UNIVERSITY OF KWAZULU-NATAL

SYNTHESIS, CHARACTERIZATION AND ANTI-OXIDANT ACTIVITY OF PRENYLATED AND FLUORINE BASED FLAVONOIDS

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SYNTHESIS, CHARACTERIZATION AND ANTI-OXIDANT ACTIVITY OF PRENYLATED AND FLUORINE BASED FLAVONOIDS

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2013

Supervisor: Prof. N.A. Koorbanally

PREFACE

This study represents original work by the author and has not been submitted in any other form to another university. Where the use of work pertaining to others has been duly acknowledged in the text.

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As the Candidate's supervisor, I have approved this thesis for submission.

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DECLARATION – PLAGIARISM

I, **WESLEY GUY CHELSAN OGLE,** declare that the experimental work described in this dissertation was carried out at the School of Chemistry and Physics, University of KwaZulu-Natal, Westville campus under the supervision of Prof. N. A. Koorbanally, and that:

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To my Lord and savior, Jesus Christ, there is none like you. You are the reason for the season and all things shall come to pass but your word will remain.

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I would like to thank each individual of the technical staff for their friendly nature and assistance with my lab work during my studies.

I would like to thank the National Research Foundation for financial support through a Masters Innovations Skills Scholarship.

List of Abbreviations

°C	degrees Celsius
^{13}C NMR	carbon-13 nuclear magnetic resonance spectroscopy
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
$CDCl_3$	deuterated chloroform
d	doublet
DCM	dichloromethane
dd	double doublet
dt	doublet triplet
EtOAc	ethyl actetate
EtOH	ethanol
GC-MS	chromatography coupled with mass spectrometry
HMBC	heteronuclear multiple bond coherence
hrs	hours
HSQC	heteronuclear single quantum coherence
Hz	hertz
IR	infrared
m	multiplet
m.p.	melting point
MeOH	methanol
min	minutes
MOM	methoxymethylene
NOESY	nuclear overhauser effect spectroscopy
s	singlet
t	triplet
td	triplet of doublets
TLC	thin layer chromatography
UV	ultraviolet

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Abstract

Twenty flavonoids **II-XXI** were successfully synthesized using the Claisen-Schmidt condensation reaction between 2-hydroxy and 3-hydroxyacetophenone with various substituted fluorobenzaldehydes. The twenty flavonoids consisted of sixteen chalcones, eight of which were new novel prenyl chalcones (**XIV-XXI**), and four flavanones (**X-XIII**). The compounds were produced in yields of between 54-90%. It was shown in **II-XIII** that the rate of reaction is influenced electronically by the substitution patterns of the fluorine atom on the B-ring, in the order; 2',4'-difluoro > 2'-fluoro> 4'-fluoro > 3'-fluoro. All compounds were characterized by NMR, IR, UV and mass spectral analyses. Compounds **II-IX** bearing hydroxyl groups were subjected to antioxidant screening using the DPPH free radical scavenging assay. Antioxidant activities of these compounds were established as moderate to low in comparison to the standard, ascorbic acid. The difluoro compounds **V** and **IX** with fluorine on the *ortho* and *para* positions in the B-ring showed the highest activities, possibly due to both the position and number of fluorine atoms in the molecule.

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Chapter 1. Introduction

1.1 Introduction to flavonoids

Flavonoids are a large class of compounds known to contain the presence of hydroxyl groups. They are considered secondary metabolites; which are compounds that are not directly involved in the growth and/or development of organisms, but rather known for their pharmacological nature in plants. Flavonoids show an absorption in the yellow region of the visible spectrum. They are found in almost all plants and mainly concentrated in the leaves and flowers of plants. To date over four thousand different types of flavonoid derivatives have been identified (Cook and Samman, 1996). There are a wide variety of flavonoids, but common to all is the presence of a phenylbenzopyrone structure, (Figure 1) that links two aromatic rings together through three carbons atoms. In most cases, the three carbon atoms that link the two rings together can either exist in the form of an oxygenated pyran ring or in an open chain structure (Grotewold, 2006). The major classes of flavonoids include flavonols, flavanones, catechins, anthocyanidins, flavones, isoflavones, dihydroflavonols and chalcones (Cook and Samman, 1996; Rodriguez *et al*., 2001).

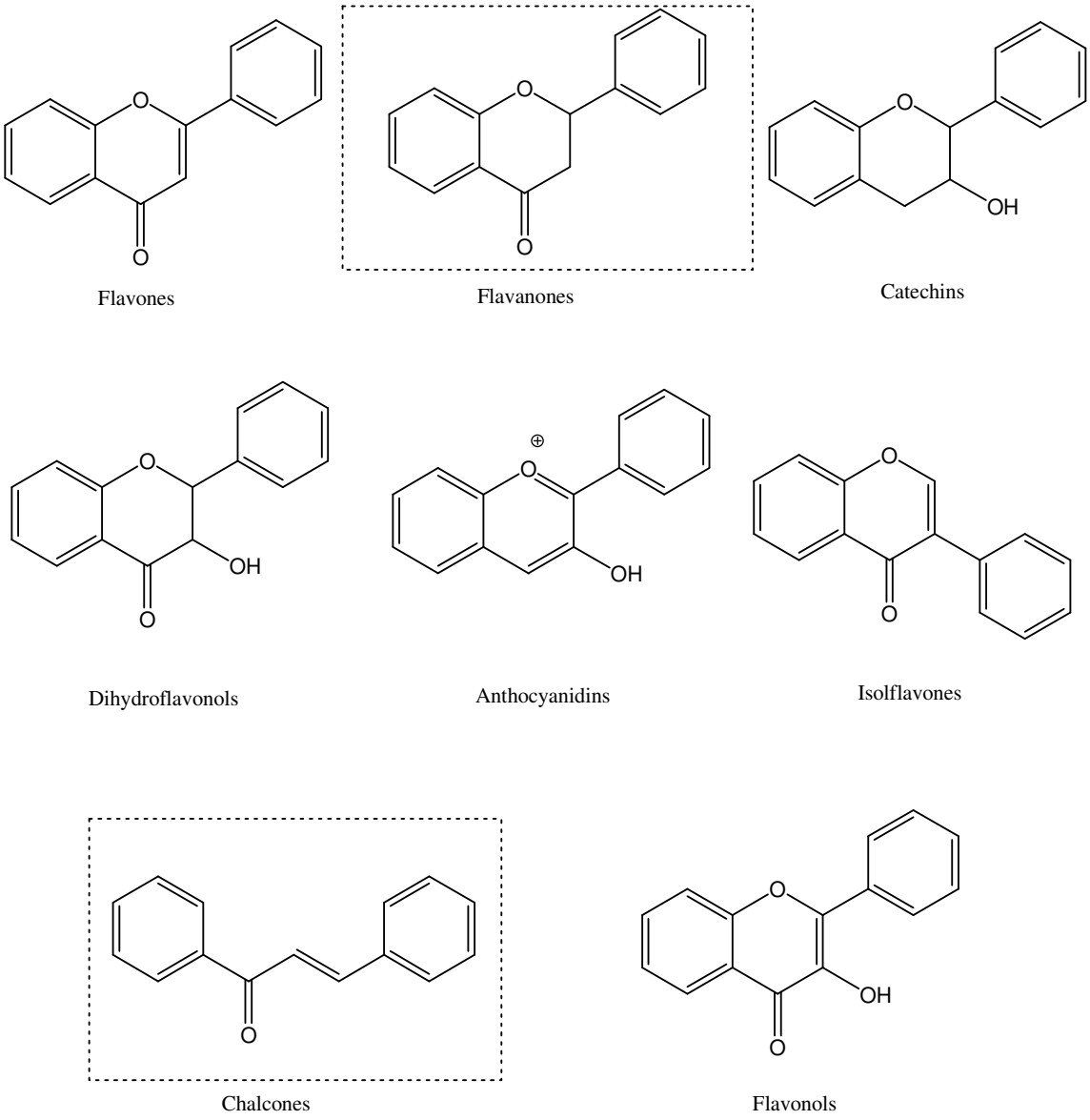


Figure 1 Structures of the major classes of flavonoids species

The pharmacological activity of flavonoids is dependent on their physical properties as well as the relative positions of various moieties and atoms in the molecule. As a result, many derivatives and analogs of flavonoids are produced synthetically (Grotewold, 2006). In this study, two major classes of flavonoids were synthesised; these are the chalcones and flavanones as highlighted in Figure 1.

1.1.1 The structure and numbering system of chalcones

Chalcones are a group of organic molecules which are known to be effective lead compounds in drug synthesis (Anto *et al*., 1995; Won *et al*., 2005; Go *et al*., 2005). They possess a 1, 3-diphenyl-2-propen-1-one structural framework linking both ring A and B, hence they exist chemically as open chain flavonoids (Figure 2). The three carbon atoms that join the two aromatic rings together are in the form of an α, β–unsaturated carbonyl system (Nowakowska, 2007).

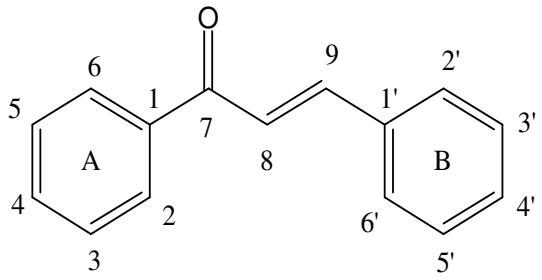


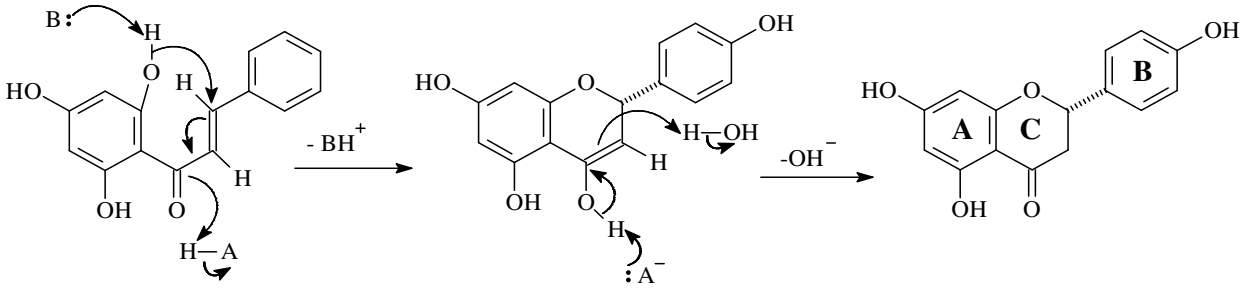
Figure 2 Basic structure and numbering of a chalcone

Chalcones occur naturally in many different polyhdroxylated forms. The radical quenching properties of the hydroxyl groups and aromatic rings are said to be the main active sites during biological treatment (Nowakowska, 2007).

1.1.2 The structure of flavanones

Flavanones are known as direct derivatives of chalcones (Cortes-Concepcion *et al*., 2010).Unlike chalcones, flavanones have a three-ring skeleton structure, and each ring is referred to as either an A-, B- or C-ring (Scheme 1) (Grotewold, 2006). In nature, plants use enzymes such as *chalconeisomerase* to chemically convert chalcones into their corresponding flavanone products, provided there is a hydroxyl moiety attached on the 2-position of the A ring of the chalcone

(Hintermann and Dittmer, 2012).The mechanism of isomerization occurs under basic conditions, whereby a base removes a proton from the hydroxyl group located at the 2-position. (**1**).Cyclisation takes place with the lone pair of electrons on the oxygen atom attacking C-3 producing intermediate (**i**). A second proton is abstracted from the hydroxyl group at C-4, followed by the abstraction of a proton from water, which leads to the flavanone (**2**). A typical example can be seen by the formation of the anti-cancer drug, Naringenin (Scheme 1) (Ahmad *et al.*, 2013).



1

2',4',6'-trihydroxychalcone

(i)

2

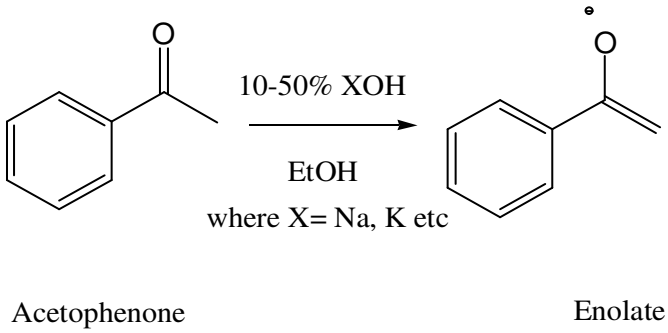
Naringenin

Scheme 1 The mechanism for the conversion of 2',4',6'-trihydroxyacetophenone to its flavanone, Naringenin where B= Base, H-A= Acid and A = conjugate base (Ahmad *et al.*, 2010)

1.1.3 Synthesis of chalcones

1.1.3.1 The base catalyzed Claisen-Schmidt condensation

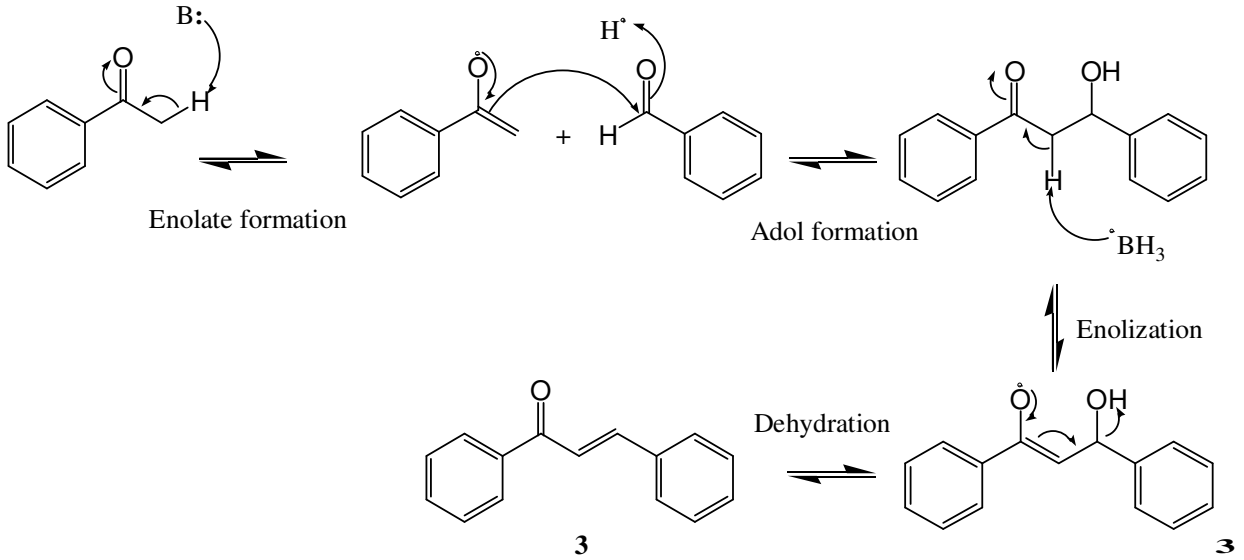
The most useful and practical method for chalcone synthesis is the use of the Claisen-Schmidt condensation reaction (Sebti *et al*., 2002; Clayden *et al*., 2007).The Claisen-Schmidt condensation reaction is referred to as the ester analogue to the Aldol condensation reaction between two ketones possessing alpha hydrogens. This process usually involves the reaction between aldehydes and ketones normally with ethanol as a solvent and under basic conditions (10-50% m/m base). Strong bases such as potassium hydroxide and sodium hydroxide are strong enough to pull off the weakly acidic alpha protons of a ketone, thereby forming an enolate ion capable of nucleophillic attack (Scheme 2) (Clayden*et al*., 2007).



Scheme 2 The formation of an enolate ion under basic conditions

The mechanism for using the Claisen condensation reaction has been studied for decades and is well understood. The reaction is often carried out using a phenyl ketone such as an acetophenone with that of an aldehyde such as benzaldehyde. In solution, a base pulls of the weakly acidic alpha hydrogen from acetophenone to form an enolate anion. The enolate anion, which acts as a base, rapidly attacks the carbonyl carbon of the benzaldehyde to form a β-hydoxyketone, intermediate. Subsequently, a conjugate base pulls off the remaining alpha hydrogen by means of

a process called enolization which is followed by dehydration to remove water. This produces a conjugated enone product, in this case a chalcone (**3**) as seen in Scheme 3 (Clayden *et al*., 2007).

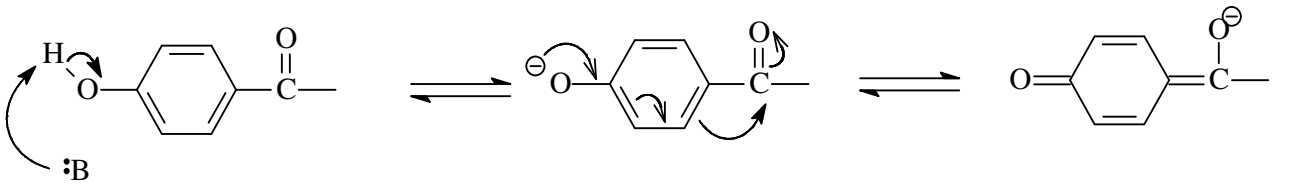


Scheme 3 Mechanism showing the formation of a simple chalcone

Reports show that yields between 55-90% can be expected using the Claisen-Schmidt condensation, however the yields may be influenced by the various substituents and their positions on both the A and B rings (Batovska *et al*., 2009). Electron withdrawing (EW) groups often tend to withdraw electron density away from the carbonyl carbon making it more susceptible to nucleophillic attack. The opposite is true for electron donating (ED) groups, making the carbonyl carbon less electrophilic and un-reactive.

Benzaldehyde and acetophenone reactants contain many difference functional groups and moieties and hence it is possible to synthesise a variety of chalcones by varying the functional groups and moieties as well as varying their substitution pattern before carrying out the

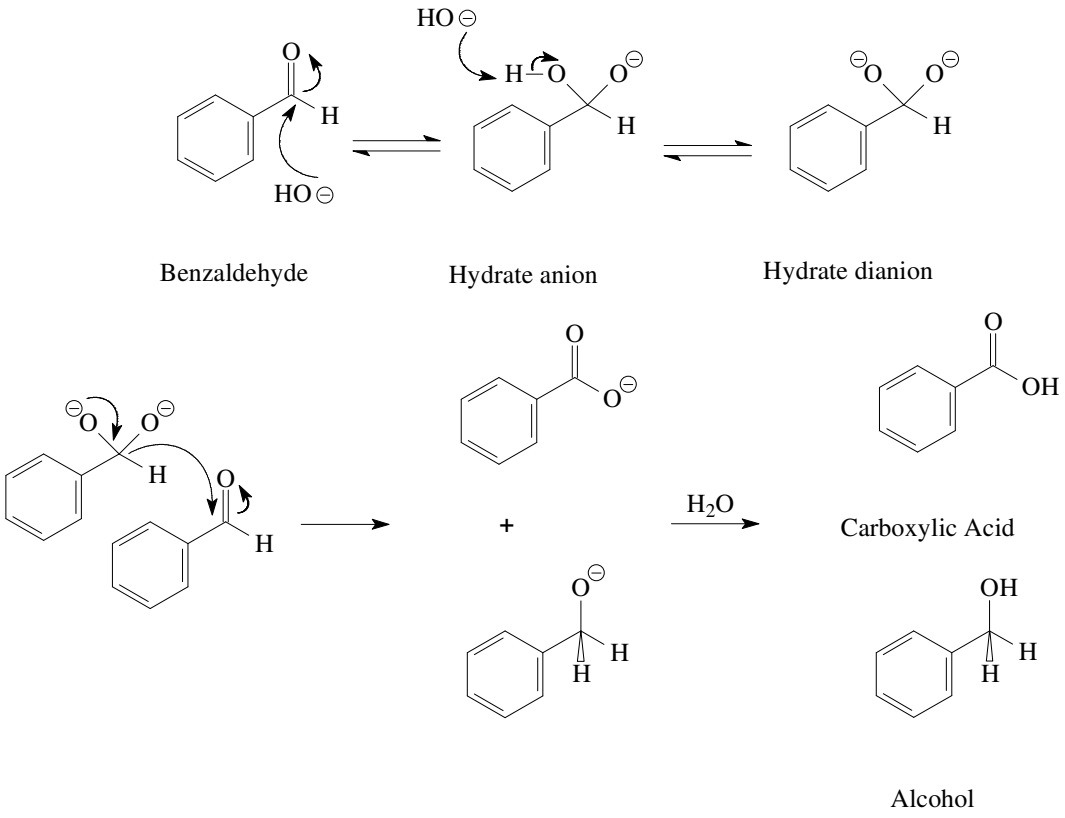
condensation reaction. Hydroxyl groups are the common functional group in flavonoids(Cook and Samman, 1996; Agati *et al*., 2012; Heim *et al*., 2002).The conversion of the chalcone (**3**) in Scheme 3 to its corresponding flavanone derivative requires a hydroxyl group at the 2-position of the A ring. The details for this mechanism are explained in Scheme 1. The major disadvantage of having functional groups is the possibility of side reactions. Under basic conditions a base is capable of pulling off a proton from a hydroxyl group on either the benzaldehyde or acetophenone starting materials. Taking 4-hydroxyacetophonenone as an example, the lone pair of electrons on the oxygen are delocalized onto the carbonyl oxygen, deactivating the carbonyl carbon whose ability to act as an enolate ion is lost in the delocalisation. Moreover, by removing a proton from the molecule, a negative charge is rendered on the entire molecule and hence this can no longer act as an electrophile. The mechanism of this process was first discovered in the early1900s (Scheme 4) (Petrov *et al*., 2008).The yields of polyhydroxy acetophenones are as a result very poor.



4-hydroxyacetophenone deactivated acetophenone

Scheme 4 Mechanism showing the deactivation of 4-hydroxyacetophenone under basic conditions

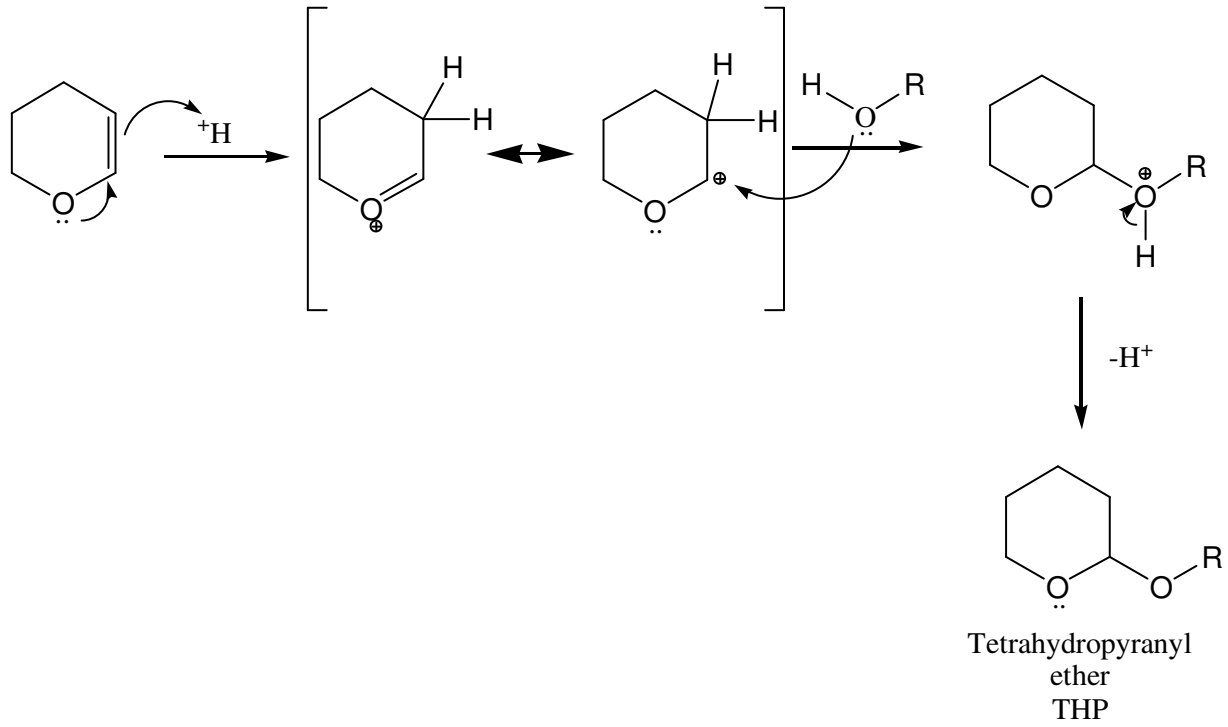
Another disadvantage of the Claisen-Schimdt condensation is the possibility of self condensation occurring between the benzaldehyde starting material. Under basic conditions, instead of abstracting the alpha acidic proton on acetophenone, the base can attack the carbonyl carbon of the benzaldehyde molecule. This subsequently forms hydrate anions and hydrate dianions. These hydrate anions and dianions further react with benzaldehyde to form carboxylic acids and alcohols respectively (Clayden *et al*., 2007). As a result, there is an overall loss of chalcone product. This process is well known as the Cannizaro reaction (Scheme 5).



Scheme 5 The mechanism of the Cannizaro reaction

Protecting groups are often used for the sole purpose of preventing side reactions and at the same time improving yields. There are numerous protecting groups that are available to protectalcohols. These include benzyl bromide, dioxolane, trimethylsilyl chloride and dihydropyran (Clayden *et al*., 2007). Dihydropyran can be used to protect the free hydroxyl group of acetopheone because of its stability in alkaline media. It has a built in trigger mechanism that makes it easy to remove by hydrolysis using a weak acid. The mechanism below shows that under acidic catalytic conditions the double bond of dihydropyran abstracts a proton from solution and subsequently the lone pair of electrons form a new double with the adjacent carbon and oxygen atoms. This results in an electrophillic intermediate resonance structure. The lone pairs on the hydroxyl group of the molecule that is being protected then attacks this intermediate which forms a tetrahydropyranyl protecting group (THP) as seen in Scheme 6 (Clayden *et al*., 2007; Green *et al*., 1999).

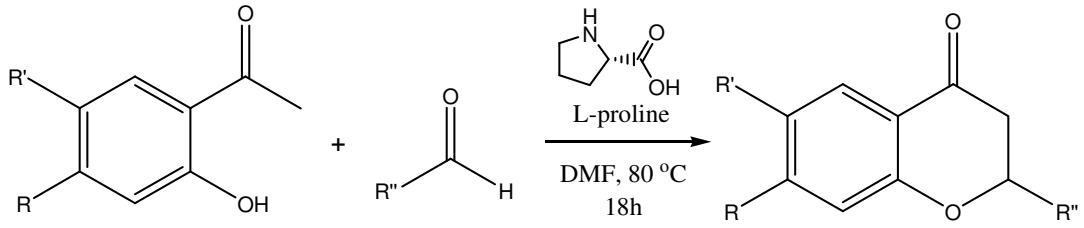
The disadvantage of using protecting groups means that an additional reaction step is required and this generally results in contamination or decrease in yield. However in contrast, protecting groups can be very useful in preventing the isomerization of a chalcone containing a hydroxyl group in the 2-position into its corresponding flavanone derivative.



Scheme 6 The mechanism for dihydropyran protection of alcohols

1.1.3.2 The use of organic and inorganic catalysts for flavonoid synthesis

The conventional methods of using bases such as NaOH, KOH and $Ba(OH)_2$ has often shifted at times due to their respective limitations. Organo-catalysts have been employed for the purpose of maximizing yields and reaction efficiency of flavonoid synthesis. The use of L-proline (structure has been inserted in scheme 7) as an organo-catalyst has been recently explored by Chandrasekhar *et al.* (2005). L-proline acts as a strong base which pulls off weakly acidic protons from acetophenone molecules. An enolate ion is formed (Scheme 7) and the usual work up and mechanism that takes place is as described in Scheme 3.



- where R, R' and R" = various substituents

Scheme 7 The synthesis of flavanones using L-proline as an organo-catalyst

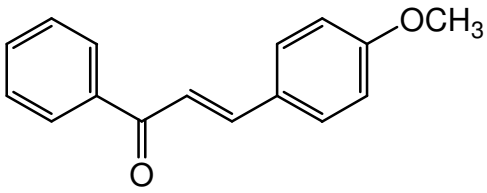
The reaction takes place in dimethyl formide (DMF) as a solvent which is reacted for eighteen hours at 80°C.Various flavanones and chalcones have been previously synthesized in yields as high as 67-93% using L-proline, indicating its popularity as a catalyst in the synthesis of chalcones (Chandrasekhar *et al*., 2005).

The use of lithium layered double hydroxides, $[LiAl_2(OH)_6](CO_3)0.5{\cdot}nH_2O$, have been previously investigated in the inorganic synthesis of flavanones. Selectivity and reaction rates were increased up to 68% after 20minutes of reaction time with different weight loadings of lithium and oxide as compared to normal basic conditions using the Claisen-Schmidt condensation reaction (Eddarir *et al*., 2003).

1.1.3.3 The use of heterogeneous catalysts for flavonoid synthesis.

The use of hydroxyapatite as a heterogeneous solid catalyst for Claisen-Schmidt condensation reactions has proven very useful in flavonoid synthesis. Several chalcones with yields as high as 87% were synthesized using various weight loadings of sodium nitrate and hydroxyapatite ($NaNO_3$/HAP). The addition of a quaternary ammonium salt (benzyltriethylammonium chloride, BTEAC) was reported to increase the rate (>25%) and overall yields of the reaction. A major environmental benefit of using this method is the fact that the catalyst is recyclable and reusable, making it environmentally beneficial as the need for greener chemistry increases (Sebti *et al*., 2002).

Table 1 Comparison of the efficiency of using BTEAC on the rate and yields of 4-methoxychalcone

Structure of product	**Yield (% (time, h)) $NaNO_3$/HAP without BTEAC**	**Yield (% (time, h)) $NaNO_3$/HAP with BTEAC**
	80 (**16**)	87(**12**)

1.1.3.4 The use of ionic liquids for flavonoid synthesis

A new approach in flavonoid synthesis is the use of ionic liquids. Ionic liquids, like that of certain heterogeneous catalysts, represent an alternative to the traditional use of volatile and hazardous solvents. The use of acyclic SO_3H-functionalized ionic liquids has been employed as catalysts for the synthesis of several variously substituted chalcones with yields between 89 to 93%. Synonymous to hydroxyapatite solid catalysts, the following ionic liquids which have been used for chalcone synthesis, are considered recyclable and reusable (Figure 3) (Dong *et al*., 2008a).

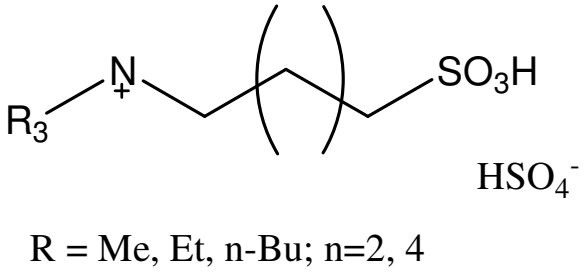


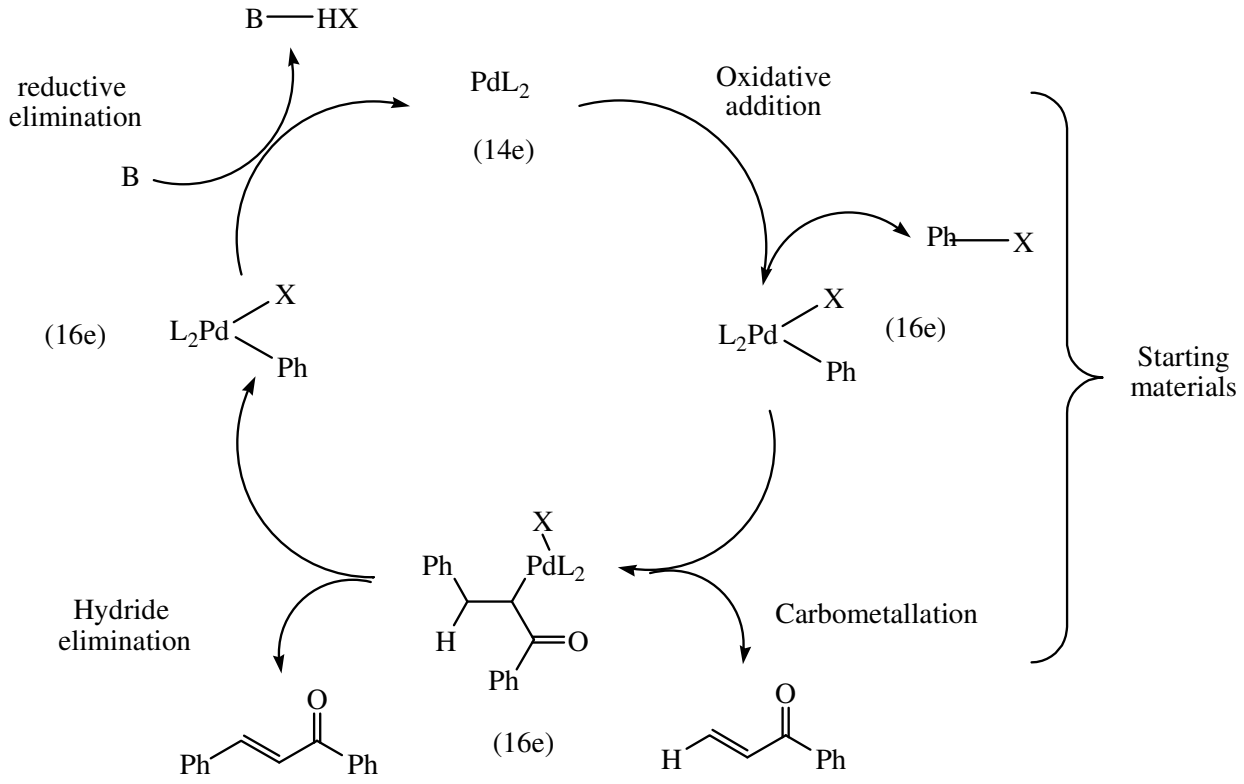
Figure 3 The structures of a few Ionic liquids used in the Claisen-Schmidt condensation

The major drawbacks experienced with the use of exotic catalysts such as ionic liquids and heterogeneous catalysts are the fact that they require a commendable amount of energy, time and effort to synthesize.

1.1.3.5 The use of metal catalysts in flavonoid synthesis.

Palladium (Pd) is just one of many transition metals which play an important role in flavonoid syntheses. It has the ability to catalyze the formation of new carbon-carbon bonds which proves essential in organic synthesis.

The Heck reaction is a palladium catalyzed reaction which couples unsaturated double bonds with aryl groups or vinyl halides. It allows these groups to react and can be carried out in organic solvents, ionic liquids or solvent free conditions (Scheme 8) (Clayden *et al*., 2007; Bianco *et al.*, 2003; Marvaniya *et al*., 2011).



Scheme 8 Diagram displaying the synthesis of a chalcone using Palladium as a catalyst in the Heck reaction, where B= base, L= ligand and X = halide (Clayden *et al*., 2007)

The use of the Heck reaction between an aryl vinylic ketone and an aryl iodide was carried out using triethlylamine, triphenyl phosphine, acetonitrile and $Pd(OAc)_2$ as a palladium catalyst. The intermediate product (**ii**), in 94% yield, was used to produce 2,4'-dihydroxy-4-methoxyychalcone

(**4**) and its flavanone derivative, 4'-hydroxy-7-methoxyflavanone (**5**), in satisfactory yields following a series of follow up reactions (Figure 4) (Bianco *et al*., 2003).

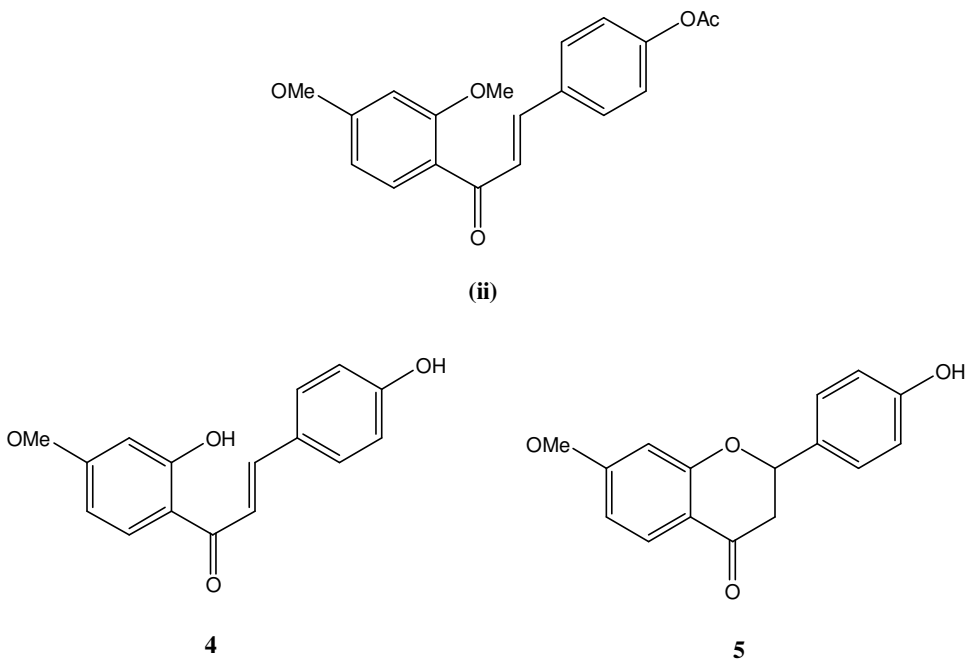
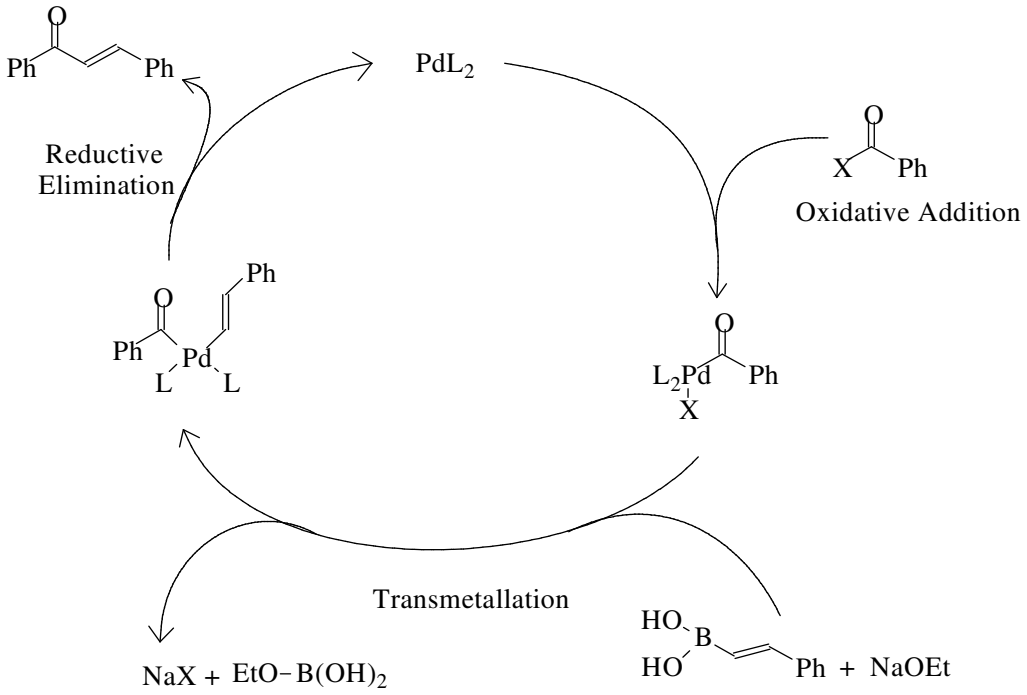


Figure 4 The structure of 2, 4'-dihydroxy 4-methoxyychalcone (4) and its flavanone derivative, 4'-hydroxy-7-methoxyflavanone (5) produced via the Hecks reaction.

Another example of using palladium as metal catalyst in flavonoid synthesis is the Suzuki cross coupling reaction between acyl halides with boronic esters. This technique has emerged over the past two decades as a powerful tool of introducing acyl functionalities to natural products and is more preferred over the traditional approach of the Friedels-Crafts acylation reaction (Blangetti *et al*., 2013). The process involves three stages: oxidative addition, transmetallation and, reductive elimination (Scheme 9).



Scheme 9 The Suzuki cross coupling reaction for the synthesis of a chalcone with palladium as a catalyst, where X= halide (Clayden *et al*., 2007)

Although both the Heck and Suzuki cross coupling reactions are very selective and produce exceptional yields, the starting materials used during their synthesis are not commercially available and needs to be synthesised. Furthermore the use of a palladium catalyst can be costly.

1.1.3.6 Other types of catalysts and catalytic supports.

Ultrasound accelerated Claisen condensation reactions have been previously used to synthesize several antibacterial chalcones. The use of a carbon catalyst (Na-Norit and Cs-Norit), when subjected to sonochemical irradiation, enhanced the effect of the yields of the afforded chalcones. Sonic activation is considered to exert a positive effect on the activation of carbon

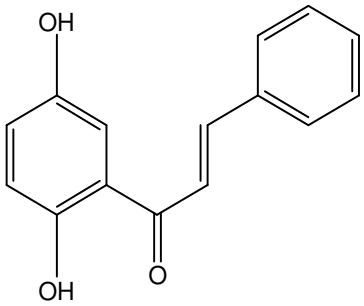
doped catalysts as opposed to non-sonic activated catalysts. This particular reaction thrives in the absence of solvents. Yields as high as 75% have been reported after 4 hours of reaction. The use of cesium doped alkaline carbons (Cs-Norit), with the absence of solvent, produced chalcones without side reactions such as the Cannizzaro reaction (Calvino *et al*., 2006).

1.1.4 Biological activity of flavonoids

Chalcones are known to have a range of bioactivities including anti-oxidant, anti-inflammatory, anti-cancer and antibacterial activities.

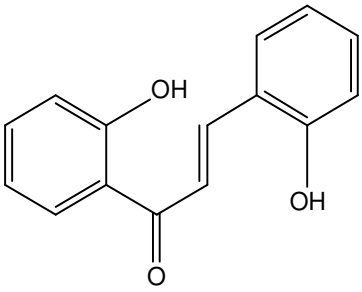
1.1.4.1 Anti-oxidant activity

Superoxide and peroxide radicals are known to participate in promoting tumor production. Several chalcones and flavanones have been found to promote antioxidant activities and scavenge free radicals. Investigation of two separate cytotoxic studies showed that, 2,5-dihydroxychalcone (**6**) exhibited potency towards superoxide production when compared to several un-substituted chalcones. Similarly, the 2,2'-dihydroxychalcone analogue (**7**) reported the highest potency for the inhibition of lipid peroxidation (Figure 5) (Anto *et al*., 1995; Hsieh *et al*., 1998).



2,5-dihydroxychalcone

6



2, 2'-dihydroxychalcone

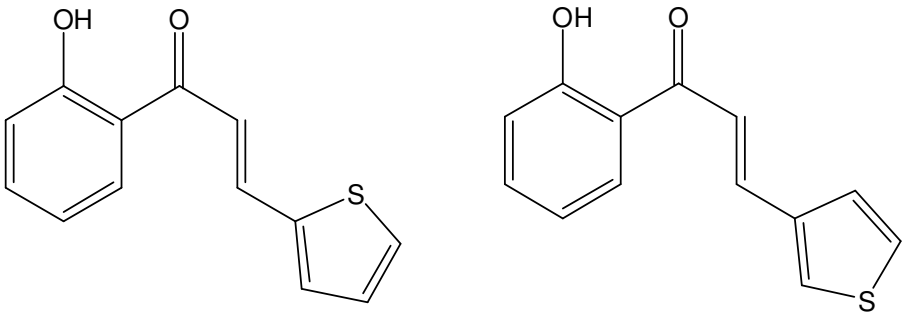
7

Figure 5 Dihydroxychalcones with known potential anti-oxidant activities

The presence of hydroxyl groups on chalcones increase antioxidant and free radical scavenging activities when compared to un-substituted chalcones (Hsieh *et al*., 1998).

1.1.4.2Anti-inflammatory activity

Inflammatory cells are capable of releasing numerous chemical mediators which are responsible for activation of mast cells, marcrophages, neutrophils and microligial cells. These cells are believed to be responsible for inflammatory responses and can affect the central nervous system (CNS). Chalcones such as2-hydroxy-2'-thienylchalcone (**8**) and 2-hydroxy-3'-thienylchalcone (**9**) (Figure 6) have shown good activity against the inhibition of superoxide anions generation in rat neutrophil cells (Won *et al.,* 2005). These chalcones also showed moderate to high inhibitory activities against glucuronidase and lysozyme production in rat neutrophils stimulated with formyl-Met-Leu-Phe cytochalasin B (Won *et al*., 2005).

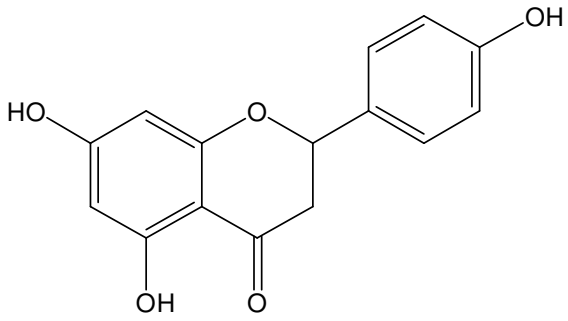


8 **9**

Figure 6 Hydroxy chalcones showing potential anti-inflammatory activities

1.1.4.3Anti-cancer activity

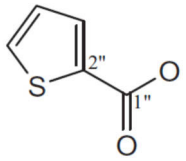
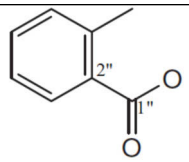
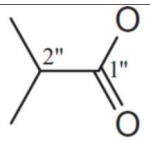
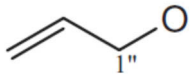
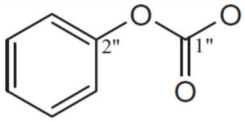
The flavanone, naringenin (**2**) is considered a mild anti-cancer agent. Recently, Yoon *et al*. (2013) investigated a set of new novel derivatives of Naringenin and their effects on human colon cancer cells. Modification atthe 7-poisition on the A ring of the flavanone with bulky moieties (Table 2) improved the overall anti-cancer activity of the chalcones in an *invitro* cyclin dependent kinase assay (CDK2) targeting human colon cancer cells (Yoon *et al*., 2013).



2

Figure 7 The structure of Naringenin (2)

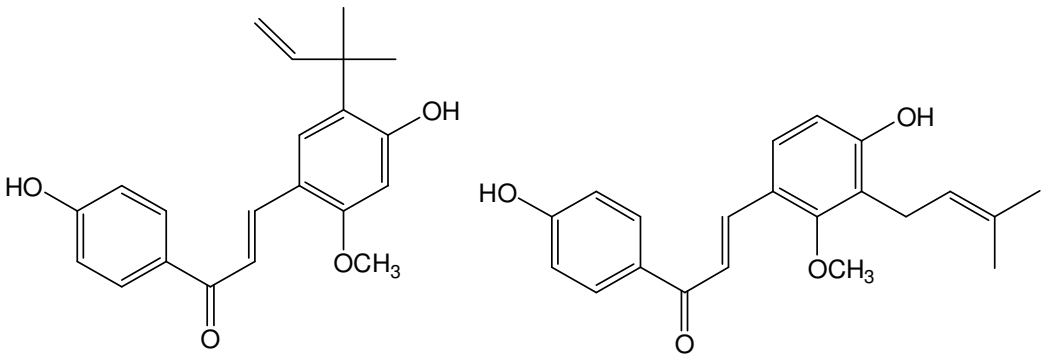
Table 2 The anti-cancer flavanone, Naringenin and its derivatives by modification on the 7-position.

Derivative	R-groups
Naringenin	OH
N-1	
N-2	
N-3	
N-4	
N-5	

1.1.4.4 Anti-bacterial activity

The derivatives licochalcone A (**10**) and C (**11**) are reported to possess antibacterial activities against Gram negative bacteria. The bacteriostatic effect of the chalcones is dependent on the presence of the free hydroxyl groups located in the 4'-position on ring A. When the moiety was placed on the Bring, no change in bacterial activity was observed (Figure 8) (Nowakowska, 2007).

The presences of α-β unsaturated carbonyl systems in chalcones are highly reactive. In the case of bacteria, thiol groups are an essential part of bacteria's protein coat structure. It was found that these carbonyl systems undergo conjugate addition with these thiol groups, which serve as binding sites. Once bound, the chalcones may inactivate these sites. This process often results in cell apoptosis and premature cell death. The antimicrobial efficiency can be varied with modifications in the chalcone structure (Srinath, 2012).



10 **11**

Figure 8 The structures of licochalcone A (10) and licochalcone C (11)

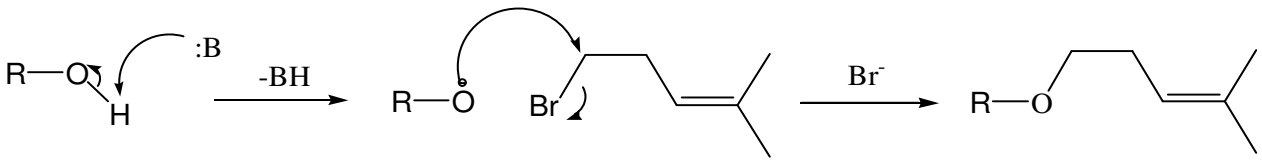
1.2 Introduction to prenylated flavonoids

The concept of prenylation involves the addition of hydrophobic moieties such as prenyl or isoprenoid groups to a molecule. These groups can be of varying length and in particular provide an added feature in terms of their biological properties. Their ability to interact with biological membranes and proteins of target molecules are associated with an increase in bioactivity, in particular antibacterial activities (Reddy *et al*., 2010; Sugamoto *et al*., 2011; Chi *et al*., 2001). Typically, the two major prenylating agents used in organic synthesis are 3-methyl-2-butene bromide and 3-methyl-2-butenal (Figure 9). The use of the former is known as prenylation whereas the latter, which forms a benzyopyran system, is termed chromenylation (Narender and Reddy, 2007).

3-methyl-2-butene bromide 3-methyl-2-butenal

Figure 9 The prenylating agents, 3-methyl-2-butene bromide and 3-methyl-2-butenal

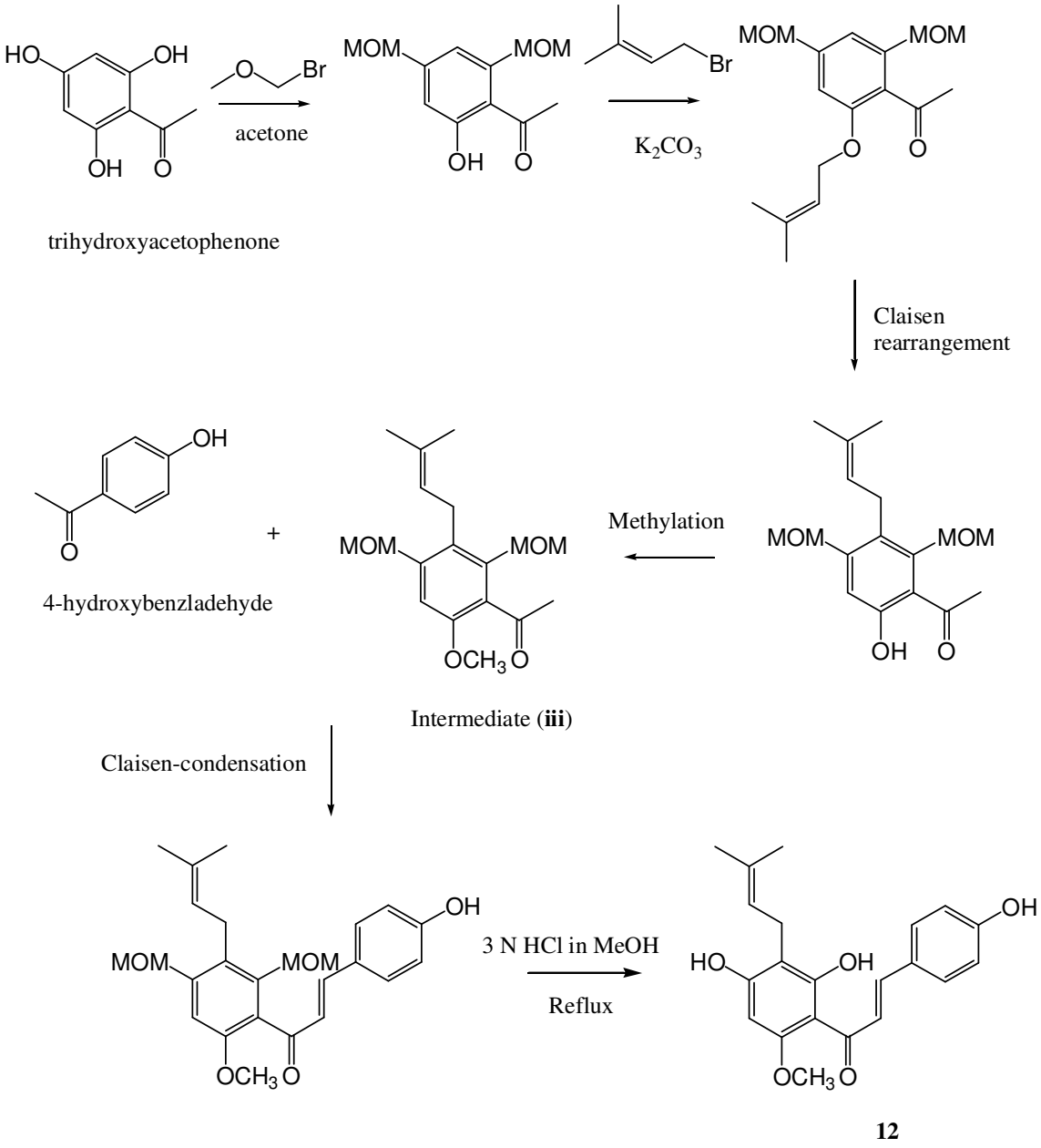
In this study, focus is centered on the prenylation of chalcones using 3-methyl-2-butene bromide as the prenylating agent. Prenylation with this reagent can only occur if there is a free hydroxyl group available on a flavonoid species. The mechanism takes the form of a S_N1 process whereby a mild base pulls off a proton from the hydroxyl group of the chalcone. The charged oxygen atom then attacks the electrophilic carbon of the C-Br bond thereby forming the prenylated product (Scheme 10).



Scheme 10 The mechanistic pathway of prenylation, using3-methyl-2-butene bromide under basic conditions. R= aromatic ring.

1.2.1 Synthesis of prenylated flavonoids

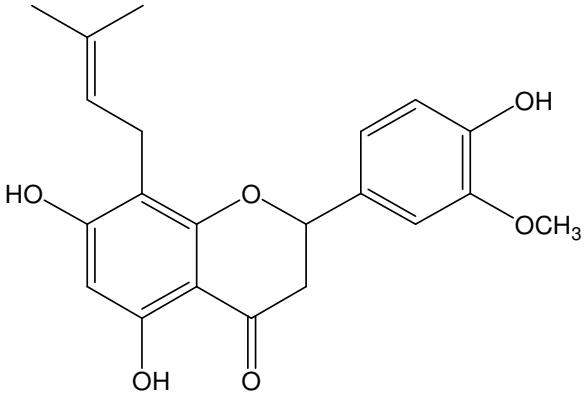
Prenylated flavonoids occur naturally and can be isolated from various medicinal plants. However, many synthetic analogues have been made (Vogel *et al*., 2008).An example is Xanthohumol (**12**), a prenylated chalcone considered to be an effective chemopreventive agent (Stevens and Page, 2004).In the synthesis of Xanthohumol (Scheme 11) trihydroxyacetophenone is protected with methoxymethylene bromide followed by the addition of the prenyl group with3-methyl-2-butene bromide. The prenylated acetophenone undergoes a Claisen-rearrangement forming compound. This is followed by methylation to form the methoxylated intermediate (**iii**), which is then condensed with 4'-hydroxybenzaldehyde producing the protected chalcone, which is deprotected under acidic conditions to produce Xanthohumol (Vogel *et al*., 2008).



12

Scheme 11 The synthesis of Xanthohumol (12)

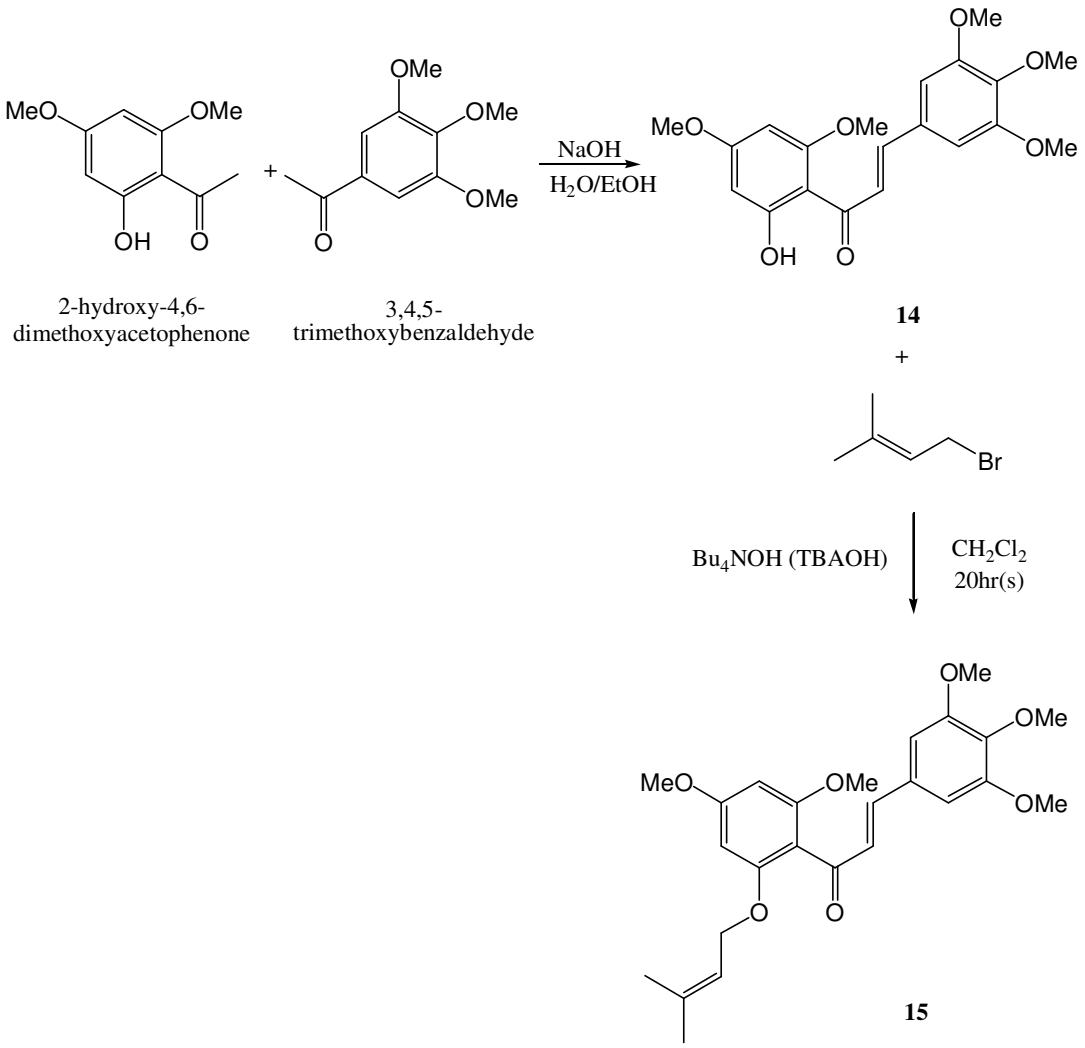
Similarly, the prenylated flavanone, Exiguaflavanone K (**13**), known to exhibit mild vasodilator effects, has been synthesized with the omission of the methylation step seen above and the use of 3'-methoxy-4'-hydroxybenzaldheyde instead of4'-hydroxybenzaldheyde during the condensation step (Figure 10) (Dong *et al*., 2008b).



13

Figure 10 The structure of Exiguaflavanone K (13)

Alternately, flavonoids have been synthesized first followed by prenylation reactions.Neves *et al* (2012) demonstrated the use of the base-catalyzed reaction between 2-hydroxy-4,6-dimethoxyacetophenoneand 3,4,5-trimethoxybenzaldehydeto afford the intermediate compound **14**. Compound **14** was used as a precursor to produce the synthetic chalcone analogue, to which prenyl bromide was added in the presence of tetrabutylammonium hydroxide (TBAOH; Bu_4NOH) and dichloromethane at room temperature to produce **15** in satisfactory yields(Scheme 12) (Neves *et al*., 2012).



Scheme 12 Scheme showing the prenylation of chalcone (14) to form the anti-tumour compound (15)

Other conventional methods include the use of boron trifluoride etherate in dioxane treated with 2-methyl-3-buten-2-ol, the Heck reaction using 2-iodophenol, 3-methyl-1-butene, palladium acetate and triethylamine and the Stille reaction of a doubly protected 2,4-bis-(methoxymethoxy)-3-iodoacetophenone with prenyltributylstannane in DMF using $[Pd(PPh_3)_4]$. Yields as high as 76 % have been reported (Grealis *et al*., 2013).

1.2.2 Biological activity of prenylated flavonoids

Some of the most common reported bioactivities of prenylated flavonoids are anti-inflammatory (Chi *et al*., 2001),anticancer (Neves *et al*., 2012), anti-allergic (Chi *et al*., 2001), antimicrobial (Sohn *et al*., 2004), antioxidant(Rodriguez *et al*., 2001), and antibacterial (Sugamoto *et al*., 2011).

1.2.2.1 Anti-inflammatory

Several naturally occurring flavonoids isolated from various medicinal plants have shown anti-inflammatory activities. Enzymes such as arachadonic acid-metabolizing enzymes are mediators in the growth of epithelial cells that may result in inflammation and possibly cancer. The isolation and biological evaluation of the prenylated flavonoids, Kurarinone (**16**), sophoraflavanone G (**17**) and Kurarudin (**18**), showed potent activity against the AA-metabolizing enzymes in a bioactive study as compared to their non-prenyl analogues (Chi *et al*., 2001).

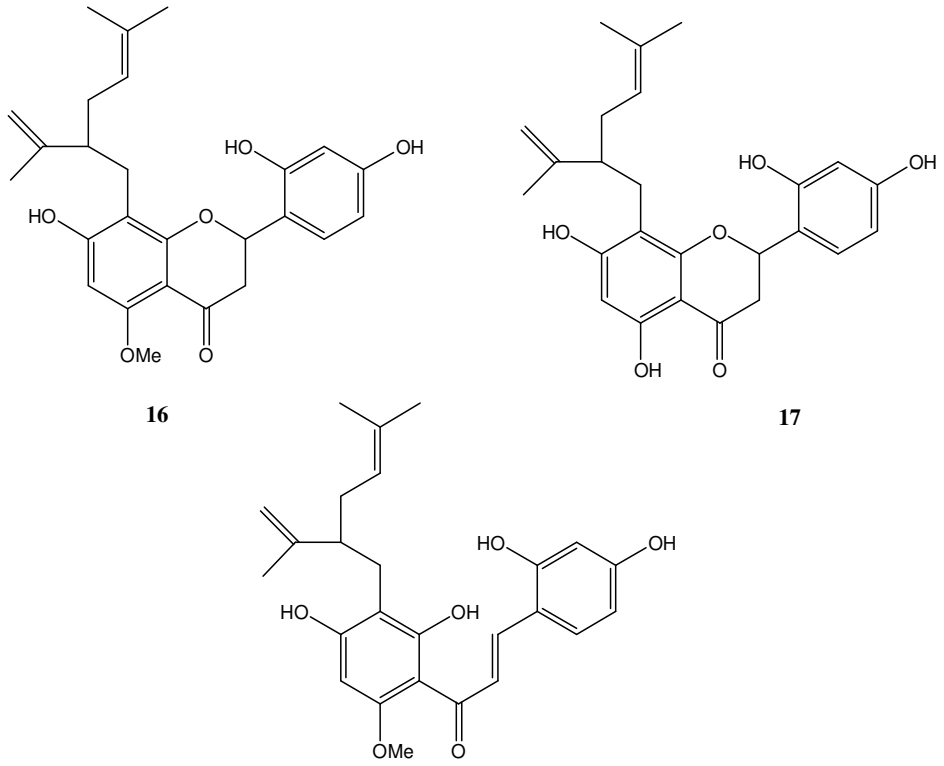


Figure 11 The anti-inflammatory flavonoids, Kurarinone (16), Sophoraflavanone G (17) and Kurarudin (18)

1.2.2.2 Antimicrobial

Studies performed on 18 different prenylated flavonoids obtained from five different plants showed promise as antibacterial agents against both fungal and bacterial microorganisms. Of these, the sophoraflavanone D (**19**) (Figure 12) exhibited good antifungal and strong antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* respectively. Similarly, its analogue sophoraflavanone G (**17**) known to possess antioxidant activity, showed strong antibacterial activity at concentrations as low as 5µg mL^{-1} (Sohn *et al*., 2004).

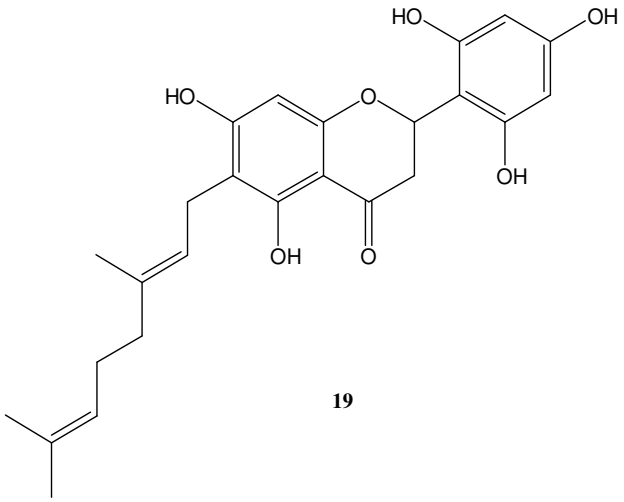


Figure 12 The structure of sophoraflavanone D (19)

1.2.2.3 Anticancer

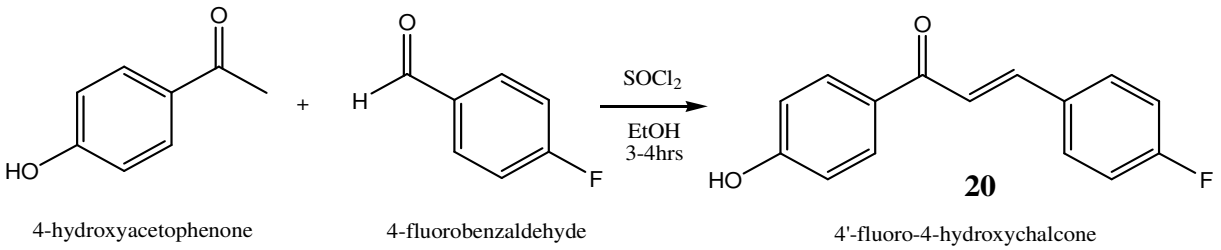
Prenyl chalcones showed *in vitro* activity on cancerous MCF-7 cells. In comparison to non-prenyl chalcones, the presence of a prenyl moiety at C-2 or C-3 on the chalcone skeleton showed an overall increase in the inhibitory effect in theMCF-7 anticancer assay. The chalcone with a prenyl moiety on the 2-position proved to be the most active derivative against the human tumor cell lines (Neves *et al*., 2012).

1.3 Fluorinated chalcones and flavanones

The use of halogens in medicinal chemistry is widely applied in pharmaceuticals. In particular, fluorine^{19}F tends to provide favourable properties such as lipophillic and hydrophobic characteristics required for certain biological activities (Srinath, 2012). Complementary to this, the replacement of a C-H with a C-F bond allows for an increase in metabolic stability and also prevents metabolic degradation (Kirk, 2006). Indeed, fluorinated molecules are amongst the most important of drugs in the pharmaceutical industry. Therefore in this study the synthesis of fluorine based flavonoids was also investigated with the aim of adding to the plethora of fluorinated drugs already on the market.

1.3.1 Synthesis of fluorinated flavonoids

The synthesis of fluorinated flavonoids is often carried out by various conventional methods. The Claisen-Schmidt condensation reaction is the simplest method employed as there is no difference between the synthesis of normal flavonoids with those having fluorine substituents. Most fluorine groups, either in the form of single or trifluoro, have been previously attached on their respective precursors. The synthesis of the anti-inflammatory chalcone, 4'-fluoro-4-hydroxychalcone (**20**) was carried out under acidic conditions using thionyl chloride and ethanol between 4-hydroxyacetophenone and 4-fluorobenzaldehyde (Scheme 13) (Hasan*et al*., 2012).



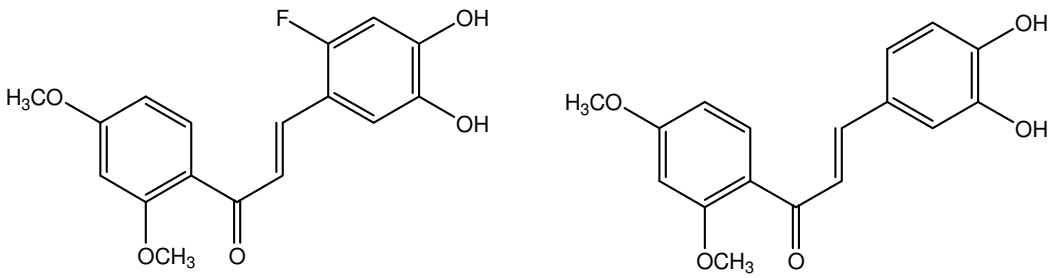
Scheme 13 The acid catalyzed synthesis of 4'-fluoro-4-hydroxychalcone (20)

A yield of 92% was obtained possibly due to the prevention of self condensation between the fluorobenzaldehydes which would have occurred had it been under normal basic conditions as explained in chapter 1.

Apart from basic and acidic conditions, there are several instances where phase catalysts and exotic solvent systems have been employed for the synthesis of fluorinated chalcones and flavanones (Chen *et al*., 2011; Kavala *et al*., 2012).

1.3.2 Biological properties of fluorinated flavonoids

Several flavonoid analogues containing fluorine have been synthesized and tested for their antioxidant and anti-inflammatory activities. The development of derivatives with2,4-dihydroxy-3',4'-dimethoxychalconeas the skeleton structure containing various substituted fluorine atoms was carried out (Nakamura *et al*., 2002). All derivatives showed anti peroxidation and 5-lipoxygenase inhibitory activity using rat basophilic leukemia cells, better than their non-fluorinated derivatives. 5-Lipoxygenase enzymes are chemical mediators for the production of leukotrienes which cause inflammation and hypersensitivity. The fluorinated derivative6-fluoro-3',4'-dihydroxy-2,4-dimethoxychalcone (**21**)showed the most potent activity in these assays (Figure 13).

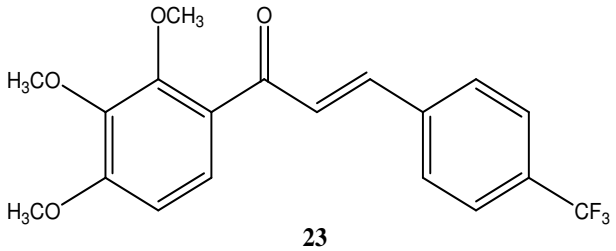


21 **22**

Figure 13 The anti-inflammatory chalcone (21) and its non-fluorinated derivative (22)

Studies show that poly-fluorinated flavonoids are more active than their mono fluorinated derivatives and may be better lead compounds in drug synthesis. The difluoro chalcone derivatives proved to be more effective against human pancreatic cancer cells and breast cancer cells than their monosubstituted and hydroxylated derivatives in a biological comparative study (Padhye *et al*., 2010).

The trifluoromethyl methoxy chalcone (**23**) synthesized by Liu *et al*. (2001), showed excellent promise as an antimalarial compound. The trifluoromethyl species alters the structure biosterically and provides different bioactivities (Figure 14).



23

Figure 14 The structure of the antimalarial chalcone, 4'-trifluoromethyl-2,3,4-trimethoxychalcone (23)

1.3.3 Prenylated and fluorine based flavonoids

The benefits of prenylation have been mentioned in the previous chapter (Chapter 1). The replacement of C-H and C-O bonds with C-F bonds allow for biosteric enhancements and in particular improved metabolic stability (Kirk, 2006). Hence, an increase in lipophillicity and interaction with biological membranes as provided by the prenyl group in conjunction with the metabolic stability of fluorine can render molecules quite active in biological systems. New types of hybrid drug molecules with multiple properties and characteristics can be synthesized and tested in biological assay with a view to identifying lead compounds for drug development.

In this proposed study, focus is centered on the synthesis of prenylated and fluorine based flavonoids, in particular, chalcones and flavanones.

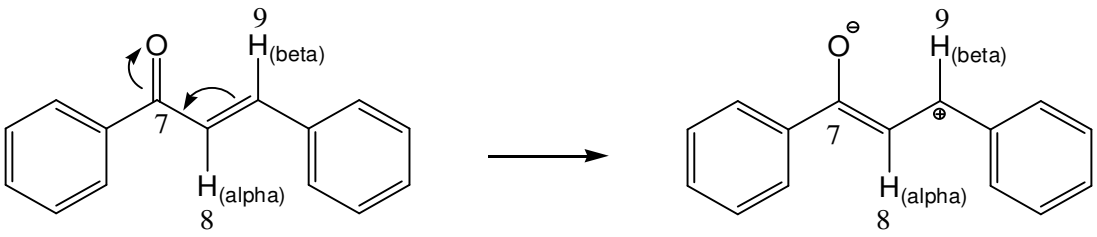
1.3.4 Characterization of flavonoids

The principal tool used for the characterization of flavonoids is Nuclear Magnetic Resonance (NMR) Spectroscopy. In conjunction with other techniques which include Infra-red spectroscopy (IR), Ultraviolet-visible spectroscopy (UV -vis), and Gas Chromatography coupled with Mass spectrometry (GC-MS), flavonoids can be structurally identified.

1.3.4.1 Identification using NMR spectroscopy

Chalcones consist of anα-β-unsaturated carbonyl chain which bridges both phenyl rings, the phenyl ring closest to the carbonyl group being acetophenone derived and that next to the double bond being benzaldehyde derived. Typical in all chalcones is the presence of a pair of doublets assigned to these olefinic protons which couple with each other. Most chalcones tend to adopt a *trans* geometry, usually to minimize steric effects and therefore characteristic *J* coupling values

between 15-17Hz for these doublets are evident (Go *et al*, 2005; Clayden *et al*, 2007; Srinath, 2012). This distinctive feature is used as a primary means of identification. If these protons are situated *cis* to each other, they would have the same splitting pattern but a different *J* value (8-10 Hz), which is rather more difficult to identify the chalcones as *ortho* coupling in aromatic rings have the same coupling constant. Resonance structures show that the *beta* carbon should appear more deshielded than the *alpha* carbon due to the pi pair of electrons being delocalized between the three atoms, leaving the α-carbon more deshielded than the alpha carbon (Scheme 14) (Clayden *et al*, 2007).



Scheme 14 The delocalized resonance structure of the olefinic bond in chalcones

Depending also on the type of substituents present, the chemical shifts of both the *alpha* and *beta* protons can also vary when compared to un-substituted chalcones.

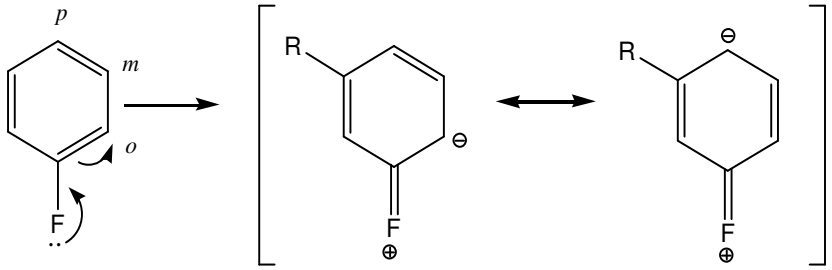
^{19}F tends to have the ability to couple with proton nuclei due to its 99% natural abundance (Gerig, 2001). Similarly, fluorine has the ability to couple with carbon and this feature can be seen in the carbon spectrum, despite ^{13}C having a relatively low abundance of 1%. Fluorine couples to carbon differently when placed in the *ipso*, *ortho, meta* and *para* positions of the aromatic ring resulting in the carbon resonances being split with different coupling constants (Table 3). This can help in the assignment of the protons as if the carbon resonances are identified by their coupling constants, the HSQC spectrum can aid with the assignment of the

corresponding protons. A direct carbon-fluorine bond (C-F) has a characteristic large *J* coupling value of approximately 246 Hz. The respective signal making up the doublet could easily be mistaken for two separate carbon resonances. This can be clarified in the HMBC spectrum where several correlations, typically to the aromatic protons are evident for both these signals making up the doublet.

The ability of fluorine to donate a lone pair of electrons toward the aromatic ring results in the *ortho* and *para* carbonsand protons being more shielded than the *meta* carbons and protons (Scheme 15) (Kavala *et al*., 2012).

Table 3 ^{13}C NMR chemical shift and coupling constant data for the B-ring of 2'-fluoro flavanone.

Position of fluorine	**^{13}C NMR**
Ortho	116 (d, *J* = 21Hz)
Meta	130 (d, *J* = 8Hz)
Para	123 (d, *J* = 4Hz)
ipso(C-F)	160 (d, *J* = 246Hz)

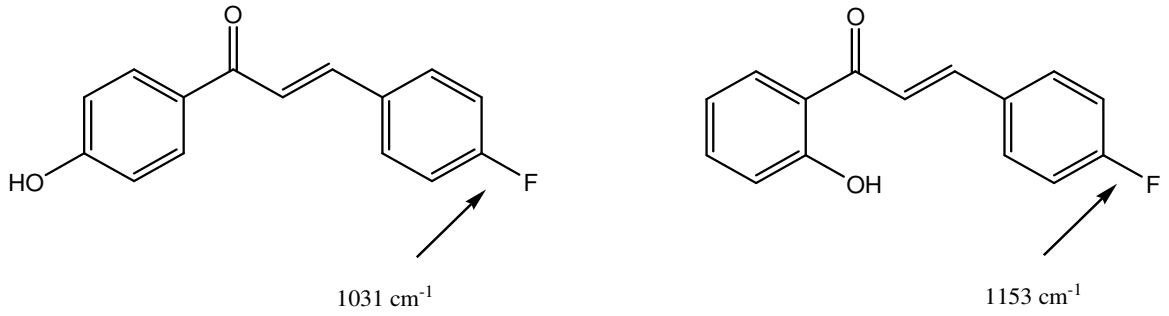


Scheme 15 Resonance structures that result when a fluorine atom is substituted on an aromatic ring

1.3.4.2 Identification using Infra-Red (IR) spectroscopy

The carbonyl group is the most predominant feature in the IR spectrum for the identification of most flavonoids. In the case of flavanones, the presence of the C=O group resonates as a sharp peak usually at around 1680 to 1720 cm^{-1}.Chalcones on the other hand contain an α,β unsaturated carbonyl group, which resonates at a lower frequency as a result of the conjugative effect of the double bond. Resonance structures as that shown in Scheme 13 result in the carbonyl group having more single bond character than a pure ketone and hence the carbonyl stretching band in chalcones can be found between 1650-1680 cm^{-1} (Sherman, 1992).

The frequencies at which other bands absorb may depend on conjugation, ring size and electronic effects of substituents present on the flavonoid structure. A variation in the C-F stretching frequency can be observed between4'-fluoro-4-hydroxychalcone (**24**) and 4'-fluoro-2-hydroxychalcone (**25**) illustrating the effect the position of the hydroxyl group has on the C-F stretching band (Figure 15) (Hasan *et al*., 2012; Ivkovic *et al*., 2013).



24 **25**

Figure 15 The variation in C-F stretching between 4'-fluoro-4-hydroxychalcone (24) and -4'-fluoro-2-hydroxychalcone (25)

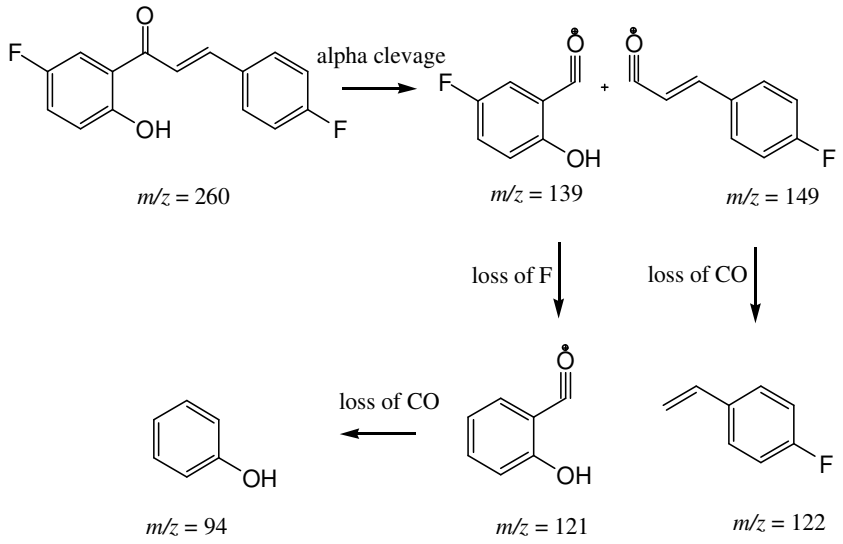
1.3.4.3 Identification using ultraviolet spectroscopy

Chalcones tend to have two absorption bands, one minor and one major for each of rings A and B. The major bands reported for a series of non-substituted 2-hydroxychalcones appeared in the upper region of the UV spectrum (316 nm). Electron donating groups tend to cause a red shift between these bands whereas the opposite is observed for electron withdrawing groups. The minor bands often absorbin the lower regions (<300 nm) of the visible spectrum and are sometimes neglected due to their relatively small peak intensities. Similarly, flavanones may have an additional absorption band in addition to their major band at 303-304nm and minor band between 240 to 285 nm. The absorption values may also depend largely on the solvent systems used (Matsushima and Kageyama, 1985;Pinheiro and Justino, 2012).

UV also proves very useful in differentiating between 2-hydroxychalcones and their flavanone derivatives due to differences which are observed in band intensity. Flavanones tend to have three strong predominant absorption bands as opposed to the two of chalcones due to the presence of the closed benzopyran ring system which increases conjugation (Matsushima and Kageyama, 1985; Srinath, 2012).

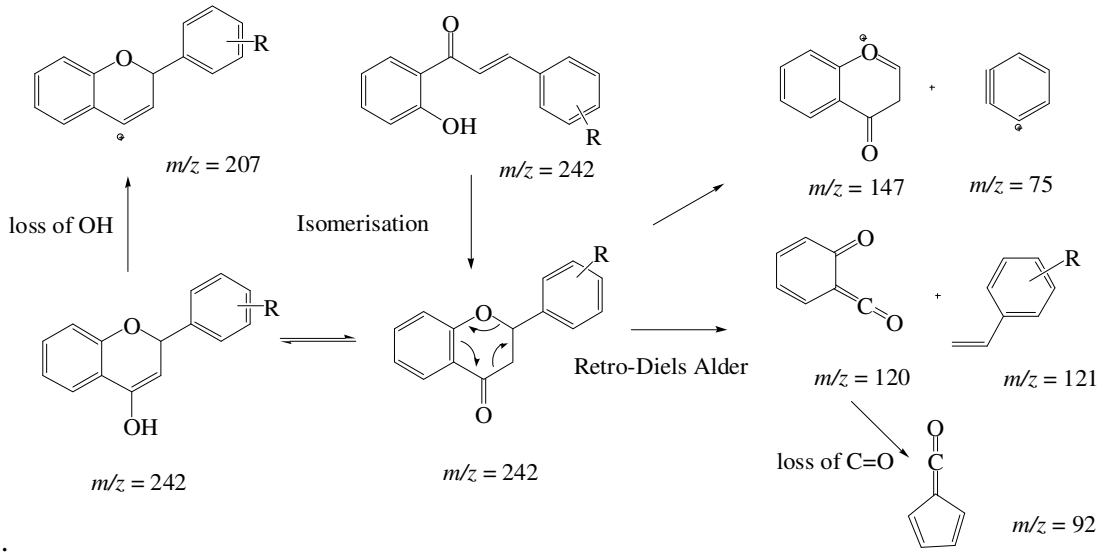
1.3.4.4 Identification by Mass spectrometry

Since fluorine is not as distinctive as chlorine and bromine, it is imperative to understand the fragmentation patterns of the structure as a whole rather than its abundance with a comparable isotope. Generally, chalcones undergo *alpha* cleavage which occurs on both sides of the carbonyl carbon and as a result a distinctive pattern is observed. A typical example of α-cleavage can be seen in the fragmentation pattern of 4',4-difluoro-2-hydroxychalcone (Scheme 16) resulting in the characteristic fragmentation masses at m/z = 121 and m/z = 149 (Hasan *et al*., 2007).



Scheme 16 The fragmentation pattern of 4',4-difluoro-2-hydroxychalcone

The stable fragments can be used to identify the location of the fluorine atom. In the case of hydroxyl substituents present in the 2-position, thermal isomerization can take place converting the chalcone to its corresponding flavanone derivative. Unlike the chalcone, flavanones undergo retro Diels Alder cleavage. A characteristic peak can be observed at *m/z*=120 in the mass spectrum (Scheme 17) (Itagak *et al*., 1966).



Scheme 17 The fragmentation pathway of 2-hydroxychalcone where R = F

1.3.5 Aim and objectives of this study

Since the physical and biological properties of flavonoids depend on the different types of substituents in its structure, the aim of this project was to synthesize a small library of flavonoid compounds, each with different modifications on both the A and B ring with regard to prenylation and fluorination and explore their physical and biological properties. With regard to the latter, the antioxidant properties of selected molecules were determined to investigate the effect different fluorine substitution has on hydroxylated chalcones.

Specific objectives of this study

1. To synthesize various substituted fluorine and prenylated flavonoids using the conventional Claisen-Schmidt condensation reaction from the precursors, 2-hydroxy and 3-hydroxyacetophenone.
2. To fully characterize these compounds using a wide range of spectroscopic techniques including 1D and 2D NMR, IR, UV, GCMS and HRMS.
3. To investigate and compare the effects that the fluorine and prenyl moieties may have on the physical and antioxidant properties of these compounds.

Chapter 2. Experimental

2.1 General Procedure

Melting point determinations were carried out using a Stuart Smart scientific melting point apparatus. UV analyses were performed using a UV-vis Shimadzu series 200 spectrophotometer. ^{1}H and ^{13}C NMR, gradient heteronuclear single quantum coherence (HSQC), gradient heteronuclear multiple-bond correlation (HMBC), and nuclear overhauser effect spectroscopy (NOESY) spectra were all recorded using a Bruker Advance III 400 MHz spectrometer. All spectra were recorded at room temperature with chemical shifts recorded in deuterated chloroform ($CDCl_3$) against the internal standard, tetramethylsilane (TMS). IR spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer with universal ATR sampling accessory. GC-MS data were gathered using an Agilent Technologies GC-MSD apparatus equipped with a DB-5SIL MS (30 m x 0.25 mm i.d., 0.25 μm film thickness) fused silica capillary column. Helium (2 mL min^{-1}) was used as a carrier gas and methanol was used to dissolve the samples. Polarization angle values were obtained using a Bellingham and Stanley ADP 410 Polarimeter.

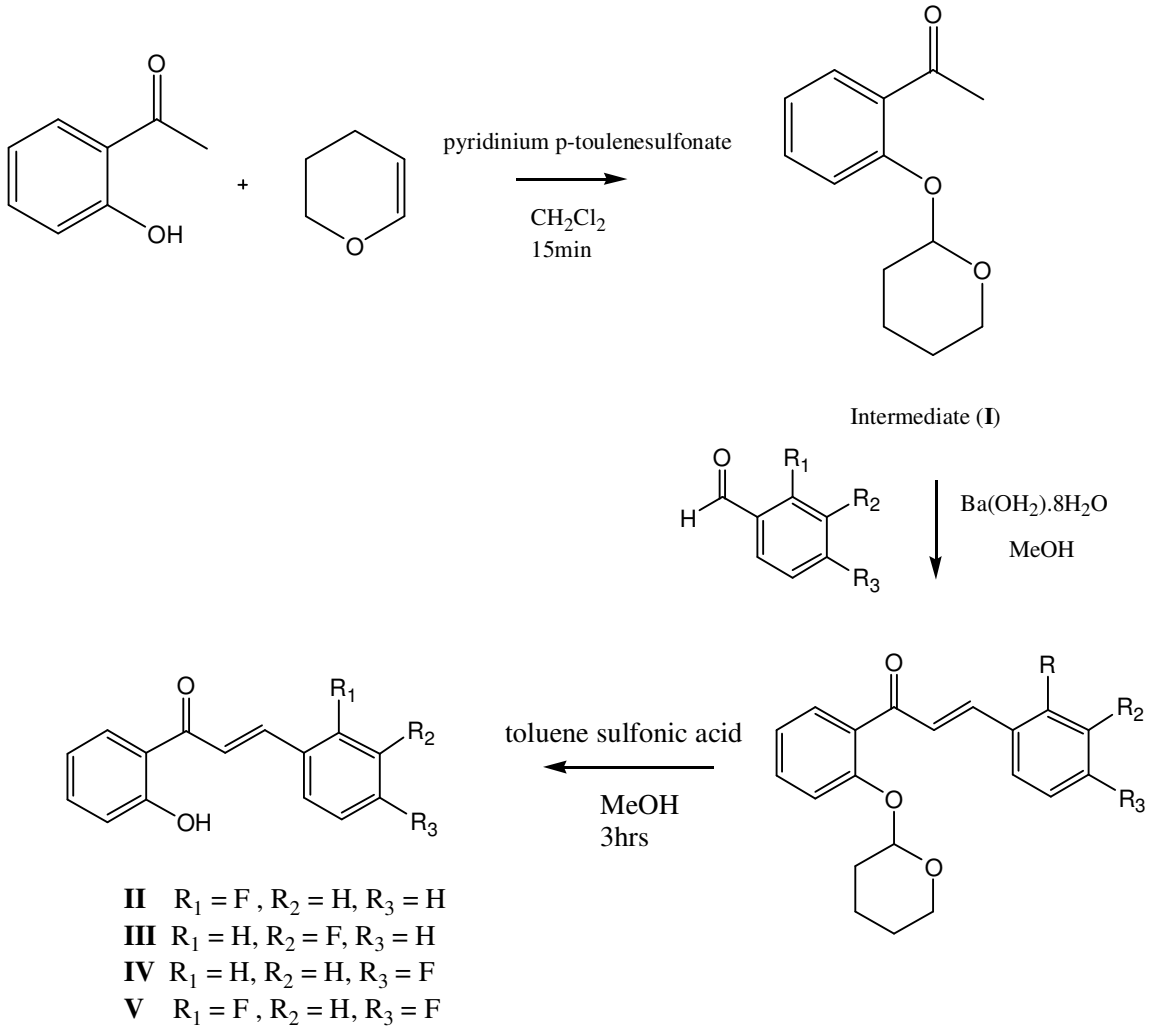
2.2 Flavonoid synthesis

2.2.1 Preparation of fluorine substituted 2-hydroxychalcones

In a 100 mL round bottom flask, four equivalents (0.200 mol; 17.0 mL) dihydropyran in 60 mL of dichloromethane was added dropwise to a stirring mixture of 2-hydroxyacetophenone (0.0500 mol; 6.80 g) and pyridinium *p*-toulenesulfonate (0.00250 mol; 630 mg) in 40 mL of dichloromethane. The solution was stirred for 15 min at room temperature (25 ºC) and completion of the reaction monitored by Thin-Layer Chromatography (TLC). The resultant crude oil product, intermediate (**I**), was stored in a cool dry place (Scheme 18).

For the synthesis of the chalcones, an equimolar mixture of Intermediate (**I**) (0.00500 mol; 1.10 g) and substituted fluorobenzaldehydes (**1-4**) (0.00500 mol) were added to a 100 mL round bottom flask, after which, one equivalent of barium hydroxide octahydrate (0.00500 mol; 1.58 g) in 25 mL absolute methanol, was added with constant stirring. The mixture was refluxed for a 24 hr period at room temperature (25 ºC) and monitored using TLC. The remaining methanol was evaporated off under reduced pressure to provide a protected chalcone precipitate, which were dissolved in 20 mL methanol, treated with toluene sulfonic acid (0.00125 mol; 215 mg) and refluxed for 3hrs until deprotection was confirmed by TLC. Remaining methanol was evaporated and the precipitates that formed were filtered, washed with 2 x 25 mL de-ionised water and under vacuum.

The crude solids were purified by column chromatography with hexane: ethyl acetate (8:2) as the mobile phase. In all cases, the product eluted in the first three fractions to afford pure yellow solid compounds (**II-V**) (Scheme 18)

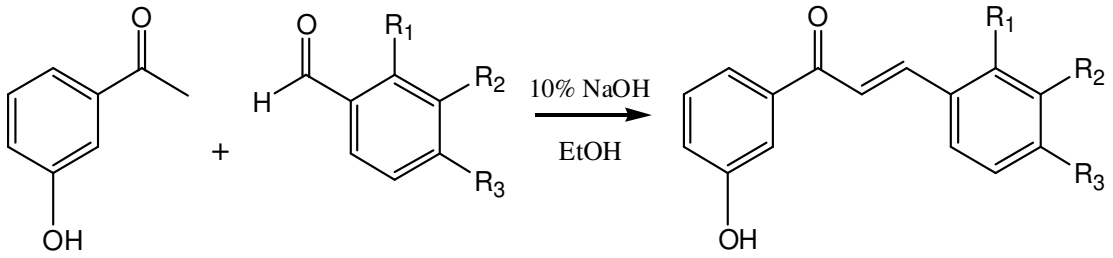


II $R_1 = F$, $R_2 = H$, $R_3 = H$
III $R_1 = H$, $R_2 = F$, $R_3 = H$
IV $R_1 = H$, $R_2 = H$, $R_3 = F$
V $R_1 = F$, $R_2 = H$, $R_3 = F$

Scheme 18 Synthesis of 2-hydroxychalcones II-V

2.2.2 Preparation of fluorine substituted 3-hydroxychalcones

An equimolar mixture of 3-hydroxyacetophenone (0.00500 mol, 680 mg) and substituted fluorobenzaldehydes (0.00500 mol) were added to separate 50 mL round bottom flasks. To each flask, 10% (m/m) NaOH (10 mL) in absolute ethanol was added with continuous stirring. The solutions were refluxed at room temperature until the reaction had completed in each case. This was monitored by TLC. The resultant mixtures were neutralized using 10 mL of 0.1 M HCl and then extracted using 3 x 20 mL dichloromethane (DCM). The combined extracts were concentrated and then purified using column chromatography with hexane: ethyl acetate (7:3) as the mobile phase. In all cases, the first four fractions afforded deep yellow solid compounds (**VI-IX**) (Scheme 19).

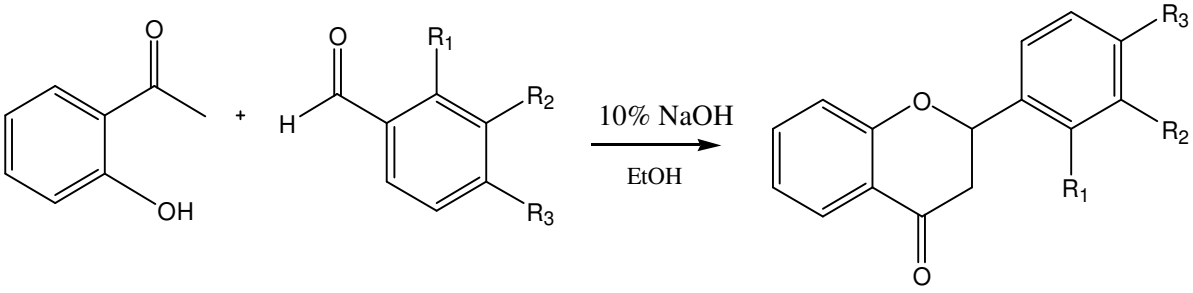


VI $R_1 = F$, $R_2 = H$, $R_3 = H$
VII $R_1 = H$, $R_2 = F$, $R_3 = H$
VIII $R_1 = H$, $R_2 = H$, $R_3 = F$
IX $R_1 = F$, $R_2 = H$, $R_3 = F$

Scheme 19 Synthesis of 3-hydroxychalcones VI-IX

2.2.3 Preparation of fluorine substituted flavanones

An equimolar mixture of 2-hydroxyacetophenone (0.0100 mol, 1.36 g) and fluorobenzaldehydes (0.0100 mol) were added to separate 50 mL round bottom flasks. To each flask, 10 % (m/m) sodium hydroxide in absolute ethanol (10 mL) was added dropwise with continuous stirring. The solutions were refluxed at room temperature until the reaction had completed in each case. This was monitored by TLC. The resultant precipitates were filtered, washed with 3 x 30 mL de-ionised water and purified using column chromatography with hexane:ethyl acetate (7:3) as the mobile phase. Compounds **X-XIII** eluted in fractions 3-5 as pale green and yellow crystalline solids (Scheme 20).

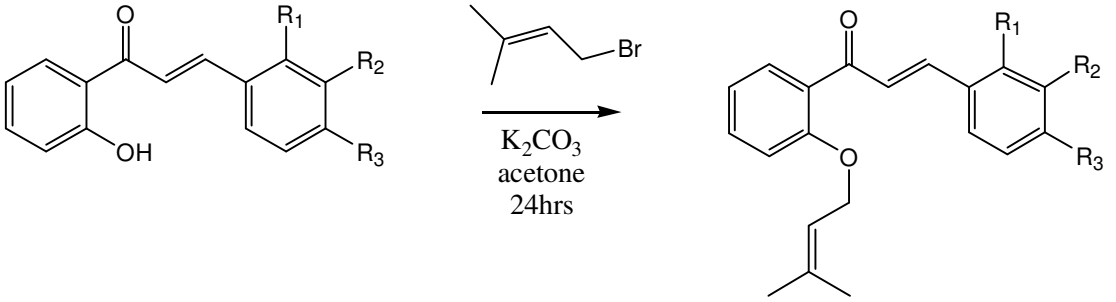


X $R_1 = F$, $R_2 = H$, $R_3 = H$
XI $R_1 = H$, $R_2 = F$, $R_3 = H$
XII $R_1 = H$, $R_2 = H$, $R_3 = F$
XIII $R_1 = F$, $R_2 = H$, $R_3 = F$

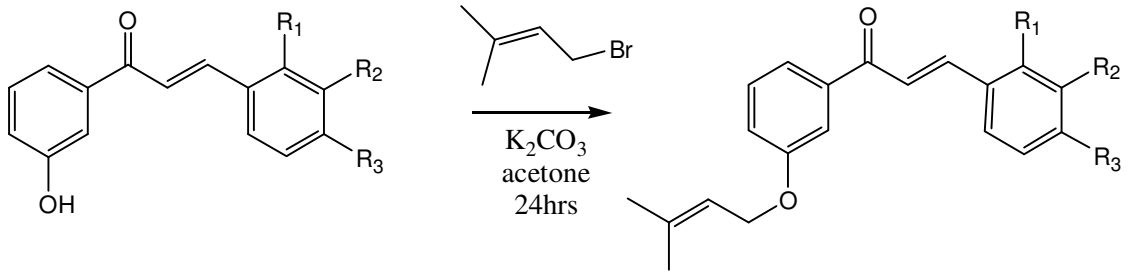
Scheme 20 Synthesis of fluorine substituted flavanones X-XIII

2.2.4 Prenylation of hydroxychalcones

In separate round bottom flasks, 2.5 equivalents of ignited potassium carbonate (0.00500 mol, 700 mg) were added to stirring solutions containing chalcones **II-IX** (0.00200 mol) with prenyl bromide (0.00200 mol, 300 mg). Each mixture was stirred on a magnetic stirrer for a period of 24hrs. Completion of the reaction was confirmed using TLC. Each flask was then treated with 10 mL of deionised water and the organic components extracted with 3 x 10 mL ethyl acetate. The extracts were combined and purified using column chromatography with hexane:ethyl acetate (8:2). Pure prenyl compounds (**XIV-XXI**) eluted in fractions 2-3 (Scheme 21).



XIV R_1= F , R_2 = H, R_3= H
XV R_1= H, R_2 = F, R_3 = H
XVI R_1= H, R_2 = H, R_3 = F
XVII R_1= F , R_2 = H, R_3 = F

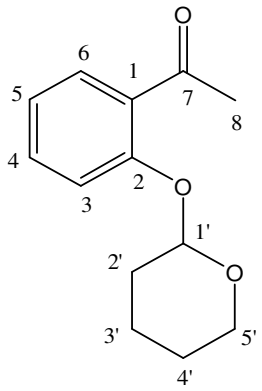


XVIII R_1= F , R_2 = H, R_3= H
XIX R_1= H, R_2 = F, R_3 = H
XX R_1= H, R_2 = H, R_3 = F
XXI R_1= F , R_2 = H, R_3 = F

Scheme 21 The prenylation of 2-hydroxy and 3-hydroxychalones

2.3 Spectroscopic data

I) 2-tetrahydropyranoacetophenone; $C_{13}H_{16}O_3$ (220.11 g mol^{-1})



Physical description: Brown oil

UV Data: λ_{max} (nm) (log ε): 252 (5.38), 326 (4.84).

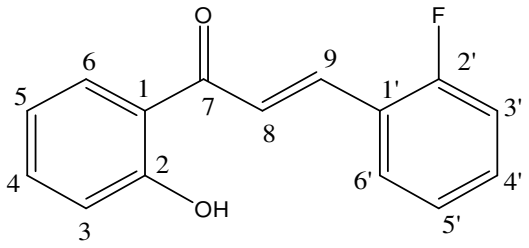
IR Data: ν_{max} (cm^{-1}): 2941 (-CH), 1638 (C=O), 1217 (Ar-F), 1023 (C-O).

^{1}H NMR Data: (400 MHz, $CDCl_3$): δ 7.68 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H, H-6), 7.44 (td, *J* = 8.5 Hz, 1.5 Hz, 1H, H-4), 6.93 (d, *J* = 8.5 Hz, H-3), 6.85 (td, *J* = 8.0 Hz, 1.0 Hz, 1H, H-5), 4.90-4.72 (m, 1H, H-1'), 3.90-3.38, (m, 2H, H-5a/5b), 2.56 (s, 3H, H-8), 1.90-1.40 (m, 6H, H-2'ab/3'ab/4'ab).

^{13}C NMR Data: (100 MHz, $CDCl_3$):δ 204.6 (C-7), 162.3 (C-2), 136.4 (C-1), 130.9 (C-6), 119.7 (C-4), 119.0 (C-5), 118.3 (C-3), 94.5 (C-1'), 62.9 (C-5'), 30.8 (C-8), 26.6 (C-2'), 25.6 (C-4'), 19.7 (C-3').

MS Data: *m/z* (rel.int.): 136 (48) [M^+-THP], 121 (100), 93 (18), 85 (100), 57 (15).

II) 2'-fluoro-2-hydroxychalcone; $C_{15}H_{11}O_2F$ (242.25 g mol^{-1})



Physical description: Dark yellow solid

Yield: 80 % (0.968 g)

Melting point: 81-82 ^{o}C

UV Data: λ_{max} (nm) (log ε): 312 (5.39)

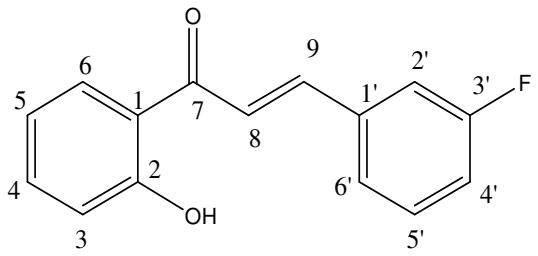
IR Data ν_{max} (cm^{-1}): 3691 (OH), 2957 (-CH), 1635 (C=O), 1567 (C=C), 1056 (C-O)

^{1}H NMR Data: (400 MHz, $CDCl_3$): δ8.01 (d, *J* = 15.6 Hz, 1H, H-9), 7.94 (dd, *J* = 8.04 Hz, 1.0 Hz, 1H, H-6), 7.80 (d, *J* = 15.6 Hz, 1H, H-8), 7.67 (td, *J* = 8.5 Hz, 1.5 Hz, 1H, H-6'), 7.54 (td, *J* = 8.6 Hz, 1.5 Hz, 1H, H-4), 7.48-7.43 (m, 1H, H-4'), 7.24 (t, *J* = 7.6 Hz, 1H, H-5'), 7.17 (dd, *J* = 10.5 Hz, 8.0 Hz, 1H, H-3'), 7.05 (d, *J* = 8.0 Hz, 1H, H-3), 6.98 (t, *J* = 7.5 Hz, 1H, H-5)

^{13}C NMR Data: (100 MHz, $CDCl_3$): δ 193.9 (C-7), 163.7 (C-2), 162.8 (d, *J* = 255.3 Hz, C-2'), 138.3 (C-9), 136.6, (C-4), 132.2 (d, *J* = 8.8 Hz, C-4'), 130.2 (d, *J* = 2.9 Hz, C-6'), 129.8 (C-6), 124.6 (d, *J* = 3.7 Hz, C-5'), 123.0 (C-8) 122.7 (d, *J* = 8.1 Hz, C-1'), 120.0 (C-1), 118.8 (C-5), 118.5 (C-3), 116.4 (d, *J* = 22.0 Hz, C-3')

MS Data: *m/z* (rel. int.): 242 (93) [M^+], 222 (52), 147 (33), 120 (89), 92 (100).

III) 3'-fluoro-2-hydroxychalcone; $C_{15}H_{11}O_2F$ (242.25 g mol^{-1})



Physical Data: Light yellow solid

Yield: 56 % (0.677 g)

Melting point: 107-108 ^{o}C

UV Data: λ_{max} (nm) (log ε): 311 (5.47)

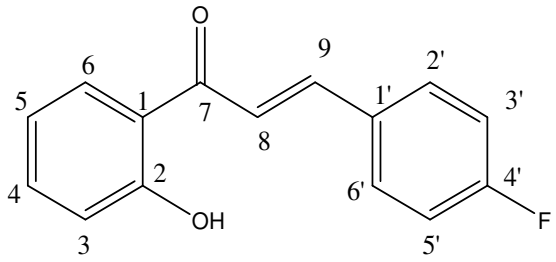
IR Data: ν_{max} (cm^{-1}): 3692 (OH), 2949 (-CH), 1637 (C=O), 1577 (C=C), 1217 (Ar-F), 1057 (C-O)

^{1}H NMR Data: (400 MHz, $CDCl_3$): δ7.84 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H, H-6), 7.79 (d, *J* = 15.6 Hz, 1H, H-9), 7.57 (d, *J* = 15.6 Hz, 1H, H-8), 7.45 (td, *J* = 8.5 Hz, 1.5 Hz, 1H, H-4), 7.35 (m, 2H, H-2' and H-5'), 7.38-7.25 (m, 1H, H-6'), 7.10-7.00 (m, 1H, H-4'), 6.97 (d, *J* = 7.5 Hz, 1H, H-3), 6.89 (d, *J* = 8.0 Hz, 1H, H-5)

^{13}C NMR Data: (100 MHz, $CDCl_3$): δ 193.4 (C-7), 163.7 (C-2), 163.7 (d, *J* = 247.9 Hz, C-3'), 144.2 (d, *J* = 2.9 Hz, C-9), 136.9 (d, *J* = 8.1 Hz, C-1'), 136.7 (C-4), 130.7 (d, *J* = 8.1 Hz, C-5'), 129.7 (C-6), 124.9 (d, *J* = 2.9 Hz, C-6'), 121.6 (C-8) 120.1 (C-1), 119.1 (C-5), 118.7 (C-3), 117.7 (d, *J* = 21.3 Hz, C-4'), 114.7 (d, *J* = 22.0 Hz, C-2')

MS Data: *m/z* (rel. int.): 242 (100) [M^+], 147 (41), 120 (70), 92 (88).

IV) 4'-fluoro-2-hydroxychalcone; $C_{15}H_{11}O_2F$ (242.25 g mol^{-1})



Physical description: Yellow fine crystals

Yield: 73 % (0.883 g)

Melting point: 118-120 ^{o}C

UV Data: λ_{max} (nm) (log ε): 319 (5.68)

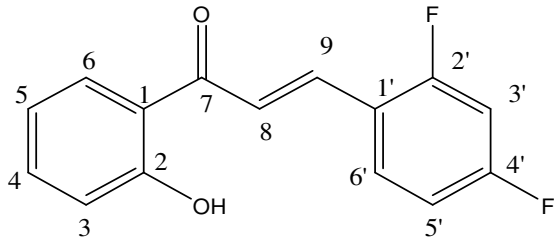
IR Data: ν_{max} (cm^{-1}): 3710 (OH), 2888 (-CH), 1636 (C=O), 1572 (C=C), 1202 (Ar-F)

^{1}H NMR Data: (400 MHz, $CDCl_3$): δ7.84 (d, *J* = 5.5 Hz, 1H, H-6), 7.81 (d, *J* = 15.6 Hz, 1H, H-9), 7.60 (dd, *J* = 8.5 Hz, 5.0 Hz, 2H, H-2'/6'), 7.52 (d, *J* = 15.6 Hz, 1H, H-8), 7.44 (td, *J* = 8.5 Hz, 1.5 Hz, 1H, H-4), 7.06 (t, *J* = 8.5 Hz, 2H, H-3'/5'), 6.97 (d, *J* = 8.5 Hz, 1H, H-3), 6.88 (t, *J* = 8.0 Hz, 1H, H-5)

^{13}C NMR Data: (100 MHz, $CDCl_3$): δ 193.5 (C-7), 163.6 (C-2), 162.7 (d, *J* = 248.7 Hz, C-4'), 144.3 (C-9), 136.6, (C-4), 130.9 (C-1'), 130.6 (d, *J* = 8.8 Hz, C-2'/6'), 129.6 (C-6), 119.9 (C-1), 119.8 (d, *J* = 2.9 Hz, C-8), 118.9 (C-5), 118.6 (C-3), 116.2 (d, *J* = 22.0 Hz, C-3'/5')

MS Data: *m/z* (rel. int.): 242 (100) [M^+], 225 (14), 147 (22), 120 (63), 92 (81).

V) 2',4'-difluoro-2-hydroxychalcone; $C_{15}H_{10}O_2F_2$ (260.24 g mol^{-1})



Physical description: Bright yellow solid

Yield: 84 % (1.098 g)

Melting point: 115-116 ^{o}C

UV Data: λ_{max} (nm) (log ε): 315 (5.07)

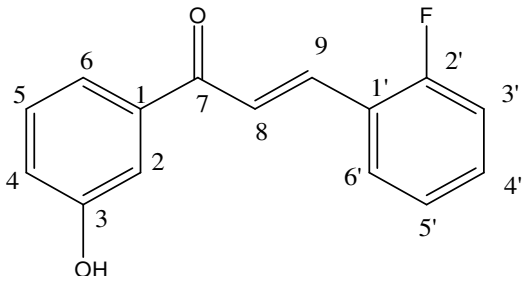
IR Data: ν_{max} (cm^{-1}): 3693 (OH), 2956 (-CH), 1635 (C=O), 1571 (C=C), 1057 (C-O)

^{1}H NMR Data: (400 MHz, $CDCl_3$): δ7.95 (d, *J* = 15.6 Hz,, 1H, H-9), 7.91 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H, H-6), 7.74 (d, *J* = 15.6 Hz, 1H, H-8), 7.66 (dt, *J* = 8.5 Hz, 6.5 Hz, 1H, H-6'), 7.53 (td, *J* = 8.5 Hz, 1.5 Hz, 1H, H-4), 7.05 (d, *J* = 8.5 Hz, 1H, H-6'), 7.02-6.90 (m, 3H, H-3', H-5' and H-5)

^{13}C NMR Data: (100 MHz, $CDCl_3$): δ 193.8 (C-7), 165.2 (dd, *J* = 242.8 Hz, *J* = 12.5 Hz, C-2'), 163.6 (C-2), 160.5 (dd, *J* = 245.8 Hz, 12.5 Hz, C-4'), 137.3 (C-9), 136.6 (C-4), 131.5 (dd, *J* = 9.5 Hz, 4.4 Hz, C-6'), 129.7 (C-6), 122.5 (dd, *J* = 8.1 Hz, 2.2 Hz, C-8), 119.9 (C-1) 119.3 (dd, *J* = 10.9 Hz, 3.7 Hz, C-1'), 119.0 (C-5), 118.7 (C-3), 112.3 (dd, *J* = 22.1 Hz, 3.7 Hz, C-5'), 105.0 (t, *J* = 25.7 Hz, C-3')

MS Data: *m/z* (rel. int.): 260 (100) [M^+], 240 (66), 147 (22), 120 (85), 92 (100).

VI) 2'-fluoro-3-hydroxychalcone; $C_{15}H_{11}O_2F$ (242.25 g mol^{-1})



Physical description: Dark orange solid

Yield: 90 % (1.089 g)

Melting point: 118-120 ^{o}C

UV Data: λ_{max} (nm) (log ε): 301 (5.53)

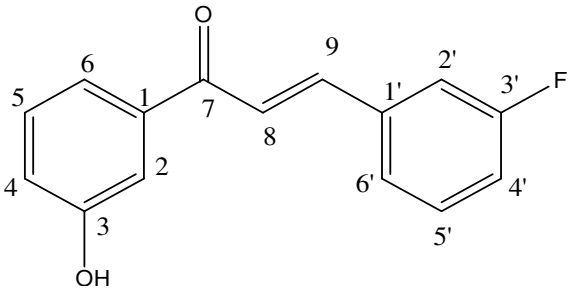
IR Data: ν_{max} (cm^{-1}): 3388 (OH), 1655 (C=O), 1573 (C=C), 1220 (Ar-F)

^{1}H NMR Data: (400 MHz, $CDCl_3$): δ7.92 (d, *J* = 15.8 Hz, 1H, H-9), 7.64 (d, *J* = 15.8 Hz, 1H, H-8), 7.66-7.62 (m, 2H, H-6' and H-6), 7.60 (d, *J* = 7.8 Hz, 1H, H-4), 7.40 (t, *J* = 7.8 Hz, 1H, H-5), 7.35 -7.45 (m, 1H, H-4'), 7.20 (t, *J* = 7.27 Hz, 1H, H-5'), 7.18-7.10 (m, 2H, H-2 and H-3')

^{13}C NMR Data: (100 MHz, $CDCl_3$): δ 191.1 (C-7), 162.0 (d, *J* = 255.3 Hz, C-2'), 156.6 (C-3), 139.3 (C-1), 138.4 (d, *J* = 2.2 Hz, C-9), 132.2 (d, *J* = 8.8 Hz, C-4'), 129.9 (C-5), 129.9 (d, *J* = 2.9 Hz, C-6'), 124.6 (d, *J* = 3.7 Hz, C-5'), 124.5 (d, *J* = 3.7 Hz, C-8), 123.0, (d, *J* = 11.0 Hz, C-1), 121.0 (C-4), 120.7 (C-2), 116.4 (d, *J* = 22.7 Hz, C-3'), 115.2 (C-6)

MS Data: *m/z* (rel. int.): 242 (100) [M^+], 223 (30), 149 (33), 121 (37), 93 (11).

VII) 3'-fluoro-3-hydroxychalcone; $C_{15}H_{11}O_2F$ (242.25 g mol^{-1})



Physical description: Pale yellow solid

Yield: 54 % (0.656 g)

Melting point: 91-93 ^{o}C

UV Data: λ_{max} (nm) (log ε): 301 (5.12)

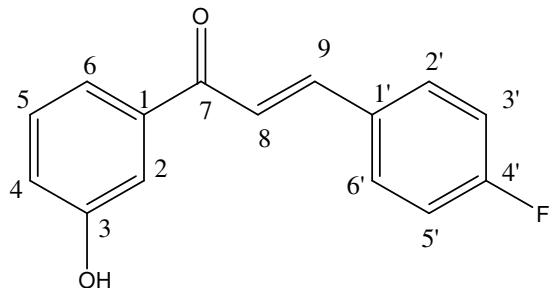
IR Data: ν_{max} (cm^{-1}): 3398 (OH), 2970 (-CH), 1662 (C=O), 1577 (C=C), 1213 (Ar-F)

^{1}H NMR Data: (400 MHz, $CDCl_3$): δ7.77 (d, *J* = 15.8 Hz, 1H, H-9), 7.60 (d, *J* = 7.8 Hz, 1H, H-4), 7.60-7.52 (m, 1H, H-6), 7.50 (d, *J* = 15.8 Hz, 1H, H-8), 7.43-7.38 (m, 3H, H-5, H-6' and H-5'), 7.35 (d, *J* = 9.03 Hz, 1H, H-2'), 7.20-7.15 (m, 2H, H-2 and H-4')

^{13}C NMR Data: (100 MHz, $CDCl_3$): δ 190.9 (C-7), 162.9 (d, *J* = 246.5 Hz, C-3'), 156.8 (C-3), 144.0 (d, *J* = 2.9 Hz, C-9), 139.2 (C-1), 137.2 (d, *J* = 7.3 Hz, C-1'), 130.6 (d, *J* = 8.1 Hz, C-5'), 130.0 (C-5), 124.9 (d, *J* = 2.9 Hz, C-6'), 123.2 (C-8) 121.1 (C-4), 120.8 (C-2), 117.5 (d, *J* = 21.3 Hz, C-4'), 115.4 (C-6), 114.6 (d, *J* = 21.3 Hz, C-2')

MS Data: *m/z* (rel. int.): 242 (100) [M^+], 149 (26), 121 (33), 93 (15).

VIII) 4'-fluoro-3-hydroxychalcone; $C_{15}H_{11}O_2F$ (242.25 g mol^{-1})



Physical Data: Dark yellow solid

Yield: 81 % (0.986 g)

Melting point: 127-128 ^{o}C

UV Data: λ_{max} (nm) (log ε): 309 (5.51)

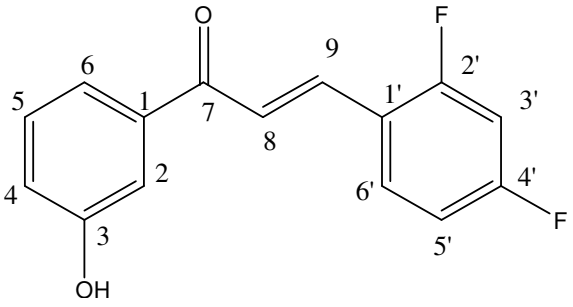
IR Data: ν_{max} (cm^{-1}): 3333 (-OH), 2579 (-CH), 1652 (C=O), 1223 (Ar-F)

^{1}H NMR Data: (400 MHz, $CDCl_3$): δ7.80 (d, *J* = 15.8 Hz, 1H, H-9), 7.65 (dd, *J* = 9.0 Hz, 5.0 Hz, 2H, H-2'/6'), 7.64-7.55 (m, 2H, H-4 and H-6), 7.44 (d, *J* = 15.55 Hz, 1H, H-8), 7.40 (t, *J* = 8.03 Hz, 1H, H-5), 7.13 (t, *J* = 8.03 Hz, 2H, H-3'/5'), 7.15-7.10 (m, 1H, H-2)

^{13}C NMR Data: (100 MHz, $CDCl_3$): δ 190.6 (C-7), 164.1 (d, *J* = 252.4 Hz, C-4'), 156.6 (C-3), 144.3 (C-9), 139.5 (C-1), 131.0 (d, *J* = 2.9 Hz, C-1'), 130.5 (d, *J* = 8.8 Hz, 2C, C-2'/6'), 129.9 (C-5), 121.7 (d, *J* = 2.9 Hz, C-8), 121.0 (C-4), 120.5 (C-2), 116.2 (d, *J* = 22.0 Hz, 2C, C-3'/5'), 115.1 (C-6)

MS Data: *m/z* (rel. int.): 242 (100) [M^+], 225 (15), 149 (22), 121 (33), 93 (7).

IX) 2',4'-fluoro-3-hydroxychalcone; $C_{15}H_{10}O_2F_2$ (260.24 g mol^{-1})



Physical description: Bright yellow solid

Yield: 86 % (1.12 g)

Melting point: 112-113 ^{o}C

UV Data: λ_{max} (nm) (log ε): 307 (5.06)

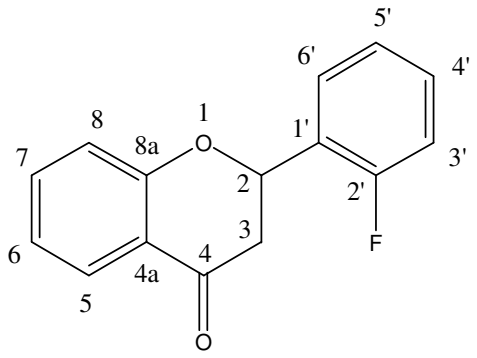
IR Data: ν_{max} (cm^{-1}): 3377 (OH), 2962 (-CH), 1654 (C=O), 1573 (C=C), 1264 (Ar-F), 1053 (C-O)

^{1}H NMR Data: (400 MHz, $CDCl_3$): δ7.86 (d, *J* = 16.0 Hz, 1H, H-9), 7.64 (dt, *J* = 8.5 Hz, 6.27 Hz, 1H, H-6'), 7.62-7.55 (m, 3H, H-8, H-4 and H-6), 7.40 (t, *J* = 8.0 Hz, 1H, H-5), 7.12 (dd, *J* = 10.6 Hz, 8.0 Hz, 1H, H-2), 7.00-6.85 (m, 2H, H-5' and H-3')

^{13}C NMR Data: (100 MHz, $CDCl_3$): δ 190.8 (C-7), 164.4 (dd, *J* = 255.3 Hz, 12.5 Hz, C-4'), 162.0 (dd, *J* = 257.5 Hz, 11.7 Hz, C-2'), 156.6 (C-3), 139.3 (C-1), 136.9 (C-9), 131.3 (dd, *J* = 10.3 Hz, 4.4 Hz, C-6'), 129.8 (C-5), 124.2 (dd, *J* = 7.3 Hz, 2.2 Hz, C-8), 121.0 (C-4) 120.8 (C-2), 119.4 (dd, *J* = 11.7 Hz, 3.7 Hz, C-1'), 115.2 (C-6), 112.3 (dd, *J* = 21.3 Hz, 3.7 Hz, C-5'), 104.8 (t, *J* = 25.7 Hz, C-3')

MS Data: *m/z* (rel. int.): 260 (100) [M^+], 241 (26), 167 (33), 139 (22).

X) 2'-fluoroflavanone; $C_{15}H_{11}O_2F$ (242.25 g mol^{-1})



Physical description: Yellow-green crystalline powder

Yield: 64 % (0.772 g)

Melting point: 79-82 ^{o}C

α_D **=** (+) 0.03 (c = 0.1, MeOH)

UV Data: λ_{max} **(nm) (log ε):** 256 (5.64), 333 (5.19)

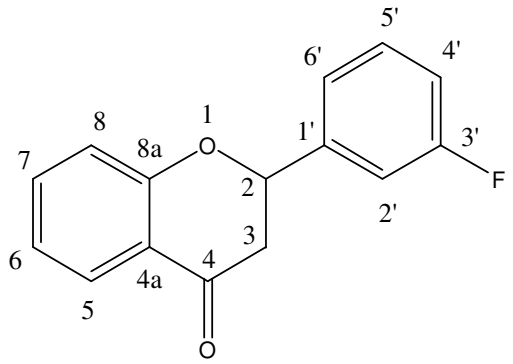
IR Data: ν_{max} **(cm^{-1}):**1629 (C=O), 1219 (Ar-F), 1037 (C-O)

^{1}H NMR Data: (400 MHz, $CDCl_3$): δ7.73 (dd, *J* = 8.0 Hz, 1.25 Hz, 1H, H-5), 7.63 (td, *J* = 7.5 Hz, 1.5 Hz, 1H, H-6'), 7.51 (td, *J* = 8.53 Hz, 1.6 Hz, 1H, H-7), 7.38-7.32 (m, 1H, H-4'), 7.22 (t, *J* = 7.5 Hz, 1H, H-5'), 7.07 (t, *J* = 8.5 Hz, 1H, H-3'), 7.02 (d, *J* = 9.5 Hz, 1H, H-8), 6.90 (t, *J* = 8.0 Hz, 1H, H-6), 5.65 (d, *J* = 9.3 Hz, 1H, H-2), 3.50 (dd, *J* = 17.6 Hz, 3.7 Hz, 1H, H-3a), 3.41 (dd, *J* = 17.6 Hz, 9.3 Hz, 1H, H-3b)

^{13}C NMR Data: (100 MHz, $CDCl_3$): δ 205.6 (C-4), 162.8 (C-8a), 159.2 (d, *J* = 245.8 Hz, C-2'), 137.3 (C-7), 130.3 (C-5), 129.7 (d, *J* = 13.2 Hz, C-1'), 129.2 (d, *J* = 8.8 Hz, C-4'), 127.4 (d, *J* = 5.9 Hz, C-6'), 124.5 (d, *J* = 3.7 Hz, C-5'), 119.3 (C-4a), 119.2 (C-6), 118.7 (C-8), 115.3 (d, *J* = 21.3 Hz, C-3'), 64.2 (d, *J* = 2.9 Hz, C-2), 45.7 (C-3)

MS Data: ***m/z*** **(rel. int.):** 242 (30) [M^+], 222 (16), 147 (33), 120 (100), 92 (89).

XI) 3'-fluoroflavanone; $C_{15}H_{11}O_2F$ (242.25 g mol^{-1})



Physical description: Yellow-green crystalline powder

Yield: 72 % (0.864 g)

Melting point: 92-93 ^{o}C

α_D = (-) 0.03 (c = 0.1, MeOH)

UV Data: λ_{max} (nm) (log ε): 257 (5.48), 330 (5.02)

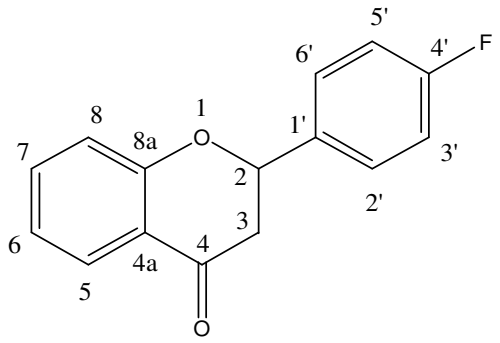
IR Data: ν_{max} (cm^{-1}):1688 (C=O), 1600 (C=C), 1225 (Ar-F)

^{1}H NMR Data: (400 MHz, $CDCl_3$): δ7.71 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H, H-5), 7.51 (td, *J* = 8.5 Hz, 1.5 Hz, 1H, H-7), 7.40-7.30 (m, 1H, H-5'), 7.05-6.95 (m, 2H, H-2' and H-6'), 7.05-7.00 (m, 2H, H-4' and H-8), 6.91 (t, *J* = 8.0 Hz, 1H, H-6), 5.38 (dd, *J* = 9.0 Hz, 1H, H-2) 3.44 (dd, *J* = 17.6 Hz, 9.0 Hz, 1H, H-3a), 3.37 (dd, *J* = 17.6 Hz, 3.5 Hz, 1H, H-3b)

^{13}C NMR Data: (100 MHz, $CDCl_3$): δ 205.3 (C-4), 163.6 (d, *J* = 246.5 Hz, C-3'), 162.6 (C-8a), 145.4 (d, *J* = 6.6 Hz, C-1'), 137.1 (C-7), 130.2 (d, *J* = 8.1 Hz, C-5'), 130.0 (C-5), 121.3 (d, *J* = 2.9 Hz, C-6'), 119.3 (C-4a), 119.2 (C-6), 118.7 (C-8), 114.7 (d, *J* = 21.3 Hz, C-4'), 112.8 (d, *J* = 22.7 Hz, C-2'), 69.2 (d, *J* = 1.5 Hz, C-2), 47.1 (C-3)

MS Data: *m/z* (rel.int.): 242 (100) [M^+], 147 (44), 120 (74), 92 (70).

XII) 4'-fluoroflavanone; $C_{15}H_{11}O_2F$ (242.25 g mol^{-1})



Physical description: Yellow-green crystalline powder

Yield: 86 % (1.03 g)

Melting point: 108-110 ^{o}C

α_D = (+) 0.03 (c = 0.1, MeOH)

UV Data: λ_{max} (nm) (log ε): 257 (5.44), 333 (5.02)

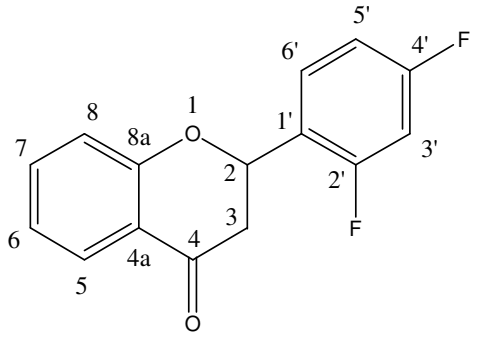
IR Data: ν_{max} (cm^{-1}): 2906 (-CH), 1631 (C=O), 1211 (Ar-F)

^{1}H NMR Data: (400 MHz, $CDCl_3$): δ7.71 (dd, *J* = 8.5 Hz, 1.5 Hz, 1H, H-5), 7.51 (td, *J* = 8.5 Hz, 1.5 Hz, 1H, H-7), 7.42 (dd, *J* = 8.5 Hz, 5.1 Hz, 2H, H-2'/6'), 7.10 (t, *J* = 8.5 Hz, 2H, H-3'/5'), 7.02 (d, *J* = 8.5 Hz, 1H, H-8), 6.91 (t, *J* = 8.0 Hz, 1H, H-6), 5.36 (dd, *J* = 9.0 Hz, 3.0 Hz, 1H, H-2), 3.45 (dd, *J* = 17.6 Hz, 9.0 Hz, 1H, H-3a), 3.38 (dd, *J* = 17.6 Hz, 3.0 Hz, 1H, H-3b)

^{13}C NMR Data: (100 MHz, $CDCl_3$): δ 205.4 (C-4), 162.6 (C-8a), 162.1 (d, *J* = 245.8 Hz, C-4'), 138.6 (d, *J* = 2.9 Hz, C-1'), 137.2 (C-7), 130.1 (C-5), 127.6 (d, *J* = 8.8 Hz, 2C, C-2'/6'), 119.3 (C-4a), 119.2 (C-6), 118.7 (C-8), 115.5 (d, *J* = 21.3 Hz, 2C, C-3'/5'), 69.3 (C-2), 47.2 (C-3)

MS Data: *m/z* (rel. int.): 242 (100) [M^+], 147 (26), 120 (67), 92 (85).

XIII) 2',4'-difluoroflavanone; $C_{15}H_{11}O_2F_2$ (260.24 g mol^{-1})



Physical description: Yellow-green crystalline powder

Yield: 70% (0.903 g)

Melting point: 97-98 ^{o}C

α_D = (+) 0.02 (c = 0.1, MeOH)

UV Data: λ_{max} (nm) (log ε): 257 (5.56), 334 (5.11)

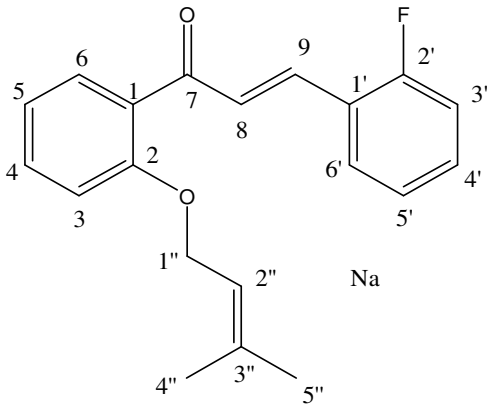
IR Data: ν_{max} (cm^{-1}): 3694 (OH),2963 (-CH), 1608 (C=O), 1242 (Ar-F), 1054 (C-O)

^{1}H NMR Data: (400 MHz, $CDCl_3$): δ7.71 (dd, *J* = 8.1 Hz, 1.0 Hz, 1H, H-5), 7.61 (dt, *J* = 8.6 Hz, 6.5 Hz, 1H, H-6'), 7.52 (td, *J* = 8.5 Hz, 1.4 Hz, 1H, H-7), 7.03 (d, *J* = 8.0 Hz, 1H, H-8),7.00-6.92 (m, 1H, H-5'), 6.91-6.88 (m, 1H, H-6), 6.83 (td, *J* = 11.0 Hz, 2.5 Hz 1H, H-3'), 5.61 (dd, *J* = 9.0 Hz, 2.5 Hz, 1H, H-2), 3.48 (dd, *J* = 17.6 Hz, 2.5 Hz, 1H, H-3b), 3.37 (dd, *J* = 17.6 Hz, 9.0 Hz, 1H, H-3a)

^{13}C NMR Data: (100 MHz, $CDCl_3$): δ 205.6 (C-4), 162.8 (C-8a), 162.8 (dd, *J* = 248.7 Hz, 12.5 Hz, C-4'), 159.7 (dd, *J* = 248.0 Hz, 11.7 Hz, C-2'), 137.4 (C-7), 130.1 (C-5), 128.6 (dd, *J* = 9.3 Hz, 5.9 Hz, C-6'), 125.7 (dd, *J* = 13.9 Hz, 3.7 Hz, C-1'), 119.3 (C-4a), 119.2 (C-6), 118.8 (C-8), 111.7 (dd, *J* = 20.5 Hz, 3.7 Hz, C-5'), 103.8 (t, *J* = 25.7 Hz, C-3'), 63.7 (d, *J* = 2.2 Hz, C-2), 45.4 (C-3)

MS Data: *m/z* (rel. int.): 260 (93) [M^+], 240 (100), 147 (26), 140 (56), 120 (93), 92 (100).

