UNIVERSITY OF KWAZULU-NATAL

DESIGN, SYNTHESIS AND SPECTRAL CHARACTERIZATION OF QUINAZOLINE AND BENZOXAZINE DERIVATIVES AS NOVEL DNA GYRASE INHIBITORS

BY

NARVA DESHWAR KUSHWAHA M.Sc. Pharm.Chem.

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A thesis submitted to the School of Health Science, Discipline of Pharmaceutical science, Department of Pharmaceutical Chemistry, University of KwaZulu-Natal, Westville, for the degree of Doctor of Philosophy.

This thesis has been prepared according to **Format 4** (Thesis by publications) as outlined in the guidelines of College of Health Sciences, University of KwaZulu-Natal. The chapters consist of an overall introduction, chapters in discrete research papers and a final discussion. One chapter has been published, one chapter submitted in peer reviewed internationally accepted journal and remaining chapters have been written in manuscript format.

As the candidate's supervisor, I have approved this thesis for examination/submission.

Supervisor: A/Prof. R Karpoormath

Signed: _____ Date: 08/October/2020

ABSTRACT

Tuberculosis (TB) has remained one of the leading causes of the death worldwide and recently surpassed HIV/AIDS as lethal disease caused by a single infectious agent. Further, development of resistance against frontline anti-tubercular drugs has worsened the existing alarming condition. Therefore, there is an urgent need to develop novel, more effective, inexpensive and accessible antitubercular agents possessing broad spectrum of potency short duration of drug regimen, less side effects, which can counter the drug resistant TB and reduce the burden on the society. Global scientific communities and pharmaceutical industries are aggressively involved in research to develop a novel broad spectrum anti-tubercular agent to address this rising threat to human kind. In continuation of our work, focused in developing new anti-TB agents, we have attempted to develop some potential quinazoline based DNA gyrase and topoisomerase IV inhibitors as potential anti-tubercular agents. In addition, we have developed novel green and efficient catalyst-free, mild one-pot tandem synthetic strategy to synthesize benzoxazine derivatives, that can be further exploited as building blocks for the synthesis of multifaceted molecular structures, especially for anti-tuberculosis agents.

Chapter 1 gives a brief overview on drug discovery and medicinal chemistry, history of antibiotic expansion, development of resistance in bacteria, history of anti-TB drugs discovery, line of treatment for TB, anti-tubercular drugs and their specific targets, classification of TB drugs, DNA gyrase and topoisomerase IV as a key target for anti-tubercular agents, marketed drugs and recently reported DNA gyrase inhibitors, importance of benzoxazine and quinazoline scaffold as well as significance of fluorine containing heterocycles in medicinal chemistry.

Chapter 2 describes, the development of a novel methodology which is green, efficient catalyst-free and is a mild one-pot, multicomponent synthetic strategy to construct substituted 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine. The reaction proceeds *via* in-situ formation of Schiff-base followed by base mediated alkylation with phenacyl bromide/substituted phenacyl bromide, finally leading to intramolecular cyclization to give a mixture of diastereomers with excellent diastereoselectivity (up to dr = 99:1), which were isolated as single diastereomer in moderate to excellent yields (41-92%). Besides, this new versatile methodology provides a wide scope for the synthesis of different functionally substituted benzoxazine scaffolds and can be further exploited as building blocks for the synthesis of multifaceted molecular structures, especially for pharmaceutical applications.

In **Chapter 3,** 15 novel fluorinated quinazoline derivatives have been synthesized and characterized with Infrared (IR) and Nuclear Magnetic Resonance (NMR) spectroscopic methods. This chapter also describes the influence of various substituents on the core scaffold (Fluorinated quinazoline) on its molecular conformations, intermolecular interactions and on the photoluminescent properties. Hirshfeld surfaces was used to investigate the structure-directing effects of functional groups in controlling their solid-state behaviour.

In **Chapter 4,** a total 21 novel quinazoline derivatives (**10a-q** and **17a-c**) were synthesized in good to moderate yields. The synthesized compounds were well-characterized by spectroscopic studies (IR and NMR) and evaluated for their preliminary *in vitro* screening against *Mycobacterium tuberculosis* H37Rv strain, which was conducted at TB Discovery Research, Infectious Disease Research Institute (IDRI), USA. The only notable % zone of inhibition was observed against *Mycobacterium tuberculosis* strain H37Rv for compounds **10m** which showed 33% inhibition after 24 h incubation which can be considered for further study which includes MIC, MBC etc.

In **Chapter 5,** total 23 novel *N/O*-methylated quinazoline derivatives (**10a-o, 16a-d** and **16aa-ad**) were synthesized in good to moderate yields. All synthesized compounds were well-characterized by spectroscopic studies (IR and NMR) and evaluated for preliminary *in-vitro* screening for anti-mycobacterium activity at 20 μM concentration against *Mycobacterium tuberculosis* H37Rv strain at TB Discovery Research, Infectious Disease Research Institute (IDRI), USA. The % zone of inhibition for compounds **16a**, against *Mycobacterium tuberculosis* strain H37Rv was found to be 34% after 24 h incubation.

Chapter 6 describes, the development of novel quinazoline based DNA gyrase inhibitors as potential antibacterial agents. Bacterial type II topoisomerase (DNA gyrase and topoisomerase IV) control the topological state of DNA during replication and are validated targets for antibacterial agents. Type II topoisomerase is essential in all bacteria. It is also present in eukaryotic cells but unlike the prokaryotic enzymes eukaryotic topoisomerase II is homodimeric, this difference in structure makes highly attractive targets in antibacterial drug discovery. Fluoroquinolones are an example of very active gyrase-based drugs, but the rise in bacterial resistance to these agents alarm the risk. We have replaced the central core quinolone with quinazoline ring and synthesized 22 derivatives and evaluated against DNA gyrase and topoisomerase IV enzyme of *Escherichia coli*. The most potent compound (**10l**) displayed balanced IC_{50} value of 0.49 and 13.22 μM for DNA Gyrase and topoisomerase IV of *Escherichia coli* respectively. This result is intresting for the further studies as it showed

promising well-balanced duel inhibiton in the low micromolar range against DNA gyrase and topoisomerase IV in *E. coli*.

DECLARATION 1: PLAGIARISM

I, **Narva Deshwar Kushwaha**, declare that

i. The research reported in this dissertation, except where otherwise indicated, is my original work.

ii. This dissertation has not been submitted for any degree or examination at any other university.

iii. This dissertation does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

iv. This dissertation does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then:

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Signed: Narvadeshwar Kushwaha. Date: 14/July/2020

DECLARATION 2: PUBLICATIONS

DETAILS OF CONTRIBUTION TO PUBLICATIONS that form part and/or include research presented in this thesis (include publications in preparation, submitted, *in press* and published and give details of the contributions of each author to the experimental work and writing of each publication).

Publications

1. Narva Deshwar Kushwaha, Babita Kushwaha, Rajshekhar Karpoormath*, Mavela Cleopus Mahlalela, Suraj Raosaheb Shinde. One-pot, multicomponent, diastereoselective, green synthesis of 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine analogues. Published to *The J. Org. Chem. 2020, 85, 12, 8221–8229.(doi.org/10.1021/acs.joc.0c00463).*

   Contributions: I developed the novel method, optimized the condition and did the experimental and characterization as well as writing up of manuscript under the guidance of Prof. Rajshekhar Karpoormath (Supervisor). Babita Kushwaha has contributed in experimental, characterization of the target molecules as well as writing up of manuscript. The other co-authors assisted me in synthesis of the target molecules.

2. Narva Deshwar Kushwaha, S. J. Zamisa, Babita Kushwaha, Anamika Sharma, Francis Kayambaa, Srinivas Reddy Merugu, Ab Majeed Ganai, Fernando Albericio, Rajshekhar Karpoormath*. Synthesis, Crystal structure, spectroscopic and photophysical studies of novel fluorinated quinazoline derivatives. *Submitted to Crystal Growth & Design.*

   Contributions: I did all the experimental work, characterization and writing up of the manuscript under supervision of Prof. Rajshekhar Karpoormath. S. J. Zamisa assisted me in solving the crystal structure of derivatives by single X-ray diffractometer and writing up of manuscript. Babita Kushwaha has contributed in experimental and characterization of the target molecules. Anamika Sharma assisted in theoretical calculation writing up of manuscript. Rest all co-authors assisted me in writing up of manuscript.

3. Narva Deshwar Kushwaha, Babita Kushwaha, Nisar Sayyad, Srinivasulu Cherukupalli, Aaron Korkegian, Yulia Ovechkina, Tanya Parish, Rajshekhar Karpoormath*. Design, synthesis and spectral characterization of novel quinazoline derivatives as an antitubercular agent. *Manuscript*.

Contributions: I designed the scheme and did the experimental work, characterization as well as writing up of the manuscript under supervision of Prof. Rajshekhar Karpoormath. Babita Kushwaha assisted me in experimental, characterization of the target molecules as well as writing up of manuscript. Rest co-authors assisted me in experimental and writing up of results and discussion. Aaron Korkegian carried out singlepoint evaluation of compounds efficacy against *M. tuberculosis*.

4. Narva Deshwar Kushwaha, Babita Kushwaha, Vincent A. Obakachi, Aaron Korkegian, Yulia Ovechkina, Tanya Parish, Rajshekhar Karpoormath*. Design, synthesis and spectral characterization of *N/O*-methylated quinazoline derivatives as an antitubercular agent. *Manuscript in preparation*.

   Contributions: I designed the scheme and did the experimental work, characterization as well as writing up of the manuscript under supervision of Prof. Rajshekhar Karpoormath. Babita Kushwaha contributed in experimental, characterization of the target molecules as well as writing up of manuscript. Rest co-authors assisted me in experimental and characterization of the target molecules. Aaron Korkegian carried out singlepoint evaluation of compounds efficacy against *M. tuberculosis*.

5. Narva Deshwar Kushwaha, Babita Kushwaha, Ruchika Chauhan, Balakumar Chandrasekaran, Meenu Ghai, Srinivas Reddy Merugu, Rajshekhar Karpoormath*. Discovery of quinazoline-based DNA Gyrase Inhibitors as Potential Anti-Tubercular Agents. *Manuscript in preparation*.

   Contributions: I designed the scheme and did the experimental work, characterization as well as writing up of the manuscript under supervision of Prof. Rajshekhar Karpoormath. Rest co-authors assisted me in experimental and writing up of manuscript. Meenu Ghai facilitated the genetic laboratory, Ruchika Chauhan and Babita Kushwaha carrying out DNA gyrase enzyme inhibition assay.

Conference contributions

1. **Poster presentation:** Design and synthesis of novel carbazolo-thiazoles as potential anti mycobacterial agents using a molecular hybridization approach†. College of Health Sciences Research Symposium, held at Nelson R Mandela School of Medicine Campus, Durban, South Africa, from 5th to 6th October **2017**.
2. **Oral presentation**: Copper-catalyzed Self-condensation of Benzamide: Formation of Quinazolinone via Domino Reaction. College of Health Sciences Research Symposium, held at Nelson R Mandela School of Medicine Campus, Durban, South Africa, from 11th to 12th October **2018**.

3. **Poster presentation:** Synthesis of 4,6-disubstituted pyrazolo[3,4-*d*] pyrimidine analogues: Cyclin-dependent kinase 2 (CDK2) inhibition, molecular docking and anticancer evaluation. College of Health Sciences Research Symposium, held at Nelson R Mandela School of Medicine Campus, Durban, South Africa, on 1st November **2019**.

Other publications

1. Nisar Sayyad, Zamani Cele, Rajeshwar Reddy Aleti, Milan Bera, Srinivasulu Cherukupalli, Balakumar Chandrasekaran, **Narva Deshwar Kushwaha,** and Rajshekhar Karpoormath*. Copper-Catalyzed Self-Condensation of Benzamide: Domino Reactions towards Quinazolinones. *Eur. J. Org. chem.* **2018**, *2018*, 5382-5388.
2. Srinivasulu Cherukupalli, Balakumar Chandrasekaran, Vladimír Kryštof, Rajeshwar Reddy Aleti, Nisar Sayyad, Srinivas Reddy Merugu, **Narva Deshwar Kushwaha,** Rajshekhar Karpoormath*. Synthesis, anticancer evaluation, and molecular docking studies of some novel 4,6-disubstituted pyrazolo[3,4-d] pyrimidines as cyclin-dependent kinase 2 (CDK2) inhibitors. *Bioorg. Chem.* **2018**, 79, 46-59.

Signed: Narvadeshwar Kushwaha. Date: 14/July/2020

Dedicated

to

My Mother, a strong and gentle soul,
who has taught me spirituality and believing
in God,
My Father for his unconditional perpetual
care, who has taught me to believe in hard
work and honesty,
My beloved Wife for her support and loves
all the way, without whom none
of my success would be possible
My Brothers for their unconditional care,
continuous support, who have raised me to be
the

person I am today

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LIST OF ABBREVIATIONS

ACN	: Acetonitrile
AIDS	: Acquired immune deficiency syndrome
API	: Active Pharmaceutal Ingredient
Ar	: Aromatic ring
ATP	: Adenosine triphosphate
ATR	: Attenuated total reflectance
BH_3	: Trihydridoboron
brs	: Broad singlet
BSA	: Bovine serum albumin
$CDCl_3$	: Deuterated chloroform
CF_3	: Trifluoromethyl
$CHCl_3$	: Chloroform
CH_3CN	: Acetonitrile
CH_3I	: Methyl iodide
CIF	: Crystallographic information file
cm^{-1}	: Centimeters
^{13}C NMR	: Carbon -13 nuclear magnetic resonance
COSY	: Correlation spectroscopy
Cs_2CO_3	: Caesium carbonate
CuI	: Copper (I) iodide
2D	: Two-dimensional
d	: Doublet
DCM	: Dichloromethane
DFT	: Density functional theory
DFP	: Difluorophenyl
DHFR	: Dihydrofolate reductase
DIPEA	: Diisopropylethylamine
DMA	: Dimethylacetamide
DMAP	: Dimethylaminopyridine
DMF	: Dimethylformamide
DMHQ	: 1,3-dimethyl-2,3-dihydroquinazolinonyl
DMSO-*d6*	: Deuterated dimethyl sulphoxide
DNA	: Deoxyribonucleic acid

DOTS : Directly observed treatment, short-course

DSSCs : Dye-sensitized solar cells

DTT : Dithiothreitol

EDC.HCl : 1-Ethyl-3-(3-dimetylaminopropyl) carbodimide hydrochloride

EDTA : Ethylenediaminetetraacetic acid

EGFR : Epidermal growth factor receptor

EtOH : Ethanol

FDA : Food and Drug Administration

Fe : Iron

^{19}F NMR : fluorine -19 nuclear magnetic resonance spectroscopy

FTIR : Fourier transform infrared spectroscopy

Gyr : Gyrase

h : Hours

HATU : Hexafluorophosphate Azabenzotriazole tetramethyl Uronium

HIV : Human immunodeficiency virus

HMBC : Heteronuclear multiple bond coherence

HOMO : Highest occupied molecular orbital

^{1}H NMR : Proton nuclear magnetic resonance

HSQC : Heteronuclear single quantum coherence

IC_{50} : The drug concentration causing 50% inhibition

ICT : Intramolecular charge transfer

IDRI : Infectious disease research institute

IR : Infrared Spectroscopy

IUPAC : International Union of Pure and Applied Chemistry

J : Coupling constant

$J_{C\text{-}F}$: Carbon-Fluorine coupling

KBr : Potassium bromide

KCl : Potassium chloride

K_2CO_3 : Potassium carbonate

kDa : Kilodaltons

kDNA : Kinetoplast Deoxyribonucliec acid

$KHCO_3$: Potassium hydrogen carbonate

$KMnO_4$: Potassium permanganate

KOH : Potassium hydroxide

LUMO : Lowest unoccupied molecular orbital

m : Multiplet
MBC : Minimum bactericidal concentration
MDR : Multi drug resistant
MDR-TB : Multi drug resistant tuberculosis
MeOH : Methanol
$MgCl_2$: Magnesium chloride
MHz : Megahertz
MIC : Minimum inhibitory concentration
mL : Millilitre
mp : Melting point
Na_2CO_3 : Sodium carbonate
$NaHCO_3$: Sodium hydrogen carbonate
NaH : Sodium hydride
NaOH : Sodium hydroxide
Na_2SO_4 : Sodium sulphate
NH_4Cl : Ammonium chloride
NLO : Non-linear optics
NMR : Nuclear magnetic resonance
NOESY : Nuclear overhauser effect spectroscopy
OADC : Oleic Albumin Dextrose Catalase
OD : Optical density
OLEDS : Organic-light emitting diodes
OPV : Organic photovoltaic devices
OTFT : Organic field effect transistors
PAS : *para*-aminosalicylic acid
POCl3 : Phosphoryl chloride
ppm : Parts per million
*p*TSA : *p*-Toluenesulfonic acid
q : Quartet
RR-TB : Rifampicina resistant tuberculosis
R&D : Research and development
rpm : Revolutions per minute
RSA : Republic of South Africa
RT : Room temperature
s : Singlet

SDS	: Sodium Dodecyl sulphate
S_N2	: Substitution nucleophilic (bi-molecular)
Str.	: Stretching
t	: Triplet
TAE	: Tris-acetate EDTA (Ethylenediaminetetraacetic acid)
TB	: Tuberculosis
*t*BuONa	: Sodium tert-butoxide
TD-DFT	: Time-dependent density-functional theory
TDR-TB	: Totally drug resistant tuberculosis
TEA	: Triethylamine
THF	: Tetrahydrofuron
TMS	: Tetramethylsilane
Topo IV	: Topoisomerase IV
UV	: Ultraviolet
UV/vis	: Ultravoilet-visible
WHO	: World Health Organization
XDR	: Extensively drug resistant
XDR-TB	: Extensively drug resistant tuberculosis

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CHAPTER 1

1. General Introduction

1.1. Drug discovery and medicinal chemistry

The field of Medicinal chemistry along with pharmacology has played a crucial role in the discovery of new medicines, which has inturn improved the quality of life for the human kind. Since last century medicinal chemists have been using perception in designing the molecules to exhibit biological activity.[1] It is originally stated by eminent Chemist, Professor Alfred Burger, Medicinal Chemistry still "*...remains a challenging science which provides profound satisfaction to its practitioners...*".[2] The IUPAC defines Medicinal Chemistry as "*...a chemistry-based discipline, also involving aspects of biological, medical and pharmaceutical sciences. It is concerned with the invention, discovery, design, identification and preparation of biologically active compounds, the study of their metabolism, the interpretation of their mode of action at the molecular level and the construction of structure-activity relationships*".[3]

Several pharmaceutical companies are investing millions of dollars in medicinal chemistry programs. However, the correct approach is key differentiator for fast and efficient drug discovery which involves interrogation of hypothesis in a cycle involving design, synthesis, test and analysis (**Figure 1**). There are several stages for approval of the drug for the market (**Figure 1**) of which most stages are performed in industry. Public sector including academia is involved mainly in biochemical pathways, early stage compound identification/generation and target identification.[4]

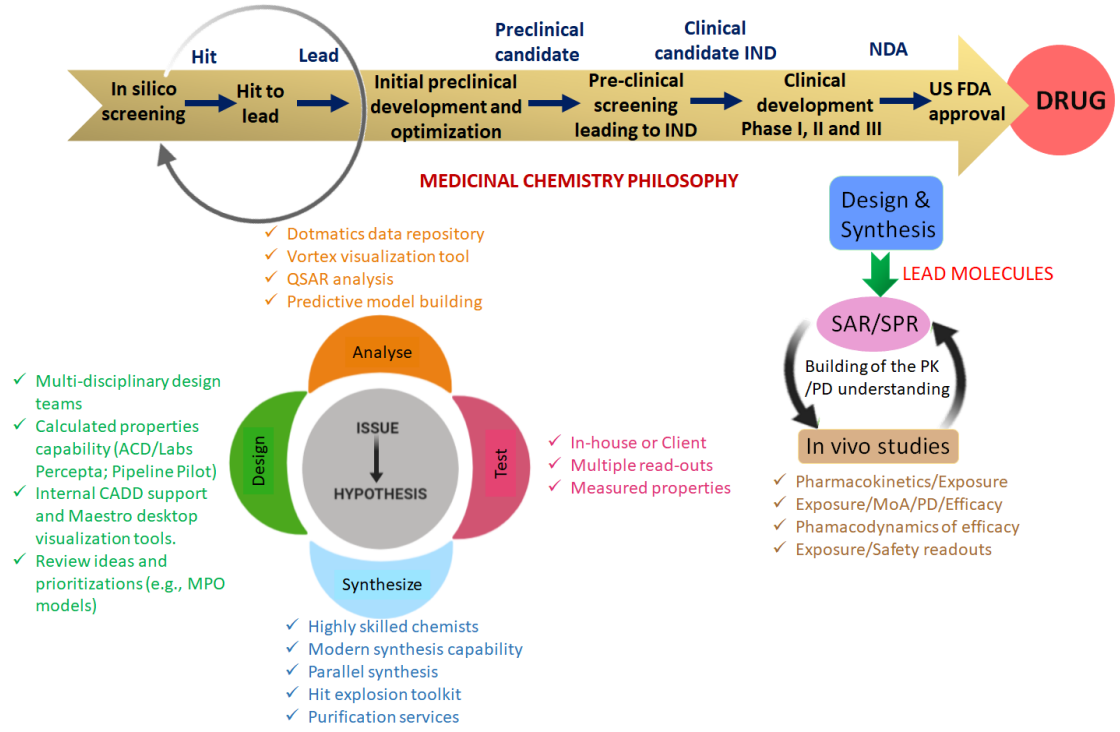

Figure 1: Stages in drug development and several approaches in medicinal chemistry.

The synthesis of antibiotics dates back to a century. The complete lineage for the development of antibiotics has been summarized in **Figure 2**.

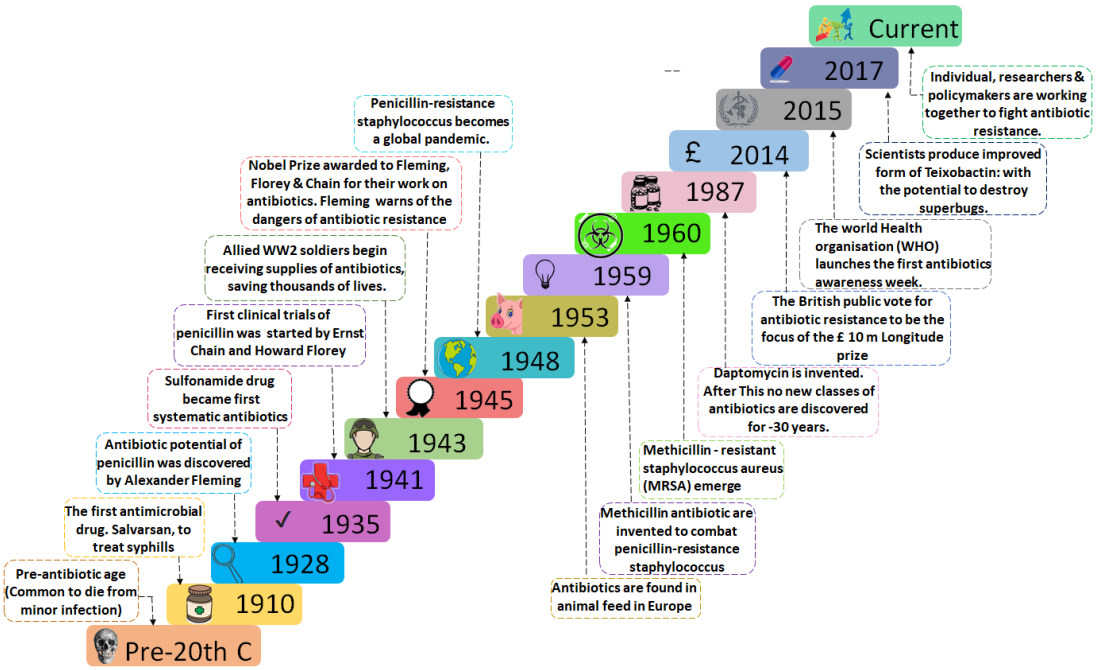

Figure 2: History of antibiotic development.

Over the years antibiotic drug resistance has become a major challenge currently faced by research and development (R&D) centers, pharmaceutical industries and medicinal chemists (**Figure 3**). Microorganisms are diverse organisms consisting of bacteria, fungi, archaea, protozoa, etc., responsible for several infectious diseases in humans and animals.

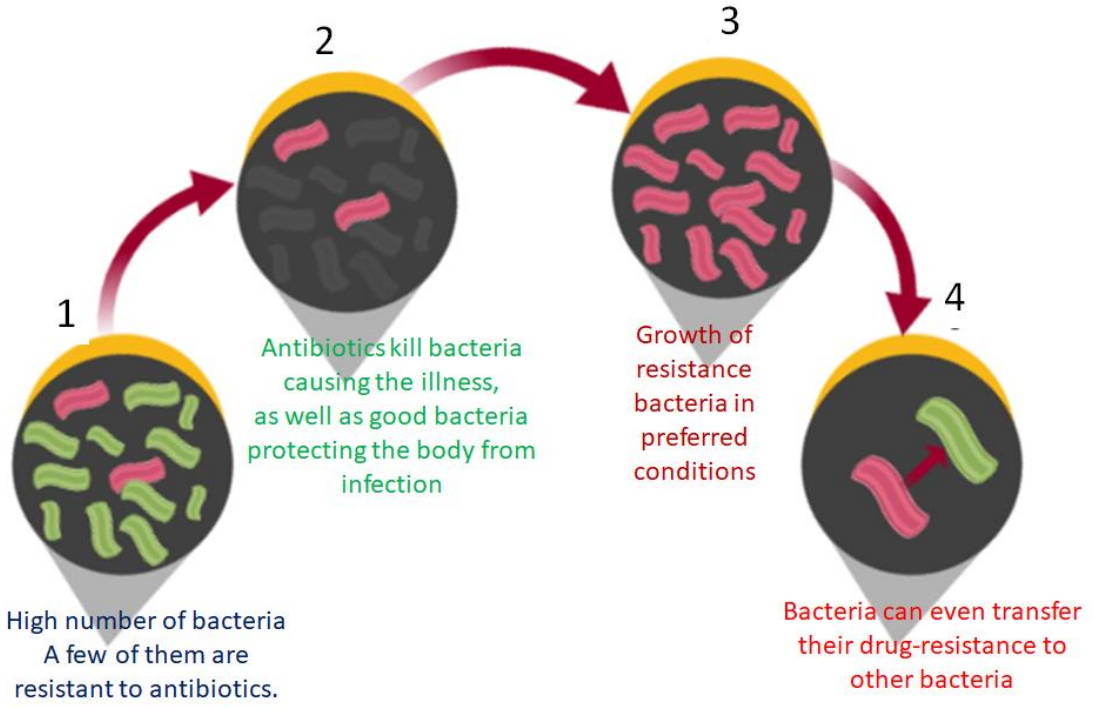

Figure 3: Development of resistance in bacteria.

According to the World Health Organization (WHO), several million deaths occure every year from bacterial infections alone, such as Scarlet fever (*Streptococcus pyogenes*), Food poisoning (*Escherichia coli*), Pneumonia (*Streptococcus pneumoniae*), Syphilis (*Treponema pallidum*), Tuberculosis (*Mycobacterium tuberculosis*) etc.[5] Emergence of HIV has further complicated the treatment and management of patience due to microbial co-infectious, especially *Mycobacterium tuberculosis* (*M. tuberculosis*) alone leading to 1.5 million deaths annually.[6] It is well documented that TB is more prevalent in people with HIV due to their compromised immunity responsible for several millon deaths annually.[7-9] According to WHO in 2017 alone, 10.0 million fell sick and 1.3 million died due to this life-threatening ailment.[10] The WHO estimates (2016), about 124,000 people in South Africa (about 330 daily), which is about 80 %, were found to be infected with HIV. South Africa has the highest TB incidence rate in the world at 340 persons per 100 000 population, with a budget expenditure of 271 million US $.[11] It has become country's leading death cause even greater than HIV.

TB results from bacterial infection which is a formidable, contagious and airborne disease. The causative organism for this fatal disease was unknown until 24th March 1882 when Dr Robert Koch revealed the discovery of bacillus *M. tuberculosis*, as the main causative bacteria of TB. This day is now commemorated as World TB Day every year.[12] During late 18th centuary, TB TB was raging in America and Europe with one death for seven people. Koch discovery of *M. tuberculosis* as the causative microorganism opened the broad idea of finding the cure for TB including its diagnosis. *M. tuberculosis* genome comprises of approximately 3950 genes of which ~10% (nearly 461 genes) are required for growth and survival of the bacillus in vitro under standard aerobic growth conditions.[13]

1.2. Treating TB

Several remarkable drug discoveries have been made worldwide after the discovery of *M. tuberculosis* (**Figure 4**).[14] Pyrazinamide was the first synthesized anti TB drug but was only in full use after 1972 along with isoniazid, rifampicin and ethambutol.

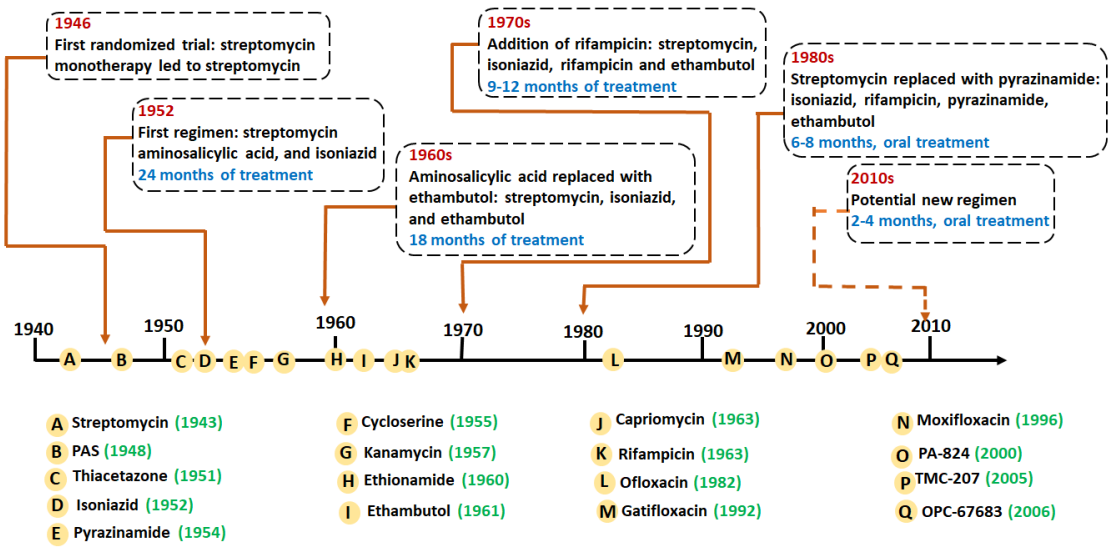

Figure 4: Time line depicting the discovery of various Anti-TB drugs.

In this field, there has been outstanding growth achieved for the treatment of TB after the introduction of *Streptomycin* in 1947. However, its potential as drug was completely utilized along with isoniazid in 1952. Following the drug discovery program, ethambutol (1961) and rifampin (1962) were introduced as the first line treatment TB drugs.[11, 15] In addition, second line drugs like *para*-aminosalicylic acid (PAS), ethionamide, cycloserine, amikacin and capreomycin have been accepted by FDA, but are known to elicit severe adverse reactions frequently.[16] Fluoroquinolones, delamanid, bedaquiline, ethionamide, rifabutin, macrolides

related drugs and some rifampin related congeners are the recent additions to anti-TB drug regimen. **Figure 5** shows the development of TB drugs.

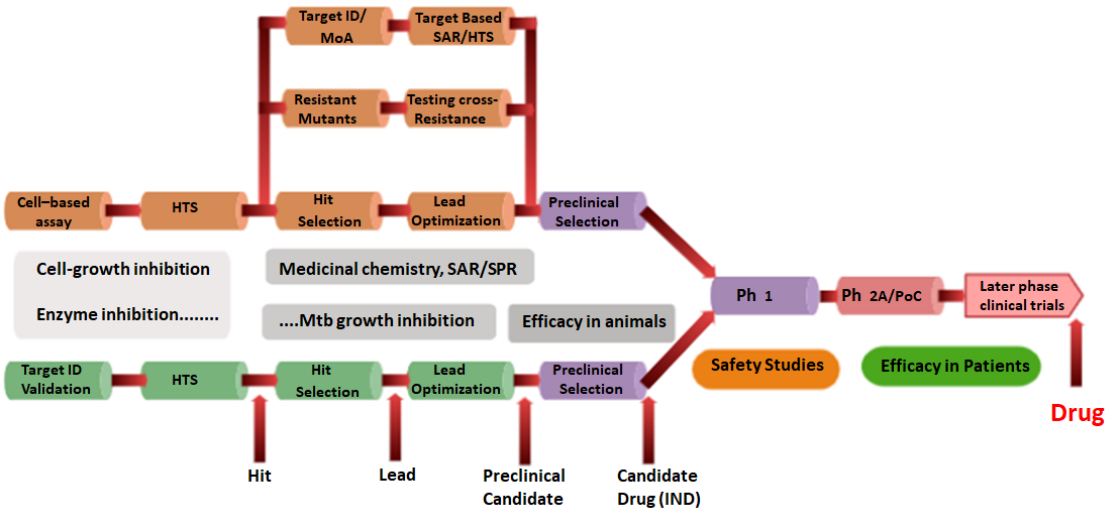

Figure 5: Schematic representation of anti-TB Drug development against *M. tuberculosis*.

The treatment for TB by standard combination of four anti-microbial drugs (isoniazid, rifampicin ethambutol and pyrazinamide)is performed under directly observed treatment short course (DOTS) for a span of six months (**Figure 6**).[17, 18] Due to constant increment in the field of drug discovery and the line of treatment for TB, the decrement of mortality rate has been witnessed in recent years with 53 million lives saved until 2017.[19] However, there is an urgency for the development of new TB drugs due to the rapid emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB strains, which are posing a serious threat to mankind.[20] Drug resistance in *M. tuberculosis* was predicted based upon two mechanisms viz., acquired drug resistance and primary drug resistance.[18, 20] Currently, delamanid finds application against MDR-TB and bedaquiline in treating both XDR-TB and MDR-TB.[21, 22]

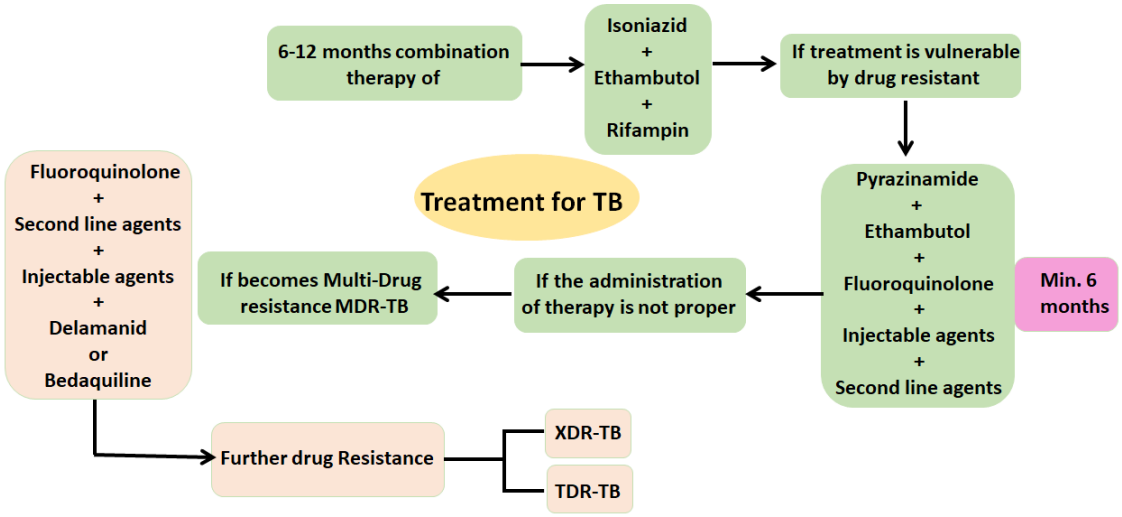

Figure 6: TB drug regimen for treatment.

1.3. Classification of TB drugs and targets

Anti-TB drugs are broadly classified as bactericidal and bacteriostatic with various targets onto bacteria which includes inhibitors of cell wall, protein synthesis, nucleic acid and membrane energy metabolism as shown in **Figure 7**. Each category comprises of drugs from first line and second line of treatment as shown in **Figure 8.**[23-25] Apart from the above, p-aminosalicylic acid[26] which is a prodrug targeting dihydrofolate reductase (DHFR) in M. tuberculosis and Clofazimine (initially referred to as B.663.254) effective against MDR-TB are also known for treatment of TB.[27]

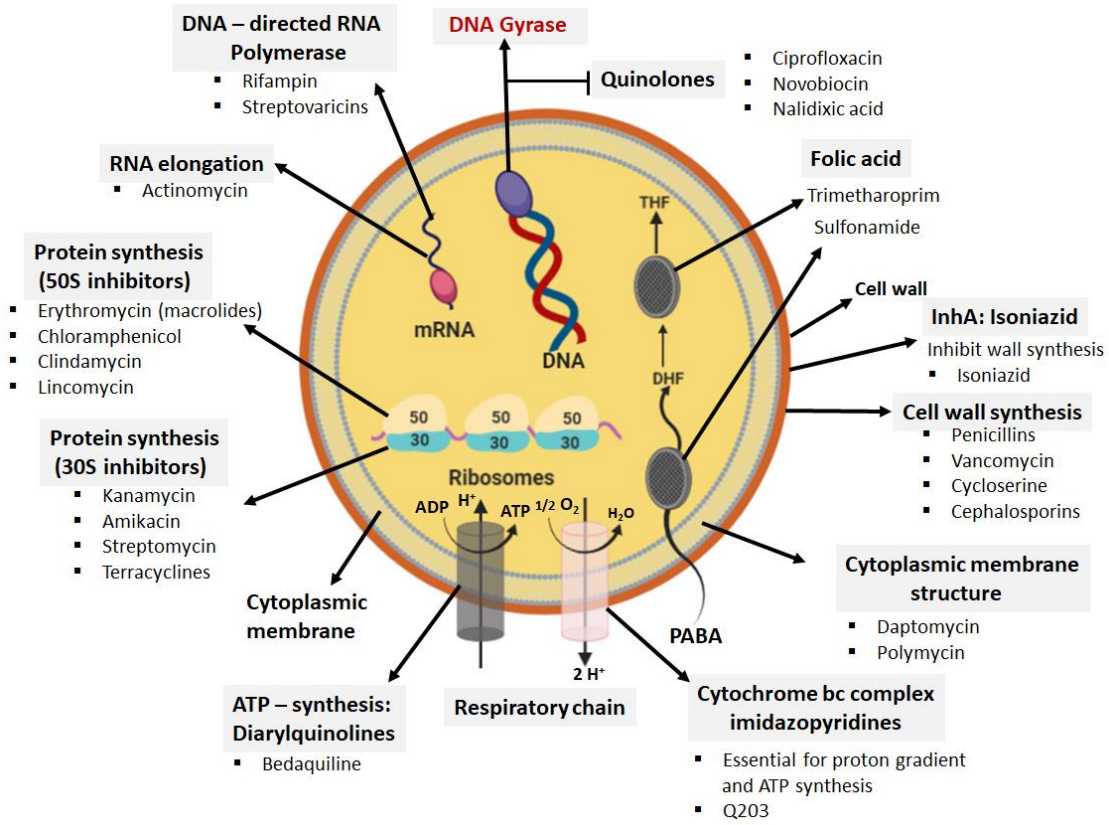

Figure 7: Antibiotics and their specific targets.

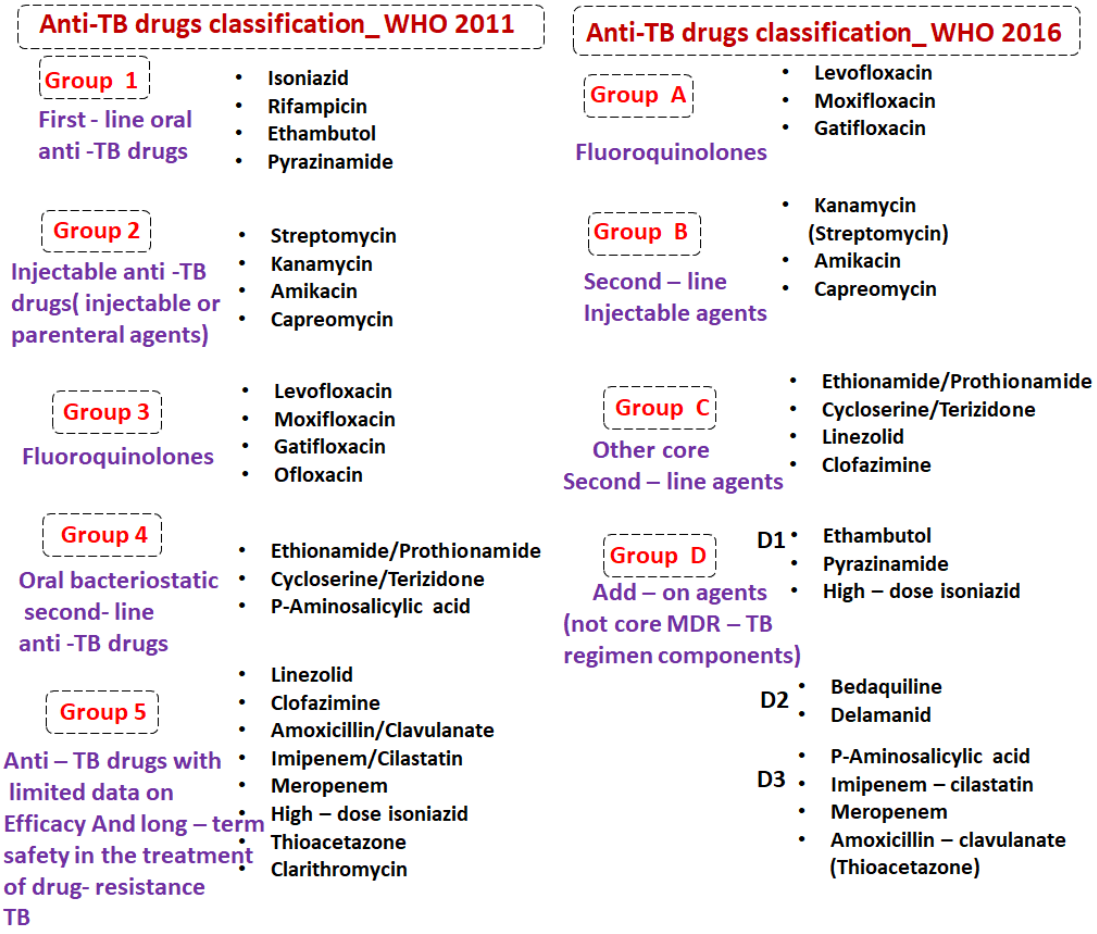

Figure 8: Classification of anti-TB drugs.[23-25]

1.4. Mechanism of bacterial drug resistance

In order to combat the bacterial resistance of TB, it is crucial to understand the drug resistance mechanism which they develop to overcome the damage which is caused by antibiotic treatments. This adaptive mechanism plays a key role for microbial survival and evaluation. Drug resistance can be due to enzymatic inactivation of the antibiotic molecule, decreased cell wall permeability to antibiotics, modification of a target site to prevent antibiotic interaction, promotion of an efflux mechanism to remove the antibiotic from the cell (**Figure 9**). The hunt for newer anti-TB drugs has been epicenter since last few decades due to constant increment of MDR/XDR-TB cases.

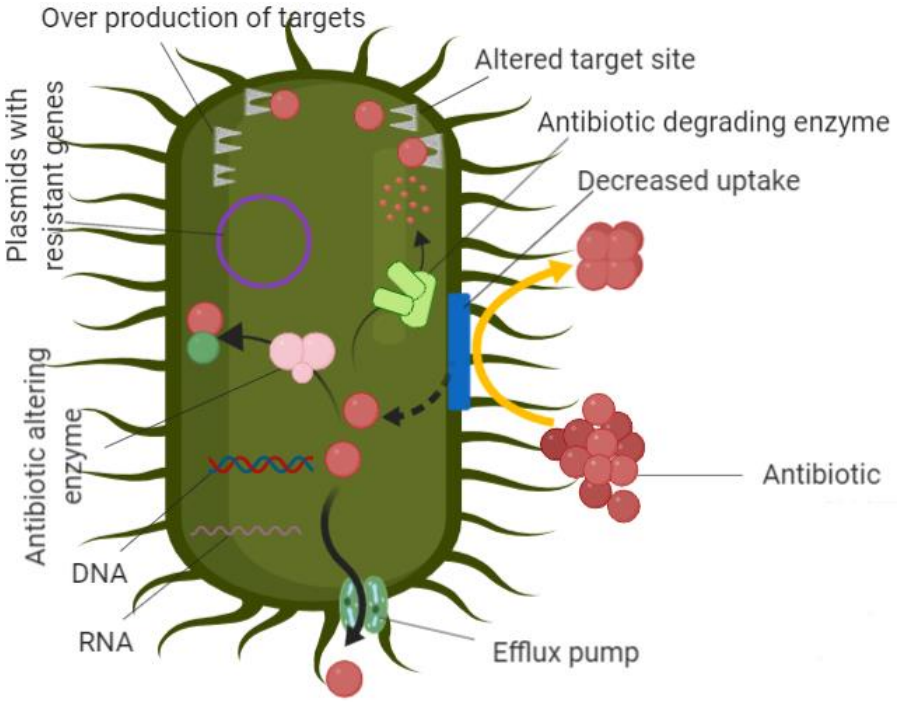

Figure 9: Different mechanism for drug resistance.

1.5. DNA topoisomerases as key target

DNA topoisomerases are set of enzymes which are responsible for changing the topology of DNA.[28, 29] These enzymes are found in both eukaryotic and prokaryotic cells and hence are essential for survival. They are divided mainly into 2 types, I and II [29, 30] (**Figure 10**). In general, all topoisomerases are known to relax super coiled DNA but only type II (also known as DNA gyrase) introduces negative supercoils which in turn requires ATP hydrolysis.[31] DNA gyrase comprises of two subunits A and B which forms heterodimer structure (A_2B_2 complex). DNA Gyrase A also known as Gyr A is involved in nicking and ligation of DNA (N-terminal with 59-64 KDa) and DNA protein interaction (C-terminal 33 kDa). DNA Gyrase B also known as Gyr B is the powerhouse in DNA replication as it has a key role in controlling ATPase activity (N-terminal with 43 KDa) and interacts with both Gyr A and DNA (C-terminal 47 kDa).[32] The mechanism of supercoiling of DNA Gyrase has been demonstrated by a generic model known as "two-gate mechanism" which makes it an attractive antibacterial target.[30] Currently, there are two main groups of antibiotics targeting DNA Gyrase. Firstly, coumarine (natural antibiotic) which are known to inhibit DNA Gyrases by competing with ATP for binding to Gyr B[33] and quinolones (synthetic antibiotics) which react with N-terminal of Gyr A to inhibit DNA segregation and induce irreversible DNA damage.[34] Although DNA Gyrase is the main target for quinolones in Gram-negative bacteria but in case of Gram-positive organisms' topoisomerase IV is also the preferred target. Quinolones are known to interact with DNA

mainly by enzymatic interaction and disrupting the DNA cleavage-religation process[32] which has been revealed by X-ray structures of fragments of gyrase (and topo IV) complexed with DNA and quinolone drugs.[35] However, a small category of TB drugs (fluoroquinolones, like moxifloxacin and gatifloxacin) targets DNA Gyrase for the treatment of MDR-TB.[36]

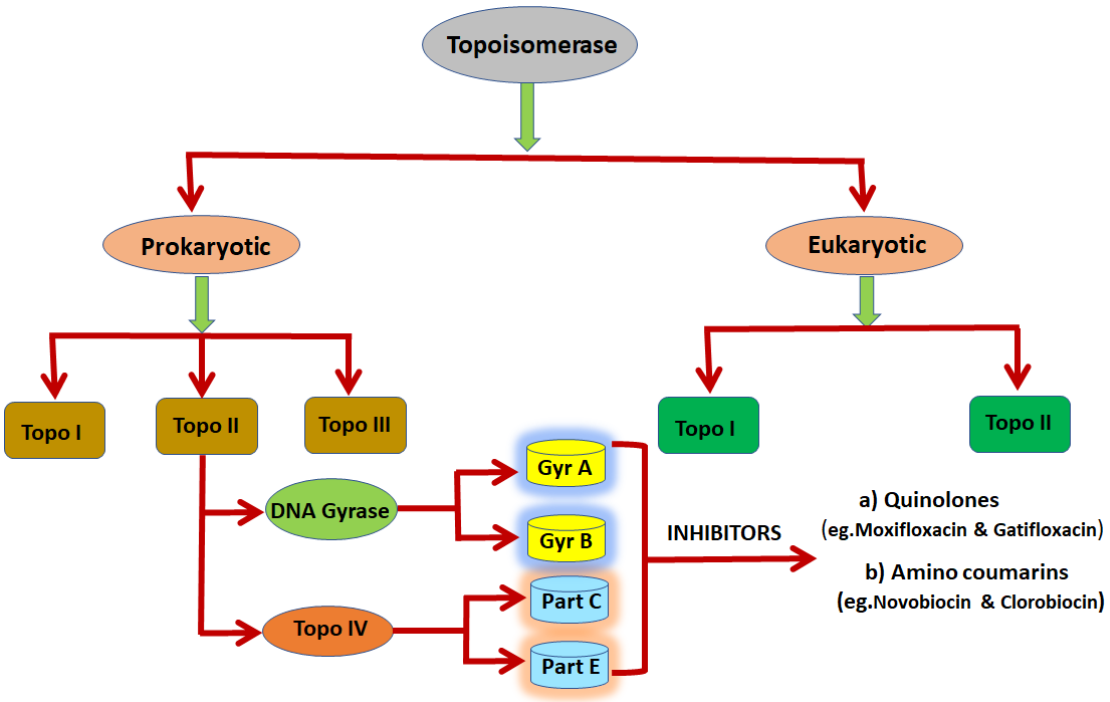

Figure 10: Topoisomerase and their subunit with Inhibitors.

1.6. DNA Gyrase and topoisomerase IV inhibitors

DNA gyrase and topoisomerase IV are the established and validated targets of aminocoumarin and quinolones/fluoroquinolones (**Figure 11**).[32, 37] Although these two types of inhibitors target different parts of the enzymes. Well known and broadly used synthetic antibiotics (quinolones/fluoroquinolones) target GyrA and ParC subunits, while natural product aminocoumarins (novobiocin and clorobiocin) target GyrB and ParE subunits. Over the past few years, revalent research has been underway by many research groups to discover novel DNA gyrase inhibitors (**Figure 11**)[38-41] with improved enzyme affinities, more effective antibacterial activities, and favourable pharmacokinetic.

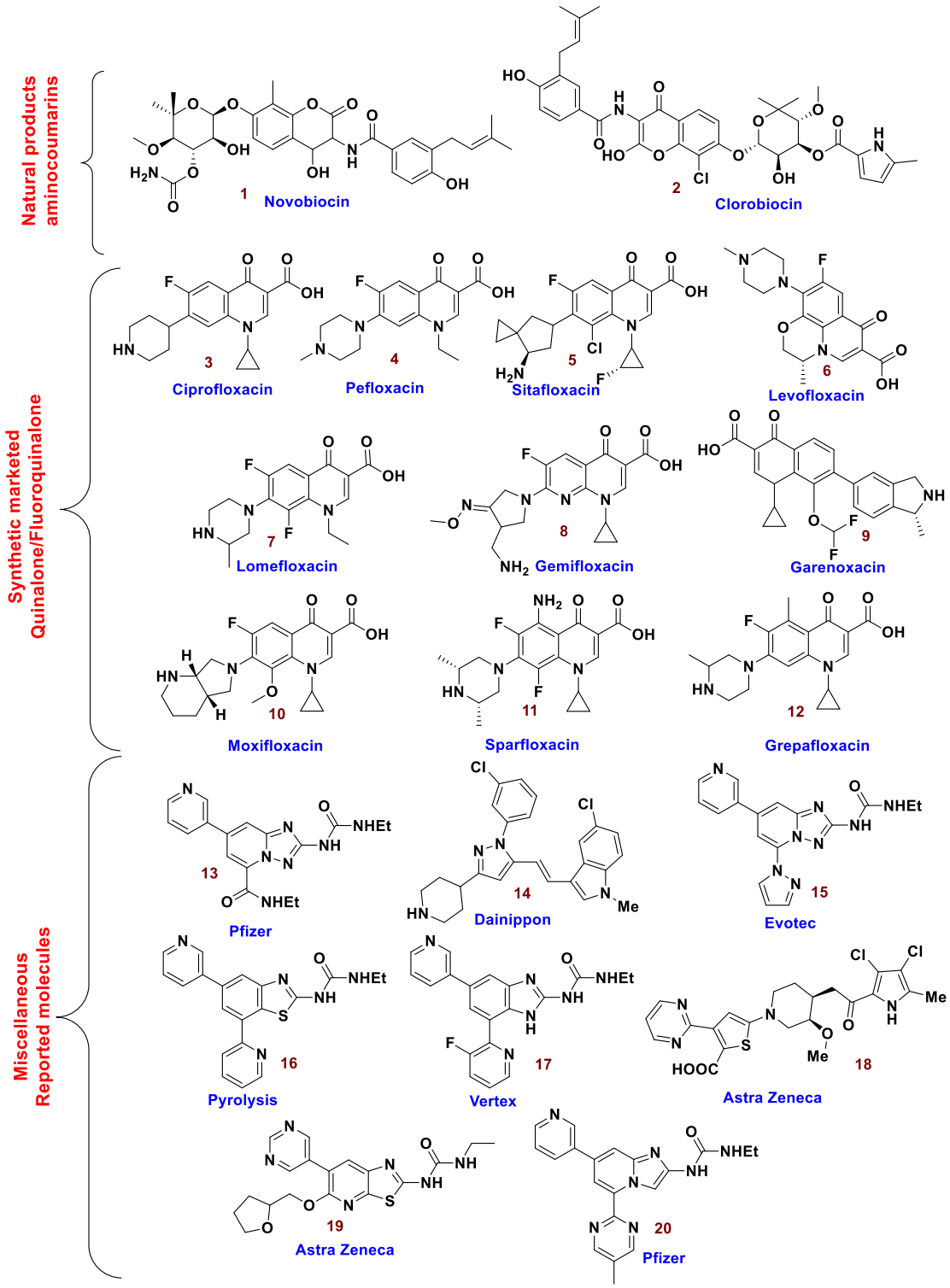

Figure 11: Marketed drugs and recently reported DNA gyrase inhibitors.[32, 37-41]

1.7. Benzoxazine: An important scaffold for medicinal chemistry

Benzoxazines are important class of heterocyclic scaffolds known for their widespread pharmacological and biological significance (**Figure 12**),[42-47] and have therefore attracted considerable interest in design and development of new greener synthetic strategies for the construction of these heterocycles. It is well documented that benzoxazine moiety has been used as a building block in developing new pharmaceutical lead compounds, which have displayed wide range for pharmaceutical applications such as neuroprotective agents,[48, 49] antidiabetic,[50] antiarrhythmics against ischemia-reperfusion injury,[51] calcium antagonist,[52] potassium channel modulators,[53] and antihyperlipidemic agents[54] etc. Owing to broader range of pharmacological properties, enormous number of synthetic approaches have been developed to synthesize novel 1,4-benzoxazine derivatives (**Figure 13**).

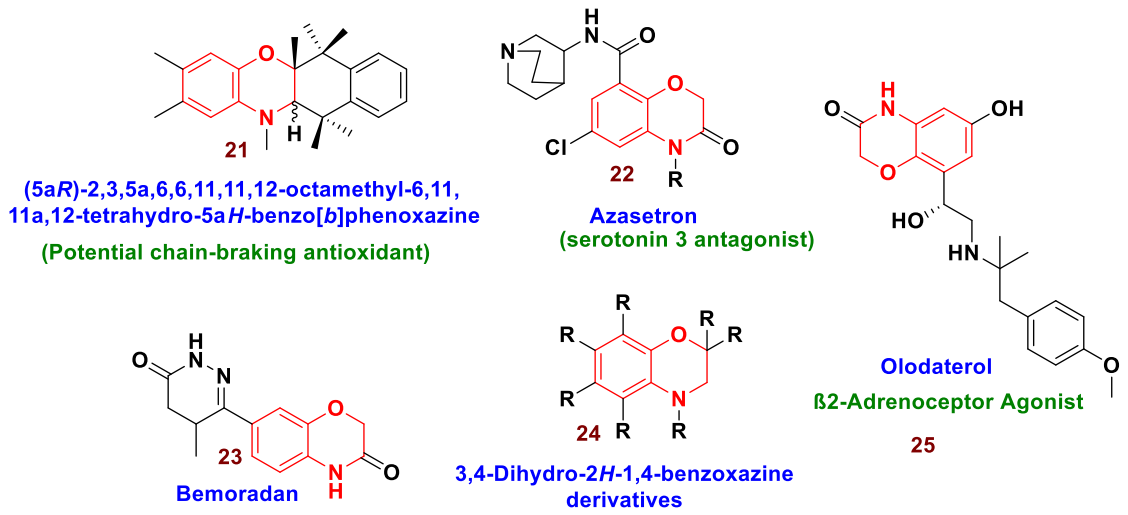

Figure 12: Commercial drugs bearing benzoxazines moiety.[42-47]

Traditionally, the reported methods used multistep synthetic approaches for the synthesis of 1,4-benzoxazine moiety (**Figure 13**) such as; **a**) cyclocondensation of amino phenols with α-halogeno acyl bromides along with reduction of carbonyl with BH_3, **b**) alkylation of *o*-nitrophenol with haloester followed by reductive cyclization,[55] **c**) intramolecular copper-catalysed *O*-arylation of *β*-aminoalcohols[56] and **d**) epoxide ring opening with *O*-halosulfonamides followed by cyclization was used to render these 1,4 benzoxazine moieties.[57] **e**) Recently, in 2017 Cuie Wang and co-workers reported a new method for the synthesis of 1,4 benzoxazine by the cyclization of Schiff-base with α-haloketones using DMAP as catalyst in DMF at 120°C[58] and **f**) in the following year Abhijit Mall *et al.* (2018) reported an efficient strategy for the synthesis of 3,4-dihydro 1,4 benzoxazine derivatives *via* Lewis acid catalysed

S_N2 type ring opening of activated aziridine with 2-halophenol followed by Cu(I)-catalysed cyclization.[46]

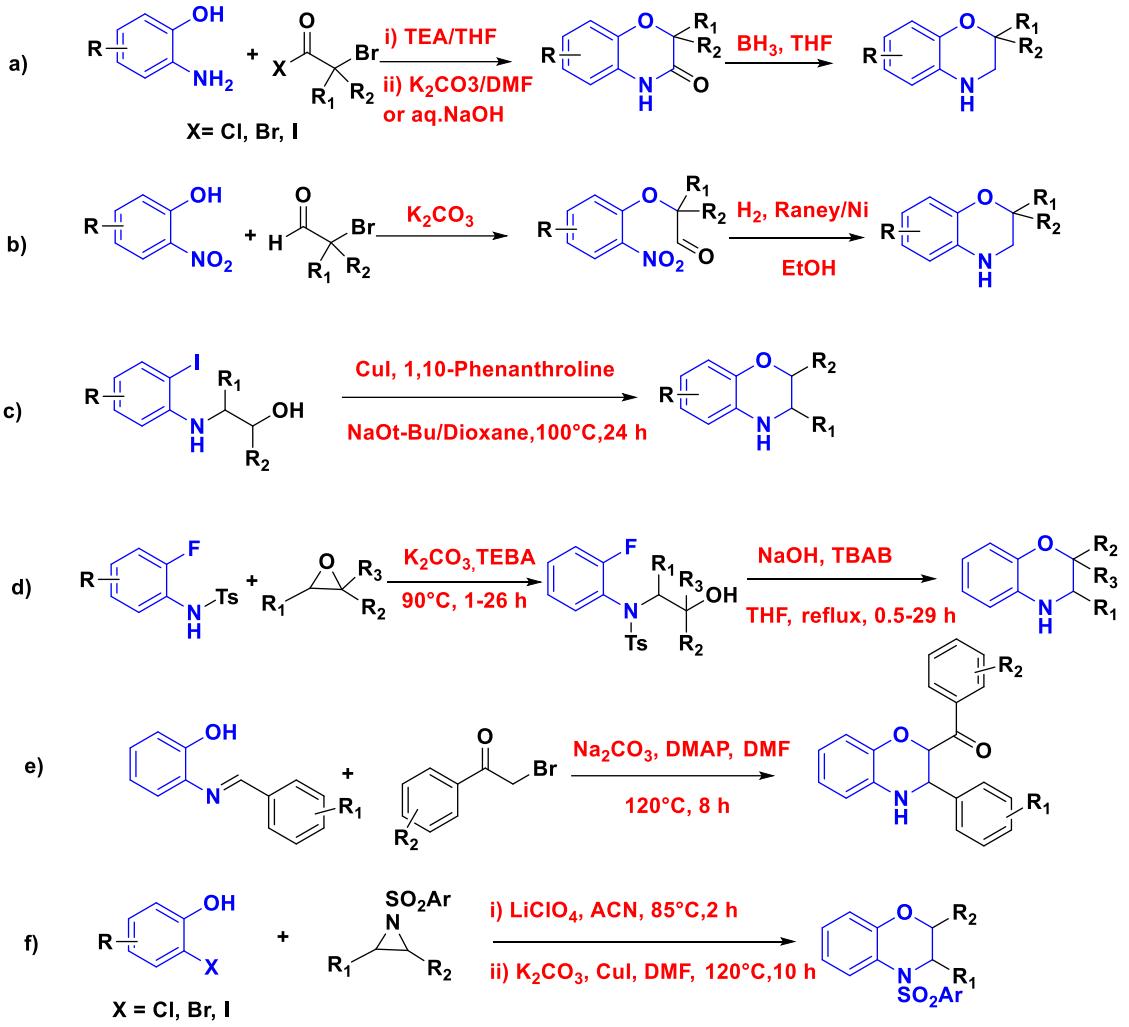

Figure 13: Some reported approach for the synthesis of 1,4 benzoxazine derivatives.[46, 55-58]

1.8. Benzoxazine and TB

Benzoxazine based core moieties are also known to exhibit activity against *M. tuberculosis.* Undoubtedly levofloxacin and ofloxacin are the well-known and noteworthy marketed drugs containing benzoxazine heterocycle as its core moiety (**Figure 14**) have been extensively used as anti-tuberculosis agent.[59, 60] Some benzoxazine analogues have been reported in literature to be highly effective against in-vitro anti-tubercular with minimum inhibitory concentration as shown in **Figure 14**.[61]

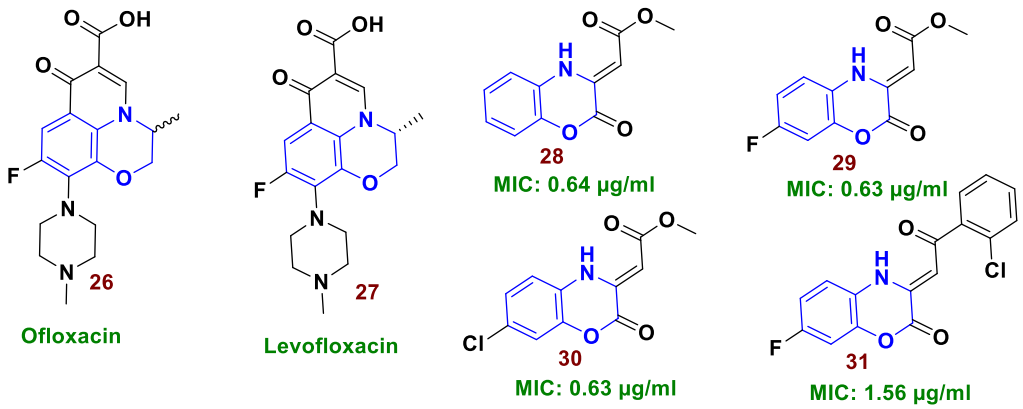

Figure 14: Benzoxazine based marketed drugs and recent reported derivatives with potent anti-tubercular activity.[21, 59-61]

1.9. Quinazoline: An important scaffold for medicinal chemistry

Quinazoline is one of the most predominant skeletons in organic chemistry which finds application in medicinal chemistry.[62-65] The first synthesis of quinazoline dates to late 1890s with extensive studies on the quinazoline (1, 3-diazanaphthalene) structure in 1903 by Gabriel and was isolated from Chinese plant aseru. Quinazoline derivatives are present in high concentration in *Rutaceae* plant family.[66] However, the name was proposed by Widdege in 1887.[67, 68] However, since then several protocols/methods have been proposed to synthesize quinazoline derivatives. Quinazoline derivatives synthesis are based on the substitution on ring.[69] Several commercial drugs bearing quinazoline core unit are known in market (**Figure 15**). Quinazoline derivatives are well documented as known sedatives, but are also known to exhibit anti-inflammatory,[70] antimicrobial,[71, 72] anticancer,[73-75] anticonvulsant,[76] and antifungal activities.[77]

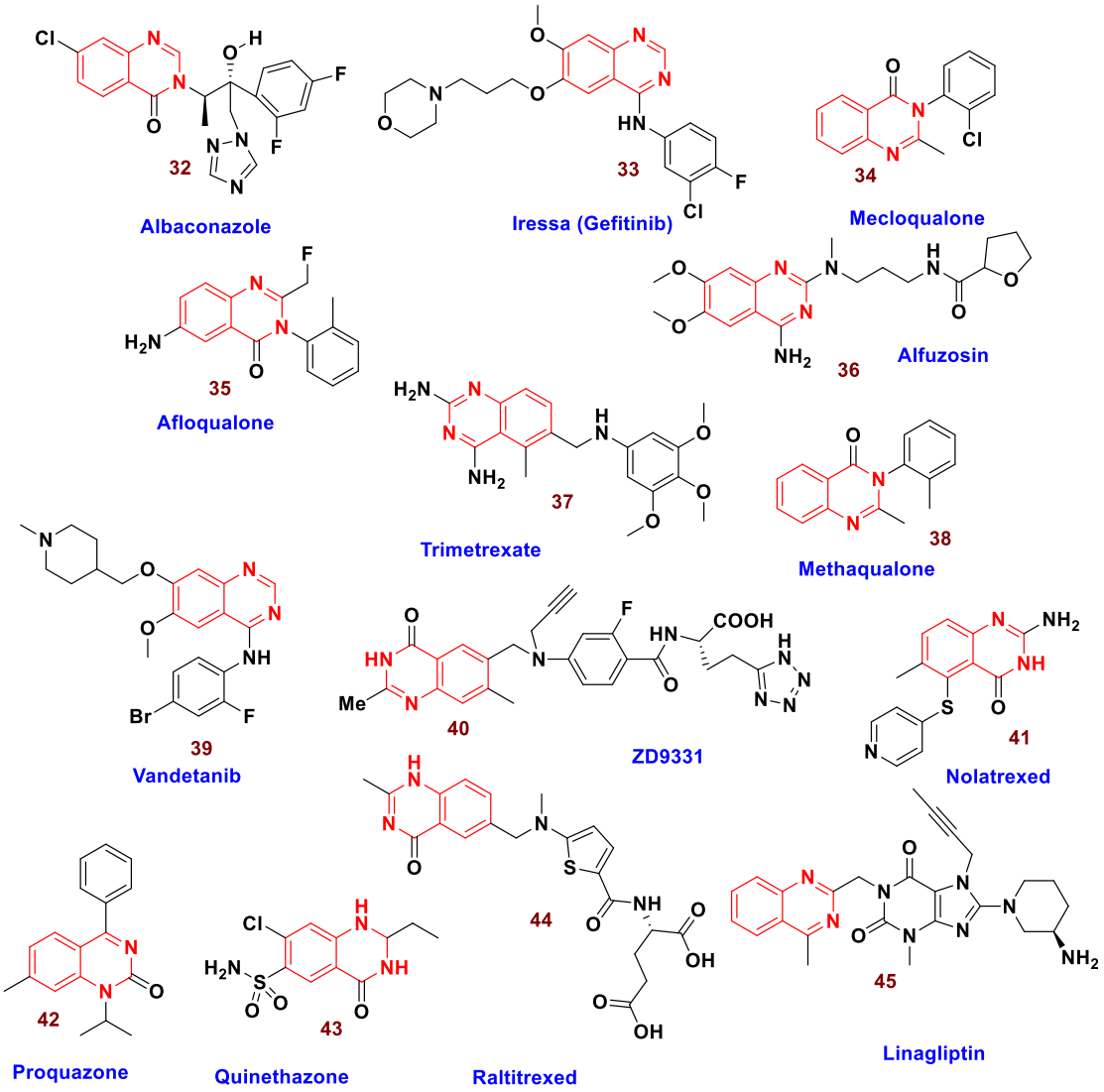

Figure 15: Commercial drugs bearing quinazoline moiety.

1.10. Quinazoline and TB

Quinazoline based molecules are also known to exhibit activity against *M. tuberculosis*.[78] Some quinazoline analogues have been reported in literature to be highly effective against *in-vitro* anti-tubercular with minimum inhibitory concentration (MIC) as shown in **Figure 16**.[79] In another report, several quinazoline derivatives have been shown to display significant anti-tubercular activity against *M. tuberculosis* H37Rv with substantial low cytotoxicity.[80]. Tryptanthrin analogues have been known to show potency against multi-resistant TB strains. These derivatives are reported to be close in efficacy compared to known anti-tubercular compounds streptomycin and ethambutol.[81] Several other reports have also reported the synthesis of quinazoline based derivatives having high anti-tubercular activity.[82, 83]

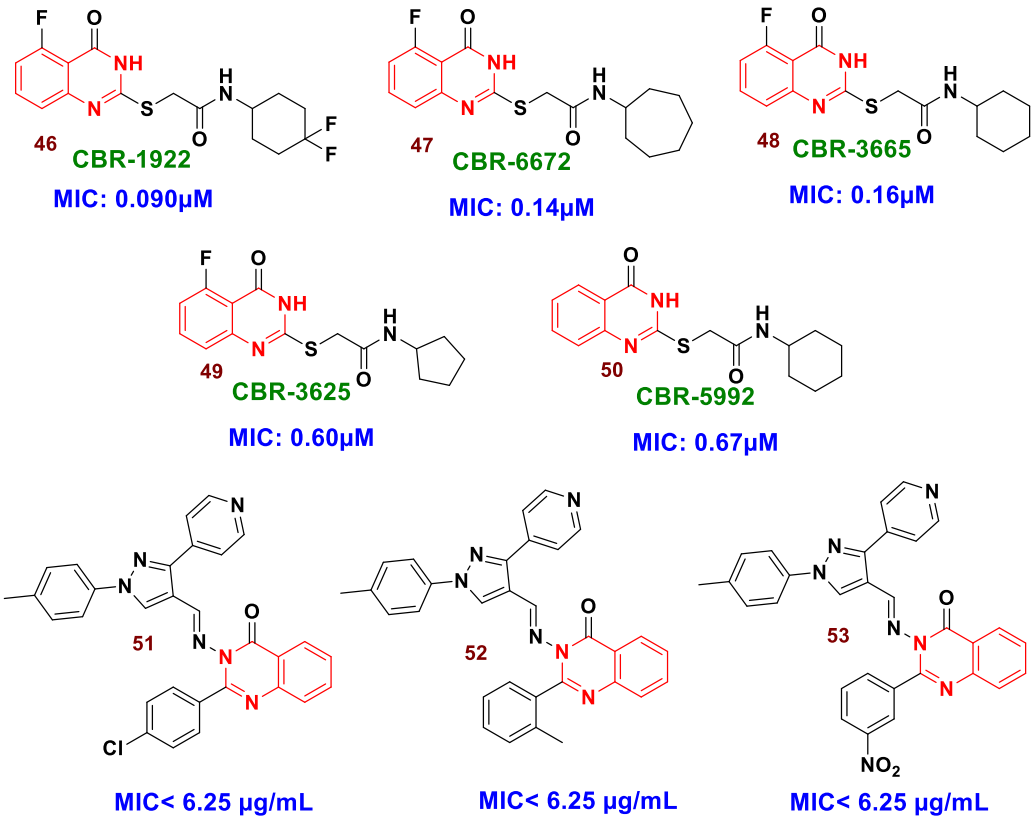

Figure 16: Quinazoline based derivatives with potent anti-tubercular activity.[79, 83]

1.11. Significance of fluorine in medicinal chemistry

Fluorine being small (van der Waals radius 1.47 Å) and most electronegative element in the Periodic Table (3.98 Pauling scale), has been influencing organic chemistry since decades.[84, 85] However, since last few decades it has become kingpin in medicinal chemistry as it alters the biological properties of the drugs. Till date, 20-25% drugs approved by food and drug administration (FDA) contain fluorine (F) or CF_3. In 2018 alone, 17 drugs bearing F or CF_3 has been approved by FDA.[86] Fluorine is known to influence molecular conformation, owing to the large dipole moment of the C-F bond. Fluorine is quite comparable with hydrogen counterparts and is known to cause significantly less steric perturbations and increases the lipophilicity. In addition, fluorine containing molecules are also known to increase the membrane permeability of the compounds as it reduces the basicity of the molecule.[87, 88]

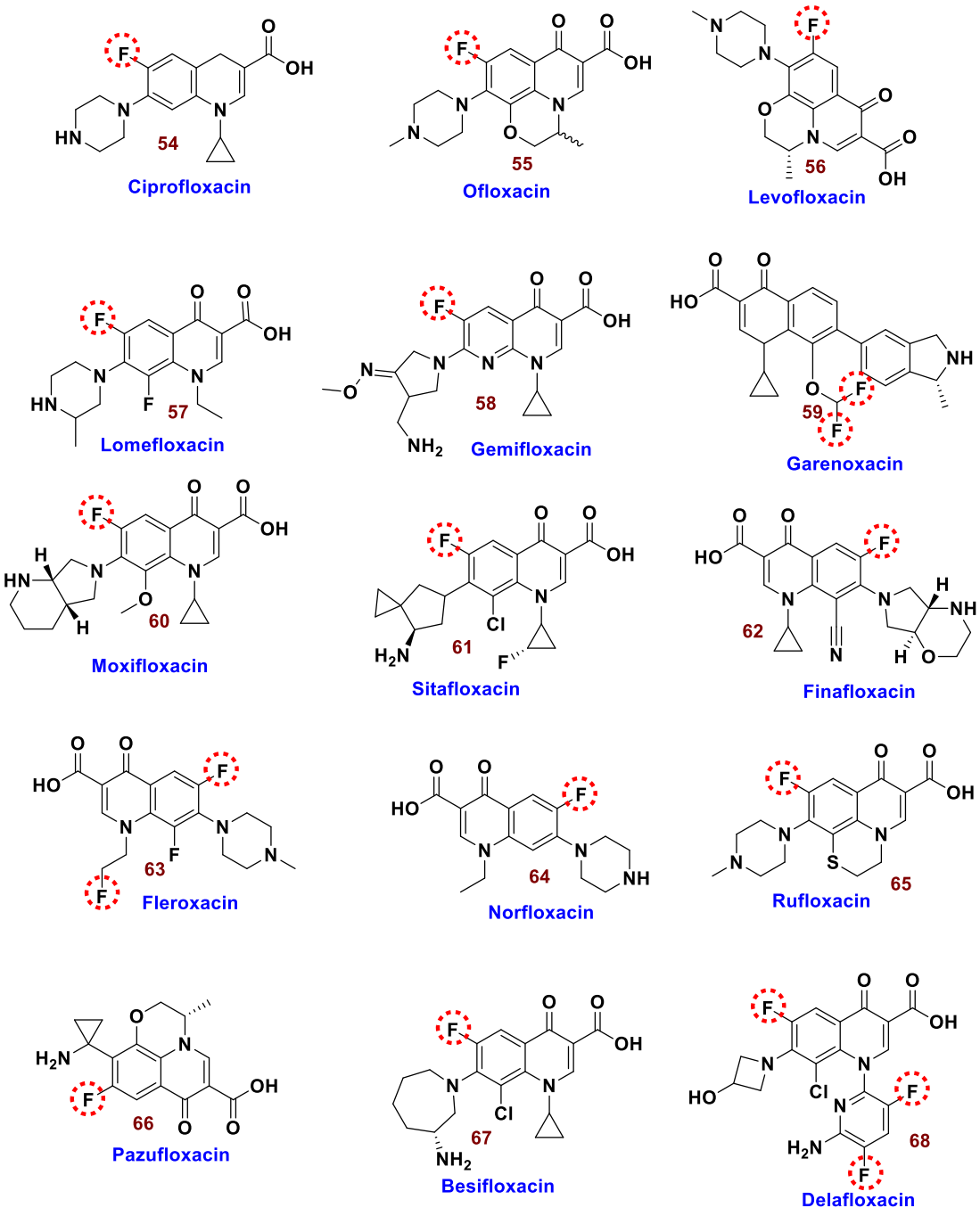

Figure 17: Fluorine containing DNA Gyrase and topoisomerase IV inhibitors (marketed drugs).

In view of the above literature, we realize that DNA Gyrase for *M. tuberculosis* inhibition (for anti-tubercular) has not been explored much. Owing to the high rate of antibiotic resistance against M. tuberculosis there is an urgency to look for new targets. DNA Gyrase provides us with an opportunity to synthesize quinazoline based derivatives which are expected to possess anti-tubercular activity.

2. Objectives of the Present Research Work

The aims and objectives of the present research work are-

1. To carryout widespread literature survey for designing of quinazoline and benzoxazine based new chemical entities as potential antitubercular agents and type II topoisomerase (DNA gyrase and topoisomerase IV) inhibitors.
2. To develop a convenient and efficient method for the synthesis of novel quinazoline and benzoxazine based scaffold.
3. To generate a library of novel quinazoline and benzoxazine based analogues using the developed synthetic methodology.
4. To purify the synthesized compounds by chromatographic techniques using combi flash column chromatography.
5. To establish the structure of synthesized compounds by spectral characterization (IR, ^{1}H NMR, ^{13}C NMR 2D-NMR) and also with single crystal X- ray crystallography.
6. To carry out the preliminary biological evaluation of the synthesized compounds for their antitubercular activity and type II topoisomerase (DNA gyrase and topoisomerase IV) inhibition.

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CHAPTER 2

One-pot, multicomponent, diastereoselective, green synthesis of 3,4-dihydro-2H-benzo[b][1,4]oxazine analogues

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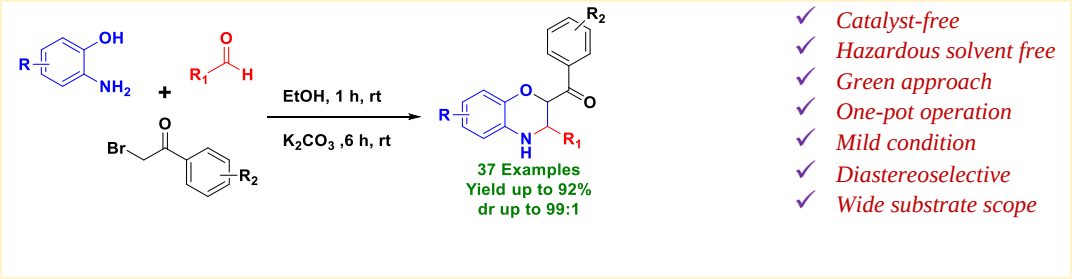
Graphical Abstract



Abstract

A novel green and efficient catalyst-free, the mild one-pot, multicomponent synthetic strategy has been developed to construct substituted 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine. This reaction proceeds *via* in-situ formation of Schiff-base followed by base mediated alkylation with phenacyl bromide/substituted phenacyl bromide, finally leading to intramolecular cyclization to give a mixture of diastereomers with excellent diastereoselectivity (up to dr = 99:1), which were isolated as single diastereomer in moderate to excellent yields (41-92%). Besides, this new versatile methodology provides a wide scope for the synthesis of different functionally substituted benzoxazine scaffolds and can be further exploited as building blocks for the synthesis of multifaceted molecular structures, especially for pharmaceutical applications.

Keywords

1, 4-benzoxazine, Diastereoselective, Green, one-pot, multicomponent synthesis.

1. Introduction

Benzoxazines are important heterocyclic scaffolds known for their extensive pharmacological and biological significance.[1-4] It is well documented that benzoxazine moiety has been used as a building block in developing new pharmaceutical lead compounds, which have displayed wide range for pharmaceutical applications such as neuroprotective agents,[5, 6] antidiabetic,[7] antiarrhythmics against ischemia-reperfusion injury,[8] calcium antagonist,[9] potassium channel modulators,[10] and antihyperlipidemic agents[11]etc. The medicinal significance of benzoxazine skeleton is further validated by its presence in several marketed pharmaceutical drugs[1-4, 12-14] as displayed in **Figure 1**. Undoubtedly one of the most well-known and noteworthy marketed drug containing benzoxazine heterocycle as its core moiety is levofloxacin (**Figure 1**). It is an FDA approved potent antibiotic for the treatment and management of various human diseases such as pneumonia, acute bacterial sinusitis, urinary tract infections and acute pyelonephritis.[15, 16] In addition, 1,4-benzoxazine scaffold has also found its application in agricultural industry in developing potential herbicides[17] (**Figure 1**).

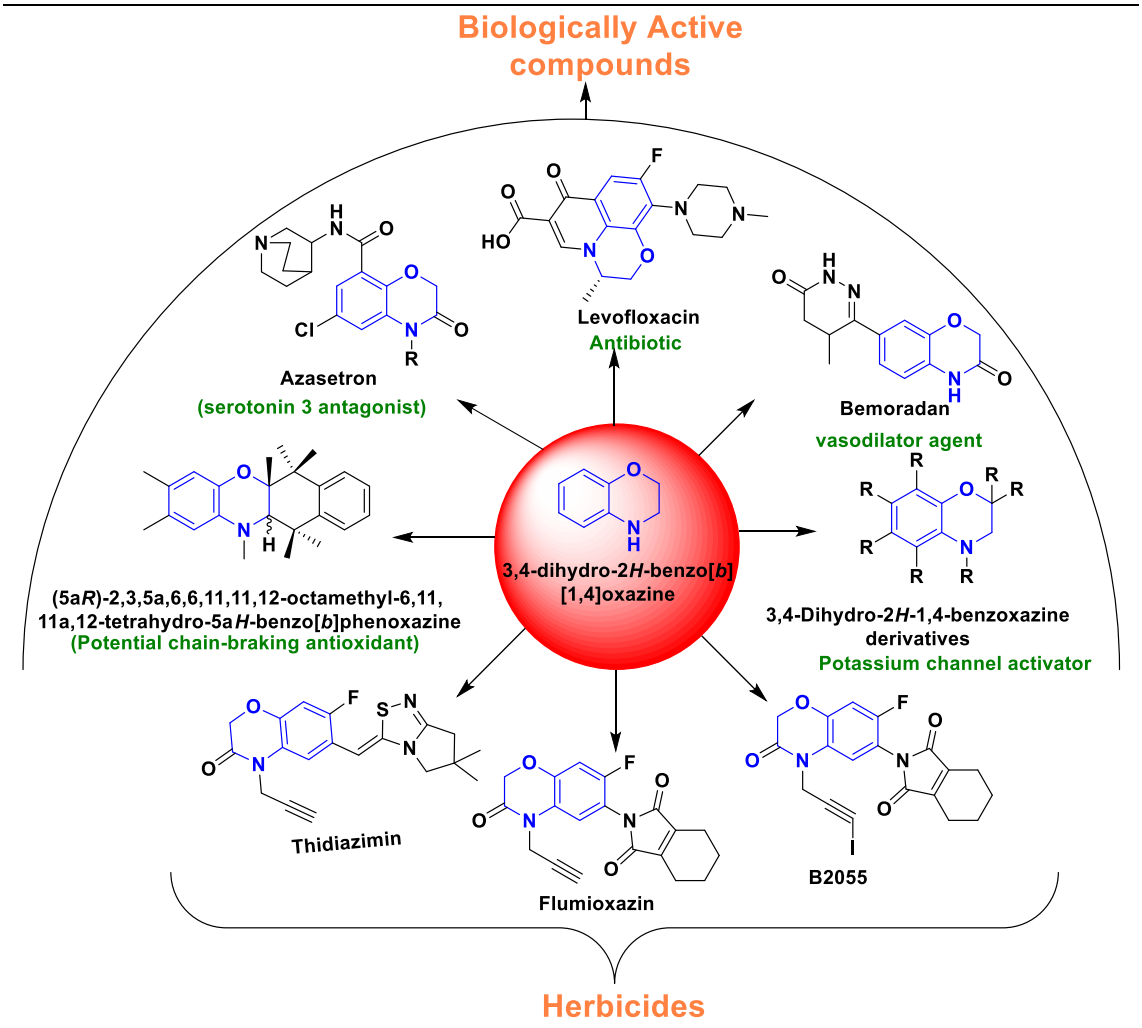


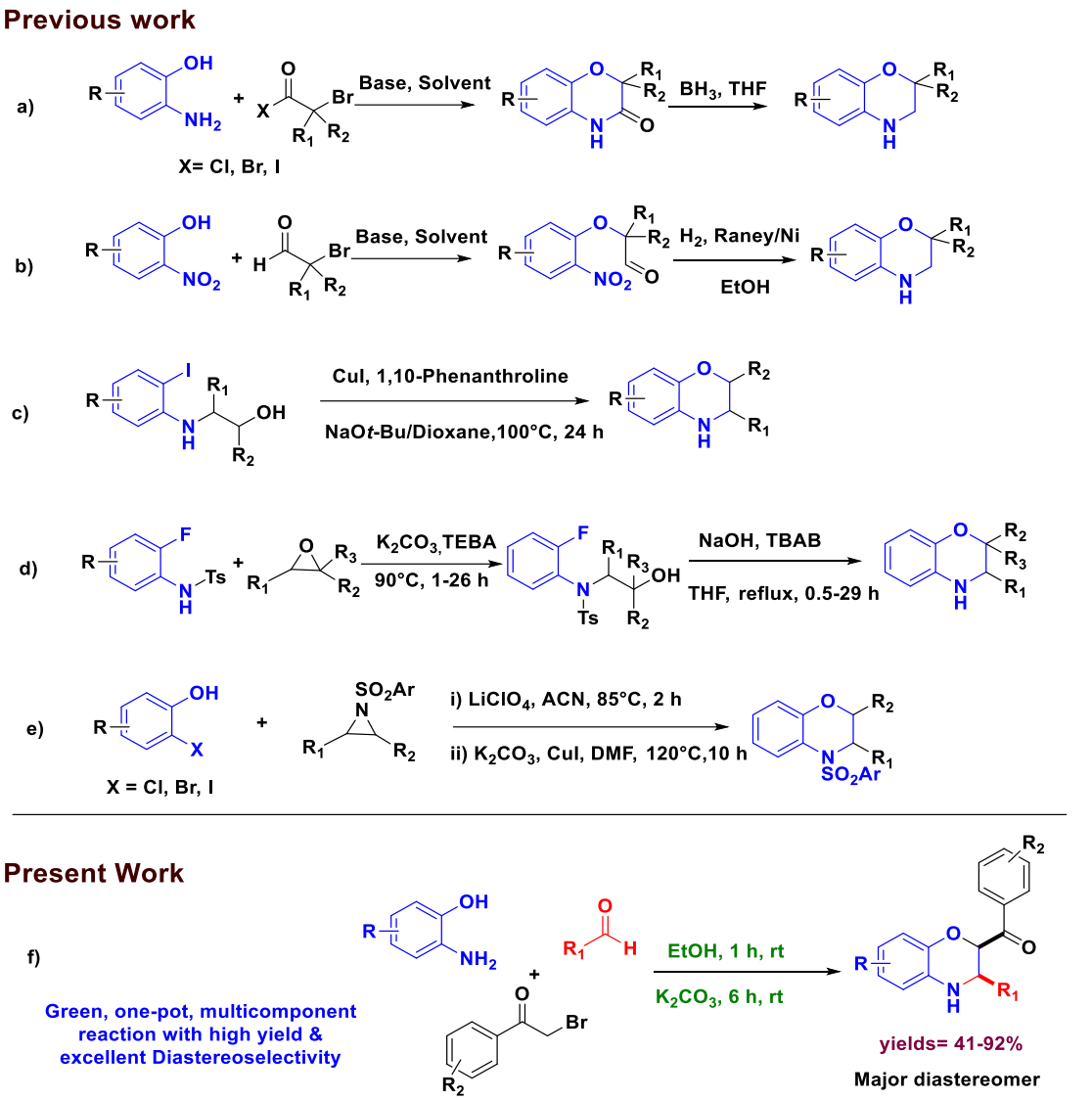
Figure 1: Some important marketed pharmaceuticals and agrochemicals containing 1, 4-benzoxazine as core moiety.

Further, 1, 4-benzoxazine is also widely used as a building block for the synthesis of more complex molecular structures, active pharmaceutical ingredients, herbicides and pesticides.[17, 18] Thus, have attracted considerable intrest of chemists in designing and developing new greener synthetic strategies to construct different functionally substituted 1,4-benzoxazine scaffolds.

The previous reported methods used multistep synthetic approaches for the synthesis of 1,4-benzoxazine moiety (Scheme 1) such as **a**) cyclocondensation of amino phenols with α-halogeno acyl bromides futher reduction of carbonyl with BH_3, **b**) alkylation of *o*-nitrophenol with haloester followed by reductive cyclization,[19] **c**) intramolecular copper-catalysed *O*-arylation of *β*-aminoalcohols[20] and **d**) epoxide ring opening with *O*-halosulfonamides and then cyclization was carried out to render 1,4 benzoxazine moieties.[21] and **e**) Recently, in 2018 Abhijit Mall *et al.* reported an efficient strategy for the synthesis of 3,4-dihydro 1,4 benzoxazine derivatives *via* Lewis acid catalysed S_N2 type ring opening of activated aziridine with 2-

halophenol followed by Cu(I)-catalysed cyclization.[22] However, all of the above mentioned multistep methods/procedures had drawbacks such as high temperature, long reaction time, low yield, lack of diastereomer selectivity, use of expensive catalyst and hazardous solvents, non-eco-friendly and most importantly the method were not versatile enough to synthesize differentially substituted 1,4 benzoxazine. Hence, an alternate, efficient route of synthesis was needed. Scheme 1 presents the previously reported methods (a-e) and our present work (f).

Keeping in mind the shortcomings of the previously reported methods, we envisaged to develop a simple, yet efficient, low cost, multicomponent, one pot, catalyst-free, green alternative method to synthesize 1,4-benzoxazine skeleton with diverse functionality and diastereoselectivity. The reaction proceeds via in situ formation of Schiff base, followed by mild base mediated *O*-alkylation and finally intramolecular cyclization to yield a mixture of diastereomers with excellent diastereoselectivity, which were isolated as single diastereomer in moderate to excellent yields (41-92%).



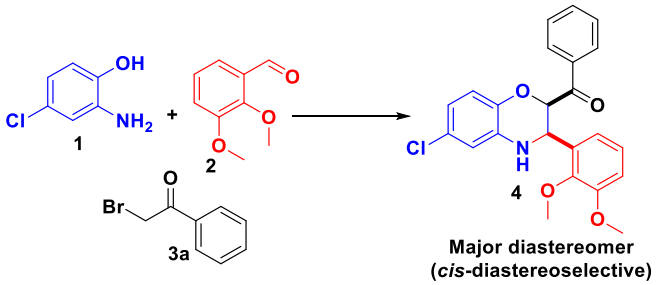
Scheme 1: **a-e**) Previous work for the synthesis of 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine, **f**) present work: One-pot, multicomponent, catalyst-free, diastereospecific, green approach (K_2CO_3/EtOH/ rt/7 h) for the synthesis of 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine.

2. Results & Discussion

Our one pot study commenced by reacting 2-amino-4-chlorophenol, aldehydes and alpha bromoketones in the presence of mild base Na_2CO_3, in DMF at 120°C for 5 h. The progress of the reaction was monitored by TLC and it was observed that the reaction was not clean, had several spots including that of starting material. Thus, indicating that the reaction did not go to completion. In order to obtain the desired product with improved yields and diastereoselectivity, further optimization of the reaction was initiated by changing various reaction parameters including base, temperature and solvents as shown in **Table 1**. Thus, we decided to first start by screening several bases (organic and inorganic) and it was observed that the use of K_2CO_3 led to

the completion of the reaction with slight improved yield of 47%, (**Table 1**, entry2). However, the reaction was not clean, and the TLC displayed several spots. Further solvent screening was performed, and it was observed that ethanol resulted in improved yield (56%) at 90°C (**Table 1**, entry 3), but the reaction was still not clean. From these results we believed that higher temperature could be responsible for the formation of undesired side products. In order to improve the yield as well as to have a clean reaction, the reaction was carried out at lower temperature (60°C) in ethanol, K_2CO_3 for 5 h, which resulted in significantly improved yield of 68% (**Table 1**, entry 4). Encouraged by these results we then decided to perform this reaction at room temperature (rt) and it was noted that after for 5 hours an intense single spot of the desired product was observed, but still the reaction was incomplete. Thus, the reaction was further continued for 7 h, resulting in a clean, single spot of the corresponding cyclic product **4** with excellent *cis*-diastereoselectivity, which was isolated with a significant improved yield of 91% (**Table 1**, entry 5). Its configuration was determined by ^{1}H-^{1}H NOESY analysis.[23] Hence, the best optimized reaction conditions for the synthesis of differently functionalized 1,4-benzoxazines was K_2CO_3 in ethanol at room temperature (rt) for 7 h (**Table 1**, entry 5).

Table 1. Optimization of the Reaction Conditions[a].



Entry	Base	Solvent	Time (h)	Temp (°C)	Yield of 4 (%)[b,c]
1.	Na_2CO_3	DMF	5	120	43
2.	K_2CO_3	DMF	5	120	47
3.	K_2CO_3	EtOH	5	90	56
4.	K_2CO_3	EtOH	5	60	68
5.	K_2CO_3	EtOH	7	rt	91
6.	Na_2CO_3	EtOH	7	rt	51
7.	Cs_2CO_3	EtOH	7	rt	86
8.	NaOH	EtOH	7	rt	45
9.	TEA	EtOH	7	rt	48
10.	DIPEA	EtOH	7	rt	52
11.	$NaHCO_3$	EtOH	7	rt	Trace
12.	K_2CO_3	MeOH	7	rt	84
13.	K_2CO_3	ACN	7	rt	64
14.	K_2CO_3	Acetone	7	rt	49
15.	K_2CO_3	Dioxane	7	rt	60
16.	K_2CO_3	THF	7	rt	57
17.	K_2CO_3	DMF	7	rt	52
18.	K_2CO_3	DCM	7	rt	Trace
19.	K_2CO_3	H_2O	7	rt	Trace
20.	K_2CO_3	Toluene	7	rt	Trace

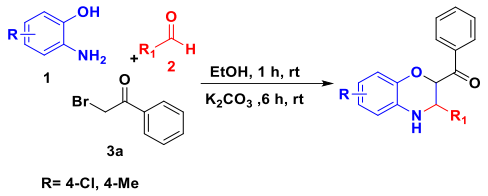
[a]Reaction conditions: **1** (1 equiv), **2** (1 equiv), **3a** (1 equiv), base (1.5 equiv), solvent (2 mL). [b]Diastereomeric ratio of 4 from the ^{1}H NMR of crude reaction mixture was >5:1 in all reactions. [c]Isolated yield of major diastereomer.

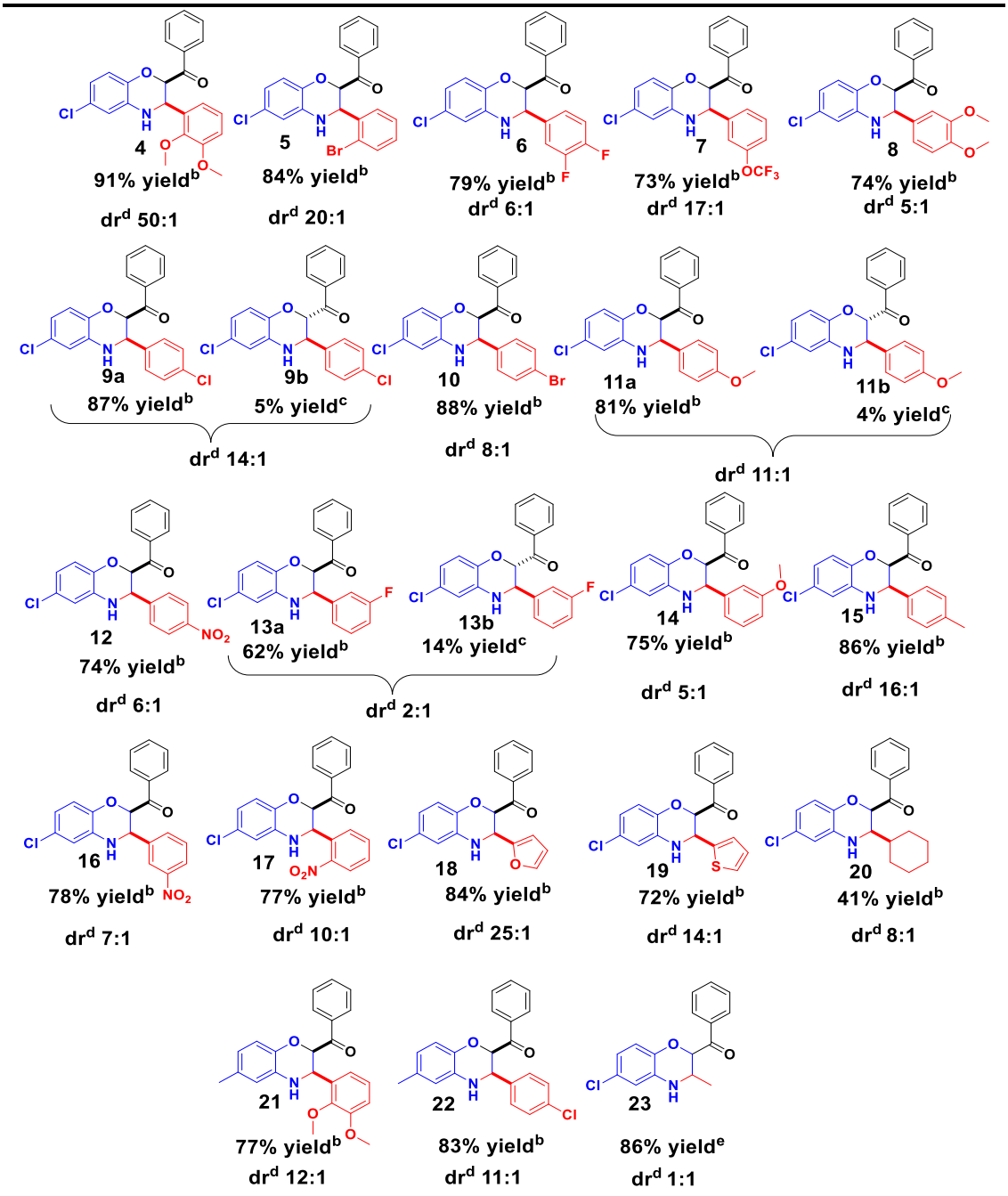
To expand the scope of this protocol, aliphatic and various substituted aryl/heteroaryl aldehydes (**2**) possessing both electron donating (-CH_3, -OCH_3) and withdrawing groups (-NO_2, -Cl, -Br, -F) were reacted with chloro, methyl, and nitro substituted 2-aminophenols (**1**) and phenacyl bromide (**3a**) under optimized reaction condition. The chloro and methyl substituted 2-aminophenol gave excellent results yielding desired product as a mixture of diastereomers resepectively. These mixtures were further purified and isolated as diastereomerically pure compounds **4-19** and **21-22** (**Table 2**) in moderate to excellent yields (62-91%). However, no desired product was obtained with nitro-substituted 2-aminophenol, only *O*-alkylated intermediate was formed, which could be attributed to the strong ring deactivating aspects of meta nitro group with respect to amine (NH_2). Furthermore, All the substituted aryl/hetroaryl

aldehydes gave admirable yields (62-91%), while alicylic aldehyde (compound **20**) presented relatively lower yield 41%. Further in the case of linear aliphatic aldehyde, the diastereomeric mixtures (combined yield 86%; dr = 3:2) could not be separated due to indistinguishable R*f* difference (compound 23). All the synthesized derivatives were well-characterized by IR and NMR. In addition, it was observed that halo and nitro substituted aryl aldehydes were well tolerated and their corresponding desired products (**5, 6, 9a, 10, 12, 13a, 16, 17** and **22**) were obtained in good to excellent yields (62-88%). In all the above reactions the major diastereomeric product was isolated in high yields, which provided the scope for further functionalization and their applications as building blocks in pharmaceuticals.

Remarkably, in most of the cases (**4-6, 8, 10, 12, 14-19** and **22**) the major diastereomers precipitated from the reaction mixtures, which was filtered, washed with water and *n*-pentane to remove impurities, followed by drying under vacuum. However, in the case of **9**, both the diastereomeric mixtures (major and minor) precipitated, which were then separated as **9a** and **9b** by using combi-flash column chromatography. However, in the case of **7, 11a, 11b, 13a, 13b, 20 21** and **23** no precipitation of the product was observed, hence the crude reaction mixture was concentrated and diluted with water and then extracted with ethyl acetate. These diastereomers were then purified and separated using combi-flash column chromatography. Structures of compound **9b**, **15** and **17** were further confirmed by single crystal X-ray analysis (See appendix 1), and the relative configuration of other products were deduced by analogy.

Table 2. Substrate scope of aldehydes with substituted 2-aminophenol[a].



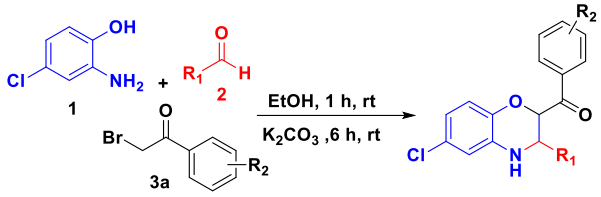


[a]Reaction conditions: Substituted 2-aminophenol [(**1**);1 equiv], substituted aldehydes [(**2**);1 equiv], phenacyl bromides [(**3a**);1 equiv], K_2CO_3 (1.5 equiv), EtOH (2 mL). [b]Isolated yields of major diastereomer. [c]Isolated yield of minor diastereomer. [d]Diastereomeric ratios determined by

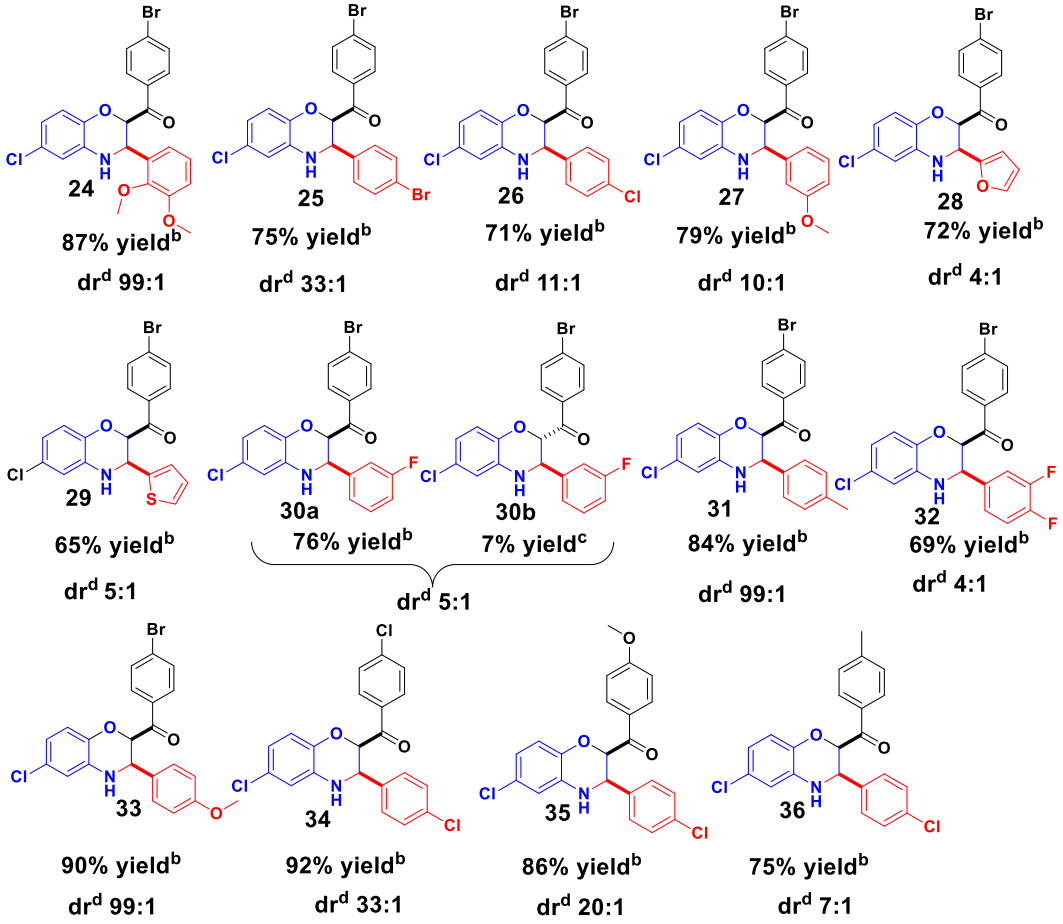
[1]H NMR of the crude reaction mixture. [e]Isolated combined yield of diastereomeric mixture (*cis* and *trans*).

Next to widen the scope and versatility of this new methodology, substituted phenacyl bromide (**3**) was treated with 2-amino-4-chlorophenol (**1**) and various substituted aryl/hetero aryl aldehydes (**2**) under optimized condition to obtain corresponding substituted 1, 4-benzoxazine analogues in good to excellent yields as summarised in **Table 3**. The electron donating groups at ortho/meta/para position of benzaldehyde resulted in desired products (**24**, **27**, **31** and **33**), respectively with excellent yields (79-90%) and diastereoselectivity, while the electron-withdrawing groups comparatively gave slightly lower yields (69-76%) and less diastereoselectivity (**25**, **26**, **30a** and **32**). In addition, we had performed a reaction with ethyl α-bromo acetate, but the reaction did not go to completion and resulted only in the formation of an intermediate compound, which did not undergo intramolecular cyclization to yield the desired product.

Table 3. Substrate scope of aldehyde with substituted phenacyl bromide[a].



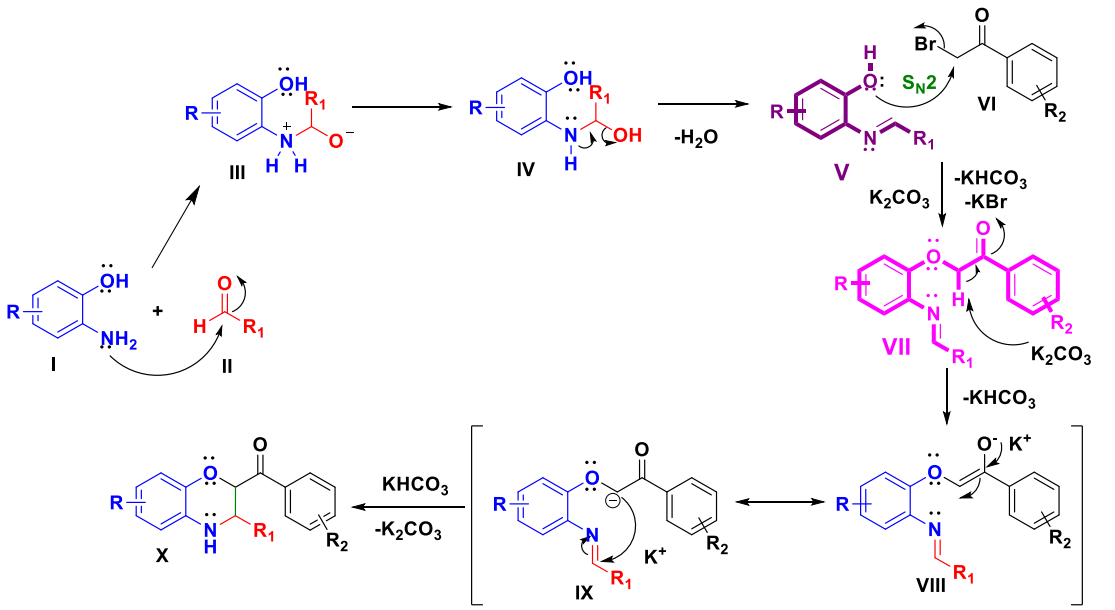
R_2= 4-Br, 4-Me, 4-Cl, 4-OMe



[a]Reaction conditions: 2-amino-4-chlorophenol [(**1**);1 equiv], substituted aldehydes [(**2**);1 equiv], substituted phenacyl bromides [(**3a**);1 equiv], K_2CO_3 (1.5 equiv), EtOH (2 mL).[b]Isolated yields of major diastereomer. [c]Isolated yield of minor diastereomer. [d]Diastereomeric ratios have been determined by ^{1}H NMR analysis of the crude reaction mixture.

A plausible mechanism as outlined in Scheme 2 was proposed on the basis of our experimental observations and from the previously reported literature.[24-25] The reaction proceeds *via* the nucleophilic attack by the amine of **I** (amino phenol) on the carbonyl carbon of the aldehyde (**II**) leading to the formation the intermediate **III**, which further undergoes proton shift, followed by dehydration to give a Schiff base (**V**). Further, the in-situ reaction proceeds *via* base mediated S_N2 type substitution reaction, wherein the hydroxyl group on the Schiff base (**V**) acts as a nucleophile and attacks the α-carbon of the phenacyl bromide (**VI**) generating a corresponding

O-alkylated intermediate (**VII**). The acidic proton of **VII** is abstracted by the base K_2CO_3 resulting in the generation of a carbanion **VIII** or **IX** (Keto-enol tautomer), which further undergoes base mediated intramolecular cyclization to yield respective 1,4-benzoxazines (**X**). To validate the plausible mechanism, both the key intermediates **V** and **VII** were isolated and confirmed by ^{1}H and ^{13}C NMR (See Appendix 1). Thus, confirming the plausible mechanism as presented in scheme 2.



Scheme 2: Plausible reaction pathway via insitu formation of the intermediates **V** and **VII** (as highlighted), which were isolated and charecterized.

3. Conclusion

In conclusion, we have developed a simple, yet efficient one-pot, multicomponent, green, catalyst-free, and diastereoselective synthesis of 1,4-benzoxazines in modrate to excellent yields. This one-pot, in-situ reaction proceeds by the formation of a Schiff base followed by base mediated *O*-alkylation with the phenacyl bromide and finally catalyst free intramolecular cyclization. Further, this versatile novel methodology provides a wide scope for the synthesis of differentially substituted/functionalised 1,4-benzoxazine analogues, which can be exploited by the researchers in academia, pharmaceutical and agrochemical industries in developing new building blocks or for the synthesis of new active pharmaceutical ingredients (API's), drugs and pesticides.

4. Experimental

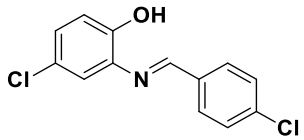
4.1. General consideration

All the fine chemicals, reagents and solvents were purchased from Sigma Aldrich and Merck and were used without further purification unless otherwise stated. The progress of the reactions and the purity of the compounds were monitored by thin-layer chromatography (TLC) on pre-coated silica gel plates procured from E. Merck and Co. (Darmstadt, Germany) visualized by UV lamp (254 or 365 nm). Purification was performed by using combi-flash (Combi*Flash*® NextGen 300+) column chromatography. The melting points of the synthesized compounds have been determined and uncorrected using a digital Stuart SMP10 melting point Apparatus. The Fourier transform infrared (FTIR) spectra were recorded in the spectral range of 400-4000 cm^{-1} on a Bruker Alpha FT-IR spectrometer using the ATR technique. The NMR spectra (^{1}H & ^{13}C) were recorded using $CDCl_3$ and DMSO-d_6 on Bruker AVANCE III 400 and 600 MHz spectrometer. Chemical shifts were determined relative to internal standard TMS at δ 0.0 parts per million (ppm) and the coupling constants were reported in Hertz. The multiplicities of the NMR resonances were abbreviated as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet) and brs (broad singlet). Elemental analysis was performed on Vario EL cube instrument. High resolution mass spectrometry (HRMS) in positive-ion mode. X-ray crystallography analysis was performed on Bruker SMART APEX II, X-ray diffractometer.

4.2. Chemistry

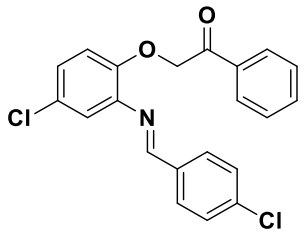
4.2.1. Synthesis and Spectral characterization of intermediate compounds (V and VII);

*4.2.1.1. Synthesis of (E)-4-chloro-2-((4-chlorobenzylidene)amino)phenol (**V**);*



A mixture of 2-amino-4-chlorophenol (0.2 g, 1 equiv) and 4-chlorobenzaldehyde (1 equiv) in ethanol (2 mL) was stirred for 1 h at room temperature, precipitate was formed filtered and washed with pentane to afford pure title Schiff base intermediate. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 8.60 (s, 1H), 7.84 (d, J = 8.30 Hz, 2H), 7.46 (d, J = 8.40 Hz, 2H), 7.27 – 7.25 (m, 1H), 7.15 (dd, J = 8.66 Hz, J = 2.35 Hz, 1H), 7.05 (s, 1H), 6.94 (d, J = 8.74 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25°C) δ 156.9, 151.0, 138.3, 136.0, 134.0, 130.2, 129.4, 128.9, 125.2, 116.34, 116.31.

*4.2.1.2. Synthesis of (E)-2-(4-chloro-2-((4-chlorobenzylidene)amino)phenoxy)-1-phenylethan-1-one (**VII**);*



To the solution of (E)-4-chloro-2-((4-chlorobenzylidene)amino)phenol (0.2 g, 1 equiv), in ethanol (2 mL), potassium carbonate (1.5 equiv) and phenacyl bromide (1 equiv) were added. The resultant mixture was stirred for 30 min at ambient temperature then diluted with water and extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under vaccum to get crude intermediate which was purified by column chromatography to afford solid title intermediate. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 8.59 (s, 1H), 7.97 (d, *J* = 7.53 Hz, 2H), 7.83 (d, *J* = 8.37 Hz, 2H), 7.59 (t, *J* = 7.37 Hz, 1H), 7.49 – 7.44 (m, 3H), 7.25 – 7.24 (m, 1H), 7.14 (dd, *J* = 8.65 Hz, *J* = 2.05 Hz, 1H), 7.04 (s, 1H), 6.92 (d, *J* = 8.65 Hz, 1H), 4.44 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25°C) δ 191.4, 156.9, 151.0, 138.3, 136.0, 134.1, 134.09, 134.03, 131.0, 130.2, 129.6, 129.4, 129.07, 129.01, 128.9, 126.7, 125.2, 116.3, 31.0.

4.2.2. General procedure A for the synthesis of compounds (4-6, 8, 10, 12, 14-19, 22, 24-29 and 31-36);

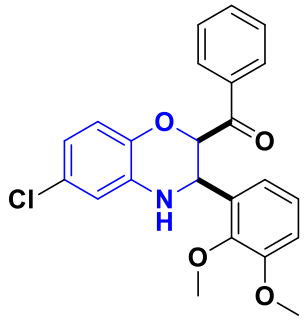
A mixture of substituted 2-aminophenol (0.2 g, 1 equiv) and corresponding aldehydes (1 equiv) in ethanol (2 mL) was stirred for 1 h at room temperature, then potassium carbonate (1.5 equiv) and phenacyl bromide/substituted phenacyl bromide (1 equiv) were added and further continued with the stirring for 6 h at ambient temperature. The solid precipitate was formed in reaction mixture which was directly filtered and washed with water followed by *n*-pentane to afford pure solid of title products as major diastereomer.

4.2.3. General procedure B for the synthesis of compounds (7, 9a-b, 11a-b, 13a-b, 20, 21, 23 and 30a-b);

A mixture of substituted 2-aminophenol (0.2 g, 1 equiv) and corresponding aldehydes (1 equiv) in ethanol (2 mL) was stirred for 1 h at room temperature, then potassium carbonate (1.5 equiv) and phenacyl bromide/substituted phenacyl bromide (1 equiv) were added and continued the stirring for 6 h at ambient temperature. The solvent was removed under reduced pressure, diluted with water and extracted with ethyl acetate (3 x 10 mL). The combined organic phase

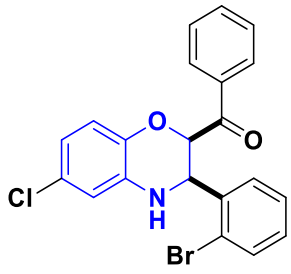
was dried over anhydrous Na2SO4 and evaporated under reduced pressure to afford a mixture of two diastereomers (major and minor). The mixtures were separated by combi flash column chromatography using EtOAc/Hexane as an eluent to afford title products.

*4.2.2.1. (6-Chloro-3-(2,3-dimethoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**4**);*



Off white solid, (521 mg, 91% yield). mp: 188-190°C; FTIR (ATR, V_{max}, cm^{-1}): 3417 (N-H str.), 2971 (Ar-H str.), 1683 (C=O str.), 1508 (Ar C=C str.), 1269 (C-N str.), 1062 (C-O-C str.), 685 (C-Cl str.); ^1H NMR (400 MHz, $CDCl_3$, 25°C) δ 8.07 (d, J = 8.12 Hz, 2H), 7.58 (t, J = 7.22 Hz, 1H), 7.50 – 7.44 (m, 2H), 6.97 (t, J = 7.42 Hz, 1H), 6.86 (d, J = 7.84 Hz, 2H), 6.75 (d, J = 8.04 Hz, 1H), 6.63 – 6.61 (m, 2H), 5.66 (d, J = 2.91 Hz, 1H), 5.24 (t, J = 3.39 Hz, 1H), 4.24 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H).$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$,25°C) δ 195.1, 152.4, 145.8, 141.2, 134.6, 133.8, 133.5, 133.3, 128.9, 128.5, 126.5, 119.2, 118.5, 117.5, 114.2, 112.3, 78.1, 60.5, 55.8, 49.4.Anal.Calcd for $C_{23}H_{20}ClNO_4$: C, 67.40; H, 4.92; N, 3.42; O, 15.61. Found: C, 67.16; H, 4.90; N, 3.60; O, 18.67.

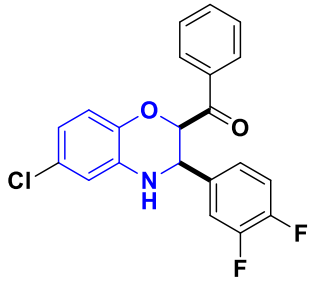
*4.2.2.2. (3-(2-Bromophenyl)-6-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**5**);*



Yellow solid, (504 mg, 84% yield). mp: 130-134°C; FTIR (ATR, V_{max}, cm^{-1}): 3409 (N-H str.), 2938 (Ar-H str.), 1672 (C=O str.), 1496 (Ar C=C str.), 1292 (C-N str.), 1183 (C-O-C str.), 752 (C-Cl str.), 690 (C-Br str.); ^1H NMR (400 MHz, $CDCl_3$, 25°C) δ 7.99 (d, J = 7.79 Hz, 2H), 7.57 - 7.53 (m, 2H), 7.43 – 7.36 (m, 3H), 7.28 (d, J = 7.52 Hz, 1H), 7.17 – 7.12 (m, 1H), 6.66 (d, J = 2.32 Hz, 1H), 6.62 (d, J = 8.56 Hz, 1H), 6.53 (dd, J = 8.45 Hz, J = 2.39 Hz, 1H), 5.53 (dd, J =

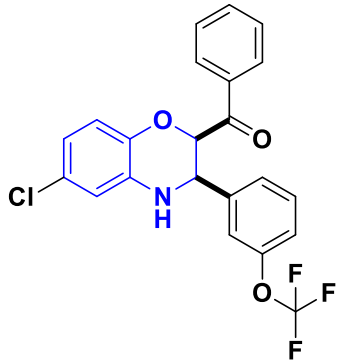
4.60 Hz, *J* = 2.35 Hz, 1H), 5.50 (d, *J* = 2.40 Hz, 1H), 4.45 (d, *J* = 4.56 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25°C) δ 195.62, 140.0, 139.6, 134.8, 133.7, 133.6, 133.1, 129.6, 129.2, 129.1, 128.5, 128.0, 127.4, 122.3, 118.3, 114.5, 77.4, 53.2. Anal.Calcd for $C_{21}H_{15}BrClNO_2$: C, 58.83; H, 3.53; N, 3.27; O, 7.46. Found: C, 57.75; H, 3.51; N, 3.30; O, 9.70.

*4.2.2.3. (6-Chloro-3-(3,4-difluorophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**6**);*



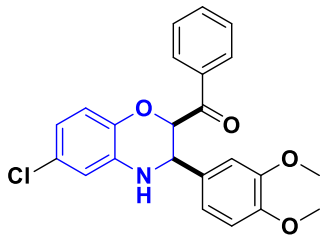
Off white solid, (425 mg, 79% yield). mp: 140-144°C; FTIR (ATR, V_{max}, cm^{-1}): 3349 (N-H str.), 2977 (Ar-H str.), 1681 (C=O str.), 1490 (Ar C=C str.), 1291 (C-N str.), 1116 (C-F str.), 1059 (C-O-C str.), 692 (C-Cl str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 7.95 (d, *J* = 7.85 Hz, 2H), 7.64 (t, *J* = 6.95 Hz, 1H), 7.53 – 7.45 (m, 3H), 7.40 – 7.33 (m, 1H), 7.22 – 7.20 (m, 1H), 6.87 (d, *J* = 3.92 Hz, 1H), 6.71 – 6.69 (m, 2H), 6.50 (dd, *J* = 8.54 Hz, *J* = 2.43 Hz, 1H), 5.97 (d, *J* = 3.57 Hz, 1H), 4.83 (t, *J* = 3.54 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6, 25°C) δ 194.8, 150.4 – 147.9 (dd, J_{C-F}= 246.20 Hz, J_{C-F} = 12.64 Hz, 1C), 149.9 – 147.3 (dd, J_{C-F} = 246.20 Hz, J_{C-F} = 12.64 Hz, 1C), 140.6, 137.9 – 137.8 (d, J_{C-F}= 8.38 Hz, 1C), 137.9, 134.52 – 134.50 (d, J_{C-F} = 2.98 Hz, 1C), 133.6, 128.7, 128.6, 125.1, 124.05 – 124.01 (d, J_{C-F} = 3.42 Hz, 1C), 117.4 – 117.2 (d, J_{C-F} = 17.68 Hz, 1C), 117.1, 116.3, 116.1, 113.2, 77.3, 52.4. Anal.Calcd for $C_{21}H_{14}ClF_2NO_2$: C, 65.38; H, 3.66; N, 3.63; O, 8.29. Found: C, 66.52; H, 4.54; N, 3.73; O, 10.91.

*4.2.3.1. (6-Chloro-3-(3-(trifluoromethoxy)phenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**7**);*



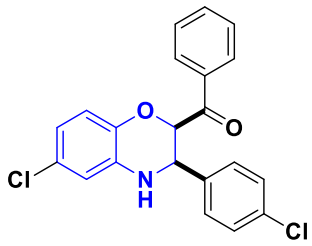
Yellow solid, (438 mg, 73% yield). R_f 0.6 (6% ethyl acetate in hexane); mp 83-87°C; FTIR (ATR, V_{max}, cm^{-1}): 3349 (N-H str.), 3061 (Ar-H, str.), 1674 (C=O str.), 1492 (Ar C=C str.), 1254 (C-N str.), 1160 (C-F str.); 1062 (C-O-C str.), 691 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 7.82 (s, 2H), 7.52 – 7.37 (m, 5H), 7.09 (s, 2H), 6.77 – 6.63 (m, 3H), 5.33 (s, 1H), 4.83 (s, 1H), 4.45 (s, 1H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25°C) δ 194.7, 149.5, 141.1, 135.1, 133.8, 133.7, 130.2, 128.8, 128.6, 127.1, 126.0, 121.7, 120.8, 120.1, 119.1, 118.6, 118.0, 114.7, 78.3, 54.9. Anal.Calcd for $C_{22}H_{15}ClF_3NO_3$: C, 60.91; H, 3.49; N, 3.23; O, 11.06. Found: C, 61.96; H, 3.54; N, 3.16; O, 14.11.

*4.2.2.4. (6-Chloro-3-(3,4-dimethoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**8**);*



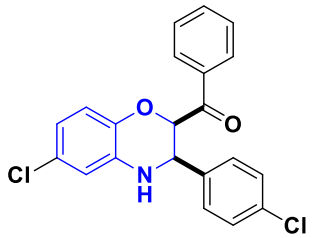
Off white solid, (424 mg, 74% yield). mp: 145-150°C; FTIR (ATR, V_{max}, cm^{-1}): 3350 (N-H str.), 2973 (Ar-H str.), 1690 (C=O str.), 1491 (Ar C=C str.), 1246 (C-N str.), 1026 (C-O-C str.), 698 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 7.81 (d, J = 7.87 Hz, 2H), 7.51 (t, J = 7.23 Hz, 1H), 7.36 (t, J = 7.73 Hz, 2H), 6.87 (d, J = 8.21 Hz, 1H), 6.82 – 6.80 (m, 2H), 6.73 (d, J = 8.21 Hz, 1H), 6.68 (d, J = 2.05 Hz, 1H), 6.63 (dd, J = 8.40 Hz, J = 2.13 Hz, 1H), 5.26 (d, J = 6.50 Hz, 1H), 4.72 (d, J = 6.21 Hz, 1H), 4.20 (s, 1H), 3.80 (s, 3H), 3.78 (s, 3H) .^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25°C) δ 194.9, 149.3, 149.2, 141.4, 135.6, 134.2, 133.7, 130.3, 128.9, 128.6, 127.0, 120.1, 118.4, 117.9, 114.6, 111.4, 110.7, 78.9, 56.0, 55.4. Anal.Calcd for $C_{23}H_{20}ClNO_4$: C, 67.40; H, 4.92; N, 3.42; O, 15.61. Found: C, 67.54; H, 5.12; N, 3.40; O, 19.47.

*4.2.3.2. (6-Chloro-3-(4-chlorophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**9a**);*



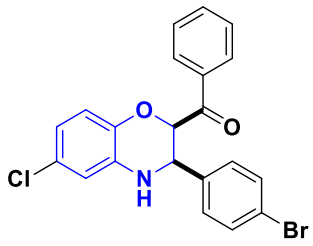
Off white solid, (468 mg, 87% yield). R_f 0.45 (6% ethyl acetate in hexane); mp: 159-162°C; FTIR (ATR, V_{max}, cm^{-1}): 3407 (N-H str.), 2974 (Ar-H str.), 1687 (C=O str.), 1522 (Ar C=C str.), 1205 (C-N str.), 691 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 7.85 (d, J = 7.64 Hz, 2H), 7.54 (t, J = 7.13 Hz, 1H), 7.39 (d, J = 7.63 Hz, 2H), 7.28 – 7.23 (m, 4H), 6.76 (d, J = 8.52 Hz, 1H), 6.66 (d, J = 2.16 Hz, 1H), 6.61 (dd, J = 7.48 Hz, J = 2.35 Hz, 1H), 5.26 (d, J = 5.56 Hz, 1H), 4.86 (d, J = 4.20 Hz, 1H), 4.22 (s, 1H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25°C) δ 194.6, 141.2, 137.3, 135.2, 134.4, 133.9, 133.8, 129.1, 129.03, 129.0, 128.7, 127.2, 118.6, 118.0, 114.7, 78.7, 54.5. Anal.Calcd for $C_{21}H_{15}Cl_2NO_2$: C, 65.64; H, 3.93; N, 3.65; O, 8.33. Found: C, 64.20; H, 3.88; N, 3.66; O, 10.58.

*4.2.3.3. (6-Chloro-3-(4-chlorophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**9b**);*



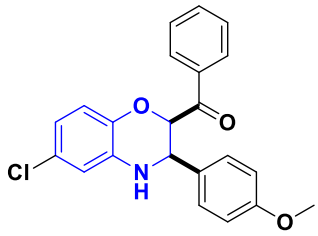
Off white solid, (27 mg, 5% yield). R_f 0.4 (8% ethyl acetate in hexane); mp: 190-193°C; FTIR (ATR, V_{max}, cm^{-1}): 3341 (N-H str.), 2977 (Ar-H str.), 1688 (C=O str.), 1492 (Ar C=C str.), 1256 (C-N str.), 1088 (C-O-C str.), 684 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 7.69 (d, J= 7.46 Hz, 2H), 7.54 (t, J = 7.42 Hz, 1H), 7.38 (t, J = 7.74 Hz, 2H), 7.12 (d, J = 8.40 Hz, 2H), 6.99 (d, J = 7.40 Hz, 2H), 6.93 (d, J = 8.12 Hz, 1H), 6.72 - 6.69 (m, 2H), 5.62 (d, J = 2.92 Hz, 1H), 4.96 (t, J = 2.84 Hz, 1H), 4.38 (d, J = 1.93 Hz, 1H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 40°C) δ 194.7, 141.5, 137.0, 135.9, 134.3, 133.8, 133.5, 128.9, 128.8, 128.7, 128.6, 127.6, 118.8, 118.2, 114.6, 78.9, 55.7. Anal.Calcd for $C_{21}H_{15}Cl_2NO_2$: C, 65.64; H, 3.93; N, 3.65; O, 8.33. Found: C, 65.49; H, 3.97; N, 3.71; O, 12.99.

*4.2.2.5. (3-(4-Bromophenyl)-6-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**10**);*



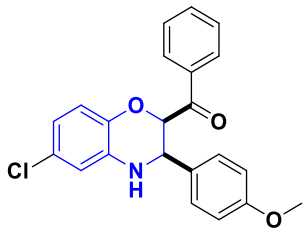
Off white solid, (528 mg, 88% yield). mp: 118-122°C; FTIR (ATR, V_{max}, cm^{-1}): 3328 (N-H str.), 2977 (Ar-H str.), 1672 (C=O str.), 1488 (Ar C=C str.), 1228 (C-N str.), 1063 (C-O-C str.), 689 (C-Cl str.), 510 (C-Br str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 7.85 (d, J = 8.38 Hz, 2H), 7.55 (t, J = 7.46 Hz, 1H), 7.41 – 7.38 (m, 4H), 7.20 (d, J = 8.31 Hz, 2H), 6.76 (d, J = 8.68 Hz, 1H), 6.67 – 6.66 (m, 1H), 6.61 (dd, J = 8.52 Hz, J = 1.97 Hz, 1H), 5.26 (d, J = 5.41 Hz, 1H), 4.83 (t, J = 3.06 Hz, 1H), 4.25 (s, 1H).$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25°C) δ 194.7, 141.2, 137.9, 135.2, 134.0, 133.8, 132.1, 129.4, 129.1, 128.8, 127.2, 122.6, 118.7, 118.1, 114.8, 78.7, 54.6. Anal.Calcd for $C_{21}H_{15}BrClNO_2$: C, 58.83; H, 3.53; N, 3.27; O, 7.46. Found: C, 58.75; H, 3.48; N, 3.35; O, 10.87.

*4.2.3.4. (6-Chloro-3-(4-methoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**11a**);*



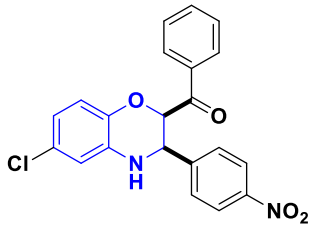
Yellow solid, (429 mg, 81% yield). R_f 0.4 (15% ethyl acetate in hexane); mp: 90-92°C; FTIR (ATR, V_{max}, cm^{-1}): 3340 (N-H str.), 2923 (Ar-H str.), 1669 (C=O str.), 1500 (Ar C=C str.), 1225 (C-N str.), 1054(C-O-C str.), 692 (C-Cl str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 7.93 (d, J = 7.50 Hz, 2H), 7.62 (t, J = 7.34 Hz, 1H), 7.49 (t, J = 7.77 Hz, 2H), 7.29 (d, J = 8.58 Hz, 2H), 6.85 (d, J = 8.60 Hz, 2H), 6.75 (d, J = 1.44 Hz, 1H), 6.72 (d, J = 8.52 Hz, 1H), 6.69 (d, J = 2.36 Hz, 1H), 6.50 (dd, J = 8.46 Hz, J = 2.38 Hz, 1H), 5.83 (d, J = 4.28 Hz, 1H), 4.67 (t, J = 2.71 Hz, 1H), 3.68 (s, 3H).$^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6, 25°C) δ 195.0, 158.7, 140.9, 135.1, 134.7, 133.6, 131.4, 128.7, 128.5, 128.4, 124.9, 116.9, 115.8, 113.8, 113.1, 77.6, 55.0, 53.1. Anal.Calcd for $C_{22}H_{18}ClNO_3$: C, 69.57; H, 4.78; N, 3.69; O, 12.64. Found: C, 69.63; H, 4.94; N, 3.72; O, 14.36.

*4.2.3.5. (6-Chloro-3-(4-methoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**11b**);*



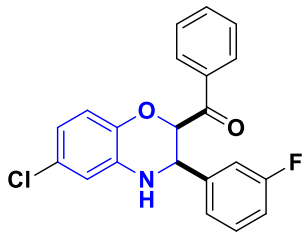
Yellow solid, (22 mg, 4% yield). R_f 0.32 (18% ethyl acetate in hexane); mp:184-188°C; FTIR (ATR, V_{max}, cm^{-1}): 3349 (N-H str.), 2982 (Ar-H str.), 1686 (C=O str.), 1503 (Ar C=C str.), 1248 (C-N str.), 1040 (C-O-C str.), 686 (C-Cl str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 7.67 (d, J = 7.35 Hz, 2H), 7.56 (t, J = 7.41 Hz, 1H), 7.40 (t, J = 7.71 Hz, 2H), 6.89 – 6.83 (m, 4H), 6.72 (d, J = 2.50 Hz, 1H), 6.68 (d, J = 8.54 Hz, 2H), 6.55 (dd, J = 8.71 Hz, J = 2.85 Hz, 1H), 5.99 (d, J = 3.22 Hz, 1H), 4.83 (t, J = 2.93 Hz, 1H), 3.62 (s, 3H).^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6, 25°C) δ 195.3, 159.1, 141.5, 136.2, 136.1, 133.6, 130.9, 128.9, 128.8, 128.6, 125.6, 117.5, 116.3, 113.8, 113.5, 77.6, 55.4, 54.4. Anal.Calcd for $C_{22}H_{18}ClNO_3$: C, 69.57; H, 4.78; N, 3.69; O, 12.64. Found: C, 69.35; H, 4.94; N, 3.77; O, 14.07.

*4.2.2.6. (6-Chloro-3-(4-nitrophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**12**);*



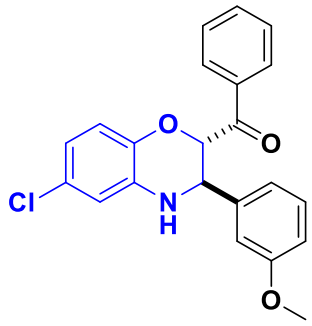
Light yellow solid, (408 mg, 74% yield). mp 187-190°C; FTIR (ATR, V_{max}, cm^{-1}): 3334 (N-H str.), 2977 (Ar-H str.), 1685 (C=O str.), 1490 (Ar C=C str.), 1343 (Ar-NO_2 Str.), 1222 (C-N str.), 1057 (C-O-C str.), 685 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 40°C) δ 8.13 – 7.89 (m, 4H), 7.53 – 7.41 (m, 5H), 6.70 – 6.61 (m, 3H), 5.32 (s, 1H), 5.10 (s, 1H), 4.36 (s, 1H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 40°C) δ 194.4, 148.0, 146.8, 140.9, 135.0, 134.1, 133.3, 129.1, 128.8, 128.5, 127.6, 124.1, 119.2, 118.3, 115.1, 78.7, 54.4. Anal.Calcd for $C_{21}H_{15}ClN_2O_4$: C, 63.89; H, 3.83; N, 7.10; O, 16.21. Found: C, 63.18; H, 3.72; N, 7.11; O, 18.63.

*4.2.3.6. (6-Chloro-3-(3-fluorophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**13a**);*



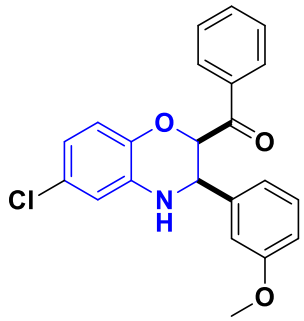
Off white solid, (318 mg, 62% yield). R_f 0.42 (6% ethyl acetate in hexane); mp: 177-180°C; FTIR (ATR, V_{max}, cm^{-1}): 3370 (N-H str.), 2976 (Ar-H str.), 1688 (C=O str.), 1490 (Ar C=C str.), 1247 (C-N str.), 1191 (C-F str.), 1078 (C-O-C str.), 689 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 7.69 (dd, J = 7.24 Hz, J = 1.66 Hz, 2H), 7.52 (t, J = 7.59 Hz, 1H), 7.37 (t, J = 7.59 Hz, 2H), 7.15 – 7.09 (m, 1H), 6.93 (d, J = 9.19 Hz, 1H), 6.88 – 6.84 (m, 2H), 6.80 – 6.76 (m, 1H), 6.72 – 6.70 (m, 2H), 5.62 (d, J = 3.08 Hz, 1H), 4.98 (t, J = 3.98 Hz, 1H), 4.40 (d, J = 2.08 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 40°C) δ 194.8, 164.1 – 161.7 (d, $J_{C\text{-}F}$ = 247.08 Hz, 1C), 141.5, 141.0, 136.0, 133.7, 133.5, 130.2 – 130.1 (d, $J_{C\text{-}F}$ = 8.35 Hz, 1C), 128.7 – 128.6 (d, $J_{C\text{-}F}$ = 6.61 Hz, 1C), 127.6, 123.2, 118.9, 118.3, 115.4, 115.2, 114.8 – 114.5 (d, $J_{C\text{-}F}$ = 22.33 Hz, 1C), 114.7, 78.8, 55.8. HRMS (ESI-TOF) calcd for $C_{21}H_{16}ClFNO_2$ $[M + H]^+$ 368.0854, found 368.1180.

*4.2.3.7. (6-Chloro-3-(3-methoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**13b**);*



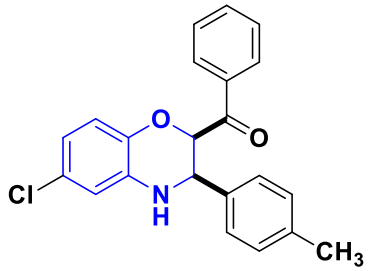
Yellow semi solid, (72 mg, 14% yield). R_f 0.35 (10% ethyl acetate in hexane); FTIR (ATR, V_{max}, cm^{-1}): 3337 (N-H str.), 3070 (Ar-H str.), 1685 (C=O str.), 1593 (Ar C=C str.), 1221 (C-N str.), 687 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 8.06 (d, J = 8.08 Hz, 2H), 7.74 (t, J = 7.76 Hz, 1H), 7.59 (t, J = 8.41 Hz, 2H), 7.43 – 7.40 (m, 1H), 7.31 – 7.28 (m, 2H), 7.14 – 7.09 (m, 1H), 6.96 (d, J = 8.53 Hz, 1H), 6.89 (d, J = 2.34 Hz, 1H), 6.81 (dd, J = 8.41, J = 2.22 Hz, 1H), 5.54 (d, J = 5.05 Hz, 1H), 5.05 (d, J = 5.57 Hz, 1H), 4.67 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25°C) δ 194.7, 164.1 – 161.7 (d, $J_{C\text{-}F}$ = 244.81 Hz, 1C), 141.5 - 141.4 (d, J = 7.26 Hz, 1C), 141.0, 135.0, 133.8, 133.7, 130.4, 128.8 – 128.6, 128.3 127.0, 123.1, 118.3, 117.9, 115.4 – 115.2 (d, $J_{C\text{-}F}$ = 21.09 Hz, 1C), 114.6, 78.4, 54.9. Anal.Calcd for $C_{21}H_{15}ClFNO_2$: C, 68.58; H, 4.11; Cl, 9.64; F, 5.17; N, 3.81; O, 8.70. Found: C, 66.97; H, 3.98; N, 3.80; O, 10.73.

*4.2.2.7. (6-Chloro-3-(3-methoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**14**);*



Off white solid, (398 mg, 75% yield). mp: 177-180°C; FTIR (ATR, V_{max}, cm^{-1}): 3364 (N-H str.), 2976 (Ar-H str.), 1687 (C=O str.), 1493 (Ar C=C str.), 1254 (C-N str.), 1054 (C-O-C str.), 690 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 7.64 (d, J = 7.40 Hz, 2H), 7.48 (t, J = 7.40 Hz, 1H), 7.32 (t, J = 7.76 Hz, 2H), 7.07 (t, J = 7.92 Hz, 1H), 6.91 (d, J = 9.24 Hz, 1H), 6.71 – 6.67 (m, 4H), 6.58 (s, 1H), 5.66 (d, J = 3.16 Hz, 1H), 4.92 (t, J = 2.74 Hz, 1H), 4.34 (d, J = 1.4 Hz, 1H), 3.59 (s, 3H).$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25°C) δ 194.84, 159.6, 141.5, 139.3, 136.0, 133.9, 133.2, 129.6, 128.8, 126.9, 119.6, 118.6, 117.8, 114.4, 113.9, 112.9, 78.3, 56.0, 55.10. Anal.Calcd for $C_{22}H_{18}ClNO_3$; C, 69.57; H, 4.78; N, 3.69; O, 12.64. Found: C, 68.66; H, 4.71; N, 3.73; O, 15.16.

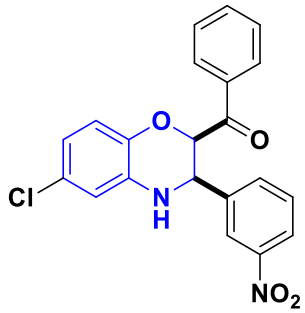
*4.2.2.8. (6-Chloro-3-(p-tolyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**15**);*



Off white solid, (438 mg, 86% yield). mp: 177-180°C; FTIR (ATR, V_{max}, cm^{-1}): 3395 (N-H str.), 2974 (Ar-H str.), 1689 (C=O str.), 1495 (Ar C=C str.), 1257 (C-N str.), 1057 (C-O-C str.), 684 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 7.83 (d, J = 8.58 Hz, 2H), 7.50 (t, J = 7.40 Hz, 1H), 7.36 (t, J = 7.75 Hz, 2H), 7.19 (d, J = 7.99 Hz, 2H), 7.06 (d, J = 7.96 Hz, 2H), 6.77 (d, J = 8.48 Hz, 1H), 6.64 (d, J = 2.28 Hz, 1H), 6.60 (dd, J = 8.40 Hz, J = 2.36 Hz, 1H), 5.27 (d, J = 5.88 Hz, 1H), 4.79 (d, J = 5.64 Hz, 1H), 4.19 (s, 1H), 2.26 (s, 3H).$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25°C) δ 194.85, 141.2, 138.3, 135.3, 135.2, 134.0, 133.5, 129.5, 128.5, 127.3, 126.8,

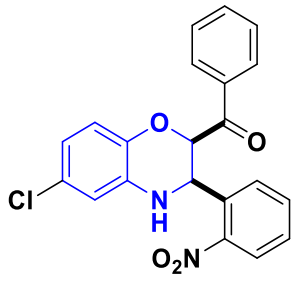
118.2, 117.8, 114.4, 78.9, 54.9, 21.0. Anal.Calcd for $C_{22}H_{18}ClNO_2$: C, 72.63; H, 4.99; N, 3.85; O, 8.79. Found: C, 72.22; H, 5.18; N, 3.92; O, 11.31.

*4.2.2.9. (6-Chloro-3-(3-nitrophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**16**);*



Off white solid, (430 mg, 78% yield). mp:180-184°C; FTIR (ATR, V_{max}, cm^{-1}): 3324 (N-H str.), 2976 (Ar-H str.), 1682 (C=O str.), 1490 (Ar C=C str.), 1356 (Ar-NO_2 str.), 1249 (C-N str.), 1058 (C-O-C str.), 681 (C-Cl str.); ^{1}H NMR (600 MHz, $CDCl_3$, 50°C) δ 8.02 (d, J = 8.10 Hz, 1H), 7.90 (s, 1H), 7.74 (d, J = 7.68 Hz, 2H), 7.53 (t, J = 7.41 Hz, 1H), 7.49 (d, J = 7.74 Hz, 1H), 7.40 – 7.34 (m, 3H), 6.95 (d, J = 8.16 Hz, 1H), 6.75 – 6.73 (m, 2H), 5.60 (d, J = 2.82 Hz, 1H), 5.11 (t, J = 3.06 Hz, 1H), 4.46 (s, 1H).^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 50°C) δ 194.4, 148.4, 141.4, 141.0, 135.8, 133.8, 133.6, 133.3, 129.7, 128.87, 128.84, 128.1, 123.2, 122.8, 119.2, 118.5, 114.9, 78.9, 55.8. Anal.Calcd for $C_{21}H_{15}ClN_2O_4$: C, 63.89; H, 3.83; N, 7.10; O, 16.21. Found: C, 63.31; H, 3.79; N, 7.32; O, 17.98.

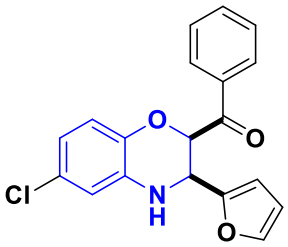
*4.2.2.10. (6-Chloro-3-(2-nitrophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**17**);*



Green solid, (425 mg, 77% yield). mp: 189-191°C; FTIR (ATR, V_{max}, cm^{-1}): 3406 (N-H str.), 2976 (Ar-H str.), 1673 (C=O str.), 1494 (Ar C=C str.), 1338 (Ar-NO_2 str.), 1245 (C-N str.), 1058 (C-O-C str.), 694 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 8.03 – 7.98 (m, 3H), 7.59 (d, J = 4.11 Hz, 2H), 7.55 (d, J = 8.07 Hz, 1H), 7.48 – 7.46 (m, 1H), 7.44 – 7.40 (m, 2H), 6.67 (d, J = 2.0 Hz, 1H), 6.59 (d, J = 8.51 Hz, 1H), 6.51 (dd, J = 8.60 Hz, J = 2.26 Hz, 1H), 5.85 (d, J = 5.56 Hz, 1H), 5.58 (s, 1H), 4.58 (d, J = 5.44 Hz, 1H).^{13}C{^{1}H} NMR (100 MHz,

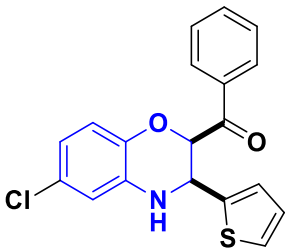
$CDCl_3$, 25°C) δ 194.7, 147.7, 139.5, 137.1, 134.4, 133.8, 133.7, 133.6, 129.9, 129.2, 128.6, 128.5, 127.7, 124.9, 118.4, 118.3, 114.6, 77.5, 49.8. Anal.Calcd for $C_{21}H_{15}ClN_2O_4$: C, 63.89; H, 3.83; N, 7.10; O, 16.21. Found: C, 63.47; H, 3.79; N, 7.08; O, 16.76.

*4.2.2.11. (6-Chloro-3-(furan-2-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**18**);*



Brown solid, (398 mg, 84% yield). mp: 170-174°C; FTIR (ATR, V_{max}, cm^{-1}): 3364 (N-H str.), 2976 (Ar-H str.), 1689 (C=O str.), 1497 (Ar C=C str.), 1262 (C-N str.), 1060 (C-O-C str.), 691 (C-Cl str.); ^1H NMR (400 MHz, $CDCl_3$, 25°C) δ 7.80 (d, J = 8.01 Hz, 2H), 7.55 (t, J = 7.31 Hz, 1H), 7.42 (t, J = 7.64 Hz, 2H), 7.18 (s, 1H), 6.89 (d, J = 8.24 Hz, 1H), 6.71 – 6.69 (m, 2H), 6.18 – 6.16 (m, 1H), 6.10 (d, J = 3.20 Hz, 1H), 5.63 (d, J = 2.48 Hz, 1H), 5.06 (s, 1H), 4.35 (s, 1H).$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25°C) δ 194.7, 150.7, 142.1, 141.6, 135.5, 133.5, 133.0, 128.7, 128.6, 127.1, 119.4, 118.1, 115.5, 110.6, 108.2, 77.8, 50.1.Anal.Calcd for $C_{19}H_{14}ClNO_3$: C, 67.16; H, 4.15; N, 4.12; O, 14.13. Found: C, 70.97; H, 4.43; N, 4.42; O, 16.53.

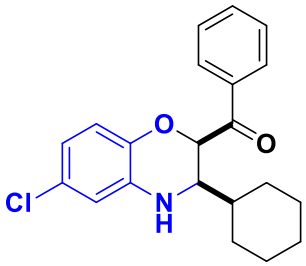
*4.2.2.12. (6-Chloro-3-(thiophen-2-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**19**);*



Off white solid, (358 mg, 72% yield). mp: 195-198°C; FTIR (ATR, V_{max}, cm^{-1}): 3366 (N-H str.), 2976 (Ar-H str.), 1688 (C=O str.), 1496 (Ar C=C str.), 1226 (C-N str.), 1057 (C-O-C str.), 694 (C-Cl str.); ^1H NMR (400 MHz, $CDCl_3$, 25°C) δ 7.79 (d, J = 7.74 Hz, 2H), 7.55 (t, J = 7.34 Hz, 1H), 7.41 (t, J = 7.64 Hz, 2H), 7.11 (d, J = 4.88 Hz, 1H), 6.94 (d, J = 8.52 Hz, 1H), 6.82 – 6.79 (m, 2H), 6.73 – 6.71 (m, 1H), 6.67 (d, J = 1.80 Hz, 1H), 5.63 (d, J = 2.28 Hz, 1H), 5.29 (s, 1H), 4.40 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25°C) δ 141.5, 133.5, 133.0, 128.8, 128.6, 127.5, 126.6, 126.1, 125.8, 119.3, 118.2, 115.3, 78.99, 51.80. The signals for the three aromatic quaternary carbons were not observed in the ^{13}C NMR spectrum. Anal.Calcd for $C_{19}H_{14}ClNO_2S$:

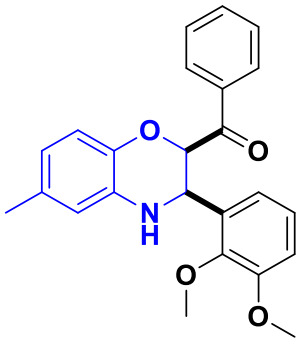
C, 64.13; H, 3.97; N, 3.94; O, 8.99; S, 9.01. Found: C, 63.34; H, 3.92; N, 4.02; O, 11.58; S, 8.73.

*4.2.3.11. (6-Chloro-3-cyclohexyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**20**);*



Off white solid, (205 mg, 41% yield). R_f 0.5 (5% ethyl acetate in hexane); mp: 110-115°C; FTIR (ATR, V_{max}, cm^{-1}): 3380 (N-H str.), 2923 (Ar-H str.), 1688 (C=O str.), 1497 (Ar C=C str.), 1219 (C-N str.), 689 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 8.04 - 8.02 (m, 2H), 7.46 – 7.42 (m, 4H), 7.09 (dd, J = 8.65 Hz, J = 2.22 Hz, 1H), 6.85 (d, J = 8.65 Hz, 1H), 5.41 (d, J = 8.59 Hz, 1H), 3.75 – 3.71 (m, 1H), 1.90 – 1.83 (m, 2H), 1.74 - 1.67 (m, 1H), 1.53 - 1.49 (m, 1H), 1.45 (d, J = 5.69 Hz, 1H), 1.27 -1.23 (m, 4H), 1.19 – 1.13 (m, 1H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25°C) δ 162.0, 143.4, 136.9, 134.9, 131.3, 128.6, 128.3, 127.8, 127.2, 126.9, 116.9, 73.1, 70.7, 39.9, 29.7, 26.55, 26.51, 26.2, 25.5. HRMS (ESI-TOF) calcd for $C_{21}H_{23}ClNO_2$ $[M + H]^+$ 356.1417, found 356.1786.

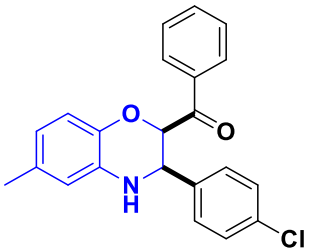
*4.2.3.12. (3-(2,3-Dimethoxyphenyl)-6-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**21**);*



Yellow solid, (488 mg, 77% yield). R_f 0.32 (21% ethyl acetate in hexane); mp: 144-147°C; FTIR (ATR, V_{max}, cm^{-1}): 3356 (N-H str.), 3070 (Ar-H str.), 1689 (C=O str.), 1596 (Ar C=C str.), 1206 (C-N str.), 1077 (C-O-C str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 8.08 (d, J = 7.91 Hz, 2H), 7.56 (t, J = 7.11 Hz, 1H), 7.44 (t, J = 7.67 Hz, 2H), 6.98 – 6.91 (m, 2H), 6.84 (d, J = 7.67 Hz, 1H), 6.74 (d, J = 7.79 Hz, 1H), 6.49 – 6.47 (m, 2H), 5.61 (d, J = 2.91 Hz, 1H), 5.24 (d, J = 2.88 Hz, 1H), 4.12 (brs, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.23 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz,

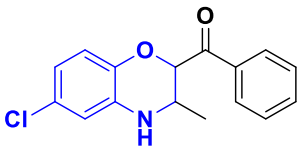
$CDCl_3$, 25°C) δ 195.5, 152.4, 146.0, 140.6, 135.0, 134.3, 133.3, 132.1, 131.3, 128.9, 128.4, 124.2, 119.6, 119.5, 116.4, 115.5, 112.1, 78.4, 60.5, 55.8, 49.7, 20.8. Anal.Calcd for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60; O, 16.43. Found: C, 74.11; H, 6.01; N, 3.66; O, 16.73.

*4.2.2.13. (3-(4-Chlorophenyl)-6-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**22**);*



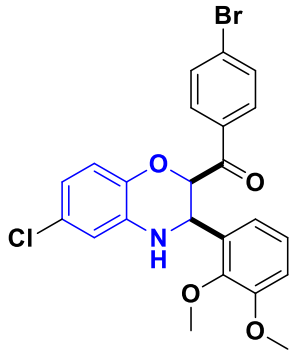
Off white solid, (490 mg, 83% yield). mp: 155-160°C; FTIR (ATR, V_{max}, cm^{-1}): 3399 (N-H str.), 1687 (C=O str.), 1596 (Ar C=C str.), 1207 (C-N str.), 690 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 7.84 (d, J = 7.68 Hz, 2H), 7.49 (t, J = 7.24 Hz, 1H), 7.35 (t, J = 7.54 Hz, 2H), 7.25 – 7.18 (m, 4H), 6.72 (d, J = 7.92 Hz, 1H), 7.47- 7.45 (m, 2H), 5.21 (d, J = 5.74 Hz, 1H), 6.49 – 6.47 (m, 2H), 5.61 (d, J = 2.91 Hz, 1H), 5.24 (d, J = 2.88 Hz, 1H), 4.12 (brs, 1H), 4.80 (d, J = 5.36 Hz, 1H), 4.06 (s, 1H), 2.20 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25°C) δ 195.0, 140.5, 137.7, 135.3, 134.0, 133.6, 132.4, 131.8, 129.0, 128.9, 128.8, 128.5, 119.5, 116.7, 115.6, 79.0, 54.93, 20.8. Anal.Calcd for $C_{22}H_{18}ClNO_2$: C, 72.63; H, 4.99; N, 3.85; O, 8.79. Found: C, 71.74; H, 5.14; N, 3.96; O, 9.72.

*4.2.3.11. (6-chloro-3-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**23**, major diastereomer);*



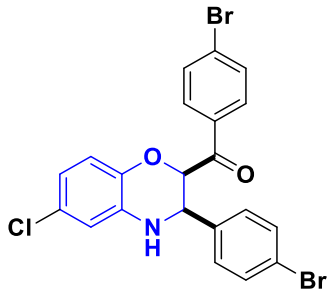
Yellow liquid, (3:2 diastereomeric mixture, combined yield 344 mg, 86%). R_f 0.4 (3.9% ethyl acetate in hexane); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 7.95 (d, J = 7.87 Hz, 2H), 7.49 – 7.47 (m, 3H), 7.42 (d, J = 2.37 Hz, 1H), 7.12 – 7.09 (m, 1H), 6.91 (d, J = 8.46 Hz, 1H), 5.25 (d, J = 6.56 Hz, 1H), 4.08 – 4.02 (m, 1H), 2.28 (s, 1H), 1.10 (d, J = 6.40 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25°C) δ 160.3, 136.0, 134.6, 134.1, 131.6, 129.0, 128.6, 127.4, 127.3, 127.1, 116.7, 76.1, 66.5, 19.0

*4.2.2.14. (4-Bromophenyl)(6-chloro-3-(2,3-dimethoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanone (**24**);*



Reddish solid, (592 mg, 87% yield). mp: 160-162°C; FTIR (ATR, V_{max}, cm^{-1}): 3402 (N-H str.), 2973 (Ar-H str.), 1691 (C=O str.), 1473 (Ar C=C str.), 1269 (C-N str.), 1060 (C-O-C str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 7.92 (d, J = 8.45 Hz, 2H), 7.59 (d, J = 8.42 Hz, 2H),7.00 - 6.96 (m, 1H), 6.87 - 6.84 (m, 2H), 6.73 (d, J = 8.80 Hz, 1H), 6.64 – 6.60 (m, 2H), 5.56 (d, J = 2.67 Hz, 1H), 5.21 (t, J = 3.16 Hz, 1H), 4.24 (d, J = 3.07 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H).$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25°C) δ 194.3, 152.4, 145.7, 140.9, 133.5, 133.4, 133.3, 131.8, 130.4, 128.8, 126.7, 124.3, 119.2, 118.5, 117.6, 114.3, 112.4, 78.2, 60.6, 55.8, 49.4. Anal.Calcd for $C_{23}H_{19}BrClNO_4$: C, 56.52; H, 3.92; N, 2.87; O, 13.09. Found: C, 56.30; H, 3.92; N, 3.08; O, 15.43.

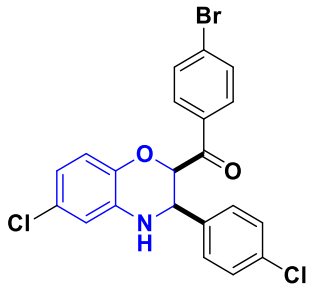
*4.2.2.15. (4-Bromophenyl)(3-(4-bromophenyl)-6-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanone (**25**);*



Yellow solid, (532 mg, 75% yield). mp: 143-146°C; FTIR (ATR, V_{max}, cm^{-1}): 3366 (N-H str.), 2976 (Ar-H str.), 1674 (C=O str.), 1486 (Ar C=C str.), 1215 (C-N str.), 1061 (C-O-C str.), 768 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 7.74 (d, J = 8.18 Hz, 2H), 7.55 (d, J = 8.56 Hz, 2H), 7.42 (d, J = 8.39 Hz, 2H), 7.20 (d, J = 8.38 Hz, 2H), 6.73 (d, J = 8.55 Hz, 1H), 6.67 (d, J = 2.23 Hz, 1H), 6.61 (dd, J = 8.65 Hz, J = 2.37 Hz, 1H), 5.18 (d, J = 5.45 Hz, 1H), 4.86 (dd, J = 5.32 Hz, J = 2.58 Hz, 1H), 4.24 (d, J = 1.88 Hz, 1H).$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25°C) δ 193.4, 140.8, 137.8, 133.8, 133.7, 132.15, 132.12, 130.5, 129.3, 129.2, 127.4, 122.6,

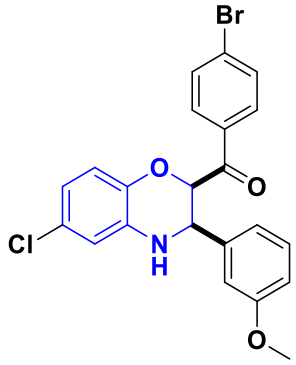
118.7, 118.1, 114.7, 78.9, 54.4. Anal.Calcd for $C_{21}H_{14}Br_2ClNO_2$: C, 49.69; H, 2.78; N, 2.76; O, 6.30. Found: C, 49.17; H, 2.77; N, 2.81; O, 9.29.

*4.2.2.16. (4-Bromophenyl)(6-chloro-3-(4-chlorophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanone (**26**);*



Yellow solid, (458 mg, 71% yield). mp: 138-140°C; FTIR (ATR, V_{max}, cm^{-1}): 3352 (N-H str.), 2976 (Ar-H str.), 1663 (C=O str.), 1489 (Ar C=C str.), 1225 (C-N str.), 1063 (C-O-C str.), 676 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 7.74 (d, J = 8.67 Hz, 2H), 7.55 (d, J = 8.45 Hz, 2H), 7.27 – 7.26 (m, 4H), 6.74 (d, J = 8.52 Hz, 1H), 6.67 (d, J = 2.31 Hz, 1H), 6.62 (dd, J = 8.88 Hz, J = 2.36 Hz, 1H), 5.19 (d, J = 5.56 Hz, 1H), 4.87 (dd, J = 5.47 Hz, J = 2.66 Hz, 1H), 4.23 (d, J = 2.66 Hz, 1H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25°C) δ 193.8, 140.8, 137.2, 134.5, 133.8, 132.1, 130.5, 129.3, 129.2, 128.9, 127.4, 118.7, 118.1, 114.7, 78.9, 54.4. Anal.Calcd for $C_{21}H_{14}BrCl_2NO_2$: C, 54.46; H, 3.05; N, 3.02; O, 6.91. Found: C, 52.80; H, 2.99; N, 2.99; O, 10.78.

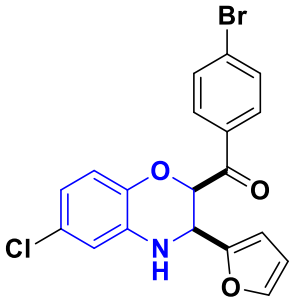
*4.2.2.17. (4-Bromophenyl)(6-chloro-3-(3-methoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanone (**27**);*



Off white solid, (507 mg, 79% yield). mp: 170-174°C; FTIR (ATR, V_{max}, cm^{-1}): 3371 (N-H str.), 2970 (Ar-H str.), 1686 (C=O str.), 1494 (Ar C=C str.), 1255 (C-N str.), 1054 (C-O-C str.), 695 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 7.46 – 7.41 (m, 4H), 7.09 (t, J = 7.61 Hz, 1H), 6.88 (d, J = 8.88 Hz, 1H), 6.72 – 6.71 (m, 2H), 6.70 – 6.69 (m, 2H), 6.60 (t, J = 1.91 Hz, 1H), 5.55 (d, J = 3.26 Hz, 1H), 4.91 (t, J = 2.81 Hz, 1H), 4.35 (d, J = 1.62 Hz, 1H), 3.62 (s,

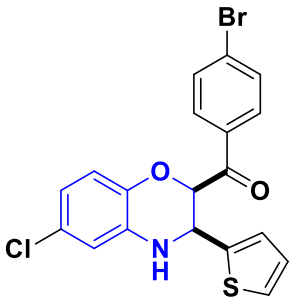
3H).$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25°C) δ 194.6, 141.4, 139.4, 134.8, 133.9, 131.7, 130.0, 129.9, 128.5, 127.2, 119.7, 118.8, 117.9, 114.6, 113.8, 113.3, 79.0, 56.1, 55.3. Anal.Calcd for $C_{22}H_{17}BrClNO_3$: C, 57.60; H, 3.74; N, 3.05; O, 10.46. Found: C, 56.72; H, 3.70; N, 3.13; O, 12.76.

*4.2.2.18. (4-Bromophenyl)(6-chloro-3-(furan-2-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanone (**28**);*



Off white solid, (422 mg, 72% yield). mp: 150-152°C; FTIR (ATR, V_{max}, cm^{-1}): 3365 (N-H str.), 2976 (Ar-H str.), 1691(C=O str.), 1490 (Ar C=C str.), 1241 (C-N str.), 1059 (C-O-C str.), 736 (C-Cl str.); ^{1}H NMR (600 MHz, $CDCl_3$, 40°C) δ 7.66 (d, J = 8.36 Hz, 2H), 7.54 (d, J = 8.33 Hz, 2H), 7.17 (s, 1H), 6.85 (d, J = 8.37 Hz, 1H), 6.71 – 6.69 (m, 2H), 6.17 (s, 1H), 6.10 (d, J = 2.82 Hz, 1H), 5.49 (d, J = 2.28 Hz, 1H), 5.05 (d, J = 2.99 Hz, 1H), 4.33 (s, 1H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$, 40°C) δ 194.3, 150.8, 142.2, 141.5, 134.4, 133.0, 131.9, 130.3, 128.7, 127.3, 119.5, 118.0, 115.6, 110.7, 108.3, 78.4, 50.2. Anal.Calcd for $C_{19}H_{13}BrClNO_3$: C, 54.51; H, 3.13; N, 3.35; O, 11.46. Found: C, 52.68; H, 3.09; N, 3.30; O, 14.04.

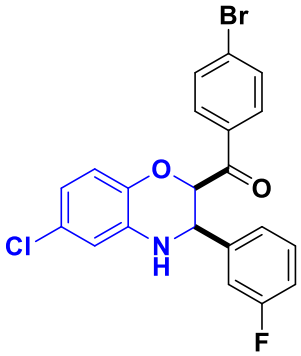
*4.2.2.19. (4-Bromophenyl)(6-chloro-3-(thiophen-2-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanone (**29**);*



Off white solid, (395 mg, 65% yield). mp: 150-152°C; FTIR (ATR, V_{max}, cm^{-1}): 3348 (N-H str.), 2976 (Ar-H str.), 1679 (C=O str.), 1492 (Ar C=C str.), 1233 (C-N str.), 1060 (C-O-C str.), 711 (C-Cl str.); ^{1}H NMR (600 MHz, $CDCl_3$, 40°C) δ 7.75 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 8.02, Hz, 2H), 7.21 (d, J = 4.20 Hz, 1H), 6.97 (s, 1H), 6.88 (s, 1H), 6.77 (d, J = 8.04 Hz, 1H), 6.65 – 6.63

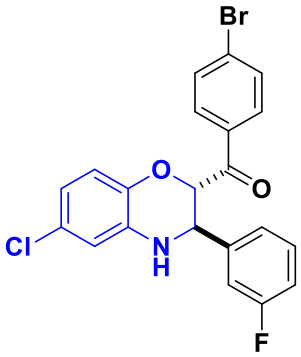
(m, 2H), 5.31 (d, *J* = 4.98 Hz, 1H), 5.17 (d, *J* = 4.03 Hz, 1H), 4.32 (s, 1H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$, 40°C) δ 193.8, 141.6, 141.2, 134.1, 133.1, 132.1, 130.4, 129.2, 127.3, 127.2, 126.2, 126.0, 119.2, 118.0, 115.2, 78.9, 51.2. Anal.Calcd for $C_{19}H_{13}BrClNO_2S$: C, 52.49; H, 3.01; N, 3.22; O, 7.36; S, 7.37. Found: C, 52.24; H, 2.96; N, 3.56; O, 9.91; S, 6.89.

4.2.3.11. (4-Bromophenyl)(6-chloro-3-(3-fluorophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanone (30a);



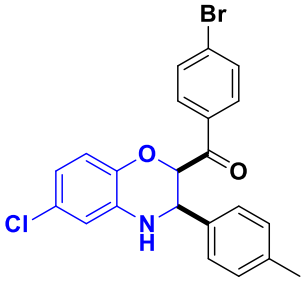
Light yellow solid, (530 mg, 76% yield). R_f 0.7 (3% ethyl acetate in hexane); mp: 135-138°C; FTIR (ATR, V_{max}, cm^{-1}): 3398 (N-H str.), 2976 (Ar-H str.), 1678 (C=O str.), 1491 (Ar C=C str.), 1218 (C-N str.), 1112 (C-F str.), 1064 (C-O-C str.), 687 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 7.75 (d, *J* = 8.14 Hz, 2H), 7.54 (d, *J* = 8.39 Hz, 2H), 7.28 – 7.26 (m, 1H), 7.10 – 7.04 (m, 2H), 6.98 – 6.94 (m, 1H), 6.74 (d, *J* = 8.24 Hz, 1H), 6.68 (d, *J* = 1.83 Hz, 1H), 6.62 (dd, *J* = 8.24 Hz, *J* = 1.83 Hz, 1H), 5.23 (d, *J* = 5.16 Hz, 1H), 4.90 (d, *J* = 3.22 Hz, 1H), 4.27 (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25°C) δ 194.0, 164.3 – 161.8 (d, J_{C-F} = 248.02 Hz, 1C), 141.5 – 141.4 (d, J_{C-F} = 6.50 Hz, 1C), 140.7, 133.8, 133.6, 132.0, 130.6, 130.5, 129.3, 127.4, 123.2 – 123.1 (d, J_{C-F} = 2.86 Hz, 1C), 118.7, 118.1, 115.7 – 115.5 (d, J_{C-F} = 20.96 Hz, 1C), 114.7, 114.6 – 114.4 (d, J_{C-F}= 22.05 Hz, 1C), 78.8, 54.5. Anal.Calcd for $C_{21}H_{14}BrClFNO_2$: C, 56.47; H, 3.16; N, 3.14; O, 7.16. Found: C, 56.63; H, 3.18; N, 3.01; O, 8.32.

4.2.3.12. (4-Bromophenyl)(6-chloro-3-(3-fluorophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanone (30b);



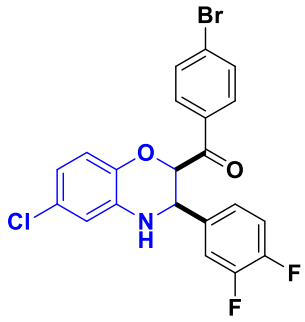
Light yellow solid, (49 mg, 7% yield). R_f 0.6 (5% ethyl acetate in hexane); mp: 135-138°C; FTIR (ATR, V_{max}, cm^{-1}): 3366 (N-H str.), 2964 (Ar-H str.), 1686 (C=O str.), 1490 (Ar C=C str.), 1256 (C-N str.), 1063 (C-O-C str.), 788 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 7.53 – 7.47 (m, 4H), 7.16 – 7.11 (m, 1H), 6.91 – 6.86 (m, 3H), 6.81 (d, J = 9.68 Hz, 1H), 6.72 – 6.70 (m, 2H), 5.51 (d, J = 3.32 Hz, 1H), 4.97 (s, 1H), 4.41 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25°C) δ 194.4, 164.1, 141.2, 140.8, 134.5, 133.6, 131.9, 130.4, 130.2, 128.8, 127.7, 123.2, 118.9, 118.2, 115.6 – 115.4 (d, $J_{C\text{-}F}$ = 22.10 Hz, 1C), 114.6, 114.5, 79.2, 55.7. HRMS (ESI-TOF) calcd for $C_{21}H_{15}BrClFNO_2$ $[M + H]^+$ 445.9959, found 446.0160.

*4.2.2.20. (4-Bromophenyl)(6-chloro-3-(p-tolyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanone (**31**);*



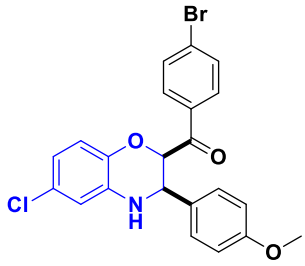
Reddish solid, (520 mg, 84% yield). mp: 175-177°C; FTIR (ATR, V_{max}, cm^{-1}): 3374 (N-H str.), 2976 (Ar-H str.), 1679 (C=O str.), 1489 (Ar C=C str.), 1285 (C-N str.), 1061 (C-O-C str.), 677 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 7.70 (d, J = 8.50 Hz, 2H), 7.51 (d, J = 8.48 Hz, 2H), 7.18 (d, J = 7.98 Hz, 2H), 7.08 (d, J = 7.93 Hz, 2H), 6.76 (d, J = 8.50 Hz, 1H), 6.65 (d, J = 2.26 Hz, 1H), 6.61 (dd, J = 8.56 Hz, J = 2.27 Hz, 1H), 5.20 (d, J = 5.91 Hz, 1H), 4.77 (d, J = 5.77 Hz, J = 1.76 Hz, 1H), 4.22 (s, 1H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25°C) δ 194.1, 141.0, 138.6, 135.2, 134.14, 134.1, 131.9, 130.5, 129.6, 129.0, 127.4, 127.1, 118.3, 117.9, 114.5, 79.1, 55.1, 21.2. Anal.Calcd for $C_{22}H_{17}BrClNO_2$: C, 59.68; H, 3.87; N, 3.16; O, 7.23. Found: C, 59.55; H, 3.94; N, 3.43; O, 9.52.

*4.2.2.21. (4-Bromophenyl)(6-chloro-3-(3,4-difluorophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanone (**32**);*



Brown solid, (448 mg, 69% yield). mp: 139-143°C; FTIR (ATR, V_{max}, cm^{-1}): 3344 (N-H str.), 2921 (Ar-H str.), 1689 (C=O str.), 1493 (Ar C=C str.), 1224 (C-N str.), 1114 (C-F str.), 1060 (C-O-C str.), 768 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 7.75 (d, J = 7.19 Hz, 2H), 7.55 (d, J = 7.63 Hz, 2H), 7.19 - 7.05 (m, 3H), 6.73 – 6.60 (m, 3H), 5.11 (d, J = 4.31 Hz, 1H), 4.86 (d, J = 3.18 Hz, 1H), 4.30 (brs, 1H).$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25°C) δ 193.7, 151.8 – 149.2 (dd, $J_{C\text{-}F}$ = 250.08 Hz, $J_{C\text{-}F}$ = 13.37 Hz, 1C), 151.5 – 148.9 (dd, $J_{C\text{-}F}$ = 250.08 Hz, $J_{C\text{-}F}$ = 12.90 Hz, 1C), 140.7, 135.98 – 135.93 (d, $J_{C\text{-}F}$ = 4.46 Hz, 1C), 133.6, 133.5, 132.1, 130.5, 129.4, 127.5, 123.7 – 123.6 (dd, $J_{C\text{-}F}$ = 3.61 Hz, $J_{C\text{-}F}$ = 3.61 Hz, 1C), 118.8, 118.1, 117.8 -117.6 (d, $J_{C\text{-}F}$ = 17.91 Hz, 1C), 116.7 – 116.5 (d, $J_{C\text{-}F}$ = 18.47 Hz, 1C), 114.8, 78.7, 53.9. HRMS (ESI-TOF) calcd for $C_{21}H_{14}BrClF_2NO_2$ $[M + H]^+$ 463.9865, found 464.0126.

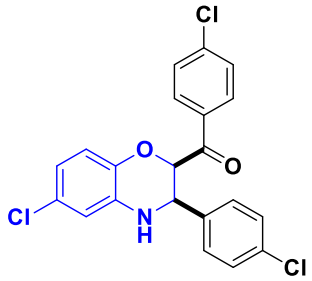
*4.2.2.22. (4-Bromophenyl)(6-chloro-3-(4-methoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanone (**33**);*



Red solid, (578 mg, 90% yield). mp: 142-145°C; FTIR (ATR, V_{max}, cm^{-1}): 3368 (N-H str.), 2929 (Ar-H str.), 1681 (C=O str.), 1491 (Ar C=C str.), 1224 (C-N str.), 1061 (C-O-C str.), 794 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 7.69 (d, J = 8.62 Hz, 2H), 7.51 (d, J = 8.62 Hz, 2H), 7.21 (d, J = 8.68 Hz, 2H), 6.80 - 6.77 (m, 3H), 6.66 – 6.61 (m, 2H), 5.17 (d, J = 6.25 Hz, 1H), 4.74 (d, J = 6.13 Hz, 1H), 4.19 (brs, 1H), 3.74 (s, 3H).$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25°C) δ 194.1, 159.9, 141.1, 134.2, 132.0, 130.5, 129.9, 129.0, 128.8, 127.1, 118.4, 117.9, 114.6,

114.4, 79.2, 55.4, 54.9. Anal.Calcd for $C_{22}H_{17}BrClNO_3$: C, 57.60; H, 3.74; N, 3.05; O, 10.46. Found: C, 56.13; H, 3.65; N, 3.57; O, 14.18.

*4.2.2.23. (6-Chloro-3-(4-chlorophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(4-chlorophenyl)methanone (**34**);*

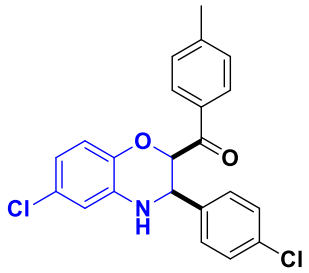


Light yellow solid, (538 mg, 92% yield). mp: 148-150°C; FTIR (ATR, V_{max}, cm^{-1}): 3356 (N-H str.), 2908 (Ar-H str.), 1664 (C=O str.), 1585 (Ar C=C str.), 1223 (C-N str.), 795 (C-Cl str.); ^1H NMR (400 MHz, $CDCl_3$, 25°C) δ 7.74 (d, J = 8.45 Hz, 2H), 7.29 (d, J = 8.45 Hz, 2H), 7.20 – 7.18 (m, 4H), 6.66 (d, J = 8.52 Hz, 1H), 6.59 (d, J = 1.87 Hz, 1H), 6.53 (dd, J = 8.50 Hz, J = 1.82 Hz, 1H), 5.11 (d, J = 5.44 Hz, 1H), 4.78 (d, J = 5.18 Hz, 1H), 4.18 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25°C) δ 193.5, 140.7, 140.4, 137.1, 134.4, 133.6, 133.3, 130.3, 129.08, 129.0, 128.8, 127.3, 118.5, 118.0, 114.6, 78.8, 54.3. Anal.Calcd for $C_{21}H_{14}Cl_3NO_2$: C, 60.24; H, 3.37; N, 3.35; O, 7.64. Found: C, 59.62; H, 3.35; N, 3.37; O, 8.26.

*4.2.2.24. (6-Chloro-3-(4-chlorophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(4-methoxyphenyl)methanone (**35**);*

Off white solid, (498 mg, 86% yield). mp: 145-148°C; FTIR (ATR, V_{max}, cm^{-1}): 3339 (N-H str.), 2931 (Ar-H str.), 1665 (C=O str.), 1591 (Ar C=C str.), 1230 (C-N str.), 745 (C-Cl str.); ^1H NMR (400 MHz, $CDCl_3$, 25°C) δ 7.86 (d, J = 8.70 Hz, 2H), 7.28 – 7.23 (m, 4H), 6.86 (d, J = 8.70 Hz, 2H), 6.78 (d, J = 8.50 Hz, 1H), 6.67 (s, 1H), 6.62 (d, J = 8.51 Hz, 1H), 5.21 (d, J = 5.72 Hz, 1H), 4.83 (d, J = 7.04 Hz, 1H), 4.27 (s, 1H), 3.85 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25°C) δ 192.7, 164.2, 141.3, 137.4, 134.3, 133.9, 131.5, 129.07, 129.05, 128.1, 127.1, 118.5, 118.0, 114.7, 114.0, 78.6, 55.6, 54.6. Anal.Calcd for $C_{22}H_{17}Cl_2NO_3$: C, 63.78; H, 4.14; N, 3.38; O, 11.59. Found: C, 63.38; H, 4.03; N, 3.46; O, 12.09.

*4.2.2.25. (6-Chloro-3-(4-chlorophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(p-tolyl)methanone (**36**);*



Off white solid, (416 mg, 75% yield). mp: 149-152°C; FTIR (ATR, V_{max}, cm^{-1}): 3334 (N-H str.), 2921 (Ar-H str.), 1672 (C=O str.), 1602 (Ar C=C str.), 1235 (C-N str.), 800 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 7.84 (d, J = 7.68 Hz, 2H), 7.49 (t, J = 7.24 Hz, 1H), 7.35 (t, J = 7.54 Hz, 2H), 7.25 – 7.18 (m, 4H), 6.72 (d, J = 7.92 Hz, 1H), 7.47- 7.45 (m, 2H), 5.21 (d, J = 5.74 Hz, 1H), 6.49 – 6.47 (m, 2H), 5.61 (d, J = 2.91 Hz, 1H), 5.24 (d, J = 2.88 Hz, 1H), 4.12 (brs, 1H), 4.80 (d, J = 5.36 Hz, 1H), 4.06 (s, 1H), 2.20 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25°C) δ 194.0, 144.9, 141.1, 137.2, 134.2, 133.7, 132.6, 129.3, 129.0, 128.99, 128.91, 127.0, 118.4, 117.9, 114.6, 78.5, 54.5, 21.7. Anal.Calcd for $C_{22}H_{17}Cl_2NO_2$: C, 66.35; H, 4.30; N, 3.52; O, 8.03. Found: C, 66.68; H, 4.47; N, 3.42; O, 8.63.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

NOESY spectra of compound 4

Spectral characterization of intermediates v and vii.

Copies of ^{1}H, ^{13}C NMR, HRMS, Elemental Analysis and IR spectra.

X-ray crystallographic analysis of **9b** (CIF)

X-ray crystallographic analysis of **15** (CIF)

X-ray crystallographic analysis of **17** (CIF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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CHAPTER 3

Synthesis, Crystal structure, spectroscopic and photophysical studies of novel fluorinated quinazoline derivatives

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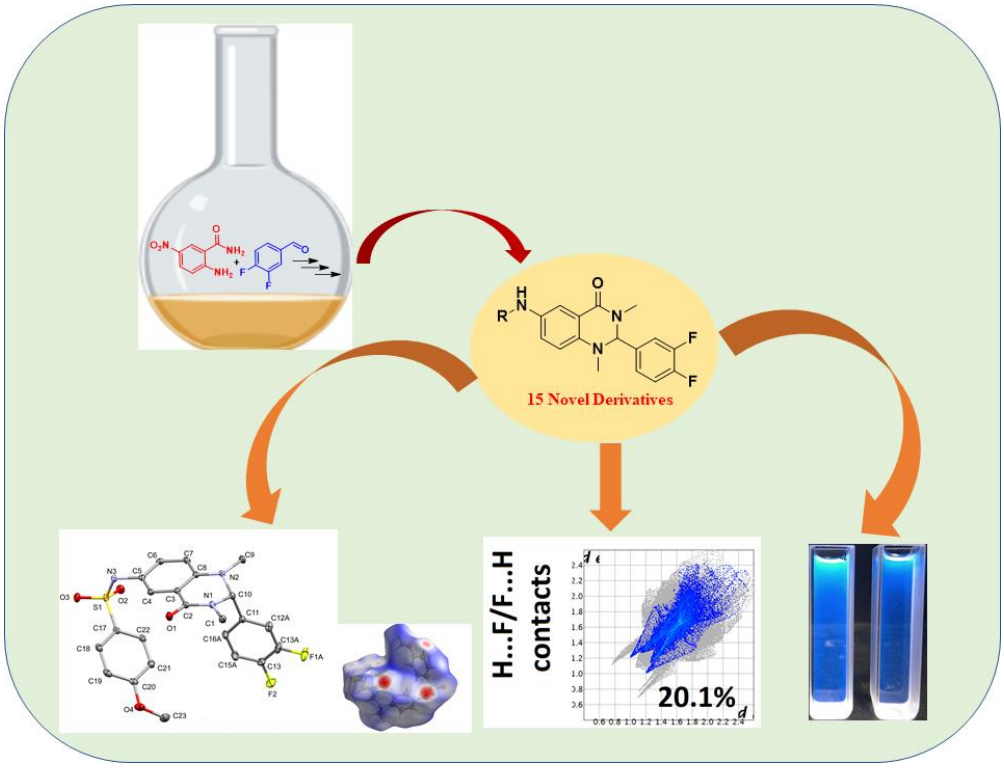
Graphical Abstract



Abstract

Fifteen fluorinated quinazoline derivatives have been synthesized and well-characterized with Infrared (IR) and Nuclear Magnetic Resonance (NMR) spectroscopic methods (^{1}H, ^{13}C, COSY, HMBC, HSQC and NOESY). In addition, crystal structure of 4 derivatives (**13b**, **13e**, **13f** and **13g**) were solved by single X-ray diffractometer. In this chapter, we have described the influence of various substituents on the core scaffold (Fluorinated quinazoline) on its molecular conformations, intermolecular interactions and on the photoluminescent properties. Hirshfeld surfaces was used to investigate the structure-directing effects of functional groups in controlling their solid-state behaviour. The photo-physical properties of all compounds have been studied including UV and fluorescence.

Keywords

Quinazoline, Crystal structure, fluorescence.

1. Introduction

In the past two decades there has been considerable efforts to develop new fluorophores with intramolecular charge transfer (ICT) emissions, as they have significant applications in non-linear optics (NLO),[1] organic-light emitting diodes (OLEDs), luminescence sensors,[2] emissive material for sensor,[3] dye-sensitized solar cells (DSSCs)[4] and field effect transistors.[5]

Quinazolines are important class of heterocyclic compounds and continue to attract significant attention in research because of their interesting photophysical (electronic absorption and emission) properties and wide pharmacological applications. Quinazoline is a π-deficient, nitrogen containing fused benzo-pyrimidine aromatic ring system. This π-deficient aromatic ring is responsible for the intramolecular charge transfer (ICT) property.[6-8] In general, quinazoline scaffold along with ICT has a significant impact on the luminescence properties and is also required for nonlinear optical (NLO) processes. The nitrogen atom of quinazoline ring plays a critical role in the formation of supramolecular assemblies[9] and sensors,[10] by allowing protonation, hydrogen bond formation and chelation.

Further, quinazoline ring is present as a core moiety in a wide variety of bioactive natural products and some important marketed pharmaceutical drugs such as gefitinib,[11] lapatinib[12] and erlotinib[13] (**Figure 1**). From literature it is quite evident that analogues of quinazoline also display a broad array of activities such as anti-cancer,[14] antiviral,[15] anti-tubercular,[16] antimalarial,[17] anticonvulsant,[18] anti-inflammatory[19] and anti-hypertensive.[20] Owing to the comprehensive application of this pharmacophore, it has attracted the attention of organic chemists to develop novel synthetic approaches to synthesize novel functionalized quinazolines and their derivatives.[21, 22]

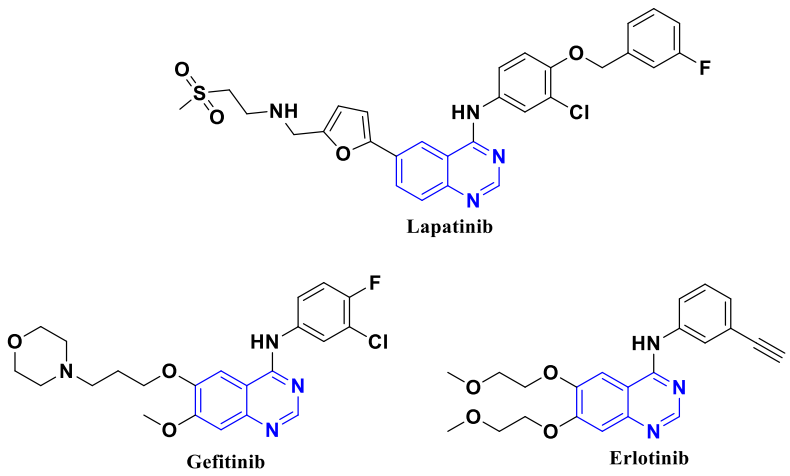
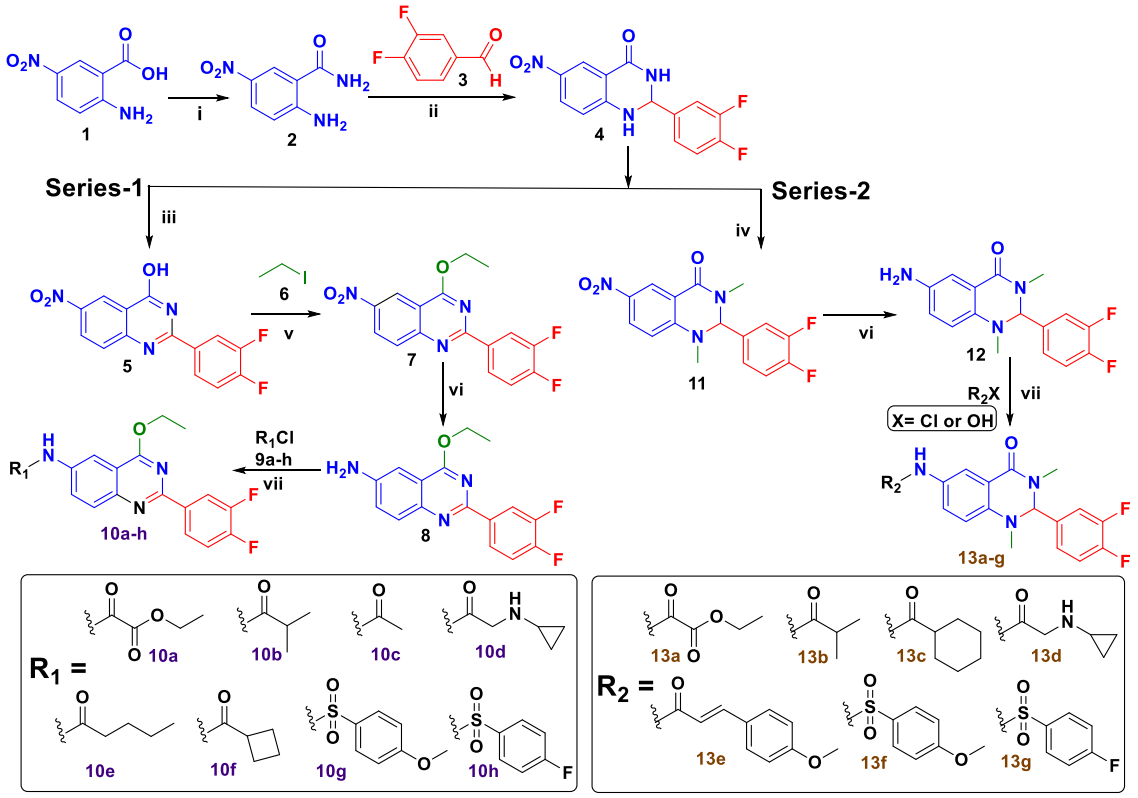


Figure 1: Structures of some biologically active quinazoline cores.

Additionally, presence of fluorine in organic molecules has considerable importance in both material science as well as pharmaceuticals. Introducing fluorine into the molecules provides a unique way of achieving distinctive modification with minimal changes in structural configuration. Fluorinated organic compounds have potential application in organic light-emitting diodes (OLEDs),[23, 24] organic photovoltaic devices (OPV)[25] and organic field effect transistors (OTFT).[26] In addition it is well documented that replacing a hydrogen atom of the natural substrate with fluorine may enhance biological activity[27] along with several biological properties such as solubility, lipophilicity, metabolic stability and binding selectivity.[28] With this in mind, we envisaged to synthesize novel fluorinated quinazoline derivatives and study the influence of the various substituents on the molecular conformation and intermolecular interactions on the photoluminescent properties.

2. Result and Discussion

2.1. Synthesis and spectral characterization



Scheme 1: *Reagents and conditions:* **i)** 28% aqueous ammonia solution, EDC.HCl, HOBt, DMF, 3–5 h; **ii)** *p*TSA, MeOH, 70°C, 16 h; **iii)** $KMnO_4$, DMSO, 100°C, 16 h; **iv)** CH_3I, K_2CO_3, DMF, 0°C - rt, 16 h; **v)** K_2CO_3, DMF, 0°C - rt, 24 h; **vi)** Fe, NH_4Cl, Dioxane: EtOH: H_2O

(7:5:3), 100°C, 5 h; **vii)** TEA, DCM, 0°C - rt, 4 h. **or** Pyridine, DCM, 0°C - rt, 16 h. **or** EDC.HCl, HOBT, DIPEA, DMF, rt, 16 h.

A brief description of synthetic route for all compounds is presented in Scheme 1. 2-amino-5-nitrobenzamide (**2**) was synthesized adopting the procedure described by M. Tobe *et al*.[29] where acid was converted to amide by treatment with aqueous ammonia in the presence of coupling reagent (EDC.HCl and HOBt) in DMF which was then cyclized with aldehyde (**3**) in presence of dehydrating agent *p*TSA in methanol followed by oxidation of 2-(3,4-difluorophenyl)-6-nitro-2,3-dihydroquinazolin-4(1*H*)-one (**4**) with $KMnO_4$ in DMSO. The obtained 6-nitroquinazolin-4-ol (**5**) was alkylated with iodoethane in presence of K_2CO_3 in DMF at ambient temperature for 24 h and then reduced with Fe/NH_4Cl, yielding 2-(3,4-difluorophenyl)-4-ethoxyquinazolin-6-amine (**8**) which was condensed with various acid chloride in presence of TEA in DCM and numerous sulfonyl chloride along with pyridine in DCM at 0°C - rt for 16 h yielding a series of corresponding final compounds (**10a-h**).

In the other series, compound (**4**) was alkylated with iodomethane in presence of K_2CO_3 in DMF at ambient temperature for 16 h followed by reduction with Fe/NH_4Cl in dioxane, ethanol and water (3:2:1) to yield 6-amino-2-(3,4-difluorophenyl)-1,3-dimethyl-2,3-dihydroquinazolin-4(1*H*)-one (**12**) which was treated with various acid, acid chlorides, and sulfonyl chlorides to yield another series of corresponding final compounds (**13a-g**).

The structures of all the new compounds were confirmed by spectroscopic data obtained from UV, IR, NMR (^1H, ^{13}C, ^{19}F and 2D). All derivatives and intermediates were evaluated using IR spectroscopy[30-33]. The stretching frequencies of C-F in all cases were observed in the region between 1050–1150 cm^{-1}.[31] The stretching frequencies around 1250 – 1350 cm^{-1} in case of **2, 4, 5,** and **7** indicated the presence of nitro (NO_2) group[30]. The frequencies with medium to strong intensities in the range of 1450–1650 cm^{-1} is assigned for C=N stretching[32, 33]. The stretching frequencies in the region 1600–1750 cm^{-1} and 3200–3400 cm^{-1} in some of derivatives (**10a-f** and **13a-e**) indicates the presence of amide C=O and N-H group, respectively.[31] In the IR spectra of **10g**, **10h**, **13f** and **13g** show broad band in the regions of 3200–3400 cm^{-1} are assigned for N-H stretching and high intense bands in the ranges 1250–1350 and 1100-1200 cm^{-1} for asymmetric and symmetric stretching modes of O=S=O group[33].

In case of ^1H NMR spectrum of compound **2**, two singlets at 8.18 and 7.36 clearly indicating different chemical environments of amide protons along with broad singlet at 7.87 of amine protons. Construction of **4** *via* cyclization was confirmed by appearance of singlet chiral proton at 6.09 ppm along with singlets at 8.79 and 8.57 ppm for adjacent NH and disappearance of amide and amine protons (**Figure 2A** and **2B**). Formation of **5** by oxidation was confirmed by

disappearance of singlet at 6.09 along with adjacent NH protons at 8.79 and 8.57 ppm, in addition, the presence of informative broad singlet at around 12.93 ppm confirms the presence of OH proton (**Figure 2B** and **2C**). The synthesis of alkylated compound **7** was confirmed by disappearance of -OH proton with appearance of quartet and triplet of -CH_2, -CH_3 at 4.80 ppm (J = 7.08 Hz) and 1.62 ppm (J = 7.19 Hz), respectively (**Figure 2C** and **2D**). The conversion of nitro to amine (**8**) was confirmed by appearance of broad singlet of -NH_2 at around 5.88 ppm (**Figure 2D** and **2E**).

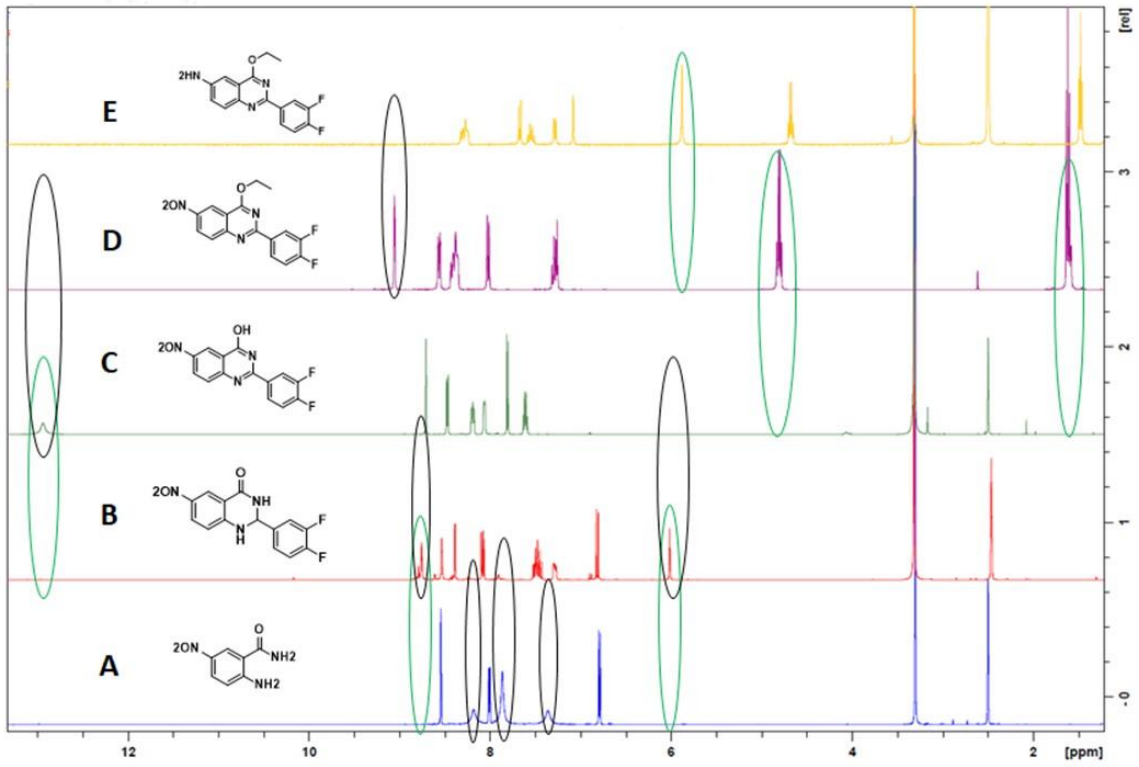


Figure 2: Consecutive validation of intermediate compounds by ^{1}H NMR overlapping.

Further, the formation of **11** by N-methylation was confirmed by appearance of two singlets at 2.97 and 2.89 of -CH3 protons as well as disappearance of two -NH protons. (**Figure 3A** and **3B**). The reduction of compound **11** was confirmed by the appearance of broad singlet of -NH_2 protons at around 4.75 ppm. (**Figure 3B** and **3C**).

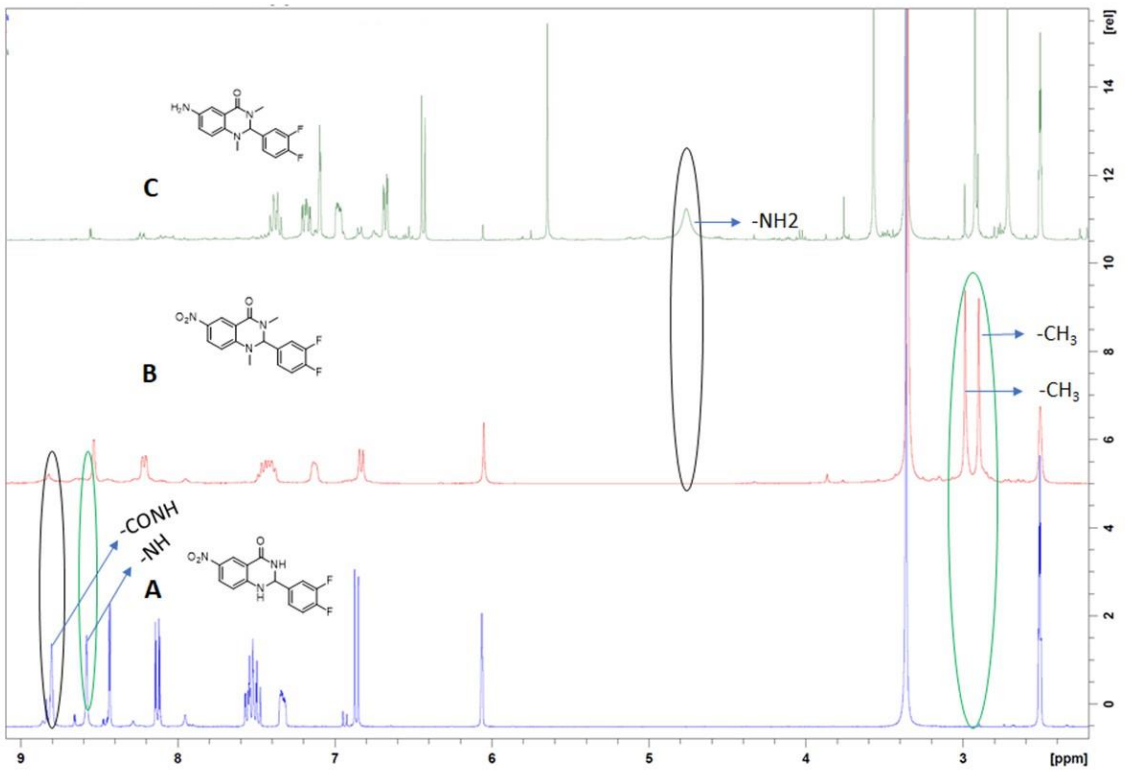


Figure 3: Successive confirmation of intermediate compounds by ^{1}H NMR overlapping.

The ^{1}H NMR spectrum of the final compounds (**10a-10h**) displayed some characteristic signals at around δ 11.16-10.12 ppm for N-H proton, and δ 4.79-4.65, 1.51-1.37 ppm for ethyl (-CH_2CH_3) protons although the ^{1}H spectrum of the other series final compounds (**13a-13g**) showed distinct signals at around δ 10.69-9.68 ppm for N-H, 2.91-2.84 and 2.81-2.73 ppm for methyl (-CH_3) protons.

These findings were further verified from their respective ^{13}C NMR spectra of the title compounds. Formation of **4** was supported by appearance of new carbon signal at around δ 65.12 and conversion to **5** was supported by disappearance of signal at 65.12 ppm along with appearance of quaternary carbon in de-shielded region at around 153.33 ppm. The alkylated product **7** was supported by presence of carbon signals at around δ 64.2 and 14.41 ppm which are assign for ethoxy (-CH_2-CH_3) and the N- methylated product **11** was supported by presence of carbon signals at 35.40 and 31.71 ppm which confirm the presence of methyl groups.

The ^{13}C NMR spectrum of the final compounds (**10a-10h** and **13a-13g**) displayed some characteristic double doublet signals at around δ 154−147 and 151−146 ppm which showed $J_{C\text{-}F}$ 254-242 Hz, 15-10 Hz and 248-241 Hz, 13-10 Hz respectively, verified the presence of two

fluorine atoms in aromatic ring which was also confirmed by ^{19}F NMR spectrum while the various aromatic carbons resonated around δ 169.6−100.8 ppm.

2.2. 2D NMR (NOESY, COSY, HSQC, and HMBC) investigation of 13b, 13e, 13f and 13g

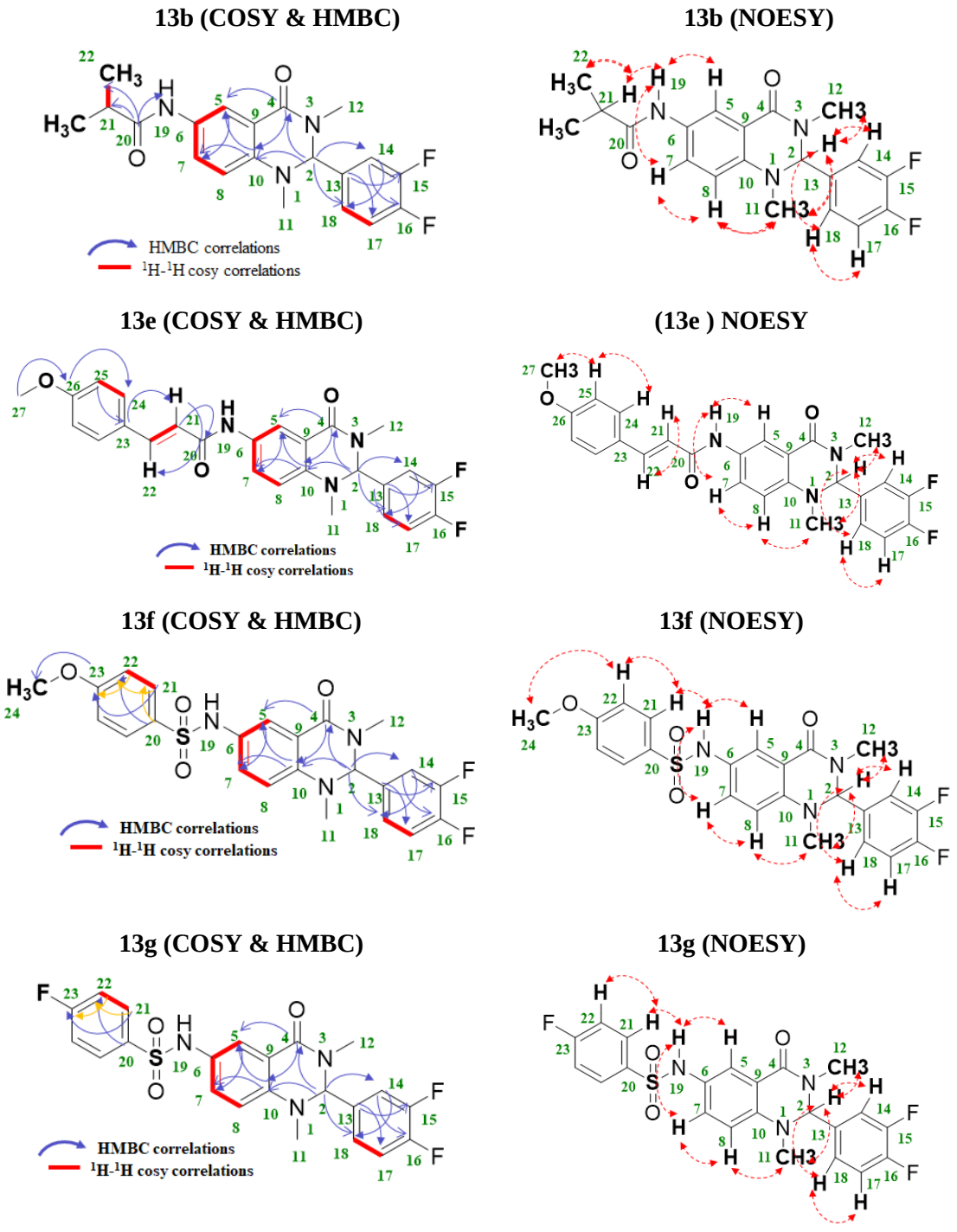


Figure 4: 2D *(NOESY, COSY, HSQC, and HMBC)* correlations of compounds **13b**, **13e**, **13f** and **13g**.

The solution phase conformational investigation of compounds **13b**, **13e**, **13f** and **13g** was carried out using 2D NMR (HMBC, HSQC, COSY and NOESY) analysis which are depicted in **figure 4**. Each molecule composed of 3,4 difluoro phenyl (DFP), 1,3-dimethyl-2,3-dihydroquinazolinone (DMHQ) and amide (**13b** and **13e**) or sulphonamide (**13f** and **13g**) moieties. The HMBC study of all molecules revealed that chiral carbon (2C) has correlation with 4C, 10C, 14C and 18C through the bond and the NOESY study revealed that chiral proton (2H) showing connectivity with 11H, 12H, 14H and 18H through the space. It indicates that chiral proton is in the centre of 11H, 12H, 14H and 18H. Furthermore, the 2D NMR study also revealed the absence of characteristic NOESY correlation between the proton of DMHQ and alkyl or aryl group of amide chain in compounds **13b**, **13e** and **13g** suggesting the non-existence of proximity. This indicate that the substituted amide groups of these compounds may away from DMHQ ring in solution phase. For **13f** the 2D NOESY failed to provide desired information about through space proton-proton connectivity between the aromatic proton of DMHQ ring and sulphonamide ring which is suggesting that the molecule is not in U shape in solution phase as confirmed by crystal structure.

2.3. Crystal structure descriptions of 13b, 13e, 13f, and 13g

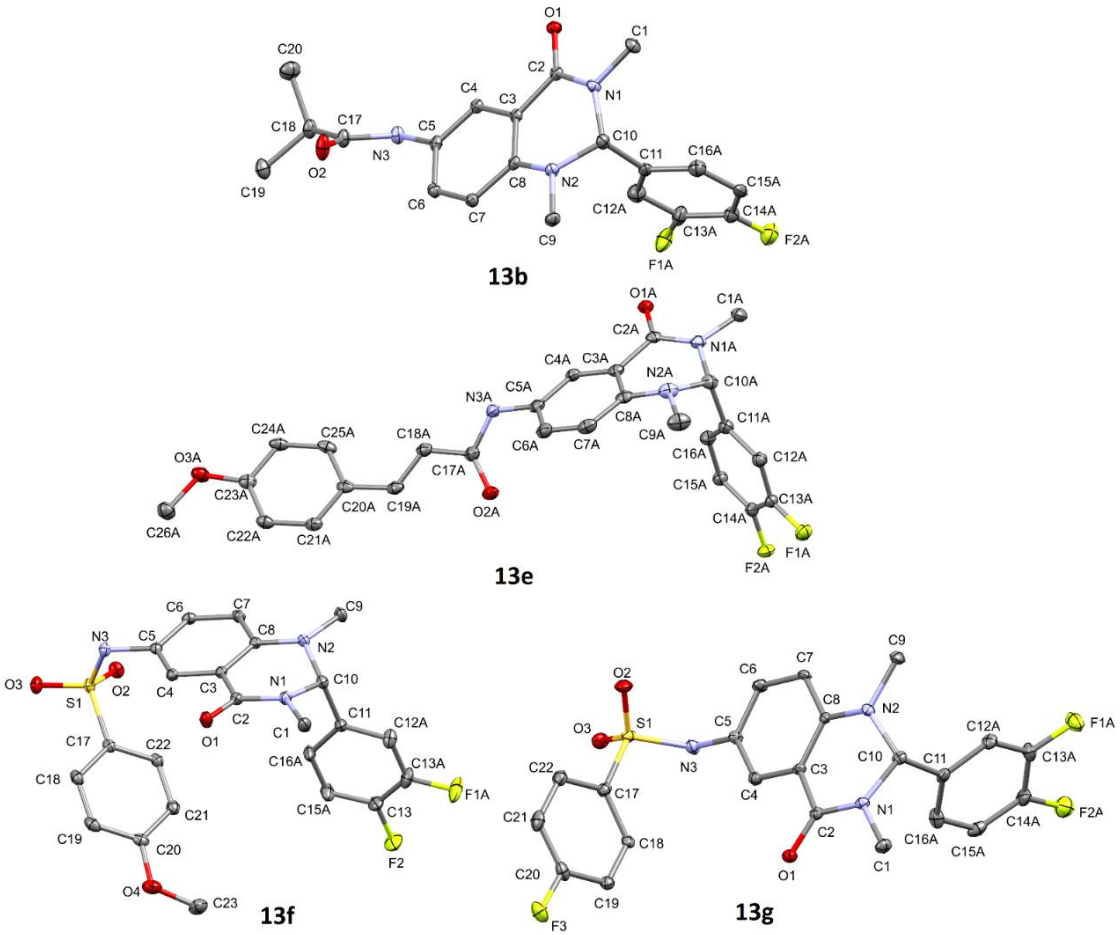


Figure 5: *ORTEP* diagrams of compounds **13b**, **13e**, **13f**, and **13g** drawn at 50% thermal ellipsoid probability. All hydrogen atoms, solvent molecules in **13b** and **13e** including one of the two quinazoline molecules of compound 13e have been omitted for clarity.

The fluorinated quinazoline molecules of compounds **13b**, **13e**, **13f**, and **13g** observed in their respective asymmetric units, are depicted in **Figure 5**. Each molecule composes of a 3,4-difluorophenyl (DFP), 1,3-dimethyl-2,3-dihydroquinazolinonyl (DMHQ), amide (**13b** and **13e**), sulfonamide (**13f** and **13g**) moieties. The DMHQ moiety in all the compounds was found to be non-planar with root mean squared deviation of 10 fitted atoms of the fused rings ranging from 0.110 Å to 0.123 Å. Furthermore, the DFP groups were almost orthogonal with respect to the core DMHQ unit with dihedral angle between the two moieties ranging from 84.823° to 96.556°. Interestingly, it appears that the presence of the electron donating substituent on the sulphonamide unit in **13f** narrows C5—N3—S1—C17 torsion angle from -74.661 (**13g**) to

56.3215(7) which results in **13f** having a bended, U-shaped molecular structure. All bond angles and distances are comparable to those of closely related structures.[34, 35]

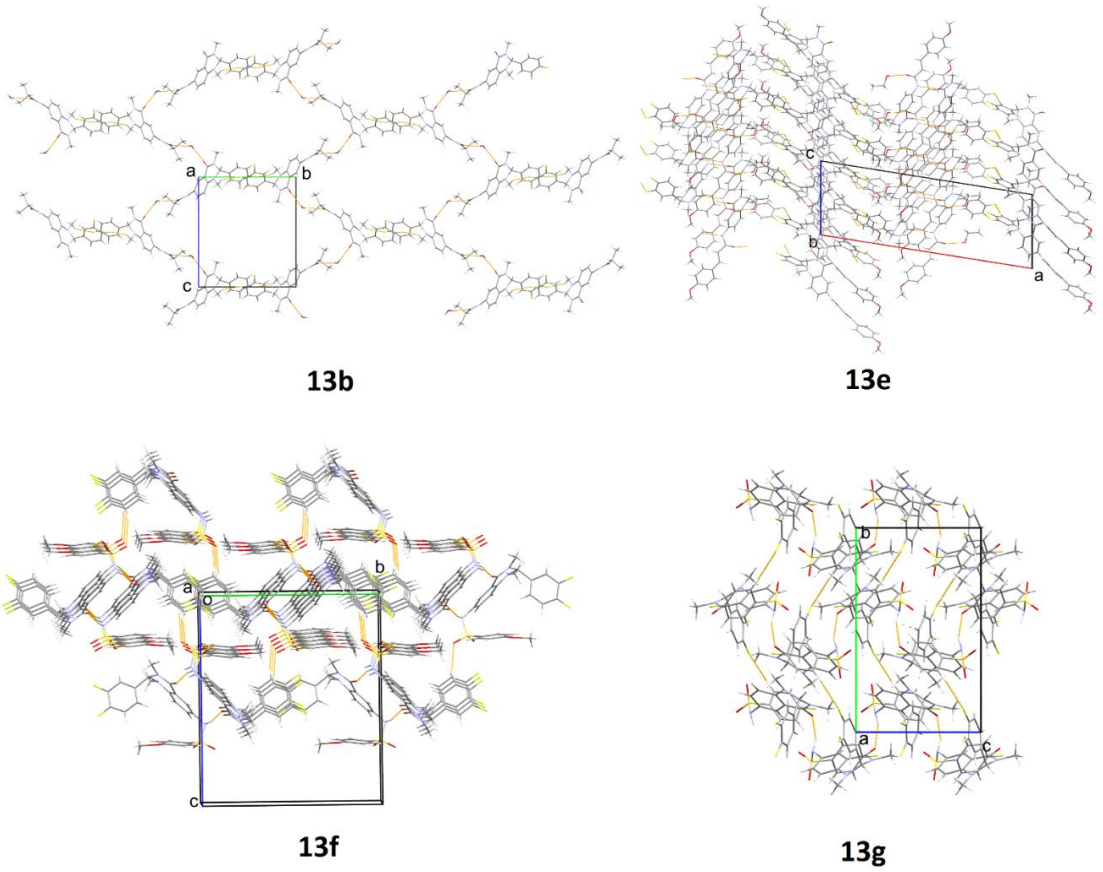


Figure 6: Selected hydrogen bonding patterns (shown as dashed orange bonds) found in crystal packing of compounds **13b**, **13e**, **13f**, and **13g**.

Selected intermolecular hydrogen bonding parameters observed in **13b, 13e, 13f,** and **13g** are listed in **Table 1** whilst the hydrogen bonding patterns are depicted in **Figure 6**. Classical intermolecular N—H…O hydrogen bonds between the amide (**13b** and **13e**) and sulphonamide (**13f**) link two neighbouring molecules to form 14-membered ring with a graphset notation $R_2^2(14)$. Another N—H…O hydrogen bonding pattern observed in **13e** and **13g** sew together neighbouring molecules to form chains that propagate along the crystallographic c axis. Since **13b** and **13e** contained polar, protic solvent molecules, O—H…O hydrogen bonds were also observed in their respective crystal packing. The methanol molecule in **13e** forms a dimer via O—H…O hydrogen bonds with the carbonyl oxygen of the amide functional group. On the other hand, the water molecule in **13b** links the DMHQ's and amide's carbonyl oxygen atoms of neighbouring molecules via O—H…O hydrogen bonds to form a 2-D supramolecular structure shown in **Figure 6**. Non-classical C—H…F hydrogen bonding patterns also exist in

13e and **13g** between the aromatic hydrogens and DFP moieties' fluorine atoms of neighbouring molecules. Linking molecules in this manner results in the formation of 2-D supramolecular architectures which extend along the crystallographic ac planes. Lastly, the C—H…O hydrogen bonds between the aromatic hydrogens (H19 and H15B) and O2 and O3 atoms of neighbouring sulphonamide moieties also form 2-D supramolecular structures which grow along the crystallographic ab planes.

Table 1: Selected hydrogen-bonding parameters (Å, º) for **13b**, **13e, 13f**, and **13g**.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
*Compound **13b***				
O3—H3*A*···O2^{i}	0.87	1.91	2.756 (2)	164
O3—H3*B*···O1	0.87	1.96	2.811 (2)	166
N3—H3···O1^{ii}	0.88	2.02	2.897 (2)	177
*Compound **13e***				
N3*A*—H3*A*···O1*A*^{i}	0.88	1.98	2.854 (3)	173
N3*B*—H3*B*···O1*B*^{ii}	0.88	2.01	2.855 (3)	160
C12*C*—H12*C*···F1*A*^{iii}	0.95	2.31	3.248 (8)	171
O4—H4···O2*A*	0.84	1.92	2.753 (3)	169
*Compound **13f***				
C19—H19···O2^{i}	0.95	2.35	3.2967 (2)	174
C15*B*—H15*B*···O3^{ii}	0.95	2.36	3.228 (5)	151
N3—H3···O1^{iii}	0.88 (1)	1.96 (1)	2.817 (1)	166
*Compound **13g***				
N3—H3···O1^{i}	0.88	1.95	2.739 (8)	149
C21—H21···F2*B*^{ii}	0.95	2.23	3.05 (2)	144
C16*B*—H16*B*···F1*B*^{iii}	0.95	1.18	2.02 (2)	143

Symmetry codes: 13b (i) *x*, −*y*−1/2, *z*−1/2; (ii) −*x*+1, −*y*, −*z*; **13e** (i) −*x*+1, −*y*+1, −*z*+2; (ii) *x*, −*y*+3/2, *z*−1/2; (iii) −*x*, −*y*+1, −*z*+2; **13f** (i) *x*−1, *y*, *z*; (ii) −*x*+3/2, *y*+1/2, −*z*+1/2; (iii) −*x*+1, −*y*+1, −*z*. **13g** (i) *x*, −*y*+1, *z*+1/2; (ii) *x*−1/2, *y*−1/2, *z*; (iii) *x*, −*y*+1, *z*−1/2.

2.4. Hirshfeld Surface Analysis

The molecular interactions of compounds **13b**, **13e, 13f**, and **13g** were studied by Hirshfeld surface analysis, which detailed the proximity of intermolecular interactions in their respective crystal packing. The Hirshfeld d_{norm} surface maps and the corresponding fingerprint plots for the H···H, H···O/O···H, C···H/H···C, and F···H/ H···F interactions are depicted in **Figure 7** and **8**, respectively. The red areas on the Hirshfeld surfaces around the DMHQ moiety highlight the reciprocal O···H/H···O contacts which are represented by a pair of broad spikes in the lower left (donor) area of the fingerprint plot and they are attributed to the N—H…O and C—H···O hydrogen bonds. Generally, the sulfonamides have larger O…H/H…O contribution to the d_{norm} surface than the amide derivatives due to a higher number of oxygen atoms. The H···H contacts were found to be the major contributor to the Hirshfeld surfaces with the amide derivatives having higher percentage values than the sulfonamides. Interestingly, it appears that the presence of the sterically demanding *iso*-propyl group in **13b** results in the highest H…H and H…F/F…H contributions in this series. As for the sulfonamides, the decrease in the H···H and H…F/F…H contributions from 34.1% (**13f**) to 27.3% (**13g**) and from 16% (**13f**) to 14.5% (**13g**) could be attributed to the widening of the C5—N3—S1—C17 torsion angle from 56.3(1) (**13f**) to -74.6(6) (**13g**).

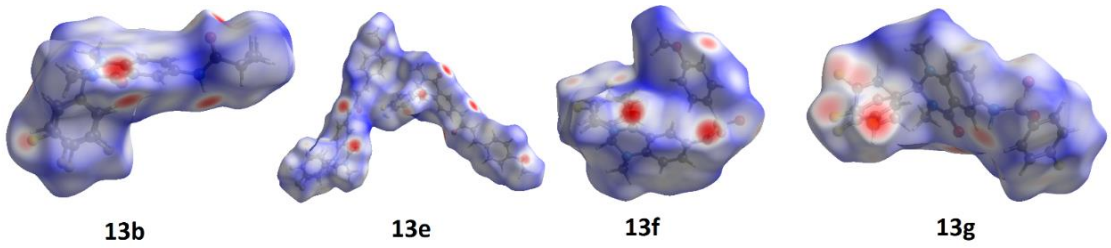


Figure 7: d_{norm} mapped on Hirshfeld surfaces.

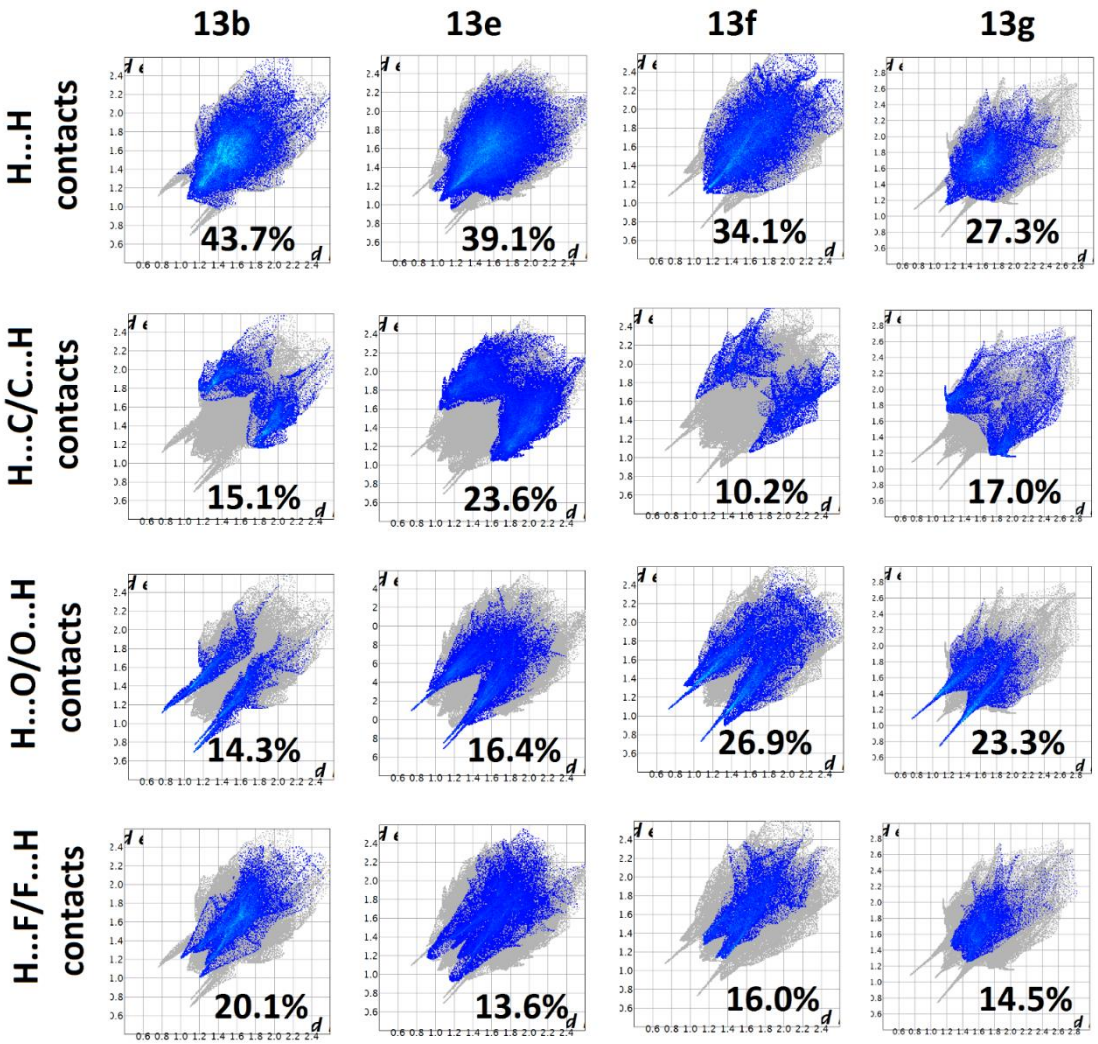


Figure 8: 2D fingerprint plots depicting relative contributions of various intermolecular contacts.

2.5. Photophysical studies

The UV-vis and fluorescence data were acquired in acetonitrile at 25°C and are summarized in **Table 2**. All compounds appear to have a λ_{max} ranging from 264 to 354 nm along with one or two maxima at shorter wavelengths. Alkylation of compound **5** results in a hypsochromic shift from 354 nm to 327 nm (**7**) and reduction of the NO_2 group to NH_2 causes a slight absorption bathochromic shift to 330 nm and an emission at 442 nm (**8**). Converstion of the amino group to various amide derivatives (**10a-f**) and (**13a-e**) results in an absorption hypsochromic shift from 330 nm (**8**) to 264-327 nm (**10a-f**) and 302-321 nm (**13a-e**). Intriguingly, increasing the carbon chain (**10e**) on the amide group and introducing a cyclic, bulky unit (**10f**) has little or no effect on the absorption λ_{max} relative to **10c**. However, it appears that having an acyclic, bulky group results in a significant bathochromic shift from 307 nm (**10c**) to 321 nm (**10b**). A similar trend

was observed for **13b** and **13c**. Having the cyclopropylamino amide unit in **10d** results in the disappearance of the absorption band around 300 nm whilst a significant bathochromic shift was observed for **13d** (321 nm) relative to other amides derivatives of **series-2**. The presence of an electron donating group (-OMe) on the amide units in **10g** causes an absorption bathochromic shift from 301 nm (**10h**) to 310 nm, whereas a large hypsochromic shift was observed from 354 nm (**13g**) to 309 nm (**13f**). The presence of nitro groups in **5** and **7**, oxalyl amide units in **10a** and **13a** including conjugated amide in **13e**, appear to quench the fluorescence ability of quinazoline. It was also noted that the presence of sulphonamide units in **10g-h** luminescence at a shorter wavelength range (380-385 nm) compared to that containing the amide units in **10a-f** (399-447 nm). In case of **13a-g**, there is an overlay in the emission wavelength maxima for the amides (437-456 nm) and sulphonamides (402-443 nm). Compounds **10c-h** (70-183 nm) have lower Stokes shift values relative that of compound **8** (112 nm) and **13b-g** (98-154 nm) with the exception of compound **10d** (183 nm).

Table 2: Summarized details from UV and fluorescence spectra of compounds **5**, **7**, **8**, **10a-h** and **13a-g**.

Compound	UV/vis λ_{max}, nm	Emission λ_{max}, nm	Stokes shift, nm
5	214, 354	-	
7	258, 327	-	
8	259, 330	442	112
10a	260, 327	-	
10b	225, 321	-	
10c	251, 307	399	92
10d	264	447	183
10e	252, 308	400	92
10f	252, 309	401	92
10g	252, 310	380	70
10h	249, 301	384	83
13a	252, 319	-	-
13b	220, 310	454	144
13c	220, 302	456	154
13d	225, 321	437	116
13e	218, 307	-	-
13f	252, 309	443	134
13g	215, 354	402	98

2.6. Theoretical calculation

Gaussian09 program package was employed for theoretical calculations. Geometry optimization of the structures was performed by using density functional theory (DFT) employing the B3LYP (Becke three parameters Lee–Yang–Parr exchange correlation functional), which combines the hybrid exchange functional of Becke with the gradient-correlation functional of Lee, Yang and Parr using 6-311G++(d,p) basis set was performed in gas phase. No solvent corrections were made with these calculations as gas phase calculations frequently correspond quite well with crystal structures. Starting geometries for were taken from X-ray refined data. All the distorted geometry was removed while generating the input file. The optimized geometry results in the free molecule state were compared to those in the crystalline state. No negative vibrational modes were obtained. The DFT calculated structure and geometric parameters (bond lengths and bond angles) agreed with each other. All optimized structures had a C1 point group.

The bond length between C9-O3 and N8-H54 in case of **13f**, was found to be 1.225 Å and 1.014 Å which is slightly higher than carbonyl (C=O) (usually 1.22 Å) and NH of sulphonamide, indicating presence of inter molecular H-bonding. Similar pattern of H-bonding was also determined in case of **13b**, **13e** and **13g** as shown by the increase of bond length compared to usual.

Frontier Orbital Energy and TD DFT calculations

Molecular Total Energy and Frontier Orbital energy levels were calculated using DFT (**Table 3**). Energy gap (ΔE) has been calculated for all 4 crystals as shown in the **Table 3**.

Table 3: Total energy and frontier orbital energy [B3LYP/6-311++G (d, p)].

--	13b	13e	13f	13g
E_{total} (Hartree)	-1366.01639120	-1594.66296551	-1952.49439920	-1937.20477708
E_{HOMO}	-0.21182	-0.20315	-0.21891	-0.22316
E_{LUMO}	-0.06395	-0.06965	-0.06343	-0.06602
ΔE^a (eV)	4.33	3.63	4.23	4.27

[a]$\Delta E = E_{LUMO} - E_{HOMO}$.

The energy gap between HOMO and LUMO was calculated by the B3LYP method using the 6-311G++(d,p) basis set. The compounds showed an energy gap (ΔE) for HOMO → LUMO in a range from 3.63-4.33 eV (**Table 3**). HOMO and LUMO are important factors that affect bioactivity, chemical reactivity and electron affinity and ionization potential. Thus, study of the

frontier orbital energy can provide useful information about the biological and chemical reaction mechanism. TD-DFT calculations have also been performed to bring insight into the absorption spectra of the derivatives to calculate the excited states.

Table 4: Calculation of absorption spectra using TD-DFT calculations.

Compound	Transitions from	Calculated		*f*
		λ_{max} (nm)	λ_{max} (eV)	
13b	HOMO-LUMO	367.93	3.37	0.0453
	HOMO-LUMO+1	324.41	3.82	0.0402
	HOMO-LUMO+2	300.08	4.13	0.0507
13e	HOMO-LUMO	380.20	3.26	0.6693
	HOMO-LUMO+1	361.48	3.43	0.0495
	HOMO-LUMO+2	327.36	3.79	0.0033
13f	HOMO-LUMO	349.13	3.55	0.0409
	HOMO-LUMO+1	313.46	3.96	0.0040
	HOMO-LUMO+2	305.50	4.06	0.0991
13g	HOMO-LUMO	344.95	3.59	0.0442
	HOMO-LUMO+1	311.03	3.99	0.1482
	HOMO-LUMO+2	303.23	4.09	0.0041

Electronic transition properties including λ_{max} were calculated for all 4 crystals using TD-DFT calculations using Gaussian09 and the values of λ_{max} (both in nm and eV) and oscillator strength have been calculated as shown in **Table 4**. From the calculated absorption spectrum, in case of **13b**, three intense bands were observed corresponding to transitions from HOMO to LUMO (367.93 nm), HOMO to LUMO+1 (324.41 nm) and HOMO to LUMO+2 (300.08 nm). In case of **13g** the most prominent transition was observed from HOMO to LUMO+1 (311.03 nm) based on the oscillator strength whereas in case of **13e** HOMO to LUMO was the most intense one at 380.20 nm. In case of **13f**, shows one intense band envelope based on the oscillator strength, at λ_{max} = 305.50 nm compared to other two signals at 349.13 and 313.46 nm. This intense band refers to the transition from HOMO to LUMO+2.

3. Conclusion

In this chapter, fifteen compounds based on fluorinated quinazoline derivatives have been synthesized and well-characterized with Infrared (IR) and Nuclear Magnetic Resonance (NMR) spectroscopic methods (^{1}H, ^{13}C, COSY, HMBC, HSQC and NOESY). Additionally, crystal structure of 4 derivatives (**13b**, **13e**, **13f** and **13g**) were solved by single X-ray diffractometer and compare the confirmation of molecules in solution- phase using 2D NOESY experiments.

The influence of various substituents on the core scaffold (Fluorinated quinazoline) on its molecular conformations, intermolecular interactions and on the photoluminescent properties has been described. Hirshfeld surfaces was used to investigate the structure-directing effects of functional groups in controlling their solid-state behaviour. Among the series, compounds (**8**, **10c-h**, **13b-d** and **13f-g**) displayed good photoluminescent properties.

4. Experimental

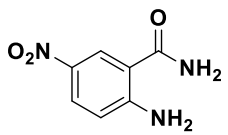
4.1. General consideration

All the fine chemicals, reagents and solvents were purchased from Sigma Aldrich and Merck and were used without further purification unless otherwise stated. The progress of the reactions and the purity of the compounds were monitored by thin-layer chromatography (TLC) on pre-coated silica gel plates procured from E. Merck and Co. (Darmstadt, Germany) visualized by UV lamp (254 or 365 nm). Purification was performed by using combi-flash (Combi*Flash*® NextGen 300+) column chromatography. The melting points of the synthesized compounds have been determined and uncorrected using a digital Stuart SMP10 melting point Apparatus. The Fourier transform infrared (FTIR) spectra were recorded in the spectral range of 400-4000 cm^{-1} on a Bruker Alpha FT-IR spectrometer using the ATR technique. The NMR spectra (**(**^{1}H, ^{13}C, ^{19}F, & 2D) were recorded using $CDCl_3$ and DMSO-d_6 on Bruker AVANCE III 400 and 600 MHz spectrometer. Chemical shifts were determined relative to internal standard TMS at δ 0.0 parts per million (ppm) and the coupling constants were reported in Hertz. The multiplicities of the NMR resonances were abbreviated as s (singlet), d (doublet), dd (doublet of doublet), (t (triplet), q (quartet), m (multiplet) and brs (broad singlet). X-ray crystallography analysis was performed on Bruker SMART APEX II, X-ray diffractometer.

4.2. Chemistry

4.2.1. Synthesis and spectral characterization of intermediate compounds (2, 4, 5, 7, 8, 11 and 12);

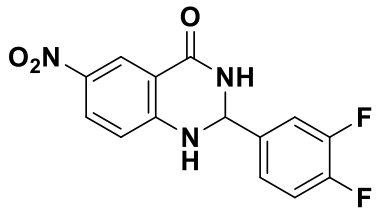
*4.2.1.1. Synthesis of 2-amino-5-nitrobenzamide (**2**);*



To the solution of 2-amino-5-nitrobenzoic acid (30 g, 164.83 mmol) and HOBt (26.70 g, 197.80 mmol) in DMF (150 mL) was added EDC.HCl (37.78 g, 197.80 mmol). The mixture was stirred

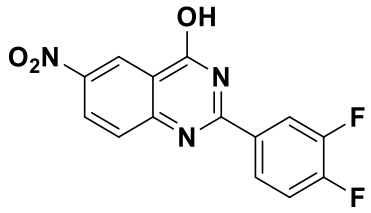
at ambient temperature for 2 h then cooled to 0°C. Then a 28% ammonia solution was added and stirred for another 2 h at room temperature: the reaction mixture was monitored by TLC. After consumption of starting material, the mixture poured into ice cold water, the precipitate was filtered and dried under vacuum, washed with pentane followed by diethyl ether to afford yellow solid product (24.9 g, 83%); mp: 128-134°C; FTIR (ATR, V_{max}, cm^{-1}): 3412.37 (N-H str. of NH_2), 3300.44 (N-H str.), 3198 (Ar-H str.), 1667.46 (C=O str.), 1613.56 (Ar C=C str.), 1314.55 (Ar-NO_2 str.); 1H NMR (600 MHz, DMSO-d_6, 25°C) δ 8.54 (s, 1H), 8.18 (brs, 1H), 8.00 (d, J = 8.99 Hz, 1H), 7.86 (brs, 2H), 7.36 (brs, 1H), 6.79 (d, J = 9.17 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 169.6, 155.6, 134.8, 127.4, 126.3, 115.9, 112.0.

*4.2.1.2. Synthesis of 2-(3,4-difluorophenyl)-6-nitro-2,3-dihydroquinazolin-4(1H)-one (**4**);*



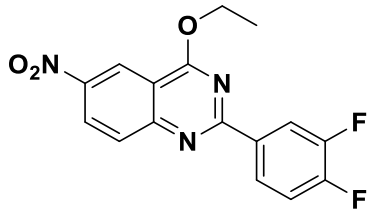
To the solution of 2-amino-5-nitrobenzamide (10 g, 55.20 mmol) and 3,4-difluorobenzaldehyde (6.12 mL, 55.20 mmol) in methanol (20 mL) was added catalytic amount of *p*-toluenesulfonic acid (1.05 g, 5.52 mmol). The resultant mixture was reflux for 16 h, precipitate was formed, filtered and washed with methanol to afford yellow solid product (13.2 g, 78%). mp: 294-296°C; UV/vis (CH_3CN): λ_{max} = 344 nm; FTIR (ATR, V_{max}, cm^{-1}): 3477.23 (N-H str.), 3357.74 (N-H str.), 2973.94 (Ar-H str.), 1682.62 (C=O str.), 1487 (Ar C=C str.), 1324.68 (Ar-NO_2 str.), 1057 (C-F str.); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 8.79 (brs, 1H), 8.57 (brs, 1H), 8.42 (d, J = 3.33 Hz, 1H), 8.11 (dd, J = 8.97 Hz, J = 2.77 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.33 – 7.30 (m, 3H), 6.85 (d, J = 9.08 Hz, 1H), 6.05 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 161.2, 151.8, 150.4 – 148.6 (dd, $J_{C\text{-}F}$ = 246.5 Hz, $J_{C\text{-}F}$ = 14.3 Hz, 1C), 150.1 – 148.4 (dd, $J_{C\text{-}F}$ = 245.6 Hz, $J_{C\text{-}F}$ = 12.5 Hz, 1C), 138.7, 137.4, 129.0, 124.1, 123.4 – 123.4 (dd, $J_{C\text{-}F}$ = 6.6 Hz, $J_{C\text{-}F}$ = 3.31 Hz, 1C), 117.7 – 117.6 (d, $J_{C\text{-}F}$ = 17.3 Hz, 1C), 115.9 – 115.8 (d, $J_{C\text{-}F}$ = 17.3 Hz, 1C), 114.4, 112.6, 65.1. ^{19}F NMR (376 MHz, DMSO-d_6, 25°C) δ -137.74 (d, $J_{F\text{-}F}$ = 22.21 Hz, 1F), -138.35 (d, $J_{F\text{-}F}$ = 22.21 Hz, 1F).

*4.2.1.3. Synthesis of 2-(3,4-difluorophenyl)-6-nitroquinazolin-4-ol (**5**);*



To the solution of 2-(3,4-difluorophenyl)-6-nitro-2,3-dihydroquinazolin-4(1H)-one (8 g, 26.20 mmol) in DMSO (50 mL) was added potassium permanganate (12.42 g, 78.62 mmol). The mixture was heated at 100°C for 16 h and monitored by TLC after consumption of starting material cooled to room temperature and filtered through celite. The filtrate was poured into water and stirred for 30 min precipitate was formed, filtered and washed with diethyl ether to afford title compound (5.6 g, 70%). mp 296-298°C; UV/vis (CH_3CN): λ_{max} = 354 nm; FTIR (ATR, V_{max}, cm^{-1}): 2973.93 (Ar-H str.), 2868.71 (Ar-H str.), 1674.85 (C=O str.), 1569.82 (Ar C=C str), 1339.13 (Ar-NO_2 str.), 1056.77 (C-F str.); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 12.93 (brs, 1H), 8.70 (d, J = 2.81 Hz, 1H), 8.47 (dd, J = 9.10 Hz, J = 2.47 Hz, 1H), 8.21 – 8.17 (m, 1H), 8.06 (t, J = 4.26 Hz, 1H), 7.80 (d, J = 9.11 Hz, 1H), 7.63 – 7.58 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6, 70°C) δ 161.3, 153.3, 152.7 – 151.0 (dd, $J_{C\text{-}F}$ = 252.7 Hz, $J_{C\text{-}F}$ = 12.5 Hz, 1C), 152.3, 150.1 – 148.3 (dd, $J_{C\text{-}F}$ = 245.9, $J_{C\text{-}F}$ = 15.3 Hz, 1C), 144.7, 129.0, 128.4, 125.7 – 125.6 (dd, $J_{C\text{-}F}$ = 7.41 Hz, $J_{C\text{-}F}$ = 2.9 Hz, 1C), 121.8, 120.8, 118.0 – 117.8 (d, $J_{C\text{-}F}$ = 17.6 Hz, 1C), 117.4 – 117.3 (d, $J_{C\text{-}F}$ = 19.4 Hz, 1C). ^{19}F NMR (376 MHz, DMSO-d_6, 25°C) δ -132.80 (d, $J_{F\text{-}F}$ = 23.21 Hz, 1F), -137.27 (d, $J_{F\text{-}F}$ = 23.25 Hz, 1F).

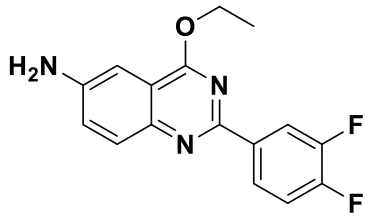
4.2.1.4. Synthesis of 2-(3,4-difluorophenyl)-4-ethoxy-6-nitroquinazoline (7);



To the solution of 2-(3,4-difluorophenyl)-6-nitroquinazolin-4-ol (3.4 g, 11.21 mmol) in DMF (30 mL) was added potassium carbonate (2.32 g, 16.81 mmol), followed by iodoethane (1.35 mL, 16.81 mmol). The resultant suspension was stirred at room temperature for 16 h then poured into ice cold water, precipitate was formed filtered under vacuum and washed with methanol to afford title compound (2.87 g, 77%). mp: 230-232°C; UV/vis (CH_3CN): λ_{max} = 327 nm; FTIR (ATR, V_{max}, cm^{-1}): 3093.47 (Ar-H str.), 2992.85 (Ar-H str.), 1592.53 (C=N str.), 1495.42 (Ar C=C str.), 1276.13 (Ar-NO_2 str.), 1110.78 (C-F str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 9.05 (s, 1H), 8.56 (d, J = 9.45 Hz, 1H), 8.43 – 8.35 (m, 2H), 8.02 (d, J = 8.95 Hz, 1H),

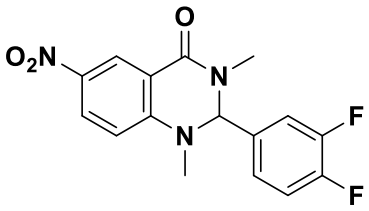
7.31 – 7.25 (m, 1H), 4.80 (q, J = 7.08 Hz, 2H), 1.62 (t, J = 7.19 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ 167.9, 161.3, 154.6, 154.2 – 151.6 (dd, $J_{C\text{-}F}$ = 254.0 Hz, $J_{C\text{-}F}$ = 12.2 Hz, 1C), 151.9 – 149.3 (dd, $J_{C\text{-}F}$ = 248.9 Hz, $J_{C\text{-}F}$ = 12.9 Hz, 1C), 145.2, 134.5 – 134.4 (dd, $J_{C\text{-}F}$ = 5.79 Hz, $J_{C\text{-}F}$ = 3.03 Hz, 1C), 129.6, 127.4, 125.6 – 125.5 (dd, $J_{C\text{-}F}$ = 7.3 Hz, $J_{C\text{-}F}$ = 4.1 Hz, 1C), 121.0, 118.2 – 118.0 (d, $J_{C\text{-}F}$ = 19.1 Hz, 1C), 117.5 – 117.3 (d, $J_{C\text{-}F}$ = 18.1 Hz, 1C), 114.7, 64.2, 14.4. ^{19}F NMR (376 MHz, DMSO-d_6, 25°C) δ -133.14 (d, $J_{F\text{-}F}$ = 21.68 Hz, 1F), -137.21 (d, $J_{F\text{-}F}$ = 20.48 Hz, 1F).

*4.2.1.5. Synthesis of 2-(3,4-difluorophenyl)-4-ethoxyquinazolin-6-amine (**8**);*



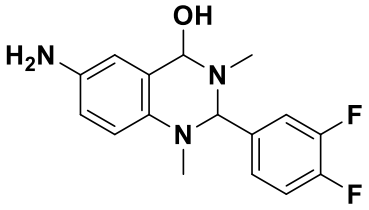
2-(3,4-difluorophenyl)-4-ethoxy-6-nitroquinazoline (2.5 g, 7.54 mmol) was added into the mixture of dioxane (28 mL), ethanol (20 mL) and water (12 mL) followed by ammonium chloride (2.4 g, 45.27 mmol). To the resultant mixture iron powder (1.26 g, 22.63 mmol) was added with vigorous stirring and then heated at 100°C for 5 h. The reaction mixture was cool to room temperature and filtered through celite and washed with 10% MeOH/DCM. The filtrate was concentrated under reduce pressure and diluted with water then extracted with 10% IPA/$CHCl_3$ (3 X 50 mL). Organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduce pressure to afford greenish solid product (2.2 g, 92%). mp: 148-150°C; UV/vis (CH_3CN): λ_{max} = 330 nm; FTIR (ATR, V_{max}, cm^{-1}): 3443.08 (N-H str.), 2988.98 (Ar-H str.), 1588.08 (C=N str.), 1519.27 (Ar C=C str.), 1426.90 (N-H bend), 1101.85 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 8.32 – 8.24 (m, 2H), 7.67 (d, J = 9.22 Hz, 1H), 7.58 – 7.51 (m, 1H), 7.28 (dd, J = 8.93 Hz, J = 2.42 Hz, 1H), 7.08 (d, J = 2.47 Hz, 1H), 5.88 (s, 2H), 4.68 (q, J = 7.03 Hz, 2H), 1.48 (t, J = 7.45 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 164.4, 151.9, 150.7, 149.2, 148.3, 143.6, 135.8, 128.4, 124.5, 123.9, 117.5 – 117.3 (d, $J_{C\text{-}F}$ = 17.7 Hz, 1C), 116.1, 115.8 – 115.6 (d, $J_{C\text{-}F}$ = 18.8 Hz, 1C), 100.8, 62.2, 14.2. ^{19}F NMR (376 MHz, DMSO-d_6, 25°C) δ -137.68 (d, $J_{F\text{-}F}$ = 22.50 Hz, 1F), -138.51 (d, $J_{F\text{-}F}$ = 22.11 Hz, 1F).

*4.2.1.6. Synthesis of 2-(3,4-difluorophenyl)-1,3-dimethyl-6-nitro-2,3-dihydroquinazolin-4(1H)-one (**11**);*



To the solution of 2-(3,4-difluorophenyl)-6-nitro-2,3-dihydroquinazolin-4(1H)- one (4 g, 13.10 mmol) in DMF was added potassium carbonate (9.04 g, 65.52 mmol) followed by iodomethane (4.09 mL, 65.52 mmol) at 0°C. The resultant mixture was stirred at room temperature for 24 h then poured into ice cold water precipitate was formed, filtered to get crude solid product. The crude was dissolved into DMSO (10 mL) and added water (50 mL) precipitate was formed filtered and dried under vacuum to afford yellow solid product (4.0g, 91%); mp 220-222°C; ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 8.52 (d, J = 1.69 Hz, 1H), 8.20 (dd, J = 8.90 Hz, J = 1.87 Hz, 1H), 7.48 – 7.37 (m, 2H), 7.13 (s, 1H), 6.82 (d, J = 9.34 Hz, 1H), 6.04 (s, 1H), 2.97 (s, 3H), 2.89 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 159.3, 151.2 – 148.6 (dd, $J_{C\text{-}F}$ = 246.5 Hz, $J_{C\text{-}F}$ = 10.6 Hz, 1C), 150.1, 137.6, 134.6, 129.3, 124.0, 122.8, 118.6 – 118.4 (d, $J_{C\text{-}F}$ = 17.4 Hz, 1C), 115.7 – 115.6 (d, $J_{C\text{-}F}$ = 17.9 Hz, 1C), 113.4, 112.2, 77.0, 35.4. 31.71.

*4.2.1.7. Synthesis of 6-amino-2-(3,4-difluorophenyl)-1,3-dimethyl-1,2,3,4-tetrahydroquinazolin-4-ol (**12**);*



The title compound was synthesized from 2-(3,4-difluorophenyl)-1,3-dimethyl-6-nitro-1,2,3,4-tetrahydroquinazolin-4-ol (4.52 g, 13.56 mmol) as described in the procedure for **8**. Brown liquid, yield: (2.9 g, 70%). ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 7.40 – 7.33 (m, 1H), 7.20 – 7.14 (m, 1H), 7.08 (d, J = 2.54 Hz, 1H), 6.98 – 6.95 (m, 1H), 6.67 (dd, J = 8.62 Hz, J = 2.67 Hz, 1H), 6.42 (d, J = 8.59 Hz, 1H), 5.63 (s, 1H), 4.75 (s, 2H), 2.91 (s, 3H), 2.70 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 151.0 – 148.5 (dd, $J_{C\text{-}F}$ = 245.91 Hz, $J_{C\text{-}F}$ = 12.76 Hz, 1C), 150.8 – 148.2 (dd, $J_{C\text{-}F}$ = 247.61 Hz, $J_{C\text{-}F}$ = 12.76 Hz, 1C), 142.0, 137.6, 135.5, 133.5, 120.6, 118.7, 118.2 – 118.0 (d, $J_{C\text{-}F}$ = 17.89 Hz, 1C), 116.1 – 115.9 (d, $J_{C\text{-}F}$ = 7.24 Hz, 1C), 115.6 , 113.0, 78.0, 37.0, 32.7.

4.2.2. General procedure for synthesis and spectral characterization of derivatives (10a-c and 13a-c), (10d and 13d) and (10g-h and 13f-g);

4.2.2.1. General procedure A for synthesis of derivatives (10a-c and 13a-c);

To the suspension of 2-(3,4-difluorophenyl)-4-ethoxyquinazolin-6-amine (**8**)/ 6-amino-2-(3,4-difluorophenyl)-1,3-dimethyl-2,3-dihydroquinazolin-4(1H)-one (**12**) (1.0 equiv) in DCM, were added triethyl amine (1.5 equiv), followed by appropriate acid chloride (1.5 equiv) at 0°C. The resultant mixture was stirred at room temperature for 2 h, quenched with sodium bicarbonate solution and extracted with DCM (3 x 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduce pressure to get crude product which were purified by combi-flash column chromatography using MeOH/DCM as an eluent to afford the respective title products.

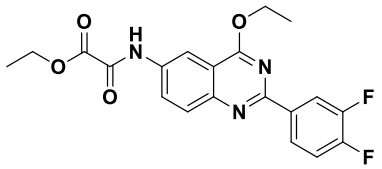
4.2.2.2. Procedure B for synthesis of derivative (10d and 13d);

To the solution of 2-(3,4-difluorophenyl)-4-ethoxyquinazolin-6-amine (**8**)/6-amino-2-(3,4-difluorophenyl)-1,3-dimethyl-2,3-dihydroquinazolin-4(1H)-one (**12**) (1.0 equiv) in DCM (10 mL) was added triethyl amine (1.5 equiv), followed by 2-bromoacetyl bromide (1.2 equiv) at 0°C. The resultant mixture was stirred at room temperature for 2 h, precipitate was formed, filtered and washed with pentane to afford salt of 2-bromo-N-(2-(3,4-difluorophenyl)-4-ethoxyquinazolin-6-yl) acetamide and 2-bromo-N-(2-(3,4-difluorophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)acetamide, respectively which were dissolved separately in DMF then added potassium carbonate (1.5 equiv), followed by cyclopropanamine (1.5 equiv) at room temperature. The resultant mixture was stirred at room temperature for 16 h, then diluted with ethyl acetate and washed with cold brine solution (3 x 10 mL). The organic layer dried over anhydrous Na_2SO_4, filtered and evaporated under reduce pressure to yield crude product which were recrystallized with ethanol to afford the pure title products.

4.2.2.3. General procedure C for synthesis of derivatives (10g-h and 13f-g);

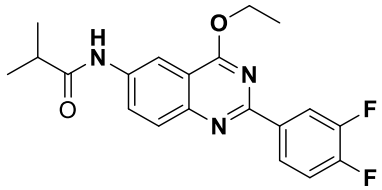
To the solution of 2-(3,4-difluorophenyl)-4-ethoxyquinazolin-6-amine (**8**)/6-amino-2-(3,4-difluorophenyl)-1,3-dimethyl-2,3-dihydroquinazolin-4(1H)-one (**12**) (1.0 equiv) in DCM were added pyridine (8.0 equiv), followed by appropriate sulfonyl chloride (1.5 equiv) at 0°C. The resultant mixture was stirred at room temperature for 16 h, quenched with 2N-HCl solution and extracted with DCM (3 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to yield the crude, which were triturated with diethyl ether, filtered to yield the title products.

*4.2.2.1.1. Ethyl 2-((2-(3,4-difluorophenyl)-4-ethoxyquinazolin-6-yl) amino)-2-oxoacetate (**10a**);*



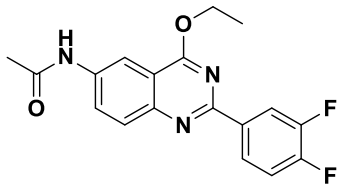
Yellow solid, yield: 67%, mp: 225-227°C; UV/vis (CH_3CN): λ_{max} = 327 nm; FTIR (ATR, V_{max}, cm^{-1}): 3338.84 (N-H str.), 1704.49 (C=O str.), 1564.65 (Ar C=N str.), 1430.34 (C=C str.), 1095.83 (C-F str.); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 11.00 (s, 1H), 8.63 (s, 1H), 8.39 – 8.35 (m, 2H), 8.25 (d, J = 8.22 Hz, 1H), 7.96 (d, J = 9.21 Hz, 1H), 7.59 – 7.54 (m, 1H), 4.79 (q, J = 7.10 Hz, 2H), 4.38 (q, J = 7.27 Hz, 2H), 1.54 (t, J = 6.87 Hz, 3H), 1.37 (t, J = 6.82 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 165.9, 160.2, 156.0, 155.6, 152.3 – 149.9 (dd, J_{C-F} = 250.1 Hz, J_{C-F} = 13.6 Hz, 1C), 150.7 – 148.2 (dd, J_{C-F} = 243.7 Hz, J_{C-F} = 12.7 Hz, 1C), 148.0, 136.2, 135.1 – 135.0 (d, J_{C-F} = 4.19 Hz, 1C), 128.1, 127.7, 124.8 – 124.7 (d, J_{C-F} = 4.1 Hz, 1C), 117.7 – 117.5 (d, J_{C-F} = 17.0 Hz, 1C), 116.5 – 116.3 (d, J_{C-F} = 19.0 Hz, 1C), 114.5, 112.4, 63.0, 62.5, 14.1, 13.8. ^{19}F NMR (376 MHz, DMSO-d_6, 25°C) δ -136.06 (d, J_{F-F} = 22.27 Hz, 1F), -138.19 (d, J_{F-F} = 22.49 Hz, 1F).

*4.2.2.1.2. N-(2-(3,4-Difluorophenyl)-4-ethoxyquinazolin-6-yl)isobutyramide (**10b**);*



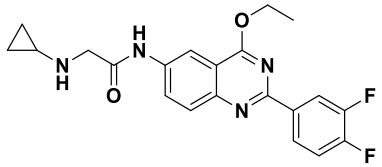
Off white solid, yield: 66%, mp: 222-225°C; UV/vis (CH_3CN): λ_{max} = 321 nm; FTIR (ATR, V_{max}, cm^{-1}): 3268.11 (N-H str.), 2970.48 (Ar-H str.), 1655.45 (C=O str.), 1565.48 (C=N str.), 1518.32 (Ar C=C str.), 1096.54 (C-F str.); ^{1}HNMR (400 MHz, DMSO-d_6, 25°C) δ 10.29 (s, 1H), 8.60 (d, J = 2.30 Hz, 1H), 8.40 – 8.32 (m, 2H), 8.03 (dd, J = 9.02 Hz, J = 2.40 Hz, 1H), 7.91 (d, J = 9.02 Hz, 1H), 7.63 – 7.56 (m, 1H), 4.75 (q, J = 7.56 Hz, 2H), 2.68 – 2.62 (m, 1H), 1.51 (t, J = 6.97 Hz, 3H), 1.14 (d, J = 6.83 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 175.7, 165.8, 155.4, 150.8 – 148.2 (dd, J_{C-F} = 243.67 Hz, J_{C-F} = 16.72 Hz, 1C), 149.7, 147.2, 138.2, 135.2, 128.1, 127.1, 124.67, 117.7 – 117.5 (d, J_{C-F} = 17.89 Hz, 1C), 116.4 – 116.2 (d, J_{C-F} = 18.97 Hz, 1C), 114.9, 110.3, 62.9, 35.0, 19.4, 14.2. ^{19}F NMR (376 MHz, DMSO-d_6, 25°C) δ -136.31 (d, J_{F-F} = 23.15 Hz, 1F), -138.21 (d, J_{F-F} = 22.33 Hz, 1F).

*4.2.2.1.3. N-(2-(3,4-Difluorophenyl)-4-ethoxyquinazolin-6-yl)acetamide (**10c**);*



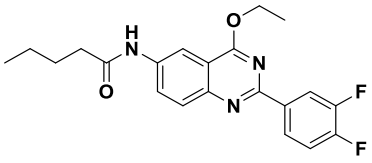
Yellow solid, Yield: 43%, mp: 230-232°C; UV/vis (CH_3CN): λ_{max} = 307 nm; FTIR (ATR, V_{max}, cm^{-1}): 3263.95 (N-H str.), 2984.45 (Ar-H str.), 1680.83 (C=O str.), 1542.92 (C=N str.), 1517.22 (Ar C=C str.), 1096.44 (C-F str.); ^{1}HNMR (400 MHz, DMSO-d_6, 25°C) δ 10.37 (s, 1H), 8.49 (d, J = 2.44 Hz, 1H), 8.36 – 8.28 (m, 2H), 8.00 (dd, J = 9.06 Hz, J = 2.66 Hz, 1H), 7.88 (d, J = 9.03 Hz, 1H), 7.60 – 7.54 (m, 1H), 4.72 (q, J = 7.08 Hz, 2H), 2.11 (s, 3H), 1.49 (t, J = 7.24 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 168.7, 165.7, 155.3, 152.3 – 149.6 (dd, $J_{C\text{-}F}$ = 250.38 Hz, $J_{C\text{-}F}$ = 14.26 Hz, 1C), 150.8 – 148.2 (dd, $J_{C\text{-}F}$ = 244.8 Hz, $J_{C\text{-}F}$ = 13.4 Hz, 1C), 147.2, 138.0, 135.2, 128.2, 126.8, 124.6, 117.7 – 117.5 (d, $J_{C\text{-}F}$ = 17.46 Hz, 1C), 116.4 – 116.2 (d, $J_{C\text{-}F}$ = 18.45 Hz, 1C), 114.8, 110.1, 62.9, 24.0, 14.1.

*4.2.2.2.1. 2-(Cyclopropylamino)-N-(2-(3,4-difluorophenyl)-4-ethoxyquinazolin-6 yl)acetamide (**10d**);*



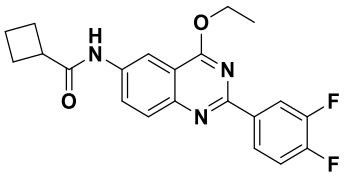
Yellow solid, yield: 74%, mp: 170-173°C; UV/vis (CH_3CN): λ_{max} = 264 nm; FTIR (ATR, V_{max}, cm^{-1}): 3294.63 (N-H str.), 2968.45 (Ar-H str.), 1685.93 (C=O str.), 1578.51 (C=N str.), 1515.79 (Ar C=C str.), 1094.47 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 10.24 (s, 1H), 8.58 (d, J = 2.37 Hz, 1H), 8.39 – 8.30 (m, 2H), 8.07 (dd, J = 9.09 Hz, J = 2.40 Hz, 1H), 7.91 (d, J = 8.92 Hz, 1H), 7.62 – 7.55 (m, 1H), 7.74 (q, J = 7.13 Hz, 2H), 3.40 (s, 2H), 2.22 – 2.17 (m, 1H), 1.50 (t, J = 7.73 Hz, 3H), 0.40 – 0.35 (m, 2H), 0.32 – 0.29 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 171.1, 165.7, 155.3, 152.3 – 149.7 (dd, $J_{C\text{-}F}$ = 247.09, $J_{C\text{-}F}$ = 11.49 Hz, 1C), 150.8 – 148.2 (dd, $J_{C\text{-}F}$ = 245.70 Hz, $J_{C\text{-}F}$ = 13.00 Hz, 1C), 147.3, 137.6, 135.4 – 135.1 (dd, $J_{C\text{-}F}$ = 5.79 Hz, $J_{C\text{-}F}$ = 3.18 Hz, 1C), 128.2, 127.1, 124.6 – 124.6 (d, $J_{C\text{-}F}$ = 4.11 Hz, 1C), 117.6 – 117.5 (d, $J_{C\text{-}F}$ = 17.54 Hz, 1C), 116.4 – 116.2 (d, $J_{C\text{-}F}$ = 18.48 Hz, 1C), 114.8, 110.4, 62.9, 52.7, 30.0, 14.1, 6.1.

*4.2.2.1.4. N-(2-(3,4-Difluorophenyl)-4-ethoxyquinazolin-6-yl)pentanamide (**10e**);*



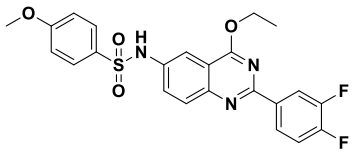
Light yellow solid, Yield: 75%, mp: 230-232°C; UV/vis (CH_3CN): λ_{max} = 308 nm; FTIR (ATR, V_{max}, cm^{-1}): 3284.73 (N-H str.), 2964.35 (Ar-H str.), 1656.81 (C=O str.), 1566.42 (C=N str.), 1519.99 (Ar C=C str.), 1095.14 (C-F str.); ^{1}HNMR (400 MHz, DMSO-d_6, 25°C) δ 10.33 (s, 1H), 8.56 (d, J = 2.26 Hz, 1H), 8.39 – 8.30 (m, 2H), 8.01 (dd, J = 9.09 Hz, J = 2.42 Hz, 1H), 7.90 (d, J = 9.06 Hz, 1H), 7.62 – 7.55 (m, 1H), 4.74 (q, J = 7.17 Hz, 2H), 2.37 (t, J = 7.43 Hz, 2H), 1.65 – 1.57 (m, 2H), 1.50 (t, J = 6.90 Hz, 3H), 1.39 – 1.30 (m, 2H), 0.91 (t, J = 7.81 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 171.7, 165.7, 155.2, 152.2 – 149.6 (dd, $J_{C\text{-}F}$ = 250.35 Hz, $J_{C\text{-}F}$ = 13.49 Hz, 1C), 150.7 – 148.2 (dd, $J_{C\text{-}F}$ = 245.2 Hz, $J_{C\text{-}F}$ = 13.4 Hz, 1C), 147.1, 138.0, 135.26 – 135.20 (dd, $J_{C\text{-}F}$ = 5.9 Hz, $J_{C\text{-}F}$ = 5.9 Hz, 1C), 128.1, 126.8, 124.6, 117.6 – 117.4 (d, $J_{C\text{-}F}$ = 21.9 Hz, 1C), 116.3 – 116.1 (d, $J_{C\text{-}F}$ = 18.4 Hz, 1C), 114.8, 110.1, 62.8, 36.1, 27.1, 21.8, 14.1, 13.7. ^{19}F NMR (376 MHz, DMSO-d_6, 25°C) δ -136.31 (d, $J_{F\text{-}F}$ = 22.75 Hz, 1F), -138.20 (d, $J_{F\text{-}F}$ = 22.14 Hz, 1F).

*4.2.2.1.5. N-(2-(3,4-Difluorophenyl)-4-ethoxyquinazolin-6-yl)cyclobutanecarboxamide (**10f**):*



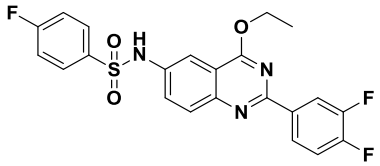
Yellow solid, Yield: 79%, mp: 214-216°C; UV/vis (CH_3CN): λ_{max} = 309 nm; FTIR (ATR, V_{max}, cm^{-1}): 3276 (N-H str.), 2966.05 (Ar-H str.), 1654.34 (C=O str.), 1564.29 (C=N str.), 1518.00 (Ar C=C str.), 1097.10 (C-F str.); ^{1}HNMR (400 MHz, DMSO-d_6, 25°C) δ 10.12 (s, 1H), 8.48 (d, J = 2.25 Hz, 1H), 8.27 – 8.21 (m, 2H), 7.98 (dd, J = 9.12 Hz, J = 2.46 Hz, 1H), 7.81 (d, J = 8.97 Hz, 1H), 7.54 – 7.47 (m, 1H), 4.65 (q, J = 6.82 Hz, 2H), 3.31 – 3.22 (m, 1H), 2.31 – 2.21 (m, 2H), 2.18 – 2.10 (m, 2H), 2.10 – 1.91 (m, 1H), 1.89 – 178 (m, 1H), 1.48 (t, J = 7.58 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 173.3, 165.7, 155.2, 152.2 – 149.6 (dd, $J_{C\text{-}F}$ = 250.7 Hz, $J_{C\text{-}F}$ = 14.1 Hz, 1C), 150.7 – 148.2 (d, $J_{C\text{-}F}$ = 243.7 Hz, $J_{C\text{-}F}$ = 12.0 Hz, 1C), 147.1, 138.1, 135.2 – 135.1 (dd, $J_{C\text{-}F}$ = 6.3 Hz, $J_{C\text{-}F}$ = 3.1 Hz, 1C), 128.1, 126.9, 124.5, 117.6 – 117.4 (d, $J_{C\text{-}F}$ = 17.6 Hz, 1C), 116.3 – 116.1 (d, $J_{C\text{-}F}$ = 18.7 Hz, 1C), 114.8, 110.2, 62.8, 24.5, 17.7, 14.1. ^{19}F NMR (376 MHz, DMSO-d_6, 25°C) δ -136.35 (d, $J_{F\text{-}F}$ = 22.38 Hz, 1F), -138.23 (d, $J_{F\text{-}F}$ = 22.52 Hz, 1F).

*4.2.2.3.1. N-(2-(3,4-Difluorophenyl)-4-ethoxyquinazolin-6-yl)-4-methoxybenzenesulfonamide (**10g**);*



Yellow solid, Yield: 68%, mp: 195-200°C; UV/vis (CH_3CN): λ_{max} = 310 nm; FTIR (ATR, V_{max}, cm^{-1}): 3232.25 (N-H str.), 2971.00 (Ar-H str.), 1561.08 (C=N str.), 1495.96 (Ar C=C str.), 1261.54 (SO_2 asym.), 1150.66 (SO_2 sym.), 1091.42 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 10.69 (brs, 1H), 8.32 – 8.24 (m, 2H), 7.84 (d, J = 9.08 Hz, 1H), 7.77 – 7.73 (m, 3H), 7.69 (dd, J = 9.03 Hz, J = 2.51 Hz, 1H), 7.58 – 7.51 (m, 1H), 7.06 (d, J = 8.86 Hz, 2H), 4.68 (q, J = 7.52 Hz, 2H), 3.73 (s, 3H), 1.47 (t, J = 7.19 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 165.7, 162.6, 155.9, 152.4 – 149.8 (dd, $J_{C\text{-}F}$ = 248.4 Hz, $J_{C\text{-}F}$ = 13.8 Hz, 1C), 150.8 – 148.3 (dd, $J_{C\text{-}F}$ = 245.2 Hz, $J_{C\text{-}F}$ = 13.8 Hz, 1C), 147.6, 136.8, 135.0, 130.7, 128.9, 127.3, 124.8, 117.8 – 117.6 (d, $J_{C\text{-}F}$ = 18.1 Hz, 1C), 116.5 – 116.3 (d, $J_{C\text{-}F}$ = 18.1 Hz, 1C), 114.9, 114.5, 110.9, 63.1, 55.6, 14.1.

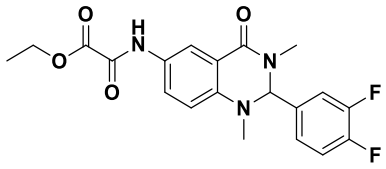
*4.2.2.3.2. N-(2-(3,4-Difluorophenyl)-4-ethoxyquinazolin-6-yl)-4-fluorobenzenesulfonamide (**10h**);*



Yellow solid, Yield: 76%, mp: 220-222°C; UV/vis (CH_3CN): λ_{max} = 301 nm; FTIR (ATR, V_{max}, cm^{-1}): 3246.72 (N-H str.), 2995.45 (Ar-H str.), 1576.03 (C=N str.), 1506.43 (Ar C=C str.), 1266.07 (SO_2 asym.), 1151.71 (SO_2 sym.), 1100.66 (C-F str.); ^{1}HNMR (400 MHz, DMSO-d_6, 25^0C) δ 10.84 (s, 1H), 8.36 – 8.28 (m, 2H), 7.89 – 7.84 (m, 3H), 7.78 (d, J = 2.42 Hz, 1H), 7.70 (dd, J = 8.98 Hz, J = 2.50 Hz, 1H), 7.61 – 7.55 (m, 1H), 7.40 (t, J = 8.32 Hz, 2H), 4.71 (q, J = 7.09 Hz, 2H), 1.48 (t, J = 6.91 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 165.7 – 163.2 (d, $J_{C\text{-}F}$ = 250.8 Hz, 1C), 165.6, 155.9, 152.4 – 149.7 (dd, $J_{C\text{-}F}$ = 249.2 Hz, $J_{C\text{-}F}$ = 15.7 Hz, 1C), 150.7 – 148.2 (dd, $J_{C\text{-}F}$ = 245 .1 Hz, $J_{C\text{-}F}$ = 14.6 Hz, 1C), 147.8, 136.3, 135.53 – 135.5 (d, $J_{C\text{-}F}$ = 2.96 Hz, 1C), 134.93 – 134.0 (d, $J_{C\text{-}F}$ = 9.02 Hz, 1C), 129.8 – 129.7 (d, $J_{C\text{-}F}$ = 10.06 Hz, 1C), 129.0, 127.5, 124.74 – 124.71 (d, $J_{C\text{-}F}$ = 4.0 Hz, 1C), 117.6 – 117.5 (d, $J_{C\text{-}F}$ = 18.00 Hz, 1C), 116.7, 116.5, 116.5 – 116.3 (d, $J_{C\text{-}F}$ = 18.63 Hz, 1C), 114.8, 111.5, 63.0, 14.0. ^{19}F NMR (376

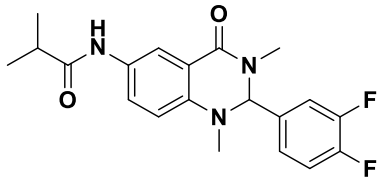
MHz, DMSO-d_6, 25°C) δ -105.43 (s, 1F), -135.95 (d, $J_{F\text{-}F}$ = 21.59 Hz, 1F), -138.13 (d, $J_{F\text{-}F}$ = 22.08 Hz, 1F).

*4.2.2.1.6. Ethyl 2-((2-(3,4-difluorophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)amino)-2-oxoacetate (**13a**);*



Yellow solid, Yield: 72%, mp: 110-115°C; UV/vis (CH_3CN): λ_{max} = 319 nm; FTIR (ATR, V_{max}, cm^{-1}): 3337.34 (N-H str.), 2898.96 (Ar-H str.), 1692.16 (C=O str.), 1663.24 (Amide C=O str.), 1099.09 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 10.69 (S, 1H), 8.21 (d, J = 2.48 Hz, 1H), 7.73 (dd J = 8.60 Hz, J = 2.61 Hz, 1H), 7.44 – 7.37 (m, 1H), 7.28 – 7.23 (m, 1H), 7.02 – 7.00 (m, 1H), 6.64 (d, J = 9.07 Hz, 1H), 5.82 (s, 1H), 4.29 (q, J = 7.08 Hz, 2H), 2.90 (s, 3H), 2.81 (s, 3H), 1.30 (t, J = 7.21 Hz, 3H), ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 161.0, 160.6, 155.0, 150.9 – 148.3 (dd, $J_{C\text{-}F}$ = 246.0 Hz, $J_{C\text{-}F}$ = 15.1 Hz, 1C), 150.5 – 147.9 (dd, $J_{C\text{-}F}$ = 247.9 Hz, $J_{C\text{-}F}$ = 13.2 Hz, 1C), 143.0, 134.7 – 134.6 (d, $J_{C\text{-}F}$ = 5.22 Hz, 1C), 128.4, 126.6, 122.8, 119.9, 118.2 – 118.0 (d, $J_{C\text{-}F}$ = 17.6 Hz, 1C), 115.6 – 115.4 (d, $J_{C\text{-}F}$ = 17.1Hz, 1C), 115.4, 112.5, 77.0, 62.2, 34.9, 31.9, 13.8. ^{19}F NMR (376 MHz, DMSO-d_6, 25°C) δ -137.34 (d, $J_{F\text{-}F}$ = 22.27 Hz, 1F), -138.10 (d, $J_{F\text{-}F}$ = 22.11 Hz, 1F).

