UNIVERSITY OF KWAZULU-NATAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF FLUORINATED DERIVATIVES OF 2-STYRYLCHROMONES AND 2-THIOXO IMIDAZOLE DICARBOXYLATE ESTERS

2012

MEHBUB I KHALIL MOMIN

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2-STYRYLCHROMONES AND

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2012

A thesis submitted to the school of Chemistry, Faculty of Science and Agriculture,University of KwaZulu-Natal, Westville, for the degree of Doctor of Philosophy.

This Thesis has been prepared according to **Format 4** as outlined in the guidelines from the Faculty of Science and Agriculture which states:

This is a thesis in which chapters are written as a set of discrete research papers, with an overall introduction and final discussion. Where one (or all) of the chapters have alreadybeen published. Typically these chapters will have been published in internationallyrecognized, peer- reviewed journals.

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

Supervisor:

Signed: --------------------------------Name: ------------------------- Date: --------------

ABSTRACT

Two classes of fluorinated derivatives were synthesized in this work to test the effects of the fluorinated drugs in antibacterial, antioxidant and anti-platelet activity. These two classes were the 2-styrylchromones and the 2-thioimidazoles. The 2-styrylchromones were tested for their antibacterial activity and the 3-hydroxypentadien-1one intermediates were tested for their antioxidant activity. The 2-thioimidazoles were tested for the ability to inhibit platelet aggregation *in vitro*.

A total of ten 2-styrylchromones together with their intermediates were synthesized of which six were new(**A5a-A5f**). The two intermediates to each of the six compounds were also new and together with the 2-styrylchromones resulted in thirty compounds being synthesised and characterised. The synthesis was based on the Baker-Venkataraman rearrangement using substituted cinnamic acids and hydroxyacetophenones.All the 2-styrylchromones were screened for their antibacterial activity using Gram-positive bacteria (*Staphylococcus aureus,scuii* and *xylosus* and *Bacillussubtilis*) and Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*and *Klebsiella pneumonia*). The compounds were most effective against *B. subtilis* followed by *S. aureus* and a single strain of *E. coli* (ATCC 25922). Difluorination on the phenyl ring was shown to enhance antibacterial activity and fluorine substitution at the 6-position was shown to be far superior to substitution at the 7-position. In comparison to tetracycline, the activity indices of the fluorinated styrylchromones ranged from 0.50 to 0.75 against *B. subtilis*.

The fluoro and methoxy analogues of (2Z, 4E)-3-hydroxy-1-(2-hydroxyphenyl)-5-(phenyl) penta-2, 4-dien-1-one, the intermediates to the 2-styrylchromones were tested for their ability to act as antioxidants since they contained a 3-hydroxy group in the backbone of their

structure. They were screened by the 2, 2-diphenyl-1-pycryl-hydrazyl (DPPH) radical scavenging assay and Ferric Reducing Power assay (FRAP).All the methoxylated analogues showedbetter activity thanthe fluorinated analogues and comparable to that of ascorbic acid.

Seven fluorinated derivatives of diethyl-2-(benzylthio)-2,3-dihydro-1H-imidazole-4,5-dicarboxylate (**B6a-B6g**) as well as a nitro and chloro derivative (**B6h-B6i**) also known as 2-thiomidazole derivativeswere prepared in five steps from glycine, ethyl formate, diethyl oxalate, potassium thiocyanate and substituted benzyl bromides. The synthesized compounds exhibited concentration dependent anti-platelet aggregation activity on both the thrombin and ADP induced platelet aggregation. The 4-nitro and 4-fluoro compounds exhibited the highest activity from the compounds tested, with estimatedIC$_{50}$ values of 1.05 and 0.99 mM for the thrombin-induced and ADP-induced platelet aggregation respectively. Three of the compounds, the 3,4-difluoro(**B6c**), 4-nitro(**B6h**) and 3-chloro(**B6i**) derivatives have reasonable activity in both of the assays and could have potential as broad spectrum antiplatelet inhibitors. With the exception of **B6c**, the fluoro derivatives were not as active as the nitro and chloro compounds.

All the reactions in this work were monitored by ^{1}H and ^{13}C NMR at each step and all compounds were characterized using 1D and 2D NMR as well as MS, IR and UV data. All the synthesised compounds were fully characterised unambiguously and the respective carbon and proton resonances were assigned with the aid of HSQC, HMBC and NOESY data. In addition, crystal structures of two 2-styrylchromones and three of its cinnamate ester intermediates as well as the 2-thioimidazole provide a full structural analysis of the compounds synthesised.

STRUCTURES OF COMPOUNDS

A-3a

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

A-3b

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

A-3c

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

A-3d

Chemical Formula: $C_{17}H_{12}F_2O_3$
Exact Mass: 302.0755

A-3e

Chemical Formula: $C_{17}H_{12}F_2O_3$
Exact Mass: 302.0755

A-3f

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

A-3g

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

A-3h

Chemical Formula: $C_{18}H_{16}O_4$
Exact Mass: 296.1049

A-3i

Chemical Formula: $C_{19}H_{18}O_5$
Exact Mass: 326.1154

A-3j

Chemical Formula: $C_{18}H_{14}O_5$
Exact Mass: 310.0841

A-4a

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

A-4b

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

A-4c

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

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A-4h

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Exact Mass: 296.1049

A-4i

Chemical Formula: $C_{19}H_{18}O_5$
Exact Mass: 326.1154

A-4j

Chemical Formula: $C_{18}H_{14}O_5$
Exact Mass: 310.0841

A-5a

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

A-5b

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

A-5c

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

A-5d

Chemical Formula: $C_{17}H_{10}F_2O_2$
Exact Mass: 284.0649

A-5e

Chemical Formula: $C_{17}H_{10}F_2O_2$
Exact Mass: 284.0649

A-5f

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

A-5g

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

A-5h

Chemical Formula: $C_{18}H_{14}O_3$
Exact Mass: 278.0943

A-5i

Chemical Formula: $C_{19}H_{16}O_4$
Exact Mass: 308.1049

A-5j

Chemical Formula: $C_{18}H_{12}O_4$
Exact Mass: 292.0736

B-2

Chemical Formula: $C_4H_{10}ClNO_2$
Exact Mass: 139.0400

B-3

Chemical Formula: $C_5H_9NO_3$
Exact Mass: 131.0582

B-5

Chemical Formula: $C_9H_{12}N_2O_4S$
Exact Mass: 244.0518

B-6a

Chemical Formula: $C_{16}H_{17}FN_2O_4S$
Exact Mass: 352.0893

B-6b

Chemical Formula: $C_{16}H_{17}FN_2O_4S$
Exact Mass: 352.0893

B-6c

Chemical Formula: $C_{16}H_{16}F_2N_2O_4S$
Exact Mass: 370.0799

B-6d

Chemical Formula: $C_{16}H_{13}F_5N_2O_4S$
Exact Mass: 424.0516

B-6e

Chemical Formula: $C_{17}H_{17}F_3N_2O_4S$
Exact Mass: 402.0861

B-6f

Chemical Formula: $C_{18}H_{16}F_6N_2O_4S$
Exact Mass: 470.0735

B-6g

Chemical Formula: $C_{17}H_{17}F_3N_2O_5S$
Exact Mass: 418.0810

B-6h

Chemical Formula: $C_{16}H_{17}N_3O_6S$
Exact Mass: 379.0838

B-6i

Chemical Formula: $C_{16}H_{17}ClN_2O_4S$
Exact Mass: 368.0598

ABBREVIATIONS

^{13}C NMR	(C-13) nuclear magnetic resonance spectroscopy
^{1}H NMR	proton (H-1) nuclear magnetic resonance spectroscopy
^{19}F NMR	fluorine-19 (F-19) nuclear magnetic resonance spectroscopy
Ac	acetate
EtOH	ethanol
MeOH	methanol
aq	aqueous
br	broad
c	concentration
cc	column chromatography
CD$_3$OD	deuterated methanol
CDCl$_3$	deuterated chloroform
DMSO-d$_6$	deuterated dimethyl sulfoxide
D2O	deuterated water
COSY	correlated spectroscopy
d	doublet
dd	double of doublets
DEPT	distortionless enhancement by polarization transfer
DNA	deoxyribonucleic acid
DNP	dictionary of natural products
EIMS	electron impact mass spectroscopy
HMBC	heteronuclear multiple bond coherence
HPLC	high pressure liquid chromatography
HREIMS	high resolution electron impact mass spectroscopy
HSQC	heteronuclear single quantum coherence
Hz	hertz
IR	infrared
m	multiplet
Me	methyl
Mp	melting point
MS	mass spectroscopy

NOESY	nuclear overhauser effect spectroscopy
RSA	radical scavenging activity
s	singlet
t	triplet
td	triplet of doublets
TCA	trichloroacetic acid
TGI	total growth inhibition
TLC	thin layer chromatography
UV	ultraviolet
MIC	minimum inhibitory concentration
SC	styrylchromone

DECLARATIONS

DECLARATION 1 – PLAGIARISM

I, Mehbub I Khalil Momin declare that

1. The research reported in this thesisis my original research, except where otherwise indicated.

2. This thesis has not been submitted for any degree or examination at any other university.

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

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

   a. Their words have been re-written but the general information attributed to them have been referenced

   b. Where their exact words have been used, then their writing has been placed in italics and inside quotation marks, and referenced.

5. This thesis does not contain text, graphics or tables copied and pasted from the Internet, unless specifically acknowledged, and the source being detailed in the thesis and in the References sections.

Signed ………………………………………………………

DECLARATION 2-PUBLICATIONS

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

Publication 1

Momin, M.I.K., Ramjugernath, D., Chenia, H. and Koorbanally, N.A., Synthesis, crystal structure and evaluation of novel fluorinated 2-styrylchromones as antibacterial agents.submitted to *the European Journal of Medicinal Chemistry.*

Publication 2

Momin, M.I.K., Ramjugernath, D.and Koorbanally, N.A., Structure elucidation of a series of fluoro- and methoxy-2-styrylchromones using 1D and 2D NMR spectroscopy. To be submitted to *Magnetic Resonance in Chemistry.*

Publication 3

Momin, M.I.K., Ramjugernath,D., Islam, S.and Koorbanally, N.A., Antioxidant activity of 3-hydroxy-1-(2-hydroxyphenyl)-5-(phenyl)-2,4-pentadien-1-one analogues.To be submitted to *Pharmaceutical Biology.*

Publication 4

Momin, M.I.K., Ramjugernath,D., Mosa, R.A., Opoku, A.R.and Koorbanally, N.A., Synthesis, and *in vitro* antiplatelet aggregation screening for novel fluorinated diethyl-2-(benzylthio)-2,3-dihydro-1H-imidazole-4,5-dicarboxylate derivatives. Submitted to *Journal of Pharmacy and Pharmacology.*

Publication 5

Momin, M.I.K., Pawar, S., Koorbanally, N.A., Su, H. and Ramjugernath, D., 2-Acetylphenyl (2E)-3-(4-fluorophenyl) acrylate, Acta Crystallographica Section E, 2012, E68, o3049. (*Published*)

Publication 6

Momin, M.I.K., Koorbanally, N.A., Su, H. and Ramjugernath, D., (E)-2-acetyl-4-fluorophenyl-3-(4-fluorophenyl) acrylate. To be submitted to *Acta Crystallographica Section E.*

Publication 7

Momin, M.I.K., Koorbanally, N.A., Su, H. and Ramjugernath, D., (E)-2-acetylphenyl- 3-(4-methoxyphenyl) acrylate. To be submitted to *Acta Crystallographica Section E.*

Publication 8

Momin, M.I.K., Koorbanally, N.A., Su, H. and Ramjugernath, D., 2'-Fluro-2-styrylchromone. To be submitted to *Acta Crystallographica Section E.*

From all the above publications, my role included carrying out all the experimental workand contributing to the writing of the publications along with my supervisor. The other co-authors contribution was that of an editorial natureandchecking on the scientific content and my correct interpretation. Based on their expertise, they have added minor parts to the manuscripts.

Signed: ………………………………..

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I would also like to thank my parents, and sister. They have given me their unequivocal support throughout, as always, for which my mere expression of thanks likewise does not suffice. Mostly, I want to acknowledge almighty for his abundance of love and blessings that He has showered upon me.

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Chapter 1. Introduction

1.1.   An introduction to Fluorine pharmaceuticals

Fluoride is relatively abundant (0.065%) in the earth's crust and the most abundant of all the halogens. It was first isolated in 1886 by the French chemist Henry Moissan, which earned him the Nobel Prize in 1906. The importance of fluorinated organic molecules has grown over the last 50 years, particularly in the pharmaceutical and agrochemical industries(Sandford et al., 2000; Key et al., 1997), highlighting the active nature of research in this particular area. Fluorine has unique properties since it is a very small atom with a high electronegativity and low polarisability (Sasaki et al., 2004; 2010). The presence of one (or more) fluorine atom(s) in place of hydrogen in anorganic compound confers upon themproperties and reactivity which are significantly different from those of the hydrogenated compound because the length of the C-F bond is almost the same as the length of the C-H bond (1.39 and 1.09 Årespectively).

The fluorinated analogues have three lone pairs around the fluorine substituent and combined with its high electronegativity, makes fluorinated analogues more reactive than the non-fluorinated compounds. Biologically important compounds in which the hydrogen or oxygen in C–H or C–O bonds have been replaced with fluorine haveresulted in molecules with special advantages. For example, fluorination increases the activity and selectivity of cortisone and fluorination in pyrimidines like 5-fluorouracil is effective in the treatment of cancer (Kirk et al., 2006).

Prior to the synthesis of 5-fluorouracilin1957, which was developed into an anti-tumour drug Thalidomide, there were no drugs containing fluorineon the market. Since then, the situation changed dramatically with over 150 fluorinated drugs beingpresent today(Hangmann et

al.,2008),representing approximately 20% of all pharmaceuticals(Kirk et al., 2006; Isanbor et al., 2006; Muller et al., 2007). Apart from the pharmaceutical market, fluorine compounds have also found application in agrochemicals, where these compounds have an even higher proportionthan the pharmaceuticals (Muller et al., 2007).Presently,pharmaceutical research involving fluorinated molecules is routine(Park et al., 2001) and some fluorinated drugs are among the most popular, for example, the anti-depressant fluoxetine (Prozac), the anti-cholesterol atorvastatin (Lipitor) or the anti-bacterial ciprofloxacin (Ciprobay) (Figure1-1).

Figure1-1 Examples of some popular fluorine drugs

1.1.1 Nomenclature

Organic fluorine compoundsare named according to the rules of theInternational Union for Pure and Applied Chemistry (IUPAC).However, for highly fluorinated molecules with several carbon atoms, this nomenclature can be confusing. The term "perfluoro" may be used when all hydrogen atoms bonded to the carbon skeleton in a particular substituent have been replaced by fluorine. This does not apply to functional groups with hydrogen (e.g., CHO or

COOH). Fluorine on aromatic or aliphatic moieties, like other halides are termed fluoro, for example 4-fluoronitrobenzene contains a fluorine at C-4 and 2, 2-difluoropentane contains two fluorine atoms at C-2 of the pentane chain. The methyl and methoxy functional groups where fluorine has replaced all of the hydrogens is termed trifluoromethyl ($-CF_3$) and trifluoromethoxy ($-OCF_3$). Likewise, an acetate group where fluorine has replaced hydrogen is termed trifluoroacetate (CF_3COO-).

1.1.2 Electronic effect of fluorine

The C-F bond is the strongest single bond in organic chemistry, in comparison to C-C, C-H, C-O and C-Cl bonds(Table 1-1) (Park et al., 2001;O' Hagan et al., 2008).This can be explained by the high electronegativity of the fluorine atom which strongly attracts the covalent electron density, rendering the C-F bond highly polarised. The electron density is displaced towards the fluorine. Thus, the high strength of the bond is due to an electrostatic attraction between $C^{\delta+}$ and $F^{\delta-}$ rather than a normal covalent bond with electron sharing (Park et al., 2001).

Table 1-1Dissociation energies of various C-X bonds (O' Hagan et al., 2008)

Bond	Dissociation energy (kcalmol^{-1})
C-F	105.4
C-O	84.0
C-C	83.1
C-Cl	78.5
C-H	98.8

1.1.3 Steric influence of fluorine

The fluorine atom is smaller than oxygen, nitrogen and chlorine with a Van der Waals radius of 1.47 Å (O = 1.52; N = 1.55 and Cl = 1.75 Å) (Bondi et al., 1964) and has been found to be a good substituent to replace hydrogen (1.20 Å) in organic molecules (O' Hagan et al., 2008).The substitution of fluorine for hydrogen does not result in steric hindrance at all (Wodzinska et al., 2008) and in crystal structures, hydrogen and fluorine are often interchangeable. Thus, despite the difference in size, fluorine is a good hydrogen mimic and has been widely used in this regard in medicinal chemistry (O' Hagan et al., 1997). Replacing hydrogen with fluorine allows modification of the electronic environment without altering the steric environment of the molecule.   There is however some evidence that replacing a hydrogen atom with fluorine can induce a change in the geometry of the molecule (Liu et al., 2008).

An example of the effect that fluorine can have on adjacent functional groups is illustrated by the pK_a of amines and carboxylic acids. Ethylamine has a pK_a of 10.58 but 1-fluoroethylamine has a pK_a of 9.19, 1,1-difluoroethylamine a pK_a of 7.45 and 1,1,1-trifluoroethylamine has a pK_a of 5.40. When hydrogen is replaced with fluorine the molecule becomes more acidic. This is due to its inductive withdrawal effects which weaken the N-H bond. The same effect is seen in carboxylic acids (CH_3COOH has a pKa of 4.76; CH_2FCOOH 2.60; CHF_2COOH 1.40 and CF_3COOH 0.51).

The CF_3 group though is not a good CH_3 mimic. CF_3 is far bigger than CH_3 and experimental evidence indicates that it is actually closer to an isopropyl group and sometimes acts more like *tert*-butyl in terms of steric impact (Riggi et al., 1995).

1.1.4 Hydrogen bonding to fluorine

Fluorine is highly electronegative and the C-F bond highly polarised with three lone pairs being present around the fluoro substituent. This makes fluorine an ideal hydrogen bond acceptor. However H····F contacts are rare as revealed by structures deposited in the Cambridge Structural Database (Dunitz et al., 1997) and fluorine forms hydrogen bonds only in the absence of a better acceptor (Abraham et al., 1989).

1.1.5 The chemical properties of fluorinated compounds

The influence of fluorine is greatest in highly fluorinated and perfluorinated compounds and these compounds have a high thermal stability and chemical resistance and are physiologically inert (Sandford et al., 2000). This makes them suitable inmany applications for which hydrocarbonsare not. Properties that are exploited commercially include high thermal and chemical stability, low surface tension, and good dielectric properties. This can be seen in fluoropolymers, perfluorinated oils and inert fluids (Boday et al., 2012). These differences from hydrocarbon based organic moleculesis due to the very small inter-and intra-molecular forces for perfluoro-carbon molecules. However, the partially fluorinated molecules arequite polar and have appreciable molecular interactions owing to strong electrostatic bond dipole interactions. Organic molecules which are fluoro substituted are affected by both electron withdrawal by induction and electron donation by resonance since fluorine can do both.

1.1.6 Fluorine and lipophilicity

To crosslipid membranes, a drug needs to be sufficiently lipophilic and therefore this property is important in medicinal chemistry. However, if a drug is too lipophilic, this would reduce its water solubility and its bioavailability and therefore the right proportion of lipophilicity is needed in order for a drug to be successful. Selective fluorinationis a good way to introduce lipophilicity into a molecule and the introduction of one or more fluorine atoms can increase the lipophilicity in an incremental manner.An Increase in lipophilicity results in a concurrent increase in hydrophobicity. Aromatic fluorination is known to always increase the liphophilicity of molecules (Filler et al., 2009; Boiko et al., 2010).

1.1.7 Effects of fluorine on Biological activity

In the area of medicinal chemistry, incorporation of fluorine into organic compounds have had an exceptional impact. Fluorinated compounds have been used as antivirals (Filler et al., 2009), antibacterials (Hardy et al., 1987), in the treatment of HIV (Marquez et al., 1990), malaria (Simpson et al., 2000), obesity (Vermes et al., 2000), mental illness (Park et al., 1994), cancer (Klijn et al., 2001; Feldman et al., 2001), Alzheimer's disease (Zhang et al., 2005) and as herbicides and insecticides(Key et al., 1997). The incorporation of fluorine into a biologically active compound alters the electronic, lipophilic and steric parameters and can critically increase the intrinsic activity, the chemical and metabolic stability, and bioavailability (Dinoiu et al., 2006).

Fluorinated compounds find pharmaceutical applications as steroids.For example 9α-fluoro-11-β-hydroxycorticoids exhibited anti-inflammatory activity (Fried et al., 1954); broad spectrum antibiotics such as ciprofloxacin and temafloxacin(Filler et al., 2009); antifungal agents such asfluconazole and voricon-azole (Kuznetsovaet al., 2008; Sabo et al., 2000),

effective in the treatment of dermal and vaginal infections; anticancer agents such as tamoxifen, an estrogenantagonist used in the treatment of hormone dependent breast cancer (Klijn et al., 2001)., fludarbine, a purine antimetabolite, effective in the treatment of B-Cellchronic lymphocytic leukemia (Isanbor et al., 2006; Rummel et al., 1999) and flutamide, an anti-androgen used in the treatment of prostate cancer (Feldman et al., 2001); antimalarials such as mefloquin(Simpson et al., 2000); haloperidol, an antipsychotic drug used in the treatment of schizophrenia and acute psychotic states (Park et al., 1994); fluoxetine and citalopram, antidepressant drugs (Hiemke et al., 2000); and cardioprotective effects showed by the pinacidil-derivative flocalin(Figure 1-2) (Voitychuk et al., 2012).

Figure 1-2 Examples of fluorinated drugs

Two other fields where fluorine molecules have been widely used are in aneasthesia and Positron Emission Tomography (PET). Inhalation anesthetics are almost entirely dependent on fluorine chemistry. Fluoroxene ($CF_3CF_2OCH=CH_2$), isoflurane ($CF_3CClOCHF_2$), sevoflurane (($CF_3)_2CHOCH_2F$) and desfluorane ($CF_3CHFOCHF_2$) have almost revolutionized the field of anesthesiology because of their low blood-gas partition coefficients and their minimal levels of metabolism, which minimize side effects and shortens the recovery time of patients (Key et al., 1997).

Fluoxetine

Citalopram

Haloperidol

Figure 1-2 continued... Examples of fluorinated drugs

Positron Emission Tomography (PET) is non invasive nuclear medical imaging technique that makes use of ^{18}F isotope tracers. ^{18}F is used since it has a longer half-life compared to the other commonly used radionuclides. PET scans show biological processes, providing information on metabolic processes (Persur, 2008). The fluorinated compound 2-deoxy-2-[^{18}F] fluoro-D-glucose or [^{18}F] FDG is the most frequently used radiopharmaceutical.

1.2.   Introduction to 2-styrylchromones

Chromones are one of the most abundant classes of naturally occurring compounds found especially in plants. They are oxygen-containing heterocyclic compounds with a benzoannelated γ-pyrone ring, the parent compound being chromone (Figure 1-3) (Douglas et al., 2003). The 2-styrylchromones (Figure 1-3) are a new class of flavonoids, structurally

related to the flavones (2-phenylchromones) and characterized by the attachment of a styryl group to the C2-position instead of a phenyl group as in the flavonoids.

Chromone derivatives are relatively non-toxic and some are beneficial in our diets, for example the flavonoids, where polyhydroxy flavonoids are known antioxidants contained in a wide variety of fruit and vegetables and in red wine.These antioxidants are known to fight off damaging free radicals which cause harm to normal cells. Chromone derivatives also find application as drugs on the market such asnedocromil for the treatment of asthma (Barnes et al., 2006; Beecher et al., 2003).

| **1** | **2** | **3** |
| Chromone | Flavone | 2-styrylchromones |

Figure 1-3 The basic structure of a chromone, flavone and 2-styrylchromone

Unlike the flavonoids, 2-styrylchromones are not that common in nature, with hormothamnione**(4)**and 6-desmethoxyhormothamnione**(5)** (Figure 1-4) being the first and to the best of our knowledge the only naturally occurring styrylchromones which were isolated from the marine blue green algae, cryptophyte, *Chrysophaeumtaylori* and which demonstrated cytotoxic activity against leukemia cells (Gerwick et al., 1989).

Hormothamnione6-desmethoxyhormothamnione

4   5

Figure 1-4 Natural 2-styrylchromones

The biological activities of 2-styrylchromones have recently been reviewed by Gomes et al. (2010). The 2-styrylchromones were shown to be A_3 adenosine receptor antagonists (Karton et al., 1996), have hepatoprotective activity (Fernandes et al., 2003), be potent antioxidants (Filipe et al., 2004), have anti allergic properties (Doria, et al., 1979), antiviral activity (Desideri, et al., 2000), anticancer activity (Marinho et al., 2008; Momoi et al., 2005; Gerwick et al., 1987) and to display xanthine oxidase inhibition to treat for example gout, hypertension and hepatitis linked to xanthine oxidase actitivity (Fernandes, 2002).

1.2.1   Synthesis

The synthesis of 2-styrylchromones was reviewed by Silva et al. (2004). They can be synthesised by two basic methods, the aldol condensation and the Baker-Venkataramanrearrangment. Both these methods make use of 2'-hydroxyacetophenones, with the aldol condensation making use ofcinnamaldehydes (Pinto et al., 1996; 2004; Silva et al., 1994; 1996; 1998; 2004) and the Baker-Venkataraman rearrangement using cinnamoyl chlorides (Pinto et al., 1996; 1998; 1999; 2000; Reddy et al., 1996; Santos et al., 2003).

Both methods result in 2,4-pentadien-1-ones as the intermediate, with the Baker-Venkataraman rearrangment having a 3-hydroxyl group, which makes these intermediates susceptible to cyclisation with acid. For the cyclisation step, halogens such as I_2 and Br_2 with DMSO are used for both intermediates, whereas acids such as hydrochloric acid and *p*-toluenesulphonic acid is used only for the 3-hydroxy intermediate that results from the Baker-Venkataraman rearrangement. This makes the Baker-Venkataraman rearrangement a more desirable synthetic route as it precludes the use of I_2 or Br_2 and the cyclisation can be carried out using the relatively mild *p*-toluene sulphonic acid.