XIV) 2'-fluoro-2-oxyprenylchalcone; $C_{20}H_{19}O_2F$ (310.36 g mol^{-1})



Physical description: Yellow gummy oil

Yield: 82 % (0.510 g)

UV Data: λ_{max} (nm) (log ε): 253 (5.13), 300 (5.42)

IR Data: ν_{max} (cm^{-1}): 2922 (-CH), 1658 (C=O), 1599 (C=C), 1227 (Ar-F)

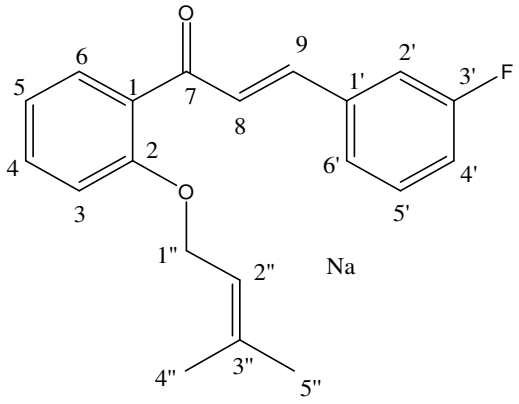
^{1}H NMR Data: (400 MHz, $CDCl_3$): δ7.79 (d, *J* = 16.0 Hz, 1H, H-9), 7.73 (dd, *J* = 7.6 Hz, 1.5 Hz, 1H, H-6), 7.62 (d, *J* = 16.0 Hz, 1H, H-8), 7.61 (td, *J* = 8.5 Hz, 1.5 Hz, 1H, H-6'), 7.48 (td, *J* = 8.6 Hz, 1.5 Hz, 1H, H-4), 7.40-7.32 (m, 1H, H-4'), 7.17 (t, *J* = 7.5 Hz, 1H, H-5'), 7.14-7.04 (m, 2H, H-5 and H-3'), 7.02 (d, *J* = 8.5 Hz, 1H, H-3), 5.50 (t, *J* = 6.5 Hz, 1H, H-2"), 4.63 (d, 7.0 Hz, 2H, H-1"), 1.75 (s, 1H, H-5"), 1.73 (s, 1H, H-4")

^{13}C NMR Data: (100 MHz, $CDCl_3$): δ 192.3 (C-7), 161.9 (d, *J* = 254.6 Hz, C-2'), 157.9 (C-2), 138.8 (C-3"), 134.6 (d, *J* = 3.1 Hz, C-9), 133.2 (C-4), 131.4 (d, *J* = 8.8 Hz, C-4'), 131.0 (C-6), 129.7 (d, *J* = 5.9 Hz, C-6'), 129.2 (C-1), 129.1 (d, *J* = 2.9 Hz, C-8), 124.3 (d, *J* = 3.7 Hz, C-5'), 123.4 (d, *J* = 11.7 Hz, C-1'), 120.8 (C-5), 119.3 (C-2"), 116.1 (d, *J* = 22.0 Hz, C-3'), 113.1 (C-3), 65.6 (C-1"), 25.8 (C-5"), 18.3 (C-4")

MS Data: *m/z* (rel. int.): 310 (7) [M^+], 242 (89), 222 (28), 147 (30), 120 (74), 92 (22), 69 (100)

HRMS (*m/z*): 333.1268 (calcd for $C_{20}H_{19}O_2FNa$, 333.1267)

XV) 3'-fluoro-2-oxyprenylchalcone; $C_{20}H_{19}O_2F$ (310.36 g mol^{-1})



Physical description: Orange gummy oil

Yield: 60 % (0.372 g)

UV Data: λ_{max} (nm) (log ε): 228 (5.43), 299 (5.53)

IR Data: ν_{max} (cm^{-1}): 2923 (-CH), 1657 (C=O), 1597 (C=C), 1229 (Ar-F)

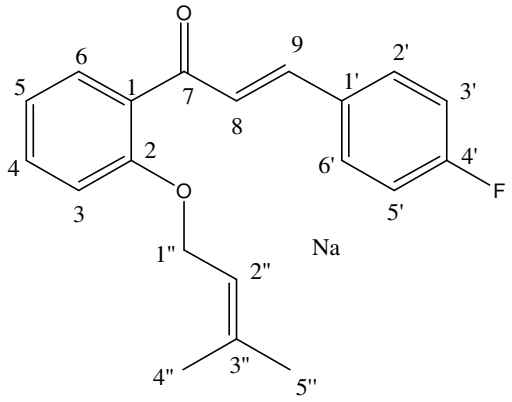
^{1}H NMR Data: (400 MHz, $CDCl_3$): δ7.76 (dd, *J* = 7.8 Hz, 1.8 Hz, 1H, H-6), 7.61 (d, *J* = 15.8 Hz, 1H, H-9), 7.57 (d, *J* = 15.8 Hz, 1H, H-8), 7.49 (td, *J* = 8.7 Hz, 2.0 Hz, 1H, H-4), 7.40-7.32 (m, 2H, H-5' and H-6'), 7.32-7.30 (m, 1H, H-2'), 7.12-7.06(m, 1H, H-4'), 7.03 (t, *J* = 7.8 Hz, 1H, H-3), 7.05-7.03 (m, 1H, H-5), 5.53 (t, *J* = 6.8 Hz, 1H, H-2"), 4.64 (d, *J* = 6.8 Hz, 2H, H-1"), 1.78 (s, 1H, H-5"), 1.75 (s, 1H, H-4")

^{13}C NMR Data: (100 MHz, $CDCl_3$): δ 192.0 (C-7), 162.9 (d, *J* = 246.5 Hz, C-3'), 158.2 (C-2), 140.5 (d, *J* = 2.9 Hz, C-9), 138.9 (C-3"), 137.8 (d, *J* = 7.3 Hz, C-1'), 133.6 (C-4), 130.9 (C-6), 130.3 (d, *J* = 8.1 Hz, C-5'), 128.9 (C-1), 128.6 (C-8), 124.6 (d, *J* = 2.9 Hz, C-6'), 120.9 (C-5), 119.1 (C-2"), 116.8 (d, *J* = 22.0 Hz, C-4'), 114.1 (d, *J* = 22.3 Hz, C-2'), 113.0 (C-3), 65.6 (C-1"), 25.8 (C-5"), 18.3 (C-4")

MS Data: *m/z* (rel. int.): 310 (15) [M^+], 241 (100), 225 (19), 147 (52), 121 (26), 69 (19)

HRMS (*m/z*): 333.1269 (calcd. for $C_{20}H_{19}O_2FNa$ 333.1267)

XVI) 4'-fluoro-2-oxyprenylchalcone; $C_{20}H_{19}O_2F$ (310.36 g mol^{-1})



Physical description: Orange gummy oil

Yield: 63 % (0.390 g)

UV Data: λ_{max} (nm) (log ε): 228 (5.56), 307 (5.63)

IR Data: ν_{max} (cm^{-1}): 2924 (-CH), 1656 (C=O), 1594 (C=C)

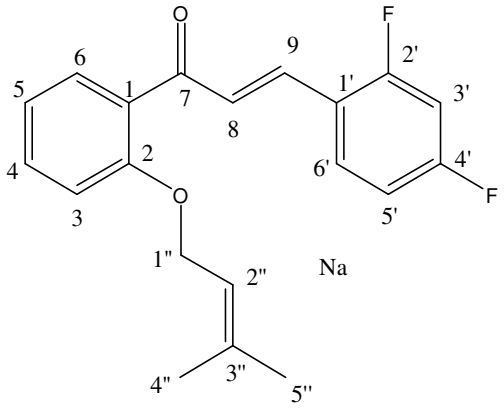
^{1}H NMR Data: (400 MHz, $CDCl_3$): δ7.72 (dd, *J* = 7.8 Hz, 1.8 Hz, 1H, H-6), 7.61 (d, *J* = 15.8 Hz, 1H, H-9), 7.57 (dd, *J* = 10.2 Hz, 8.5 Hz, 2H, H-2'/6'), 7.48 (d, *J* = 15.8 Hz, 1H, H-8), 7.46 (td, *J* = 8.8 Hz, 2.1 Hz, 1H, H-4), 7.09 (t, *J* = 8.5 Hz, 2H, H-3'/5'), 7.08-7.02 (m, 2H, H-3 and H-5), 5.51 (t, *J* = 6.8 Hz, 1H, H-2''), 4.63 (d, *J* = 6.5 Hz, 2H, H-1''), 1.76 (s, 1H, H-5''), 1.74 (s, 1H, H-4'')

^{13}C NMR Data: (100 MHz, $CDCl_3$): δ 192.2 (C-7), 163.9 (d, *J* = 250.9 Hz, C-4'), 158.0 (C-2), 141.1 (C-9), 138.6 (C-3''), 133.2 (C-4), 131.8 (d, *J* = 3.7 Hz, C-1'), 130.8 (C-6), 130.1 (d, *J* = 8.8 Hz, 2C, C-2'/6'), 129.1 (C-1), 127.3 (d, *J* = 2.2 Hz, C-8), 120.7 (C-5), 119.4 (C-2''), 116.2 (d, *J* = 22.0 Hz, 2C, C-3'/5'), 113.4 (C-3), 65.5 (C-1''), 25.7 (C-5''), 18.6 (C-4'')

MS Data: *m/z* (rel. int.): 310 (19) [M^+], 241 (100), 147 (26), 120 (33), 69 (19)

HRMS (*m/z*): 333.1274 (calcd. for $C_{20}H_{19}O_2FNa$, 333.1267)

XVII) 2',4'-difluoro-2-oxyprenylchalcone; $C_{20}H_{18}O_2F_2$ (328.36 g mol^{-1})



Physical description: Yellow solid

Yield: 74 % (0.484 g)

Melting point: 54-55 ^oC

UV Data: λ_{max} (nm) (log ε): 228 (5.36), 307 (549)

IR Data: ν_{max} (cm^{-1}): 2927 (-CH), 1649 (C=O), 1594 (C=C), 1267 (Ar-F)

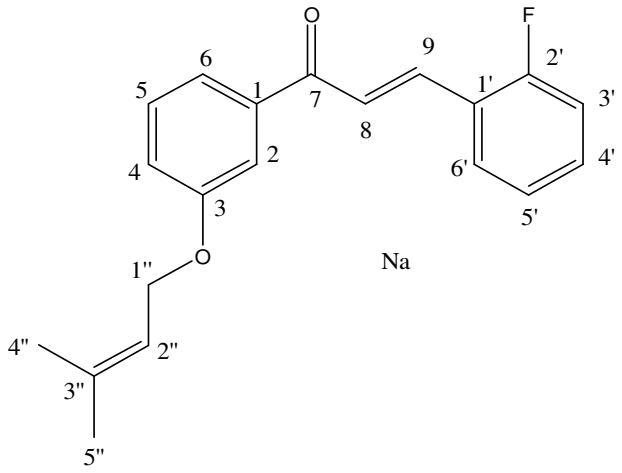
^{1}H NMR Data: (400 MHz, $CDCl_3$): δ 7.78-7.70 (m, 1H, H-6), δ7.72 (d, *J* = 15.6 Hz, 1H, H-9), 7.60-7.56 (m, 1H, H-6'), 7.58 (d, *J* = 15.6 Hz, 1H, H-8), 7.48 (td, *J* = 8.5 Hz, 1.5 Hz, 1H, H-4), 7.05 (t, *J* = 7.5 Hz, 1H, H-5), 7.01 (d, *J* = 8.6 Hz, 1H, H-3), 6.95-6.84 (m, 2H, H-3' and H-5'), 5.49 (t, *J* = 6.5 Hz, 1H, H-2"), 4.64 (d, *J* = 6.5 Hz, 2H, H-1"), 1.75 (s, 1H, H-5"), 1.73 (s, 1H, H-4")

^{13}C NMR Data: (100 MHz, $CDCl_3$):δ 192.3 (C-7), 163.1 (dd, *J* = 243.7 Hz, 12.5 Hz, C-2'), 160.1 (dd, *J* = 240.4 Hz, 12.0 Hz, C-4'), 138.4 (C-3"), 133.6, (C-9), 133.3 (C-4), 131.9 (C-6), 130.2 (dd, *J* = 9.5 Hz, 4.4 Hz, C-6'), 129.2 (dd, *J* = 5.7 Hz, 2.9 Hz, C-8), 129.1 (C-1), 121.0 (C-5), 119.50 (C-2"), 119.48 (dd, *J* = 12.4 Hz, 3.8 Hz, C-1'), 113.0 (C-3), 111.7 (dd, *J* = 21.3 Hz, 3.7 Hz, C-5'), 104.6 (t, *J* = 25.7 Hz, C-3'), 66.2 (C-1"), 25.5 (C-5"), 18.7 (C-4")

MS Data: *m/z* (rel. int.): 328 (7) [M^+], 260 (100), 240 (56), 147 (30), 69 (15)

HRMS (*m/z*): 351.1177 (calcd. for $C_{20}H_{19}O_2F_2Na$ 351.1173)

XVIII) 2'-fluoro-3-oxyprenylchalcone; $C_{20}H_{19}O_2F$ (310.36 g mol^{-1})



Physical description: Pale yellow-green solid

Yield: 66 % (0.408 g)

Melting point: 56-57 ^{o}C

UV Data: λ_{max} (nm) (log ε): 294 (5.52)

IR Data: ν_{max} (cm^{-1}): 2933 (-CH), 1657 (C=O), 1574 (C=C), 1246 (Ar-F), 1009 (C-O)

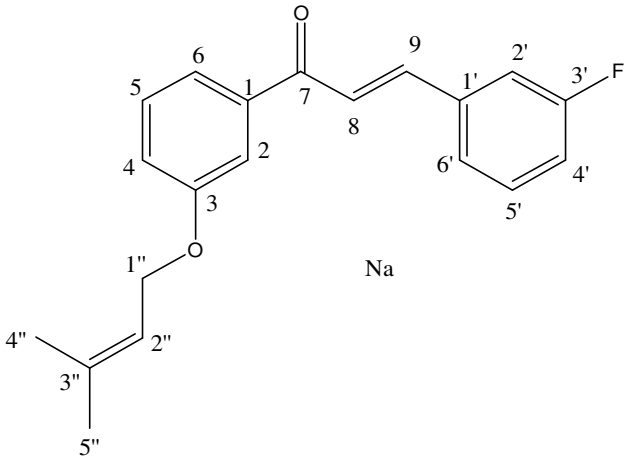
^{1}H NMR Data: (400 MHz, $CDCl_3$): δ7.93 (d, *J* = 15.6 Hz, 1H, H-9), 7.65 (td, *J* = 8.5 Hz, 1.5 Hz, 1H, H-6'), 7.63 (d, *J* = 15.6 Hz, 1H, H-8), 7.61-7.59 (m, 2H, H-4 and H-6), 7.42 (t, *J* = 8.0 Hz, 1H, H-5), 7.42-38 (m, 1H, H-4'), 7.21 (t, *J* = 7.2 Hz, 1H, H-5'), 7.17-7.14 (m, 2H, H-2 and H-3'), 5.53 (t, *J* = 6.5 Hz, 1H, H-2''), 4.62 (d, *J* = 6.5 Hz, 2H, H-1''), 1.82 (s, 1H, H-5''), 1.79 (s, 1H, H-4'')

^{13}C NMR Data: (100 MHz, $CDCl_3$): δ 190.4 (C-7), 161.5 (d, *J* = 254.6 Hz, C-2'), 159.5 (C-3), 139.3 (C-1), 138.7 (C-3''), 137.6 (d, *J* = 5.2 Hz, C-9), 131.8 (d, *J* = 8.8 Hz, C-4'), 129.8 (d, *J* = 5.7 Hz, C-6'), 129.6 (C-5), 124.7 (d, *J* = 7.3 Hz, C-5'), 124.5 (d, *J* = 3.7 Hz, C-8), 123.0 (d, *J* = 11.7 Hz, C-1'), 121.1 (C-4), 120.2 (C-2), 119.0 (C-2''), 116.2 (d, *J* = 22.0 Hz, C-3'), 113.6 (C-6), 64.8 (C-1''), 25.9 (C-5''), 18.1 (C-4'')

MS Data: *m/z* (rel. int.): 310 (19) [M^+], 242 (100), 223 (33), 121 (22), 69 (19)

HRMS Data: 333.1261 (calcd. for $C_{20}H_{19}O_2FNa$ 333.1267)

XIX) 3'-fluoro-3-oxyprenylchalcone; $C_{20}H_{19}O_2F$ (310.36 g mol^{-1})



Physical description: Pale yellow solid

Yield: 68 % (0.419 g)

Melting point: 51-52 ^{o}C

UV Data: λ_{max} (nm) (log ε): 295 (5.53)

IR Data: ν_{max} (cm^{-1}): 2907 (-CH), 1662 (C=O), 1577 (C=C), 1018 (C-O)

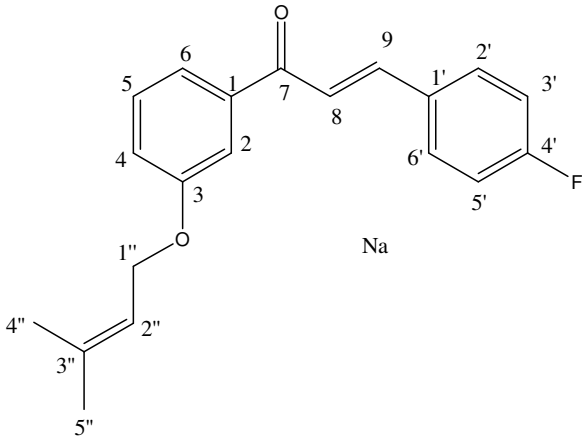
^{1}H NMR Data: (400 MHz, $CDCl_3$): δ7.76 (d, *J* = 16.2 Hz, 1H, H-9), 7.60 (d, *J* = 8.0 Hz, 1H, H-4), 7.59-7.55 (m, 1H, H-6), 7.51 (d, *J* = 15.6 Hz, 1H, H-8), 7.42-7.38 (m, 3H, H-5, H-5' and H-6'), 7.35 (d, *J* = 9.5 Hz, 1H, H-2'), 7.16 (dd, *J* = 8.5 Hz, 3.0 Hz, 1H, H-2), 7.14-7.10 (m, 1H, H-4'), 5.52 (t, *J* = 7.0 Hz, 1H, H-2''), 4.60 (d, *J* = 7.0 Hz, 2H, H-1''), 1.82 (s, 1H, H-5''), 1.78 (s, 1H, H-4'')

^{13}C NMR Data: (100 MHz, $CDCl_3$): δ 190.0 (C-7), 163.1 (d, *J* = 246.5 Hz, C-3'), 159.4 (C-3), 143.1 (d, *J* = 2.2 Hz, C-9), 139.3 (C-1), 138.8 (C-3''), 137.4 (d, *J* = 8.1 Hz, C-1'), 130.8 (d, *J* = 8.1 Hz, C-5'), 129.5 (C-5), 124.4 (d, *J* = 2.9 Hz, C-6'), 123.1 (C-8), 121.0 (C-4), 120.2 (C-2), 119.2 (C-2''), 117.0 (d, *J* = 21.3 Hz, C-4'), 114.5 (d, *J* = 22.7 Hz, C-2'), 113.8 (C-6), 64.1 (C-1''), 25.7 (C-5''), 18.3 (C-4'')

MS Data:*m/z* (rel. int.): 310 (7) [M^+], 242 (100), 223 (7), 149 (15), 121 (7), 69 (26)

HRMS (*m/z*): 333.1252 (calcd. for $C_{20}H_{19}O_2FNa$ 333.1267)

XX) 4'-fluoro-3-oxyprenylchalcone; $C_{20}H_{19}O_2F$ (310.36 g mol^{-1})



Physical description: Yellow crystalline powder

Yield: 75 % (0.462 g)

Melting point: 69-71 ^{o}C

UV Data: λ_{max} (nm) (log ε): 303 (5.50)

IR Data: ν_{max} (cm^{-1}): 2935 (-CH), 1656 (C=O), 1579 (C=C), 1228 (Ar-F), 1011 (C-O)

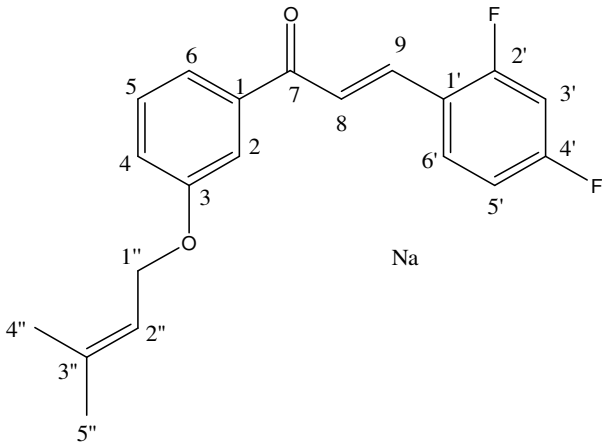
^{1}H Data: NMR (400 MHz, $CDCl_3$): δ7.78 (d, *J* = 15.6 Hz, 1H, H-9), 7.65 (dd, *J* = 11.6 Hz, 9.0 Hz, 2H, H-2'/6'), 7.60 (d, *J* = 7.5 Hz, 1H, H-4), 7.58-7.56 (m, 1H, H-6), 7.46 (d, *J* = 15.6 Hz, 1H, H-8), 7.41 (t, *J* = 7.5 Hz, 1H, H-5), 7.15 (dd, *J* = 8.5 Hz, 3.1 Hz, 1H, H-2), 7.12 (t, *J* = 8.5 Hz, 2H, H-3'/5'), 5.53 (t, *J* = 6.5 Hz, 1H, H-2''), 4.60 (d, *J* = 6.5 Hz, 2H, H-1''), 1.82 (s, 1H, H-5''), 1.79 (s, 1H, H-4'')

^{13}C NMR Data: (100 MHz, $CDCl_3$): δ 190.6 (C-7), 164.5 (d, *J* = 252.4 Hz, C-4'), 159.3 (C-3), 143.7 (C-9), 139.7 (C-1), 138.8 (C-3''), 131.1 (d, *J* = 2.9 Hz, C-1'), 130.3 (d, *J* = 8.1 Hz, 2C, C-2'/6'), 129.6 (C-5), 121.9 (d, *J* = 2.2 Hz, C-8), 121.0 (C-4), 120.0 (C-2), 119.2 (C-2''), 116.1 (d, *J* = 21.0 Hz, 2C, C-3'/5'), 113.8 (C-6), 65.1 (C-1''), 25.9 (C-5''), 18.2 (C-4'')

MS Data: *m/z* (rel. int.): 310 (14) [M^+], 242 (89), 149 (40), 121 (63) 69 (100).

HRMS (*m/z*): 333.1257 (calcd. for $C_{20}H_{19}O_2FNa$, 333.1267)

XXI) 2',4'-difluoro-3-oxyprenylchalcone; $C_{20}H_{18}O_2F_2$ (328.36 g mol^{-1})



Physical description: Yellow solid

Yield: 71 % (0.467 g)

Melting point: 76-77 ^{o}C

UV Data: λ_{max} (nm) (log ε): 300 (5.32)

IR Data: ν_{max} (cm^{-1}): 2895 (-CH), 1659 (C=O), 1583 (C=C), 1247 (Ar-F), 1098 (C-O)

^{1}H NMR Data: (400 MHz, $CDCl_3$): δ7.85 (d, *J* = 15.6 Hz, 1H, H-9), 7.65 (dt, *J* = 8.5 Hz, 6.5 Hz, 1H, H-6'), 7.57 (d, *J* = 15.6 Hz, 1H, H-8), 7.58-7.55 (m, 2H, H-2 and H-6), 7.42 (t, *J* = 7.5 Hz, 1H, H-5), 7.16 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H, H-4), 7.00-6.94 (m, 1H, H-5'), 6.92-6.85 (m, 1H, H-3'), 5.33 (t, *J* = 6.5 Hz, 1H, H-2''), 4.60 (d, *J* = 6.5 Hz, 2H, H-1''), 1.83 (s, 1H, H-5''), 1.79 (s, 1H, H-4'')

^{13}C NMR Data: (100 MHz, $CDCl_3$): δ 190.3 (C-7), 164.2 (dd, *J* = 253.8 Hz, 12.5 Hz, C-4'), 161.3 (dd, *J* = 254.5 Hz, 11.7 Hz, C-2'), 159.3 (C-3) 139.3 (C-1), 138.8 (C-3''), 136.5 (C-9) 130.9 (dd, *J* = 10.3 Hz, 5.1 Hz, C-6'), 129.7 (C-5), 124.2 (dd, *J* = 2.9 Hz, 2.2 Hz, C-8), 121.02 (C-4), 120.2 (C-2), 119.6 (dd, *J* = 11.7 Hz, 3.7 Hz, C-1'), 119.2 (C-2''), 113.8 (C-6), 112.2 (dd, *J* = 21.3 Hz, 3.7 Hz, C-5'), 104.8 (t, *J* = 25.67 Hz, C-3'), 65.3 (C-1''), 25.9 (C-5''), 18.4 (C-4'').

MS Data: *m/z* (rel. int.): 328 (7) [M^+], 260 (100), 240 (56), 147 (30), 69 (15).

HRMS (*m/z*): 351.1174 (calcd. for $C_{20}H_{18}O_2F_2Na$ 351.1173)

2.4 Anti-oxidant activity

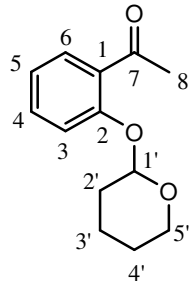
In this study, the comparison in anti-oxidant activity of variously substituted fluorine containing 2-hydroxy and 3-hydroxychalcones was examined using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) method.

The DPPH scavenging activity of compounds **II-IX** were determined spectrophotometrically using the stable free radical DPPH. Stock solutions of each compound were prepared by dissolving 10 mg of the compound in 10 mL of methanol (1.00 mg mL^{-1}). The stock solutions were used to prepare a series of eight concentrations (500, 250, 100, 50 and 10 μg mL^{-1}). A solution of DPPH was prepared by dissolving 1.97 mg of DPPH in 50 mL of methanol (0.1 mM) and protected from light by covering the volumetric flask with aluminum foil. An aliquot of each dilution of the compound (200 μL) was mixed with methanolic solution of DPPH (2.00 mL) in glass test tubes. The mixtures were shaken vigorously and set in a dark cupboard at ambient temperature for 30 min. The absorbance was then measured at 517 nm against methanol as a blank. The percent scavenging activity of the compounds were calculated using the following formula:

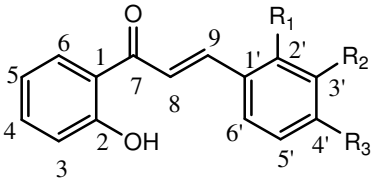
$$\text{Scavenging activity (\%)} = 100 \text{ x } \frac{Abs(\text{control}) - Abs\ (\text{sample})}{Abs\ (\text{control})}$$

Chapter 3. Results and Discussion

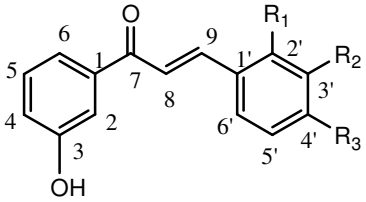
Twenty-one compounds of which include one intermediate (compound **I**) and eight novel prenyl chalcones (**XIV-XXI**)were successfully synthesized using both the Claisen-Schmidt condensation reaction and prenylation. All chalcones have fluorine substituted at the 2', 3', 4' and 2',4' positions on the B ring, in combination with a hydroxyl group at the 2-position (**II-V**) and the 3-position (**VI-IX**) as well as an oxyprenyl group at the 2-position (**XIV-XVII**) and the 3-position (**XVIII-XXI**). In addition, four flavanones with the same fluorine substitution pattern on the B-ring were synthesized (**X-XIII**).



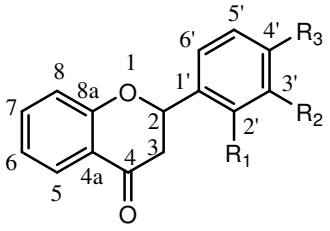
I



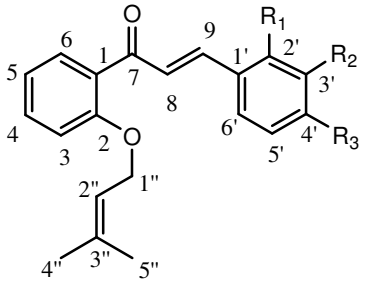
II $R_1 = F$, $R_2 = H$, $R_3 = H$
III $R_1 = H$, $R_2 = F$, $R_3 = H$
IV $R_1 = H$, $R_2 = H$, $R_3 = F$
V $R_1 = F$, $R_2 = H$, $R_3 = F$



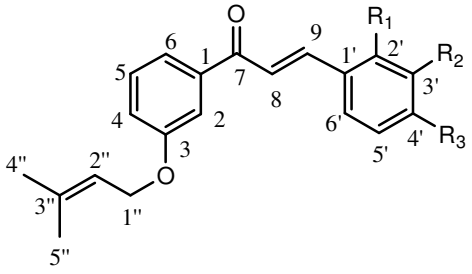
VI $R_1 = F$, $R_2 = H$, $R_3 = H$
VII $R_1 = H$, $R_2 = F$, $R_3 = H$
VIII $R_1 = H$, $R_2 = H$, $R_3 = F$
IX $R_1 = F$, $R_2 = H$, $R_3 = F$



X $R_1 = F$, $R_2 = H$, $R_3 = H$
XI $R_1 = H$, $R_2 = F$, $R_3 = H$
XII $R_1 = H$, $R_2 = H$, $R_3 = F$
XIII $R_1 = F$, $R_2 = H$, $R_3 = F$



XIV $R_1 = F$, $R_2 = H$, $R_3 = H$
XV $R_1 = H$, $R_2 = F$, $R_3 = H$
XVI $R_1 = H$, $R_2 = H$, $R_3 = F$
XVII $R_1 = F$, $R_2 = H$, $R_3 = F$



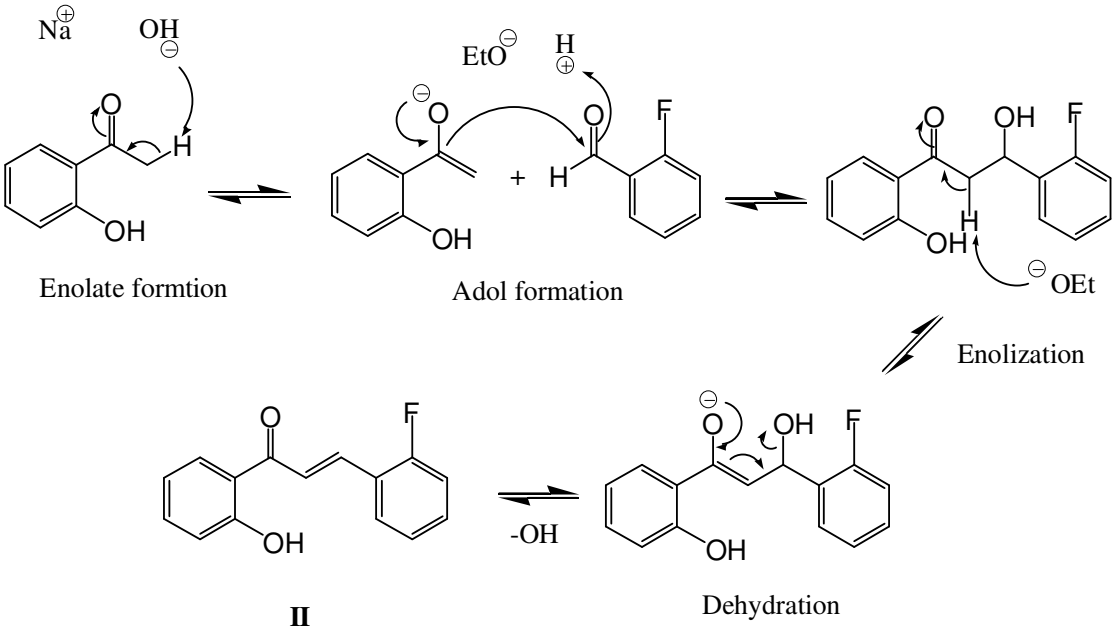
XVIII $R_1 = F$, $R_2 = H$, $R_3 = H$
XIX $R_1 = H$, $R_2 = F$, $R_3 = H$
XX $R_1 = H$, $R_2 = H$, $R_3 = F$
XXI $R_1 = F$, $R_2 = H$, $R_3 = F$

Figure 16 The molecular structures of all 20 compounds and one intermediate (I) synthesized in this study

3.1 Chemistry

The synthesis of the chalcones were carried out using the Claisen-Schmidt condensation reaction between substituted hydroxyl acetophenones and various susbstituted fluorobenzaldehydes. The mechanism for this reaction is explained in detail in chapter 1. The reaction involves four steps; firstly the formation of an enolate ion using aqueous sodium hydroxide [10% (m/m) NaOH] in ethanol, secondly the nucleophillic attack on the carbonyl group of fluorobenzaldehyde by the enolate ion (also known as Aldol formation), thirdly the process of enolization and lastly the dehydration step which subsequently forms the chalcone (**II**).

II



Scheme 22 The mechanistic pathway for the formation of compound II

3.1.1 The hydroxyfluorinated chalcones

The yields obtained for the hydroxyl fluorinated chalcones **II-IX** were between 70-90 % (Table 4), with the exception of the two *meta* positioned fluoro derivatives whose yields were lower at 56 % and 54 % for **III** and **VII** respectively. In addition, **VII** took five days to complete. Thus, weakly deactivating substituents on the aromatic aldehydes render the carbonyl carbon of the aldehyde less reactive than substitution at the *ortho* and *para* positions. The best yield was obtained by 2'-fluoro-3-hydroxychalcone (**VI**) of 90 % although taking twice as long to achieve it, and 2'-fluoro-2-hydroxychalcone (**II**) also had a high yield (80 %) in half the time. This may be due to the inductive effects of fluorine, withdrawing electron density from the aldehydic carbon and increasing its reactivity. Compounds **V** and **IX**, with two fluorine atoms also showed high yields of 84 % and 81 % respectively. The fact that the *meta* positioned fluorine atoms diminished reactivity of the benzaldehydes indicates that there must be some electronic factor associated with it, since the *para* fluoro derivatives were also synthesized in good yields of 73 % and 81 %.

In general, the 3-hydroxyfluorinated derivatives took longer to reach completion (48-120 hrs) than the 2-hydroxyfluorinated chalcones, which all reacted in 24 hrs. An exception was the difluorinated 3-hydroxychalcone which reached completion in 24 hrs. This suggests that hydroxy substitution at the 2-position of the acetophenone renders it a better nucleophile than substitution at the 3-position.

In general, the rate of reaction decreased in the order of 2',4'-difluoro > 2'-fluoro > 4'-fluoro > 3'-fluoro substitution with regard to fluorine substitution on the phenyl ring B and 2-OH > 3-OH with regard to hydroxyl substitution on the phenyl ring A. This relationship is consistent with

previous investigations on rate studies between analogues of variously substituted chalcones (Clayden e*t al*., 2007; Gasull *et al*., 2000).

Table 4 The percentage yields and melting points of the compounds synthesised

No.	Reaction time (hrs)	% Yield	M.p. (°C)	Literature m.p. (°C)
(**II**)	24	80	81-82	82-83 (Ivkovic *et al*., 2013)
(**III**)	24	56	107-108	109-110 (Dias *et al*., 2013)
(**IV**)	24	73	118-120	84-88 (Ivkovic *et al*., 2013)
(**V**)	24	84	115-116	46-48 (Singh *et al*, 2011)
(**VI**)	48	90	118-120	-
(**VII**)	120	54	91-93	-
(**VIII**)	72	81	127-128	135-136 (Butcher *et al*., 2007)
(**IX**)	24	81	112-113	-
(**X**)	72	64	78-82	147-148(Kavala *et al*., 2012)
(**XI**)	48	72	92-93	-
(**XII**)	3	86	108-110	79-80 (Chen *et al*., 2011)
(**XIII**)	24	70	97-98	-
(**XIV**)	24	82	-	*
(**XV**)	24	60	-	*
(**XVI**)	24	63	-	*
(**XVII**)	24	74	54-55	*
(**XVIII**)	24	66	56-57	*
(**XX**)	24	68	51-52	*

(**XIX**)	24	75	69-72	*
(**XXI**)	24	71	76-77	*

*Eight Novel compounds.

In order to make the 2-hydroxychalcones, an extra protection step was needed as attempts to make the 2-hydroxychalcones under the same basic conditions as that used for the synthesis of the 3-hydroxychalcones resulted in the flavanones being formed (discussed below). In order to prevent cyclisation from occurring, the 2-hydroxy group was protected using dihydropyran as a protecting agent. The protection was carried out using pyridinium *p*-toluene sulfonate as a mild base in methylene chloride with refluxing at room temperature for 15 minutes.

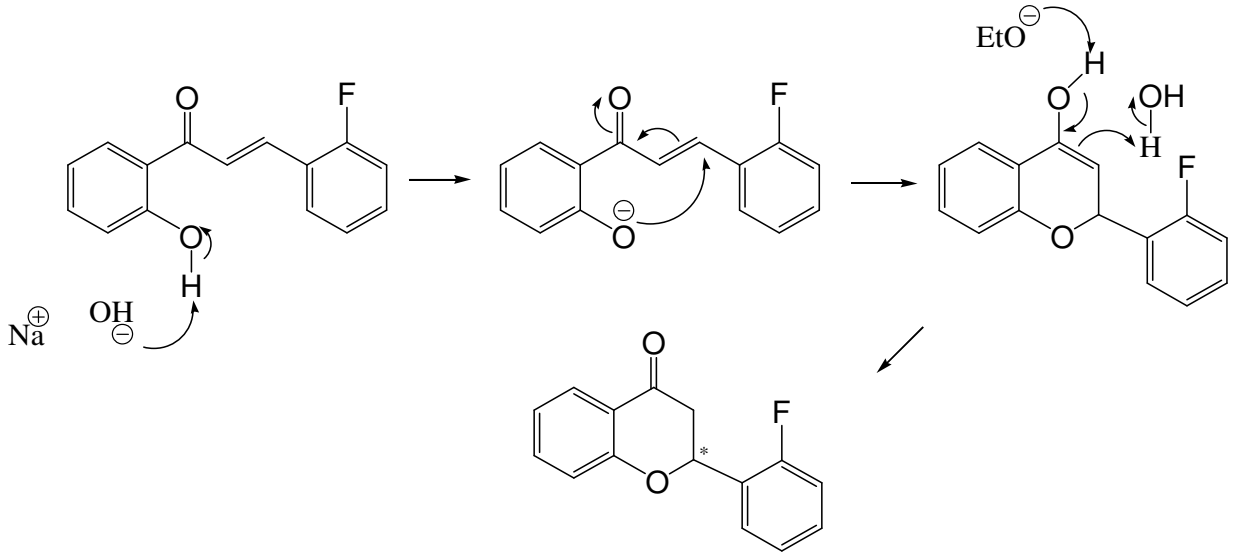
The protected acetophenone product that formed was reacted with various substituted fluorobenzaldehydes using barium hydroxide octahydrate in methanol [$Ba(OH)_2.8H_2O$/MeOH] as opposed to sodium hydroxide in ethanol used previously. The protected chalcones were de-protected using toluene sulfonic acid producing chalcones **II-V**. The completion of the condensation reaction between the protected acetophenone and various fluorobenzaldehydes needed just 24 hrs for all compounds. This reaction time was significantly shorter than the synthesis of the 3-hydroxychalcones using sodium hydroxide in ethanol (NaOH/EtOH). The use of barium hydroxide octahydrate in methanol [$Ba(OH)_2.8H_2O$/MeOH] may be a more efficient base in the synthesis of chalcones and protection of the free hydroxyl groups may also add to the increase in the rate of reaction.

The melting points of all the fluorinated hydroxyl chalcones ranged between 80-130 ºC, with the majority melting between 105-120 ºC. The melting points of **IV**, **V** and **VIII** did not compare well with literature (Ivkovik *et al.*, 2013, Singh *et al.*, 2011, Butcher *et al.*, 2007). We have

checked the melting point twice and proved the structure by means of NMR analysis below and are confident in our findings.

3.1.2 The fluorinated flavanones

The starting material 2-hydroxyacetophenone was treated in the same manner as 3-hydroxacetophenone in an attempt to synthesize various fluorine substituted 2-hydroxychalcones. However under the same basic conditions cyclization took place and instead the flavanone derivatives, compounds **X** to **XIII** were produced. The process of cyclization is common for chalcones containing a hydroxyl moiety on the 2-position of the A-ring. The mechanism of this process is explained in detail in chapter 1. The base responsible for removing the alpha proton of acetophenone also abstracts the proton of the hydroxyl group. The negatively charged oxygen atom acts as a nucleophile and reacts with the neighboring double bond of the α,β unsaturated carbonyl system of the chalcone. As a result, cyclization occurs to produce a racemic mixture of both *R*- and *S*- flavanones which was confirmed by optical rotation studies. Cyclization of compound **II** into the flavanone derivative **X** is shown below.



X

Scheme 23 The cyclization of compound II into its flavanone derivative X

Previous investigations show under similar conditions chalcones have been obtained without the process of cyclization. Furthermore, the process of cyclization is generally carried out with an additional reaction step (French *et a*l., 2010; Akcok and Cagˇır, 2010; Safavi *et al*., 2012). In this work, cyclization occurs simultaneously in a concerted mechanism. The percentage yields which were as high as 86 % corresponded with those reported in literature. Reaction times and yields were influenced by the variation in the position of the fluorine atom on the B-ring. The *para* fluoro flavanone formed in just 3 hrs whereby the *ortho* fluoro derivative formed in 3 days. The *o*,*p*-difluoro flavanone formed in 24 hrs. Thus, substitution of fluorine at the *para* position seems to increase the rate of reaction probably due to conjugation through the three ring system and its ability to form several stable resonance structures compared to the other substitution patterns.

The melting points of the flavanones **X-XIII** were all lower than their corresponding chalcones, possibly due to less intermolecular interaction since the three carbon chain, which was present in chalcones is now cyclized in the flavanones. This indicates that the chalcone skeleton allows for greater intermolecular interactions than the flavanones, the melting points of which range between 78-110 ºC.

3.1.3 Prenylation

Chalcones **II** to **IX** were prenylated with prenylbromide and ignited potassium carbonate as base in acetone for 24hours. Prenylation occurred at the oxygen atom of the hydroxyl groups for both 2- and 3-hydroxychalcones. All prenyl chalcones were synthesized in yields between 60-82 % (Table 4).The rate of prenylation was not affected by the position of the hydroxyl groups on the A-ring nor the electronic influence of the fluorine atoms on the B-ring since there was no significant difference in yields between the 2-oxyprenyl and 3-oxyprenylfluorinated chalcones.

The melting points of the prenyl chalcones were significantly lower than either the free hydroxy chalcones or the flavanones synthesized thereof. Compounds **XIV-XVI**, the two oxyprenyl chalcones with a mono substituted fluorine at either the *ortho*, *meta* or *para* position were all obtained as oils. The remainder of the chalcones melted between 50-77 ºC. This is because there are more intermolecular hydrogen bonds with the hydroxy derivatives than with the prenyl derivatives.

3.1.4 Physical appearance

Overall all chalcones appeared as different shades of yellow. The 2-hydroxychalcones appeared more deeply colored as opposed to the 3-hydroxychalcones probably due to the increased conjugation with the hydroxyl group in the *ortho* position. The prenylated derivatives appeared in the form of yellow oils with the exception of the difluoro derivative, which was a yellow solid. The flavanones appeared as green colored crystalline solids..

3.2 Characterization

3.2.1 Ultra-violet (UV) spectroscopy

All the chalcones (**II-V**) showed major absorptions in the range of 305-320 nm. This absorbance was a result of conjugation ofthe α,β-unsaturated carbonyl system with the aromatic B-ring. These values corresponded with those of literature as well as with other structural analogues (Matsushima and Kageyama, 1985; Pinheiro and Justino, 2012). The prenylated chalcones (**XIV-XXI**) showed major absorption bands at slightly lower values (approximately 300 nm)at a similar peak intensity to the non-prenylated chalcones. The flavanones (**X-XIII**) had their first absorption band at the lower end of the UV spectrum between 240-260 nm. Their absorbance values were within the expected range of 240–285 nm (Pinheiro and Justino, 2012). Their respective peaks appeared sharp in nature with relatively high intensities as compared to the prenyl and non-prenyl chalcones. Their second bands appeared much shorter and broader at around 330 to 340 nm.Based on this observation, it was possible to differentiate and distinguish the flavanones from the prenyl and non-prenyl chalcones. This can be seen in Figure 17 using compounds **II**, **X**, and **XIV** as examples. The various substitution patterns of the fluorine atom had no significant effect on the nature of absorbance in all compounds.

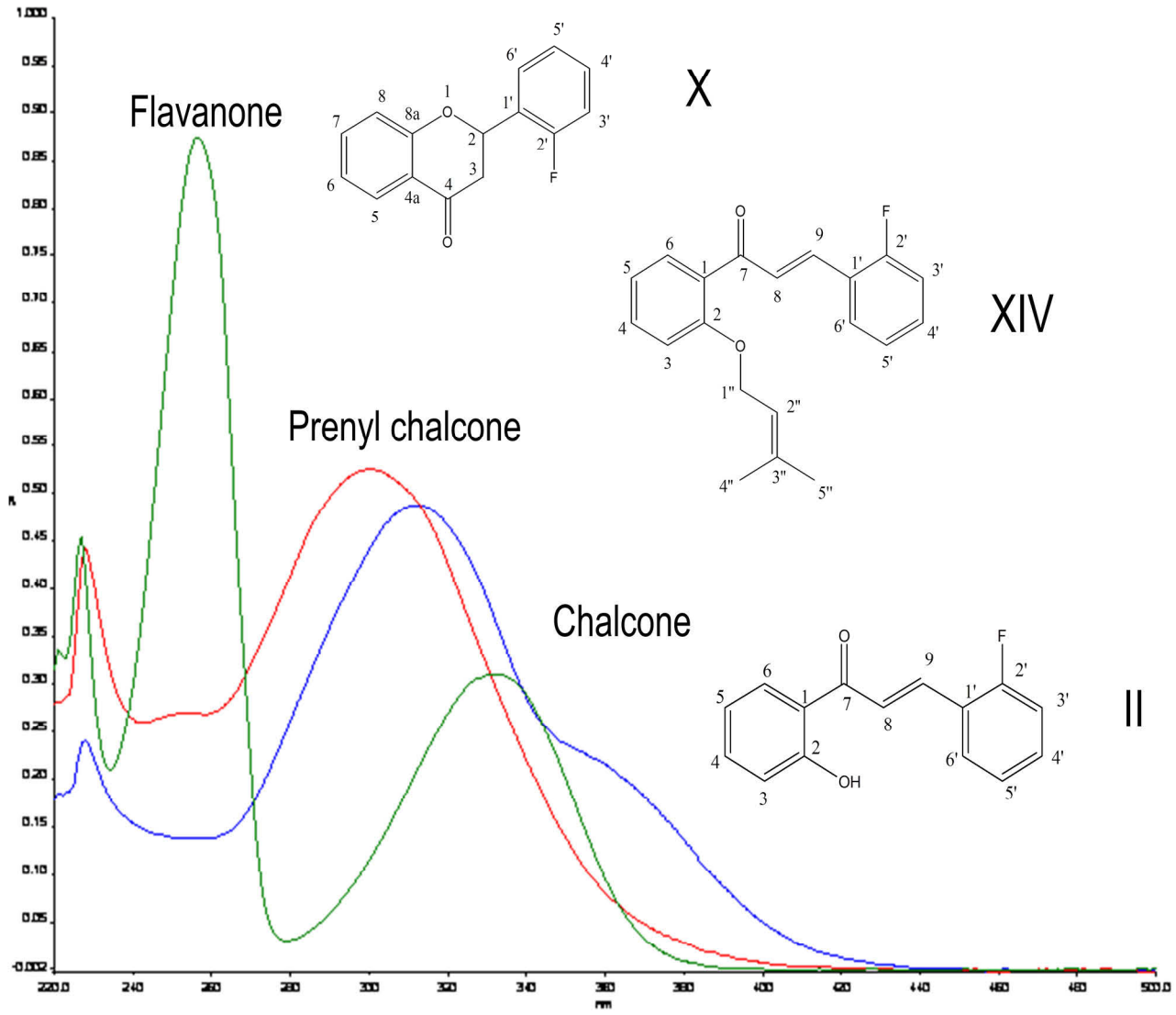


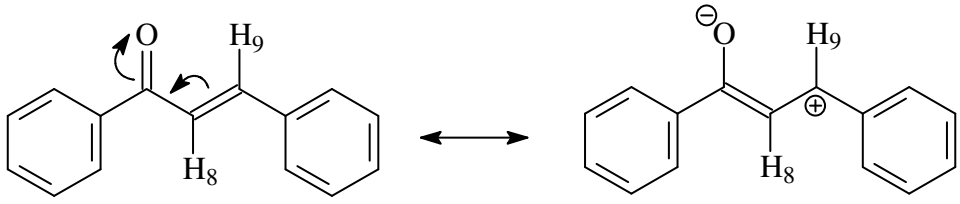
Figure 17 Comparison in peak absorbance between compounds II, X and XIV

3.2.2 Infra-Red (IR) spectroscopy

Infra-red spectroscopy was used to identify the presence of different functional groups in all the compounds. The infrared spectra of chalcones **VI** to **IX** showed broad peaks with small intensities between 3300 to 3400 cm^{-1}. This was typical for the presence of free hydroxyl groups (-OH). However, the 2-hydroxychalcones (**II-V**) did not show this as distinctly as the 3-

hydroxychalcones, possibly because of hydrogen bonding to the carbonyl group. In the flavanones (**X-XIII**) and the prenyl chalcones (**XIV-XXI**), the disappearance of the O-H stretching band confirmed their successful formation.

The carbonyl stretching bands in the chalcones occur in the range of 1665 to 1650 cm^{-1} which is indicative of a conjugated unsaturated ketone system resulting in more single bond character and lower wavenumbers (Scheme 24). The carbonyl stretching frequency of the flavanones (with the exception of the 3'-fluoro derivative) occurred at an even lower frequency range at approximately1630 cm^{-1} for three of the compounds probably due to an increase in single bond character in the benzopyran system. The 3-fluoro flavanone derivative showed a C=O stretching band at 1688 cm^{-1}.

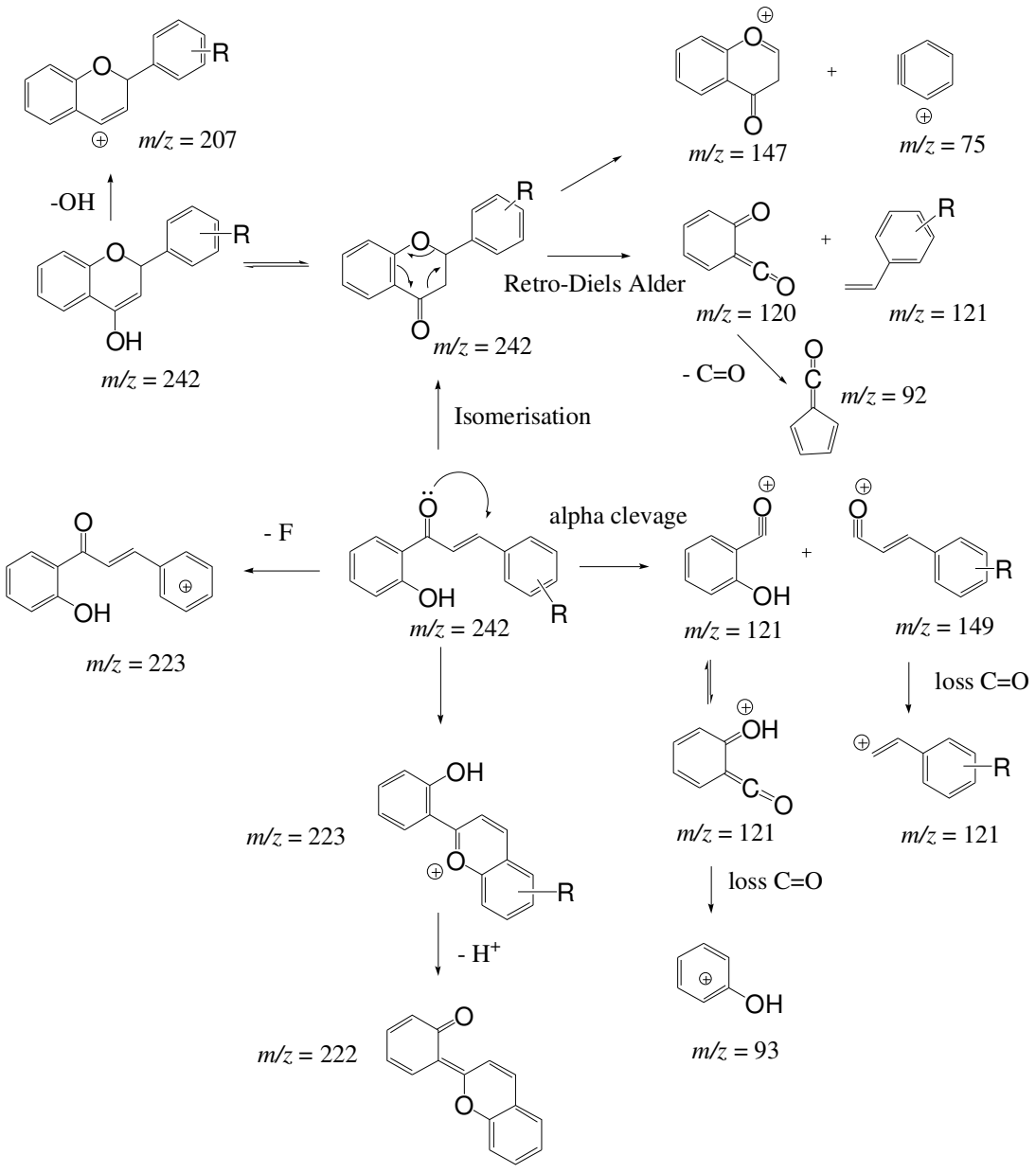


Scheme 24 The electron distribution between the double bond and carbonyl carbon

3.2.3 Mass spectrometry (MS)

The mass spectra of all compounds showed similar fragmentation patterns. The molecular ion peak was observed for all molecules and the fragmentation pattern followed one of two pathways, either alpha cleavage or a Retro Diels Alder fragmentation. In the case of the 3-hydroxychalcones and their prenyl derivatives, **VI-IX** and **XVIII-XXI**, these compounds underwent alpha cleavage on both sides of the carbonyl carbon to produce characteristic peaks at *m/z* = 149 and *m/z* = 121. In the case of the 2-hydroxychalcones and their prenyl derivatives, **II-**

V and **XIV-XVII**, alpha cleavage did not occur as expected; instead thermal isomerization took place in the GC converting these compounds into their respective flavanones before undergoing Retro Diels Alder cleavages to give characteristic peaks at *m/z* = 120 and *m/z* = 92. The only difference the prenyl chalcones have in comparison to their non-prenyl derivatives is the presence of a mass peak at *m/z* = 69, which accounts for the fragmentation mass of the prenyl moiety. However, common to all mass spectra is the loss of 19 mass units which is a result of the loss of a fluorine atom implying that the fluorine atom is very labile (Scheme 25).



Scheme 25 The general fragmentation pathway for chalcones (values refer to R = F)

3.3 Nuclear-Magnetic Resonance (NMR) spectroscopy

3.3.1 Characterization of compounds II to IX (chalcones)

*Identification of intermediate **I***

The Claisen-Schmidt condensation of 2-hydroxyacetopheone with fluorobenzaldehyde required the protection of the 2-hydroxy group to prevent cyclization to the flavanone. The intermediate **I**, was identified by the overlap of methylene protons (-CH_2) in the ^{1}H NMR spectrum at δ_H1.90-1.40 (m, 6H, H-2'/3'/4'). These protons indicate the attachment of the THP moiety on the oxygen atom to C-2, appearing in the ^{13}C NMR spectrum at δ_C 162.3. In the carbon spectrum, the carbon resonance C-5' at δ_C 62.9 is typical of a C-O bond and the C-1' resonance at δ_C 94.5 typical of an acetal carbon resonance. There are five carbon resonances in the ^{13}C NMR spectrum assigned to the aromatic ring as well as a deshielded carbon resonance at δ_C 204.6 indicative of a ketone group at C-7. This information was sufficient to confirm the protection of 2-hydroxyacetophenone with a THP group.

*Identification of the α,β-unsaturated carbonyl system in **II***

The two olefinic *trans* protons of compound **II** are characterized by the presence of a large coupling constant of 15.6 Hz which is seen at both δ_H 8.01 and δ_H 7.80. A carbonyl resonance is also seen at δ_C 193.9 (C-7) in the ^{13}C NMR spectrum. HMBC correlations between both H-8 and H-9 with that of the carbonyl resonance C-7, indicate the presence of an α,β-unsaturated carbonyl system. Delocalisation of electrons amongst the three carbon atoms of C-7, C-8 and C-9, resulted in the C-9 carbon resonance being more dieshielded than C-8. Hence C-9 was allocated to δ_C 138.3 and C-8 to δ_C 122.9 in the ^{13}C NMR spectrum. The H-8 and H-9 proton

resonances were then identified by HSQC correlations with the respective doublets and *J* values of 15.6 Hz.

Structural elucidation of the A-ring in ***II***

There are two aromatic rings present in the structure of compound **II**. The first one being adjacent to the carbonyl group of C-7 and the other which is a fluorinated aromatic ring, adjacent to the unsaturated double bond at Δ^8 (the C-8/9 double bond). The ring closest to the carbonyl group (ring A) shows four aromatic resonances at δ_H 6.98 (t, *J* = 7.5 Hz, 1H), δ_H 7.05 (d, *J* = 8.0 Hz, 1H), δ_H 7.54 (td, *J* = 8.6 Hz, 1.5 Hz, 1H) and δ_H 7.94 (dd, *J* = 8.0 Hz, 1.0 Hz). The electron donating effect of the lone pairs on the oxygen atom of the hydroxyl group at C-2 result in the *ortho* and *para* positions being more shielded than the *meta* position. Hence, the doublet at δ_H 7.05 was attributed to H-3 and the triplet at δ_H 6.98 to H-5. Furthermore, the triplet of H-5 arises due to adjacent coupling with both H-4 and H-6.

The *meta* protons at both δ_H 7.94 (H-6) and 7.54 (H-4) are more deshielded. The triplet of doublets observed for H-4 is as a result of adjacent coupling to both the protons of H-5 and H-3 as well as the *meta* coupling to the proton at H-6 (*J* = 1.5 Hz). Similarly, the double doublets of H-6 are as a result of adjacent coupling to H-5 and *meta* coupling to H-4. HMBC correlations between C-7 and H-6, and between C-2and H-4, were used to confirm the assignment of H-6 and H-4 respectively.

Structural elucidation of the B-ring in ***II***

The second aromatic ring (ring B), which is closest to the double bond, shows four aromatic protons resonances. The *ortho* and *para* positioned protons appeared more shielded with respect to the fluorine atom at C-2 due to electron donation. The proton at δ_H 7.24 appeared as a triplet (*J* = 7.6 Hz) and is assigned to H-5' due largely to coupling with the adjacent protons H-4' and H-6'. The double doublet on the other handseen at δ_H 7.17 (*J* = 10.5 Hz, *J* = 8.0 Hz, 1H) was assigned to H-3' due to coupling with the neighbouring H-4' (*J*= 8.0 Hz) and also with the fluorine atom (*J* = 10.5 Hz). The protons *meta* to the fluorine atom,H-6' and H-4' appeared more downfield as a triplet of doublets at δ_H 7.67 (*J* = 8.5 Hz, 1.5 Hz, 1H) and multiplet at δ_H 7.48-7.43 respectively with the triplet of H-6' arising as a result of *ortho* coupling to H-5', and *meta* coupling to the F atom and H-4', the *ortho* coupling and the *meta* coupling to F having the same coupling constant, resulting in the triplet as coalescence of the double doublet resonance.

The fluorinated and oxygenated aromatic carbon resonances appeared at δ_C 163.7 for C-2 and as a doublet at δ_C162.8 with a large coupling constant value of *J* = 255.3 Hz for C-2'. The *ortho* positioned C-3' carbon resonance relative to the fluorine atom appeared as a doublet with a coupling constant of *J* = 22.0 Hz; the *meta* positioned resonances C-4' and C-6' occur at δ_C132.2 (d, *J* = 8.8 Hz) and at δ_C 130.2 (d, *J* = 2.9 Hz) respectively; and the carbon *para* to fluorine occured at δ_C 124.6 (d, *J* = 3.7 Hz).

*Identification of quaternary carbons, C-1 and C-1' in **II***

TheH-5' and H-8 proton resonances show HMBC correlations to a tertiary carbon at δ_C 122.7 which seems to overlap with the carbon resonance assigned to C-8. This resonance was therefore assigned to C-1' with the remaining tertiary carbon resonance at δ_C120.0 assigned to C-1. The ^{1}H and ^{13}C NMR resonances of compound **II** matched those reported from literature (Ivkovic *et al*., 2013).

*Comparison of compound **II** with **IV** (the para substituted fluoro derivative)*

In compound **IV** the fluorine atom in this case is in the *para* position on the B-ring. In the absence of an NMR active atom, there should be a pair doublets for the protons, H-2'/6' and H-3'/5'. However since fluorine is NMR active, H-3'/5' is split by both the fluorine atom and the protons H-2'/6' with similar coupling constants appearing as a triplet, which is actually a coalesced double doublet at δ_H 7.06 (J = 8.5 Hz). The H-2'/6' resonance is also coupled to fluorine in addition to H-3'/5'. The signal appears as an expected double doublet at δ_H 7.60 (J = 8.5 Hz, 5.0 Hz). The coupling constant values of J = 8.8 Hz and J = 22.0 Hz for the carbon resonances of C-2'/6' at δ_C 130.6 and C-3'/5' at δ_C 116.2 respectively, confirmed the assignment of these particular resonances. Furthermore, HMBC correlations showed coupling between the protons H-2'/6' with the olefinic carbon C-9, which further confirmed the assignment of these resonances.

*Comparison of compound **II** with **V** (the o,p-difluorinated derivative)*

In the difluorinated compound **V**, the H-3' and H-5' proton resonances overlaped with H-5 as a multiplet at δ_H 6.90 to 7.00. The H-6' resonance however appeared as a doublet of triplets since it couples with the adjacent H-5' proton as well as with both the fluorine atoms, (J = 8.5 Hz, 6.5 Hz). The doublet of triplets can be difficult to see as both resonances overlaped and to distinguish the two triplets the first, third and fifth peaks resemble the first triplet and the second, fourth and sixth peaks resemble the other doublet.

Both the C-2' and C-4' carbon resonances occurred as double doublets with J = 242.8 Hz and J = 12.5 Hz for C-2', and J = 245.8 and 12.5 Hz for C-4' at δ_C 165.2 and 160.5 respectively. The C-3' carbon resonance appeared as a triplet at δ_C 105.0 with a J value of 25.7 Hz as it couples with both fluorine atoms equivalently. However, since carbons C-5' and C-6' couple with each fluorine atom non-equivalently, each of these signals appear as pairs of double doublets at δ_C 131.5 (J = 9.5 Hz, 4.4 Hz) and at δ_C 112.3 (J = 22.1, 3.7 Hz). The remaining C-1' carbon resonance appeared at δ_C 119.3 (J = 10.9 Hz, 3.7 Hz).

*Comparison of the A-rings of compound **II** with **VI** (the 3-hydroxychalcone)*

When comparing the A-ring of the 2-hydroxychalcones for e.g. compound **II** against the 3-hydroxychalcones e.g. compound **VI**, it can be seen that the *ortho*/*para* carbon resonances of C-2, C-4 and C-6at δ_C 121.0, 120.7 and 115.2 respectively all appear more shielded than the *meta* carbon resonances of C-5 at δ_C 129.9 and C-1 at δ_C 139.3. This is due to electronic effects of the

3-hydroxy group which were consistent with compound **II** that was discussed earlier; where C-3 and C-5 were more deshielded than their *meta* positioned C-4 and C-6 carbon resonances. Further to this, the *meta* positioned C-1 of compound **VI** occurs at δ_C 139.3 also due to the electronic effects discussed earlier as opposed to C-1 in compound **II** which resonated at δ_C 120.0 and was also *ortho* positioned to the hydroxyl group.

Cross correlations in the HSQC spectrum indicate that the protons H-4 and H-6 are more deshielded than H-5. This pattern is unusual as these resonances were expected to appear more shielded than H-5 due to their *ortho*/*para* nature. This could probably be due to through space interactions between the oxygen atom of the 3-hydroxy group with the carbonyl oxygen of at C-7. However there is no conclusive evidence for this type of relationship. On the contrary, the H-2 proton resonance as expected appeared more shielded at δ_H 7.10-7.18 in the ^{1}H NMR spectrum. These values were consistent with those reported from literature (See Table 1).

3.3.2 Characterization of compounds X to XIII (flavanones)

Formation of the flavanone derivative, compound **X** in this particular case, was indicated by the resonances of the deshielded H-2 proton doublet at δ_H 5.65 (J = 9.28 Hz, 1H, H-2). The protons H-3a and H-3b appeared at δ_H 3.50 (dd, J = 17.56 Hz, 3.76 Hz, 1H, H-3a) and δ_H 3.41 (dd, J = 17.56 Hz, 9.28 Hz, 1H, H-3b). Furthermore, the $J_{3a,3b}$ coupling constant values were established as J = 17.56Hz being the largest, the $J_{2,3b}$ = 9.28 Hz and the smallest $J_{2,3a}$= 3.76 Hz. In the case of $J_{2,3a}$, this splitting pattern was not seen for H-2. However, in compound **XII**, this pattern was

evident where H-2 was observed as a double doublet at δ_H 5.36 (J = 9.03 Hz, 3.01 Hz, 1H, H-2) (Figure 18).

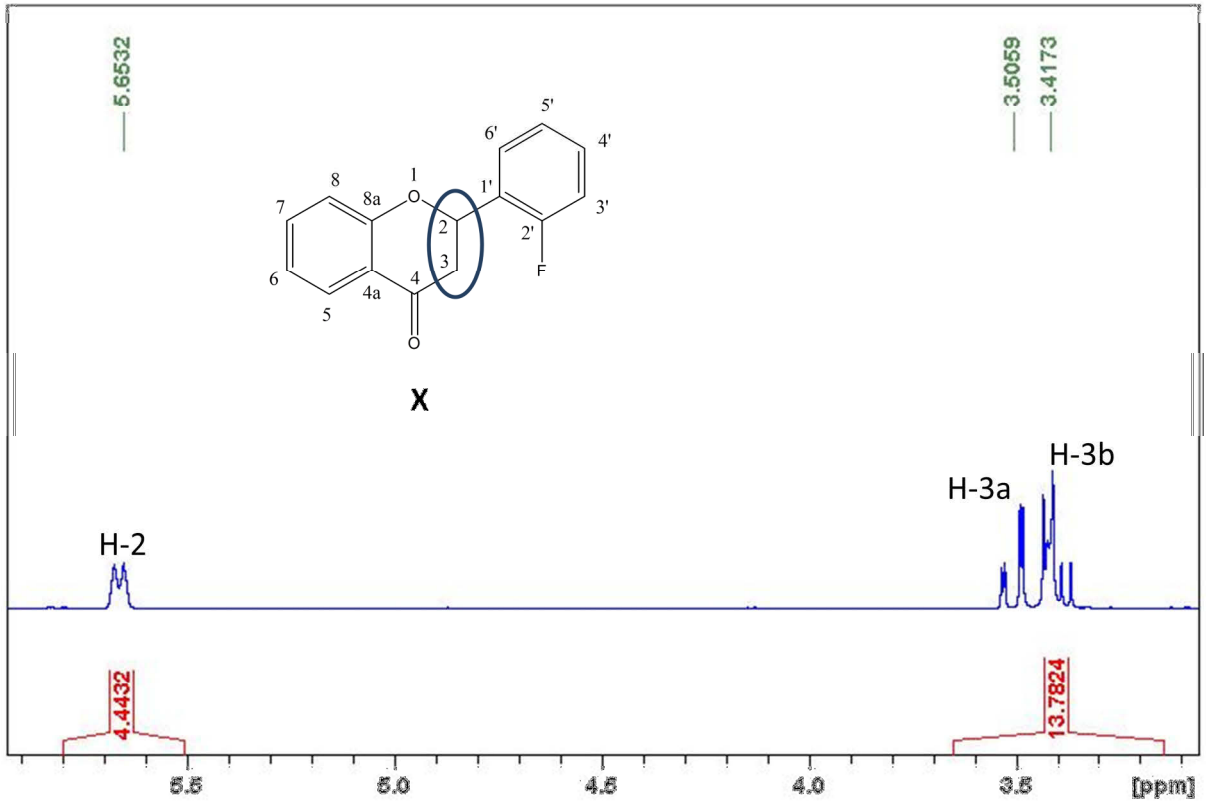


Figure 18 Expanded ^{1}H NMR spectrum of 2-fluoroflavanone (X)

Looking at the ^{13}C NMR spectrum, C-2 resonates at δ_C 64.2, C-3 at δ_C 45.7 and lastly the carbonyl carbon at δ_C 205.6. In general comparison to the chalcones, the carbonyl group of the flavanones appeared more deshielded much like that of a ketone. HMBC correlations between H-3a/3b and both C-2 and C-4 confirmed these assignments.

3.3.3 Characterization of compounds XIV to XXI (prenyl chalcones)

The formation of the prenyl chalcone, compound **XIV**, was indicated by the presence of the deshielded triplet of H-2" at δ_H 5.50 (J = 6.52 Hz, 1H), the doublet of H-1" at δ_H 4.63 (J = 7.0 Hz, 2H) and the presence of two singlet methyl peaks at δ_H 1.76 and 1.74 (Figure 19). The olefinic carbons, C-2" and C-3", at δ_C 119.3 and δ_C 138.8 respectively, which overlap with the aromatic carbon resonances in the ^{13}C NMR spectrum. The resonances of the oxygenated methylene carbon resonance and of both methyl carbons are more distinct at δ_C 65.6 (C-1"), 25.8 (C-5") and 18.3 (C-4"). The assignments of the above were supported by HMBC correlations seen between both the methyl proton resonances with C-2" and C-3". The methylene resonance, H-1" also showed HMBC correlations to C-2" and C-3" in addition to the oxygenated aromatic carbon resonance of C-2 at δ_C 157.9. Hence this relationship confirmed that prenylation had occurred at the oxygen atom. Moreso, NOESY correlations between H-2" and 3H-5" were used to distinguish the methyl resonance3H-5"from 3H-4". In addition, the methyl resonance 3H-4" also showed a NOESYcorrelations to the methylene protons 2H-1" to further support this argument.

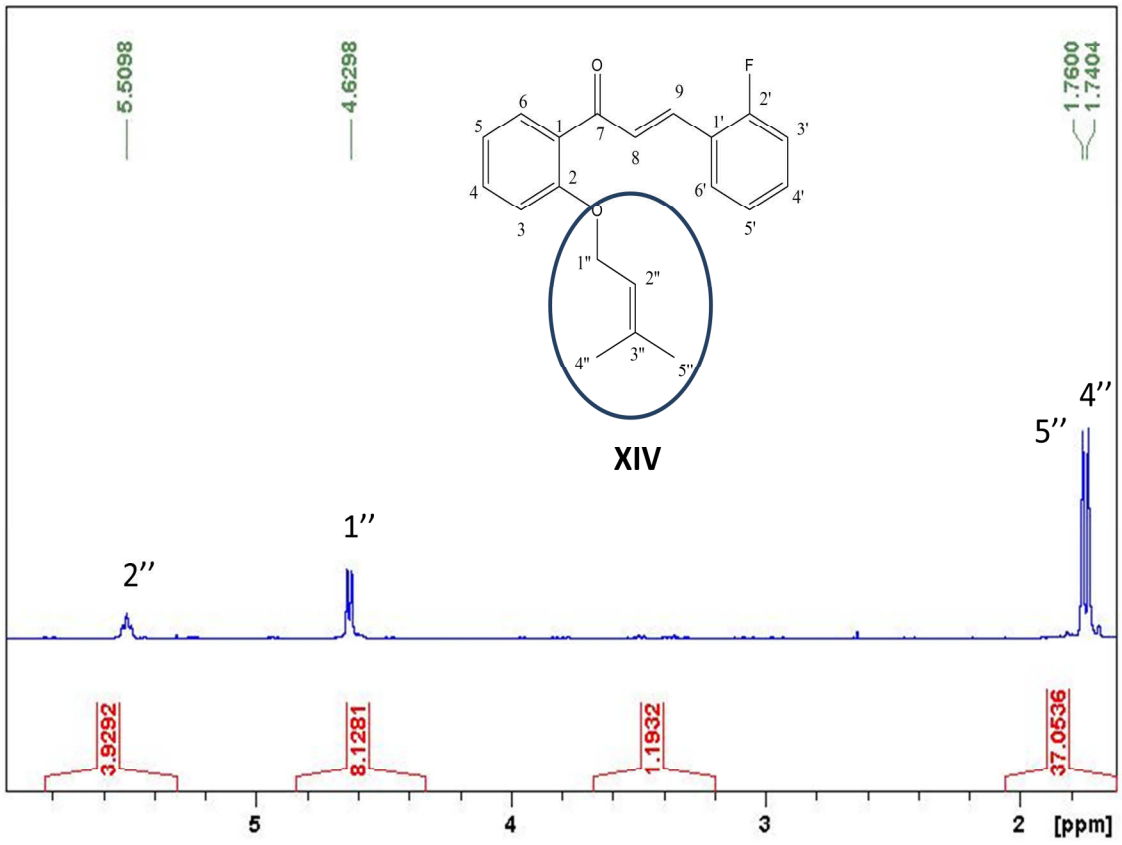


Figure 19 Expanded^{1}H NMR spectrum of 2'-fluoro-2-oxyprenylchalcone (XIV)

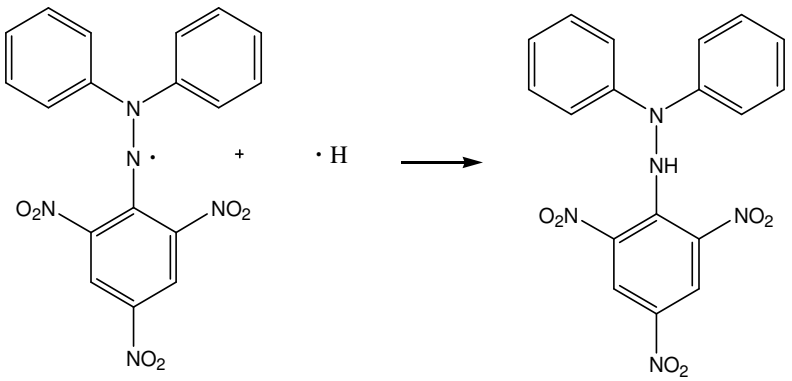
Chapter 4. Antioxidant study

4.1 Methodology for bioassays

There are several methods used for establishing the anti-oxidant activity of a compound. The most widely used include; 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging, ferric reducing anti-oxidant power (FRAP) and the nitric oxide radical assay.

4.1.1 DPPH radical scavenging assay

The simplest and most popular of the above mentioned methods is the use of the stable free radical (DPPH). DPPH is a stable free radical that is characterized by virtue of the delocalization of an extra electron over the entire molecule, which prevents dimerisation that occurs in most other free radicals (Molyneux, 2004). It is deep violet in color and as a result has a characteristic absorption band at approximately 517 nm in alcoholic solution. When DPPH is mixed in solution with a compound showing anti-oxidant potential, the DPPH molecule is reduced by accepting a hydrogen radical to form a stable DPPHH molecule. As a consequence a color change from deep violet to yellow is usually observed resulting in a decrease in absorbance and hence an increase in reducing ability (Patel and Patel, 2011). The reaction of this process is illustrated below:



Deep-violet Yellow

Scheme 26 The reaction of DPPH with a hydrogen radical to form DPPHH

Compounds containing hydroxyl groups are often considered most effective against oxidants and scavenging of free radicals. They are capable of donating hydrogen radicals that can react with DPPH. The donor molecules themselves are stabilized based on the resonance structures formed. This stability depends vastly on the surrounding substituents and moieties.

4.1.2 Ferric reducing anti-oxidant power assay

The FRAP assay is a robust, colorimetric method which uses antioxidants as reductants. The process is based on a redox reaction which measures the ability of a compound to reduce Fe^{3+} to Fe^{2+}. In the case of ferric chloride, a color change from dark green to blue is observed when mixed with a compound possessing anti-oxidant potential. The solution is measured at a wavelength of 700 nm where a strong anti-oxidant is indicated by a high absorbance value whereas the opposite is true for weak anti-oxidants (Selvakumar *et al*., 2011).

4.1.3 Nitric oxide radical assay

The free radical of nitric oxide is a constituent known to cause inflammation. It acts as a chromophore by reacting with oxygen containing compounds to produce nitrite ions which can be measured using a solution known as Griess reagent (Kankate *et al*., 2010). The radicals are generated from sodium nitroprusside in buffer saline solution at a pH of approximately 7.4 which reacts with a sample. The solution is measured at 546 nm where a decrease in absorbance accounts for compounds containing good anti-oxidant activity compared to that of a control sample (Umamaheswari and Chatterjee, 2000).

4.2 Antioxidant activity of chalcones II-IX using the DPPH assay

Research shows that the presence of hydroxy groups on molecules is responsible for anti-oxidant activity. Chalcones **II** to **IX** which possess hydroxy groups at either the 2-position or the 3-position were tested for their potential anti-oxidant activities using the stable free radical DPPH. A comparison in anti-oxidant activity of the various substituted fluorine containing 2-hydroxy and 3-hydroxychalcones was made to ascertain whether the fluoro groups substituted at different positions on the B ring would have an impact on the anti-oxidant activity. Ascorbic was used as a reference point since it is a good anti-oxidant and measurements were taken in triplicate.

*Scavenging ability of compounds **II** to **IX** in comparison to ascorbic acid*

The scavenging ability of compounds **II** to **IX** at donating a hydrogen to react which DPPH are shown in Table 5 and Figure 20. As expected, ascorbic acid shows excellent anti-oxidant activity over a wide concentration range. Moreso, it has good scavenging activity even at low concentrations (97.4% at 10 µg mL^{-1}). Hence, ascorbic acid served as an appropriate reference

material for comparison. Compounds **II** to **IX** showed moderate to low anti-oxidant activities compared to ascorbic acid even at high concentrations (500 µg mL^{-1}). The difference in activity can be rationalized by the fact that ascorbic acid has two hydroxyl groups present in its structure in the form of a catechol moiety unlike chalcones **II** to **IX** which only contain one hydroxyl group. Compounds with a catechol moiety are known to possess potent antioxidant activity.

The efficiency of the DPPH assay is dependent on the donation of a hydrogen (H) radical by a compound together with its reactivity with DPPH to form the DPPHH molecule. Thus, the more hydrogens a compound can donate, the greater the extent of the reaction with DPPH. The constraint is that the radical must be able to be stabilized by delocalization on the aromatic ring. The catechol moiety is the ideal structure that is capable of losing a hydrogen atom and at the same time being able to stabilize the resultant radical (Murti, *et al*., 2013).

Table 5 DPPH free radical scavenging activities of compounds II-XI

	Scavenging activity (%)				
Compound	**500 µg mL^{-1}**	**250 µg mL^{-1}**	**100 µg mL^{-1}**	**50 µg mL^{-1}**	**10 µg mL^{-1}**
Ascorbic acid	97.6±0.12	97.8±0.19	97.6±0.09	97.5±0.2	97.4±0.18
II	36.0 ±0.03	34.7±0.2	37±0.12	36.6±±0.03	37.6±0.14
III	27.5±0.06	28.9±0.1	29.5±0.15	28.8±0.06	27.0 ±0.16
IV	43.7±0.09	44.1±0.05	44.9±0.05	44.7±0.09	43.7 ±0.01
V	45.1±0.03	44.8±0.02	44.1±0.05	44.6±0.03	44.0 ±0.11
VI	29.2±0.13	30.6±0.12	29.3±0.09	24.0 ±0.03	29.0 ±0.12
VII	39.3±0.25	37.8±0.18	40.0 ±0.01	38.0 ±0.13	38.0 ±0.08
VIII	45.2±0.01	45.4±0.2	45.3±0.08	44.7±0.12	45.0 ±0.12
IX	45.1±0.05	45.8±0.14	45.2±0.21	44.7±0.14	45.1±0.21

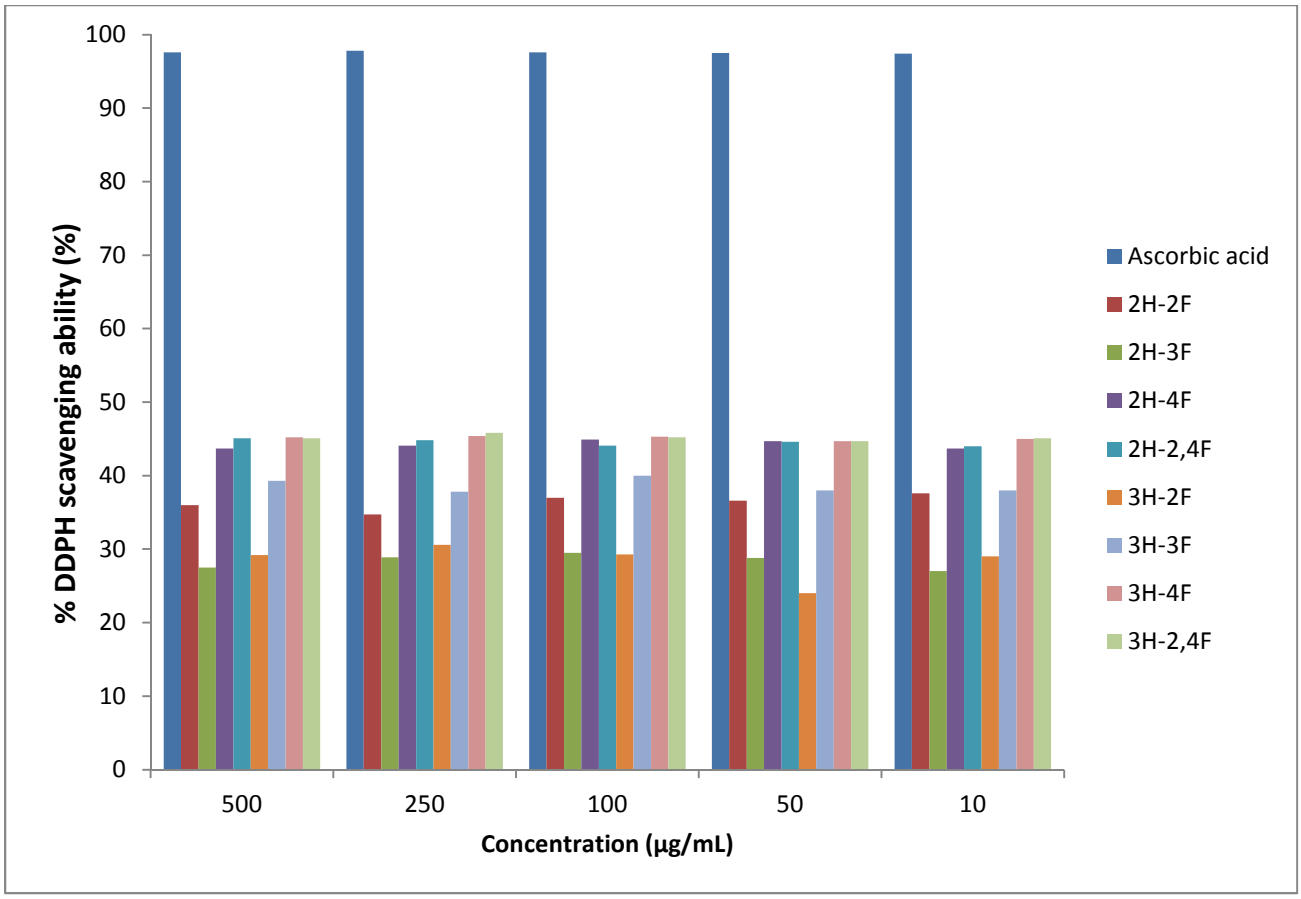


Figure 20 The scavenging ability of compounds II to IX in comparison to ascorbic acid at various concentrations

*Comparison of scavenging ability between compounds **II** to **IX***

The difluoro-compounds **V** and **IX** both showed the highest anti-oxidant activities amongst all compounds tested, with an average absorbance of 43.7% and 45.1% respectively at 500 µg mL^{-1}. These compounds contain fluorine atoms on the both *ortho* and *para* positions of the B-ring. This is followed by the 4-fluoro substituted compounds **IV** and **VIII**, which has approximately the same activity as **V** and **IX**. The lowest anti-oxidant activity was shown by the 2-hydroxy *meta* substituted fluoro derivative **III** and the 3-hydroxy *ortho* substituted derivative **VI**. The

ortho fluoro-2-hydroxychalcone (**II**) and the *meta* fluoro-3-hydroxychalcone (**VII**) showed activity in between that of **IV/V/VIII/IX** and **III/VI**.

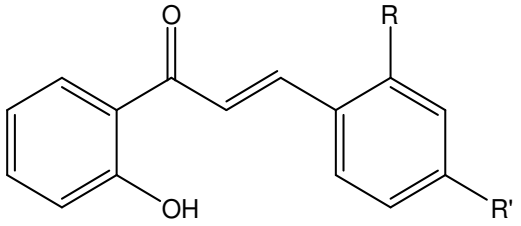
This is indicative that the 2',4'-difluoro and the 4'-fluoro chalcones are best able to stabilize the radical that results upon loss of a proton. The 2'-fluoro and the 3'-fluoro chalcones are not capable of stabilizing the radical as much and hence has the weakest anti-oxidant potential.

*Comparison of scavenging ability between compounds **II** to **IX** with analogues from literature*

Structural analogues of chalcones **II-IX** have been synthesized previously and structure activity studies carried out to determine which substitution patterns provide the best anti-oxidant activity. Previous studies show that having a hydroxyl group in the *ortho* position of the A-ring is more favorable in terms of anti-oxidant activity as opposed to a hydroxyl group in the *meta* position (Xue *et al*., 2013).

The 2-hydroxy-2'-methoxychalcone (**26**) (Figure 21), did not show DPPH activity at 50 µg mL^{-1} even after 60 minutes of reaction (Detsi *et al*., 2009). However, 2'-fluoro-2-hydroxychalcone (**II)** in this study showed 36.6 % scavenging ability at the same concentration in half the amount of reaction time, indicating that fluorine is somehow able to stabilize the resultant radical when loss of a hydrogen atom occurs better than the methoxy group. This could also be due to the electronegative properties of the fluorine atom compared to the electon donating methoxy group. In comparing 4'-chloro-2-hydroxychalcone (**27**) with 4'-fluoro-2-hydroxychalcone (**IV**), the

activity of the two compounds were similar with **27** showing 40.8% as opposed to 44.9% for **IV** (Detsi *et al*., 2009).



26. R = OCH_3 R' = H
27. R = H R' = Cl

Figure 21 The molecular structures of compounds (26) and (27)

The potential of the difluoro chalcones **V** and **IX** as promising antioxidants can be further investigated as possible lead compounds in antioxidant activity even though they are not as potent as ascorbic acid. In particular, **V** and **IX** may have other beneficial uses as pharmaceuticals, for example as anti-inflammatory drugs and therefore combining the two effects in one drug can be very beneficial. Substitution of di, tri and polyhdroxy groups on the A-ring may enhance activity as previous investigations of similar compounds suggest hydroxyl groups are the main components responsible for antioxidant activity, particularly on the A-ring.

Chapter 5. Conclusion

A series of twenty flavonoid compounds **II-XXI** were synthesized using the Claisen-Schmidt condensation reaction. The base-catalyzed (NaOH/EtOH) reaction between 3-hydroxyacetophonone and various substituted fluorobenzaldehydes led to the formation of chalcones **VI-IX**, however under the same conditions, the 2-hydroxyacetophenone precursors resulted in flavanones **X-XIII**, which were also characterised. In order to synthesize the 2-hydroxy fluorinated chalcones, dihydropyran was shown to be a good protecting agent for 2-hydroxyacetophenone to protect the 2-hydroxy group and prevent a nucleophilic ring closure catalyzed by abstraction of the proton from the hydroxy group. It was also shown that the base-catalyzed $Ba(OH)_2$ reaction in methanol with fluorobenzadehyde(s) led to the successful formation of chalcones **II-V**. All chalcones were subjected to prenylation (**XIV-XXI**) under basic conditions using prenyl bromide and the reaction worked well with the chalcones and subsequent to chalcone formation rather than reacting the acetophenone with prenyl bromide prior to the condensation reaction.

The yields of all compounds were recorded between 54 to 90 % and reaction times were reported to have occurred as fast as 3 hours with the majority of reactions occurring in 24 hrs with some reactions taking 3-5 days. The reaction times for **II-XIII** were shown to be dependent on the substitution patterns of fluorine in the B-ring. The rate of reaction was highest with the presence of two fluorine atoms, at the 2' and 4' positions of the B-ring, followed by the 2'-fluoro, 4'-fluoro and 3' fluoro substitutions. Similarly, percentage yields were affected in the same manner.

All compounds were successfully characterized by 1D and 2D NMR, IR, UV spectroscopy and GC-MS. The structures of the eight novel compounds, **XIV** to **XXI**, were further characterized by HRMS to determine their exact masses. All known compounds and their values corresponded well with those reported in literature.

Anti-oxidant activities of chalcones **II** to **IX** was carried out using the DPPH radical scavenging assay and the compounds showed moderate to low anti-oxidant activities in comparison to the standard, ascorbic acid. In comparison to each other, both difluoro chalcones, **V** and **XI**, showed the highest activities largely due to the electronic nature of the fluorine atom which is strongest at the *ortho* and *para* positions of the B-ring. The anti-oxidant activity was shown to decrease in the order *ortho* and *para* >*para*>*ortho* >*meta*. Structural analogues reported in literature confirm a similar pattern.

Future screening of the remaining compounds as well as chalcones **II-IX** is required to ascertain whether or not that these compounds may possess any potential antibacterial, anticancer or anti-inflammatory activities.

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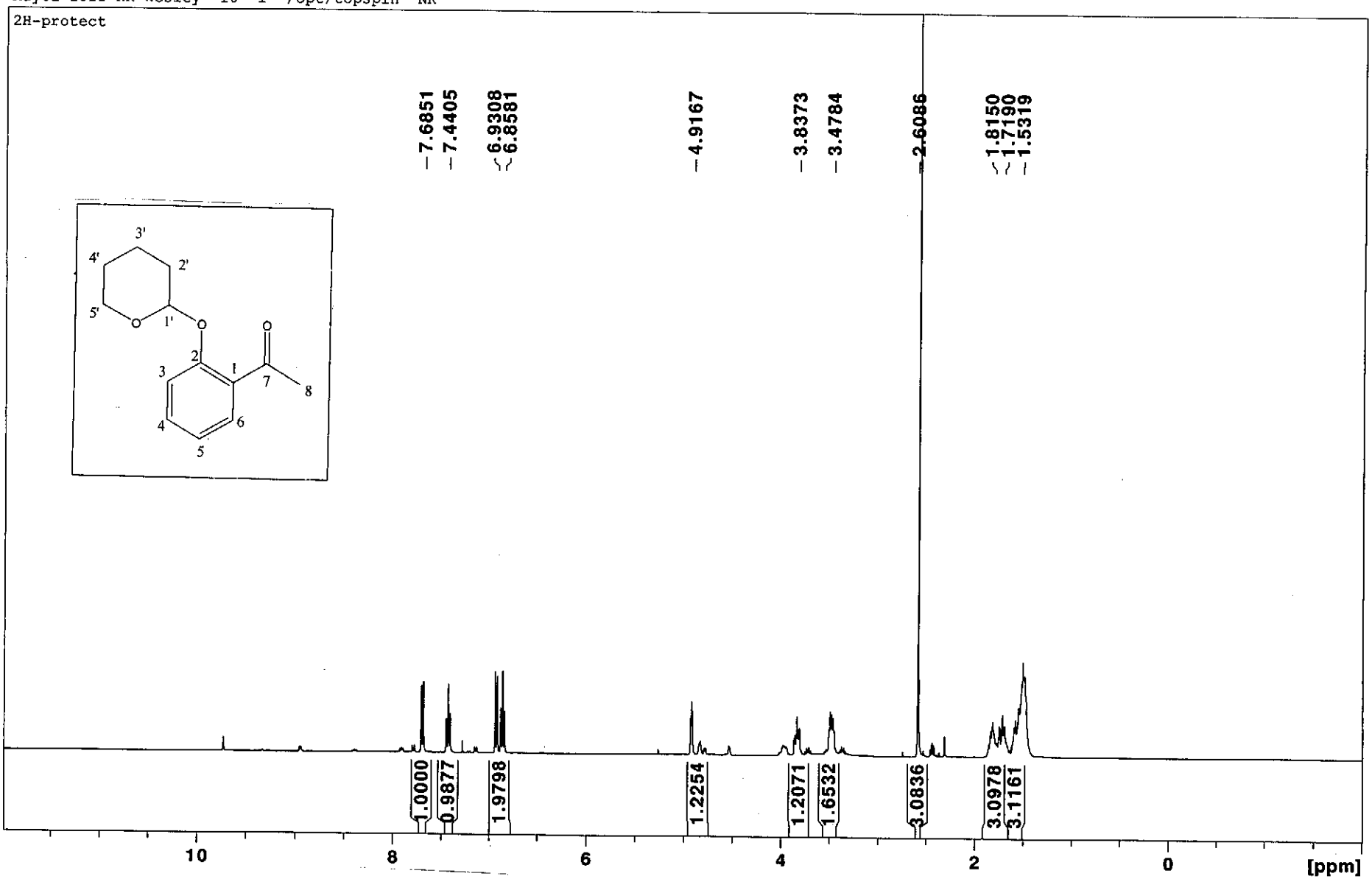
UNIVERSITY OF KWAZULU-NATAL

SYNTHESIS AND CHARACTERIZATION OF PRENYLATED AND FLUORINE BASED FLAVONOIDS

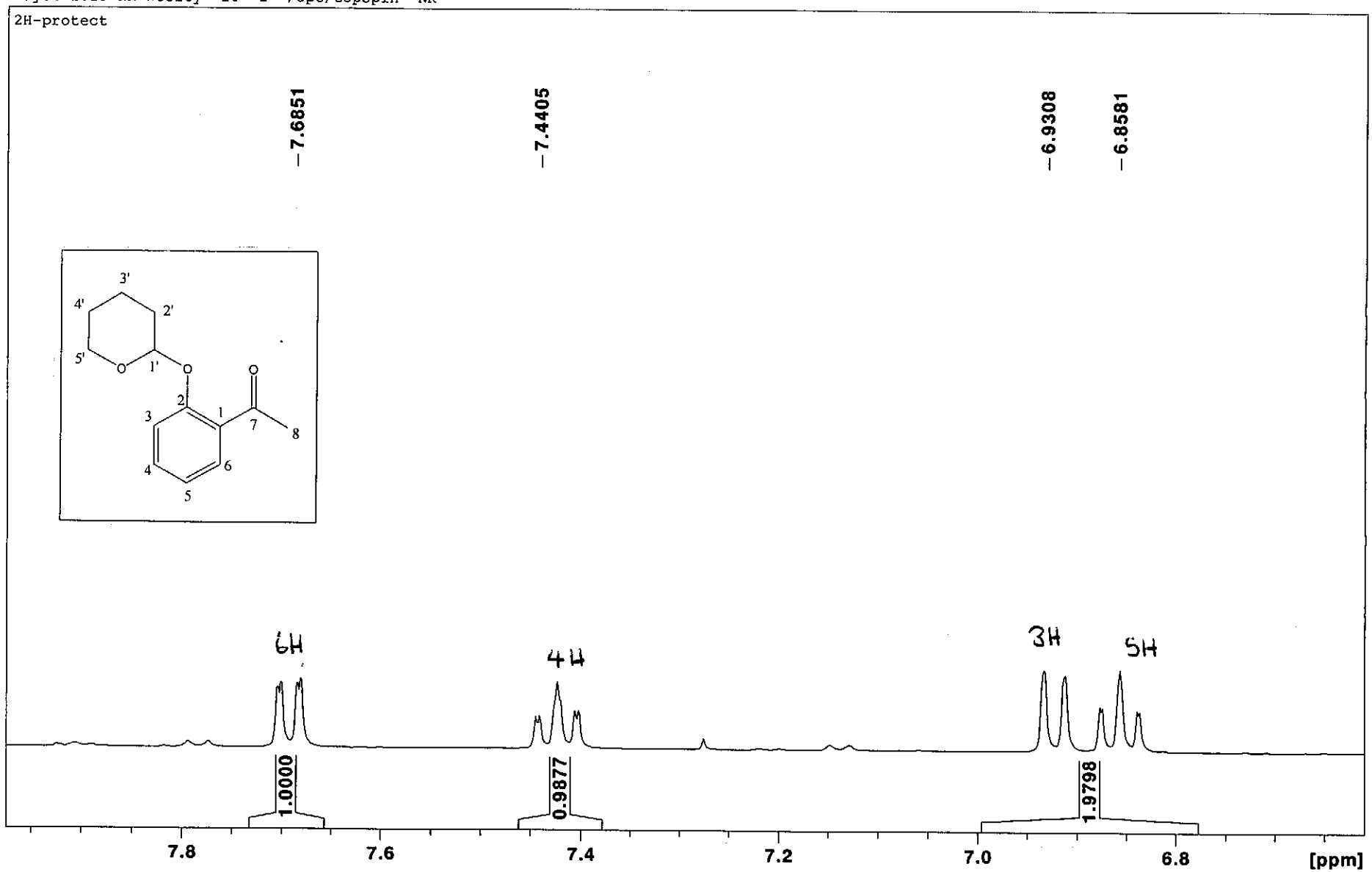
Appendix 1 Spectra

2013

WESLEY GUY CHESLAN OGLE



^{1}H NMR spectrum of 2-tetrahydropyranoacetophenone, (I)



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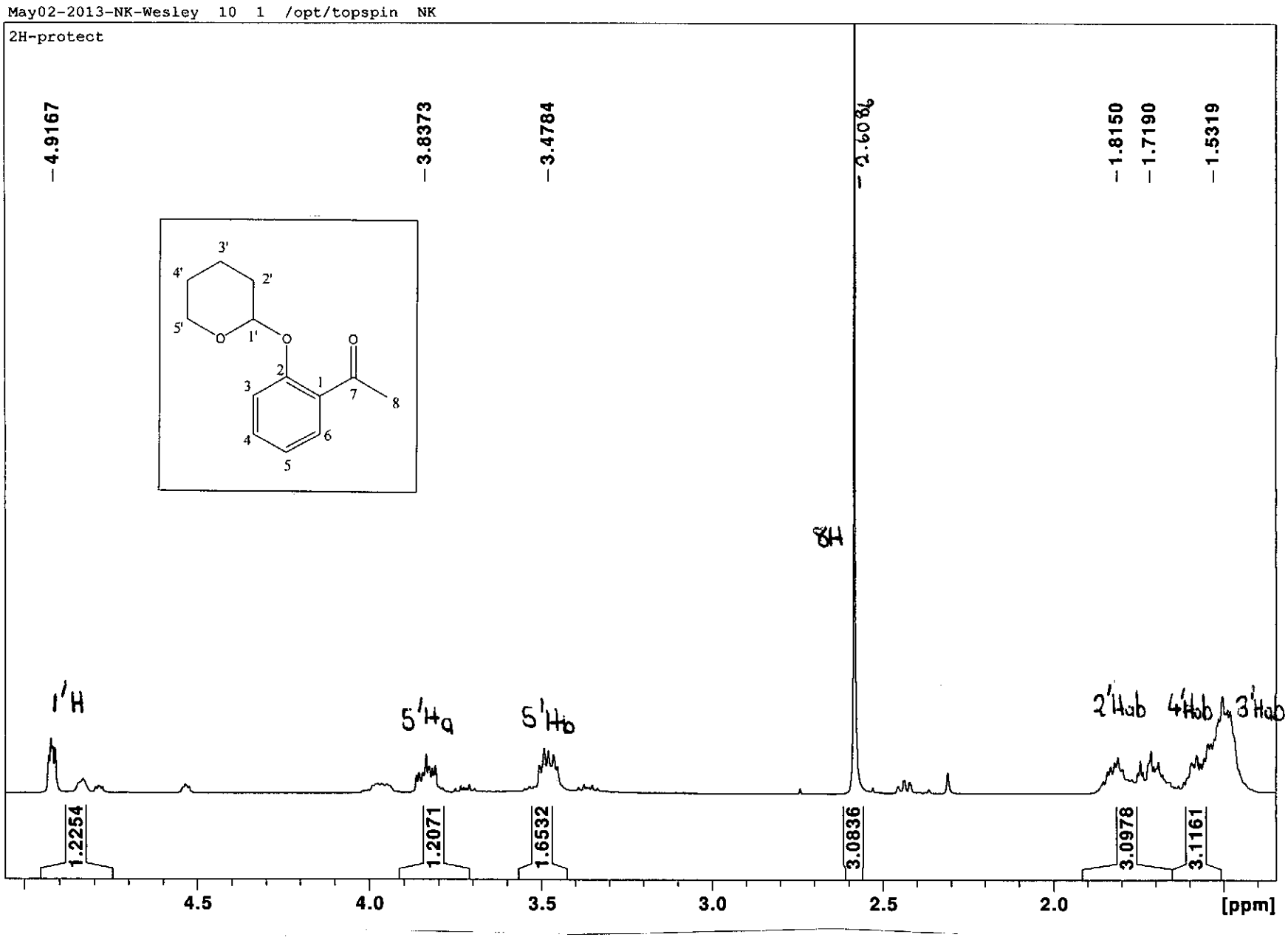

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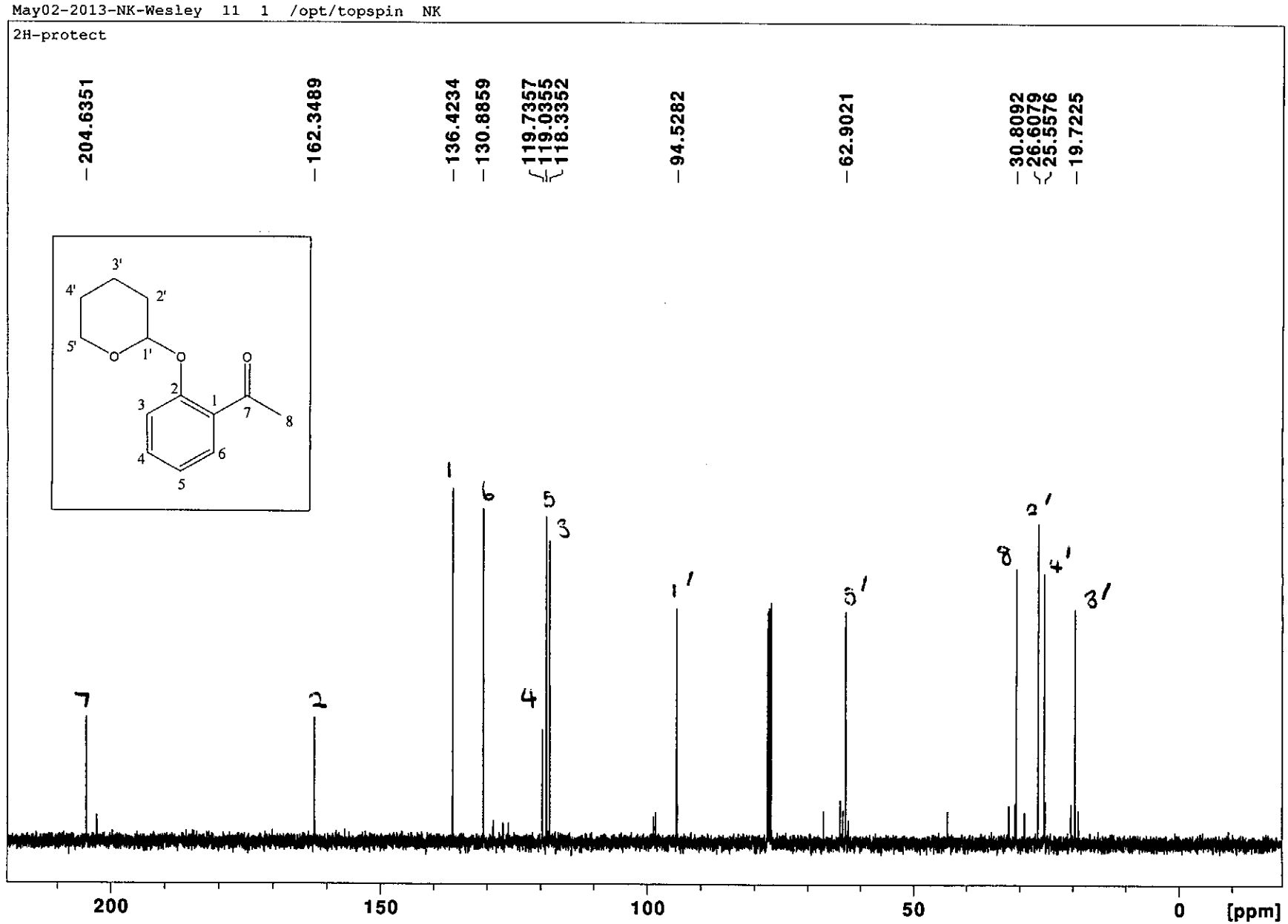
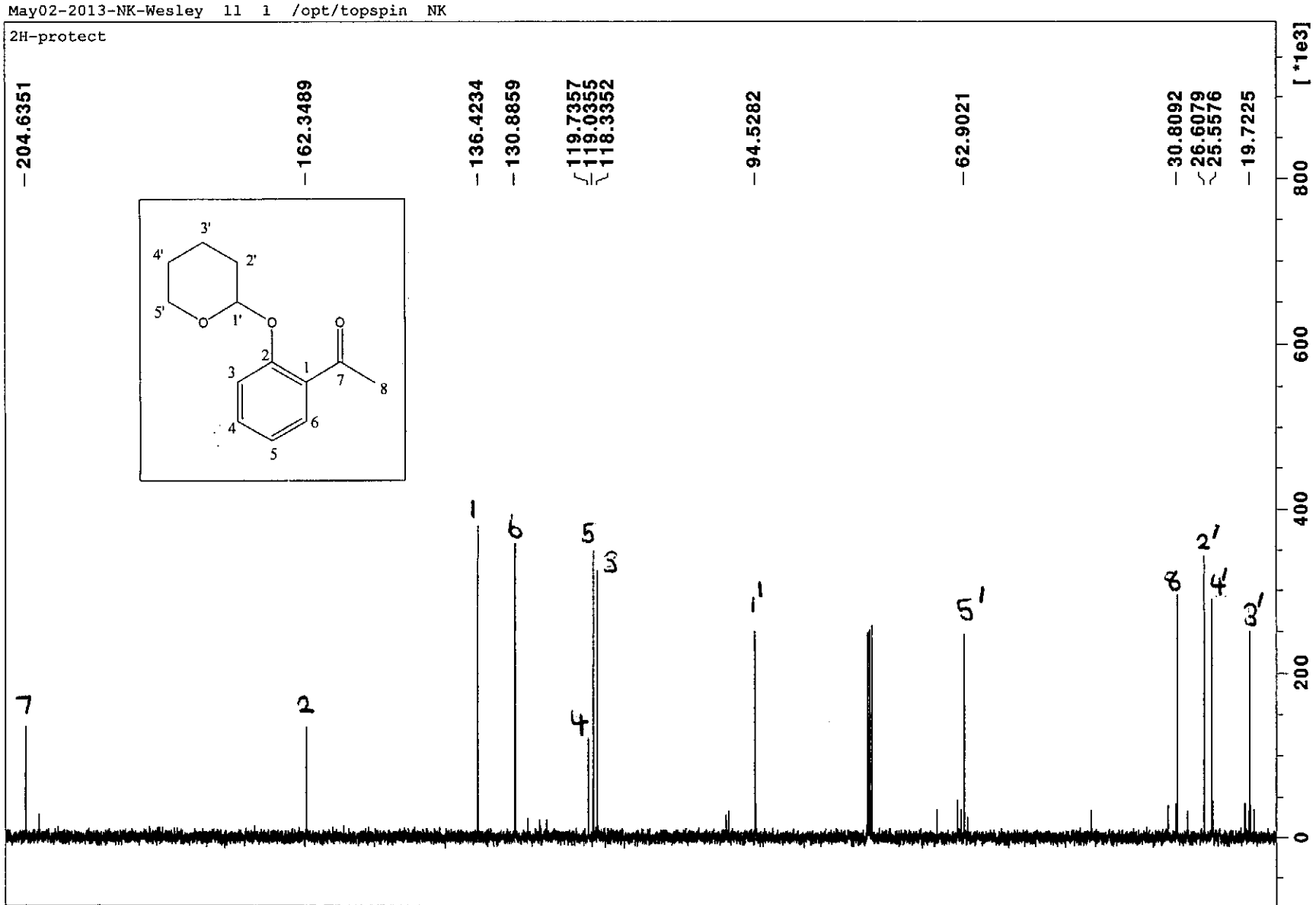


^{13}C NMR spectrum of 2-tetrahydropyranoacetophenone, (I)



^{13}C NMR spectrum of 2-tetrahydropyranoacetophenone, (I)

λmax(252nm) – 0.3833 log ε = 5.28 (1)
λmax(326nm) – 0.1379 log ε = 4.84 (2)

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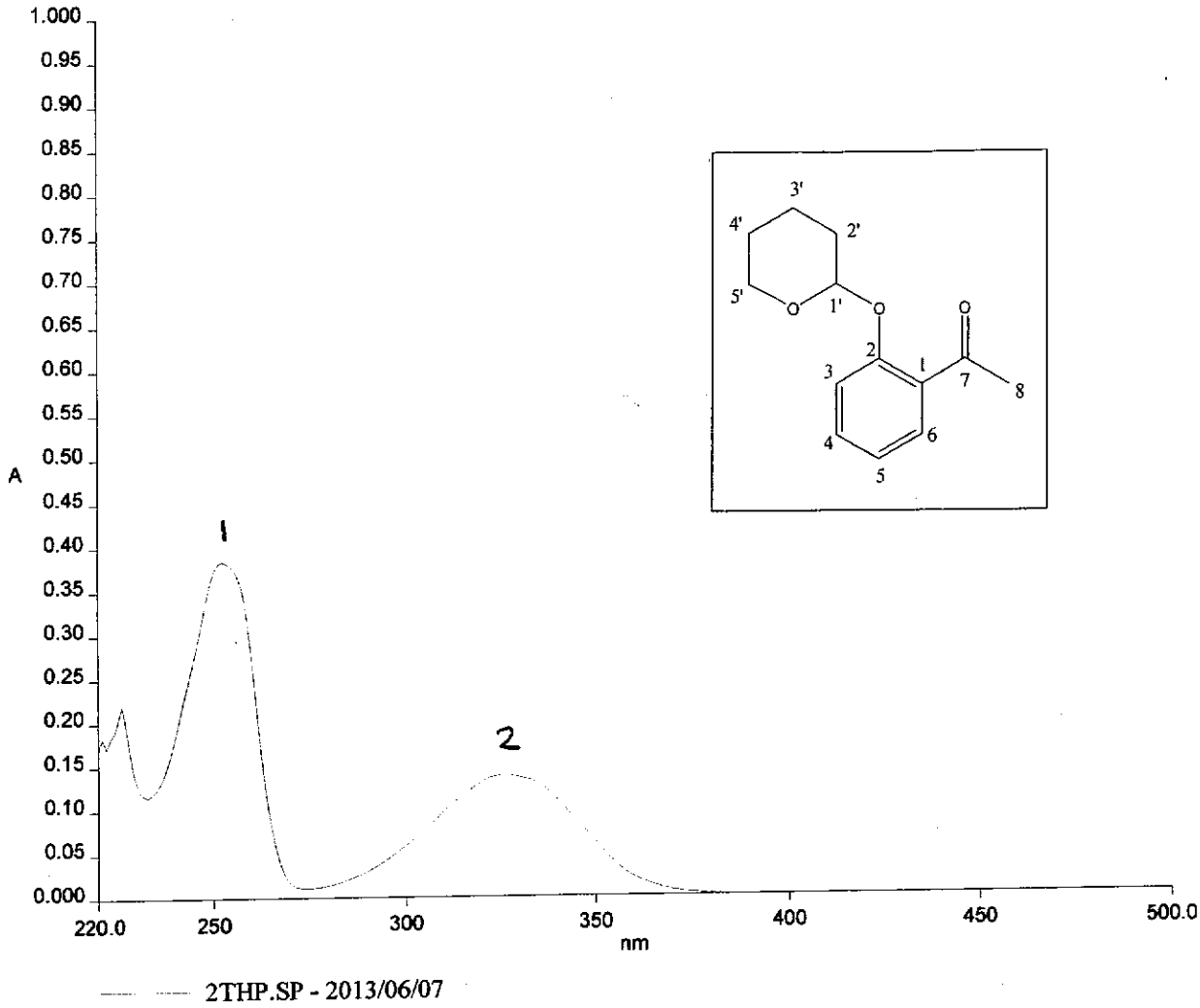
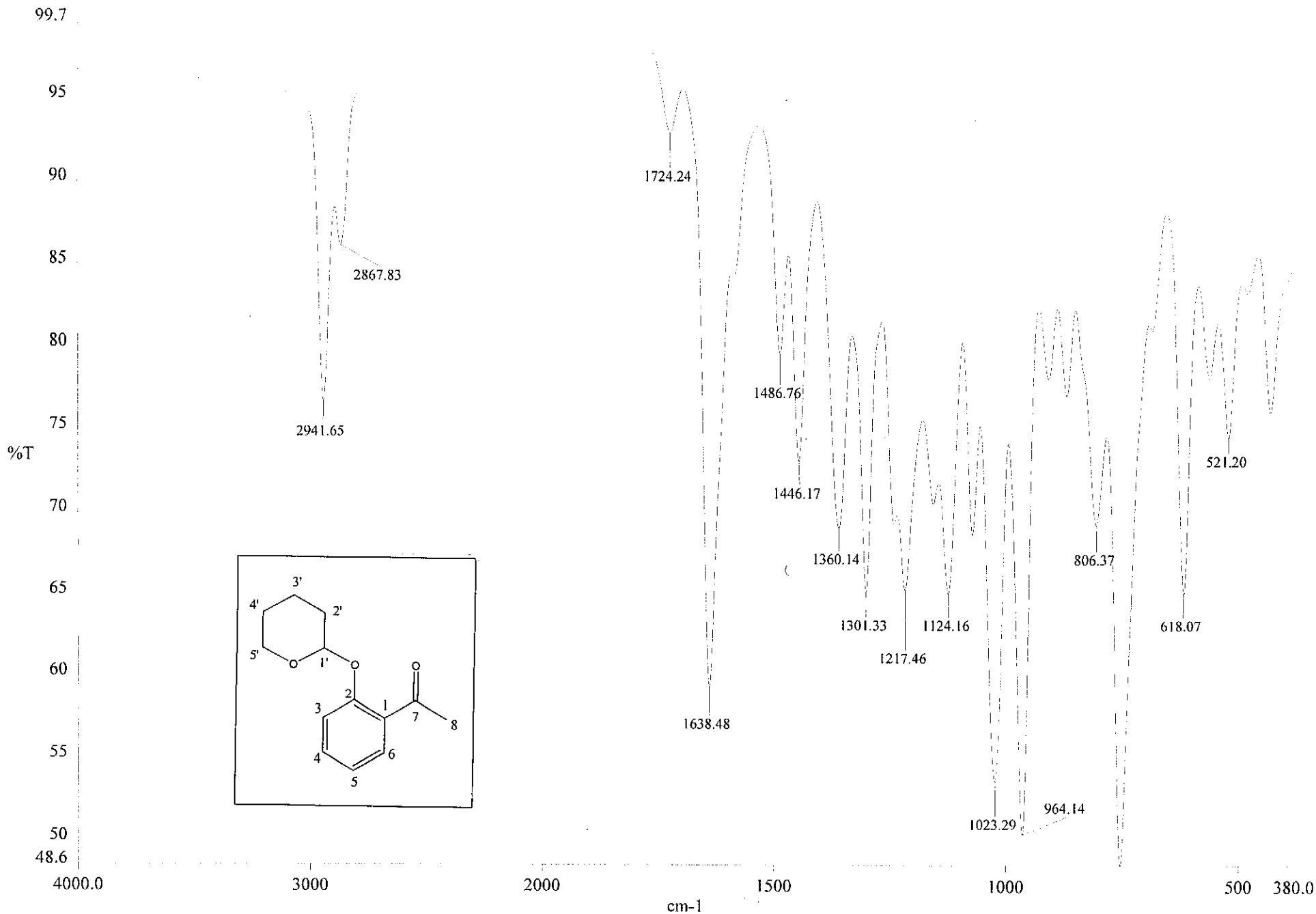


Ultra violet (UV) spectrum of 2-tetrahydropyranoacetophenone, (I)



Infra-Red (IR) spectrum of 2-tetrahydropyranoacetophenone, (I)

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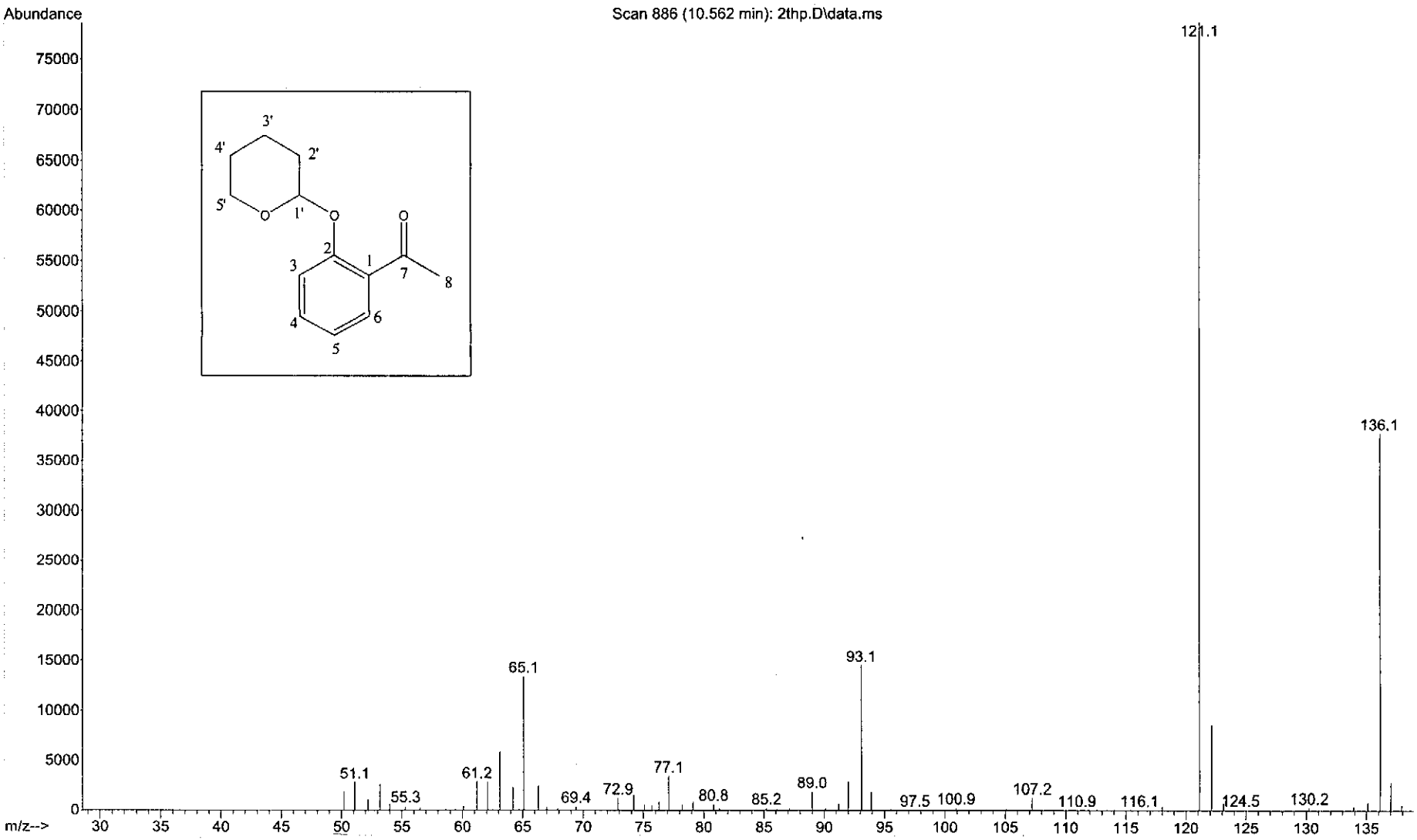

GC-MS spectrum of 2-tetrahydropyranoacetophenone, (I)

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Sample Name: 2thp
Misc Info  :
Vial Number: 10
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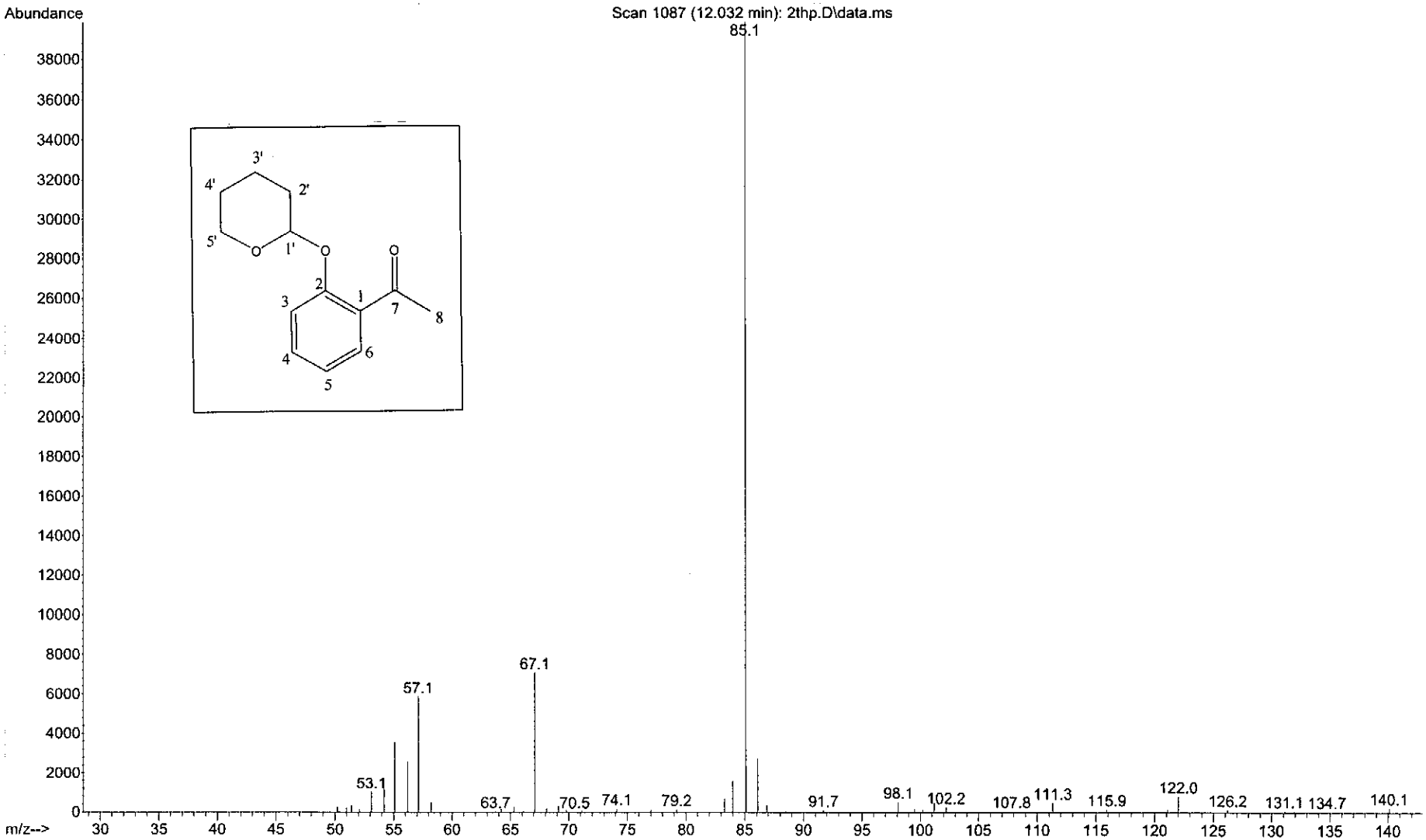
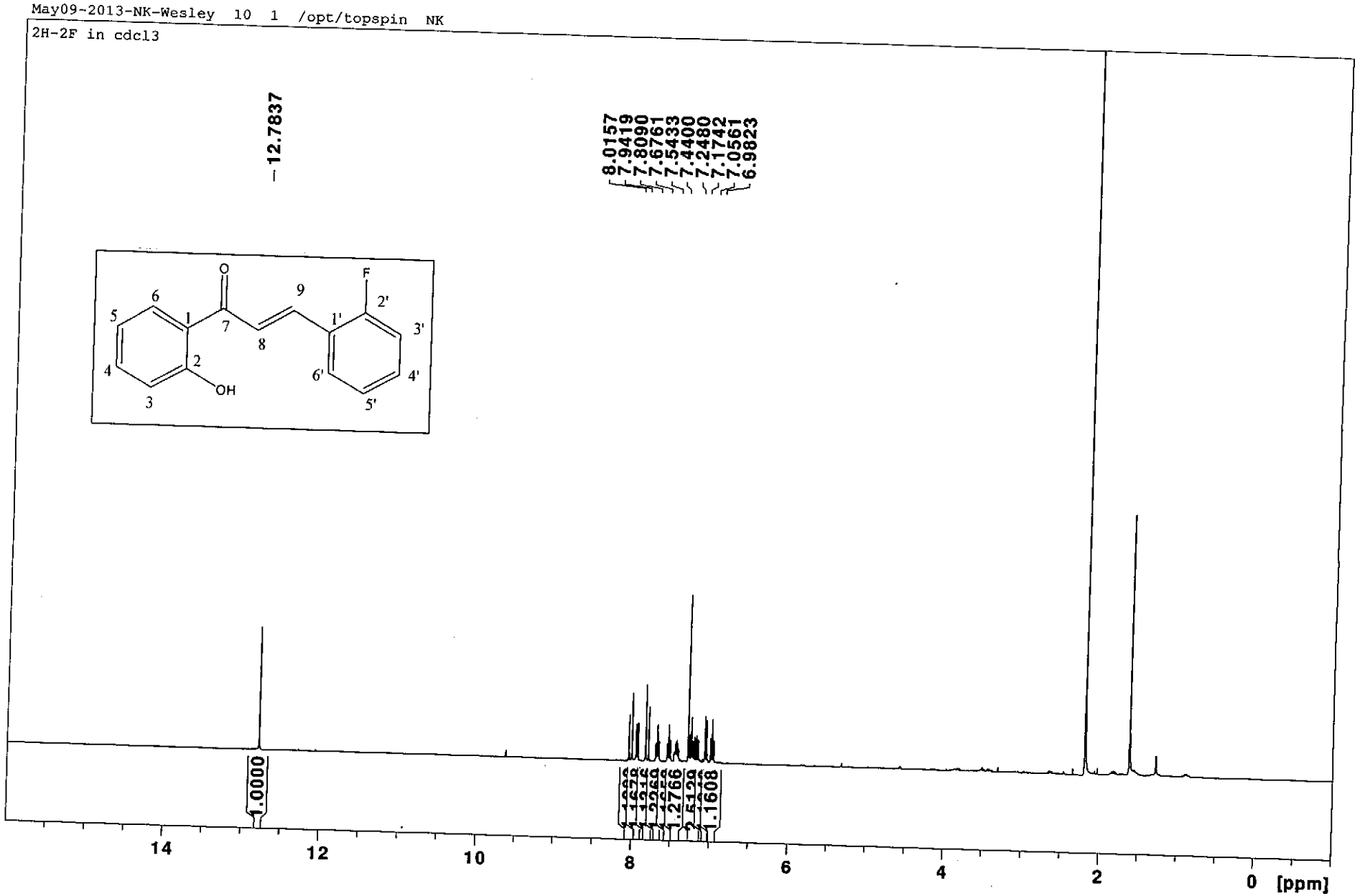
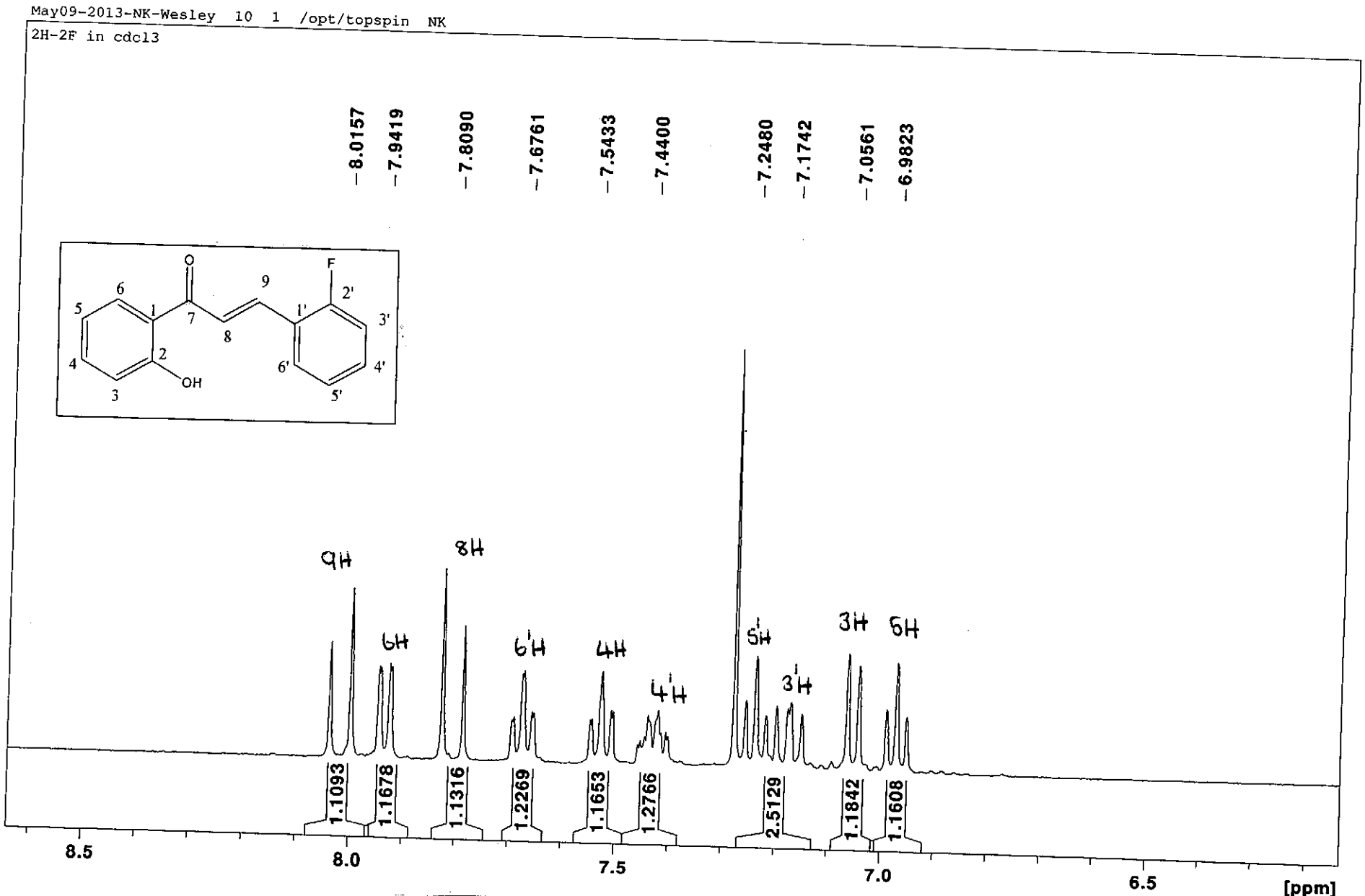


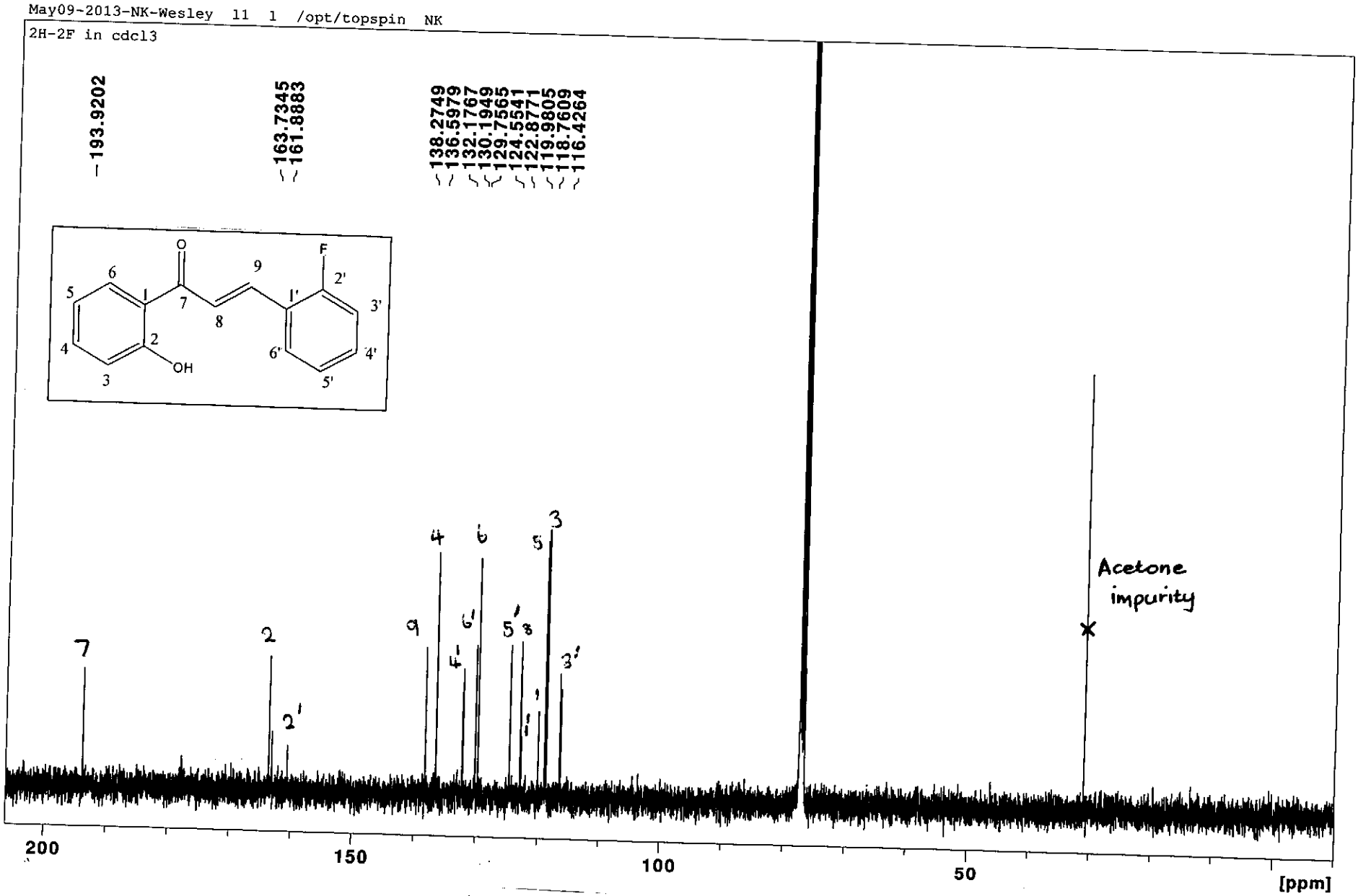
GC-MS spectrum of 2-tetrahydropyranoacetophenone, (I)



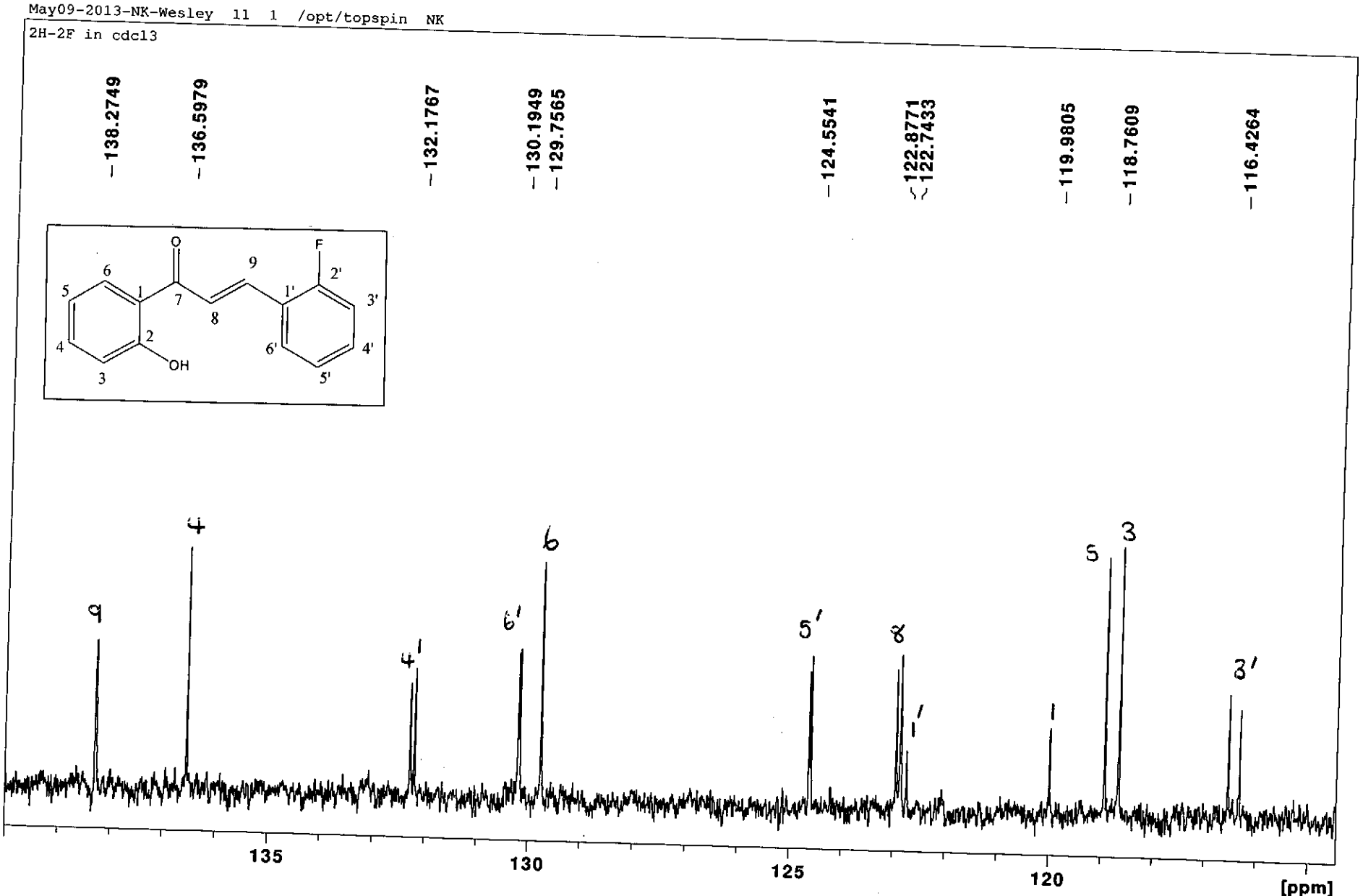
^{1}H NMR spectrum of 2'-fluoro-2-hydroxychalcone, (II)



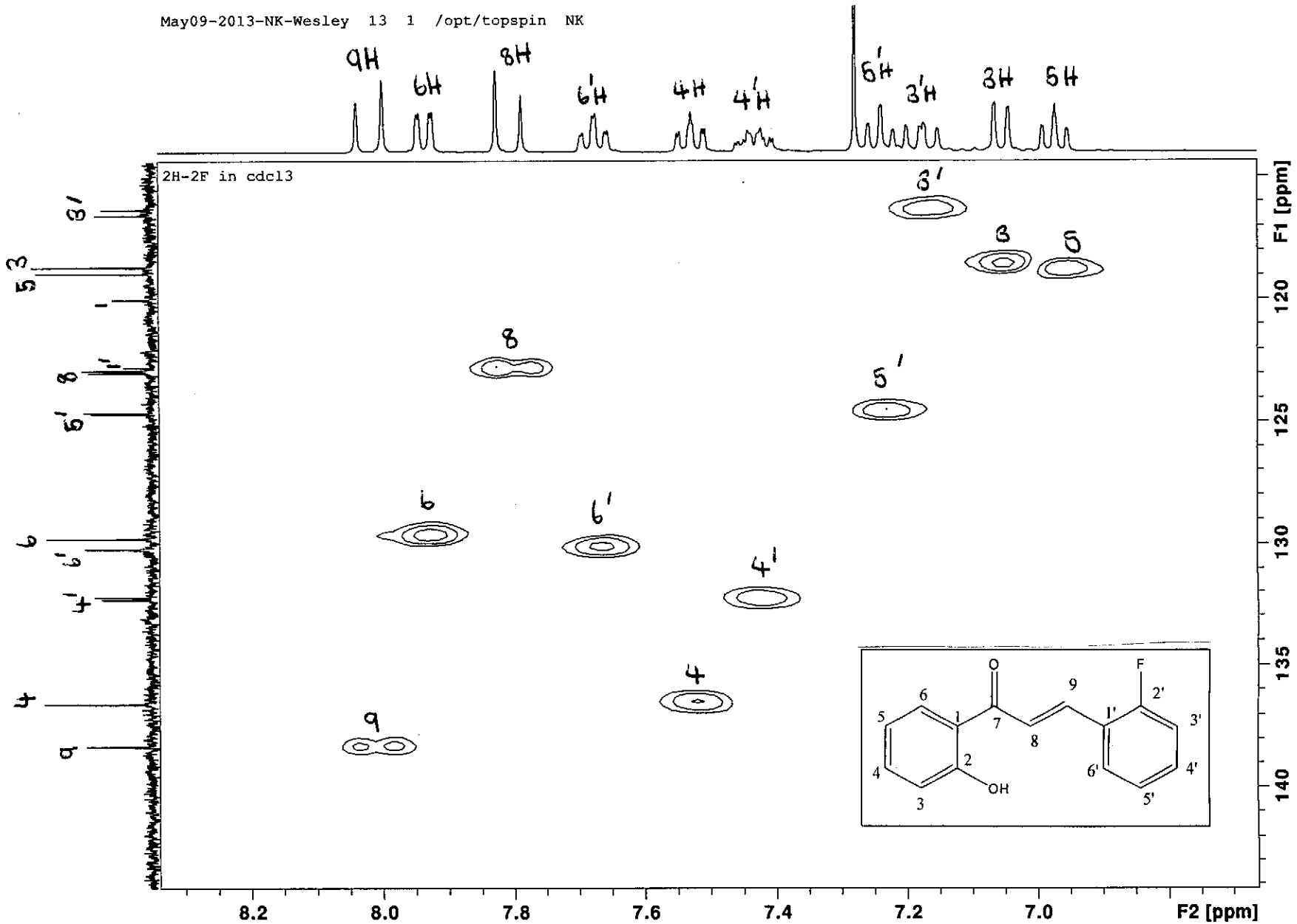
^{1}H NMR spectrum of 2'-fluoro-2-hydroxychalcone, (II)