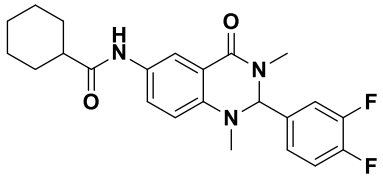
*4.2.2.1.7. N-(2-(3,4-Difluorophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)isobutyramide (**13b**);*



Yellow solid, Yield: 69%, mp: 177-180°C; UV/vis (CH_3CN): λ_{max} = 310 nm; FTIR (ATR, V_{max}, cm^{-1}): 3271.56 (N-H str.), 2964.64 (Ar-H str.), 1663.45 (C=O str.), 1631.36 (C=O str.), 1513.08 (Ar C=C str.), 1099.84 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 9.70 (s, 1H), 8.01 (d, J = 2.44 Hz, 1H), 7.64 (dd, J = 8.74 Hz, J = 2.62 Hz, 1H), 7.44 – 7.37 (m, 1H), 7.26 – 7.21 (m, 1H), 7.01 – 6.98 (m, 1H), 6.58 (d, J = 8.91 Hz, 1H), 5.78 (s, 1H), 2.90 (s, 3H), 2.78 (s, 3H), 2.56 – 2.51 (m, 1H), 1.08 (d, J = 6.72 Hz, 6H).^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 161.3, 150.4 – 148.2 (dd, $J_{C\text{-}F}$ = 245.7 Hz, $J_{C\text{-}F}$ = 12.9 Hz, 1C), 150.4 – 147.9 (dd, $J_{C\text{-}F}$ = 246.4 Hz, $J_{C\text{-}F}$ = 13.6

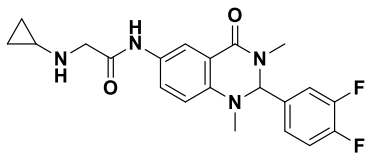
Hz, 1C), 141.9, 134.7, 130.7, 125.4, 122.89 – 122.82 (d, $J_{C\text{-}F}$ = 6.9 Hz, 1C), 118.7, 118.1 – 118.0 (d, $J_{C\text{-}F}$ = 17.2 Hz, 1C), 115.8, 115.6 – 115.4 (d, $J_{C\text{-}F}$ = 17.0 Hz, 1C), 112.6, 77.1, 35.0, 34.8, 32.0, 19.5. ^{19}F NMR (376 MHz, DMSO-d_6, 25°C) δ -137.45 (d, $J_{F\text{-}F}$ = 22.54 Hz, 1F), -138.26 (d, $J_{F\text{-}F}$ = 22.77 Hz, 1F).

*4.2.2.1.8. N-(2-(3,4-Difluorophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)cyclohexanecarboxamide (**13c**):*



Off white solid, Yield: 81%, mp: 240-244°C; UV/vis (CH_3CN): λ_{max} = 302 nm; FTIR (ATR, V_{max}, cm^{-1}): 3309.15 (N-H str.), 2924.78 (Ar-H str.), 1666 (C=O str.), 1639.73 (C=O str.), 1499.5 (Ar C=C str.), 1109.27 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 9.68 (s, 1H), 8.02 (d, J = 2.75 Hz, 1H), 7.61 (dd, J = 8.65 Hz, J = 2.64 Hz, 1H), 7.44 – 7.37 (m, 1H), 7.26 – 7.21 (m, 1H), 7.01 – 6.98 (m, 1H), 6.57 (d, J = 8.94 Hz, 1H), 5.77 (s, 1H), 2.89 (s, 3H), 2.77 (s, 3H), 2.30 – 2.22 (m, 1H), 1.78 – 1.72 (m, 4H), 1.65 – 1.62 (m, 1H), 1.44 – 1.36 (m, 2H), 1.30 – 1.26 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 173.8, 161.3, 150.8 – 148.2 (dd, $J_{C\text{-}F}$ = 247.1 Hz, $J_{C\text{-}F}$ = 13.0 Hz, 1C), 150.4 – 147.8 (dd, $J_{C\text{-}F}$ = 246.7 Hz, $J_{C\text{-}F}$ = 12.0 Hz, 1C), 141.8, 134.7, 130.8, 125.3, 122.8 – 122.7 (dd, $J_{C\text{-}F}$ = 6.9 Hz, $J_{C\text{-}F}$ = 3.4 Hz, 1C), 118.6, 118.1 – 117.9 (d, $J_{C\text{-}F}$ = 17.3 Hz, 1C), 115.8, 115.6 – 115.4 (d, $J_{C\text{-}F}$ = 17.2 Hz, 1C), 112.6, 77.1, 56.0, 44.7, 35.0, 31.9, 29.15, 22.2. ^{19}F NMR (376 MHz, DMSO-d_6, 25°C) δ -137.46 (d, $J_{F\text{-}F}$ = 22.49 Hz, 1F), -138.27 (d, $J_{F\text{-}F}$ = 22.21 Hz, 1F).

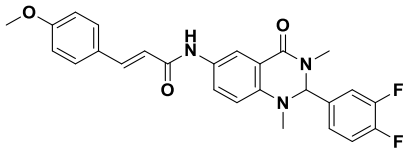
*4.2.2.2.2. 2-(Cyclopropylamino)-N-(2-(3,4-difluorophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl) acetamide (**13d**);*



Yellow solid, Yield: 71%, mp: 160-162°C; UV/vis (CH_3CN): λ_{max} = 321 nm; FTIR (ATR, V_{max}, cm^{-1}): 3287.39 (N-H str.), 2969.97 (Ar-H str.), 1655.16 (C=O str.), 1636.82 (C=O str.), 1515.19 (Ar C=C str.), 1111.38 (C-F str.) ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 9.68 (s, 1H), 8.04 (d, J = 2.72 Hz, 1H), 7.63 (dd, J = 8.82 Hz, J = 2.59 Hz, 1H), 7.44 – 7.37 (m, 1H), 7.26 – 7.21 (m,

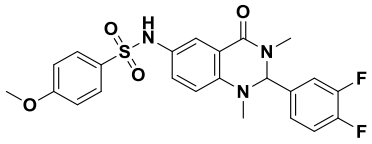
1H), 7.01 – 6.99 (m, 1H), 6.60 (d, *J* = 8.89 Hz, 1H), 5.78 (s, 1H), 3.29 (s, 2H), 2.90 (s, 3H), 2.78 (s, 3H), 2.18 – 2.13 (m, 1H), 0.39 – 0.34 (m, 2H), 0.31 – 0.26 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 169.9, 161.3, 150.8 – 148.2 (dd, $J_{C\text{-}F}$ = 246.8 Hz, $J_{C\text{-}F}$ = 12.1 Hz, 1C), 150.4 – 147.9 (dd, $J_{C\text{-}F}$ = 248.0 Hz, $J_{C\text{-}F}$ = 11.5 Hz, 1C), 142.1, 134.74 – 134.70 (d, $J_{C\text{-}F}$ = 3.2 Hz, 1C), 130.0, 125.5, 122.85 – 122.82 (d, $J_{C\text{-}F}$ = 3.2 Hz, 1C), 118.7, 118.1 – 118.0 (d, $J_{C\text{-}F}$ = 18.2 Hz, 1C), 115.8, 115.6 – 115.4 (d, $J_{C\text{-}F}$ = 17.5 Hz, 1C), 112.6, 77.1, 52.5, 35.0, 32.0, 30.1, 6.0. ^{19}F NMR (376 MHz, DMSO-d_6, 25°C) δ -137.43 (d, $J_{F\text{-}F}$ = 22.40 Hz, 1F), -138.23 (d, $J_{F\text{-}F}$ = 21.28 Hz, 1F).

*4.2.3. Synthesis of (E)-N-(2-(3,4-difluorophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-3-(4-methoxyphenyl)acrylamide (**13e**);*



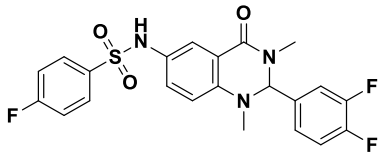
To the solution of 6-amino-2-(3,4-difluorophenyl)-1,3-dimethyl-2,3-dihydroquinazolin-4(1H)-one (0.2 g, 0.65 mmol) in DMF (10 mL) were added DIPEA (0.229 mL, 1.31 mmol), EDC.HCl (0.188 g, 0.98 mmol) and HOBT (0.133 g, 0.98 mmol), stirred for 10 min. then (E)-3-(4-methoxyphenyl)acrylic acid (0.129 g, 0.72 mmol). The resultant mixture was stirred at room temperature for 16 h, poured into ice cold water precipitate formed was filtered to get crude solid, which was purified by column chromatography on silica gel (100−200 mesh) using MeOH/DCM as an eluent to afford the pure yellow solid, Yield: 85%, mp: 170-175°C; UV/vis (CH_3CN): λ_{max} = 307 nm; FTIR (ATR, V_{max}, cm^{-1}): 3232.25 (N-H str.), 3231.03 (N-H str.), 1668.54 (C=O str.), 1636.89 (C=O str.), 1603.68 (Ar C=C str. alkene), 1510.78 (Ar C=C str.), 1111.09 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 10.04 (s, 1H), 8.11 (d, *J* = 2.84 Hz, 1H), 7.75 (dd, *J* = 8.79 Hz, *J* = 2.42 Hz, 1H), 7.56 (d, *J* = 8.33 Hz, 2H), 7.50 (d, *J* = 15.7 Hz, 1H), 7.45 – 7.38 (m, 1H), 7.28 – 7.23 (m, 1H), 7.03 – 6.99 (m, 3H), 6.67 (d, *J* = 15.26 Hz, 1H), 6.62 (s, 1H), 5.80 (s, 1H), 3.80 (s, 3H), 2.91 (s, 3H), 2.80 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 163.4, 161.3, 160.5, 150.8 – 148.3 (dd, $J_{C\text{-}F}$ = 244.1 Hz, $J_{C\text{-}F}$ = 9.5 Hz, 1C), 150.5 – 147.9 (dd, $J_{C\text{-}F}$ = 247.5 Hz, $J_{C\text{-}F}$ = 12.9 Hz, 1C), 142.0, 139.4, 134.7, 130.7, 129.2, 127.3, 125.3, 122.8, 119.7, 118.5, 118.2 – 118.0 (d, $J_{C\text{-}F}$ = 17.4 Hz, 1C), 115.8, 115.6 – 115.4 (d, $J_{C\text{-}F}$ = 17.3 Hz, 1C), 114.4, 112.7, 77.1, 55.2, 35.0, 32.0. ^{19}F NMR (376 MHz, DMSO-d_6, 25°C) δ -137.41 (d, $J_{F\text{-}F}$ = 20.87 Hz, 1F), -138.20 (d, $J_{F\text{-}F}$ = 22.37 Hz, 1F).

*4.2.2.3.3. N-(2-(3,4-Difluorophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-4-methoxybenzenesulfonamide (**13f**);*



Yellow solid, Yield: 81%, mp: 225-230°C; UV/vis (CH_3CN): λ_{max} = 309 nm; FTIR (ATR, V_{max}, cm^{-1}): 3144.97 (N-H str.), 2998.25 (Ar-H str.), 1637.23 (C=O str.), 1507.04 (Ar C=C str.), 1251.94 (SO_2 asym.), 1154.55 (SO_2 sym.), 1021.06 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 9.72 (S, 1H), 7.57 (d, J = 9.48 Hz, 1H), 7.44 (d, J =2.47 Hz, 1H), 7.41 – 7.36 (m, 1H), 7.16 – 7.07 (m, 2H), 7.02 (d, J = 8.66 Hz, 2H), 6.95 – 6.93 (m, 1H), 6.52 (d, J = 8.79 Hz, 1H), 5.76 (s, 1H), 3.78 (s, 3H), 2.85 (s, 3H), 2.73 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 162.3, 160.9, 150.9 – 148.3 (dd, J_{C-F} = 246 .12 Hz, J_{C-F} = 12.55 Hz, 1C), 150.5 – 147.9 (dd, J_{C-F} = 246.2 Hz, J_{C-F} = 12.06 Hz, 1C), 143.3, 134.5, 130.9, 128.9, 128.3, 128.2, 122.8, 121.5, 118.1 – 117.9 (d, J_{C-F} = 16.6 Hz, 1C), 115.9, 115.4 – 115.2 (d, J_{C-F} = 18.4 Hz, 1C), 114.1, 113.0, 77.0, 55.5, 34.93, 31.9. ^{19}F NMR (376 MHz, DMSO-d_6, 25°C) δ -137.27 (d, J_{F-F} = 21.33 Hz, 1F), -138.03 (d, J_{F-F} = 22.03 Hz, 1F).

*4.2.2.3.4. N-(2-(3,4-Difluorophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-4-fluorobenzenesulfonamide (**13g**);*



Yellow solid, Yield: 58%, mp: 180-185°C ; UV/vis (CH_3CN): λ_{max} = 354 nm; FTIR (ATR, V_{max}, cm^{-1}): 2987.92 (Ar-H str.), 1636.31 (C=O str.), 1514.22 (Ar C=C str), 1317.80 (SO_2 asym.), 1148.41 (SO_2 sym.), 1092.03 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 9.89 (s, 1H), 7.71 – 7.67 (m, 2H), 7.44 – 7.34 (m, 4H), 7.15 – 7.08 (m, 2H), 6.96 – 6.93 (m, 1H), 6.54 (d, J = 8.81 Hz, 1H), 5.77 (s, 1H), 2.84 (s, 3H), 2.74 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 165.5 – 163.0 (d, J_{C-F} = 251.7 Hz, 1C), 160.7, 150.95 – 148.3 (dd, J_{C-F} = 246.7 Hz, J_{C-F} = 11.7 Hz, 1C), 150.5 – 147.9 (dd, J_{C-F} = 247.2 Hz, J_{C-F} = 12.6 Hz, 1C), 143.6, 135.5 – 135.4 (d, J_{C-F} = 2.4 Hz, 1C), 134.5, 129.8 – 129.7 (d, J_{C-F} = 10.3 Hz, 1C), 128.8, 127.6, 122.9 – 122.8 (dd, J_{C-F} = 6.3 Hz, J_{C-F} = 3.3 Hz, 1C), 121.9, 118.1 – 118.0 (d, J_{C-F} = 18.2 Hz, 1C), 116.3 – 116.1 (d, J_{C-F} = 23.0 Hz, 1C), 115.8, 115.3 – 115.2 (d, J_{C-F} = 16.9 Hz, 1C), 113.1, 76.9, 34.8, 31.8. ^{19}F NMR

(376 MHz, DMSO-d_6, 25°C) δ -106.25 (s, 1F), -137.25 (d, J_{F-F} = 21.54 Hz, 1F), -138.08 (d, J_{F-F} = 20.17 Hz, 1F).

4.3. Structure Determination

Colourless, X-ray quality crystals were obtained by slow evaporation using DMSO for **13b** and **13f** whereas ethanol for **13e** and **13g**. Crystal evaluation and data collection were done on a Bruker Smart APEX2 diffractometer with a Mo Kα radiation source (λ = 0.71073 Å) equipped with an Oxford Cryostream low-temperature apparatus. Initial cell matrix determination was done using 36 frames (0.5° phi-scan) from three series of scans at an exposure time of ten seconds per frame. Each of the three series of scans was collected at different starting angles and the *APEXII*[36] program suite used to index the reflections. The total number of images was based on results from the program *COSMO*[37] whereby the expected redundancy was to be 4.0% and completeness of 100% out to 0.75 Å. Cell parameters were retrieved using *APEXII* and refined using *SAINT*[38] on all observed reflections. Data reduction was performed using *SAINT* software, and the scaling and absorption corrections were applied using *SADABS*[39] multi-scan technique. The structures were solved by the direct method using the *SHELXS*[40] program and refined. The visual crystal structures were presented using, *MERCURY*[41][6] and *Olex2*[42] system software. Non-hydrogen atoms were first refined isotropically and then by anisotropic refinement with full-matrix least squares based on F^2 using *SHELXL*[43]. All hydrogens were positioned geometrically, allowed to ride on their parent atoms, and refined isotropically. In all crystal structures, the 3,4-difluorophenyl moieties exhibited disorder over two positions which was resolved using PART instructions. The major component was found to have a site occupancy of 70.3% and 76% (**13e**), 58.1% (**13b**), 52.8% (**13f**) and 55% (**13g**). Crystal data and structural refinement information are summarized in **Table 5**.

Table 5: Crystallographic data and structural refinement details of **13b**, **13e**, **13f**, and **13g**.

	13b	**13e**	**13f**	**13g**
Chemical formula	$4(C_{20}H_{21}F_2N_3O_2)\cdot 3(H_2O)$	$8(C_{26}H_{23}F_2N_3O_3)\cdot 3(C_2H_6O)$	$C_{23}H_{21}F_2N_3O_4S$	$C_{22}H_{18}F_3N_3O_3S$
M_r	1547.63	3845.98	473.49	461.45
Crystal system, space group	Monoclinic, $P2_1/c$	Monoclinic, $P2_1/c$	Monoclinic, $P2_1/n$	Monoclinic, $C2/c$
Temperature (K)	100	103	100	100
a, *b*, *c* (Å)	9.4635 (2), 13.2122	29.2357 (7), 16.0622 (4),	7.8508 (1),	26.6621 (9),

	(3), 14.9413 (3)	10.0866 (2)	15.7287 (2), 18.4655 (3)	15.6874 (5), 10.1580 (4)
β (°)	92.210 (1)	99.026 (1)	98.257 (1)	109.399 (2)
V (Å^3)	1866.78 (7)	4677.9 (2)	2256.54 (6)	4007.5 (2)
Z	1	1	4	8
μ (mm^{-1})	0.11	0.10	0.20	0.22
Crystal size (mm)	0.36 × 0.24 × 0.17	0.29 × 0.18 × 0.11	0.26 × 0.18 × 0.13	0.31 × 0.22 × 0.14
T_{min}, T_{max}	0.698, 0.746	0.677, 0.746	0.703, 0.746	0.620, 0.746
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	23526, 4632, 3901	37523, 8667, 7337	35588, 5717, 4723	31843, 4985, 4703
R_{int}	0.021	0.041	0.028	0.049
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.669	0.606	0.673	0.669
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.047, 0.129, 1.05	0.065, 0.151, 1.18	0.036, 0.098, 1.03	0.137, 0.313, 1.16
No. of reflections	4632	8667	5717	4985
No. of parameters	324	749	351	342
No. of restraints	140	111	14	59
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.99, −0.60	0.88, −0.47	0.36, −0.44	1.27, −0.79

4.4. Hirshfeld Surface Analysis

Hirshfeld surface calculations were performed on compounds **13b**, **13e**, **13f** and **13g** using *CrystalExplorer17*[44] whereby all Hirshfeld surfaces including 2D fingerprint [45-47]plots were generated using a high standard surface resolution. All bond lengths to hydrogen were automatically modified to typical standard neutron values (C—H = 1.083 Å, and O—H = 0.983 Å) when the crystallographic information file (CIF) of the respective compound was read into the *CrystalExplorer*17 program.[48] The Hirshfeld surface maps are that of normalized contact

distance, d_{norm}, which is defined in terms of the distance to the nearest atoms outside (d_e), the distance to the nearest atoms inside (d_i) and the van der Waals radii of the two atoms external and internal to the surface.[49] The d_{norm} ranges used to map the Hirshfeld surfaces were -0.6316 to 1.4140 (**13b**), -0.6457 to 1.5251 (**13e**), -0.6022 to 1.5912 (**13f**) and -1.2575 to 1.5440 (**13g**).

4.5. Theoretical calculation

A crystal unit was selected as the initial structure from the obtained crystals for theoretical calculations. DFT-B3LYP/6-311G++(d,p) methods in Gaussian09 were used to optimize the structures. No solvent corrections were made with these calculations. Vibration analysis showed that the optimized structure indeed represents a minimum on the potential energy surface (no negative eigenvalues). TD-DFT calculations were performed using the same basis set as above to analyse the UV spectrum.

Supplementary information

CCDC numbers 1956040, 1956041, 1956042 and1956043 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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CHAPTER 4

Design, synthesis and spectral characterization of novel quinazoline derivatives as an anti-tubercular agent

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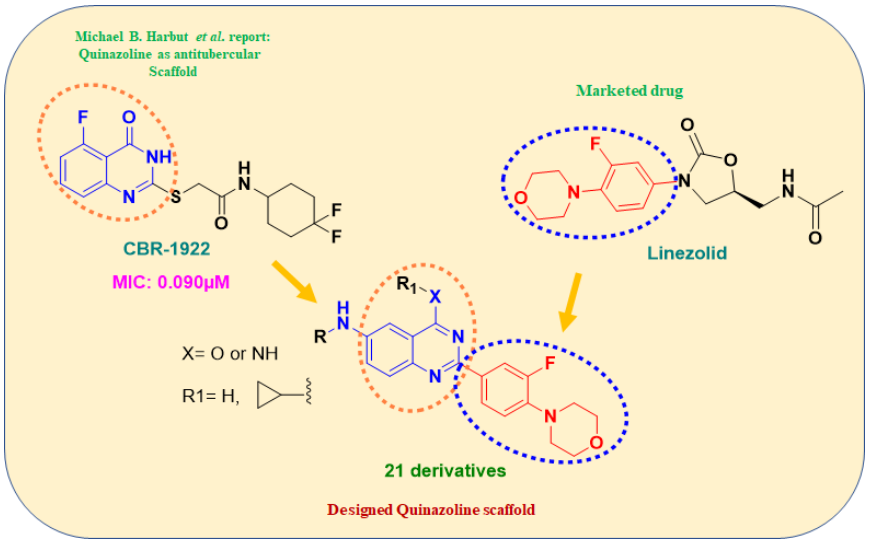
Graphical Abstract



Abstract

A novel series of quinazoline derivatives (**10a-q** and **17a-c**) were designed and synthesized in good to moderate yields. The synthesized compounds were well-characterized by spectroscopic studies (NMR and IR) and evaluated for preliminary screening for their *in-vitro* anti-mycobacterium activity at 20 µM concentration against *Mycobacterium tuberculosis* H37Rv strain. In general, the compounds did not show significant anti-mycobacterium activity. The only notable % zone of inhibition was observed against *Mycobacterium tuberculosis* strain H37Rv for compounds **10m** which showed 33% inhibition after 24 h incubation which can be considered for further study which includes MIC, MBC and enzyme inhibition study. These new compounds may serve as starting points for the designing of new series of inhibitors that prevent the growth of *Mycobacterium tuberculosis*.

Keywords

Antimycobacterial activity; quinazoline derivatives; *mycobacterium tuberculosis* H37Rv.

1. Introduction

Tuberculosis (TB)[1] is one of the oldest diseases that has affected humans for several thousands of years. The main cause remained unknown until Dr. Robert Koch declared about his discovery of bacillus Mycobacterium tuberculosis on March 24, 1882 which is commemorated every year as World TB Day[2]. TB is the second leading cause of death and ranks after human immunodeficiency virus (HIV). Republic of South Africa (RSA) is one of the leading countries with the uppermost problem of TB and HIV. World Health Organization (WHO) estimates out of 500 000 incident cases about 330 000 (66%) people were infested with both HIV and TB infection[3-6]. There have been several approaches adopted to develop newer and more efficacious drugs for its treatment. In 1993, World Health Organization (WHO) declared TB as a global health emergency. In November 2017, the governments of Brazil, the Russian Federation, India, China and South Africa announced the establishment of a collaborative TB research network, the aim of which is to accelerate TB research and innovation through cooperation mechanisms[7-9].

TB is considered as a contagious disease and attacks lungs of the infected human[10, 11]. Depending upon the stage of infection, *M. tuberculosis* resides in a variable microenvironment. It has a unique ability to survive against neutrophils, monocytes, macrophages and dendritic cells from the host cells by preventing the fusion between lysosomes and phagosomes. *M. tuberculosis* prolongs its survival by inhibiting the host cell apoptosis[12].

Heterocyclic chemistry in literature has been well documented for its immense application in medicinal chemistry towards hunt for new drugs. Owing to the drug resistance against available antibiotics in market, a need for the new drugs is high demand in the current scientific world[13]. Amongst, quinazoline is a class of heterocyclic compound which comprises of two conjoined aromatic rings with two nitrogen atoms as integral part of the ring and one carbon oxidized with keto-oxygen[14]. The first synthesis of quinazoline derivative dates to 1860s, involving reaction between anthranilic acid and various cyanogens[15]. Earlier these class of compounds found application only as sedatives. However, since the last century until recently, quinazoline and its related derivatives have gained immense acknowledgement in the field of medicinal chemistry owing to their wide and versatile spectrum of biological activity[1, 16] (**Figure 1**)[17].

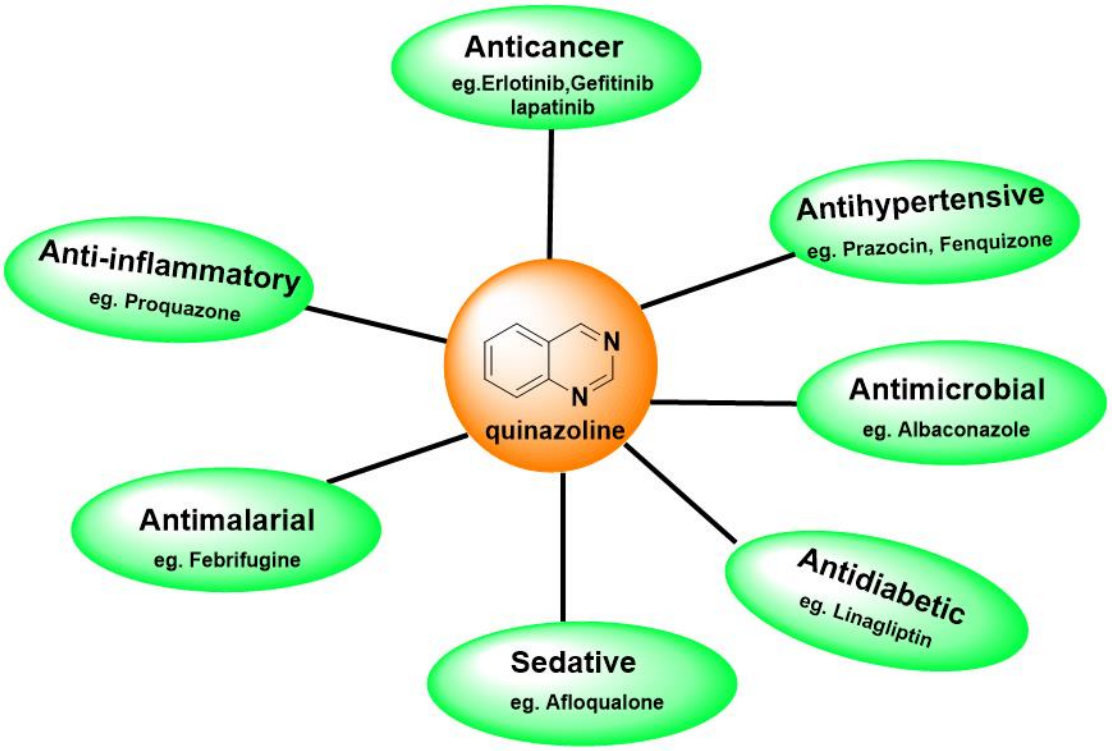


Figure 1: General structure of quinazoline ring with their biological goal.

They are well known in literature as antiviral, antiallergic, antidiabetic, anticancer and antimicrobial agents[12, 18-21]. Recently, they have also been known to possess coronary vasodilatory and histamine receptor type 3 inverse agonism[22, 23]. Several drugs are based on quinazoline unit (**Figure 2**) like erlotinib (in the treatment of several types of tumors)[24], prazosin (as an R-adrenergic blocker)[25], gefitinib (epidermal growth factor receptor (EGFR) inhibitor)[26, 27] and linagliptin (dipeptidyl peptidase-4 inhibitor), febrifugine (antimalarial) etc. have been approved by Food and Drug Administration (FDA). Wide applicability of quinazoline based derivatives as drugs prompted chemists towards development of strategies for easy synthesis. Motivated by this, in the present study, quinazoline based derivatives were synthesized, fully characterized and preliminary evaluation conducted for anti-tuberculosis activity.

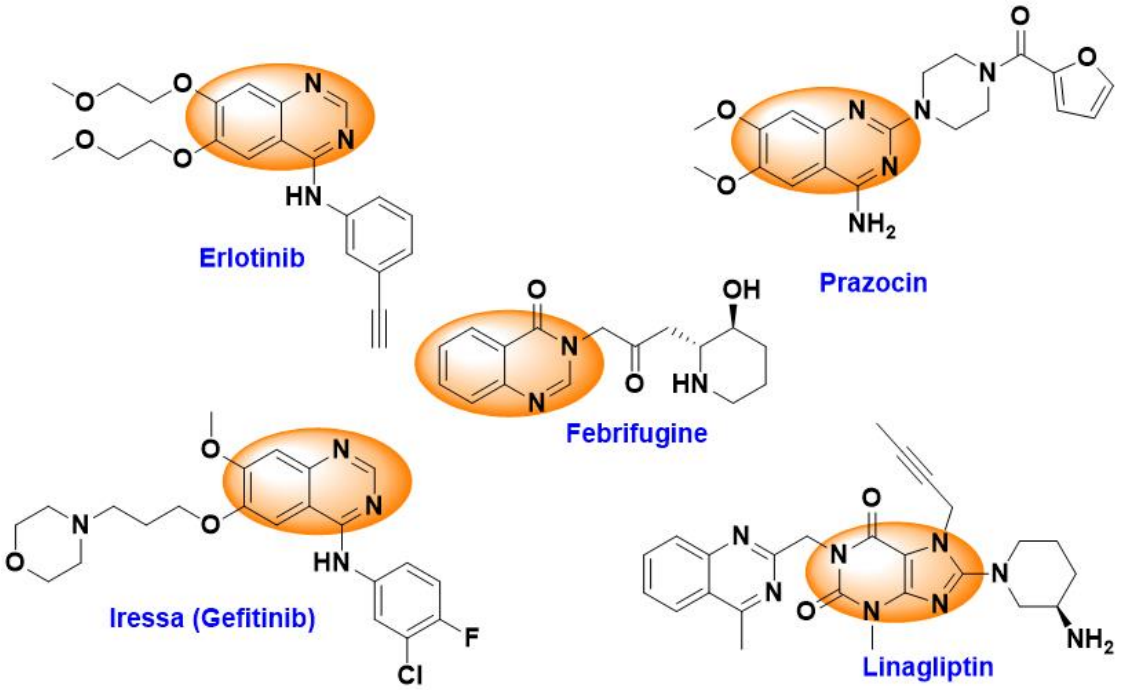


Figure 2: Commercial drugs containing quinazoline ring.

2. Results and Discussion

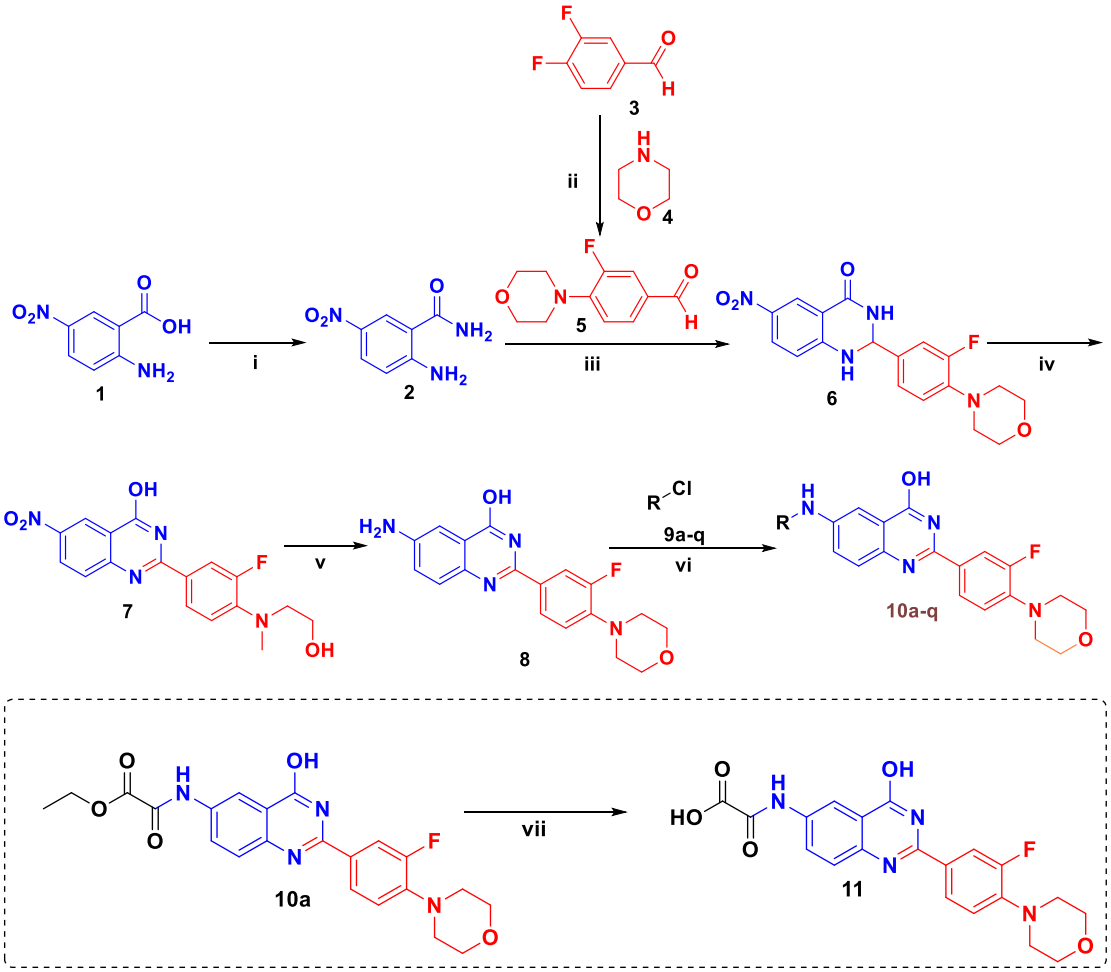
2.1. Chemistry

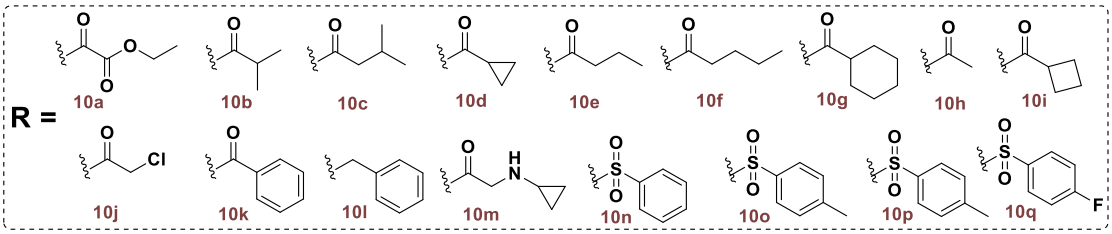
The synthesis of novel quinazoline derivatives (**10a-q** and **17a-c**) and their respective intermediates were achieved through effective and easy synthetic routes as depicted in Scheme 1 and 2. **2** was synthesized as per our previous report (**Chapter 3**), while **5** was obtained by nucleophilic substitution of 3,4-difluorobenzaldehyde with morpholine. Compounds **2** and **5** were condensed in presence of *p*TSA in methanol to yield (2-(3-fluoro-4-morpholinophenyl)-6-nitro-2,3-dihydroquinazolin-4(1H)-one) (**6**) which was subjected to oxidation with $KMnO_4$ in DMSO to yield 2-(3-fluoro-4-morpholinophenyl)-6-nitroquinazolin-4-ol (**7**). The nitro reduction of **7** was performed in presence of Fe/NH_4Cl to afford 6-amino-2-(3-fluoro-4-morpholinophenyl)quinazolin-4-ol (**8**). Subsequently, a series of compounds (**10a-q**) were synthesized by reacting **8** with the acid/sulphonyl chloride in presence of TEA in DCM at 0°C to rt for 4 h and pyridine in DCM at 0°C to rt for 16 h correspondingly. The compound **10a** was further hydrolyzed by 2N NaOH in ethanol at rt for 16 h to give 2-((2-(3-fluoro-4-morpholinophenyl)-4-hydroxyquinazolin-6-yl)amino)-2-oxoacetic acid (**11**) as illustrated in Scheme 1.

In addition, compound (**7**) was chlorinated with $POCl_3$ at 130°C for 16 h to yield 4-(4-(4-chloro-6-nitroquinazolin-2-yl)-2-fluorophenyl) morpholine (**12**). Further, **12** was substituted with cyclopropyl amine in presence of K_2CO_3/DMF at rt for 16 h to afford N-cyclopropyl-2-(3-fluoro-4-morpholinophenyl)-6-nitroquinazolin-4-amine (**14**) which in presence of Fe/NH_4Cl undergoes nitro reduction to yield N^4-cyclopropyl-2-(3-fluoro-4-morpholinophenyl) quinazoline-4,6-diamine (**15**). Further, another series of derivatives (**17a-c**) was synthesized by reaction of **15** with acid/sulphonyl chloride by using similar condition as mentioned in Scheme 1.

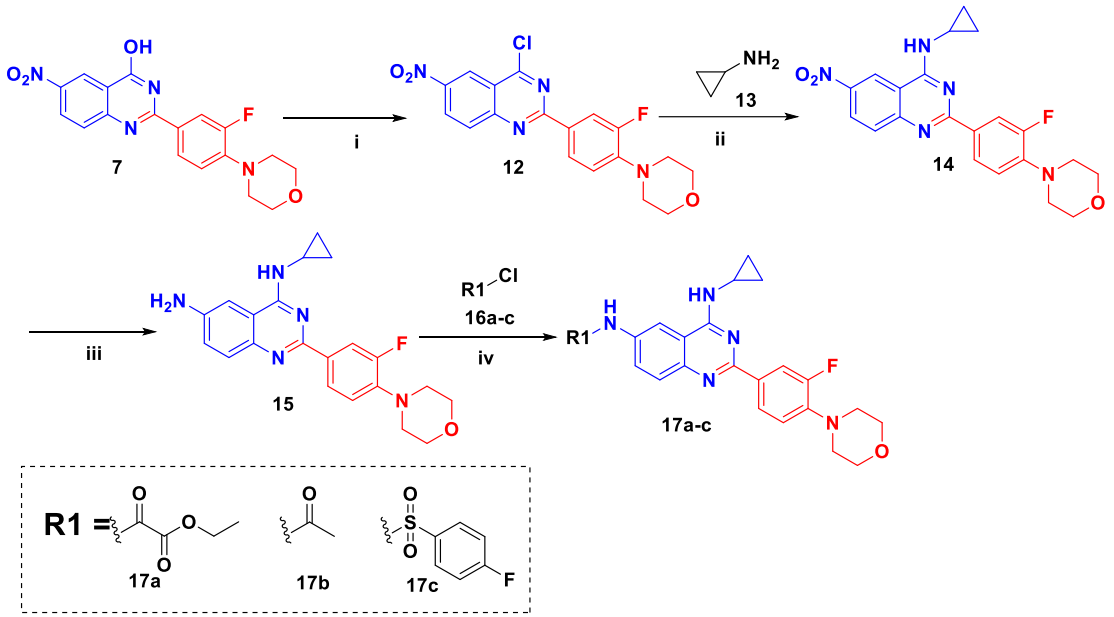
The structures of all intermediates (**5-8, 12** and **14-15**) and their corresponding final derivatives (**10a-q** and **17a-c**) were established using IR and NMR (^1H and ^{13}C). All the newly synthesized intermediates and their corresponding final derivatives show the acceptable analysis of predicted structures which are summarized in experimental section. The conversion of **3** to **5** was confirmed by the appearance of two triplet signal of 4H at around 3.86 ppm and 3.24 ppm in NMR spectra. The IR spectrum of intermediate compound **6** clearly showed characteristic absorption band around 3278.89 and 3198.58 cm^{-1} for amide and amine (N-H), 1662.36 cm^{-1} for carbonyl (C=O), 1334.63 cm^{-1} for nitro (NO_2) and 1111.15 cm^{-1} for C-F, which confirm the formation of **6**. These finding were further confirmed by ^1H NMR which exhibited prominent signal of chiral proton at around 5.96 ppm along with broad singlets at around 8.65 and 8.47 ppm, accounting for the adjacent N-**H** protons. Formation of **7** by oxidation of **6** was confirmed by disappearance of absorption band of amide and amine (N-H) in IR spectra and the signal of chiral proton along with N-**H** protons in NMR spectra. In addition, the presence of distinctive broad singlet at around 12.56 ppm confirms the presence of O**H** proton. The conversion of nitro to amine (**8**) was confirmed by disappearance of absorption band 1338.04 cm^{-1} of NO_2 in IR spectra and presence of broad singlet of amine (-N**H**$_2$**)** proton at around 5.63 ppm in NMR spectra. Furthermore, derivatization to the final compounds (**10a-q**) from scaffold **8** with acid/sulphonyl chloride were confirmed by disappearance of amine (N**H**$_2$) proton and appearance of most distinctive amide proton at around 9.84 - 11.10 ppm in case of (**10a-k** and **10m**) and secondary amine (N**H**) proton at around 6.87 ppm for **10l**. These finding were further supported by IR and ^{13}C NMR analysis. The stretching frequencies in the region 1652.22-1724.56 cm^{-1} and 3079.21-3393.66 cm^{-1} in IR spectra of compounds (**10a-k** and **10m**) indicate the presence of amide (C=O and N-H) group. Although IR spectrum of some derivatives (**10n-q**) showed the broad band in the region of 3067.19- 3085.09 cm^{-1}, 1483.80-1442.19 cm^{-1} and 1159.85-1165.30cm^{-1} are assigned for sulphonamide N-H, asymmetric and symmetric mode of O=S=O group, respectively.

In another series, the conversion of **7** to **12** was confirmed by the disappearance of O**H** proton in NMR spectra and supported by appearance of new absorption band around 735.50 cm^{-1} in IR for C-Cl. Subsequently, substitution of chloro with cyclopropyl amine to yield **14** was confirmed by the appearance of distinct N-**H** proton at around 9.28 ppm in NMR and disappearance of C-Cl absorption band in IR Spectra. The synthesis of intermediate (**15**) from the nitro reduction of **14** was authenticated by the presence of characteristic N**H**$_2$ proton at around 5.37 ppm in the NMR spectra as well as the disappearance of nitro (NO_2) stretching frequency 1323.02 cm^{-1} in IR spectra. The conversion to the final derivatives (**17a-c**) from intermediate **15** was confirmed by the appearance of amide (N-**H**) proton at around 10.09–10.93 ppm along with disappearance of amine (N**H**$_2$) protons. These results were further supported by IR spectral analysis. The absorption band in the region 3312.75 – 3333.80 cm^{-1} and 1666.39 – 1695.08 cm^{-1} in case of (**17a-b**) confirm the presence of amide group, while in the case of **17c** the stretching frequency around 3414.18 cm^{-1}, 1351.64 cm^{-1} and 1153.53 cm^{-1} assigned for sulphonamide N-H, asymmetric and symmetric mode of O=S=O group, respectively.





Scheme 1: *Reagents and conditions:* **i)** 28% aqueous ammonia solution, EDC.HCl, HOBt, DMF, 3–5 h; **ii)** K_2CO_3, DMF, 130°C, 16 h; **iii)** *p*TSA, MeOH, 70°C, 16 h; **iv)** $KMnO_4$, DMSO, 100°C, 16 h; **v)** Fe, NH_4Cl, Dioxane: EtOH: H_2O (7:5:3), 100°C, 5 h; **vi)** TEA, DCM, 0°C - rt, 4 h. or Pyridine, DCM, 0°C - rt, 16 h. **vii)** NaOH, EtOH, rt, 16 h.



Scheme 2: *Reagents and conditions:* **i)** $POCl_3$, 130°C, 16 h; **ii)** K_2CO_3, DMF, rt, 16 h; **iii)** Fe, NH_4Cl, Dioxane: EtOH: H_2O (7:5:3), 100°C, 5 h; **iv)** TEA, DCM, 0°C - rt, 4 h. or Pyridine, DCM, 0°C - rt, 16 h.

2.2. Biology

The synthesized derivatives have been evaluated against *M. tuberculosis* (Strain H37Rv) and the results as % inhibition have been tabulated in **Table 1**.

Table 1: Compounds tested against *M. tuberculosis* strain H37Rv.

Compound (20 µM)	% Inhibition	Compound (20 µM)	% Inhibition
10a	11	10m	33
10b	4	10n	-1
10c	6	10o	7
10d	2	10p	-2
10e	-2	10q	5
10f	0	11	0
10g	3	12	0
10h	-1	10l	13
10i	-5	17a	3
10j	-2	17b	2
10k	6	17c	25
10l	13		

Compounds of these series were preliminary tested against *M. tuberculosis* strain H37Rv with 20 µM concentration to find out percentage zone of inhibition, which are shown in **Table 1**. We used Rifampicin as a standard for this study. Compound **10m** showed 33 (≥ 30) percentage zone of inhibition, which will be further consider for the study like MIC, MBC etc.

3. Conclusion

In this chapter, we report rational design-based synthesis, spectral studies and preliminary anti-mycobacterial screening of novel quinazoline derivatives against *Mycobacterium tuberculosis* H37Rv strain. A total of 21 derivatives were synthesized, well-characterized by IR, NMR (^{1}H, ^{13}C) and screened against *Mycobacterium tuberculosis* H37Rv strain. In broader way, the synthesized novel compounds did not show significant percentage zone of inhibition. The only notable percentage zone of inhibition was shown by compound **10m** that was 33% after 24 h incubation. The further evaluation of this molecule for MIC and MBC can be of interest in future.

4. Experimental

4.1. General consideration

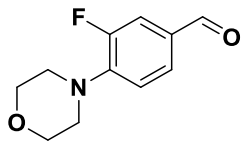
All the fine chemicals, reagents and solvents were purchased from Sigma Aldrich and Merck and were used without further purification unless otherwise stated. The progress of the reactions and the purity of the compounds were monitored by thin-layer chromatography (TLC) on pre-coated silica gel plates procured from E. Merck and Co. (Darmstadt, Germany) visualized by

UV lamp (254 or 365 nm). Purification was performed by using combi-flash (Combi*Flash*® NextGen 300+) column chromatography. The melting points of the synthesized compounds have been determined and uncorrected using a digital Stuart SMP10 melting point Apparatus. The Fourier transform infrared (FTIR) spectra were recorded in the spectral range of 400-4000 cm^{-1} on a Bruker Alpha FT-IR spectrometer using the ATR technique. The NMR spectra (**^{1}**H, and ^{13}C,) were recorded using $CDCl_3$ and DMSO-d_6 on Bruker AVANCE III 400 and 600 MHz spectrometer. Chemical shifts were determined relative to internal standard TMS at δ 0.0 parts per million (ppm) and the coupling constants were reported in Hertz. The multiplicities of the NMR resonances were abbreviated as s (singlet), d (doublet), dd (doublet of doublet), (t (triplet), q (quartet), m (multiplet) and brs (broad singlet).

4.2. Chemistry

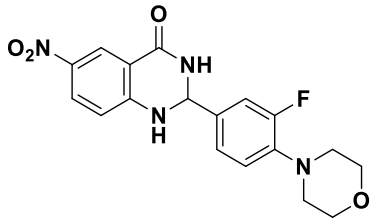
4.2.1. Synthesis and spectral characterization of compounds 5, 6, 7 and 8;

*4.2.1.1. Synthesis of 3-fluoro-4-morpholinobenzaldehyde (**5**);*



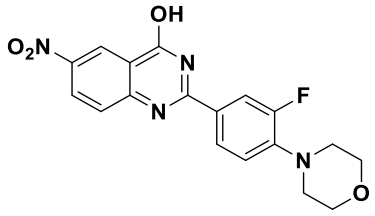
To the solution of 3,4-difluorobenzaldehyde (10 g, 70.37 mmol) in DMF (50 mL) were added K_2CO_3 (19.42 g, 140.74 mmol) followed by morpholine (7.38 mL, 84.44 mmol) at room temperature. The reaction mixture was stirred at 130°C for 16 h, monitored by TLC after consumption of starting material poured into ice cold water precipitate was formed filtered and dried under vacuum, washed with pentane to afford yellow solid product (11.45 g, 78%); mp: 63-66°C; FTIR (ATR, V_{max}, cm^{-1}): 2977.28 (Ar-H str.), 1677.18 (C=O str.), 1237.52 (C-N str.), 1110.22 (C-F str.); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 9.82 (s, 1H), 7.58 (d, J = 8.46 Hz, 1H), 7.52 (d, J = 13.50 Hz, 1H), 6.97 (t, J = 8.40 Hz, 1H), 3.86 (t, J = 5.12 Hz, 4H), 3.24 (t, J = 5.06 Hz, 4H). ^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 189.9, 155.7 – 154.0 (d, $J_{C\text{-}F}$ = 249 Hz, 1C), 145.3 – 145.2 (d, $J_{C\text{-}F}$ = 8.47 Hz, 1C), 130.55 – 130.51 (d, $J_{C\text{-}F}$ = 6.60 Hz, 1C), 128.0 – 127.9 (d, $J_{C\text{-}F}$ = 2.43 Hz, 1C), 117.79 – 117.77 (d, $J_{C\text{-}F}$ = 3.72 Hz, 1C), 116.3 – 116.1 (d, $J_{C\text{-}F}$ = 22.32 Hz, 1C), 66.8, 50.1.

*4.2.1.2. Synthesis of 2-(3-fluoro-4-morpholinophenyl)-6-nitro-2,3-dihydroquinazolin-4(1H)-one (**6**);*



To the solution of 2-amino-5-nitrobenzamide (10 g, 55.2 mmol) and 3-fluoro-4-morpholinobenzaldehyde (11.54 g, 55.2 mmol) in methanol (60 mL) was added catalytic amount of p-toluenesulfonic acid (2.1 g, 11.04 mmol). The resultant mixture was reflux for 4 h, precipitate was formed, filtered and washed with methanol to afford yellow solid product (17.3 g, 84%); mp: 255-260°C; FTIR (ATR, V_{max}, cm^{-1}): 3278.89 (N-H str.), 3198.58 (N-H str.), 2974.38 (Ar-H str.), 1662.36 (C=O str.), 1614.71 (Ar C=C str.), 1502.87 (N-H bend), 1334.63 (Ar-NO_2 str.), 1111.15 (C-F str.), 1056.88 (C-O-C str.); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 8.65 (s, 1H), 8.47 (s, 1H), 8.43 (d, J = 2.88 Hz, 1H), 8.09 (dd, J = 2.54 Hz, J = 9.22 Hz, 1H), 7.23 – 7.19 (m, 2H), 7.06 (t, J = 8.48 Hz, 1H), 6.83 (d, J = 9.28 Hz, 1H), 5.95 (s, 1H), 7.32 (t, J = 5.01 Hz, 4H), 2.99 (t, J = 4.84, Hz, 4H). ^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 161.2, 155.2 – 153.6 (d, J_{C-F} = 245 Hz, 1C), 151.9, 140.06 – 140.00 (d, J_{C-F} = 8.01 Hz, 1C), 137.2, 135.4 – 135.3 (d, J_{C-F} = 6.80 Hz, 1C), 128.9, 124.1, 122.82 – 122.81 (d, J_{C-F} = 3.35 Hz, 1C), 118.94 – 118.92 (d, J_{C-F} = 3.21 Hz, 1C), 114.3 – 114.2 (d, J_{C-F} = 22.18 Hz, 1C), 114.3, 112.6, 66.0, 65.2, 50.3.

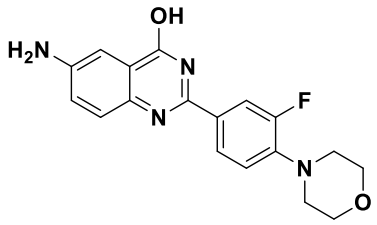
*4.2.1.3. Synthesis of 2-(3-fluoro-4-morpholinophenyl)-6-nitroquinazolin-4-ol (**7**);*



To the solution of 2-(3-fluoro-4-morpholinophenyl)-6-nitro-2,3-dihydroquinazolin-4(1H)-one (25 g, 67.3 mmol) in DMSO (100 mL) was added potassium permanganate (31.82 g, 201.41 mmol). The mixture was heated at 120°C for 24 h and monitored by TLC after consumption of starting material cooled to room temperature and filtered through celite. The filtrate was poured into ice cold water and stirred for 30 min precipitate was formed, filtered and washed with diethyl ether to afford title compound (21 g, 84%); mp: 295-297°C; FTIR (ATR, V_{max}, cm^{-1}): 3175.84 (O-H str.), 2950.24 (Ar-H str.), 2856.00 (Ar-H str.), 1676.86 (C=O str.), 1516.20 (Ar C=C str.), 1338.87 (Ar-NO_2 str.), 1243.19 (C-N str.), 1117.50 (C-F str.), 1074.99 (C-O-C str);

^{1}H NMR (600 MHz, DMSO-d_6, 70°C) δ 12.56 (brs, 1H), 8.77 (d, J = 2.05 Hz,1H), 8.46 (dd, J = 8.88 Hz, J = 2.13 Hz, 1H), 8.04 – 7.99 (m, 2H), 7.79 (d, J = 8.92 Hz, 1H), 7.11 (t, J = 8.91 Hz, 1H), 3.77 (t, J = 4.32 Hz, 4H), 3.20 (t, J = 4.05 Hz, 4H). ^{13}C NMR (150 MHz, DMSO-d_6, 70°C) δ 161.0, 154.1 – 152.5 (d, $J_{C\text{-}F}$ = 244.28 Hz, 1C), 153.8, 152.5, 144.1, 142.5 – 142.4 (d, $J_{C\text{-}F}$ = 7.81 Hz, 1C), 128.3, 127.9, 124.88 - 124.86 (d, $J_{C\text{-}F}$ = 2.27 Hz,1C), 124.16 – 124.11 (d, $J_{C\text{-}F}$ = 7.74 Hz, 1C), 121.6, 120.3, 117.9 – 117.8 (d, $J_{C\text{-}F}$ = 3.63 Hz, 1C), 115.5 – 115.4 (d, $J_{C\text{-}F}$ = 24.94 Hz 1C), 65.6, 49.5.

*4.2.1.4. Synthesis of 6-amino-2-(3-fluoro-4-morpholinophenyl)quinazolin-4-ol (**8**);*



2-(3-fluoro-4-morpholinophenyl)-6-nitroquinazolin-4-ol (6 g, 16.20 mmol) was added into the mixture of dioxane (42 mL), ethanol (30 mL) and water (18 mL) followed by ammonium chloride (8.66 g, 162.01 mmol). To the resultant mixture iron powder (4.52 g, 81 mmol) was added with vigorous stirring and then heated at 100°C for 4 h. The reaction mixture was cool to room temperature and filtered through celite and washed with 10% MeOH/DCM. The filtrate was concentrated under reduce pressure and diluted with water then extracted with 10% IPA/$CHCl_3$ (3 X 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduce pressure to afford yellow solid product (3.8 g, 68%); mp: 280-283°C; FTIR (ATR, V_{max}, cm^{-1}): 3445.93 (N-H str. of NH_2), 3305.38 (O-H str.), 3168.74 (N-H str.), 2966.17 (Ar-H str.), 1660.92 (C=O str.), 1485.46 (Ar C=C str.), 1243.61 (C-N str.), 1114.65 (C-F str.), 1042.63 (C-O-C str.); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 11.99 (brs, 1H)7.94 – 7.91 (m, 2H), 7.43 (dd, J = 8.92 Hz, J = 1.76 Hz, 1H), 7.21 (d, J = 1.76 Hz, 1H), 7.10 – 7.09 (m, 2H), 5.63 (s, 2H), 3.75 (t, J = 4.27 Hz, 4H), 3.10 (t, J = 4.31 Hz, 4H). ^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 162.1, 154.8 – 153.2 (d, $J_{C\text{-}F}$ = 242 Hz, 1C), 147.7, 145.9, 141.3 – 141.2 (d, $J_{C\text{-}F}$ = 7.9 Hz, 1C), 139.5, 128.2, 126.7 – 126.6 (d, $J_{C\text{-}F}$ = 7.80 Hz, 1C), 123.6, 122.4, 121.8, 118.3, 114.6 – 114.4 (d, $J_{C\text{-}F}$ = 24.50 Hz, 1C), 106.2, 66.0, 50.0.

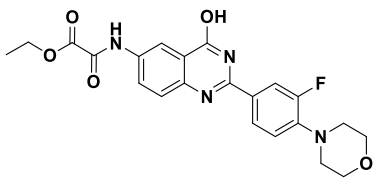
4.2.2. General procedure for synthesis and spectral characterization of derivatives (10a-l), 10m and (10n-q);

4.2.2.1. General procedure A for synthesis of derivatives (10a-10l); *To* the suspension of 6-amino-2-(3-fluoro-4-morpholinophenyl)quinazolin-4-ol (1.0 equiv) in DCM, were added triethyl amine (1.5 equiv), followed by appropriate acid chloride (9a-9l, 1.5 equiv) at 0°C. The resultant mixture was stirred at room temperature for 2 h, quenched with sodium bicarbonate solution and extracted with DCM (3 x 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduce pressure to give solid residue which were triturated with diethyl ether and filtered to afford desired title compounds (**10a-10l**).

4.2.2.2. Procedure B for synthesis of derivative (10m); To the solution of 6-amino-2-(3-fluoro-4-morpholinophenyl)quinazolin-4-ol (0.1 g, 0.29 mmol) in DCM (10 mL) was added triethyl amine (0.06 mL, 0.44 mmol), followed by 2-bromoacetyl bromide (0.038 mL, 0.44 mmol) at 0°C. The resultant mixture was stirred at room temperature for 4 h, precipitate was formed, filtered and washed with pentane to afford salt of 2-bromo-N-(2-(3-fluoro-4-morpholinophenyl)-4-hydroxyquinazolin-6-yl)acetamide (0.15 g), which was dissolved in DMF (7 mL) and were added potassium carbonate (0.12 gm, 0.88 mmol), followed by cyclopropanamine (0.04 mL, 0.58 mmol) at room temperature. The resultant mixture was stirred at room temperature for 16 h, then diluted with ethyl acetate and washed with cold brine solution (3 x 10 mL). The organic layer dried over anhydrous Na_2SO_4, filtered and evaporated under reduce pressure to yield crude product which was recrystallized with ethanol to afford the pure yellow solid product

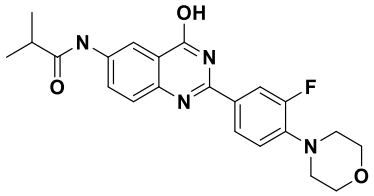
4.2.2.3. General procedure B for synthesis of derivatives (10n-10q); To the solution of 6-amino-2-(3-fluoro-4-morpholinophenyl)quinazolin-4-ol (1.0 equiv) in DCM were added pyridine (8.0 equiv), followed by appropriate sulfonyl chloride (**9m-9p,** 1.5 equiv) at 0°C. The resultant mixture was stirred at room temperature for 16 h, quenched with 2N-HCl solution and extracted with DCM (3 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to yield the crude, which was triturated with diethyl ether and filtered to afford the desired title compounds (**10n-10q**).

*4.2.2.1.1. ethyl 2-((2-(3-fluoro-4-morpholinophenyl)-4-hydroxyquinazolin-6-yl)amino)-2-oxoacetate (**10a**);*



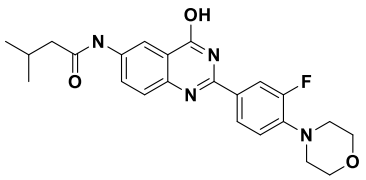
Off white solid, yield: 85%, mp: 295-297°C; FTIR (ATR, V_{max}, cm^{-1}): 3382.37 (N-H str.), 3175.43 (O-H str), 2966.20 (Ar-H str.), 1663.13 (C=O str.), 1551.62 (Ar C=C str.), 1249.99 (C-N str.), 1115.10 (C-F str), 1020.80 (C-O-C str); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 12.41 (brs, 1H), 11.10 (s, 1H), 8.64 (s, 1H), 8.10 – 7.97 (m, 3H), 7.70 (d, J = 8.60 Hz, 1H), 7.13 (t, J = 8.32 Hz, 1H), 4.33 (q, J = 5.89 Hz, 2H), 3.75 (t, J = 4.85 Hz, 4H), 3.13 (t, J = 4.68 Hz, 4H), 1.33 (t, J = 6.57 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 161.9, 160.4, 155.5, 155.1 – 152.7 (d, J_{C-F} = 243 Hz, 1C), 150.1, 145.6, 142.1, 136.6, 127.9, 127.3, 125.7 – 125.6 (d, J_{C-F} = 8.47 Hz, 1C), 124.3, 120.9, 118.4, 116.0, 115.3 – 115.0 (d, J_{C-F} = 23.79 Hz, 1C), 66.0, 62.5, 49.8, 13.8.

*3.2.2.1.2. N-(2-(3-fluoro-4-morpholinophenyl)-4-hydroxyquinazolin-6-yl)isobutyramide (**10b**);*



Yellow solid, yield: 55%, mp: 290-292°C; FTIR (ATR, V_{max}, cm^{-1}): 3274.28 (O-H str.), 3175.33 (N-H str.), 2963.45 (Ar-H str.), 1669.88 (C=O str.), 1545.57 (Ar C=C str.), 1250.41 (C-N str.), 1116.76 (C-F str.), 1045.48 (C-O-C str); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 10.03 (s, 1H), 8.35 (d, J = 2.61 Hz, 1H), 8.09 – 8.06 (m, 2H), 8.02 (d, J = 1.97 Hz, 1H), 7.85 (dd, J = 9.04 Hz, J = 2.40 Hz, 1H), 7.51 (d, J = 8.82 Hz, 1H), 7.06 (t, J = 9.11 Hz, 1H), 3.75 (t, J = 4.82 Hz, 4H), 3.09 (t, J = 4.97 Hz, 4H), 2.66 – 2.60 (m, 1H), 1.12 (d, J = 6.87 Hz, 6H). ^{13}C NMR (100 MHz, DMSO d_6, 25°C) δ 175.0, 167.3, 155.4 – 153.0 (d, J_{C-F} = 242 Hz, 1C), 154.6, 146.3, 140.8, 140.7, 135.8, 126.8, 125.0, 124.1, 121.2, 118.0, 115.1 – 114.9 (d, J_{C-F} = 22.72 Hz, 1C), 114.7, 66.1, 50.1, 34.9, 19.5.

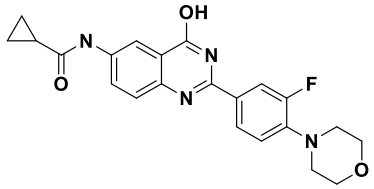
*4.2.2.1.3. N-(2-(3-fluoro-4-morpholinophenyl)-4-hydroxyquinazolin-6-yl)-3-methylbutanamide (**10c**);*



Yellow solid, yield: 75%, mp: 292-295°C; FTIR (ATR, V_{max}, cm^{-1}): 3270.09 (O-H str.), 3167.60 (N-H str.), 2960.52 (Ar-H str.), 2866.94 (Ar-H str.), 1659.23 (C=O str.), 1529.07 (Ar

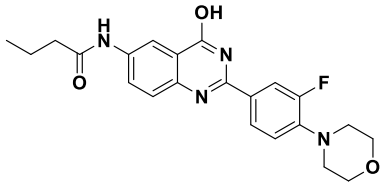
C=C str.), 1248.98 (C-N str.), 1117.72 (C-F str.), 1055.56 (C-O-C str); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 10.10 (s, 1H), 8.42 (d, J = 2.28 Hz, 1H), 8.05 - 7.99 (m, 2H), 7.86 (dd, J = 8.91 Hz, J = 2.31 Hz, 1H), 7.57 (d, J = 8.88 Hz, 1H), 7.08 (t, J = 9.05 Hz, 1H), 3.75 (t, J = 4.71 Hz, 4H), 3.11 (t, J = 4.66 Hz, 4H), 2.23 (d, J = 7.14 Hz, 2H), 2.14 - 2.08 (m, 1H), 0.95 (d, J = 6.64 Hz, 6H). ^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 170.6, 164.8, 154.8 - 153.2 (d, $J_{C\text{-}F}$ = 246 Hz, 1C), 152.2, 145.5, 141.29 - 141.24 (d, $J_{C\text{-}F}$ = 9.07 Hz, 1C), 136.4, 128.7, 127.2, 125.5, 124.1, 121.1, 118.16 – 118.13 (d, $J_{C\text{-}F}$ = 3.82 Hz, 1C), 115.0 - 114.9 (d, $J_{C\text{-}F}$ = 24.87 Hz, 1C), 114.5, 66.0, 50.0, 45.6, 25.5, 22.2.

*4.2.2.1.4. N-(2-(3-fluoro-4-morpholinophenyl)-4-hydroxyquinazolin-6-yl)cyclopropanecarboxamide (**10d**);*



Yellow solid, yield: 54%, mp: 278-280°C; FTIR (ATR, V_{max}, cm^{-1}): 3267.00 (O-H str.), 3170.92 (N-H str.), 2970.39 (Ar-H str.), 2885.24 (Ar-H str.), 1654.85 (C=O str), 1533.04 (Ar C=C str.), 1250.58 (C-N str.), 1115.19 (C-F str.), 1055.04 (C-O-C str); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 12.79 (brs, 1H), 10.49 (s, 1H), 8.46 (s, 1H), 8.00 - 7.92 (m, 3H), 7.64 (d, J = 9.18 Hz, 1H), 7.11 (t, J = 8.82 Hz, 1H), 3.75 (t, J = 4.93 Hz, 4H), 3.13 (t, J = 4.82 Hz, 4H), 1.81 – 1.79 (m, 1H) 0.85 – 0.82 (m, 4H). ^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 171.8, 162.1, 154.7 – 153.1 (d, $J_{C\text{-}F}$ = 242.87, 1C), 149.4, 144.3, 141.87 – 141.82 (d, $J_{C\text{-}F}$ = 7.34 Hz, 1C), 137.4, 127.8, 126.0, 126.0, 124.2 – 124.1 (d, $J_{C\text{-}F}$ = 2.98 Hz, 1C), 121.0, 118.36 – 118.34 (d, $J_{C\text{-}F}$ = 3.86 Hz, 1C), 115.1 – 114.9 (d, $J_{C\text{-}F}$ = 23.71 Hz, 1C), 114.1, 65.9, 49.9, 14.6, 7.3.

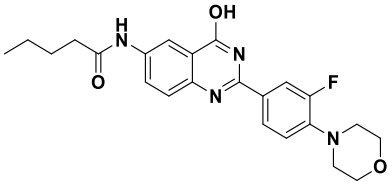
*3.2.2.1.5 N-(2-(3-fluoro-4-morpholinophenyl)-4-hydroxyquinazolin-6-yl)butyramide (**10e**);*



Yellow solid, yield: 75%, mp: 282-284°C; FTIR (ATR, V_{max}, cm^{-1}): 3275.22 (O-H str.), 3168.10 (N-H str.), 2960.50 (Ar-H str.), 2867.02 (Ar-H str.), 1654.63 (C=O str), 1530.81 (Ar C=C str.), 1248.45 (C-N str.), 1117.10 (C-F str.), 1055.15 (C-O-C str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 10.11 (s, 1H), 8.39 (s, 1H), 8.05 – 7.99 (m, 2H), 7.85 (d, J = 8.26 Hz, 1H), 7.56 (d, J = 8.66 Hz, 1H), 7.09 (t, J = 8.37 Hz, 1H), 3.75 (t, J = 3.82 Hz, 4H), 3.10 (t, J = 3.88 Hz, 4H), 2.32

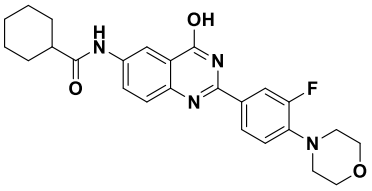
(t, *J* = 7.44 Hz, 2H), 1.66 – 1.61 (m, 2H), 0.93 (t, *J* = 7.17 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 171.2, 165.6, 155.3 – 152.9 (d, $J_{C\text{-}F}$ = 244 Hz, 1C), 145.7, 141.2, 141.1, 136.3, 129.3, 127.2, 125.3, 124.1, 121.2, 118.1, 115.1 – 114.9 (d, $J_{C\text{-}F}$ = 23.44 Hz, 1C), 114.5, 66.0, 50.1, 38.3, 18.3, 13.6.

*4.2.2.1.6. N-(2-(3-fluoro-4-morpholinophenyl)-4-hydroxyquinazolin-6-yl)pentanamide (**10f**);*



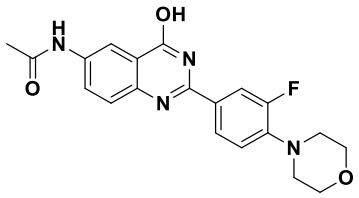
Yellow solid, yield: 65%, mp: 286-288°C; FTIR (ATR, V_{max}, cm^{-1}): 3281.07 (O-H str.), 3169.33 (N-H str.), 2960.59 (Ar-H str.), 2866.04 (Ar-H str.), 1652.22 (C=O str), 1531.89 (Ar C=C str.), 1248.96 (C-N str.), 1118.24 (C-F str.), 1055.15 (C-O-C str); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 12.33 (s, 1H), 10.23 (s, 1H), 8.50 (s, 1H), 7.99 – 7.91 (m, 3H), 7.65 (s, 1H), 7.12 (s, 1H), 3.75 (t, *J* = 4.03 Hz, 4H), 3.13 (t, *J* = 4.30 Hz, 4H), 2.35 (t, *J* = 6.96 Hz, 2H), 1.67 – 1.52 (m, 2H), 1.47 – 1.19 (m, 2H), 0.91 (t, *J* = 7.35 Hz, 3H). ^{13}C NMR (150 MHz, DMSO d_6, 65°C) δ 171.2, 161.7, 154.5 – 152.9 (d, $J_{C\text{-}F}$ = 242.34 Hz, 1C), 149.1, 141.6 – 141.5 (d, $J_{C\text{-}F}$ = 9.18 Hz, 1C), 137.3, 127.3, 126.0, 125.7, 123.9, 120.7, 118.0, 114.9 – 114.7 (d, $J_{C\text{-}F}$ = 23.78 Hz, 1C), 114.2, 65.7, 49.7, 35.8, 26.8, 21.4, 13.2.

*4.2.2.1.7. N-(2-(3-fluoro-4-morpholinophenyl)-4-hydroxyquinazolin-6-yl)cyclohexanecarboxamide (**10g**);*



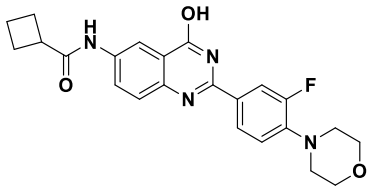
Yellow solid, yield: 45%, mp: 293-296°C; FTIR (ATR, V_{max}, cm^{-1}): 3269.25 (O-H str.), 3166.55 (N-H str.), 2971.62 (Ar-H str.), 2865.58 (Ar-H str.), 1660.06 (C=O str), 1529.93 (Ar C=C str.), 1249.56 (C-N str.), 1119.77 (C-F str.), 1055.72 (C-O-C str); ^{1}H NMR (600 MHz, DMSO-d_6, 60°C) δ 12.20 (s, 1H), 10.01 (s, 1H), 8.57 (s, 1H), 8.08 – 7.93 (m, 3H), 7.73 (s, 1H), 7.23 (s, 1H), 3.87 (t, *J* = 6.72 Hz, 4H), 2.60 (t, *J* = 6.83 Hz, 4H), 1.95 – 1.40 (m, 11H). ^{13}C NMR (150 MHz, DMSO-d_6, 60°C) δ 174.2, 161.7, 154.5 – 152.9 (d, $J_{C\text{-}F}$ = 243 Hz, 1C), 149.1, 144.15, 141.6 – 141.5 (d, $J_{C\text{-}F}$ = 7.80 Hz, 1C), 137.4, 127.3, 126.0, 125.8 – 125.7 (d, $J_{C\text{-}F}$ = 8.22 Hz, 1C), 123.9, 120.8, 118.1, 114.9 – 114.7 (d, $J_{C\text{-}F}$ = 23.83 Hz, 1C), 114.3, 65.7, 49.76, 44.6, 28.8, 25.1, 24.9.

4.2.2.1.8. N-(2-(3-fluoro-4-morpholinophenyl)-4-hydroxyquinazolin-6-yl)acetamide ***(10h);***



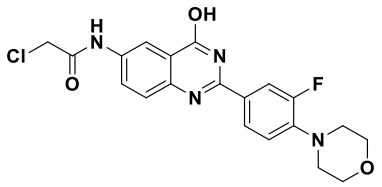
Yellow solid, yield: 90%, mp: 295-297°C; FTIR (ATR, V_{max}, cm^{-1}): 3273.13 (O-H str.), 3167.80 (N-H str.), 2972.46 (Ar-H str.), 2866.95 (Ar-H str.), 1656.52 (C=O str), 1530.92 (Ar C=C str.), 1246.14 (C-N str.), 1113.43 (C-F str.), 1055.54 (C-O-C str); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.33 (brs, 1H), 10.28 (s, 1H), 8.45 (s, 1H), 8.01 – 7.79 (m, 2H), 7.89 – 7.86 (m, 1H), 7.61 (d, J = 8.01 Hz, 1H), 7.10 (s, 1H), 3.75 (t, J = 3.97 Hz, 4H), 3.11 (t, J = 3.39 Hz, 4H), 2.09 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 168.4, 155.3 – 152.8 (d, $J_{C\text{-}F}$ = 243 Hz, 1C), 145.4, 141.4 – 141.3 (d, $J_{C\text{-}F}$ = 7.72 Hz, 1C), 136.6, 127.3, 125.4, 124.2, 121.1, 115.1 – 114.9 (d, $J_{C\text{-}F}$ = 25 Hz, 1C), 114.3, 66.0, 50.0, 24.0.

4.2.2.1.9 N-(2-(3-fluoro-4-morpholinophenyl)-4-hydroxyquinazolin-6-yl)cyclobutanecarboxamide ***(10i);***



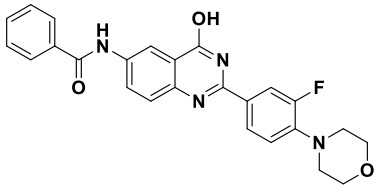
Yellow solid, yield: 68%, mp: 290-294°C; FTIR (ATR, V_{max}, cm^{-1}): 3271.92 (O-H str.), 2989.00 (Ar-H str.), 2858.87 (Ar-H str.), 1672.08 (C=O str), 1518.59 (Ar C=C str.), 1251.60 (C-N str.), 1118.67 (C-F str.); ^{1}H NMR (600 MHz, DMSO-d_6, 60°C) δ 9.84 (s, 1H), 8.41 (s, 1H), 8.02 – 7.91 (m, 3H), 7.57 (d, J = 6.34 Hz, 1H), 7.08 (s, 1H), 3.76 (t, J = 4.74 Hz, 4H), 3.31 – 3.24 (m, 1H), 3.14 (t, J = 4.27 Hz, 4H), 2.33 – 2.22 (m, 2H), 2.21 – 2.09 (m, 2H), 1.19 – 1.85 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6, 60°C) δ 172.7, 164.1, 154.6 – 153.0 (d, $J_{C\text{-}F}$ = 242 Hz, 1C), 151.6, 145.1, 141.1 – 141.0 (d, $J_{C\text{-}F}$ = 9.37 Hz, 1C), 136.4, 128.2, 126.9, 125.5, 123.9, 120.9, 117.9, 114.9 – 114.7 (d, $J_{C\text{-}F}$ = 23.76 Hz, 1C), 114.5, 78.8, 65.8, 49.8, 24.2, 17.49.

4.2.2.1.10. 2-chloro-N-(2-(3-fluoro-4-morpholinophenyl)-4-hydroxyquinazolin-6-yl)acetamide ***(10j);***



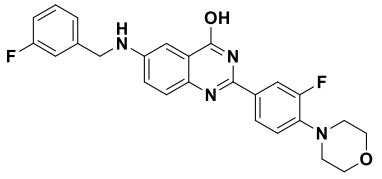
Yellow solid, yield: 68%, mp: 295-297°C; FTIR (ATR, V_{max}, cm^{-1}): 3247.85 (O-H str.), 3079.21 (N-H str.), 2967.24 (Ar-H str.), 2859.64 (Ar-H str.), 1656.18 (C=O str), 1535.39 (Ar C=C str.), 1246.48 (C-N str.), 1116.07 (C-F str.), 1046.04 (C-O-C str); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.38 (brs, 1H), 10.83 (s, 1H), 8.50 (s, 1H), 7.98 – 7.95 (m, 3H), 7.68 (s, 1H), 7.10 (s, 1H), 4.33 (s, 2H), 3.74 (t, J = 5.10 Hz, 4H), 3.12 (t, J = 5.26 Hz, 4H). ^{13}C NMR (150 MHz, DMSO-d_6, 30°C) δ 164.8, 161.9, 154.6 – 153.0 (d, $J_{C\text{-}F}$ = 244 Hz, 1C), 149.8, 144.6, 142.0 – 141.9 (d, $J_{C\text{-}F}$ = 7.78 Hz, 1C), 136.7, 127.7, 126.3, 125.5 – 125.5 (d, $J_{C\text{-}F}$ = 7.61 Hz, 1C), 124.3, 120.9, 118.33 – 118.31 (d, $J_{C\text{-}F}$ = 4.09 Hz, 1C), 115.2 – 115.0 (d, $J_{C\text{-}F}$ = 24.26 Hz, 1C), 114.6, 65.9, 49.8, 43.4.

*4.2.2.1.11. N-(2-(3-fluoro-4-morpholinophenyl)-4-hydroxyquinazolin-6-yl)benzamide (**10k**);*



Yellow solid, yield: 36%, mp: 296-298°C; FTIR (ATR, V_{max}, cm^{-1}): 3393.66 (N-H str.), 3277.16 (O-H str.), 2966.37 (Ar-H str.), 2847.14 (Ar-H str.), 1724.56 (C=O str), 1671.73 (C=O str. Keto-enol), 1535.36 (Ar C=C str.), 1253.47 (C-N str.), 1089.48 (C-O-C str); ^{1}H NMR (600 MHz, DMSO-d_6, 70°C) δ 12.13 (brs, 1H), 10.39 (s, 1H), 8.64 (s, 1H), 8.18 – 8.01 (m, 5H), 7.70 – 7.54 (m, 4H), 7.13 (s, 1H), 3.77 (t, J = 5.15 Hz, 4H), 3.17 (t, J = 5.51 Hz, 4H). ^{13}C NMR (150 MHz, DMSO-d_6, 70°C) δ 165.3, 152.8, 137.1, 134.4, 132.3, 131.2, 128.8, 128.4, 128.09, 128.02, 127.3, 127.0, 123.9, 120.7, 118.1, 115.6, 114.9 – 114.8 (d, $J_{C\text{-}F}$ = 23.10 Hz, 1C), 65.7, 49.7.

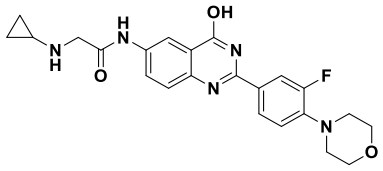
*4.2.2.1.12. 2-(3-fluoro-4-morpholinophenyl)-6-((3-fluorobenzyl)amino)quinazolin-4-ol (**10l**);*



Yellow solid, yield: 41%, mp: 200-205°C; FTIR (ATR, V_{max}, cm^{-1}): 3456.45 (O-H str.), 3163.56 (N-H str.), 2969.43 (Ar-H str.), 2865.71 (Ar-H str.), 1656.30 (C=O str keto-enol), 1591.82 (Ar

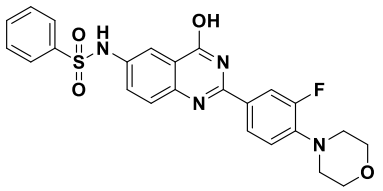
C=C str.), 1251.33 (C-N str.), 1117.52 (C-F str.), 1047.78 (C-O-C str); ^{1}HNMR (600 MHz, DMSO-d_6, 25°C) δ 12.07 (s, 1H), 7.94 – 7.91 (m, 2H), 7.48 (d, J = 8.62 Hz, 1H), 7.40 – 7.36 (m, 1H), 7.24 – 7.17 (m, 3H), 7.11 – 7.04 (m, 3H), 6.87 (t, J = 6.15 Hz, 1H), 4.41 (d, J = 6.33 Hz, 2H), 3.75 (t, J = 4.72 Hz, 4H), 3.11 (t, J = 4.52 Hz, 4H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 163.5 – 161.1 (d, $J_{C\text{-}F}$ = 244.41 Hz, 1C), 162.0, 155.3 – 152.8 (d, $J_{C\text{-}F}$ = 244.20 Hz, 1C), 147.7, 146.2, 142.89 – 142.82 (d, $J_{C\text{-}F}$ = 7.02 Hz, 1C), 141.4 – 141.3 (d, $J_{C\text{-}F}$ = 7.98 Hz, 1C), 140.0, 130.38 – 130.30 (d, $J_{C\text{-}F}$ = 8.51 Hz, 1C), 128.3, 126.5 – 126.4 (d, $J_{C\text{-}F}$ = 8.12 Hz, 1C), 123.6, 123.08 – 122.06 (d, $J_{C\text{-}F}$ = 2.50 Hz, 1C), 122.1, 121.8, 118.45 – 118.42 (d, $J_{C\text{-}F}$ = 3.35 Hz, 1C), 114.7 – 114.4 (d, $J_{C\text{-}F}$ = 23.69 Hz, 1C), 113.7 – 113.6 (d, $J_{C\text{-}F}$ = 12.78 Hz, 1C), 113.5 – 113.4 (d, $J_{C\text{-}F}$ = 11.77 Hz, 1C), 103.4, 66.0, 50.0, 45.8.

*4.2.2.2.1. Synthesis of 2-(cyclopropylamino)-N-(2-(3-fluoro-4-morpholinophenyl)-4-hydroxyquinazolin-6-yl)acetamide (**10m**);*



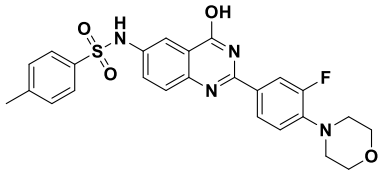
Yellow solid, yield: 29%, mp: 252-255°C; FTIR (ATR, V_{max}, cm^{-1}): 3272.51 (O-H str.), 3173.07 (N-H str.), 3078.83 (N-H str.), 2969.04 (Ar-H str.), 1662.95 (C=O str.), 1551.87 (Ar C=C str.), 1249.10 (C-N str.), 1121.91 (C-F str.), 982.33(C-O-C str); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.34 (brs, 1H), 10.11 (s, 1H), 8.53 (d, J = 2.42 Hz, 1H), 8.02 – 7.94 (m, 3H), 7.67 (d, J = 8.39 Hz, 1H), 7.14 (t, J = 9.15 Hz, 1H), 3.76 (t, J = 4.23 Hz, 4H), 3.38 (s, 2H), 3.14 (t, J = 4.47 Hz, 4H), 2.22 – 2.16 (m, 1H), 0.40 – 0.34 (m, 2H), 0.32 – 029 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 170.8, 162.0, 155.1 – 152.7 (d, $J_{C\text{-}F}$ = 243.99 Hz, 1C), 149.4, 144.6, 142.1 – 141.9 (d, $J_{C\text{-}F}$ = 8.43 Hz, 1C), 137.0, 127.9, 126.3, 125.9 – 125.8 (d, $J_{C\text{-}F}$ = 8.17 Hz, 1C), 124.2, 121.0, 118.45 – 118.41 (d, $J_{C\text{-}F}$ = 3.71 Hz, 1C), 115.2 – 114.9 (d, $J_{C\text{-}F}$ = 24.26 Hz, 1C), 114.4, 66.0, 52.7, 49.96, 30.1, 6.0.

*4.2.2.3.1. N-(2-(3-fluoro-4-morpholinophenyl)-4-hydroxyquinazolin-6-yl)benzenesulfonamide (**10n**);*



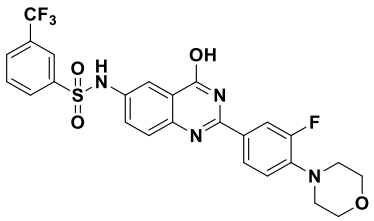
Yellow solid, yield: 44%, mp: 297-299°C; FTIR (ATR, V_{max}, cm^{-1}): 3242.21 (O-H str.), 3067.19 (N-H str.), 2853.86 (Ar-H str.), 1670.13 (C=O str. keto-enol), 1595.03 (Ar C=C str.), 1442.19 (SO_2 asym.), 1249.72 (C-N str.), 1161.71 (SO_2 sym.), 1117.84 (C-F str.), 1088.03 (C-O-C str); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 11.97 (s, 1H), 7.95 – 7.90 (m, 2H), 7.75 (dd, J = 7.17 Hz, J = 2.08 Hz, 2H), 7.65 (d, J = 2.49 Hz, 1H), 7.45 – 7.35 (m, 5H), 7.09 (t, J = 8.81 Hz, 1H), 3.74 (t, J = 4.26 Hz, 4H), 3.11 (t, J = 4.26 Hz, 4H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 162.3, 155.2 – 152.8 (d, J_{C-F} = 245 Hz, 1C), 147.7, 143.8, 142.1, 141.5 – 141.4 (d, J_{C-F} = 8.04 Hz, 1C), 130.8, 128.6, 128.5, 127.6, 126.6, 126.3, 123.8, 121.2, 118.4, 114.8 – 114.6 (d, J_{C-F} = 23.56 Hz, 1C), 113.8, 66.0, 50.0.

*4.2.2.3.2. N-(2-(3-fluoro-4-morpholinophenyl)-4-hydroxyquinazolin-6-yl)-4-methylbenzenesulfonamide (**10o**);*



Yellow solid, yield: 31%, mp: 282-284°C, FTIR (ATR, V_{max}, cm^{-1}): 3245.94 (O-H str.), 3085.09 (N-H str.), 2955.40 (Ar-H str.), 2857.50 (Ar-H str.), 1671.67 (C=O str. Of Keto-enol), 1551.91 (Ar C=C str.), 1482.76 (SO_2, asym), 1251.40 (C-N str.), 1159.85 (SO_2, sym), 1119.25 (C-F str.), 1088.37 (C-O-C str); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 11.96 (brs, 1H), 7.95 – 7.52 (m, 7H), 7.32 – 7.11 (m, 3H), 3.74 (t, J = 4.35 Hz, 4H), 3.12 (t, J = 4.62 Hz, 4H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 162.1, 155.2 – 152.7 (d, J_{C-F} = 243.63 Hz, 1C), 148.9, 143.7, 142.2, 141.8 – 141.7 (d, J_{C-F} = 8.04 Hz, 1C), 138.4, 129.4, 128.1, 127.6, 126.5, 126.2, 126.1, 124.1, 121.2, 118.4, 115.0 – 114.8 (d, J_{C-F} = 23.06 Hz, 1C), 114.4, 66.0, 49.9, 20.9.

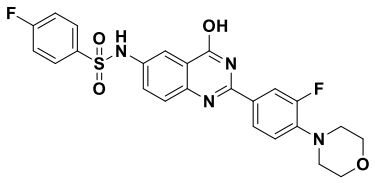
*4.2.2.3.3. N-(2-(3-fluoro-4-morpholinophenyl)-4-hydroxyquinazolin-6-yl)-3-(trifluoromethyl)benzenesulfonamide (**10p**);*



Yellow solid, yield: 32%, mp: 293-295°C; FTIR (ATR, V_{max}, cm^{-1}): 3253.07 (O-H str.), 3081.61 (N-H str.), 2966.92 (Ar-H str.), 2859.56 (Ar-H str.), 1672.36 (C=O str. keto-enol),

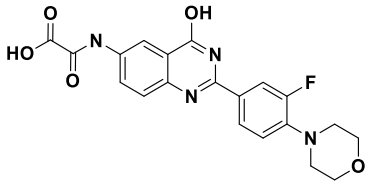
1593.75 (Ar C=C str.), 1483.63 (SO_2 asym.), 1324.08 (C-CF_3 str.), 1249.93 (C-N str.), 1161.62 (SO_2 sym.), 1123.14 (C-F str.), 1067.20 (C-O-C str); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.26 (brs, 1H), 8.02 – 7.92 (m, 5H), 7.75 – 7.72 (m, 2H), 7.55 – 7.46 (m, 2H), 7.11 (t, J = 8.59 Hz, 1H), 3.74 (t, J = 4.41 Hz, 4H), 3.12 (t, J = 3.62 Hz, 4H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 161.7, 155.1 – 152.7 (d, $J_{C\text{-}F}$ = 246 Hz, 1C), 150.0, 142.0, 140.6, 135.9, 131.0, 130.6, 129.7, 128.7, 127.7, 125.6, 124.3, 123.1, 121.2, 118.4, 115.9, 115.2 – 115.0 (d, $J_{C\text{-}F}$ = 23.31 Hz, 1C), 66.0, 49.8.

*4.2.2.3.4. 4-fluoro-N-(2-(3-fluoro-4-morpholinophenyl)-4-hydroxyquinazolin-6-yl)benzenesulfonamide (**10q**);*



Yellow solid, yield: 46%, mp: 293-296°C; FTIR (ATR, V_{max}, cm^{-1}): 3258.27 (O-H str.), 3067.49 (N-H str.), 2955.72 (Ar-H str.), 2845.25 (Ar-H str.), 1672.39 (C=O str keto-enol), 1592.48 (Ar C=C str.), 1483.80 (SO_2 asym.), 1236.36 (C-N str.), 1165.30 (SO_2 sym.), 1121.56 (C-F str.), 1089.25(C-O-C str); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.38 (brs, 1H), 10.70 (brs, 1H), 7.95 – 7.92 (m, 2H), 7.82 – 7.80 (m, 3H), 7.63 – 7.53 (m, 2H), 7.39 (t, J = 8.12 Hz, 2H), 7.10 (t, J = 8.32 Hz, 1H), 3.74 (t, J = 4.84 Hz,4H), 3.12 (t, J = 4.36 Hz, 4H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 165.6 – 163.1 (d, $J_{C\text{-}F}$ = 245 Hz, 1C), 161.8, 155.1 -152.7 (d, $J_{C\text{-}F}$ = 243.59 Hz, 1C), 150.1, 145.4, 142.1 – 142.0 (d, $J_{C\text{-}F}$ = 8.01 Hz, 1C), 135.6, 135.57 – 135.54 (d, $J_{C\text{-}F}$ = 3.41 Hz, 1C), 129.8 – 129.7 (d, $J_{C\text{-}F}$ = 9.76 Hz, 1C), 128.7, 127.4, 125.7 – 125.6 (d, $J_{C\text{-}F}$ = 7.71 Hz, 1C), 124.4, 121.3, 118.46 -118.42 (d, $J_{C\text{-}F}$ = 3.21 Hz, 1C), 116.7 – 116.5 (d, $J_{C\text{-}F}$ = 23.15 Hz, 1C), 115.6, 115.3 – 115.0 (d, $J_{C\text{-}F}$ = 23.58 Hz, 1C), 66.0, 49.9.

*4.2.2.1.1.1. Synthesis of 2-((2-(3-fluoro-4-morpholinophenyl)-4-hydroxyquinazolin-6-yl)amino)-2-oxoacetic acid (**11**);*

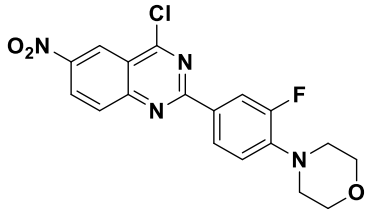


To the suspension of ethyl 2-((2-(3-fluoro-4-morpholinophenyl)-4-hydroxyquinazolin-6-yl)amino)-2-oxoacetate (0.2 g, 0.45 mmol) in ethanol was added 2N-NaOH (0.036 g, 0.908

mmol). The resultant mixture was stirred at room temperature for 16 h, diluted with water and washed with ethyl acetate .The aqueous layer was acidified with 6N-HCl , precipitate was formed , filtered and washed with diethyl ether to afford off white solid product (0.103 g, 55%); mp: 285-288°C; FTIR (ATR, V_{max}, cm^{-1}): 3671.54 (O-H str.), 2973.14 (Ar-H str.), 2867.85 (Ar-H str.), 1659.51 (C=O str.), 1249.36 (C-N str.), 1056.03 (C-O-C str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.40 (brs, 1H), 11.00 (s, 1H), 8.68 (d, J = 2.08 Hz, 1H), 8.09 (dd, J = 8.91 Hz, J = 1.91 Hz, 1H), 8.01 - 7.97 (m, 2H), 7.69 (d, J = 9.20 Hz, 1H), 7.13 (t, J = 8.57 Hz, 1H), 3.75 (t, J = 4.36 Hz, 4H), 3.13 (t, J = 4.81 Hz, 4H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 161.9, 157.7, 155.1 – 152.7 (d, J_{C-F} = 244 Hz, 1C), 142.1 – 142.0 (d, J_{C-F} = 8.55 Hz, 1C) 135.9, 127. 9, 127.2, 125.8 – 125.7 (d, J_{C-F} = 7.81 Hz, 1C), 124.4, 120.9, 118.4, 115.7, 115.3 – 115.0 (d, J_{C-F} = 23.60 Hz, 1C), 66.0, 49.9.

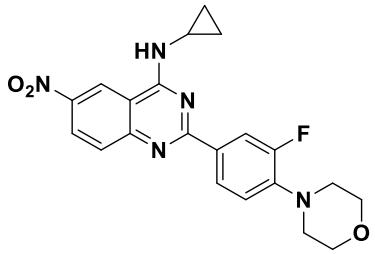
4.2.2. Synthesis and spectral characterization of compounds 12, 14, 15 and (17a-c);

4.2.2.1. Synthesis of 4-(4-(4-chloro-6-nitroquinazolin-2-yl)-2-fluorophenyl)morpholine ***(12);***



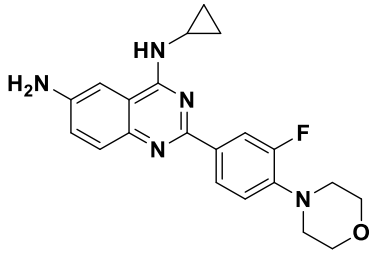
2-(3-fluoro-4-morpholinophenyl)-6-Nitroquinazolin-4-ol (4 g, 10.80 mmol) was mixed with 20 mL phosphoryl chloride and was then reflux for 16 h. After completion of reaction solvent was evaporated under reduced pressure then ice-cold water was added to residue, the formed precipitate was neutralized with ammonium hydroxide and filtered off to get crude product which was purified by column chromatography on silica gel (100−200 mesh) using MeOH/DCM as an eluent to afford the pure orange solid product (2 g, 47%); mp: 250-253°C; FTIR (ATR, V_{max}, cm^{-1}): 2963.23 (Ar-H str.), 1544.56 (Ar C=C str.), 1340.50 (Ar-NO_2 str.), 1241.01 (C-N str.), 1118.94 (C-F str.), 1042.58 (C-O-C str.), 735.50 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 9.05 (d, J = 2.50 Hz, 1H), 8.60 (dd, J = 9.17 Hz, J = 2.77 Hz, 1H), 8.26 (dd, J = 7.71 Hz, J = 1.75 Hz, 1H), 8.18 (dd, J = 14,54 Hz, J = 1.90 Hz, 1H), 8.07 (d, J = 9.26 Hz, 1H), 6.96 (t, J = 8.79 Hz, 1H), 3.89 (t, J = 4.50 Hz, 4H), 3.25 (t, J = 4.89 Hz, 4H). ^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 164.2, 161.8 – 161.7 (d, J_{C-F} = 2.89 Hz, 1C), 156.2 – 153.7 (d, J_{C-F} = 245 Hz, 1C), 154.2, 145.8, 143.6 – 143.5 (d, J_{C-F} = 8.09 Hz, 1C), 130.6, 129.3 – 129.2 (d, J_{C-F} = 8.20 Hz, 1C), 128.3, 126.25 – 126.22 (d, J_{C-F} = 2.76 Hz, 1C), 122.9 , 121.4, 117.96 – 117.93 (d, J_{C-F} = 3.14 Hz, 1C), 117.1 – 116.9 (d, J_{C-F} = 263.52 Hz, 1C), 66.9, 50.3.

*4.2.2.2. Synthesis of N-cyclopropyl-2-(3-fluoro-4-morpholinophenyl)-6-nitroquinazolin-4-amine (**14**);*



To the solution of 4-(4-(4-chloro-6-nitroquinazolin-2-yl)-2-fluorophenyl)morpholine (0.96 g, 2.46 mmol) in DMF (15 mL) was added K_2CO_3 (0.511 g, 3.70 mmol) followed by cyclopropanamine (0.25 mL, 3.70 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 h, monitored by TLC after consumption of starting material poured into ice cold water, precipitate was formed filtered and dried under vacuum, washed with diethyl ether to afford orange solid product (0.610 g, 60%); mp: 240-245°C; FTIR (ATR, V_{max}, cm^{-1}): 3392.57 (N-H str.), 2951.82 (Ar-H str.), 2856.40 (Ar-H str.), 1580.30 (Ar C=C), 1323.02 (Ar-NO_2), 1242.86 (C-N str.), 1115.79 (C-F str.), 1043.88 (C-O-C str.). ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 9.28 (s, 1H), 8.90 (s, 1H), 8.42 – 8.40 (m, 1H), 8.27 (d, J = 8.91 Hz, 1H), 8.17 – 8.13 (m, 1H), 7.80 (d, J = 8.92 Hz, 1H), 7.11 (t, J = 8.83 Hz, 1H), 3.76 (t, J = 4.75 Hz, 4H), 3.13 (t, J = 4.70 Hz, 4H). 0.90 – 0.89 (m, 2H), 0.79 – 0.74 (m, 2H).

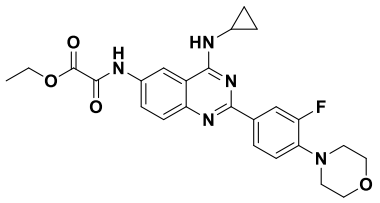
*4.2.2.3. Synthesis of N^4-cyclopropyl-2-(3-fluoro-4-morpholinophenyl)quinazoline-4,6-diamine (**15**);*



N-cyclopropyl-2-(3-fluoro-4-morpholinophenyl)-6-nitroquinazolin-4-amine (0.5 g, 1.22 mmol) was added into the mixture of dioxane (14 mL), ethanol (10 mL) and water (6 mL) followed by ammonium chloride (0.65 g, 12.22 mmol). To the resultant mixture iron powder (0.34 g, 6.10 mmol) was added with vigorous stirring and then heated at 100°C for 4 h. The reaction mixture was cool to room temperature and filtered through celite and washed with 10% MeOH/DCM. The filtrate was evaporated under reduce pressure then diluted with water and extracted with

10% MeOH/DCM (3 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduce pressure to yield crude product (0.194 g,); mp: 250-253°C; FTIR (ATR, V_{max}, cm^{-1}): 3419.04 (N-H str.) 3344.03 (N-H str.), 2960.68 (Ar-H str.), 1530.39 (Ar C=C str.), 1245.02 (C-N str.), 1106.72 (C-F str.), 1066.85 (C-O-C str.). ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 8.20 (d, J = 8.15 Hz, 1H), 8.10 (d, J = 14.53 Hz, 1H), 7.77 (d, J = 2.70 Hz, 1H), 7.49 (d, J = 8.54 Hz, 1H), 7.15 – 7.13 (m, H), 7.10 – 7.05 (m, 2H), 5.37 (brs, 2H), 3.75 (t, J = 4.32 Hz, 4H), 3.14 – 3.12 (m, 1H), 3.07 (t, J = 4.22 Hz, 4H), 0.83 – 0.82 (m, 2H), 0.66 - 0.64 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 159.3, 155.7 – 153.3 (d, $J_{C\text{-}F}$ = 249.03 Hz, 1C), 154.0, 146.4, 142.2, 140.3 – 140.2 (d, $J_{C\text{-}F}$ = 9.76 Hz, 1C), 133.98- 133.91 (d, $J_{C\text{-}F}$ = 7.40 Hz, 1C), 128.5, 123.6, 123.0, 118.2, 114.9, 114.6 – 114.4 (d, $J_{C\text{-}F}$ = 23.19 Hz, 1C), 101.7, 66.3, 50.3, 24.1, 6.2.

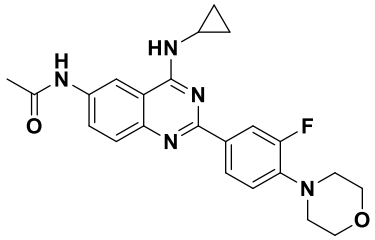
*4.2.2.3.1. Synthesis of ethyl 2-((4-(cyclopropylamino)-2-(3-fluoro-4-morpholinophenyl)quinazolin-6-yl)amino)-2-oxoacetate (**17a**):*



To the solution of N^4-cyclopropyl-2-(3-fluoro-4-morpholinophenyl)quinazoline-4,6-diamine (0.19 g, 0.50 mmol) in DCM (10 mL) were added triethyl amine (0.1 mL, 0.75 mmol), followed by ethyl 2-chloro-2-oxoacetate (0.07 mL, 0.75 mmol) at 0°C. The resultant mixture was stirred at room temperature for 2 h, quenched with sodium bicarbonate solution and extracted with DCM (3 X 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to yield crude product which was purified by column chromatography on silica gel (100−200 mesh) using MeOH/DCM as an eluent to afford the pure yellow solid (0.1 g, 41%); mp: 125-128°C; FTIR (ATR, V_{max}, cm^{-1}): 3333.80 (N-H str.), 2966.91 (Ar-H str.), 2861.88 (Ar-H str.), 1695.08 (C=O str.), 1543.68 (Ar C=C str.), 1247.24 (C-N str.), 1107.00 (C-F str.), 1048.66 (C-O-C str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 10.93 (s, 1H), 8.46 (d, J = 2.23 Hz, 1H), 8.30 – 8.26 (m, 2H), 8.18 – 8.14 (m, 1H), 7.87 (dd, J = 9.10 Hz, J = 2.15 Hz, 1H), 7.73 (d, J = 8.88 Hz, 1H), 7.12 (t, J = 8.81 Hz, 1H), 4.33 (q, J = 6.90 Hz, 2H), 3.76 (t, J = 5.00 Hz, 4H), 3.22 – 3.17 (m, 1H), 3.11 (t, J = 4.67 Hz, 4H), 1.33 (t, J = 7.35 Hz, 3H), 0.89 – 0.84 (m, 2H), 0.72 – 0.68 (m, 2H).^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 160.6, 160.5, 157.8, 155.6, 155.6 – 153.1 (d, $J_{C\text{-}F}$ = 242.77 Hz, 1C), 147.3, 141.1 – 141.0 (d, $J_{C\text{-}F}$ = 8.63 Hz, 1C), 133.7, 132.9 – 132.8 (d, $J_{C\text{-}F}$ = 7.48 Hz, 1C), 128.1, 127.6, 124.4, 118.3 – 118.2

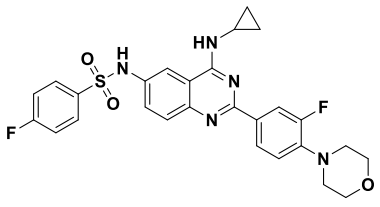
(d, J_{C-F} = 3.31 Hz, 1C), 115.2 – 114.9 (d, J_{C-F} = 22.90 Hz, 1C), 114.6, 113.5, 66.1, 62.4, 50.2, 24.3, 13.8, 6.1.

*4.2.2.3.2. Synthesis of N-(4-(cyclopropylamino)-2-(3-fluoro-4-morpholinophenyl)quinazolin-6-yl)acetamide (**17b**):*



The compound was synthesized from N^4-cyclopropyl-2-(3-fluoro-4-morpholinophenyl)quinazoline-4,6-diamine (0.15 g, 0.39 mmol) and acetyl chloride (0.04 mL, 0.59 mmol) as described in the procedure for compound **17a**. Yellow solid, yield: 31%, mp: 160-165°C; FTIR (ATR, V_{max}, cm^{-1}): 3312.75 (N-H str.), 2966.91 (Ar-H str.), 2852.03 (Ar-H str.), 1666.39 (C=O str.), 1531.44 (Ar C=C str.), 1245.58 (C-N str.), 1116.11 (C-F str.), 1045.30 (C-O-C str.); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 10.09 (s, 1H), 8.33 (s, 1H), 8.26 (d, J = 8.35 Hz, 1H), 8.20 – 8.14 (m, 2H), 7.72 – 7.68 (m, 2H), 7.11 (t, J = 9.09 Hz, 1H), 3.76 (t, J = 4.57 Hz, 4H), 3.21 – 3.16 (m, 1H), 3.10 (t, J = 4.89 Hz, 4H), 2.09 (s, 3H), 0.87 – 0.84 (m, 2H), 0.72 – 0.69 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 168.2, 160.4, 157.0, 155.1 – 153.5 (d, J_{C-F} = 242.90 Hz, 1C), 146.3, 140.9 – 140.8 (d, J_{C-F} = 7.56 Hz, 1C), 135.7, 133.09 – 133.05 (d, J_{C-F} = 8.23 Hz, 1C), 127.9, 126.7, 124.2, 118.2, 115.0 – 114.8 (d, J_{C-F} = 23.39 Hz, 1C), 113.6, 112.2, 66.0, 50.2, 24.3, 23.7, 6.7.

*4.2.2.3.3. Synthesis of N-(4-(cyclopropylamino)-2-(3-fluoro-4-morpholinophenyl)quinazolin-6-yl)-4-fluorobenzenesulfonamide (**17c**):*



To the solution of N^4-cyclopropyl-2-(3-fluoro-4-morpholinophenyl)quinazoline-4,6-diamine (0.2 g, 0.52 mmol) in DCM (10 mL) were added pyridine (0.33 mL, 4.22 mmol), followed by 4-fluorobenzenesulfonyl chloride (0.15 g, 0.79 mmol) at 0°C. The resultant mixture was stirred at room temperature for 16 h, quenched with 6N-HCl solution and extracted with DCM (3 x 20

mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to yield crude residue, which was purified by column chromatography on silica gel (100−200 mesh) using MeOH/DCM as an eluent to afford the pure yellow solid product (0.072 g, 25%); mp: 210-212°C; FTIR (ATR, V_{max}, cm^{-1}): 3414.18 (N-H str.), 3264.10 (N-H str.), 2854.40 (Ar-H str.), 1529.87 (Ar C=C str.), 1351.64 (SO_2 asym.), 1246.98 (C-N str.), 1153.53 (SO_2 sym.), 1089.19 (C-O-C str.); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 10.30 (s, 1H), 8.35 (s, 1H), 8.23 (d, J = 8.97 Hz, 1H), 8.12 (d, J = 14.97 Hz, 1H), 7.97 (s, 1H), 7.78 – 7.76 (m, 2H), 7.59 (d, J = 8.98 Hz, 1H), 7.37 – 7.34 (m, 2H), 7.26 (dd, J = 8.91 Hz, J = 1.76 Hz, 1H), 7.10 (t, J = 9.03 Hz, 1H), 3.76 (t, J = 4.70 Hz, 4H), 3.17 – 3.16 (m, 1H), 3.10 (t, J = 4.10 Hz, 4H), 0.87 – 0.85 (m, 2H), 0.71 – 0.71 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 165.1 – 163.4 (d, J_{C-F} = 253.16 Hz, 1C), 160.4, 157.8, 155.1 – 153.5 (d, J_{C-F} = 242.59 Hz, 1C), 147.5, 141.09 – 141.04 (d, J_{C-F} = 8.73 Hz, 1C), 135.7, 133.7, 132.8 – 132.7 (d, J_{C-F} = 7.31 Hz, 1C), 129.7 – 129.6 (d, J_{C-F} = 9.44 Hz, 1C), 128.6, 128.3, 124.3, 118.2, 116.4, 116.2 – 116.1 (d, J_{C-F} = 22.36 Hz, 1C), 115.0 – 114.9 (d, J_{C-F} = 25.07 Hz, 1C), 113.8, 66.0, 50.1, 24.2, 6.0.

4.3. Biology

M. tuberculosis H37Rv (ATCC 25618) was grown in Middlebrook 7H9 medium supplemented with 10% v/v oleic acid, albumin, dextrose, catalase (OADC; Becton Dickinson), 0.05% w/v Tween 80 (7H9-OADC-Tw), and 50 µg/mL hygromycin (7H9-OADC-Tw-hyg), where required. Large scale cultures were grown in 100 mL of medium in 450 cm^2 roller bottles at 37ºC and 100 rpm. *M. tuberculosis* strain CHEAM3 and DREAM8 expressing codon-optimized mCherry and DsRed from plasmids pCherry3 and pBlazeC8, respectively, were used. Assay plates containing 20 µL of 7H9-Tw-OADC medium with appropriate control compounds or test compounds were prepared in a sterile environment. 18 µL of medium was dispensed into sterile, black, 384-well, clear bottom plates (Greiner). 2 µL of control compounds, DMSO or test compounds were stamped directly into the assay plates. Controls were 100 µM rifampicin in column 1 (final assay concentration of 2 µM rifampicin), DMSO in column 2 (final assay concentration 2%) and 125 nM rifampicin in column 23 (final assay concentration of 2.5 nM). Test compounds were diluted to 0.35 mg/mL in DMSO and transferred directly into columns 3-22 of assay plates (320 compounds per plate) to yield a final assay concentration of 7 µg/mL (final concentration of 2% DMSO). *M. tuberculosis* was grown to logarithmic phase (OD590 = 0.6-0.9) and filtered through a 0.5 µm cellulose-acetate membrane filter and diluted in fresh medium to an OD of 0.06. A MultiDrop Combi (Thermo Fisher) was used to add 10 µL of M. tuberculosis culture to columns 1-23 of the assay plates; column 24 was not inoculated and used as a contamination control. Plates were incubated in sealed plastic bags in a humidified

incubator at 37 ºC for 5 days. The plate layout was arranged as 320 sample wells in columns 3-22. The remaining four columns were reserved for plate controls. OD and fluorescence were read using a Synergy 4 plate reader (BioTek) with excitation/emission of 586 nm/614 nm for mCherry and 560 nm/590 nm for DsRed. For each well, the % inhibition was calculated with reference to the average maximum growth control in column 2 (DMSO only).[28]

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CHAPTER 5

Design, synthesis and spectral characterization of *N/O*-methylated quinazoline derivatives as an antitubercular agent

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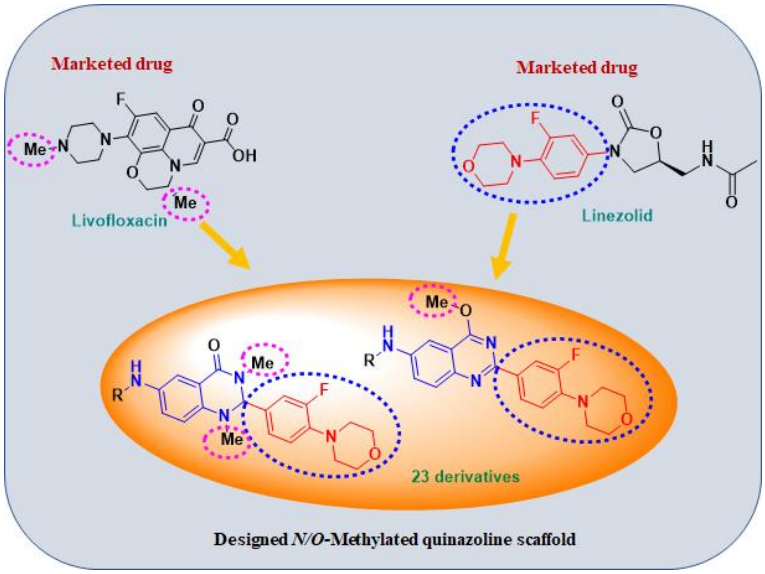
Graphical Abstract



Abstract

A novel series of *N/O*-methylated quinazoline derivatives (**10a-o, 16a-d** and **16aa-ad**) were synthesized in good to moderate yields. All synthesized compounds were well-characterized by spectroscopic studies (NMR and IR) and evaluated for preliminary *in-vitro* screening for anti-mycobacterium activity at 20 µM concentration against *Mycobacterium tuberculosis* H37Rv strain. The compounds did not show significant anti-mycobacterium activity. The only notable % zone of inhibition was observed against *Mycobacterium tuberculosis* strain H37Rv for compounds **16a** which showed 34% after 24 h incubation which can be considered for further study like MIC, MBC etc. These new compounds may serve as starting points for the designing of new series of inhibitors that prevent the growth of *Mycobacterium tuberculosis*.

Keywords

Antimycobacterial activity; *N/O*-methyl quinazoline derivatives; *mycobacterium tuberculosis* H37Rv.

1. Introduction

Methylation is significantly most prevalent in design and synthesis of biologically active molecules.[1, 2] It can be found as integral part of several commercial drugs (**Figure 1**). Wermuth precisely defines the significance of methyl group in molecular recognition as "The methyl group, so often considered as chemically inert, is able to alter deeply the pharmacological properties of a molecule".[3] Methyl group is well known for properties like London dispersion interactions, stereoelectronic effects on microtubules and biomacromolecules which intern increases the bioreceptor selectivity and potency, protects against enzyme metabolism and increases lipophilicity of the molecule.[1, 2, 4] Thus, in context of medicinal chemistry, it is considered as one of the most prevalent functionalities as to date more than 67 % of small molecule drugs contain methyl group.[5]

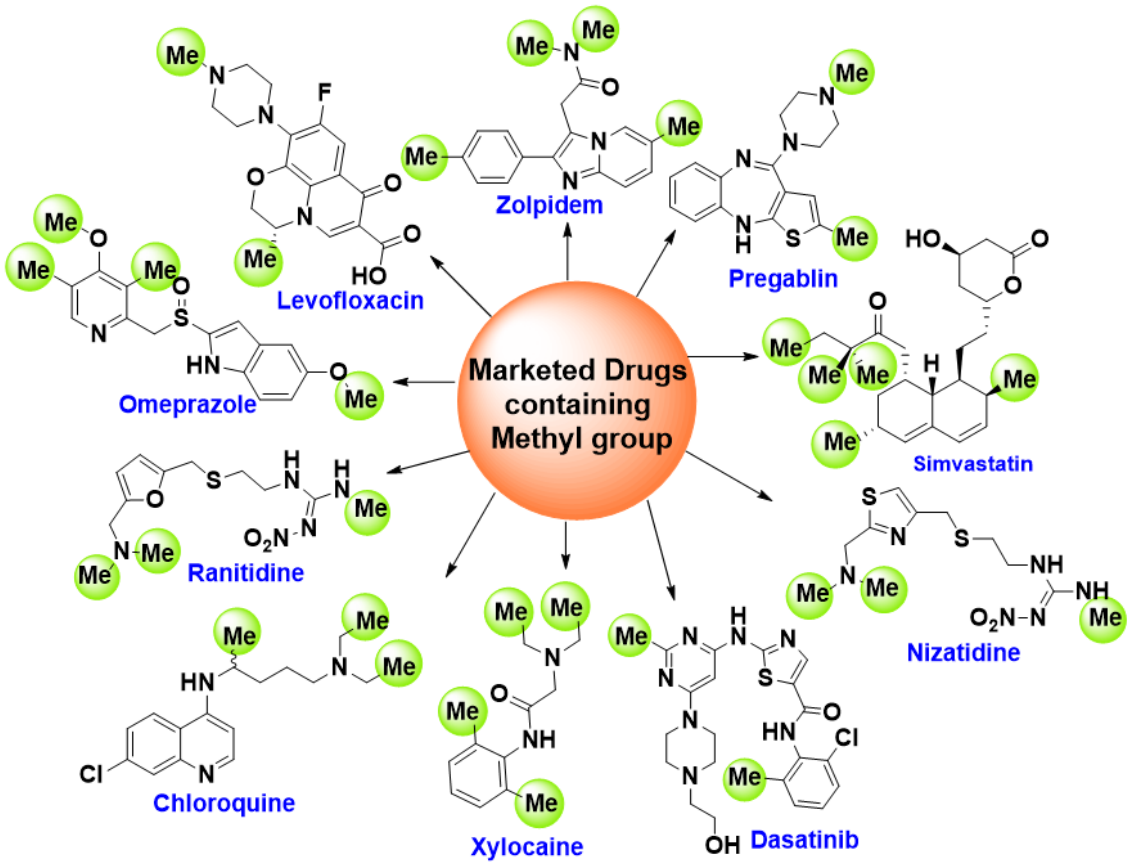


Figure 1: Drugs/Molecules containing methyl functionality.

The heterocyclic fused ring with nitrogen has drawn attention owing to their immense therapeutic potential in medicinal chemistry and drug discovery.[6] Natural products are also known to comprise of nitrogen containing heterocycles as integral part of their structure.[7] Amongst, quinazoline is well known to exist in nature.[8, 9] The first synthesis of quinazoline was

achieved successfully in 1895 by Bischler and Lang with an extension for the extensive studies in 1903 by Gabriel.[9] There are four isomeric forms of quinazoline (quinazoline, quinoxaline, cinnoline, and phthalazine) depending upon the position of nitrogen.[8, 10]

Quinazoline occurs in natural product mostly as isomeric alkaloid in root and leaves of Saxifragaceae family, mainly in *Dichroa febrifuga* (also called Chinese quinine).[11, 12] This compound was earlier known to possess anti-hypnotic and sedative action.[9] Since several decades, this class of compound has brought diverse biological importance as such as potential anticancer,[13, 14] antiviral,[15] anticonvulsant,[16] antimalarial,[17] antimicrobial,[18, 19] antidiabetic and antitubercular agents[19, 20] (**Figure 2**). This has necessitated the effort of chemists worldwide for the development of better synthetic strategies by effective methods.[21]

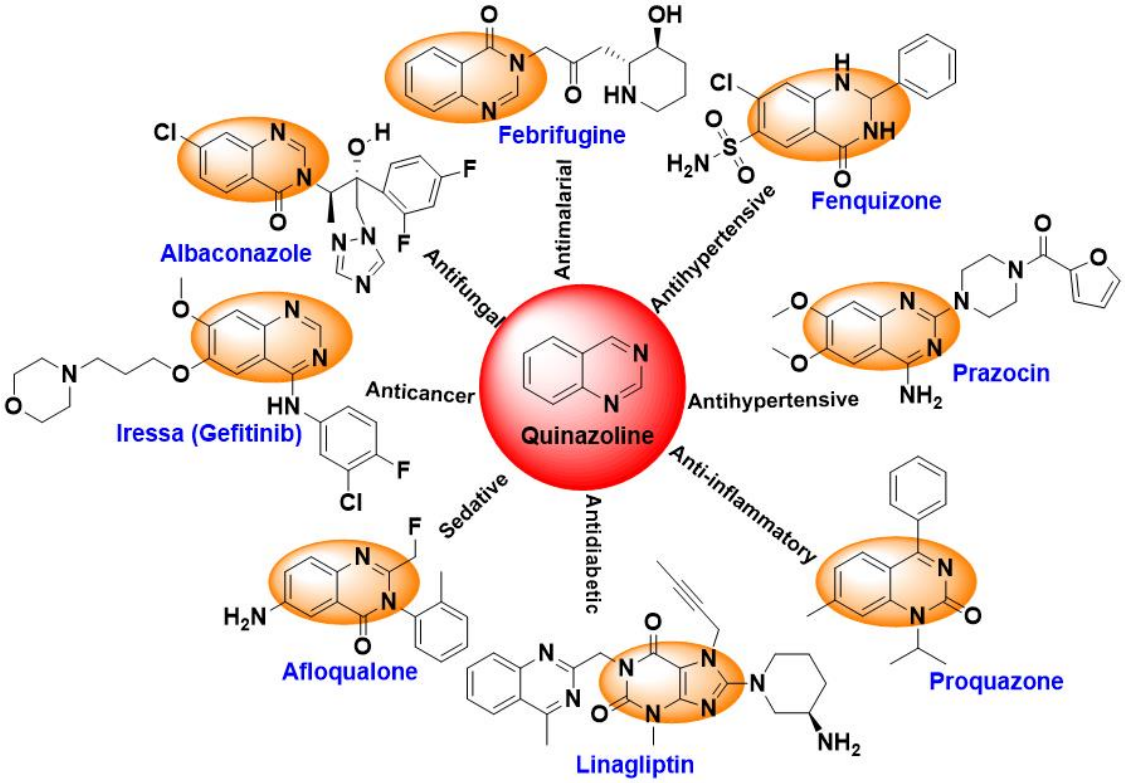


Figure 2: Quinazoline based drugs with specific activity.

Tuberculosis (TB) is one of the main lethal bacterial infection worldwide after HIV.[22] TB is caused by slow growing, acid fast bacillus *Mycobacterium tuberculosis*.[23] The active TB is currently treated with first line drugs which are unsatisfactory due to low efficacy, high toxicity, long duration of treatment and involved high cost.[24-26] In addition, its treatment has further become complicated due to emergence of drug resistance giving rise to totally drug resistant TB (TDR-TB), thus making the current drug treatment ineffective.[27, 28] This has provoked an urge for the development of new and effective therapeutic agent against TB. Quinazoline based

derivatives bearing methyl groups have been found as drugs for treatment of several ailments. Several of the marketed drugs containing quinazoline core with methyl functionality have been summed up in **Figure 3**.

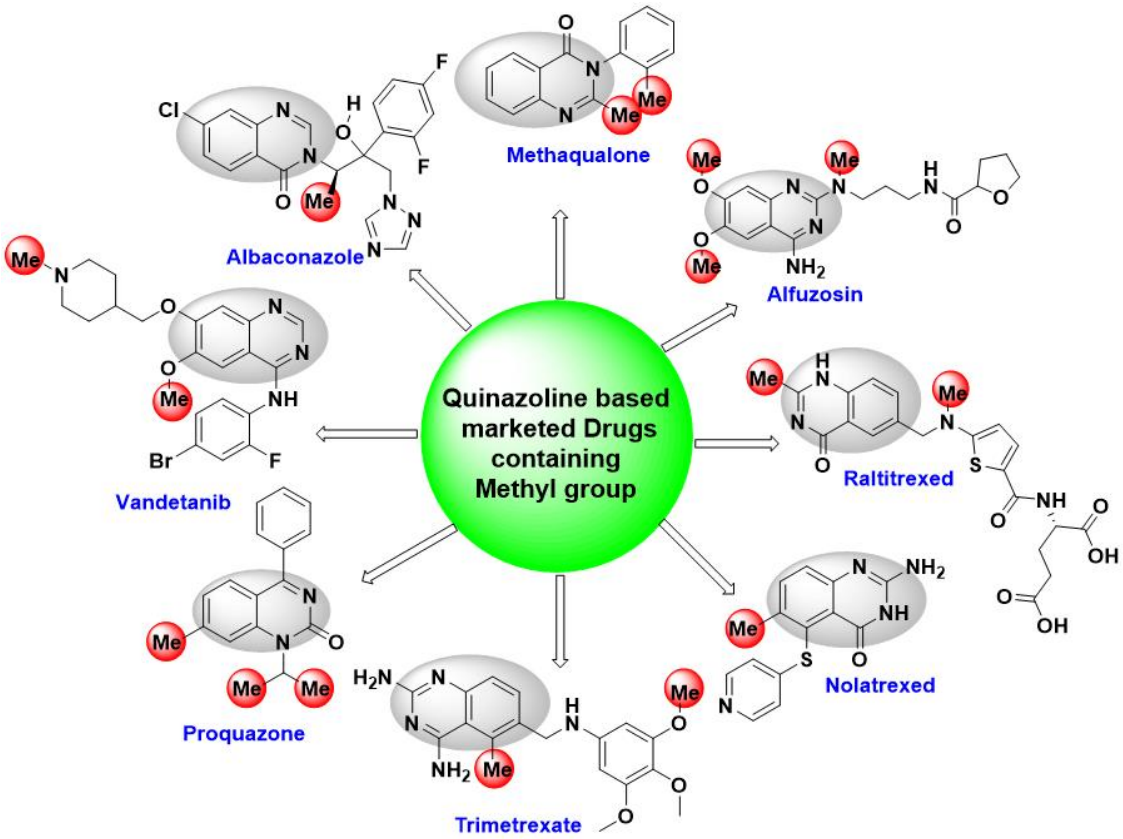


Figure 3: Quinazoline based Drugs/Molecules containing methyl functionality.

As part of the project, in this report we present the synthesis of quinazoline derivatives bearing *N*-methylation and *O*-methylation residues with complete characterization. The compounds were further evaluated for preliminary anti-TB studies.

2. Results and Discussion

2.1. Chemistry

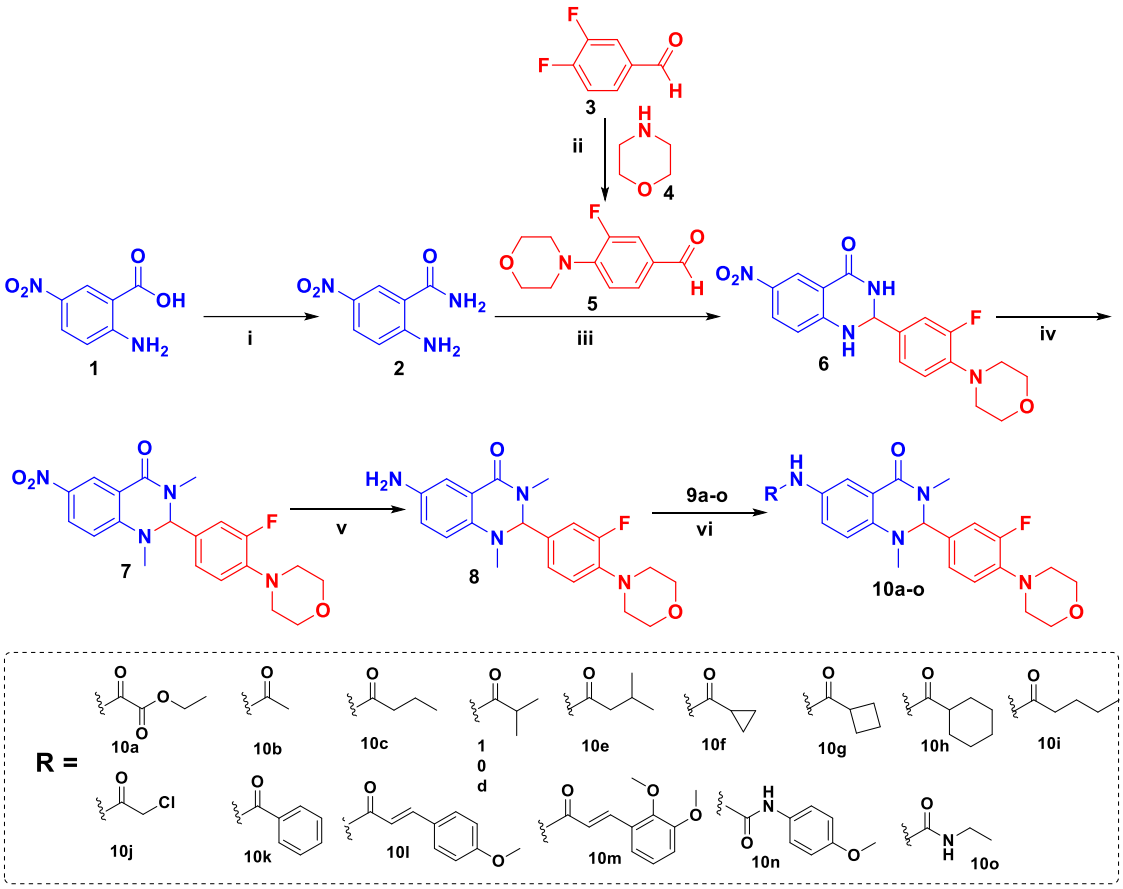
The synthesis of novel quinazoline derivatives (**10a-o, 11, 16a-d & 16aa-ad**) and their respective intermediates were achieved through effective and easy synthetic routes as depicted in Scheme 1 & 2. Intermediate **6** was synthesized as per our previous report (**Chapter 4**), which underwent methylation in presence of CH_3I/ K_2CO_3/ DMF at rt for 24 h to yield 2-(3-fluoro-4-morpholinophenyl)-1,3-dimethyl-6-nitro-2,3-dihydroquinazolin-4(1H)-one (**7**). The nitro reduction of **7** was performed in presence of Fe/NH_4Cl to afford 6-amino-2-(3-fluoro-4-

morpholinophenyl)-1,3-dimethyl-2,3-dihydroquinazolin-4(1H)-one (**8**). Afterward, a series of compounds (**10a-o**) were synthesized by reacting **8** with acid chloride/Acid/isocyanide in presence of their respective conditions illustrated in experimental section. **10a** was further subjected to hydrolysis with 2N NaOH at rt for 16 h to yield 2-((2-(3-fluoro-4-morpholinophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)amino)-2-oxoacetic acid (**11**).

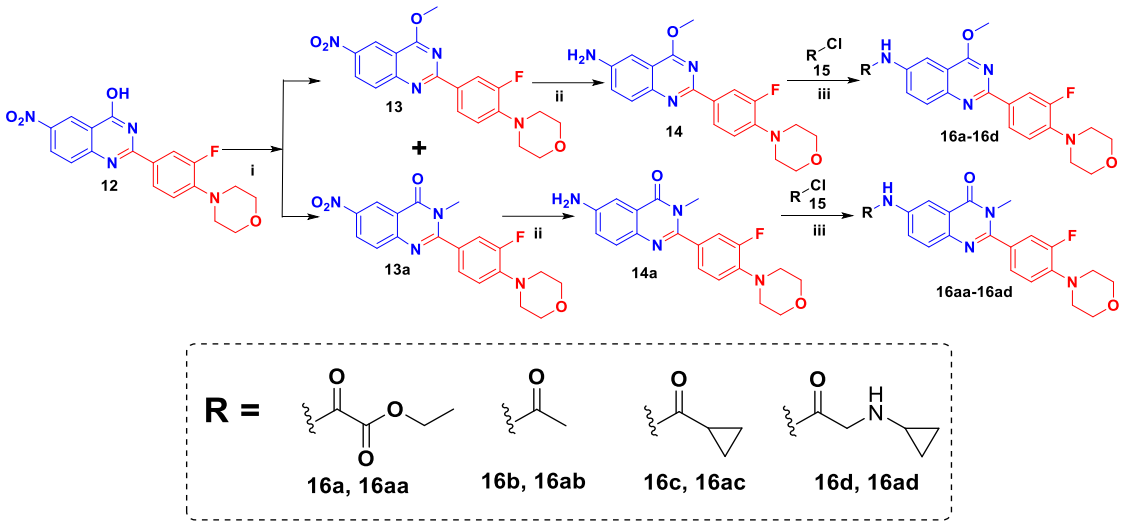
In another series, compound **12** was synthesized as per our previous report (**Chapter 4**) which was subjected to methylation in presence of CH_3I/K_2CO_3/DMF at rt for 16 h to afford mixture of regioisomers 4-(2-fluoro-4-(4-methoxy-6-nitroquinazolin-2-yl) phenyl) morpholine (**13**) and 2-(3-fluoro-4-morpholinophenyl)-3-methyl-6-nitroquinazolin-4(3H)-one (**13a**) which were separated by column chromatography. Both isomers **13** and **13a** underwent reduction with Fe/NH_4Cl to yield 2-(3-fluoro-4-morpholinophenyl)-4-methoxyquinazolin-6-amine (**14**) and 6-amino-2-(3-fluoro-4-morpholinophenyl)-3-methylquinazolin-4(3H)-one (**14a**), respectively. Each scaffold **14** & **14a** were treated with acid chloride in presence of TEA/DCM at rt for 4 h to yield a series of final derivatives (**16a-d** and **16aa-ad**).

The structure of all intermediates (**7, 8, 13, 13a, 14, 14a**) and their respective final derivatives (**10a-o**, **16a-d** and **16aa-ad**) were established by spectral (IR, ^{1}H-NMR, ^{13}C-NMR and Mass) analysis. All compounds showed the acceptable analysis of predicted structures which are summarized in experimental section. The conversion of **6** to **7** was confirmed by the appearance of two methyl proton signals at around 2.95 and 2.87 ppm and disappearance of amide and amine protons. This was further supported by ^{13}C NMR which showed two signals at around 35.44 & 31.82 assign for two methyl group. The conversion of nitro to amine (8) was confirmed by appearance of broad singlet amine ($N\underline{\mathbf{H}}_2$) proton at around 4.72 ppm in NMR spectra along with disappearance of absorption band 1315.90 cm^{-1} of nitro in IR spectra. Subsequently, derivatization of amine to the final molecules (**10a-o**) with acid chloride/ acid/ isocyanate were confirmed by the disappearance of amine ($N\underline{\mathbf{H}}_2$) proton along with appearance of most distinct amide and urea protons at around 9.59-10.68 ppm and 7.78-8.43 ppm in case of (**10a-m**) and **(10n-o**), respectively. These finding were further supported by IR and ^{13}C NMR analysis. The absorption band in the region of 1637.88-1735.49 cm^{-1} and 3225.89-3357.44 cm^{-1} in IR spectra along with signals in the range of 161.21-174.67 ppm in ^{13}C-NMR spectra of compounds (**10a-m**) indicate the presence of amide (C=O and N-H) group. While the IR spectra of **10n** and **10o** showed the absorption band in the region of 1637.44-1684.84 and 3341.01 – 3377.81 cm^{-1} accompanied with signals at around 152.80-155.33 ppm in ^{13}C NMR spectra are assign for urea (C=O and N-H) group.

In another series, conversion to **13** and **13a** from **12** was confirmed by the appearance of methoxy (O-**CH**$_3$) and methyl (N-**CH**$_3$) protons at around 4.31 and 3.60 ppm in ^{1}H NMR spectra along with carbon signals at around 54.8 and 35.0 ppm, respectively .The conversion of **13** and **14** to respective **13a** and **14a** by nitro reductions were confirm by the appearance of amine (N**H**$_2$) protons at around 5.09 ppm along with disappearance of absorption bands of nitro (NO_2) 1342.35 and 1339.08 cm^{-1} in IR spectra. Now the derivatization of **14** and **14a** to their respective derivatives **(16a-d)** and **(16aa-ad)** were confirmed by the disappearance of amine (N**H**$_2$) proton and appearance of most distinct amide proton at around 10.26-11.14 ppm. These outcomes further supported by IR and ^{13}C NMR. The presence of absorption band in the region of 1649.56-1701.67 and 3250.93-3344.55 in IR along with carbon signals at around 161.45-172.07 in ^{13}C NMR spectra indicate the presence of amide (C=O and N-H) group.



Scheme 1: *Reagents and conditions:* **i)** 28% aqueous ammonia solution, EDC.HCl, HOBt, DMF, 3–5 h; **ii)** K_2CO_3, DMF, 130°C, 16 h; **iii)** *p*TSA, MeOH, 70°C, 16 h; **iv)** CH_3I, K_2CO_3, DMF, rt, 24 h **v)** Fe, NH_4Cl, Dioxane: EtOH: H_2O (7:5:3), 100°C, 5 h; **vi)** Acid chloride, TEA, DCM, 0°C - rt, 4 h. **or** acid, HATU, DIPEA, DMF, rt, 16 h. **or** isocyanate, DIPEA, DMF, rt, 16 h.



Scheme 2: *Reagents and conditions:* **i)** CH_3I, K_2CO_3, DMF, rt, 16 h; **ii)** Fe, NH_4Cl, Dioxane: EtOH: H_2O (7:5:3), 100°C, 5 h; **iii)** TEA, DCM, 0°C - rt, 4 h.

2.2. Biology

The synthesized derivatives have been evaluated against *M. tuberculosis* (Strain H37Rv) and the results as % inhibition have been tabulated in **Table 1**.

Table 1: Compounds tested against *M. tuberculosis* strain H37Rv.

Compound (20 µM)	% Inhibition	Compound (20 µM)	% Inhibition
10a	-8	10m	2
10b	3	10n	8
10c	2	10o	4
10d	-11	11	-6
10e	-9	16a	34
10f	-6	16b	30
10g	-5	16c	28
10h	-1	16d	26
10i	-6	16aa	16
10j	17	16ab	15
10k	-6	16ac	9
10l	-1	16ad	7

Compounds of these series were preliminary tested against *M. tuberculosis* strain H37Rv with 20 µM concentration to find out percentage zone of inhibition, which are shown in **Table 1**. We used Rifampicin as a standard for this study. Compounds **16a** and **16b** showed 34 (≥ 30) percentage zone of inhibition, which will be further consider for the study like MIC, MBC etc.

3. Conclusion

In this chapter, we report synthesis, spectral studies and preliminary anti-mycobacterial screening of novel N/O methylated quinazoline derivatives against *Mycobacterium tuberculosis* H37Rv strain. Novel 23 molecules had been synthesized, well-characterized by IR, NMR (^{1}H, ^{13}C) and screened against *Mycobacterium tuberculosis* H37Rv strain. The synthesized compounds did not show significant % zone of inhibition. The only noteworthy percentage zone of inhibition was shown by compound **16a** that was 34% after 24 h incubation which can be further consider for the study like MIC, MBC etc. The development of synthesis involving library of the molecule and their assessment against *Mycobacterium tuberculosis* strain and *in-vitro* DNA gyrase enzyme inhibition assay can be of future interest.

4. Experimental

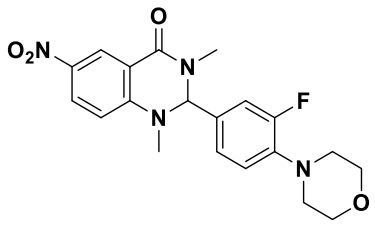
4.1. General consideration

All the fine chemicals, reagents and solvents were purchased from Sigma Aldrich and Merck and were used without further purification unless otherwise stated. The progress of the reactions and the purity of the compounds were monitored by thin-layer chromatography (TLC) on pre-coated silica gel plates procured from E. Merck and Co. (Darmstadt, Germany) visualized by UV lamp (254 or 365 nm). Purification was performed by using combi-flash (Combi*Flash*® NextGen 300+) column chromatography. The melting points of the synthesized compounds have been determined and uncorrected using a digital Stuart SMP10 melting point Apparatus. The Fourier transform infrared (FTIR) spectra were recorded in the spectral range of 400-4000 cm^{-1} on a Bruker Alpha FT-IR spectrometer using the ATR technique. The NMR spectra (**^{1}**H, and ^{13}C,) were recorded using $CDCl_3$ and DMSO-d_6 on Bruker AVANCE III 400 and 600 MHz spectrometer. Chemical shifts were determined relative to internal standard TMS at δ 0.0 parts per million (ppm) and the coupling constants were reported in Hertz. The multiplicities of the NMR resonances were abbreviated as s (singlet), d (doublet), dd (doublet of doublet), (t (triplet), q (quartet), m (multiplet) and brs (broad singlet).

4.2. Chemistry

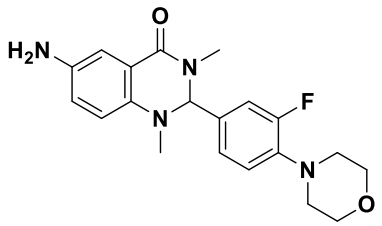
4.2.1. Synthesis and spectral characterization of compounds 7 and 8;

*4.2.1.1. Synthesis of 2-(3-fluoro-4-morpholinophenyl)-1,3-dimethyl-6-nitro-2,3-dihydroquinazolin-4(1H)-one (**7**);*



To the solution of 2-(3-fluoro-4-morpholinophenyl)-6-nitro-2,3-dihydroquinazolin-4(1H)-one (0.5 g, 1.34 mmol) in DMF (100 mL) were added potassium carbonate (0.92 g, 1.34 mmol) followed by iodomethane (0.41 mL, 6.71 mmol). The mixture was stirred for 24 h at room temperature and monitored by TLC, after consumption of starting material poured into ice cold water precipitate was formed, filtered and washed with diethyl ether to afford title compound (0.290 g, 54%); mp: 242-246°C; FTIR (ATR, V_{max}, cm^{-1}): 3084.53 (Ar str.), 2832.75 (Ar-H str.), 1654.63 (C=O str.), 1606.24 (Ar C=C str.), 1315.90 (Ar-NO_2 str.), 1288.46 (C-N str.), 1167.21 (C-F str.), 1111.39 (C-O-C str); ^{1}H NMR (400 MHz, DMSO-d_6, 70°C) δ 8.52 (d, J = 2.68 Hz, 1H), 8.18 (dd, J = 9.25 Hz, J = 2.59 Hz, 1H), 7.07 – 6.99 (m, 3H), 6.79 (d, J = 9.17 Hz, 1H), 5.94 (s, 1H), 3.68 (t, J = 4.06 Hz, 4H), 2.95 (s, 3H), 2.96 (t, J = 4.23 Hz, 4H), 2.87 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 70°C) δ 159.5, 155.6 – 153.1 (d, $J_{C\text{-}F}$ = 247.46 Hz, 1C), 150.3, 140.48 – 140.41 (d, $J_{C\text{-}F}$ = 8.0 Hz, 1C), 137.4, 130.9 – 130.8 (d, $J_{C\text{-}F}$ = 6.61 Hz, 1C), 129.3, 123.9, 122.33 – 122.30 (d, $J_{C\text{-}F}$ = 2.95 Hz, 1C), 119.5 – 119.4 (d, $J_{C\text{-}F}$ = 2.85 Hz, 1C), 114.0 – 113.8 (d, $J_{C\text{-}F}$ = 21.11 Hz, 1C), 113.5, 112.1, 77.3, 66.0, 50.1, 35.4, 31.8.

*4.2.1.2. 6-Amino-2-(3-fluoro-4-morpholinophenyl)-1,3-dimethyl-2,3-dihydroquinazolin-4(1H)-one (**8**);*



2-(3-fluoro-4-morpholinophenyl)-1,3-dimethyl-6-nitro-2,3-dihydroquinazolin-4(1H)-one (1.93 g, 4.82 mmol) was added into the mixture of dioxane (28 mL), ethanol (20 mL) and water (12

mL) followed by ammonium chloride (2.57 g, 48.20 mmol). To the resultant mixture iron powder (1.34 g, 24.10 mmol) was added with vigorous stirring and then heated at 100°C for 4 h. The reaction mixture was cool to room temperature and filtered through celite and washed with 10% MeOH/DCM. The filtrate was concentrated under reduce pressure and diluted with water then extracted with 10% MeOH/DCM (3 x 30 mL). Organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduce pressure to get solid product, which was triturated with diethyl ether to afford greenish solid product (1.08 g, 61%); mp: 180-184°C; FTIR (ATR, V_{max}, cm^{-1}): 3329.69 (N-H str.), 2860.66 (Ar-H str.), 2827.68 (Ar-H str.), 1613.08 (C=O str.), 1503.93 (Ar C=C str.), 1242.42 (C-N str.), 1111.86 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 7.08 (s, 1H), 6.95 – 6.86 (m, 3H), 6.65 (d, J = 7.02 Hz, 1H), 6.39 (d, J = 8.42 Hz, 1H), 5.54 (s, 1H), 4.72 (s, 2H), 3.68 (t, J = 4.71 Hz, 4H), 2.94 (t, J = 4.22 Hz, 4H), 2.88 (s, 3H), 2.68 (s, 3H).^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 162.0, 155.0 – 153.3 (d, $J_{C\text{-}F}$ = 246.10 Hz, 1C), 141.1, 139.56 – 139.50 (d, $J_{C\text{-}F}$ = 8.77 Hz, 1C), 137.4, 131.44 – 131.40 (d, $J_{C\text{-}F}$ = 5.03 Hz, 1C), 122.68 – 122.66 (d, $J_{C\text{-}F}$ = 2.59 Hz, 1C), 118.0, 114.5, 114.1 – 113.9 (d, $J_{C\text{-}F}$ = 21.97 Hz, 1C), 112.6, 77.8, 66.0,50.1, 36.2, 32.1.

4.2.2. General procedure for synthesis and spectral characterization of derivatives (10a-10k), (10l-10m) and (10n-10o);

4.2.2.1. General procedure A for synthesis of derivatives (10a-10k);

To the suspension of 6-amino-2-(3-fluoro-4-morpholinophenyl)-1,3-dimethyl-2,3-dihydroquinazolin-4(1H)-one (1.0 equv) in DCM were added triethyl amine (2.0 equiv), followed by appropriate acid chloride (9a-9k, equiv) at 0°C. The resultant mixture was stirred at room temperature for 2 h, quenched with sodium bicarbonate solution and extracted with DCM (3 X 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduce pressure to give solid residue which were purified by combi-flash column chromatography using EA/Hexane as an eluent to afford desired title compounds (**10a-10k**).

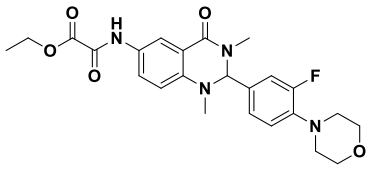
4.2.2.2. General procedure B for synthesis of derivatives (10l & 10m);

To the solution of 6-amino-2-(3-fluoro-4-morpholinophenyl)-1,3-dimethyl-2,3-dihydroquinazolin-4(1H)-one (1.0 equiv), HATU (1.5 equiv), and DIPEA (2.0 equiv) in DMF was added appropriate cinnamic acid (9l-9m, 1.5 equiv) and the solution was stirred at room temperature for 16 h then poured into ice cold water precipitate was formed, filtered and washed with diethyl ether to afford desired title compounds (**10l-10m**).

4.2.2.3 General procedure C for synthesis of derivatives (10n & 10o);

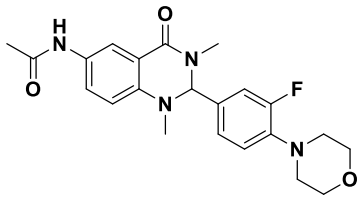
To the solution of 6-amino-2-(3-fluoro-4-morpholinophenyl)-1,3-dimethyl-2,3-dihydroquinazolin-4(1H)-one (1.0 equiv), in dry DMF were added DIPEA (1.0 equiv), followed by appropriate isocyanate (**9n-9o**, 1.2 equiv) at 0°C and the solution was stirred at room temperature for 16 h then poured into ice cold water precipitate was formed, filtered to yield crude solid which was recrystallized with ethanol to afford desired title compounds (**10n-10o**).

*4.2.2.1.1. Ethyl 2-((2-(3-fluoro-4-morpholinophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)amino)-2-oxoacetate (**10a**);*



Yellow solid, yield: 59%, mp: 182-185°C; FTIR (ATR, V_{max}, cm^{-1}): 3268.67 (N-H str.), 2972.67 (Ar-H str.), 2823.57 (Ar-H str.), 1735.49 (C=O str.), 1689.94 (C=O str.), 1539.88 (Ar C=C str.), 1241.80 (C-N str.), 1118.13 (C-F str.), 1051.52 (C-O-C str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 10.68 (s, 1H), 8.19 (d, J = 1.73 Hz, 1H), 7.71 (dd, J = 8.77 Hz, J = 1.62 Hz, 1H), 6.99 – 6.91 (m, 3H), 6.62 (d, J = 8.85 Hz, 1H), 5.72 (s, 1H), 4.29 (q, J = 6.92 Hz, 2H), 3.68 (t, J = 4.65 Hz, 4H), 2.95 (t, J = 4.23 Hz, 4H), 2.88 (s, 3H), 2.79 (s, 3H), 1.31 (t, J = 6.74 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 161.2, 160.6, 155.5 – 153.0 (d, $J_{C\text{-}F}$ = 244.56 Hz, 1C), 155.0, 143.3, 140.0 – 139.9 (d, $J_{C\text{-}F}$ = 8.29 Hz, 1C), 131.09 – 131.04 (d, $J_{C\text{-}F}$ = 5.61 Hz, 1C), 128.2, 126.5, 122.4, 119.9, 119.2, 115.5, 114.0 – 113.8 (d, $J_{C\text{-}F}$ = 21.67 Hz, 1C), 112.3, 77.3, 66.0, 62.2, 50.1, 34.9, 31.9, 13.8.

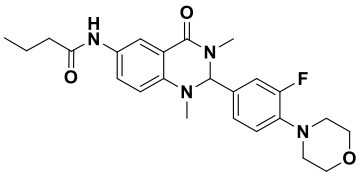
*4.2.2.1.2. N-(2-(3-Fluoro-4-morpholinophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)acetamide (**10b**);*



Yellow solid, yield: 36%, mp: 128-130°C; FTIR (ATR, V_{max}, cm^{-1}): 3292.10 (N-H str.), 2965.73 (Ar-H str.), 2861.63 (Ar-H str.), 1637.88 (C=O str.), 1616.21 (C=O str.), 1505.40 (Ar C=C str.), 1221.73 (C-N str.), 1111.61 (C-F str.), 1049.14 (C-O-C str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 9.80 (S, 1H), 7.97 (d, J = 2.18 Hz, 1H), 7.59 (dd, J = 9.06 Hz, J = 2.19 Hz, 1H), 6.98 –

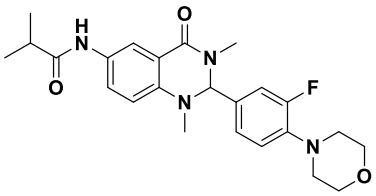
6.89 (m, 3H), 6.56 (d, *J* = 8.82 Hz, 1H), 5.67 (s, 1H), 3.68 (t, *J* = 4.66 Hz, 4H), 2.94 (t, *J* = 4.64 Hz, 4H), 2.88 (s, 3H), 2.76 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 167.7, 161.4, 155.5 – 153.0 (d, $J_{C\text{-}F}$ = 245.78 Hz, 1C), 142.1, 139.9 – 139.8 (d, $J_{C\text{-}F}$ = 8.24 Hz, 1C), 131.1 – 131.0 (d, $J_{C\text{-}F}$ = 5.75 Hz, 1C), 130.4, 125.2, 122.53 – 122.50 (d, $J_{C\text{-}F}$ = 2.66 Hz, 1C), 119.13 – 119.10 (d, $J_{C\text{-}F}$ = 4.85 Hz, 1C), 118.4, 115.8, 114.0 – 113.8 (d, $J_{C\text{-}F}$ = 20.50 Hz, 1C), 112.4, 77.4, 67.0, 50.1, 35.0, 31.9, 23.7.

*4.2.2.1.3. N-(2-(3-Fluoro-4-morpholinophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)butyramide (**10c**);*



Yellow solid, yield: 33%, mp: 125-128°C; FTIR (ATR, V_{max}, cm^{-1}): 3317.05 (N-H str.), 2964.99 (Ar-H str.), 2844.05 (Ar-H str.), 1638.11 (C=O str.), 1615.59 (C=O str.), 1507.37 (Ar C=C str.), 1240.77 (C-N str.), 1113.56 (C-F str.), 1049.84 (C-O-C str.); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 9.68 (s, 1H), 7.98 (s, 1H), 7.61 (d, *J* = 7.92 Hz, 1H), 6.97 – 6.91 (m, 3H), 6.56 (d, *J* = 8.66 Hz, 1H), 5.66 (s, 1H), 3.68 (t, *J* = 4.30, 4H), 2.95 (t, *J* = 4.26 Hz, 4H), 2.88 (s, 3H), 2.77 (s, 3H), 2.23 (t, *J* = 7.33 Hz, 2H), 1.62 – 1.58 (m, 2H), 0.91 (t, *J* = 7.90 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 170.5, 161.4, 155.0 – 153.4 (d, $J_{C\text{-}F}$ = 245.45 Hz, 1C), 142.1, 139.88 – 139.83 (d, $J_{C\text{-}F}$ = 8.19 Hz, 1C), 131.1 – 131.0 (d, $J_{C\text{-}F}$ = 5.32 Hz, 1C), 130.3, 125.2, 122.48 – 122.47 (d, $J_{C\text{-}F}$ = 2.71 Hz, 1C), 119.08 – 119.06 (d, $J_{C\text{-}F}$ = 2.62 Hz, 1C), 118.6, 115.8, 113.9 – 113.8 (d, $J_{C\text{-}F}$ = 21.22 Hz, 1C), 112.3, 77.4, 66.0, 50.1, 38.1, 35.0, 31.9, 18.5, 13.5.

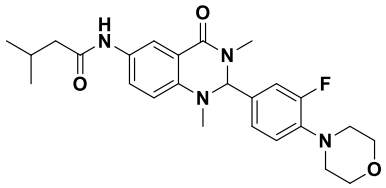
*4.2.2.1.4. N-(2-(3-Fluoro-4-morpholinophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)isobutyramide (**10d**);*



Yellow solid, yield: 52%, mp: 212-214°C; FTIR (ATR, V_{max}, cm^{-1}): 3290.53 (N-H str.), 2965.29 (Ar-H str.), 2825.54 (Ar-H str.), 1678.71 (C=O str.), 1637.45 (C=O str.), 1509.35 (Ar C=C str.), 1239.18 (C-N str.), 1117.16 (C-F str.), 1050.80 (C-O-C str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 9.68 (s, 1H), 7.99 (d, *J* = 2.50 Hz, 1H), 7.62 (dd, *J* = 8.79 Hz, *J* = 2.67 Hz, 1H), 6.98 – 6.89 (m, 3H), 6.56 (d, *J* = 8.64 Hz, 1H), 5.68 (s, 1H), 3.68 (t, *J* = 4.71 Hz, 4H), 2.95 (t, *J* = 5.04

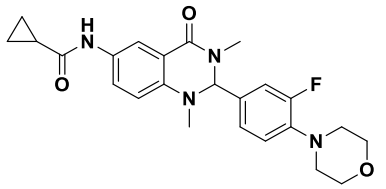
Hz, 4H), 2.88 (s, 3H), 2.76 (s, 3H), 2.56 – 2.53 (m, 1H), 1.08 (d, J = 6.68 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 174.6, 161.4, 155.5 – 153.0 (d, $J_{C\text{-}F}$ = 248.42 Hz, 1C), 142.1, 139.9 – 139.8 (d, $J_{C\text{-}F}$ = 8.57 Hz, 1C), 131.09 – 131.04 (d, $J_{C\text{-}F}$ = 5.93 Hz, 1C), 130.4, 125.3, 122.4, 119.1, 118.7, 115.8, 114.0 – 113.8 (d, $J_{C\text{-}F}$ = 22 Hz, 1C), 112.4, 77.4, 66.0, 50.1, 35.0, 32.0, 19.5.

*4.2.2.1.5. N-(2-(3-Fluoro-4-morpholinophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-3-methylbutanamide (**10e**);*



Yellow solid, yield: 61%, mp: 134-136°C; FTIR (ATR, V_{max}, cm^{-1}): 3325.89 (N-H str.), 2952.32 (Ar-H str.), 2866.13 (Ar-H str.), 1638.98 (C=O str.), 1615.05 (C=O str.), 1541.64 (Ar C=C str.), 1241.67 (C-N str.), 1115.38 (C-F str.), 1051.34 (C-O-C str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 9.72 (s, 1H), 7.98 (d, J = 2.48 Hz, 1H), 7.60 (dd, J = 8.96 Hz, J = 2.24 Hz, 1H), 6.99 – 6.89 (m, 3H), 6.56 (d, J = 8.91 H, 1H), 5.68 (s, 1H), 3.68 (t, J = 4.16 Hz, 4H), 2.95 (t, J = 4.41 Hz, 4H), 2.88 (s, 3H), 2.76 (s, 3H), 2.11 (d, J = 6.91 Hz, 2H), 2.09 – 1.98 (m, 1H), 0.92 (d, J = 6.57 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 170.1, 161.4, 155.5 – 153.0 (d, $J_{C\text{-}F}$ = 254.32 Hz, 1C), 142.2, 139.9 – 139.8 (d, $J_{C\text{-}F}$ = 8.05 Hz, 1C), 131.1 – 131.0 (d, $J_{C\text{-}F}$ = 6.02 Hz, 1C), 130.3, 125.3, 122.5, 119.14 – 119.11 (d, $J_{C\text{-}F}$ = 3.06 Hz, 1C), 118.6, 115.8, 114.0 – 113.8 (d, $J_{C\text{-}F}$ = 21.69 Hz, 1C), 112.4, 77.4, 66.0, 50.2, 45.5, 35.0, 32.0, 25.6, 22.3.

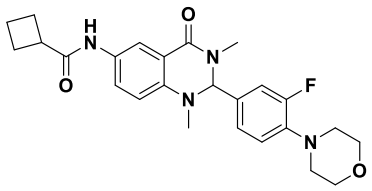
*4.2.2.1.6. N-(2-(3-Fluoro-4-morpholinophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)cyclopropanecarboxamide (**10f**);*



Yellow solid, yield: 55%, mp: 150-153°C; FTIR (ATR, V_{max}, cm^{-1}): 3310.53 (N-H str.), 2953.18 (Ar-H str.), 2854.68 (Ar-H str.), 1666.00 (C=O str.), 1638.88 (C=O str.), 1509.36 (Ar C=C str.), 1241.77 (C-N str.), 1114.26 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 10.05 (s, 1H), 7.99 (s, 1H), 7.61 (d, J = 7.06 Hz, 1H), 6.94 – 6.91 (m, 3H), 6.55 (d, J = 7.99 Hz, 1H), 5.67 (s, 1H), 3.68 (t, J = 5.03 Hz, 4H), 2.94 (t, J = 5.07 Hz, 4H), 2.88 (s, 3H), 2.76 (s, 3H), 1.67 – 1.66 (m, 1H), 0.84 – 0.68 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 171.0, 161.4, 155.5 –

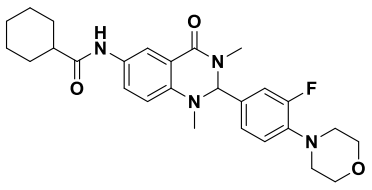
153.0 (d, $J_{C\text{-}F}$ = 246.33 Hz, 1C), 142.1, 139.9 – 139.8 (d, $J_{C\text{-}F}$ = 8.16 Hz, 1C), 131.09 – 131.04 (d, $J_{C\text{-}F}$ = 5.61 Hz, 1C), 130.5, 125.1, 122.5, 119.1, 118.4, 115.8, 114.0 – 113.8 (d, $J_{C\text{-}F}$ = 21.18 Hz, 1C), 112.4, 77.4, 66.0, 50.1, 35.0, 31.9, 14.3, 6.8.

*4.2.2.1.7. N-(2-(3-Fluoro-4-morpholinophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)cyclobutanecarboxamide (**10g**);*



Yellow solid, yield: 41%, mp: 110-112°C; FTIR (ATR, V_{max}, cm^{-1}): 3271.20 (N-H str.), 2941.81 (Ar-H str.), 2854.40 (Ar-H str.), 1638.91 (C=O str.), 1616.93 (C=O str.), 1508.28 (Ar C=C str.), 1241.46 (C-N str.), 1114.31 (C-F str.), 918.02 (C-O-C str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 9.59 (s,1H), 7.99 (d, J = 2.36 Hz, 1H), 7.63 (dd, J = 8.72 Hz, J = 2.69 Hz, 1H), 6.98 - 6.89 (m, 3H), 6.55 (d, J = 8.83 Hz, 1H), 5.68 (s, 1H), 3.68 (t, J = 4.29 Hz, 4H), 3.20 – 3.12 (m, 1H), 2.95 (t, J = 4.87 Hz, 4H), 2.88 (s, 3H), 2.76 (s, 3H), 2.25 – 2.16 (m, 2H), 2.11 – 2.04 (m, 2H), 1.97 – 1.86 (m, 1H), 1.82 – 1.75 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 172.3, 161.4, 155.5 – 153.0 (d, $J_{C\text{-}F}$ = 245.67 Hz, 1C), 142.1, 139.9 – 139.8 (d, $J_{C\text{-}F}$ = 8.03 Hz, 1C), 131.09 – 131.03 (d, $J_{C\text{-}F}$ = 5.73 Hz, 1C), 130.4, 125.3, 122.53 – 122.50 (d, $J_{C\text{-}F}$ = 2.97 Hz, 1C), 119.09 – 119. 06 (d, $J_{C\text{-}F}$ = 4.25 Hz, 1C), 118.6, 115.8, 114.0 – 113.8 (d, $J_{C\text{-}F}$ = 21. 35 Hz, 1C), 112.4, 77.4, 66.0, 50.1, 39.4, 34.9, 31.9, 24.6, 17.7.

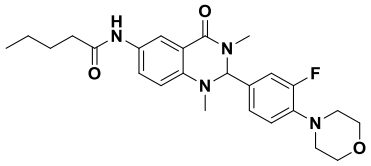
*4.2.2.1.8. N-(2-(3-Fluoro-4-morpholinophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)cyclohexanecarboxamide (**10h**);*



Yellow solid, yield: 34%, mp: 135-140°C; FTIR (ATR, V_{max}, cm^{-1}): 3296.53 (N-H str.), 2924.74 (Ar-H str.), 2852.37 (Ar-H str.), 1639.13 (C=O str.), 1616.61 (C=O str.), 1508.73 (Ar C=C str.), 1241.15 (C-N str.), 1114.65 (C-F str.), 1047.52 (C-O-C str.); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 9.64 (s, 1H), 8.01 (d, J = 2.22 Hz, 1H), 7.61 (dd, J = 8.99 Hz, J = 2.72 Hz, 1H), 6.97 – 6.89 (m, 3H), 6.55 (d , J = 8.97 Hz, 1H), 5.67 (s, 1H), 3.68 (t, J = 3.93 Hz, 4H), 2.95 (t, J = 4.35 Hz, 4H), 2.88 (s, 3H), 2.76 (s, 3H), 2.28 – 2.24 (m, 1H), 1.78 – 1.73 (m, 4 H), 1.64 – 1.62 (m, 1H), 1.43 – 1.37 (m, 2H), 129 – 1.14 (m, 3H). 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ

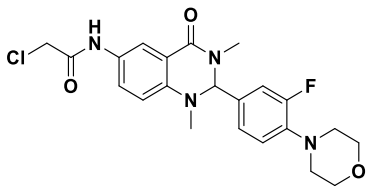
173.7, 161.4, 155.0 – 153.4 (d, J_{C-F} = 244.84 Hz, 1C), 142.0, 139.8 -139.7 (d, J_{C-F} = 8.16 Hz, 1C), 131.09 – 131.05 (d, J_{C-F} = 6.53 Hz, 1C), 130.5, 125.2,122.46 – 122.44 (d, J_{C-F} = 2.46 Hz, 1C), 119.0, 118.6, 115.8, 113.9 – 113.8 (d, J_{C-F} = 21.41 Hz, 1C), 112.3, 77.4, 66.0, 50.1, 44.7, 34.9, 31.9, 29.1, 25.3, 25.2.

*4.2.2.1.9. N-(2-(3-Fluoro-4-morpholinophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)pentanamide (**10i**);*



Yellow solid, yield: 33%, mp: 160-165°C; FTIR (ATR, V_{max}, cm^{-1}): 3335.00 (N-H str.), 2958.21 (Ar-H str.), 2852.94 (Ar-H str.), 1671.25 (C=O str.), 1636.16 (C=O str.), 1509.17 (Ar C=C str.), 1240.23 (C-N str.), 1117.32(C-F str.), 943.28 (C-O-C str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 9.73 (s, 1H), 7.98 (s, 1H), 7.61 (s, 1H), 6.94 – 6.91 (m, 3H), 6.56 (s, 1H), 5.67 (s, 1H), 3.68 (t, J = 4.65 Hz, 4H), 2.95 (t, J = 4.41 Hz, 4H), 2.88 (s, 1H), 2.76 (s, 3H), 2.23 (t, J = 4.57 Hz, 2H), 1.63 – 1.48 (m, 2H), 1.38 – 1.21 (m, 2H), 0.89 (t, J = 7.28 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 170.7, 161.4, 155.4 – 153.0 (d, J_{C-F} = 245.83 Hz, 1C), 142.1, 139.9 – 139.8 (d, J_{C-F} = 8.76 Hz, 1C), 131.09 – 131.04 (d, J_{C-F} = 5.79 Hz, 1C), 130.4, 125.2, 122.4, 119.1, 118.5, 115.8, 114.0 – 113.8 (d, J_{C-F} = 21.53 Hz, 1C), 112.4, 77.4, 66.0, 50.1, 35.9, 34.9, 31.9, 27.3, 21.8, 13.7.

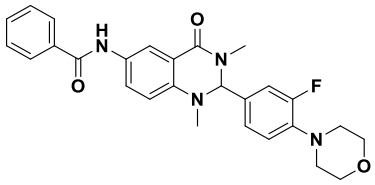
*4.2.2.1.10. 2-Chloro-N-(2-(3-fluoro-4-morpholinophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)acetamide (**10j**);*



Yellow solid, yield: 42%, mp: 175-179°C; FTIR (ATR, V_{max}, cm^{-1}): 3357.44 (N-H str.), 2969.10 (Ar-H str.), 2848.67 (Ar-H str.), 1684.34 (C=O str.), 1637.28 (C=O str.), 1516.55 (Ar C=C str.), 1237.73 (C-N str.), 1117.70 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 10.20 (s, 1H), 8.00 (s, 1H), 7.60 (d, J = 7.27 Hz, 1H), 6.98 – 6.90 (m, 3H), 6.60 (d, J = 9.17 Hz, 1H), 5.70 (s, 1H), 4.20 (s, 2H), 3.68 (t, J = 4.29 Hz, 4H), 2.95 (t, J = 4.51 Hz, 4H), 2.88 (s, 3H), 2.78 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 164.1, 161.2, 155.5 – 153.0 (d, J_{C-F} = 245.77 Hz, 1C), 142.7, 139.9 – 139.8 (d, J_{C-F} = 7.61 Hz, 1C), 131.06 – 131.00 (d, J_{C-F} = 6.08

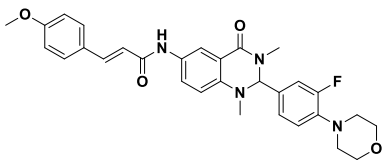
Hz, 1C), 129.3, 125.4, 122.47 – 122.45 (d, $J_{C\text{-}F}$ = 3.76 Hz, 1C), 119.17 – 119.14 (d, $J_{C\text{-}F}$ = 2.99 Hz, 1C), 118.8, 115.7, 114.0 – 113.8 (d, $J_{C\text{-}F}$ = 21.52 Hz, 1C), 112.5, 77.4, 66.0, 50.1, 43.4, 34.9, 31.9.

*4.2.2.1.11. N-(2-(3-Fluoro-4-morpholinophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)benzamide (**10k**);*



Yellow solid, yield: 44%, mp: 230-235°C; FTIR (ATR, V_{max}, cm^{-1}): 3271.33 (N-H str.), 2963.52 (Ar-H str.), 2823.78 (Ar-H str.), 1663.03 (C=O str.), 1637.11 (C=O str.), 1254.29 (C-N str.), 1117.61 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 10.16 (s, 1H), 8.19 (s, 1H), 7.96 (d, J = 7.10 Hz, 2H), 7.82 (d, J = 7.74 Hz, 1H), 7.57 – 7.51 (m, 3H), 6.97 – 6.95 (m, 3H), 6.63 (d, J = 8.38 Hz, 1H), 5.71 (s, 1H), 3.68 (t, J = 4.66 Hz, 4H), 2.95 (t, J = 3.99 Hz, 4H), 2.90 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 164.9, 161.4, 155.5 – 153.0 (d, $J_{C\text{-}F}$ = 246.26 Hz, 1C), 142.6, 139.9 – 139.8 (d, $J_{C\text{-}F}$ = 8.22 Hz, 1C), 134.8, 131.3, 131.1 – 131.0 (d, $J_{C\text{-}F}$ = 5.12 Hz, 1C), 130.0, 128.3, 127.5, 126.5, 122.5, 119.9, 119.16 – 119.13 (d, $J_{C\text{-}F}$ = 4.03 Hz, 1C), 115.7, 114.0 – 113.8 (d, $J_{C\text{-}F}$ = 21.48 Hz, 1C), 112.3, 77.4, 66.0, 50.1, 35.0, 32.0.

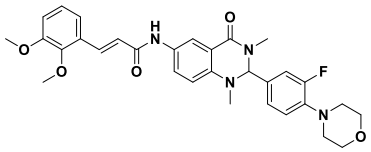
*4.2.2.2.1. (E)-N-(2-(3-Fluoro-4-morpholinophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-3-(4-methoxyphenyl)acrylamide (**10l**);*



Green solid, yield: 55%, mp: 135-140°C; FTIR (ATR, V_{max}, cm^{-1}): 3285.27 (N-H str.), 2955.21 (Ar-H str.), 2833.57 (Ar-H str.), 1639.61 (C=O str.), 1600.19 (C=O str.), 1508.51 (Ar C=C str.), 1241.62 (C-N str.), 1112.67 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 10.03 (s, 1H), 8.09 (d, J = 2.93 Hz, 1H), 7.74 (dd, J = 8.65 Hz, J = 2.44 Hz, 1H), 7.56 (d, J = 8.93 Hz, 2H), 7.50 (d, J = 15.78 Hz, 1H), 7.01 – 6.91 (m, 5H), 3.79 (s, 3H), 3.68 (t, J = 4.39 Hz, 4H), 2.95 (t, J = 4.85 Hz, 4H), 2.89 (s, 3H), 2.78 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 163.4, 161.4, 160.5, 155.5 – 153.0 (d, $J_{C\text{-}F}$ = 241.50 Hz, 1C), 142.3, 139.9 – 139.8 (d, $J_{C\text{-}F}$ = 7.75 Hz, 1C), 139.3, 131.1 – 131.0 (d, $J_{C\text{-}F}$ = 5.49 Hz, 1C), 130.5, 129.3, 127.3, 125.2, 122.5, 119.7,

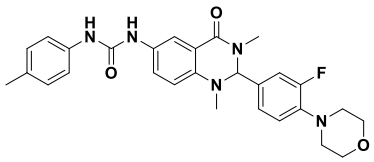
119.1, 118.5, 115.9, 114.4, 114.0 – 113.8 (d, $J_{C\text{-}F}$ = 22.33Hz, 1C), 112.5, 77.4, 66.0, 55.2, 50.2, 35.0, 32.0.

*4.2.2.2.2. (E)-3-(2,3-Dimethoxyphenyl)-N-(2-(3-fluoro-4-morpholinophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)acrylamide (**10m**);*



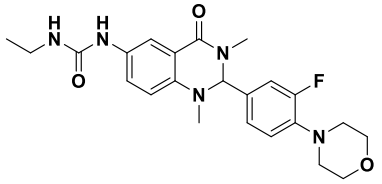
Green solid, yield: 63%, mp: 140-145°C; FTIR (ATR, V_{max}, cm^{-1}): 3340.83 (N-H str.), 2828.03 (Ar-H str.), 1639.51 (C=O str.), 1613.31 (C=O str.), 1504.26 (Ar C=C str.), 1264.21 (C-N str.), 1117.46 (C-F str.), 1067.07 (C-O-C str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 10.14 (s, 1H), 8.11 (s, 1H), 7.78 (s, 1H), 7.74 (d, J = 16.37 Hz, 1H), 7.19 – 7.10 (m, 3H), 6.97 – 6.93 (m, 3H), 6.81 (d, J = 16.52 Hz, 1H), 6.62 (d, J = 8.77 Hz, 1H), 5.70 (s, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.68 (t, J = 4.30 Hz, 4H), 2.95 (t, J = 4.43 Hz, 4H), 2.89 (s, 3H), 2.79 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 2°C) δ 163.2, 161.4, 155.5 – 153.0 (d, $J_{C\text{-}F}$ = 246.05 Hz, 1C), 152.9, 147.5, 142.4, 139.9, 134.1, 131.1 – 131.0 (d, $J_{C\text{-}F}$ = 5.65 Hz, 1C), 130.3, 128.3, 125.2, 124.4, 123.5, 122.5, 119.1, 118.7, 118.5, 115.8, 114.0 – 113.8 (d, $J_{C\text{-}F}$ = 21.34 Hz, 1C), 114.0, 112.5, 77.4, 66.0, 60.6, 55.7, 50.1, 34.9, 32.0.

*4.2.2.3.1. 1-(2-(3-Fluoro-4-morpholinophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-3-(p-tolyl)urea (**10n**);*



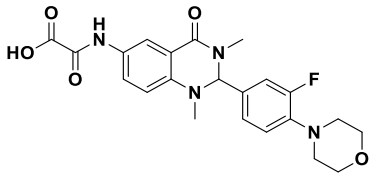
Light pink solid, yield: 38%, mp: 132-137°C; FTIR (ATR, V_{max}, cm^{-1}): 3377.81 (N-H str.), 2839.33 (Ar-H str.), 1684.84 (C=O str.), 1630.31 (C=O str.), 1513.25 (Ar C=C str.), 1240.47 (C-N str.), 1114.18 (C-F str.); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 8.43 (s, 1H), 8.41 (s, 1H), 7.86 (d, J = 8.43 Hz, 2H), 7.06 (d, J = 8.13 Hz, 2H), 6.97 – 6.91 (m, 3H), 6.56 (d, J = 8.81 Hz, 1H), 5.67 (s, 1H), 3.68 (t, J = 4.57 Hz, 4H), 2.95 (t, J = 4.21 Hz, 4H), 2.89 (s, 3H), 2.77 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 161.5, 155.0 – 153.4 (d, $J_{C\text{-}F}$ = 247.69 Hz, 1C), 152.8, 141.5, 139.87 – 139.82 (d, J = 7.67 Hz, 1C), 137.2, 131.14 – 131.11 (d, $J_{C\text{-}F}$ = 5.61 Hz, 1C), 130.8, 130.4, 129.0, 124.8, 122.56 – 120.54 (d, $J_{C\text{-}F}$ = 3.32 Hz, 1C), 119.07 – 119.05 (d, $J_{C\text{-}F}$ = 3.20 Hz, 1C), 118.2, 118.0, 116.2, 114.0 – 113.8 (d, $J_{C\text{-}F}$ = 21.21 Hz, 1C), 112.7, 77.5, 66.1, 50.1, 35.1, 32.0, 20.2.

*4.2.2.3.2. 1-Ethyl-3-(2-(3-fluoro-4-morpholinophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea (**10o**);*



Green solid, yield: 42%, mp: 155-160°C; FTIR (ATR, V_{max}, cm^{-1}): 3341.01 (N-H str.), 2965.13 (Ar-H str.), 1637.44 (C=O str.), 1613.00 (C=O str.), 1505.40 (Ar C=C str.), 1240.37 (C-N str.), 1113.63 (C-F str.); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 8.23 (s, 1H), 7.78 (d, J = 2.21 Hz, 1H), 7.40 (dd, J = 8.78 Hz, J = 2.16 Hz, 1H), 6.96 – 6.89 (m, 3H), 6.51 (d, J = 8.69 Hz, 1H), 5.95 (t, J = 5.55 Hz, 1H), 5.64 (s, 1H), 3.68 (t, J = 4.51 Hz, 4H), 3.11 – 3.06 (m, 2H), 2.95 (t, J = 4.32 Hz, 4H), 2.88 (s, 3H), 2.74 (s, 3H), 1.04 (t, J = 7.38 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 161.5, 155.3, 155.0 – 153.4 (d, $J_{C\text{-}F}$ = 246.42 Hz, 1C), 140.9, 139.79 – 139.74 (d, $J_{C\text{-}F}$ = 8.05 Hz, 1C), 131.8, 131.1 – 131.0 (d, $J_{C\text{-}F}$ = 5.02 Hz, 1C), 124.3, 122.54 – 122.52 (d, $J_{C\text{-}F}$ = 2.66 Hz, 1C), 119.0 – 118.9 (d, $J_{C\text{-}F}$ = 2.63 Hz, 1C), 117.4, 116.2, 114.0 – 113.8 (d, $J_{C\text{-}F}$ = 21.17 Hz, 1C), 112.7, 77.5, 66.0, 50.1, 35.1, 33.9, 31.9, 15.4.

*4.2.2.1.1.1. Synthesis of 2-((2-(3-fluoro-4-morpholinophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)amino)-2-oxoacetic acid (**11**);*

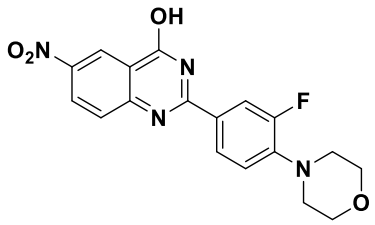


To the suspension of ethyl 2-((2-(3-fluoro-4-morpholinophenyl)-1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)amino)-2-oxoacetate (0.2 g, 0.425 mmol) in ethanol was added 2N-NaOH (0.034 g, 0.85 mmol). The resultant mixture was stirred at room temperature for 16 h, diluted with water and washed with ethyl acetate. The aqueous layer was acidified with 6N-HCl, precipitate was formed, filtered and washed with diethyl ether to afford yellow solid product (0.145 g, 77%). mp 143-145°C; FTIR (ATR, V_{max}, cm^{-1}): 3296.46 (N-H str.), 2954.69 (Ar-H str.), 2827.00 (Ar-H str.), 1685.98 (C=O str.), 1637.87 (C=O str.), 1506.53 (Ar C=C str.), 1240.55 (C-N str.), 1110.68 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 10.62 (s, 1H), 8.24 (s, 1H), 7.71 (d, J = 8.04 Hz, 1H), 6.96 – 6.92 (m, 3H), 6.61 (d, J = 6.60 Hz, 1H), 5.71 (s, 1H), 3.68 (t, J = 4.03 Hz, 4H), 2.95 (t, J = 4.27 Hz, 4H), 2.88 (s, 3H), 2.71 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) 162.1, 161.2, 156.3, 155.5 – 150.0 (d, $J_{C\text{-}F}$ = 244 Hz, 1C), 143.2, 140.0 – 139.9, (d, $J_{C\text{-}F}$ = 8.54 Hz, 1C), 131.1 – 131.0 (d, $J_{C\text{-}F}$ = 5.39 Hz, 1C), 128.5, 126.4,

122.4, 119.8, 119.2, 115.5, 114. 0 – 113.8 (d, $J_{C\text{-}F}$ = 22.10 Hz, 1C), 112.3, 77.4, 60.0, 50.1, 34.9, 31.9.

4.2.3. Synthesis and spectral characterization of compounds 12, 13, 13a, 14 and 14a;

*4.2.3.1. Synthesis of 2-(3-fluoro-4-morpholinophenyl)-6-nitroquinazolin-4-ol (**12**);*



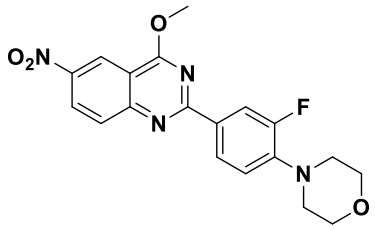
To the solution of 2-(3-fluoro-4-morpholinophenyl)-6-nitro-2,3-dihydroquinazolin-4(1H)-one (25 g, 67.3 mmol) in DMSO (100 mL) was added potassium permanganate (31.82 g, 201.41 mmol). The mixture was heated at 120°C for 24 h and monitored by TLC after consumption of starting material cooled to room temperature and filtered through celite. The filtrate was poured into ice cold water and stirred for 30 min precipitate was formed, filtered and washed with diethyl ether to afford title compound (21 g, 84%); mp: 295-297°C; FTIR (ATR, V_{max}, cm^{-1}): 3703.90 (O-H str.), 2972.62 (Ar-H str.), 2865 (Ar-H str.), 1675.24 (C=O str.), 1613.70 (Ar C=C str.), 1338.04 (Ar-NO_2 str.), 1242.16 (C-N str.), 1116.63 (C-F str), 1055.57 (C-O-C str); ^{1}H NMR (600 MHz, DMSO-d_6, 70°C) δ 12.56 (brs, 1H), 8.77 (d, J = 2.05 Hz,1H), 8.46 (dd, J = 8.88 Hz, J = 2.13 Hz, 1H), 8.04 – 7.99 (m, 2H), 7.79 (d, J = 8.92 Hz, 1H), 7.11 (t, J = 8.91 Hz, 1H), 3.77 (t, J = 4.32 Hz, 4H), 3.20 (t, J = 4.05 Hz, 4H). ^{13}C NMR (150 MHz, DMSO-d_6, 70°C) δ 161.0, 154.1 – 152.5 (d, $J_{C\text{-}F}$ = 244.28 Hz, 1C), 153.8, 152.5, 144.1, 142.5 – 142.4 (d, $J_{C\text{-}F}$ = 7.81 Hz, 1C), 128.3, 127.9, 124.88 - 124.86 (d, $J_{C\text{-}F}$ = 2.27 Hz,1C), 124.16 – 124.11 (d, $J_{C\text{-}F}$ = 7.74 Hz, 1C), 121.6, 120.3, 117.9 – 117.8 (d, $J_{C\text{-}F}$ = 3.63 Hz, 1C), 115.5 – 115.4 (d, $J_{C\text{-}F}$ = 24.94 Hz 1C), 65.6, 49.5.

*4.2.3.2. Synthesis of 4-(2-fluoro-4-(4-methoxy-6-nitroquinazolin-2-yl)phenyl)morpholine (**13**) & 2-(3-fluoro-4-morpholinophenyl)-3-methyl-6-nitroquinazolin-4(3H)-one (**13a**);*

To a mixture of 2-(3-fluoro-4-morpholinophenyl)-6-nitroquinazolin-4-ol (3.5 g, 9.45 mmol) in DMF (30 mL), were added K_2CO_3 (3.91 g, 28.35 mmol) followed by iodomethane (1.18 mL, 18.90 mmol) at room temperature. The reaction mixture was stirred for 16 h at ambient temperature and poured into ice cold water, precipitate was formed, filtered and washed with pentane to afford a mixture of titled compounds which was separated by combi-flash column

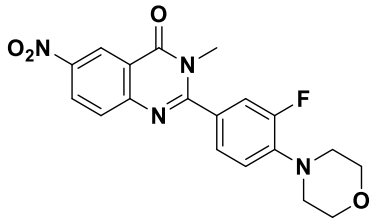
chromatography using EA/Hexane as eluent. Both fractions were collected separately and evaporated under vacuum to afford title compounds.

*Spectral characterization of **13**;*



Yellow solid, yield: 44%, mp: 248-250°C; FTIR (ATR, V_{max}, cm^{-1}): 2961.70 (Ar-H str.), 2867.90 (Ar-H str.), 1588.50 (Ar C=C str.), 1342.35 (Ar-NO_2 str.), 1247.20 (C-N str.), 1115.54 (C-F str.), 1055.50 (C-O-C str); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 9.00 (d, J = 2.68 Hz, 1H), 8.52 (dd, J = 9.25 Hz, J = 2.56 Hz, 1H), 8.31 (dd, J = 8.52 Hz, J = 2.24 Hz, 1H), 8.23 (dd, J = 14.37 Hz, J = 2.24 Hz, 1H), 7.98 (d, J = 9.25 Hz, 1H), 6.99 (t, J = 9.06 Hz, 1H), 4.31 (s, 3H), 3.90 (t, J = 4.57 Hz, 4H), 3.23 (t, J = 4.64 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ 167.9, 162.2, 156.3 – 153.9 (d, J_{C-F} = 245 Hz, 1C), 154.7, 144.8, 143.0 – 142.9 (d, J_{C-F} = 8.34 Hz, 1C), 131.0 – 131.1 (d, J_{C-F} = 8.00 Hz, 1C), 129.3, 127.3, 125.73 – 125.71 (d, J_{C-F} = 2.64 Hz, 1C), 121.0, 117.95 – 117.92 (d, J_{C-F} = 4.03 Hz, 1C), 116.9 – 116.7 (d, J_{C-F} = 23.25 Hz, 1C), 114.3, 67.0, 54.8, 50.5.

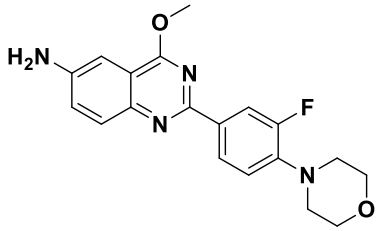
*Spectral characterization of **13a**;*



Yellow solid, yield: 44%, mp: 230-233°C; FTIR (ATR, V_{max}, cm^{-1}): 2971.90 (Ar-H str.), 2866.73 (Ar-H str.), 1676.67 (C=O str.), 1612.26 (Ar C=C str.), 1339.08 (Ar-NO_2 str.), 1238.89 (C-N str.), 1112.82 (C-F str.), 1055.41 (C-O-C str); ^{1}H NMR (600 MHz, $CDCl_3$, 25°C) δ 9.15 (d, J = 3.05 Hz, 1H), 8.51 (dd, J = 9.07 Hz, J = 2.19 Hz, 1H), 7.80 (d, J = 9.06 Hz, 1H), 7.36 – 7.34 (m, 2H), 7.04 (t, J = 8.23 Hz, 1H), 3.89 (t, J = 4.51 Hz, 4H), 3.60 (s, 3H), 3.20 (t, J = 4.60 Hz, 4H). ^{13}C NMR (150 MHz, $CDCl_3$, 25°C) δ 161.9, 158.1, 155.3 – 154.0 (d, J_{C-F} = 248 Hz, 1C), 151.3, 145.8, 142.48 – 142.43 (d, J_{C-F} = 7.70 Hz, 1C), 129.1, 128.5, 127.9 – 127.8 (d, J_{C-F} = 8.35 Hz, 1C), 125.16 – 125.14 (d, J_{C-F} = 4.48 Hz, 1C), 123.66 – 123.64 (d, J_{C-F} = 6.01 Hz, 1C),

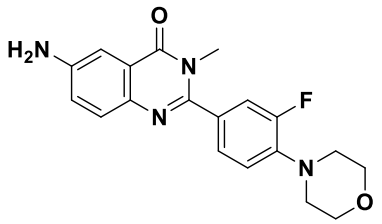
120.5, 118.63 – 118.60 (d, J_{C-F} = 4.00 Hz, 1C), 116.9 – 116.8 (d, J_{C-F} = 25 Hz, 1C), 66.9, 50.5, 35.0.

*4.2.3.3. Synthesis of 2-(3-fluoro-4-morpholinophenyl)-4-methoxyquinazolin-6-amine (**14**);*



The title compound was synthesized from 4-(2-fluoro-4-(4-methoxy-6-nitroquinazolin-2-yl)phenyl)morpholine (2.0 g, 5.20 mmol) as described in the procedure for **8**. Brown solid, yield: 65%; ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 8.17 (dd, J = 8.14 Hz, J = 2.09 Hz, 1H), 8.07 (dd, J = 14.97 Hz, J = 1.95 Hz, 1H), 7.64 (d, J = 8.82 Hz, 1H), 7.27 – 7.25 (m, 1H), 7.10 – 7.09 (m, 1H), 7.06 – 7.05 (m, 1H), 5.79 (s, 2H), 4.16 (s, 3H), 3.76 (t, J = 4.71 Hz, 4H), 3.09 (t, J = 4.80 Hz, 4H).

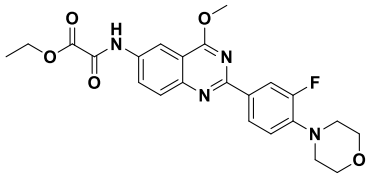
*4.2.3.4. Synthesis of 6-amino-2-(3-fluoro-4-morpholinophenyl)-3-methylquinazolin-4(3H)-one (**14a**);*



The title compound was synthesized from 2-(3-fluoro-4-morpholinophenyl)-3-methyl-6-nitroquinazolin-4(3H)-one (3.8 g, 9.88 mmol) as described in the procedure for **8**. Brown solid, yield: 67%; mp: 240-243°C; ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 8.17 (dd, J = 8.30 Hz, J = 1.79 Hz, 1H), 8.07 (dd, J = 14.96 Hz, J = 1.93 Hz, 1H), 7.64 (d, J = 8.92 Hz, 1H), 7.26 (dd, J = 8.97 Hz, J = 2.51 Hz, 1H), 7.12 – 7.07 (m, 2H), 5.09 (s, 2H), 4.16 (s, 3H), 3.76 (t, J = 5.03 Hz, 4H), 3.09 (t, J = 4.74 Hz, 4H).

4.2.4. Synthesis and spectral characterization of derivatives (16a-16d) and (16aa-16ad);

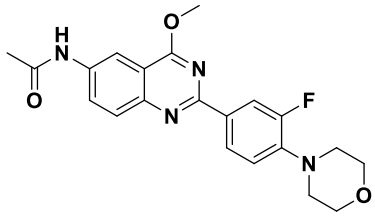
*3.2.4.1. Synthesis of ethyl 2-((2-(3-fluoro-4-morpholinophenyl)-4-methoxyquinazolin-6-yl)amino)-2-oxoacetate (**16a**);*



The compound was synthesized from 2-(3-fluoro-4-morpholinophenyl)-4-methoxyquinazolin-6-amine (0.1 g, 0.28 mmol) and ethyl 2-chloro-2-oxoacetate (0.04 mL, 0.42 mmol) as described in general procedure A.

Off white solid, yield: 50%, mp: 230-232°C; FTIR (ATR, V_{max}, cm^{-1}): 3332.74 (N-H str.), 2951.85 (Ar-H str.), 2859.92 (Ar-H str.), 1701.67 (C=O str.), 1549.48 (Ar C=C str.), 1248.80 (C-N str.), 1116.84 (C-F str.), 1047.02 (C-O-C str); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 11.14 (s, 1H), 8.65 (d, J = 2.24 Hz, 1H), 8.23 (dd, J = 8.33 Hz, J = 1.72 Hz, 1H), 8.17 (dd, J = 9.20 Hz, J = 2.05 Hz, 1H), 8.13 (dd, J = 14.89 Hz, J = 1.29 Hz, 1H), 7.90 (d, J = 9.28 Hz, 1H), 7.13 (t, J = 8.83 Hz, 1H), 4.34 (q, J = 6.75 Hz, 2H), 4.23 (s, 3H), 3.77 (t, J = 4.13 Hz, 4H), 3.13 (t, J = 4.55 Hz, 4H), 1.34 (t, J = 7.03 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 166.1, 160.2, 157.1, 155.6, 155.1 – 153.5 (d, J_{C-F} = 244.77 Hz, 1C), 148.2, 141.58 – 141.53 (d, J_{C-F} = 8.41 Hz, 1C), 135.7, 131.3 – 131.2 (d, J_{C-F} = 7.04 Hz, 1C), 128.0, 127.7, 124.5, 118.42 – 118.40 (d, J_{C-F} = 3.65 Hz, 1C), 115.2 – 115.0 (d, J_{C-F} = 23.18 Hz, 1C), 114.3, 112.4, 66.0, 62.4, 54.2, 50.0, 13.7.

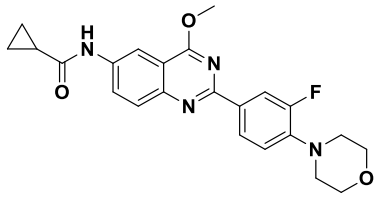
*4.2.4.2. Synthesis of N-(2-(3-fluoro-4-morpholinophenyl)-4-methoxyquinazolin-6-yl)acetamide (**16b**);*



The compound was synthesized from 2-(3-fluoro-4-morpholinophenyl)-4-methoxyquinazolin-6-amine (0.2 g, 0.56 mmol) and acetyl chloride (0.06 mL, 0.84 mmol) as described in general procedure A. Yellow solid, yield: 29%, mp: 250-252°C; FTIR (ATR, V_{max}, cm^{-1}): 3313.78 (N-H str.), 2960.89 (Ar-H str.), 1665.78 (C=O str.), 1544.43 (Ar C=C str.), 1240.93 (C-N str.), 1115.63 (C-F str.), 983.48 (C-O-C str); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 10.31 (s, 1H), 8.53 (d, J = 1.32 Hz, 1H), 8.21 (d, J = 8.39 Hz, 1H), 8.11 (d, J = 14.32 Hz, 1H), 7.91 (dd, J = 8.86 Hz, J = 1.95 Hz, 1H), 7.84 (d, J = 8.89 Hz, 1H), 7.12 (t, J = 8.96 Hz, 1H), 4.21 (s, 3H), 3.76 (t, J = 4.20 Hz, 4H), 3.11 (t, J = 4.15 Hz, 4H), 2.11 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 168.7, 166.0, 156.3, 155.1 – 153.5 (d, J_{C-F} = 245.06 Hz, 1C), 147.4, 141.4 – 141.3 (d,

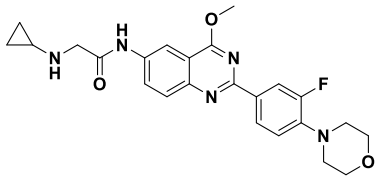
J_{C-F} = 7.67 Hz, 1C), 137.6, 131.58 – 131.53 (d, J_{C-F} = 7.56 Hz, 1C), 121.0, 126.7, 124.3, 118.4, 115.0 – 114.9 (d, J_{C-F} = 21.44 Hz, 1C), 114.6, 110.1, 66.0, 54.0, 50.1, 24.0.

*4.2.4.3. Synthesis of N-(2-(3-fluoro-4-morpholinophenyl)-4-methoxyquinazolin-6-yl)cyclopropanecarboxamide (**16c**);*



The compound was synthesized from 2-(3-fluoro-4-morpholinophenyl)-4-methoxyquinazolin-6-amine (0.1 g, 0.28 mmol, 1 equiv) and cyclopropanecarbonyl chloride (0.038 mL, 0.42 mmol, 1.5 equiv) as described in general procedure A. Yellow solid, yield: 27%, mp: 255-260°C; FTIR (ATR, V_{max}, cm^{-1}): 3269.32 (N-H str.), 2968.41 (Ar-H str.), 2857.07 (Ar-H str.), 1655.94 (C=O str.), 1535.45 (Ar C=C str.), 1244.51 (C-N str.), 1122.08 (C-F str.), 960.69 (C-O-C str); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 10.56 (s, 1H), 8.53 (s, 1H), 8.19 (d, J = 8.57 Hz, 1H), 8.08 (d, J = 14.56 Hz, 1H), 7.93 (dd, J = 8.53 Hz, J = 1.61 Hz, 1H), 7.83 (d, J = 8.90 Hz, 3H), 7.09 (t, J = 9.13 Hz, 1H), 4.19 (s, 3H), 3.75 (t, J = 4.26 Hz, 4H), 3.10 (t, J = 4.54 Hz, 4H), 1.83 – 1.80 (m, 1H), 0.86 – 0.83 (m, 4H). ^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 172,0, 166.0, 156.3, 155.1 – 153.5 (d, J_{C-F} = 244.05 Hz, 1C), 147.3, 141.4 – 141.3 (d, J_{C-F} = 8.74 Hz, 1C), 137.5, 131.58 – 131.54 (d, J_{C-F} = 7.37 Hz, 1C), 127.9, 126.7, 124.3, 118.3, 115.0 – 114.9 (d, J_{C-F} = 23.45 Hz, 1C), 114.6, 110.2, 66.0, 54.0, 50.1, 14.6, 7.4.

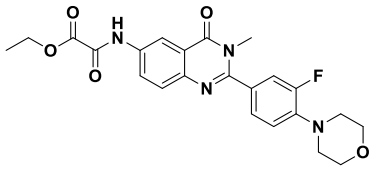
*4.2.4.4. Synthesis of 2-(cyclopropylamino)-N-(2-(3-fluoro-4-morpholinophenyl)-4-methoxyquinazolin-6-yl)acetamide (**16d**);*



To the solution of 2-(3-fluoro-4-morpholinophenyl)-4-methoxyquinazolin-6-amine (0.2 g, 0.56 mmol) in DCM (10 mL) was added triethyl amine (0.117 mL, 0.84 mmol), followed by 2-bromoacetyl bromide (0.074 mL, 0.84 mmol) at 0°C. The resultant mixture was stirred at room temperature for 4 h, precipitate was formed, filtered and washed with pentane to afford salt of 2-bromo-*N*-(2-(3-fluoro-4-morpholinophenyl)-4-methoxyquinazolin-6-yl)acetamide (0.4 g), which was dissolved in DMF (10 mL) and were added potassium carbonate (0.23 gm, 1.69 mmol), followed by cyclopropanamine (0.06 mL, 0.84 mmol) at room temperature. The resultant mixture was stirred at room temperature for 16 h, then diluted with ethyl acetate and

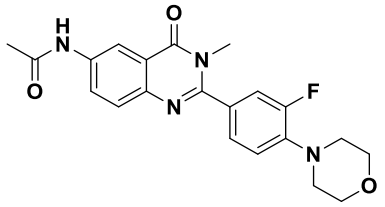
washed with cold brine solution (3 X 10 mL).The organic layer dried over anhydrous Na_2SO_4, filtered and evaporated under reduce pressure to yield crude product which was recrystallized with ethanol to afford the pure yellow solid product; yield: 37%, mp: 186-188°C; FTIR (ATR, V_{max}, cm^{-1}): 3250.93 (N-H str.), 2959.62 (Ar-H str.), 1662.75 (C=O str.), 1578.47 (Ar C=C str.), 1250.36 (C-N str.), 1116.64 (C-F str.), 1046.31 (C-O-C str); ^{1}H NMR (600 MHz, $CDCl_3$, 25°C) δ 9.21 (s, 1H), 8.36 (s, 1H), 8.28 (d, J = 8.44 Hz, 1H), 8.23 (d, J = 14.79 Hz, 1H), 7.93 – 7.88 (m, 2H), 7.00 (t, J = 8.00 Hz, 1H), 4.25 (s, 3H), 3.89 (t, J = 5.38 Hz, 4H), 3.54 (s, 2H), 3.20 (t, J = 5.38 Hz, 4H), 2.33 – 2.32 (m, 1H), 0.56 – 0.55 (m, 2H), 0.47 – 0.46 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$, 25°C) δ 170.3, 166.8, 158.1, 156.3 – 154.7 (d, J_{C-F} = 241.75 Hz, 1C), 149.0, 141.9 – 141.8 (d, J_{C-F} = 9.30 Hz, 1C), 135.7, 133.0, 128.8, 126.6, 124.8 – 124.7 (d, J_{C-F} = 2.48 Hz, 1C), 118.1, 116.3 – 116.2 (d, J_{C-F} = 24.31 Hz, 1C), 115.6, 111.9, 67.1, 54.1, 53.4, 50.8, 31.7, 6.7.

*4.2.4.5. Synthesis of ethyl 2-((2-(3-fluoro-4-morpholinophenyl)-3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)amino)-2-oxoacetate (**16aa**);*



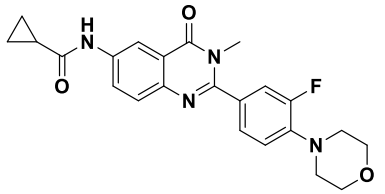
The compound was synthesized from 6-amino-2-(3-fluoro-4-morpholinophenyl)-3-methylquinazolin-4(3H)-one (0.2 g, 0.56 mmol) and ethyl 2-chloro-2-oxoacetate (0.08 mL, 0.84 mmol) as described in general procedure A. Off white solid, yield: 34%, mp: 225-227°C; FTIR (ATR, V_{max}, cm^{-1}): 3287.76 (N-H str.), 2951.72 (Ar-H str.), 1715.87 (C=O str.), 1673.56 (C=O str.), 1511.60 (Ar C=C str.), 1118.90 (C-F str.), 1055.67 (C-O-C str); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 11.09 (s, 1H), 8.66 (d, J = 2.19 Hz, 1H), 8.12 (dd, J = 8.66 Hz, J = 2.41 Hz, 1H), 7.65 (d, J = 8.81 Hz, 1H), 7.50 (dd, J = 13.82 Hz, J = 1.43 Hz, 1H), 7.44 (d, J = 8.48 Hz, 1H), 7.13 (t, J = 8.98 Hz, 1H), 4.33 (q, J = 7.73 Hz, 2H), 3.76 (t, J = 4.47 Hz, 4H), 3.40 (s, 3H), 3.11 (t, J = 4.19 Hz, 4H), 1.33 (t, J = 7.23 Hz, 3H).^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 161.4, 160.3, 155.6, 154.5 – 152.9 (d, J_{C-F} = 244.63 Hz, 1C), 144.1, 143.8, 140.8 – 140.7 (d, J_{C-F} = 8.07 Hz, 1C), 135.9, 128.78 – 128.73 (d, J_{C-F} = 8.44 Hz, 1C), 127.7, 127.7, 125.39 – 125.37 (d, J_{C-F} = 2.82 Hz, 1C), 120.1, 118.44 – 118.42 (d, J_{C-F} = 3.09 Hz, 1C), 116.5 – 116.4 (d, J_{C-F} = 12.67 Hz, 1C), 116.1, 66.0, 62.4, 50.1, 34.0, 13.8.

*4.2.4.6. Synthesis of N-(2-(3-fluoro-4-morpholinophenyl)-3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)acetamide (**16ab**);*



The compound was synthesized from 6-amino-2-(3-fluoro-4-morpholinophenyl)-3-methylquinazolin-4(3H)-one (0.2 g, 0.56 mmol) and acetyl chloride (0.06 mL, 0.84 mmol) as described in general procedure A. Yellow solid, yield: 22%, mp: 270-273°C; FTIR (ATR, V_{max}, cm^{-1}): 3344.55 (N-H str.), 2969.43 (Ar-H str.), 1691.42 (C=O str.), 1647.42 (C=O str.), 1585.55 (Ar C=C str.), 1234.53 (C-N str.), 1114.01 (C-F str.), 1053.57 (C-O-C str); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 10.26 (s, 1H), 8.48 (s, 1H), 7.93 (d, J = 8.31 Hz, 1H), 7.60 (d, J = 8.76 Hz, 1H), 7.49 (d, J = 14.10 Hz, 1H), 7.43 (d, J = 7.89 Hz, 1H), 7.13 (t, J = 8.78 Hz, 1H), 3.76 (t, J = 4.29 Hz, 4H), 3.39 (s, 3H), 3.10 (t, J = 4.29 Hz, 4H), 2.09 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 168.5, 161.5, 154.5 – 152.9 (d, J_{C-F} = 244.59 Hz, 1C), 153.3, 142.7, 140.7 – 140.6 (d, J_{C-F} = 8.14 Hz, 1C), 137.8, 128.9 – 128.8 (d, J_{C-F} = 7.68 Hz, 1C), 127.7, 125.8, 125.3, 120.2, 118.45 – 118.43 (d, J_{C-F} = 3.41 Hz, 1C), 116.5 – 116.4 (d, J_{C-F} = 22.97 Hz, 1C), 114.0, 66.0, 50.12, 3.94, 24.0.

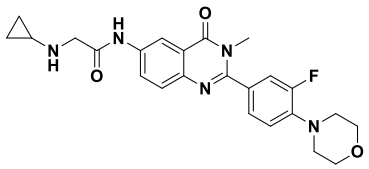
*4.2.4.7. Synthesis of N-(2-(3-fluoro-4-morpholinophenyl)-3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)cyclopropanecarboxamide (**16ac**);*



The compound was synthesized from 6-amino-2-(3-fluoro-4-morpholinophenyl)-3-methylquinazolin-4(3H)-one (0.3 g, 0.84 mmol, 1 equiv) and cyclopropanecarbonyl chloride (0.09 mL, 1.26 mmol, 1.5 equiv) as described in general procedure A. Yellow solid, yield: 53%, mp: 294-296°C; FTIR (ATR, V_{max}, cm^{-1}): 3343.88 (N-H str.), 2961.08 (Ar-H str.), 1649.56 (C=O str.), 1619.80 (C=O str.), 1580.70 (Ar C=C str.), 1236.56 (C-N str.), 1114.58 (C-F str.), 1052.69 (C-O-C str); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 10.52 (s, 1H), 8.48 (d, J = 2.65 Hz, 1H), 7.96 (dd, J = 8.67 Hz, J = 2.12 Hz, 1H), 7.59 (d, J = 8.93 Hz, 1H), 7.49 (dd, J = 13.72 Hz, J = 1.17 Hz, 1H), 7.42 (dd, J = 8.62 Hz, J = 1.03 Hz, 1H), 7.12 (t, J = 8.71 Hz, 1H), 3.76 (t, J = 4.78 Hz, 4H), 3.39 (s, 3H), 3.10 (t, J = 4.46 Hz, 4H), 1.83 – 1.79 (m, 1H), 0.85 – 0.82 (m, 4H). ^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 171.8, 161.5, 154.5 – 152. 9 (d, J_{C-F} = 246.05 Hz, 1C), 153.2, 142.6, 140.7 – 140.6 (d, J_{C-F} = 8.29 Hz, 1C), 137.9, 128.9 – 128.8 (d, J_{C-F} = 8.41 Hz,

1C), 127.7, 125.8, 125.34 – 125 .33 (d, J_{C-F} = 2.37Hz, 1C), 120.2, 118.42 – 118.40 (d, J_{C-F} = 3.27 Hz, 1C), 116.5 – 116.3 (d, J_{C-F} = 22.80 Hz, 1C), 114.1, 66.0, 50.1, 33.9, 14.6, 7.3.

*4.2.4.8. Synthesis of 2-(cyclopropylamino)-N-(2-(3-fluoro-4-morpholinophenyl)-3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)acetamide (**16ad**);*



To the solution of 6-amino-2-(3-fluoro-4-morpholinophenyl)-3-methylquinazolin-4(3H)-one (0.2 g, 0.56 mmol) in DCM (10 mL) was added triethyl amine (0.117 mL, 0.84 mmol), followed by 2-bromoacetyl bromide (0.074 mL, 0.84 mmol) at 0°C. The resultant mixture was stirred at room temperature for 4 h, precipitate was formed, filtered and washed with pentane to afford crude salt of 2-bromo-*N*-(2-(3-fluoro-4-morpholinophenyl)-3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)acetamide (0.5 g), which was dissolved in DMF (10 mL) and were added potassium carbonate (0.23 gm, 1.69 mmol), followed by cyclopropanamine (0.06 mL, 0.84 mmol) at room temperature. The resultant mixture was stirred at room temperature for 16 h, then diluted with ethyl acetate and washed with cold brine solution (3 x 10 mL).The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduce pressure to yield crude product which was recrystallized with ethanol to afford the pure yellow solid product; yield: 35%, mp: 186-188°C; FTIR (ATR, V_{max}, cm^{-1}): 3314.18 (N-H str.), 2962.20 (Ar-H str.), 1650.68 (C=O str.), 1620.65 (C=O str.), 1578.13 (Ar C=C str.), 1236.42 (C-N str.), 1115.21 (C-F str.); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 9.26 (s, 1H), 8.25 (d, *J* = 8.68 Hz, 1H), 8.07 (s, 1H), 7.62 (d, *J* = 9.07 Hz, 1H), 7.25 – 7.22 (m, 2H), 6.96 (t, *J* = 8.11 Hz, 1H), 3.83 (t, *J* = 4.47 Hz, 4H), 3.47 (s, 5H), 3.11 (t, J = 4.41 Hz, 4H), 2.26 – 2.24 (m, 1H), 0.48 -0.41 (m, 4H). ^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 170.4, 162.5, 155.8 – 154.1 (d, J_{C-F} = 248.2 Hz, 1C), 153.8, 143.8, 141.68 – 141.63 (d, J_{C-F} = 8.32 Hz, 1C), 136.8, 129.1 – 129.0 (d, J_{C-F} = 7.78 Hz, 1C), 128.6, 126.5, 124.93 – 124.92 (d, J_{C-F} = 2.84 Hz, 1C), 120.8, 118.63 – 118.61 (d, J_{C-F} = 2.89 Hz, 1C), 116.8 – 116.6 (d, J_{C-F} = 23.87 Hz, 1C), 115.2, 66.9, 53.2, 50.6, 34.5, 31.6, 6.6.

4.3. Biology

M. tuberculosis H37Rv (ATCC 25618) was grown in Middlebrook 7H9 medium supplemented with 10% v/v oleic acid, albumin, dextrose, catalase (OADC; Becton Dickinson), 0.05% w/v Tween 80 (7H9-OADC-Tw), and 50 µg/mL hygromycin (7H9-OADC-Tw-hyg), where required. Large scale cultures were grown in 100 mL of medium in 450 cm^2 roller bottles at 37 ºC and 100 rpm. *M. tuberculosis* strain CHEAM3 and DREAM8 expressing codon-optimized

mCherry and DsRed from plasmids pCherry3 and pBlazeC8, respectively, were used. Assay plates containing 20 µL of 7H9-Tw-OADC medium with appropriate control compounds or test compounds were prepared in a sterile environment. 18 µL of medium was dispensed into sterile, black, 384-well, clear bottom plates (Greiner). 2 µL of control compounds, DMSO or test compounds were stamped directly into the assay plates. Controls were 100 µM rifampicin in column 1 (final assay concentration of 2 µM rifampicin), DMSO in column 2 (final assay concentration 2%) and 125 nM rifampicin in column 23 (final assay concentration of 2.5 nM). Test compounds were diluted to 0.35 mg/mL in DMSO and transferred directly into columns 3-22 of assay plates (320 compounds per plate) to yield a final assay concentration of 7 µg/mL (final concentration of 2% DMSO). *M. tuberculosis* was grown to logarithmic phase (OD590 = 0.6-0.9) and filtered through a 0.5 µm cellulose-acetate membrane filter and diluted in fresh medium to an OD of 0.06. A MultiDrop Combi (Thermo Fisher) was used to add 10 µL of M. tuberculosis culture to columns 1-23 of the assay plates; column 24 was not inoculated and used as a contamination control. Plates were incubated in sealed plastic bags in a humidified incubator at 37ºC for 5 days. The plate layout was arranged as 320 sample wells in columns 3-22. The remaining four columns were reserved for plate controls. OD and fluorescence were read using a Synergy 4 plate reader (BioTek) with excitation/emission of 586 nm/614 nm for mCherry and 560 nm/590 nm for DsRed. For each well, the % inhibition was calculated with reference to the average maximum growth control in column 2 (DMSO only).

5. References

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CHAPTER 6

Discovery of Quinazoline-based DNA Gyrase Inhibitors as Potential Anti-Tubercular Agents

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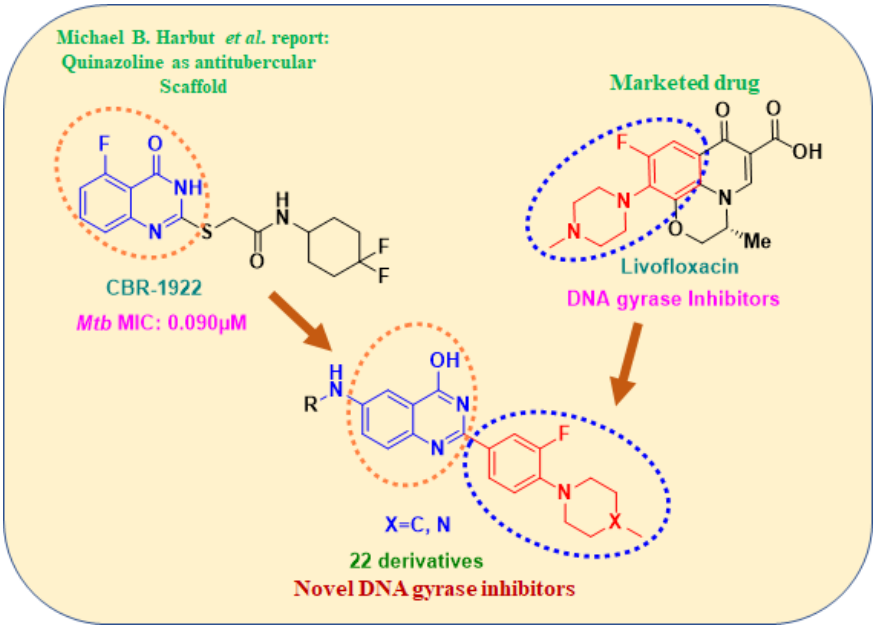
Graphical Abstract



Abstract

A novel series of quinazoline derivatives (**9a-j** and **10a-l**) were designed and synthesized in good to moderate yields. The synthesized compounds were well-characterized by spectroscopic studies (NMR and IR) and evaluated against DNA gyrase and topoisomerase IV enzyme of *Escherichia coli*. Among the series, compound **10l** bearing carboxylic acid group was found to be most active with IC_{50} value of 0.49 and 13.22 μM for DNA Gyrase and topoisomerase IV, respectively. In addition, **9f**, **9i**, **9j**, **10c**, **10j** and **10k** were also exhibited excellent activity against DNA Gyrase while comparatively less activity against topoisomerase IV. These results provide a basis for structure-based optimization toward dual DNA gyrase and topoisomerase IV inhibition.

Keywords

Quinazoline derivatives, DNA gyrase inhibition, Topoisomerase IV inhibition.

1. Introduction

The increasing antibiotic resistance of bacteria is becoming a major health problem worldwide. The rising demand for antibiotics in hospitals and veterinary purpose has led to the accumulation of antibiotics in the aqueous environment, which exert selective pressure for resistant bacteria in the environment.[1] The developing countries always battled against life threatening infectious diseases especially tuberculosis (TB) and HIV/AIDS,[2-4] due to multidrug resistant,[5] these diseases become more threatening (**Figure 1**). TB ranks second, standing next to HIV in terms of lethality.[6] Rifampicin was introduced in 1970s, as a first line drug used in case of TB due to its sterilizing capacity and bactericidal effect,[7, 8] However, it has been known to develop resistance towards curing TB. The global report of TB with multidrug-resistant TB (MDR-TB) was estimated to be 3.9% newly diagnosed and 21 % with previous history of TB.[8] MDR-TB is technically due to the resistance of *Mycobacterium tuberculosis* against rifampicin and isoniazid.[9,10] In addition, Rifampicin-resistant TB (RR-TB) is detected by genotypic/phenotypic methods against other first-line anti-TB drugs (with/without resistance) and hence posing a threat to control TB.[11-13].Consequently, the discovery of anti-*Mycobacterium tuberculosis* (anti-Mtb) drug is promising. Hence there is a need for novel anti-Mtb compounds that must have activity against resistant bacterial strains. However, the search for new compound remains a significant challenge for the future.[14]

Bacterial DNA type II topoisomerases (DNA gyrase and topoisomerase IV) are well-established validated targets in antibacterial drug discovery. These enzymes are vital for control of the topological state of DNA during cell division and DNA replication.[15] In general, DNA gyrase introduces negative supercoils in DNA in front of the replication fork, although topoisomerase IV is important for decatenation during DNA replication. DNA gyrase is consists of two A subunits (GyrA) and two B subunits (GyrB), whereas topoisomerase IV composed of two C subunits (ParC) and two E subunits (ParE), which are homologous to GyrA and GyrB, correspondingly.[16] The resemblances in the structure of DNA gyrase and topoisomerase IV offer an remarkable opportunity for the dual targeting of these enzymes by novel antibacterial compounds, in that way reducing the possibility of bacteria to develop target based resistance against them.[17]

The DNA gyrase inhibitors (**Figure 2**) i.e., quinolones/fluoroquinolones mainly target GyrA subunit of the DNA Gyrase complex while the Novobiocin targets the GyrB subunit. Due to the clinical success of the fluoroquinolone class of antibacterial, DNA Gyrase has fascinated a great deal of interest from both industrial and academic institutions.[16-18]

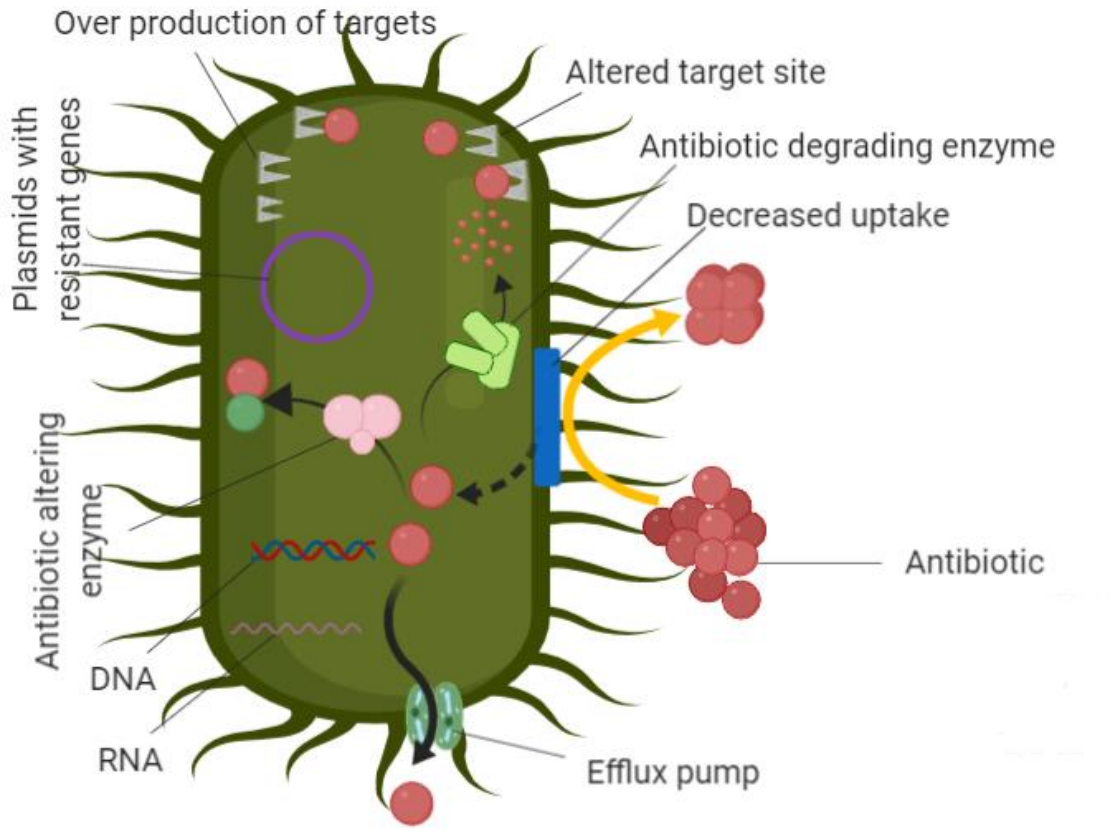


Figure 1: Mechanism of antibiotic resistance.

Synthetic chemists always desire for the simple synthetic protocols to synthesize biologically active derivatives[19]. Several heterocyclic derivatives are well documented to possess pharmacological advantage for drug designing. Sir James Black (Nobel Laureate; winner of 1988 Nobel Prize in Physiology and Medicine) once stated, "*the most fruitful basis for the discovery of a new drug is to start with an old drug*".[20]

Heterocyclic chemistry with nitrogen as integral part of fused ring are frequently found in natural products. They have also been part of the synthetic drugs and functional materials.[21] *N*-Heterocycles are frequently found in natural products, synthetic drugs, and functional materials. Developing novel, efficient, and practical methods for the synthesis of *N*-heterocycles is very important in organic chemistry. Among the existing *N*-heterocycles, many quinazolines have attracted great attention because they possess distinctive biological activities and physical activity ranging from anticancer, anti-inflammatory, antipsychotic, antidiabetic, antileishmanial, and antibacterial activities.[22-27] A series of 2-substituted quinazolines with broad-spectrum antibacterial activity, inhibiting RNA synthesis and translation in a number of bacterial species were reported.[28, 29]

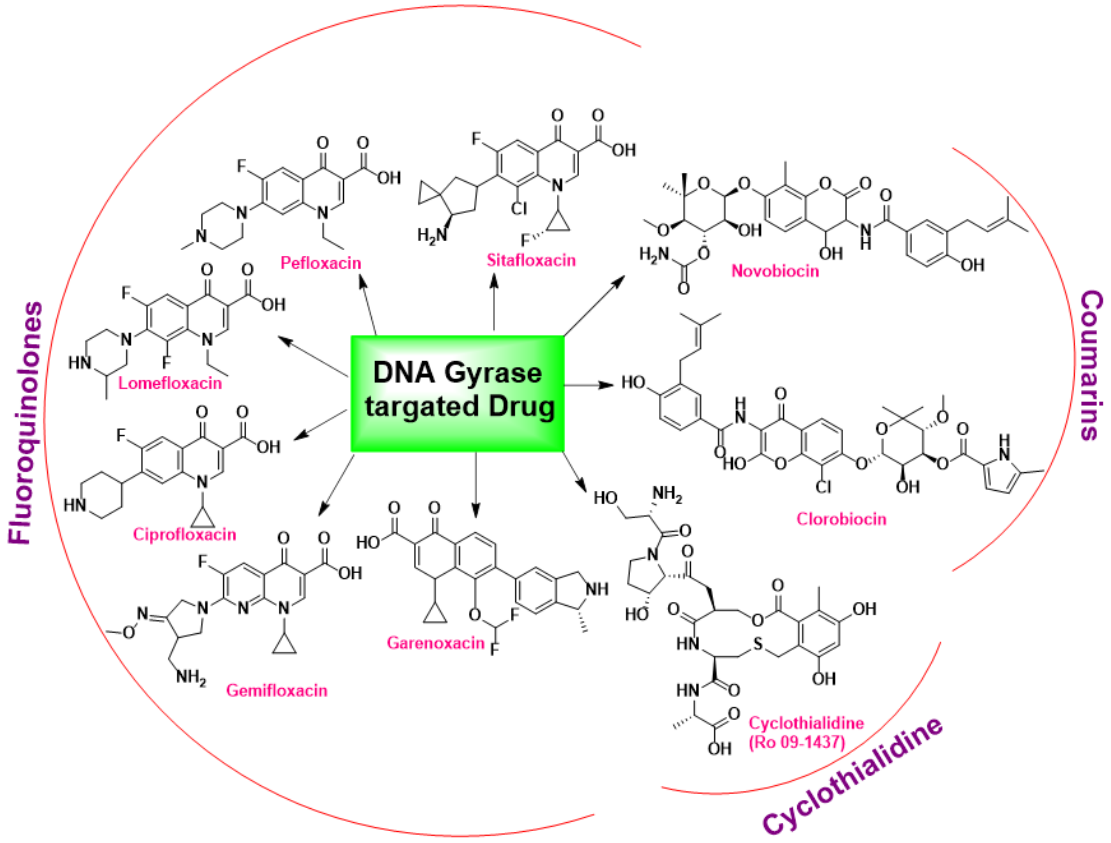


Figure 2: Commercial drugs targeting DNA Gyrase.[16]

Piperazine/piperidine derivatives have also gained immense acknowledgment due to various types of biological properties like antifungal, antibacterial, anti-cancer, anti-HIV, antimalarial etc.[30-32] Owing to all the significance, it is an essential starting material in the pharmaceutical industry.[33] Substitution at one of the nitrogen atoms also enhances the biological significance (**Figure 3**). It is also well documented that bis-heterocyclic derivatives possess better antibacterial activity than heterocyclic compounds alone.

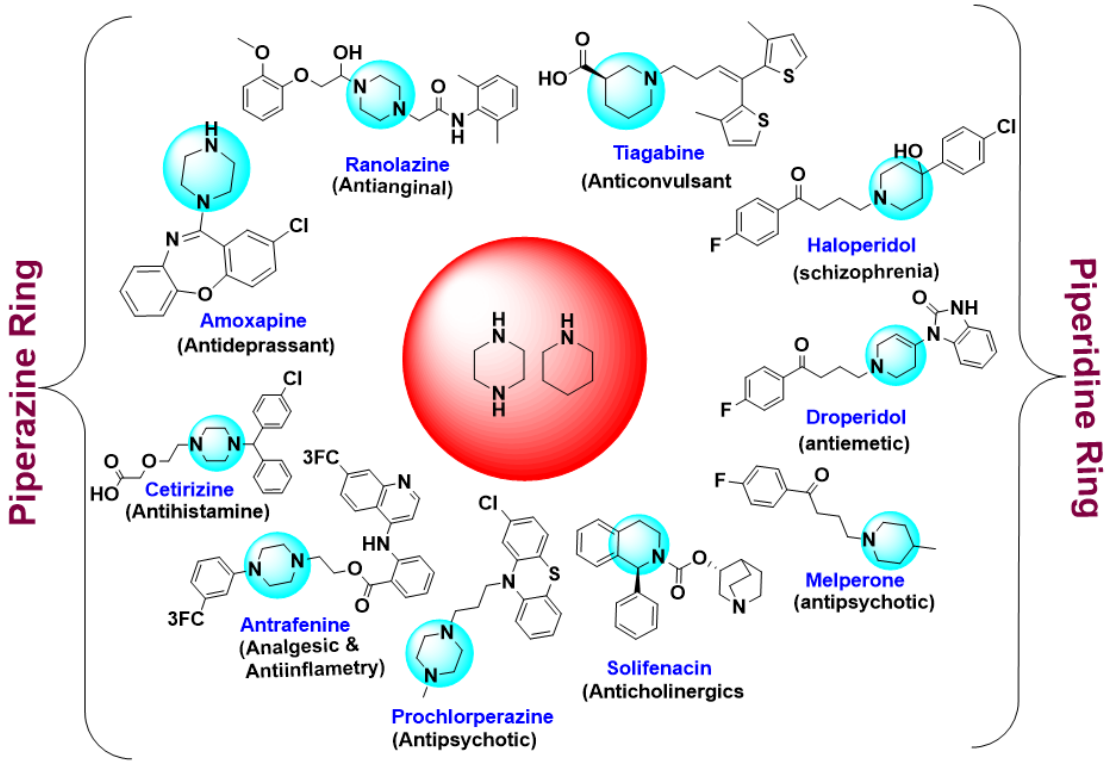


Figure 3: Significance of piperazine and piperidine in drug discovery.

With all this in mind, we propose the fusion of piperazine/4-methyl piperidine and quinazoline to synthesize a series of molecules containing both moieties.

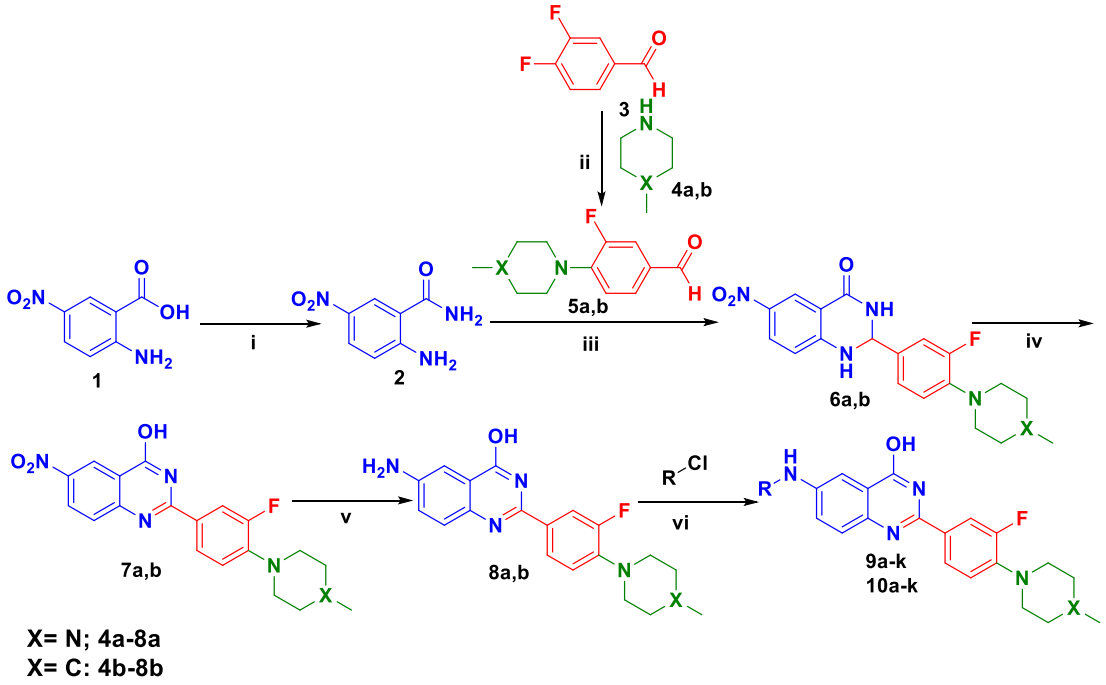
2. Results and discussion

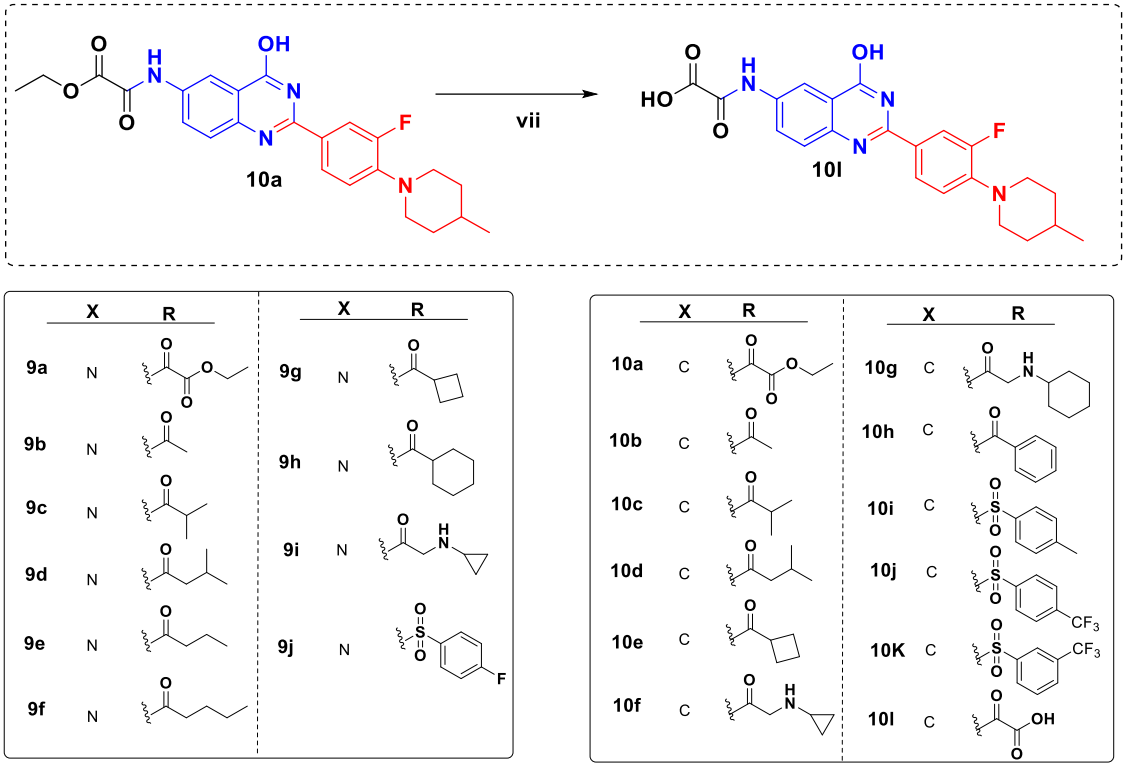
2.1. Chemistry

The synthesis of novel quinazoline derivatives (**9a-j & 10a-k**) and their corresponding intermediates were attained through effective and easy synthetic routes as depicted in Scheme-**I**. Intermediate **2** was synthesized as per our previous report (**Chapter-3**) while **5a-b** were obtained by nucleophilic substitution of 3,4-difluorobenzaldehyde with 1-methylpiperazine and 4-methylpiperidine, respectively. **6a-b** were achieved by the condensation of **5a-b** with **2** in presence of dehydrating agent (*p*TSA) in DMA at 130°C for 16 h, which were subjected to oxidation with $KMnO_4$ in DMSO to yield (**7a-b**). The nitro reduction of **7a-b** was performed in presence of Fe/NH_4Cl to afford (**8a-b**). Subsequently, two series of final derivatives (**9a-j**) and (**10a-k**) were synthesized by reacting **8a-b** with the acid/sulphonyl chloride in presence of TEA in DCM at 0°C to rt for 4 h and pyridine in DCM at 0°C to rt for 16 h correspondingly.

The structure of all intermediates (**5a-b, 6a-b, 7a-b, 8a-b,**) and their respective final derivatives (**9a-j & 10a-k**) were characterized by spectral (IR, ^{1}H-NMR, and ^{13}C-NMR) analysis. All

compounds showed adequate analysis of their predicted structures, which are summarized in experimental section. The conversion of **3** to **5a** and **5b** was confirmed by the appearance of methyl protons at around 2.33 ppm and 0.96 ppm along with most distinct signals of aldehyde protons at around 9.78 ppm and 9.76 ppm correspondingly. Further, the formation of **6a-b** was confirmed by the appearance of amide and amine protons at around 8.69 ppm and 8.59-8.51 ppm correspondingly along with most distinct chiral protons at around 5.95 ppm. The conversion of **6a-b** to **7a-b** were confirmed by the disappearance of amide and amine along with chiral protons and appearance of distinct O**H** proton at around 12.82 ppm in NMR spectra. Furthermore, the formation of **8a-b** was confirmed by the appearance of amine (N**H**$_2$) protons at around 5.61-5.63 ppm in ^{1}H-NMR while disappearance of nitro (NO_2) absorption band 1334.58 – 1340.58 cm^{-1} in IR spectra. Subsequently, the derivatization of **8a** and **8b** to **9a-i** and **10a-h**, respectively were confirmed by the vanishing of amine (N**H**$_2$) proton and same time entrance of amide proton at around 10.04 - 11.10 ppm in ^{1}H-NMR spectra. The absorption band of amide (C=O and N-H) around 1655.79 - 1671.43 cm^{-1} and 3081.67 - 3174.32 cm^{-1} in IR spectra along with signals of carbonyl carbon at around 161.9 – 175.4 ppm in ^{13}C-NMR spectra confirmed the presence of amide group. In case of **9j** and **10i-k** derivatives showed the signals at around 10.60 -10.81 ppm in ^{1}H-NMR spectrum and broad band in the region of 3079.22 - 3088.14 cm^{-1}, 1316.94 - 1485.10 cm^{-1} and 1158.44 - 1234.94 cm^{-1} are assigned for N-H, asymmetric and symmetric mode of O=S=O group, respectively confirmed the presence of sulphonamide.



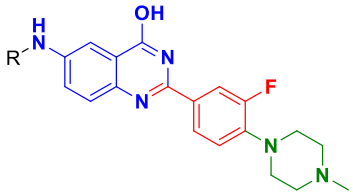


Scheme 1: *Reagents and conditions:* **i)** 28% aqueous ammonia solution, EDC.HCl, HOBt, DMF, 3–5 h; **ii)** K_2CO_3, DMF, 130°C, 16 h; **iii)** *p*TSA, DMA, 130°C, 16 h; **iv)** $KMnO_4$, DMSO, 100°C, 16 h; **v)** Fe, NH_4Cl, Dioxane: EtOH: H2O (7:5:3), 100°C, 5 h; **vi)** TEA, DCM, 0°C - rt, 4 h. or Pyridine, DCM/DMF, 0°C - rt, 16 h. **vii)** NaOH, EtOH, rt, 16 h.

2.2. Biology

All the quinazoline based synthesized derivatives (**9a-i** and **10a-l**) were evaluated for their inhibitory activity against DNA gyrase (supercoiling assay) and topoisomerase IV (decatenation assays). The results measured as IC_{50} values, have been tabulated in **Table 1**.

Table 1: Inhibition of *E. coli* DNA Gyrase and Topoisomerase IV by quinazoline-based compounds.



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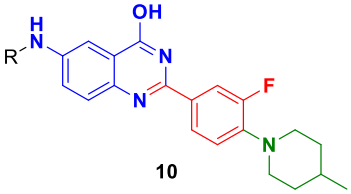

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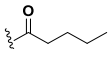
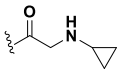
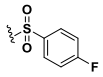
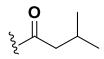
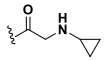
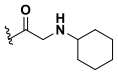
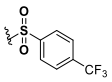
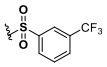
Compound	R	IC_{50} (µM) [a]	
		DNA gyrase (*E.coli*)	Topoisomerase IV (*E.coli*)
Ciprofloxacin	-	0.16	10.23
9a		1.46	15.58
9b		1.46	45.83
9c		1.37	101.60
9d		1.50	29.48
9e		1.81	16.39
9f		0.22	183.20
9g		1.49	24.91
9h		1.48	94.95
9i		1.98	31.31
9j		0.52	235.00
10a		1.44	87.57
10b		1.46	109.20
10c		0.60	23.79

10d		nd	30.02
10e		nd	25.91
10f		1.79	95.43
10g		2.54	58.17
10h		nd	20.49
10i		nd	427.00
10j		0.34	239.20
10k		0.22	17.87
10l		0.49	13.22

[a]Concentration of compound (mean ± SD) that inhibits the enzyme activity by 50%. nd = not determined.

Most of the compounds showed good inhibitory activity against DNA gyrase and topoisomerases IV with IC_{50} values ranging 0.22-2.54 µM and 13.22-427.00 µM, respectively. Among the series, compound **10l** bearing carboxylic acid group was found to be most active with IC_{50} value of 0.49 and 13.22 µM for DNA Gyrase and topoisomerase IV, respectively. In addition, **9f**, **9i**, **9j**, **10c**, **10j** and **10k** were also exhibited excellent activity against DNA Gyrase while comparatively less activity against topoisomerase IV. Comparing the IC_{50s} for DNA Gyrase inhibition, all the derivatives showed moderate to high potency. However, in case of topoisomerase IV, the inhibition was found to be low to moderate.

3. Conclusion

In conclusion, we have described a series of novel quinazoline derivatives which were first time designed and synthesized via convenient procedure. In this chapter, we have synthesized 22 molecules and all the structures of new compounds were characterized by spectroscopic method (IR and NMR) and their inhibitory activities on DNA gyrase and topoisomerase IV from *E. coli* were measured. All compounds (**9a-9j** and **10a-l**) displayed IC_{50} value lower than 2 µM for DNA gyrase and the most active compound **10l** had an IC_{50} of 0.49 µM. Overall, compounds **9a**, **9e**, **10c**, **10k** and **10l** are particularly motivating for further studies because they showed

promising balanced inhibition in the low micromolar range against both DNA gyrase and topoisomerase IV from *E. coli*.

4. Experimental

4.1. General consideration

All the fine chemicals, reagents and solvents were purchased from Sigma Aldrich and Merck and were used without further purification unless otherwise stated. The progress of the reactions and the purity of the compounds were monitored by thin-layer chromatography (TLC) on pre-coated silica gel plates procured from E. Merck and Co. (Darmstadt, Germany) visualized by UV lamp (254 or 365 nm). Purification was performed by using combi-flash (Combi*Flash*® NextGen 300+) column chromatography. The melting points of the synthesized compounds have been determined and uncorrected using a digital Stuart SMP10 melting point Apparatus. The Fourier transform infrared (FTIR) spectra were recorded in the spectral range of 400-4000 cm^{-1} on a Bruker Alpha FT-IR spectrometer using the ATR technique. The NMR spectra (**^{1}**H, and ^{13}C,) were recorded using $CDCl_3$ and DMSO-d_6 on Bruker AVANCE III 400 and 600 MHz spectrometer. Chemical shifts were determined relative to internal standard TMS at δ 0.0 parts per million (ppm) and the coupling constants were reported in Hertz. The multiplicities of the NMR resonances were abbreviated as s (singlet), d (doublet), dd (doublet of doublet), (t (triplet), q (quartet), m (multiplet) and brs (broad singlet). *Escherichia coli* DNA gyrase, *E. coli* DNA topoisomerase IV, relaxed DNA (pHOT1) and supercoiled DNA (pBR322) were obtained from TopoGEN (TopoGEN. USA) and the stock solution of compound was prepared at in DMSO.

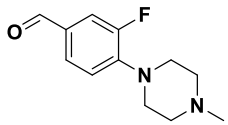
4.2. Chemistry

4.2.1. Synthesis and spectral characterization of compounds 5a, 5b, 6a, 6b, 7a, 7b and 8a, 8b;

4.2.1.1 General procedure for synthesis of 5a and 5b;

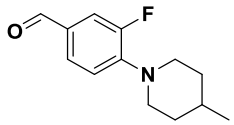
To the solution of 3,4-difluorobenzaldehyde (1 equiv) in DMF was added K_2CO_3 (2 equiv) followed by 4a or 4b (1.2 equiv) at room temperature. The reaction mixture was stirred at 130°C for 16 h, cooled to room temperature, diluted with ethyl acetate and washed with cold brine solution. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give solid residue which was triturated with pentane and filtered to afford corresponding title products.

*3-Fluoro-4-(4-methylpiperazin-1-yl)benzaldehyde (**5a**);*



Yellow solid (2.6 g, 83%); mp: 65-67°C; FTIR (ATR, V_{max}, cm^{-1}): 2932.71 (Ar-H str.), 1679.30 (C=O str.), 1561.14 (Ar C=C str.), 1247.01 (C-N str), 1137.56 (C-F str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 9.78 (s, 1H), 7.54 (dd, J = 8.25 Hz, J = 2.05 Hz, 1H), 7.48 (dd, J = 13.17 Hz, J = 1.99 Hz, 1H), 6.95 (t, J = 7.96 Hz, 1H), 3.26 (t, J = 5.11 Hz, 4H), 2.56 (t, J = 4.84 Hz, 4H), 2.32 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ 189.9, 155.9 – 153.5 (d, $J_{C\text{-}F}$ = 248 Hz, 1C), 145.4 – 145.3 (d, $J_{C\text{-}F}$ = 8.53 Hz, 1C), 130.1 – 130.0 (d, $J_{C\text{-}F}$ = 6.16 Hz, 1C), 128.04 – 128.02 (d, $J_{C\text{-}F}$ = 3.26 Hz, 1C), 118.0 – 117.9 (d, $J_{C\text{-}F}$ = 3.86 Hz, 1C), 116.1 – 115.9 (d, $J_{C\text{-}F}$ = 22.10 Hz, 1C), 54.9, 49.7, 46.1.

*3-Fluoro-4-(4-methylpiperidin-1-yl)benzaldehyde (**5b**);*

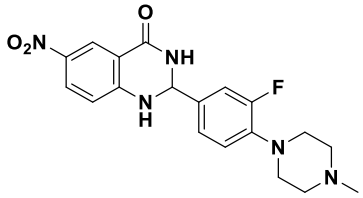


Brown liquid (17 g, 72%); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 9.76 (s, 1H), 7.52 – 7.44 (m, 2H), 6.94 (t, J = 8.45 Hz, 1H), 3.64 – 3.61 (m, 2H), 2.82 – 2.76 (m, 2H), 1.73 – 1.70 (m, 2H), 1.60 – 1.49 (m, 1H), 1.40 – 1.30 (m, 2H), 0.96 (d, J = 6.49 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ 189.9, 155.8 – 153.3 (d, $J_{C\text{-}F}$ = 252.40 Hz, 1C), 146.1, 129.4, 128.0, 118.0, 116.0 – 115.8 (d, $J_{C\text{-}F}$ = 22.8 Hz, 1C), 51.1, 34.1, 30.7, 21.8.

4.2.1.2. General procedure for synthesis of 6a and 6b;

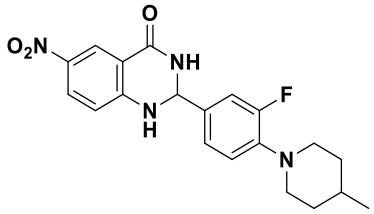
To the solution of 2-amino-5-nitrobenzamide (1 equiv) and 5a or 5b (1 equiv) in DMA was added catalytic amount of *p*-toluenesulfonic acid (0.2 equiv). The resultant mixture was heated at 130°C for 16 h, cooled to room temperature and poured into ice cold water, precipitate was formed filtered and washed with diethyl ether to afford corresponding title products.

*2-(3-Fluoro-4-(4-methylpiperazin-1-yl)phenyl)-6-nitro-2,3-dihydroquinazolin-4(1H)-one (**6a**);*



Yellow solid (16.0 g, 75%); mp: 255-257°C; FTIR (ATR, V_{max}, cm^{-1}): 3269.81 (N-H str.), 2919.54 (Ar-H str.), 1649.88 (C=O str.), 1504.18 (Ar C=C str.), 1326.42 (Ar-NO_2 str.), 1250.24 (C-N str.), 1119.39 (C-F str.); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 8.69 (s, 1H), 8.54 (s, 1H), 8.42 (d, J = 2.65 Hz, 1H), 8.09 (dd, J = 9.10 Hz, J = 2.94 Hz, 1H), 7.21 – 7.17 (m, 2H), 7.05 (t, J = 8.56 Hz, 1H), 6.83 (d, J = 9.08 Hz, 1H), 5.95 (s, 1H), 3.01 (t, J = 4.31 Hz, 4H), 2.48 (t, J = 4.42 Hz, 4H), 2.23 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 161.3, 155.2 – 153.6 (d, J_{C-F} = 244.52 Hz, 1C), 152.0, 140.1 – 140.0 (d, J_{C-F} = 8.44 Hz, 1C), 137.2, 135.19 – 135.15 (d, J_{C-F} = 6.54 Hz, 1C), 128.9, 124.1, 122.78 – 122.76 (d, J_{C-F} = 2.74 Hz, 1C), 119.12 – 119.10 (d, J_{C-F} = 3.23 Hz, 1C), 114.3, 114.2 – 114.1 (d, J_{C-F} = 20.92 Hz, 1C), 112.6, 65.2, 54.4, 49.7, 45.5.

*2-(3-Fluoro-4-(4-methylpiperidin-1-yl)phenyl)-6-nitro-2,3-dihydroquinazolin-4(1H)-one (**6b**);*

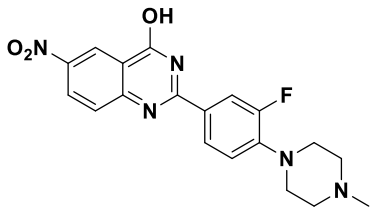


Yellow solid (20.1 g, 94%); mp: 224-228°C; FTIR (ATR, V_{max}, cm^{-1}): 3353.37 (N-H str.), 3264.91 (N-H str.), 2922.23 (Ar-H str.), 1650.20 (C=O str.), 1506.10 (Ar C=C str.), 1324.54 (Ar-NO_2 str.), 1235.94 (C-N str), 1109.95 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 8.69 (s, 1H), 8.51 (s, 1H), 8.41 (d, J = 2.73 Hz, 1H), 8.10 (dd, J = 9.10 Hz, J = 2.83 Hz, 1H), 7.20 – 7.15 (m, 2H), 7.05 (t, J = 8.21 Hz, 1H), 6.82 (d, J = 9.25 Hz, 1H), 5.94 (s, 1H), 3.31 – 3.27 (m, 2H), 2.64 – 2.59 (m, 2H), 1.69 – 1.66 (m, 2H), 1.51 – 1.44 (m, 1H), 1.31 – 1.22 (m, 2H), 0.93 (d, J = 6.53 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 161.1, 155.2 – 153.6 (d, J = 248.48 Hz, 1C), 151.8, 140.8 – 140.7 (d, J = 11.86 Hz, 1C), 137.1, 134.6, 128.7, 124.0, 122.6 – 122.5 (d, J = 2.98 Hz, 1C), 119.2, 114.2, 114.0 – 113.9 (d, J = 22.5 Hz, 1C), 112.6, 65.2, 50.4, 33.7, 29.8, 29.5.

4.2.1.3. General procedure for synthesis of 7a and 7b;

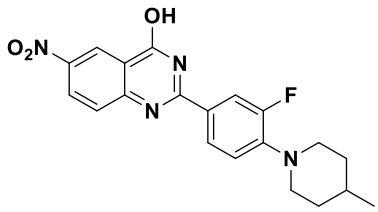
To the solution of 6a or 6b (1 equiv) in DMSO was added potassium permanganate (3 equiv) at 0°C. The mixture was heated at 100°C for 16 h then cooled to room temperature and filtered through celite. The filtrate was poured into ice cold water and stirred for 30 min precipitate was formed, filtered and washed with diethyl ether to afford title compounds.

*2-(3-Fluoro-4-(4-methylpiperazin-1-yl)phenyl)-6-nitroquinazolin-4-ol (**7a**);*



Red solid (10 g, 62%); mp: 267-270°C; FTIR (ATR, V_{max}, cm^{-1}): 3258.70 (O-H str.), 2932.84 (Ar-H str.), 1671.87 (C=O str.), 1539.90 (Ar C=C str.), 1334.18 (Ar-NO_2 str.), 1242.63 (C-N str), 1138.10 (C-F str.); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 8.77 (d, J = 2.39 Hz, 1H), 8.49 (dd, J = 9.05 Hz, J = 2.65 HZ, 1H), 8.05 – 8.00 (m, 2H), 7.81 (d, J = 8.83 Hz, 1H), 7.12 (t, J = 8.97 Hz, 1H), 3.20 (t, J = 5.31 Hz, 4H), 2.52 (t, J = 4.34 Hz, 4H), 2.26 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 161.7, 154.3 – 152.7 (d, $J_{C\text{-}F}$ = 244.3 Hz, 1C), 153.0, 144.2, 142.8, 128.7, 128.3, 125.1, 124.3, 122.0, 120.5, 118.4, 115.7 – 115.6 (d, $J_{C\text{-}F}$ = 24.5 Hz, 1C), 54.2, 49.1, 45.4.

*2-(3-Fluoro-4-(4-methylpiperidin-1-yl)phenyl)-6-nitroquinazolin-4-ol (**7b**):*



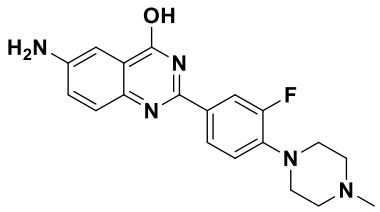
Yellow solid (6.9 g, 69%); mp: 293-295°C; FTIR (ATR, V_{max}, cm^{-1}): 3177.84 (O-H str.), 2923.58 (Ar-H str.), 1670.88 (C=O str.), 1575.63 (Ar C=C str.), 1340.58 (Ar-NO2 str.), 1240.75 (C-N str.), 1131.27 (C-F str.), ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.82 (s, 1H), 8.79 (d, J = 2.68 Hz, 1H), 8.52 (dd, J = 9.21 Hz, J = 3.01 Hz, 1H), 8.07 – 8.00 (m, 2H), 7.85 (d, J = 8.83 Hz, 1H), 7.14 (t, J = 8.69 Hz, 1H), 3.56 (d, J = 12.22 Hz, 2H), 2.83 – 2.77 (m, 2H), 1.73 – 1.70 (m, 2H), 1.59 – 1.52 (m, 1H), 1.33 – 1.23 (m, 2H), 0.95 (d, J = 6.25 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 154.0 -152.4 (d, $J_{C\text{-}F}$ = 242.59 Hz, 1C), 153.9, 114.1, 143.28, 143.23,

128.0, 124.9, 123.28, 123.22, 121.7, 120.3, 118.2, 115.5 – 115.3 (d, $J_{C\text{-}F}$ = 24.27 Hz, 1C), 49.6, 33.4, 29.6, 21.2.

4.2.1.4. General procedure for synthesis of 8a and 8b;

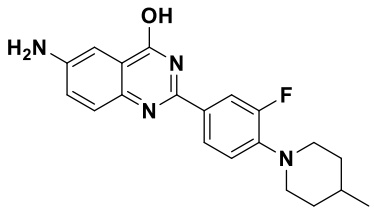
7a or **7b** (1 equiv) was added into the mixture of dioxane, ethanol and water (7:5:3) followed by ammonium chloride (10 equiv). To the resultant mixture iron powder (5 equiv) was added with vigorous stirring and then heated at 100°C for 4 h. The reaction mixture was cool to room temperature, filtered through celite and washed with ethyl acetate. The filtrate was concentrated under reduce pressure then diluted with ethyl acetate and washed with saturated sodium bicarbonate solution. Organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated under reduce pressure to afford title products.

*6-Amino-2-(3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)quinazolin-4-ol (**8a**);*



Yellow solid (4.3 g, 46%); mp: 255-260°C; FTIR (ATR, V_{max}, cm^{-1}): 3313.65 (O-H str.), 3175.40 (N-H str.), 2968.46 (Ar-H str.), 1620.47 (C=O str. Keto-enol), 1513.82 (Ar C=C str.), 1255.06 (C-N str), 1136.72 (C-F str.); ^{1}H NMR (600 MHz, DMSO-d_6, 25°C) δ 11.97 (s, 1H), 7.92 – 7.89 (m, 2H), 7.43 (d, J = 9.39 Hz, 1H), 7.21 (d, J = 2.23 Hz, 1H), 7.10 – 7.06 (m, 2H), 5.61 (s, 2H), 3.11 (t, J = 4.91 Hz, 4H), 2.47 (t, J = 4.36 Hz, 4H), 2.22 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6, 25°C) δ 162.0, 154.8 – 153.2 (d, $J_{C\text{-}F}$ = 243.9 Hz, 1C), 147.6, 145.9, 141.4 – 141.3 (d, $J_{C\text{-}F}$ = 8.9 Hz, 1C), 139.6, 128.2, 126.3 – 126.2 (d, $J_{C\text{-}F}$ = 7.4 Hz, 1C), 123.5, 122.4, 121.8, 118.54 – 118.52 (d, $J_{C\text{-}F}$ = 3.4 Hz, 1C), 114.5 – 114.4 (d, $J_{C\text{-}F}$ = 24.2 Hz, 1C), 106.2, 54.4, 49.4, 45.6.

*6-Amino-2-(3-fluoro-4-(4-methylpiperidin-1-yl)phenyl)quinazolin-4-ol (**8b**);*



Yellow solid (4.1 g, 74%); mp: 240-243°C; FTIR (ATR, V_{max}, cm^{-1}): 3447.17 (N-H str.), 3352.05 (O-H str.), 2918.11 (Ar-H str.), 1647.06 (C=O str. Keto-enol), 1485.40 (Ar C=C str.), 1236.68 (C-N str), 1062.47 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 11.99 (s, 1H), 7.92 – 7.86 (m, 2H), 7.42 (d, J = 8.88 Hz, 1H), 7.19 (d, J = 3.00 Hz, 1H), 7.10 – 7.06 (m, 2H), 5.63 (s, 2H), 3.46 (d, J = 12.17 Hz, 2H), 2.72 (t, J = 12.48 Hz, 2H), 1.71 (d, J = 11.89 Hz, 2H), 1.55 – 1.48 (m, 1H), 1.34 – 1.22 (m, 2H), 0.95 (d, J = 6.61 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 162.0, 155.2 – 152.8 (d, J_{C-F} = 244.2 Hz, 1C), 147.6,145.9, 142.2 – 142.1 (d, J_{C-F} = 8.80 Hz, 1C), 13.6, 128.2, 125.9 – 125.8 (d, J_{C-F} = 8.05 Hz, 1C), 123.56 – 123.53 (d, J_{C-F} = 3.75 Hz, 1C), 122.5, 121.8, 118.77 – 118.73 (d, J_{C-F} = 3.54 Hz, 1C), 114.5 – 114.2 (d, J_{C-F} = 23.5 Hz, 1C), 106.2, 50.2, 33.7, 30.0, 21.7.

4.2.1.5. General procedure for synthesis, and spectral characterization of derivatives (9a-h, 10a-e and 10h), (9i, 10f-g) and (9j, 10i-k);

4.2.1.5.1 General procedure A for synthesis of derivatives (9a-h, 10a-e and 10h);

To the suspension of 6-amino-2-(3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)quinazolin-4-ol (**8a**)/ 6-amino-2-(3-fluoro-4-(4-methylpiperidin-1-yl)phenyl)quinazolin-4-ol (**8b**) (1.0 equiv) in DCM, were added triethyl amine (1.5 equiv), followed by appropriate acid chloride (1.5 equiv) at 0°C. The resultant mixture was stirred at room temperature for 2 h, quenched with sodium bicarbonate solution and extracted with DCM (3 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduce pressure to give solid residue which were triturated with diethyl ether and filtered to afford desired title compounds.

4.2.1.5.2. General procedure B for synthesis of derivatives (9i, 10f-g);

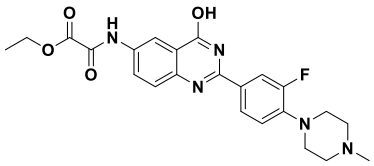
To the solution of 6-amino-2-(3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)quinazolin-4-ol (**8a**)/ 6-amino-2-(3-fluoro-4-(4-methylpiperidin-1-yl)phenyl)quinazolin-4-ol (**8b**) (1 equiv) in DCM (10 mL) was added triethyl amine (1.5 equiv), followed by 2-bromoacetyl bromide (1.2 equiv) at 0°C. The resultant mixture was stirred at room temperature for 2 h, precipitate was formed, filtered and washed with pentane to afford salt of 2-bromo-*N*-(2-(3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)-4-hydroxyquinazolin-6-yl)acetamide and 2-bromo-*N*-(2-(3-fluoro-4-(4-methylpiperidin-1-yl)phenyl)-4-hydroxyquinazolin-6-yl)acetamide, respectively which were dissolved separately in DMF and were added potassium carbonate (1.5 equiv), followed by appropriate amine (1.5 equiv) at room temperature. The resultant mixture was stirred at room temperature for 16 h, then diluted with ethyl acetate and washed with cold brine solution (3 x 10 mL). The organic layer dried over anhydrous Na_2SO_4, filtered and evaporated under reduce

pressure to yield crude product which was recrystallized with ethanol to afford the pure title products.

4.2.1.5.3. General procedure C for synthesis of derivatives (9j, 10i-k);

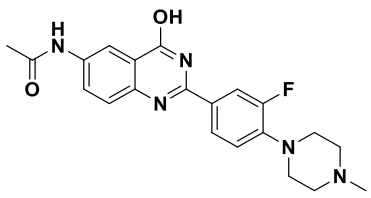
To the solution of 6-amino-2-(3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)quinazolin-4-ol (**8a**)/ 6-amino-2-(3-fluoro-4-(4-methylpiperidin-1-yl)phenyl)quinazolin-4-ol (**8b**) (1.0 equiv) in DCM were added pyridine (8.0 equiv), followed by appropriate sulfonyl chloride (1.5 equiv) at 0°C. The resultant mixture was stirred at room temperature for 16 h, quenched with 2N-HCl solution and extracted with DCM (3 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to yield the crude, which was triturated with diethyl ether and filtered to afford the desired title products.

*4.2.1.5.1.1. Ethyl 2-((2-(3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)-4-hydroxyquinazolin-6-yl)amino)-2-oxoacetate (**9a**);*



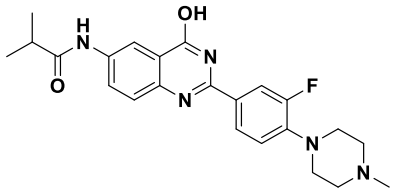
Yellow solid, yield:15%, mp: 265-268°C; FTIR (ATR, V_{max}, cm^{-1}): 3334.94 (O-H str.), 3172.30 (N-H str.), 2930.68 (Ar-H str.), 1713.33 (C=O str.), 1660.71 (C=O str.), 1590.85 (Ar C=C str.), 1256.98 (C-N str.); 1167.10 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.41 (s, 1H), 11.10 (s, 1H), 8.64 (d, J = 2.61 Hz, 1H), 8.09 (dd, J = 8.91 Hz, J = 2.51 Hz, 1H), 8.02 – 7.96 (m, 2H), 7.70 (d, J = 8.85 Hz, 1H), 7.13 (t, J = 8.84 Hz, 1H), 4.33 (q, J = 6.87 Hz, 2H), 3.18 (t, J = 4.78 Hz, 4H), 2.56 (t, J = 3.76 Hz, 4H), 2.29 (s, 3H), 1.33 (t, J = 7.52 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 161.9, 160.4, 155.6, 155.0 – 152.6 (d, $J_{C\text{-}F}$ = 243.2 Hz, 1C), 150.1, 145.6, 141.8, 135.6, 128.0, 127.3, 125.7 – 125.6 (d, $J_{C\text{-}F}$ = 7.91 Hz, 1C), 124.4, 120.9, 118.7, 116.0, 115.2 – 115.0 (d, $J_{C\text{-}F}$ = 24.1 Hz, 1C), 62.5, 53.9, 48.7, 44.8, 13.8.

*4.2.1.5.1.2. N-(2-(3-Fluoro-4-(4-methylpiperazin-1-yl)phenyl)-4-hydroxyquinazolin-6-yl)acetamide (**9b**);*



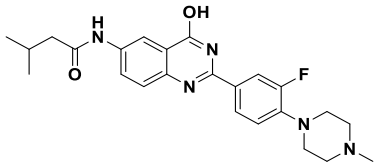
Light yellow solid, yield: 30%, mp: 250-252°C; FTIR (ATR, V_{max}, cm^{-1}): 3270.75 (O-H str.), 3172.40 (N-H str.), 2928.50 (Ar-H str.), 1660.77 (C=O str.), 1549.98 (Ar C=C str.), 1250.87 (C-N str.), 1117.81(C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.32 (s, 1H), 10.27 (s, 1H), 8.49 (d, J = 2.24 Hz, 1H), 8.00 – 7.95 (m, 2H), 7.90 – 7.87 (m, 1H), 7.65 (d, J = 8.86 Hz, 1H), 7.13 (t, J = 9.05 Hz, 1H), 3.17 (t, J = 5.83 Hz, 4H), 2.55 (t, J = 4.73 Hz, 4H), 2.28 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 168.5, 162.0, 155.1 – 152.6 (d, J_{C-F} = 246.2 Hz, 1C), 149.3, 144.4, 141.9 – 141.8 (d, J_{C-F} = 8.37 Hz, 1C), 137.5, 127.8, 126.0, 125.7 – 125.6 (d, J_{C-F} = 8.39 Hz, 1C), 124.1, 121.0, 118.6, 115.1 – 114.8 (d, J_{C-F} = 22.8, 114.0, 54.2, 49.1, 45.3, 24.0.

*4.2.1.5.1.3. N-(2-(3-Fluoro-4-(4-methylpiperazin-1-yl)phenyl)-4-hydroxyquinazolin-6-yl)isobutyramide (**9c**);*



Off white solid,yield: 54%, mp: 298-300°C; FTIR (ATR, V_{max}, cm^{-1}): 3275.40 (O-H str.), 3174.32 (N-H str.), 2958.33 (Ar-H str.), 1658.33 (C=O str.), 1550.86 (Ar C=C str.), 1252.26 (C-N str.), 1153.22 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 10.14 (s, 1H), 8.50 (d, J = 2.69 Hz, 1H), 8.00 – 7.92 (m, 3H), 7.65 (d, J = 8.99 Hz, 1H), 7.12 (t, J = 8.63 Hz, 1H), 3.15 (t, J = 4.93 Hz, 4H), 2.66 – 2.59 (m, 1H), 2.23 (s, 3H), 1.13 (d, J = 7.01 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 175.4, 162.0, 155.1 – 152.6 (d, J_{C-F} = 243.5 Hz, 1C), 149.3, 144.4, 142.1 – 142.0 (d, J_{C-F} = 7.9 Hz, 1C), 137.6, 127.8, 126.2, 125.6 – 125.5 (d, J_{C-F} = 7.64 Hz, 1C), 124.2, 120.9, 118.59 – 118.55 (d, J_{C-F} = 3.5 Hz, 1C), 115.1 – 114.8(d, J_{C-F} = 23.9 Hz, 1C), 114.3, 54.4, 49.4, 45.7, 35.0, 19.4.

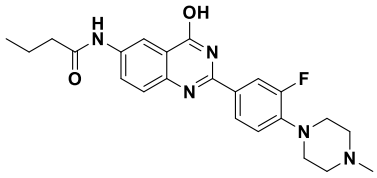
*4.2.1.5.1.4. N-(2-(3-Fluoro-4-(4-methylpiperazin-1-yl)phenyl)-4-hydroxyquinazolin-6-yl)-3-methylbutanamide (**9d**);*



Light Yellow solid, yield: 64%, mp: 296-298°C; FTIR (ATR, V_{max}, cm^{-1}): 3269.85 (O-H str.), 3173.08 (N-H str.), 2956.05 (Ar-H str.), 1670.05 (C=O str.), 1515.71 (Ar C=C str.), 1257.36 (C-N str), 1139.44 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.27 (brs, 1H), 10.17 (s,

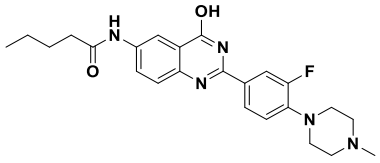
1H), 8.51 (d, *J* = 2.37 Hz, 1H), 7.99 – 7.97 (m, 1H), 7.94 – 7.88 (m, 2H), 7.64 (d, *J* = 8.79 Hz, 1H), 7.09 (t, *J* = 8.64 Hz,1H), 3.13 (t, *J* = 5.21 Hz, 4H), 2.46 (t, *J* = 4.97 Hz, 4H), 2.23 (d, *J* =7.28 Hz, 2H), 2.22 (s, 3H), 2.14 – 2.10 (m, 1H), 0.95 (d, *J* = 6.52 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 171.3, 162.5, 155.5 – 153.1 (d, $J_{C\text{-}F}$ = 244.80 Hz, 1C), 149.8, 148.2, 142.5, 137.9, 128.3, 126.6, 126.0, 124.6, 121.4, 119.0, 115.5 – 115.3 (d, $J_{C\text{-}F}$ = 22.94 Hz, 1C), 114.7, 54.9, 49.9, 46.2, 46.1, 26.0, 22.7.

*4.2.1.5.1.5. N-(2-(3-Fluoro-4-(4-methylpiperazin-1-yl)phenyl)-4-hydroxyquinazolin-6-yl)butyramide (**9e**);*



Light Yellow solid, yield: 40%, mp: 297-299°C; FTIR (ATR, V_{max}, cm^{-1}): 3275.50 (O-H str.), 3172.68 (N-H str.), 2958.61 (Ar-H str.), 1656.93 (C=O str.), 1530.38 (Ar C=C str.), 1253.03 (C-N str), 1012.45 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.31 (s, 1H), 10.19 (s, 1H), 8.50 (d, *J* = 2.44 Hz, 1H), 7.99 – 7.94 (m, 2H), 7.90 (dd, *J* = 8.79 Hz, *J* = 2.53 Hz, 1H), 7.65 (d, *J* = 8.83 Hz, 1H), 7.12 (d, *J* = 8.76 Hz, 1H), 3.15 (t, *J* = 6.16 Hz, 4H), 2.49 (t, *J* = 5.8 Hz, 4H), 2.33 (t, *J* = 6.79 Hz, 2H), 2.23 (s, 3H), 1.67 – 1.61 (m, 2H), 0.93 (t, *J* = 7.80 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 171.3, 162.0, 155.1 – 152.7 (d, $J_{C\text{-}F}$ = 243.47 Hz, 1C), 149.3, 142.0 – 141.9 (d, $J_{C\text{-}F}$ = 10.1 Hz, 1C), 137.5, 127.8, 126.1, 125.6 – 125.5 (d, $J_{C\text{-}F}$ = 7.8 Hz, 1C), 124.1, 121.0, 118.5, 115.1 – 114.8 (d, $J_{C\text{-}F}$ = 24.2 Hz, 1C), 114.1, 54.4, 49.4, 45.6, 38.3, 18.5, 13.6.

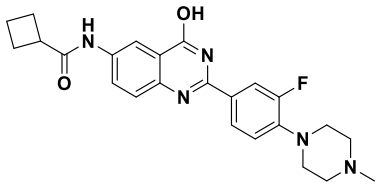
*4.2.1.5.1.6. N-(2-(3-Fluoro-4-(4-methylpiperazin-1-yl)phenyl)-4-hydroxyquinazolin-6-yl)pentanamide (**9f**);*



Light yellow solid, yield: 46%, mp: 294-296°C; FTIR (ATR, V_{max}, cm^{-1}): 3279.92 (O-H str.), 3173.41 (N-H str.), 2957.51 (Ar-H str.), 1656.26 (C=O str.), 1532.80 (Ar C=C str.), 1252.37 (C-N str.), 1154.99 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.31 (s, 1H), 10.19 (s, 1H), 8.50 (d, *J* = 2.14 Hz, 1H), 7.99 – 7.94 (m, 2H), 7.90 (dd, *J* = 8.82 Hz, *J* = 2.51 Hz, 1H), 7.65 (d, *J* = 8.78 Hz, 1H), 7.12 (t, *J* = 8.78 Hz, 1H), 3.15 (t, *J* = 4.81 Hz, 4H), 2.48 – 2.45 (m, 4H), 2.35

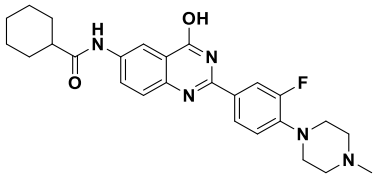
(t, *J* = 7.71 Hz, 2H), 2.23 (s, 3H), 1.64 – 1.57 (m, 2H), 1.39 – 1.30 (m, 2H), 0.91 (t, *J* = 7.73 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 171.6, 162.1, 155.1 – 152.7 (d, $J_{C\text{-}F}$ = 244.92 Hz, 1C), 149.4, 144.4, 142.1 – 142.0 (d, $J_{C\text{-}F}$ = 7.34 Hz, 1C), 137.5, 127.9, 126.2, 125.6 – 125.5 (d, $J_{C\text{-}F}$ = 7.75 Hz, 1C), 124.2, 121.0, 118.6, 115.1 – 114.9 (d, $J_{C\text{-}F}$ = 23.4 Hz, 1C), 114.2, 54.5, 49.4, 45.7, 36.2, 27.2, 21.8, 13.7.

*4.2.1.5.1.7. N-(2-(3-Fluoro-4-(4-methylpiperazin-1-yl)phenyl)-4-hydroxyquinazolin-6-yl)cyclobutanecarboxamide (**9g**);*



Light yellow solid, yield: 64%, mp: 297-299°C; FTIR (ATR, V_{max}, cm^{-1}): 3271.96 (O-H str.), 3173.79 (N-H str.), 2955.54 (Ar-H str.), 1671.43 (C=O str.), 1518.89 (Ar C=C str.), 1256.38 (C-N str), 1141.95 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.30 (s, 1H), 10.04 (s, 1H), 8.50 (s, 1H), 7.99 – 7.91 (m, 3H), 7.64 (d, *J* = 8.68 Hz, 1H), 7.11 (t, *J* = 8.70 Hz, 1H), 3.26 – 3.22 (m, 1H), 3.14 (t, *J* = 4.89 Hz, 4H), 2.47 (t, *J* = 4.78 Hz, 4H), 2.30 – 2.25 (m, 2H), 2.22 (s, 3H), 2.16 – 2.08 (m, 2H), 2.01 – 1.89 (m, 1H), 1.86 – 1.79 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 173.1, 162.0, 155.1 – 152.6 (d, $J_{C\text{-}F}$ = 245.04 Hz, 1C), 149.3, 144.3, 142.08 – 142.0 (d, $J_{C\text{-}F}$ = 7.87 Hz, 1C), 124.1, 121.0, 118.5, 115.0 – 114.8 (d, $J_{C\text{-}F}$ = 24.61 Hz, 1C), 114.3, 54.4, 49.4, 45.7, 30.6, 24.6, 17.7.

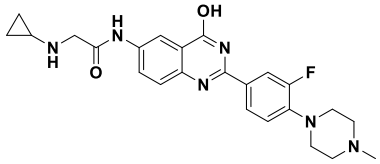
*4.2.1.5.1.8. N-(2-(3-Fluoro-4-(4-methylpiperazin-1-yl)phenyl)-4-hydroxyquinazolin-6-yl)cyclohexanecarboxamide(**9h**);*



Light yellow solid, yield: 65%, mp: 296-298°C; FTIR (ATR, V_{max}, cm^{-1}): 3379.60 (O-H str.), 3173.77 (N-H str.), 2929.33 (Ar-H str.), 1655.79 (C=O str.), 1532.07 (Ar C=C str.), 1253.27 (C-N str.), 1153.50 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.30 (s, 1H), 10.13 (s, 1H), 8.51 (d, *J* = 2.58Hz, 1H), 8.0 – 7.90 (m, 3H), 7.64 (d, *J* = 8.84 Hz, 1H), 7.12 (t, *J* = 8.32 Hz, 1H), 3.15 (t, *J* = 4.95 Hz, 4H), 2.47 (t, *J* = 4.81 Hz, 4H), 2.40 – 2.32 (m, 1H), 1.84 – 1.75 (m, 2H), 1.67 – 1.64 (m, 1H), 1.48 – 1.39 (m, 2H), 1.33 – 1.18 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 174.5, 162.0, 155.1 – 152.7 (d, $J_{C\text{-}F}$ = 245.7 Hz, 1C), 149.3, 144.3, 142.0 – 141.9 (d, $J_{C\text{-}F}$ = 8.7 Hz, 1C), 137.6, 127.8, 126.2, 125.6 – 125.5 (d, $J_{C\text{-}F}$ = 8.3 Hz, 1C), 124.2,

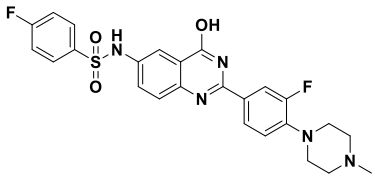
120.9, 118.6 – 118.5 (d, J_{C-F} = 3.7 Hz, 1C), 115.1 – 114.8 (d, J_{C-F} = 23.6 Hz, 1C), 114.2, 54.4, 49.4, 45.6, 44.9, 29.0, 25.3, 25.1.