1.2.1.1 Aldol condensation / Oxidative cyclisation.

This method involves the base catalyzed aldol reaction of cinnamaldehydes (**6**) with 2-hydroxyacetophenones (**7**) to produce a 2'-hydroxycinnamylideneacetophenone (**8**) intermediate.This reaction is carried out with a strong base such as sodium hydroxide in methanol at room temperature, which is followed by oxidative cyclisation of **8** into (*E*)-2-styrylchromones (**9**) (Silva et al., 1998; Santos et al., 2003).More attention has been devoted in the literature to the oxidative reagents for the cyclisation. These reagents are anhydrous potassium carbonate (Pinto et al., 1996), DMSO with either I_2 or Br_2 in catalytic amounts(Pinto et al., 1994; 1999; Silva et al., 1994; 1996),ethanolicsulphuric acid (Reddy et al., 1996).A catalytic amount of iodine with DMSO was reported as the most successful oxidative cyclisation reagent (Silva et al., 2004) and the reaction is normally refluxed for 30 minutes to 2 hours respectively (Scheme 1-1**Error! Reference source not found.**)(Silva et al., 1998). This particular reaction also results in halogenation of the most activated position of the 2-styrylchromone when a one molar equivalent of halogen is used (Pinto et al., 1994; 1996)

It was also reported that reacting the 6'-benzyloxy-2'-hydroxycinammylideneacetophenone intermediate for longer reaction times (2 hours) results in a debenzylation reaction as well producing 5'-hydroxy-2-styrylchromones.

Reagents and conditions: (i) NaOH-H₂O, MeOH, rt. (ii) I2 (cat.) or Br₂ (cat.), DMSO, reflux, 30 min.

Scheme 1-1 Aldol condensation and oxidative cyclisation leading to the synthesis of 2-styrylchromones

1.2.1.2 Baker-Venkataraman rearrangement

The Baker-Venkataraman rearrangement is one of the most common methods used to synthesize flavonoids. In forming the 2-styrylchromones, it begins with the *O*-acylation of 2-hydroxyacetophenones (**10**) followed by a base catalyzed rearrangement of the formed esters (**12**) into 5-aryl-3-hydroxy-1-(2-hydroxyaryl)-2,4-pentadiene-1-ones (**13**). The third and last step of the synthesis is thecyclodehydration of the β-hydroxyketones into the desired 2-styrylchromones (**14**)(Scheme 1-2) (Priceet al., 1993).

This reaction was reduced to two steps by Reddy et al. (1996) producing **(13)** from **(10)**and **(11)**, using potassium carbonate in acetone and refluxing for 12 hours, which probably works via the same mechanism as the three step reaction without producing the esterified intermediate. A one step reaction involving the synthesis was reported by the same group using the same reagents, but with thiopheneacroyl chlorides instead of cinnamoylchlorides and refluxing for 16 hours (Miya et al., 1998; 2012).A second step was necessary to hydrolyse the ester from the undesired position, but the styrylchromone was produced in one step with a longer reaction time (Scheme 1-3).

Instead of using cinnamoyl chlorides, cinnamic acid anhydrides (**20**) were also reported to be used with a Ba(OH)$_2$ base in a microwave reaction (Scheme 1-4) (Goel et al., 2006).

Reagents and Conditions: (i) DCC, 4-Pyrrolidinopyridine, CH$_2$Cl$_2$, rt. X=OH; (ii) K$_2$CO$_3$, acetone, reflux, 12 h, X=Cl; (iii) a. H$_2$SO$_4$, reflux, 3h; b. p-toluenesulfonic acid or I$_2$, DMSO, 90-100 °C, 2-3 h; (iv)NaOH or KOH

Scheme 1-2 The Baker-Venkataraman rearrangement for the synthesis of 2-styrylchromones (Price et al., 1993; Reddy et al., 1996)

1.2.2   Reactivity.

Due to the conjugated unsaturated system of the styrylchromone moiety and the 2-ene-4-one moiety in the 2-styrylchromone backbone, they have been shown to participate in pericyclic reactions as dienes and dienophiles forming xanthones and polyaromatic compounds and in reactions with azo compounds forming azoles and with thiourea or diamino imines forming pyrimidines.

Scheme 1-3 One step synthesis of 2-styrylchromones (Miya et al., 1998)

1.2.2.1 Styrylchromones as dienes and dienophiles

Using daylight with chloroform as the solvent, styrylchromones were converted to xanthones by an intramolecular Diels-Alder reaction followed by an oxidative process, with a *E* to *Z* isomerisation occurring prior to this (Scheme 1-5) (Silva et al., 1996). Xanthones were also reported to be formed with pyrrolidine enamines via a [4+2] cycloaddition reaction (Scheme 1-6) (Kelkar et al., 2000). The pyrolidine enamines were formed *in situ* with the corresponding ketones as a solvent and a catalytic amount of pyrrolidine. The styrylchromone **25** was completely converted to the xanthone, probably via the intermediate **27** since this was isolated in some of the reactions, which gets converted to the xanthone via

migration of the exocyclic double bond and subsequent oxidation (Kelkar et al., 2000). Somewhat surprisingly, with 2-butanone as the solvent, the expected 1,2-dimethylxanthones were not formed directly as was the case with acetone forming 1-methylxanthones. The subsequent migration of the double bond and oxidative aromatisation did not occur. However, the 1-methylidene-2-methyltetrahydroxanthones (**30**) were easily converted to the 1,2-dimethylxanthones (**31**) by reaction with a strong acid (Kelkar et al., 2000).

Reagents and conditions: (i) Ba(OH)$_2$/ DMSO, hυ, 40 °C, 40 sec.; (ii) PTSA, hυ, 40 °C, 60 sec.

Scheme 1-4: The synthesis of 2-styrylchromones using microwave reactions with anhydrides and acetophenones (Goel et al., 2006)

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Scheme 1-5 IntramolecularDiels Alder reaction of 2-styrylchromones to produce
xanthones(Silva et al., 1996)

Scheme 1-6 Diels Alder reaction of 2-styrylchromones with pyrrolidineenamines (Kelkar et
al., 2000)

The reaction of 2-styrylchromones (**23**) with *ortho*-benzoquinodimethanes (**32**) generated *in situ*with 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxideproducedcycloadducts (**33**) which could be dehydrogenated to 2-[2-(3-arylnaphthyl)] chromones (**34**). They were also prepared in a one pot synthesis with *ortho*-benzoquinodibromomethane (**35**) generated *in situ* from α,α,α',α'-tetrabromo-*o*-xylene (Scheme 1-7) (Silva et al., 1999a).

1.2.2.2 2-Styrylchromone reactions with azo compounds

2-Styrylchromones react with diazomethane, behaving as dipolarophiles, producing pyrazolines (**37**) via the intermediate **36**with **38** occurring as a minor component of the reaction (Scheme 1-8) (Pinto et al., 1998). They can also form 1,2,3-triazoles, either in a one pot synthesis with sodium azide or from the brominated compounds **39** and **41** with sodium azide (Silva et al., 1999; 2004) (Scheme 1-9).

1.2.2.3 Styrylchromone reactions with hydrazine

It was shown that the chromones can react with hydrazine hydrate togive 5(3)-(2-hydroxyphenyl) pyrazoles (Takagi et al., 1986).In the reaction of 2-styrylchromones (**44**) with methyl hydrazine, only the styrylpyrazole (**46**) was formed but with hydrazine hydrate an additional two compounds, **47** and **48** were formed together with the expected styrylpyrazole (**45**) (Pinto et al., 1997) (Scheme 1-10).

1.2.2.4 Styrylchromone reactions with diamino imines and thioureas

The styrylchromones (**49**) were shown to react with thiourea and guanidine to produce the styrylpyrimidines **50** and **51**(Karale et al., 2003) (Scheme 1-11).

R= H, CH₃; R₁= H, CH₃, OCH₃, Cl.

(i) 1,2,4-Trichlorobenzene; (ii) (a) NBS, benzoylperoxide, CCl₄or (b) Et₃N;(iii) DMF.

Scheme 1-7 Diels Alder reactions of 2-styrylchromones with *ortho*-benzoquinodimethanes (Silva et al., 1999a)

R = H,OB_Z
R₁= H,Me,OMe,Cl.

Scheme 1-8 The reaction of 2-styrylchromones with diazomethane (Pinto et al., 1998)

Scheme 1-9 The reaction of 2-styrylchromones with sodium azide (Silva et al., 1999; 2004)

R = H, CH₃; R₁ = H, Me, OCH₃, C(CH₃)₃

Scheme 1-10 Reaction of 2-styrylchromones with hydrazines (Pinto et al., 1997)

21

$R = H, CH_3, OCH_3$; (i) $H_2NC(NH)NH2.HCl$; (ii) H2NCSNH2

Scheme 1-11 The reaction of 2-stryrylchromones with thiourea and guanidine (Karale et al., 2003)

1.2.3 Biological activity of 2-styrylchromones

The biological activities of 2-styrylchromones have recently been reviewed by Gomes et al. (2010). The 2-styrylchromones were shown to be A_3 adenosine receptor antagonists (Karton et al., 1996), have hepatoprotective activity (Fernandes et al., 2003), be potent antioxidants (Filipe et al., 2004), have anti allergic properties (Doria et al., 1979), antiviral activity (Desideri et al., 2000), anticancer activity (Marinho et al., 2008;Momoi et al., 2005, Gerwick et al., 1987) and shown to display xanthine oxidase inhibition to treat for example gout, hypertension and hepatitis linked to xanthine oxidase activity(Fernandes et al., 2002).

1.2.3.1 Antioxidant activity

The polyhydroxylated 2-styrylchromones were found to be potent hepatoprotectors against pro-oxidant hepatotoxicity exerted by *tert* butyl hydroperoxide in freshly isolated rat hepatocytes, with the best activity being shown withtwo hydroxyl groups present on the benzene ring and with one or two hydroxyl groups on the benzopyronering (Fernandes et al.,

2003).The polyhydroxylated 2-styrylchromones were also shown to be good antioxidants, capable of scavenging activity against reactive oxygen and reactive nitrogen species (ROS and RNS).The most potent activity was shown by 5,7-dihydroxy and 7-hydroxy substitution in the A-ring (Gomes et al., 2007).Polyhdroxylated styrylchromones with two hydroxyl groups on the styryl moiety and an additional hydroxyl group at C-5 on the benzopyrone ring were shown to have an even betterinhibitory effect on the Cu^{2+}- induced peroxidation of low-density lipoproteins (LDL) than the flavonoid quercetin (Filipe et al., 2004).

1.2.3.2 Antiviral (rhinovirus and norovirus) activity

Human rhinoviruses (HRVs) are the most frequent cause of the common cold and responsible for several chronic conditions, such as asthma and sinusitis(Wimalasundera et al., 1997), whereas Human noroviruses (NoV) are responsible for acute gastroenteritis (Rocha-Pereira et al., 2010).The 6-fluoro-2-styrylchromone and its 3-hydroxy and 3-methoxy derivatives were shown to be effective against serotype 1Bof the HRV (Desideri et al. 2000; 2003; Conti et al., 2005) and 5-hydroxy-2-styrylchromone and 4'-methoxy-2-styrylchromonewith an estimated IC_{50} of 7 μM was found to have the best activity against the human NoV (Rocha-Pereira et al., 2010).

1.2.3.3 Anticanceractivity

The highly oxygenated hormothamnione(Figure 1-4) witha methyl group at C-3 and methoxy groups at the 6, 7 and 8 positions and hydroxy groups at C-5, C-3' and C-5' showed potent cytotoxicity against the P388 lymphocytic leukemia and HL-60 human promyelocytic leukemia cells by inhibiting RNA synthesis, while its 6-desmethoxy analogue with a hydrogen at C-6 instead of the methoxy group showed good cytotoxicity to 9 KB cells (Gerwick et al., 1986; 1989). The 4'-methoxy-2-styrylchromone and the 3',4',5'-trimethoxy-2-

styrylchromone (Figure 1-5) showed good cytotoxic activity against four human tumor cell lines (squamous cell carcinoma HSC-2, HSC-3,submandibular gland carcinoma HSGandpromyelocytic leukemia HL-60) (Momoi et al., 2005).

Figure 1-53', 4', 5'-trimethoxy-2-styrylchromone

1.2.3.4   Anti-inflammatory activity

Cyclooxygenases (COXs) are the key enzymes in the biosynthesis of prostaglandins involved in inflammatory responses. The 3',4'-dihydroxy and 4'-hydroxy 2-styrylchromone compounds showed COX-1 and COX-2 as well as LTB4 inhibition making them potential anti-inflammatory compounds (Gomes et al., 2009).

Several 2-styrylchromone-6-carboxylic acids displayed anti-allergic activity when administered orally to rats in the passive cutaneous anaphylaxis test (Doria et al., 1979).

The 2-styrylchromonols and 2-styrylfuranochromones have been described as A3 adenosine receptor antagonists which have the potential for the treatment of allergic, inflammatory and possibly ischemic disorders with the 2-styryl analogue **(52)** (Figure 1-6) of the natural furanochromone visnagin showing a strong affinity to the A3 receptor (Karton et al., 1996).

24

52

Figure 1-6 2-styrylfuranochromone with A3 adenosine receptor antagonist activity

1.2.4   Structural elucidation of 2-styrylchromones

The 2-styrylchromones are highly conjugated molecules and the ultraviolet (UV) spectrum contains characteristic absorption bands in the region 262-345 nm corresponding to an α, β, γ, δ- unsaturated conjugated carbonyl system (Rao et al., 2011). Due to the delocalisation of electrons in this unsaturated carbonyl system, the carbonyl stretching frequency in the IR spectrum occurs at 1620-1650 cm^{-1} exhibiting more single bond character.   The CH stretching bands of the olefinic bonds are observed between 1580-1620 cm^{-1} (Desideri et al., 2003).

The ^{1}H NMR spectra of the 2-styrylchromones contain aromatic and olefinic resonances between δ 6.1 and δ 7.8. In many cases, the H-3 resonance can be seen as a singlet between δ 6.10 - 6.25 for the benzyloxy 2-styrylchromones and more downfield at between δ 6.20 - 6.50 for the hydroxy 2-styrylchromones.   The H$_\alpha$ and H$_\beta$ proton resonances of the styryl moiety occur between δ 6.50 - 7.18 for the H$_\alpha$ proton resonances and more downfield between δ 7.36-7.74 for the H$_\beta$ proton resonances.   These resonances occur as doublets with a large coupling constant of approximately 16 Hz for the *trans* olefinic protons and in many cases overlap with the aromatic resonances which resonate between δ 6.20 to δ 7.80 (Santos et al., 2003).

The basic 2-styrylchromone nucleus contains seventeen carbon atoms and their resonances in the ^{13}C NMR spectrum are mainly concentrated in the region δ 100-140. The carbonyl resonance is easily detected at δ 176-183 due to the unsaturated carbonyl system. The C_β resonance is also distinguishable at δ 136 - 139 as is the C-2 resonances at δ 160 -163, however this overlaps with the oxygenated aromatic resonances. Other aromatic proton resonances can be seen at δ 100-130 (Santos et al., 2003).

1.3. Introduction to imidazole-2-thiones

Imidazole-2-thiones are planar five membered cyclic compounds consisting of three carbon and two nitrogen atoms in the ring and an exocyclic sulphur bond. They are based on the parent compound, imidazole, a basic molecule, which readily forms salts with acids (Turner et al., 1949) and found in a number of biological important molecules including purine, histamine and histidine. They are therefore important components of nucleic acids and proteins, histidine playing an important role in the structure and binding of hemoglobin (Bhatnagar et al., 2011).

Imidazole-2-thiones can exist in two tautomeric forms, a thione **(53)** and a thiol **(54)** (Figure 1-7). Ionization of the compounds occurs in the thione form in the crystalline state and in solution (Jayaram et al., 2008). The length of the C-N bond is 1.345 Å, very close to the length of the C-N partial double bond in nitrogen-containing heterocyclic systems (1.352 Å).

Figure 1-7 Tautomeric forms of imidazole-2-thiones.

These compounds are weak organic bases, readily protonated when dissolved in acids. Having both nitrogen and sulfur atoms in their core structure, they belong to the so-called "ambifunctional nucleophilic compounds" and are readily involved in reactions with electrophilic agents. The ambidentate anion of compounds with a thioamide group, generated by proton abstraction results in a triatomic functionality with the negative charge being unevenly distributed between the nitrogen and sulphur atoms (Figure 1-8)(Cumper et al., 1972).

Figure 1-8 Ambifunctional nucleophilic compounds

The interaction of imidazole-2-thione with electrophilic reagents normally involves the readily polarized and highly nucleophilic sulphur atom. In the case of polar electrophiles, however, the new bond is formed with the more electronegative nitrogen atom (Svetlik et al., 1990).

1.3.1 Synthesis

Recent reviews by Dawood et al. (2010) and Savjani et al. (2011) containthe different synthetic procedures and starting materials that have been used to synthesise the imidazole-2-thiones, which can be substituted at almost all positions on the imidazole-2-thione skeleton. They can be formed from α-bromoketones with substituted hydrazines and potassium thiocyanate (Lagoja et al., 2003), fromα-hydroxyketones, thiourea and ammonium

thiocyanate (Maduskuie et al., 1995), from benzil and thiourea (Muccioli et al., 2006) and from phenylglycine methyl ester with phenyl or alkyl isothiocynate (Muccioli et al., 2006) to name a few. The imidazole-2-thiones are extremely reactive and can be alkylated and arylated at both sulphur and nitrogen using a variety of reagents (Trzhtsinskayaand Abramova, 1991) added to activate double bonds such as 2-cyanoethene (Bagrii et al., 1978; Trzhtsinskaya et al., 1992), acetylene (Skvortsova et al., 1974), aliphatic and alicyclic ketones and acetophenones (Hozien et al., 2000).

1.3.1.1 Synthesis with α-bromoketones, substituted hydrazines and potassium thiocyanate

The N-substituted 1-amino-2,3-dihydro-1*H*-imidazole-2-thiones (**58**)were synthesized in good yields in a one-step reaction from easily available starting materials like hydrazines (**55**), R-bromoketones(**56**), and potassium thiocyanate(**57**)in the presence of acetic acid at 30°C (Scheme 1-12) (Lagoja et a., 2003).

Scheme 1-12 Reaction withα-bromoketones, substituted hydrazines and potassium
thiocyanate (Lagoja et al., 2003)

1.3.1.2 Synthesis fromα-hydroxyketones and thiourea, and from diketones and

ammonium thiocyanate

The 4,5-disubstituted-2-mercaptoimidazole(**59**)was synthesized by a condensation reaction with the α-hydroxy ketone(**60**)and thioureainthe presence of N,N-dimethylformamide or hexanol. The diketone (**61**) reacted with ammonium thiocyanate and n-hexanol also gave the N-susbstituted thioimidazole (**62**) (Scheme 1-13) (Maduskuie et al., 1995).

Scheme 1-13 Condensation reaction with α-hydroxy ketone and thiourea, and diketones and ammonium thiocyanate

1.3.1.3 Synthesis from benzil and thiourea

A 5-disubstituted-4-keto derivative of 2-thioimidazole (**63**) was synthesized using microwave reactions with benzil (**64**) and thiourea (**65**) (Scheme 1-14). The advantages of this reaction are that it is rapid and results in moderate to good yields (Muccioli et al., 2006).

Reagents and conditions: (a) DMSO/aq KOH, nine microwaves pulses (750 W)

Scheme 1-14 Microwave assisted reaction of benzil and thiourea (Muccioli et al., 2006)

1.3.1.4 Synthesis from phenylglycine methyl ester with phenyl or alkyl isothiocynate

The 3-substituted-4-keto-5-phenyl-2-thioimidazoles (**66**) were synthesized with phenylglycinemethyl ester(**67**) with the desired phenyl or alkyl isothiocyanates(**68**)in the presence of pyridine, leading first to a 3-substituted (thio)urido-phenyl aceticacid which is then cyclised by refluxing under acidic conditions (Scheme 1-15)(Muccioli et al., 2006).

Scheme 1-15 Reaction withphenylglycine methyl ester and phenyl or alkyl isothiocynate
(Muccioli et al., 2006)

1.3.1.5 Synthesis from methyl or phenyl isothiocyanate and α-amino acids via 2-thiohydantoins

The 2-thioimidazoles can be formed from methyl or phenyl isothiocyanates and α amino acids forming thiohydantoic acid (**69**) which is cyclized to the 2-thiohydantoins (**70**) with acid. The 2-thiohydantoins arethen reduced by borohydrides to 4-hydroxyimidazolidine-2-thiones (**71**), which form imidazole-2-thiones (**72**) by the elimination of water with acid (Scott et al., 1968) (Scheme 1-16).

Scheme 1-16 Synthesis with methyl or phenyl isothiocyanate and α-amino acids via a 2-thiohydantoin intermediate (Scott et al., 1968)

1.3.1.6 Preparation from imidazolium salts and elemental sulphur

Imidazolium salts (**73**) reacted with elemental sulphur, potassium *tert* butoxide and sodium hydride produced the 2-thioimidazoles (**74**) in good yields (Sauerbrey et al., 2012). They were subsequently phosphanylated with diorganochlorophosphane at C-4 on the 2-thioimidazole skeleton (**75**) (Scheme 1-17).

Scheme 1-17 Preparation of thioimidazole-2-thiones using imidazolium salts and elemental sulphur (Sauerbrey et al., 2012)

1.3.1.7 Preparation by intramolecular vinylic substitution

A series of 1, 3, 4-trisubstituted imidazole-2-thiones (**76**) were prepared by the intramolecular vinylic substitution reaction with *N, N'*-trisubstituted thiones (**77**) with a vinylic bromide moiety and potassium carbonate in dimethyl formamide (DMF) (Shen et al., 2009) (Scheme 1-18).

Scheme 1-18 Preparation by an intramolecular vinylic substitution reaction (Shen et al., 2009)

1.3.2 Reactions of imidazole-2-thiones

A literature search on Scifinder Scholar (2012) shows that the imidazole-2-thiones are extremely reactive and can be alkylated and arylated at both sulphur and nitrogen using a variety of reagents (Trzhtsinskayaand Abramova, 1991), added to activated double bonds such as 2-cyanoethene (Bagrii and Vasilenko, 1978; Trzhtsinskaya et al., 1992), acetylene (Skvortsova et al., 1974), and aliphatic and alicyclic ketones and acetophenones (Hozien et al., 2000).However, apart from the reaction with acetylene, most of the other references were

only available as abstracts despite several attempts at obtaining them and the details for these are not commented on in this work.

For the reaction with acetylene, 2-mercaptobenzimidazole (**78**) was reacted with acetylene and potassium hydroxide to produce the S-vinyl product (**79**). Reaction with acetylene using metal catalysts such as cuprous chloride and cadmium acetate produced the divinyl product substituted at both the sulphur and the nitrogen (**80**)(Scheme 1-19)(Skvortsova et al., 1974).

Scheme 1-19 Reactions of imidazole-2-thiones with acetylene (Skvortsova et al., 1974)

1.3.3 Biological activity of imidazole-2-thiones

The imidazole-2-thiones have also shown a wide range of biological activities, having antiulcer(Tsuji et al., 1989), anti-inflammatory(Buhler et al., 2011; Selig et al., 2011; Tsuji et al., 1989; Makita et al., 2000), antiarthritic, analgesic (Sharpe et al., 1985), antihyperthyroid (Doerge et al., 1993), anti-hypercholesterolemic (Billheimer et al., 1990; Maduskuie et al., 1995), antibacterial, antifungal(Saeed et al., 2007) and anti-HIV activity (Yasser et al., 2003) as well asbeing platelet aggregation inhibitors (Hayashi et al., 1989). The related 4-nitro-5-thioimidazole derivatives have also showed antitumour activity (Iradyan et al., 1988).

1.3.3.1 Antiulcer, anti-inflammatory, antiarthritic and analgesic activity

The tri- and tetra-substituted imidazole-2-thione derivatives (**81**) and their corresponding sulphoxides (**82**) (Figure 1-9) were tested for anti-inflammatory activity using the p38α MAPK assaywhere thesulphides were shown to have a higher affinity for the enzyme than the sulphoxides (Buhler et al., 2011). In a related study, observing the steric effects of the *S*-substituted methyl group, it was shown that a loss of steric hindrance increased the inhibitory potency of the compounds to the enzyme up to two-fold when compared to the dihydrothiazoline compounds (Selig et al., 2011).

81   **82**

R_1 = acyl or fluorobenzylacyl
R_2 = methyl or H

Figure 1-9 Tri- and tetrasubstituted thioimidazole-2-thiones and their sulphoxide derivatives

The 4,5-dipyridyl-S-substituted ether(**83**)(Figure 1-10)was shown toexhibit activity on human cytosolic phospholipase A2, which plays a role in inflammation (Makita et al., 2000).

83

Figure 1-10 A 4,5-dipyridyl-S-substituted ether of imidazole-2-thione

A series of 4,5-diaryl-2-(alkyloxy substituted thio)imidazole derivatives with chloro, fluoro or methoxy substitution on the phenyl groups and alkyl, alkenyl, fluoralkyl and thioethers and esters substituted on the sulphur were tested for both their anti-inflammatory and analgesic activity. The best analgesic and anti arthritic activity was seen when sulphur was substituted with fluoroalkyl groups and when the phenyl groups at C-4 and C-5 were *para* substituted.The derivative tiflamizole (**84**) (Figure 1-11) was eight times more potent than indomethacinin the rat adjuvant induced arthritis assay and with its high efficacy, could be the drug of choice prescribed for inflammation (Sharpe et al., 1985).

84

Figure 1-11 Tiflamizole

The diphenyl thioimidazole (**85**) **(**Figure 1-12**)** with a methylpyridinyl group attached to the sulphur has shown excellent antiulcer and anti-inflammatory activities (Tsuji et al., 1989).