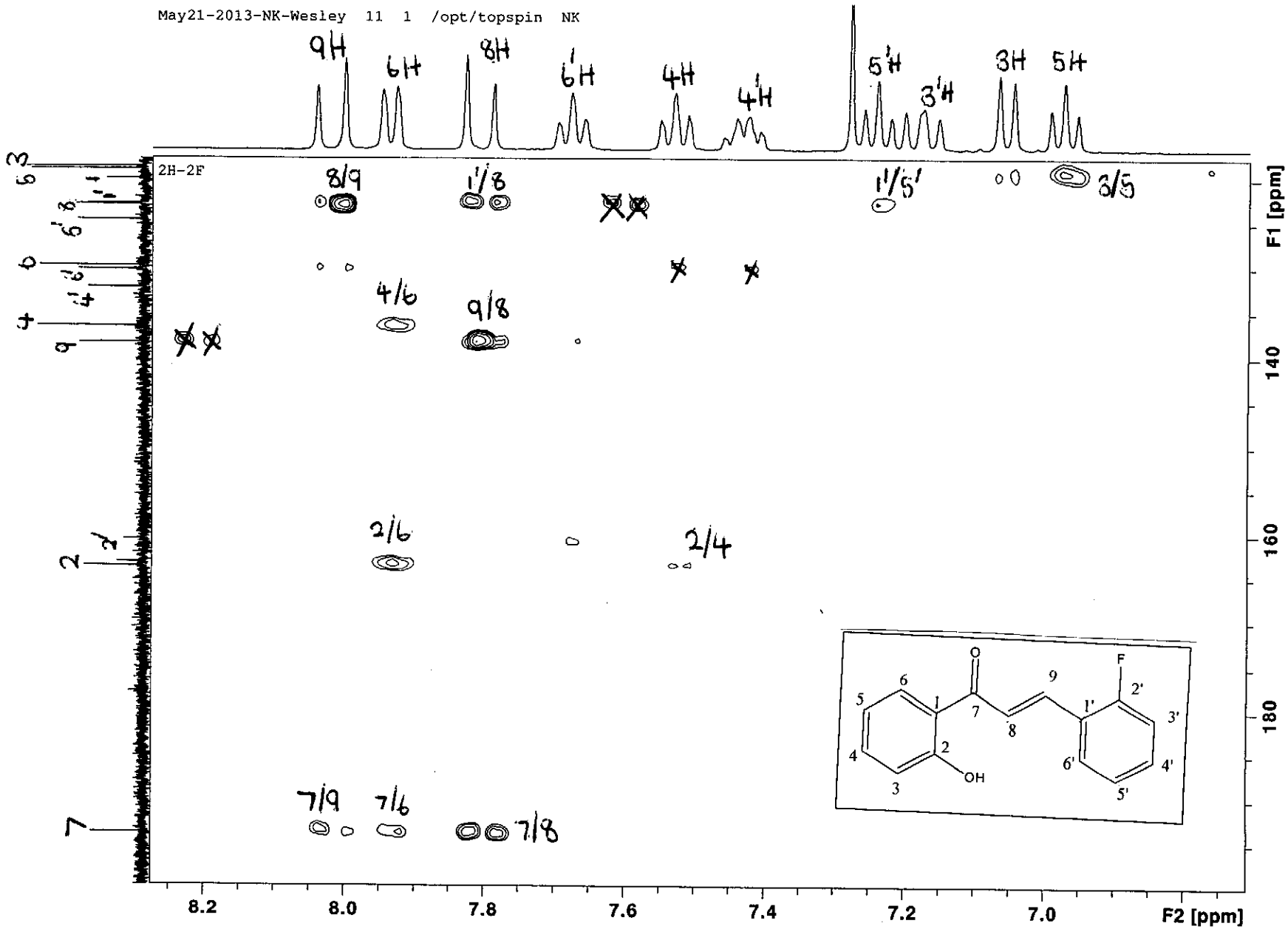
^{13}C NMR spectrum of 2'-fluoro-2-hydroxychalcone, (II)



^{13}C NMR spectrum of 2'-fluoro-2-hydroxychalcone, (II)



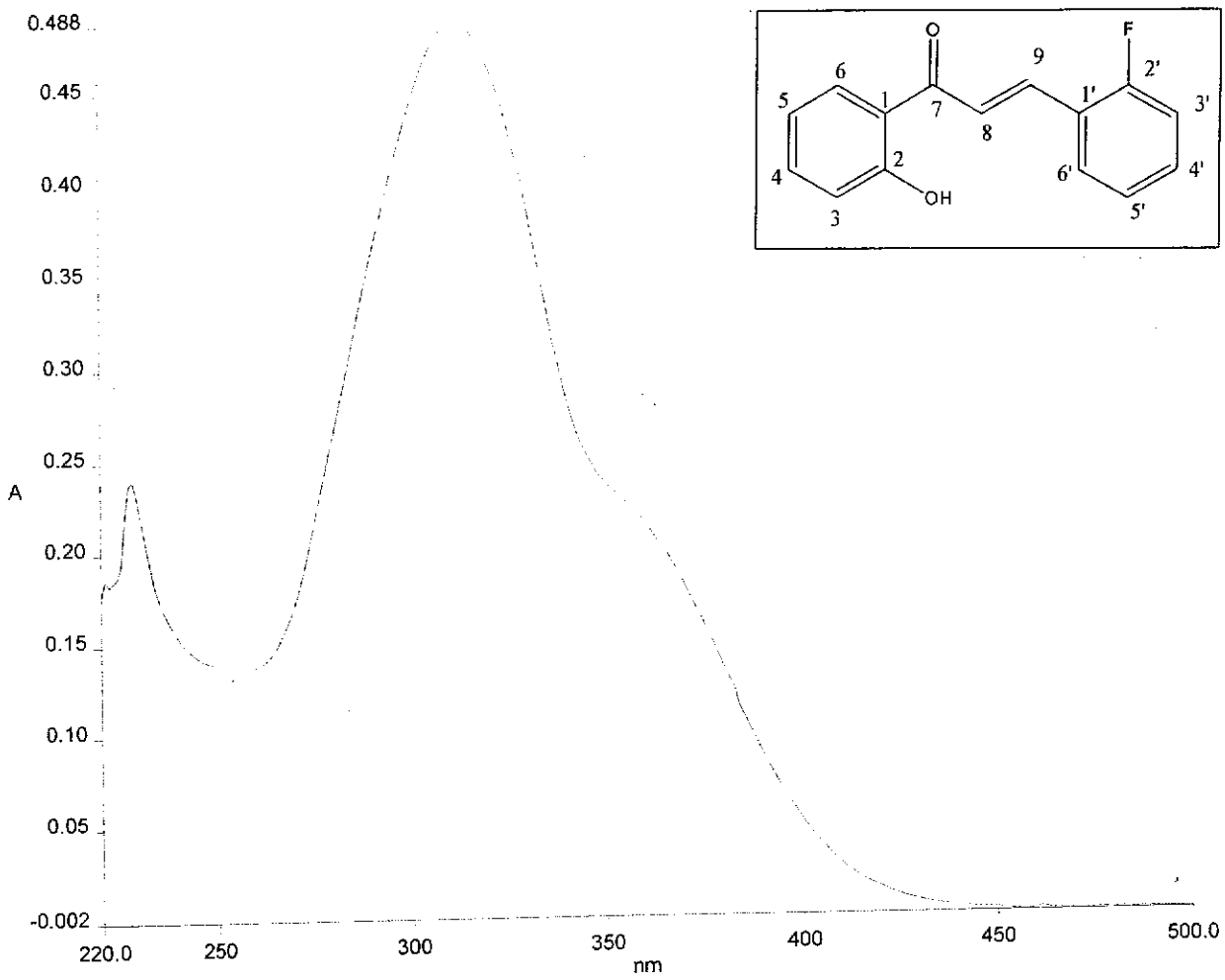
HSQC spectrum of 2'-fluoro-2-hydroxychalcone, (II)



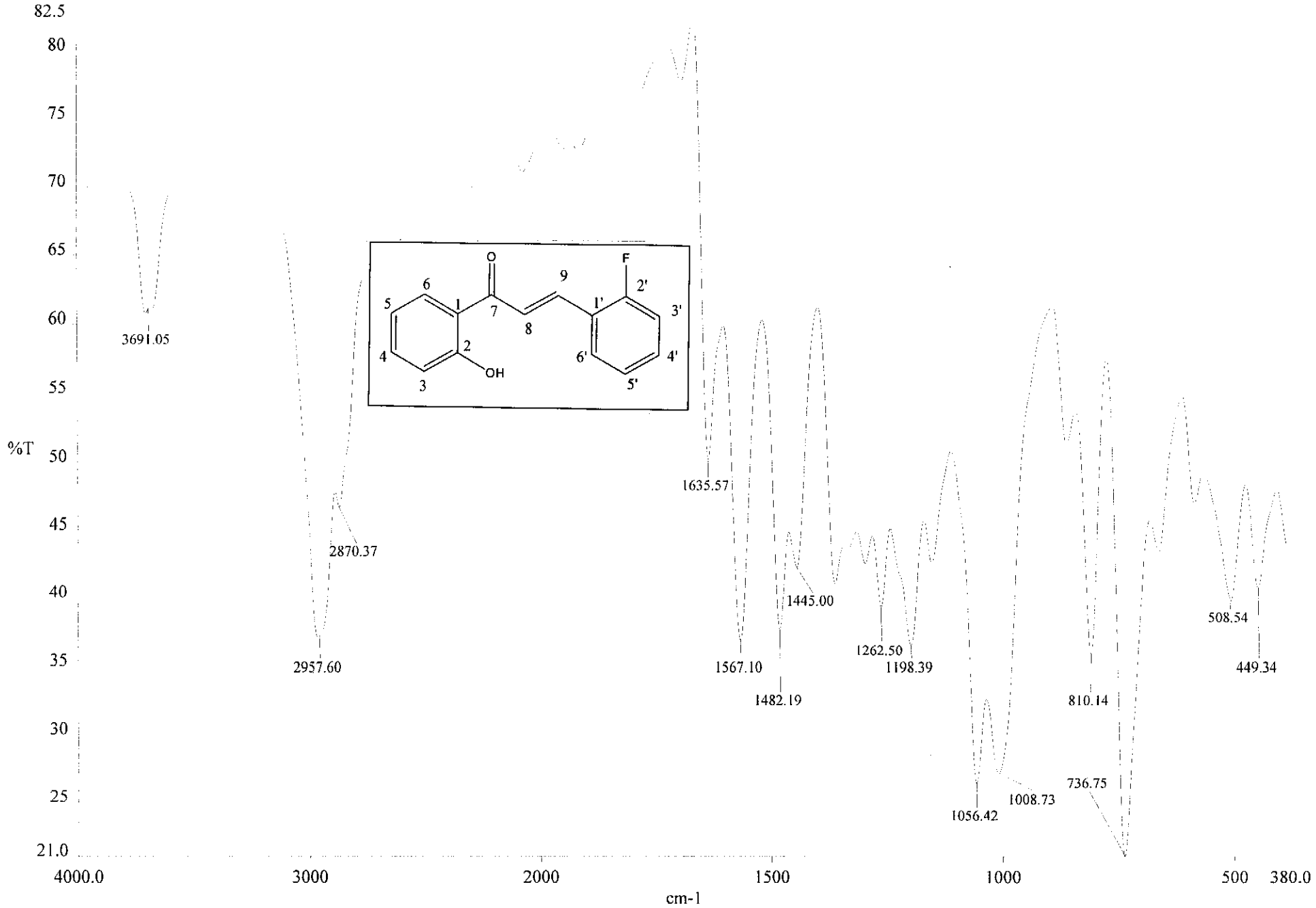
HMBC spectrum of 2'-fluoro-2-hydroxychalcone, (II)

λmax – (312nm) (0.487) log ε = 5.39

Date: 2013/05/20 Time: 11:55:42 AM



Ultra violet (UV) spectrum of 2'-fluoro-2-hydroxychalcone, (II)



Infra-Red (IR) spectrum of 2'-fluoro-2-hydroxychalcone, (II)

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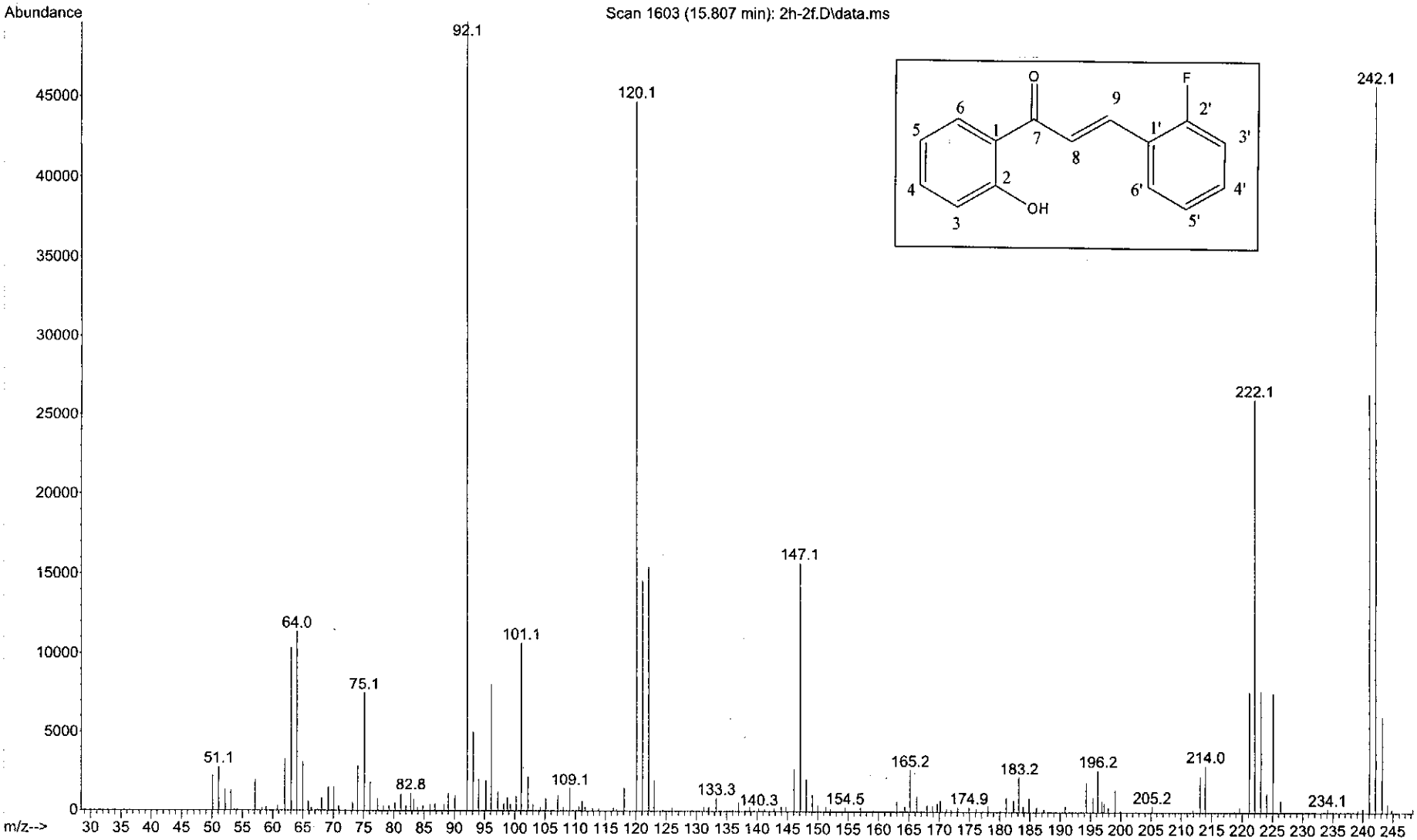
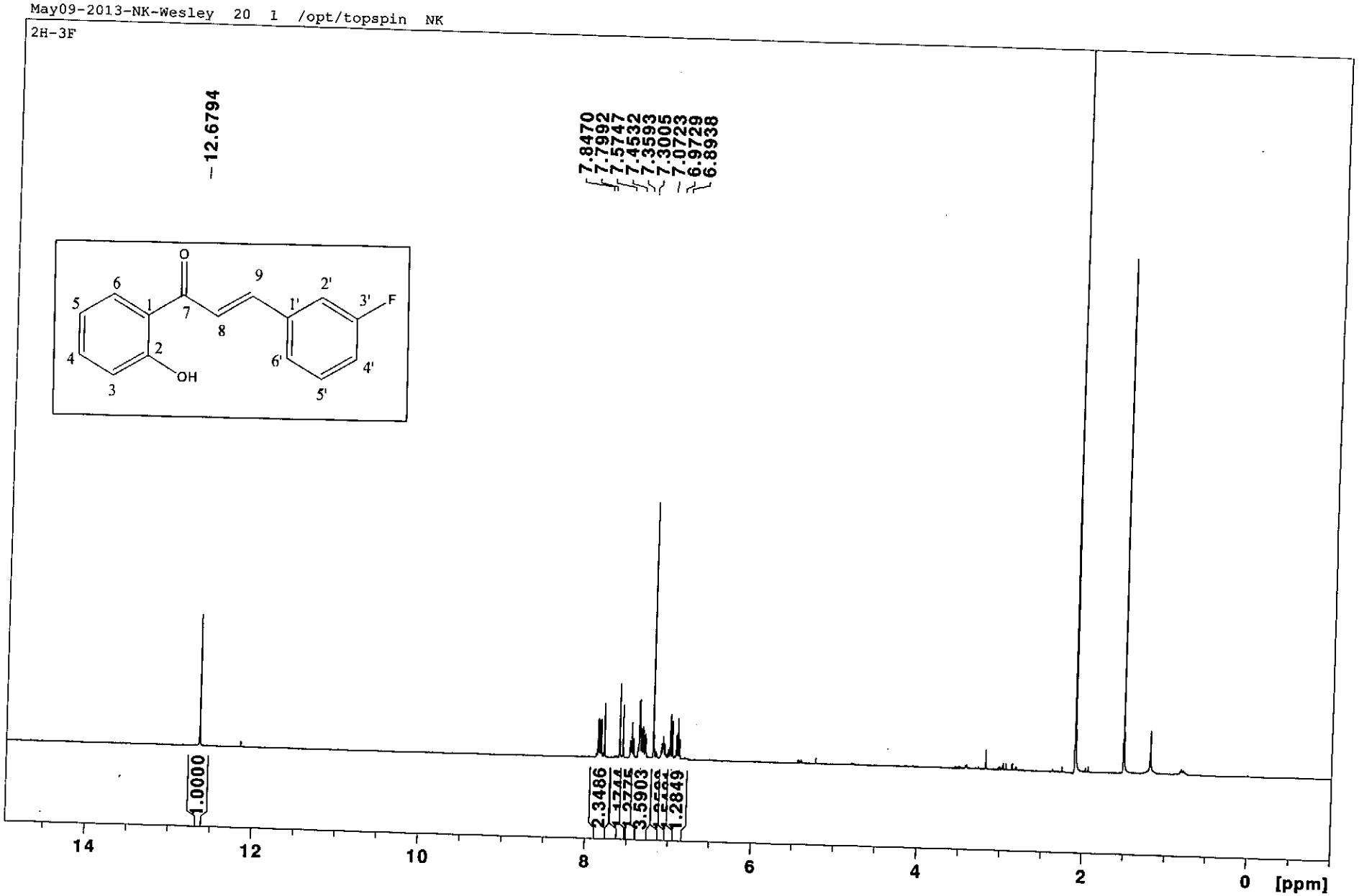
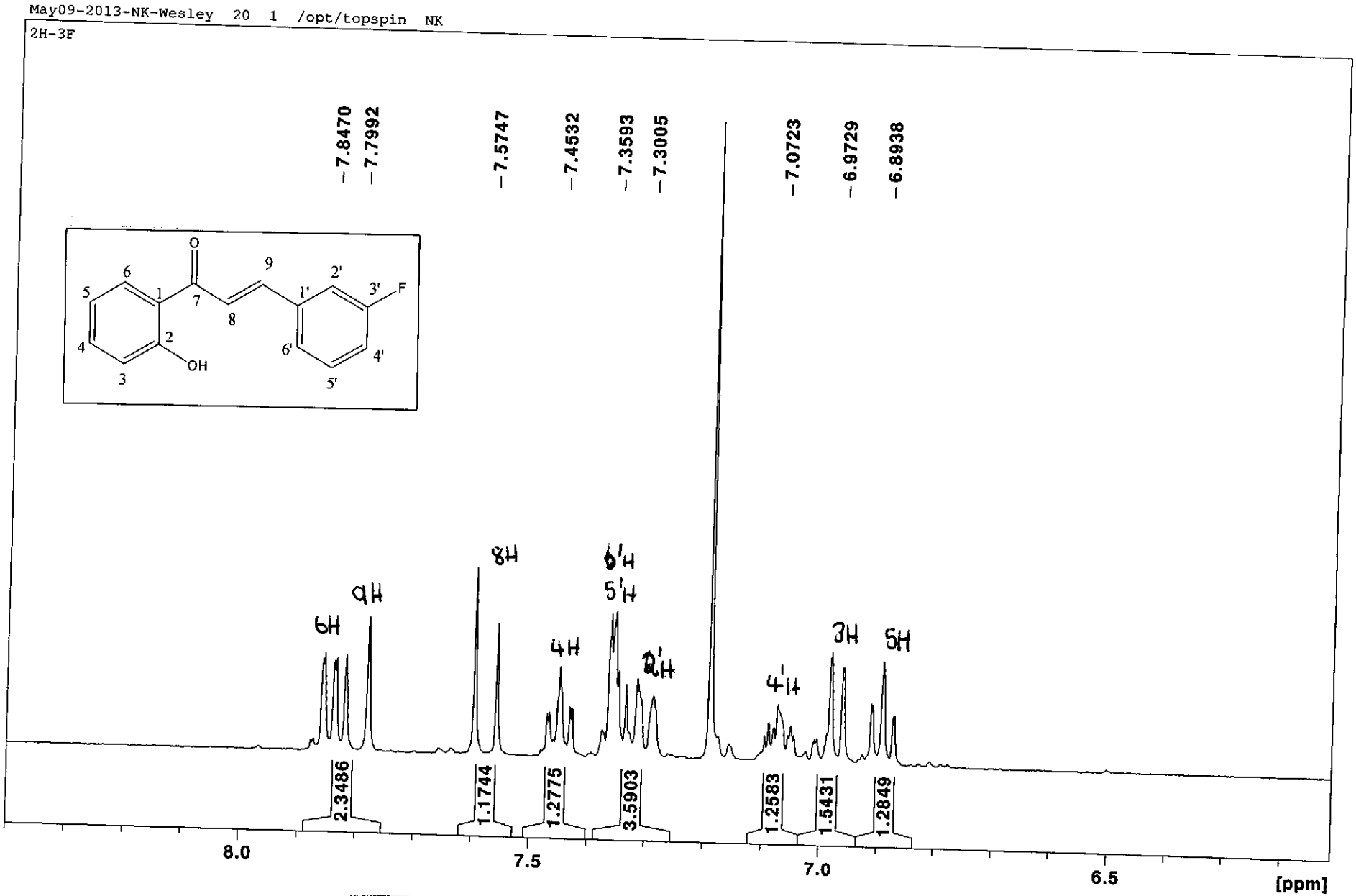


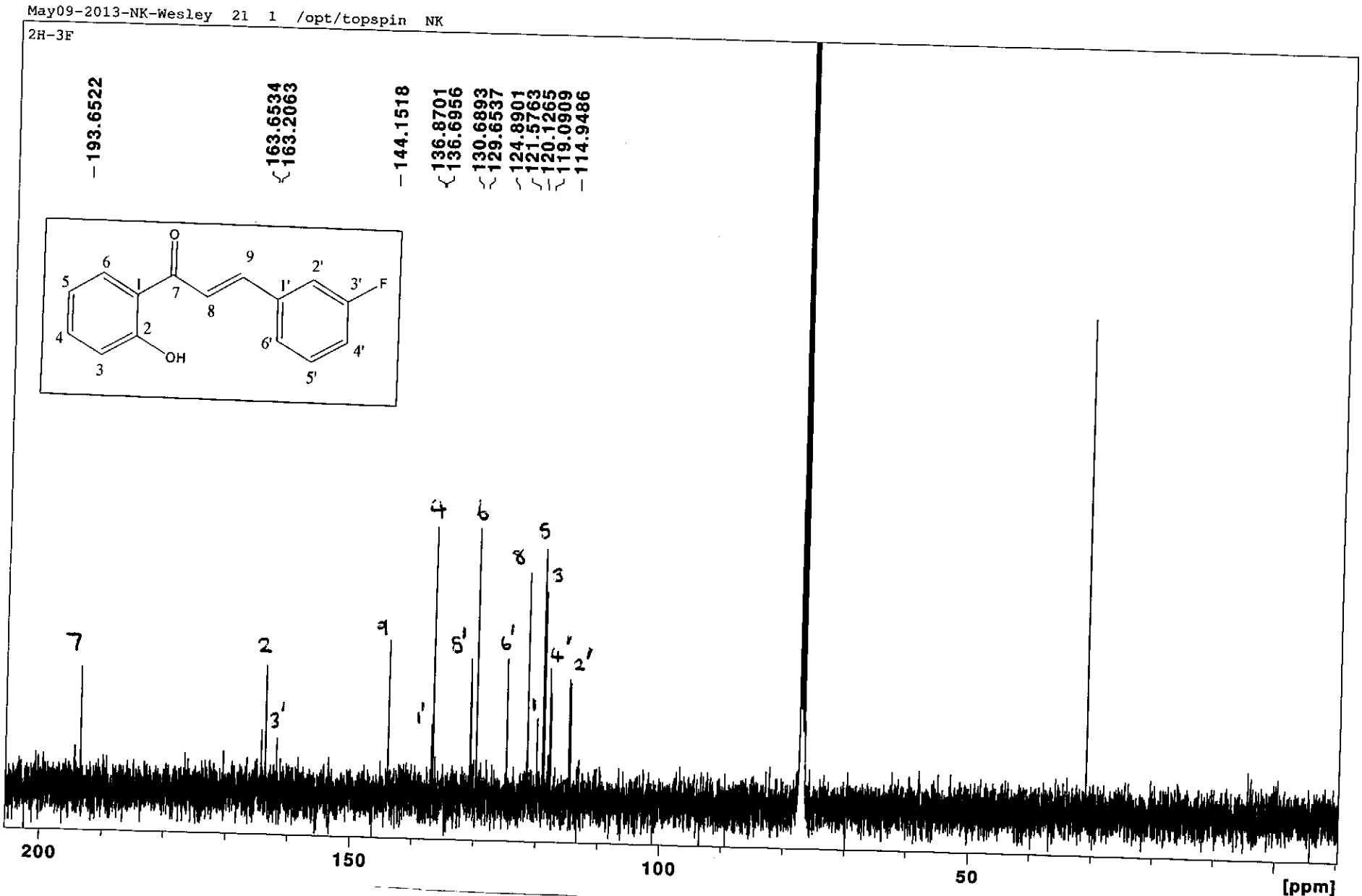
GC-MS spectrum of 2'-fluoro-2-hydroxychalcone, (II)



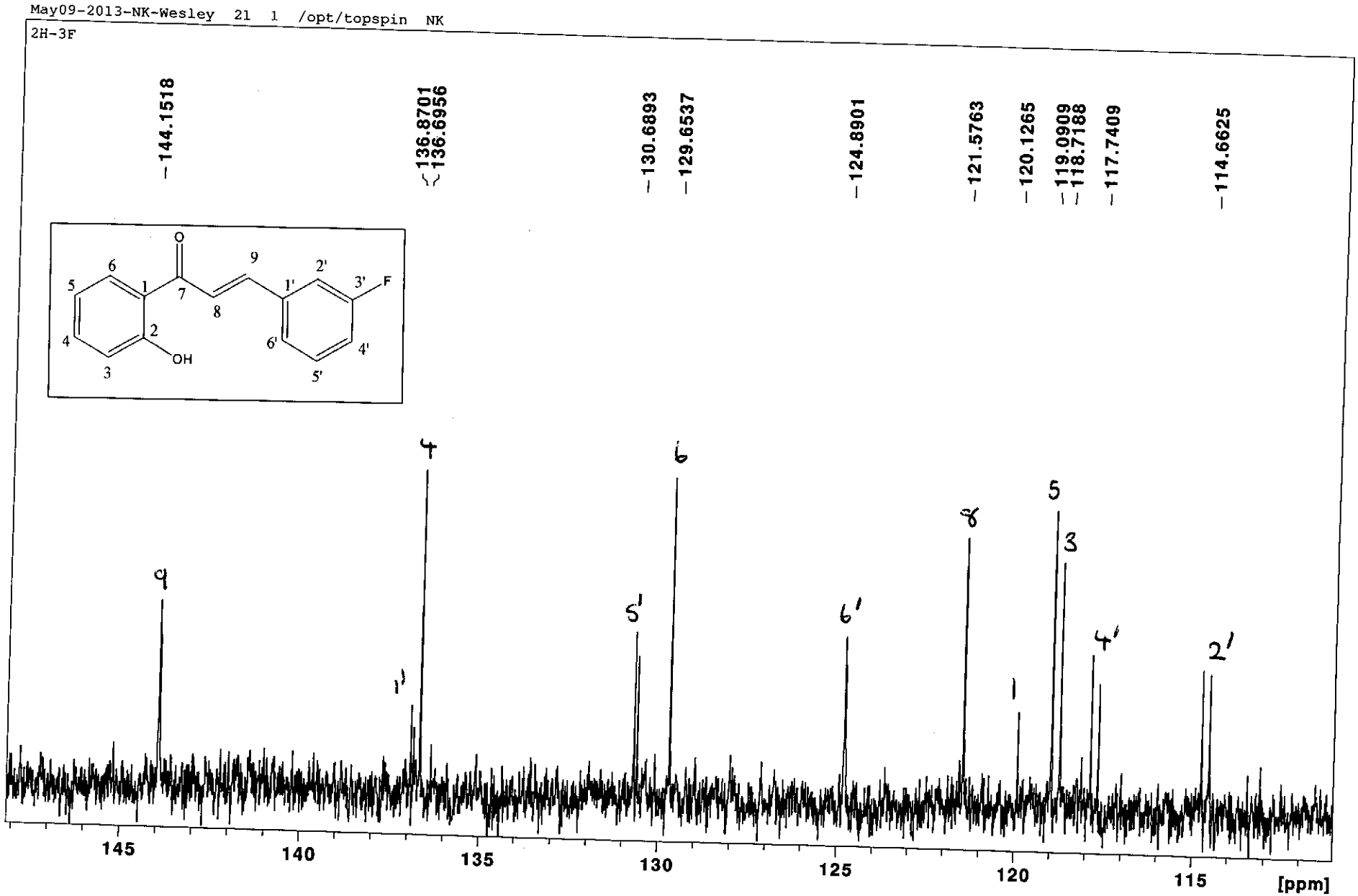
^{1}H NMR spectrum of 3'-fluoro-2-hydroxychalcone, (III)



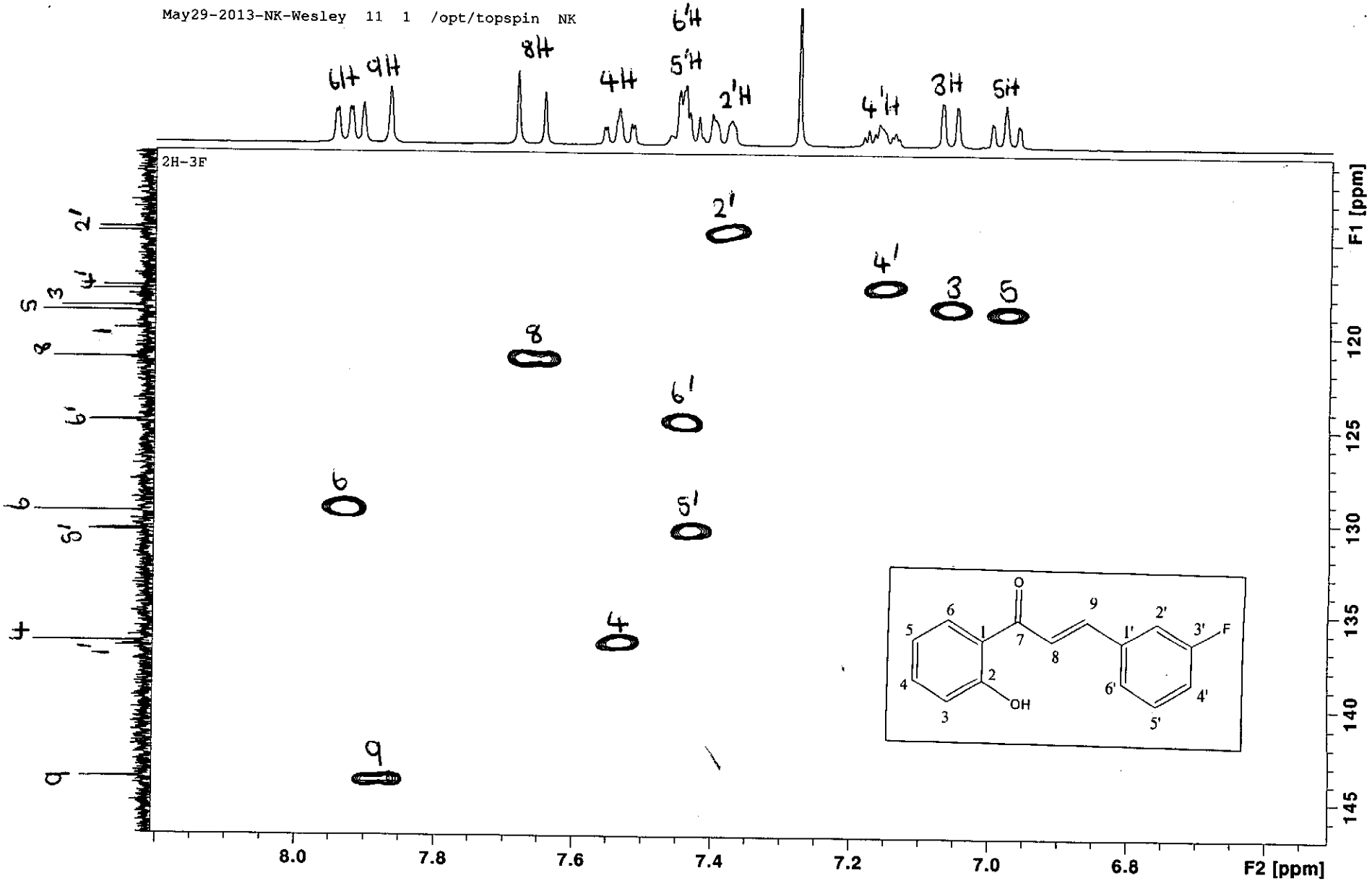
^{1}H NMR spectrum of 3'-fluoro-2-hydroxychalcone, (III)



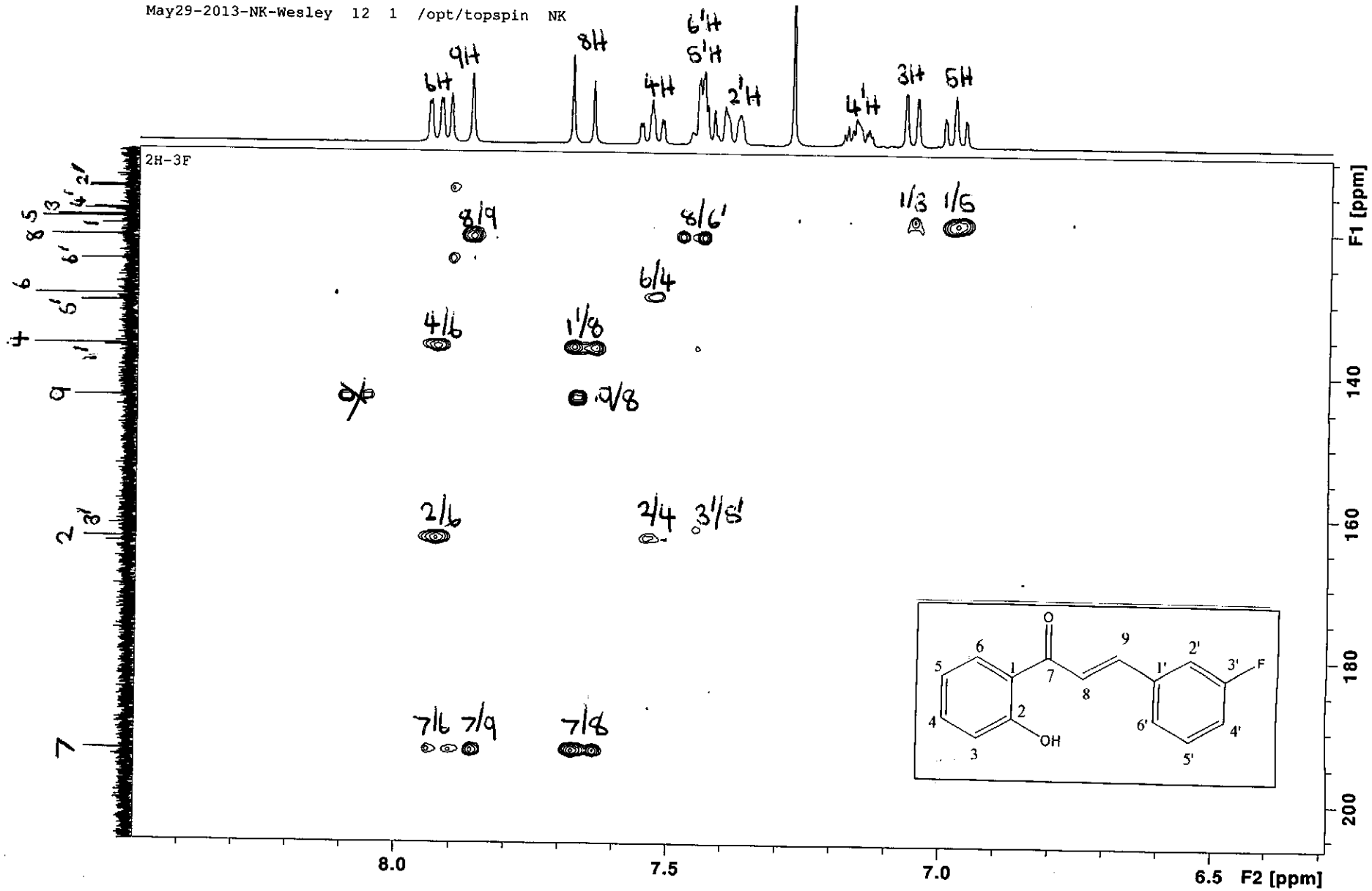
^{13}C NMR spectrum of 3'-fluoro-2-hydroxychalcone, (III)



^{13}C NMR spectrum of 3'-fluoro-2-hydroxychalcone, (III)



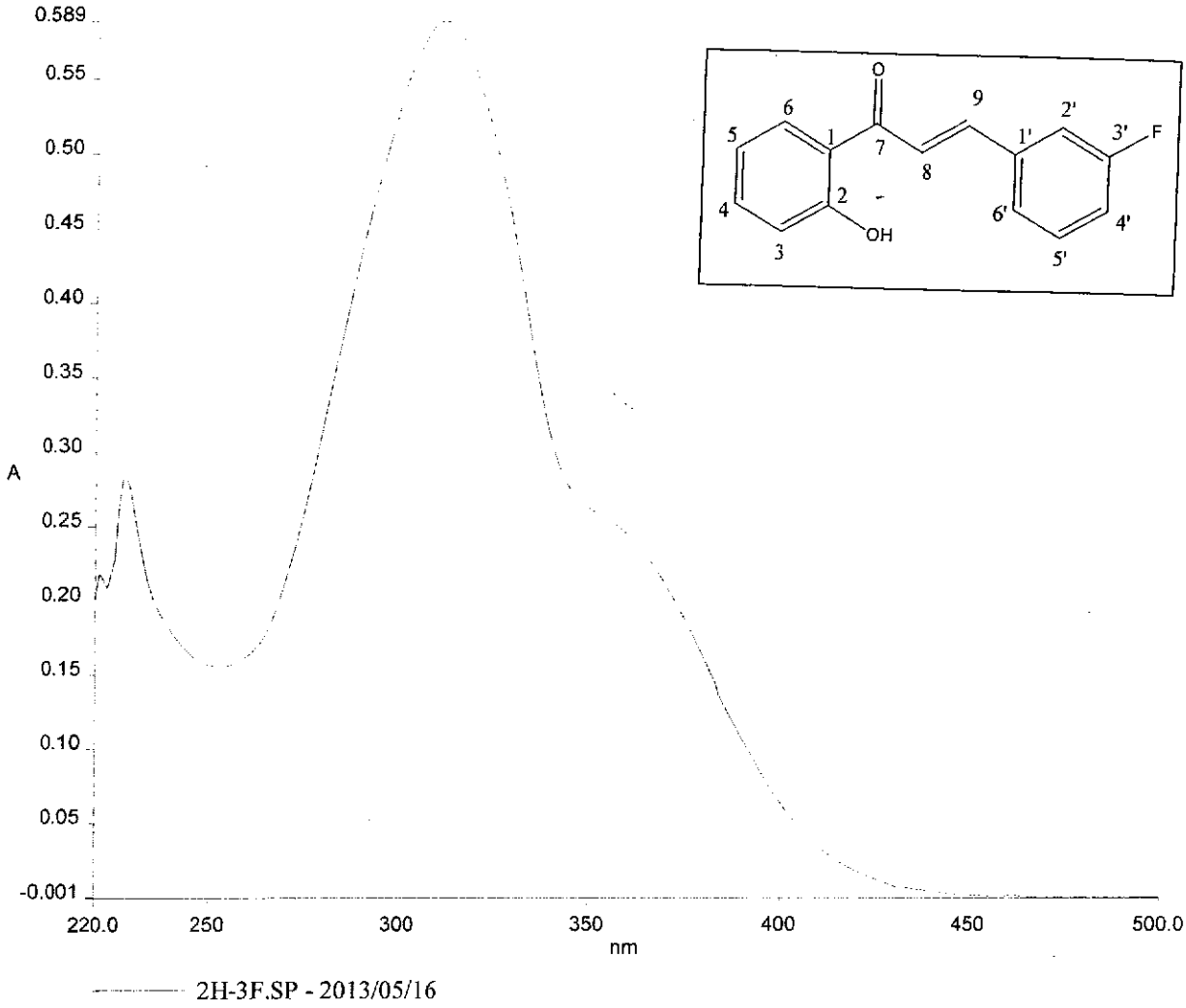
HSQC spectrum of 3'-fluoro-2-hydroxychalcone, (III)



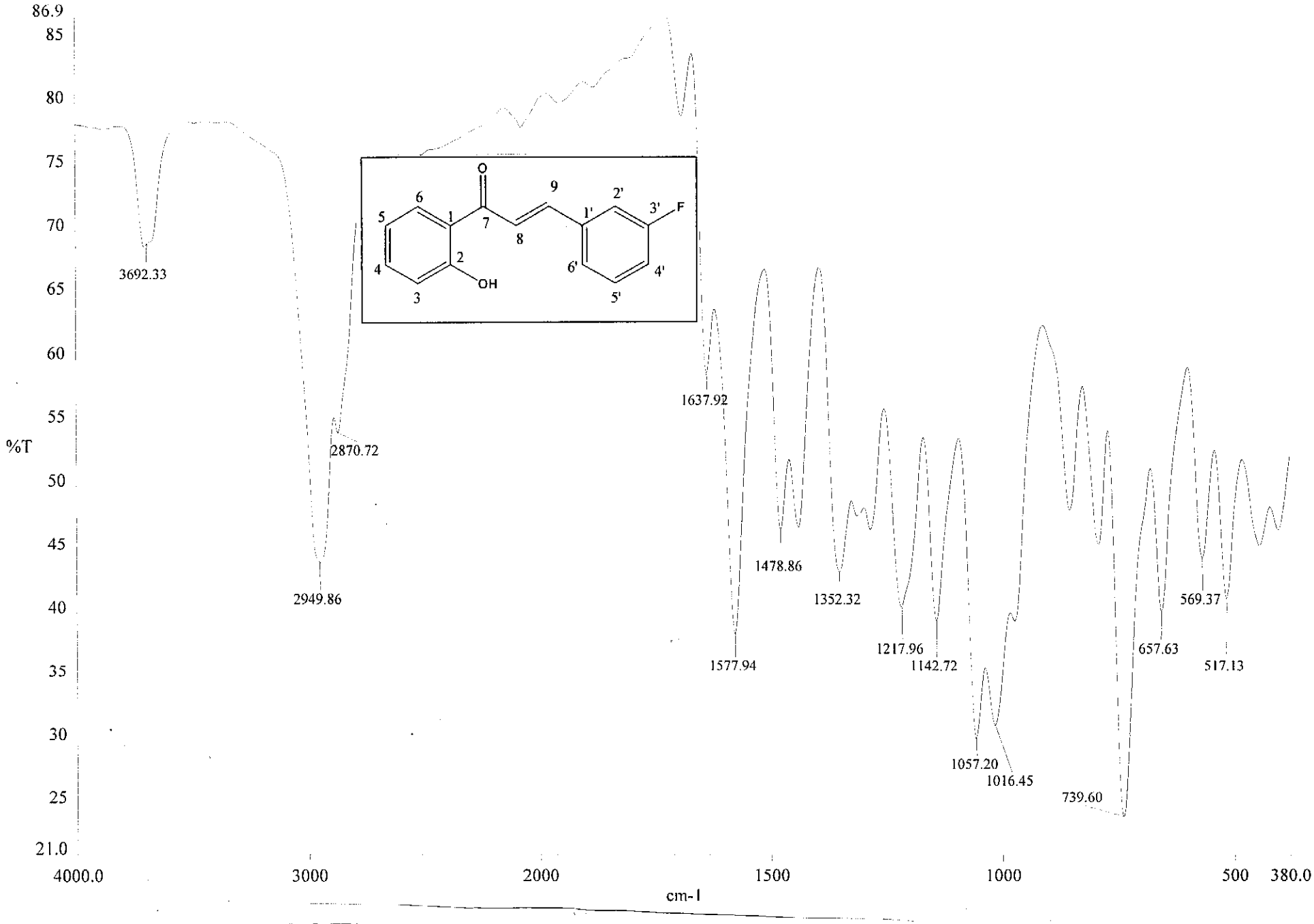
HMBC spectrum of 3'-fluoro-2-hydroxychalcone, (III)

λmax – (311 nm) – 0.5886 log ε = 5.47

Date: 2013/05/20 Time: 11:58:16 AM



Ultra violet (UV) spectrum of 3'-fluoro-2-hydroxychalcone, (III)



Infra-Red (IR) spectrum of 3'-fluoro-2-hydroxychalcone, (III)

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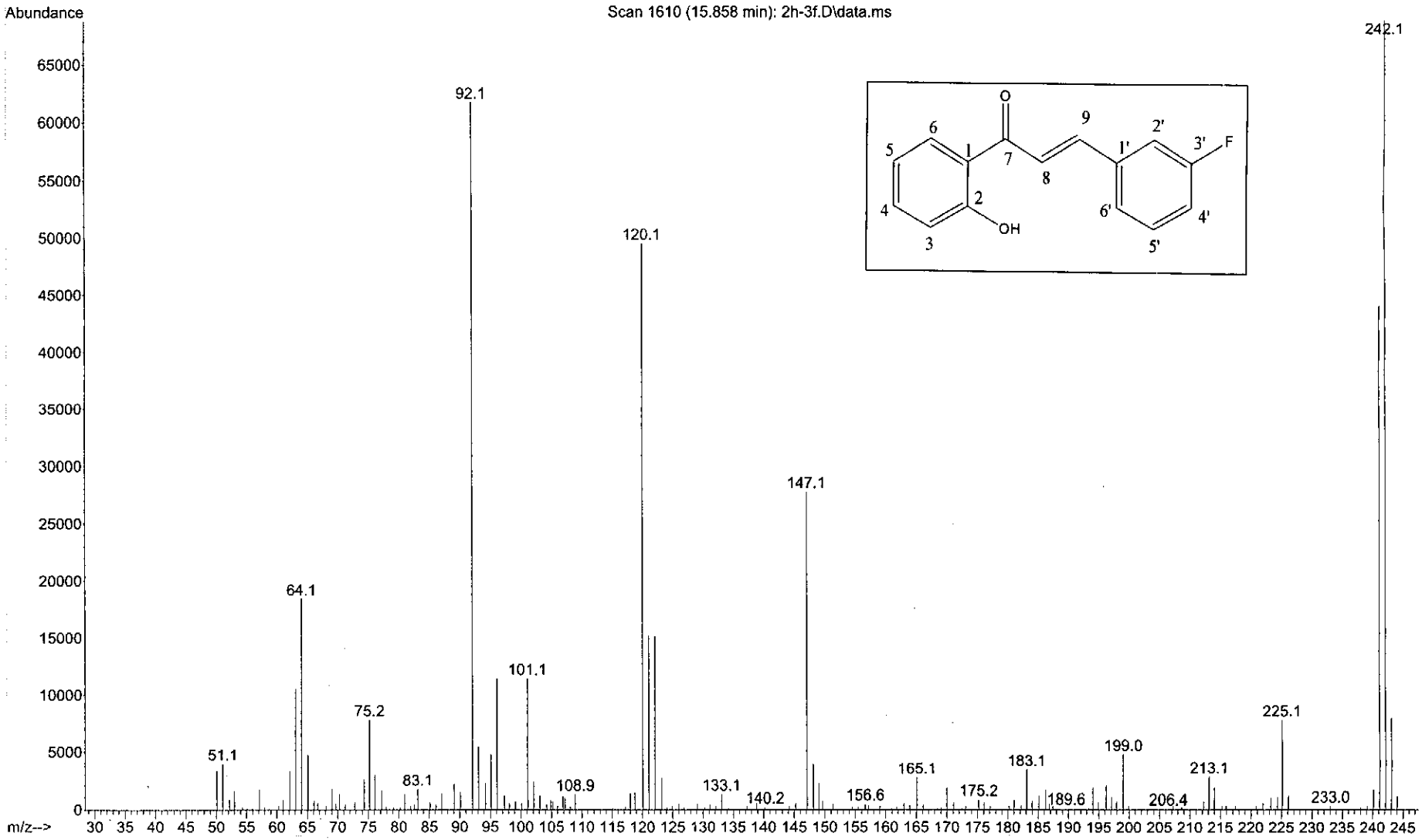
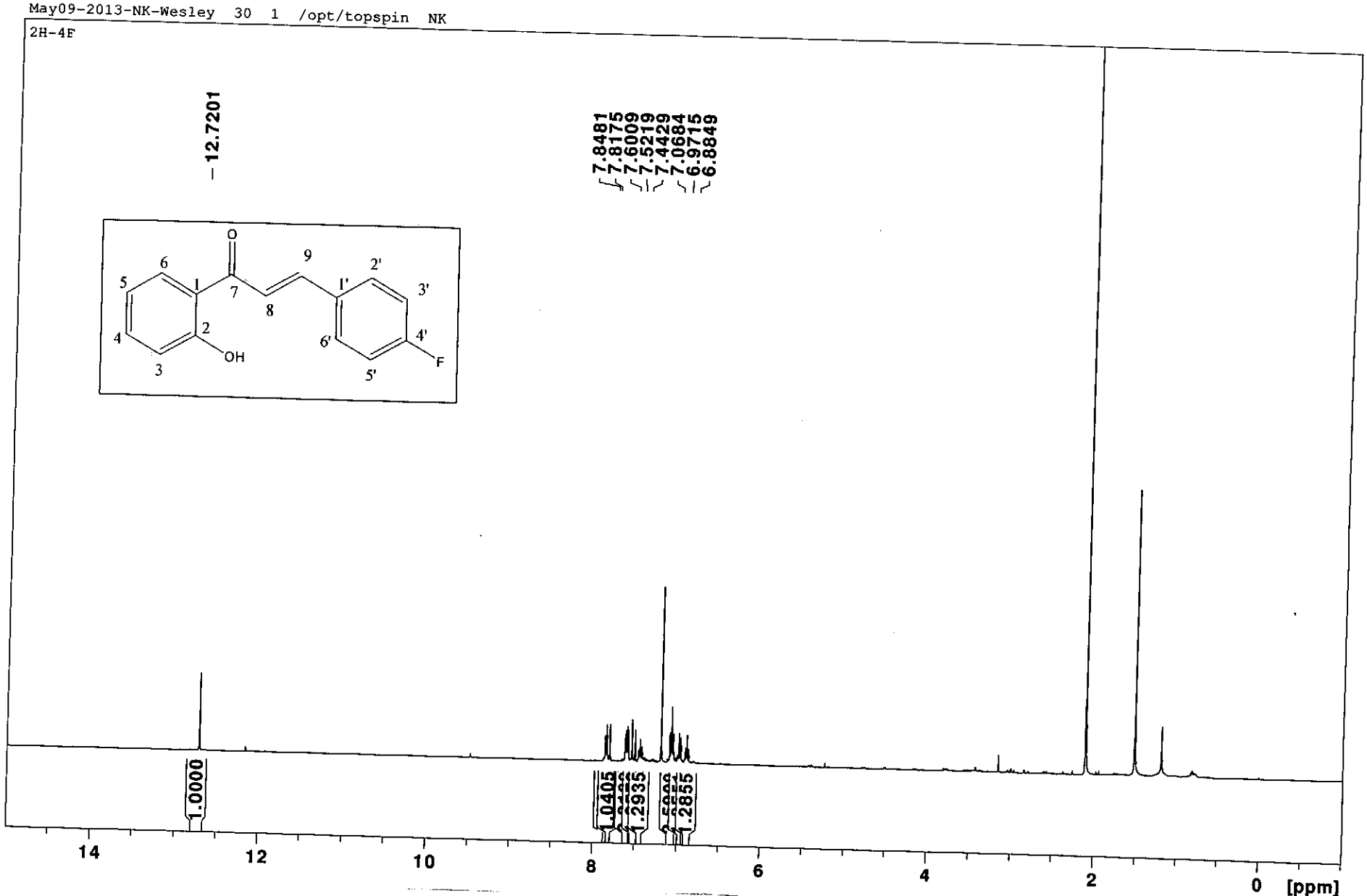
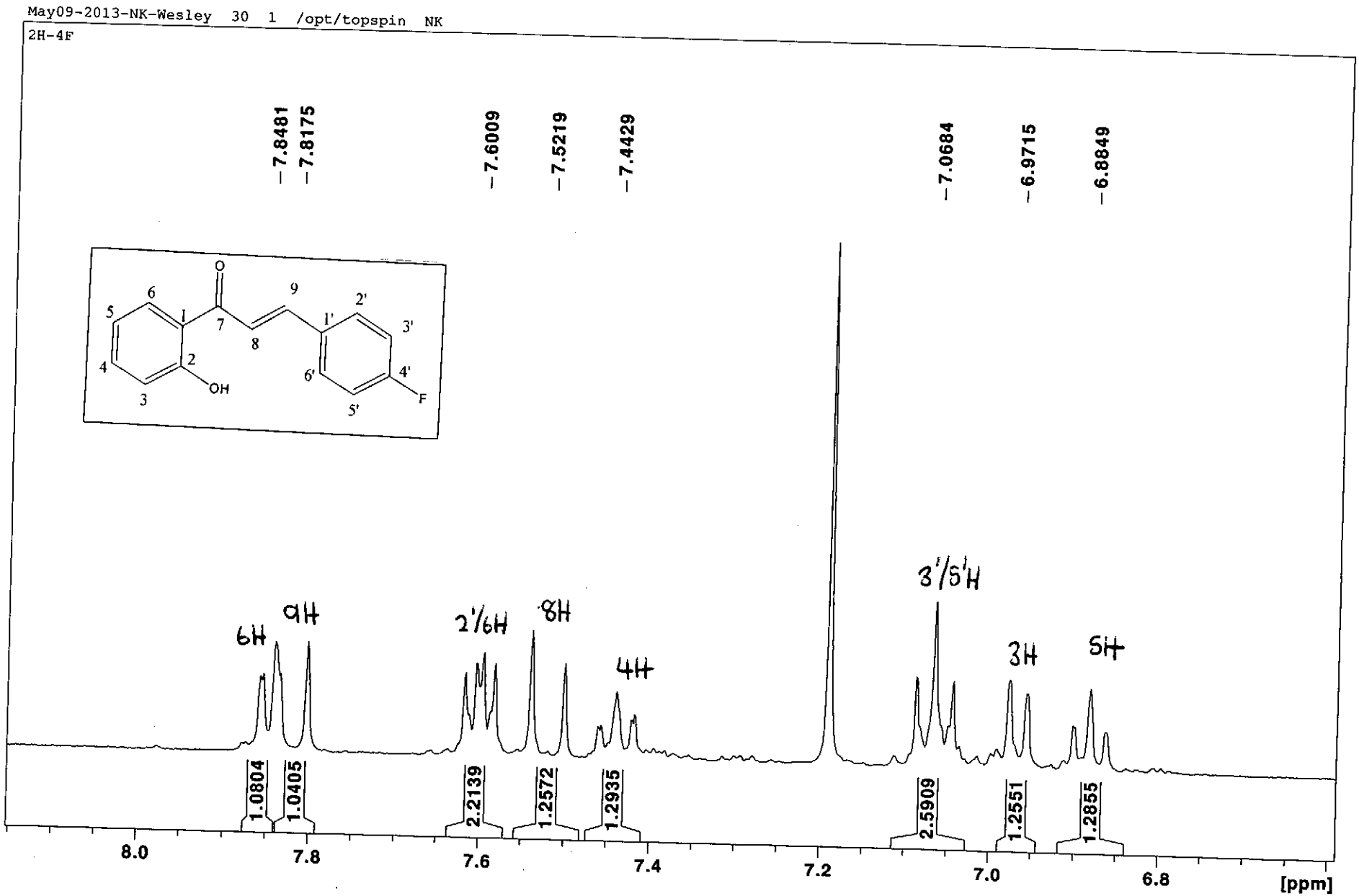


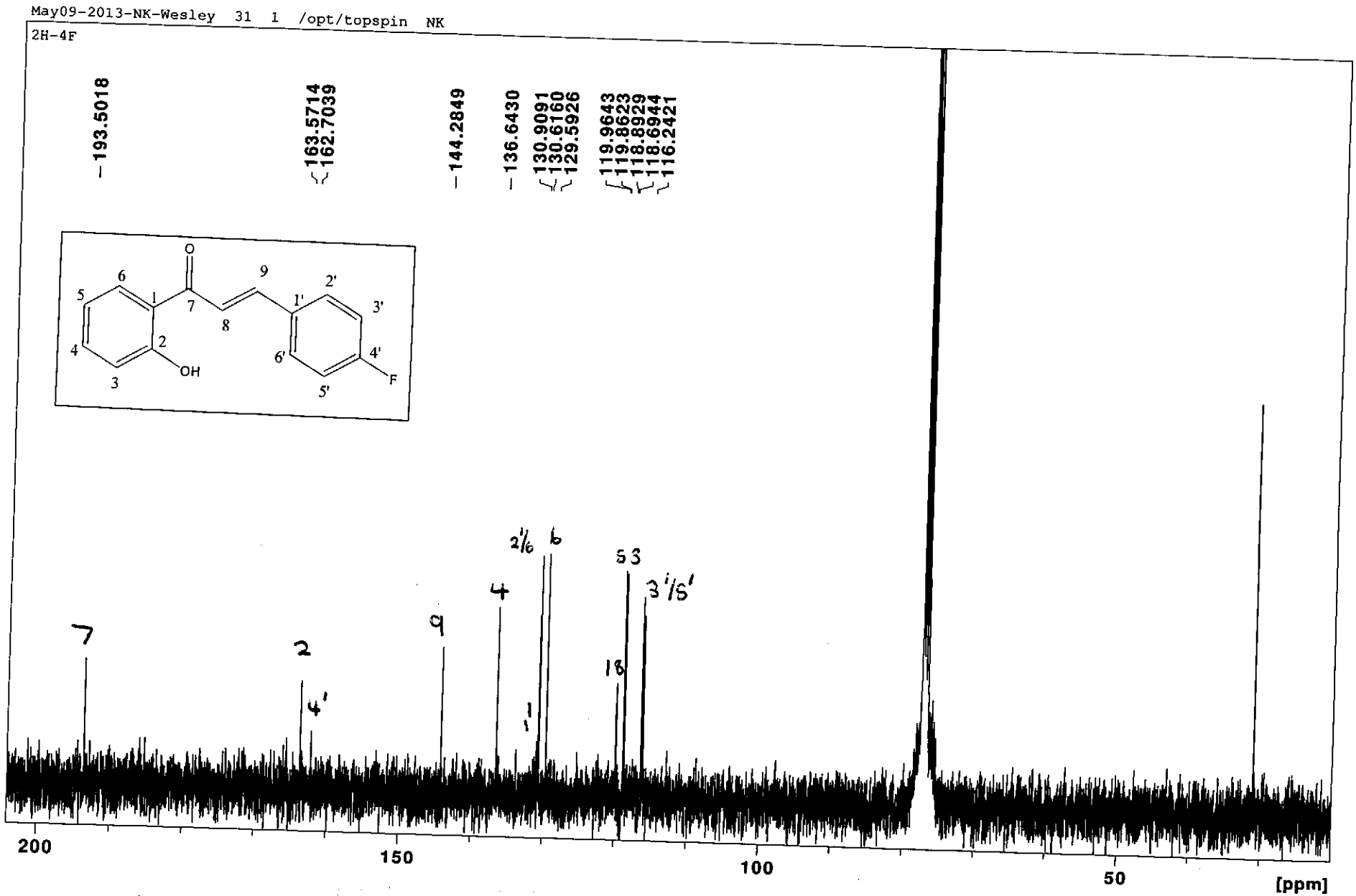
GC-MS spectrum of 3'-fluoro-2-hydroxychalcone, (III)



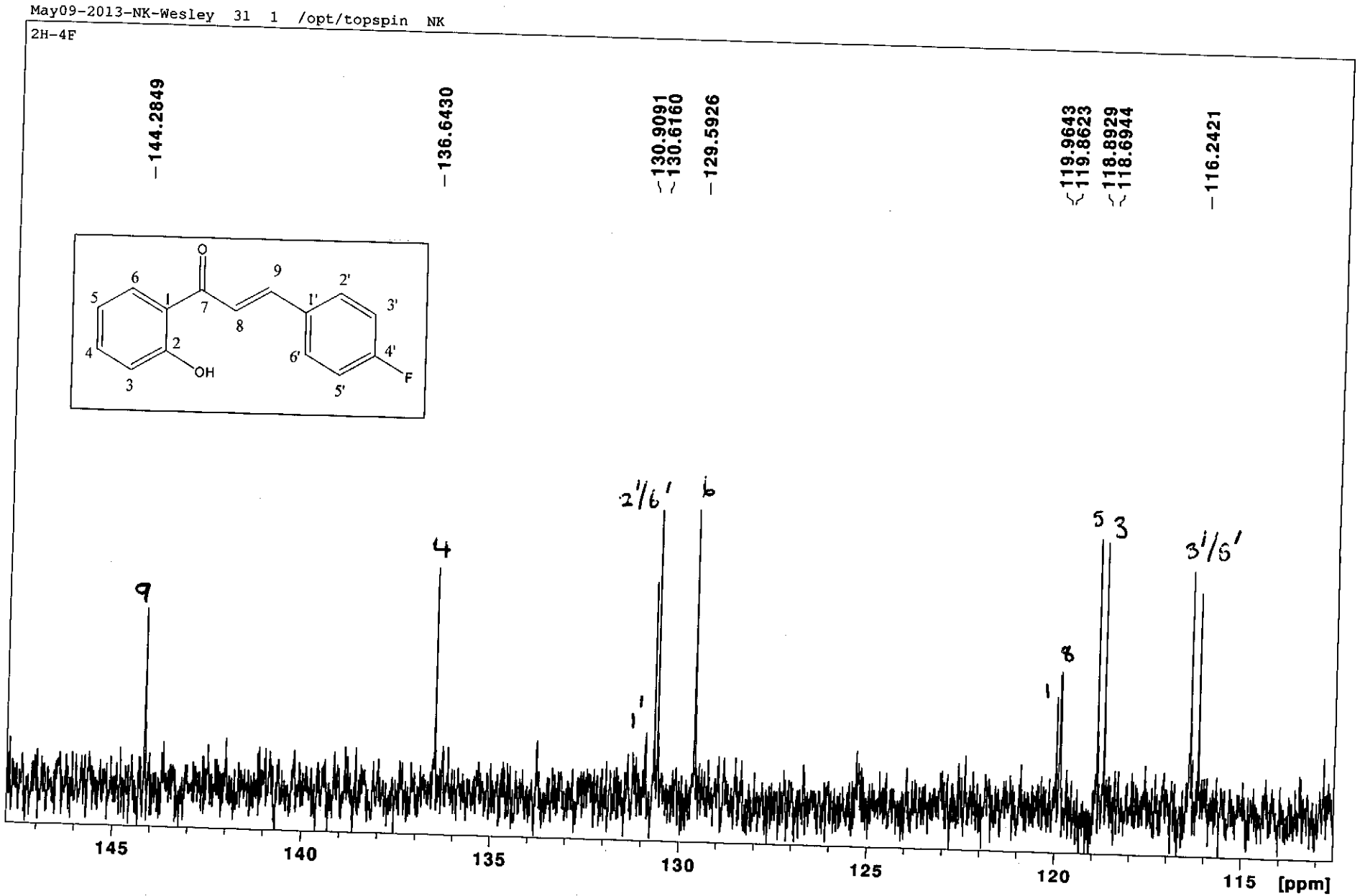
^{1}H NMR spectrum of 4'-fluoro-2-hydroxychalcone, (IV)



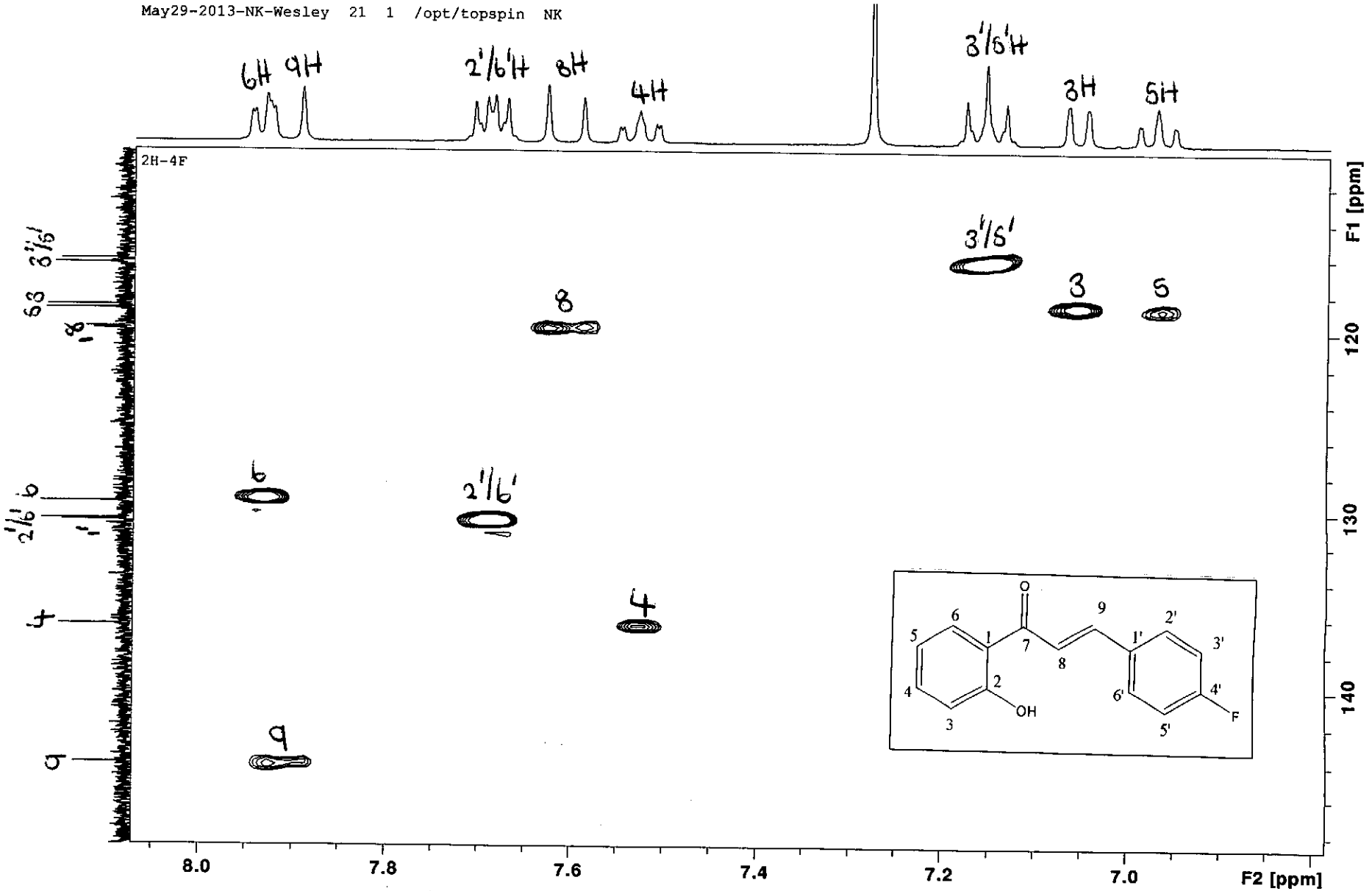
^{1}H NMR spectrum of 4'-fluoro-2-hydroxychalcone, (IV)



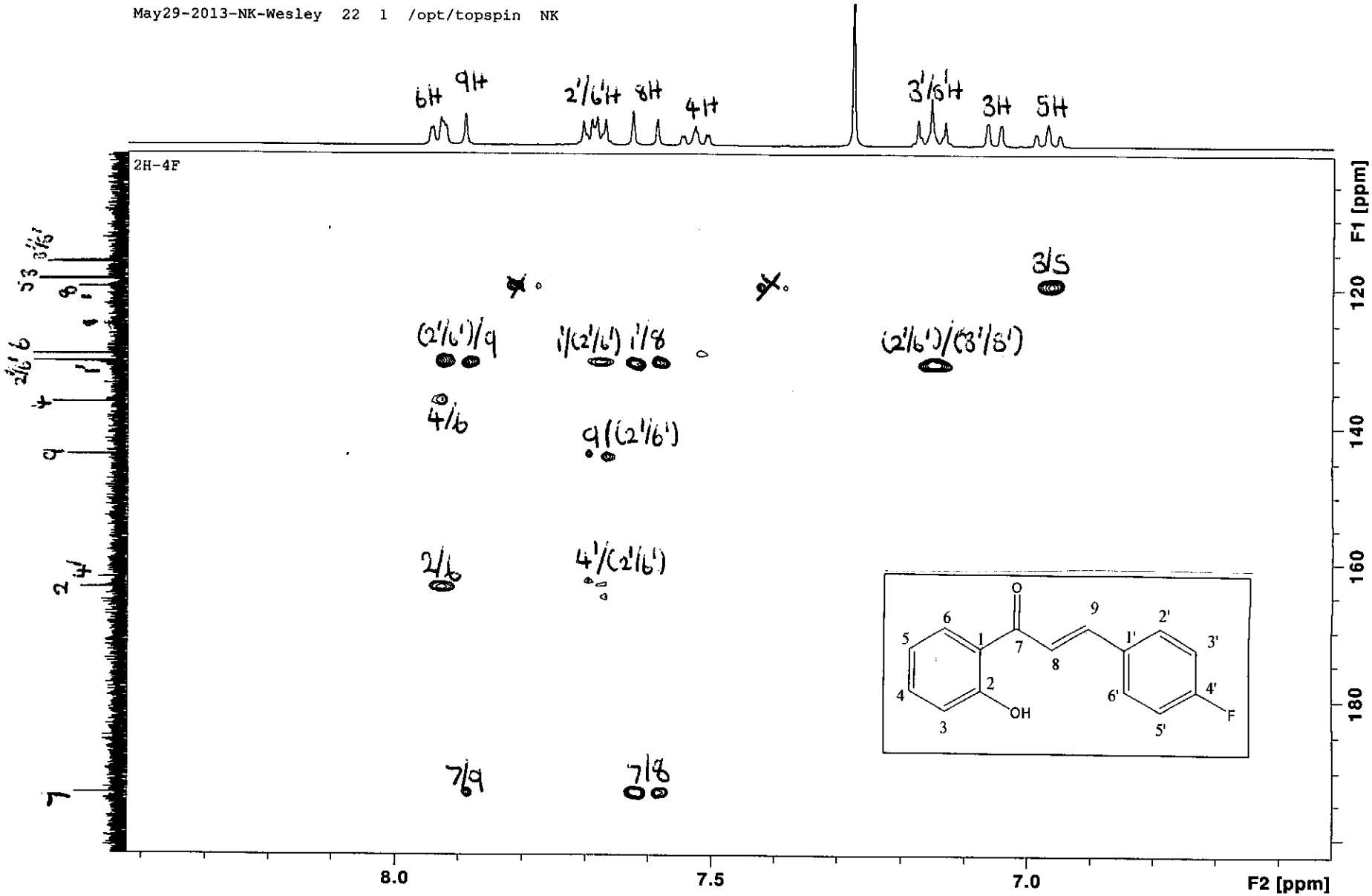
^{13}C NMR spectrum of 4'-fluoro-2-hydroxychalcone, (IV)



^{13}C NMR spectrum of 4'-fluoro-2-hydroxychalcone, (IV)



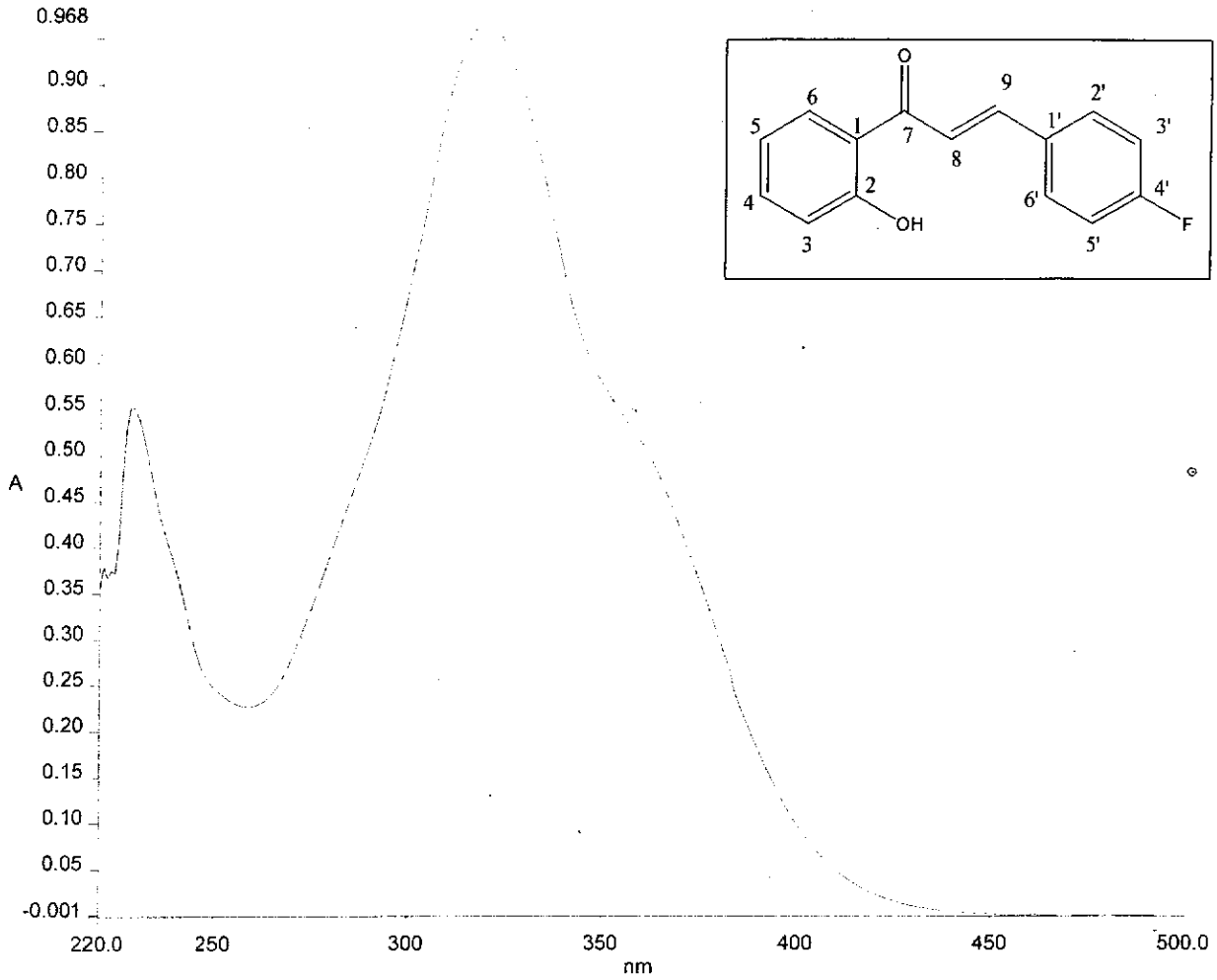
HSQC spectrum of 4'-fluoro-2-hydroxychalcone, (IV)



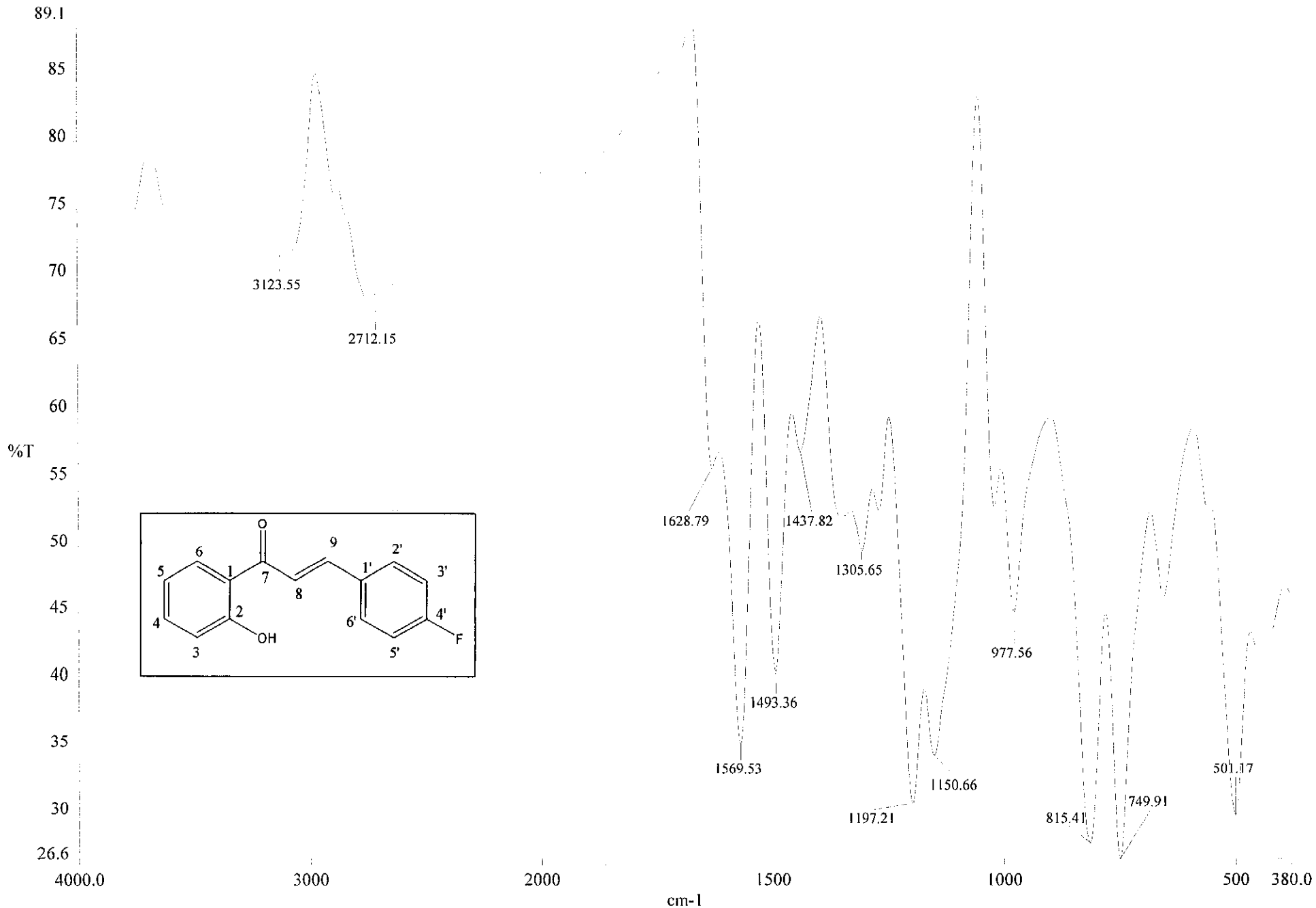
HMBC spectrum of 4'-fluoro-2-hydroxychalcone, (IV)

λmax (319 nm) - 0.967 log ε = 4.13

Date: 2013/05/20 Time: 11:58:44 AM



Ultra violet (UV) spectrum of 4'-fluoro-2-hydroxychalcone, (IV)



Infra-Red (IR) spectrum of 4'-fluoro-2-hydroxychalcone, (IV)

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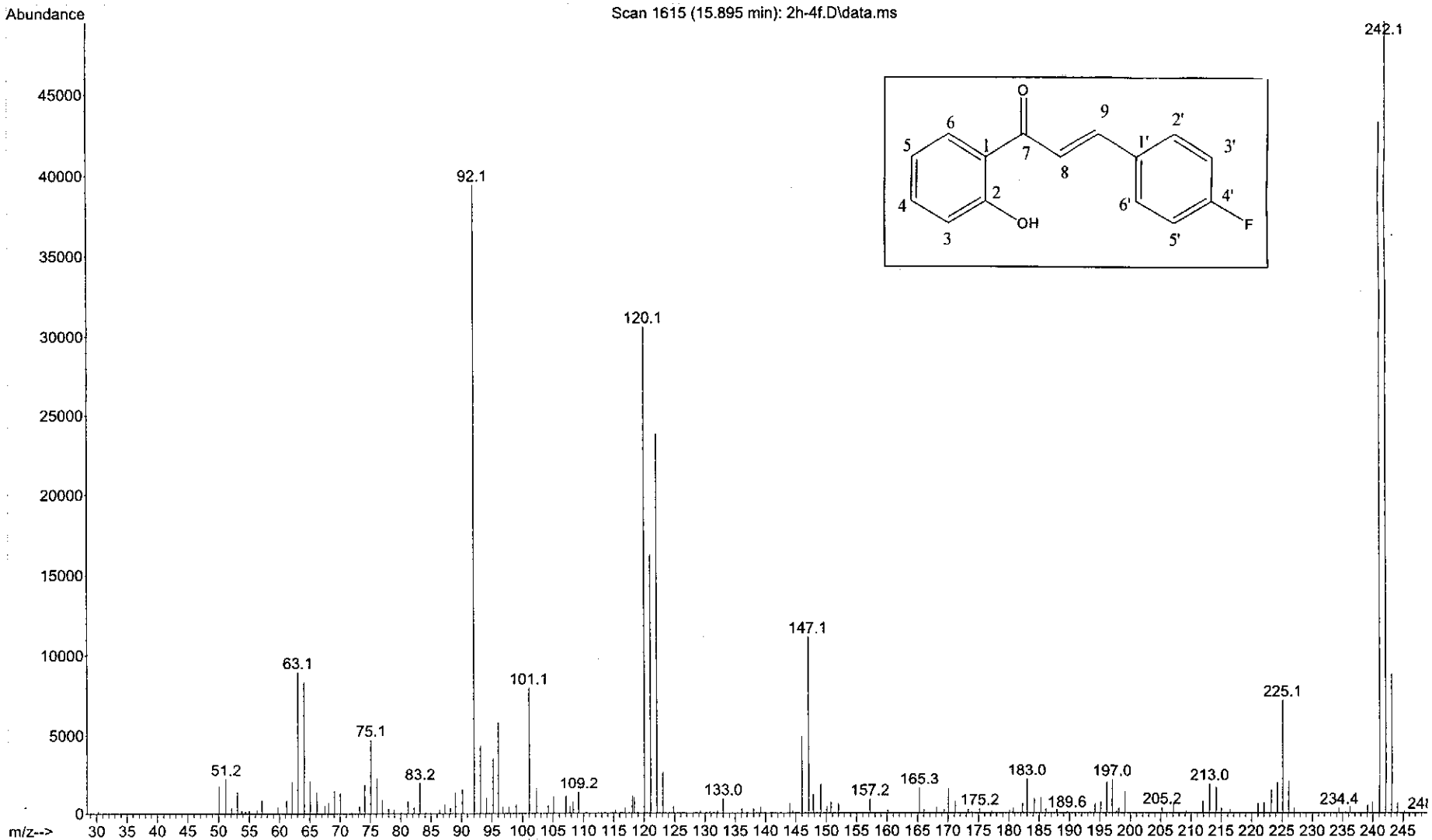
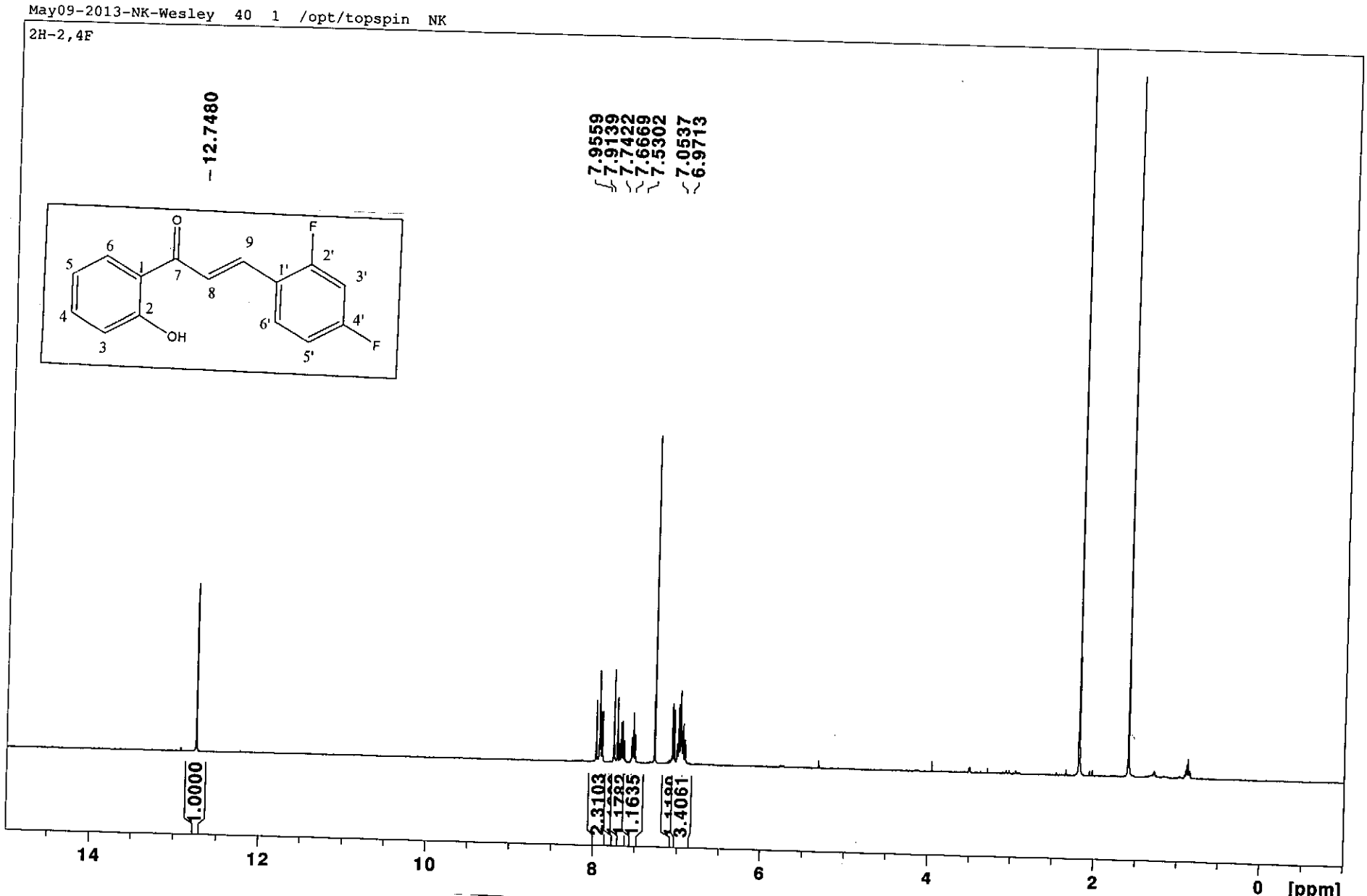
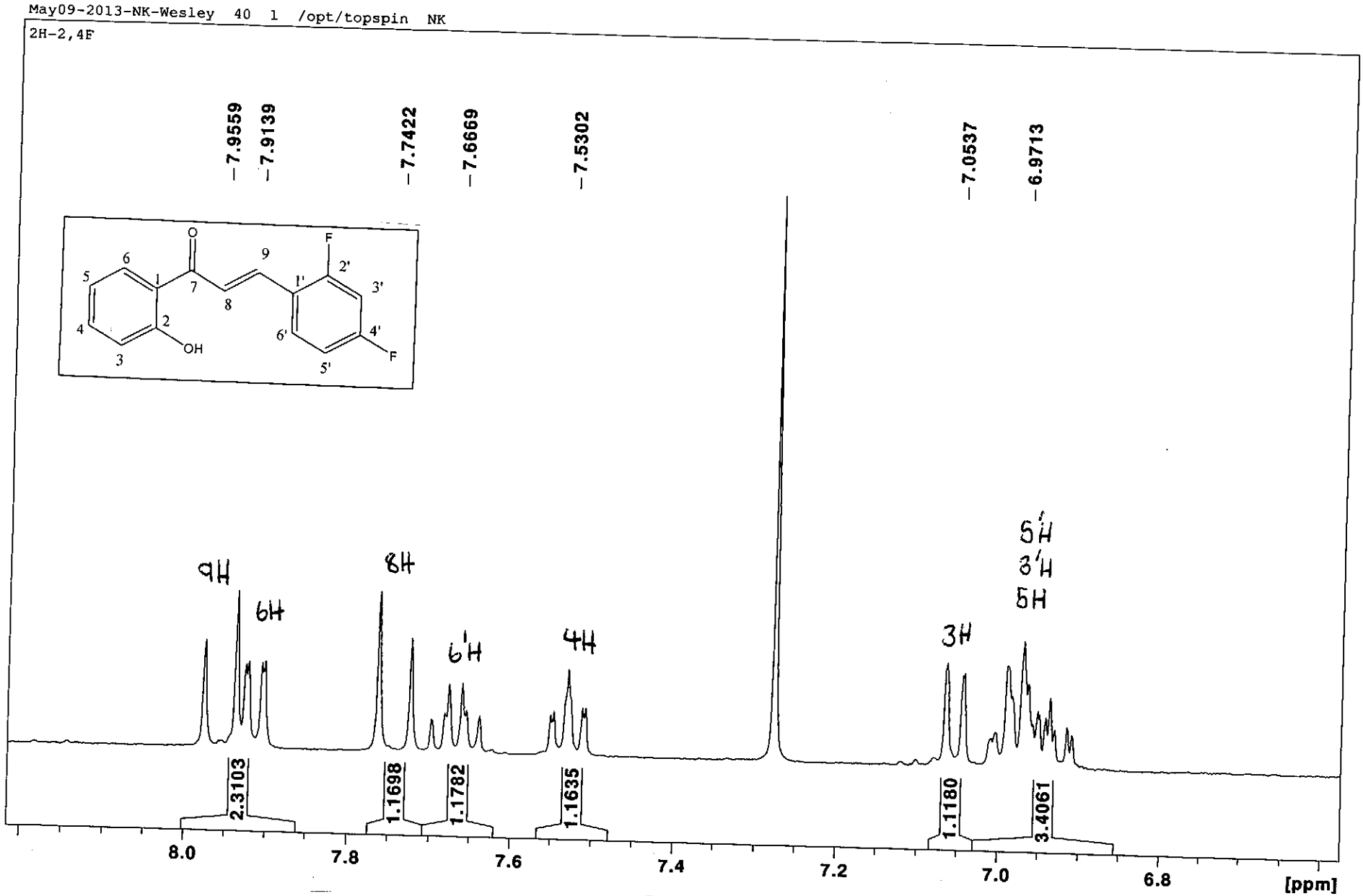


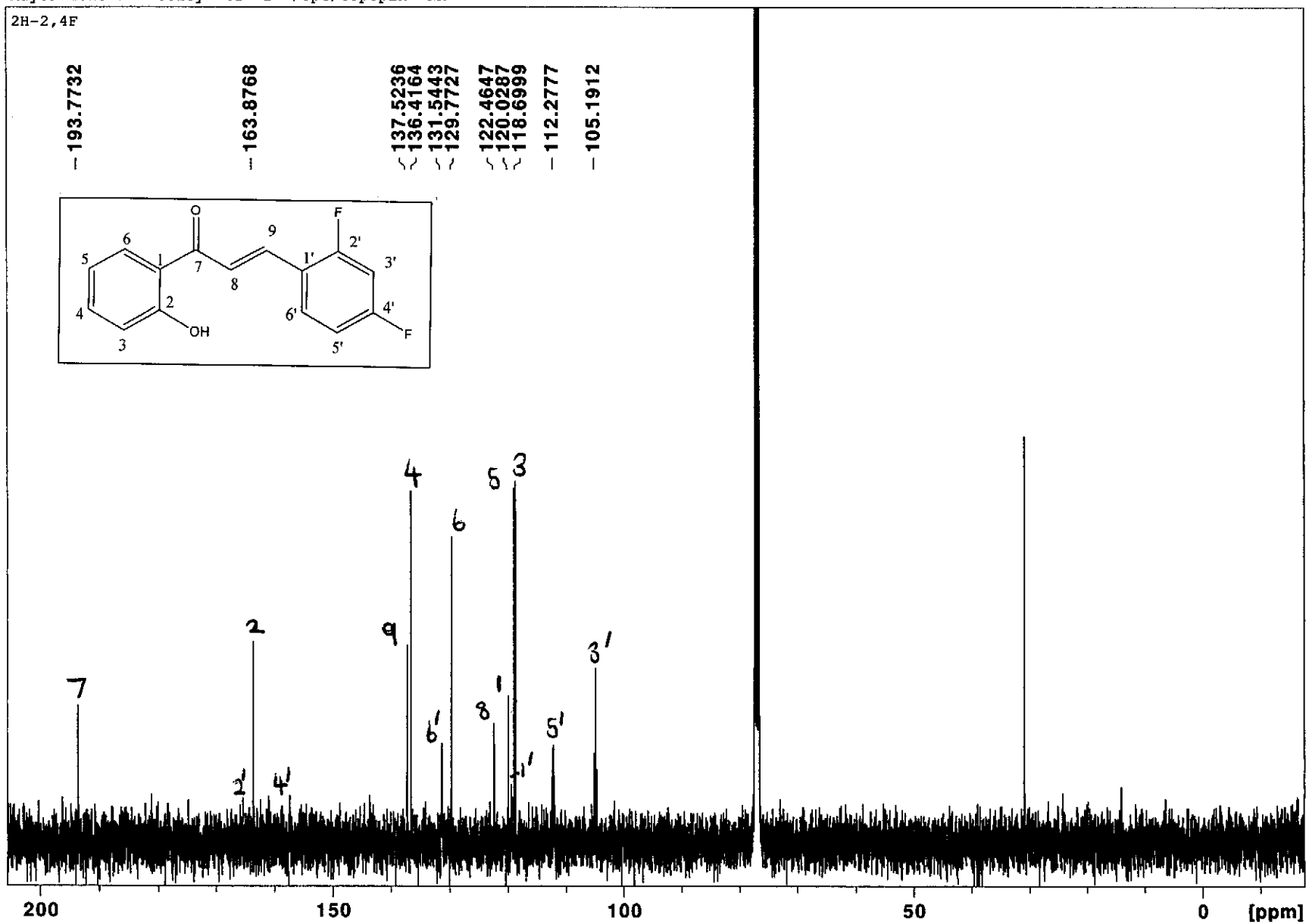
GC-MS spectrum of 4'-fluoro-2-hydroxychalcone, (IV)



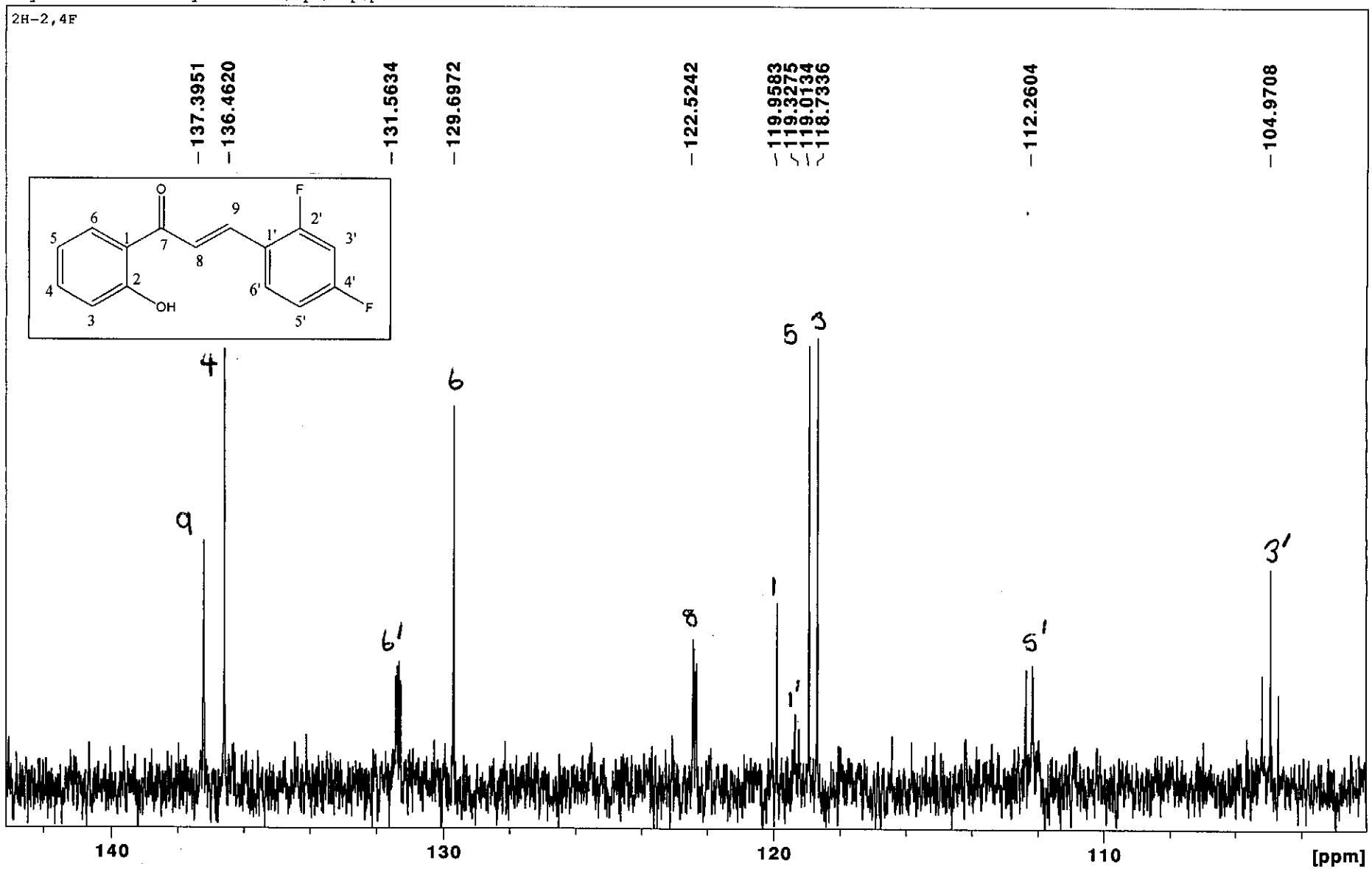
^{1}H NMR spectrum of 2', 4'-difluoro-2-hydroxychalcone, (V)



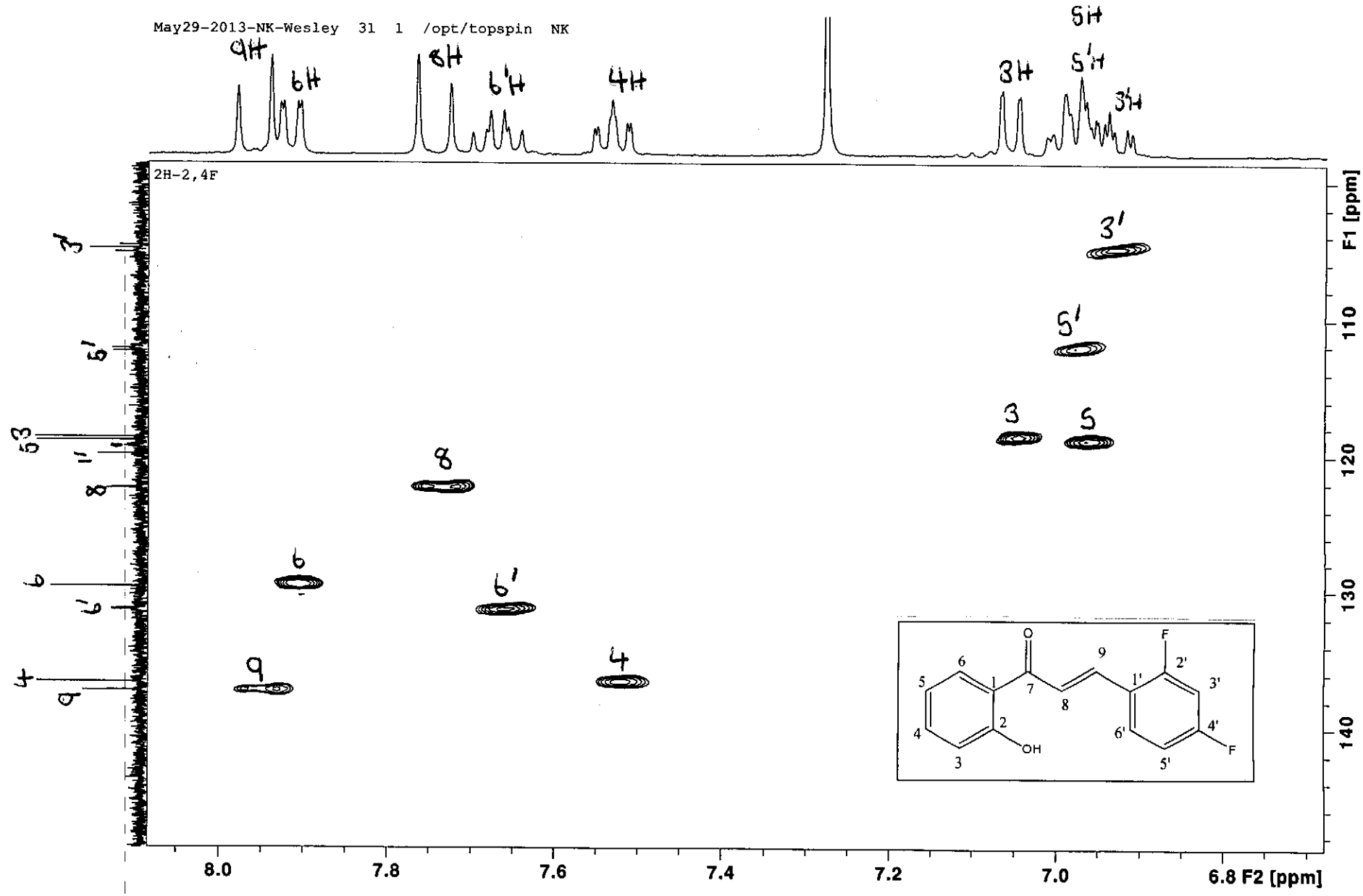
^{1}H NMR spectrum of 2', 4'-difluoro-2-hydroxychalcone, (V)



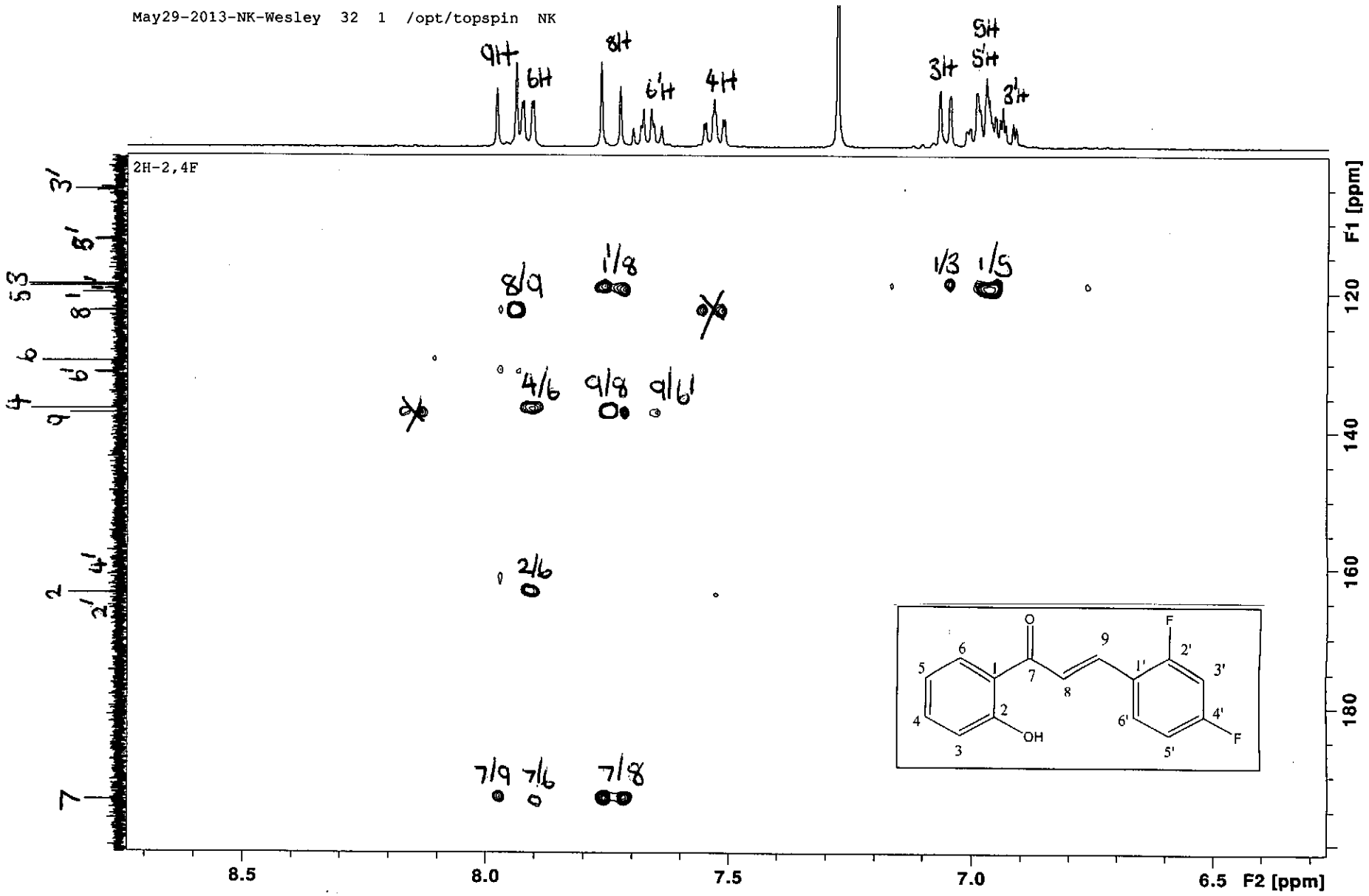
^{13}C NMR spectrum of 2', 4'-difluoro-2-hydroxychalcone, (V)



^{13}C NMR spectrum of 2', 4'-difluoro-2-hydroxychalcone, (V)



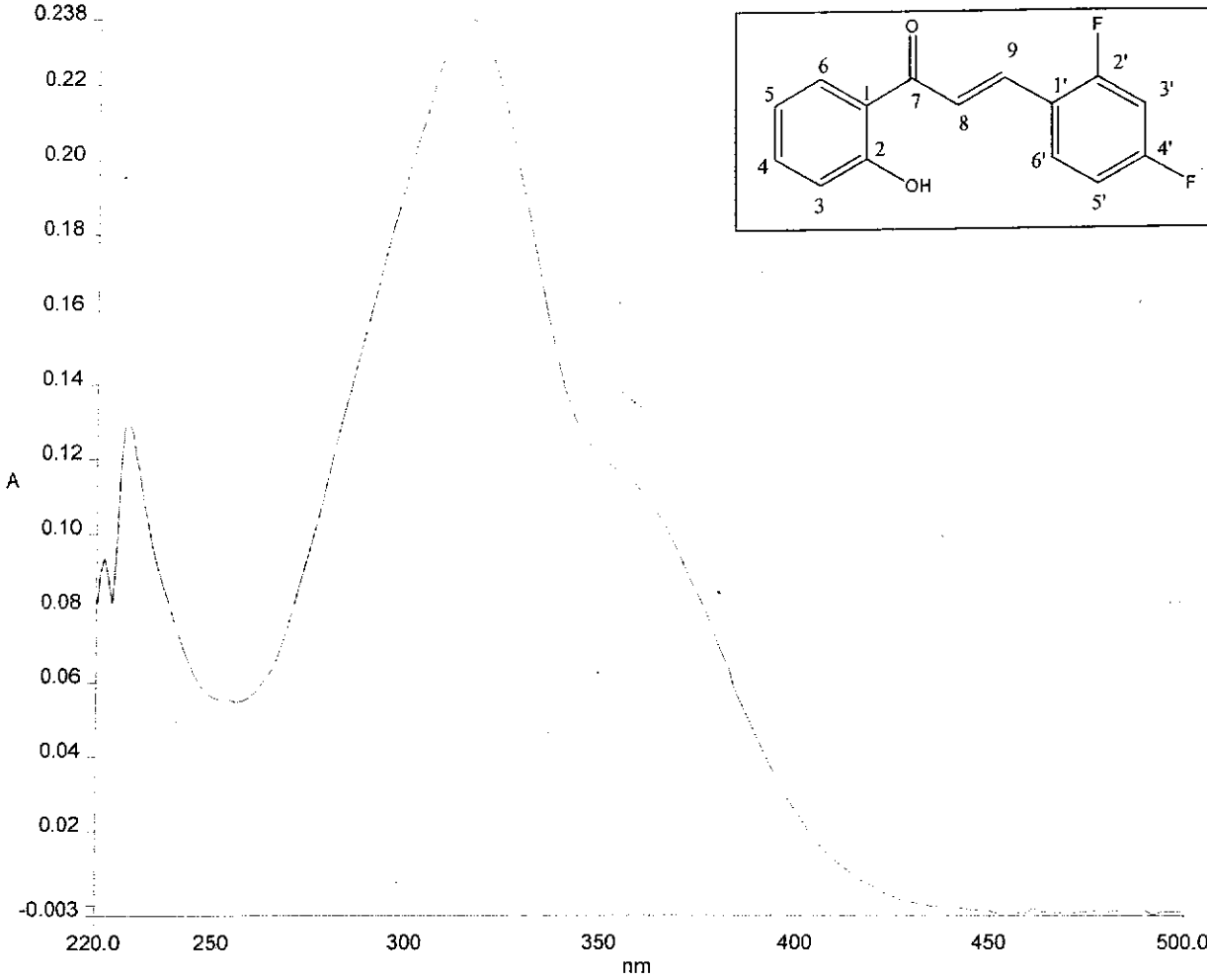
HSQC spectrum of 2', 4'-difluoro-2-hydroxychalcone, (V)



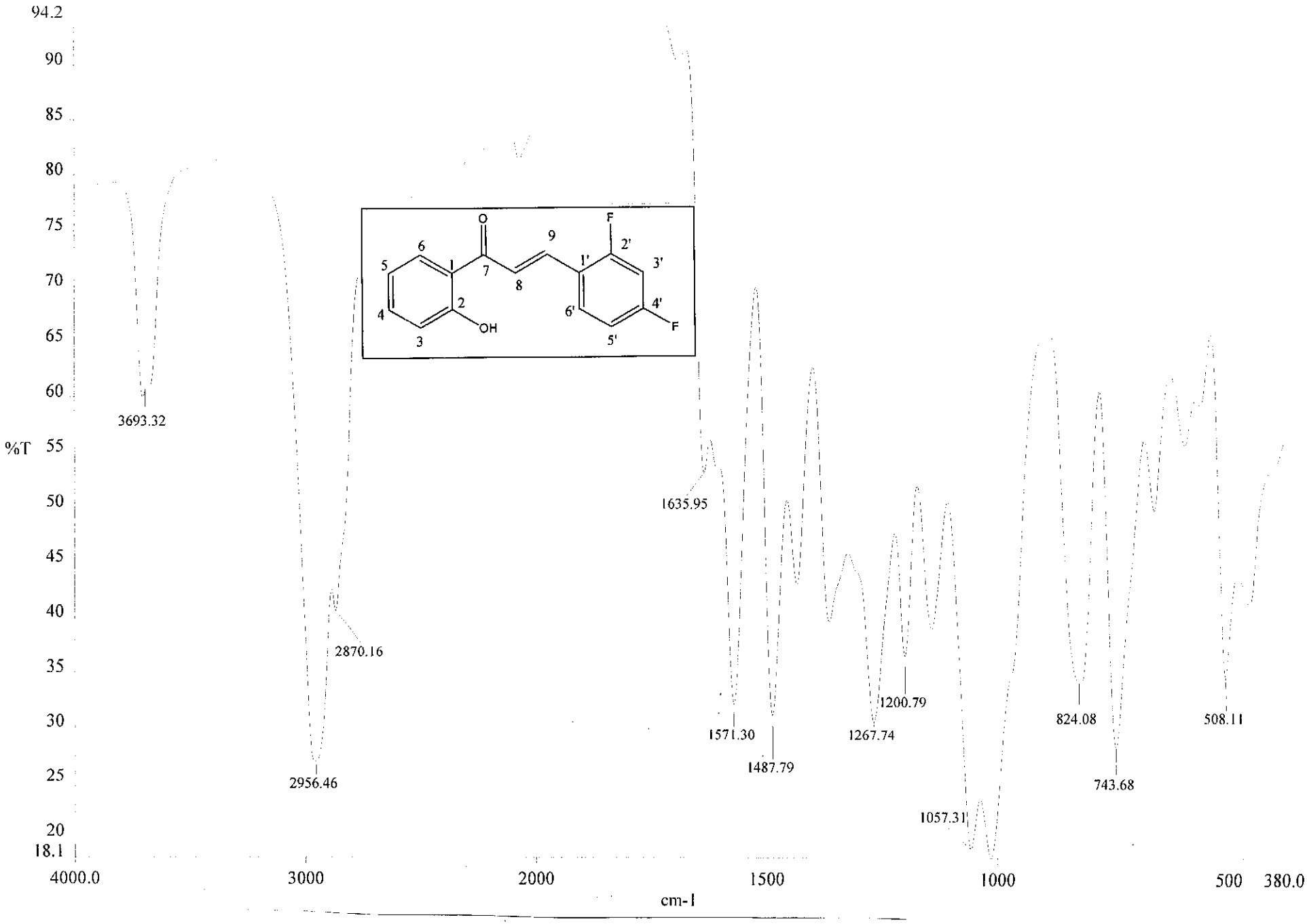
HMBC spectrum of 2', 4'-difluoro-2-hydroxychalcone, (V)

λmax (315nm) - 0.287 log ε = 3.07

Date: 2013/05/20 Time: 12:02:18 PM



Ultra violet (UV) spectrum of 2', 4'-difluoro-2-hydroxychalcone, (V)



Infra-Red (IR) spectrum of 2', 4'-difluoro-2-hydroxychalcone, (V)

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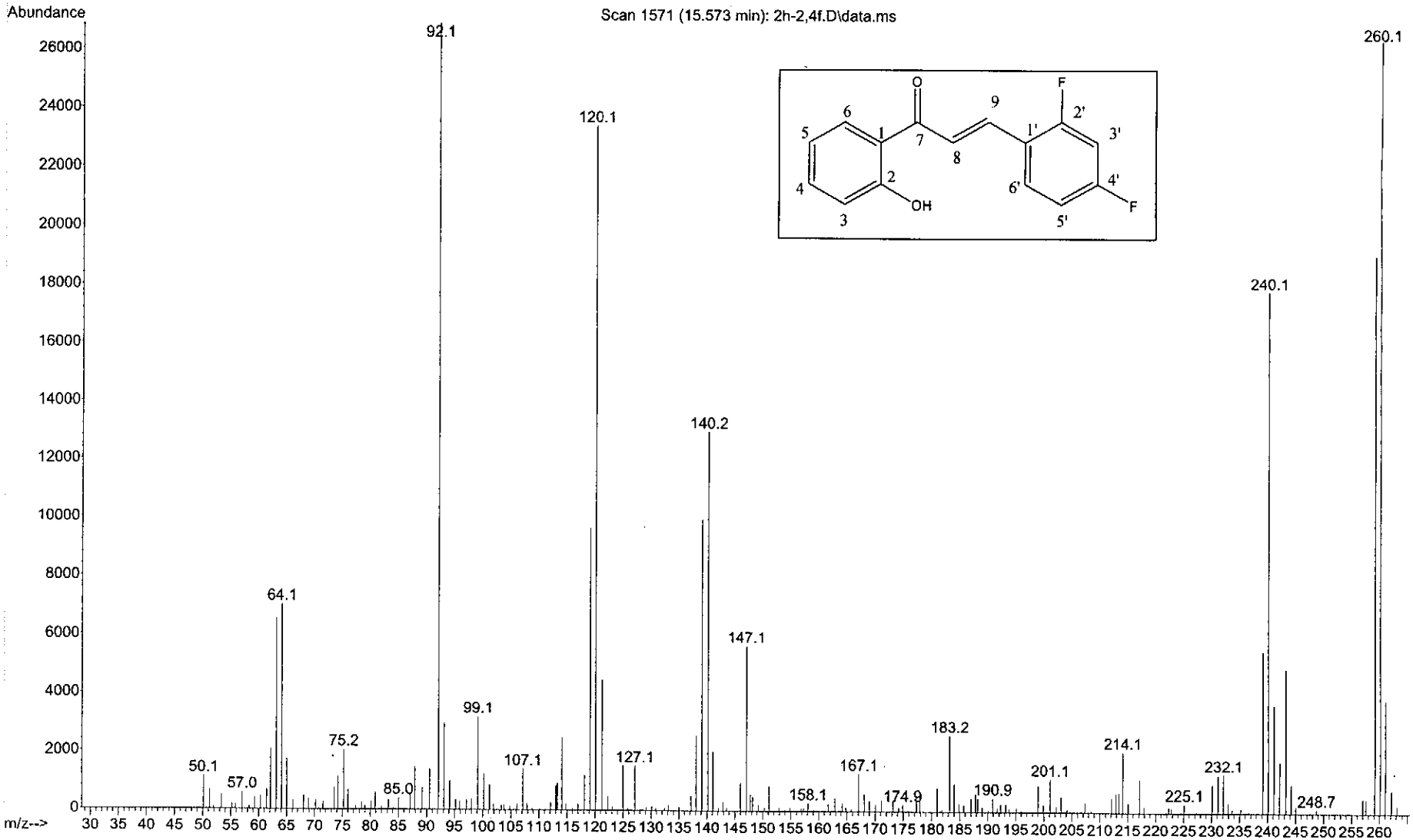
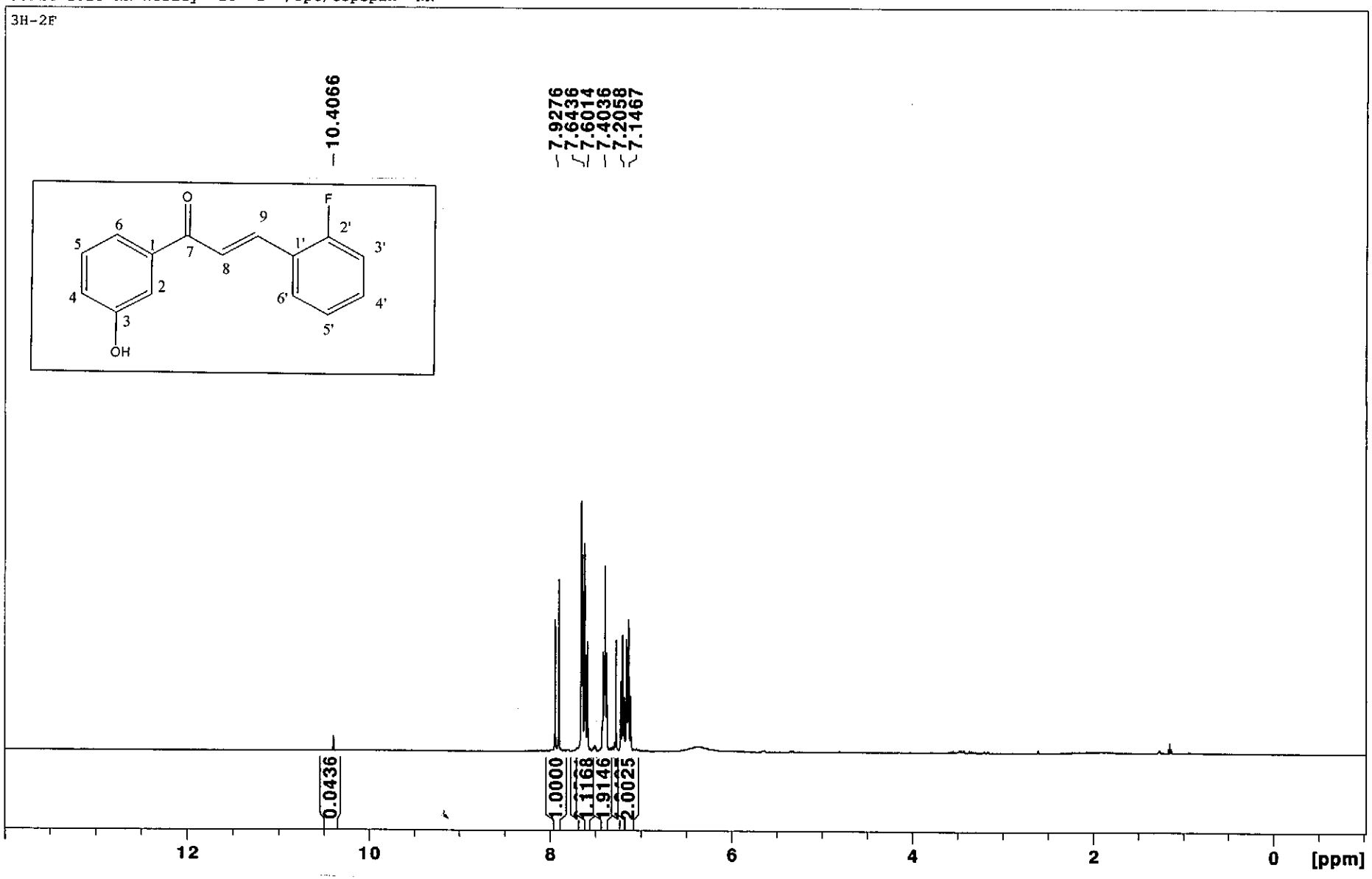
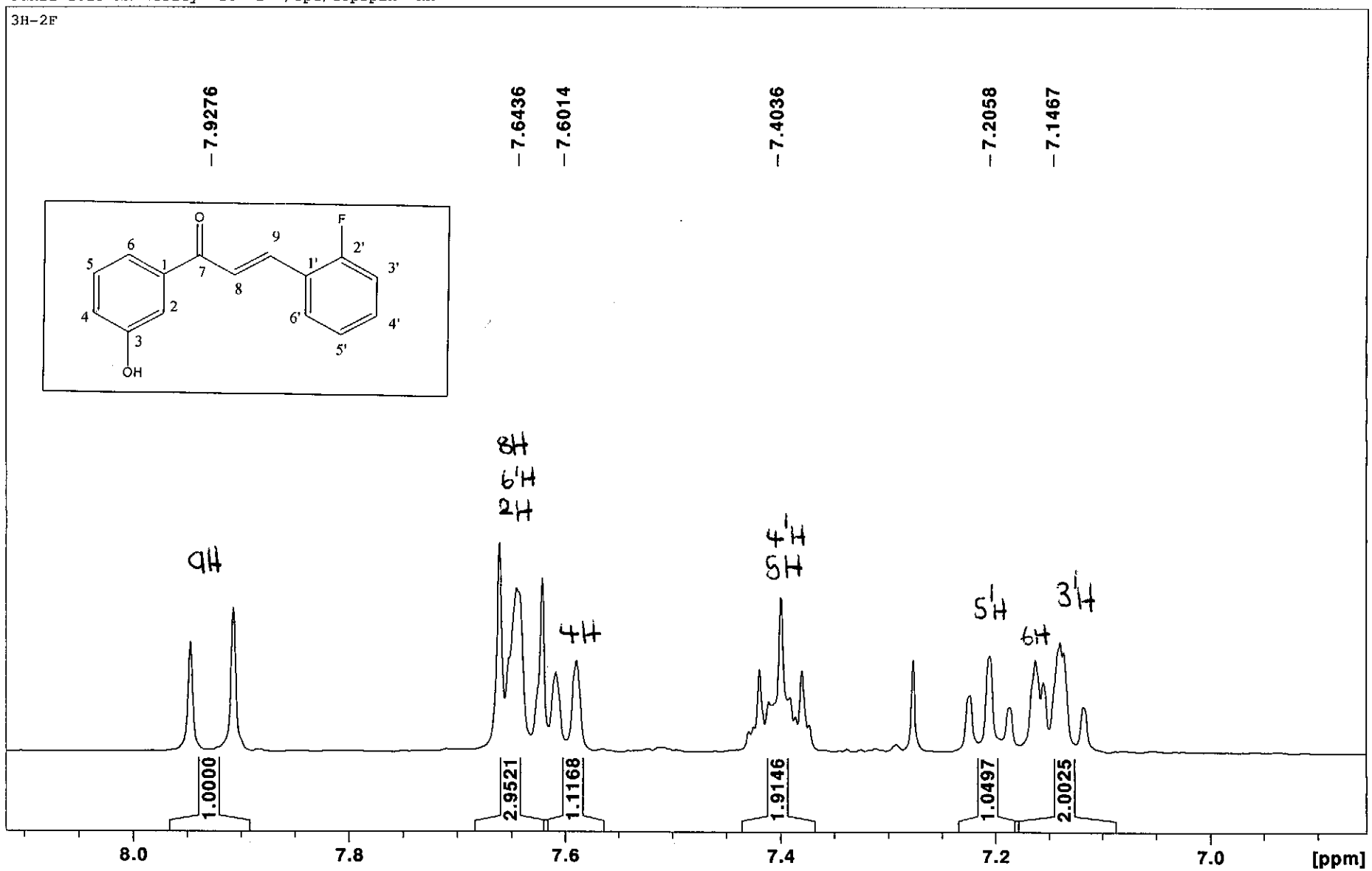


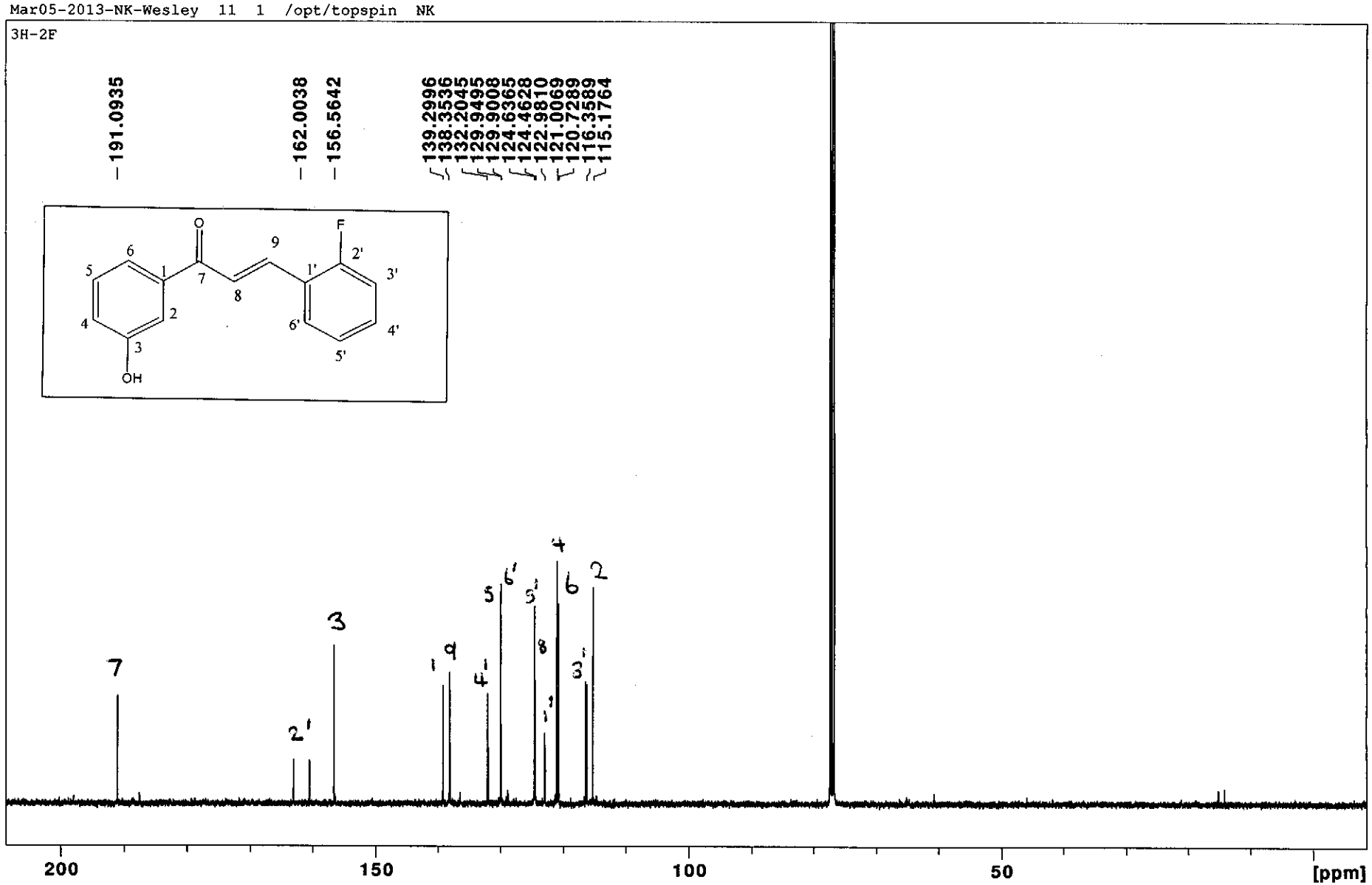
GC-MS spectrum of 2', 4'-difluoro-2-hydroxychalcone, (V)



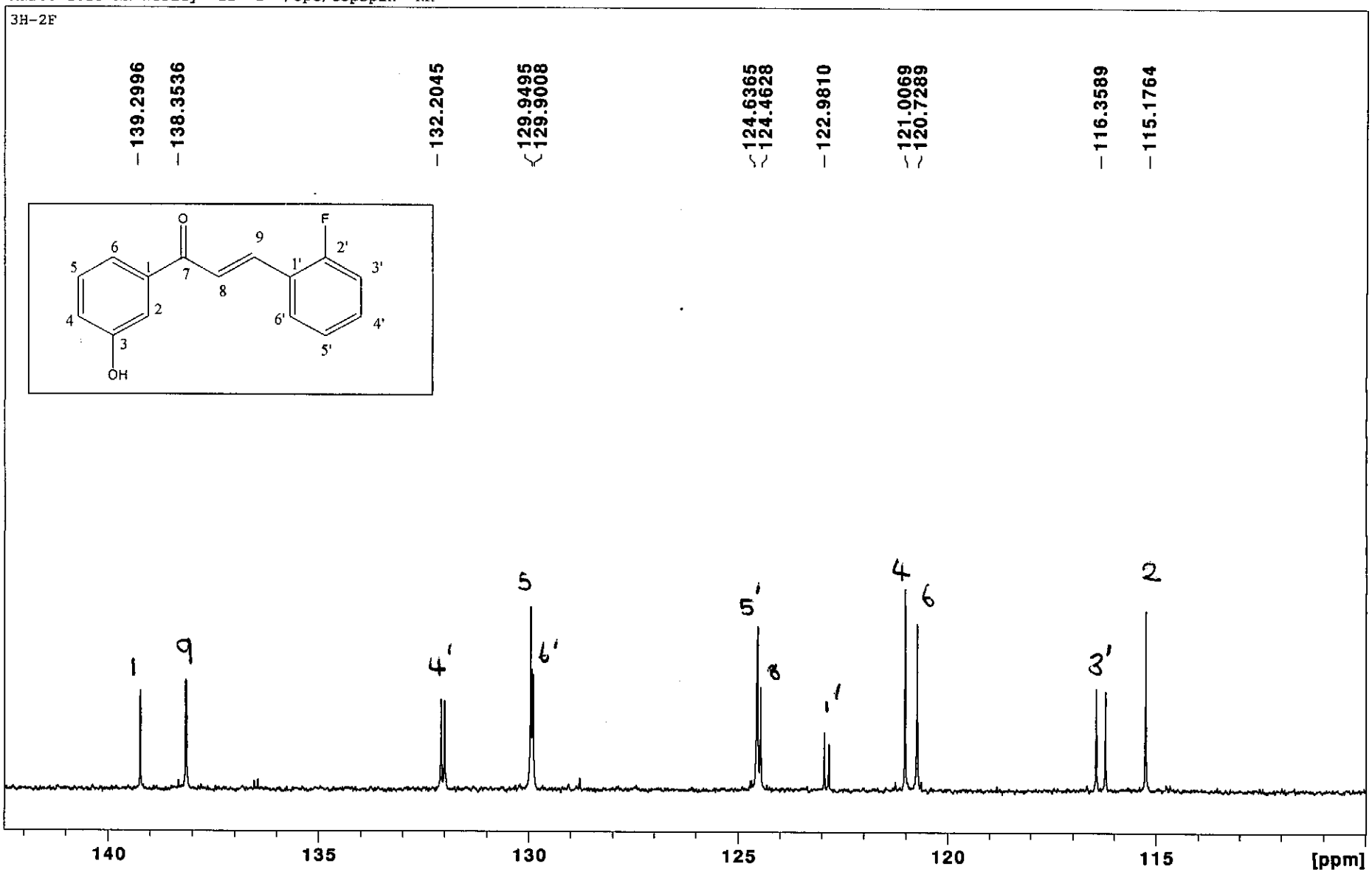
^{1}H NMR spectrum of 2'-fluoro-3-hydroxychalcone, (VI)



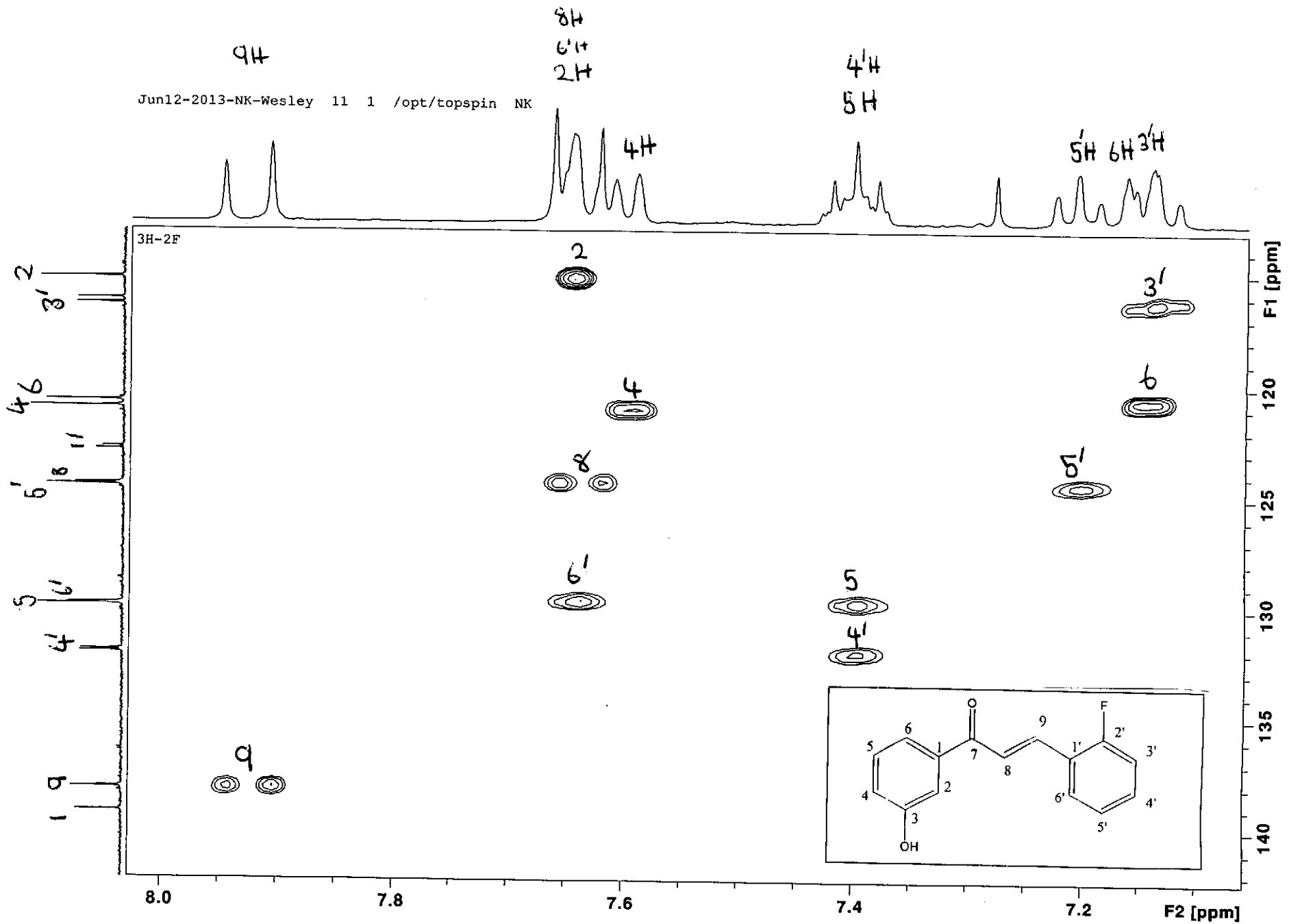
^{1}H NMR spectrum of 2'-fluoro-3-hydroxychalcone, (VI)