*4.2.1.5.2.1. 2-(Cyclopropylamino)-N-(2-(3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)-4-hydroxyquinazolin-6-yl)acetamide (**9i**);*



Light yellow solid, yield: 42%, mp: 250-252°C; FTIR (ATR, V_{max}, cm^{-1}): 3280.09 (O-H str.), 3181.76 (N-H str.), 2928.76 (Ar-H str.), 1664.34 (C=O str.), 1551.08 (Ar C=C str.), 1252.84 (C-N str.), 1116.95 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.30 (s, 1H), 10.14 (s, 1H), 8.52 (d, J = 2.54 Hz, 1H), 8.00 – 7.97 (m, 2H), 7.95 – 7.94 (m, 1H), 7.66 (d, J = 8.81 Hz, 1H), 7.11 (t, J = 8.19 Hz, 1H), 3.40 (s, 2H), 3.15 (t, J = 4.33 Hz, 4H), 2.51 (t, J = 4.66 Hz, 4H), 2.25 (s, 3H), 2.23 – 2.18 (m, 1H), 0.41 – 0.36 (m, 2H), 0.35 – 0.31 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 171.1, 162.5, 155.5 – 153.1 (d, J_{C-F} = 242.7 Hz, 1C), 149.9, 145.1, 142.5 – 142.4 (d, J_{C-F} = 7.81 Hz, 1C), 137.4, 128.4, 126.8, 126.1 – 126.0 (d, J_{C-F} = 7.9 Hz, 1C), 124.7, 121.5, 119.1, 115.6 – 115.3 (d, J_{C-F} = 24.2 Hz, 1C), 114.8, 54.8, 53.1, 49.7, 46.0, 30.5, 6.4.

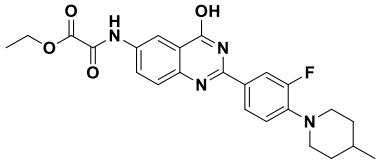
*4.2.1.5.3.1. 4-Fluoro-N-(2-(3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)-4-hydroxyquinazolin-6-yl)benzenesulfonamide (**9j**);*



Light yellow solid, yield: 49%, mp: 265-267°C; FTIR (ATR, V_{max}, cm^{-1}): 3260.14 (O-H str.), 3079.22 (N-H str.), 2956.61 (Ar-H str.), 1669.60 (C=O str. Keto-enol), 1591.19 (Ar C=C str.), 1485.10 (SO_2 asym.), 1252.64 (C-N str), 1234.94 (SO_2 sym.), 1154.16 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.37 (s, 1H), 10.64 (s, 1H), 7.97 – 7.91 (m, 2H), 7.84 – 7.79 (m, 3H), 7.62 (d, J = 8.68 Hz, 1H), 7.58 – 7.52 (m, 1H), 7.40 (t, J = 8.75 Hz, 2H), 7.11 (t, J = 8.86 Hz, 1H), 3.16 (t, J = 5.26 Hz, 4H), 2.53 (t, J = 4.40 Hz, 4H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 165.6 – 163.1 (d, J_{C-F} = 251.7 Hz, 1C), 161.8, 155.0 – 152.6 (d, J_{C-F} = 243.6 Hz, 1C), 150.1, 145.4, 142.1 – 142.0 (d, J_{C-F} = 8.12 Hz, 1C), 135.6, 135.6 – 135.5 (d, J_{C-F} = 2.80 Hz, 1C), 129.7 – 129.6 (d, J_{C-F} = 9.94 Hz, 1C), 128.6, 127.4, 125.4 – 125.3 (d, J_{C-F} = 7.92 Hz,

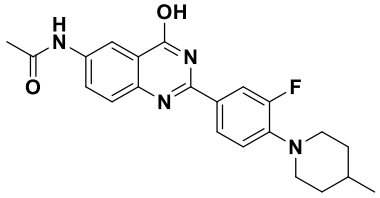
1C), 124.3, 121.2, 118.6, 116.7 – 116.5 (d, J_{C-F} = 24.09 Hz, 1C), 115.6, 115.2 – 115.0 (d, J_{C-F} = 3.38 Hz, 1C), 54.3, 49.2, 45.4.

*4.2.1.5.1.9. Ethyl 2-((2-(3-fluoro-4-(4-methylpiperidin-1-yl)phenyl)-4-hydroxyquinazolin-6-yl)amino)-2-oxoacetate (**10a**);*



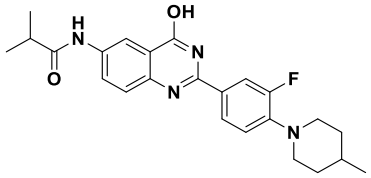
Yellow solid, yield: 63%, mp: 297-299°C; FTIR (ATR, V_{max}, cm^{-1}): 3334.94 (O-H str.), 3172.71 (N-H str.), 2921.56 (Ar-H str.), 1710.28 (C=O str.), 1659.26 (C=O str.), 1515.84 (Ar C=C str.), 1250.62 (C-N str.), 1181.71 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.36 (s, 1H), 11.09 (s, 1H), 8.63 (d, J = 2.34 Hz, 1H), 8.09 (dd, J = 8.83 Hz, J = 2.46 Hz, 1H), 7.99 – 7.94 (m, 2H), 7.69 (d, J = 8.69 Hz, 1H), 7.11 (t, J = 8.55 Hz, 1H), 4.33 (q, J = 7.35 Hz, 2H), 3.50 (d, J = 12,29 Hz, 2H), 2.78 – 2.72 (m,2H), 1.71 (d, J = 10.82 Hz, 2H), 1.57 – 149 (m, 1H), 1.33 (t, J = 7.11 Hz, 3H), 1.30 – 1.222 (m, 2H), 0.95 (d, J = 6.46 Hz, 3H).^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 162.0, 160.4, 155.5, 155.1 – 152.6 (d, J_{C-F} = 247.8 Hz, 1C), 150.2, 145.7, 142.9 – 142.8 (d, J_{C-F} = 8.72 Hz, 1C), 135.5, 127.9, 127.3, 124.9 – 124.8 (d, J_{C-F} = 7.72 Hz, 1C), 124.3, 120.9, 118.7, 116.1, 115.1 – 114.9 (d J_{C-F} = 23.8 Hz, 1C), 62.5, 50.1, 33.7, 30.0, 21.7, 13.8.

*4.2.1.5.1.10 N-(2-(3-Fluoro-4-(4-methylpiperidin-1-yl)phenyl)-4-hydroxyquinazolin-6-yl)acetamide (**10b**);*



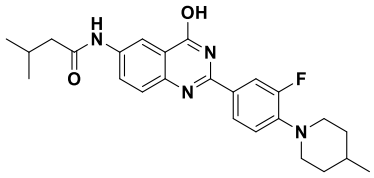
Off white solid, yield: 60%, mp: 295-298°C; FTIR (ATR, V_{max}, cm^{-1}): 3273.47 (O-H str.), 3170.62 (N-H str.), 2912.98 (Ar-H str.), 1661.23 (C=O str.), 1538.86 (Ar C=C str.), 1242.35 (C-N str.), 1194.11 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 10.08 (s, 1H), 8.30 (d, J = 2.30 Hz, 1H), 8.05 – 7.97 (m, 2H), 7.78 (dd, J = 8.87 Hz, J = 2.45 Hz, 1H), 7.49 (d, J = 8.78 Hz, 1H), 7.05 (t, J = 8.74 Hz, 1H), 3.46 – 3.43 (m, 2H), 2.74 – 2.68 (m, 2H), 2.70 (s, 3H), 1.73 – 1.70 (m, 2H), 1.52 – 1.50 (m, 1H), 1.35 – 1.25 (m, 2H), 0.95 (d, J = 6.53 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 168.7, 168.0, 155.4 – 153.0 (d, J_{C-F} = 243.62 Hz, 1C), 147.0, 141.44, 135.2, 126.6, 124.4, 123.9, 121.3, 118.2, 115.0 – 114.7 (d, J_{C-F} = 23.1 Hz, 1c), 114.6, 50.4, 33.9, 30.0, 23.9, 21.7.

*4.2.1.5.1.11. N-(2-(3-Fluoro-4-(4-methylpiperidin-1-yl)phenyl)-4-hydroxyquinazolin-6-yl)isobutyramide (**10c**);*



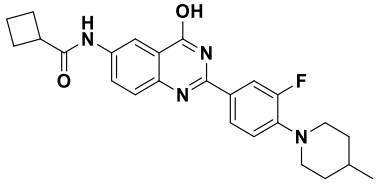
Off white solid, yield: 46%, mp: 292-295°C; FTIR (ATR, V_{max}, cm^{-1}): 3276.53 (O-H str.), 3172.50 (N-H str.), 2918.24 (Ar-H str.), 1659.47 (C=O str.), 1542.85 (Ar C=C str.), 1243.35 (C-N str.), 1135.21 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.28 (s, 1H), 10.14 (s, 1H), 8.49 (d, J =2.46 Hz, 1H), 7.98 – 7.92 (m, 3H), 7.64 (d, J = 8.87 Hz, 1H), 7.11 (t, J = 8.78 Hz, 1H), 3.51 – 3.48 (m, 2H), 2.78 – 2.72 (m, 2H), 2.66 – 2.59 (m, 1H), 1.73 – 1.70 (m, 2H), 1.55 – 149 (m, 1H), 1.34 – 1.25 (m, 2H), 1.13 (d, J = 6.95 Hz, 6H), 0.95 (d, J = 6.56 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 175.5, 162.1, 155.1 – 152.7 (d, J_{C-F} = 242.0 Hz, 1C), 149.7, 144.5, 142.8 – 142.7 (d, J_{C-F} = 8.25 Hz, 1C), 137.6, 127.8, 126.3, 125.2 – 125.1 (d, J_{C-F} = 8.04 Hz, 1C), 124.2, 121.0, 118.77 – 118.73 (d, J_{C-F} = 3.43 Hz, 1C), 115.0 – 114.8 (d, J_{C-F} = 23.93 Hz, 1C), 114.4, 50.1, 35.0, 33.7, 30.0, 21.7, 19.4.

*4.2.1.5.1.12. N-(2-(3-Fluoro-4-(4-methylpiperidin-1-yl)phenyl)-4-hydroxyquinazolin-6-yl)-3-methylbutanamide (**10d**);*



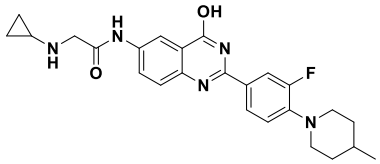
Yellow solid, yield: 34%, mp: 293-295°C; FTIR (ATR, V_{max}, cm^{-1}): 3276.06 (O-H str.), 3176.62 (N-H str.), 2948.55 (Ar-H str.), 1661.94 (C=O str.), 1524.70 (Ar C=C str.), 1244.25 (C-N str.), 1131.48 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.29 (s, 1H), 10.17 (s, 1H), 8.50 (d, J = 2.24 Hz, 1H), 7.98 – 7.88 (m, 3H), 7.64 (d, J = 8.82 Hz, 1H), 7.11 (t, J = 8.48 Hz, 1H), 3.51 – 3.48 (m, 2H), 2.78 – 2.72 (m, 2H), 2.23 (d, J = 6.98 Hz, 2H), 2.14 – 2.07 (m, 1H), 1.73 – 1.70 (m, 2H), 1.55 – 1.51 (m, 1H), 1.33 – 1.22 (m, 2H), 0.95 (d, J = 6.33Hz, 9H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 170.9, 162.0, 155.1 – 152.7 (d, J_{C-F} = 243.08 Hz, 1C), 149.4, 144.5, 142.8 – 142.7 (d, J_{C-F} = 8.17 Hz, 1C), 137.4, 127.8, 126.2, 125.2 – 125.1 (d, J_{C-F} = 7.71 Hz, 1C), 124.2, 120.9, 118.74 – 118.71 (d, J_{C-F} = 3.5 Hz, 1C), 115.0 – 114.8 (d, J_{C-F} = 24.37 Hz, 1C), 114.2, 50.1, 45.6, 33.7, 30.0, 25.6, 22.2, 21.7.

*4.2.1.5.1.13. N-(2-(3-Fluoro-4-(4-methylpiperidin-1-yl)phenyl)-4-hydroxyquinazolin-6-yl)cyclobutanecarboxamide (**10e**);*



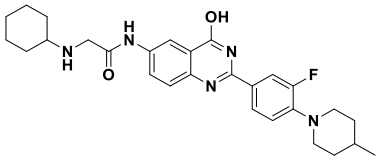
Off white solid, yield: 34%, mp: 297-299°C; FTIR (ATR, V_{max}, cm^{-1}): 3272.78 (O-H str.), 3178.12 (N-H str.), 2917.41 (Ar-H str.), 1664.91 (C=O str.), 1518.11 (Ar C=C str.), 1249.12 (C-N str.), 1133.35 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.28 (s, 1H), 10.04 (s, 1H), 8.50 (s, 1H), 7.97 – 7.92 (m, 3H), 7.64 (d, J = 9.34 Hz, 1H), 7.11 (t, J = 9.0 Hz, 1H), 3.51 – 3.48 (m, 2H), 3.26 – 3.24 (m, 1H), 2.78 – 2.72 (m, 2H), 2.28 – 2.21 (m, 2H), 2.14 – 2.08 (m, 2H), 2.01 – 1.90 (m, 1H), 1.86 – 1.81 (m, 1H), 1.73 – 1.70 (m, 2H), 1.60 – 1.45 (m, 1H), 1.33 – 1.25 (m, 2H), 0.95 (d, J = 6.26 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 173.1, 162.1, 155.1 – 152.7 (d, J_{C-F} = 242.4 Hz, 1C), 149.4, 144.4, 142.7 – 142.6 (d, J_{C-F} = 10.65 Hz, 1C), 137.5, 127.8, 126.2, 125.2 – 125.1 (d, J_{C-F} = 11.02 Hz, 1C), 124.1, 121.0, 118.7, 115.0 – 114.8 (d, J_{C-F} = 23.98 Hz, 1C), 114.3, 50.1, 39.6, 33.7, 30.0, 24.6, 21.7, 17.7.

*4.2.1.5.2.1. 2-(Cyclopropylamino)-N-(2-(3-fluoro-4-(4-methylpiperidin-1-yl)phenyl)-4-hydroxyquinazolin-6-yl)acetamide (**10f**);*



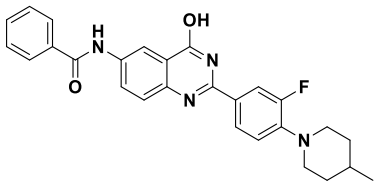
Off white solid, yield: 40%, mp: 283-285°C; FTIR (ATR, V_{max}, cm^{-1}): 3275.71 (O-H str.), 3174.42 (N-H str.), 2919.54 (Ar-H str.), 1660.96 (C=O str.), 1533.07 (Ar C=C str.), 1237.71 (C-N str.), 1131.61 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.22 (brs, 1H), 10.11 (s, 1H), 8.52 (d, J = 2.49 Hz, 1H), 7.97 – 7.92 (m, 3H), 7.65 (d, J = 8.91 Hz, 1H), 7.10 (t, J = 8.52 Hz, 1H), 3.50 – 3.47 (m, 2H), 2.77 – 2.71 (m, 2H), 2.22 – 2.16 (m, 1H), 1.72 – 1.69 (m, 2H), 1.54 – 1.48 (m, 1H), 1.33 – 1.21 (m, 2H), 0.94 (d, J = 6.62 Hz, 3H), 0.40 – 0.35 (m, 2H), 0.34 – 0.29 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 170.8, 162.1, 155.1 – 152.7 (d, J_{C-F} = 243.72 Hz, 1C), 144.6, 142.8, 142.7, 136.9, 127.9, 126.3, 125.2 – 125.1 (d, J_{C-F} = 7.41 Hz, 1C), 124.2, 121.0, 118.1, 115.0 – 114.8 (d, J_{C-F} = 23.5 Hz, 1C), 114.4, 52.7, 50.1, 33.7, 30.1, 30.0, 21.7, 6.1.

*4.2.1.5.2.2. 2-(Cyclohexylamino)-N-(2-(3-fluoro-4-(4-methylpiperidin-1-yl)phenyl)-4-hydroxyquinazolin-6-yl)acetamide (**10g**);*



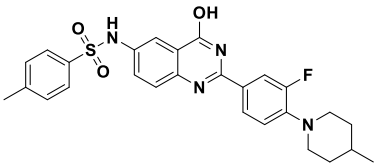
Yellow solid, yield: 61%, mp: 292-295°C; FTIR (ATR, V_{max}, cm^{-1}): 3267.58 (O-H str.), 3081.67 (N-H str.), 2918.66 (Ar-H str.), 1659.56 (C=O str.), 1528.97 (Ar C=C str.), 1239.18 (C-N str.), 1131.65 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 10.15 (s, 1H), 8.52 (d, J = 2.71 Hz, 1H), 7.99 – 7.93 (m, 3H), 7.66 (d, J = 8.79 Hz, 1H), 7.11 (t, J = 8.48 Hz, 1H), 3.51 – 3.48 (m, 2H), 3.35 (s, 2H), 2.78 – 2.72 (m,2H), 2.45 – 2.37 (m, 1H), 1.84 – 1.81 (m, 2H), 1.73 – 1.66 (m, 4H), 1.56 – 1.50 (m, 2H), 1.34 – 1.25 (m, 2H), 1.22 – 1.16 (m, 2H), 1.14 – 1.04 (m, 3H), 0.95 (d, J = 6.59 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 170.9, 162.0, 155.1 – 152.7 (d, J_{C-F} = 243.55 Hz, 1C), 149.5, 144.6, 142.7 – 142.6 (d, J_{C-F} = 8.20 Hz, 1C), 136.7, 127.9, 126.2, 125.1 – 125.0 (d, J_{C-F} = 8.61 HZ, 1C), 124.2, 120.9, 118.7 - 118.6 (d, J_{C-F} = 3.87 Hz, 1C), 115.0 – 114.7 (d, J_{C-F} = 24.33 Hz, 1C), 114.3, 56.2, 50.15, 50.1, 33.7, 32.7, 30.0, 25.6, 24.3, 21.7.

*4.2.1.5.1.14. N-(2-(3-Fluoro-4-(4-methylpiperidin-1-yl)phenyl)-4-hydroxyquinazolin-6-yl)benzamide (**10h**);*



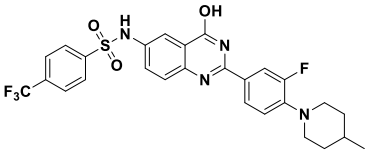
Yellow solid, yield: 27%, mp: 298-300°C; FTIR (ATR, V_{max}, cm^{-1}): 3278.50 (O-H str.), 3168.84 (N-H str.), 2935.86 (Ar-H str.), 1662.05 (C=O str.), 1522.68 (Ar C=C str.), 1244.15 (C-N str.), 1134.34 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.33 (s, 1H), 10.56 (s, 1H), 8.68 (d, J = 2.49 Hz, 1H), 8.17 (dd, J = 8.95 Hz, J = 2.52 Hz, 1H), 8.01 – 7.92 (m, 4H), 7.70 (d, J = 8.53 Hz, 1H), 7.62 – 7.54 (m, 3H), 7.14 – 7.07 (m, 1H), 3.50 (d, J = 12.10 Hz, 2H), 2.78 – 2.71 (m, 2H), 1.71 (d, J = 12.75 Hz, 2H), 1.54 – 1.50 (m, 1H), 1.34 – 1.25 (m, 2H), 0.95 (d, J = 6.34 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 165.7, 162.2, 155.2 – 152.7 (d, J_{C-F} = 246 Hz, 1C), 154.3, 149.7, 144.9, 142.7, 137.3, 134.6, 131.8, 129.5, 128.4, 127.7, 127.2, 125.1, 124.2, 120.9, 118.8, 115.6, 50.1, 33.7, 30.0, 21.7.

*4.2.1.5.3.2. N-(2-(3-Fluoro-4-(4-methylpiperidin-1-yl)phenyl)-4-hydroxyquinazolin-6-yl)-4-methylbenzenesulfonamide (**10i**);*



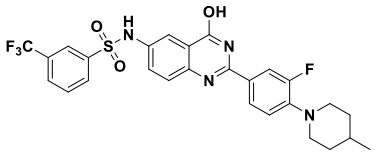
Off white solid, yield: 21%, mp: 298-300°C; FTIR (ATR, V_{max}, cm^{-1}): 3255.53 (O-H str.), 3087.02 (N-H str.), 2936.03 (Ar-H str.), 1669.12 (C=O str.), 1547.04 (Ar C=C str.), 1354.95 (SO2, asym), 1243.21 (C-N str.), 1158.44 (SO2 sym), 1131.21 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.33 (s, 1H), 10.60 (s, 1H), 7.94 – 7.88 (m, 2H), 7.80 (d, J = 2.51 Hz, 1H), 7.66 (d, J = 8.20 Hz, 2H), 7.59 (d, J = 8.91 Hz, 1H), 7.54 (dd, J = 8.86 Hz, J = 2.53 Hz, 1H), 7.34 (d, J = 8.15 Hz, 2H), 7.08 (t, J = 8.82 Hz, 1H), 3.49 – 3.46 (m, 2H), 2.76 – 2.70 (m, 2H), 2.30 (s, 3H), 1.71 – 1.68 (m, 2H), 1.56 – 1.47 (m, 1H), 1.31 – 1.21 (m, 2H), 0.93 (d, J = 6.67 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 162.2, 155.5 – 153.1 (d, J_{C-F} = 242.8 Hz, 1C), 150.4, 143.9, 143.3, 136.8, 136.3, 130.2, 129.0, 127.4, 127.1, 125.4, 124.7, 121.6, 119.1, 115.5 – 115.3 (d, J_{C-F} = 20.1 Hz, 1C), 50.5, 34.2, 30.4, 22.1, 21.3.

*4.2.1.5.3.3. N-(2-(3-Fluoro-4-(4-methylpiperidin-1-yl)phenyl)-4-hydroxyquinazolin-6-yl)-4-(trifluoromethyl)benzenesulfonamide (**10j**);*



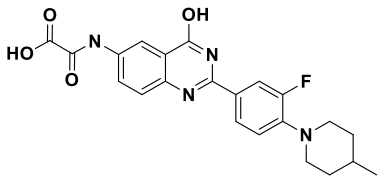
Off white solid, yield: 30%, mp: 295-297°C; FTIR (ATR, V_{max}, cm^{-1}): 3265.95 (O-H str.), 3087.89 (N-H str.), 2945.30 (Ar-H str.), 1670.02 (C=O str.), 1547.90 (Ar C=C str.), 1325.51 (SO2 asym), 1243.57 (C-N str.), 1168.68 (Sym.), 1136.01 (C-F str.), ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.37 (s, 1H), 10.89 (s, 1H), 7.99 – 7.97 (m, 4H), 7.94 – 7.89 (m, 2H), 7.81 (d, J = 2.48 Hz, 1H), 7.62 (d, J = 8.73 Hz, 1H), 7.55 (dd, J = 9.8 Hz, J = 2.55 Hz, 1H), 7.08 (t, J = 9.03 Hz, 1H), 3.49 – 3.46 (m, 2H), 2.76 – 2.70 (m, 2H), 1.70 – 1.68 (m, 2H), 1.55- 1.47 (m, 1H), 1.31 – 1.21 (m, 2H), 0.93 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 161.7, 155.0 – 152.6 (d, J_{C-F} = 243.39 Hz, 1C), 150.3, 145.7, 143.0, 142.9 – 142.8 (d, J_{C-F} = 8.83 Hz, 1C), 135.1, 132.8 – 132.5 (d, J_{C-F} = 32.1 Hz, 1C), 128.7, 127.6, 127.4, 126.73 – 126.7 (d, J_{C-F} = 3.61 Hz, 1C), 124.8 – 124.7 (d, J_{C-F} = 7.86 Hz, 1C), 124.6, 124.3, 121.2, 118.7, 115.8, 115.1 – 114.9 (d, J_{C-F} = 24.8 Hz, 1C), 50.1, 33.7, 30.0, 21.7.

*4.2.1.5.3.4 N-(2-(3-Fluoro-4-(4-methylpiperidin-1-yl)phenyl)-4-hydroxyquinazolin-6-yl)-3-(trifluoromethyl)benzenesulfonamide (**10k**);*



Off white solid, yield: 30%, mp: 295-297°C; FTIR (ATR, V_{max}, cm^{-1}): 3250.14 (O-H str.), 3088.14 (N-H str.), 2921.53 (Ar-H str.), 1670.57 (C=O str.), 1550.10 (Ar C=C str.), 1316.94, (SO2, asym.), 1242.04 (C-N str.), 1161.90 (SO2 sym.), 1132.25 (C-F str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.37 (s, 1H), 10.81, (s, 1H), 8.04 – 8.01 (m, 2H), 7.94 – 7.89 (m, 2H), 7.83 – 7.79 (m, 2H), 7.62 (d, J = 8.78 Hz, 1H), 7.53 (dd, J = 8.77 Hz, J = 2.46 Hz, 1H), 7.09 (t, J = 8.72 Hz, 1H), 3.48 (d, J = 12.01 Hz, 2H), 2.74 (t, J = 12.07 Hz, 2H), 1.71 – 1.68 (m, 2H), 1.54 – 1.49 (m, 1H), 1.34 – 1.22 (m, 2H), 0.94 (d, J = 6.40 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 162.1, 155.5 – 153.0 (d, J_{C-F} = 243.1 Hz, 1C), 150.8, 146.2, 143.3, 140.7, 135.5, 131.6, 131.1, 130.5 – 130.2 (d, J_{C-F} = 32.5 Hz, 1C), 130.3, 129.2, 128.1, 125.2 – 125.1 (d, J_{C-F} = 7.96 Hz, 1C), 124.8, 123.65 – 123.6 (d, J_{C-F} = 3.84 Hz, 1C), 121.6, 119.2 – 119.1 (d, J_{C-F} = 3.40 Hz, 1C), 116.5, 115.6 – 115.3 (d, J_{C-F} = 23.85 Hz, 1C), 50.4, 34.1, 30.4, 22.1.

*4.2.1.5.1.9.1 Synthesis of 2-((2-(3-fluoro-4-(4-methylpiperidin-1-yl)phenyl)-4-hydroxyquinazolin-6-yl)amino)-2-oxoacetic acid (**10l**):*



To the suspension of ethyl 2-((2-(3-fluoro-4-(4-methylpiperidin-1-yl)phenyl)-4-hydroxyquinazolin-6-yl)amino)-2-oxoacetate (0.15 g, 0.33 mmol) in THF and EtOH was added aqueous lithium hydroxide (0.023 g, 0.99 mmol). The resultant mixture was stirred at room temperature for 4 h, then solvent was evaporated under reduce pressure, diluted with water and washed with ethyl acetate. The aqueous layer was acidified with 6N-HCl, and extracted with ethyl acetate (3 x 10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduce pressure to afford yellow solid product (0.099 g, 70%); mp: 275-277°C; ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ 12.36 (s, 1H), 11.03 (s, 1H), 8.67 (d, J = 2.80 Hz, 1H), 8.09 (dd, J = 8.84 Hz, J = 2.56 Hz, 1H), 8.00 – 7.94 (m, 2H), 7.69 (d, J = 8.85 Hz, 1H), 7.11 (t, J = 8.94 Hz, 1H), 3.52 – 3.49 (m, 2H), 2.79 – 2.73 (m, 2H), 1.73 – 1.70 (m, 2H), 1.55 – 1.50 (m, 1H), 1.34 – 1.22 (m, 2H), 0.95 (d, J = 6.66 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25°C) δ 162.0, 161.8, 156.9, 155.0 – 152.6 (d, J = 244.8 Hz, 1C), 150.1, 145.4, 142.8 – 142.7 (d, J = 7.99 Hz, 1C), 135.7, 127.8, 127.2, 124.9 – 124.8 (d, J = 7.7 Hz, 1C), 124.3, 120.8, 118.7, 115.8, 115.1 – 114.9 (d, J = 23.7 Hz, 1C), 50.1, 33.7, 30.0, 21.7.

4.3. Biology

4.3.1. Evaluation of inhibitory activities on E. coli DNA gyrase and topoisomerase IV

Synthesized quinazoline derivatives were evaluated for their inhibitory activity against DNA gyrase and topoisomerase IV from E. coli in supercoiling and decatenation assays, respectively. These assays were performed based on established protocols attained from the supplier, TopoGEN, Inc. (Buena Vista, Colorado, USA). All of the reactions (DNA gyrase and Topo isomerase IV activities) loaded on a 1% agarose, TAE (40 mM Tris-acetate, 0.01 M EDTA, pH 8.3) gel and run for 3–4 hr at 50 V. The gel was stained with 0.5 µg mL^{-1} ethidium bromide in TAE for 30 min while rocking, then destained for 10 min in deionized water. The images were captured on a Gel doc XR imaging system from BIO-RAD. at a wavelength of 300 nm. The intensity of the reaction product, for gyrase, and the decatenation product of topoisomerase were quantitated using Image Lab software and IC_{50} values were determined by non-linear regression analysis in Graph Pad Prism 8.

4.3.1.1. Evaluation of inhibitory activities on E. coli DNA gyrase (supercoiling and relaxation)

Supercoiling of relaxed plasmid DNA (pHOT1) was examined in a reaction volume of 20 µl contains of assay buffer (35 mM Tris pH 7, 24 mM KCl, 4 mM $MgCl_2$, 2 mM DTT, 1.8 mM spermidine, 6.5% glycerol, 0.1 mg/ml acetylated BSA, 1 mM ATP), and 0.2 mg of relaxed DNA (pHOT1 a derivative of pBR322 < 3KB) substrate. Drug compounds with different concentrations (100, 10, 1µM) in DMSO were added and after that the reactions were initiated with 2 units of E. coli gyrase (TopoGEN). In order to compare the results optimum concentration of ciprofloxacin (10 µM) has been used as standard. The reaction proceeded for incubation with shaking on a mini-orbital shaker for 1 hour at 37°C. After the incubation, added 0.1volume of 10% SDS and 10 µl of proteinase K (20mg/ml) and digest for 30 min. at 37°C. Then add 0.1volume of 10x loading dye (0.25% bromophenol and 50 % glycerol), followed by organic extraction using chloroform: isoamyl alcohol mixture (24:1 ratio), vortex briefly, separate blue coloured upper aqueous phase and load onto 1% agrose gel.

The gyrase relaxation activity was assayed with corresponding supercoiled DNA using supercoiling buffer (without ATP and spermidine). Different concentrations of test compound (100, 10, 1µM) were prepared in DMSO and added to the reaction mix prior to enzyme addition. For the comparison, ciprofloxacin was tested in the same experiment as standard. The reaction proceeded for incubation for 1 hour at 37°C. After the incubation, added 0.1volume of

10% SDS and 10 µL of proteinase K (20mg/mL) and digest for 30 min. at 37°C. Then add 0.1volume of 10x loading dye (0.25% bromophenol and 50 % glycerol), followed by organic extraction using chloroform: isoamyl alcohol mixture (24:1 ratio), vortex briefly, separate blue colored upper aqueous phase and load onto 1% agrose gel. The loaded DNA was stained with 0.5 µg mL^{-1} ethidium bromide for 30 minutes and distain with distilled water for 10 min at room temperature. The photo visualized and documented with Gel doc XR imaging system from BIO-RAD. Quantification of the intensity of the bands was performed using Image Lab software provided by BIO-RAD.com and IC50 was determined using Graph Pad Prism 8.

4.3.1.2. Evaluation of inhibitory activities on E. coli topoisomerase IV (relaxation and decatenation)

The inhibition activities of topoisomerase IV enzyme were assayed with corresponding assay buffer using relaxation and decatenation of supercoiled DNA and kinetoplast DNA substrate, respectively. The reaction mixture(20µl) for relaxation consist of Assay buffer (40 mM Tris pH 7.5, 6 mM $MgCl_2$, 10 mM DTT, 100 mM potassium glutamate, 50 mg/ml acetylated BSA, 1 mM ATP) and 0.2mg supercoiled DNA. Different concentration of test compound in DMSO were added and reactions were initiated with 2 Units of *E. coli* TopoIV after that incubated for 30 mins at 37°C. The stop reaction and extraction procedure were same as above for the DNA gyrase.

Decatenation was assayed in a reaction volume of 20 µl of containing 40 mM Tris pH 7.5, 6 mM $MgCl_2$, 10 mM DTT, 100 mM potassium glutamate, 50 mg/ml acetylated BSA, 1 mM ATP, and 0.2 mg kDNA substrate. Test compound with different concentration (in DMSO) were added and the reactions were initiated with 2 units of E. coli topoIV (Topogen) that were incubated for 30 min at 37°C. After incubation follow the same procedure as mention in *E. coli* DNA gyrase.

5. References

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CHAPTER 7

1. SUMMARY AND CONCLUSION

Tuberculosis (TB) and other microbial infections are becoming a major health problem due to the rapidly emerging drug resistance as well as co-infection. Tuberculosis is one of the leading cause of death from a single infectious agent. Keeping TB as a main target, the work in this thesis is divided into 6 chapters and in total 110 derivatives have been synthesized. **Chapter 1** briefly describes, drug discovery and medicinal chemistry, history of antibiotic expansion, development of resistance in bacteria, history of TB drugs discovery, line of treatment for TB, anti-tuberculosis drugs and their specific targets and classification of TB drugs. In addition, we have also explored DNA gyrase and topoisomerase IV as a key target for anti-bacterial agents, marketed drugs and recently reported DNA gyrase inhibitors. This led us to explore heterocycles (Benzoxazine and quinazoline) as potential anti-TB targets.

In **Chapter 2**, we have developed a simple, yet efficient one-pot, multicomponent, green, catalyst-free, and diastereospecific tandem synthesis of 1,4-benzoxazines in excellent yields. This one-pot, in-situ reaction proceeds by the formation of a Schiff base followed by base mediated *O*-alkylation with the phenacyl bromide and finally catalyst free intramolecular cyclization. Further, this versatile novel methodology provides a wide scope for the synthesis of differentially substituted/functionalised 1,4-benzoxazine analogues, which can be exploited by the researchers in academia, pharmaceutical and agrochemical industries in developing new building blocks for the synthesis of new active pharmaceutical ingredients (API's), drugs and pesticides.

In **chapter 3**, 15 compounds based on fluorinated quinazoline derivatives have been synthesized and well-characterized with Infrared (IR) and Nuclear Magnetic Resonance (NMR) spectroscopic methods (^{1}H, ^{13}C, COSY, HMBC, HSQC and NOESY). Additionally, crystal structure of 4 derivatives (**13b**, **13e**, **13f** and **13g**) were solved by single X-ray diffractometer and the confirmation of molecules in solution- phase, using 2D NOESY experiments, was compared. The influence of various substituents on the core scaffold (Fluorinated quinazoline) on its molecular conformations, intermolecular interactions and on the photoluminescent properties has been described. Hirshfeld surfaces was used to investigate the structure-directing effects of functional groups in controlling their solid-state behaviour. Among the series, compounds (**8**, **10c-h**, **13b-d** and **13f-g**) displayed good photoluminescent properties.

In **Chapter 4**, we report rational design-based synthesis, spectral studies and preliminary anti-mycobacterial screening of novel quinazoline derivatives against *Mycobacterium tuberculosis* H37Rv strain. A total of 21 derivatives were synthesized, well-characterized by IR, NMR and screened against *Mycobacterium tuberculosis* H37Rv strain. The notable percentage zone of inhibition was shown by compound **10m** that was 33% after 24 h incubation.

In **Chapter 5**, we report synthesis, spectral studies and preliminary anti-mycobacterial screening of novel N/O methylated quinazoline derivatives against *Mycobacterium tuberculosis* H37Rv strain. Novel 23 molecules had been synthesized, well-characterized by IR, NMR and screened against *Mycobacterium tuberculosis* H37Rv strain. The percentage zone of inhibition by **16a** was 34% after 24 h incubation which can be further consider for the study like MIC, MBC etc.

In **Chapter 6**, we have replaced the central core quinolone with quinazoline ring and synthesized 22 derivatives. All derivatives were characterized by IR and NMR and evaluated against DNA gyrase and topoisomerase IV enzyme of *Escherichia coli* using Ciprofloxacin as reference drug. Among the series, compound **10l** bearing carboxylic acid group was found to be most active with IC_{50} value of 0.49 and 13.22 μM for DNA Gyrase and topoisomerase IV, respectively. In addition, **9f**, **9i**, **9j**, **10c**, **10j** and **10k** were also exhibited excellent activity against DNA Gyrase while comparatively less activity against topoisomerase IV. These results provide a basis for structure-based optimization toward dual DNA gyrase and topoisomerase IV inhibition.

FUTURE WORK

In this project, we have developed a novel green and efficient catalyst-free, the mild one-pot tandem synthetic method to construct 1, 4-benzoxazine which can be further exploited to synthesize novel potential anti-tubercular agents. Moreover, we have already synthesized 29 benzoxazine based molecules that can be screened against *Mycobacterium tuberculosis* and evaluated against DNA gyrase and topoisomerase IV for *E. coli*. The most potent molecules can be effectively used in developing further lead compounds through three-dimensional quantitative structure relationship (3D-QSAR) models.

Additionally, one of the quinazoline series showing satisfactory inhibitory activities against DNA gyrase and topoisomerase IV. All other quinazoline series tend to show inhibitory activities against DNA gyrase and topoisomerase IV. This motivate us to evaluate all other quinazoline based series against DNA gyrase and topoisomerase IV of Gram-negative bacteria.

APPENDIX – I

SUPPLEMENTARY INFORMATION

CHAPTER 2

One-pot, multicomponent, diastereoselective green synthesis of 3,4-dihydro-2H-benzo[b][1,4]oxazine analogues

Narva Deshwar Kushwaha, Babita Kushwaha, Rajshekhar Karpoormath* Mavela Cleopus Mahlalela, Suraj Raosaheb Shinde

Department of Pharmaceutical Chemistry, Discipline of Pharmaceutical Sciences, College of Health Sciences, University of KwaZulu-Natal, Westville Campus, Durban 4000, South Africa

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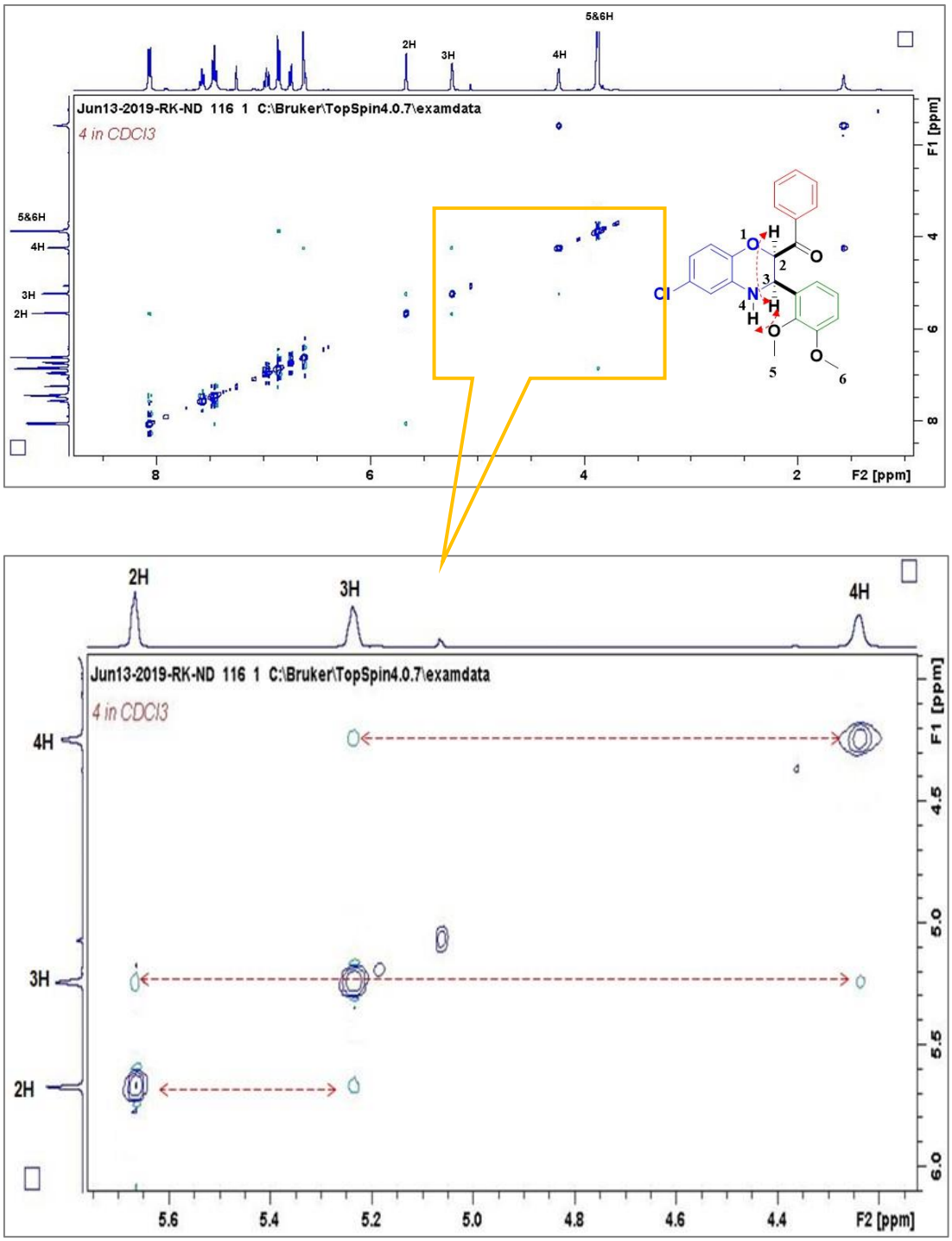
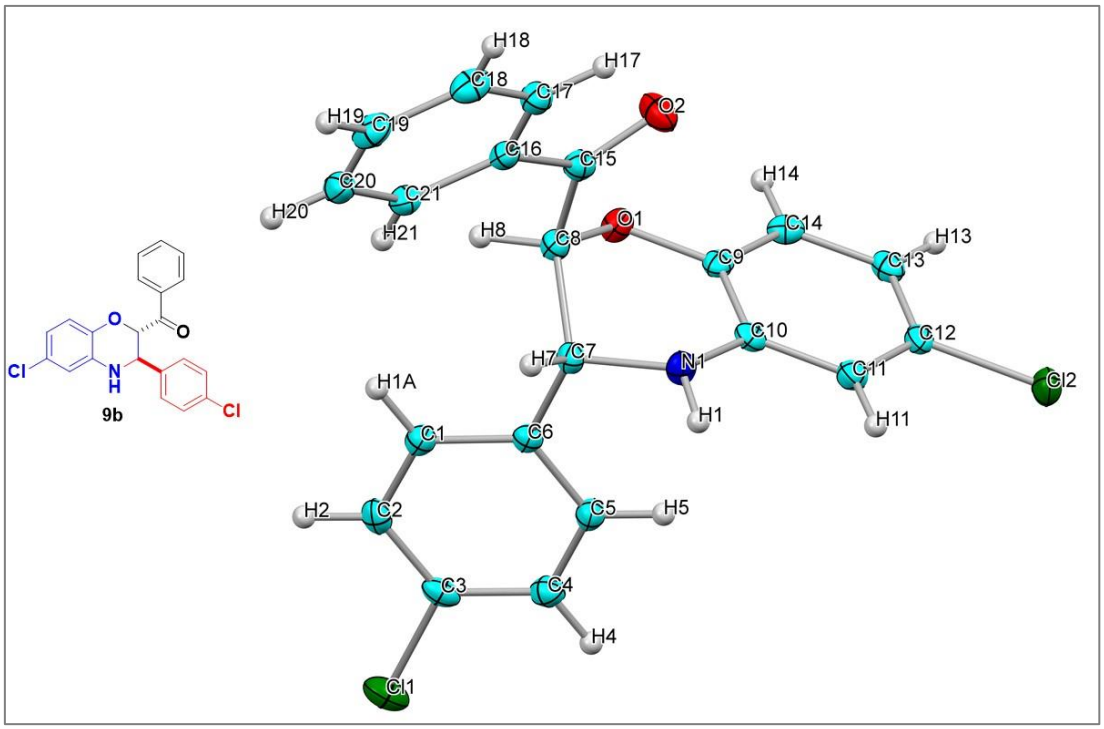
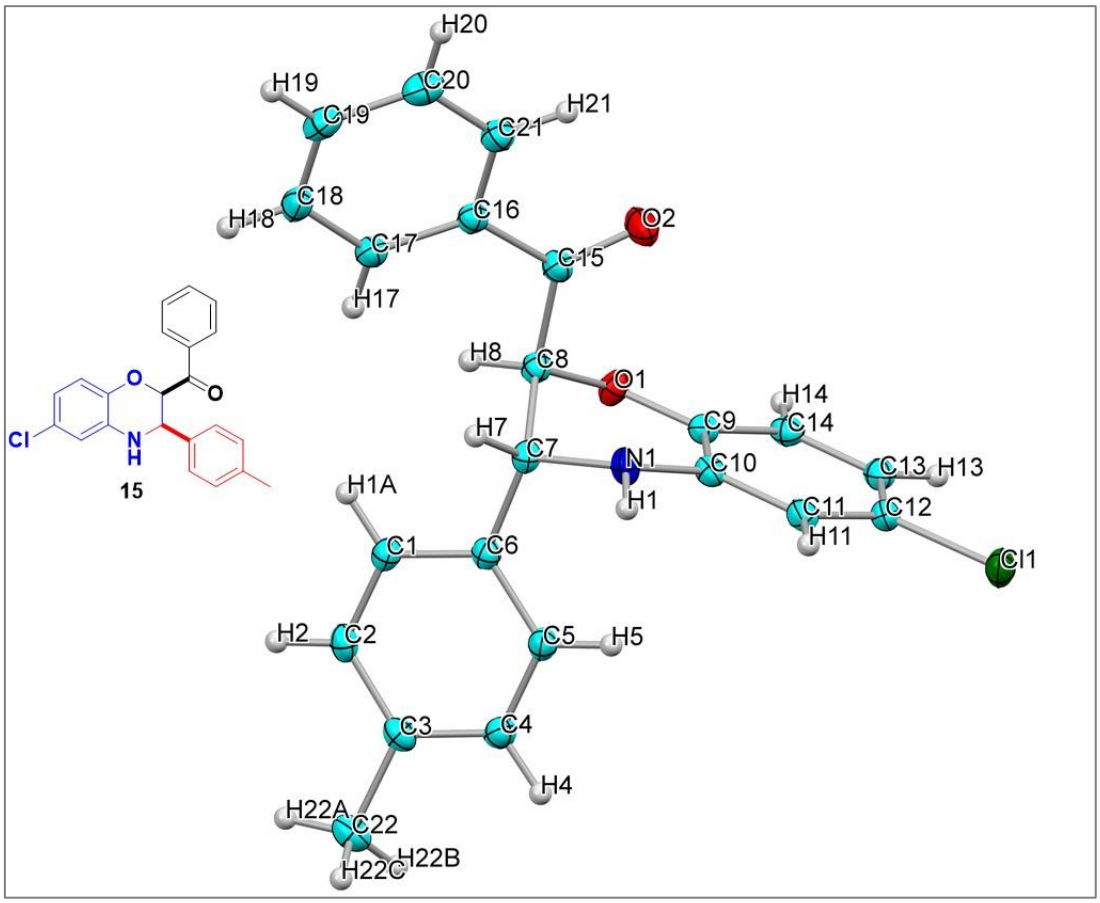


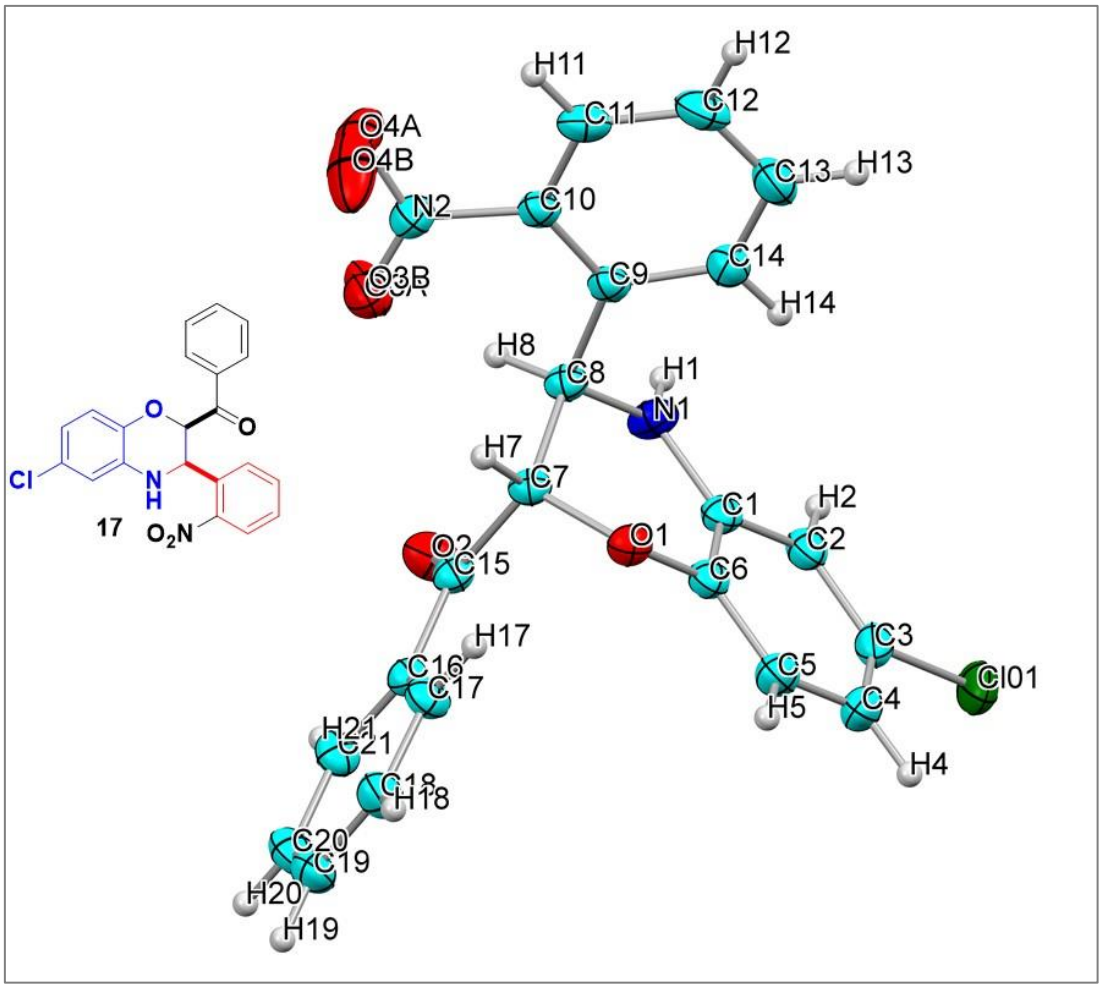
NOESY spectrum of compound 4 (Chapter 2)



Crystal structure of compound 9b (CCDC No. 1966293) (Chapter 2)



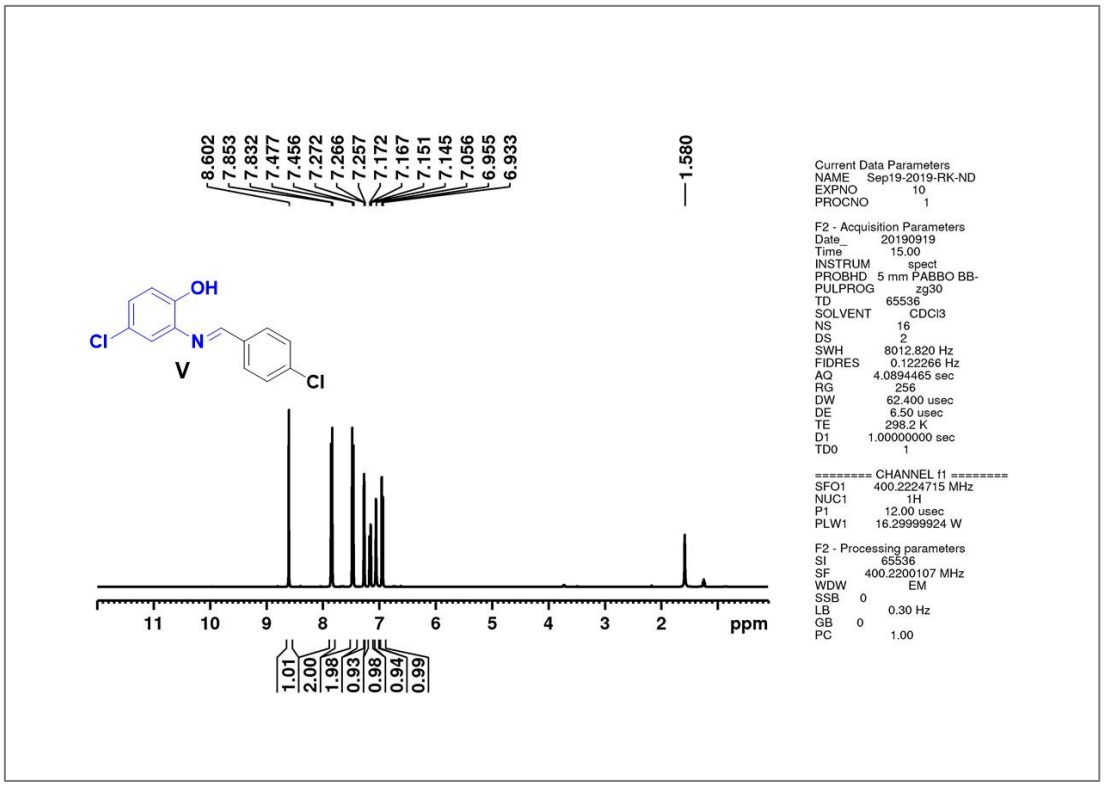
Crystal structure of compound 15 (CCDC No. 1966294) (Chapter 2)



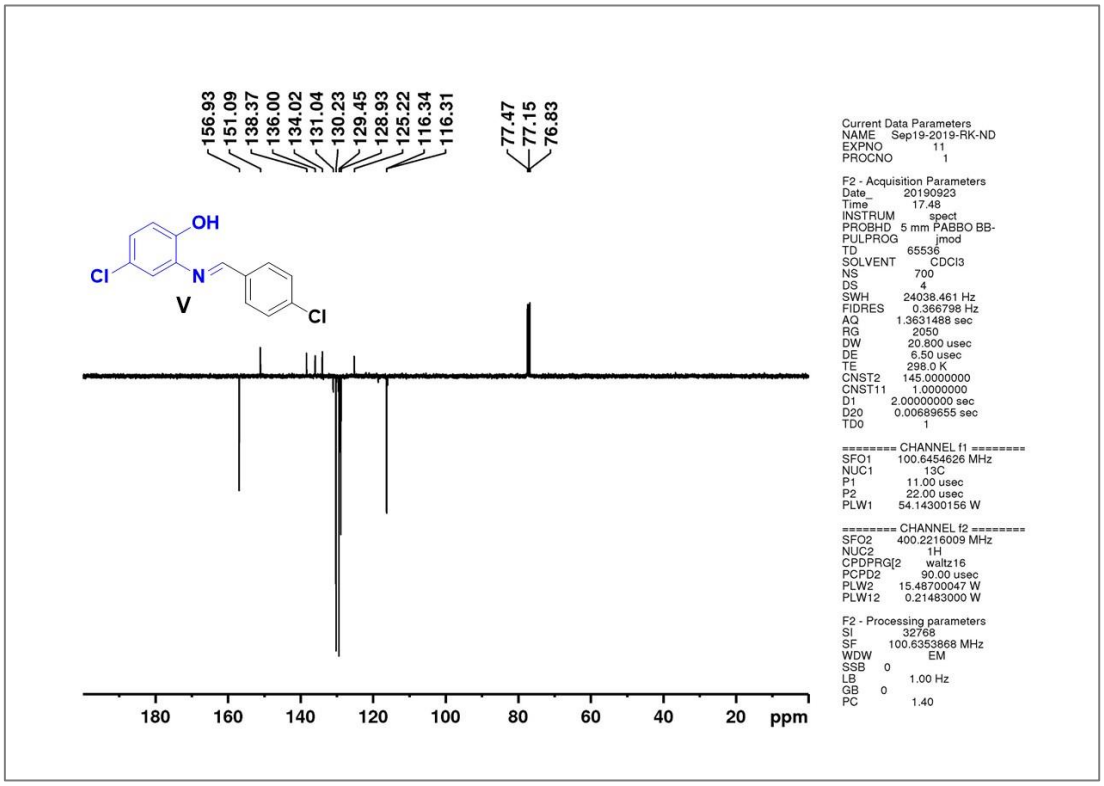
Crystal structure of compound 17 (CCDC No. 1997747) (Chapter 2)

Table S1: X-ray crystallographic data and structure refinement.

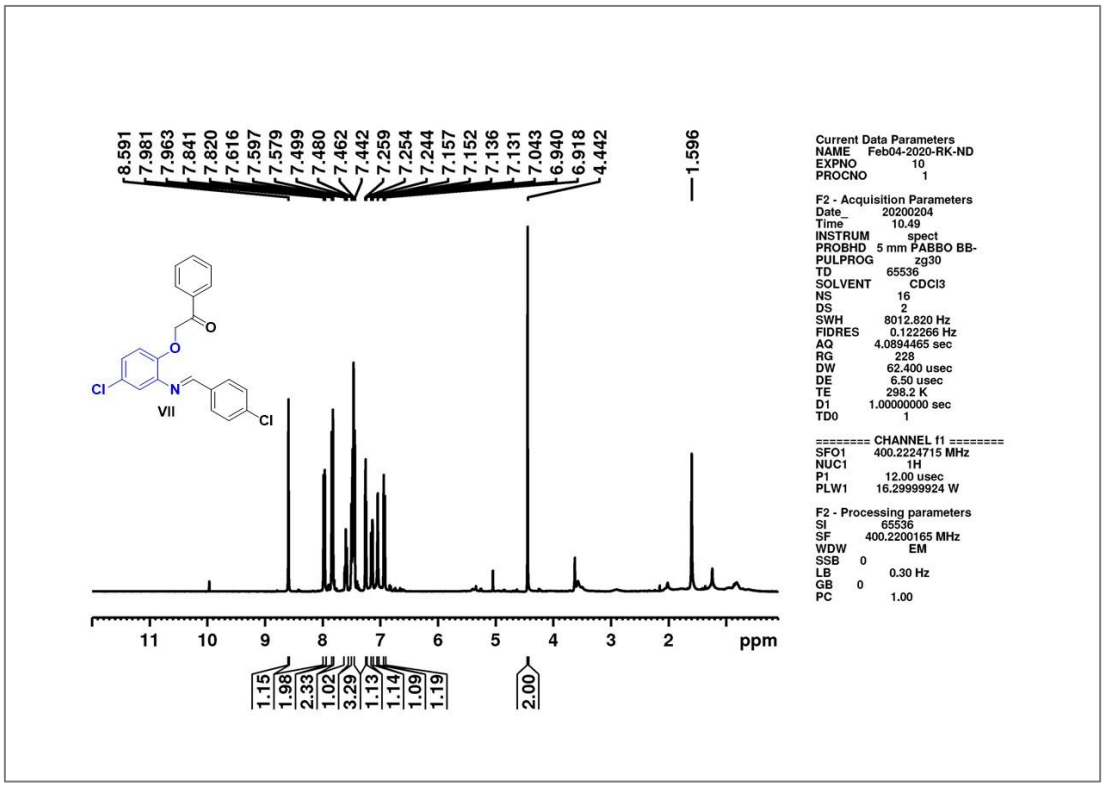
Crystal parameters	**9b**	**15**	**17**
Empirical formula	$C_{21}H_{15}Cl_2NO_2$	$C_{22}H_{18}ClNO_2$	$C_{21}H_{15}ClN_2O_4$
Formula weight	384.24	363.82	394.80
Temperature/K	100.15	100.00	149.98
Crystal system	monoclinic	monoclinic	monoclinic
Space group	$P2_1/n$	$P2_1/n$	$P2_1/n$
a/Å	10.4411(2)	10.4686(3)	9.59130(10)
b/Å	15.0003(3)	14.9205(4)	11.3803(2)
c/Å	11.6037(2)	11.6719(3)	17.0706(2)
α/°	90	90	90
β/°	111.5660(10)	111.0760(10)	100.5990(10)
γ/°	90	90	90
Volume/$Å^3$	1690.14(6)	1701.15(8)	1831.50(4)
Z	4	4	4
$\rho_{calc}g/cm^3$	1.510	1.421	1.432
μ/mm^{-1}	0.400	0.241	0.240
F(000)	792.0	760.0	816.0
Crystal size/mm^3	0.29 × 0.24 × 0.16	0.36 × 0.24 × 0.16	0.36 × 0.27 × 0.23
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.65 to 55.332	4.49 to 56.938	4.324 to 55.224
Index ranges	$-13 \le h \le 10$, $-17 \le k \le 19$, $-15 \le l \le 15$	$-13 \le h \le 13$, $-19 \le k \le 19$, $-15 \le l \le 15$	$-12 \le h \le 12$, $-14 \le k \le 14$, $-21 \le l \le 22$
Reflections collected	12982	20903	25266
Independent reflections	3846 [R_{int} = 0.0359, R_{sigma} = 0.0359]	4271 [R_{int} = 0.0196, R_{sigma} = 0.0154]	4221 [R_{int} = 0.0171, R_{sigma} = 0.0128]
Data/restraints/parameters	3846/0/239	4271/1/240	4221/20/272
Goodness-of-fit on F^2	1.026	1.042	1.027
Final R indexes [I>=2σ (I)]	R_1 = 0.0308, wR_2 = 0.0753	R_1 = 0.0324, wR_2 = 0.0859	R_1 = 0.0339, wR_2 = 0.0862
Final R indexes [all data]	R_1 = 0.0424, wR_2 = 0.0799	R_1 = 0.0368, wR_2 = 0.0897	R_1 = 0.0390, wR_2 = 0.0905
Largest diff. peak/hole / e $Å^{-3}$	0.34/-0.26	0.35/-0.25	0.37/-0.36



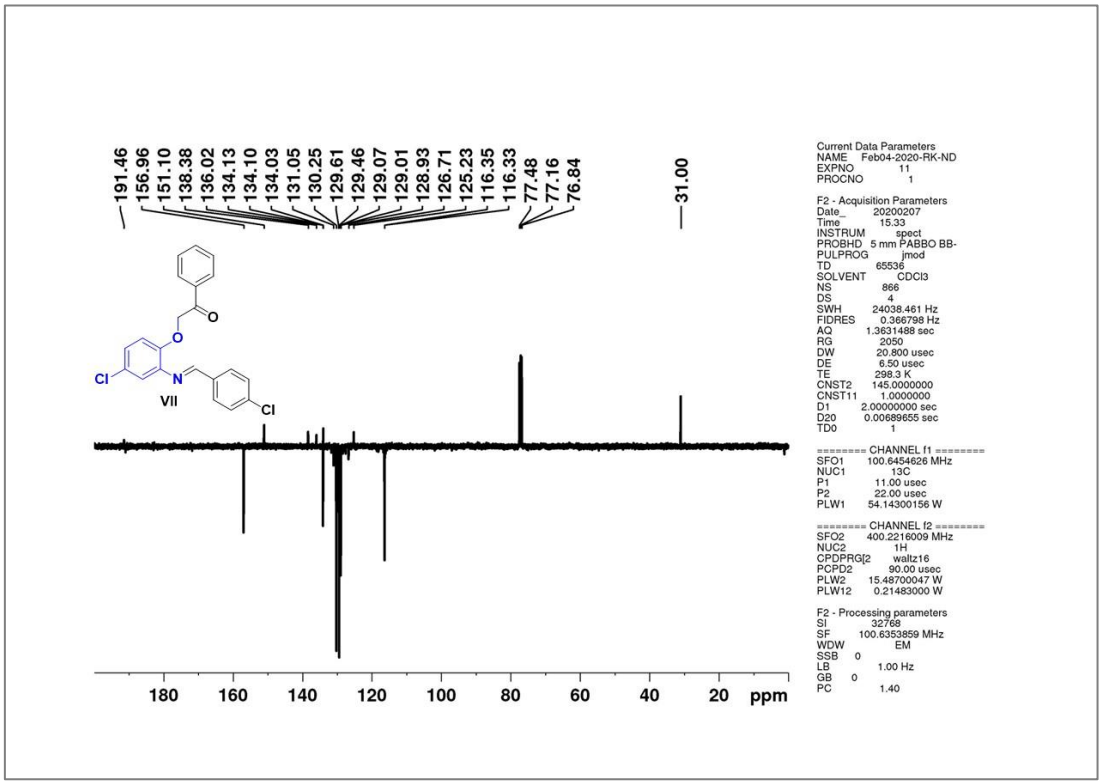
^{1}H NMR spectrum of intermediate compound V (Chapter 2)



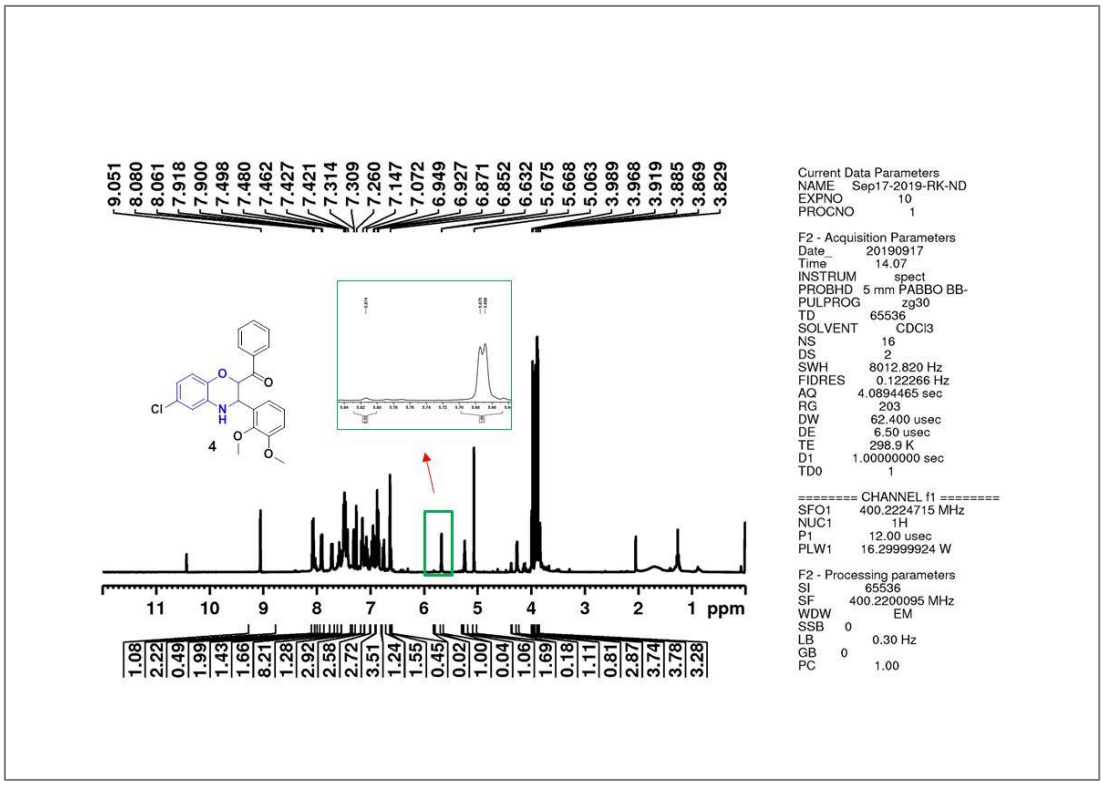
^{13}C{^{1}H} NMR spectrum of intermediate compound V (Chapter 2)



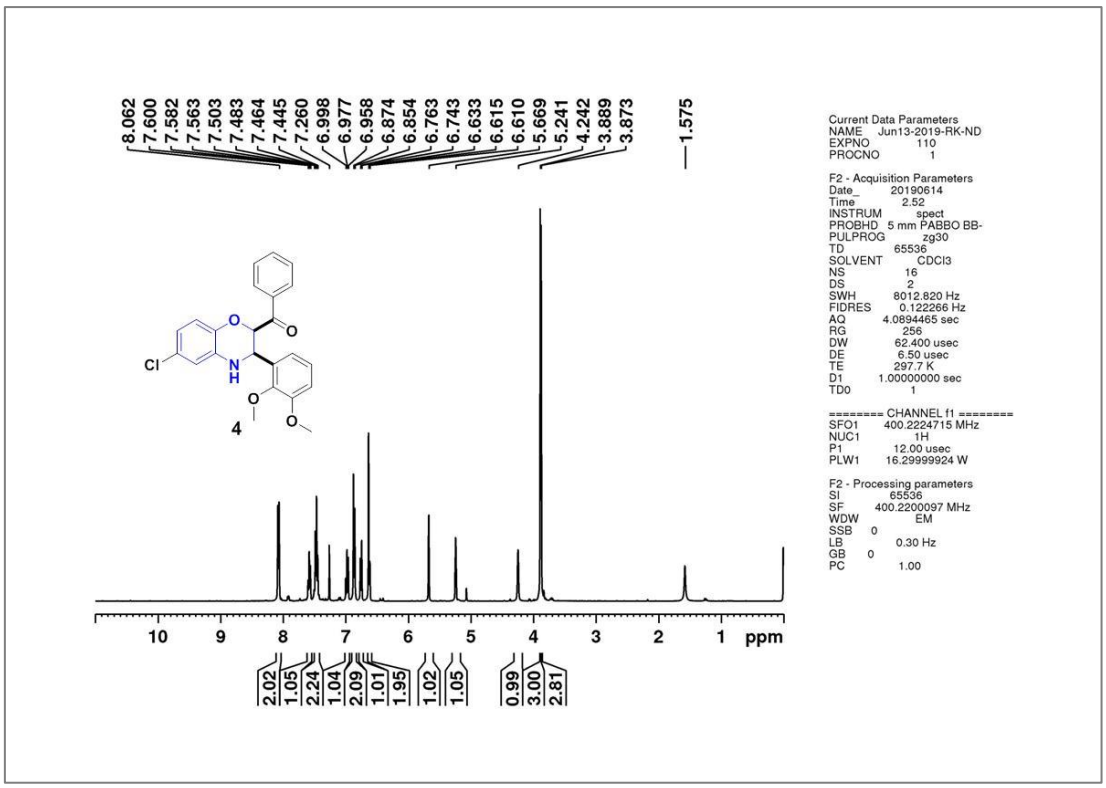
^{1}H NMR spectrum of intermediate compound VII (Chapter 2)



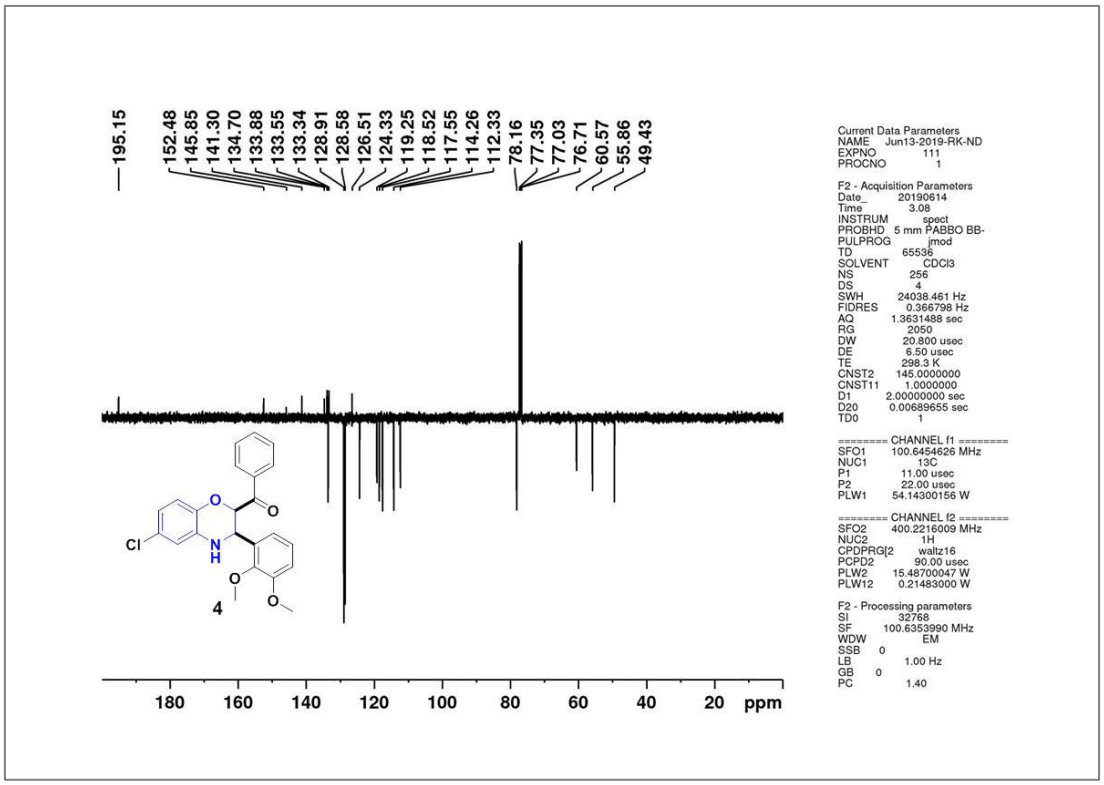
^{13}C{^{1}H} NMR spectrum of intermediate compound VII (Chapter 2)



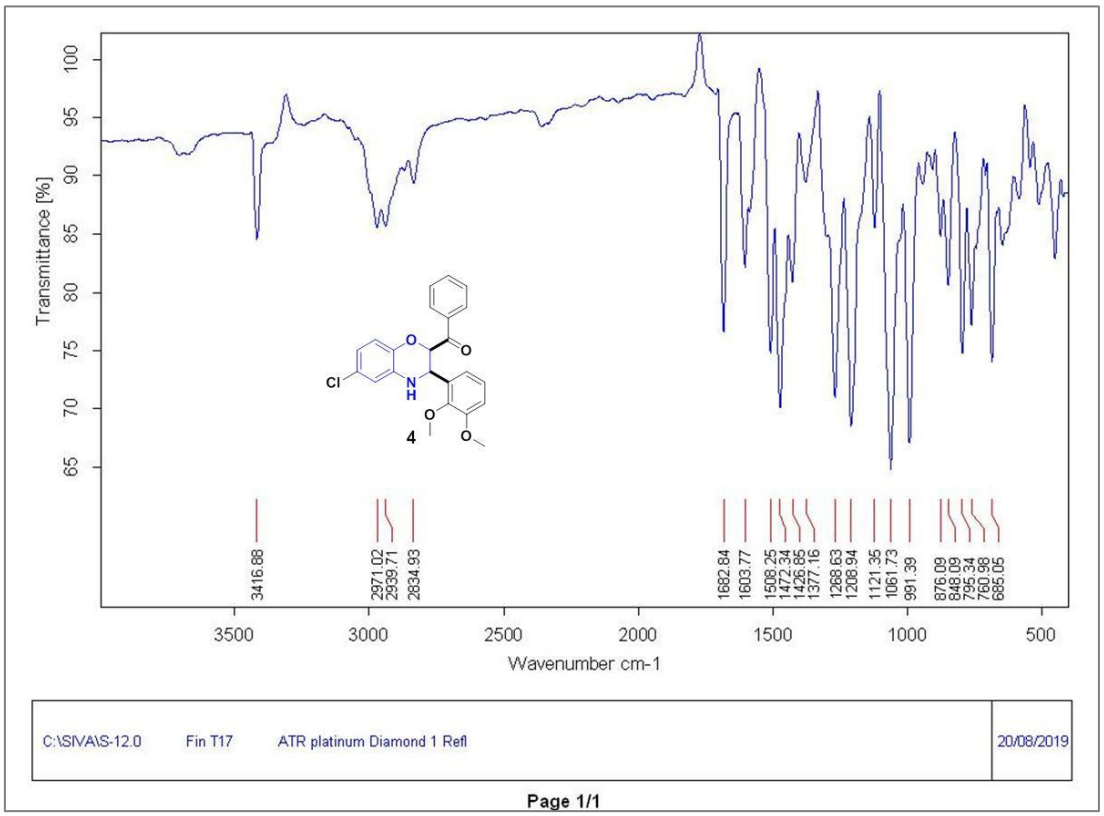
^{1}H NMR spectrum of crude compound 4 (Chapter 2)



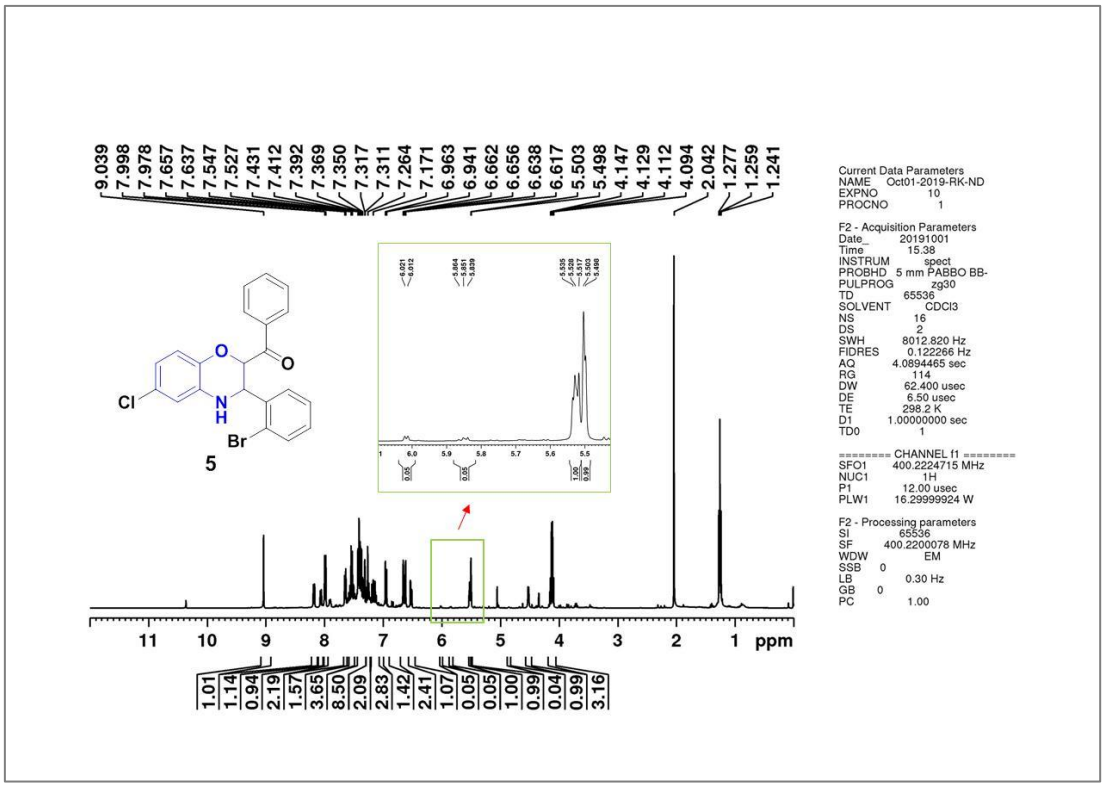
^{1}H NMR spectrum of compound 4 (Chapter 2)



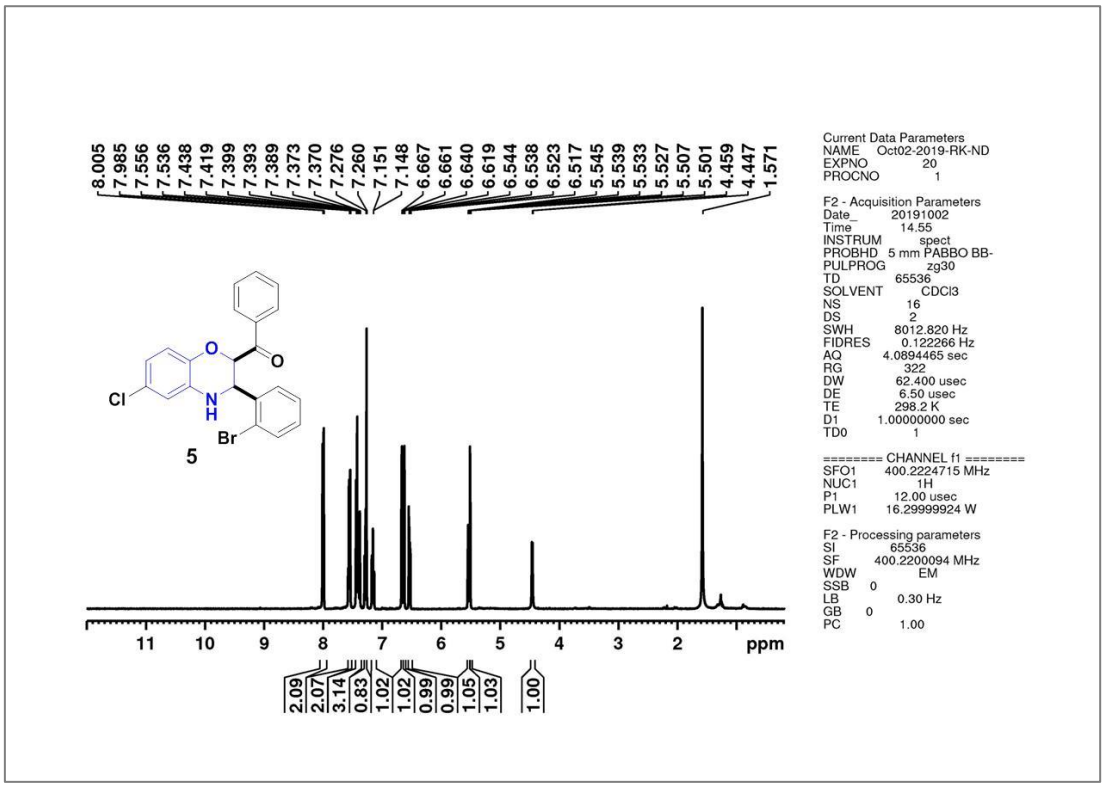
$^{13}C\{^{1}H\}$ NMR spectrum of compound 4 (Chapter 2)



IR spectrum of compound 4 (Chapter 2)



^{1}H NMR spectrum of crude compound 5 (Chapter 2)



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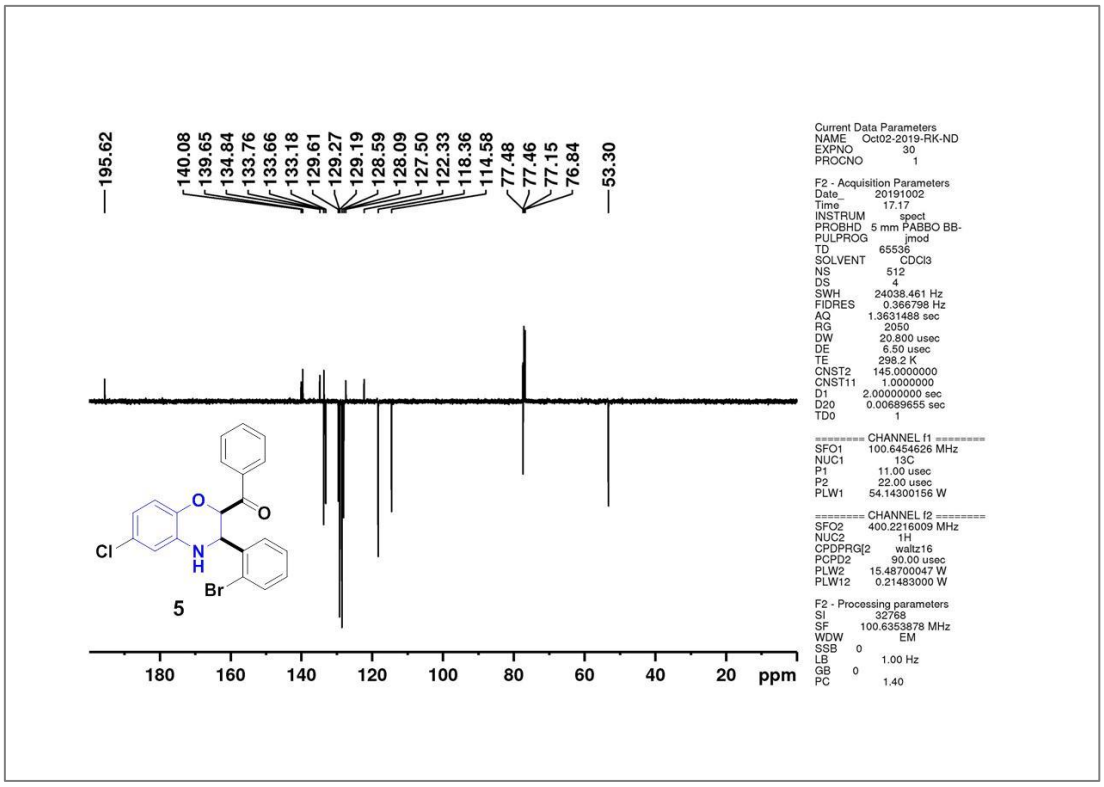
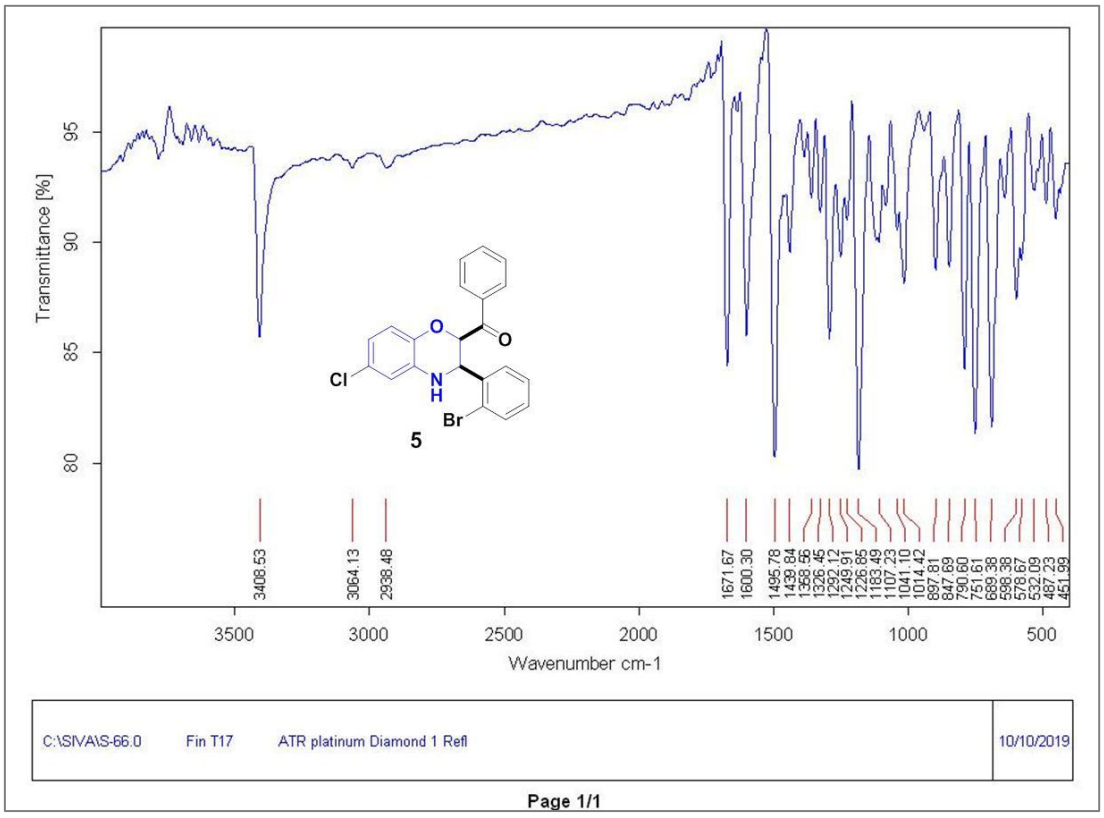


$^{13}C\{^{1}H\}$ NMR spectrum of compound 5 (Chapter 2)



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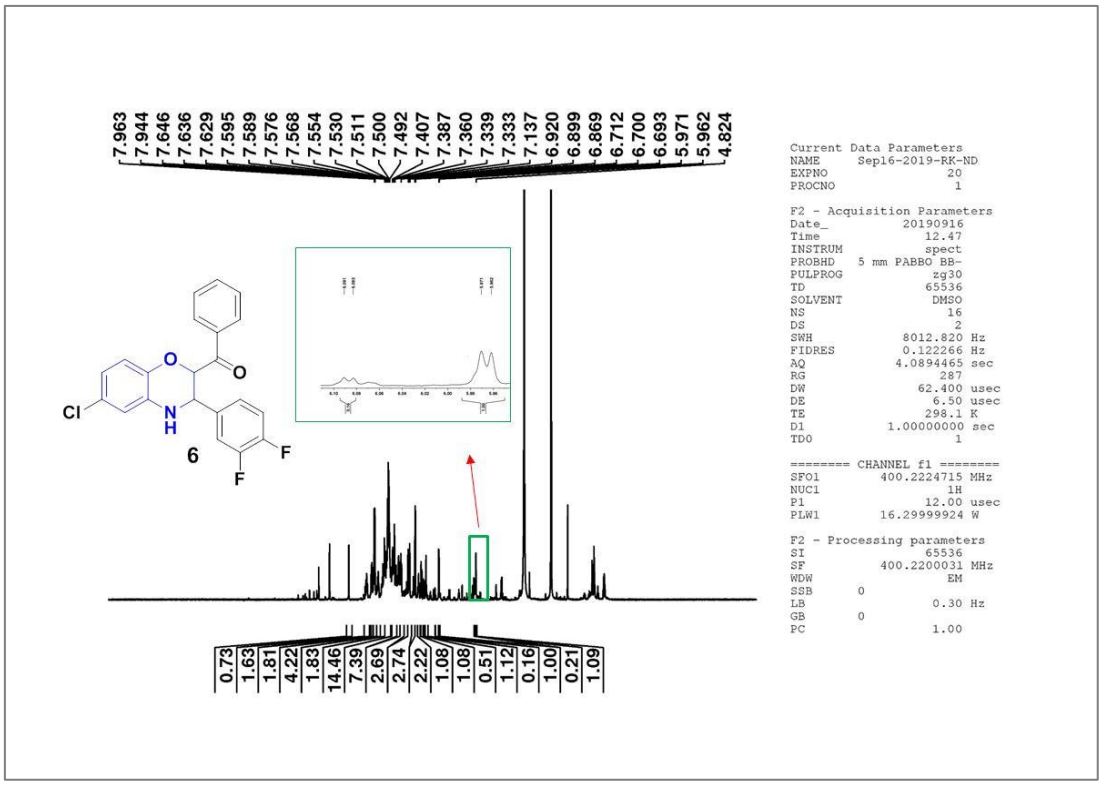
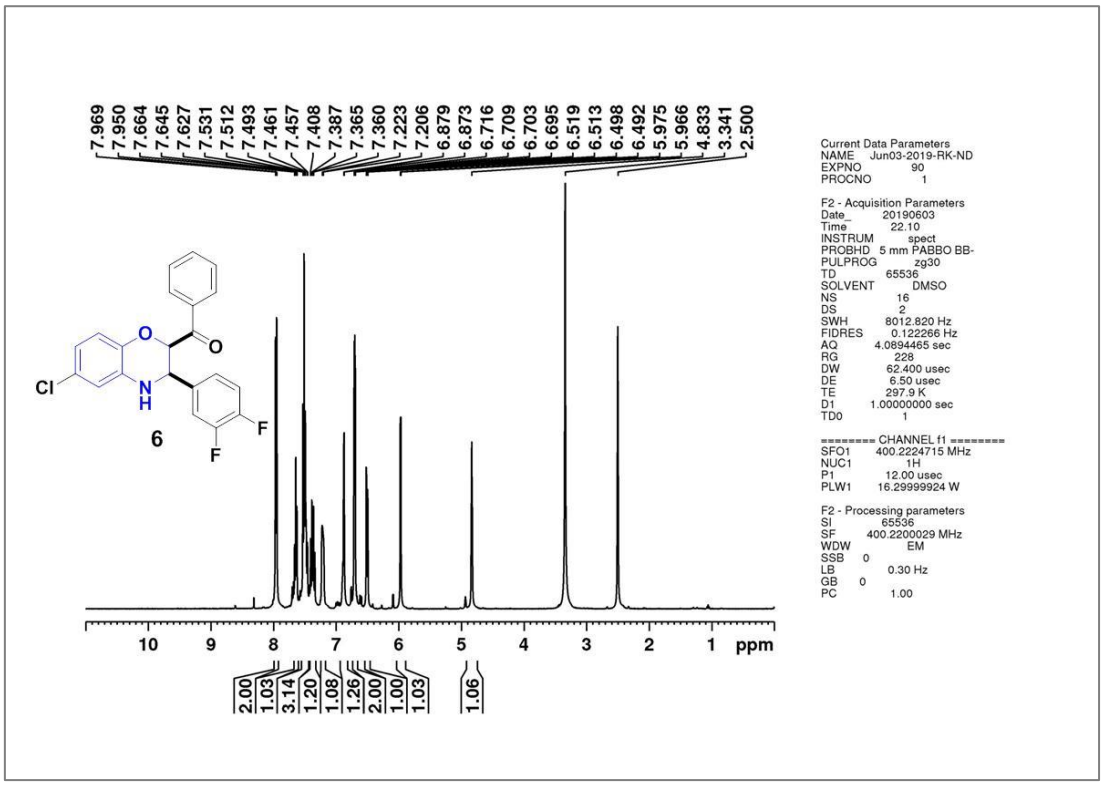


[1]H NMR spectrum of crude compound 6 (Chapter 2)



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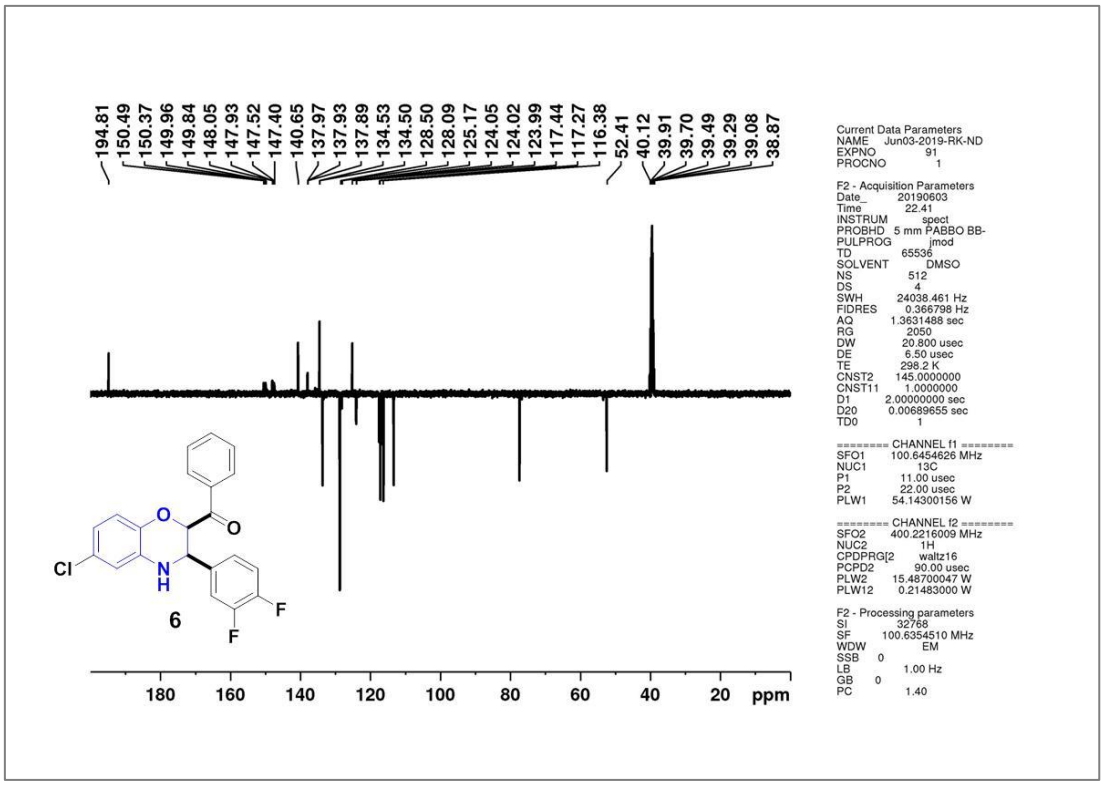

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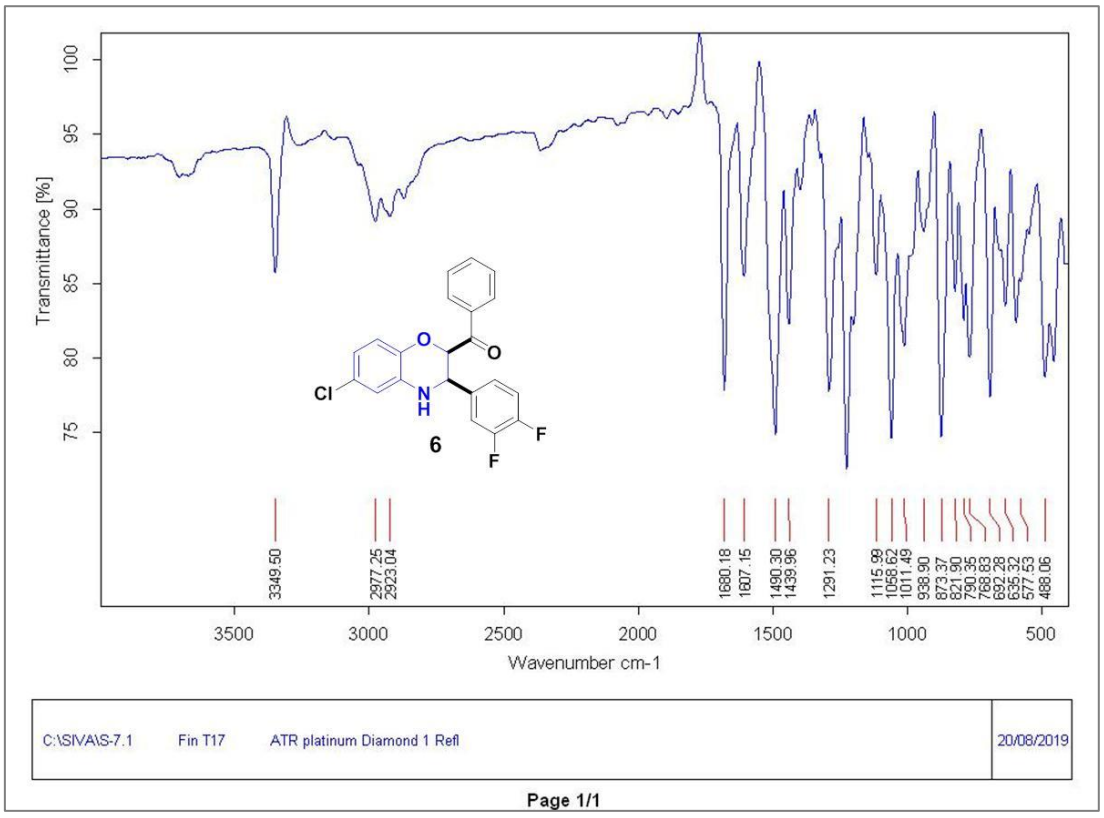

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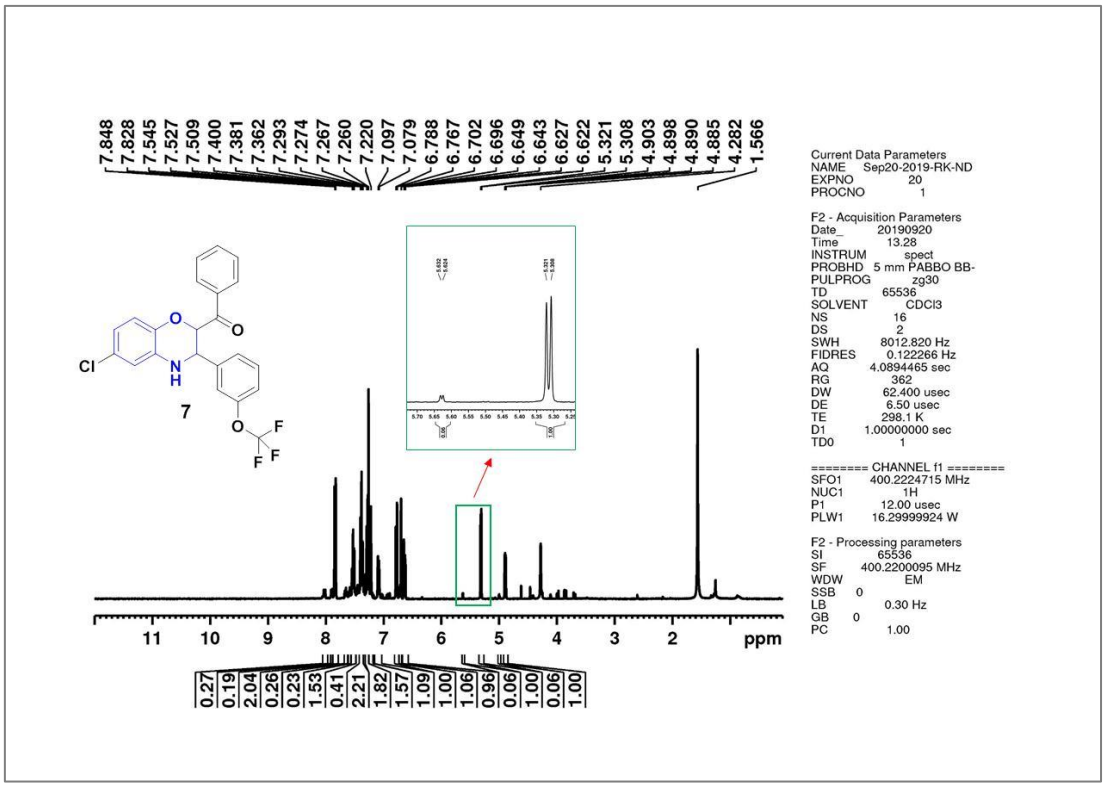
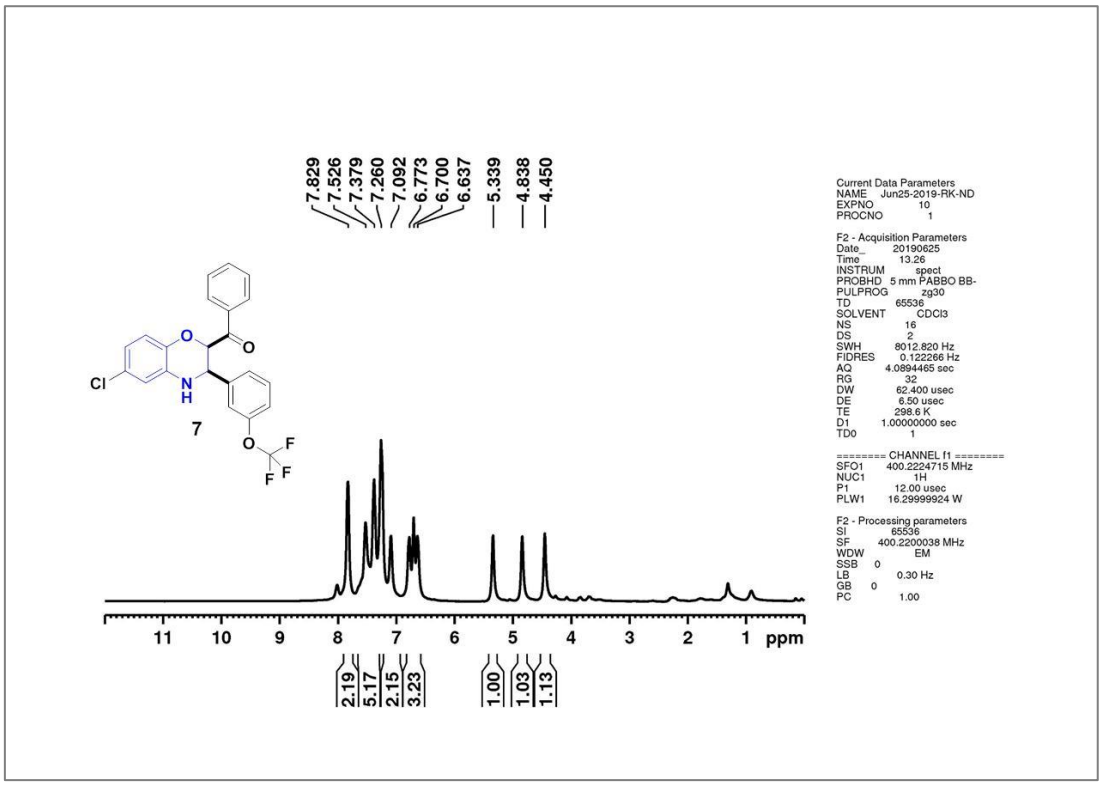
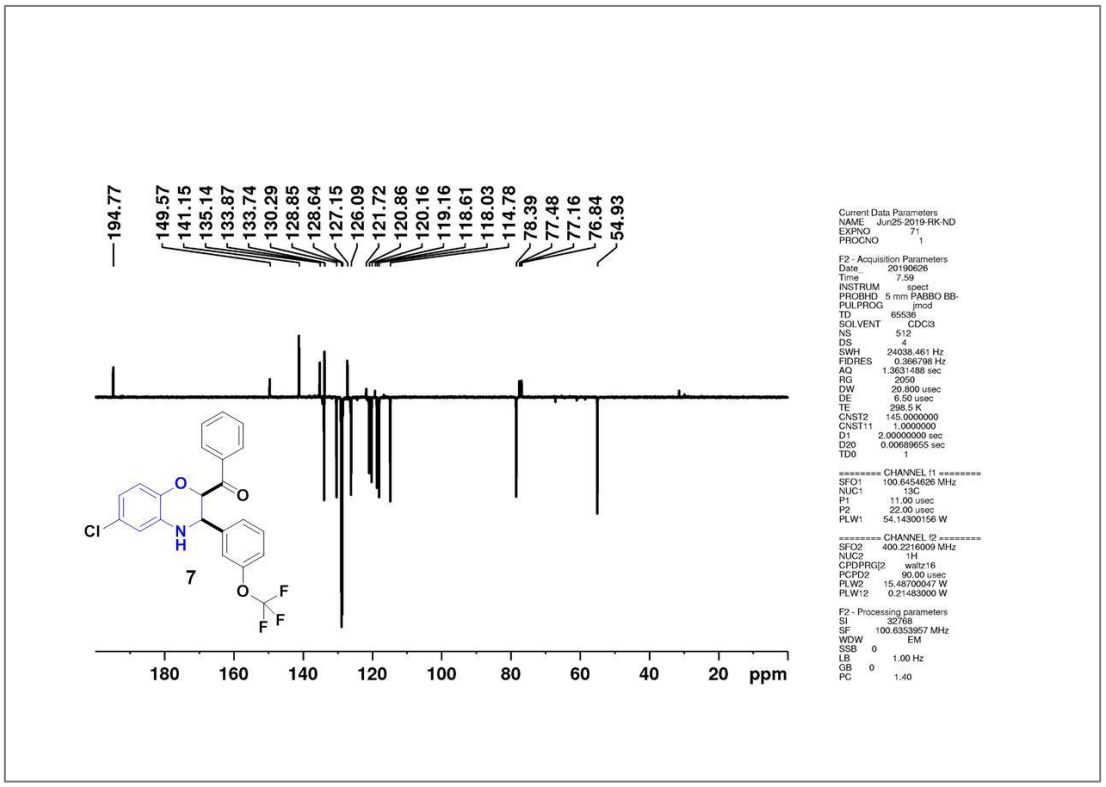


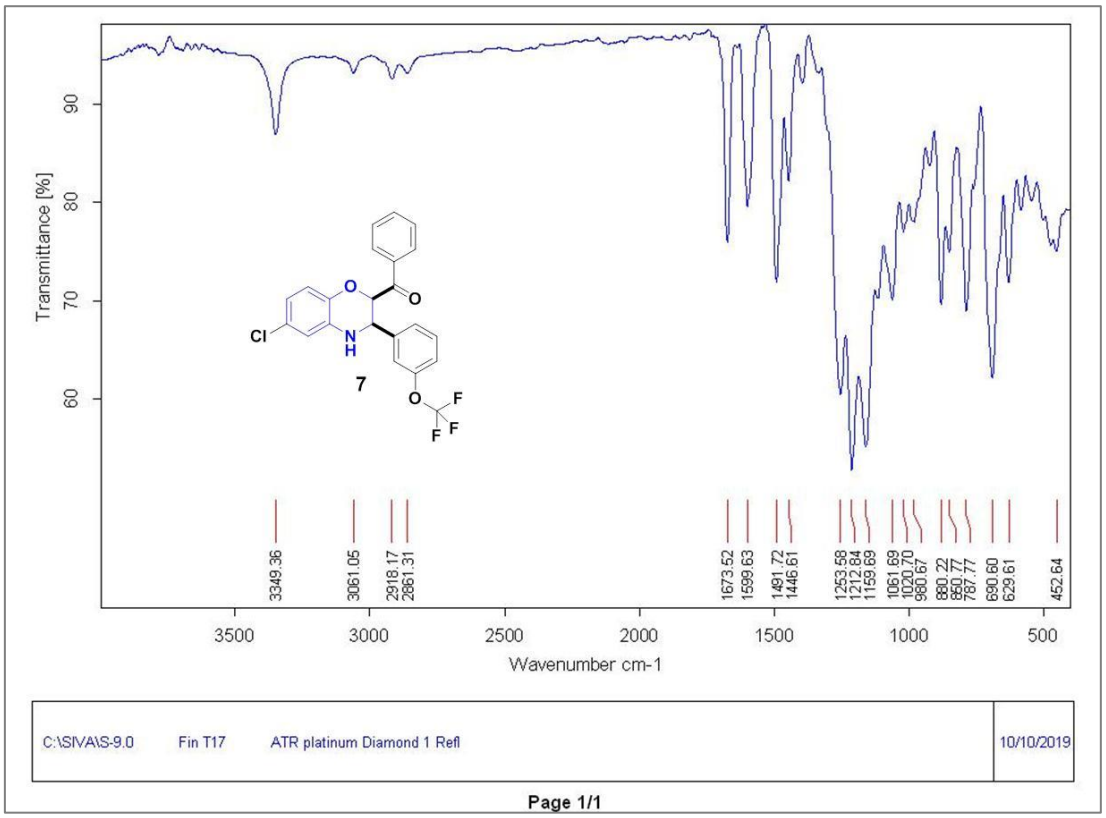
[1]H NMR spectrum of crude compound 7 (Chapter 2)



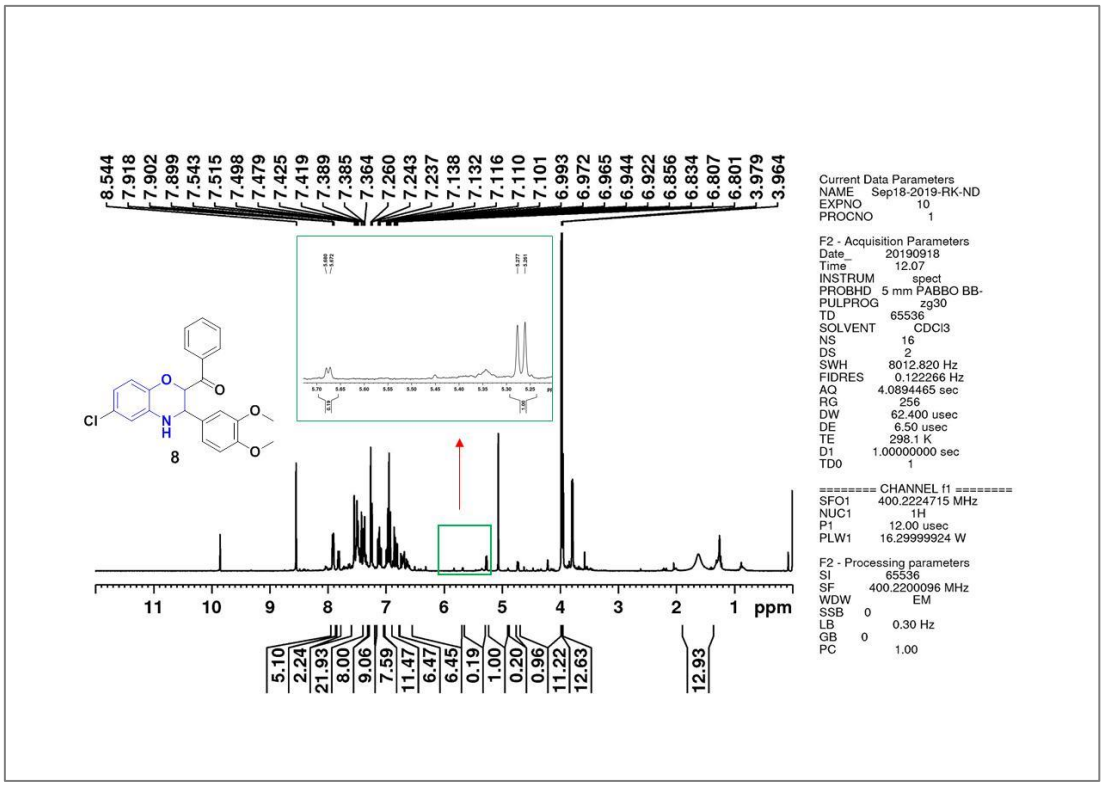
[1]H NMR spectrum of compound 7 (Chapter 2)



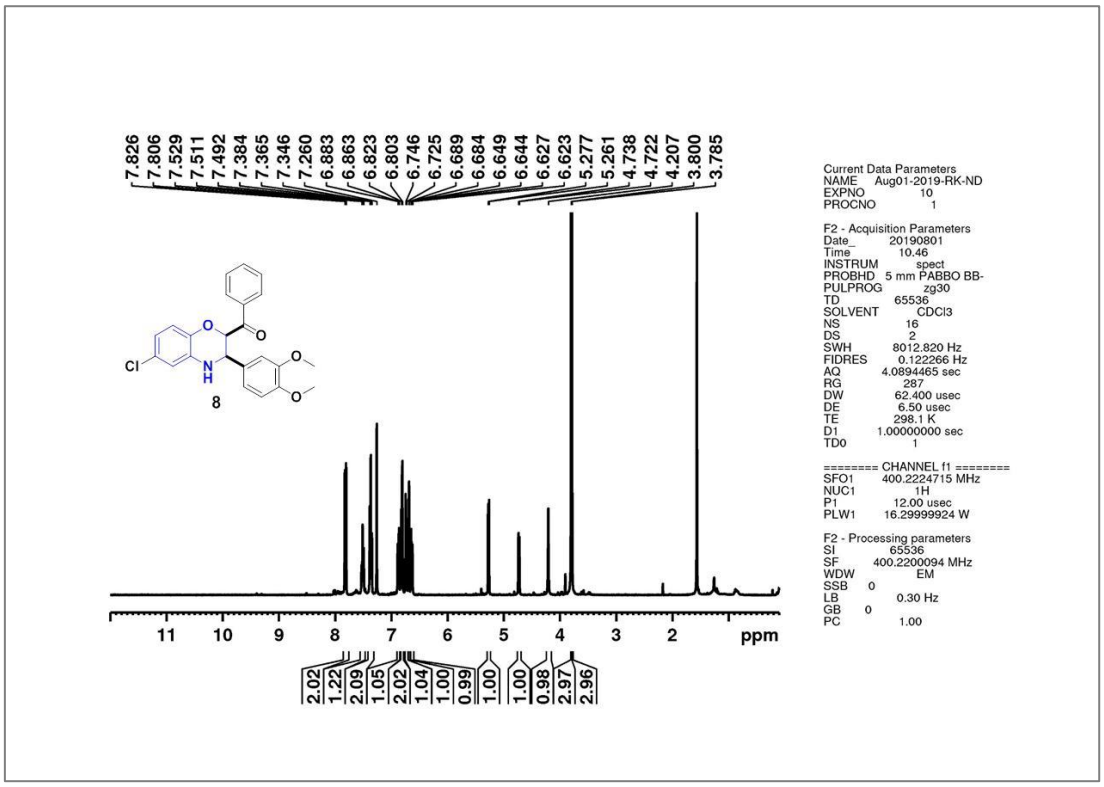
$^{13}C\{^{1}H\}$ NMR spectrum of compound 7 (Chapter 2)



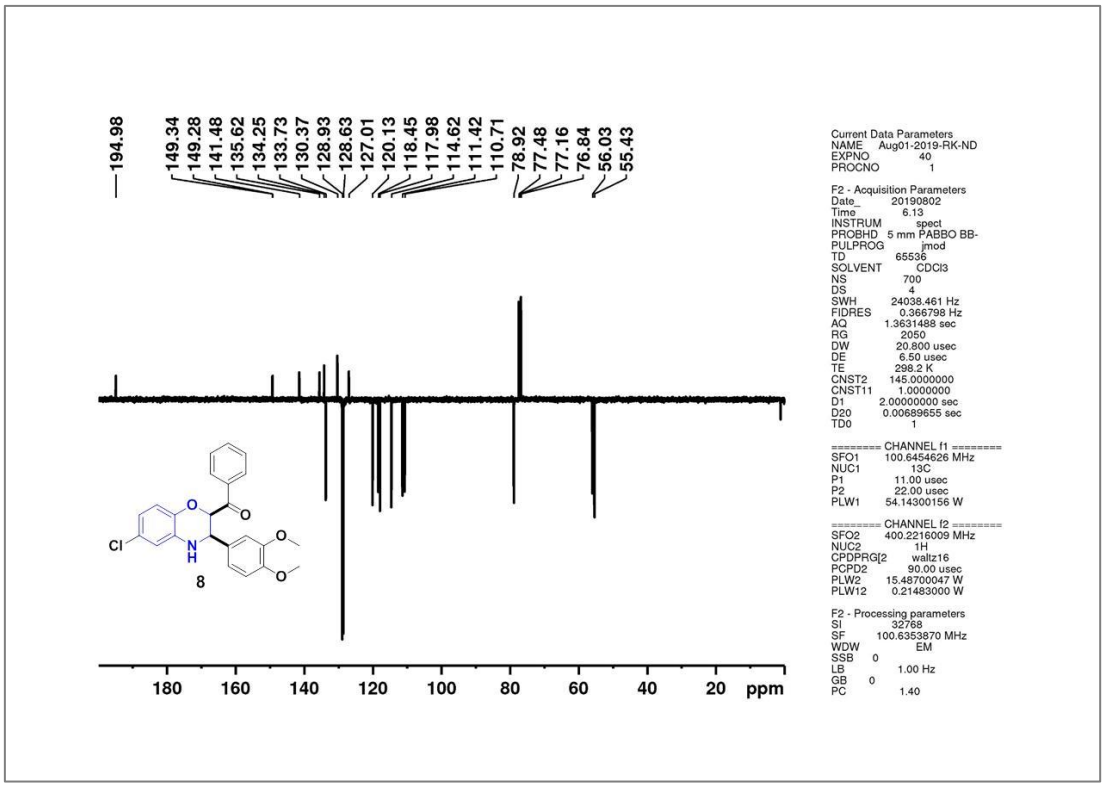
IR spectrum of compound 7 (Chapter 2)



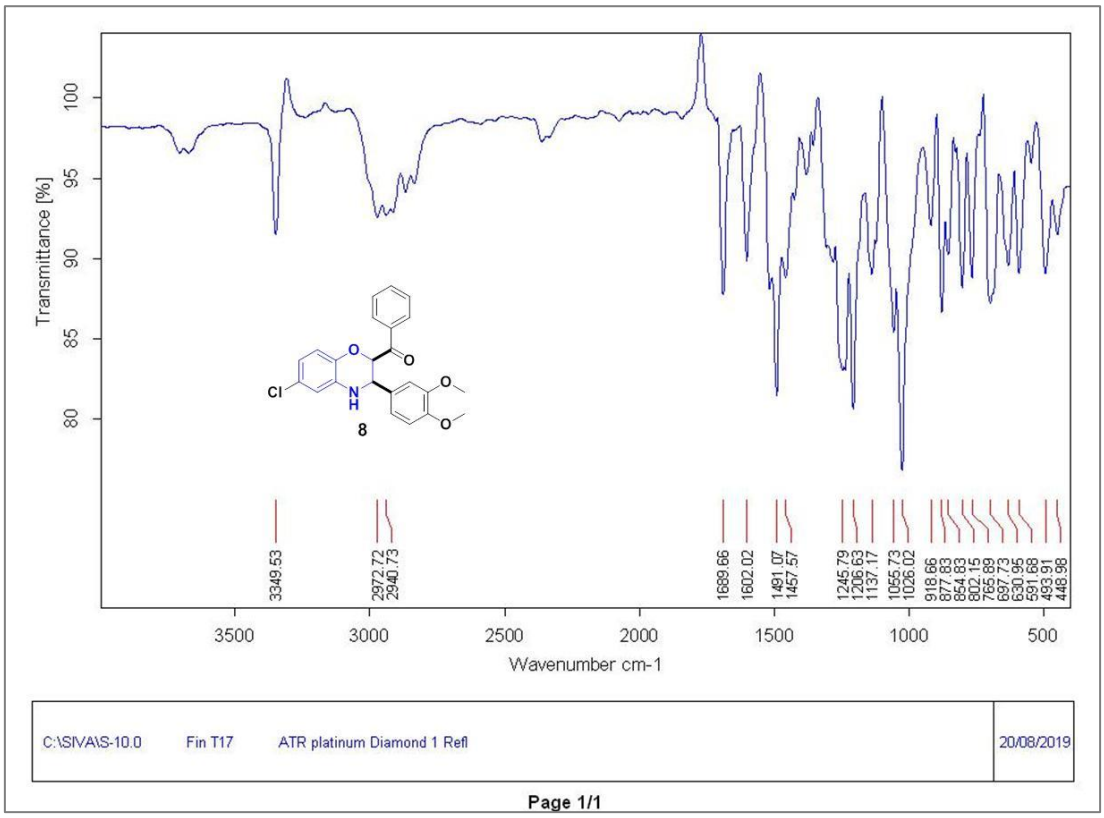
[1]H NMR spectrum of crude compound 8 (Chapter 2)



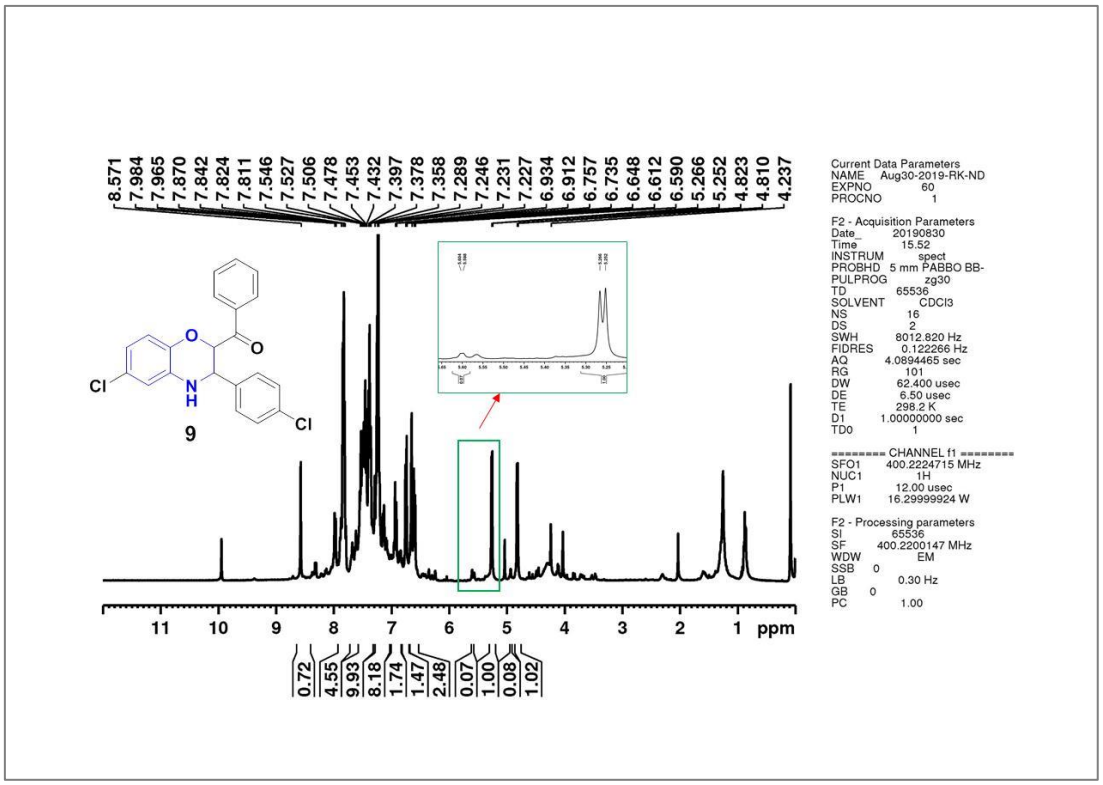
[1]H NMR spectrum of compound 8 (Chapter 2)



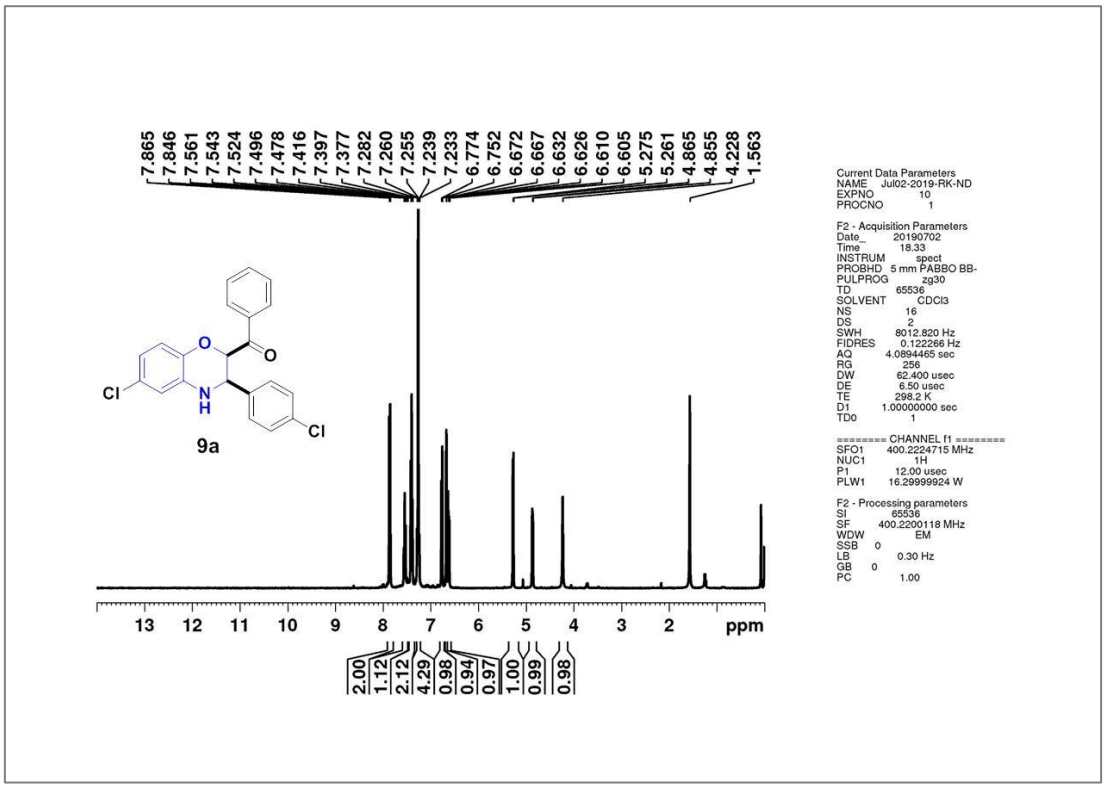
$^{13}C\{^{1}H\}$ NMR spectrum of compound 8 (Chapter 2)



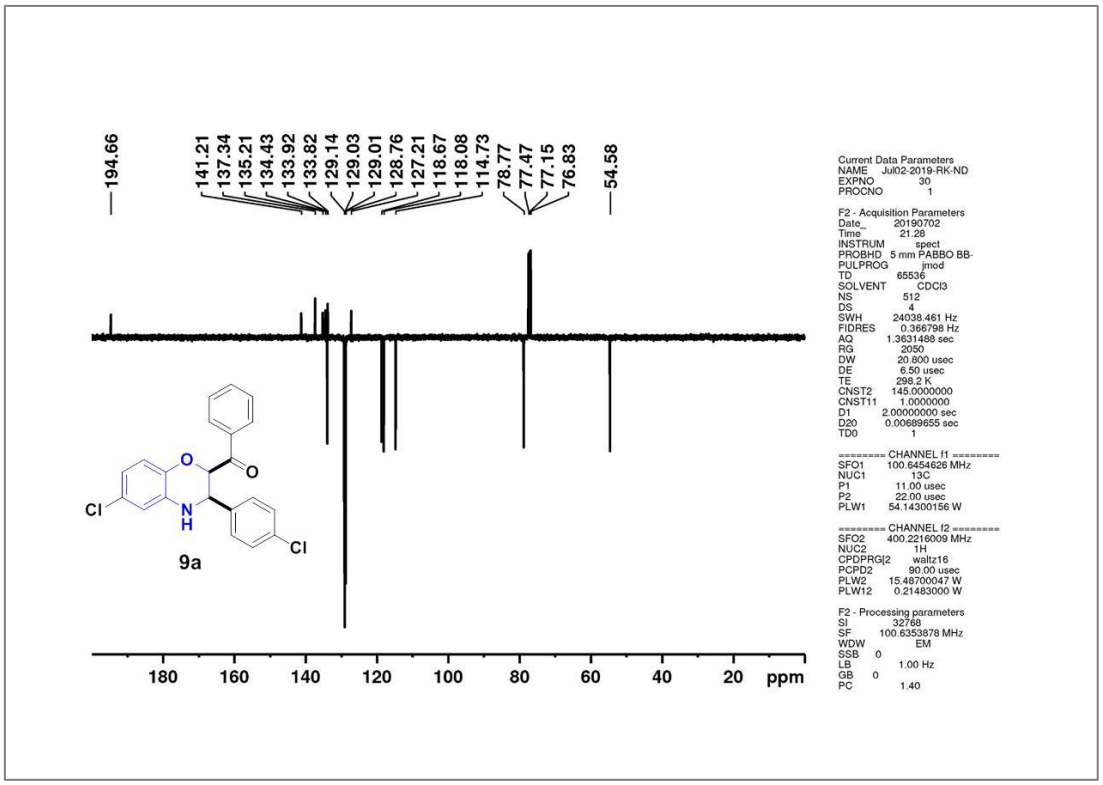
IR spectrum of compound 8 (Chapter 2)



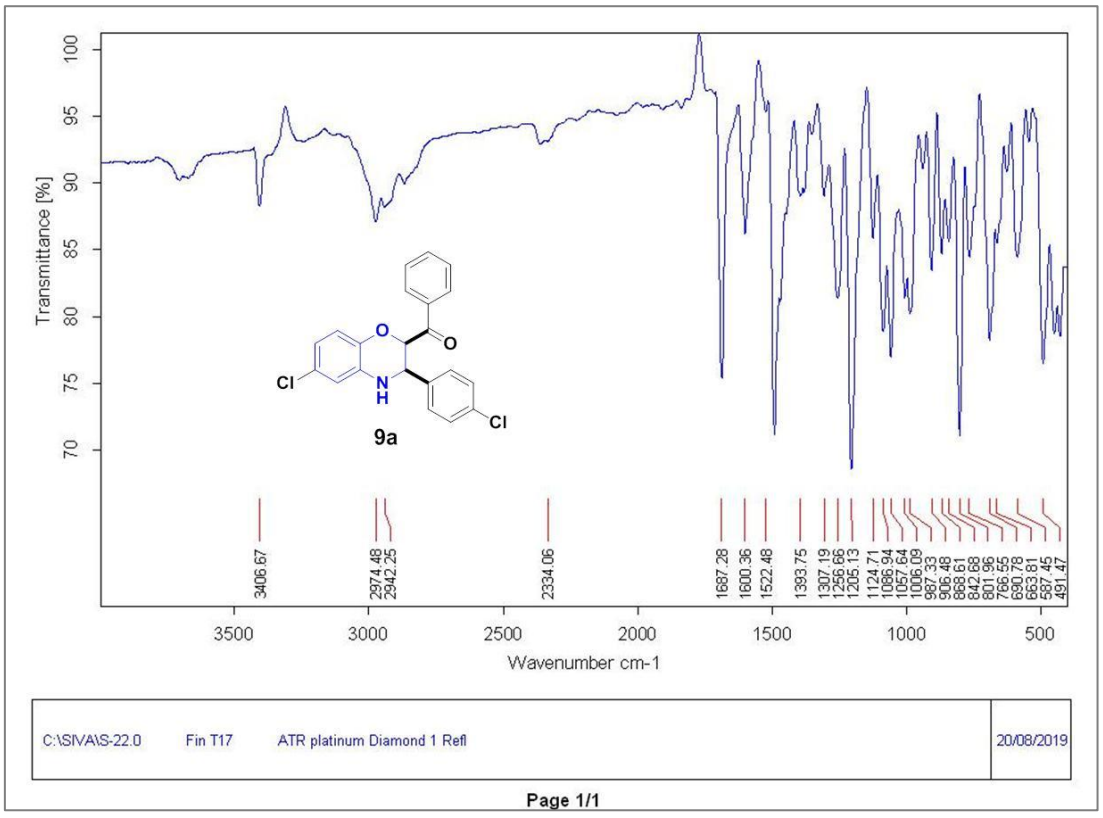
^{1}H NMR spectrum of crude compound 9 (Chapter 2)



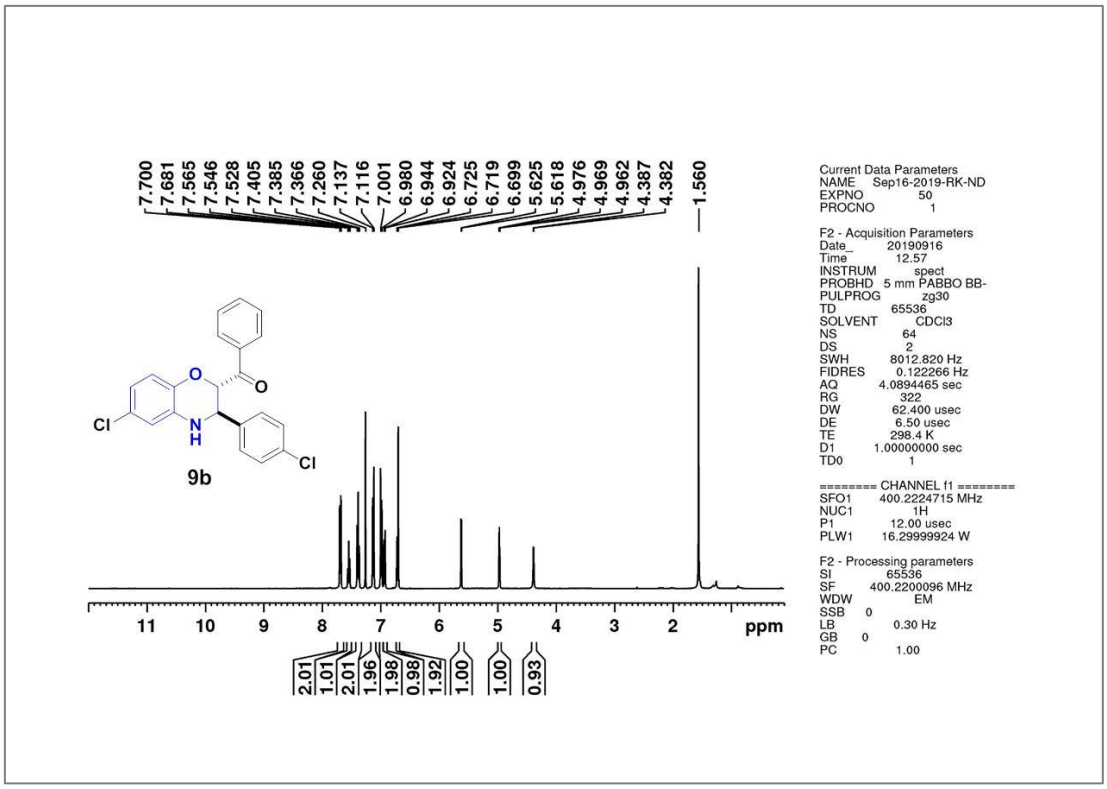
^{1}H NMR spectrum of compound 9a (Chapter 2)



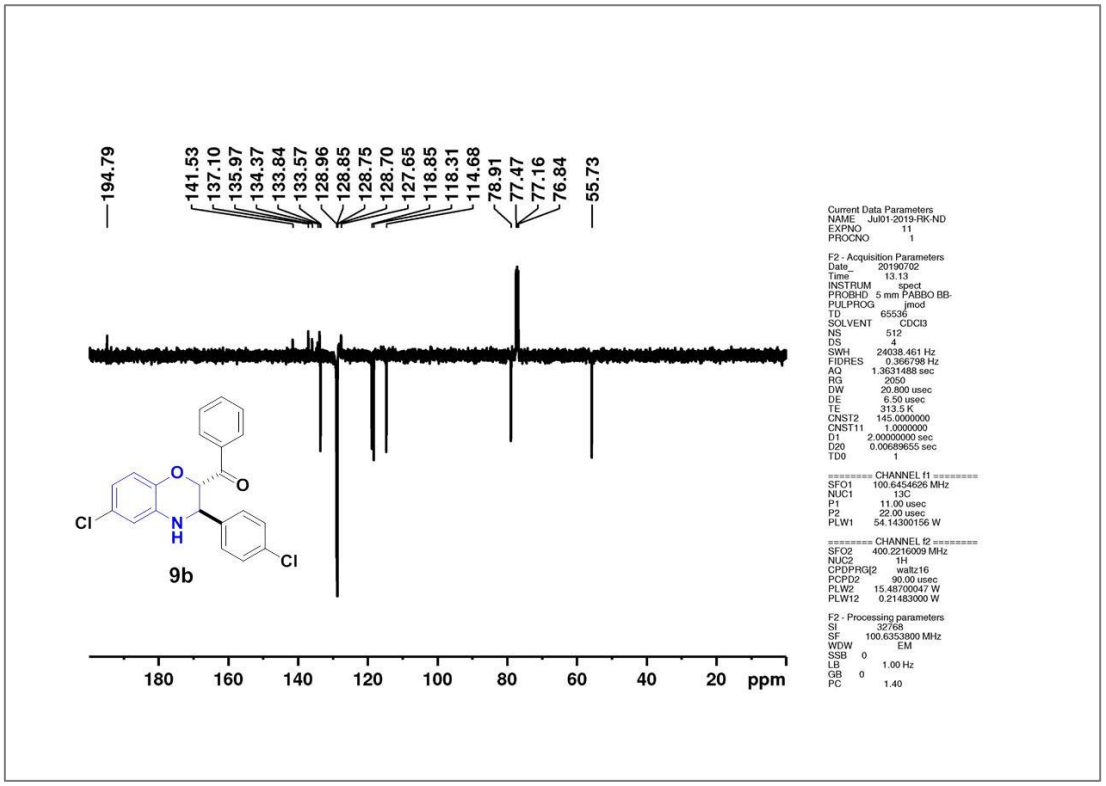
$^{13}C\{^{1}H\}$ NMR spectrum of compound 9a (Chapter 2)



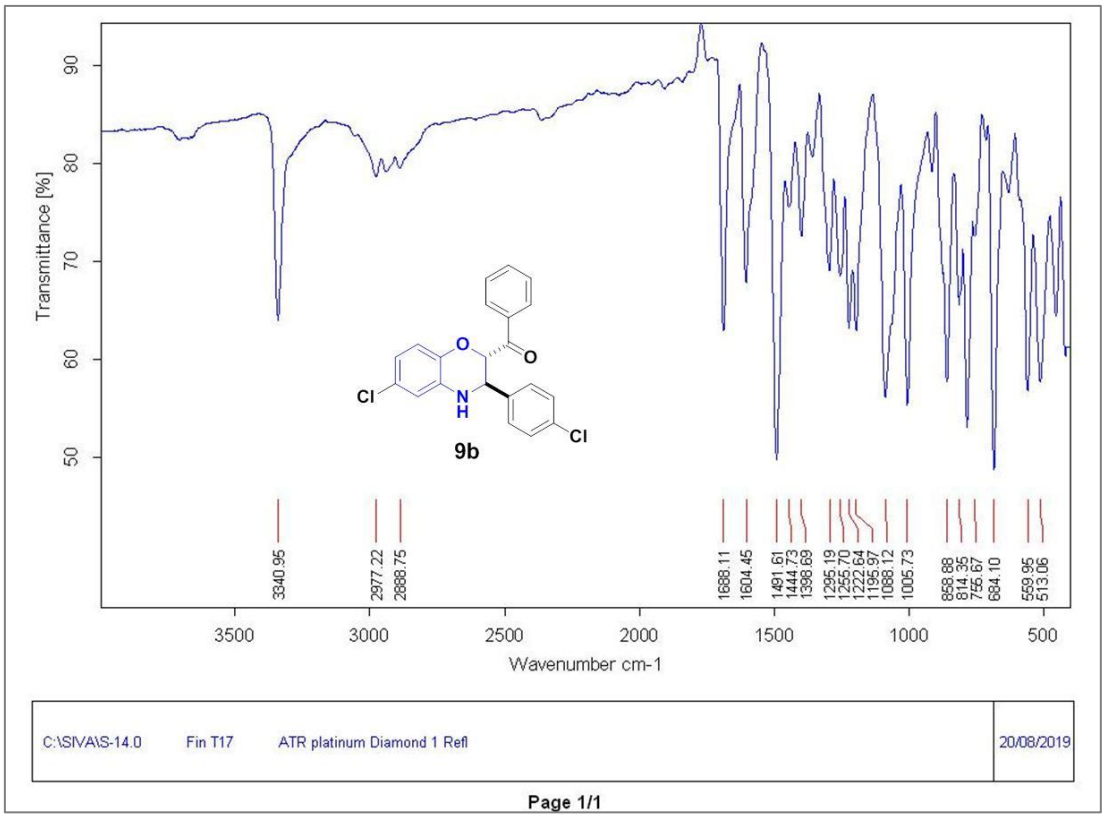
IR spectrum of compound 9a (Chapter 2)



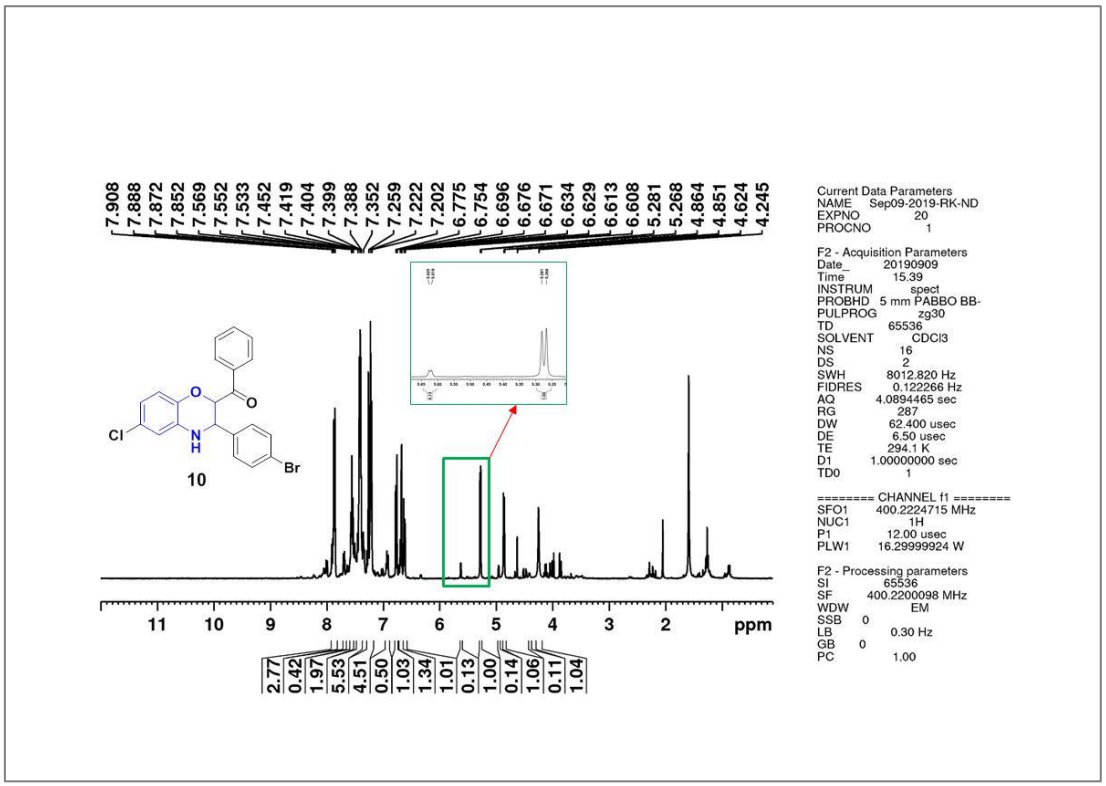
^{1}H NMR spectrum of compound 9b (Chapter 2)



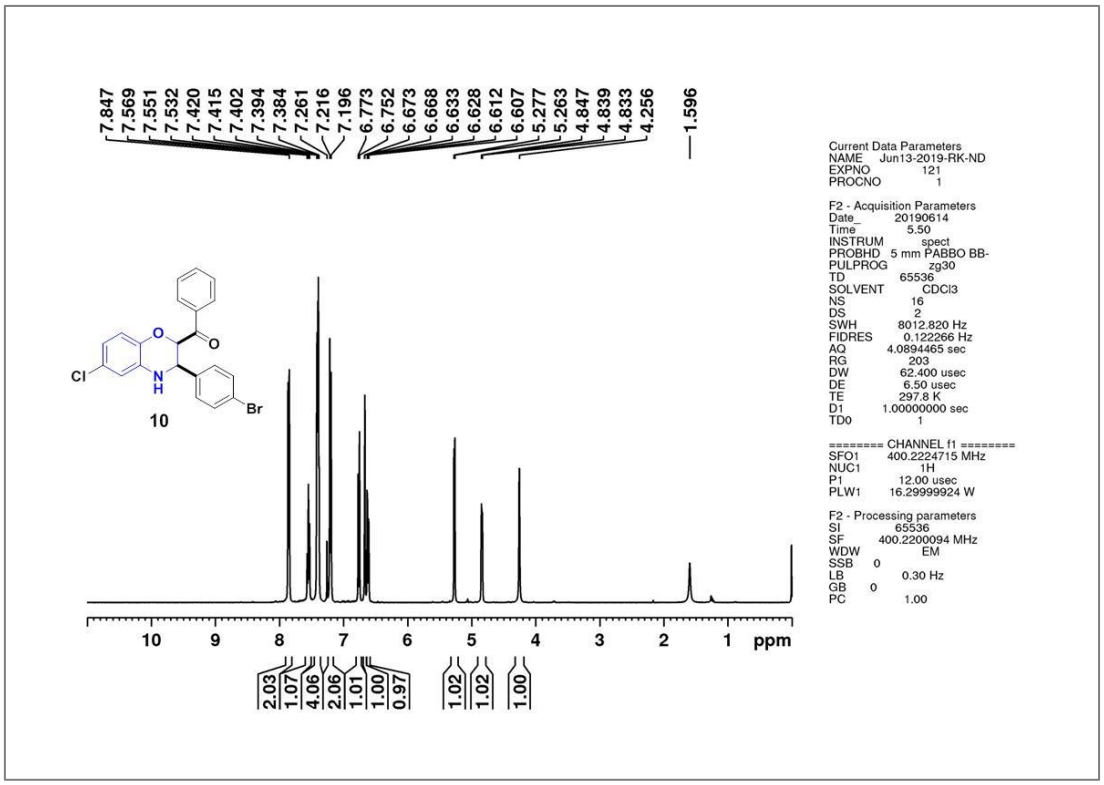
^{13}C{^{1}H} NMR spectrum of compound 9b (Chapter 2)



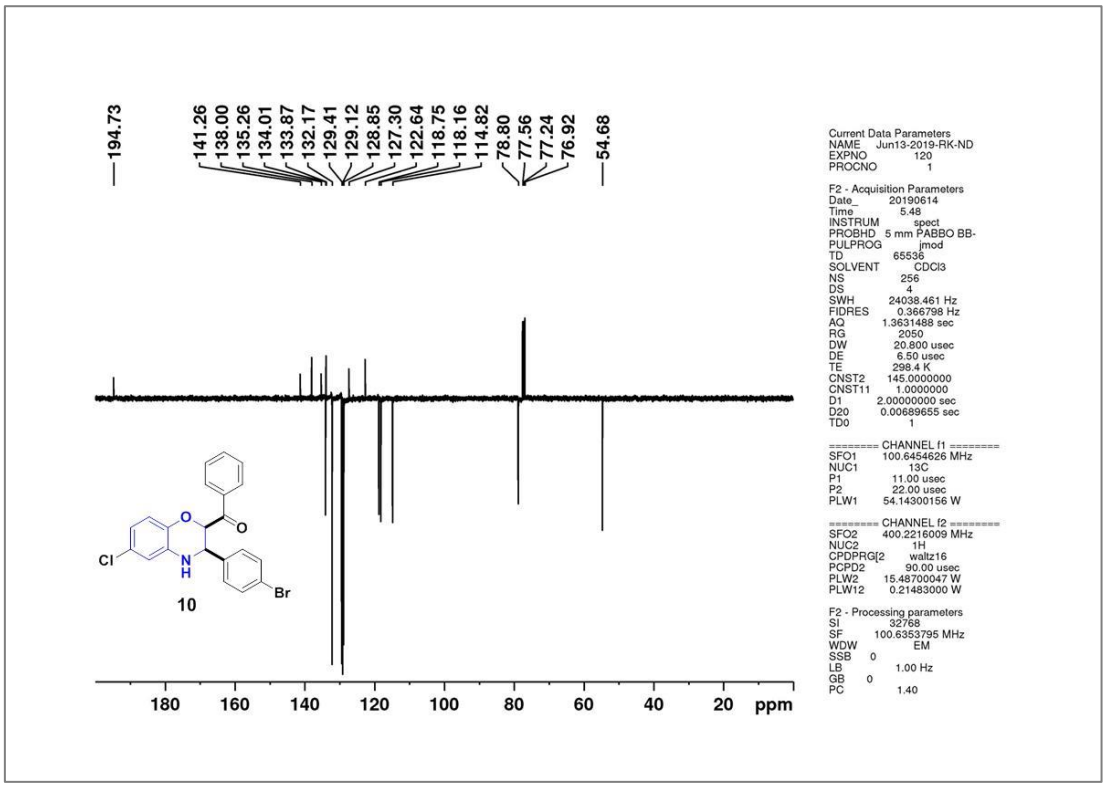
IR spectrum of compound 9b (Chapter 2)



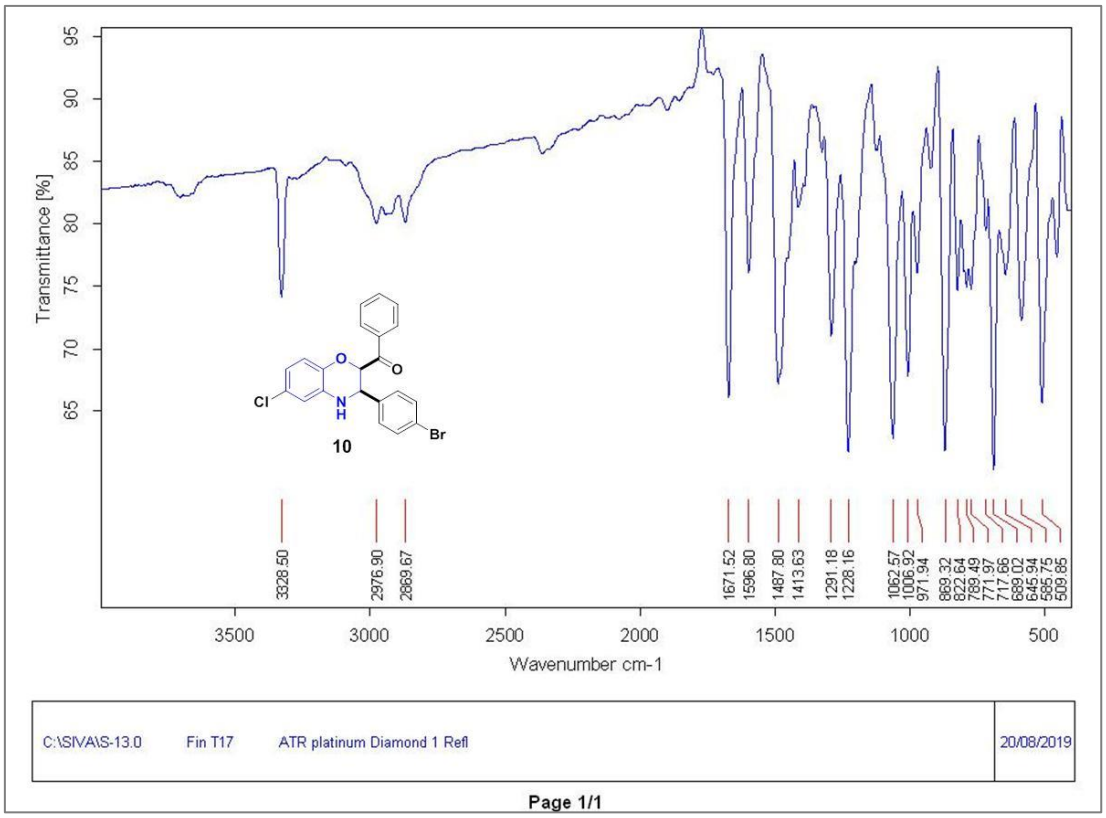
^{1}H NMR spectrum of crude compound 10 (Chapter 2)



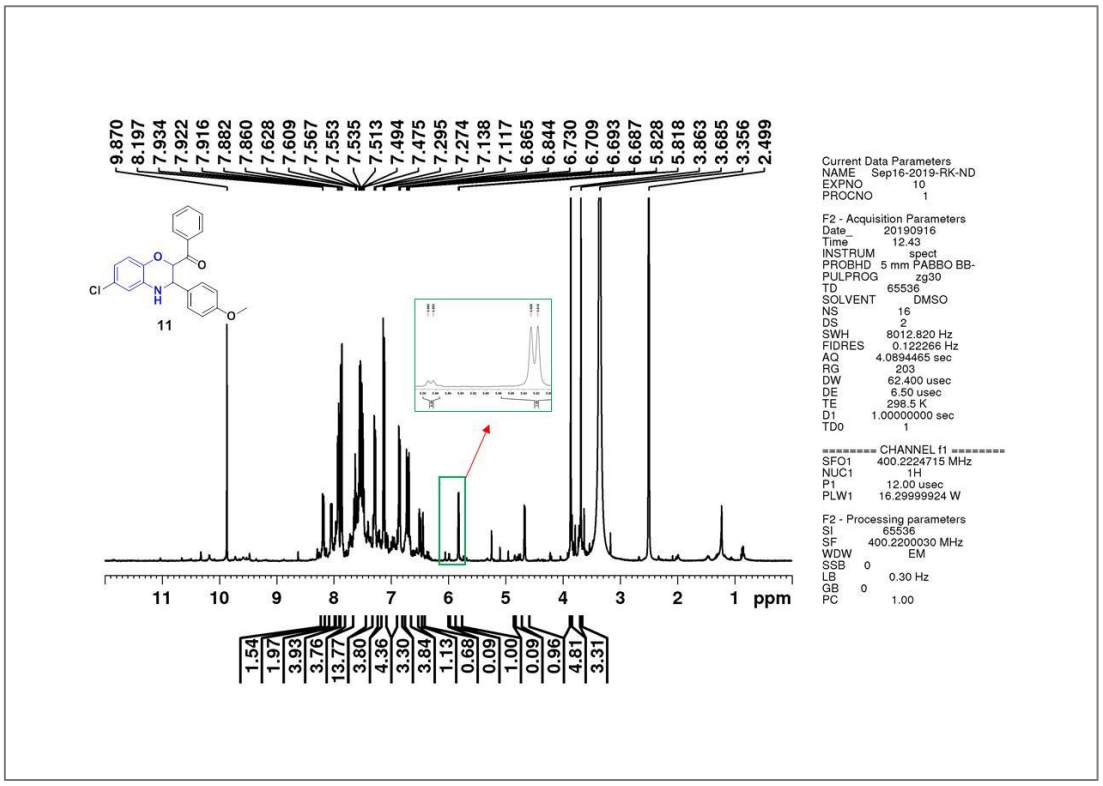
^{1}H NMR spectrum of compound 10 (Chapter 2)



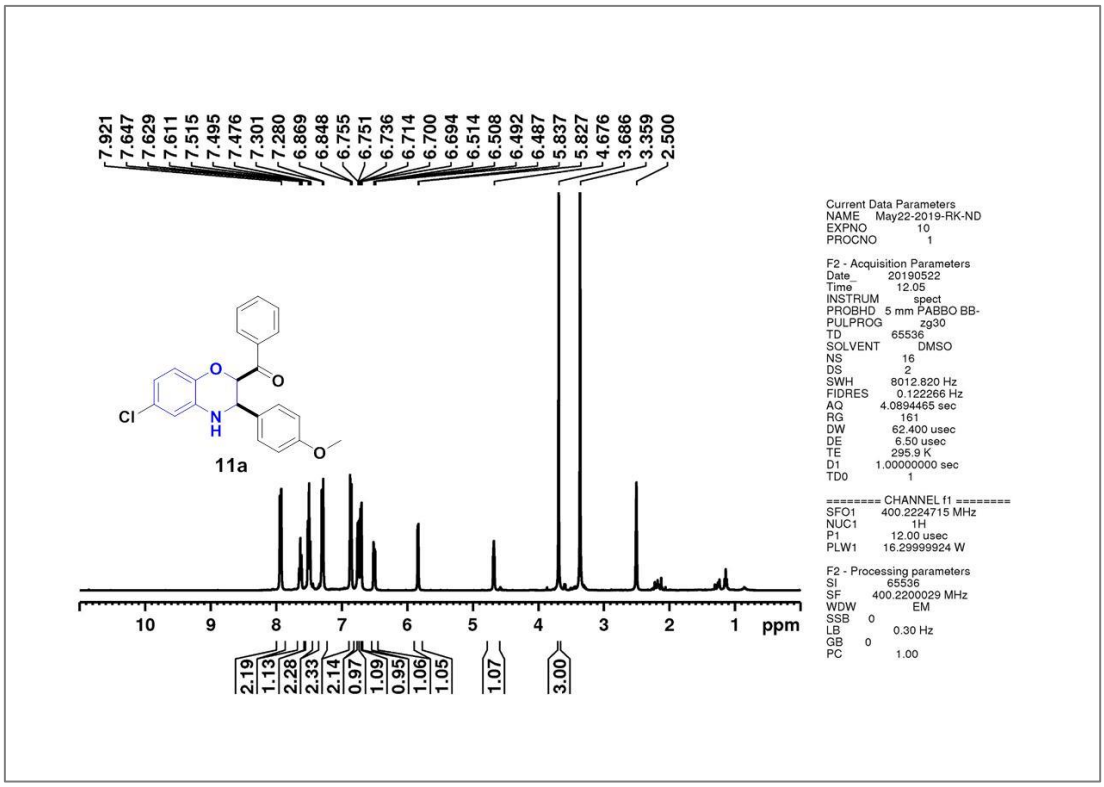
^{13}C{^{1}H} NMR spectrum of compound 10 (Chapter 2)



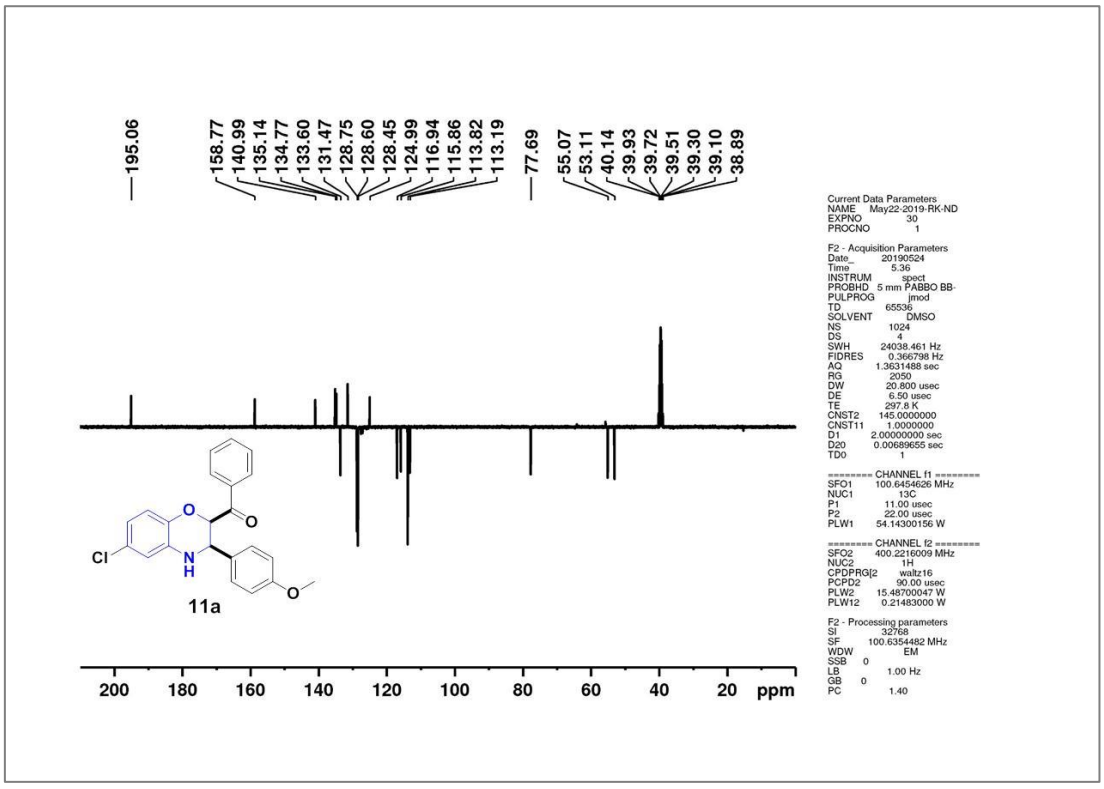
IR spectrum of compound 10 (Chapter 2)



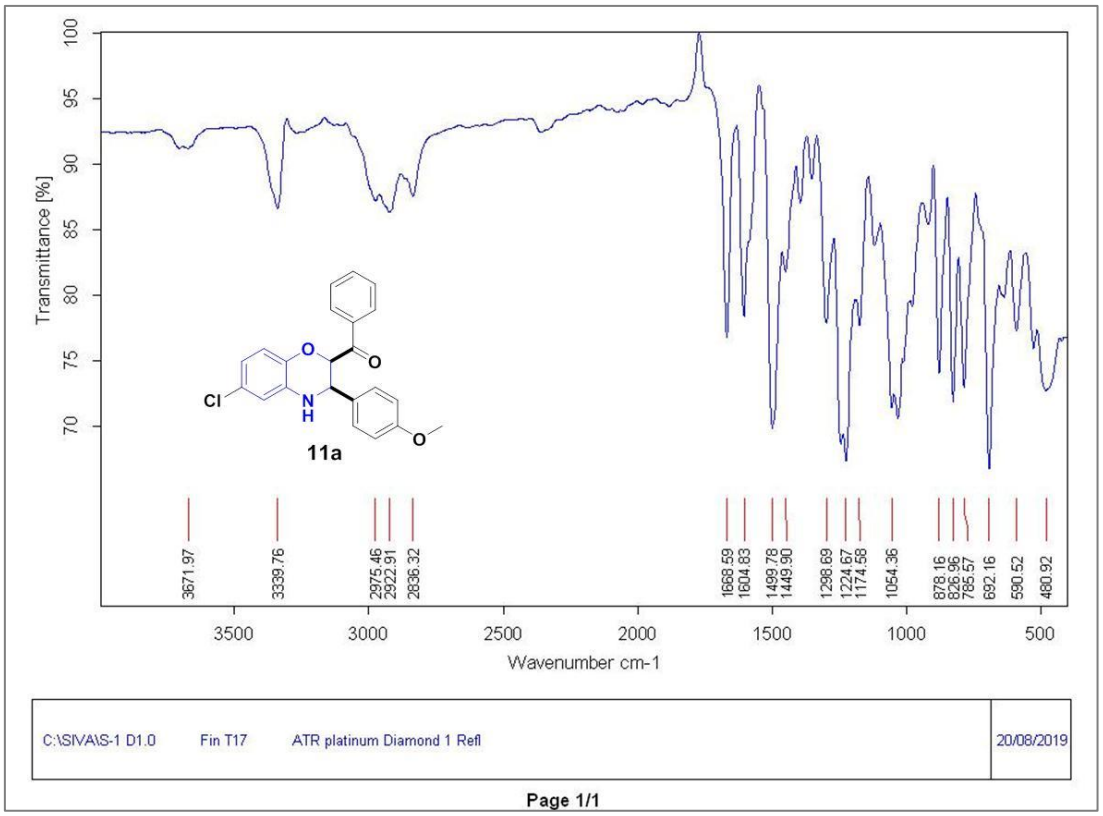
^{1}H NMR spectrum of crude compound 11 (Chapter 2)



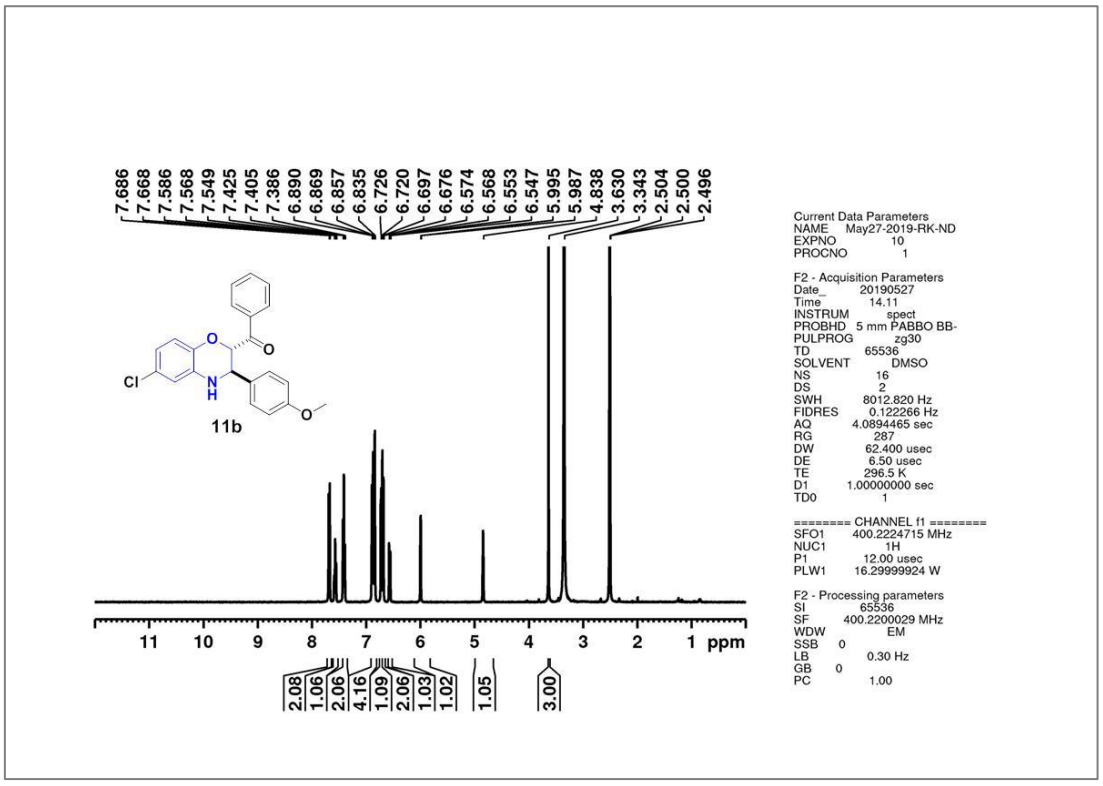
^{1}H NMR spectrum of compound 11a (Chapter 2)



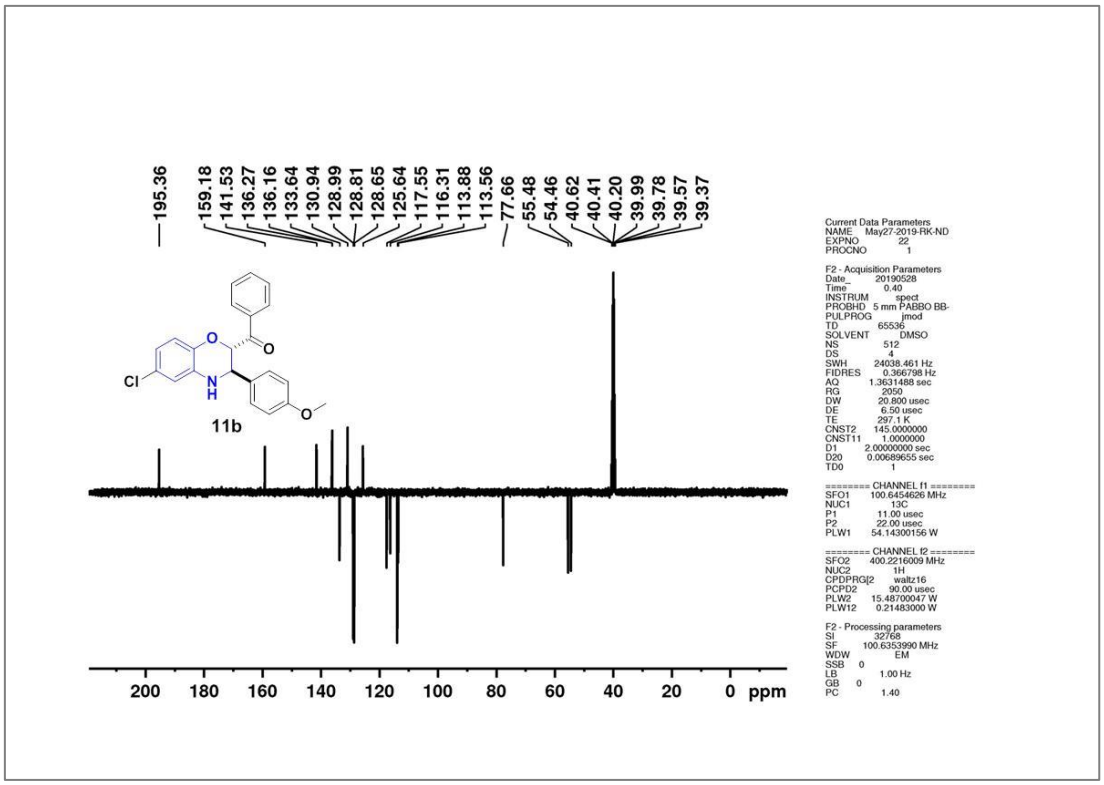
^{13}C{^{1}H} NMR spectrum of compound 11a (Chapter 2)



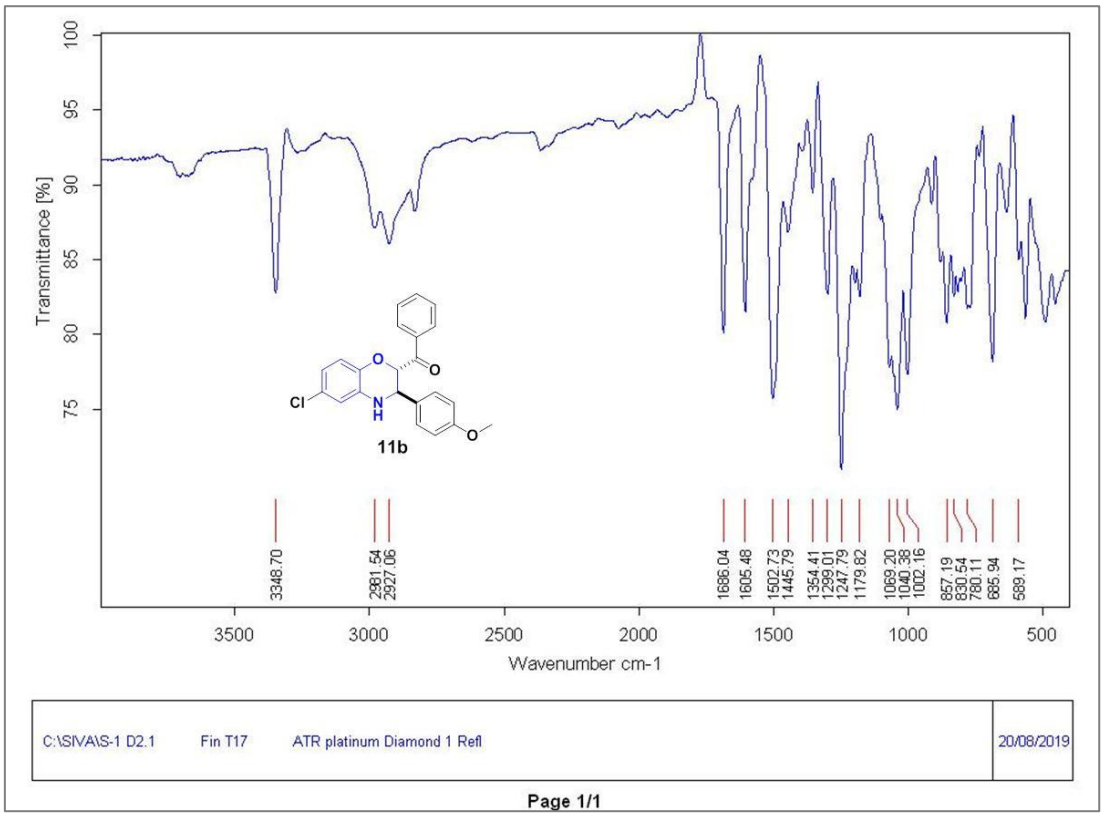
IR spectrum of compound 11a (Chapter 2)



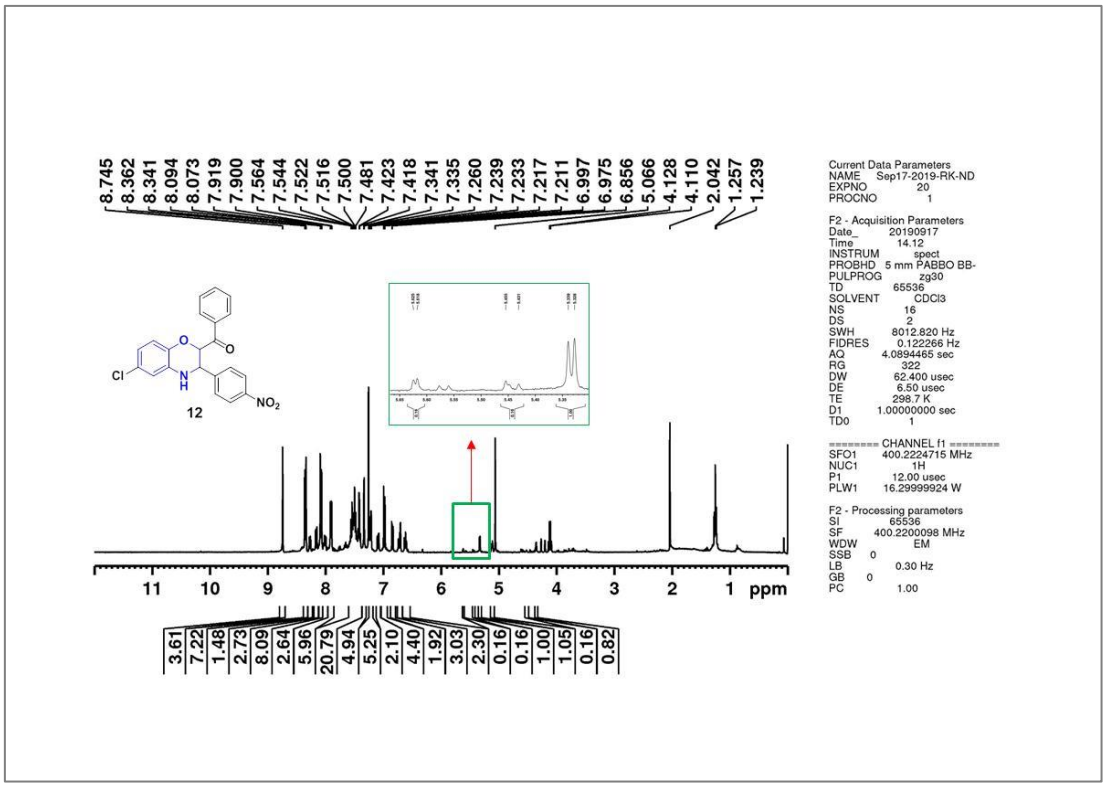
^{1}H NMR spectrum of compound 11b (Chapter 2)



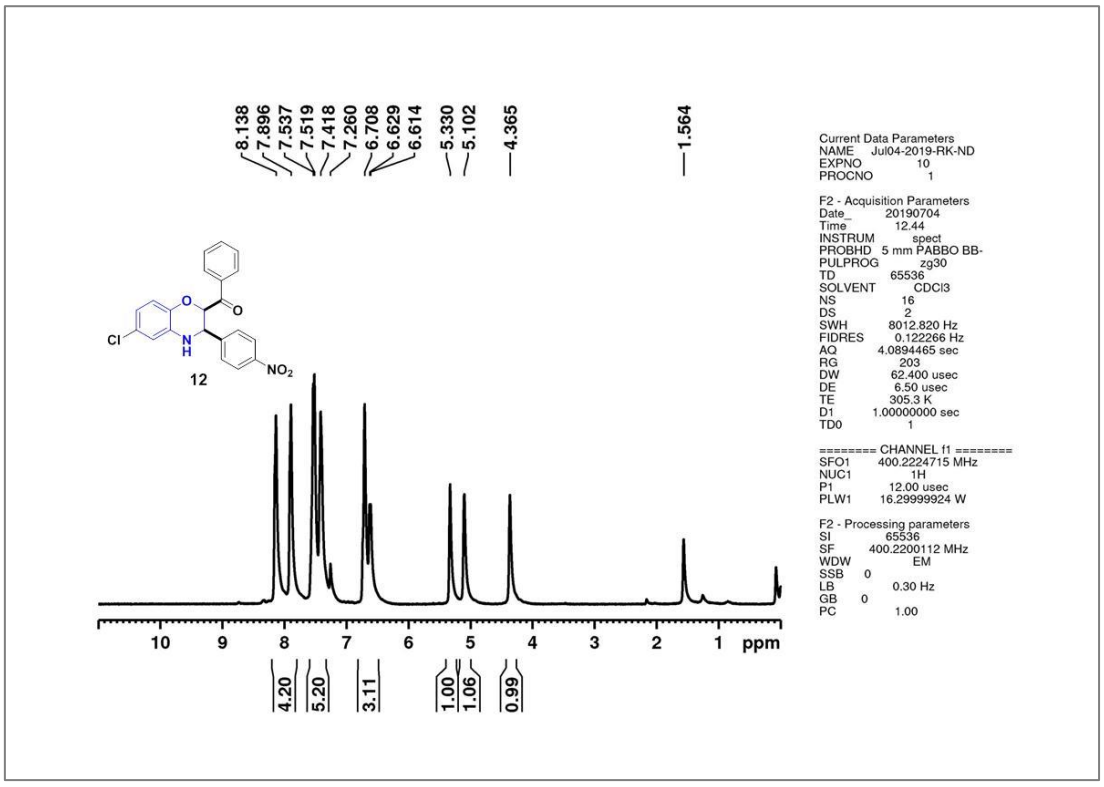
$^{13}C\{^{1}H\}$ NMR spectrum of compound 11b (Chapter 2)



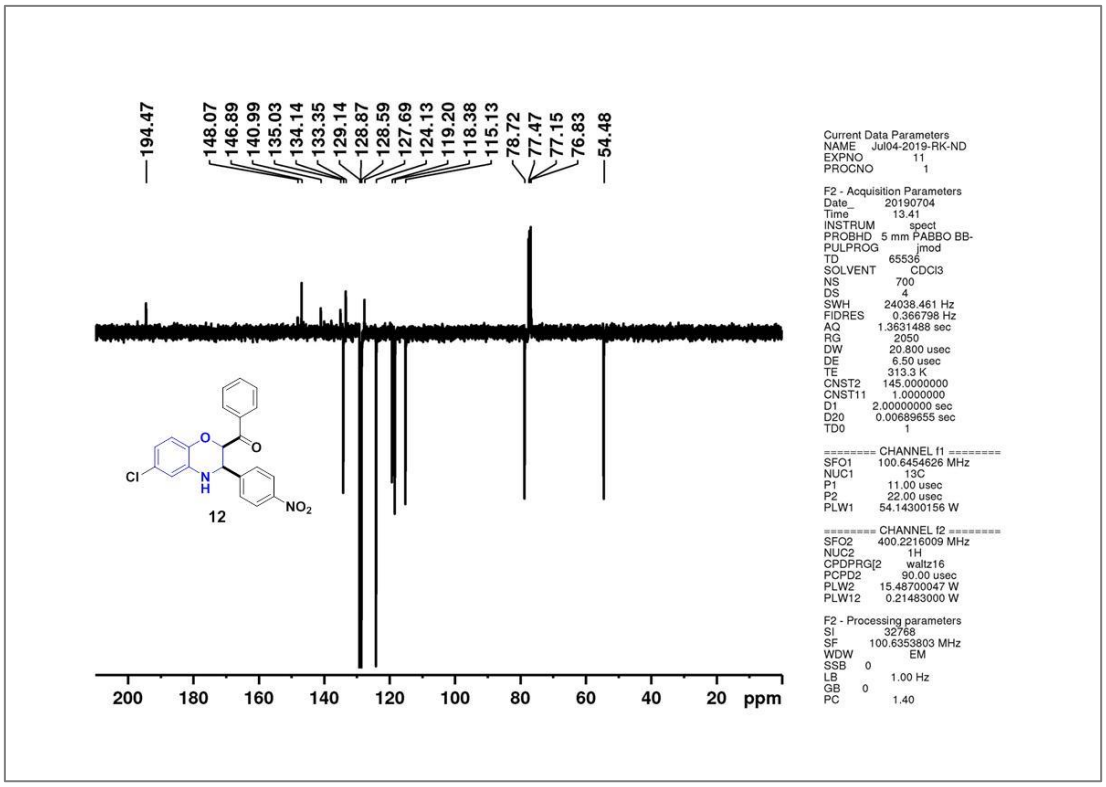
IR spectrum of compound 11b (Chapter 2)



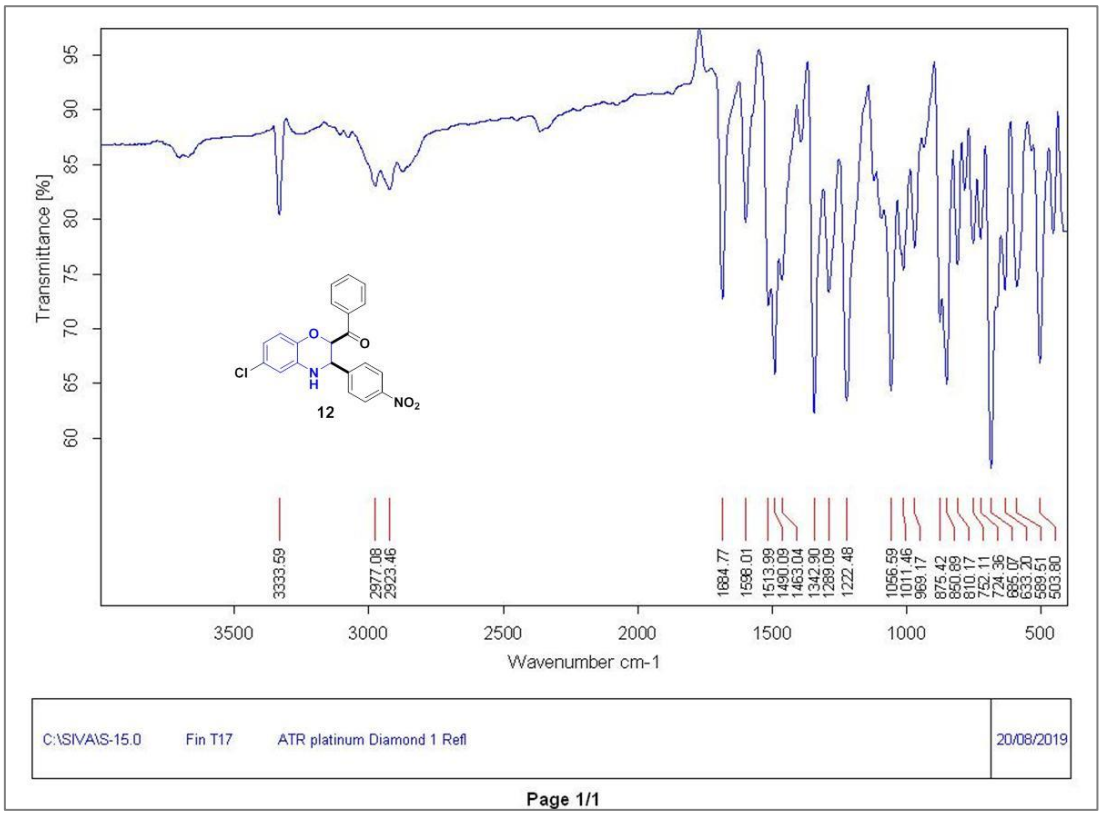
^{1}H NMR spectrum of crude compound 12 (Chapter 2)



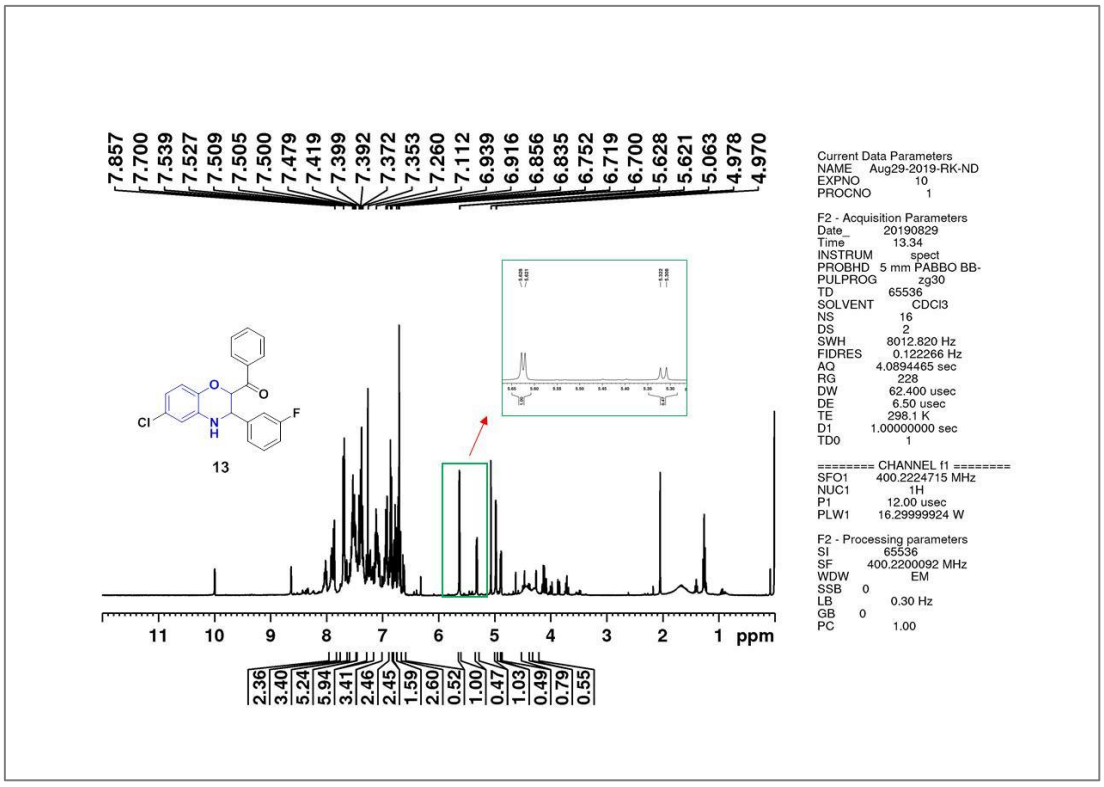
^{1}H NMR spectrum of compound 12 (Chapter 2)



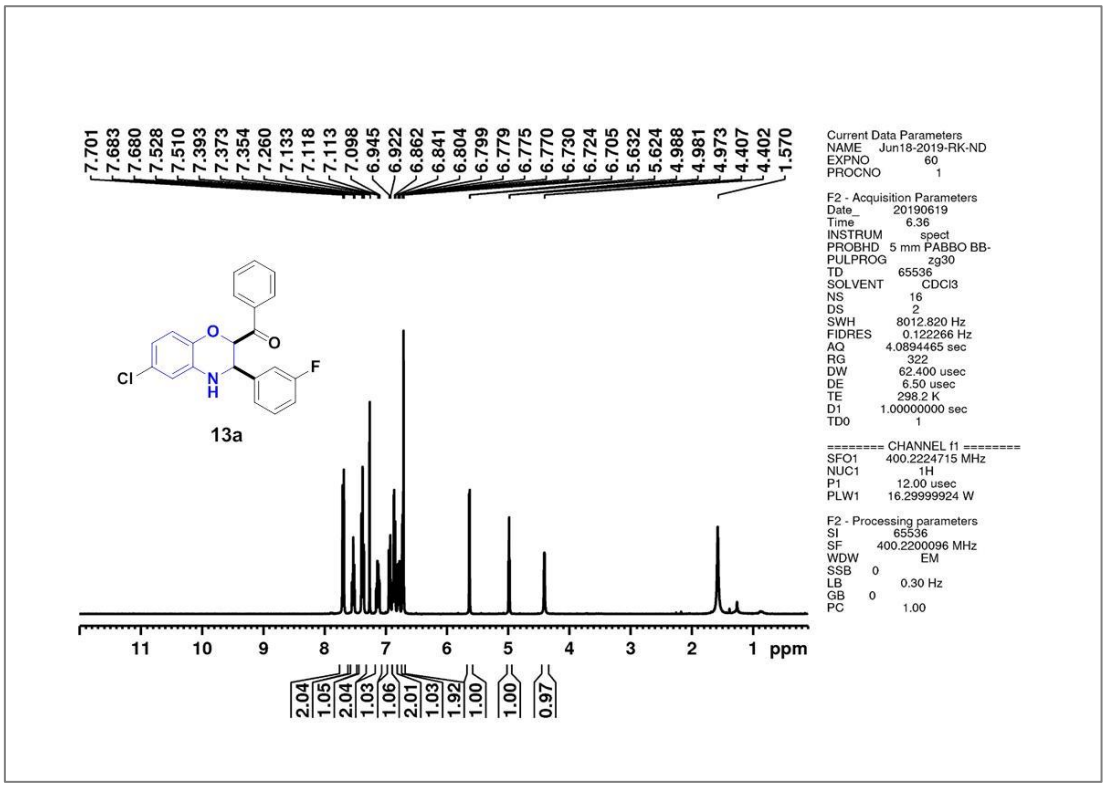
$^{13}C\{^{1}H\}$ NMR spectrum of compound 12 (Chapter 2)



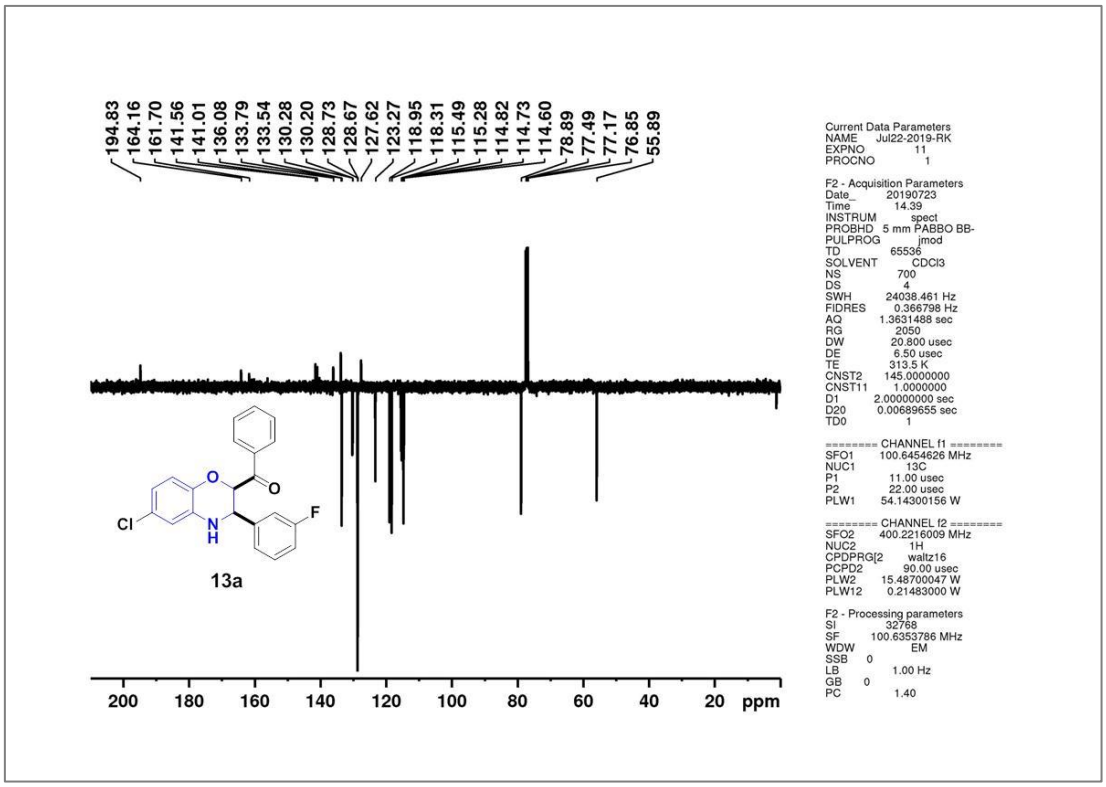
IR spectrum of compound 12 (Chapter 2)



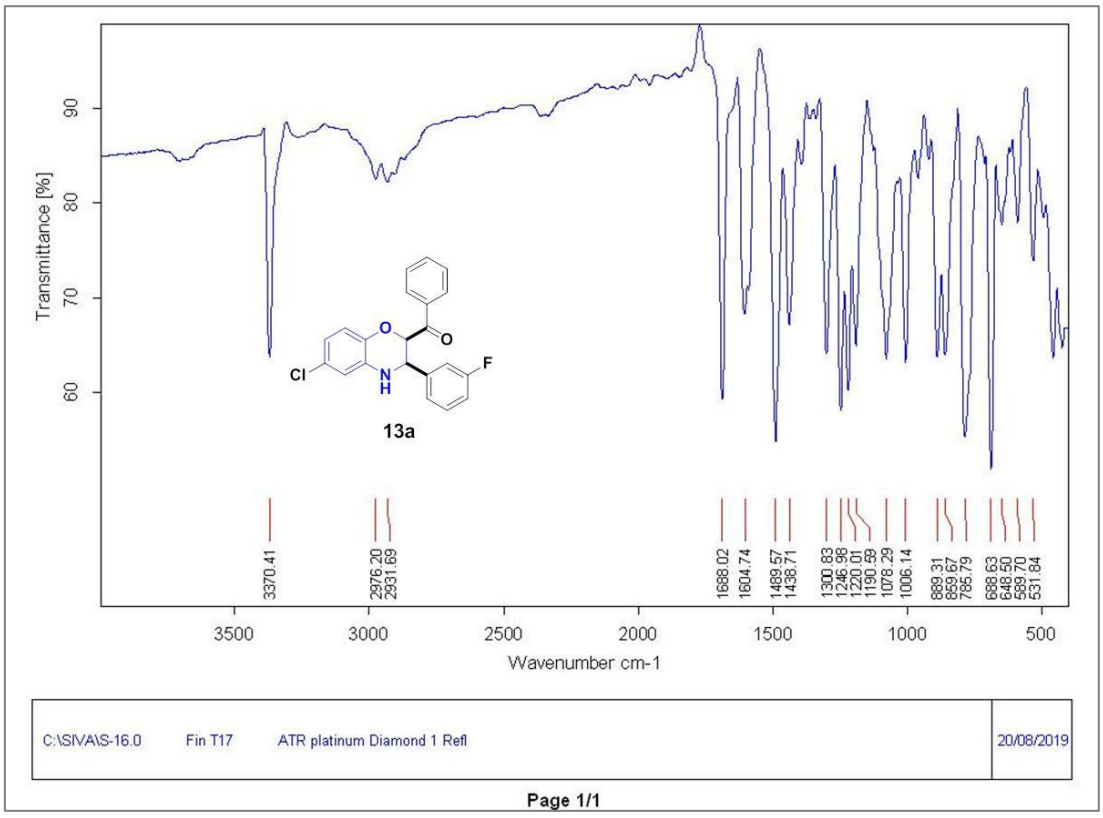
^{1}H NMR spectrum of crude compound 13 (Chapter 2)



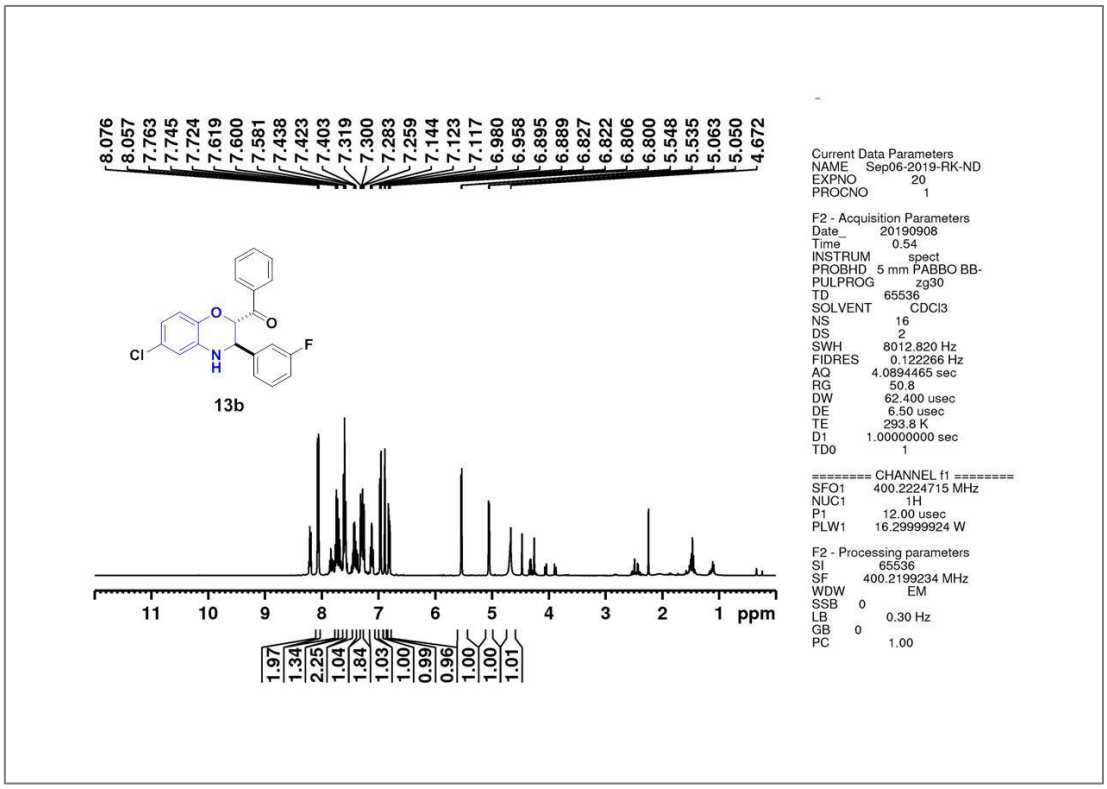
^{1}H NMR spectrum of compound 13a (Chapter 2)



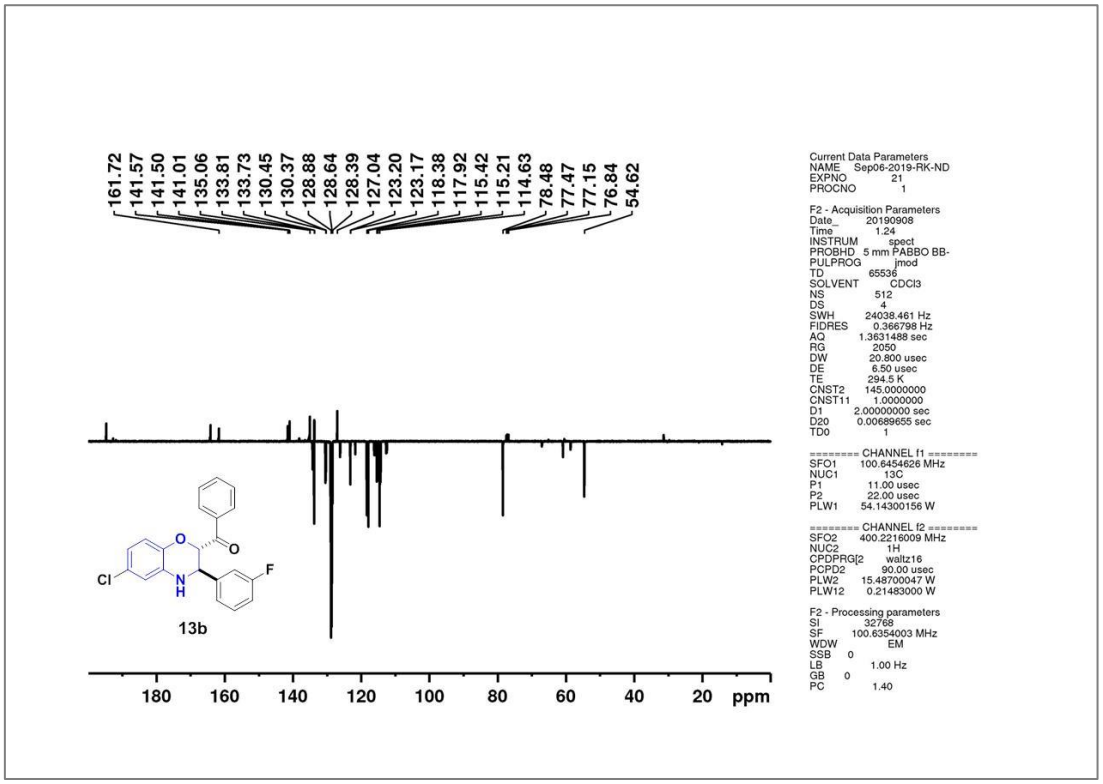
$^{13}C\{^{1}H\}$ NMR spectrum of compound 13a (Chapter 2)



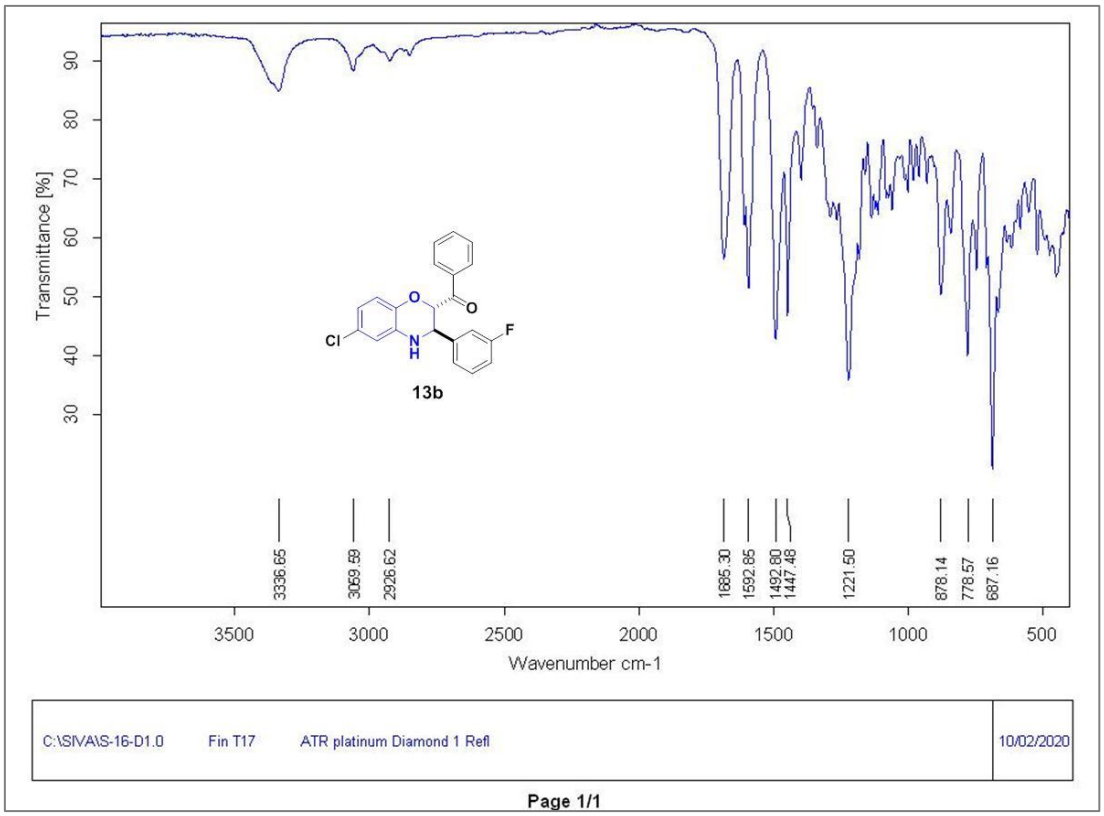
IR spectrum of compound 13a (Chapter 2)



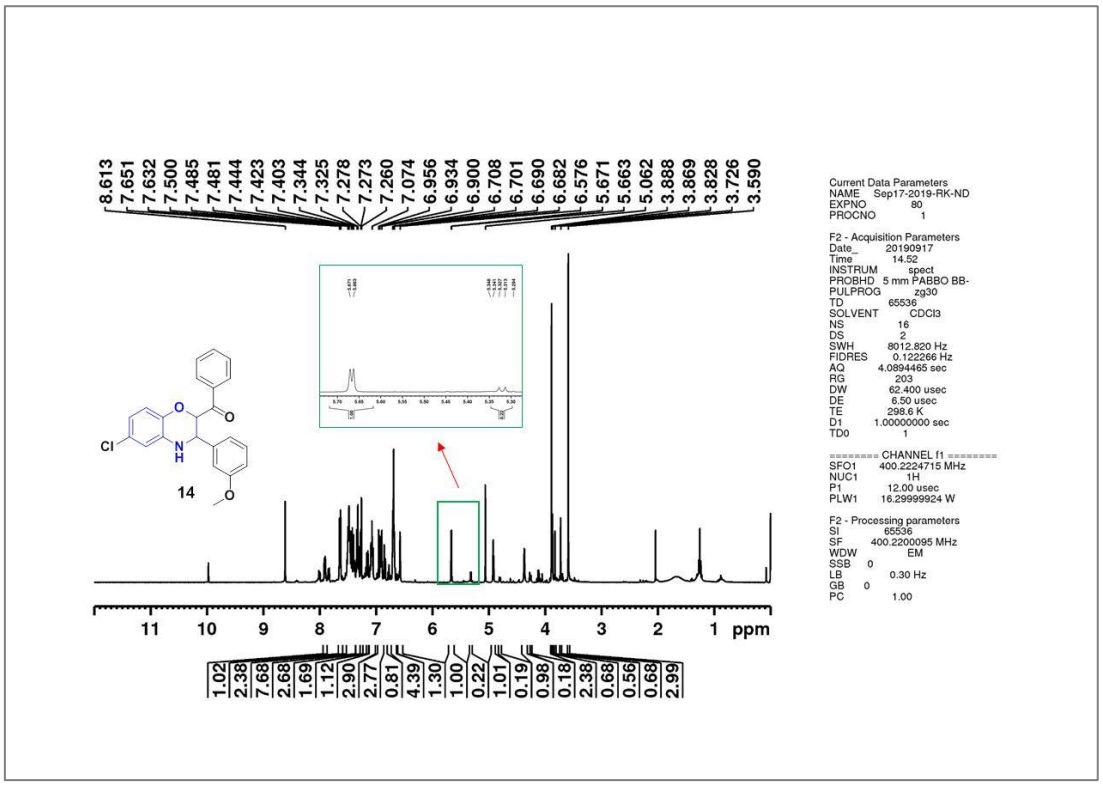
^{1}H NMR spectrum of compound 13b (Chapter 2)



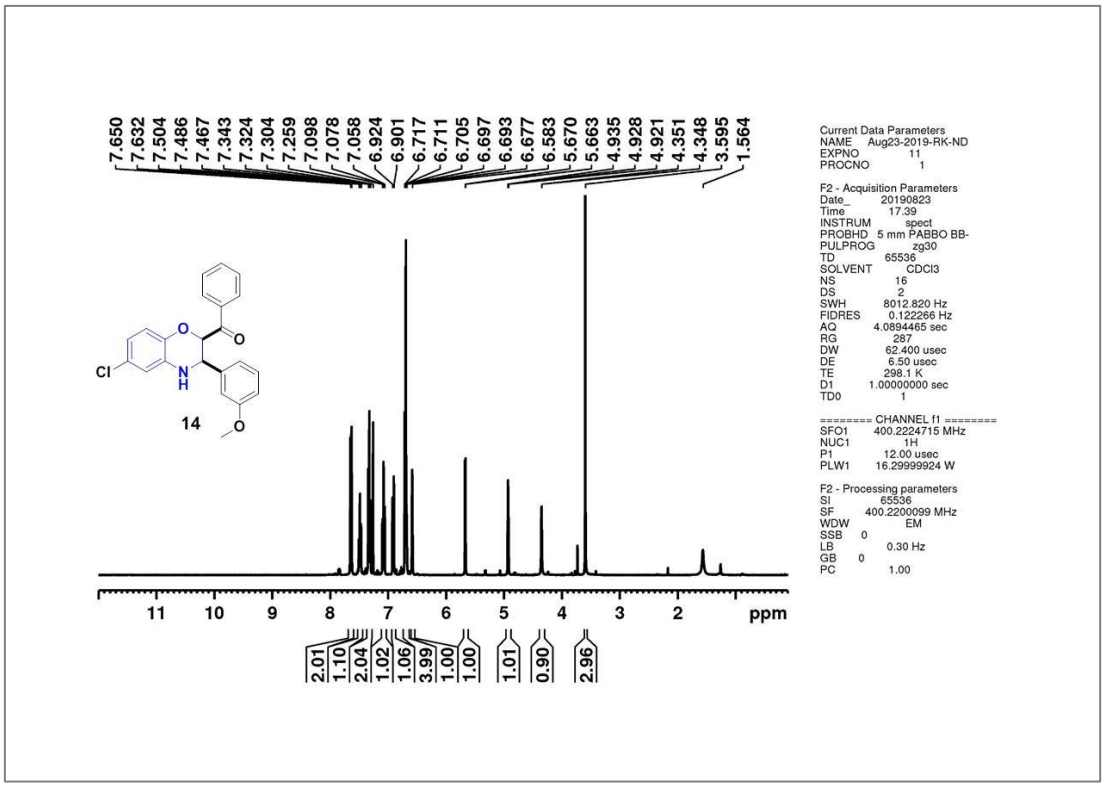
^{13}C{^{1}H} NMR spectrum of compound 13b (Chapter 2)



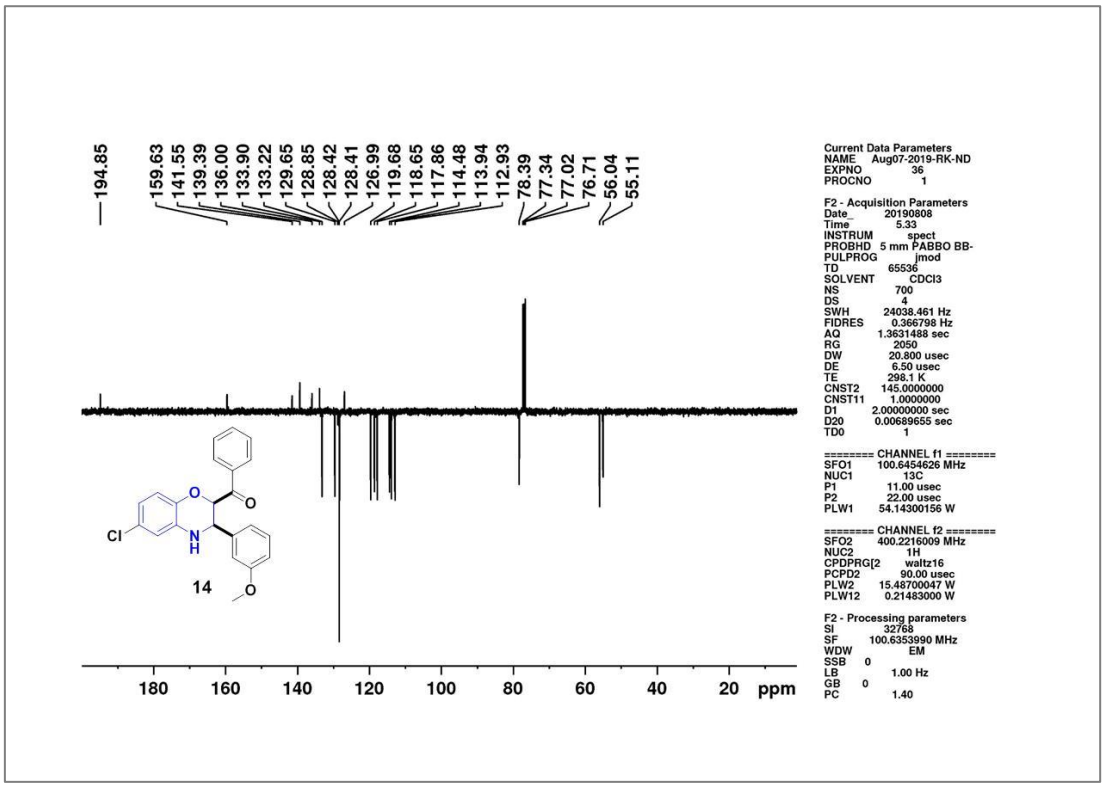
IR spectrum of compound 13b (Chapter 2)



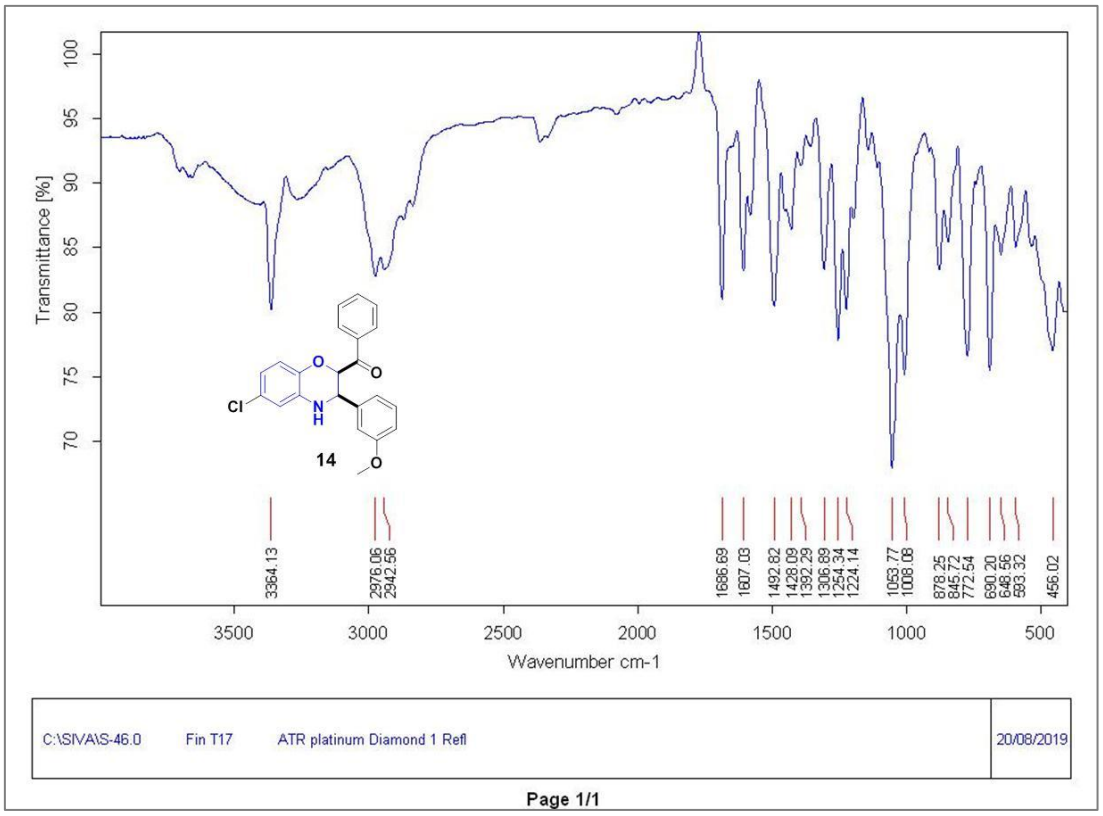
^{1}H NMR spectrum of crude compound 14 (Chapter 2)



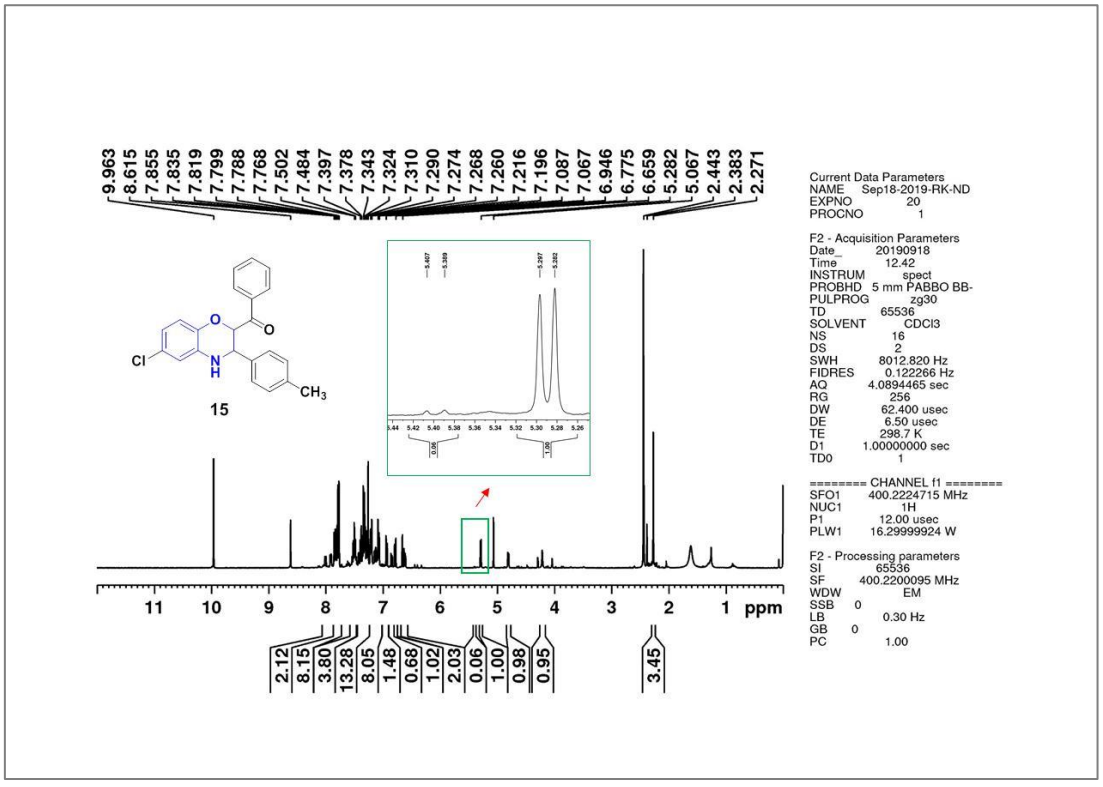
^{1}H NMR spectrum of compound 14 (Chapter 2)



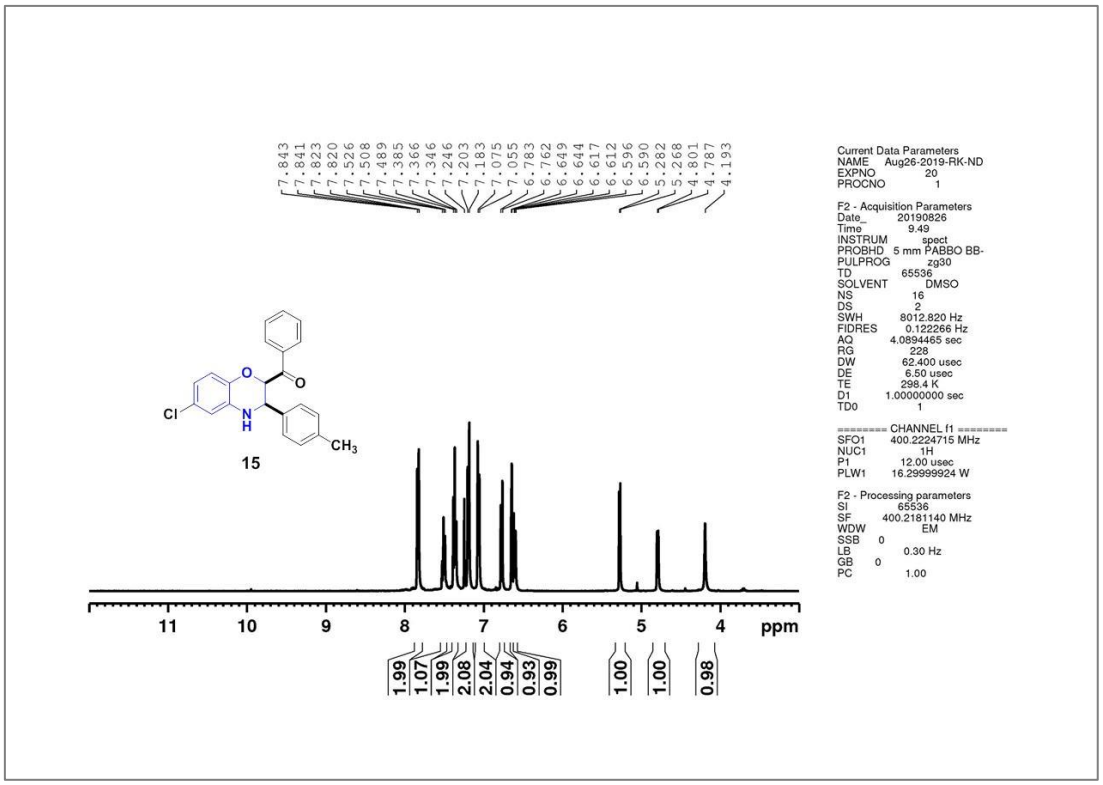
^{13}C{^{1}H} NMR spectrum of compound 14 (Chapter 2)



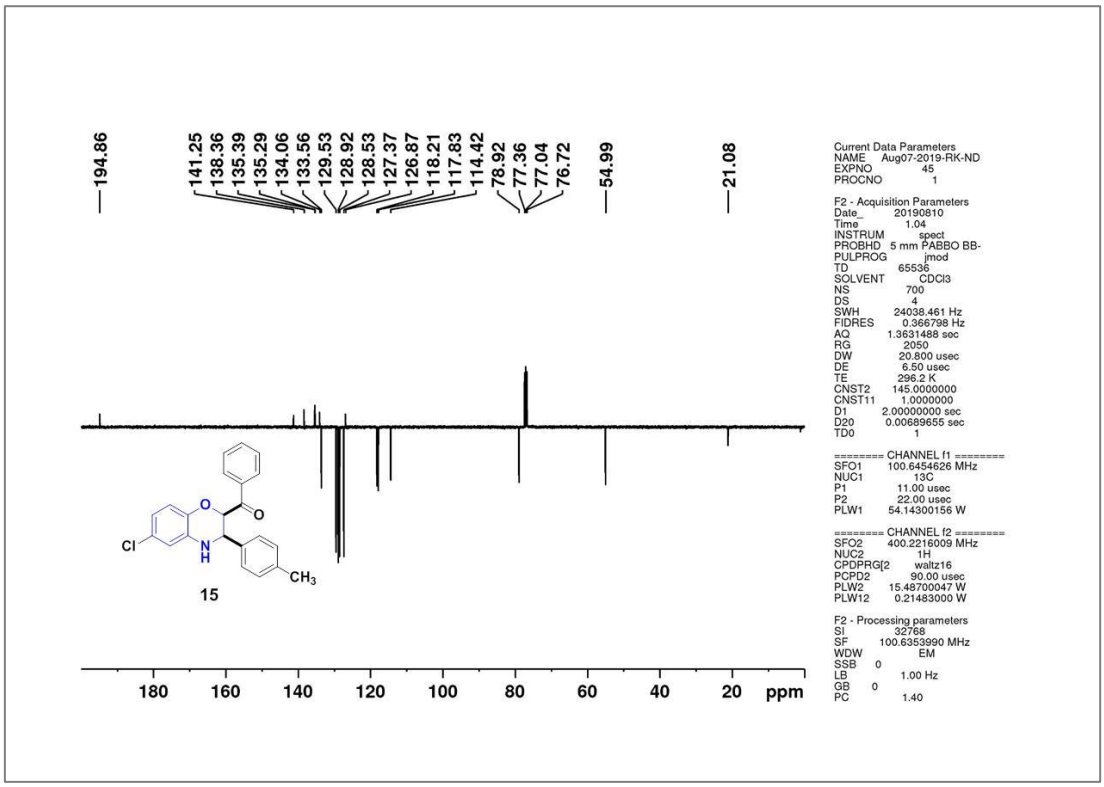
IR spectrum of compound 14 (Chapter 2)



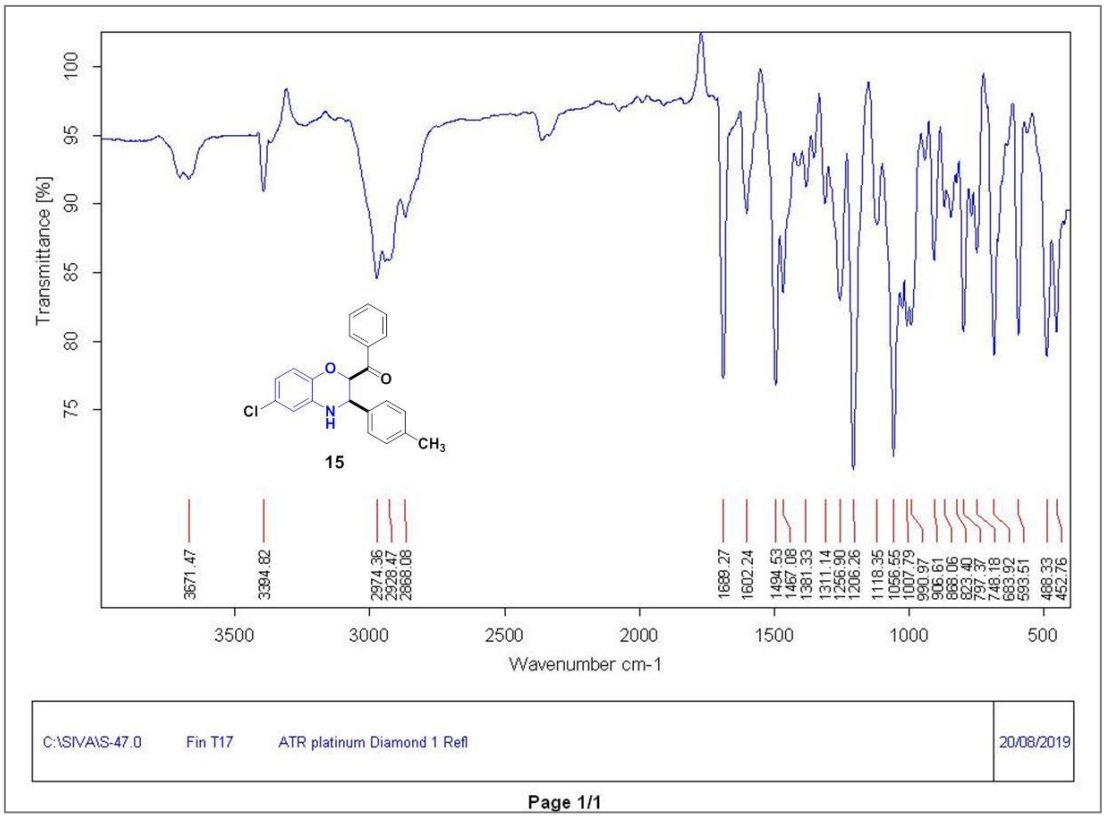
^{1}H NMR spectrum of crude compound 15 (Chapter 2)



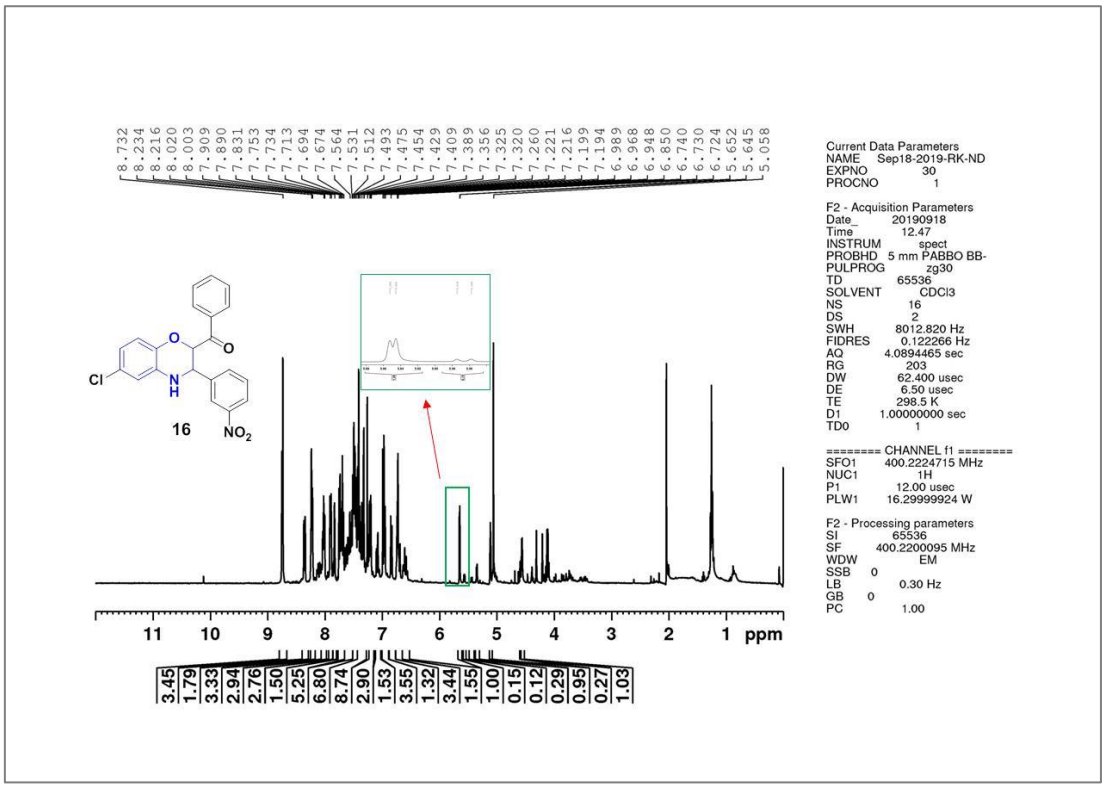
^{1}H NMR spectrum of compound 15 (Chapter 2)



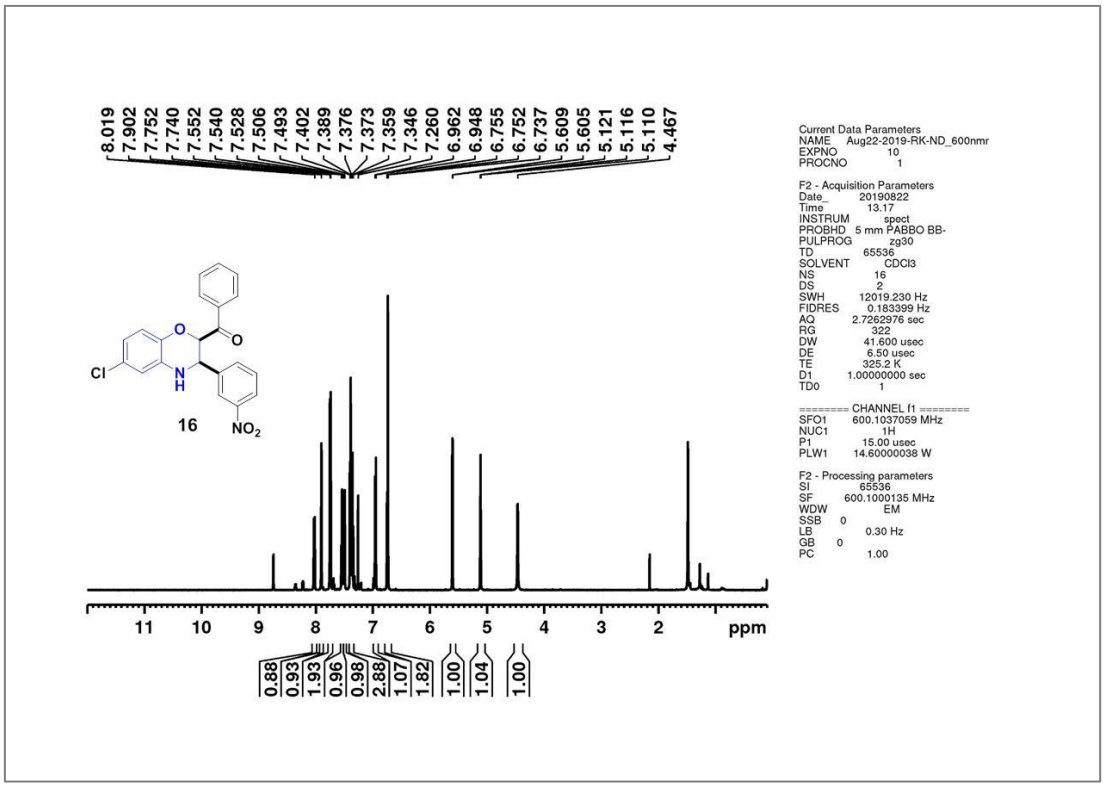
^{13}C{^{1}H} NMR spectrum of compound 15 (Chapter 2)



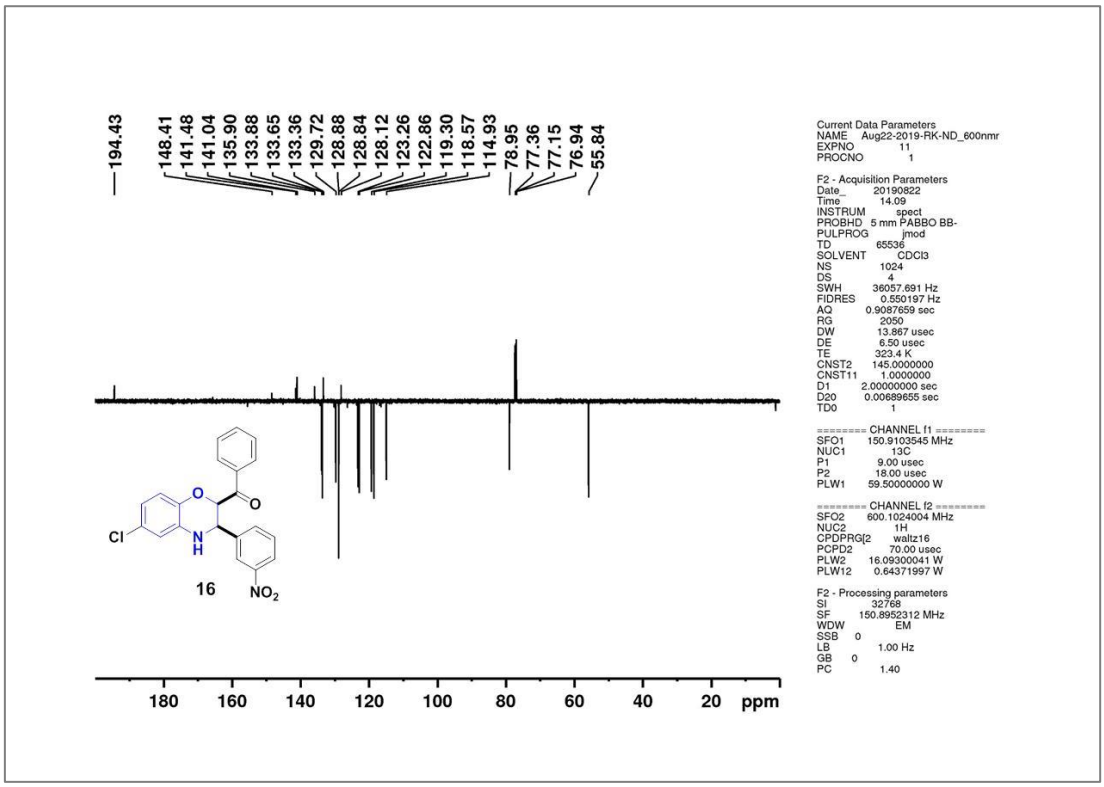
IR spectrum of compound 15 (Chapter 2)



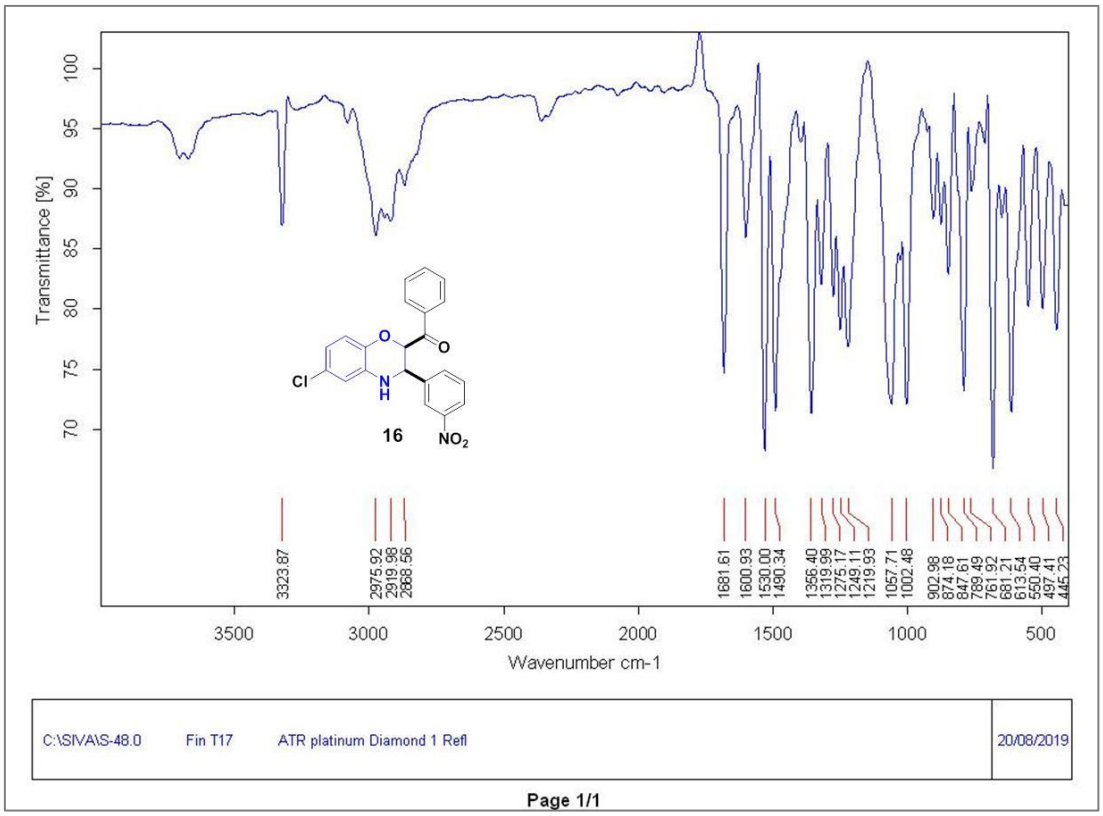
^{1}H NMR spectrum of crude compound 16 (Chapter 2)



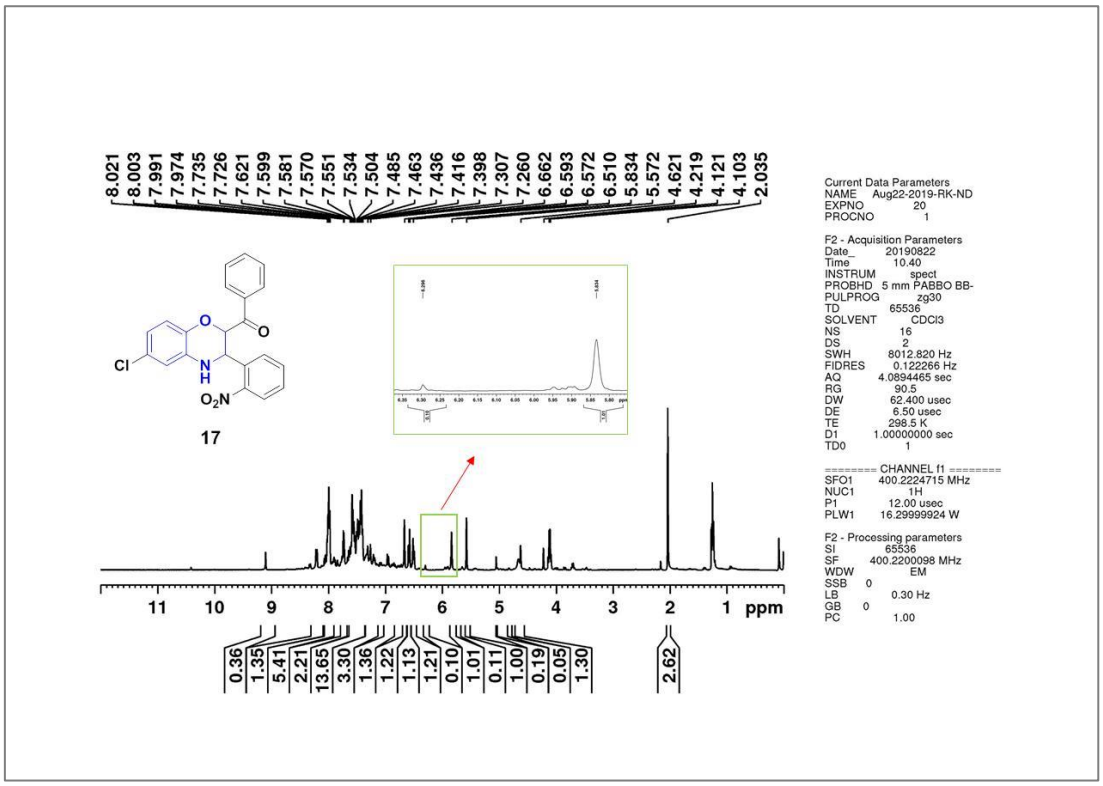
^{1}H NMR spectrum of compound 16 (Chapter 2)



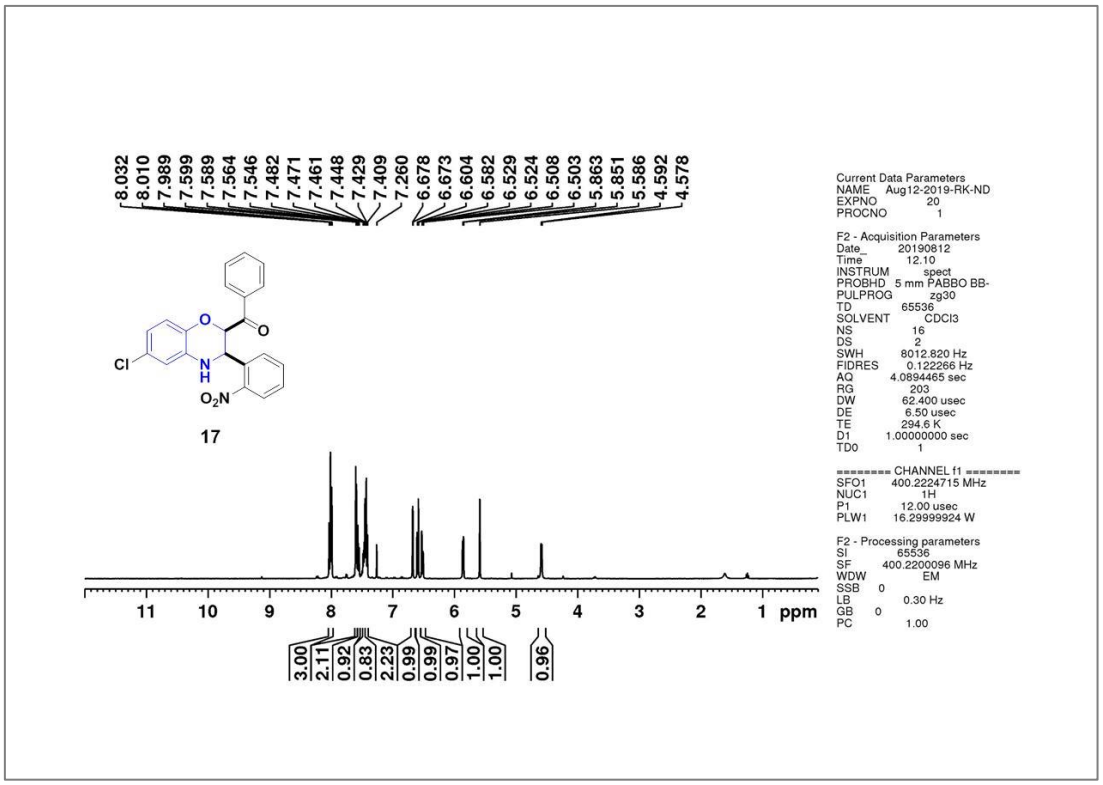
^{13}C{^{1}H} NMR spectrum of compound 16 (Chapter 2)



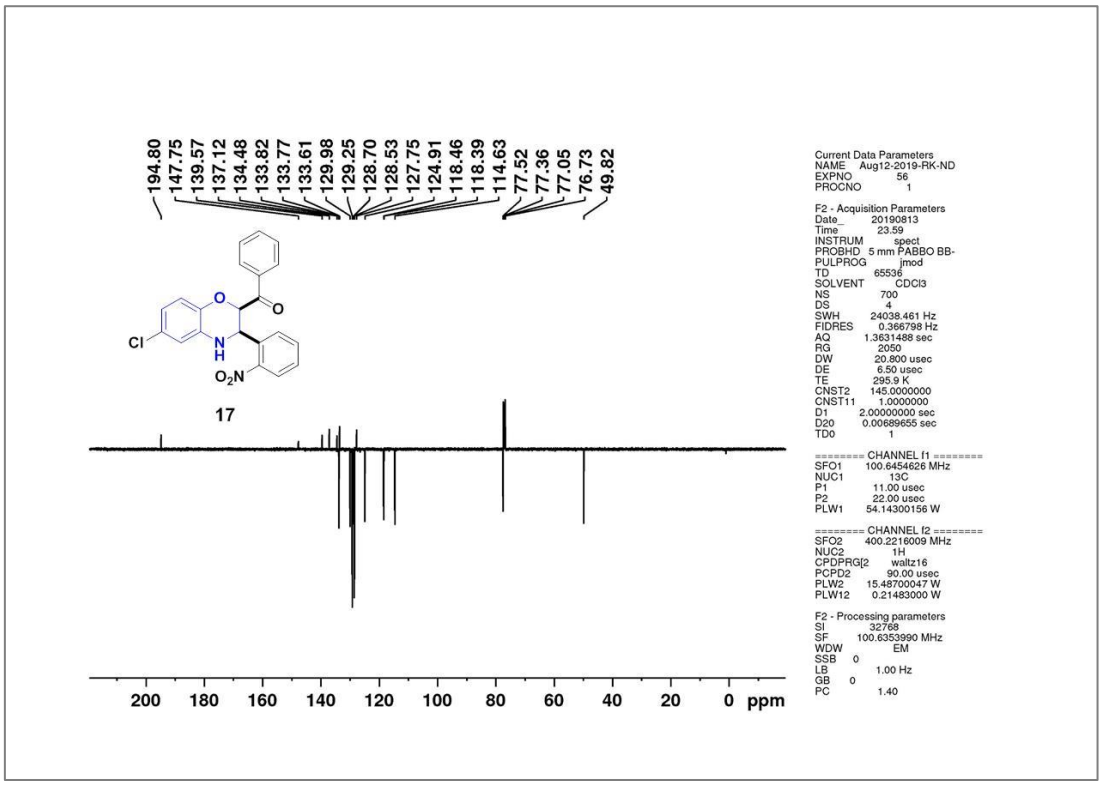
IR spectrum of compound 16 (Chapter 2)



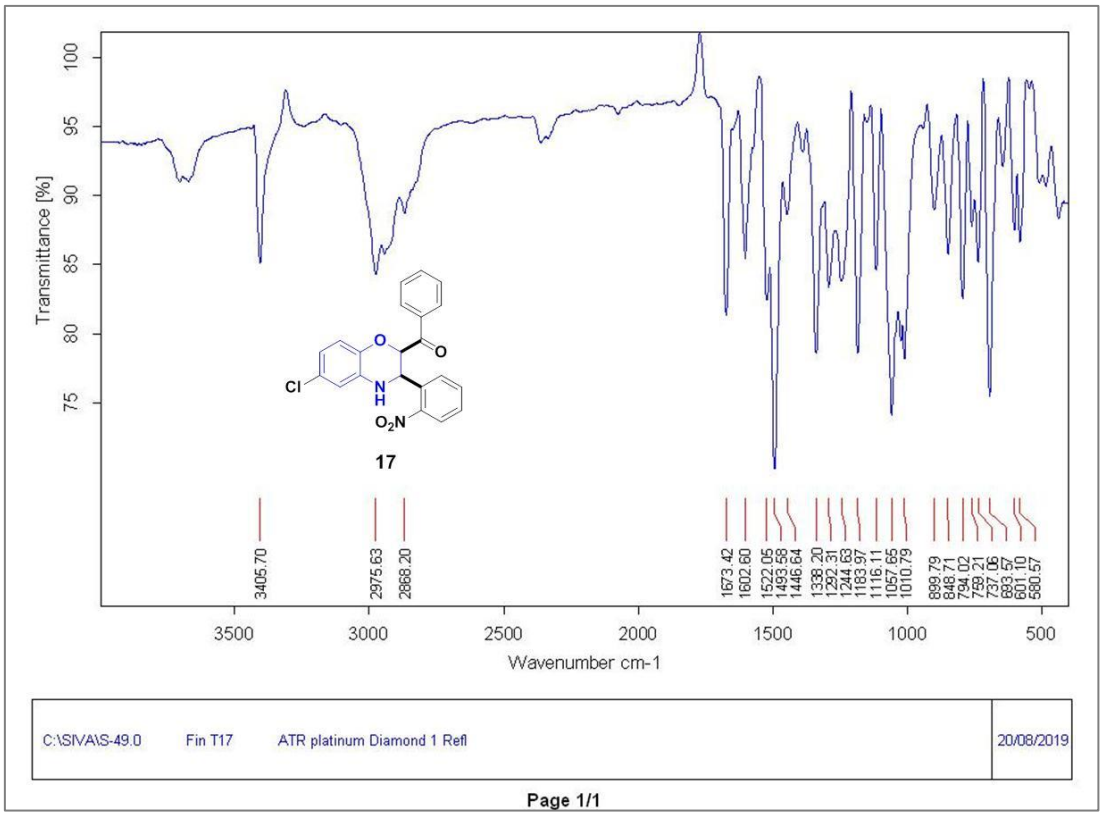
^{1}H NMR spectrum of crude compound 17 (Chapter 2)



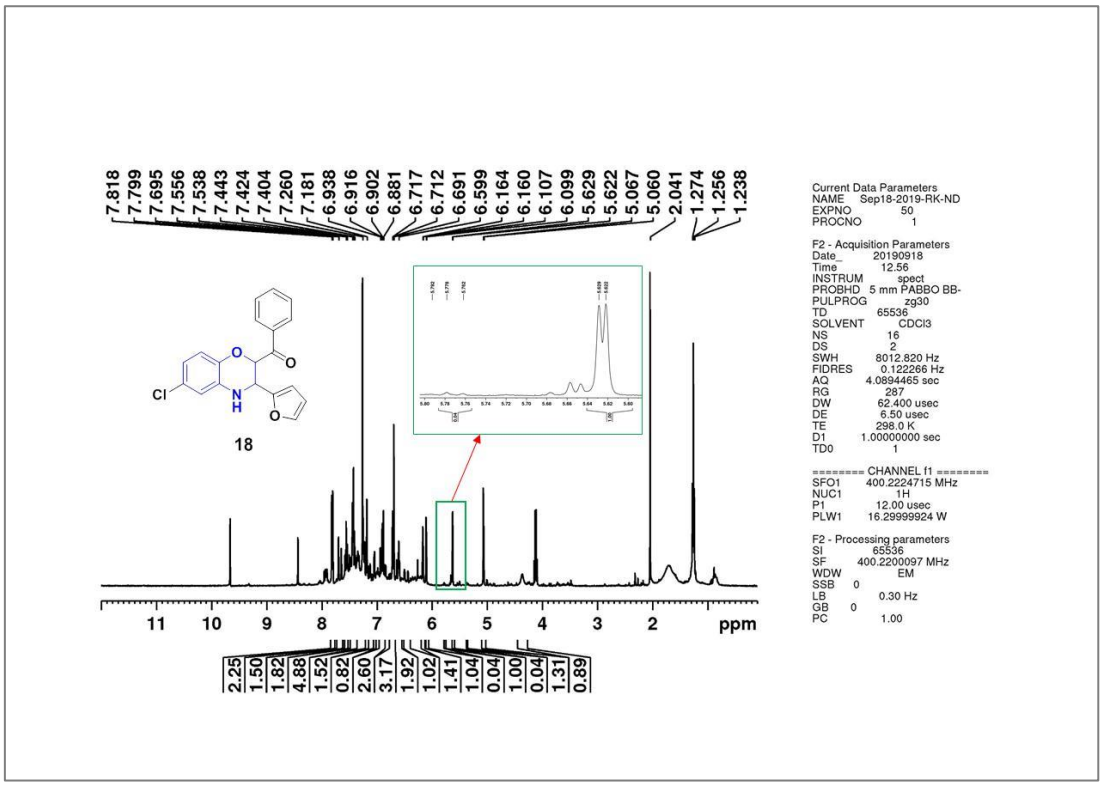
^{1}H NMR spectrum of compound 17 (Chapter 2)



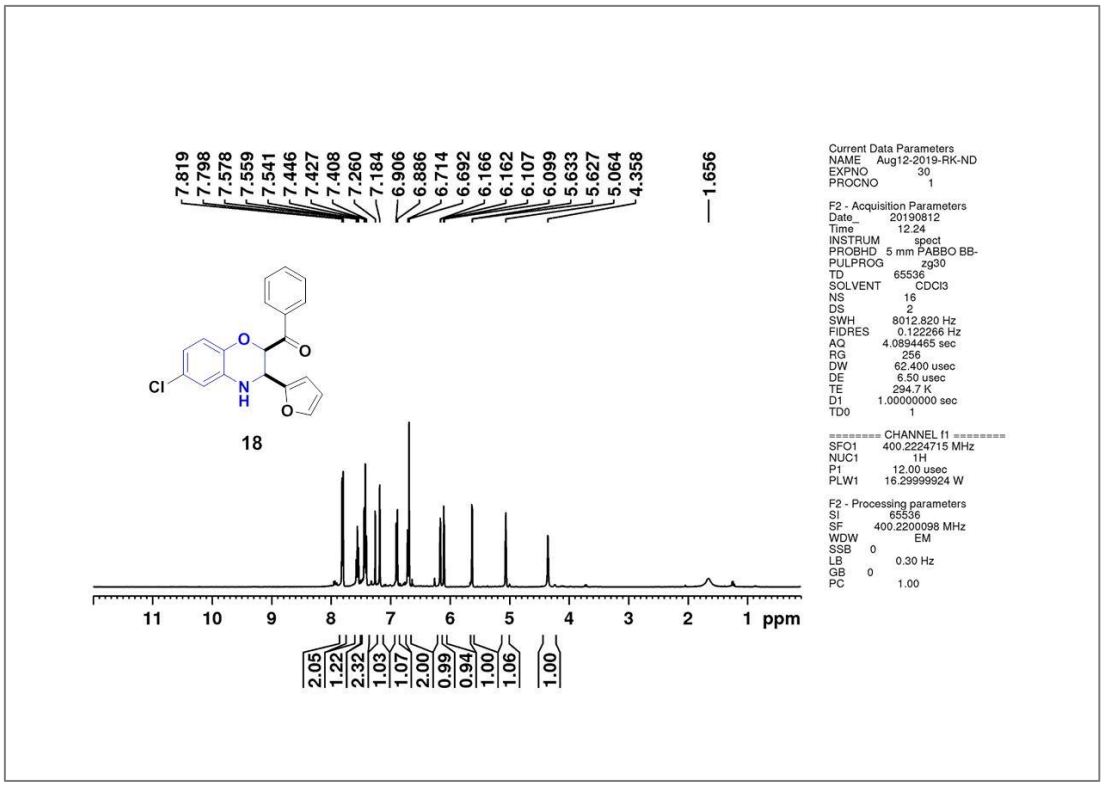
^{13}C{^{1}H} NMR spectrum of compound 17 (Chapter 2)



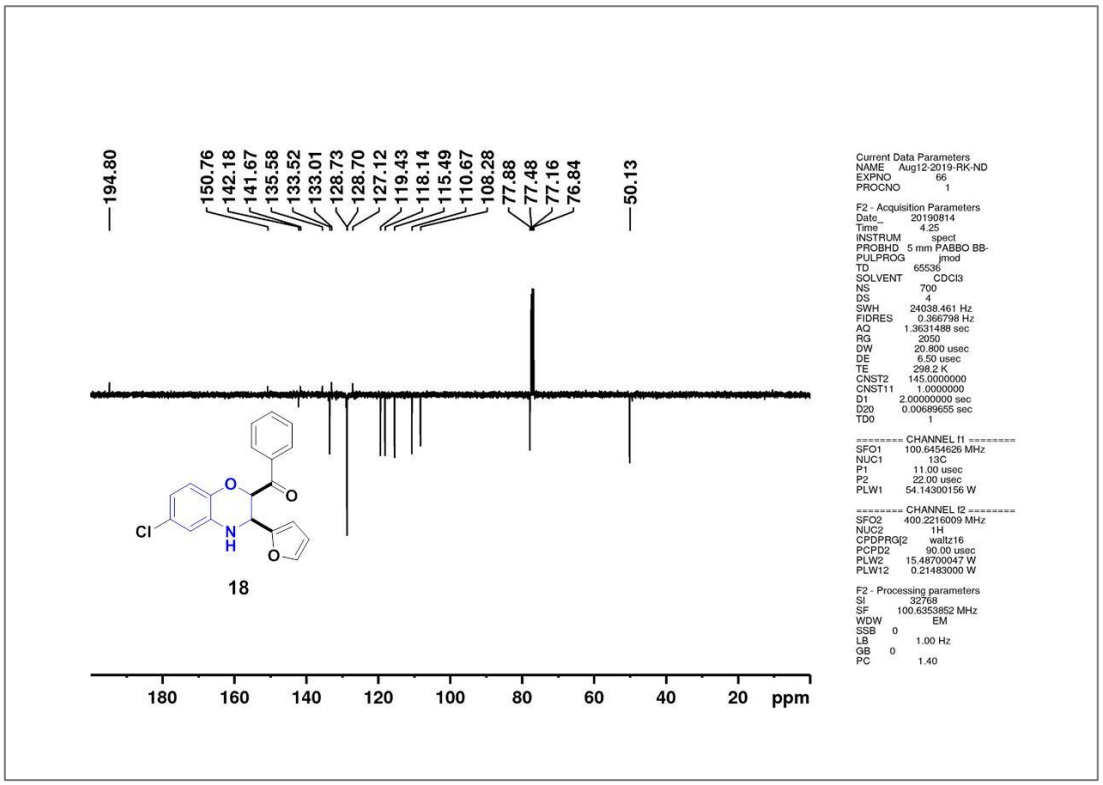
IR spectrum of compound 17 (Chapter 2)



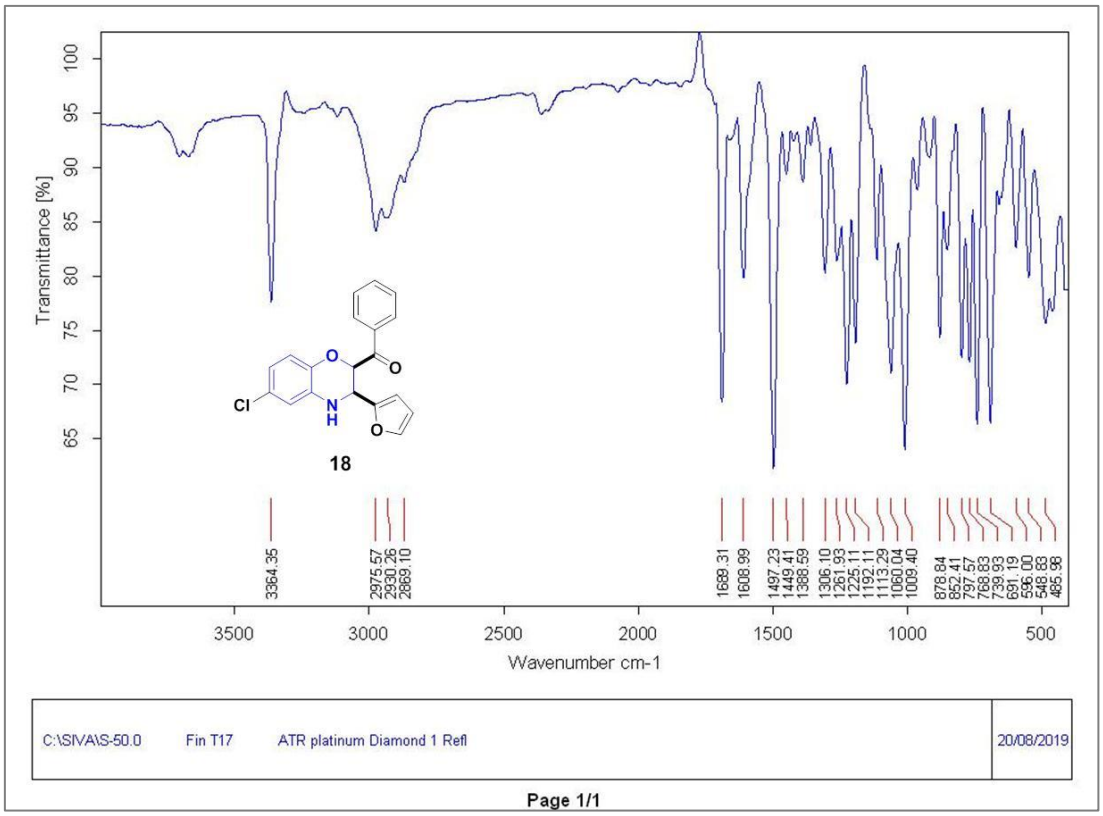
^{1}H NMR spectrum of crude compound 18 (Chapter 2)



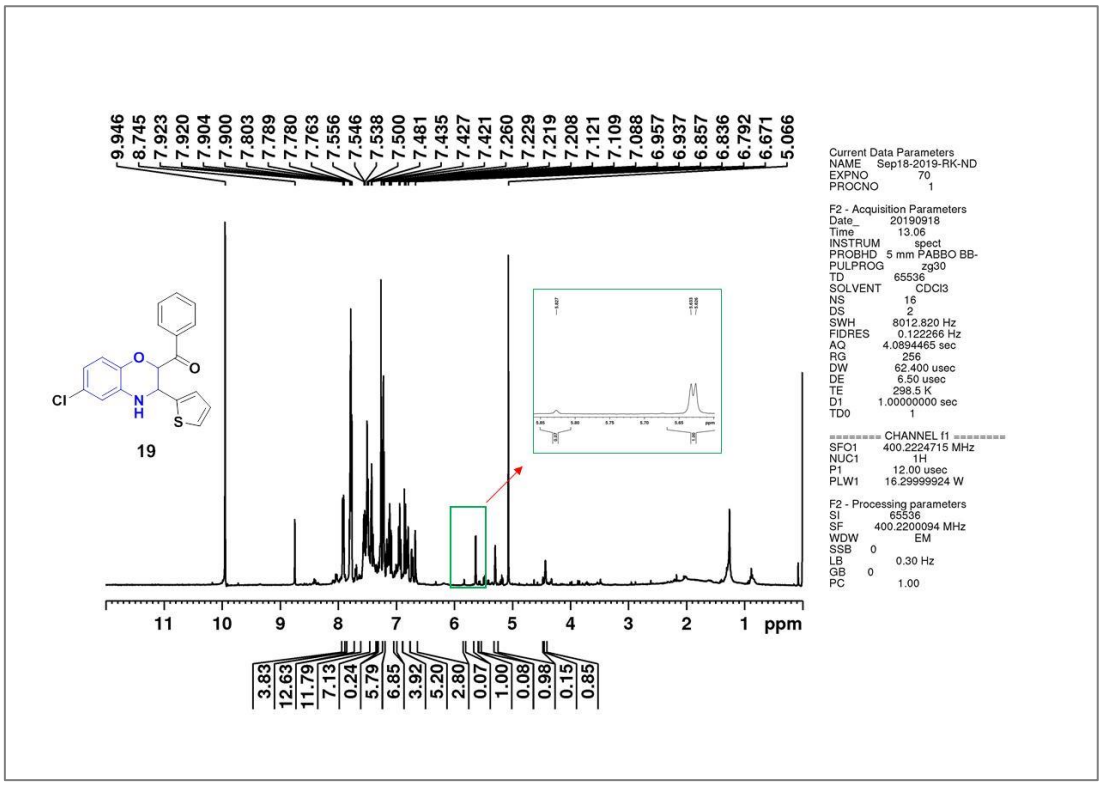
^{1}H NMR spectrum of compound 18 (Chapter 2)



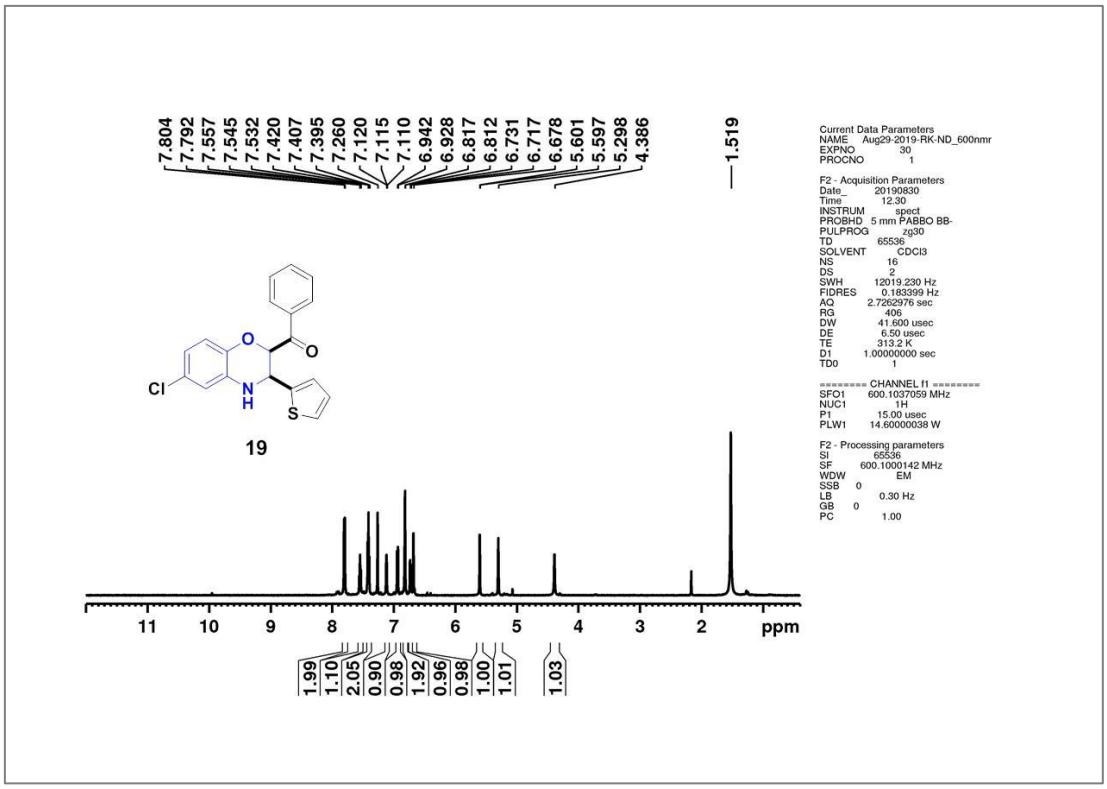
^{13}C{^{1}H} NMR spectrum of compound 18 (Chapter 2)



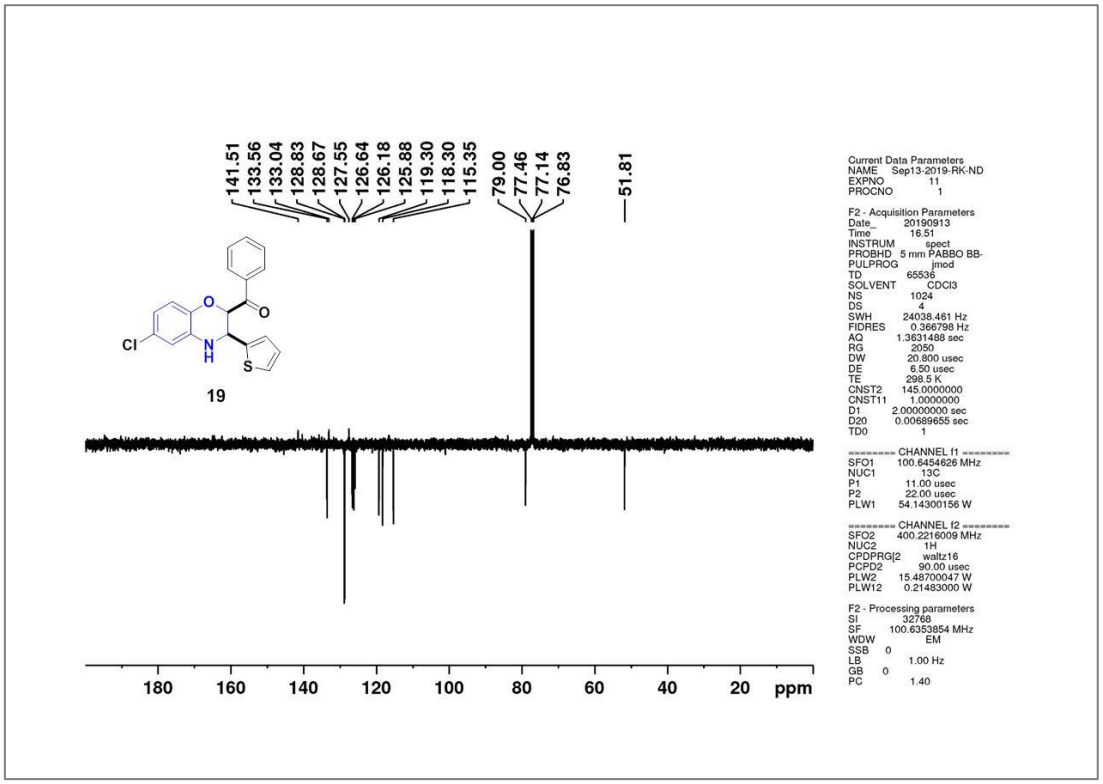
IR spectrum of compound 18 (Chapter 2)



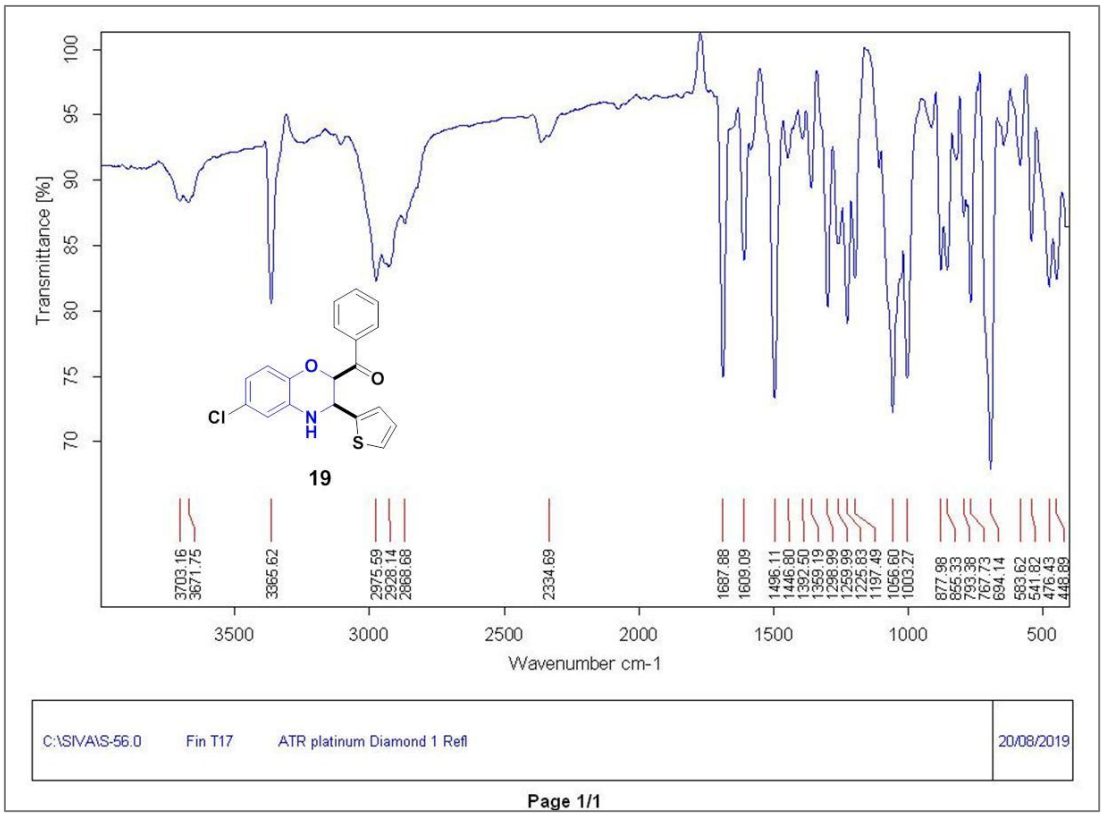
^{1}H NMR spectrum of crude compound 19 (Chapter 2)