85

Figure 1-12 Dipehnyl-*S*-methylpyridinyl thioimidazole-2-thiones

1.3.3.2 Antihyperthyroid, antihypertensiveand anti-hypercholesterolemic activity

N-substituted imidazolylethanols (**86**)(Figure 1-13)synthesized from their corresponding diphenylimidazoles with β-halo alcohols (Cl, Br) were shown to have antihypertensive properties (Povstyanoi et al., 1979).

R = H, Me, Ph, p-C$_6$H$_4$NO$_2$
R1 = Me, PhCH$_2$

86

Figure 1-13 Imidazolylethanols

A series of *N*-substituted imidazoline-2-thiones and benzimidazoline-2-thione (**87-91**) (Figure 1-14) derivatives were synthesized and tested to treat hyperthyroidism. The 1,3-disubstituted thiourea derivative (**90**) was the most potent and could represent a new class of potential antihyperthyroid drugs (Doerge et al., 1993).

Figure 1-14 Imidazole-2-thiones and their benzo derivatives tested for antihyperthyroid activity

The 4,5-diaryl-2-substituted thioimidazoles(**92**)where R$_1$ and R$_2$ are H, F, Cl, CF$_3$ or alkyl and R$_3$ is H, CH$_3$ or ethyl with A being an alkylene group of 7-20 carbon atoms was synthesized along with their sulphoxide derivatives (Figure 1-15). These compounds were shown to inhibit the intestinal absorption of cholesterol thereby having the potential to inhibit artherosclerosis (Billheimer et al., 1990).

36

R$_1$ = and R$_2$ = H, F, Cl, CF$_3$ or alkyl
R$_3$ = H, CH$_3$ or CH$_2$CH$_3$
A = alkylene groups of 7-20 carbon atoms
n = 0, 1, 2

Figure 1-15 Anti-hypercholesterolemic imidazole-2-thiones

Kruse et al. (1987) reported the dopamine β-hydroxylase activity of 52 thione analogues, identifying compounds which could be used for cardiovascular disorders related to hypertension. Among these, the *N*-substituted alkyl phenyl groups with hydroxyl, nitro and fluoro groups (**93-97**) (Figure 1-16) were amongst the most potent (Kruse et al., 1987).

Figure 1-16N-substituted thioimidazole-2-thione dopamine β-hydroxylase inhibitors

The 2-thioimidazoles substituted with an alkyl imidazole at the sulphur atom were seen to inhibitdiet-induced elevation of plasma cholesterol in rats.Among the compounds that were tested, **98** (Figure 1-17) showedthe best inhibition (Bridge et al., 1992).

98

Figure 1-17 Plasma cholesterol inhibiting 2-thioimidazole

1.3.3.3 Antibacterial, antifungal and anti-HIV activity

The imidazolyl ethanols (**86**) **(**Figure 1-13**)** mentioned for their antihypertensive properties above also showed fungicidal and bactericidal activities (Povstyanoi et al., 1979).   The *N,N,*4'-trisubstituted imidazole-2-thiones with chloro, bromo, methyl and methoxy substitution at various positions were screened for their antibacterial activity against *Escherichia coli*, *Pseudomonas areuginosa*, *Staphylococcus aureus*, and *Bacillus subtilis*. The chloro derivative (**99**) (Figure 1-18) showed the broadest spectrum of activity being active against all of the strains tested (Saeed et al., 2007).   The same set of compounds was also tested for antifungal activity against *Trichophyton longifusus*, *Candida albicans*, *Aspergillus flavus*, *Microsporum canis*, *Fusariumsolani*, and *C. glabrata*.   The results showed that only the chloro and bromo substituted compounds exhibited slight activity (Saeed et al., 2007).

99

Figure 1-18 Antibacterial *N,N,*4'-trisubstituted imidazole-2-thiones

The 4,5,*N*-substituted 2-methylsulfanyl 1H-imidazoles with alkyl or benzyl ethers at the N and benzyl, cyclohexamethyl, ethyl and isopropyl groups at C-4 and C-5 (**100** and **101**) (Figure 1-19) were tested for their anti-HIV activity in MT4 cell cultures infected with wild type HIV-1 (strain IIIB). Compounds with an isopropyl group at C-4 (**101f-g**) showed the best activity in this assay comparable to that of nevirapine (Yasser et al., 2003).

100   **101**

100,101	R$_1$	R$_2$	R$_3$	101	R$_1$	R$_2$	R$_3$
a	Ph	Et	Me	e	Ph	*i*-Pr	Me
b	Ph	Et	Ph	f	Ph	*i*-Pr	Ph
c	C$_6$H$_5$	Et	Me	g	C$_6$H$_5$	*i*-Pr	Me
d	C$_6$H$_5$	Et	Ph	h	C$_6$H$_5$	*i*-Pr	Ph

Figure 1-19 Anti-HIV alkylated imidazole-2-thiones

1.3.3.4 Platelet aggregation inhibition

A series of 4,5-diphenyl S-benzylated esters were tested for their blood platelet anti aggregation activity where compound (**102**)(Figure 1-20) showed the best activity (Meanwell et al., 1991).

102

Figure 1-20 4,5-Diphenyl S-benzylated ester with blood platelet aggregation inhibiting activity

Hayashi et al. (1989) synthesized substituted imidazole derivatives (**103**)(Figure 1-21) with *S*-substituted pyridinyl methyl groups which were found to be useful as blood platelet agglutination inhibitors.

103

R_1 and R_2 = H, phenyl or substituted phenyl

Figure 1-21 *S*-substituted pyridinyl methyl imidazole-2-thiones with blood platelet antiagglutination activity

1.3.3.5 Enzyme inhibitors

The 4,5-diphenylimidazole-2-thione (**104**)(Figure 1-22)showed α-glucosidase and α-amylase inhibitory activity (Balba et al., 2011). Glycosidase inhibitors have the potential to be used in the treatment of diabetes, HIV and metastatic cancer while amylase inhibitors are used for the treatment of diabetes, obesity and hyperlipemia.

104

Figure 1-224,5-Diphenylimidazole-2-thione with α-glucosidase and α-amylase inhibitory activity

1.3.3.6 Antitumour activity of related 5-thio(sulfo)imidazoles

The *S*-substituted derivatives of 4-nitro-5-thio(sulfo)imidazole were tested for their antitumor activity in a threonine dependent strain of *E.coli* P-678 and a lysine dependent strain of *Actinomyces rimosus* 222 by testing the frequency of mutations in the test cultures and on the mutations induced by UV rays. Compounds **105-110** (Figure 1-23) showed the best antitumour activity of all the tested compounds (Iradyan et al., 1988).

Figure 1-235-Thio (sulfo) imidazoles with antitumour activity

1.3.4 Structural elucidationof diethyl-2-(benzylthio)-2,3-dihydro-1H-imidazole-4,5-dicarboxylates

The ^{1}H-NMR spectra of these compoundsshow characteristic resonances for the benzyl proton between δ 4.27-4.62 with the N-H resonance of the imidazole moiety being variably observed between δ 5.88-11.32 and the aromatic resonances of the benzyl group being observed between δ 7.00- 7.50. The two ethoxy groups show the typical pattern of triplets and quartets for the methyl and methylene groups respectively at δ 1.28-1.37 and δ 4.28-4.37.

The ^{13}C-NMR spectra also has characteristic resonances, especially C-2 of the imidazole ring and the benzylic carbon, C-7", which appears at δ 144 and δ 37-38 consistently. The aromatic carbon resonances appear at δ 115-140 with the C-1" carbon resonance bonded to the benzylic carbon appearing consistently at δ 138-140. The carbon resonances for the two ethyl ester groups at positions 4 and 5 appear as equivalent resonances at δ 157-163, 61-62 and 14-15 for the carbonyl, the methylene and the methyl resonances respectively. The C-4/5 resonances are not easily detected in the ^{13}C NMR spectrum, but appear at δ 127-129 detectable.

1.4.   Aims and objectives

This project was funded in part by the Fluorine Expansion Initiative (FEI) of South Africa and part of FEIs plan and our broad objective was to increase the capacity of the local South African fluorine pharmaceutical market.   Our aim was to develop fluorinated pharmaceuticals, which can be developed into drugs that could be marketed in South Africa. To this end, we chose the 2-styrylchromone and 2-thioimidazole nucleus and aimed to investigate the potential of inserting fluorine into these molecules by using fluorine precursors in the synthesis.

We synthesized the 2-styrylchromones with the specific aim of testing these compounds for antibacterial and antioxidant activity since these screens are readily available at UKZN in the School of Biological and Conservation Sciences. The 2-thioimidazoles were synthesized with the aim of testing these compounds for antiplatelet activity in conjunction with our collaborators in the Department of Biochemistry and Microbiology at the University of Zululand in South Africa.

1.4.1 Specific aims and objectives

The objectives were two fold, (i) to synthesize the two classes of compounds mentioned above and (ii) to test these compounds in bioassays aimed at antibacterial and antioxidant activity in the case of the 2-styrylchromones and antiplatelet activity in the case of the 2-thioimidazoles.

To achieve these, we had the following specific objectives:

1. To synthesize novel target molecules using known procedures modified to suit our starting materials.
2. To characterize the synthesized compounds using spectroscopic and other structure determination techniques such as X-ray crystallography.
3. To test the synthesized compounds in standard known bioassays and compare the activity of the synthesized compounds with known drugs.

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Chapter 2. Synthesis, Crystal Structure and Evaluation of Novel Fluorinated 2-Styrylchromones as Antibacterial Agents

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Abstract

A range of fluorinated 2-styrylchromones (**5a-g**) of which six are new (**5a-f**) were prepared in three steps using the Baker-Venkataraman rearrangement together with two methoxyderivatives (**5h-i**) and a methylenedioxy derivative (**5j**), and screened for their antibacterial activity using Gram-positive bacteria (*Staphylococcus aureus,Scuii* and *Xylosus* as well as *Bacillussubtilis*) and Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*and *Klebsiella pneumonie*).The compounds were most effective against *B. subtilis* followed by *S. aureus* and a single strain of *E. coli* (ATCC 25922). Difluorination of the phenyl ring was shown to enhance antibacterial activity and fluorine substitution at the 6-position was shown to be much superior to substitution at the 7-position. In comparison to tetracycline, the activity indices of the fluorinated styrylchromones ranged from 0.50 to 0.75 against *B. subtilis*. The crystal structure of 6-fluorostyrylchromone is also presented and the molecule was shown to be planar.

2.1.   Introduction

Fluorinated compounds have a wide range of medical applications such as anti-inflammatory, antiviral, anti-HIV, antibacterial, anticancer, antimalarial, antidepressants, antipsychotics, anaesthetics and steroids (Park et al., 2001; Kirk and Filler, 1996).   Introducing fluorine atoms into drug molecules can also alter the rate and route of drug metabolism (Park et al., 2001) and stereoelectronic factors associated with the fluorine atom can lead to changes in the biological action of molecules in comparison to its analogues substituted with hydroxy groups or hydrogen atoms (O' Hagan and Rzepa, 1997).   The substitution of fluorine for hydrogen or hydroxy groups can lead to changes in the mechanism of the drug as well as enzyme inhibition (O' Hagan and Rzepa, 1997).   The small size of the fluorine atom, the enhanced lipophilicity it imparts to the molecules and the electronegativity of the atom often results in improved therapeutic drugs (Kirk and Filler, 1996).   As part of an ongoing study on fluorinated pharmaceutical compounds, we have chosen to explore the antibacterial effects of fluorinated 2-styrylchromones.

The biological activities of 2-styrylchromones have recently been reviewed by Gomes et al. (2010).   The 2-styrylchromones were shown to be A_3 adenosine receptor antagonists (Karton et al., 1996), have hepatoprotective activity (Fernandes et al., 2003), be potent antioxidants (Filipe et al., 2004), have anti allergic properties (Doria, et al., 1979), antiviral activity (Desideri, et al., 2000),   anticancer activity (Marinho et al., 2008; Momoi et al., 2005; Gerwick, 1987) and shown to display xanthine oxidase inhibition to treat for example gout, hypertension and hepatitis linked to xanthine oxidase inhibition (Fernandes et al., 2002).

 The synthesis of these compounds has been reviewed by Silva et al. (2004) and involves the aldol condensation between cinnammaldehydes and 2-hydroxyacetophenones followed by an

oxidative cyclisation (Silva et al., 1998) or the Baker-Venkataraman rearrangement, involving the O-acylation of 2'-hydroxyacetophenones with cinnamic acids, followed by rearrangement of the ester and then cyclisation into the styrylchromone (Pinto et al., 2000a). They can also be made directly from 2'-hydroxyacetophenones with cinnamoyl chlorides (Reddy and David, 1996).

The 2-styrylchromones have a structure analogous to the flavonoids, with an extra two carbon olefinic bond between the chromone and the phenyl ring. Thus, instead of a phenyl group attached to C-2 of the chromone ring as in the flavonoids, a styryl group is attached in stead (see **5** in Scheme 2-1). Due to the double bond in the backbone of the structure, the 2-styrylchromones are reactive molecules, acting as dienes in the pericylic reactions of xanthones (Pinto et al., 2005), dienophiles forming flavones with ortho benzoquinodimethane (Silva et al., 1999a) and are readily transformed into pyrazolines (Pinto et al., 1998; Toth et al., 1993), 1,2,3-triazoles (Silva et al., 1999b), pyrazoles (Takagi et al., 1986; Pinto et al., 1997; Pinto, et al., 2000b) and pyrimidines (Karale, et al., 2003).

To our knowledge, there have only beenonly two studies on fluorinated styrylchromones, where the 6-fluoro-2-styrylchromones have shown anti-rhinovirus activity (Conti et al., 2005) and the 4'-fluoro-, the 4'-trifluoromethyl- and 4'-trifluoromethoxy-2-styrylchromones were shown to have antitumour activity (Shaw, et al., 2009). We report here on the synthesis and antibacterial activity of a series of fluorinated 2-styrylchromones as well as the novel crystal structure of the 6-fluoro-2-styrylchromone.

2.2. Results and Discussion

Chemistry

Seven new fluorinated 2-styrylchromones were prepared in good overall yields of between 60 and 90% with only one compound (**5e**) having a yield of 45%. The synthesis was carried out according to the three-step sequence shown in Scheme 2-1 and based on the Baker-Venkataraman rearrangement (Pinto, et al., 2000a) with modifications. This involved the formation of the desired 2-cinnamoyloxyacetophenone esters from substituted *ortho*-hydroxyacetophenones and cinnamic acid derivatives in pyridine using $POCl_3$ as a condensing agent. A strong base such as potassium hydroxid then abstracts a proton from the methyl ketone and the resultant carbanion attacks the ester carbonyl groupresulting in the conversion of the cinnamoyloxyacetophenones to the ketoenols. Cyclisation to the chromone was achieved with the strong acid catalyst *para*-toluene sulphonic acid, which protonates the β-hydroxy group, increasing the electrophilicity of the β-carbon, which is attacked by the 2'-hydroxy group, ultimately resulting in formation of a chromone ring. The cinnamic acids, **2a-c** and **2h-i** were prepared by an aldol condensation and elimination reaction from the corresponding benzaldehydes and malonic acid before being reacted with the corresponding acetophenones.

The series of 2-styrylchromones synthesized contained a single fluorine atom on the *ortho*, *meta* and *para* positions (**5a-c**) of the phenyl ring, two fluorine atoms at the 3' and 5' positions on the phenyl ring (**5d**), fluorine atoms on both of the aromatic rings (at the 7 and 4' positions) (**5e**), as well as a single fluorine atom on the 7- (**5f**) and 6- (**5g**) positions on the chromone ring. These substitution patterns were chosen to observe the effect of fluorine at different positions on the phenyl ring as well as the effect of fluorine on the chromone ring. The difluorinated compounds would provide information on multiple sites of the molecule as

well as substitution on both the phenyl and chromone rings simultaneously. Two methoxylated 2-styrylchromones, the 4'-methoxy- and the 3',4'-dimethoxy-2-styrylchromones as well as the 3',4'-methylenedioxy-2-styrylchromone (**5h-j**) were also synthesized to test alongside the fluorinated styrylchromones for comparison.

a	2'-F	b	3'-F	c	4'-F	d	3',5'-F	e	7,4'-F
f	7-F	g	6-F	h	4'-OCH$_3$	i	3',4'-OCH$_3$	j	3',4'-OCH$_2$O

Scheme 2-1 The preparation of 2-styrylchromones **5a-j** from their corresponding acetophenones and cinnamic acids (i) Pyridine, POCl$_3$, rt. 4-5 h. (ii) DMSO, KOH, rt. 2h (iii) DMSO, PTSA, 90-95 °C, 2-3h.

The structures of the prepared compounds were elucidated using 1D and 2D NMR spectroscopy along with mass spectrometry and IR spectroscopy. Compounds **5g-j** and their intermediates have all been prepared previously (Conti et al., 2005; Momoi et al., 2005), but only the NMR data for only **4g** and **5g** (Conti et al., 2005), **3h** and **4h** (Pinto, 1998) and **3i** and **4i** (Santos et al., 2009) are available in the literature. Furthermore, only the ^{1}H NMR data is given for **5g** (Conti et al., 2005) while only the ethylene resonance is reported for **5h-j** in Momoi et al. (2005). The NMR data for **3g**, **3j**, **4j** and **5g-j** are therefore also reported here

along with the new compounds **5a-f** and their intermediates, **3a-f** and **4a-f**to provide a complete set of NMR data for all the synthesized 2-styrylchromones and their intermediates.

Synthesis of the cinnamoyloxyacetophenone (**3a**) was established by the presence of α and β unsaturated proton resonances in the ^{1}H NMR spectrum at δ_H 6.76 and 8.00 as two doublets with large coupling constants of 16.16 Hz, typical of *trans* olefinic protons, a methyl singlet at δ_H 2.55, an aromatic 8H signal between δ_H 7.11 to 7.85. The structure of **3a** was further supported by two carbonyl resonances in the ^{13}C NMR spectrum at δ_C 197.74 for the ketone and δ_C 165.10 for the ester carbonyl group.The aromatic carbon to which fluorine was attached was detected at δ_C 161.80 ($J = 252.60$ Hz).The fluorine NMR resonance at δ -113.57 was used to confirm the presence of fluorine on the aromatic ring and the structure confirmed by the detection of the molecular ion at *m/z* 284 in the EIMS.All of the other intermediates **3b-j** had similar NMR data and their structures were elucidated in the same manner as **3a**. The aromatic oxygenated carbon resonance in **3h** was recorded at δ_C 161.91 with similar resonances occurring in **3i-j**.

Conversion to the ketoenol (**4a**) was indicated by the disappearance of the methyl singlet resonance and the appearance of a singlet proton resonance at δ_H 6.32 for the olefinic α proton. This was supported by the enol carbon resonance at δ_C 173.63 and the keto resonance at δ_C 196.25. The fluorinated carbon resonance could be seen at δ_C 164.87 with a coupling constant of 247.22 Hz and the olefinic C-O resonance at δ_C 162.68. The ^{19}F NMR resonance at δ -112.32 and the molecular ion at *m/z* 284 in the mass spectrum further confirmed the structure. The structures of the other intermediates, **4b-j** were elucidated in a similar manner.

Cyclisation to the 2-styrylchromones was indicated by a marked shift in the H-6' resonance from δ_H 7.69 in **4a** to δ_H 8.17 as H-5 in **5a**. Further to this, only a single chromene carbonyl resonance could be seen at δ_C 178.37 in the ^{13}C NMR spectrum. The C-2 resonance was evident at δ_C 161.47 and the doublet C-F resonance at 161.17 (J = 253.27), which was supported by the ^{19}F NMR resonance at δ -115.39. The structures of **5b-j** were confirmed similarly. The structures of all intermediates and final products were further confirmed by 2D NMR spectroscopy and by the presence of the molecular ion using mass spectrometry.

In addition, the crystal structure of **5g**, 6-fluoro-2-styrylchromone, the most active compound, was carried out to determine the extent to which the molecule was planar. As can be seen in Figure 2-1 and from the data inTable 2-1, the molecule is almost planar with the bond angles between 116 and 124°. The compound crystallizes with four planar molecules in the symmetric unit and contains four molecules per unit cell. The molecular conformation is stabilized by a C-F distance of 1.363 Å and a C=O distance of 1.239Å (Table 2-1). It is postulated that the planarity of the molecule makes it very suitable to fit into enzyme pockets of substrates allowing for greater interaction between the molecule and enzyme.

Antibacterial activity

The fluorinated derivatives were most effective against Gram-positive bacteria, particularly *B. subtilis* and *S. aureus*, with that against *B. subtilis* being more predominant. The two methoxy derivatives were effective only against *B. subtilis*, with the dimethoxy derivative also being active against a strain of *S. aureus* (ATCC 29212), while the methylenedioxy **5j** derivative displayed no anti-bacterial activity against both Gram-negative and Gram-positive bacteria.

Figure 2-1ORTEP diagram of a crystal of 6-fluorostyrylchromone at 50% probability level

Table 2-1 Selected bond angles and bond lengths for 6-fluorostyrylchromone

No.	Atom1	Atom2	Atom3	Angle	Atoms	Length(A^0)
1	O2	C1	C6	122.2	C1-O2	1.374
2	O2	C1	C2	116.1	O2-C9	1.372
3	F1	C4	C5	119.0	C1-C6	1.388
4	F1	C4	C3	117.8	F1-C4	1.363
5	C9	O2	C1	118.7	C7-O1	1.239
6	O1	C7	C8	124.0	C6-C5	1.394
7	O1	C7	C6	121.5	C10-C11	1.331

Thus, in comparing the methoxy and fluoro derivatives, the latter were far superior in their activity to the methoxy compounds. Limited anti-bacterial activity was observed with Gram-negative bacteria (Table 2-2), with *K. pneumoniae* and *P. aeruginosa* being completely resistant to all of the tested compounds. Although the addition of fluorine to the benzene ring resulted in anti-bacterial action against *E.* coli ATCC 25922, it was not effective against the *E. coli* ATCC 25218 strain (Table 2-2) and the activity appeared to be strain-specific. The difluorinated styrylchromones showed a broader spectrum, with only **5d** and **5e** being effective against both *E. coli* strains tested (Table 2-2), indicating that multiple fluorinations on the 2-styrylchromone backbone could lead to enhanced activity against *E. coli*. However, fluorination on the chromone ring only resulted in no activity against *E. coli*.

The 3',5' derivative (**5d**) showed the greatest activity of all the compounds substituted on the phenyl ring. This compound also showed activity against both *E. coli* strains tested. This could therefore indicate that the activity of the 2-styrylchromones increases with increased fluorine substitution on the phenyl ring. Fluorination at position 7 on the chromone ring resulted in the compound being active against *B. subtilis* alone. This activity increased slightly with additional fluorine substitution at the 4'-position, as activity was now experienced with *S. scuii* and both of the *E. coli* strains with **5e**. However, both compounds with fluorine substitution at the 7-position showed no activity against *S. aureus*. In contrast, the **5g** derivative, with fluorine at position-6 of the chromone ring, was the most effective of all the tested compounds, with an observable inhibitory effect against all of the Gram-positive bacteria (Table 2-2). In fact, it was the only compound that showed any activity against *E. faecium*. This compound however did not show any activity against of the Gram negative bacteria. In another study, the **5g** derivative (6-fluorinated) also showed anti-rhinovirus

activity by interfering with the replication of HRV serotype 14 and serotype 1B (Conti et al., 2005).

Table 2-2 *In vitro* anti-bacterial activity of 200 μg/ml of 2-styrylchromone derivatives using the disk diffusion method

Comp.	Diameter of inhibition zone (mm)									
Comp.	*B. subtilis* ATCC 6633	*E. faecium* ATCC 51299	*S. aureus* ATCC 29212	*S. aureus* ATCC 43300	*S. scuii* ATCC 29062	*S. xylosus* ATCC 35033	*E. coli* ATCC 25922	*E. coli* ATCC 25218	*K. pneumoniae* ATCC 700603	*P. aeruginosa* ATCC 35032
5-a	20	-	14	10	-	-	14	-	-	-
5-b	22	-	15	16	-	-	12	-	-	-
5-c	24	-	8	8	-	-	12	-	-	-
5-d	25	-	19	13	-	-	14	10	-	-
5-e	27	-	-	-	12	-	12	14	-	-
5-f	18	-	-	-	-	-	-	-	-	-
5-g	20	10	12	11	8	10	-	-	-	-
5-h	21	-	-	-	-	-	-	-	-	-
5-i	23	-	9	-	-	-	-	-	-	-
5-j	-	-	-	-	-	-	-	-	-	-
*AMP10	38	24	25	20	34	32	20	0	0	0
**TE30	36	22	28	32	25	36	27	23	12	14

*AMP (Concentration: 10ug/ml): Ampicilin control,

** TE (Concentration: 30ug/ml): Tetracycline control.

Although an activity index of greater than or equal to 1, relative to tetracycline susceptibility is ideal, in the present study activity indices ranged from 0 (no activity) to 0.75 (Table 2-3). Activity indices ranging from 0.27 – 0.56 were obtained following testing of the 6-F derivative (**5g**) against Gram-positive bacteria.Gram-positive organisms appeared to be more susceptible to the fluorine and methoxy derivatives compared to Gram-negative bacteria. This may be related to their mode of antimicrobial action, which remains to be elucidated.

The low activity indices obtained do not preclude the use of these derivatives as anti-bacterial agents.Further studies combined with standard antimicrobial agents is needed to investigate the synergistic activity of the 2-styrylchromones such as those carried out by Sweeney and Zurenko (2003).