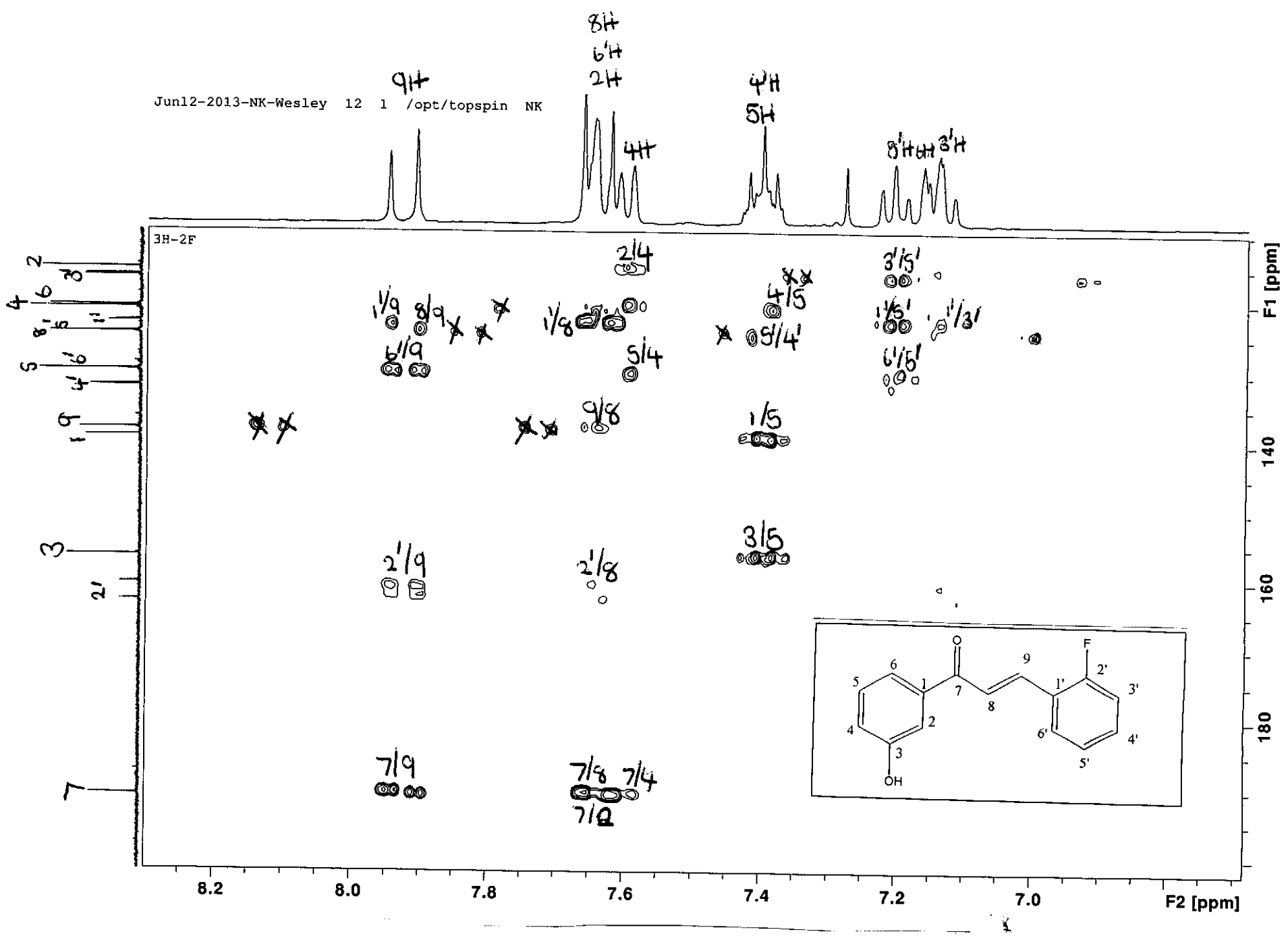
^{13}C NMR spectrum of 2'-fluoro-3-hydroxychalcone, (VI)



^{13}C NMR spectrum of 2'-fluoro-3-hydroxychalcone, (VI)



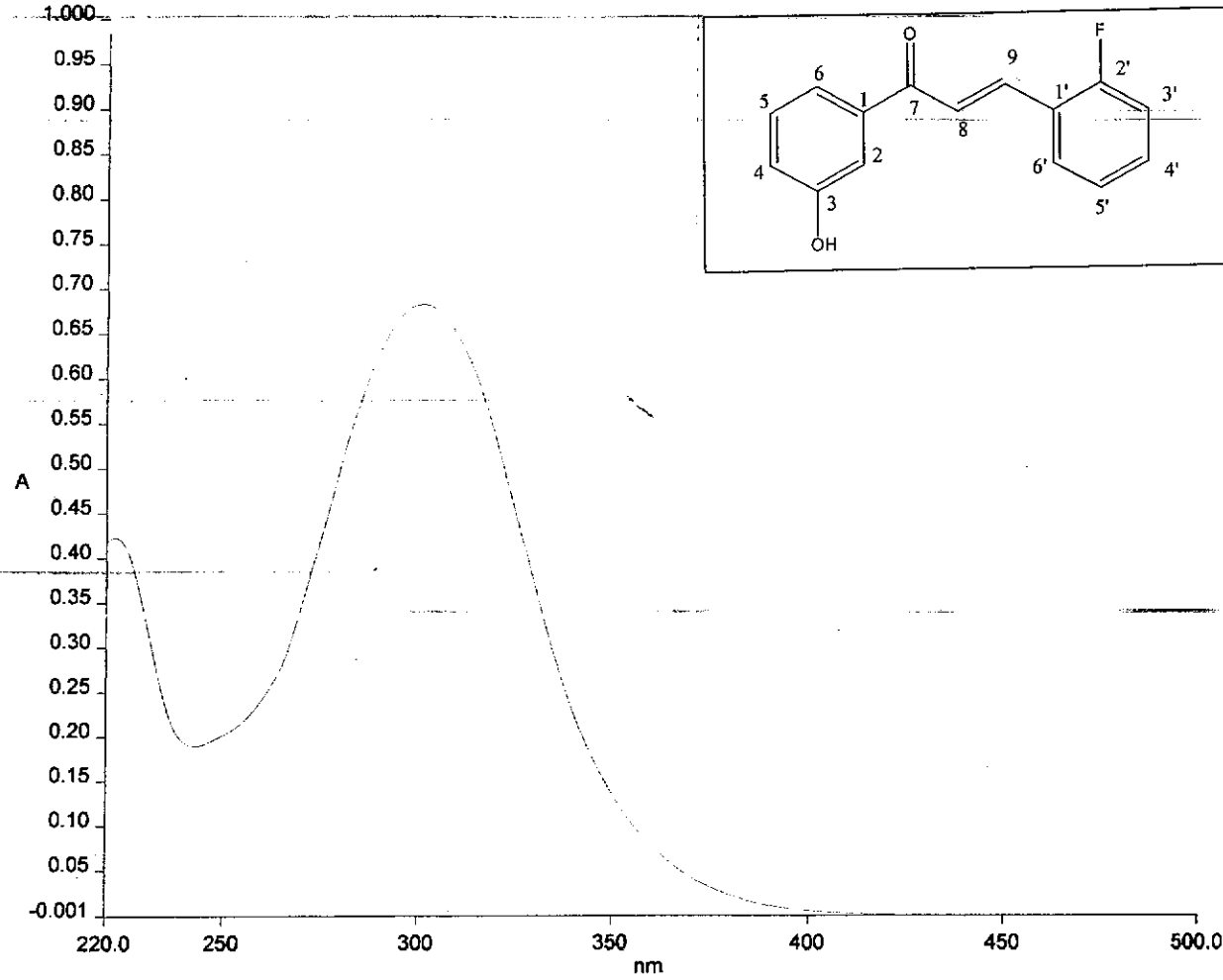
HSQC spectrum of 2'-fluoro-3-hydroxychalcone, (VI)



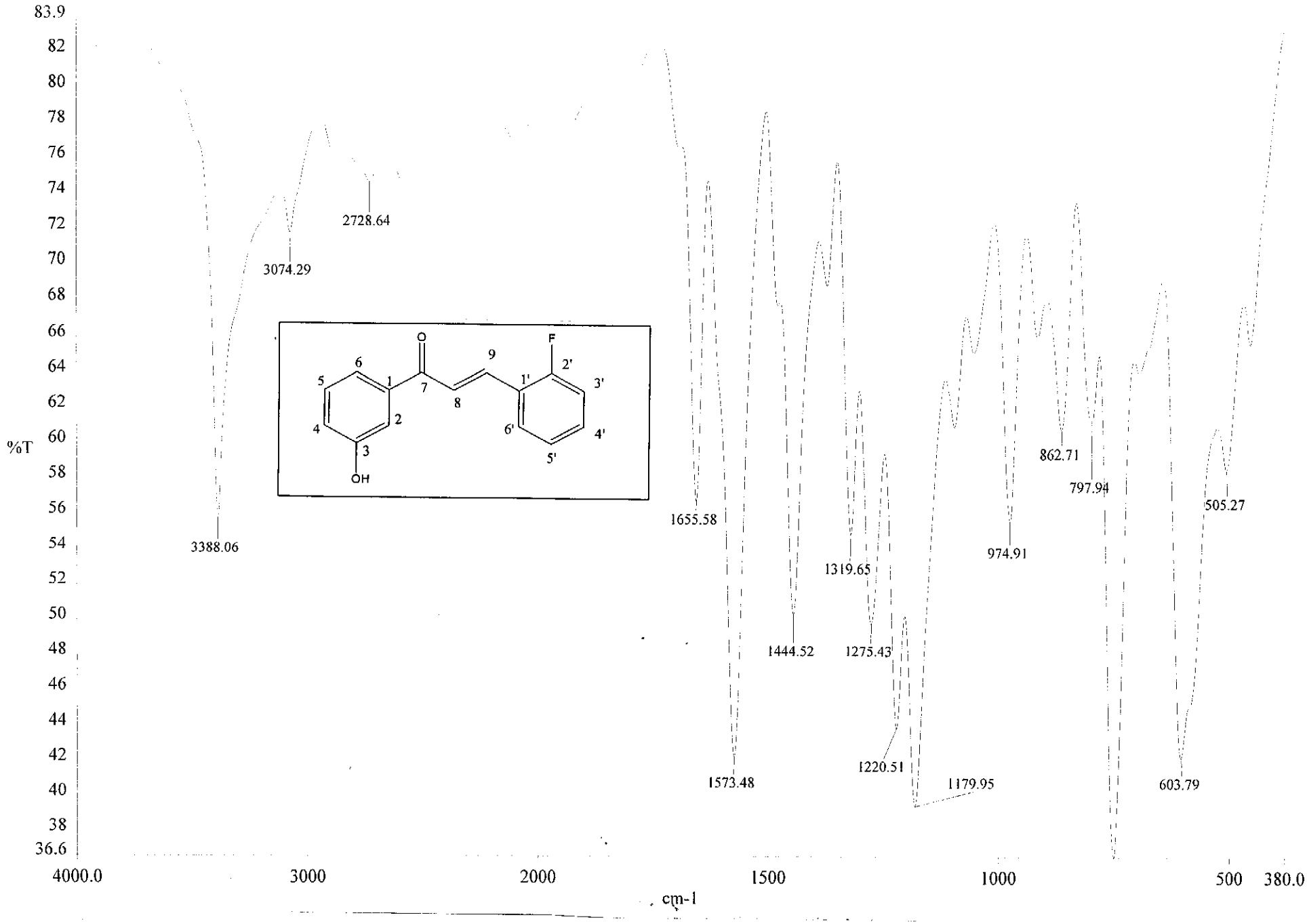
HMBC spectrum of 2'-fluoro-3-hydroxychalcone, (VI)

λmax (301nm) – 0.6822 log ε = 5.53

Date: 2013/06/14 Time: 09:30:32 AM



Ultra violet (UV) spectrum of 2'-fluoro-3-hydroxychalcone, (VI)



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Infra-Red (IR) spectrum of 2'-fluoro-3-hydroxychalcone, (VI)

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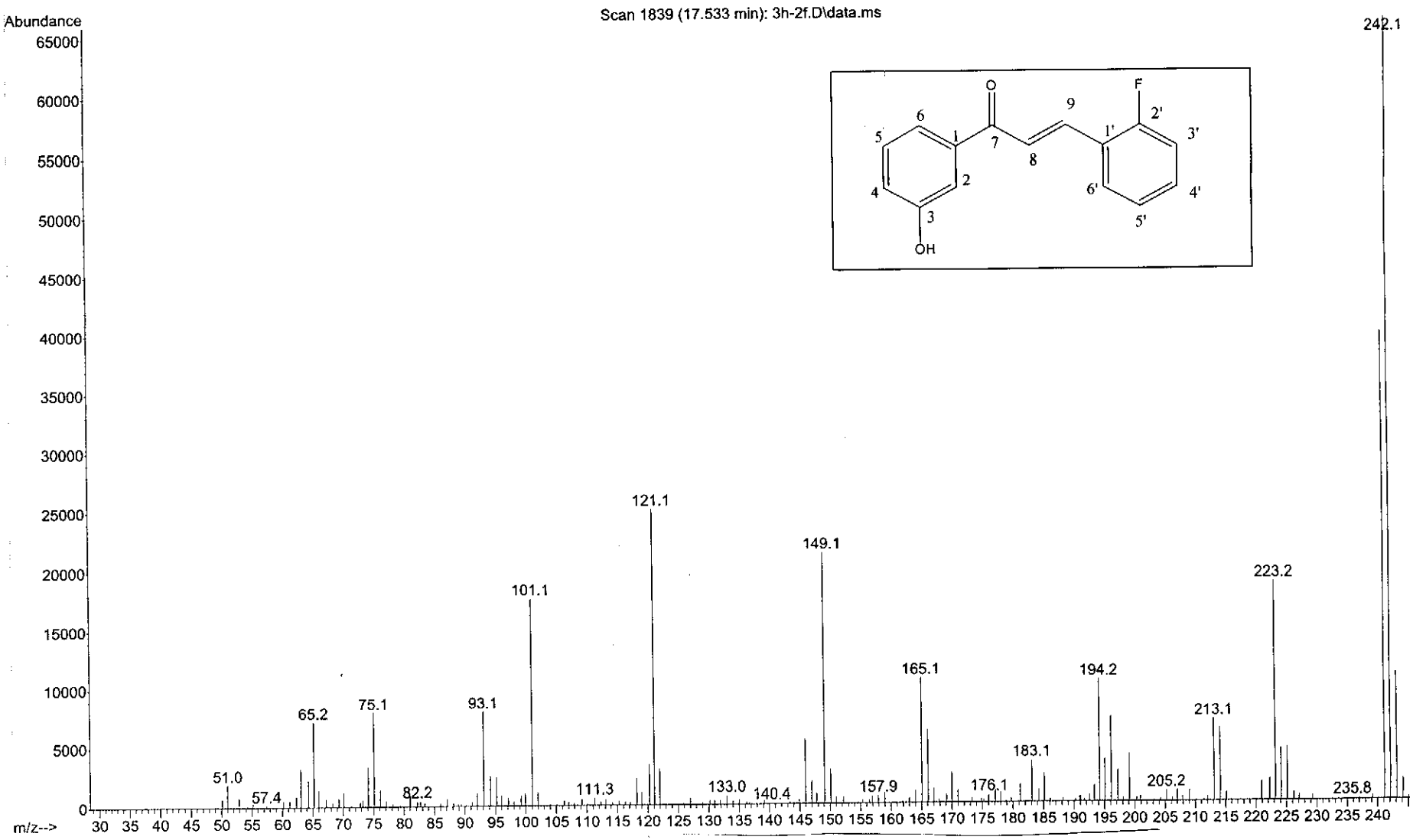
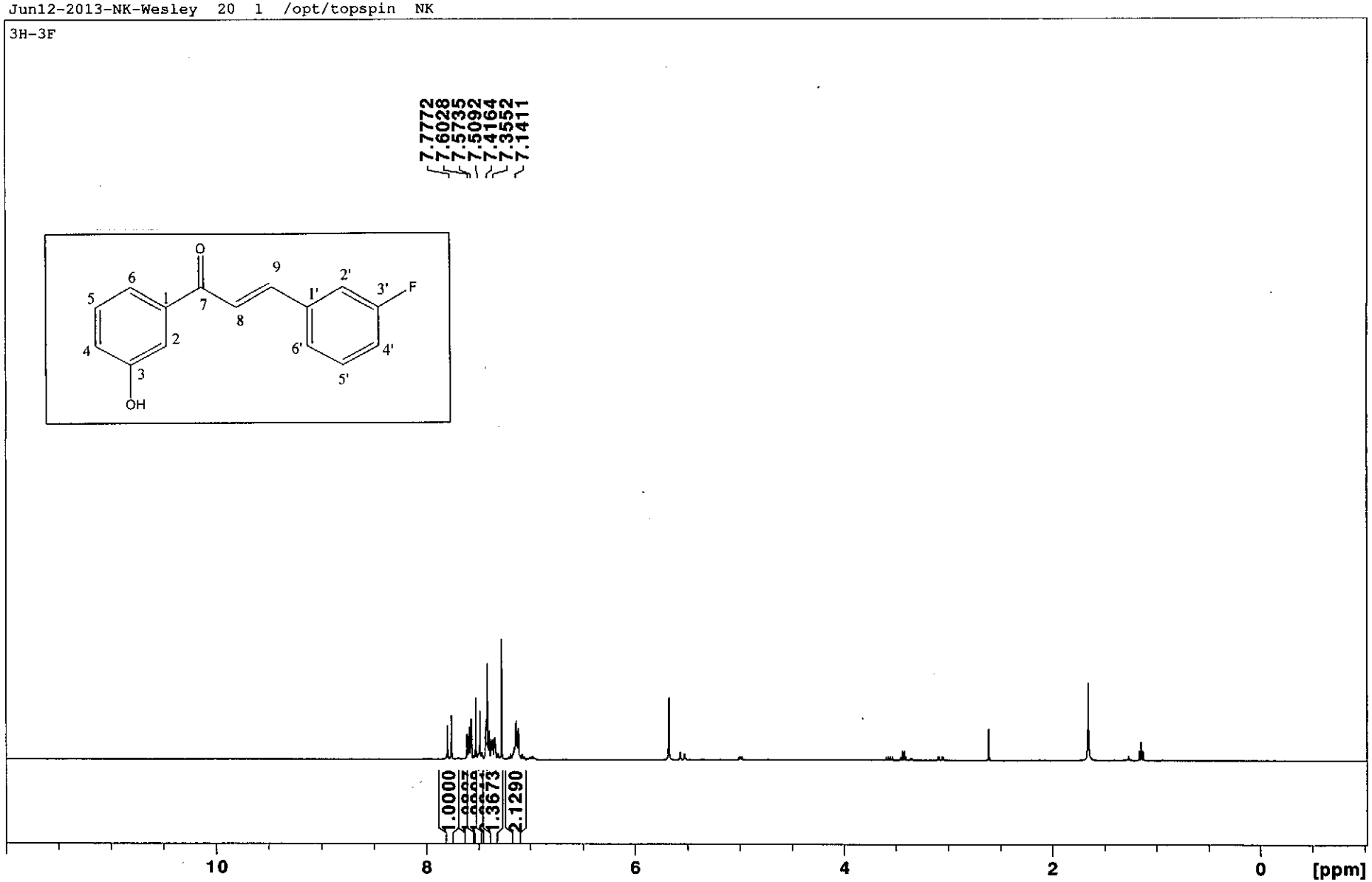
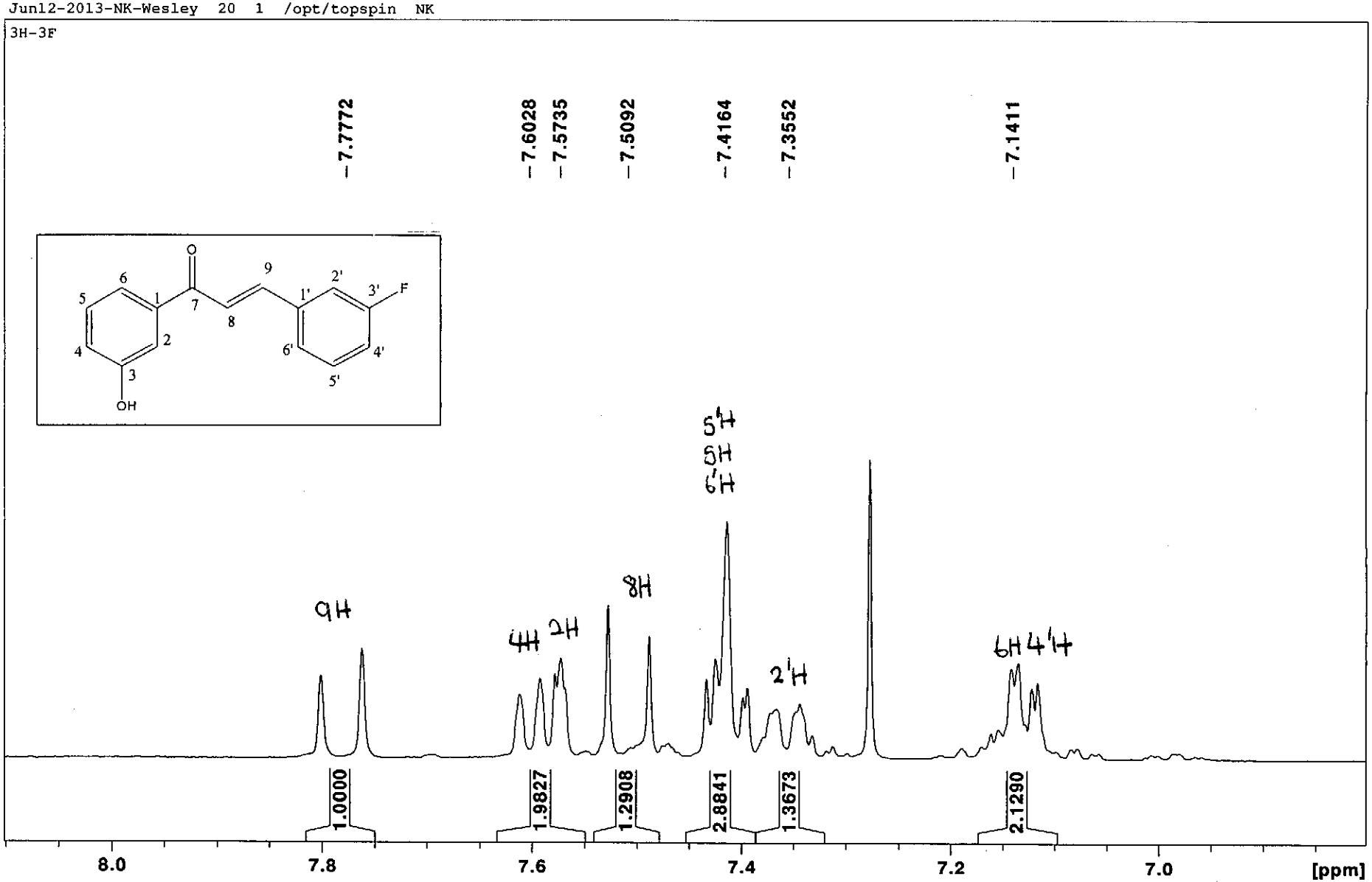


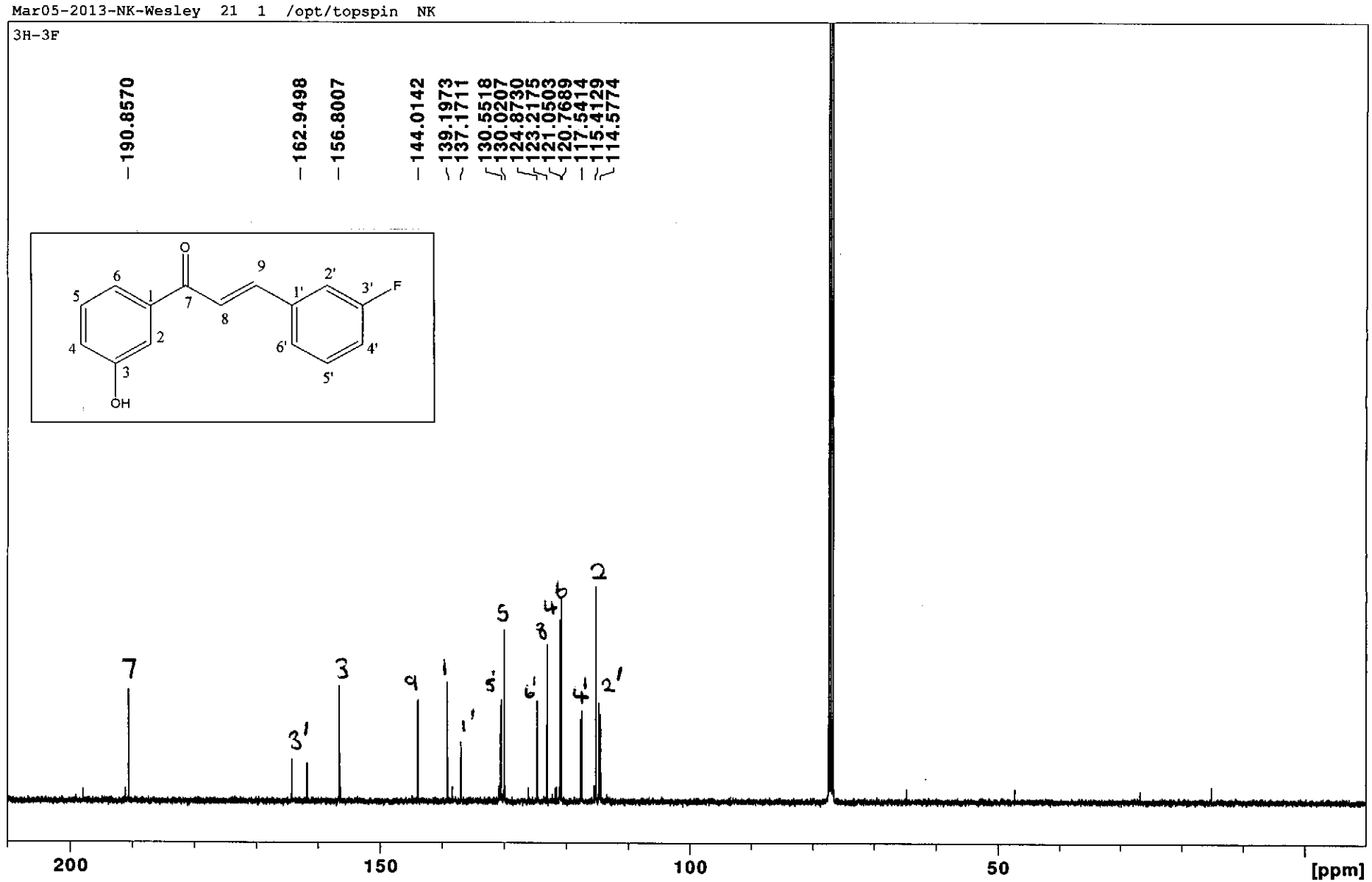
GC-MS spectrum of 2'-fluoro-3-hydroxychalcone, (VI)



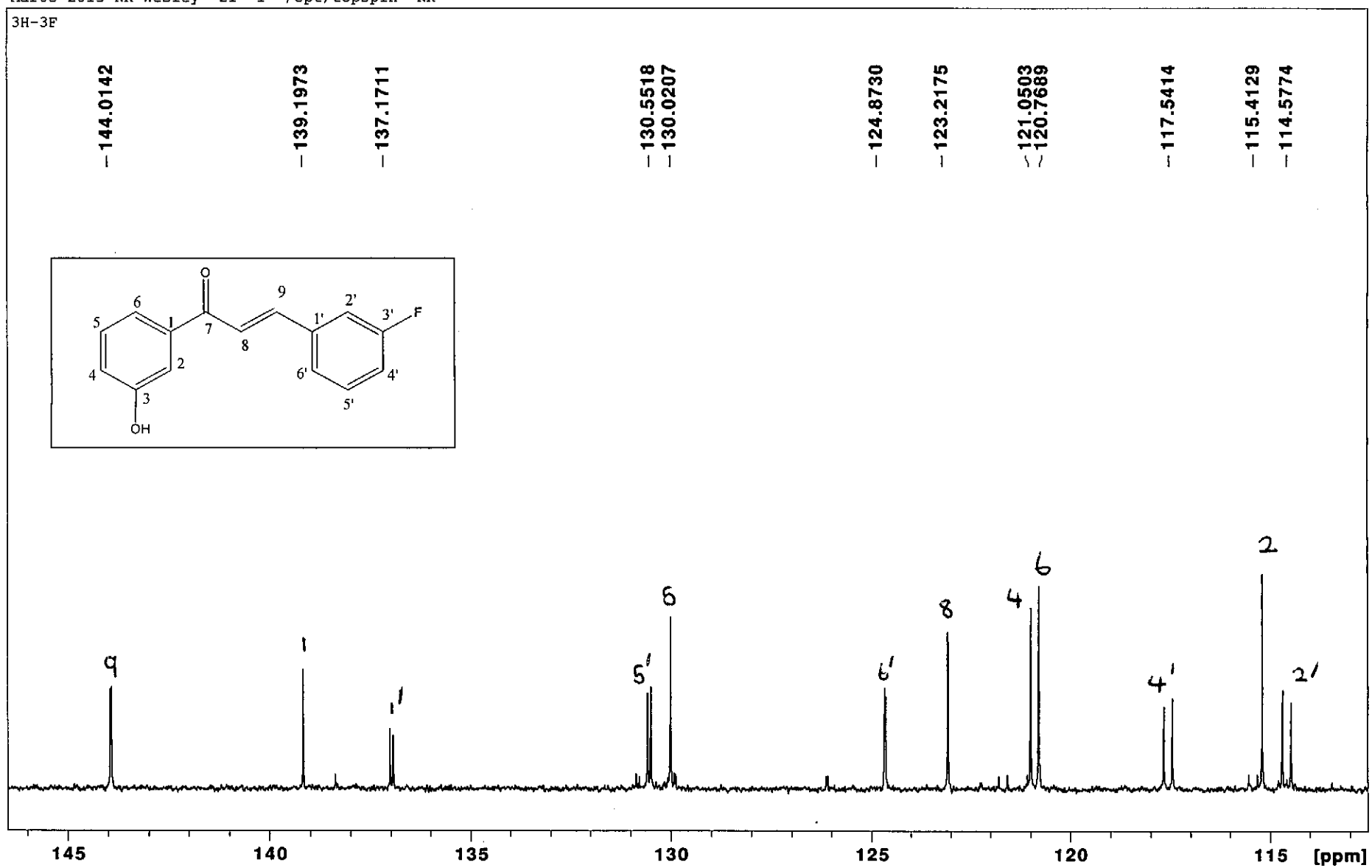
^{1}H NMR spectrum of 3'-fluoro-3-hydroxychalcone, (VII)



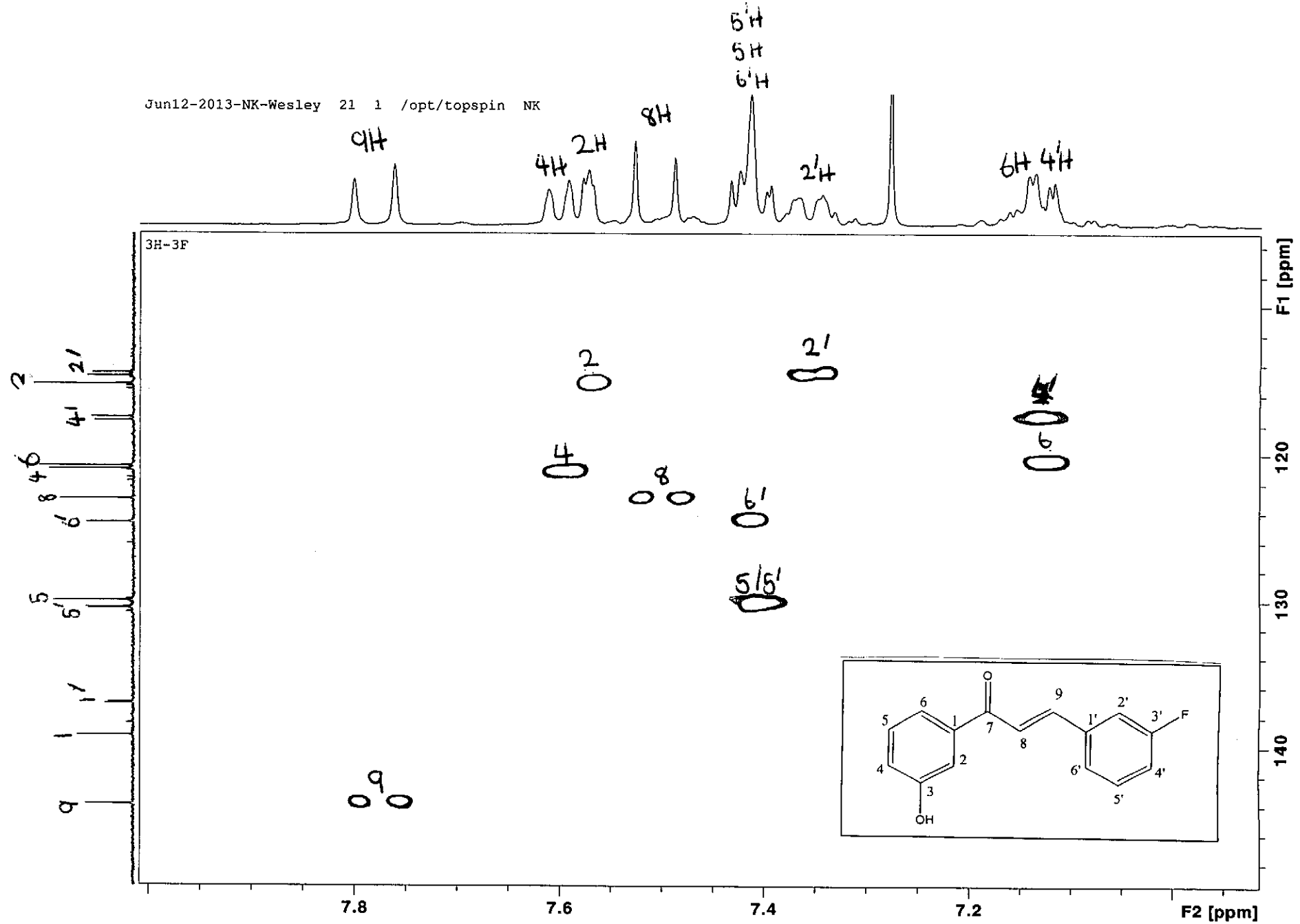
^{1}H NMR spectrum of 3'-fluoro-3-hydroxychalcone, (VII)



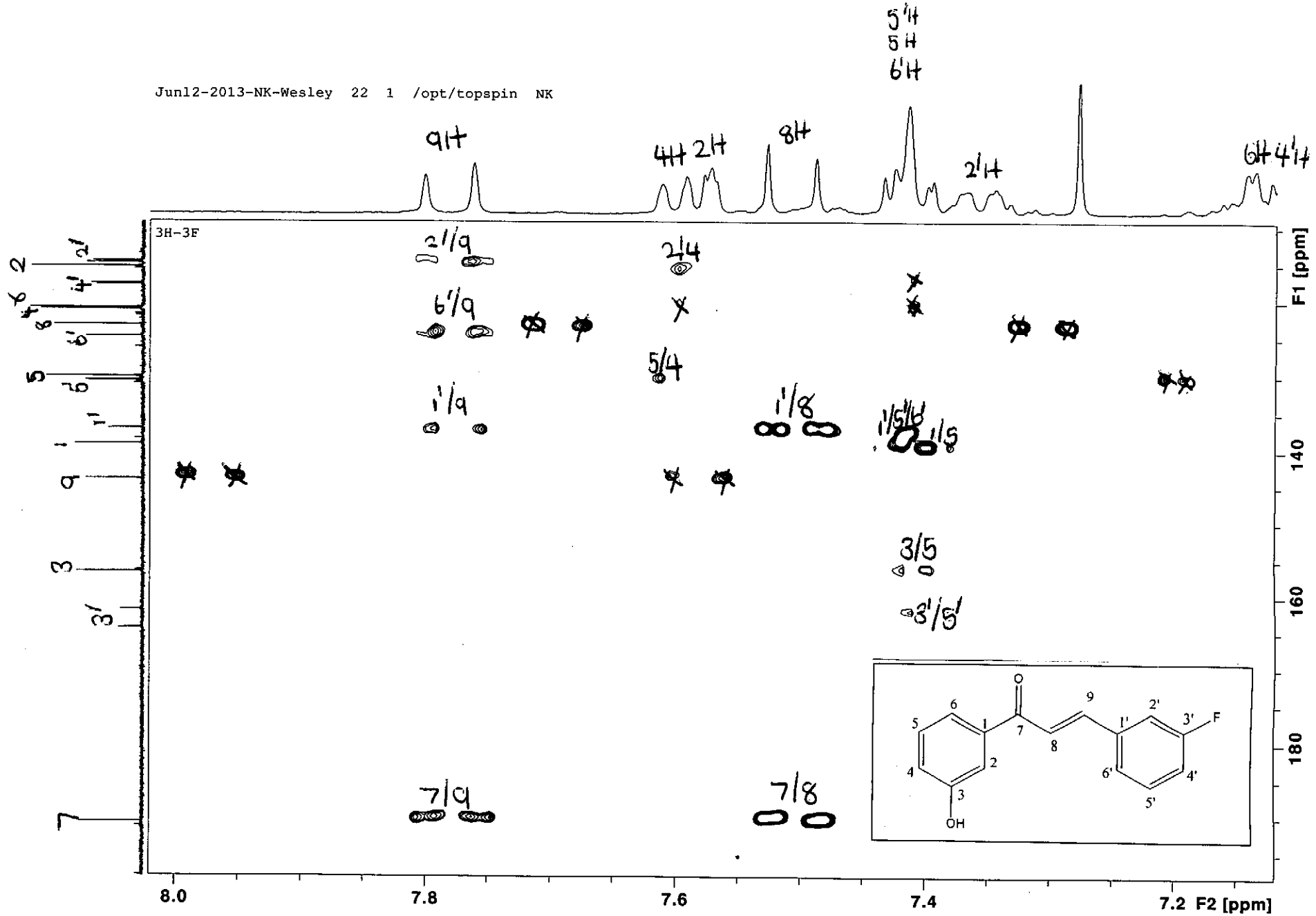
^{13}C NMR spectrum of 3'-fluoro-3-hydroxychalcone, (VII)



^{13}C NMR spectrum of 3'-fluoro-3-hydroxychalcone, (VII)



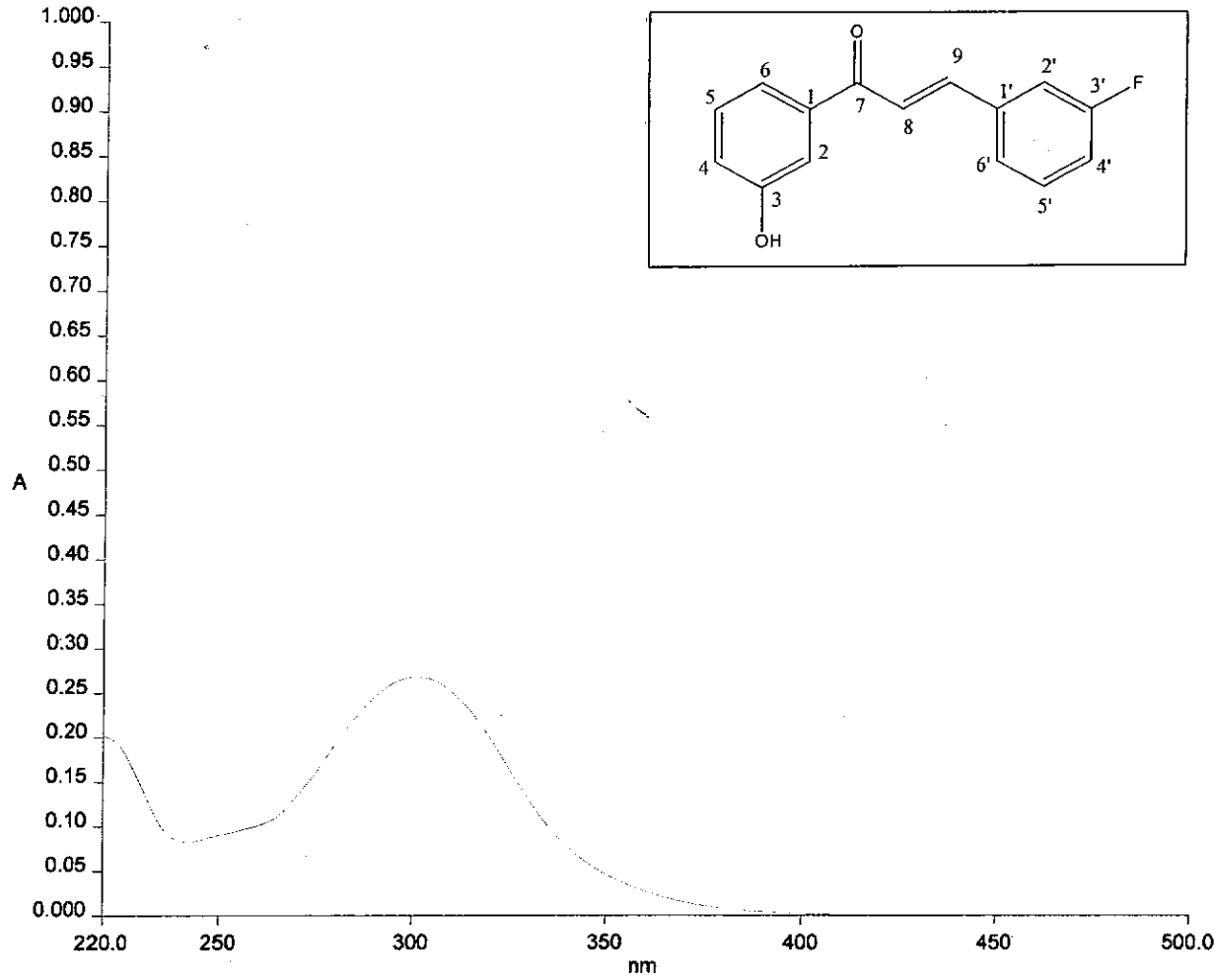
HSQC spectrum of 3'-fluoro-3-hydroxychalcone, (VII)



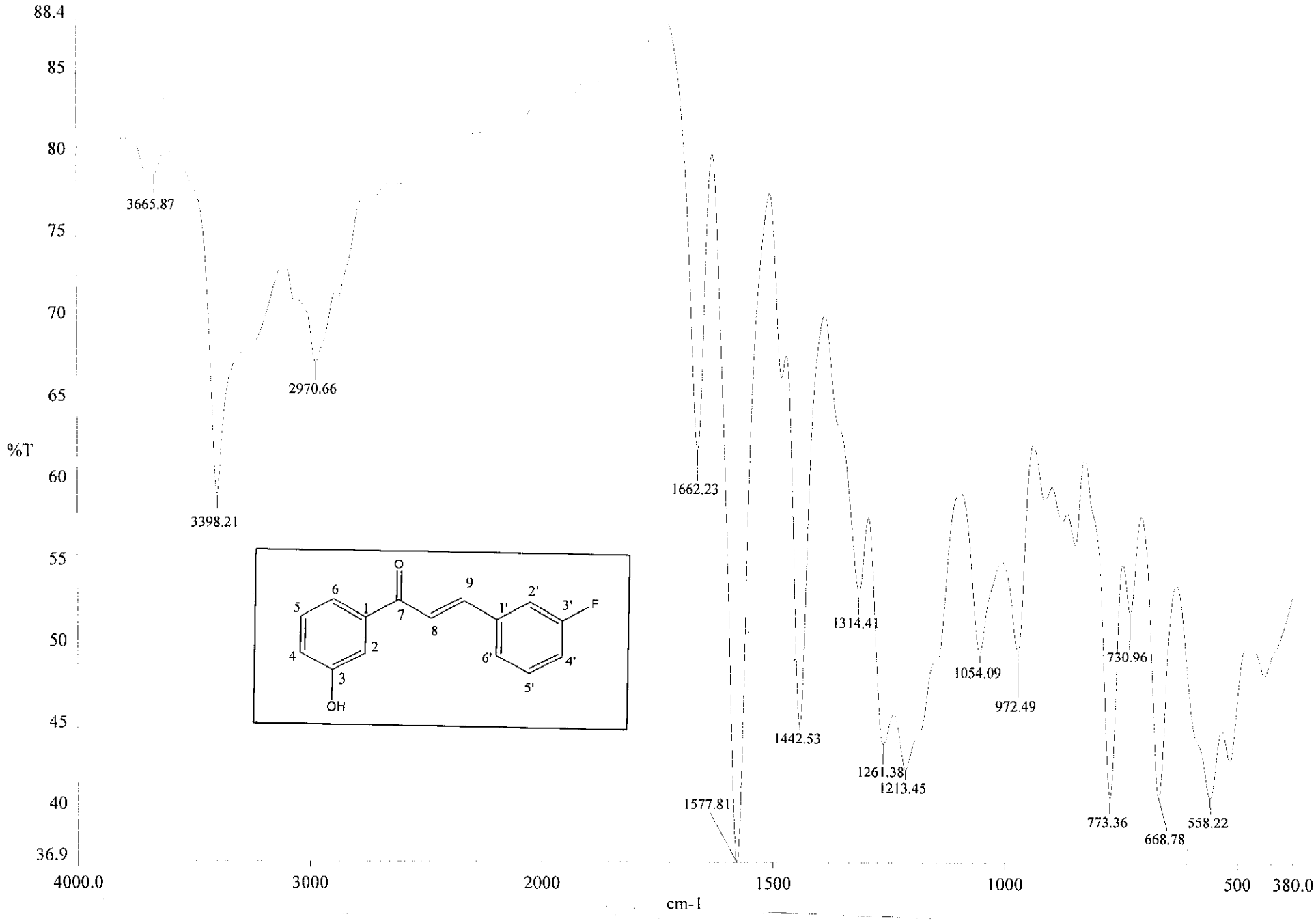
HMBC spectrum of 3'-fluoro-3-hydroxychalcone, (VII)

λmax(EtOH) = 0.2670 log ε = 6.12

Date: 2013/06/14 Time: 09:32:26 AM



Ultra violet (UV) spectrum of 3'-fluoro-3-hydroxychalcone, (VII)



Infra-Red (IR) spectrum of 3'-fluoro-3-hydroxychalcone, (VII)

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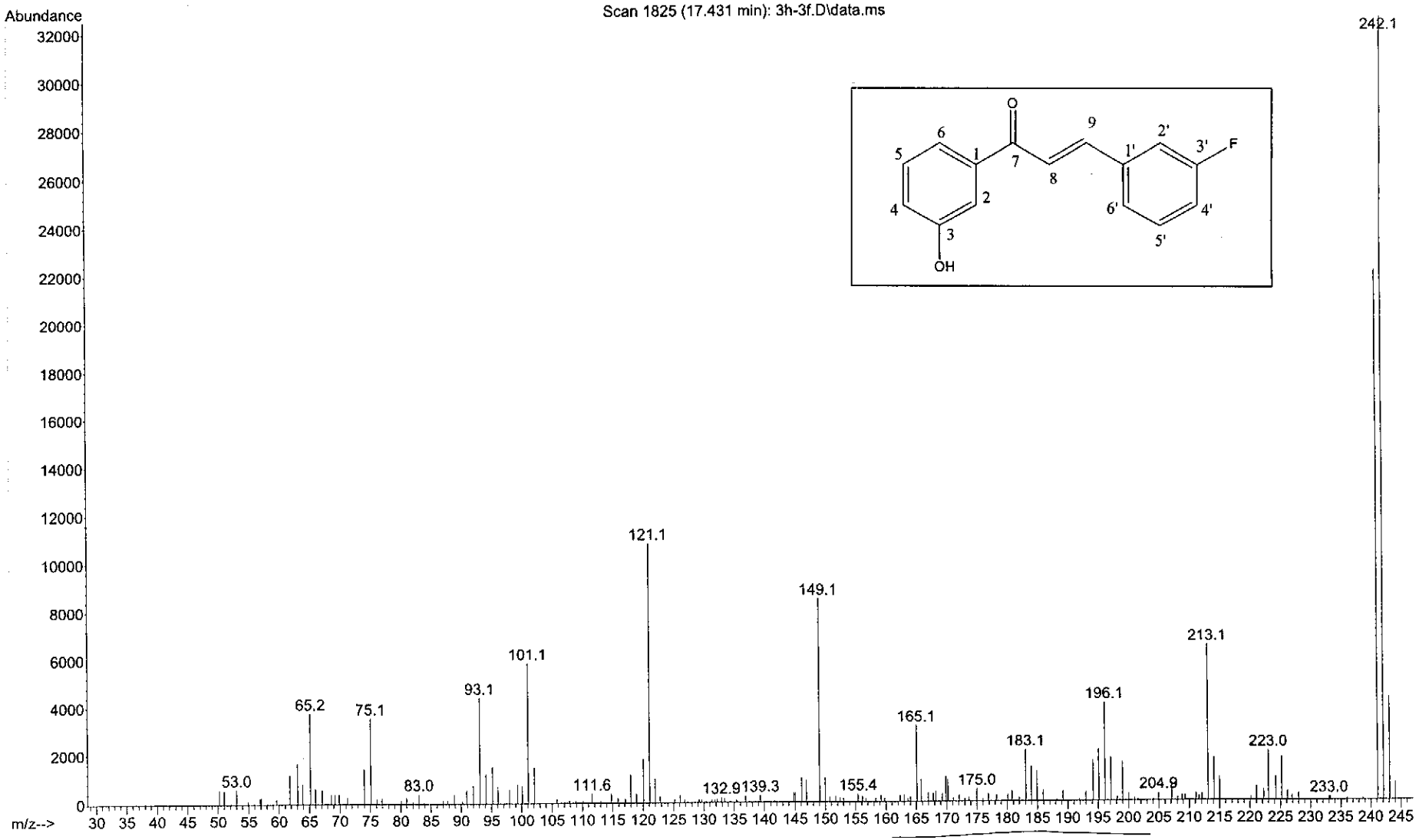
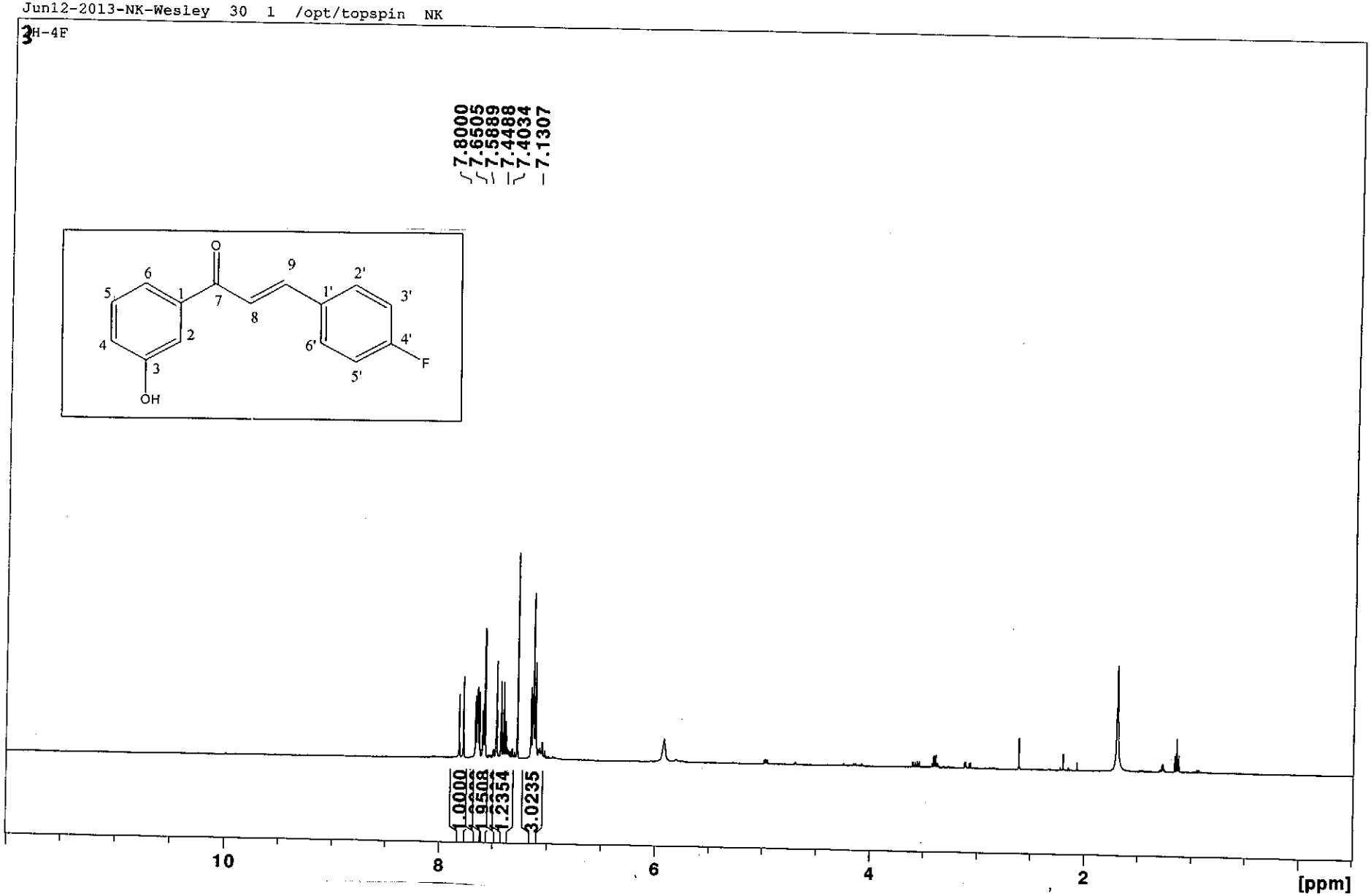
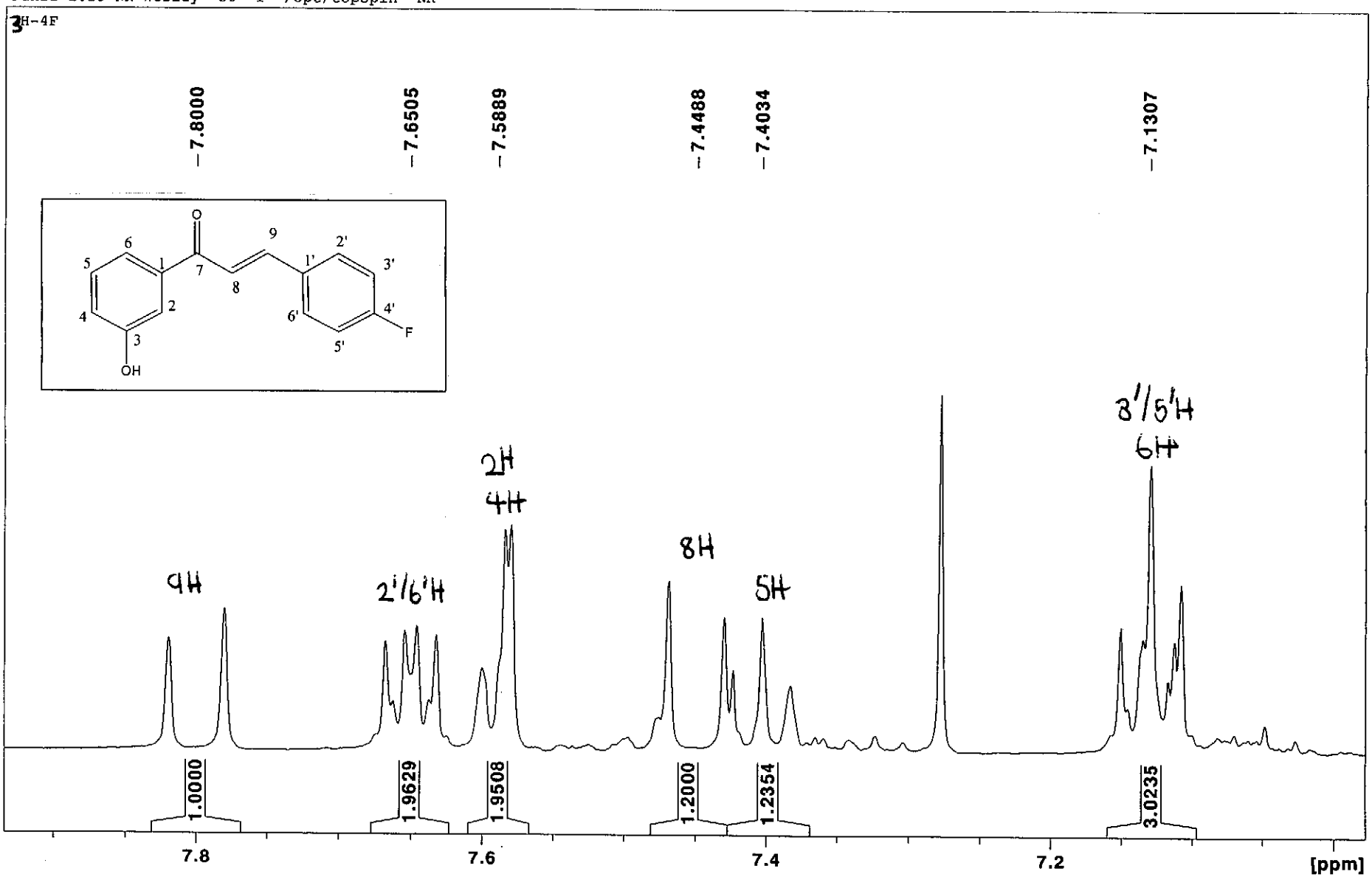
Sample Name: 3h-3f
Misc Info :



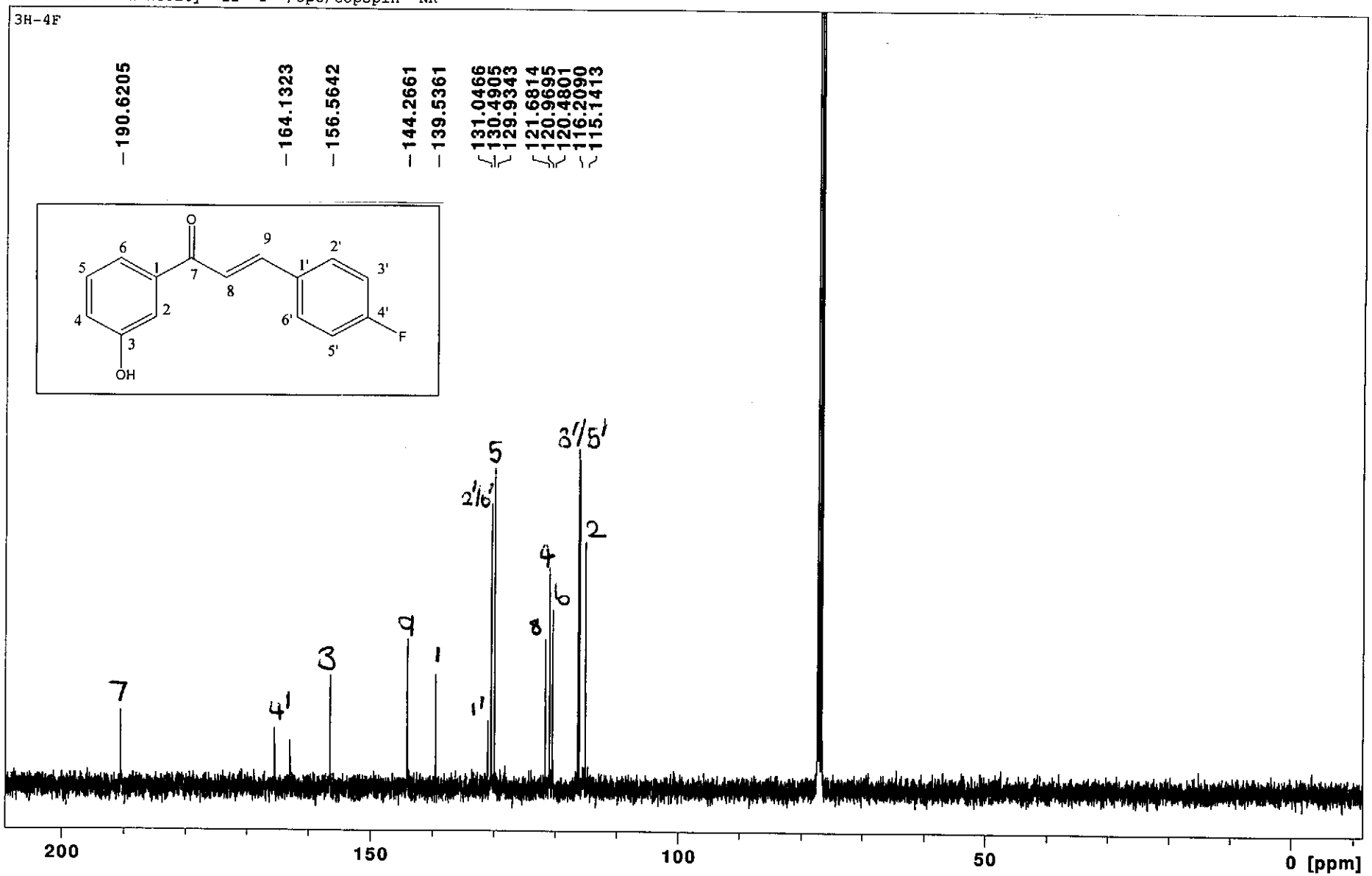
GC-MS spectrum of 3'-fluoro-3-hydroxychalcone, (VII)



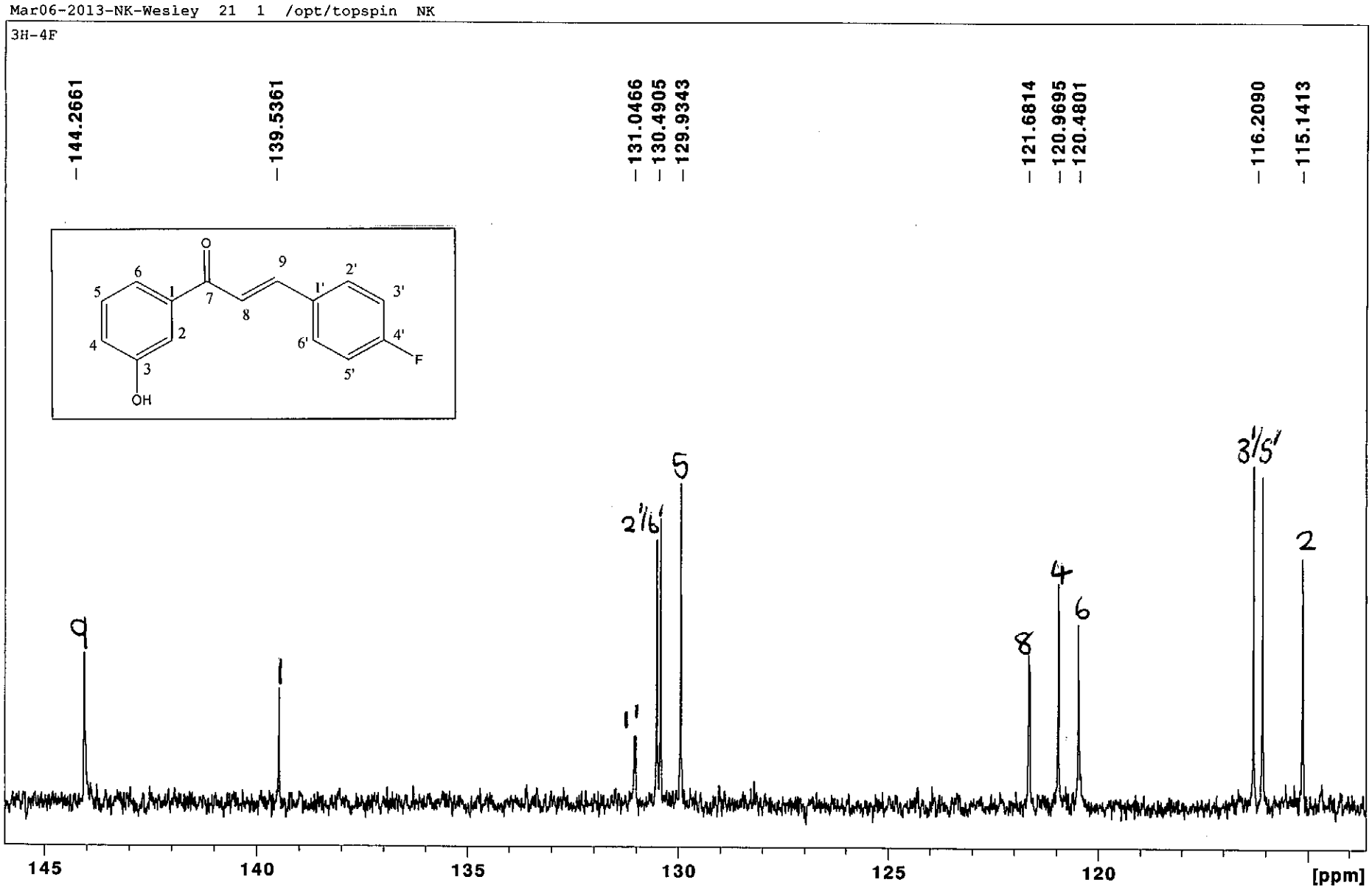
^{1}H NMR spectrum of 4'-fluoro-3-hydroxychalcone, (VIII)



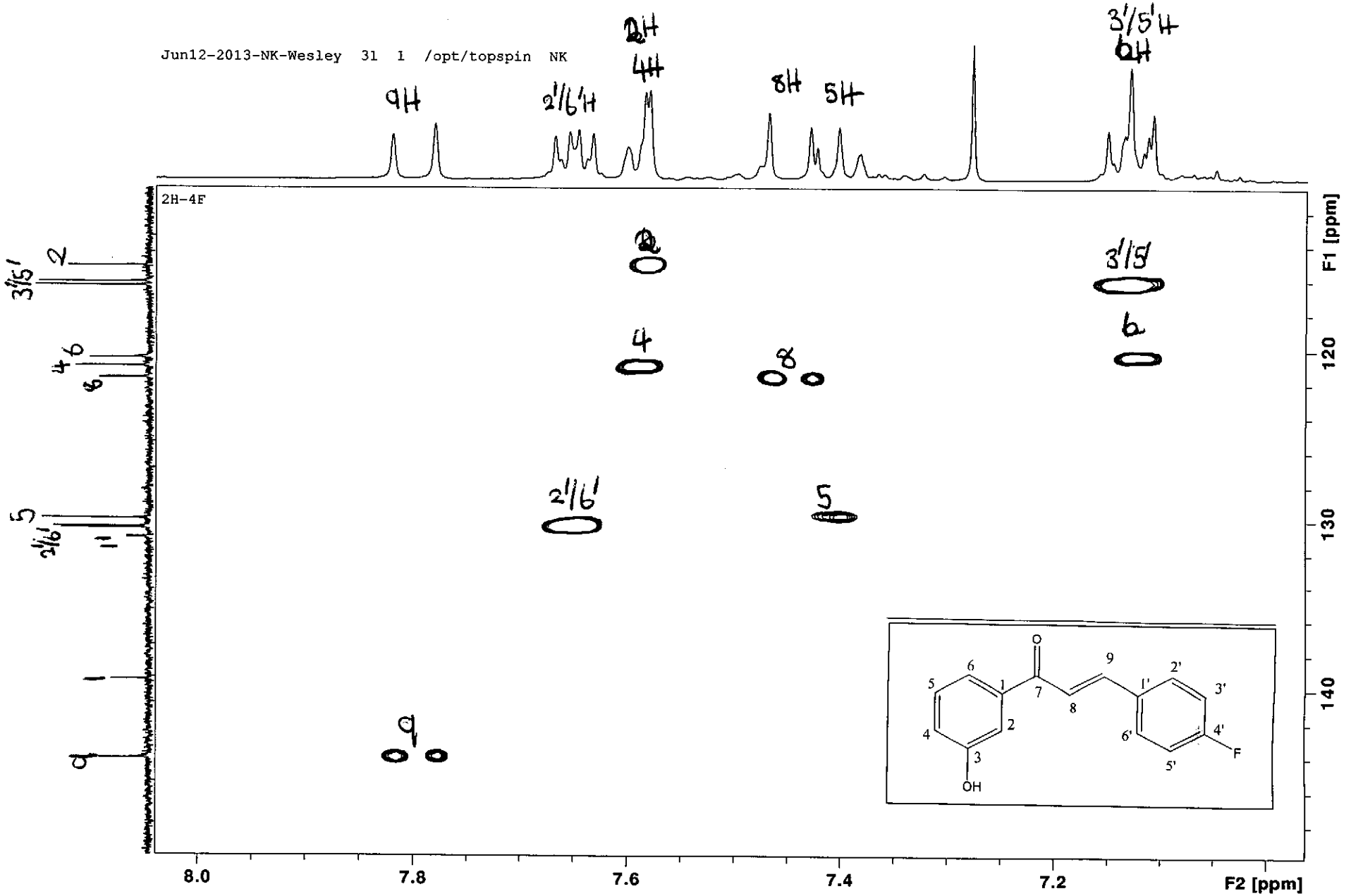
^{1}H NMR spectrum of 4'-fluoro-3-hydroxychalcone, (VIII)



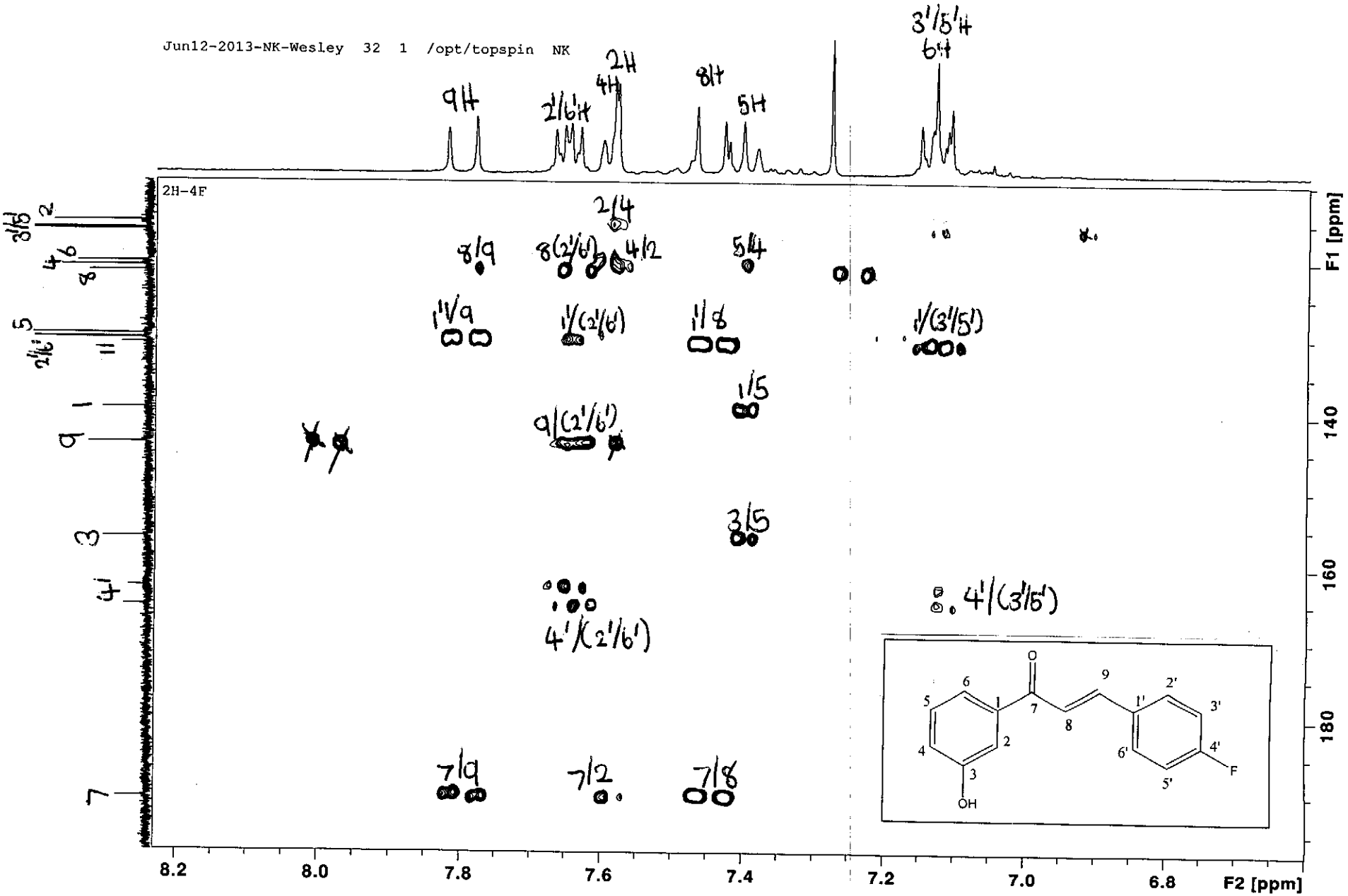
^{13}C NMR spectrum of 4'-fluoro-3-hydroxychalcone, (VIII)



^{13}C NMR spectrum of 4'-fluoro-3-hydroxychalcone, (VIII)



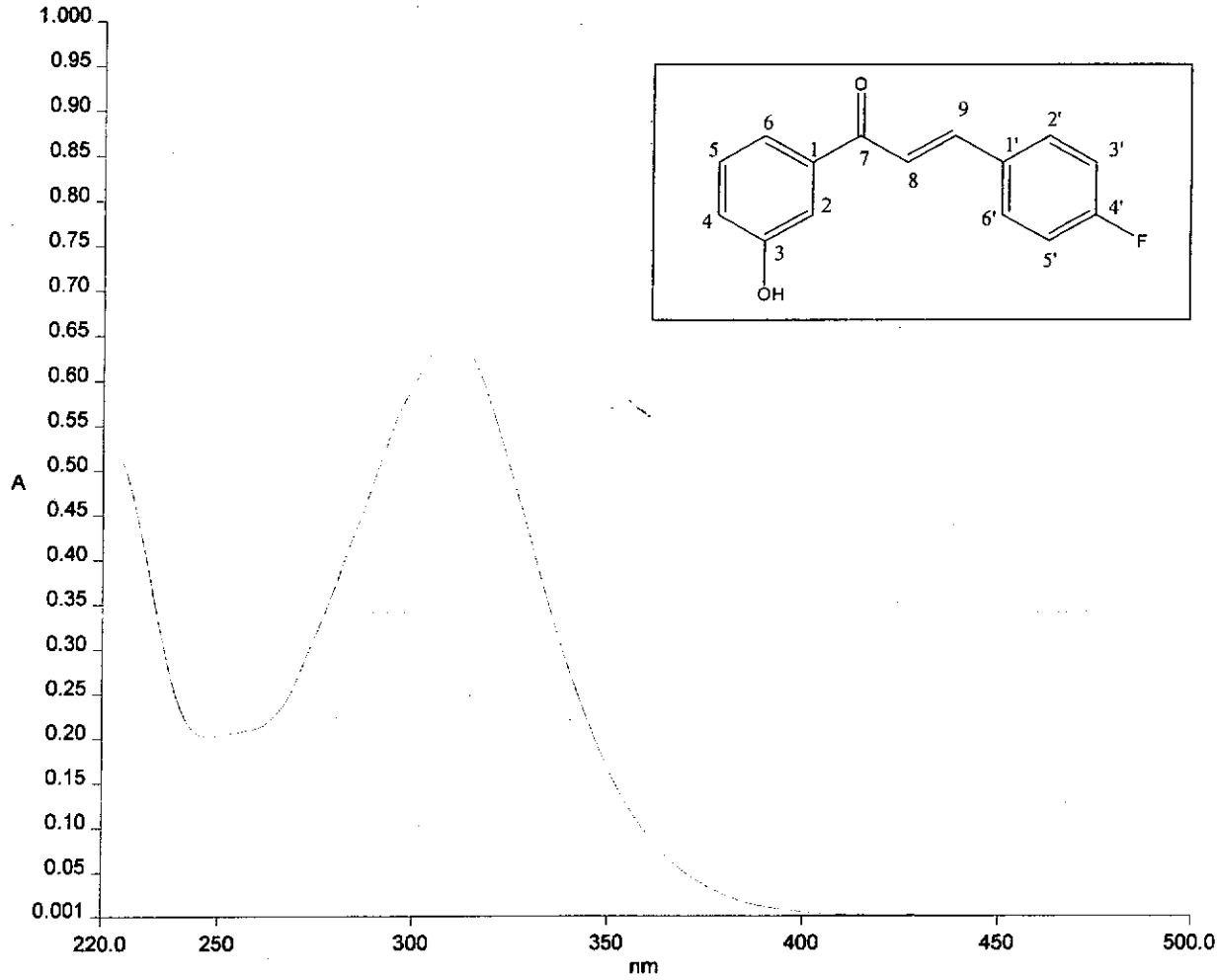
HSQC spectrum of 4'-fluoro-3-hydroxychalcone, (VIII)



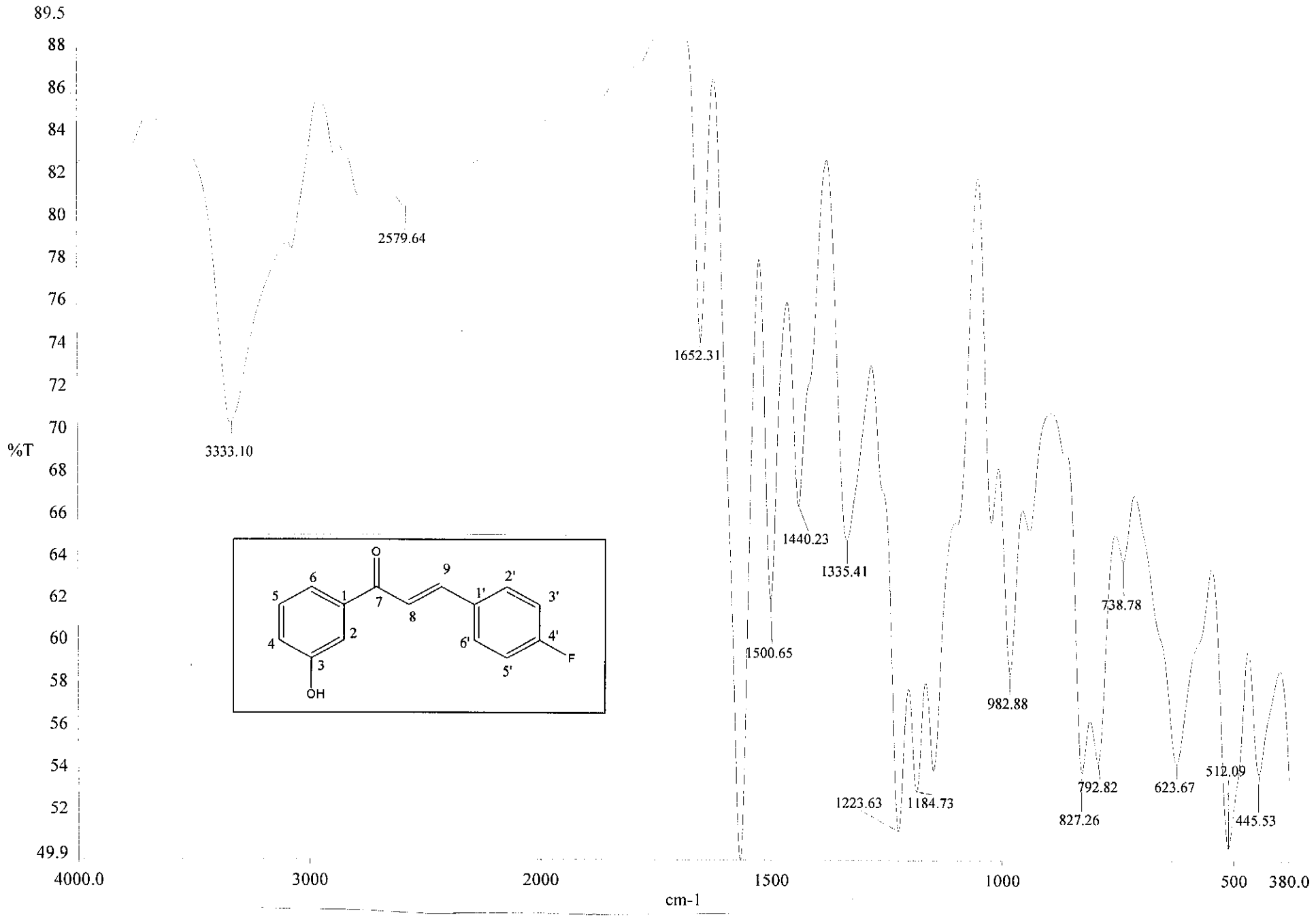
HMBC spectrum of 4'-fluoro-3-hydroxychalcone, (VIII)

λmax (309nm) = 0.641 log ε = 5.61

Date: 2013/06/14 Time: 09:33:08 AM



Ultra violet (UV) spectrum of 4'-fluoro-3-hydroxychalcone, (VIII)



Infra-Red (IR) spectrum of 4'-fluoro-3-hydroxychalcone, (VIII)

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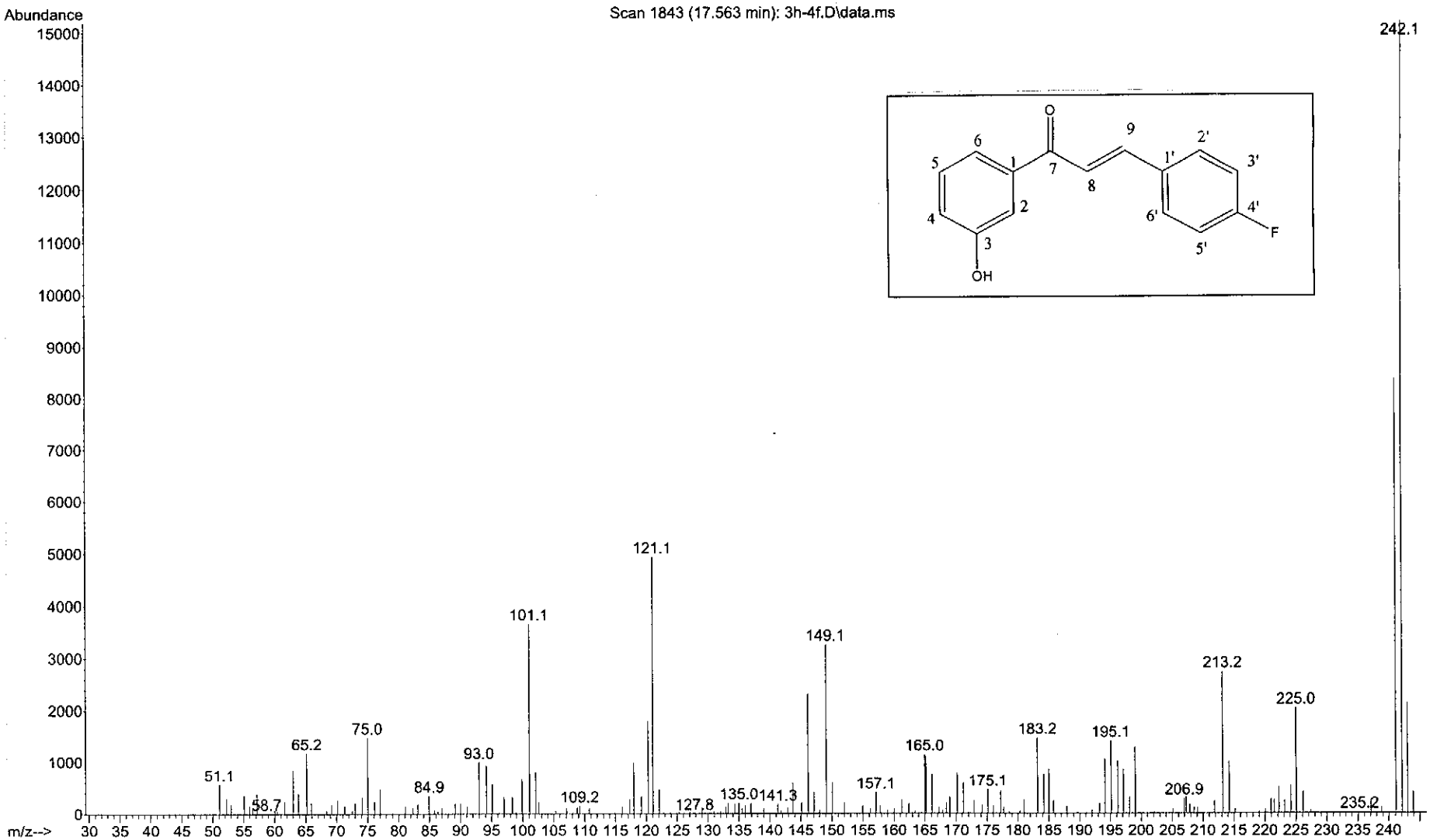
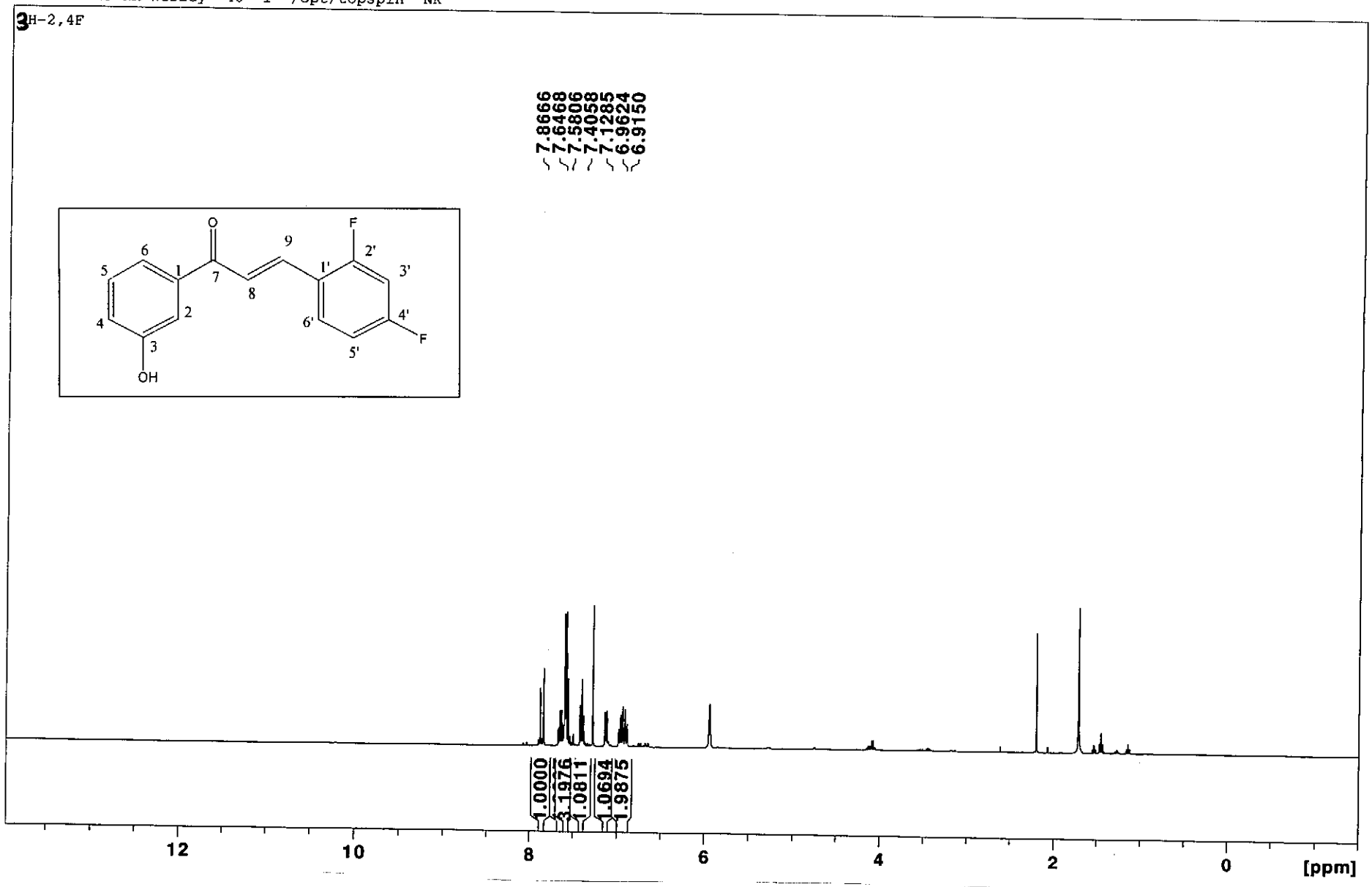
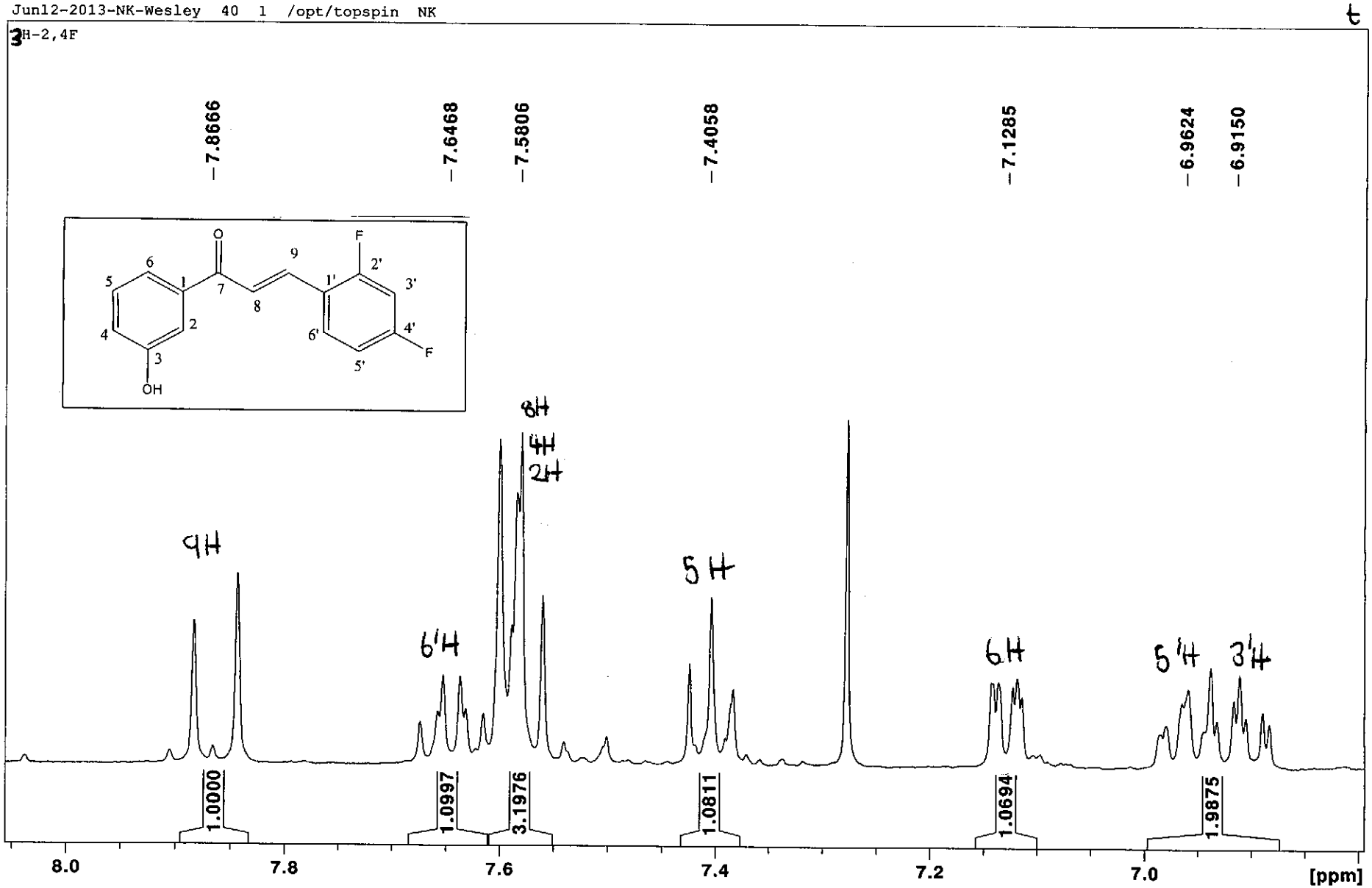


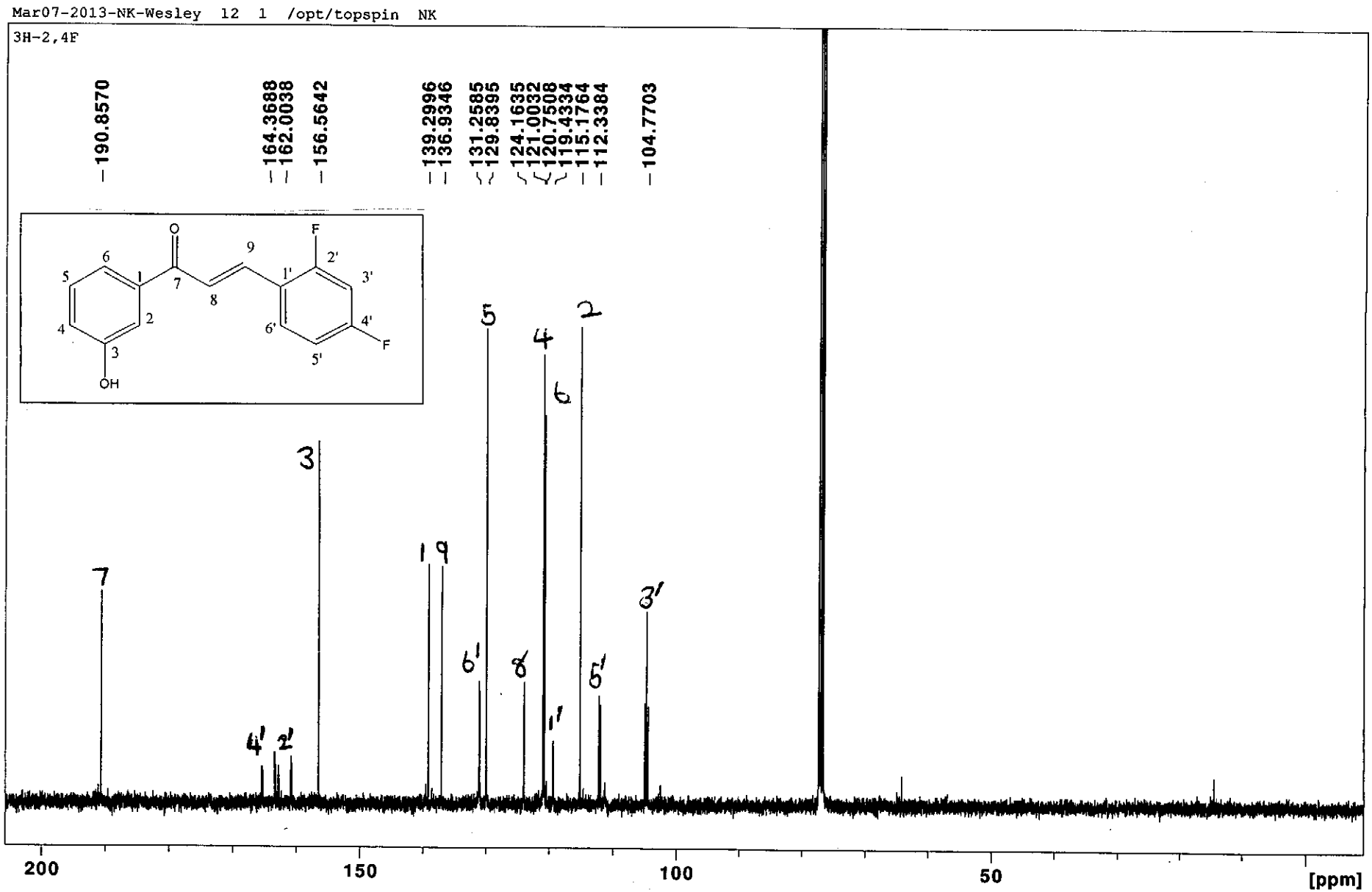
GC-MS spectrum of 4'-fluoro-3-hydroxychalcone, (VIII)



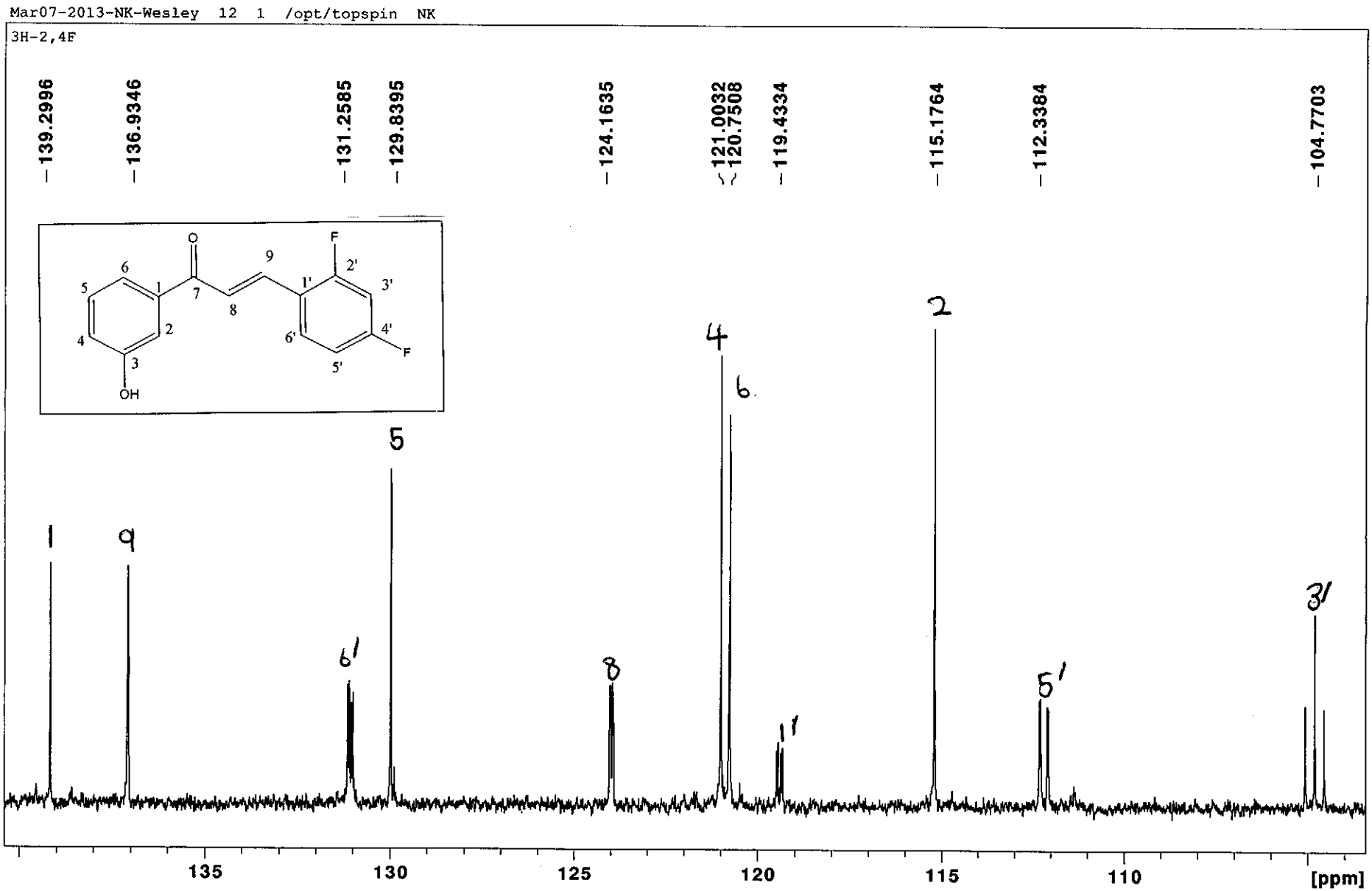
^{1}H NMR spectrum of 2', 4'-fluoro-3-hydroxychalcone, (IX)



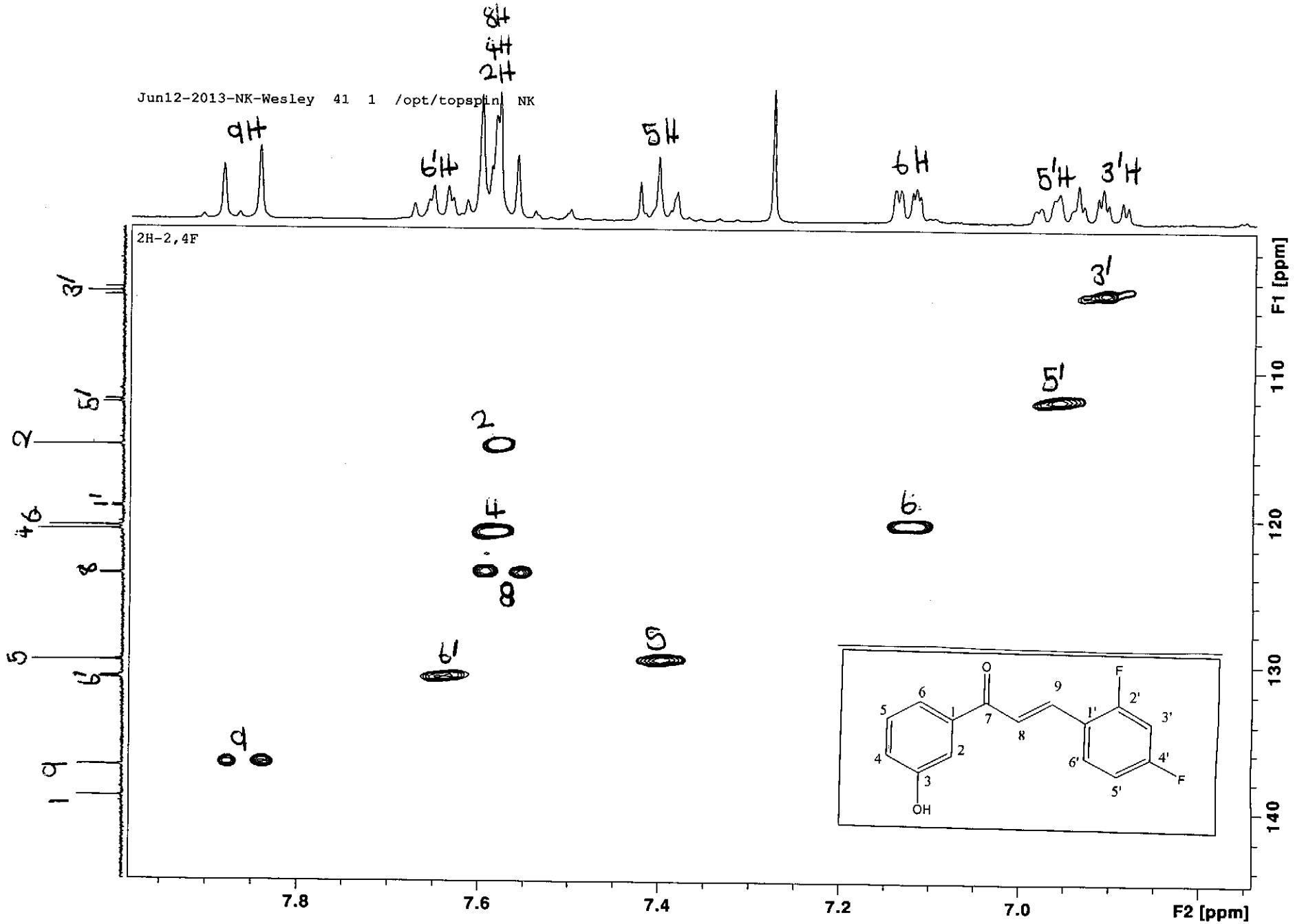
^{1}H NMR spectrum of 2', 4'-fluoro-3-hydroxychalcone, (IX)



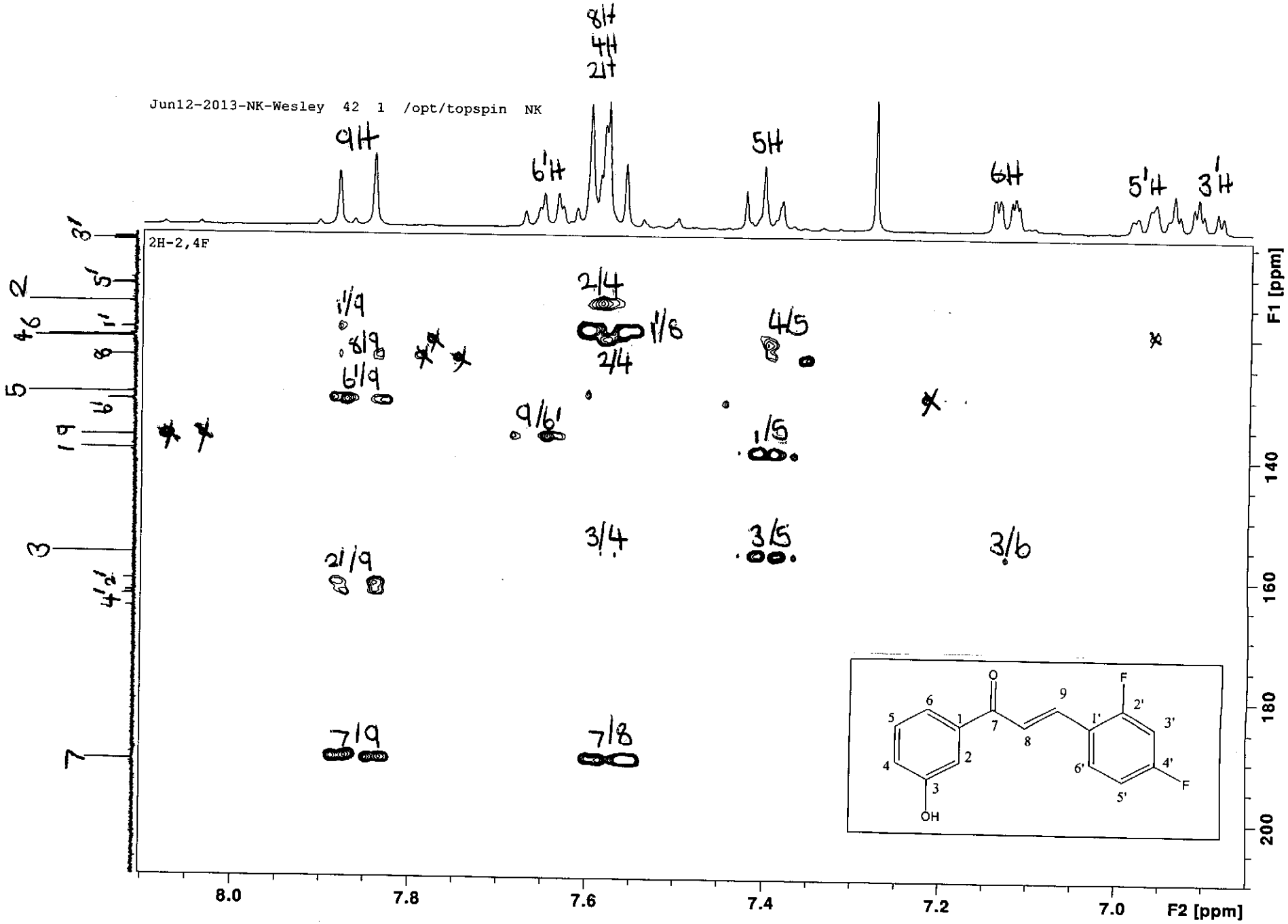
^{13}C NMR spectrum of 2', 4'-fluoro-3-hydroxychalcone, (IX)



^{13}C NMR spectrum of 2', 4'-fluoro-3-hydroxychalcone, (IX)



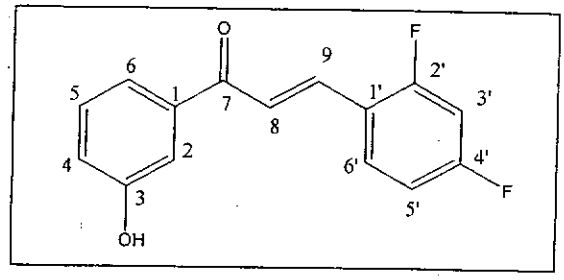
HSQC spectrum of 2', 4'-fluoro-3-hydroxychalcone, (IX)



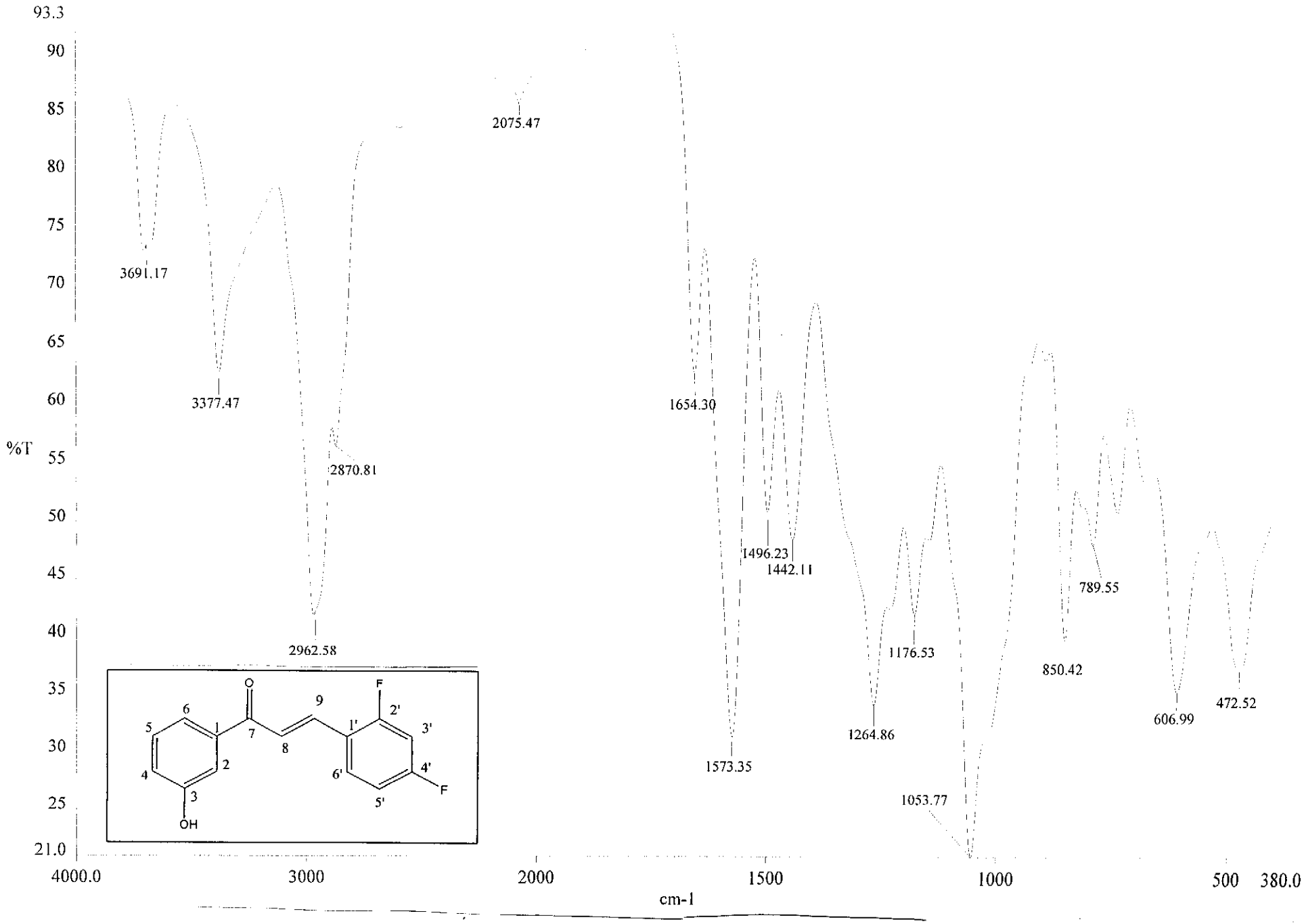
HMBC spectrum of 2', 4'-fluoro-3-hydroxychalcone, (IX)

λmax (307nm) = 0.2460 log ε = 5.06

Date: 2013/06/14 Time: 09:35:30 AM



Ultra violet (UV) spectrum of 2', 4'-fluoro-3-hydroxychalcone, (IX)



Infra-Red (IR) spectrum of 2', 4'-fluoro-3-hydroxychalcone, (IX)

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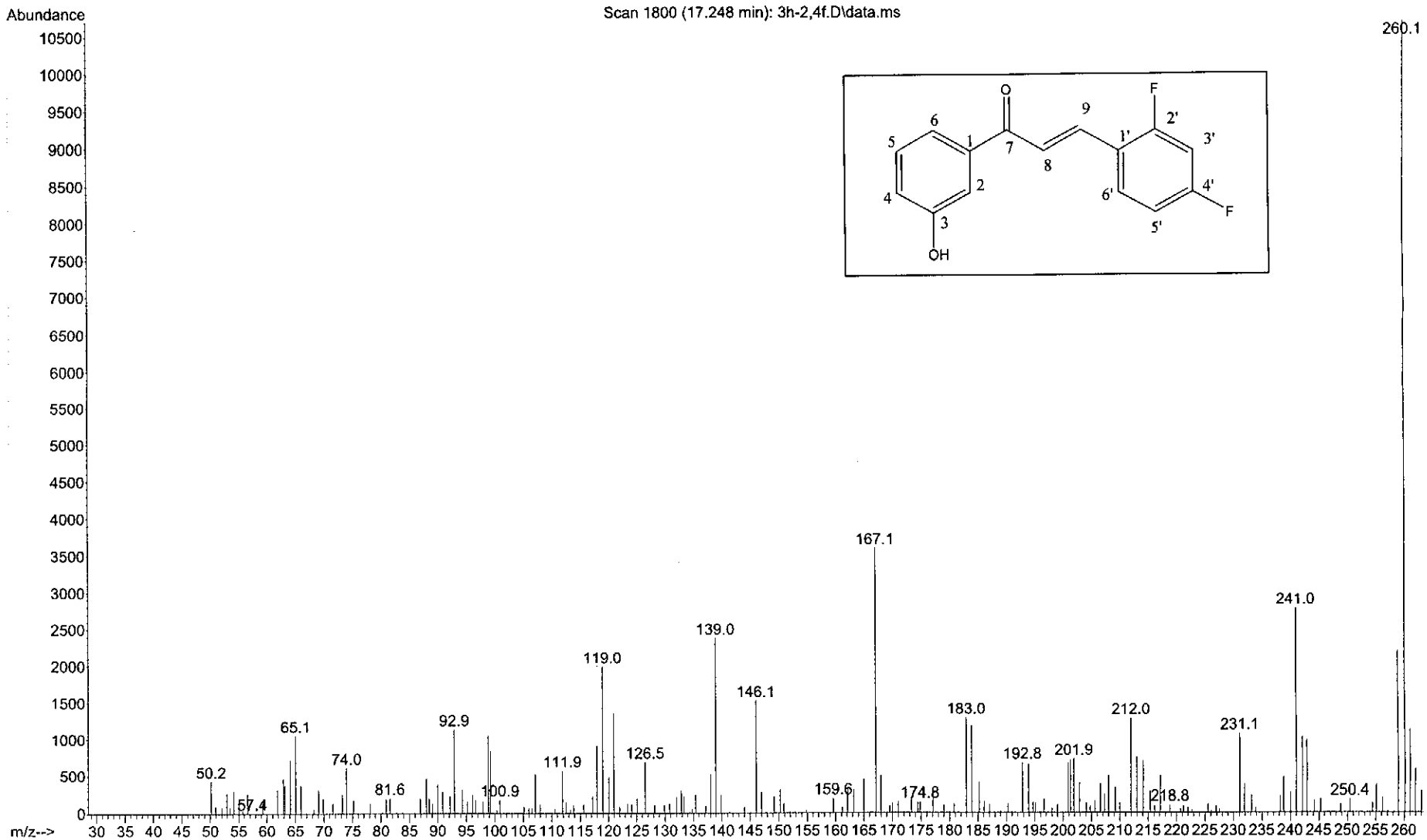
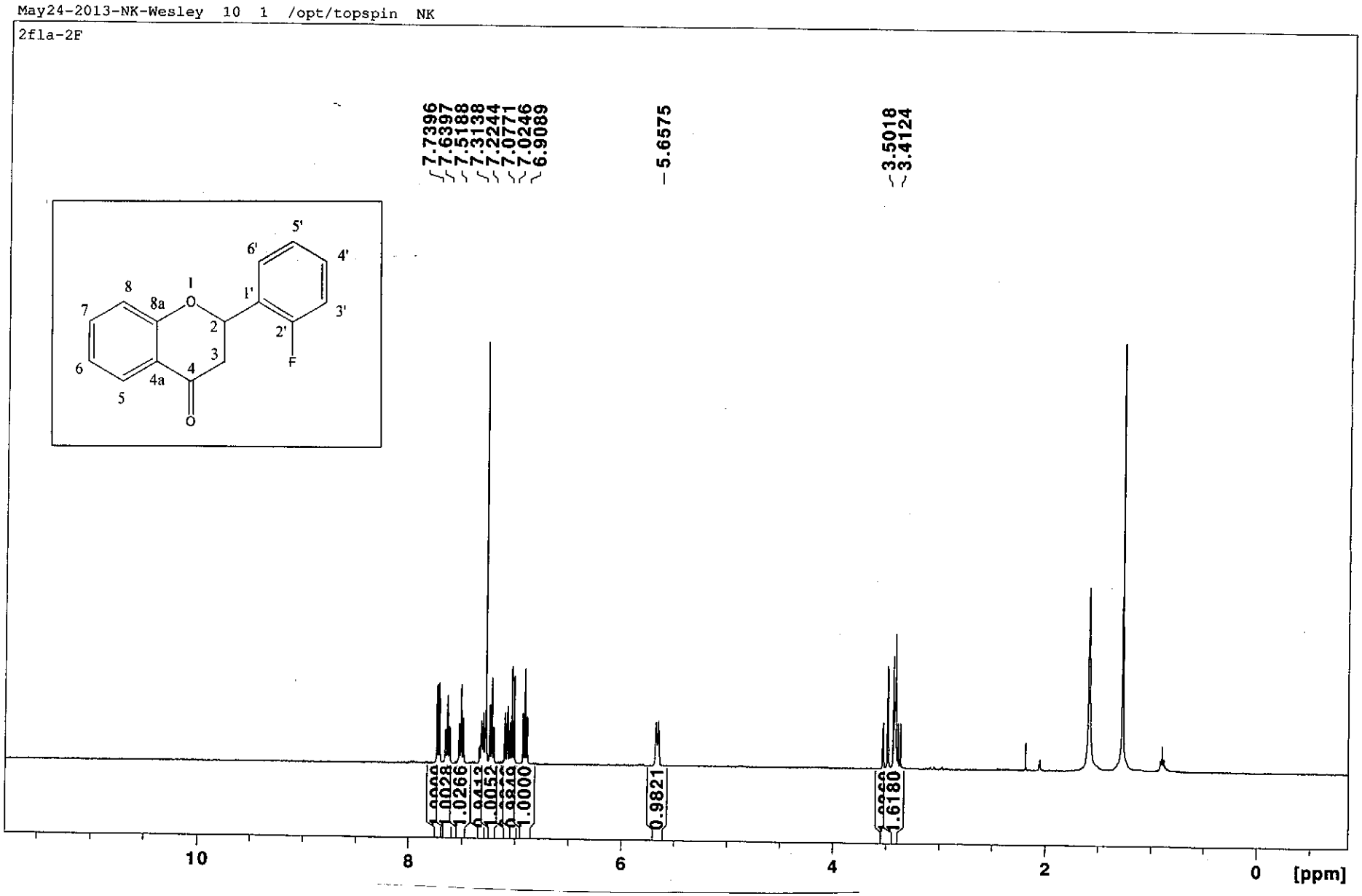
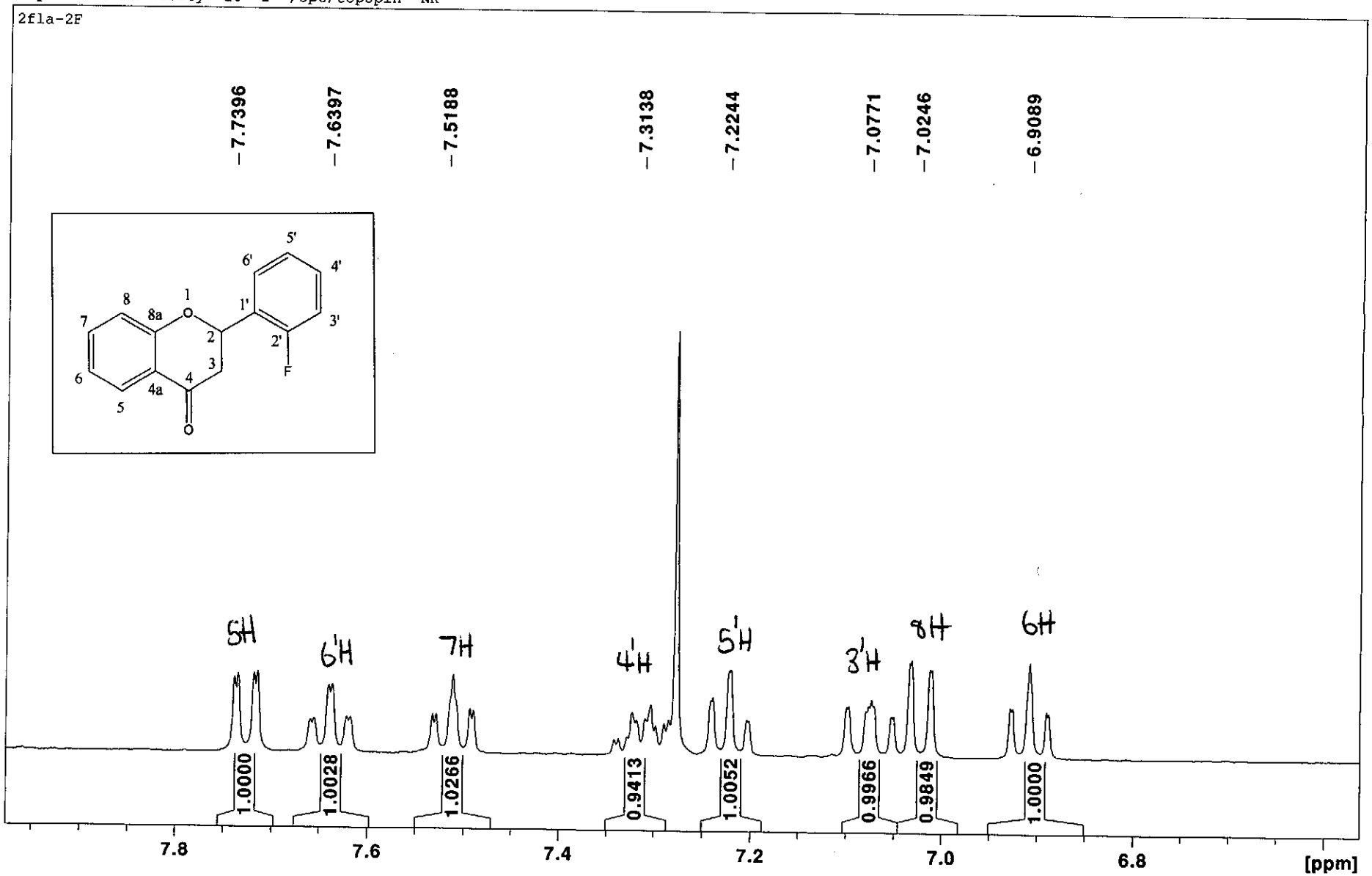


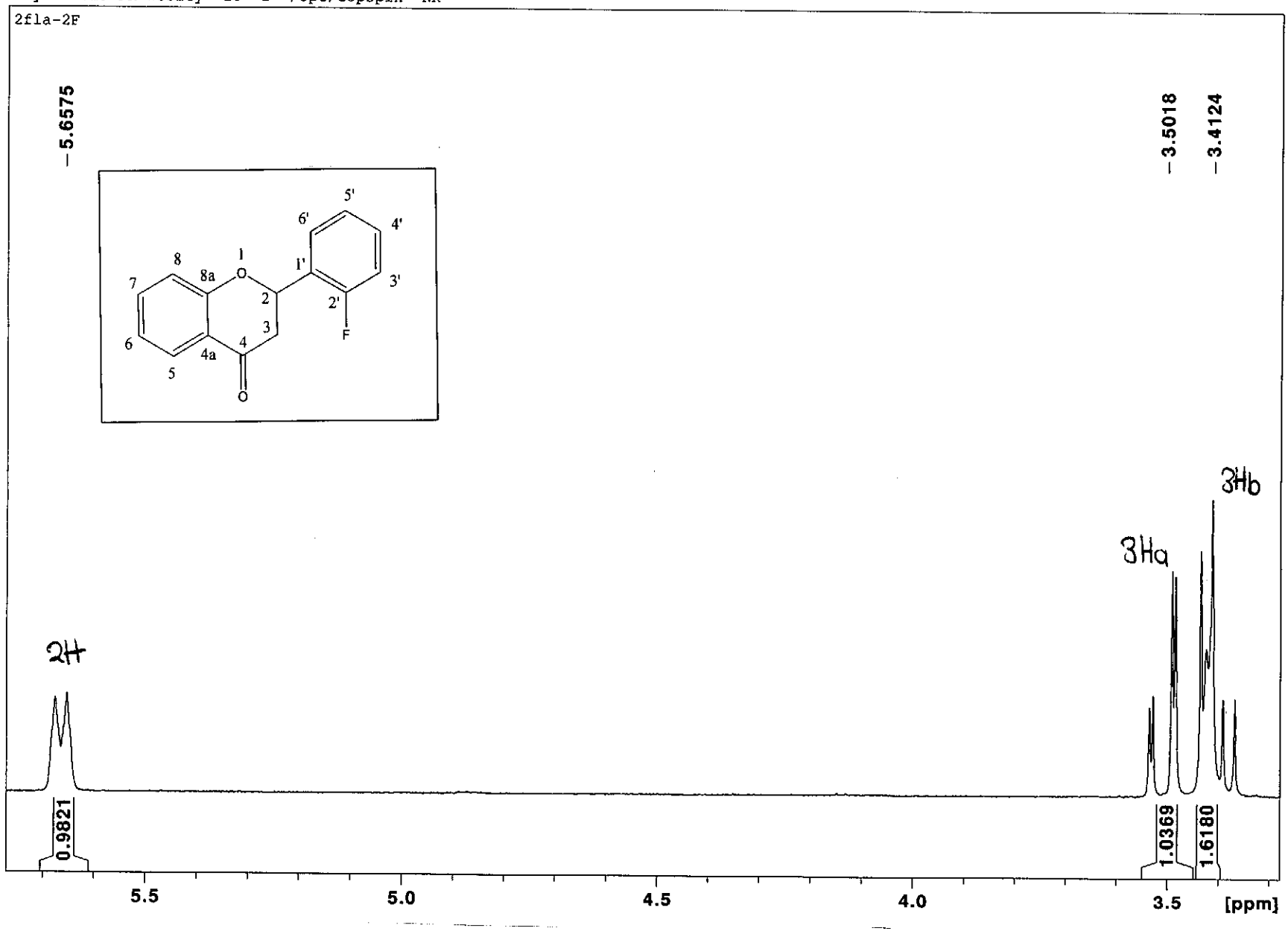
GC-MS spectrum of 2', 4'-fluoro-3-hydroxychalcone, (IX)



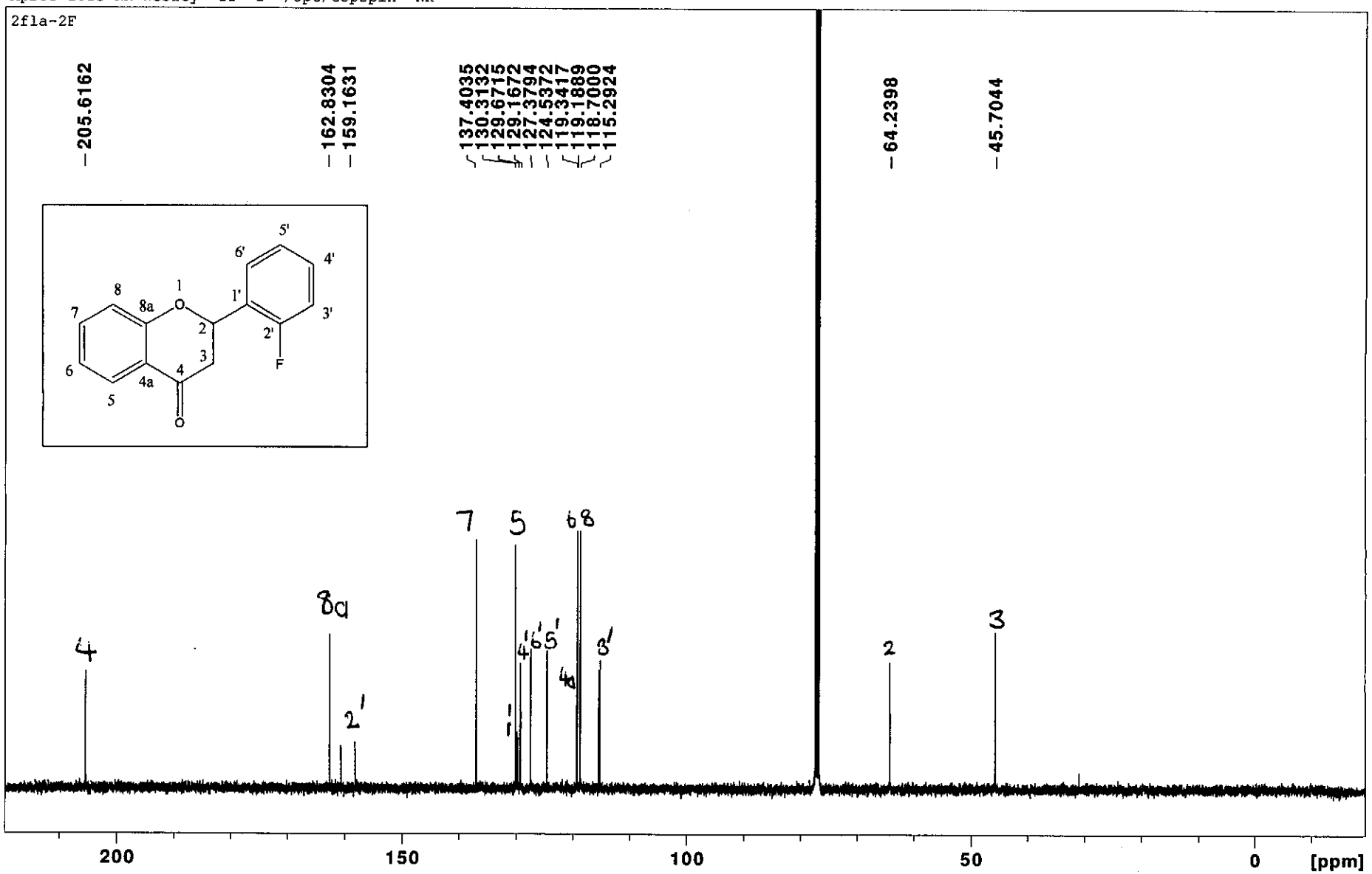
^{1}H NMR spectrum of 2'-fluoroflavanone, (X)



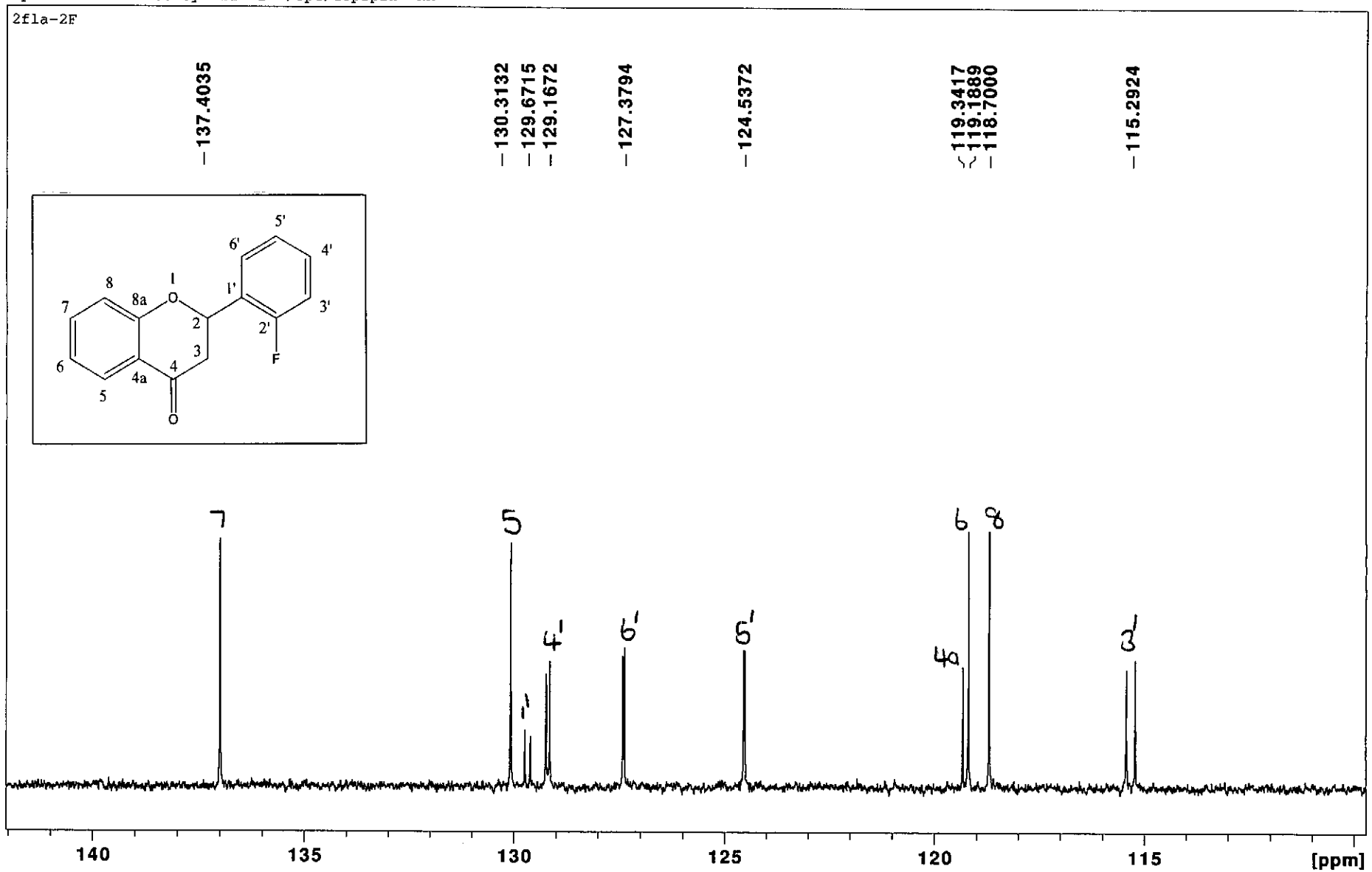
^{1}H NMR spectrum of 2'-fluoroflavanone, (X)



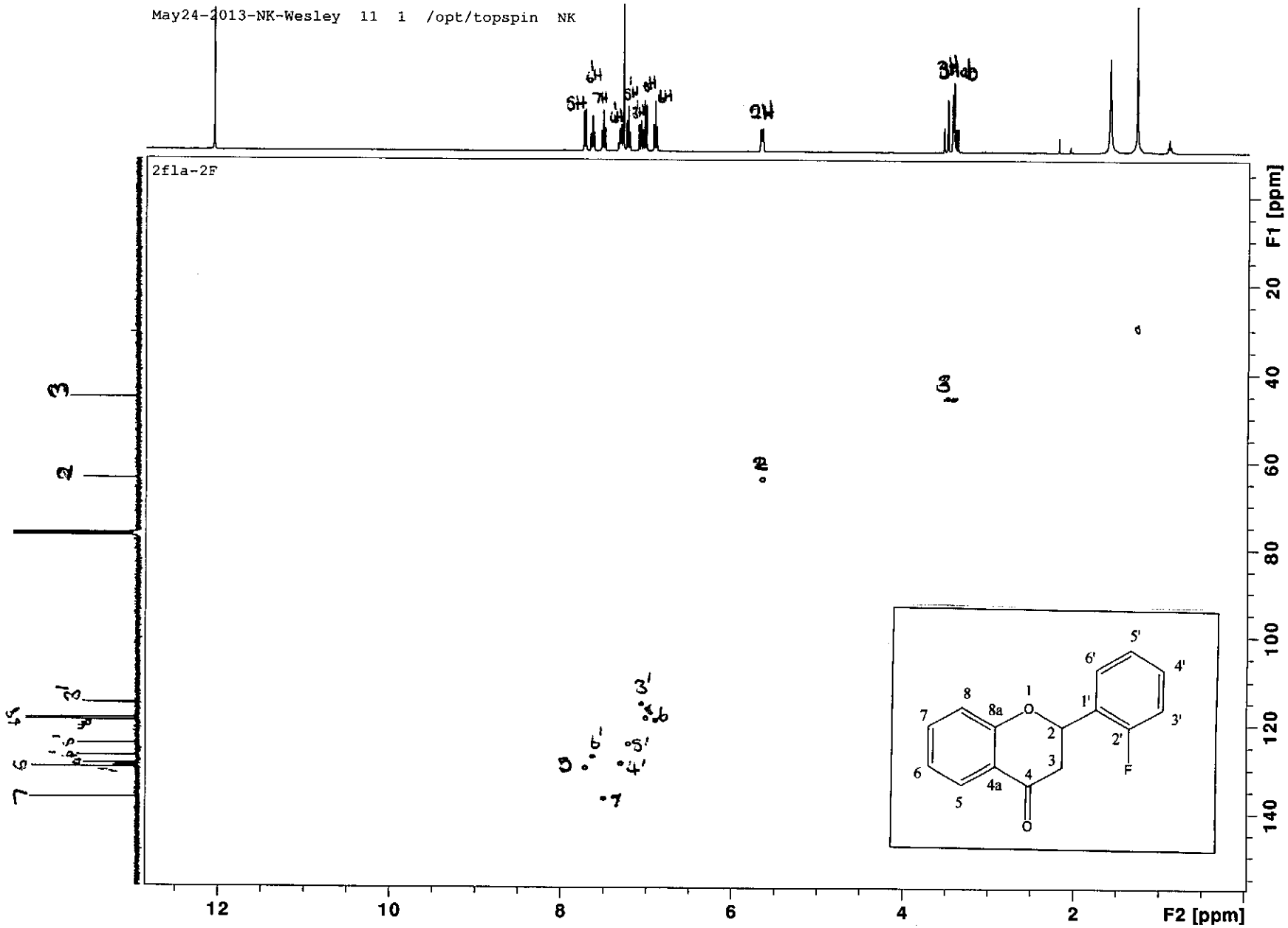
^{1}H NMR spectrum of 2'-fluoroflavanone, (X)