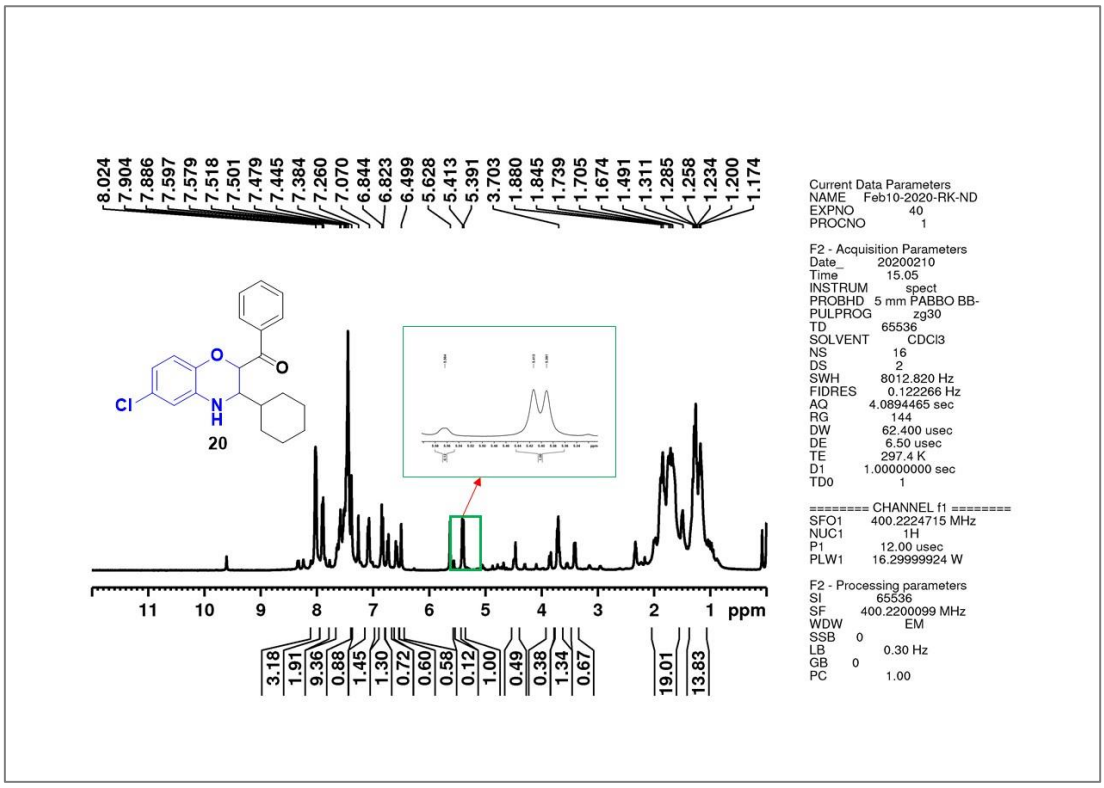
^{1}H NMR spectrum of compound 19 (Chapter 2)



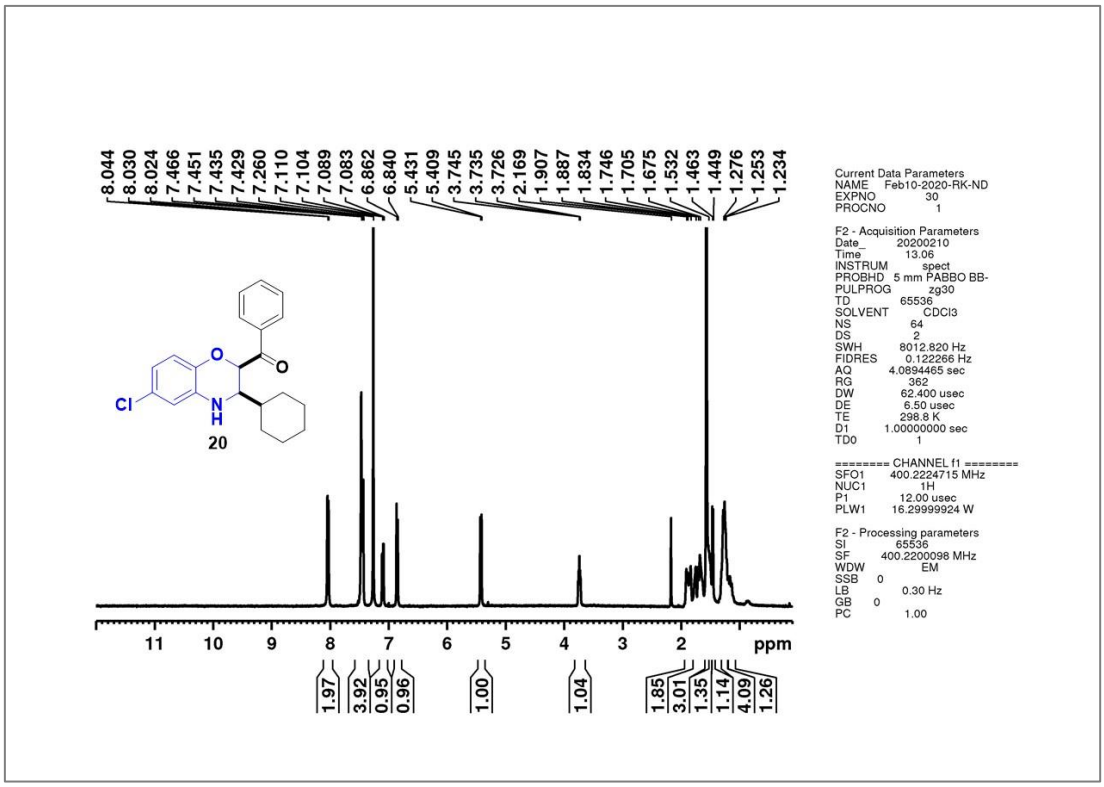
^{13}C{^{1}H} NMR spectrum of compound 19 (Chapter 2)



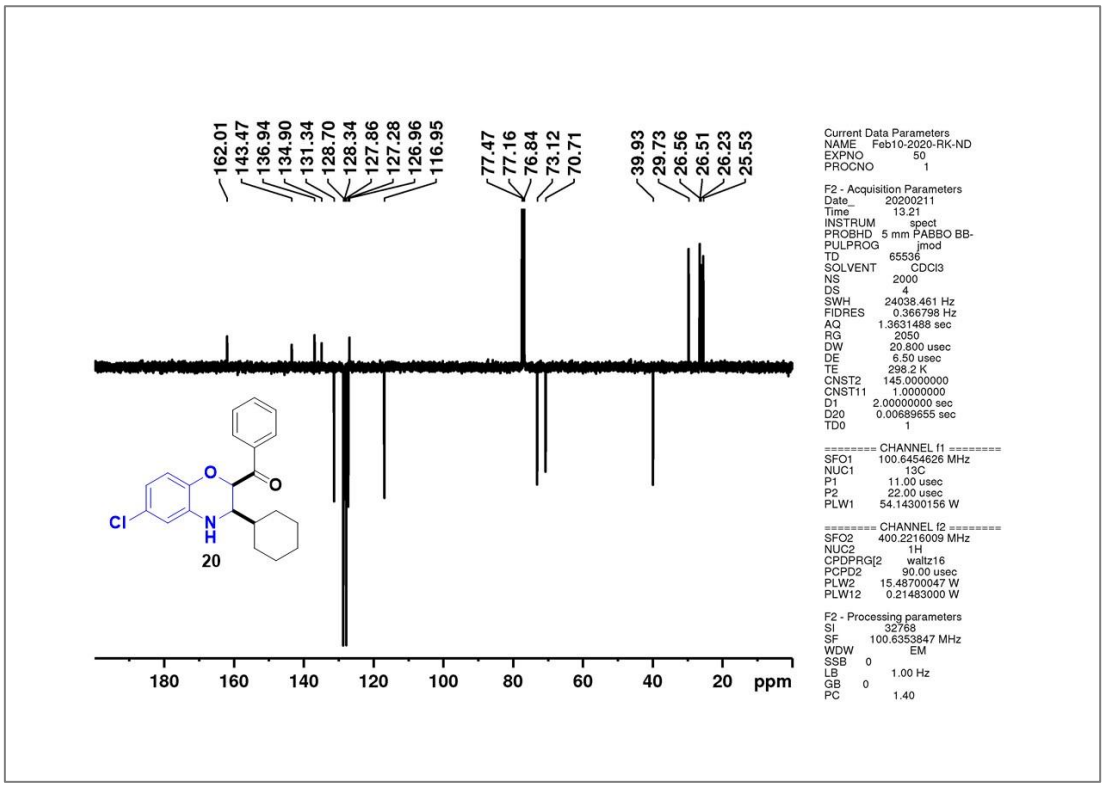
IR spectrum of compound 19 (Chapter 2)



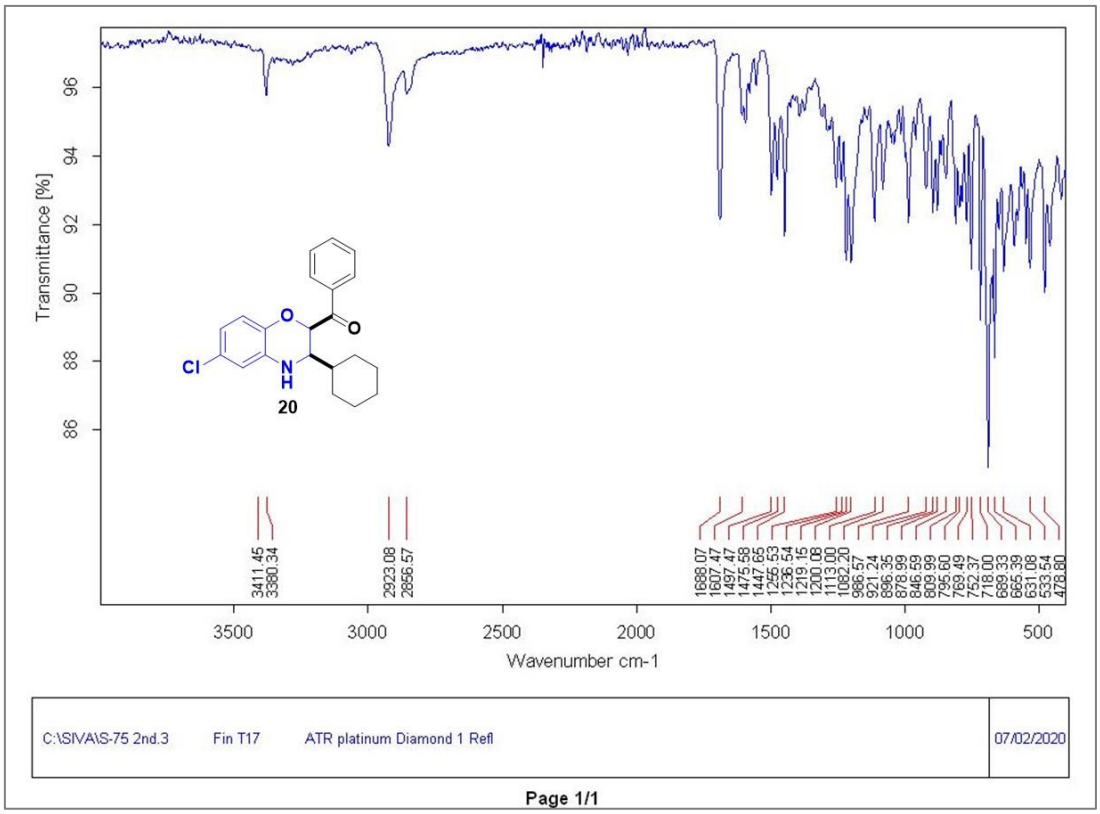
^{1}H NMR spectrum of crude compound 20 (Chapter 2)



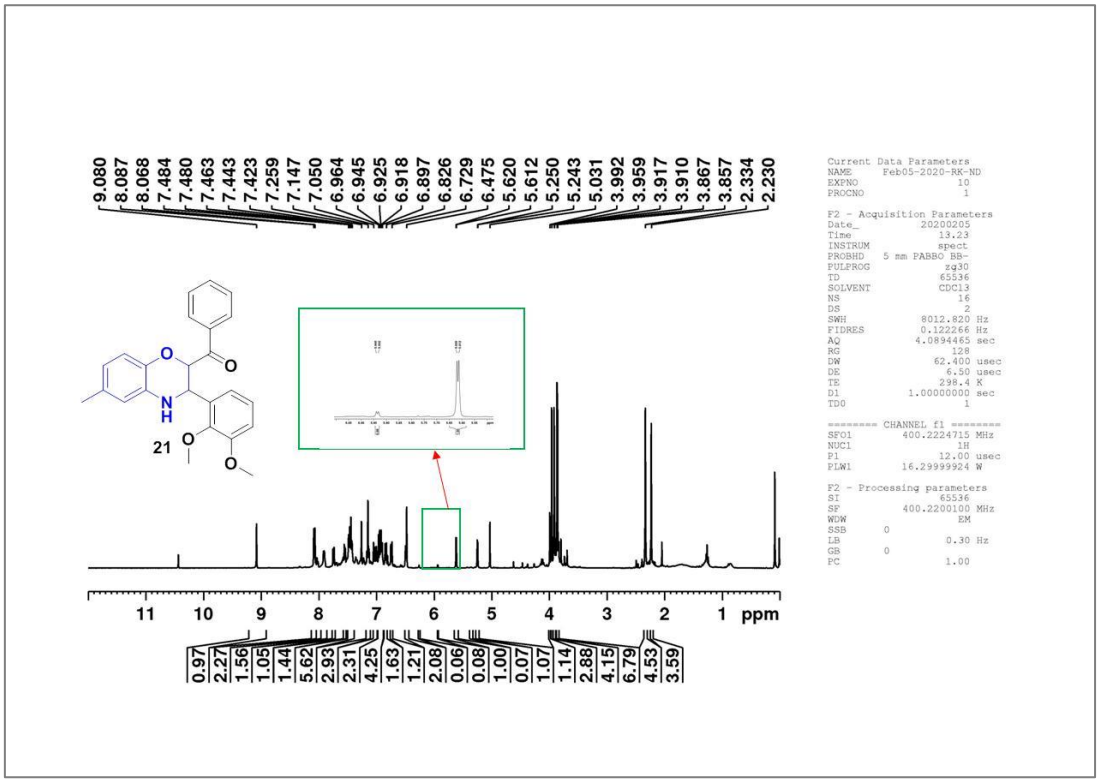
^{1}H NMR spectrum of compound 20 (Chapter 2)



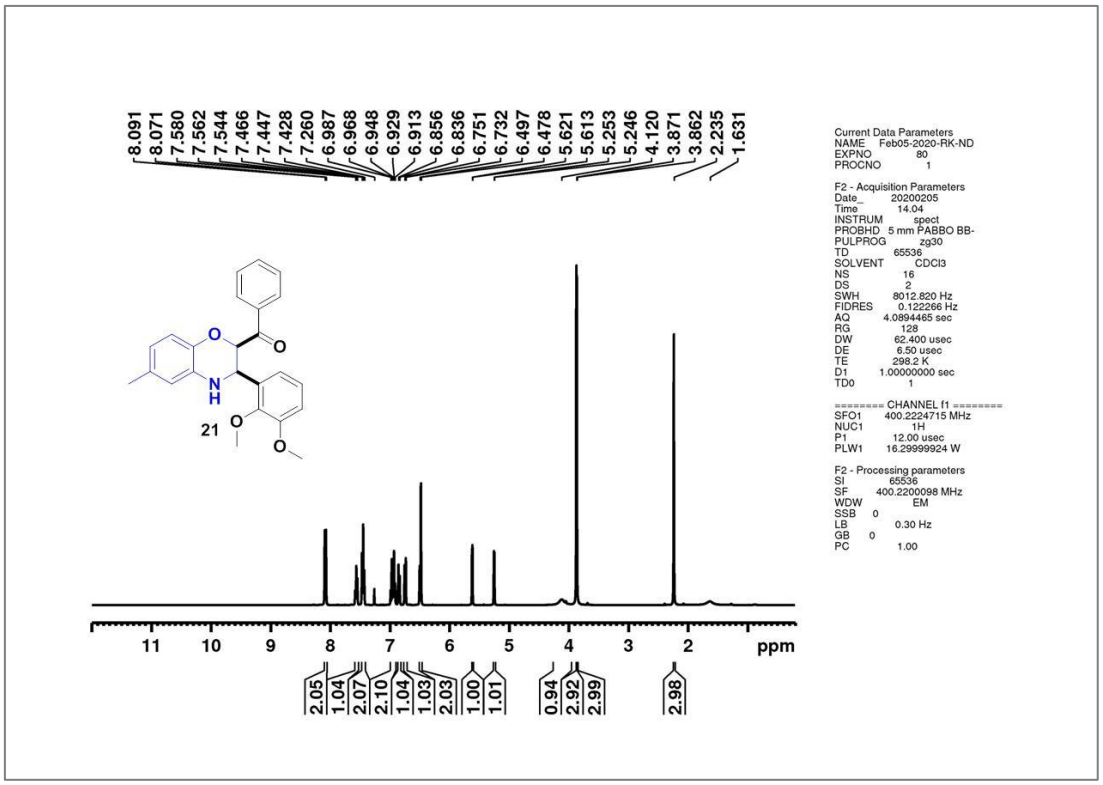
^{13}C{^{1}H} NMR spectrum of compound 20 (Chapter 2)



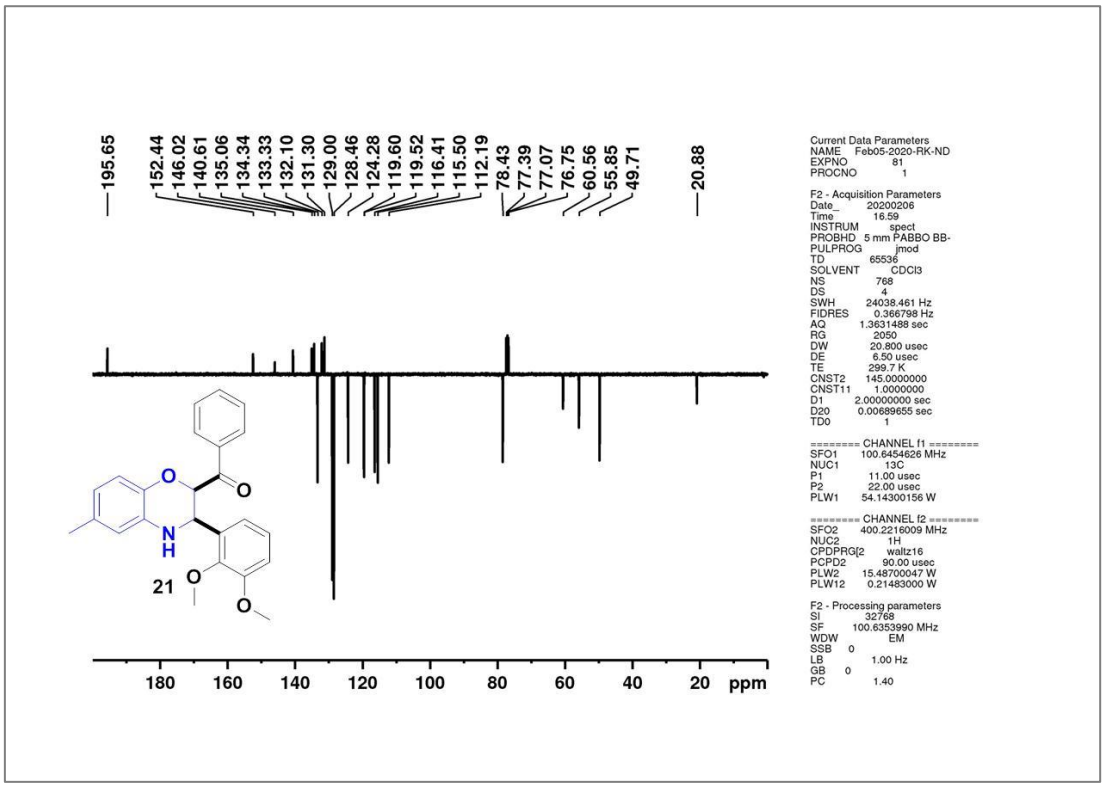
IR spectrum of compound 20 (Chapter 2)



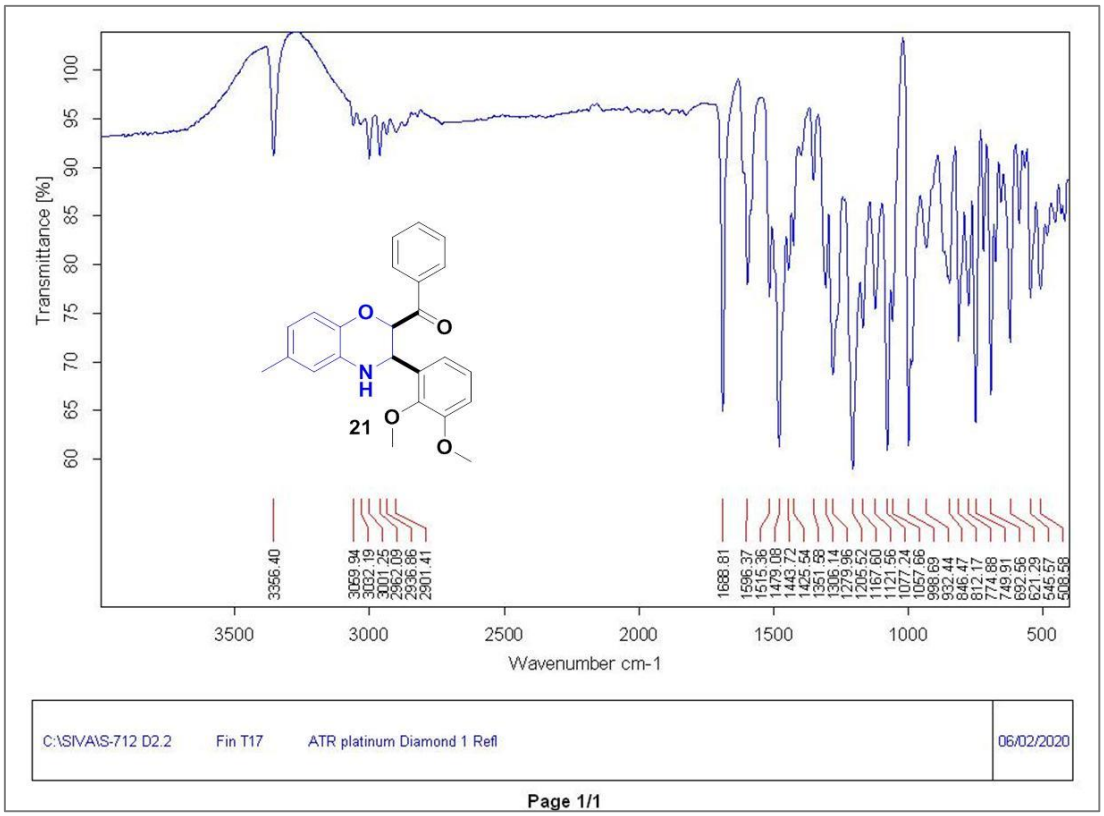
^{1}H NMR spectrum of crude compound 21 (Chapter 2)



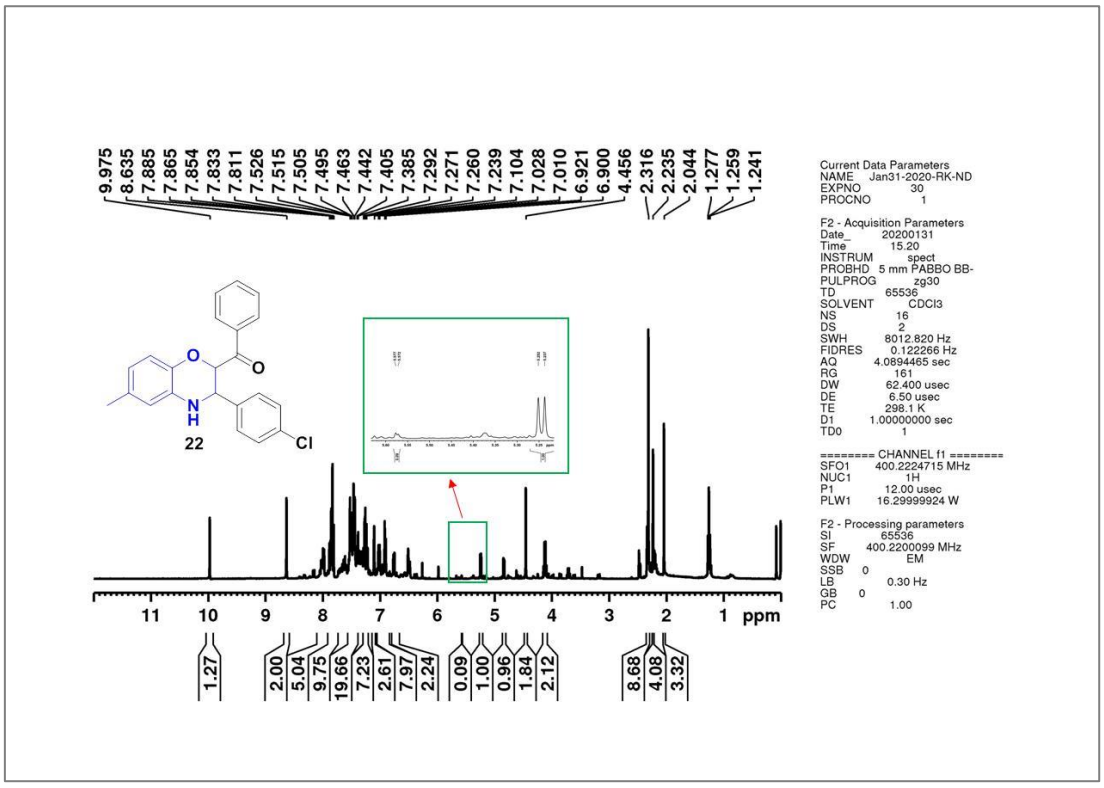
^{1}H NMR spectrum of compound 21 (Chapter 2)



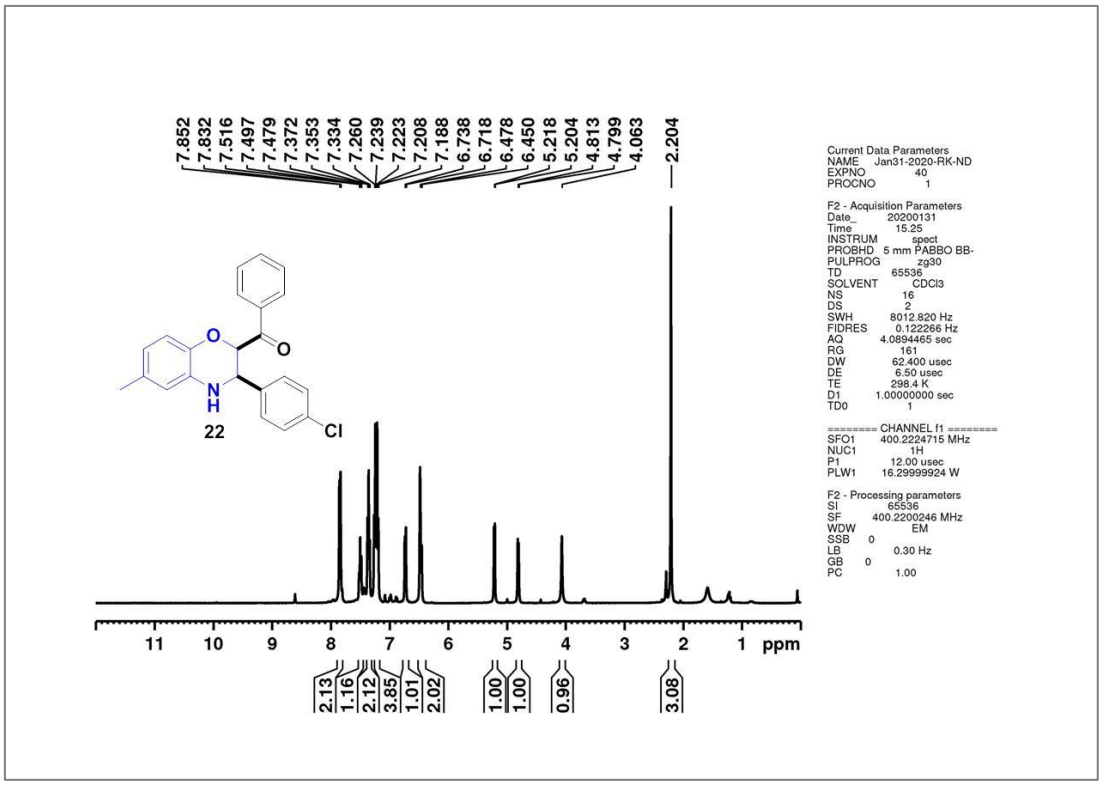
^{13}C{^{1}H} NMR spectrum of compound 21 (Chapter 2)



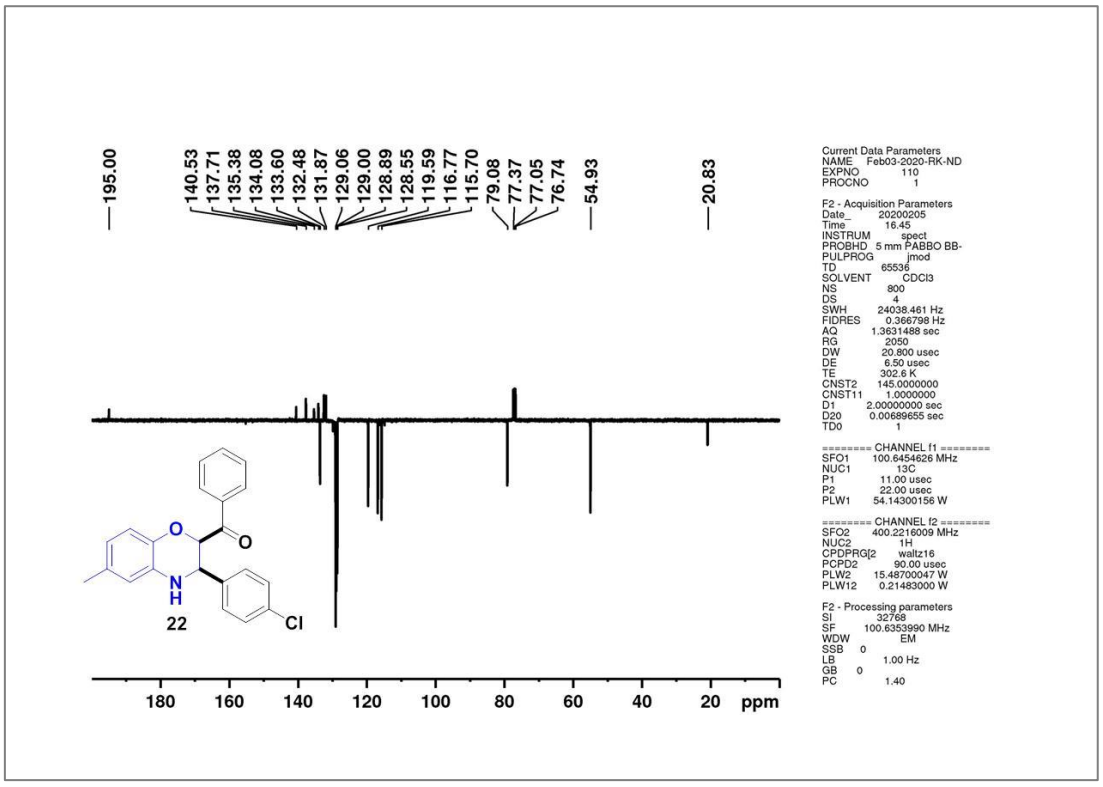
IR spectrum of compound 21 (Chapter 2)



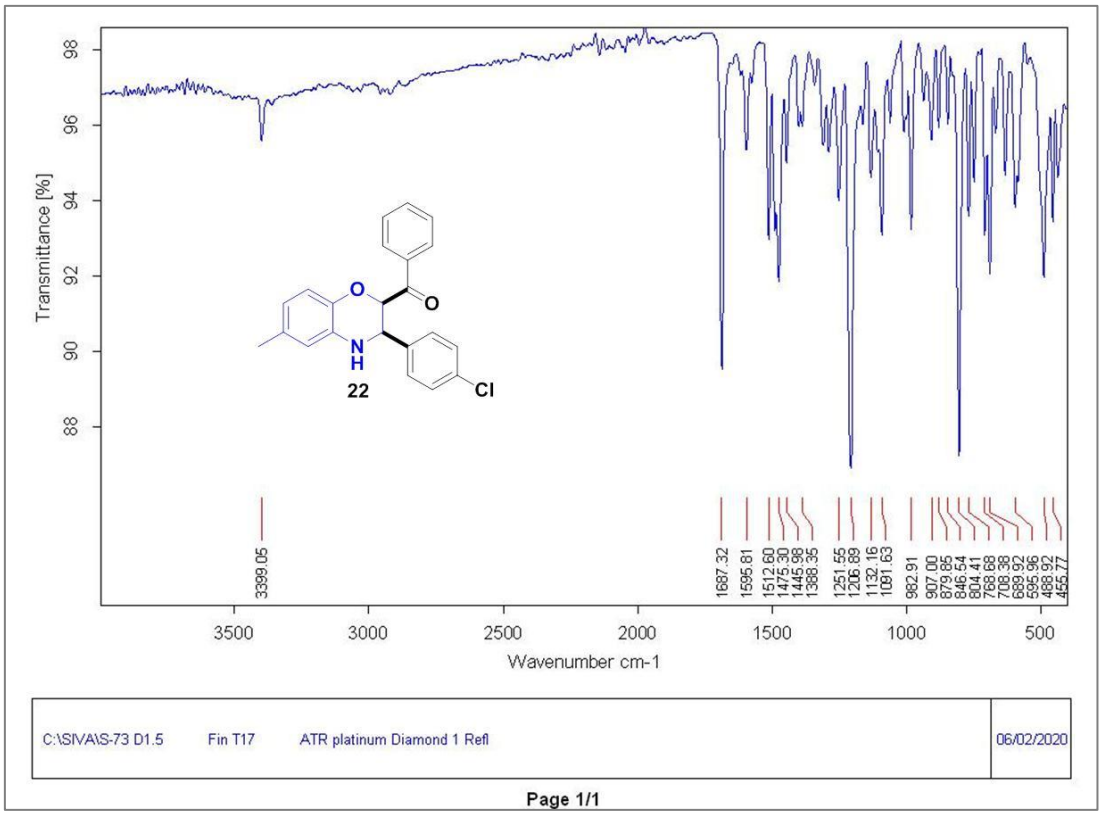
^{1}H NMR spectrum of crude compound 22 (Chapter 2)



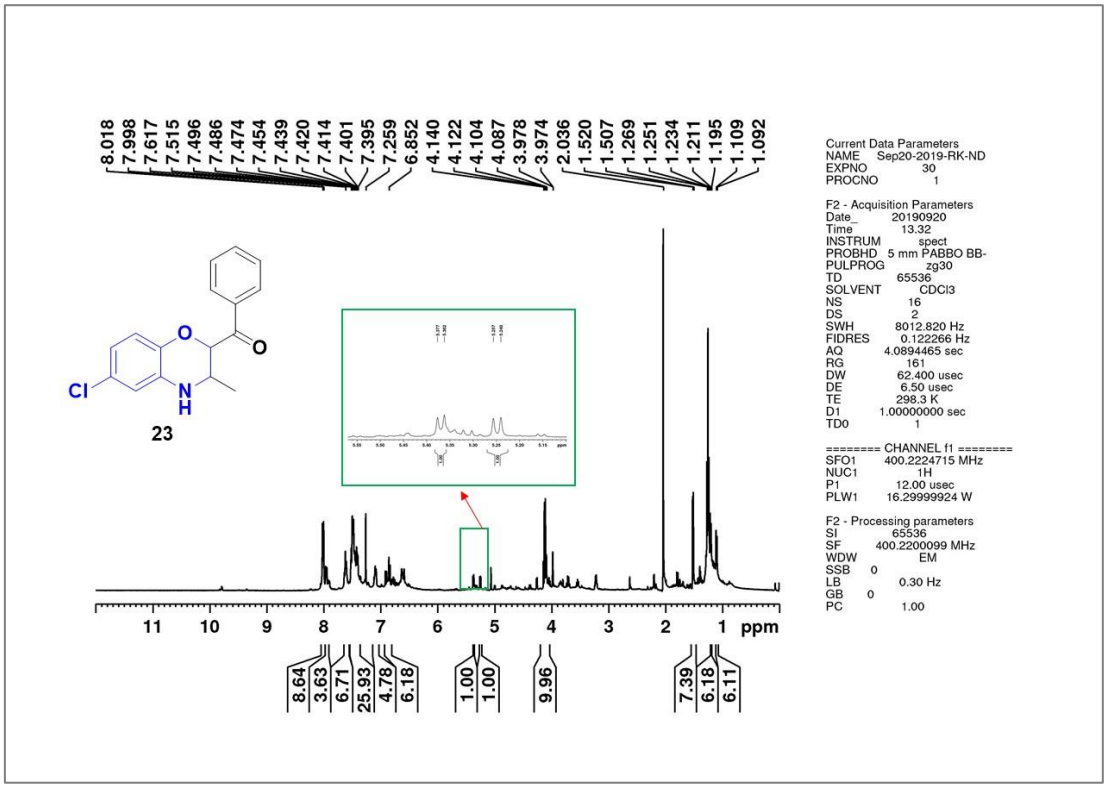
^{1}H NMR spectrum of compound 22 (Chapter 2)



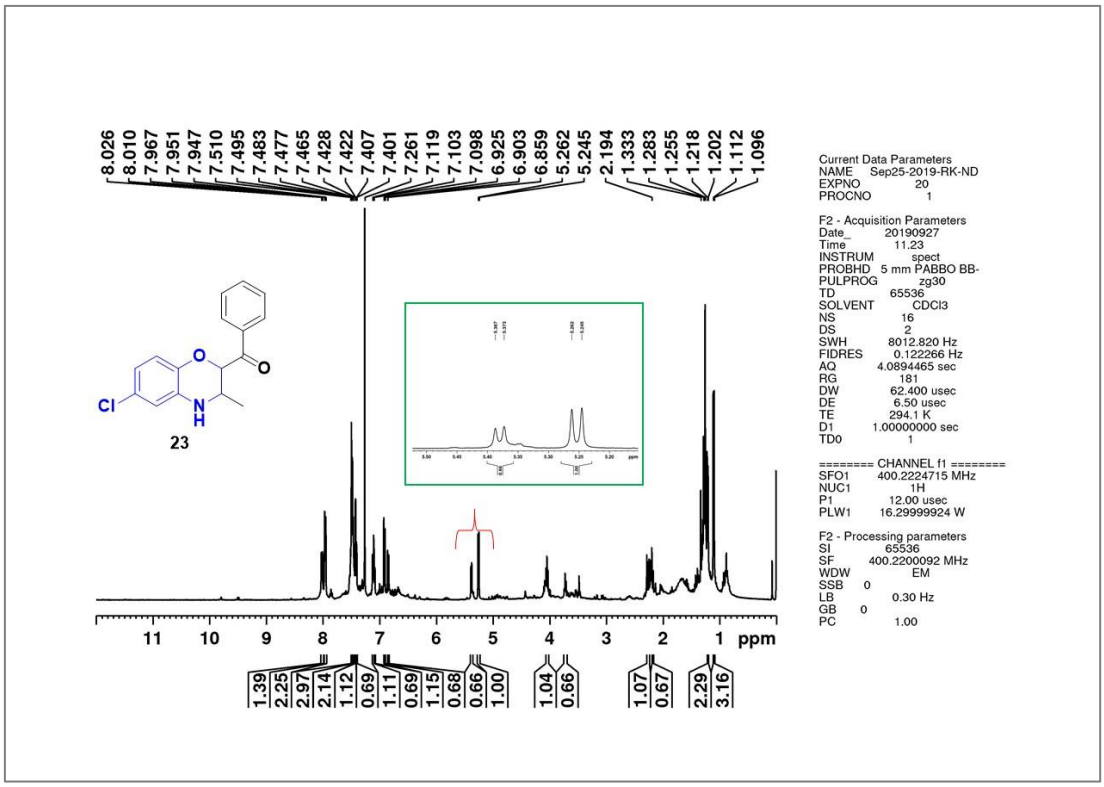
^{13}C{^{1}H} NMR spectrum of compound 22 (Chapter 2)



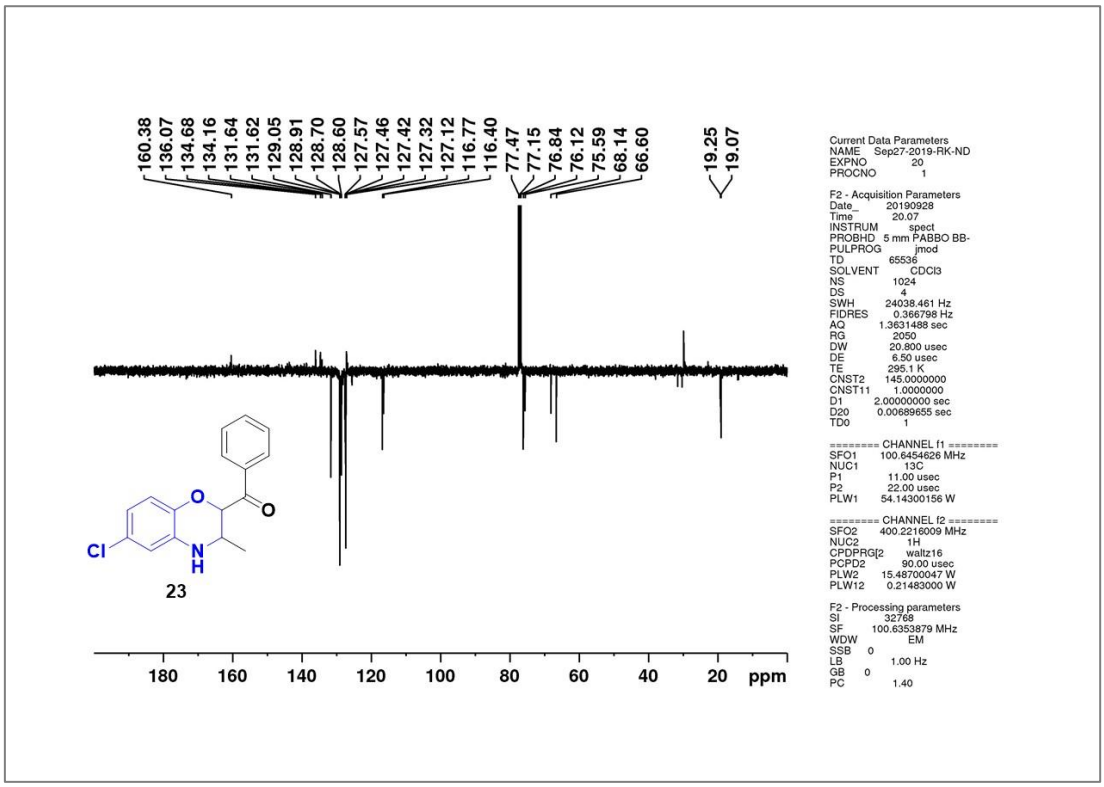
IR spectrum of compound 22 (Chapter 2)



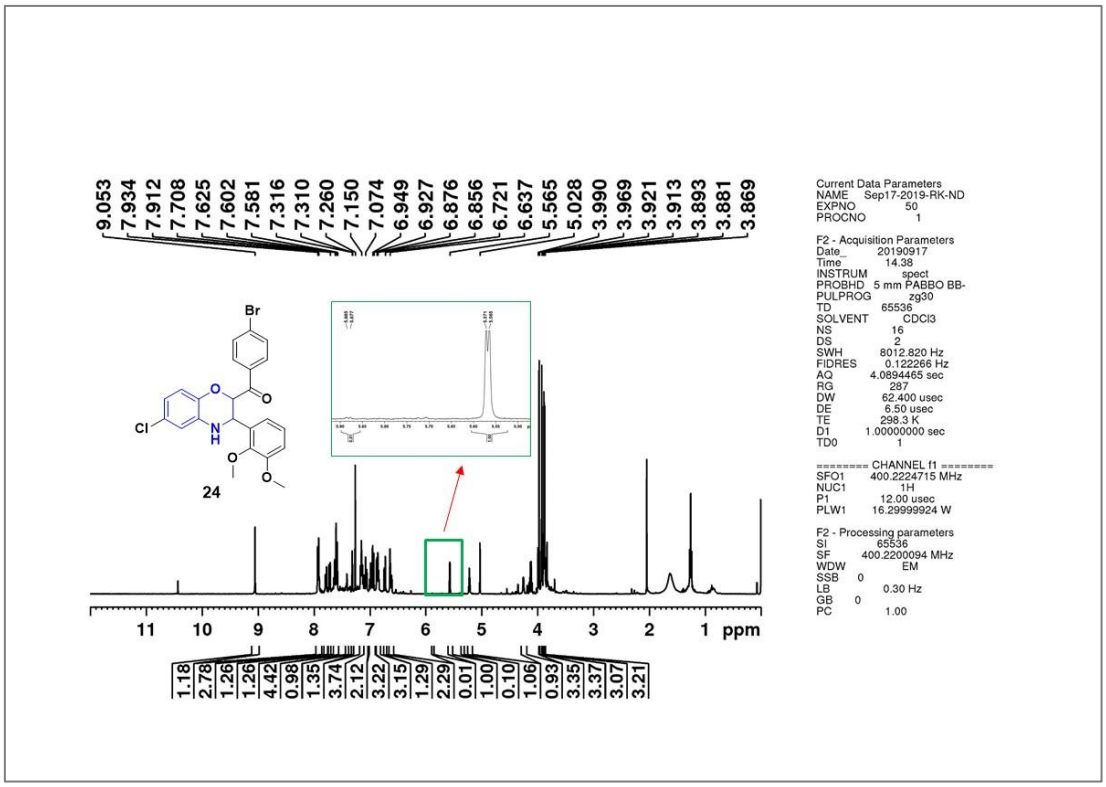
^{1}H NMR spectrum of crude compound 23 (Chapter 2)



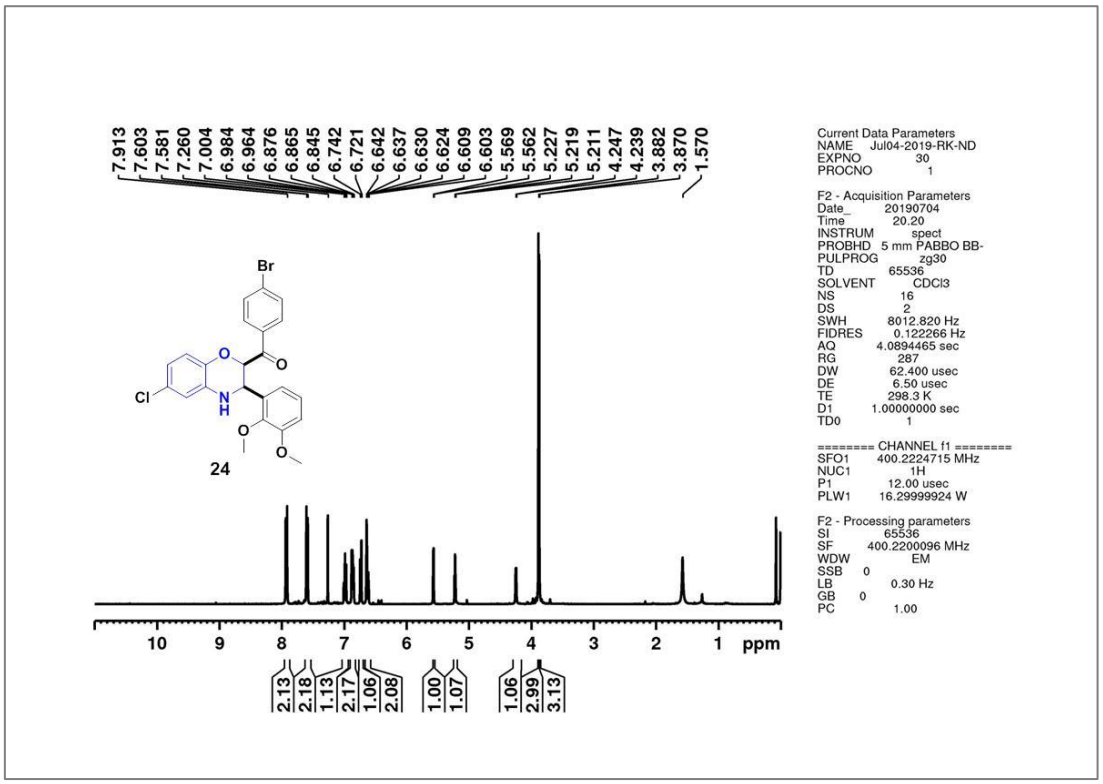
^{1}H NMR spectrum of compound 23 (Chapter 2)



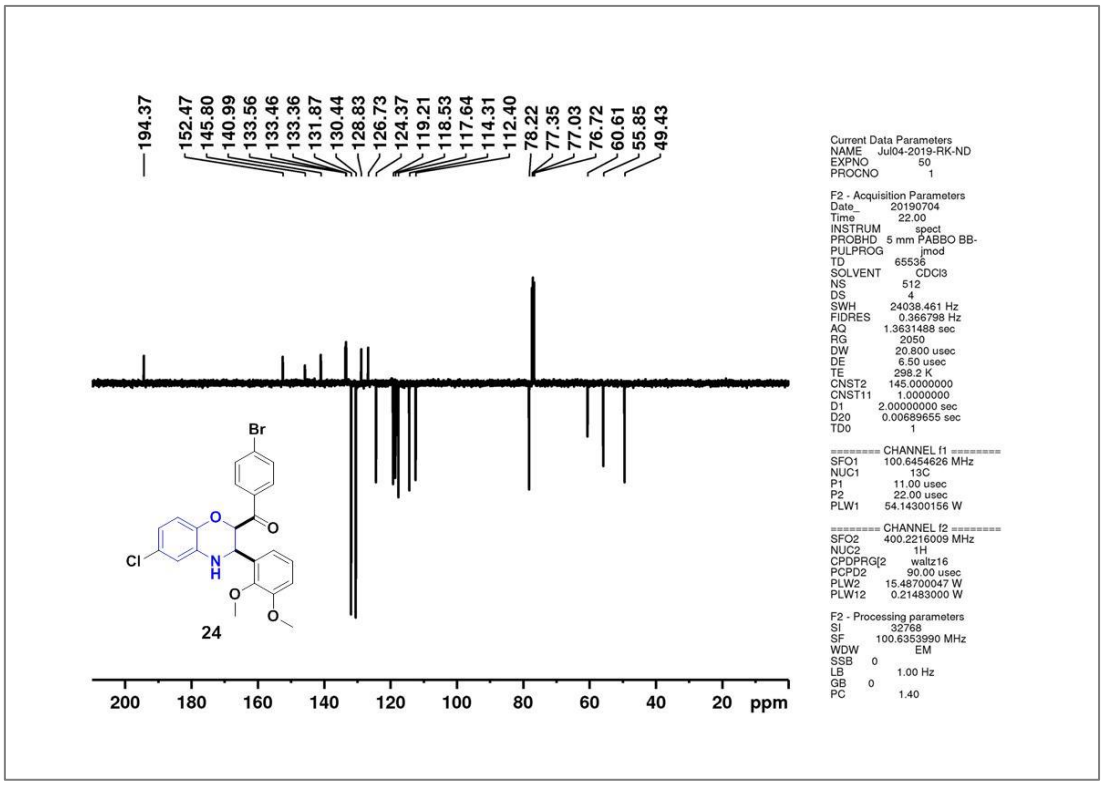
^{13}C{^{1}H} NMR spectrum of compound 23 (Chapter 2)



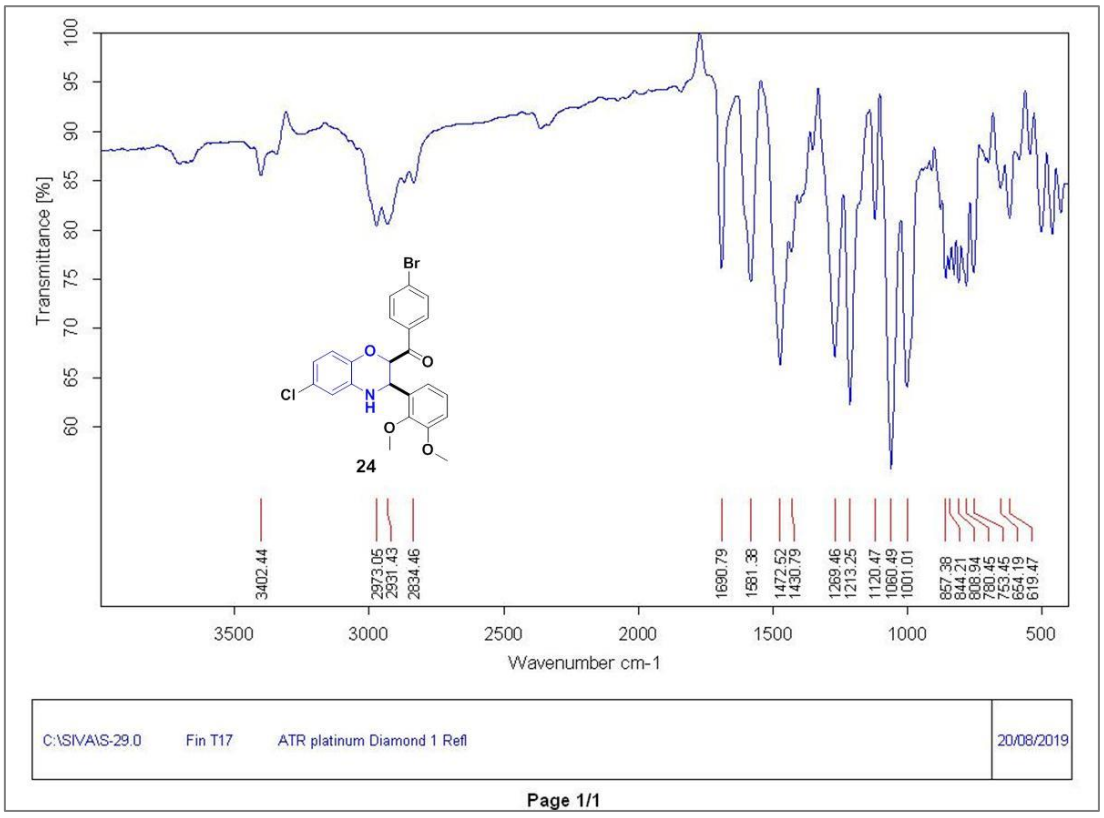
^{1}H NMR spectrum of crude compound 24 (Chapter 2)



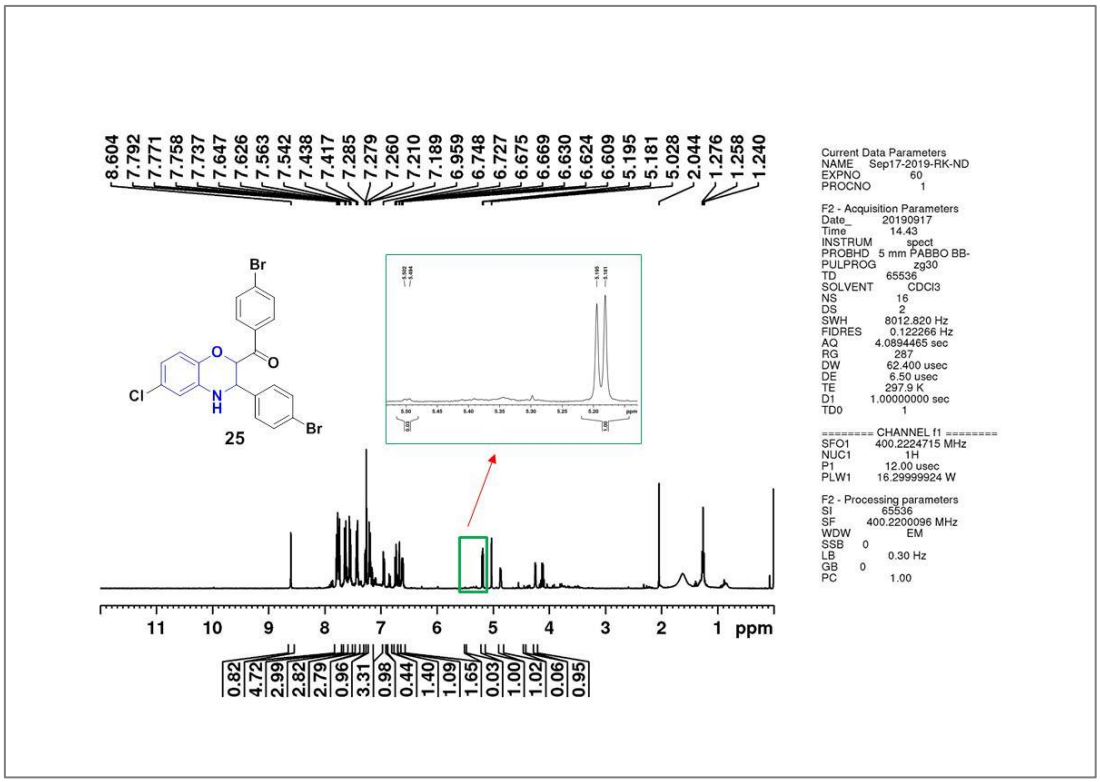
^{1}H NMR spectrum of compound 24 (Chapter 2)



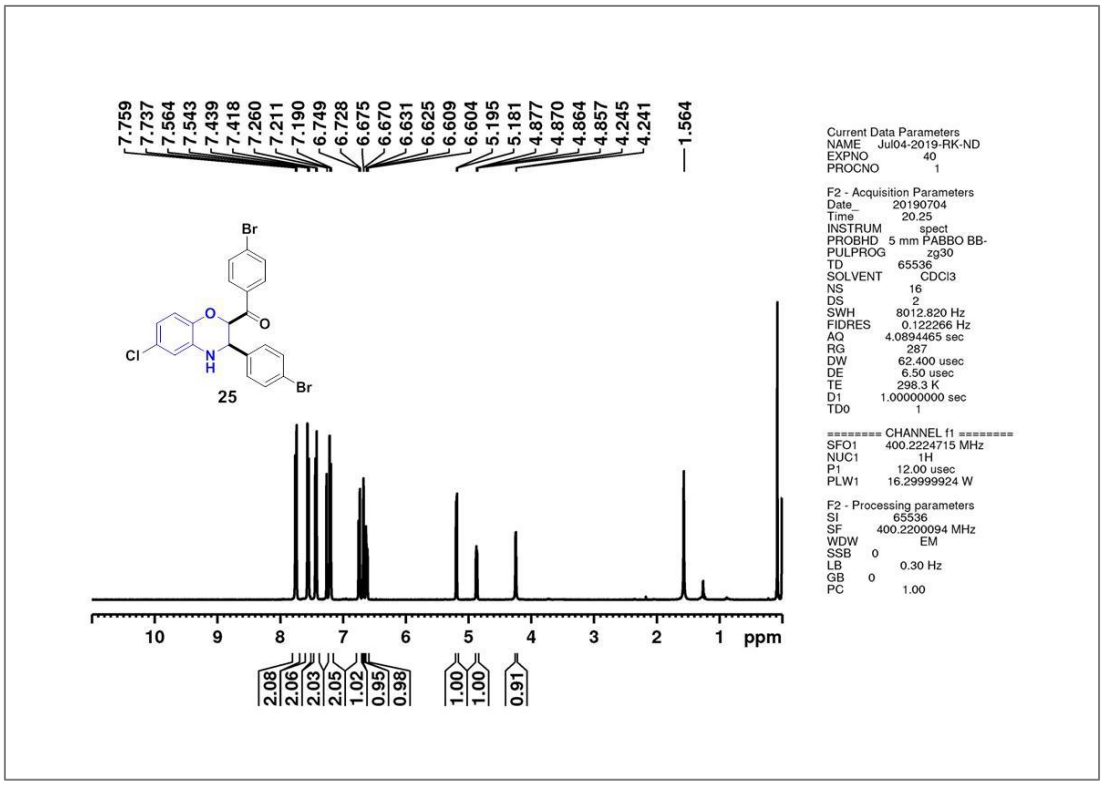
$^{13}C\{^{1}H\}$ NMR spectrum of compound 24 (Chapter 2)



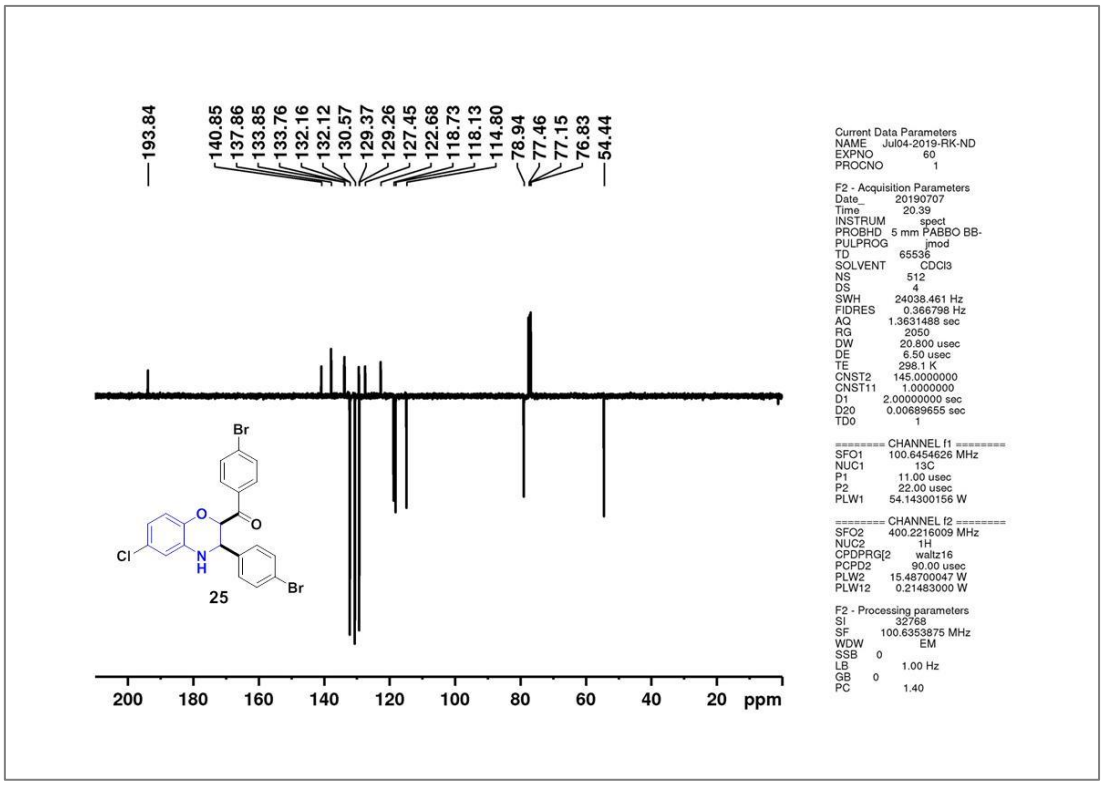
IR spectrum of compound 24 (Chapter 2)



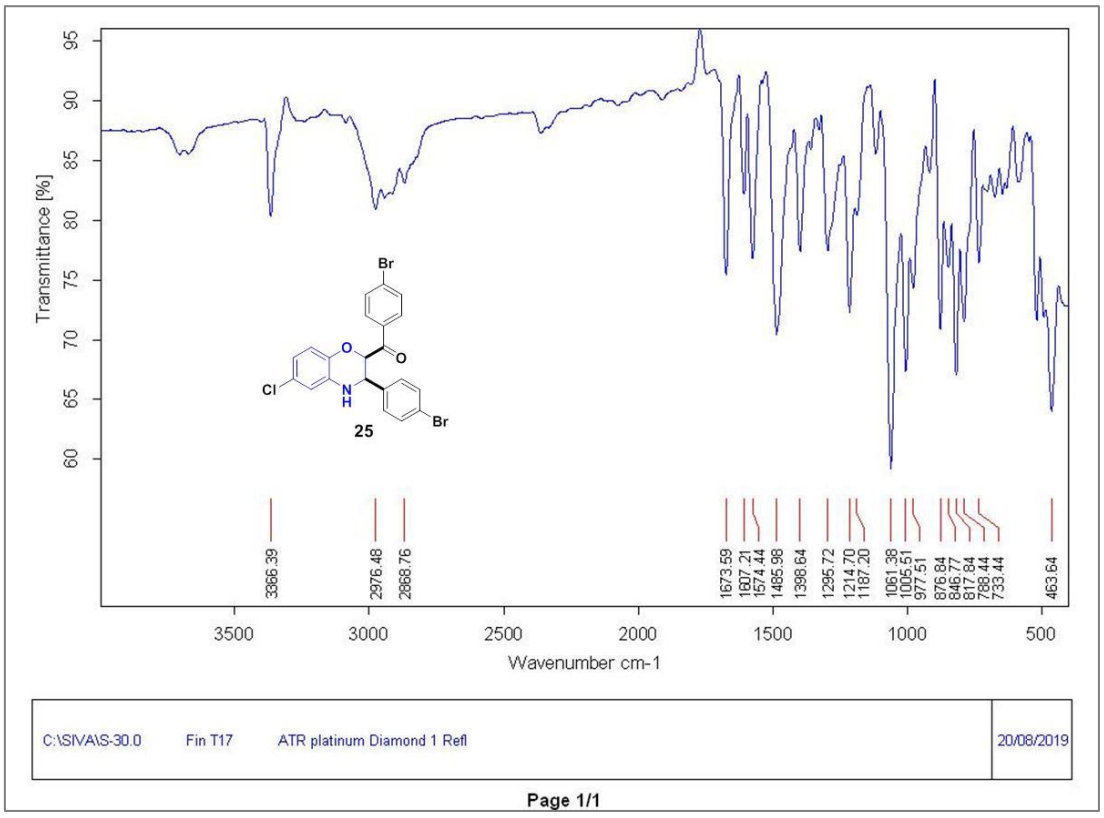
^{1}H NMR spectrum of crude compound 25 (Chapter 2)



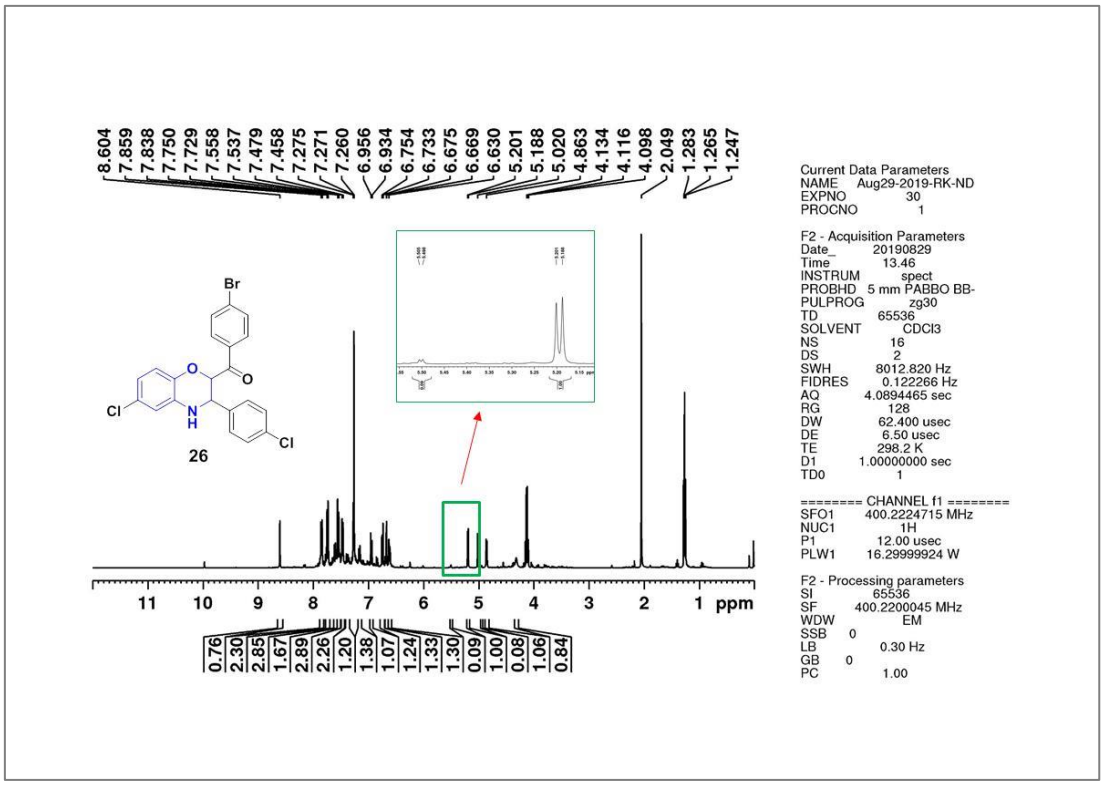
^{1}H NMR spectrum of compound 25 (Chapter 2)



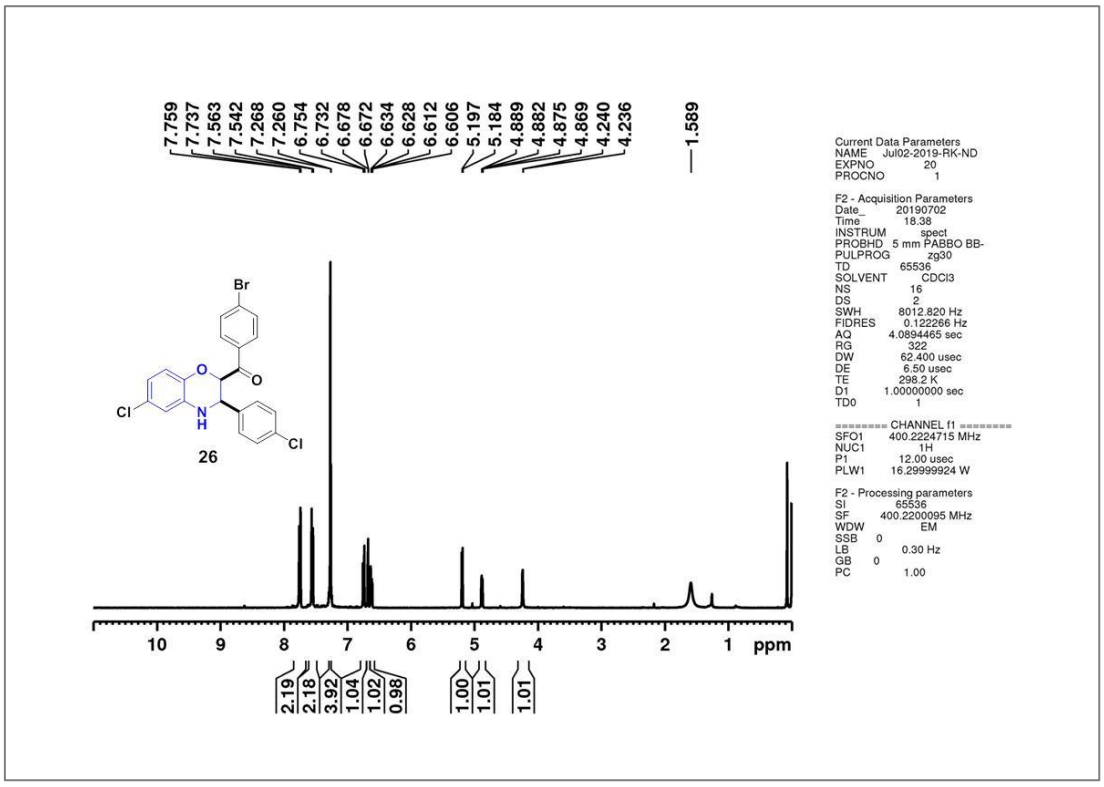
$^{13}C\{^{1}H\}$ NMR spectrum of compound 25 (Chapter 2)



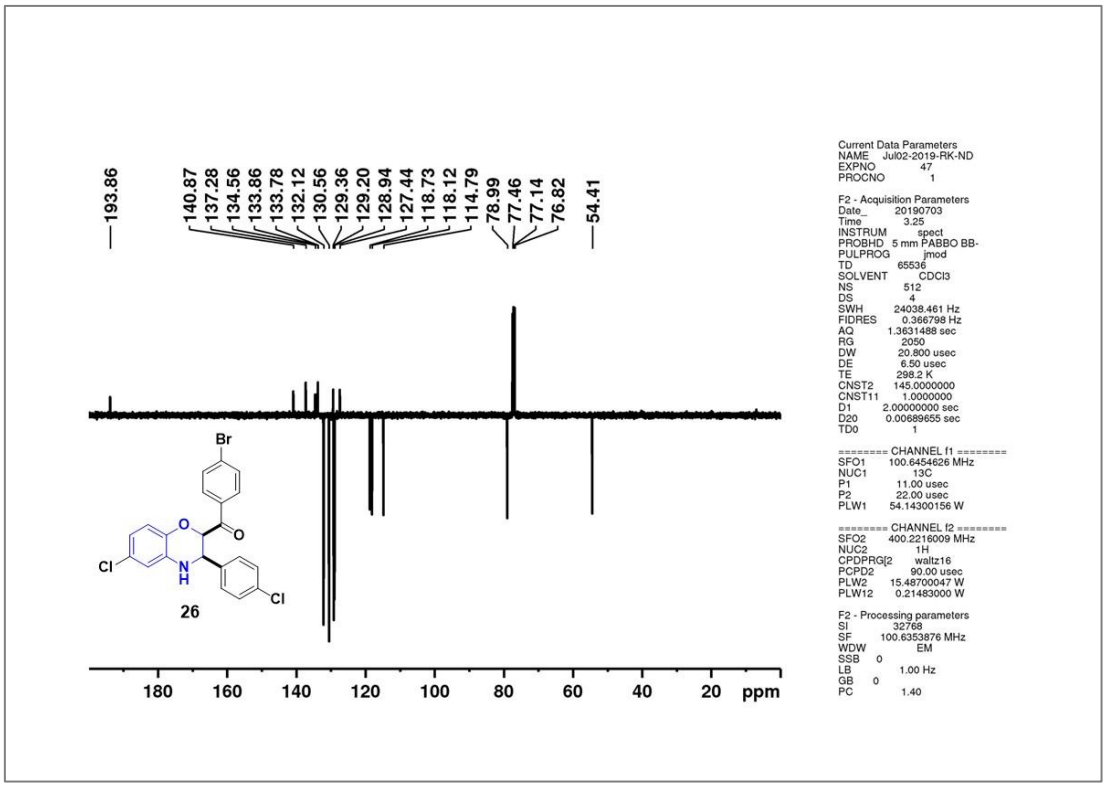
IR spectrum of compound 25 (Chapter 2)



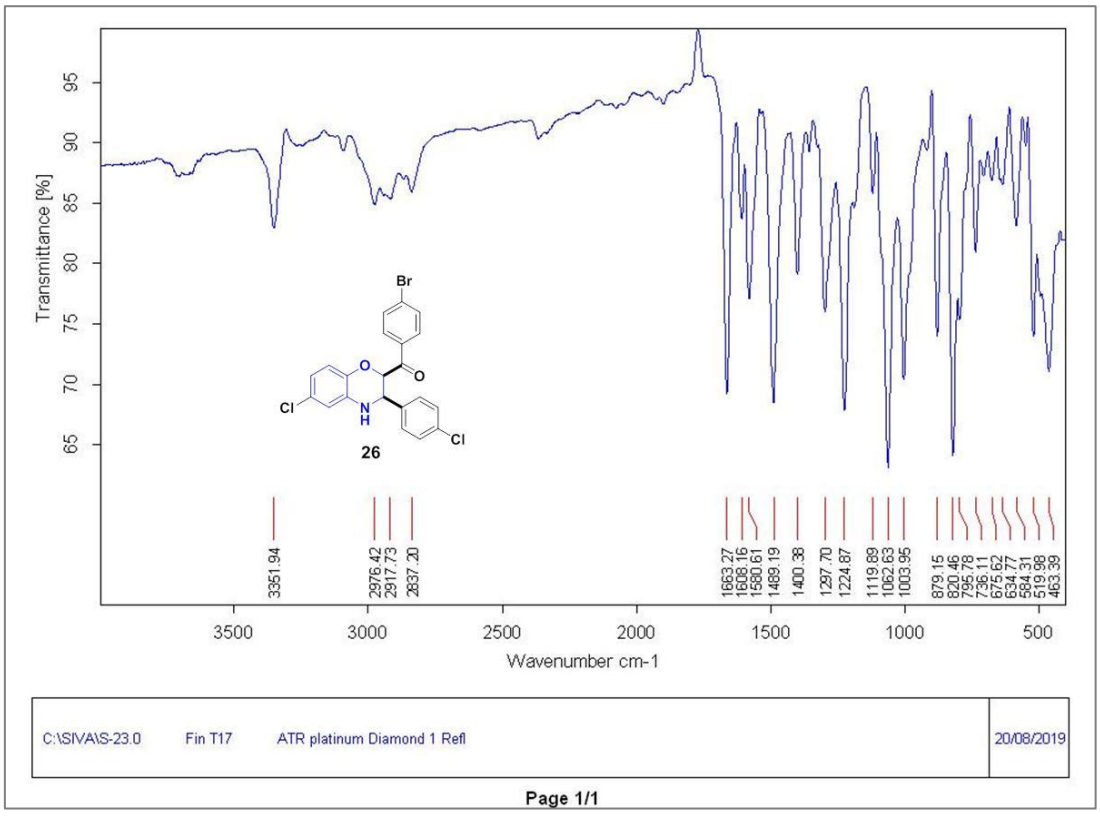
[1]H NMR spectrum of crude compound 26 (Chapter 2)



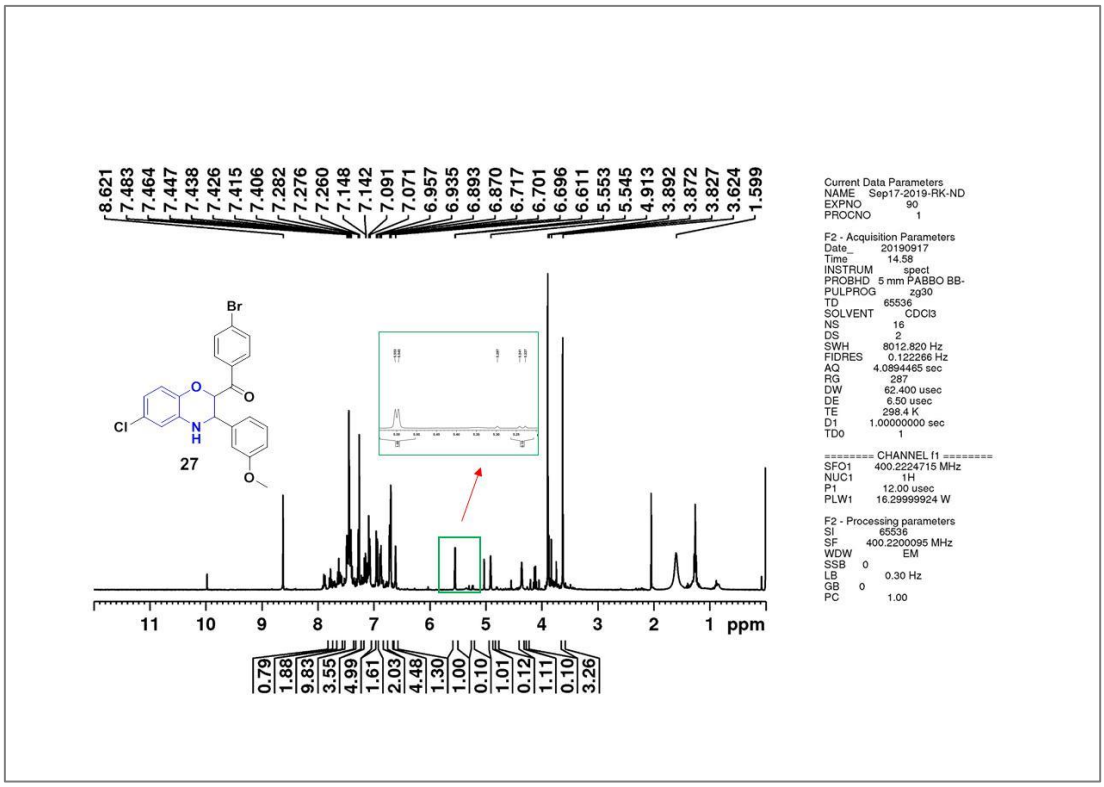
[1]H NMR spectrum of compound **26** (Chapter 2)



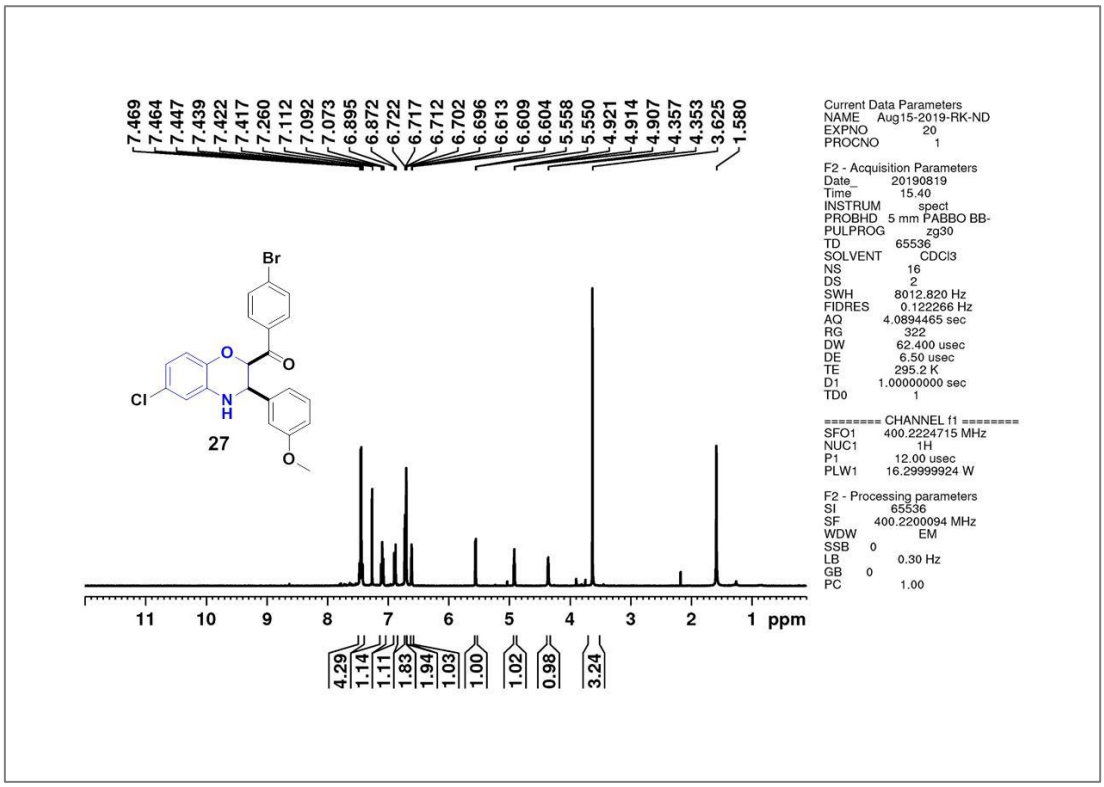
$^{13}C\{^{1}H\}$ NMR spectrum of compound 26 (Chapter 2)



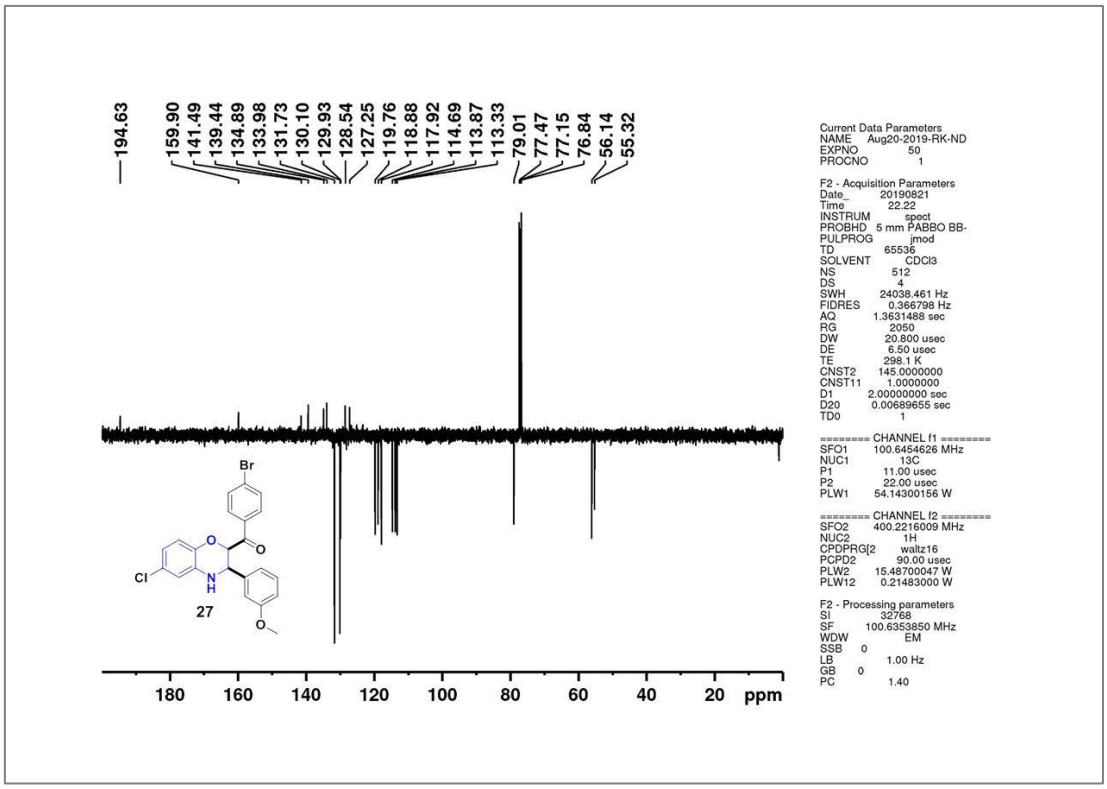
IR spectrum of compound 26 (Chapter 2)



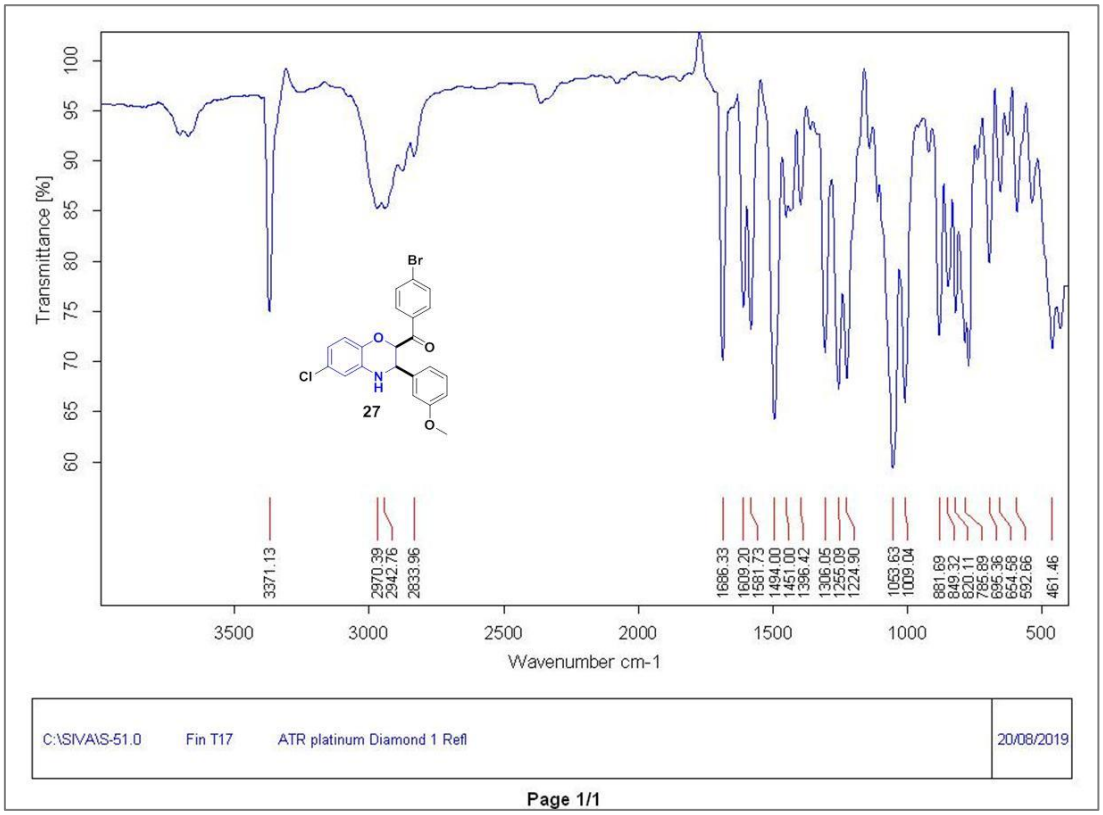
^{1}H NMR spectrum of crude compound 27 (Chapter 2)



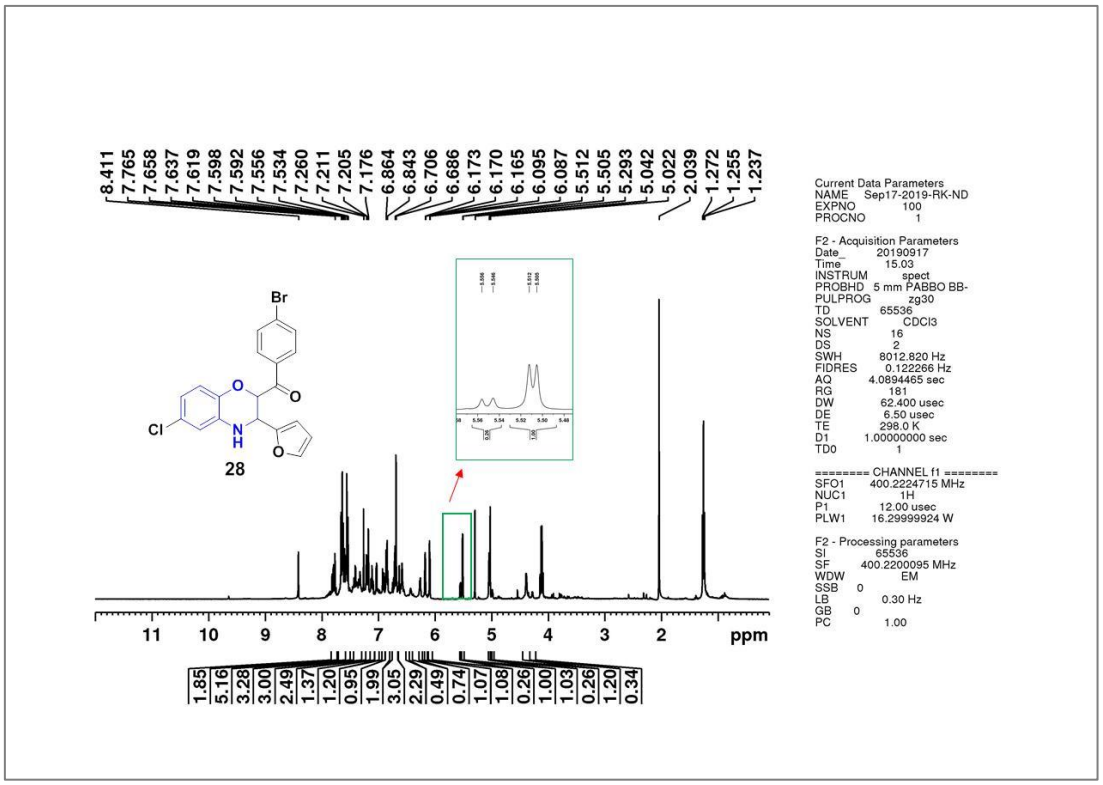
^{1}H NMR spectrum of compound 27 (Chapter 2)



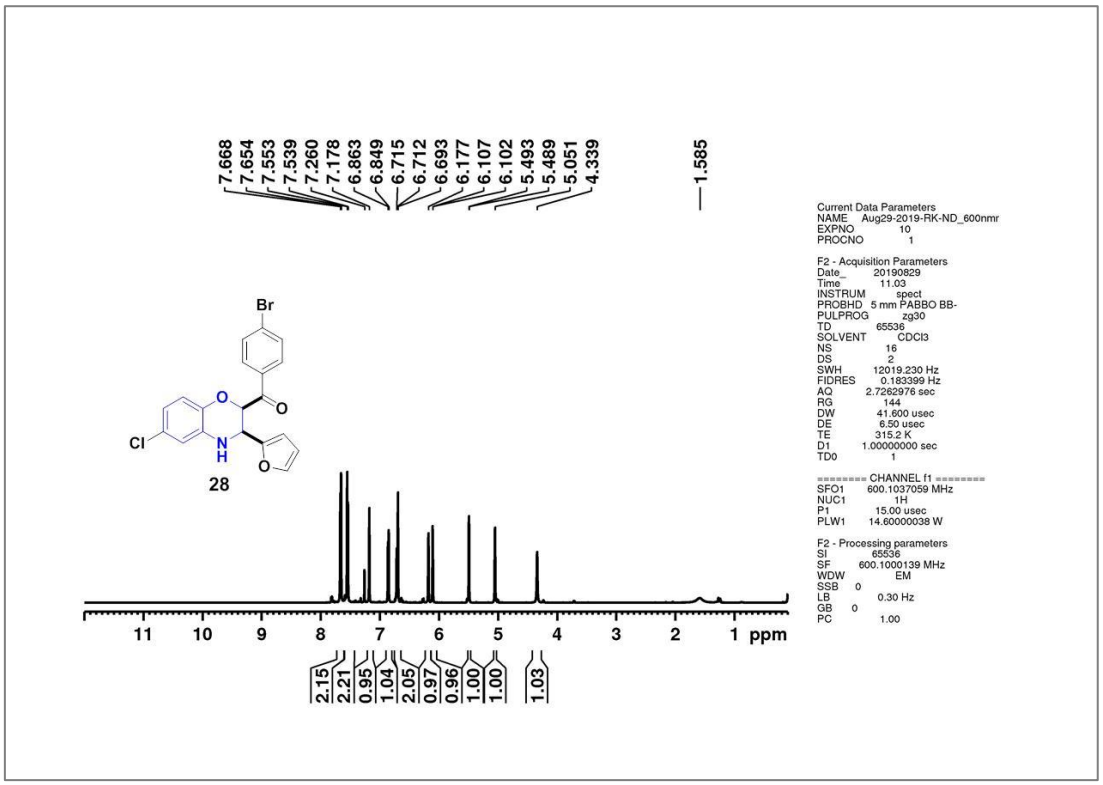
$^{13}C\{^{1}H\}$ NMR spectrum of compound 27 (Chapter 2)



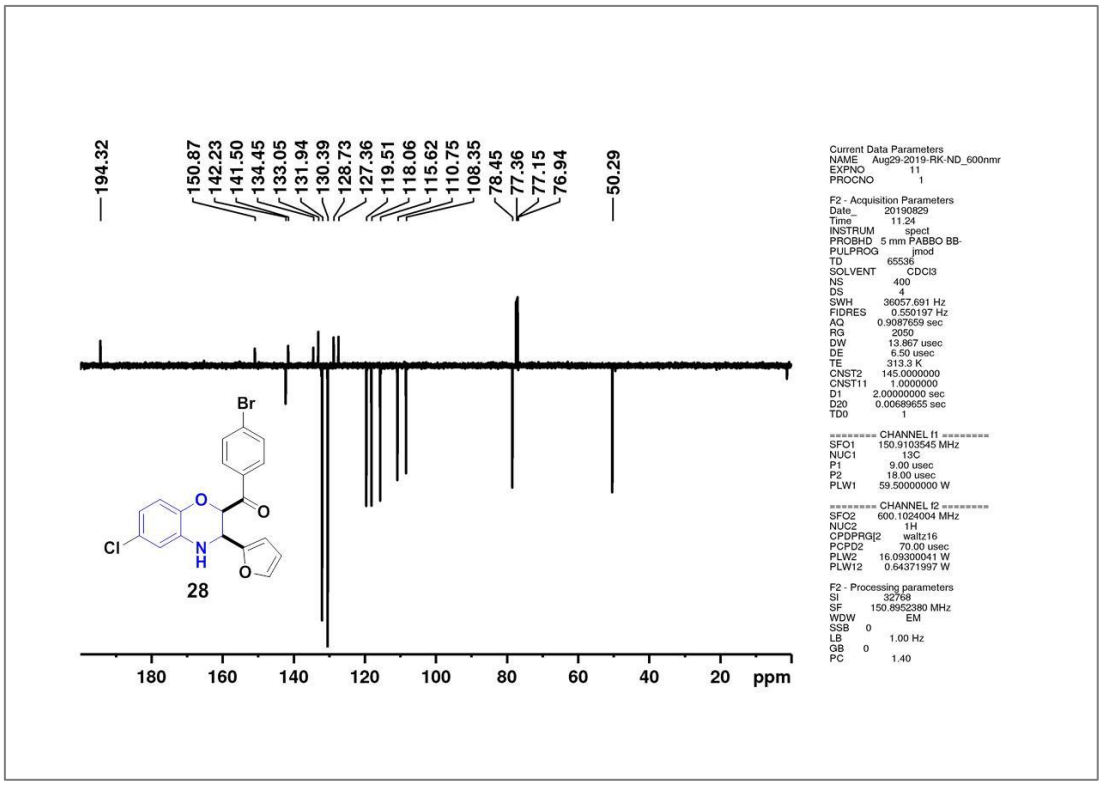
IR spectrum of compound 27 (chapter 2)



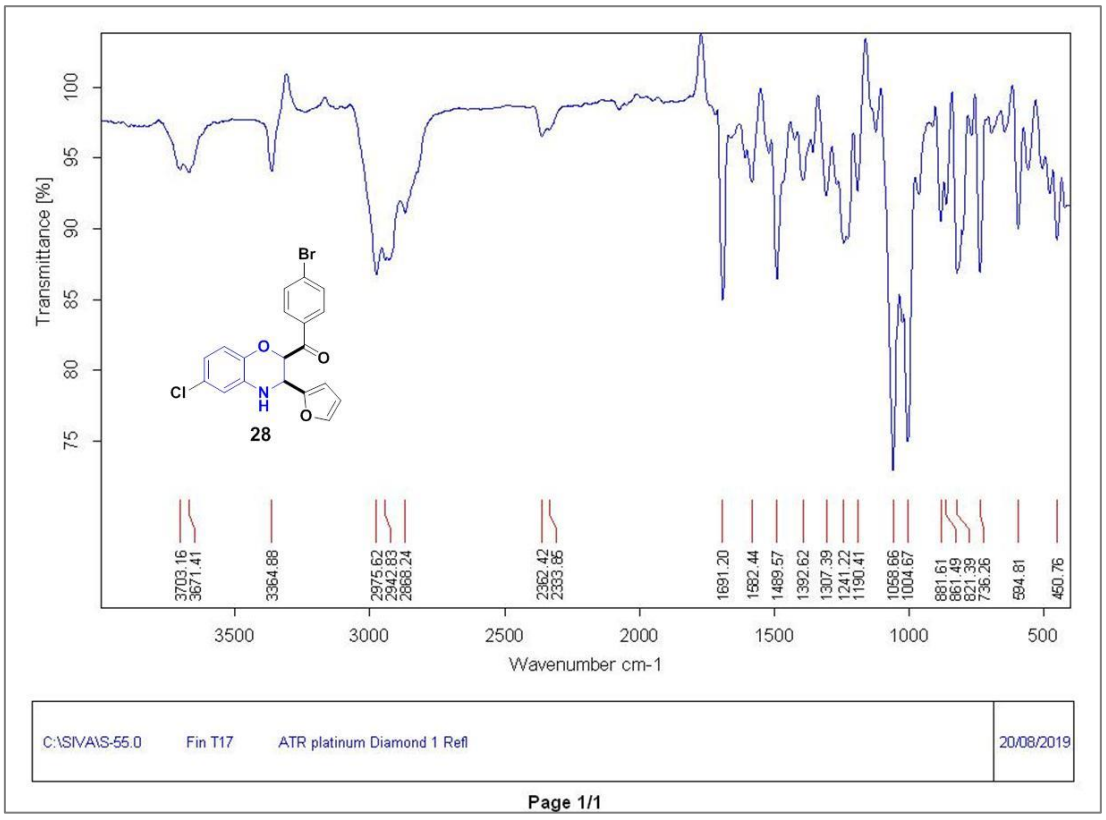
^{1}H NMR spectrum of crude compound 28 (Chapter 2)



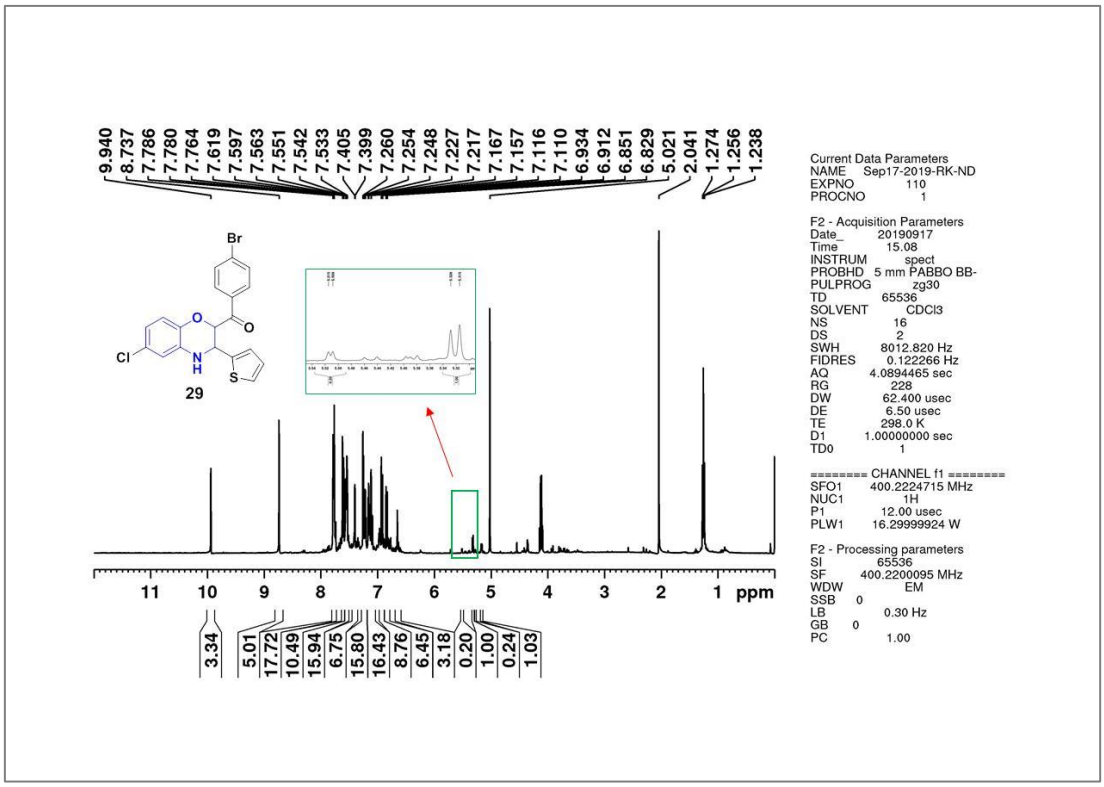
^{1}H NMR spectrum of compound 28 (Chapter 2)



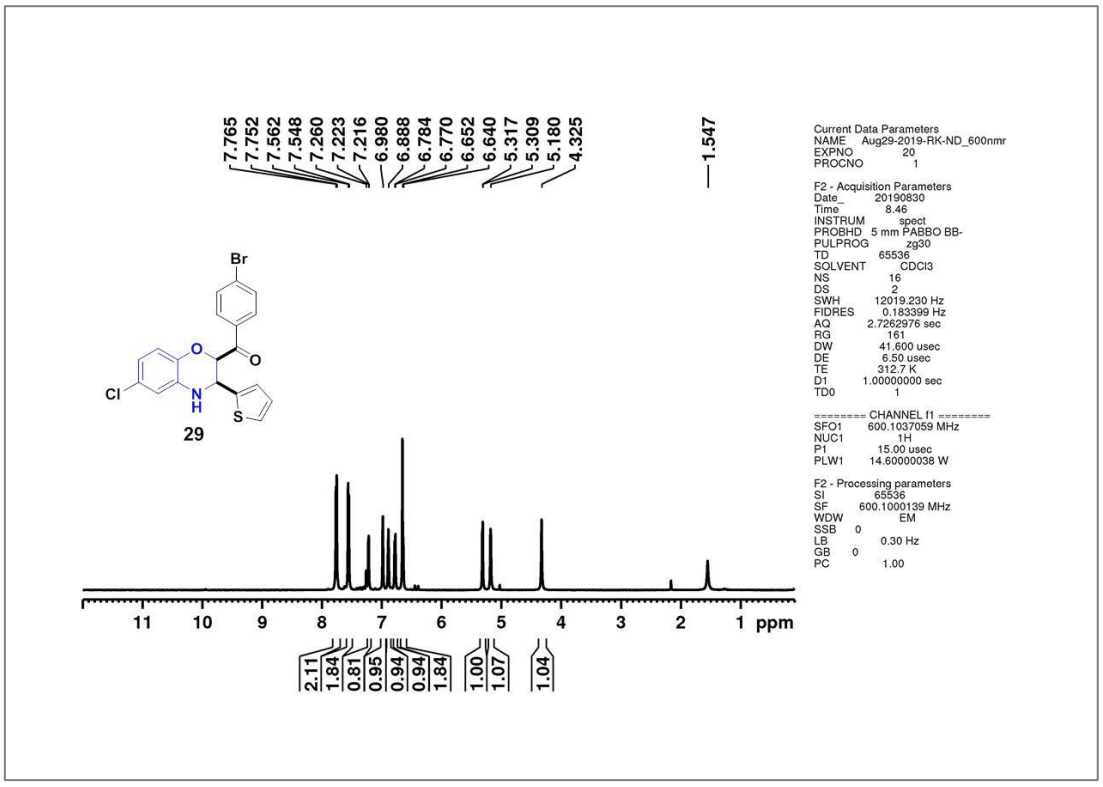
$^{13}C\{^{1}H\}$ NMR spectrum of compound 28 (Chapter 2)



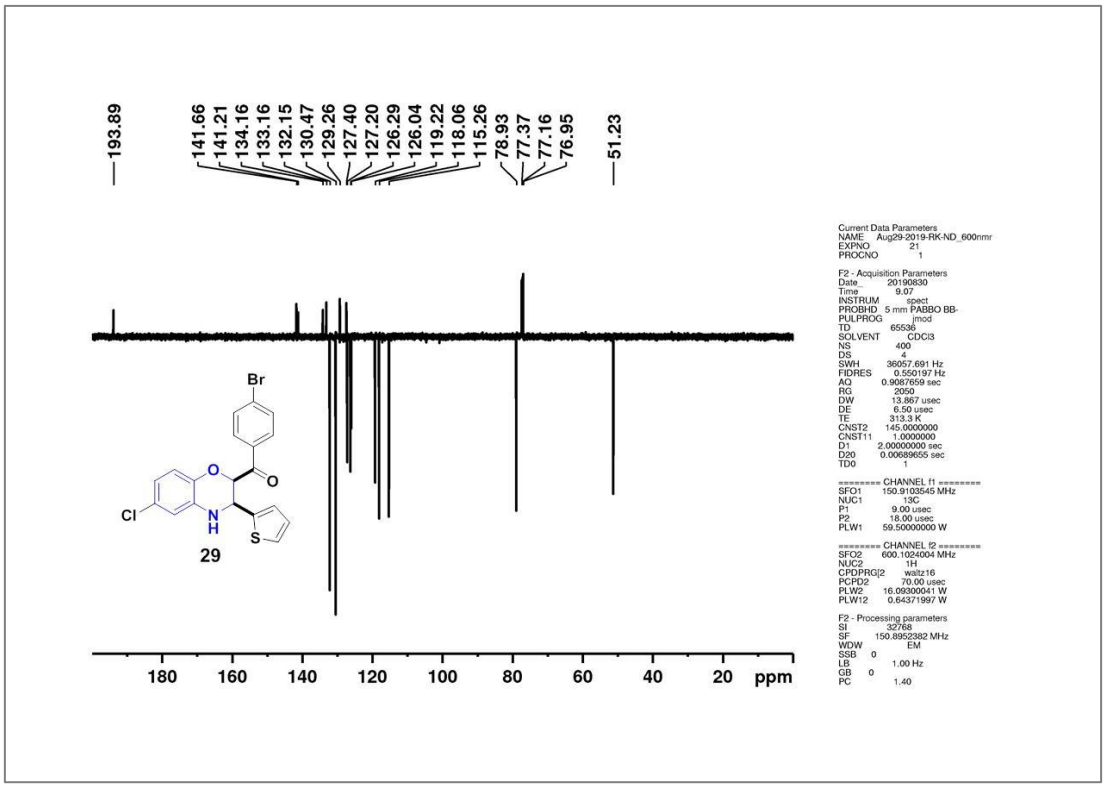
IR spectrum of compound 28 (Chapter 2)



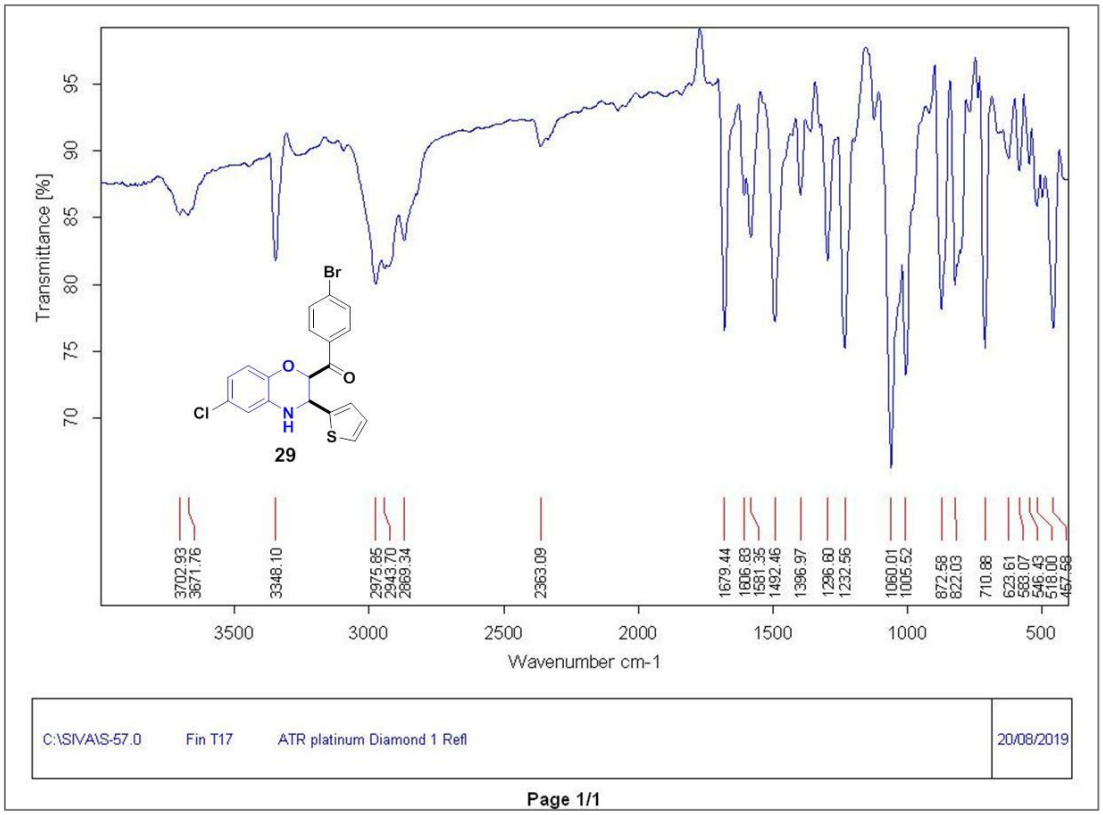
^{1}H NMR spectrum of crude compound 29 (Chapter 2)



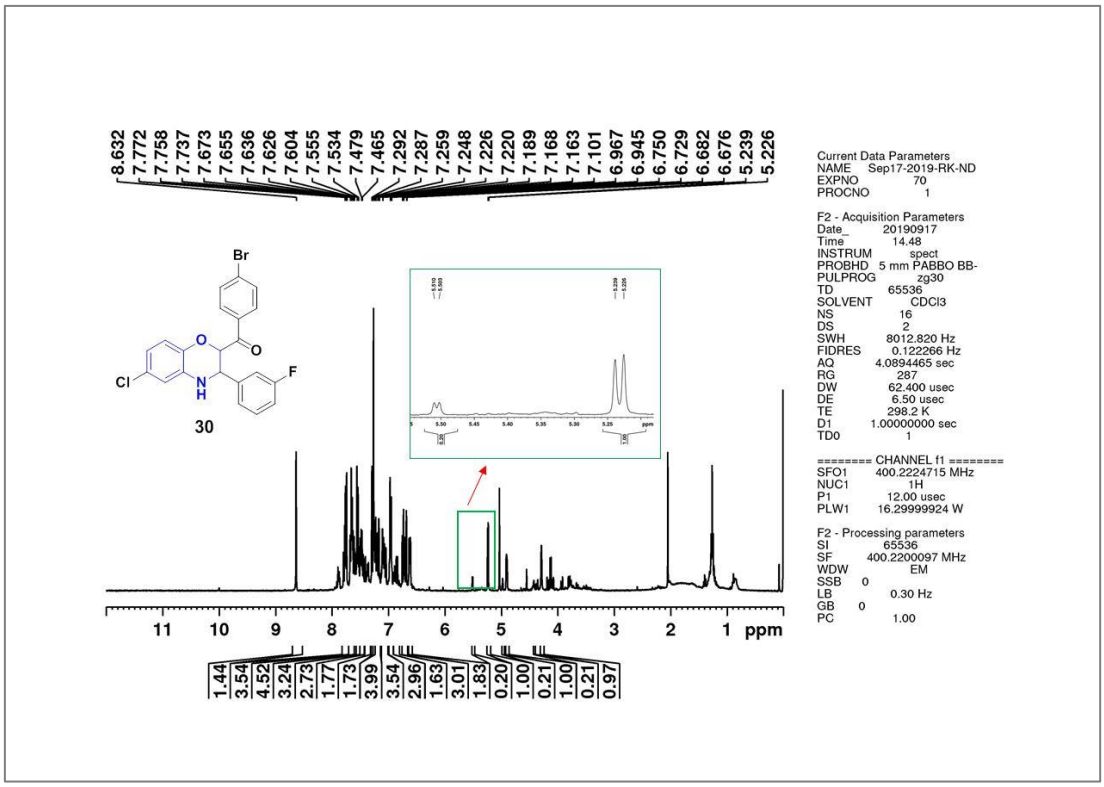
^{1}H NMR spectrum of compound 29 (Chapter 2)



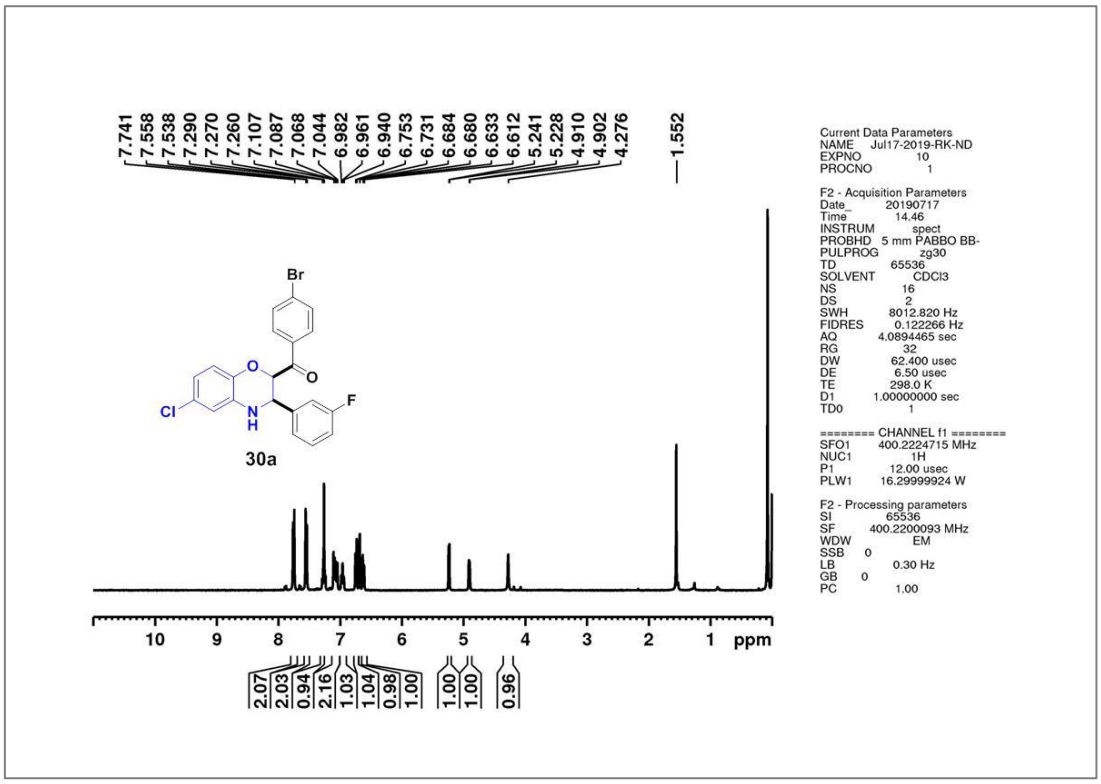
$^{13}C\{^{1}H\}$ NMR spectrum of compound 29 (Chapter 2)



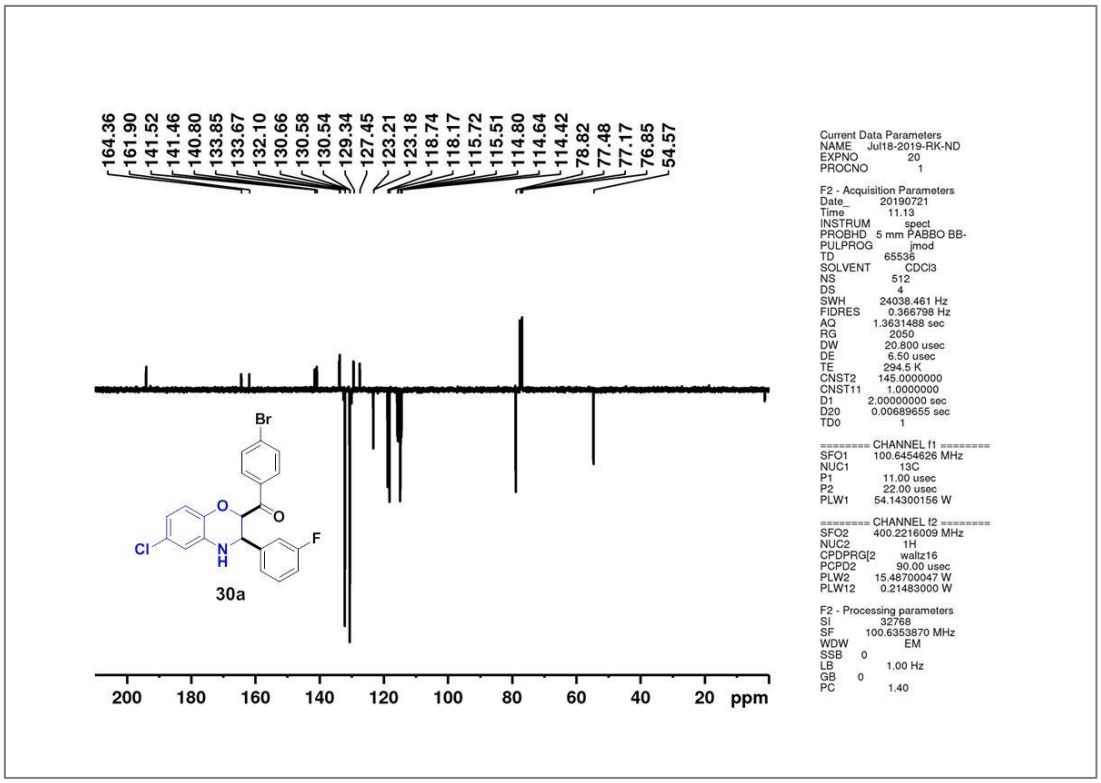
IR spectrum of compound 29 (chapter 2)



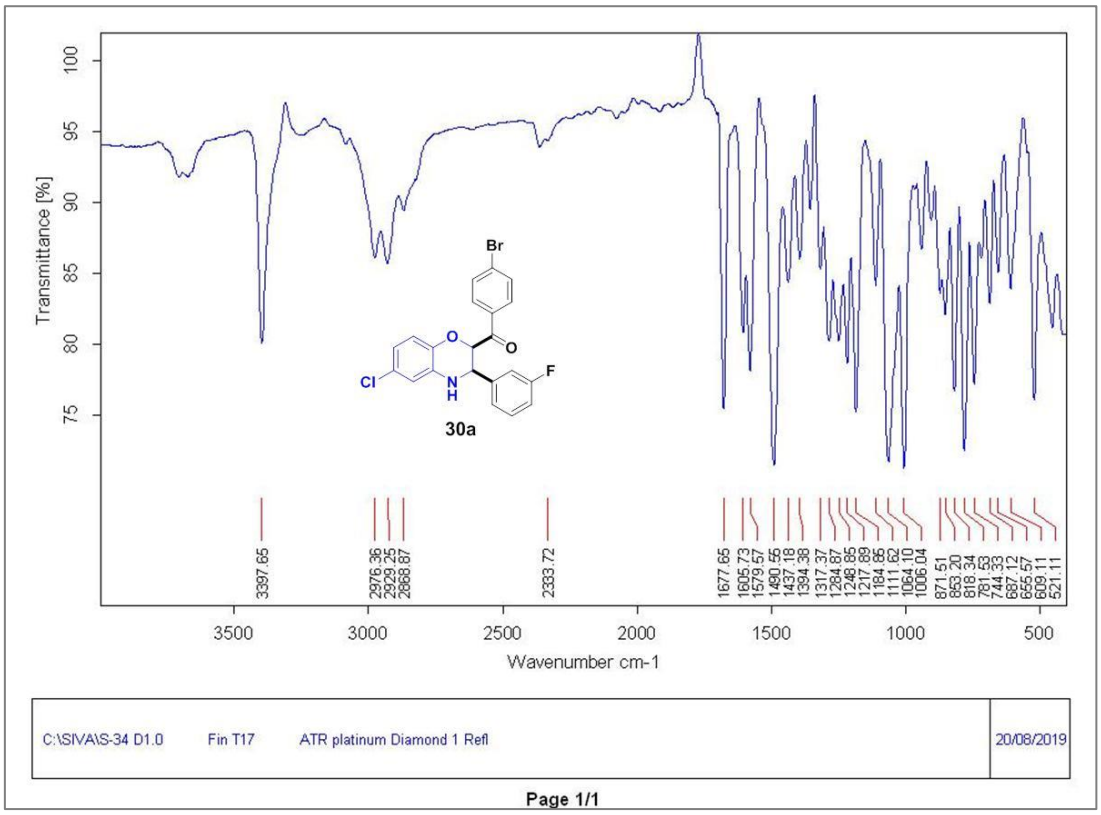
^{1}H NMR spectrum of crude compound 30 (Chapter 2)



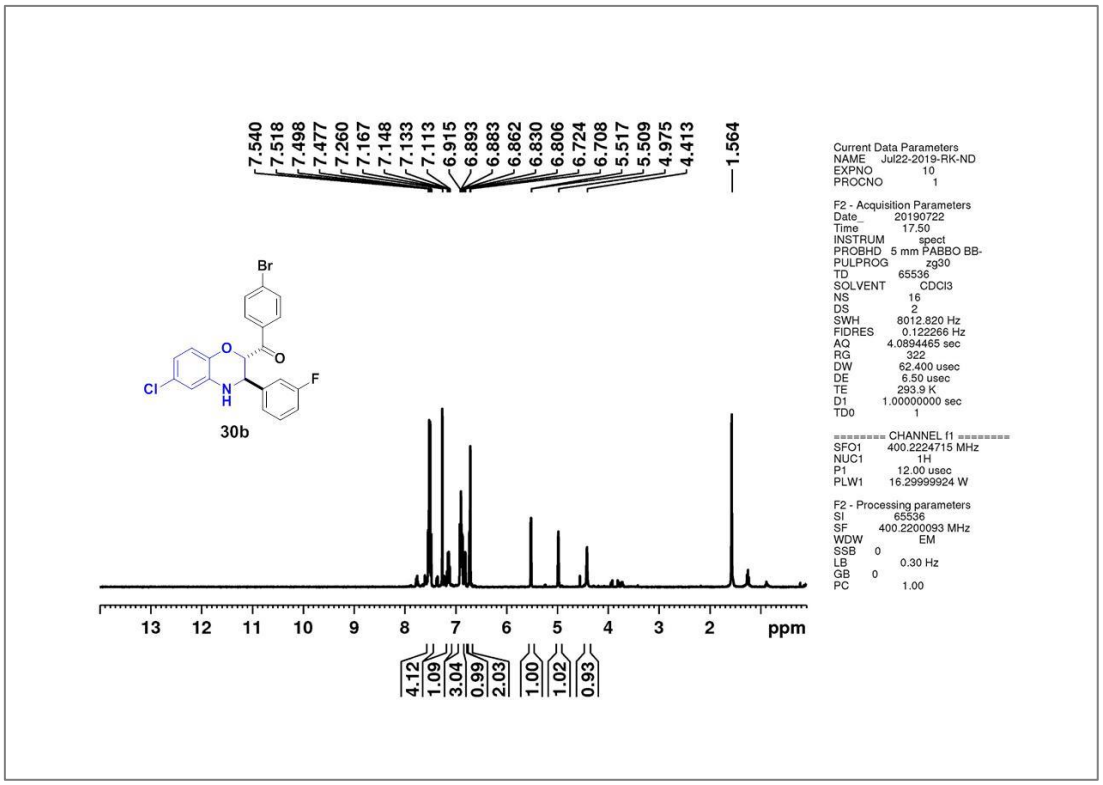
^{1}H NMR spectrum of compound 30a (Chapter 2)



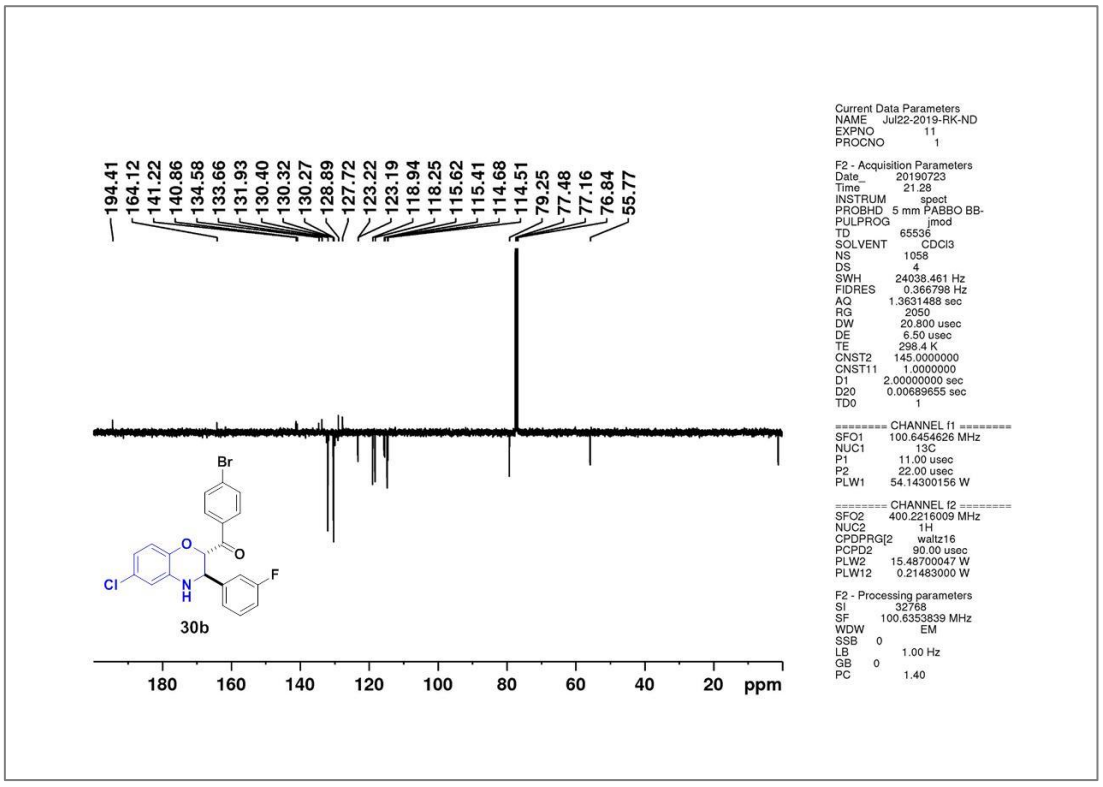
$^{13}C\{^{1}H\}$ NMR spectrum of compound 30a (Chapter 2)



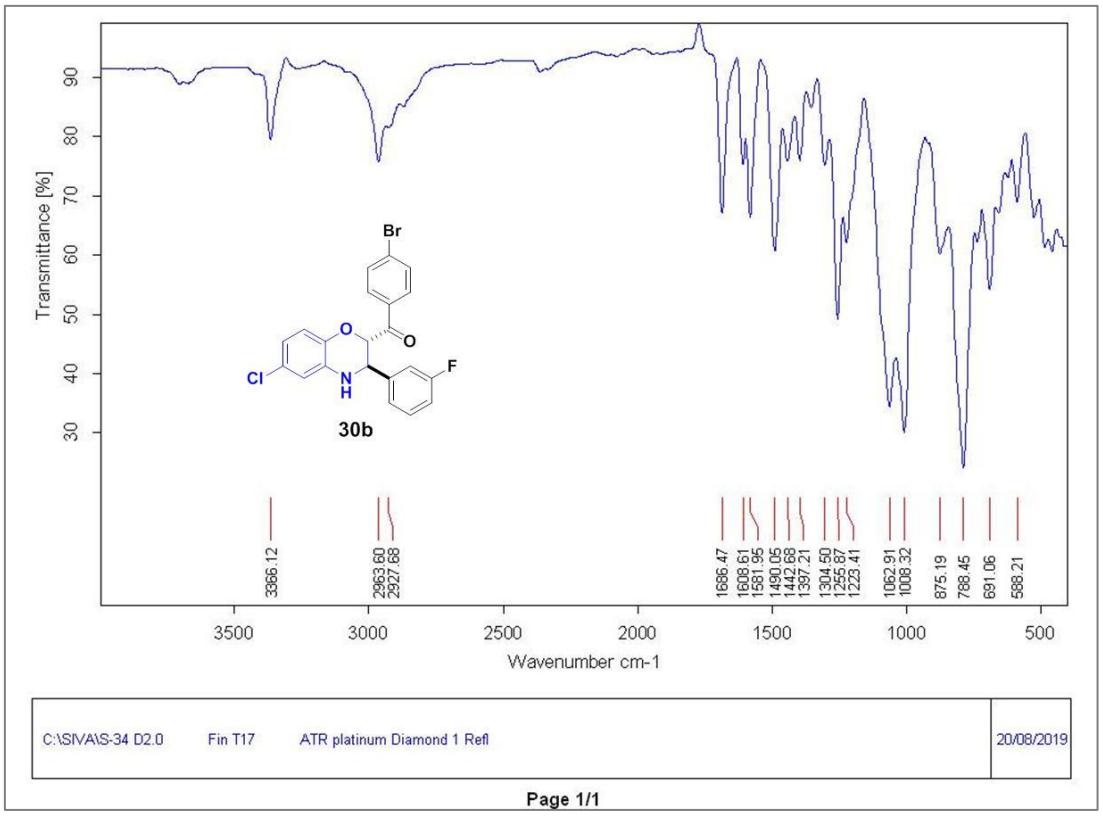
IR spectrum of compound 30a (Chapter 2)



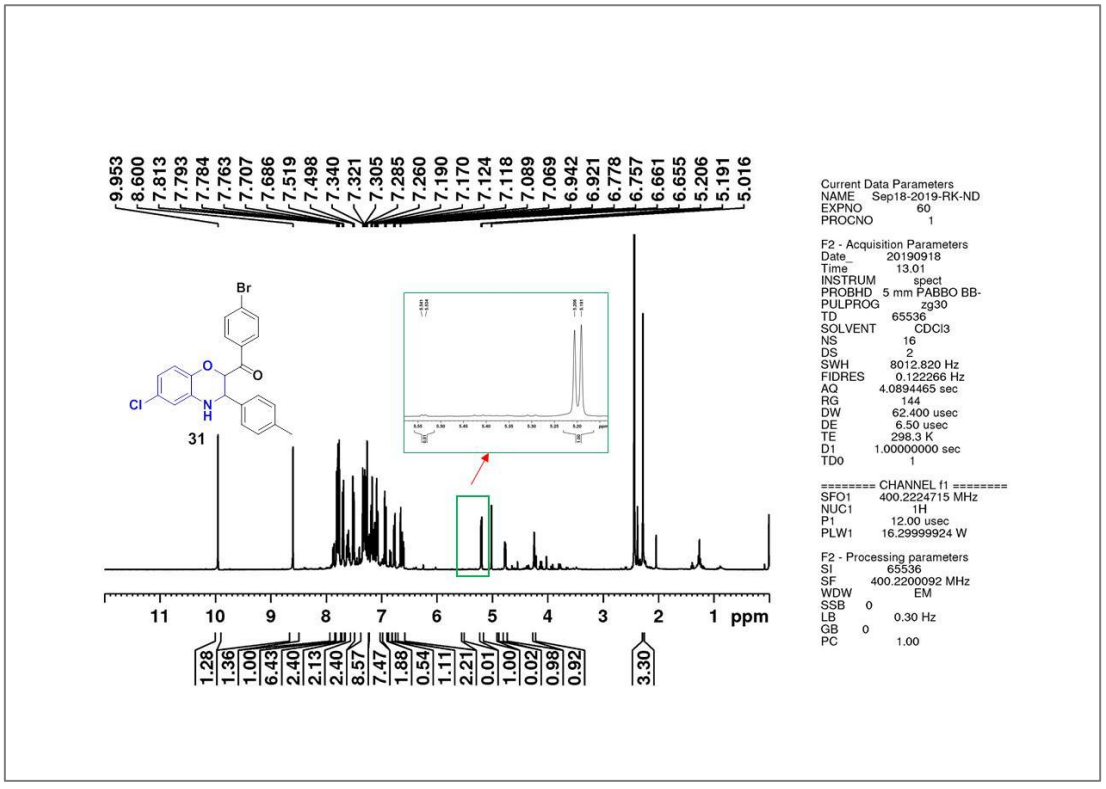
^{1}H NMR spectrum of compound 30b (Chapter 2)



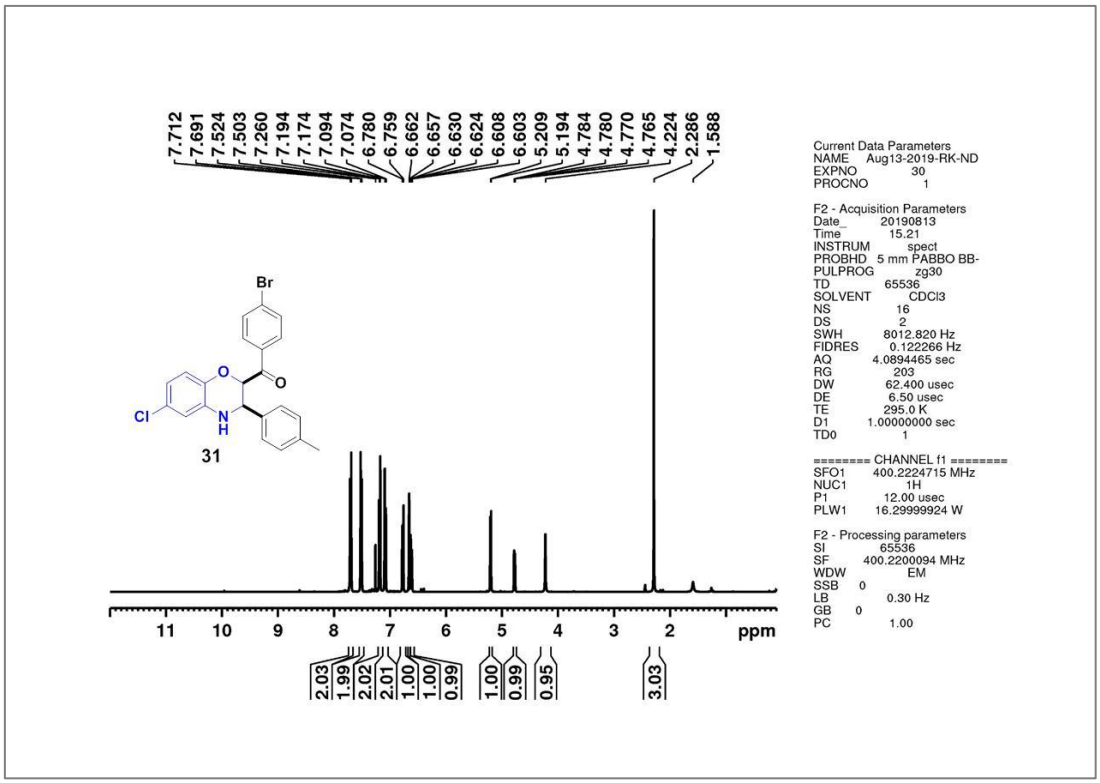
^{13}C{^{1}H} NMR spectrum of compound 30b (Chapter 2)



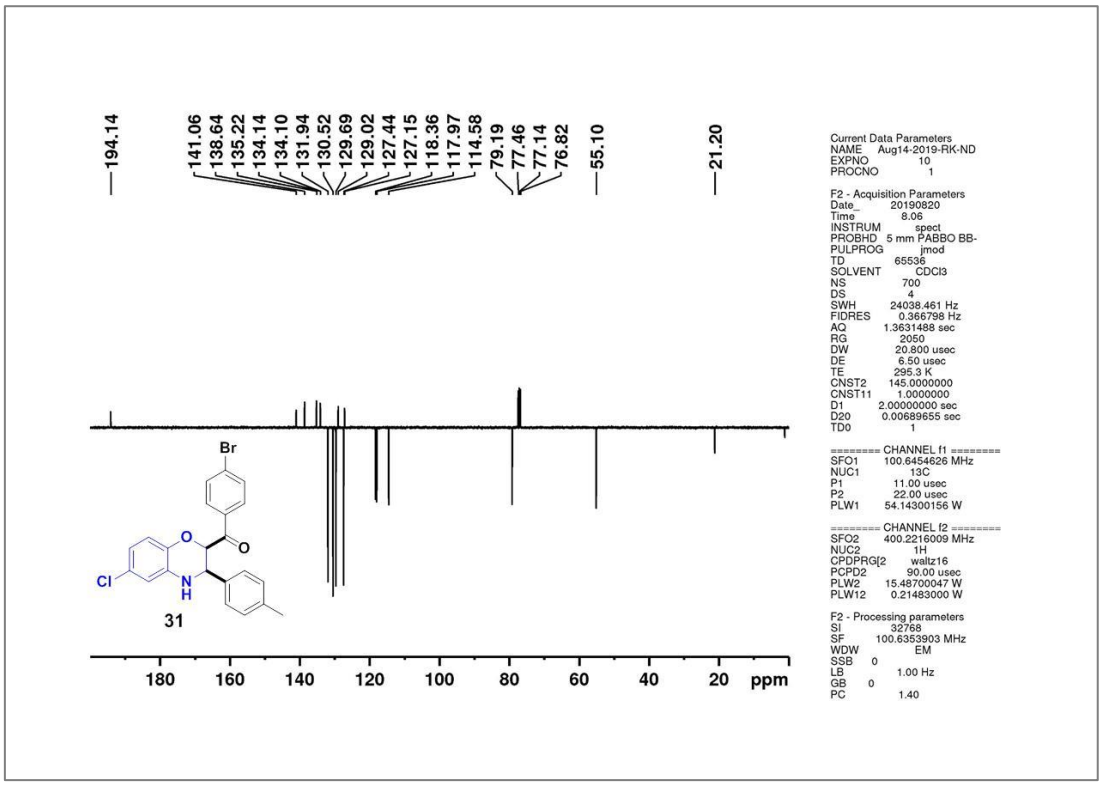
IR spectrum of compound 30b (Chapter 2)



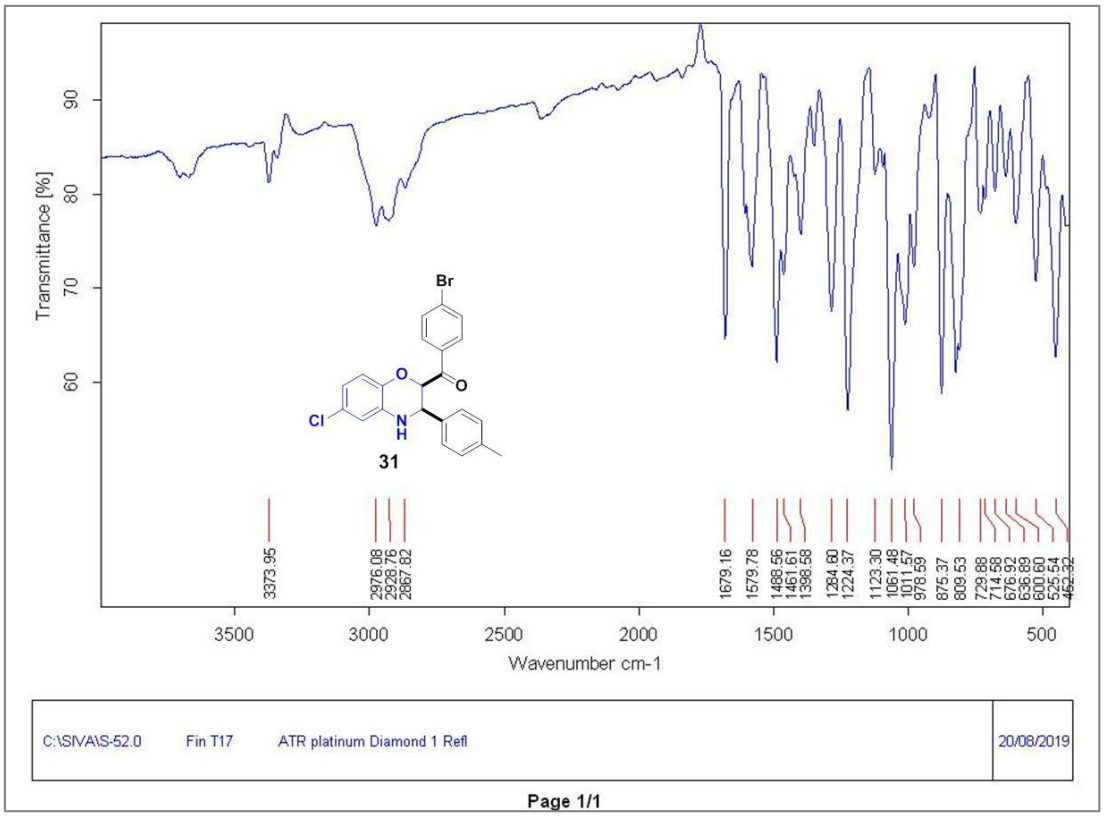
^{1}H NMR spectrum of crude compound 31 (Chapter 2)



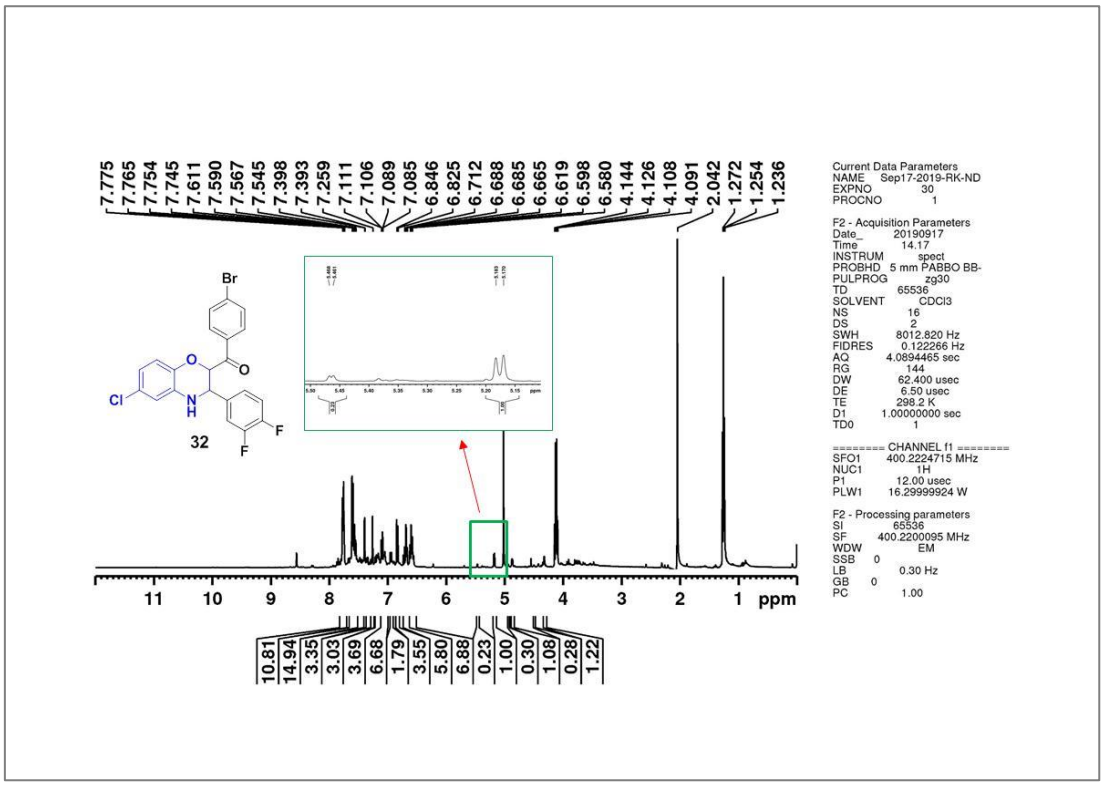
^{1}H NMR spectrum of compound 31 (Chapter 2)



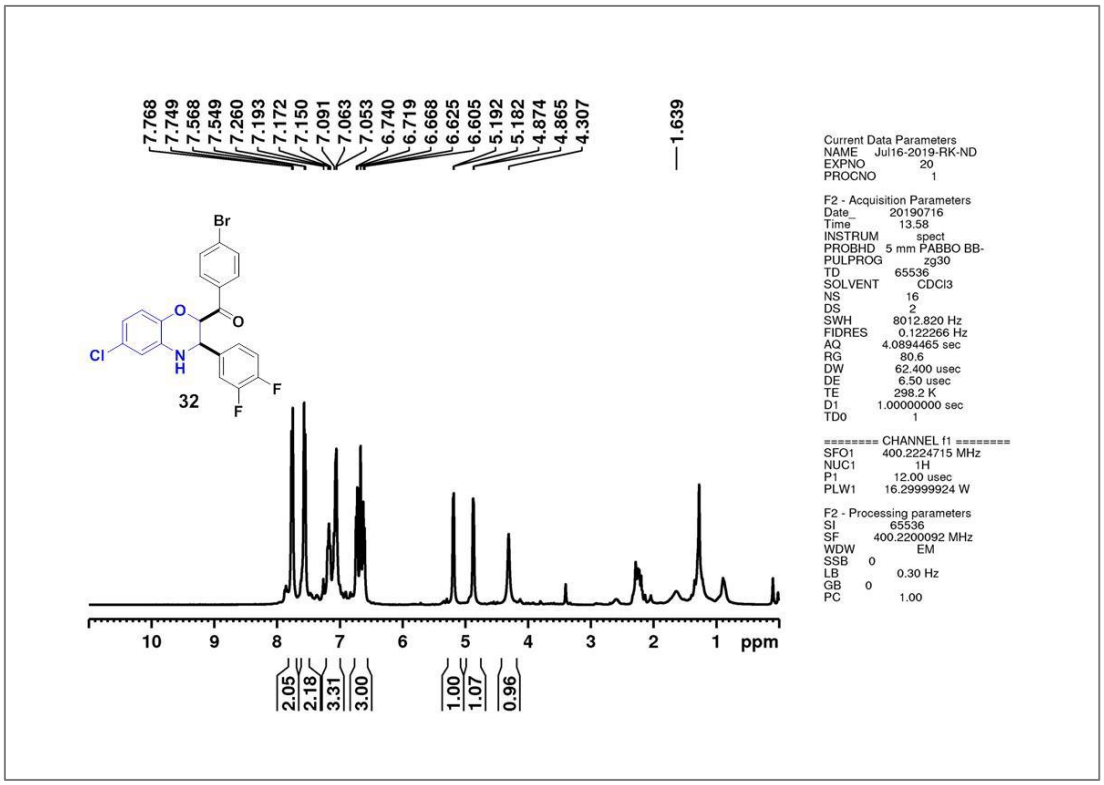
^{13}C{^{1}H} NMR spectrum of compound 31 (Chapter 2)



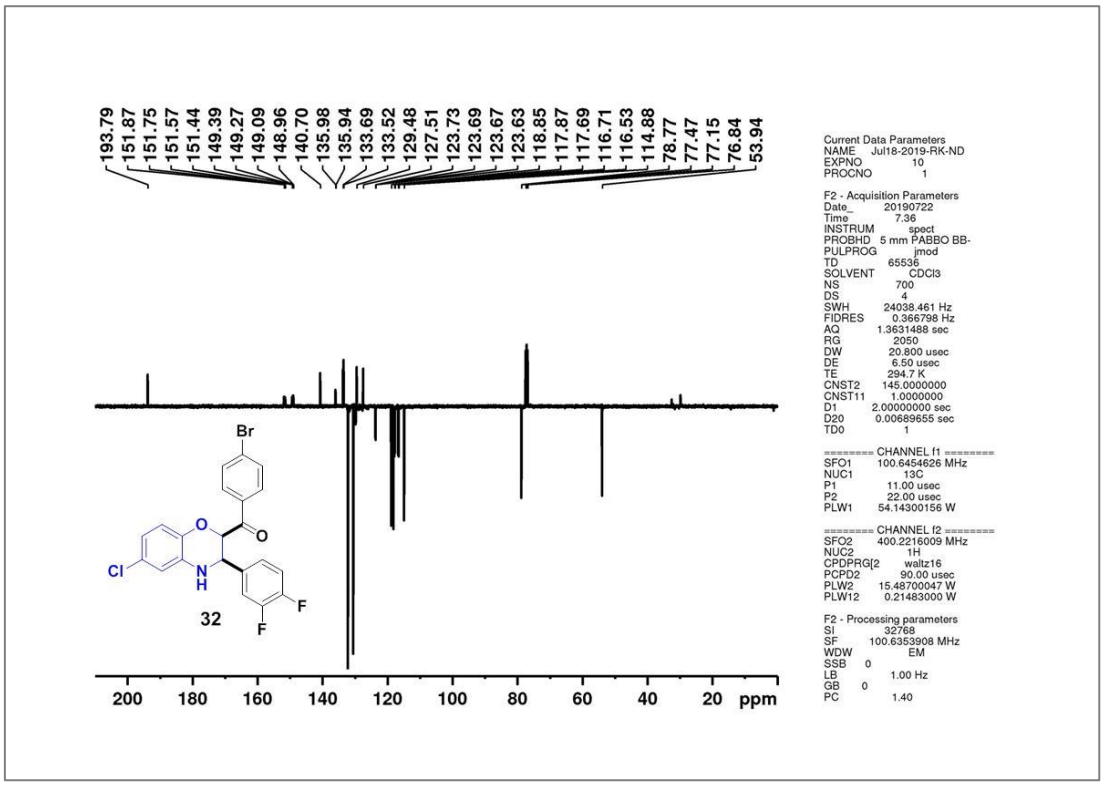
IR spectrum of compound 31 (Chapter 2)



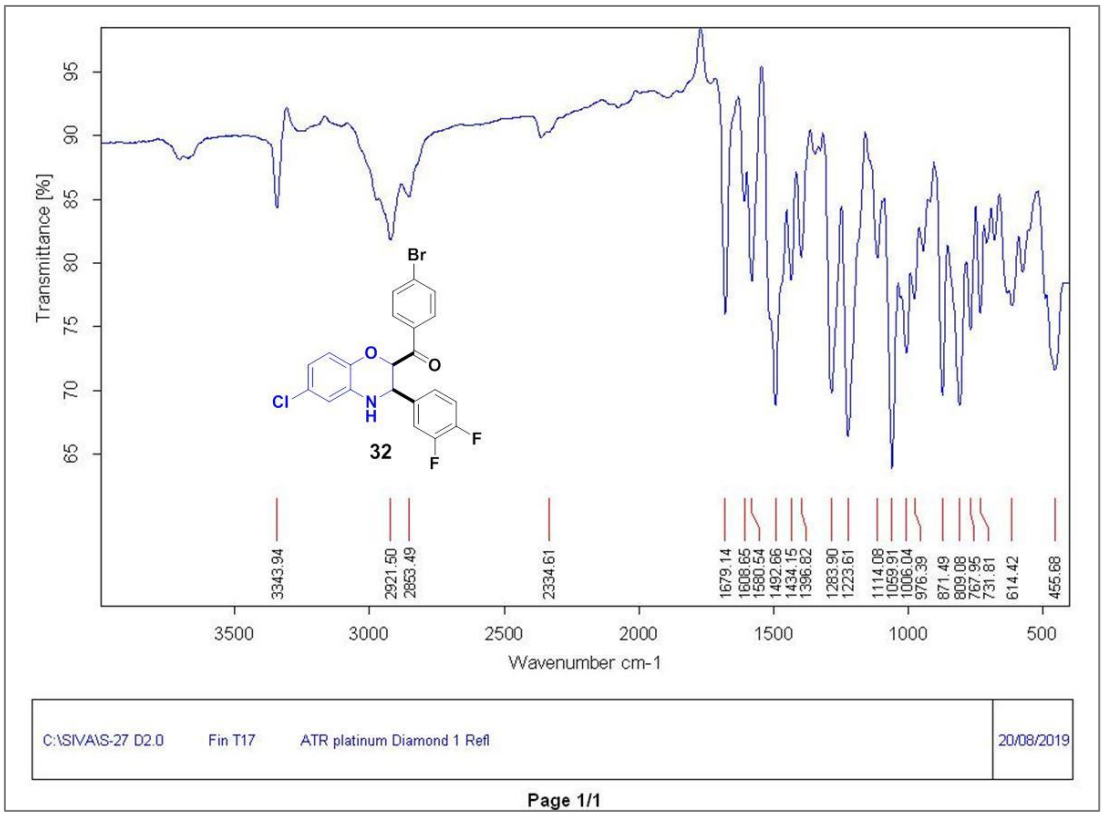
^{1}H NMR spectrum of crude compound 32 (Chapter 2)



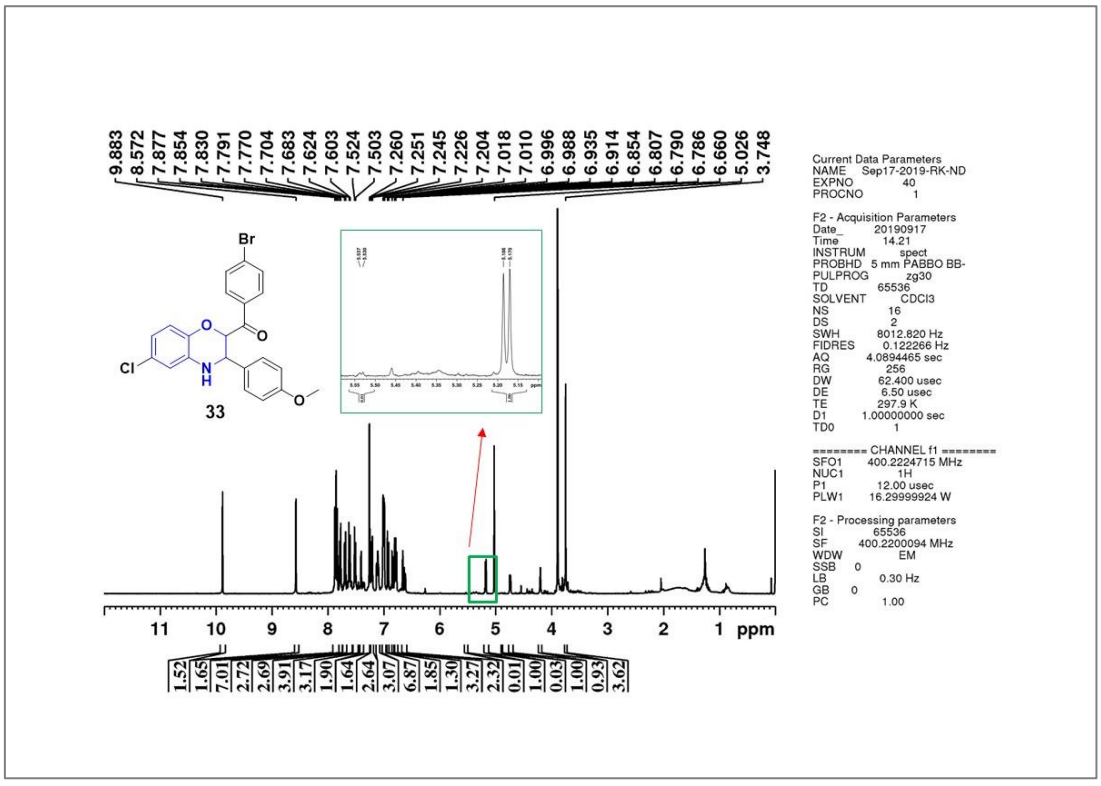
^{1}H NMR spectrum of compound 32 (Chapter 2)



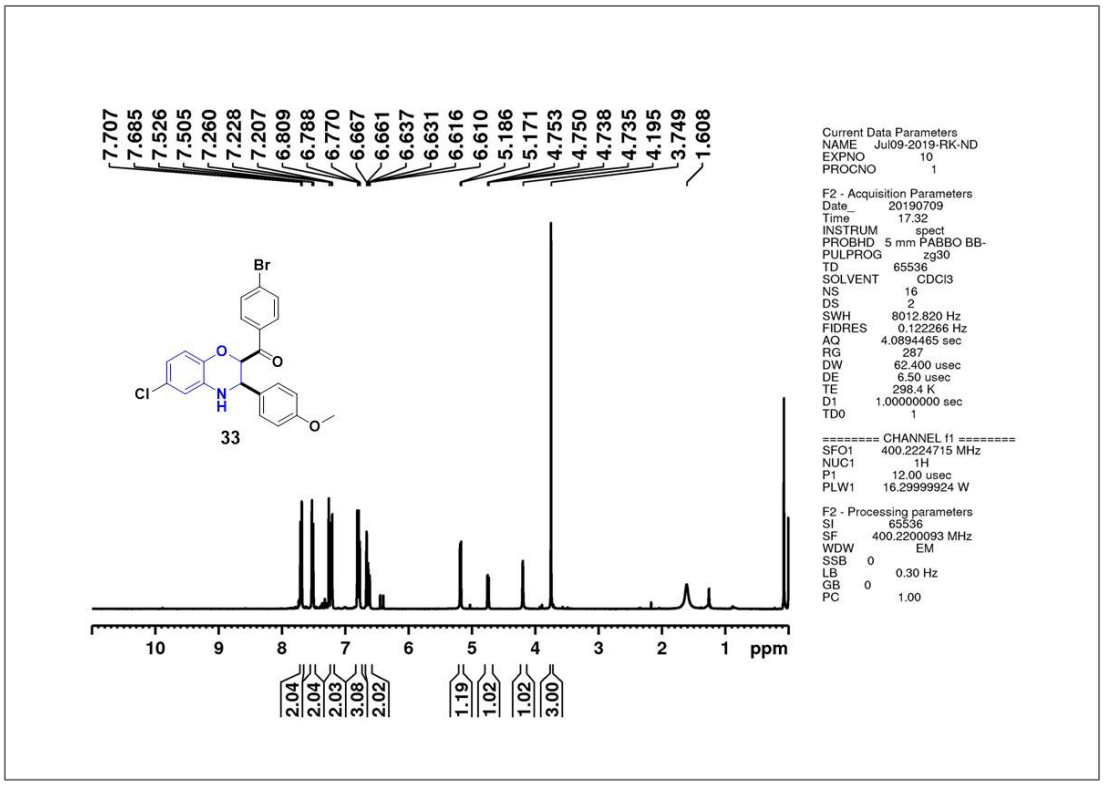
^{13}C{^{1}H} NMR spectrum of compound 32 (Chapter 2)



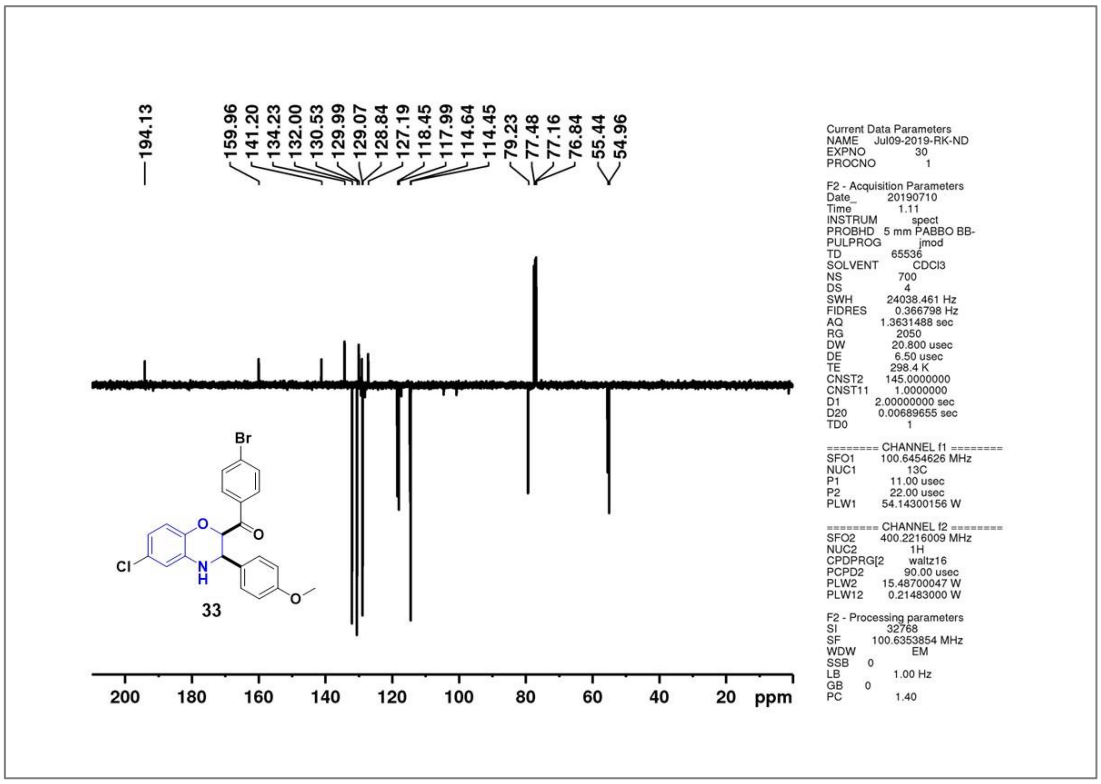
IR spectrum of compound 32 (Chapter 2)



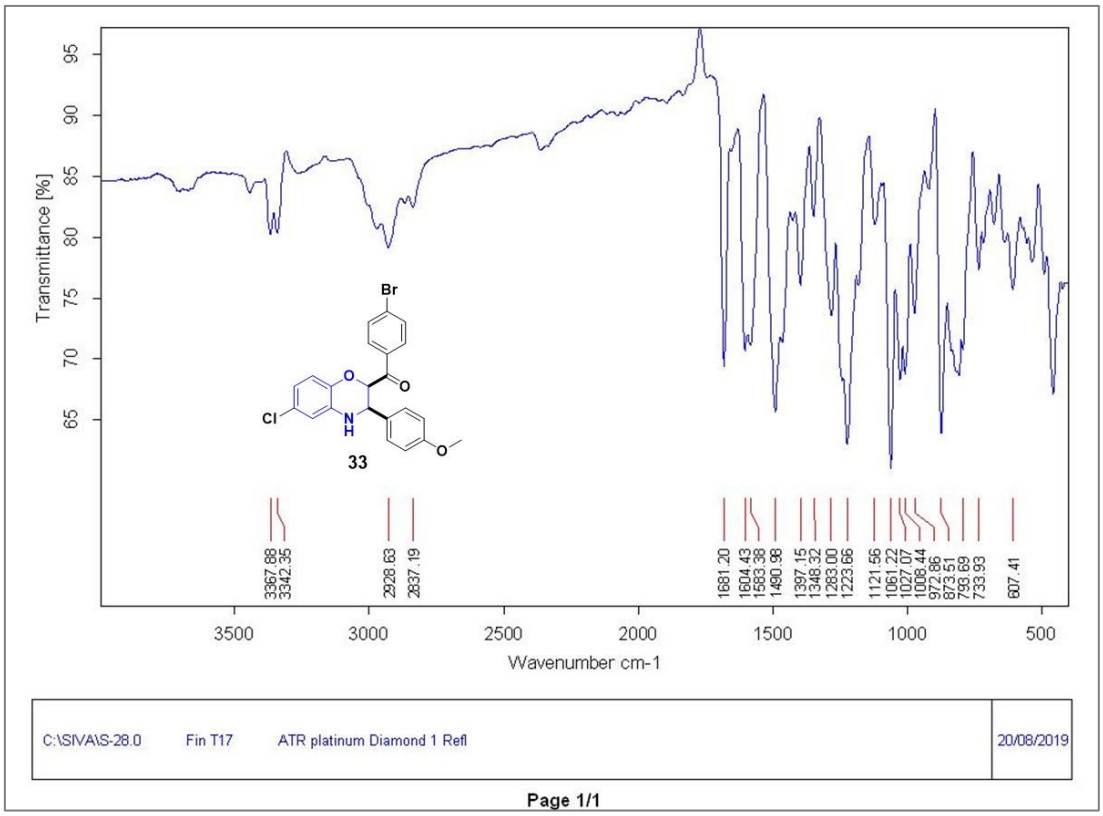
^{1}H NMR spectrum of crude compound 33 (Chapter 2)



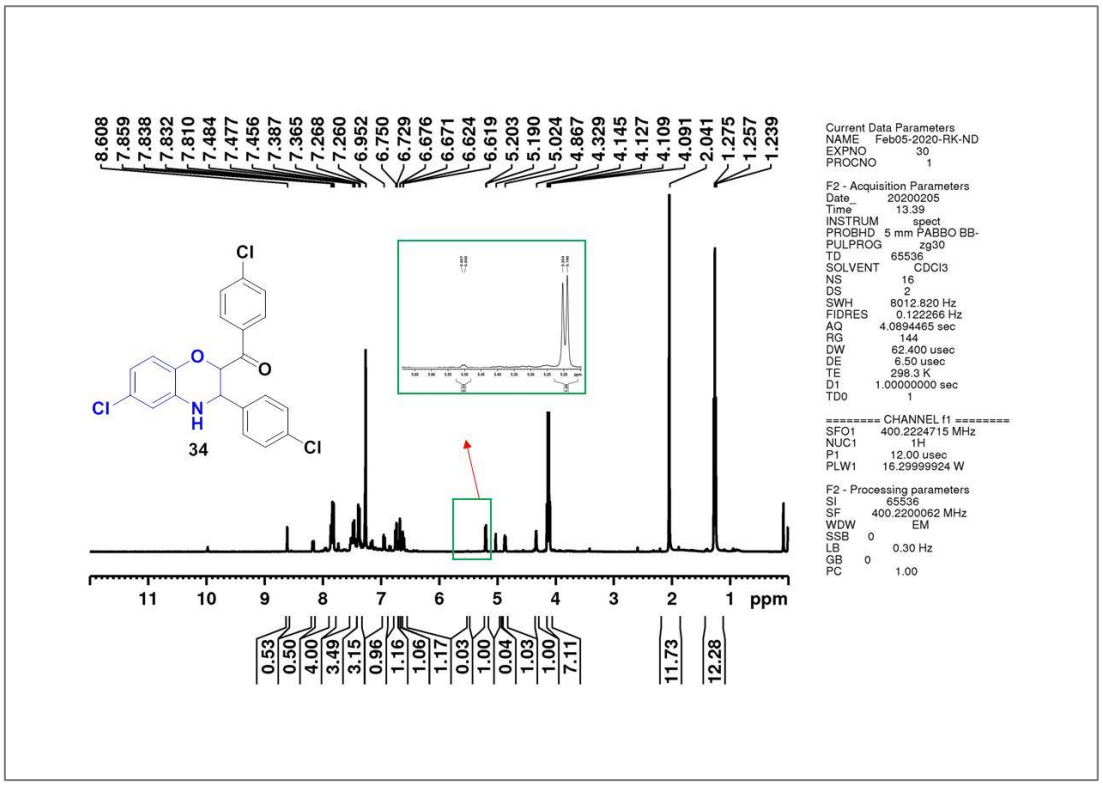
^{1}H NMR spectrum of compound 33 (Chapter 2)



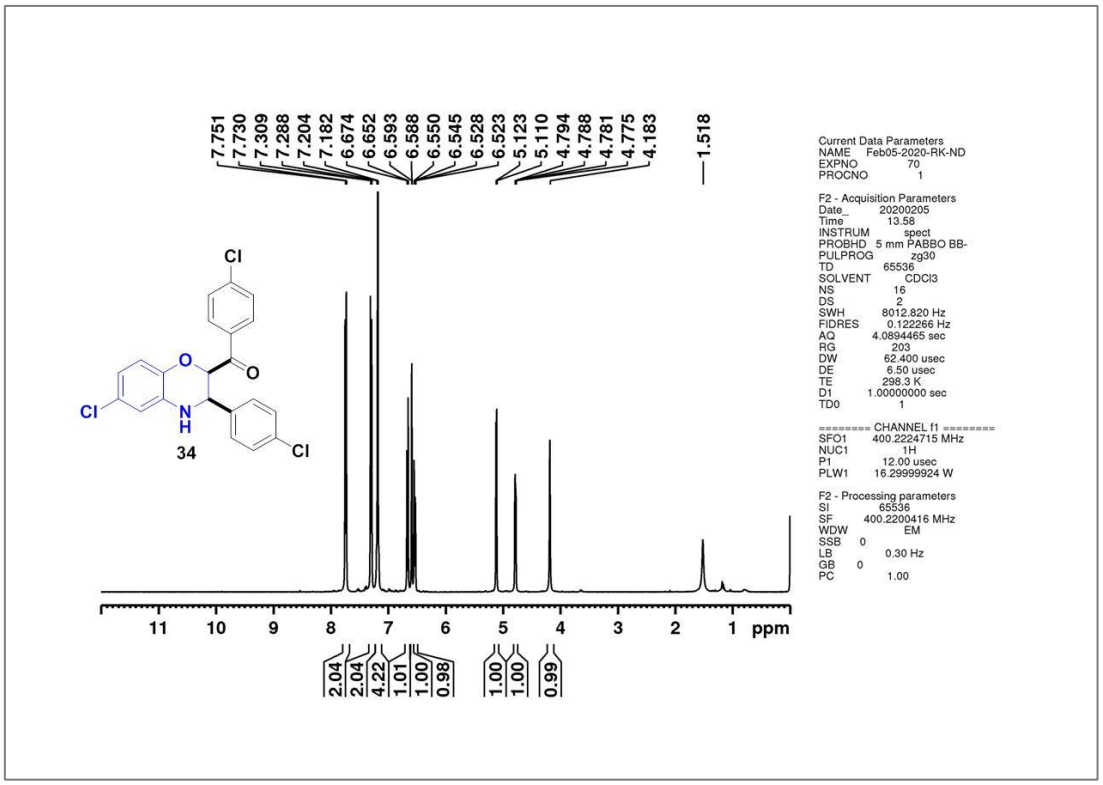
^{13}C{^{1}H} NMR spectrum of compound 33 (Chapter 2)



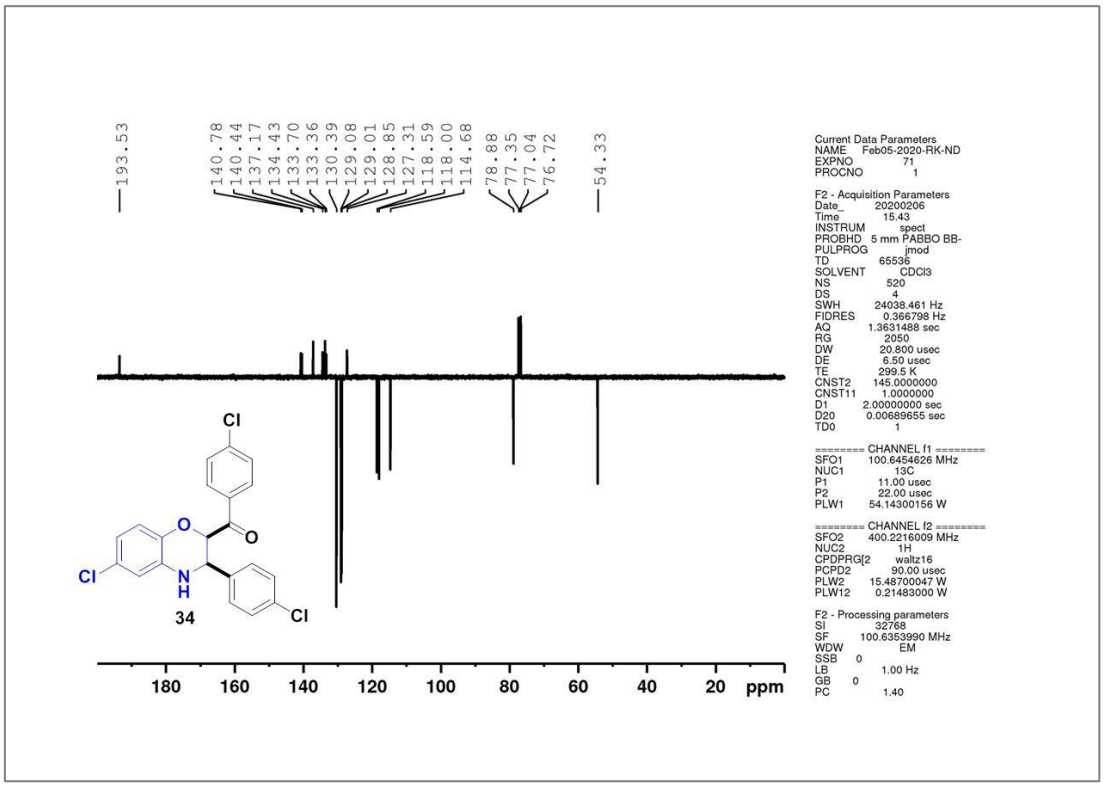
IR spectrum of compound 33 (Chapter 2)



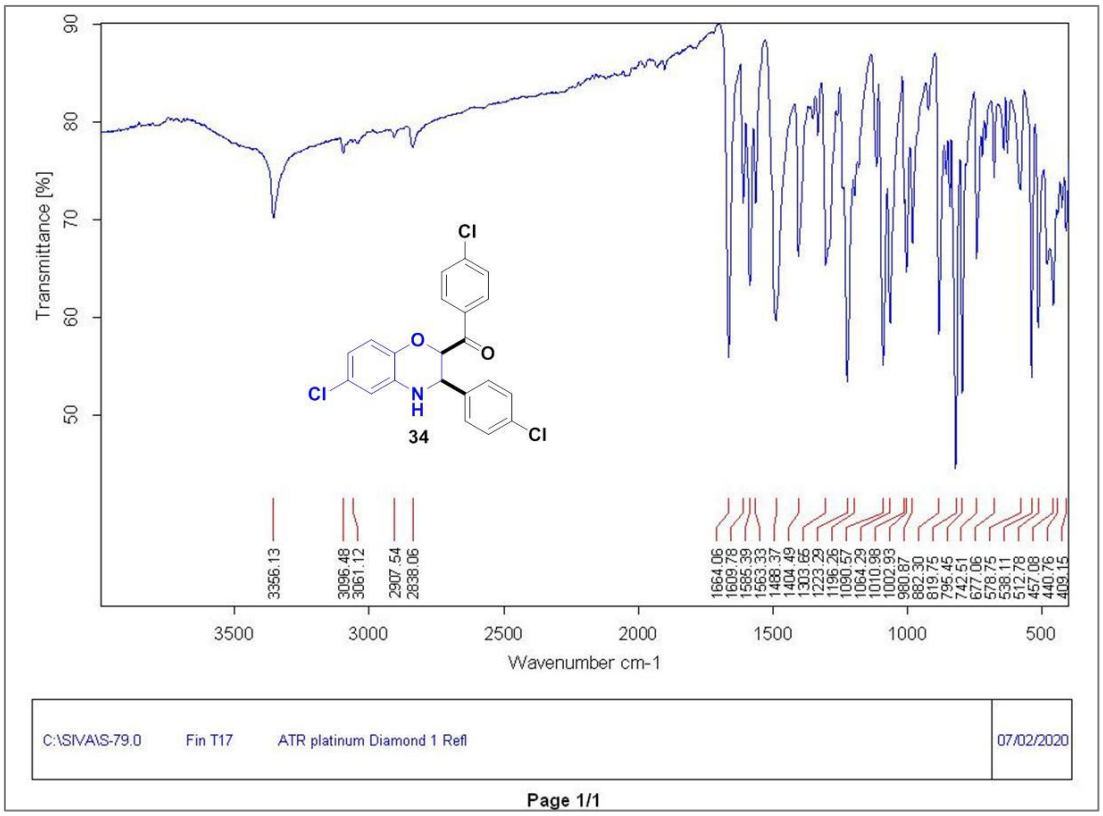
^{1}H NMR spectrum of crude compound 34 (Chapter 2)



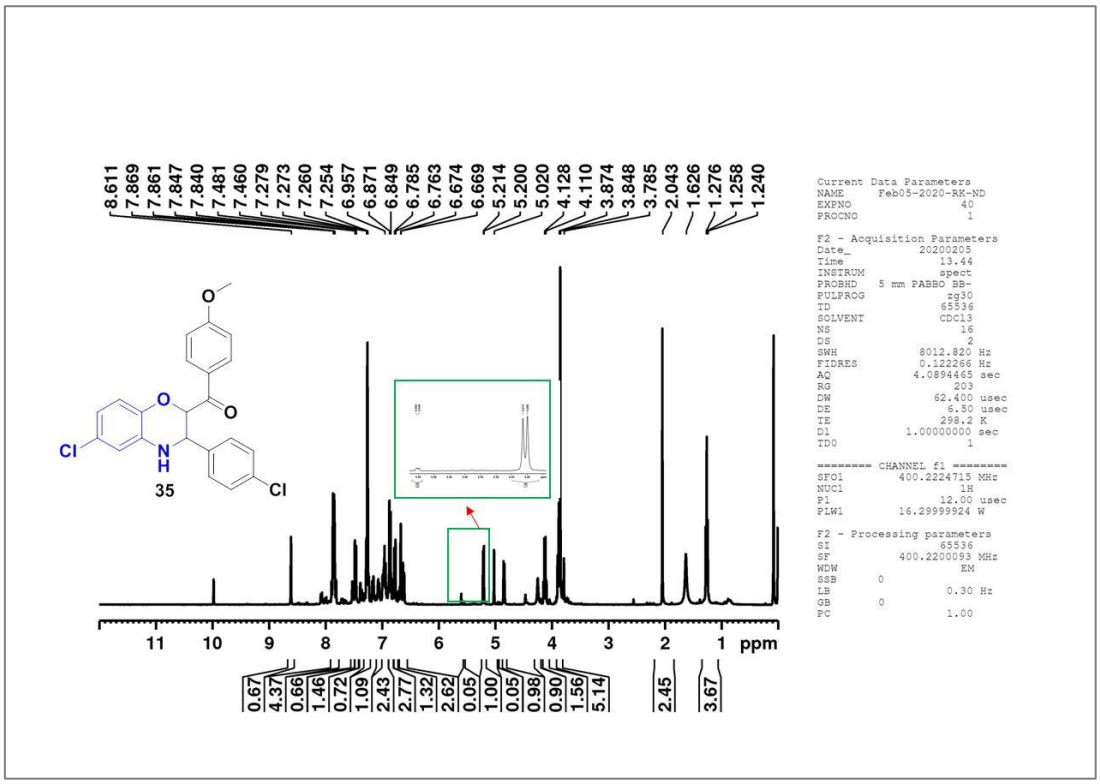
^{1}H NMR spectrum of compound 34 (Chapter 2)



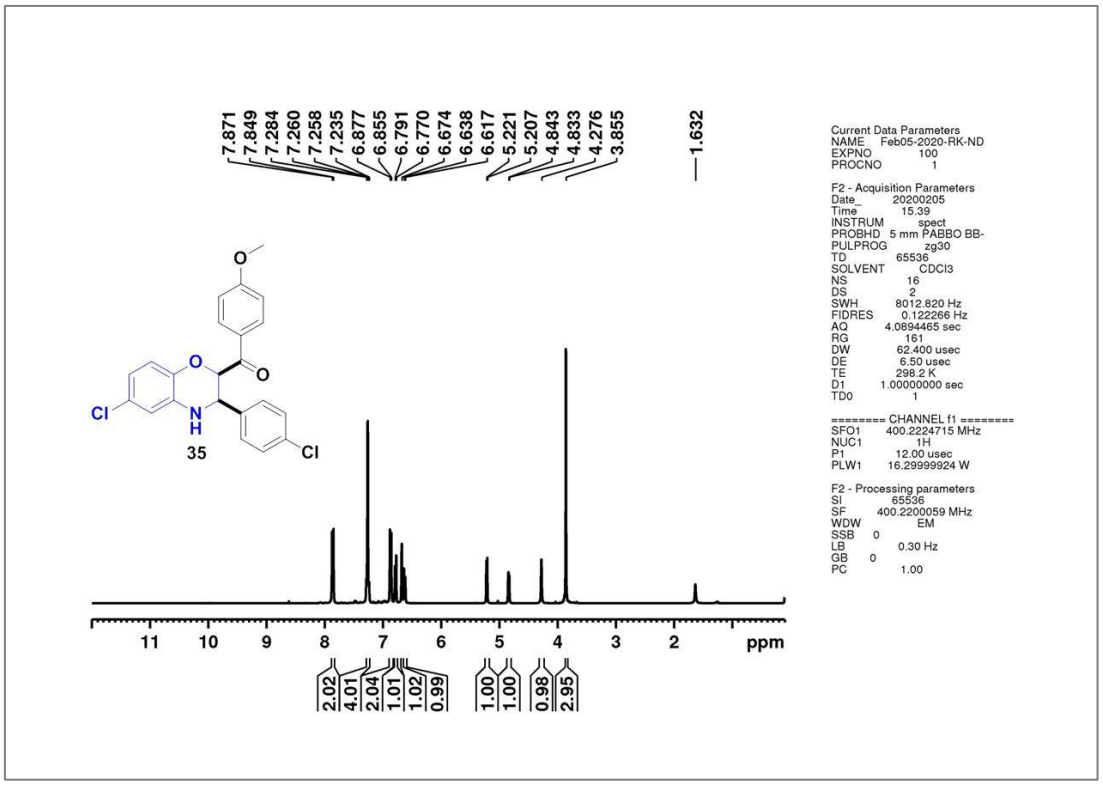
^{13}C{^{1}H} NMR spectrum of compound 34 (Chapter 2)



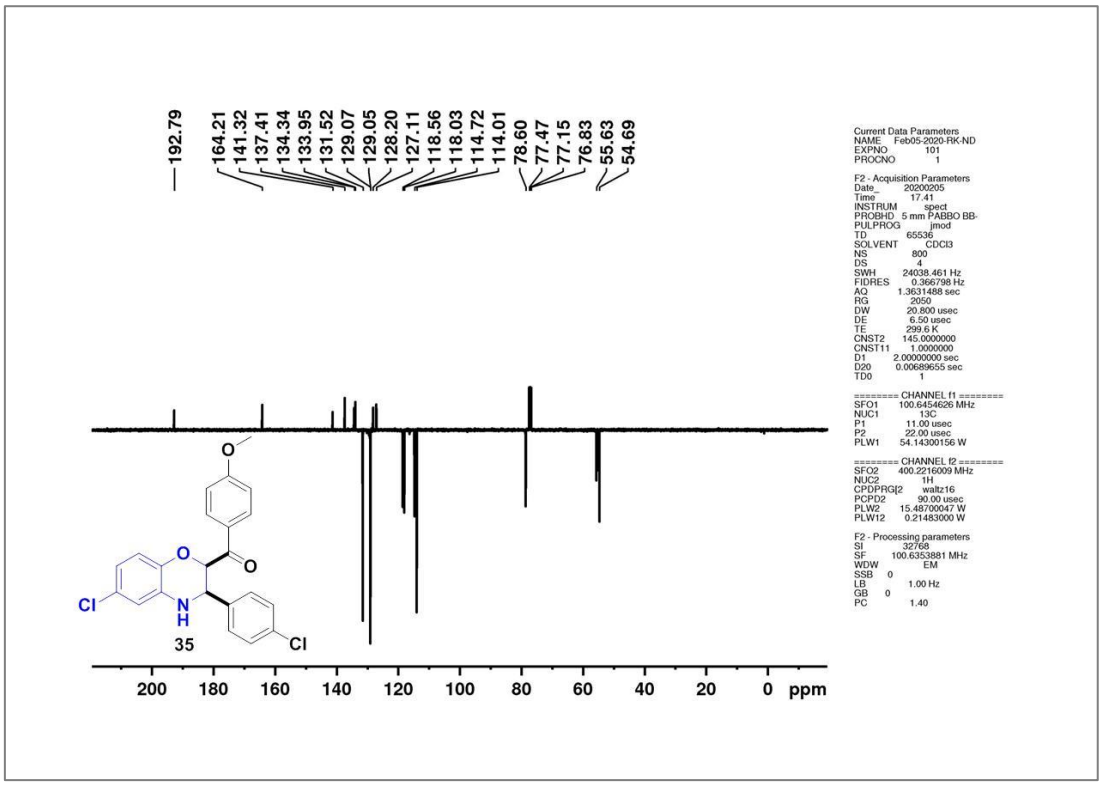
IR spectrum of compound 34 (Chapter 2)



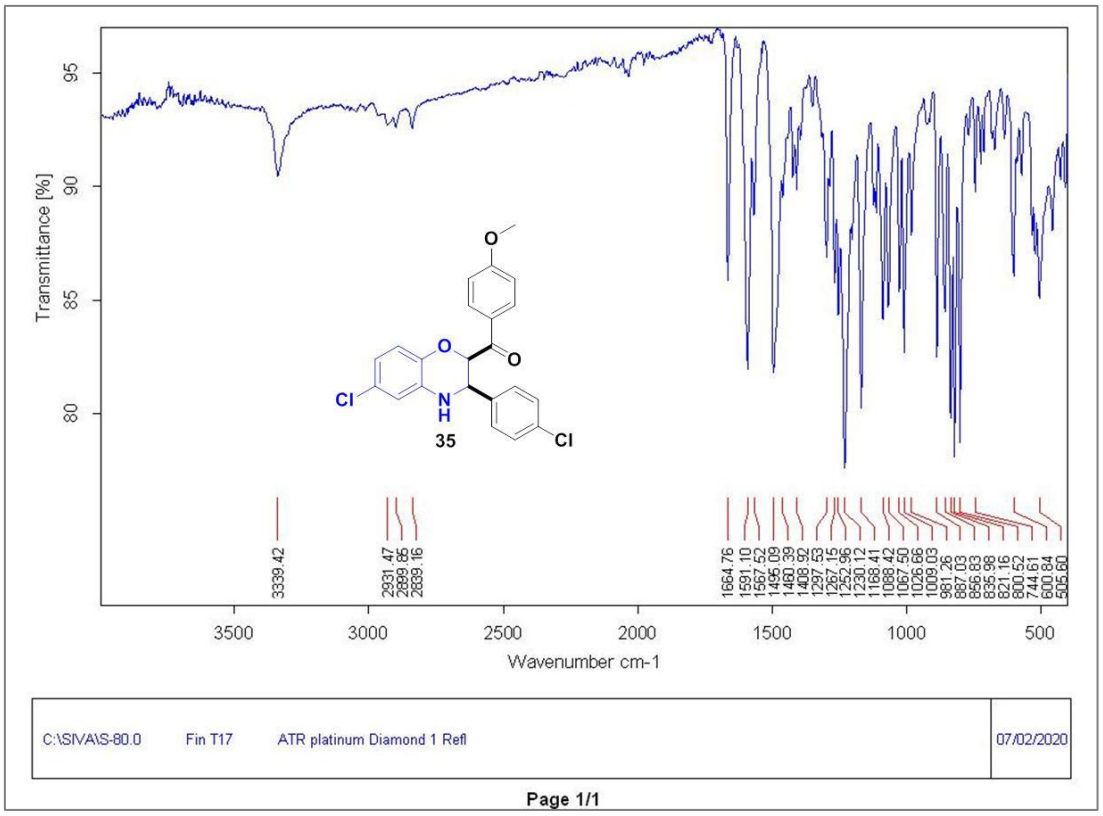
^{1}H NMR spectrum of crude compound 35 (Chapter 2)



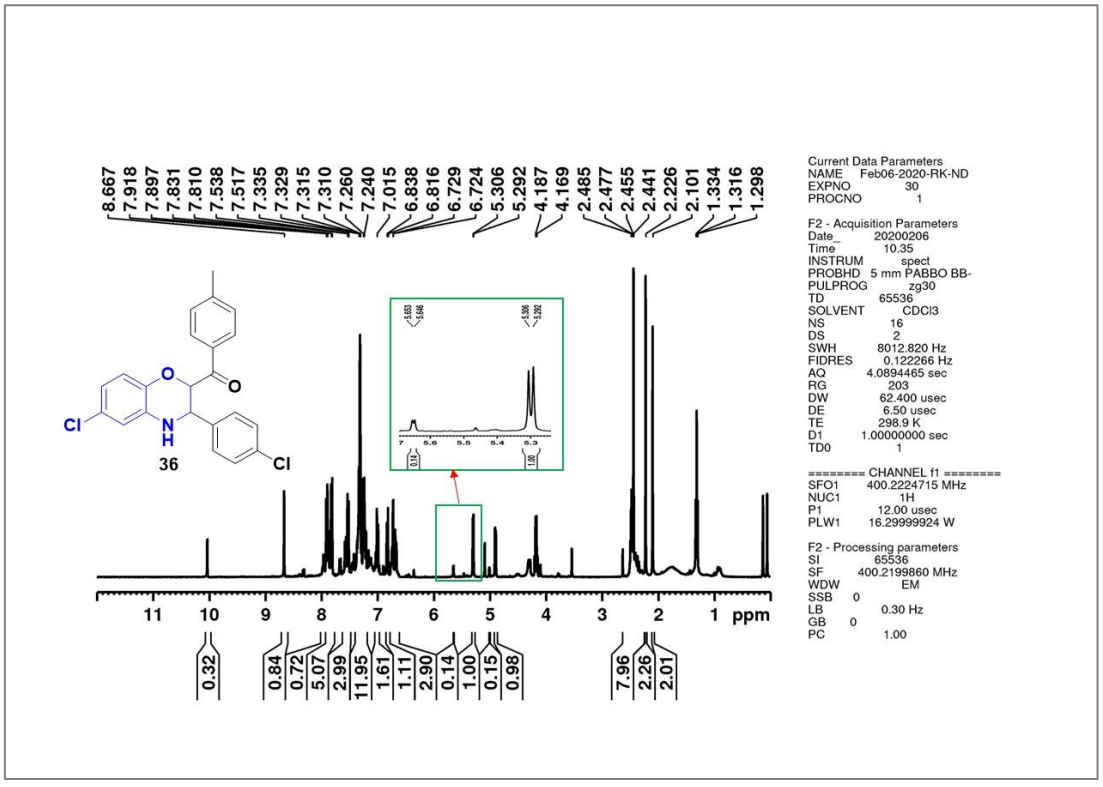
^{1}H NMR spectrum of compound 35 (Chapter 2)



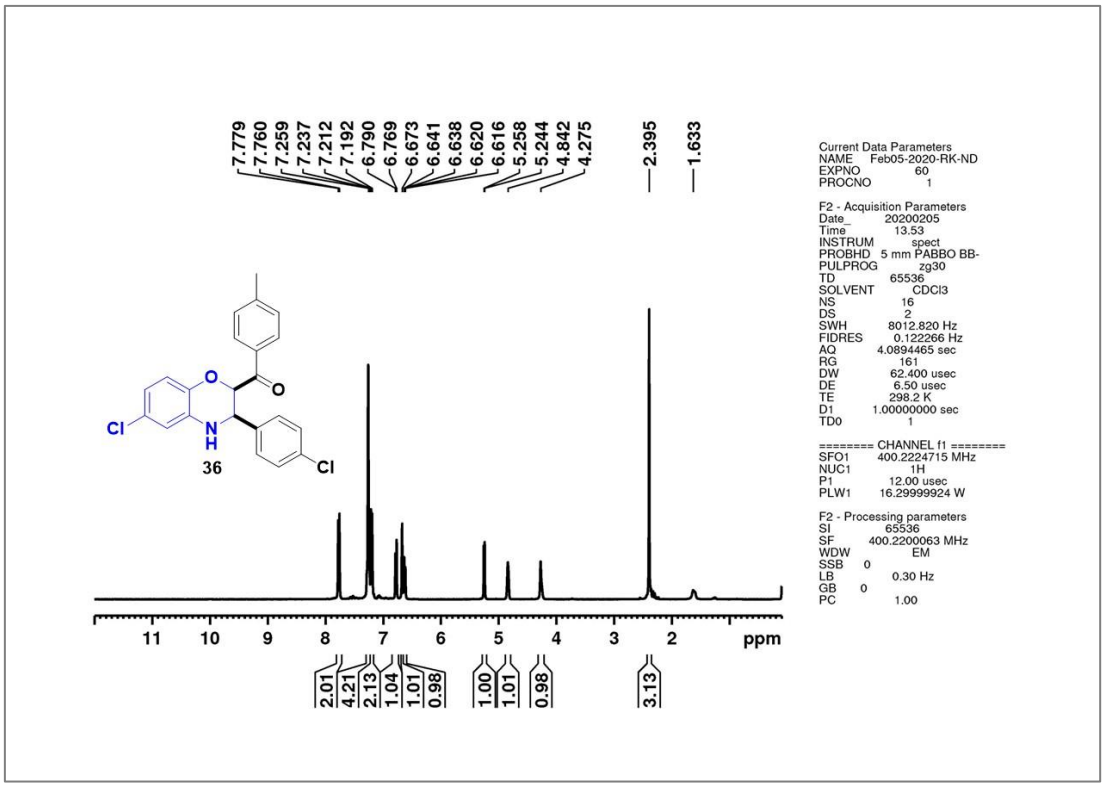
^{13}C{^{1}H} NMR spectrum of compound 35 (Chapter 2)



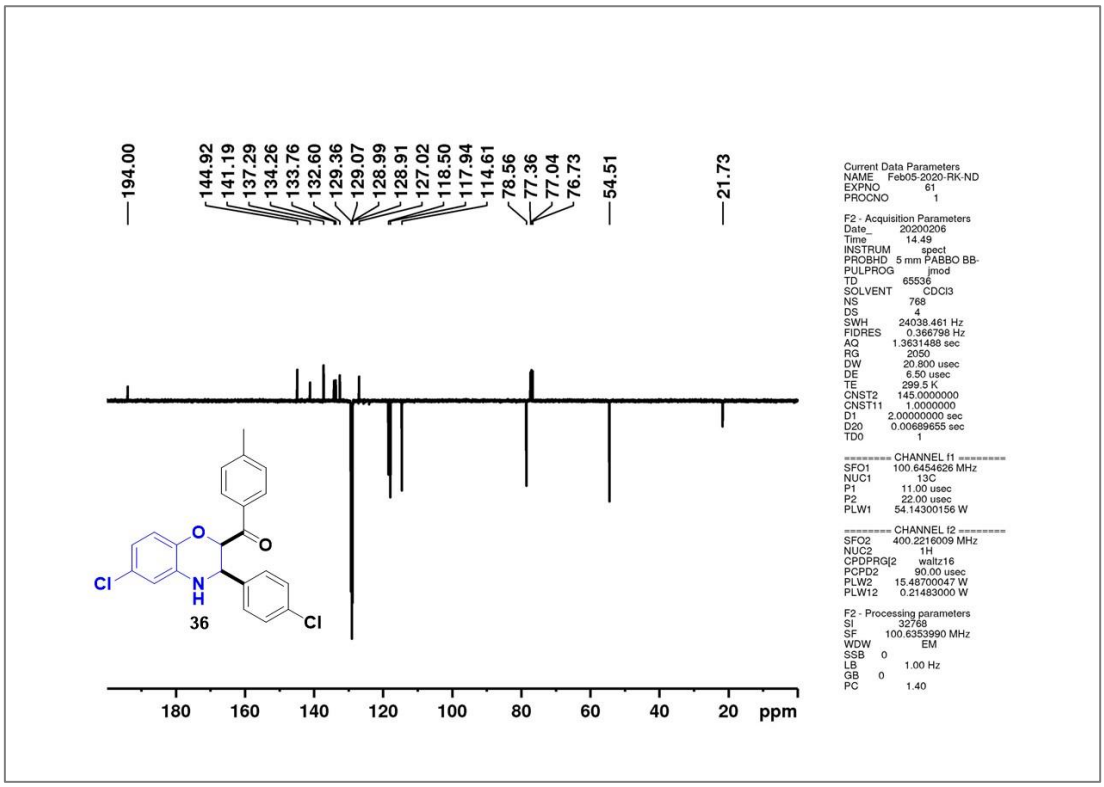
IR spectrum of compound 35 (Chapter 2)



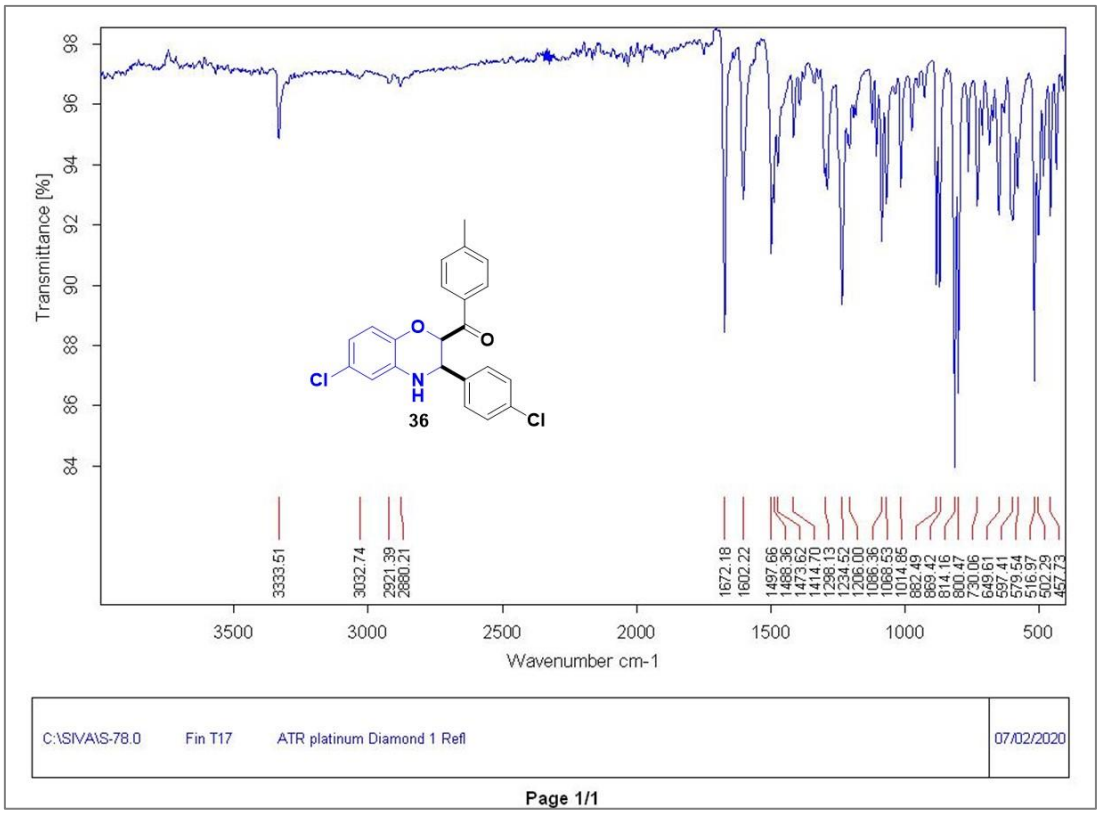
^{1}H NMR spectrum of crude compound 36 (Chapter 2)



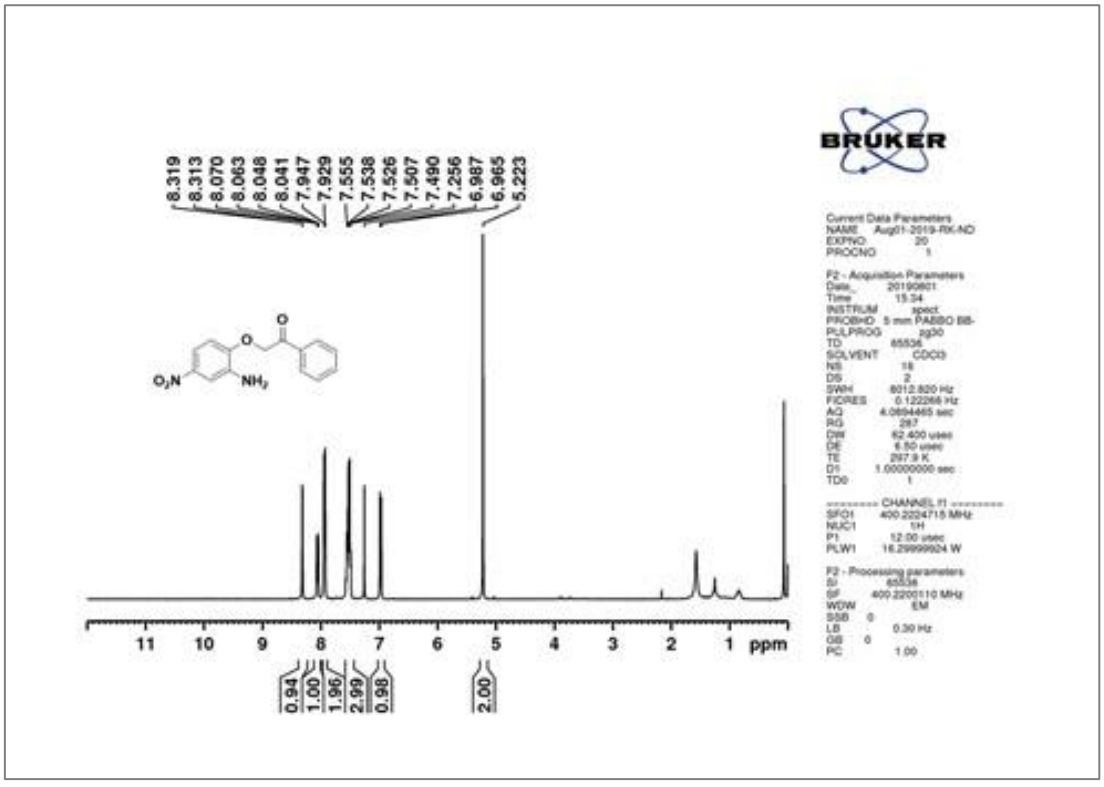
^{1}H NMR spectrum of compound 36 (Chapter 2)



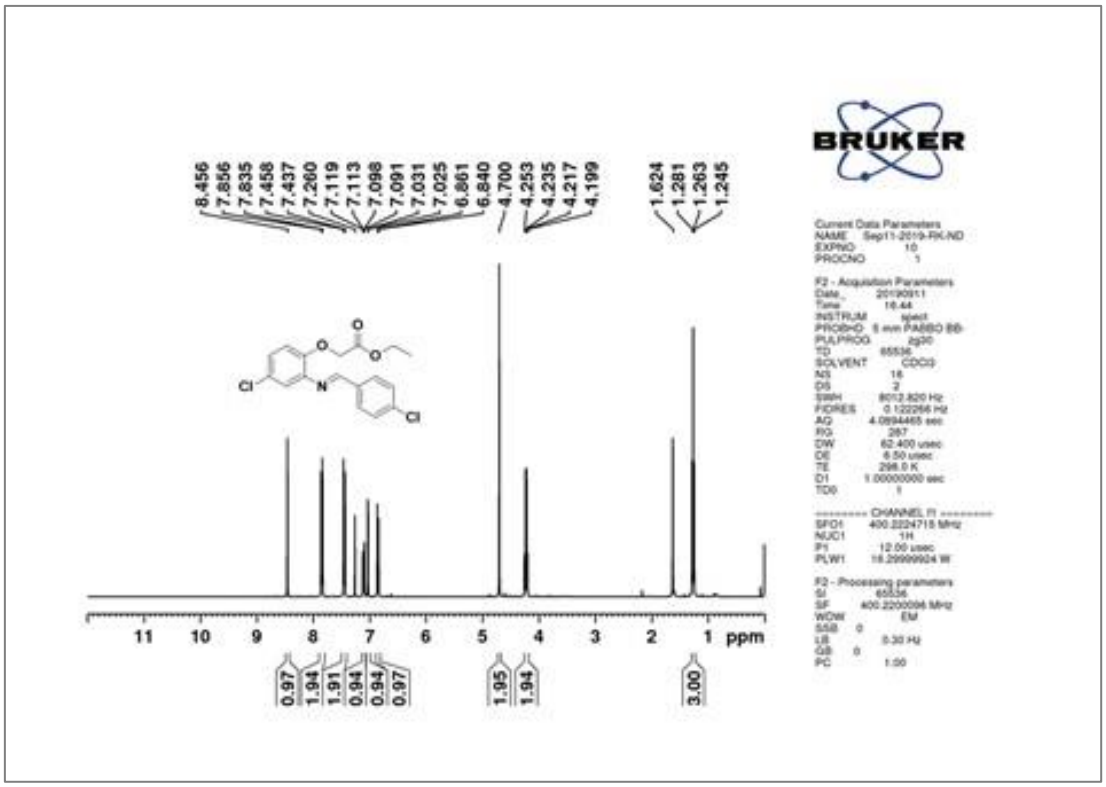
^{13}C{^{1}H} NMR spectrum of compound 36 (Chapter 2)



IR spectrum of compound 36 (Chapter 2)



^{1}H NMR spectrum of intermediate compound (with 2-amino-4-nitrophenol) (Chapter 2)



^{1}H NMR spectrum of intermediate compound (with ethyl α-bromoacetate) (Chapter 2)

Generic Display Report

Analysis Info

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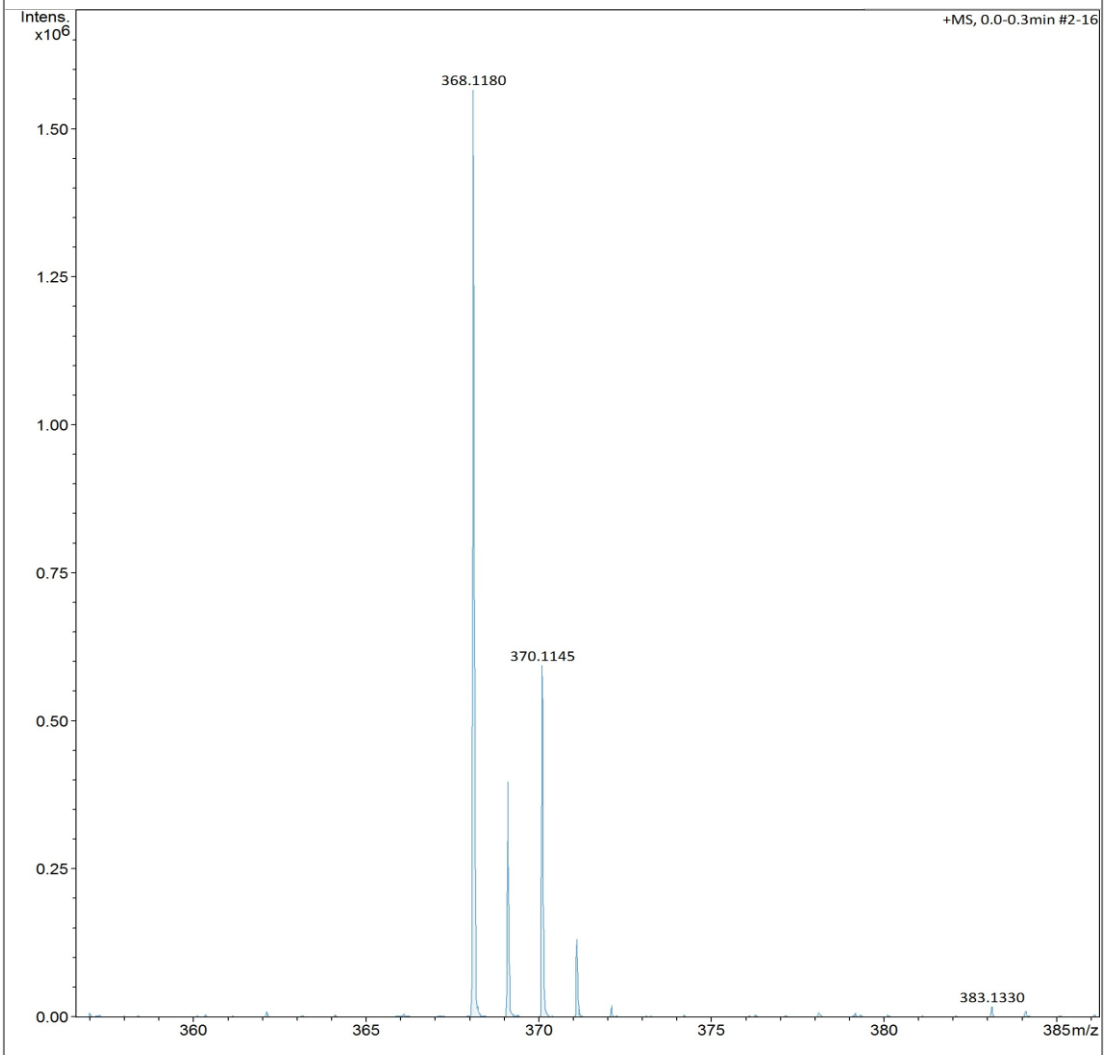
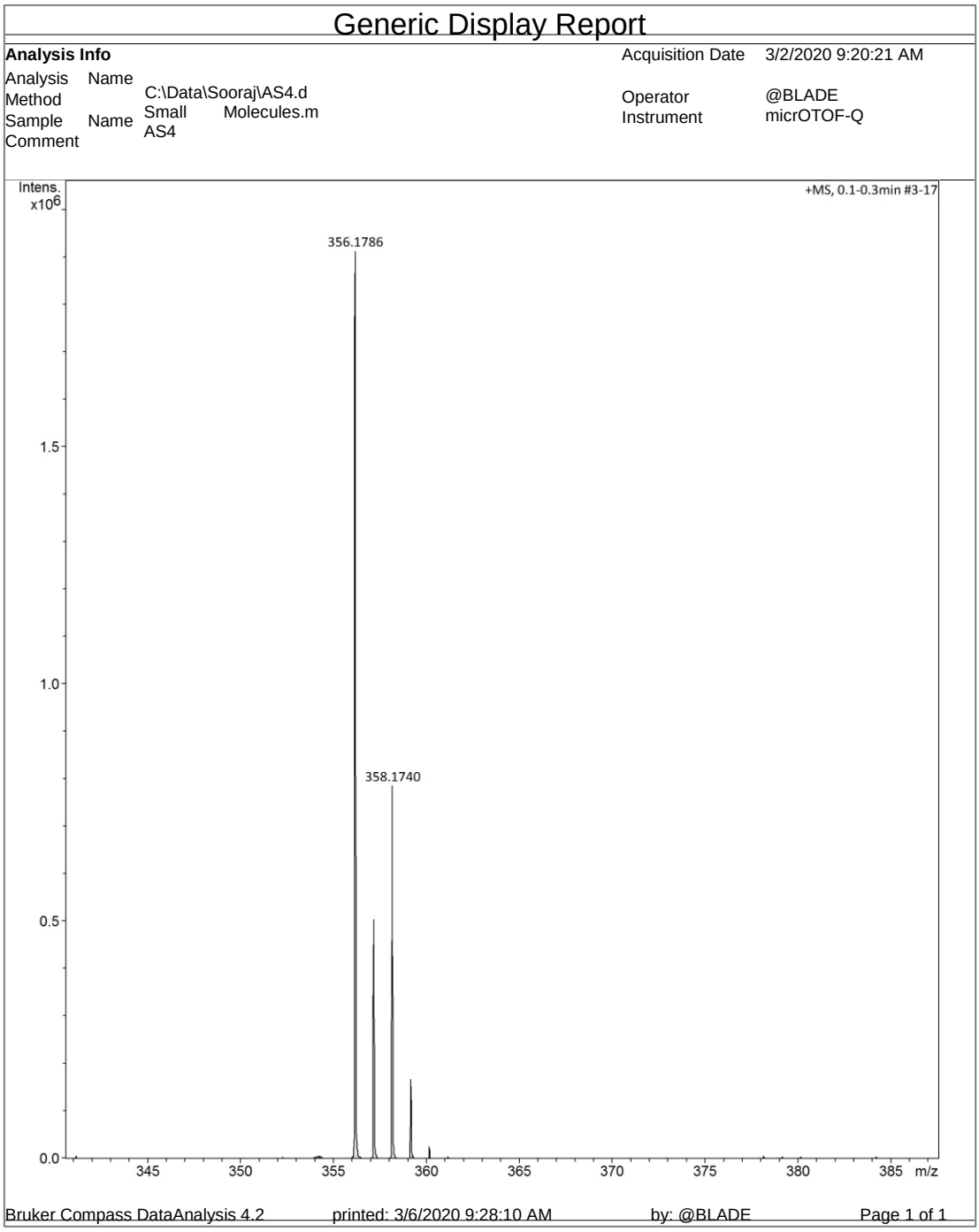
Sample Name	AS1	Instrument	micrOTOF-Q
Comment			

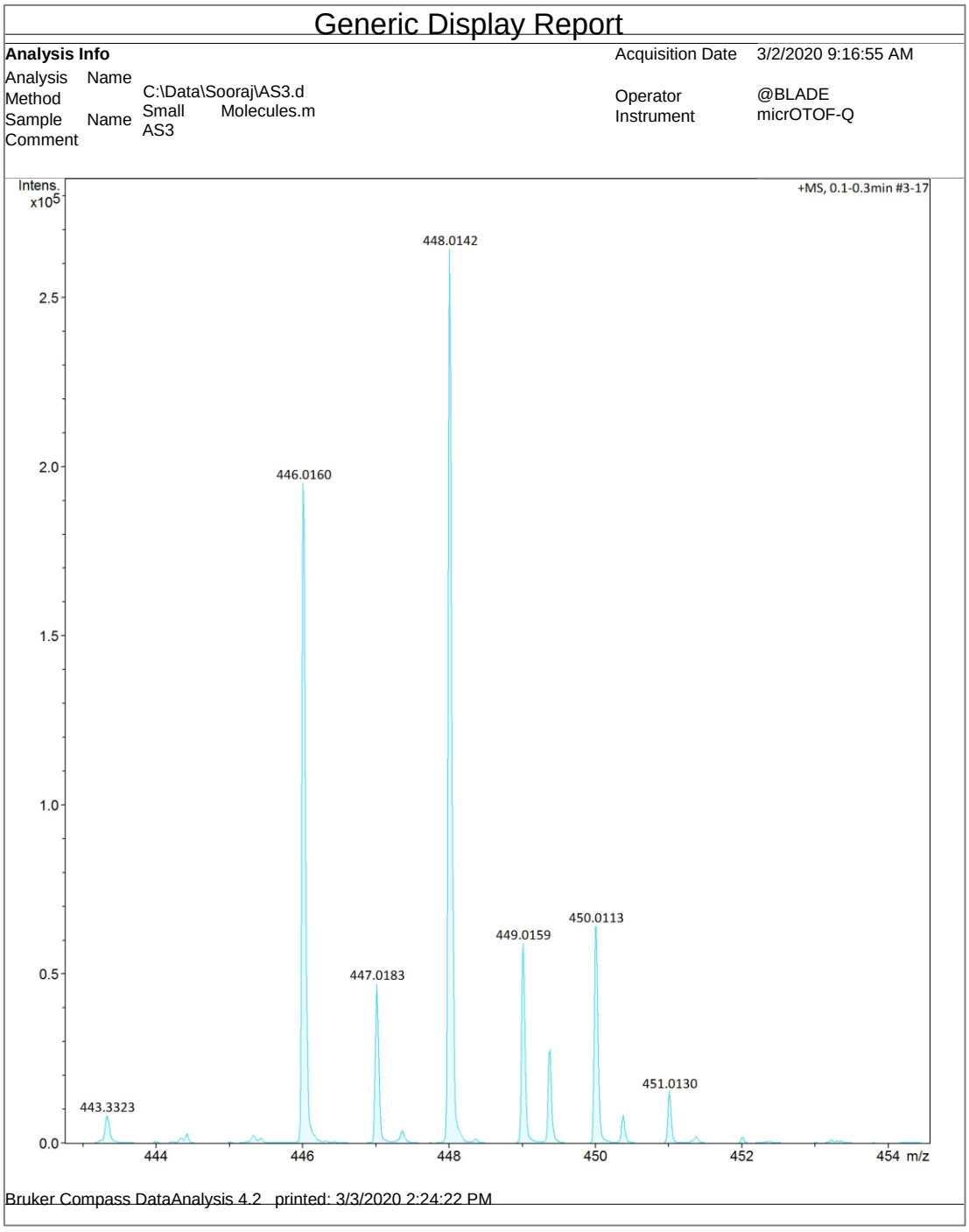


Bruker Compass DataAnalysis 4.2 printed: 3/6/2020 9:30:01 AM

HRMS spectrum of compound 13a (Chapter 2)



HRMS spectrum of compound 20 (Chapter 2)



HRMS spectrum of compound 30b (chapter 2)

Display Report

Analysis Info

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Method Small Molecules.m
Sample Name S_27
Comment

Acquisition Date 3/9/2020 11:22:59 AM

Operator @BLADE
Instrument micrOTOF-Q 228888.10139

Acquisition Parameter

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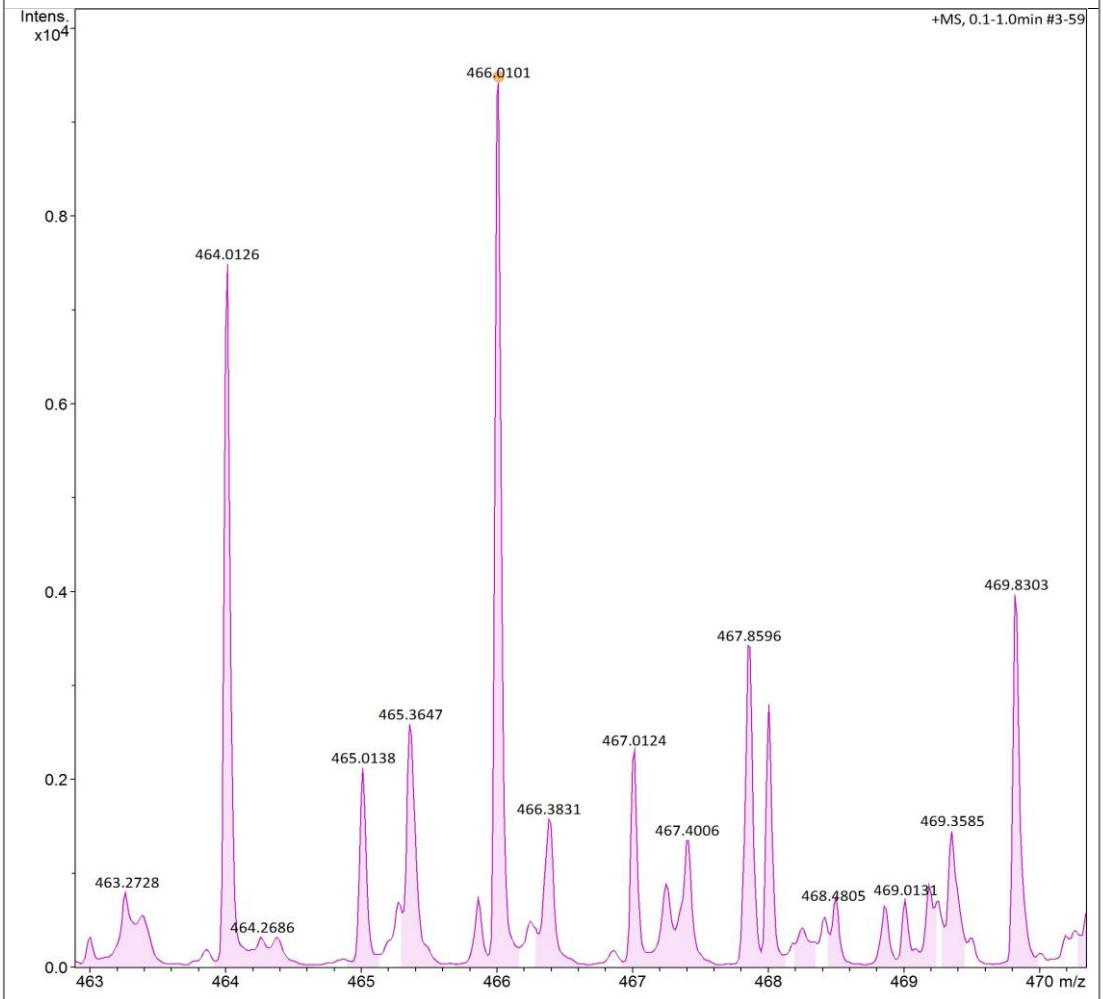

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HRMS spectrum of compound 32 (Chapter 2)

Document: BATCH 8 151019 (VarioELcube) from: 2019/10/16 09:51

INSTALLATION TEST - 25_03_2019
varioELcube serial
number: 19181072

Text report

No.	Name	Manuscript compound ID	N [%]	C [%]	H [%]	S [%]
1	s 14 02	9a	3.66	64.20	3.882	0.000
2	S22	9b	3.71	65.49	3.973	0.033
3	S10	8	3.40	67.54	5.120	0.000
4	S12	4	3.60	67.16	4.900	0.000
5	S13	10	3.35	58.75	3.487	0.000
6	S 1 D1	11a	3.72	69.63	4.947	0.000
7	S 1D2	11b	3.77	69.35	4.940	0.000
8	S 15	12	7.11	63.18	3.729	0.000
9	S46	14	3.73	68.66	4.711	0.000
10	S47	15	3.92	72.22	5.185	0.000
11	S48	16	7.32	63.31	3.790	0.000
12	S 49 D1	17	7.08	63.47	3.796	0.000
13	S50	18	4.42	70.97	4.431	0.000
14	S 56	19	4.02	63.34	3.923	8.737
15	S 66	5	3.30	57.75	3.511	0.000
16	S 28	23	3.57	56.13	3.656	0.000
17	S 29	24	3.08	56.30	3.929	0.000
18	S 30	25	2.81	49.17	2.773	0.000
19	S 23	26	2.99	52.80	2.994	0.000
20	S 51	27	3.13	56.72	3.709	0.000
21	S 52	31	3.43	59.55	3.942	0.000
22	S 55	28	3.30	52.68	3.091	0.000
23	S 57	29	3.56	52.24	2.961	6.896

Document: 2020 batch 8 02032020 (VarioELcube) from: --.--.-- (modified)

INSTALLATION TEST - 25_03_2019
varioELcube serial
number: 19181072

Text report

No.	Name	Manuscript compound ID	N [%]	C [%]	H [%]	S [%]
1	S_72	21	3.66	74.11	6.017	0.048
2	S_73	22	3.97	71.64	5.145	0.072
3	S_78	33	3.42	66.68	4.479	0.021
4	S_79	34	3.37	59.62	3.356	0.005
5	S_80	35	3.46	63.36	4.062	0.006
6	S_72(2)	21	3.67	74.30	6.010	0.000
7	S_73(2)	22	3.96	71.74	5.146	0.034
8	S_78(2)	33	3.42	66.86	4.503	0.009
9	S_79(2)	34	3.36	59.58	3.324	0.000
10	S_80(2)	35	3.46	63.38	4.033	0.000

Name: eassuperuser, Access: varioELcube superuser Mon Mar 2 11:22:57 2020

varioEL cube V4.0.16 (366251fb2)2018-07-25, CHNS Mode, Ser. No.: 19181072 Elementar Analysensysteme GmbH

Page 1 (of 1)

Document: 2020 batch 9 04032020 (VarioELcube) from: 2020/03/04 16:05

INSTALLATION TEST - 25_03_2019
varioELcube serial
number: 19181072

Text report

No.	Name	Manuscript compound ID	N [%]	C [%]	H [%]	S [%]
1	S_7	6	3.73	66.52	4.545	0.499
2	S_16_D2	13b	3.80	66.97	3.982	0.050
3	S_34_D1	30a	3.01	56.63	3.186	0.015
4	S_9_D1	7	3.16	61.96	3.547	1.354
5	S_7b	6	3.77	68.66	4.806	11.142
6	S_16_D2b	13b	3.73	67.20	3.863	1.778
7	S_34_d1b	30a	3.00	56.36	3.064	1.715

Name: eassuperuser, Access: varioELcube superuser Wed Mar 4 16:07:38 2020

varioEL cube V4.0.16 (366251fb2)2018-07-25, CHNS Mode, Ser. No.: 19181072 Elementar Analysensysteme GmbH

Page 1 (of 1)

Document: oxygen batch 3 06/11/19 (VarioELcube) from: 2019/11/13 09:47

INSTALLATION TEST - 25_03_2019
varioELcube serial
number: 19181072

Text report

No.	Name	Manuscript compound ID	O [%]
1	S10	8	19.477
2	S12	4	18.675
3	S13	10	10.870
4	S15	12	18.632
5	S22	9b	12.996
6	S23	26	10.781
7	S28	23	14.189
8	S29	24	15.433
9	S30	25	9.294
10	S46	14	15.160
11	S47	15	11.319

Name: eassuperuser, Access: varioELcube superuser Fri Nov 15 13:11:57 2019

varioEL cube V4.0.16 (366251fb2)2018-07-25, O Mode, Ser. No.: 19181072
Elementar Analysensysteme GmbH

Document: oxygen batch 4 13/11/19 (VarioELcube) from: 2019/11/13 14:43

INSTALLATION TEST - 25_03_2019
varioELcube serial
number: 19181072

Text report

No.	Name	Manuscript compound ID	O [%]
1	S48	16	17.988
2	S50	18	16.539
3	S51	27	12.767
4	S52	31	9.528
5	S55	28	14.047
6	S56	19	11.588
7	S57	29	9.910
8	S66	5	9.709
9	S_1_D1	11a	14.368
10	S_1_D2	11b	14.079
11	S_14_D2	9a	10.580
12	S_49_D1	17	16.767

Name: eassuperuser, Access: varioELcube superuser Fri Nov 15 13:12:55 2019

varioEL cube V4.0.16 (366251fb2)2018-07-25, O Mode, Ser. No.: 19181072 Elementar Analysensysteme GmbH

Page 1 (of 1)

Document: oxygen batch 2 12/03/20 (VarioELcube) from: 2020/03/12 16:48

INSTALLATION TEST - 25_03_2019
varioELcube
serial number: 19181072
Text report

No.	Name	Manuscript compound ID	O [%]	Date Time
1	s73a	22	10.169	2020/03/12 13:04
2	S72A	21	16.737	2020/03/12 13:15
3	S78A	33	9.445	2020/03/12 13:27
4	S79A	34	8.387	2020/03/12 13:38
5	S80A	35	12.090	2020/03/12 13:50
6	S7A	6	11.026	2020/03/12 14:01
7	S16A	13b	10.885	2020/03/12 14:15
8	S34D1A	30a	8.409	2020/03/12 14:27
9	S73B	22	9.790	2020/03/12 14:39
10	S7B	6	10.918	2020/03/12 14:51
11	S9D1A	7	14.119	2020/03/12 15:02
12	S9D1B	7	14.303	2020/03/12 15:14
13	S78B	33	8.990	2020/03/12 15:25
14	S79B	34	8.336	2020/03/12 15:37
15	S16B	13b	10.735	2020/03/12 15:48
16	S34D1B	30a	8.324	2020/03/12 16:00
17	S73C	22	9.728	2020/03/12 16:11
18	S78C	33	8.639	2020/03/12 16:23
19	S79C	34	8.264	2020/03/12 16:43

Parameter report

Temperatures		
	Pyrol. tube	1170
	CO col.standby	40
	Desorpt.Mid.	40
	Cool temp.	60
Time values		

Elemental analysis report

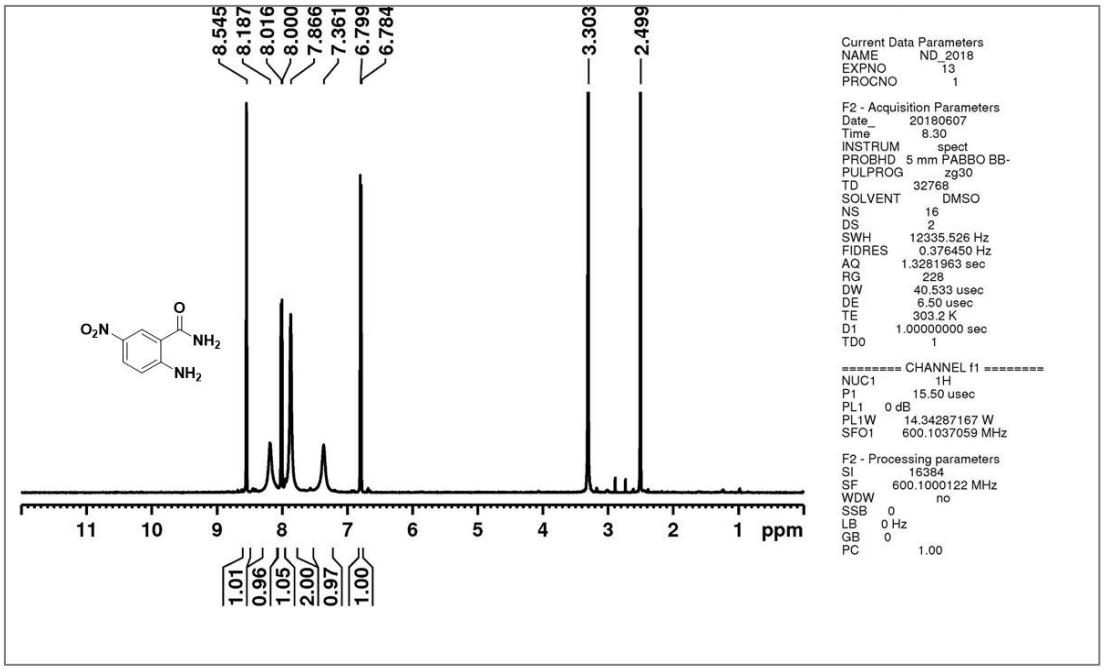
APPENDIX – II

SUPPLEMENTARY INFORMATION

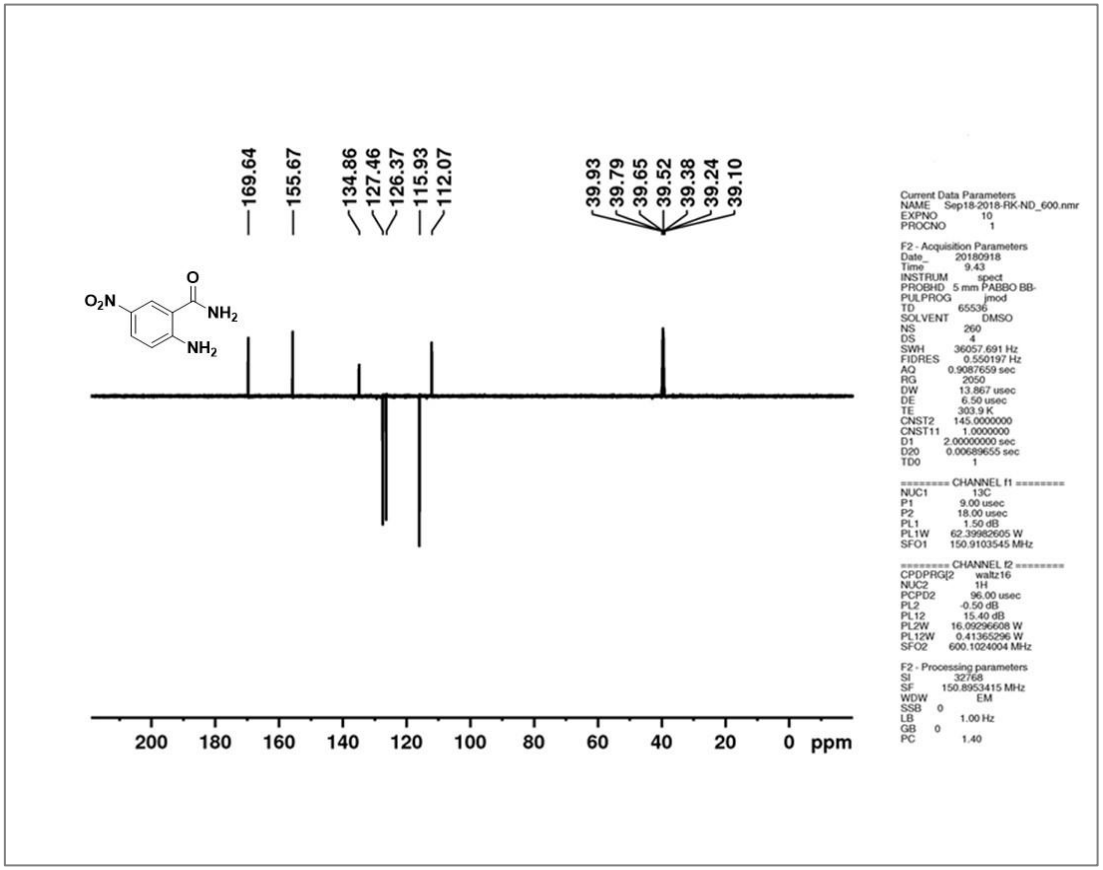
CHAPTER 3

Synthesis, Crystal structure, spectroscopic and photophysical studies of novel fluorinated quinazoline derivatives

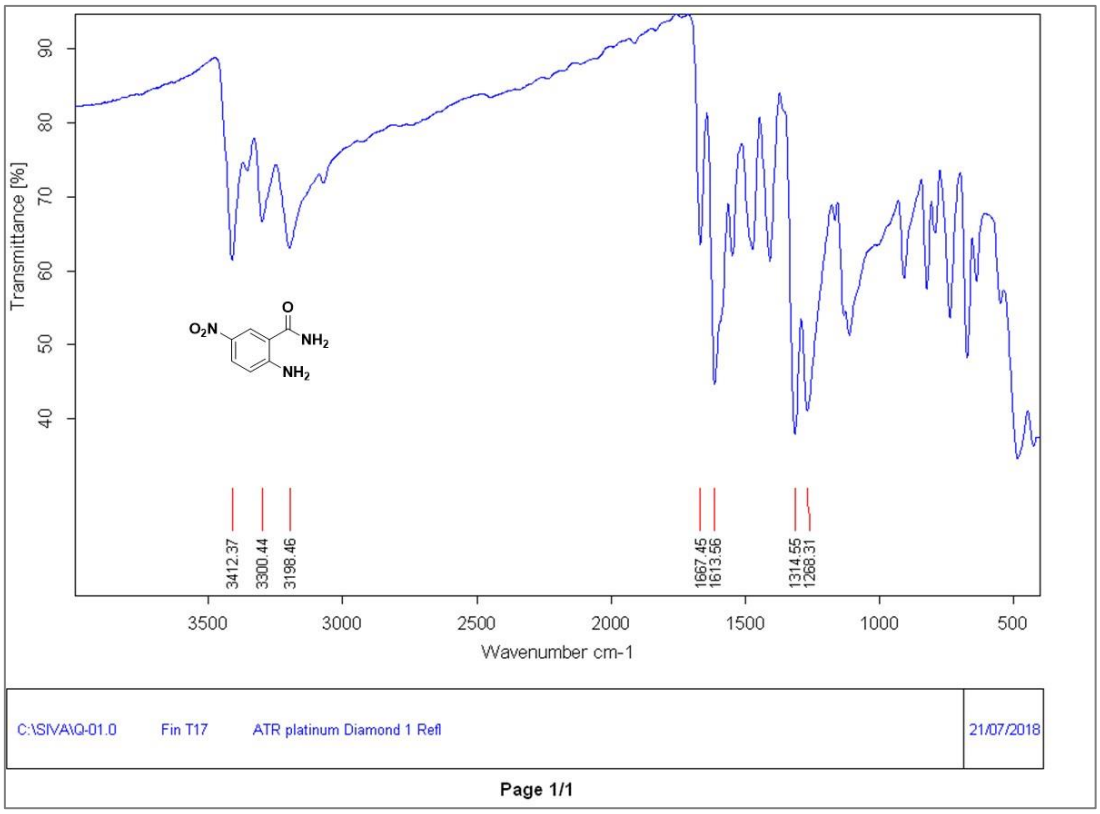
Department of Pharmaceutical Chemistry, Discipline of Pharmaceutical Sciences, College of Health Sciences, University of KwaZulu-Natal (Westville), Durban-4000, South Africa



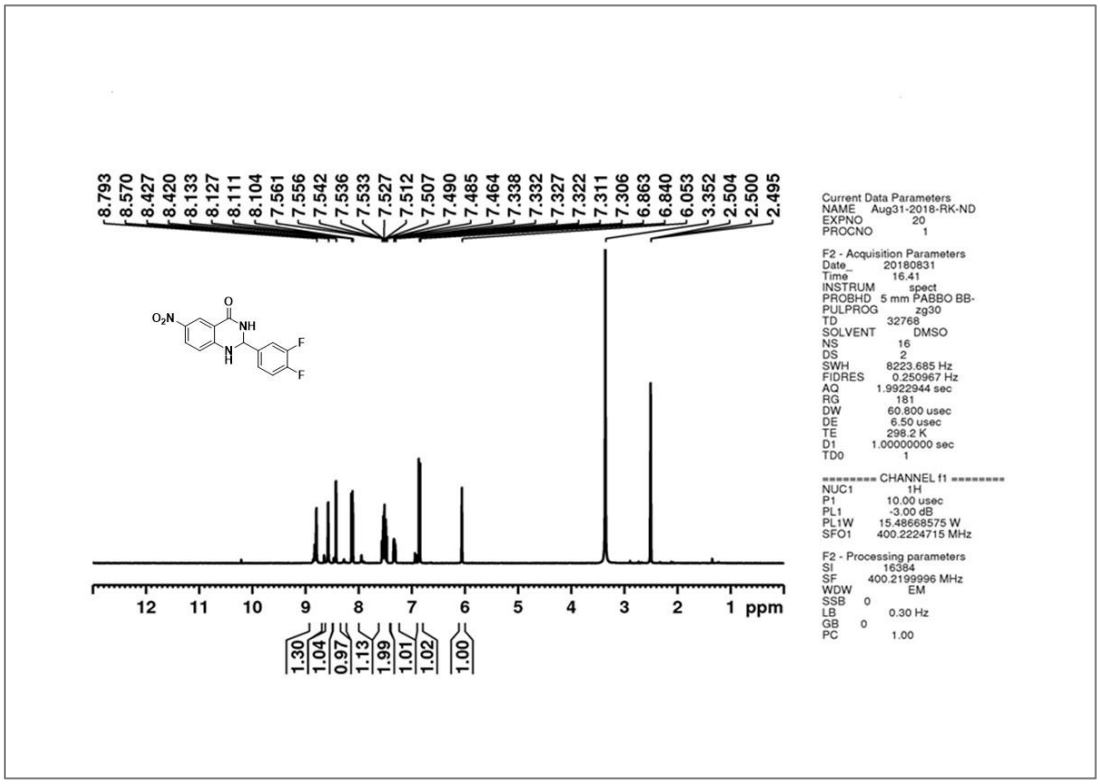
^{1}H NMR spectrum of compound 2 (Chapter 3)



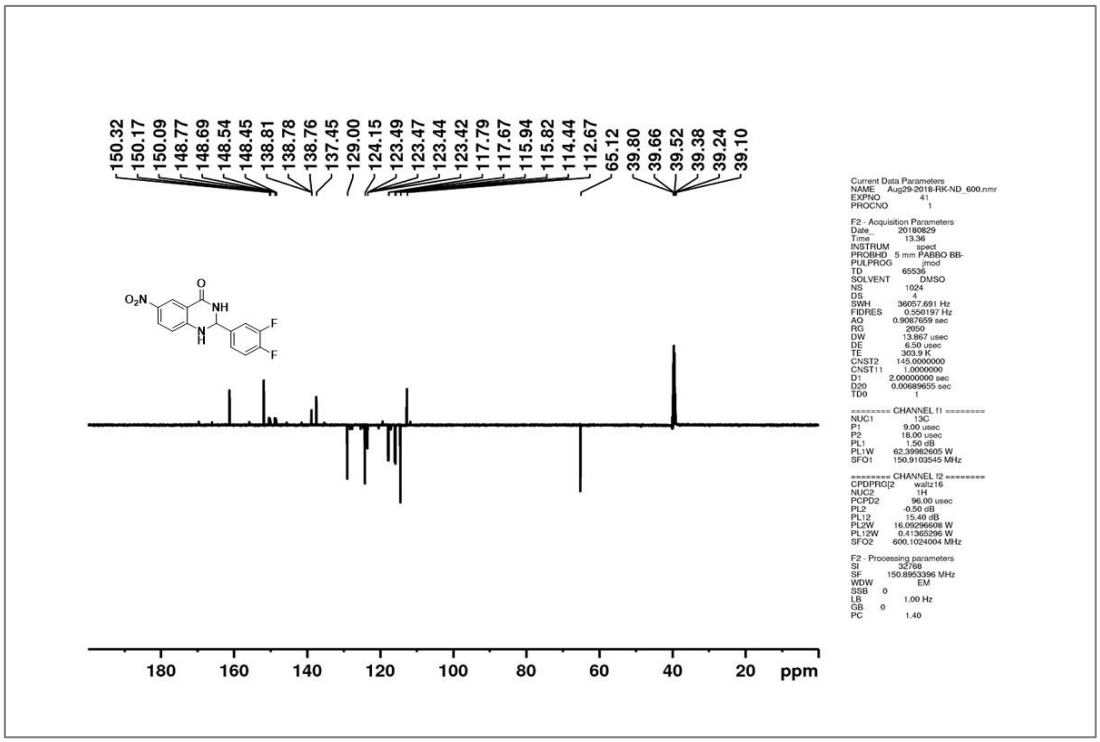
^{13}C NMR spectrum of compound 2 (Chapter 3)



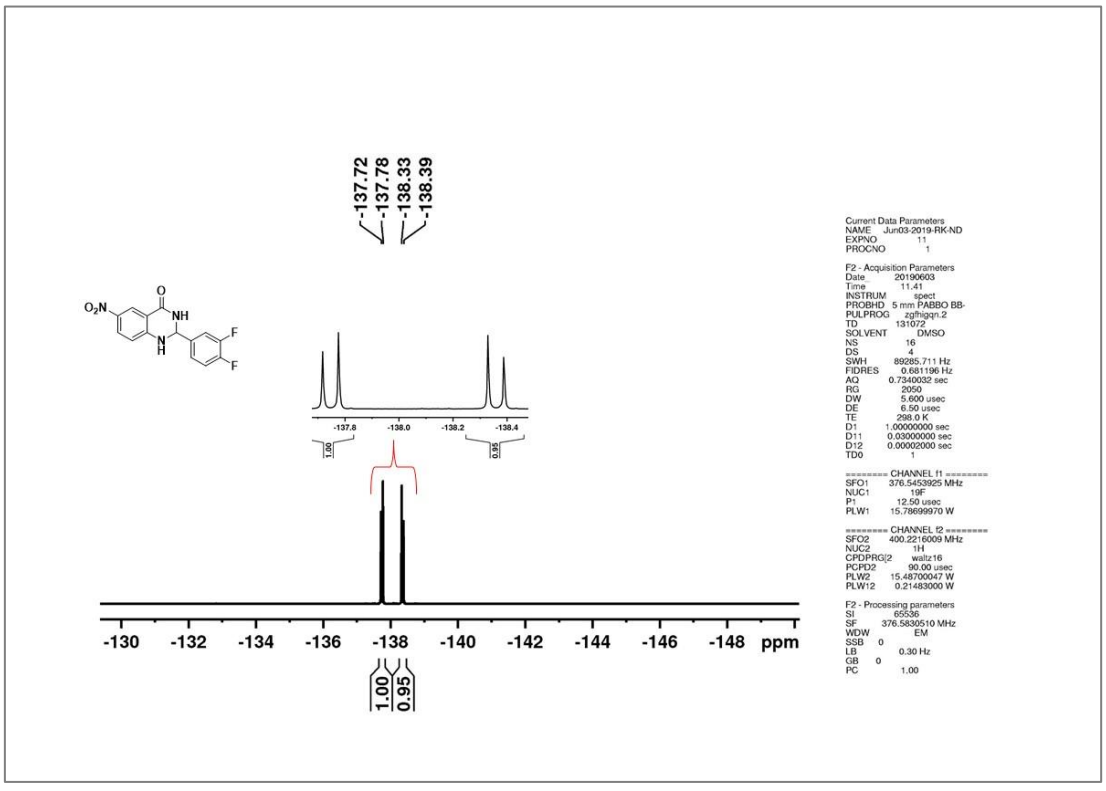
IR spectrum of compound 2 (Chapter 3



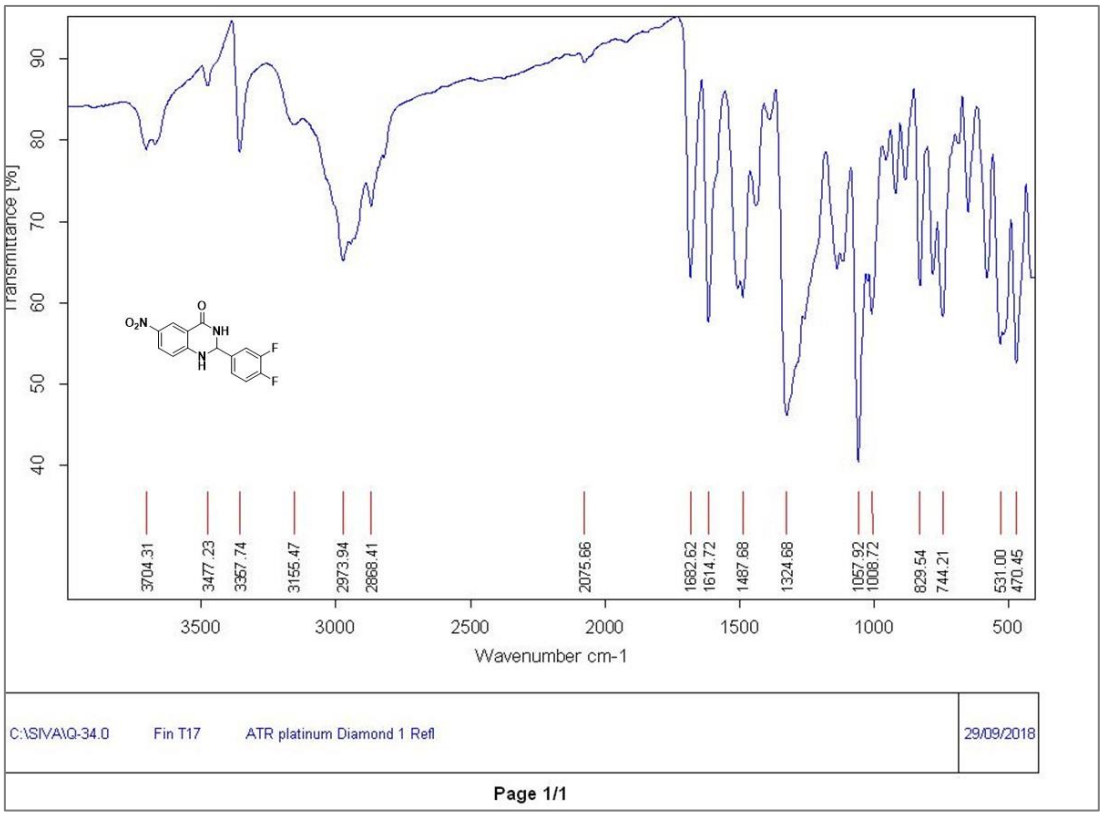
^{1}H NMR spectrum of compound 4 (Chapter 3)



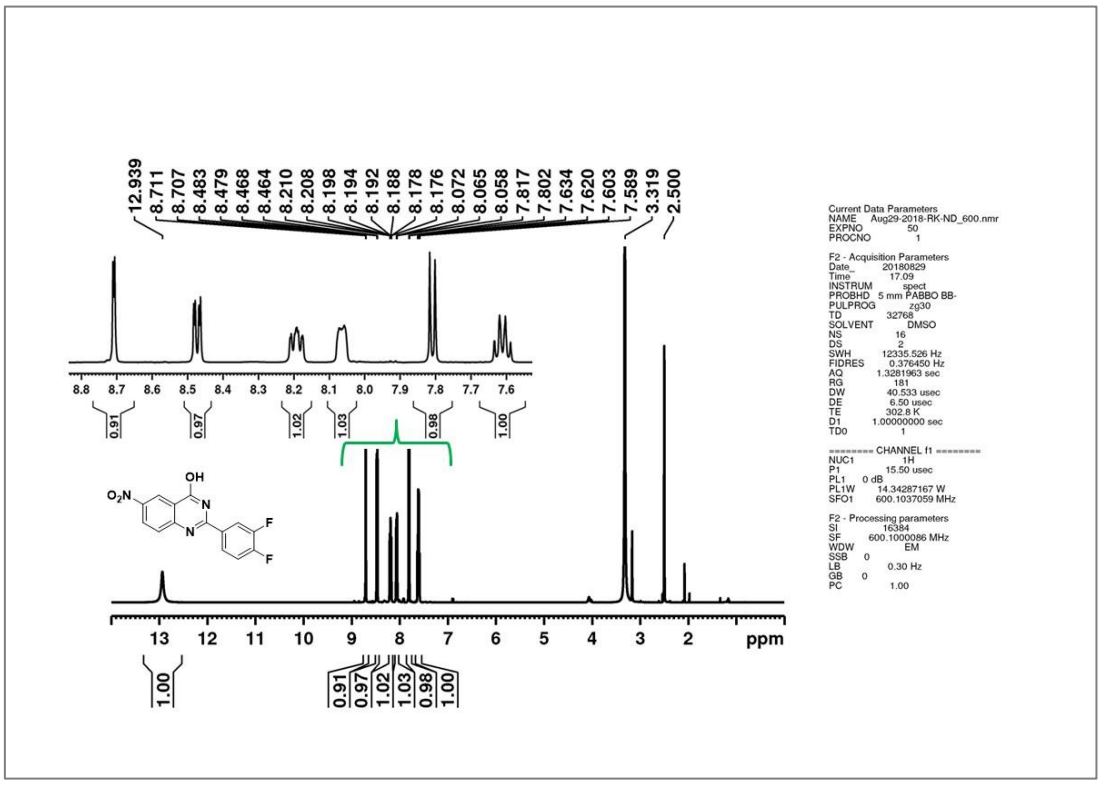
^{13}C NMR spectrum of compound 4 (Chapter 3)



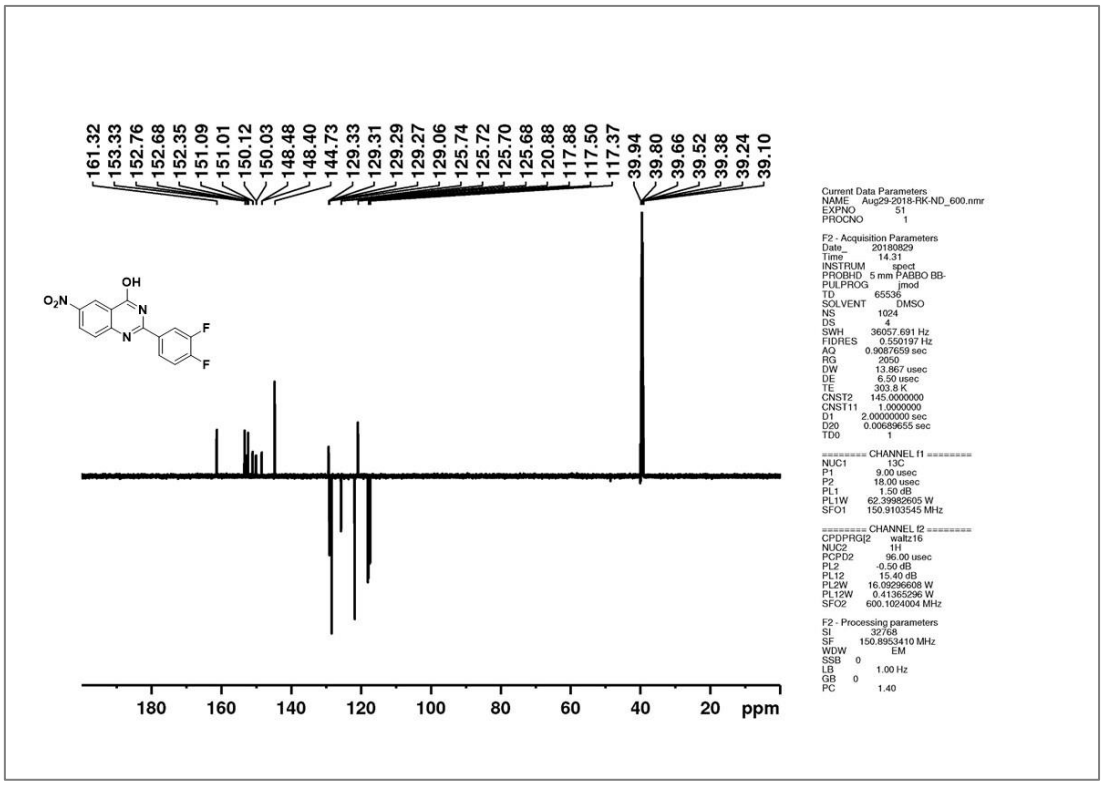
^{19}F NMR spectrum of compound 4 (Chapter 3)



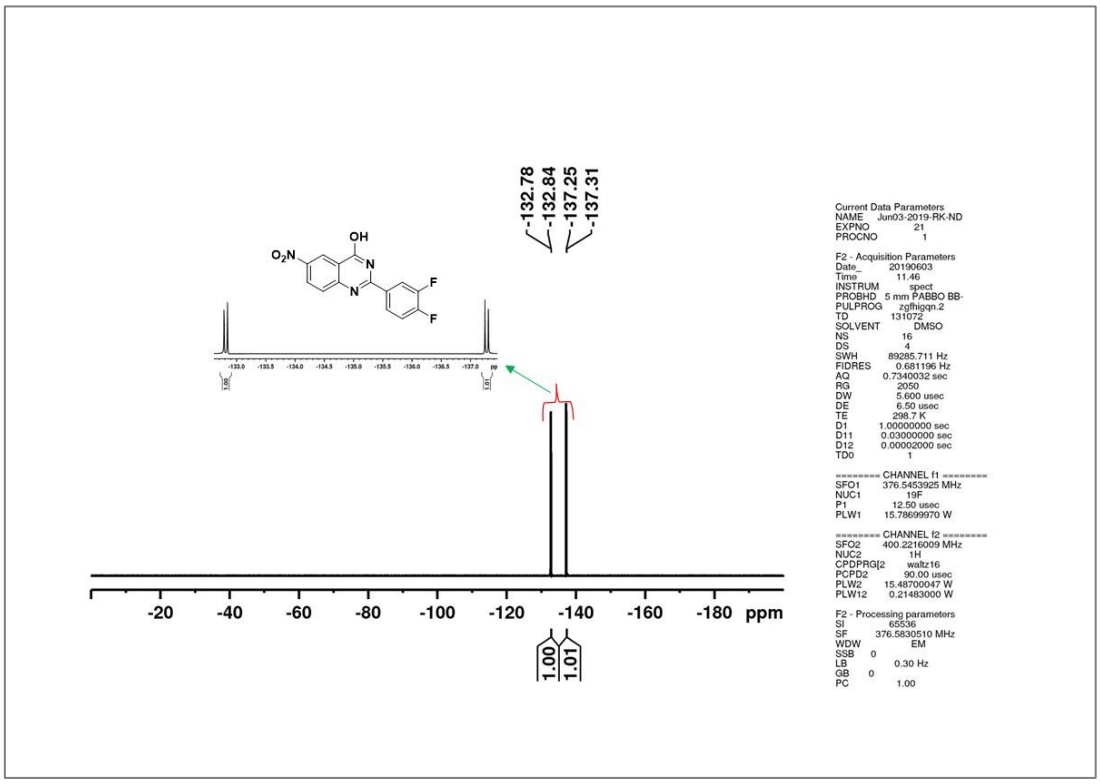
IR spectrum of compound 4 (Chapter 3



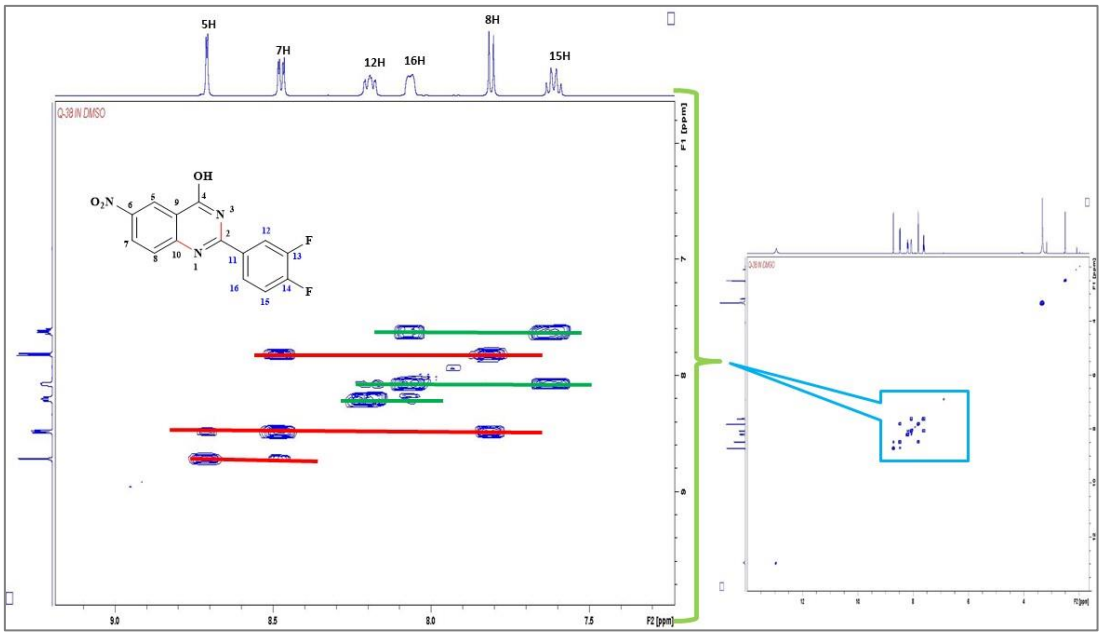
^{1}H NMR spectrum of compound 5 (Chapter 3)



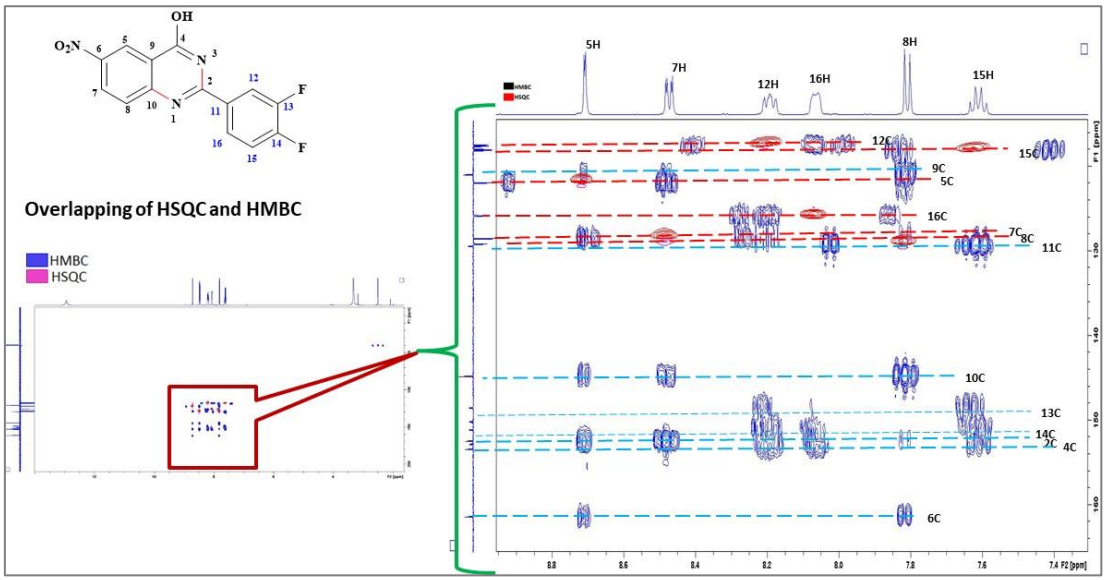
^{13}C NMR spectrum of compound 5 (Chapter 3)



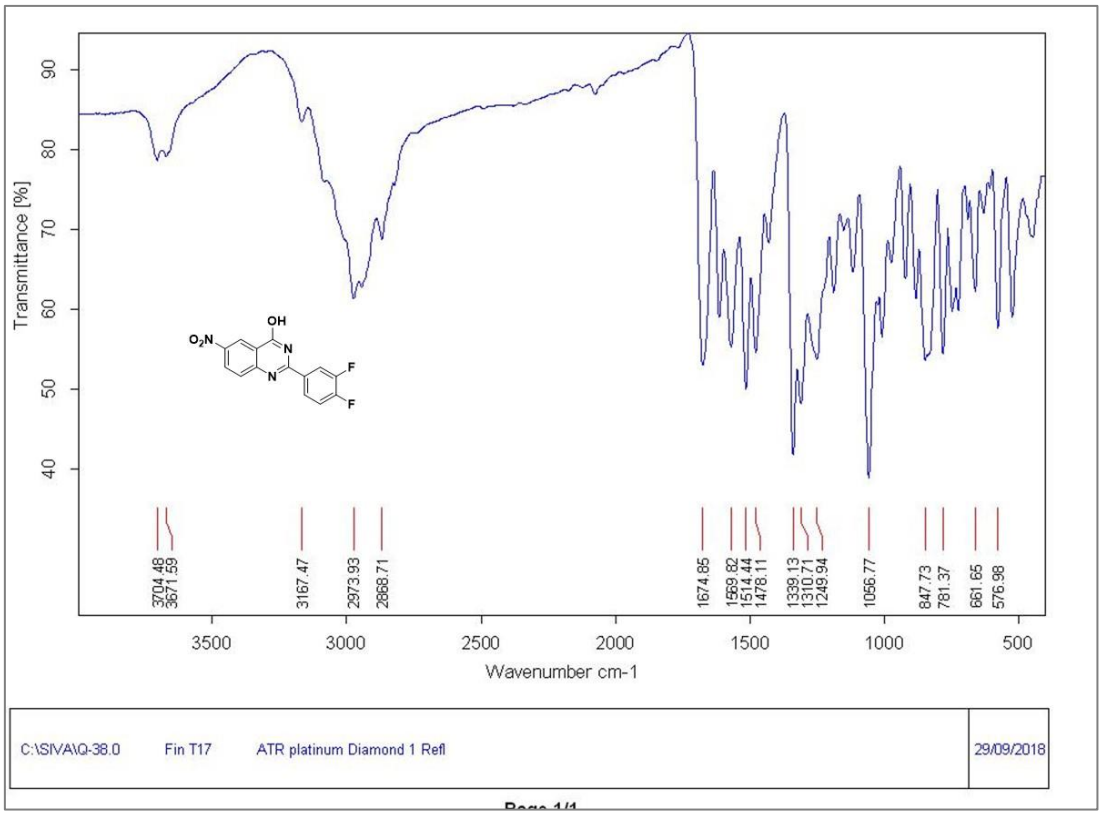
^{19}F NMR spectrum of compound 5 (Chapter 3)



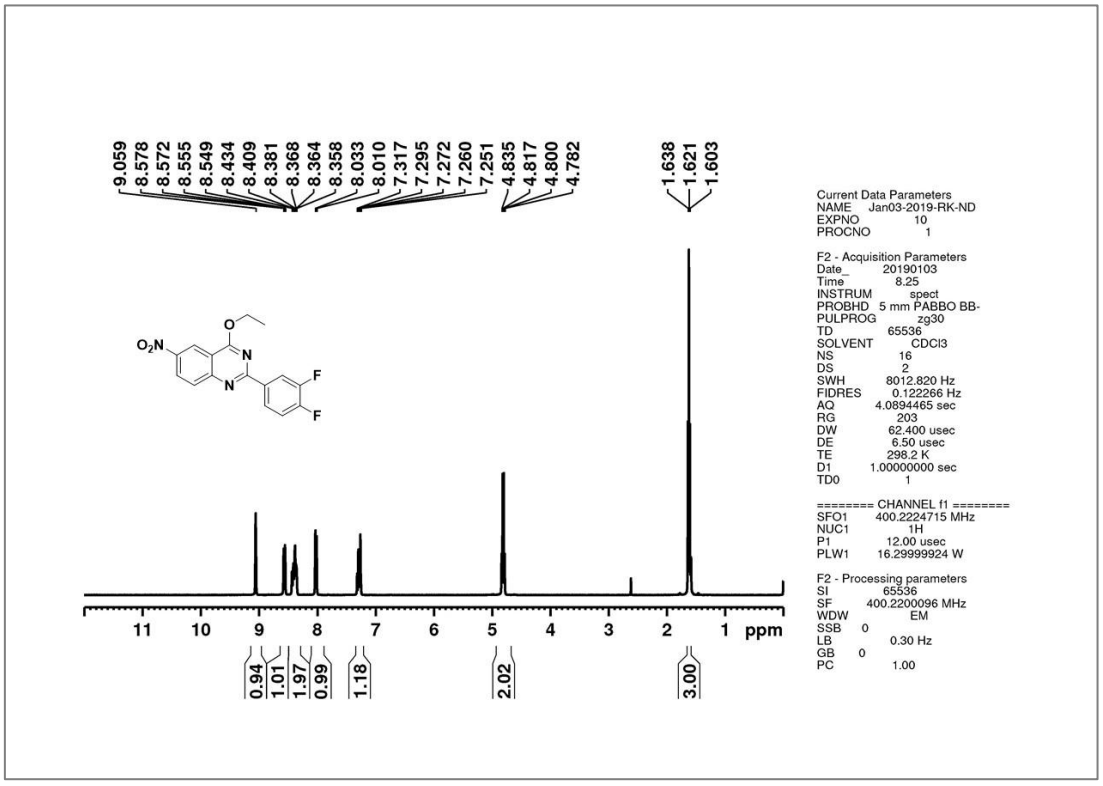
Cosy spectrum of compound 5 (Chapter 3)



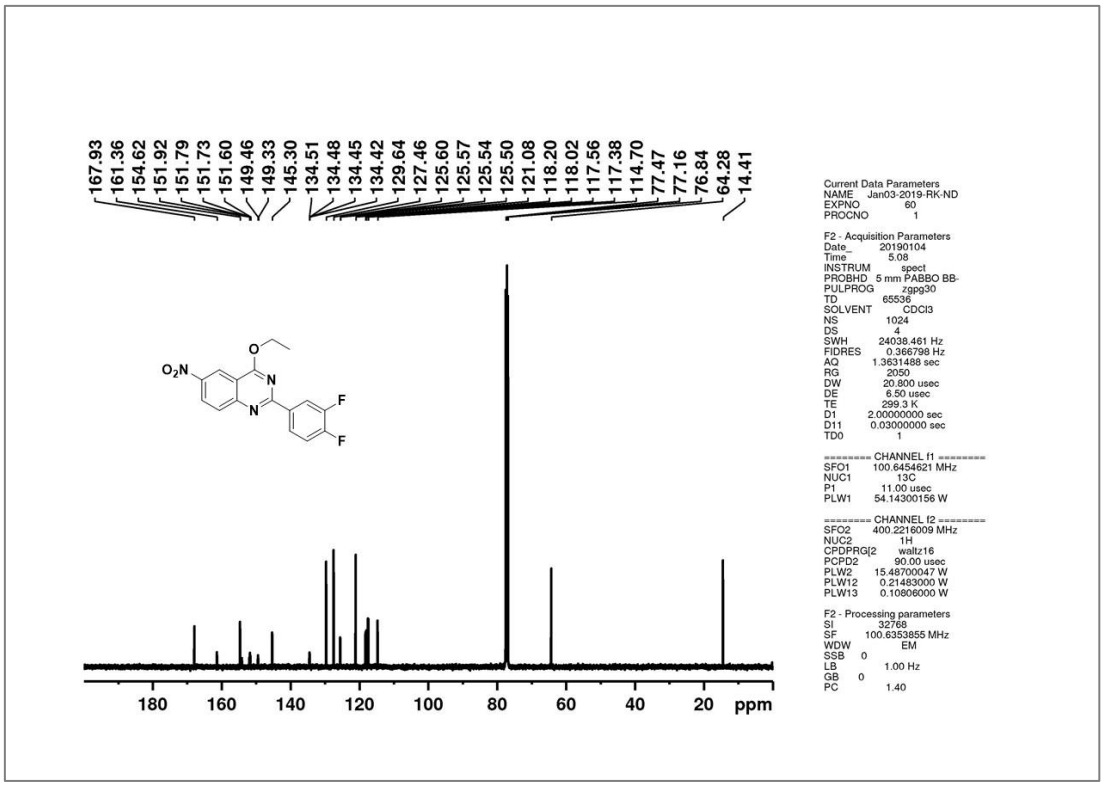
HMBC & HSQC spectrum of compound 5 (Chapter 3)



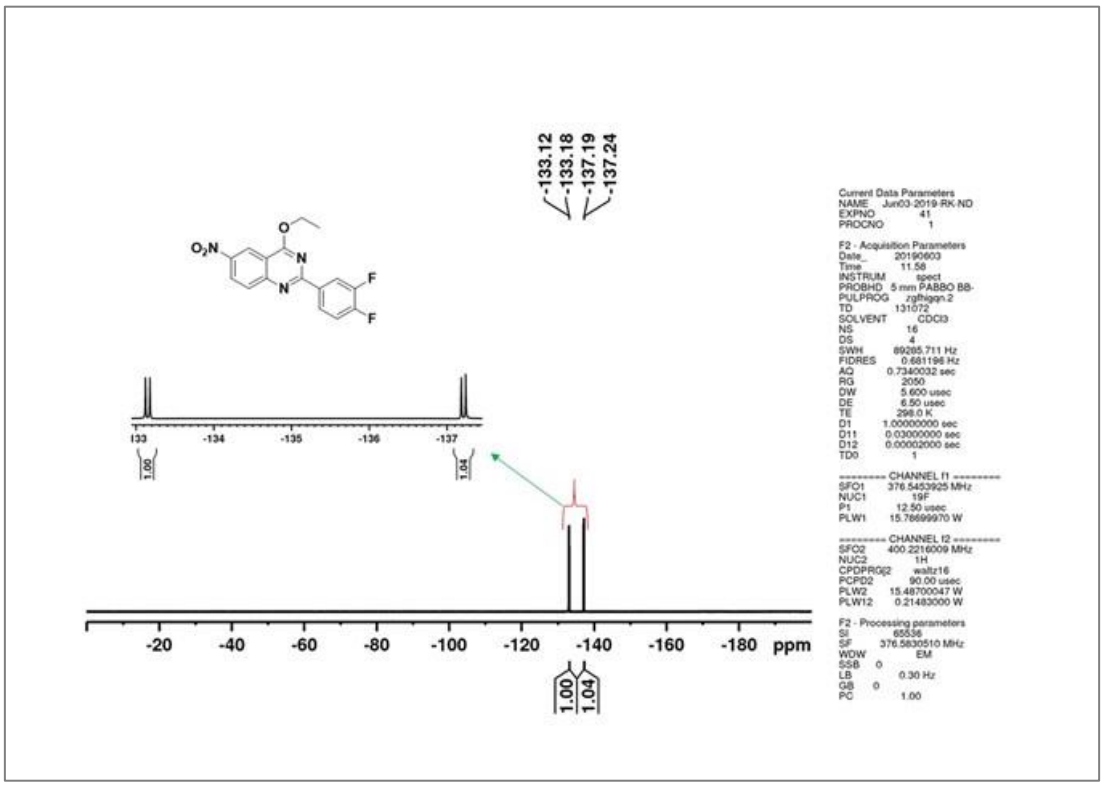
IR spectrum of compound 5 (Chapter 3)