Table 2-3 Activity indices of 200 µg/ml 2-styrylchromone derivatives in comparison to tetracycline

Comp.	*B. subtilis* ATCC 6633	*E. faecium* ATCC 51299	*S. aureus* ATCC 29212	*S. aureus* ATCC 43300	*S. scuii* ATCC 29062	*S. xylosus* ATCC 35033	*E. coli* ATCC 25922	*E. coli* ATCC 25218	*K. pneumoniae* ATCC 700603	*P. aeruginosa* ATCC 35032
5-a	0.56	0	0.50	0.31	0	0	0.52	0	0	0
5-b	0.61	0	0.54	0.50	0	0	0.44	0	0	0
5-c	0.67	0	0.29	0.02	0	0	0.44	0	0	0
5-d	0.69	0	0.68	0.41	0	0	0.42	0.44	0	0
5-e	0.75	0	0	0	0.48	0	0.44	0.61	0	0
5-f	0.50	0	0	0	0	0	0	0	0	0
5-g	0.56	0.46	0.43	0.34	0.32	0.27	0	0	0	0
5-h	0.58	0	0	0	0	0	0	0	0	0
5-i	0.64	0	0.32	0	0	0	0	0	0	0
5-j	0	0	0	0	0	0	0	0	0	0
*TE30	1	1	1	1	1	1	1	1	1	1

* TE (Concentration: 30ug/ml): Tetracycline control

2.3.   Experimental

Chemistry

General Experimental Procedures

Reagents and chemicals used in this study were purchased from Sigma Aldrich via Capital Lab, South Africa and were reagent grade. All organic solvents were redistilled and dried according to standard procedures. NMR spectra were recorded using a Bruker Avance[III] 400 MHz spectrometerat room temperature with chemical shifts (δ) recorded against the internal

standard, tetramethylsilane (TMS). IR spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer with universal ATR sampling accessory. For GC-MS analyses, the samples were analysed on an Agilent GC–MSD apparatus equipped with DB-5SIL MS (30 m x 0.25 mm i.d., 0.25 μm film thickness) fused-silica capillary column. Helium (at 2 ml/min) was used as a carrier gas. The MS was operated in the EI mode at 70 eV.Melting points were recorded on an Ernst Leitz Wetziar micro-hot stage melting point apparatus.

Typical procedure for the preparation of cinnamic acids

For the preparation of the cinnamic acids **2a-c** and **2h-i**, the procedure in Qian (2010) was adopted with slight modifications   The required aromatic aldehydes (3.2 mmol), malonic acid (3.87 mmol) and piperidine (0.387 mmol) was dissolved in pyridine and stirred at 80-90°C for 4-5 hours. The pyridine was removed under vacuum and the reaction mixture poured into water and washed with HCl. The precipitate formed was filtered and washed thrice with hexane, after which it was dried under vacuum to afford the cinnamic acids**2a-c** and **2h-i** (Scheme 2-1).

Typical procedure for the synthesis of substituted 2-(cinnamoyloxy)acetophenones

Phosphorous oxychloride (15.6 mmol) was added to a solution of the appropriate 2-hydroxyacetophenone (12.0 mmol) and the appropriate cinnamic acid (15.6 mmol) in dry pyridine. The solution was stirred at 60–70 °C for 3h, and then poured into ice and water, and the reactionmixture acidified with hydrochloric acid (pH3-4). The obtained solid was removed by filtration and dissolved inethyl acetate (100 ml) and purified by silica gel column chromatography using a 7:3 mixture of ethyl acetate:*n*-hexane as the eluent. The solvent was evaporated to dryness and the residue recrystallized from ethanol, resulting in compounds **3a-j**.

Typical procedure for the synthesis of substituted 3-hydroxy-1-(2-hydroxyphenyl)-5-(phenyl)-2,4-pentadien-1-ones

Potassium hydroxide powder (0.05 mmol, 2.8 g) was added to a solution of 2-cinnamoyloxy)acetophenones **3a–j** (10 mmol) in dimethyl sulfoxide (15 ml). The solution was stirred at room temperature until complete disappearance of the startingmaterial, which was monitored by TLC. A typical reaction time was 2h. The solution was then poured into ice water and HCl and the pH adjusted to 5. The obtained solid was removed by filtration, dissolved in ethyl acetate (150 ml) and purified by silica gel chromatography using ethyl acetate:*n*-hexane (7:3) as the eluent. The solvent was evaporated to dryness and the residue recrystallized from ethanol, resulting in **4a-j**.

Typical procedure for the synthesis of substituted 2-styrylchromones

p-Toluenesulfonic acid (3.42 mmol) was added to a solution of the appropriate 3-hydroxy-1-(2-hydroxyphenyl)-5-(phenyl)-2,4-pentadien-1-ones **4a–j** (6.5 mmol) in dimethyl sulfoxide (20 ml). The reaction mixture was heated at 90 °C for 2h, and then poured into ice andwater andstirred for 10 min. The obtained solid was removed by filtration, dissolved in chloroform (100 ml) and washed with a 20% aqueous solution of sodium thiosulphate. The solvent was evaporated to dryness and the residue was purified by silica gel chromatography, using chloroform: *n*-hexane (7:3) as the eluent, to produce **5a-j**.

2-(2'-Fluorocinnamoyloxy) acetophenone (3a) brownsolid residue (90% yield);mp 68-70° C; IR (KBr)υ_{max}:1682 (br C=O),1627 (C=C),1612 (aromatic C-C),1483,1456,1284 (C-F),1227cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.00 (d, *J*=16.16 Hz, 1H),7.85 (dd , *J*=7.85, 1.58 Hz, 1H), 7.59 (td, *J*=7.92, 1.65 Hz, 1H),7.54 (td, *J*=7.64, 1.58 Hz, 1H), 7.39 (m), 7.33 (td,

J=7.64, 0.84 Hz, 1H),7.19 (dd, J= 8.0, 0.84 Hz, 1H), 7.18 (t,J= 7.50 Hz, 1H), 7.11 (dd, J=10.25, 8.80 Hz, 1H), 6.76 (d,J=16.16 Hz, 1H), 2.55 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 197.74 (C=O), 165.10 (C=O), 161.80 (d, J_{CF} = 252.60 Hz), 149.09, 139.95 (d, J= 2.72 Hz), 133.36, 132.21 (d, J= 14.23 Hz), 131.29, 130.16, 129.43 (d, J= 2.65 Hz), 126.12, 124.56 (d, J= 3.62 Hz), 123.77, 122.17 (d, J= 11.56 Hz), 119.42 (d, J= 6.93 Hz), 116.32 (d, J= 21.72 Hz), 29.77 (CH$_3$);^{19}F NMR (CDCl$_3$, 376.5 MHz) δ-113.57; EIMS (probe) 70 eV, m/z(rel. int.): 284 M[+] (3), 149 (100), 121 (63), 101 (65), 75 (15); calculated molecular mass: 284.28.

2-(3'-Fluorocinnamoyloxy) acetophenone (3b) brown solid residue (68% yield): mp 55-56 °C;IR(KBr)υ$_{max}$: 1733 and 1673 (C=O),1637 (C=C),1444,1136 (C-F),1073cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.83 (dd, J= 7.56, 1.64 Hz, 1H), 7.82 (d, J= 15.96 Hz, 1H,Hβ), 7.55 (td, J=7.84, 1.64 Hz, 1H), 7.35 (m, 2H), 7.33 (td, J= 7.66, 0.84 Hz, 1H), 7.27 (d, J= 9.64 Hz , 1H), 7.17 (dd, J= 8.0, 0.68 Hz, 1H), 7.10 (tt, J=8.20, 2.0 Hz, 1H), 6.55 (d, J= 15.96 Hz, 1H, Hα), 2.55 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 100 MHz) δ197.68 (C=O),164.90 (ester C=O), 163.02 (d, J_{CF} = 245.63 Hz), 148.99, 145.83 (d, J= 2.73 Hz), 136.27 (d, J=7.85 Hz), 133.39, 131.21, 130.56 (d, J= 8.04 Hz), 130.19, 126.17, 124.42 (d, J= 2.87 Hz), 123.76, 118.31, 117.71 (d, J= 21.25 Hz), 114.63 (d, J= 21.88 Hz),29.97(CH$_3$);^{19}F NMR (CDCl$_3$, 376.5 MHz) δ -112.27; EIMS (probe) 70 eV, m/z(rel. int.): 284 M[+] (3), 149 (100), 121 (60), 101(55), 75(11);calculated molecular mass: 284.28.

2-(4'-Fluorocinnamoyloxy) acetophenone (3c) cream solid residue (72% yield); mp 80-82°C; IR(KBr) υ$_{max}$: 1729 (C=O), 1670 (C=O), 1624 (C=C), 1590, 1446, 1221 (C-F), 1202, 1159, 1050 cm^{-1};^{1}H NMR (CDCl$_3$, 400 MHz) δ7.84 (d, J= 15.96 Hz, 1H, Hβ),7.81 (dd, J=8.00, 1.60 Hz, 1H), 7.58 (dd, J= 8.60, 5.42 Hz,2H), 7.53 (dd,J=8.00, 1.52 Hz,

1H),7.33(td,J=8.06,0.72 Hz, 1H),7.17(dd, J= 8.06, 0.72 Hz, 1H), 7.09 (t, J=8.60 Hz, 2H),6.58 (d, J= 15.96 Hz, 1H, Hα), 2.54(s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 100 MHz) δ197.78 (C=O), 165.14 (C=O), 163.02 (d, J_{CF} = 250.70 Hz), 149.07, 145.99, 133.36, 131.30, 130.43 (d, J= 8.37 Hz), 130.32 (d, J= 3.55 Hz), 130.15, 126.10, 123.78, 116.58 (d, J= 2.37 Hz), 116.20 (d, J= 21.85 Hz),29.71 (CH$_3$);^{19}F NMR (CDCl$_3$, 376.5 MHz) δ -108.54; EIMS (probe) 70 eV, (*m/z*, rel. int.) 284 M$^+$(21), 149(100), 121(25), 101(20); calculated molecular mass: 284.28.

2-(3',5'-Difluorocinnamoyloxy) acetophenone (3d) brown solid residue (70% yield); mp 58-59°C;IR(KBr)υ_{max}: 1729 (C=O), 1682 (C=O), 1249 (C-F), 1201, 1122 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ7.82 (dd, J=7.92,1.04 Hz,1H), 7.75 (d,J=15.96 Hz, 1H, Hβ), 7.55 (td,J=7.60, 1.06 Hz, 1H), 7.34 (t, J=7.60 Hz, 1H),7.16 (dd, J = 7.92, 0.80 Hz, 1H), 7.08 (m, 2H), 6.85 (tt, J=8.68, 2.28 Hz, 1H), 6.64 (d, J=15.96 Hz, 1H, Hα), 2.54 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 100 MHz) δ197.60 (C=O), 164.58 (C=O), 163.03 (d, J_{CF} = 248.29 Hz, 2C), 148.86, 144.47,137.27 (d, J= 9.54 Hz), 133.47, 131.00,130.28,126.26, 123.74, 119.72, 111.52 (d, J= 26.08 Hz, 2C), 105.92 (t, J= 24.44 Hz), 29.51 (CH$_3$); ^{19}F NMR (CDCl$_3$, 376.5 MHz) δ -108.75; EIMS (probe) 70 eV, (*m/z*, rel. int.):302 M$^+$(3), 167(100), 139(79), 119(60); calculated molecular mass: 302.27.

*4-fluoro-2-(4'-Fluorocinnamoyloxy) acetophenone (3e)*off white solid residue (68% yield); mp 60-62°C; IR (KBr)υ_{max}:1724 (C=O),1679 (C=O),1361 (C-O), 1225 (C-F), 1143 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ7.87 (dd,J= 8.75, 6.34 Hz, 1H),7.84 (d, J=15.96 Hz, 1H, Hβ),7.58 (dd, J = 5.40, 1.98 Hz, 2H), 7.10 (dd, J = 8.70, 2.48 Hz, 2H), 7.03 (td,J=8.75, 2.45 Hz, 1H), 6.92(dd, J= 8.90,2.45 Hz,1H), 6.56(d, J= 15.96 Hz, 1H, Hα), 2.53 (s,3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 196.11 (C=O), 165.11 (C=O), 164.99 (d, J_{CF} = 254.07 Hz),164.35 (d, J_{CF} = 250.95 Hz), 151.16, 146.55, 132.20 (d, J= 10.14 Hz), 130.47 (d, J= 8.47 Hz, 2C),

130.17 (d, J= 3.0 Hz), 127.62 (d, J= 3.51 Hz), 116.26 (d, J= 21.94 Hz, 2C), 116.11 (d, J= 2.24 Hz), 113.24 (d, J= 21.20 Hz), 111.70 (d, J= 23.99 Hz), 29.73 (CH$_3$); ^{19}F NMR (CDCl$_3$, 376.5 MHz) δ -103.81, -103.17; EIMS (probe) 70 eV (m/z, rel. int.)302 M$^+$ (3), 149(100), 121(92), 101(75); calculated molecular mass: 302.27.

4-fluoro-2-cinnamoyloxy acetophenone (3f) brownsolid residue (86% yield); mp 98-100 °C; IR(KBr)υ$_{max}$:1730 (C=O),1678 (C=O),1634,1598,1247 (C-F),1100,886cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ7.88(d, J=15.92 Hz, 1H, Hβ), 7.86 (dd, J= 8.60, 5.40 Hz, 1H),7.58 (dd, J= 7.50, 1.90 2H),7.44 (m, 2H), 7.41 (m, 1H), 7.03 (ddd,J=8.60, 7.87, 2.48 Hz, 1H),6.94 (dd, J = 8.90, 2.48 Hz, 1H), 6.63(d, J=15.92 Hz, 1H, Hα), 2.53 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 196.13 (C=O), 166.44 (d, J_{CF} = 255.80 Hz), 164.75 (C=O), 151.00, 145.40, 133.86, 132.29 (d, J = 10.15 Hz), 131.08, 129.04 (2C), 128.51 (2C), 127.00, 116.29, 113.43 (d, J = 21.13 Hz), 111.73 (d, J = 24.07 Hz), 29.83 (CH$_3$);^{19}F NMR (CDCl$_3$, 376.5 MHz) δ-103.91; EIMS (probe) 70 eV (m/z, rel. int.) 284 M$^+$ (3), 131(100), 103(71), 77 (39), 51(11);calculated molecular mass: 284.28.

5-fluoro-2-cinnamoyloxy acetophenone (3g) brownsolid residue(90% yield); mp 81-83°C; IR (KBr)υ$_{max}$: 1731 (C=O), 1681 (C=O), 1632, 1581, 1131 (C-F), 983 cm^{-1};^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.88(d, J=15.92 Hz, 1H, Hβ),7.58 (m, 2H), 7.49 (dd, J=8.70, 3.04 Hz, 1H),7.40 (m, 1H), 7.39 (m, 2H), 7.23 (dd, J = 7.80, 3.04 Hz, 1H),7.15(dd,J = 8.70, 4.65 Hz, 1H), 6.64 (d, J=15.92 Hz, 1H, Hα), 2.53 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 100 MHz) δ196.35 (C=O), 165.22 (C=O), 159.90 (d, J_{CF} = 245.12 Hz), 147.79, 145.03, 133.90,132.63 (d, J= 6.10 Hz), 131.04, 129.04 (2C), 128.48 (2C),125.44 (d, J= 7.96 Hz), 120.08 (d, J= 23.26 Hz), 116.51 (d, J= 20.48 Hz), 116.61, 29.78 (CH$_3$); ^{19}F NMR (CDCl$_3$, 376.5 MHz) δ-115.35; EIMS (probe)

70 eV (*m/z*, rel. int.) 284 M$^+$ (30), 266(8), 145(25), 131(100), 103(44), 77 (21); calculated molecular mass: 284.28.

2-(4'-methoxycinnamoyloxy) acetophenone (3h) off white solid residue (91% yield); mp 97-99 °C; IR (KBr) υ_{max}: 1711 (C=O), 1680 (C=O), 1600 (C=C), 1509, 1581, 1246, 1189 cm$^-$^{1}; ^{1}H NMR (CDCl$_3$, 400 MHz)δ 7.83 (d, *J* =15.92 Hz, 1H), 7.80 (dd, *J* = 8.04, 1.55 Hz, 1H), 7.53 (d, *J* = 8.72 Hz, 2H), 7.51 (td, *J* = 7.55, 1.55 Hz, 1H), 7.31 (td, *J* = 8.04, 0.76 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 6.91 (dd, *J* = 8.72, 2.64 Hz, 2H), 6.52 (d, *J* = 15.92 Hz, 1H), 3.84 (s, 3H, OCH$_3$), 2.54 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 197.90 (C=O), 165.53 (C=O), 161.91, 149.28, 147.15, 133.26, 131.54, 130.23 (2C), 130.04, 126.78, 125.95, 123.81, 114.45 (2C), 114.10, 55.43, 29.92; EIMS (probe) 70 eV (*m/z*, rel. int.) 296 M$^+$(7), 161 (100), 133 (49), 118 (16), 90 (15), 77 (16);calculated molecular mass: 296.10.

2-(3',4'-methoxycinnamoyloxy) acetophenone (3i) off white solid residue(56% yield); mp 99-101 °C; IR (KBr)υ_{max}: 1728 (C=O), 1683 (C=O), 1633 (C=C), 1515, 1254 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz)δ 7.82 (d, *J* = 15.88 Hz, 1H), 7.81 (dd, *J* =7.80, 1.72 Hz, 1H), 7.54 (td, *J* = 7.92, 1.56 Hz, 1H), 7.31 (td, *J* = 7.55, 0.90 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.16 (dd, *J* = 8.24, 1.88 Hz, 1H), 7.10 (d, *J*= 1.88 Hz, 1H), 6.87 (d, *J* = 8.24 Hz, 1H), 6.52 (d, *J* = 15.88 Hz, 1H), 3.91 (s, 6H, 2 x OCH$_3$), 2.55 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 197.90 (C=O), 165.48 (C=O), 151.67, 149.30, 149.23, 147.36, 133.29, 131.49, 130.06, 127.03, 125.98, 123.81, 123.31, 114.34, 111.05, 109.82, 55.94, 56.00, 29.86; EIMS (probe) 70 eV (*m/z*, rel. int.) 326 M$^+$(20), 191 (100), 163 (36), 148 (19), 77 (22);calculated molecular mass: 326.10.

*2-(3',4'-methylenedioxycinnamoyloxy) acetophenone (3j)*off white solid residue (59% yield), mp 99-100 °C, IR (KBr) υ_{max}: 1715 (C=O), 1679 (C=O), 1600 (C=C), 1449, 1202 (C-F), 925 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz)δ 7.80 (dd, J = 7.92, 1.56 Hz, 1H), 7.78 (d, J = 15.88 Hz, 1H), 7.53 (td, J = 7.92, 1.56 Hz, 1H), 7.31 (td, J = 7.92, 1.56 Hz, 1H), 7.16 (d, J = 7.92 Hz, 1H), 7.08 (d, J = 1.56 Hz, 1H), 7.05 (dd, J = 7.94, 1.56 Hz, 1H), 6.82 (d, J = 7.94 Hz, 1H), 6.47 (d, J = 15.88 Hz, 1H), 6.00 (s, 2H, OCH$_2$O), 2.54 (s, 3H, CH$_3$);^{13}C NMR (CDCl$_3$, 100 MHz) δ 197.84 (C=O), 165.39 (C=O), 150.17, 149.21, 148.47, 147.11, 133.28, 131.47, 130.06, 128.49, 125.99, 125.18, 123.79, 114.60, 108.64, 106.70, 101.70 (OCH$_2$O), 29.86; EIMS (probe) 70 eV (*m/z*, rel. int.) 310 M$^+$(12), 175(100), 145(64), 117(24), 89(40), 63(16); calculated molecular mass: 310.30.

*3-Hydroxy-1-(2-hydroxyphenyl)-5-(2-fluorophenyl)-2,4-pentadien-1-one (4a)*pale yellowsolid residue (93% yield); mp 158-160°C, IR (KBr)υ_{max}:1680 (C=O), 1626, 1581, 1483, 1283 (C-F), 1227 (C-O) cm^{-1};^{1}H NMR (CDCl$_3$, 400 MHz) δ14.55 (s, 3-OH), 12.17(s, 2'-OH), 7.73(d, J= 16.00 Hz, 1H Hβ),7.69 (dd, J=8.01, 1.44 Hz, 1H),7.54 (td, J=7.65, 1.48 Hz, 1H), 7.43 (ddd,J= 8.48, 7.08, 1.44 Hz, 1H), 7.32 (m, 1H), 7.16(t, J=7.56 Hz, 1H),7.09(t, J= 8.20 Hz, 1H),6.97(dd, J=8.48, 0.68 Hz, 1H),6.88 (td, J = 8.12, 0.84 Hz, 1H), 6.70 (d, J= 16.00 Hz, 1H, Hα), 6.32 (s,1H);^{13}C NMR (CDCl$_3$, 100 MHz)δ 196.47 (C=O), 174.03 (C3),162.63, 161.41 (d, J_{CF} = 253.82 Hz),136.18, 132.62 (d, J= 2.23 Hz),131.38 (d, J= 8.82 Hz), 129.23 (d, J = 3.00 Hz),128.56, 124.84 (d, J = 7.77 Hz), 124.52 (d, J = 3.57 Hz),123.11 (d, J = 11.54 Hz), 119.06,119.04,118.76, 116.29 (d, J = 21.90 Hz), 97.41 (C2);^{19}F NMR (CDCl$_3$, 376.5 MHz) δ -114.18;EIMS (probe) 70 eV (*m/z*, rel. int.) 284 M$^+$ (26), 264(7), 149(100), 121 (59), 101(20); calculated molecular mass: 284.28.

3-Hydroxy-1-(2-hydroxyphenyl)-5-(3-fluorophenyl)-2,4-pentadien-1-one **(4b)** yellow solid residue (72% yield), mp 115-117°C, IR (KBr)υ_{max}:1641 (C=O), 1626 (C=C), 1581, 1488, 1429, 1294 (C-F),1236 cm^{-1};^{1}H NMR (CDCl$_3$, 400 MHz) δ14.55 (s, 3-OH), 12.15(s, 2'-OH), 7.68(dd, *J*=8.01, 2.01 Hz, 1H), 7.58(d, *J*=15.78 Hz, 1H, Hβ), 7.44 (ddd,*J*=8.53, 7.05, 1.54 Hz, 1H), 7.34 (dd, *J*= 7.92, 5.70 Hz, 1H), 7.30 (d, *J*=7.76 Hz, 1H), 7.24 (m, 1H), 7.06 (m, 1H), 6.89 (ddd, *J*=8.01, 7.05, 0.90 Hz, 1H), 6.97 (dd, *J*= 7.90, 0.90 Hz, 1H),6.56 (d, *J*=15.78 Hz, 1H, Hα), 6.32 (s, 1H); ^{13}C NMR (CDCl$_3$,100MHz) δ196.25 (C=O), 173.63,164.87 (d, *J*$_{CF}$ = 247.22 Hz),162.68,138.32 (d, *J*= 2.51 Hz),137.28 (d, *J*= 7.75 Hz), 136.00, 130.50 (d, *J*= 8.23 Hz), 128.53, 124.06 (d, *J*= 2.75 Hz), 123.51,119.05, 119.01, 118.81, 116.90 (d, *J*= 21.60 Hz), 114.05 (d, *J*= 20.01 Hz), 97.44 (C2);^{19}F NMR (CDCl$_3$, 376.5 MHz) δ-112.32; EIMS (probe) 70 eV (*m/z*, rel. int.) 284 M$^+$(25), 149 (100), 265 (8), 121 (88), 101 (17); calculated molecular mass: 284.28.

3-Hydroxy-1-(2-hydroxyphenyl)-5-(4-fluorophenyl)-2,4-pentadien-1-one **(4c)** pale yellow solid residue (92% yield); mp 130-132 °C, IR (KBr) υ_{max}: 1683 (C=O), 1627 (C=C), 1598, 1572, 1489, 1156 (C-F) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ14.62 (s, 3-OH), 12.17(s, 2'-OH),7.68 (dd,*J*=8.05,1.44 Hz, 1H), 7.60 (d, *J*=15.95 Hz, 1H, Hβ),7.52 (dd, *J*= 8.85, 5.36 Hz, 2H),7.44 (ddd, *J*=8.52, 7.10, 1.44 Hz, 1H), 7.08 (t, *J*=8.85 Hz, 2H),6.97 (dd, *J*=8.52, 0.85 Hz, 1H),6.88(ddd, *J*= 8.05, 7.10, 0.85 Hz, 1H), 6.49(d, *J*=15.95 Hz, 1H, Hα), 6.29(s,1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ196.03 (C=O), 174.25 (C3), 163.78 (d, *J*$_{CF}$ = 250.26 Hz), 162.64, 138.53,135.87, 130.23 (d, *J* = 3.52 Hz), 129.81 (d, *J* = 8.21 Hz, 2C), 128.47, 121.88, 119.04 (2C), 118.79, 116.15 (d, *J* = 21.85 Hz, 2C), 96.98 (C2); ^{19}F NMR (CDCl$_3$, 376.5 MHz) δ -109.55; EIMS (*m/z*, rel. int.) 284 M$^+$(21), 149 (100), 121 (71), 265 (4),163 (16), 101 (18); calculated molecular mass: 284.28.

3-Hydroxy-1-(2-hydroxyphenyl)-5-(3,5-difluorophenyl)-2,4-pentadien-1-one (4d) light brown

solid residue (91% yield), mp 130-132 °C, IR (KBr)υ_{max}: 1698 (C=O),1658 (C=C),1119 (C-

F), 962, 843 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 14.46 (s, 3-OH), 12.10(s, 2'-OH), 7.67

(dd,*J*=8.05,1.40 Hz, 1H), 7.51(d, *J*=15.70 Hz, 1H, Hβ),7.45 (ddd, *J*= 8.47, 7.24, 1.62 Hz,

1H), 7.04 (dd, *J*=8.22, 2.16 Hz, 2H), 6.98 (dd, *J*= 8.47, 1.06 Hz, 1H), 6.89 (ddd, *J*= 8.05,

7.24, 1.06 Hz, 1H), 6.80(tt, *J*=8.76, 2.16 Hz, 1H),6.55(d, *J*= 15.70 Hz, 1H, Hα), 6.32 (s,1H);

^{13}C NMR (CDCl$_3$, 100 MHz) δ196.42 (C=O), 172.84 (C$_3$), 163.29 (dd, J_{CF}= 247.76, 13.10

Hz, 2C), 162.73, 138.30 (t, *J* = 9.54 Hz),136.97,136.17,128.56,124.80,119.14,118.94, 118.85,

110.48 (dd, *J*= 18.53, 6.83 Hz, 2C),105.07 (d, *J* = 25.60 Hz),97.89 (C2);^{19}F NMR (CDCl$_3$,

376.5 MHz) δ -109.10;   EIMS (*m/z*, rel. int.)302 M^{+} (28), 167(100), 121(76), 285(10),

139(29), 121(76); calculated molecular mass: 302.27.