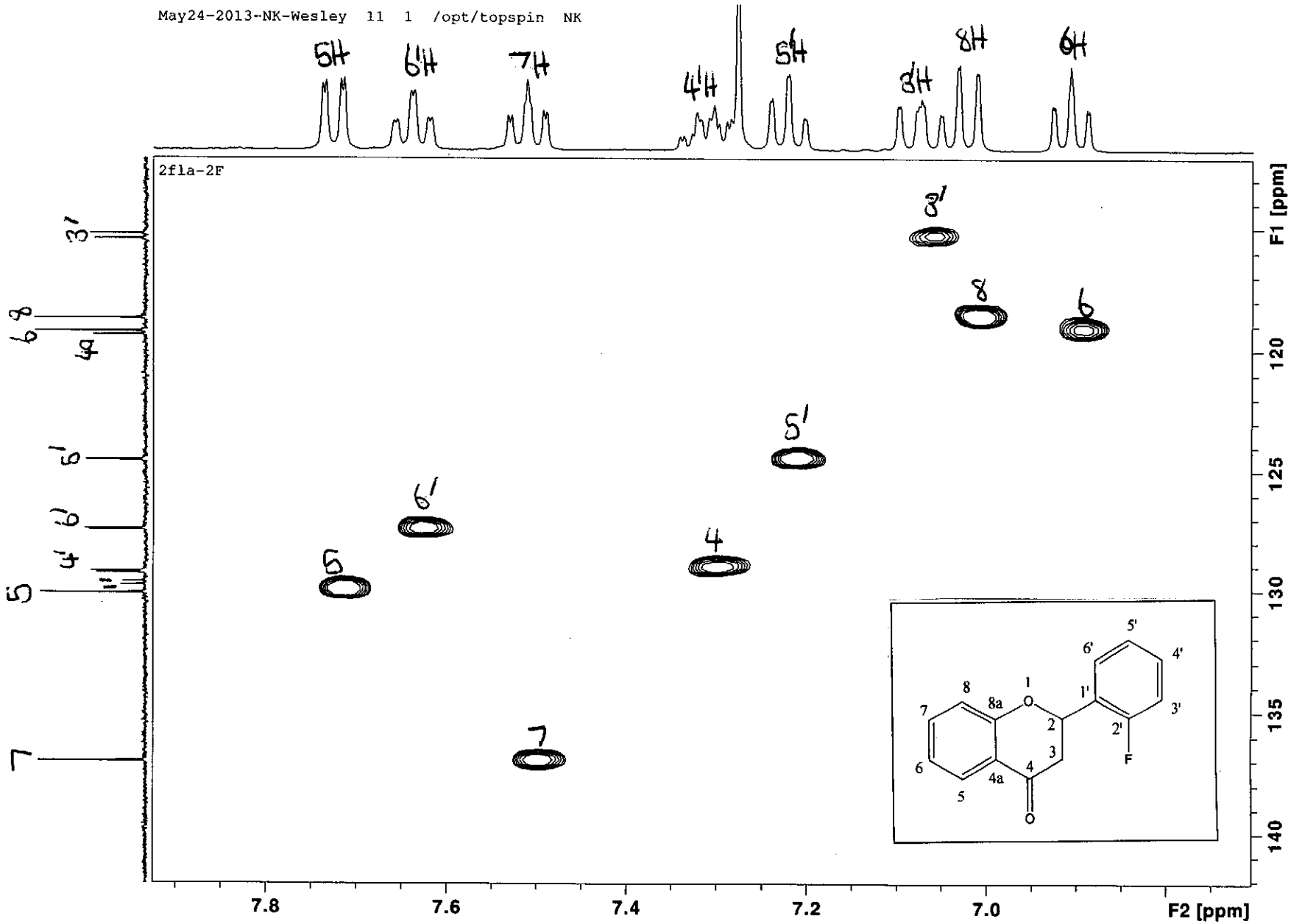
^{13}C NMR spectrum of 2'-fluoroflavanone, (X)



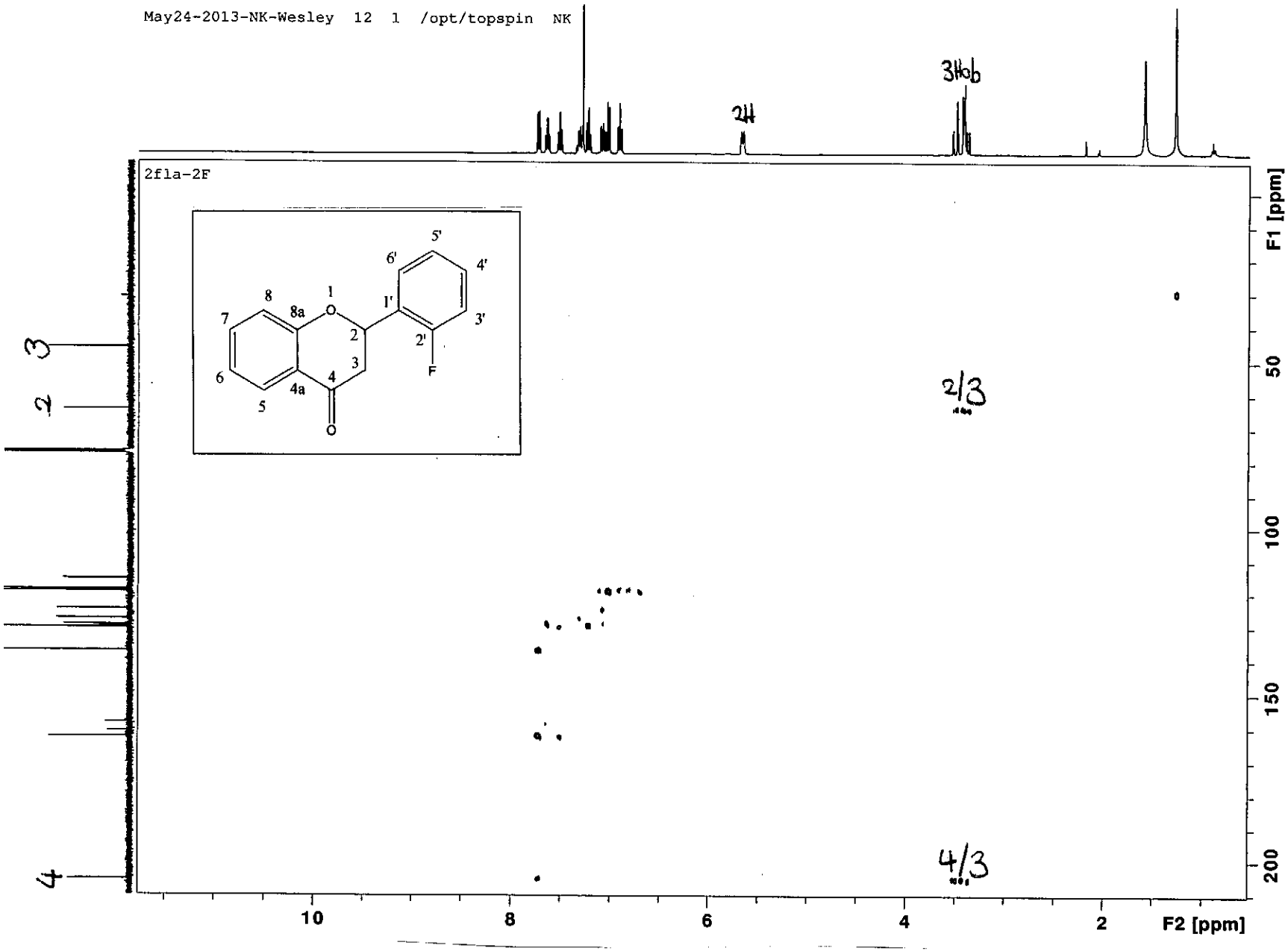
^{13}C NMR spectrum of 2'-fluoroflavanone, (X)



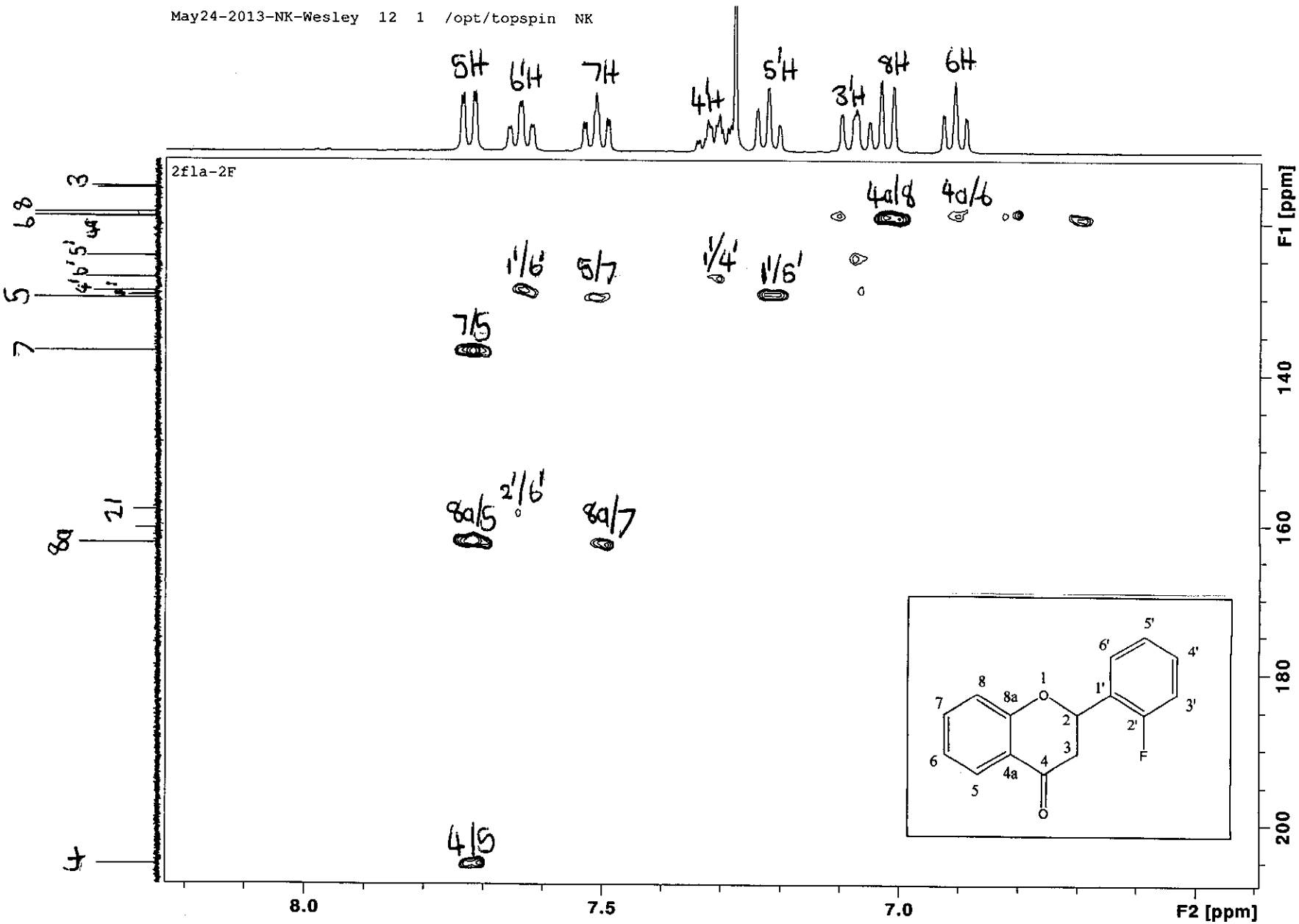
HSQC spectrum of 2'-fluoroflavanone, (X)



HSQC spectrum of 2'-fluoroflavanone, (X)



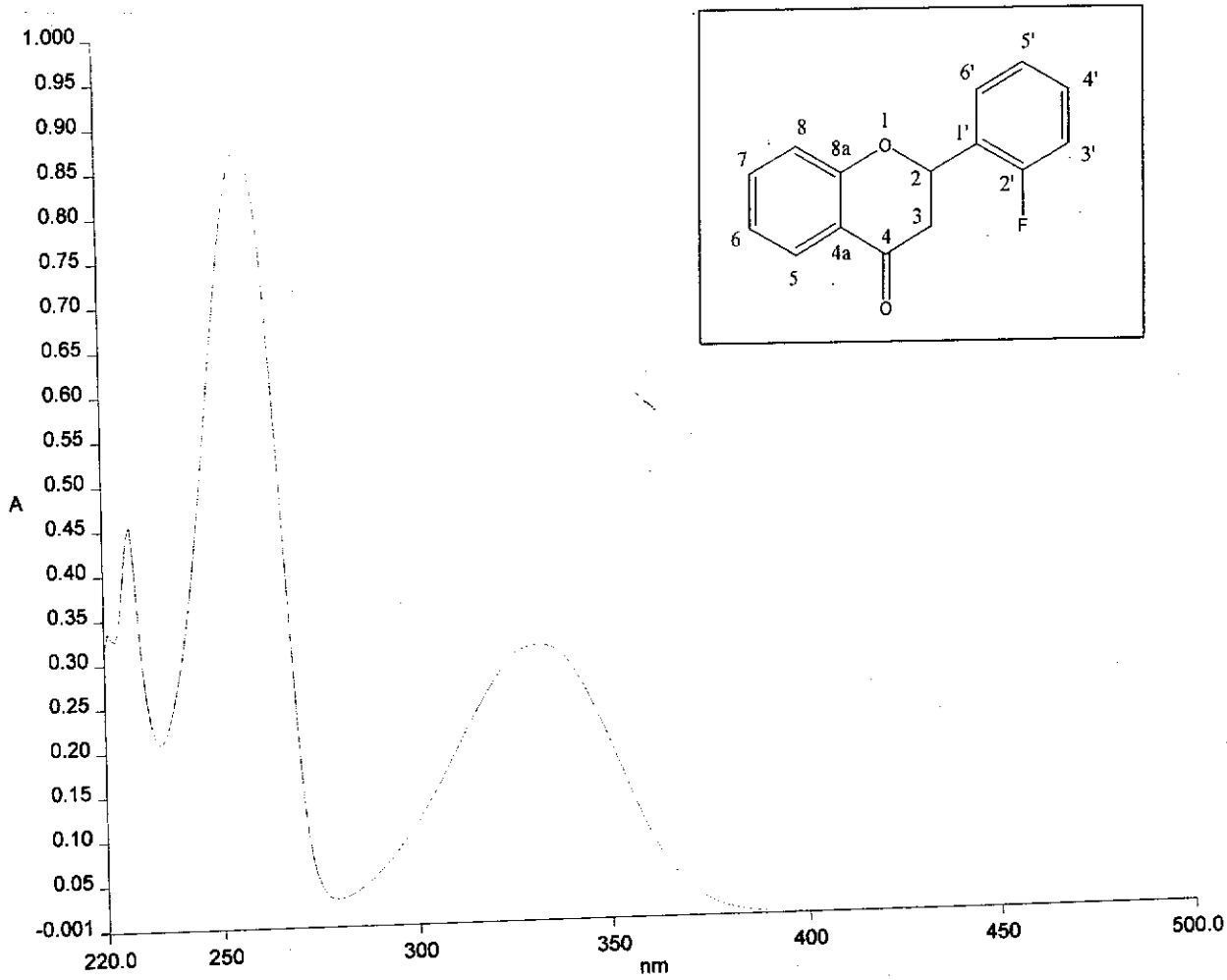
HMBC spectrum of 2'-fluoroflavanone, (X)



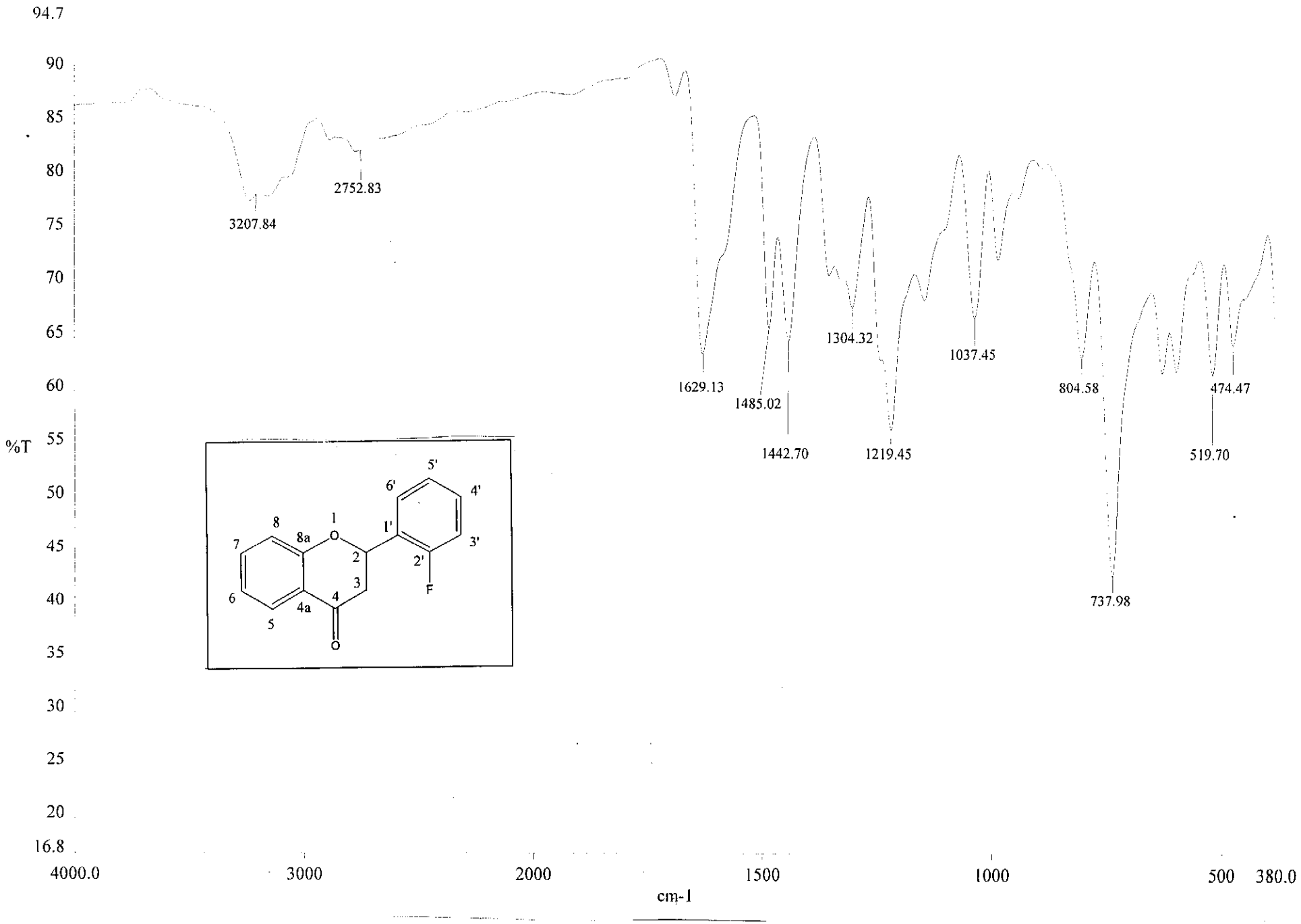
HMBC spectrum of 2'-fluoroflavanone, (X)

$\lambda max(256nm) - 0.8756$ $\log \varepsilon = 5.64$
$\lambda max(333nm) - 0.3097$ $\log \varepsilon = 5.19$

Date: 2013/06/07 Time: 09:46:54 AM



Ultra violet (UV) spectrum of 2'-fluoroflavanone, (X)



Infra-Red (IR) spectrum of 2'-fluoroflavanone, (X)

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Instrument :   5973n
Sample Name: MeOH 2fla-2f
Misc Info  :
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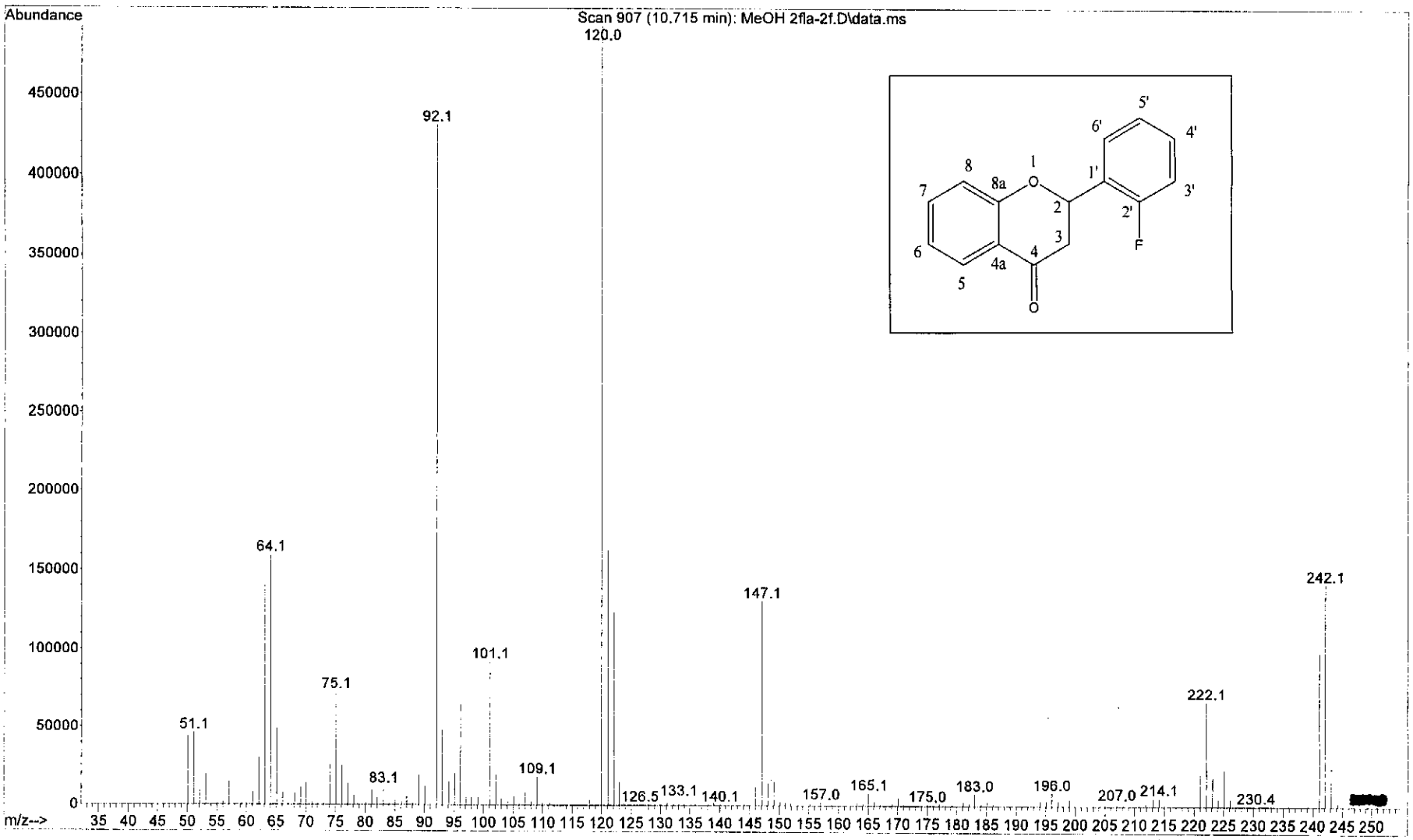
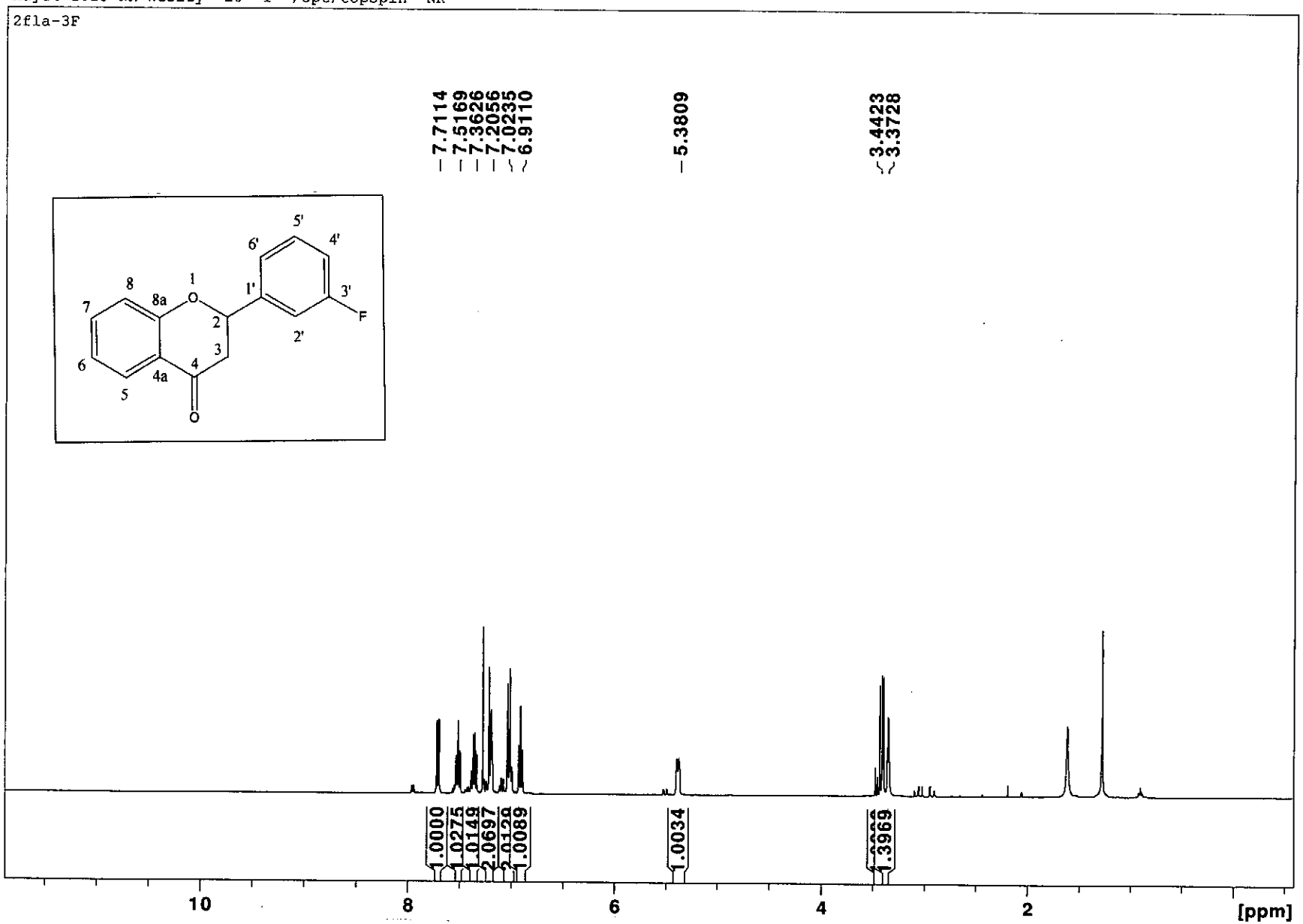
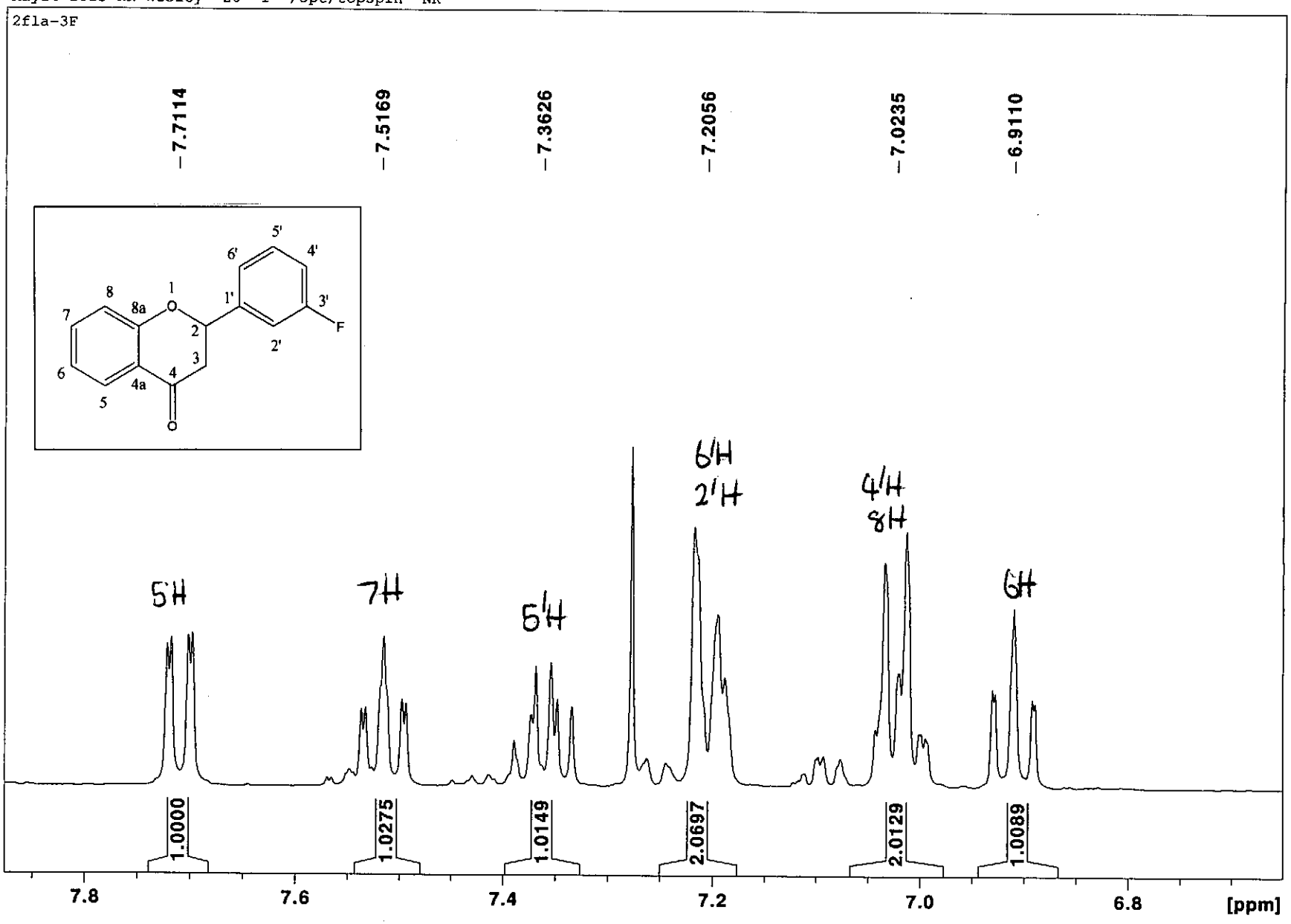


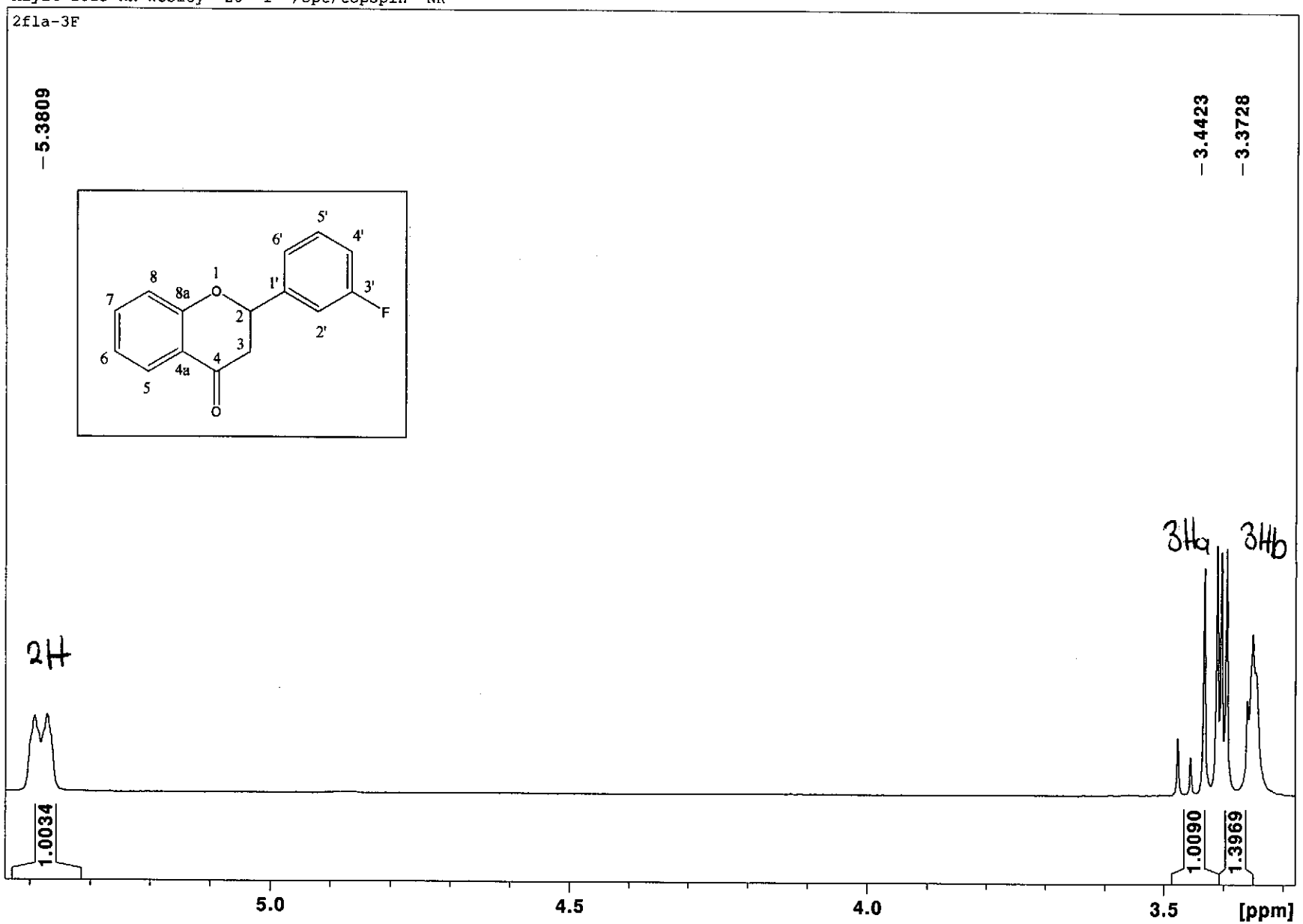
GC-MS spectrum of 2'-fluoroflavanone, (X)



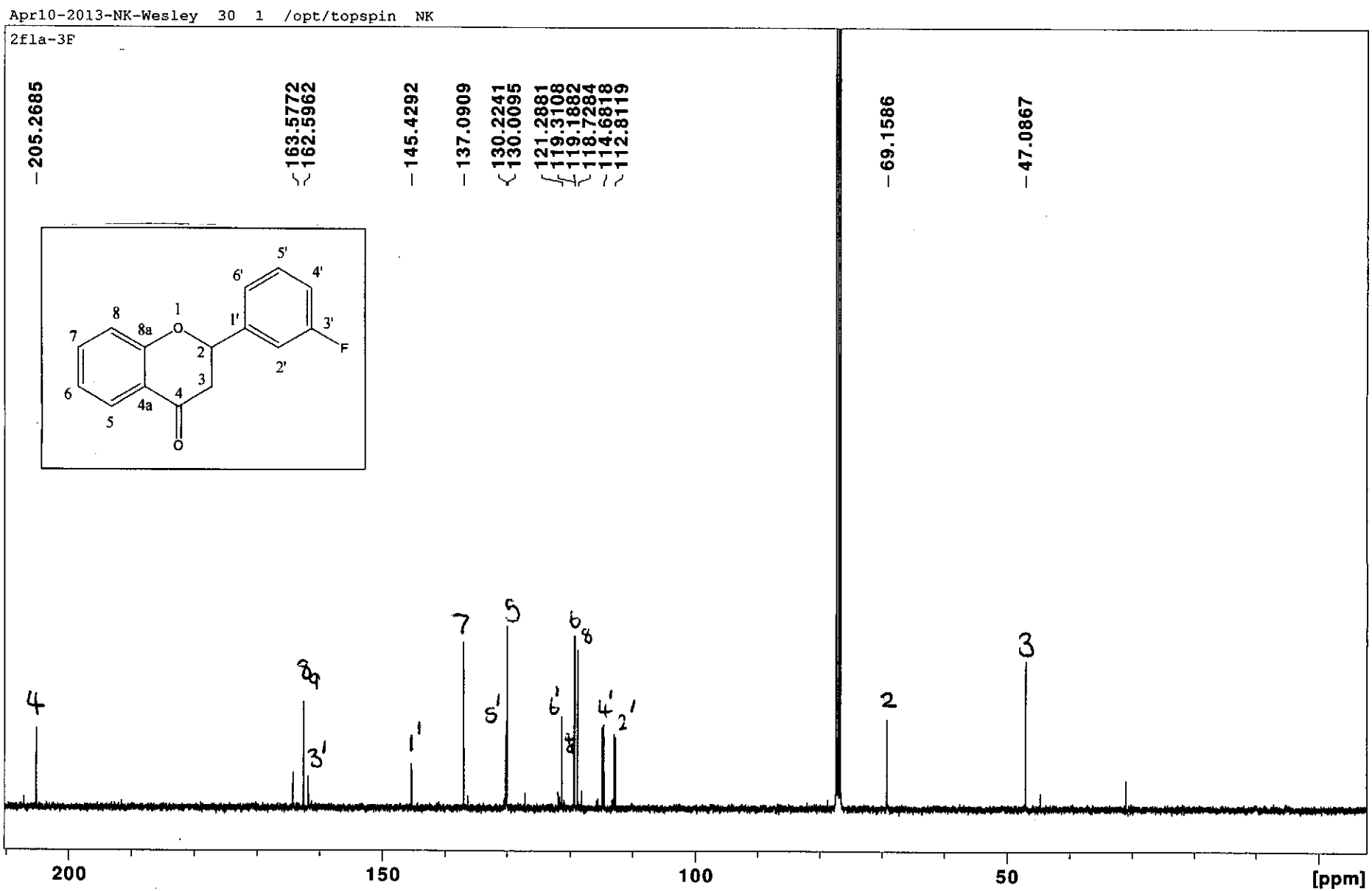
^{1}H NMR spectrum of 3'-fluoroflavanone, (XI)



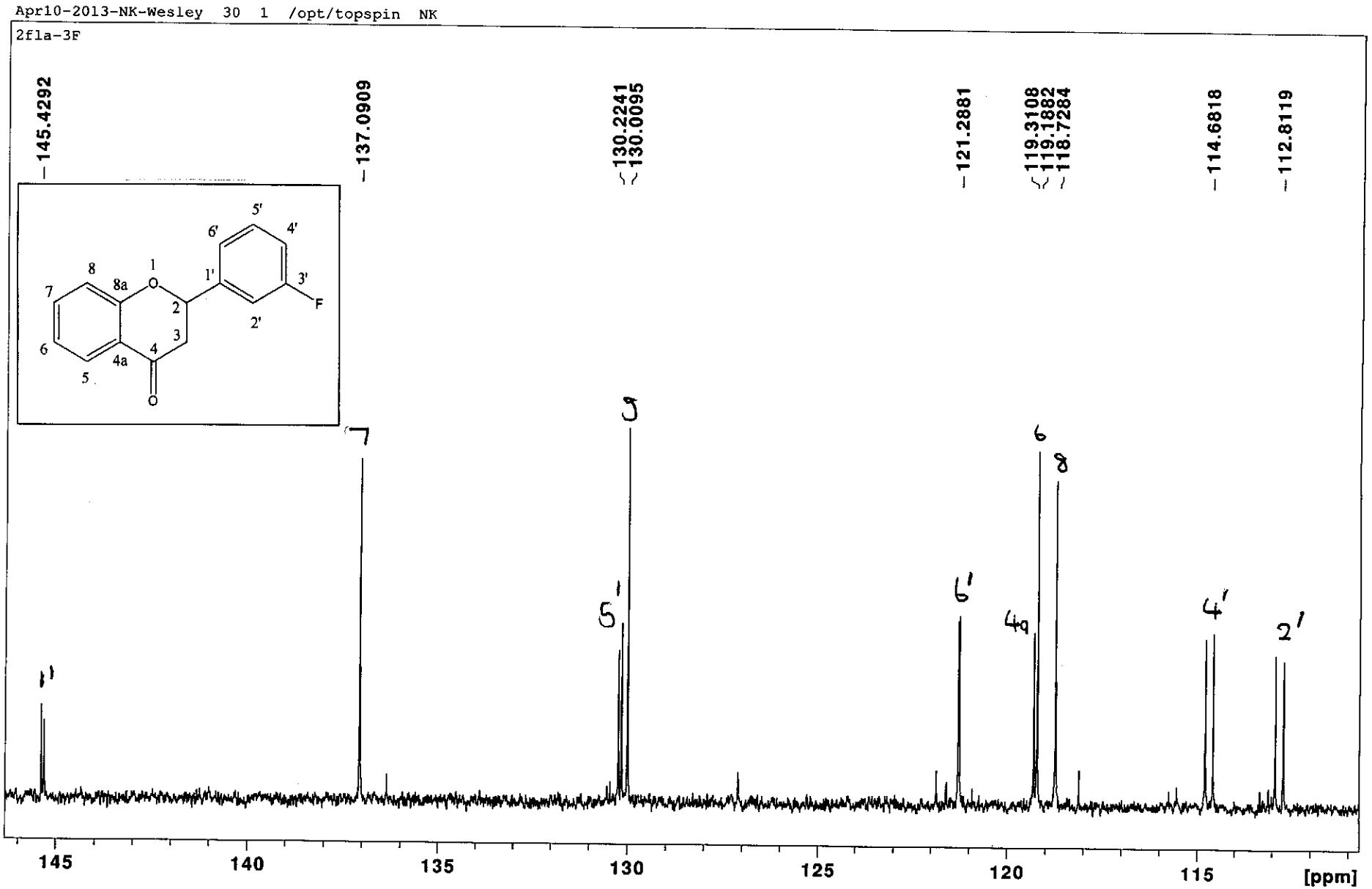
^{1}H NMR spectrum of 3'-fluoroflavanone, (XI)



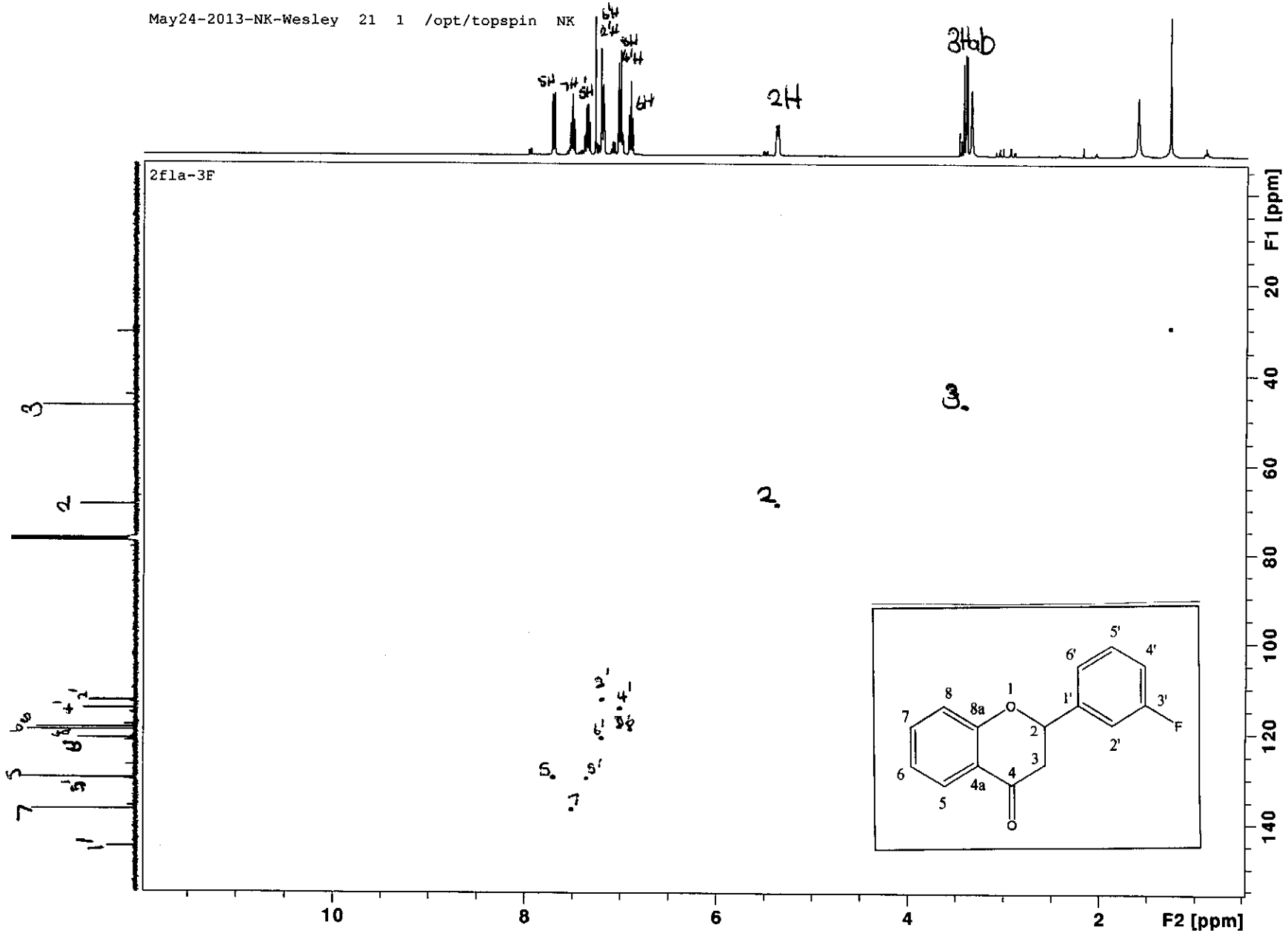
^{1}H NMR spectrum of 3'-fluoroflavanone, (XI)



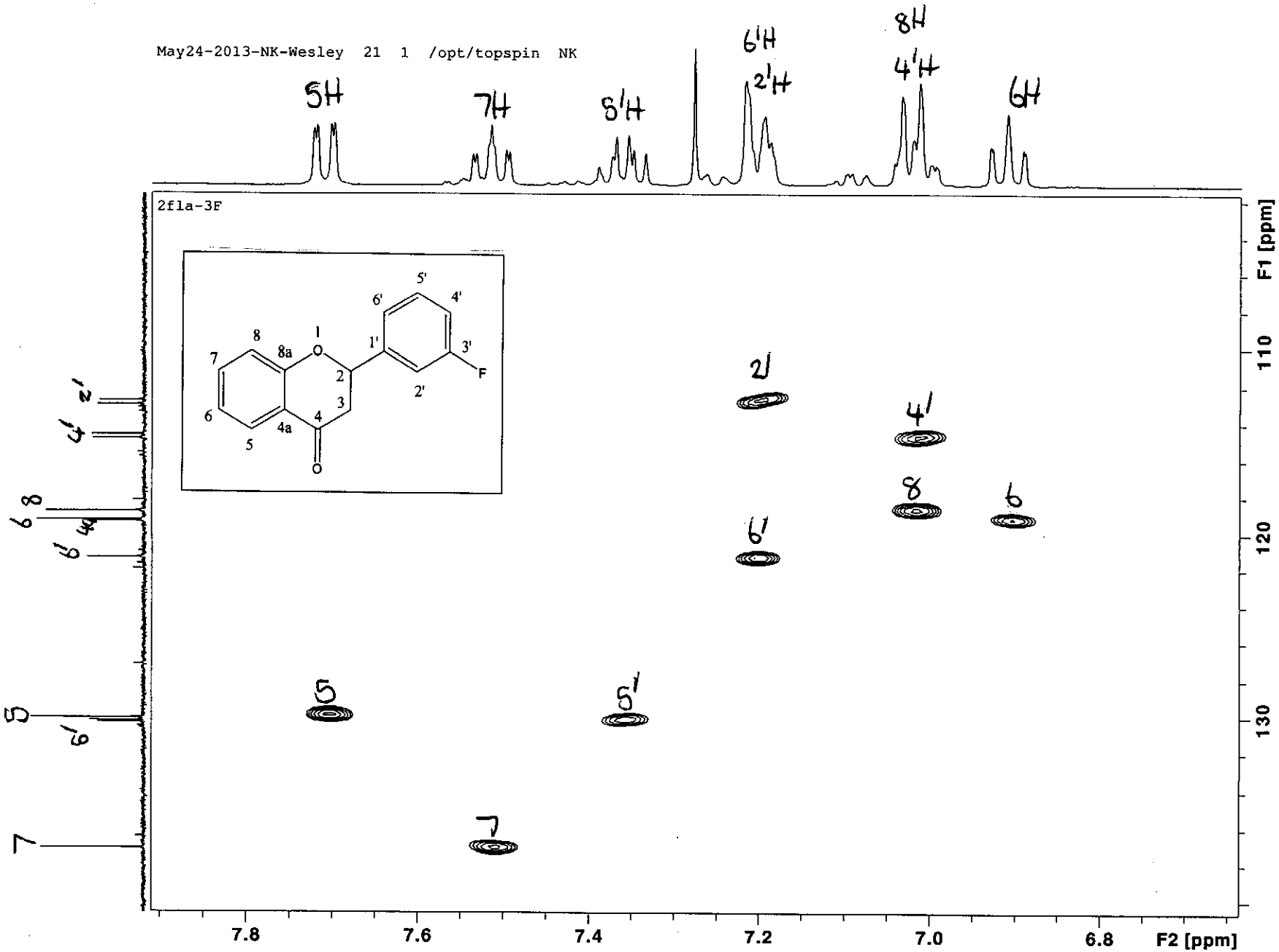
^{13}C NMR spectrum of 3'-fluoroflavanone, (XI)



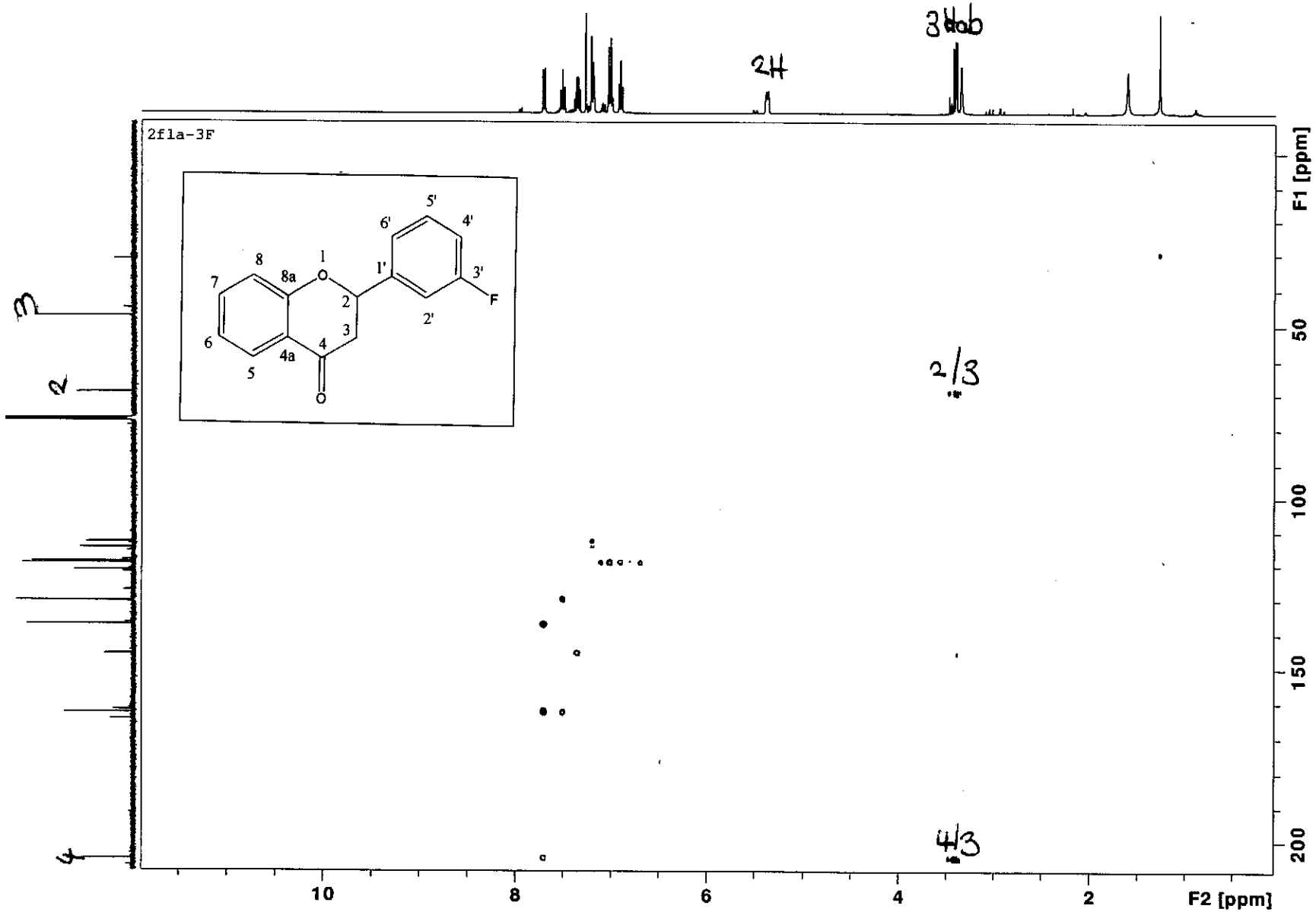
^{13}C NMR spectrum of 3'-fluoroflavanone, (XI)



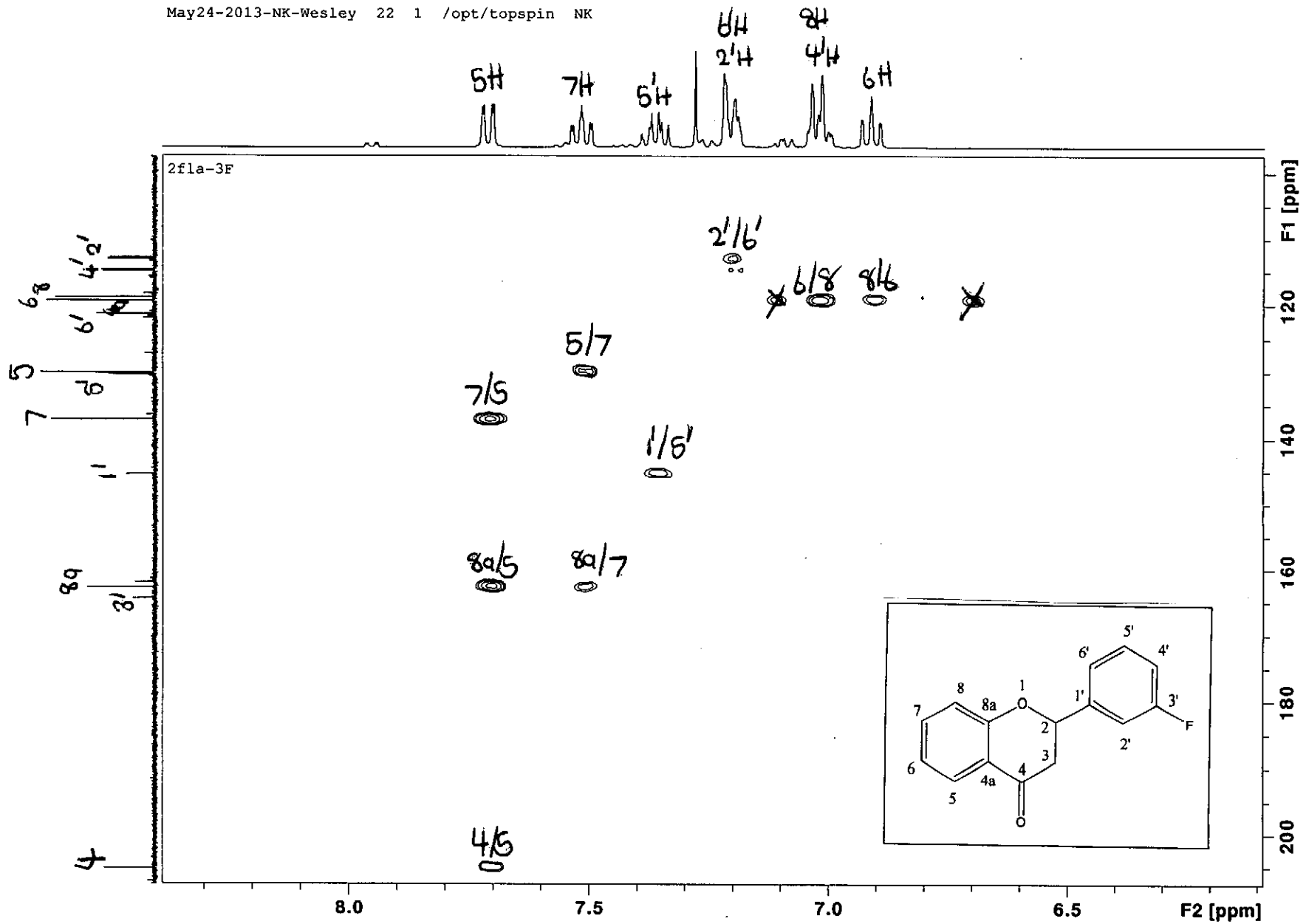
HSQC spectrum of 3'-fluoroflavanone, (XI)



HSQC spectrum of 3'-fluoroflavanone, (XI)



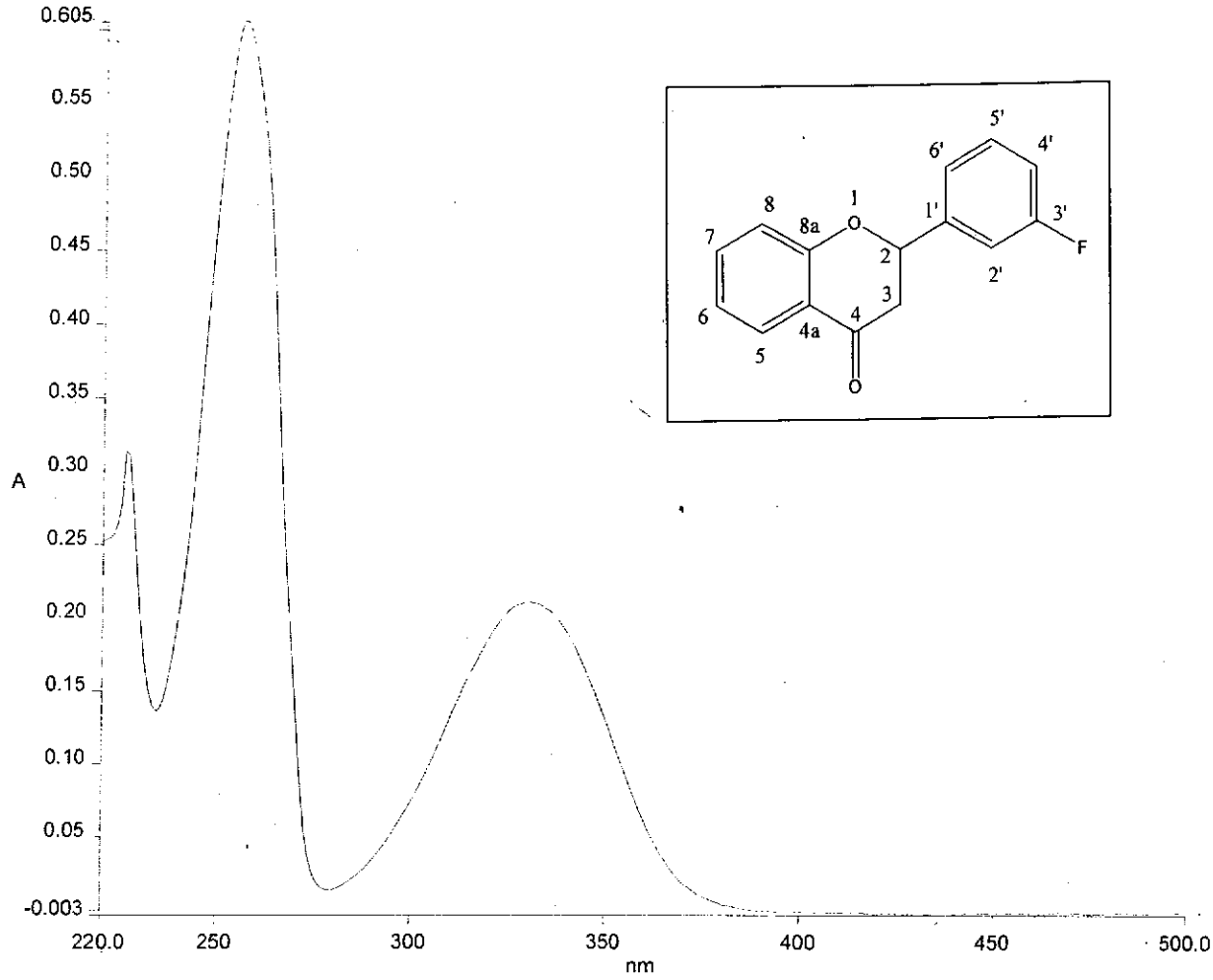
HMBC spectrum of 3'-fluoroflavanone, (XI)



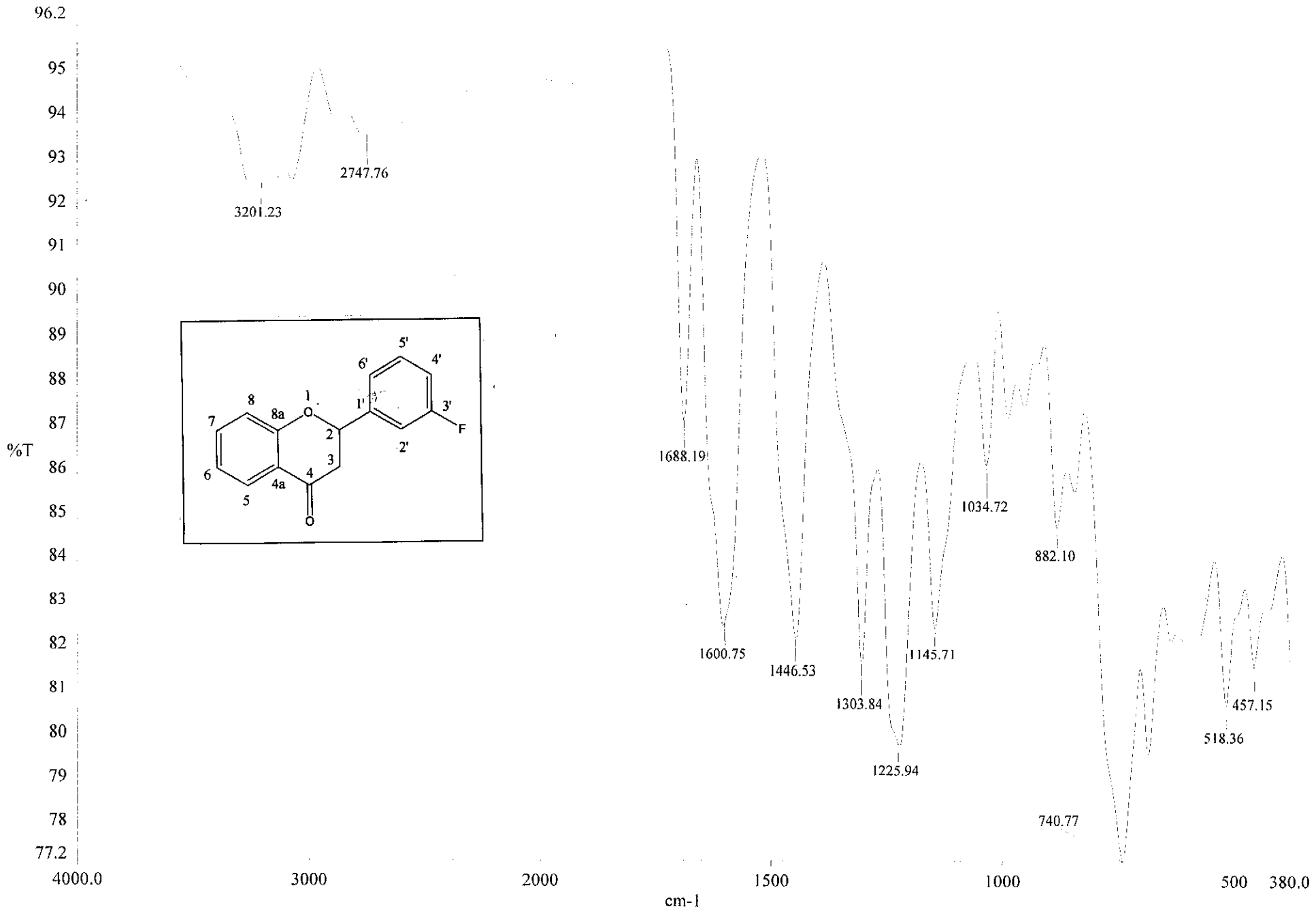
HMBC spectrum of 3'-fluoroflavanone, (XI)

λmax (330nm) – 0.2107

Date: 2013/05/23 Time: 11:21:07 AM



Ultra violet (UV) spectrum of 3'-fluoroflavanone, (XI)



Infra-Red (IR) spectrum of 3'-fluoroflavanone, (XI)

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...         3f.D
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Sample Name: 2fla-3f
Misc Info  :
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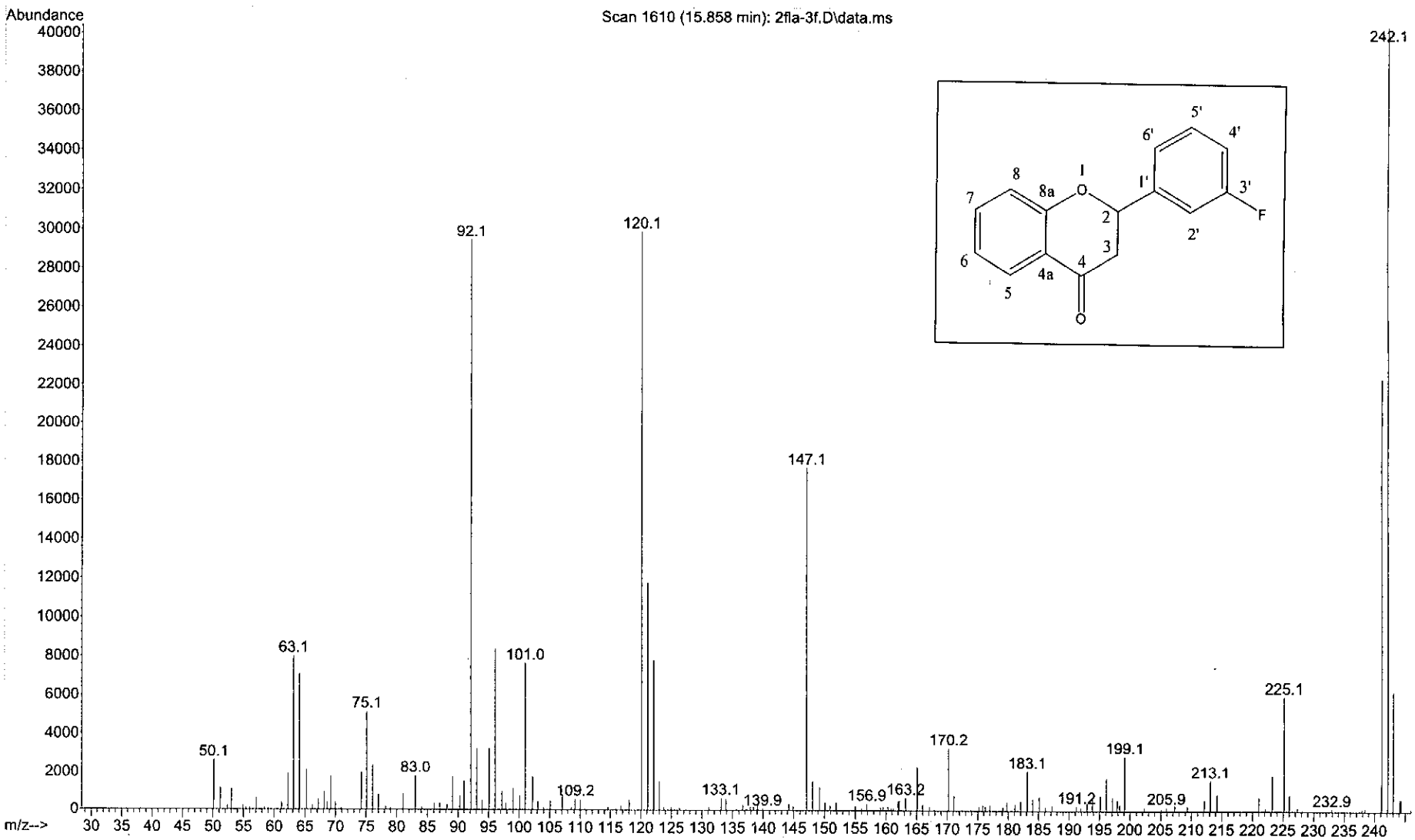
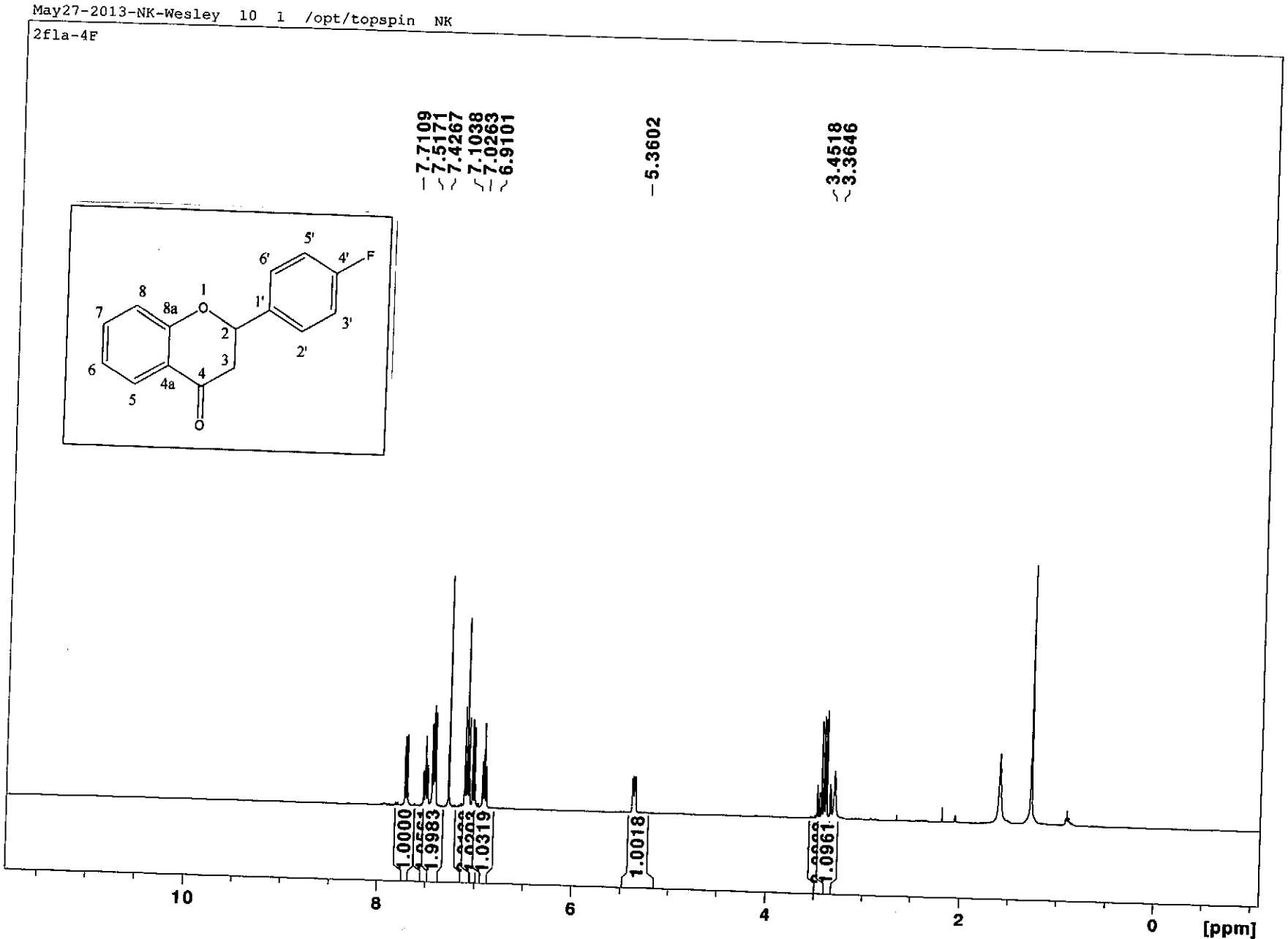
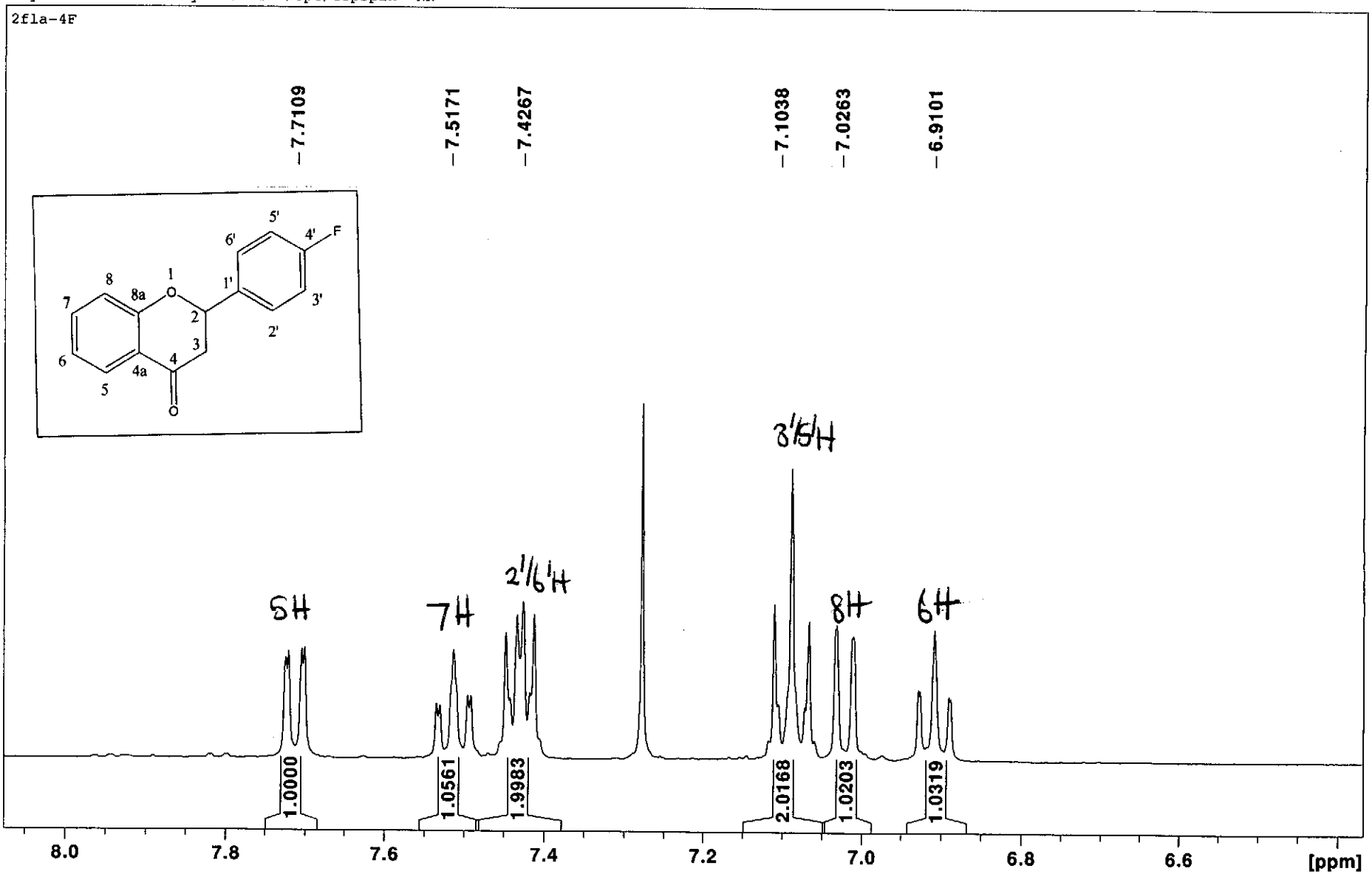


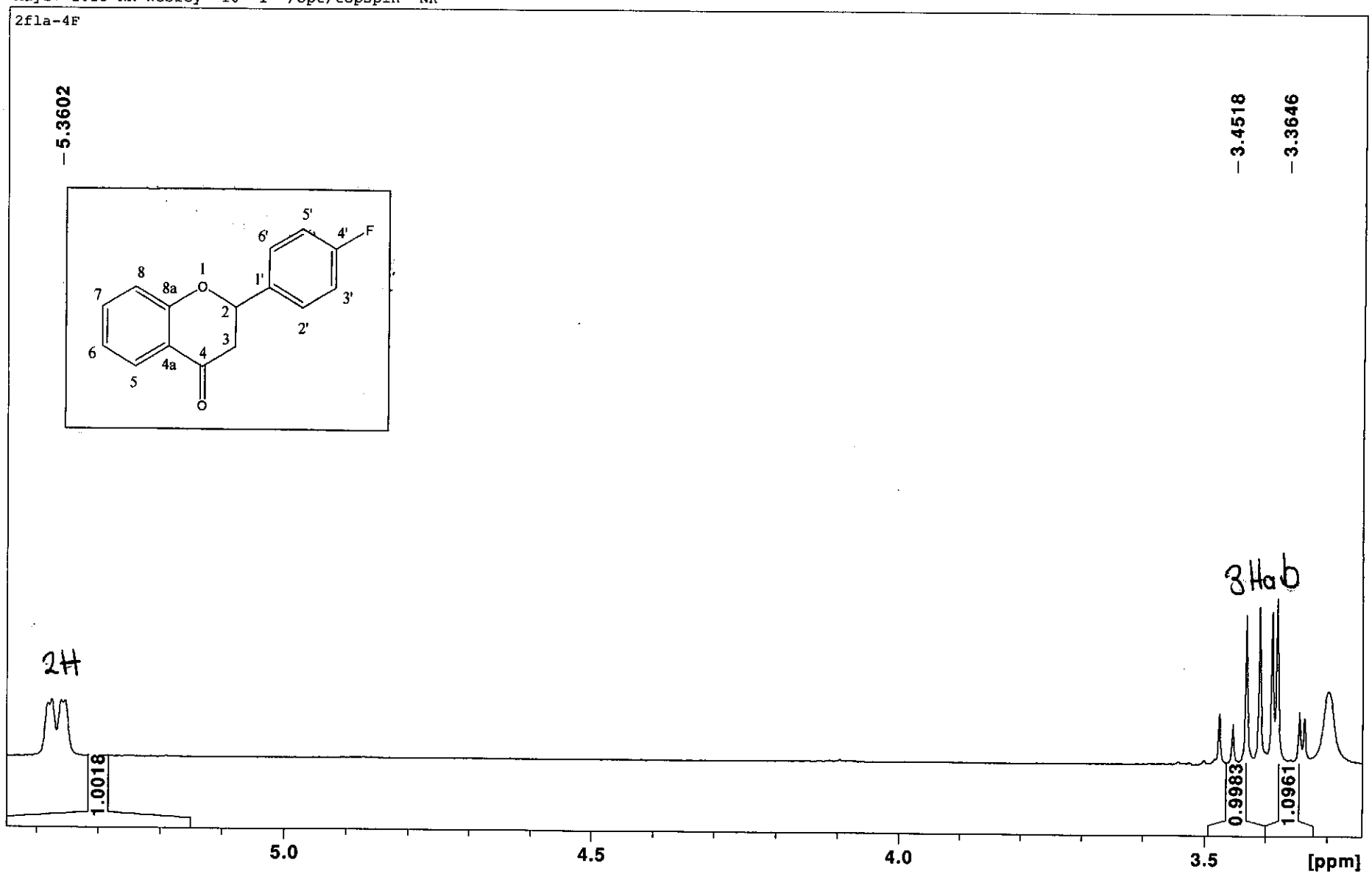
GC-MS spectrum of 3'-fluoroflavanone, (XI)



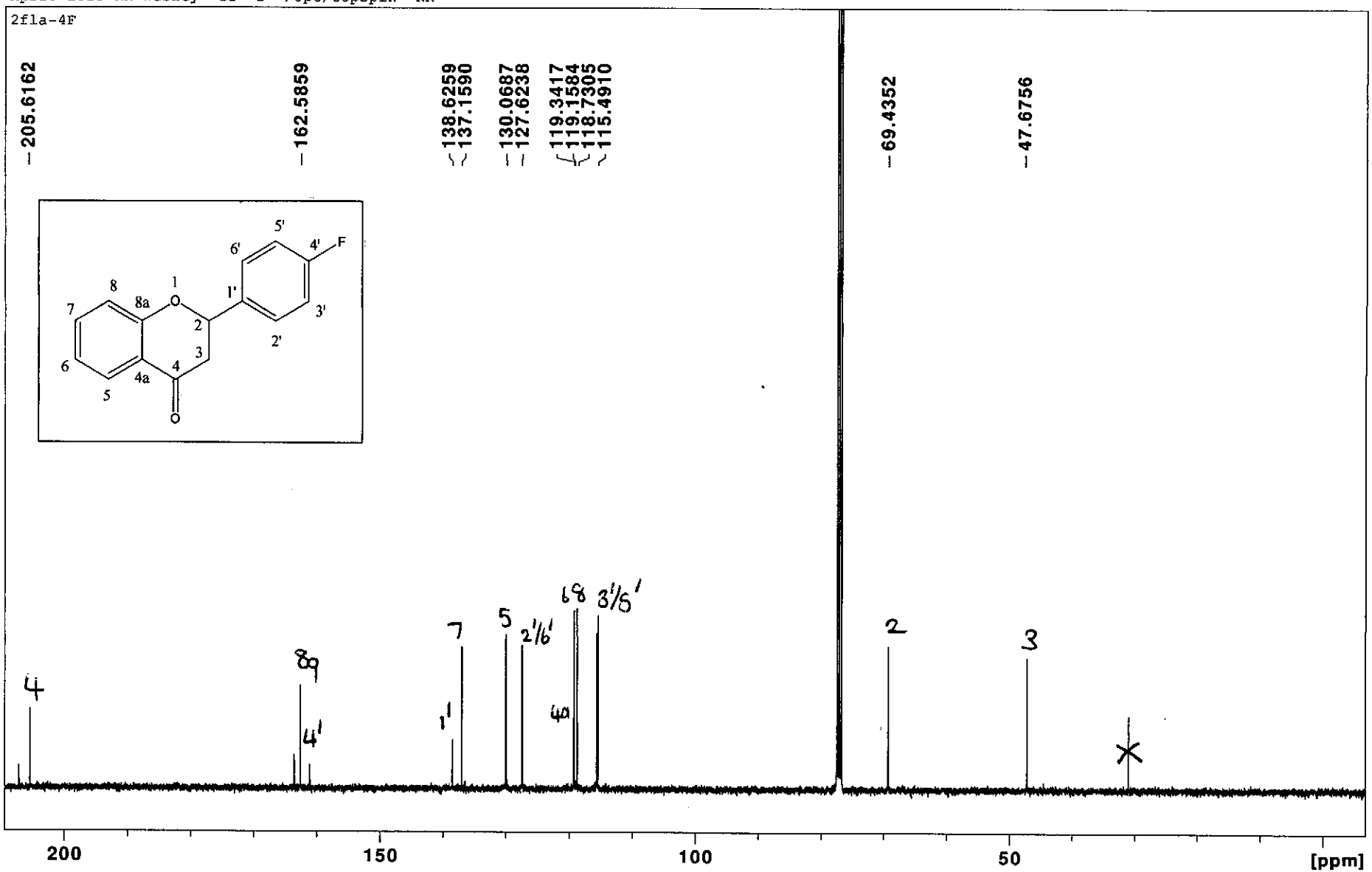
^{1}H NMR spectrum of 4'-fluoroflavanone, (XII)



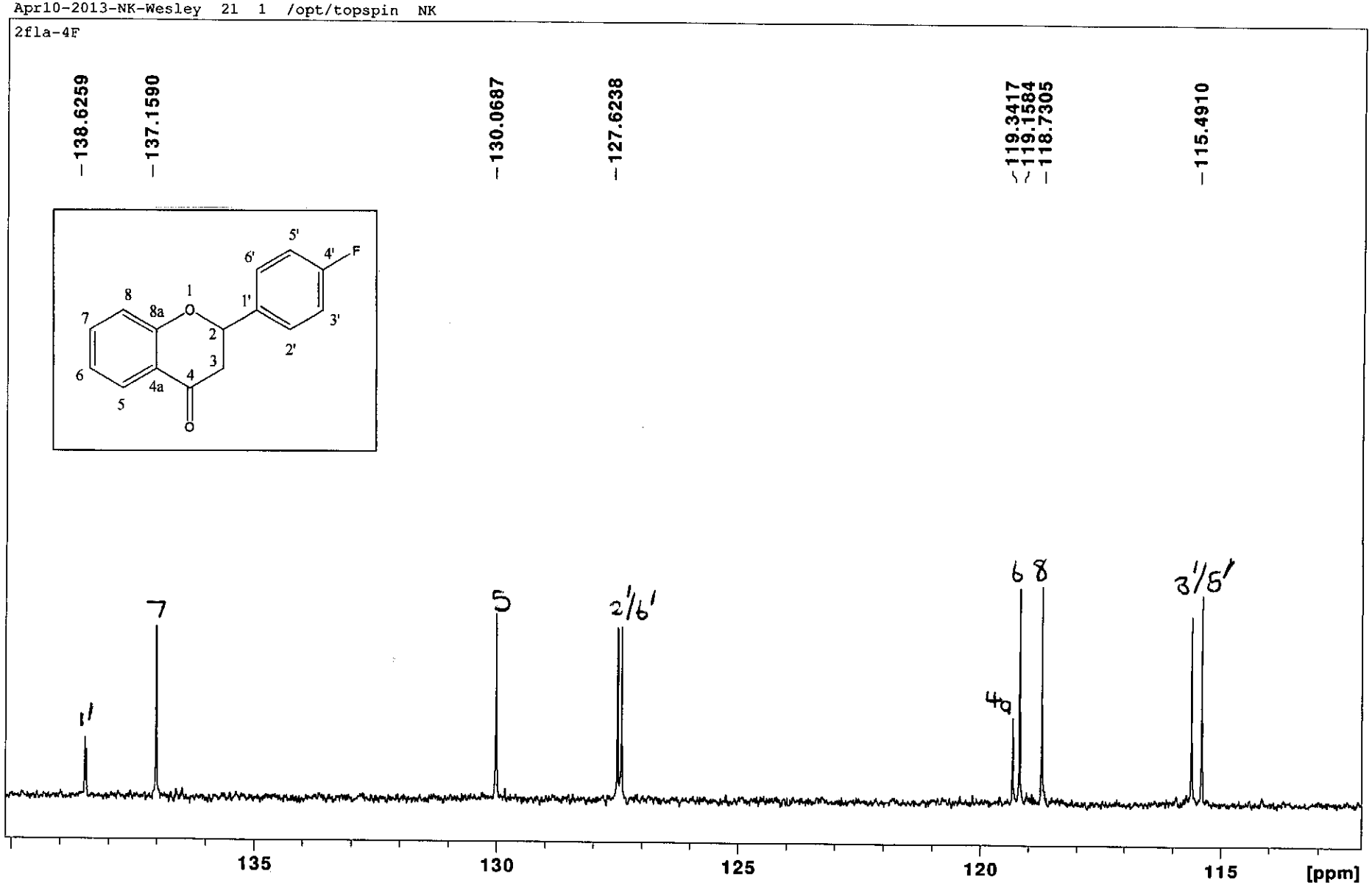
^{1}H NMR spectrum of 4'-fluoroflavanone, (XII)



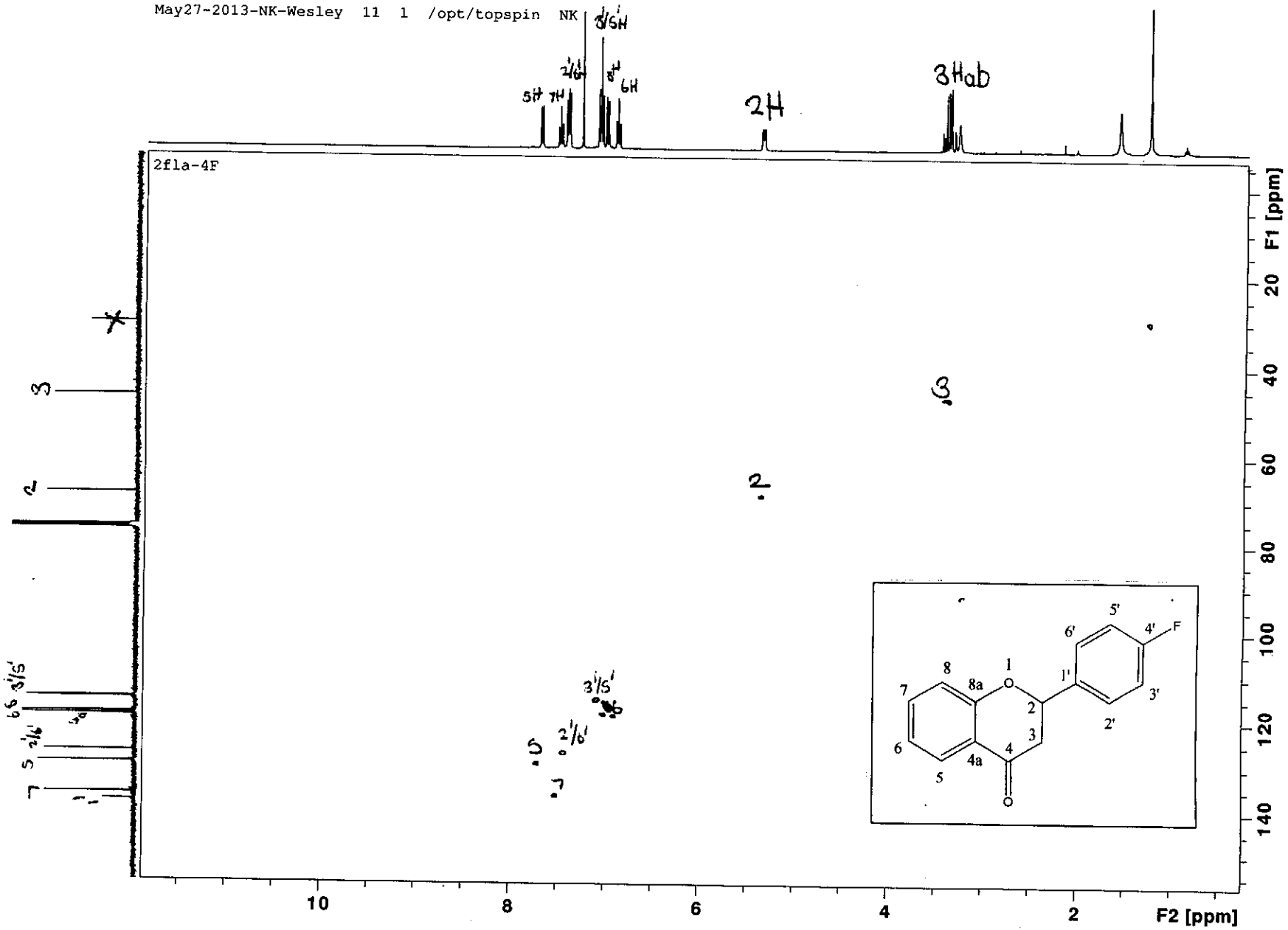
^{1}H NMR spectrum of 4'-fluoroflavanone, (XII)



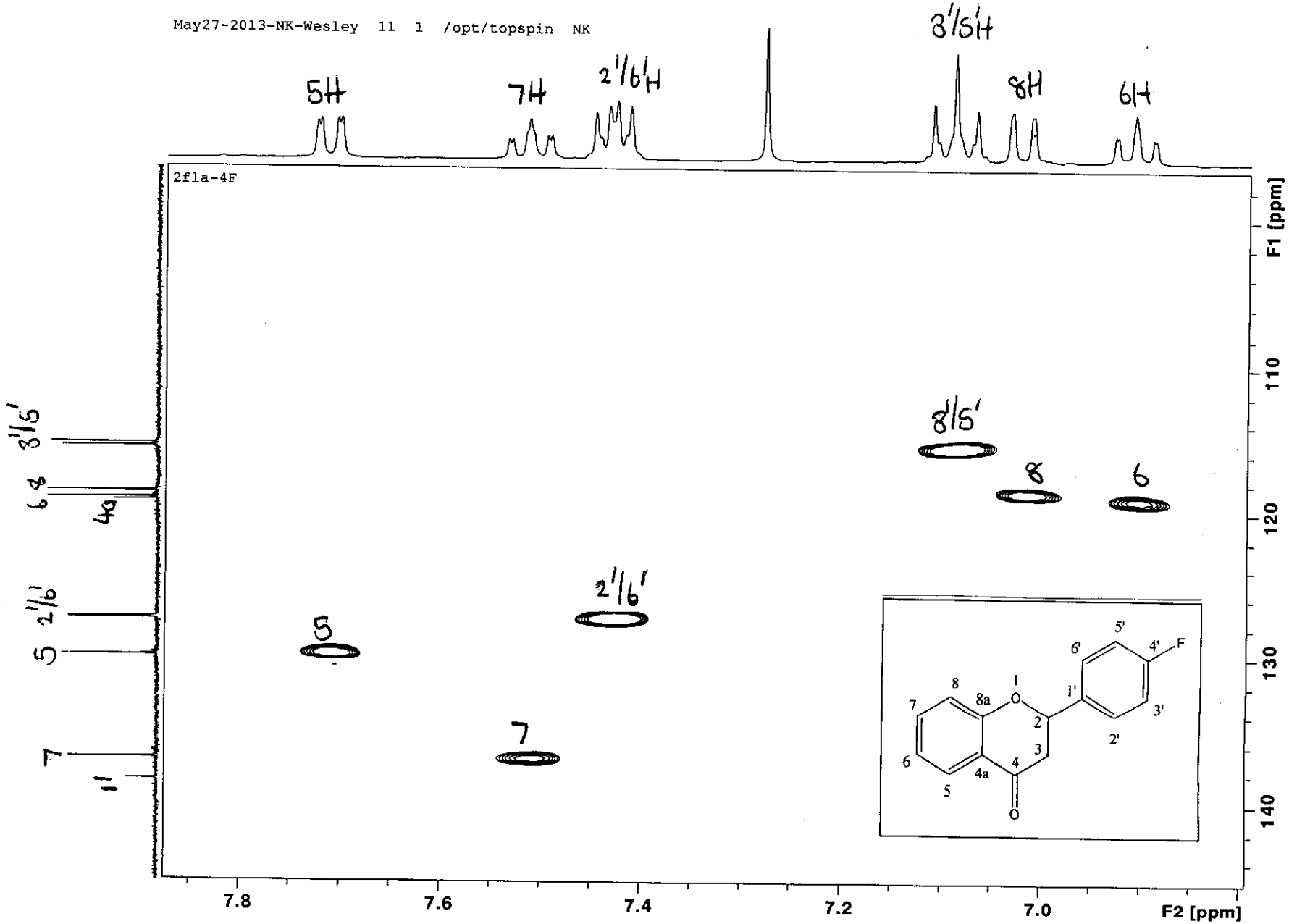
^{13}C NMR spectrum of 4'-fluoroflavanone, (XII)



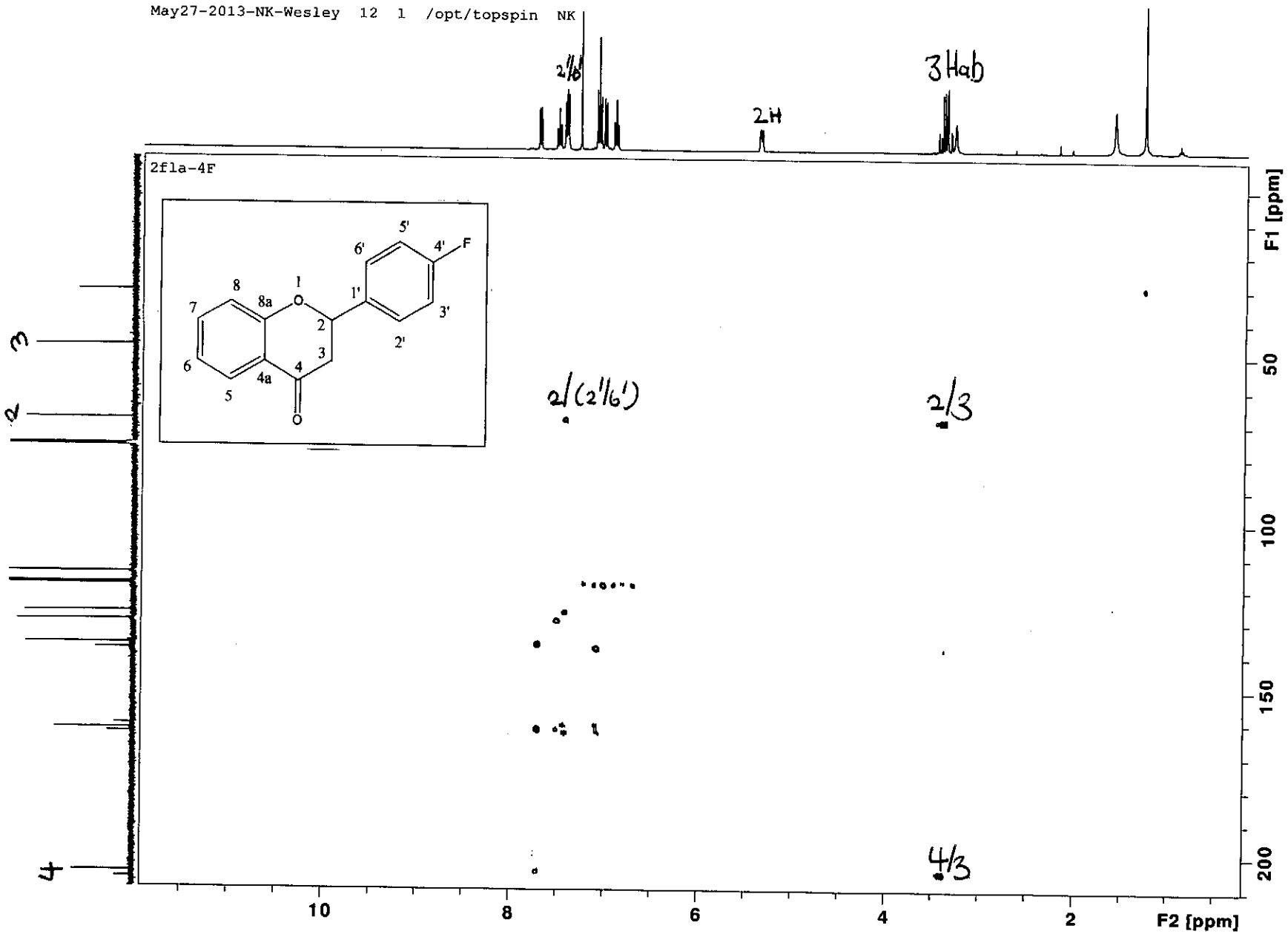
^{13}C NMR spectrum of 4'-fluoroflavanone, (XII)



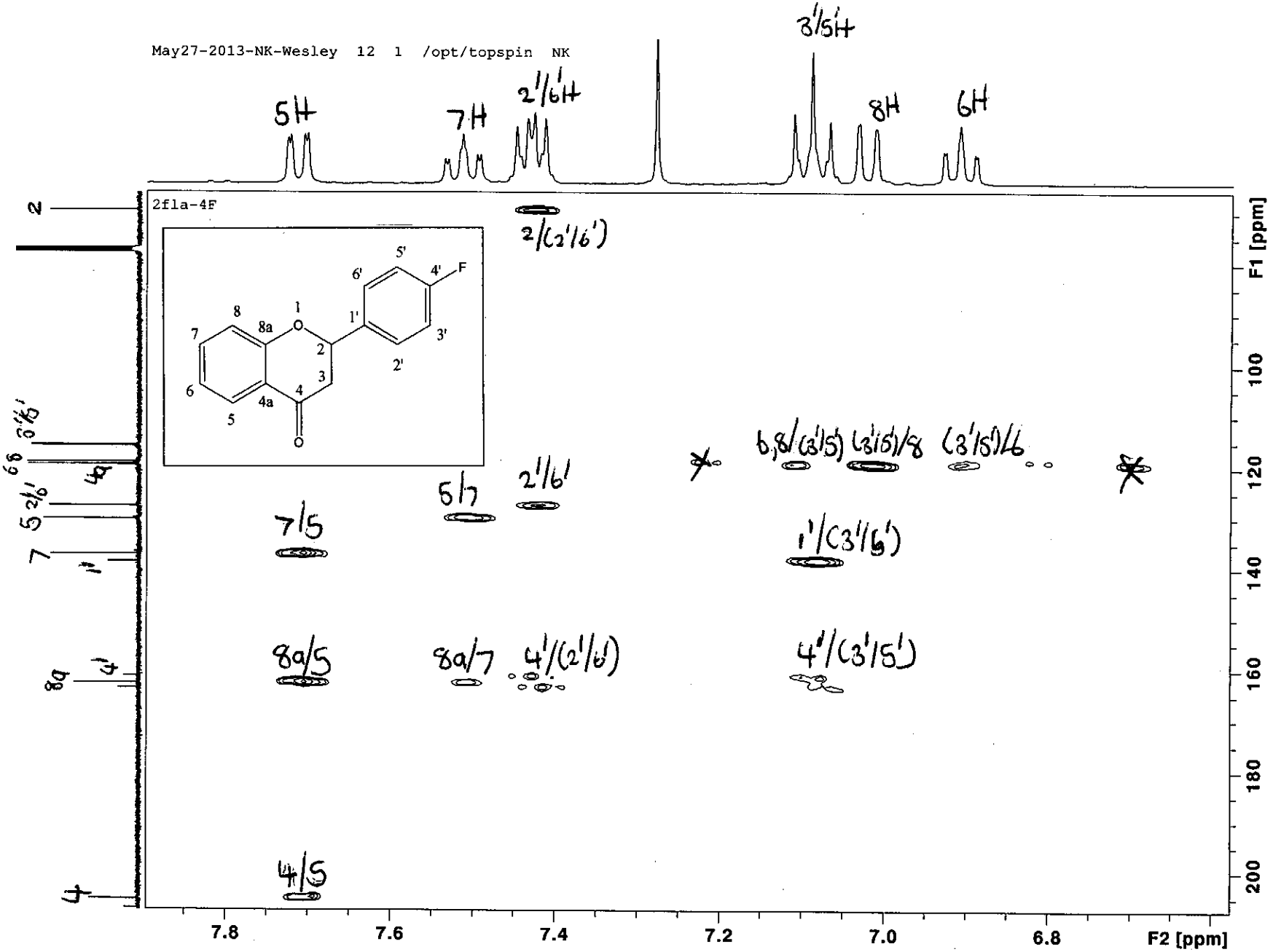
HSQC spectrum of 4'-fluoroflavanone, (XII)



HSQC spectrum of 4'-fluoroflavanone, (XII)



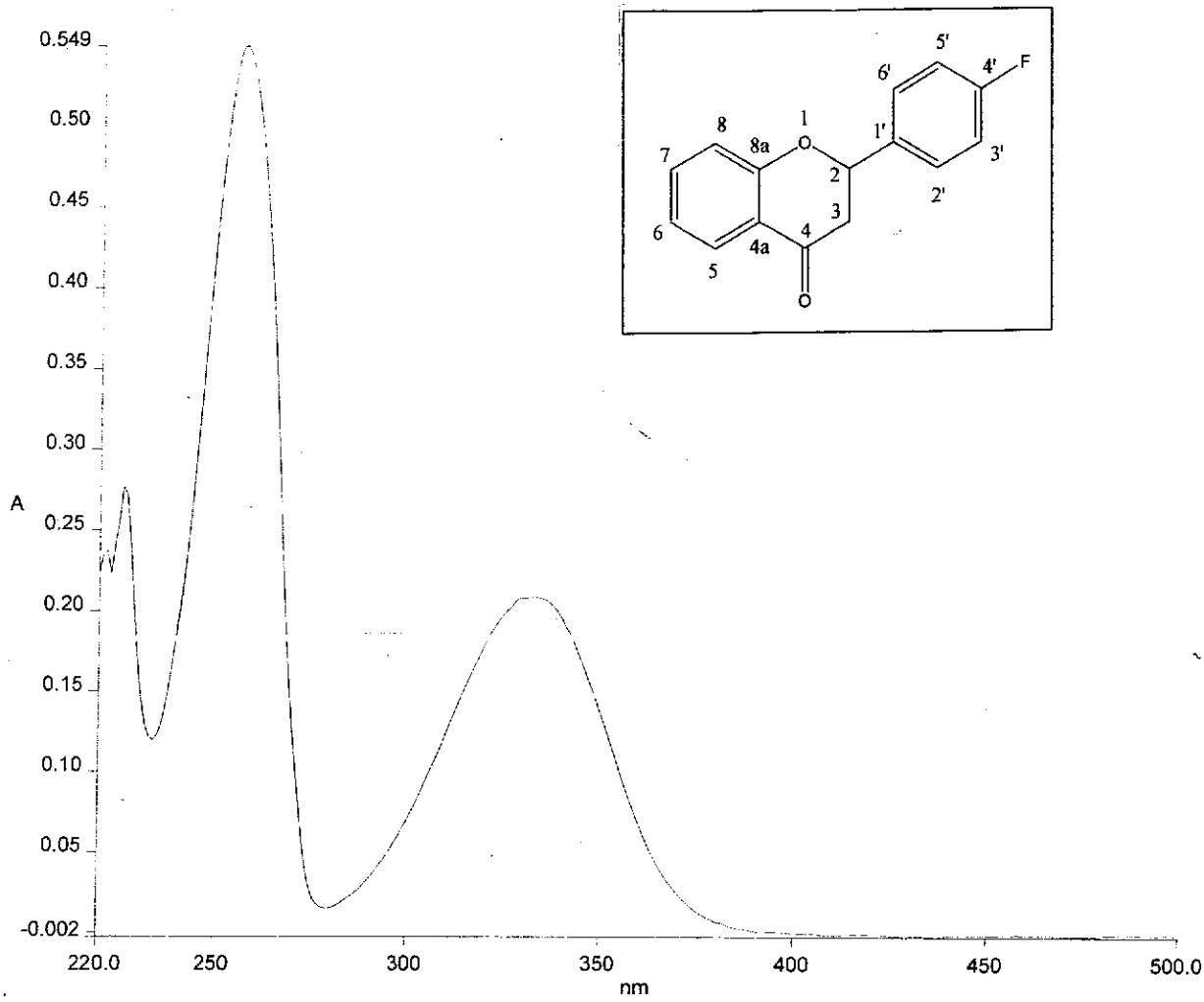
HMBC spectrum of 4'-fluoroflavanone, (XII)



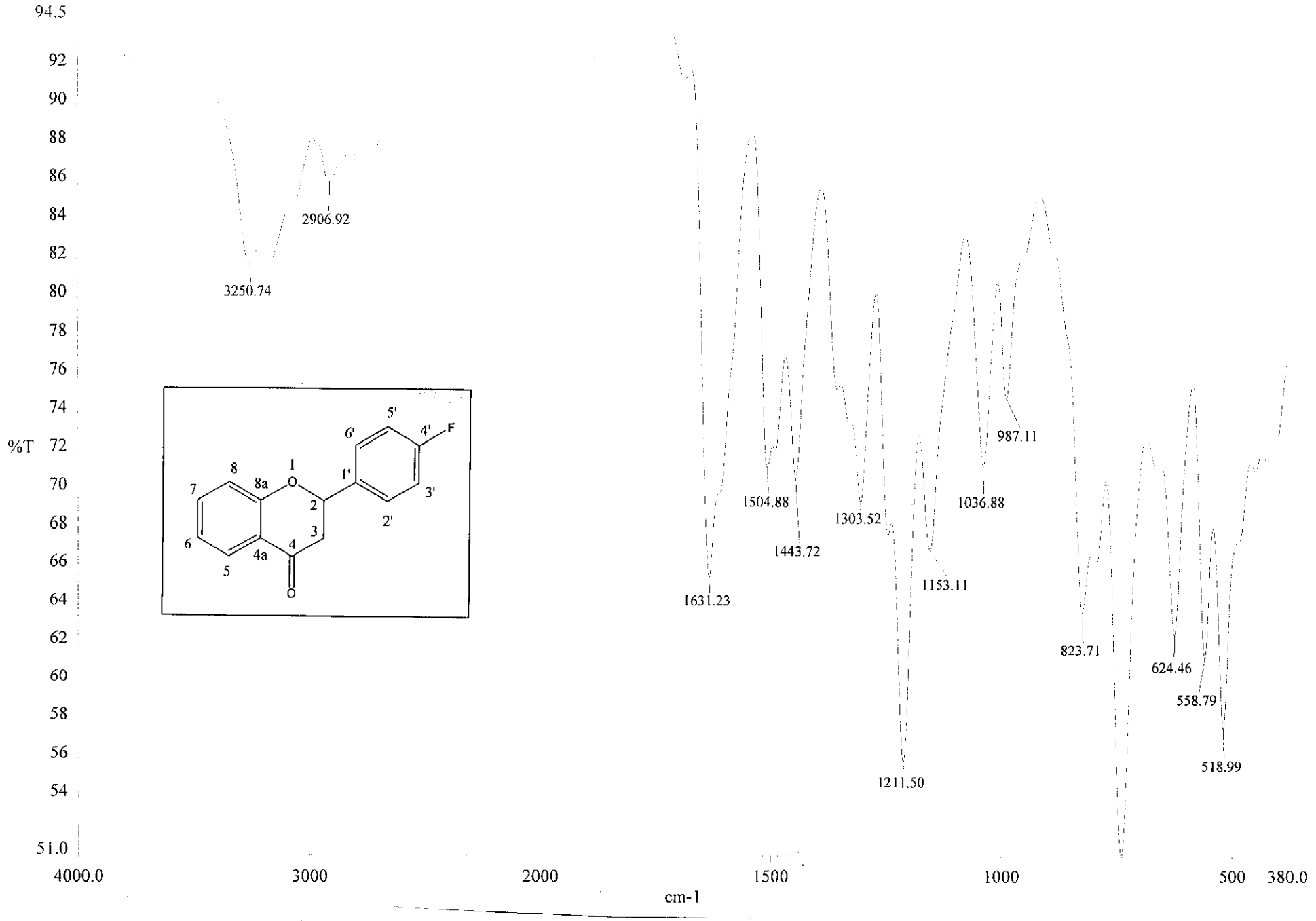
HMBC spectrum of 4'-fluoroflavanone, (XII)

λmax (333nm) - 0.267 log ε = 5.02

Date: 2013/05/23 Time: 11:23:15 AM



Ultra violet (UV) spectrum of 4'-fluoroflavanone, (XII)



Infra-Red (IR) spectrum of 4'-fluoroflavanone, (XII)

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Misc Info  :
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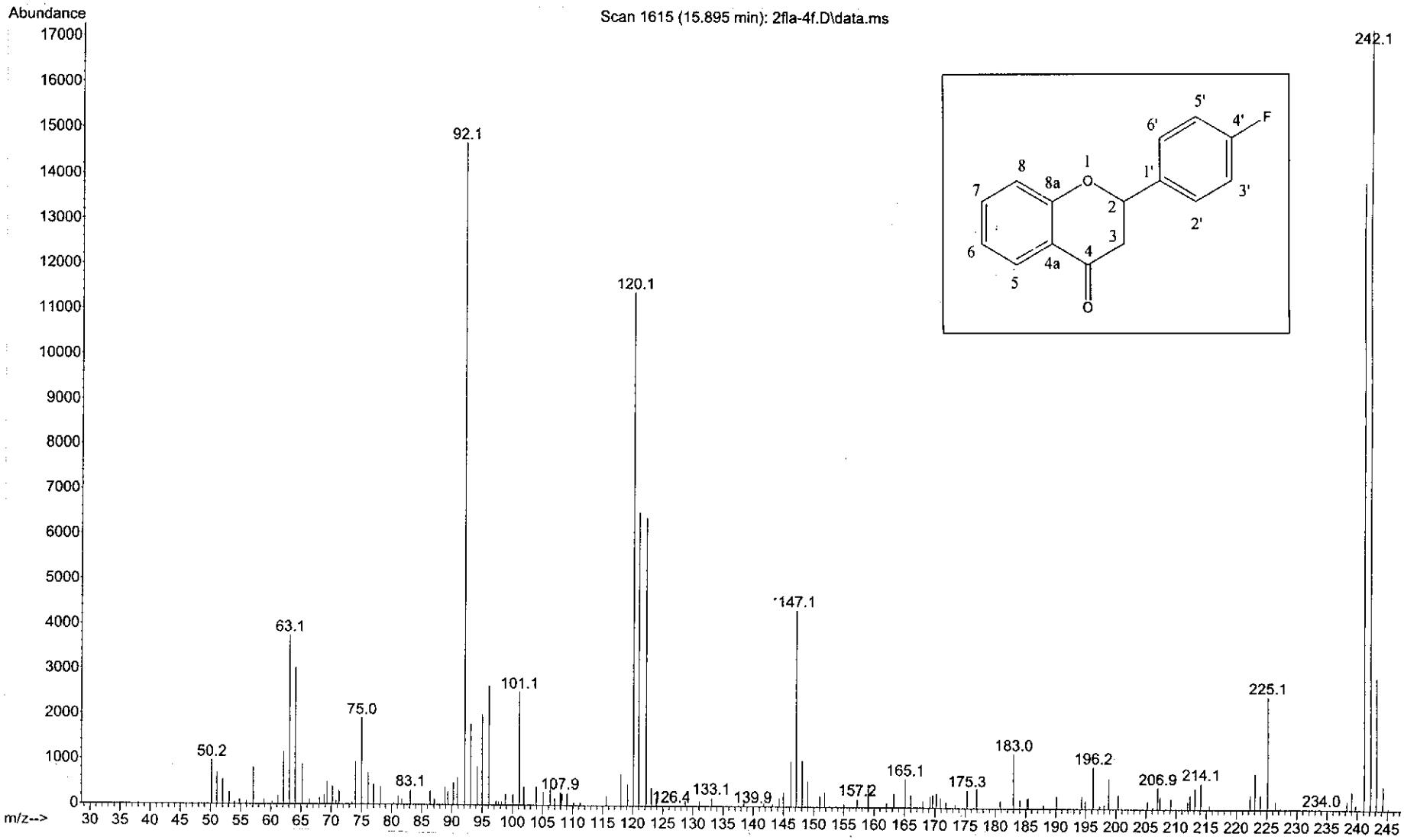
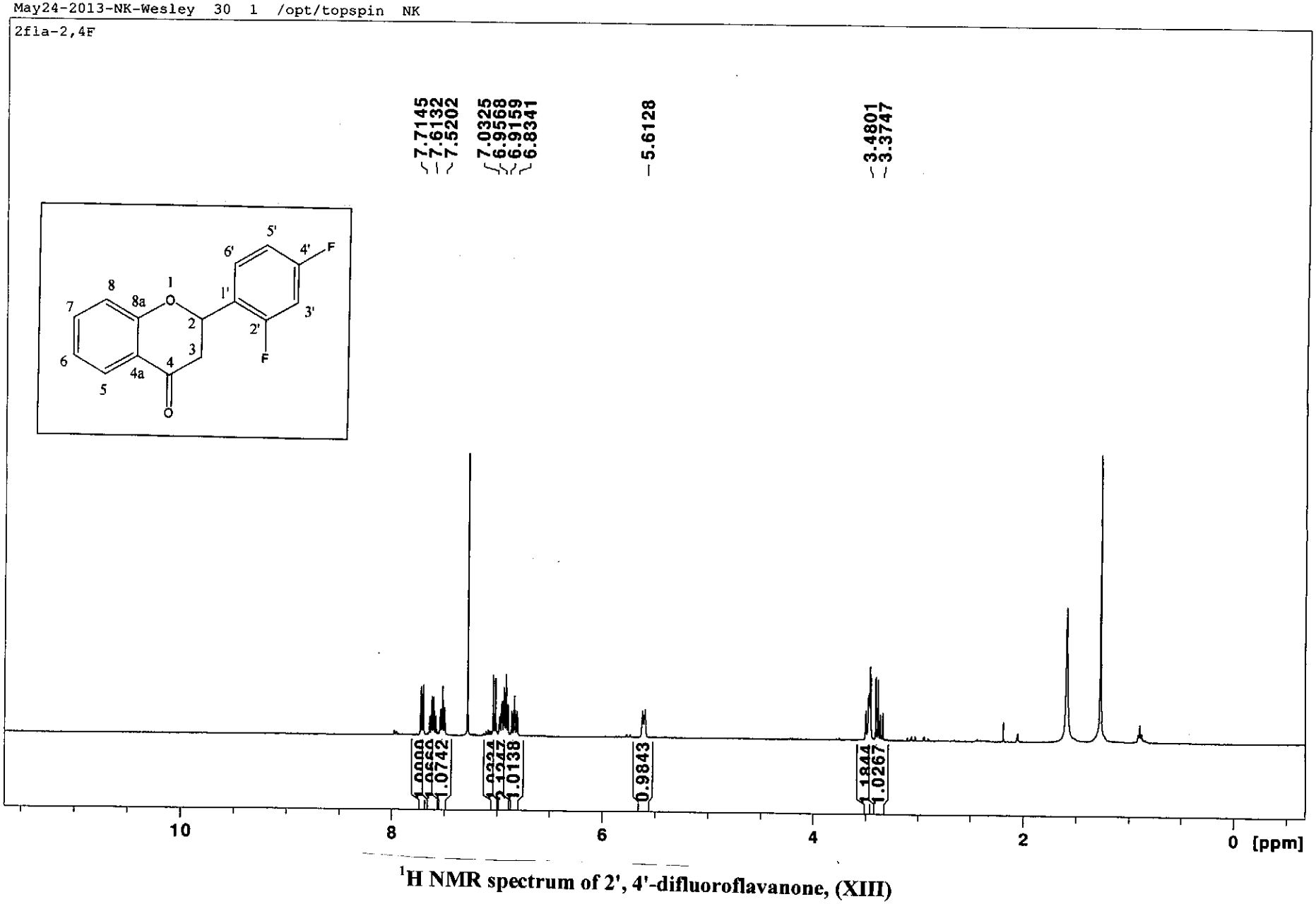
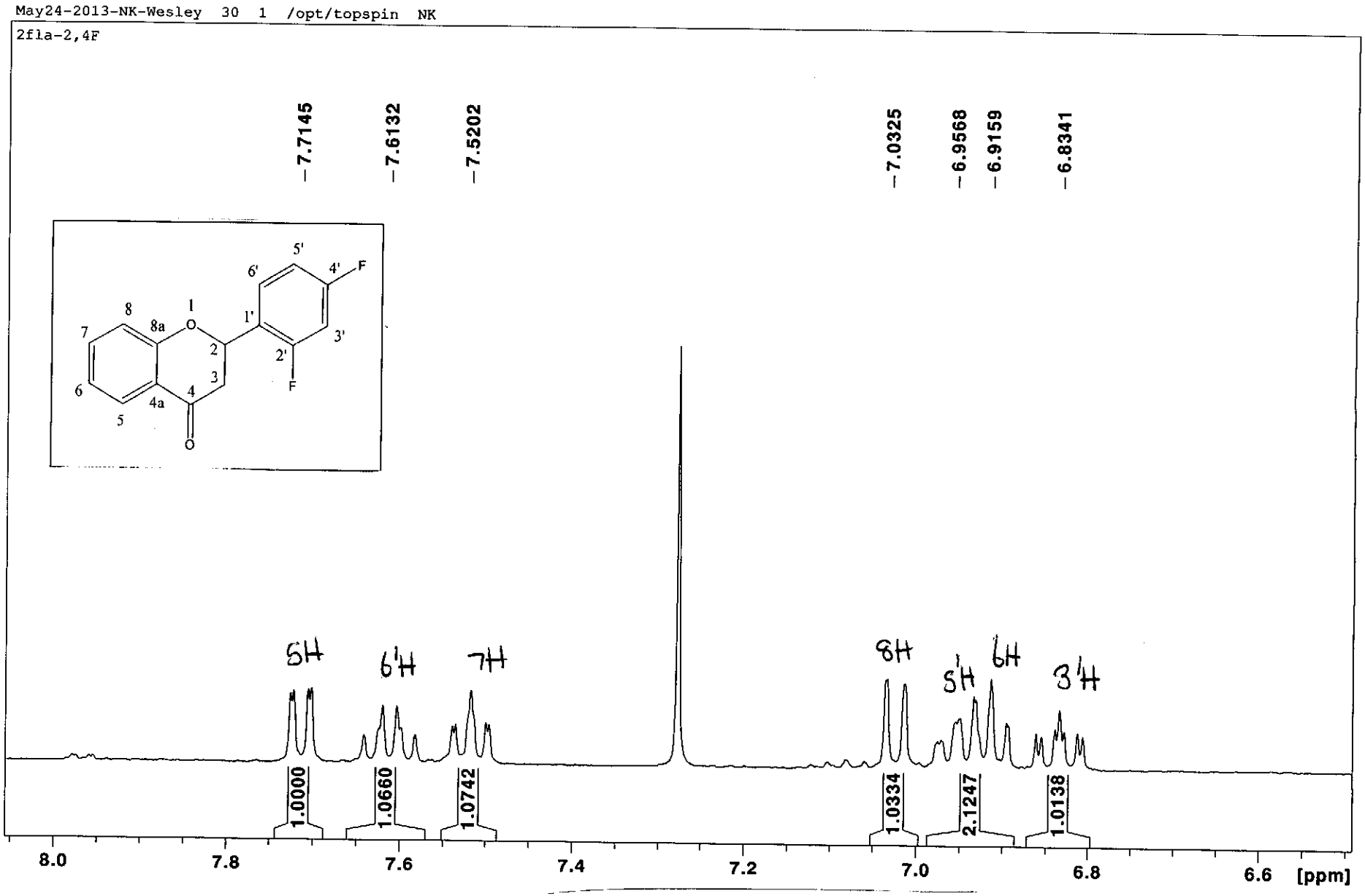


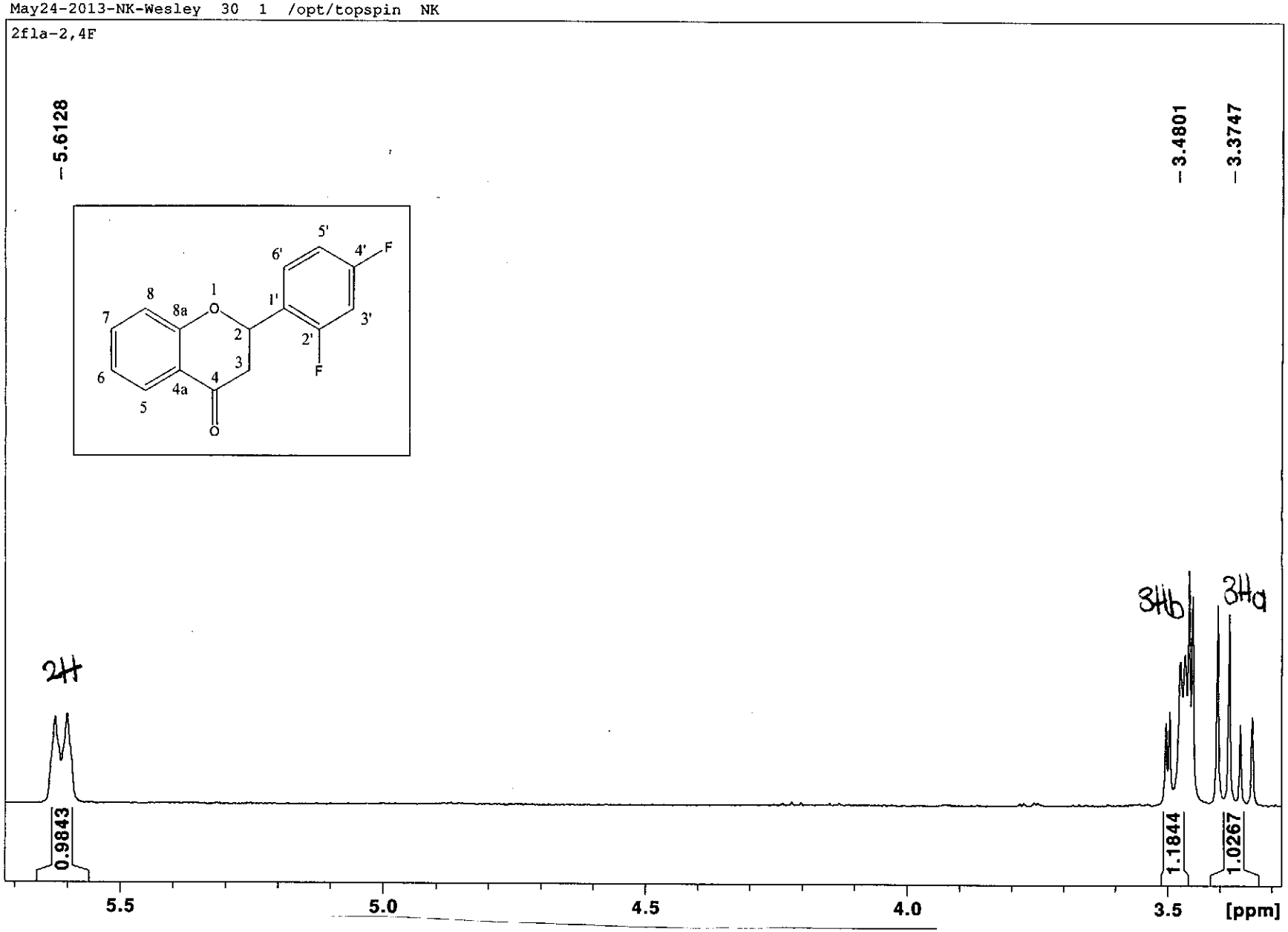
GC-MS spectrum of 4'-fluoroflavanone, (XII)



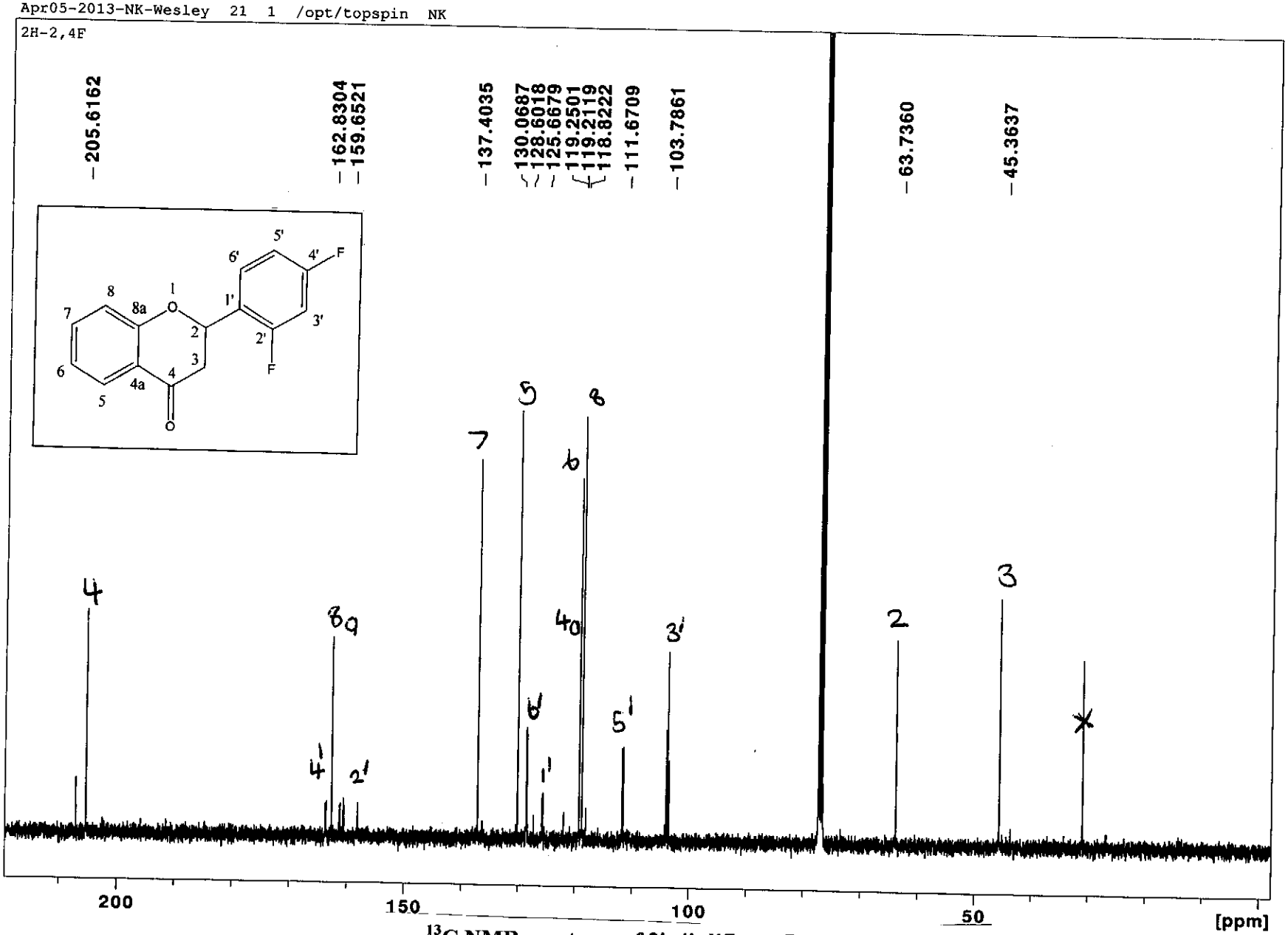
^{1}H NMR spectrum of 2', 4'-difluoroflavanone, (XIII)



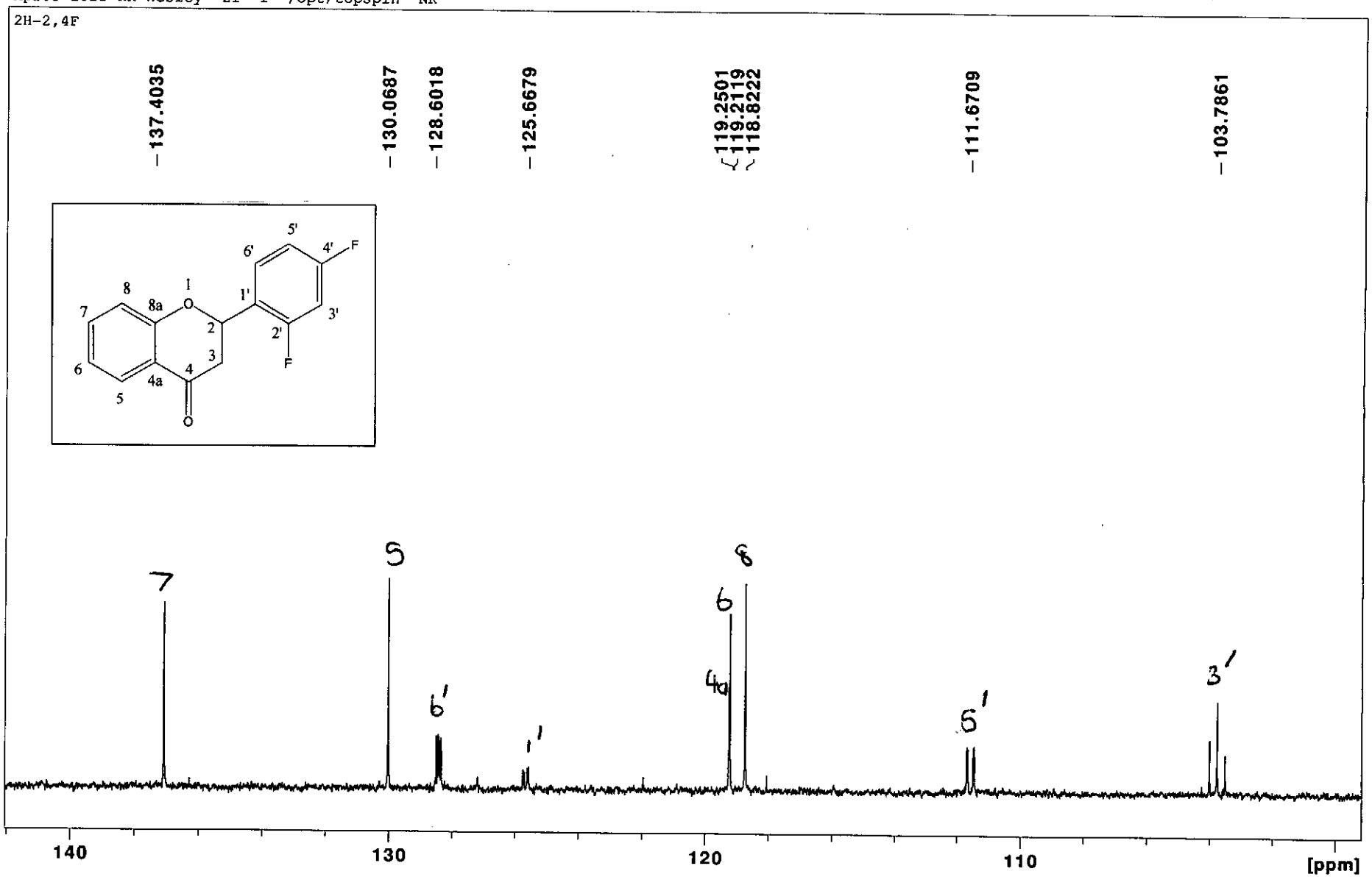
^{1}H NMR spectrum of 2', 4'-difluoroflavanone, (XIII)



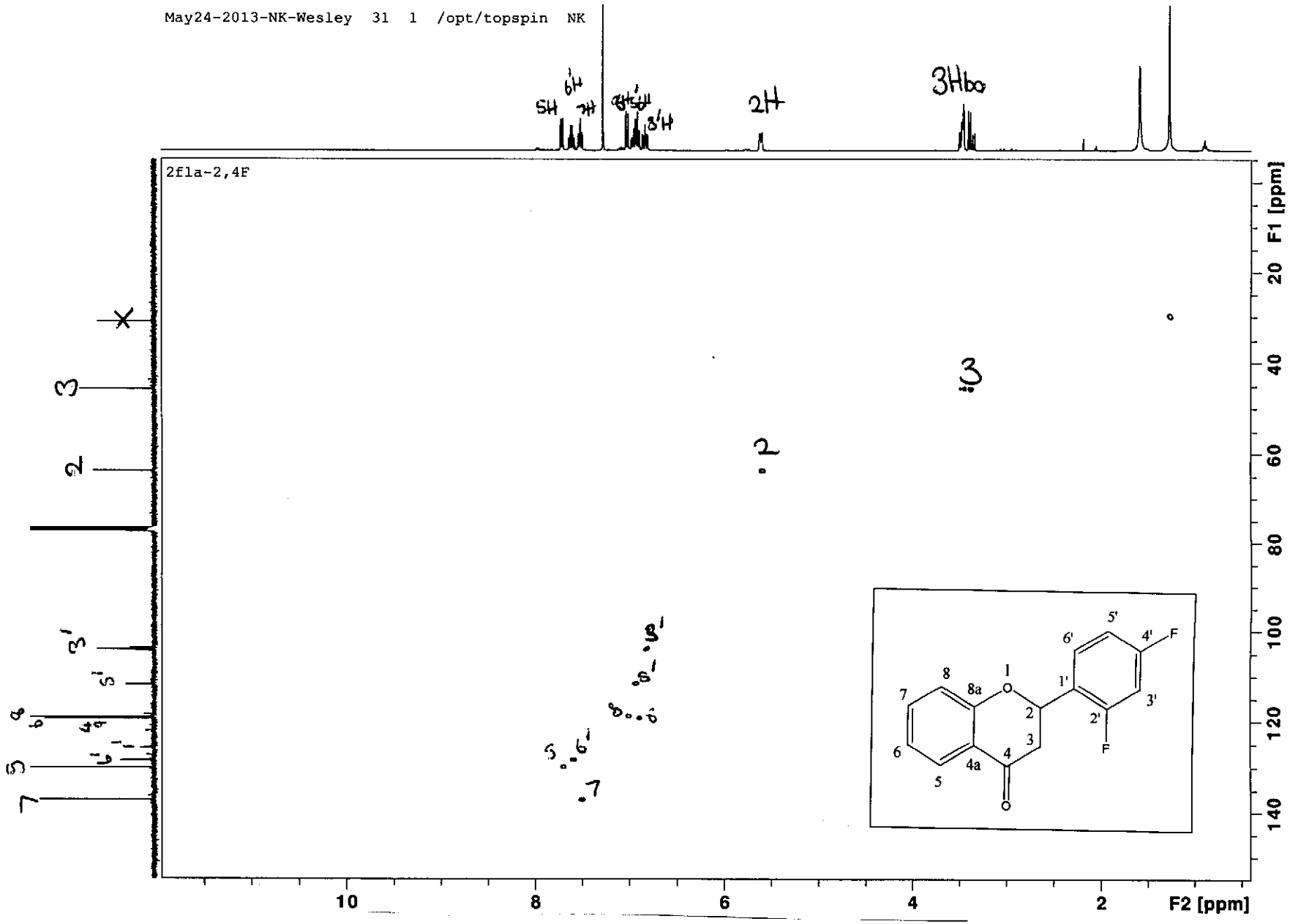
^{1}H NMR spectrum of 2', 4'-difluoroflavanone, (XIII)