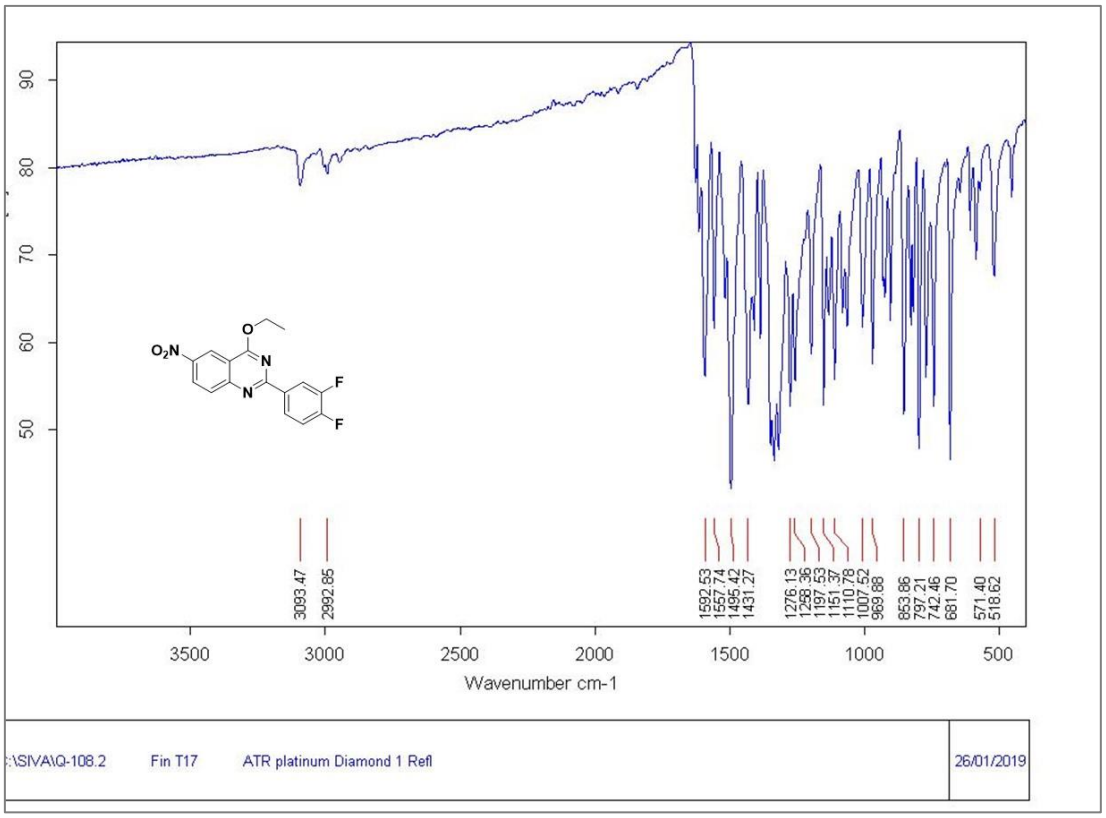
^{1}H NMR spectrum of compound 7 (Chapter 3)



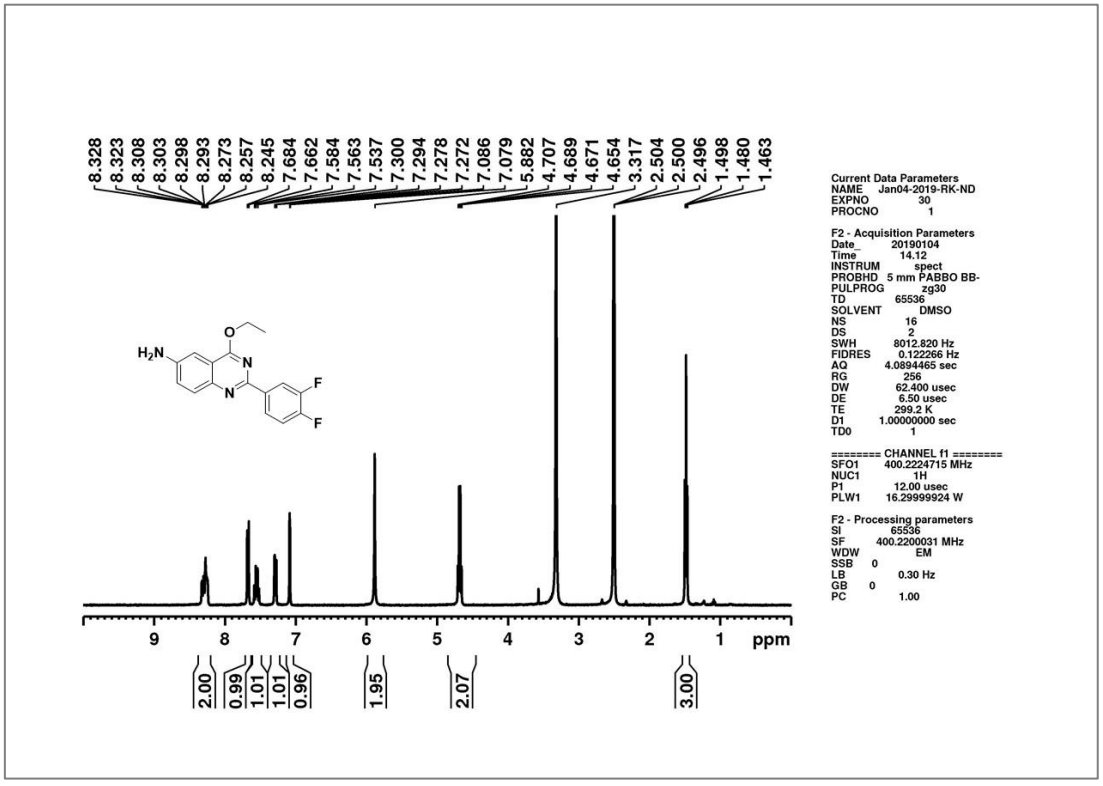
^{13}C NMR spectrum of compound 7 (Chapter 3)



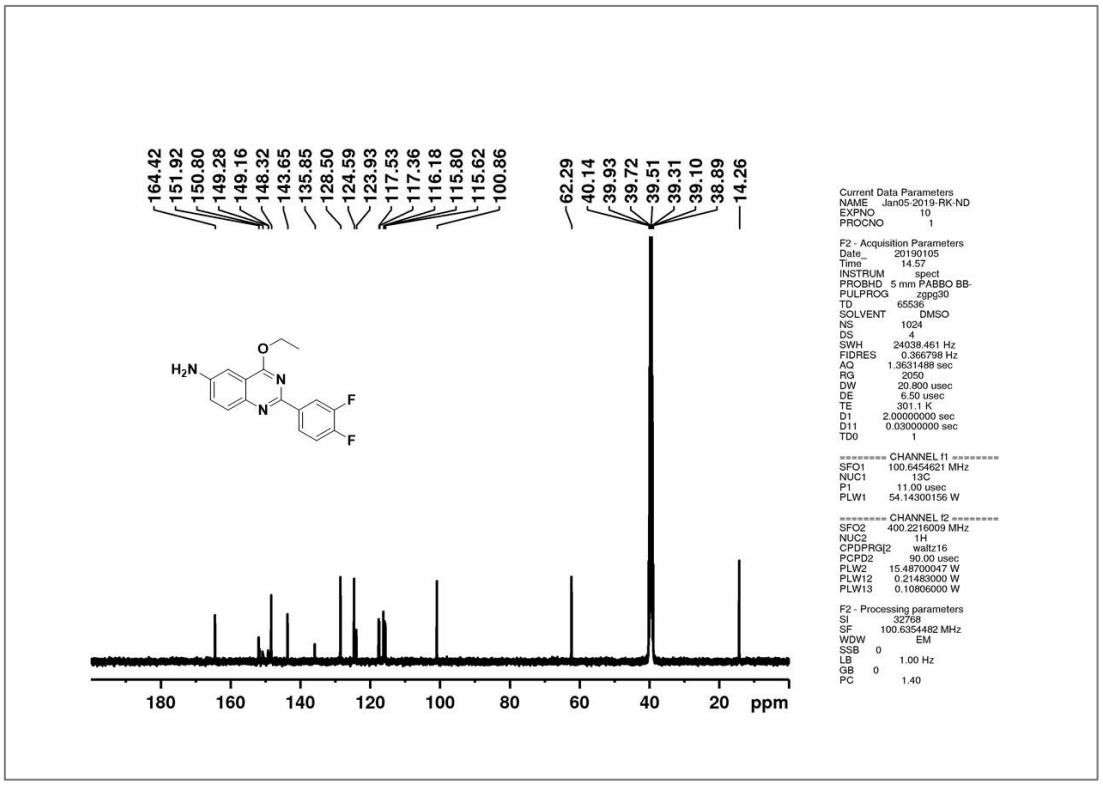
^{19}F NMR spectrum of compound 7 (Chapter 3)



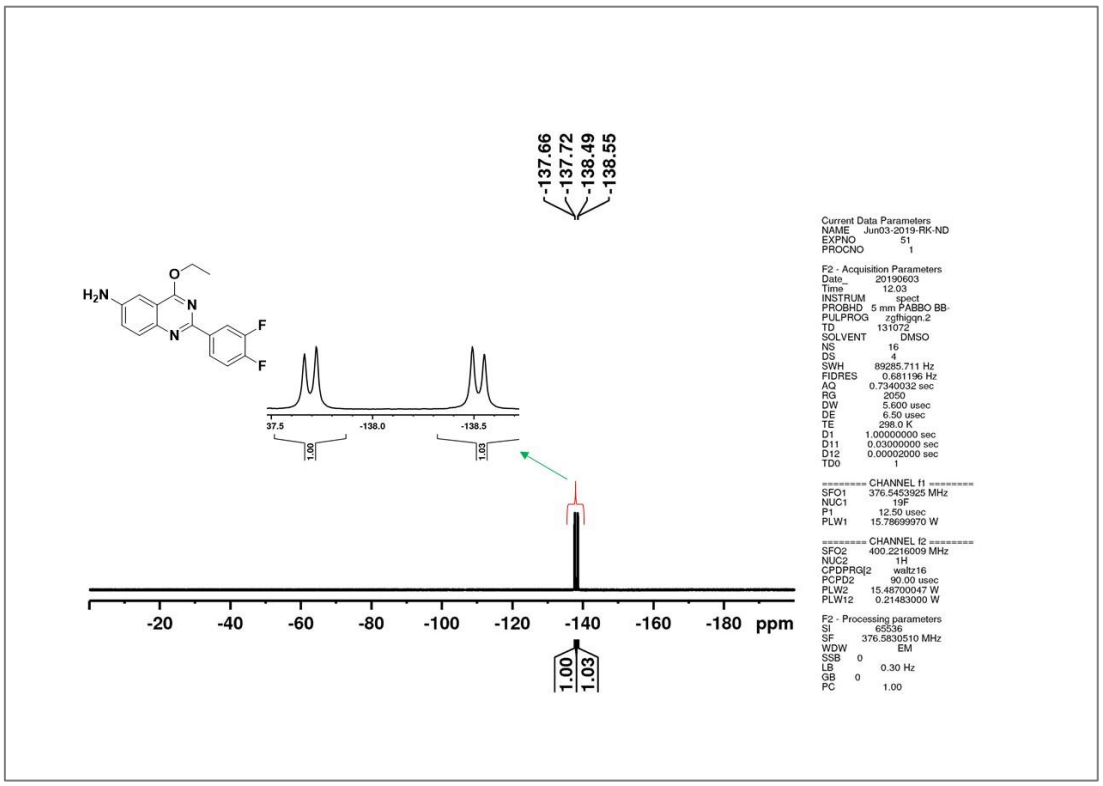
IR spectrum of compound 7 (Chapter 3)



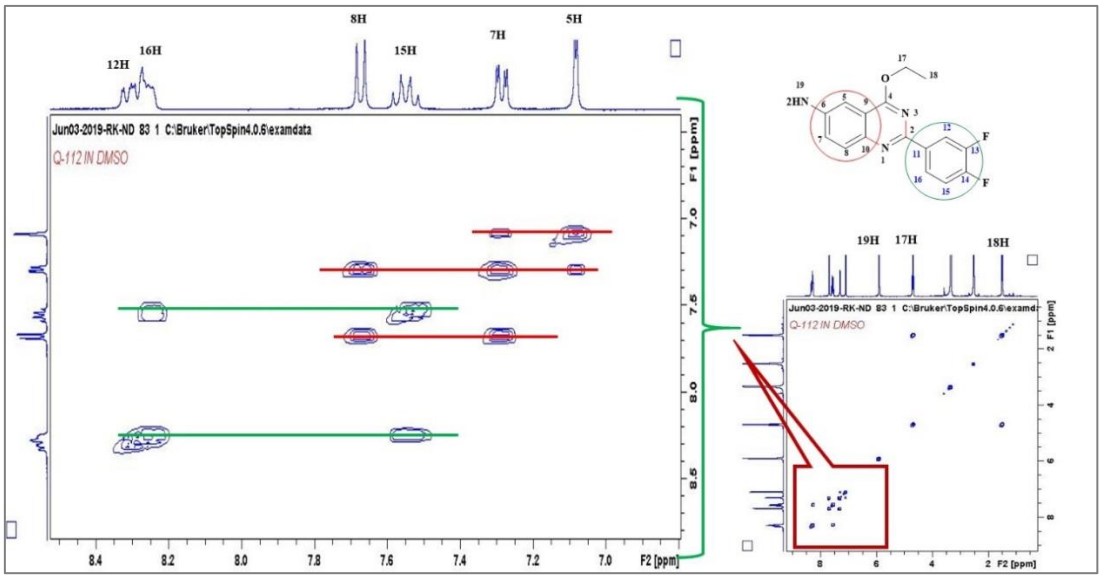
^{1}H NMR spectrum of compound 8 (Chapter 3)



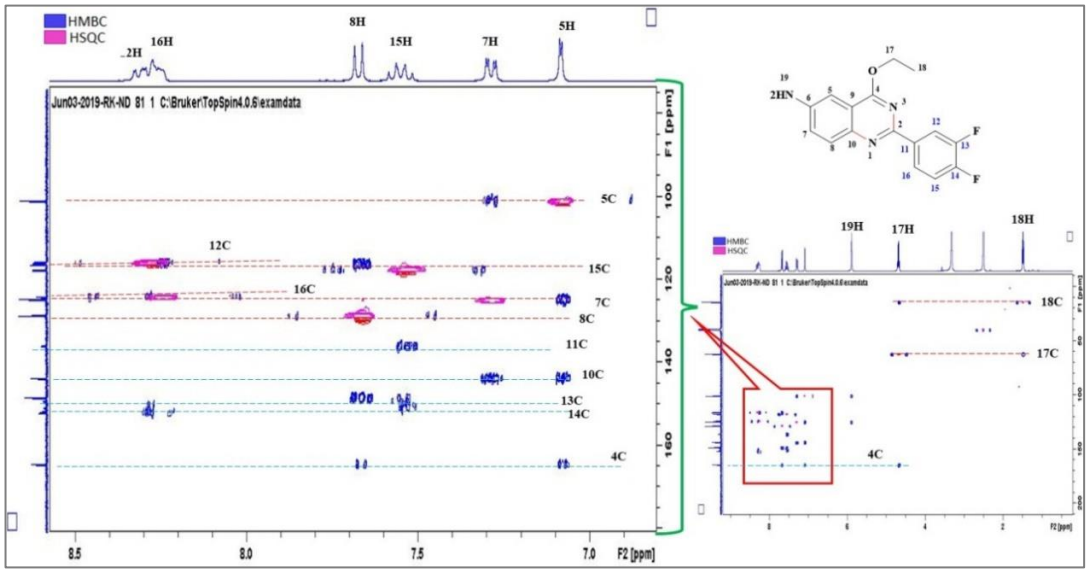
^{13}C NMR spectrum of compound 8 (Chapter3)



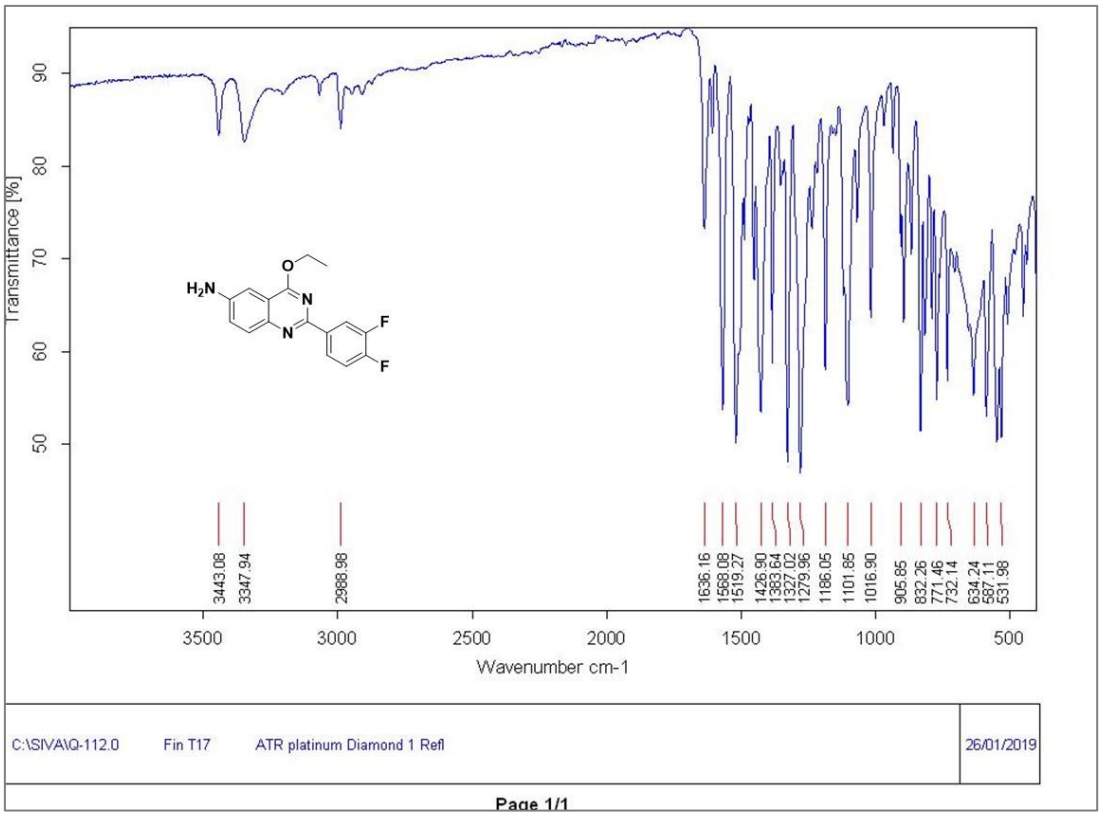
^{19}F NMR spectrum of compound 8 (Chapter 3)



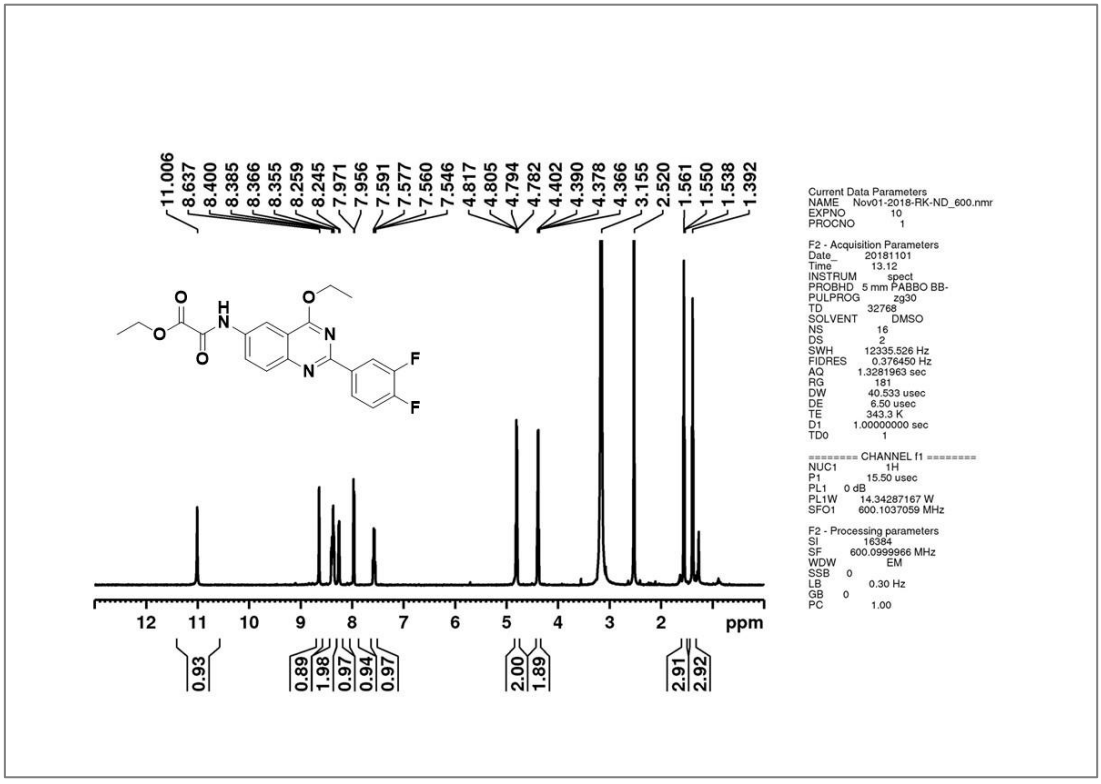
Cosy spectrum of compound 8 (Chapter 3)



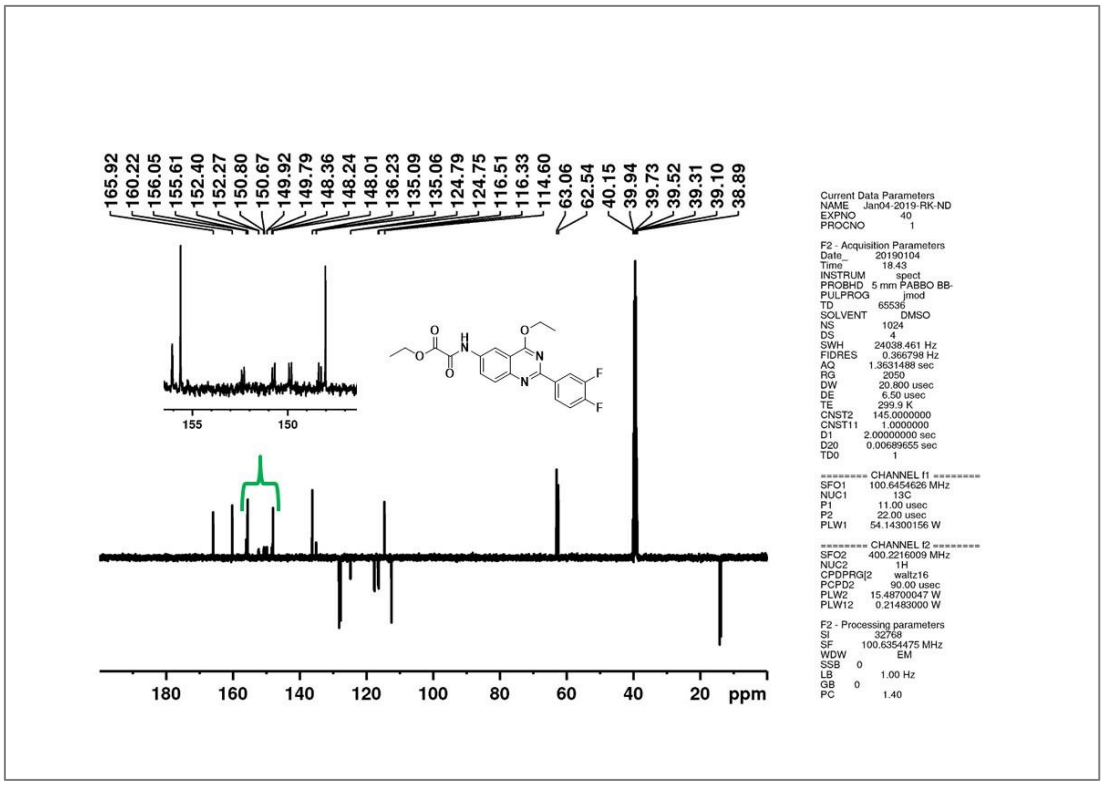
HMBC & HSQC spectrum of compound 8 (Chapter 3)



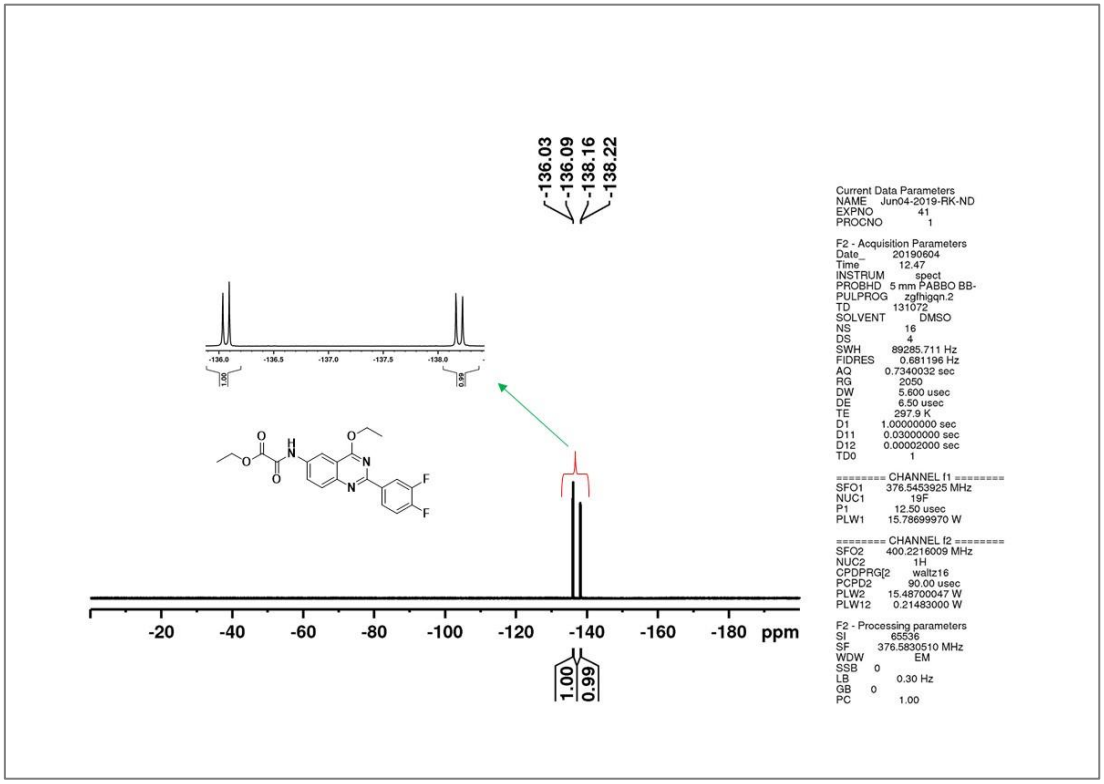
IR spectrum of compound 8 (Chapter 3)



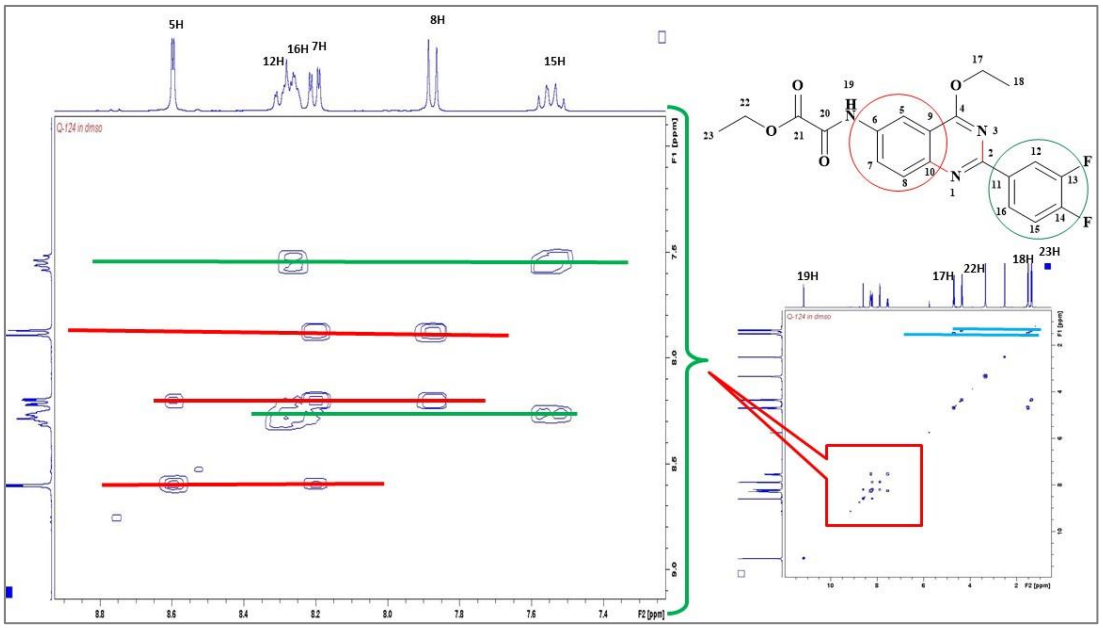
^{1}H NMR spectrum of compound 10a (Chapter 3)



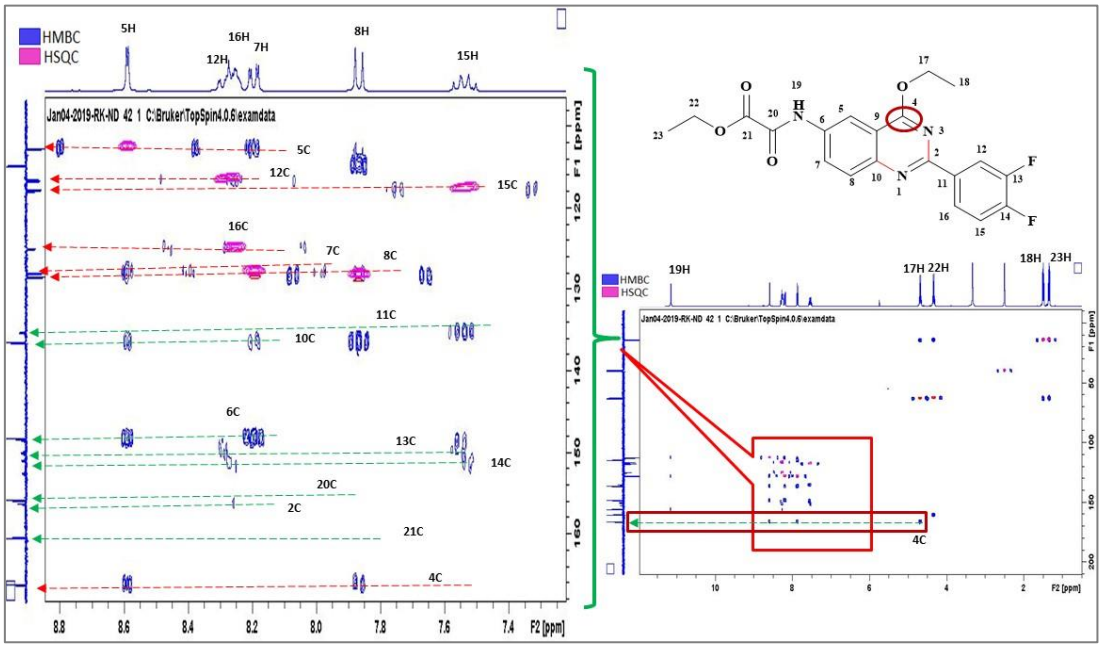
^{13}C NMR spectrum of compound 10a (Chapter 3)



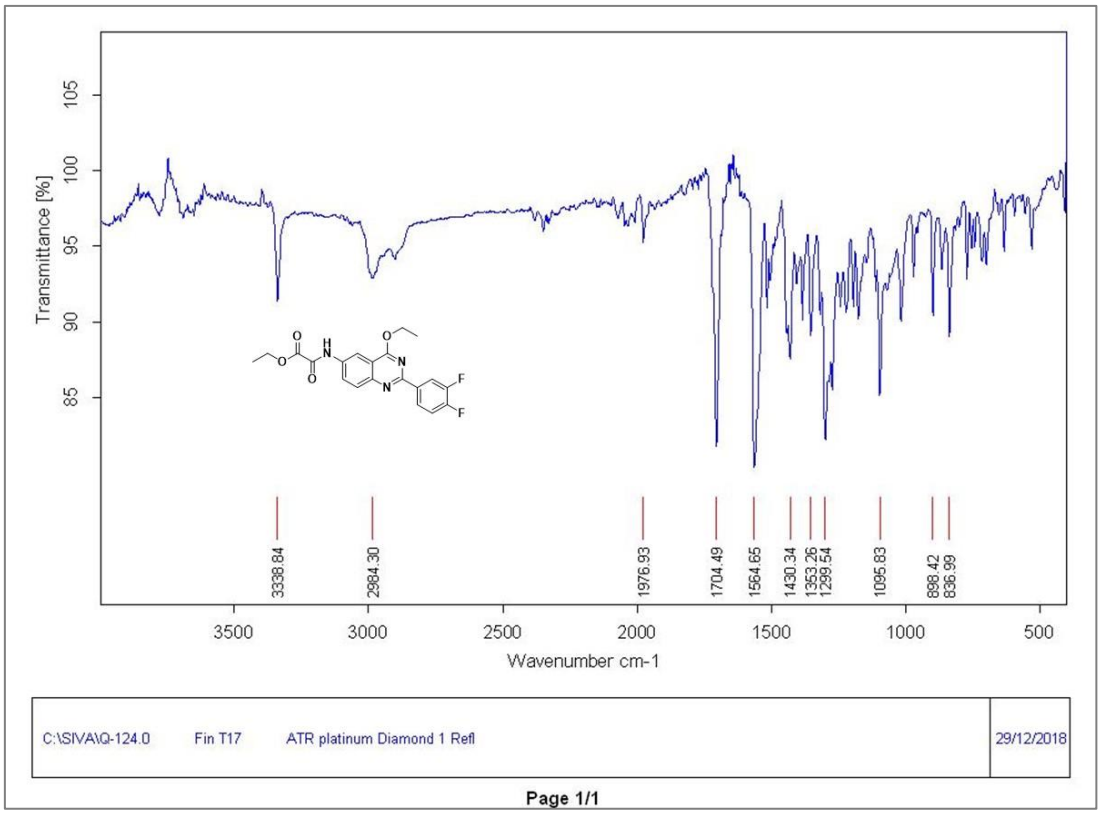
^{19}F NMR spectrum of compound 10a (Chapter 3)



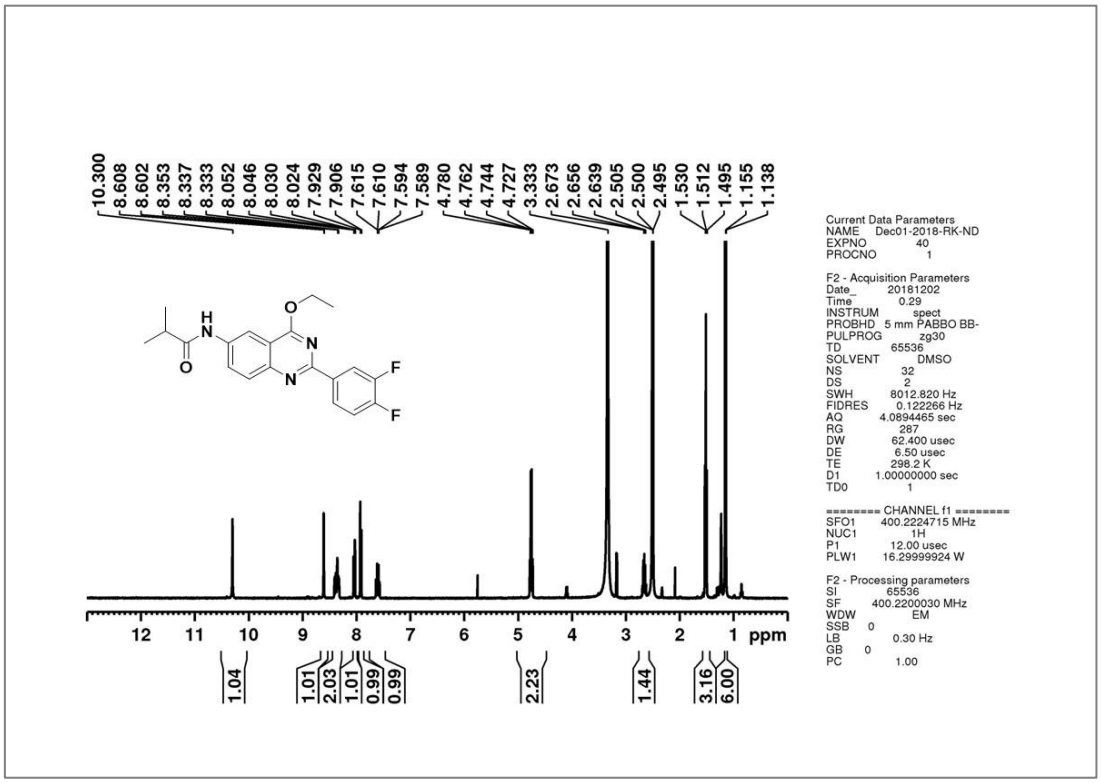
Cosy spectrum of compound 10a (Chapter 3)



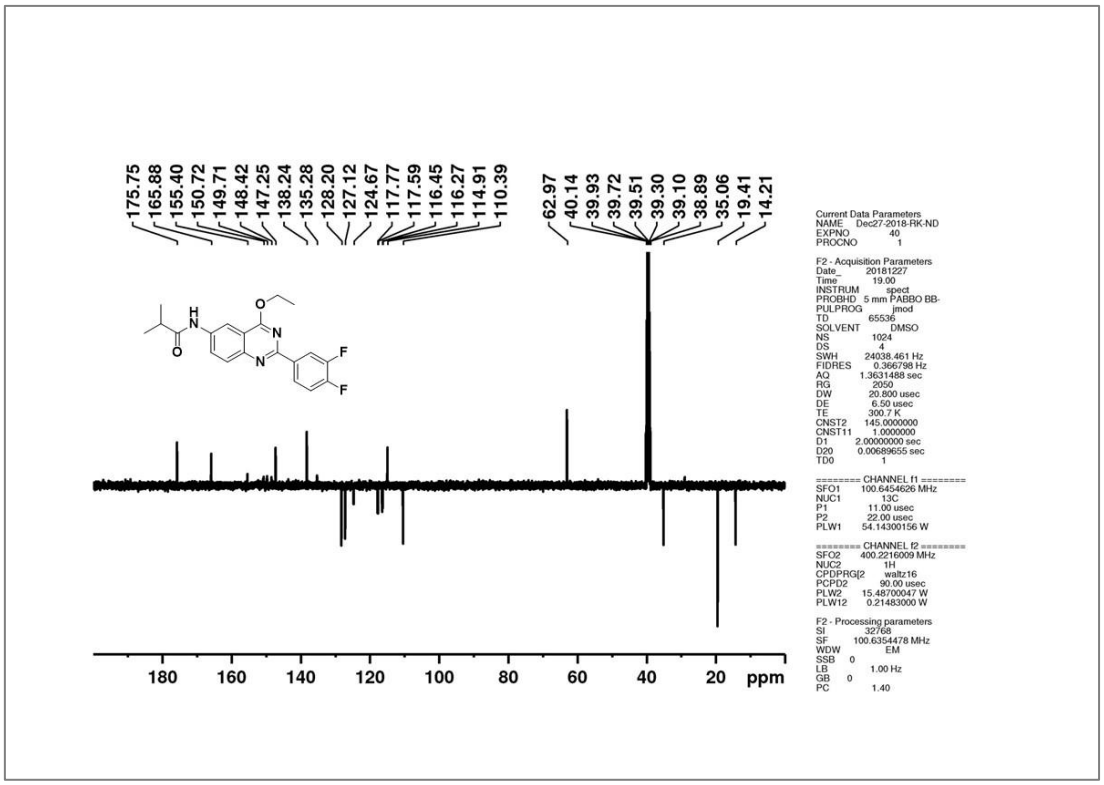
HMBC & HSQC spectrum of compound 10a (Chapter 3)



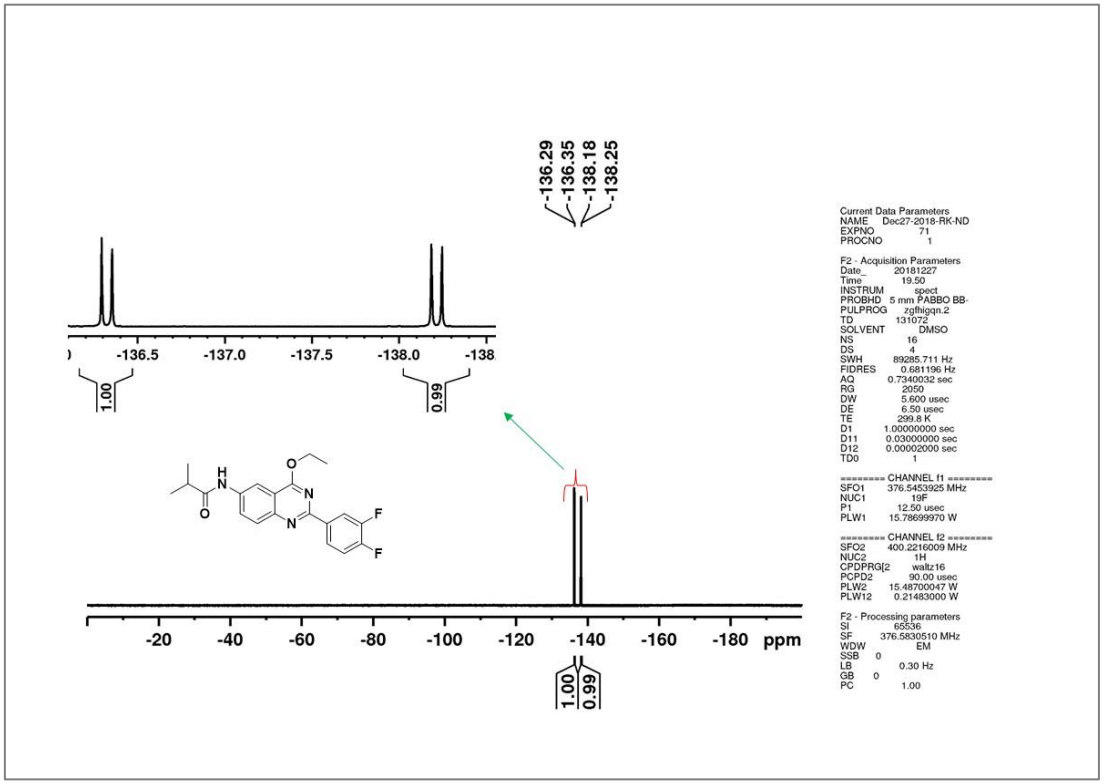
IR spectrum of compound 10a (Chapter 3)



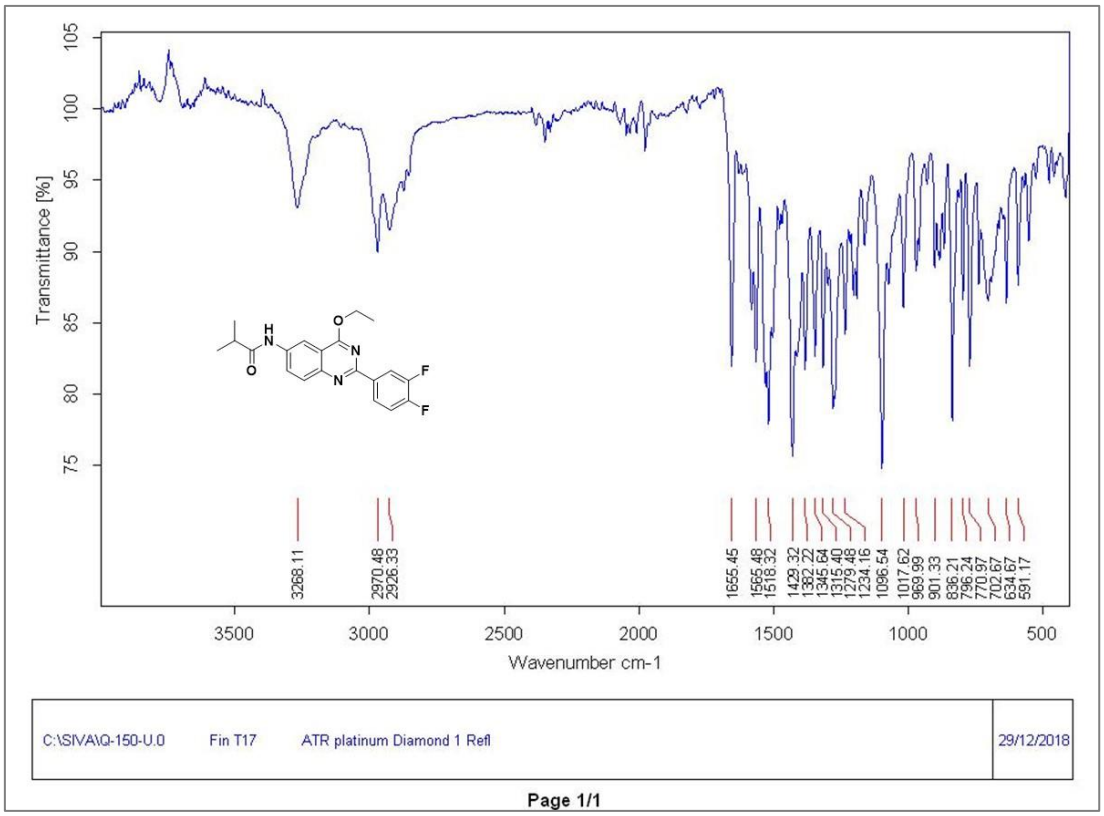
^{1}H NMR spectrum of compound 10b (Chapter 3)



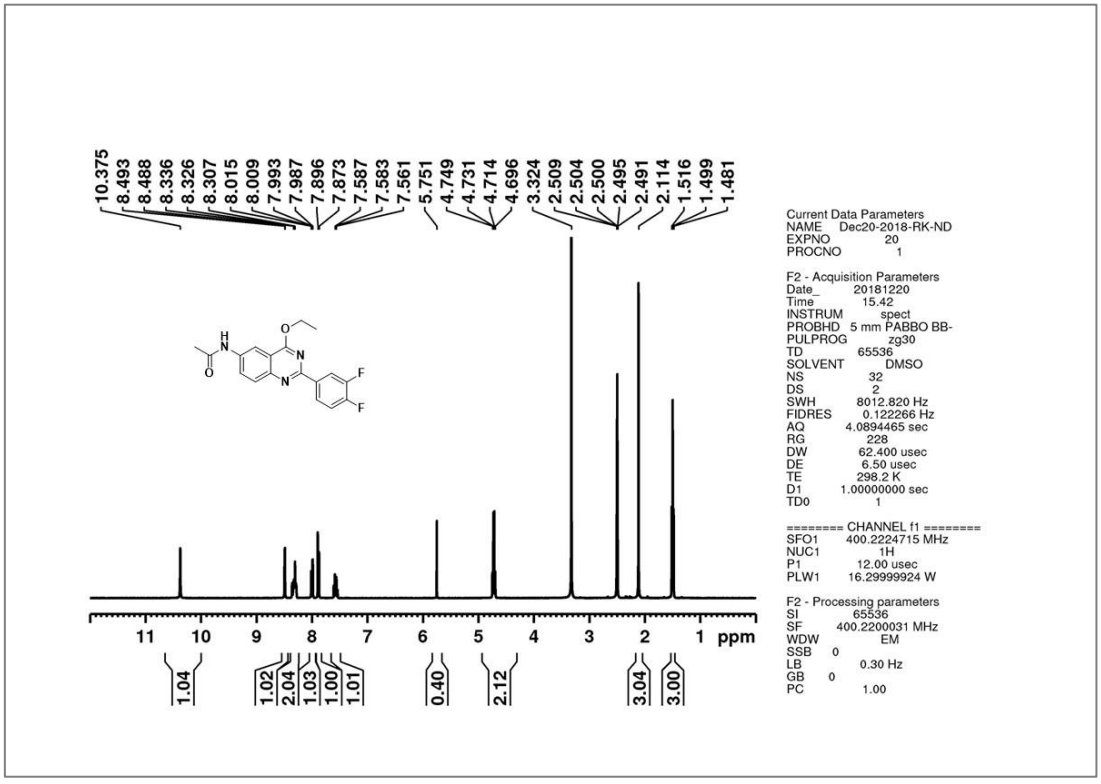
^{13}C NMR spectrum of compound 10b (Chapter 3)



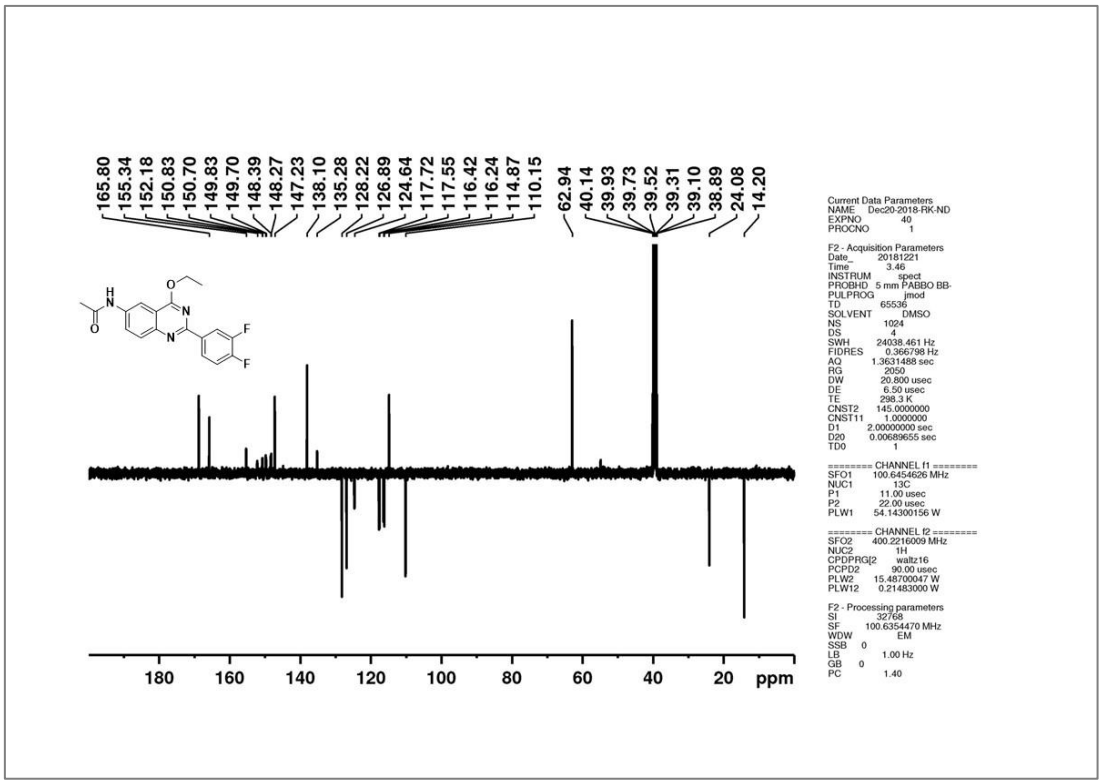
^{19}F NMR spectrum of compound 10b (Chapter 3)



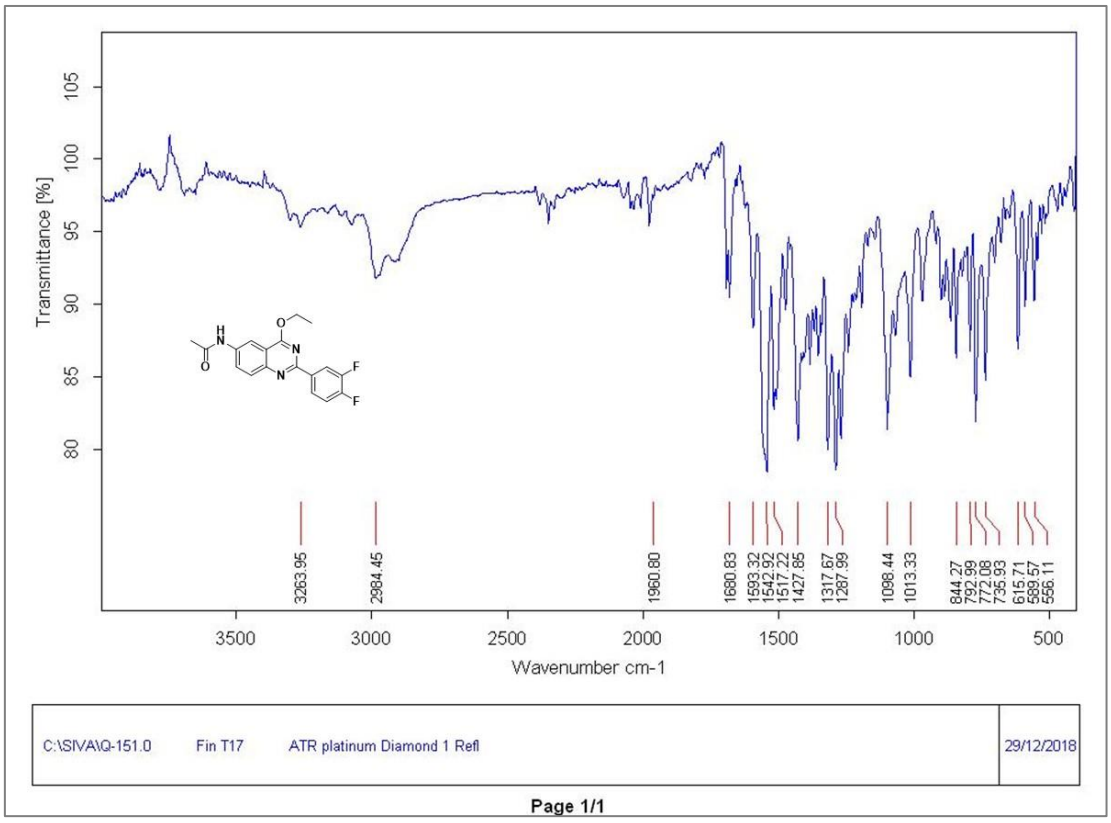
IR spectrum of compound 10b (Chapter 3)



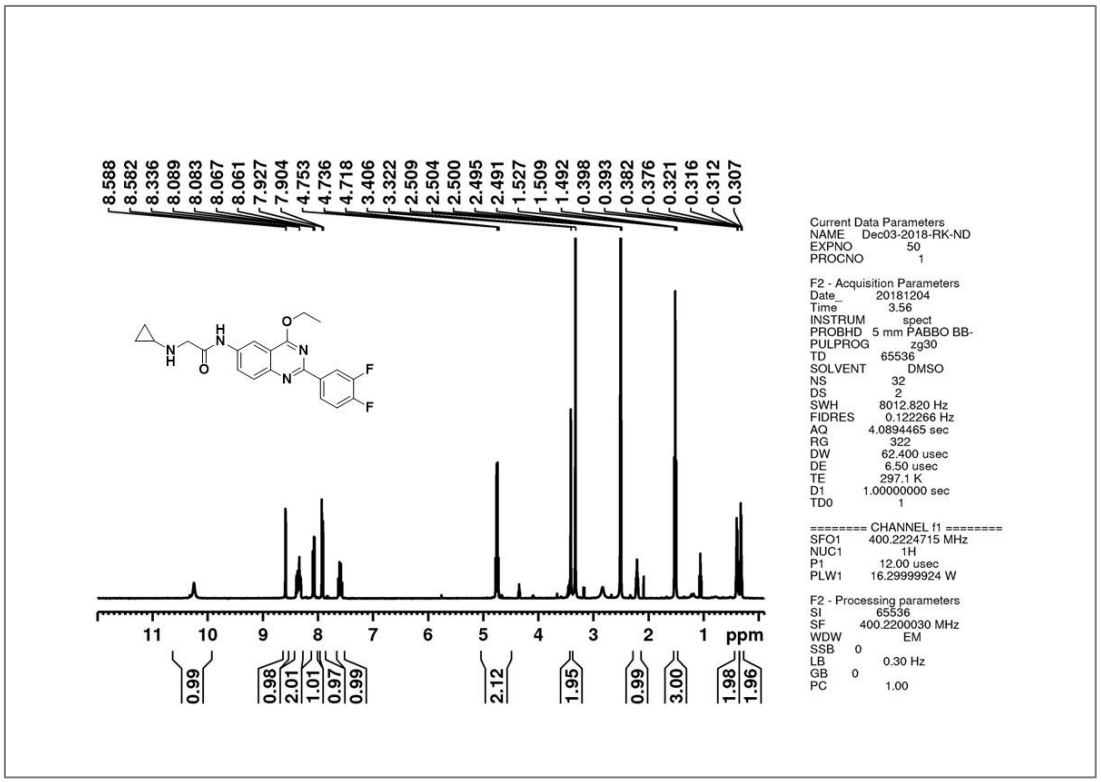
^{1}H NMR spectrum of compound 10c (Chapter 3)



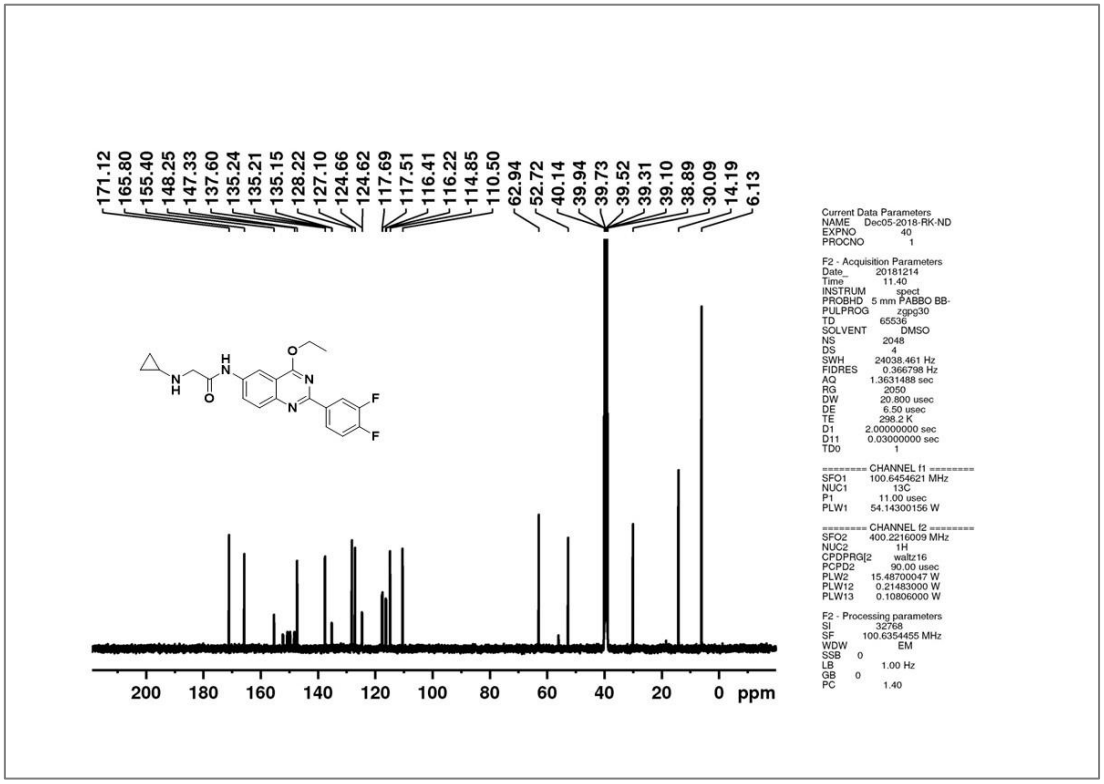
^{13}C NMR spectrum of compound 10c (Chapter 3)



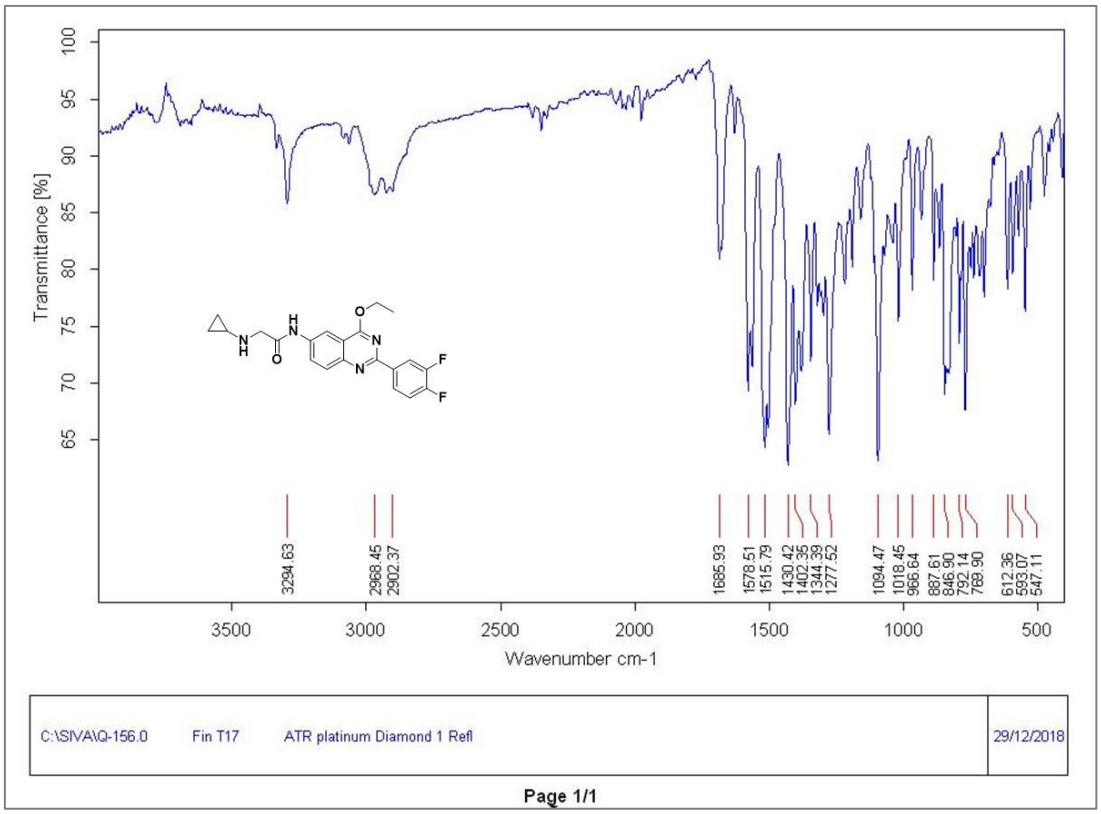
IR spectrum of compound 10c (Chapter 3)



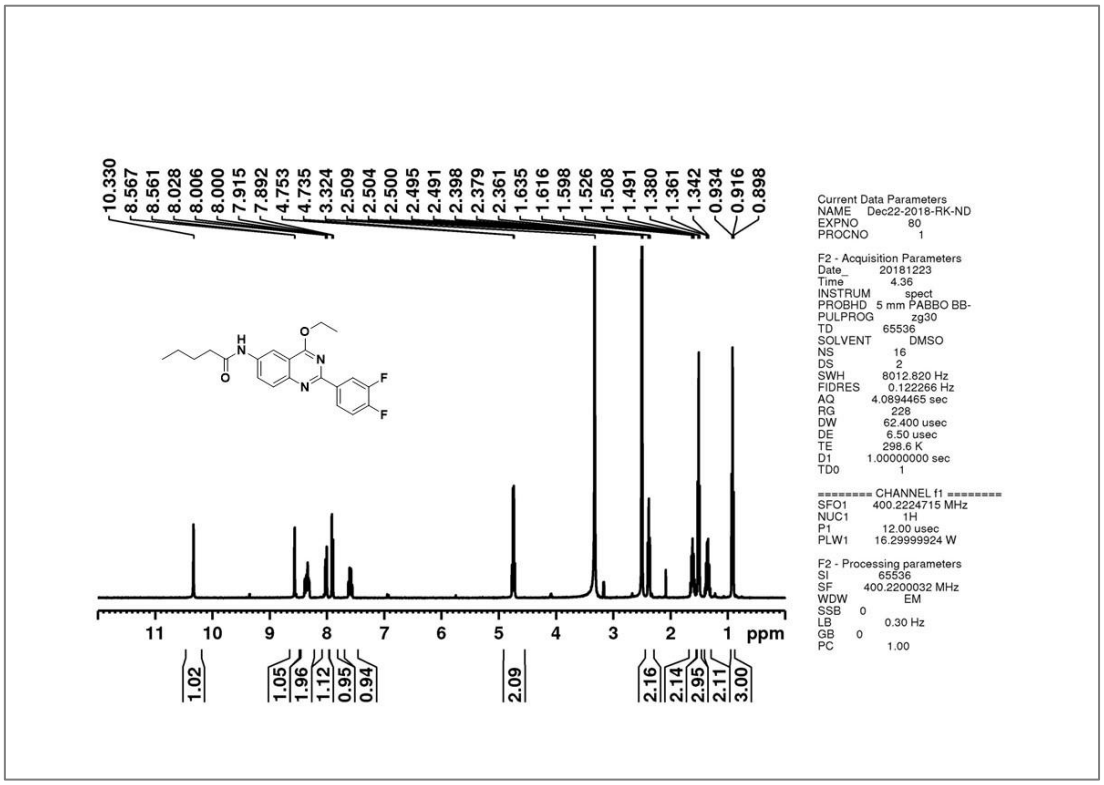
^{1}H NMR spectrum of compound 10d (Chapter 3)



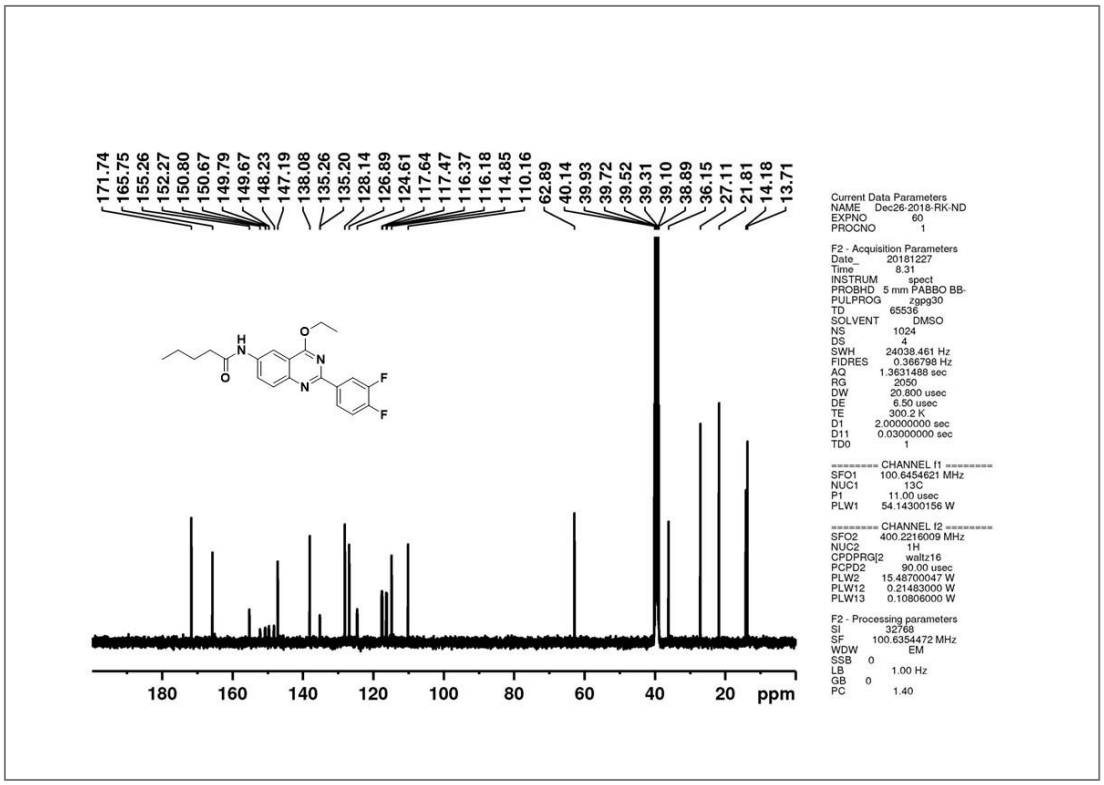
^{13}C NMR spectrum of compound 10d (Chapter 3)



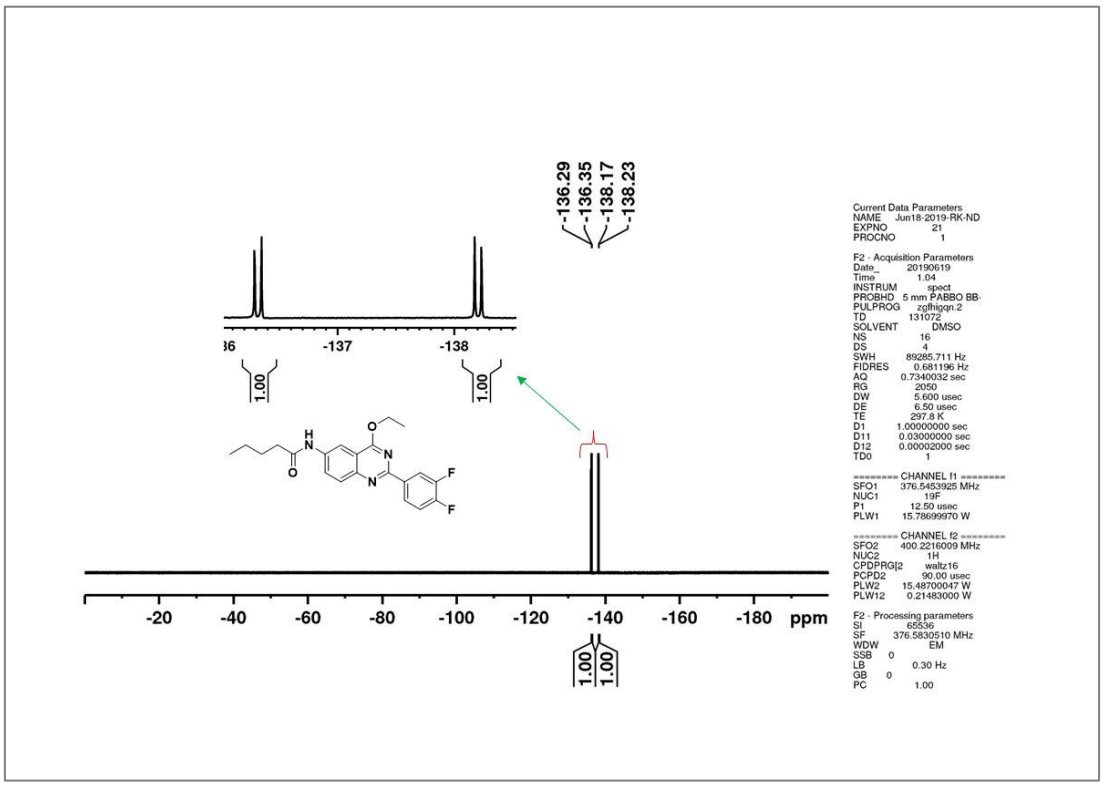
IR spectrum of compound 10d (Chapter 3)



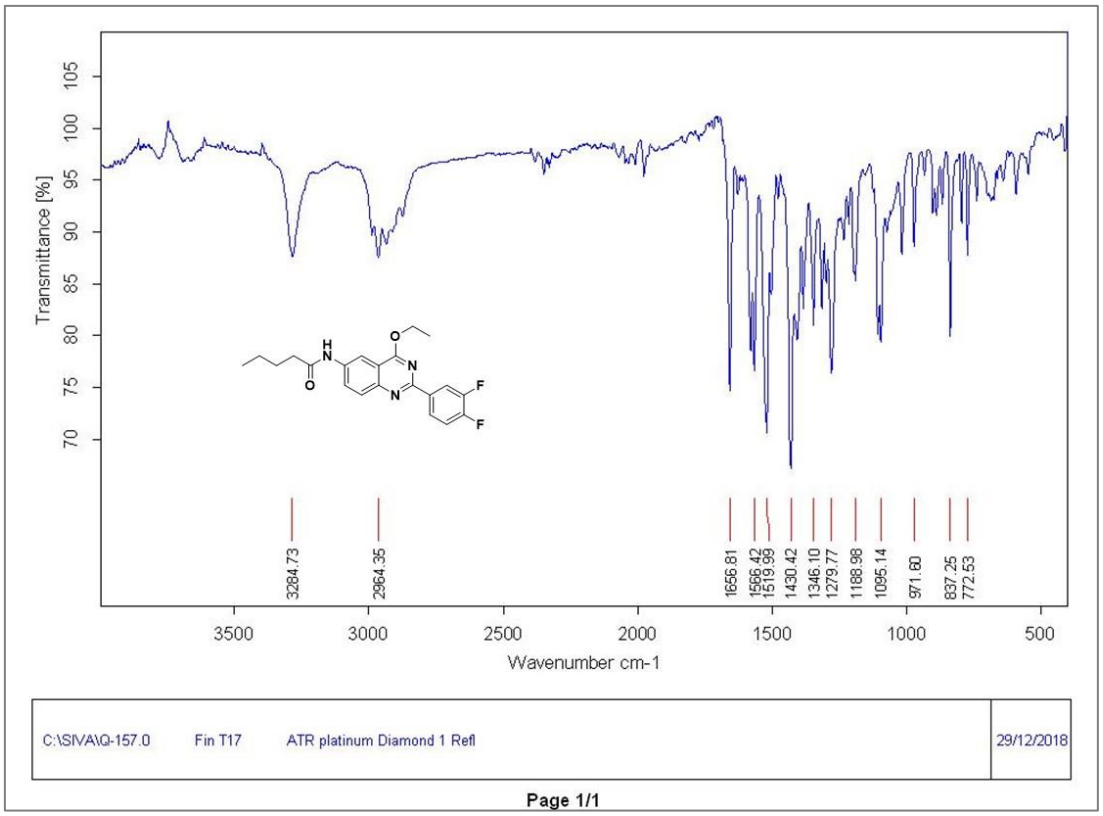
^{1}H NMR spectrum of compound 10e (Chapter 3)



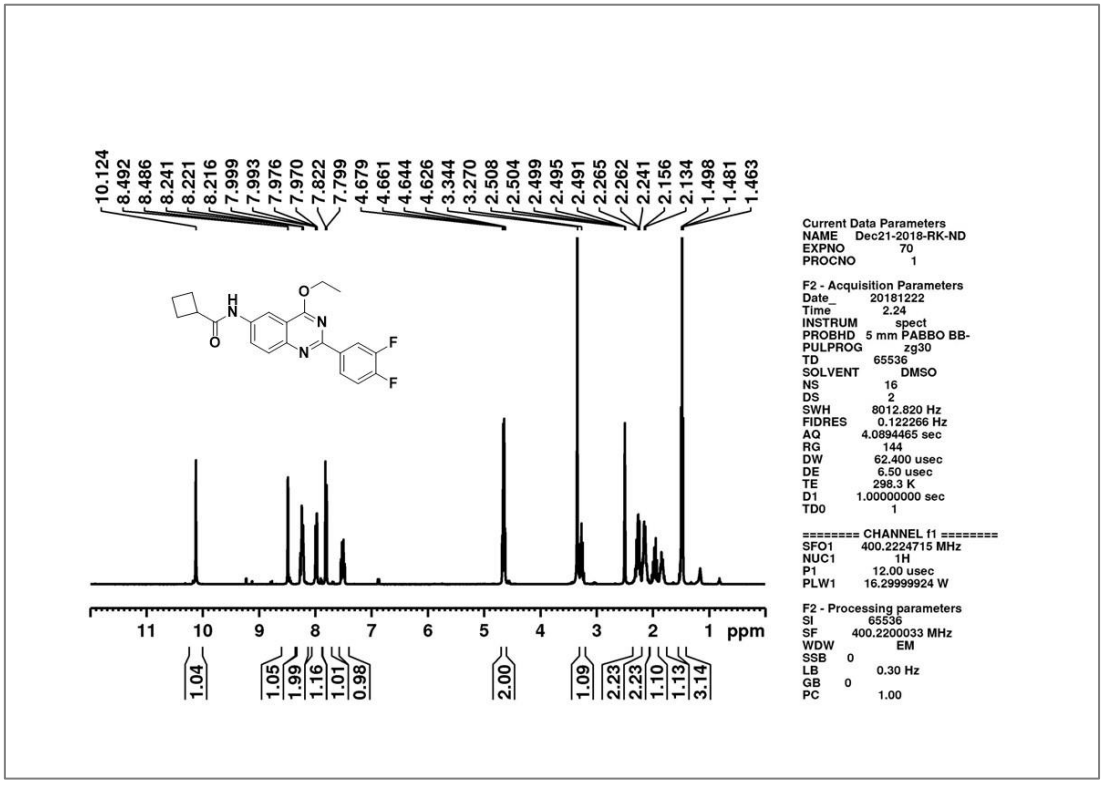
^{13}C NMR spectrum of compound 10e (Chapter 3)



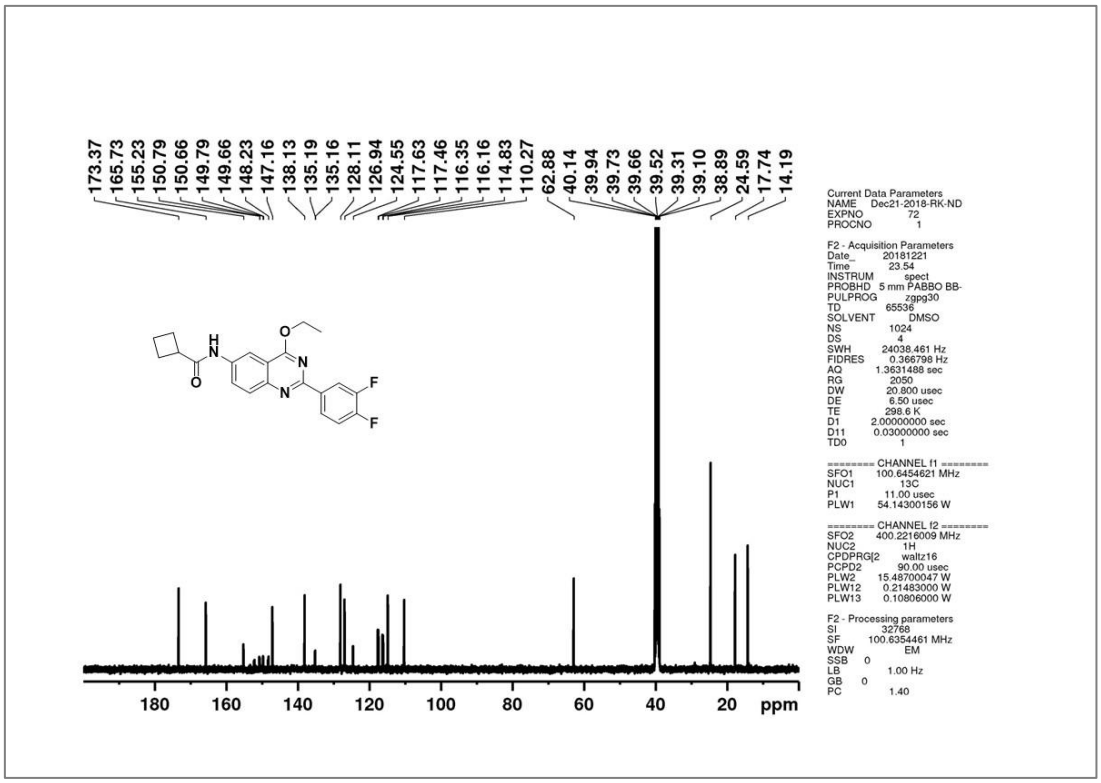
^{19}F NMR spectrum of compound 10e (Chapter 3)



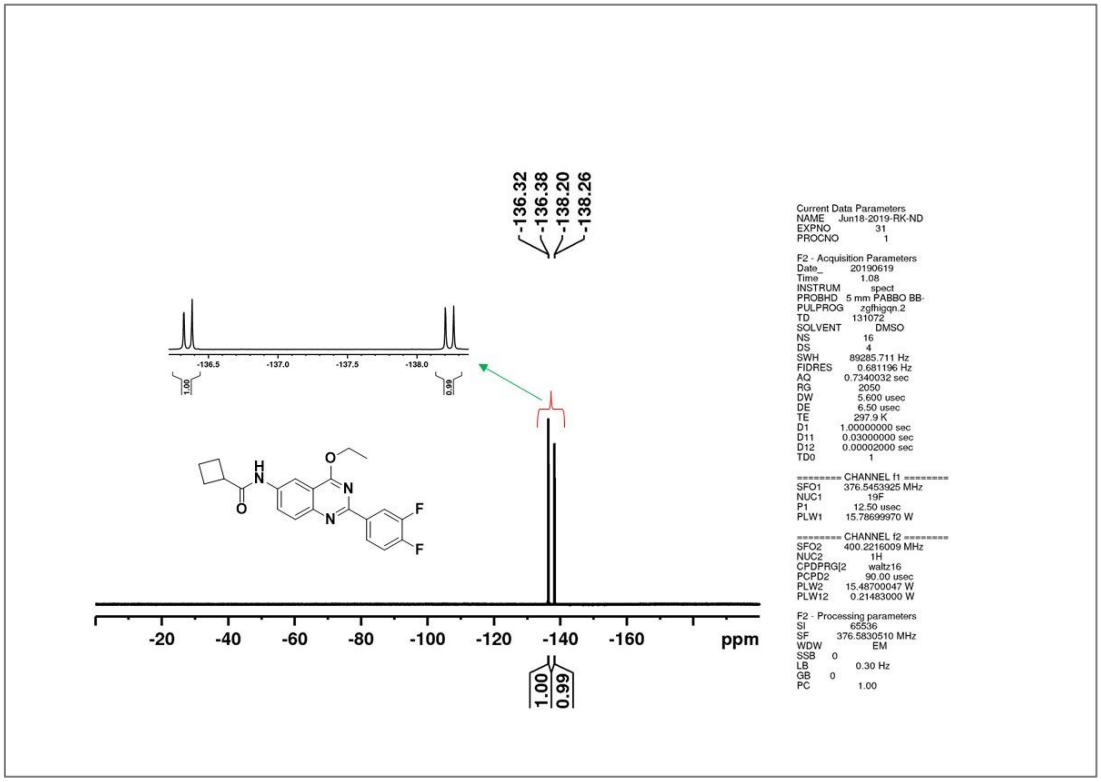
IR spectrum of compound 10e (Chapter 3)



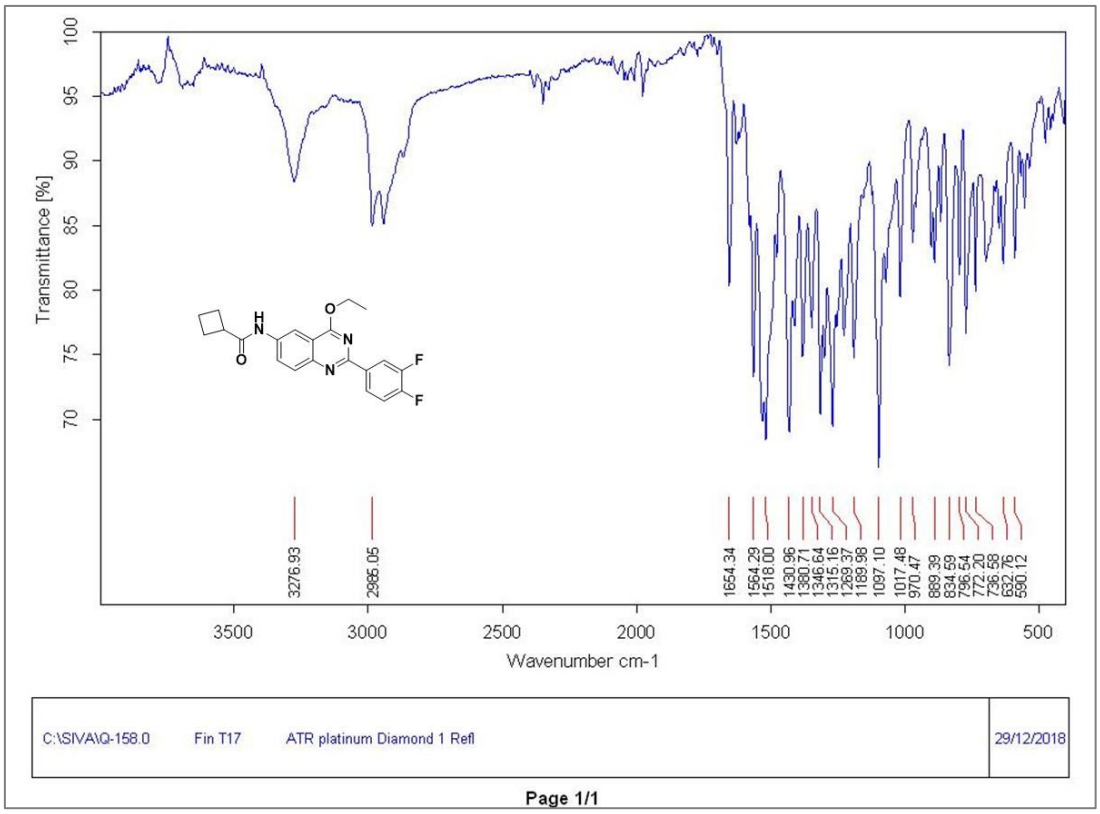
^{1}H NMR spectrum of compound 10f (Chapter 3)



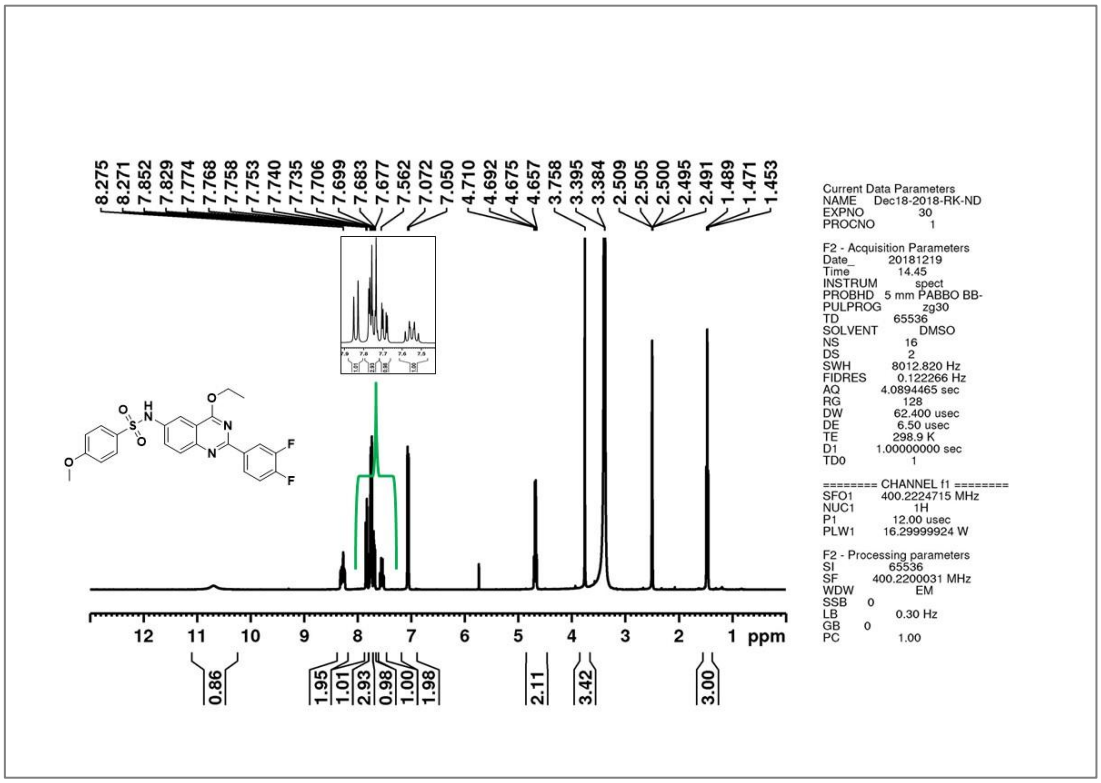
^{13}C NMR spectrum of compound 10f (Chapter 3)



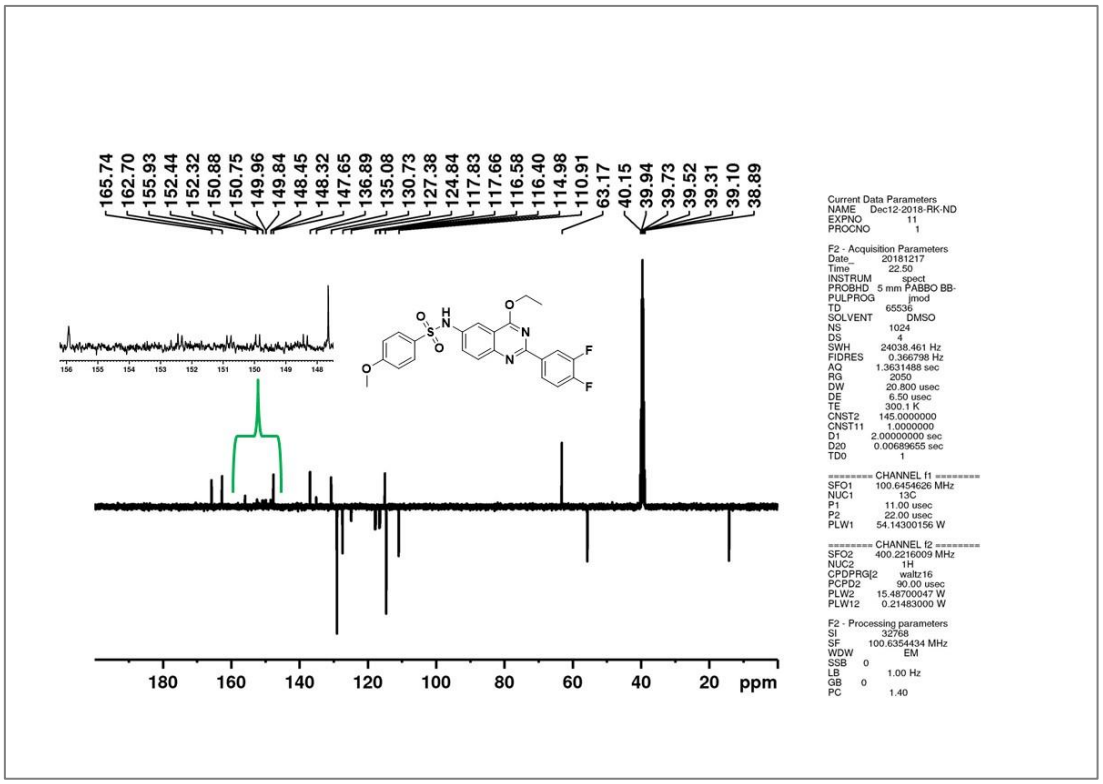
^{19}F NMR spectrum of compound 10f (Chapter 3)



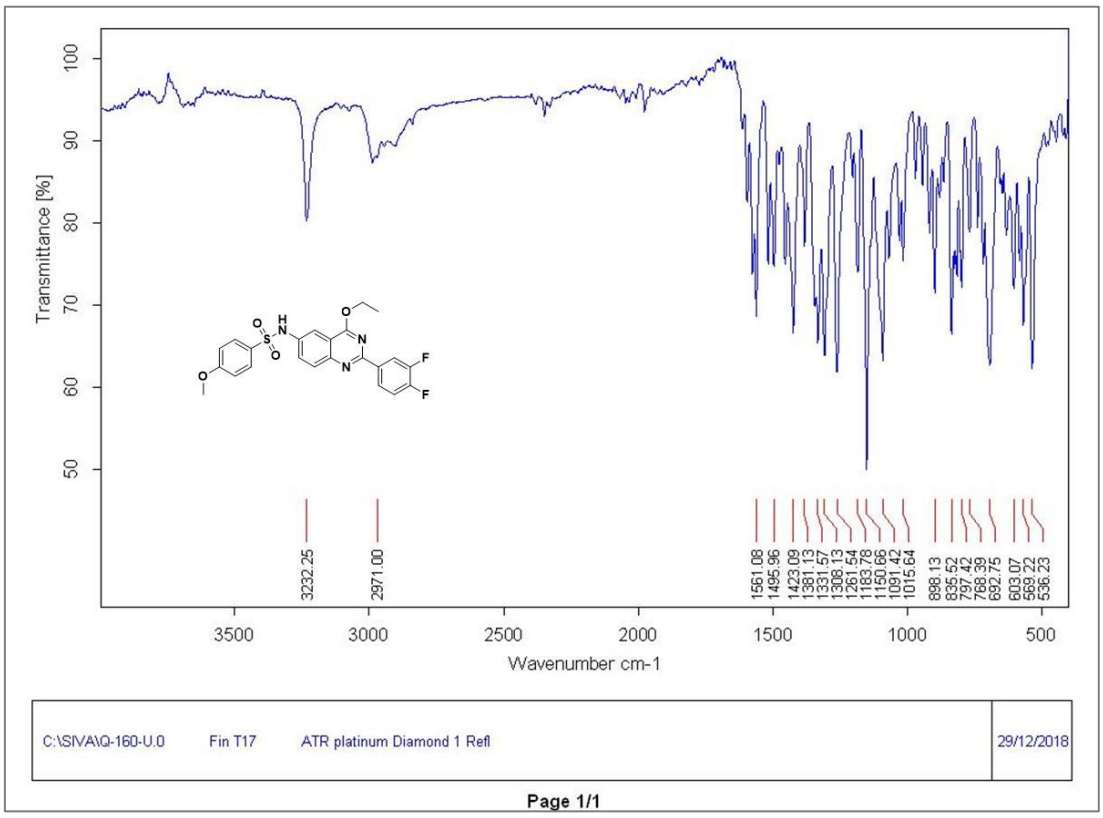
IR spectrum of compound 10f (Chapter 3)



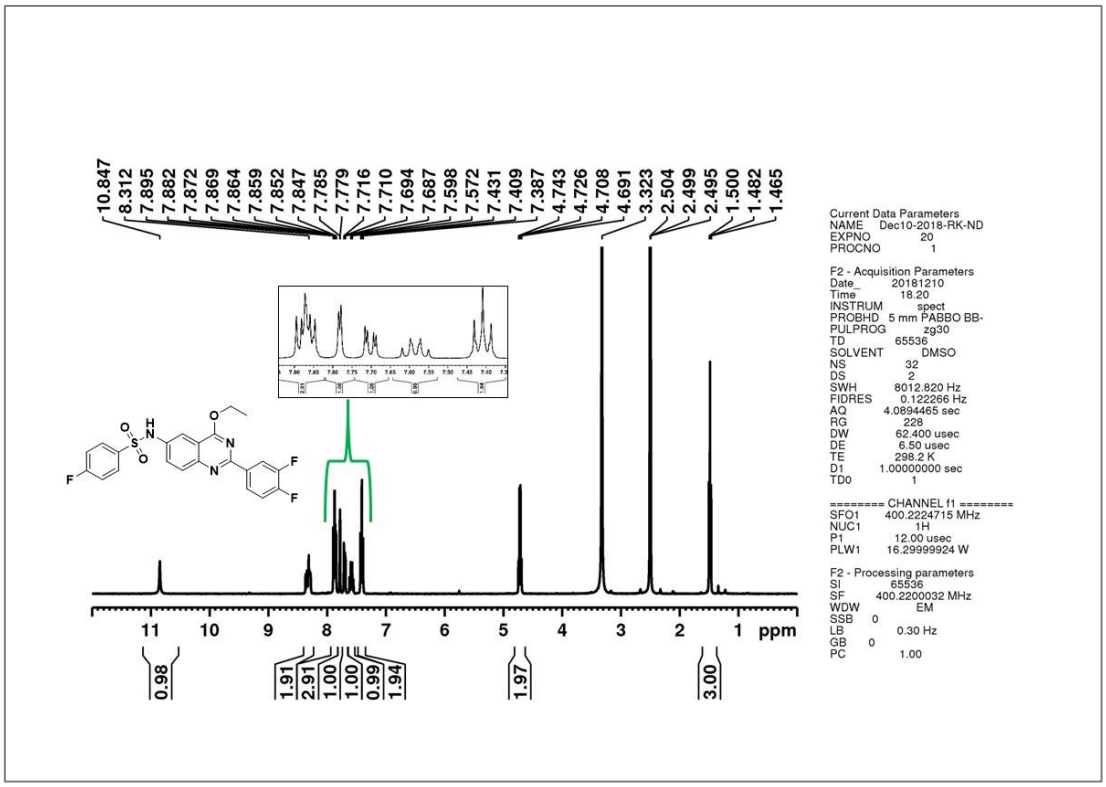
^{1}H NMR spectrum of 10g (Chapter 3)



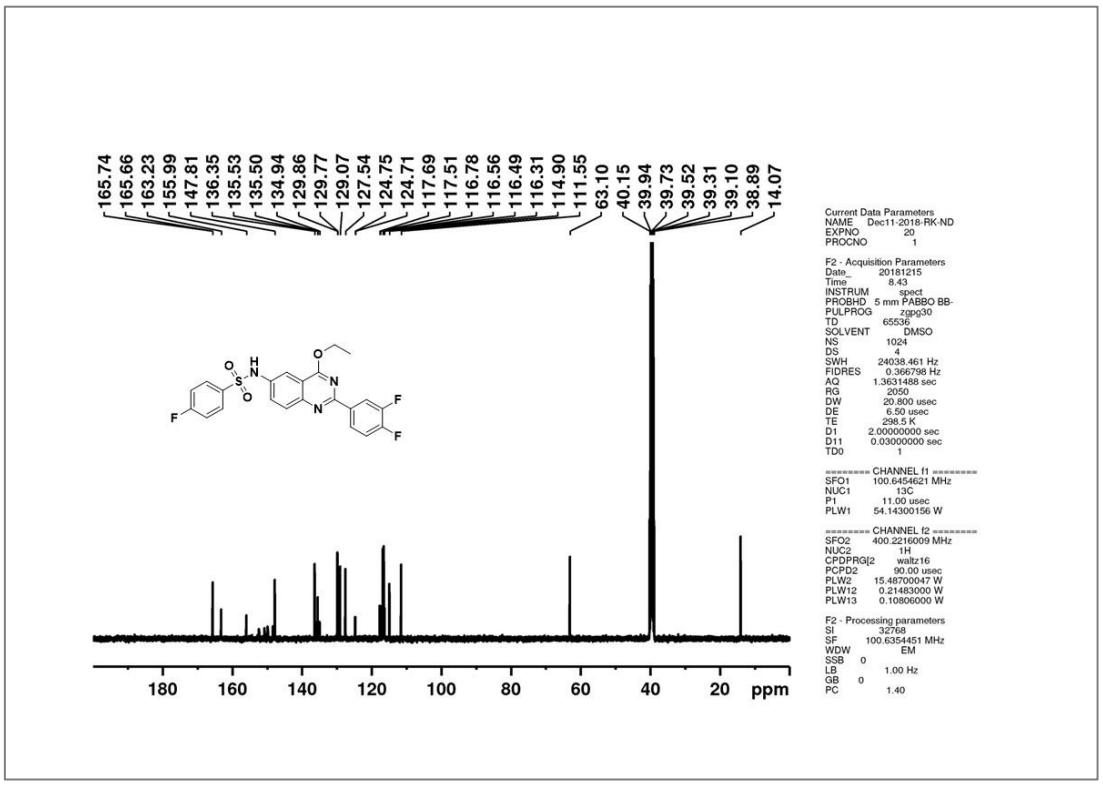
^{13}C NMR spectrum of 10g (Chapter 3)



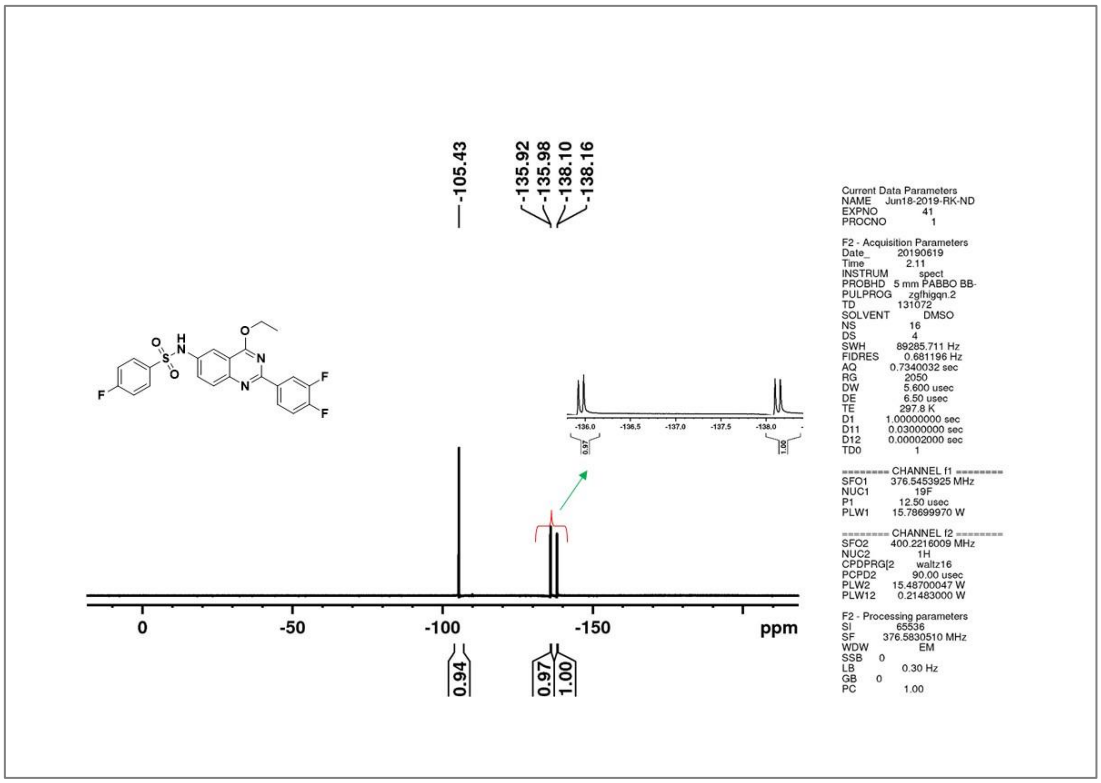
IR spectrum of compound 10g (Chapter 3)



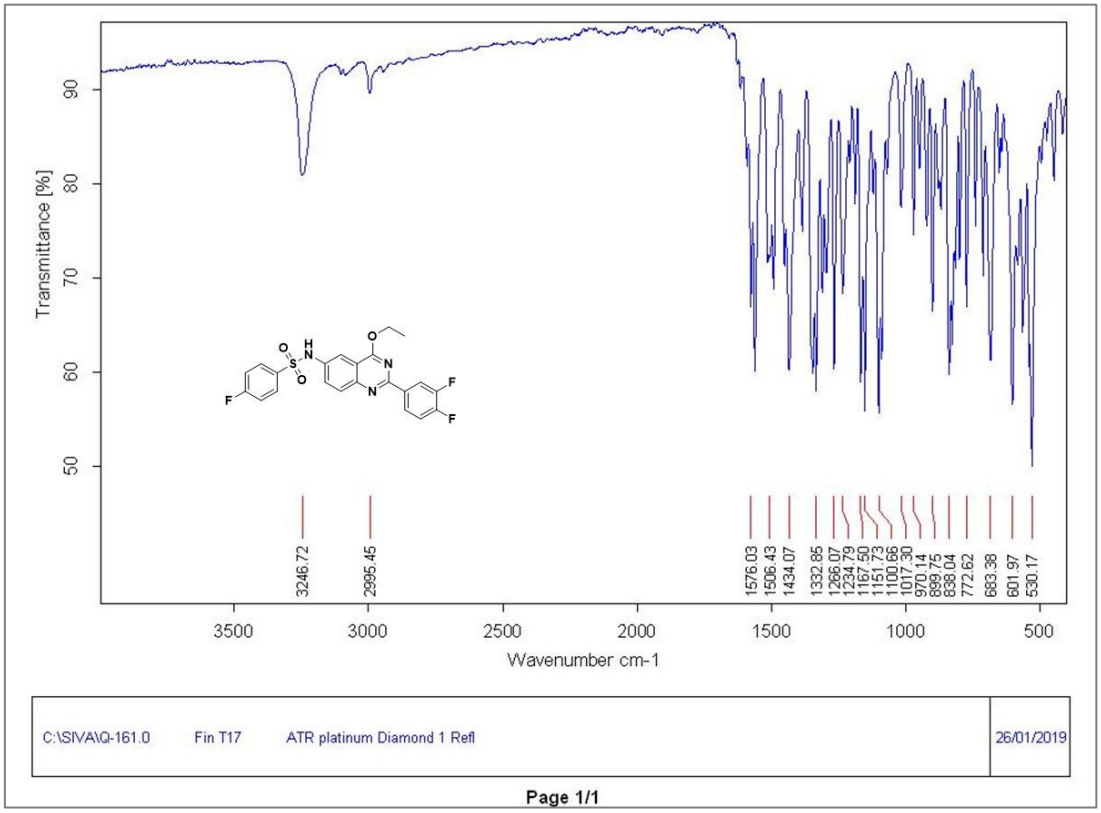
^{1}H NMR spectrum of 10h (Chapter 3)



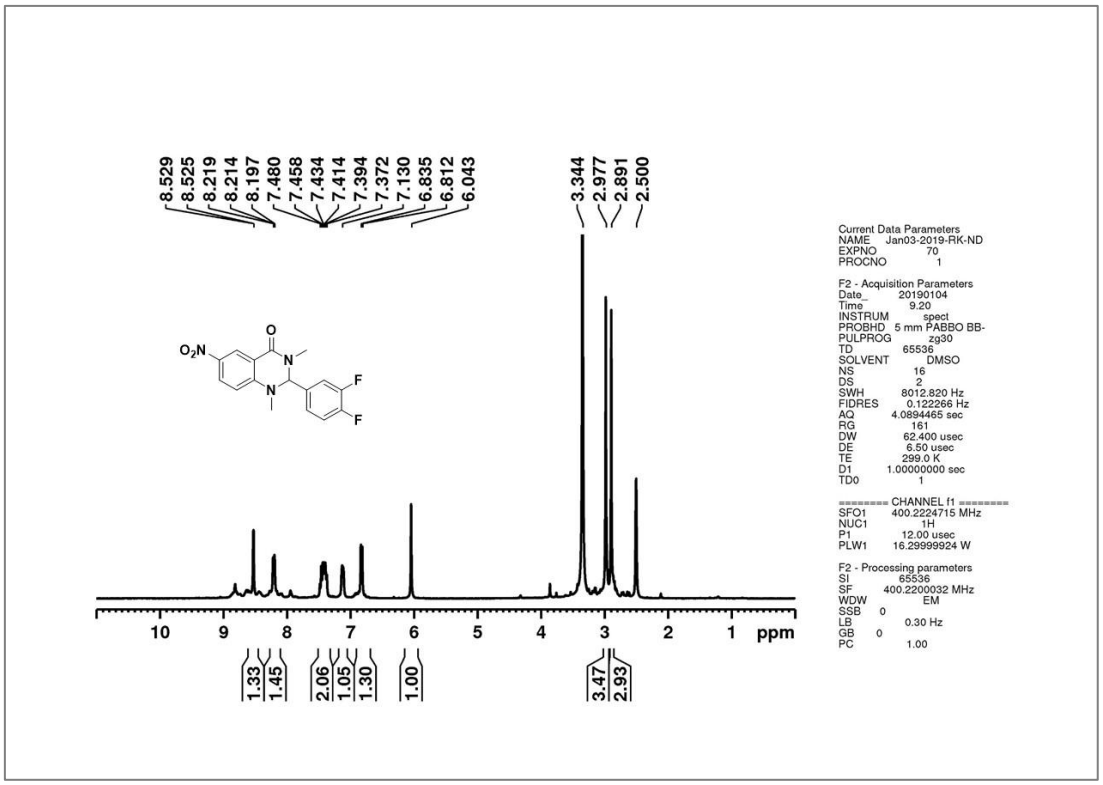
^{13}C NMR spectrum of compound 10h (Chapter 3)



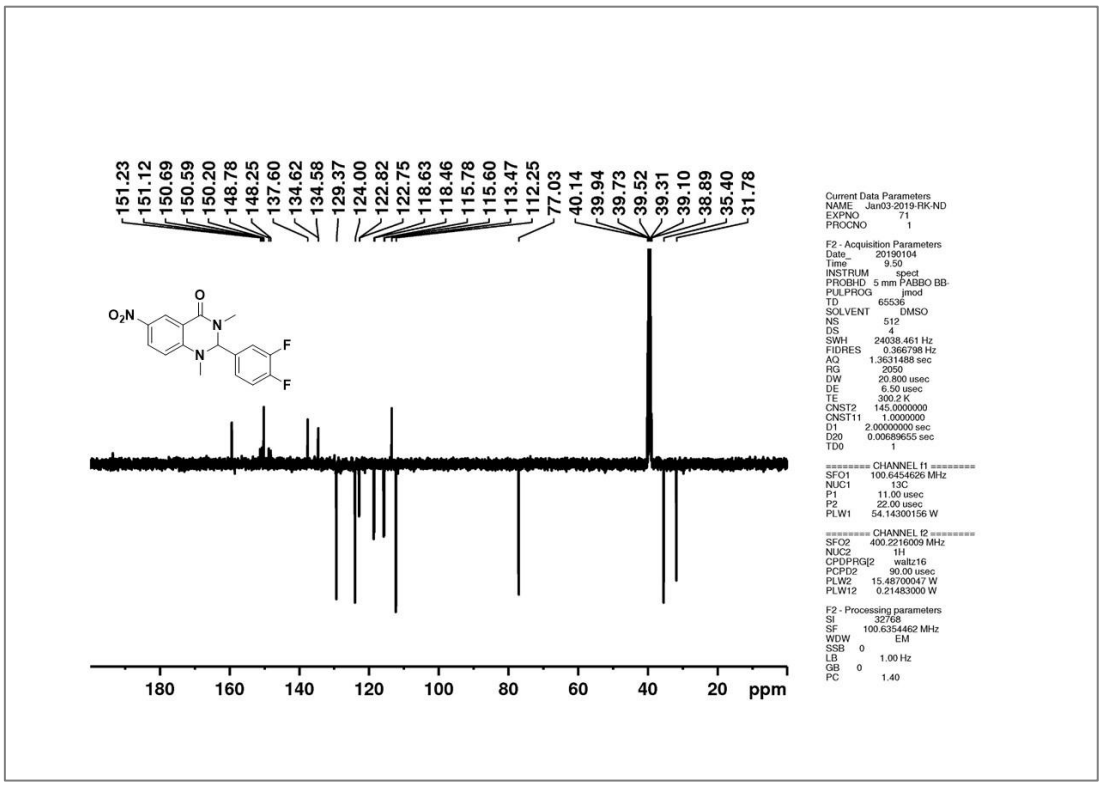
^{19}F NMR spectrum of compound 10h (Chapter 3)



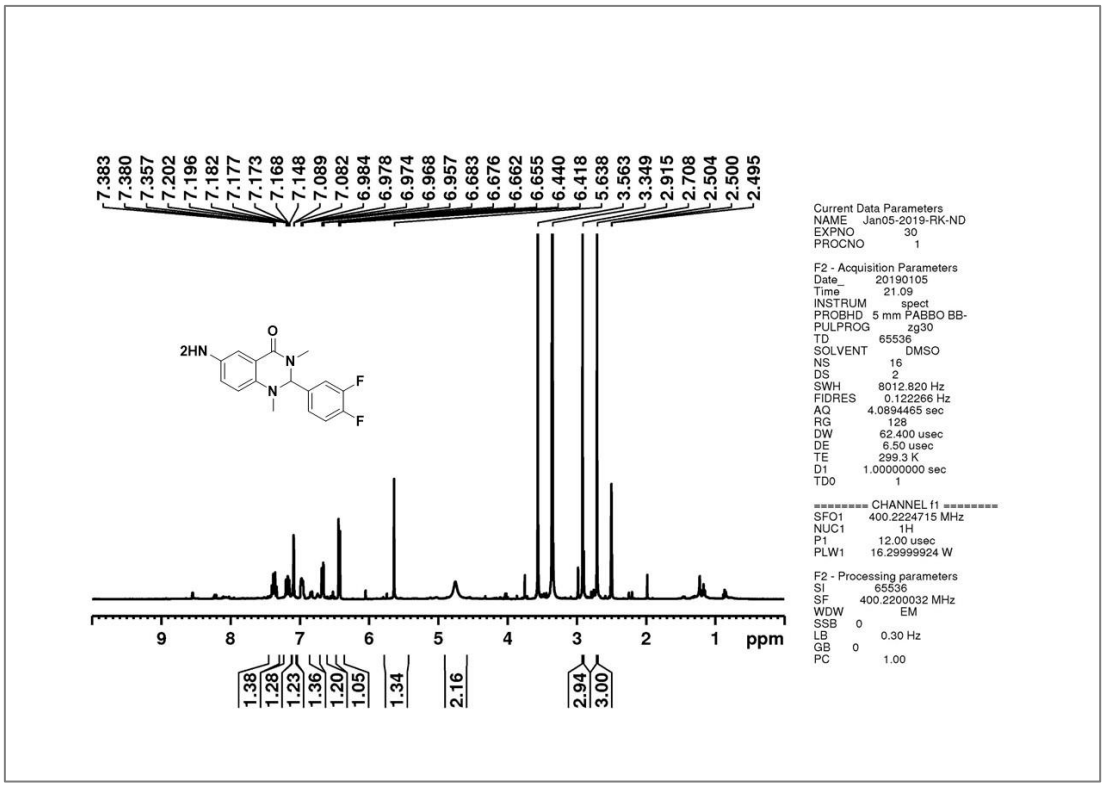
IR spectrum of compound 10h (Chapter 3)



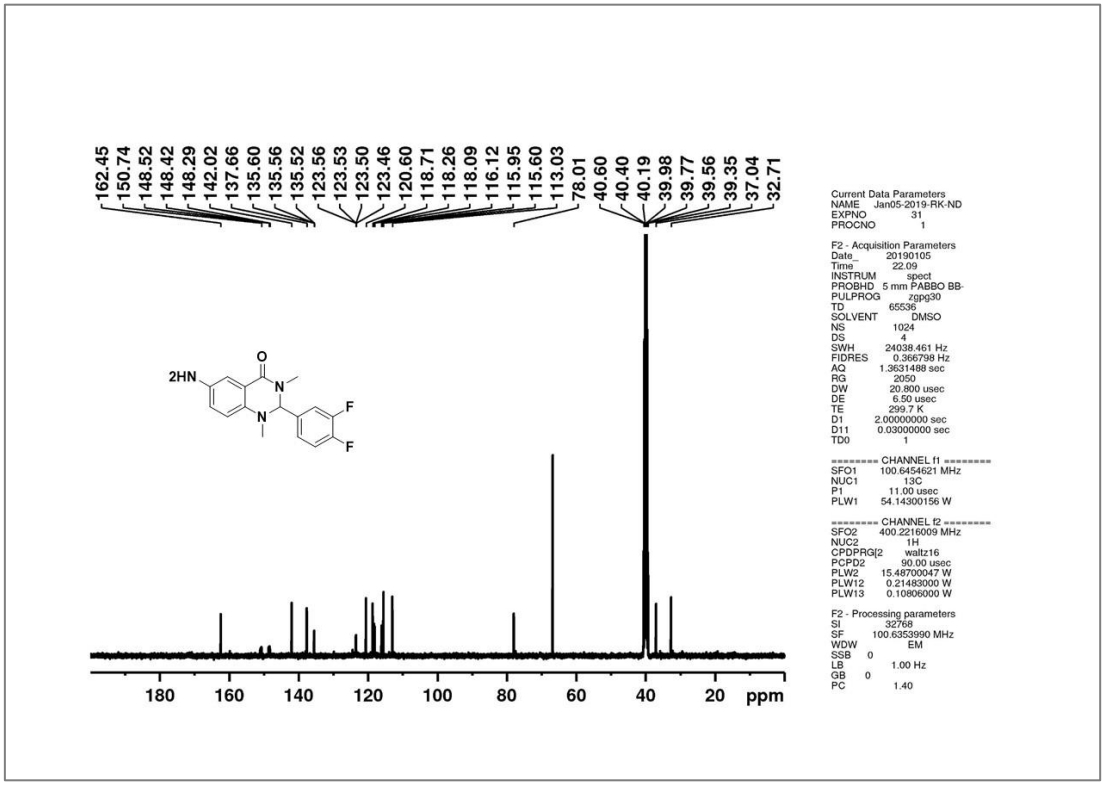
^{1}H NMR spectrum of 11 (Chapter 3)



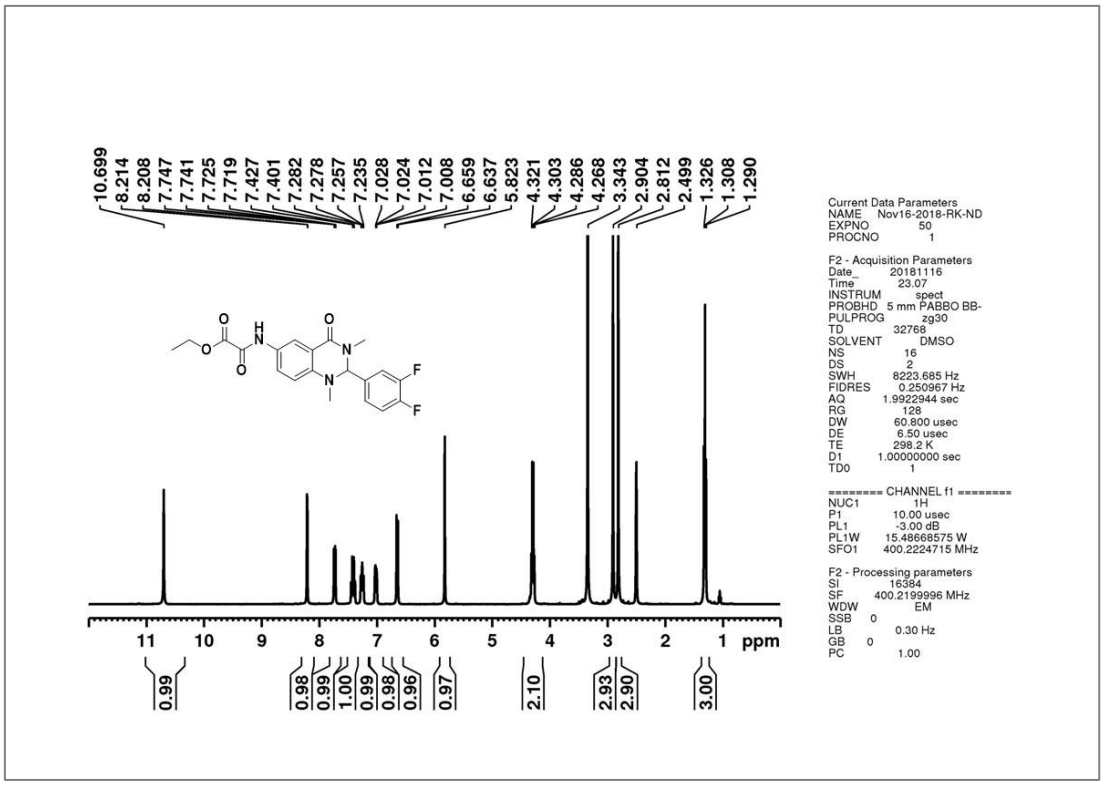
^{13}C NMR spectrum of compound 11 (Chapter 3)



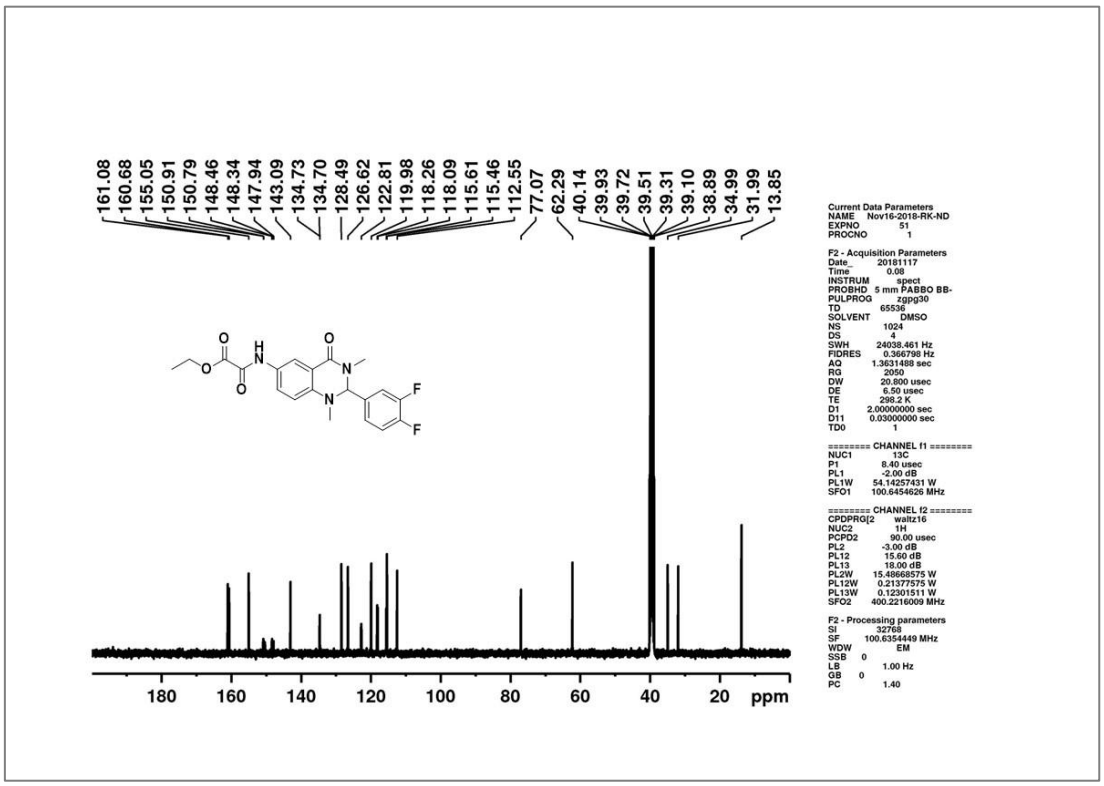
^{1}H NMR spectrum of compound 12 (Chapter 3)



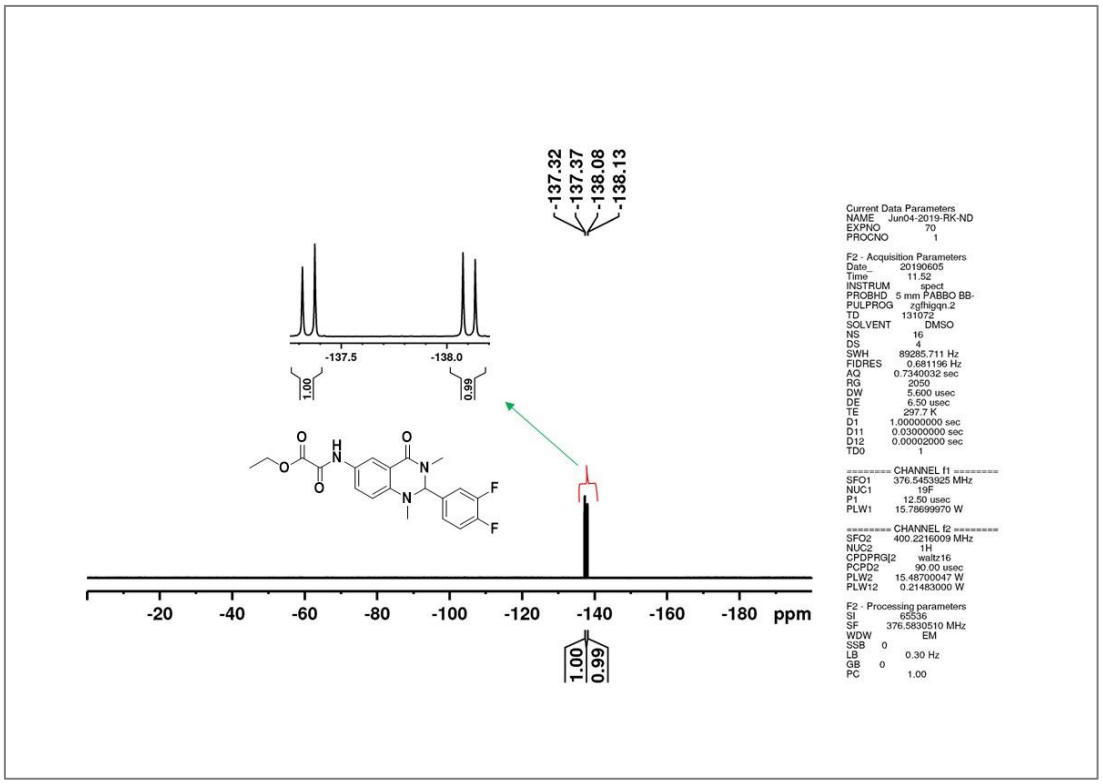
^{13}C NMR spectrum of compound 12 (Chapter 3)



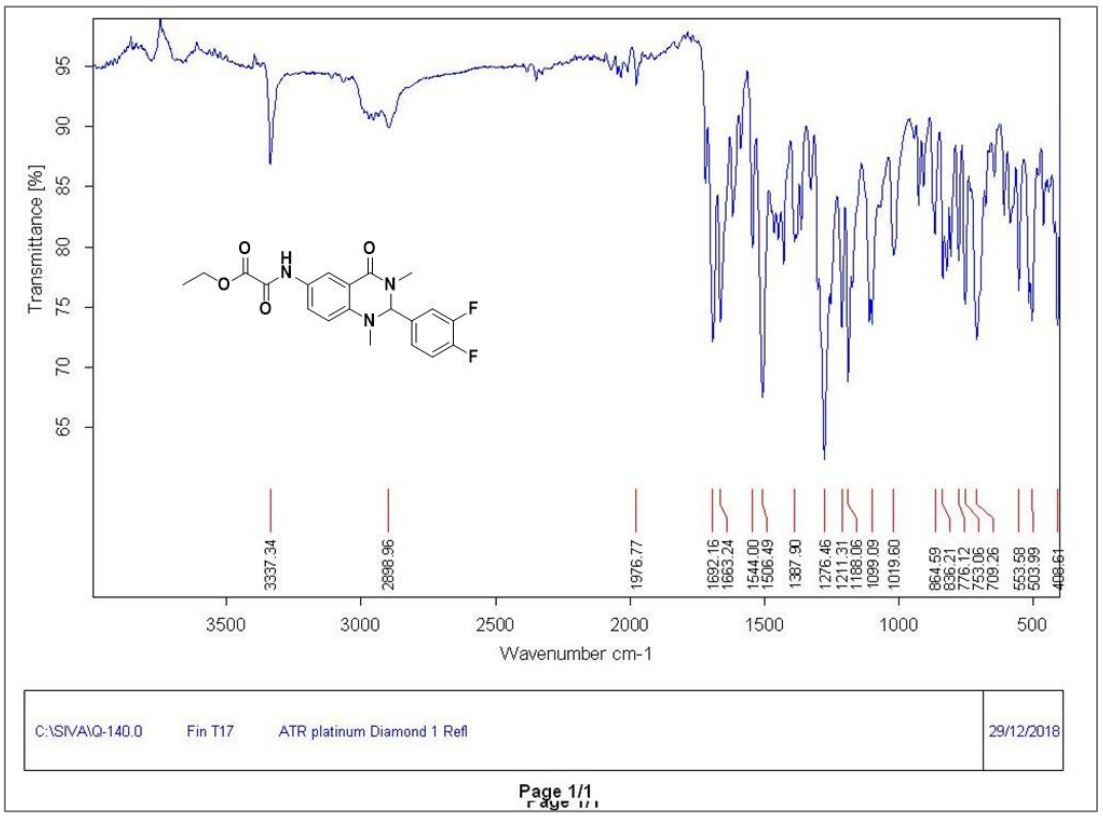
^{1}H NMR spectrum of compound 13a (Chapter 3)



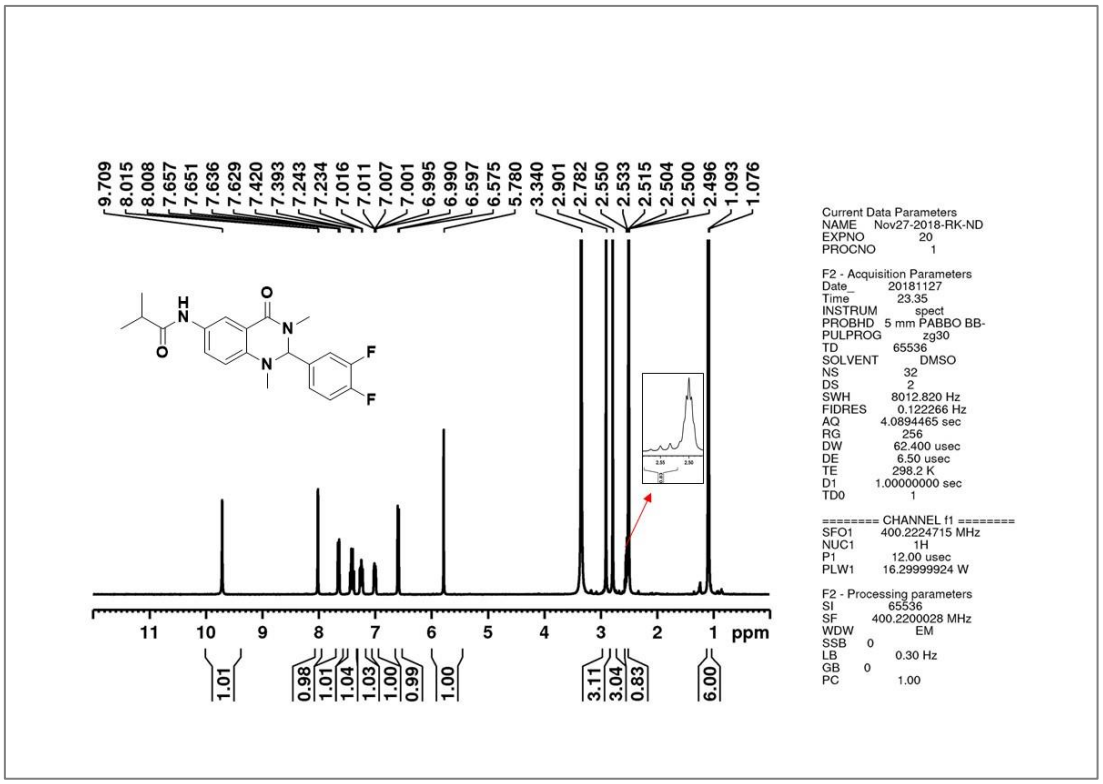
^{13}C NMR spectrum of compound 13a (Chapter 3)



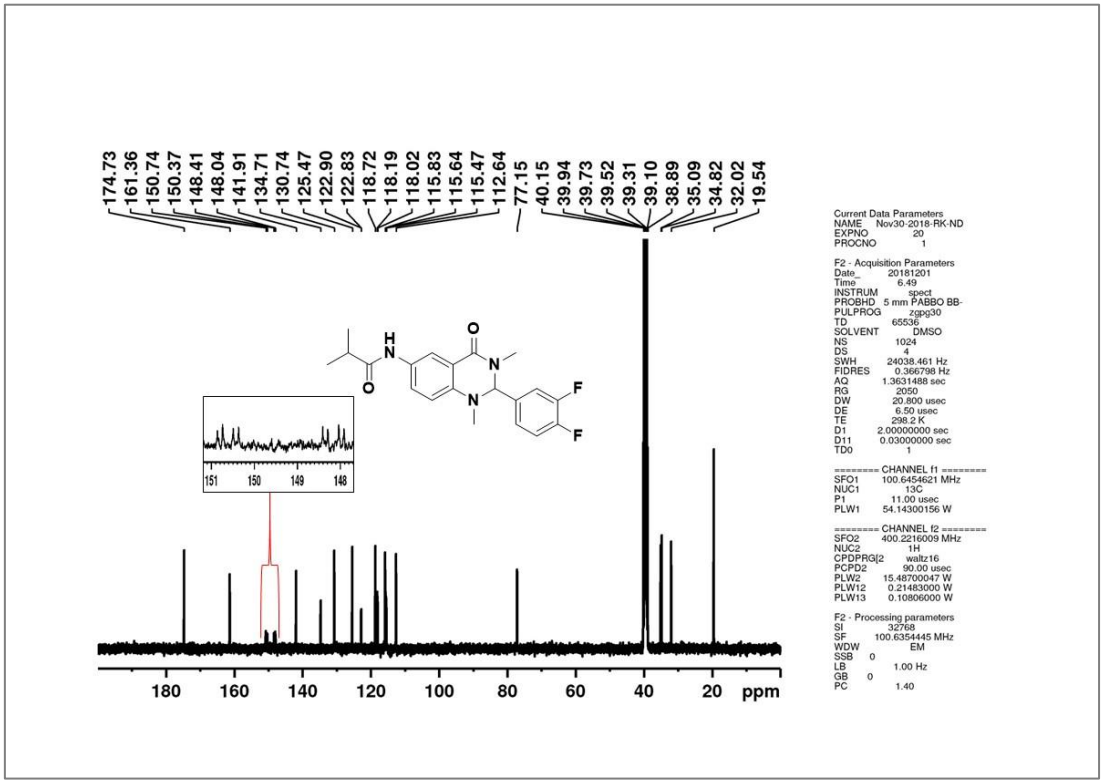
^{19}F NMR spectrum of compound 13a (Chapter 3)



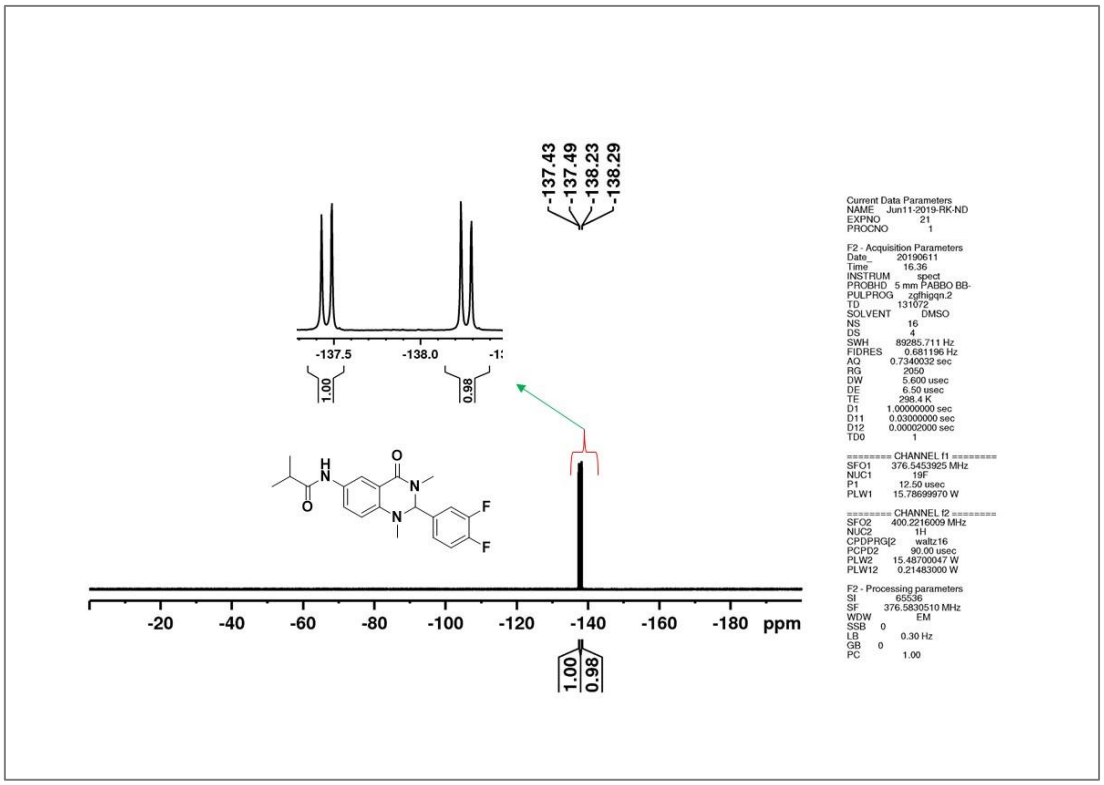
IR spectrum of compound 13a (Chapter 3)



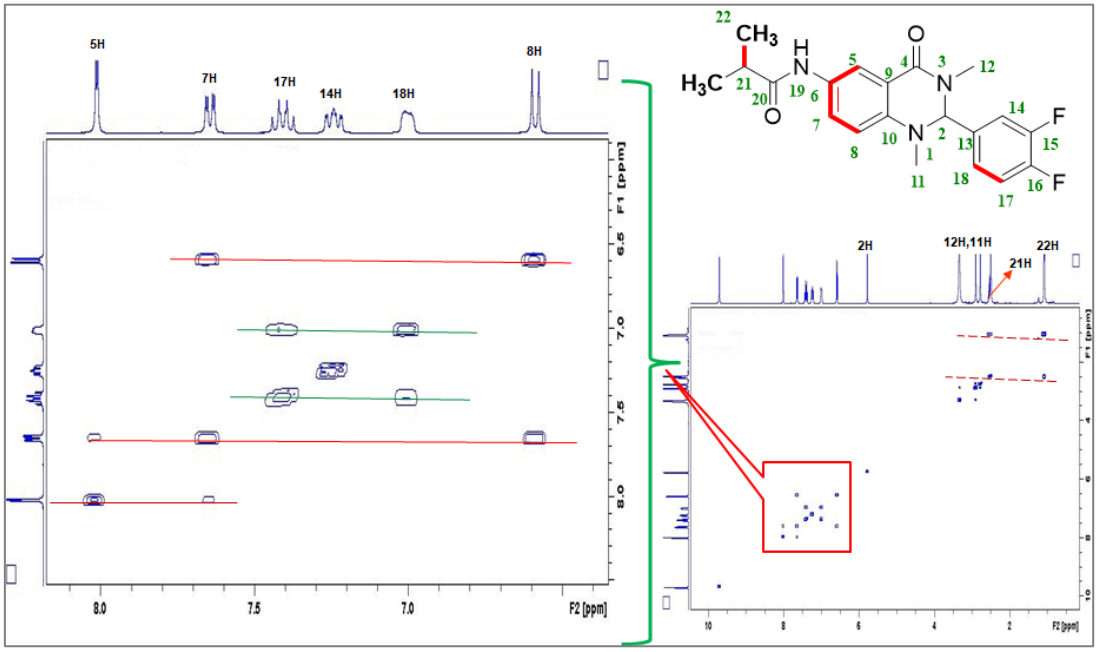
[1]H NMR spectrum of compound 13b (Chapter 3)



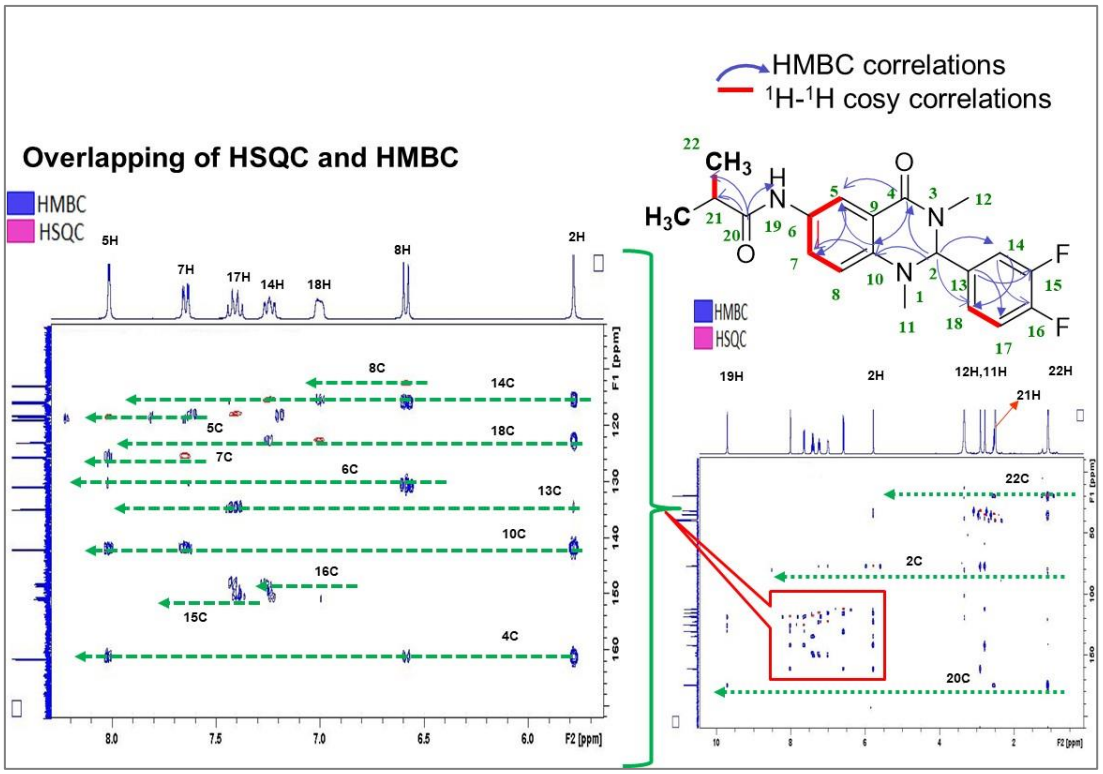
[13]C NMR spectrum of compound 13b (Chapter 3)



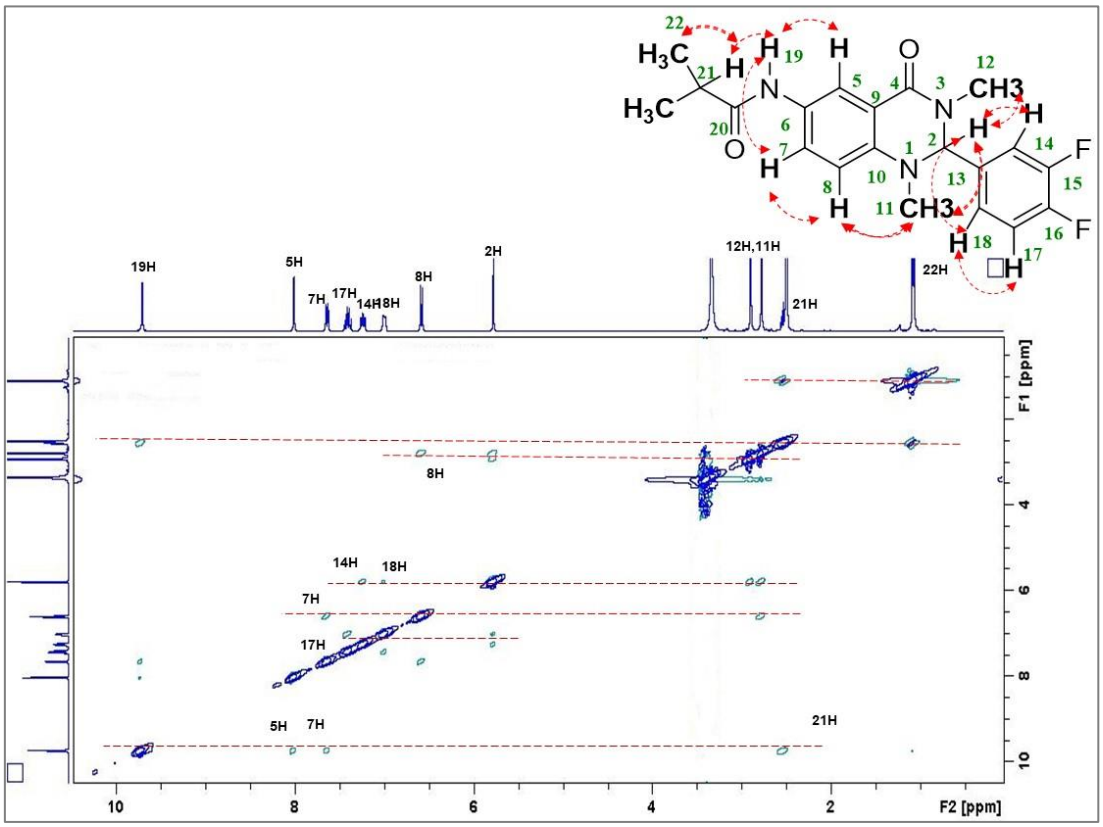
^{19}F NMR spectrum of compound 13b (Chapter 3)



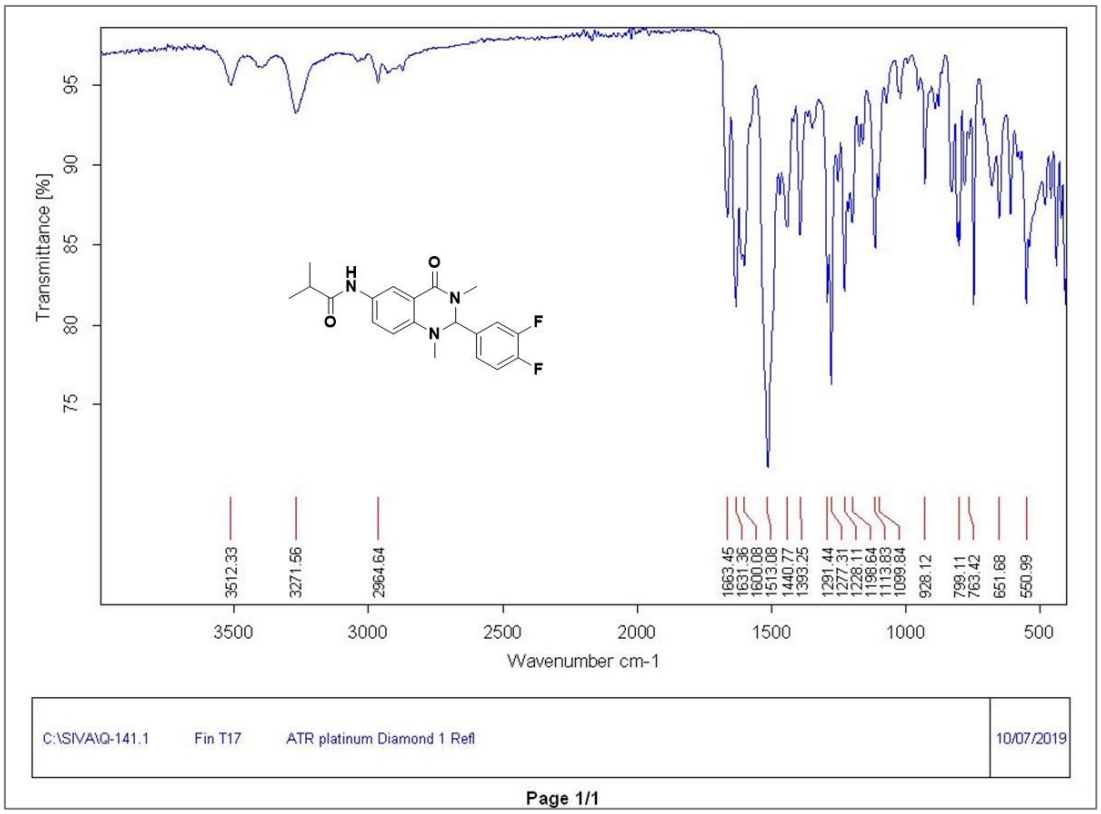
COSY spectrum of compound 13b (Chapter 3)



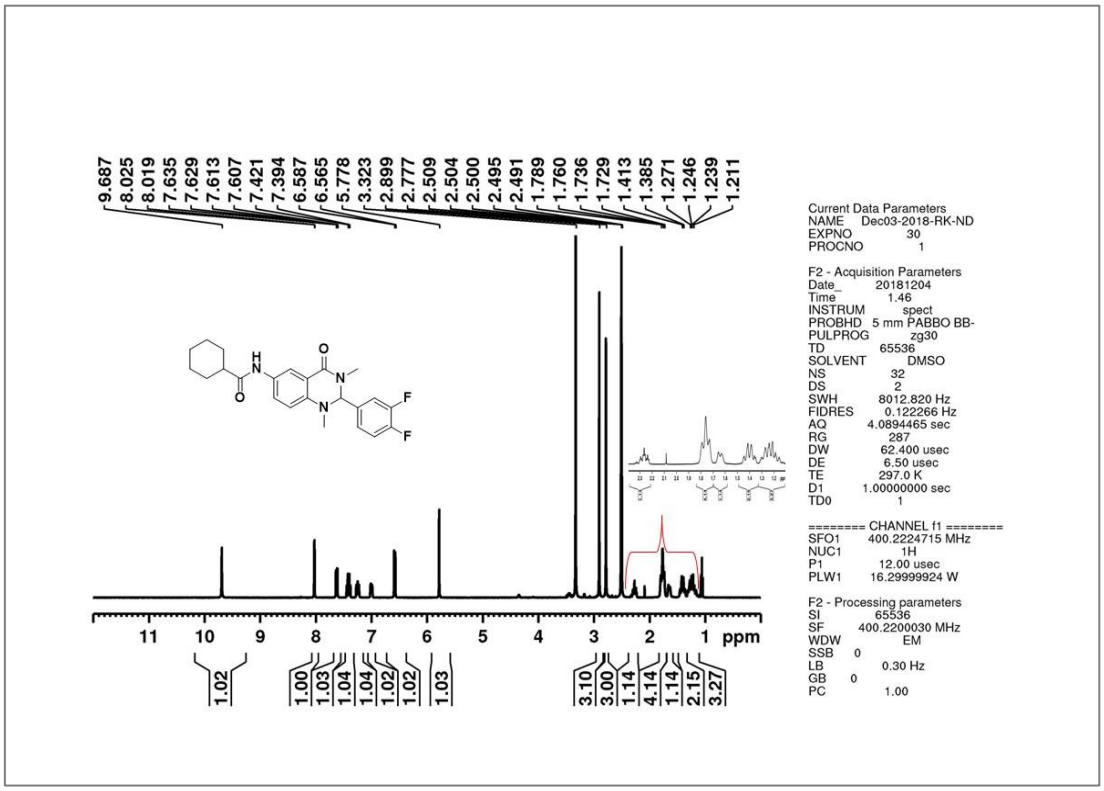
HMBC & HSQC spectrum of compound 13b (Chapter 3)



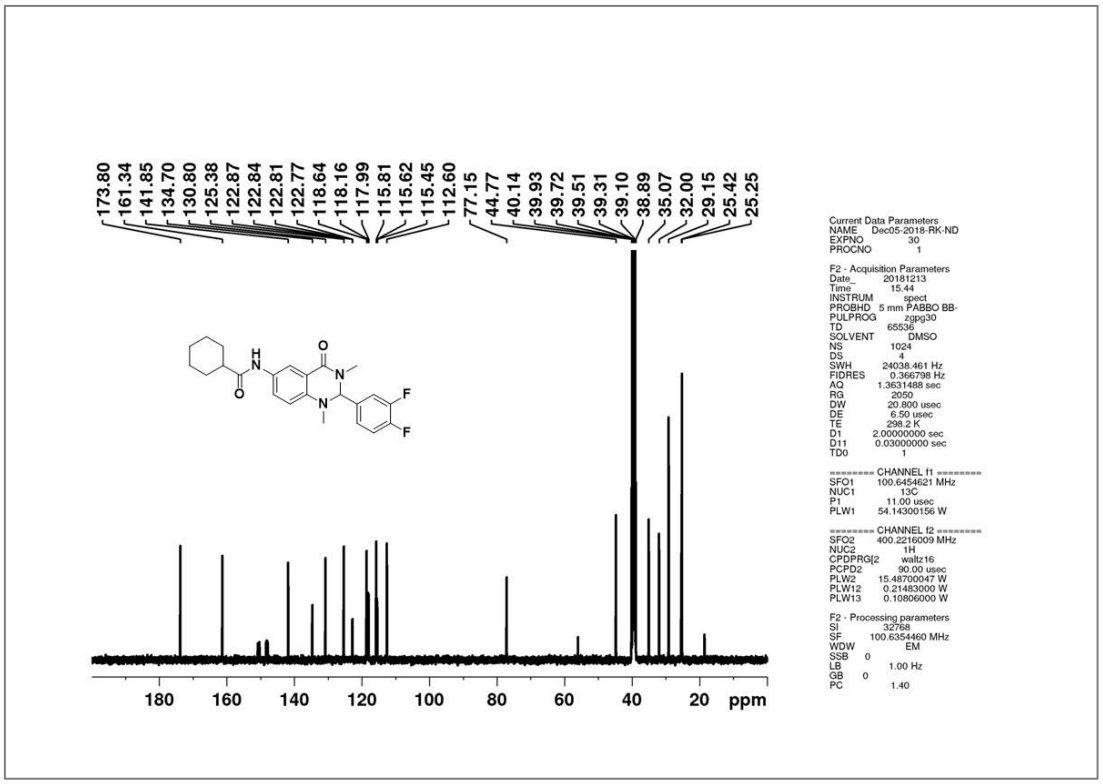
NOESY spectrum of compound 13b (Chapter 3)



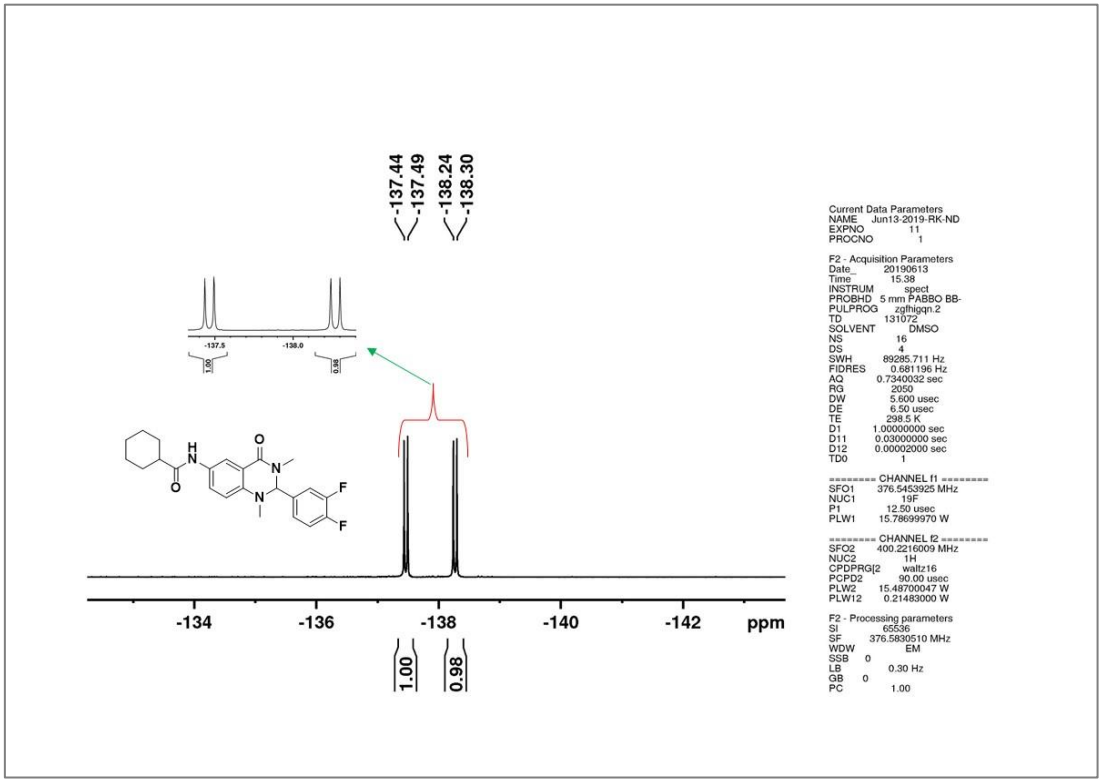
IR spectrum of compound 13b (Chapter 3)



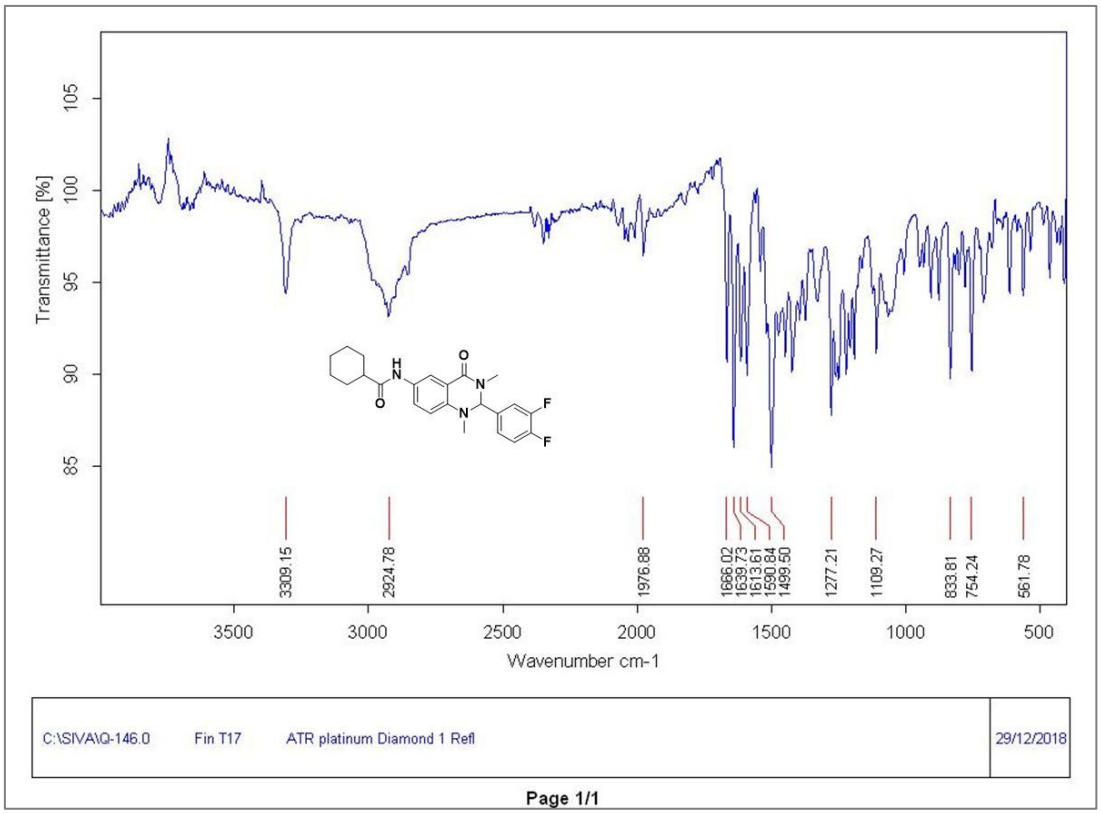
^{1}H NMR spectrum of compound 13c (Chapter 3)



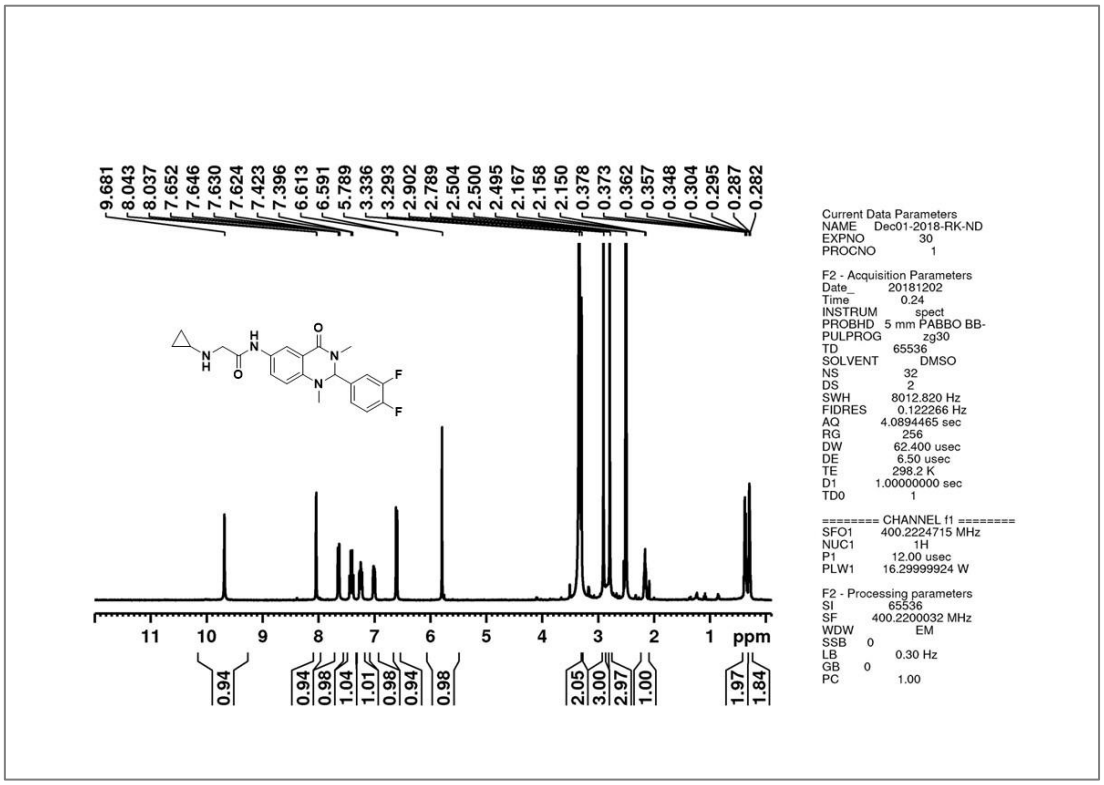
^{13}C NMR spectrum of compound 13c (Chapter 3)



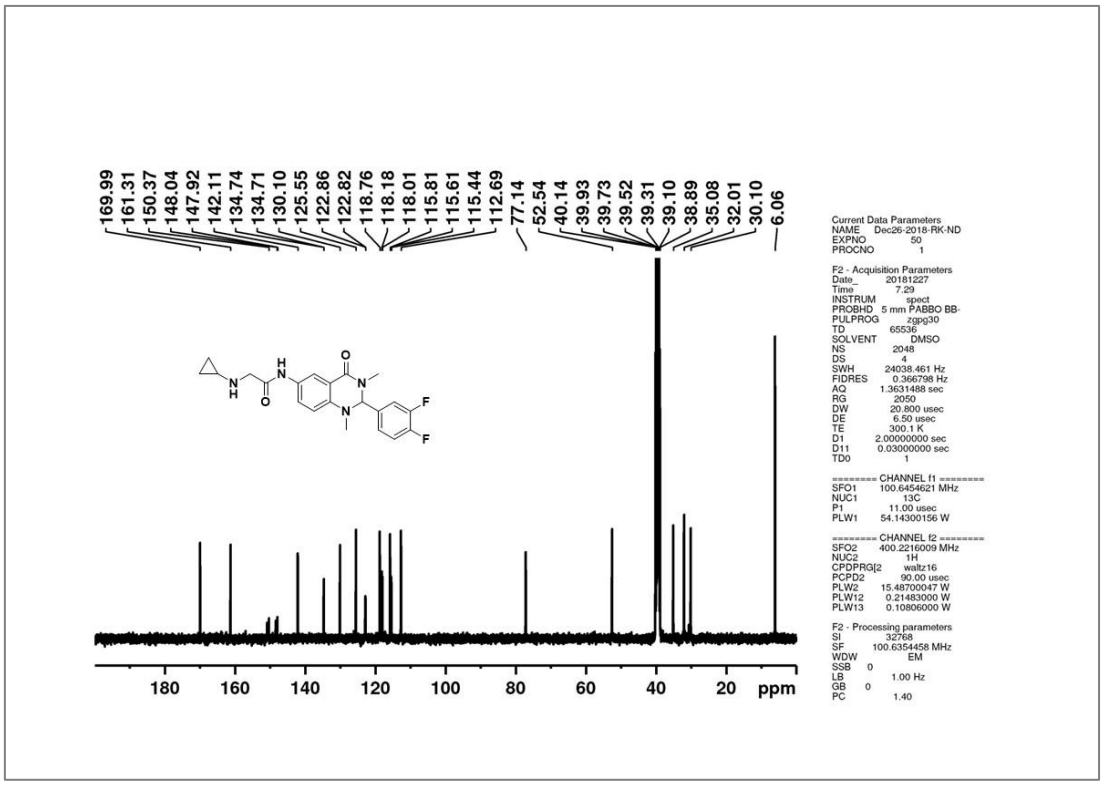
^{19}F NMR spectrum of compound 13c (Chapter 3)



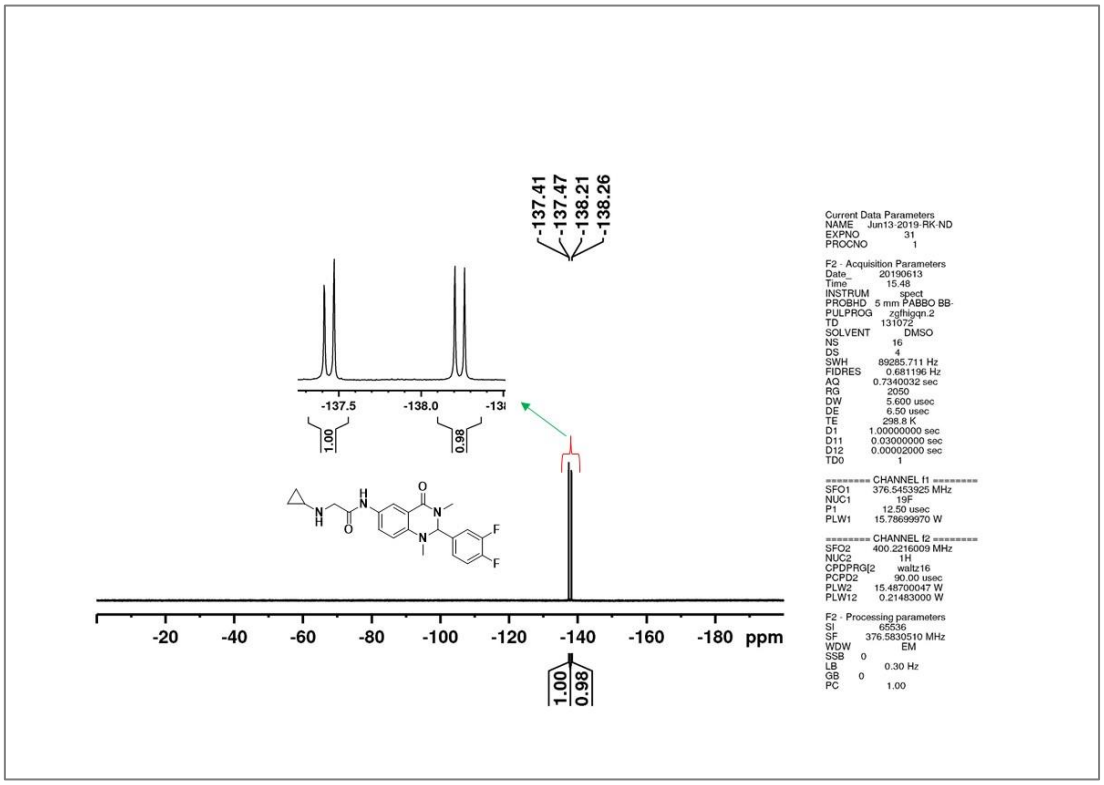
IR spectrum of compound 13c (Chapter 3)



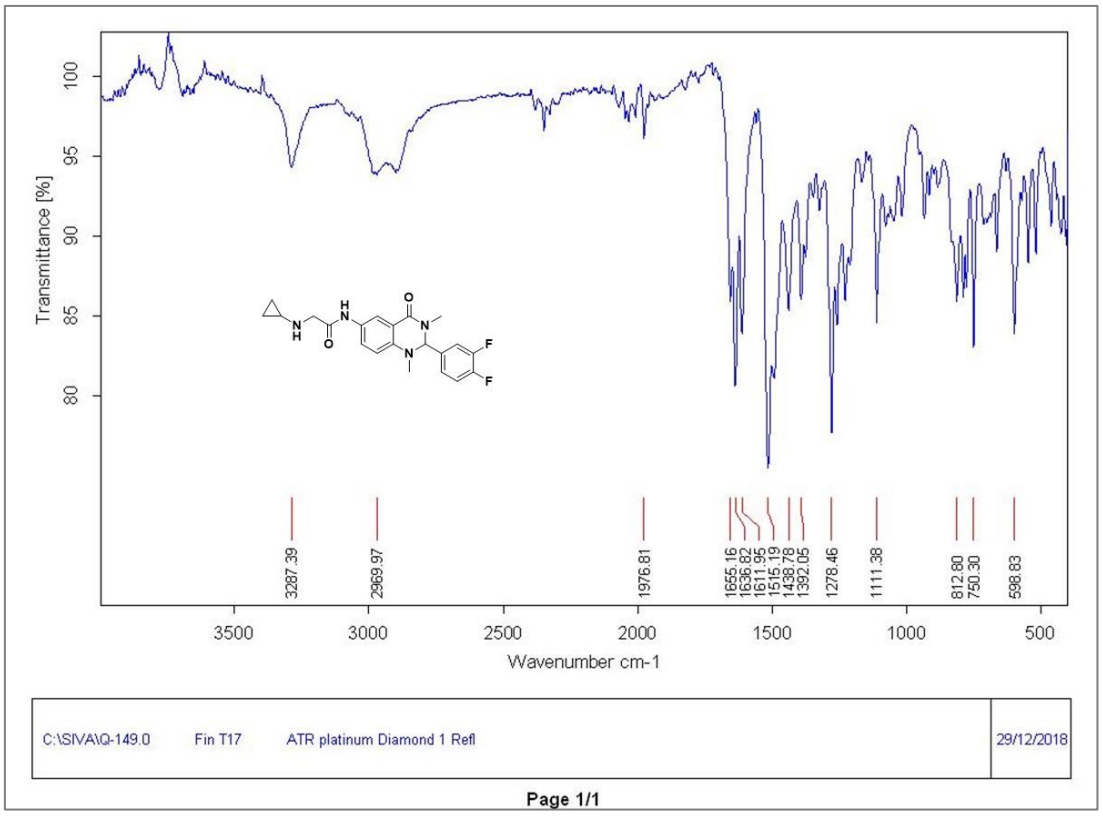
^{1}H NMR spectrum of compound 13d (Chapter 3)



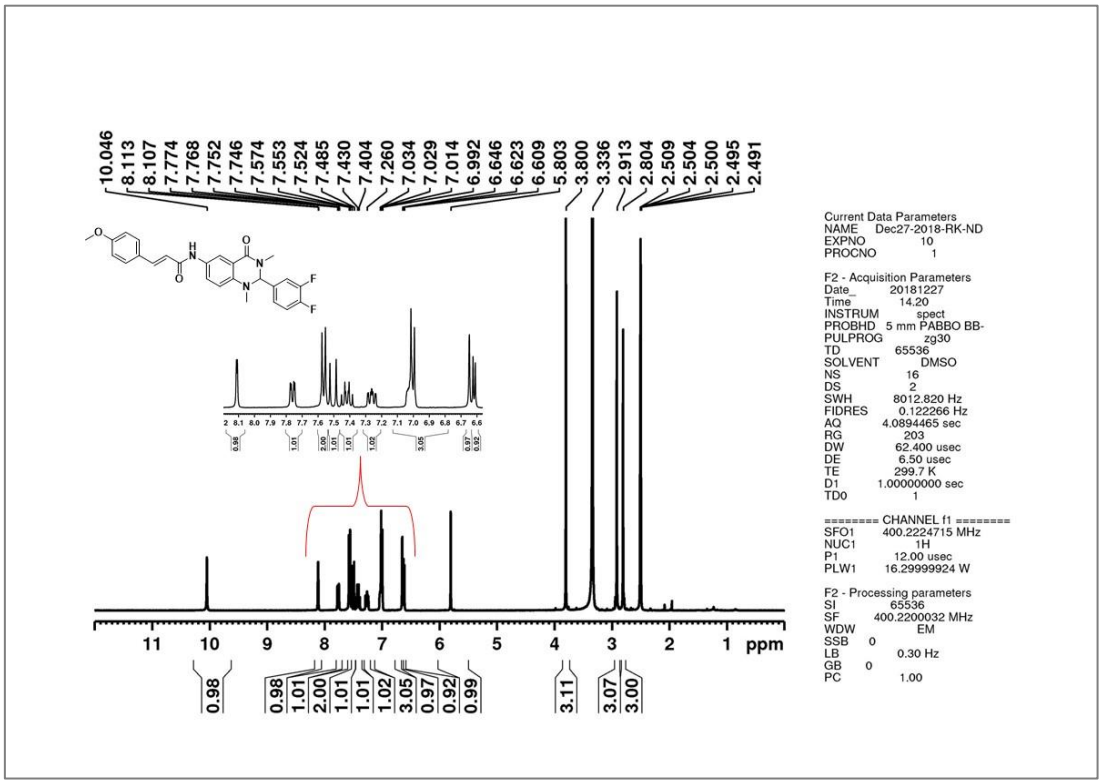
^{13}C NMR spectrum of compound 13d (Chapter 3)



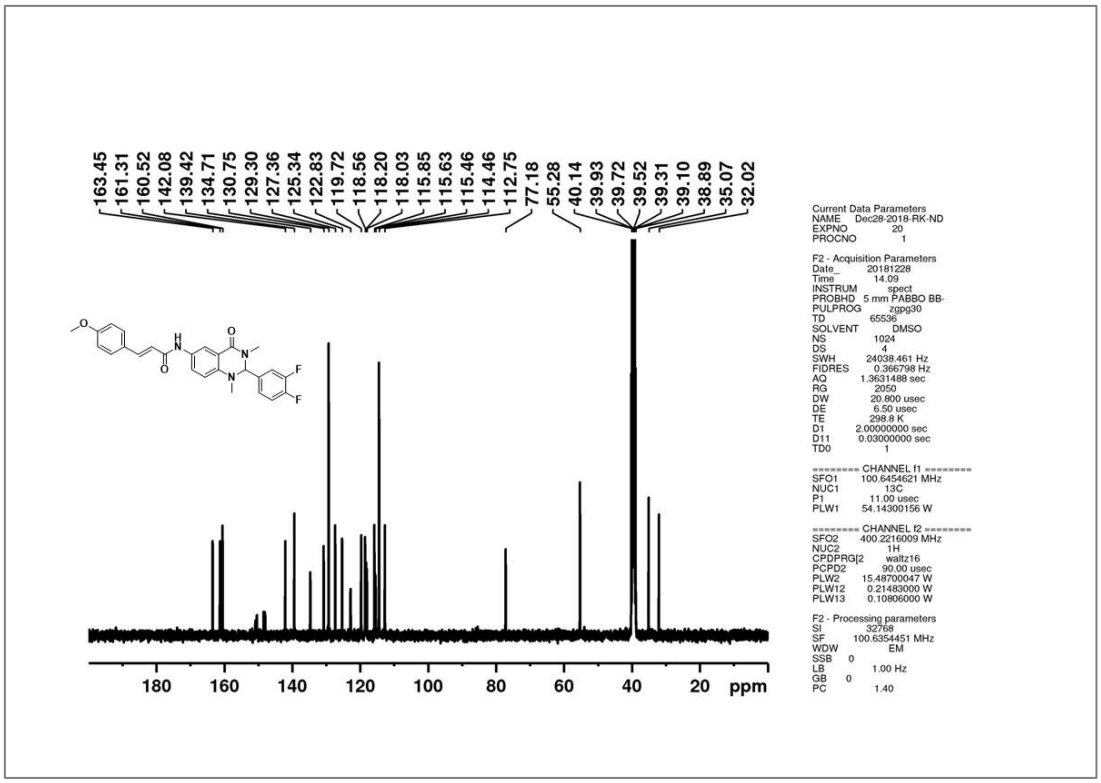
^{19}F NMR spectrum of compound 13d (Chapter 3)



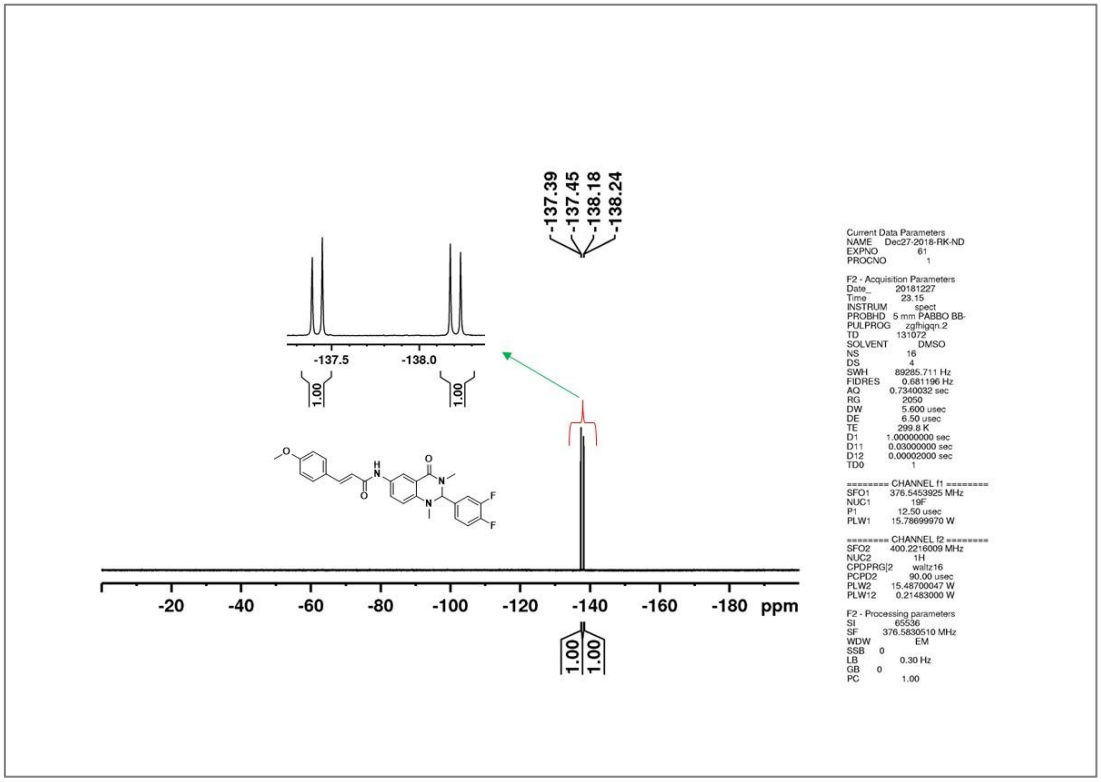
IR spectrum of compound 13d (Chapter 3)



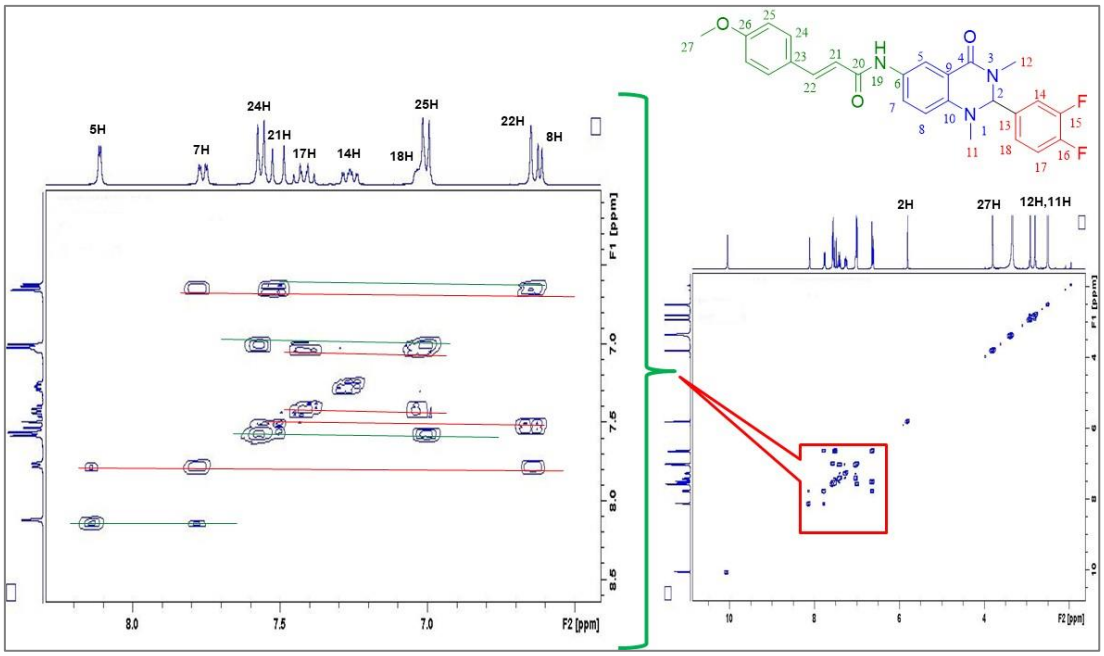
^{1}H NMR spectrum of compound 13e (Chapter 3)



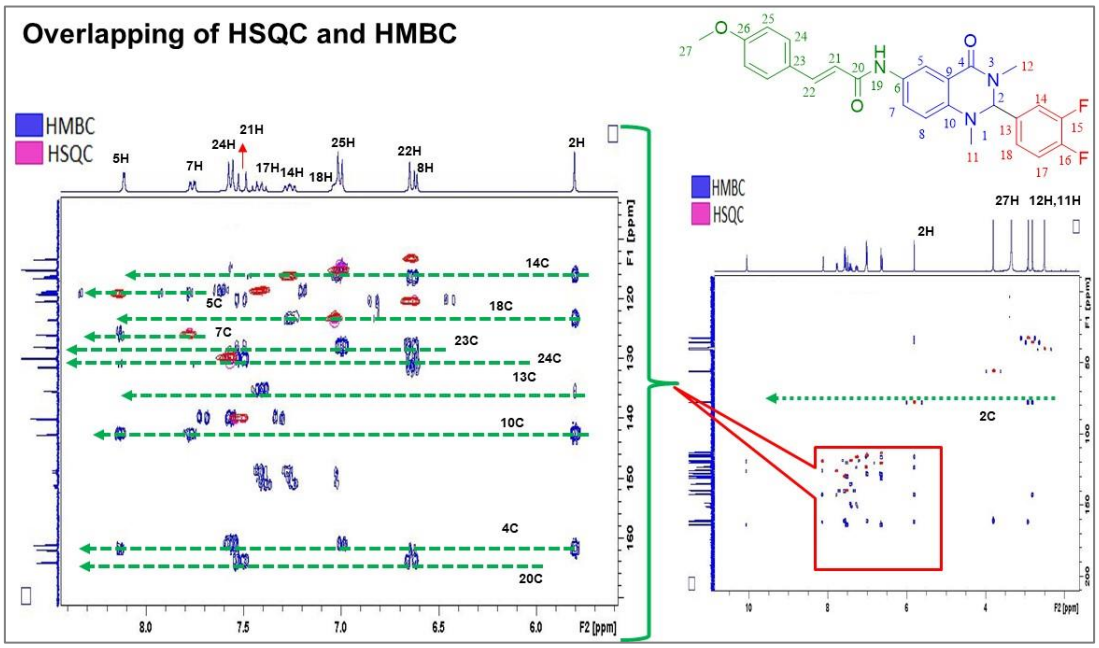
^{13}C NMR spectrum of compound 13e (Chapter 3)



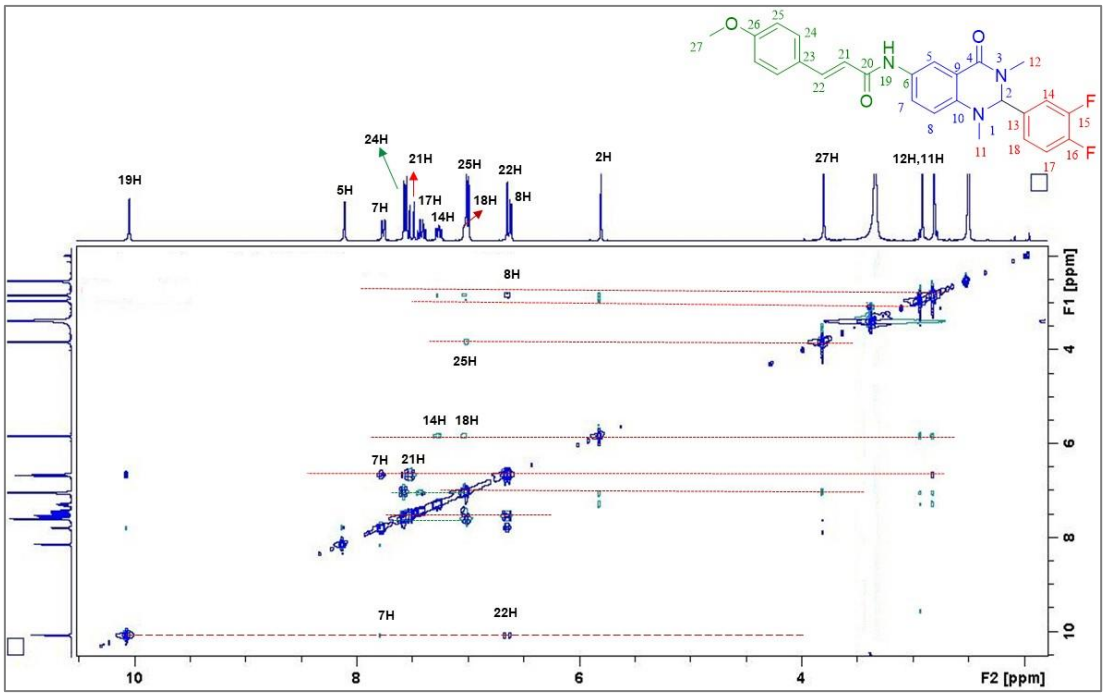
^{19}F NMR spectrum of compound 13e (Chapter 3)



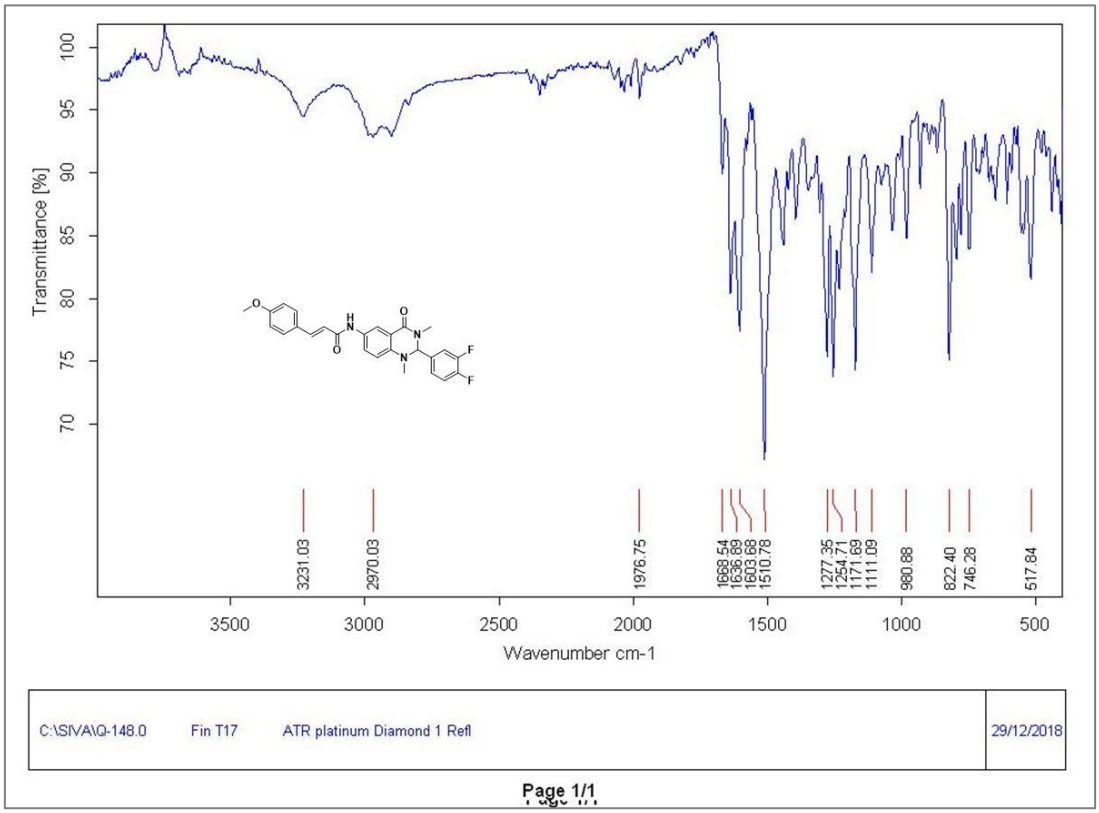
COSY spectrum of compound 13e (Chapter 3)



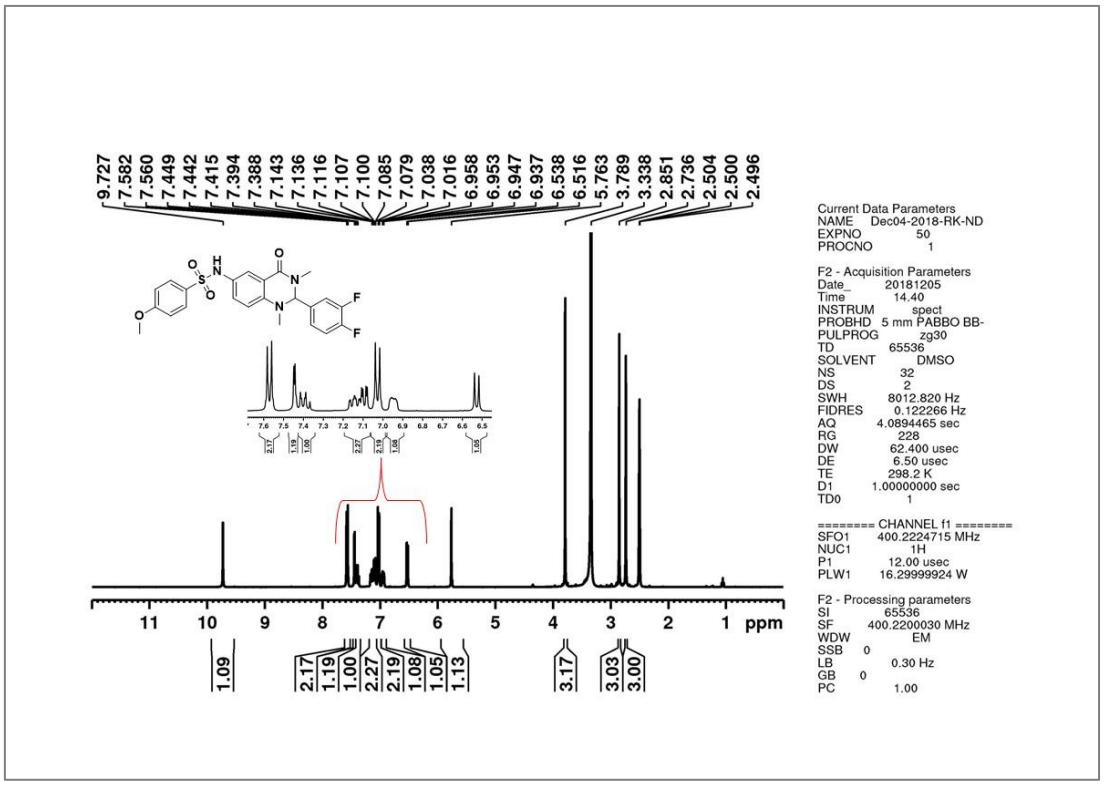
HMBC & HSQC spectrum of compound 13e (Chapter 3)



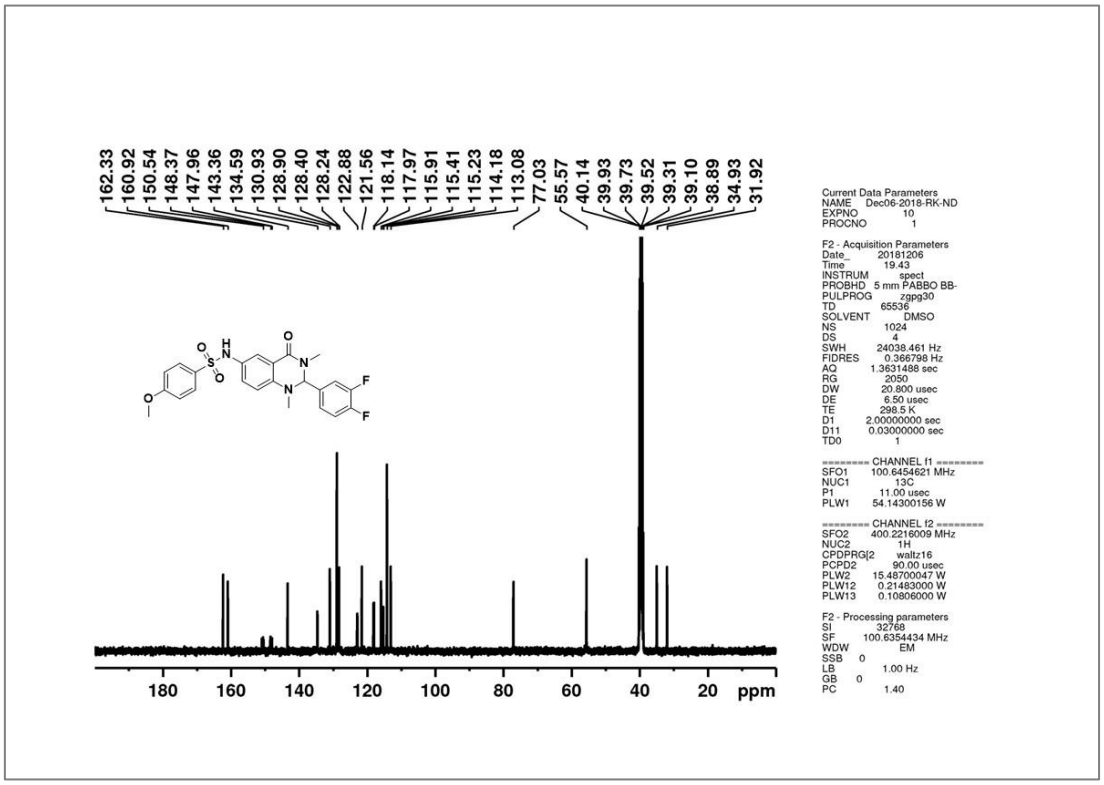
NOESY spectrum of compound 13e (Chapter 3)



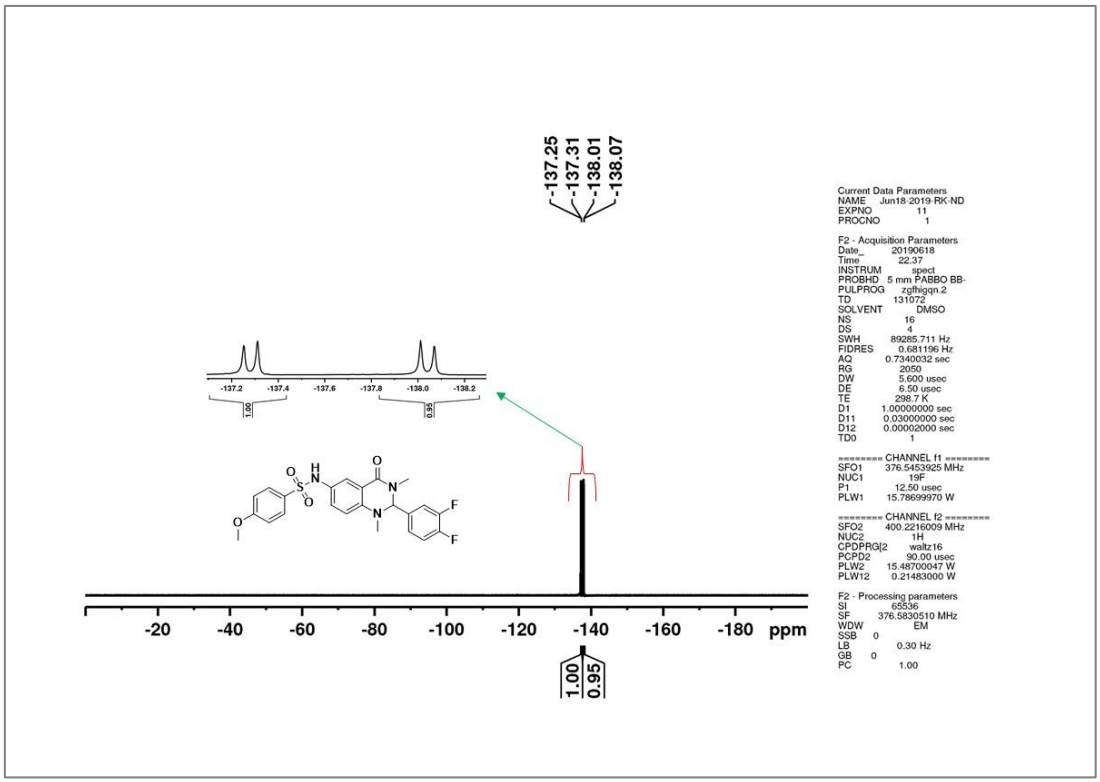
IR spectrum of compound 13e (Chapter 3)



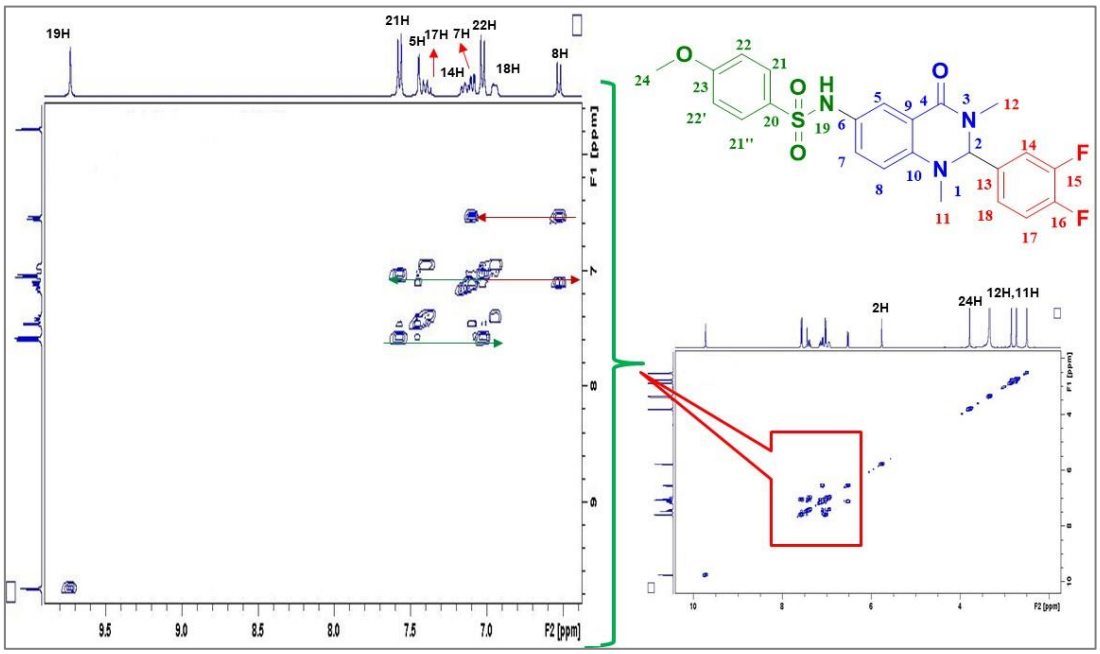
^{1}H NMR spectrum of compound 13f (Chapter 3)



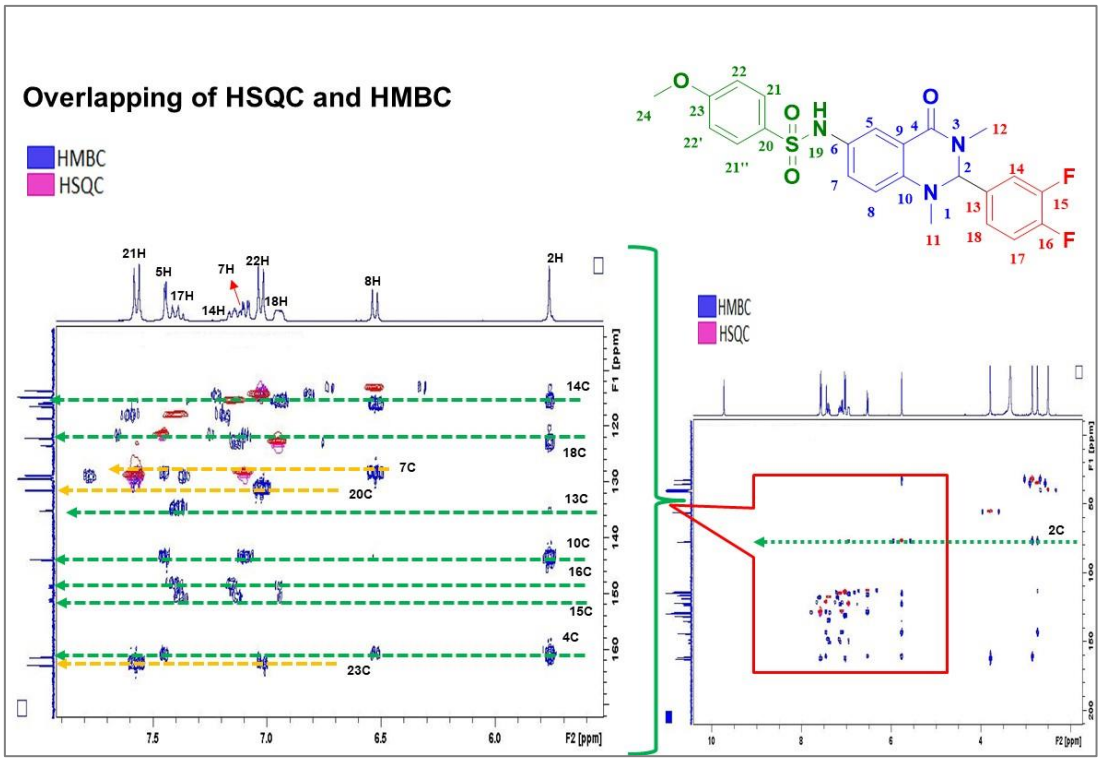
^{13}C NMR spectrum of compound 13f (Chapter 3)



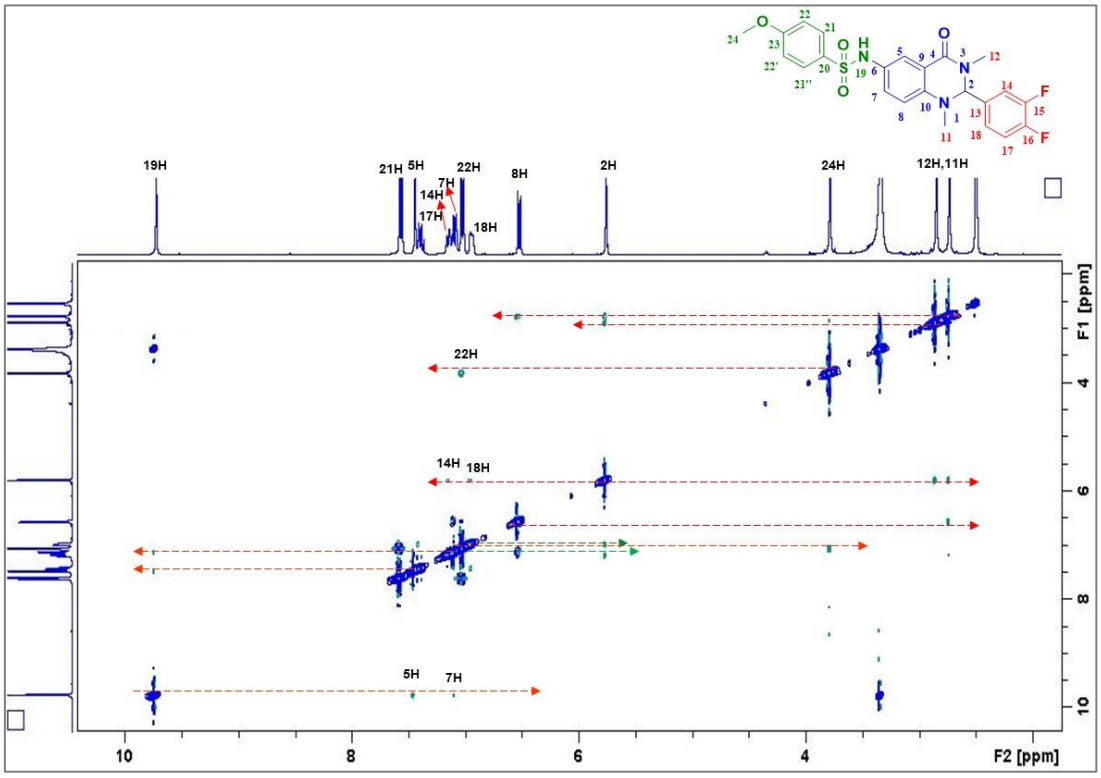
^{19}F NMR spectrum of compound 13f (Chapter 3)



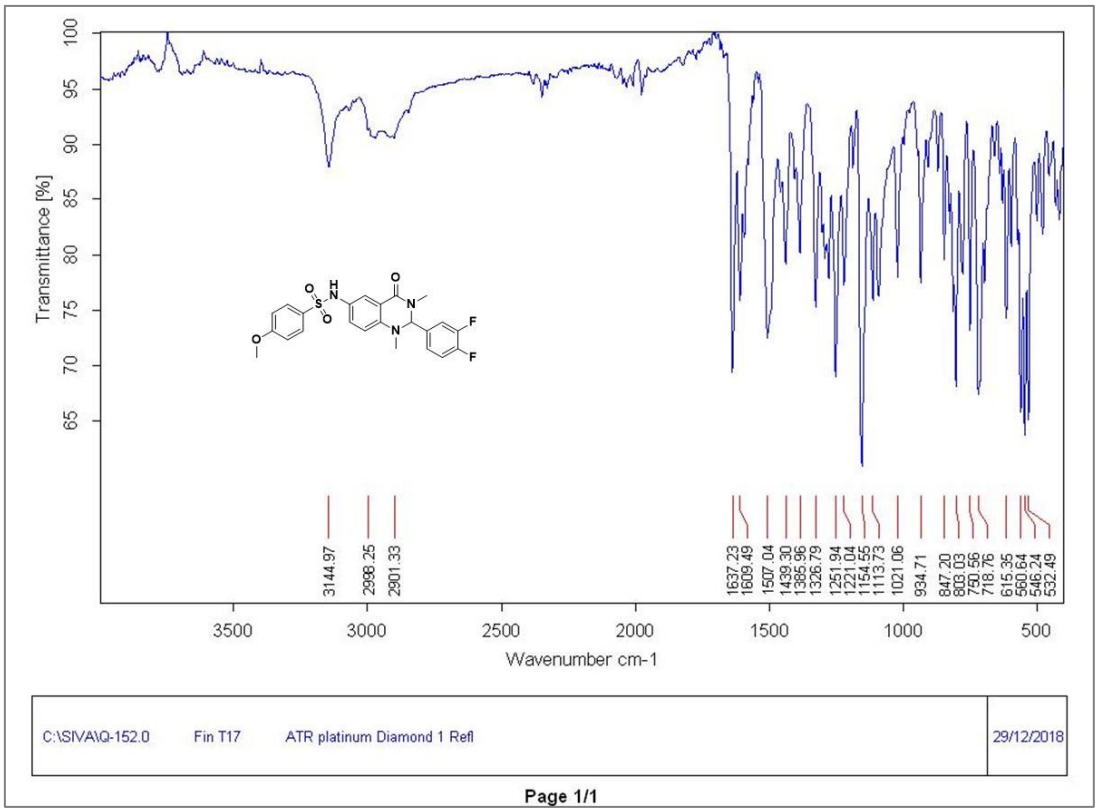
COSY spectrum of compound 13f (Chapter 3)



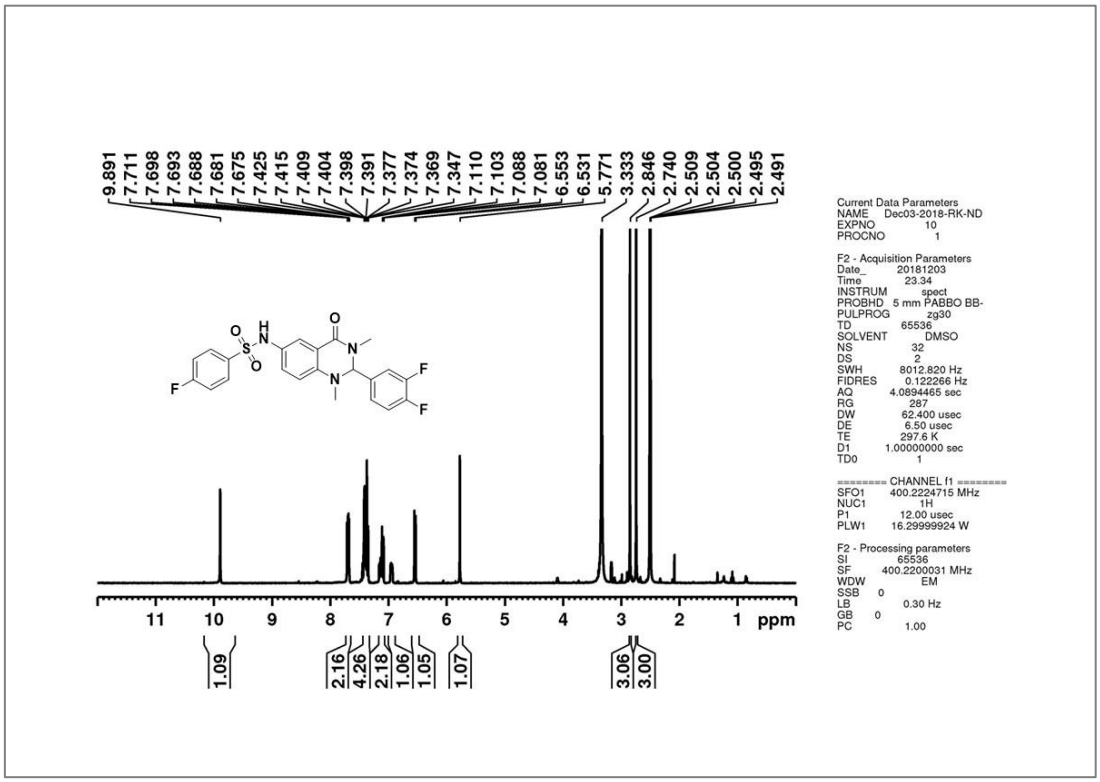
HMBC & HSQC spectrum of compound 13f (Chapter 3)



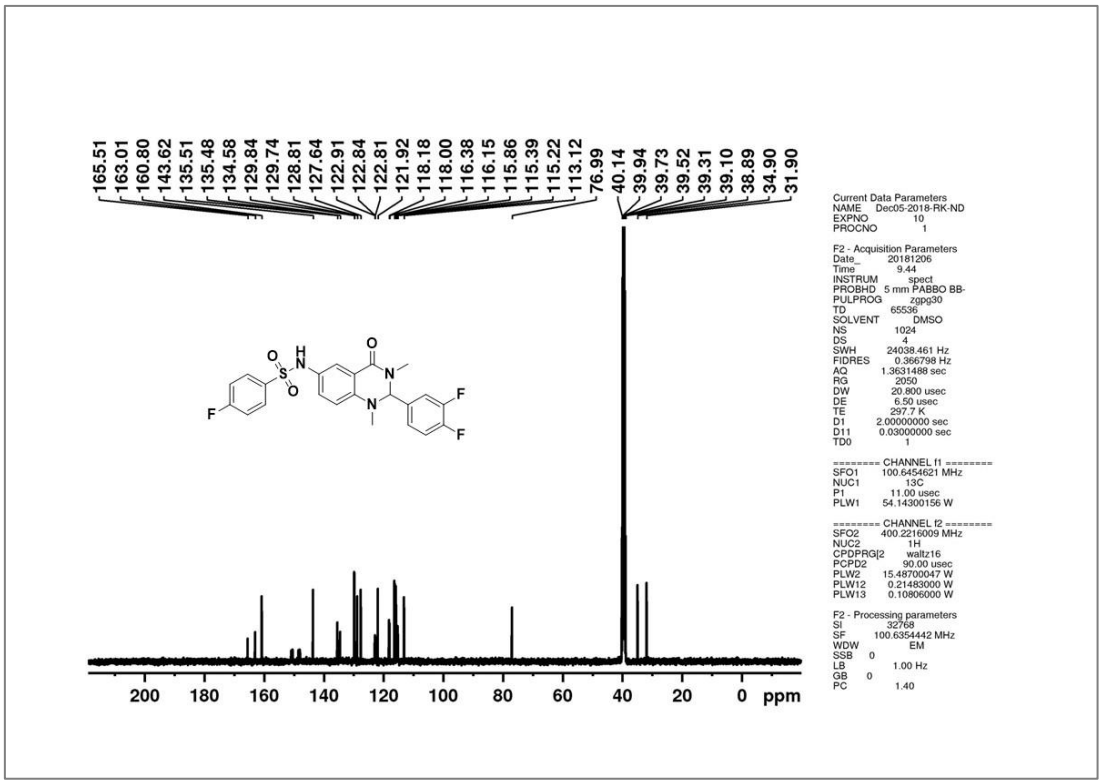
NOESY spectrum of compound 13f (Chapter 3)



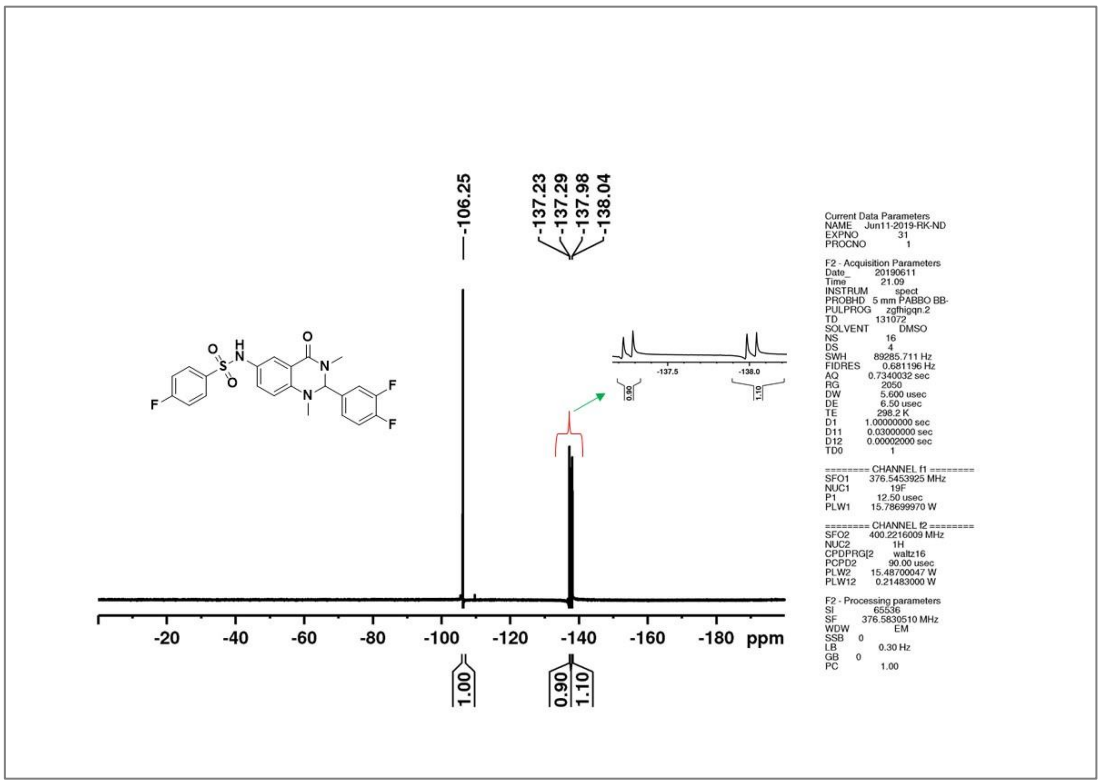
IR spectrum of compound 13f (Chapter 3)



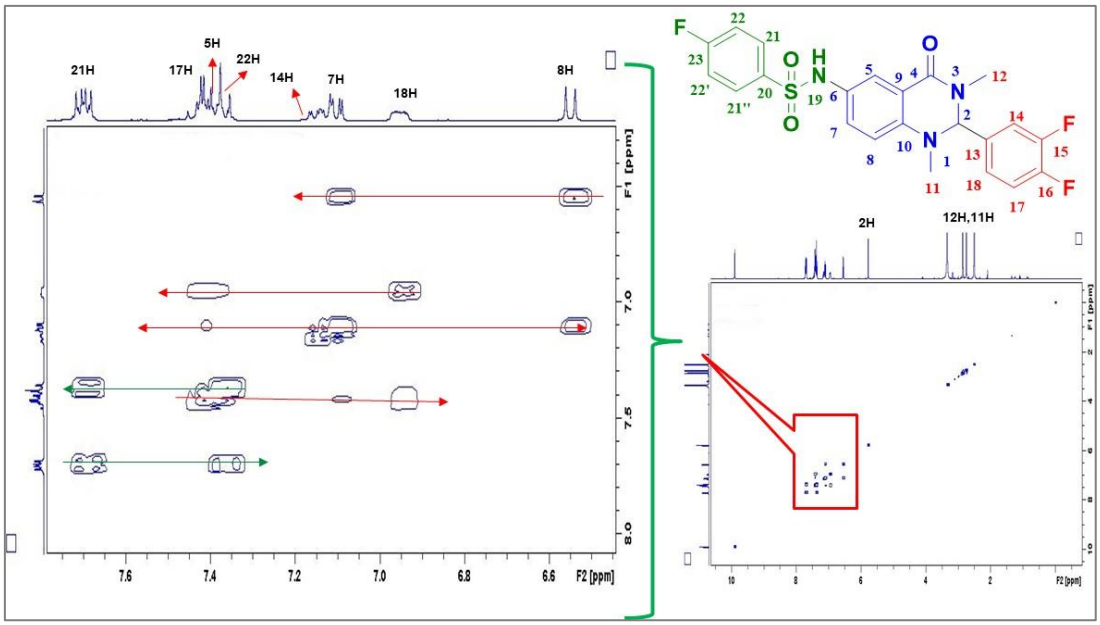
^{1}H NMR spectrum of compound 13g (Chapter 3)



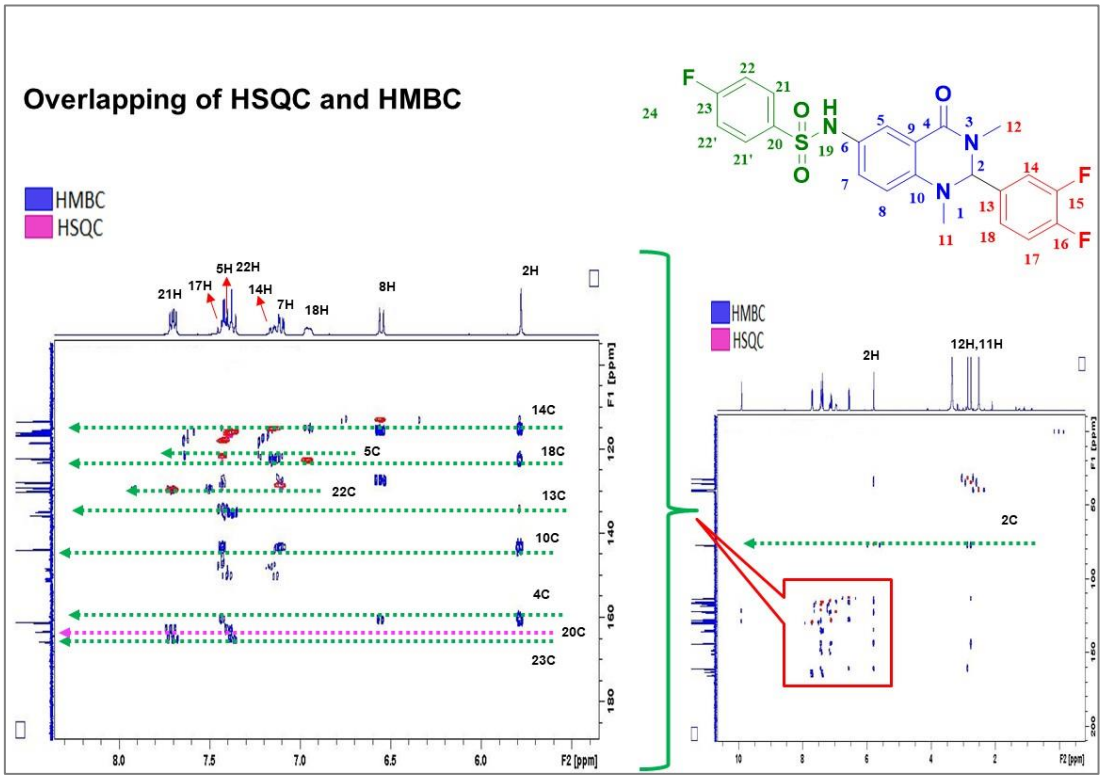
^{13}C NMR spectrum of compound 13g (Chapter 3)



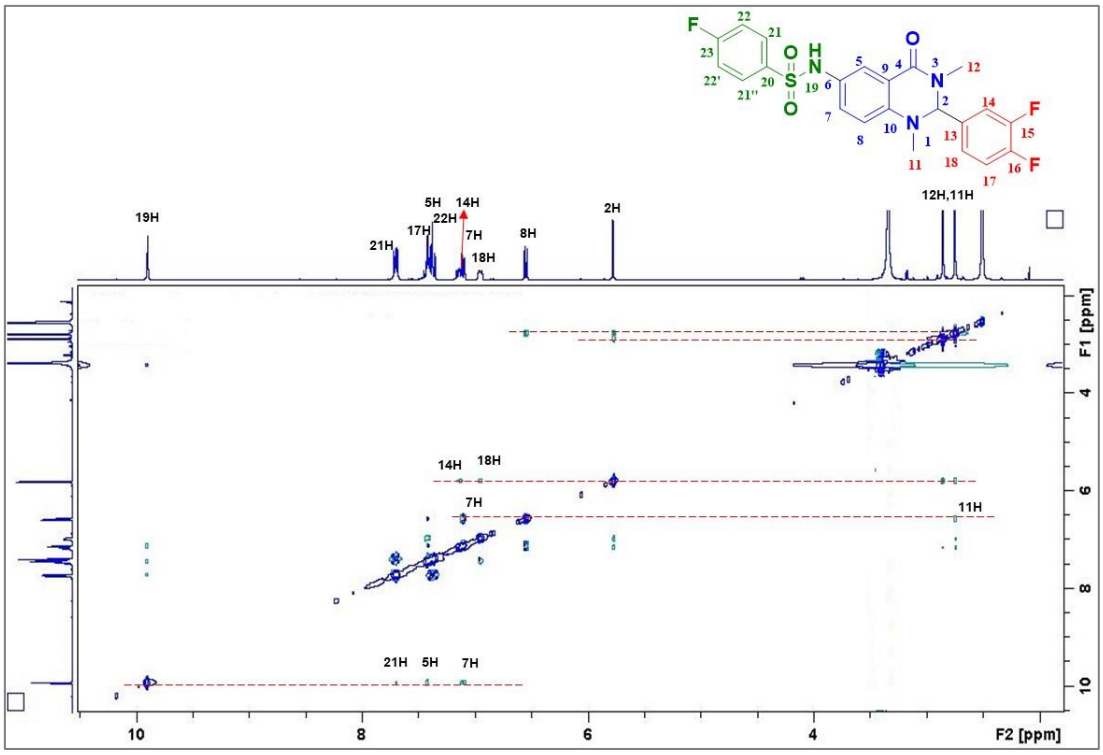
^{19}F NMR spectrum of 13g (Chapter 3)



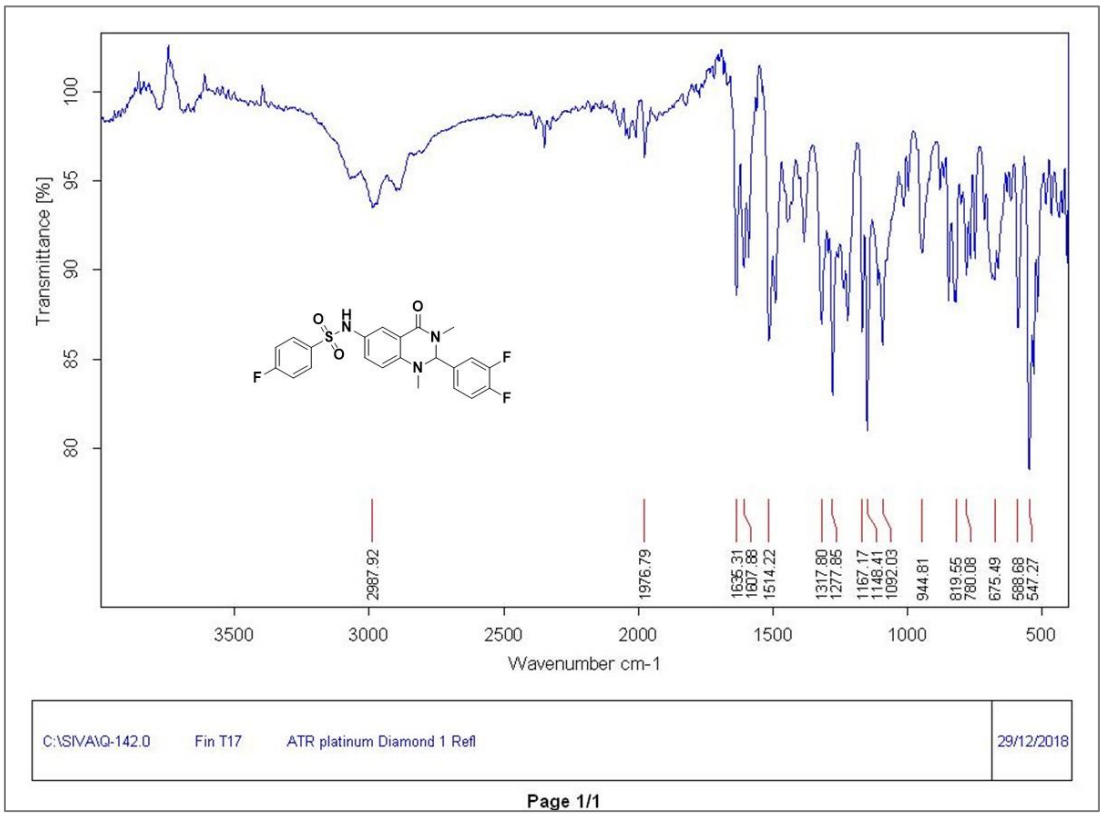
COSY spectrum of compound 13g (Chapter 3)



HMBC & HSQC spectrum of compound 13g (Chapter 3)



NOESY spectrum of compound 13g (Chapter



IR spectrum of compound 13g (Chapter 3)

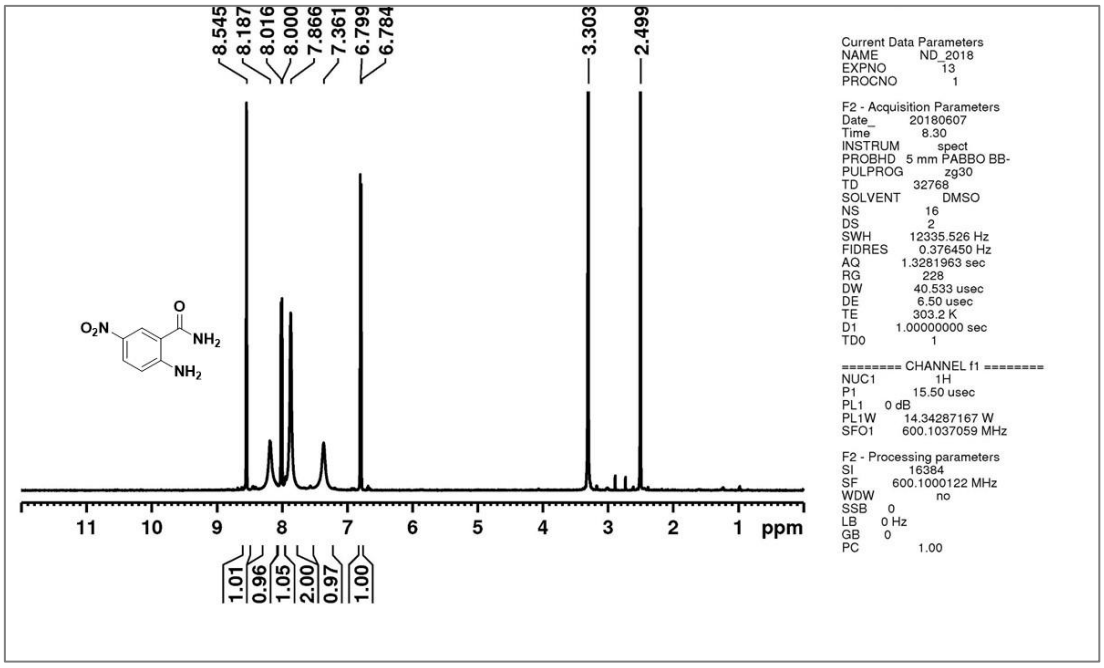
APPENDIX – III

SUPPLEMENTARY INFORMATION

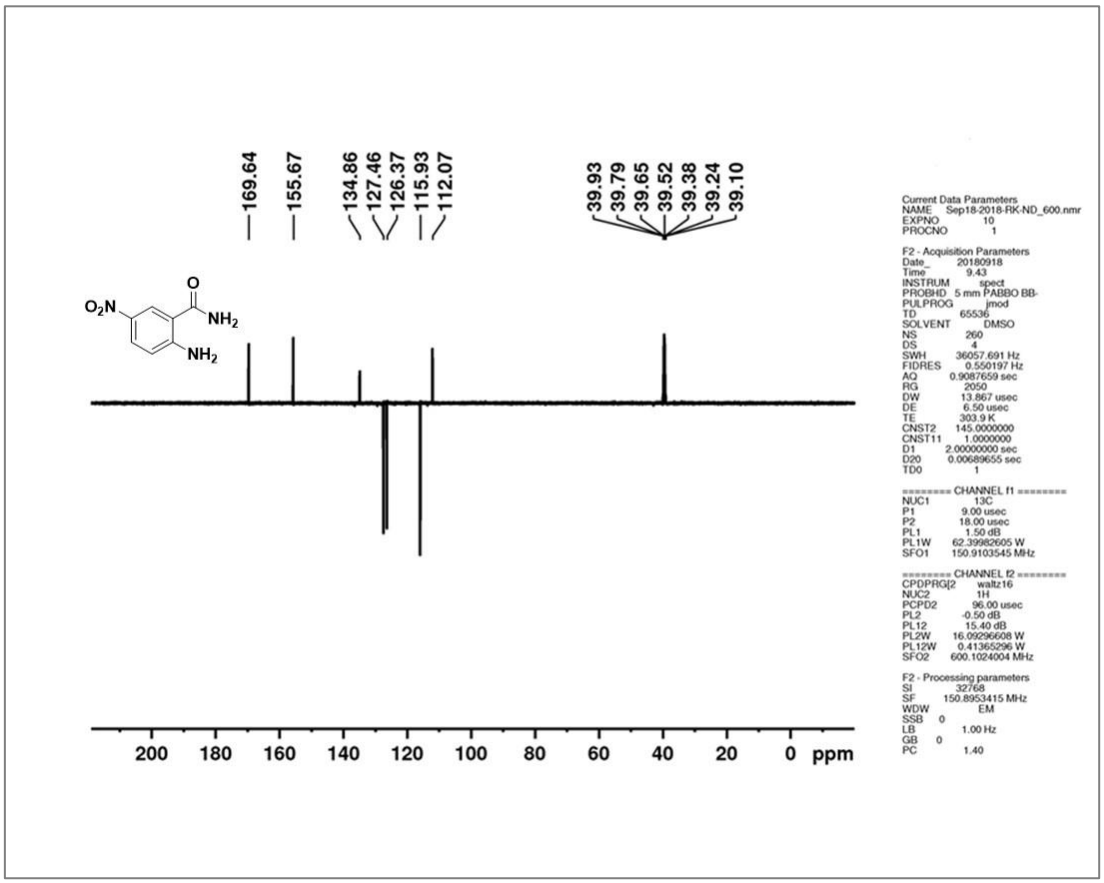
CHAPTER 4

Design, synthesis and spectral characterization of novel quinazoline derivatives as an anti-tubercular agent

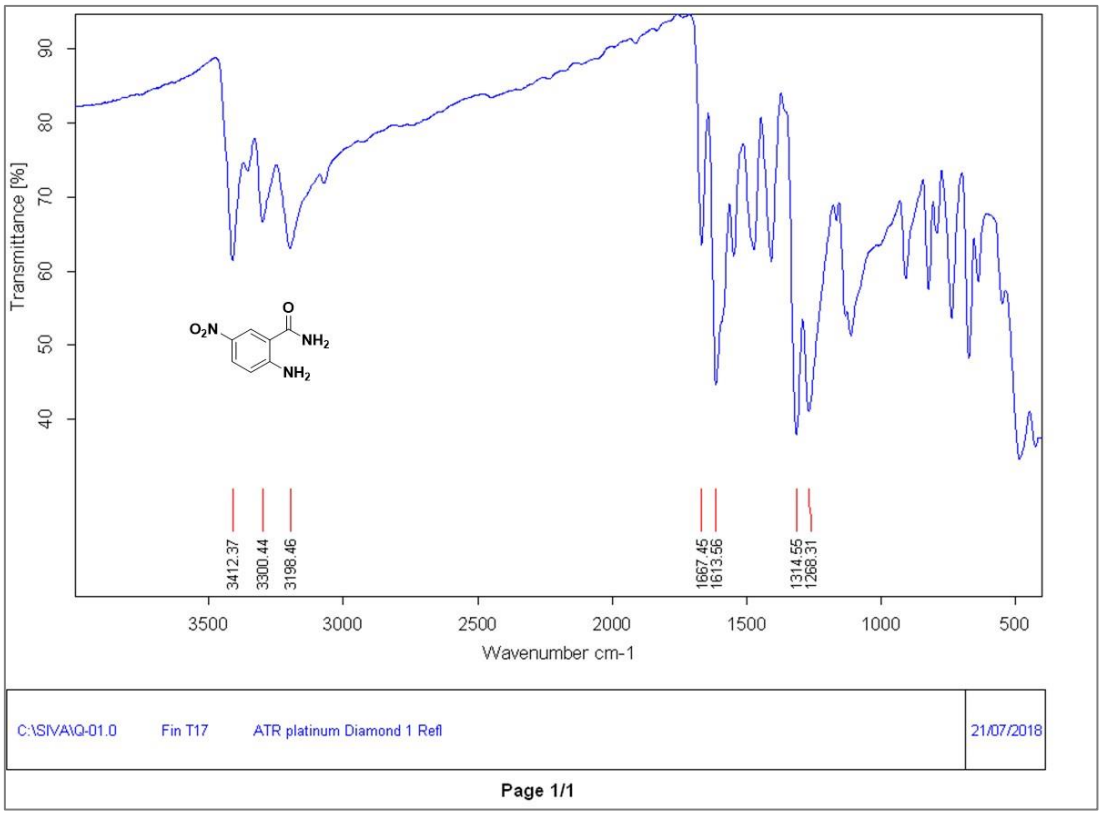
Department of Pharmaceutical Chemistry, Discipline of Pharmaceutical Sciences, College of Health Sciences, University of KwaZulu-Natal (Westville), Durban-4000, South Africa



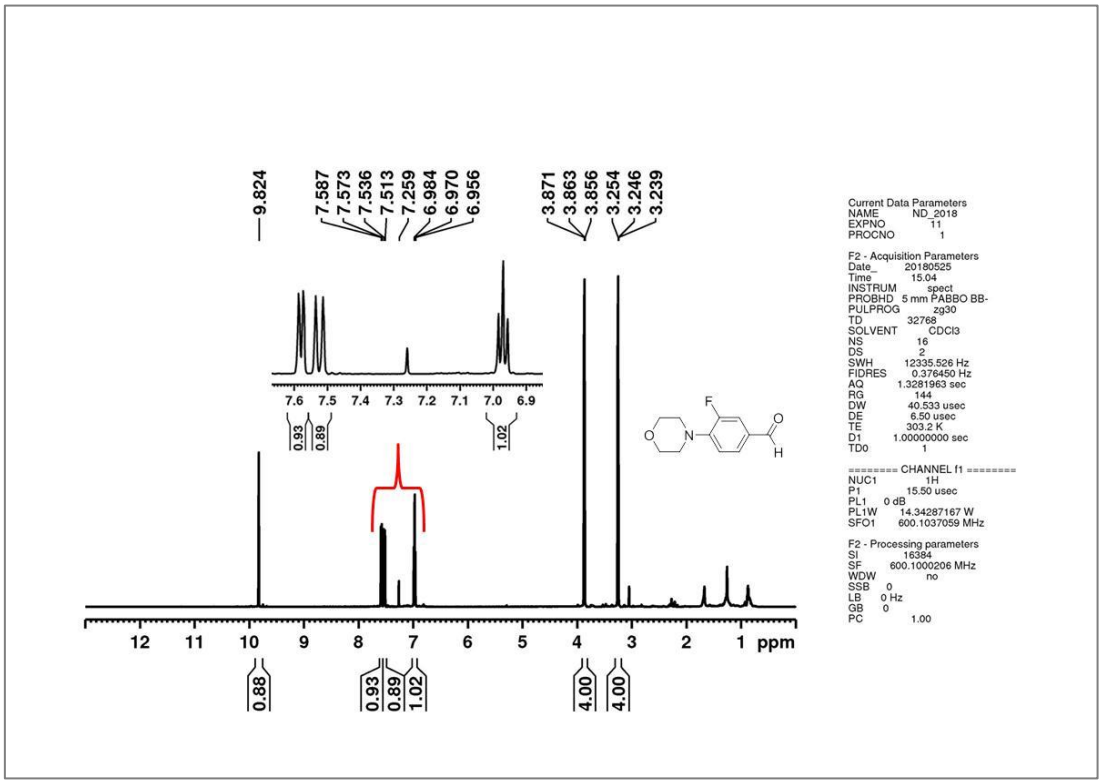
^{1}H NMR spectrum of compound 2 (Chapter 4)



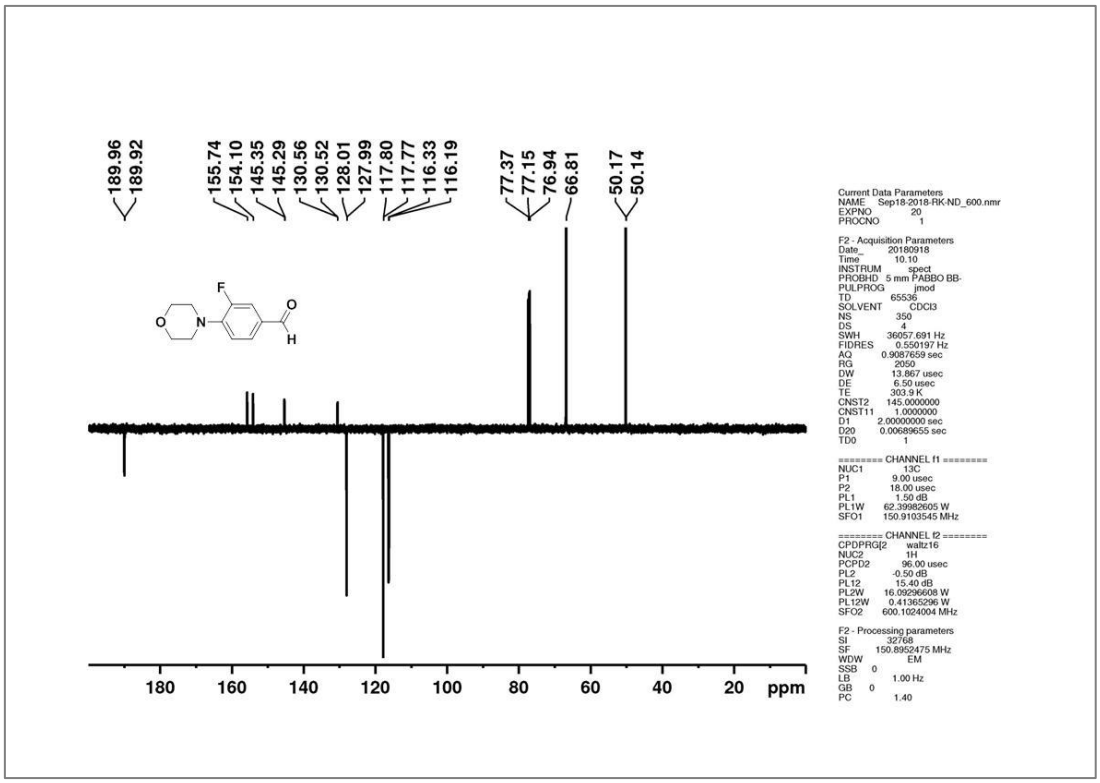
^{13}C NMR spectrum of compound 2 (Chapter 4)



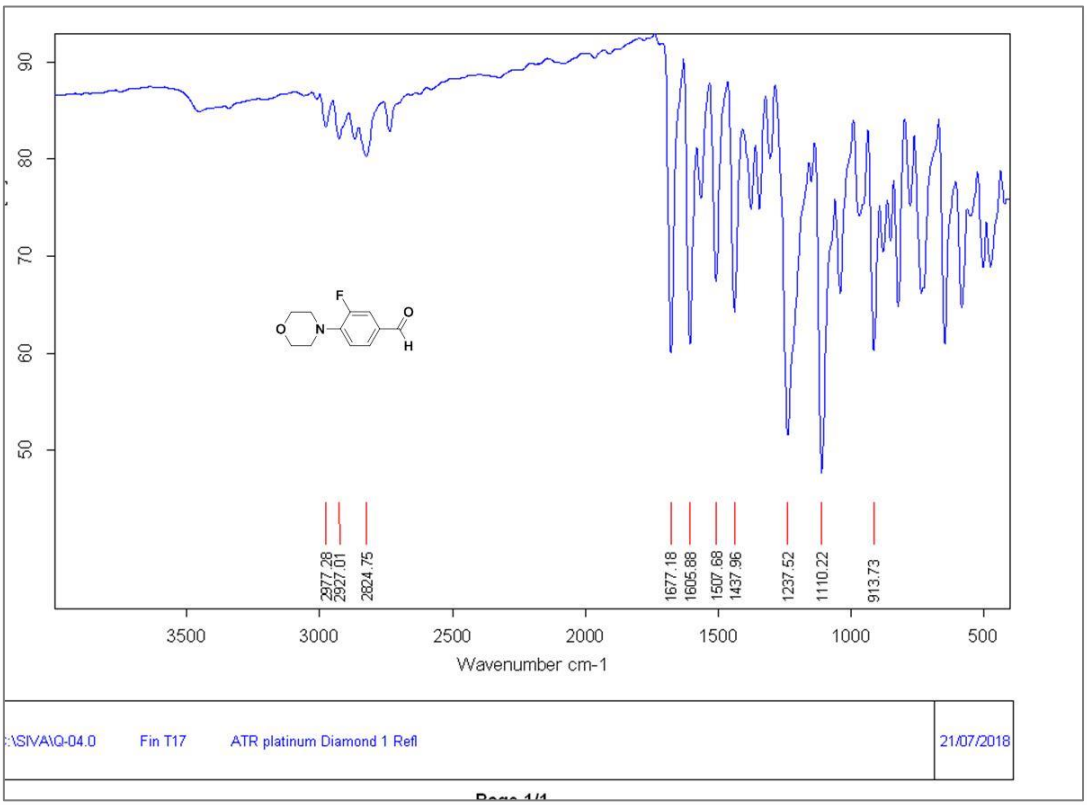
IR spectrum of compound 2 (Chapter 4)



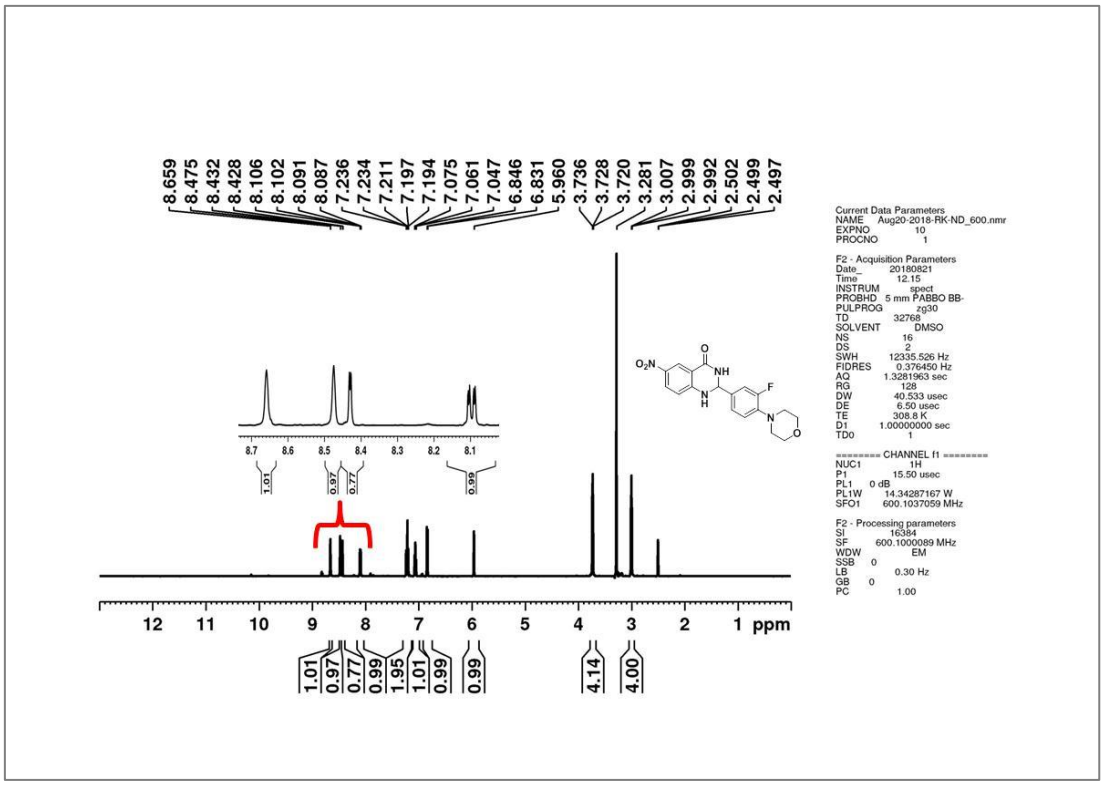
^{1}H NMR spectrum of compound 5 (Chapter 4)



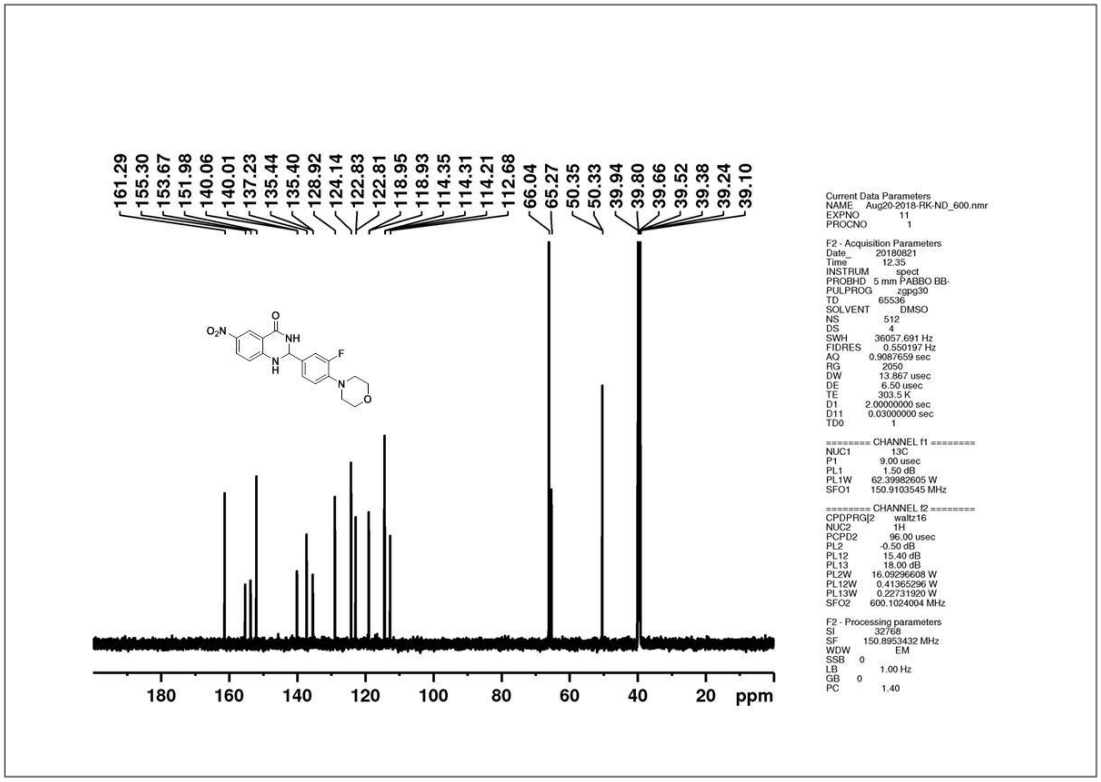
^{13}C NMR spectrum of compound 5 (Chapter 4)



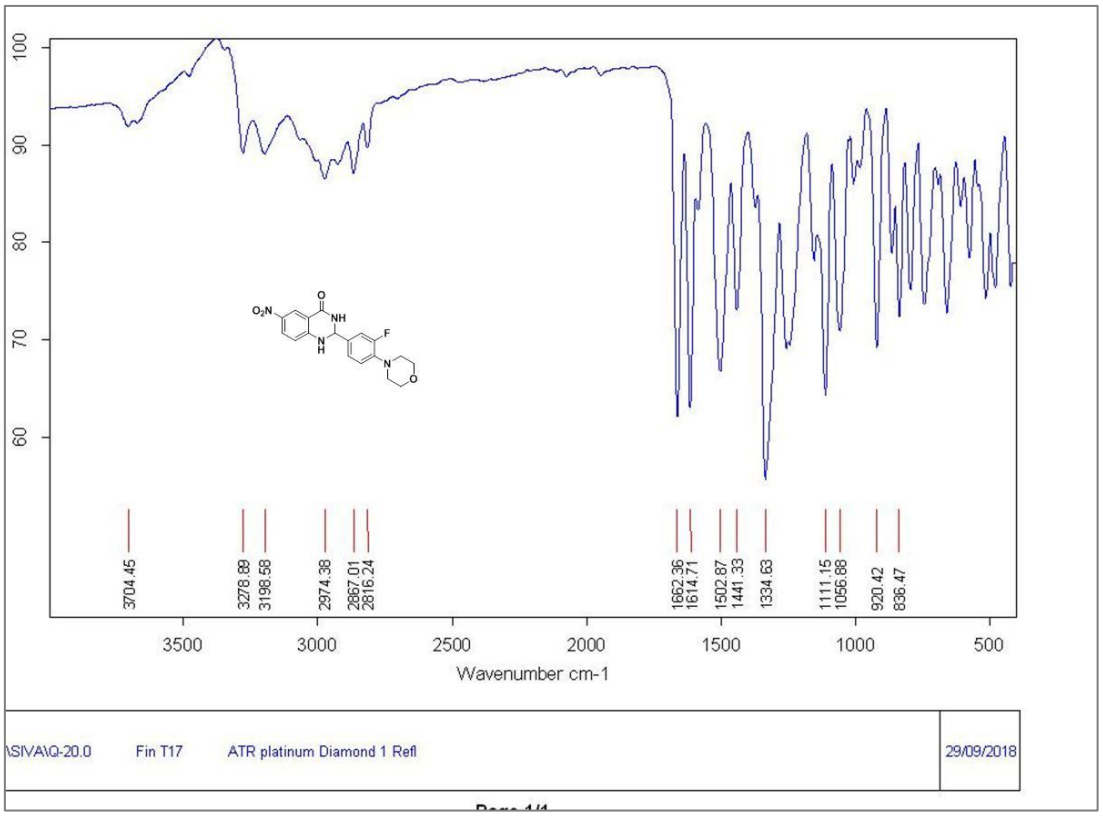
IR spectrum of compound 5 (Chapter 4)



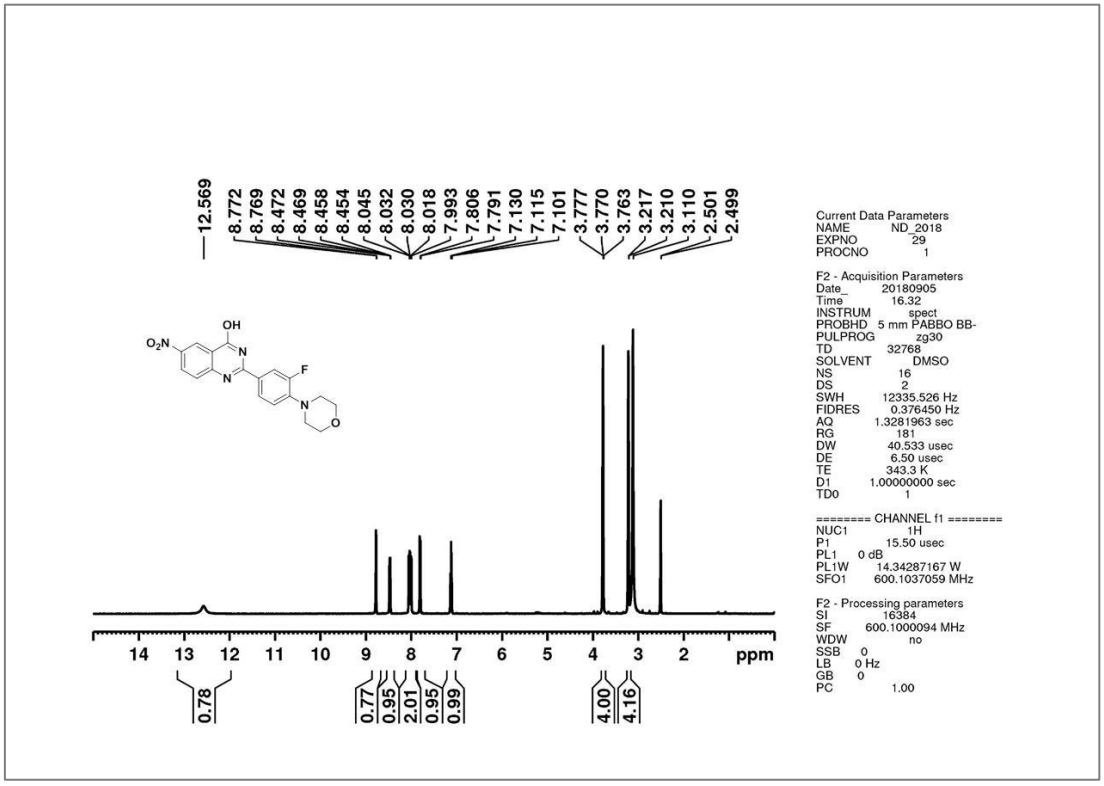
^{1}H NMR spectrum of compound 6 (Chapter 4)



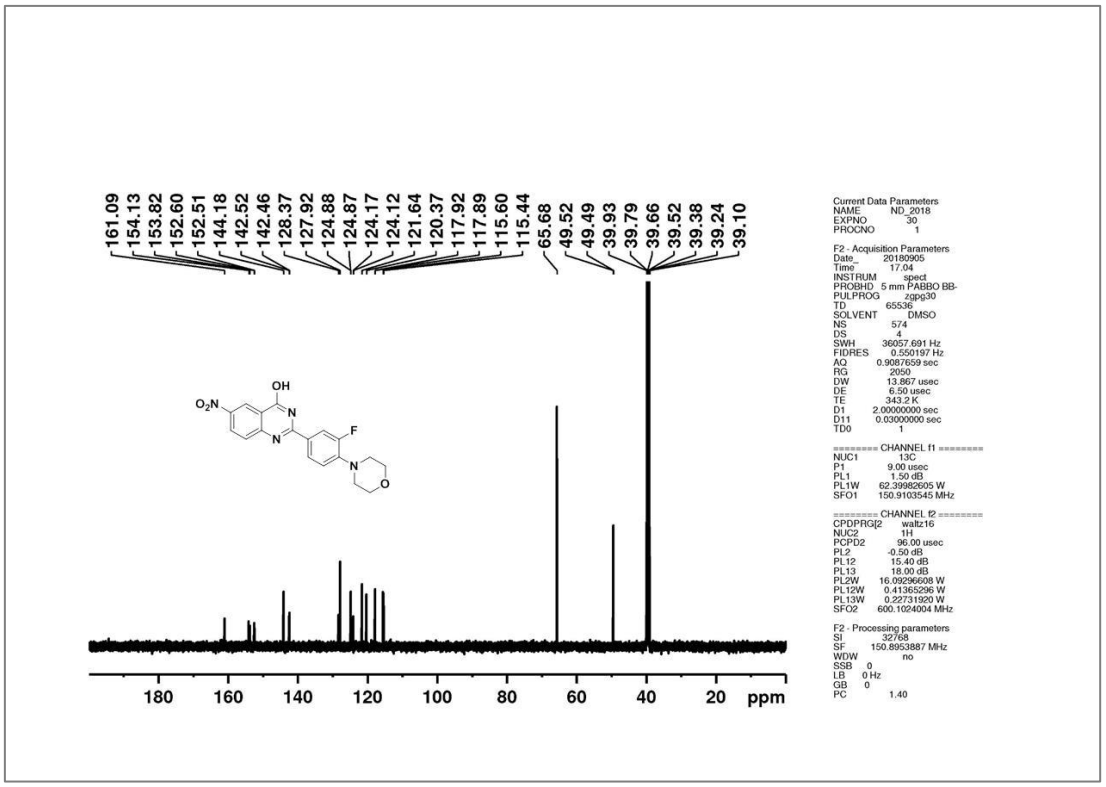
^{13}C NMR spectrum of compound 6 (Chapter 4)



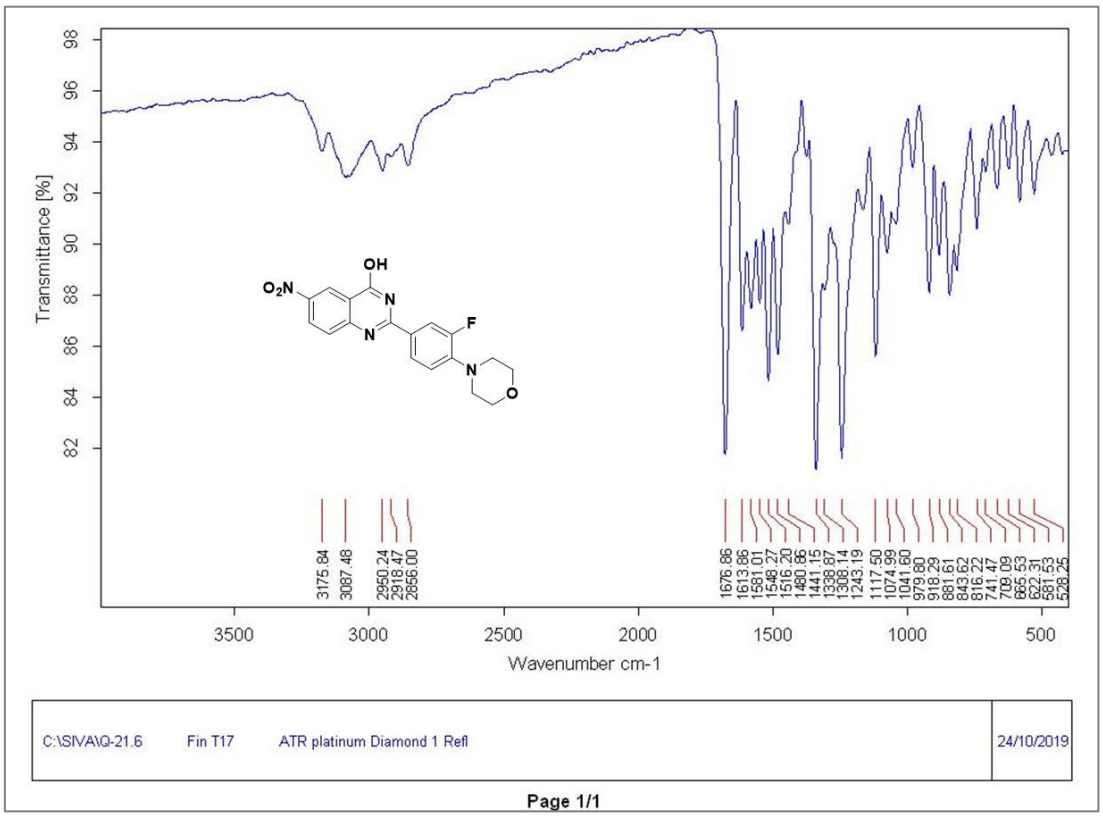
IR spectrum of compound 6 (Chapter 4)



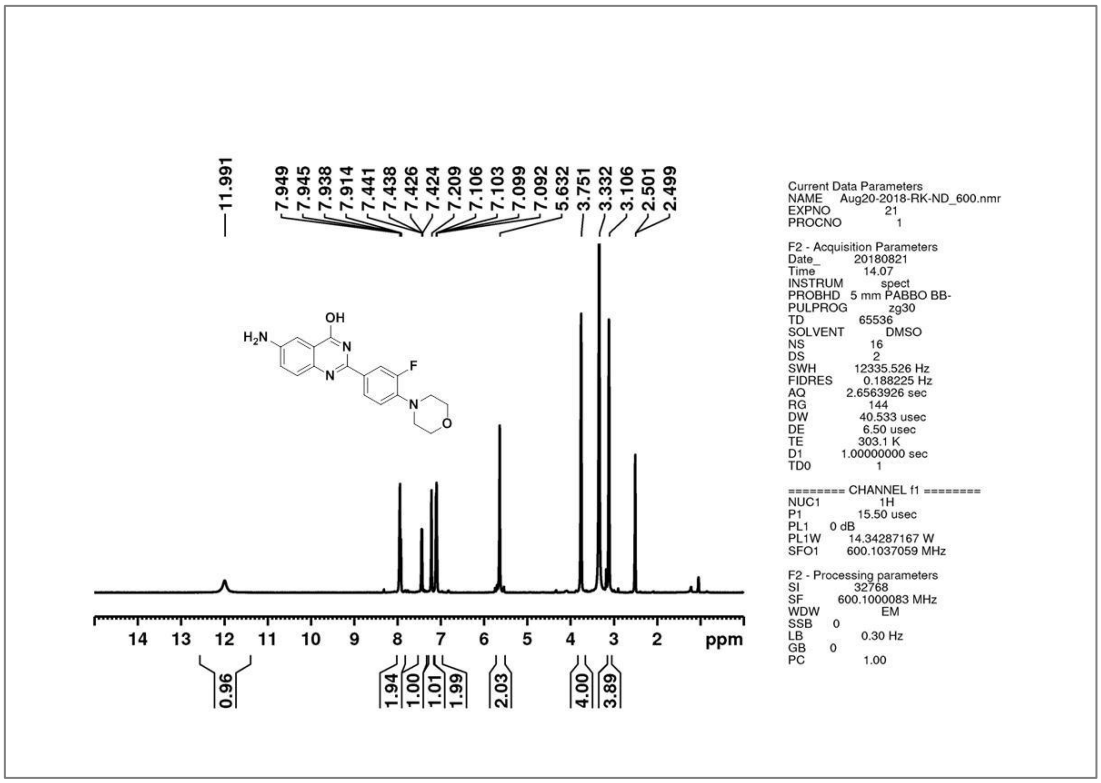
^{1}H NMR spectrum of compound 7 (Chapter 4)



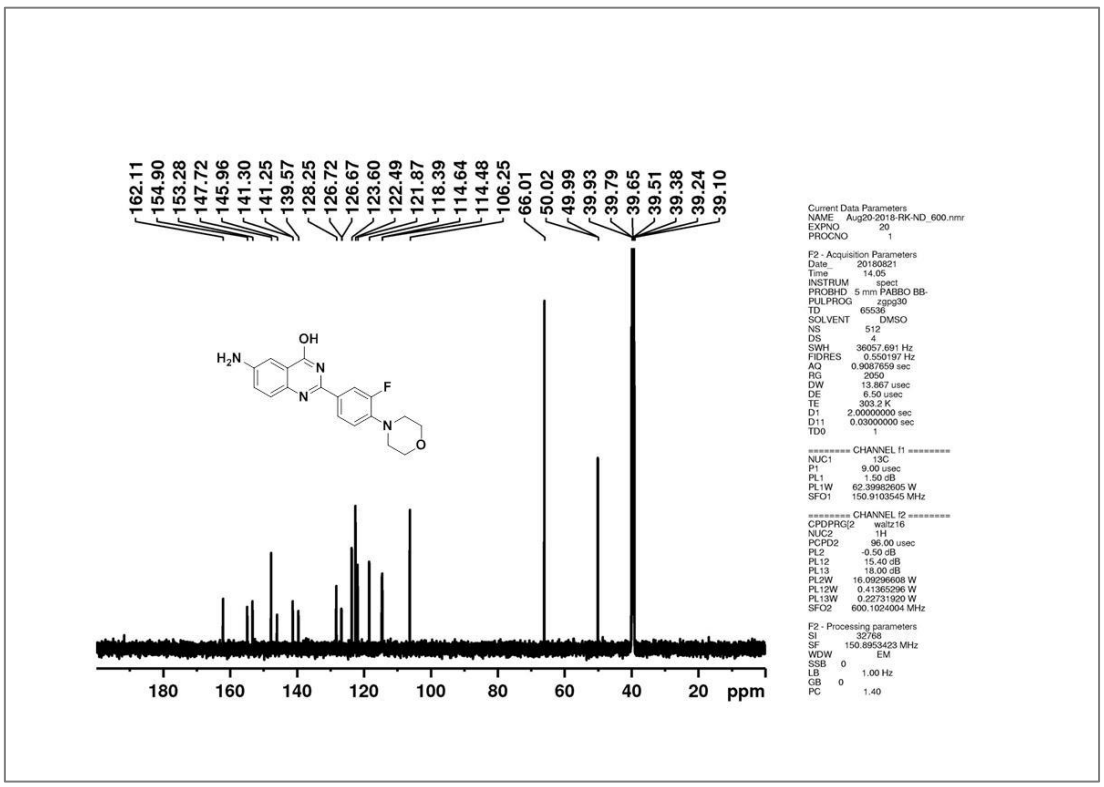
^{13}C NMR spectrum of compound 7 (Chapter 4)



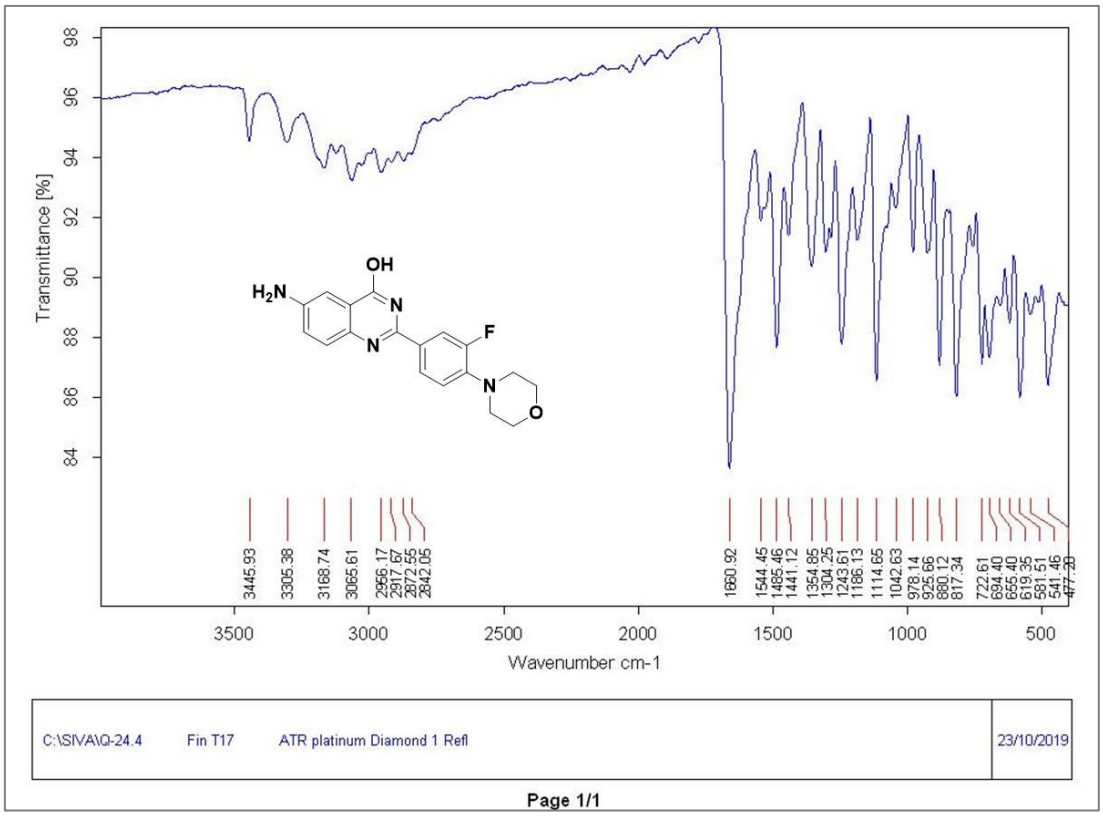
IR spectrum of compound 7 (Chapter 4)



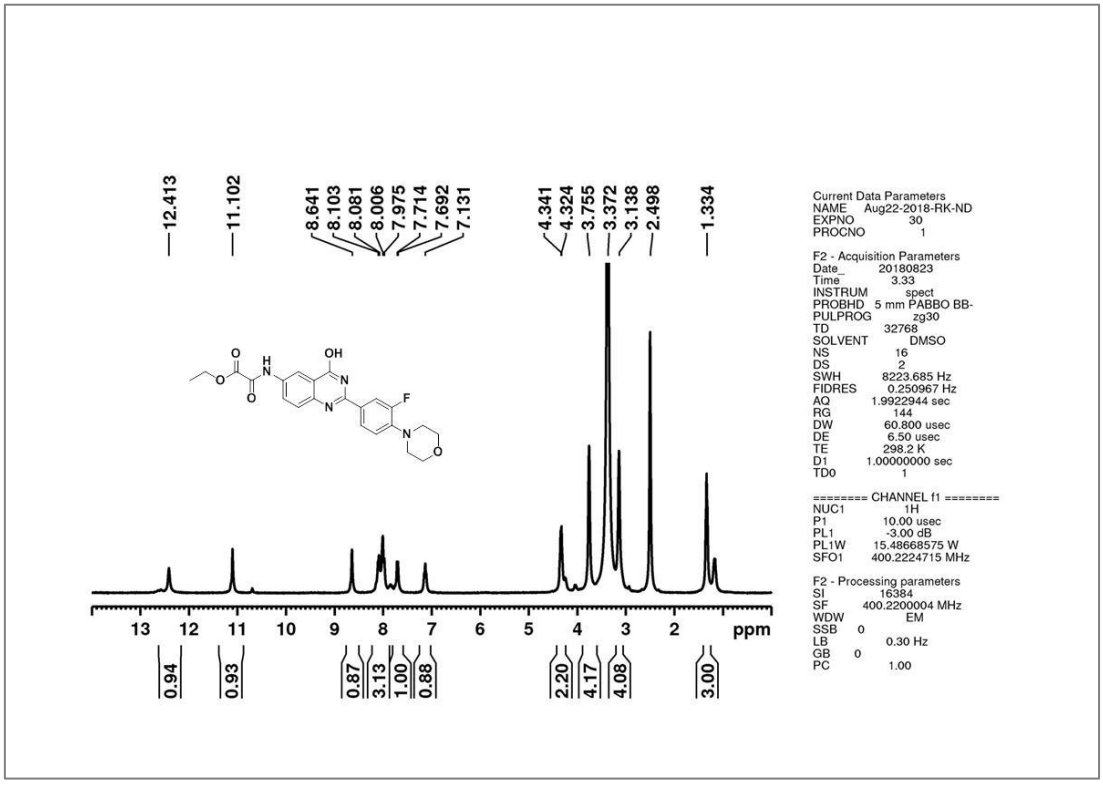
^{1}H NMR spectrum of compound 8 (Chapter 4)