3-Hydroxy-1-(4-fluoro-2-hydroxyphenyl)-5-(4-fluorophenyl)-2,4-pentadien-1-one (4e) yellow

solid residue (82%yield); mp143-145°C; IR (KBr)υ_{max}:1726 (C=O),1629 (C=C),1234 (C-F),

1157, 975, 824, 803, 789 cm^{-1};^{1}H NMR (CDCl$_3$,400MHz)δ 14.42 (s, 3-OH), 12.47 (s, 2'OH),

7.60(d,*J*=15.90 Hz, 1H, Hβ),7.68 (dd,*J*=8.98, 6.40 Hz,1H),7.52(dd,*J*=8.72 5.40 Hz, 2H), 7.08

(t,*J*=8.58 Hz, 2H),6.65 (dd, *J*= 10.37, 2.50 Hz, 1H), 6.60(ddd,*J*= 8.77, 8.16,2.15 Hz, 1H),

6.51 (d, *J* = 15.90 Hz, 1H, Hα),6.20 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 194.87 (C=O),

174.21 (C3),166.40 (d,J_{CF}= 212.10 Hz), 165.16 (d, *J* = 14.10 Hz), 162.98 (d, J_{CF}=250.55 Hz),

138.72,130.65 (d, *J* =11.90 Hz),130.41 (d, *J* =10.83 Hz),129.85 (d, *J*=8.55 Hz, 2C), 121.70,

116.17 (d, *J* =21.88 Hz, 2C), 115.95, 107.31 (d, *J* = 22.57 Hz),105.30 (d, *J* = 23.57 Hz),

96.76 (C2); ^{19}FNMR (CDCl$_3$, 376.5 MHz)δ-100.64, -109.57; EIMS (*m/z*, rel. int.) 302 M^{+}

(41), 149 (100), 283 (18), 207 (11), 163 (35), 139 (95), 121 (37), 101 (35); calculated

molecular mass: 302.27.

3-Hydroxy-1-(4-fluoro-2-hydroxyphenyl)-5-(phenyl)-2,4-pentadien-1-one **(4f)** yellowsolid residue (64% yield); mp 143-145°C; IR (KBr)υ_{max}: 1632 (C=O), 1579 (C=C), 1178 (C-F) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 14.48 (s, 3-OH), 12.55 (s, 2'-OH), 7.68 (dd, *J*= 8.94, 6.42 Hz, 1H),7.64(d, *J*= 15.80 Hz, 1H, Hβ), 7.53 (dd, *J*= 8.06, 2.05 Hz, 2H), 7.38 (m,3H),6.65 (dd, *J*=10.30, 2.50 Hz, 1H), 6.60(td, *J* = 8.0, 2.50 Hz, 1H), 6.57 (d, *J*= 15.80 Hz, 1H, Hα),6.21 (s,1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ194.85 (C=O),174.42 (C3), 165.17 (d,*J*$_{CF}$= 209.24 Hz), 165.08 (d, *J* = 14.07 Hz), 140.14, 134.92, 130.47 (d, *J* = 11.65 Hz), 130.18, 128.99 (2C), 128.02 (2C), 122.00, 115.95, 107.29 (d, *J* = 22.65 Hz), 105.27 (d, *J* = 23.41 Hz), 96.78 (C2); ^{19}F (CDCl$_3$, 376.5 MHz) δ -100.72;EIMS (*m/z*, rel. int.) 284 M$^+$(33), 131 (100), 265 (14), 139 (64), 103 (42), 77 (39), 51 (11); calculated molecular mass: 284.28.

3-Hydroxy-1-(5-fluoro-2-hydroxyphenyl)-5-phenyl-2,4-pentadien-1-one **(4g)** yellow solid residue (90% yield); mp 118-120°C; IR (KBr):1632(C=O),1550,1487,1248,1180,960,781,754 cm^{-1};^{1}H NMR (CDCl$_3$, 400 MHz) δ14.59 (s, 3-OH), 11.94 (s, 2'-OH), 7.66 (d, *J*= 15.81 Hz, 1H Hβ), 7.54(dd , *J*= 7.88, 2.20 Hz, 2H), 7.40 (m, 3H), 7.34 (dd,*J*= 9.0, 3.08 Hz, 1H), 7.17 (ddd, *J*= 9.16, 7.88, 3.00 Hz, 1H), 6.93 (dd, *J*= 9.08, 4.68 Hz, 1H),6.58 (d, *J*= 15.81 Hz, 1H, Hα),6.20(s,1H);^{13}C NMR (CDCl$_3$, 100 MHz) δ194.82 (d, *J* = 2.72 Hz, C=O), 175.23 (C3), 158.72, 155.12 (d,*J*$_{CF}$= 236.79 Hz), 140.67, 134.84, 130.42, 129.02 (2C), 128.10 (2C), 123.19 (d, *J* = 23.38 Hz), 121.86, 119.95 (d, *J* = 7.41 Hz), 118.72 (d, *J* = 6.50 Hz), 113.46 (d, *J* = 23.53 Hz), 96.81 (C2); ^{19}F (CDCl$_3$, 376.5 MHz) δ -124.33;EIMS (probe) 70 eV (*m/z*, rel. int.) 284 M$^+$(5), 131 (100), 103 (80), 77 (35); calculated molecular mass: 284.28.

3-Hydroxy-1-(2-hydroxyphenyl)-5-(4-methoxyphenyl)-2,4-pentadien-1-one **(4h)** yellowsolid residue (90% yield); mp 167-169 °C; IR (KBr)υ_{max}:1645 (C=O),1599, 1514, 1462, 1258, 963, 828, 749 cm^{-1};^{1}H NMR (CDCl$_3$, 400 MHz) δ14.72 (s, 3-OH),12.24 (s, 2'-OH), 7.67 (dd,

J=7.95, 1.60 Hz, 1H),7.61 (d, J= 15.76 Hz, 1H),7.49 (d, J = 8.80 Hz, 2H), 7.42 (ddd, J= 8.50, 7.50, 1.60 Hz, 1H),6.96 (dd,J=8.50, 2.10 Hz, 1H), 6.91 (d, J = 8.80 Hz, 2H), 6.89 (m, 1H), 6.45 (d, J= 15.76 Hz, 1H),6.26 (s,1H),3.83 (s, 3H, OCH$_3$);^{13}C NMR (CDCl$_3$, 100 MHz) δ195.32 (C=O),174.91 (C3), 162.26, 161.12, 139.49, 135.33, 129.77, 129.44 (2C), 128.83, 119.41, 118.85, 118.69, 118.44, 114.16 (2C), 96.13, 55.15;EIMS (probe) 70 eV (*m/z*, rel. int.) 296 M[+](14), 161(100), 207(18), 133(77), 118(29); calculated molecular mass: 296.10.

*3-Hydroxy-1-(2-hydroxyphenyl)-5-(3,4-dimethoxyphenyl)-2,4-pentadien-1-one(4i)*yellow solid residue (84% yield); mp 130-132°C; IR(KBr): 1685(C=O), 1621, 1564, 1488, 1252, 1161;^{1}H NMR (CDCl$_3$, 400 MHz) δ14.71 (s, 3-OH),12.23 (s, 2'-OH), 7.67 (dd, J= 8.08, 1.45 Hz,1H),7.59 (d, J = 15.68 Hz, 1H, Hβ),7.42 (ddd, J= 8.52, 8.30, 1.45 Hz, 1H),7.11 (dd, J = 8.30, 1.90 Hz, 1H), 7.06 (d,J= 1.82 Hz, 1H),6.96 (dd, J = 8.43, 0.68 Hz,1H), 6.87 (d, J = 8.30 Hz, 1H), 6.85 (td, J = 8.30, 0.68 Hz, 1H), 6.45 (d, J= 15.68 Hz, 1H, Hα), 6.28 (s,1H),3.92 (s, 3H, OCH$_3$), 3.91 (s, 3H, OCH$_3$); ^{13}C NMR (CDCl$_3$, 100 MHz) δ195.62 (C=O),175.00 (C3), 162.54,151.13, 149.31, 139.98, 135.64, 128.39, 128.02, 122.60, 119.91, 119.12, 118.96, 118.74, 111.19, 109.67, 96.48 (C2), 56.01, 55.93;EIMS (probe) 70 eV (*m/z*, rel. int.) 326 M[+](15), 191 (100), 207 (16), 163 (49), 148 (19), 133 (18), 77 (23);calculated molecular mass: 326.12.

3-Hydroxy-1-(2-hydroxyphenyl)-5-(3,4-methelenedioxyphenyl)-2,4-pentadien-1-one (4j) light yellow solid residue (94%yield); mp165-167°C; IR (KBr)υ_{max}:1693 (C=O), 1621, 1602, 1566, 1484, 1446, 1239 (C-O), 1171, 1035, 925 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ14.68 (s, 3-OH), 12.24 (s, 2'-OH), 7.66 (dd, J=8.01, 1.56 Hz, 1H), 7.55 (d, J=15.64 Hz, 1H Hβ), 7.42 (ddd, J = 8.45, 8.01, 1.56 Hz, 1H), 7.04 (bd, J = 0.35 Hz), 7.02 (dd, J= 8.00, 1.20 Hz,1H), 6.96 (dd,J=8.45, 0.50 Hz, 1H), 6.87 (td, J = 8.01, 0.50 Hz, 1H), 6.81 (d, J=8.00 Hz,

1H),6.39 (d, J= 15.64 Hz, 1H, Hα),6.26 (s,1H), 6.00 (s, 2H, OCH$_2$O); ^{13}C NMR (CDCl$_3$, 100 MHz) δ195.69(C=O), 174.83 (C3), 162.55, 149.57(C4'), 148.47(C3'), 139.73, 135.68, 129.50, 128.42, 124.56, 120.13, 119.09, 118.99, 118.73, 108.70, 106.31, 101.61 (OCH$_2$O), 96.61 (C2); EIMS (probe) 70 eV (*m/z*, rel. int.) 310 M$^+$ (18), 175(100), 207(28), 145(87), 157(42), 117 (44), 89(52), 43(62); calculated molecular mass: 310.30.

2'-Fluoro-2-styrylchromone (5a) light yellowsolid residue (68% yield); mp 150-152 °C; UV λ$_{max}$ (CH$_3$OH) nm (log ε): 325 (3.37); IR (KBr) υ$_{max}$: 1682 (C=O), 1625, 1589 (C-C), 1562, 1464, 1391 (C-F), 1125, 968 cm^{-1};^{1}H NMR (CDCl$_3$, 400 MHz) δ8.17 (dd,J= 7.94, 1.56 Hz, 1H),7.72 (d, J=16.24 Hz, 1H, Hβ), 7.66 (ddd,J= 8.56, 7.20, 1.56 Hz,1H),7.59 (td, J= 7.60, 1.50 Hz, 1H), 7.53 (d,J=8.28 Hz,1H),7.37 (td, J = 7.92, 0.80 Hz, 1H) ,7.32 (m, 1H), 7.17 (t,J=7.92 Hz,1H), 7.11 (ddd, J = 9.20, 8.20, 2.36 Hz, 1H), 6.87 (d, J=16.24 Hz, 1H, Hα), 6.32 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 178.46 (C=O), 161.47, 161.17 (d, J_{CF}=253.27 Hz, C2'), 156.02,133.88,131.25 (d, J= 8.67 Hz), 129.47 (d, J= 3.10 Hz, Cβ), 128.39 (d, J= 2.72 Hz), 125.69, 125.06, 124.56 (d, J= 3.57 Hz),124.13, 123.09 (d, J = 11.68 Hz), 122.67 (d, J = 6.52 Hz, Cα), 117.93, 116.23 (d, J= 21.81 Hz), 111.21; ^{19}F NMR (CDCl$_3$, 376.5 MHz) δ -115.39; EIMS (*m/z*, rel. int.) 265 (M$^+$-1)(100), 237(12), 207(20), 146(36), 92(25); HRMS (*m/z*) M$^+$ 266.0733 (calculated for C$_{17}$H$_{11}$FO$_2$: 266.0743).

3'-Fluoro-2-styrylchromone (5b) brown solid residue (62% yield), mp 105-108 °C; UV λ$_{max}$ (CH$_3$OH) nm (log ε): 325 (3.34); IR (KBr) υ$_{max}$:1694 (C=O), 1622, 1579 (C-C),1465,1389 (C-F),1247,1122,967,775 cm^{-1};^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.18 (dd, J = 7.92, 1.32 Hz, 1H), 7.68 (dt, J = 8.60, 1.64 Hz, 1H), 7.55 (d, J = 16.00 Hz, 1H), 7.52 (d, J = 8.60 Hz, 1H), 7.36 (m, 3H), 7.26 (m, 1H), 7.06 (t, J = 8.04 Hz, 1H), 6.77 (d, J = 16.00 Hz, 1H), 6.34 (s,

1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 178.51 (C=O), 163.15 (d, *J* = 245.48 Hz, C3'), 161.22, 156.00, 137.28 (d, *J* = 7.84 Hz), 135.57 (d, *J* = 2.77 Hz, Cβ), 133.89, 130.54 (d, *J* = 8.30 Hz), 125.76, 125.14, 124.09, 123.61 (d, *J* = 2.67 Hz), 121.67 (Cα), 117.87, 116.69 (d, *J* = 21.60 Hz), 113.99 (d, *J* = 21.99 Hz), 111.15; ^{19}F NMR (CDCl$_3$, 376.5 MHz) δ-112.42; EIMS (*m/z*, rel. int.) 265 (M$^+$-1) (100), 237(6), 209(8), 173(16), 146(40), 121(20), 92(27); HRMS (*m/z*): 266.0726 M$^+$ (calculated for C$_{17}$H$_{11}$FO$_2$: 266.0743).

4'–Fluoro-2-styrylchromone (5c) off white solid residue (70% yield), mp 158-160°C; UV λ$_{max}$ (CH$_3$OH) nm (log ε): 328 (3.39); IR (KBr):1691 (C=O), 1623, 1594, 1506, 1466, 1391 (C-F), 1224, 969, 817 cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 400 MHz) δ8.01 (dd, *J*= 7.92, 1.44 Hz, 1H), 7.82 (m, 1H), 7.79(m, 2H), 7.70 (d, *J* = 16.16 Hz, 1H, Hβ), 7.69 (d,*J*= 8.48 Hz,1H),7.47 (t, *J* = 7.44 Hz, 1H), 7.28(t,*J*=8.78 Hz, 2H), 7.16 (d, *J*=16.16 Hz, 1H, Hα), 6.46 (s, 1H); ^{13}C NMR (DMSO-d$_6$, 100 MHz) δ 177.42 (C=O), 162.88 (d, *J*$_{CF}$ =240.60 Hz, C4'),161.64, 155.43, 135.38 (Cβ), 134.35, 131.60 (d, *J* = 3.22 Hz), 130.02 (d, *J* = 8.11 Hz, 2C), 125.31, 124.76, 123.39, 120.38 (Cα),118.20, 115.97 (d, *J* = 24.34 Hz, 2C), 110.06; ^{19}F NMR (DMSO-d$_6$, 376.5 MHz) δ-110.72;EIMS (*m/z*, rel. int.) 265 (M$^+$-1) (100), 237(8), 207(13), 173(10), 146(39), 120(18), 92 (20); HRMS (*m/z*): 266.0721 M$^+$ (calculated for C$_{17}$H$_{11}$FO$_2$: 266.0743).

*3',5'-Difluoro-2-styrylchromone (5d)*light brown solid residue (92% yield); mp 114-116 °C; UV λ$_{max}$(CH$_3$OH) nm (log ε)322 (3.49); IR (KBr) υ$_{max}$:1701 (C=O), 1615,1586,1465,1390 (C-F),1309,1272,1117 (C-F),966,847,751 cm^{-1};^{1}H NMR (CDCl$_3$, 400 MHz) δ8.18 (dd, *J*= 7.92, 1.56 Hz, 1H),7.72 (ddd,*J*= 8.55, 7.20, 1.56 Hz,1H),7.55 (d,*J*=8.30 Hz,1H), 7.53 (d, *J*=15.96 Hz, 1H, Hβ), 7.43 (td, *J* = 7.92, 0.68 Hz, 1H),7.12 (m, 3H), 6.85 (tt,*J*=8.70, 2.35

Hz,1H),6.80 (d, J=15.96 Hz, 1H, Hα), 6.34 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ178.37 (C=O), 163.47 (d, J_{CF}=248.84 Hz, C3'), 160.59, 155.97,138.28 (d, J = 9.50 Hz),134.22 (d, J = 3.02 Hz, Cβ),133.99,125.79, 125.25, 124.11,122.98(Cα), 117.87, 111.70, 110.41, 110.20 (d, J = 11.25 Hz), 110.15 (d, J = 25.90 Hz), 104.96 (d, J = 25.31 Hz);^{19}F NMR (CDCl$_3$, 376.5 MHz) δ -108.99; EIMS (*m/z*, rel. int.) 284 M$^+$ (100), 267(82), 191(40), 164(63), 121(58), 92(65),64(21); HRMS (*m/z*): 284.0633 M$^+$ (calculated for C$_{17}$H$_{10}$F$_2$O$_2$: 284.0649).

7,4'-Difluro-2-styrylchromone (5e) pale yellow solid residue(45% yield); mp 182-184°C; UV λ$_{max}$ (CH$_3$OH) nm (log ε) 322 (3.54); IR(KBr): 1659 (C=O),1621 (C=C), 1598,1511,1438,1377 (C-F),1233,1140,1112, 967 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.18 (dd, J=8.80, 6.35 Hz, 1H), 7.56 (dd,J= 8.60, 5.56, Hz, 2H), 7.53 (d, J= 16.00 Hz, 1H, Hβ), 7.20 (dd, J= 9.04, 2.40 Hz, 1H), 7.12 (m, 1H), 7.10 (t, J= 8.60 Hz, 2H), 6.67 (d, J = 16.00 Hz, 1H, Hα), 6.28 (s, 1H);^{13}C NMR (CDCl$_3$, 100 MHz) δ177.41 (C=O),167.07(d, J_{CF}= 210.10 Hz),164.97 (d, J_{CF}= 251.55 Hz), 161.82, 156.88, 135.83, 131.15 (d, J= 3.56 Hz), 129.52 (d, J= 8.19 Hz, 2C), 128.22 (d, J= 10.51 Hz), 120.96, 119.67, 116.21 (d, J= 21.88 Hz, 2C), 113.73 (d, J= 22.45 Hz), 110.63, 104.60 (d, J= 25.49 Hz); ^{19}F NMR (CDCl$_3$, 376.5 MHz) δ -102.96, -109.89; EIMS (*m/z*, rel. int.) 283 (M$^+$-1) (100), 267(56), 255(8), 227(13), 173(13), 146(50), 120(10);HRMS (*m/z*): 284.0642 (calculated for C$_{17}$H$_{10}$F$_2$O$_2$: 284.0649).

7-Fluoro-2-strychromone (5f) off white solid residue (94% yield); mp 116-118 °C; UV λ$_{max}$ (CH$_3$OH) nm (log ε) 312 (3.35); IR (KBr)υ$_{max}$:1667 (C=O),1599,1538, 1438, 1382 (C-F stretch), 1143, 1012, 960 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ8.19 (dd, J=8.85, 6.35 Hz, 1H), 7.59 (d, J = 15.96 Hz, 1H, Hβ),7.58 (dd, J = 8.10, 1.48 Hz, 2H),7.41 (m, 3H), 7.21 (dd, J=9.13, 2.40 Hz, 1H), 6.76 (d, J= 15.96 Hz, 1H, Hα), 7.10 (td, J = 8.60, 2.40 Hz, 1H), 6.29

(s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 177.48 (C=O),164.48 (d, J_{CF} = 240.00 Hz), 162.01,157.05 (d, J = 13.20 Hz), 137.19 (Cβ), 134.88, 130.00, 129.05 (2C),128.20 (d, J = 10.64 Hz),127.72 (2C), 121.00, 119.89 (Cα),113.69 (d, J = 22.56 Hz),110.62, 104.63 (d, J = 25.39 Hz);^{19}F NMR (CDCl$_3$, 376.5 MHz) δ-103.04; EIMS (*m/z*, rel. int.) 265 (M$^+$-1) (100), 250(36), 237(5), 209(7), 128(29), 102(8); HRMS (*m/z*): 266.0730 (calculated for C$_{17}$H$_{11}$FO$_2$: 266.0743).

6-Fluoro-2-styrylchromone (*5g*) light green solid residue (89% yield); mp 108-110° C; IR (KBr): 1710 (C=O), 1628,1567,1478,1445,1378,1284,1172,967,818,751 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.81 (dd, *J*=8.20, 3.15 Hz, 1H), 7.58 (d, *J*=16.08 Hz, 1H, Hβ),7.56 (d, *J*= 8.0 Hz, 2H),7.52 (dd, *J* = 9.10, 4.15 Hz, 1H), 7.40 (m, 3H), 6.77 (d, *J*=16.08 Hz,1H, Hα), 6.31 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 177.62 (d, *J* = 2.28 Hz, C=O), 161.99, 159.50 (d, J_{CF}=245.09 Hz), 152.20, 137.35 (Cβ), 134.88, 130.02, 129.05 (2C), 127.73 (2C), 125.47 (d, *J* = 7.10 Hz), 121.76 (d, *J* = 25.13 Hz), 120.03 (Cα), 119.89 (d, *J* = 7.89 Hz), 110.69 (d, *J* = 23.42 Hz), 109.89; ^{19}F NMR (CDCl$_3$, 376.5 MHz) δ -115.51; EIMS (*m/z*, rel. int.) 265 (M$^+$ -1) (100), 249(43), 237(9), 209(12), 128(56); calculated molecular mass: 266.67.

4'-Methoxy-2-styrylchromone (5h) yellow solid residue (90% yield); mp 167-169 °C; UV λ$_{max}$ (CH$_3$OH) nm (log ε) 354 (3.33); IR (KBr)υ$_{max}$:1645 (C=O), 1599, 1514, 1462, 1258, 963, 828, 749 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.18 (dd, *J* = 7.95, 1.60 Hz, 1H), 7.65 (ddd, *J* = 8.56, 7.12, 1.60 Hz, 1H), 7.55 (d, *J* = 15.96 Hz, 1H, Hβ), 7.52 (d, *J* = 8.56 Hz), 7.48 (d, *J* = 8.70 Hz, 2H), 7.36 (t, *J* = 7.95 Hz, 1H), 6.92 (d, *J* = 8.70 Hz, 2H), 6.64 (d, *J* = 15.96 Hz, 1H, Hα), 6.28 (s, 1H), 3.84 (s, 3H, OCH$_3$); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 178.48 (C=O), 162.25, 161.11, 156.03, 136.65 (Cβ), 133.60, 129.29 (2C), 125.69, 124.91,

124.15, 117.85(Cα), 117.90, 117.85, 114.48 (2C), 109.94, 55.42 (O$\underline{C}$H$_3$); EIMS (*m/z*, rel. int.) 277 (M$^+$-1) (100), 247(21), 207(19), 158(38), 115(55); calculated molecular mass: 278.30.

3',4'-Dimethoxy-2-styrylchromone (5i) yellow solid residue (55% yield); mp 162-163 °C; UV λ$_{max}$ (CH$_3$OH) nm (log ε)367 (3.18); IR (KBr)υ$_{max}$: 1682 (C=O), 1617, 1558, 1509, 1464, 1381, 1261, 1138, 1025, 965, 780, 759 cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 400 MHz) δ8.01 (dd, *J* = 7.88, 1.72 Hz, 1H), 7.81(ddd, *J* = 8.20, 7.16, 1.72 Hz, 1H), 7.70(d, *J*=8.20 Hz, 1H), 7.65 (d, *J*=16.04 Hz, 1H, Hβ), 7.47 (ddd, *J*=7.88, 7.16, 0.68 Hz, 1H), 7.36(d,*J* = 1.72 Hz, 1H),7.27(d, *J*=8.28, 1.72 Hz, 1H), 7.11(d, *J*=16.04 Hz, 1H, Hα), 7.02(d,*J*=8.28 Hz, 1H), 6.40 (s, 1H), 3.80 (s, 3H, OCH$_3$),3.83 (s, 3H, OCH$_3$); ^{13}C NMR (DMSO-d$_6$, 100 MHz) δ 177.02 (C=O), 162.26, 155.44, 150.53, 149.00, 136.87, 134.21, 127.79, 125.22, 124.74, 123.42, 122.31, 118.11, 118.01, 111.67, 109.92, 109.17, 55.54 (2 x O$\underline{C}$H$_3$); EIMS (*m/z*, rel. int.) 308 (M$^+$) (100), 277(22), 250(10), 221(14), 188(70), 121(19);calculated molecular mass: 308.33.

3',4'-Methylenedioxy-2-styrylchromone (5j) yellow solid residue (92% yield); mp 209-210 °C; UV λ$_{max}$ (CH$_3$OH) nm (log ε)329 (3.36); IR (KBr)υ$_{max}$: 1694 (C=O), 1625, 1461, 1499, 1447, 1383, 1251, 845 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.17 (d, *J* = 7.62 Hz, 1H), 7.65 (ddd, *J* = 8.11, 7.14, 0.98 Hz, 1H), 7.51 (d, *J* = 7.82 Hz, 1H), 7.50 (d, *J* = 16.06 Hz, 1H, Hβ), 7.37 (t, *J* = 7.53, 1H), 7.08 (s, 1H), 7.05 (d, *J* = 8.06 Hz, 1H), 6.81 (d, *J*= 8.06 Hz, 1H), 6.59 (d, *J* = 16.06, 1H, Hα), 6.28 (s, 1H), 6.01 (s, 2H, OCH$_2$O); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 178.45 (C=O), 161.98, 156.01, 149.32 (C4'),148.52 (C3'), 136.67, 133.65, 129.53, 125.70, 124.95, 123.91, 123.25, 118.35, 117.80, 110.17, 108.69, 106.15, 101.60 (OCH$_2$O); EIMS (*m/z*, rel. int.) 291 (M$^+$-1) (100), 275(55), 233(18), 205(24), 172(67), 114(29);calculated molecular mass: 292.29.