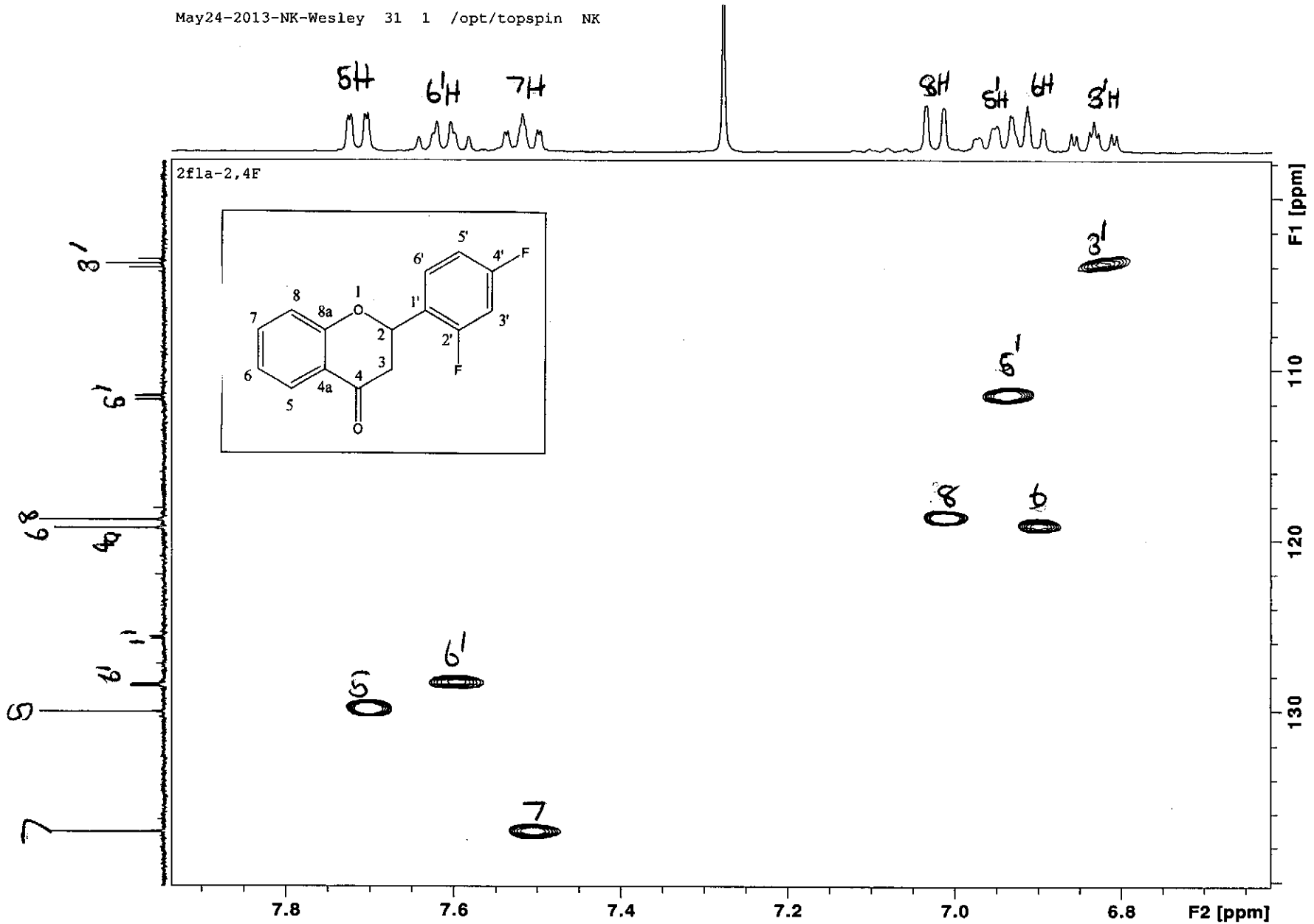
^{13}C NMR spectrum of 2', 4'-difluoroflavanone, (XIII)



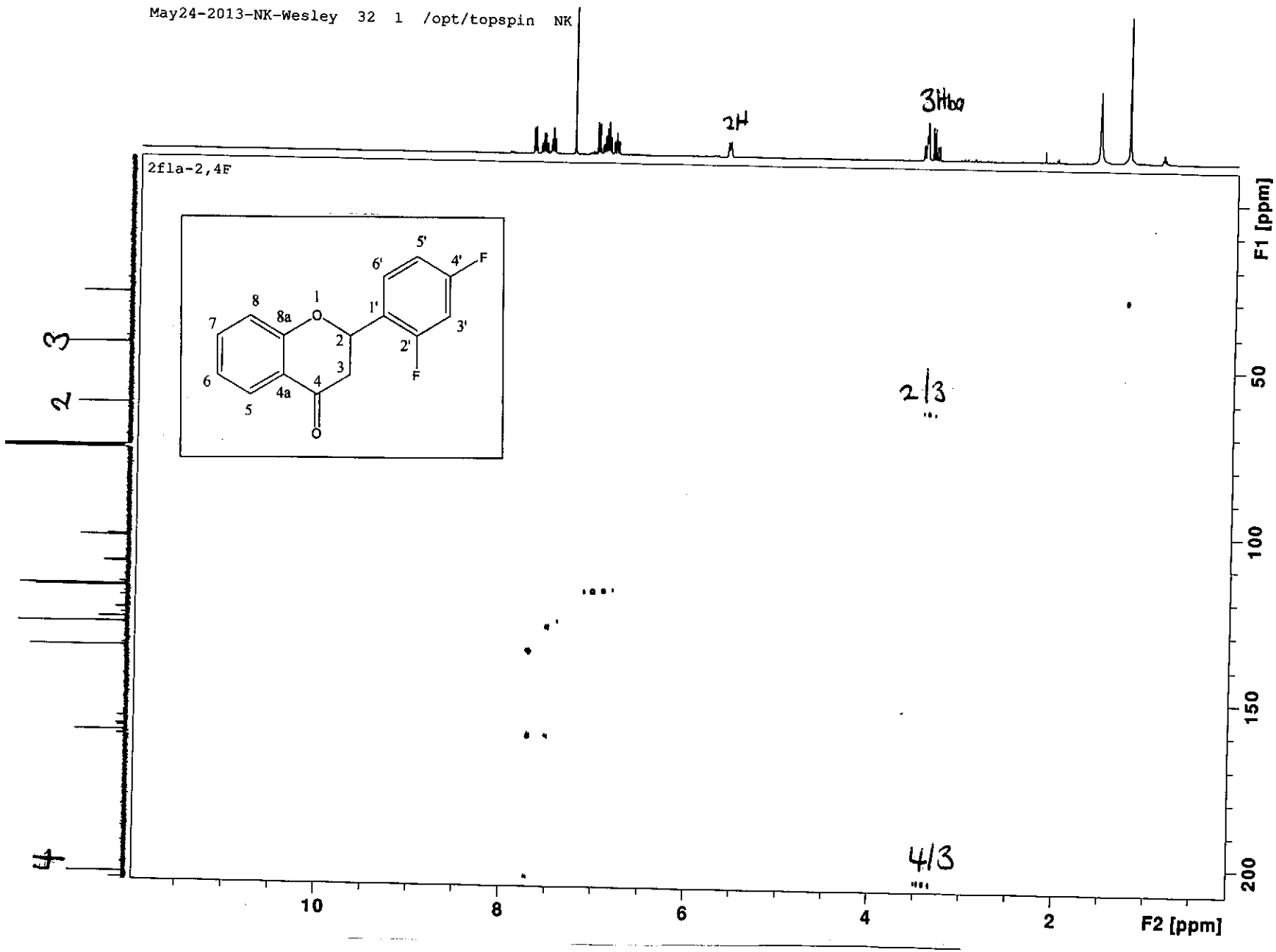
^{13}C NMR spectrum of 2', 4'-difluoroflavanone, (XIII)



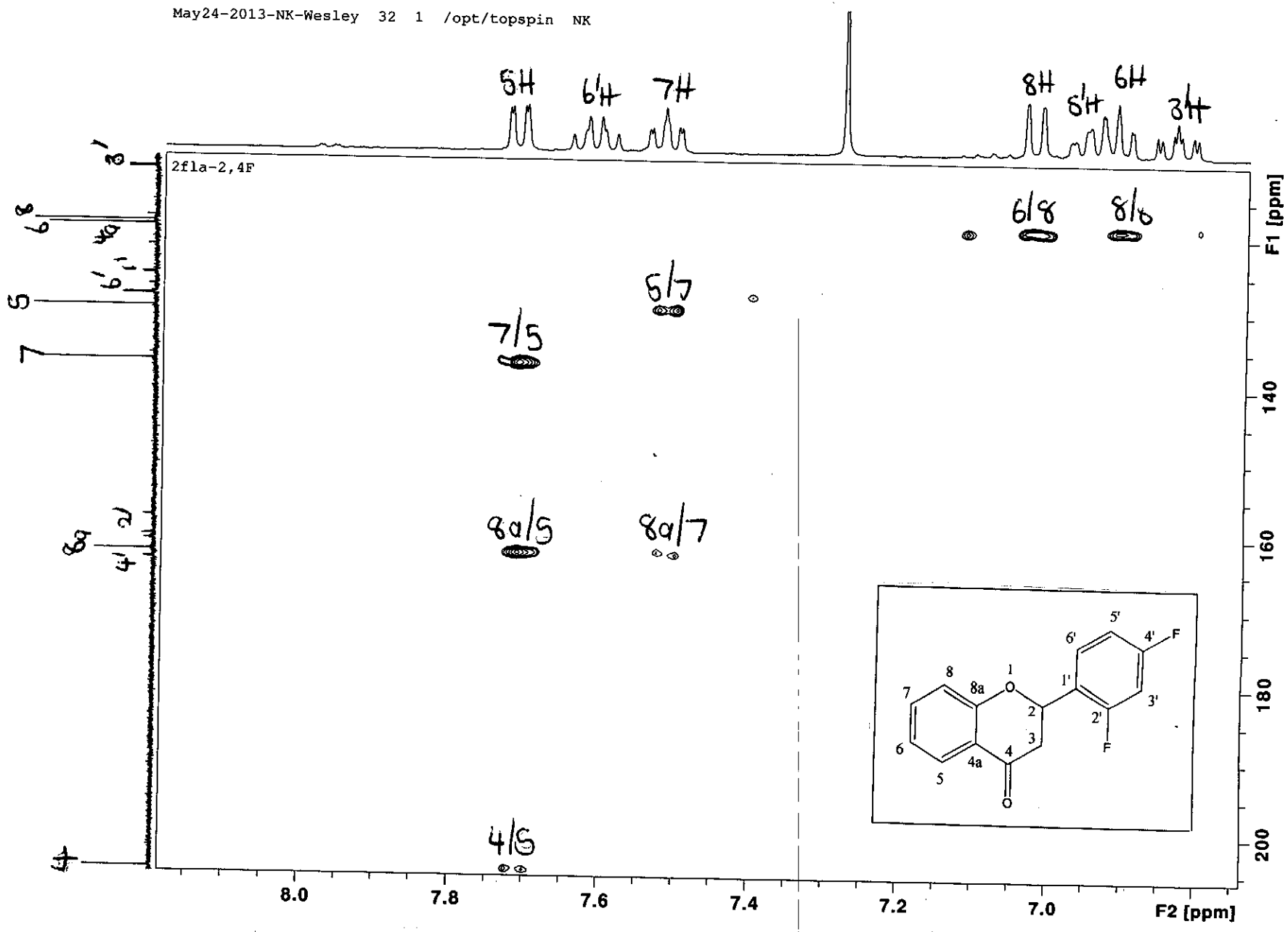
HSQC spectrum of 2', 4'-difluoroflavanone, (XIII)



HSQC spectrum of 2', 4'-difluoroflavanone, (XIII)



HMBC spectrum of 2', 4'-difluoroflavanone, (XIII)

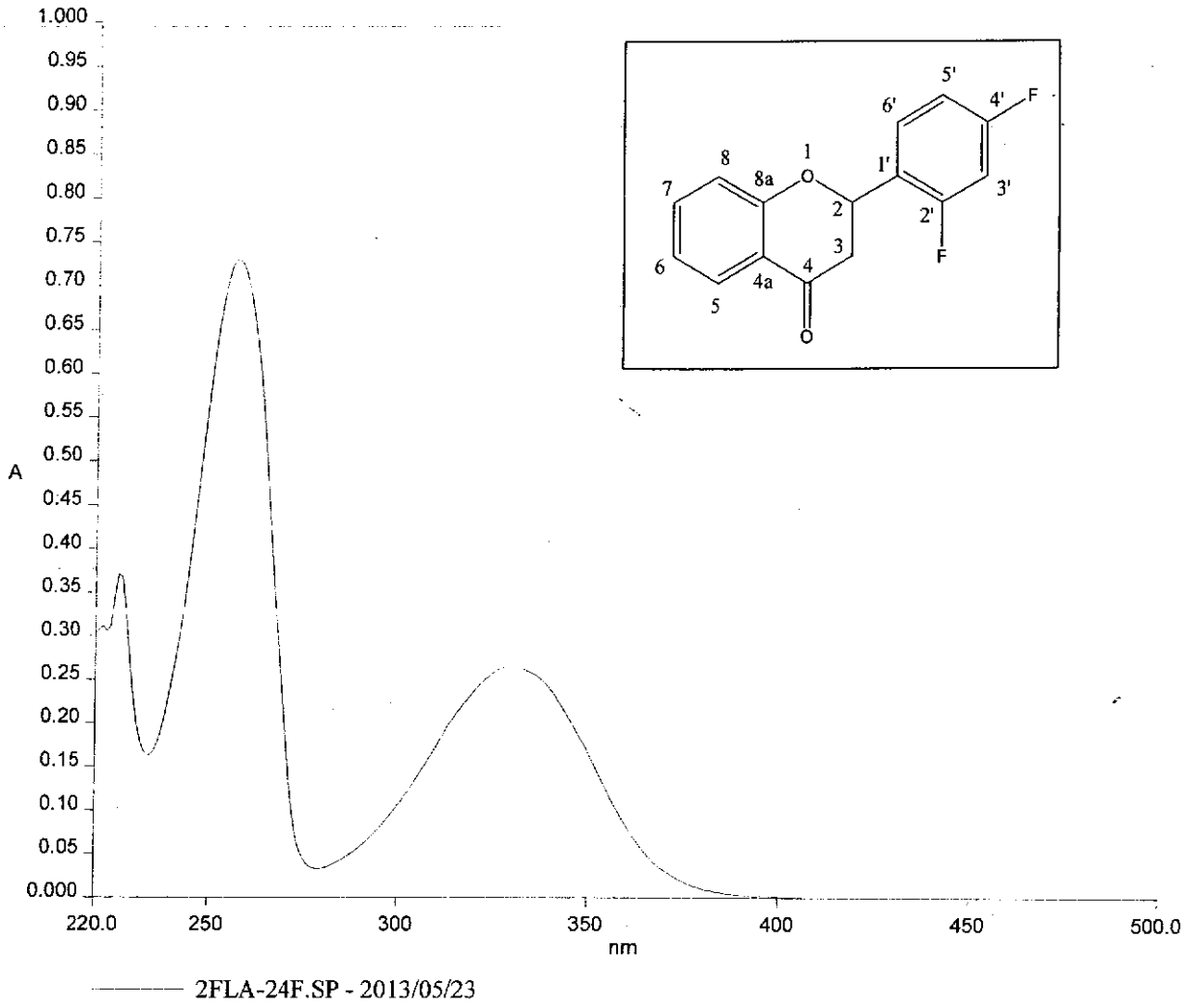


HMBC spectrum of 2', 4'-difluoroflavanone, (XIII)

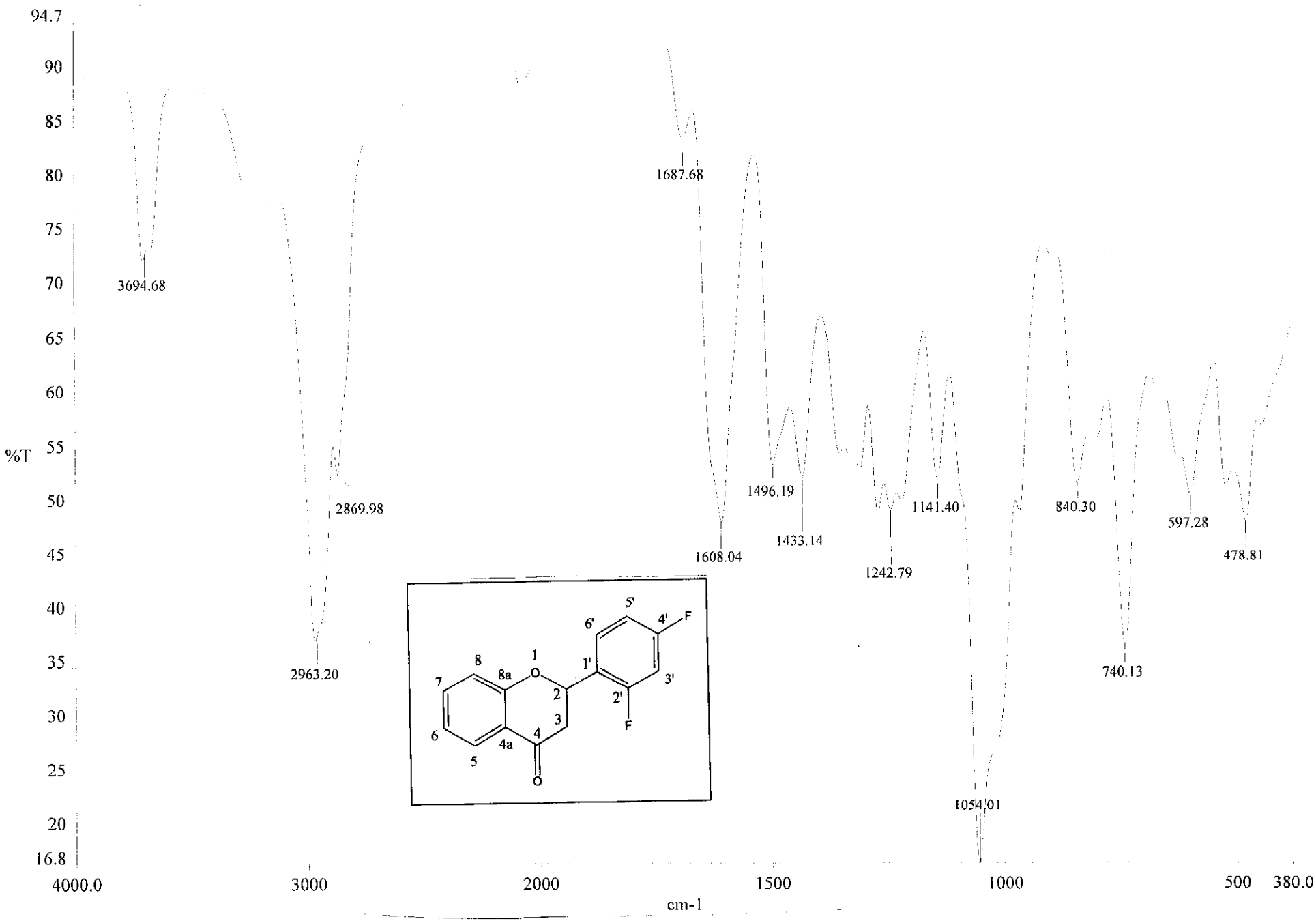
λmax(334nm)=0.2596

log ε = 5.11

Date: 2013/05/23 Time: 11:15:07 AM



Ultra violet (UV) spectrum of 2', 4'-difluoroflavanone, (XIII)



Infra-Red (IR) spectrum of 2', 4'-difluoroflavanone, (XIII)

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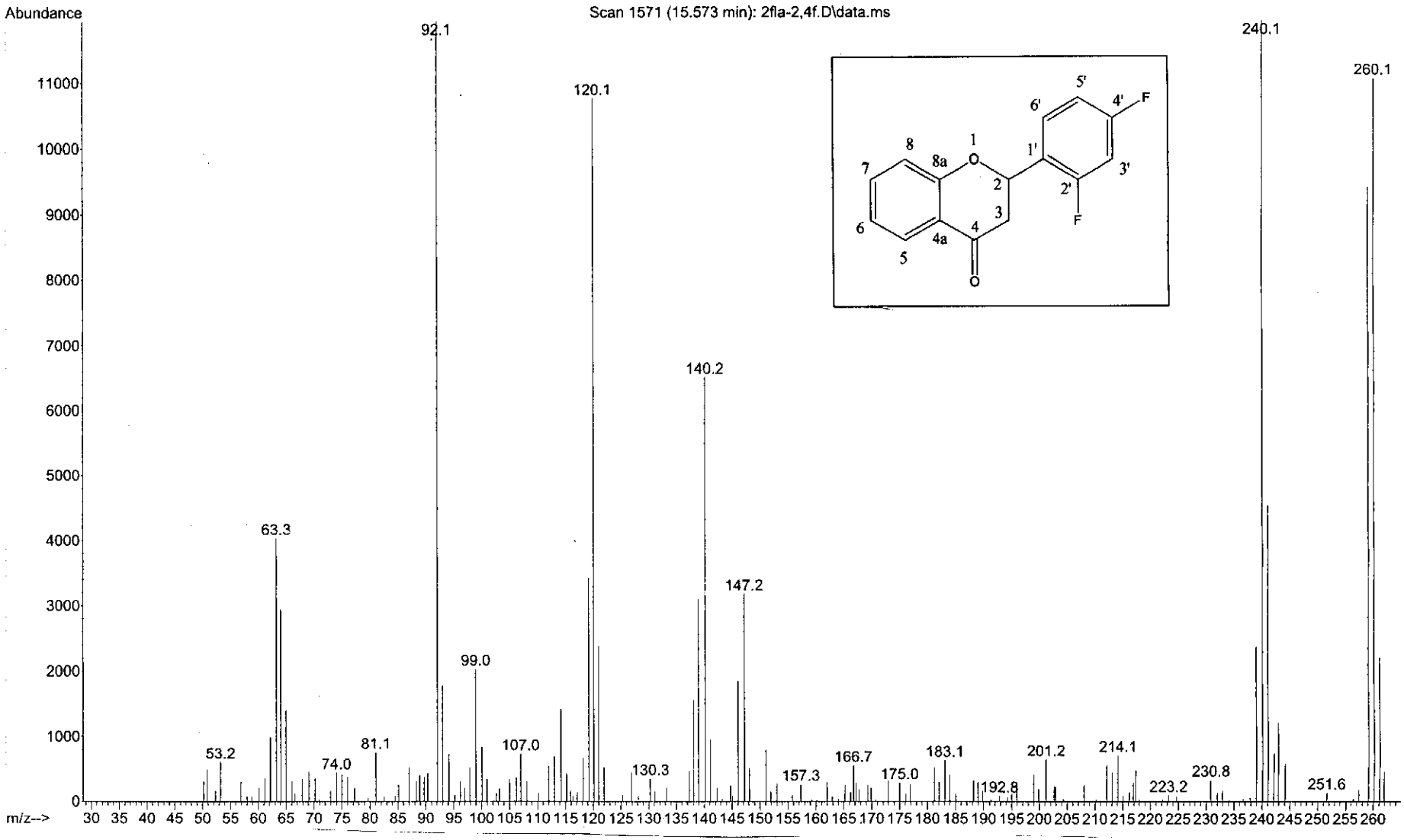
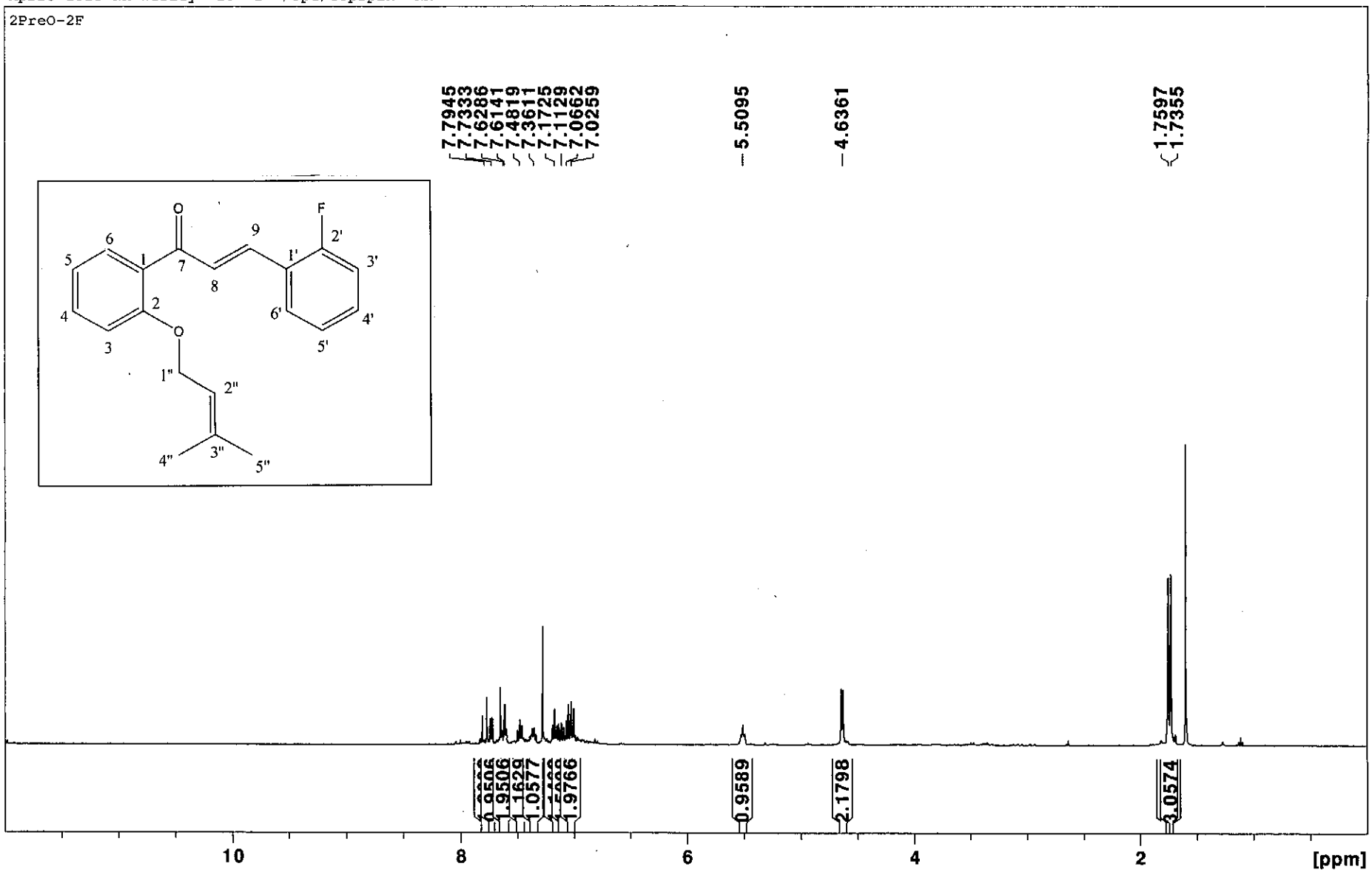
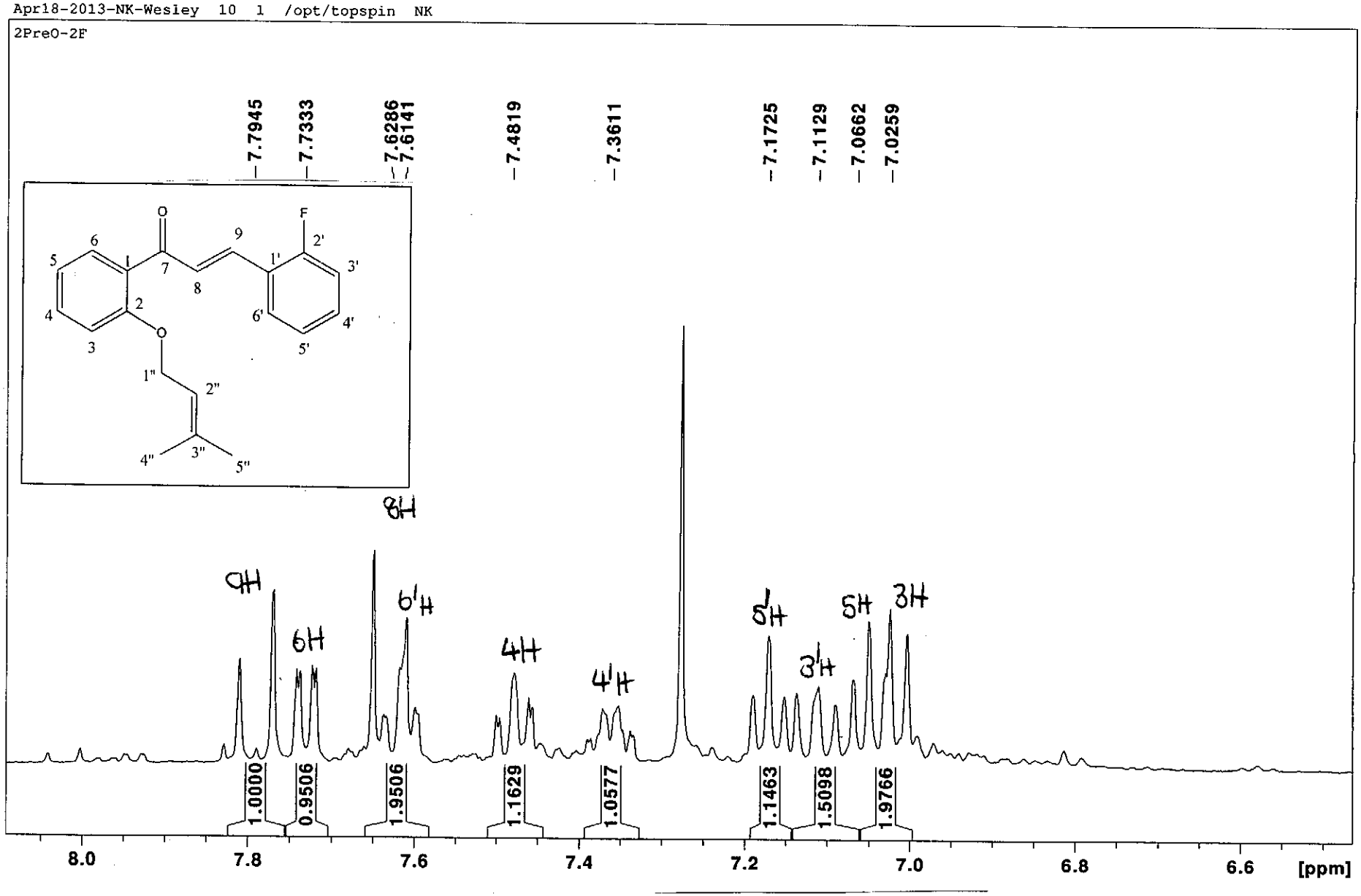


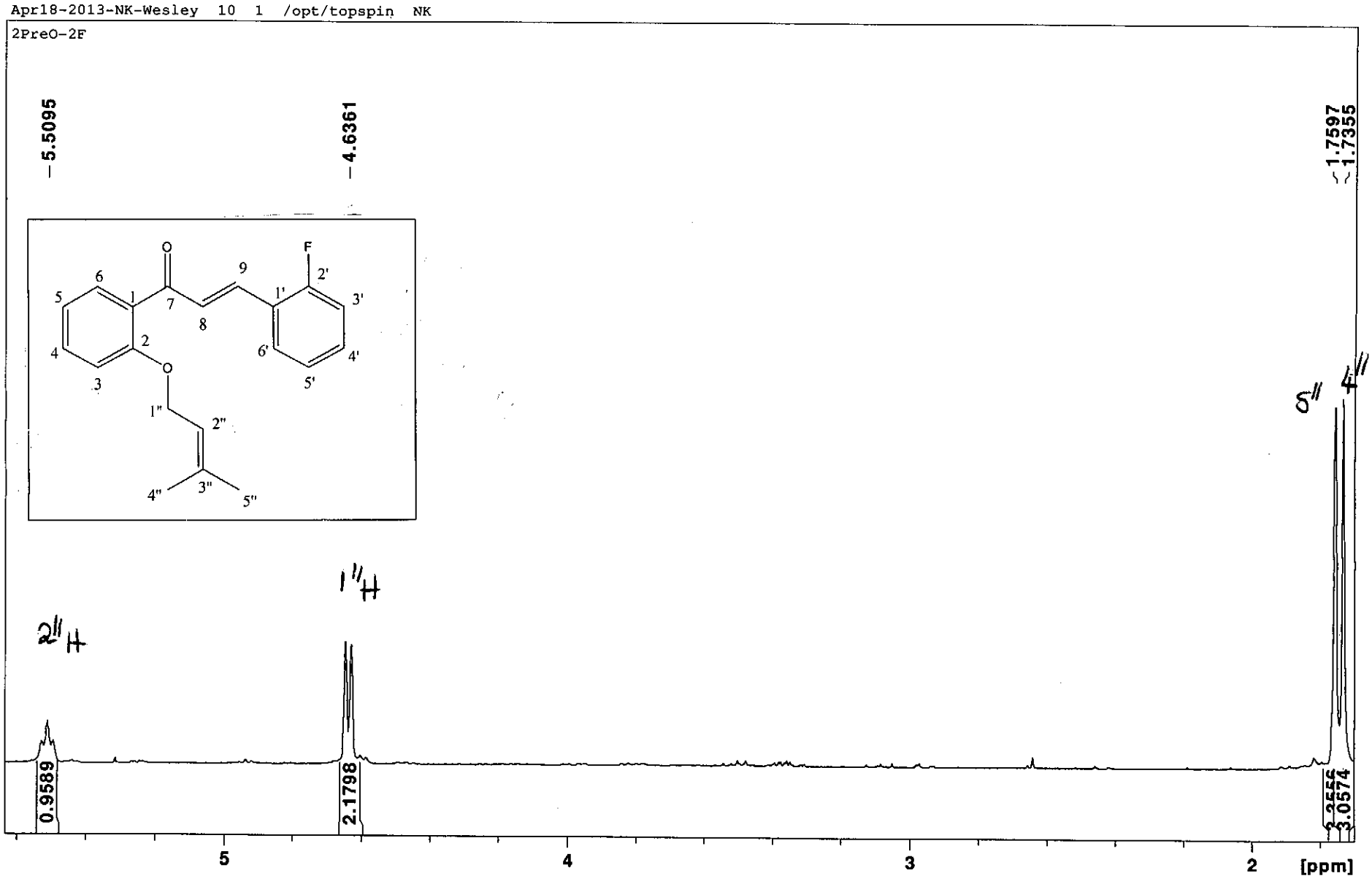
GC-MS spectrum of 2', 4'-difluoroflavanone, (XIII)



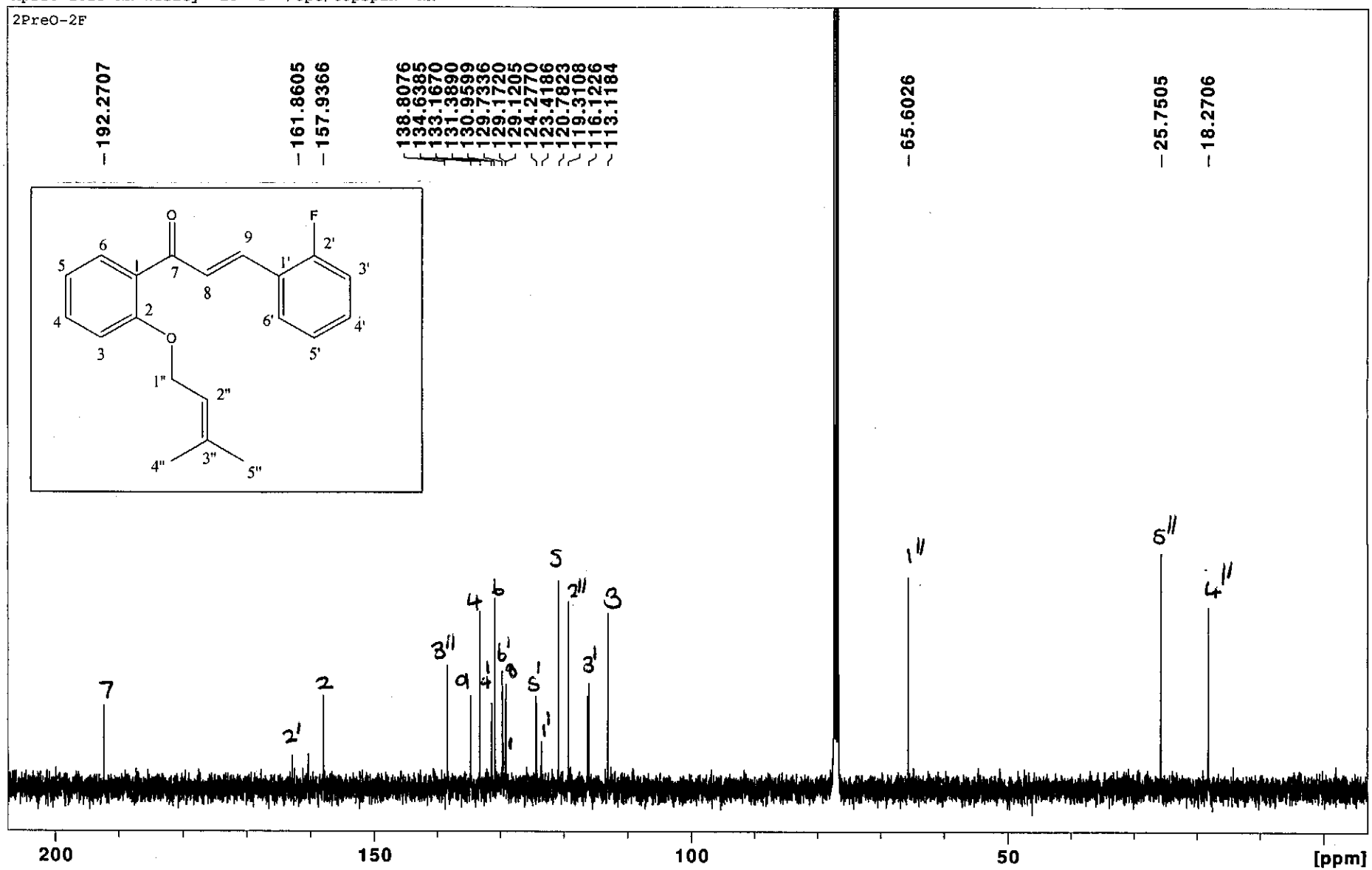
^{1}H NMR spectrum of 2'-fluoro-2-oxyprenylchalcone, (XIV)



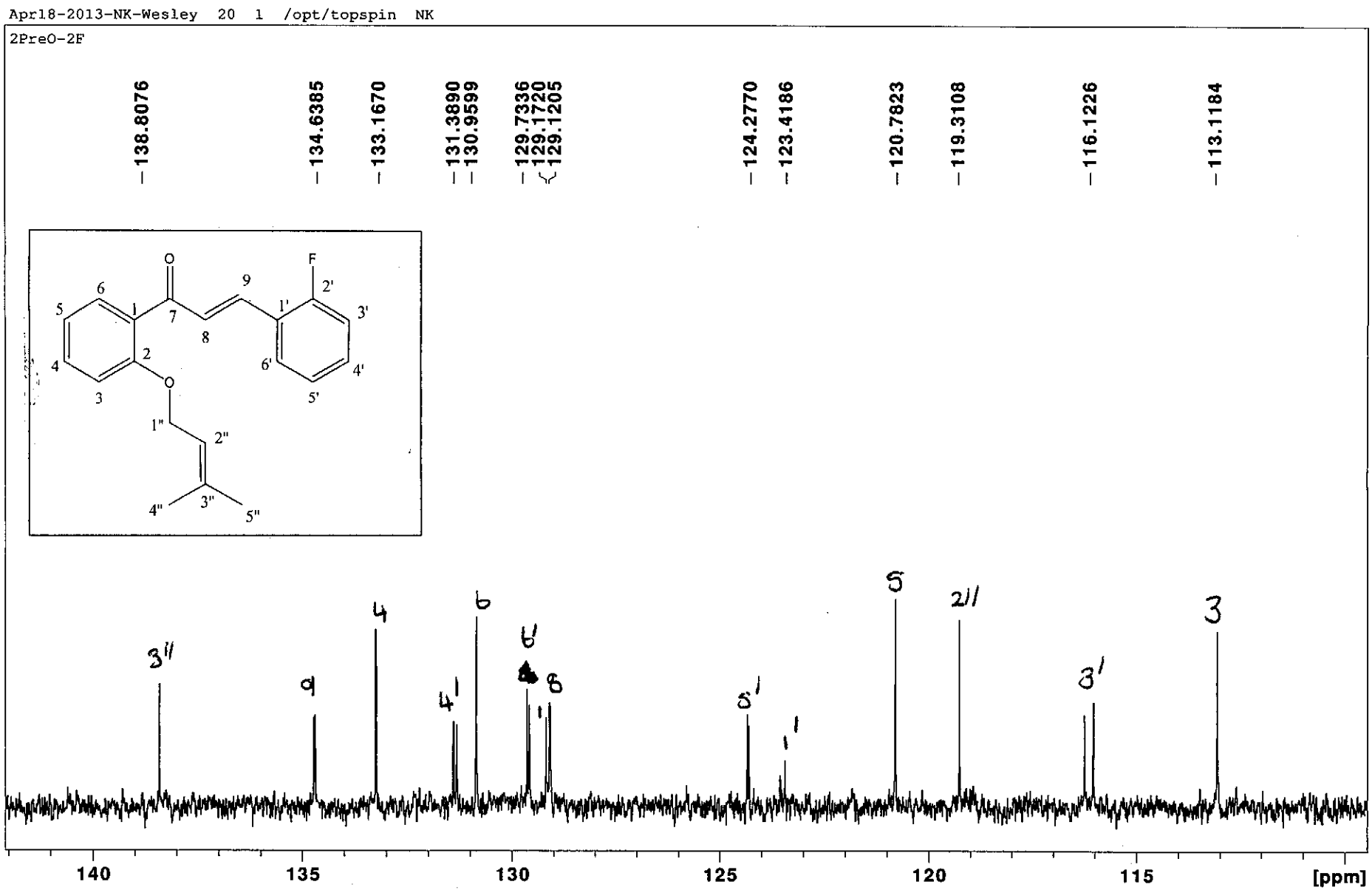
^{1}H NMR spectrum of 2'-fluoro-2-oxyprenylchalcone, (XIV)



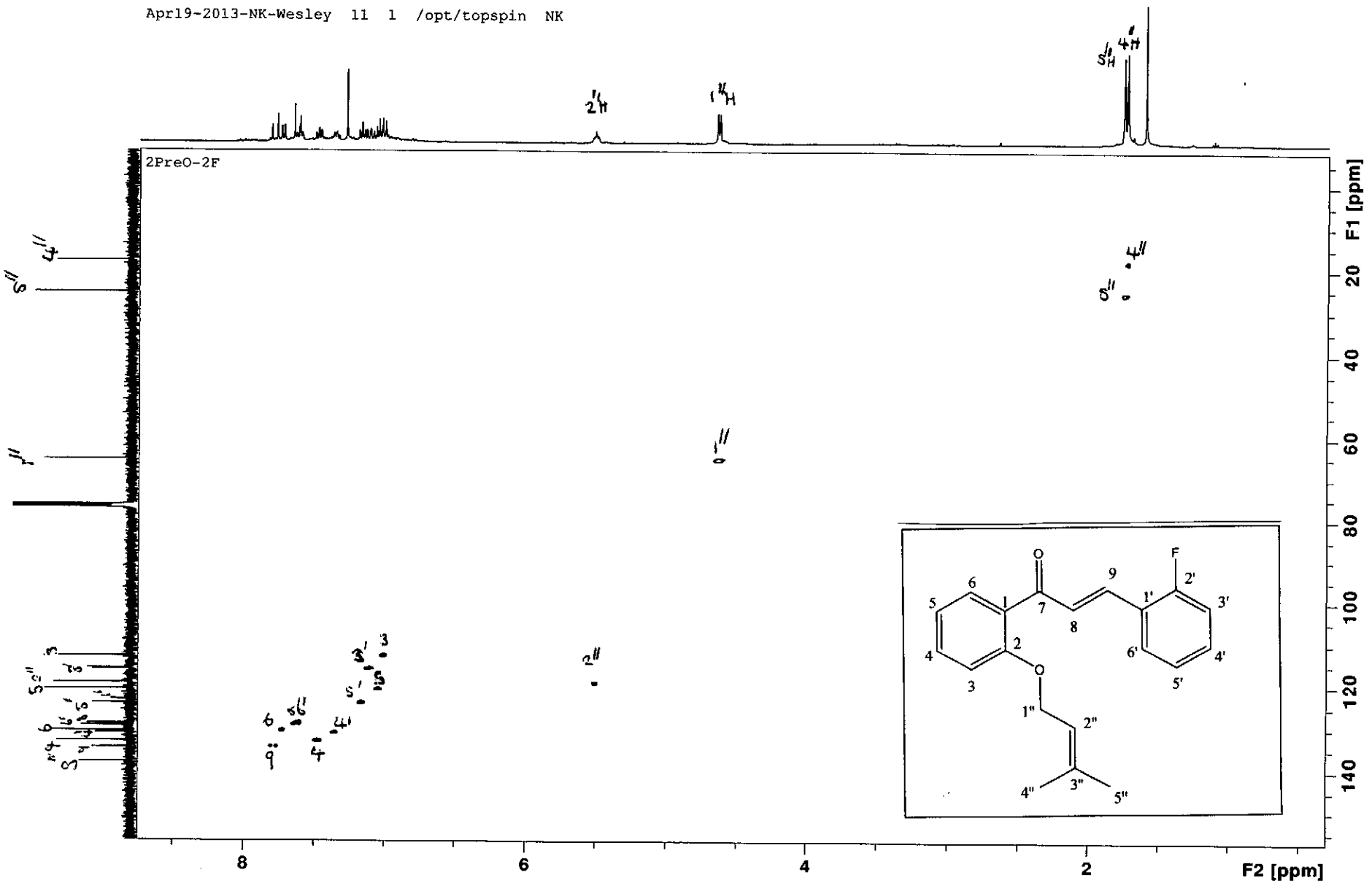
^{1}H NMR spectrum of 2'-fluoro-2-oxyprenylchalcone, (XIV)



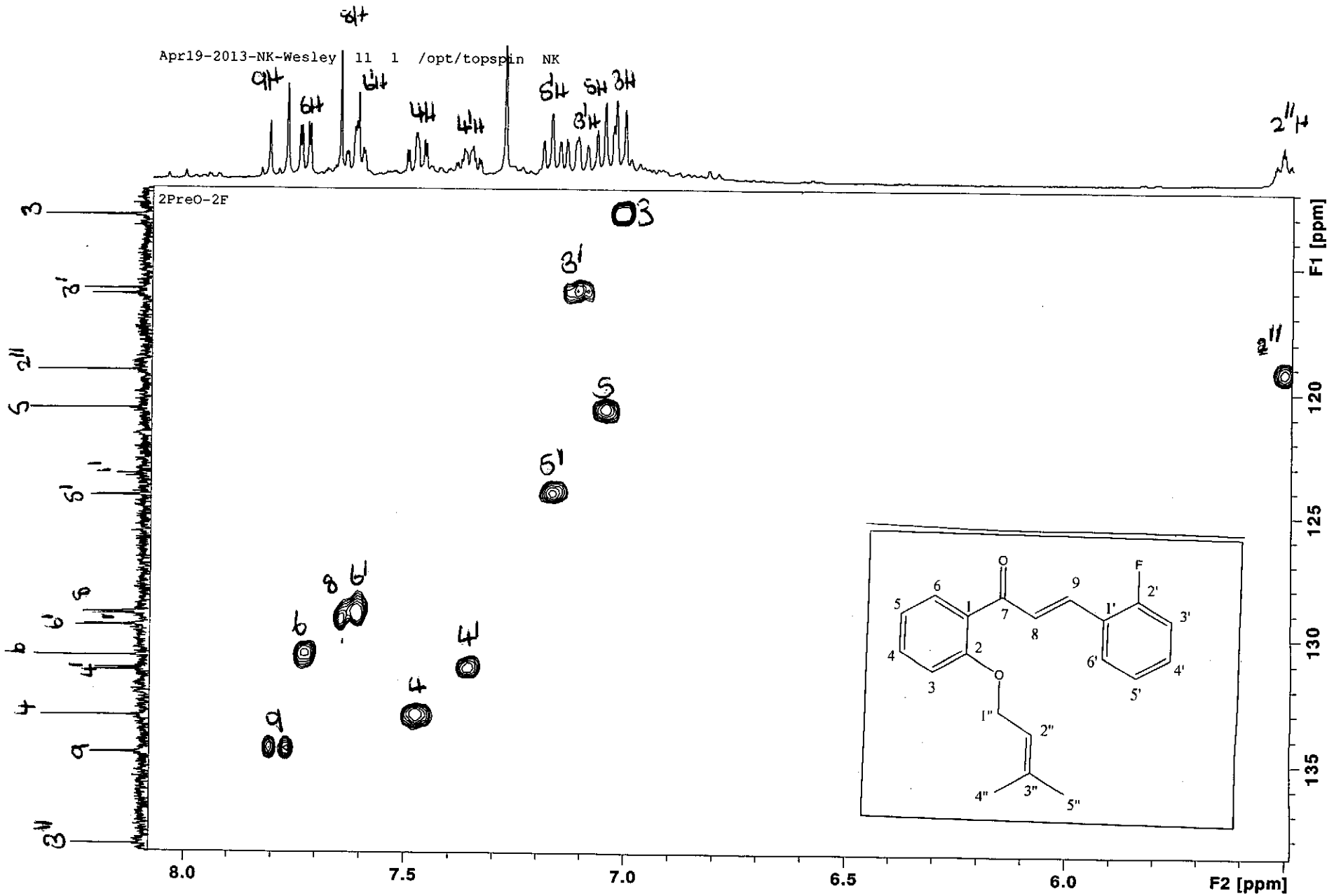
^{13}C NMR spectrum of 2'-fluoro-2-oxyprenylchalcone, (XIV)



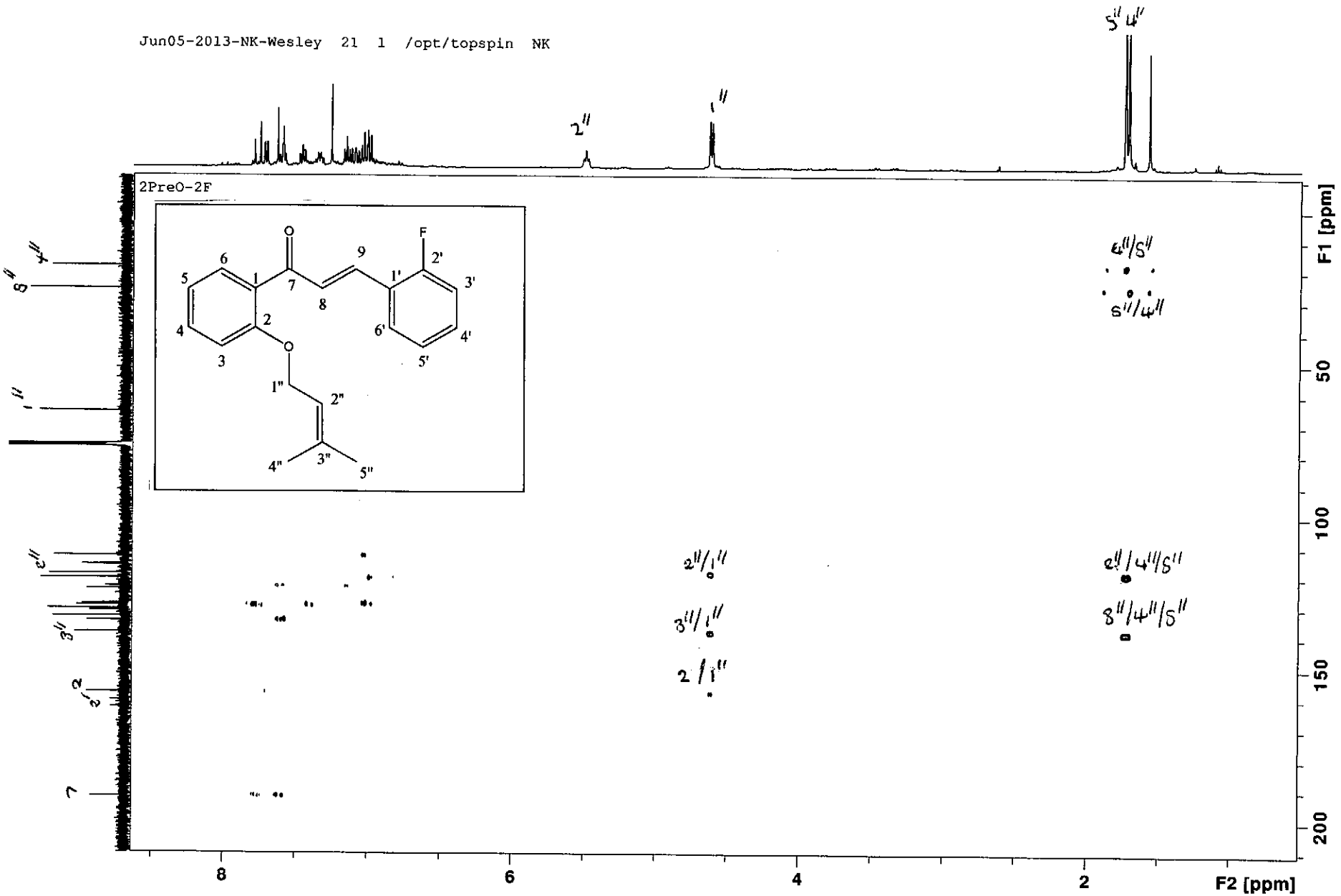
^{13}C NMR spectrum of 2'-fluoro-2-oxyprenylchalcone, (XIV)



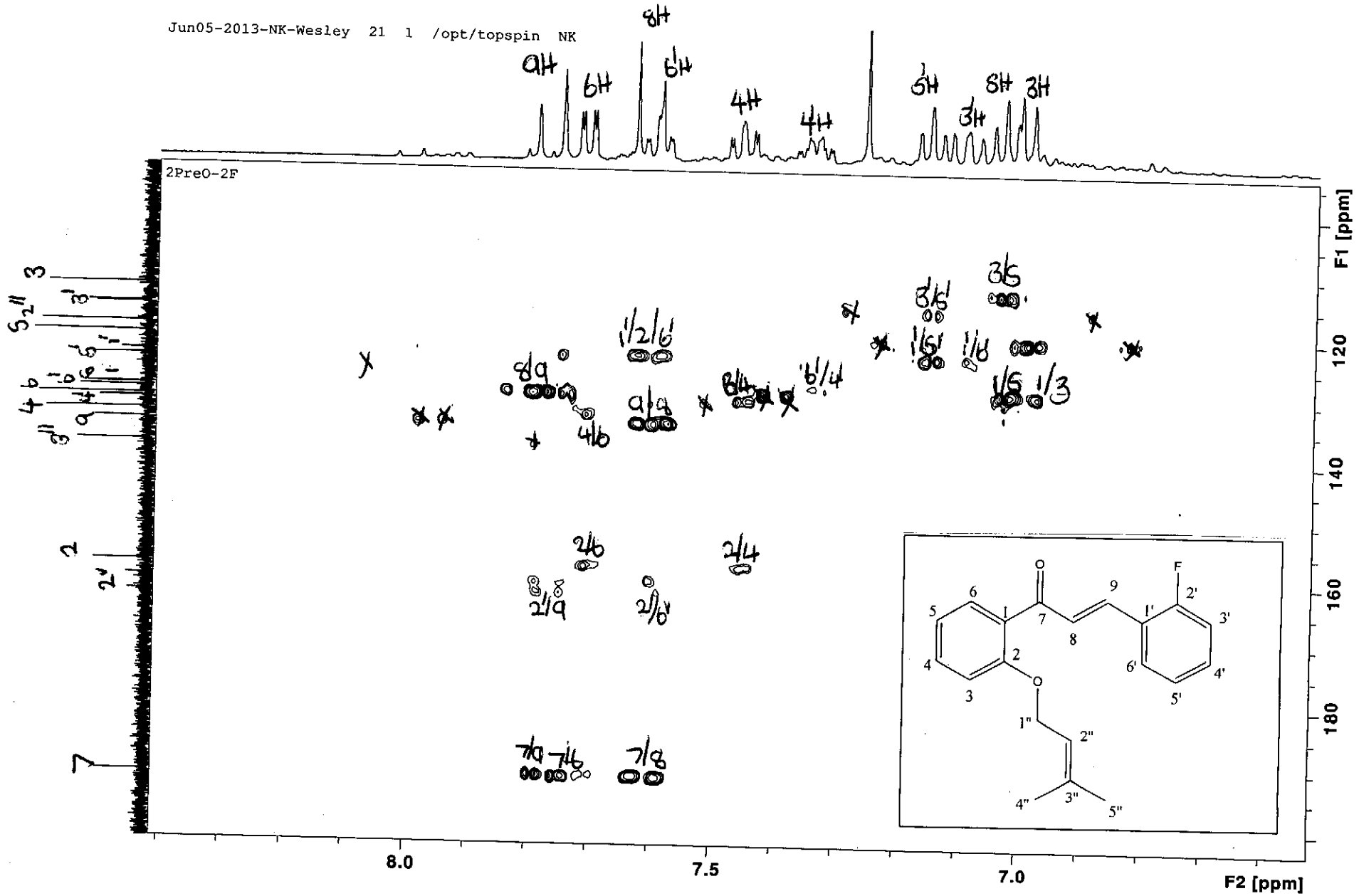
HSQC spectrum of 2'-fluoro-2-oxyprenylchalcone, (XIV)



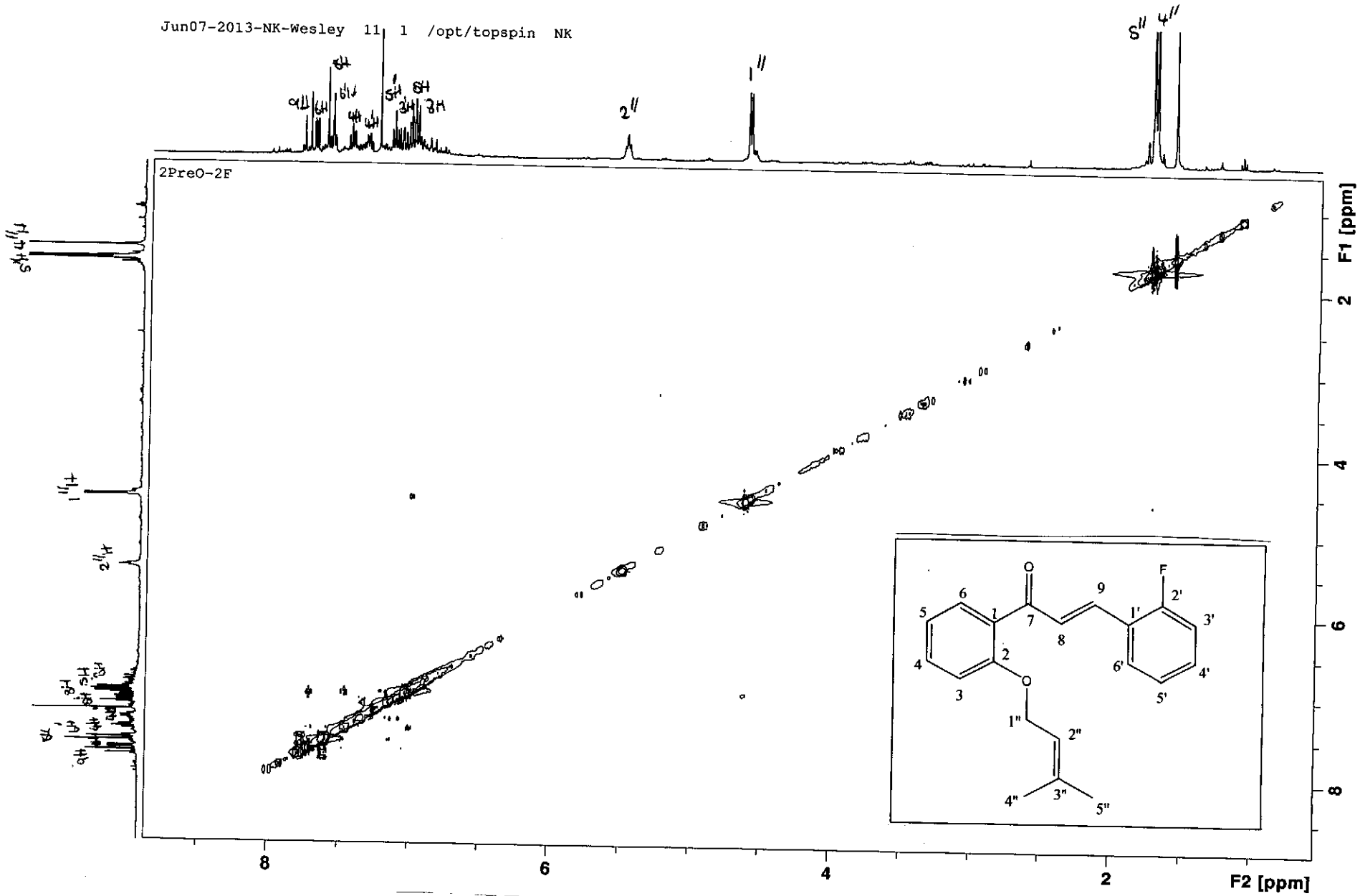
HSQC spectrum of 2'-fluoro-2-oxyprenylchalcone, (XIV)



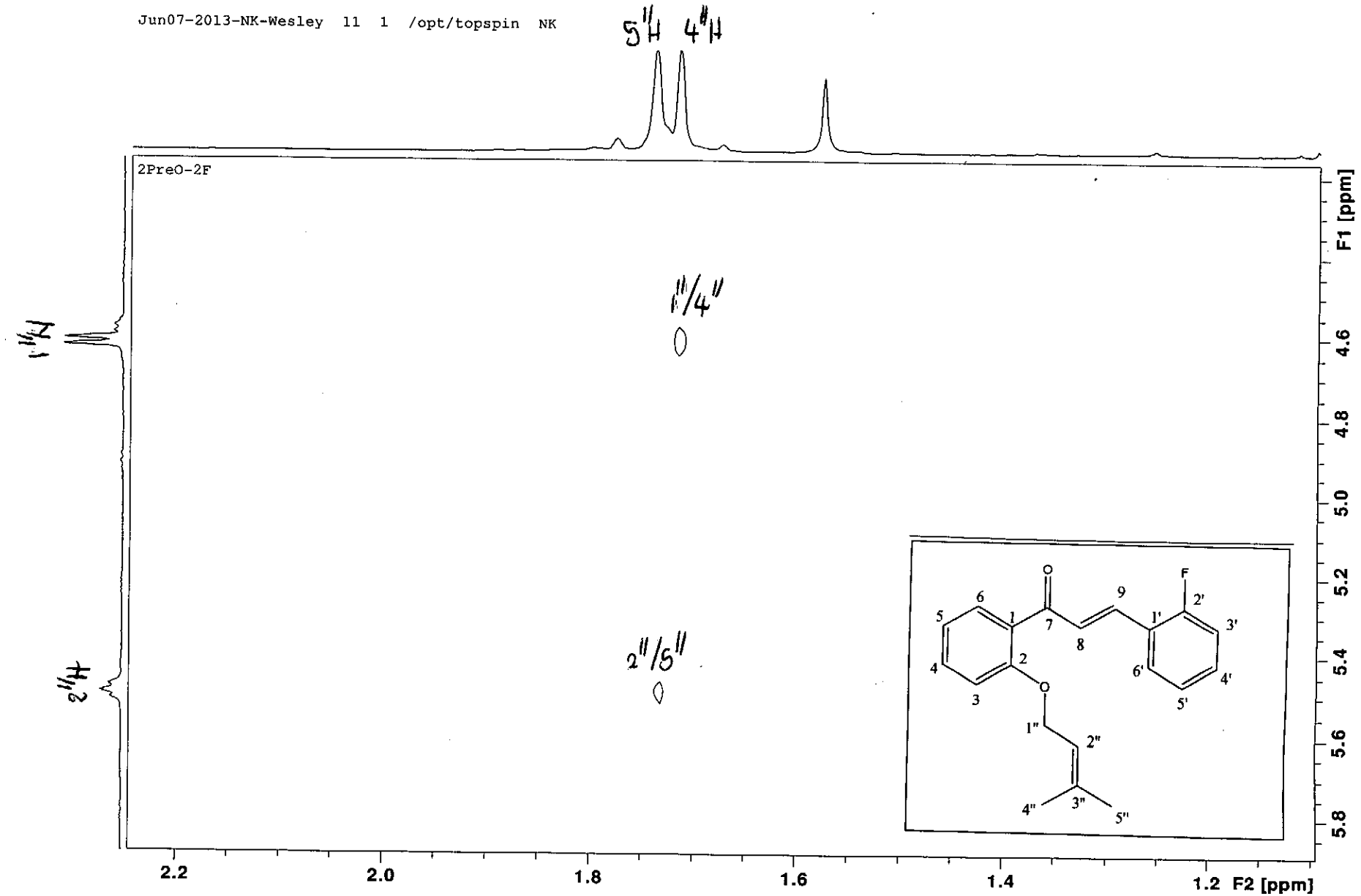
HMBC spectrum of 2'-fluoro-2-oxyprenylchalcone, (XIV)



HMBC spectrum of 2'-fluoro-2-oxyprenylchalcone, (XIV)



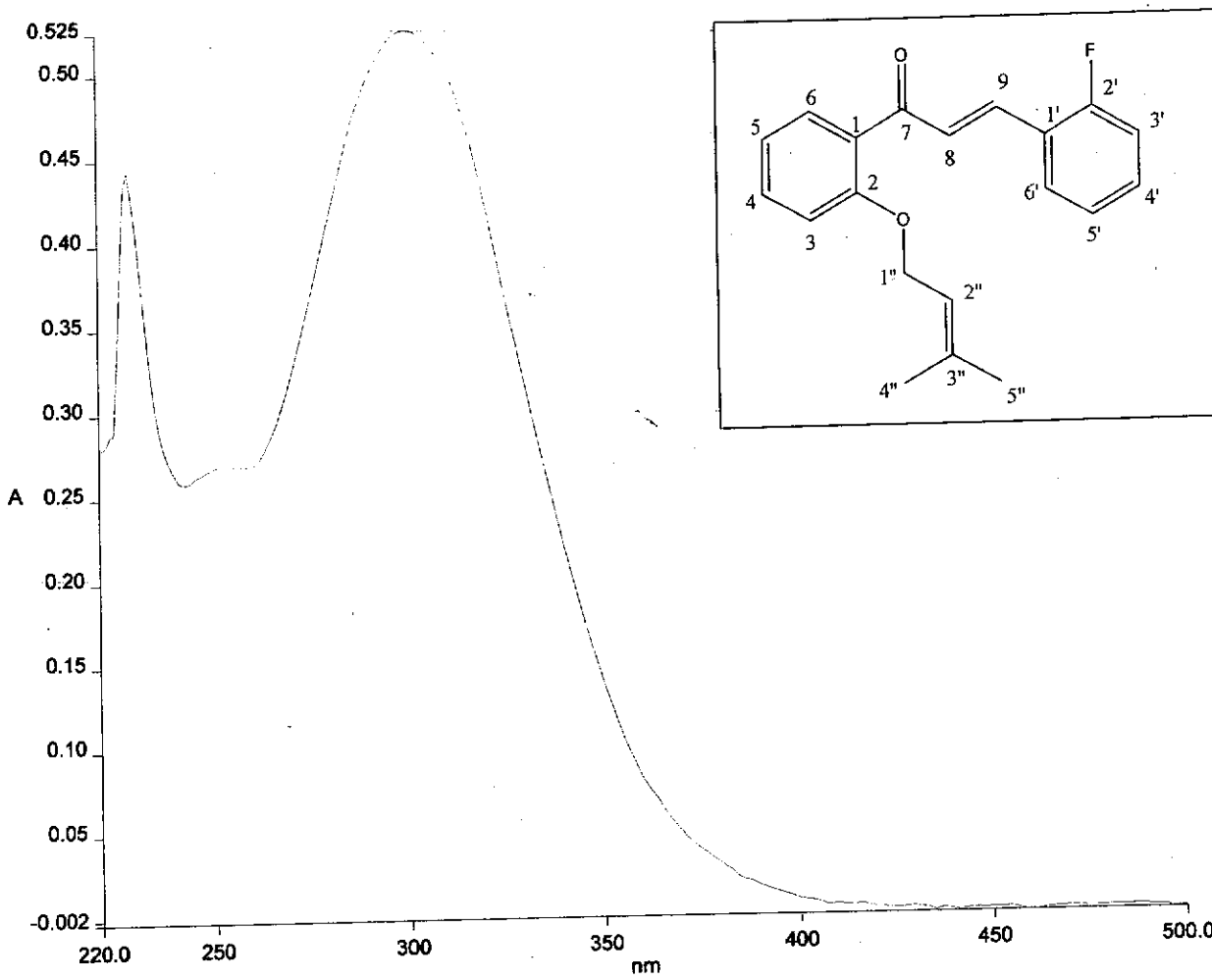
NOESY spectrum of 2'-fluoro-2-oxyprenylchalcone, (XIV)



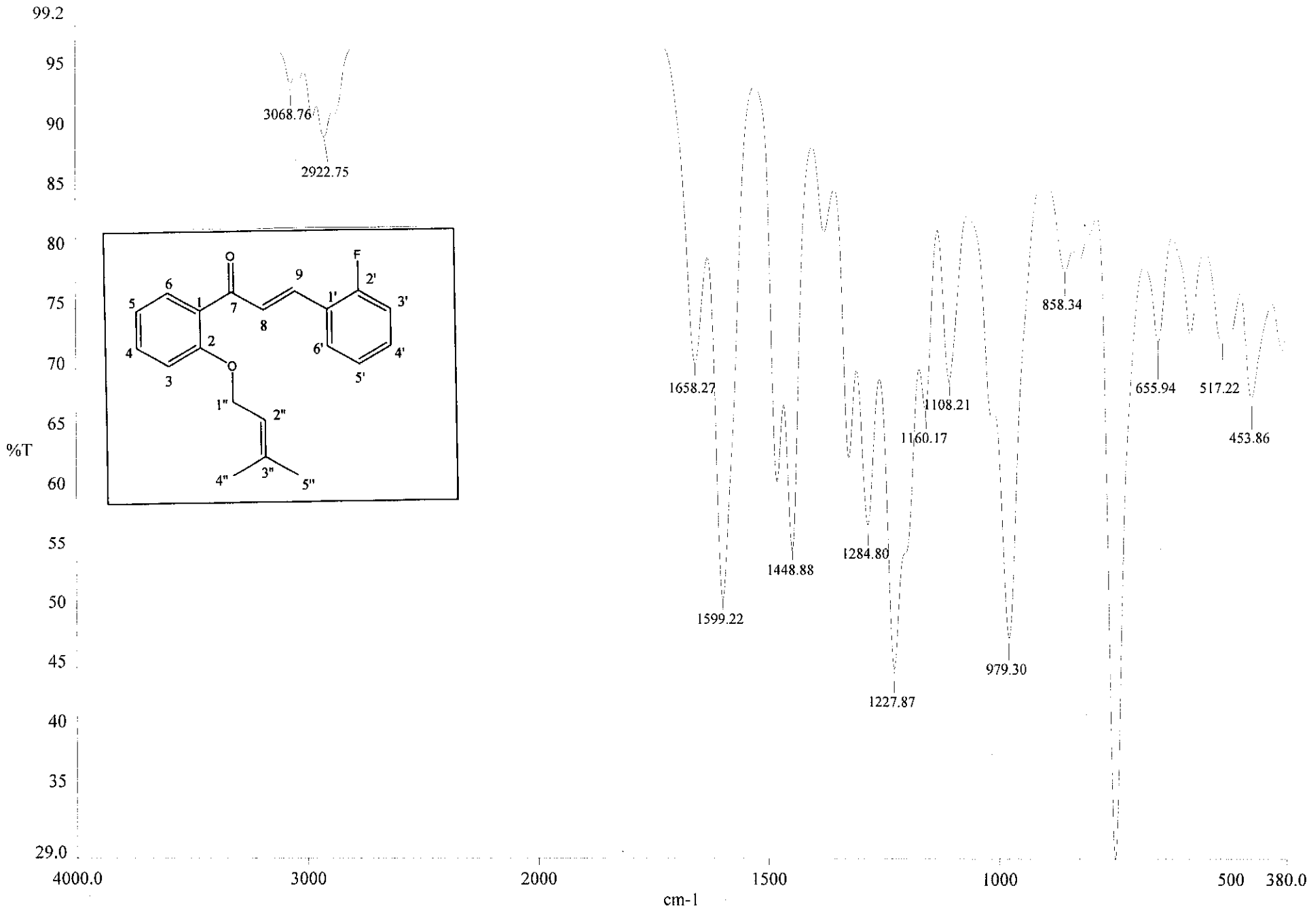
NOESY spectrum of 2'-fluoro-2-oxyprenylchalcone, (XIV)

λmax (258nm) - 0.2691 log ε = 0.13
λmax (300nm) - 0.5249 log ε = 0.42

Date: 2013/06/07 Time: 09:42:13 AM



Ultra violet (UV) spectrum of 2'-fluoro-2-oxyprenylchalcone, (XIV)



Infra-Red (IR) spectrum of 2'-fluoro-2-oxyprenylchalcone, (XIV)

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Instrument :   5973n
Sample Name: MeOH 2preo-2f
Misc Info  :
Vial Number: 10
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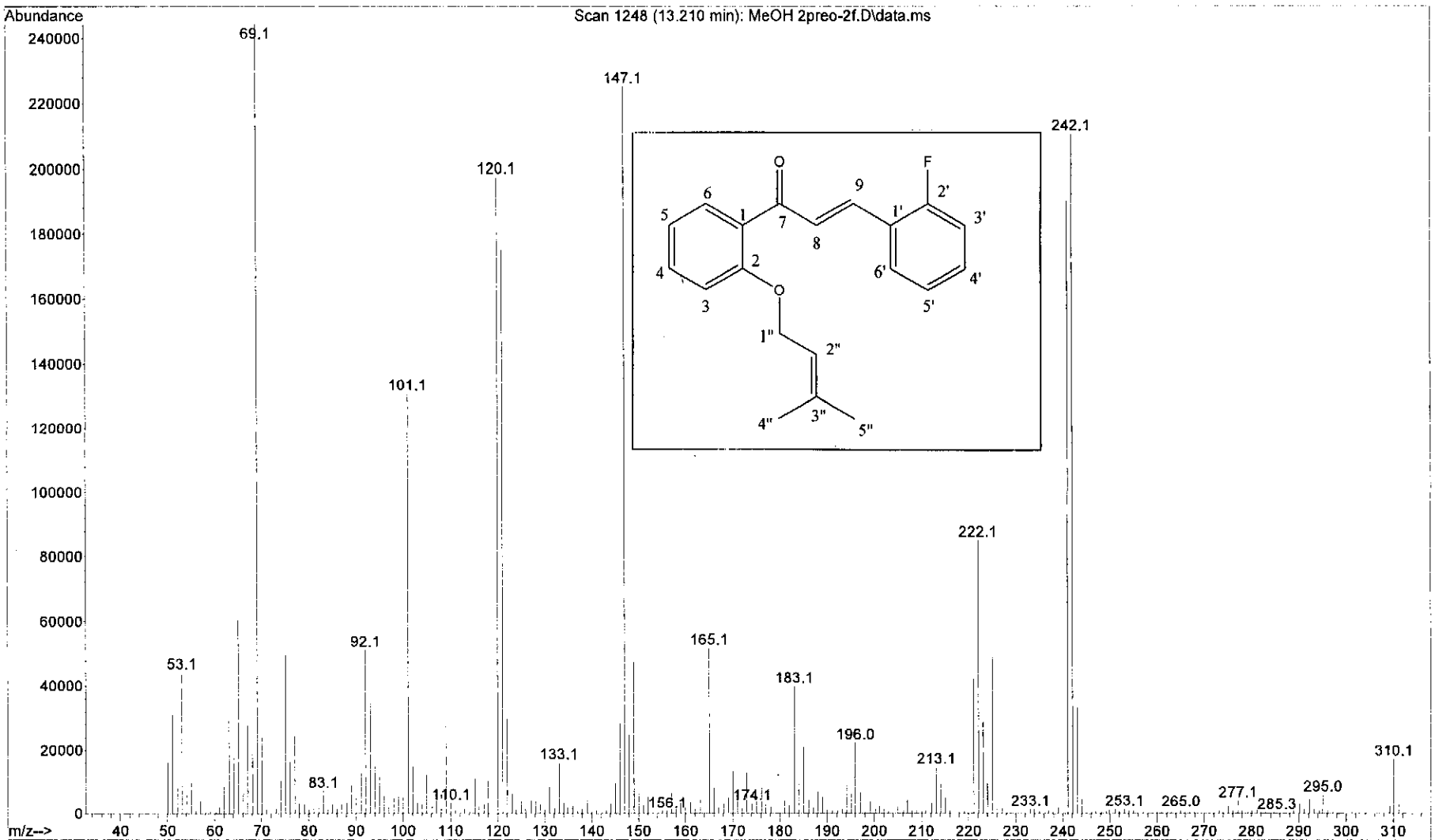


GC-MS spectrum of 2'-fluoro-2-oxyprenylchalcone, (XIV)

Elemental Composition Report

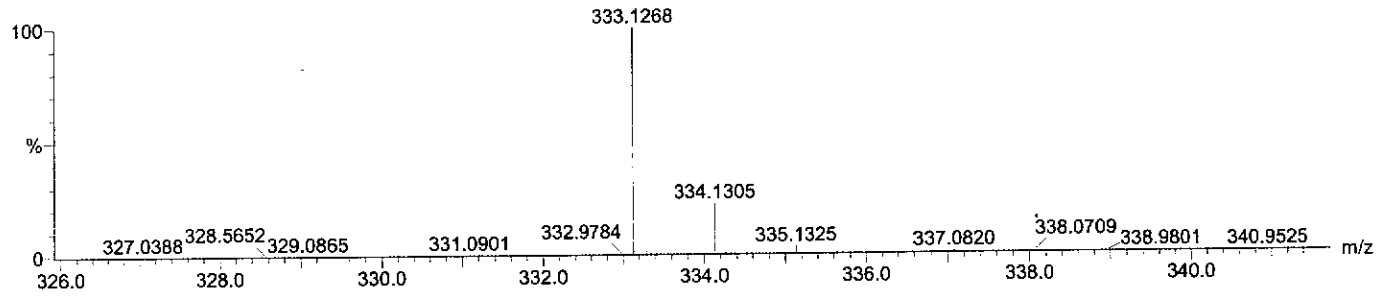
Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

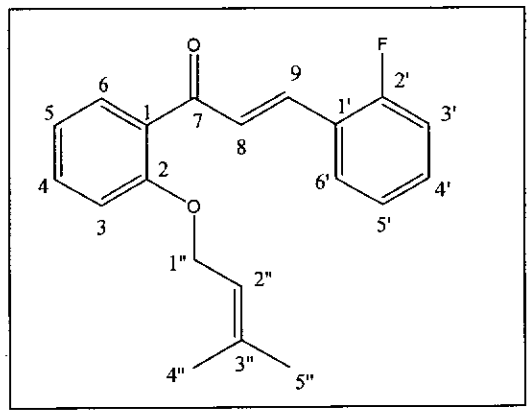
Monoisotopic Mass, Even Electron Ions
9 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 15-20 H: 15-20 O: 0-5 F: 0-1 Na: 0-1

2PreO-2F 15 (0.240) Cm (1:16)
TOF MS ES+

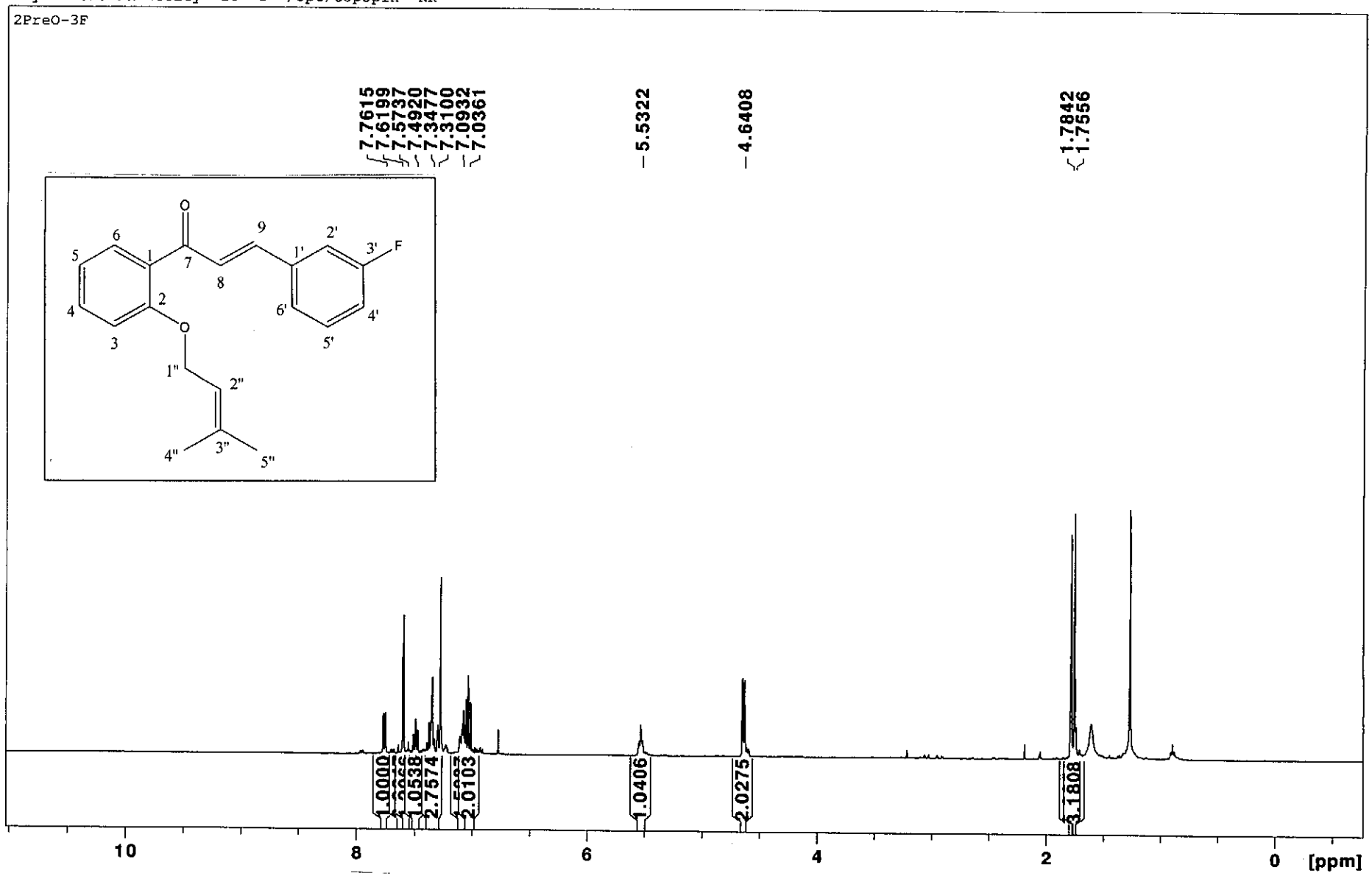
2.97e+004



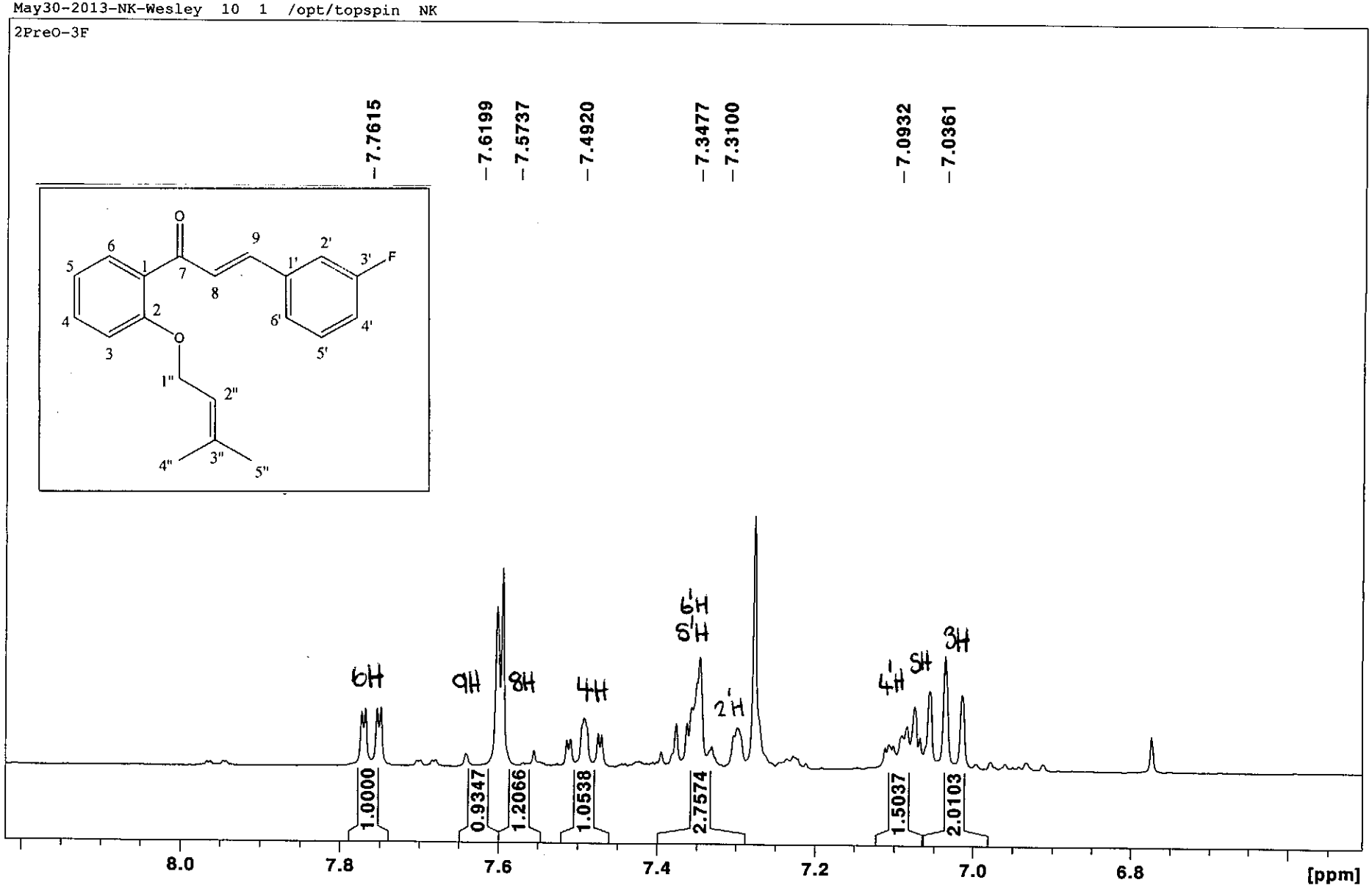
Minimum:				-1.5						
Maximum:		5.0	5.0	100.0						
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula			
333.1268	333.1267	0.1	0.3	10.5	477.3	0.0	C20	H19	O2	F Na



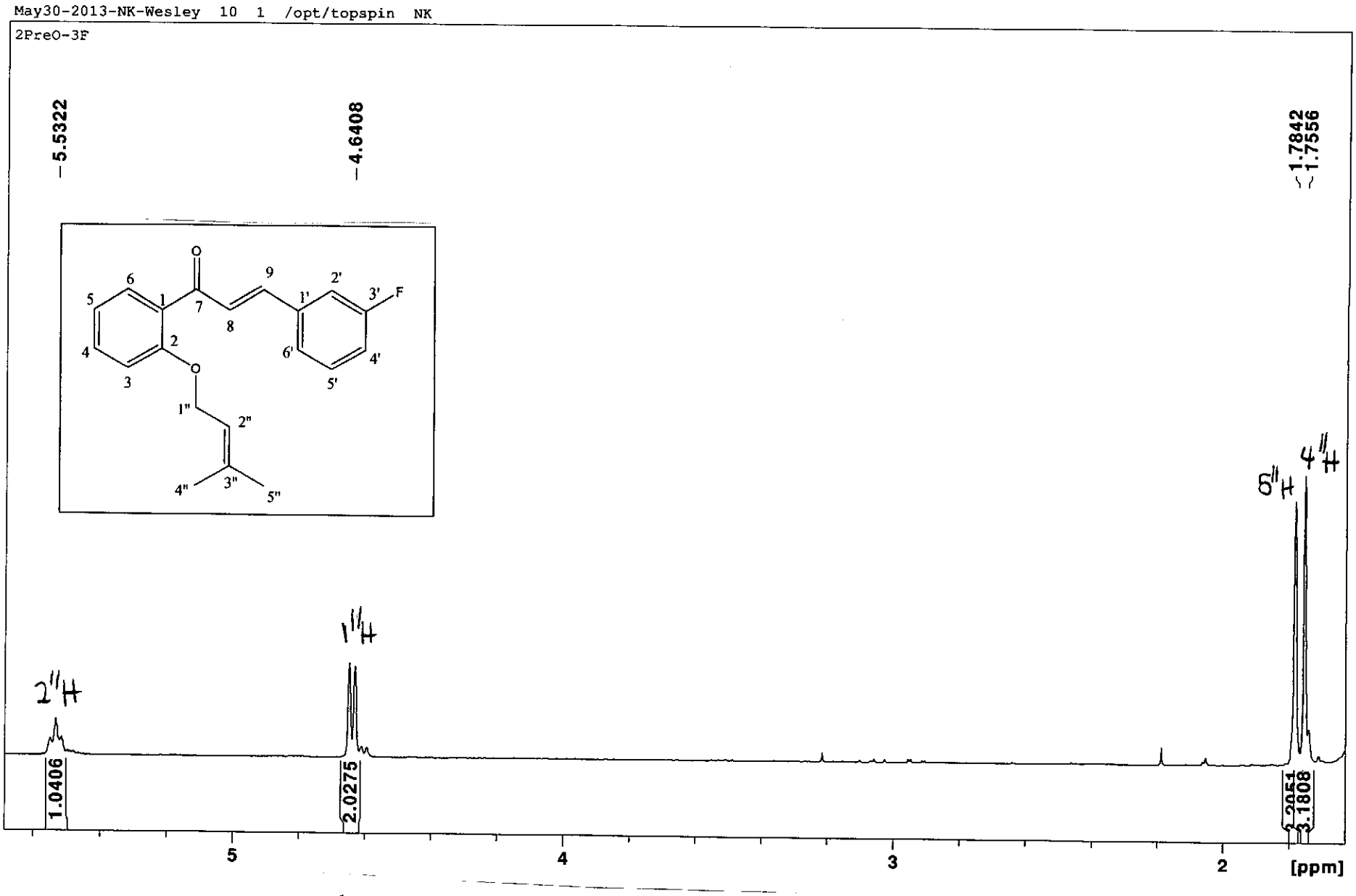
HR-MS spectrum of 2'-fluoro-2-oxyprenylchalcone, (XIV)



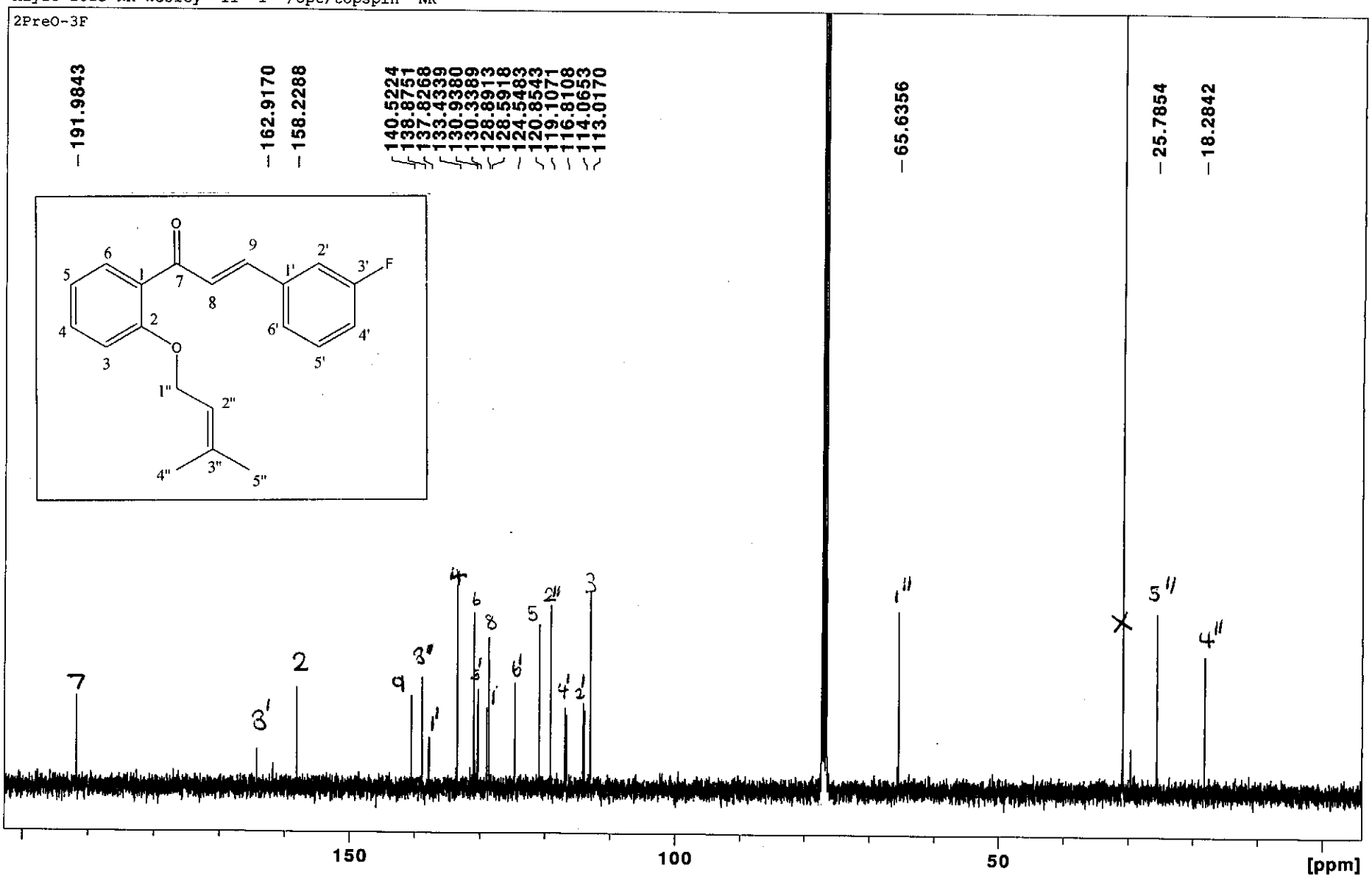
^{1}H NMR spectrum of 3'-fluoro-2-oxyprenylchalcone, (XV)



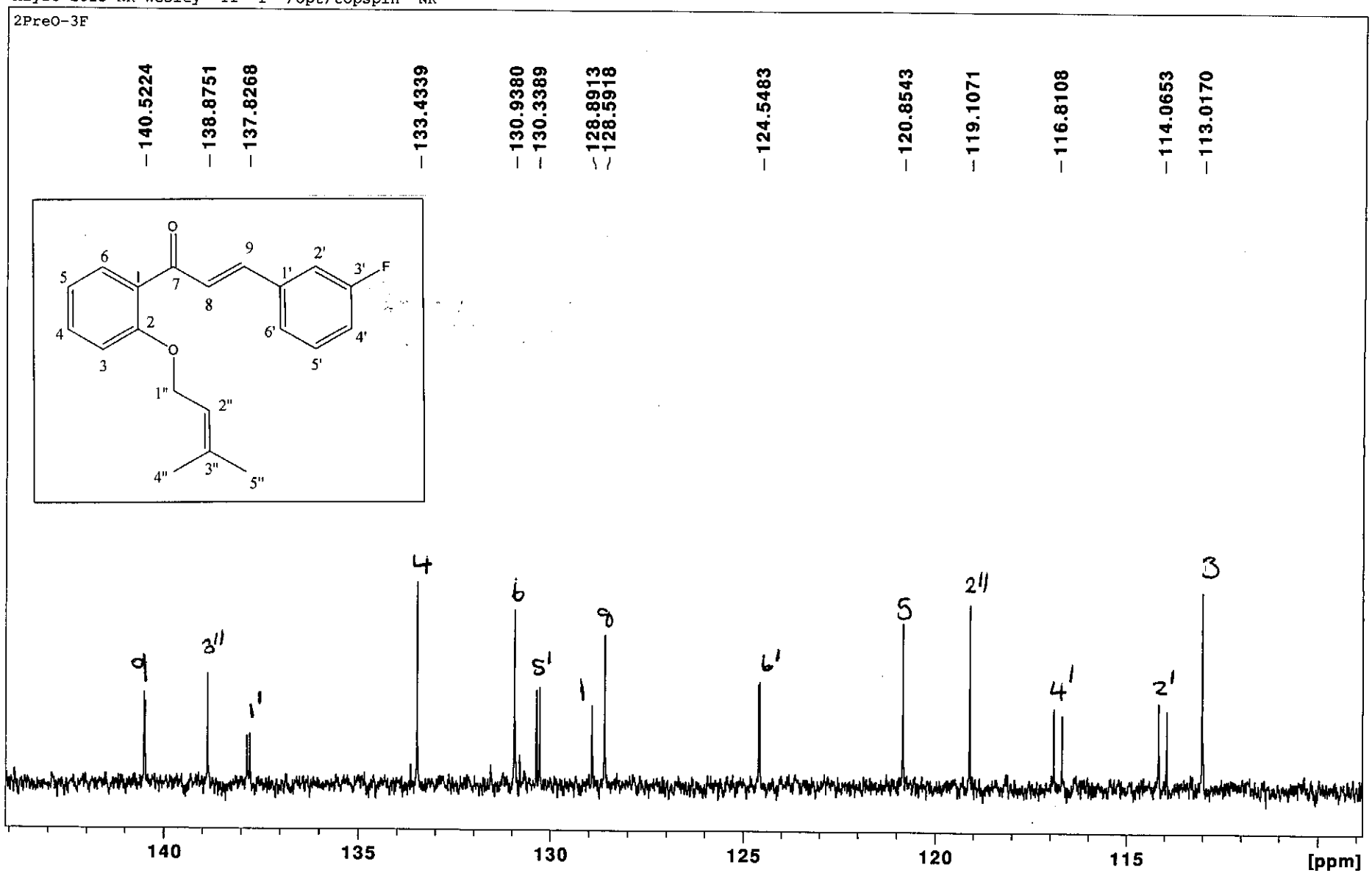
^{1}H NMR spectrum of 3'-fluoro-2-oxyprenylchalcone, (XV)



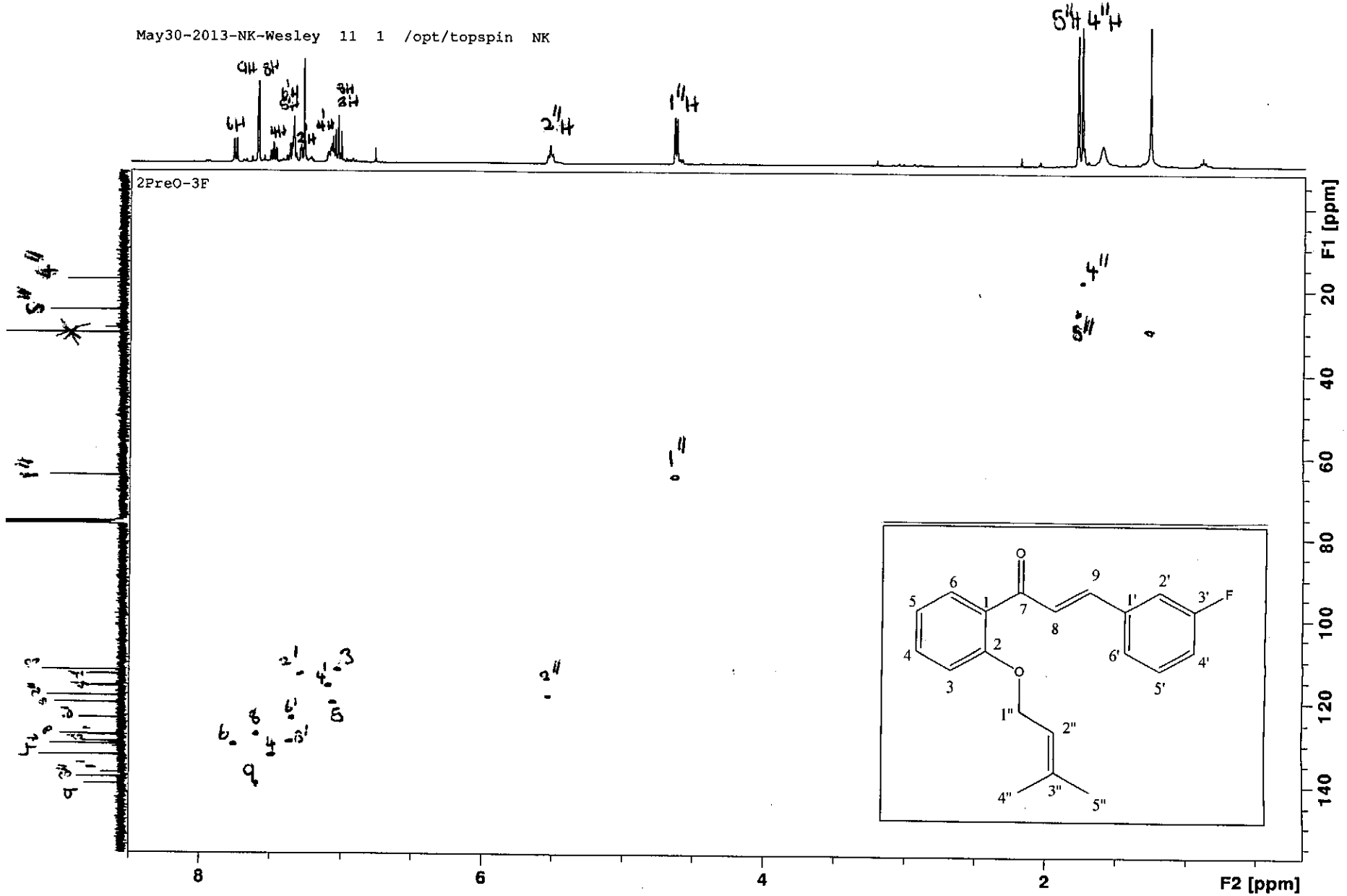
^{1}H NMR spectrum of 3'-fluoro-2-oxyprenylchalcone, (XV)



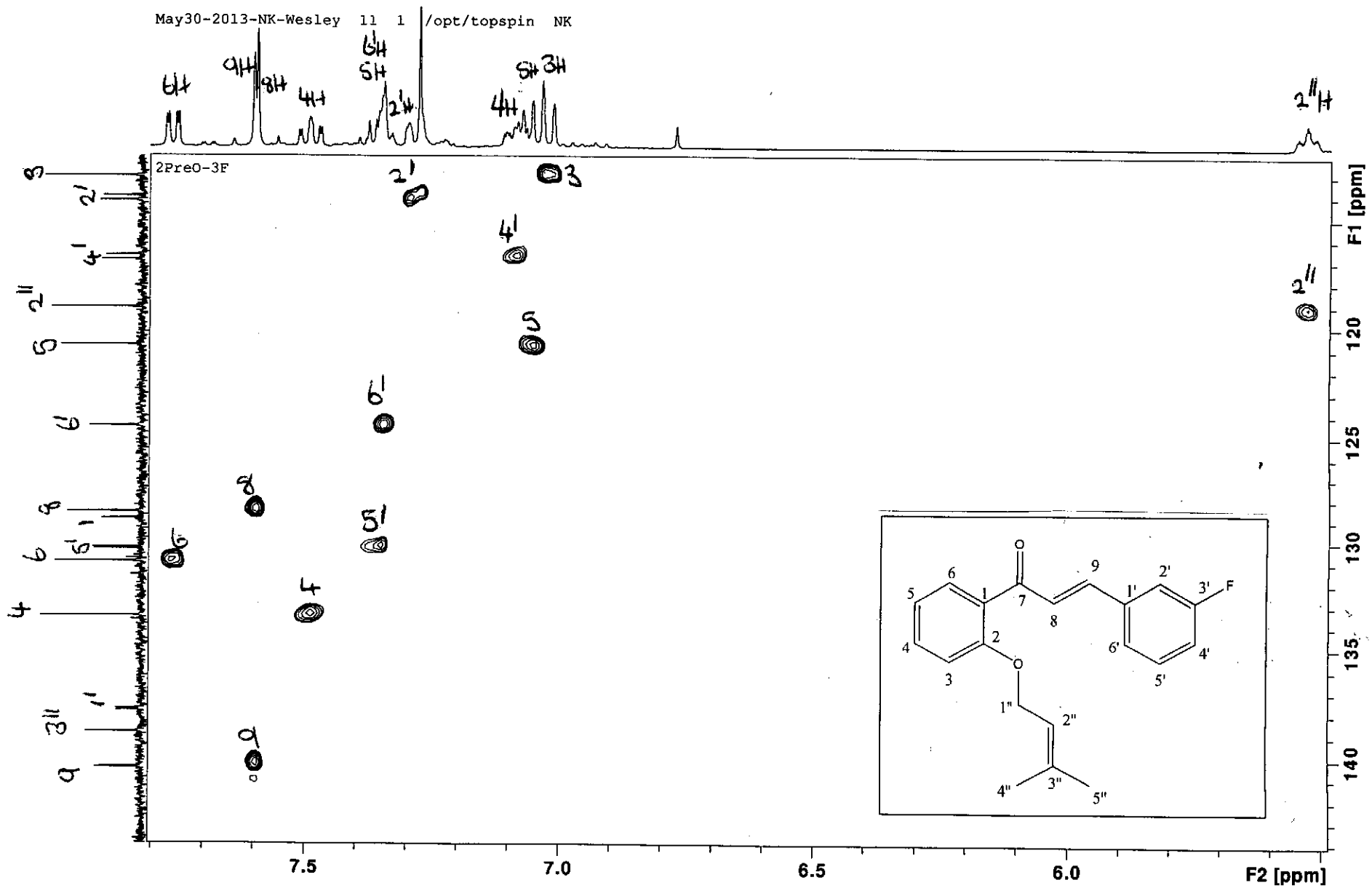
^{13}C NMR spectrum of 3'-fluoro-2-oxyprenylchalcone, (XV)



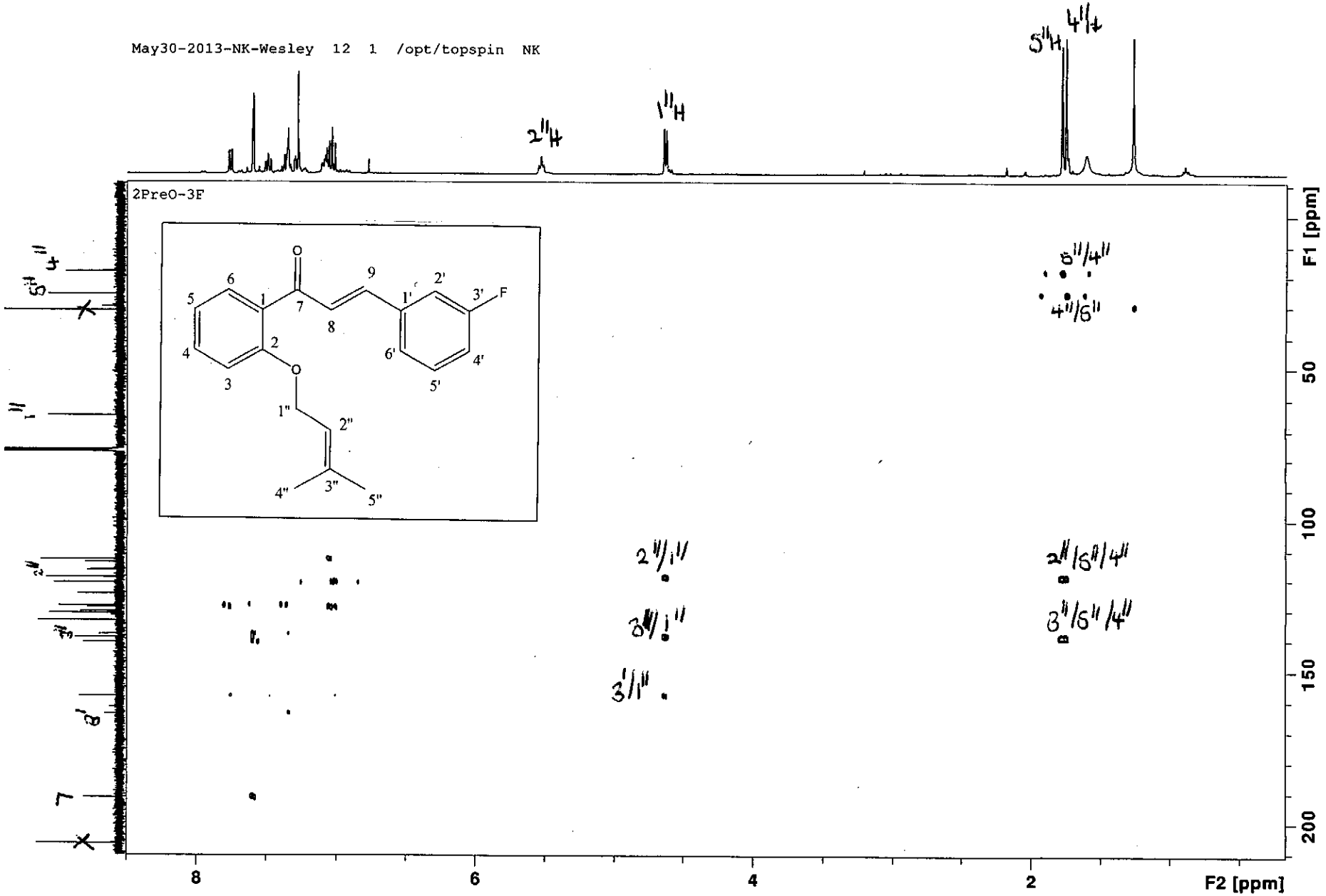
^{13}C NMR spectrum of 3'-fluoro-2-oxyprenylchalcone, (XV)



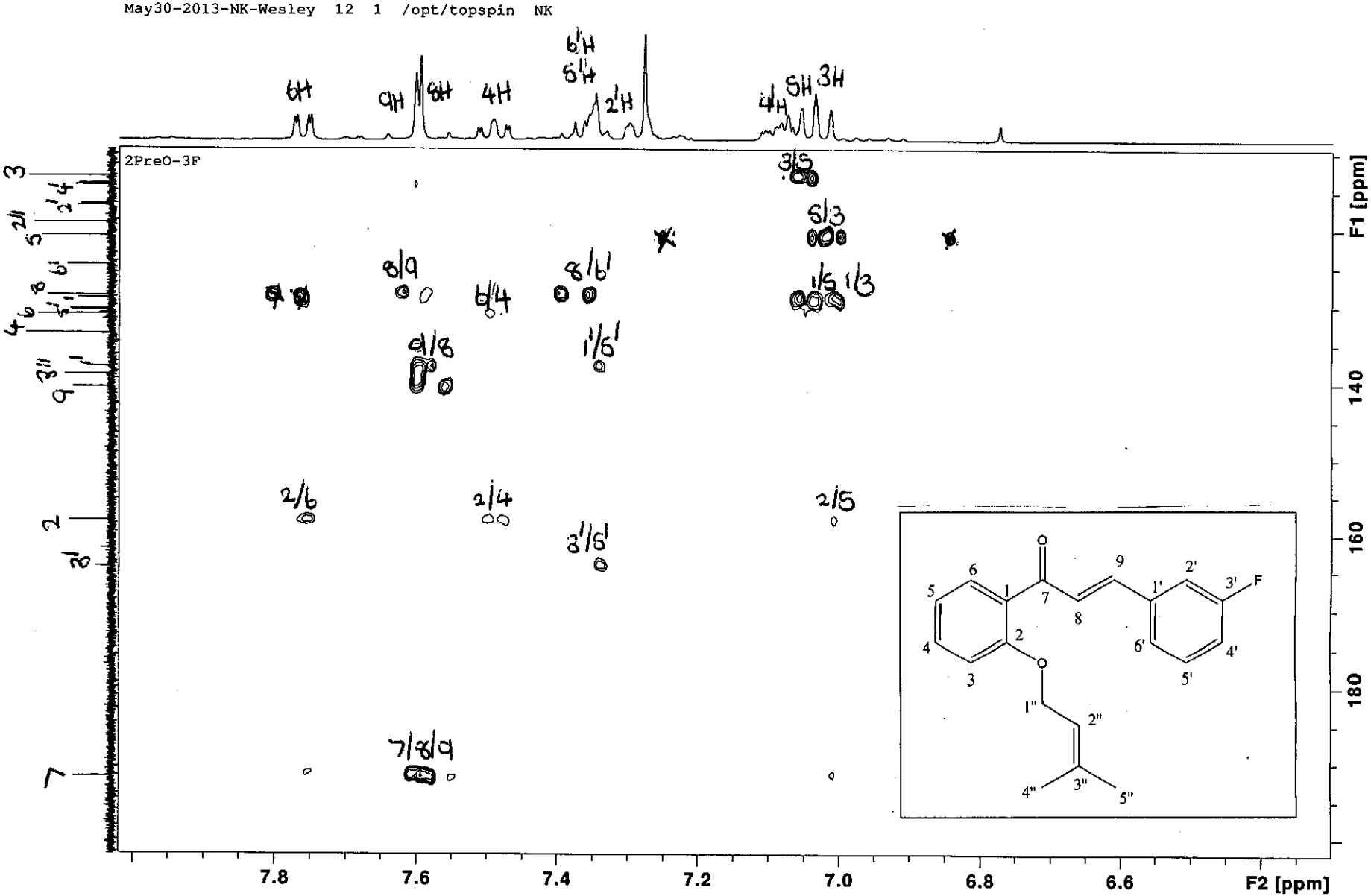
HSQC spectrum of 3'-fluoro-2-oxyprenylchalcone, (XV)



HSQC spectrum of 3'-fluoro-2-oxyprenylchalcone, (XV)



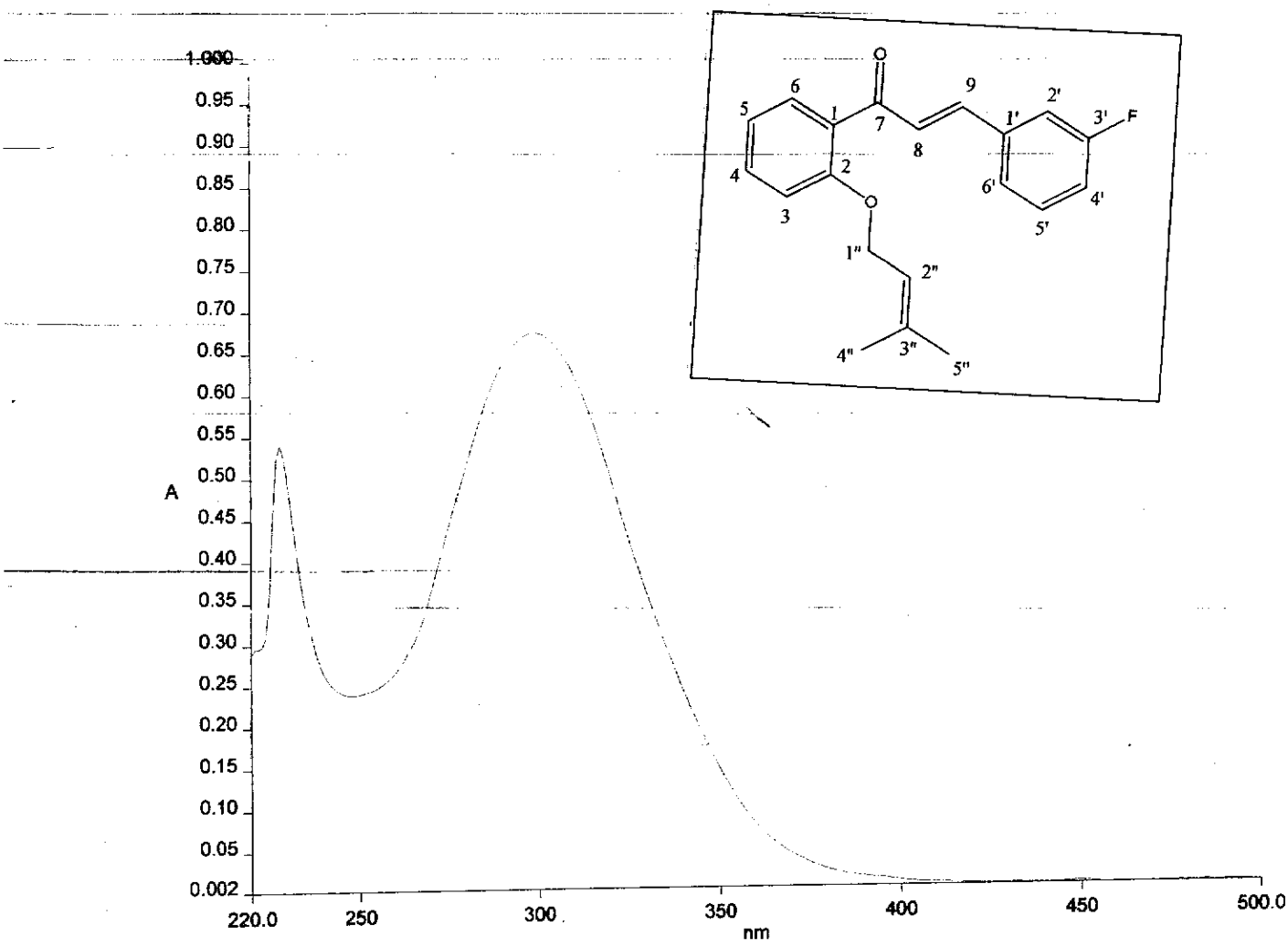
HMBC spectrum of 3'-fluoro-2-oxyprenylchalcone, (XV)



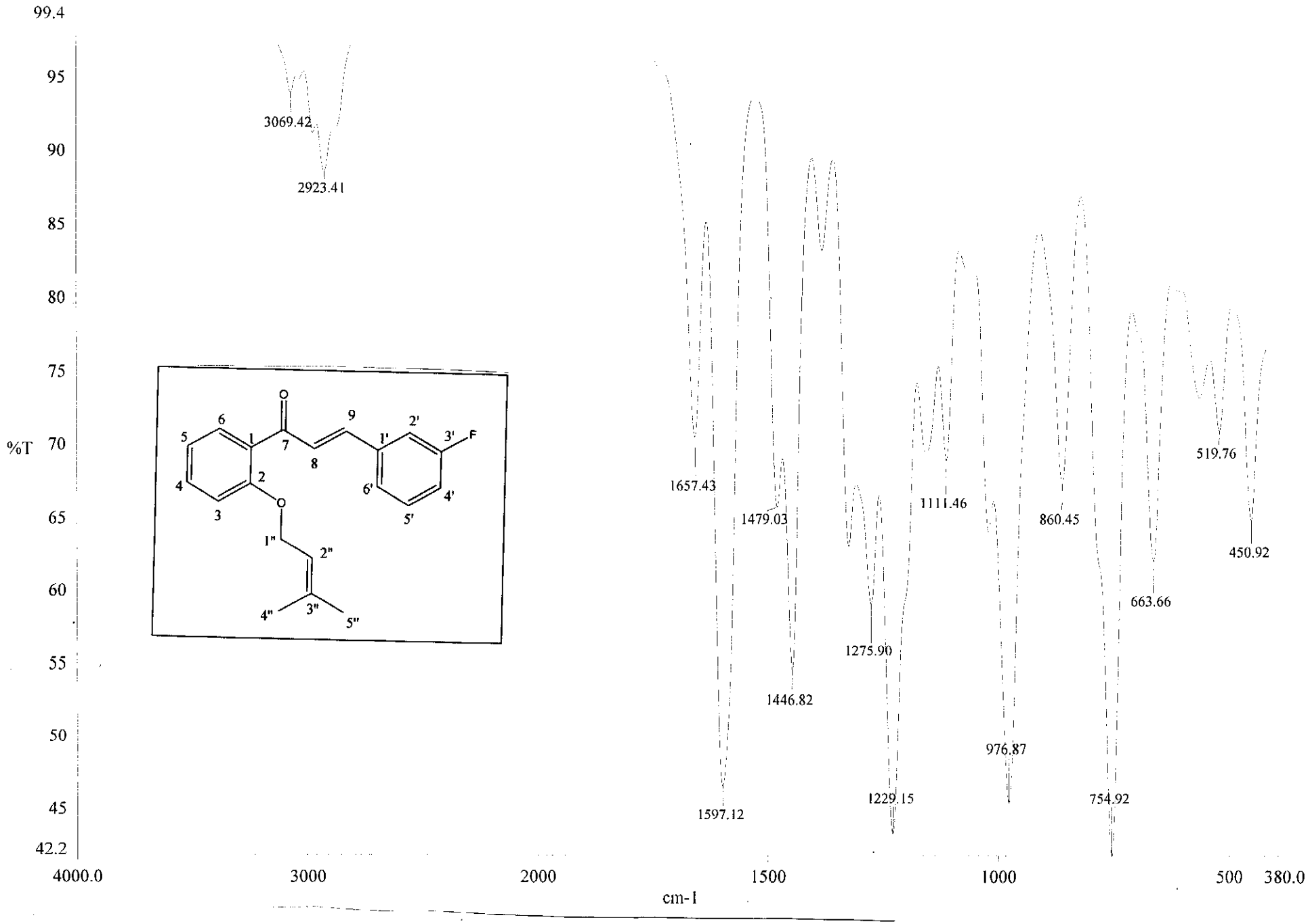
HMBC spectrum of 3'-fluoro-2-oxyprenylchalcone, (XV)

λmax(299nm) - 0.6712 log ε = 5.53

Date: 2013/06/07 Time: 09:45:03 AM



Ultra violet (UV) spectrum of 3'-fluoro-2-oxyprenylchalcone, (XV)



Infra-Red (IR) spectrum of 3'-fluoro-2-oxyprenylchalcone, (XV)

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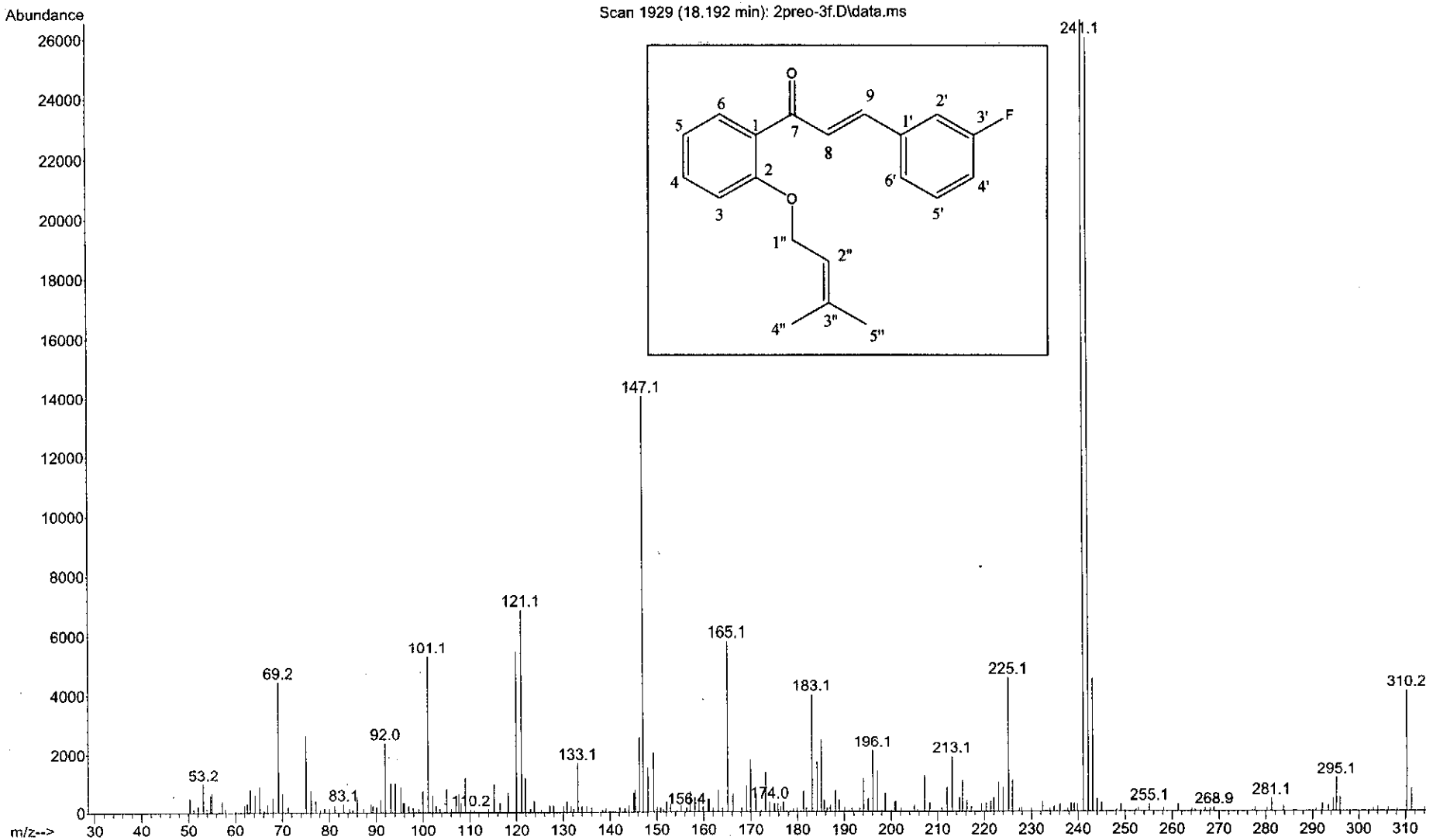


GC-MS spectrum of 3'-fluoro-2-oxyprenylchalcone, (XV)

Elemental Composition Report

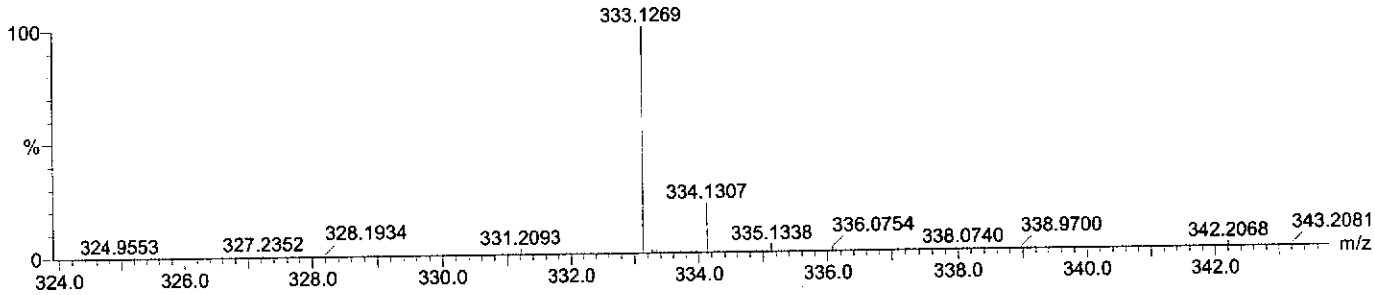
Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

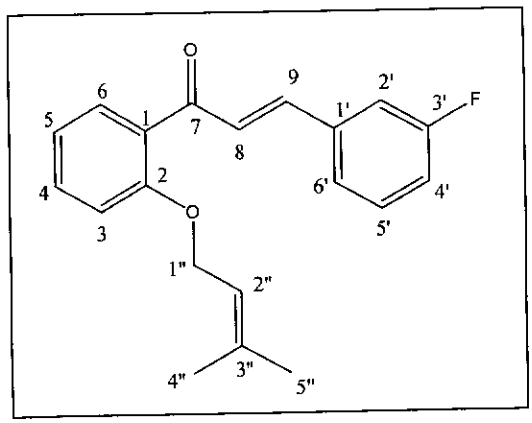
Monoisotopic Mass, Even Electron Ions
9 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 15-20 H: 15-20 O: 0-5 F: 0-1 Na: 0-1

2PreO-3F 8 (0.119) Cm (1:16)
TOF MS ES+

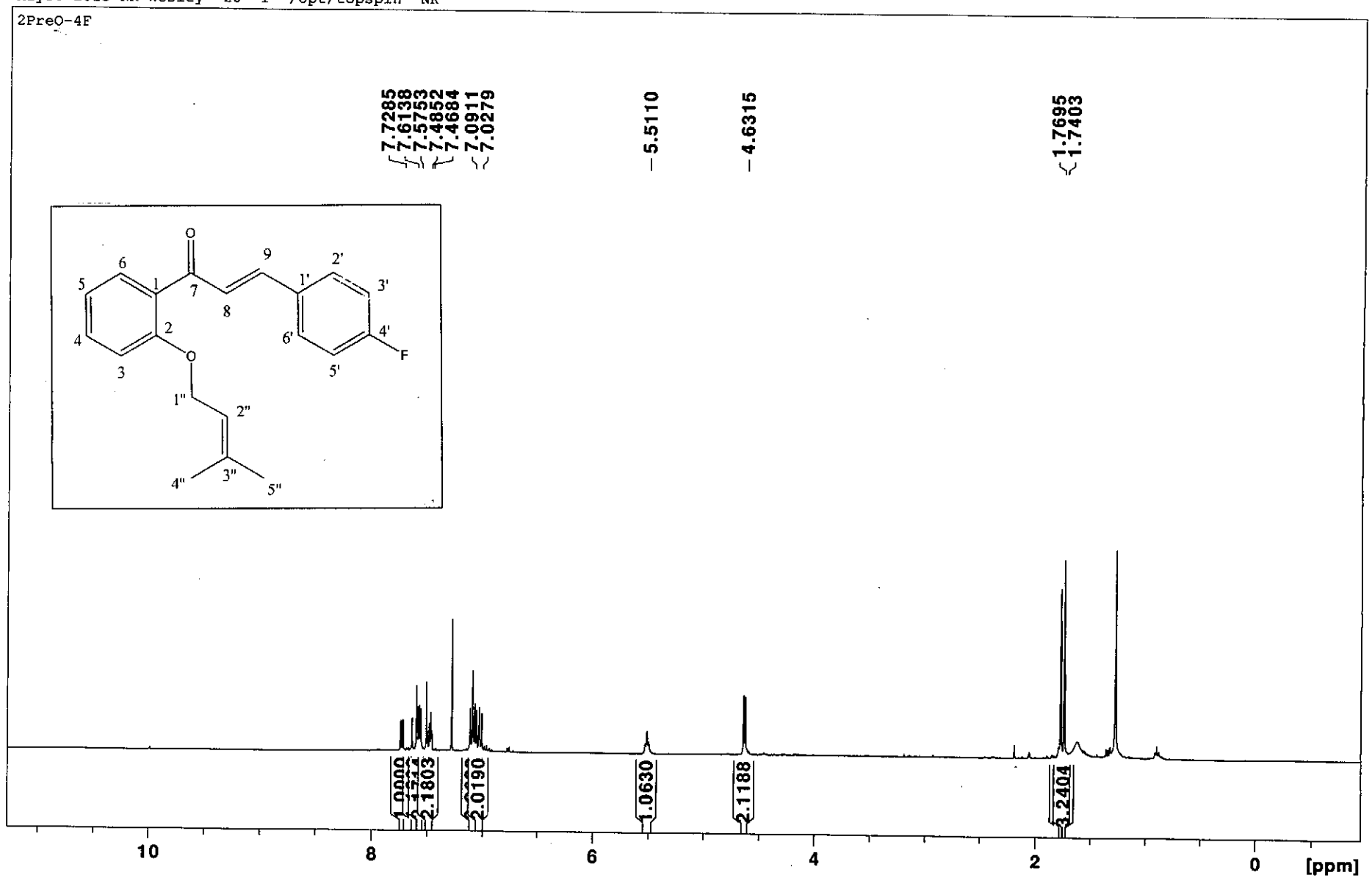
1.74e+004



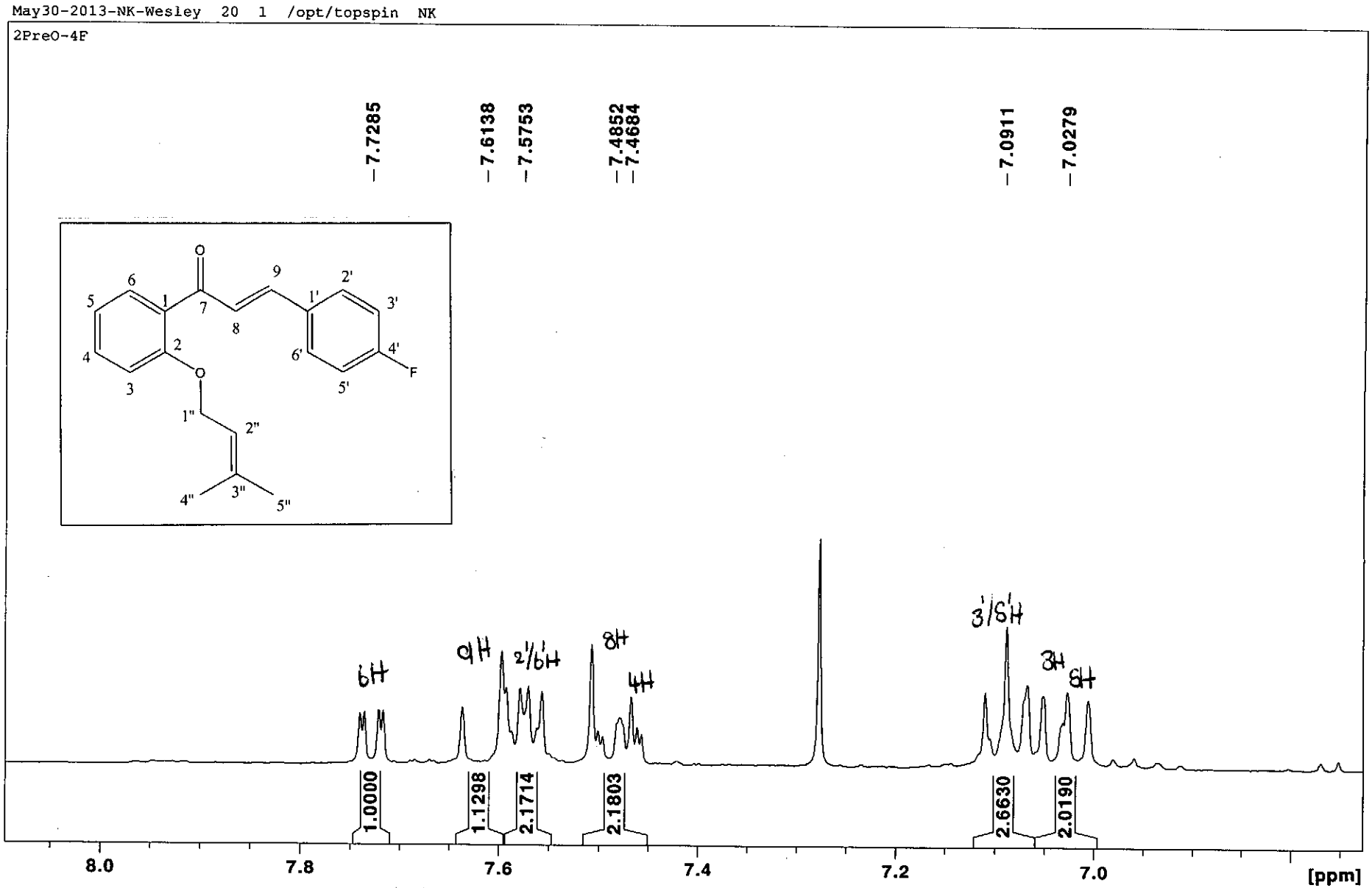
Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
333.1269	333.1267	0.2	0.6	10.5	419.7	0.0	C20 H19 O2 F Na



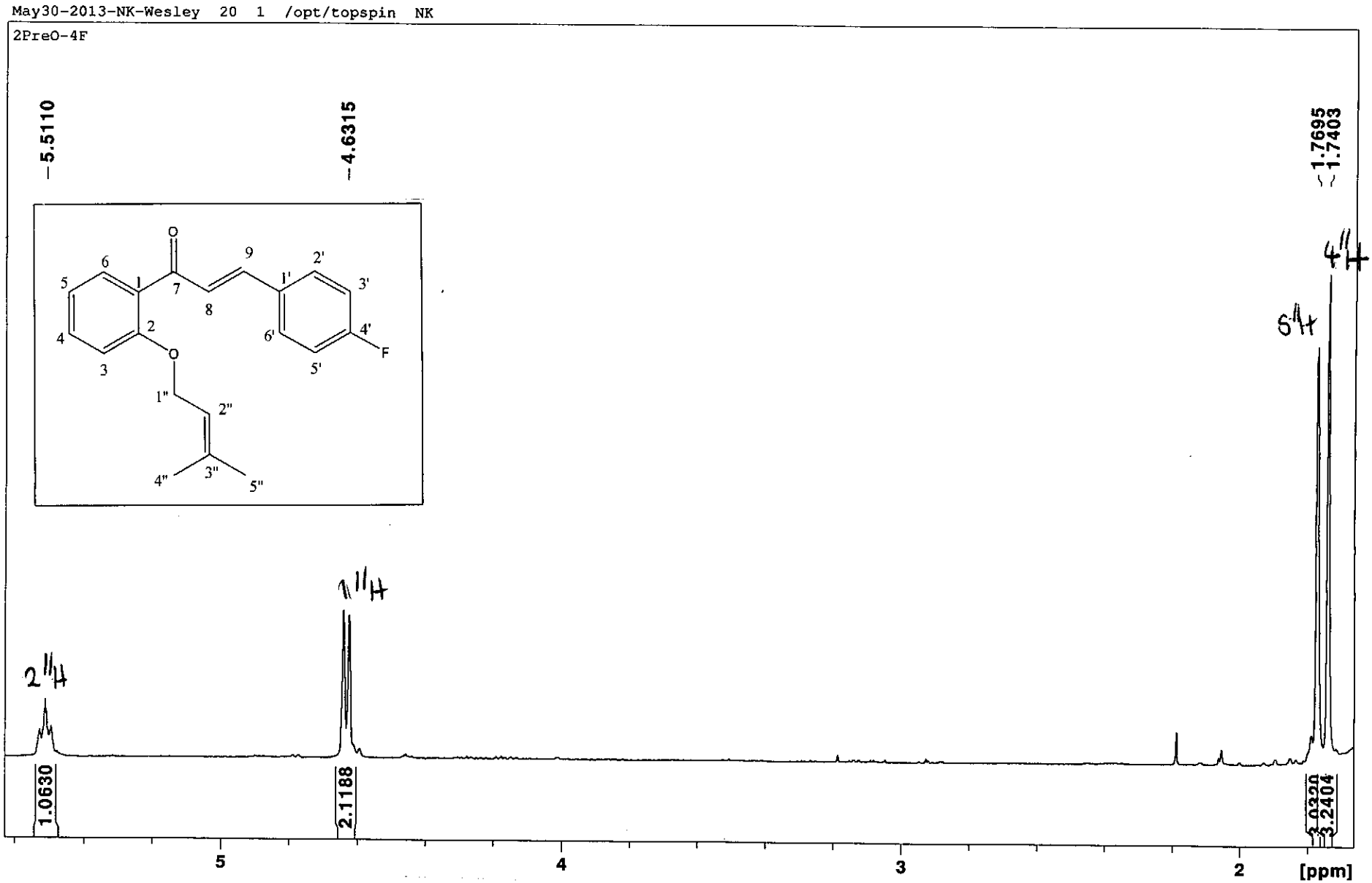
HR-MS spectrum of 3'-fluoro-2-oxyprenylchalcone, (XV)