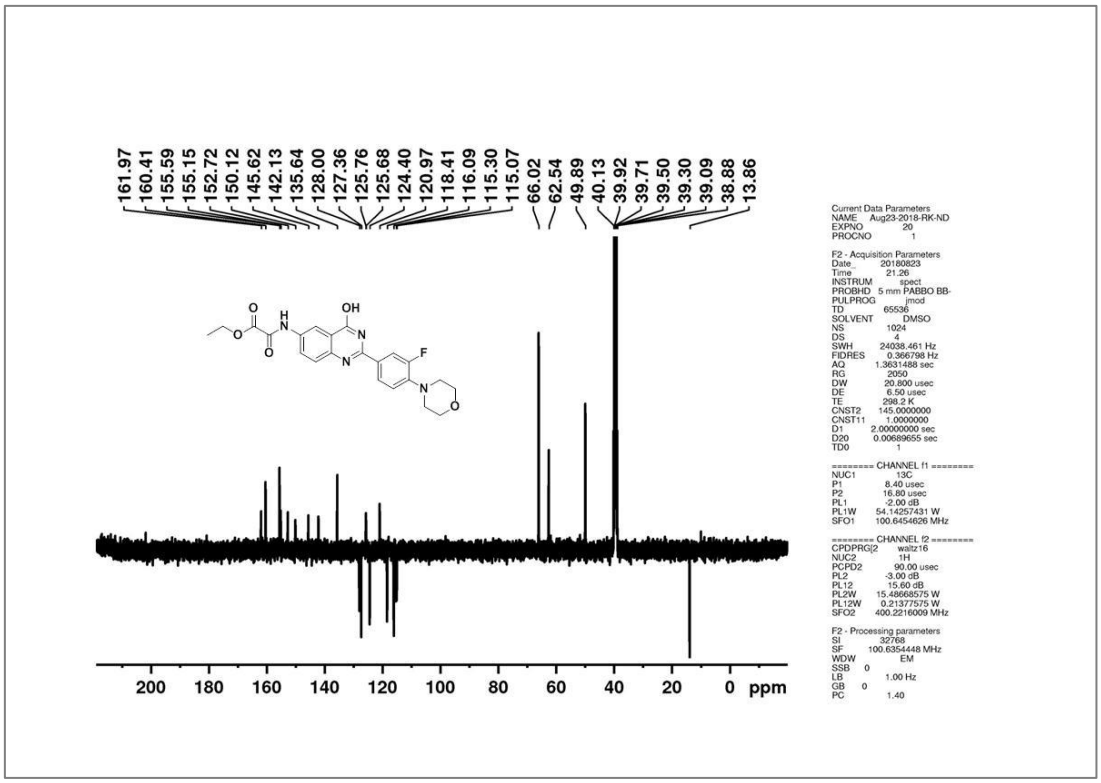
^{13}C NMR spectrum of compound 8 (Chapter 4)



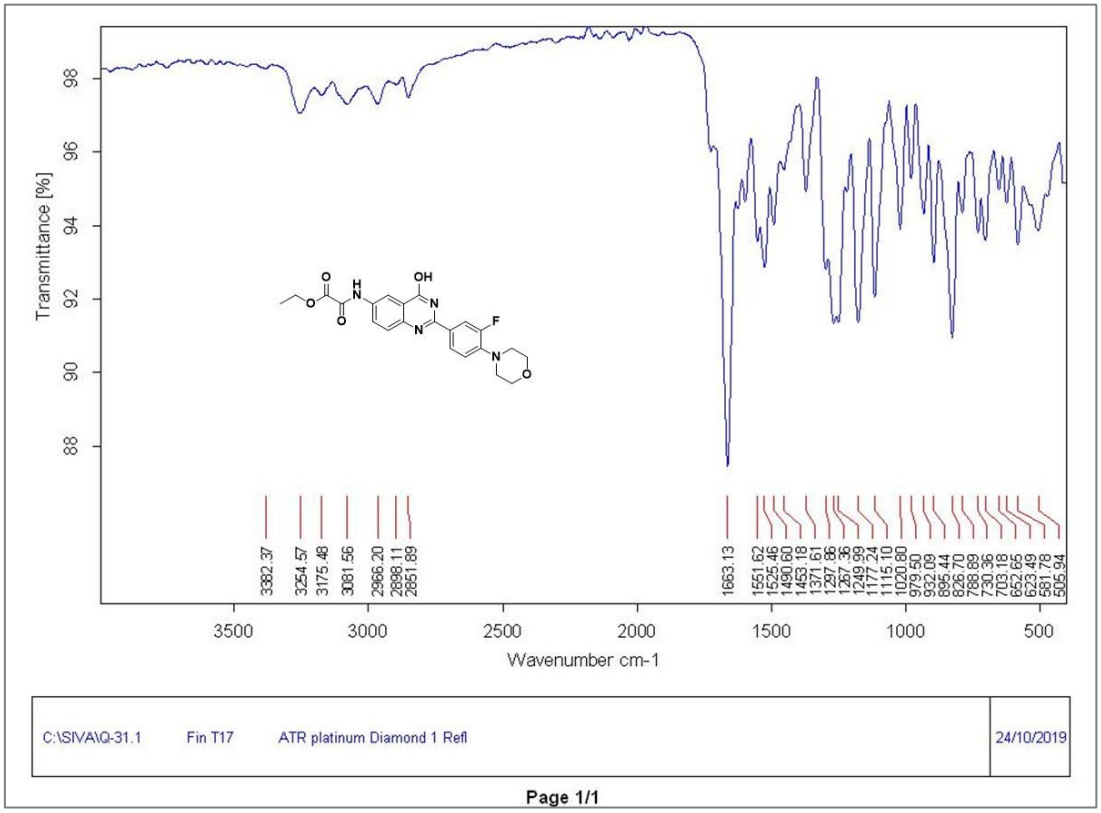
IR spectrum of compound 8 (Chapter 4)



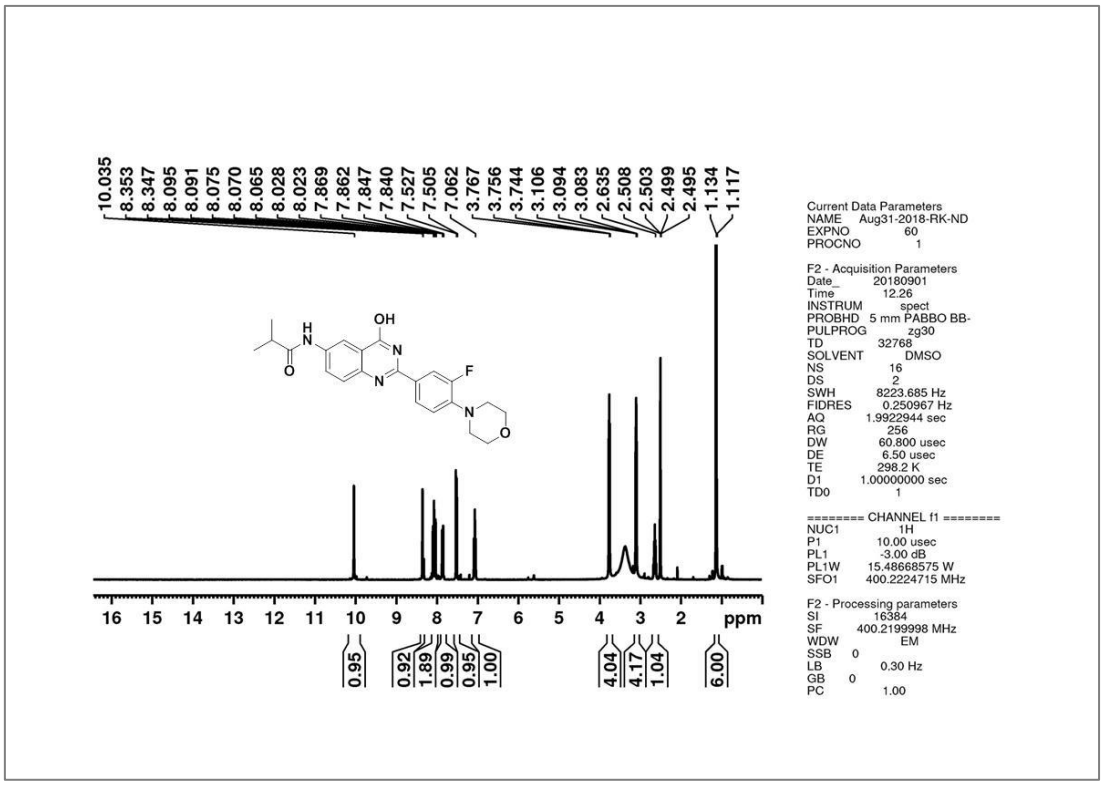
^{1}H NMR spectrum of compound 10a (Chapter 4)



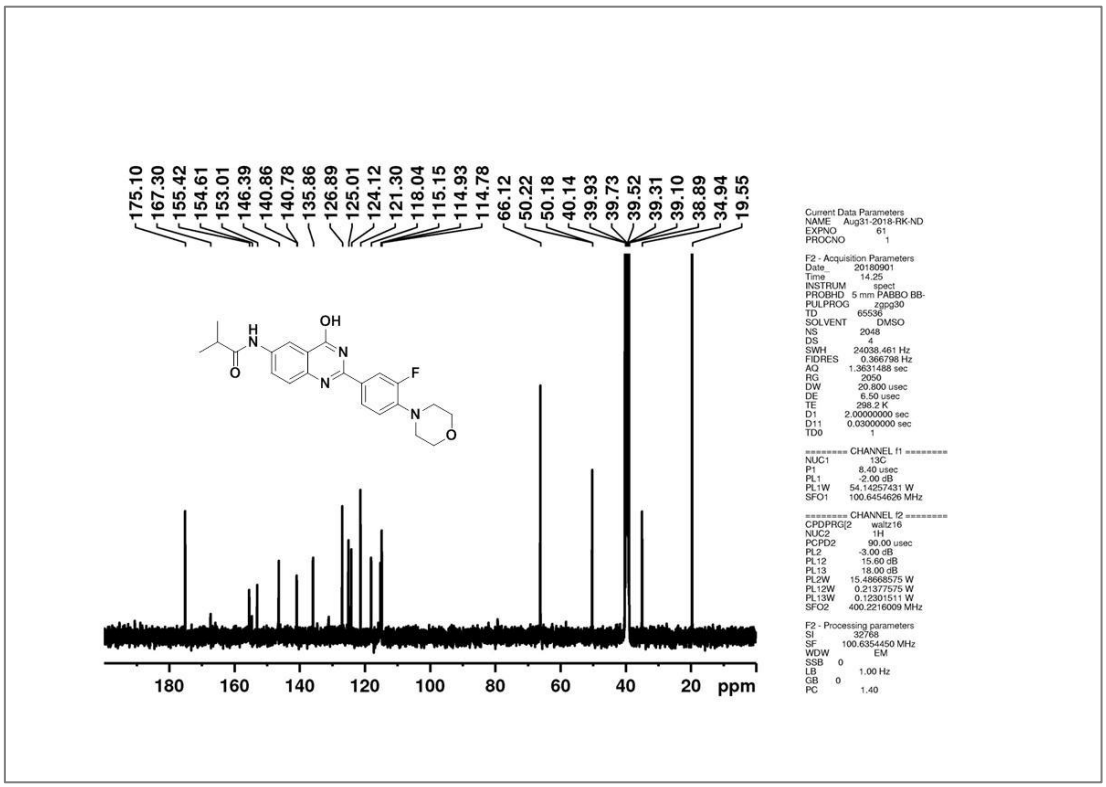
^{13}C NMR spectrum of compound 10a (Chapter 4)



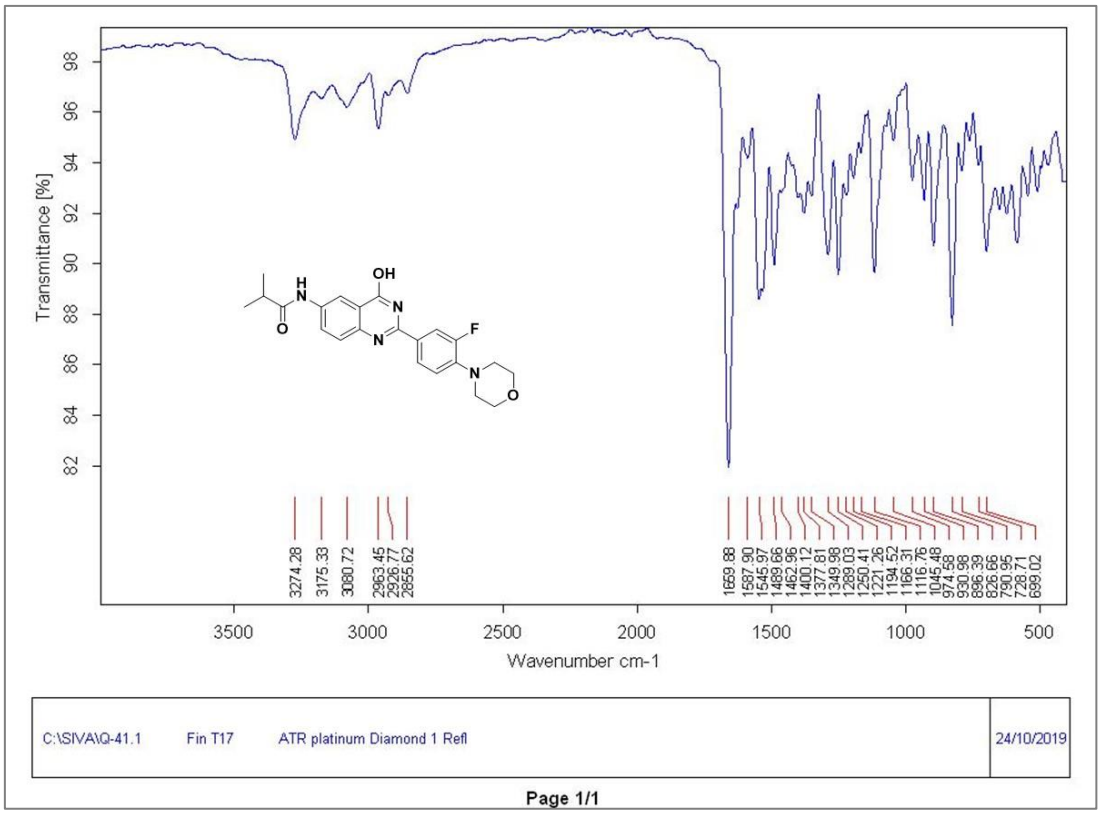
IR spectrum of compound 10a (Chapter 4)



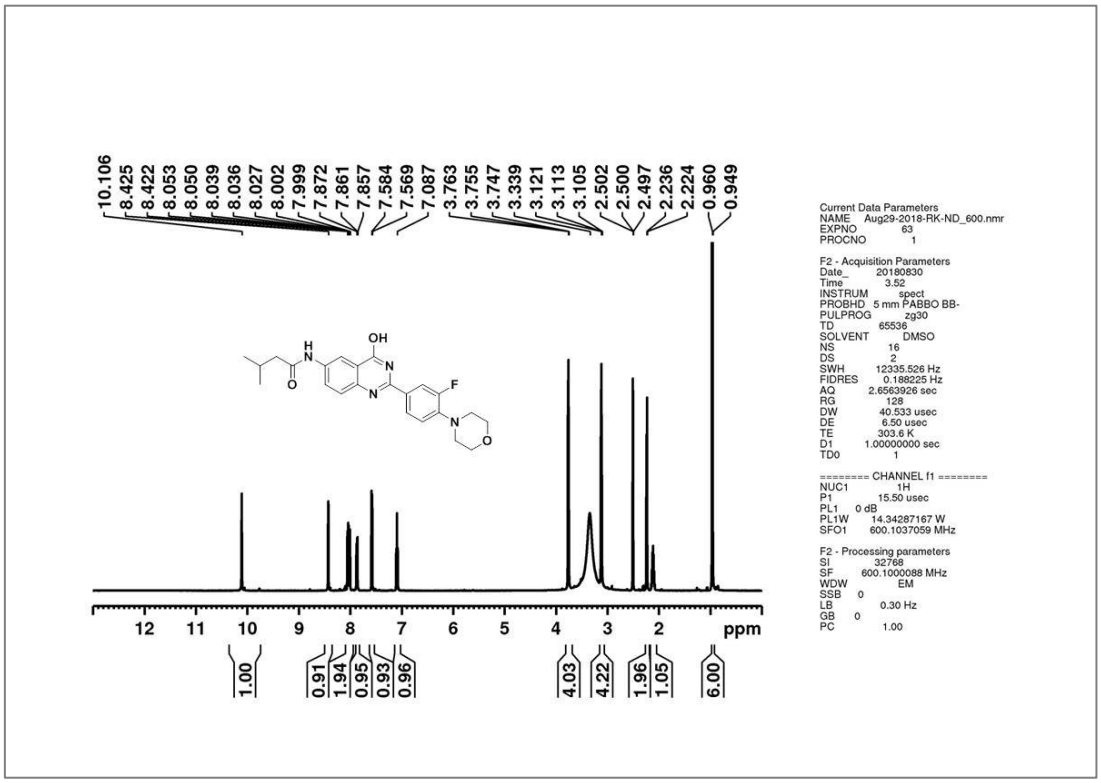
[1]H NMR spectrum of compound 10b (Chapter 4)



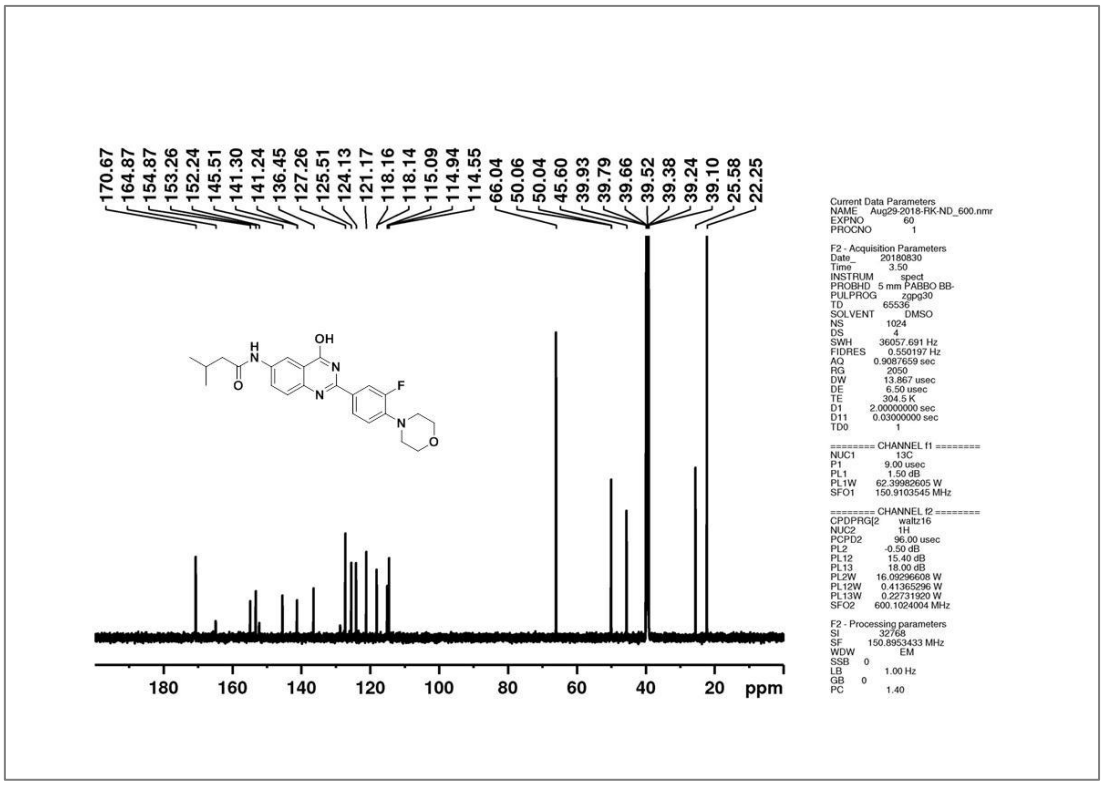
[13]C NMR spectrum of compound 10b (Chapter 4)



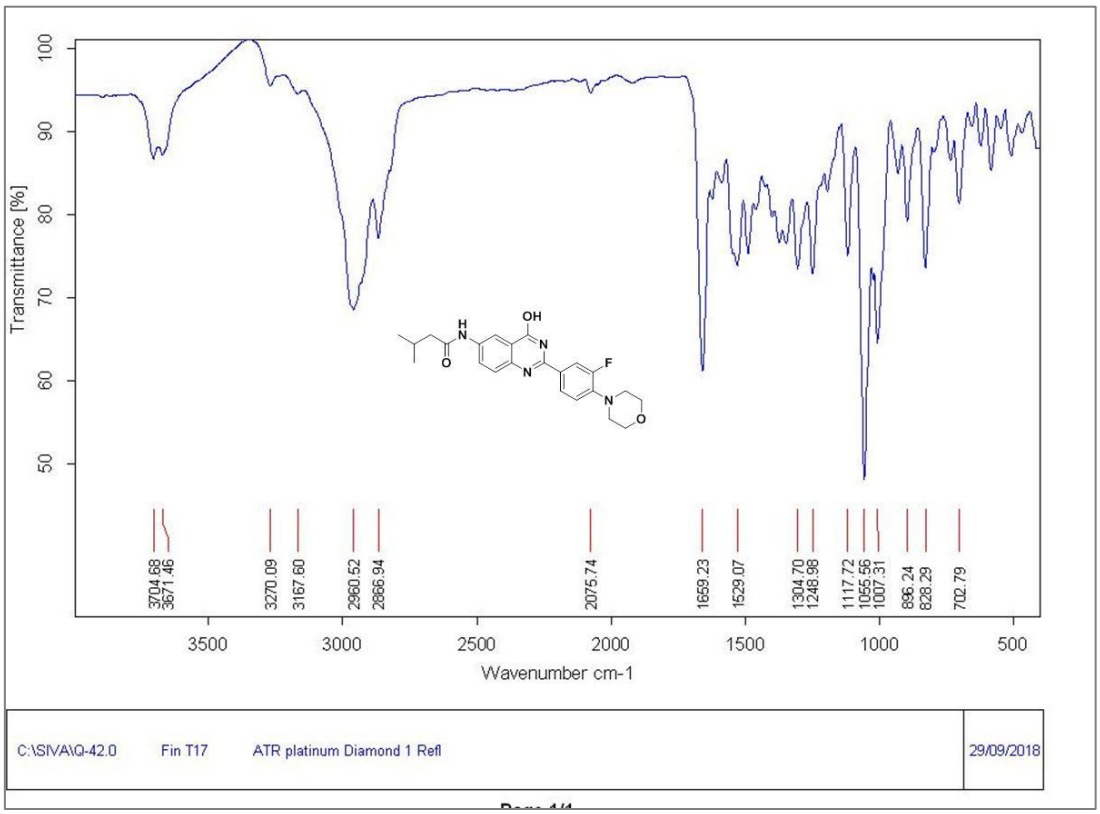
IR spectrum of compound 10b (Chapter 4)



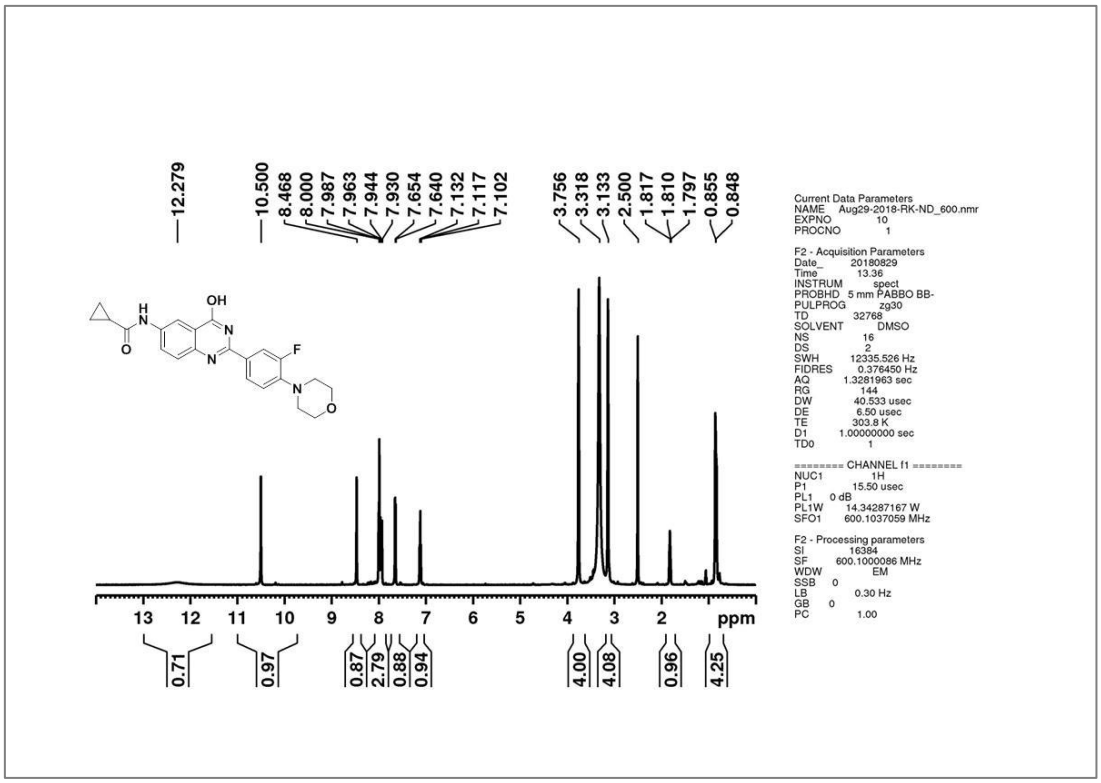
^{1}H NMR spectrum of compound 10c (Chapter 4)



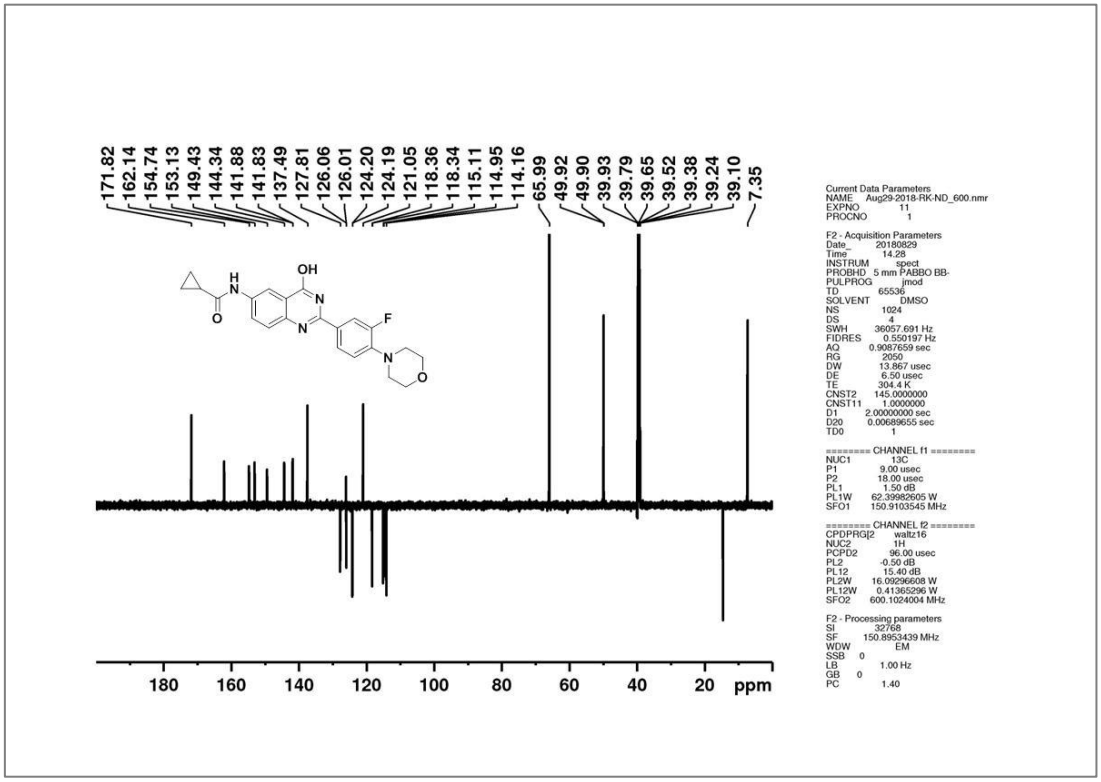
^{13}C NMR spectrum of compound 10c (Chapter 4)



IR spectrum of compound 10c (Chapter 4)



[1]H NMR spectrum of compound 10d (Chapter 4)



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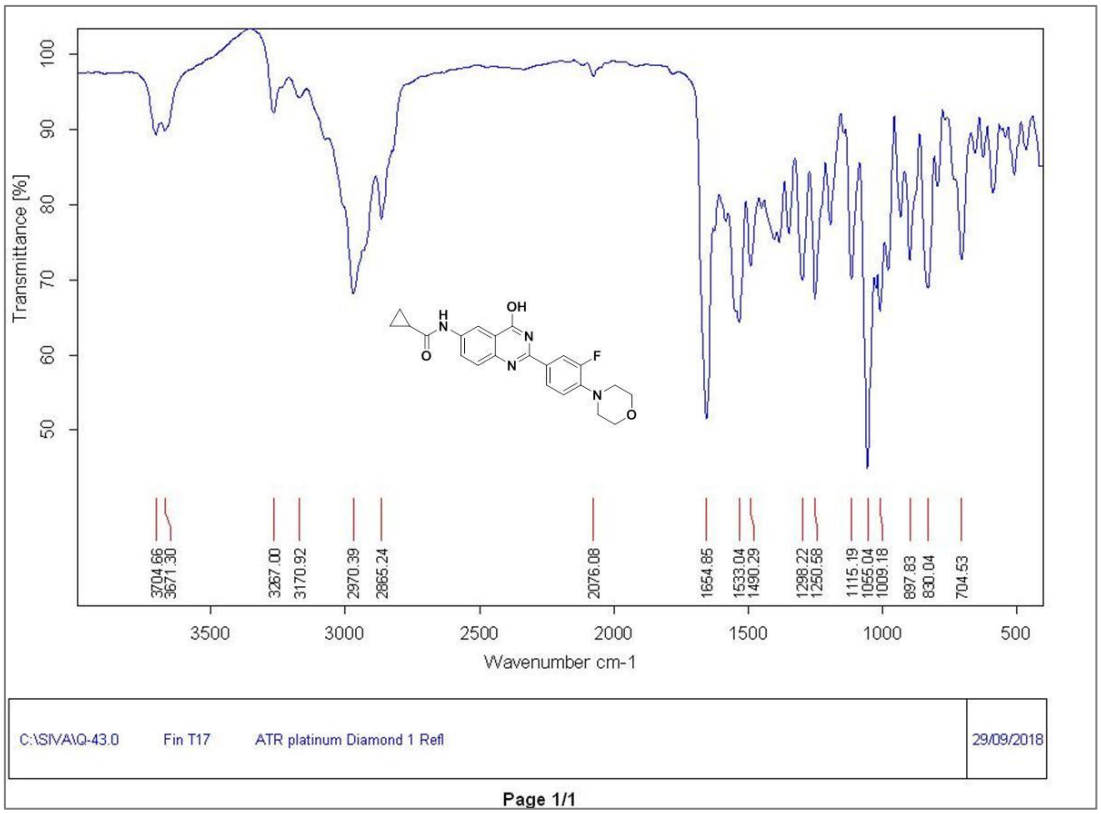
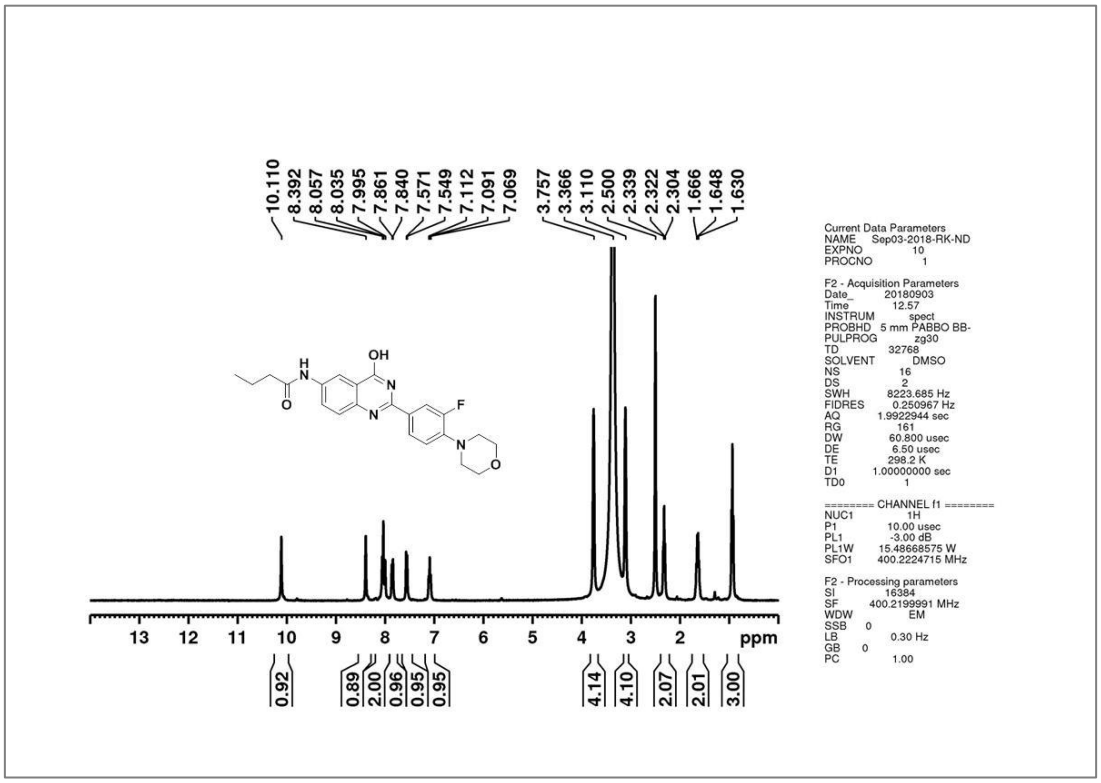
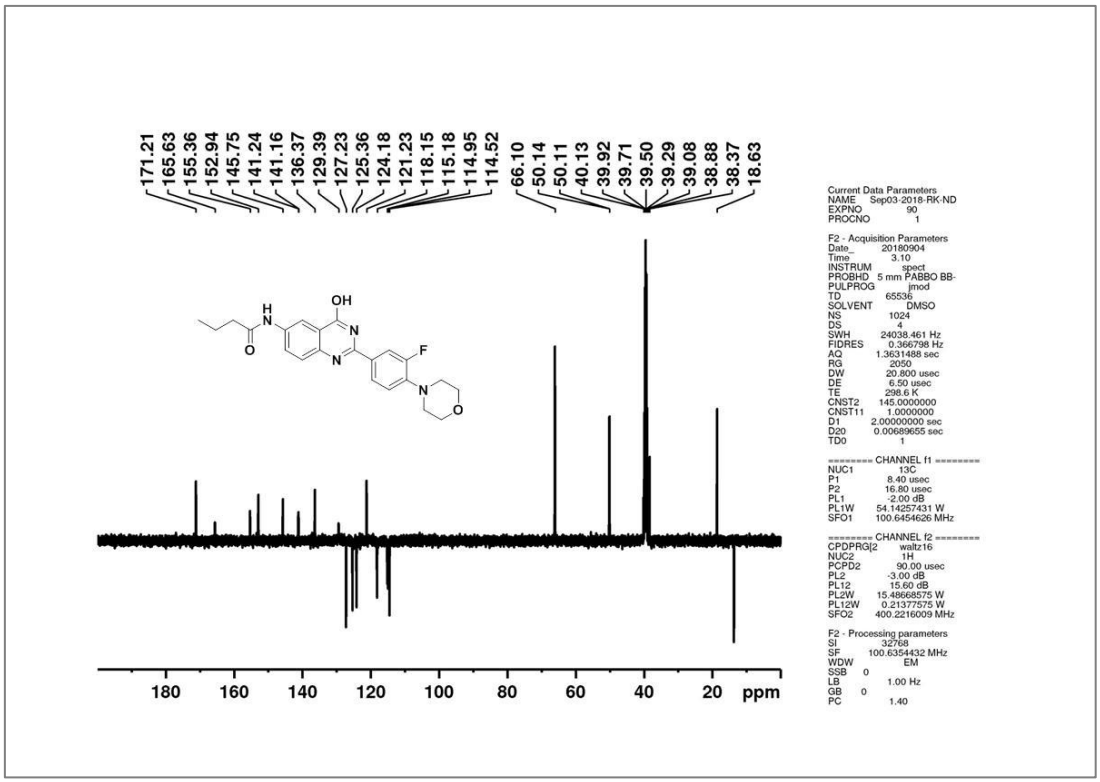


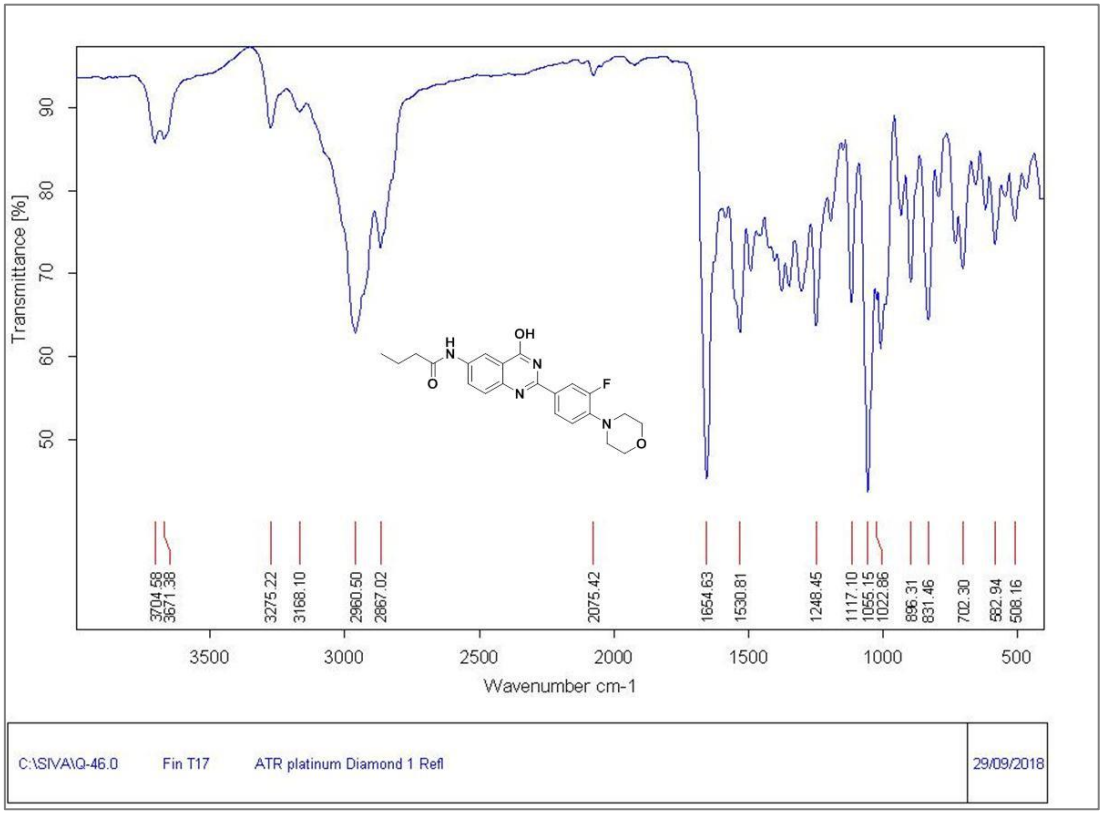
IR spectrum of compound 10d (Chapter 4)



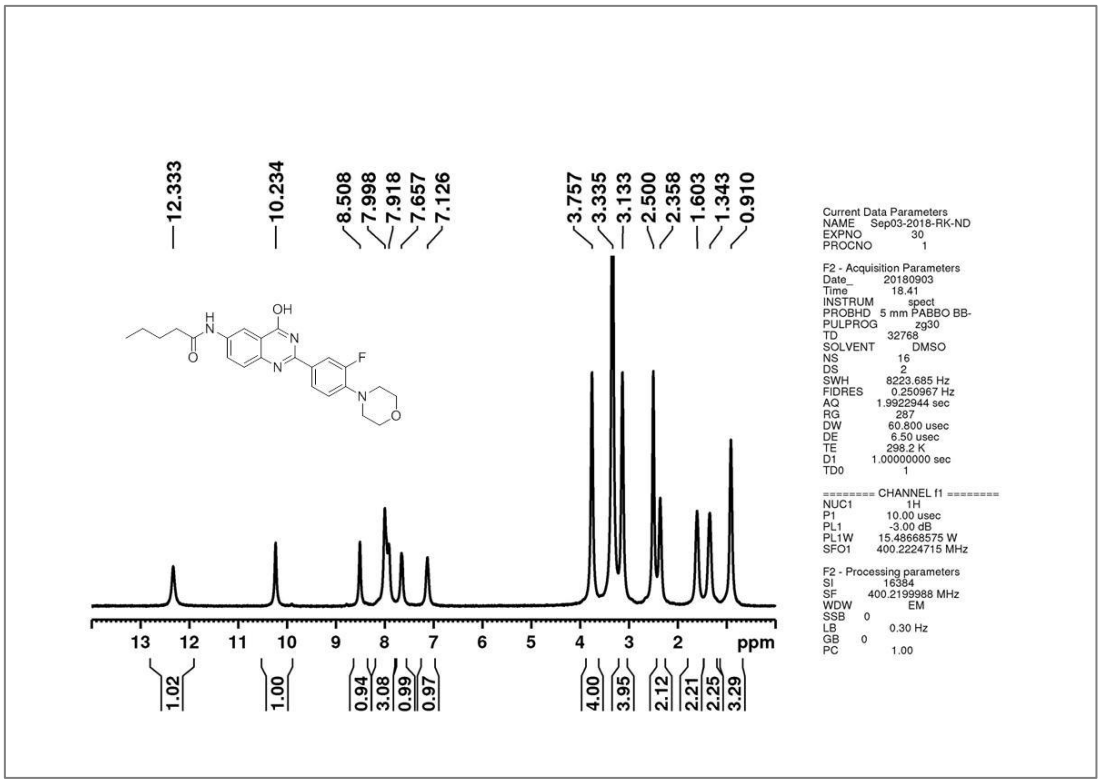
^{1}H NMR spectrum of compound 10e (Chapter 4)



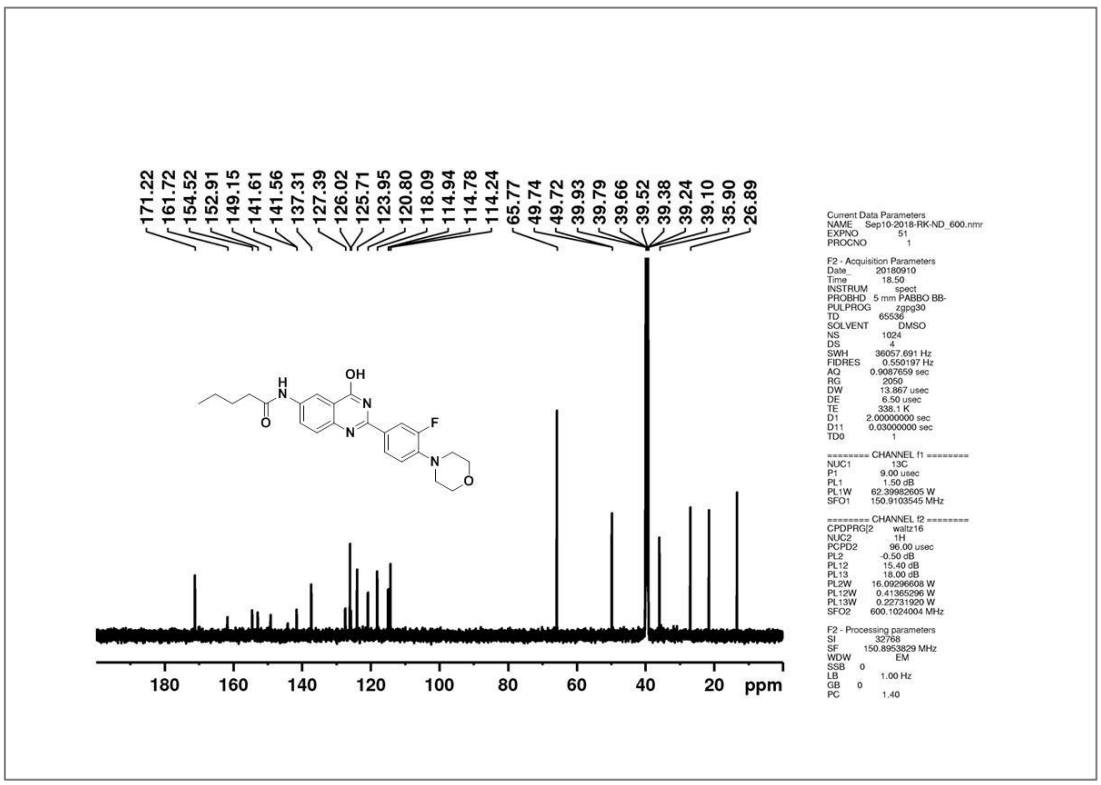
^{13}C NMR spectrum of compound 10e (Chapter 4)



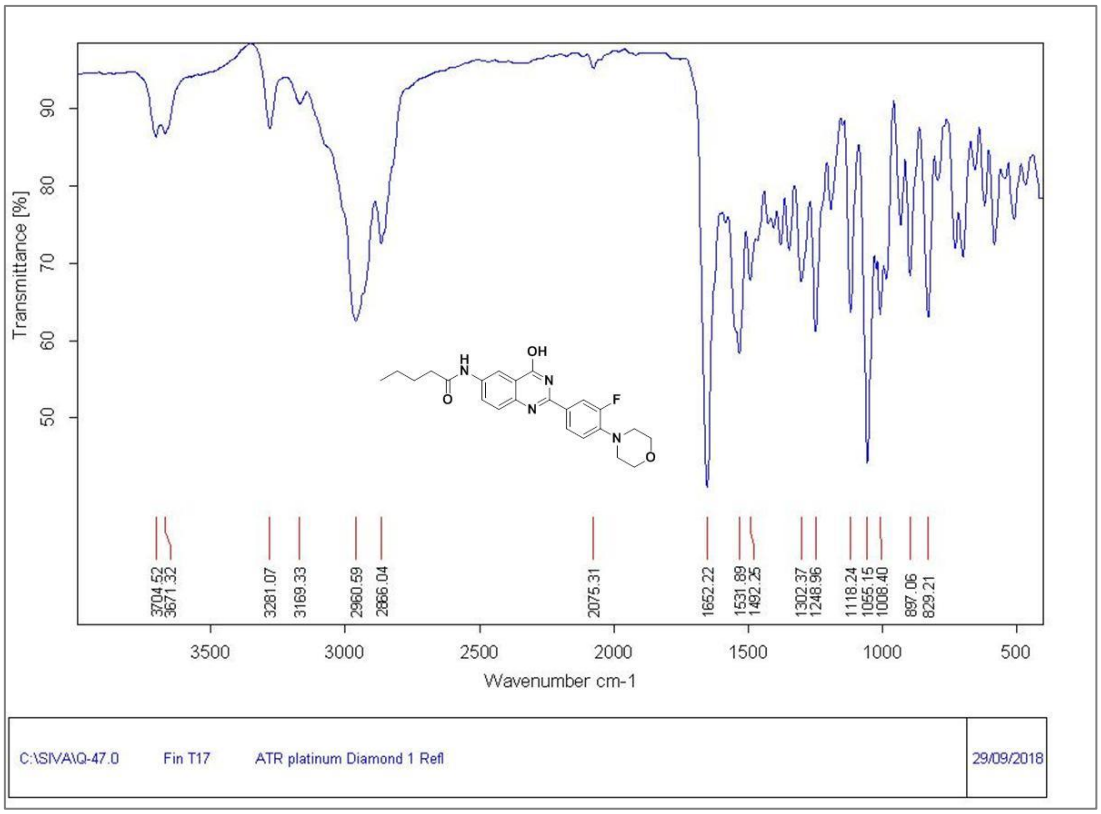
IR spectrum of compound 10e (Chapter 4)



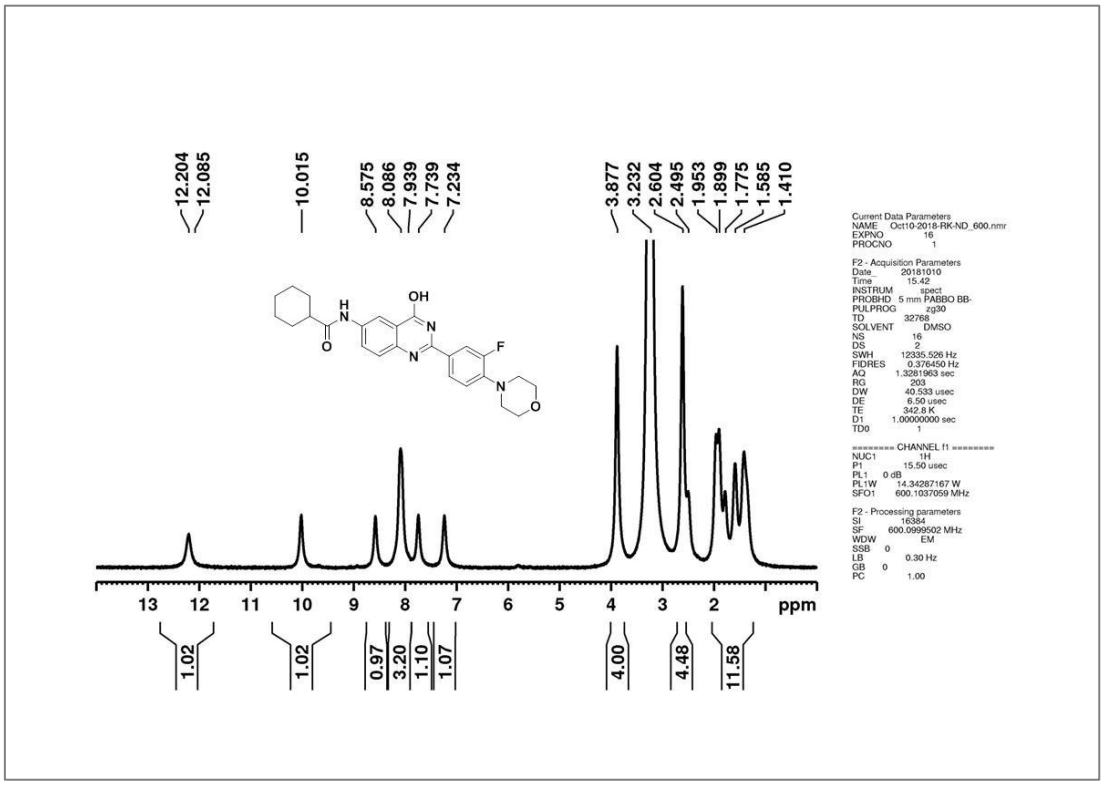
^{1}H NMR spectrum of compound 10f (Chapter 4)



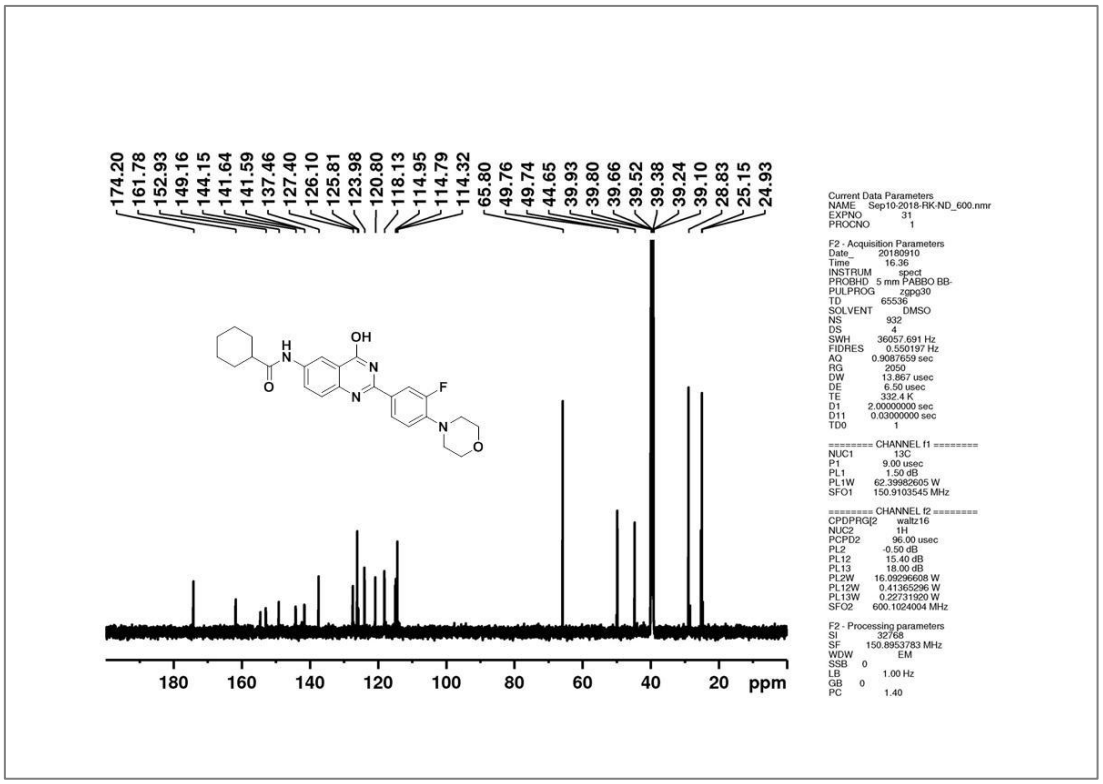
^{13}C NMR spectrum of compound 10f (Chapter 4)



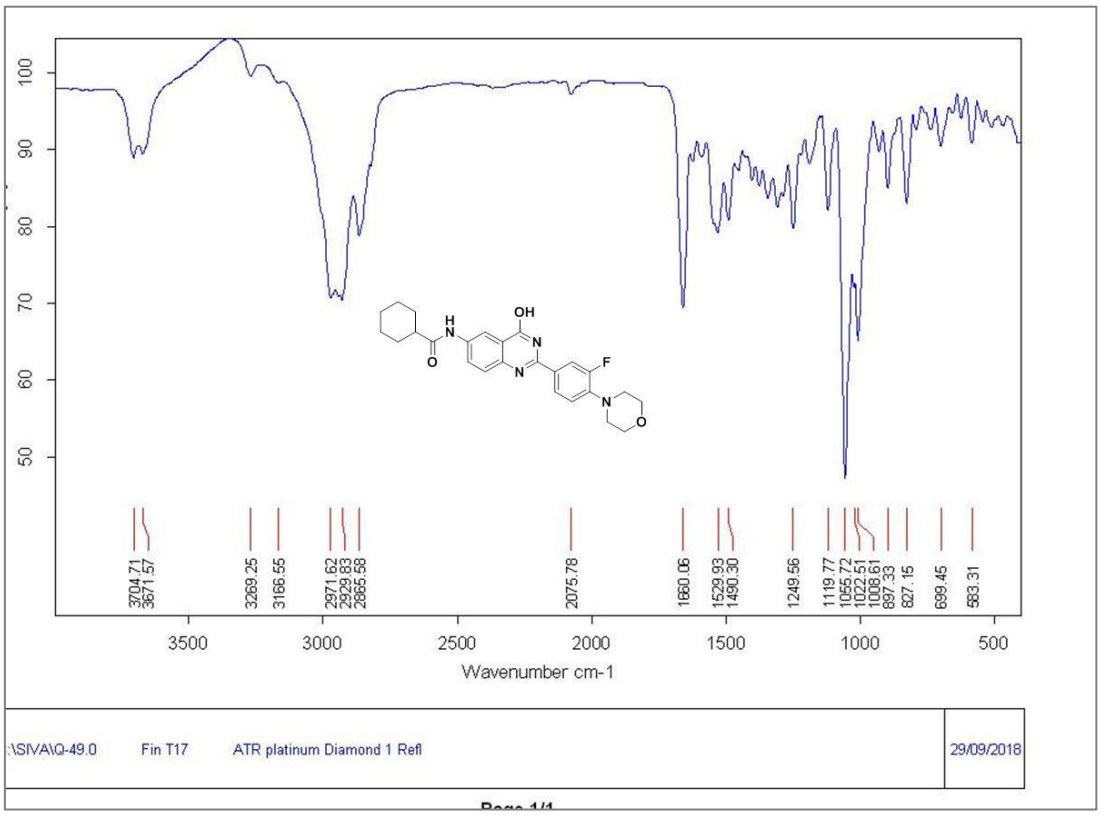
IR spectrum of compound 10f (Chapter 4)



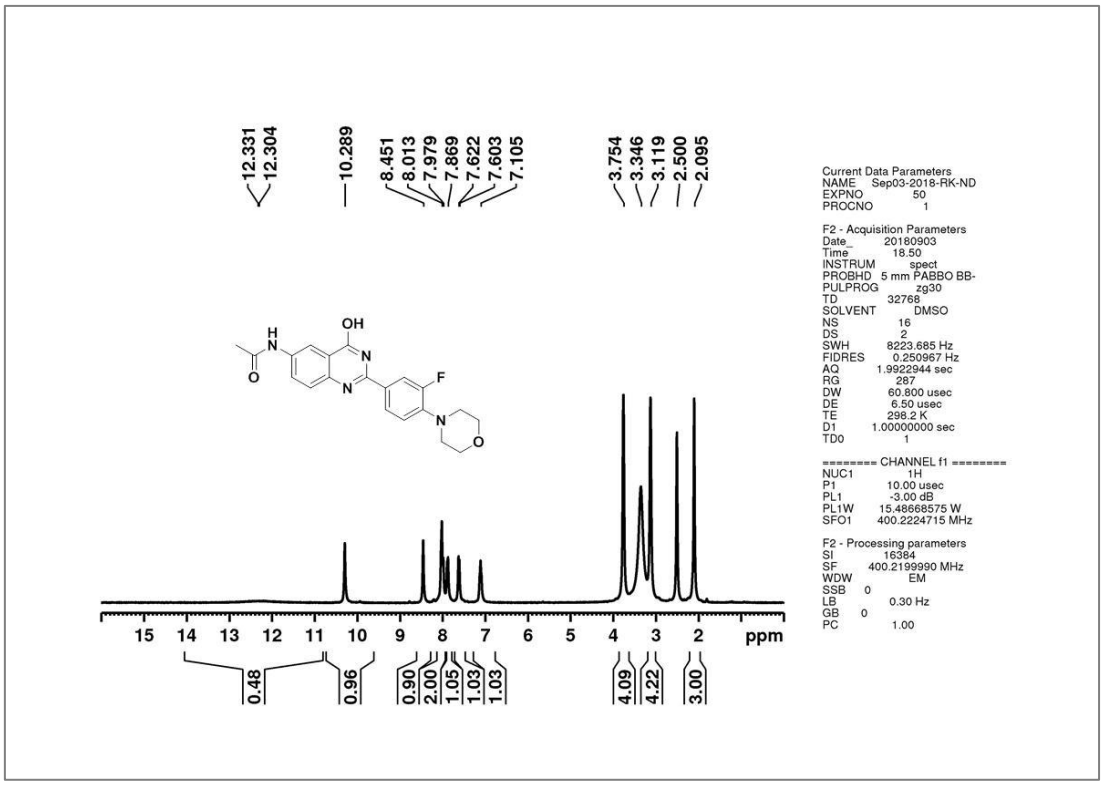
^{1}H NMR spectrum of compound 10g (Chapter 4)



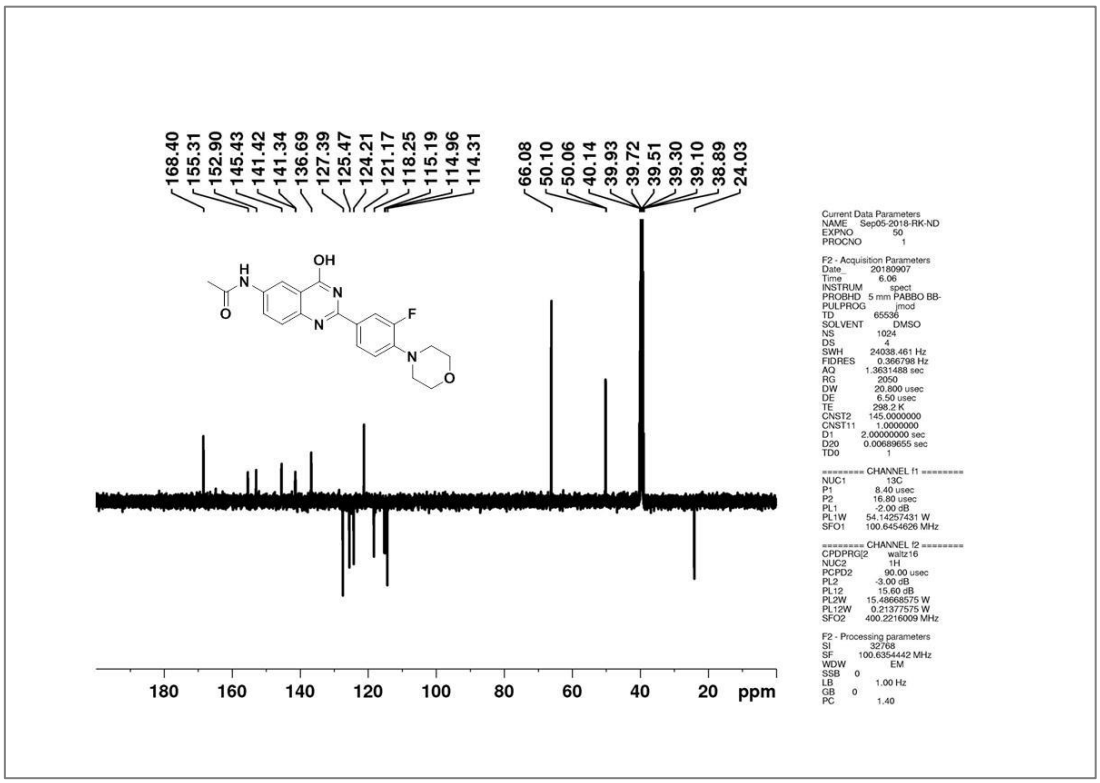
^{13}C NMR spectrum of compound 10g (Chapter 4)



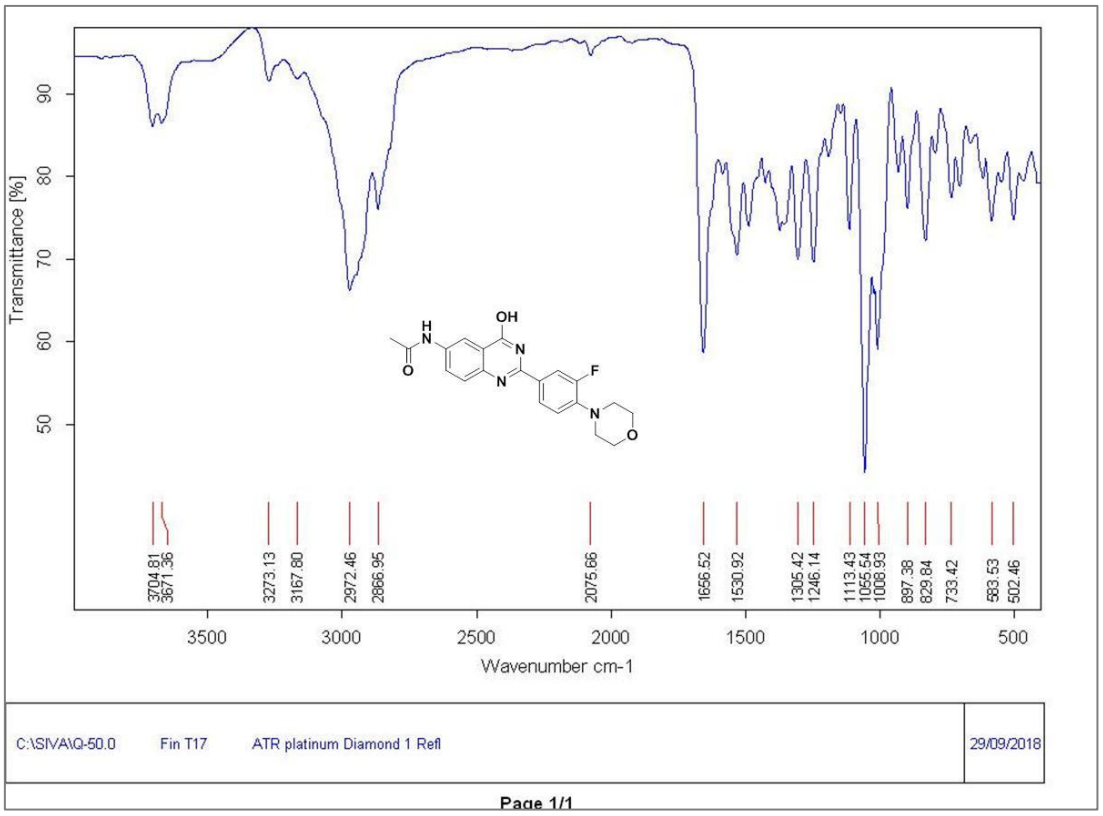
IR spectrum of compound 10g (Chapter 4)



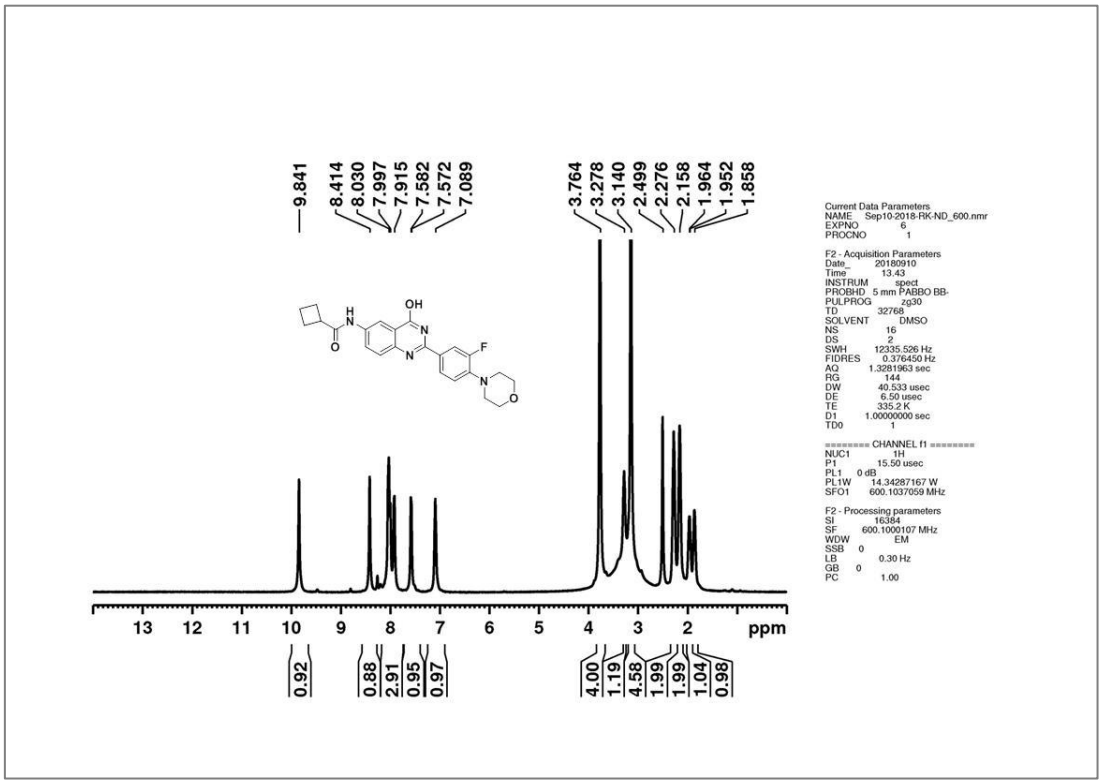
[1]H NMR spectrum of compound 10h (Chapter 4)



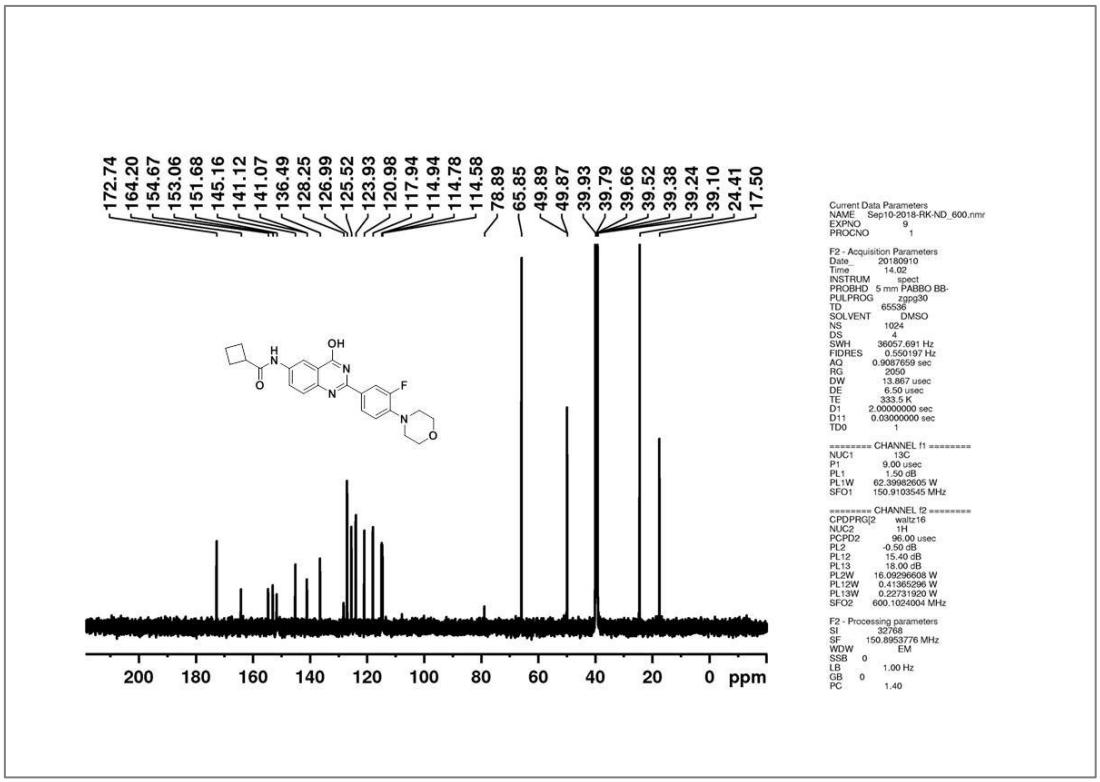
[13]C NMR spectrum of compound 10h (Chapter 4)



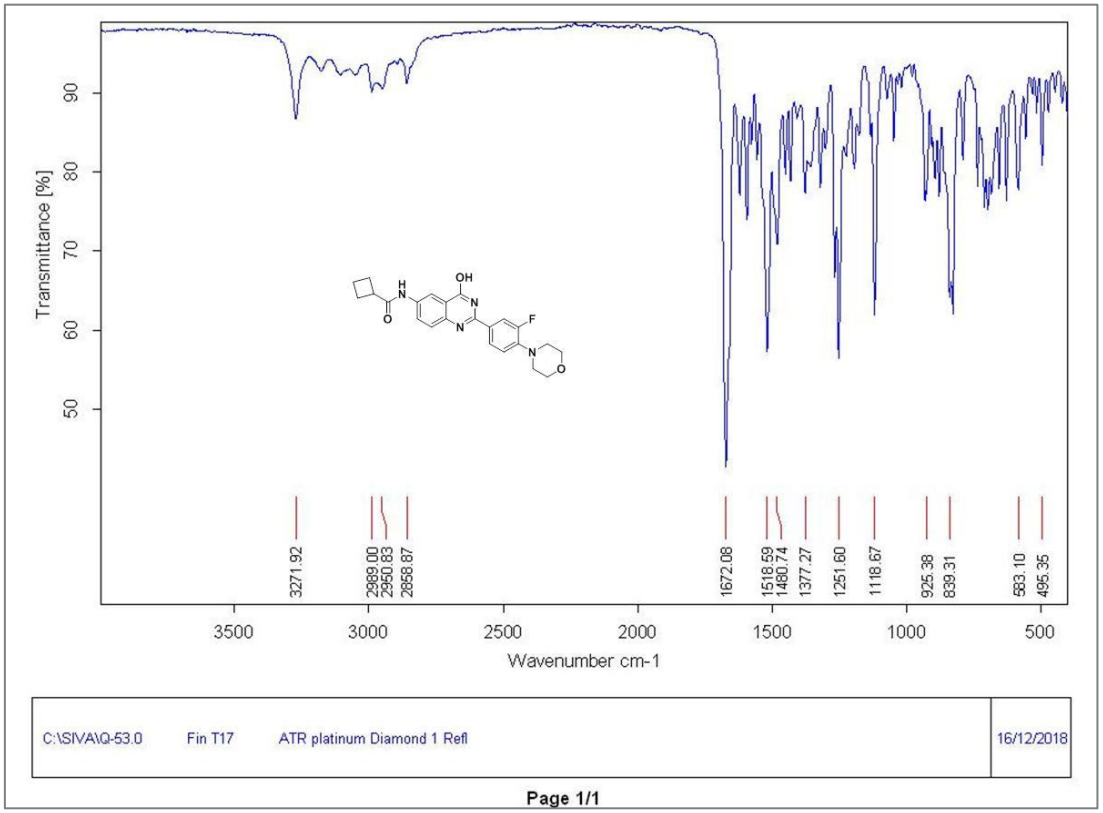
IR spectrum of compound 10h (Chapter 4)



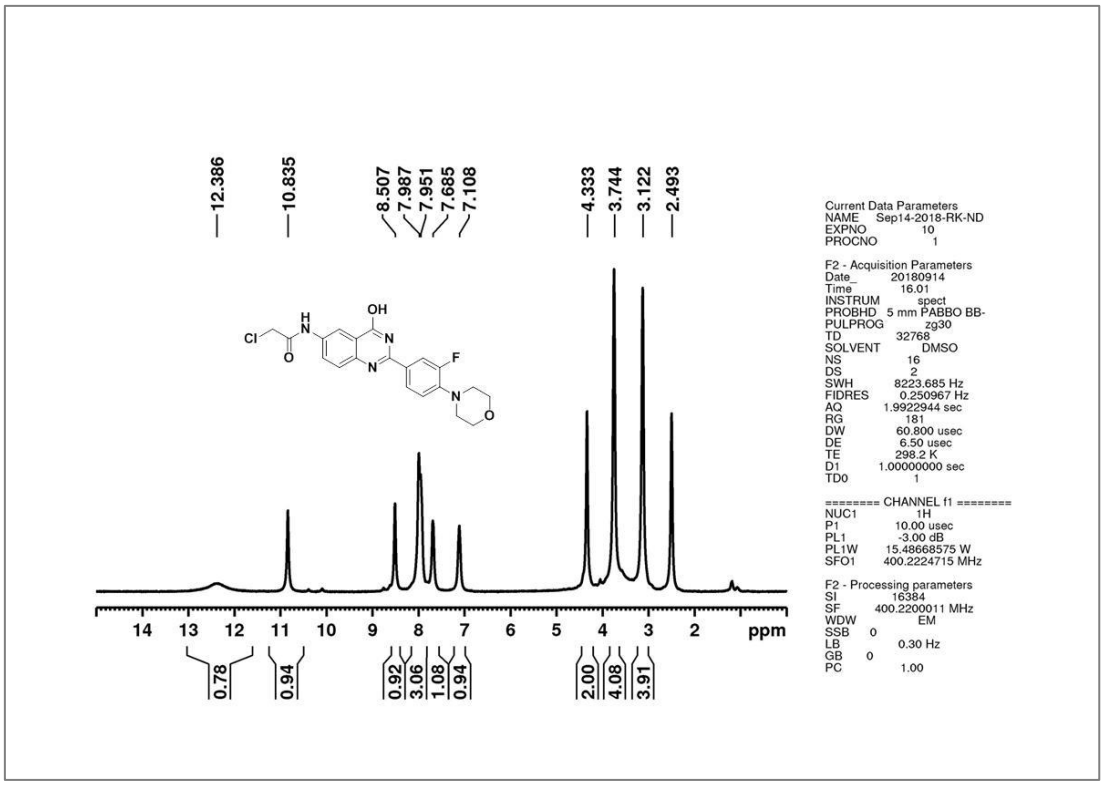
^{1}H NMR spectrum of compound 10i (Chapter 4)



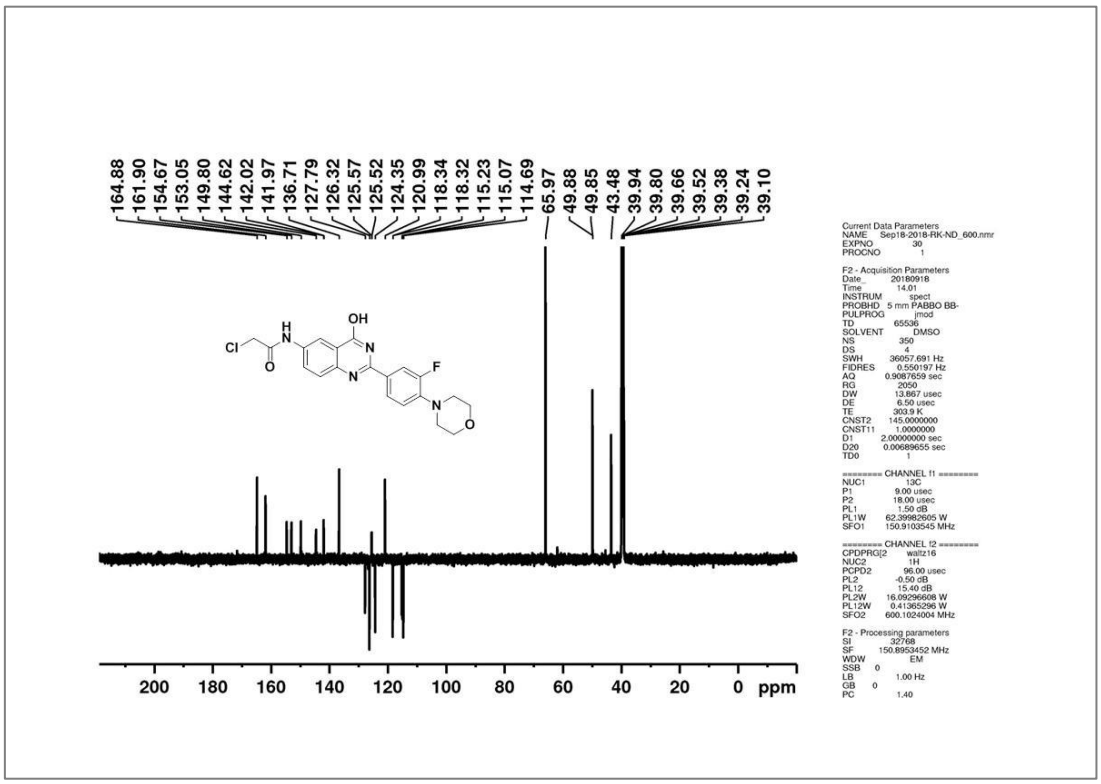
^{13}C NMR spectrum of compound 10i (Chapter 4)



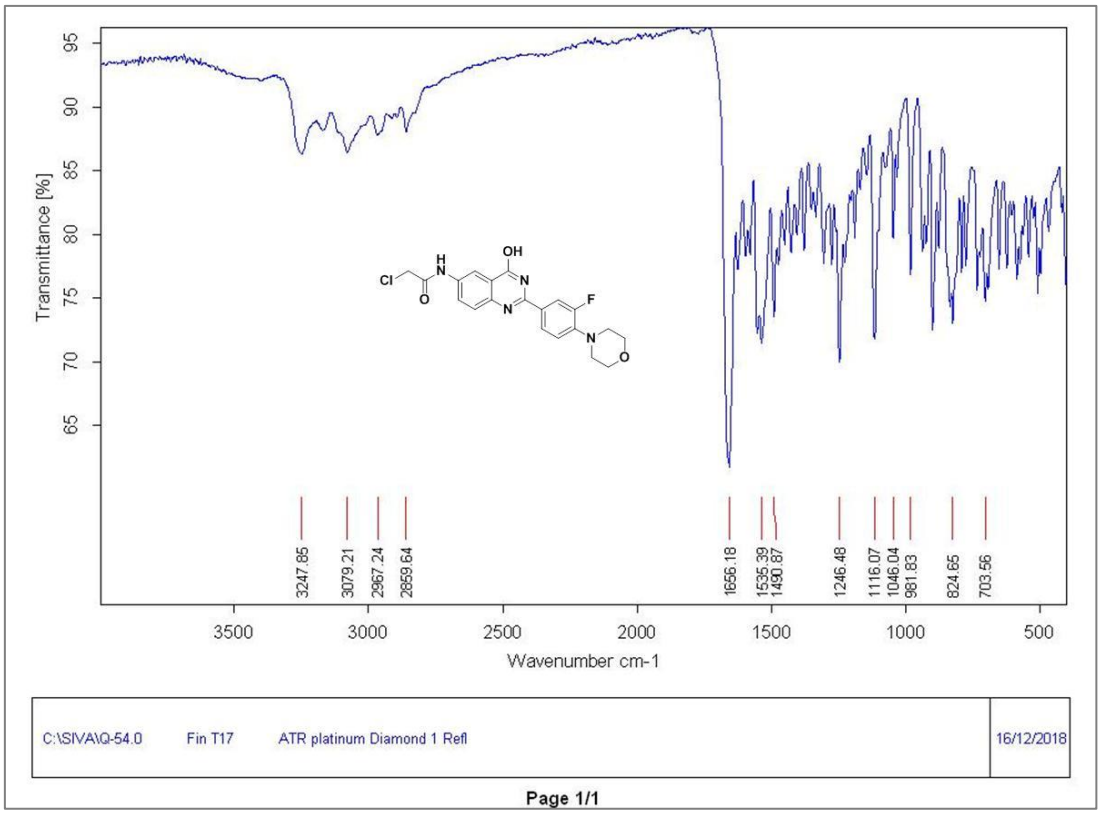
IR spectrum of compound 10i (Chapter 4)



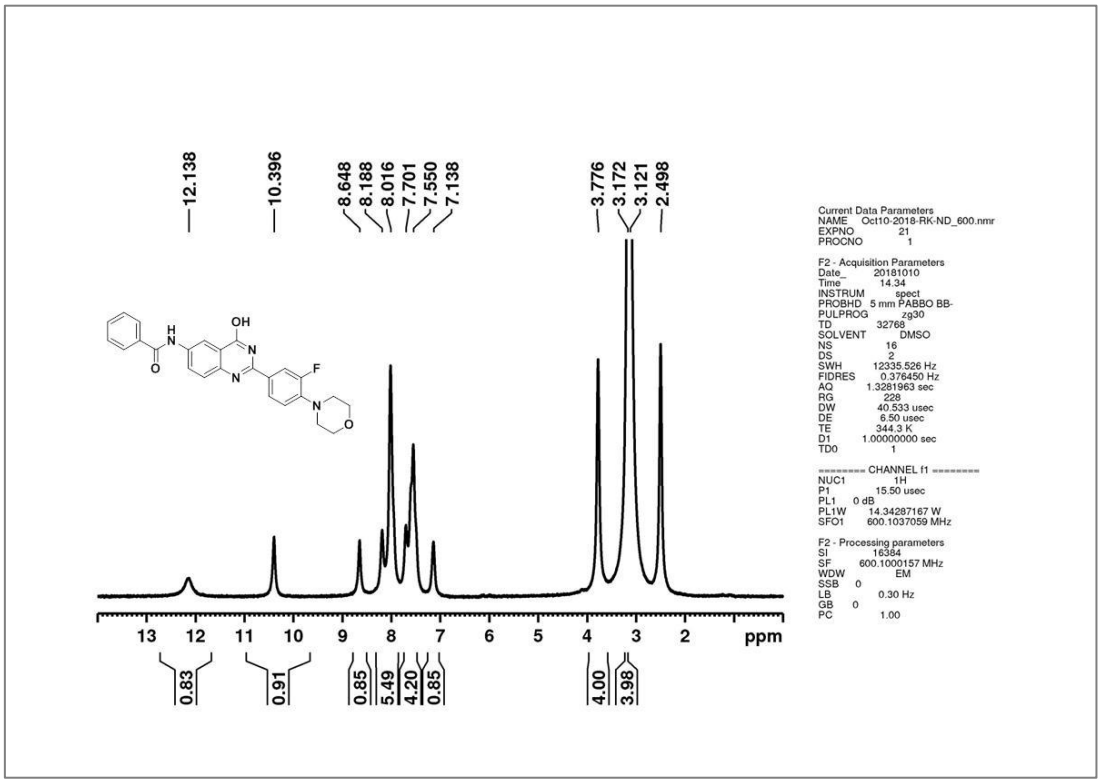
^{1}H NMR spectrum of compound 10j (Chapter 4)



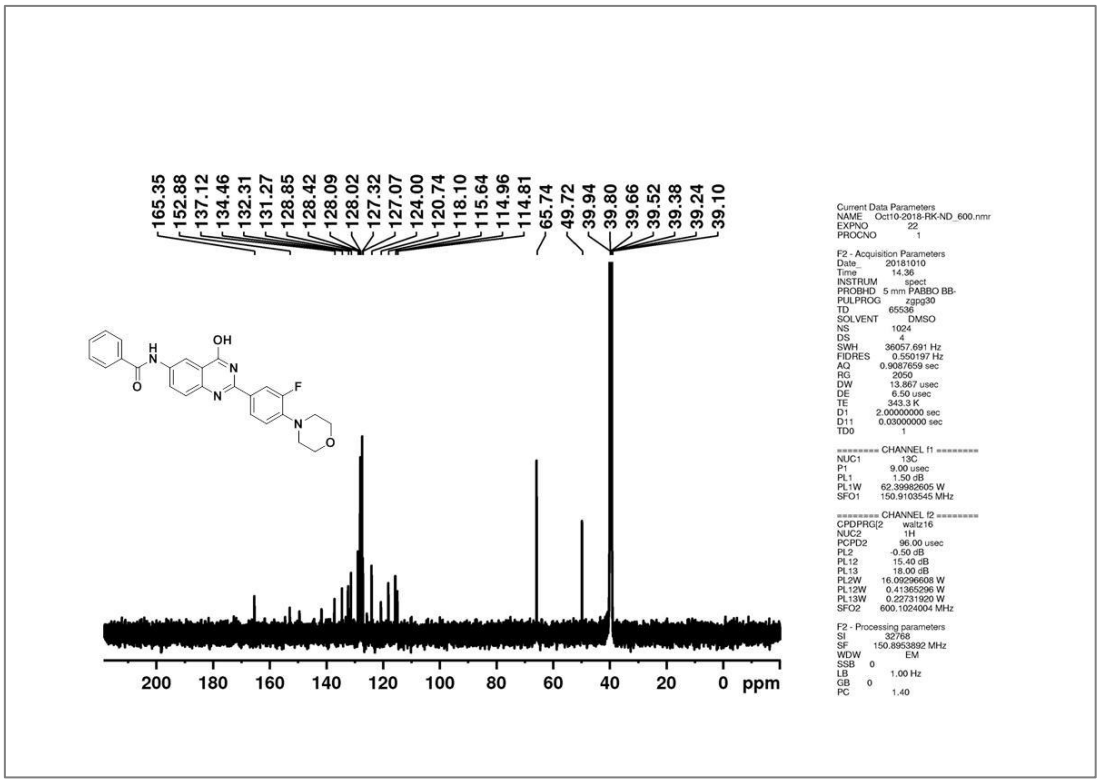
^{13}C NMR spectrum of compound 10j (Chapter 4)



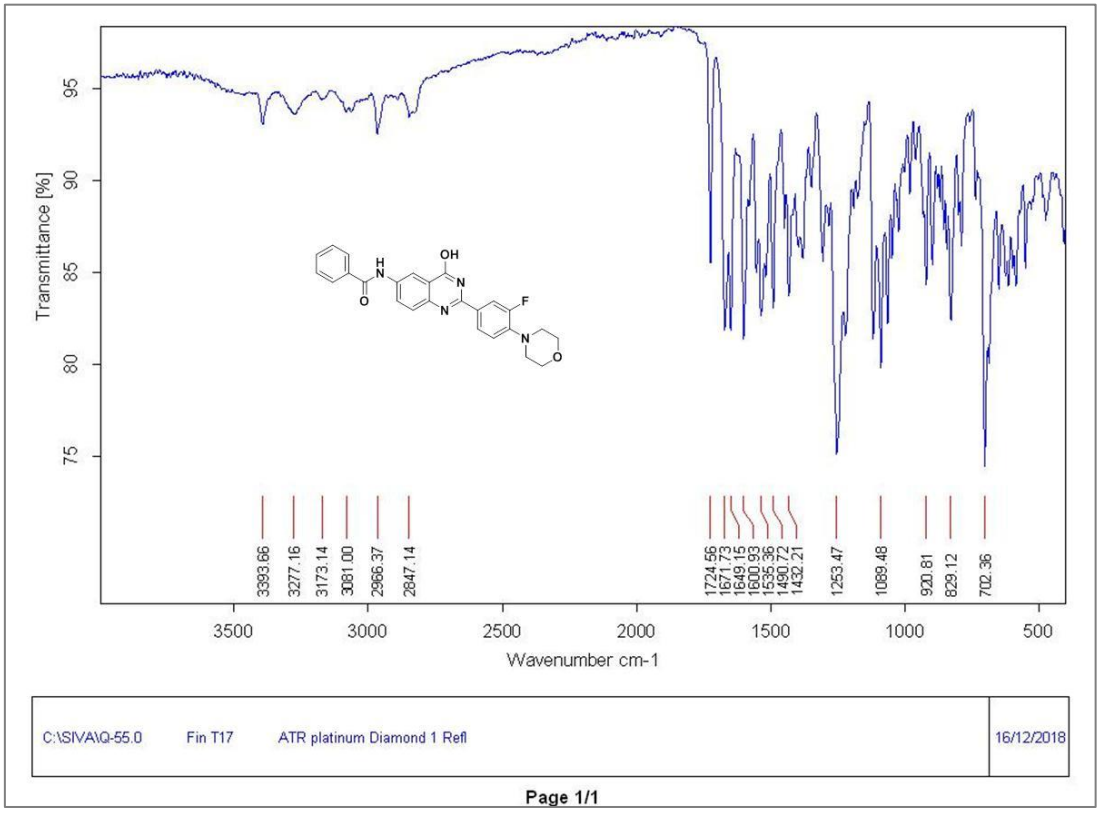
IR spectrum of compound 10j (Chapter 4)



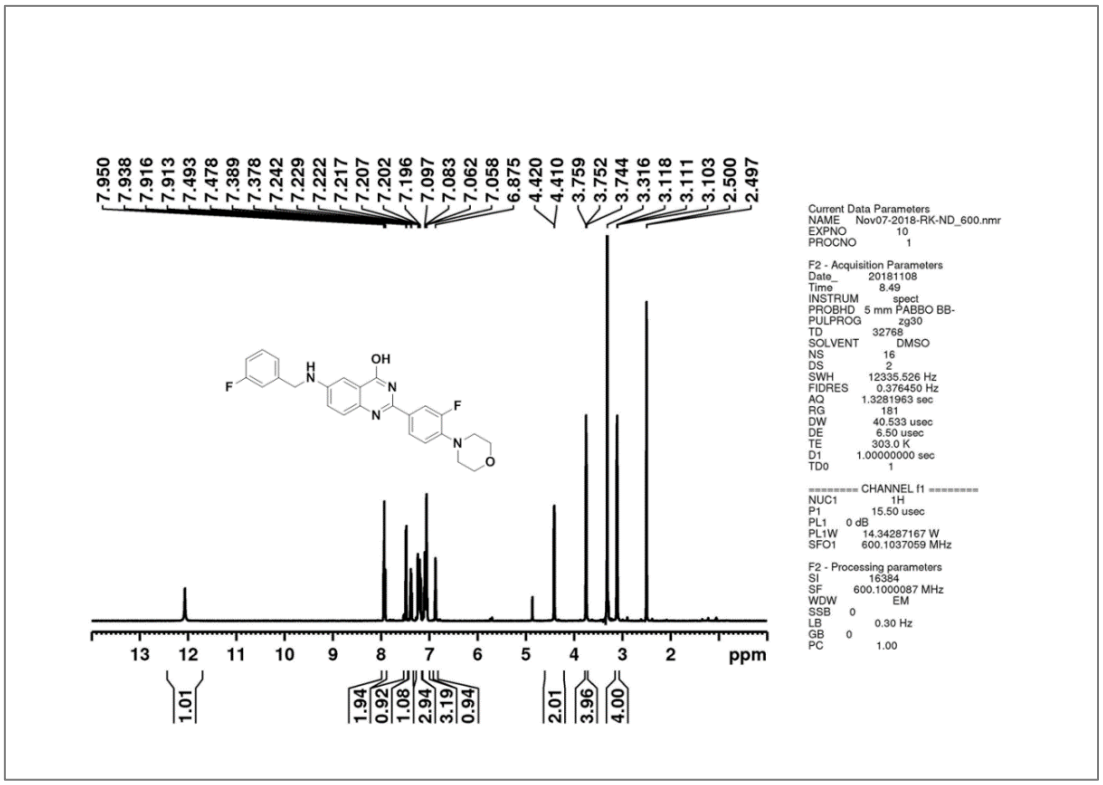
^{1}H NMR spectrum of compound 10k (Chapter 4)



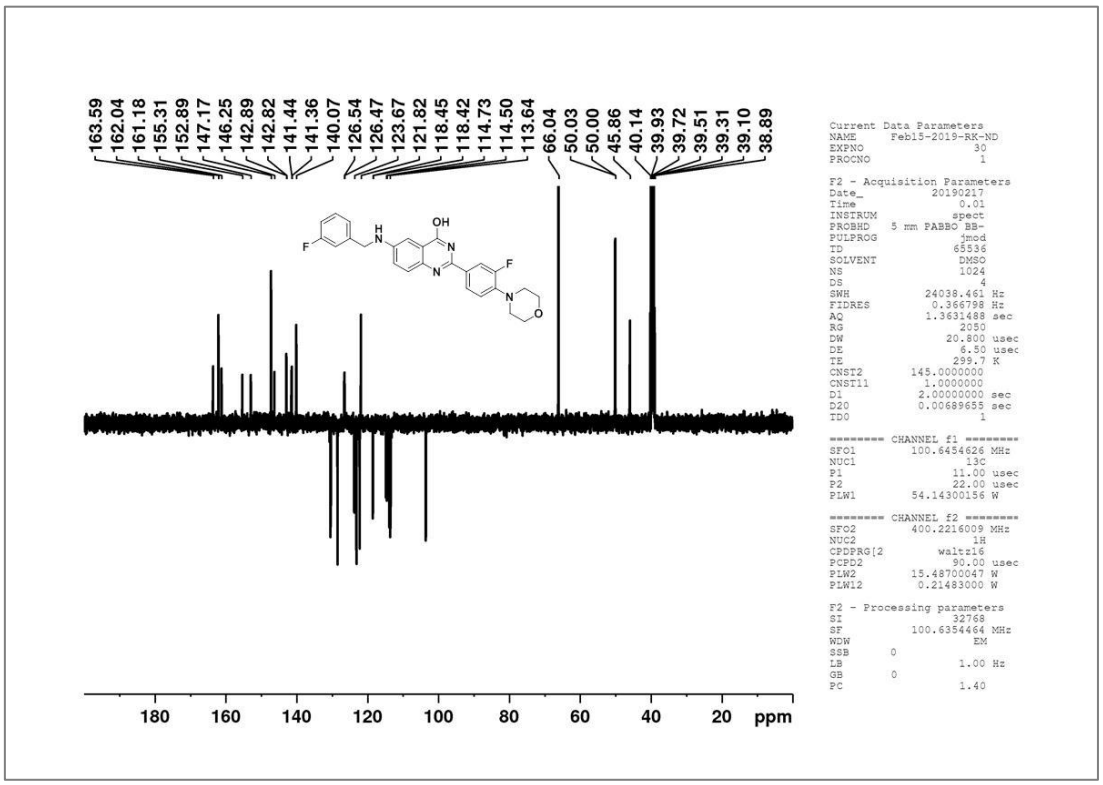
^{13}C NMR spectrum of compound 10k (Chapter 4)



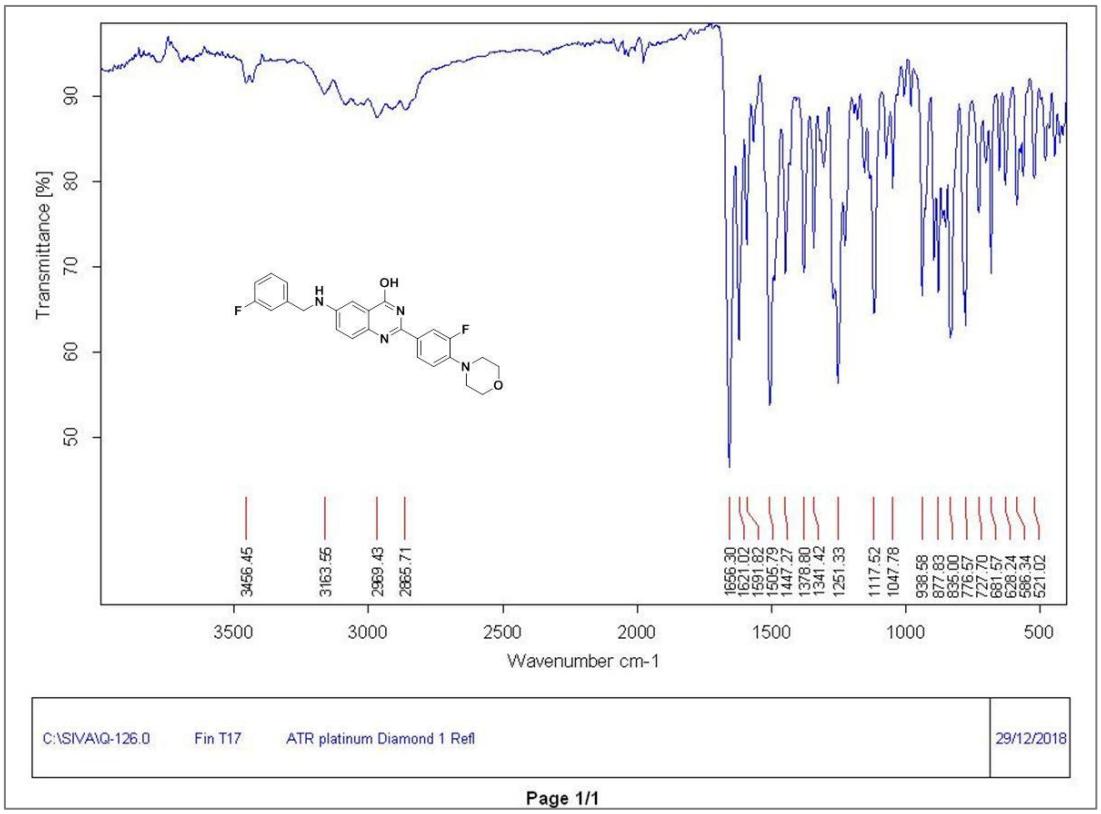
IR spectrum of compound 10k (Chapter 4)



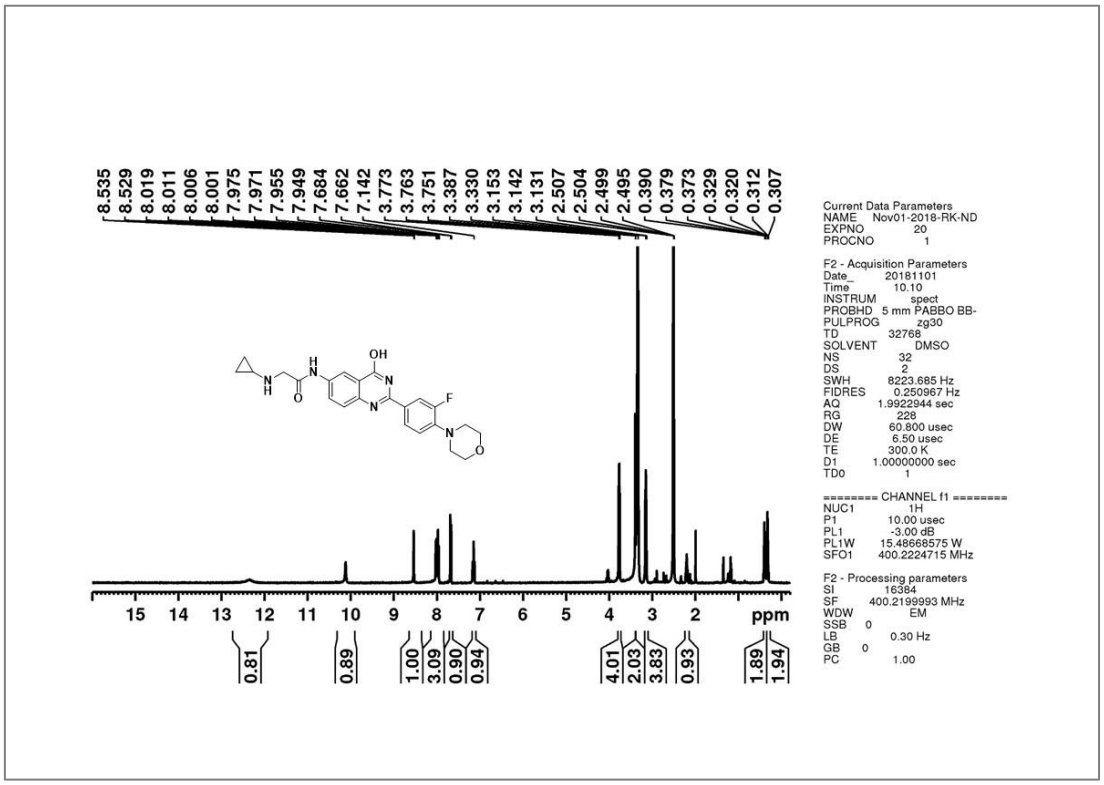
^{1}H NMR spectrum of compound 10l (Chapter 4)



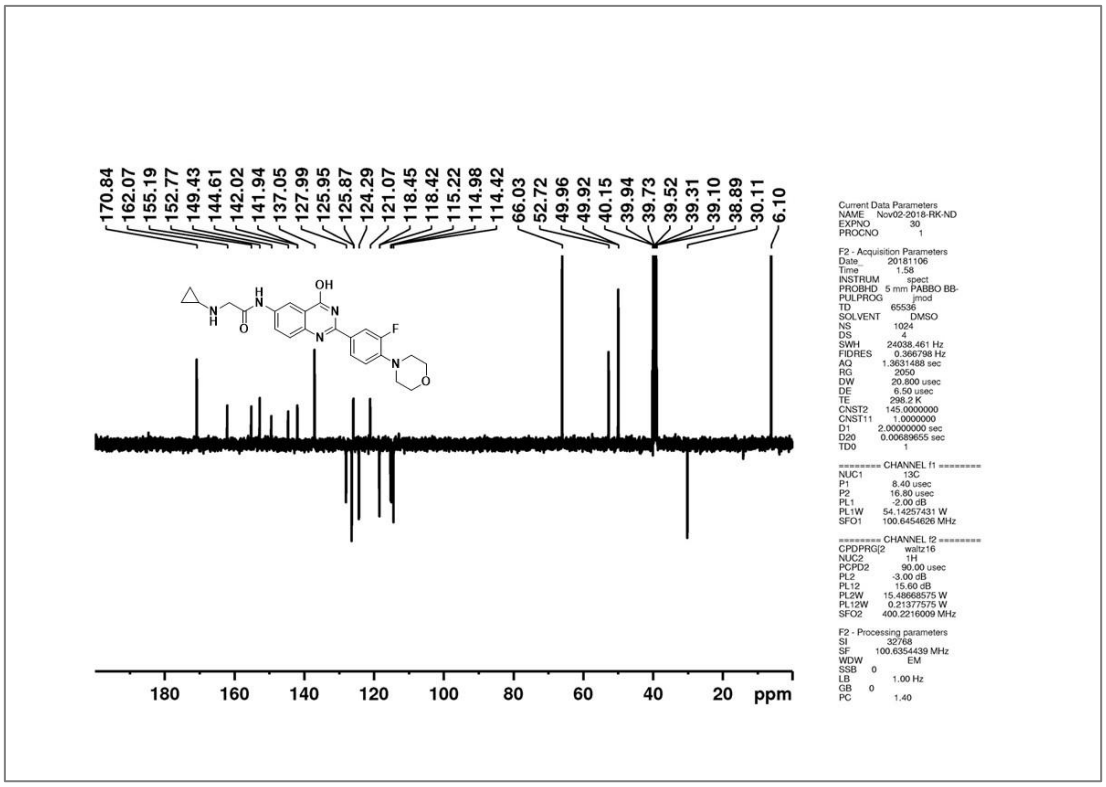
^{13}C NMR spectrum of compound 10l (Chapter 4)



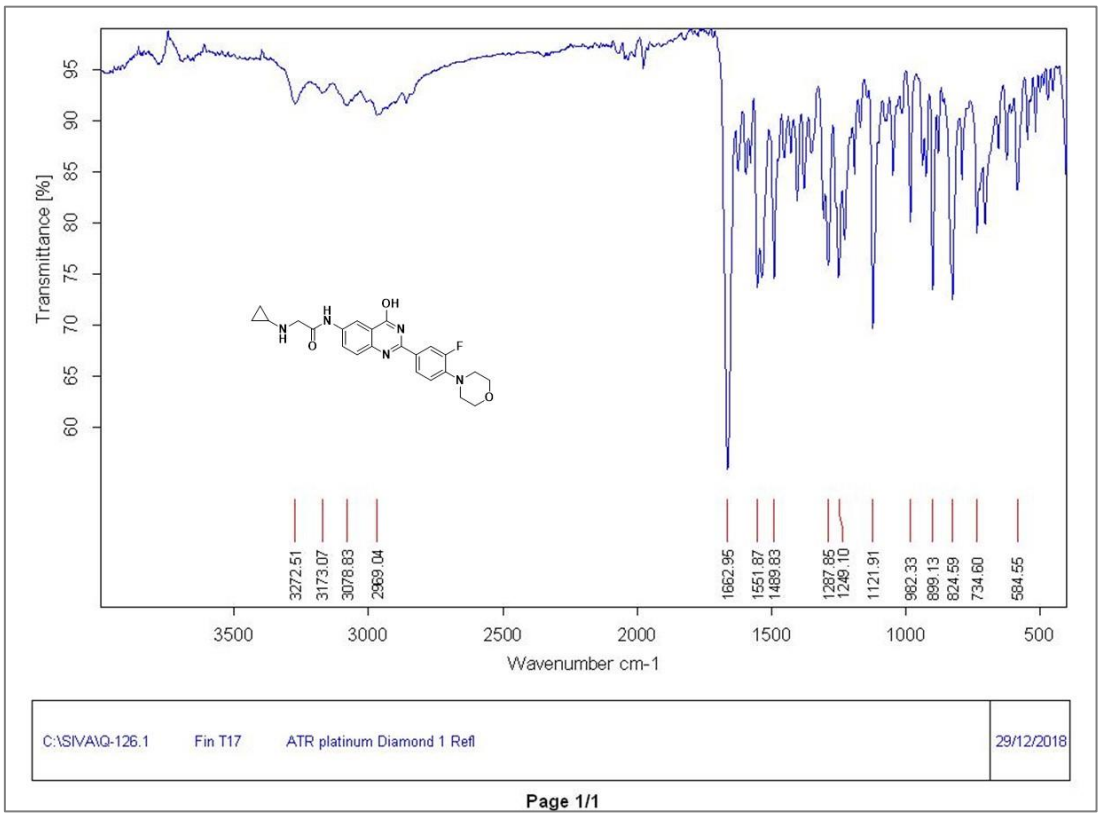
IR spectrum of compound 10l (Chapter 4)



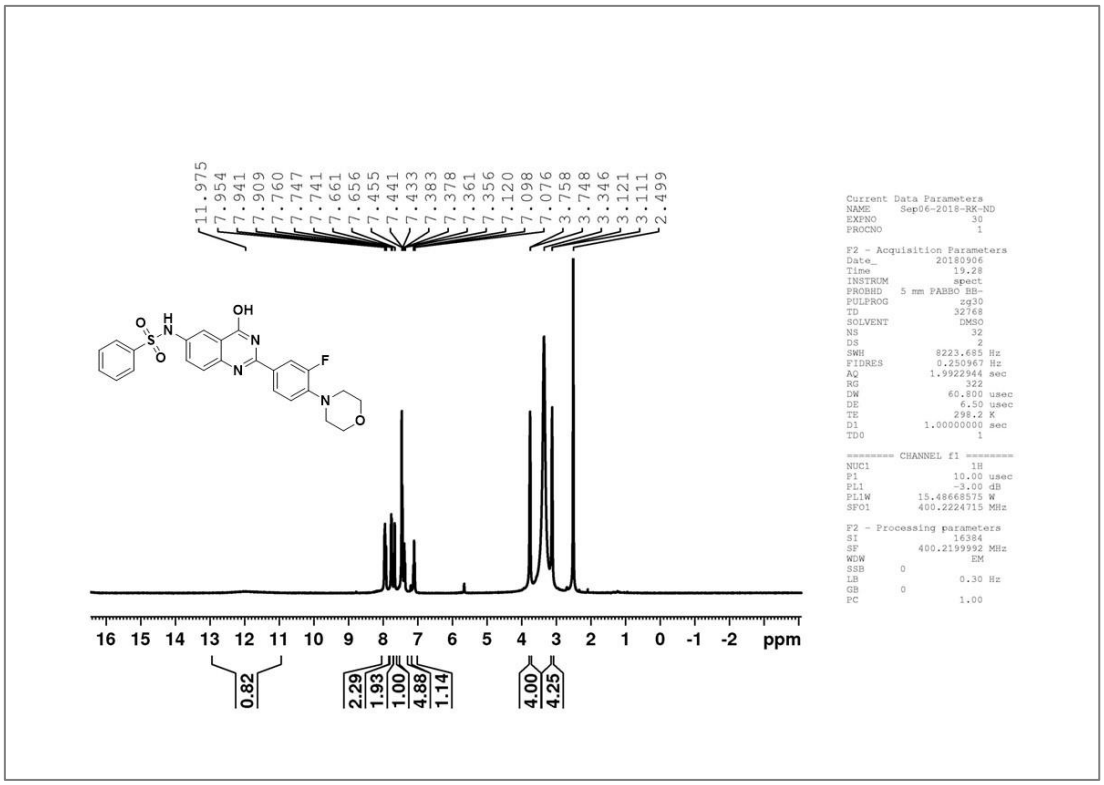
^{1}H NMR spectrum of compound 10m (Chapter 4)



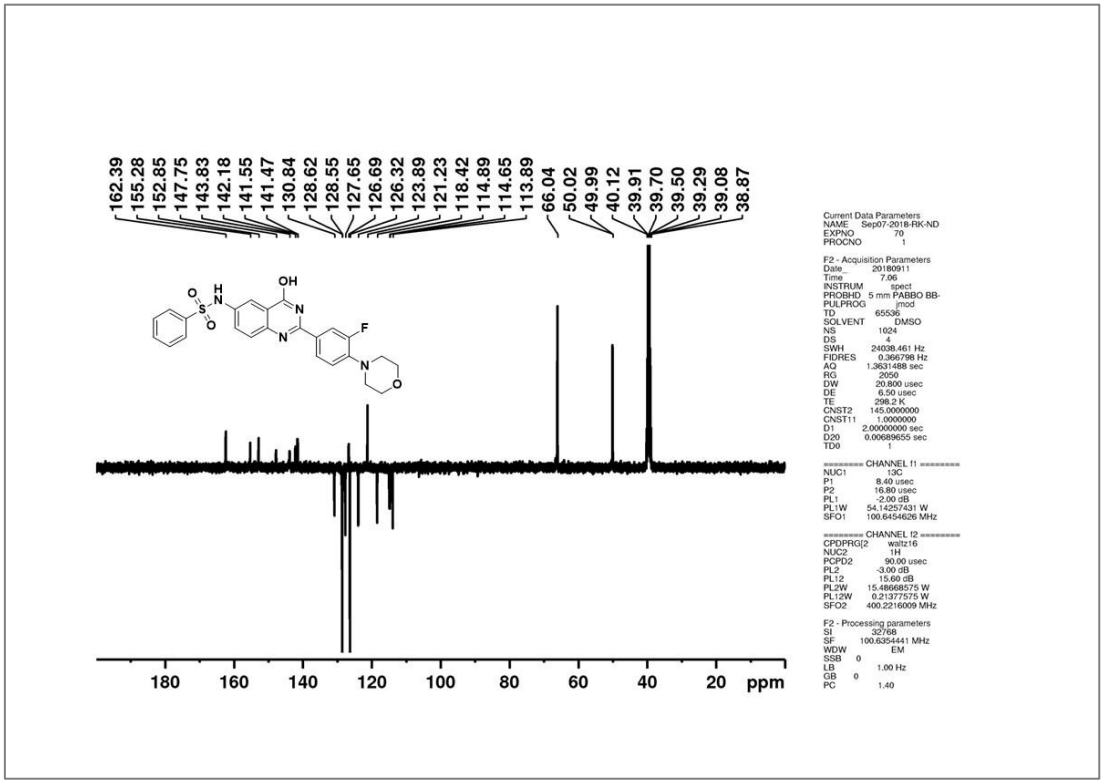
^{13}C NMR spectrum of compound 10m (Chapter 4)



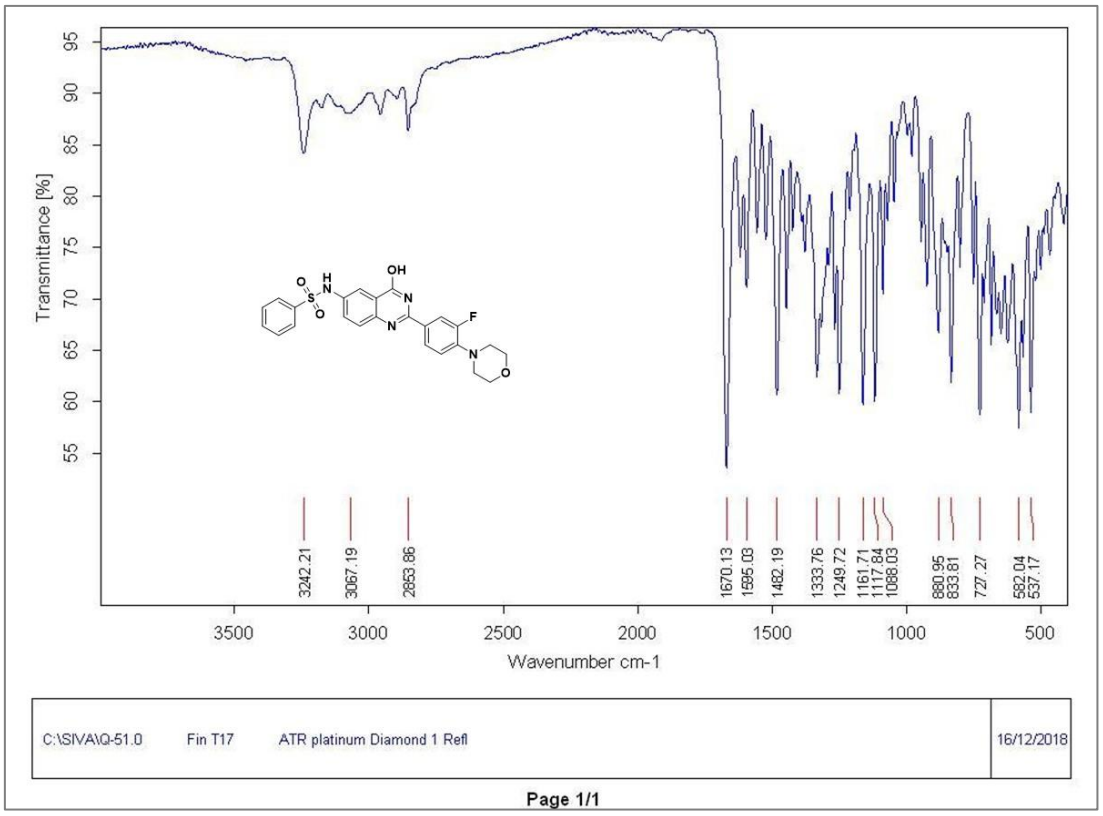
IR spectrum of compound 10m (Chapter 4)



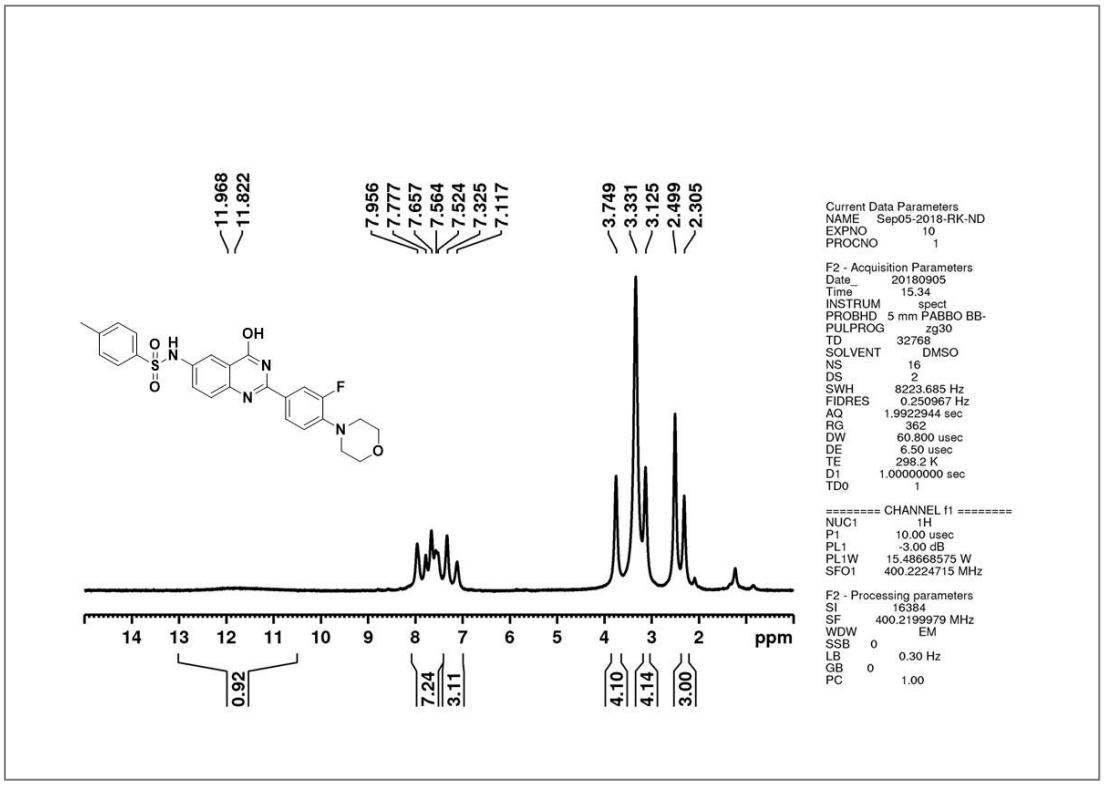
[1]H NMR spectrum of compound 10n (Chapter 4)



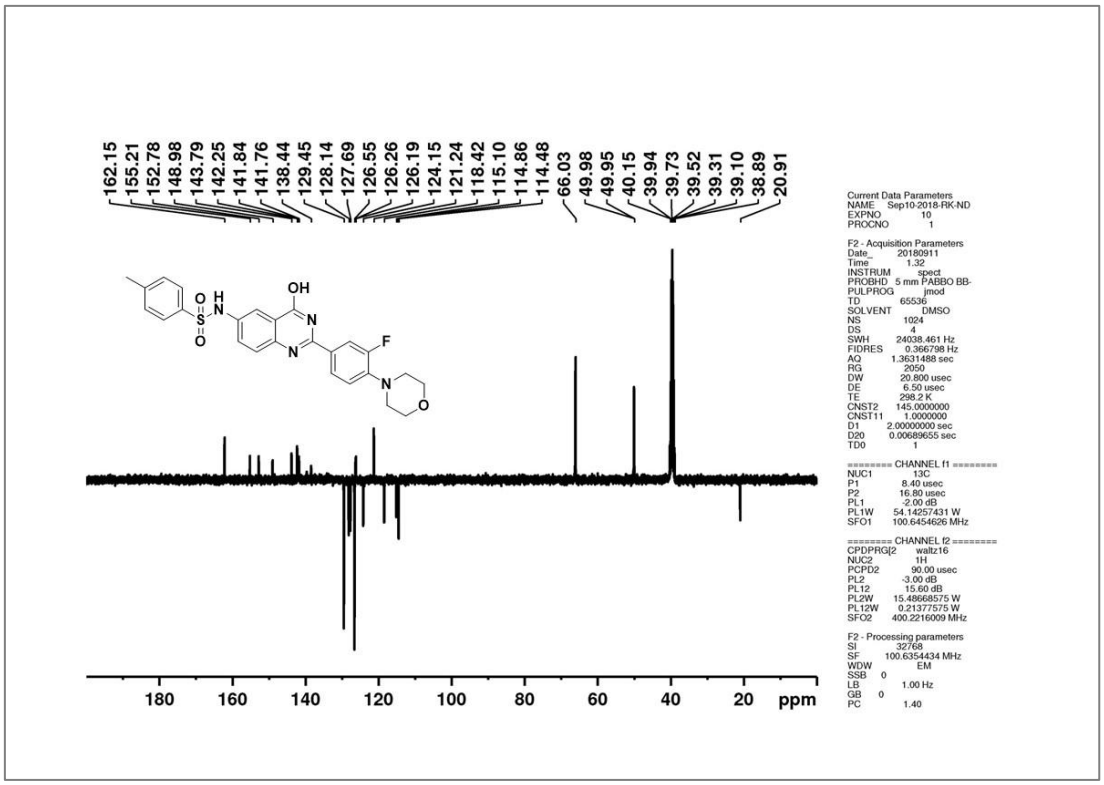
[13]C NMR spectrum of compound 10n (Chapter 4)



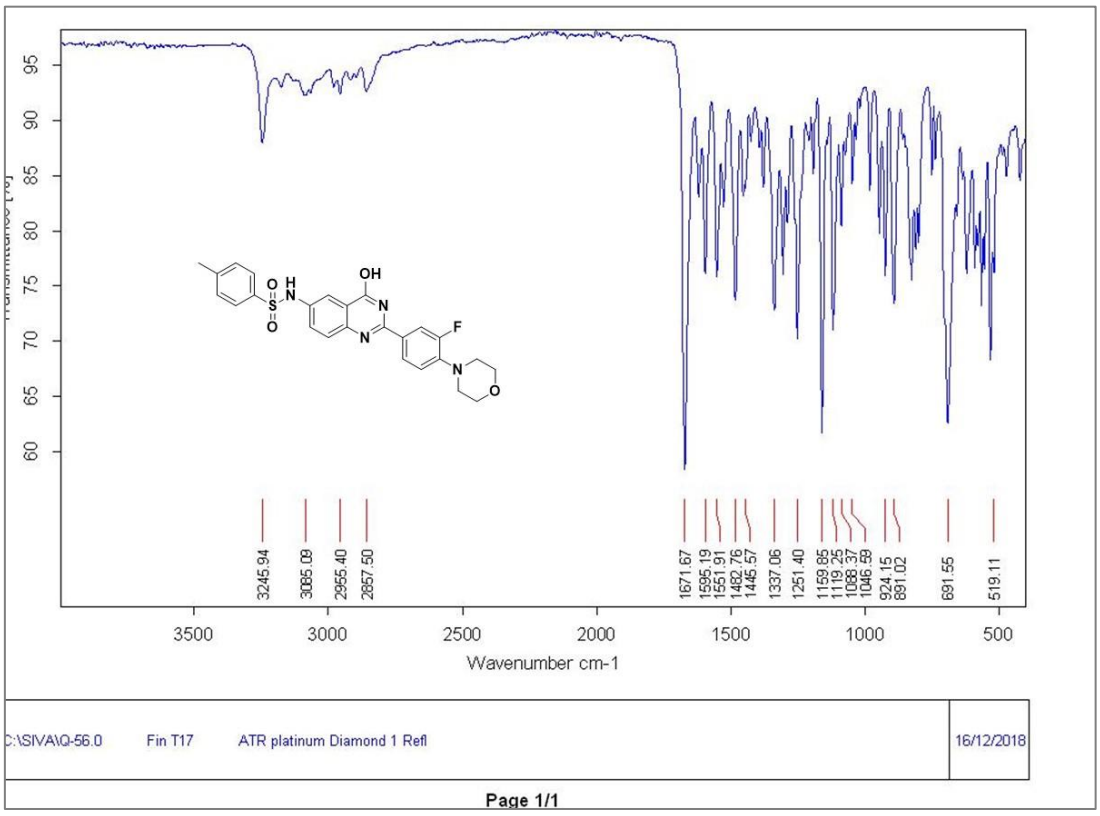
IR spectrum of compound 10n (Chapter 4)



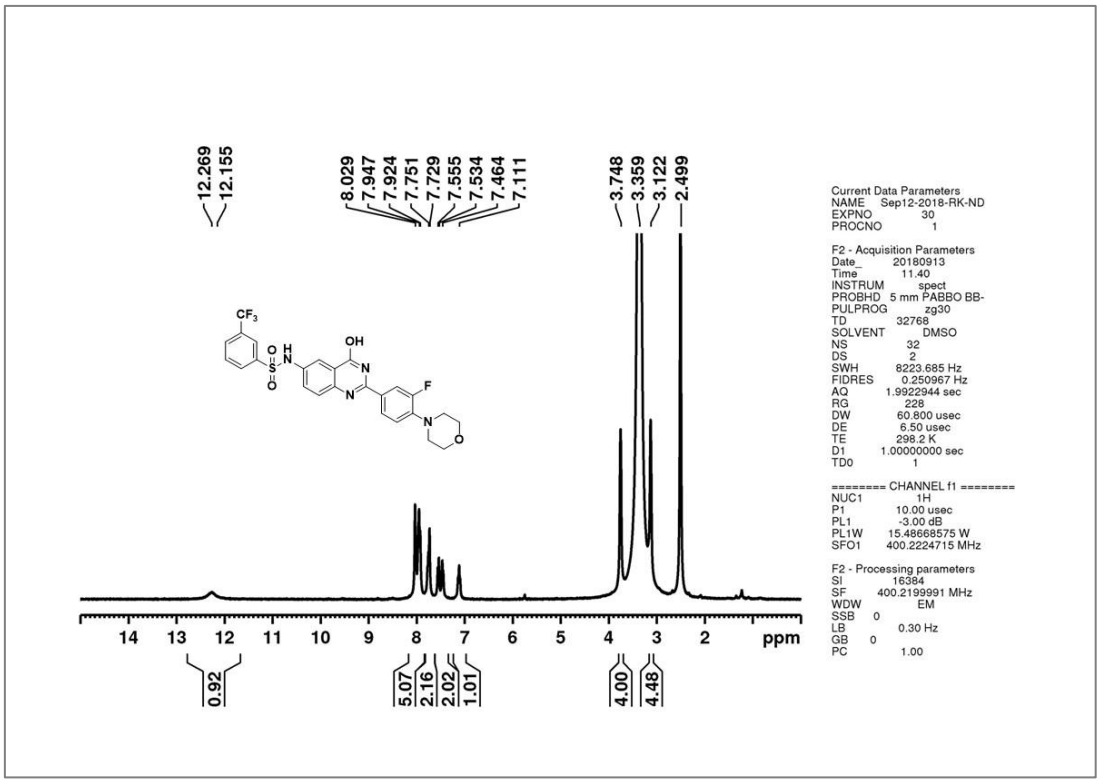
^{1}H NMR spectrum of compound 10o (Chapter 4)



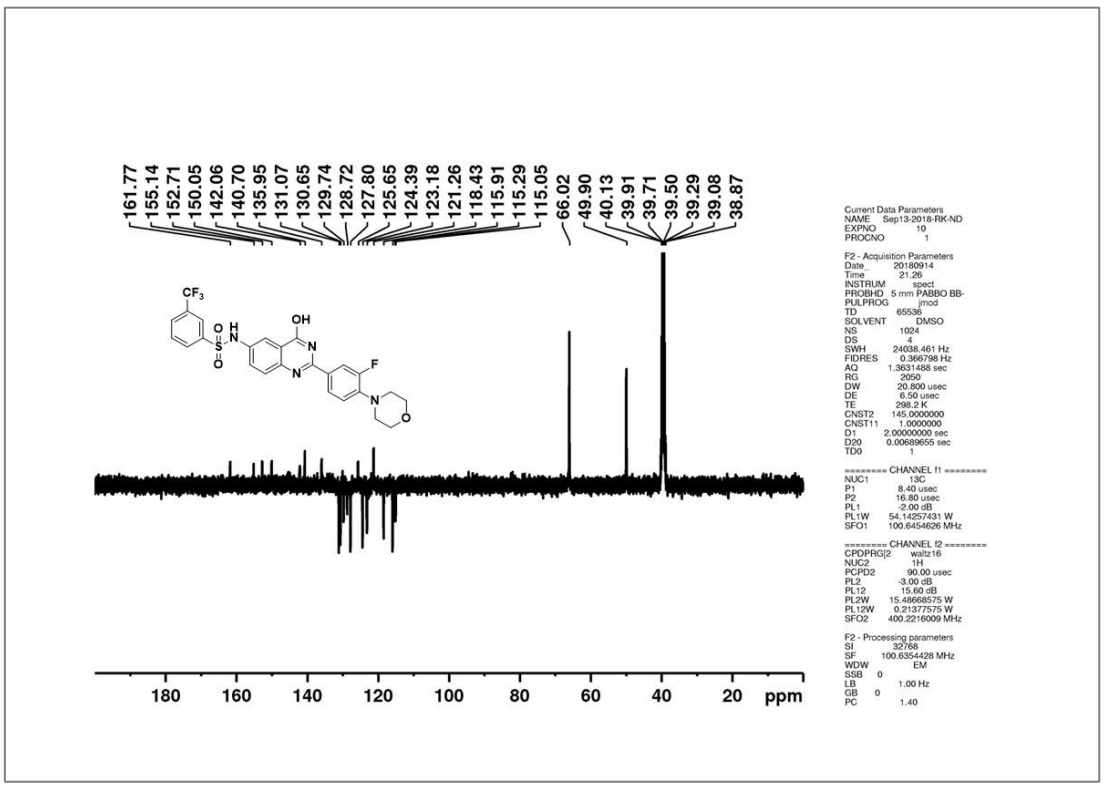
^{13}C NMR spectrum of compound 10o (Chapter 4)



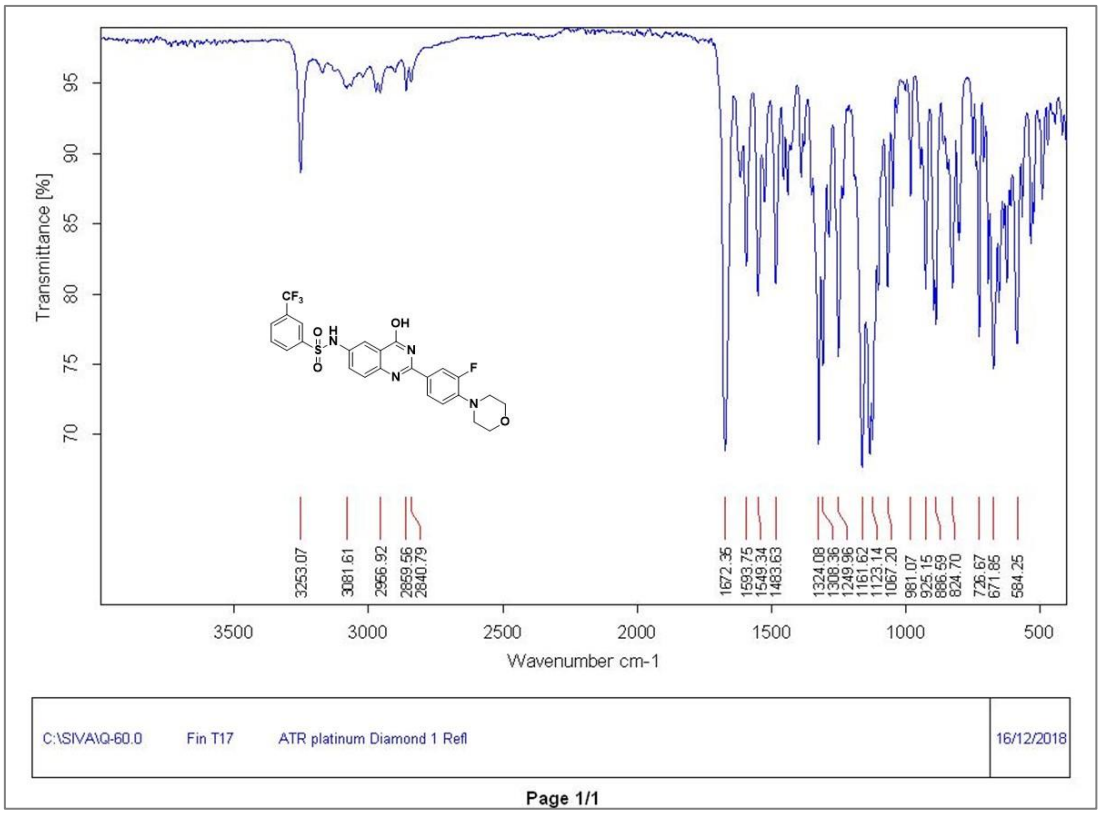
IR spectrum of compound 10o (Chapter 4)



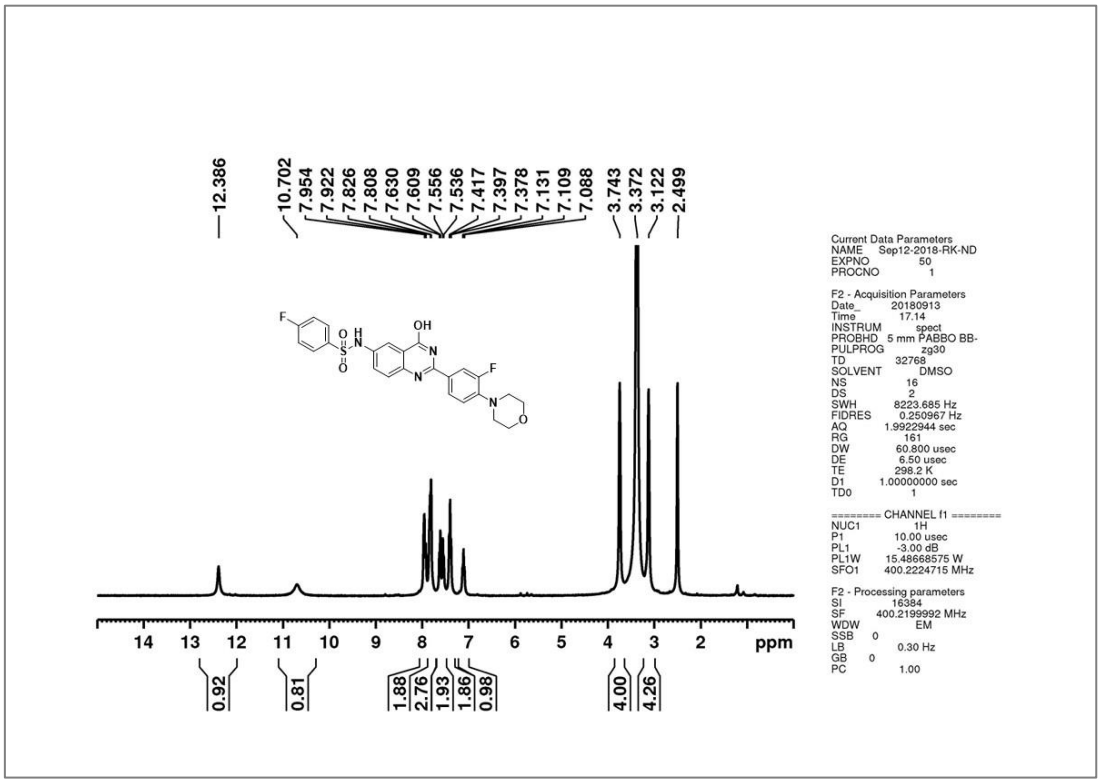
[1]H NMR spectrum of compound 10p (Chapter 4)



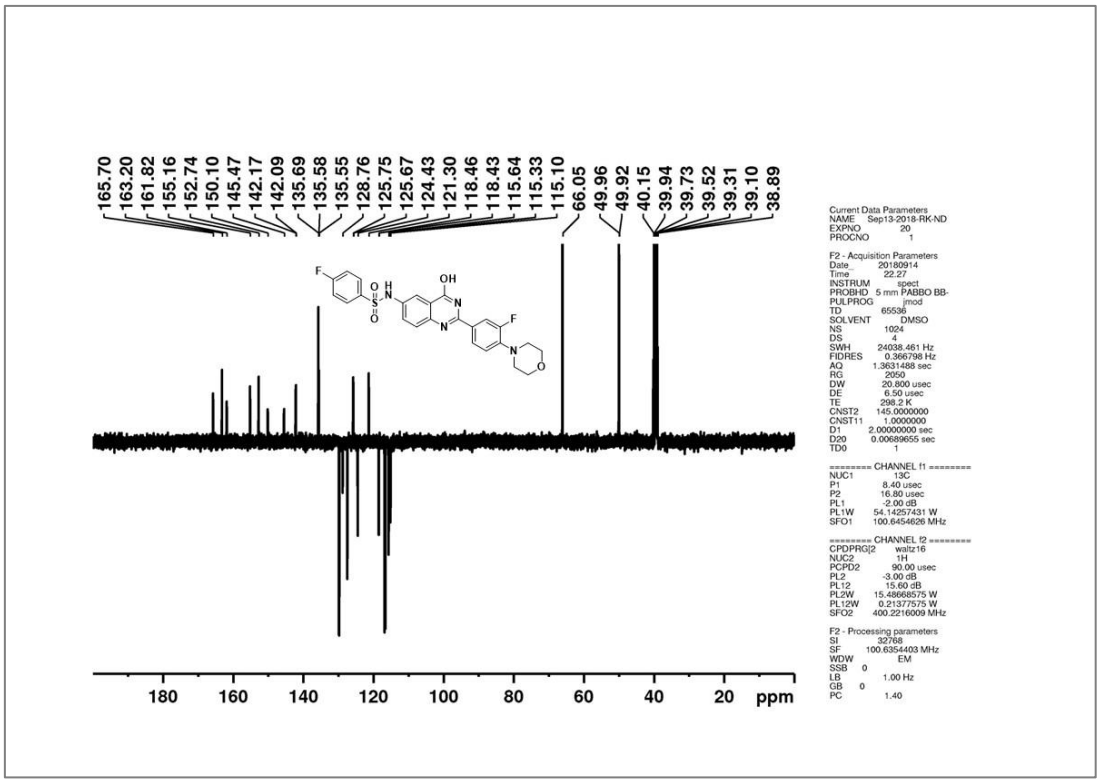
[13]C NMR spectrum of compound 10p (Chapter 4)



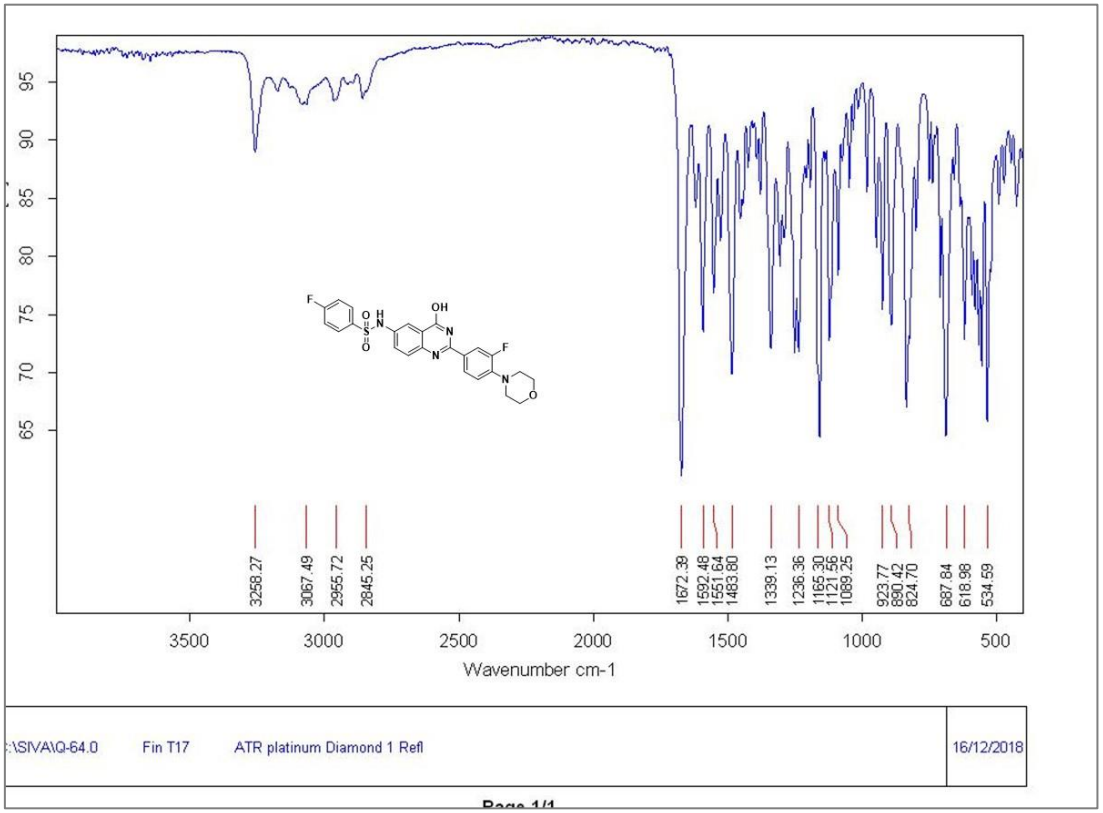
IR spectrum of compound 10p (Chapter 4)



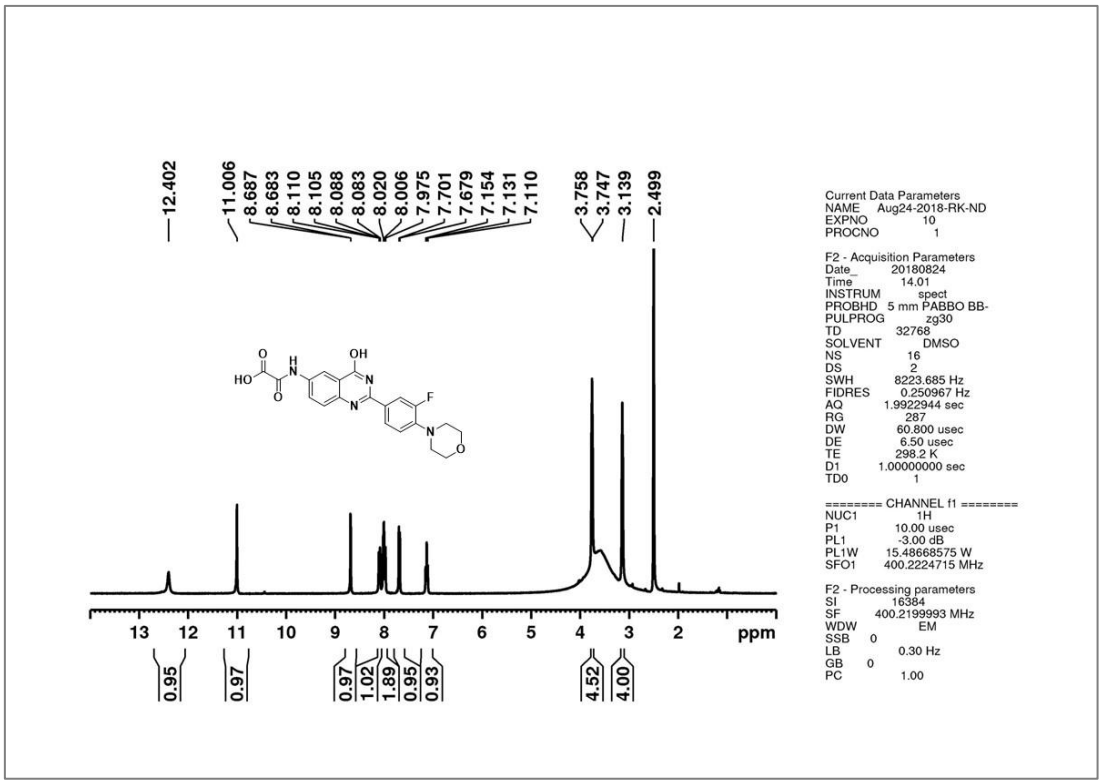
^{1}H NMR spectrum of compound 10q (Chapter 4)



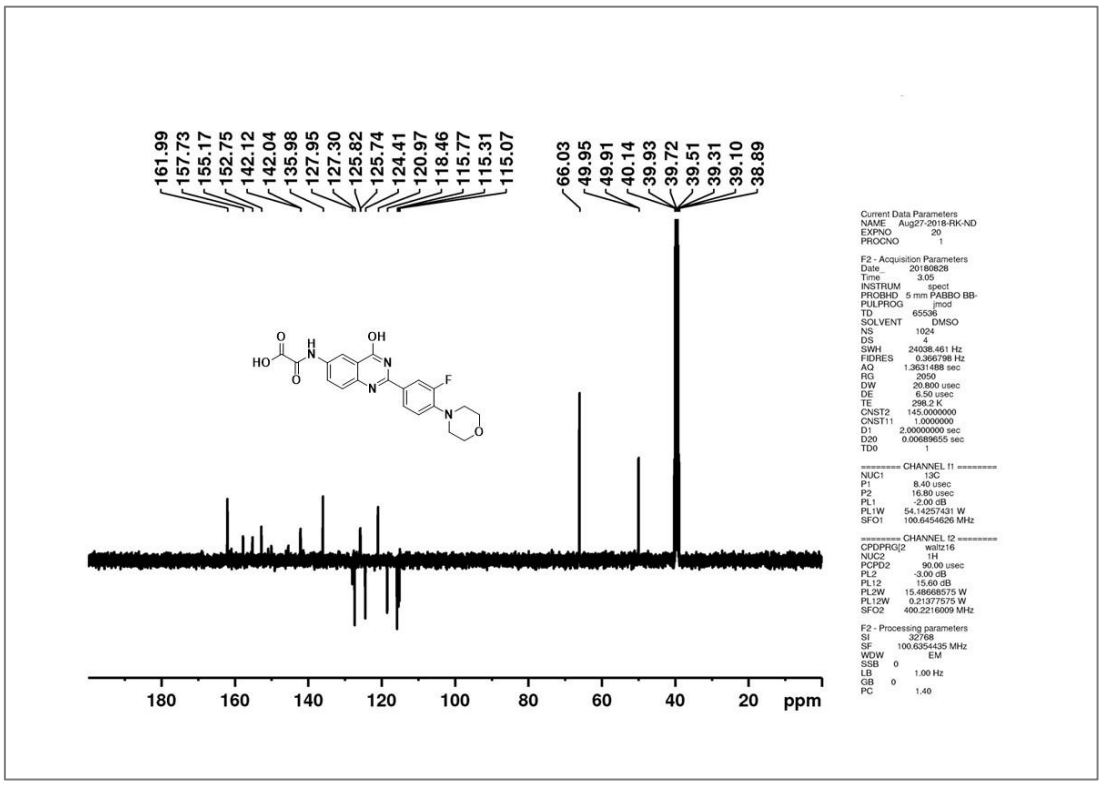
^{13}C NMR spectrum of compound 10q (Chapter 4)



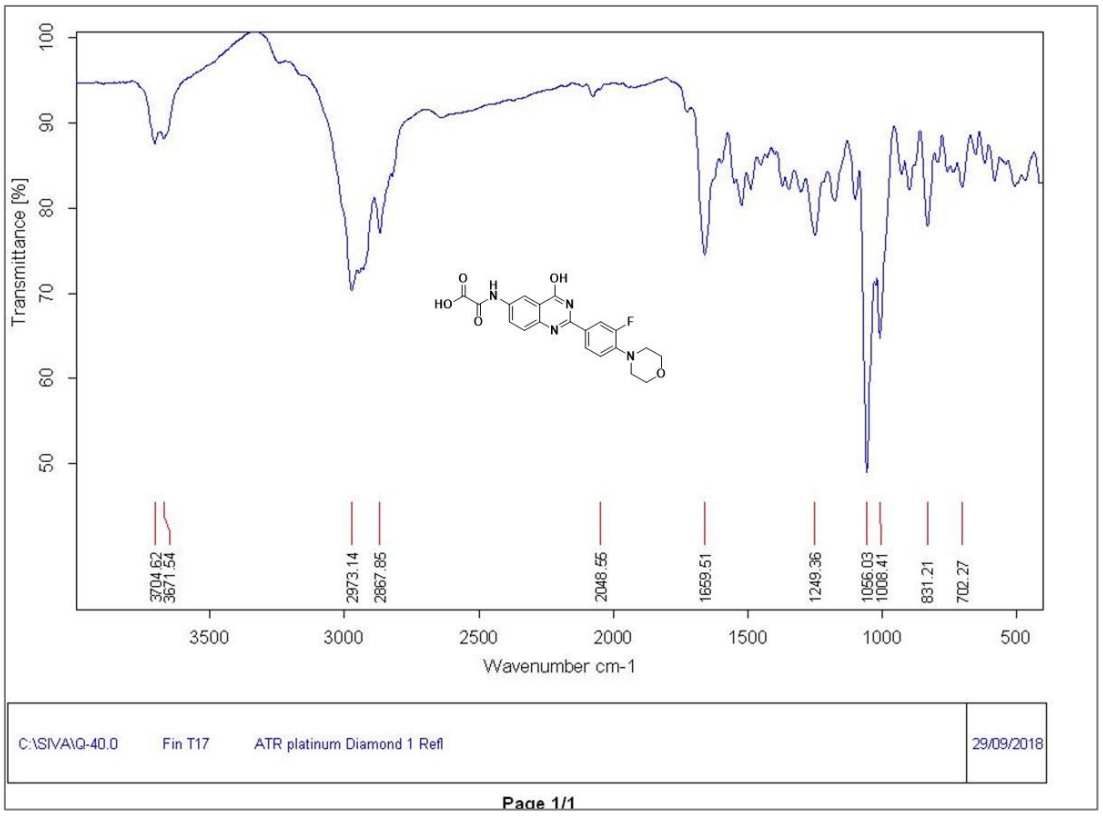
IR spectrum of compound 10q (Chapter 4)



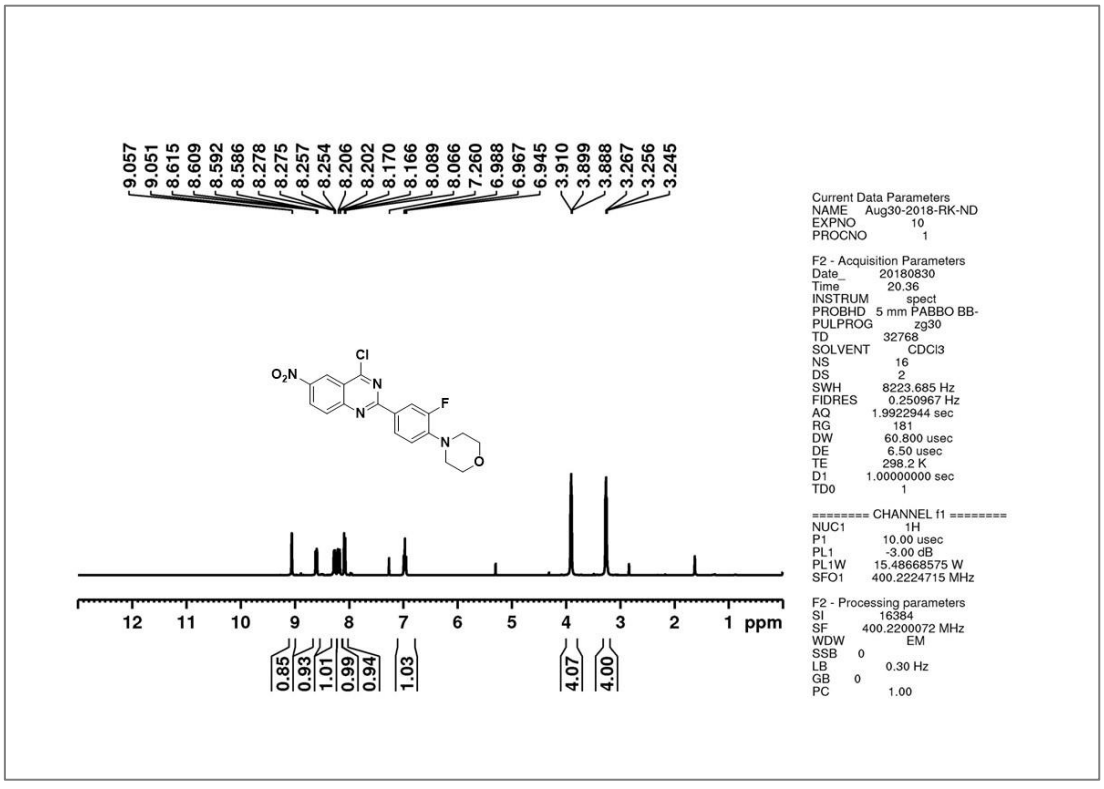
^{1}H NMR spectrum of compound 11 (Chapter 4)



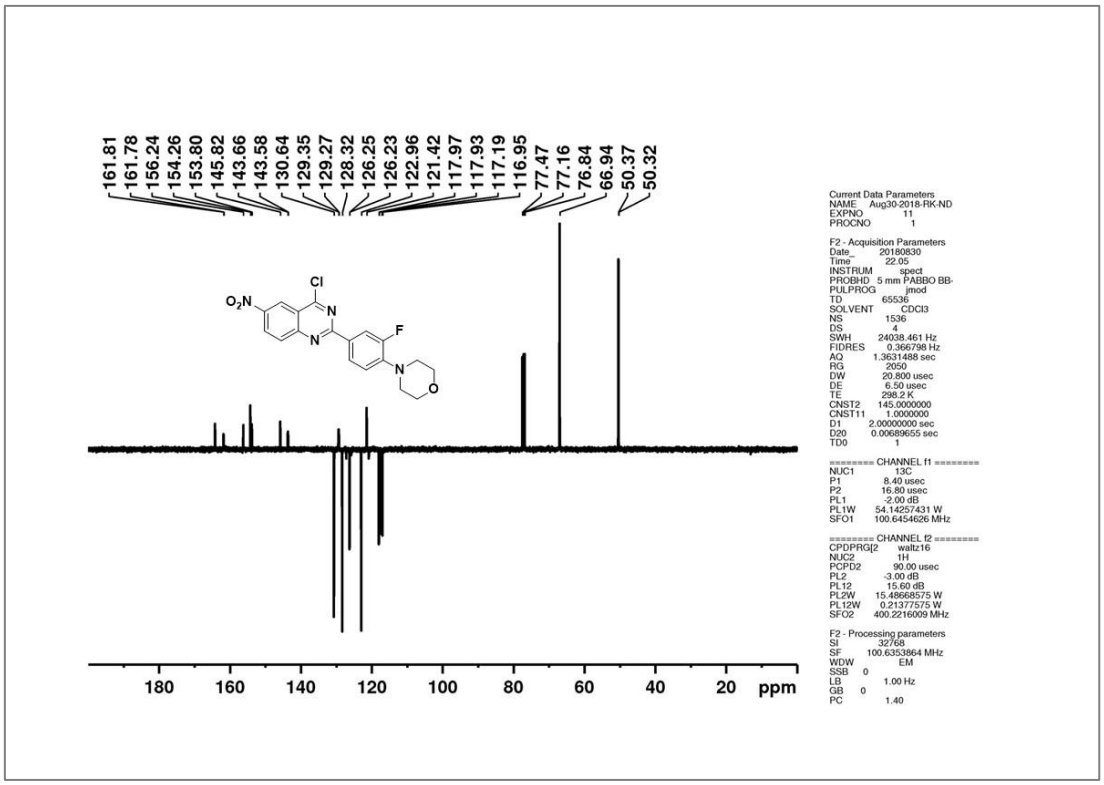
^{13}C NMR spectrum of compound 11 (Chapter 4)



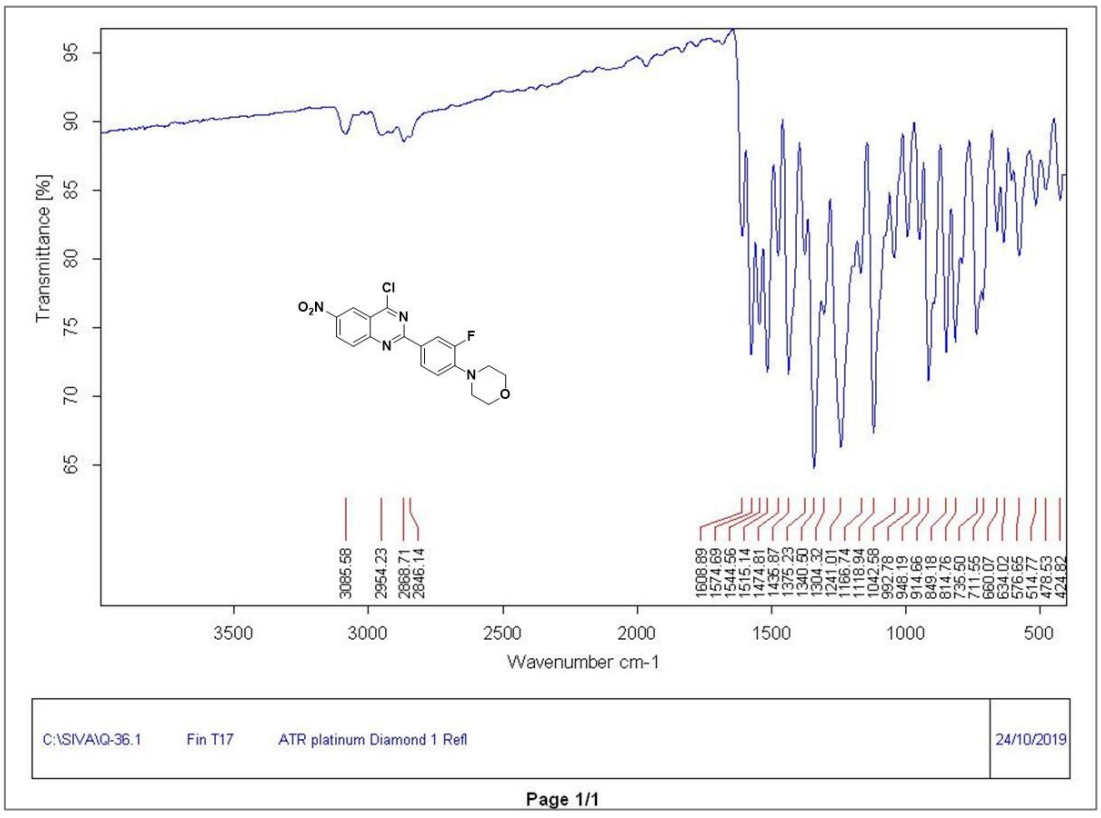
IR spectrum of compound 11 (Chapter 4)



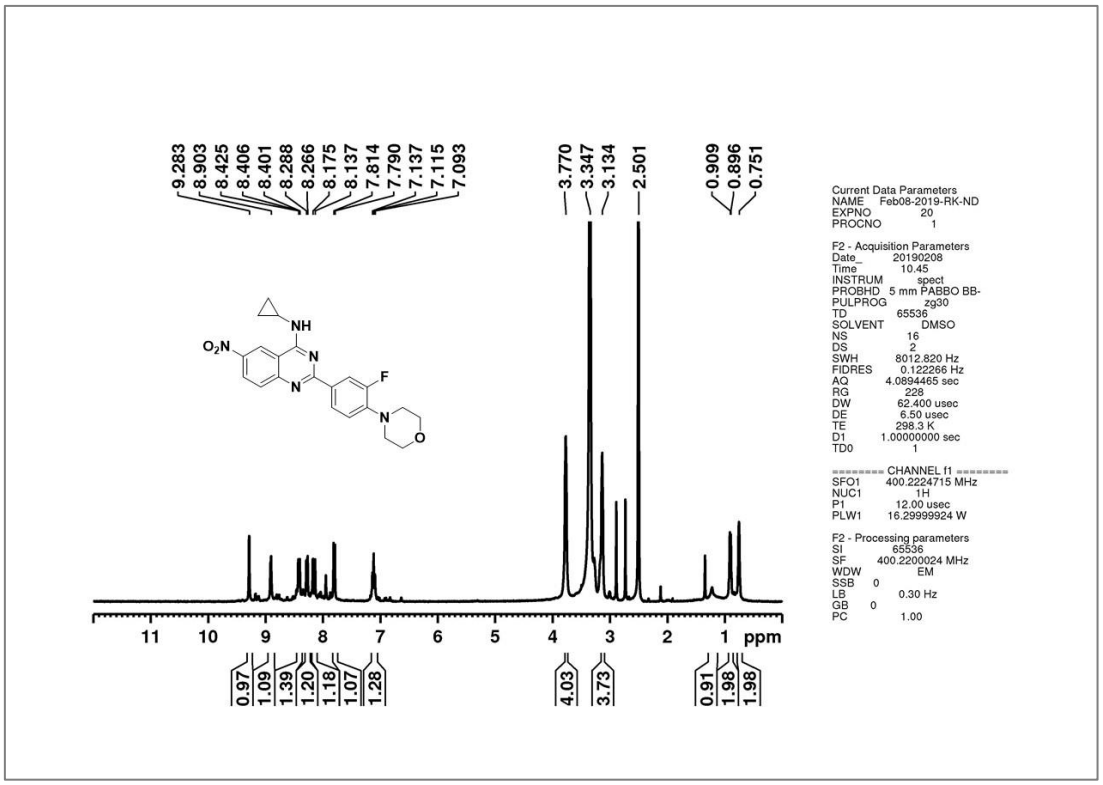
^{1}H NMR spectrum of compound 12 (Chapter 4)



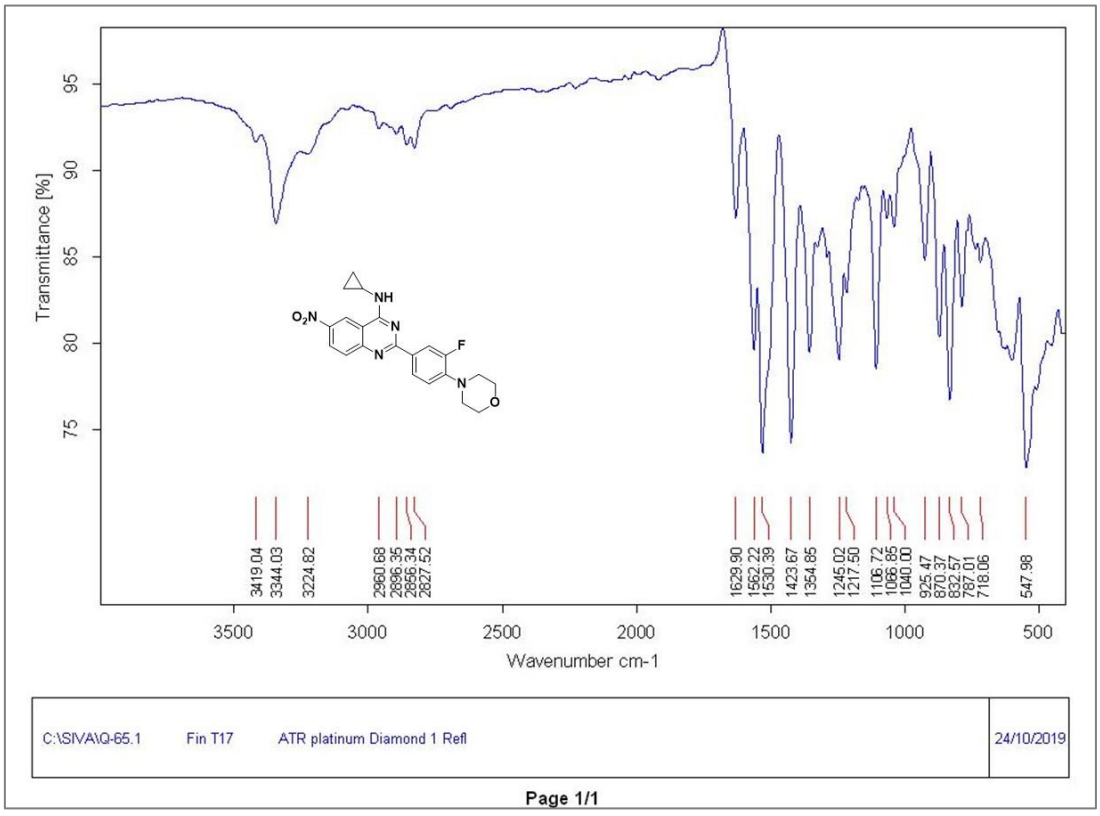
^{13}C NMR spectrum of compound 12 (Chapter 4)



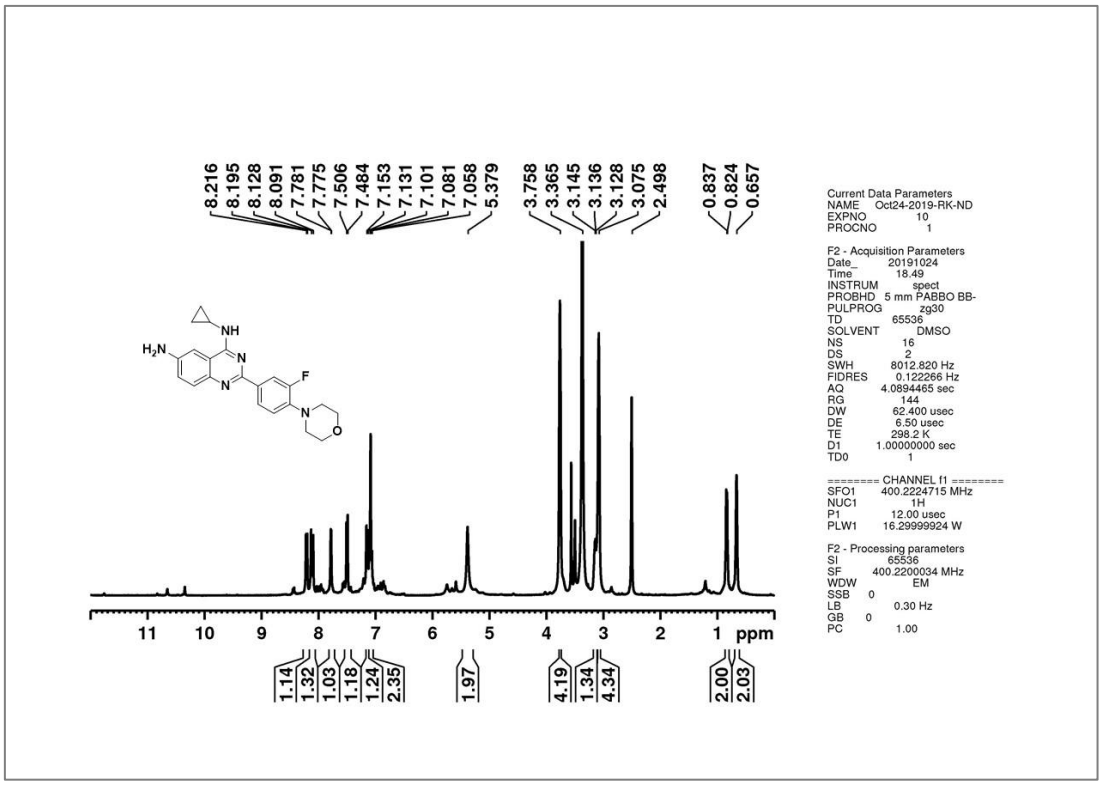
IR spectrum of compound 12 (Chapter 4)



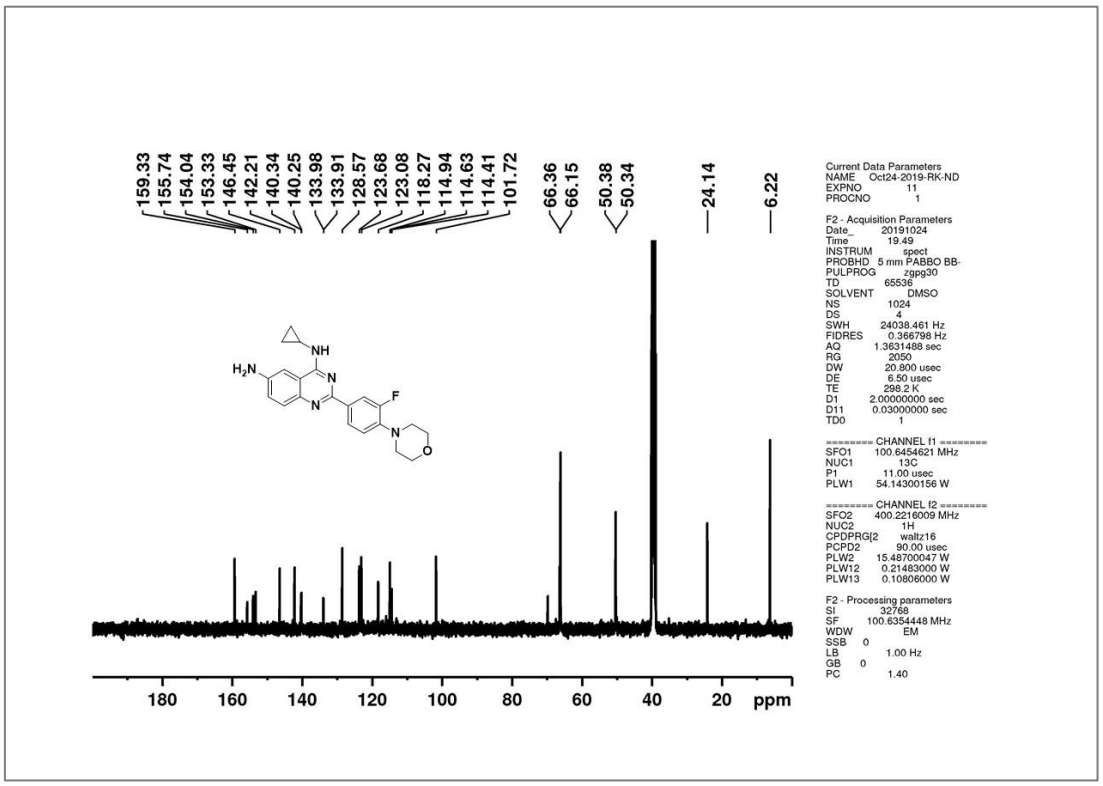
^{1}H NMR spectrum of compound 14 (Chapter 4)



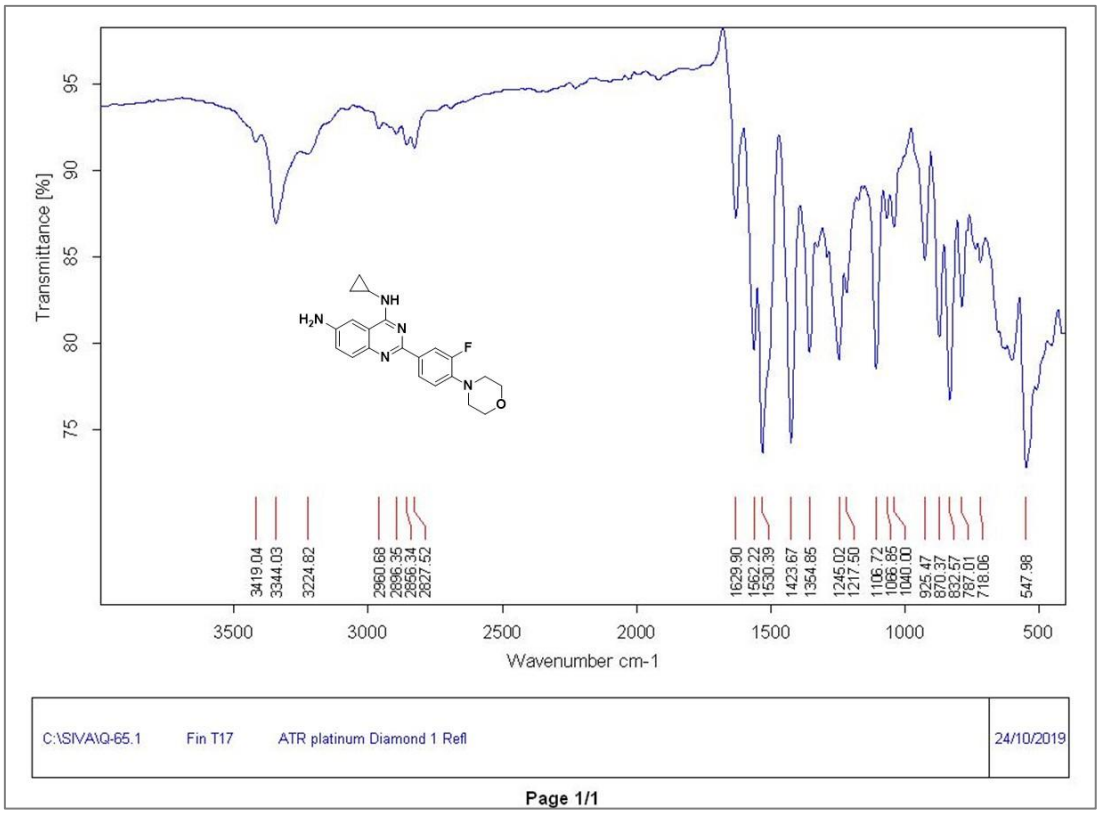
IR spectrum of compound 14 (Chapter 4)



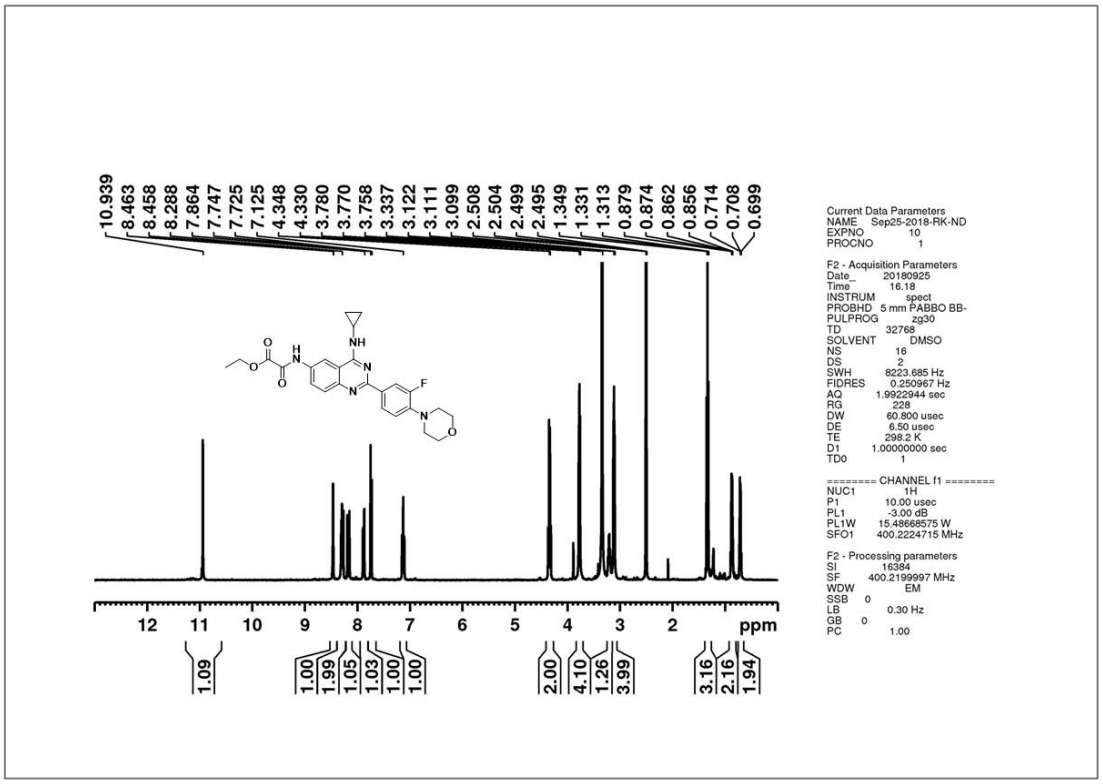
^{1}H NMR spectrum of compound 15 (Chapter 4)



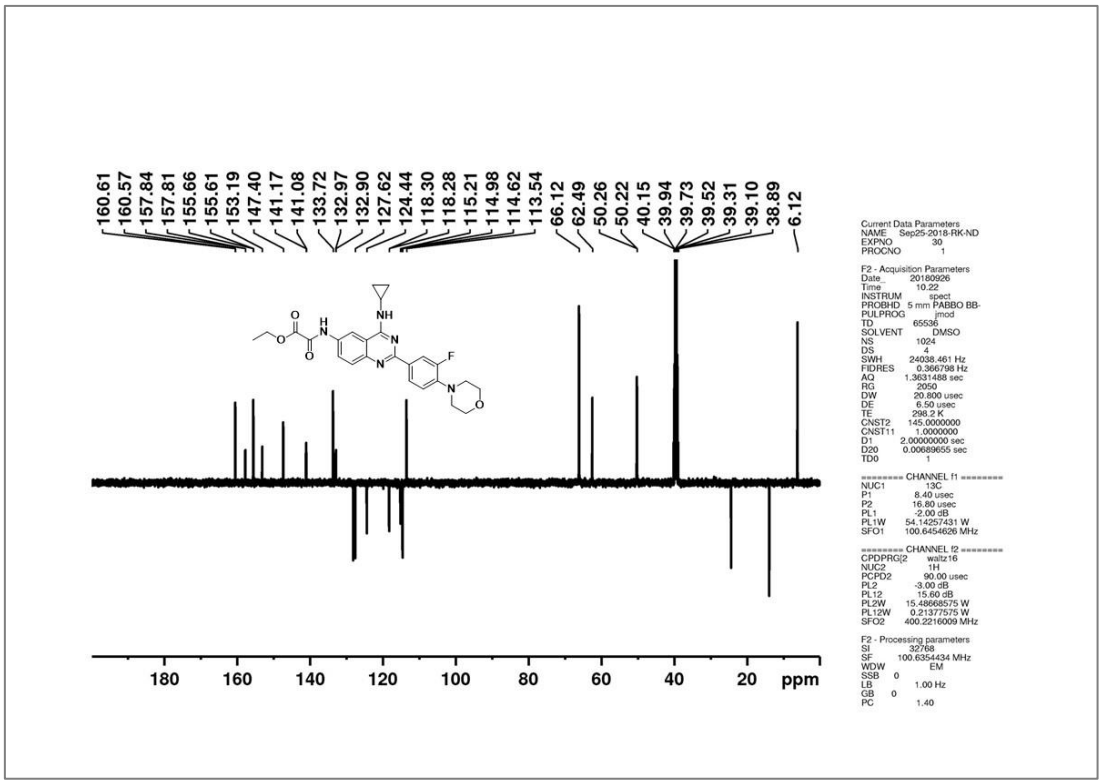
^{13}C NMR spectrum of compound 15 (Chapter 4)



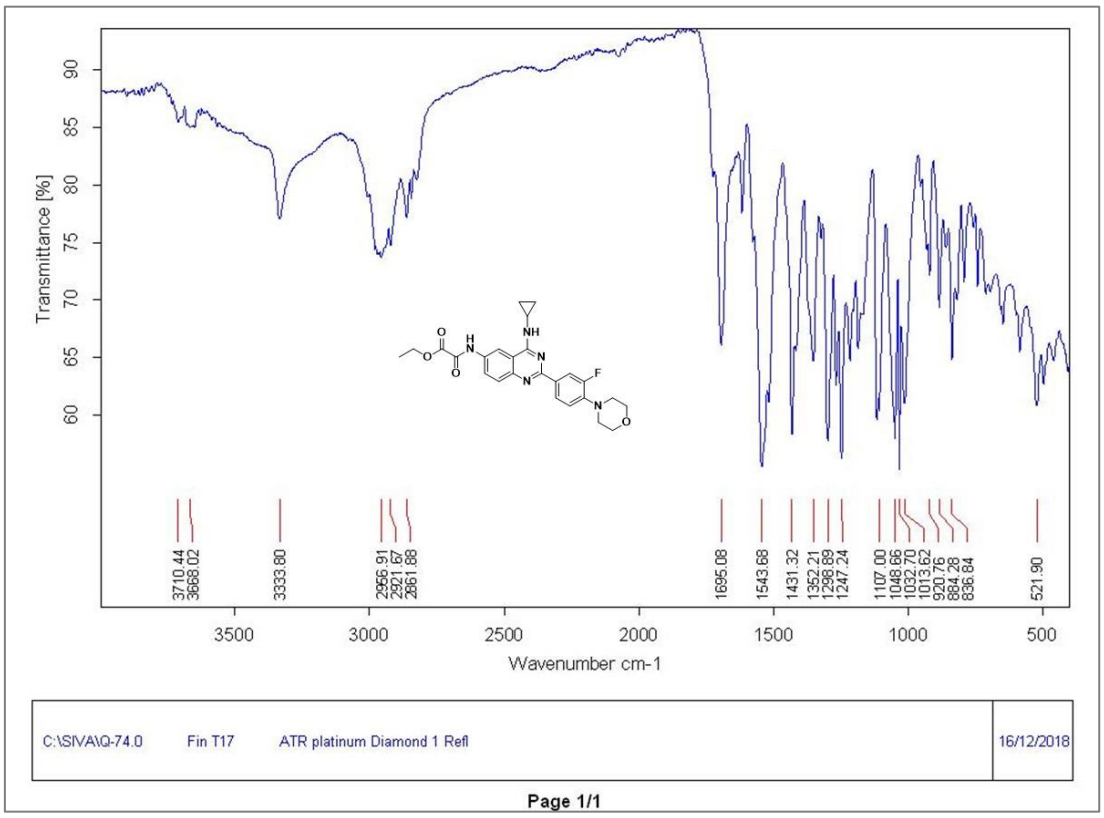
IR spectrum of compound 15 (Chapter 4)



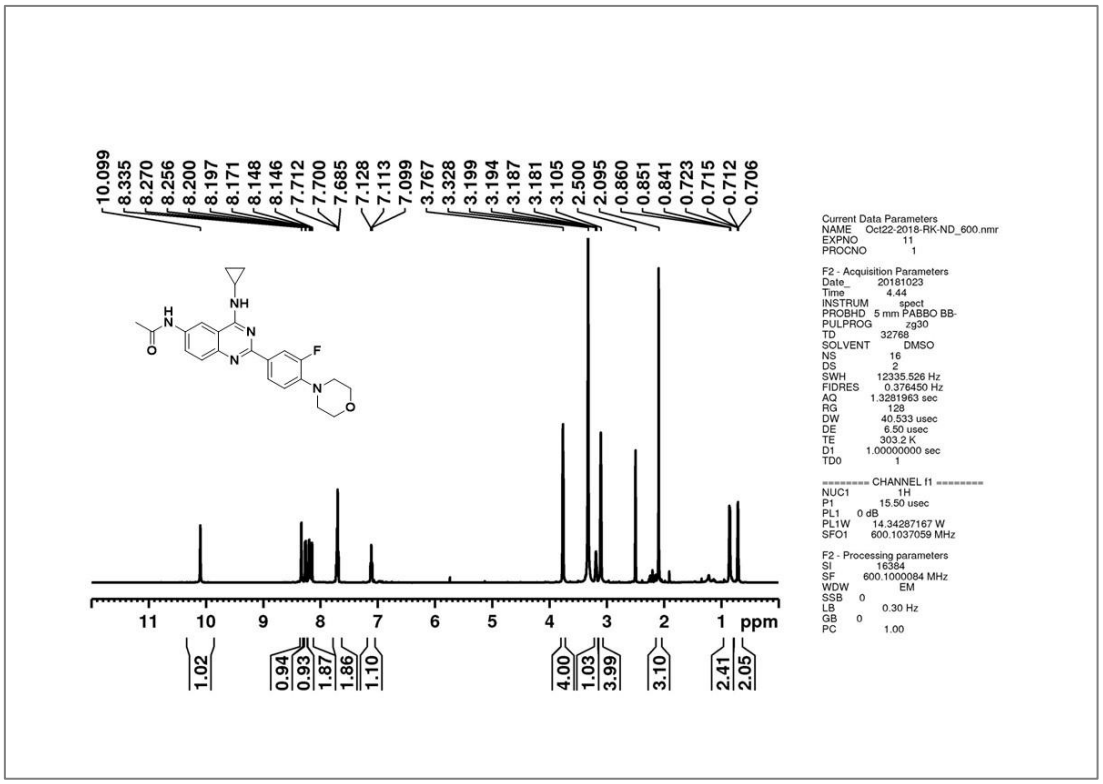
^{1}H NMR spectrum of compound 17a (Chapter 4)



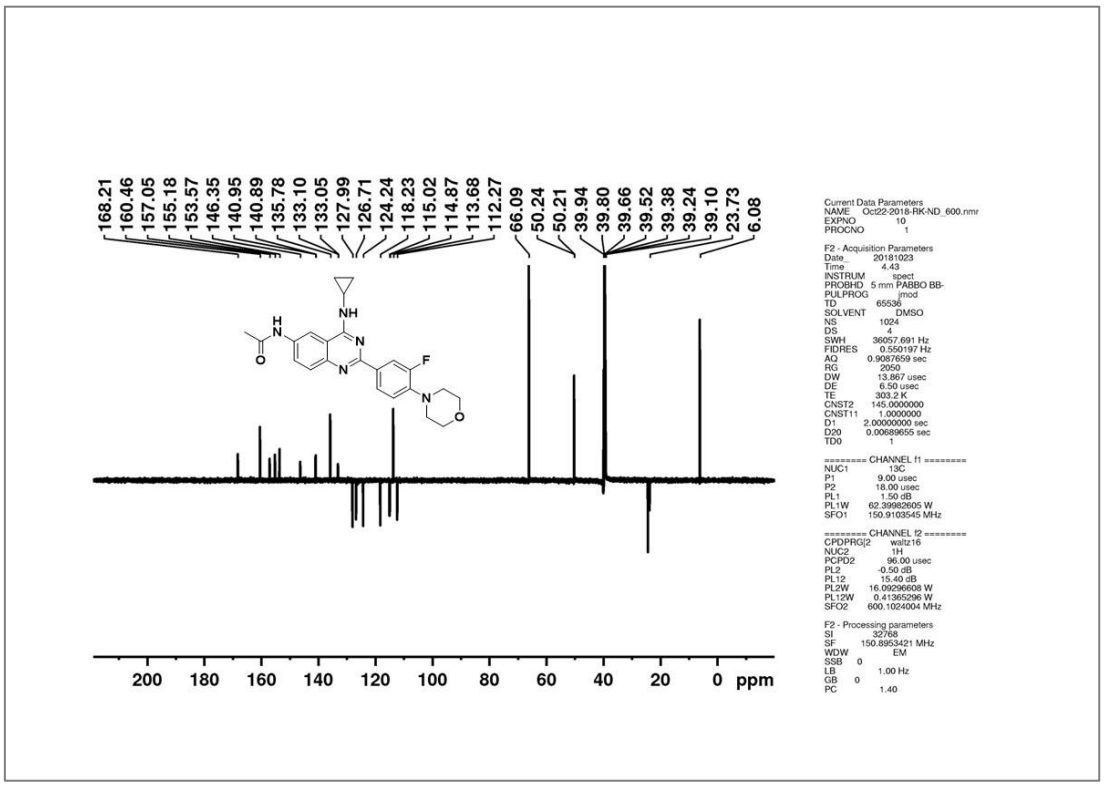
^{13}C NMR spectrum of compound 17a (Chapter 4)



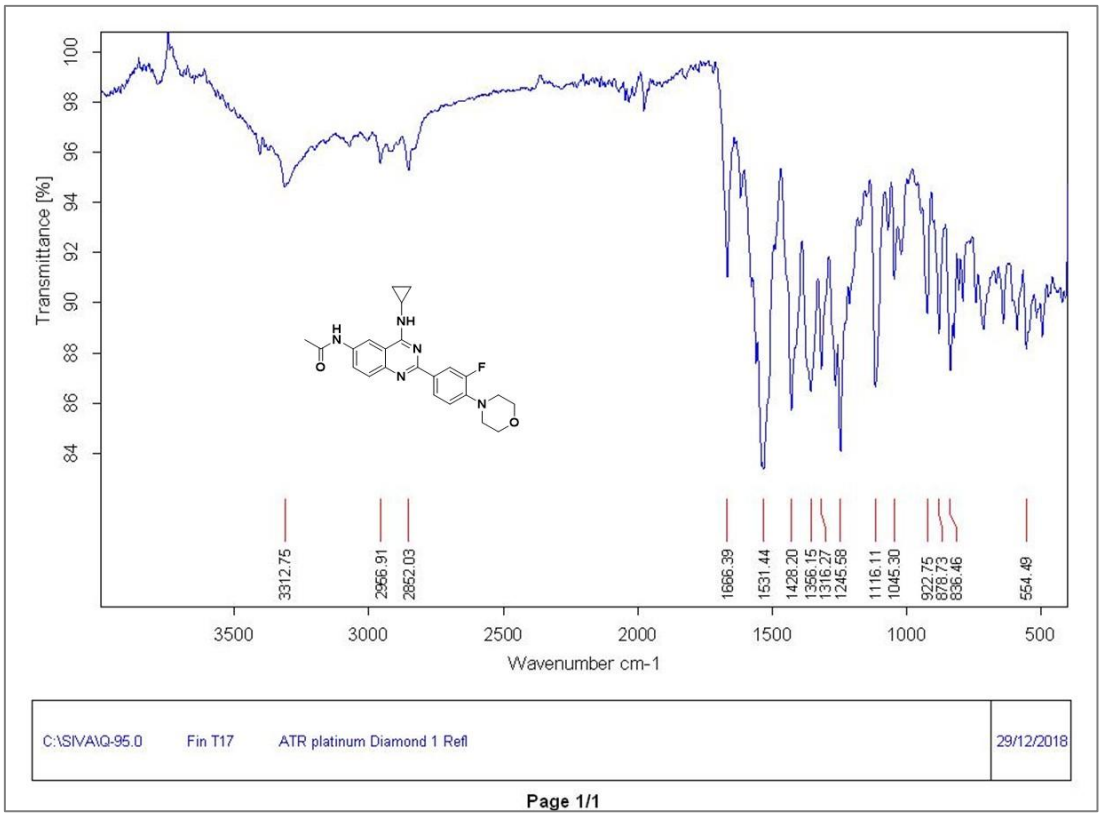
IR spectrum of compound 17a (Chapter 4)



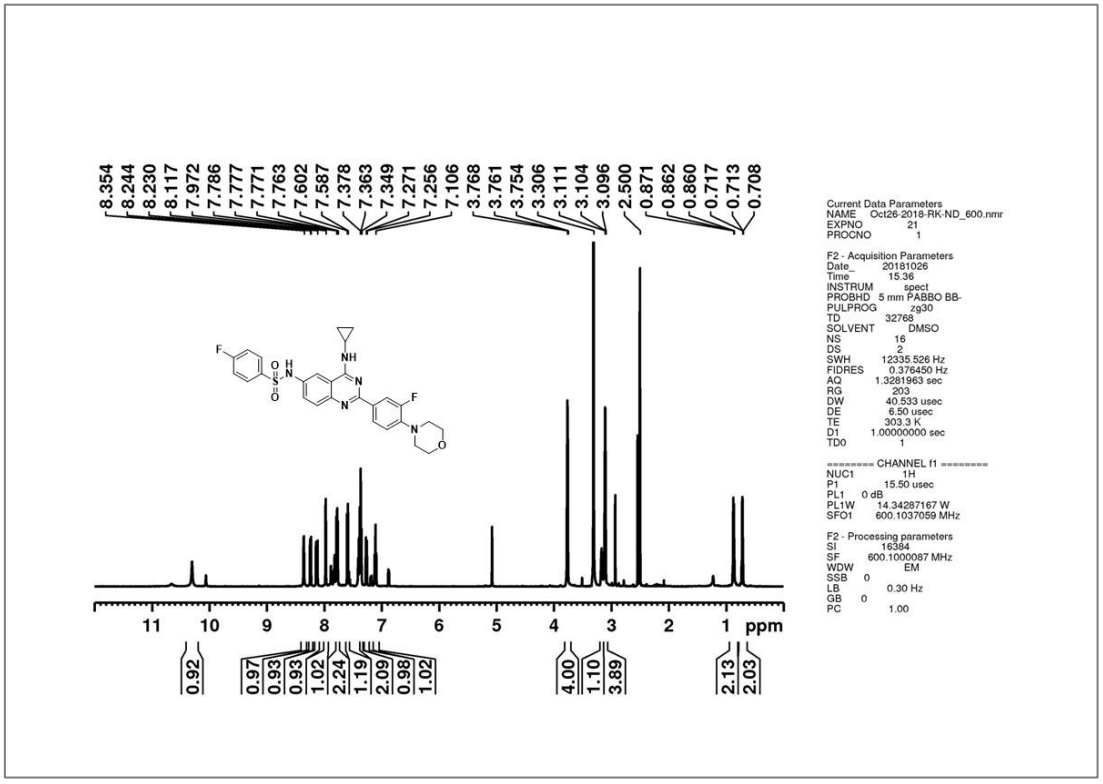
^{1}H NMR spectrum of compound 17b (Chapter 4)



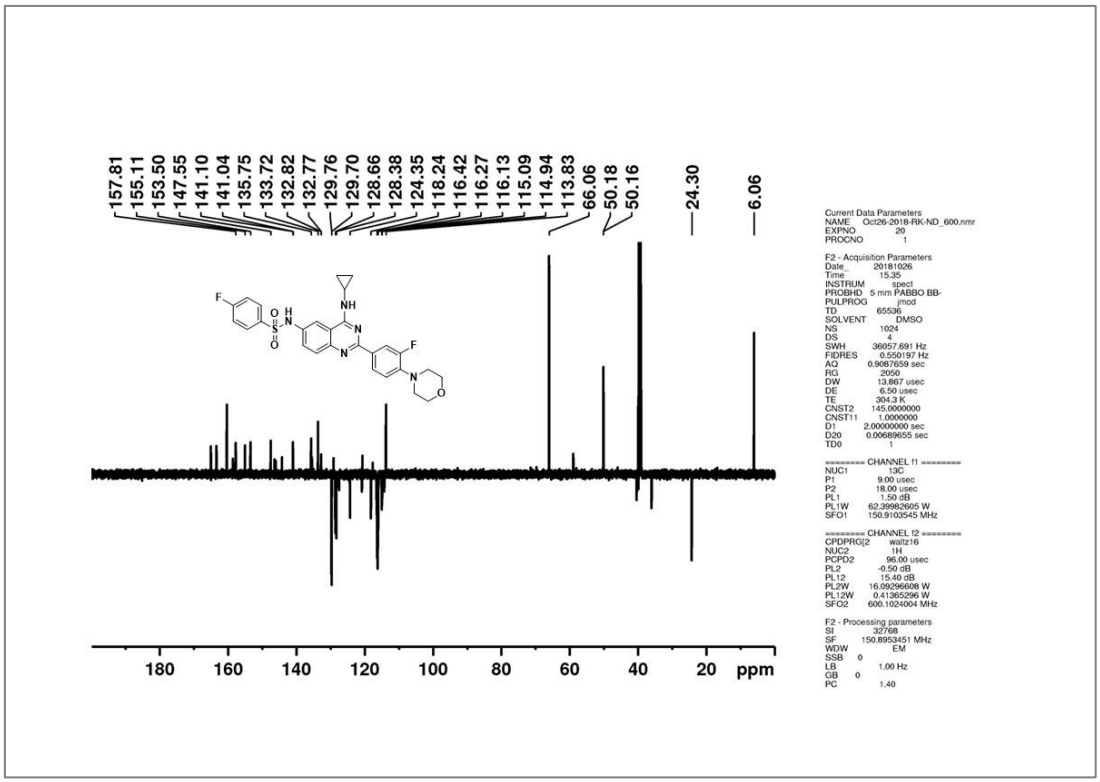
^{13}C NMR spectrum of compound 17b (Chapter 4)



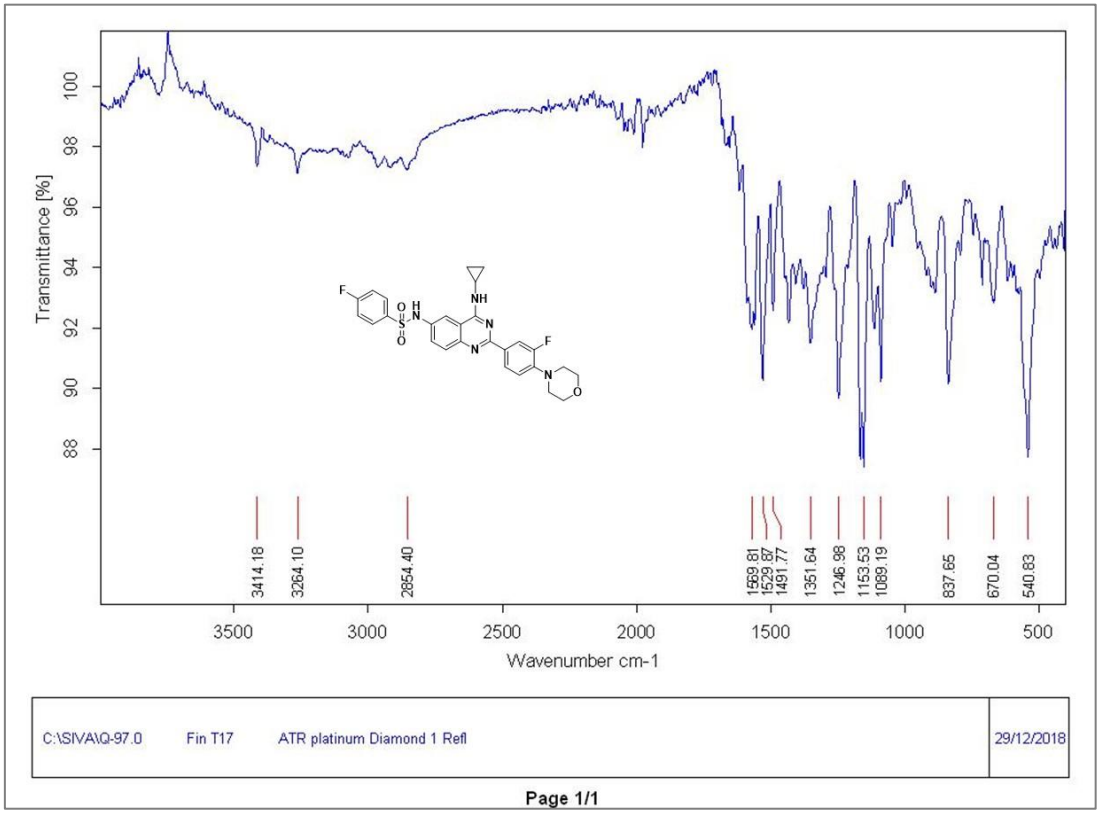
IR spectrum of compound 17b (Chapter 4)



^{1}H NMR spectrum of compound 17c (Chapter 4)



^{13}C NMR spectrum of compound 17c (Chapter 4)



IR spectrum of compound 17c (Chapter 4)

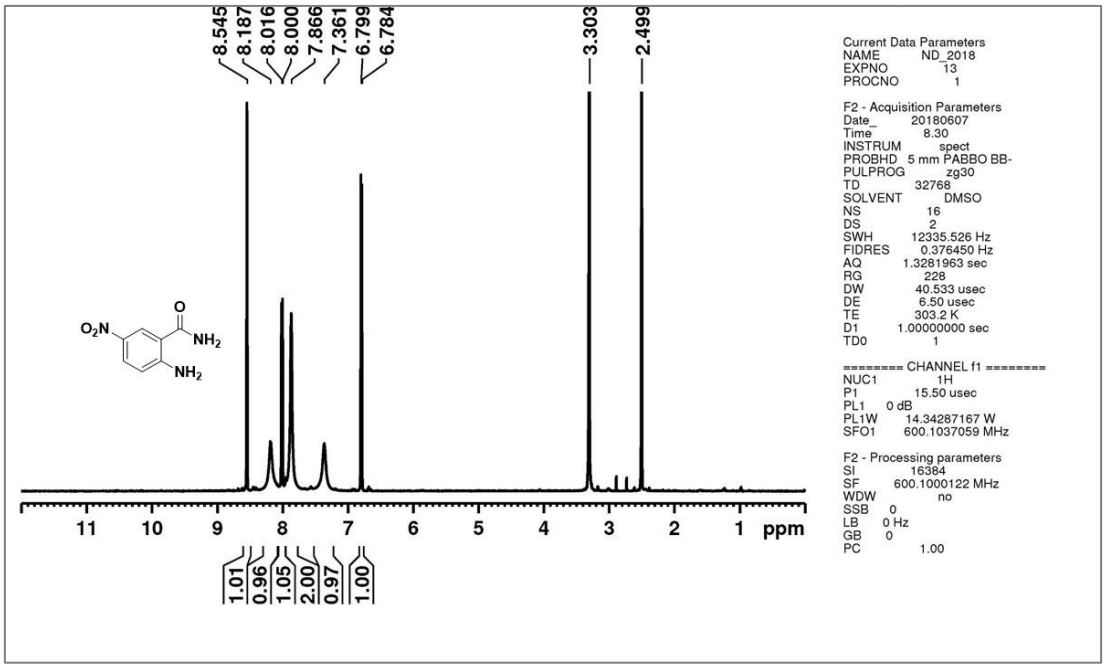
APPENDIX – IV

SUPPLEMENTARY INFORMATION

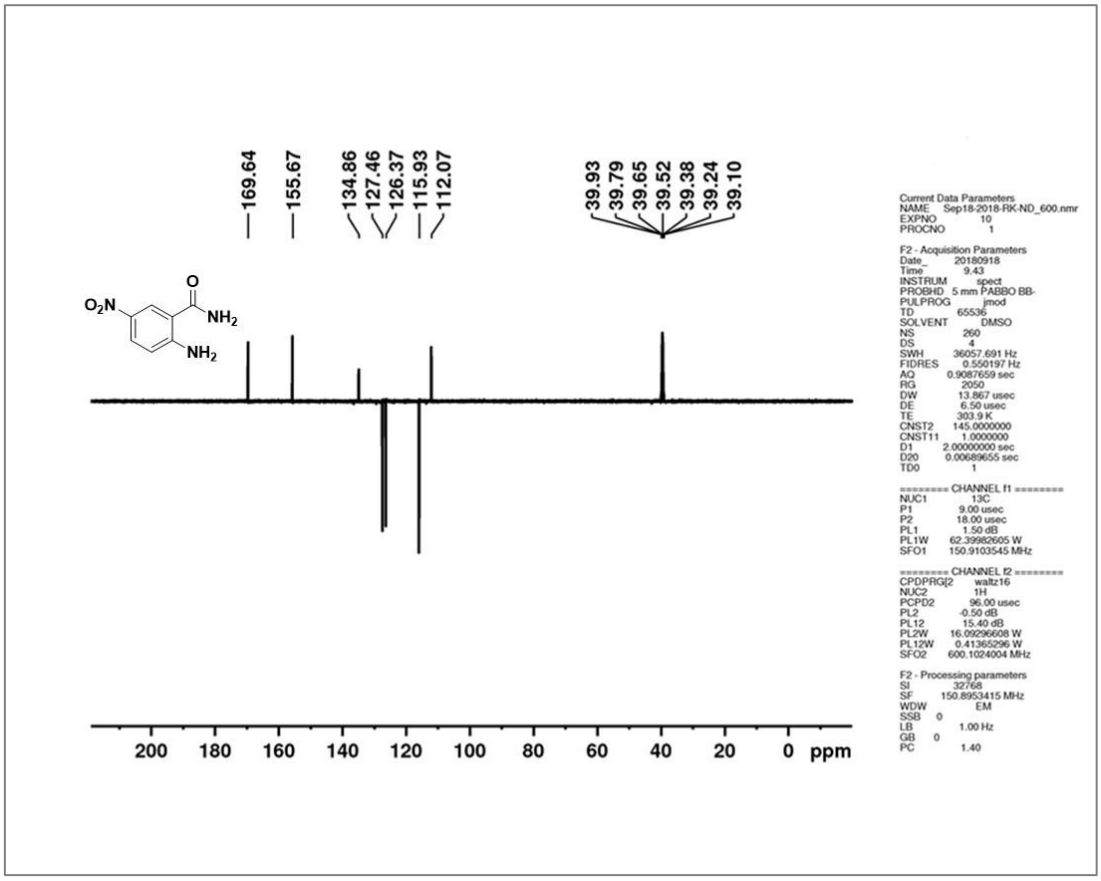
CHAPTER 5

Design, synthesis and spectral characterization of *N/O*-methylated quinazoline derivatives as an antitubercular agent

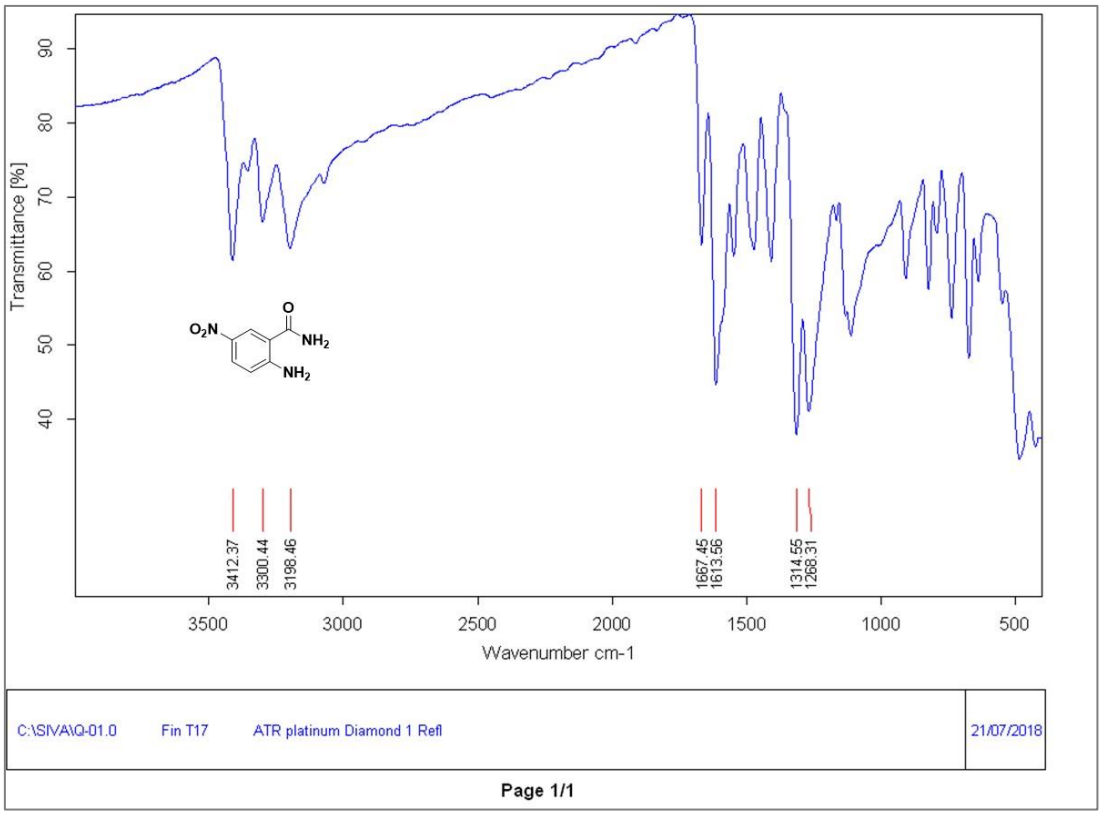
Department of Pharmaceutical Chemistry, Discipline of Pharmaceutical Sciences, College of Health Sciences, University of KwaZulu-Natal (Westville), Durban-4000, South Africa



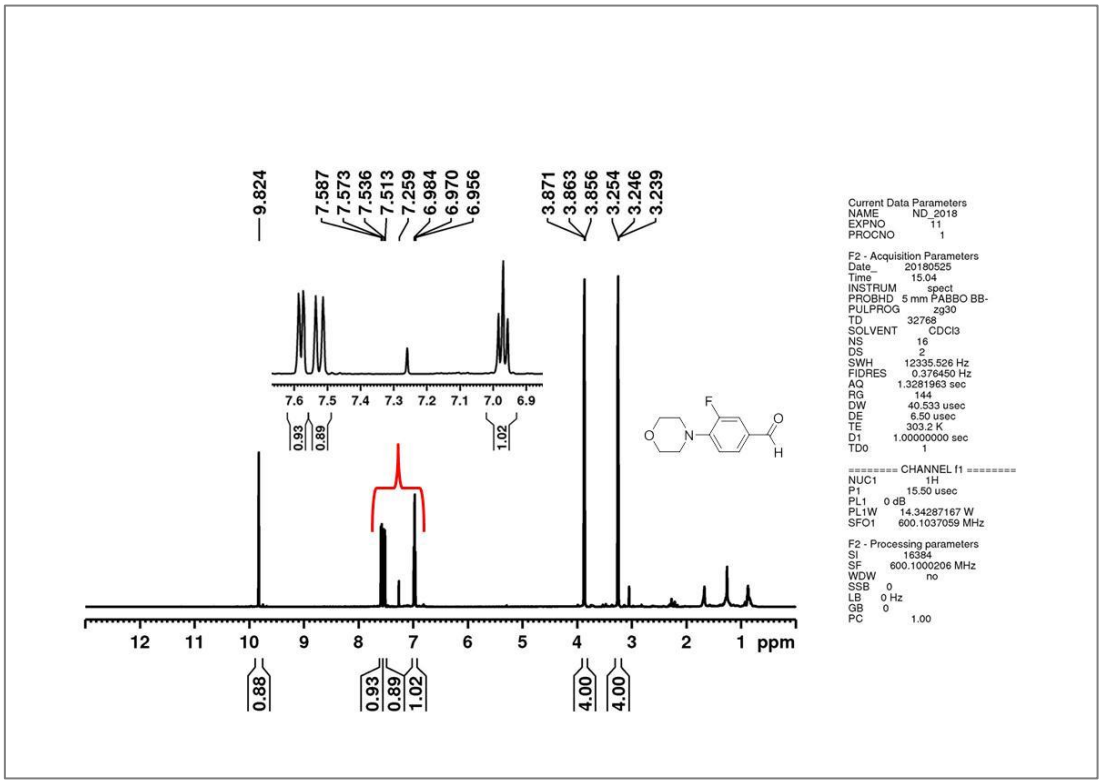
^{1}H NMR spectrum of compound 2 (Chapter 5)



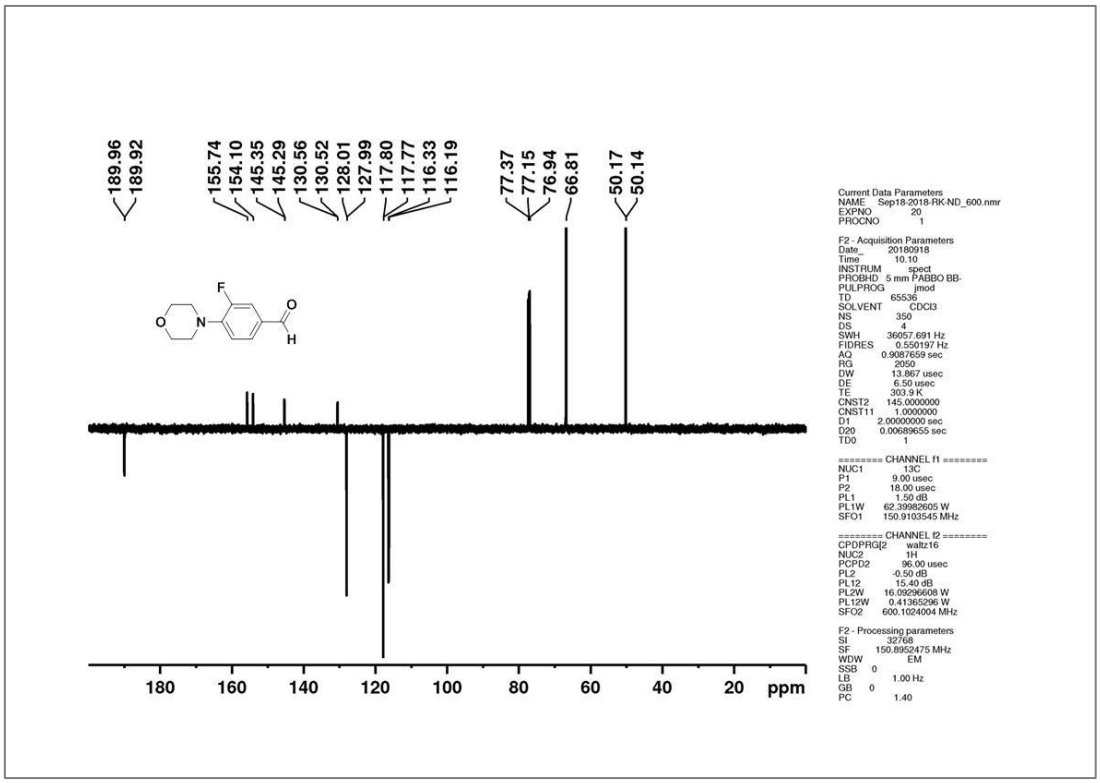
^{13}C NMR spectrum of compound 2 (Chapter 5)



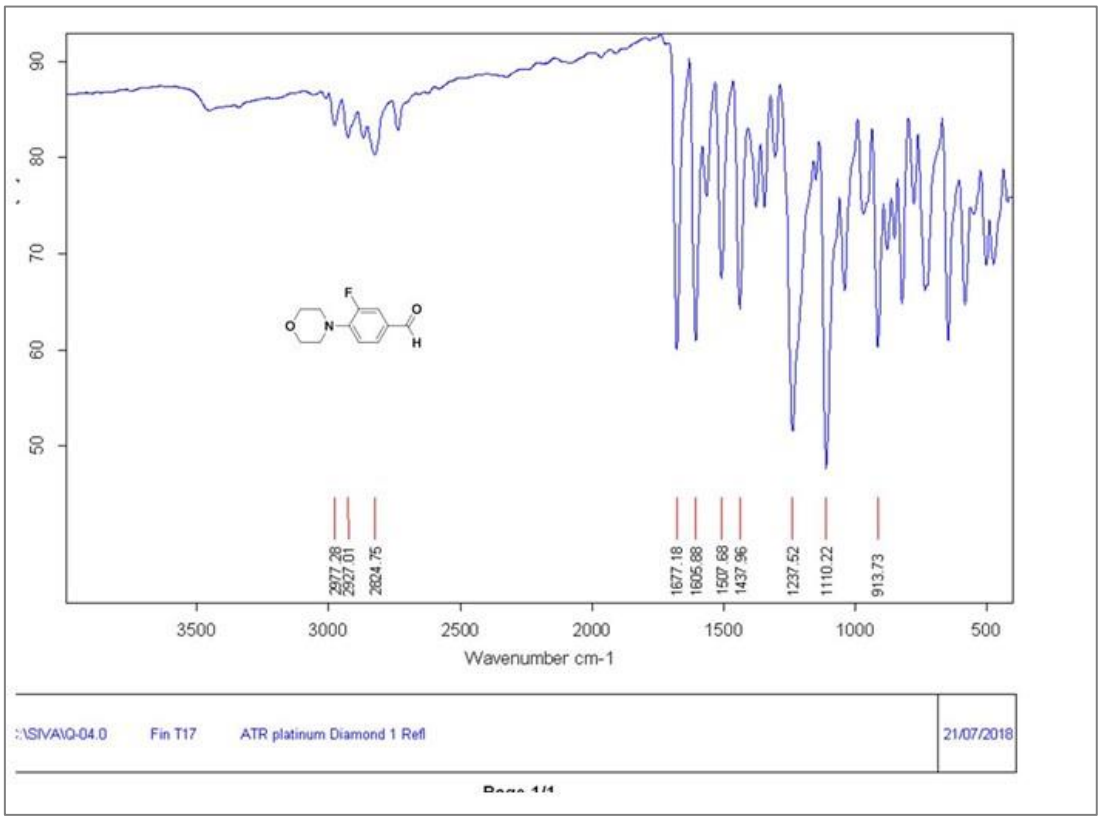
IR spectrum of compound 2 (Chapter 5)



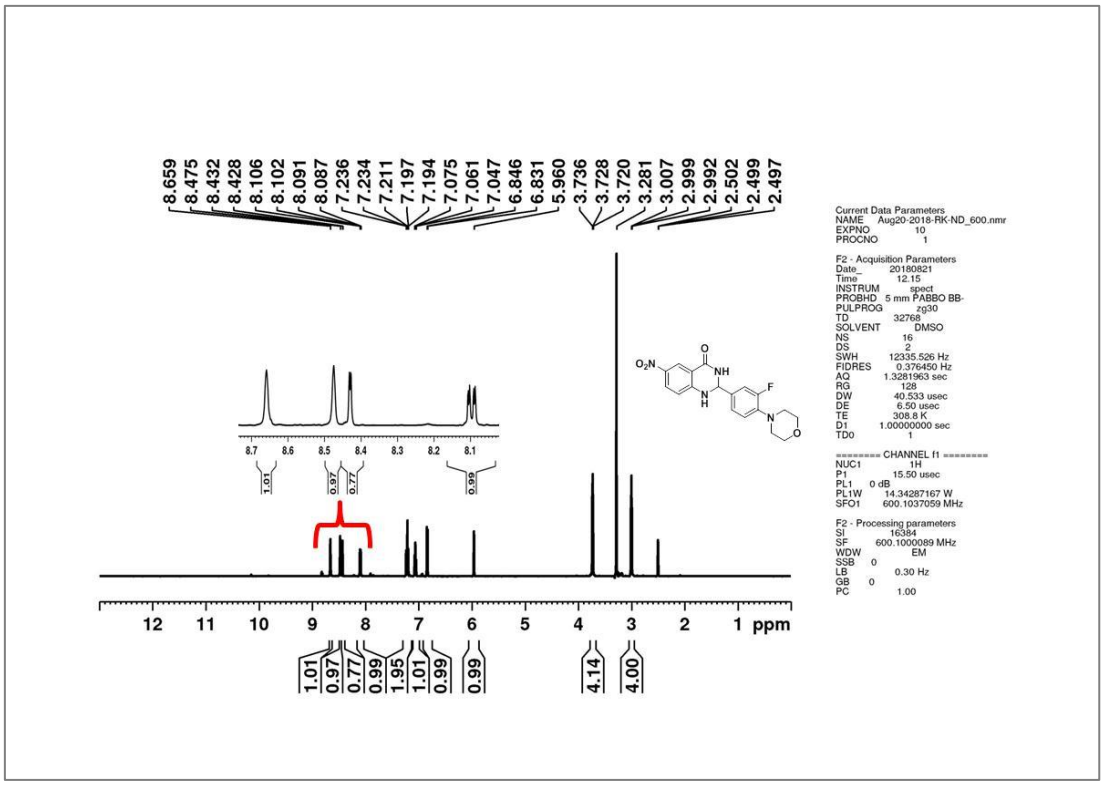
^{1}H NMR spectrum of compound 5 (Chapter 5)



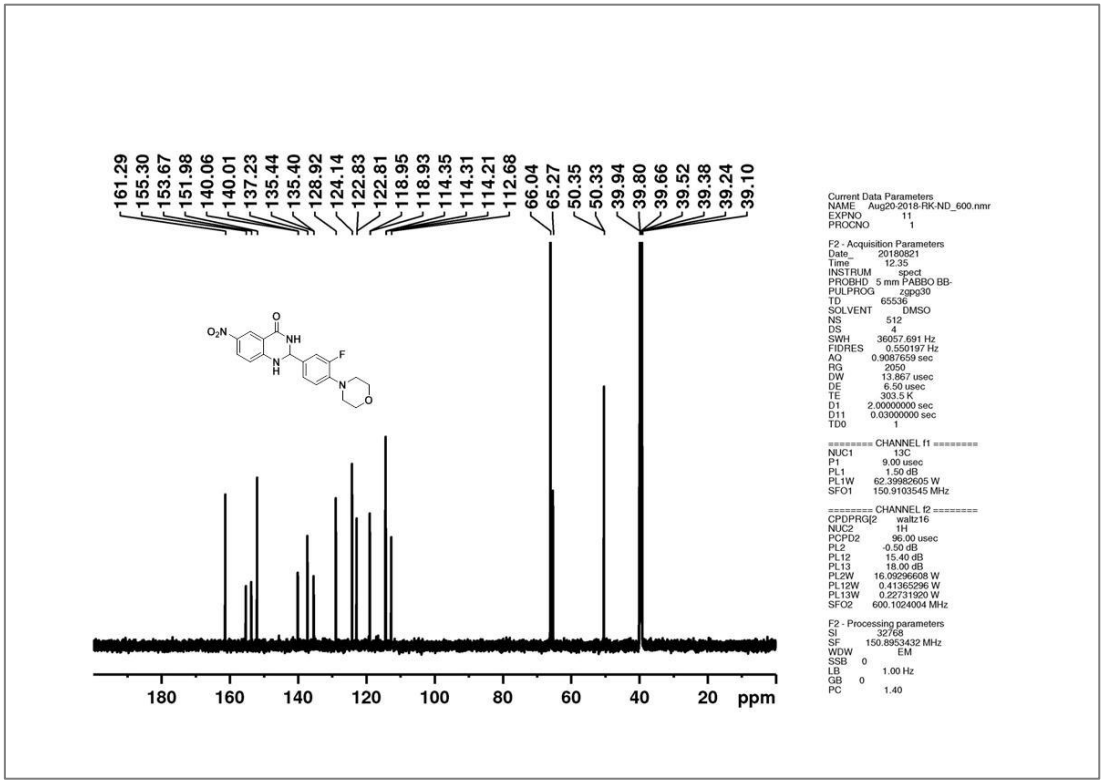
^{13}C NMR spectrum of compound 5 (Chapter 5)



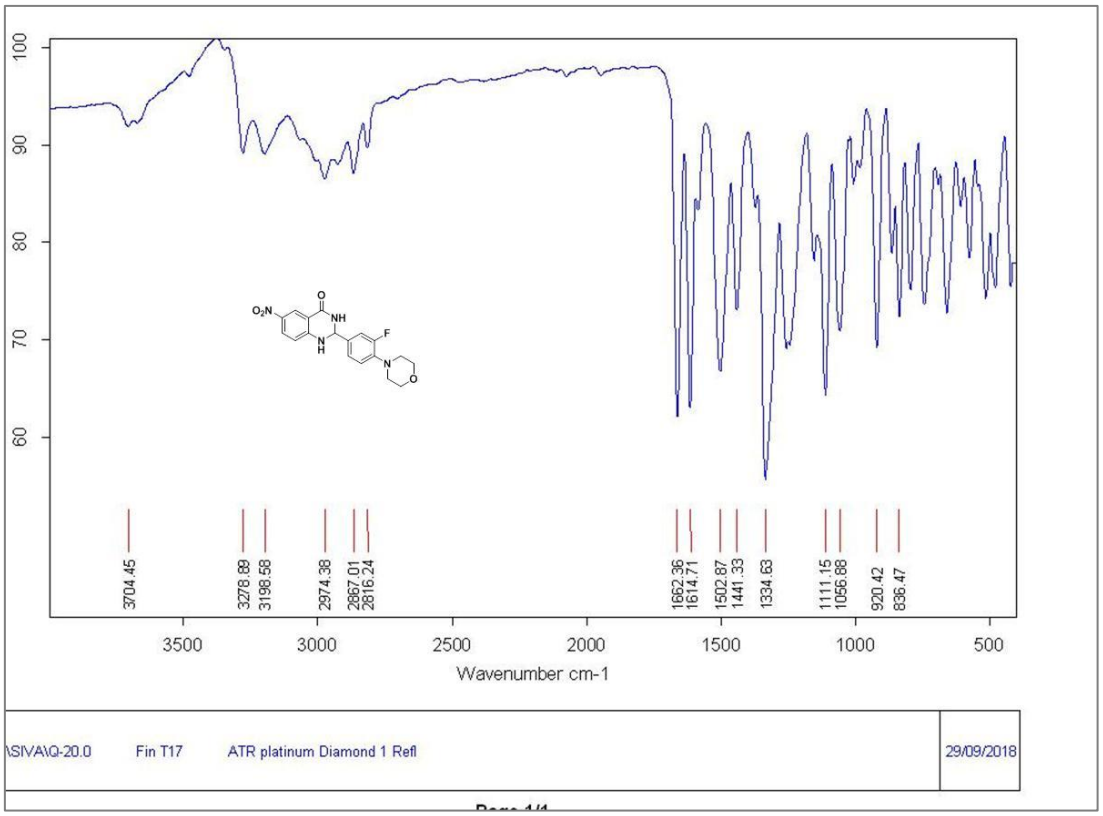
IR spectrum of compound 5 (Chapter 5)



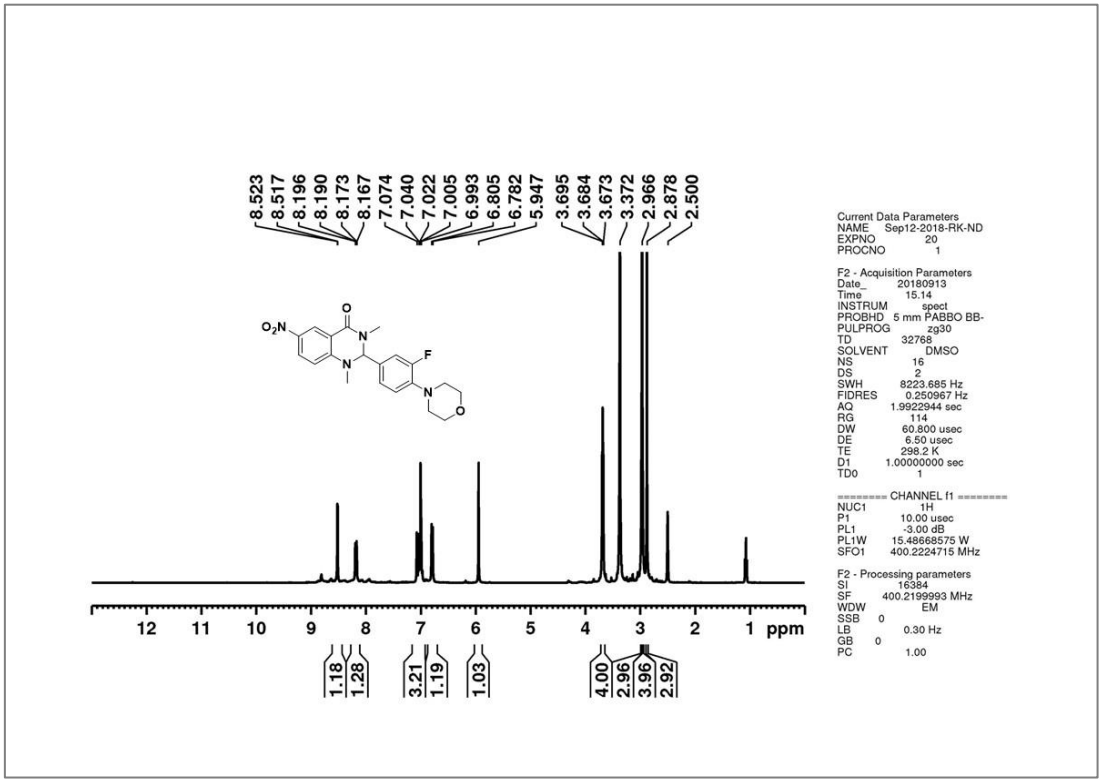
^{1}H NMR spectrum of compound 6 (Chapter 5)



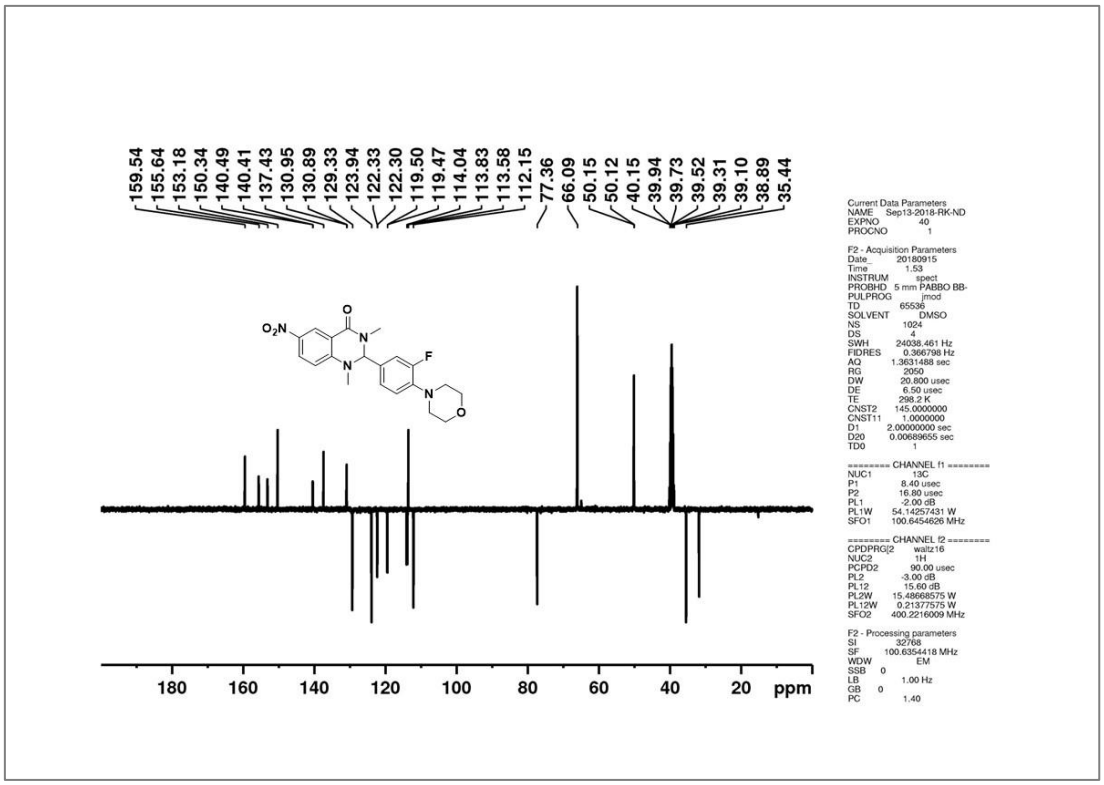
^{13}C NMR spectrum of compound 6 (Chapter 5)



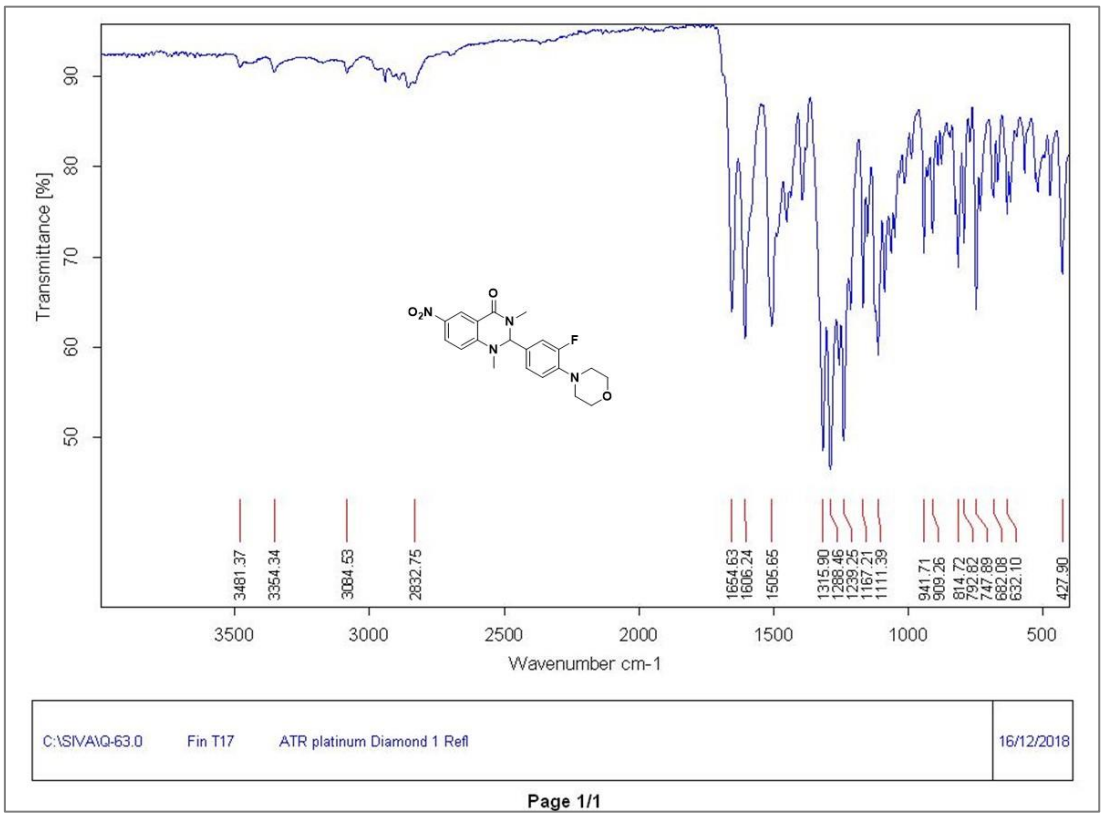
IR spectrum of compound 6 (Chapter 5)



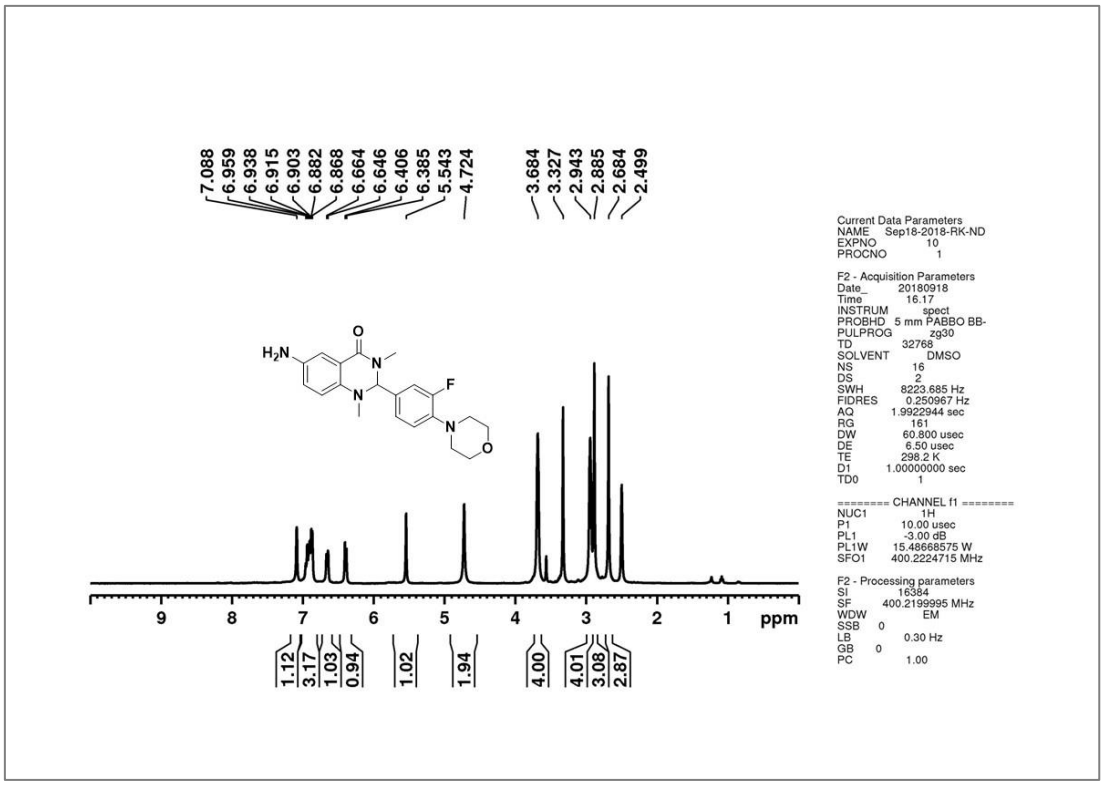
^{1}H NMR spectrum of 7 compound (Chapter 5)



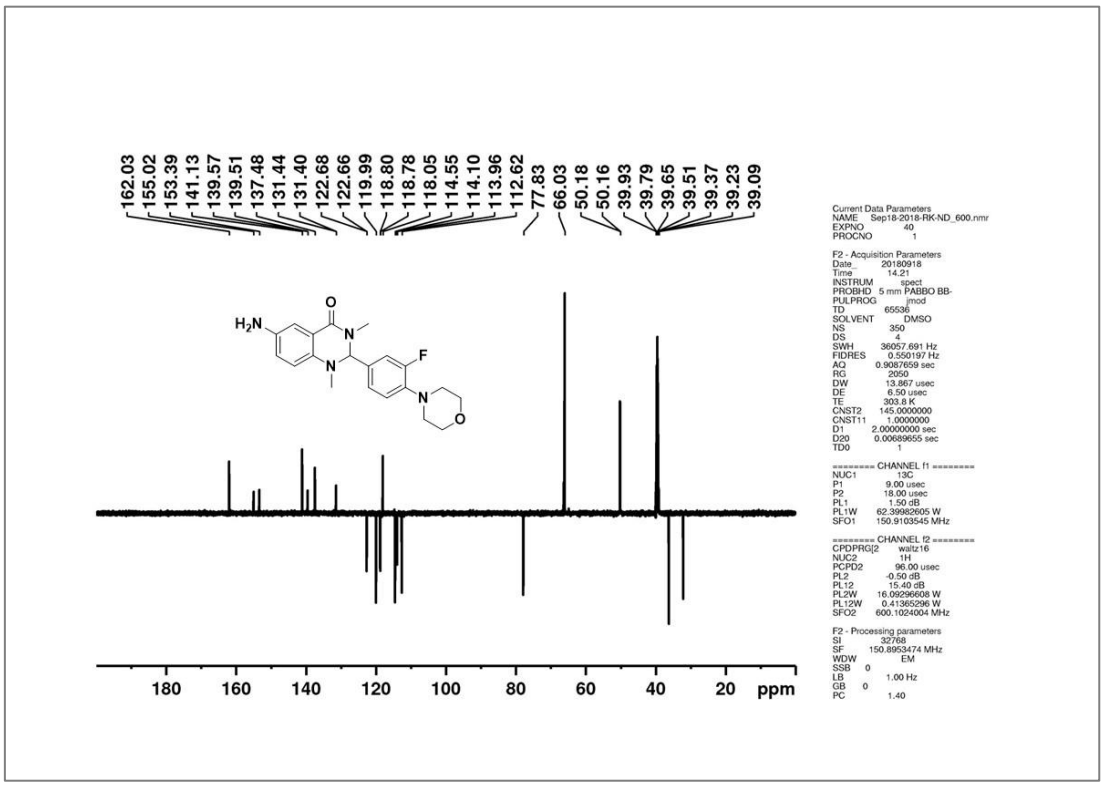
^{13}C NMR spectrum of compound 7 (Chapter 5)



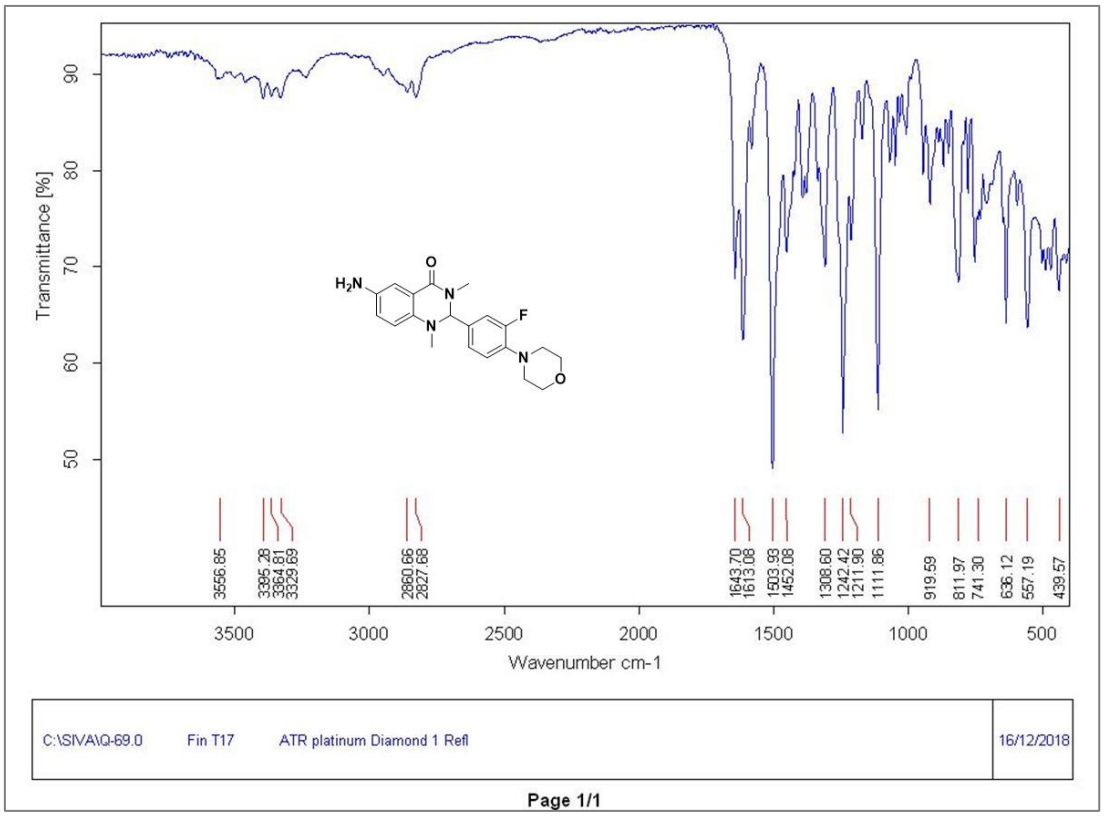
IR spectrum of compound 7 (Chapter 5)



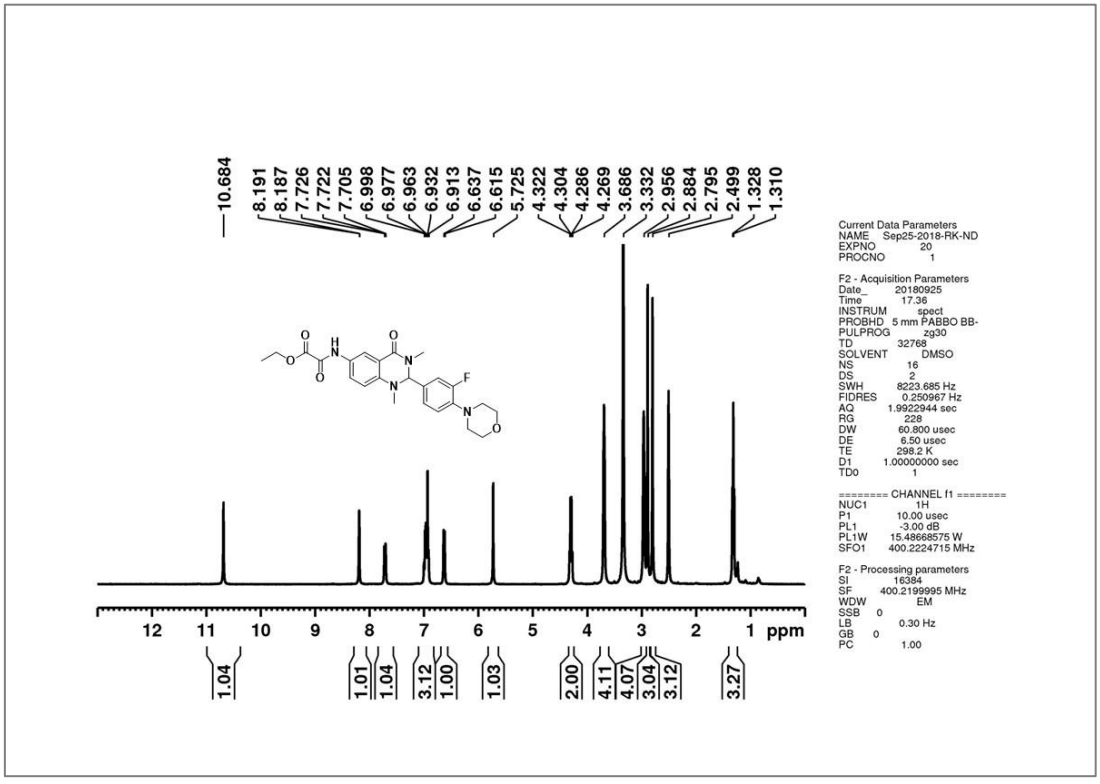
[1]H NMR spectrum of compound 8 (Chapter 5)



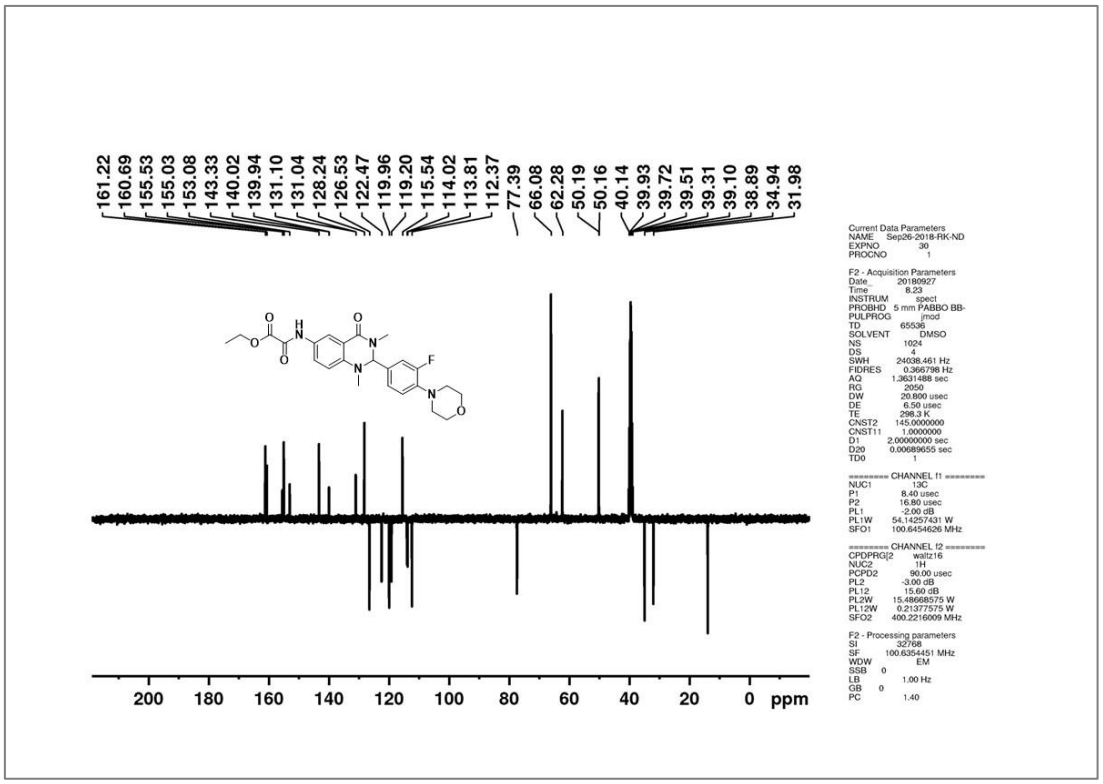
[13]C NMR spectrum of compound 8 (Chapter 5)



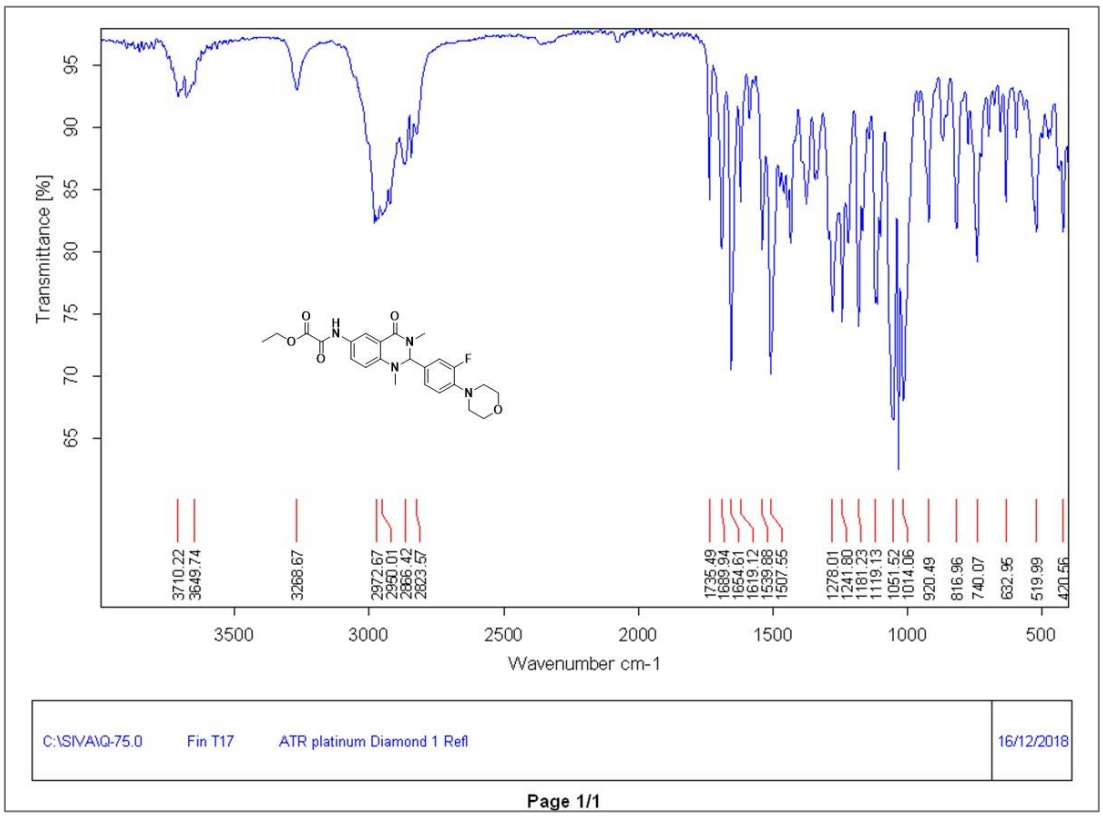
IR spectrum of compound 8 (Chapter 5)



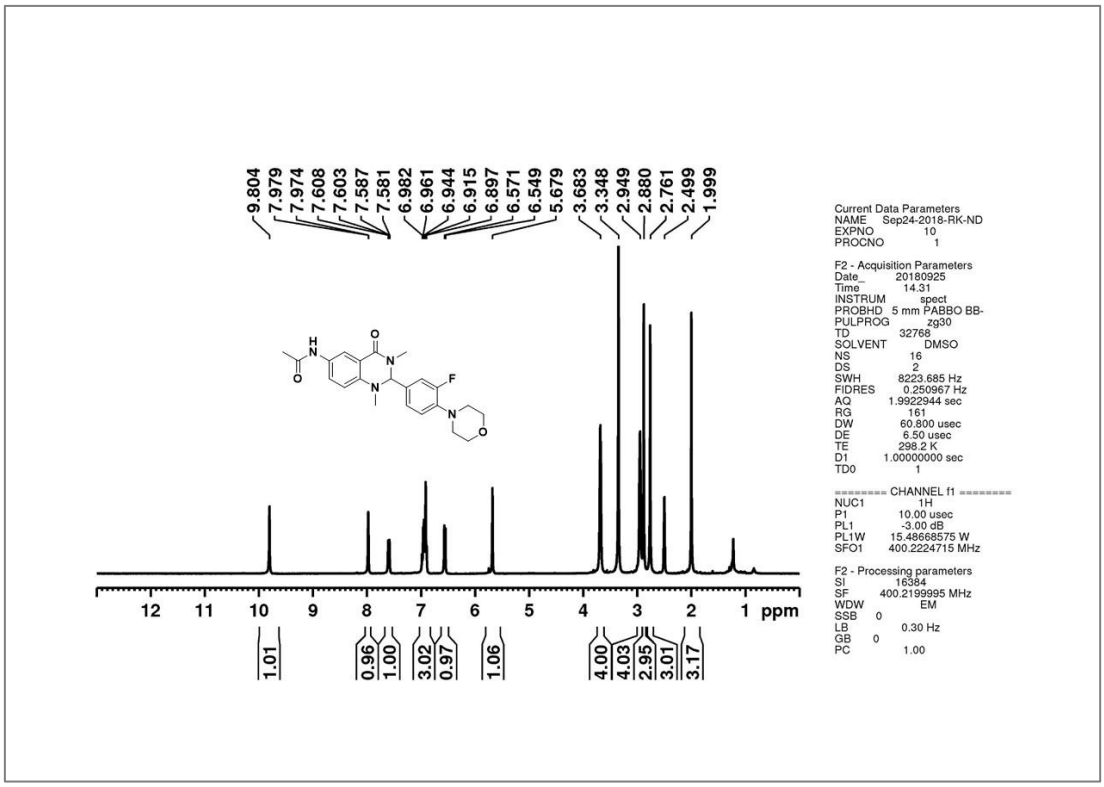
^{1}H NMR spectrum of compound 10a (Chapter 5)



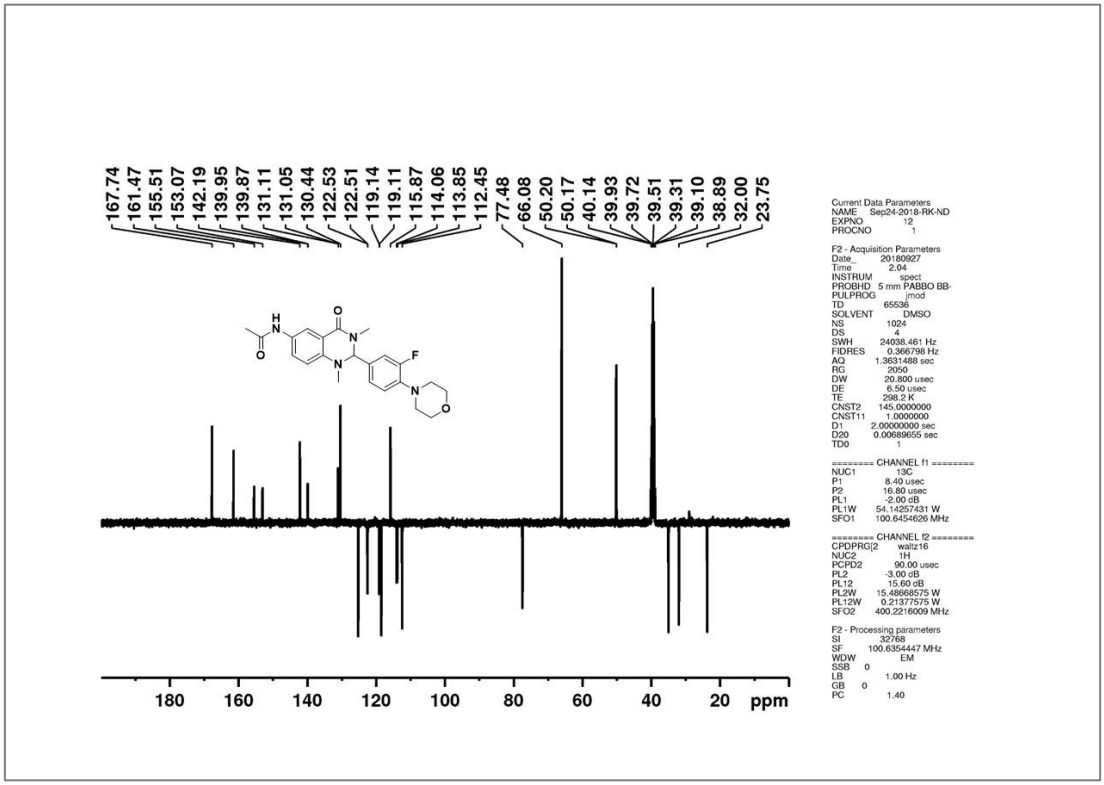
^{13}C NMR spectrum of compound 10a (Chapter 5)



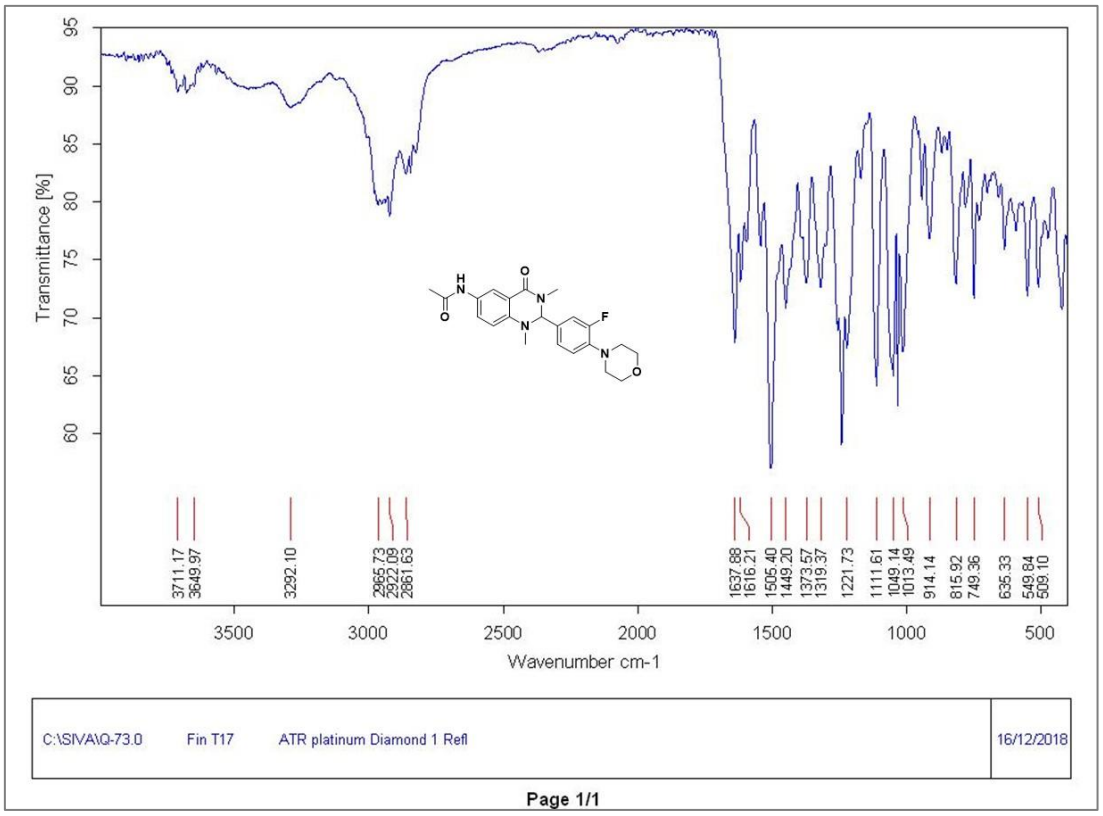
IR spectrum of compound 10a (Chapter 5)



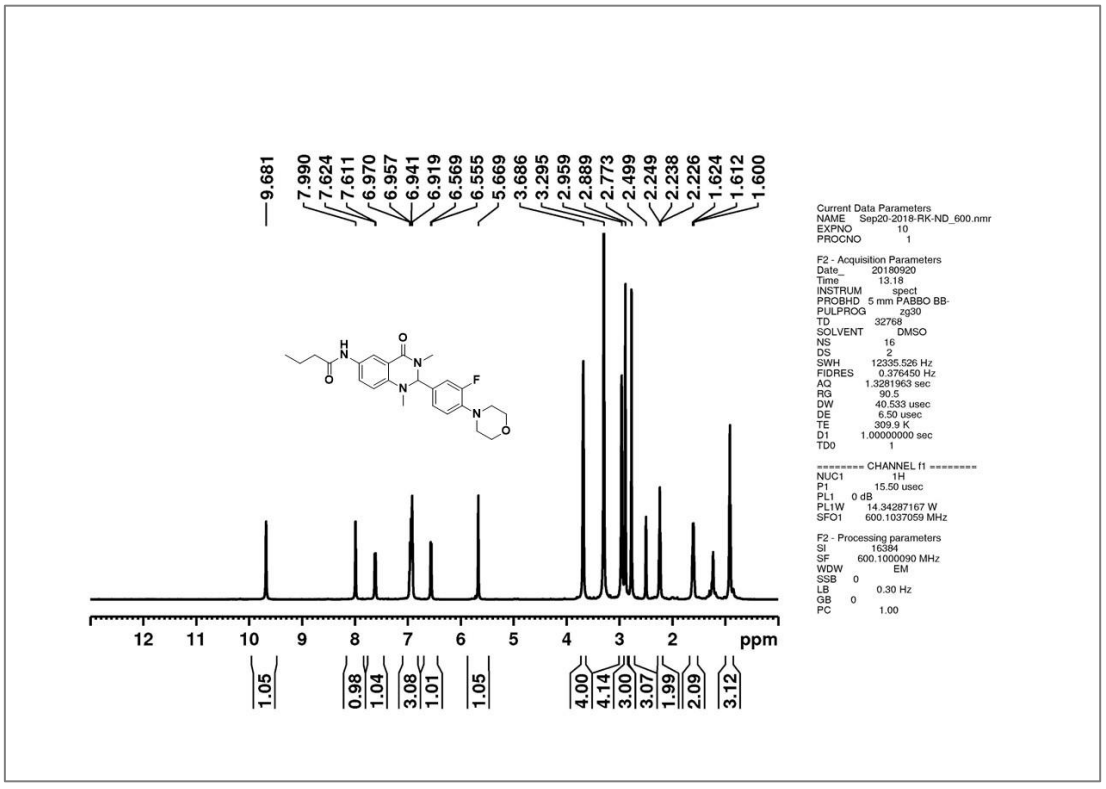
[1]H NMR spectrum of compound 10b (Chapter 5)



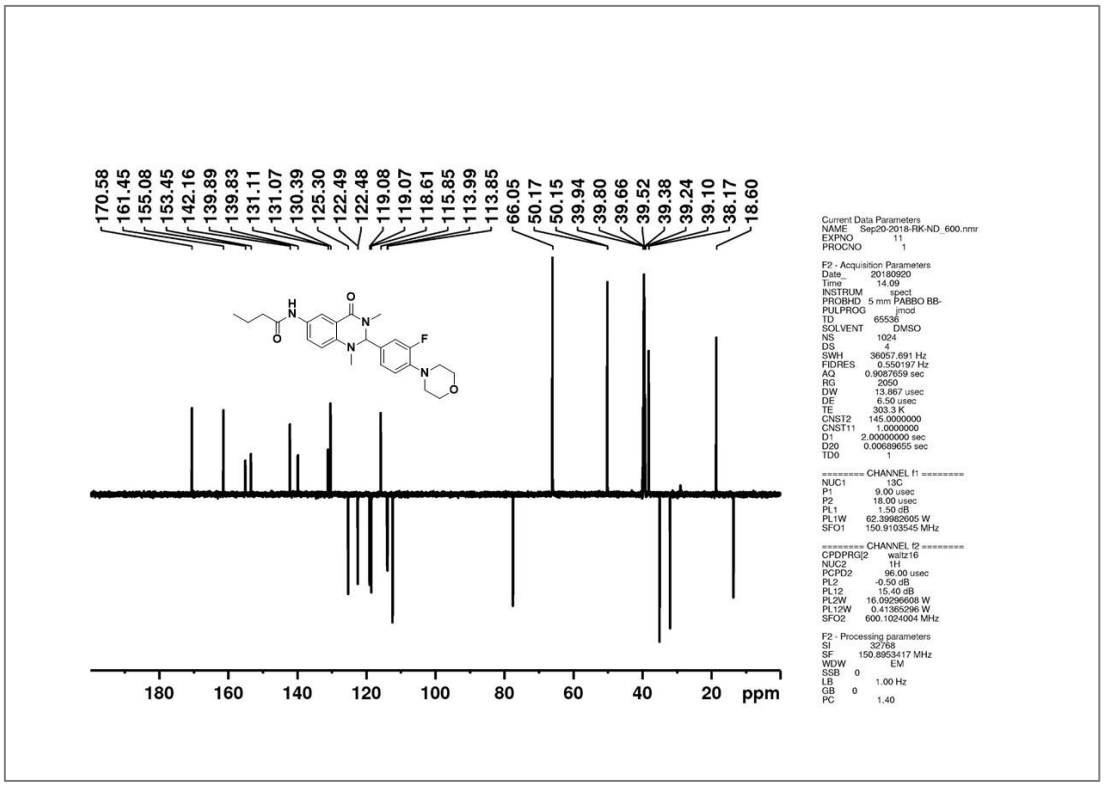
[13]C NMR spectrum of compound 10b (Chapter 5)



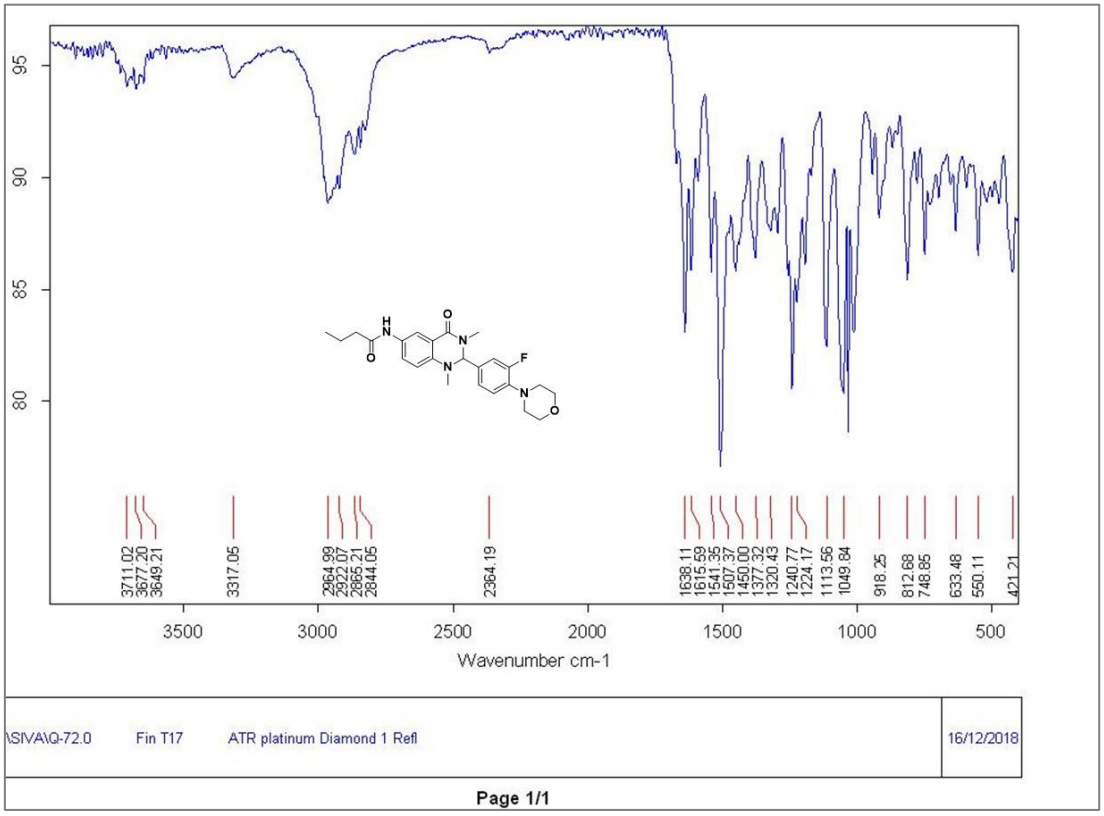
IR spectrum of compound 10b (Chapter 5)



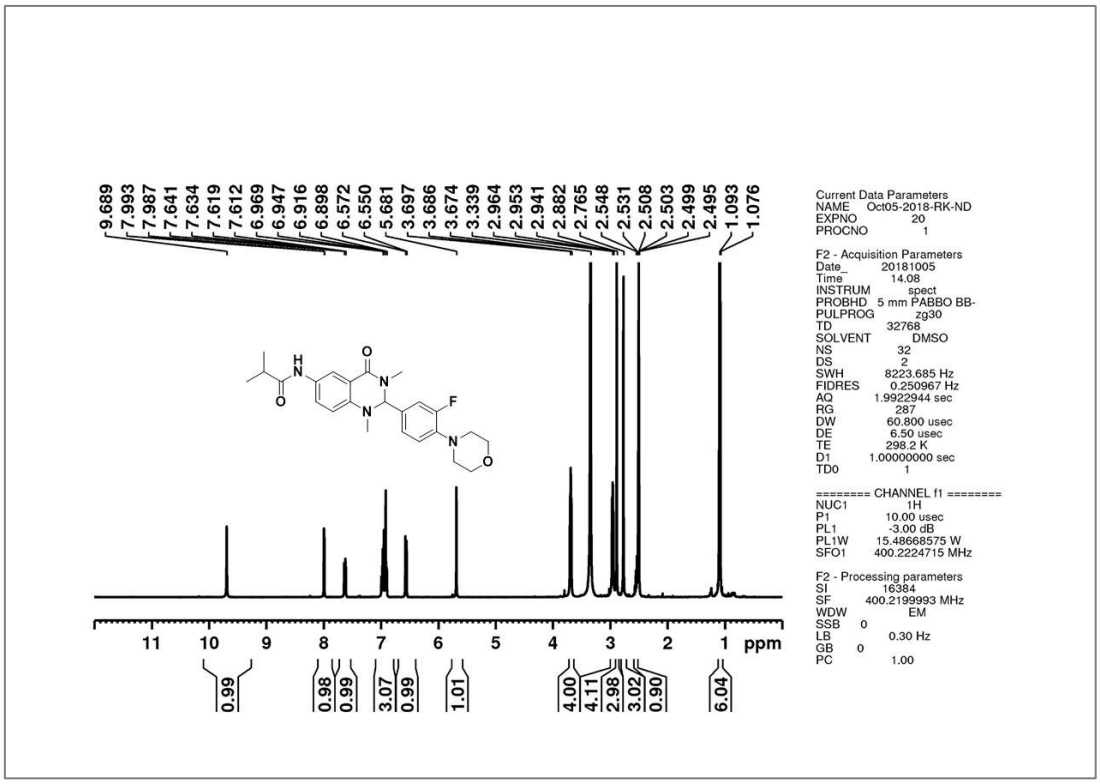
^{1}H NMR spectrum of compound 10c (Chapter 5)



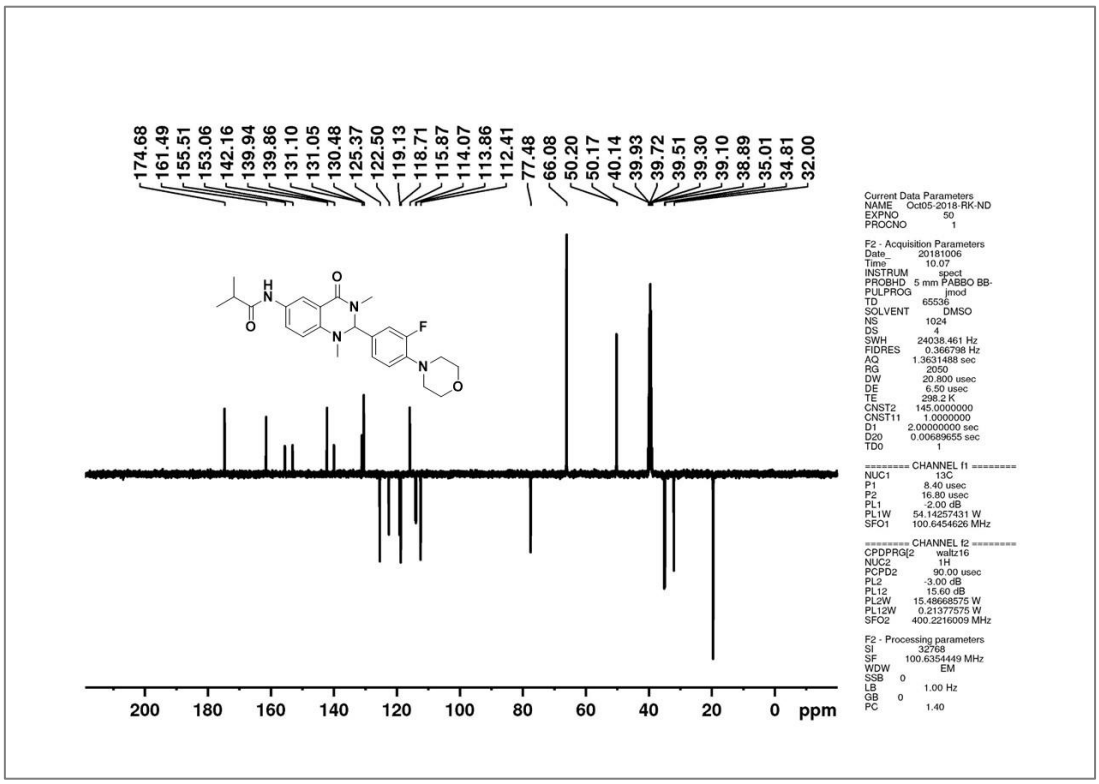
^{13}C NMR spectrum of compound 10c (Chapter 5)