X-ray Crystallographic Study

Single-crystal X-ray diffraction data were collected on a Bruker KAPPA APEX II DUO diffractometer using graphite-monochromated Mo-Kα radiation (χ = 0.71073 Å). Data collection was carried out at 173(2) K. Temperature was controlled by an Oxford Cryostream cooling system (Oxford Cryostat). Cell refinement and data reduction were performed using the program SAINT (SAINT, Version 7.60a, 2006). The data were scaled and absorption correction performed using SADABS (Sheldrick, 1997). The structure was solved by direct methods using SHELXS-97 (Sheldrick, 1997) and refined by full-matrix least-squares methods based on F^2 using SHELXL-97 (Sheldrick, 1997) and using the graphics interface program X-Seed (Barbour, 2001; Atwood and Barbour, 2003). The programs X-Seed and POV-Raywere both used to prepare molecular graphic images. All non-hydrogen atoms were refined anisotropically andall hydrogen atoms could be found in the difference electron density maps but were placed in idealised positions and refined in riding models with U_{iso} set at 1.2 times those of their parent atoms and at a distance(C-H) of 0.95 Å. The structure was refined to an R factor of 0.0503.

Antibacterial Assay

In vitro evaluation of antibacterial activity was carried out on all synthesized fluorinated and oxygenated 2-styrylchromones by the disc diffusion method as described by Bauer et al. (1966) against the Gram positive bacteria, *Bacillus subtilis*, *Enterococcus faecium* and three *Staphylococcus* species, *aureus,scuii* and *xylosus*, and the Gram negative bacteria, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. The standard antibiotics, tetracycline (Te) and ampicillin (Amp) were used for controls and for comparison. Briefly, Mueller Hilton agar was prepared (38 g in 1 L of water) and poured

into prelabeled sterile Petri dishes, which was then allowed to set and dry at room temperature. The bacterial organisms were standardized using a turbidity standard and then swabbed onto the agar plates. Paper discs with dissolved sample and a control disc was placed onto the agar plates and the inoculum spots allowed to dry at room temperature before being inverted and incubated at 35-37 ℃ for 18 hours. The diameter of inhibition zone was then measured in mm. The tests were done in triplicate and the results reported as means of at least three determinations. The results are summarized in Table 2-2 and Table 2-3.

The activity index of the product 2-styrylchromoneswas calculated as follows: Activity index (A.I.) = zone of inhibition of compound / zone of inhibition obtained for standard antibiotic drug

2.4. Conclusion

Several new fluorinated 2-styrylchromones (**5a-5f**) were synthesized along with a known fluorinated compound, two methoxylated compounds and a methylenedioxy derivative. The compounds were characterized and screened for their antibacterial activity. In general, the fluorinated compounds displayed antibacterial activity against Gram-positive bacteria more than Gram-negative bacteria, with the fluorinated styrylchromones being most active against *B. subtilis* followed by *S. aureus* and then a single strain of *E. coli* (ATCC 25922), but not the *E.coli* (ATCC 25218) strain, indicating that their activity toward *E. coli* is strain specific. However, the styrylchromones with two fluorine substitutions showed activity against both *E. coli* strains, indicating that a broader spectrum could be obtained with multiple fluorinations on the styrylchromone backbone. Furthermore, the 3',5'-difluorostyrylchromone (**5d**) showed the best activity from all the compounds fluorinated on the phenyl ring, also indicating that more fluorine substitutions on the styrylchromone could lead to enhanced

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activity. Activity of the styrylchromones substituted on the chromone ring was specific to fluorination at the 6-position, which showed the best activity amongst all the compounds tested. Fluorination at the 7-position was only active against one bacterial strain, *B. subtilis*. Thus, the position and number of fluorine substituents on either the phenyl or the chromone ring has an effect on the antibacterial activity of the 2-styrylchromones. It is worthwhile exploring the effect of hydroxy, methoxy and fluorine substitution on the phenyl ring together with fluorine substitution at the 6-position, as these compounds may show enhanced activity.

Acknowledgments

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Chapter 3. Structure elucidation of a series of fluoro- and methoxy-2-styrylchromones using 1D and 2D NMR spectroscopy

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Abstract

Fluoro- and methoxy-2-styrylchromonederivatives have been synthesised by the Baker–Venkataraman method in a three step synthesis starting with acetophenones and (*E*) cinnamic acids and proceeding through substituted (*E*) cinnamoyloxyacetophenone and substituted 3-hydroxy-2,4-pentadien-1-one intermediates. Full structural elucidation of the substituted (*E*) cinnamoyloxyacetophenones and 3-hydroxy-2,4-pentadienone intermediates and the 2-styrylchromone derivatives are presented. The structure elucidation were carried out using extensive 1D (^{1}H, ^{13}C) and 2D(COSY, HSQC and HMBC) NMR spectroscopic studies.

3.1.   Introduction

2-Styrylchromones (2-SC) are a chemical family of oxygen heterocyclic compounds, similar to the flavonoids (2-phenylchromones), but with a vinyl group bridging the chromone ring to the phenyl moiety. Many derivatives of 2-styrylchromones have been synthesised (Silva et al., 2004) and their occurrence in nature has also been reported (Gerwick et al., 1989). There have also been numerous reports on the biological activity of the synthesised derivatives of 2-styrylchromones, which has recently been reviewed by Gomes et al. (2010) and these compounds have been seen to have antioxidant (Filipe et al., 2004), antiviral (Desideri, et al., 2000), anticancer (Gerwick et al., 1987; Momoi et al., 2005; Marinho et al., 2008), anti-allergic (Doria, et al., 1979)and hepatoprotective activities (Fernandes, 2003) as well as A_3 adenosine receptor antagonists (Karton, 1996)and xanthine oxidase inhibitors (Fernandes, 2002).

Although the NMR data for 2-styrylchromones are always reported in the synthetic publications that also report the biological activity, they are never assigned to particular protons or carbon atoms. We have noticed only one publication on the structural elucidation of these compounds in which the nitro derivatives were described (Barros and Silva, 2009). To the best of our knowledge there are no publications in which the structural elucidation of these compounds has been discussed with substituents on the aromatic rings which donate electrons by resonance into the aromatic rings. Furthermore, the structural elucidation of fluorinated molecules is more challenging due to the ^{19}F nucleus being NMR active and coupling with both the protons and the carbon atoms. We herein report the structural elucidation of seven fluorinated, two methoxylated and a methylenedioxy derivative of 2-styrylchrome along with their (*E*) cinnamoyloxyacetophenone and 3-hydroxy-2,4-pentadien-1-one intermediates. The structural elucidation and NMR data reported here can

help one identify newly isolated or synthesised derivatives of 2-styrylchromones, especially fluorinated derivatives.

3.2. Experimental

Synthesis

The synthesis of the 2-styrylchromones (**5a-j**) along with the (*E*) cinnamoyloxyacetophenone (**3a-j**) and 3-hydroxy-2,4-pentadienone (**4a-j**) intermediates were carried out using the Baker-Venkataraman rearrangment in a three step reaction according to Scheme 2-1and is reported in Chapter 2. Essentially, the substituted 2-hydroxyacetophenones (**1**) were reacted with substituted (*E*) cinnamic acids (**2**) in pyridine and phosphorus oxychloride (POCl$_3$) at room temperature for 4-5 h producing the (*E*) cinnamoyloxyacetophenone intermediates (**3a-j**), which were then converted to the 3-hydroxy-2,4-pentadienone intermediates (**4a-j**) with potassium hydroxide in dimethyl sulphoxide (DMSO) by being stirred at room temperature for 2 h. Final conversion to the 2-styrylchromone derivatives (**5a-j**) was carried out using *para*-toluene sulphonic (PTSA) acid in DMSO by reflux at 90-95 °C for 2-3 h. The compounds were named similarly for each of the intermediates and the 2-styrylchromone according to their substitution pattern, for example, 2-(2'-fluoro(*E*)cinnamoyloxy) acetophenone (**3a**), 3-hydroxy-1-(2-hydroxyphenyl)-5-(2-fluorophenyl)-2,4-pentadien-1-one (**4a**) and 2'-fluoro-2-(*E*)styrylchromone (**5a**).

NMR spectra

The ^{1}H and ^{13}C NMR spectra were recorded at 298 K with 5-10 mg samples dissolved in 0.5 ml of CDCl$_3$ in 5-mm NMR tubes using a Bruker Avance^{III}400 MHz NMR spectrometer(9.4 T; Bruker, Germany) (400.22 MHz for ^{1}H, 100.63 MHz for ^{13}C and 376.58 Hz for ^{19}F. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. The ^{1}H and ^{13}C

chemical shifts of the deuterated solvent were δ 7.24 and 77.0 referenced to the internal standard, TMS, respectively. For the ^{19}F NMR spectra, the chemical shift of trifluorotoluene (TFT, 0.05% in $CDCl_3$) was referenced at δ -62.73. For the ^{1}H NMR analyses, 16 transients were acquired with a 1s relaxation delay using 32K data points. The 90° pulse duration was 10.0 μs, and the spectral width was 8223.68 Hz. The ^{13}C NMR spectra were obtained with a spectral width of 24038.46 Hz using 64K data points. The 90° pulse duration was of 8.40 μs. For the ^{19}F NMR spectra, the spectral width was 89285.71 Hz using 131K data points and the 90° pulse duration was 12.50 μs. For the two dimensional experiments including COSY, NOESY, HSQC and HMBC, all data were acquired with 4K × 128 data points ($t_2 \times t_1$). The mixing time for the NOESY experiment was 0.3s, and the long range coupling time for HMBC was 65 ms. All data were analysed using Bruker Topspin 2.1 (2008) software.

3.3.   Results and Discussion

Compounds **3-5** are fully characterised in Table 3-1 to Table 3-7 with their ^{1}H and ^{13}C NMR assignments unambiguously assigned using splitting patterns, chemical shifts and 2D NMR data from HSQC, HMBC and NOESY spectra. An extensive discussion on the splitting patterns and chemical shifts of the compounds are presented below for the intermediates and the 2-styrylchromone molecules. The discussion is divided into several parts, discussing the carbon chain linking the two aromatic units together and discussing the two aromatic rings in detail. This is done in detail for the intermediate **3** and then a comparison to **4** and **5** is done, pointing out salient features and resonances that have changed as well as the proton and carbon resonances that indicate that the products have been formed.

The acetyl group and the α, β unsaturated ester of the intermediate 3

In **3a**, the α and β proton resonances are characteristic and occur at δ_H 6.76 and 8.00 respectively as two doublets with large coupling constants of 16.16 Hz characteristic of *trans* olefinic protons. Their corresponding carbon resonances were present at δ_C 119.42 ($J = 6.93$ Hz, C-α) and 139.95 ($J = 2.72$ Hz, C-β). The C-β resonance is more deshielded than the C-α resonance because of conjugation between the double bond and the carbonyl group; the enolate anion resonance structure showing electron density being removed from C-β. The coupling constants experienced in **3a** for these two resonances are attributed to that of the fluorine atom three and four bonds away from C-β and C-α respectively. This small coupling in the carbon resonances was also seen in **3b** (3"-F) with the C-β resonance and **3c** (4"-F) and **3e** (4',4"-diF) with the C-α resonance, but not in **3d** (3",5"-diF), **3f** (4'-F) and **3g** (5'-F), the remaining fluorinated acetophenone derivatives. The ^{1}H and ^{13}C chemical shifts of these resonances (C-α and C-β) were similar in all of the other cinnamoyloxy acetophenone derivatives (**3b-3j**). The acetophenone methyl resonance occurred at δ_H 2.55 as an intense singlet, also consistent with all the other derivatives **3b-3j** and the acetophenone carbonyl resonance (C-1) was present at δ_C 197.74, distinguished from the other ester carbonyl resonance (C=O) at δ_C 165.10 because the latter showed HMBC correlations to both the α and β proton resonances.

The acetophenone aromatic ring

The proton resonances of **3a-3d** (the unsubstituted acetophenone ring) are all similar with H-3' and H-6' appearing as doublet doublets at δ_H 7.19 ($J = 8.00, 0.84$ Hz) and δ_H 7.85 ($J = 7.85$, 1.58 Hz) respectively. The H-3' resonance *ortho* to the oxygenated position is more shielded because of electron donation from the oxygen atom by resonance and the H-6' resonance

more deshielded since this same electron donation by resonance results in the *meta* position becoming electron deficient. The H-4' and H-5' proton resonances both appear as triplets of doublets at δ_H 7.54 (J = 7.64, 1.58 Hz) and δ_H 7.33 (J = 7.64, 0.84 Hz) since they experience the same coupling constant with each of their adjacent protons resulting in the triplet, which is split into doublets due to *meta* coupling, hence the second small coupling constant. Only in **3b** does H-5' appear as a multiplet because of overlap with other resonances. The C-3' to C-6' carbon resonances for **3a-d** are all similar and occur between δ_C 123.77 and 130.16. The C-1' carbon resonance occurs at δ_C 131.29 and was assigned because of HMBC correlations to H-3' and H-5'. The oxygenated aromatic resonance C-2' was assigned to δ_C 149.09 because of HMBC correlations to H-6' and H-4'.

In **3e** and **3f**, where a fluorine atom is substituted at the 4'-position, the H-3' resonance also occurs as a double doublet as in **3a-d**, but now the *meta* coupling is much larger at 2.45 Hz, the first coupling constant of 8.90 Hz occurring because of H-F *ortho* coupling. The H-5' resonance occurs as a triplet of doublets as for **3a-d** since the H-F *ortho* coupling constant is similar to the H-H *ortho* coupling constant at J = 8.75 Hz, but as for H-3', the *meta* coupling constant is larger than that for **3a-d** at J = 2.45 Hz. The H-6' resonance occurs as a double doublet, but distinctly different from the double doublet in **3a-d** because of the larger *meta* H-F coupling constant of 6.34 Hz in addition to the *ortho* H-H coupling constant of 8.75 Hz. The H-6' resonance also overlaps with the H-β resonance as well in these two compounds.

In the ^{13}C NMR spectrum, C-4' occurs as a doublet with J = 254.07 Hz at δ_H 164.99 in **3e**. The coupling constant is so large that the two resonances which make up the doublet could easily be mistaken for two separate resonances. The carbon resonances however can be identified from the HMBC spectrum where both the resonances making up the doublet show

HMBC correlations to a nearby proton resonance; in the case of **3e**, C-4' to H-6'. To verify this, coupling constants of approximately 220-250 Hz are normally observed. Two bonds away from fluorine, F-C coupling of 23.99 and 21.20 Hz are observed respectively at δ_C 111.70 and 113.34 for the two doublets assigned to C-3' and C-5'. Their chemical shifts are more shielded than their corresponding carbon resonances in **3a-d** due to electron donation by resonance from the fluorine, shielding the carbon atoms more than that of hydrogen. Three bonds away from fluorine, F-C coupling of 11.22 Hz is observed at δ_C 150.90 for C-2' and 10.14 Hz at δ_C 132.20 for C-6'. F-C coupling four bonds away at δ_C 127.62 for C-1' is also observed with a coupling constant of 3.51 Hz in **3e**, however this is not seen in **3f**.

When the fluoro group moves to the 5' position in **3g**, the H-3' resonance is now *meta* to the fluorine atom, which by resonance deshields the *meta* hydrogen resulting in it appearing at δ_H 7.49 in **3g** as opposed to δ_H 6.92-6.94 in **3e** and **3f**. The multiplicity is retained as a double doublet with $J = 8.70$ and 3.04 Hz for the H-H and H-F coupling respectively. The H-4' proton resonance coincides with the solvent peak appearing as a triplet of doublets at δ_H 7.23 with $J = 7.80$ and 3.04 Hz, the triplet being due to similar coupling between H-4'-F and H-4'-H-3', similar to the H-5' resonance in **3e**. Due to the fluoro group being placed adjacent to H-6', shielding this proton through electron donation by resonance, the H-6' proton resonance moves from being the most deshielded resonance in **3e** at δ_H 7.87, where it was *meta* to both the oxygenated moiety and the fluorine atom, to the most shielded of the aromatic resonances at δ_H 7.15 in **3g**. The resonance retains its multiplicity as a double doublet since it couples to fluorine with a similar coupling constant to that of hydrogen with $J = 8.70$ and 4.65 Hz. In the ^{13}C NMR spectrum, all the carbon resonances on the aromatic ring appear as doublets except for C-2', which is *para* to the fluorinated carbon and appears at δ_C 147.79. The fluorinated carbon is present at δ_C 159.90 with $J = 245.12$ Hz. The carbon *meta* to the

fluorine C-1' occurs at δ_C 132.63 (J = 6.10 Hz), followed by the other *meta* carbon C-3', at δ_C 125.44 (J = 7.96 Hz), both being more deshielded than the two *ortho* carbon atoms at δ_C 120.08 (J = 23.26, C-6') and δ_C 116.51 (J = 20.48, C-4').

In the ^{1}H and ^{13}C NMR spectra of the methoxy and methylenedioxy derivatives **3h-3j**, H-3' to H-6', Hα and Hβ and C-1, C-2, C-1' to C-6', C-α, C-β and the ester C=O were all similar to **3a-3d**.

The cinnamoyl aromatic ring

In the absence of any substituents on this ring as in **3f** and **3g**, the H-3"/4"/5" resonances overlap at δ_H 7.44 and appear as a multiplet in **3f** and the H-2"/6" resonance appears as a double doublet with J = 7.56 and 3.88 in **3f**. Their carbon resonances apppear between δ_C 128.48 and δ_C 133.90 with the C-2"/6" and C-3"/5" resonances being equivalent. For the 4"-methoxy derivative **3h**, a characteristic pair of doublets is seen as for other *para*-substituted aromatic compounds at δ_H 7.53 for H-2"/6" and δ_H 6.91 for H-3"/5" with a coupling constant of 8.72 Hz. The H-3"/5" resonance is more shielded than that of H-2"/6" because of the electron donating effects of the methoxy group by resonance to the *ortho* positions. The carbon resonances of C-2"/6" and C-3"/5" occur at δ_C 130.23 and 114.45, the C-3"/5" resonance being more shielded due to the resonance effects explained above. The oxygenated C-4" resonance appears at δ_C 161.91 and C-1" appears at δ_C 126.78.

When the phenyl ring is substituted at both C-3" and C-4" with oxygenated substituents, as in **3i** and **3j**, *meta* coupling is observed for H-2" at δ_H 7.10 (J = 1.88 Hz) in **3i** and *ortho* coupling is observed for H-5" at δ_H 6.87 (J = 8.24 Hz) with H-6" experiencing both *ortho* and

meta coupling at δ_H 7.16 (J = 8.24, 1.88 Hz). The carbon resonances of the two carbon atoms *ortho* to the methoxy groups, C-2" and C-5" occur more upfield at δ_C 109.82 and δ_C 111.05 while C-6" *meta* positioned to the 4"-methoxy substituent appears slighlty more downfield at δ_C 123.31. The two aromatic C-O resonances C-3" and C-4" occur at δ_C 149.23 and 149.30 respectively. The two methoxy resonances in **3i** overlap at δ_H 3.91 with corresponding carbon resonances at δ_C 55.94 and 56.00. The methylenedioxy group proton resonance occurs at δ_H 6.01 with a corresponding carbon resonance of δ_C 101.70.

In **3a-e**, fluorination occurred at either 2", 3", 4" or was difluorinated at the 3" and 5" positions. For the 2"-fluoro derivative **3a**, the H-5" proton only experiences coupling from the adjacent protons and appears as a triplet at δ_H 7.18 with J = 7.50 Hz. This resonance overlaps with H-3', which may account for the *meta* coupling with H-3" not being experienced. The H-3" proton resonance at δ_H 7.11 couples with both the fluorine and the proton of H-4" and appears as a double doublet with J = 10.25 Hz (H-F coupling) and 8.80 Hz (H-H coupling). The H-4" proton resonance appears as a multiplet at δ_H 7.39 due to coupling with all of H-3", H-5", H-6" and the F. However, the only coupling constant that can be observed in this multiplet is that between H-4" and H-6" of 1.65 Hz. The H-6" proton resonance is the most deshielded of these resonances at δ_H 7.59 appearing as a triplet of doublets with J = 7.92 and 1.65 Hz. The triplet is probably caused by the *meta* F atom at C-2" and the *ortho* proton of H-5" having the same coupling constant.

The carbon resonances of the aromatic ring of **3a** with fluorine substituted at the 2" position, results in all the carbon resonances of the ring being doublets with the largest coupling occurring on the carbon directly bonded to fluorine (C-2") at δ_C 161.80 (J = 252.60 Hz), followed by *ortho* coupling of 21.72 Hz for C-3" at δ_C 116.32. For some unknown reason, C-

1", the other *ortho* carbon has a much smaller coupling constant of 11.56 Hz at δ_C 122.17. It is further noticed that while *meta* coupling of 14.23 Hz is observed for C-4" at δ_C 132.21, the same is not observed for C-6" at δ_C 129.43 which only has a coupling constant of 2.65 Hz, probably because of interference from the moiety attached to C-1". The C-5" carbon resonance, *para* to the fluourine atom has a small coupling constant of 3.62 Hz as expected at δ_C 124.56.

The same trends were observed for the 3"-fluorinated derivative **3b**, but now in the ^{13}C NMR spectrum all the usual coupling constants were observed for the *ortho* carbon resonances, C-2" and C-4" at δ_C 114.63 (J = 21.88 Hz) and 117.71 (J = 21.25 Hz), the *meta* carbon resonances, C-1" and C-5" at δ_C 136.27 (J = 7.85 Hz) and 130.56 (J = 8.04 Hz) and the *para* carbon resonance of C-6" at δ_C 124.42 (J = 2.87 Hz).

In the *para*-fluoro substituted compounds, **3c** and **3e**, instead of the usual pair of doublets with a coupling constant of approximately 8 Hz being observed as for the *para* methoxy compound **3h**, the splitting pattern is a bit more complex because of coupling to fluorine. The H-3" and H-5" protons are equivalent and their resonance appears as a triplet at δ_H 7.09 (J = 8.60 Hz). This is due to similar coupling constants between H-2"/6" and H-3"/5", and H-3"/5" and the fluorine atom. The H-2" and H-6" protons are also equivalent with their resonance appearing as a doublet of doublets, due to a smaller meta coupling constant between H-2"/6" and the fluorine atom and occurs at δ_H 7.58 (J = 8.60, 5.42 Hz). The ^{13}C NMR spectrum of **3c** shows the fluorinated carbon resonance as a doublet at δ_C 164.25 (J = 250.70 Hz) and a doublet resonance for C-3"/5" at δ_C 116.20 (J = 21.85 Hz) and C-2"/6" at δ_C 130.43 (J = 8.37 Hz). The C-1" resonance, also a doublet, overlaps with the C-2"/6"

resonance at δ_C 130.32 with a coupling constant of $J = 3.55$ Hz. This resonance can be seen more clearly in **3e** at δ_C 130.17 ($J = 3.44$ Hz).

For the 3",5"-difluorinated compound **3d**, the H-4" resonance was split into a triplet of triplets with $J = 8.68$ and 2.28 Hz. This was due to H-4" coupling to F ($J = 8.68$ Hz) and H-4" coupling to the *meta* protons H-2"/6" ($J = 2.28$ Hz). The H-2" and H-6" protons are equivalent and appear as a double doublet at δ_H 7.08 with $J = 7.92$ Hz for the H-F coupling and 1.92 Hz for the *meta* coupling with H-4". The slight variation in $J_{4",2"/6"}$ is due to the coalescing and broadening of peaks for H-2"/6", however coupling between these two resonances were verified in the COSY spectrum. In the ^{13}C NMR spectrum, the C-3" and C-5" resonances are equivalent and splits into a double doublet at δ_C 163.24 due to coupling between the fluorine attached to ($J = 248.29$ Hz) and the fluorine *meta* to it ($J = 12.83$ Hz). The C-2" and C-6" resonances are also equivalent and appear as a double doublet at δ_C 111.02 ($J = 18.80, 7.18$ Hz) arising from coupling to the fluorine *ortho* to it and the fluorine *para* to it respectively. The C-4", C-1" and C-β resonances appear as triplets at δ_C 105.92 ($J = 25.36$ Hz), δ_C 137.27 ($J = 9.44$ Hz) and δ_C 144.47 ($J = 2.81$ Hz) respectively since these carbon atoms are in the middle of the two fluorine atoms.

The substituted 3-hydroxy-2,4-pentadien-1-one intermediates (4a-j)

In these intermediates, there is a noticeable shift from the acetophenone methyl group at δ_H 2.59 in **3a** to an olefinic resonance (H-2) at δ_H 6.32 in **4a**. This is indicative that the cinnamoyloxyacetophenones (**3**) had converted to the 3-hydroxy-2,4-pentadien-1-ones (**4**). With regard to the α,β-unsaturated double bond, both the resonances shift more upfield by 0.27 Hz for the β resonance in **3a** to H-5 in **4a** and 0.06 Hz for the α resonance in **3a** to H-4 in **4a**. This is because the double bond is now conjugated with the newly formed keto-enol

moiety, shielding H-4 and H-5 more than the H-α and H-β protons in **3**. The *trans* configuration of the double bond is retained as evidenced by the large coupling constant of 16.00 Hz. The H-3' to H-6' resonances also move more upfield by 0.22, 0.11, 0.45 and 0.16 Hz for H-3', H-4', H-5' and H-6', respectively from **3a** to **4a**. This is probably due to greater electron donation by the hydroxy group as opposed to the ester group in **3a**. A further characteristic trait of the ^{1}H NMR spectra of the intermediates **4** are the two hydroxyl resonances occurring at δ_H 14.55 (3-OH) and 12.18 (2'-OH).