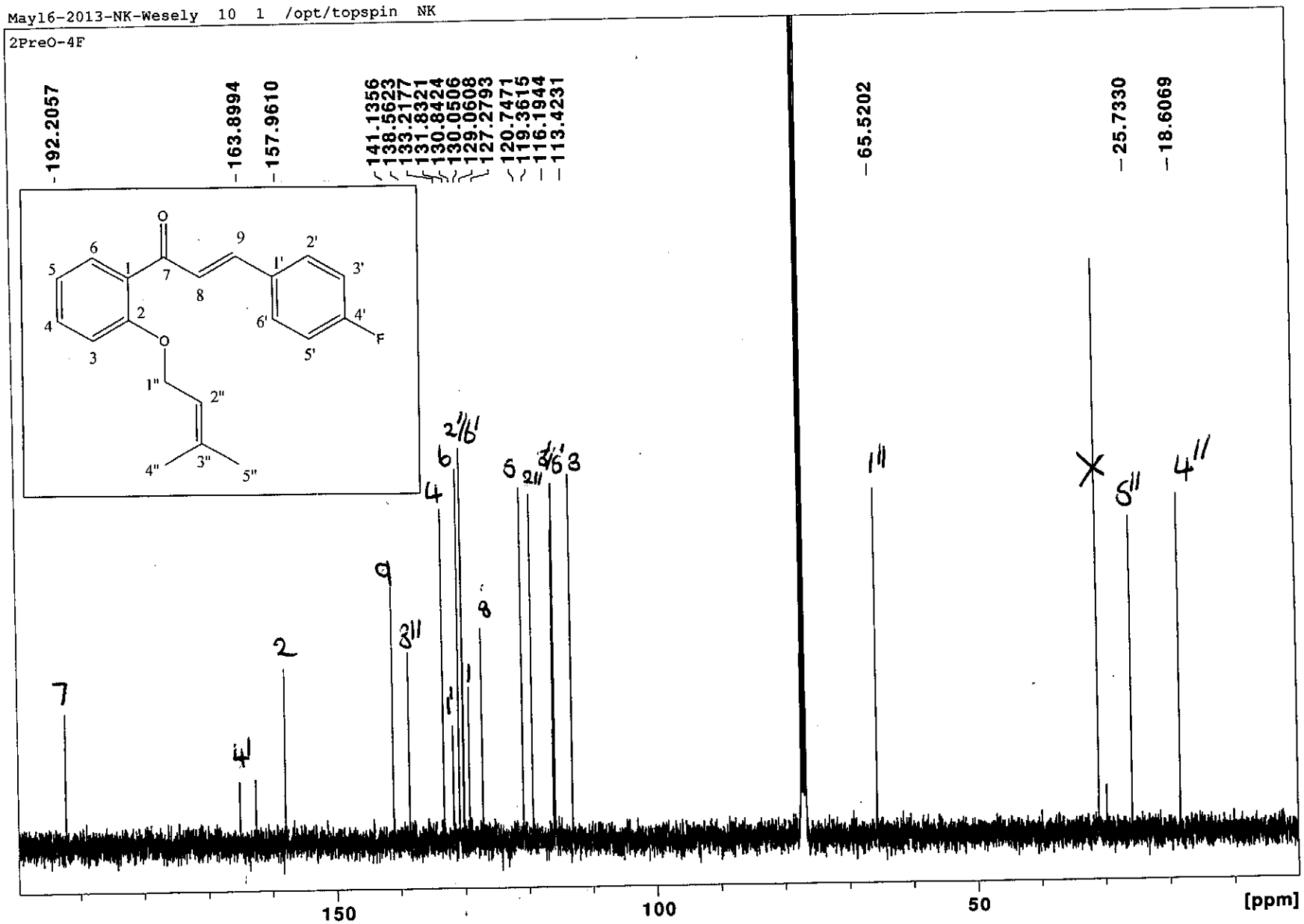
^{1}H NMR spectrum of 4'-fluoro-2-oxyprenylchalcone, (XVI)



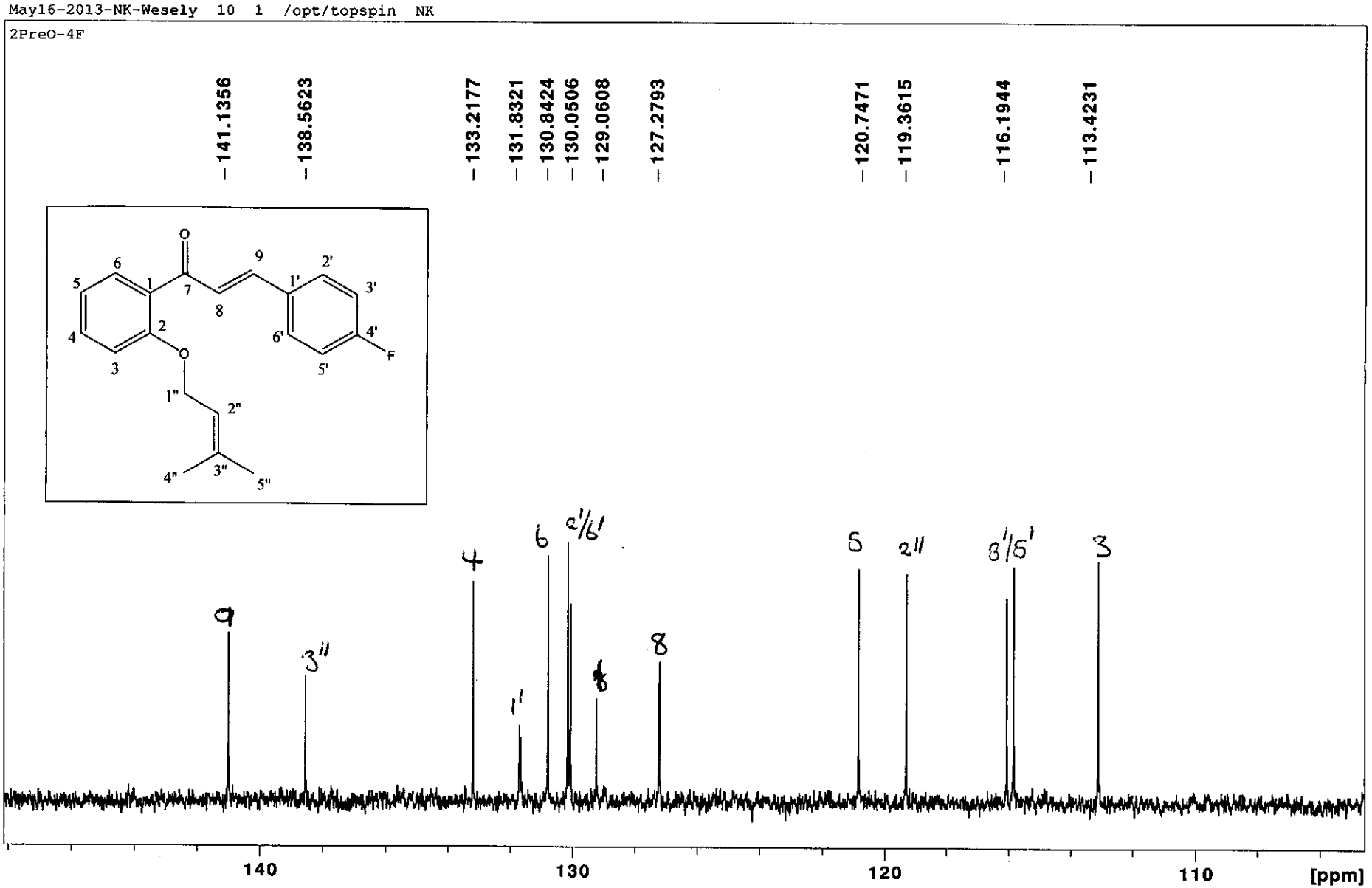
^{1}H NMR spectrum of 4'-fluoro-2-oxyprenylchalcone (XVI)



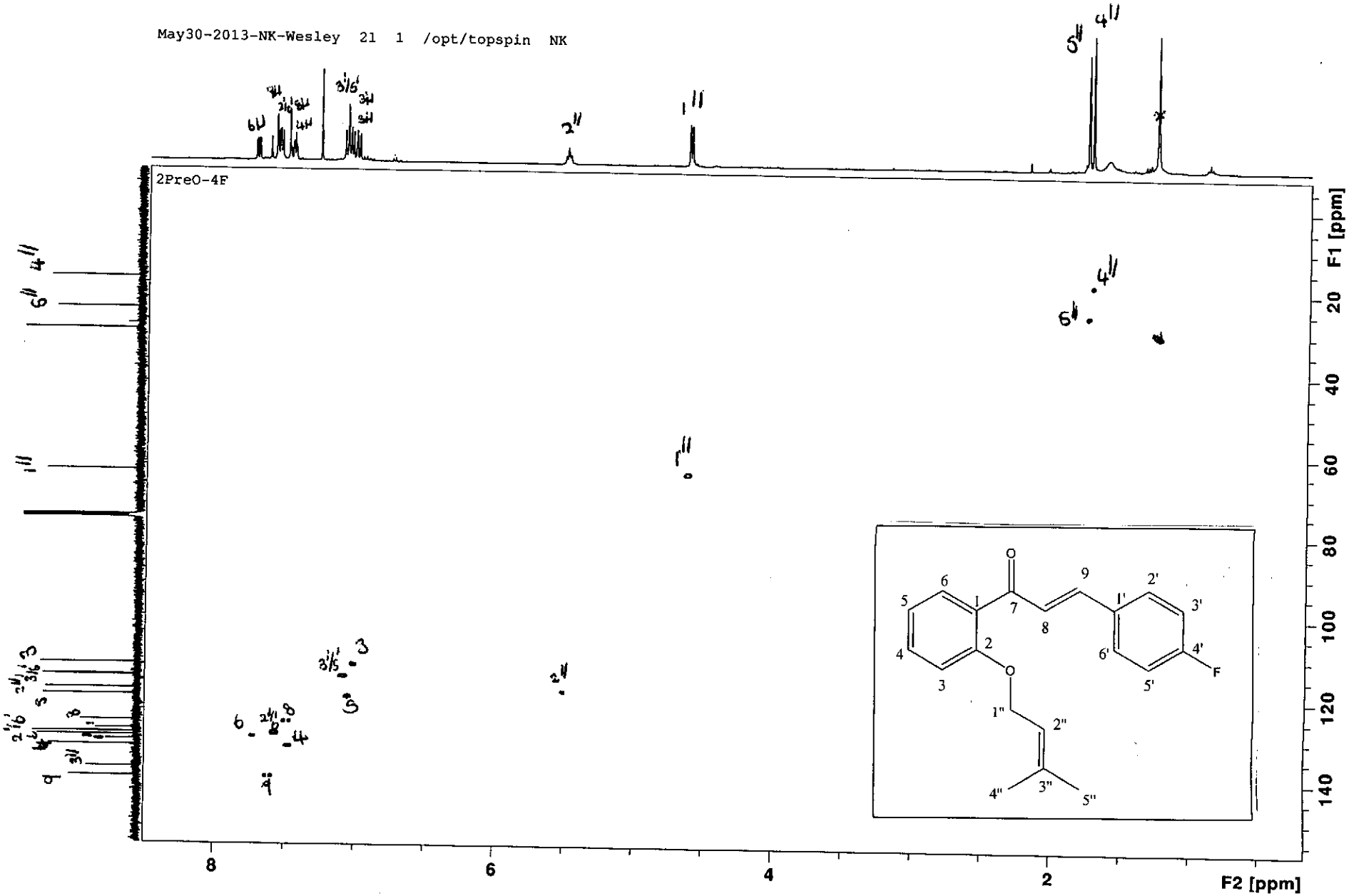
^{1}H NMR spectrum of 4'-fluoro-2-oxyprenylchalcone, (XVI)



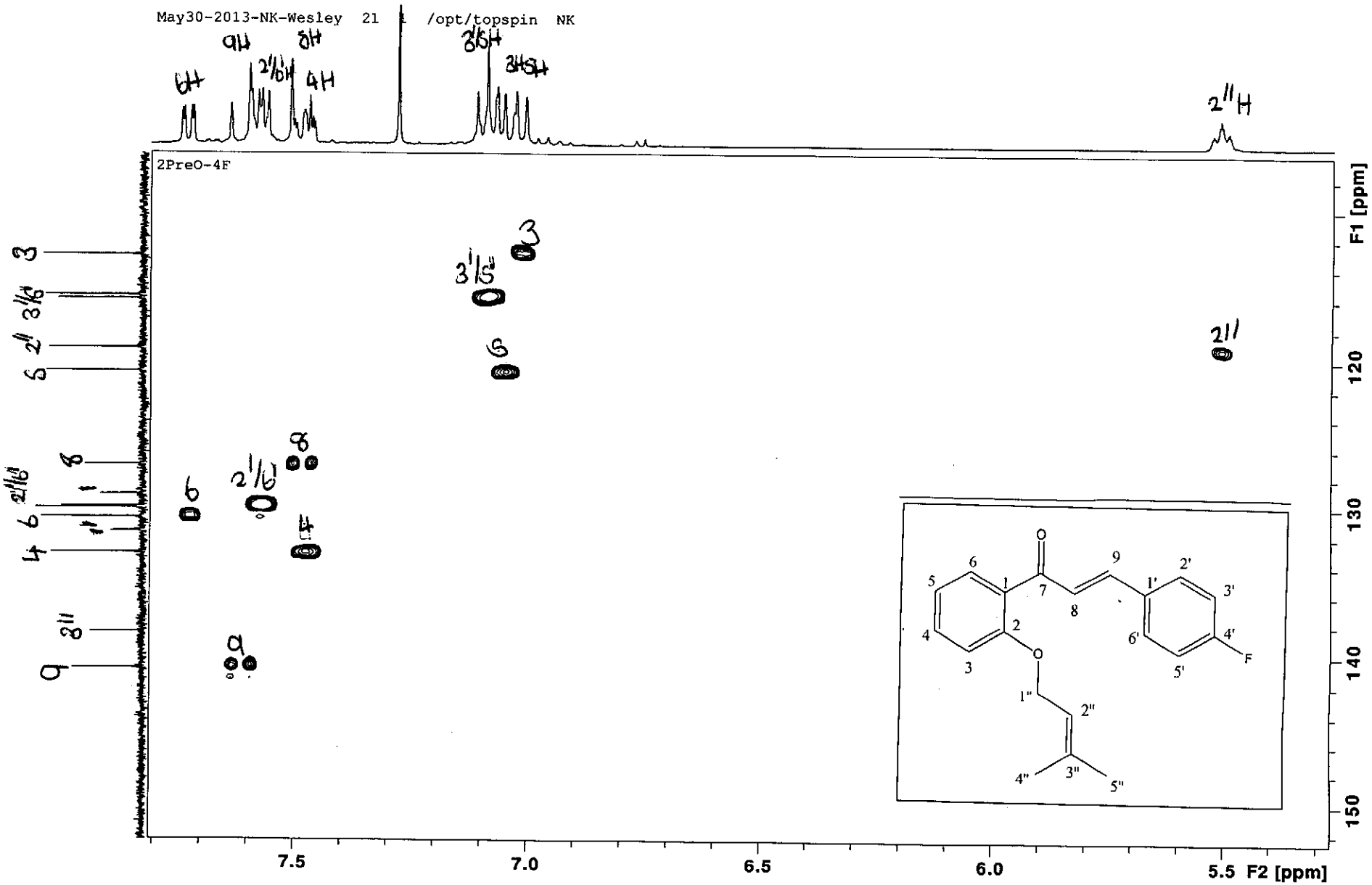
^{13}C NMR spectrum of 4'-fluoro-2-oxyprenylchalcone, (XVI)



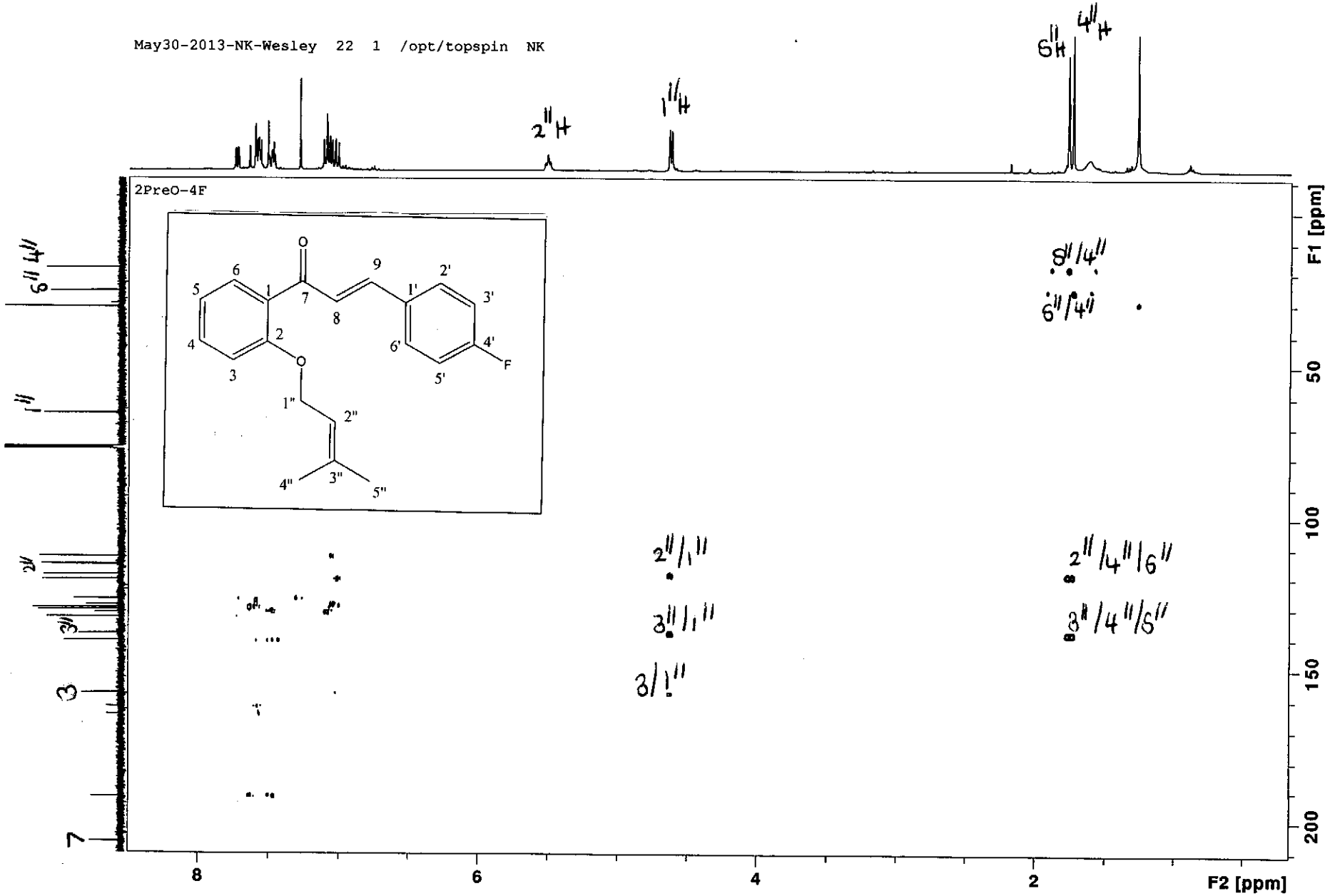
^{13}C NMR spectrum of 4'-fluoro-2-oxyprenylchalcone, (XVI)



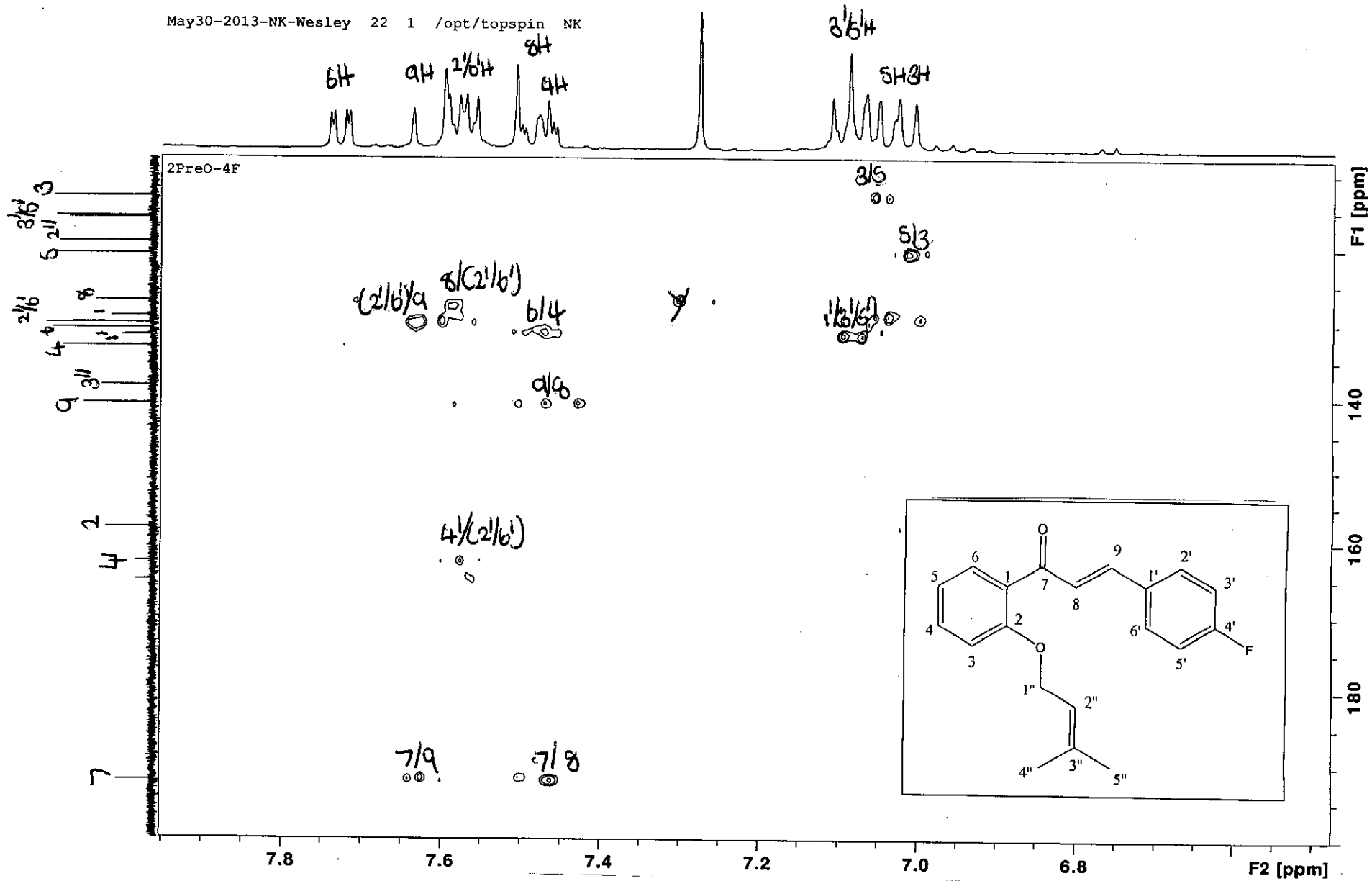
HSQC spectrum of 4'-fluoro-2-oxyprenylchalcone, (XVI)



HSQC spectrum of 4'-fluoro-2-oxyprenylchalcone, (XVI)



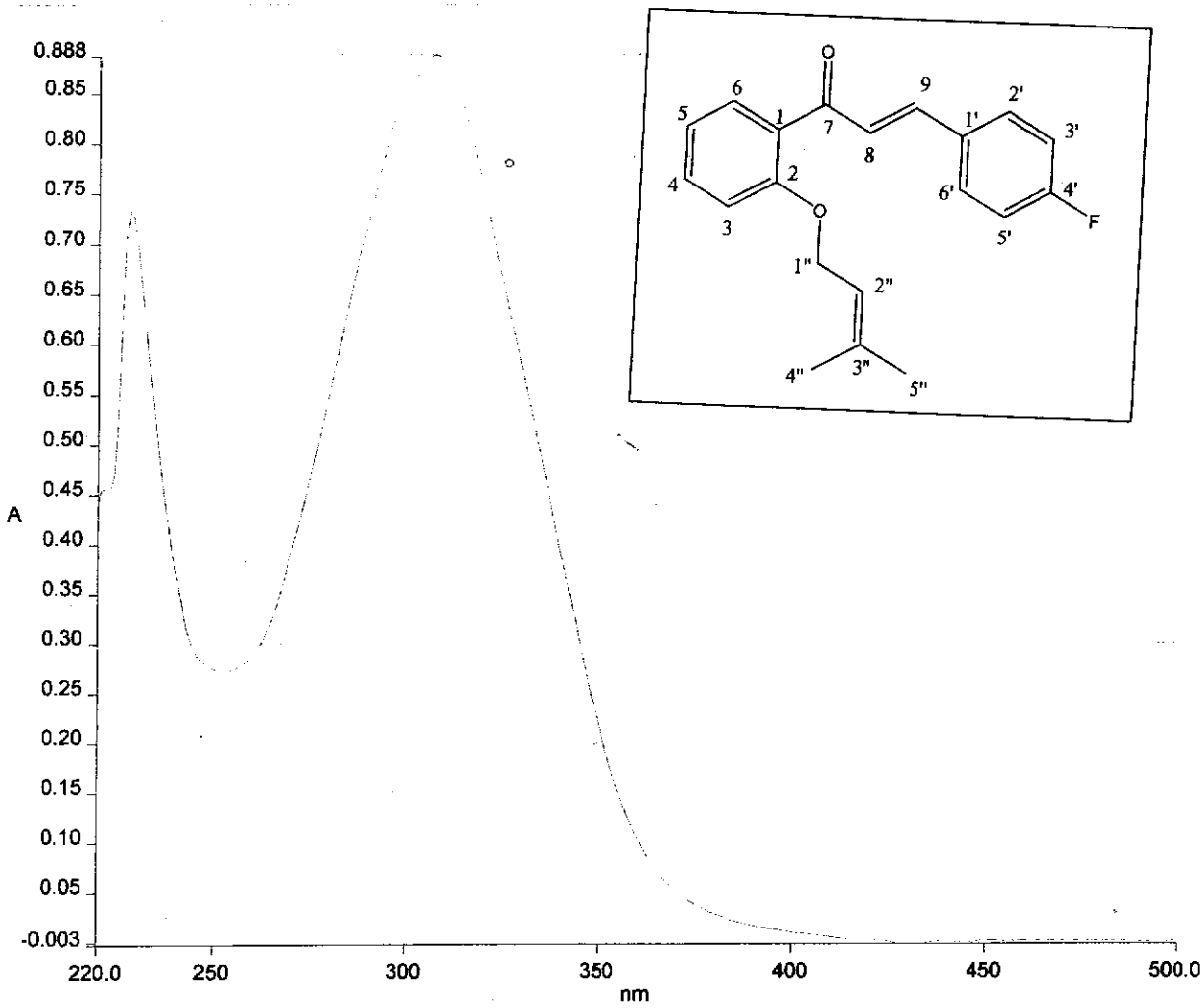
HMBC spectrum of 4'-fluoro-2-oxyprenylchalcone, (XVI)



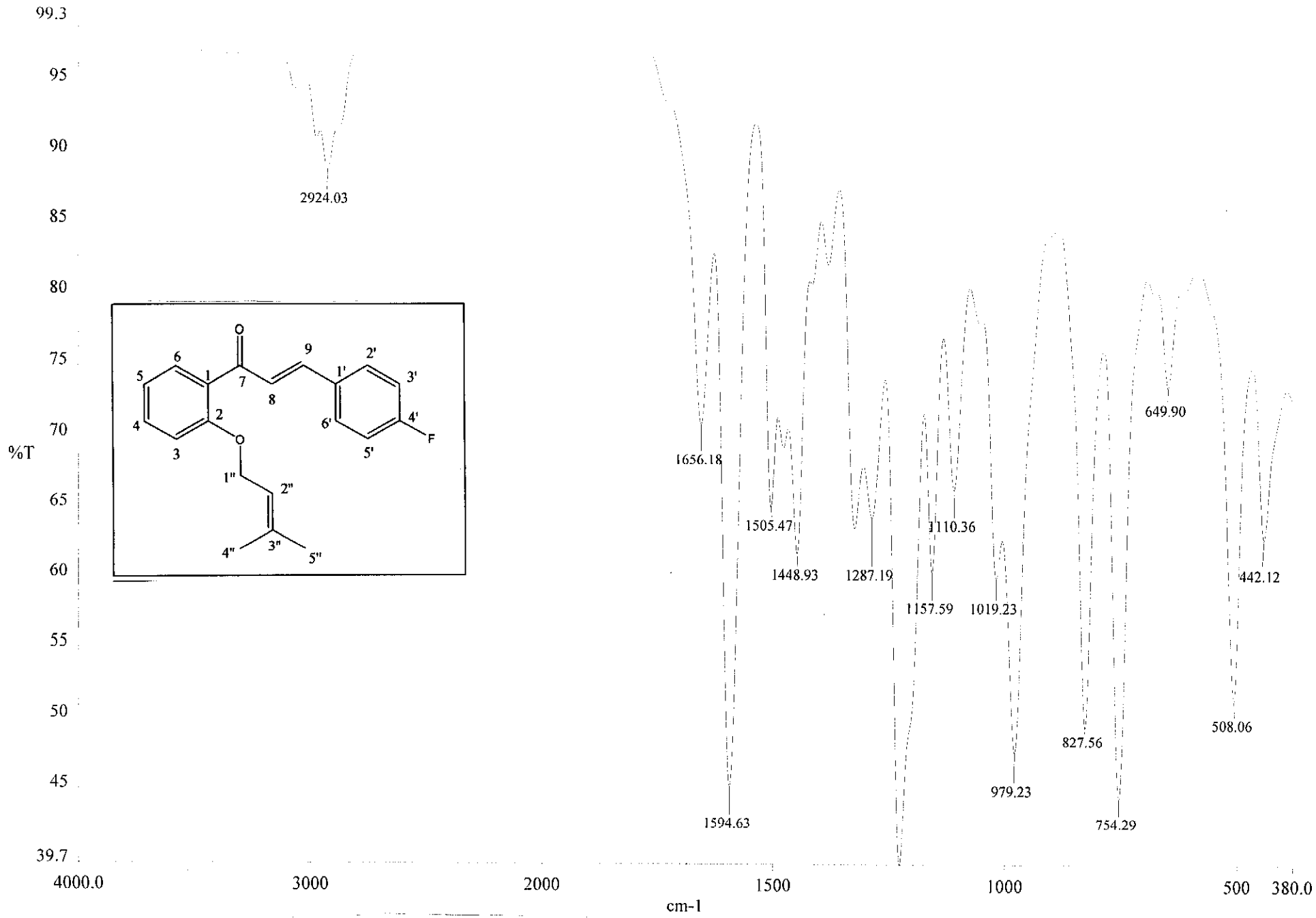
HMBC spectrum of 4'-fluoro-2-oxyprenylchalcone, (XVI)

λmax(228nm)-0.7332
λmax(307nm)-0.8877

Date: 2013/06/04 Time: 01:38:46 PM



Ultra violet (UV) spectrum of 4'-fluoro-2-oxyprenylchalcone, (XVI)



Infra-Red (IR) spectrum of 4'-fluoro-2-oxyprenylchalcone, (XVI)

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Instrument : 5973n
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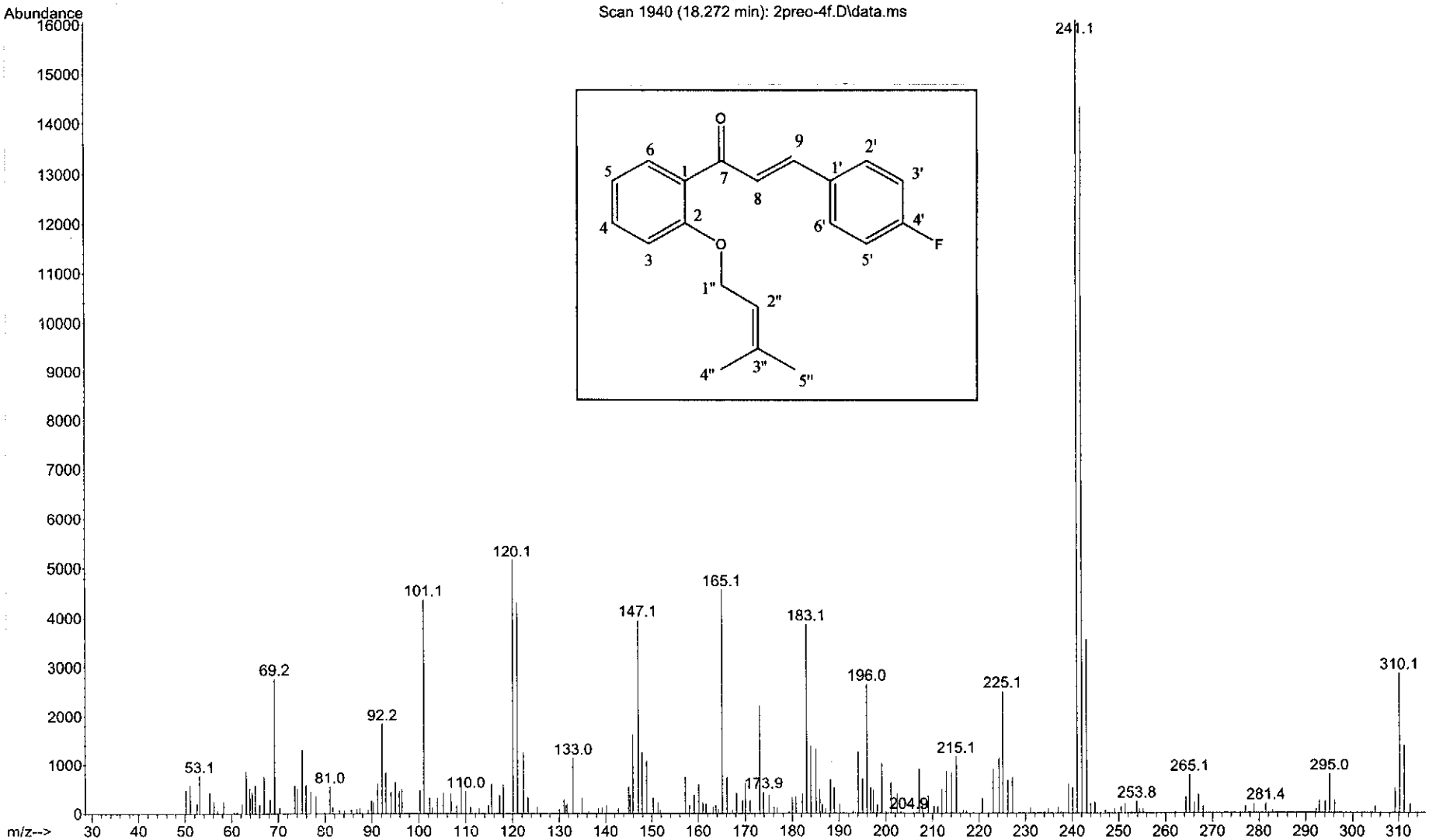
Sample Name: 2preo-4f
Misc Info :



GC-MS spectrum of 4'-fluoro-2-oxyprenylchalcone, (XVI)

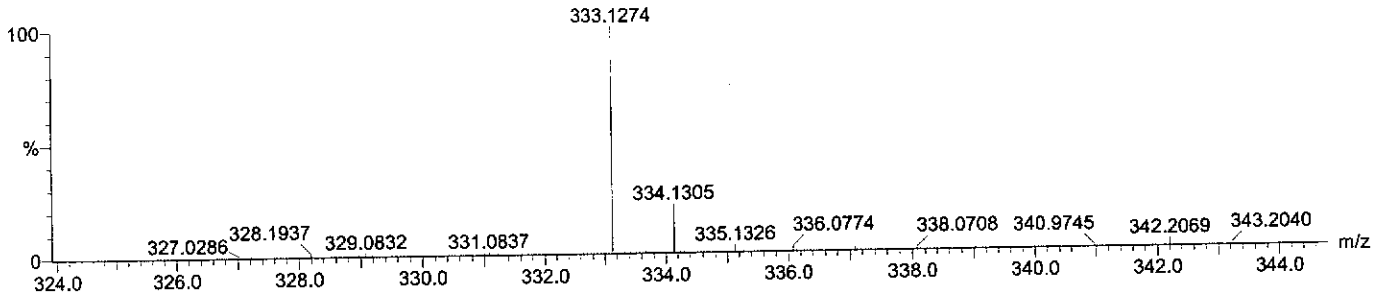
Elemental Composition Report

Single Mass Analysis

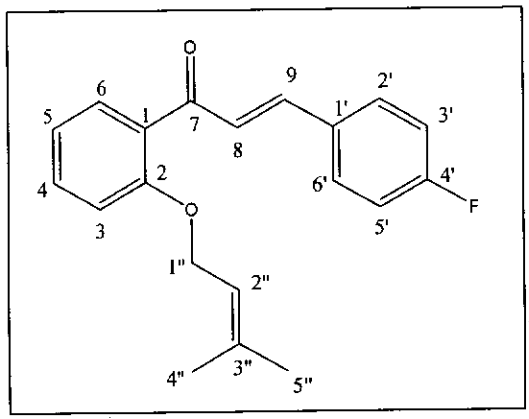
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
9 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 15-20 H: 15-20 O: 0-5 F: 0-1 Na: 0-1
2PreO-4F 12 (0.188) Cm (1:15)
TOF MS ES+

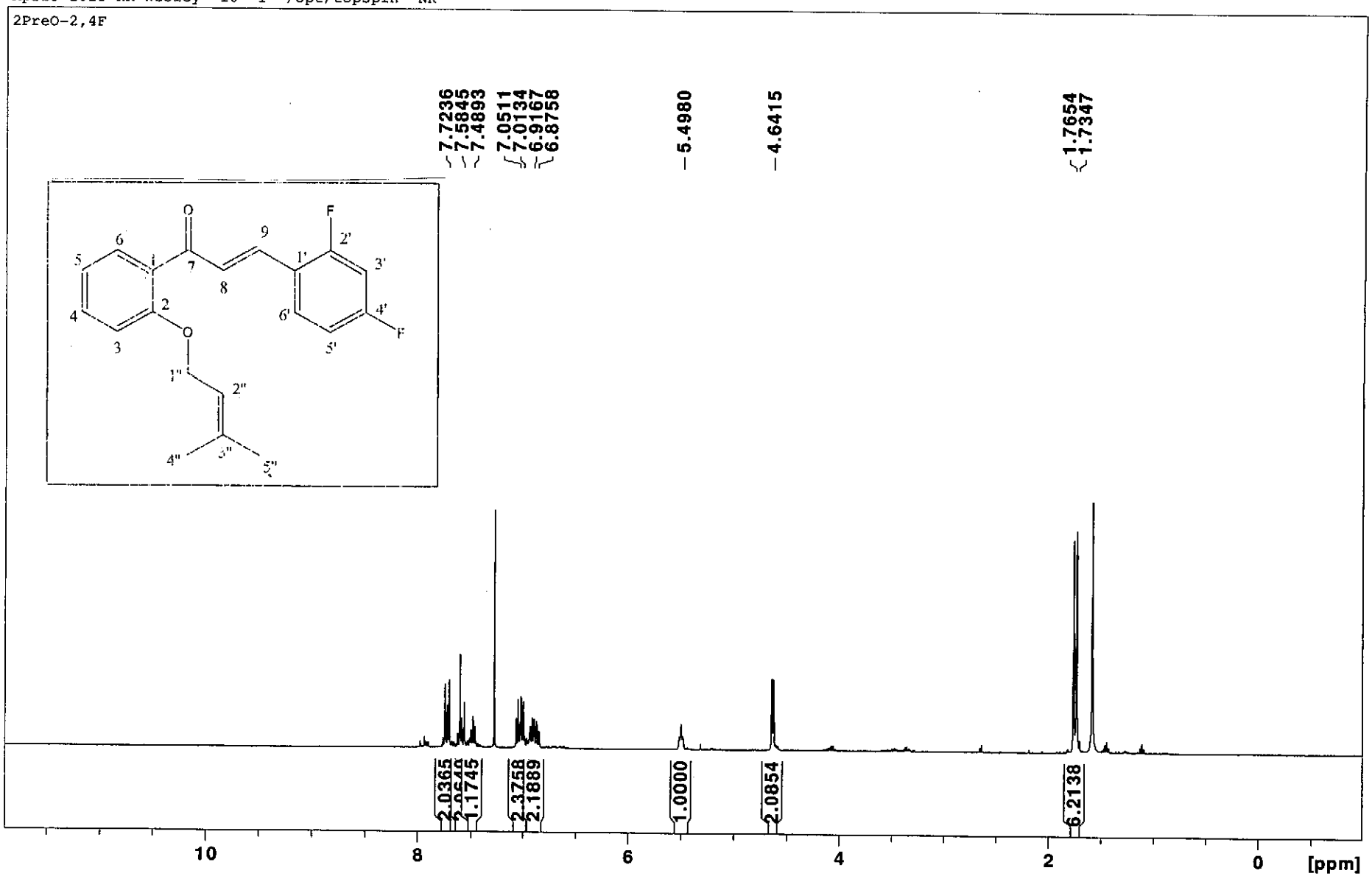
1.41e+004



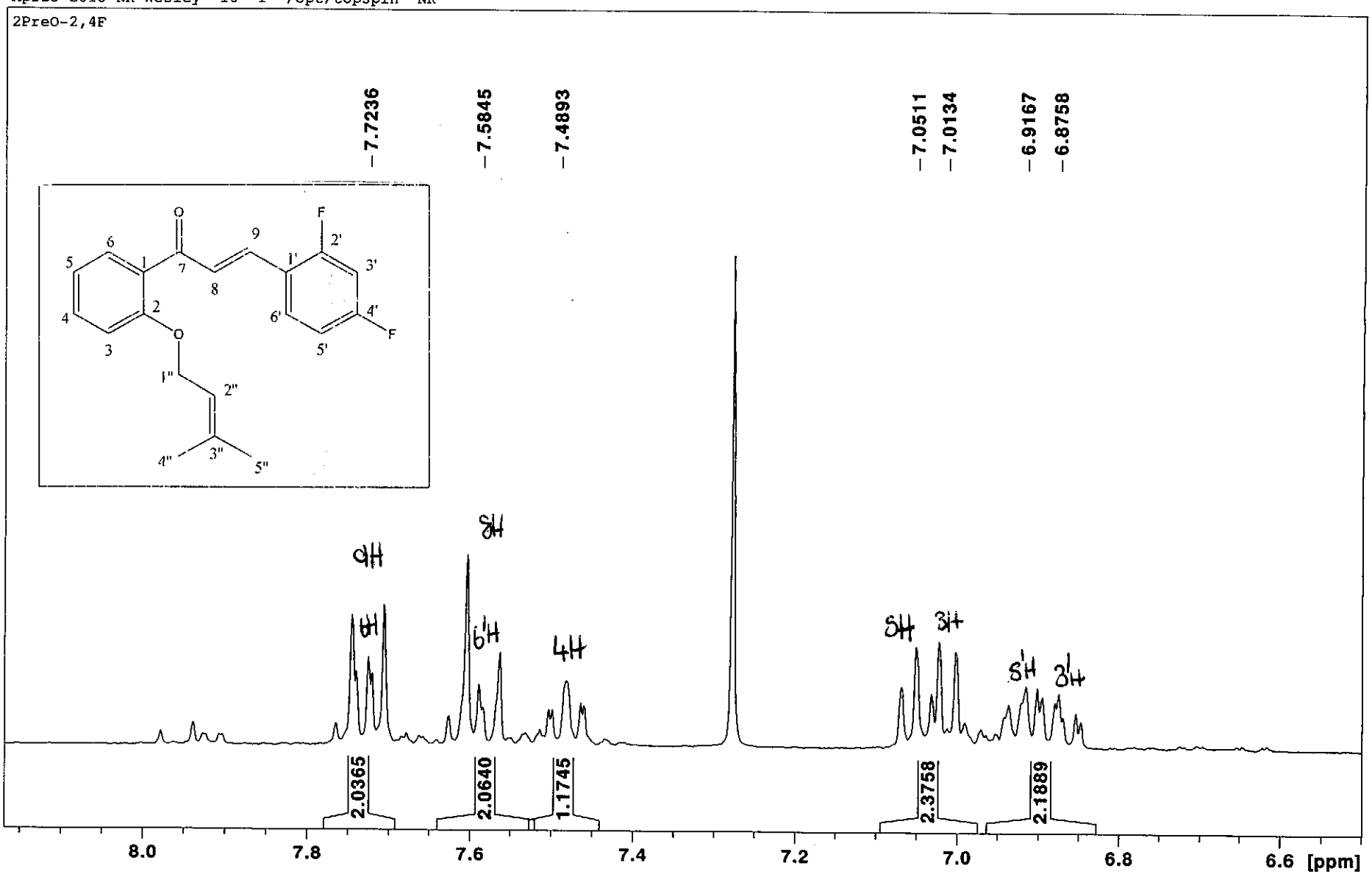
Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
333.1274	333.1267	0.7	2.1	10.5	395.1	0.0	C20 H19 O2 F Na



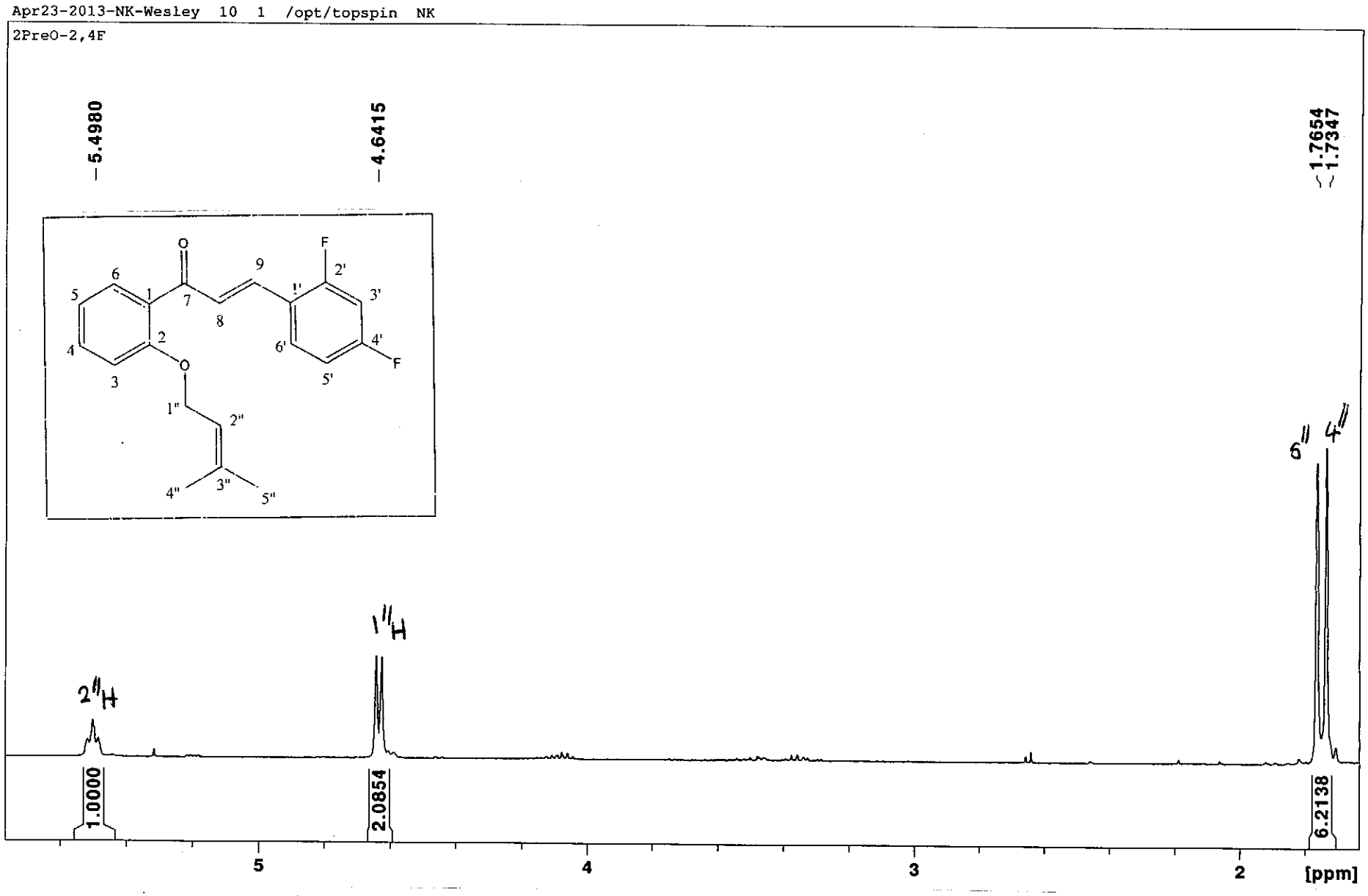
HR-MS spectrum of 4'-fluoro-2-oxyprenylchalcone, (XVI)



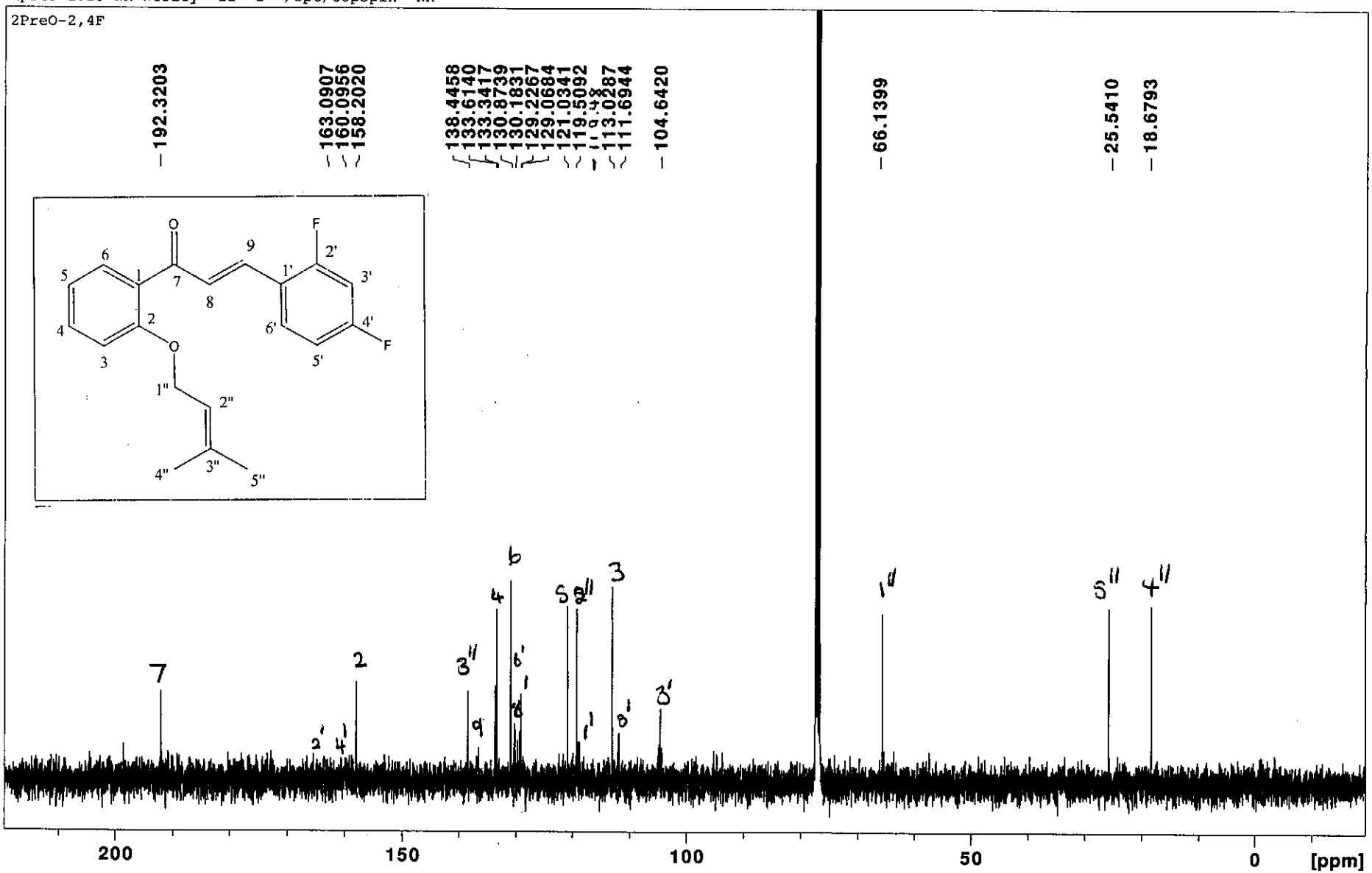
^{1}H NMR spectrum of 2',4'-difluoro-2-oxyprenylchalcone, (XVII)



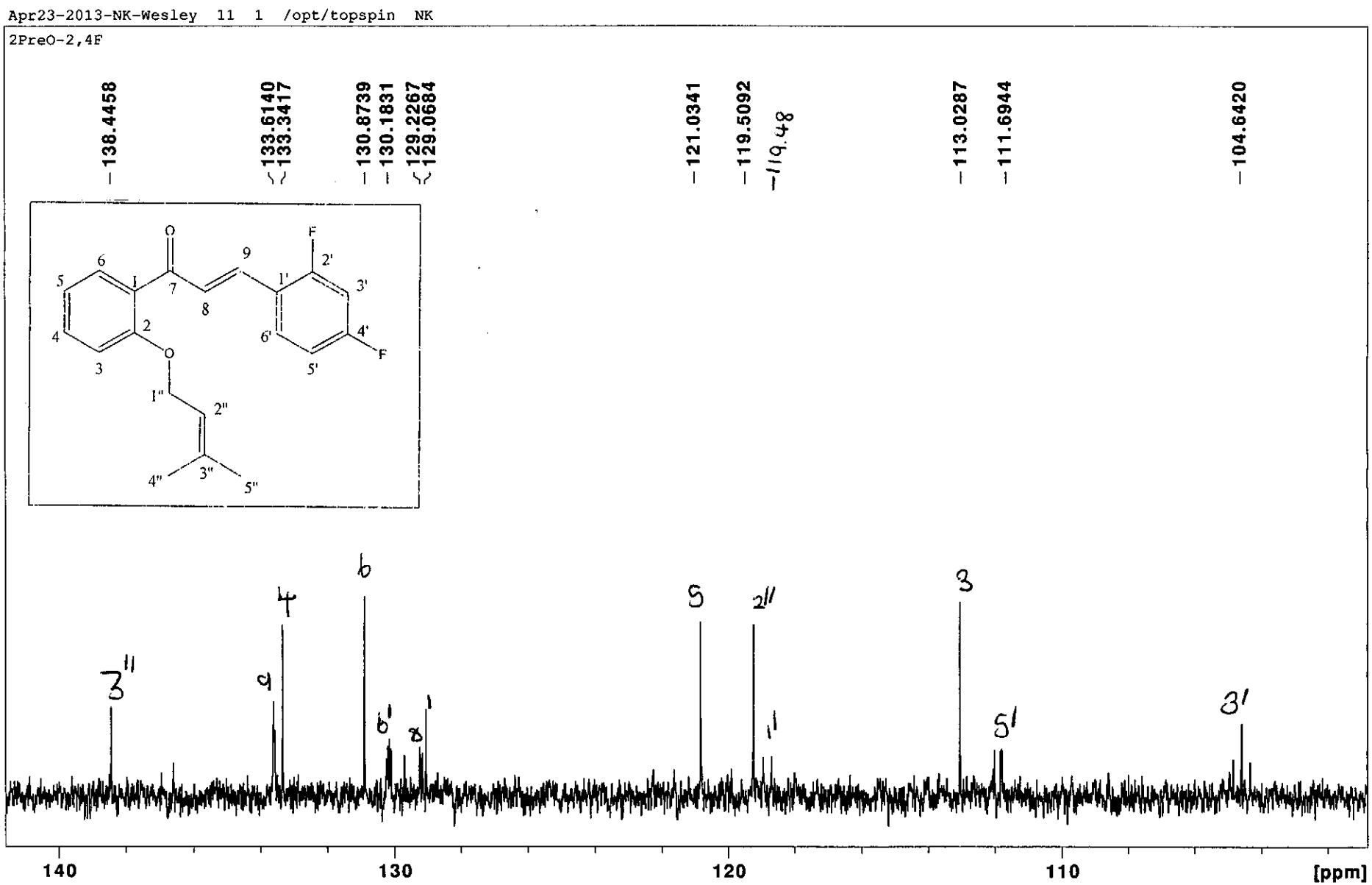
^{1}H NMR spectrum of 2',4'-difluoro-2-oxyprenylchalcone, (XVII)



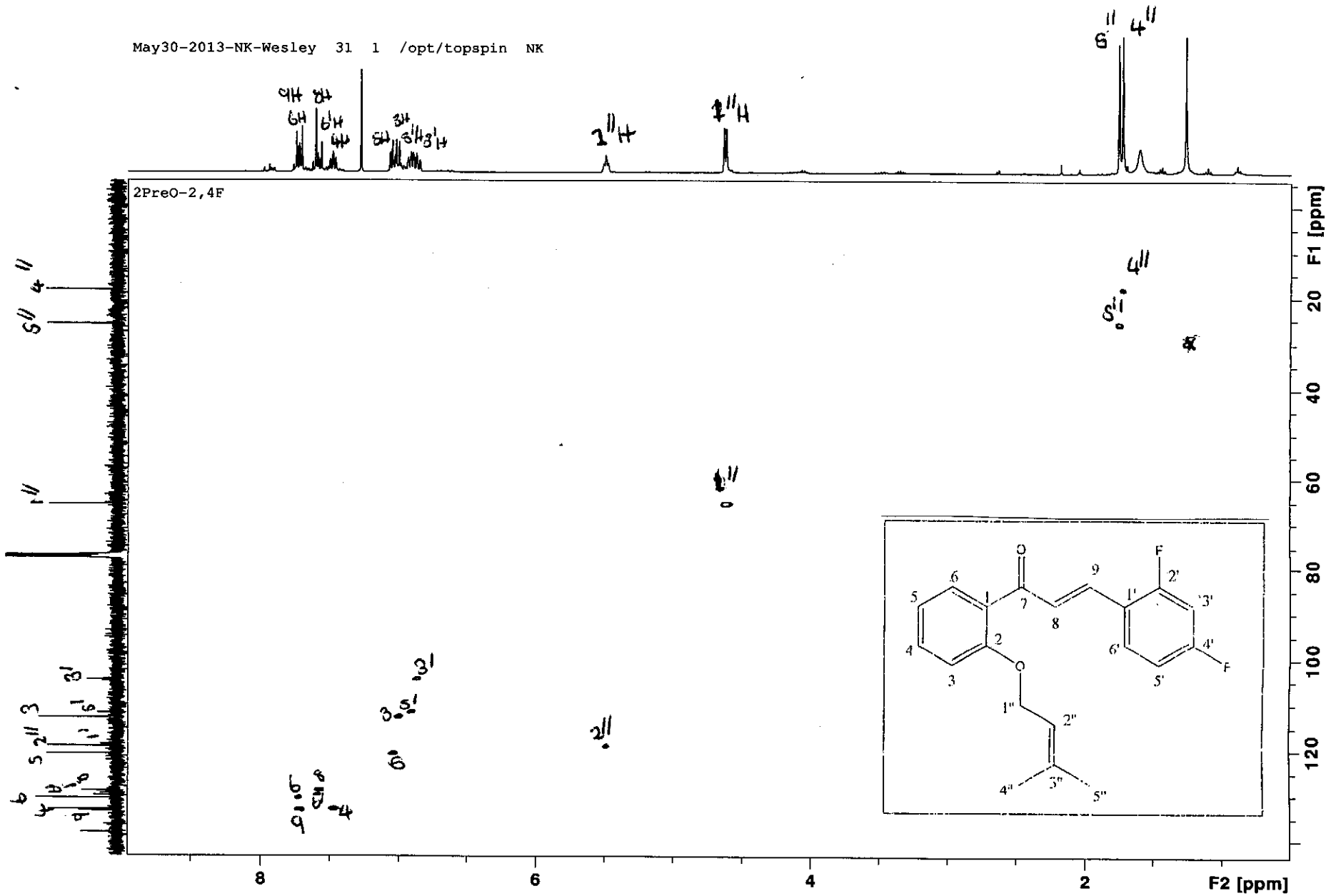
^{1}H NMR spectrum of 2',4'-difluoro-2-oxyprenylchalcone, (XVII)



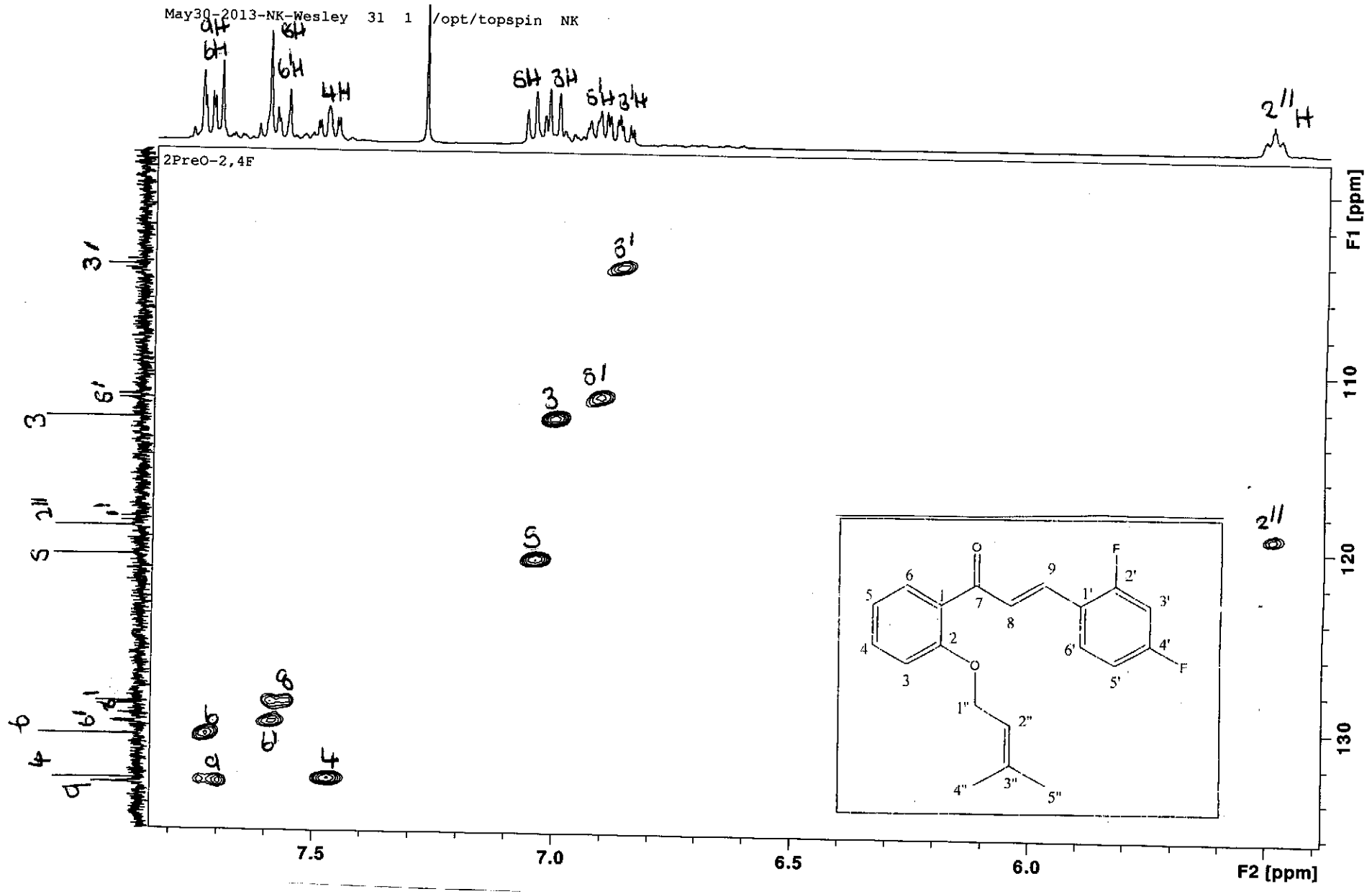
^{13}C NMR spectrum of 2',4'-difluoro-2-oxyprenylchalcone, (XVII)



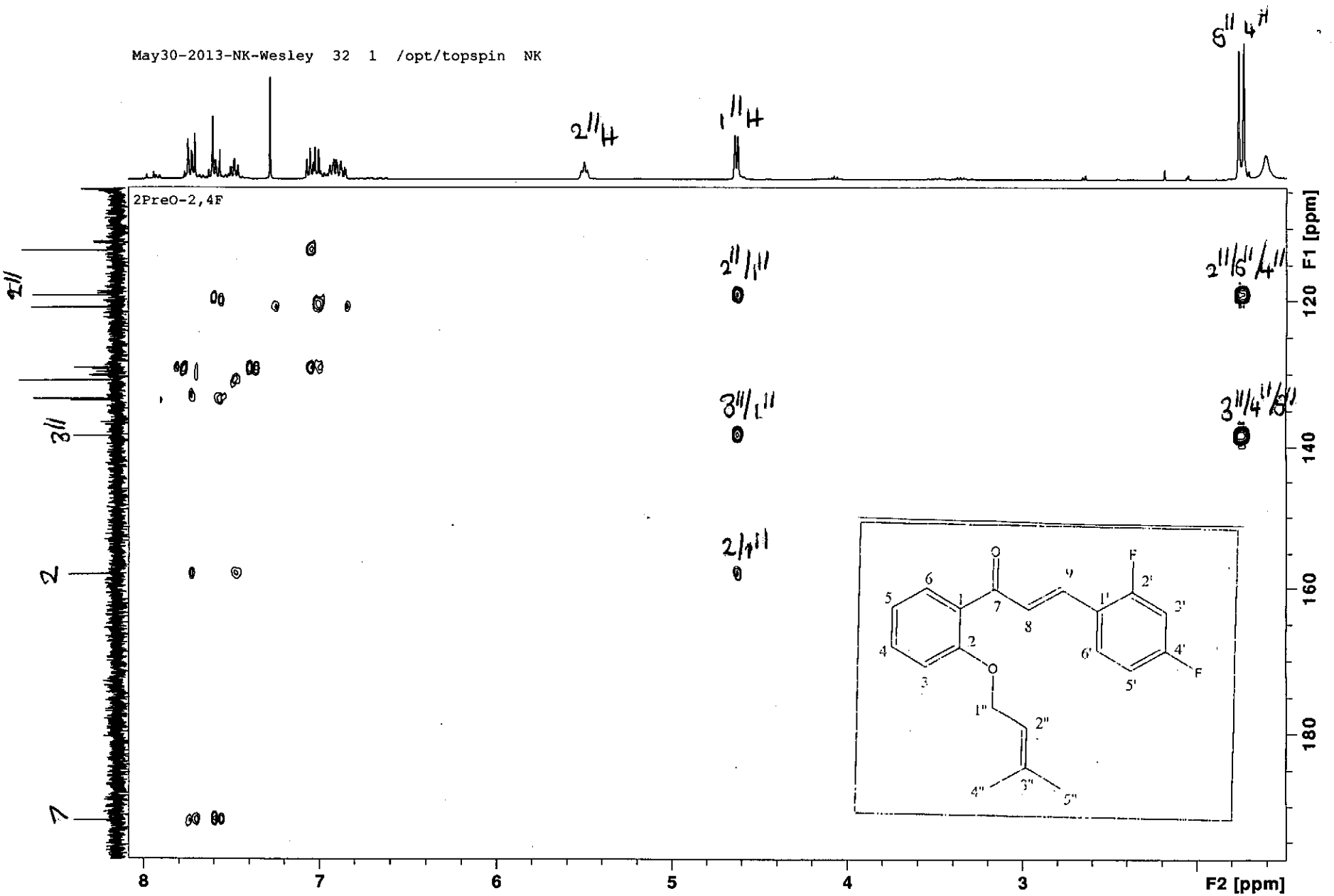
^{13}C NMR spectrum of 2',4'-difluoro-2-oxyprenylchalcone, (XVII)



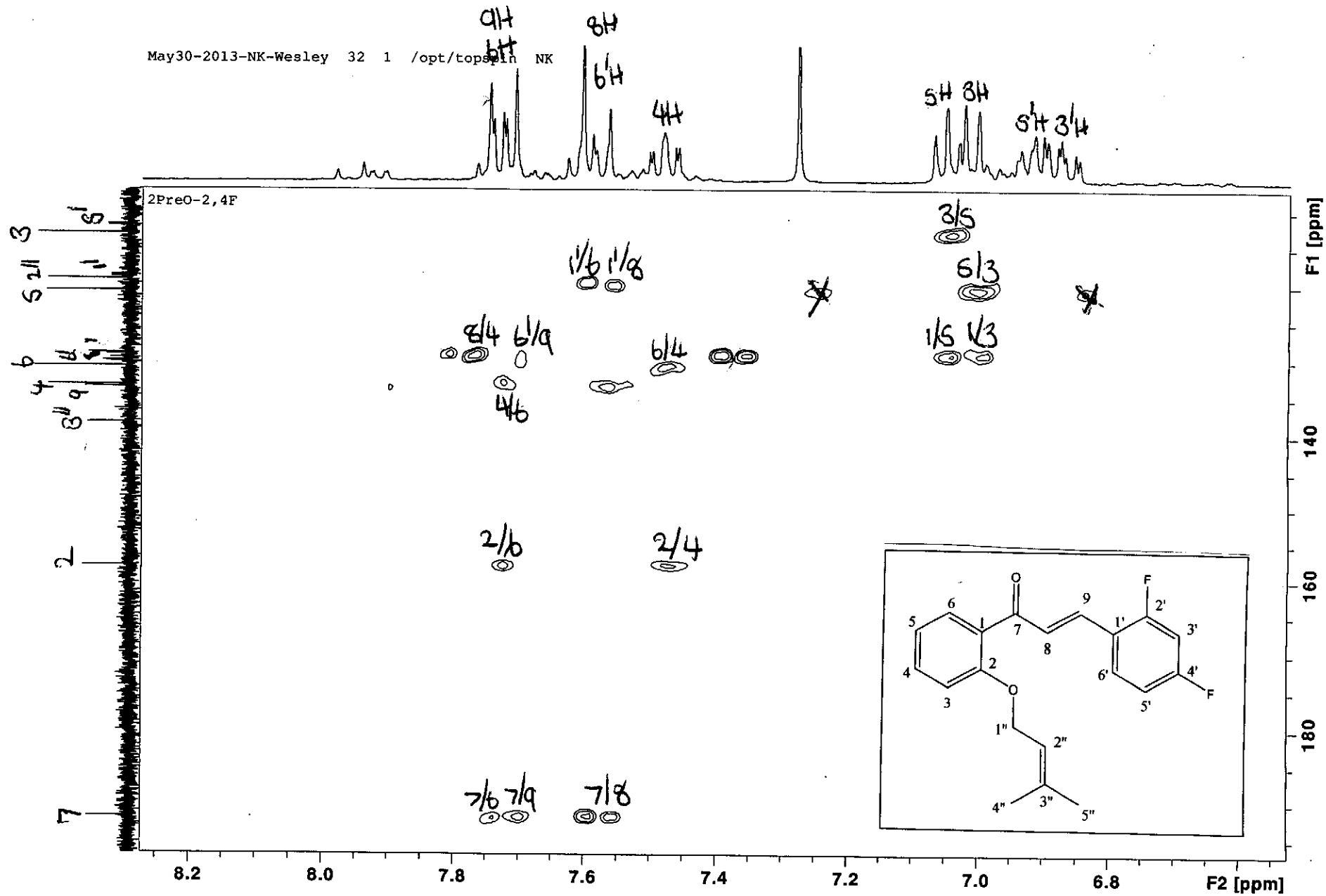
HSQC spectrum of 2',4'-difluoro-2-oxyprenylchalcone, (XVII)



HSQC spectrum of 2',4'-difluoro-2-oxyprenylchalcone, (XVII)



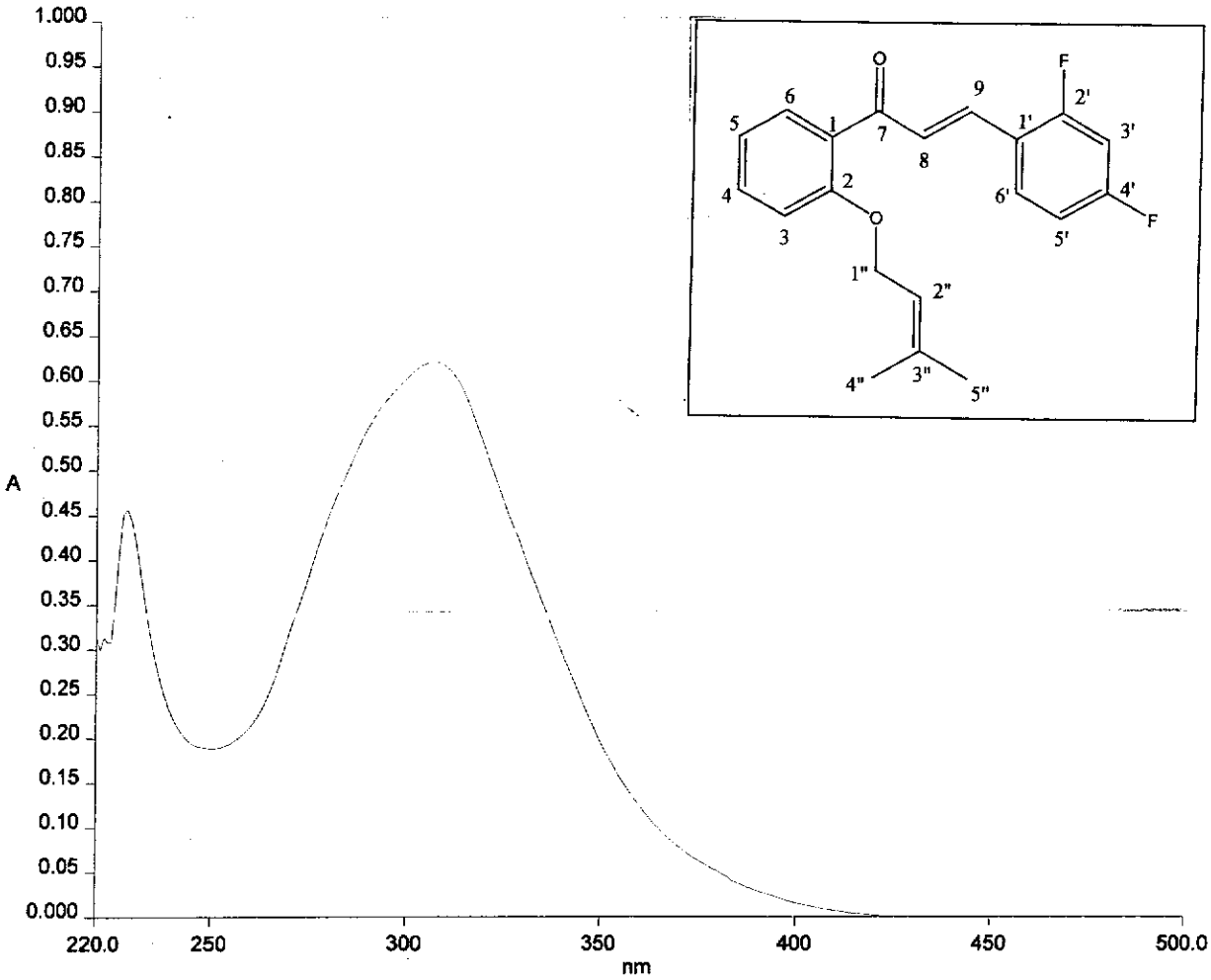
HMBC spectrum of 2',4'-difluoro-2-oxyprenylchalcone, (XVII)



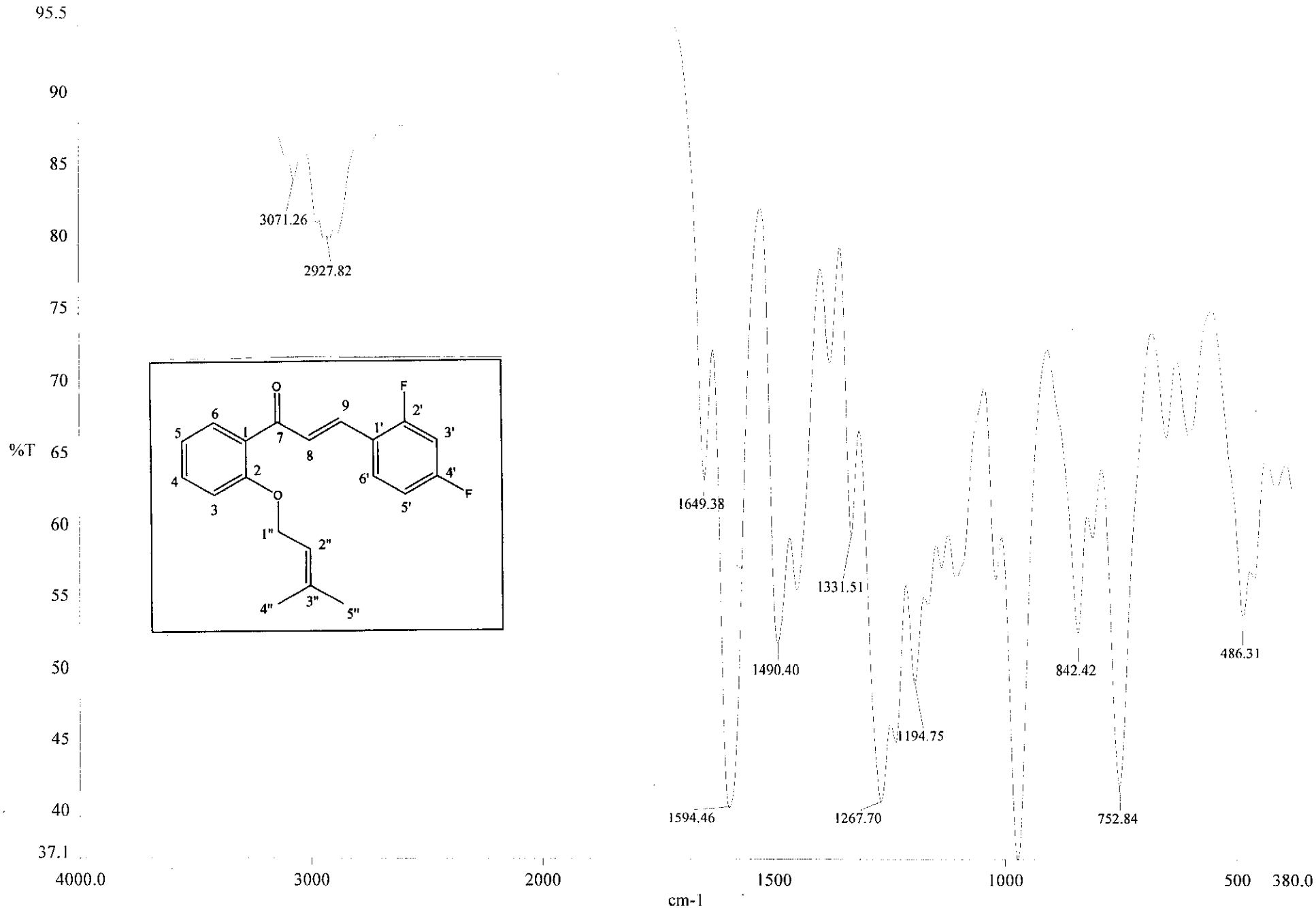
HMBC spectrum of 2',4'-difluoro-2-oxyprenylchalcone, (XVII)

λmax(226) - 0.456
λmax(307nm) - 0.6202

Date: 2013/06/04 Time: 01:27:51 PM

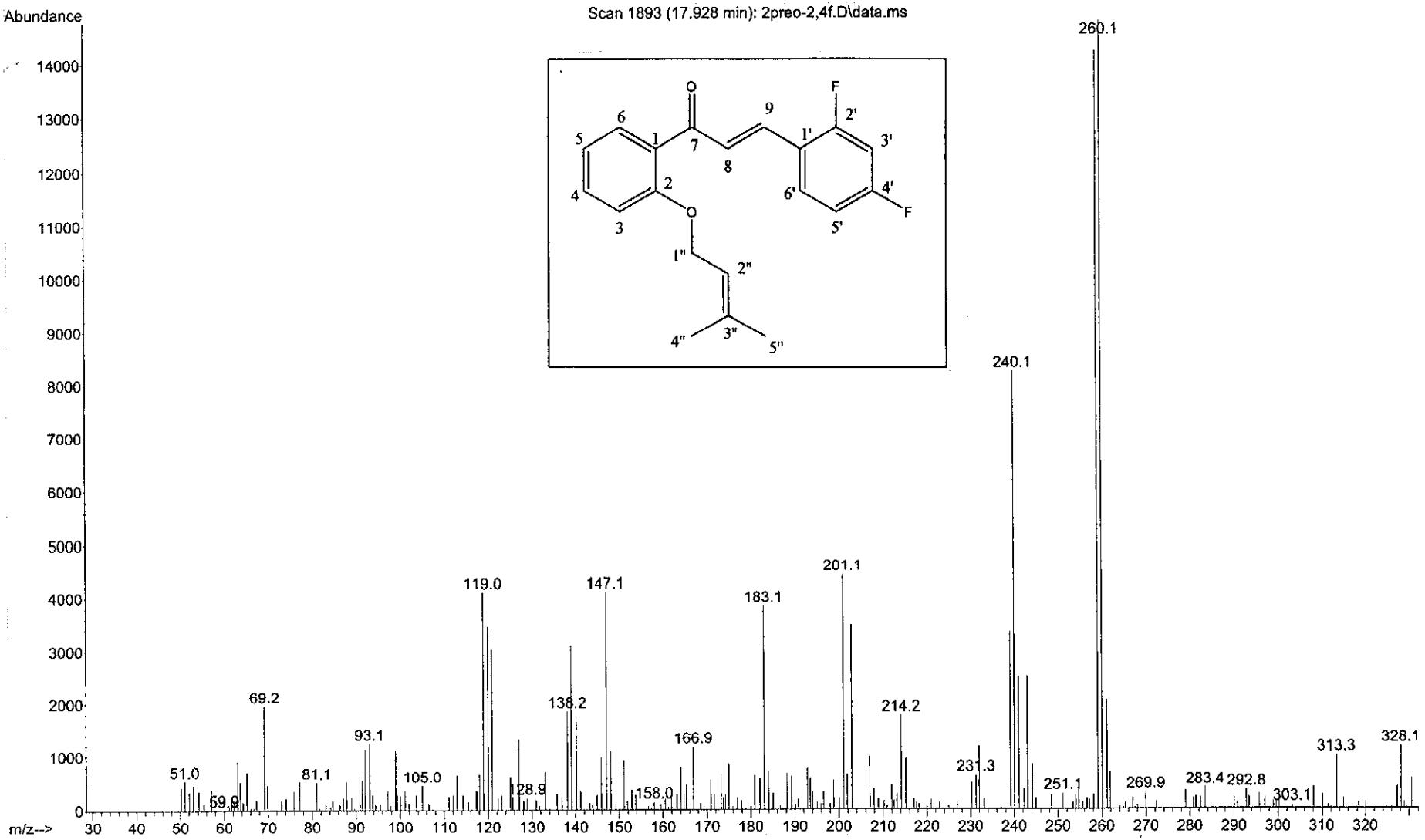


Ultra violet (UV) spectrum 2', 4'-difluoro-2-oxyprenylchalcone, (XVII)



Infra-Red (IR) spectrum of 2',4'-difluoro-2-oxyprenylchalcone, (XVII)

File :C:\msdchem\1\methods\NATPRODUCTS AUTOMATED splitless.M\2preo
... -2,4f.D
Operator : neal
Instrument : 5973n
Acquired : 5 Jul 2013 22:56 using AcqMethod NATPRODUCTS AUTOMATED SPLITLESS.M
Sample Name: 2preo-2,4f
Misc Info :



GC-MS spectrum of 2',4'-difluoro-2-oxyprenylchalcone, (XVII)

Elemental Composition Report

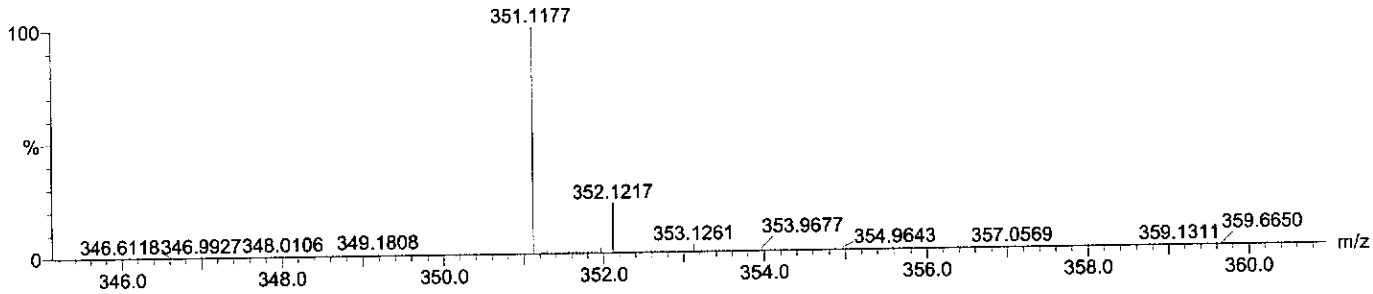
Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

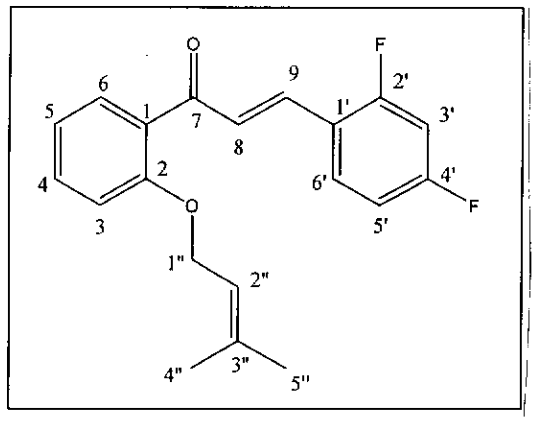
Monoisotopic Mass, Even Electron Ions
15 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 15-20 H: 15-20 O: 0-5 F: 0-2 Na: 0-1

2PreO-24F 2 (0.017) Cm (1:15)
TOF MS ES+

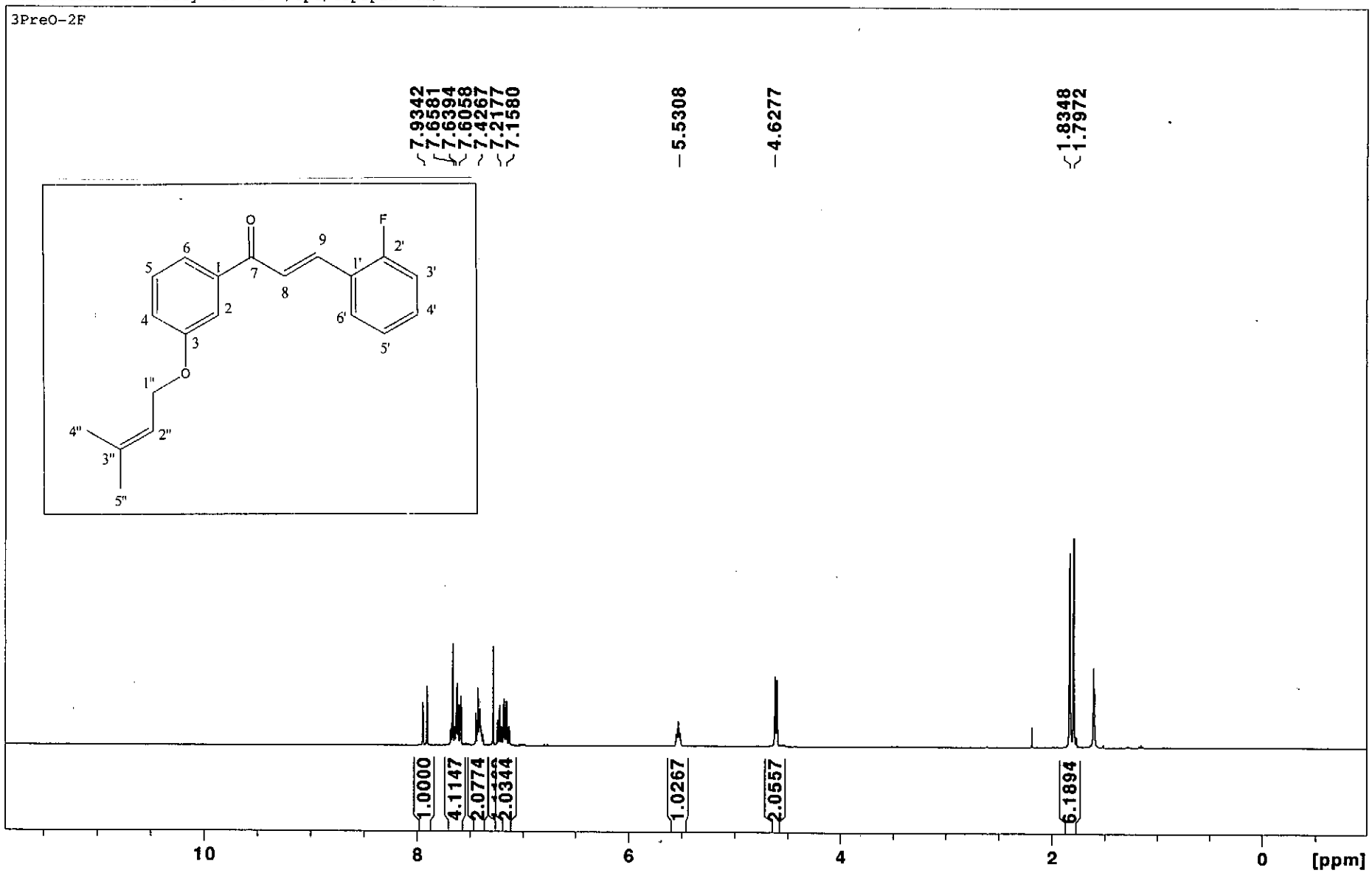
2.47e+004



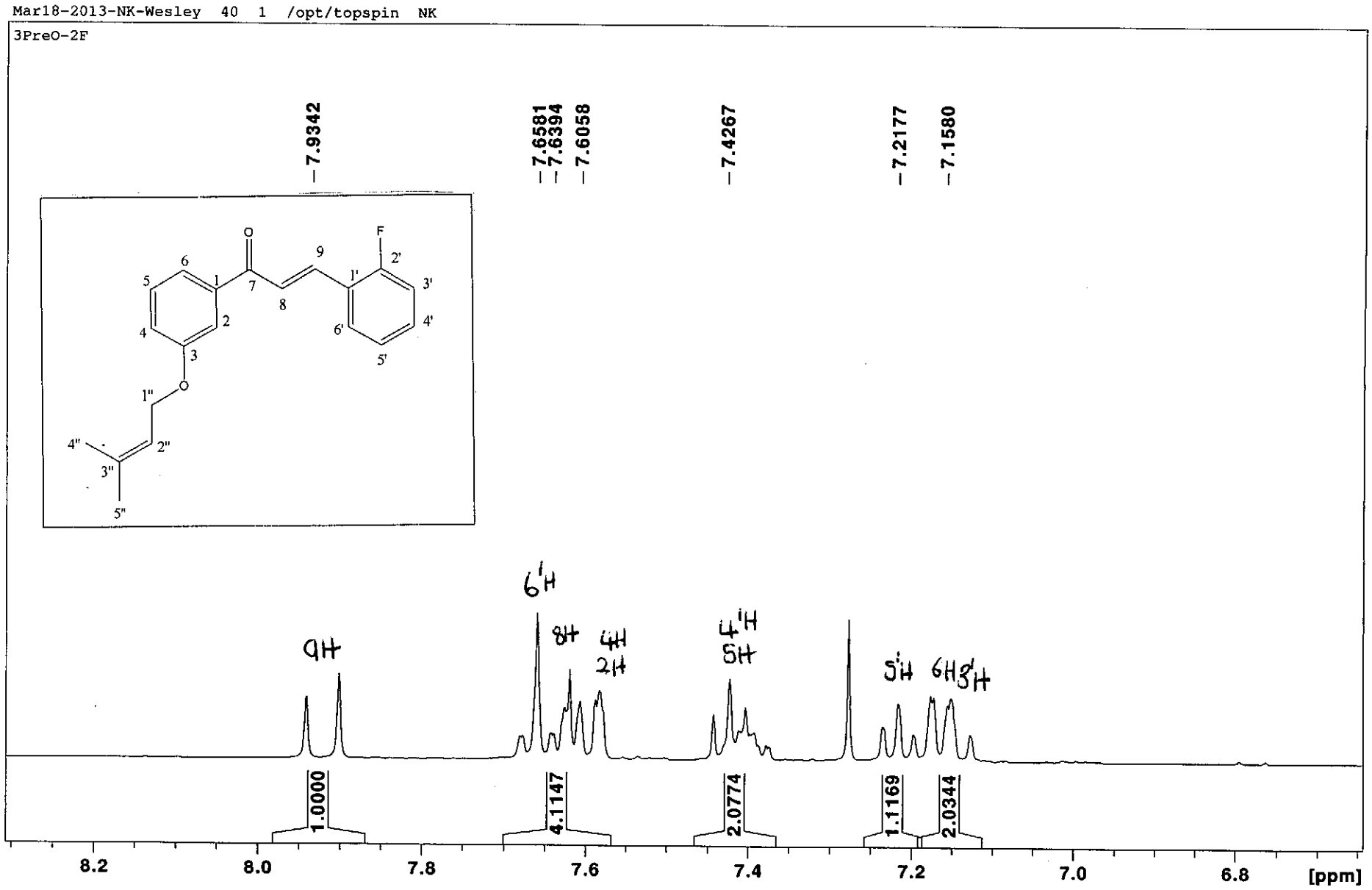
Minimum:		5.0	5.0	-1.5			
Maximum:				100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
351.1177	351.1173	0.4	1.1	10.5	438.4	0.0	C20 H18 O2 F2 Na



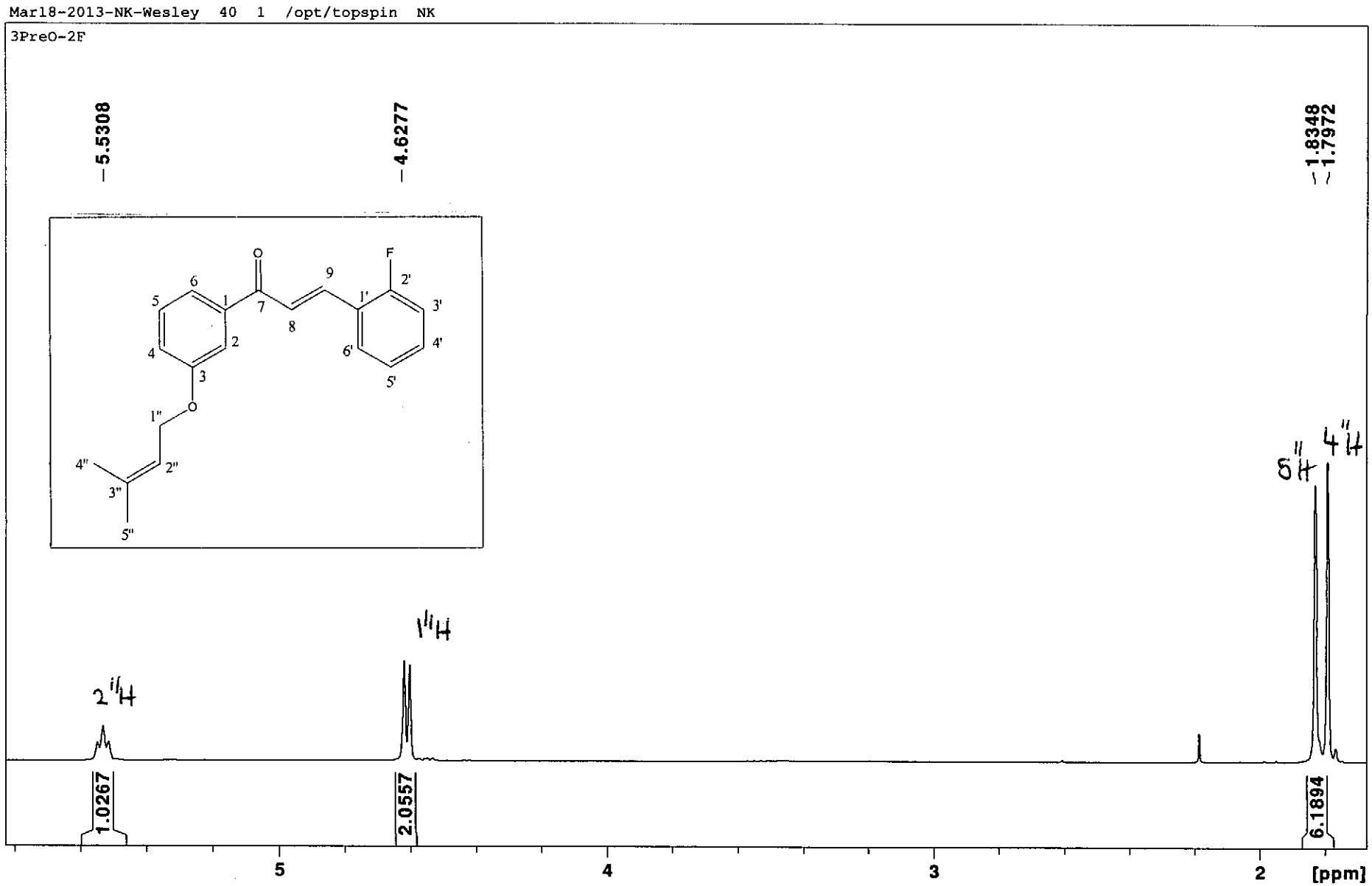
HR-MS spectrum of 2',4'-difluoro-2-oxyprenylchalcone, (XVII)



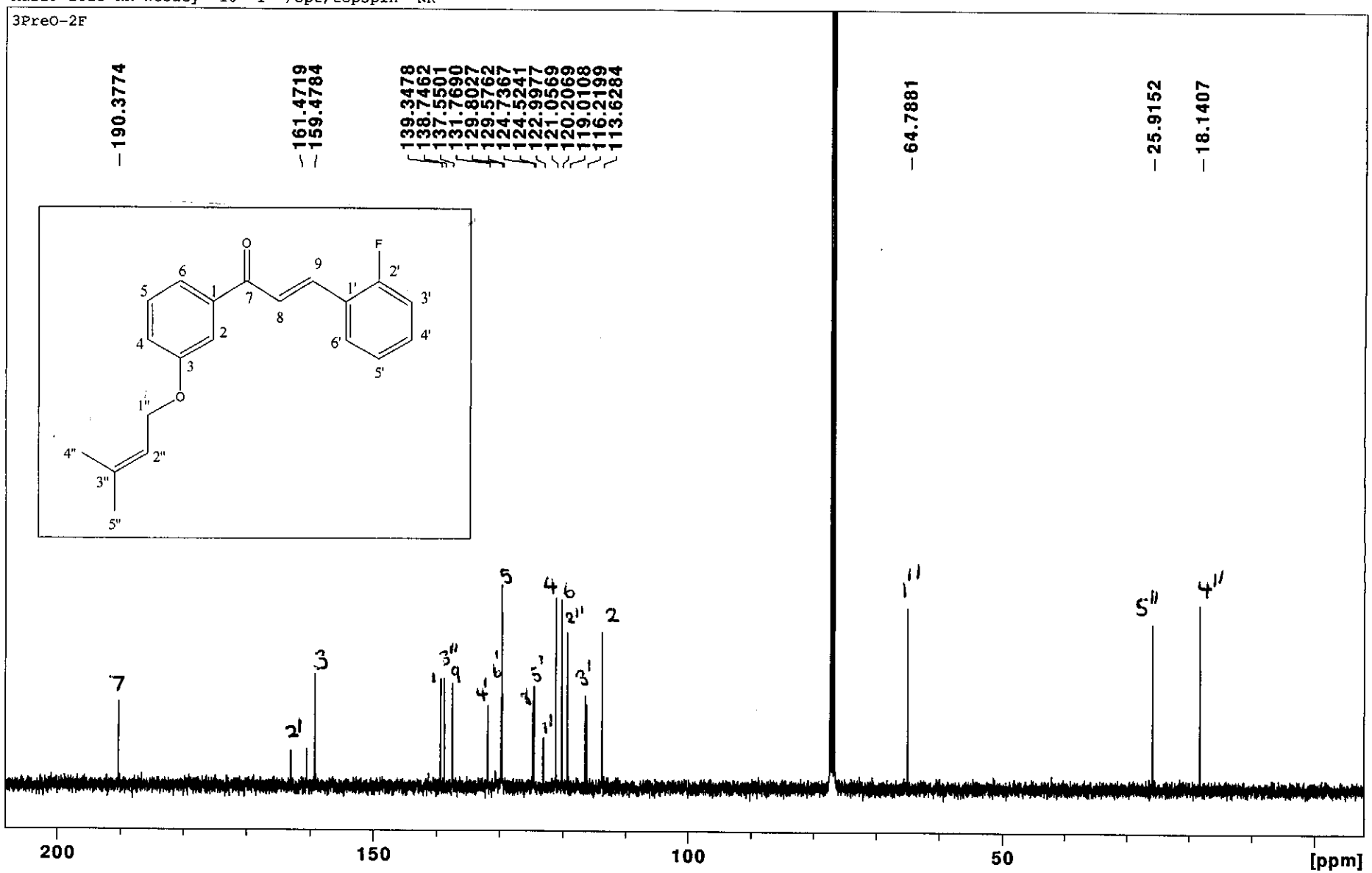
^{1}H NMR spectrum of 2'-fluoro-3-oxyprenylchalcone, (XVIII)



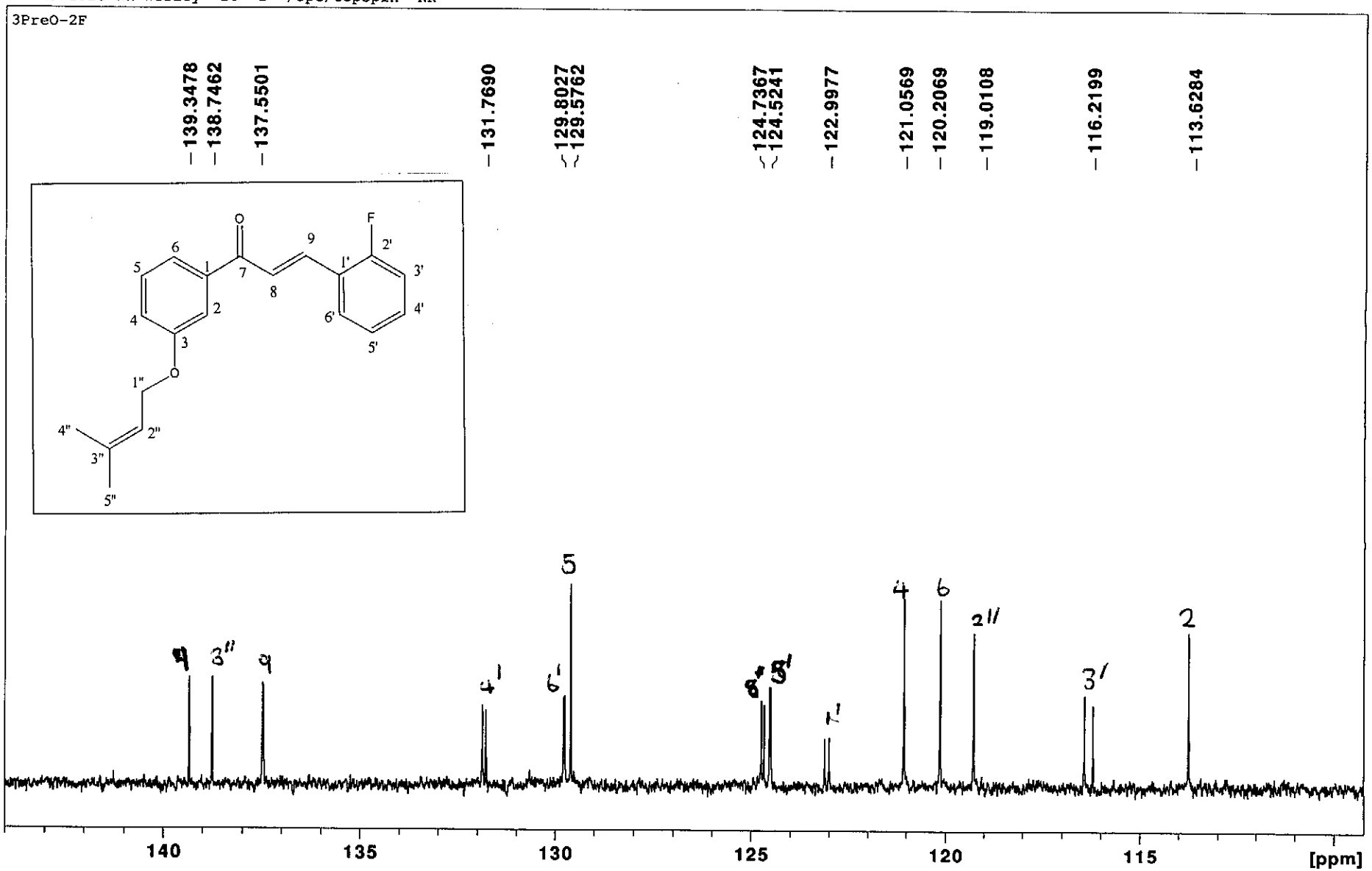
^{1}H NMR spectrum of 2'-fluoro-3-oxyprenylchalcone, (XVIII)



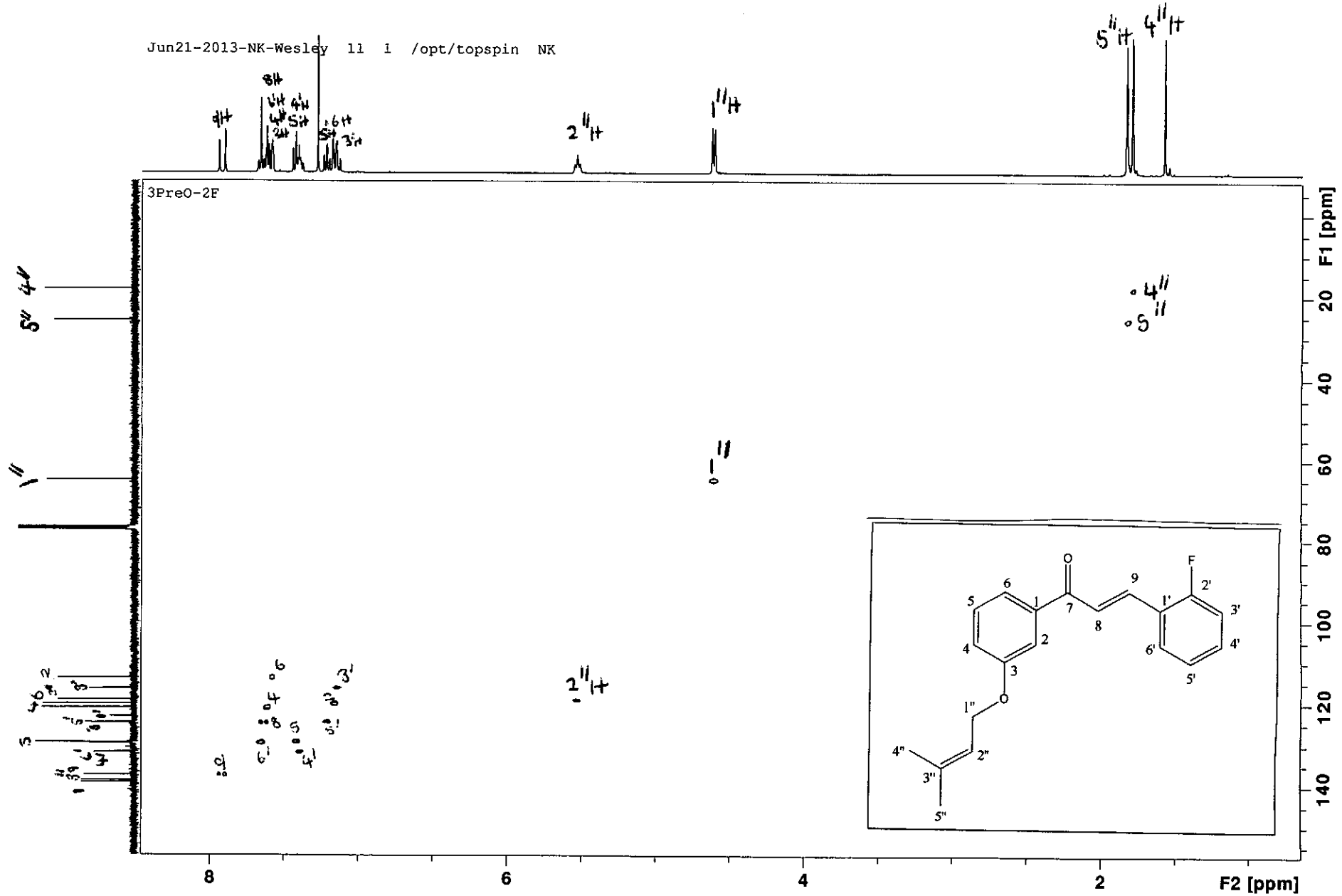
^{1}H NMR spectrum of 2'-fluoro-3-oxyprenylchalcone, (XVIII)



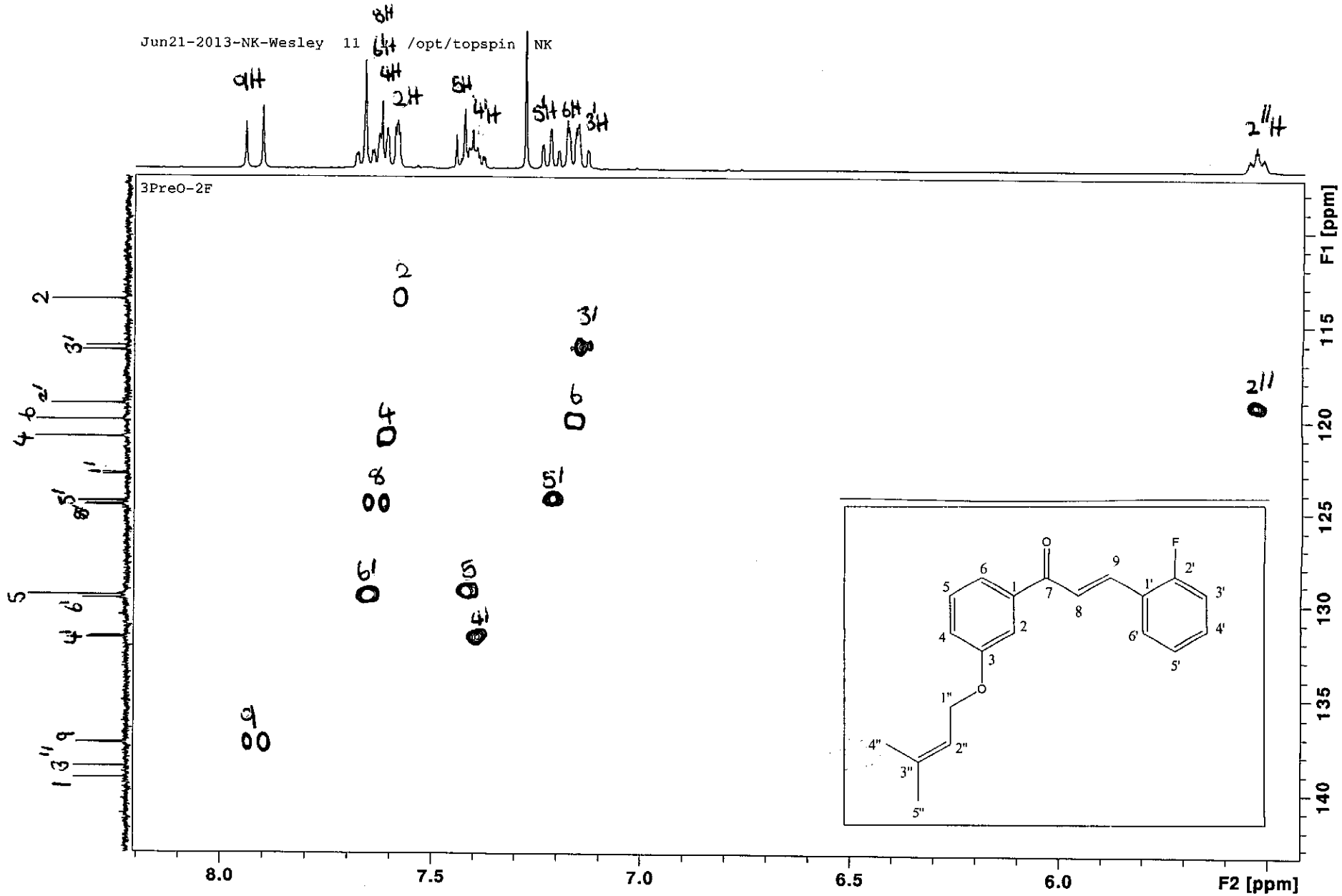
^{13}C NMR spectrum of 2'-fluoro-3-oxyprenylchalcone, (XVIII)



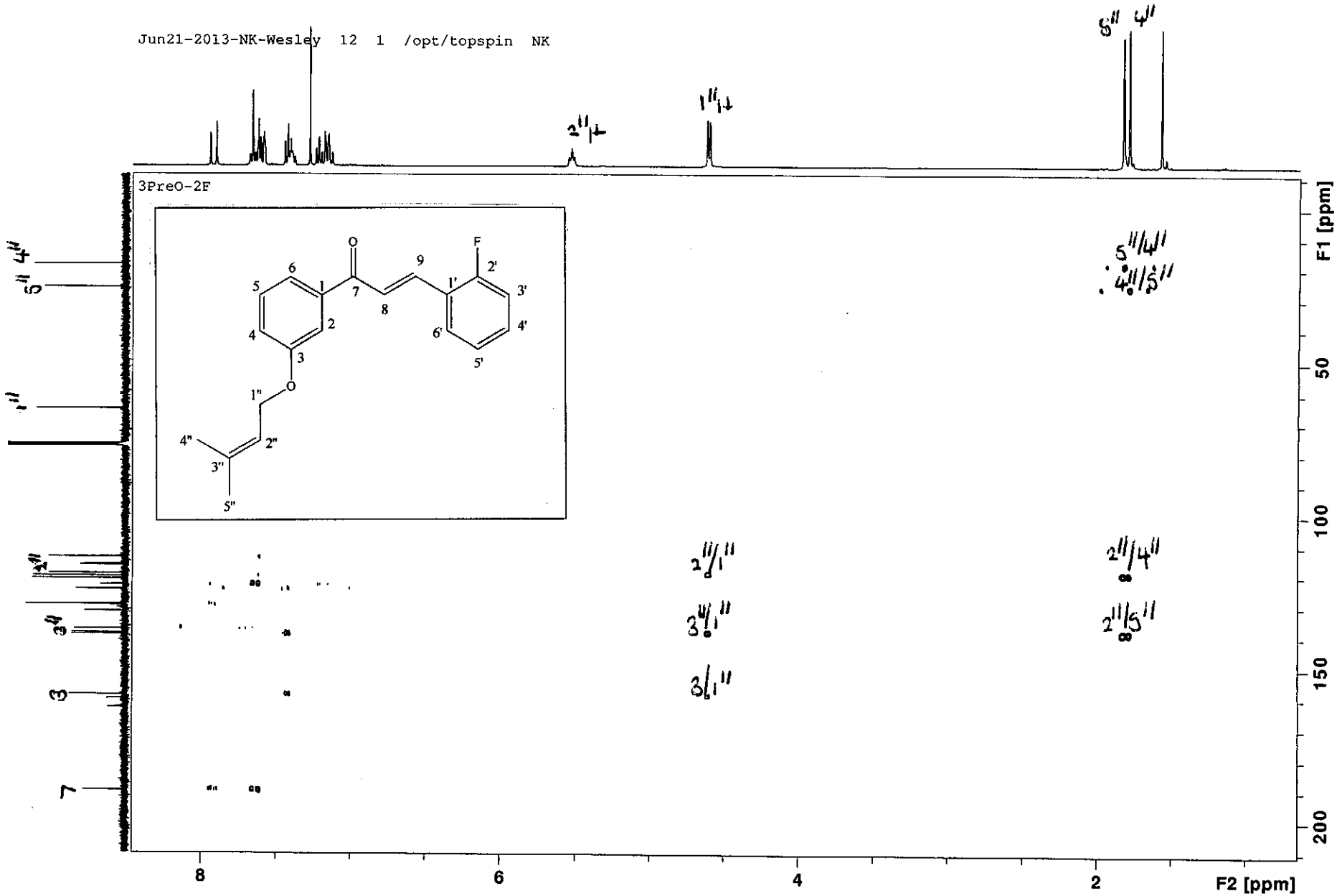
^{13}C NMR spectrum of 2'-fluoro-3-oxyprenylchalcone, (XVIII)



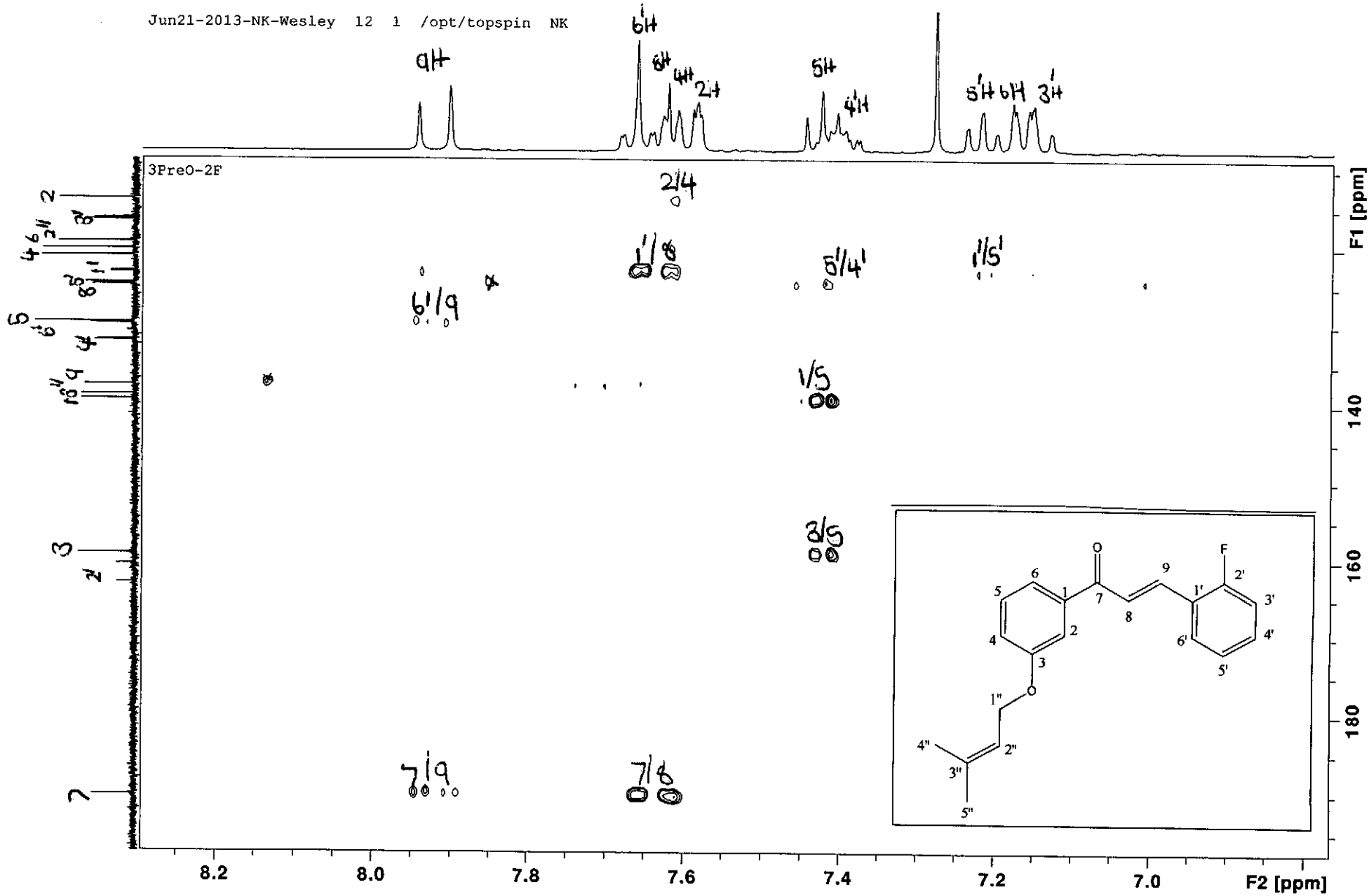
HSQC spectrum of 2'-fluoro-3-oxyprenylchalcone, (XVIII)



HSQC spectrum of 2'-fluoro-3-oxyprenylchalcone, (XVIII)



HMBC spectrum of 2'-fluoro-3-oxyprenylchalcone, (XVIII)

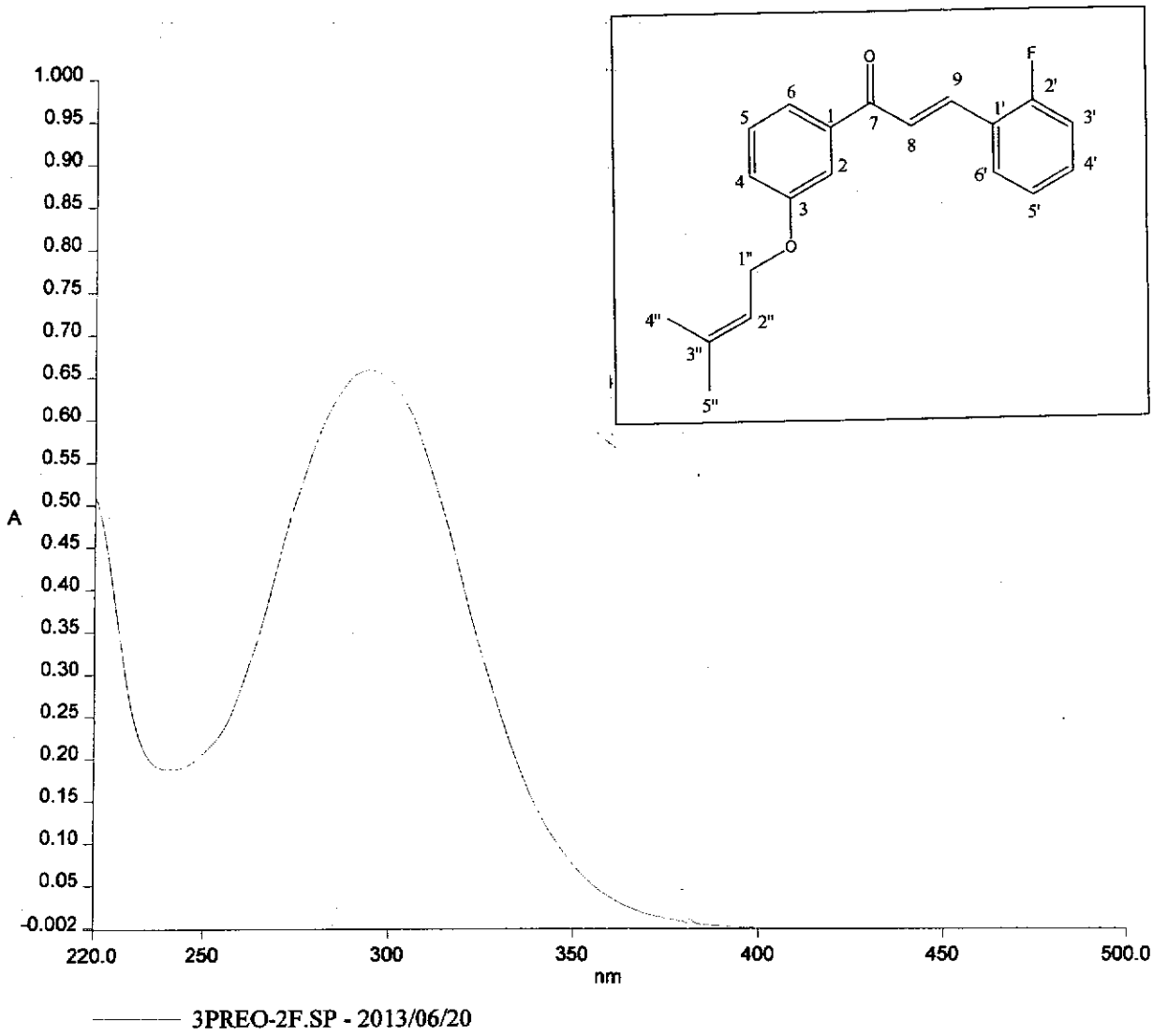


HMBC spectrum of 2'-fluoro-3-oxyprenylchalcone, (XVIII)

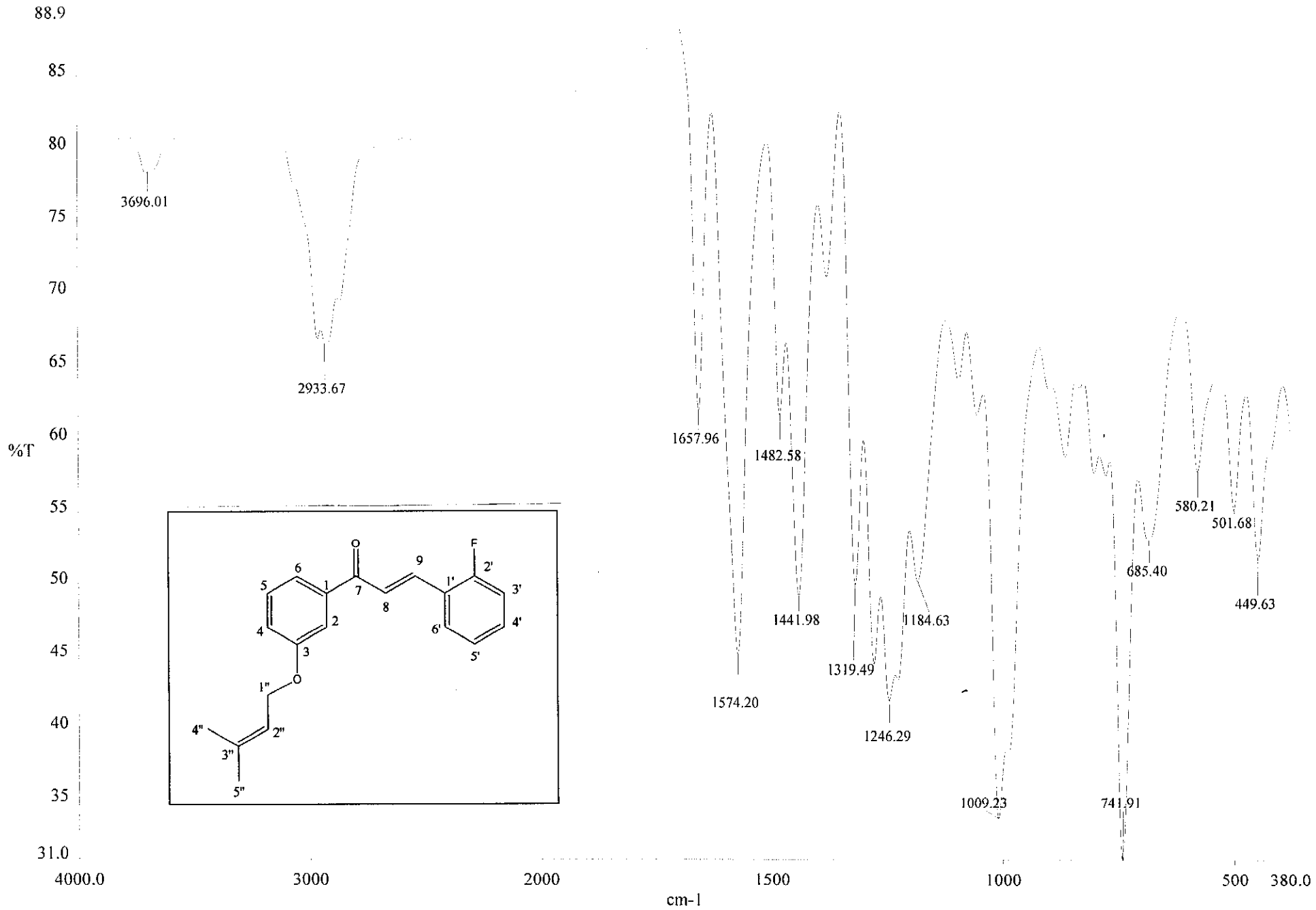
λmax(294nm) = 0.6561

log ε = 6.52

Date: 2013/06/20 Time: 11:02:32 AM



Ultra violet (UV) spectrum of 2'-fluoro-3-oxyprenylchalcone, (XVIII)