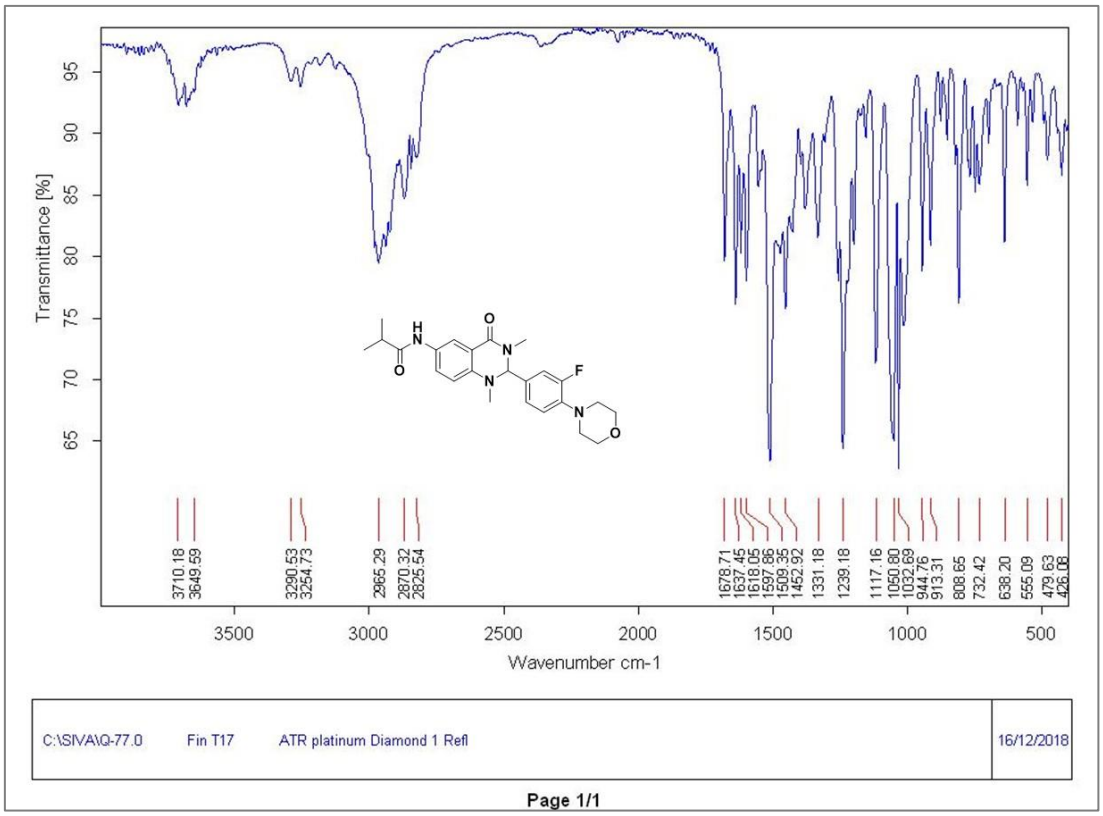
IR spectrum of compound 10c (Chapter 5)



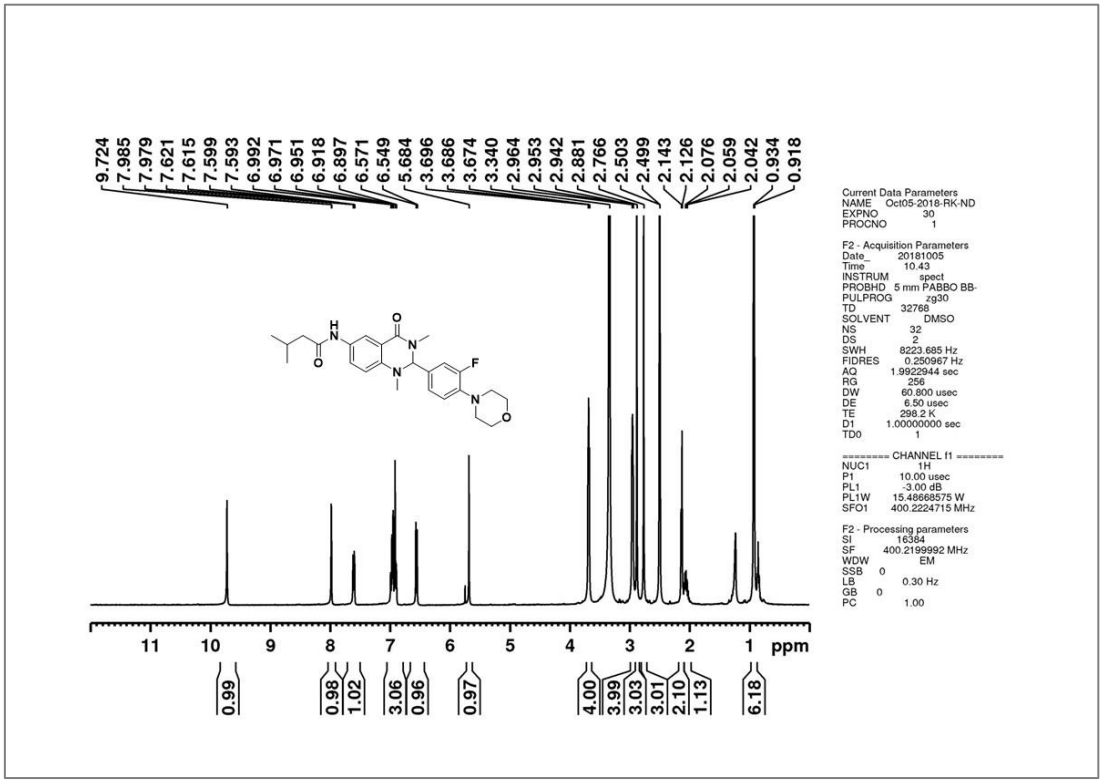
[1]H NMR spectrum of compound 10d (Chapter 5)



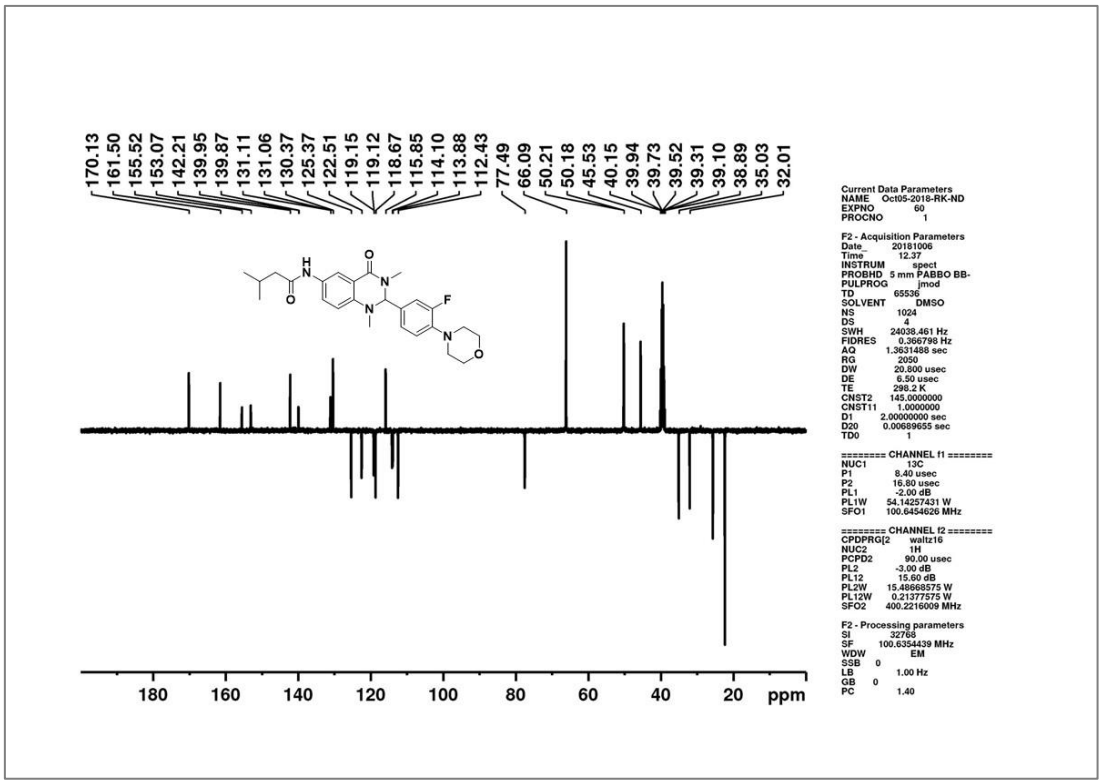
[13]C NMR spectrum of compound 10d (Chapter 5)



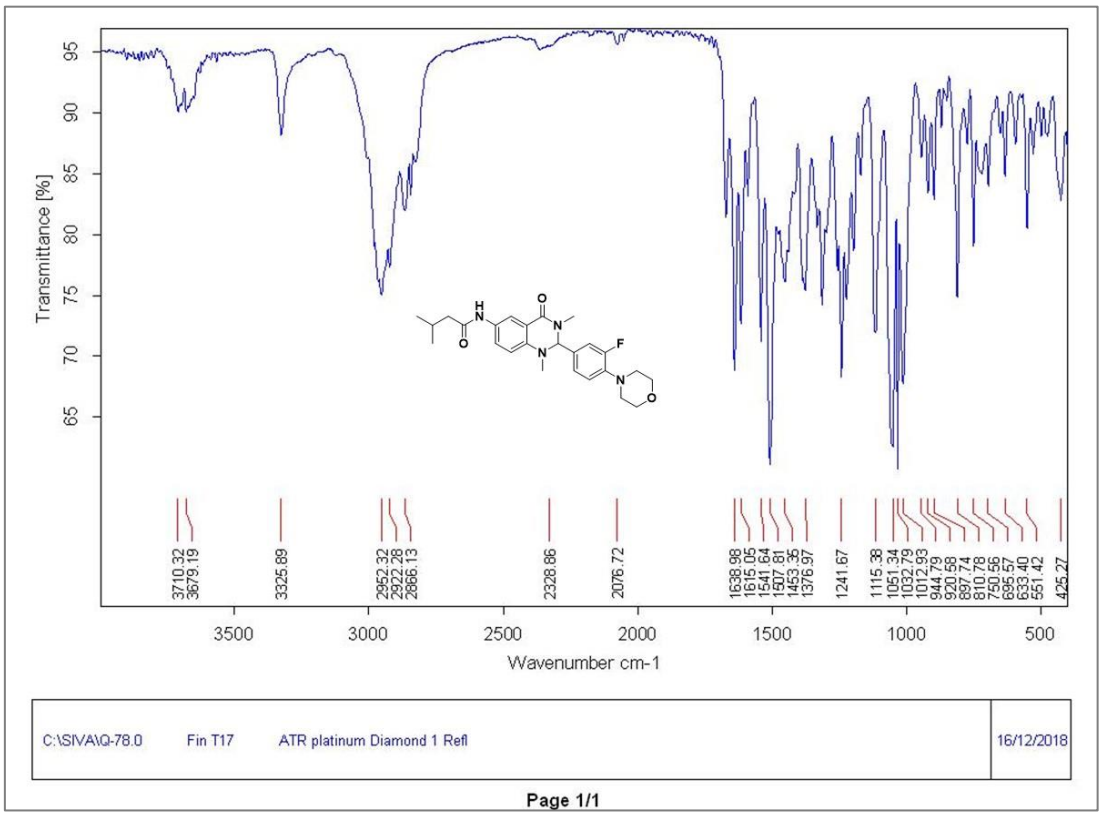
IR spectrum of compound 10d (Chapter 5)



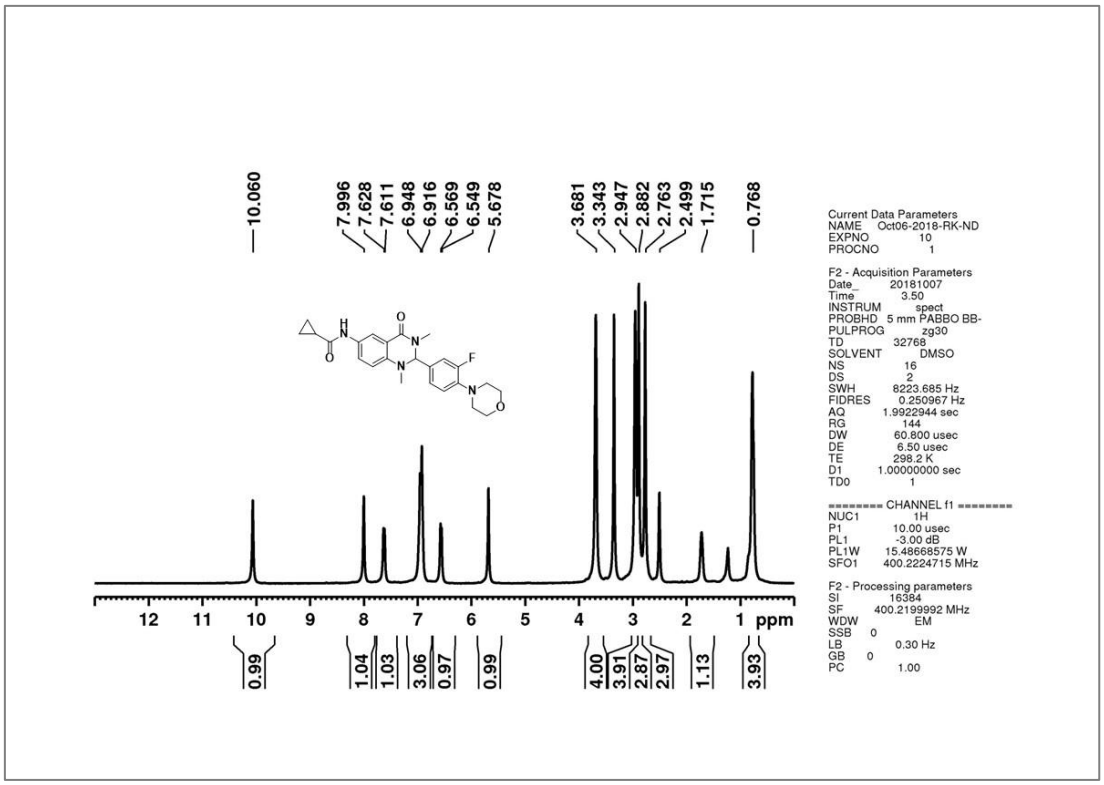
^{1}H NMR spectrum of compound 10e (Chapter 5)



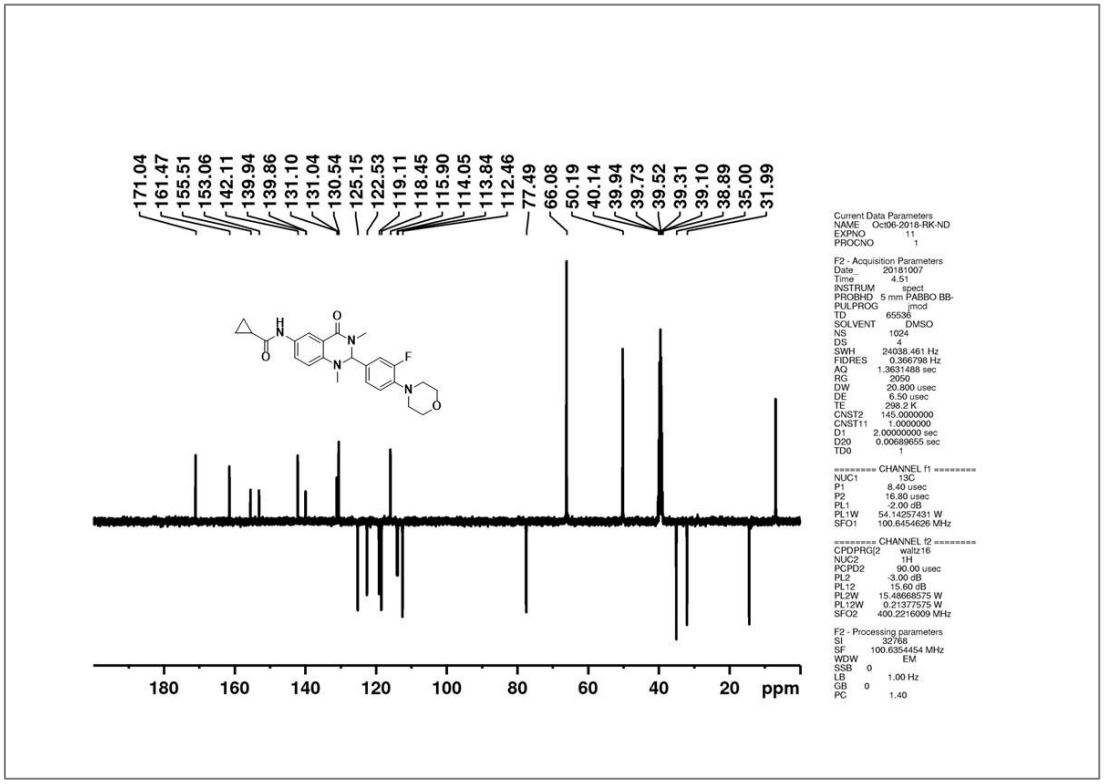
^{13}C NMR spectrum of compound 10e (Chapter 5)



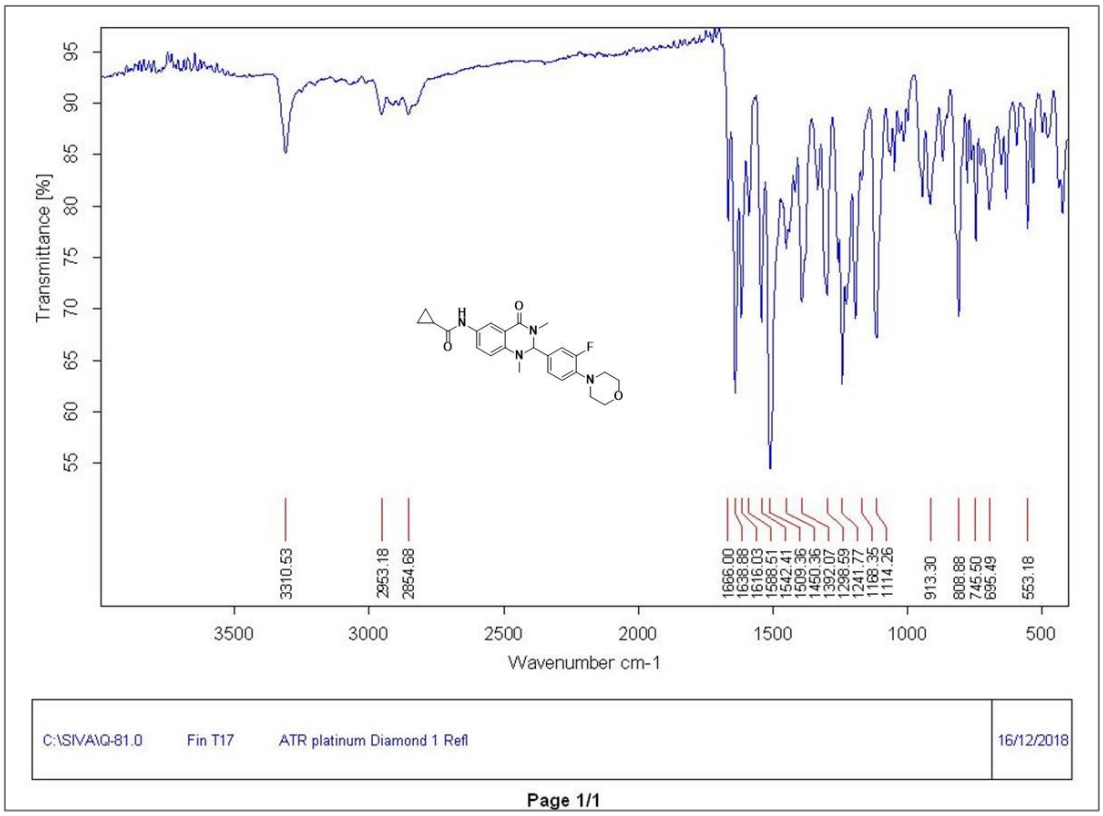
IR spectrum of compound 10e (Chapter 5)



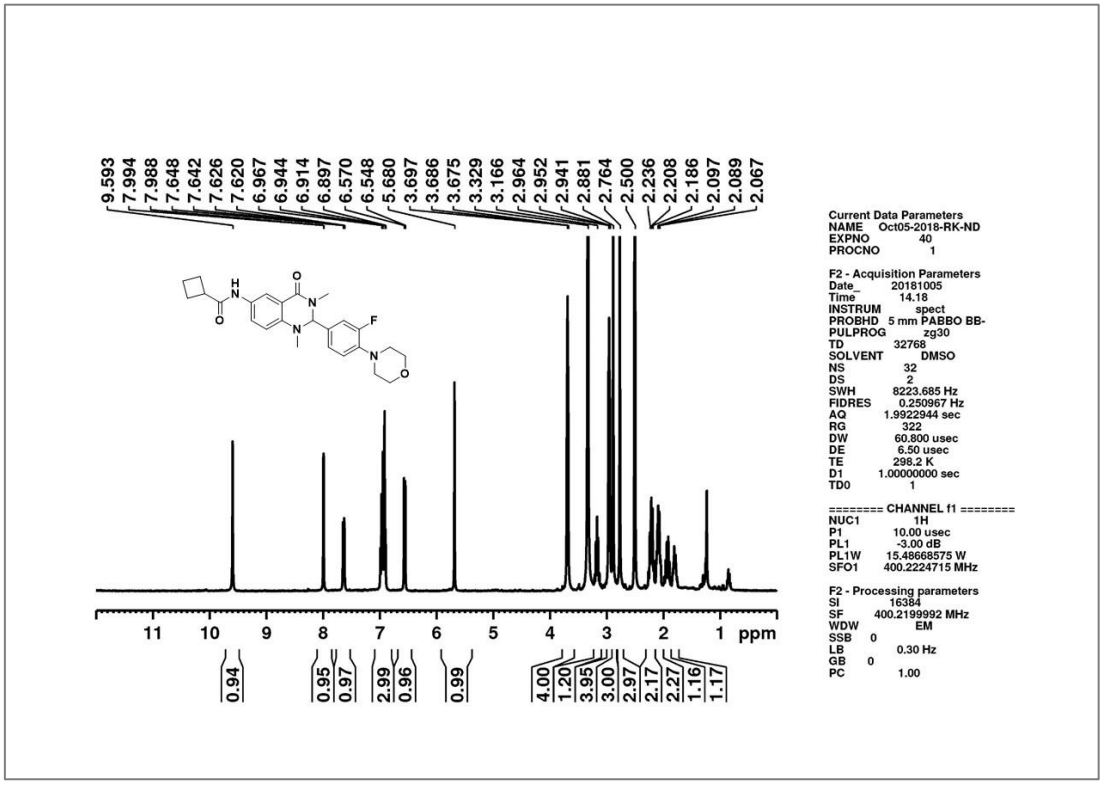
^{1}H NMR spectrum of compound 10f (Chapter 5)



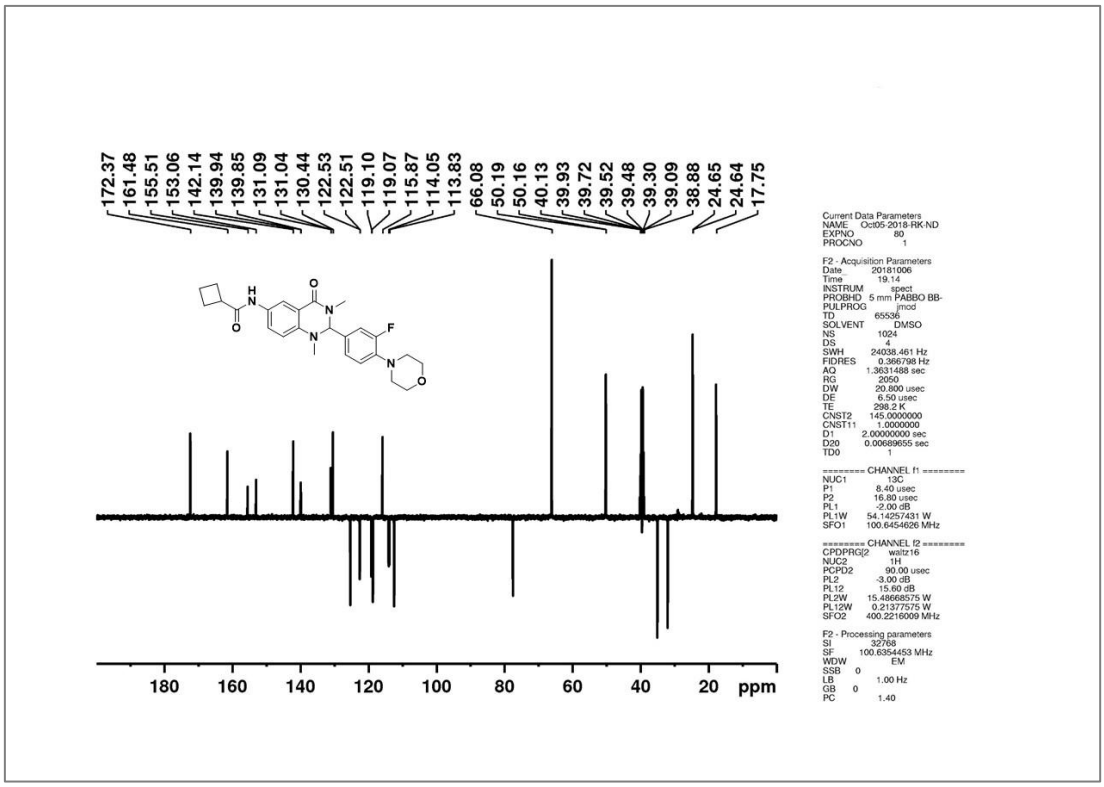
^{13}C NMR spectrum of compound 10f (Chapter 5)



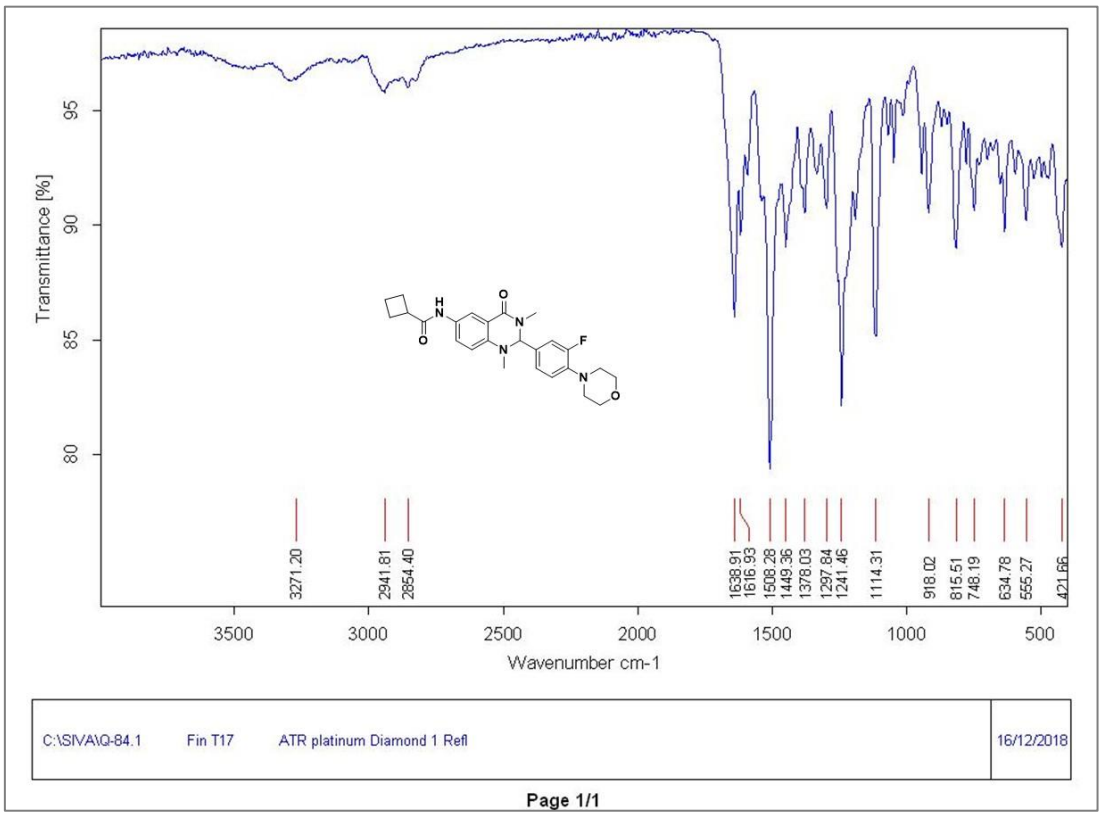
IR spectrum of compound 10f (Chapter 5)



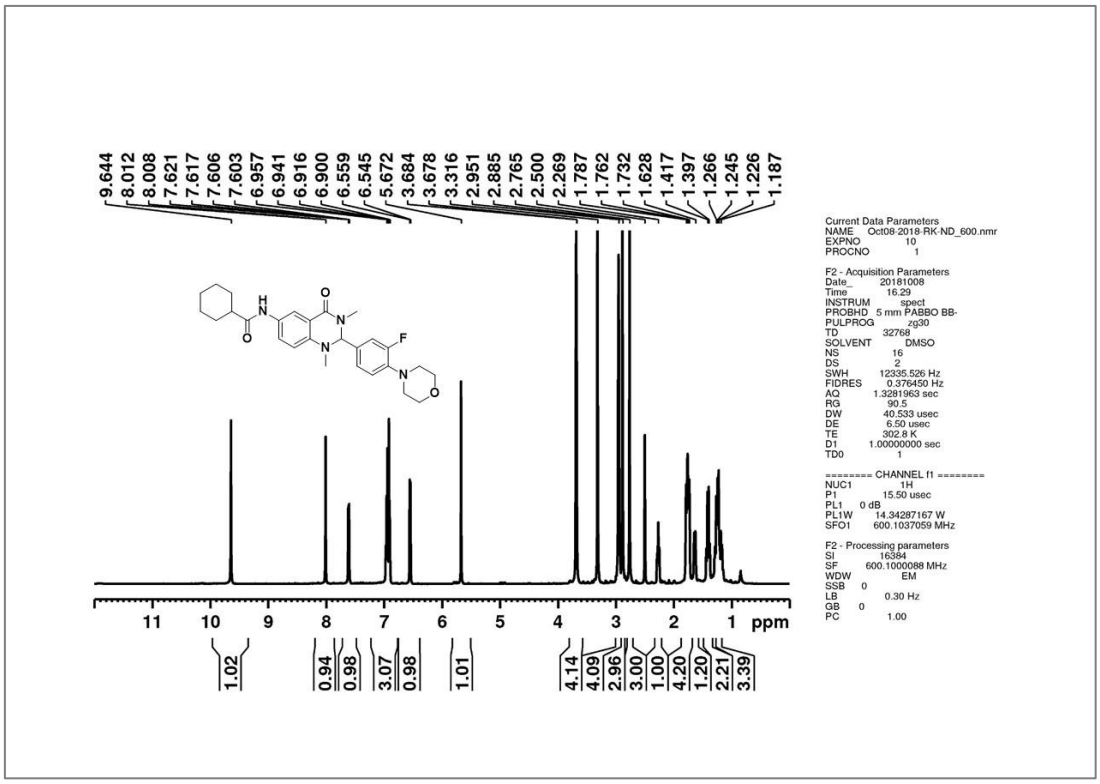
^{1}H NMR spectrum of compound 10g (Chapter 5)



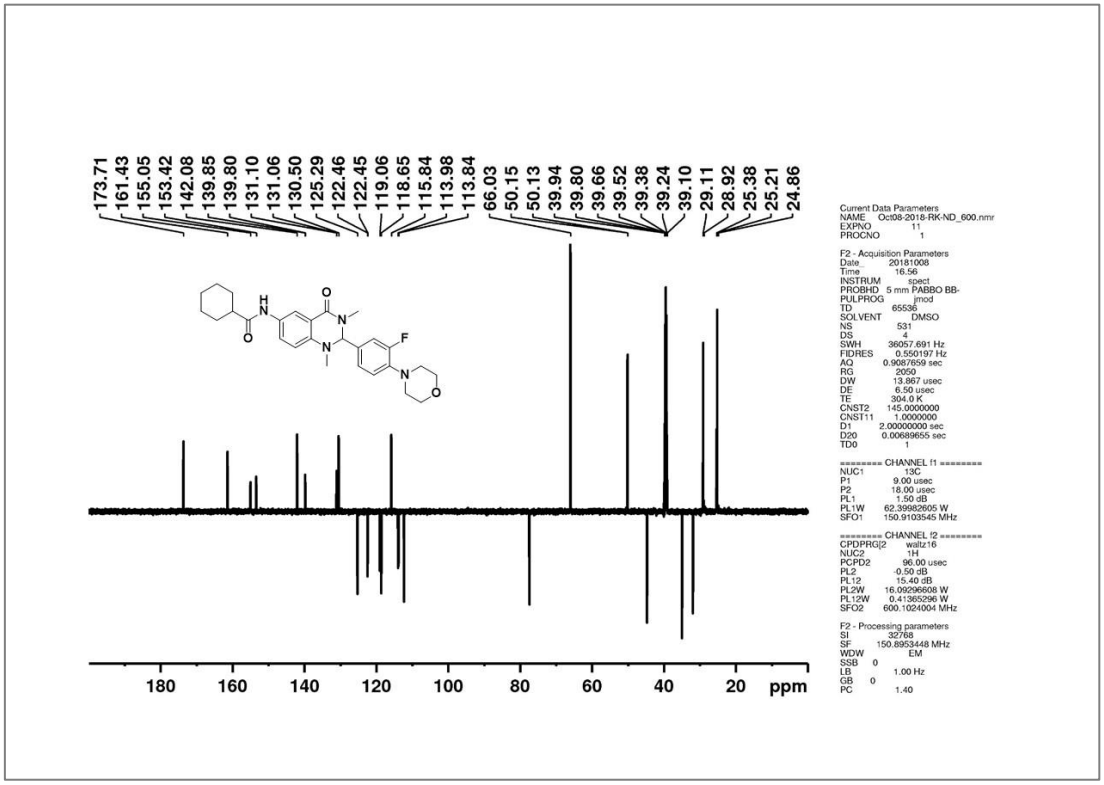
^{13}C NMR spectrum of compound 10g (Chapter 5)



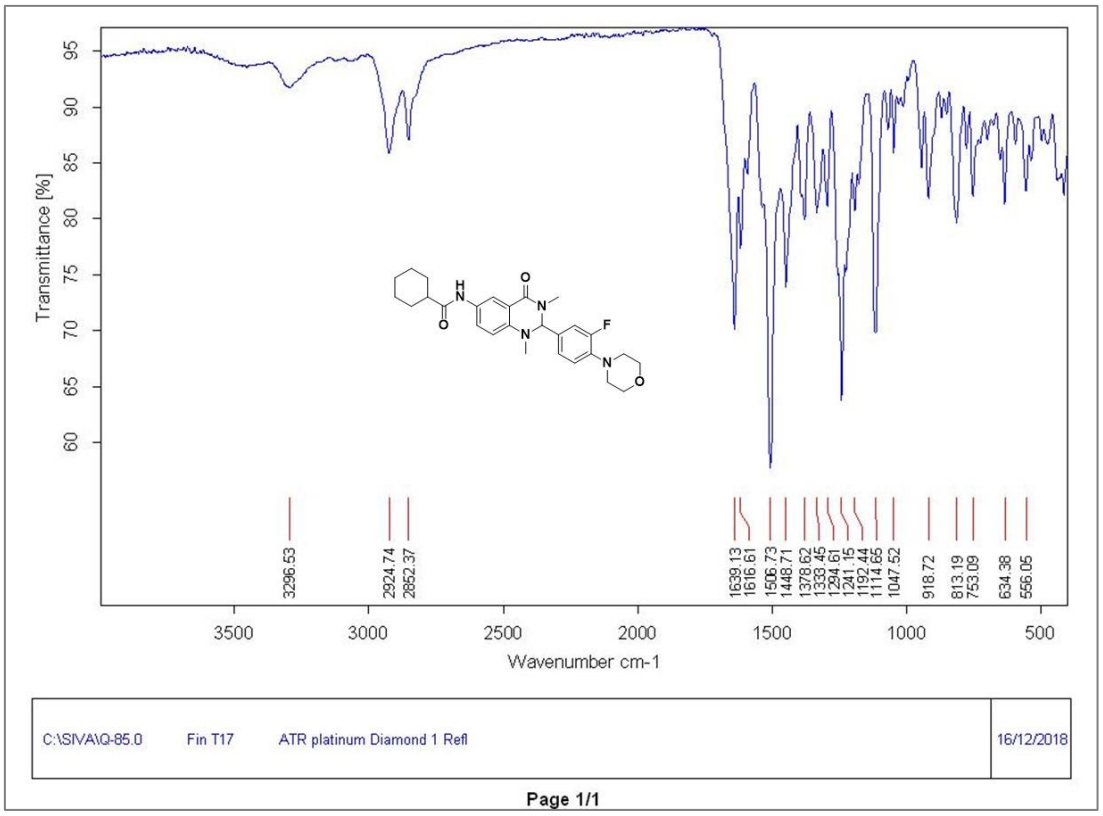
IR spectrum of compound 10g (Chapter 5)



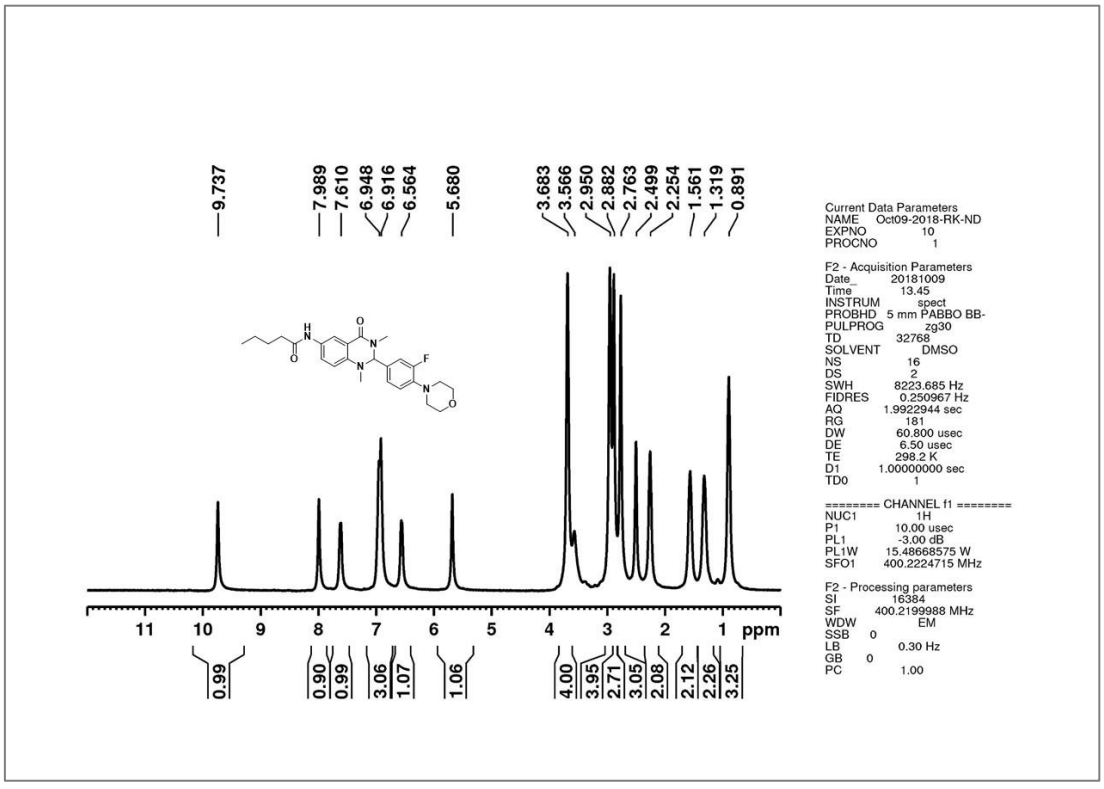
^{1}H NMR spectrum of compound 10h (Chapter 5)



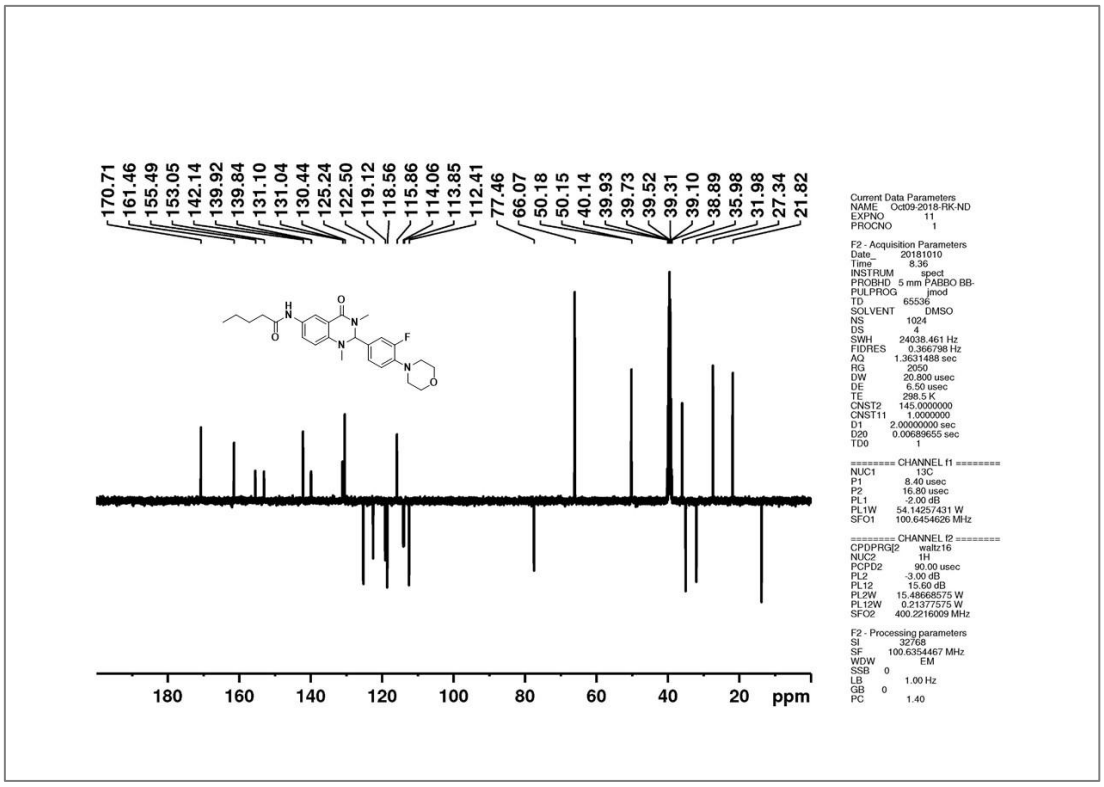
^{13}C NMR spectrum of compound 10h (Chapter 5)



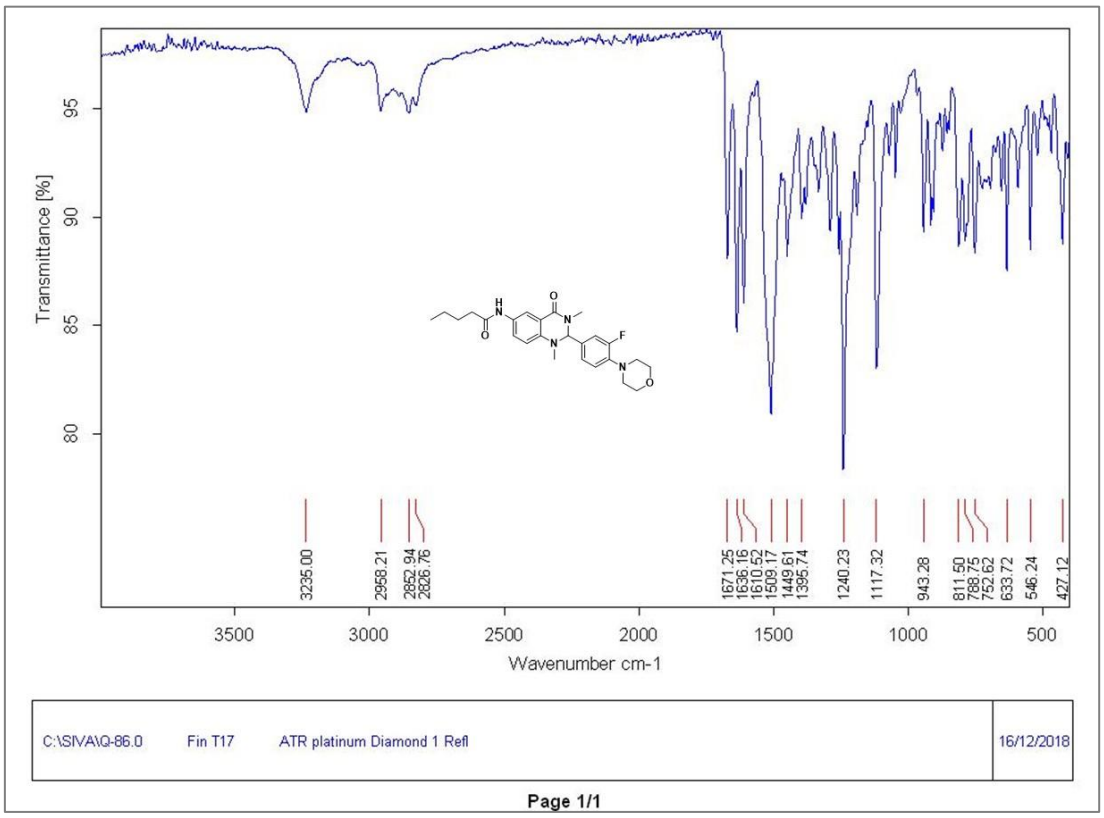
IR spectrum of compound 10h (Chapter 5)



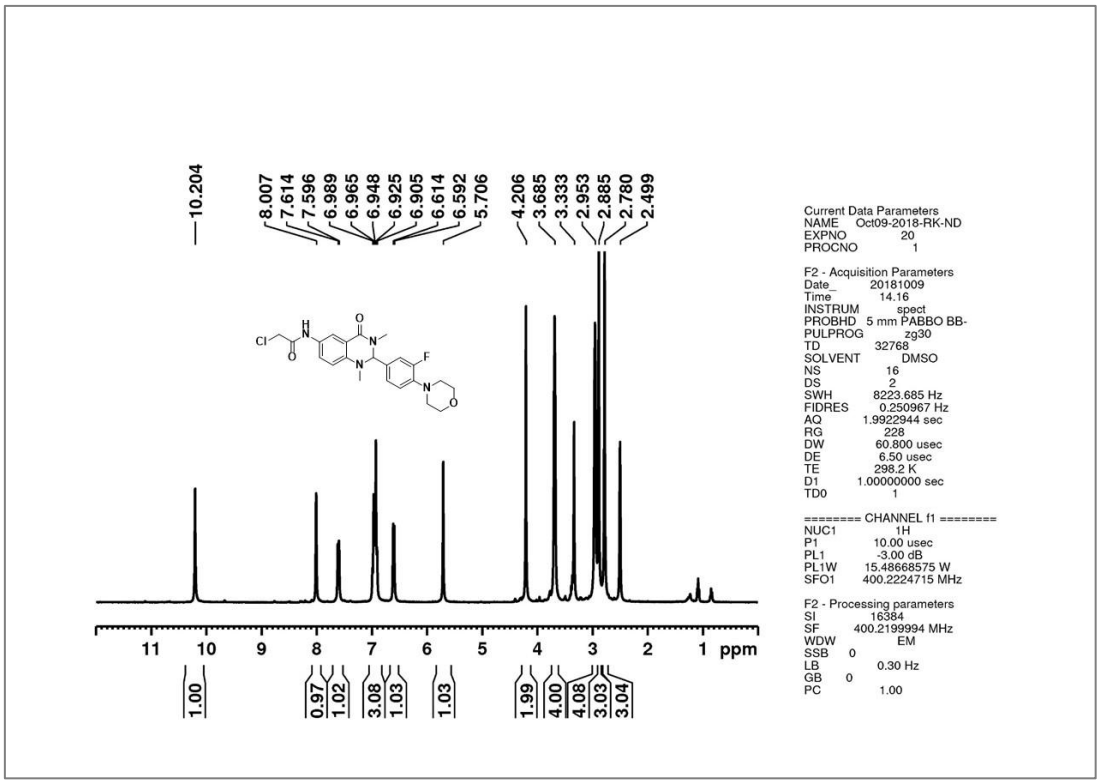
^{1}H NMR spectrum of compound 10i (Chapter 5)



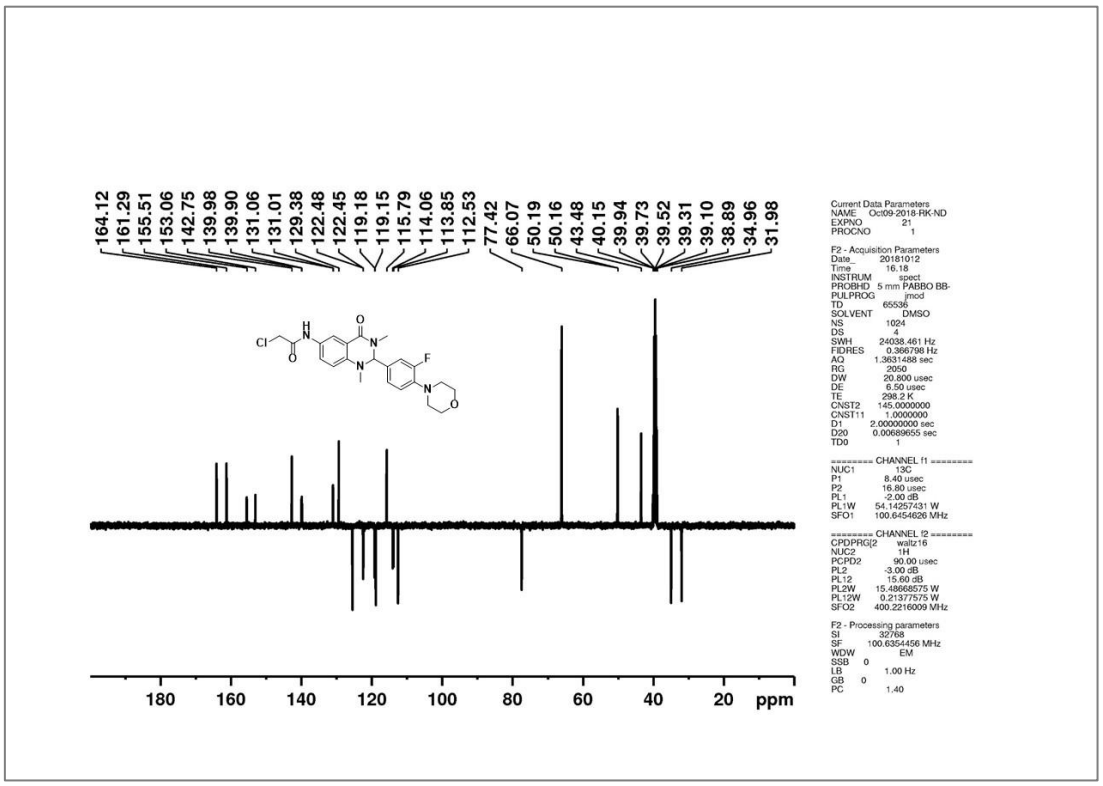
^{13}C NMR spectrum of compound 10i (Chapter 5)



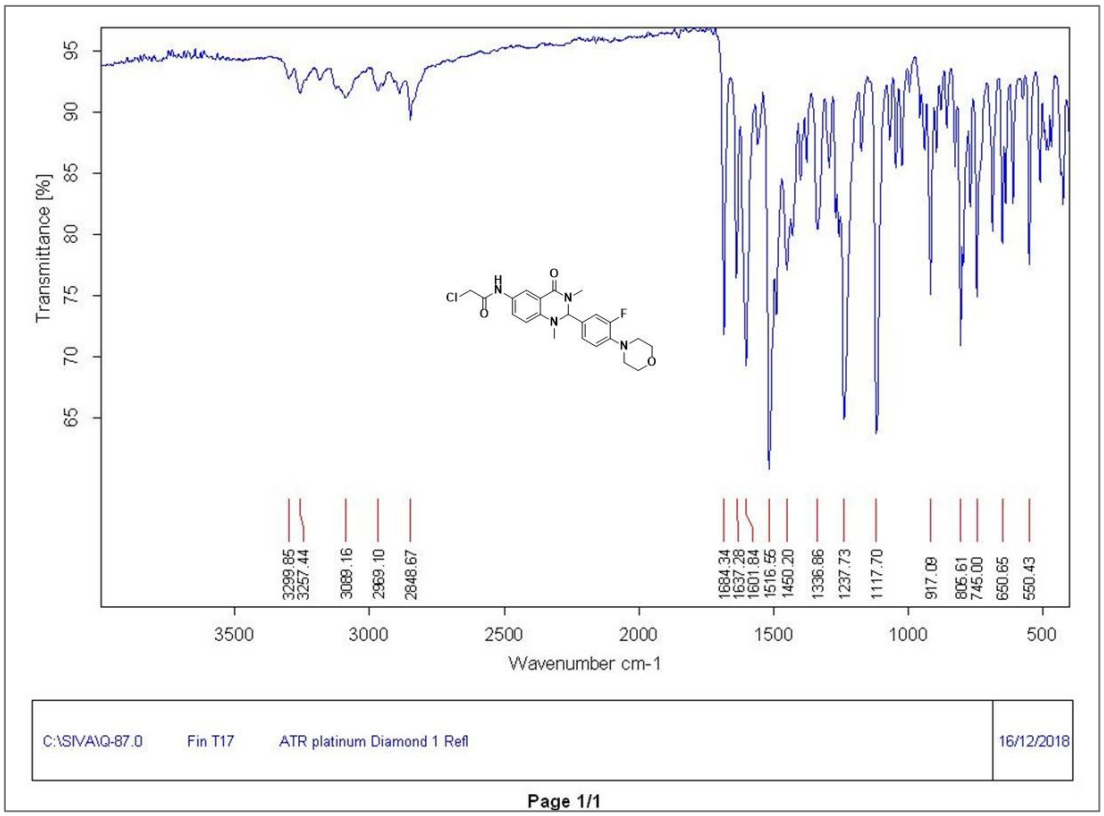
IR spectrum of compound 10i (Chapter 5)



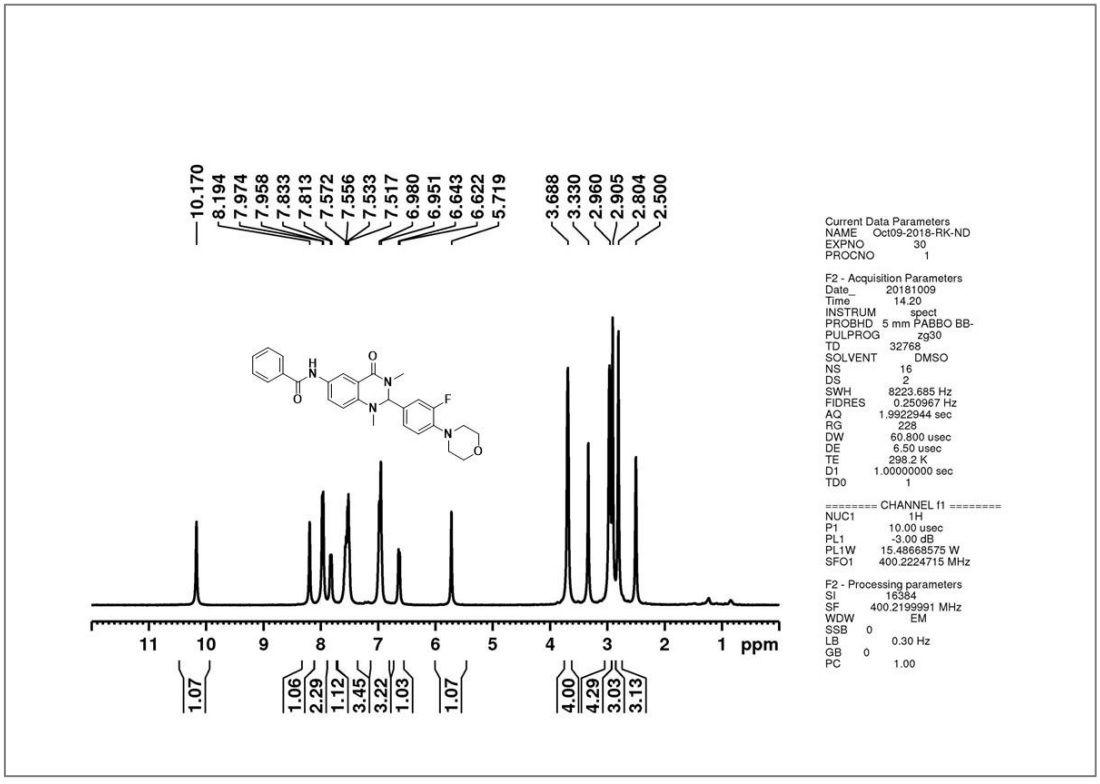
^{1}H NMR spectrum of compound 10j (Chapter 5)



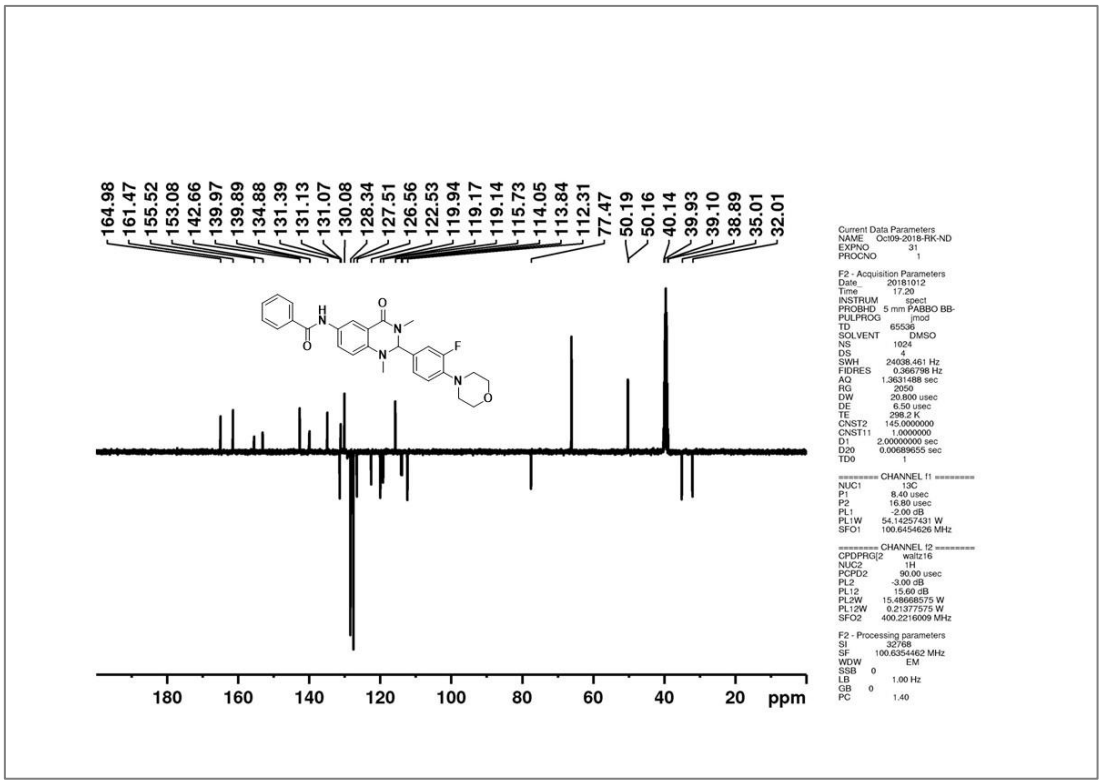
^{13}C NMR spectrum of compound 10j (Chapter 5)



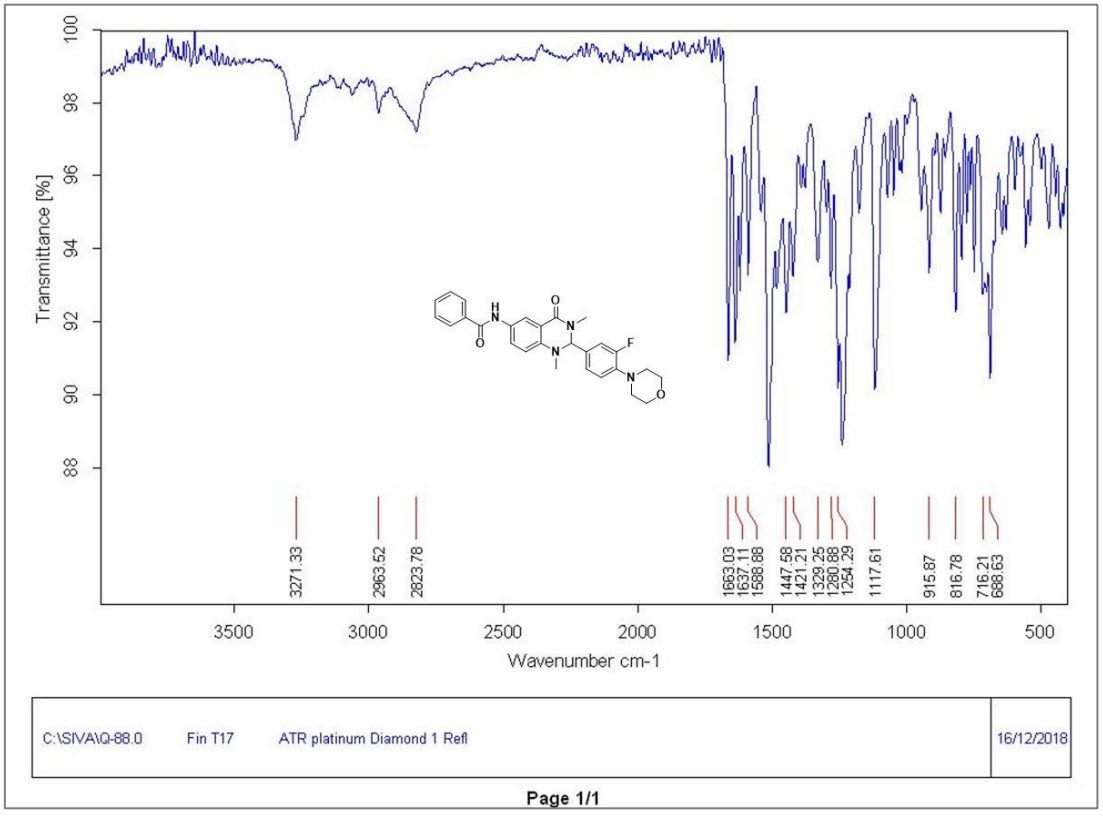
IR spectrum of compound 10j (Chapter 5)



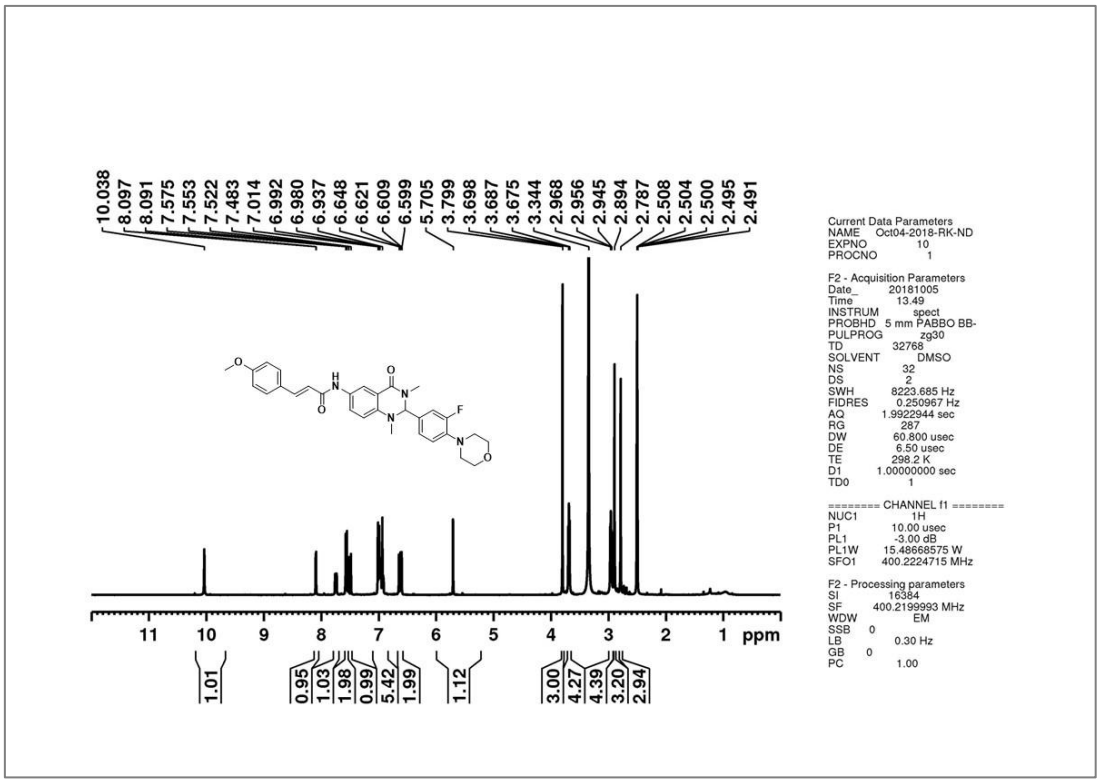
^{1}H NMR spectrum of compound 10k (Chapter 5)



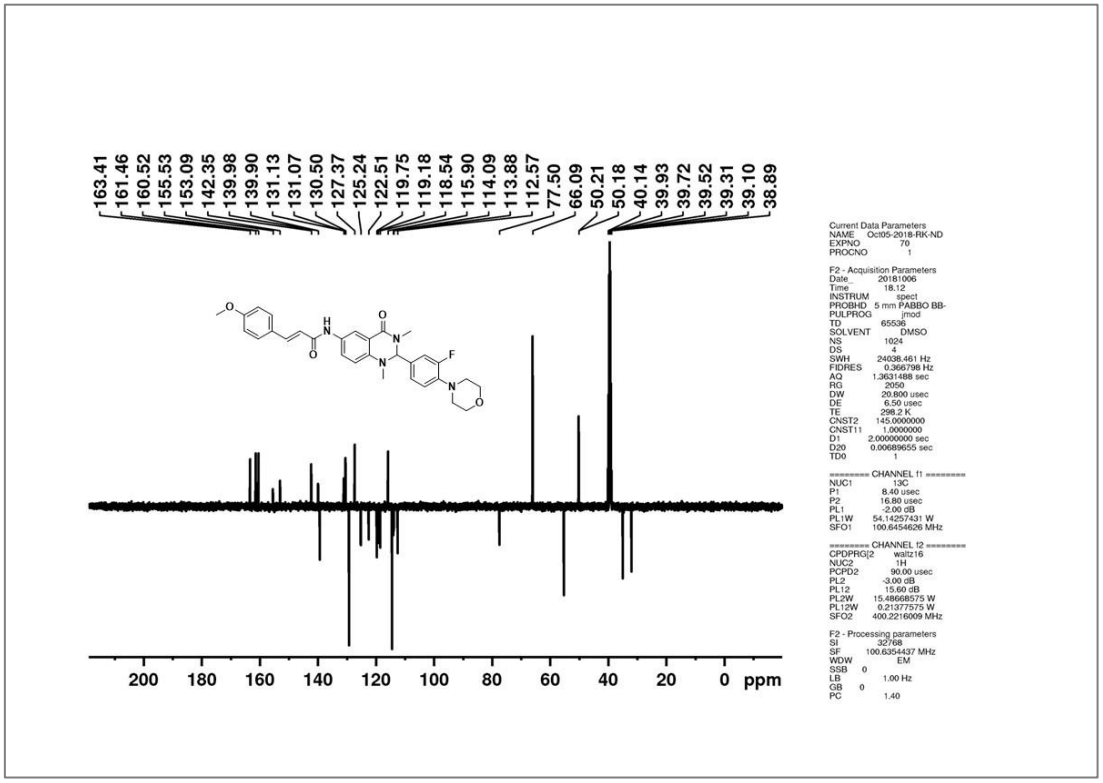
^{13}C NMR spectrum of compound 10k (Chapter 5)



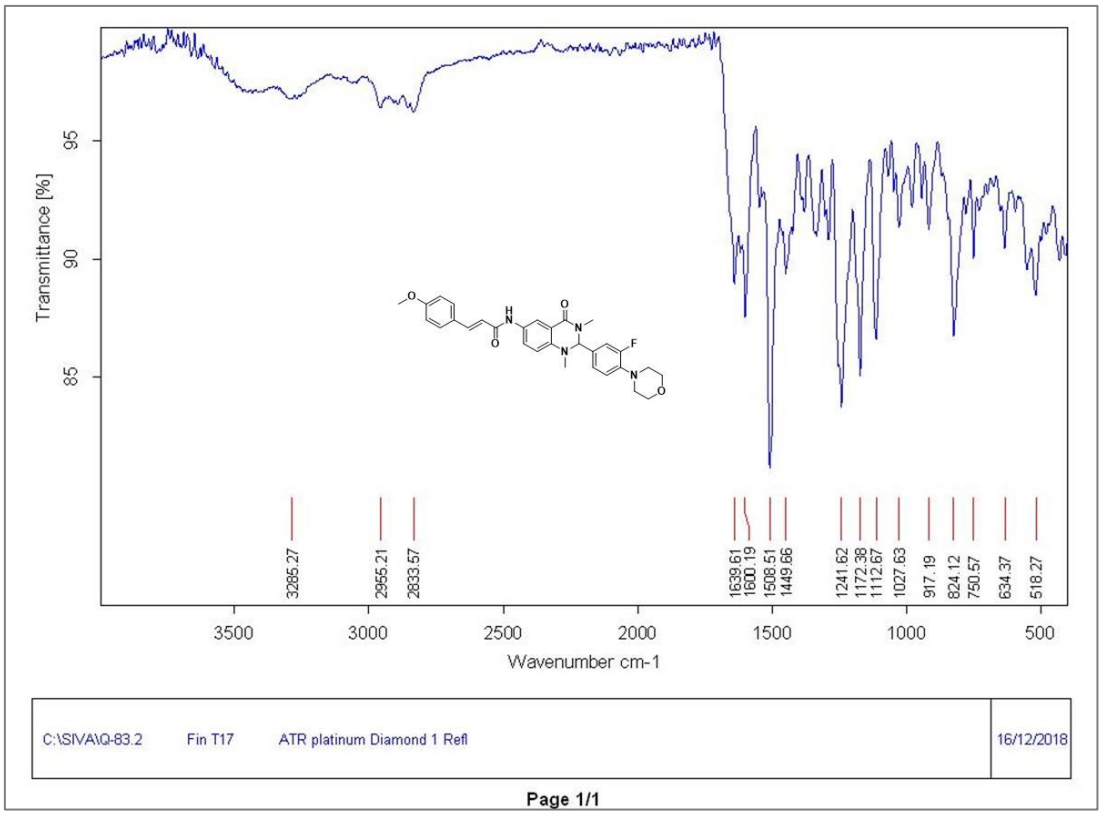
IR spectrum of compound 10k (Chapter 5)



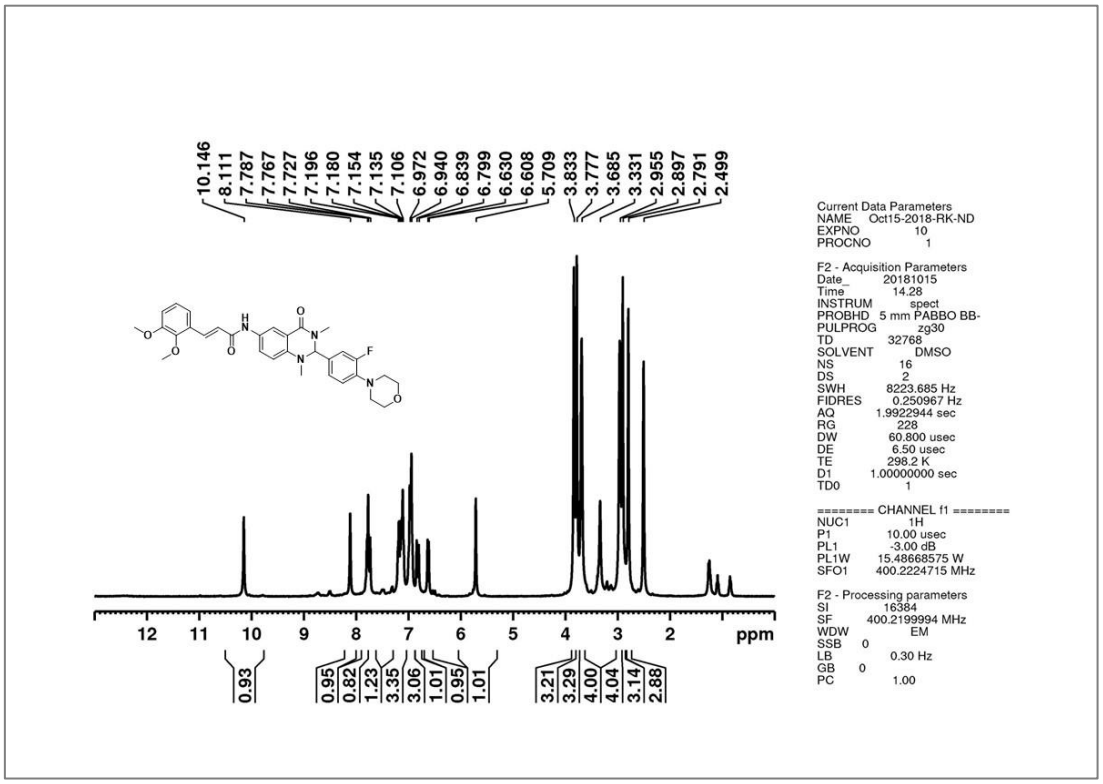
[1]H NMR spectrum of compound 10l (Chapter 5)



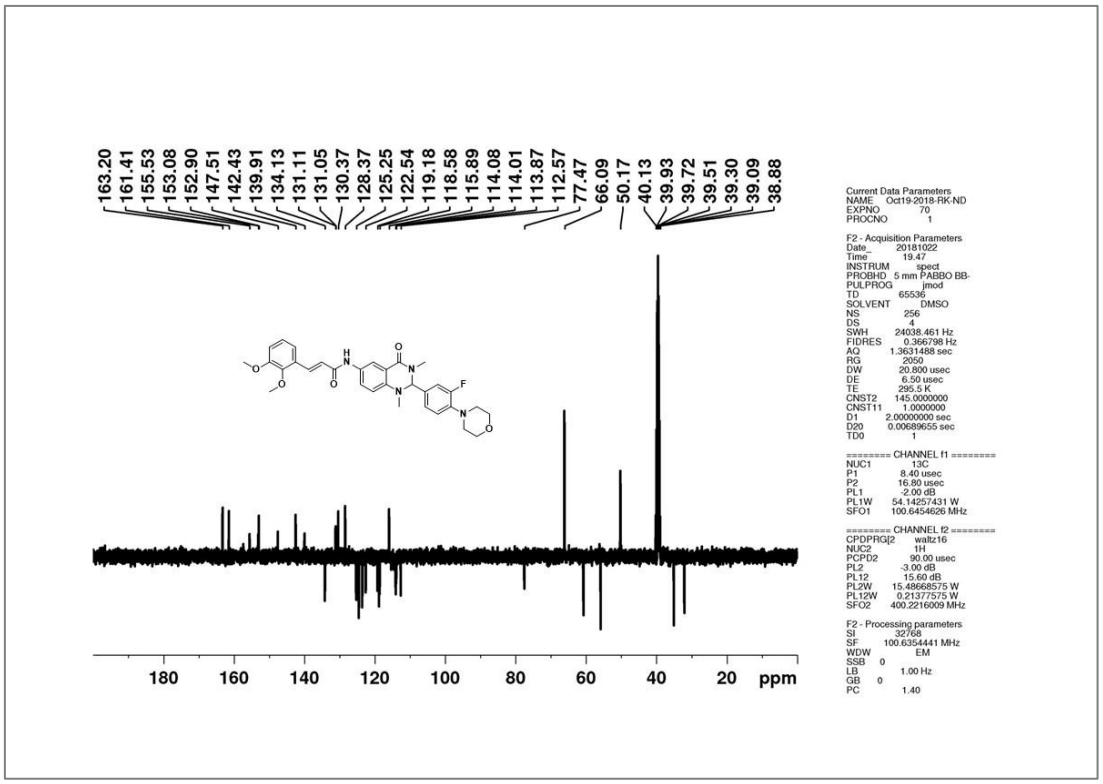
[13]C NMR spectrum of compound 10l (Chapter 5)



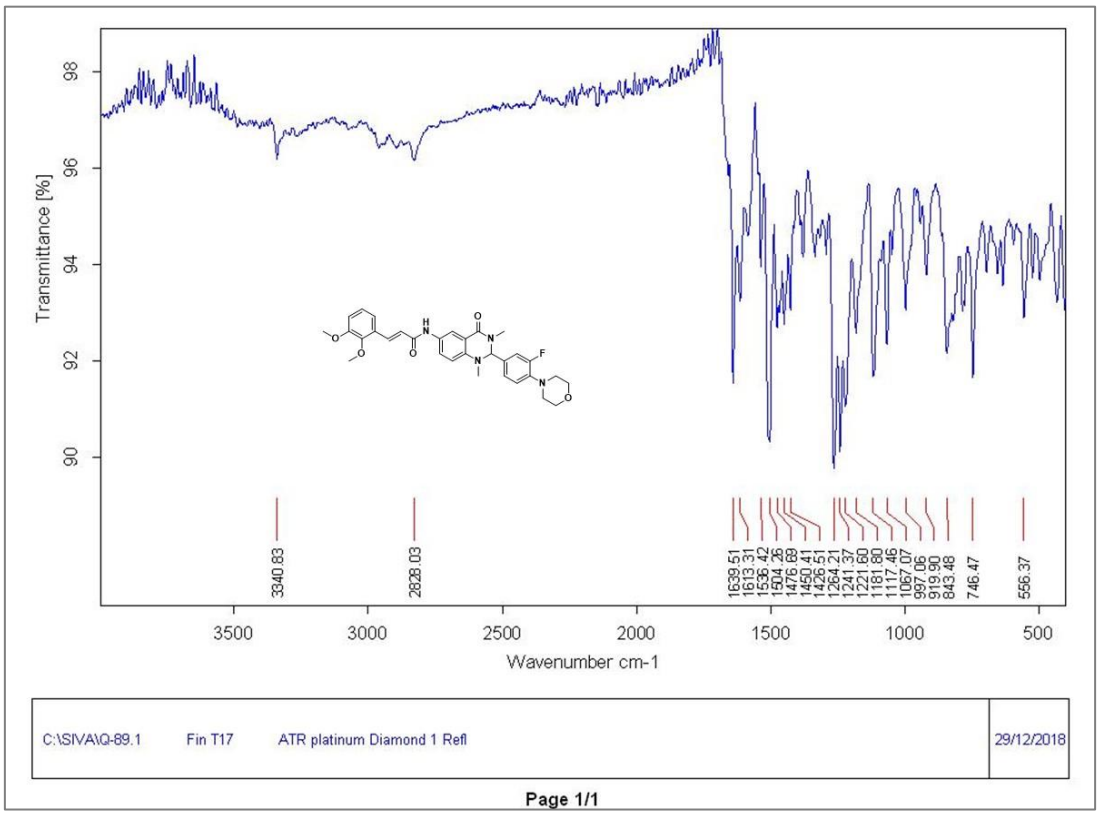
IR spectrum of compound 10l (Chapter 5)



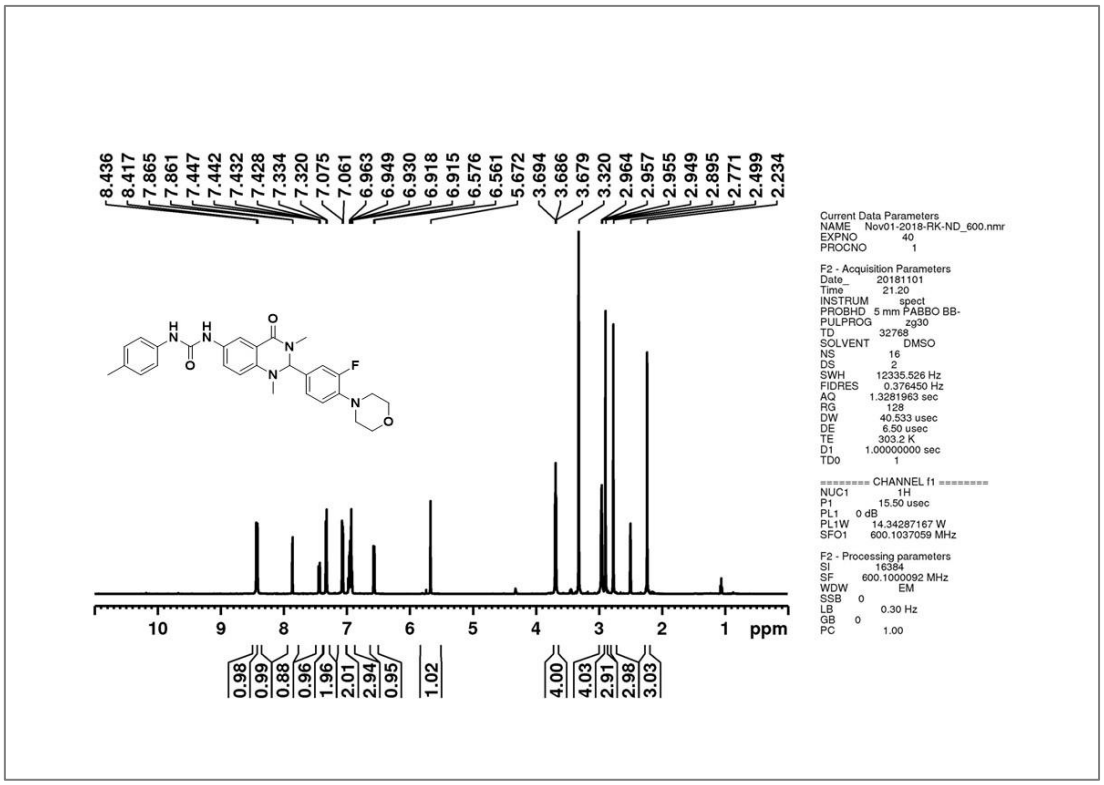
^{1}H NMR spectrum of compound 10m (Chapter 5)



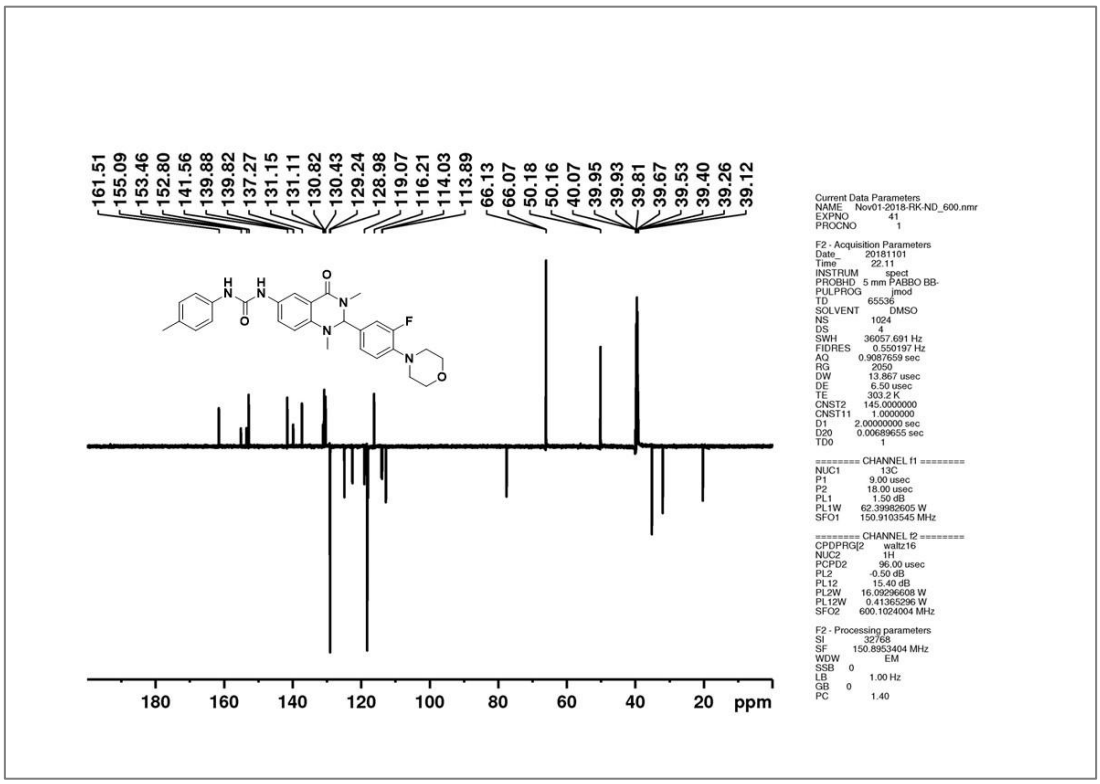
^{13}C NMR spectrum of compound 10m (Chapter 5)



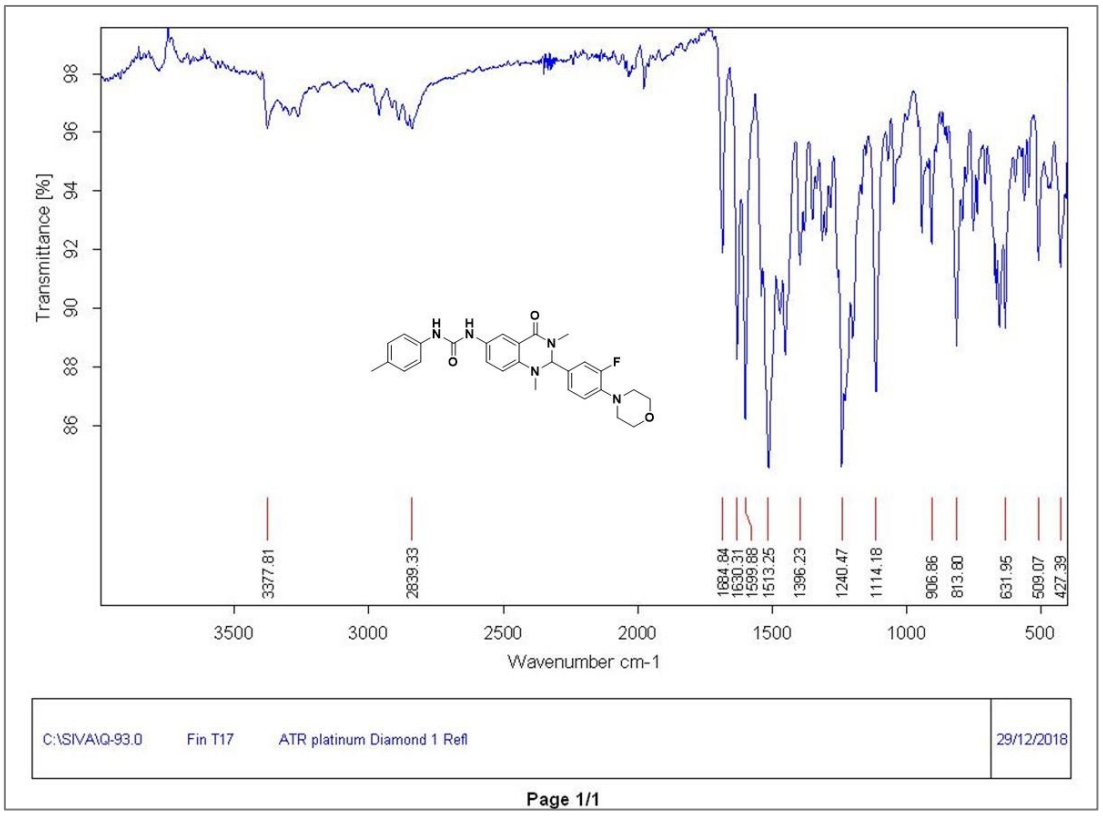
IR spectrum of compound 10m (Chapter 5)



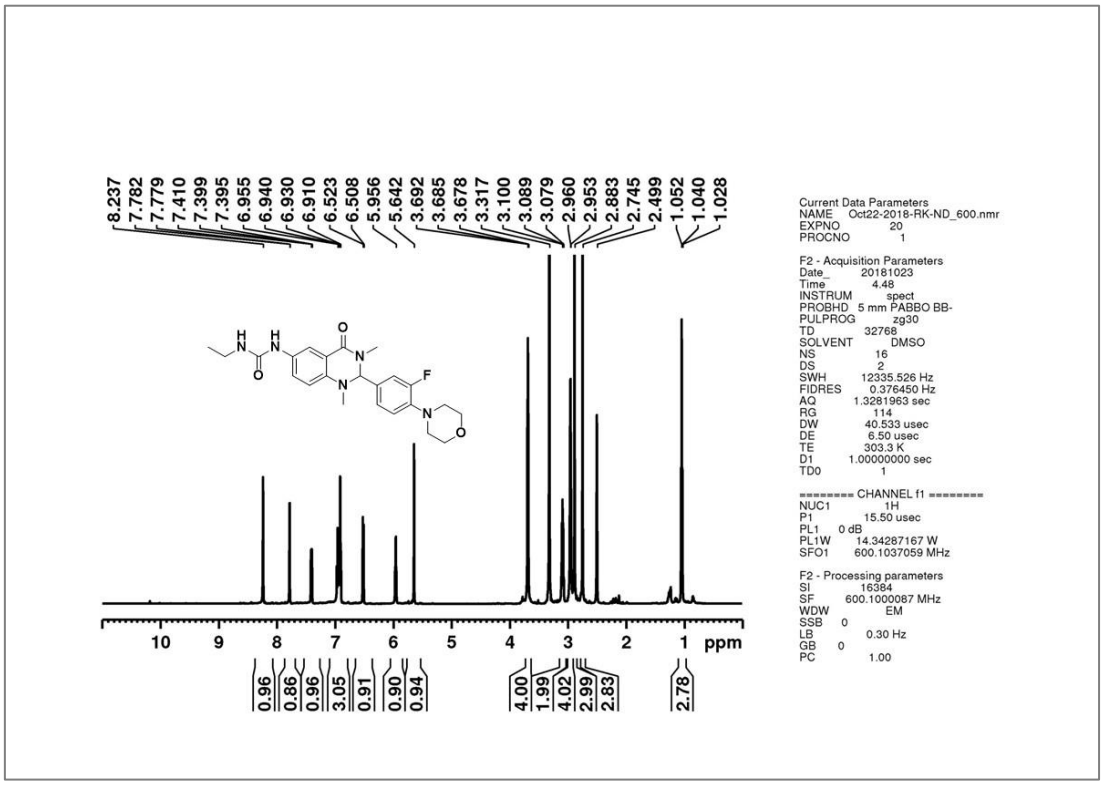
^{1}H NMR spectrum of compound 10n (Chapter 5)



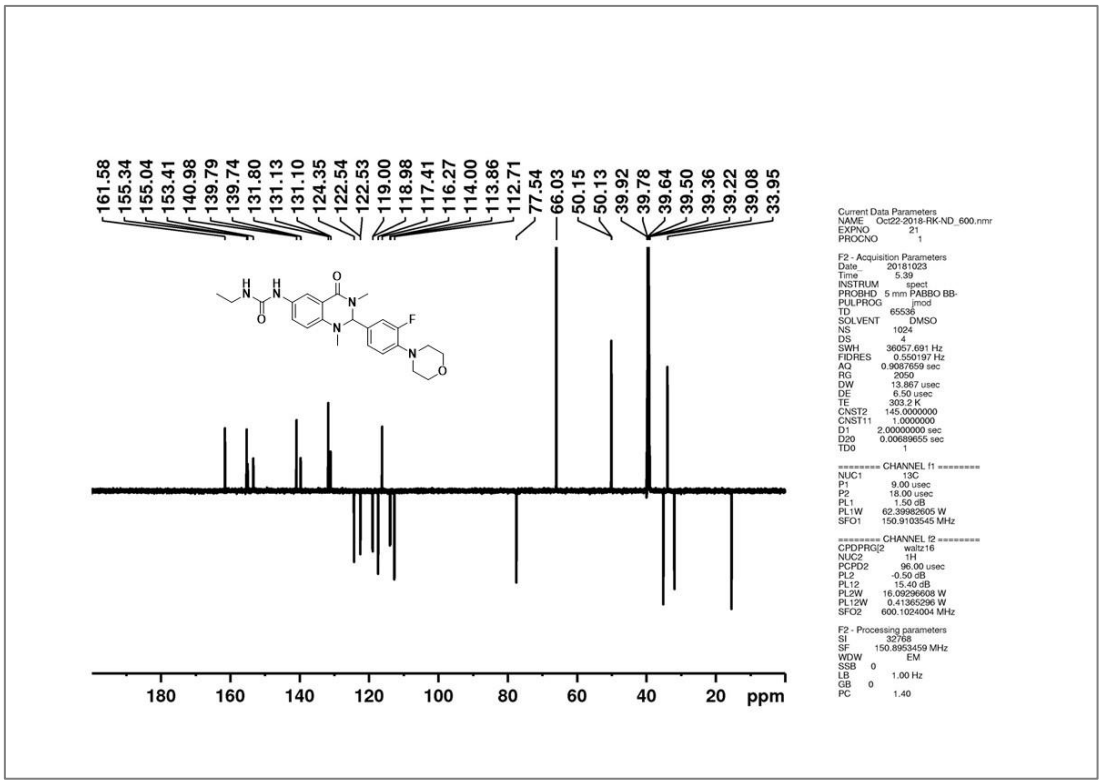
^{13}C NMR spectrum of compound 10n (Chapter 5)



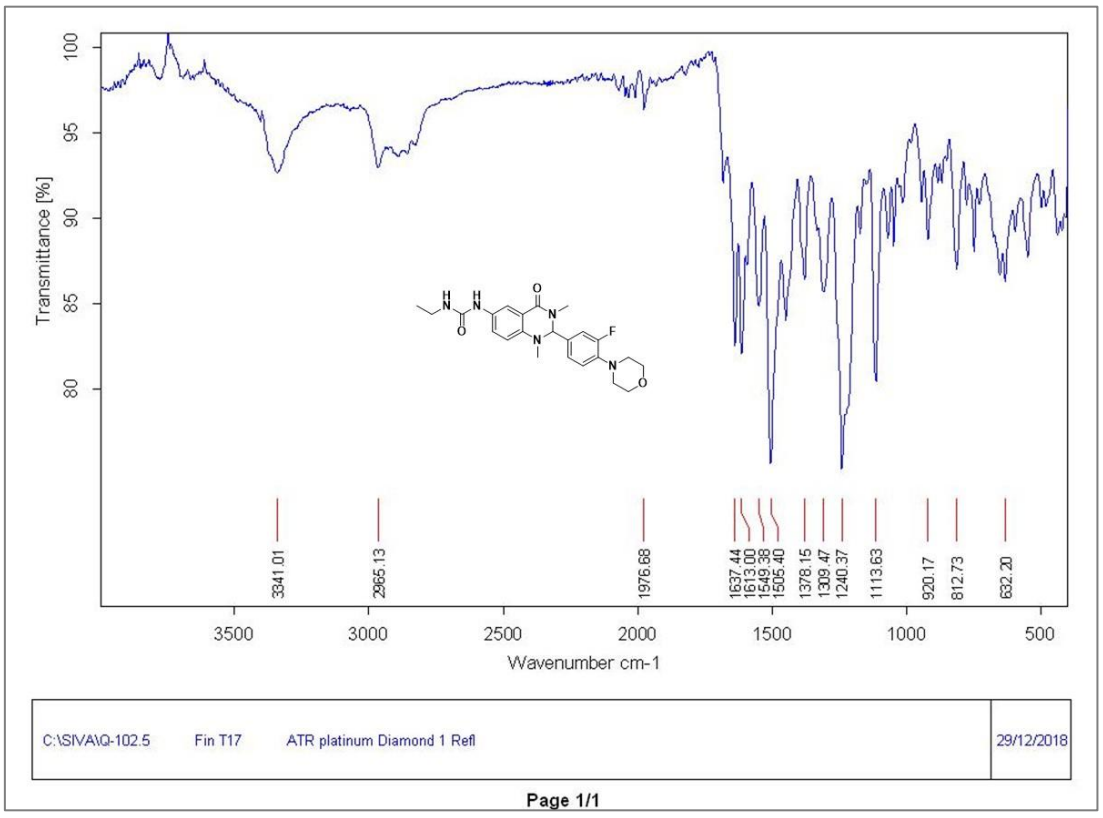
IR spectrum of compound 10n (Chapter 5)



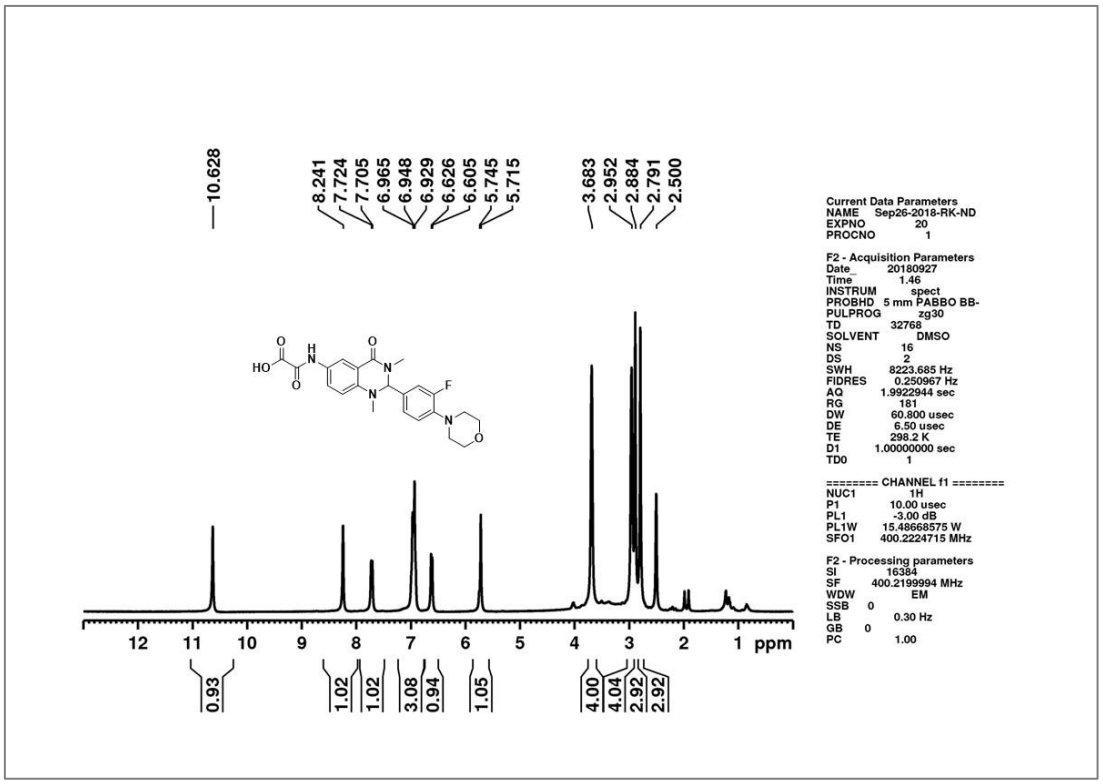
^{1}H NMR spectrum of compound 10o (Chapter 5)



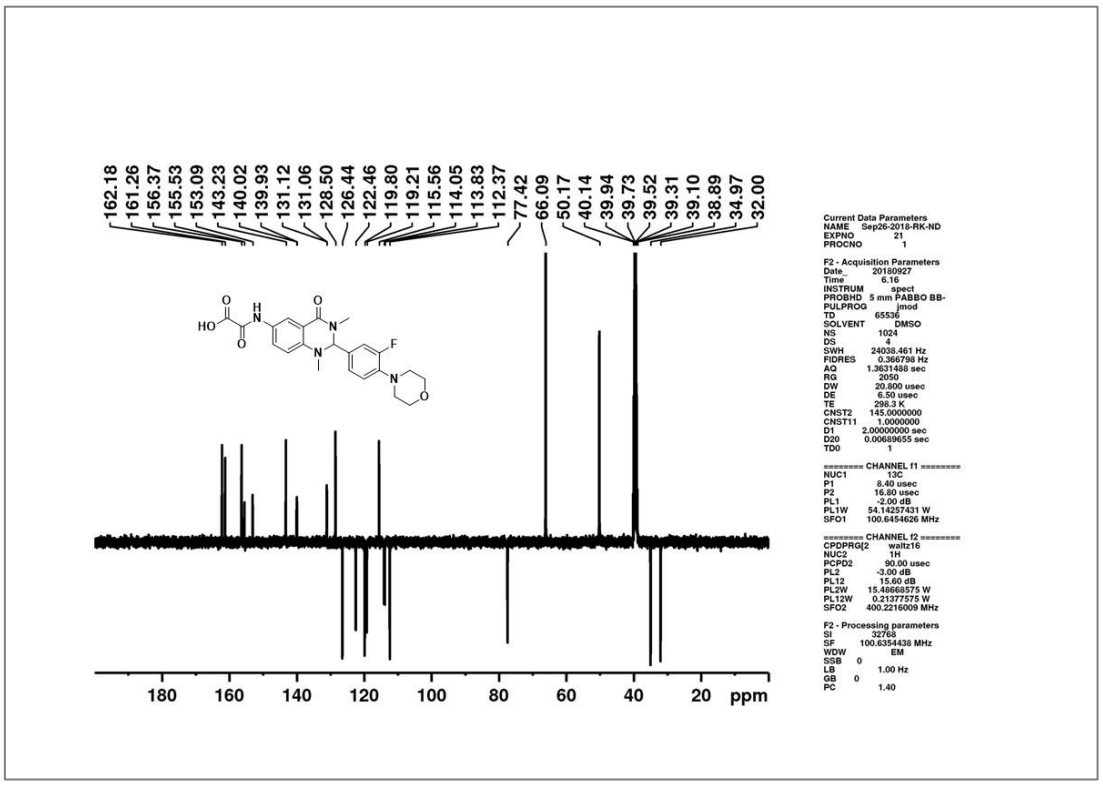
^{13}C NMR spectrum of compound 10o (Chapter 5)



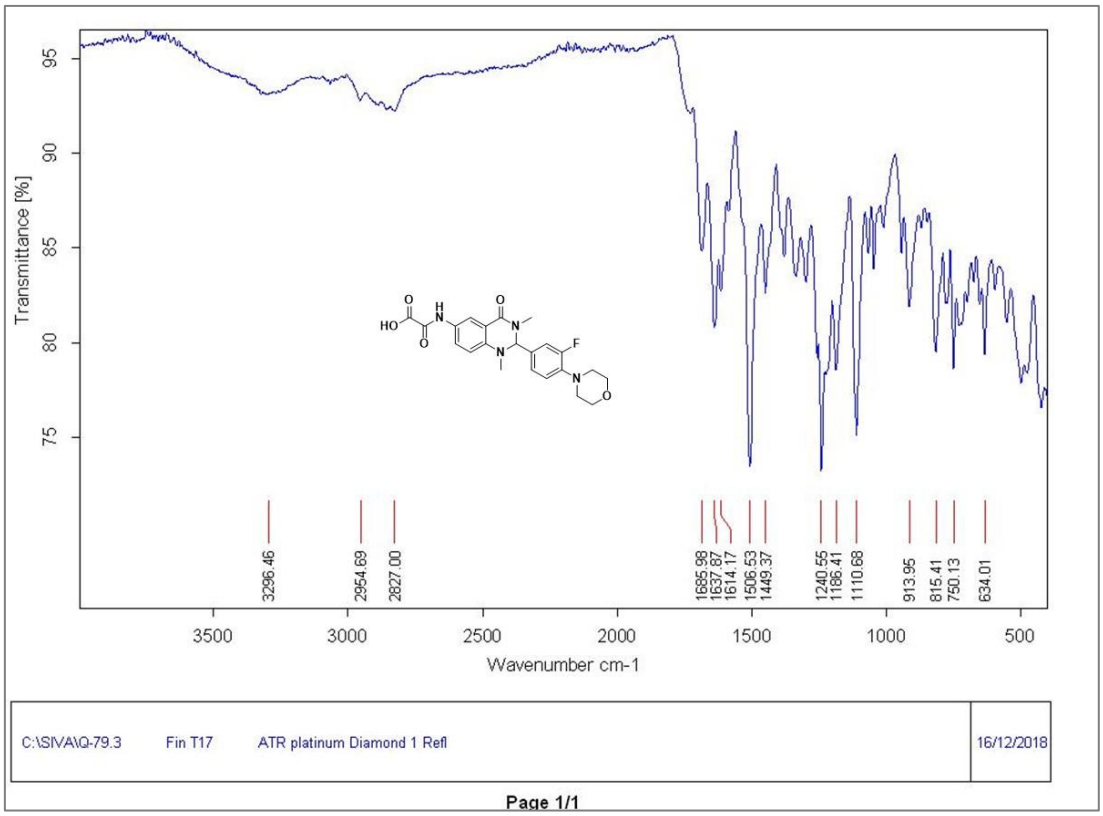
IR spectrum of compound 10o (Chapter 5)



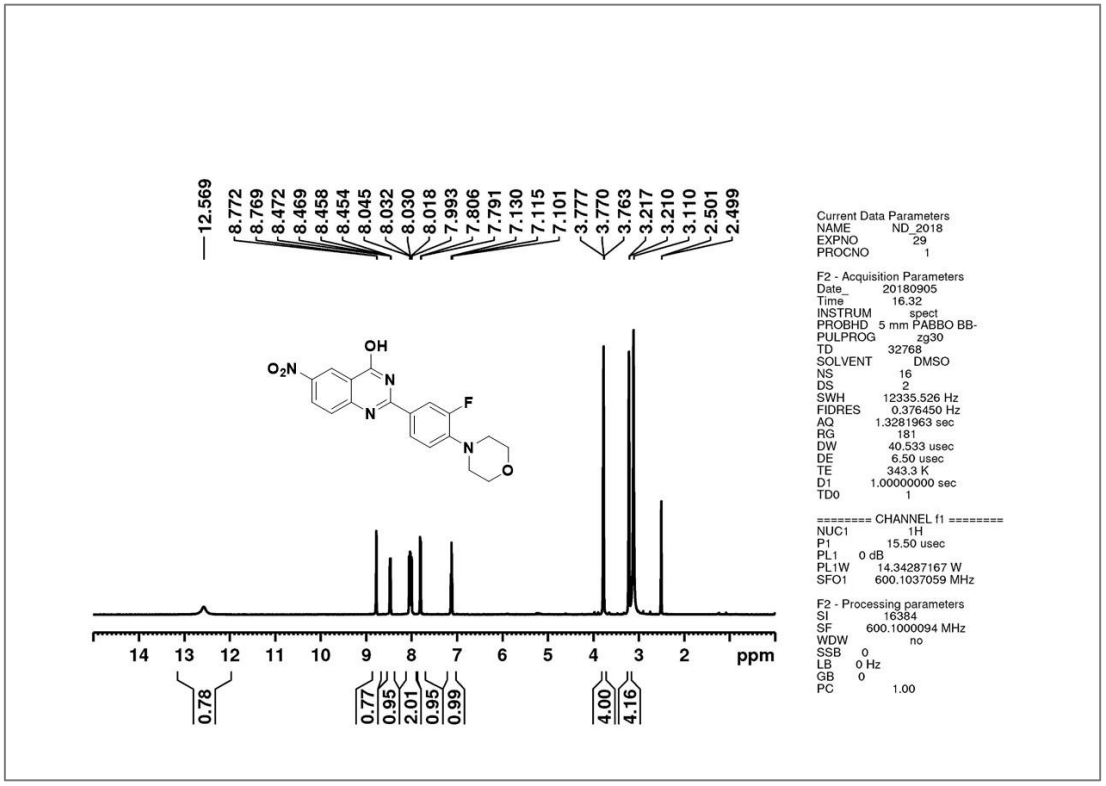
^{1}H NMR spectrum of compound 11 (Chapter 5)



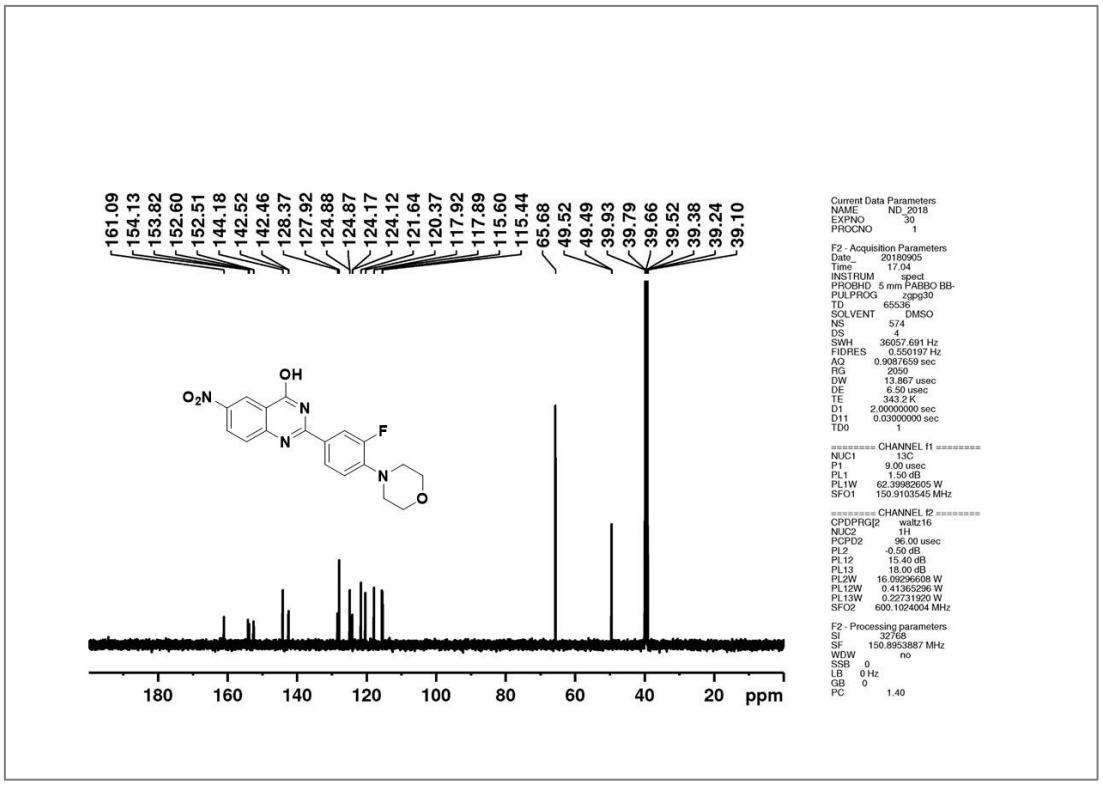
^{13}C NMR spectrum of compound 11 (Chapter 5)



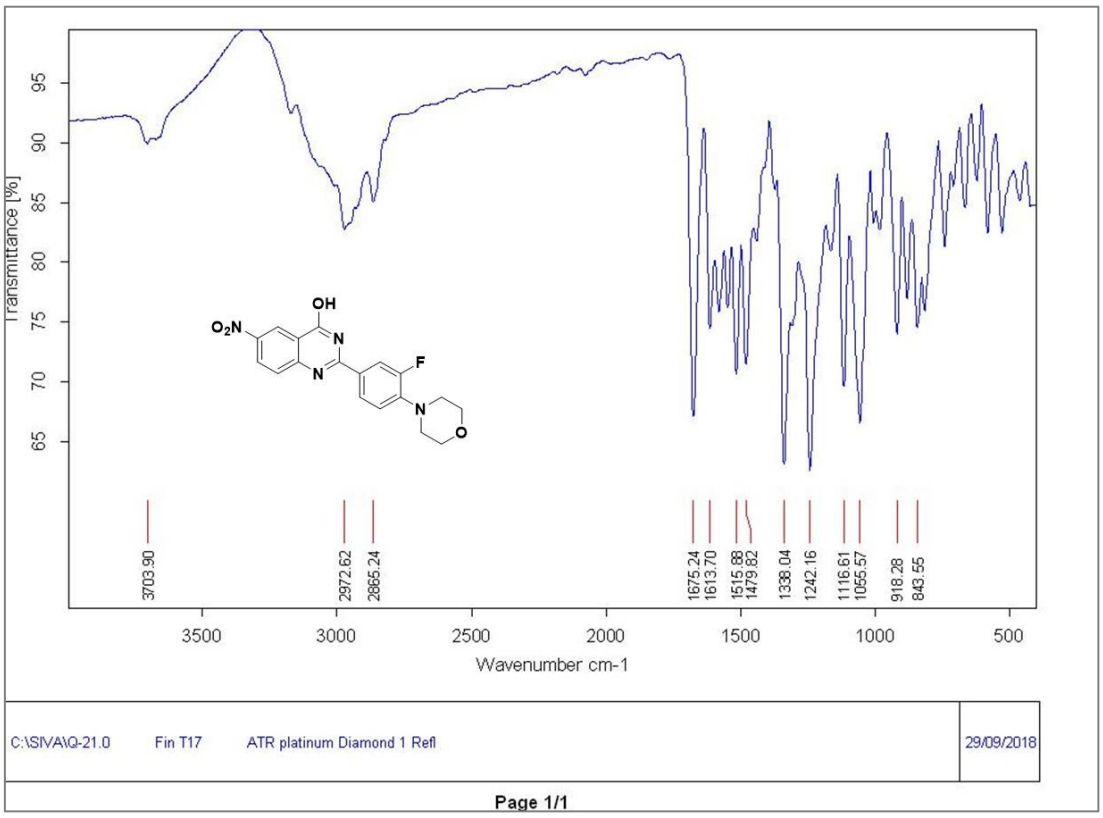
IR spectrum of compound 11 (Chapter 5)



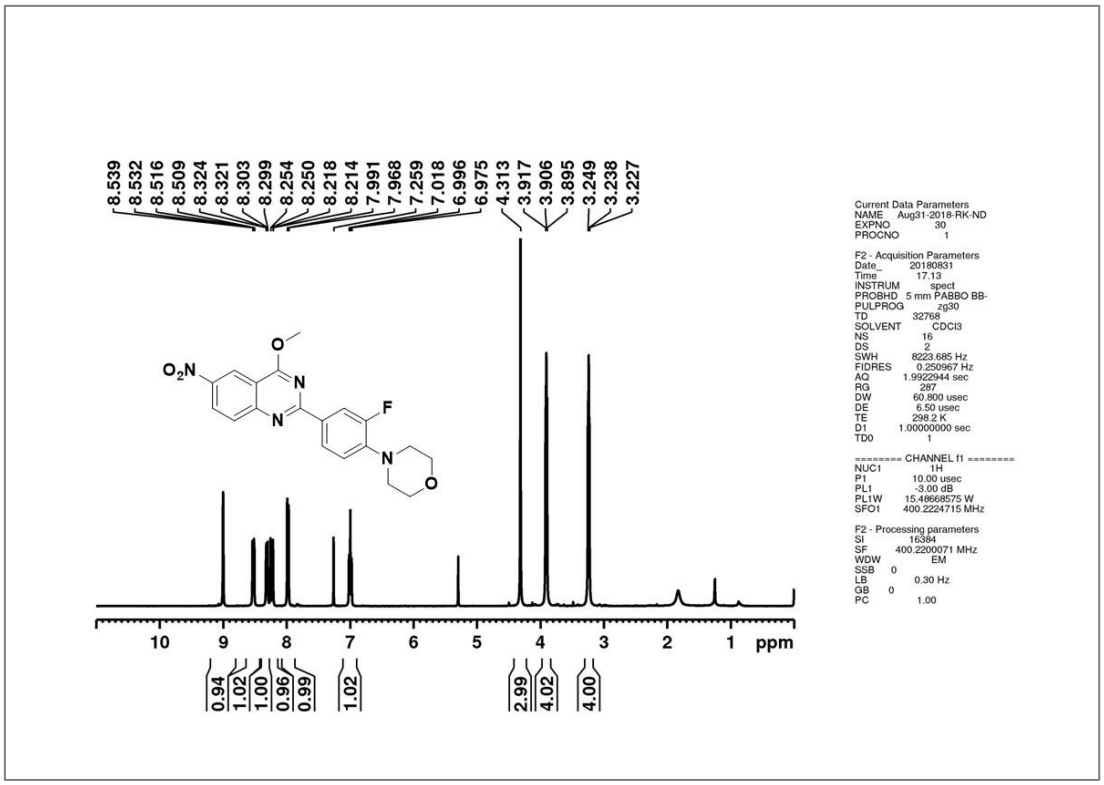
^{1}H NMR spectrum of compound 12 (Chapter 5)



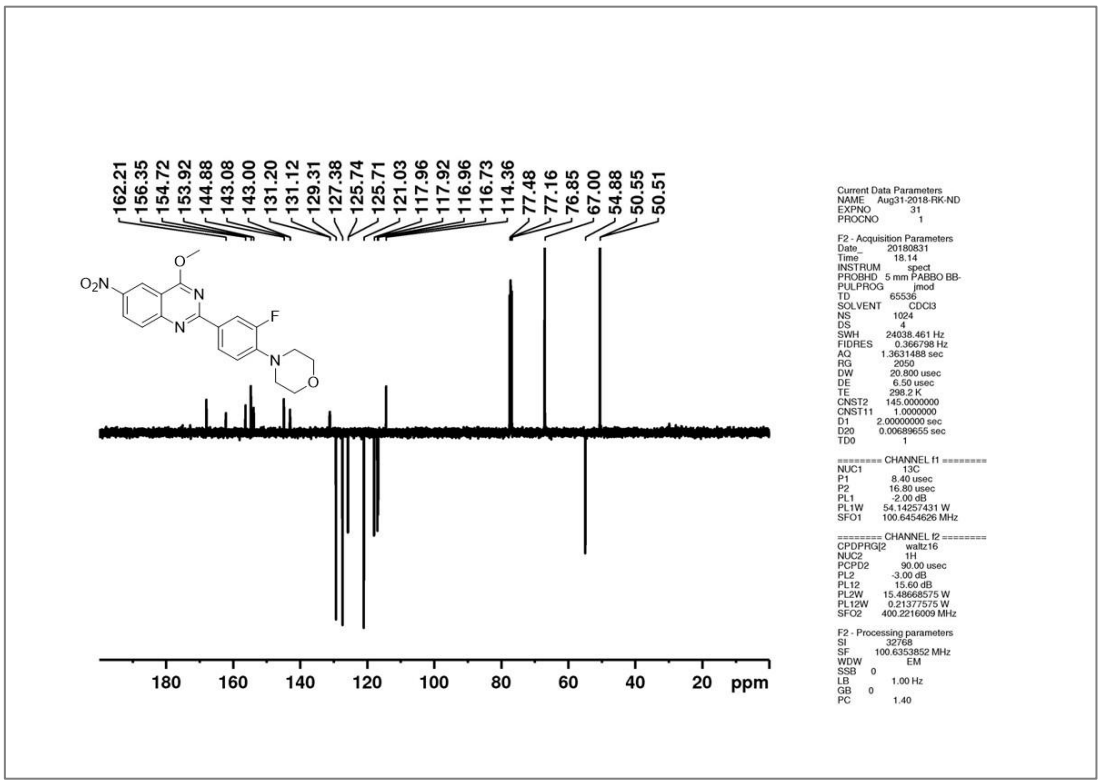
^{13}C NMR spectrum of compound 12 (Chapter 5)



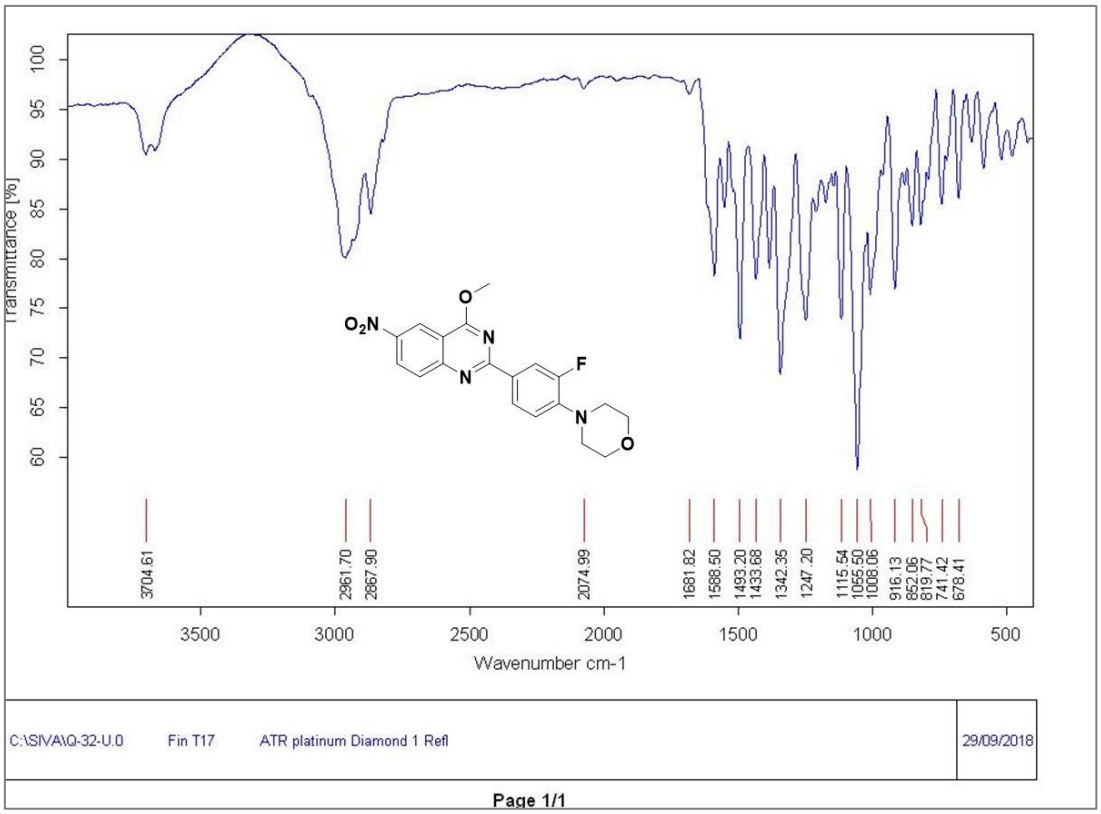
IR spectrum of compound 12 (Chapter 5)



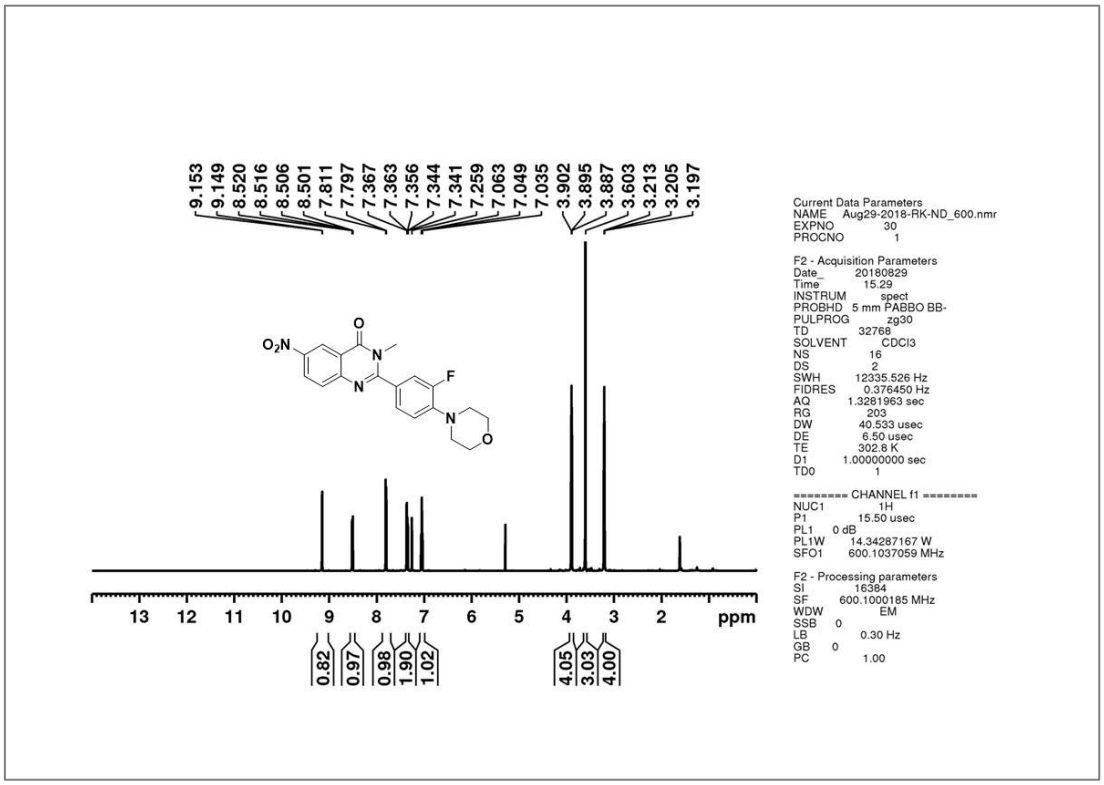
^{1}H NMR spectrum of compound 13 (Chapter 5)



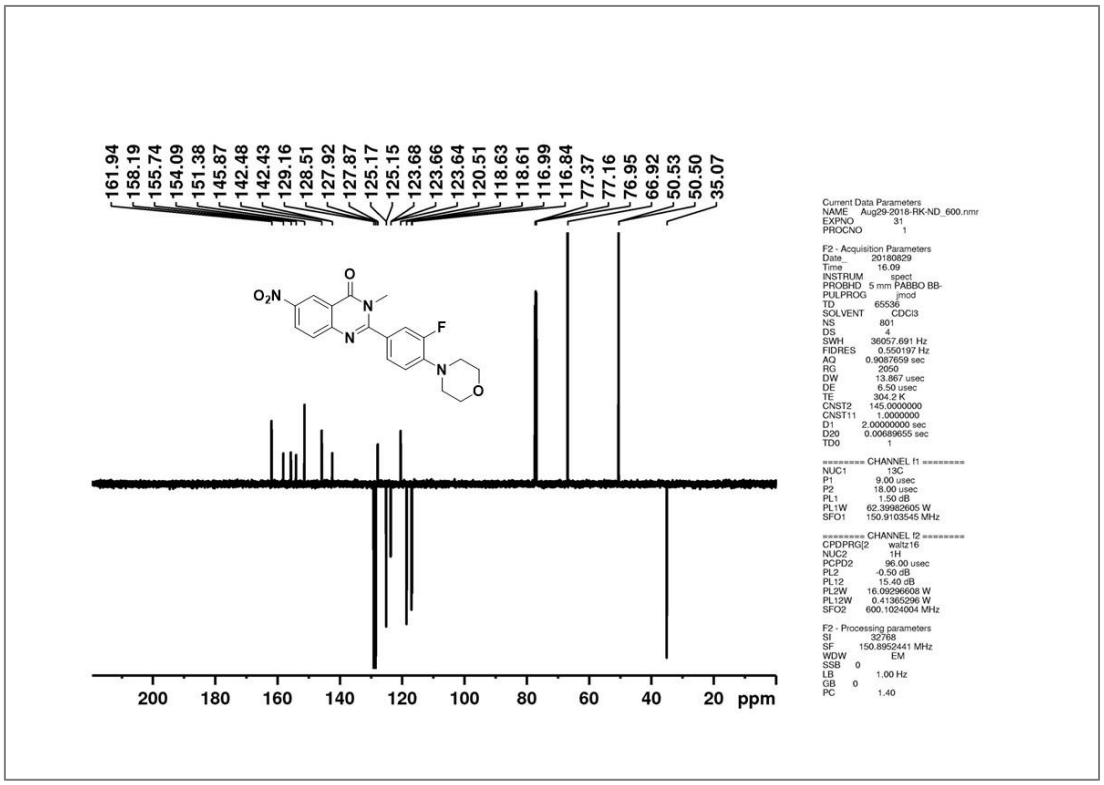
^{13}C NMR spectrum of compound 13 (Chapter 5)



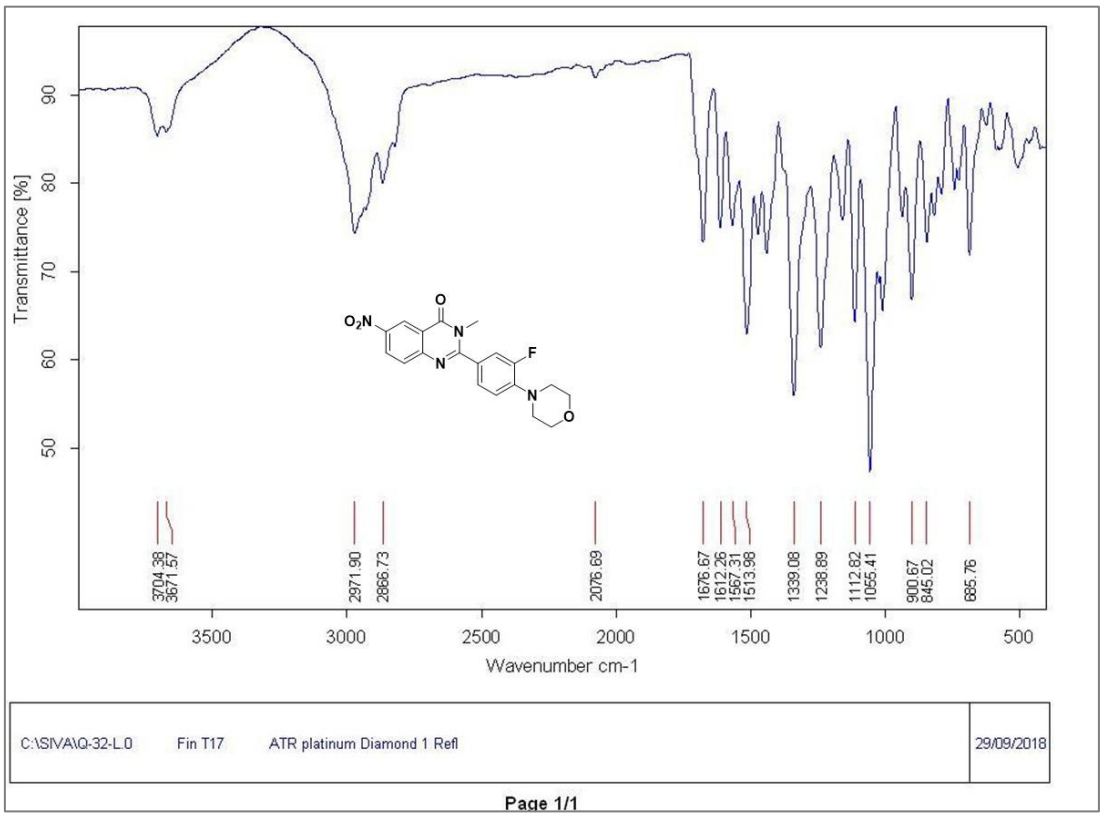
IR spectrum of compound 13 (Chapter 5)



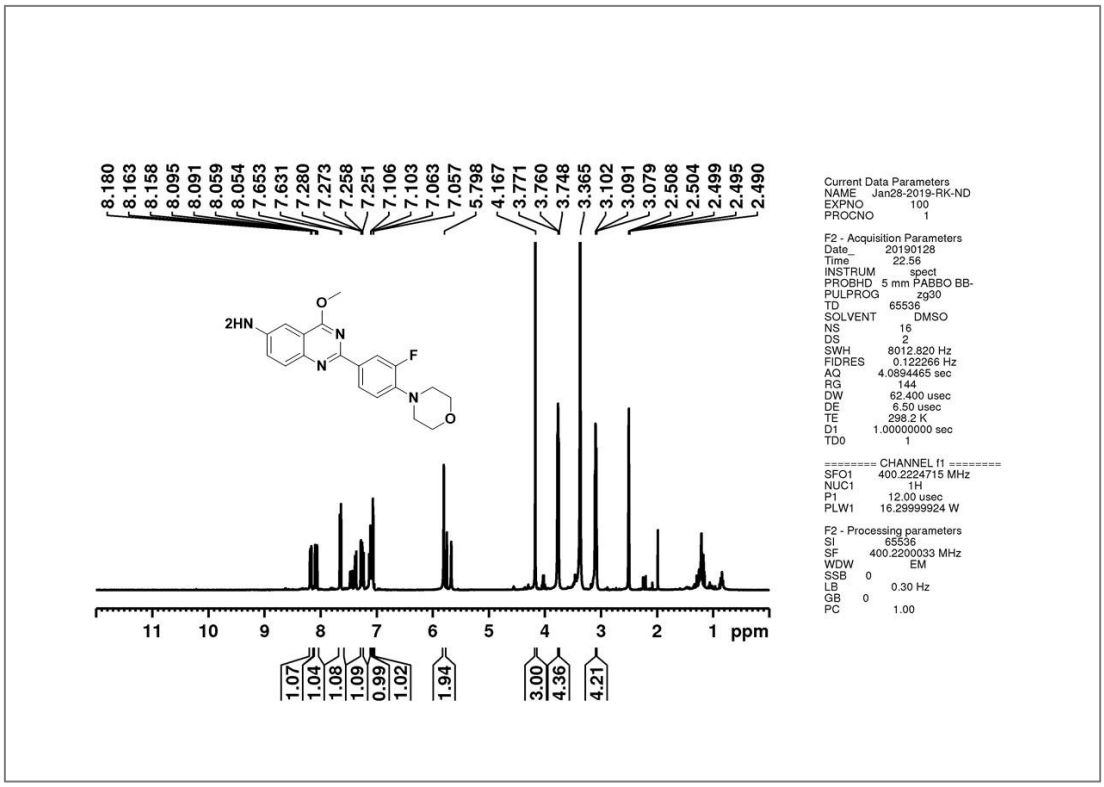
^{1}H NMR spectrum of compound 13a (Chapter 5)



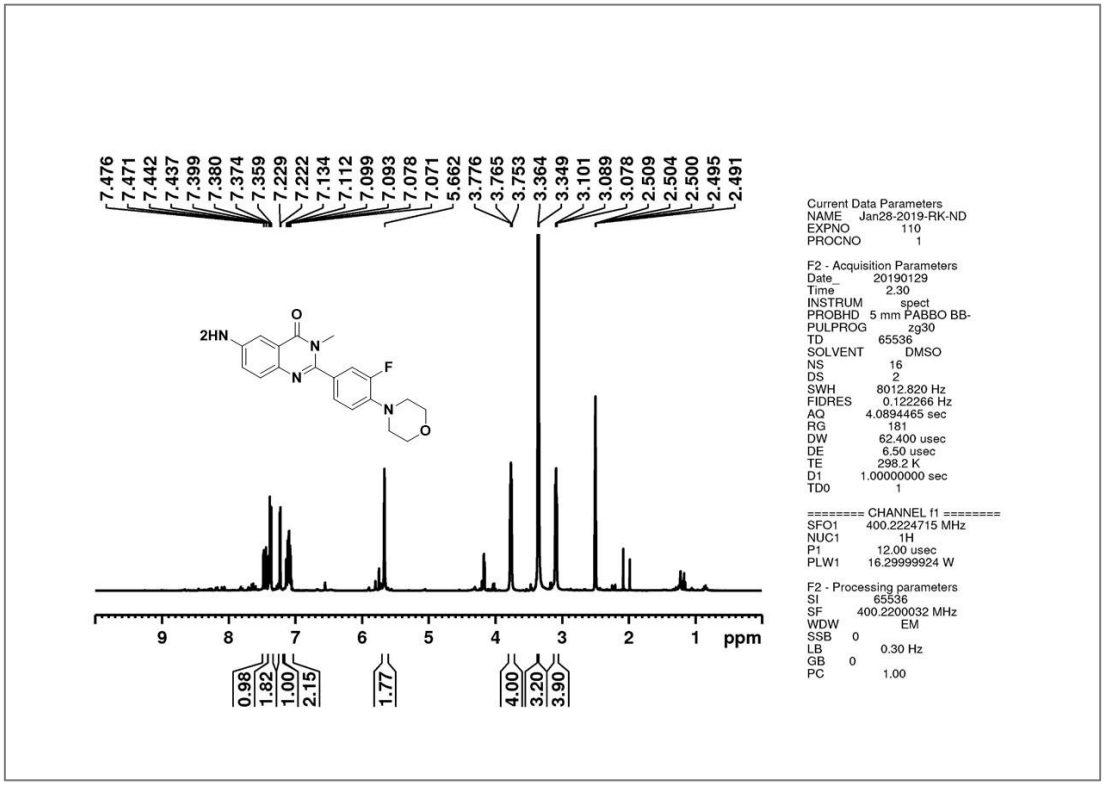
^{13}C NMR spectrum of compound 13a (Chapter 5)



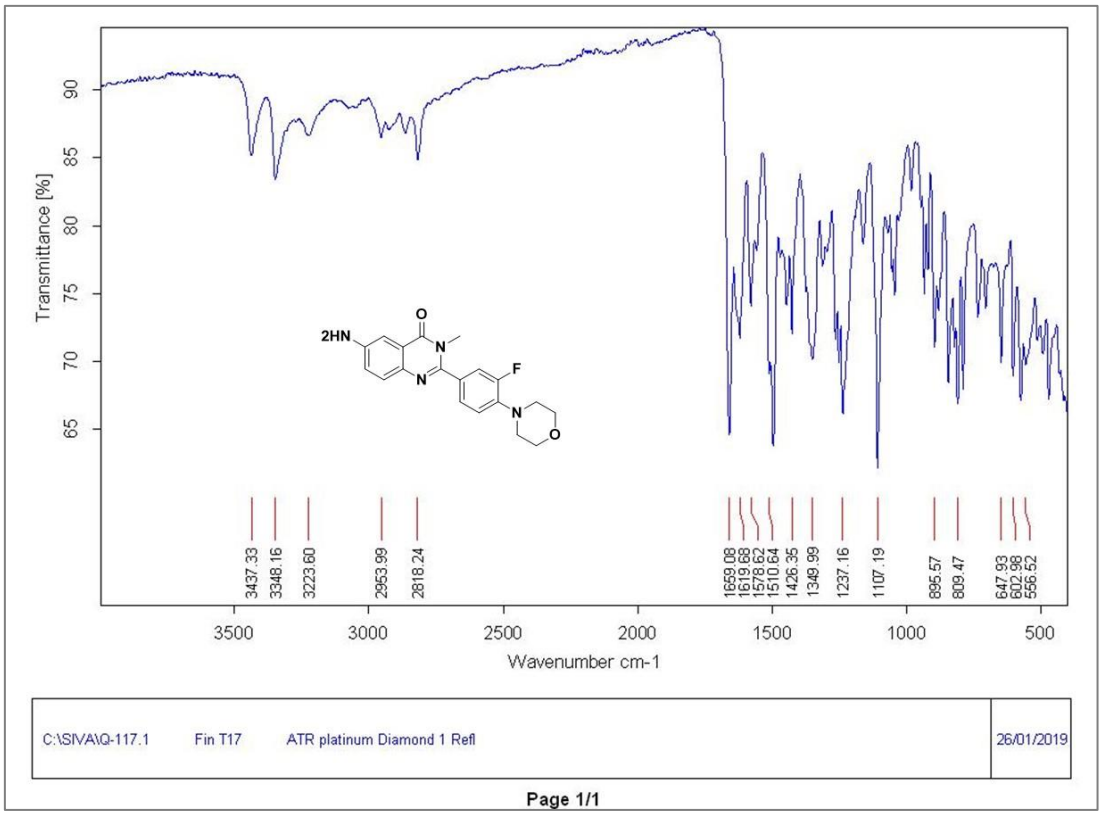
IR spectrum of compound 13a (Chapter 5)



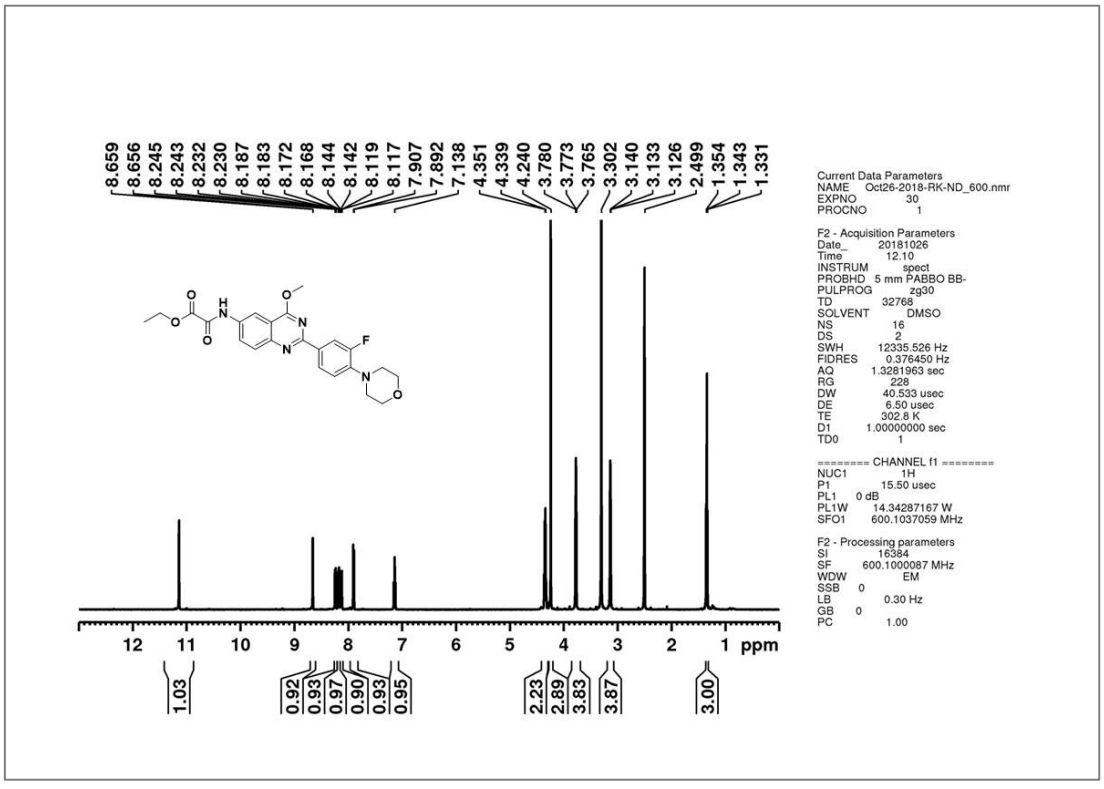
[1]H NMR spectrum of compound 14 (Chapter 5)



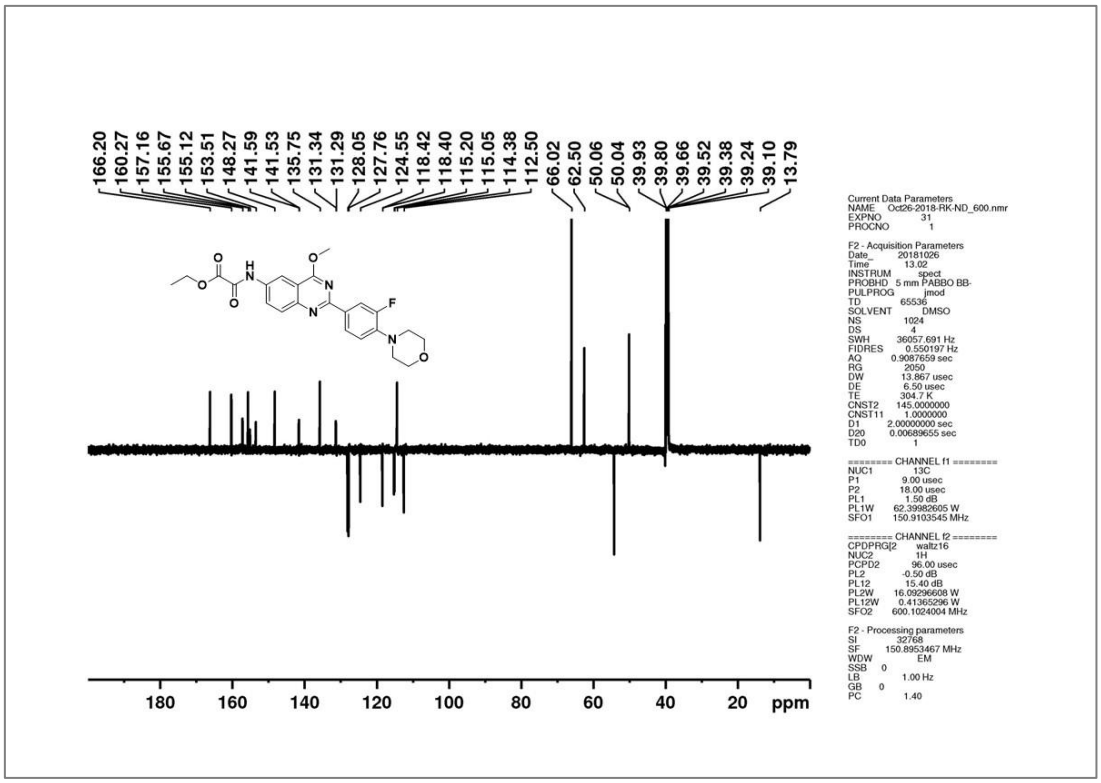
[1]H NMR spectrum of compound 14a (Chapter 5)



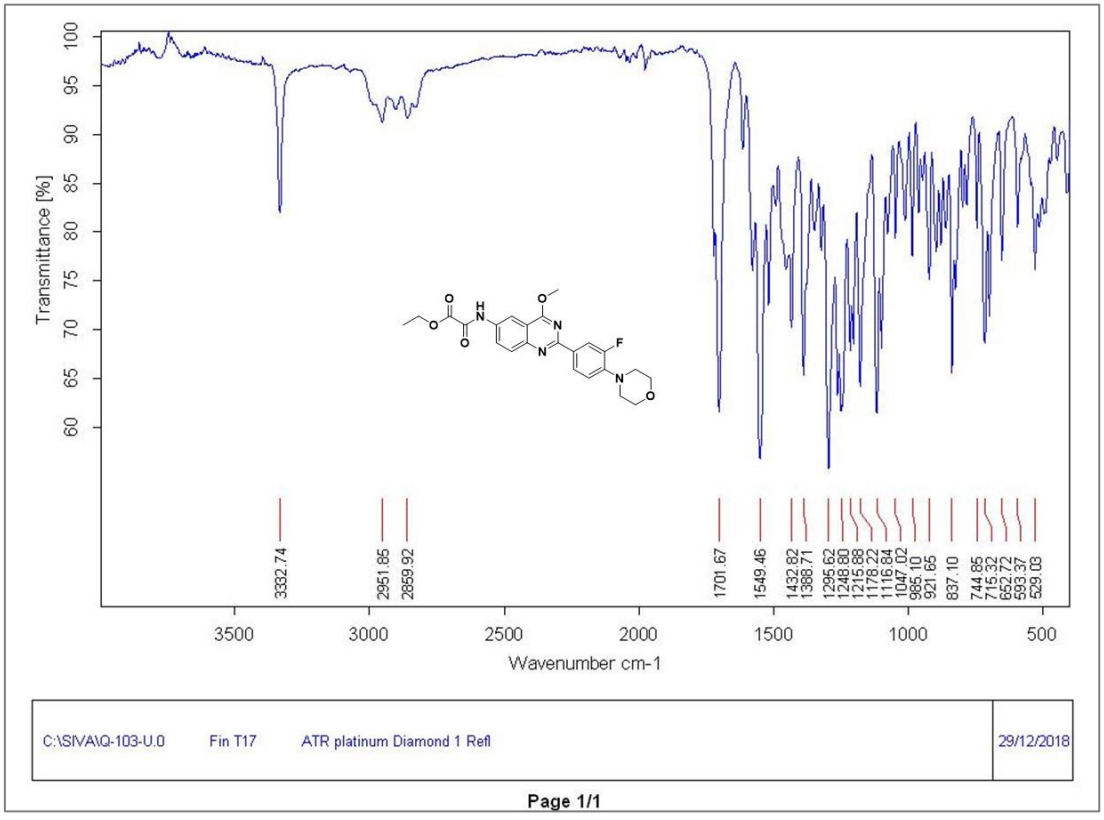
IR spectrum of compound 14a (Chapter 5)



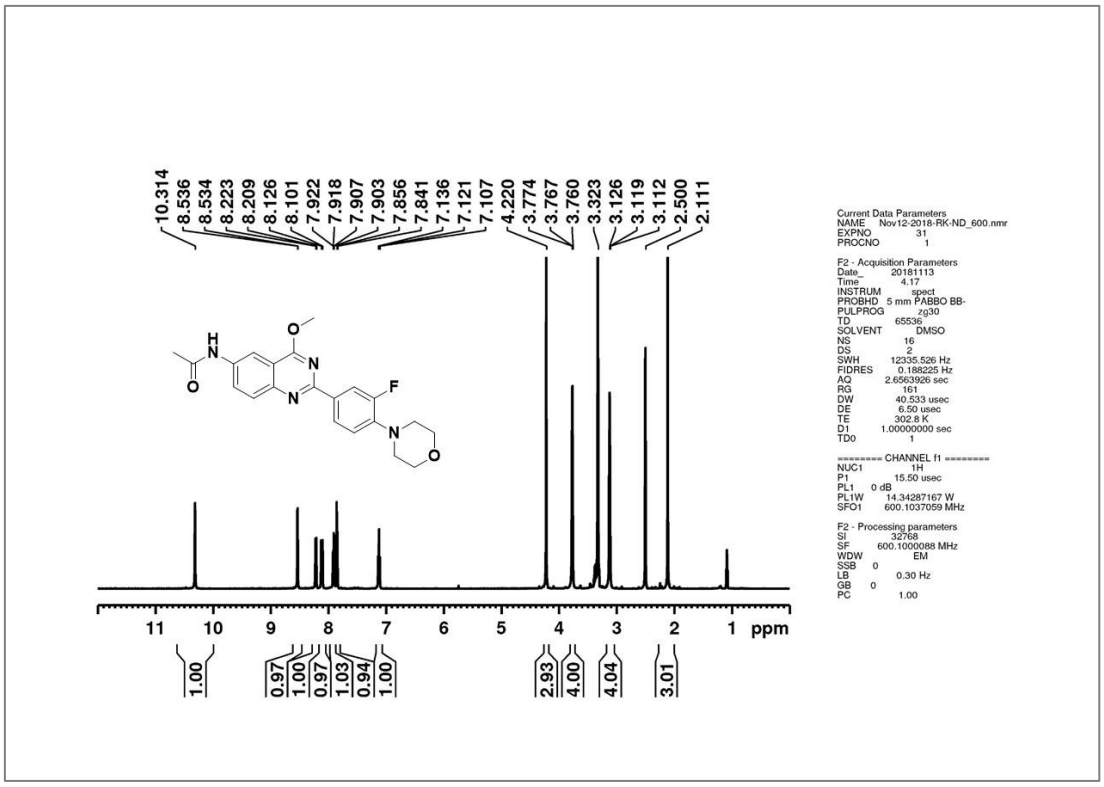
^{1}H NMR spectrum of compound 16a (Chapter 5)



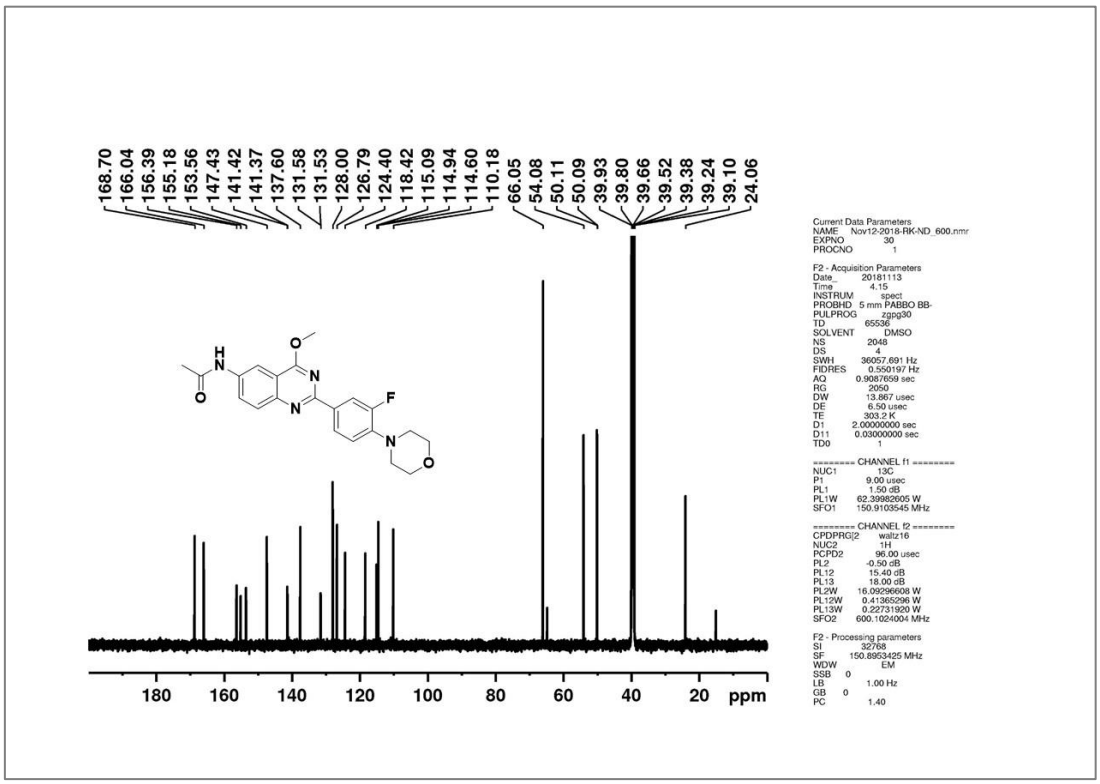
^{13}C NMR spectrum of compound 16a (Chapter 5)



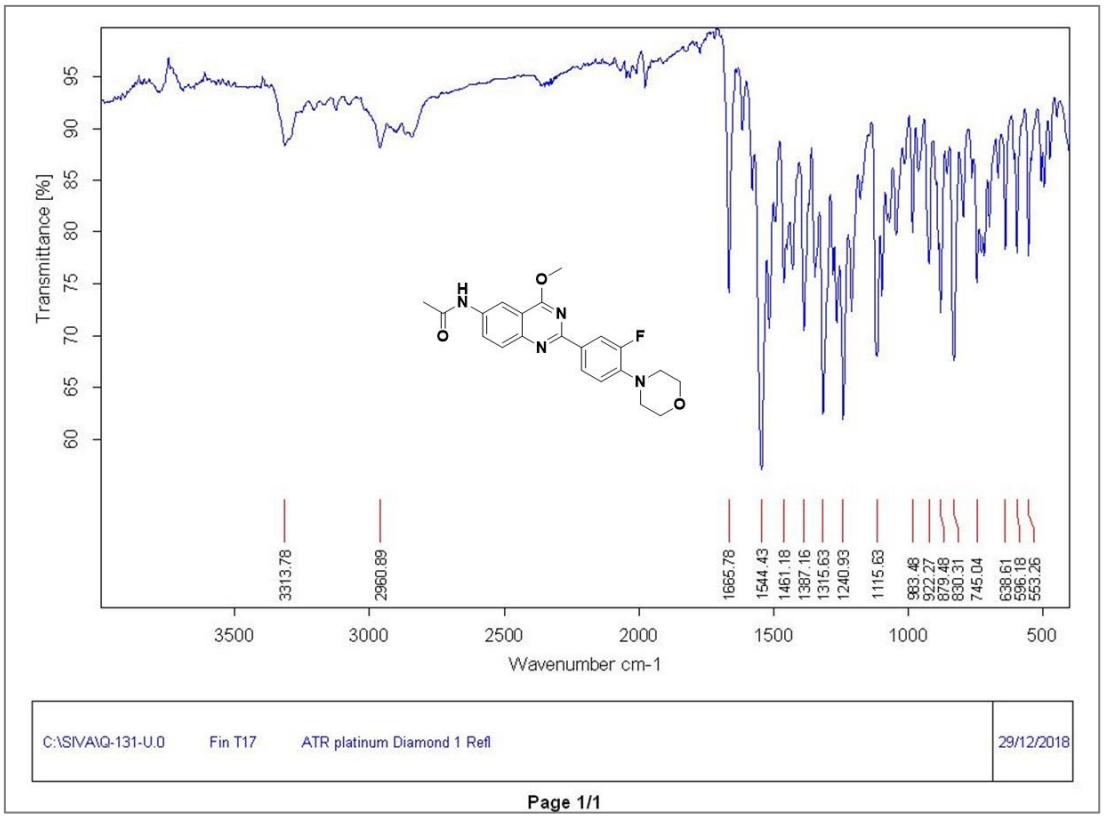
IR spectrum of compound 16a (Chapter 5)



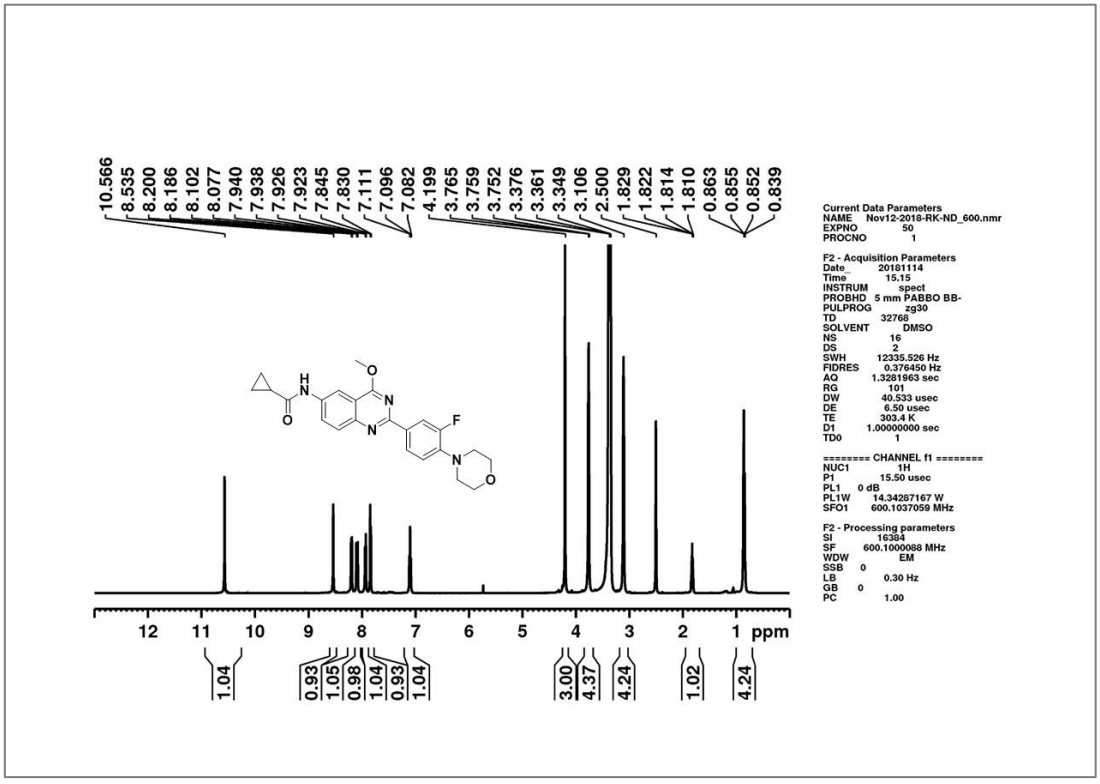
^{1}H NMR spectrum of compound 16b (Chapter 5)



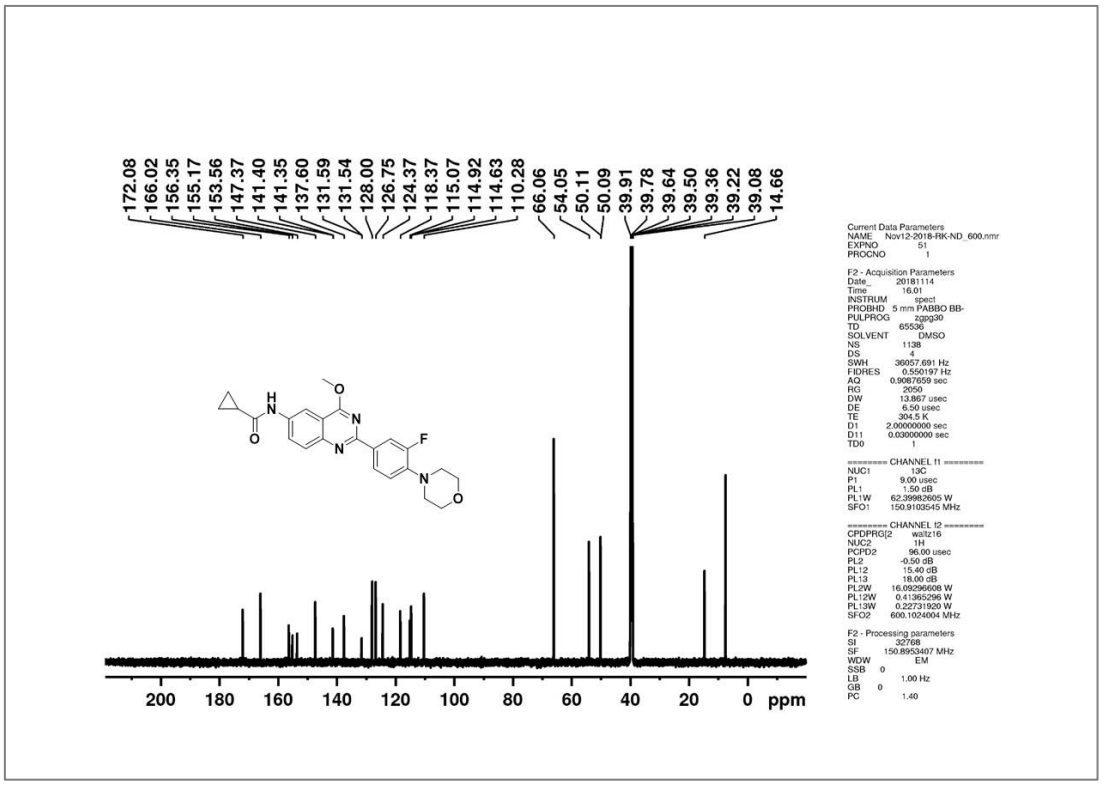
^{13}C NMR spectrum of compound 16b (Chapter 5)



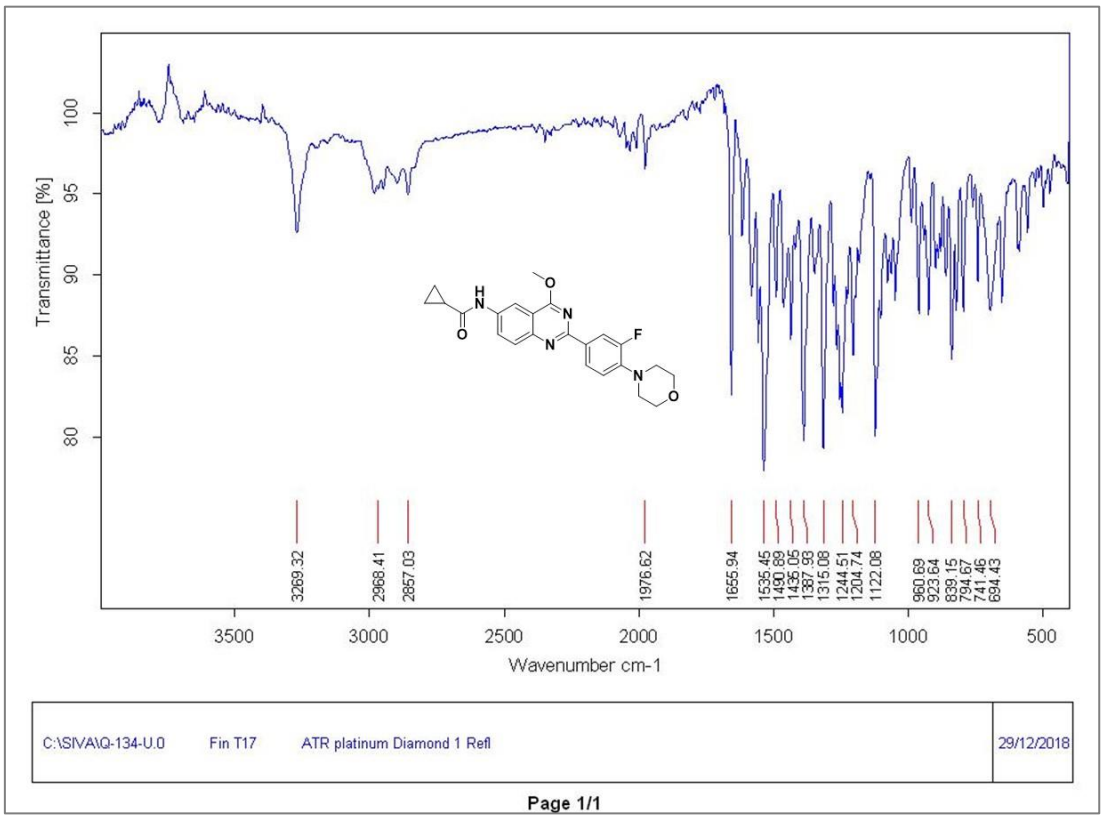
IR spectrum of compound 16b (Chapter 5)



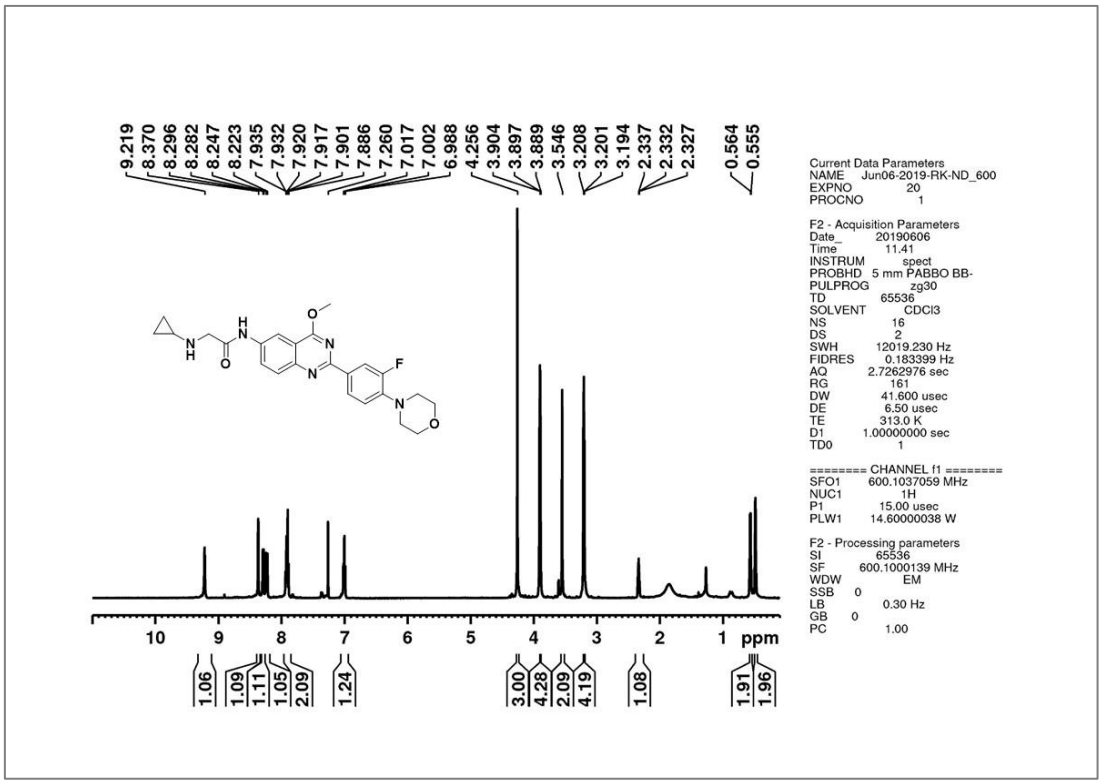
^{1}H NMR spectrum of compound 16c (Chapter 5)



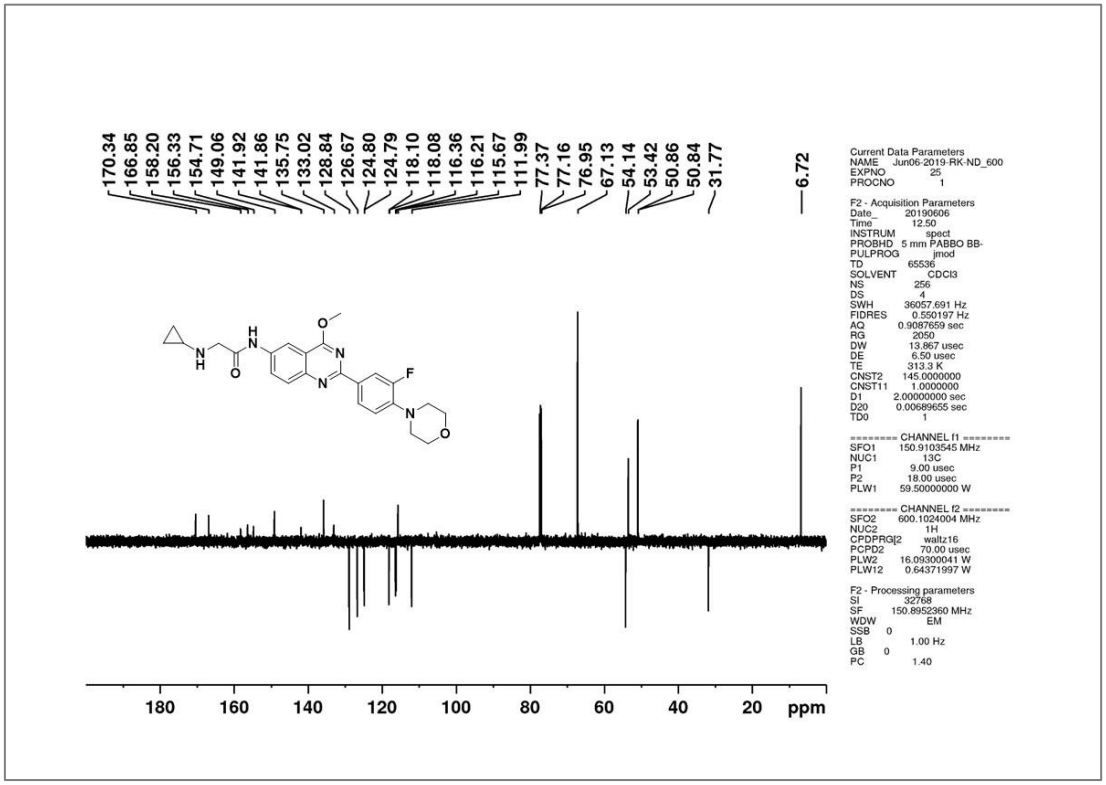
^{13}C NMR spectrum of compound 16c (Chapter 5)



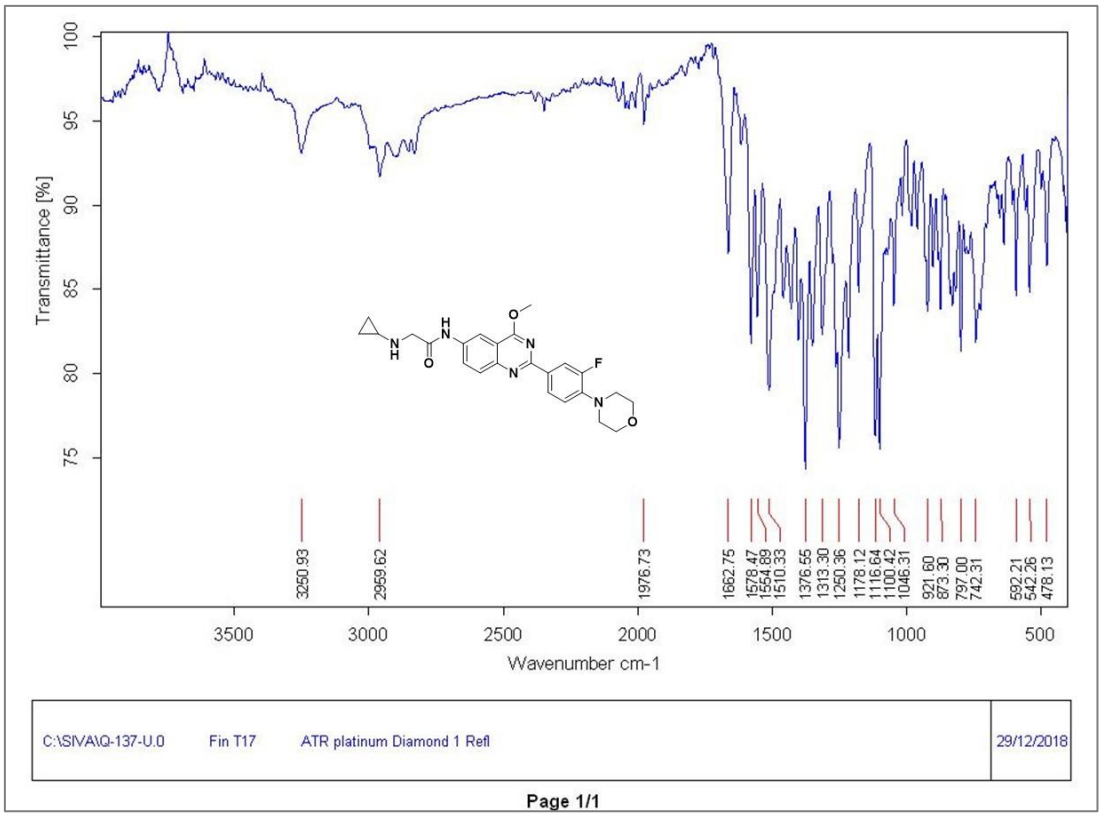
IR spectrum of compound 16c (Chapter 5)



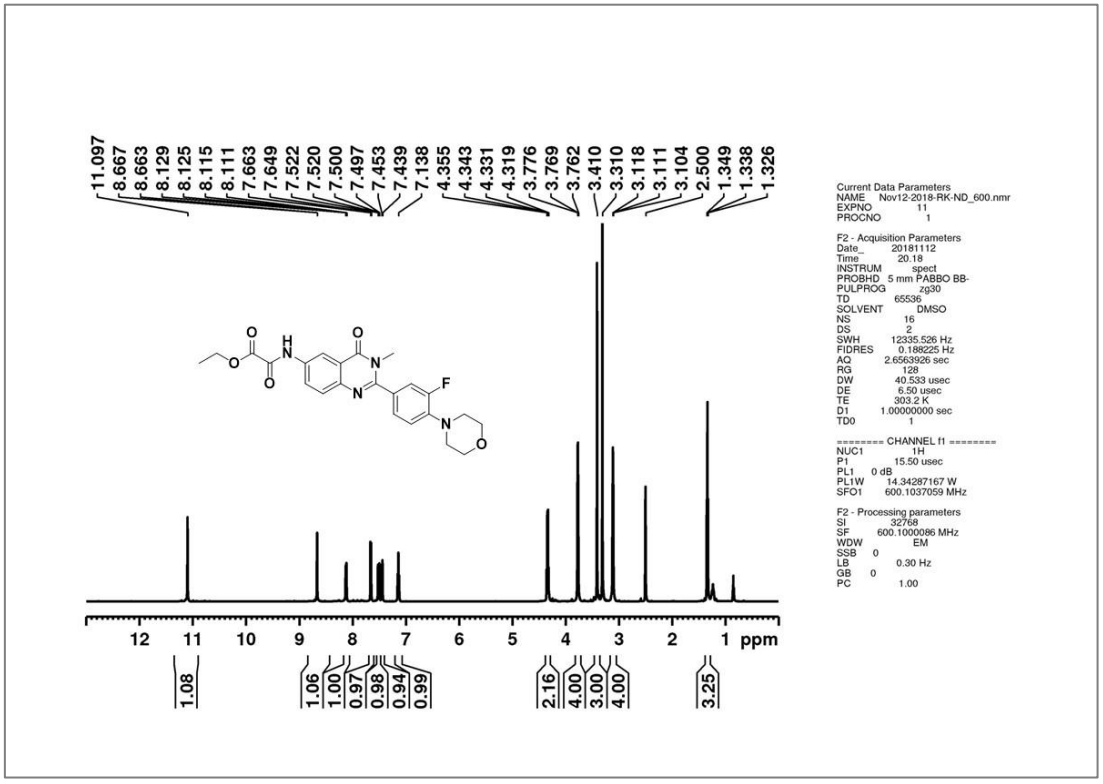
^{1}H NMR spectrum of compound 16d (Chapter 5)



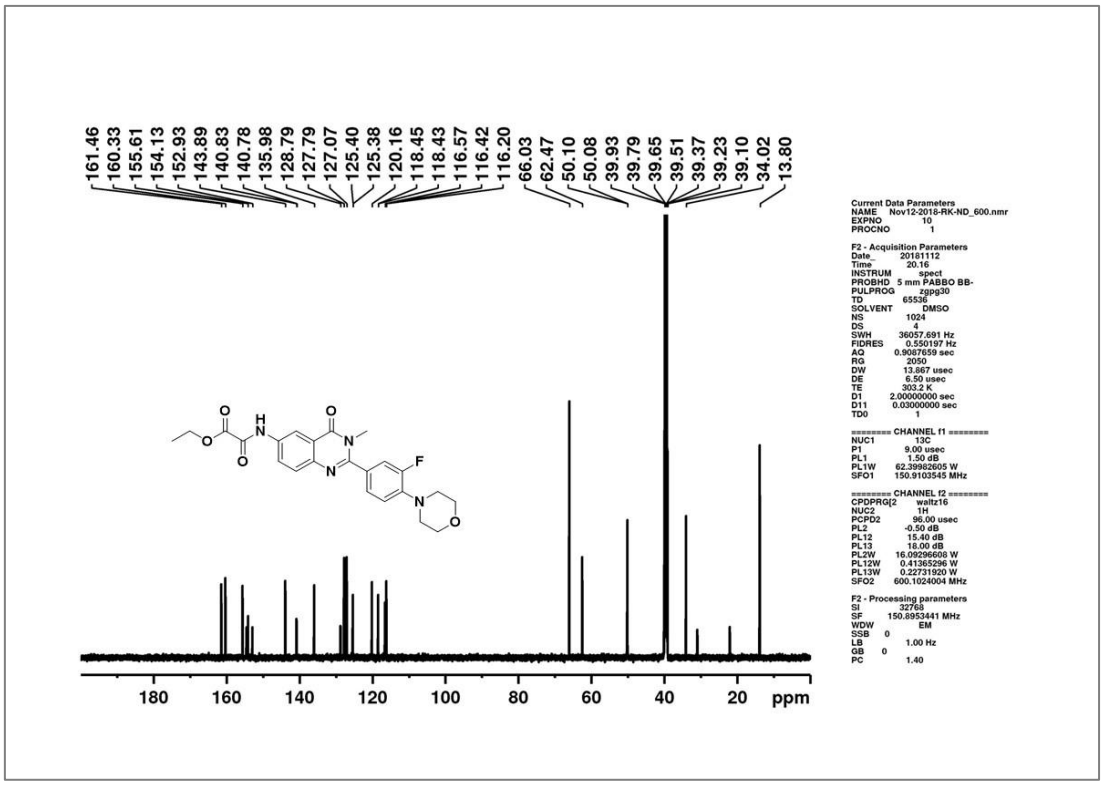
^{13}C NMR spectrum of compound 16d (Chapter 5)



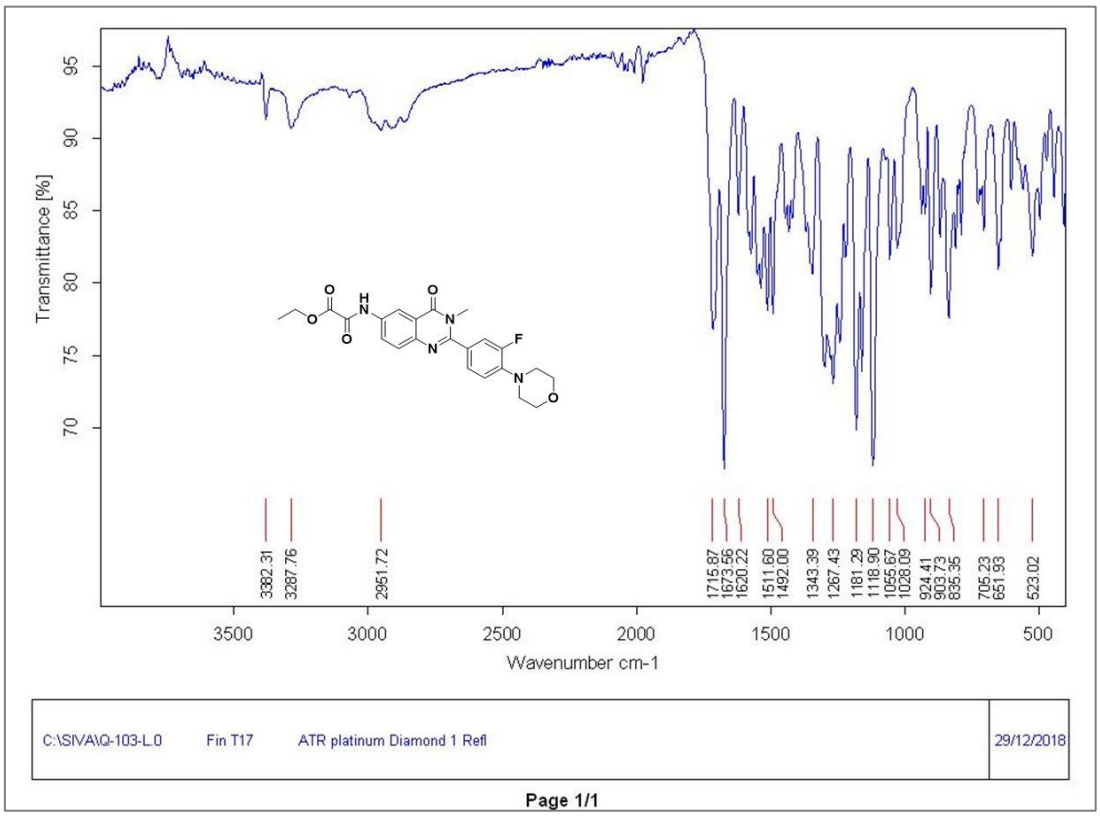
IR spectrum of compound 16d (Chapter 5)



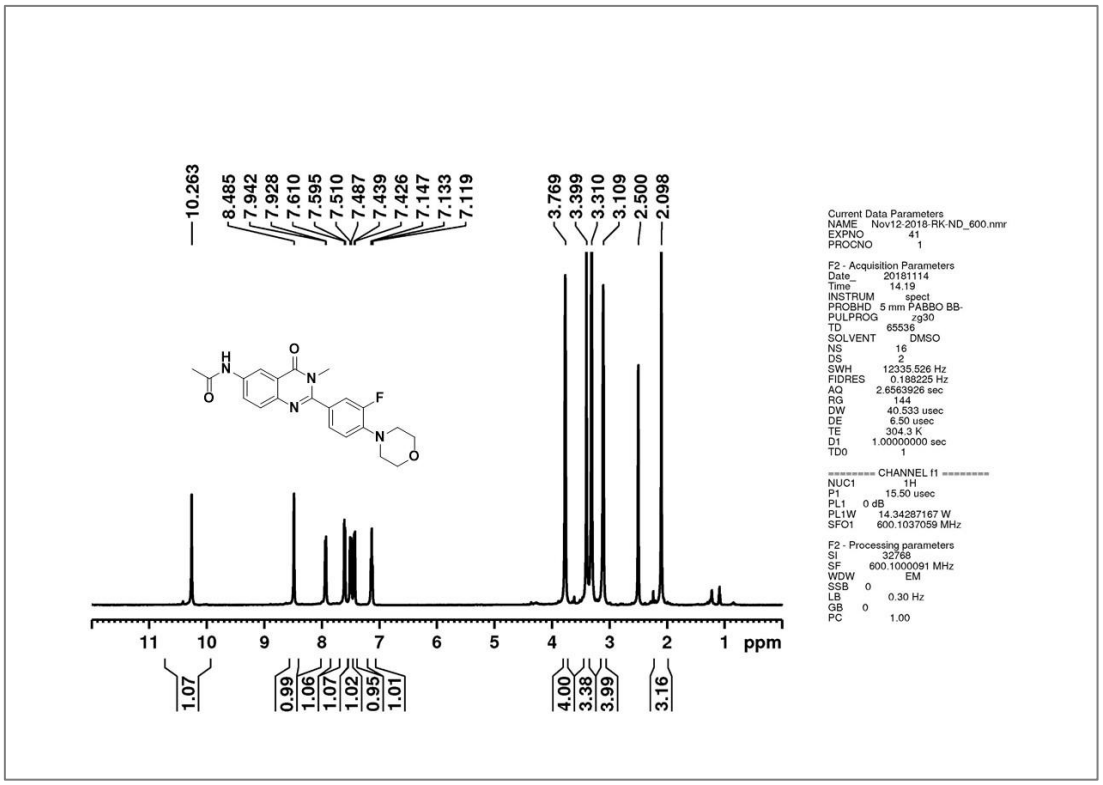
^{1}H NMR spectrum of compound 16aa (Chapter 5)



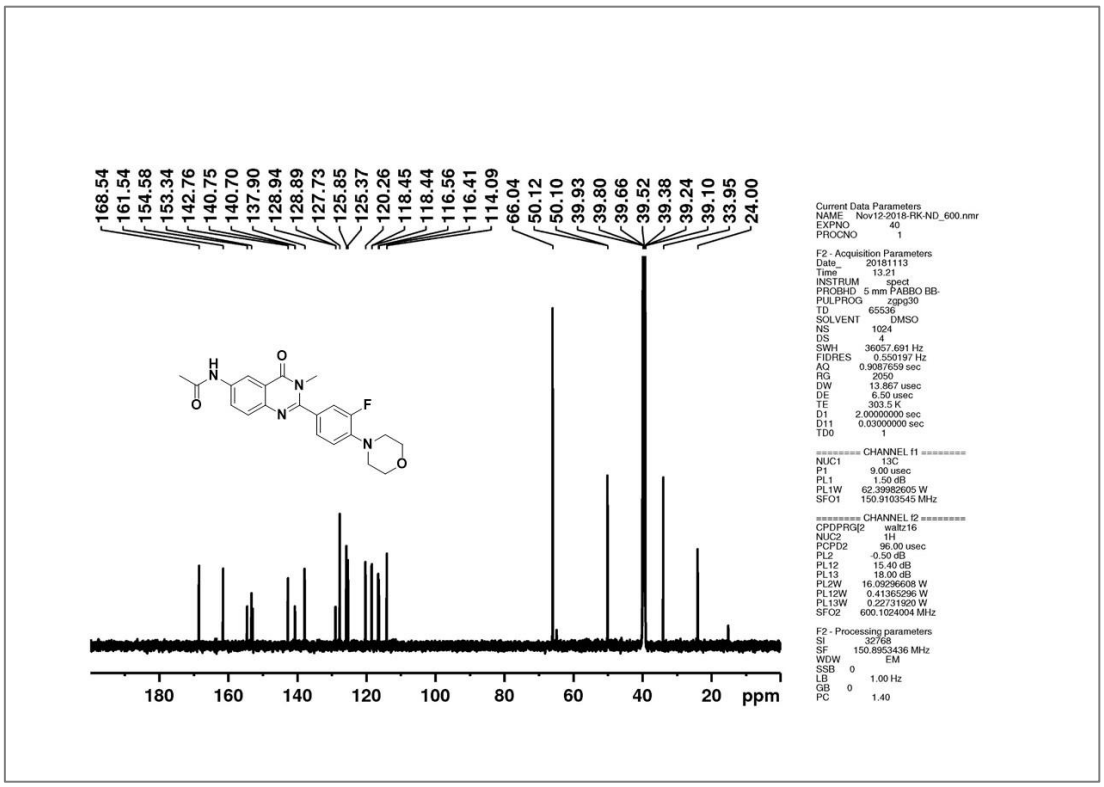
^{13}C NMR spectrum of compound 16aa (Chapter 5)



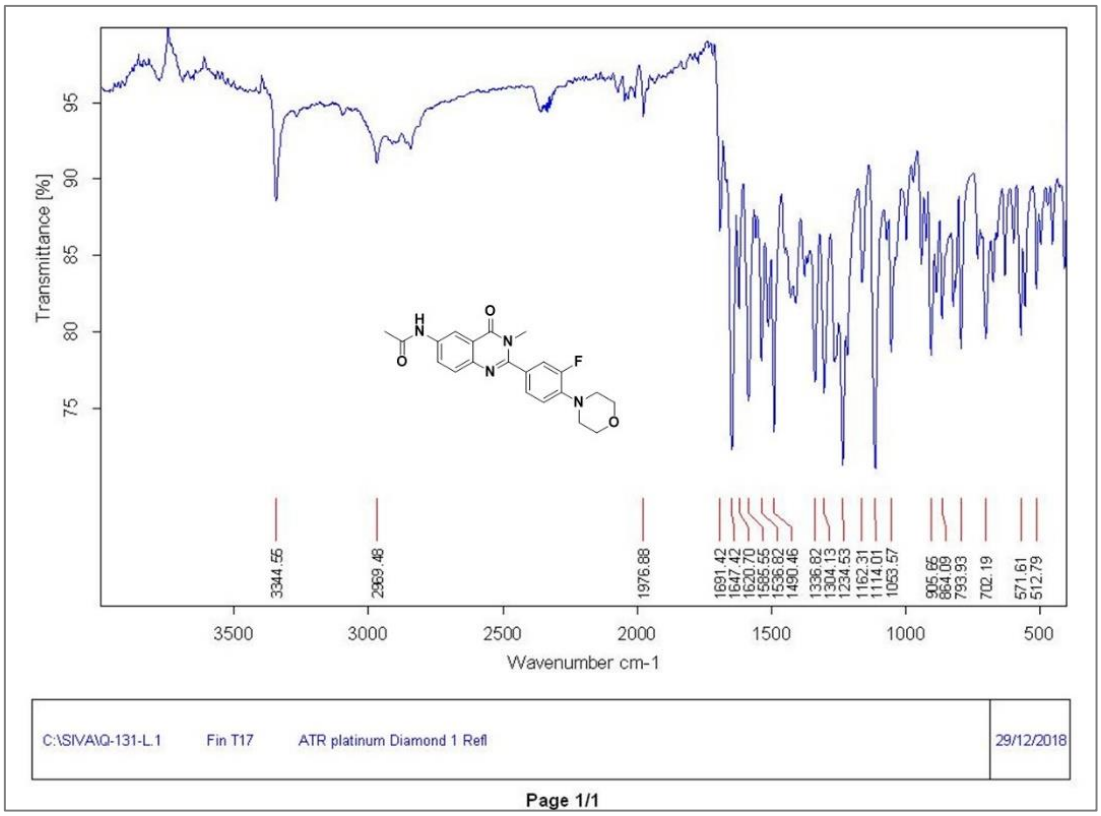
IR spectrum of compound 16aa (Chapter 5)



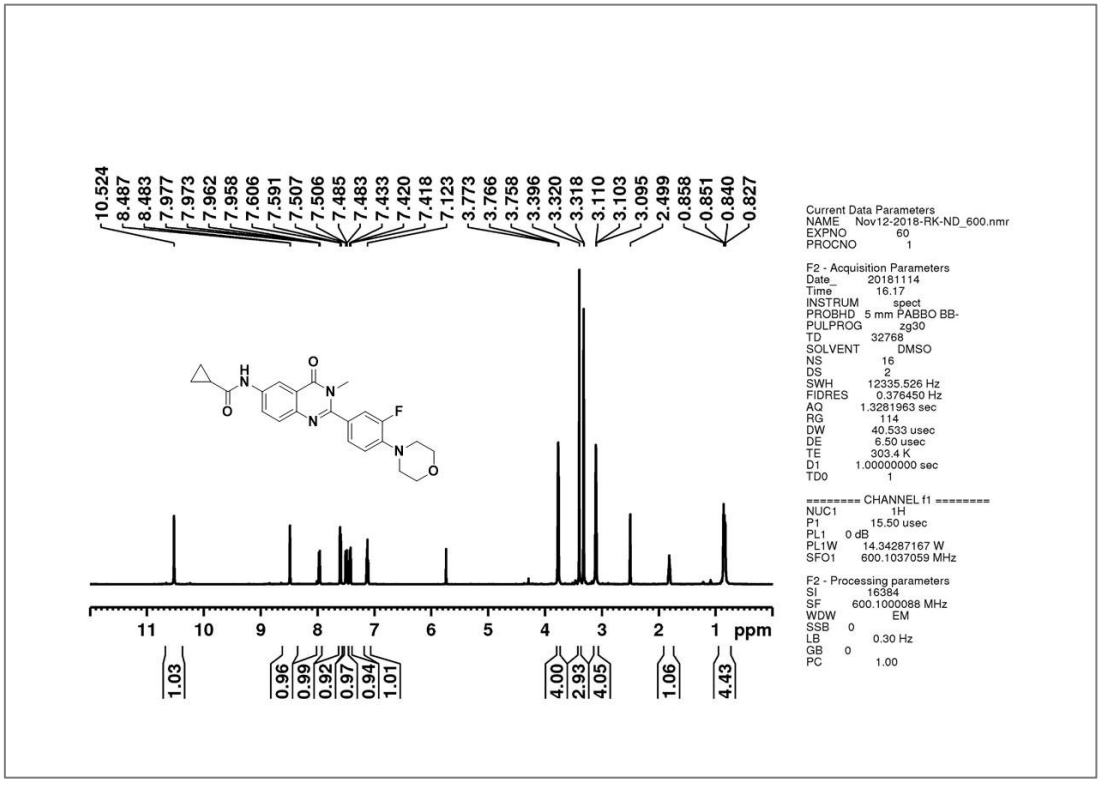
^{1}H NMR spectrum of compound 16ab (Chapter 5)



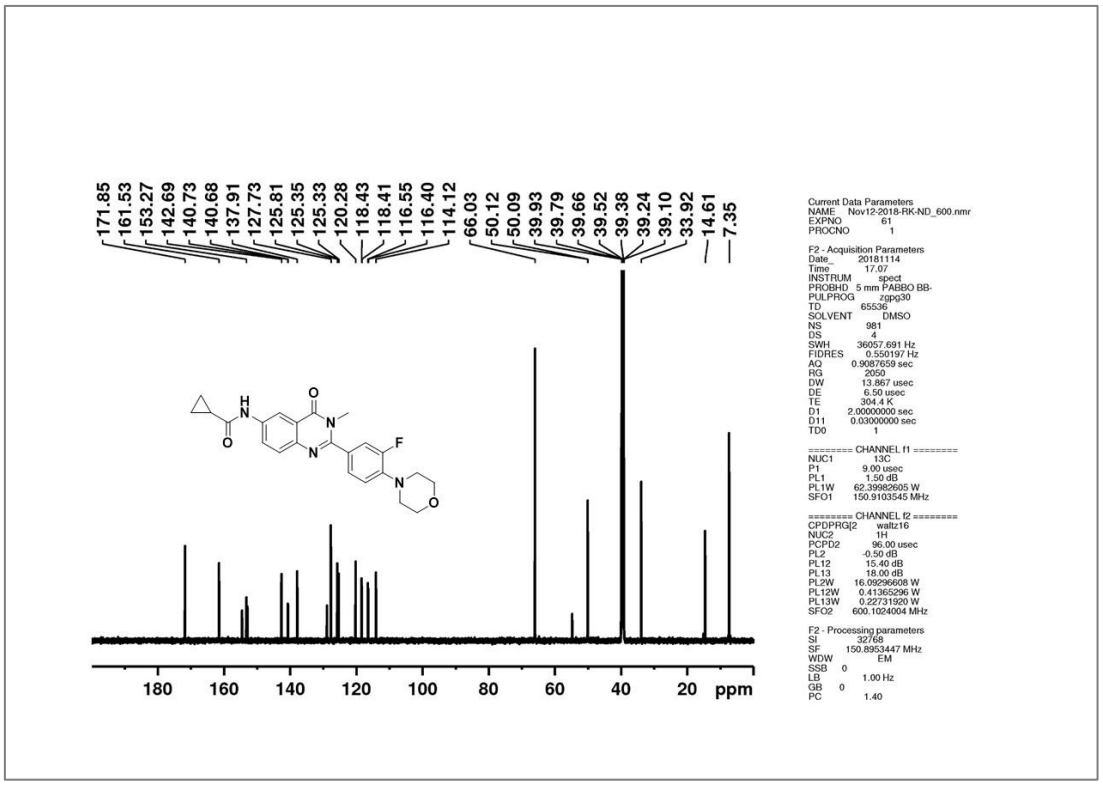
^{13}C NMR spectrum of compound 16ab (Chapter 5)



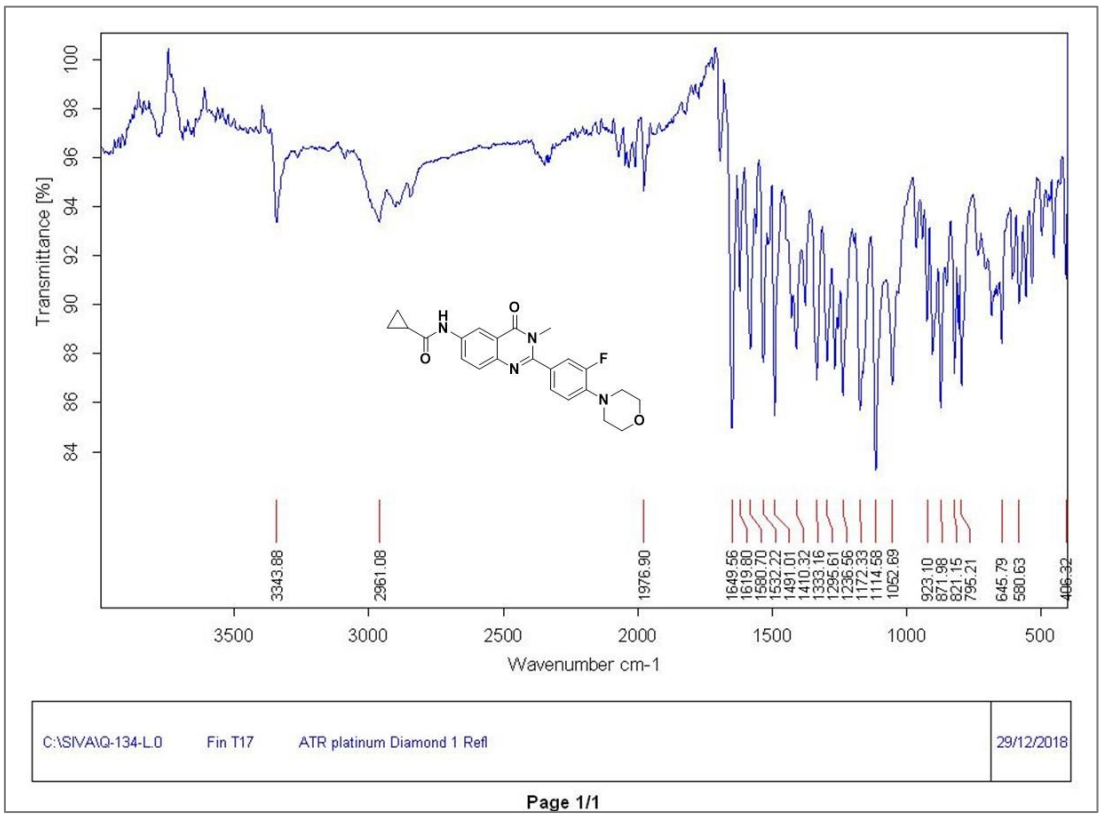
IR spectrum of compound 16ab (Chapter 5)



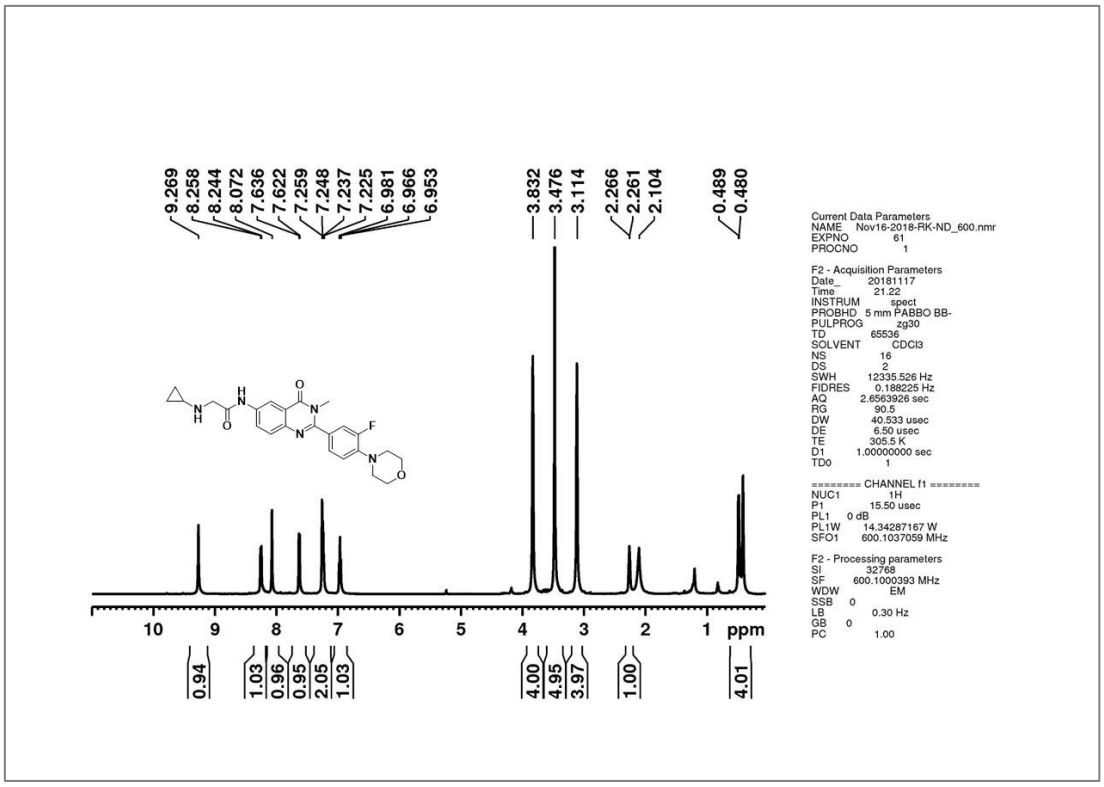
^{1}H NMR spectrum of compound 16ac (Chapter 5)



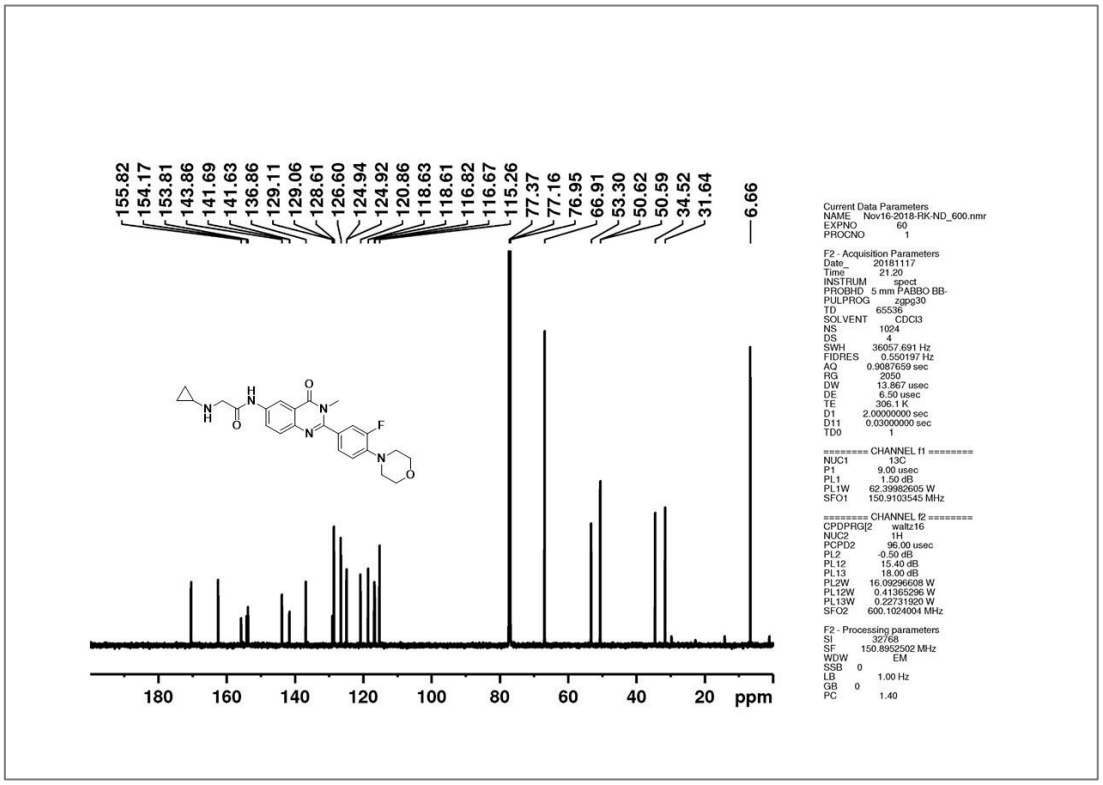
^{13}C NMR spectrum of compound 16ac (Chapter 5)



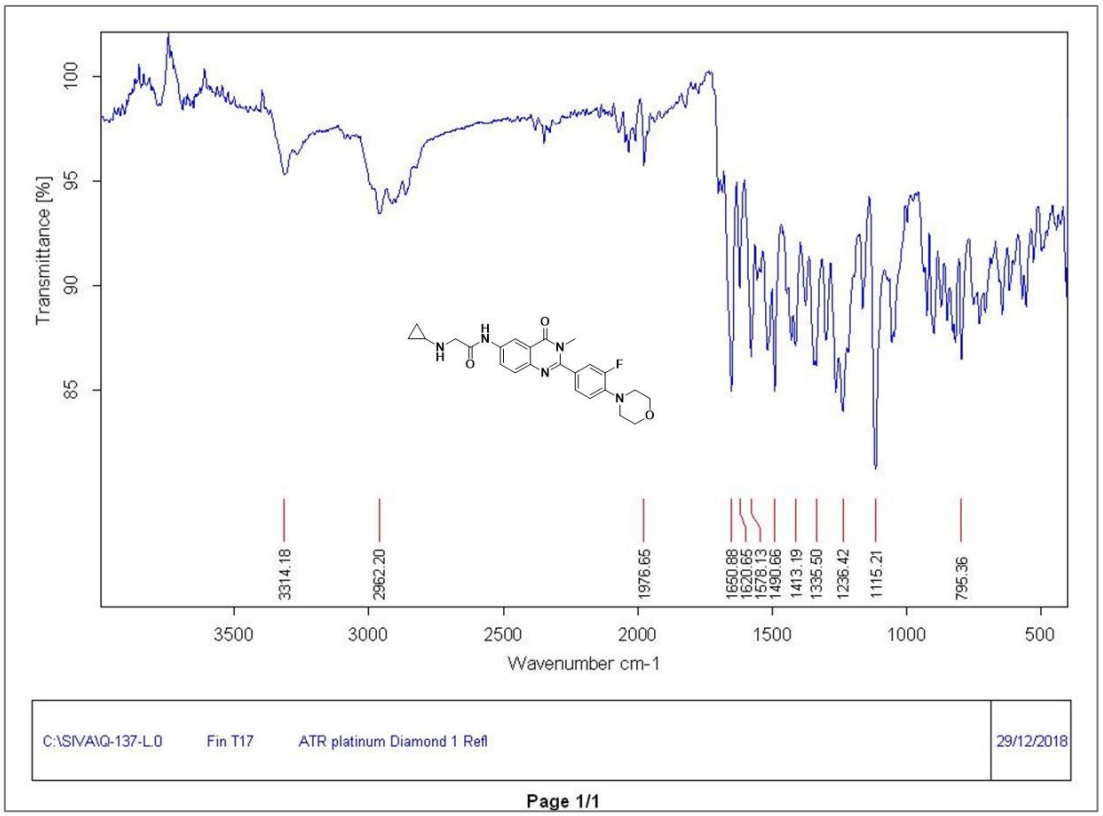
IR spectrum of compound 16ac (Chapter 5)



[1]H NMR spectrum of compound 16ad (Chapter 5)



[13]C NMR spectrum of compound 16ad (Chapter 5)



IR spectrum of compound 16ad (Chapter 5)

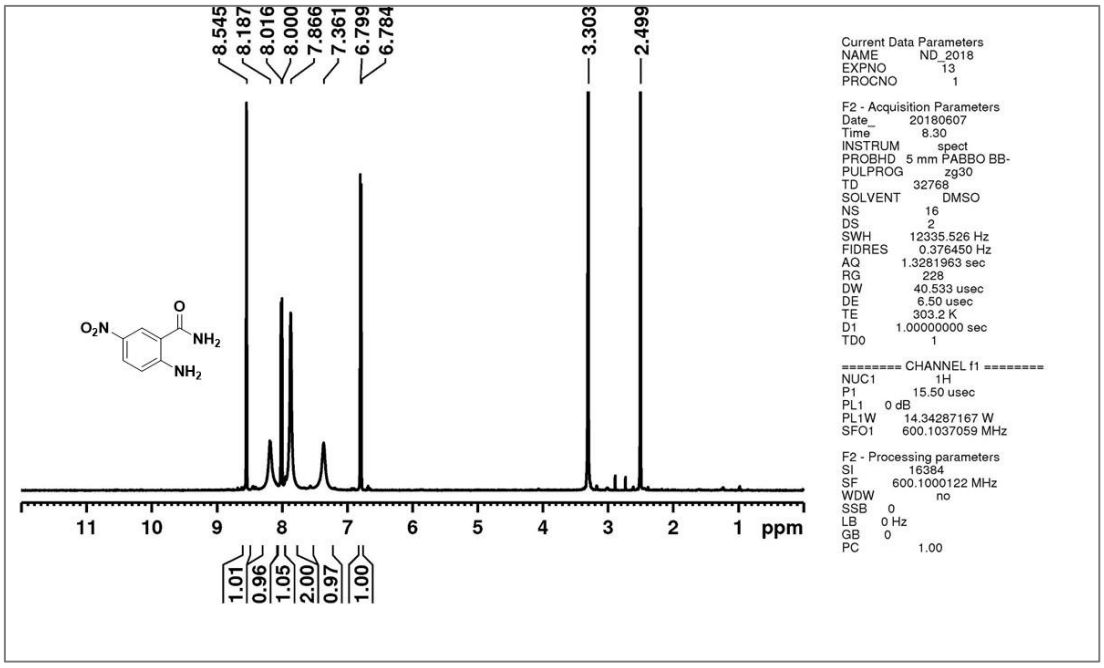
APPENDIX – V

SUPPLEMENTARY INFORMATION

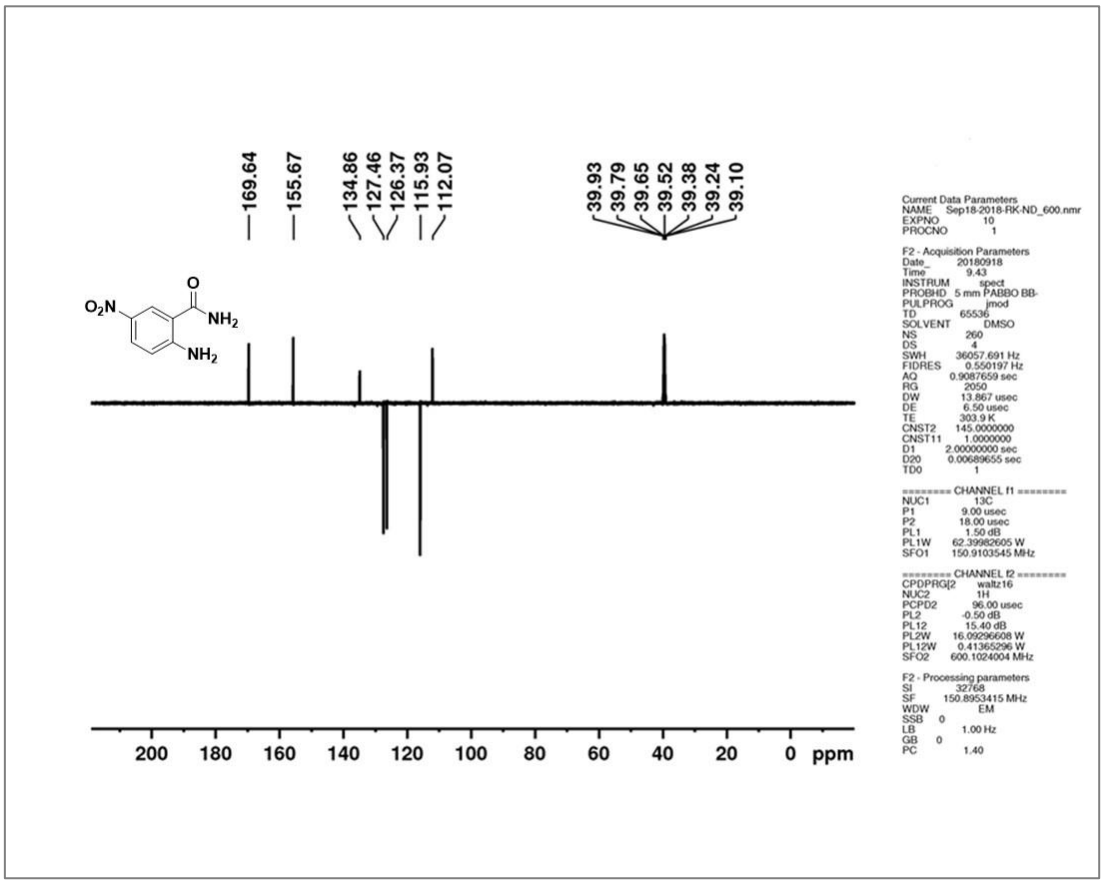
CHAPTER 6

Discovery of Quinazoline-based DNA Gyrase Inhibitors as Potential Anti-tubercular Agents

Department of Pharmaceutical Chemistry, Discipline of Pharmaceutical Sciences, College of Health Sciences, University of KwaZulu-Natal (Westville), Durban-4000, South Africa



[1]H NMR spectrum of compound 2 (Chapter 6)



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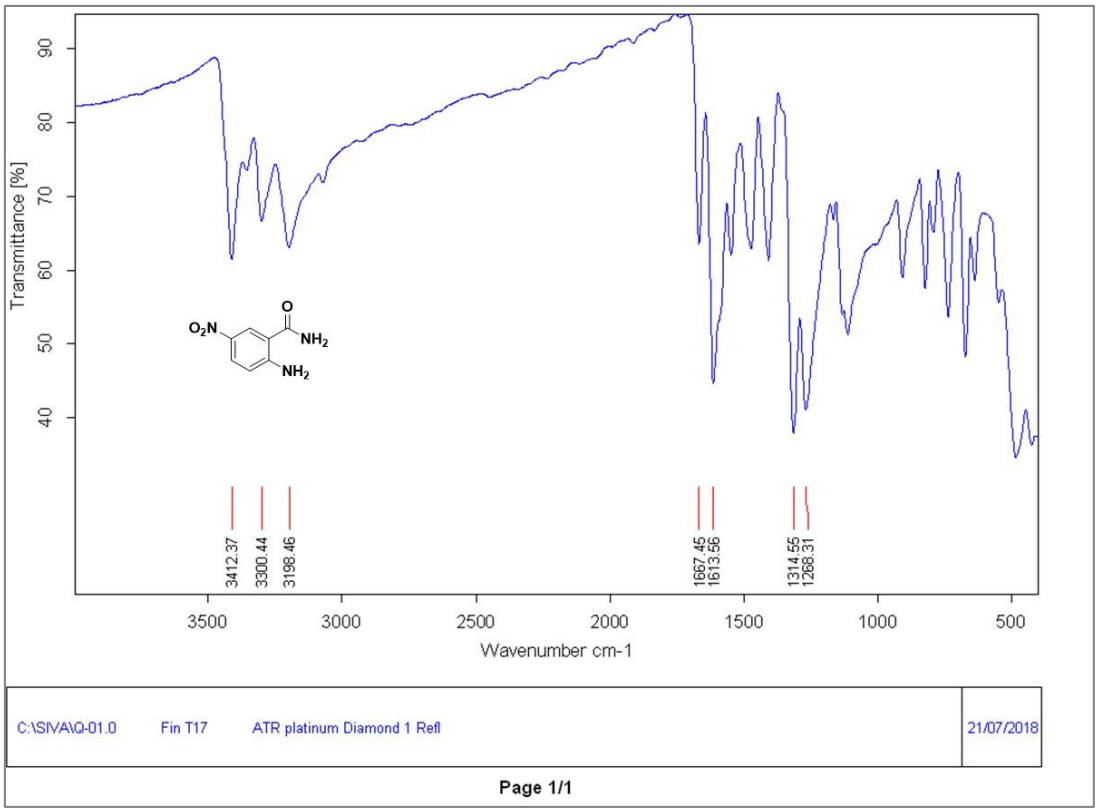
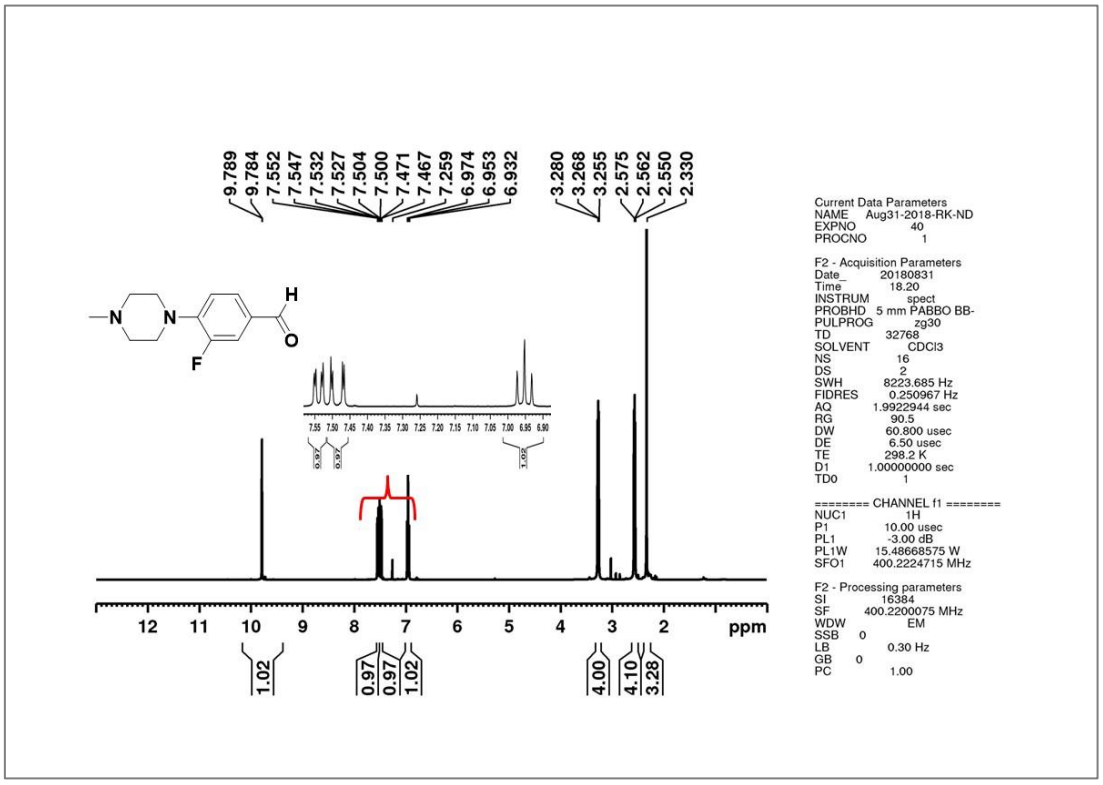
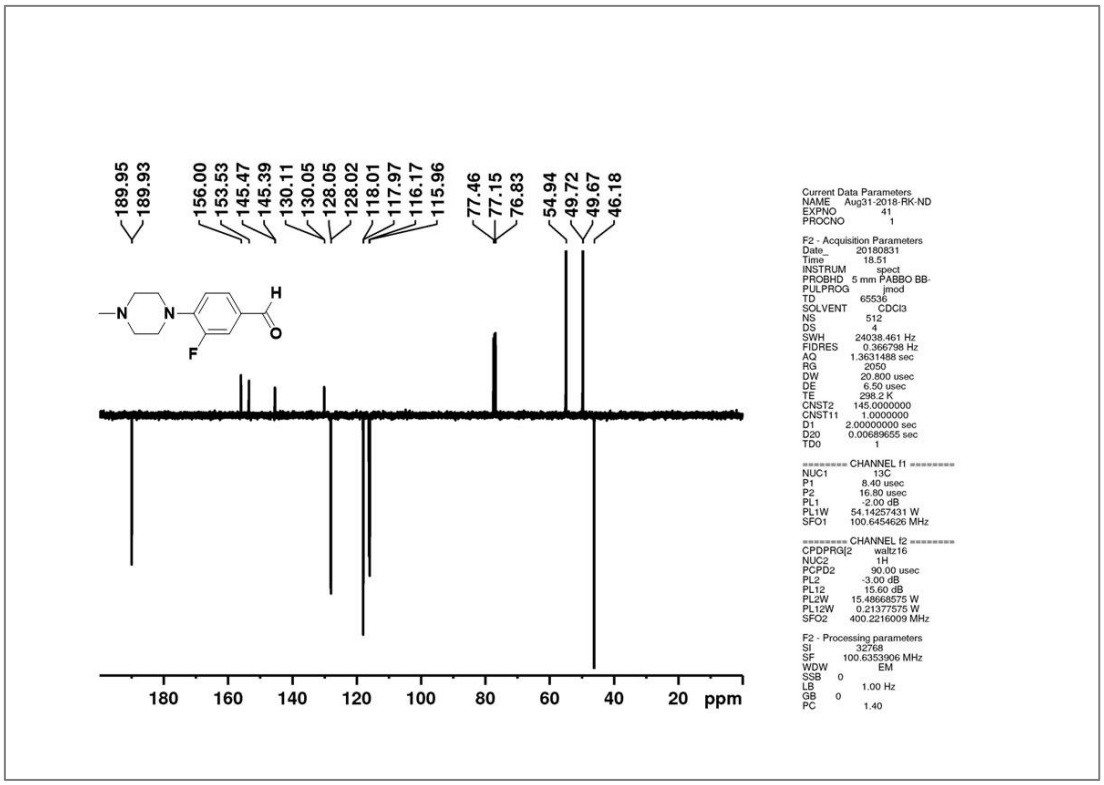


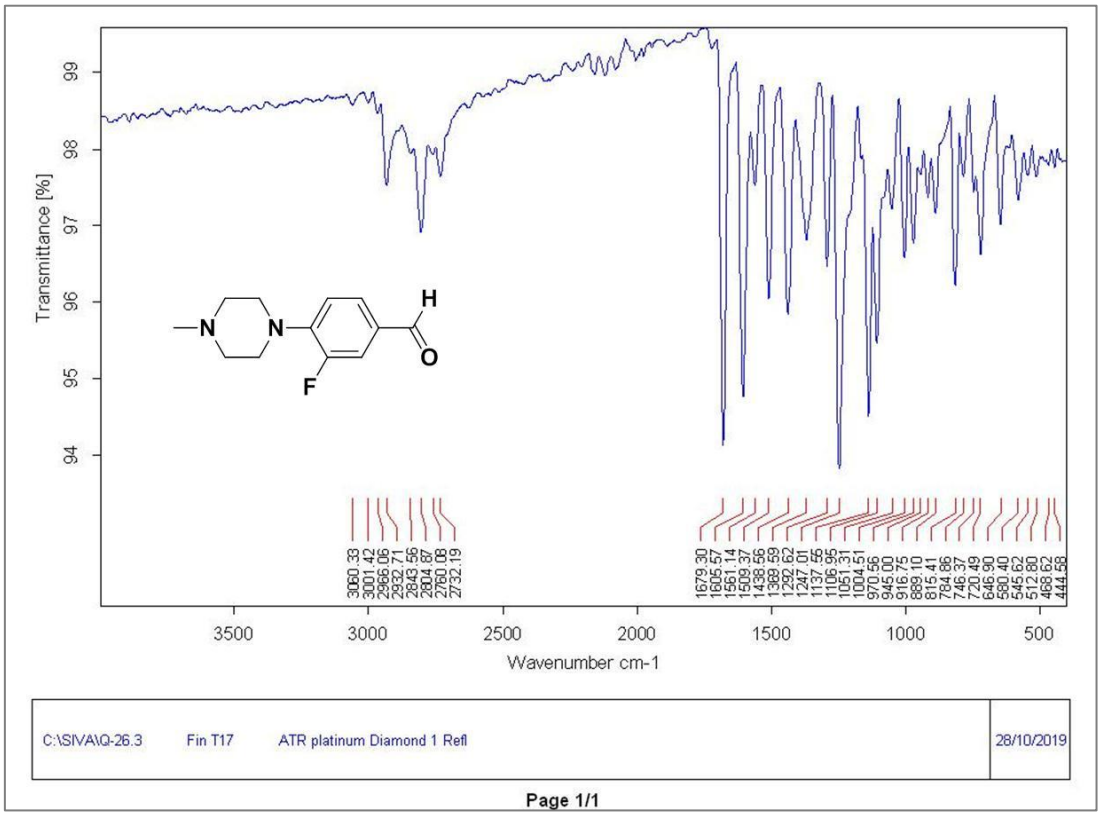
IR spectrum of compound 2 (Chapter 6)



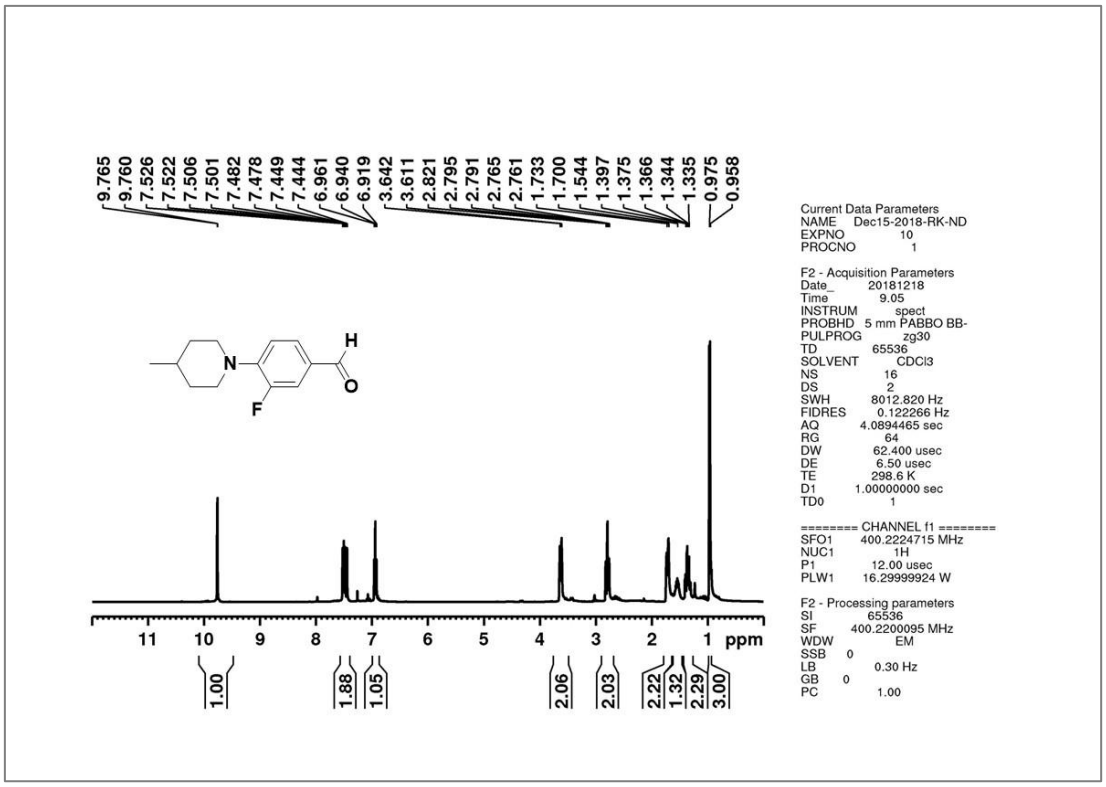
^{1}H NMR spectrum of compound 5a (Chapter 6)



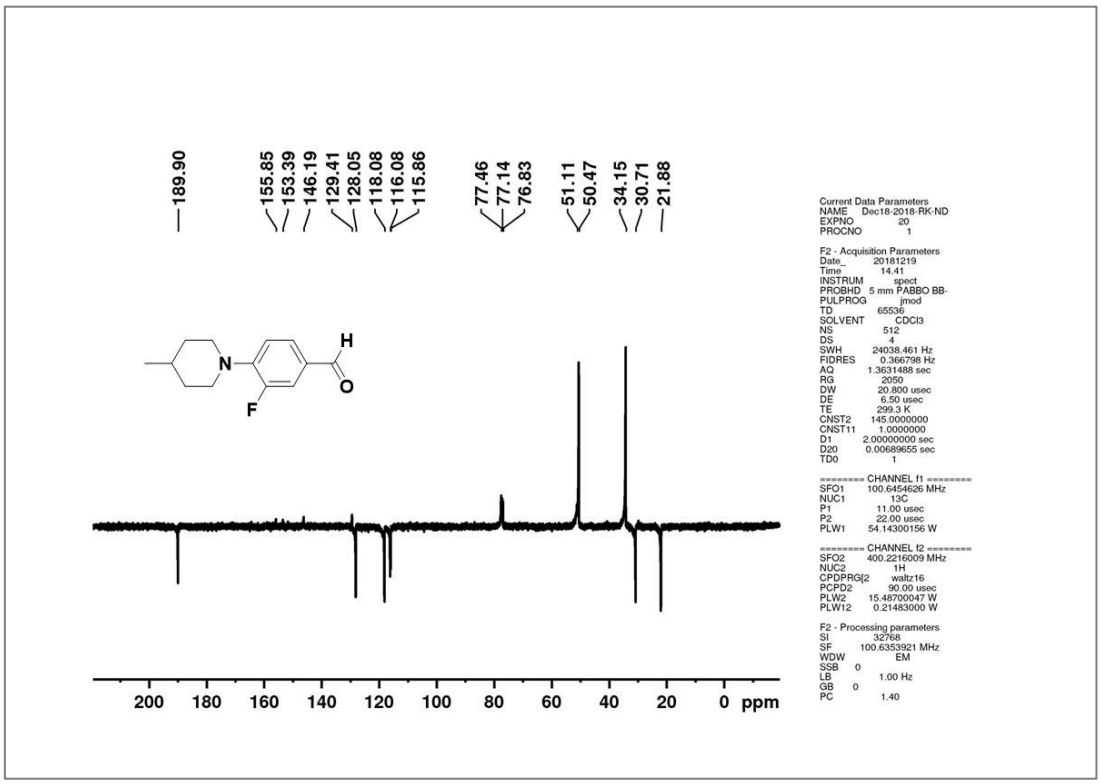
^{13}C NMR spectrum of compound 5a (Chapter 6)



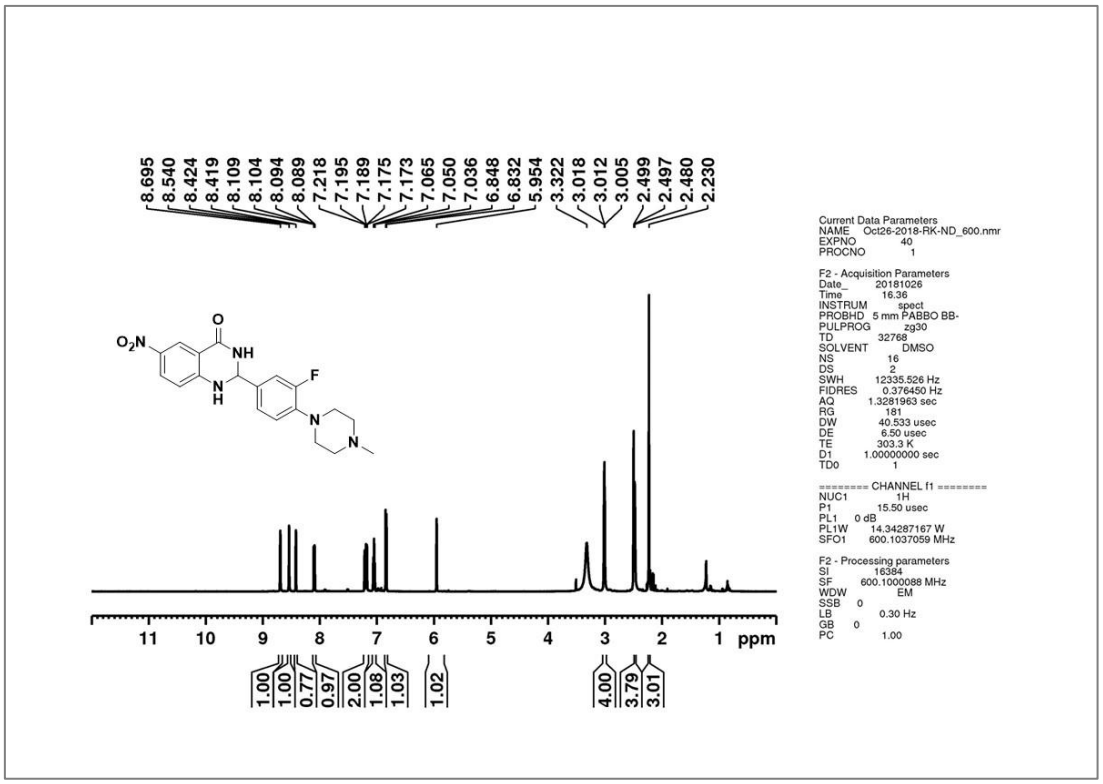
IR spectrum of compound 5a (Chapter 6)



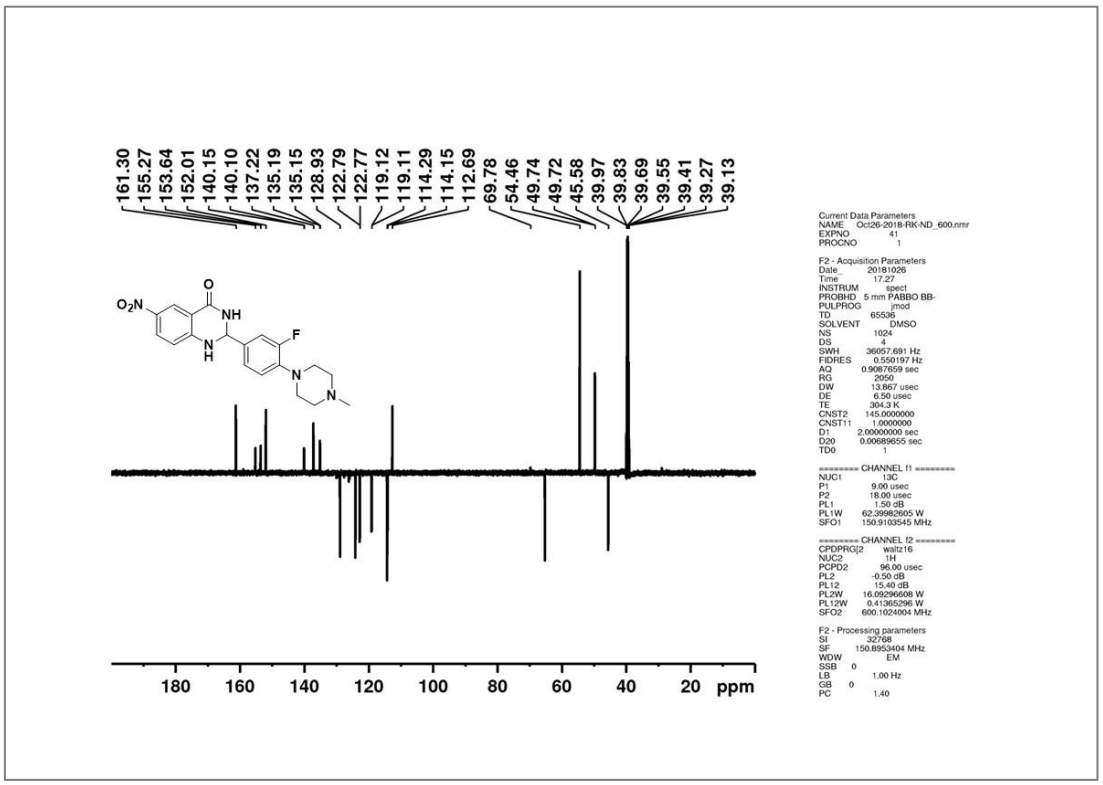
^{1}H NMR spectrum of compound 5b (Chapter 6)



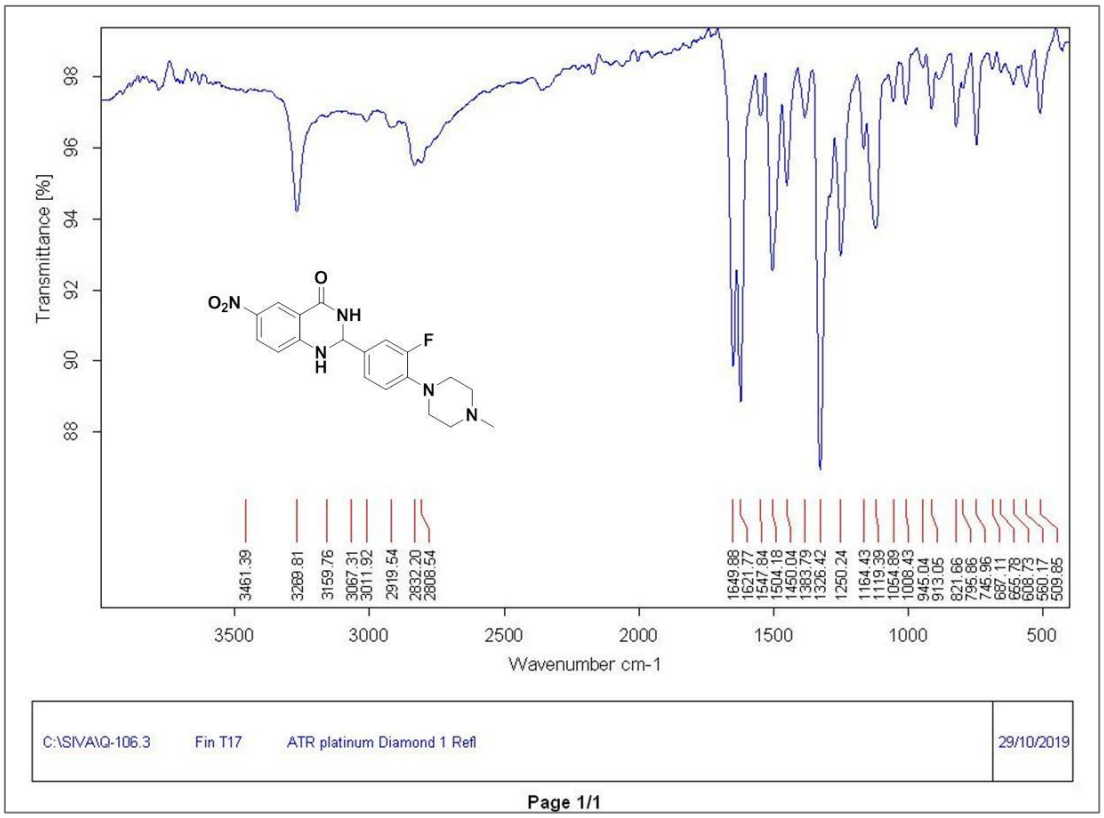
^{13}C NMR spectrum of compound 5b (Chapter 6)



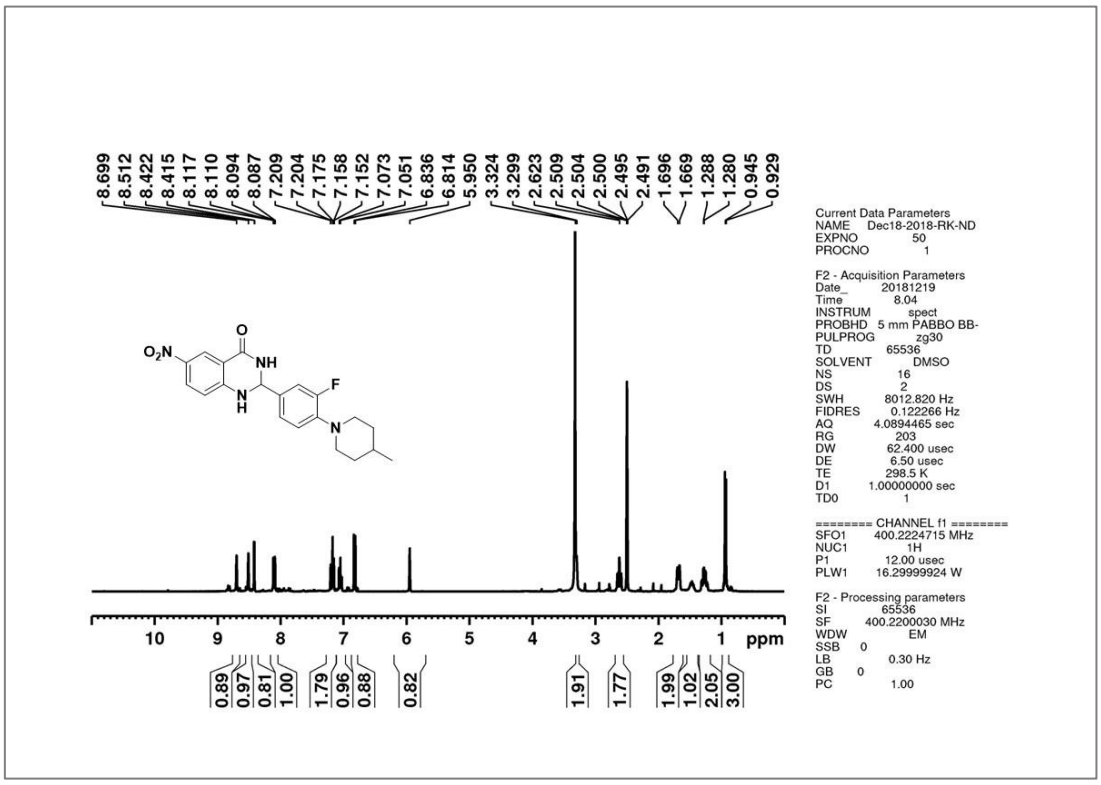
^{1}H NMR spectrum of compound 6a (Chapter 6)



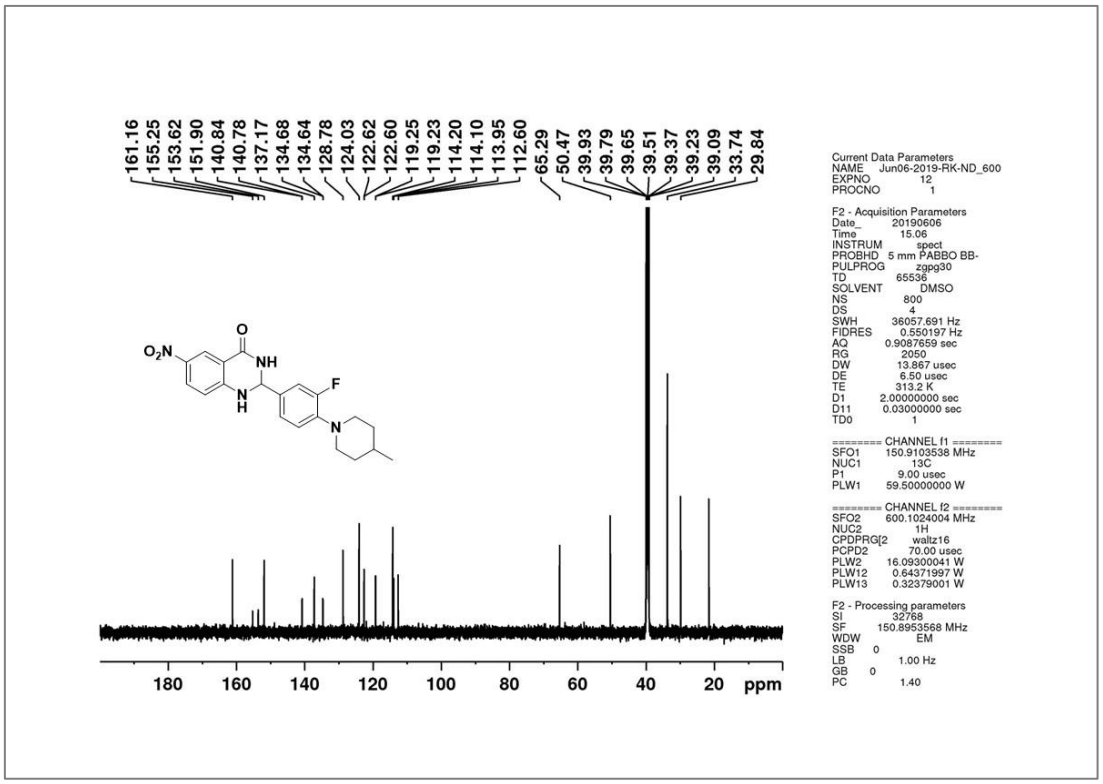
^{13}C NMR spectrum of compound 6a (Chapter 6)



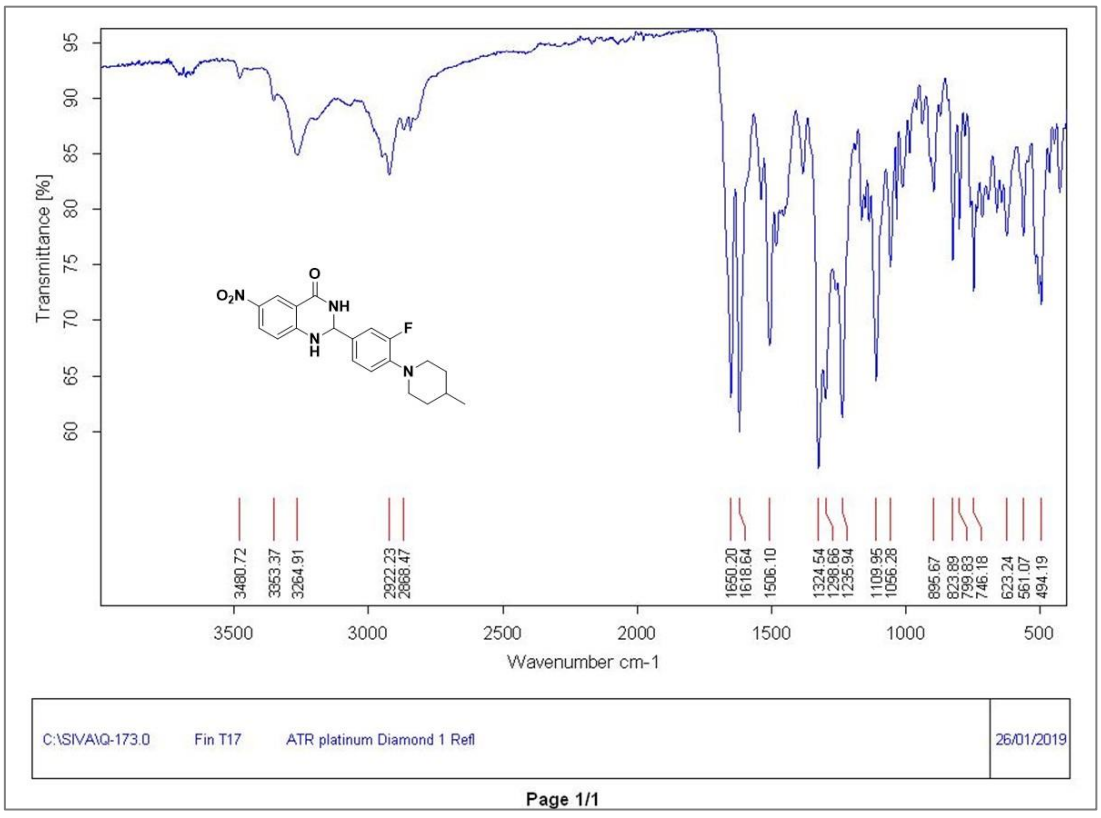
IR spectrum of compound 6a (Chapter 6)



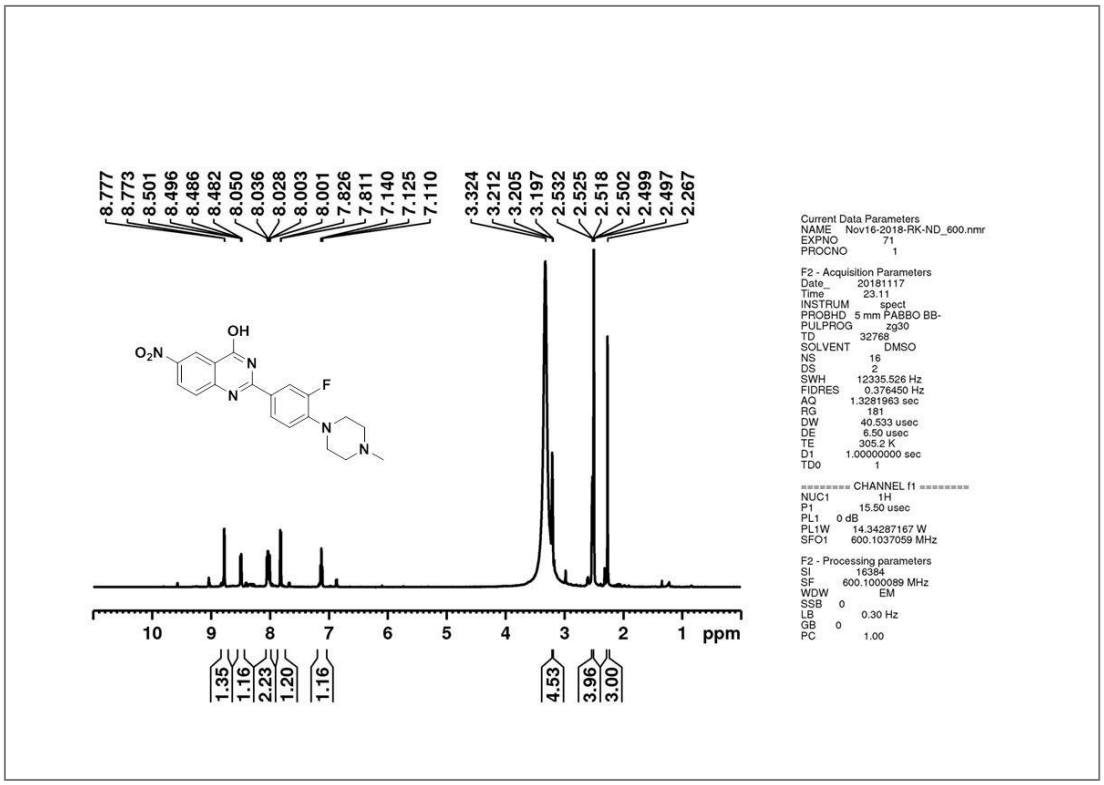
^{1}H NMR spectrum of compound 6b (Chapter 6)



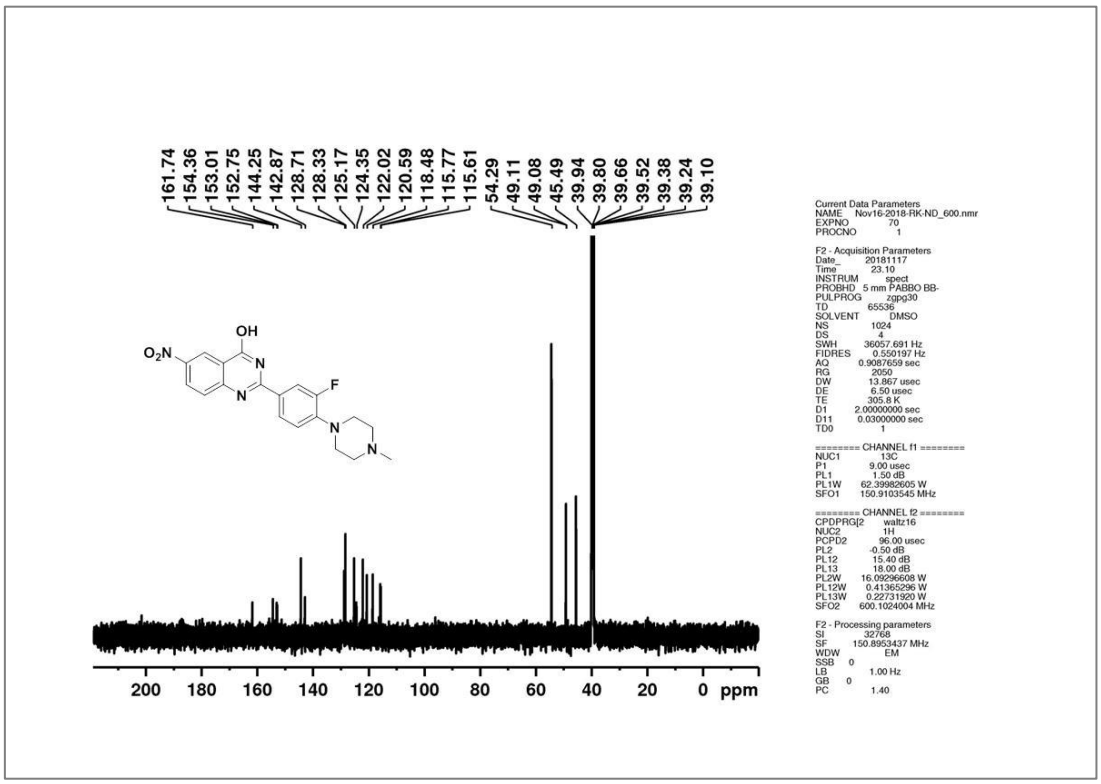
^{13}C NMR spectrum of compound 6b (Chapter 6)



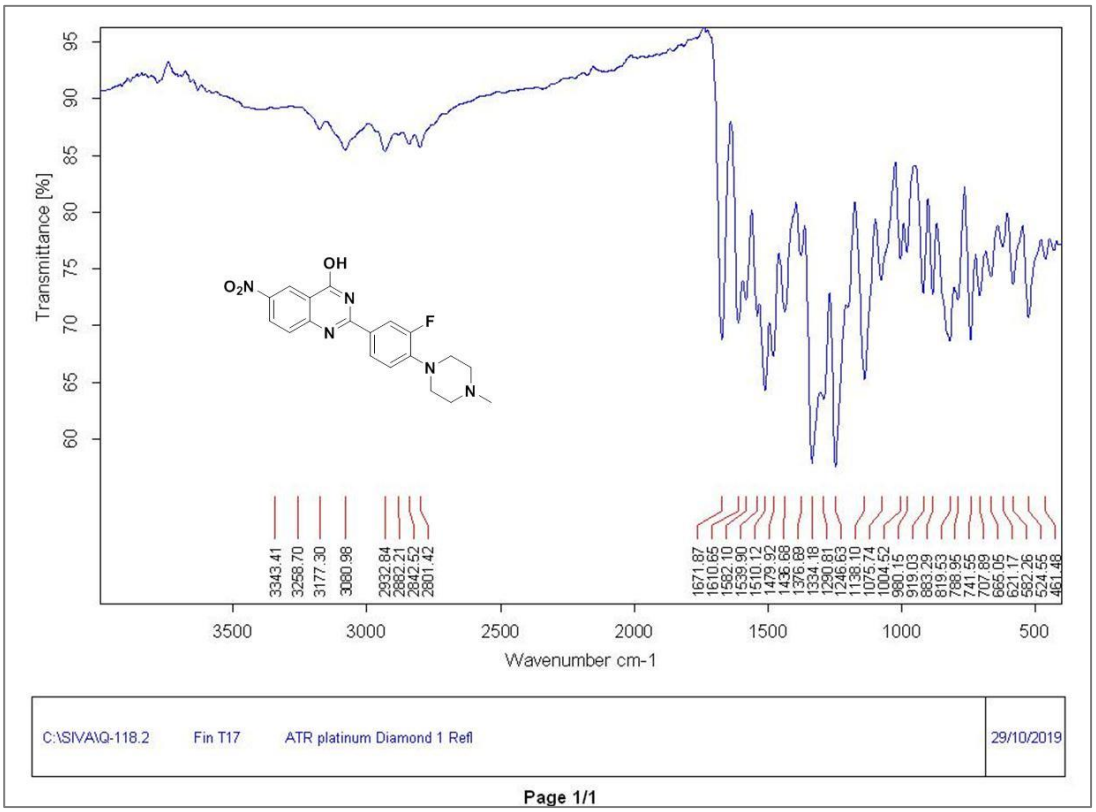
IR spectrum of compound 6b (Chapter 6)



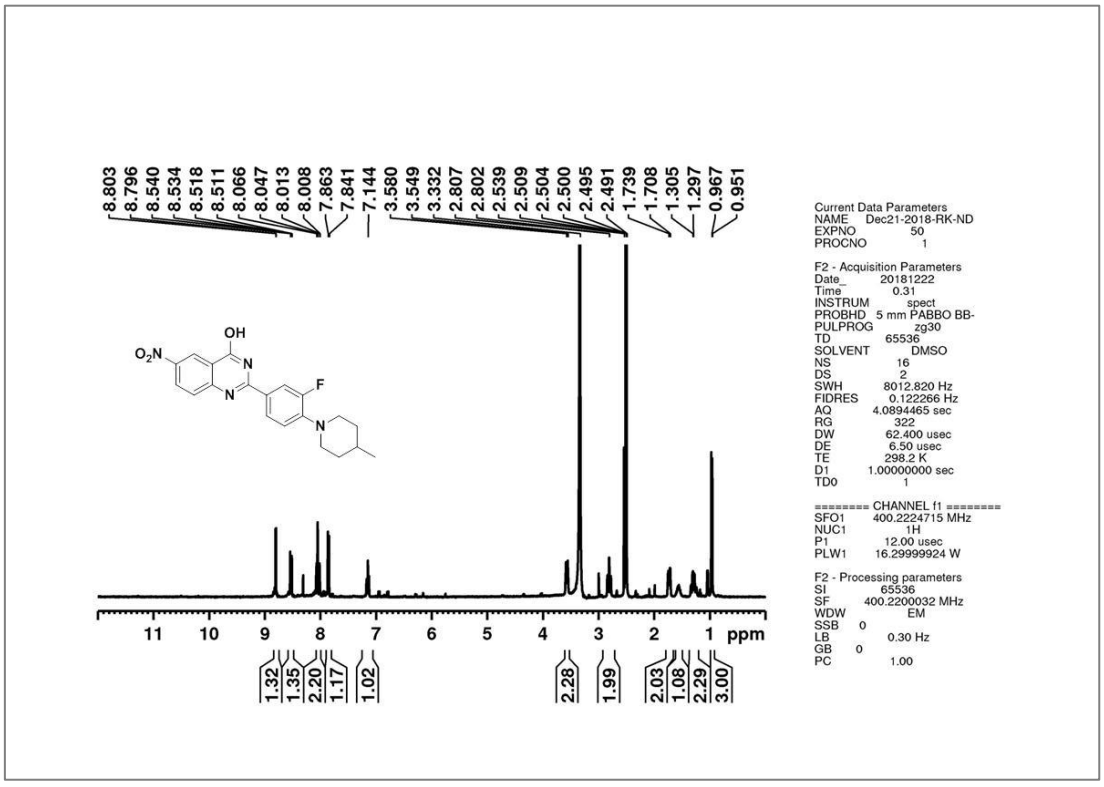
^{1}H NMR spectrum of compound 7a (Chapter 6)



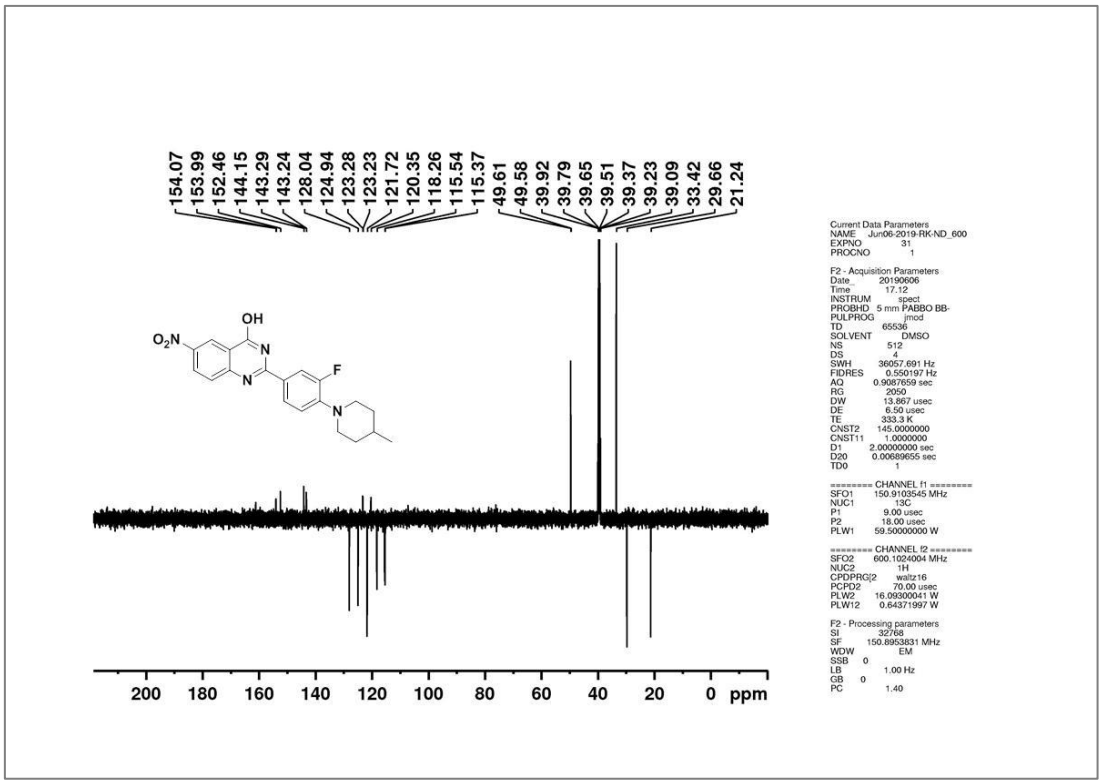
^{13}C NMR spectrum of compound 7a (Chapter 6)



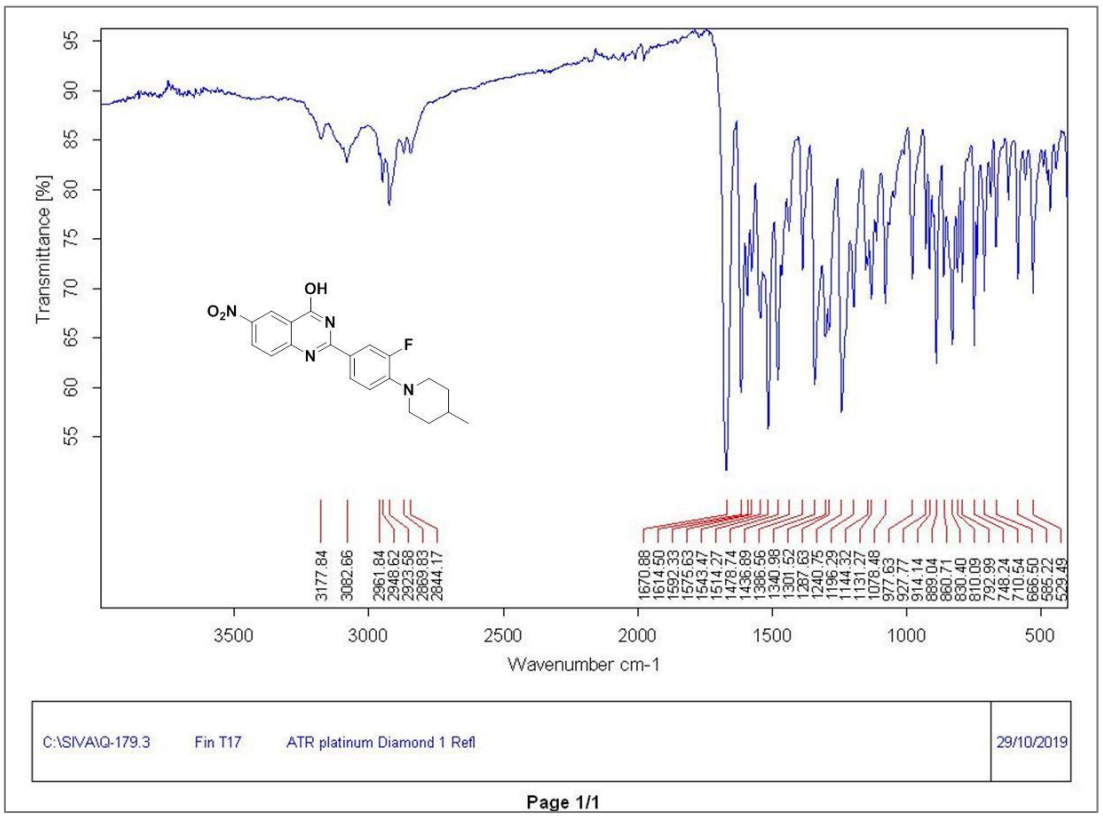
IR spectrum of compound 7a (Chapter 6)



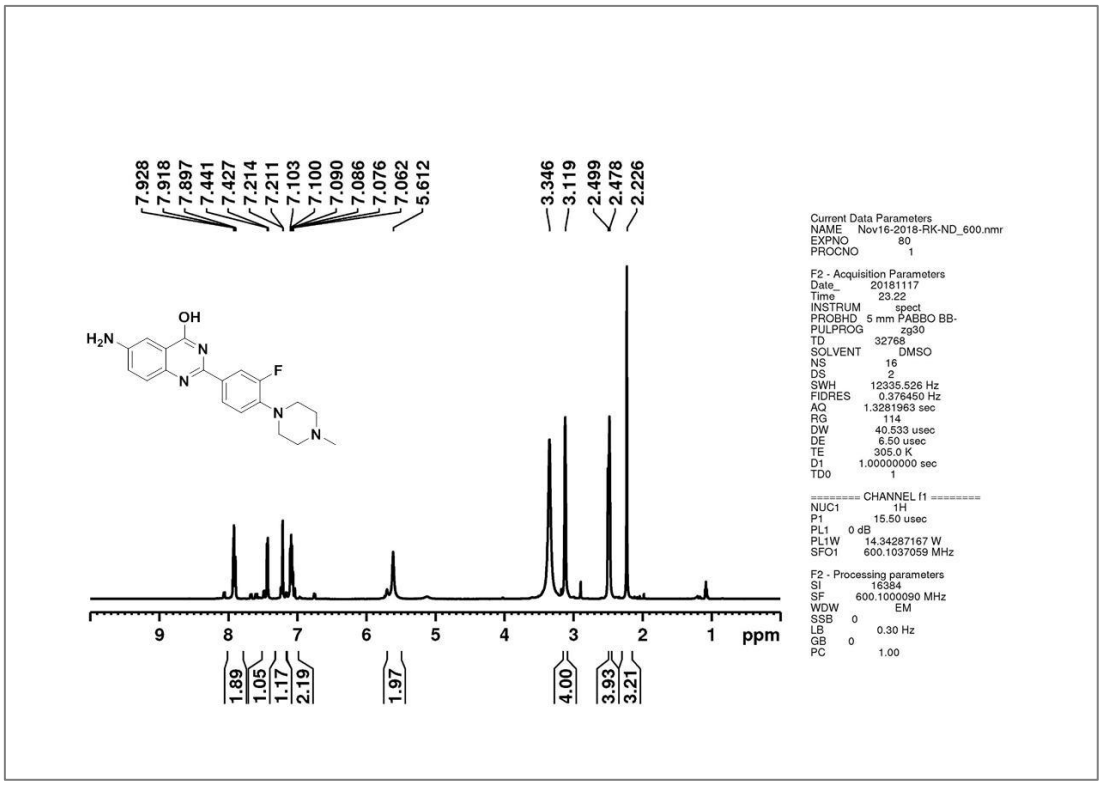
^{1}H NMR spectrum of compound 7b (Chapter 6)



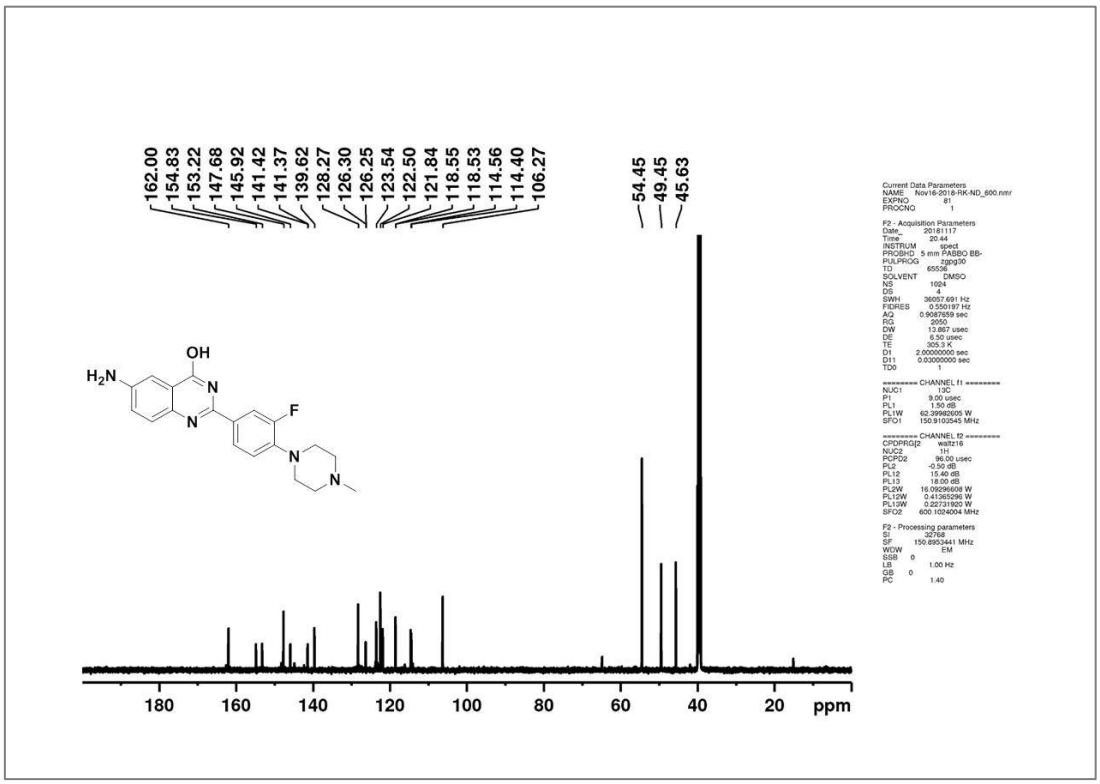
^{13}C NMR spectrum of compound 7b (Chapter 6)



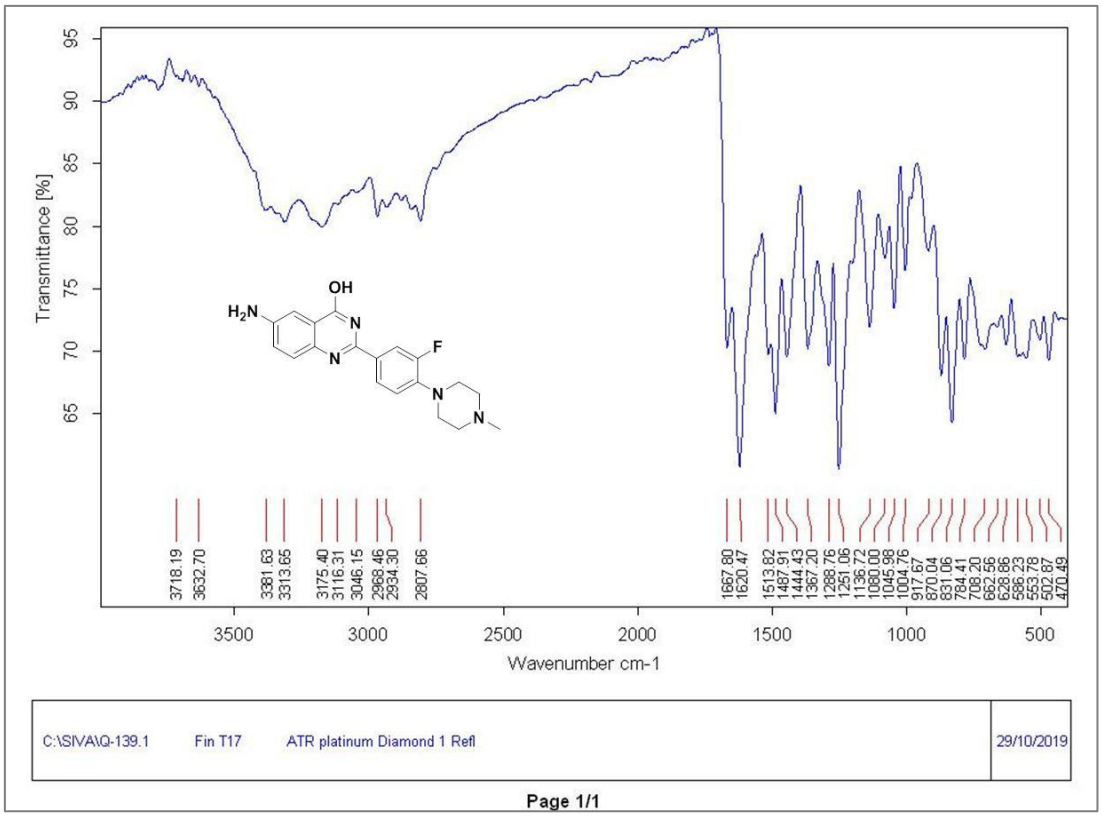
IR spectrum of compound 7b (Chapter 6)