In the ^{13}C NMR spectrum of **4a**, the appearance of the alkene carbon resonance C-2 at δ_C 97.42 and an enol carbon resonance C-3 at δ_C 174.03 instead of the methyl carbon resonance at δ_C 29.78 and the ester carbonyl resonance at δ_C 165.10 in **3a** is further evidence that **3a** had converted to **4a**. Due to the ester group being converted to a hydroxy group from **3a** to **4a**, the *ortho* and *para* positions are now some what more shielded by electron donation by resonance. As such, C-1' shifts from δ 131.29 in **3a** to δ 119.04 in **4a**, C-3' from δ 123.77 to δ 118.76 and C-5' from δ 126.12 to δ 119.06. The C-2' resonance which is bonded to the hydroxy group however shifts more upfield to the Ar-OH range at δ_C 162.67 in **4a** from the Ar-ester resonance at δ_C 149.09 in **3a**. The resonances on the aromatic ring adjacent to the Δ^4 double bond remain relatively unchanged and the ^{1}H NMR spectra of **4b-4j** contain the same differences as that pointed out between **3a** and **4a**.

The substituted 2-styrylchromones

In the substituted 2-styrylchromones **5**, the splitting patterns and chemical shifts of the phenyl rings in the ^{1}H and ^{13}C NMR spectra did not change much from those of the intermediates **3** and **4** and therefore a discussion of these will not be repeated. There was also not much change in the C-α and C-β carbon resonances as well as the H-β resonance. However, in the

formation of the chromone ring, the H-α proton experiences a slight shift more downfield to δ_H6.87 in **5a**, approximately 0.17 Hz from the corresponding resonance in **4a**.

All the proton resonances in the chromone ring are also deshielded in forming the chromone ring from the 3-hydroxy-2,4-pentadien-1-one intermediates**4**. The most characteristic and noticeable of these resonances is that of H-5 occurring at δ_H 8.17 in **5a** from 7.69 in **4a**, with the H-6, H-7 and H-8 proton resonances having significant downfield shifts between 0.23 and 0.56, at δ_H 7.37, 7.66 and 7.53 respectively in **5a** from δ_H 6.88, 7.43 and 6.97 in **4a**. These downfield shifts must occur because of delocalisation of the π electrons within the chromone skeleton, thus reducing the electron density at these specific protons. The difference in chemical shift of the H-5 proton is also due to hydrogen bonding with the C-4 carbonyl group. This is now possible since the carbonyl group is locked into position by formation of the chromone ring.

With regard to the ^{13}C NMR spectra, there is not much change in both the C-α and C-β resonances or the aromatic resonances on the chromone ring with the exception of C-6, which is *para* to the oxygen substituent forming the chromone ring. This shift is slightly downfield by approximately 7 ppm at δ_C 125.05 in **5a** from 119.06 in **4a**. The most notable shifts in the ^{13}C NMR spectrum are that of C-2, C-3 and C-4, the carbon atoms involved in forming the chromone ring from the 3-hydroxy-2,4-pentadien-1-one. In **5a**, these carbon resonances occur at δ_C 161.47, 111.21 and 178.48 for C-2, C-3 and C-4 as opposed to their corresponding resonances in **4a** at δ_C 174.03, 97.41 and 196.47 respectively. These three resonances can also be used as evidence that the 2-styrylchromone derivatives had been formed from the 3-hydroxy-2,4-pentadienone intermediates.

All structures were confirmed and assignments of the resonances of each of the proton and carbon atoms were made with aid of HSQC, HMBC and NOESY data. Selected HMBC correlations for **5a** are shown in Figure 3-1 below and the ^{1}H NMR spectrum of **5a** is shown in Figure 3-2 depicting the splitting patterns and chemical shifts of the proton resonances. Table 3-1 to Table 3-7 contain the ^{1}H, ^{13}C and ^{19}F NMR data for all the prepared compounds. The spectra were acquired in CDCl$_3$ unless otherwise stated.

Figure 3-1 Selected HMBC correlations for 2'-fluoro-2-styrylchromone (**5a**)

Figure 3-2[1]H NMR spectrum of 2'-fluoro-2-styrylchromone (**5a**) depicting chemical shifts and splitting patterns

Acknowledgements

Table 3-1 ^{1}H NMR chemical shifts (δ in ppm) for compounds **3a–j** (*J* is given in Hz)

	H-3'	H-4'	H-5'	H-6'	H-α	H-β	H-2"	H-3"	H-4"	H-5"	H-6"	CH₃	OCH₃/OCH₂O
3a	7.19 dd *J* = 8.00, 0.84	7.54 td *J* = 7.64, 1.58	7.33 td *J* = 7.64, 0.84	7.85 dd *J* = 7.85, 1.58	6.76 d *J* = 16.16	8.00 d *J* = 16.16	---	7.11 dd *J* = 10.25, 8.80	7.39 m	7.18 t *J* = 7.50	7.59 td *J* = 7.92, 1.65	2.55 s	---
3b	7.17 dd *J* = 8.00, 0.68	7.55 td *J* = 7.84, 1.64	7.35 m	7.83 dd *J* = 7.56, 1.64	6.55 d *J* = 15.96	7.82 d *J* = 15.96	7.27 d *J* = 9.64	---	7.10 tt *J* = 8.20, 2.00	7.33 td J = 7.66, 0.84	7.35 m	2.55 s	---
3c	7.17 dd *J* = 8.00, 0.72	7.53 td *J* = 8.0, 1.52	7.33 td *J* = 8.00, 0.72	7.81 dd *J* = 8.00, 1.60	6.58 d *J* = 15.96	7.84 d *J* = 15.96	7.58 dd *J*= 8.60, 5.42	7.09 t *J* = 8.60	---	7.09 t *J* = 8.60	7.58 dd J = 8.60, 5.42	2.54 s	---
3d	7.16 dd *J* = 7.92, 0.80	7.55 td *J* = 7.60, 1.00	7.34 td *J* = 7.60, 0.76	7.82 dd *J* = 7.92, 1.00	6.64 d *J* = 15.96	7.75 d *J* = 15.96	7.08 m	---	6.85 tt *J* = 8.68, 2.28	---	7.08 m	2.54 s	---
3e	6.92 dd *J* = 8.90, 2.45	---	7.03 td *J* = 8.75, 2.45	7.87 dd *J* = 8.75, 6.34	6.56 d *J* = 15.96	7.84 d *J* = 15.96	7.58 dd *J* = 8.72, 5.40	7.10 dd *J* = 8.60	---	7.10 dd *J* = 8.60	7.58 dd *J* = 8.72, 5.40	2.53 s	---
3f	6.94 dd *J* = 8.90, 2.48	---	7.03 td *J* = 8.60, 2.48	7.86 dd *J* = 8.60, 5.40	6.63 d *J* = 15.92	7.88 d *J* = 15.92	7.58 dd *J* = 7.56, 3.88	7.44 m	7.44 m	7.44 m	7.58 dd *J* = 7.56 3.88	2.53 s	---
3g	7.49 dd *J* = 8.70, 3.04	7.23 dd *J* = 7.80, 3.04	---	7.15 dd *J* = 8.70, 4.65	6.64 d *J* = 15.92	7.88 d *J* = 15.92	7.58 dd *J* = 7.44, 3.60	7.39 m	7.39 m	7.39 m	7.58 dd *J* = 7.44, 3.60	2.53 s	---
3h	7.17 d *J* = 8.00	7.51 td *J* = 7.55, 1.55	7.31 td *J* = 8.04, 0.76	7.80 dd *J* = 8.04, 1.55	6.52 d *J* = 15.92	7.83 d *J* = 15.92	7.53 d *J* = 8.72	6.91 dd *J* = 8.72	---	6.91 dd *J* = 8.72	7.53 d *J* = 8.72	2.54 s	3.84 s
3i	7.17 d *J* = 8.08, 0.90	7.54 td *J* = 7.80, 1.72	7.31 td *J* = 7.55, 0.90	7.81 dd *J* = 7.80, 1.72	6.52 d *J* = 15.88	7.82 d *J* = 15.88	7.10 d *J* = 1.88	---	---	6.87 d *J* = 8.24	7.16 dd *J* = 8.24, 1.88	2.55 s	3.91 s (6H)
3j	7.16 d *J* = 7.92	7.53 td *J* = 7.92, 1.56	7.31 td *J* = 7.92, 0.76	7.80 dd *J* = 7.92, 1.56	6.47 d *J* = 15.88	7.78 d *J* = 15.88	7.05 d *J* = 1.56	---	---	6.82 d *J* = 7.94	7.08 dd *J* = 7.94, 1.56	2.54 s	6.01 s

Table 3-2 ^{13}C NMR chemical shifts (δ in ppm) for compounds **3a–j** (J is given in Hz)

	C-1	C-2	C=O	C-α	C-β	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'	C-1"	C-2"	C-3"	C-4"	C-5"	C-6"	CH₃/OCH₂O
3a	197.74	29.77	165.10	119.42 d $J = 6.93$	139.95 d $J = 2.72$	131.29	149.09	123.77	133.36	126.12	130.16	122.17 d $J = 11.56$	161.80 d $J = 252.60$	116.32 d $J = 21.72$	132.21 d $J = 14.23$	124.56 d $J = 3.62$	129.43 d $J = 2.65$	-
3b	197.68	29.97	164.90	118.31	145.83 d $J = 2.73$	131.21	148.99	123.76	133.39	126.17	130.19	136.27 d $J =7.85$	114.63 d $J = 21.88$	163.02 d $J = 245.63$	117.71 d $J = 21.25$	130.56 d $J = 8.04$	124.42 d $J = 2.87$	-
3c	197.78	29.71	165.14	116.58 d $J = 2.37$	145.99	131.30	149.07	123.78	133.36	126.10	130.15	130.32 d $J = 3.55$	130.43 d $J = 8.37$	116.20 d $J = 21.85$	164.25 d $J=250.70$	116.20 d $J = 21.85$	130.43 d $J = 8.37$	-
3d	197.60	29.51	164.58	119.72	144.47 t $J = 2.81$	131.00	148.86	123.74	133.47	126.26	130.28	137.27t $J=9.44$	111.02d d$J=18.80,7.18$	163.24 dd$J=248.29, 12.83$	105.92t $J=25.36$	163.24 dd$J=248.29, 12.83$	111.02d d$J =18.80, 7.18$	-
3e	196.11	29.73	165.11	116.11 d $J = 2.24$	146.55	127.62 d $J = 3.51$	150.99 d $J = 11.22$	111.70 d $J = 23.99$	164.99 d $J=254.07$	113.34 d $J = 21.20$	132.20 d $J = 10.14$	130.17 d $J = 3.44$	130.47 d $J = 8.47$	116.26 d $J = 21.94$	164.35 d $J=250.95$	116.26 d $J = 21.94$	130.47d $J = 8.47$	-
3f	196.13	29.83	164.75	116.29	145.40	127.00	151.00 d $J = 11.43$	113.43 d $J = 21.13$	166.44 $J=255.80$	111.73 d $J = 24.07$	132.29 d $J = 10.15$	133.86	129.04	128.51	131.08	128.51	129.04	-
3g	196.35	29.78	165.22	116.61	145.03	132.63 d $J = 6.1$	147.79	125.44 d $J = 7.96$	116.51 d $J = 20.48$	159.90 d $J = 245.12$	120.08 d $J = 23.26$	133.90	128.48	129.04	131.04	129.04	128.48	-
3h	197.90	29.92	165.53	114.10	147.15	131.54	149.28	123.81	133.26	125.95	130.04	126.78	130.23	114.45	161.91	114.45	130.23	55.43
3i	197.90	29.86	165.48	114.34	147.36	131.49	151.67	123.81	133.29	125.98	130.06	127.03	109.82	149.23	149.30	111.05	123.31	55.94 s, 56.0 s
3j	197.84	29.86	165.39	114.60	147.11	131.47	150.17	125.18	133.28	125.99	130.06	128.49	106.70	148.47	149.21	108.64	123.79	101.70

Table 3-3[1]H NMR chemical shifts (δ in ppm) for compounds **4a–j**(J is given in Hz)

	2'-OH	H-3'	H-4'	H-5'	H-6'	H-2	3-OH	H-4	H-5	H-2"	H-3"	H-4"	H-5"	H-6"	OCH$_3$/O CH$_2$O
4a	12.17 s	6.97 dd J=8.48, 0.68	7.43ddd J = 8.48, 7.08, 1.44	6.88 td J=8.12, 0.84	7.69 dd J = 8.01, 1.44	6.32 s	14.55 s	6.70 d J = 16.00	7.73 d J = 16.00	---	7.09 t J = 8.20	7.32 m	7.16 t J = 7.56	7.54 td J = 7.65,1.48	---
4b	12.15 s	6.97 dd J =7.90, 0.90	7.44 ddd J = 8.53, 7.05, 1.54	6.89 ddd J = 8.01, 7.05, 0.90	7.68 dd J = 8.01,2.01	6.32 s	14.55 s	6.56 d J = 15.78	7.58 d J = 15.78	7.24 m	---	7.06 m	7.34 dd J = 7.92, 5.70	7.30 d J = 7.76	---
4c	12.17 s	6.97 dd J = 8.52, 0.85	7.44ddd J = 8.52, 7.10, 1.44	6.88 ddd J = 8.05, 7.10, 0.85	7.68 dd J = 8.05,1.44	6.29 s	14.62 s	6.49 d J = 15.95	7.60 d J = 15.95	7.52 dd J = 8.85, 5.36	7.08 t J =8.85	---	7.08 t J = 8.85	7.52 dd J = 8.85, 5.36	---
4d	12.10 s	6.98 dd J = 8.47,1.06	7.45 ddd J = 8.47, 7.24,1.62	6.89 ddd J = 8.05,7.24, 1.06	7.67 dd J = 8.05, 1.40	6.32 s	14.46 s	6.55 d J = 15.70	7.51 d J = 15.70	7.04 dd J = 8.22, 2.16	---	6.80 tt J = 8.76, 2.16	---	7.04 dd J = 8.22, 2.16	---
4e	12.47 s	6.65dd J =10.37, 2.50	---	6.60 ddd J = 8.77, 8.16,2.15	7.68dd J = 8.98, 6.40	6.20s	14.42 s	6.51 d J = 15.96	7.60 d J = 15.90	7.52 dd J = 8.72, 5.40	7.08 t J = 8.58	---	7.08 t J = 8.58	7.52 dd J = 8.72, 5.40	---
4f	12.55 s	6.65 dd J=10.30, 2.50	---	6.60 td J=8.0, 2.50	7.68 dd J = 8.94, 6.42	6.21 s	14.48 s	6.57 d J = 15.80	7.64 d J = 15.80	7.53 dd J = 8.06, 2.05	7.38 m	7.38 m	7.38 m	7.53 dd J = 8.06, 2.05	---
4g	11.94 s	6.93 dd J=9.08, 4.68	7.17 ddd J =9.16, 7.88, 3.00	-	7.34 dd J =9.00, 3.00	6.20 s	14.59 s	6.58 d J = 15.81	7.66 d J = 15.81	7.54 dd J=7.88 2.20	7.40 m	7.40 m	7.40 m	7.54 dd J=7.88 2.20	
4 h	12.24 s	6.96 dd J=8.50, 2.1	7.42 ddd J = 8.50, 7.50,1.60	6.89 m	7.67 dd J = 7.95, 1.60	6.26 s	14.72 s	6.45 d J = 15.76	7.61 d J = 15.76	7.49 d J=8.80	6.91 d J = 8.80	--	6.91 d J= 8.80	7.49 d J=8.80	3.83 s
4i	12.23 s	6.96 dd J=8.43, 0.68	7.42 ddd J = 8.52, 8.30,1.45	6.85 td J=8.30, 0.68	7.67 dd J = 8.08, 1.45	6.28 s	14.71 s	6.45 d J = 15.68	7.59 d J = 15.68	7.06 d J=1.82	---	---	6.87d J=8.30	7.11 dd J = 8.30, 1.90	3.91 s, 3.92s
4j	12.21 s	6.96 dd J = 8.45, 0.50	7.42 ddd J = 8.45, 8.01,1.56	6.87 td J = 8.01, 0.50	7.66 dd J = 8.01, 1.56	6.26 s	14.68 s	6.39 d J = 15.64	7.55 d J = 15.64	7.04 d (br) J=0.35	---	---	6.81 d J = 8.00	7.02 dd J = 8.00, 1.20	6.00 s

Table 3-4 ^{13}C NMR chemical shifts (δ in ppm) for compounds **4a–j** (J is given in Hz)

	C-1	C-2	C-3	C-4	C-5	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'	C-1"	C-2"	C-3"	C-4"	C-5"	C-6"	CH$_3$/ OCH$_2$O
4a	196.47	97.41	174.03	124.84d J=7.77	132.62d J=2.23	119.04	162.63	118.76	136.18	119.06	128.56	123.11d J=11.54	161.41d J = 253.82	116.29 d J=21.90	131.38 d J=8.82	124.52 d J =3.57	129.23 d J=3.00	---
4b	196.25	97.44	173.63	123.51	138.32 d J=2.51	119.01	162.68	118.81	136.00	119.05	128.53	137.28 d J=7.75	114.05 d J=20.01	164.87 d J = 247.22	116.90 d J=21.61	130.50 d J=8.23	124.06 d J = 2.75	-
4c	196.03	96.98	174.25	121.88	138.53	119.04	162.64	118.79	135.87	119.04	128.47	130.23 d J =3.52	129.81d J=8.21	116.15 d J = 21.85	163.78 d J= 250.26	116.15 d J = 21.85	129.81d J=8.21	-
4d	196.42	97.89	172.84	124.80	136.97	118.94	162.73	118.85	136.17	119.14	128.56	138.30 t J=9.54	110.48dd J= 18.53, 6.83	163.29 dd J = 247.76, 13.10	105.07 t J= 25.60	163.29 dd J = 247.76, 13.10	110.48d d J= 18.53, 6.83	-
4e	194.87	96.76	174.21	121.70	138.72	115.93	165.16 d J = 14.10	105.30 d J=23.57	166.40 d J = 212.10	107.31 d J=22.57	130.41 d J=10.83	130.65d J=11.90	129.85 d J=8.55	116.17 d J=21.88	162.98 d J= 252.55	116.17 d J=21.88	129.85 d J=8.55	-
4f	194.85	96.78	174.42	122.00	140.14	115.95	165.08 d J = 14.14	105.27 d J = 23.41	165.17 d J=209.24	107.29 J=22.65	130.47 J=11.65	134.92	128.02	128.99	130.18	128.99	128.02	-
4g	194.82 d J=2.72	96.81	175.23	121.86	140.58	118.72 d J=6.50	158.72	119.95 d J=7.41	123.19 d J=23.38	155.12 d J = 236.79	113.46 d J=23.53	134.84	128.10	129.02	130.42	129.02	128.10	-
4h	195.32	96.13	174.91	119.41	139.49	118.85	162.26	118.44	135.33	118.69	128.83	129.77	129.44	114.16	161.12	114.16	129.44	55.15
4i	195.62	96.48	175.00	119.91	139.98	119.12	162.54	118.74	135.64	118.96	128.39	128.02	109.67	151.13	149.31	111.19	122.60	56.01, 55.93
4j	195.69	96.61	174.83	120.13	139.73	119.09	162.55	118.73	135.68	118.99	128.42	129.50	106.31	149.57	148.47	108.70	124.56	101.61

Table 3-5 ^{1}H NMR chemical shifts (δ in ppm) for compounds **5a–j**(J is givenin Hz)

	H-3	H-5	H-6	H-7	H-8	H-2'	H-3'	H-4'	H-5'	H-6'	H-α	H-β	OCH$_3$/OCH$_2$O
5a	6.32 s	8.17 dd $J = 7.94$, 1.56	7.37 td $J=7.92$, 0.80	7.66 ddd $J = 8.56$, 7.20, 1.56	7.53 d $J = 8.28$	---	7.11ddd $J = 9.20$, 8.20, 2.36	7.32 m	7.17 t $J = 7.92$	7.59 td $J = 7.60$, 1.50	6.87 d $J = 16.24$	7.72 d $J = 16.24$	---
5b	6.34 s	8.18 dd $J = 7.92$, 1.32	7.36 m	7.68 dt $J = 8.60$, 1.64	7.52 d $J = 8.60$	7.26 m	---	7.06 t $J = 8.04$	7.36 m	7.36 m	6.77 d $J = 16.00$	7.55 d $J = 16.00$	---
5c*	6.46 s	8.01 dd $J = 7.92$, 1.44	7.47 t $J = 7.44$	7.82 m	7.69 d $J = 8.48$	7.79 m	7.28 t $J = 8.78$	---	7.28 t $J = 8.78$	7.79 m	7.16 d $J = 16.16$	7.70 d $J = 16.16$	---
5d	6.34 s	8.18 dd $J = 7.92$, 1.56	7.39 td $J = 7.92$, 0.68	7.72ddd $J = 8.55$, 7.20,1.56	7.51 d $J = 8.30$	7.08 dd $J = 8.08$, 1.88	---	6.81 tt $J = 8.70,2.35$	---	7.08 dd $J = 8.08$, 1.88	6.76 d $J = 15.96$	7.49 d $J = 15.96$	---
5e	6.28 s	8.18 dd $J = 8.80$, 6.35	7.12 m	---	7.20 dd $J = 9.04$, 2.40	7.56 dd $J=8.60$, 5.56	7.10 t $J = 8.60$	---	7.10 t $J = 8.60$	7.56dd $J=8.60$, 5.56	6.67 d $J = 16.00$	7.53 d $J = 16.00$	---
5f	6.29s	8.19 dd $J = 8.85$ 6.35	7.10 td $J=8.60$, 2.40	---	7.21dd $J=9.13$, 2.40	7.58 dd $J=8.10$, 1.48	7.41 m	7.39 m	7.41 m	7.58 dd $J=8.10$ 1.48	6.76 d $J = 15.96$	7.59 d $J = 15.96$	---
5g	6.31 s	7.85 dd $J =8.20$, 3.15	---	7.40 m	7.52 dd $J = 9.10, 4.15$	7.56 d $J = 8.00$	7.40 d $J = 8.00$	7.39 m	7.40 d $J = 8.00$	7.56 d $J = 8.00$	6.77 d $J = 16.08$	7.60d $J = 16.08$	---
5h	6.28 s	8.18 dd $J = 7.95$, 1.60	7.36 t $J=7.95$	7.65 ddd $J =8.56$, 7.12,1.60	7.52 d $J = 8.56$	7.48 d $J = 8.70$	6.92 d $J = 8.70$	---	6.92 d $J = 8.70$	7.48 d $J = 8.70$	6.64 d $J = 15.96$	7.55 d $J = 15.96$	3.84 s
5i*	6.40 s	8.01 dd $J = 7.88,1.72$	7.47 ddd $J = 7.88,7.16, 0.68$	7.81 ddd $J = 8.20,7.16, 1.72$	7.70 d $J = 8.20$	7.36 d $J=1.72$	---	---	7.02 d $J = 8.28$	7.27 dd $J = 8.28$, 1.72	7.11 d $J = 16.04$	7.65 d $J = 16.04$	3.80 s 3.83s
5j	6.28 s	8.17 d $J = 7.62$	7.37 t $J=7.53$	7.65ddd $J = 8.11$ 7.14,0.98	7.51 d $J = 7.82$	7.08 s	---	---	6.81 d $J = 8.06$	7.05 d $J = 8.06$	6.59 d $J = 16.06$	7.50 d $J = 16.06$	6.01

*in DMSO-d$_6$

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Table 3-6 ^{13}C NMR chemical shifts (δ in ppm) for compounds **5a–j** (J is given in Hz)

	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-α	C-β	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'	OCH₃/ OCH₂O
5a	161.47	111.21	178.48	125.69	125.05	133.88	117.93	156.02	124.13	122.67 d J = 6.51	129.47 d J = 3.10	123.09 d J = 11.68	161.17 d J = 253.27	116.23 d J=21.81	131.25 dJ=8.67	124.56 dJ =3.57	128.39 d J = 2.72	
5b	161.22	111.15	178.51	125.76	125.14	133.89	117.87	156.00	124.09	121.67	135.57 d J = 2.77	137.28 d J = 7.84	113.99 d J = 21.99	163.15 d J = 245.48	116.69 d J = 21.60	130.54 d J = 8.30	123.61 d J = 2.67	
5c*	161.68	110.06	177.13	124.76	125.31	134.35	118.20	155.43	123.39	120.38	135.38	131.59 d J=3.22	130.02 d J=8.11	115.97 d J=24.34	162.88 d J = 240.60	115.97 d J=24.34	130.02 d J =8.11	
5d	160.59	111.70	178.37	125.79	125.25	133.99	117.87	155.97	124.11	122.98	134.22 t J=3.02	138.28 t J=11.24	110.28 dd J = 18.47, 7.22	163.35 dd$J$= 247.82, 12.87	104.96 tJ = 25.41	163.35 dd$J$= 247.82, 12.87	110.28 dd J = 18.47, 7.22	
5e	161.82	110.63	177.41	128.22 d J=10.51	113.73 d J=22.45	167.07 d J=210.10	104.60 d J=25.49	156.88	120.96	119.67	135.83	131.15 d J=3.56	129.52 d J=8.19	116.21 d J=21.88	164.97 d J=251.55	116.21 d J=21.88	129.52 d J =8.19	
5f	162.01	110.62	177.48	128.20 d J=10.64	113.69 d J=22.56	164.48 d J = 252.60	104.63 d J=25.39	157.05 d J=13.20	121.00	119.89	137.19	134.88	127.72	129.05	130.00	129.05	127.72	
5g	161.99	109.89	177.62 d J = 2.28	110.69 d J=23.42	159.50 d J = 245.09	121.76 d J =25.13	119.89 d J=7.86	152.20	125.47 d J=7.10	120.03	137.35	134.88	127.73	129.05	130.02	129.05	127.73	
5h	162.25	109.94	178.48	125.69	124.91	133.60	117.85	156.03	124.15	117.90	136.65	130.95	129.29	114.48	161.11	114.48	129.29	55.42
5i*	162.26	109.17	177.02	124.74	125.22	134.21	118.11	155.44	123.42	118.01	136.87	127.79	109.92	149.00	150.53	111.67	122.31	55.54
5j	161.98	110.17	178.45	125.70	124.95	133.65	117.80	156.01	123.25	118.35	136.67	129.53	106.15	149.32	148.52	108.69	123.91	101.60

* in DMSO-d$_6$

Table 3-7 ^{19}F NMR chemical shifts (δ in ppm)of compounds **3a-g** , **4a-g** and **5a-g**

No.	3	4	5
a	-113.57	-114.18	-115.39
b	-112.27	-112.32	-112.42
c	-108.54	-109.55	-110.72
d	-108.75	109.10	-109.31
e	-103.81, -103.17	-100.64, -109.57	-102.96, -109.89
f	-103.91	-100.72	-103.04
g	-115.35	-124.33	-115.51

3.4.   References

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Chapter 4. Antioxidant activity of 3-hydroxy-1-(2-hydroxyphenyl)-5-(phenyl)-2, 4-pentadien-1-one analogues

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ABSTRACT

The fluoro aryl and methoxy aryl analogues of (2*Z*,4*E*)-3-hydroxy-1-(2-hydroxyphenyl)-5-(phenyl)penta-2,4-dien-1-one were synthesised from different combinations of substituted 2-hydroxacetophenones and (*E*)-cinnamic acids. They were then screened for their antioxidant activity by the 2, 2-diphenyl-1-picryl-hydrazyl (DPPH) radical scavenging assay and Ferric Reducing Power assay (FRAP).All the methoxylated analogues showedbetter activity thanthe fluorinated analogues and comparable to that of ascorbic acid.