Infra-Red (IR) spectrum of 2'-fluoro-3-oxyprenylchalcone, (XVIII)

```
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Instrument :   5973n
Sample Name: 3preo-2f
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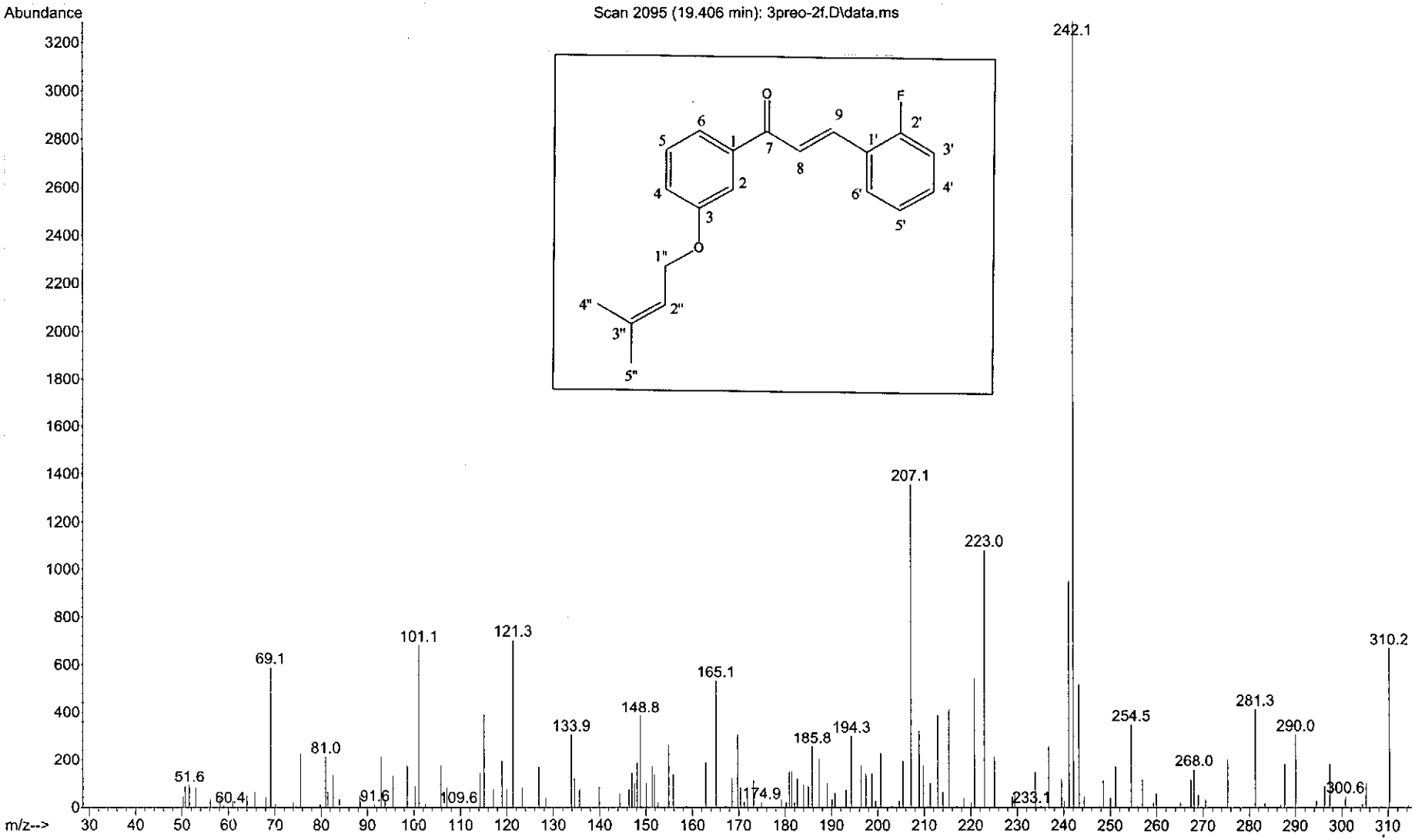


GC-MS spectrum of 2'-fluoro-3-oxyprenylchalcone, (XVIII)

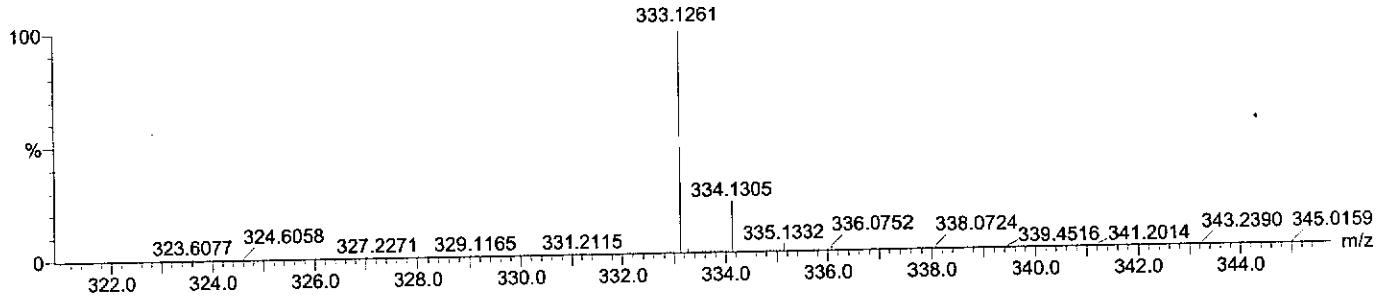
Elemental Composition Report

Single Mass Analysis

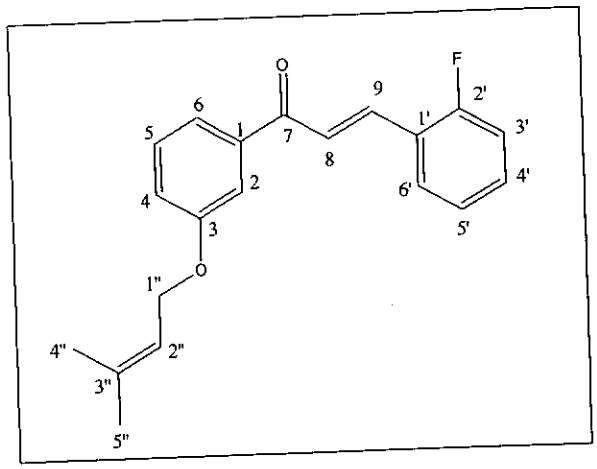
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
14 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 15-20 H: 15-20 O: 0-5 F: 0-2 Na: 0-1

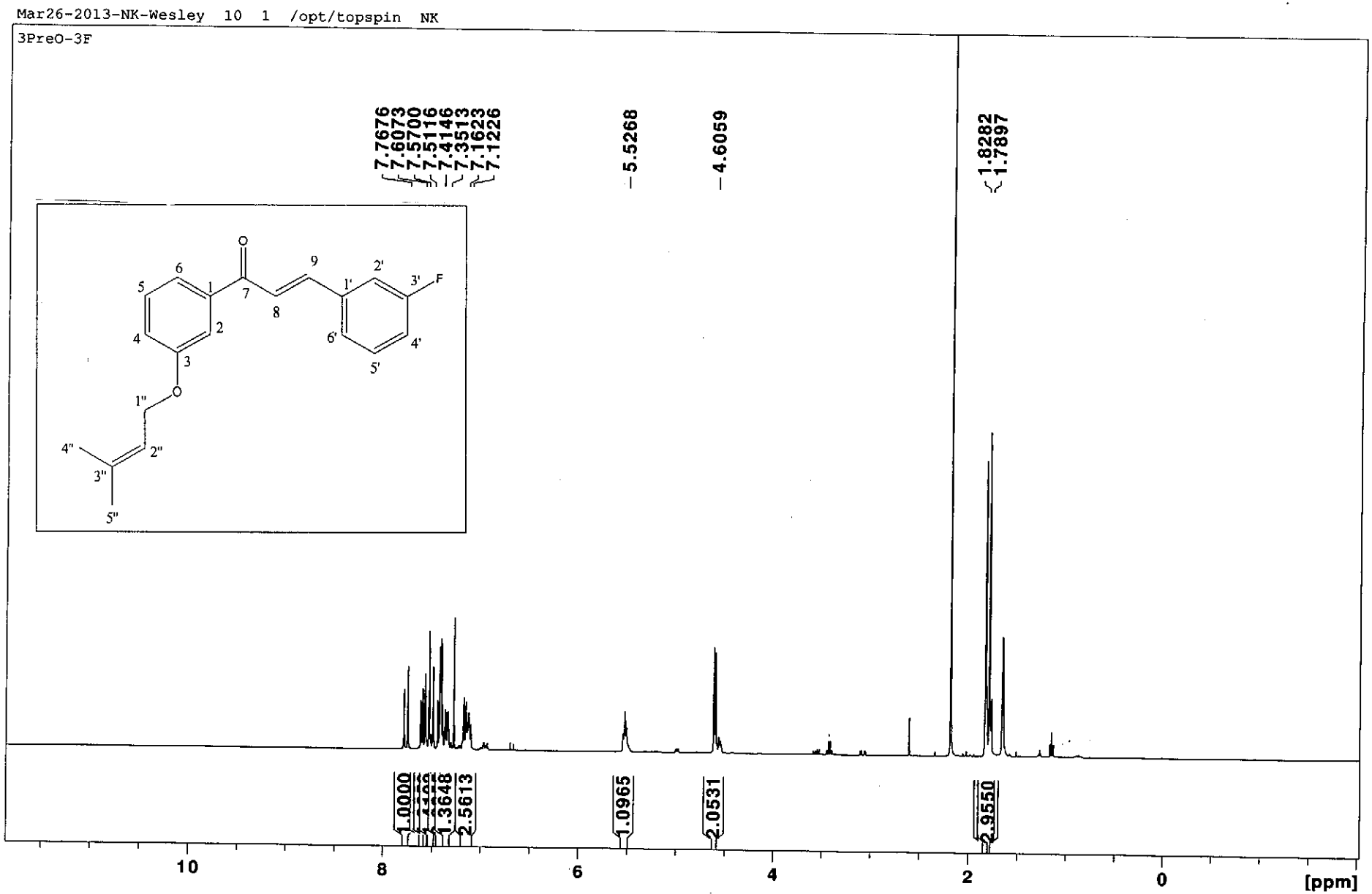
3PreO-2F 15 (0.239) Cm (1:15)
TOF MS ES+ 2.76e+004



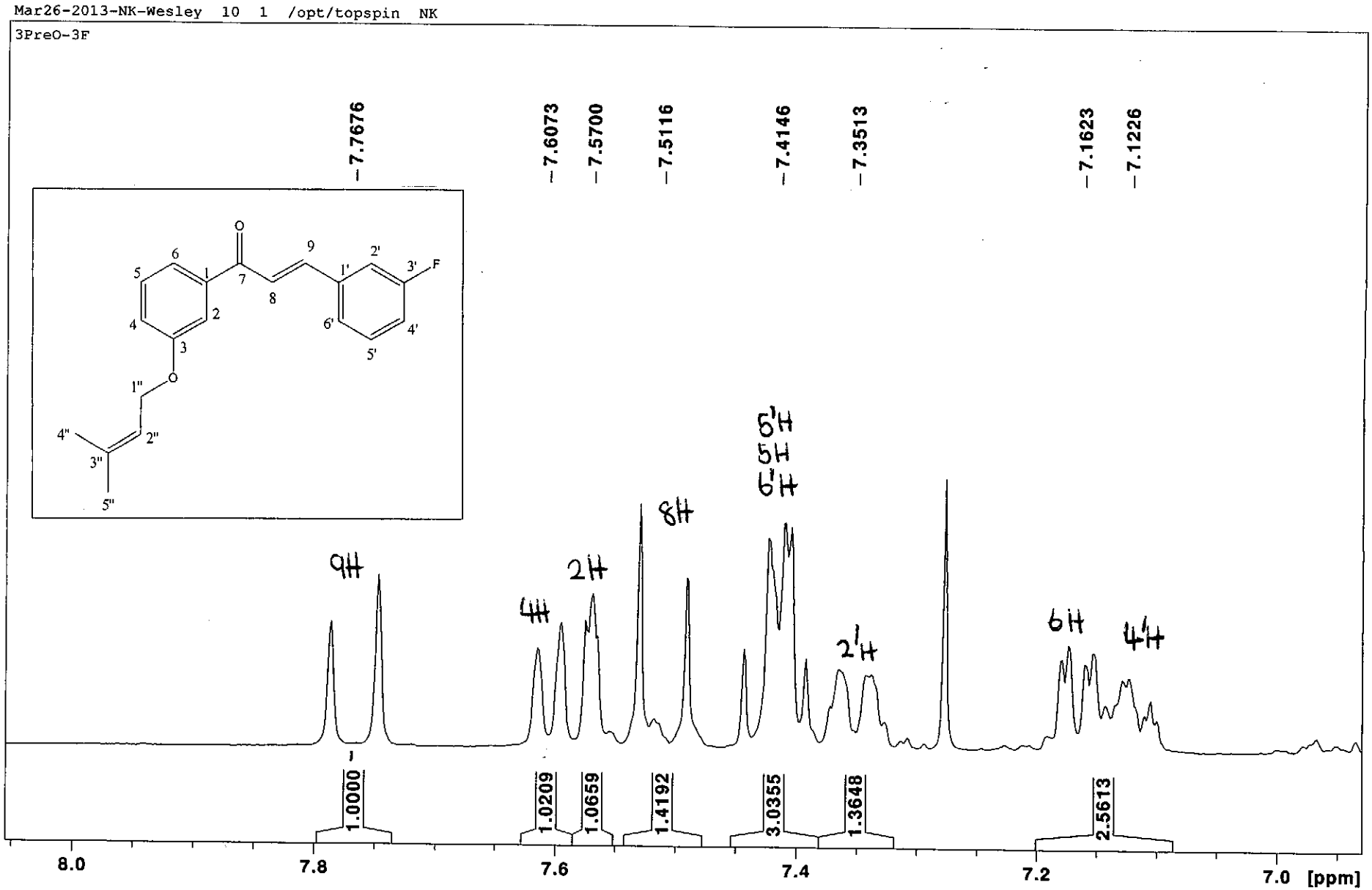
Minimum:		5.0	5.0	-1.5			
Maximum:				100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
333.1261	333.1267	-0.6	-1.8	10.5	442.3	0.0	C20 H19 O2 F Na



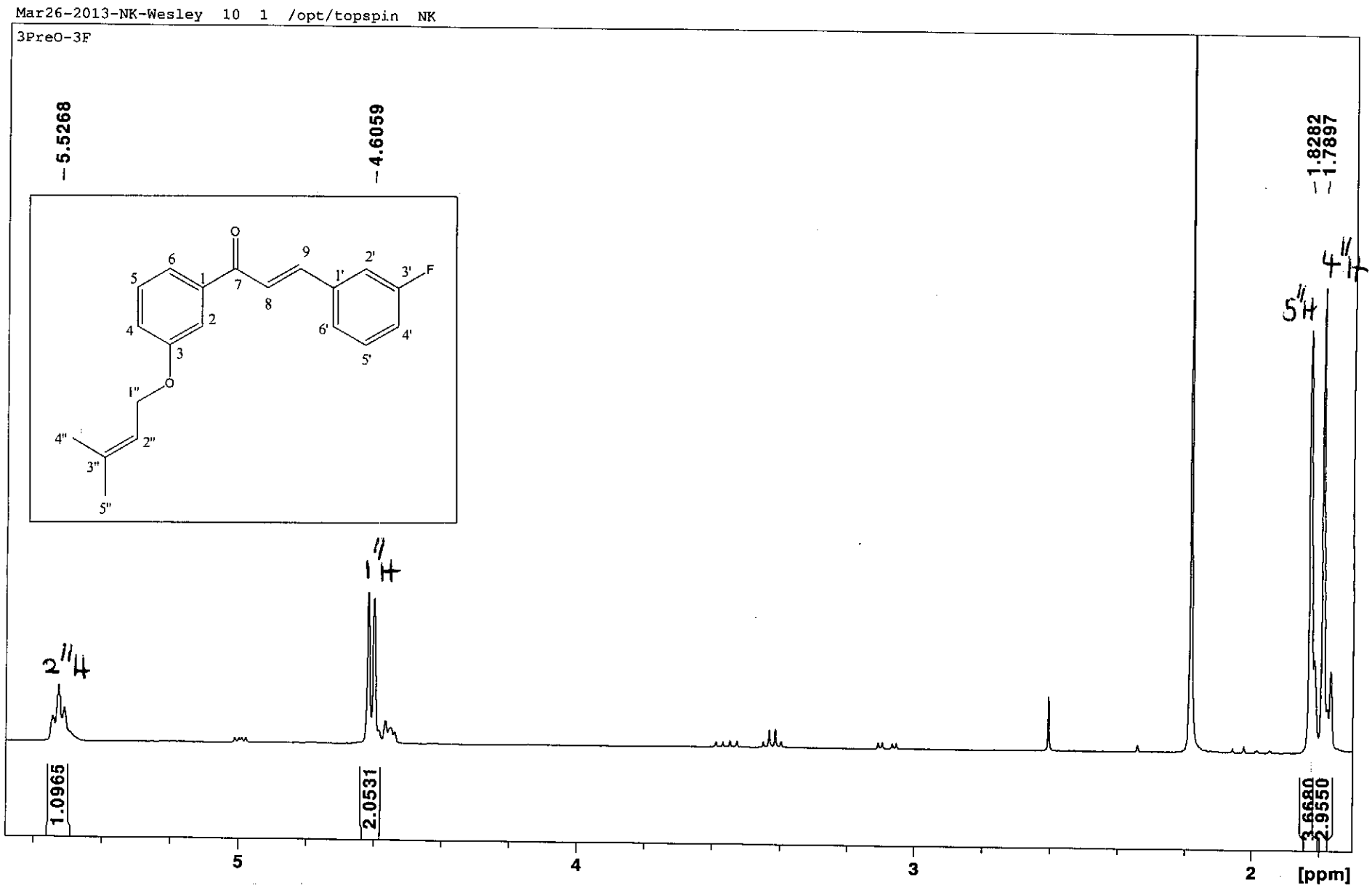
HR-MS spectrum of 2'-fluoro-3-oxyprenylchalcone, (XVIII)



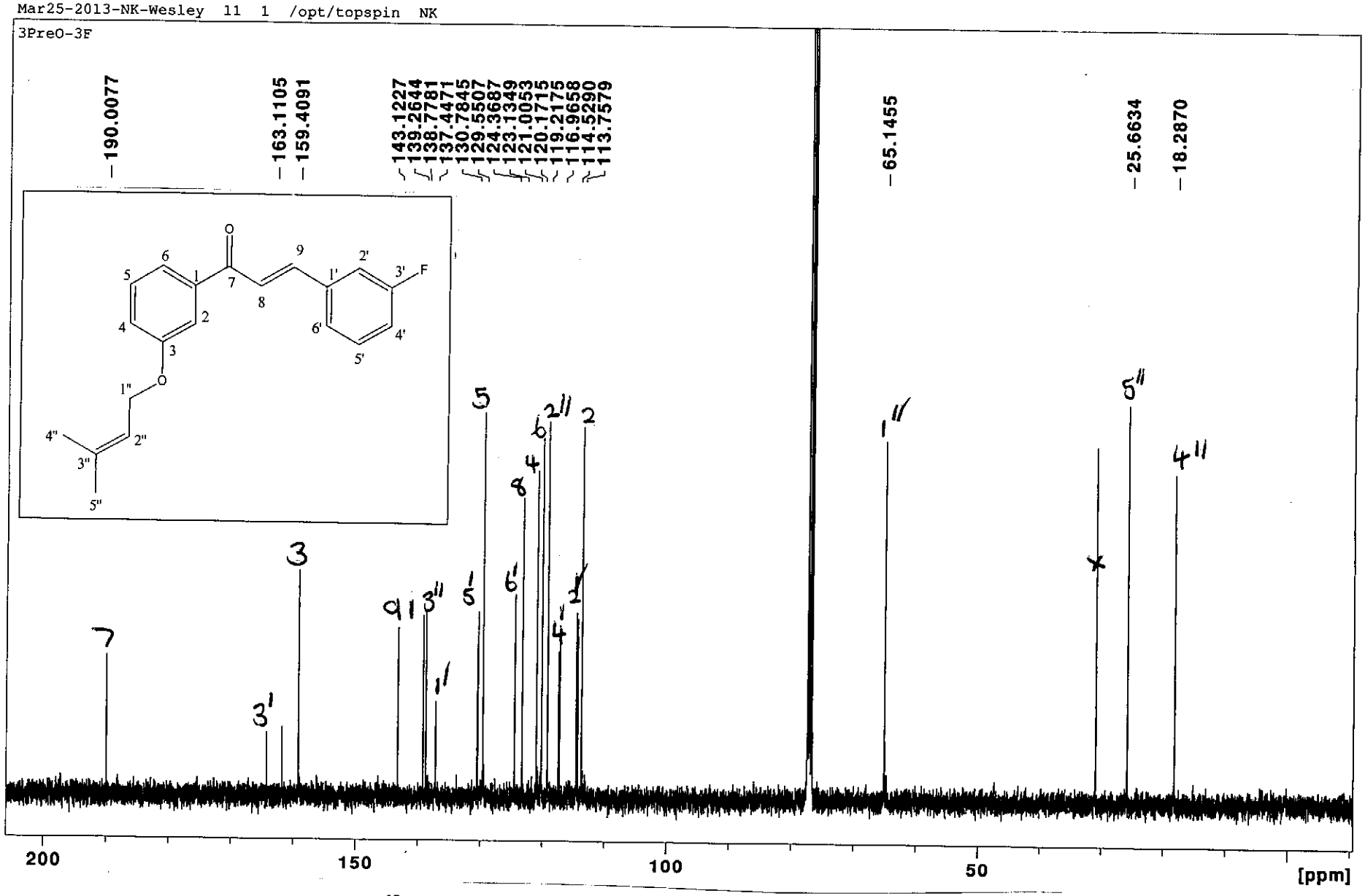
^{1}H NMR spectrum of 3'-fluoro-3-oxyprenylchalcone, (XIX)



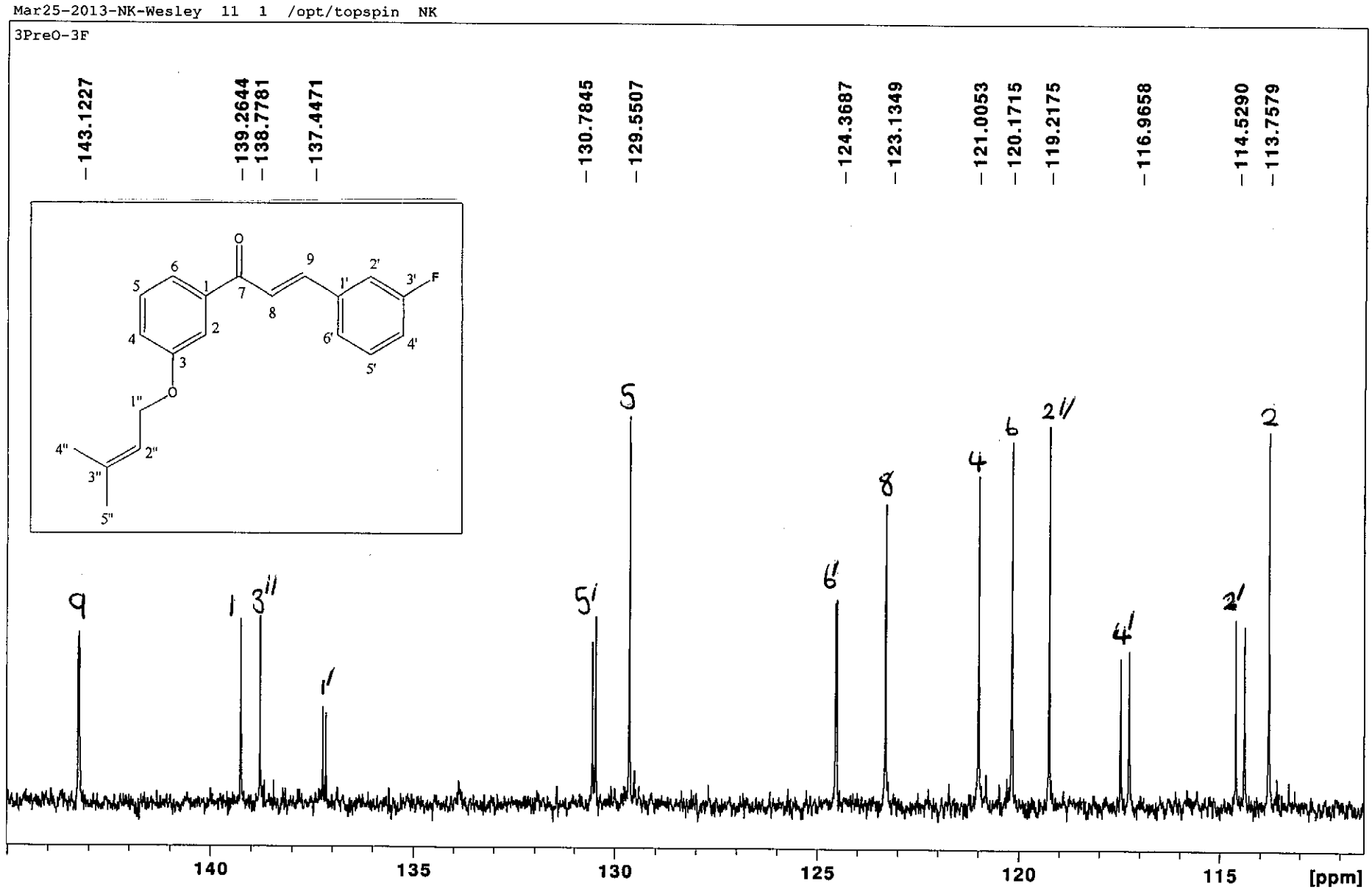
^{1}H NMR spectrum of 3'-fluoro-3-oxyprenylchalcone, (XIX)



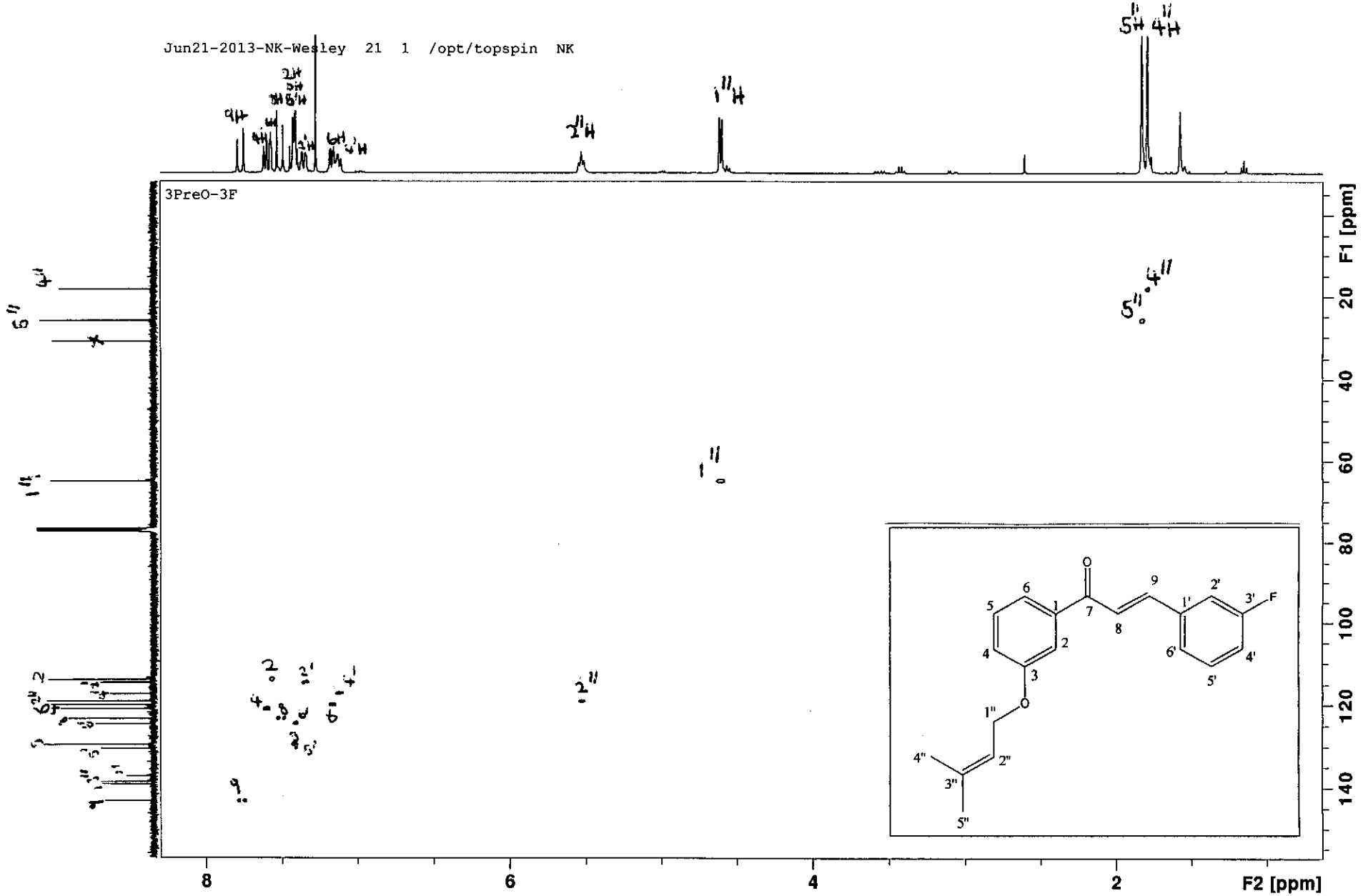
^{1}H NMR spectrum of 3'-fluoro-3-oxyprenylchalcone, (XIX)



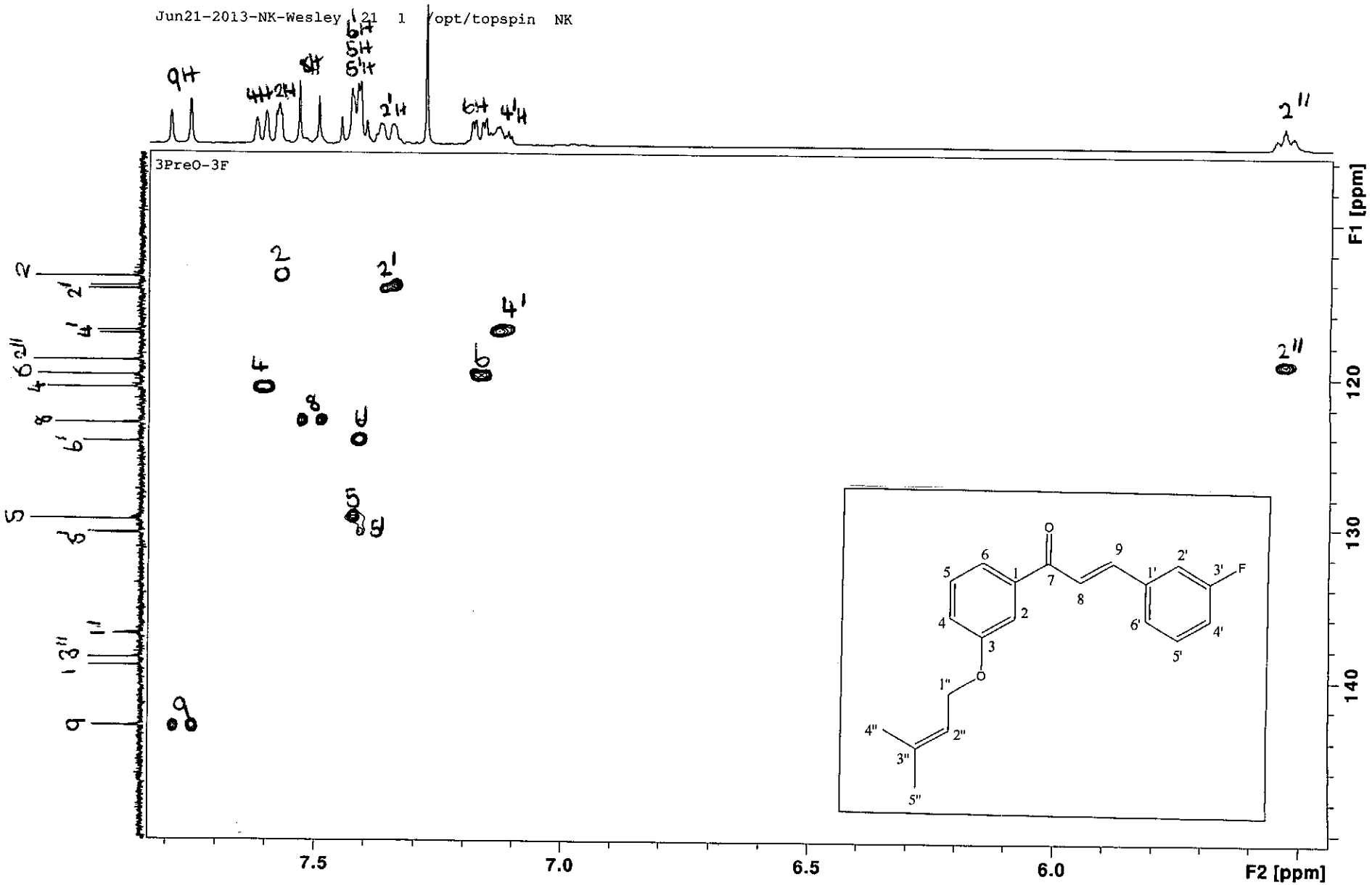
^{13}C NMR spectrum of 3'-fluoro-3-oxyprenylchalcone, (XIX)



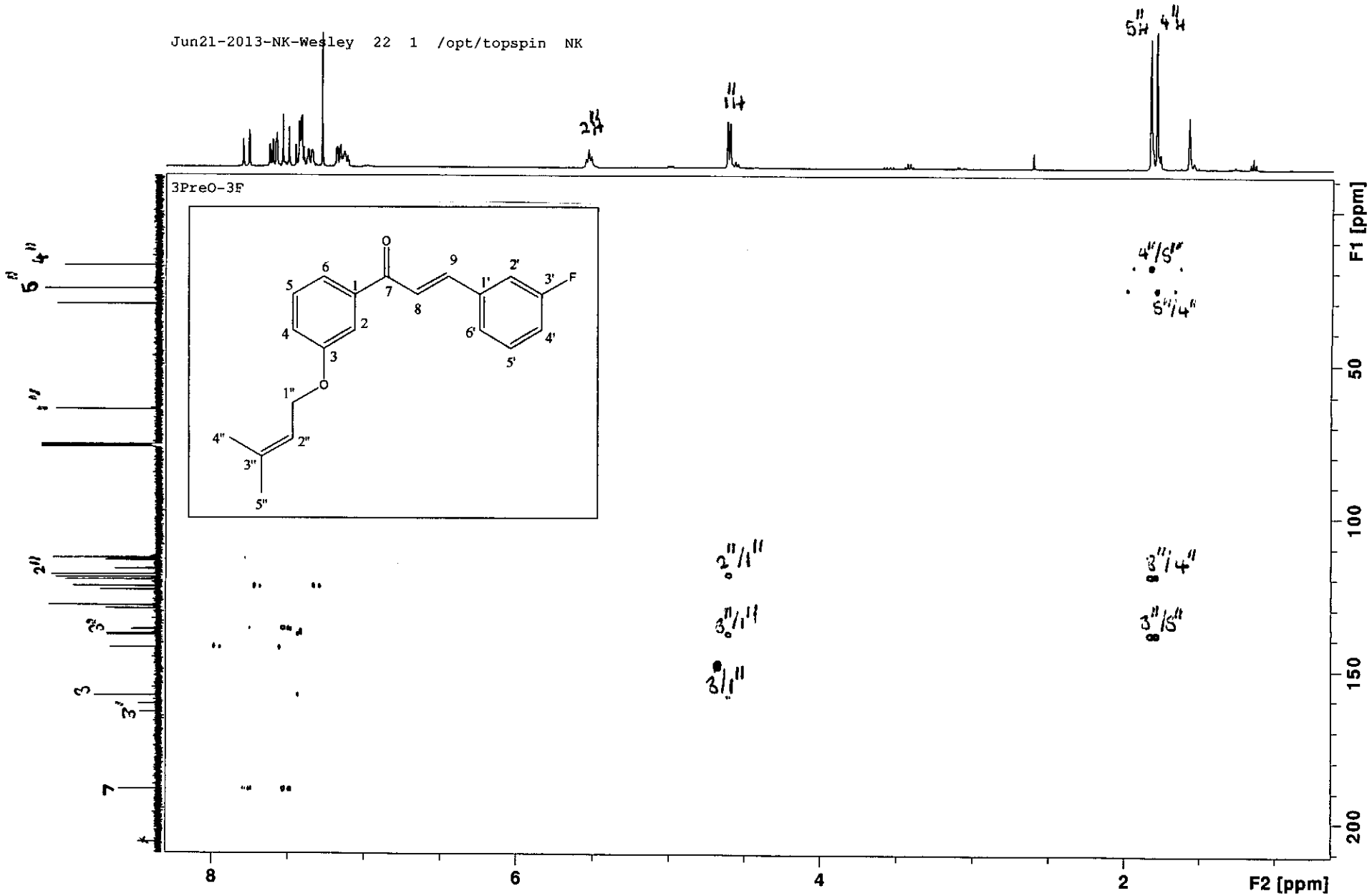
^{13}C NMR spectrum of 3'-fluoro-3-oxyprenylchalcone, (XIX)



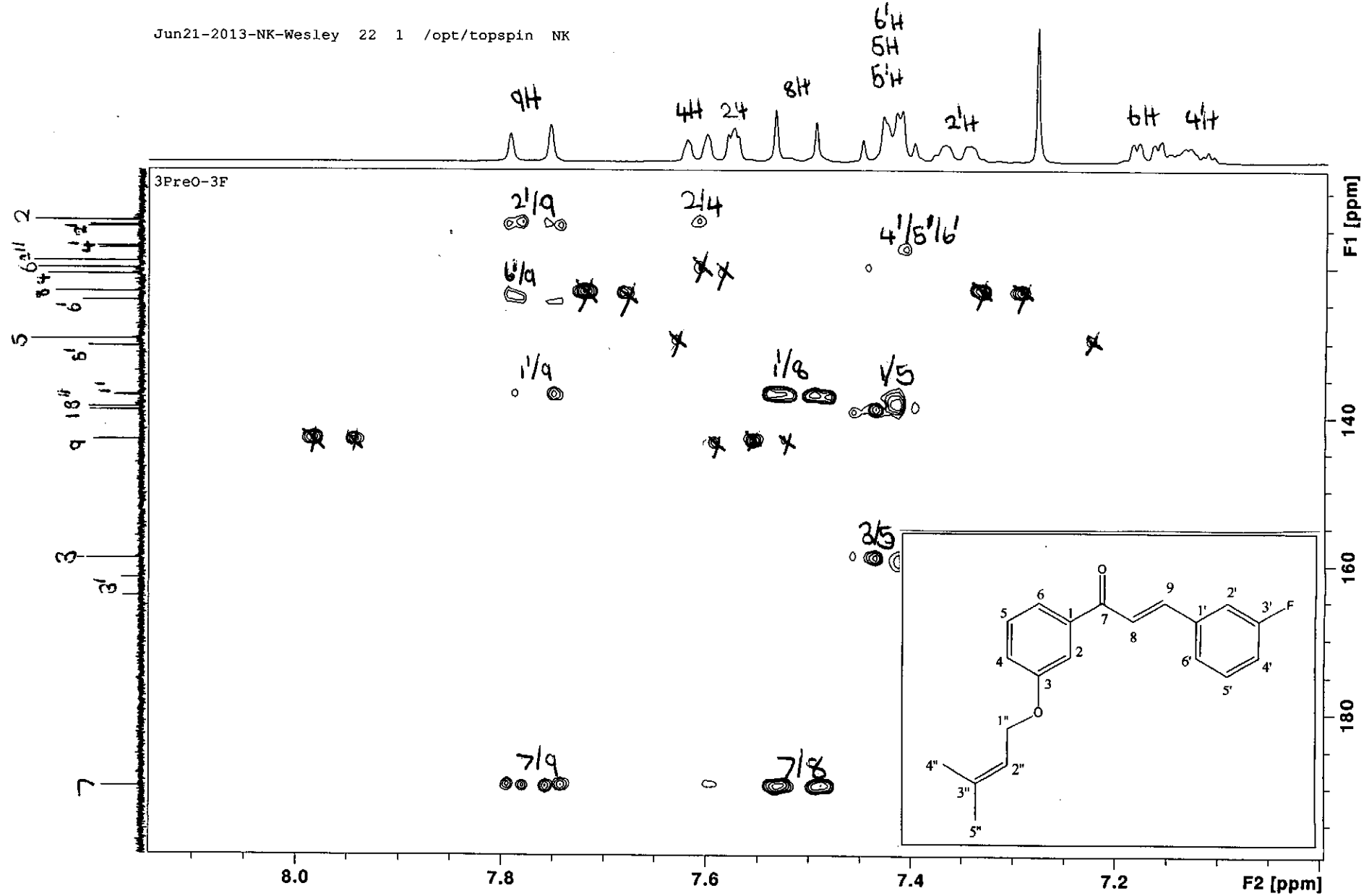
HSQC spectrum of 3'-fluoro-3-oxyprenylchalcone, (XIX)



HSQC spectrum of 3'-fluoro-3-oxyprenylchalcone, (XIX)



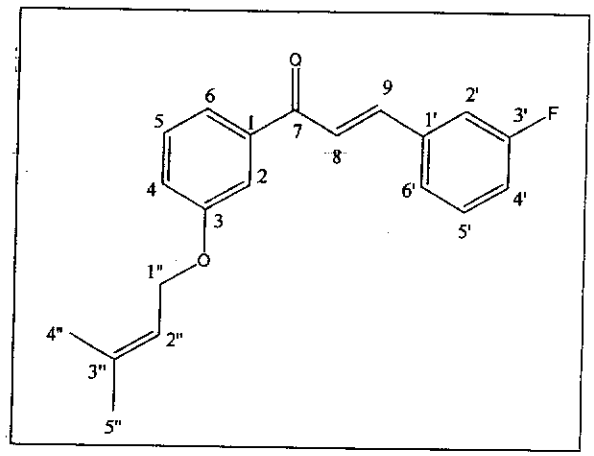
HMBC spectrum of 3'-fluoro-3-oxyprenylchalcone, (XIX)



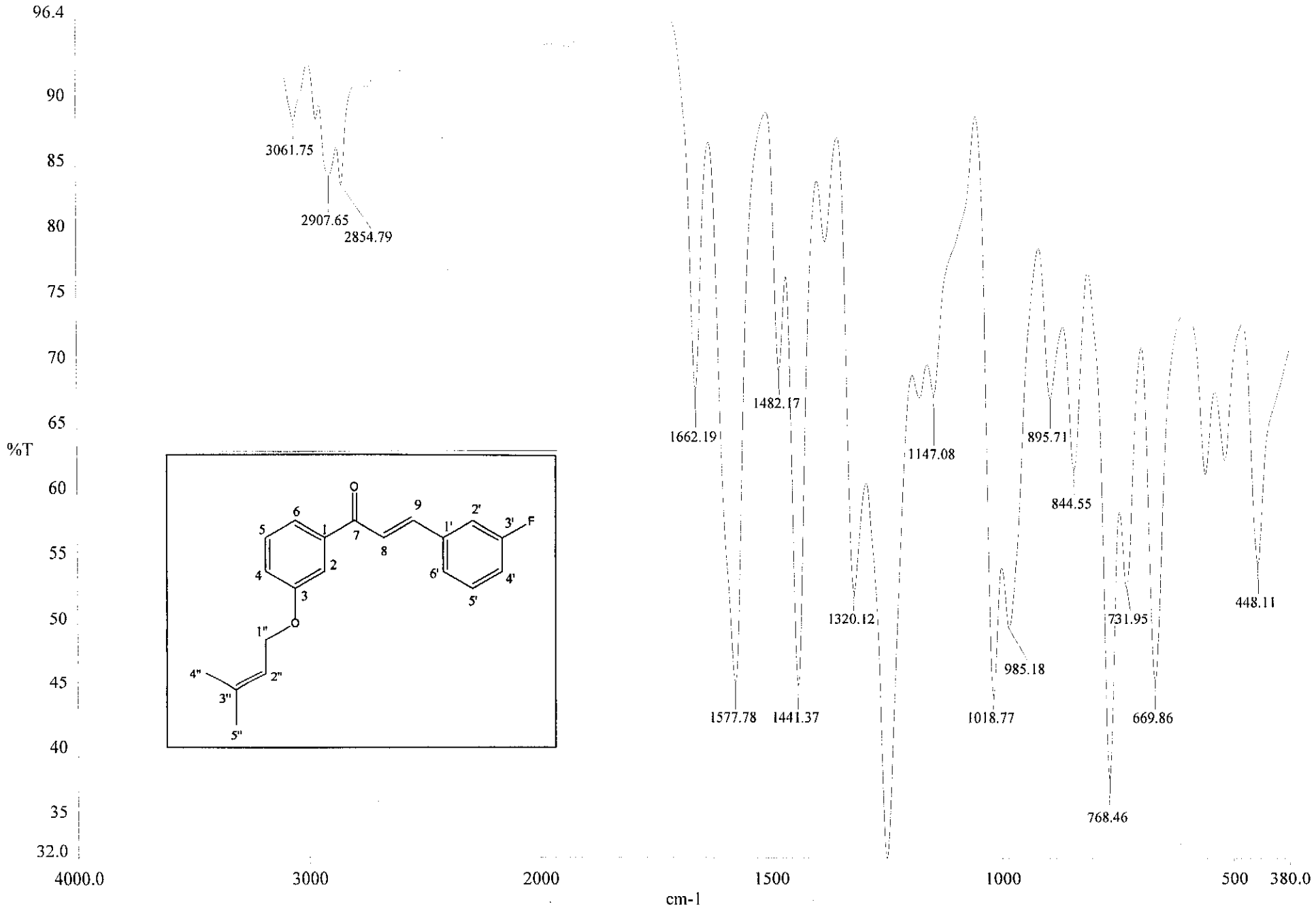
HMBC spectrum of 3'-fluoro-3-oxyprenylchalcone, (XIX)

λmax(295nm) – 0.674
log ε = 5.53

Date: 2013/06/20 Time: 11:06:42 AM

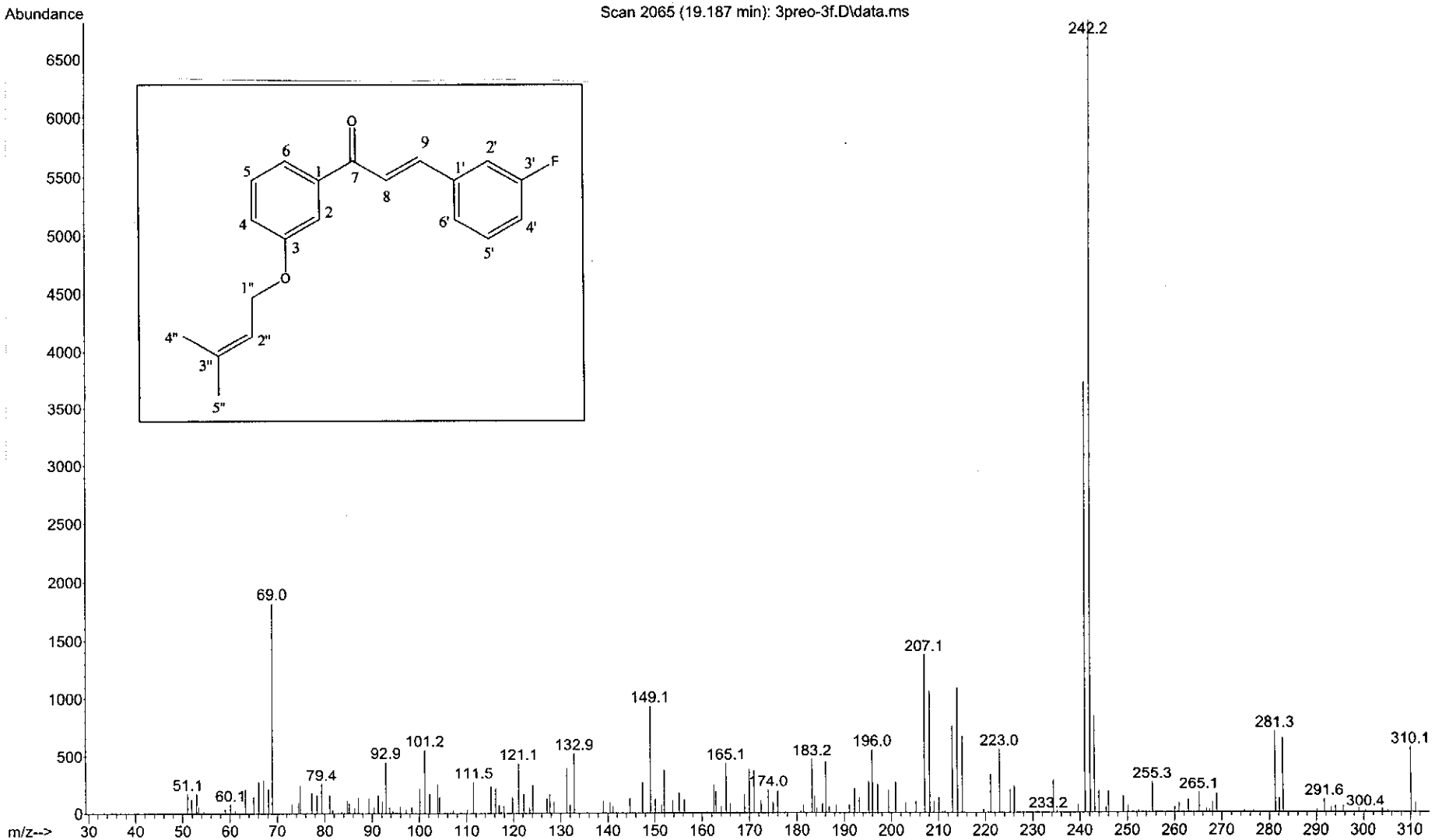


Ultra violet (UV) spectrum of 3'-fluoro-3-oxyprenylchalcone, (XIX)



Infra-Red (IR) spectrum of 3'-fluoro-3-oxyprenylchalcone, (XIX)

File :C:\msdchem\1\data\Wesley\3preo-3f.D
Operator : neal
Acquired : 21 Jun 2013 11:47 using AcqMethod NATPRODUCTS AUTOMATED SPLITLESS.M
Instrument : 5973n
Sample Name: 3preo-3f
Misc Info :
Vial Number: 3



GC-MS spectrum of 3'-fluoro-3-oxyprenylchalcone, (XIX)

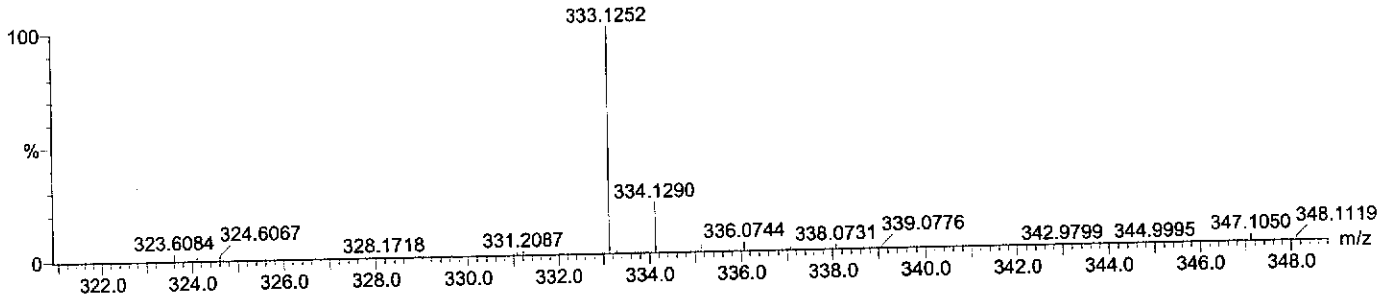
Elemental Composition Report

Single Mass Analysis

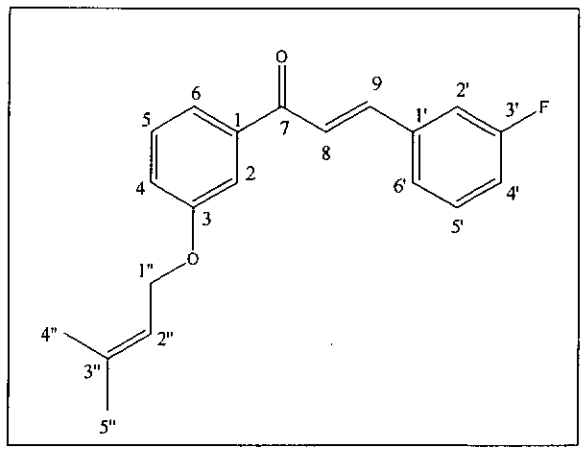
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
14 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 15-20 H: 15-20 O: 0-5 F: 0-2 Na: 0-1

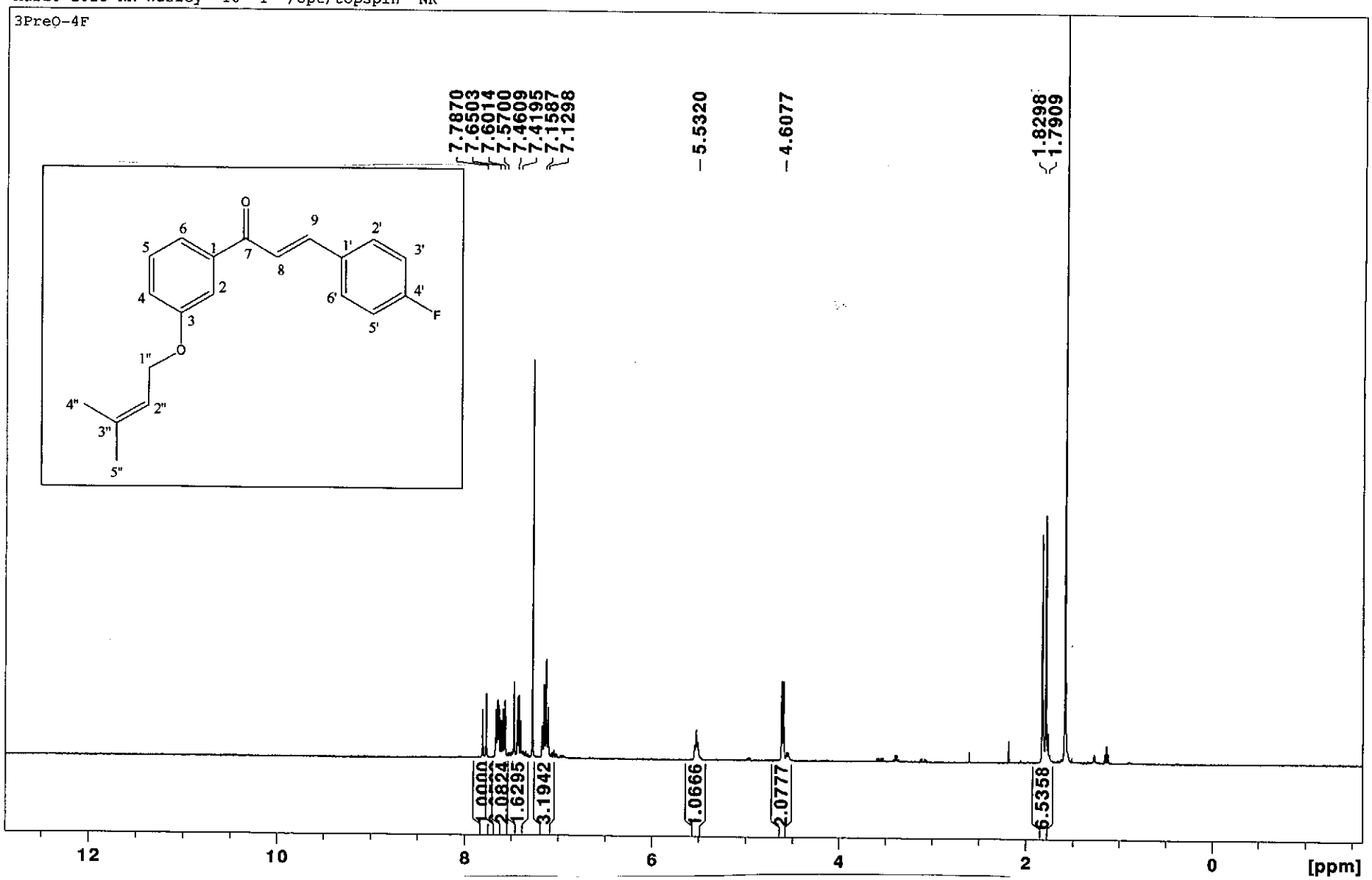
3PreO-3F 15 (0.239) Cm (1:15)
TOF MS ES+ 2.04e+004



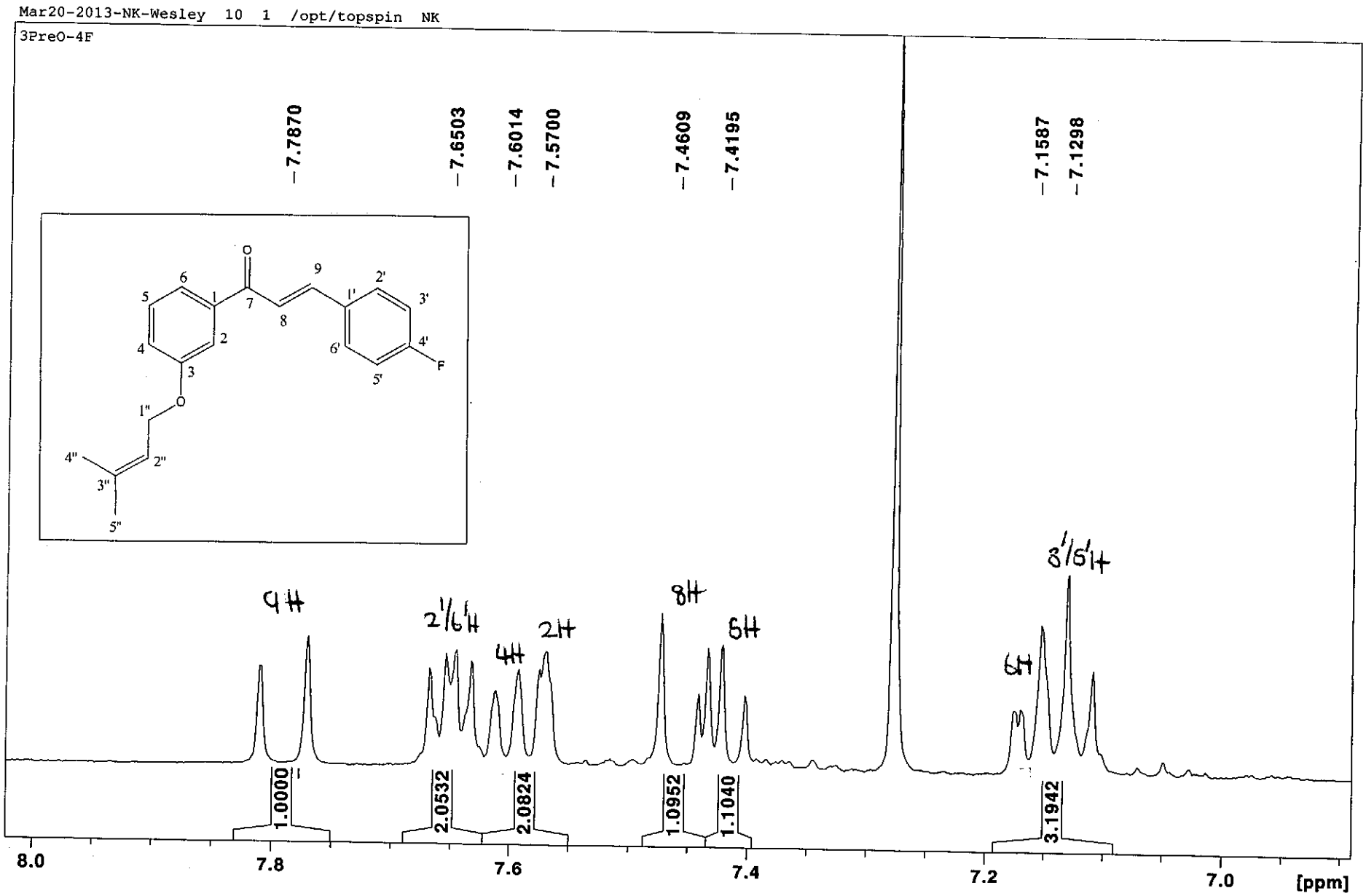
Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
333.1252	333.1267	-1.5	-4.5	10.5	434.2	0.0	C20 H19 O2 F Na



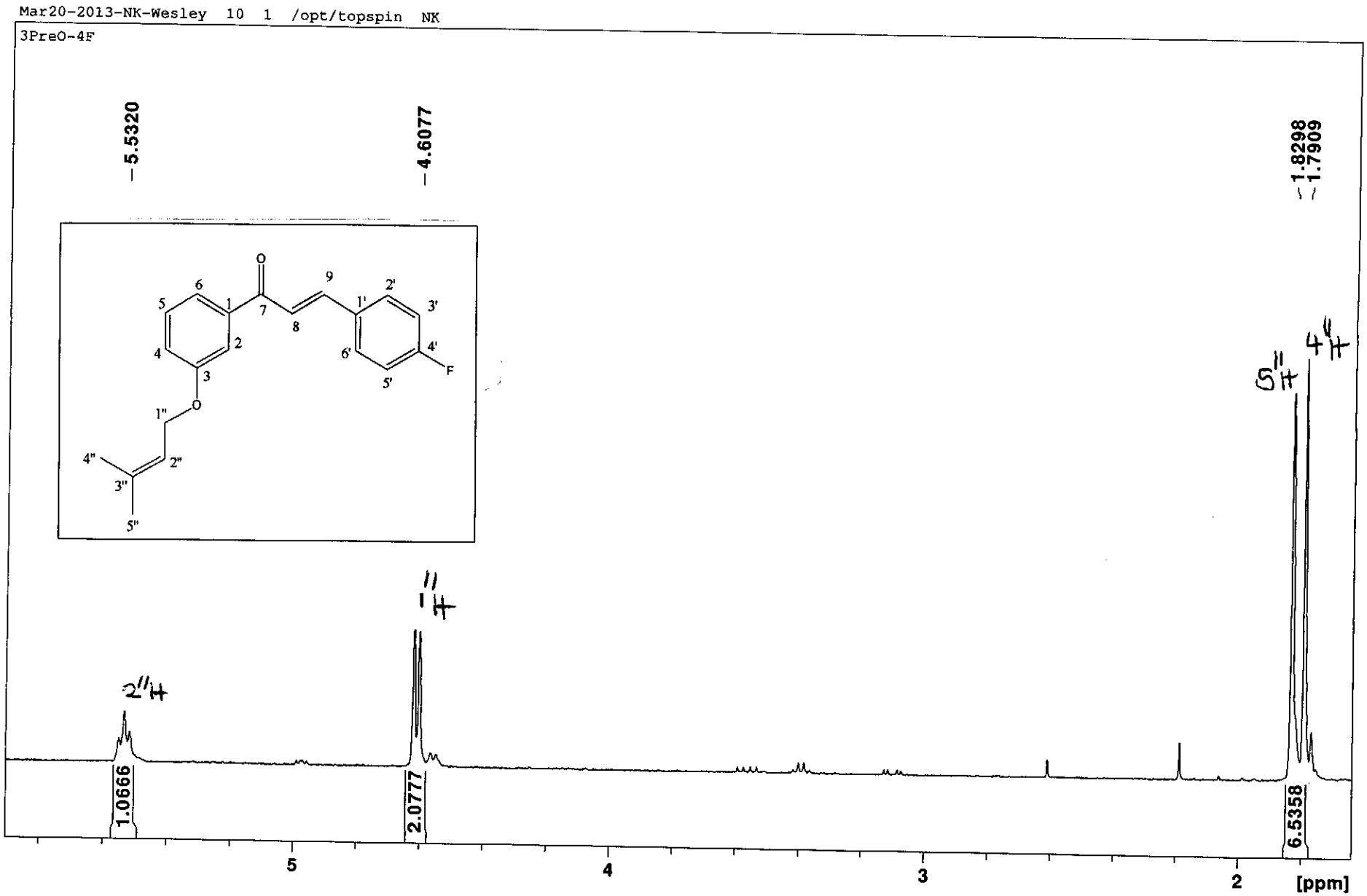
HR-MS spectrum of 3'-fluoro-3-oxyprenylchalcone, (XIX)



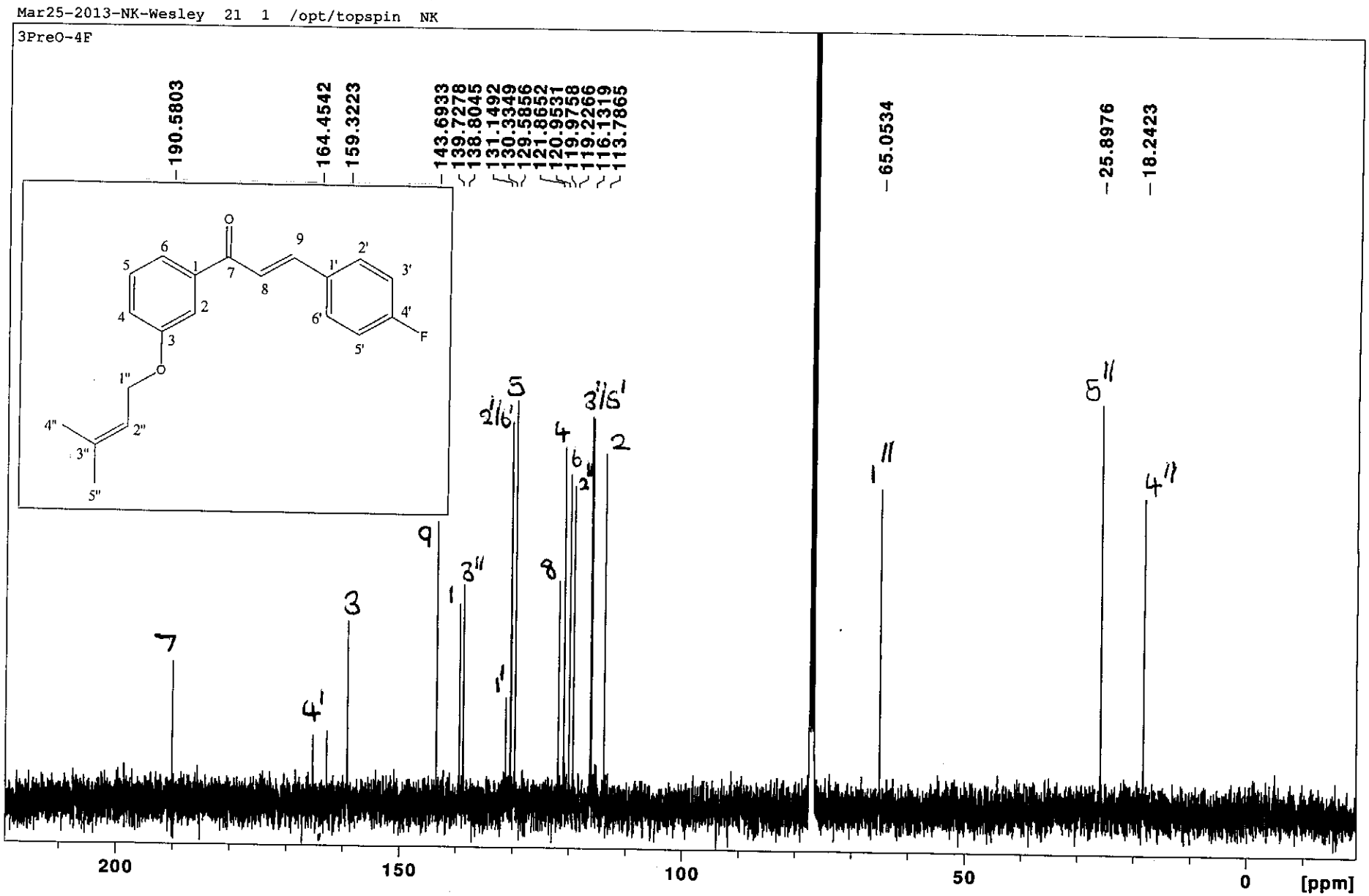
^{1}H NMR spectrum of 4'-fluoro-3-oxyprenylchalcone, (XX)



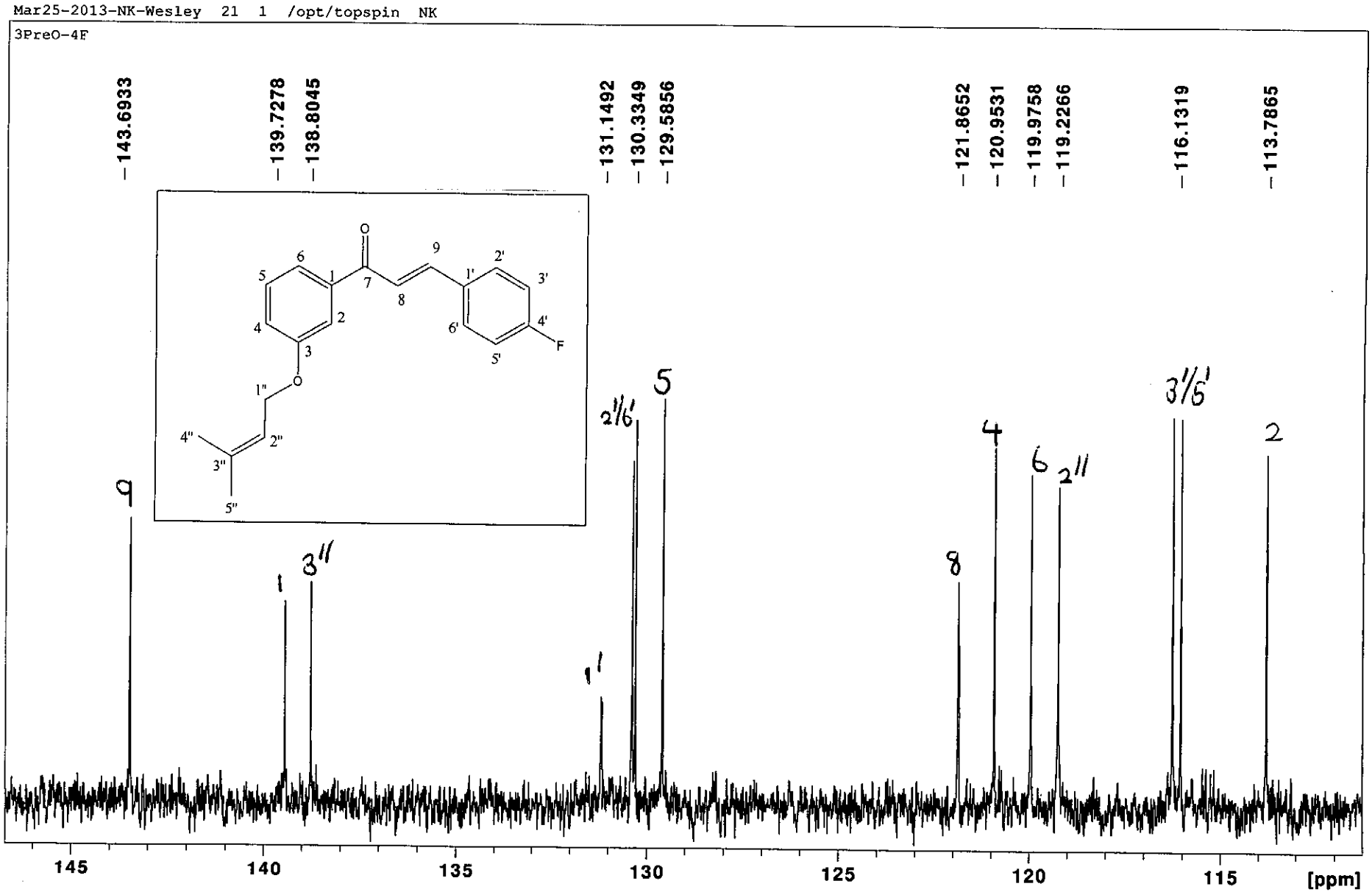
^{1}H NMR spectrum of 4'-fluoro-3-oxyprenylchalcone, (XX)



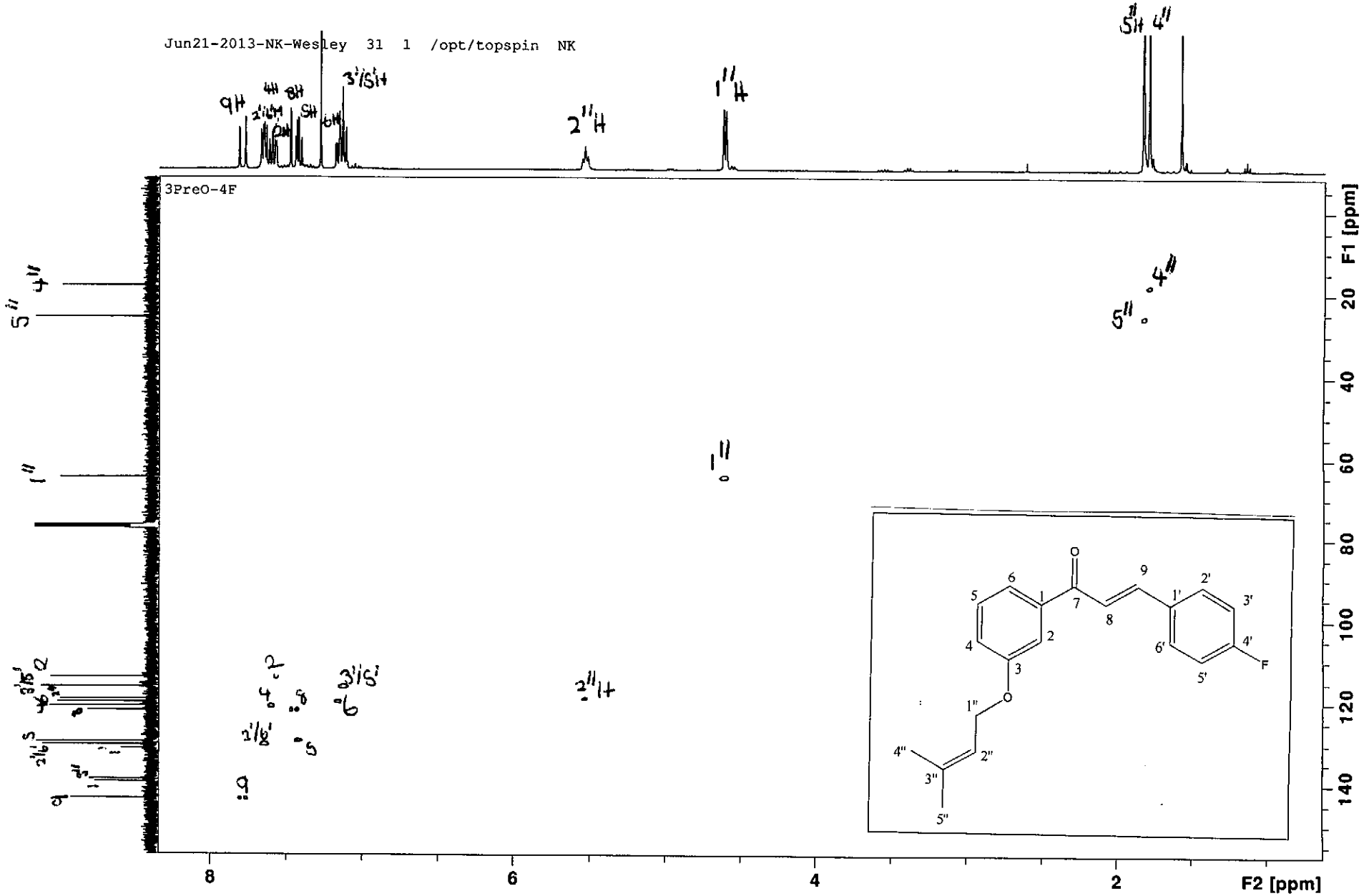
^{1}H NMR spectrum 4'-fluoro-3-oxyprenylchalcone, (XX)



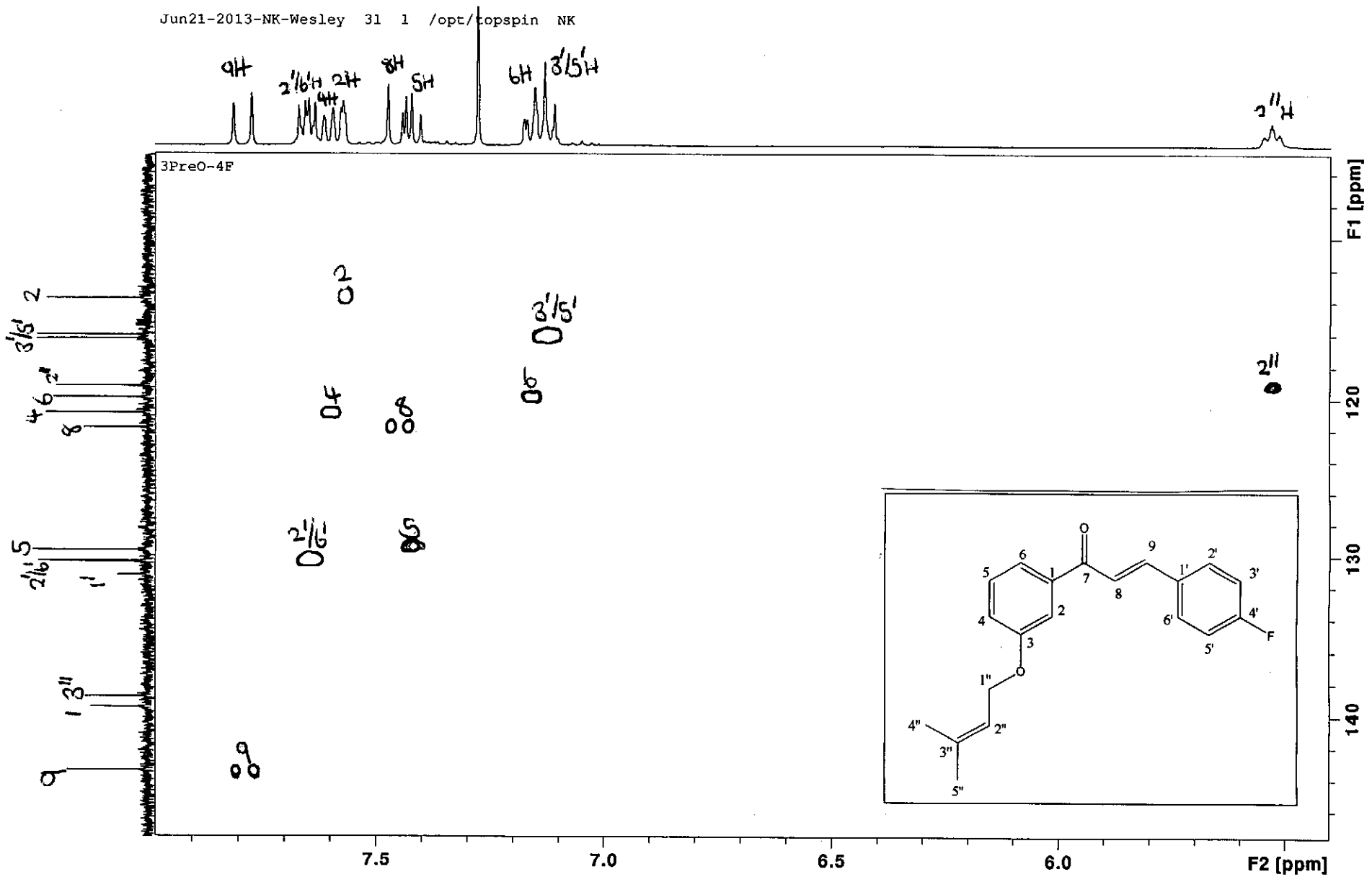
^{13}C NMR spectrum of 4'-fluoro-3-oxyprenylchalcone, (XX)



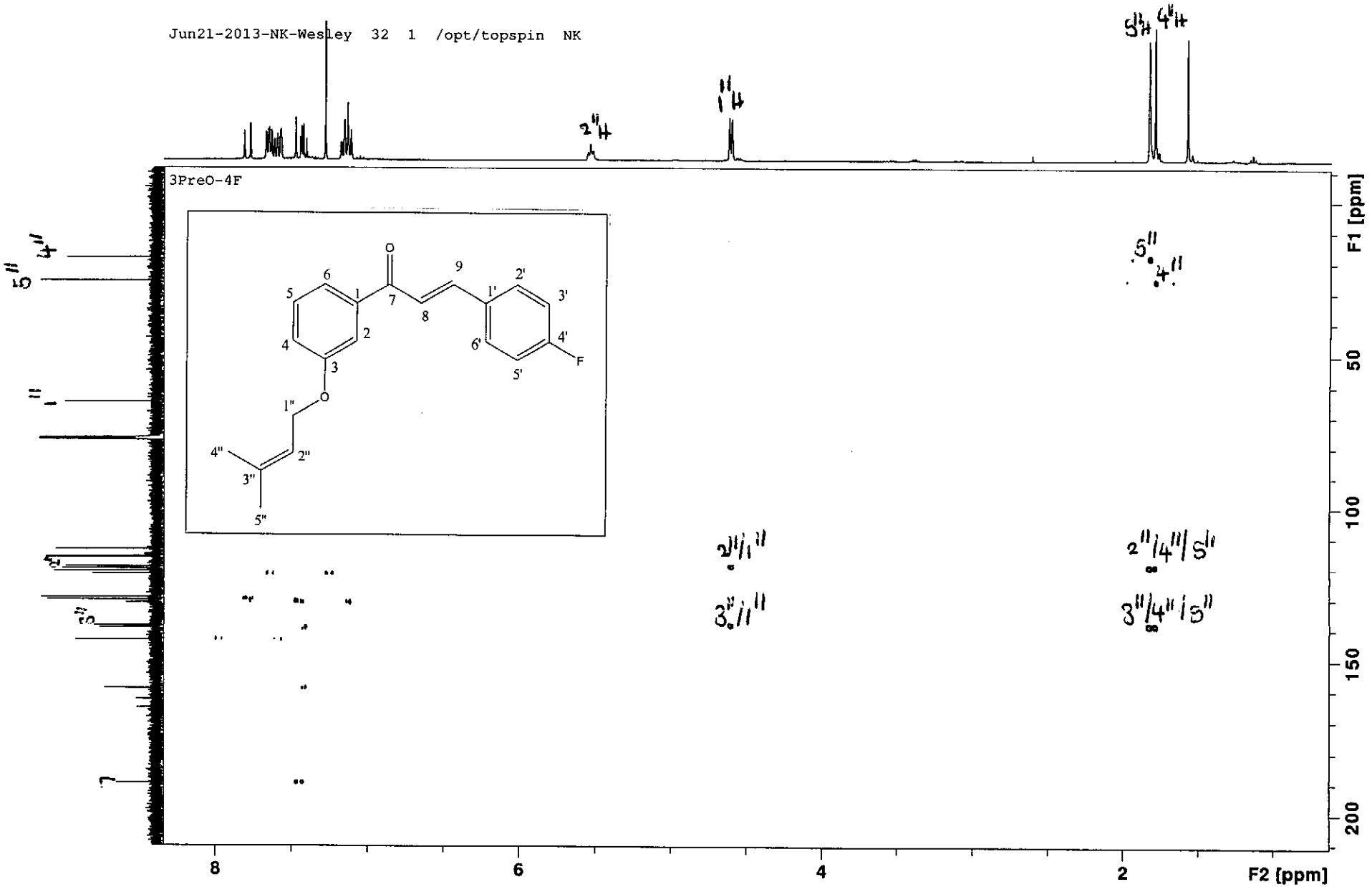
^{13}C NMR spectrum of 4'-fluoro-3-oxyprenylchalcone, (XX)



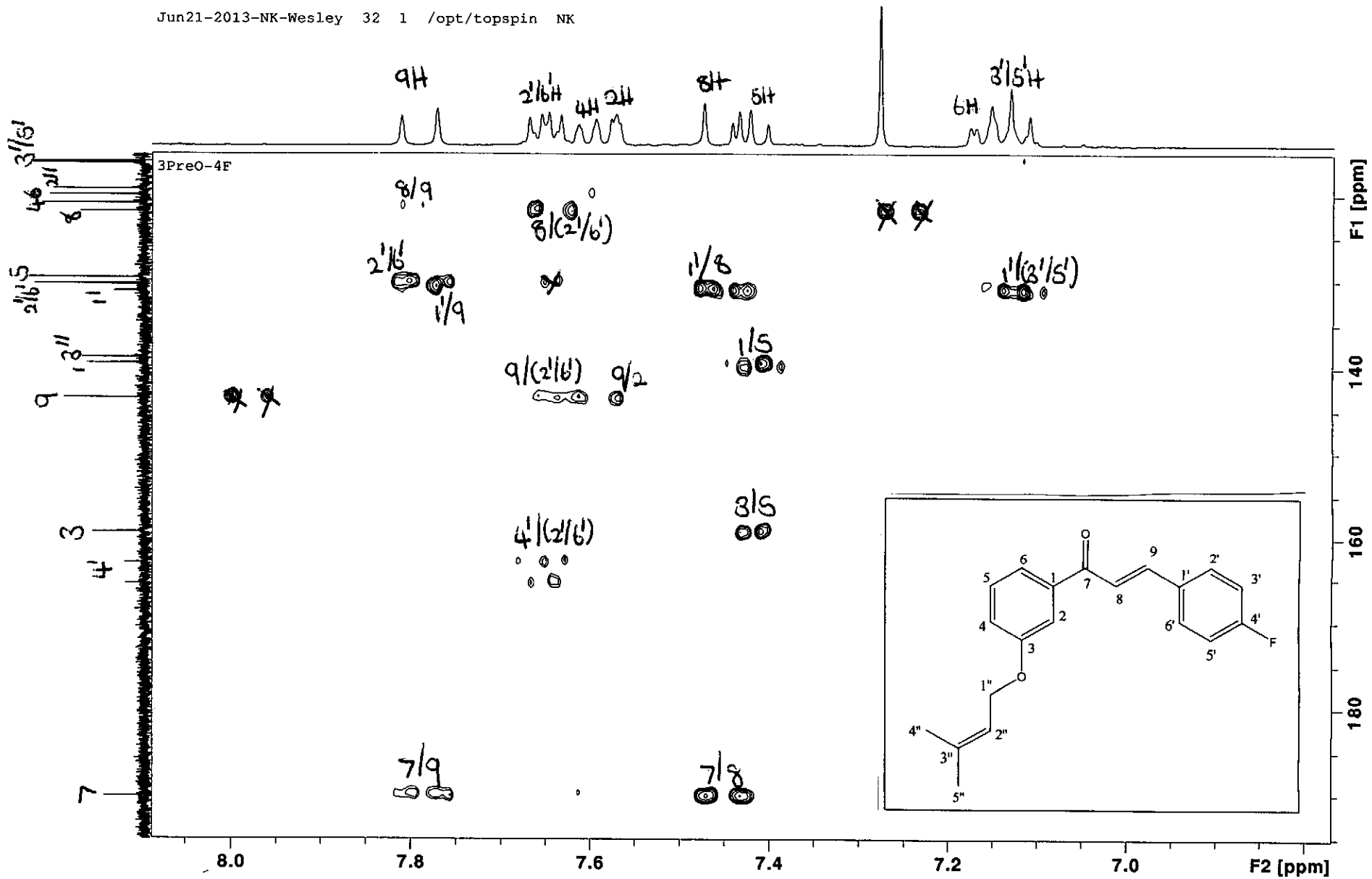
HSQC spectrum of 4'-fluoro-3-oxyprenylchalcone, (XX)



HSQC spectrum of 4'-fluoro-3-oxyprenylchalcone, (XX)



HMBC spectrum of 4'-fluoro-3-oxyprenylchalcone, (XX)

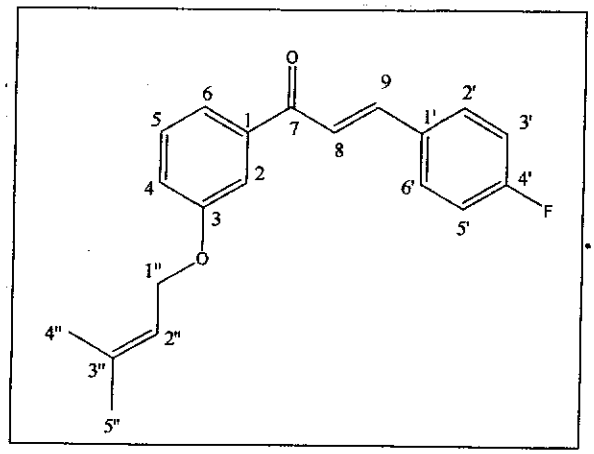


HMBC spectrum of 4'-fluoro-3-oxyprenylchalcone, (XX)

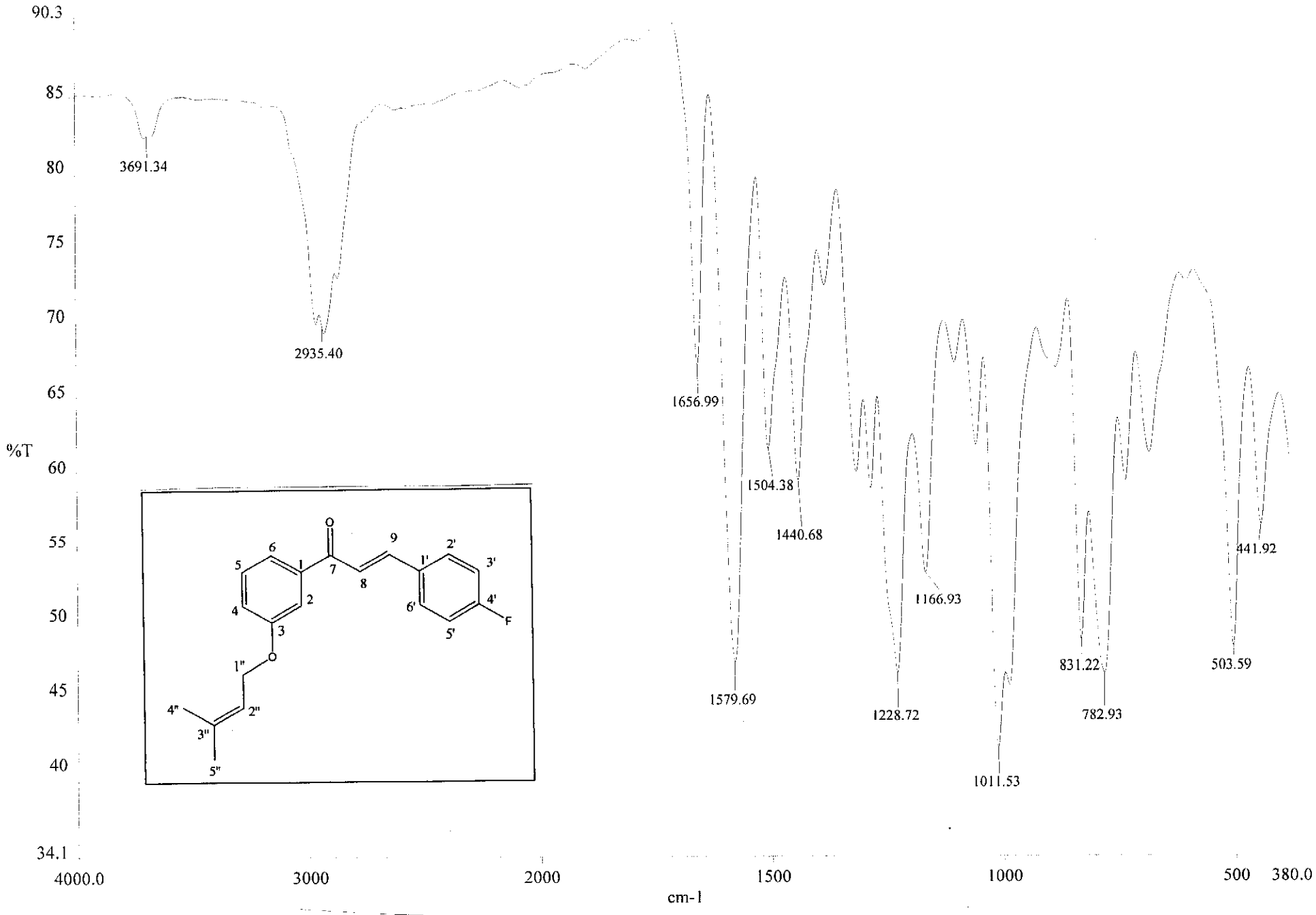
λmax (303 nm) = 0.3964

log ε = 5.30

Date: 2013/06/20 Time: 11:00:55 AM



Ultra violet (UV) spectrum of 4'-fluoro-3-oxyprenylchalcone, (XX)



Infra-Red (IR) spectrum of 4'-fluoro-3-oxyprenylchalcone, (XX)

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File       :C:\msdchem\1\data\HONOURS2013\denvar\MeOH 3preo-4f.D
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Acquired   : 14 Oct 2013  20:01     using AcqMethod NATPRODUCTS SPLIT AUTOMATED.M
Instrument :   5973n
Sample Name: MeOH 3preo-4f
Misc Info  :
Vial Number: 9
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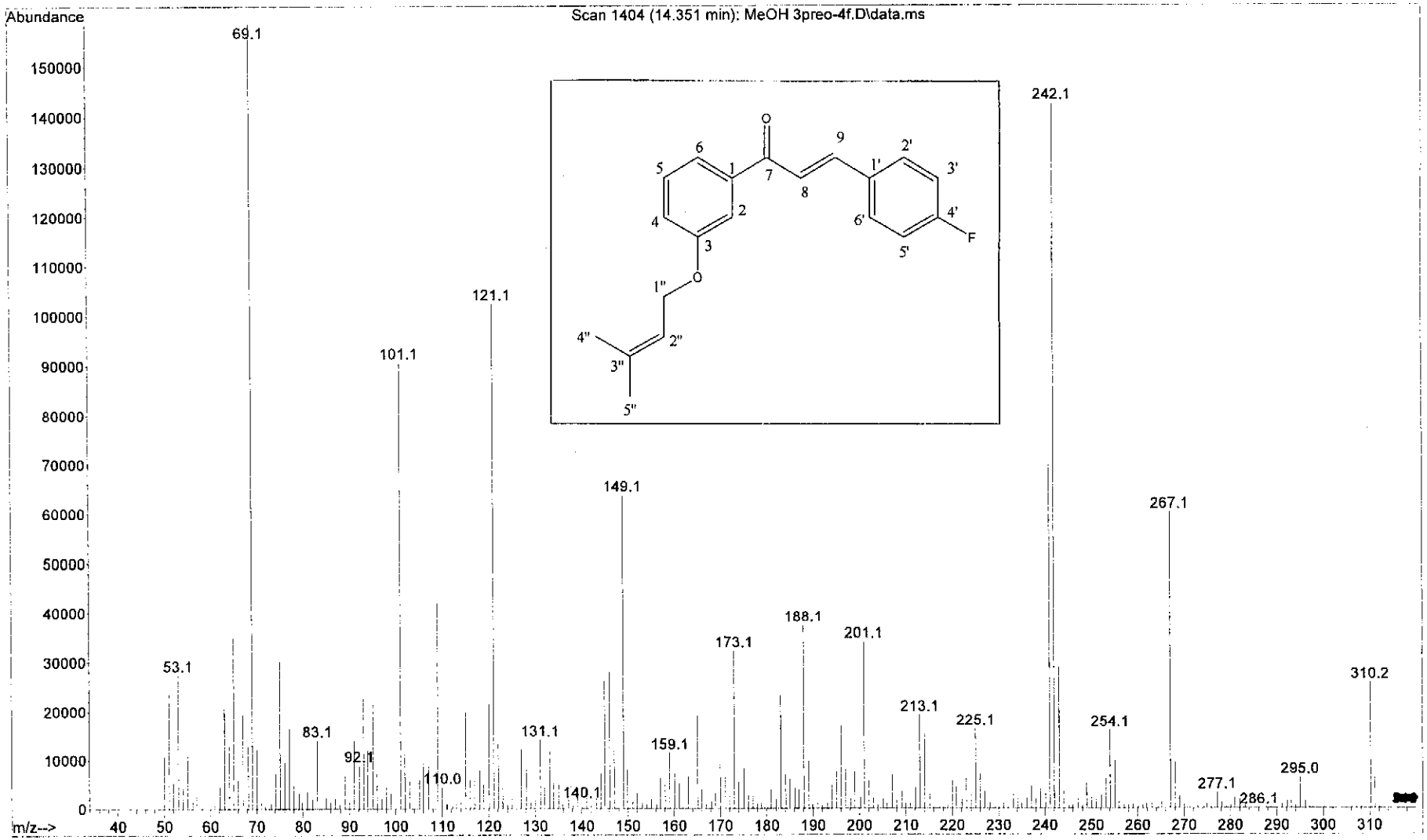


GC-MS spectrum of 4'-fluoro-3-oxyprenylchalcone, (XX)

Elemental Composition Report

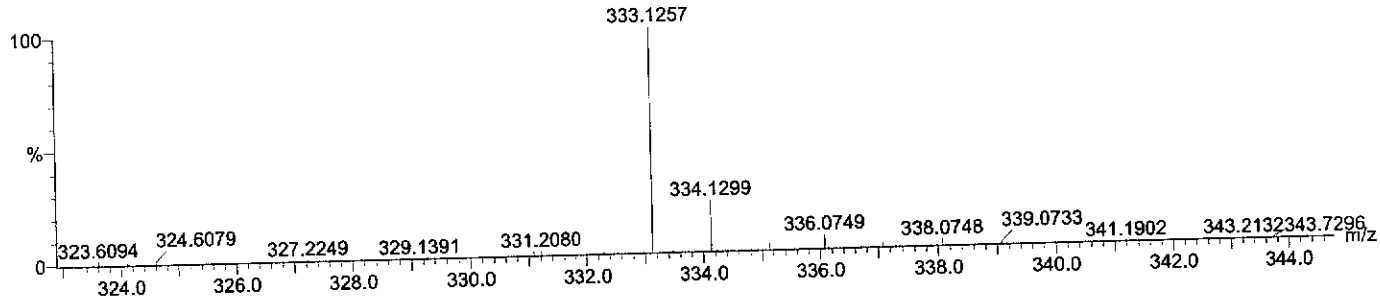
Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

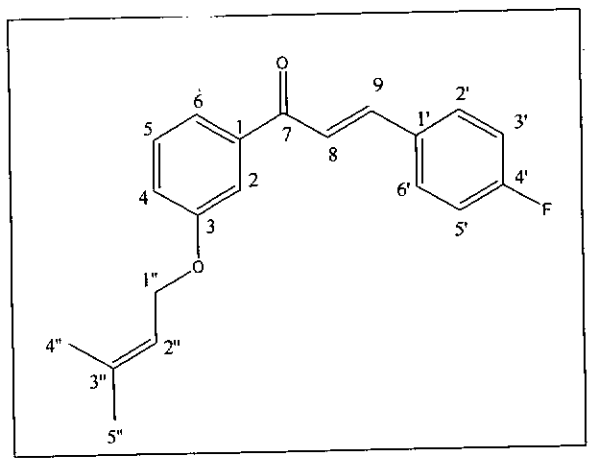
Monoisotopic Mass, Even Electron Ions
14 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 15-20 H: 15-20 O: 0-5 F: 0-2 Na: 0-1

3PreO-4F 16 (0.257) Cm (1:16)
TOF MS ES+

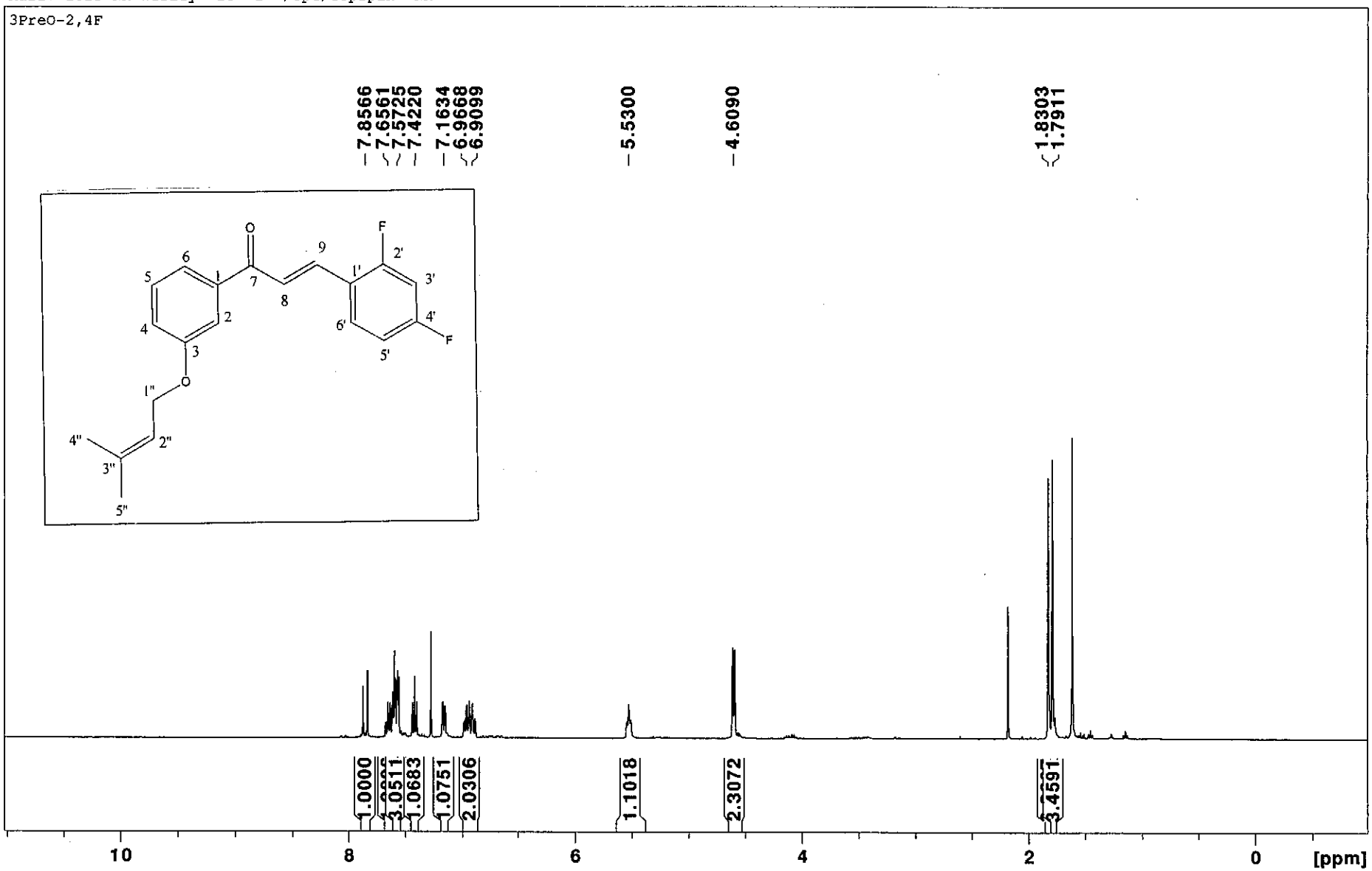
1.96e+004



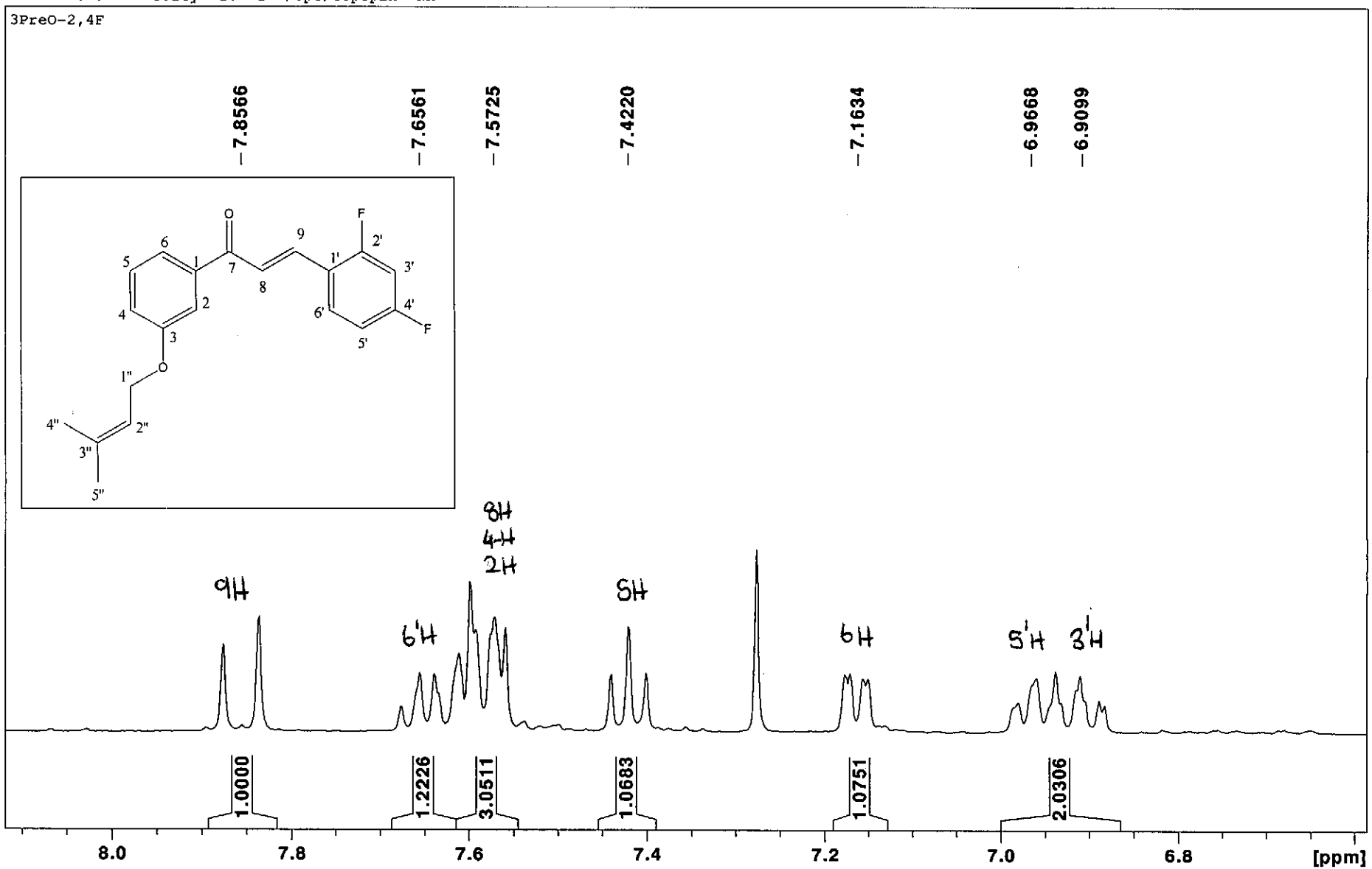
Minimum:		5.0	5.0	-1.5			
Maximum:				100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
333.1257	333.1267	-1.0	-3.0	10.5	420.9	0.0	C20 H19 O2 F Na



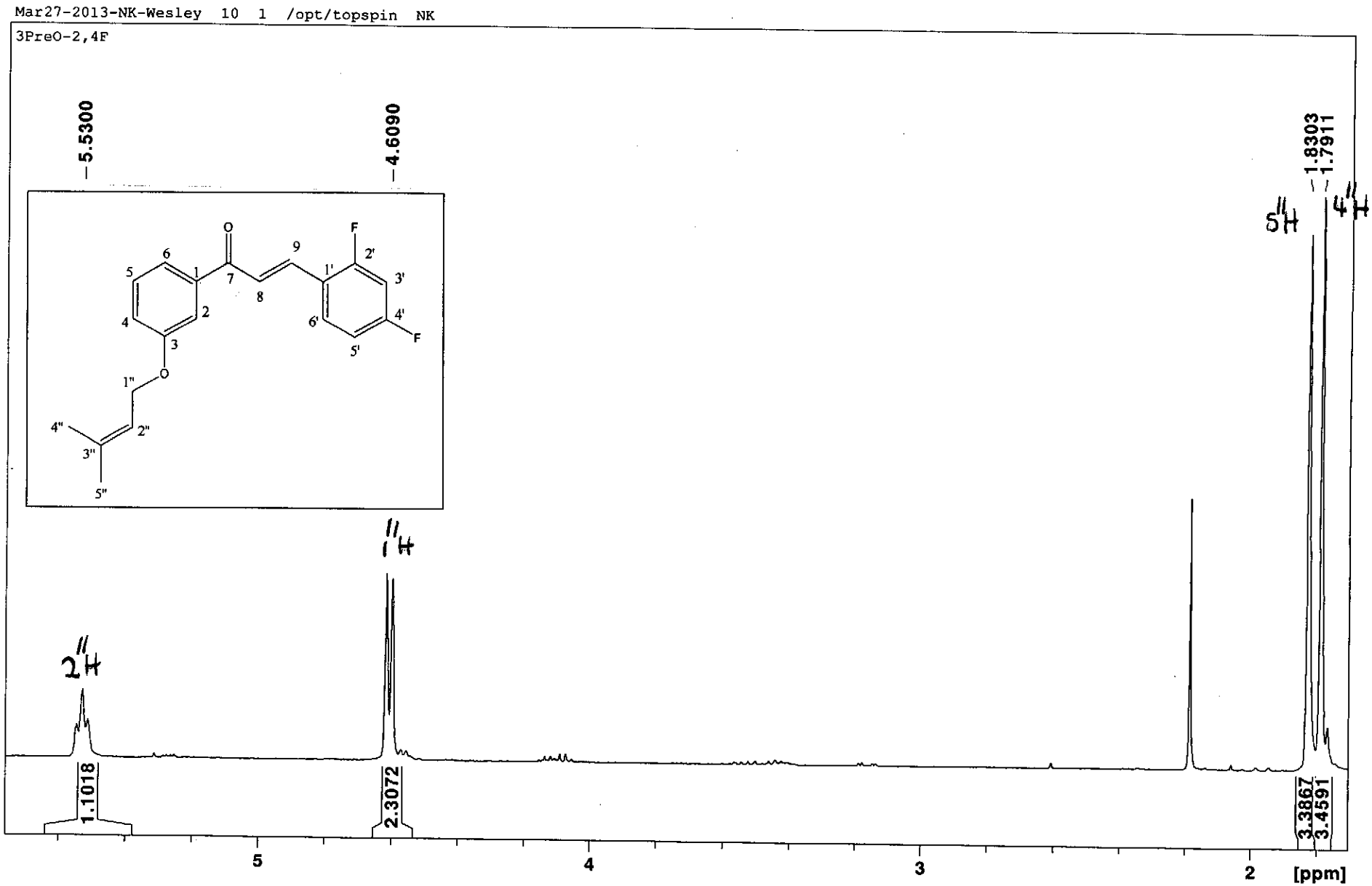
HR-MS spectrum of 4'-fluoro-3-oxyprenylchalcone, (XX)



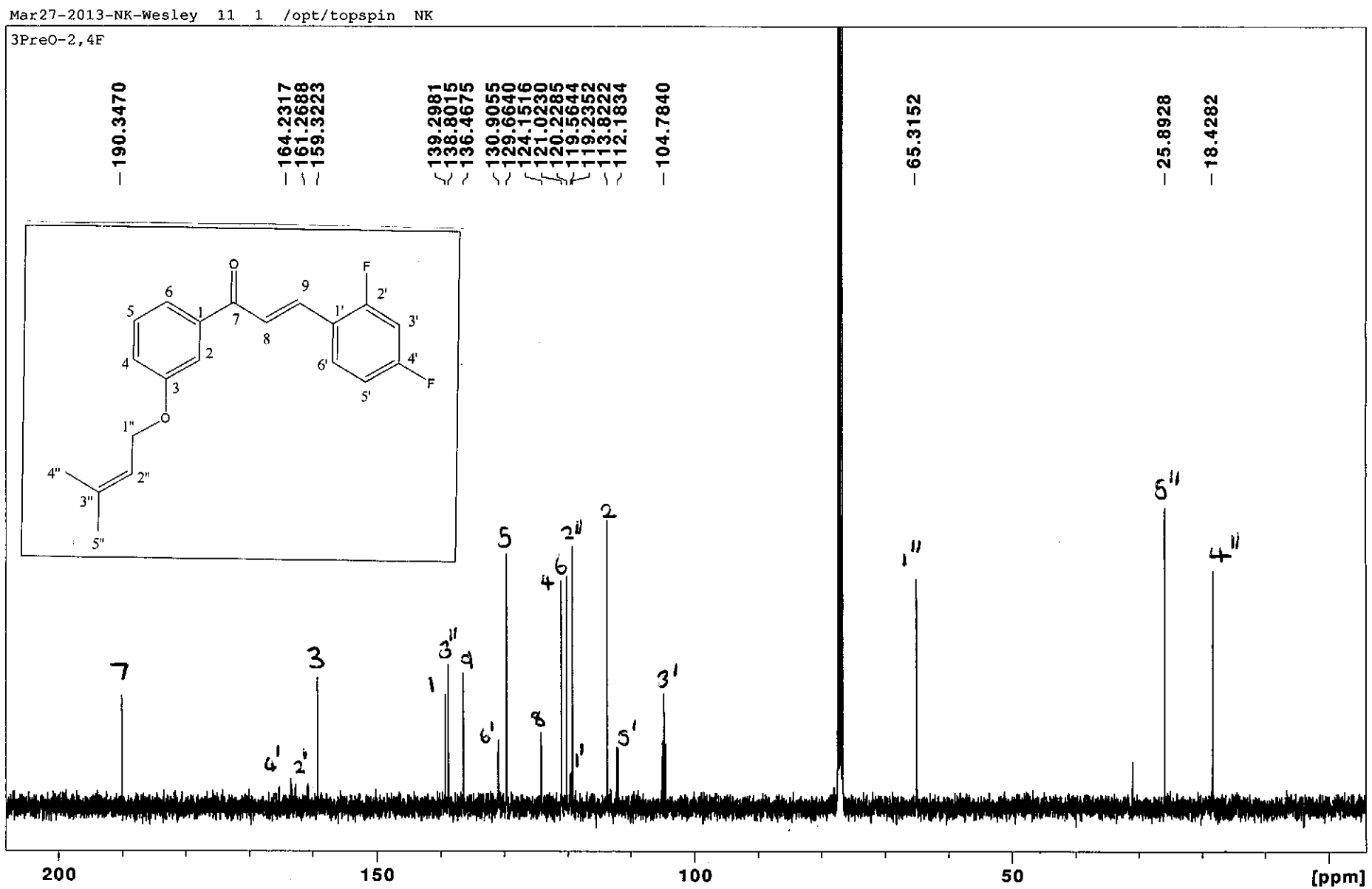
^{1}H NMR spectrum of 2',4'-difluoro-3-oxyprenylchalcone, (XXI)



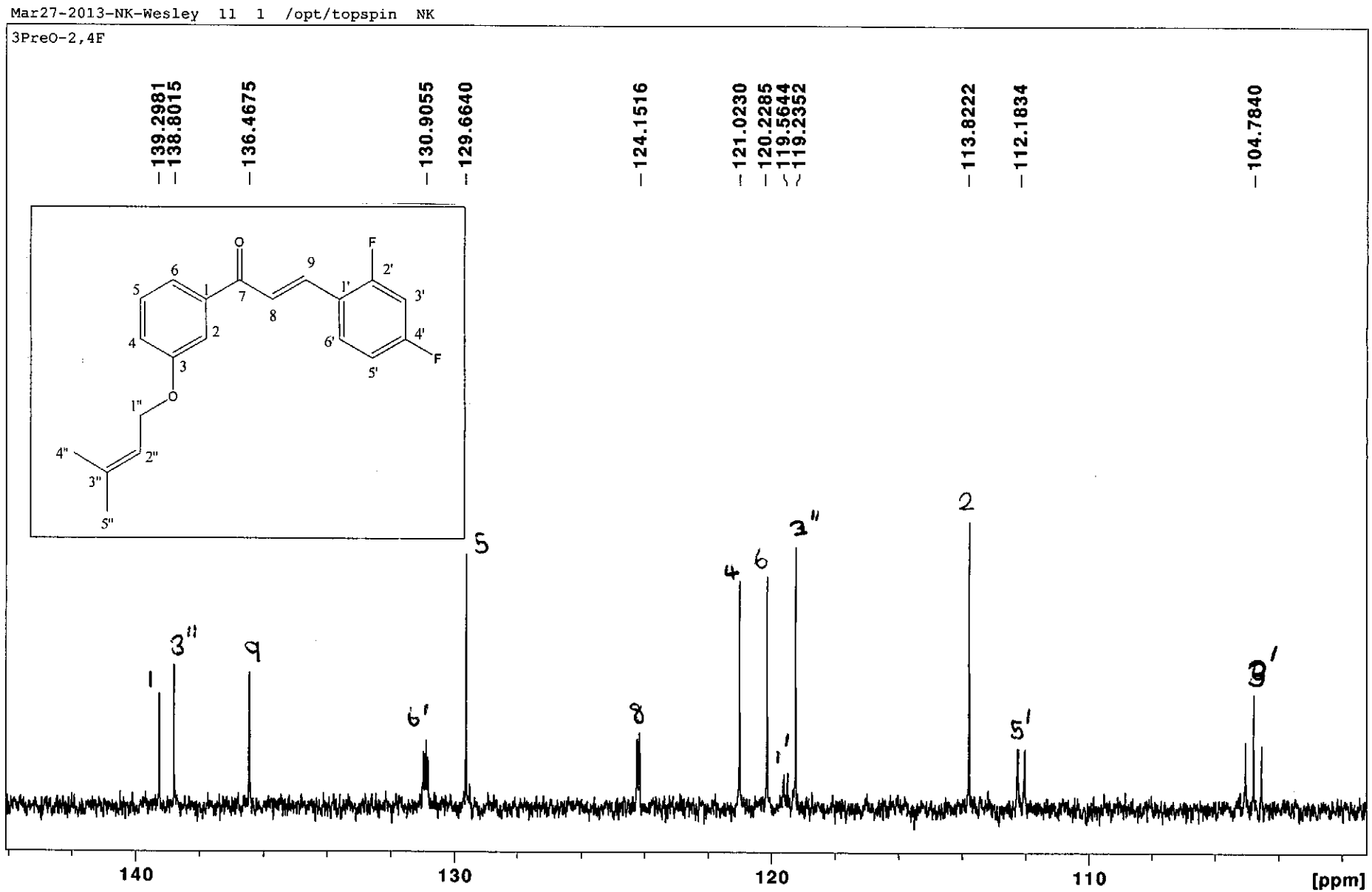
^{1}H NMR spectrum of 2',4'-difluoro-3-oxyprenylchalcone, (XXI)



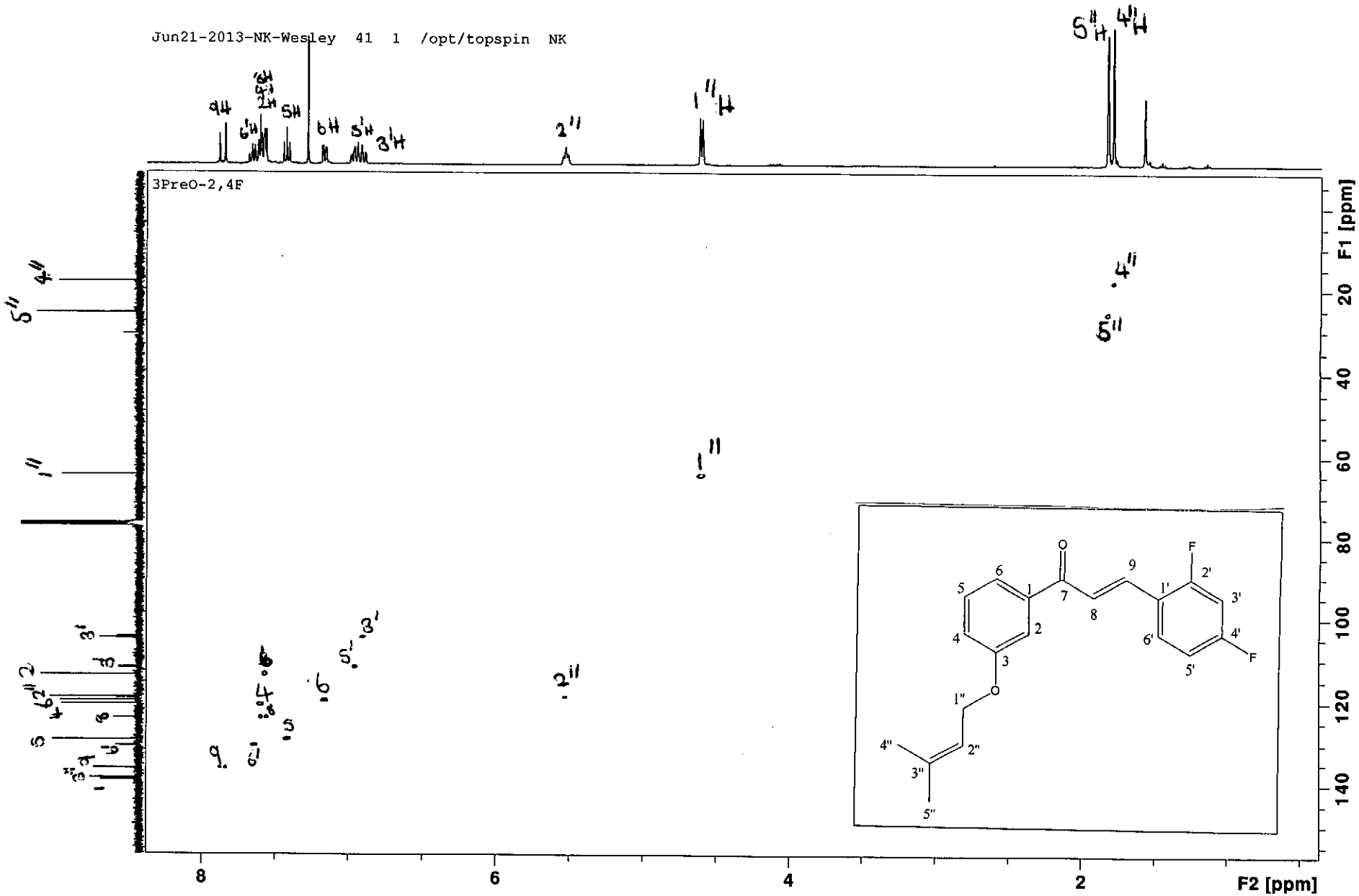
^{1}H NMR spectrum of 2',4'-difluoro-3-oxyprenylchalcone, (XXI)



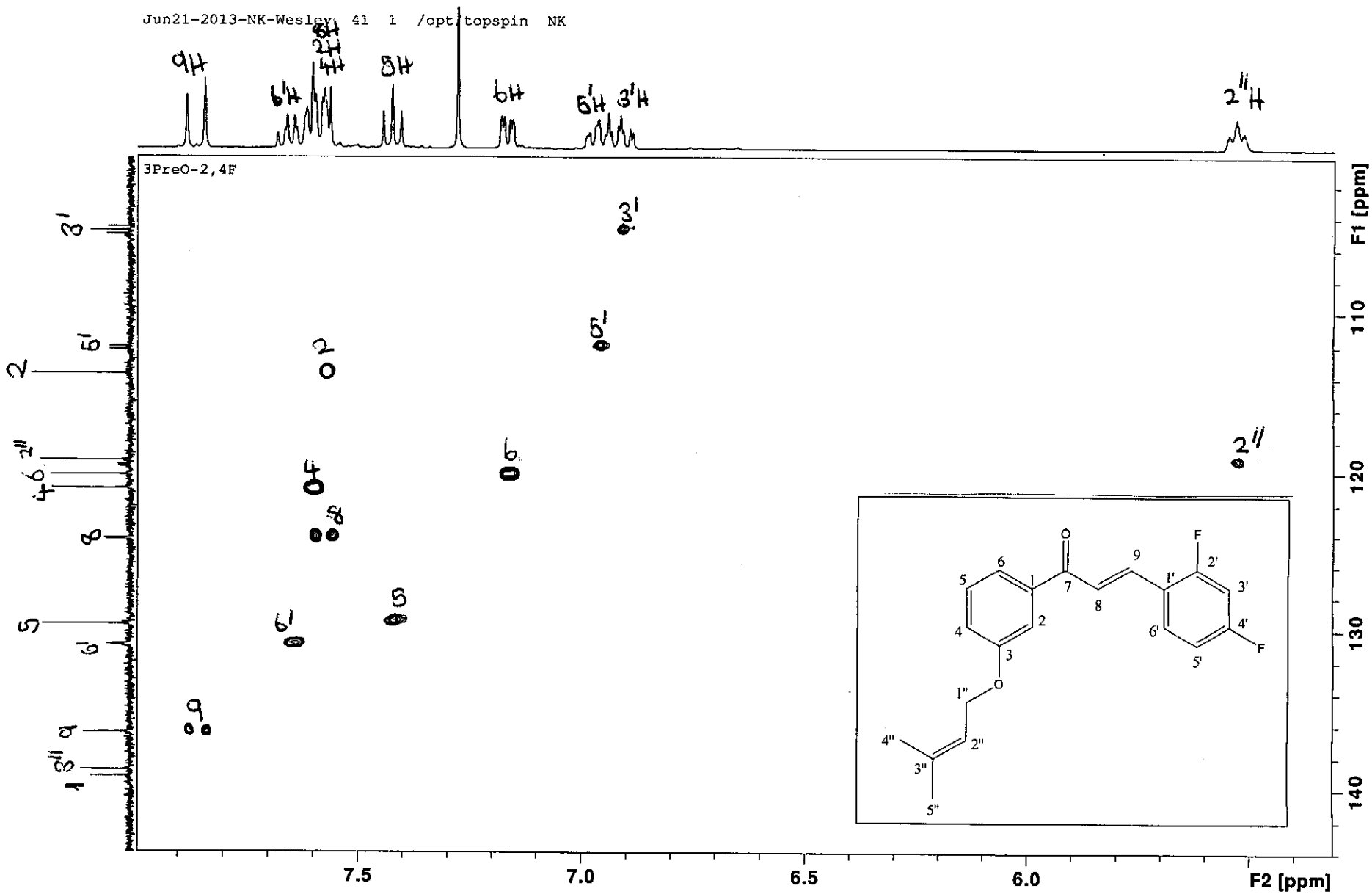
^{13}C NMR spectrum of 2',4'-difluoro-3-oxyprenylchalcone, (XXI)



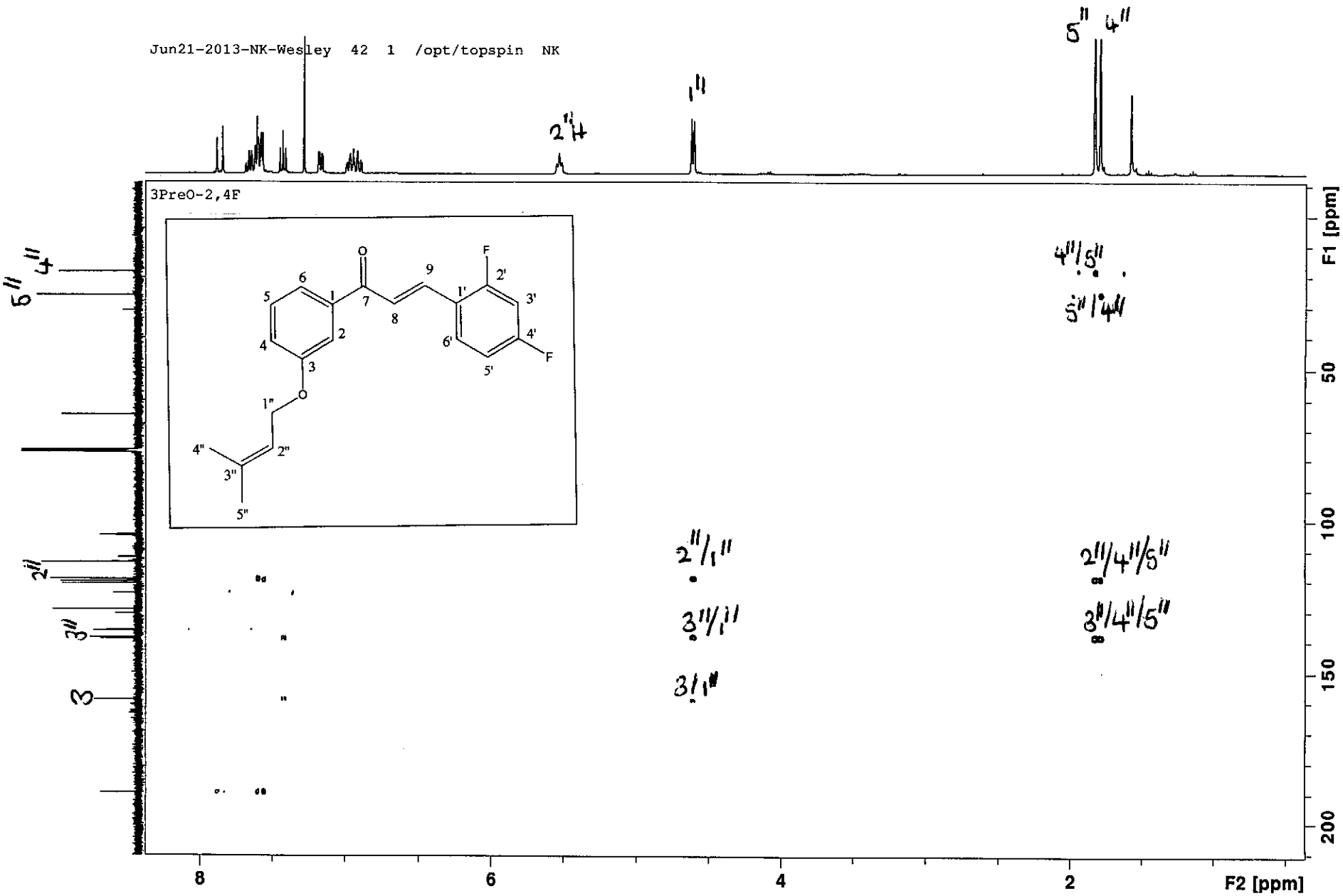
^{13}C NMR spectrum of 2',4'-difluoro-3-oxyprenylchalcone, (XXI)



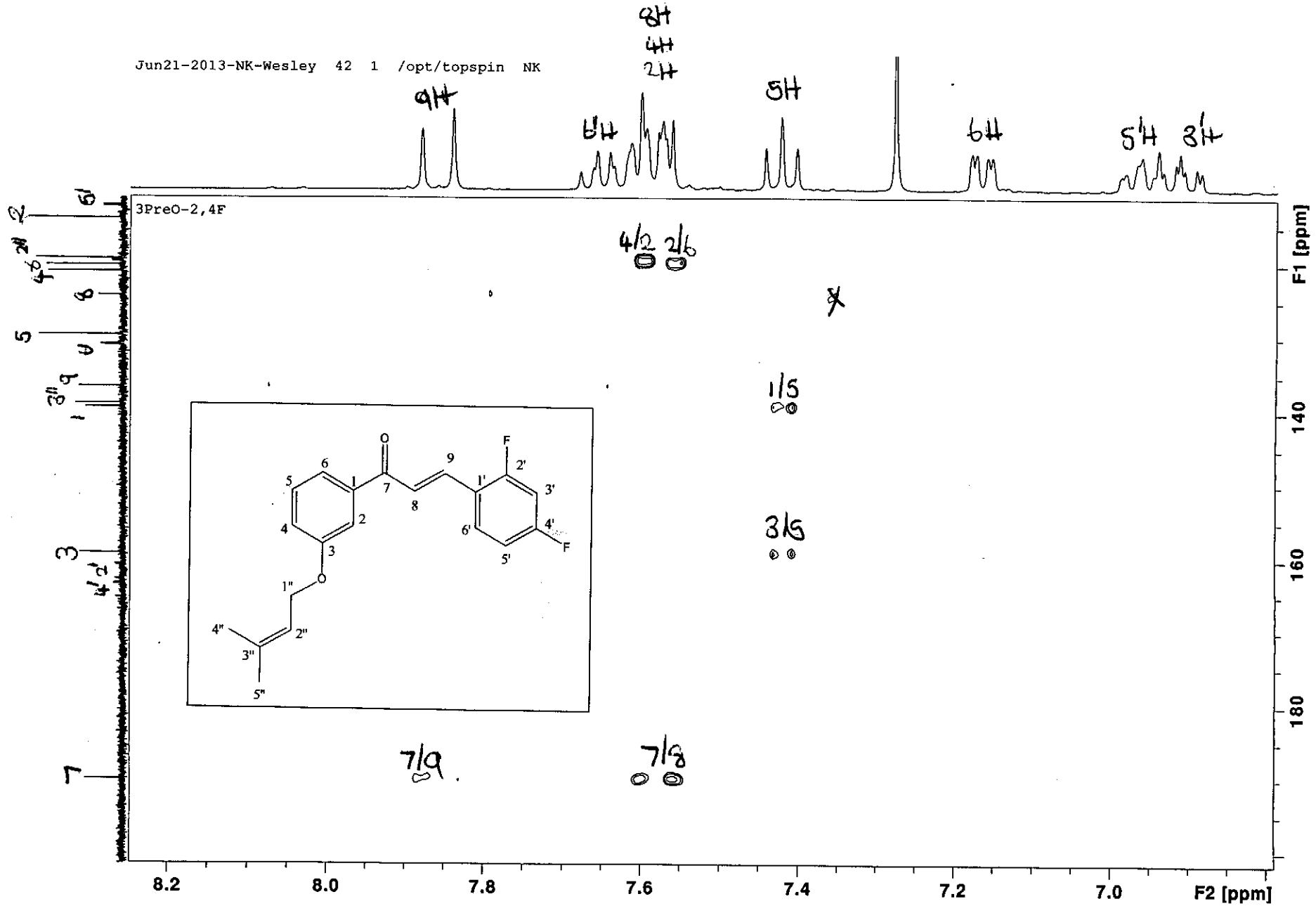
HSQC spectrum of 2',4'-difluoro-3-oxyprenylchalcone, (XXI)



HSQC spectrum of 2',4'-difluoro-3-oxyprenylchalcone, (XXI)



HMBC spectrum of 2',4'-difluoro-3-oxyprenylchalcone, (XXI)

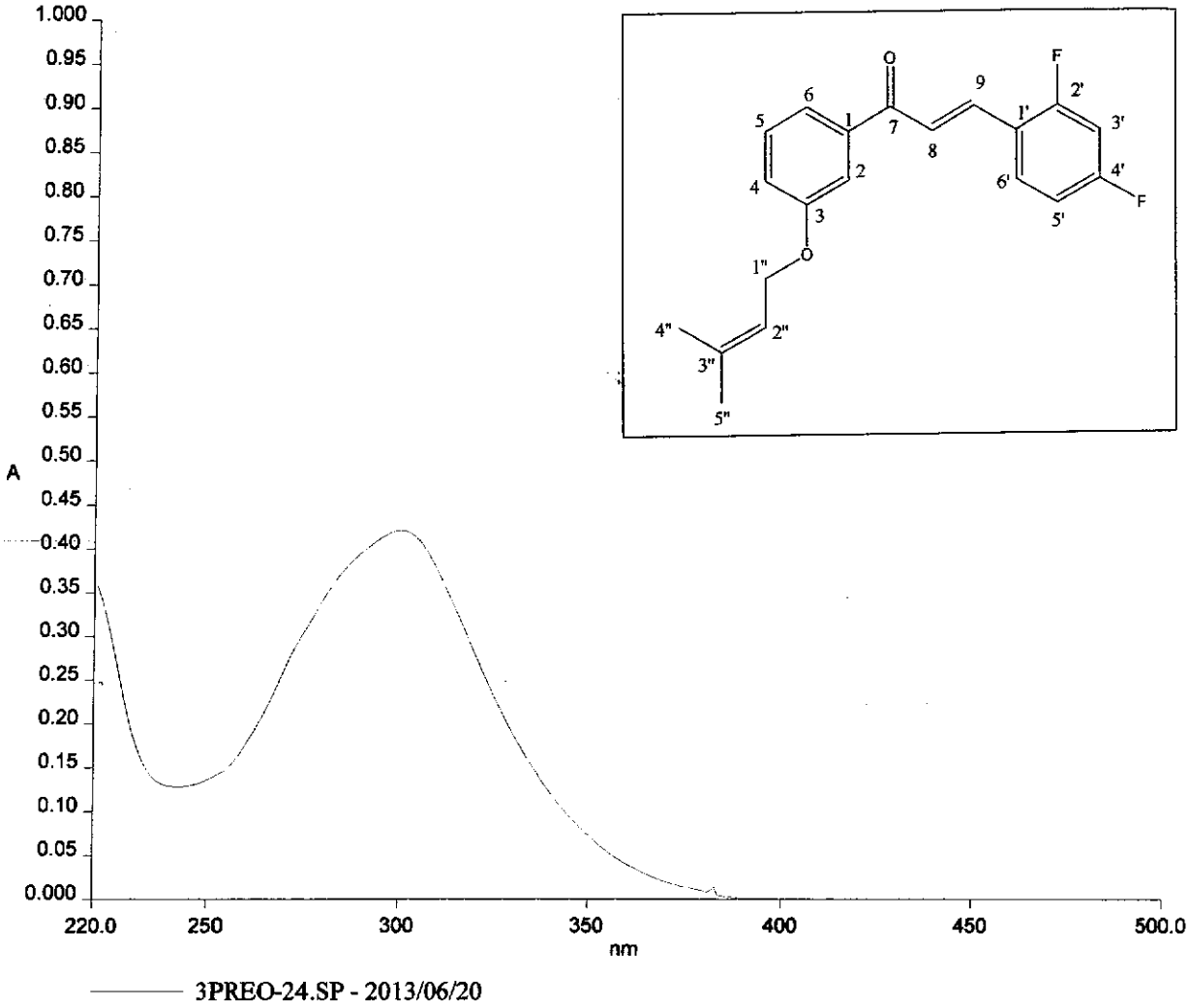


HMBC spectrum of 2',4'-difluoro-3-oxyprenylchalcone, (XXI)

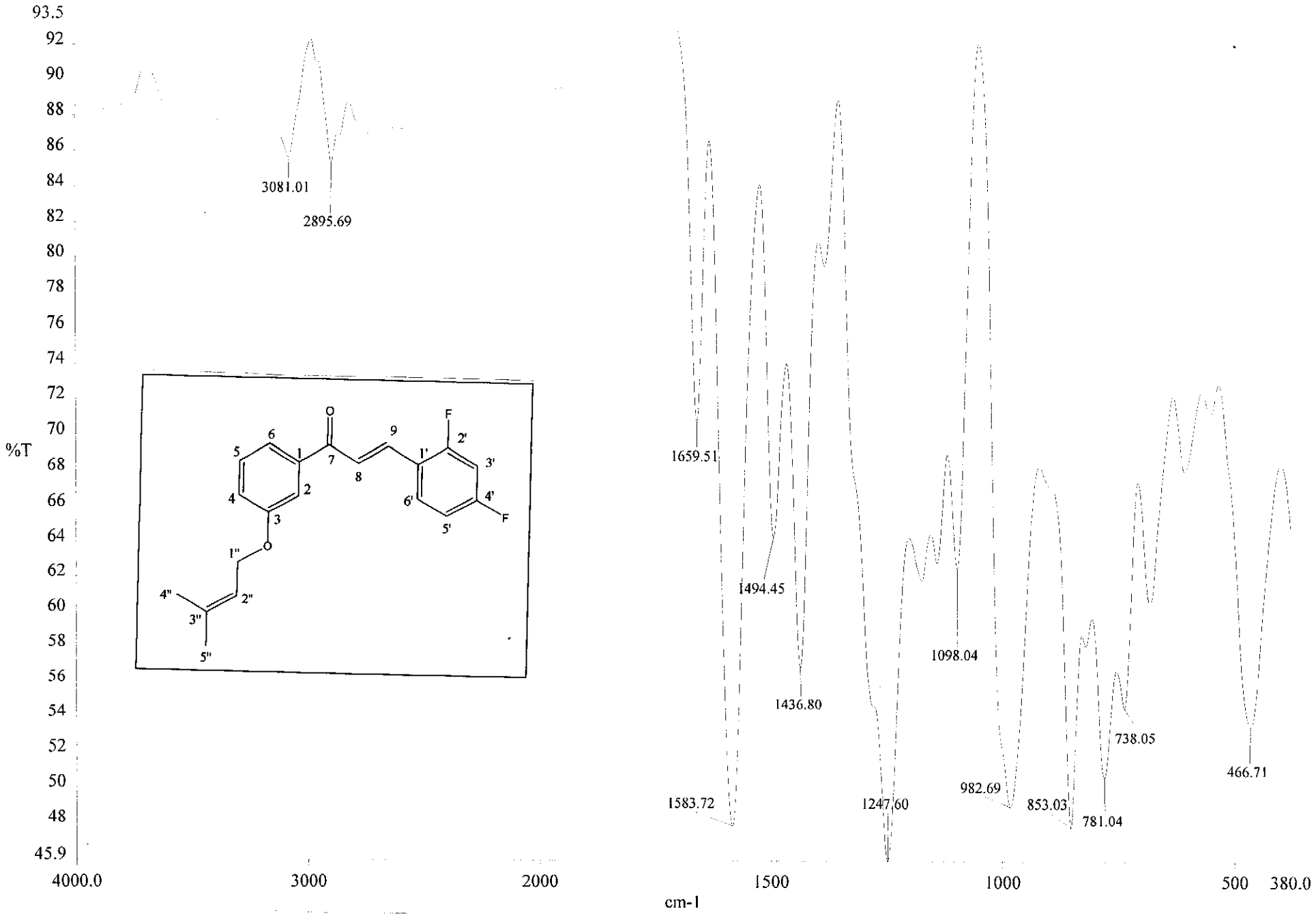
Max (300nm) – 0.4204

lgε = 5.32

Date: 2013/06/20 Time: 10:55:06 AM



Ultra violet (UV) spectrum of 2',4'-difluoro-3-oxyprenylchalcone, (XXI)



Infra-Red (IR) spectrum of 2',4'-difluoro-3-oxyprenylchalcone, (XXI)

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Operator   : neal
Acquired   : 21 Jun 2013  13:13     using AcqMethod NATPRODUCTS AUTOMATED SPLITLESS.M
Instrument :   5973n
Sample Name: 3preo-2,4f
Misc Info  :
Vial Number: 5
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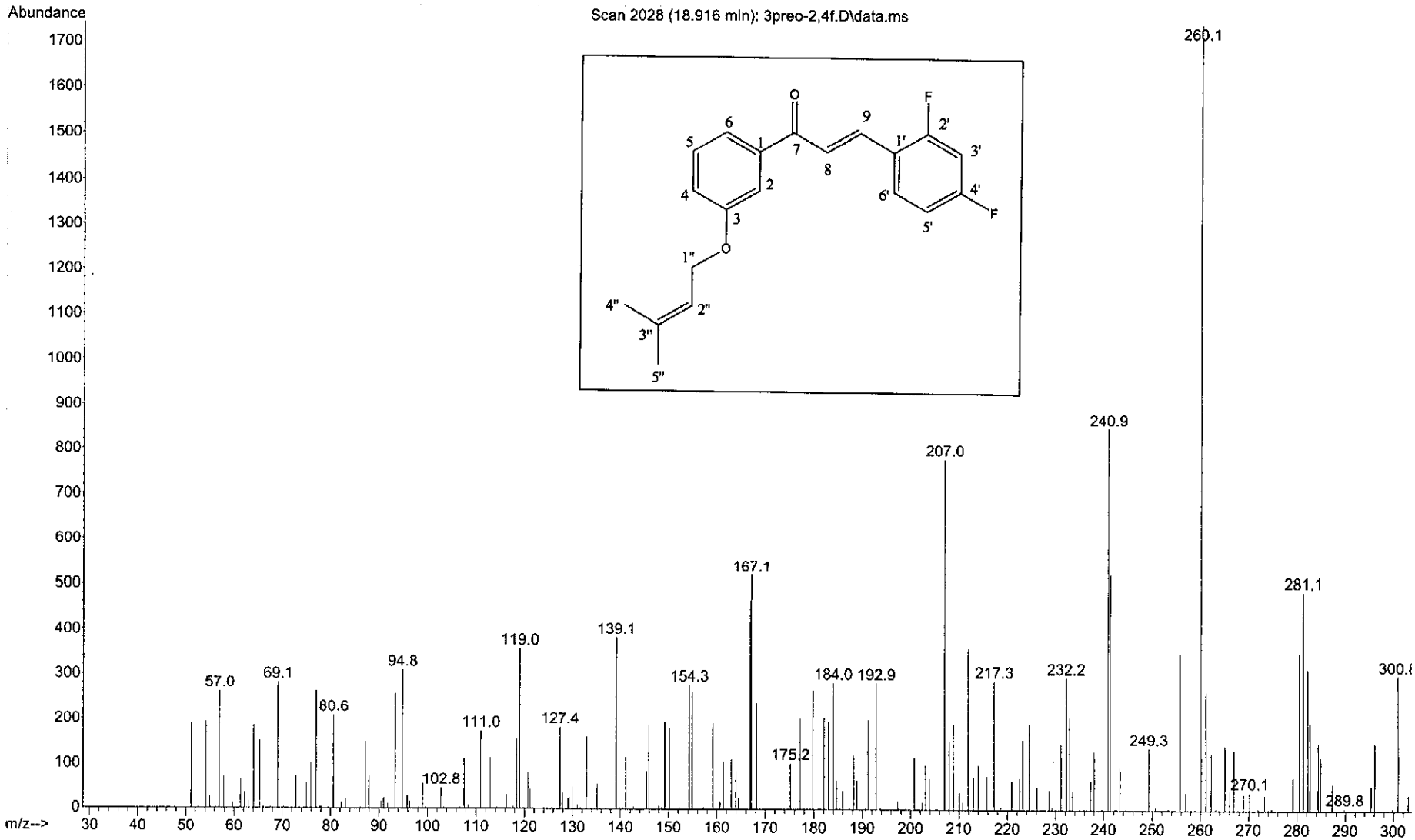


GC-MS spectrum of 2',4'-difluoro-3-oxyprenylchalcone, (XXI)

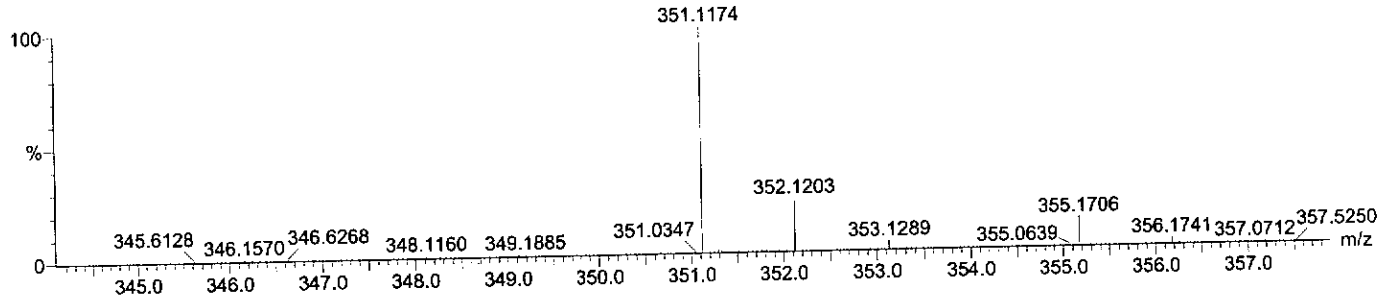
Elemental Composition Report

Single Mass Analysis

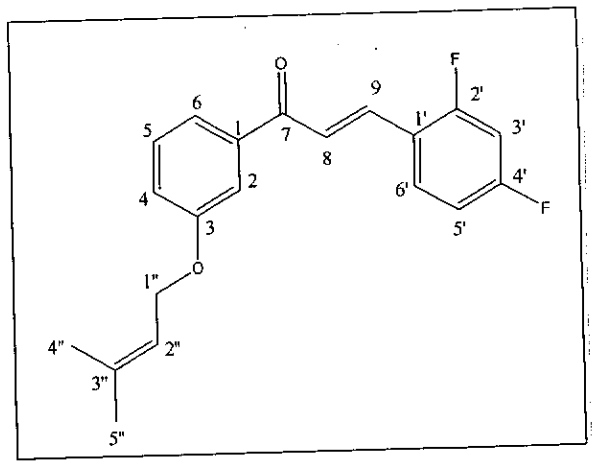
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
15 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 15-20 H: 15-20 O: 0-5 F: 0-2 Na: 0-1

3PreO-24F 2 (0.017) Cm (1:15)
TOF MS ES+ 7.79e+003



Minimum:				-1.5							
Maximum:		5.0	5.0	100.0							
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula	C20	H18	O2	F2	Na
351.1174	351.1173	0.1	0.3	10.5	375.5	0.0						



HR-MS spectrum of 2',4'-difluoro-3-oxyprenylchalcone, (XXI)