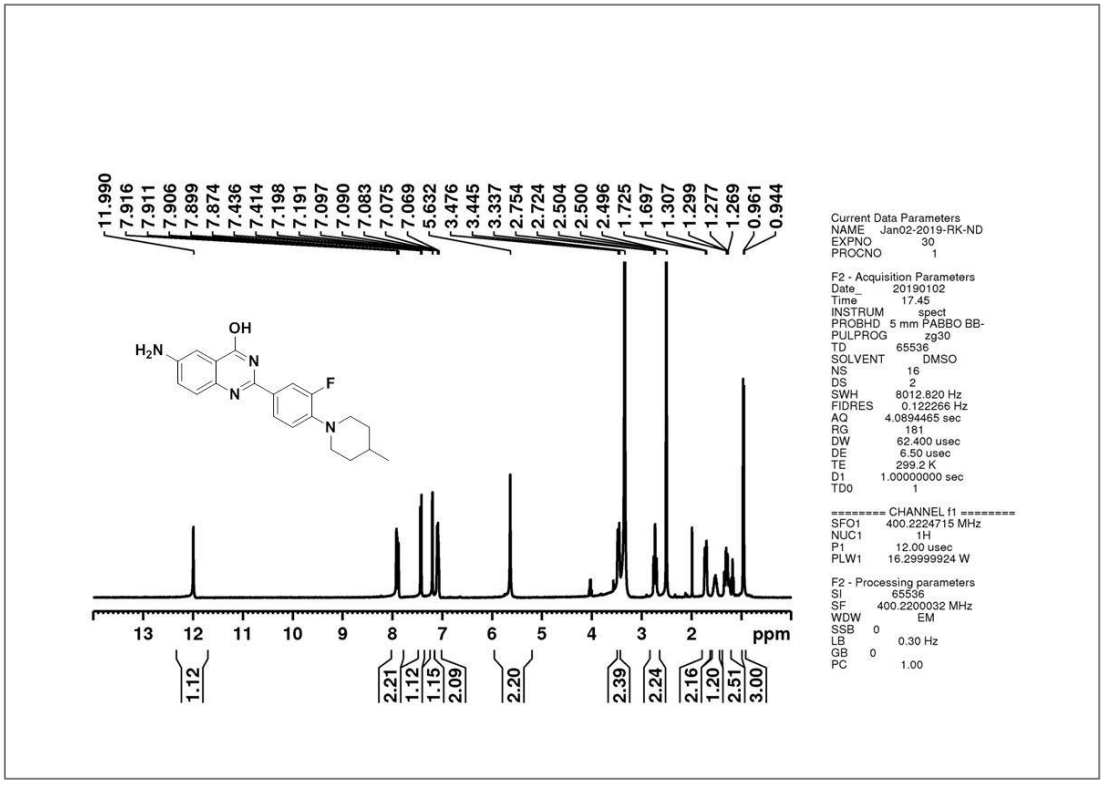
^{1}H NMR spectrum of compound 8a (Chapter 6)



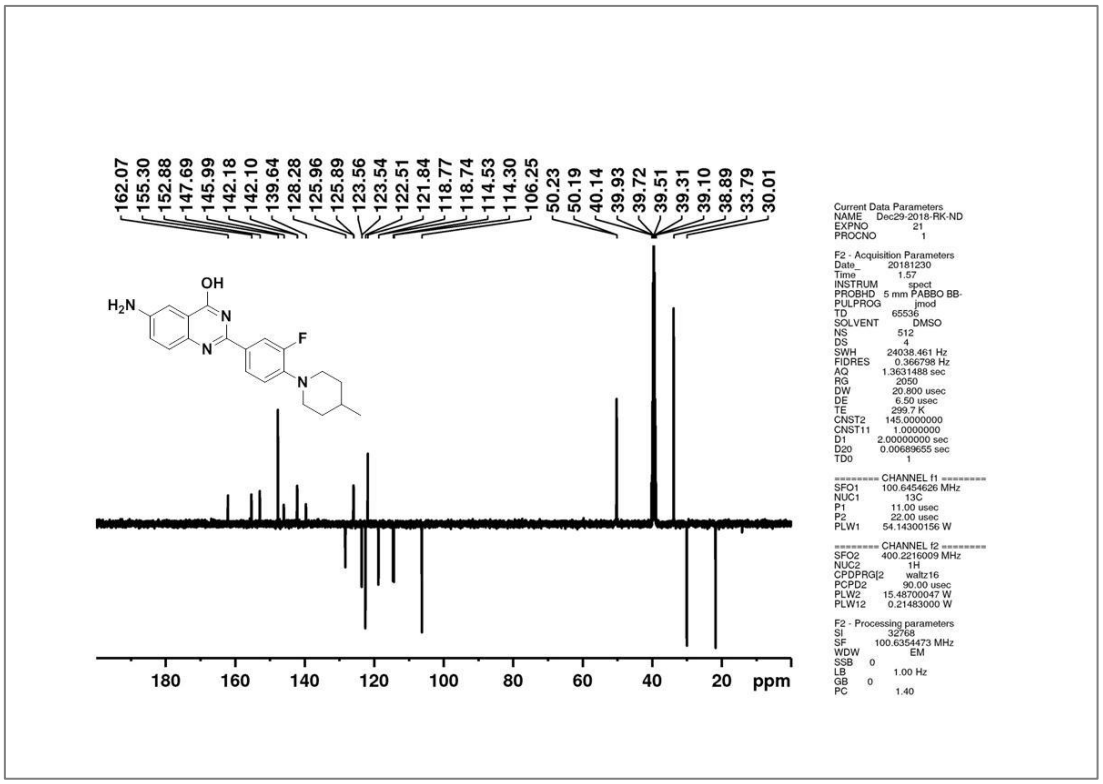
^{13}C NMR spectrum of compound 8a (Chapter 6)



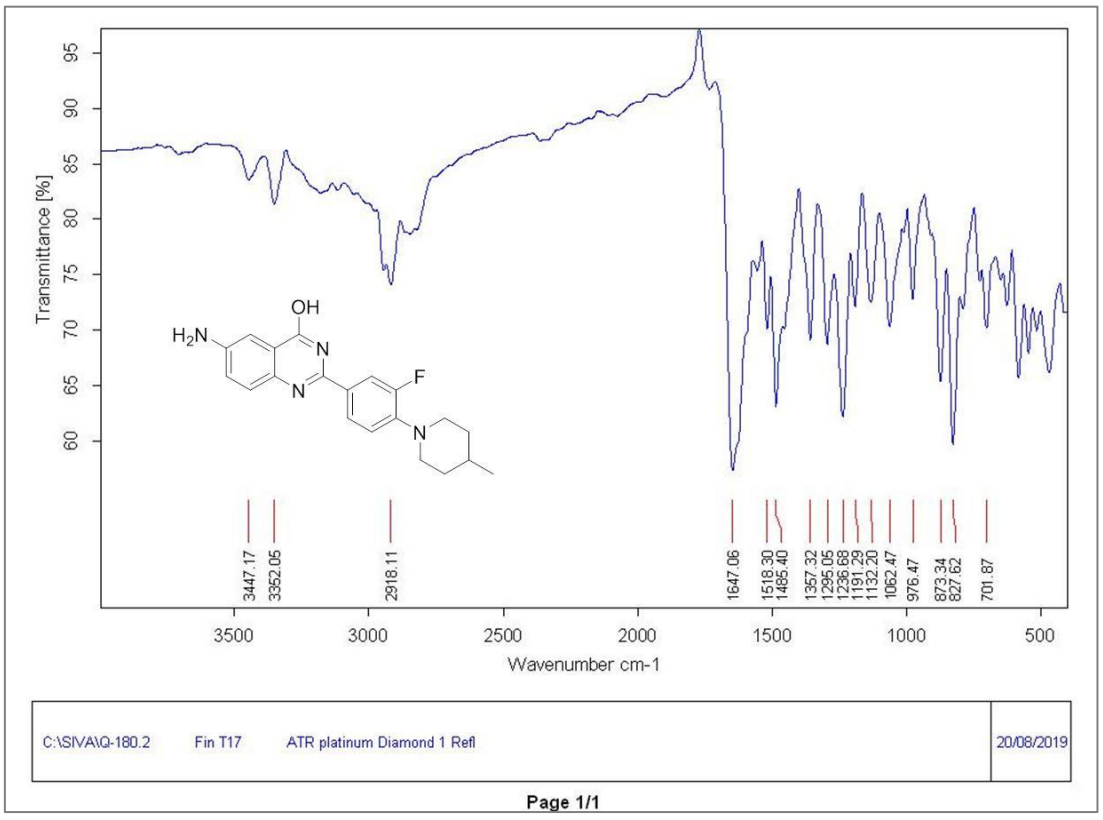
IR spectrum of compound 8a (Chapter 6)



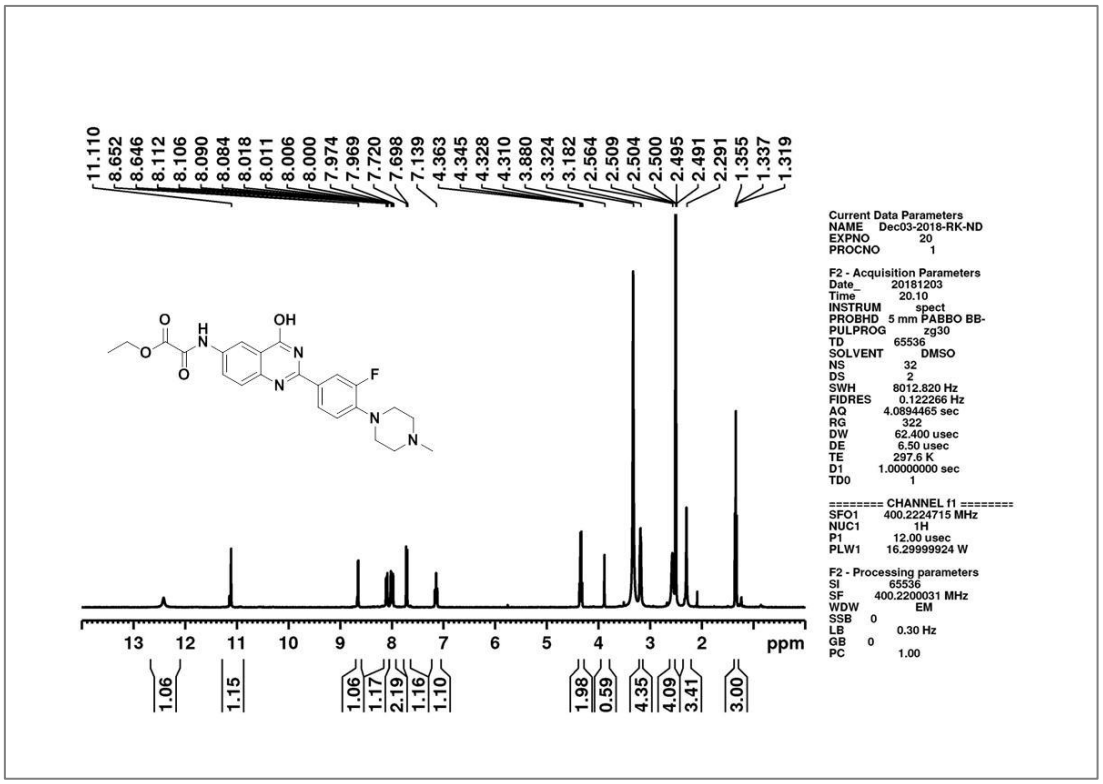
^{1}H NMR spectrum of compound 8b (Chapter 6)



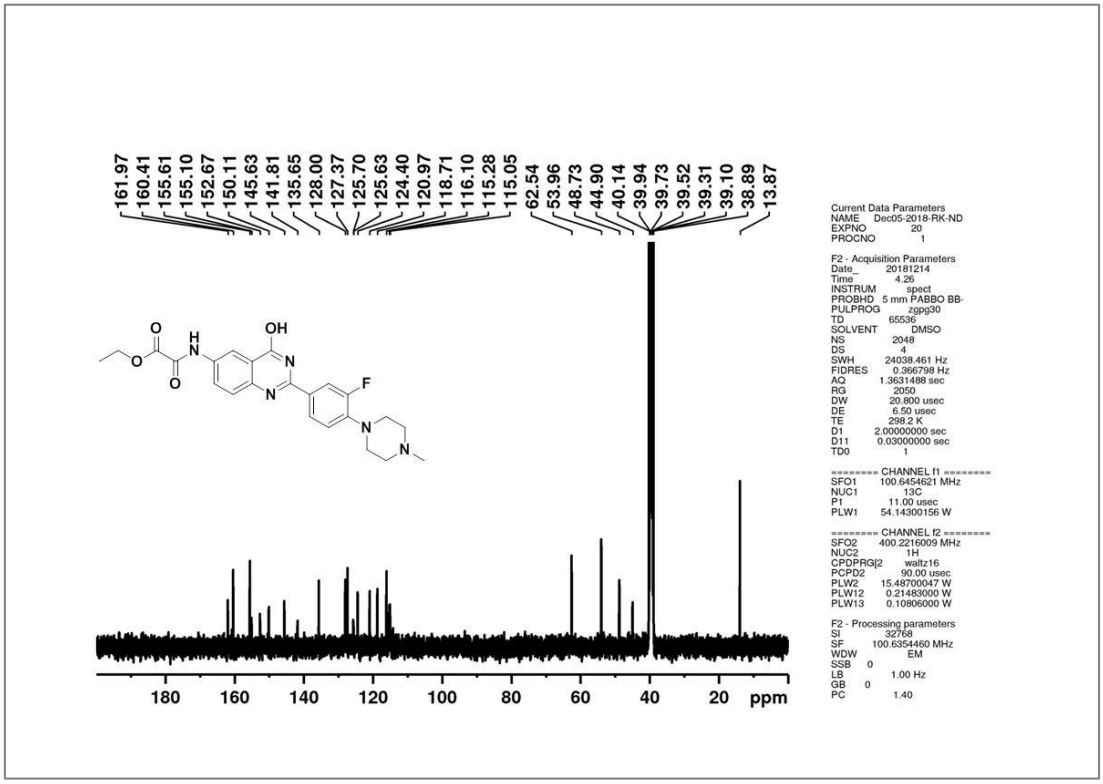
^{13}C NMR spectrum of compound 8b (Chapter 6)



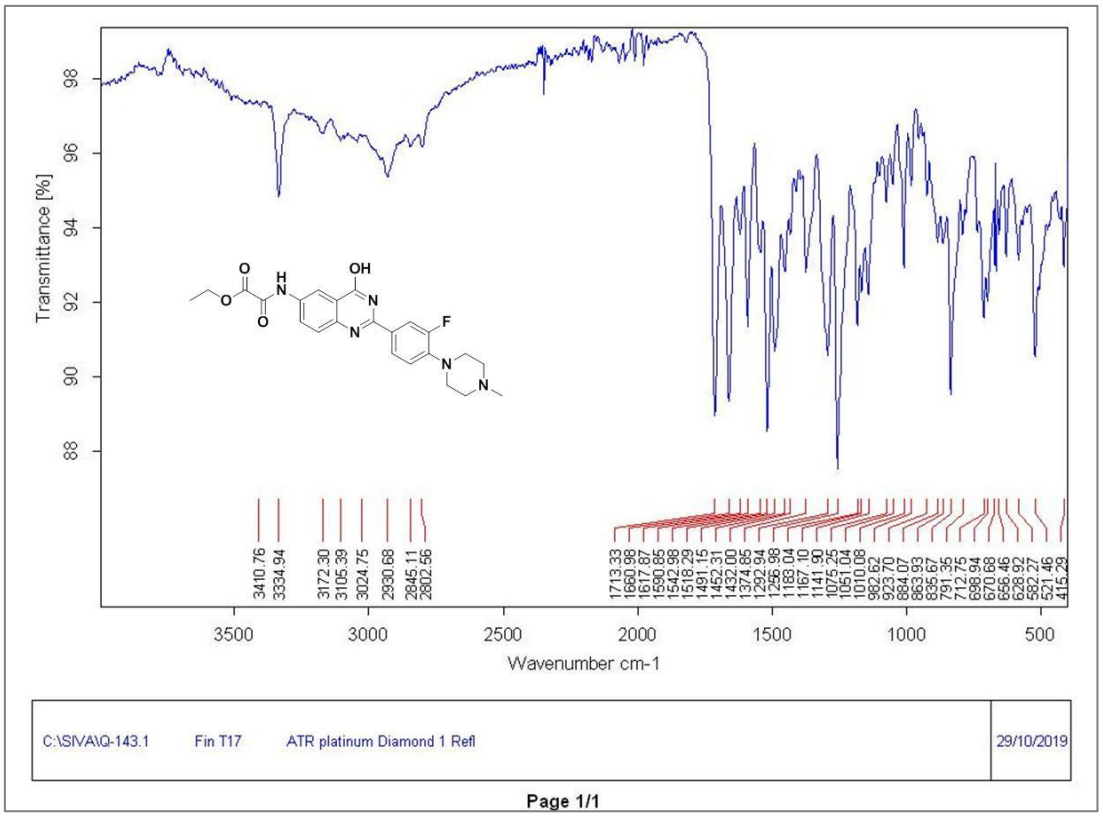
IR spectrum of compound 8b (Chapter 6)



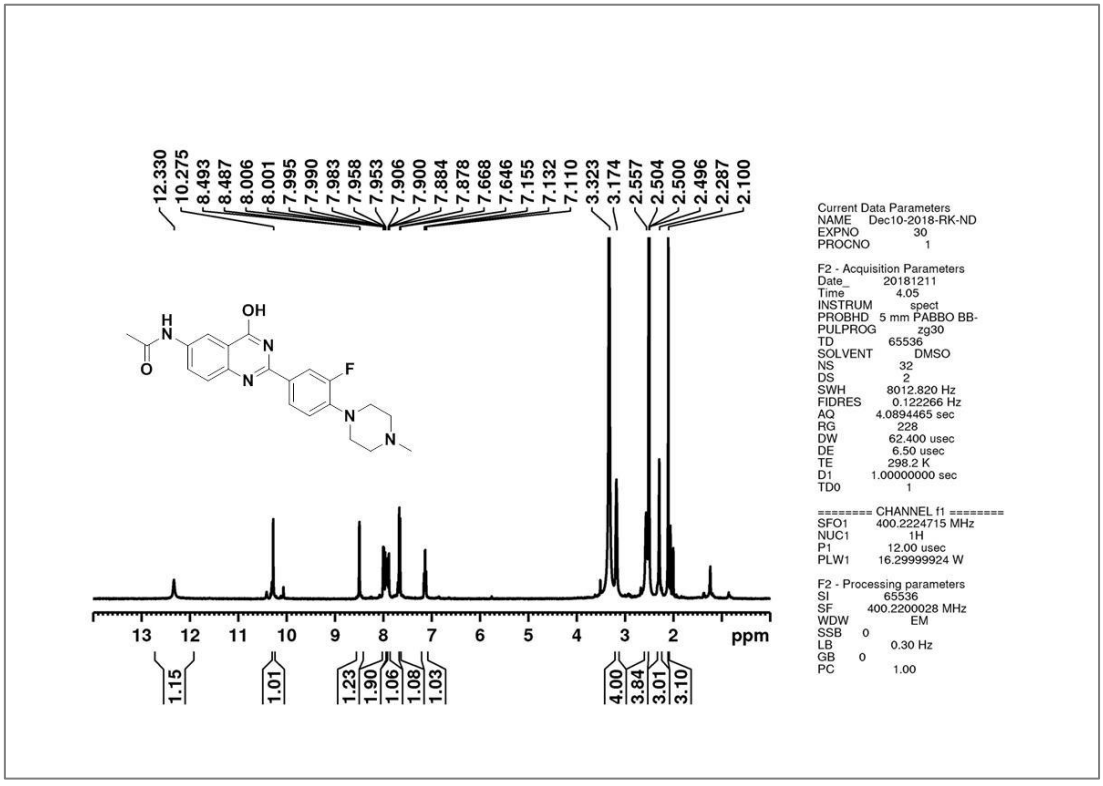
[1]H NMR spectrum of compound 9a (Chapter 6)



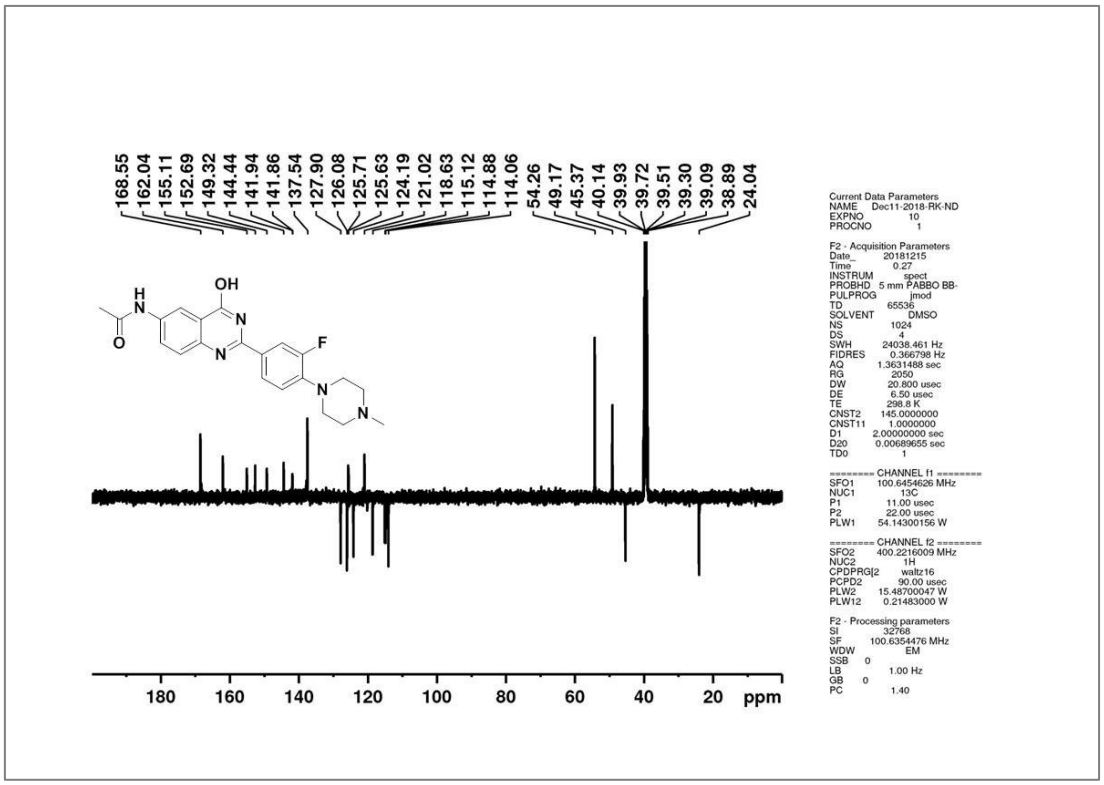
[13]C NMR spectrum of compound 9a (Chapter 6)



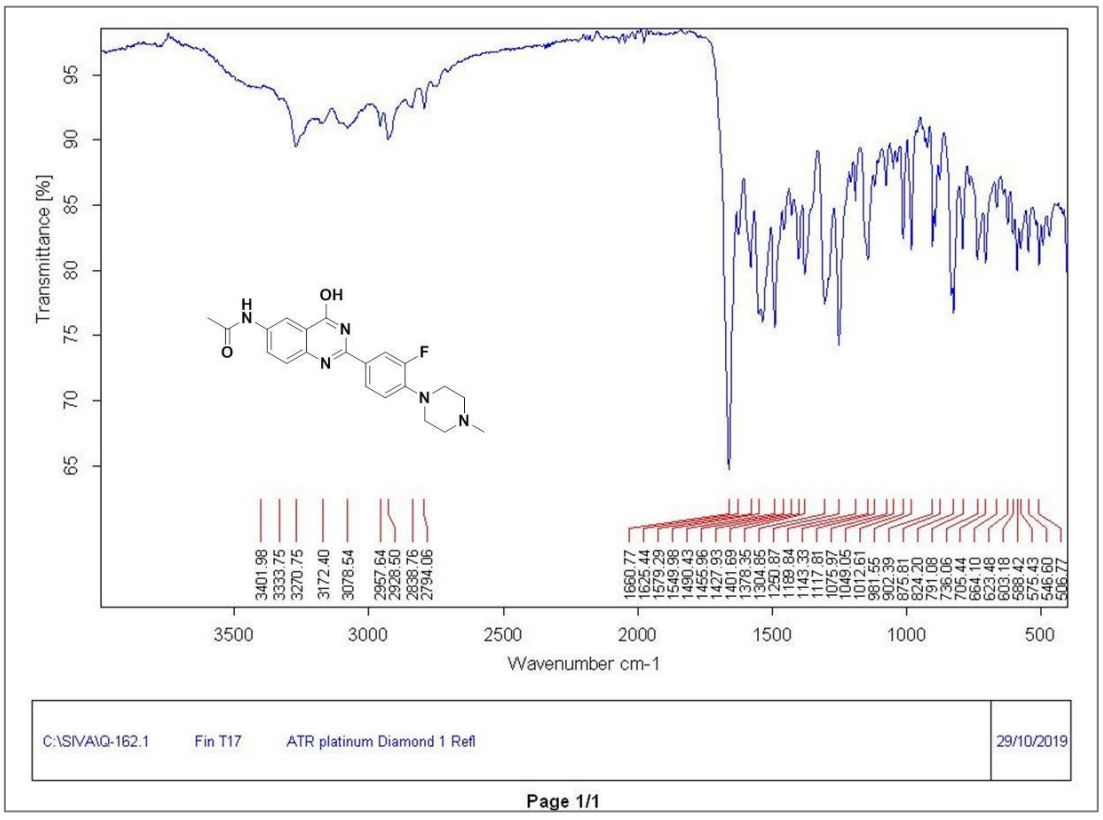
IR spectrum of compound 9a (Chapter 6)



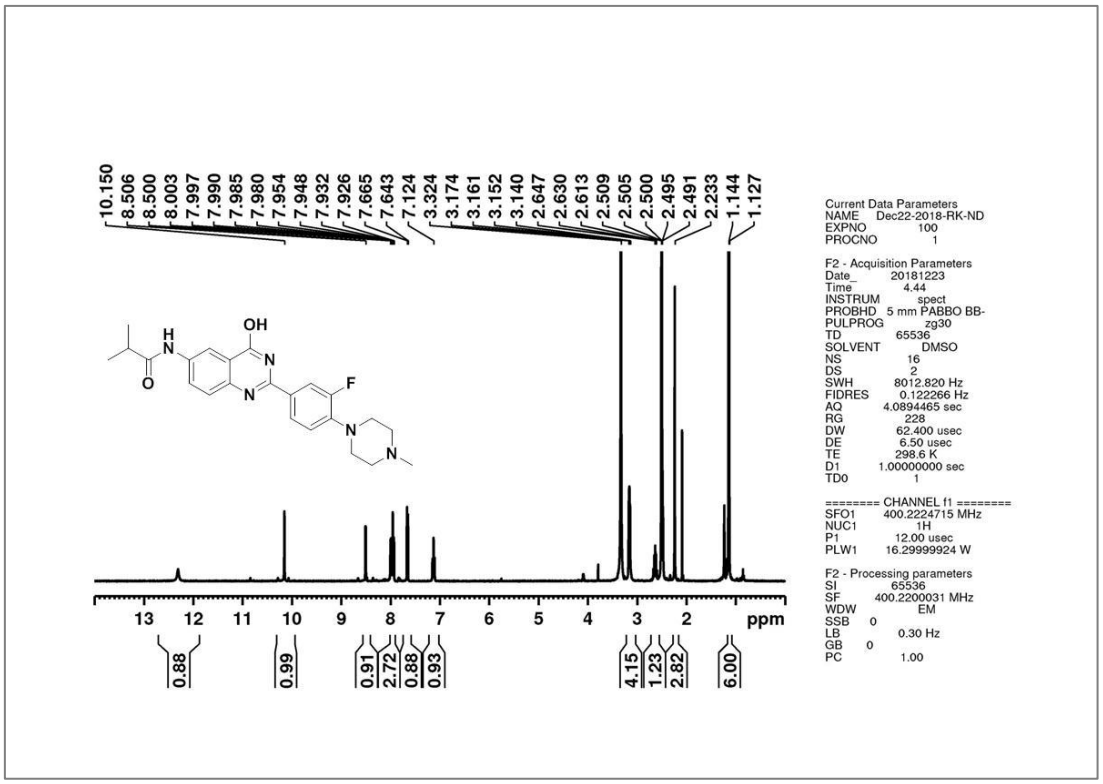
^{1}H NMR spectrum of compound 9b (Chapter 6)



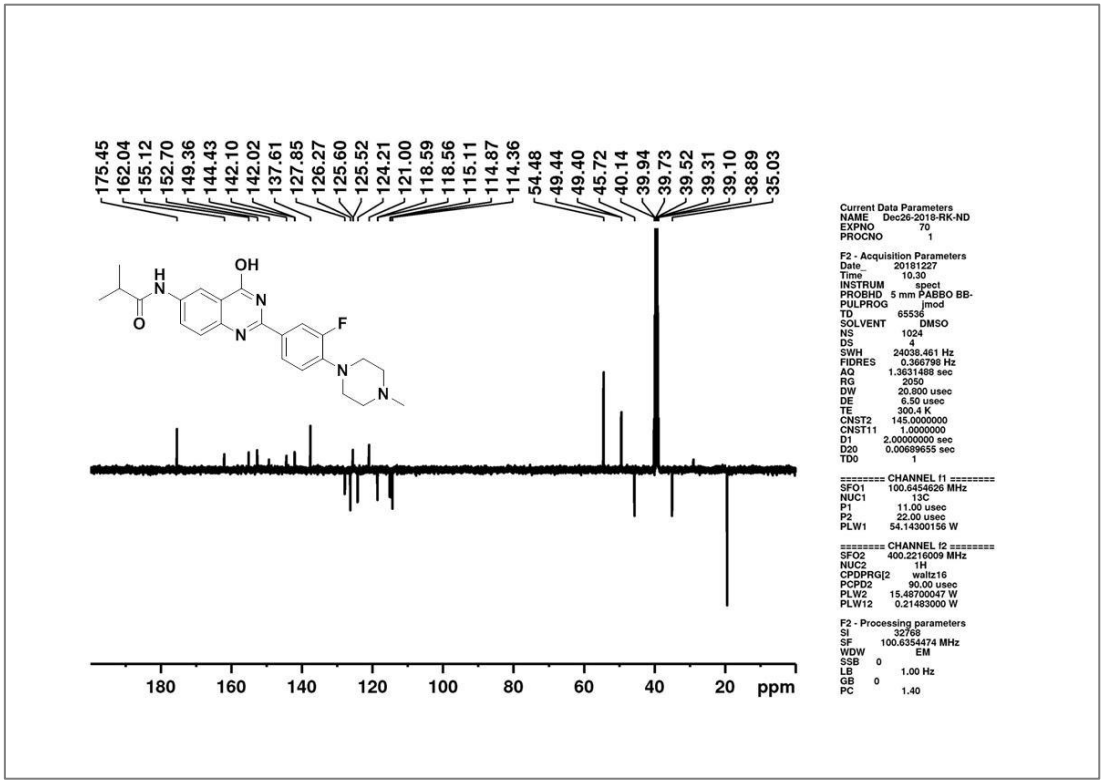
^{13}C NMR spectrum of compound 9b (Chapter 6)



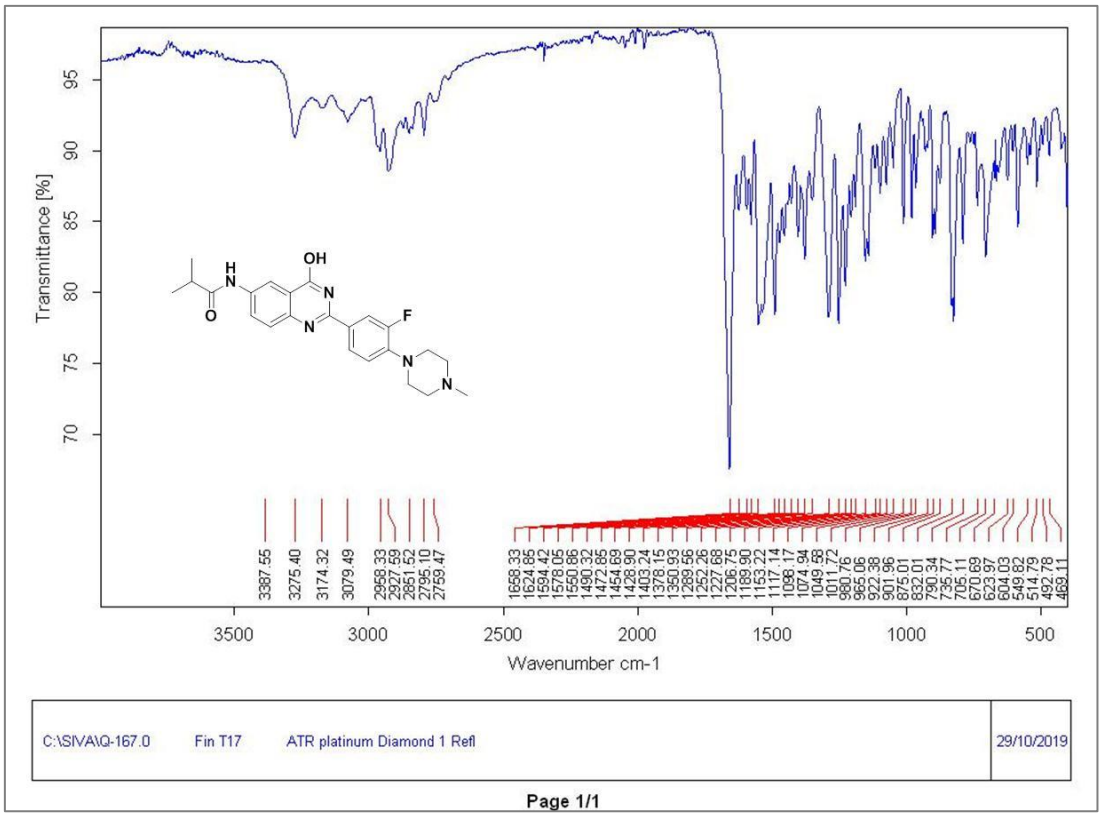
IR spectrum of compound 9b (Chapter 6)



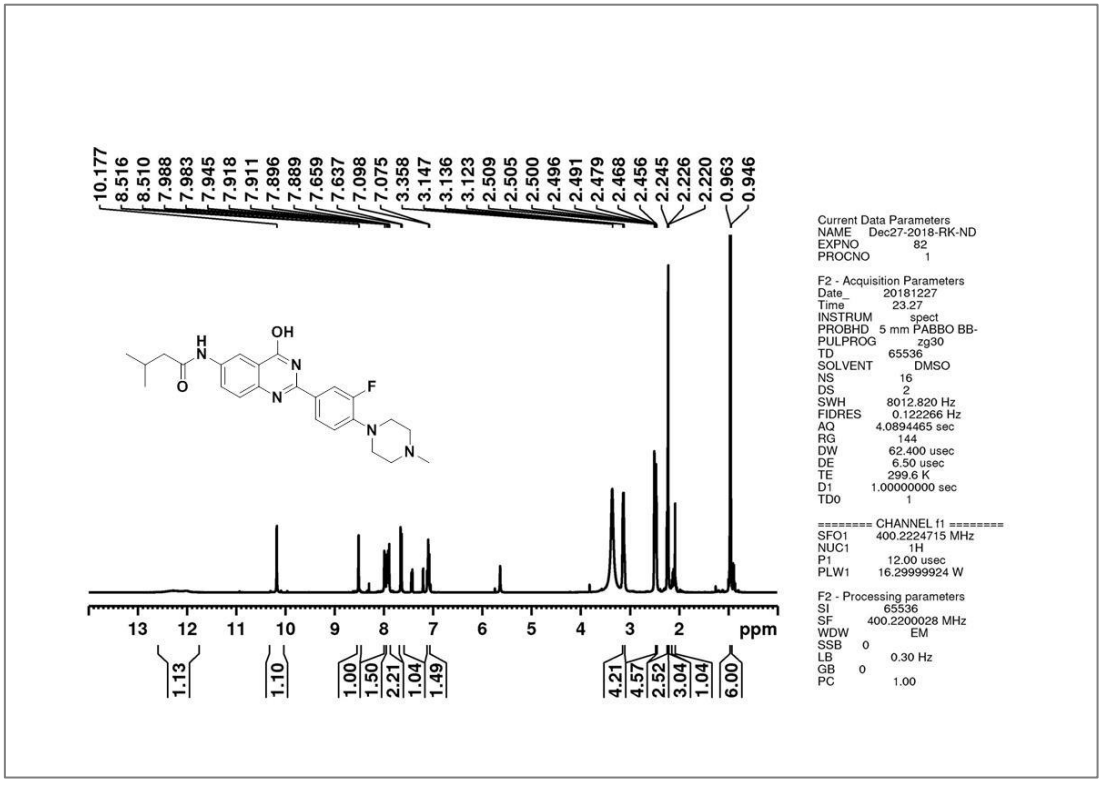
^{1}H NMR spectrum of compound 9c (Chapter 6)



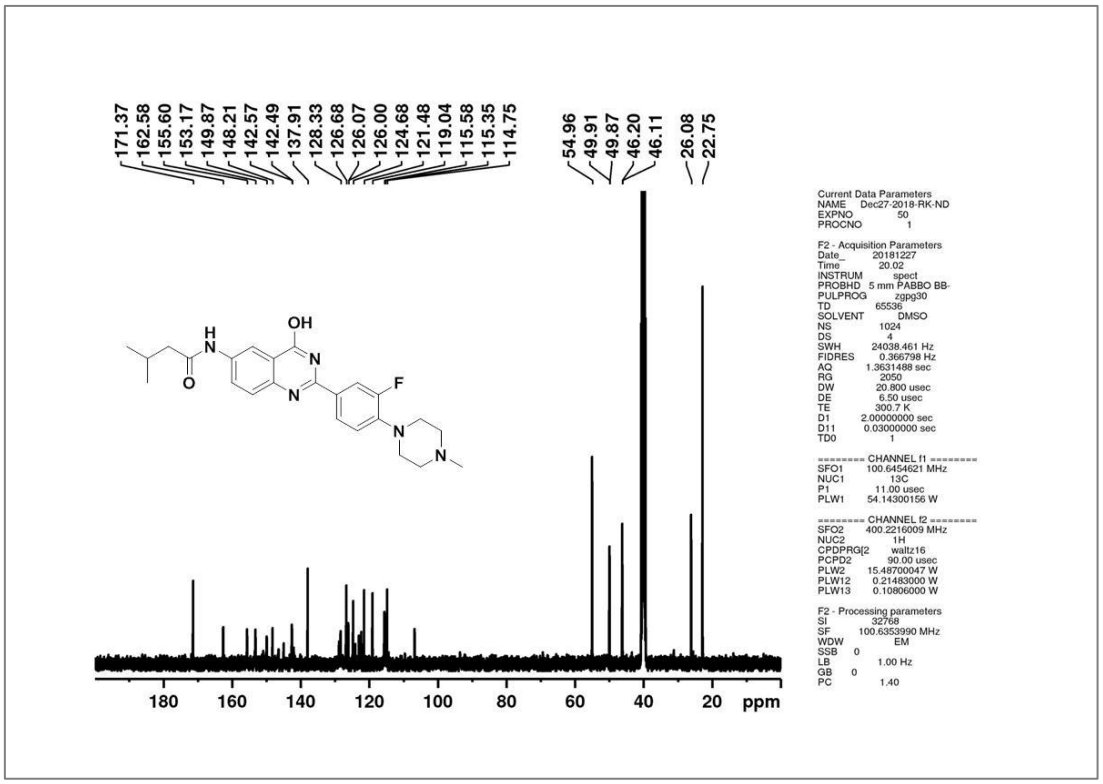
^{13}C NMR spectrum of compound 9c (Chapter 6)



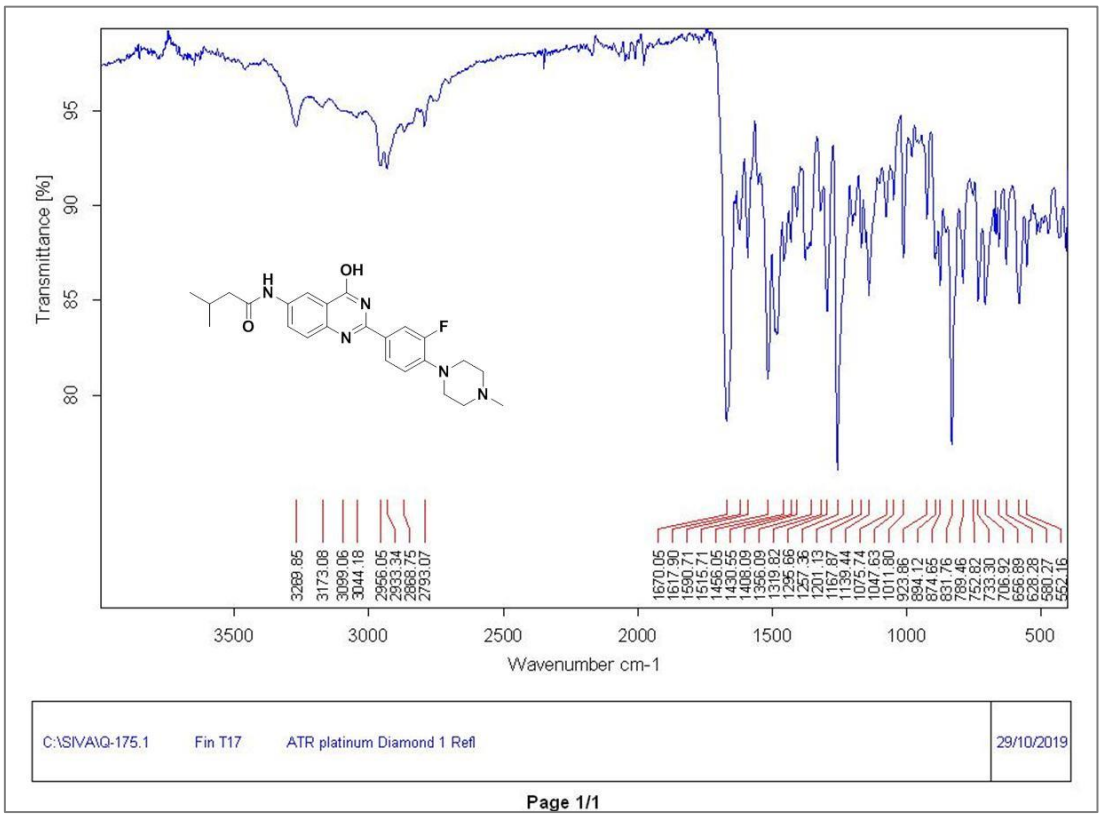
IR spectrum of compound 9c (Chapter 6)



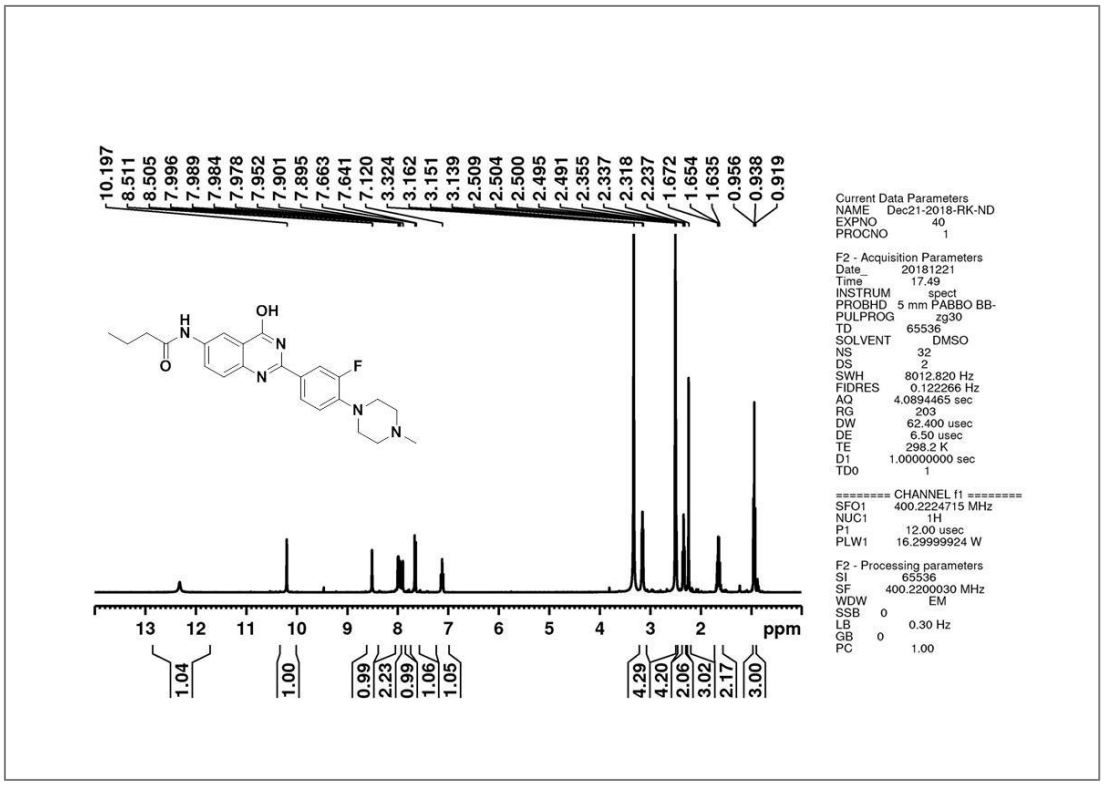
^{1}H NMR spectrum of compound 9d (Chapter 6)



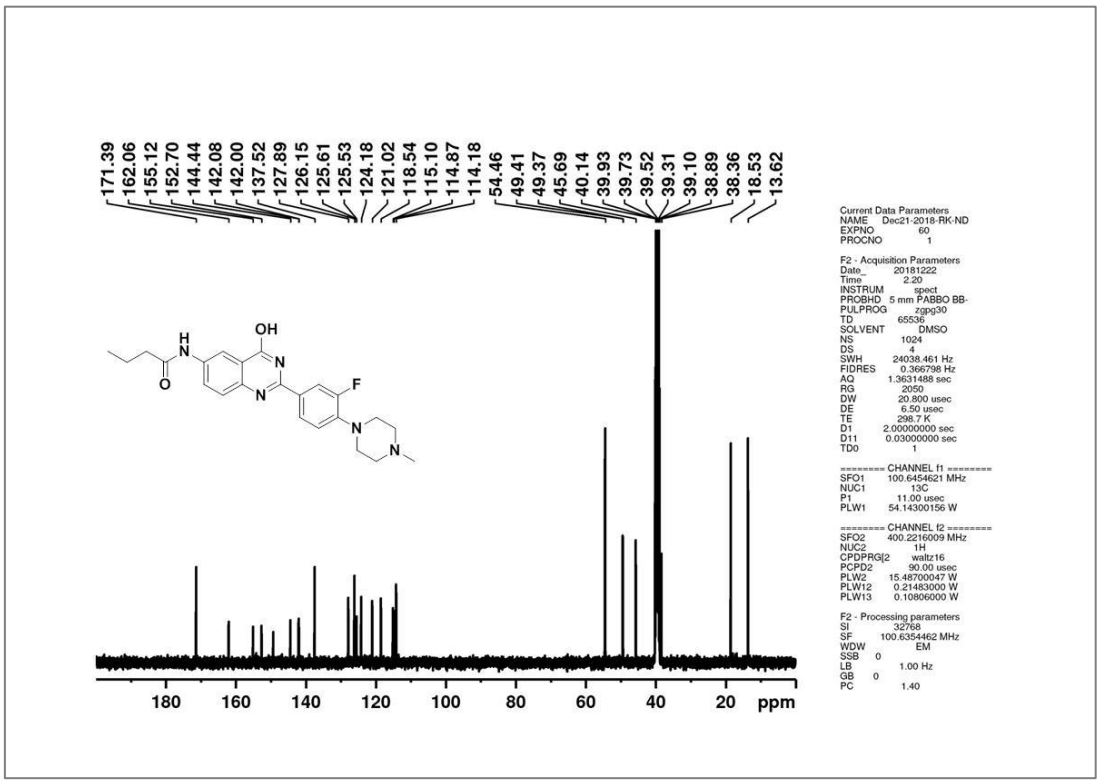
^{13}C NMR spectrum of compound 9d (Chapter 6)



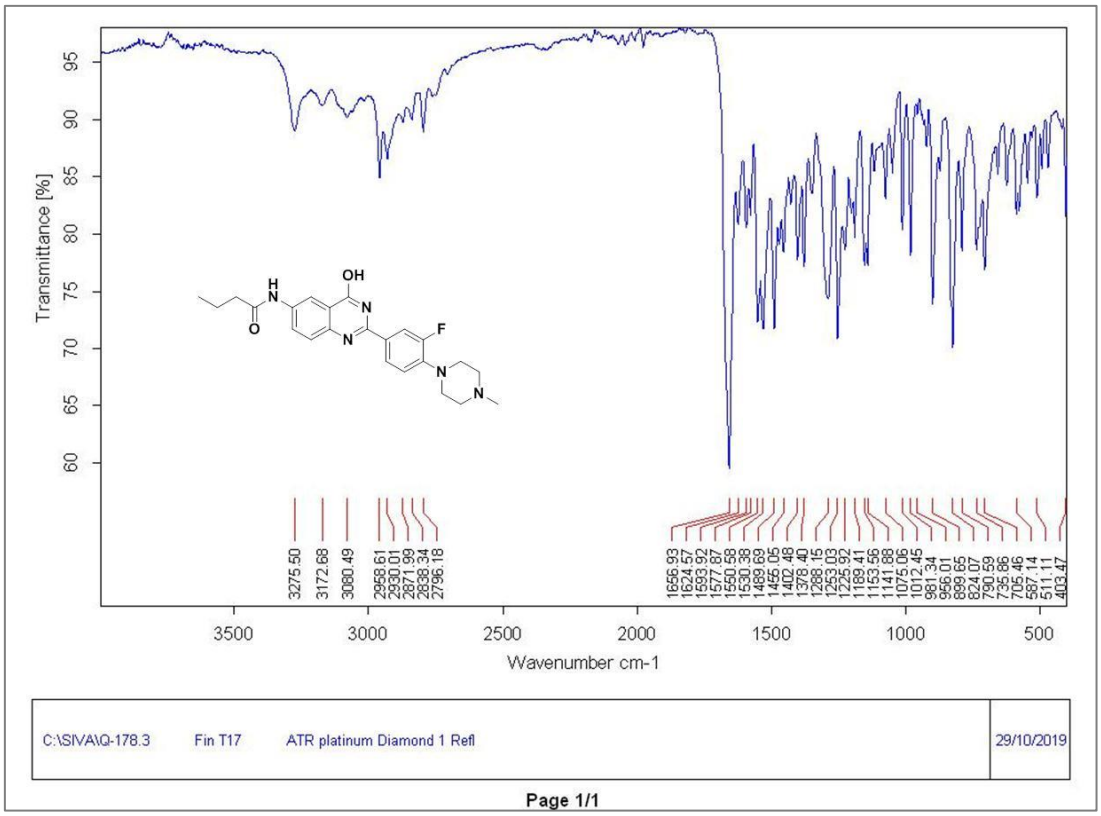
IR spectrum of compound 9d (Chapter 6)



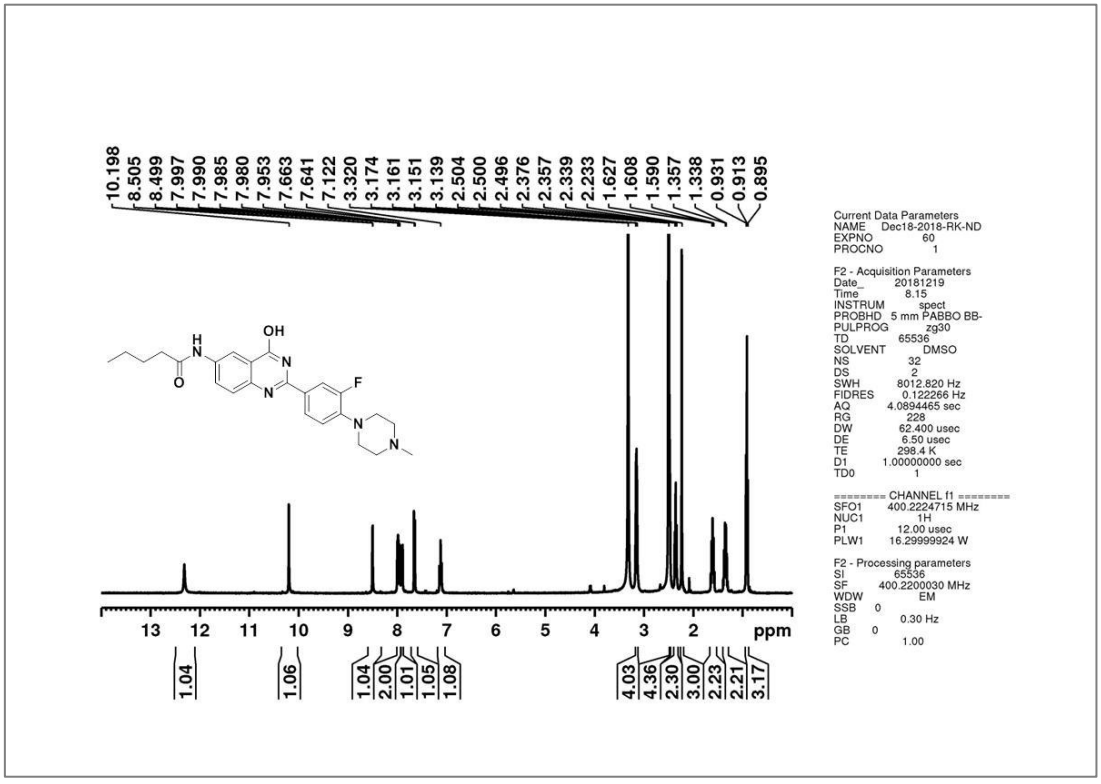
^{1}H NMR spectrum of compound 9e (Chapter 6)



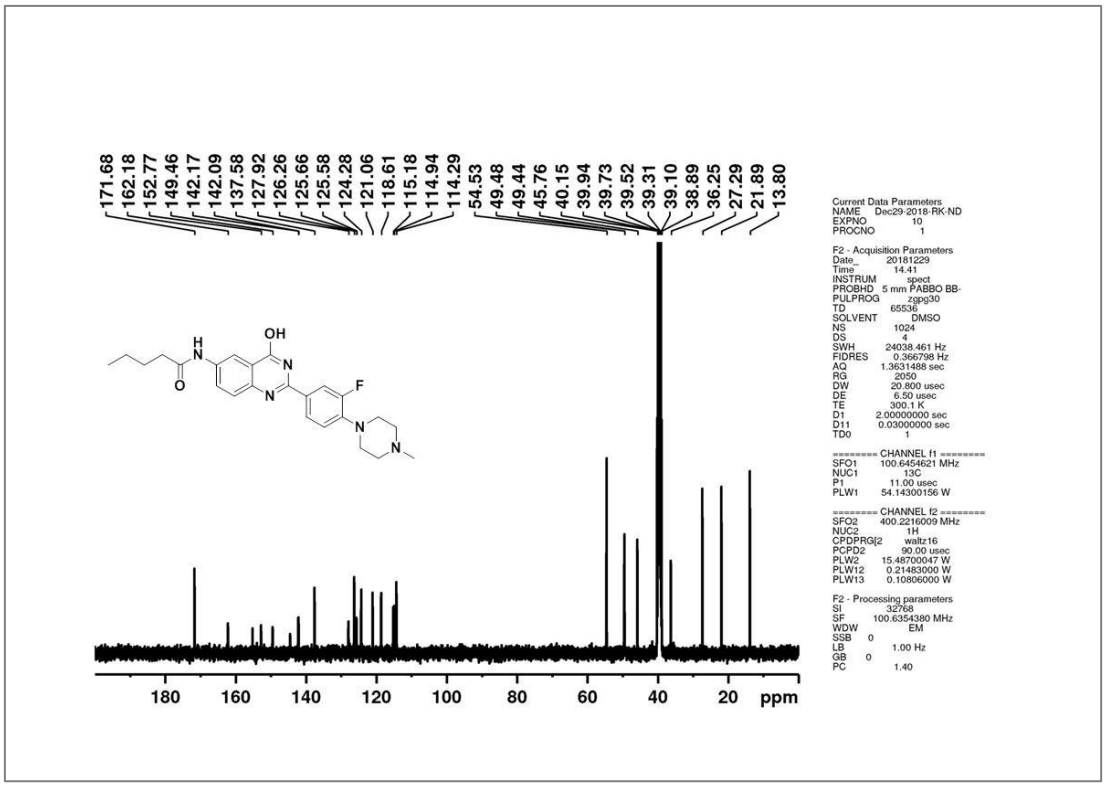
^{13}C NMR spectrum of compound 9e (Chapter 6)



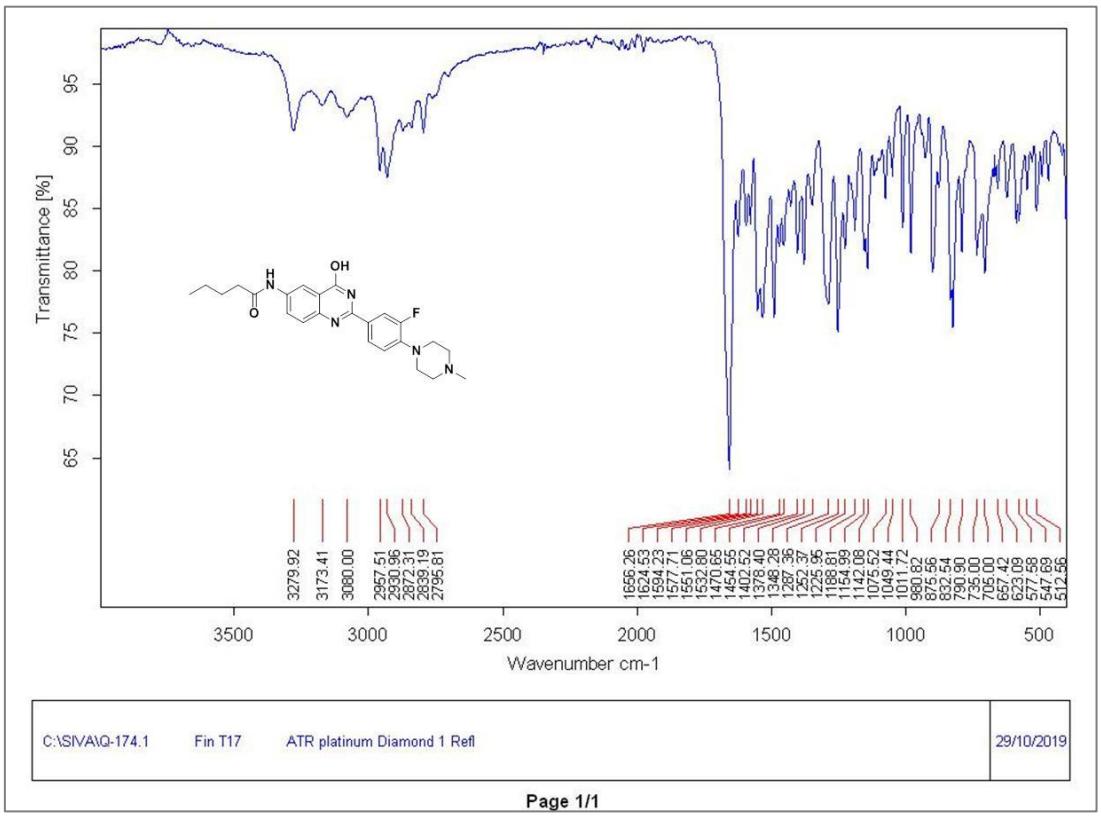
IR spectrum of compound 9e (Chapter 6)



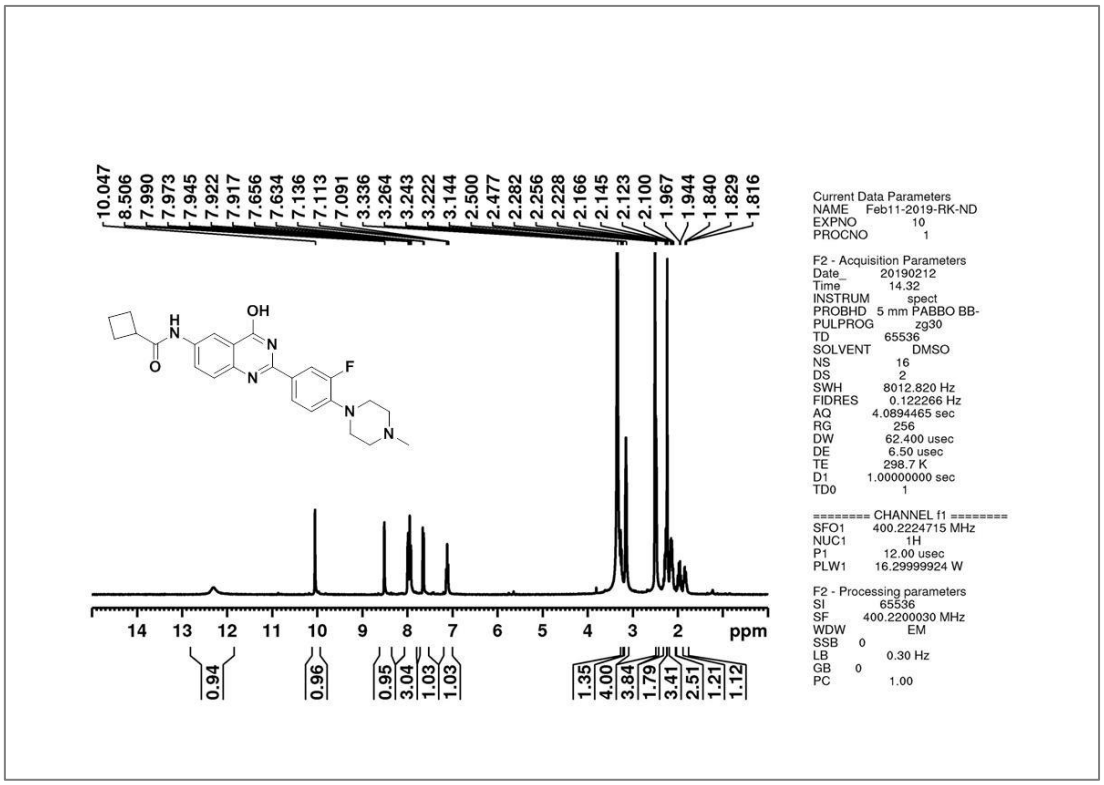
^{1}H NMR spectrum of compound 9f (Chapter 6)



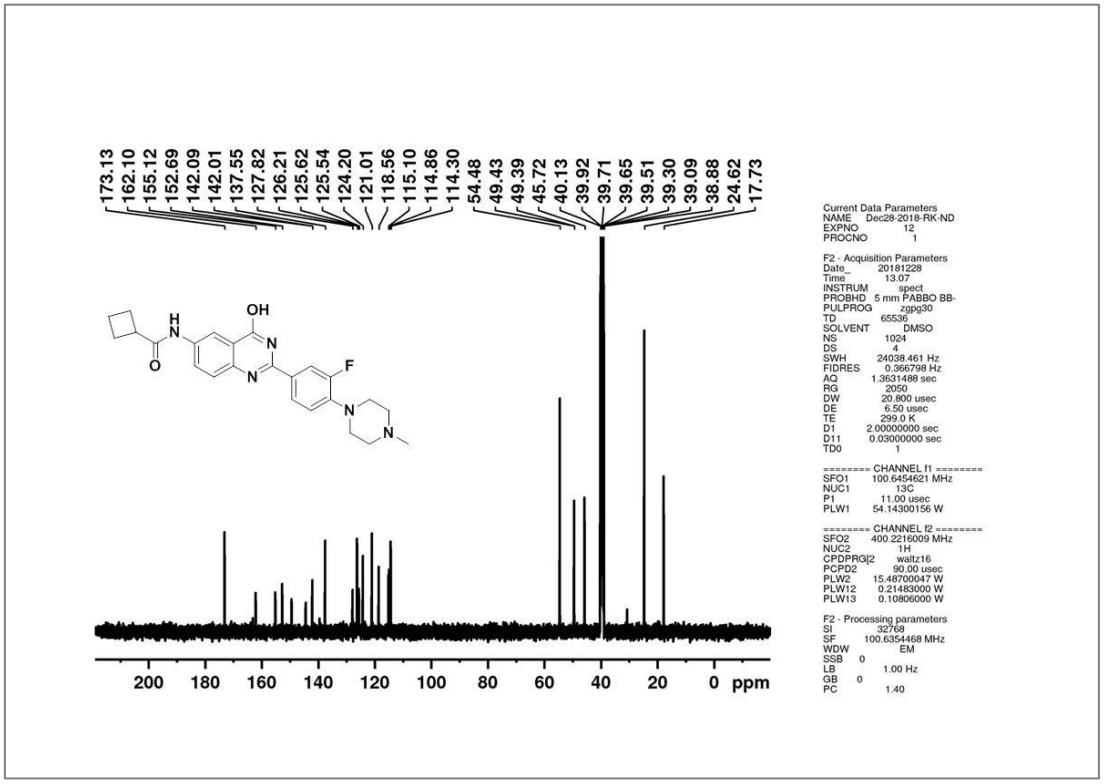
^{13}C NMR spectrum of compound 9f (Chapter 6)



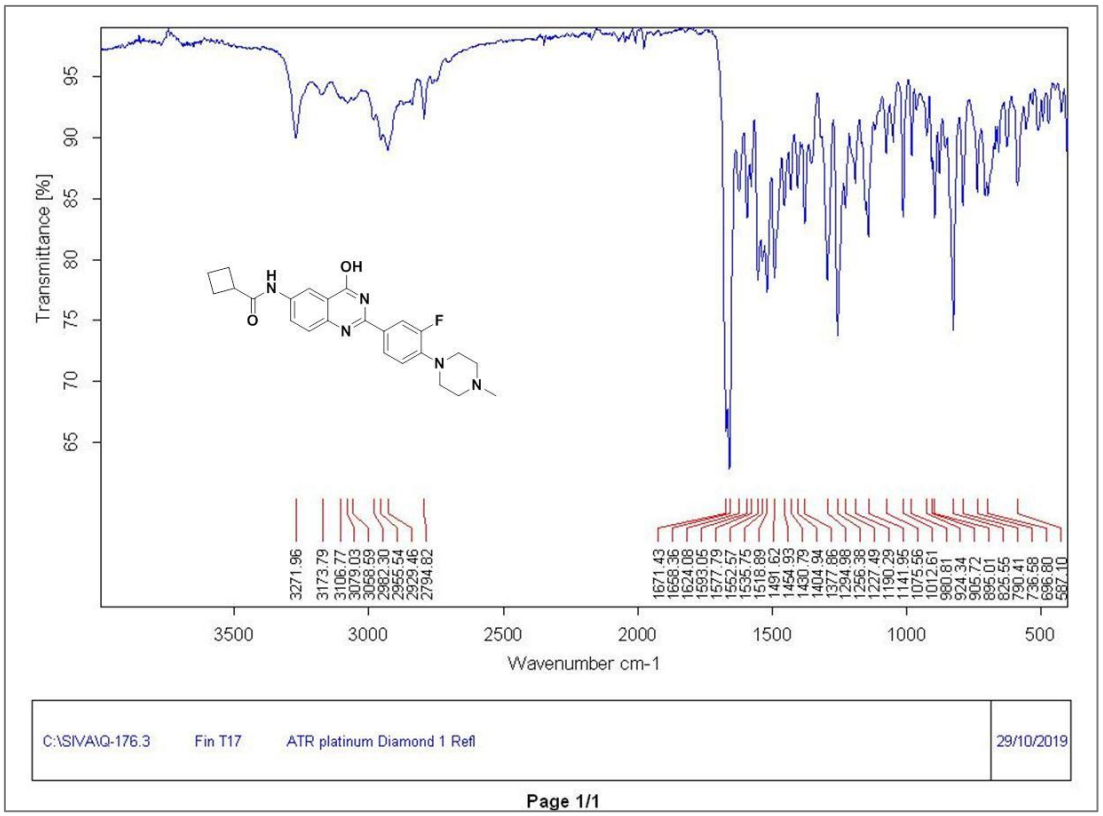
IR spectrum of compound 9f (Chapter 6)



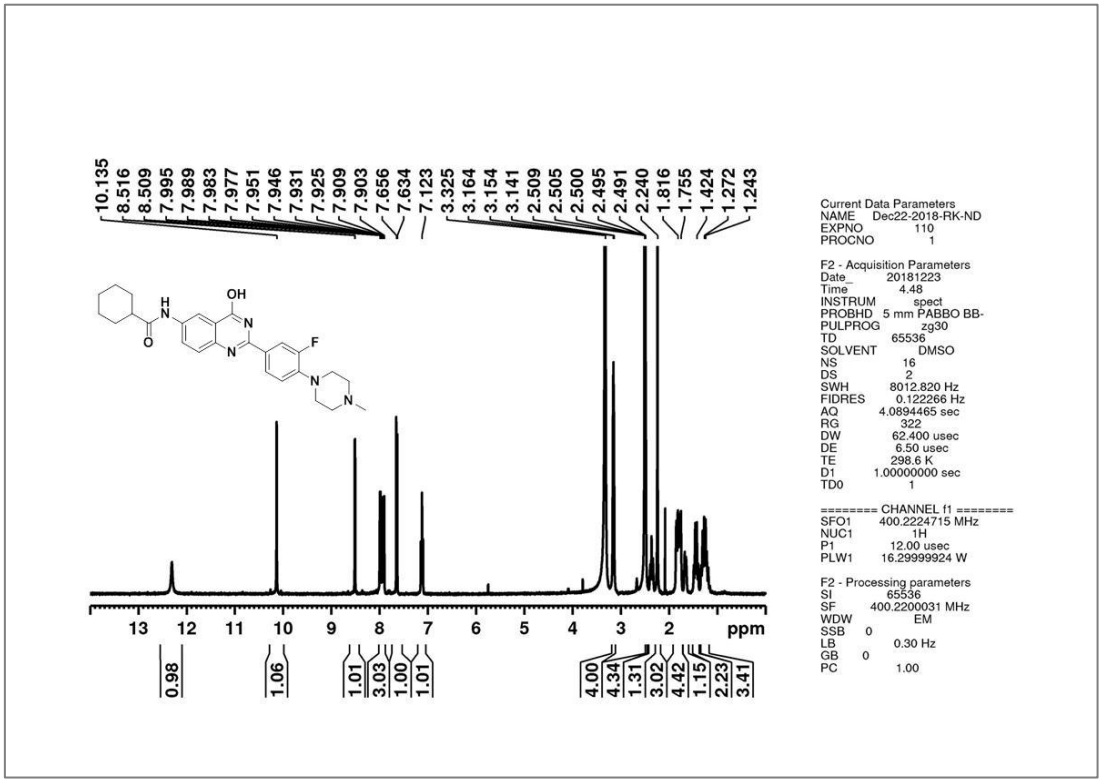
^{1}H NMR spectrum of compound 9g (Chapter 6)



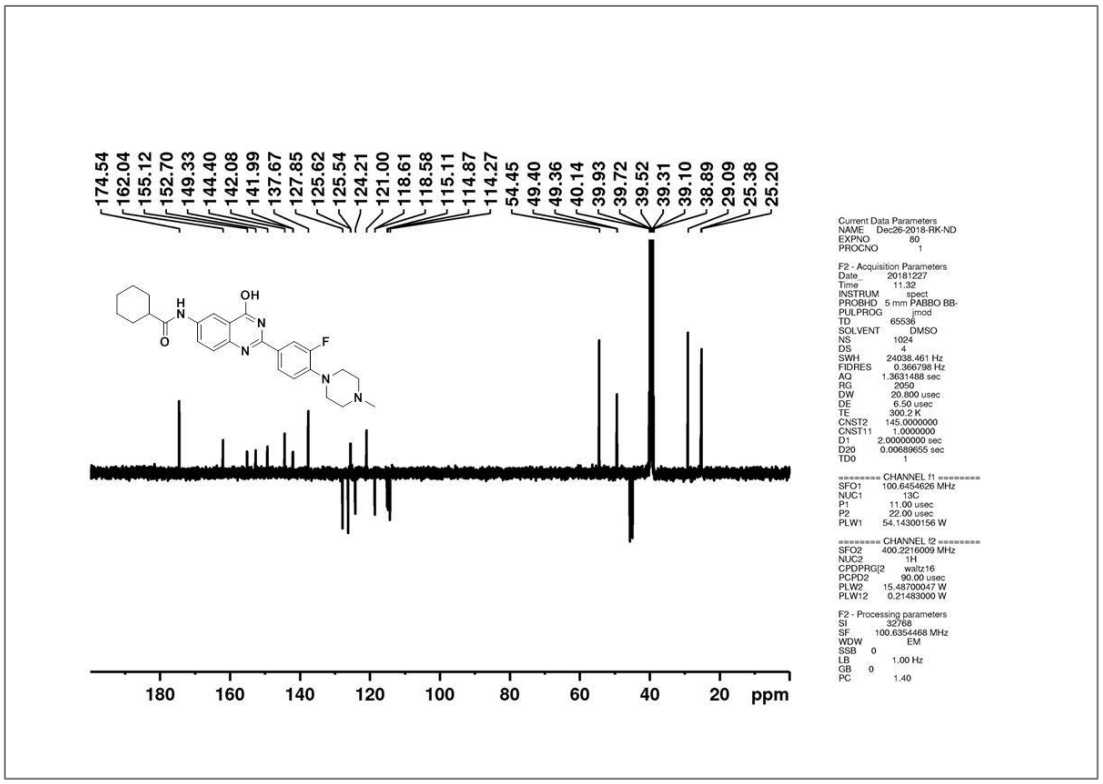
^{13}C NMR spectrum of compound 9g (Chapter 6)



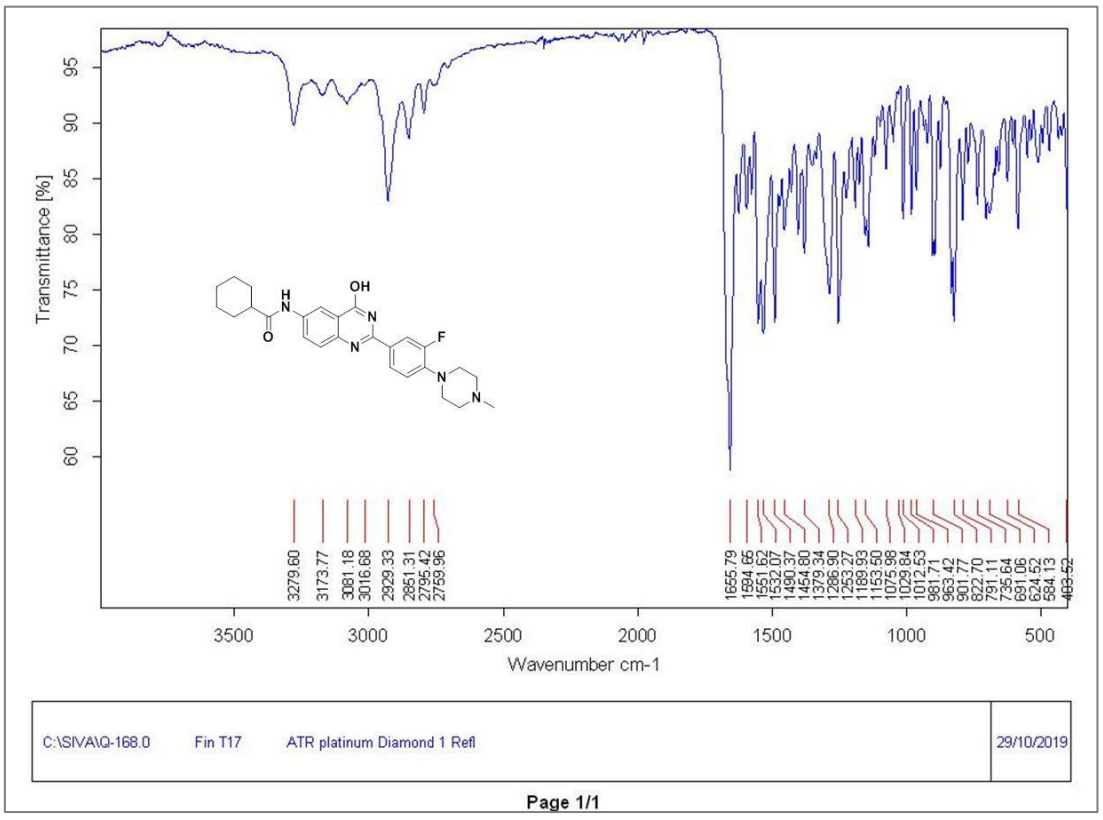
IR spectrum of compound 9g (Chapter 6)



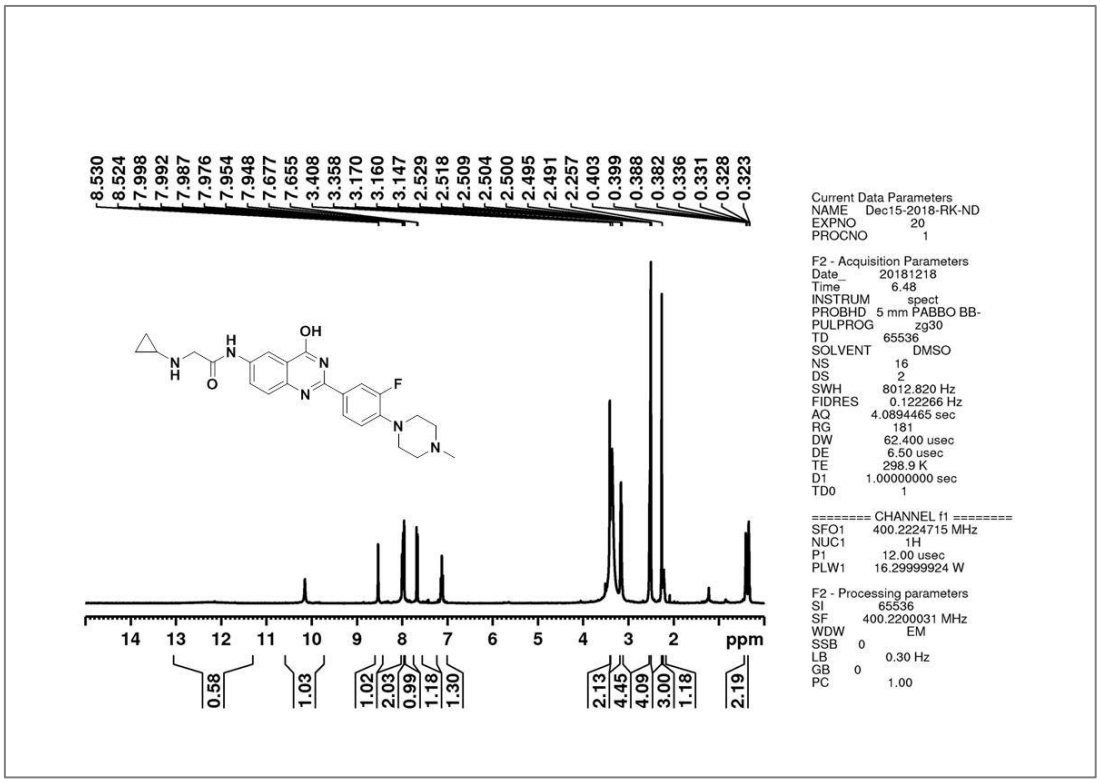
^{1}H NMR spectrum of compound 9h (Chapter 6)



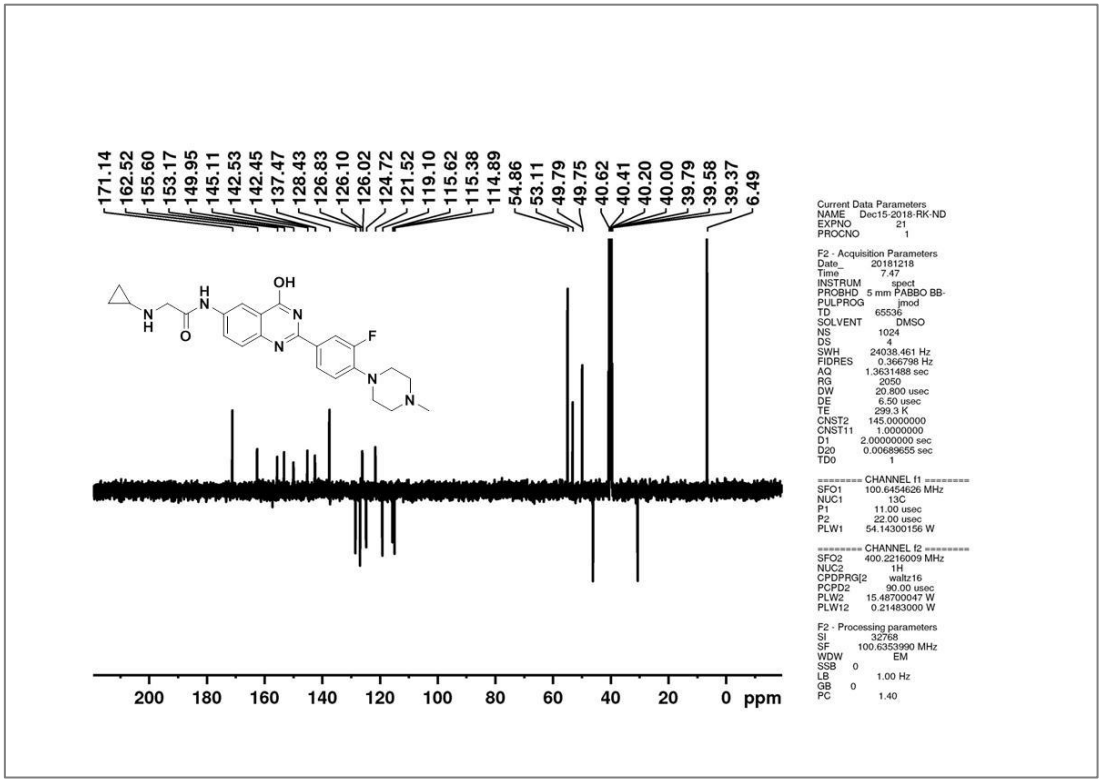
^{13}C NMR spectrum of compound 9h (Chapter 6)



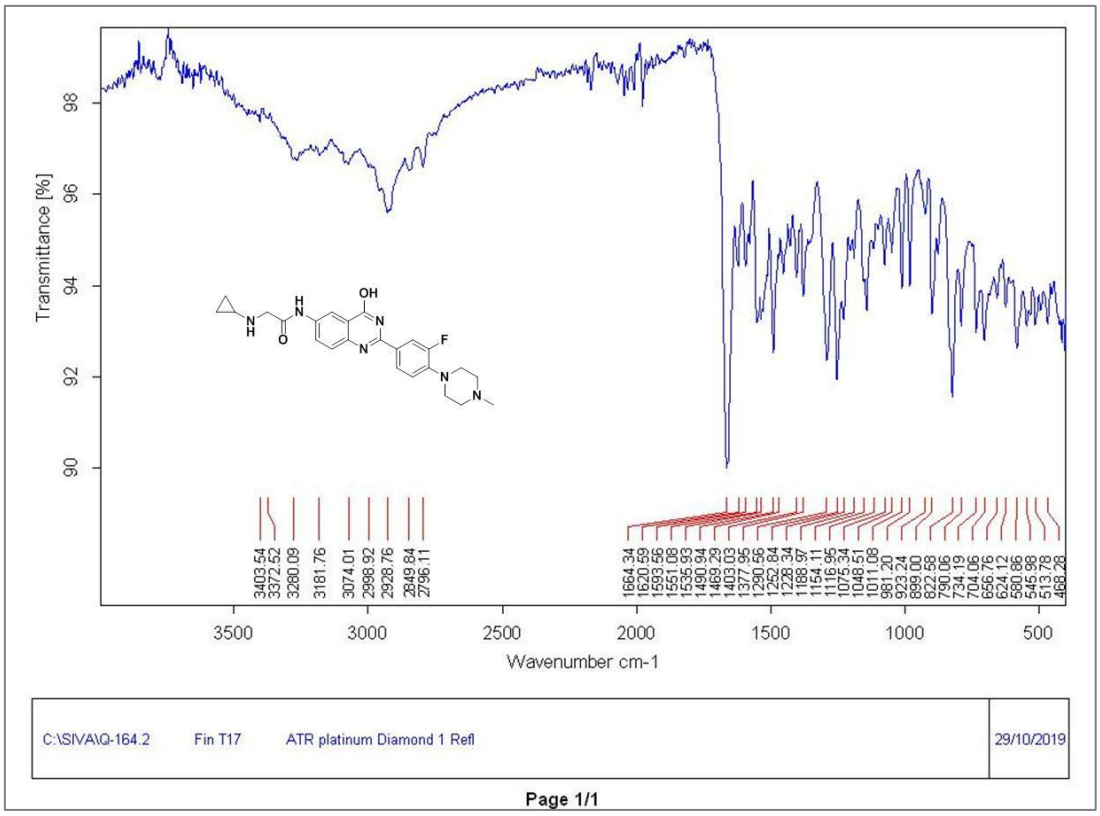
IR spectrum of compound 9h (Chapter 6)



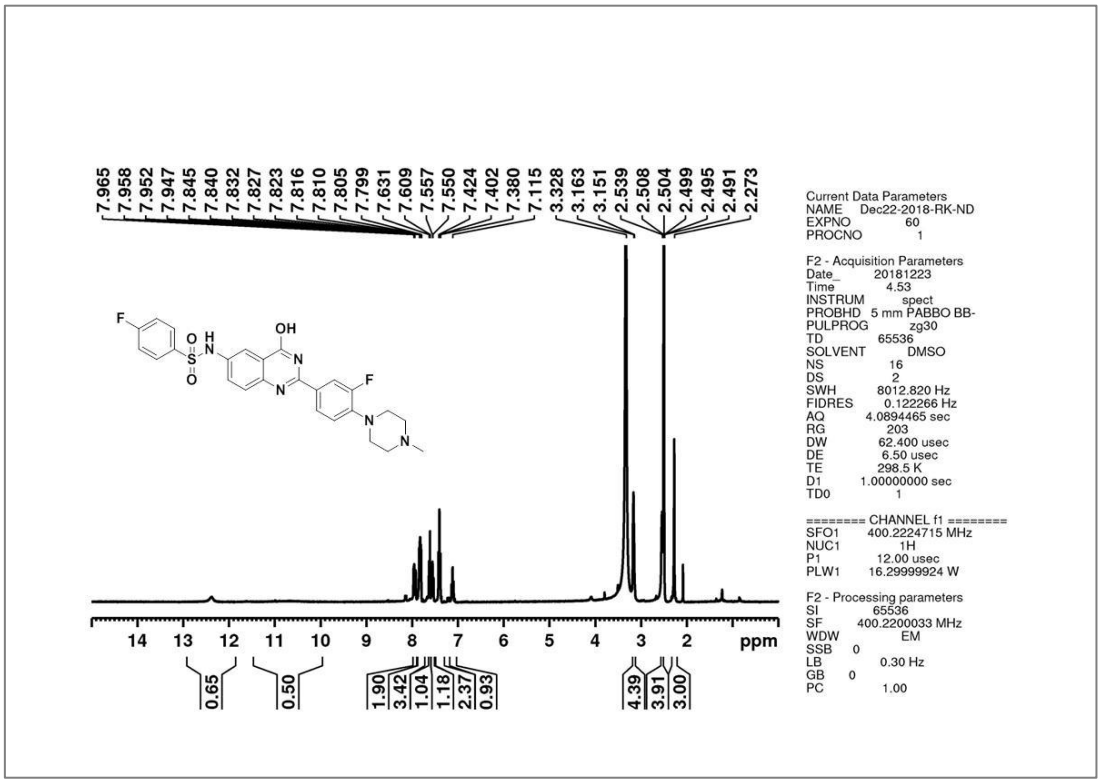
^{1}H NMR spectrum of compound 9i (Chapter 6)



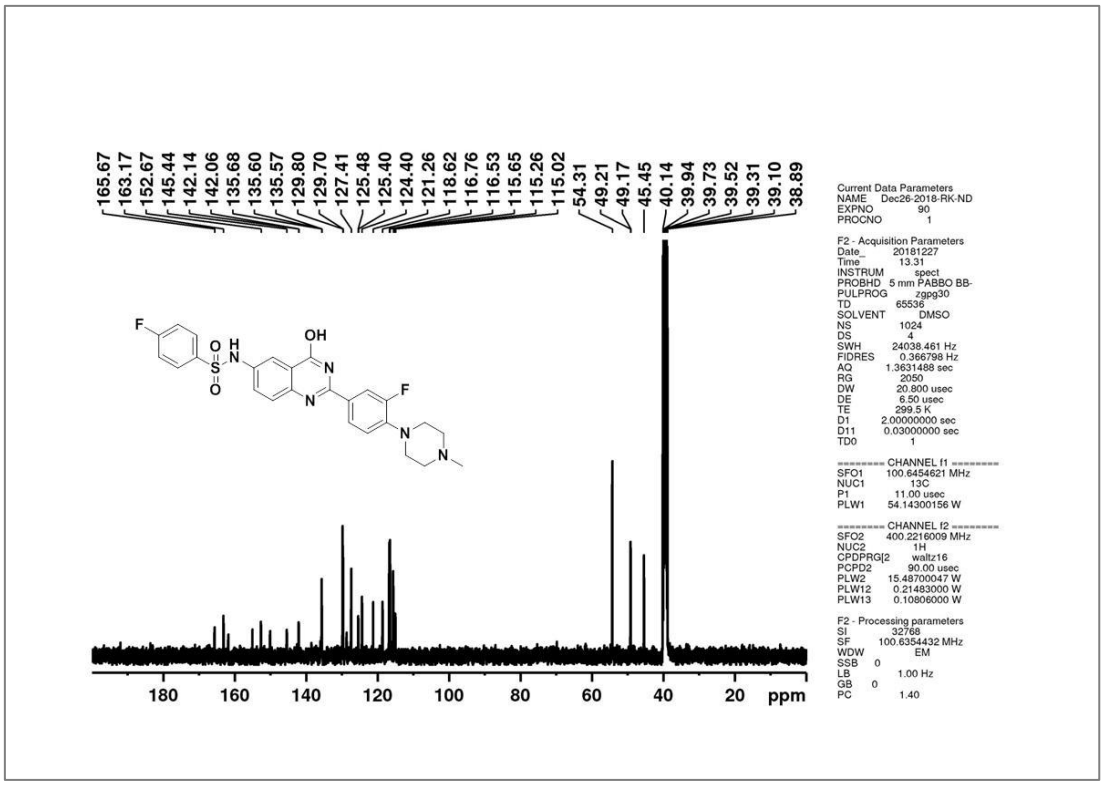
^{13}C NMR spectrum of compound 9i (Chapter 6)



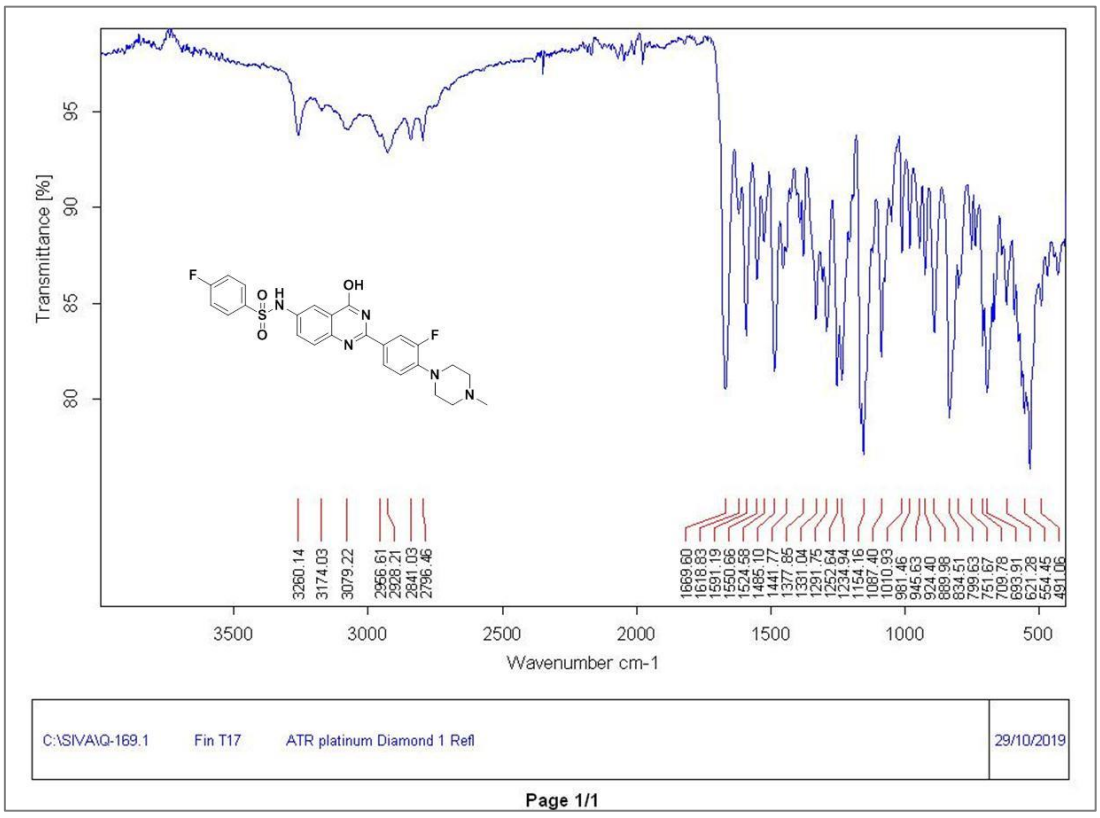
IR spectrum of compound 9i (Chapter 6)



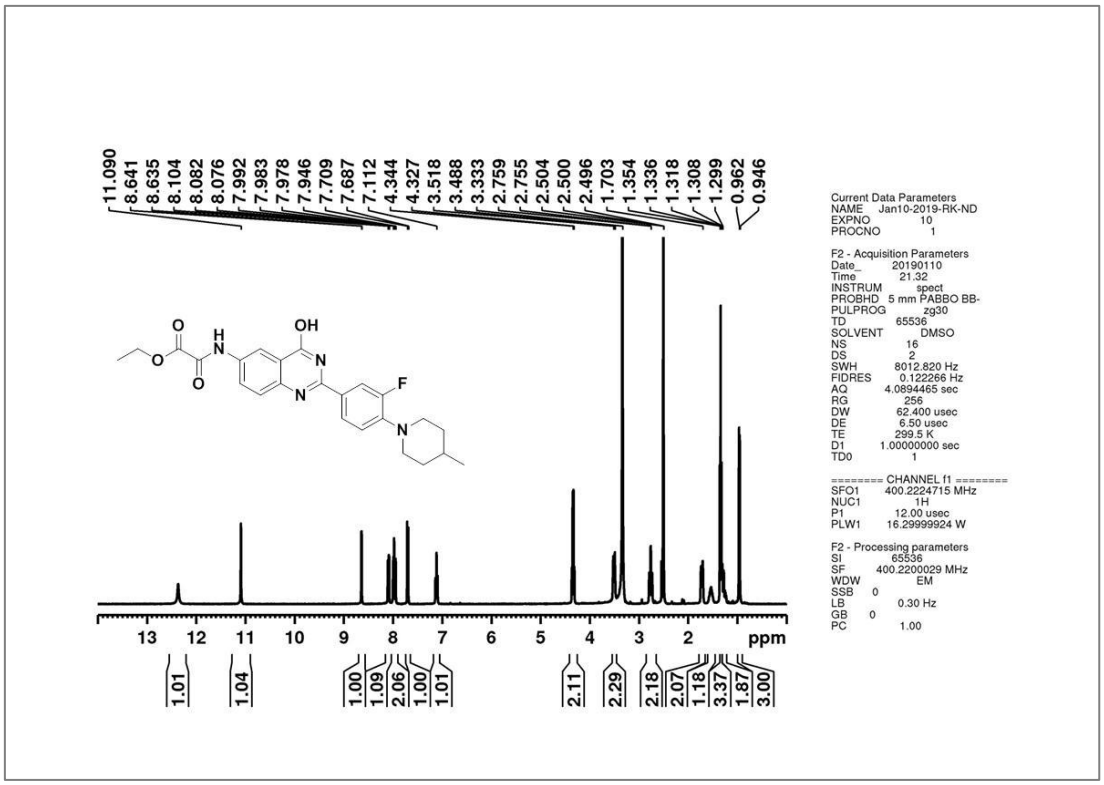
^{1}H NMR spectrum of compound 9j (Chapter 6)



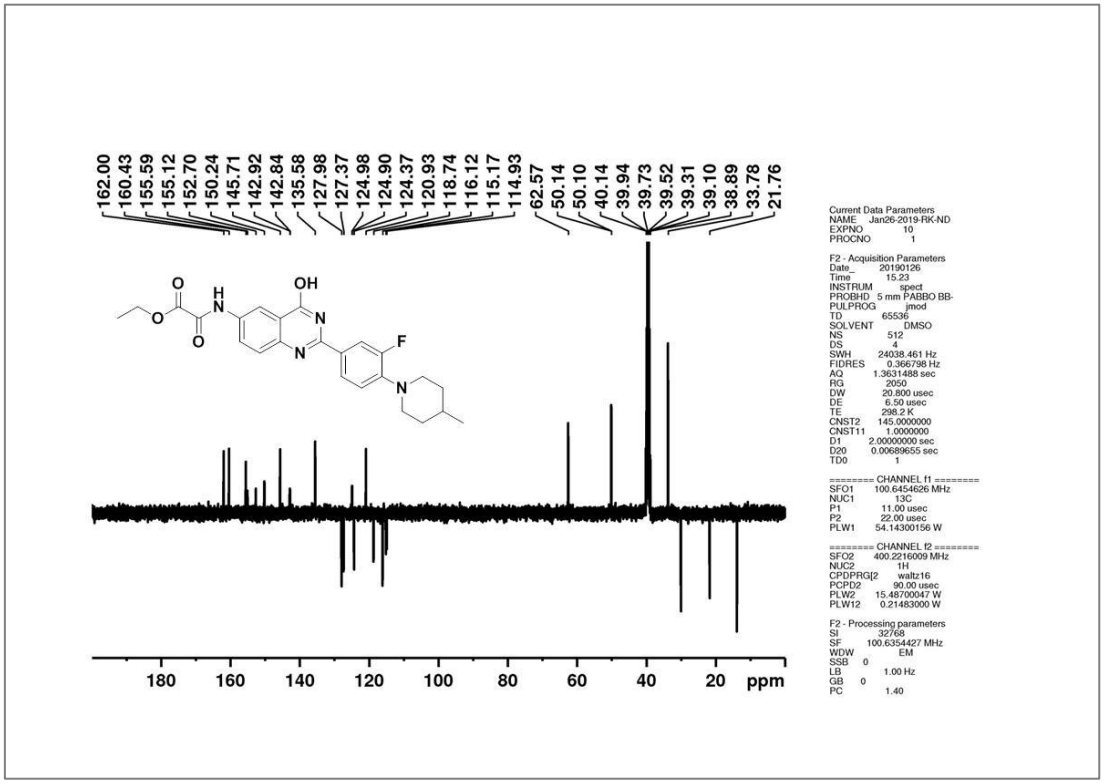
^{13}C NMR spectrum of compound 9j (Chapter 6)



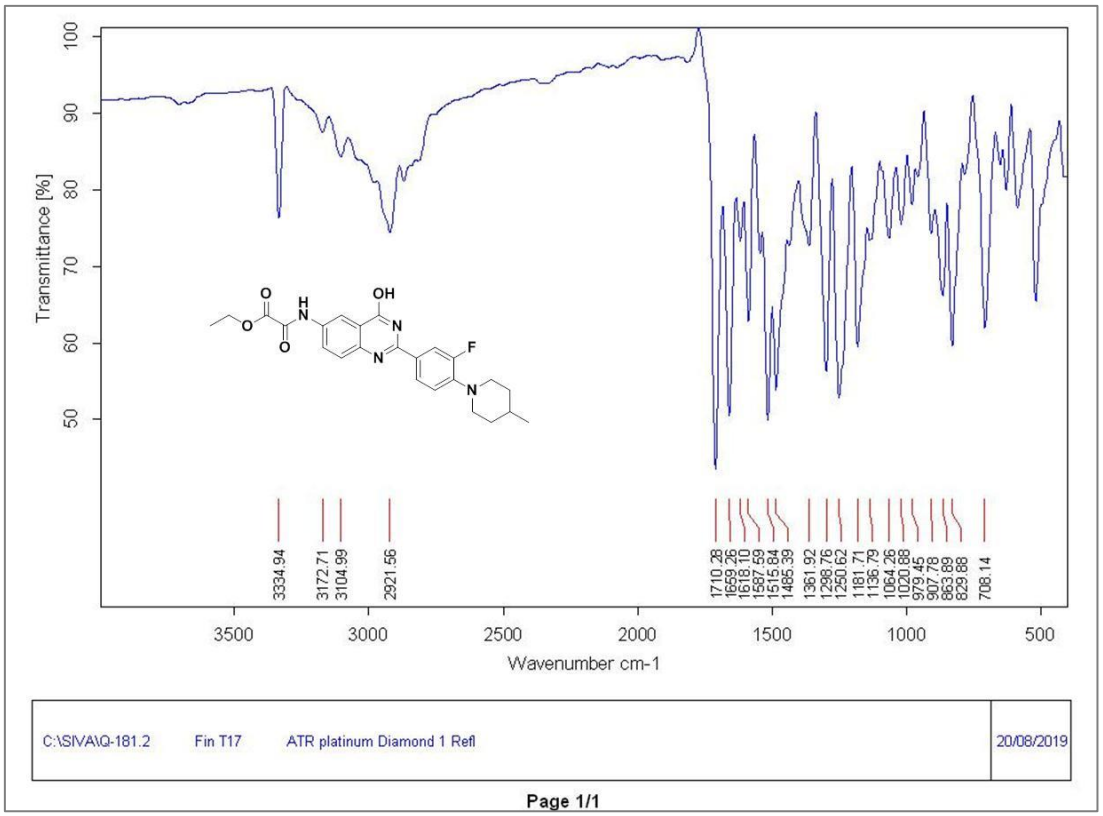
IR spectrum of compound 9j (Chapter 6)



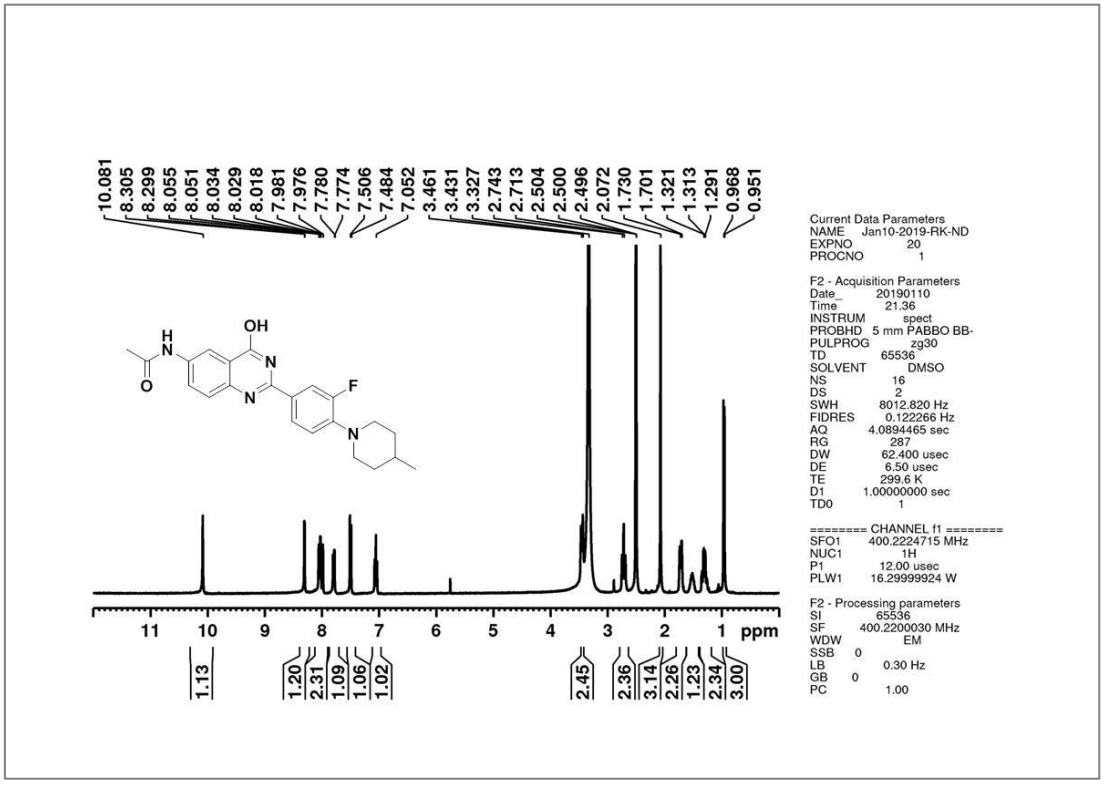
[1]H NMR spectrum of compound 10a (Chapter 6)



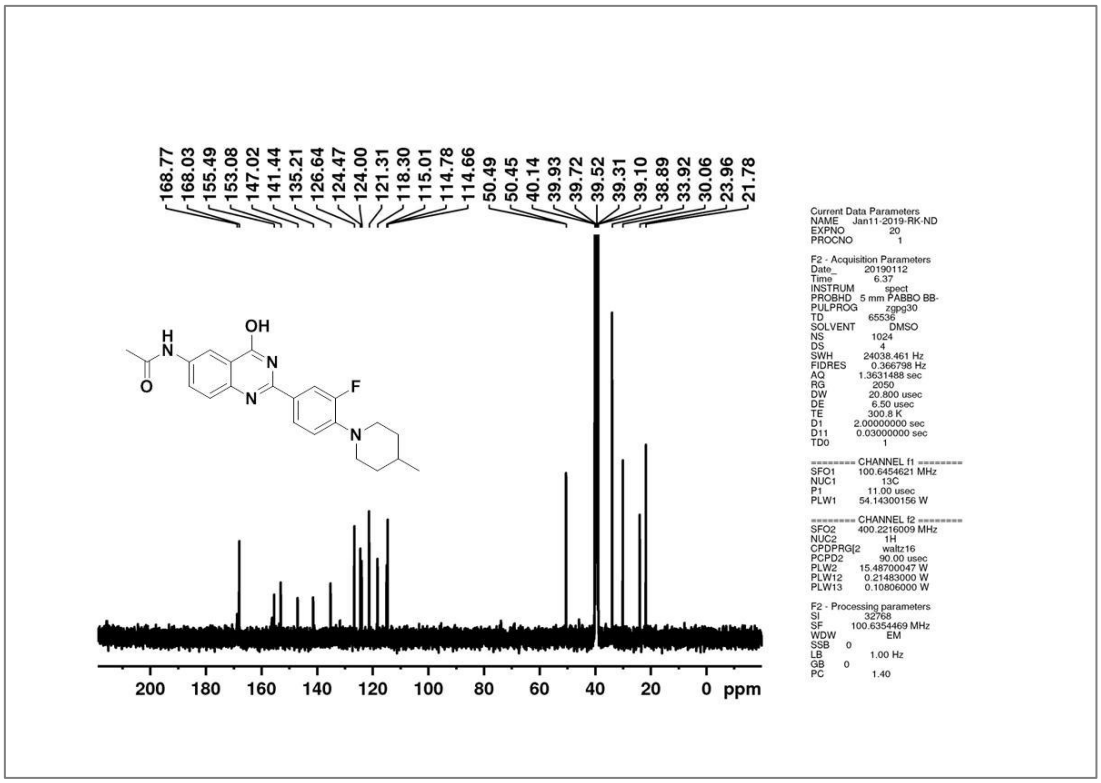
[13]C NMR spectrum of compound 10a (Chapter 6)



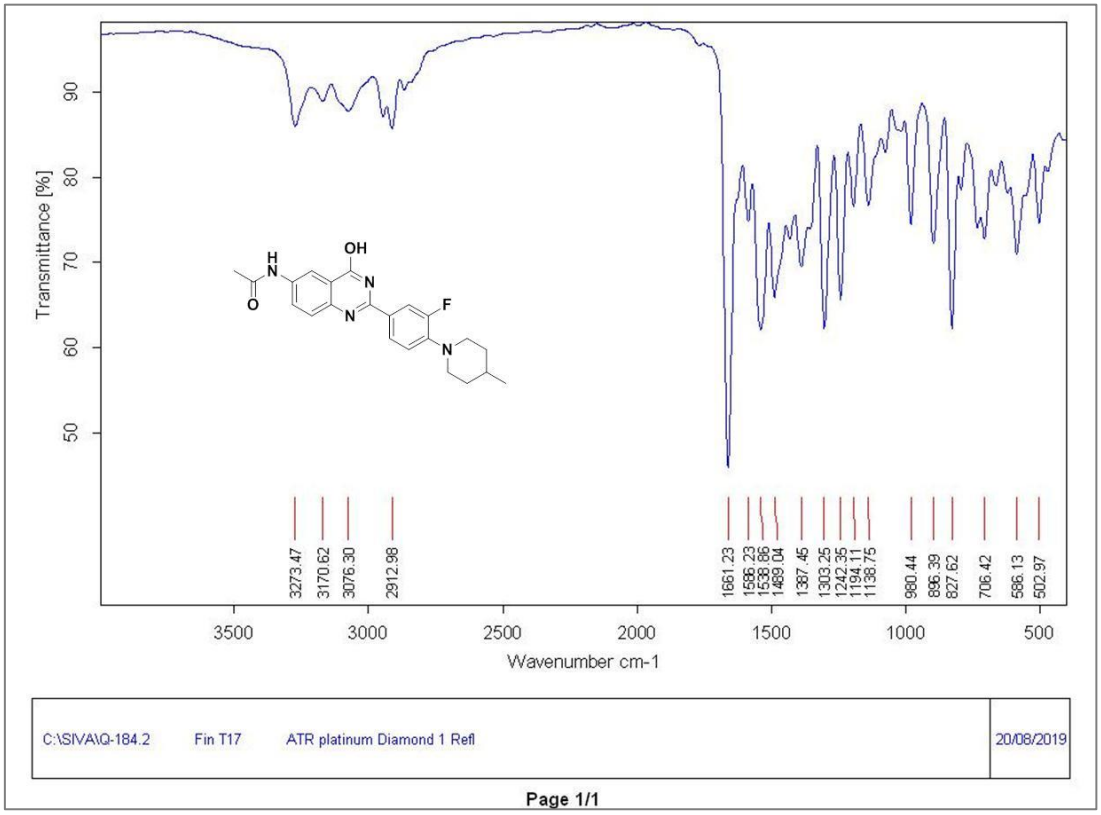
IR spectrum of compound 10a (Chapter 6)



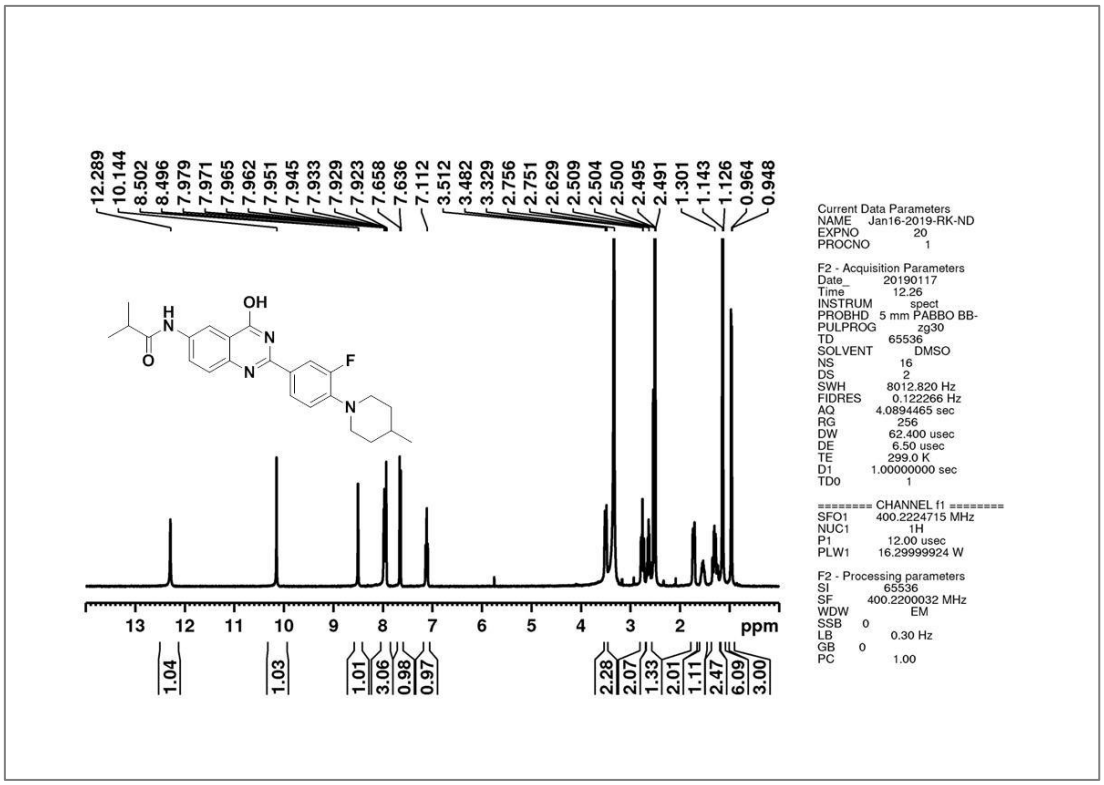
^{1}H NMR spectrum of compound 10b (Chapter 6)



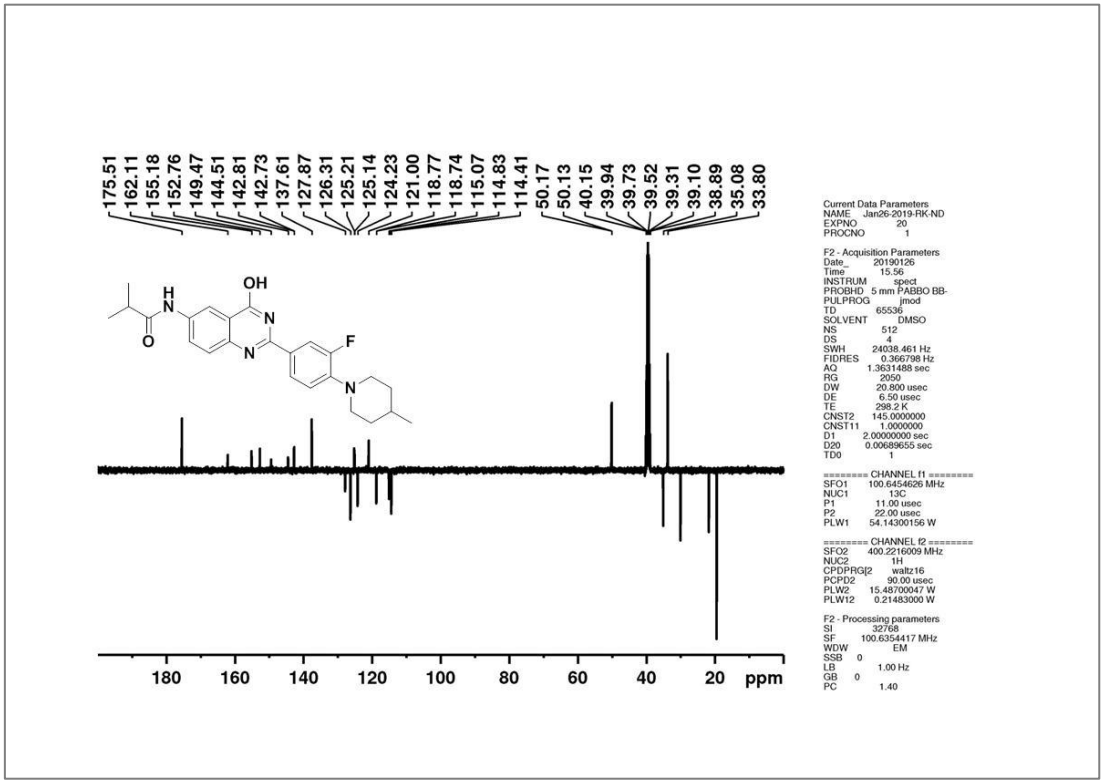
^{13}C NMR spectrum of compound 10b (Chapter 6)



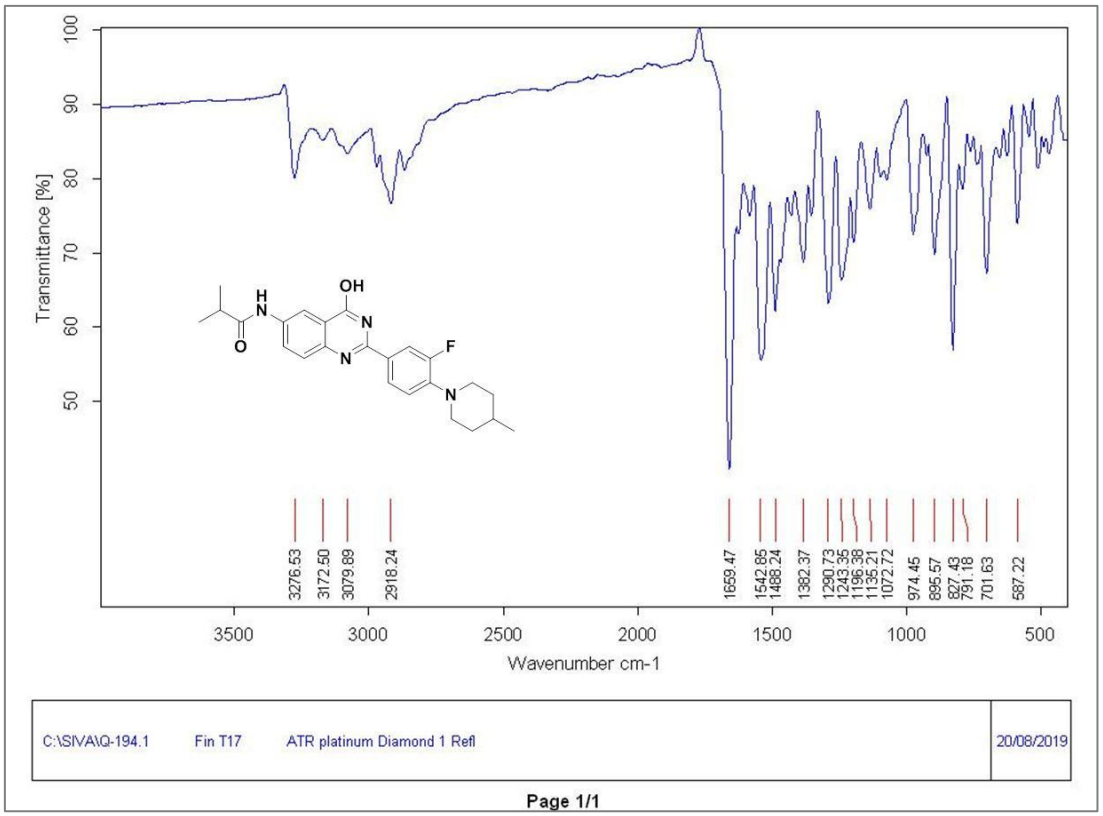
IR spectrum of compound 10b (Chapter 6)



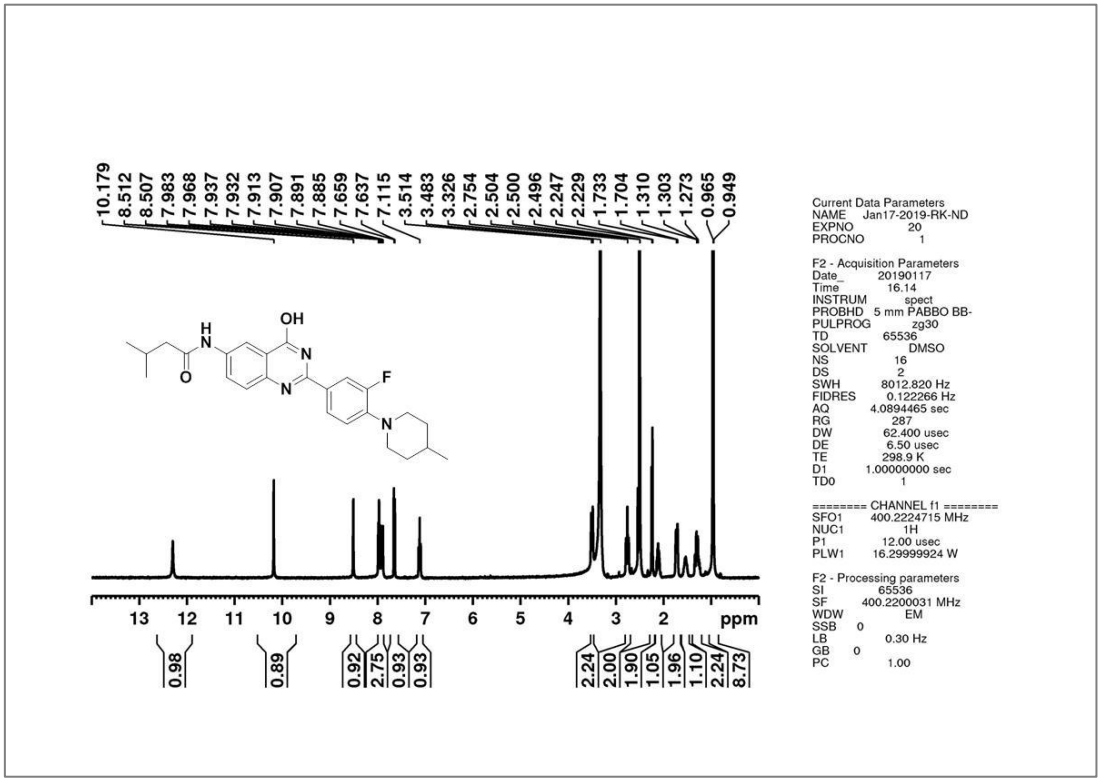
^{1}H NMR spectrum of compound 10c (Chapter 6)



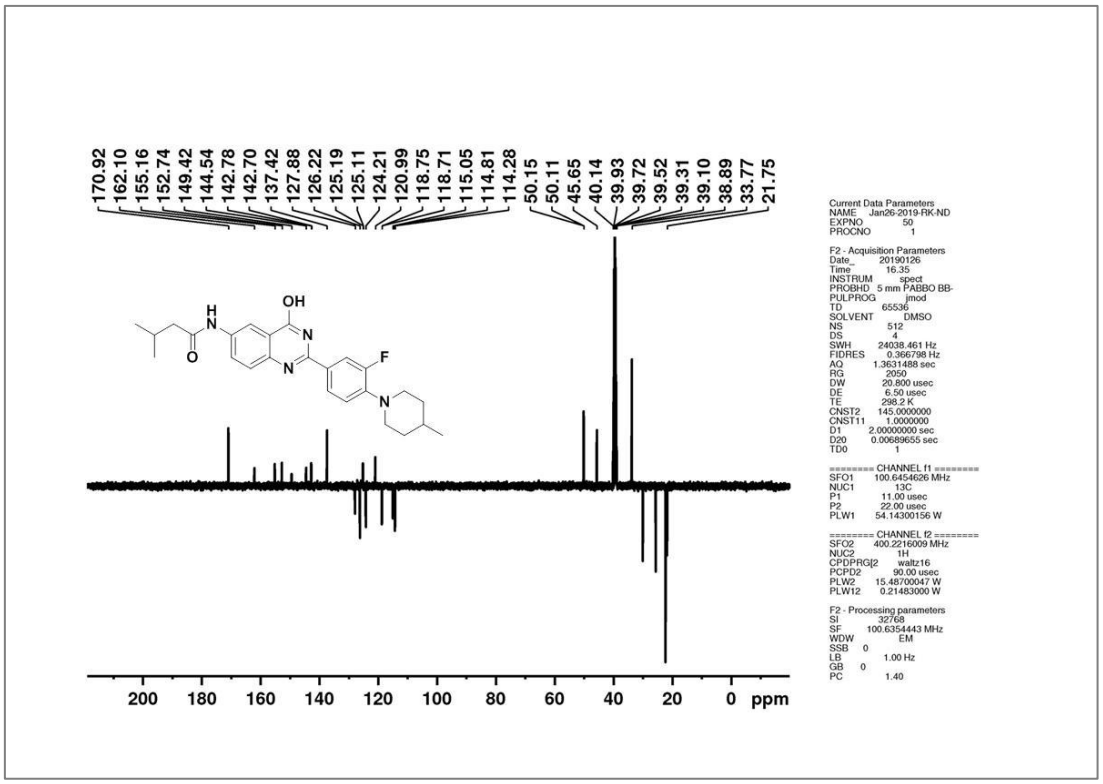
^{13}C NMR spectrum of compound 10c (Chapter 6)



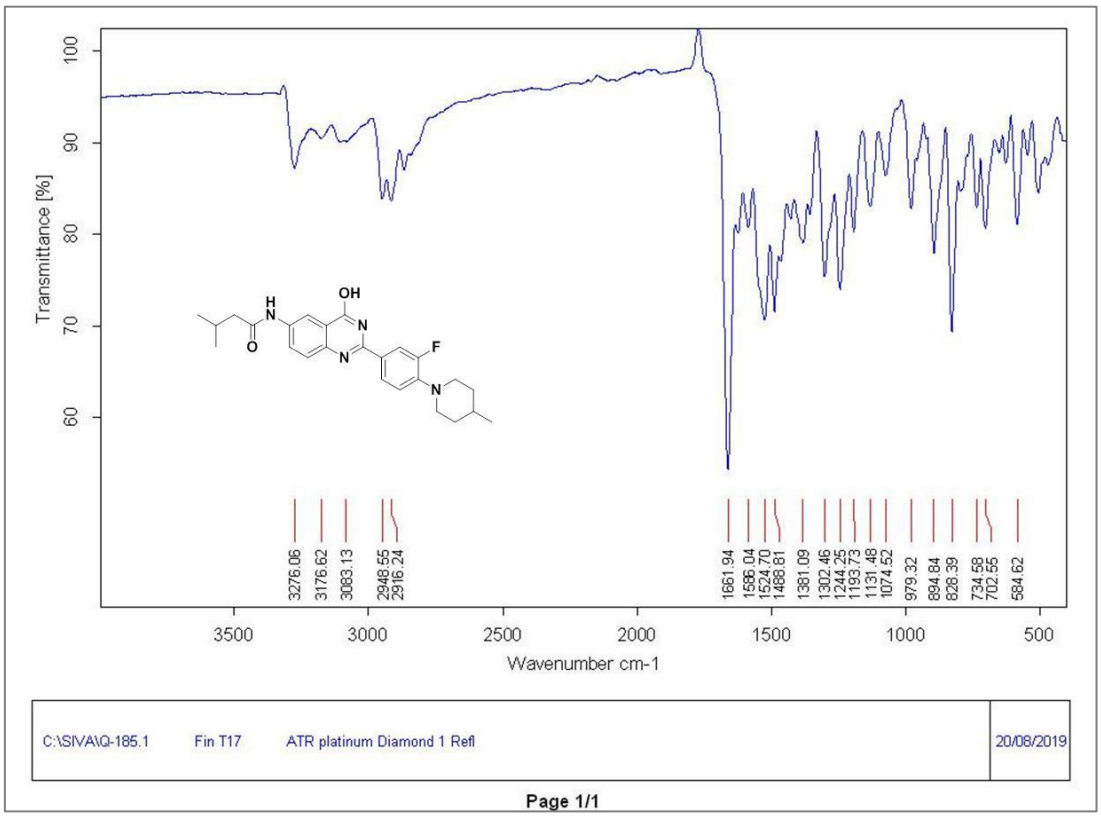
IR spectrum of compound 10c (Chapter 6)



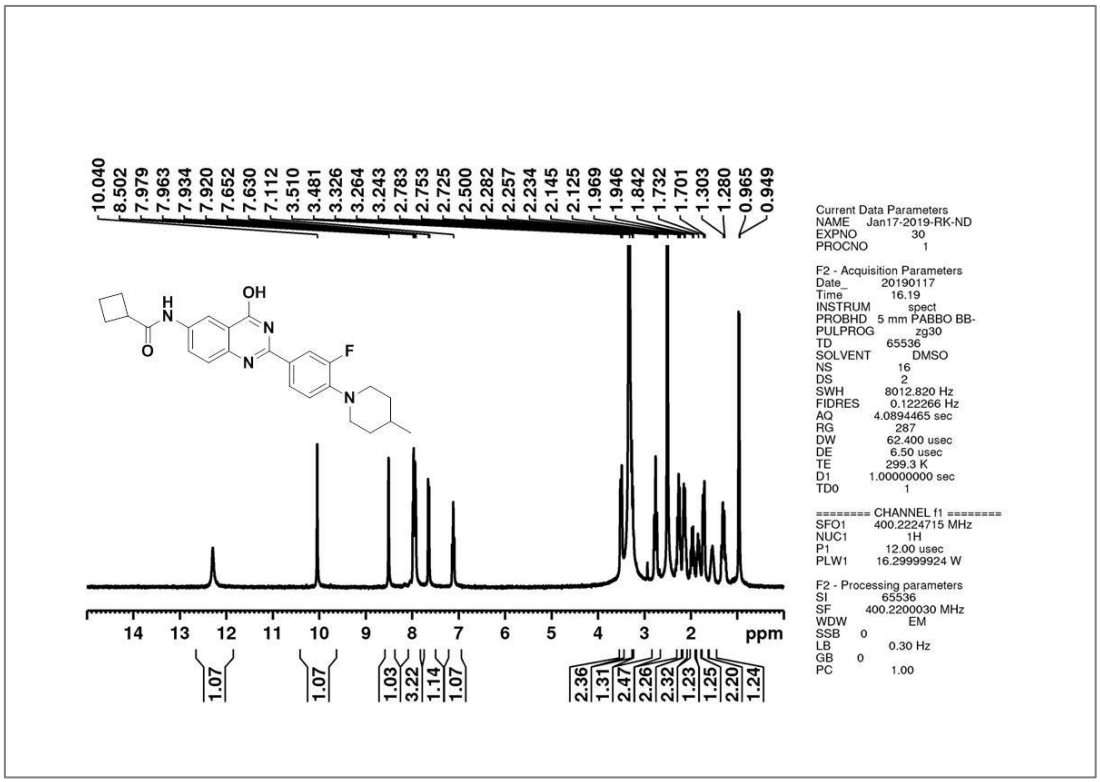
^{1}H NMR spectrum of compound 10d (Chapter 6)



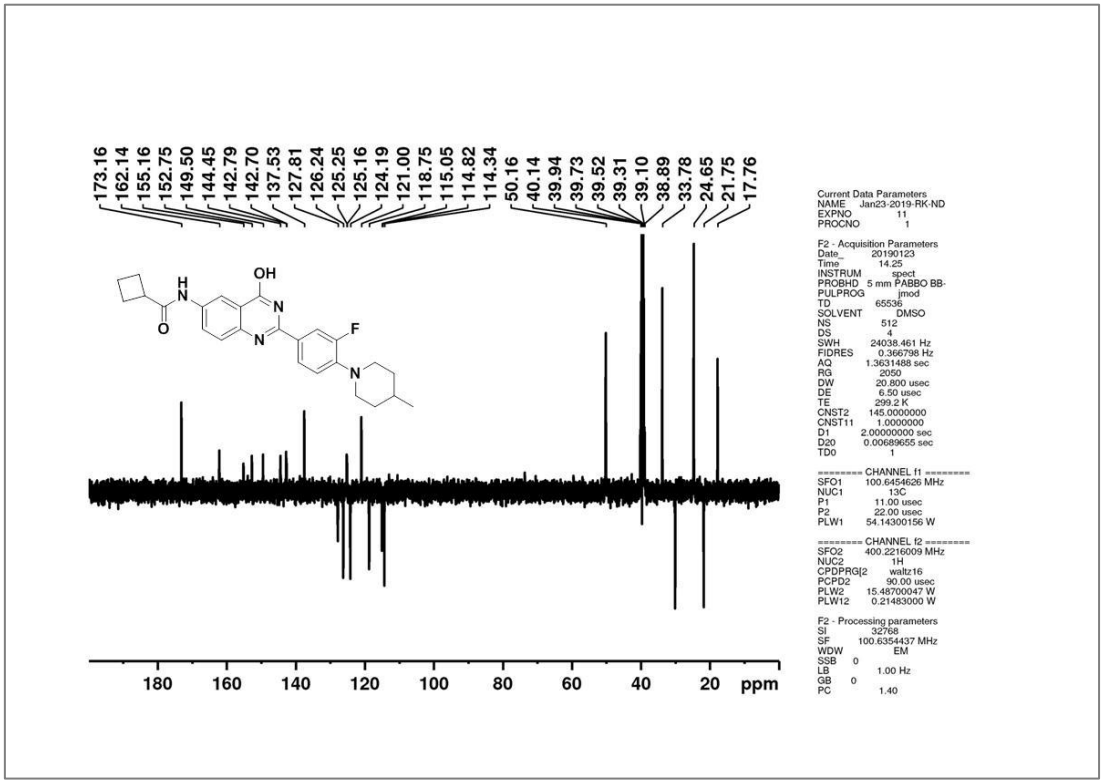
^{13}C NMR spectrum of compound 10d (Chapter 6)



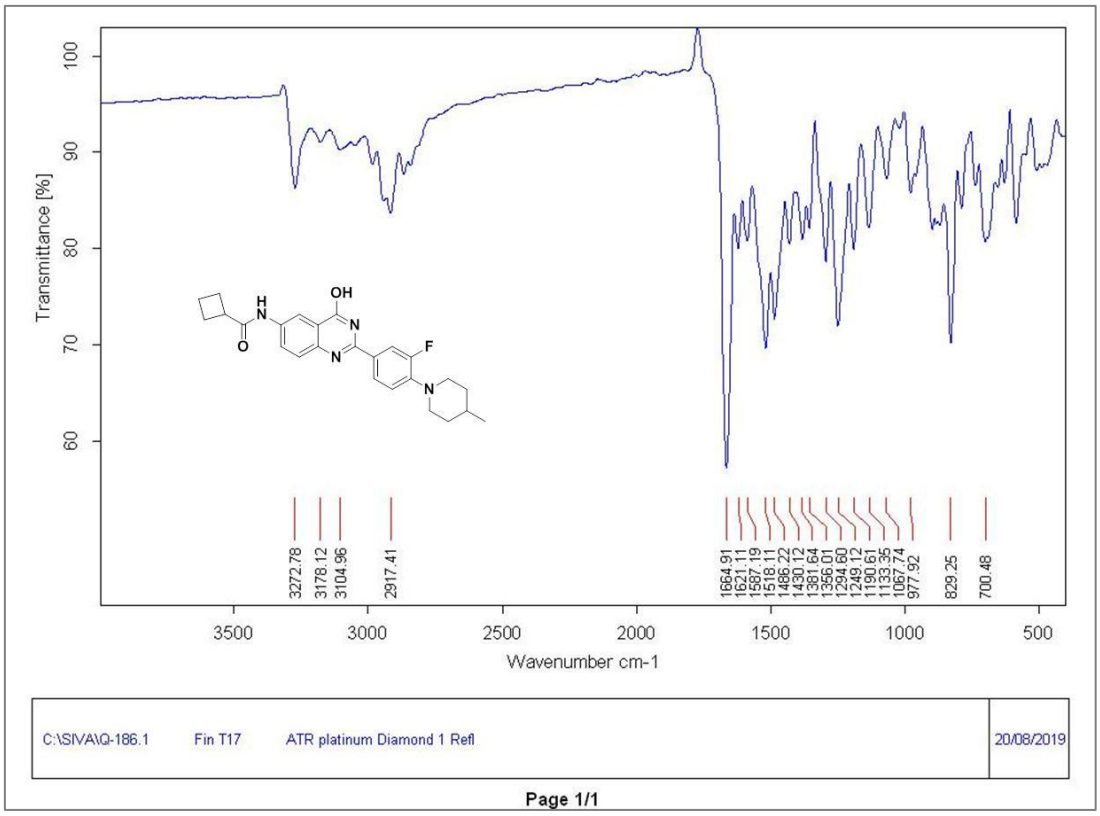
IR spectrum of compound 10d (Chapter 6)



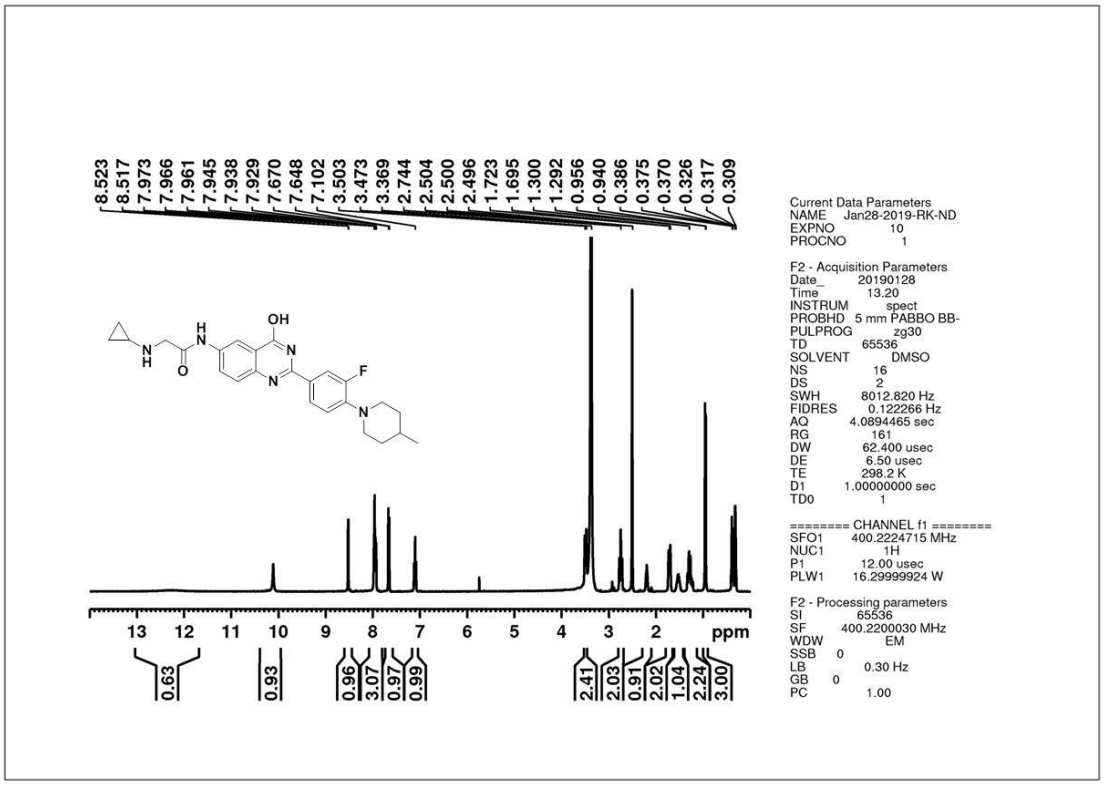
^{1}H NMR spectrum of compound 10e (Chapter 6)



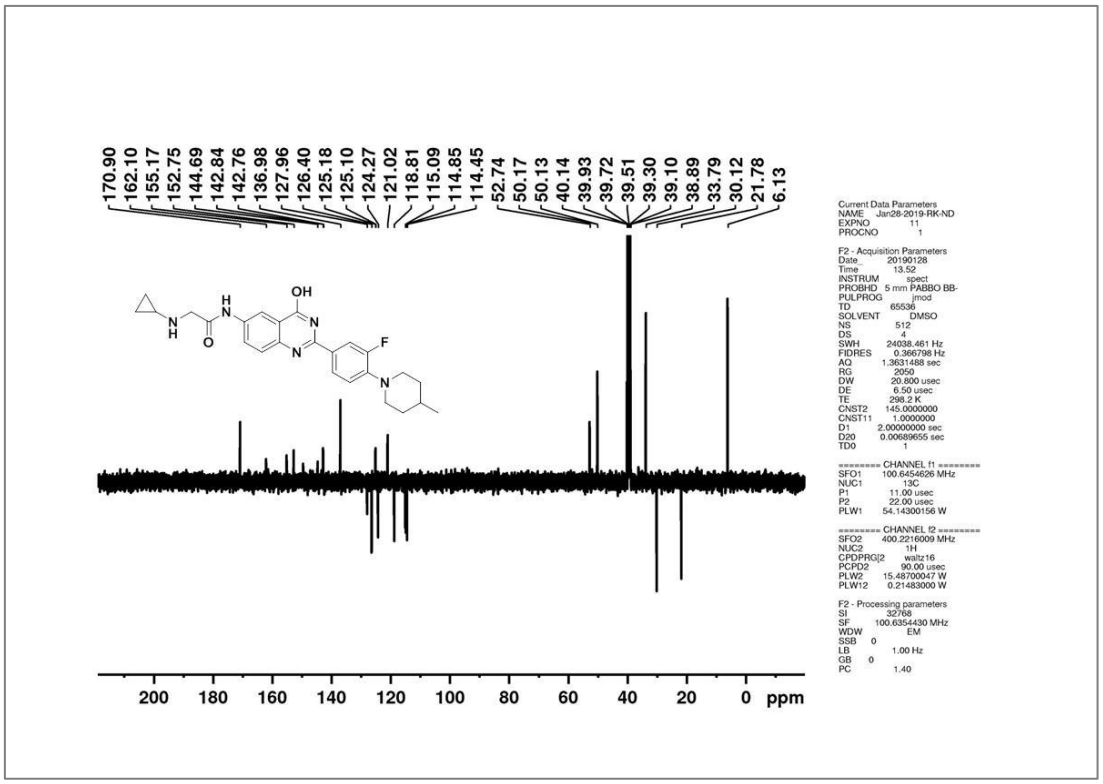
^{13}C NMR spectrum of compound 10e (Chapter 6)



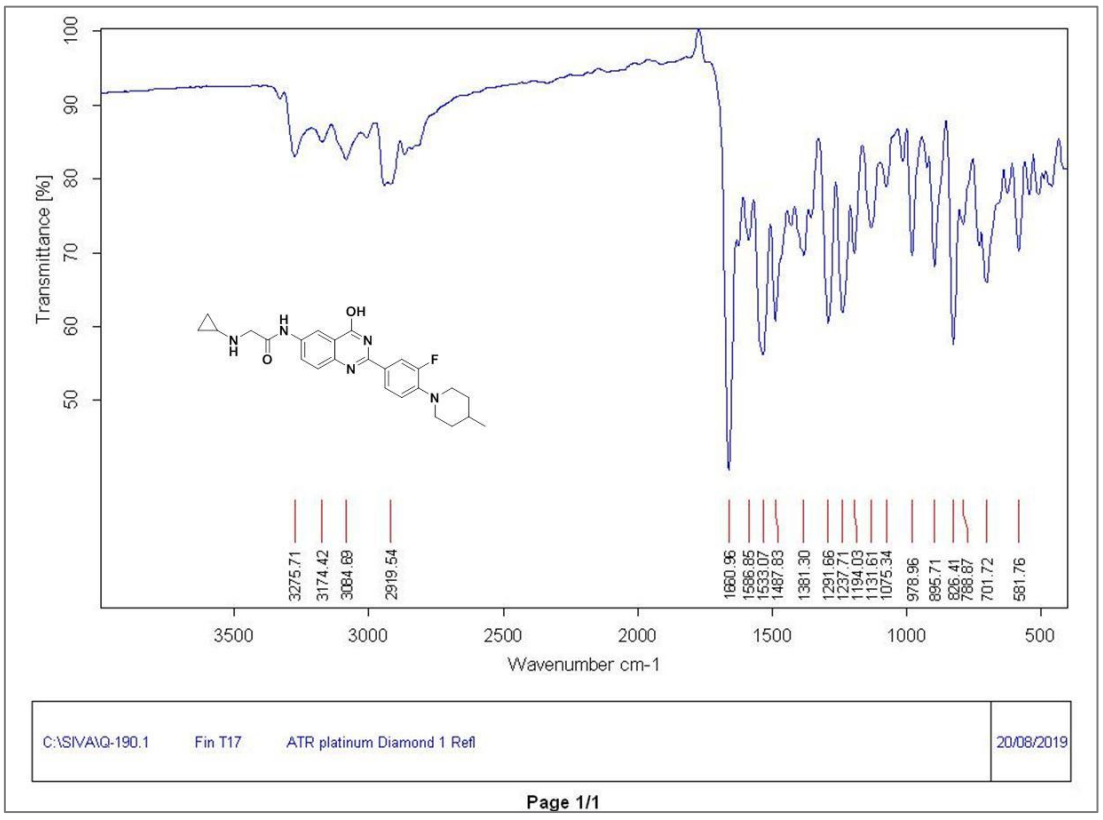
IR spectrum of compound 10e (Chapter 6)



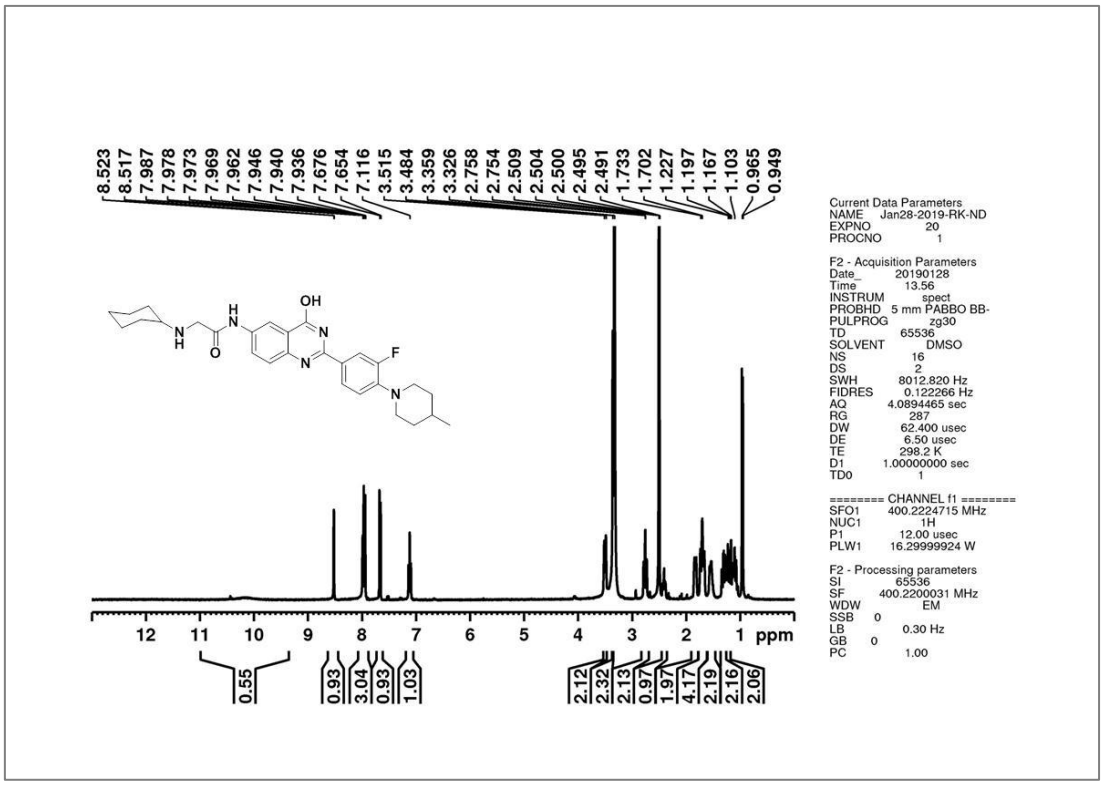
^{1}H NMR spectrum of compound 10f (Chapter 6)



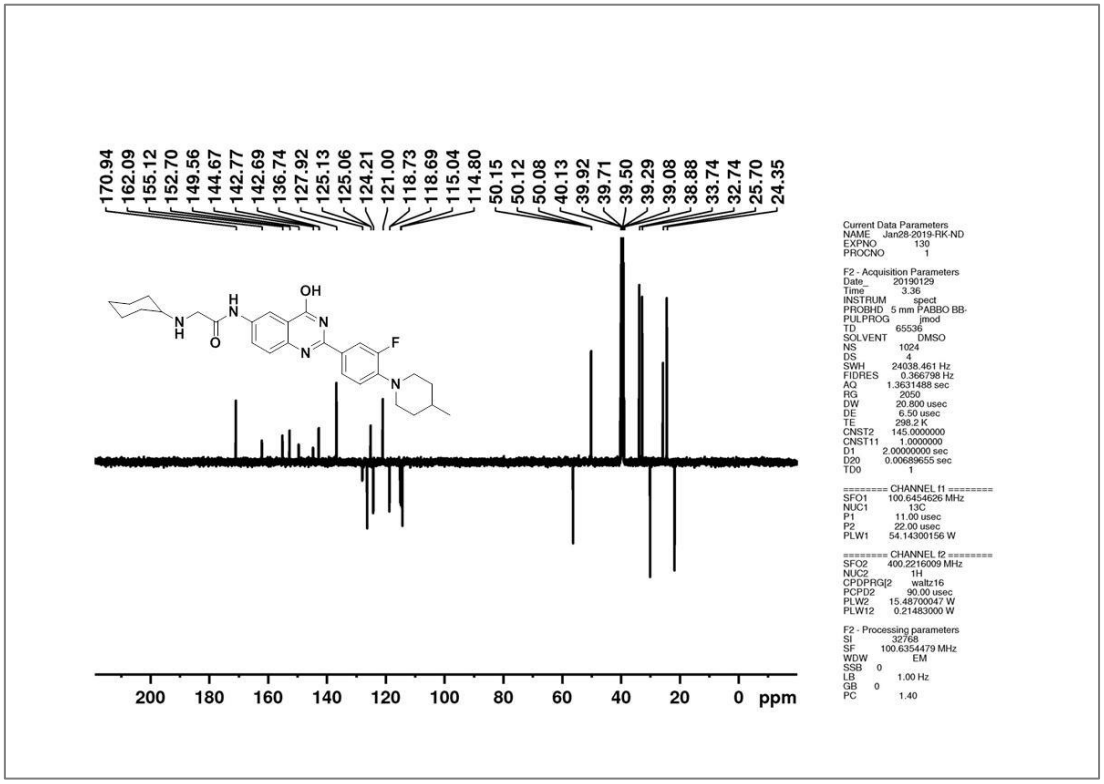
^{13}C NMR spectrum of compound 10f (Chapter 6)



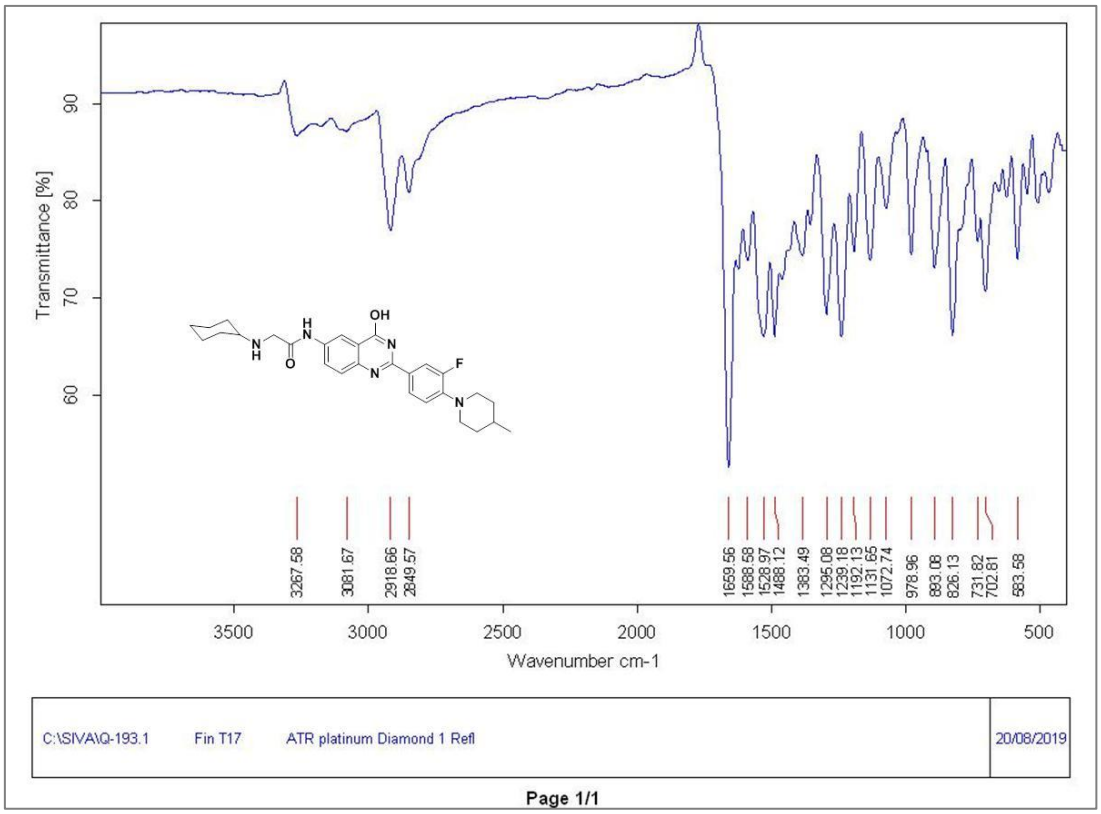
IR spectrum of compound 10f (Chapter 6)



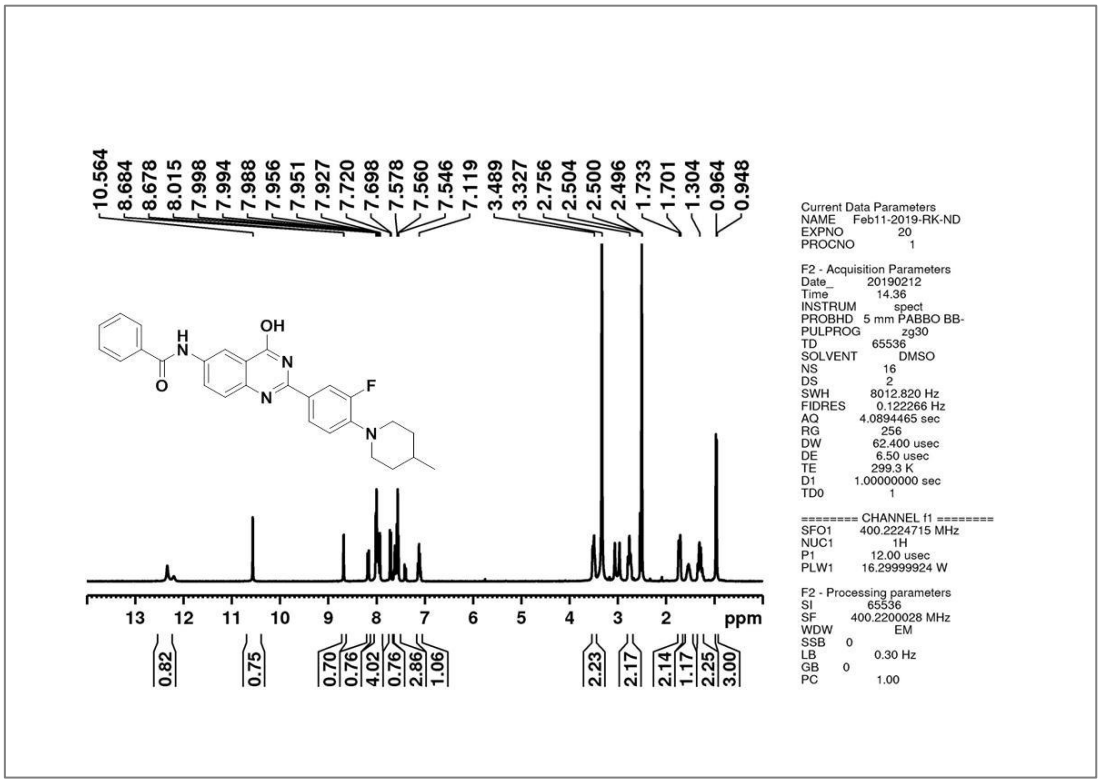
^{1}H NMR spectrum of compound 10g (Chapter 6)



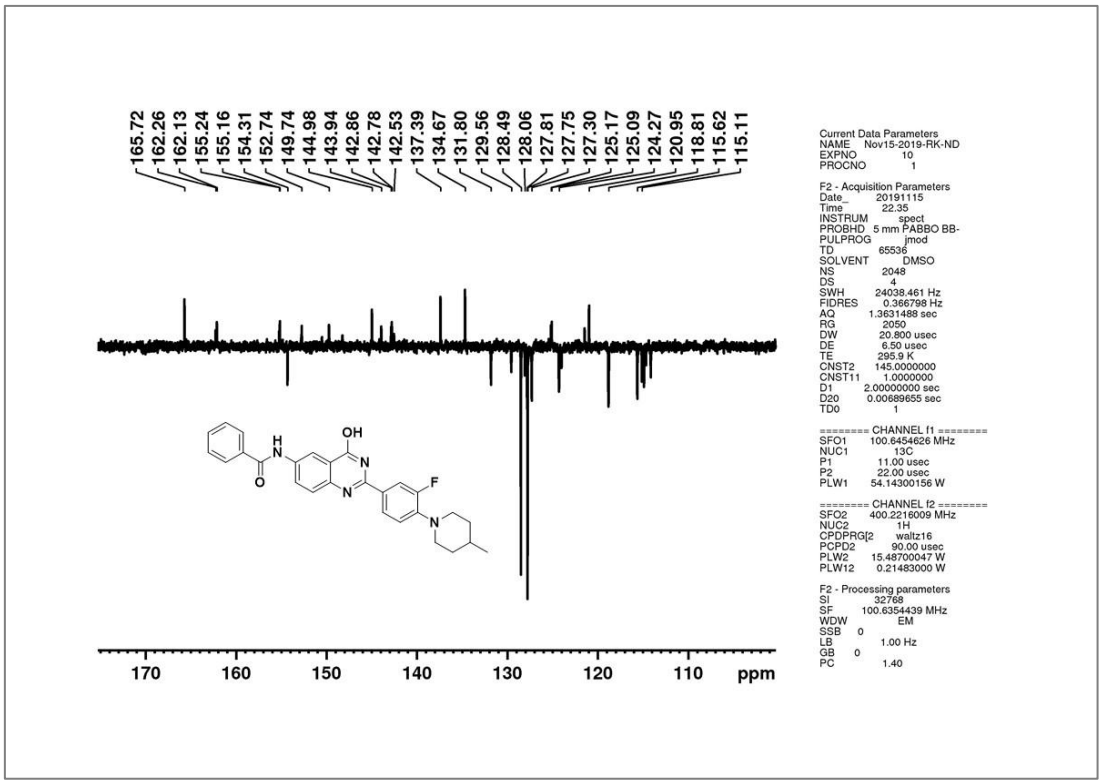
^{13}C NMR spectrum of compound 10g (Chapter 6)



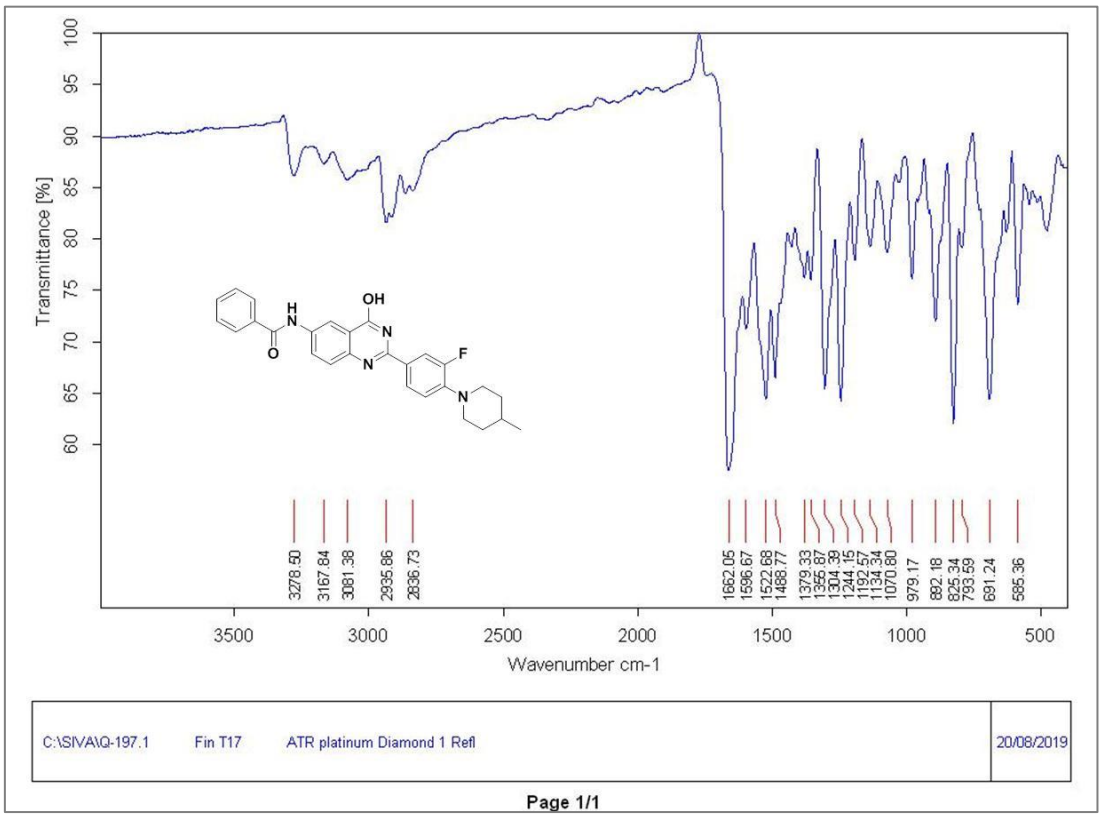
IR spectrum of compound 10g (Chapter 6)



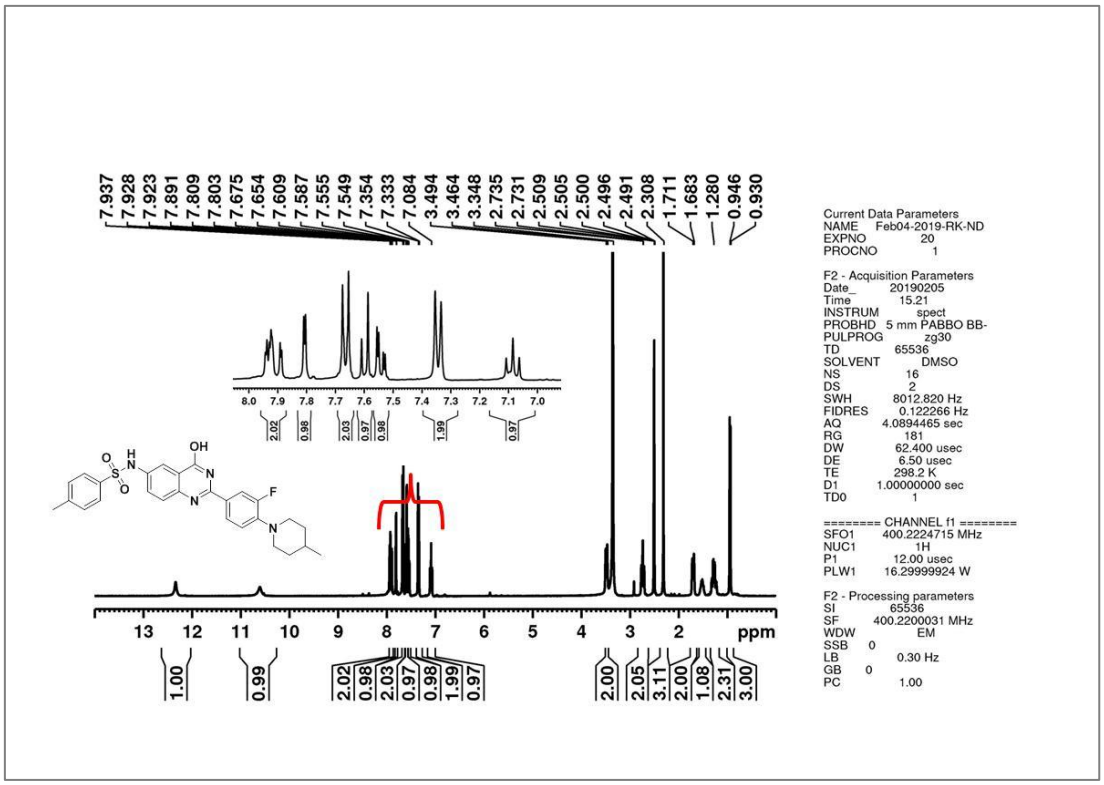
^{1}H NMR spectrum of compound 10h (Chapter 6)



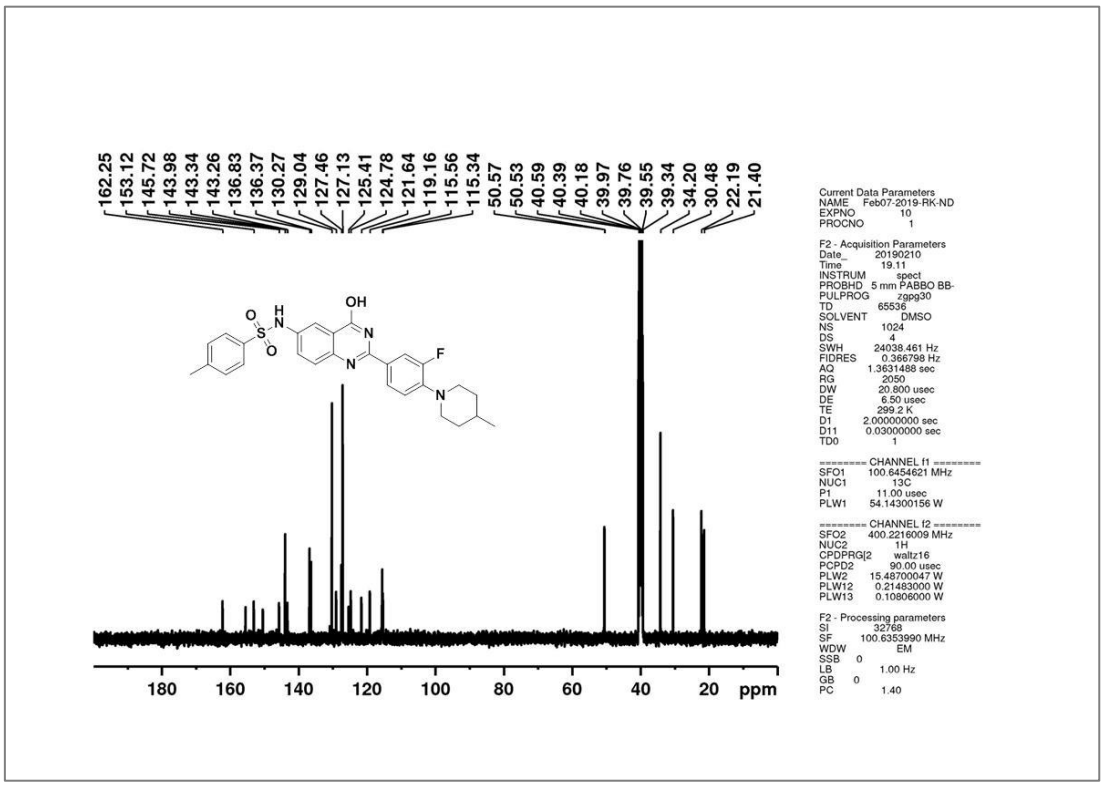
^{13}C NMR spectrum of compound 10h (Chapter 6)



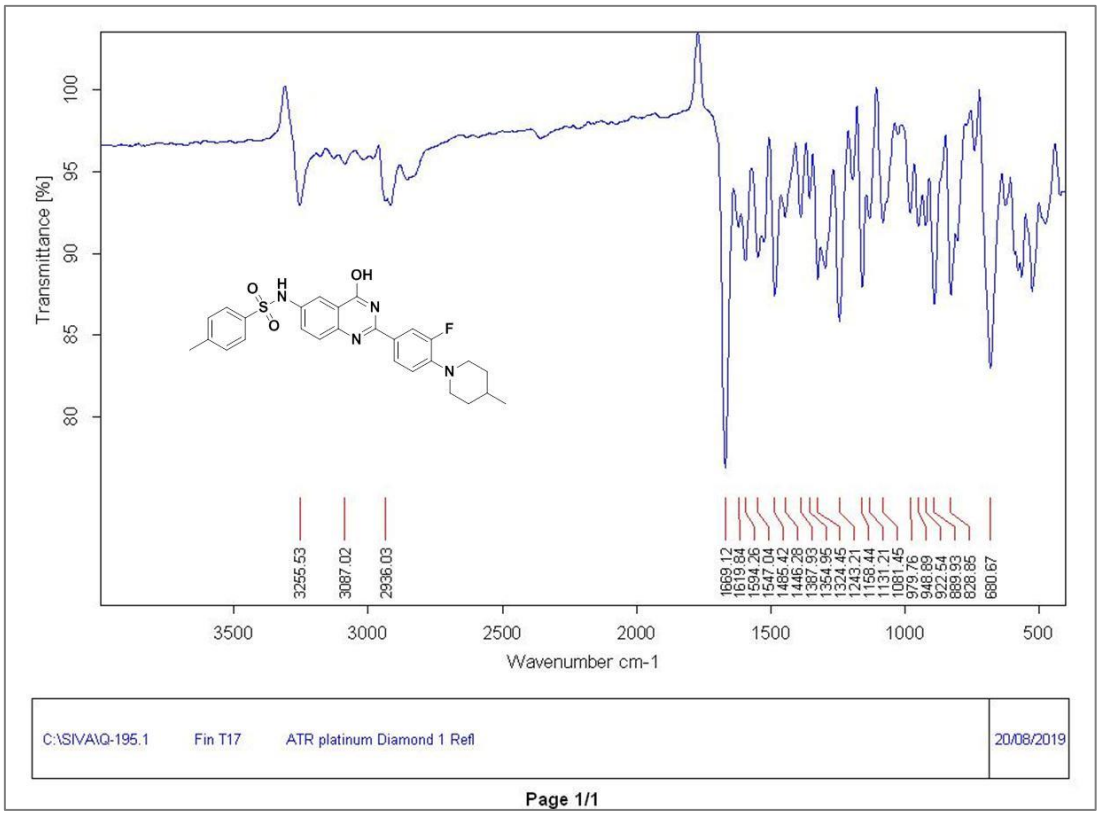
IR spectrum of compound 10h (Chapter 6)



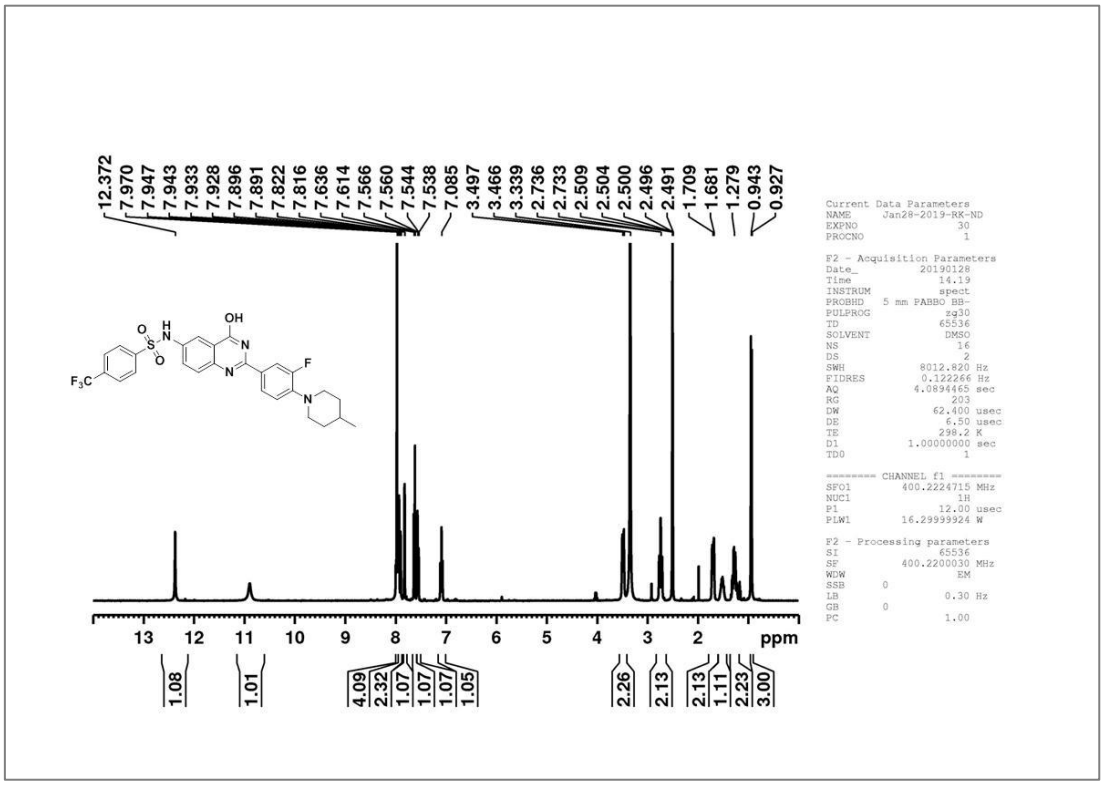
^{1}H NMR spectrum of compound 10i (Chapter 6)



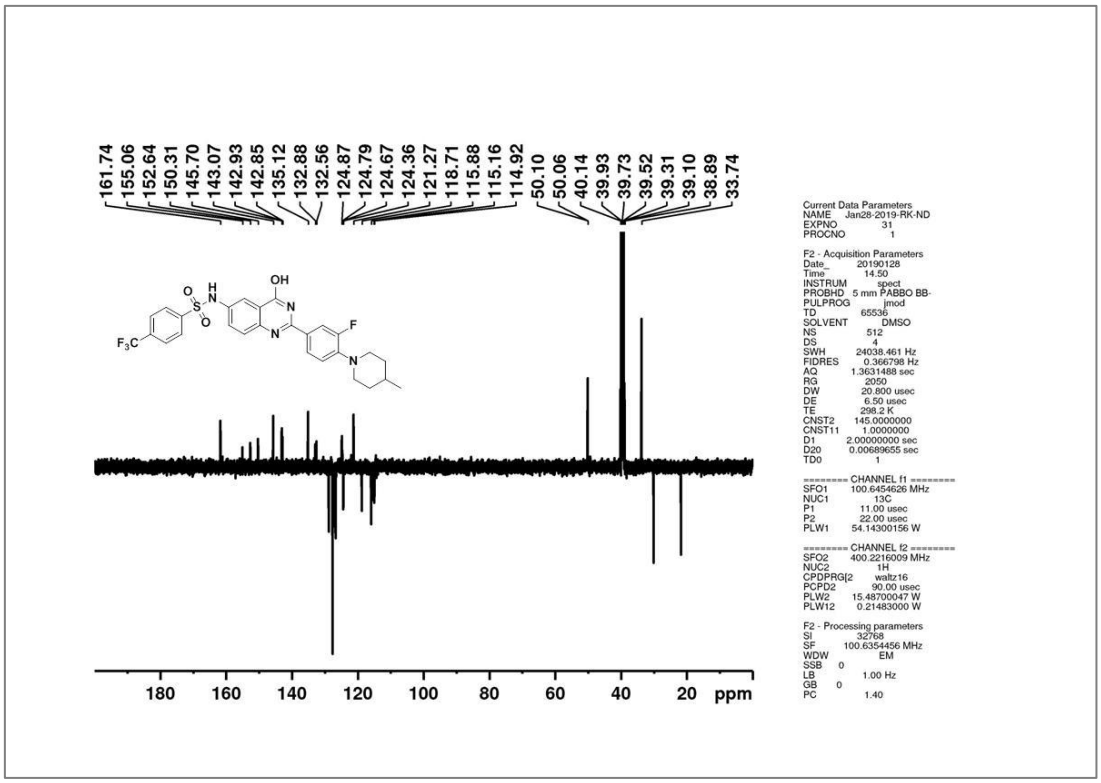
^{13}C NMR spectrum of compound 10i (Chapter 6)



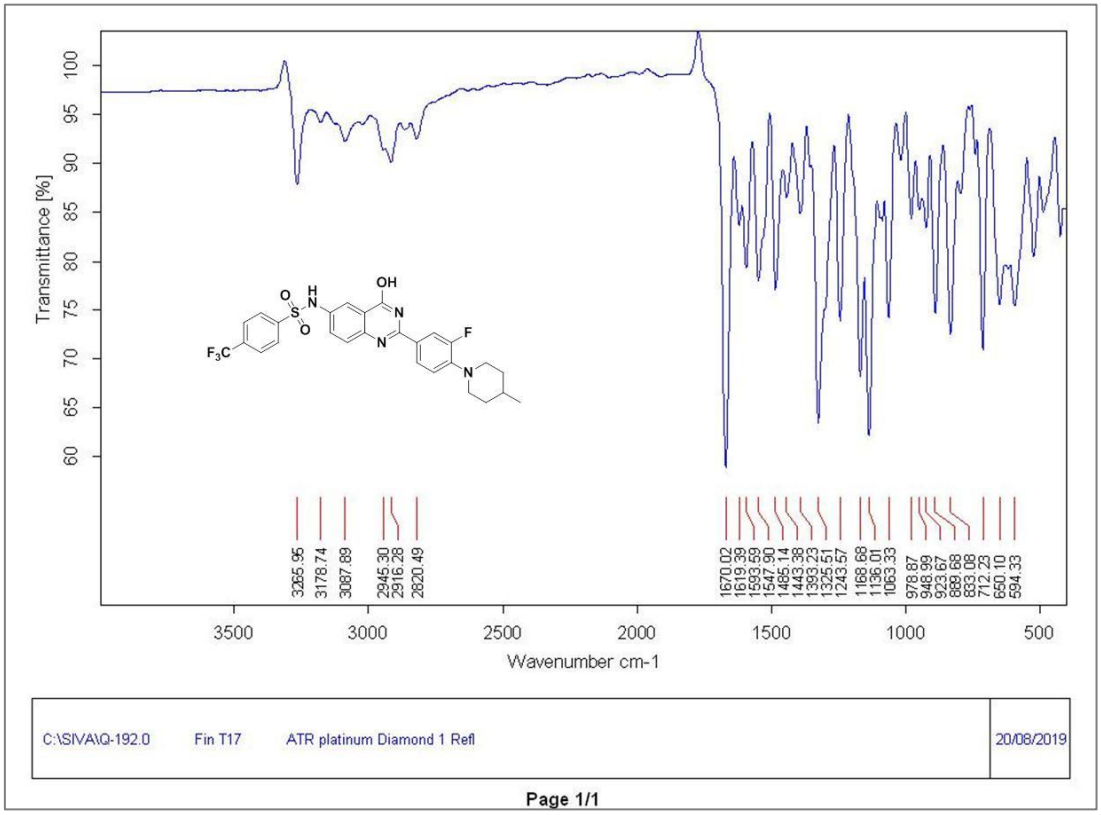
IR spectrum of compound 10i (Chapter 6)



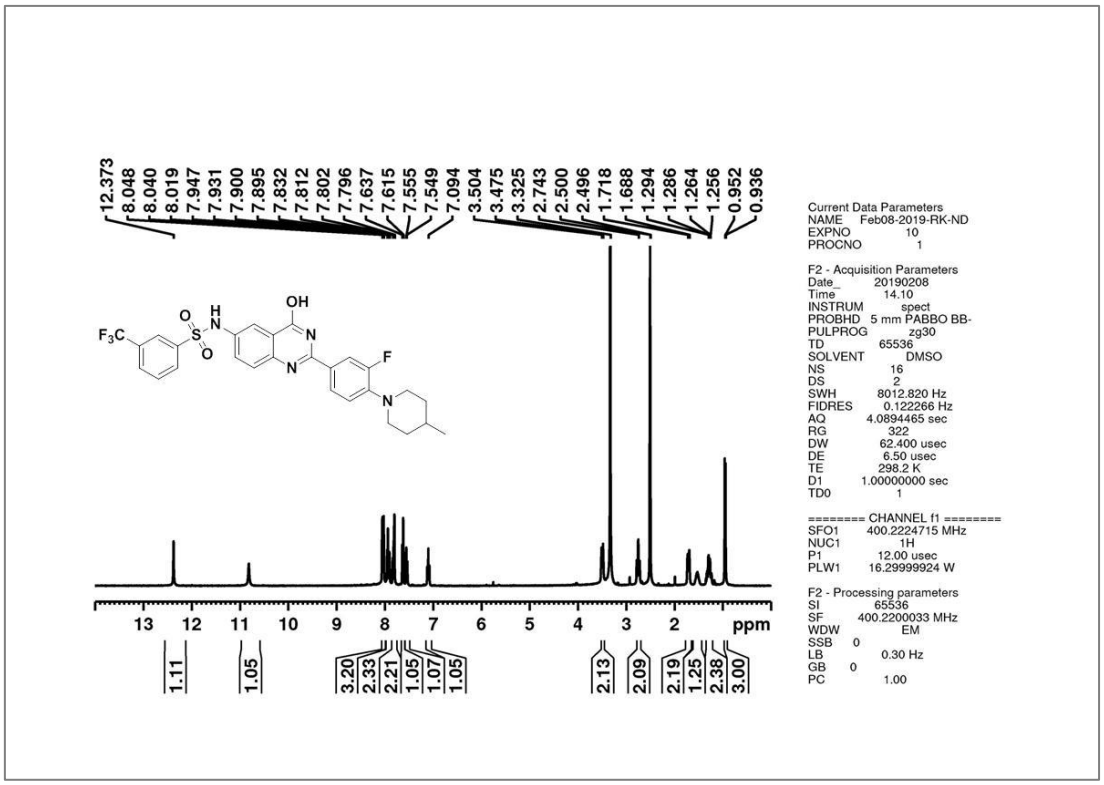
^{1}H NMR spectrum of compound 10j (Chapter 6)



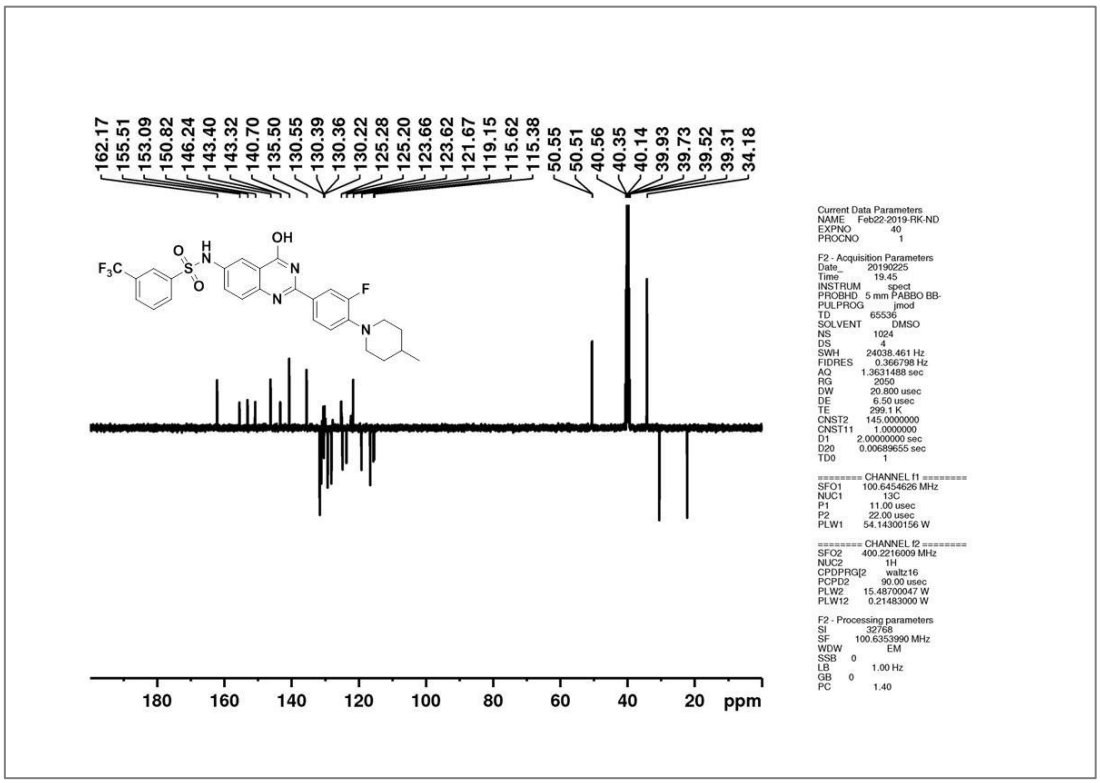
^{13}C NMR spectrum of compound 10j (Chapter 6)



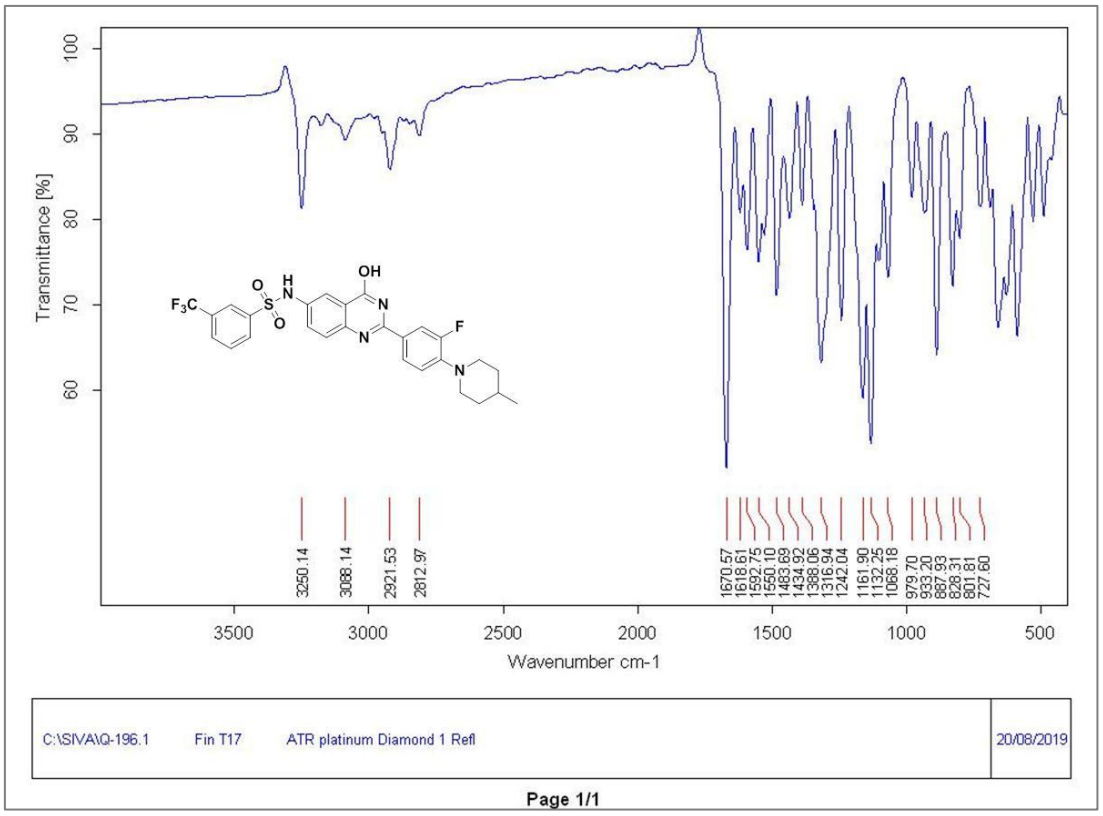
IR spectrum of compound 10j (Chapter 6)



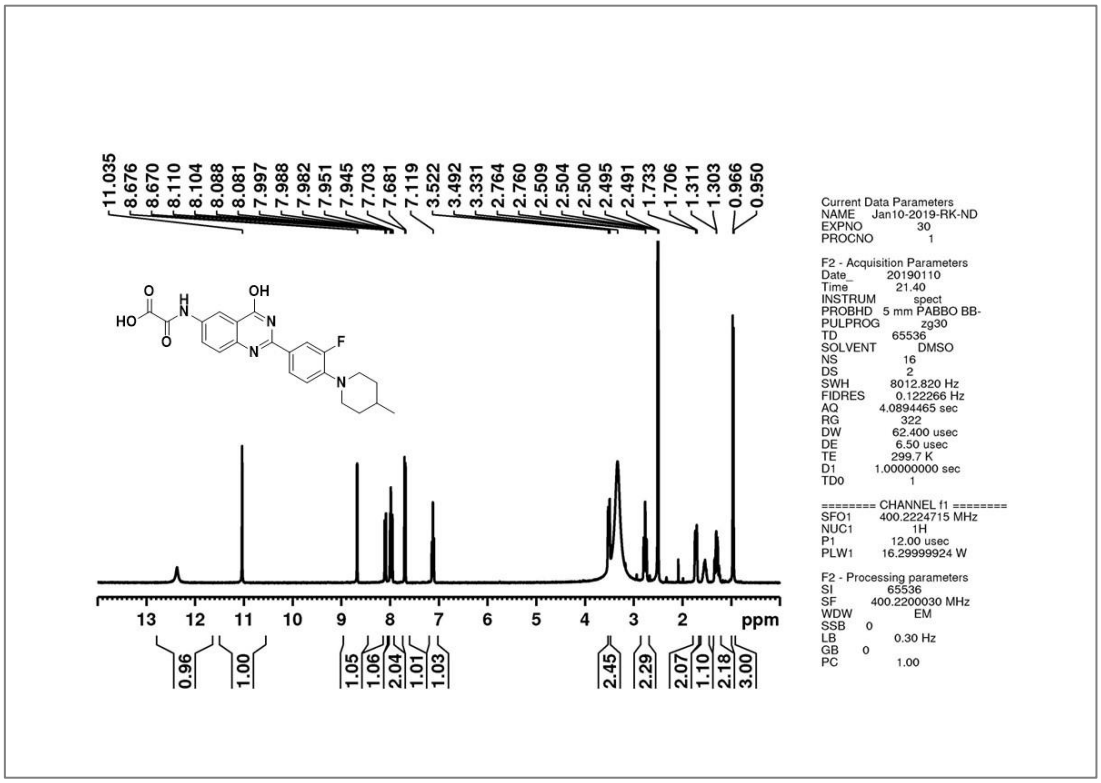
^{1}H NMR spectrum of compound 10k (Chapter 6)



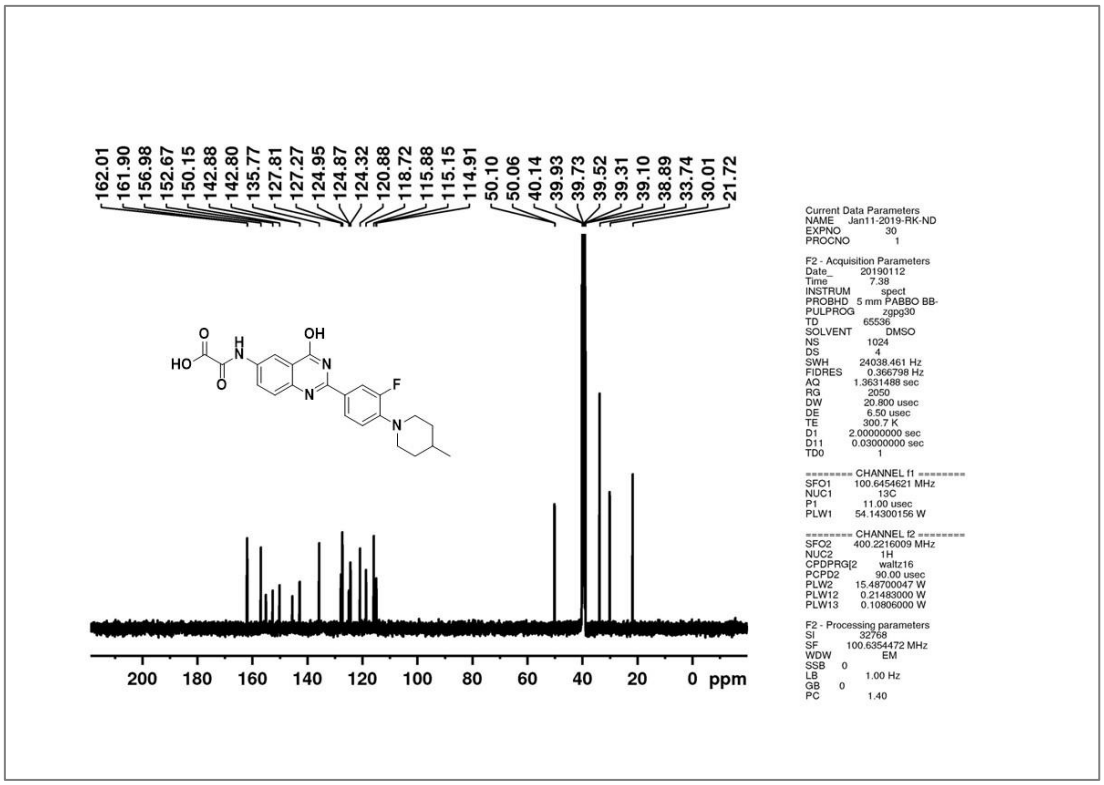
^{13}C NMR spectrum of compound 10k (Chapter 6)



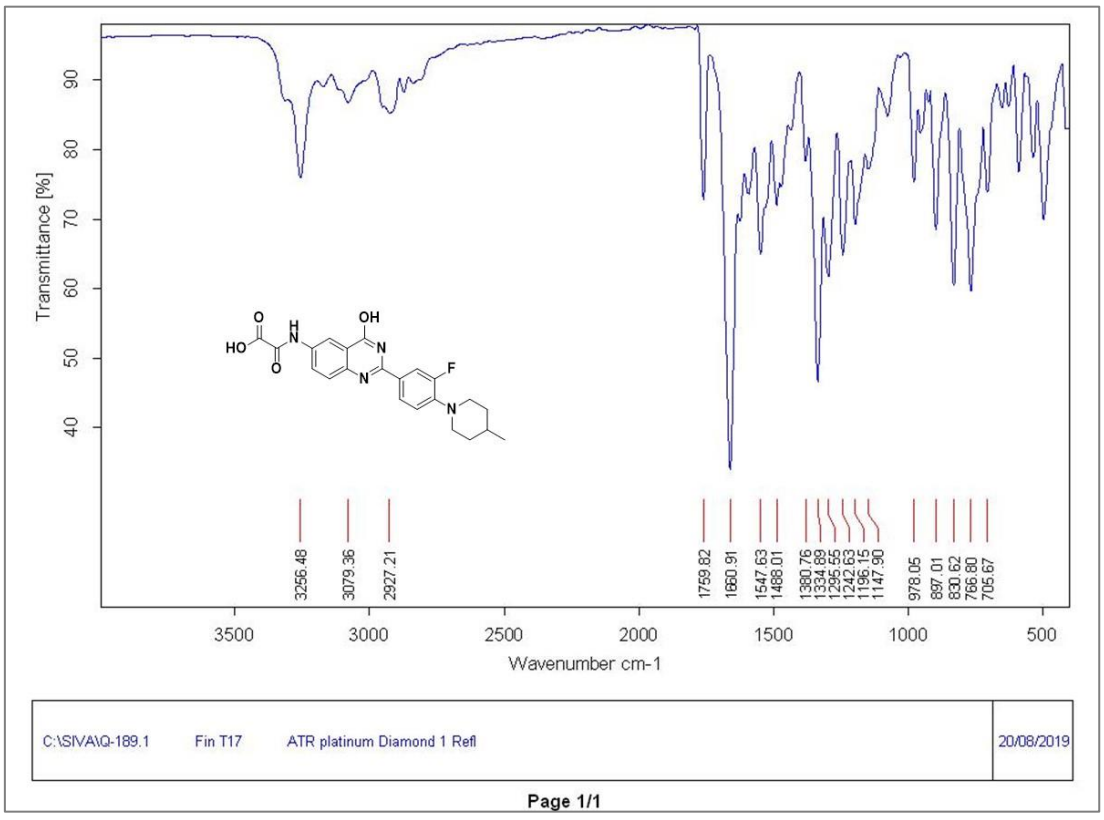
IR spectrum of compound 10k (Chapter 6)



^{1}H NMR spectrum of compound 10l (Chapter 6)



^{13}C NMR spectrum of compound 10l (Chapter 6)



IR spectrum of compound 10l (Chapter 6)

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One-Pot, Multicomponent, Diastereoselective, Green Synthesis of 3,4-Dihydro-2*H*-benzo[*b*][1,4]oxazine Analogues

Narva Deshwar Kushwaha, Babita Kushwaha, Rajshekhar Karpoormath,* Mavela Cleopus Mahlalela, and Suraj Raosaheb Shinde

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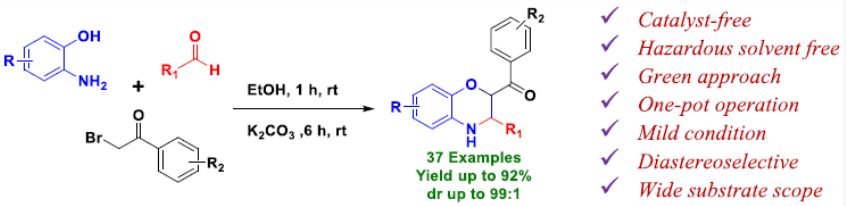

ABSTRACT: A novel green and efficient catalyst-free, mild one-pot, multicomponent synthetic strategy has been developed to construct substituted 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine. This reaction proceeds via in situ formation of Schiff-base followed by base mediated alkylation with phenacyl bromide/substituted phenacyl bromide, finally leading to intramolecular cyclization to give a mixture of diastereomers with excellent diastereoselectivity (up to dr = 99:1), which were isolated as a single diastereomer in moderate to excellent yields (41−92%). Besides, this new versatile methodology provides a wide scope for the synthesis of different functionally substituted benzoxazine scaffolds and can be further exploited as building blocks for the synthesis of multifaceted molecular structures, especially for pharmaceutical applications.

Benzoxazines are important heterocyclic scaffolds known for their extensive pharmacological and biological significance.[1−4] It is well documented that the benzoxazine moiety has been used as a building block in developing new pharmaceutical lead compounds, which have displayed a wide range for pharmaceutical applications such as neuroprotective agents,[5,6] antidiabetic,[7] antiarrhythmics against ischemia-reperfusion injury,[8] calcium antagonist,[9] potassium channel modulators,[10] and antihyperlipidemic agents,[11] etc. The medicinal significance of the benzoxazine skeleton is further validated by its presence in several marketed pharmaceutical drugs[1−4,12−14] as displayed in Figure 1. Undoubtedly one of the most well-known and noteworthy marketed drug containing benzoxazine heterocycle as its core moiety is Levofloxacin (Figure 1). It is an FDA approved potent antibiotic for the treatment and management of various human diseases such as pneumonia, acute bacterial sinusitis, urinary tract infections, and acute pyelonephritis.[15,16] In addition, the 1,4-benzoxazine scaffold has also found its application in the agricultural industry in developing potential herbicides[17] (Figure 1).

Further, 1,4-benzoxazine is also widely used as a building block for the synthesis of more complex molecular structures, active pharmaceutical ingredients, herbicides, and pesticides.[17,18] Thus, they have attracted a considerable interest of chemists in designing and developing new greener synthetic strategies to construct different functionally substituted 1,4-benzoxazine scaffolds.

The previous reported methods used multistep synthetic approaches for the synthesis of the 1,4-benzoxazine moiety (Scheme 1) such as (a) cyclocondensation of amino phenols with α-halogeno acyl bromide's further reduction of carbonyl with BH_3, (b) alkylation of *O*-nitrophenol with halo ester followed by reductive cyclization,[19] (c) intramolecular copper-catalyzed *O*-arylation of β-aminoalcohols,[20] and (d) epoxide ring opening with *O*-halosulfonamides and then cyclization was carried out to render 1,4 benzoxazine moieties.[21] (e) Recently, in 2018, Abhijit Mall et al. reported an efficient strategy for the synthesis of 3,4-dihydro 1,4 benzoxazine derivatives via Lewis acid catalyzed S_N2 type ring opening of activated aziridine with 2-halophenol followed by Cu(I)-catalyzed cyclization.[22] However, all of the above-mentioned multistep methods/procedures had drawbacks such as high temperature, long reaction time, low yield, lack of diastereomer selectivity, use of expensive catalyst and hazardous solvents, non-eco-friendly and most importantly

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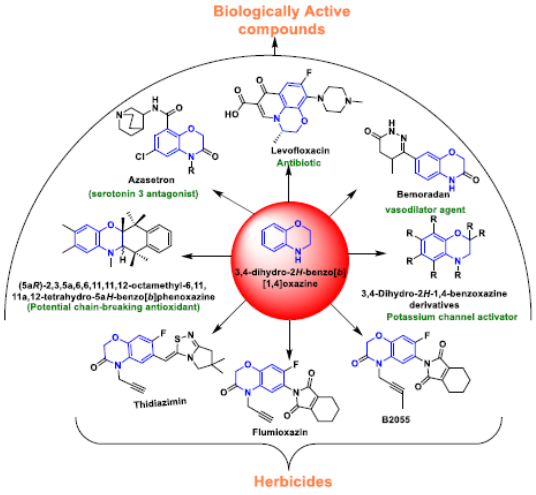
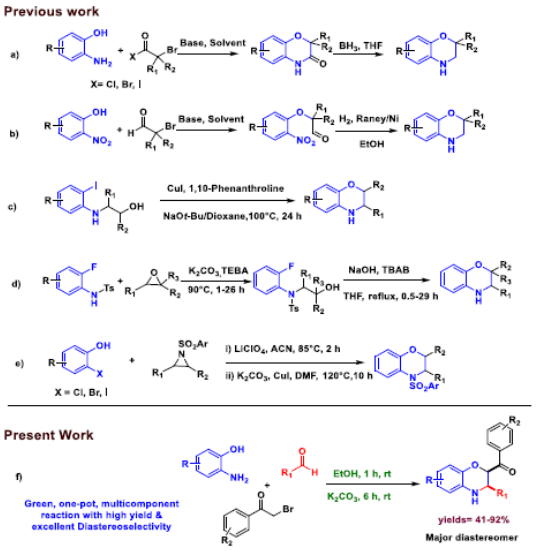


Figure 1. Some important marketed pharmaceuticals and agrochemicals containing 1,4-benzoxazine as the core moiety.

Scheme 1. (a–e) Previous Work for the Synthesis of 3,4-Dihydro-2*H*-benzo[*b*][1,4]oxazine and (f) Present Work[a]



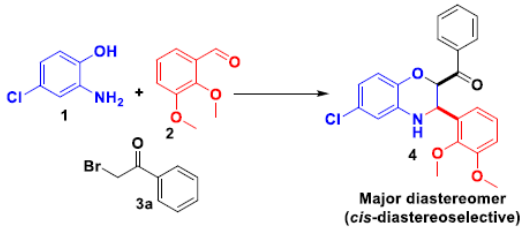
[a]One-pot, multicomponent, catalyst-free, diastereospecific, green approach (K_2CO_3/EtOH/rt/7 h) for the synthesis of 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine.

the methods were not versatile enough to synthesize differentially substituted 1,4 benzoxazine. Hence, an alternate, efficient route of synthesis was needed. Scheme 1 presents the previously reported methods (a–e) and our present work (f).

Keeping in mind the shortcomings of the previously reported methods, we envisaged to develop a simple yet efficient, low cost, multicomponent, one pot, catalyst-free, green alternative method to synthesize the 1,4-benzoxazine skeleton with diverse functionality and diastereoselectivity. The reaction proceeds via in situ formation of Schiff base, followed by mild base mediated *O*-alkylation and finally intramolecular cyclization to yield a mixture of diastereomers with excellent diastereoselectivity, which were isolated as a single diastereomer in moderate to excellent yields (41–92%).

Our one pot study commenced by reacting 2-amino-4-chlorophenol, aldehydes, and α-bromoketones in the presence of mild base Na_2CO_3, in DMF at 120 °C for 5 h. The progress of the reaction was monitored by TLC, and it was observed that the reaction was not clean and had several spots including that of the starting material. This indicates that the reaction did not go to completion. In order to obtain the desired product with improved yields and diastereoselectivity, further optimization of the reaction was initiated by changing various reaction parameters including base, temperature, and solvents as shown in Table 1. Thus, we decided to first start by screening several

Table 1. Optimization of the Reaction Conditions[a]



entry	base	solvent	time (h)	temp (°C)	yield of 4 (%)[b,c]
1.	Na_2CO_3	DMF	5	120	43
2.	K_2CO_3	DMF	5	120	47
3.	K_2CO_3	EtOH	5	90	56
4.	K_2CO_3	EtOH	5	60	68
5.	K_2CO_3	EtOH	7	rt	91
6.	Na_2CO_3	EtOH	7	rt	51
7.	Cs_2CO_3	EtOH	7	rt	86
8.	NaOH	EtOH	7	rt	45
9.	TEA	EtOH	7	rt	48
10.	DIPEA	EtOH	7	rt	52
11.	$NaHCO_3$	EtOH	7	rt	trace
12.	K_2CO_3	MeOH	7	rt	84
13.	K_2CO_3	ACN	7	rt	64
14.	K_2CO_3	acetone	7	rt	49
15.	K_2CO_3	dioxane	7	rt	60
16.	K_2CO_3	THF	7	rt	57
17.	K_2CO_3	DMF	7	rt	52
18.	K_2CO_3	DCM	7	rt	trace
19.	K_2CO_3	H_2O	7	rt	trace
20.	K_2CO_3	toluene	7	rt	trace

[a]Reaction conditions: **1** (1 equiv), **2** (1 equiv), **3a** (1 equiv), base (1.5 equiv), and solvent (2 mL). [b]Diastereomeric ratio of **4** from the ^{1}H NMR of crude reaction mixture was >5:1 in all reactions. [c]Isolated yield of major diastereomer.

bases (organic and inorganic), and it was observed that the use of K_2CO_3 led to the completion of the reaction with a slightly improved yield of 47% (Table 1, entry 2). However, the reaction was not clean and the TLC displayed several spots. Further solvent screening was performed, and it was observed that ethanol resulted in improved yield (56%) at 90 °C (Table 1, entry 3), but the reaction was still not clean. From these results we believed that higher temperature could be responsible for the formation of undesired side products. In order to improve the

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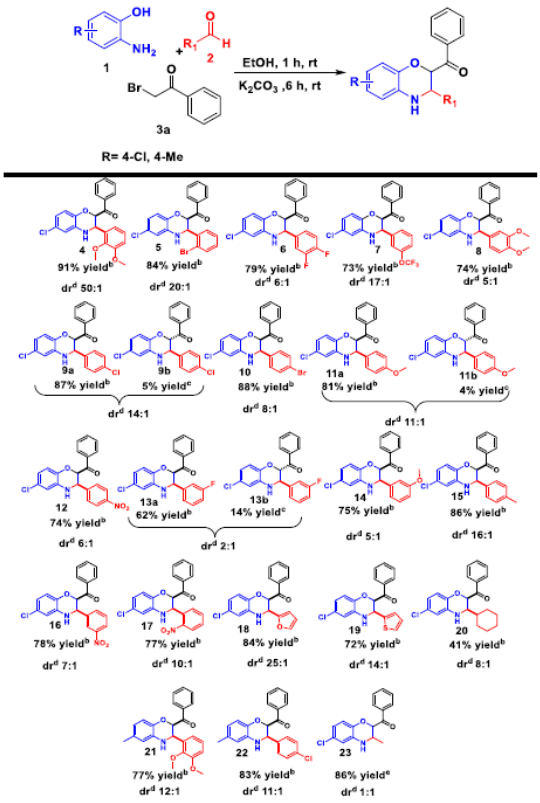
yield as well as to have a clean reaction, the reaction was carried out at lower temperature (60 °C) in ethanol, K_2CO_3 for 5 h, which resulted in a significantly improved yield of 68% (Table 1, entry 4). Encouraged by these results, we then decided to perform this reaction at room temperature (rt), and it was noted that after 5 h, an intense single spot of the desired product was observed, but still the reaction was incomplete. Thus, the reaction was further continued for 7 h, resulting in a clean, single spot of the corresponding cyclic product 4 with excellent cis-diastereoselectivity, which was isolated with a significantly improved yield of 91% (Table 1, entry 5). Its configuration was determined by ^{1}H−^{1}H NOESY analysis (see the Supporting Information, Figure S1).[23] Hence, the best optimized reaction conditions for the synthesis of differently functionalized 1,4-benzoxazines was K_2CO_3 in ethanol at room temperature (rt) for 7 h (Table 1, entry 5).

To expand the scope of this protocol, aliphatic and various substituted aryl/heteroaryl aldehydes (2) possessing both electron donating (−CH_3, −OCH_3) and withdrawing groups (−NO_2, −Cl, −Br, −F) were reacted with chloro, methyl, and nitro-substituted 2-aminophenols (1) and phenacyl bromide (3a) under optimized reaction conditions. The chloro and methyl substituted 2-aminophenol gave excellent results yielding desired products as a mixture of diastereomers, respectively. These mixtures were further purified and isolated as diastereomerically pure compounds **4**−**19** and **21** and **22** (Table 2) in moderate to excellent yields (62−91%). However, no desired product was obtained with nitro-substituted 2-aminophenol, only *O*-alkylated intermediate was formed, which could be attributed to the strong ring deactivating aspects of the meta nitro group with respect to amine (NH_2) (see the Supporting Information, Figure S152 for spectra). Furthermore, all the substituted aryl/heteroaryl aldehydes gave admirable yields (62−91%), while alicyclic aldehyde (compound **20**) presented a relatively lower yield (41%). Further in the case of linear aliphatic aldehyde, the diastereomeric mixtures (combined yield 86%; dr = 3:2) could not be separated due to indistinguishable R_f difference (compound **23**). All the synthesized derivatives were well characterized by IR and NMR. In addition, it was observed that halo- and nitro-substituted aryl aldehydes were well tolerated and their corresponding desired products (**5**, **6**, **9a**, **10**, **12**, **13a**, **16**, **17**, and **22**) were obtained in good to excellent yields (62−88%). In all the above reactions the major diastereomeric product was isolated in high yields, which provided the scope for further functionalization and their applications as building blocks in pharmaceuticals.

Remarkably, in most of the cases (**4**−**6**, **8**, **10**, **12**, **14**−**19**, and **22**), the major diastereomer precipitated from the reaction mixture, which was filtered, washed with water and *n*-pentane to remove impurities, followed by drying under vacuum. However, in the case of **9**, both the diastereomeric mixtures (major and minor) precipitated, which were then separated as **9a** and **9b** by using combi-flash column chromatography. However, in the case of **7**, **11a**, **11b**, **13a**, **13b**, **20**, **21**, and **23**, no precipitation of the product was observed; hence, the crude reaction mixture was concentrated and diluted with water and then extracted with ethyl acetate. These diastereomers were then purified and separated using combi-flash column chromatography. Structures of compound **9b**, **15**, and **17** were further confirmed by single crystal X-ray analysis (see the Supporting Information, Figures S2−S4 and Table S1), and the relative configuration of other products were deduced by analogy.

Table 2. Substrate Scope of Aldehydes with Substituted 2-Aminophenol[a]



[a]Reaction conditions: Substituted 2-aminophenol [(1); 1 equiv], substituted aldehydes [(2); 1 equiv], phenacyl bromide [(3a); 1 equiv], K_2CO_3 (1.5 equiv), EtOH (2 mL). [b]Isolated yields of major diastereomer. [c]Isolated yield of minor diastereomer. [d]Diastereomeric ratios determined by ^{1}H NMR of the crude reaction mixture. [e]Isolated combined yield of diastereomeric mixture (cis and trans).

Next to widen the scope and versatility of this new methodology, substituted phenacyl bromides (3) were treated with 2-amino-4-chlorophenol (1) and various substituted aryl/hetero aryl aldehydes (2) under optimized condition to obtain corresponding substituted 1,4-benzoxazine analogues in good to excellent yields as summarized in Table 3. The electron donating groups at ortho/meta/para position of benzaldehyde resulted in desired products (**24**, **27**, **31**, and **33**), respectively, with excellent yields (79−90%) and diastereoselectivity, while the electron-withdrawing groups comparatively gave slightly lower yields (69−76%) and less diastereoselectivity (**25**, **26**, **30a**, and **32**). In addition, we had performed a reaction with ethyl α-bromoacetate, but the reaction did not go to completion and resulted only in the formation of an intermediate compound, which did not undergo intramolecular cyclization to yield the desired product (see the Supportimg Information Figure S153 for the spectra).

A plausible mechanism as outlined in Scheme 2 was proposed on the basis of our experimental observations and from the previously reported literature.[24,25] The reaction proceeds via the

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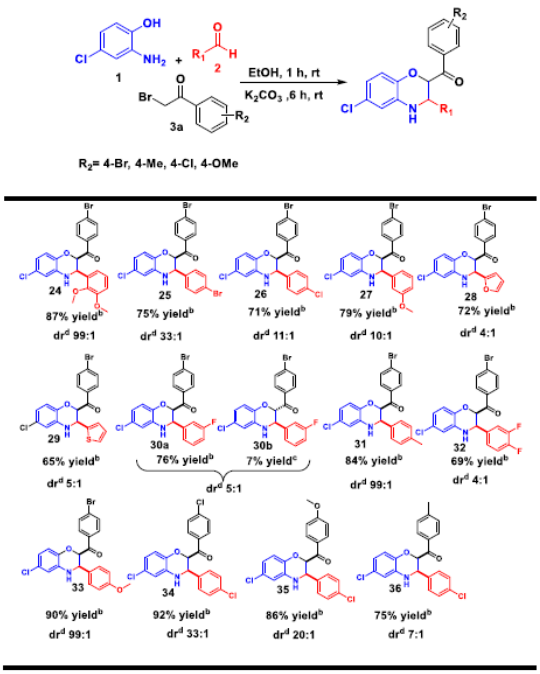
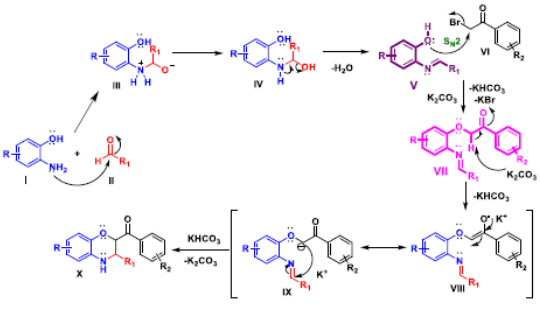
Table 3. Substrate Scope of Aldehyde with Substituted Phenacyl Bromide[a]



[a]Reaction conditions: 2-amino-4-chlorophenol [(1); 1 equiv], substituted aldehydes [(2); 1 equiv], substituted phenacyl bromides [(3a); 1 equiv], K_2CO_3 (1.5 equiv), EtOH (2 mL). [b]Isolated yields of major diastereomer. [c]Isolated yield of minor diastereomer. [d]Diastereomeric ratios have been determined by ^{1}H NMR analysis of the crude reaction mixture.

Scheme 2. Plausible Reaction Pathway via in Situ Formation of the Intermediates V and VII (as Highlighted), Which Were Isolated and Characterized



nucleophilic attack by the amine of I (amino phenol) on the carbonyl carbon of the aldehyde (II) leading to the formation the intermediate III, which further undergoes a proton shift, followed by dehydration to give a Schiff base (V). Further, the in situ reaction proceeds via a base mediated S_N2 type substitution reaction, wherein the hydroxyl group on the Schiff base (V) acts as a nucleophile and attacks the α-carbon of the phenacyl bromide (VI) generating a corresponding *O*-alkylated intermediate (VII). The acidic proton of VII is abstracted by the base K_2CO_3 resulting in the generation of a carbanion VIII or IX (keto−enol tautomer), which further undergoes base mediated intramolecular cyclization to yield respective 1,4-benzoxazines (X). To validate the plausible mechanism, both the key intermediates V and VII were isolated and confirmed by ^{1}H and ^{13}C NMR (see the Supporting Information, Figures S5−S8 for spectra). Thus, confirming the plausible mechanism as presented in Scheme 2.

In conclusion, we have developed a simple, yet efficient one-pot, multicomponent, green, catalyst-free, and diastereoselective synthesis of 1,4-benzoxazines in moderate to excellent yields. This one-pot, in situ reaction proceeds by the formation of a Schiff base followed by base mediated *O*-alkylation with the phenacyl bromide and finally catalyst free intramolecular cyclization. Further, this versatile novel methodology provides a wide scope for the synthesis of differentially substituted/functionalized 1,4-benzoxazine analogues, which can be exploited by the researchers in academia and the pharmaceutical and agrochemical industries in developing new building blocks or for the synthesis of new active pharmaceutical ingredients (APIs), drugs, and pesticides.

EXPERIMENTAL SECTION

All the fine chemicals, reagents and solvents were purchased from Sigma-Aldrich and Merck and were used without further purification unless otherwise stated. The progress of the reactions and the purity of the compounds were monitored by thin-layer chromatography (TLC) on precoated silica gel plates procured from E. Merck and Co. (Darmstadt, Germany) visualized by a UV lamp (254 or 365 nm). Purification was performed by using combi-flash (*Combi Flash* NextGen 300+) column chromatography. The melting points of the synthesized compounds have been determined and uncorrected using a digital Stuart SMP10 melting point apparatus. The Fourier transform infrared (FTIR) spectra were recorded in the spectral range of 400−4000 cm^{-1} on a Bruker Alpha FT-IR spectrometer using the ATR technique. The NMR spectra (^{1}H and ^{13}C) were recorded using $CDCl_3$ and DMSO-d_6 on Bruker AVANCE III 400 and 600 MHz spectrometers. Chemical shifts were determined relative to internal standard TMS at δ 0.0 ppm (ppm), and the coupling constants were reported in Hertz. The multiplicities of the NMR resonances were abbreviated as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet), and brs (broad singlet). Elemental analysis was performed on a Vario EL cube instrument. High-resolution mass spectrometry (HRMS) was performed using a Bruker ESI-QTOF mass spectrometer in positive-ion mode. X-ray crystallography analysis was performed on a Bruker SMART APEX II X-ray diffractometer.

General Procedure A for the Synthesis of 4−6, 8, 10, 12, 14−19, 22, 24−29, and 31−36). A mixture of substituted 2-aminophenol (0.2 g, 1 equiv) and corresponding aldehydes (1 equiv) in ethanol (2 mL) was stirred for 1 h at room temperature, then potassium carbonate (1.5 equiv) and phenacyl bromide/substituted phenacyl bromide (1 equiv) were added, and the stirring was continued further for 6 h at ambient temperature. The solid precipitate was formed in a reaction mixture which was directly filtered and washed with water followed by *n*-pentane to afford a pure solid of the title products as a major diastereomer.

General Procedure B for the Synthesis of 7, 9a, 9b, 11a, 11b, 13a, 13b, 20, 21, 23, 30a, and 30b). A mixture of substituted 2-aminophenol (0.2 g, 1 equiv) and corresponding aldehydes (1 equiv) in ethanol (2 mL) was stirred for 1 h at room temperature, then potassium carbonate (1.5 equiv) and phenacyl bromide/substituted phenacyl bromide (1 equiv) were added, and the stirring continued for 6 h at ambient temperature. The solvent was removed under reduced pressure, diluted with water, and extracted with ethyl acetate (3 × 10 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford a mixture of two diastereomers (major and minor). The mixtures were separated by

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combi flash column chromatography using EtOAc/hexane as an eluent to afford the title products.

*(E)-4-Chloro-2-((4-chlorobenzylidene)amino)phenol (**V**).* ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.60 (s, 1H), 7.84 (d, J = 8.30 Hz, 2H), 7.46 (d, J = 8.40 Hz, 2H), 7.27−7.25 (m, 1H), 7.15 (dd, J = 8.66 Hz, J = 2.35 Hz, 1H), 7.05 (s, 1H), 6.94 (d, J = 8.74 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ 156.9, 151.0, 138.3, 136.0, 134.0, 130.2, 129.4, 128.9, 125.2, 116.34, 116.31.

*(E)-2-(4-Chloro-2-((4-chlorobenzylidene)amino)phenoxy)-1-phenylethan-1-one (**VII**).* ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.59 (s, 1H), 7.97 (d, J = 7.53 Hz, 2H), 7.83 (d, J = 8.37 Hz, 2H), 7.59 (t, J = 7.37 Hz, 1H), 7.49−7.44 (m, 3H), 7.25−7.24 (m, 1H), 7.14 (dd, J = 8.65 Hz, J = 2.05 Hz, 1H), 7.04 (s, 1H), 6.92 (d, J = 8.65 Hz, 1H), 4.44 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ 191.4, 156.9, 151.0, 138.3, 136.0, 134.1, 134.09, 134.03, 131.0, 130.2, 129.6, 129.4, 129.07, 129.01, 128.9, 126.7, 125.2, 116.3, 31.0.

*(6-Chloro-3-(2,3-dimethoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**4**).* Off white solid, (521 mg, 91% yield). mp: 188−190 °C; FTIR (ATR, V_{max}, cm^{-1}): 3417 (N−H str.), 2971 (Ar−H str.), 1683 (C=O str.), 1508 (Ar C=C str.), 1269 (C−N str.), 1062 (C−O−C str.), 685 (C−Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.07 (d, J = 8.12 Hz, 2H), 7.58 (t, J = 7.22 Hz, 1H), 7.50−7.44 (m, 2H), 6.97 (t, J = 7.42 Hz, 1H), 6.86 (d, J = 7.84 Hz, 2H), 6.75 (d, J = 8.04 Hz, 1H), 6.63−6.61 (m, 2H), 5.66 (d, J = 2.91 Hz, 1H), 5.24 (t, J = 3.39 Hz, 1H), 4.24 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ 195.1, 152.4, 145.8, 141.2, 134.6, 133.8, 133.5, 133.3, 128.9, 128.5, 126.5, 119.2, 118.5, 117.5, 114.2, 112.3, 78.1, 60.5, 55.8, 49.4. Anal. Calcd for $C_{23}H_{20}ClNO_4$: C, 67.40; H, 4.92; N, 3.42; O, 15.61. Found: C, 67.16; H, 4.90; N, 3.60; O, 18.67.

*(3-(2-Bromophenyl)-6-chloro-3,4-dihydro-2H-benzo[b][1,4]-oxazin-2-yl)(phenyl)methanone (**5**).* Yellow solid, (504 mg, 84% yield). mp: 130−134 °C; FTIR (ATR, V_{max}, cm^{-1}): 3409 (N−H str.), 2938 (Ar−H str.), 1672 (C=O str.), 1496 (Ar C=C str.), 1292 (C−N str.), 1183 (C−O−C str.), 752 (C−Cl str.), 690 (C−Br str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.99 (d, J = 7.79 Hz, 2H), 7.57−7.53 (m, 2H), 7.43−7.36 (m, 3H), 7.28 (d, J = 7.52 Hz, 1H), 7.17−7.12 (m, 1H), 6.66 (d, J = 2.32 Hz, 1H), 6.62 (d, J = 8.56 Hz, 1H), 6.53 (dd, J = 8.45 Hz, J = 2.39 Hz, 1H), 5.53 (dd, J = 4.60 Hz, J = 2.35 Hz, 1H), 5.50 (d, J = 2.40 Hz, 1H), 4.45 (d, J = 4.56 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ 195.62, 140.0, 139.6, 134.8, 133.7, 133.6, 133.1, 129.6, 129.2, 129.1, 128.5, 128.0, 127.4, 122.3, 118.3, 114.5, 77.4, 53.2. Anal. Calcd for $C_{21}H_{15}BrClNO_2$: C, 58.83; H, 3.53; N, 3.27; O, 7.46. Found: C, 57.75; H, 3.51; N, 3.30; O, 9.70.

*(6-Chloro-3-(3,4-difluorophenyl)-3,4-dihydro-2H-benzo[b][1,4]-oxazin-2-yl)(phenyl)methanone (**6**).* Off white solid, (425 mg, 79% yield). mp: 140−144 °C; FTIR (ATR, V_{max}, cm^{-1}): 3349 (N−H str.), 2977 (Ar−H str.), 1681 (C=O str.), 1490 (Ar C=C str.), 1291 (C−N str.), 1116 (C−F str.), 1059 (C−O−C str.), 692 (C−Cl str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 7.95 (d, J = 7.85 Hz, 2H), 7.64 (t, J = 6.95 Hz, 1H), 7.53−7.45 (m, 3H), 7.40−7.33 (m, 1H), 7.22−7.20 (m, 1H), 6.87 (d, J = 3.92 Hz, 1H), 6.71−6.69 (m, 2H), 6.50 (dd, J = 8.54 Hz, J = 2.43 Hz, 1H), 5.97 (d, J = 3.57 Hz, 1H), 4.83 (t, J = 3.54 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6, 25 °C) δ 194.8, 150.4−147.9 (dd, J_{C-F}= 246.20 Hz, J_{C-F} = 12.64 Hz, 1C), 149.9−147.3 (dd, J_{C-F} = 246.20 Hz, J_{C-F} = 12.64 Hz, 1C), 140.6, 137.9−137.8 (d, J_{C-F}= 8.38 Hz, 1C), 137.9, 134.52−134.50 (d, J_{C-F} = 2.98 Hz, 1C), 133.6, 128.7, 128.6, 125.1, 124.05−124.01 (d, J_{C-F}= 3.42 Hz, 1C), 117.4−117.2 (d, J_{C-F} = 17.68 Hz, 1C), 117.1, 116.3, 116.1, 113.2, 77.3, 52.4. Anal. Calcd for $C_{21}H_{14}ClF_2NO_2$: C, 65.38; H, 3.66; N, 3.63; O, 8.29. Found: C, 66.52; H, 4.54; N, 3.73; O, 10.91.

*(6-Chloro-3-(3-(trifluoromethoxy)phenyl)-3,4-dihydro-2H-benzo-[b][1,4]oxazin-2-yl)(phenyl)methanone (**7**).* Yellow solid, (438 mg, 73% yield). R_f 0.6 (6% ethyl acetate in hexane); mp 83−87 °C; FTIR (ATR, V_{max}, cm^{-1}): 3349 (N−H str.), 3061 (Ar−H, str.), 1674 (C=O str.), 1492 (Ar C=C str.), 1254 (C−N str.), 1160 (C−F str.), 1062 (C−O−C str.), 691 (C−Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.82 (s, 2H), 7.52−7.37 (m, 5H), 7.09 (s, 2H), 6.77−6.63 (m, 3H), 5.33 (s, 1H), 4.83 (s, 1H), 4.45 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ 194.7, 149.5, 141.1, 135.1, 133.8, 133.7, 130.2, 128.8, 128.6, 127.1, 126.0, 121.7, 120.8, 120.1, 119.1, 118.6, 118.0, 114.7, 78.3, 54.9. Anal. Calcd for $C_{22}H_{15}ClF_3NO_3$: C, 60.91; H, 3.49; N, 3.23; O, 11.06. Found: C, 61.96; H, 3.54; N, 3.16; O, 14.11.

*(6-Chloro-3-(3,4-dimethoxyphenyl)-3,4-dihydro-2H-benzo[b]-[1,4]oxazin-2-yl)(phenyl)methanone (**8**).* Off white solid, (424 mg, 74% yield). mp: 145−150 °C; FTIR (ATR, V_{max}, cm^{-1}): 3350 (N−H str.), 2973 (Ar−H str.), 1690 (C=O str.), 1491 (Ar C=C str.), 1246 (C−N str.), 1026 (C−O−C str.), 698 (C−Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.81 (d, J = 7.87 Hz, 2H), 7.51 (t, J = 7.23 Hz, 1H), 7.36 (t, J = 7.73 Hz, 2H), 6.87 (d, J = 8.21 Hz, 1H), 6.82−6.80 (m, 2H), 6.73 (d, J = 8.21 Hz, 1H), 6.68 (d, J = 2.05 Hz, 1H), 6.63 (dd, J = 8.40 Hz, J = 2.13 Hz, 1H), 5.26 (d, J = 6.50 Hz, 1H), 4.72 (d, J = 6.21 Hz, 1H), 4.20 (s, 1H), 3.80 (s, 3H), 3.78 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ 194.9, 149.3, 149.2, 141.4, 135.6, 134.2, 133.7, 130.3, 128.9, 128.6, 127.0, 120.1, 118.4, 117.9, 114.6, 111.4, 110.7, 78.9, 56.0, 55.4. Anal. Calcd for $C_{23}H_{20}ClNO_4$: C, 67.40; H, 4.92; N, 3.42; O, 15.61. Found: C, 67.54; H, 5.12; N, 3.40; O, 19.47.

*(6-Chloro-3-(4-chlorophenyl)-3,4-dihydro-2H-benzo[b][1,4]-oxazin-2-yl)(phenyl)methanone (**9a**).* Off white solid, (468 mg, 87% yield). R_f 0.45 (6% ethyl acetate in hexane); mp: 159−162 °C; FTIR (ATR, V_{max}, cm^{-1}): 3407 (N−H str.), 2974 (Ar−H str.), 1687 (C = O str.), 1522 (Ar C = C str.), 1205 (C−N str.), 691 (C−Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.85 (d, J = 7.64 Hz, 2H), 7.54 (t, J = 7.13 Hz, 1H), 7.39 (d, J = 7.63 Hz, 2H), 7.28−7.23 (m, 4H), 6.76 (d, J = 8.52 Hz, 1H), 6.66 (d, J = 2.16 Hz, 1H), 6.61 (dd, J = 7.48 Hz, J = 2.35 Hz, 1H), 5.26 (d, J = 5.56 Hz, 1H), 4.86 (d, J = 4.20 Hz, 1H), 4.22 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ 194.6, 141.2, 137.3, 135.2, 134.4, 133.9, 133.8, 129.1, 129.03, 129.0, 128.7, 127.2, 118.6, 118.0, 114.7, 78.7, 54.5. Anal. Calcd for $C_{21}H_{15}Cl_2NO_2$: C, 65.64; H, 3.93; N, 3.65; O, 8.33. Found: C, 64.20; H, 3.88; N, 3.66; O, 10.58.

*(6-Chloro-3-(4-chlorophenyl)-3,4-dihydro-2H-benzo[b][1,4]-oxazin-2-yl)(phenyl)methanone (**9b**).* Off white solid, (27 mg, 5% yield). R_f 0.4 (8% ethyl acetate in hexane); mp: 190−193 °C; FTIR (ATR, V_{max}, cm^{-1}): 3341 (N−H str.), 2977 (Ar−H str.), 1688 (C=O str.), 1492 (Ar C=C str.), 1256 (C−N str.), 1088 (C−O−C str.), 684 (C−Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.69 (d, J = 7.46 Hz, 2H), 7.54 (t, J = 7.42 Hz, 1H), 7.38 (t, J = 7.74 Hz, 2H), 7.12 (d, J = 8.40 Hz, 2H), 6.99 (d, J = 7.40 Hz, 2H), 6.93 (d, J = 8.12 Hz, 1H), 6.72−6.69 (m, 2H), 5.62 (d, J = 2.92 Hz, 1H), 4.96 (t, J = 2.84 Hz, 1H), 4.38 (d, J = 1.93 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 40 °C) δ 194.7, 141.5, 137.0, 135.9, 134.3, 133.8, 133.5, 128.9, 128.8, 128.7, 128.6, 127.6, 118.8, 118.2, 114.6, 78.9, 55.7. Anal. Calcd for $C_{21}H_{15}Cl_2NO_2$: C, 65.64; H, 3.93; N, 3.65; O, 8.33. Found: C, 65.49; H, 3.97; N, 3.71; O, 12.99.

*(3-(4-Bromophenyl)-6-chloro-3,4-dihydro-2H-benzo[b][1,4]-oxazin-2-yl)(phenyl)methanone (**10**).* Off white solid, (528 mg, 88% yield). mp: 118−122 °C; FTIR (ATR, V_{max}, cm^{-1}): 3328 (N−H str.), 2977 (Ar−H str.), 1672 (C=O str.), 1488 (Ar C=C str.), 1228 (C−N str.), 1063 (C−O−C str.), 689 (C−Cl str.), 510 (C−Br str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.85 (d, J = 8.38 Hz, 2H), 7.55 (t, J = 7.46 Hz, 1H), 7.41−7.38 (m, 4H), 7.20 (d, J = 8.31 Hz, 2H), 6.76 (d, J = 8.68 Hz, 1H), 6.67−6.66 (m, 1H), 6.61 (dd, J = 8.52 Hz, J = 1.97 Hz, 1H), 5.26 (d, J = 5.41 Hz, 1H), 4.83 (t, J = 3.06 Hz, 1H), 4.25 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ 194.7, 141.2, 137.9, 135.2, 134.0, 133.8, 132.1, 129.4, 129.1, 128.8, 127.2, 122.6, 118.7, 118.1, 114.8, 78.7, 54.6. Anal. Calcd for $C_{21}H_{15}BrClNO_2$: C, 58.83; H, 3.53; N, 3.27; O, 7.46. Found: C, 58.75; H, 3.48; N, 3.35; O, 10.87.

*(6-Chloro-3-(4-methoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]-oxazin-2-yl)(phenyl)methanone (**11a**).* Yellow solid, (429 mg, 81% yield). R_f 0.4 (15% ethyl acetate in hexane); mp: 90−92 °C; FTIR (ATR, V_{max}, cm^{-1}): 3340 (N−H str.), 2923 (Ar−H str.), 1669 (C=O str.), 1500 (Ar C=C str.), 1225 (C−N str.), 1054 (C−O−C str.), 692 (C−Cl str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 7.93 (d, J = 7.50 Hz, 2H), 7.62 (t, J = 7.34 Hz, 1H), 7.49 (t, J = 7.77 Hz, 2H), 7.29 (d, J = 8.58 Hz, 2H), 6.85 (d, J = 8.60 Hz, 2H), 6.75 (d, J = 1.44 Hz, 1H), 6.72 (d, J = 8.52 Hz, 1H), 6.69 (d, J = 2.36 Hz, 1H), 6.50 (dd, J = 8.46 Hz, J = 2.38 Hz, 1H), 5.83 (d, J = 4.28 Hz, 1H), 4.67 (t, J = 2.71 Hz, 1H), 3.68 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6, 25 °C) δ 195.0, 158.7, 140.9, 135.1, 134.7, 133.6, 131.4, 128.7, 128.5, 128.4, 124.9, 116.9, 115.8, 113.8, 113.1, 77.6, 55.0, 53.1. Anal. Calcd for $C_{22}H_{18}ClNO_3$: C,

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69.57; H, 4.78; N, 3.69; O, 12.64. Found: C, 69.63; H, 4.94; N, 3.72; O, 14.36.

*(6-Chloro-3-(4-methoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]-oxazin-2-yl)(phenyl)methanone (**11b**).* Yellow solid, (22 mg, 4% yield). R_f 0.32 (18% ethyl acetate in hexane); mp: 184−188 °C; FTIR (ATR, V_{max}, cm^{-1}): 3349 (N−H str.), 2982 (Ar−H str.), 1686 (C=O str.), 1503 (Ar C=C str.), 1248 (C−N str.), 1040 (C−O−C str.), 686 (C−Cl str.); ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 7.67 (d, J = 7.35 Hz, 2H), 7.56 (t, J = 7.41 Hz, 1H), 7.40 (t, J = 7.71 Hz, 2H), 6.89−6.83 (m, 4H), 6.72 (d, J = 2.50 Hz, 1H), 6.68 (d, J = 8.54 Hz, 2H), 6.55 (dd, J = 8.71 Hz, J = 2.85 Hz, 1H), 5.99 (d, J = 3.22 Hz, 1H), 4.83 (t, J = 2.93 Hz, 1H), 3.62 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6, 25 °C) δ 195.3, 159.1, 141.5, 136.2, 136.1, 133.6, 130.9, 128.9, 128.8, 128.6, 125.6, 117.5, 116.3, 113.8, 113.5, 77.6, 55.4, 54.4. Anal. Calcd for $C_{22}H_{18}ClNO_3$: C, 69.57; H, 4.78; N, 3.69; O, 12.64. Found: C, 69.35; H, 4.94; N, 3.77; O, 14.07.

*(6-Chloro-3-(4-nitrophenyl)-3,4-dihydro-2H-benzo[b][1,4]-oxazin-2-yl)(phenyl)methanone (**12**).* Light yellow solid, (408 mg, 74% yield). mp 187−190 °C; FTIR (ATR, V_{max}, cm^{-1}): 3334 (N−H str.), 2977 (Ar−H str.), 1685 (C=O str.), 1490 (Ar C=C str.), 1343 (Ar-NO_2 str.), 1222 (C−N str.), 1057 (C−O−C str.), 685 (C−Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 40 °C) δ 8.13−7.89 (m, 4H), 7.53−7.41 (m, 5H), 6.70−6.61 (m, 3H), 5.32 (s, 1H), 5.10 (s, 1H), 4.36 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 40 °C) δ 194.4, 148.0, 146.8, 140.9, 135.0, 134.1, 133.3, 129.1, 128.8, 128.5, 127.6, 124.1, 119.2, 118.3, 115.1, 78.7, 54.4. Anal. Calcd for $C_{21}H_{15}ClN_2O_4$: C, 63.89; H, 3.83; N, 7.10; O, 16.21. Found: C, 63.18; H, 3.72; N, 7.11; O, 18.63.

*(6-Chloro-3-(3-fluorophenyl)-3,4-dihydro-2H-benzo[b][1,4]-oxazin-2-yl)(phenyl)methanone (**13a**).* Off white solid, (318 mg, 62% yield). R_f 0.42 (6% ethyl acetate in hexane); mp: 177−180 °C; FTIR (ATR, V_{max}, cm^{-1}): 3370 (N−H str.), 2976 (Ar−H str.), 1688 (C=O str.), 1490 (Ar C=C str.), 1247 (C−N str.), 1191 (C−F str.), 1078 (C−O−C str.), 689 (C−Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.69 (dd, J = 7.24 Hz, J = 1.66 Hz, 2H), 7.52 (t, J = 7.59 Hz, 1H), 7.37 (t, J = 7.59 Hz, 2H), 7.15−7.09 (m, 1H), 6.93 (d, J = 9.19 Hz, 1H), 6.88−6.84 (m, 2H), 6.80−6.76 (m, 1H), 6.72−6.70 (m, 2H), 5.62 (d, J = 3.08 Hz, 1H), 4.98 (t, J = 3.98 Hz, 1H), 4.40 (d, J = 2.08 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 40 °C) δ 194.8, 164.1−161.7 (d, J_{C-F} = 247.08 Hz, 1C), 141.5, 141.0, 136.0, 133.7, 133.5, 130.2−130.1 (d, J_{C-F} = 8.35 Hz, 1C), 128.7−128.6 (d, J_{C-F} = 6.61 Hz, 1C), 127.6, 123.2, 118.9, 118.3, 115.4, 115.2, 114.8−114.5 (d, J_{C-F} = 22.33 Hz, 1C), 114.7, 78.8, 55.8. HRMS (ESI-TOF) calcd for $C_{21}H_{16}ClFNO_2$ $[M + H]^+$ 368.0854, found 368.1180.

*(6-Chloro-3-(3-fluorophenyl)-3,4-dihydro-2H-benzo[b][1,4]-oxazin-2-yl)(phenyl)methanone (**13b**).* Yellow semisolid, (72 mg, 14% yield). R_f 0.35 (10% ethyl acetate in hexane); FTIR (ATR, V_{max}, cm^{-1}): 3337 (N−H str.), 3070 (Ar−H str.), 1685 (C=O str.), 1593 (Ar C=C str.), 1221 (C−N str.), 687 (C−Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.06 (d, J = 8.08 Hz, 2H), 7.74 (t, J = 7.76 Hz, 1H), 7.59 (t, J = 8.41 Hz, 2H), 7.43−7.40 (m, 1H), 7.31−7.28 (m, 2H), 7.14−7.09 (m, 1H), 6.96 (d, J = 8.53 Hz, 1H), 6.89 (d, J = 2.34 Hz, 1H), 6.81 (dd, J = 8.41, J = 2.22 Hz, 1H), 5.54 (d, J = 5.05 Hz, 1H), 5.05 (d, J = 5.57 Hz, 1H), 4.67 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C) δ 194.7, 164.1−161.7 (d, J_{C-F} = 244.81 Hz, 1C), 141.5−141.4 (d, J = 7.26 Hz, 1C), 141.0, 135.0, 133.8, 133.7, 130.4, 128.8−128.6, 128.3 127.0, 123.1, 118.3, 117.9, 115.4−115.2 (d, J_{C-F} = 21.09 Hz, 1C), 114.6, 78.4, 54.9. Anal. Calcd for $C_{21}H_{15}ClFNO_2$: C, 68.58; H, 4.11; Cl, 9.64; F, 5.17; N, 3.81; O, 8.70. Found: C, 66.97; H, 3.98; N, 3.80; O, 10.73.

*(6-Chloro-3-(3-methoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]-oxazin-2-yl)(phenyl)methanone (**14**).* Off white solid, (398 mg, 75% yield). mp: 177−180 °C; FTIR (ATR, V_{max}, cm^{-1}): 3364 (N−H str.), 2976 (Ar−H str.), 1687 (C=O str.), 1493 (Ar C=C str.), 1254 (C−N str.), 1054 (C−O−C str.), 690 (C−Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.64 (d, J = 7.40 Hz, 2H), 7.48 (t, J = 7.40 Hz, 1H), 7.32 (t, J = 7.76 Hz, 2H), 7.07 (t, J = 7.92 Hz, 1H), 6.91 (d, J = 9.24 Hz, 1H), 6.71−6.67 (m, 4H), 6.58 (s, 1H), 5.66 (d, J = 3.16 Hz, 1H), 4.92 (t, J = 2.74 Hz, 1H), 4.34 (d, J = 1.4 Hz, 1H), 3.59 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C) δ 194.84, 159.6, 141.5, 139.3, 136.0, 133.9, 133.2, 129.6, 128.8, 126.9, 119.6, 118.6, 117.8, 114.4, 113.9, 112.9, 78.3, 56.0, 55.10. Anal. Calcd for $C_{22}H_{18}ClNO_3$; C, 69.57; H, 4.78; N, 3.69; O, 12.64. Found: C, 68.66; H, 4.71; N, 3.73; O, 15.16.

*(6-Chloro-3-(p-tolyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)-(phenyl)methanone (**15**).* Off white solid, (438 mg, 86% yield). mp: 177−180 °C; FTIR (ATR, V_{max}, cm^{-1}): 3395 (N−H str.), 2974 (Ar−H str.), 1689 (C=O str.), 1495 (Ar C=C str.), 1257 (C−N str.), 1057 (C−O−C str.), 684 (C−Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.83 (d, J = 8.58 Hz, 2H), 7.50 (t, J = 7.40 Hz, 1H), 7.36 (t, J = 7.75 Hz, 2H), 7.19 (d, J = 7.99 Hz, 2H), 7.06 (d, J = 7.96 Hz, 2H), 6.77 (d, J = 8.48 Hz, 1H), 6.64 (d, J = 2.28 Hz, 1H), 6.60 (dd, J = 8.40 Hz, J = 2.36 Hz, 1H), 5.27 (d, J = 5.88 Hz, 1H), 4.79 (d, J = 5.64 Hz, 1H), 4.19 (s, 1H), 2.26 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C) δ 194.85, 141.2, 138.3, 135.3, 135.2, 134.0, 133.5, 129.5, 128.5, 127.3, 126.8, 118.2, 117.8, 114.4, 78.9, 54.9, 21.0. Anal. Calcd for $C_{22}H_{18}ClNO_2$: C, 72.63; H, 4.99; N, 3.85; O, 8.79. Found: C, 72.22; H, 5.18; N, 3.92; O, 11.31.

*(6-Chloro-3-(3-nitrophenyl)-3,4-dihydro-2H-benzo[b][1,4]-oxazin-2-yl)(phenyl)methanone (**16**).* Off white solid, (430 mg, 78% yield). mp:180−184 °C; FTIR (ATR, V_{max}, cm^{-1}): 3324 (N−H str.), 2976 (Ar−H str.), 1682 (C=O str.), 1490 (Ar C=C str.), 1356 (Ar−NO_2 str.), 1249 (C−N str.), 1058 (C−O−C str.), 681 (C−Cl str.); ^{1}H NMR (600 MHz, $CDCl_3$, 50 °C) δ 8.02 (d, J = 8.10 Hz, 1H), 7.90 (s, 1H), 7.74 (d, J = 7.68 Hz, 2H), 7.53 (t, J = 7.41 Hz, 1H), 7.49 (d, J = 7.74 Hz, 1H), 7.40−7.34 (m, 3H), 6.95 (d, J = 8.16 Hz, 1H), 6.75−6.73 (m, 2H), 5.60 (d, J = 2.82 Hz, 1H), 5.11 (t, J = 3.06 Hz, 1H), 4.46 (s, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 50 °C) δ 194.4, 148.4, 141.4, 141.0, 135.8, 133.8, 133.6, 133.3, 129.7, 128.87, 128.84, 128.1, 123.2, 122.8, 119.2, 118.5, 114.9, 78.9, 55.8. Anal. Calcd for $C_{21}H_{15}ClN_2O_4$: C, 63.89; H, 3.83; N, 7.10; O, 16.21. Found: C, 63.31; H, 3.79; N, 7.32; O, 17.98.

*(6-Chloro-3-(2-nitrophenyl)-3,4-dihydro-2H-benzo[b][1,4]-oxazin-2-yl)(phenyl)methanone (**17**).* Green solid, (425 mg, 77% yield). mp: 189−191 °C; FTIR (ATR, V_{max}, cm^{-1}): 3406 (N−H str.), 2976 (Ar−H str.), 1673 (C=O str.), 1494 (Ar C=C str.), 1338 (Ar−NO_2 str.), 1245 (C−N str.), 1058 (C−O−C str.), 694 (C−Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.03−7.98 (m, 3H), 7.59 (d, J = 4.11 Hz, 2H), 7.55 (d, J = 8.07 Hz, 1H), 7.48−7.46 (m, 1H), 7.44−7.40 (m, 2H), 6.67 (d, J = 2.0 Hz, 1H), 6.59 (d, J = 8.51 Hz, 1H), 6.51 (dd, J = 8.60 Hz, J = 2.26 Hz, 1H), 5.85 (d, J = 5.56 Hz, 1H), 5.58 (s, 1H), 4.58 (d, J = 5.44 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C) δ 194.7, 147.7, 139.5, 137.1, 134.4, 133.8, 133.7, 133.6, 129.9, 129.2, 128.6, 128.5, 127.7, 124.9, 118.4, 118.3, 114.6, 77.5, 49.8. Anal. Calcd for $C_{21}H_{15}ClN_2O_4$: C, 63.89; H, 3.83; N, 7.10; O, 16.21. Found: C, 63.47; H, 3.79; N, 7.08; O, 16.76.

*(6-Chloro-3-(furan-2-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**18**).* Brown solid, (398 mg, 84% yield). mp: 170−174 °C; FTIR (ATR, V_{max}, cm^{-1}): 3364 (N−H str.), 2976 (Ar−H str.), 1689 (C=O str.), 1497 (Ar C=C str.), 1262 (C−N str.), 1060 (C−O−C str.), 691 (C−Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.80 (d, J = 8.01 Hz, 2H), 7.55 (t, J = 7.31 Hz, 1H), 7.42 (t, J = 7.64 Hz, 2H), 7.18 (s, 1H), 6.89 (d, J = 8.24 Hz, 1H), 6.71−6.69 (m, 2H), 6.18−6.16 (m, 1H), 6.10 (d, J = 3.20 Hz, 1H), 5.63 (d, J = 2.48 Hz, 1H), 5.06 (s, 1H), 4.35 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C) δ 194.7, 150.7, 142.1, 141.6, 135.5, 133.5, 133.0, 128.7, 128.6, 127.1, 119.4, 118.1, 115.5, 110.6, 108.2, 77.8, 50.1. Anal. Calcd for $C_{19}H_{14}ClNO_3$: C, 67.16; H, 4.15; N, 4.12; O, 14.13. Found: C, 70.97; H, 4.43; N, 4.42; O, 16.53.

*(6-Chloro-3-(thiophen-2-yl)-3,4-dihydro-2H-benzo[b][1,4]-oxazin-2-yl)(phenyl)methanone (**19**).* Off white solid, (358 mg, 72% yield). mp: 195−198 °C; FTIR (ATR, V_{max}, cm^{-1}): 3366 (N−H str.), 2976 (Ar−H str.), 1688 (C=O str.), 1496 (Ar C=C str.), 1226 (C−N str.), 1057 (C−O−C str.), 694 (C−Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.79 (d, J = 7.74 Hz, 2H), 7.55 (t, J = 7.34 Hz, 1H), 7.41 (t, J = 7.64 Hz, 2H), 7.11 (d, J = 4.88 Hz, 1H), 6.94 (d, J = 8.52 Hz, 1H), 6.82−6.79 (m, 2H), 6.73−6.71 (m, 1H), 6.67 (d, J = 1.80 Hz, 1H), 5.63 (d, J = 2.28 Hz, 1H), 5.29 (s, 1H), 4.40 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C) δ 141.5, 133.5, 133.0, 128.8, 128.6, 127.5, 126.6, 126.1, 125.8, 119.3, 118.2, 115.3, 78.99, 51.80. The signals for the three aromatic quaternary carbons were not observed in the ^{13}C NMR spectrum. Anal. Calcd for $C_{19}H_{14}ClNO_2S$: C, 64.13; H, 3.97; N,

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3.94; O, 8.99; S, 9.01. Found: C, 63.34; H, 3.92; N, 4.02; O, 11.58; S, 8.73.

(6-Chloro-3-cyclohexyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(phenyl)methanone (**20**). Off white solid, (205 mg, 41% yield). R_f 0.5 (5% ethyl acetate in hexane); mp: 110−115 °C; FTIR (ATR, V_{max}, cm^{-1}): 3380 (N−H str.), 2923 (Ar−H str.), 1688 (C=O str.), 1497 (Ar C=C str.), 1219 (C−N str.), 689 (C−Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.04−8.02 (m, 2H), 7.46−7.42 (m, 4H), 7.09 (dd, J = 8.65 Hz, J = 2.22 Hz, 1H), 6.85 (d, J = 8.65 Hz, 1H), 5.41 (d, J = 8.59 Hz, 1H), 3.75−3.71 (m, 1H), 1.90−1.83 (m, 2H), 1.74−1.67 (m, 1H), 1.53−1.49 (m, 1H), 1.45 (d, J = 5.69 Hz, 1H), 1.27−1.23 (m, 4H), 1.19−1.13 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C) δ 162.0, 143.4, 136.9, 134.9, 131.3, 128.6, 128.3, 127.8, 127.2, 126.9, 116.9, 73.1, 70.7, 39.9, 29.7, 26.55, 26.51, 26.2, 25.5. HRMS (ESI-TOF) calcd for $C_{21}H_{23}ClNO_2$ $[M + H]^+$ 356.1417, found 356.1786.

(3-(2,3-Dimethoxyphenyl)-6-methyl-3,4-dihydro-2H-benzo[b]-[1,4]oxazin-2-yl)(phenyl)methanone (**21**). Yellow solid, (488 mg, 77% yield). R_f 0.32 (21% ethyl acetate in hexane); mp: 144−147 °C; FTIR (ATR, V_{max}, cm^{-1}): 3356 (N−H str.), 3070 (Ar−H str.), 1689 (C=O str.), 1596 (Ar C=C str.), 1206 (C−N str.), 1077 (C−O−C str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.08 (d, J = 7.91 Hz, 2H), 7.56 (t, J = 7.11 Hz, 1H), 7.44 (t, J = 7.67 Hz, 2H), 6.98−6.91 (m, 2H), 6.84 (d, J = 7.67 Hz, 1H), 6.74 (d, J = 7.79 Hz, 1H), 6.49−6.47 (m, 2H), 5.61 (d, J = 2.91 Hz, 1H), 5.24 (d, J = 2.88 Hz, 1H), 4.12 (brs, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.23 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$,25 °C) δ 195.5, 152.4, 146.0, 140.6, 135.0, 134.3, 133.3, 132.1, 131.3, 128.9, 128.4, 124.2, 119.6, 119.5, 116.4, 115.5, 112.1, 78.4, 60.5, 55.8, 49.7, 20.8. Anal. Calcd for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60; O, 16.43. Found: C, 74.11; H, 6.01; N, 3.66; O, 16.73.

(3-(4-Chlorophenyl)-6-methyl-3,4-dihydro-2H-benzo[b][1,4]-oxazin-2-yl)(phenyl)methanone (**22**). Off white solid, (490 mg, 83% yield). mp: 155−160 °C; FTIR (ATR, V_{max}, cm^{-1}): 3399 (N−H str.), 1687 (C=O str.), 1596 (Ar C=C str.), 1207 (C−N str.), 690 (C−Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.84 (d, J = 7.68 Hz, 2H), 7.49 (t, J = 7.24 Hz, 1H), 7.35 (t, J = 7.54 Hz, 2H), 7.25−7.18 (m, 4H), 6.72 (d, J = 7.92 Hz, 1H), 7.47- 7.45 (m, 2H), 5.21 (d, J = 5.74 Hz, 1H), 6.49−6.47 (m, 2H), 5.61 (d, J = 2.91 Hz, 1H), 5.24 (d, J = 2.88 Hz, 1H), 4.12 (brs, 1H), 4.80 (d, J = 5.36 Hz, 1H), 4.06 (s, 1H), 2.20 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C) δ 195.0, 140.5, 137.7, 135.3, 134.0, 133.6, 132.4, 131.8, 129.0, 128.9, 128.8, 128.5, 119.5, 116.7, 115.6, 79.0, 54.93, 20.8. Anal. Calcd for $C_{22}H_{18}ClNO_2$: C, 72.63; H, 4.99; N, 3.85; O, 8.79. Found: C, 71.74; H, 5.14; N, 3.96; O, 9.72.

(6-Chloro-3-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)-(phenyl)methanone (**23**, *Major Diastereomer*). Yellow liquid, (3:2 diastereomeric mixture, combined yield 344 mg, 86%). R_f 0.4 (3.9% ethyl acetate in hexane); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.95 (d, J = 7.87 Hz, 2H), 7.49−7.47 (m, 3H), 7.42 (d, J = 2.37 Hz, 1H), 7.12−7.09 (m, 1H), 6.91 (d, J = 8.46 Hz, 1H), 5.25 (d, J = 6.56 Hz, 1H), 4.08−4.02 (m, 1H), 2.28 (s, 1H), 1.10 (d, J = 6.40 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C) δ 160.3, 136.0, 134.6, 134.1, 131.6, 129.0, 128.6, 127.4, 127.3, 127.1, 116.7, 76.1, 66.5, 19.0.

(4-Bromophenyl)(6-chloro-3-(2,3-dimethoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanone (**24**). Reddish solid, (592 mg, 87% yield). mp: 160−162 °C; FTIR (ATR, V_{max}, cm^{-1}): 3402 (N−H str.), 2973 (Ar−H str.), 1691 (C=O str.), 1473 (Ar C=C str.), 1269 (C−N str.), 1060 (C−O−C str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.92 (d, J = 8.45 Hz, 2H), 7.59 (d, J = 8.42 Hz, 2H),7.00−6.96 (m, 1H), 6.87−6.84 (m, 2H), 6.73 (d, J = 8.80 Hz, 1H), 6.64−6.60 (m, 2H), 5.56 (d, J = 2.67 Hz, 1H), 5.21 (t, J = 3.16 Hz, 1H), 4.24 (d, J = 3.07 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C) δ 194.3, 152.4, 145.7, 140.9, 133.5, 133.4, 133.3, 131.8, 130.4, 128.8, 126.7, 124.3, 119.2, 118.5, 117.6, 114.3, 112.4, 78.2, 60.6, 55.8, 49.4. Anal. Calcd for $C_{23}H_{19}BrClNO_4$: C, 56.52; H, 3.92; N, 2.87; O, 13.09. Found: C, 56.30; H, 3.92; N, 3.08; O, 15.43.

(4-Bromophenyl)(3-(4-bromophenyl)-6-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanone (**25**). Yellow solid, (532 mg, 75% yield). mp: 143−146 °C; FTIR (ATR, V_{max}, cm^{-1}): 3366 (N−H str.), 2976 (Ar−H str.), 1674 (C=O str.), 1486 (Ar C=C str.), 1215 (C−N str.), 1061 (C−O−C str.), 768 (C−Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.74 (d, J = 8.18 Hz, 2H), 7.55 (d, J = 8.56 Hz, 2H), 7.42 (d, J = 8.39 Hz, 2H), 7.20 (d, J = 8.38 Hz, 2H), 6.73 (d, J = 8.55 Hz, 1H), 6.67 (d, J = 2.23 Hz, 1H), 6.61 (dd, J = 8.65 Hz, J = 2.37 Hz, 1H), 5.18 (d, J = 5.45 Hz, 1H), 4.86 (dd, J = 5.32 Hz, J = 2.58 Hz, 1H), 4.24 (d, J = 1.88 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C) δ 193.4, 140.8, 137.8, 133.8, 133.7, 132.15, 132.12, 130.5, 129.3, 129.2, 127.4, 122.6, 118.7, 118.1, 114.7, 78.9, 54.4. Anal. Calcd for $C_{21}H_{14}Br_2ClNO_2$: C, 49.69; H, 2.78; N, 2.76; O, 6.30. Found: C, 49.17; H, 2.77; N, 2.81; O, 9.29.

(4-Bromophenyl)(6-chloro-3-(4-chlorophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanone (**26**). Yellow solid, (458 mg, 71% yield). mp: 138−140 °C; FTIR (ATR, V_{max}, cm^{-1}): 3352 (N−H str.), 2976 (Ar−H str.), 1663 (C=O str.), 1489 (Ar C=C str.), 1225 (C−N str.), 1063 (C−O−C str.), 676 (C−Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.74 (d, J = 8.67 Hz, 2H), 7.55 (d, J = 8.45 Hz, 2H), 7.27−7.26 (m, 4H), 6.74 (d, J = 8.52 Hz, 1H), 6.67 (d, J = 2.31 Hz, 1H), 6.62 (dd, J = 8.88 Hz, J = 2.36 Hz, 1H), 5.19 (d, J = 5.56 Hz, 1H), 4.87 (dd, J = 5.47 Hz, J = 2.66 Hz, 1H), 4.23 (d, J = 2.66 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C) δ 193.8, 140.8, 137.2, 134.5, 133.8, 132.1, 130.5, 129.3, 129.2, 128.9, 127.4, 118.7, 118.1, 114.7, 78.9, 54.4. Anal. Calcd for $C_{21}H_{14}BrCl_2NO_2$: C, 54.46; H, 3.05; N, 3.02; O, 6.91. Found: C, 52.80; H, 2.99; N, 2.99; O, 10.78.

(4-Bromophenyl)(6-chloro-3-(3-methoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanone (**27**). Off white solid, (507 mg, 79% yield). mp: 170−174 °C; FTIR (ATR, V_{max}, cm^{-1}): 3371 (N−H str.), 2970 (Ar−H str.), 1686 (C=O str.), 1494 (Ar C=C str.), 1255 (C−N str.), 1054 (C−O−C str.), 695 (C−Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.46−7.41 (m, 4H), 7.09 (t, J = 7.61 Hz, 1H), 6.88 (d, J = 8.88 Hz, 1H), 6.72−6.71 (m, 2H), 6.70−6.69 (m, 2H), 6.60 (t, J = 1.91 Hz, 1H), 5.55 (d, J = 3.26 Hz, 1H), 4.91 (t, J = 2.81 Hz, 1H), 4.35 (d, J = 1.62 Hz, 1H), 3.62 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C) δ 194.6, 141.4, 139.4, 134.8, 133.9, 131.7, 130.0, 129.9, 128.5, 127.2, 119.7, 118.8, 117.9, 114.6, 113.8, 113.3, 79.0, 56.1, 55.3. Anal. Calcd for $C_{22}H_{17}BrClNO_3$: C, 57.60; H, 3.74; N, 3.05; O, 10.46. Found: C, 56.72; H, 3.70; N, 3.13; O, 12.76.

(4-Bromophenyl)(6-chloro-3-(furan-2-yl)-3,4-dihydro-2H-benzo-[b][1,4]oxazin-2-yl)methanone (**28**). Off white solid, (422 mg, 72% yield). mp: 150−152 °C; FTIR (ATR, V_{max}, cm^{-1}): 3365 (N−H str.), 2976 (Ar−H str.), 1691(C=O str.), 1490 (Ar C=C str.), 1241 (C−N str.), 1059 (C−O−C str.), 736 (C−Cl str.); ^{1}H NMR (600 MHz, $CDCl_3$, 40 °C) δ 7.66 (d, J = 8.36 Hz, 2H), 7.54 (d, J = 8.33 Hz, 2H), 7.17 (s, 1H), 6.85 (d, J = 8.37 Hz, 1H), 6.71−6.69 (m, 2H), 6.17 (s, 1H), 6.10 (d, J = 2.82 Hz, 1H), 5.49 (d, J = 2.28 Hz, 1H), 5.05 (d, J = 2.99 Hz, 1H), 4.33 (s, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 40 °C) δ 194.3, 150.8, 142.2, 141.5, 134.4, 133.0, 131.9, 130.3, 128.7, 127.3, 119.5, 118.0, 115.6, 110.7, 108.3, 78.4, 50.2. Anal. Calcd for $C_{19}H_{13}BrClNO_3$: C, 54.51; H, 3.13; N, 3.35; O, 11.46. Found: C, 52.68; H, 3.09; N, 3.30; O, 14.04.

(4-Bromophenyl)(6-chloro-3-(thiophen-2-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanone (**29**). Off white solid, (395 mg, 65% yield). mp: 150−152 °C; FTIR (ATR, V_{max}, cm^{-1}): 3348 (N−H str.), 2976 (Ar−H str.), 1679 (C=O str.), 1492 (Ar C=C str.), 1233 (C−N str.), 1060 (C−O−C str.), 711 (C−Cl str.); ^{1}H NMR (600 MHz, $CDCl_3$, 40 °C) δ 7.75 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 8.02, Hz, 2H), 7.21 (d, J = 4.20 Hz, 1H), 6.97 (s, 1H), 6.88 (s, 1H), 6.77 (d, J = 8.04 Hz, 1H), 6.65−6.63 (m, 2H), 5.31 (d, J = 4.98 Hz, 1H), 5.17 (d, J = 4.03 Hz, 1H), 4.32 (s, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 40 °C) δ 193.8, 141.6, 141.2, 134.1, 133.1, 132.1, 130.4, 129.2, 127.3, 127.2, 126.2, 126.0, 119.2, 118.0, 115.2, 78.9, 51.2. Anal. Calcd for $C_{19}H_{13}BrClNO_2S$: C, 52.49; H, 3.01; N, 3.22; O, 7.36; S, 7.37. Found: C, 52.24; H, 2.96; N, 3.56; O, 9.91; S, 6.89.

(4-Bromophenyl)(6-chloro-3-(3-fluorophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanone (**30a**). Light yellow solid, (530 mg, 76% yield). R_f 0.7 (3% ethyl acetate in hexane); mp: 135−138 °C; FTIR (ATR, V_{max}, cm^{-1}): 3398 (N−H str.), 2976 (Ar−H str.), 1678 (C=O str.), 1491 (Ar C=C str.), 1218 (C−N str.), 1112 (C−F str.), 1064 (C−O−C str.), 687 (C−Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.75 (d, J = 8.14 Hz, 2H), 7.54 (d, J = 8.39 Hz, 2H), 7.28−7.26 (m, 1H), 7.10−7.04 (m, 2H), 6.98−6.94 (m, 1H), 6.74 (d, J = 8.24 Hz, 1H), 6.68 (d, J = 1.83 Hz, 1H), 6.62 (dd, J = 8.24 Hz, J = 1.83 Hz, 1H), 5.23 (d, J = 5.16 Hz, 1H), 4.90 (d, J = 3.22 Hz, 1H), 4.27 (s, 1H).

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$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ 194.0, 164.3−161.8 (d, J_{C-F} = 248.02 Hz, 1C), 141.5−141.4 (d, J_{C-F} = 6.50 Hz, 1C), 140.7, 133.8, 133.6, 132.0, 130.6, 130.5, 129.3, 127.4, 123.2−123.1 (d, J_{C-F} = 2.86 Hz, 1C), 118.7, 118.1, 115.7−115.5 (d, J_{C-F} = 20.96 Hz, 1C), 114.7, 114.6−114.4 (d, J_{C-F} = 22.05 Hz, 1C), 78.8, 54.5. Anal. Calcd for $C_{21}H_{14}BrClFNO_2$: C, 56.47; H, 3.16; N, 3.14; O, 7.16. Found: C, 56.63; H, 3.18; N, 3.01; O, 8.32.

*(4-Bromophenyl)(6-chloro-3-(3-fluorophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanone (**30b**).* Light yellow solid, (49 mg, 7% yield). R_f 0.6 (5% ethyl acetate in hexane); mp: 135−138 °C; FTIR (ATR, V_{max}, cm^{-1}): 3366 (N−H str.), 2964 (Ar−H str.), 1686 (C = O str.), 1490 (Ar C=C str.), 1256 (C−N str.), 1063 (C−O−C str.), 788 (C−Cl str.); ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.53−7.47 (m, 4H), 7.16−7.11 (m, 1H), 6.91−6.86 (m, 3H), 6.81 (d, J = 9.68 Hz, 1H), 6.72−6.70 (m, 2H), 5.51 (d, J = 3.32 Hz, 1H), 4.97 (s, 1H), 4.41 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ 194.4, 164.1, 141.2, 140.8, 134.5, 133.6, 131.9, 130.4, 130.2, 128.8, 127.7, 123.2, 118.9, 118.2, 115.6−115.4 (d, J_{C-F} = 22.10 Hz, 1C), 114.6, 114.5, 79.2, 55.7. HRMS (ESI-TOF) calcd for $C_{21}H_{15}BrClFNO_2$ $[M + H]^+$ 445.9959, found 446.0160.

*(4-Bromophenyl)(6-chloro-3-(p-tolyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanone (**31**).* Reddish solid, (520 mg, 84% yield). mp: 175−177 °C; FTIR (ATR, V_{max}, cm^{-1}): 3374 (N−H str.), 2976 (Ar−H str.), 1679 (C=O str.), 1489 (Ar C=C str.), 1285 (C−N str.), 1061 (C−O−C str.), 677 (C−Cl str.); ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.70 (d, J = 8.50 Hz, 2H), 7.51 (d, J = 8.48 Hz, 2H), 7.18 (d, J = 7.98 Hz, 2H), 7.08 (d, J = 7.93 Hz, 2H), 6.76 (d, J = 8.50 Hz, 1H), 6.65 (d, J = 2.26 Hz, 1H), 6.61 (dd, J = 8.56 Hz, J = 2.27 Hz, 1H), 5.20 (d, J = 5.91 Hz, 1H), 4.77 (d, J = 5.77 Hz, J = 1.76 Hz, 1H), 4.22 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ 194.1, 141.0, 138.6, 135.2, 134.14, 134.1, 131.9, 130.5, 129.6, 129.0, 127.4, 127.1, 118.3, 117.9, 114.5, 79.1, 55.1, 21.2. Anal. Calcd for $C_{22}H_{17}BrClNO_2$: C, 59.68; H, 3.87; N, 3.16; O, 7.23. Found: C, 59.55; H, 3.94; N, 3.43; O, 9.52.

*(4-Bromophenyl)(6-chloro-3-(3,4-difluorophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanone (**32**).* Brown solid, (448 mg, 69% yield). mp: 139−143 °C; FTIR (ATR, V_{max}, cm^{-1}): 3344 (N−H str.), 2921 (Ar−H str.), 1689 (C=O str.), 1493 (Ar C=C str.), 1224 (C−N str.), 1114 (C−F str.), 1060 (C−O−C str.), 768 (C−Cl str.); ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.75 (d, J = 7.19 Hz, 2H), 7.55 (d, J = 7.63 Hz, 2H), 7.19−7.05 (m, 3H), 6.73−6.60 (m, 3H), 5.11 (d, J = 4.31 Hz, 1H), 4.86 (d, J = 3.18 Hz, 1H), 4.30 (brs, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$ 25 °C) δ 193.7, 151.8−149.2 (dd, J_{C-F} = 250.08 Hz, J_{C-F} = 13.37 Hz, 1C), 151.5−148.9 (dd, J_{C-F} = 250.08 Hz, J_{C-F} = 12.90 Hz, 1C), 140.7, 135.98−135.93 (d, J_{C-F} = 4.46 Hz, 1C), 133.6, 133.5, 132.1, 130.5, 129.4, 127.5, 123.7−123.6 (dd, J_{C-F} = 3.61 Hz, J_{C-F} = 3.61 Hz, 1C), 118.8, 118.1, 117.8−117.6 (d, J_{C-F} = 17.91 Hz, 1C), 116.7−116.5 (d, J_{C-F} = 18.47 Hz, 1C), 114.8, 78.7, 53.9. HRMS (ESI-TOF) calcd for $C_{21}H_{14}BrClF_2NO_2$ $[M + H]^+$ 463.9865, found 464.0126.

*(4-Bromophenyl)(6-chloro-3-(4-methoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanone (**33**).* Red solid, (578 mg, 90% yield). mp: 142−145 °C; FTIR (ATR, V_{max}, cm^{-1}): 3368 (N−H str.), 2929 (Ar−H str.), 1681 (C=O str.), 1491 (Ar C=C str.), 1224 (C−N str.), 1061 (C−O−C str.), 794 (C−Cl str.); ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.69 (d, J = 8.62 Hz, 2H), 7.51 (d, J = 8.62 Hz, 2H), 7.21 (d, J = 8.68 Hz, 2H), 6.80−6.77 (m, 3H), 6.66−6.61 (m, 2H), 5.17 (d, J = 6.25 Hz, 1H), 4.74 (d, J = 6.13 Hz, 1H), 4.19 (brs, 1H), 3.74 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ 194.1, 159.9, 141.1, 134.2, 132.0, 130.5, 129.9, 129.0, 128.8, 127.1, 118.4, 117.9, 114.6, 114.4, 79.2, 55.4, 54.9. Anal. Calcd for $C_{22}H_{17}BrClNO_3$: C, 57.60; H, 3.74; N, 3.05; O, 10.46. Found: C, 56.13; H, 3.65; N, 3.57; O, 14.18.

*(6-Chloro-3-(4-chlorophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(4-chlorophenyl)methanone (**34**).* Light yellow solid, (538 mg, 92% yield). mp: 148−150 °C; FTIR (ATR, V_{max}, cm^{-1}): 3356 (N−H str.), 2908 (Ar−H str.), 1664 (C=O str.), 1585 (Ar C=C str.), 1223 (C−N str.), 795 (C−Cl str.); ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.74 (d, J = 8.45 Hz, 2H), 7.29 (d, J = 8.45 Hz, 2H), 7.20−7.18 (m, 4H), 6.66 (d, J = 8.52 Hz, 1H), 6.59 (d, J = 1.87 Hz, 1H), 6.53 (dd, J = 8.50 Hz, J = 1.82 Hz, 1H), 5.11 (d, J = 5.44 Hz, 1H), 4.78 (d, J = 5.18 Hz, 1H), 4.18 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ 193.5, 140.7, 140.4, 137.1, 134.4, 133.6, 133.3, 130.3, 129.08, 129.0, 128.8, 127.3, 118.5, 118.0, 114.6, 78.8, 54.3. Anal. Calcd for $C_{21}H_{14}Cl_3NO_2$: C, 60.24; H, 3.37; N, 3.35; O, 7.64. Found: C, 59.62; H, 3.35; N, 3.37; O, 8.26.

*(6-Chloro-3-(4-chlorophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(4-methoxyphenyl)methanone (**35**).* Off white solid, (498 mg, 86% yield). mp: 145−148 °C; FTIR (ATR, V_{max}, cm^{-1}): 3339 (N−H str.), 2931 (Ar−H str.), 1665 (C=O str.), 1591 (Ar C=C str.), 1230 (C−N str.), 745 (C−Cl str.); ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.86 (d, J = 8.70 Hz, 2H), 7.28−7.23 (m, 4H), 6.86 (d, J = 8.70 Hz, 2H), 6.78 (d, J = 8.50 Hz, 1H), 6.67 (s, 1H), 6.62 (d, J = 8.51 Hz, 1H), 5.21 (d, J = 5.72 Hz, 1H), 4.83 (d, J = 7.04 Hz, 1H), 4.27 (s, 1H), 3.85 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ 192.7, 164.2, 141.3, 137.4, 134.3, 133.9, 131.5, 129.07, 129.05, 128.1, 127.1, 118.5, 118.0, 114.7, 114.0, 78.6, 55.6, 54.6. Anal. Calcd for $C_{22}H_{17}Cl_2NO_3$: C, 63.78; H, 4.14; N, 3.38; O, 11.59. Found: C, 63.38; H, 4.03; N, 3.46; O, 12.09.

*(6-Chloro-3-(4-chlorophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)(p-tolyl)methanone (**36**).* Off white solid, (416 mg, 75% yield). mp: 149−152 °C; FTIR (ATR, V_{max}, cm^{-1}): 3334 (N−H str.), 2921 (Ar−H str.), 1672 (C=O str.), 1602 (Ar C=C str.), 1235 (C−N str.), 800 (C−Cl str.); ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.84 (d, J = 7.68 Hz, 2H), 7.49 (t, J = 7.24 Hz, 1H), 7.35 (t, J = 7.54 Hz, 2H), 7.25−7.18 (m, 4H), 6.72 (d, J = 7.92 Hz, 1H), 7.47−7.45 (m, 2H), 5.21 (d, J = 5.74 Hz, 1H), 6.49−6.47 (m, 2H), 5.61 (d, J = 2.91 Hz, 1H), 5.24 (d, J = 2.88 Hz, 1H), 4.12 (brs, 1H), 4.80 (d, J = 5.36 Hz, 1H), 4.06 (s, 1H), 2.20 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ 194.0, 144.9, 141.1, 137.2, 134.2, 133.7, 132.6, 129.3, 129.0, 128.99, 128.91, 127.0, 118.4, 117.9, 114.6, 78.5, 54.5, 21.7. Anal. Calcd for $C_{22}H_{17}Cl_2NO_2$: C, 66.35; H, 4.30; N, 3.52; O, 8.03. Found: C, 66.68; H, 4.47; N, 3.42; O, 8.63.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c00463.

NOESY spectra of compound 4, spectral characterization of intermediates V and VII, and copies of ^1H, ^{13}C NMR, HRMS, elemental analysis, and IR spectra (PDF)

X-ray crystallographic analysis of **9b** (CIF)

X-ray crystallographic analysis of **15** (CIF)

X-ray crystallographic analysis of **17** (CIF)

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Notes

The authors declare no competing financial interest.

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