KEYWORDS: Antioxidant activity, 3-hydroxy-pentadien-1-ones, fluorinated aromatics, oxygenated aromatics, DPPH, FRAP

4.1. Introduction

Oxidative stress is caused by an imbalance in the ratio of antioxidants to oxidants present in the body (Bhuyan et al., 2011). Antioxidants are gaining popularity to help fight off a large number of life-style diseases such as cancer, diabetes, cardiovascular and other degenerative diseases. Some of these, for example cancer, may be caused by the deleterious effects of pollution and overexposure to harmful chemicals (Roopan et al., 2009), while others such as diabetes and cardiovascular diseases may be caused by modern lifestyles where diets rich in fatty acids and carbohydrates coupled with a lack of exercise and work or family related stress is prevalent. These conditions can cause biochemical changes in the body, causing an accumulation of harmful free radicals (Kumar, 2011).

A free radical is a highly reactive chemical species, which contains an unpaired electron (Jaslin et al., 2011). The family of free radicals generated from oxygen is called reactive oxygen species (ROS). These species cause damage to other molecules by extracting electrons from them in order to attain stability (Chanda et al., 2010). While most fruits and vegetables are rich in antioxidants such as polyphenolic compounds (e.q the flavonoids, also a major constituent in red wine), most people experiencing the effects of oxidative stress do not contain these natural antioxidant supplements in their diet and the human body does not synthesize the required antioxidants to compensate with the damaging effects of ROS (Halliwell, 1996; Uttara et al., 2009).

Although synthetic antioxidants such as tert butylated hydroxy toluene, tert butylate hydroxy anisole, gallic acid esters and tertiary butylated hydroquinones have shown the potential to neutralize free radicals, they have been criticized, mainly for having possible toxic effects, low solubility and only moderate antioxidant activity. For decades, vitamin C (ascorbic acid)

has been used as an antioxidant supplement, but nowadays even this dietary supplement is not enough to ward off the deleterious effects of the free radicals generated in our bodies. There is thus a constant need to discover newpotential sources of antioxidants (Kothari et al., 2010).

The carbonyl group and the phenolic hydroxyl and methoxyl groups in molecules can contribute to enhanced antioxidant activity (Wright, 2002., Atmani et al., 2009). Since the 3-hydroxy-pentadien-1-ones contain most or all of these functional groups, they were subjected to the 1,1-diphenyl-2-picryl hydrazyl (DPPH) radical scavenging assay and the FerricReducing Power assay (FRAP)to determination their potential to act as free radical scavengers and hence potential antioxidants.

4.2.   Materials and Methods

Chemistry

In general, different combinations of 2-hydroxyacetophenones (**1**) and cinnamic acid derivatives (**2**) were reacted with phosphorus oxychloride in pyridine at room temperature for 4-5 hours to produce substituted (*E*) cinnamoyloxyacetophenones (**3**), which were subjected to basic conditions in DMSO at room temperature for 2 hours to produce the substituted (2*Z*,4*E*)-3-hydroxy-1-(2-hydroxyaryl)-5-(aryl)penta-2,4-dien-1-ones (**4a-4j**) (Scheme 4-1). The molecules were named according to their substitution pattern on the aromatic rings: for example, **4a** was named as (2*Z*,4*E*)-3-hydroxy-1-(2-hydroxyphenyl)-5-(2-fluorophenyl)-2,4-pentadien-1-one. The structures of the molecules were confirmed by 1D and 2D NMR spectroscopy and mass spectrometry. The detailed synthesis is given in Chapter 2 and a full structural elucidation of the compounds is given in Chapter 3.

DPPH Assay

The determination of the free radical scavenging activity of **4a-4j** was carried using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay as described by Mensor et al. (2001) with a slight modification. Various concentrations (10, 25, 50, 125, and 250 μgmL^{-1}) of sample extracts in methanol were prepared. A 1.0 mLaliquot of a 0.3 mM DPPH solution in methanol was added to a 2.5 mL solution of the product or standard and allowed to stand at room temperature in a dark chamber for 30 minutes. The change in colour from deep violet tolight yellow was then measured at 518 nm on a UVspectrophotometer (Jenway 6025). The decrease in absorbance was then converted to percentage antioxidant activity (% AA) using the formula:

AA%=100 -{[(Abssample-Absblank) x100] / Abscontrol}

Blank = Methanol (1.0 mL) plus sample solution (2.0 mL), Negativecontrol=DPPH solution (1.0 mL, 0.25 mM) plus methanol (2.0 mL), Ascorbic acid and gallic acid were used as standards.The scavenging reaction between (DPPH·) and an antioxidant (HA)can be written as:

(DPPH·) + (H-A) →DPPH-H + (A·)

Ferric Reducing Power assay

The FRAP was determined according the method of Oyaizu et al. (1986). The product or standard (100μgmL^{-1}) was mixed with phosphate buffer (pH 6.6) and potassium ferricyanide. The mixture was incubated at50°C for 20 min. Trichloroacetic acid (10%, 2.5 mL) was added to themixture. A portion of the resulting mixture was mixed with $FeCl_3$(0.1%, 0.5mL) and the

absorbance was measured at 700 nm in aspectrophotometer (Jenway 6025). A higher absorbance of the reaction mixture indicated a greater reductive potential of the sample.

4.3.   Results and Discussion

Seven fluorinated and three methoxylatedanalogues of 3-hydroxy-1-(2-hydroxyphenyl)-5-(phenyl)-2,4-pentadien-1-oneswere synthesized in a two-step reaction from different combinations of (*E*) cinnamic acids and 2-hydroxyacetophenones according toScheme 4-1. The resultant compounds were evaluated for their antioxidant activity using the FRAP and DPPH assays since they contained carbonyl, hydroxy, methoxy and fluoro functional groups in the molecule.   In particular, we wanted to see whether the fluorinated derivatives had comparable activity to the methoxylated derivatives.

| a | 2"-F | b | 3"-F | c | 4"-F | d | 3",5"-F | e | 4',4"-F |
| f | 4'-F | g | 5'-F | h | 4"-OCH$_3$ | i | 3",4"-OCH$_3$ | j | 3",4"-OCH$_2$O |

Scheme 4-1 The preparation of (2*Z*,4*E*)-3-hydroxy-1-(2-hydroxyaryl)-5-(aryl)penta-2,4-dien-1-ones **4a-j** from their corresponding acetophenones and (*E*) cinnamic acids (i) Pyridine, POCl$_3$, rt. 4-5 h. (ii) DMSO, KOH, rt. 2h.

The results obtained from the FRAP assay (Table 4-1) showed that the reducing power of all compounds increased with increasing concentration, indicating that they all contained antioxidant activity and were capable of donating electrons to radicals, quenching them and rendering them inactive. The reducing power of the ten compounds tested decreased in the following order: **4i>4h>4j>4e>4d>4g>4f>4b>4c>4a**.The reducing power of the standard ascorbic acid was however better than the tested compounds.Five of the tested compounds, three fluorinated, (the 3",5"-difluoro**4d**, 4',4"-difluoro **4e** and the 4'-fluoro **4f** derivatives) and two methoxylated (the 4"-methoxy **4h** and 3",4"-methoxy **4i** derivatives) were relatively comparable to ascorbic acid having antioxidant activity of between 54 and 65% to that of ascorbic acid at low concentrations (31.1 μg mL^{-1}), with the 4',4" fluoro derivative **4i** having the highest activity. However, with increased concentration, better antioxidant activity was seen in the methoxy derivatives **4h** and **4i**, with **4i** showing the best activity from all the tested compounds, increasing from 62% to 86% to that of ascorbic acid with a two-fold increase in concentration. At higher concentrations (125 and 250 μg mL^{-1}), both methoxy derivatives **4h** and **4i** and the methylenedioxy derivative **4j** showed good activity in comparison to ascorbic acid, having activity of between 57 and 82% (125 μg mL^{-1}) and between 70 and 80% (250 μg mL^{-1}) of that of ascorbic acid.

With regard to the fluorinated compounds, **4e** substituted with fluorine on both the chromone ring at C-4' and the phenyl ring at C-4" showed the best activity, slightly higher than that with a fluorine substituted at C-4' alone as in **4f**. The activity of the 3",5"-difluoro derivative **4d** also has antioxidant activity comparable to **4e** and **4f** but **4g** with the 5'-fluoro substitution and all the derivatives with mono-fluoro substitution on the phenyl ring **4a-4c** showed much lower antioxidant activity.

Table 4-1 Antioxidant activity of **4a-j** measured by the FRAP method

	Absorbance at the given concentration			
	31.1μg mL^{-1}	62.5μg mL^{-1}	125μg mL^{-1}	250μg mL^{-1}
4a	0.15±0.03	0.41±0.02	0.48±0.02	0.82±0.01
4b	0.21±0.01	0.30±0.01	0.45±0.01	0.88±0.02
4c	0.26±0.02	0.28±0.01	0.74±0.01	0.83±0.01
4d	0.38±0.01	0.46±0.02	0.69±0.01	0.99±0.01
4e	0.42±0.02	0.53±0.02	0.93±0.02	1.12±0.03
4f	0.36±0.01	0.38±0.01	0.67±0.01	0.94±0.00
4g	0.25±0.02	0.28±0.01	0.41±0.01	0.97±0.01
4h	0.35±0.02	0.58±0.02	1.10±0.02	1.55±0.03
4i	0.40±0.01	0.85±0.04	1.51±0.02	1.83±0.02
4j	0.27±0.02	0.44±0.01	1.58±0.02	1.50±0.02
Ascorbic acid	0.65±0.03	0.99±0.01	1.93±0.02	2.15±0.03

Data are presented as means ±SD of triplicate.

The reduction of DPPH can be correlated with thenumber of available hydroxyl groups in the test samples and their ability to donate these to the DPPH radicals, quenching them and showing the probability of rendering other radicals of this type inactive. The results from this assay (Table 4-2) shows that all the fluorinated compounds did not have as good antioxidant activity as the methoxylated or the methylenedioxy derivatives. The activity of the ten compounds decreased in the following order **4i**>**4j**>**4h**>**4f**>**4a**>**4g**>**4e**>**4c**>**4d** >**4b**. The highest activity was shown by **4i**, the 3″,4″-dimethoxy derivative, which also had the highest activity in the FRAP assay and had an activity of 76% to that of ascorbic acid at the highest concentration (250 μg mL^{-1}) and 71% at the lowest concentration (31.1 μg mL^{-1}). The other

two oxygenated derivatives, **4h** and **4j** also had good activity in this assay of between 52 and 65% at 62.5 μg mL^{-1} and 66 and 73% at 250 μg mL^{-1} to that of ascorbic acid at the same concentrations. It appears that activating electron donating substituents such as the methoxy group is much better at allowing the hydroxy group on the alkene to donate its proton to the DPPH radical than the deactivating fluoro groups are. Thus, fluorine substitution at either the phenyl or the chromone ring did not make much difference to the antioxidant activity as compared to oxygenated substituents such as the methoxy group.

Table 4-2 Antioxidant activity of **4a-j** measured by the DPPH method

	Absorbance of the given concentration.			
	31.1μg mL^{-1}	**62.5μg mL^{-1}**	**125μg mL^{-1}**	**250μg mL^{-1}**
4a	12.56±0.65	26.78±0.46	38.12±0.27	48.46±0.56
4b	9.98±0.29	16.70±0.44	34.96±0.77	42.35±1.41
4c	16.44±0.47	20.04±1.05	34.31±0.63	45.98±0.60
4d	10.99±0.28	15.74±0.32	26.54±0.47	44.79±1.06
4e	19.75±0.58	21.45±0.64	30.17±0.25	47.50±0.28
4f	11.57±0.70	21.38±0.35	39.00±0.40	52.31±0.53
4g	16.72±0.15	31.83±1.16	34.96±0.81	46.30±1.10
4h	18.40±0.23	35.95±0.42	44.44±0.21	61.21±0.47
4i	34.57±0.81	43.62±0.75	59.20±0.53	70.05±0.77
4j	23.99±0.99	45.39±0.65	50.99±0.73	67.52±0.40
Ascorbic acid	48.54±0.70	69.42±0.60	86.42±0.60	92.42±0.72

Data are presented as means ± SD of triplicate.

4.4. Conclusion

The FRAP assay deals with the electron donating capacity of the molecules and reflects the reducing power of active molecules. The presence of reductants with antioxidant property causes the reduction of the Fe^{3+}/ferricynide complex to the ferrous (Fe^{2+}) ion. In the DPPH assay, DPPH is a stable free radical and accepts an electron or hydrogen radical (like O-H) to become a stable diamagnetic molecule.

In comparison to the methoxylated and methylenedioxy derivatives, the fluorinated derivatives were not as active as antioxidant agents, however in the FRAP assay, three fluorinated derivatives, the 3",5"-difluoro 4d, the 4',4"-difluoro 4e and the 4'-fluoro 4f derivatives showed comparable activity to the oxygenated derivatives 4h-4j. Amongst the three most active fluorinated compounds, 4e showed the best activity. At higher concentrations, the antioxidant activity of the methoxy and methylenedioxy derivatives were comparable to that of ascorbic acid in both the FRAP and DPPH assays. The results show that the methoxylated and methylenedioxy derivatives of (2*Z*,4*E*)-3-hydroxy-1-(2-hydroxyphenyl)-5-(phenyl)penta-2,4-dien-1-one could be considered as good alternative sources of antioxidants.

4.5. References

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Chapter 5. Synthesis, and *in vitro* antiplatelet aggregation screeningof novel fluorinated diethyl-2-(benzylthio)-2,3-dihydro-1H-imidazole-4,5-dicarboxylate derivatives

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Abstract

Objectives

To synthesise a small library of fluorinated derivatives of imidazole-2-thiones and to screen the synthesised compounds *in vitro* for antiplatelet aggregation activity to identify lead compounds which could either be used or developed further into antithrombotic drugs and to compare the activity of the fluorinated derivatives with the nitro and chloro derivatives.

Methods

Seven fluorinated derivatives of diethyl-2-(benzylthio)-2,3-dihydro-1H-imidazole-4,5-dicarboxylate (**6a-6g**) as well as a nitro and chloro derivative (6**h-6i**) were prepared in five steps from glycine, ethyl formate, diethyl oxalate, potassium thiocyanate and substituted benzyl bromides. The structures of the synthesised compounds were elucidated and verified using ^{1}H and ^{13}C NMR spectroscopy and, where appropriate, 2D NMR spectroscopy.

Key Findings

The synthesized compounds exhibited concentration dependent anti-platelet aggregation activity on both the thrombin and ADP induced platelet aggregation. The 4-nitro (**6h**) and 4-fluoro (**6b**) compounds exhibited the highest activity from the compounds tested, with estimated IC$_{50}$ values of 0.40 and 0.35mg/mL for the thrombin-induced and ADP-induced platelet aggregation respectively

Conclusions

Three of the compounds, the 3,4-difluoro(**6c**), 4-nitro(**6h**) and 3-chloro(**6i**) derivatives have reasonable activity in both of the assays and could have potential as broad spectrum antiplatelet inhibitors. With the exception of **6c**, however the fluoro derivatives were not as active as the nitro and chloro compounds.

Keywords: flourine, imidazole, antiplatelet activity, thrombin, ADP.

5.1. Introduction

The imidazole moiety is an important constituent of many biological molecules and hence has been the focus of many synthetic approaches in the quest for pharmaceutically active compounds in a wide range of medical conditions and diseases. Imidazole drugs themselves are well known to have many pharmaceutical applications (Bhatnagar et al., 2011). The imidazole-2-thiones are a subgroup of these molecules that contain a thioamide group and as such have an ambidentate anion, either on nitrogen or sulphur after proton abstraction, which makes them reactive toward electrophilic agents. This normally involves the highly polarised and nucleophilic sulphur atom, which reacts first with most electrophilic centres (Dawood et al., 2010).

Recent reviews by Dawood et al. (2010) and Savjani et al. (2011) include a number of synthetic methods that have been employed to synthesise and react these compounds, to produce a wide range of imidazole-2-thiones, substituted at almost all positions on the imidazole-2-thione skeleton. They can be formed from α-bromoketones with substituted hydrazines and potassium thiocyanate (Lagoja et al., 2003), fromα-hydroxyketones, thiourea and ammonium thiocyanate (Maduskuie et al., 1995), from benzil and thiourea (Muccioli et al., 2006), from phenylglycine methyl ester with phenyl or alkyl isothiocynate (Muccioli et al., 2006) and from diamines and CS_2 over a zinc oxide/aluminium oxide catalyst (Ballabeni et al., 1999) to name a few. The imidazole-2-thiones are extremely reactive and can be alkylated and arylated at both sulphur and nitrogen using a variety of reagents (Trzhtsinskayaand Abramova, 1991) added to activated double bonds such as 2-cyanoethene (Bagrii and Vasilenko, 1978; Trzhtsinskaya et al., 1992), acetylene (Skvortsova et al., 1974), aliphatic and alicyclic ketones and acetophenones (Hozien et al., 2000).

The imidazole-2-thiones have also shown a wide range of biological activities, having antitumor (Iradyan et al., 1987), antiulcer (Tsuji et al., 1989), *in vitro*anti-inflammatory (Selig et al., 2011; Tsuji et al., 1989), antiarthritic, analgesic (Sharpe et al., 1985), antihyperthyroid (Doerge et al., 1993), tuberculostatic (Trzhtsinskaya et al., 1992), *in vitro* antibacterial, antifungal and insecticidal activity (Saeed et al., 2007). They were also shown to possess *in vitro* anti-HIV activity, by showing non-nucleoside reverse transcriptase inhibition (Yasser et al., 2003) andhuman cytosolic phospholipase A2 activity having a role in preventing inflammation (Makita et al., 2000). They are known to be *in vitro* Acyl-CoA: Cholesterol acyltransferase(ACAT) inhibitors, limiting the absorption of dietary cholesterol (Maduskuie et al., 1995), protein kinase inhibitors responsible for preventing the gene expression of proinflammatory cytokines (Buhler et al., 2011), *in vitro* platelet aggregation inhibitors (Hayashi et al., 1989), and known to be *in vitro* anti-hypercholesteremics (Billheimer et al., 1990).

Platelets play an important role in hemostasis during tissue injury. Platelet adhesion and its activation is a normal physiological response to the accidental rupture of blood vessels. Platelets interact with activated plasma clottingfactors at the site of injury in the blood vessel, forming a mechanical plug which blocks the defect and terminates blood loss (Aruna et al., 2010; Jantan et al., 2009). However, when such activity is uncontrolled, this may cause thromboembolic artery occlusion, acute coronary syndrome, and ischemic stroke (Aruna et al., 2010). Anti-platelet aggregation (e.g. aspirin, clopidogrel and dipyridamole) are used in the treatment of cardiovascular diseases, myocardial infarction and stroke (Hankey, 2003). However, some patients are allergic to these drugs, necessitating the need for alternative antithrombotic drugs.

As part of an ongoing study on the search for fluorinated pharmaceuticals and our interest in platelet aggregation inhibitors, we have synthesised a range of fluorinated imidazole-2-thiones and tested them for their ability to inhibit platelet aggregation *in vitro*. We have also synthesised a nitro and chloro analogue to compare the activity of the fluorinated derivatives against.

5.2.   Experimental

Chemistry

General Experimental Procedures

Reagents and chemicals used in this study were purchased from Sigma Aldrich via Capital Lab, South Africa and were reagent grade. All organic solvents were redistilled and dried according to standard procedures. NMR spectra were recorded using a Bruker Avance[III] 600 MHz spectrometer at room temperature with chemical shifts (δ) recorded against the internal standard, tetramethylsilane (TMS). IR spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer with universal ATR sampling accessory. For GC-MS analyses, the samples were analysed on an Agilent GC–MSD apparatus equipped with DB-5SIL MS (30 m x 0.25 mm i.d., 0.25 μm film thickness) fused-silica capillary column. Helium (at 2 ml/min) was used as a carrier gas. The MS was operated in the EI mode at 70 eV. Optical rotation was recorded using a PerkinElmerTM, Model 341 Polarimeter. Melting points were recorded on an Ernst Leitz Wetziar micro-hot stage melting point apparatus.

Preparation of glycine ethyl ester hydrochloride (2).

A solution of glycine (**1**)(0.266 mol; 20.0g)in ethanol was added to a 1L three-necked round bottomed flask fitted with a reflux condenser carrying a calcium chloride guard tube. Thionyl chloride (0.293 mol, 21.3ml) was added slowly using a dropping funnel over a

period of 1 h at -5°C. A vigorous reaction takes place. After complete addition, the reaction mixture was refluxed for 5 h and then cooled at room temperature. A white solid separated out, which was filtered, dried and recrystallized from ethanol to afford the glycine ethyl ester hydrochloride **(2)**, in 94% yield, mp145-146. The structure was confirmed by[1]H NMR.

^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 8.50 (s, 2H, N-H), 4.18 (q, J= 7.38 Hz, 2H), 3.74 (s, 2H), 1.22 (t, J = 7.38 Hz, 3H); ^{13}C NMR (DMSO-d$_6$, 100 MHz): δ 167.51 (C=O), 61.47 (2C), 13.92.

Preparation of N-formylglycine ethyl ester (3)

A mixture of glycine ethyl ester hydrochloride **(2)** (0.122 mol, 17.0g) and ethyl formate (0.792 mol, 120.0 ml) was added to a three-necked round bottomed flask fitted with a reflux condenser. The contents of the flask were heated to 50-55°C, after which triethylamine (0.134 mol, 18.66 ml) was added and the contents refluxed for 24 h. The solution was then cooled and filtered with celite. The pure compound was obtained by completely distilling the filtrate to obtain *N*-formylglycine ethyl ester **(3)** in 93%yield with a bp of206-207°C. The structurewas confirmed by ^{1}H NMR. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.19 (s, 1H, CHO), 4.17 (q, J = 6.72 Hz, 2H), 4.01 (d, J = 5.28 Hz, 2H), 1.23 (t, J = 7.50 Hz, 3H).

Preparation of sodium 1,2-bis-ethoxycarbonyl-2-formylamino-ethenolate (4) and diethyl 2-mercapto-4,5-imidazoledicarboxylate (5)

The procedures in Jones (1952) and Anderson et al. (1989) were adapted and modified. Inadry 2L three-necked flask provided with a stirrer, dropping funnel and reflux condenser, 80 mL of anhydrous ether and 3.2 g (1.25 g per piece) of clean sodium was placed. Thereafter, absolute ethanol (15 mL) was added followed by the slow addition of diethyl oxalate (1.43 moles; 19.4ml) so that the reaction did not become too vigorous.*N*-

formylglycineethyl ester (**3**) (0.114 mol; 15.0 g) was added to the resultant solution from a droppingfunnel whilst stirring the contents of the flask. Aprecipitate formed (**4**) which turned to adark red-brown gummy mass upon standing. The mixture was then left to stand for 24h, after which 100 ml of iced water was added, and the mixture agitated until the solid dissolved. The aqueous layer was separated from the organic layer and 19.5g (0.20moles) of potassium thiocyanate followed by 25 mL of concentrated hydrochloric acid was added to the aqueous layer.The resultant solution was warmed on a water bathfor a few minutes to remove any remaining dissolvedetherand then refluxed at 40-60°C for six h during which time a heavy yellow crystallineprecipitate of diethyl 2-mercapto-4,5-imidazoledicarboxylate(**5**) separated. The mixture was cooled, filtered and washed with 10 mL of iced water. By evaporating the filtrate under reducedpressure to a volume of about 700 mL, an additional quantityof the product was obtained. The total yield of the crude productwas 12.75 g(46% yield), mp 202-204°C. The ^{1}H and ^{13}C NMR data of **5** compare well with that in Anderson et al., (1989).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.20 (s, 2H, N-H), 4.26(q, *J*=6.92Hz, 4H), 1.27(t, *J*=7.0Hz, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 164.21 (C=S), 157.71 (C=O), 123.37, 62.04, 14.28.

Preparation of diethyl-2-(benzylsulfanyl)-1H-imidazole-4,5-dicarboxylate derivatives (6a-i)

Diethyl 2-mercapto-4,5-imidazoledicarboxylate(**5**) (0.00409 mol, 1.0g) in DMF (10 mL), sodium bicarbonate (0.00595 mol, 0.50 g) and substituted benzyl halides (approximately 0.00500 mol of each) were added together in a 100 mL round bottom flask and stirred for 1.5 h. The contents were then diluted with 20 mL ofethyl acetate, followed by water to separate out the organic layer, which was further washed with water. The organic layer was

evaporated to yield the products (**6a-i**), which was recrystallized from ethanol. The yields and melting points are recorded below.

6a) *Diethyl 2-(3-fluorobenzylthio)-1H-imidazole-4,5-dicarboxylate:* Pale yellow sticky solid residue (85% yield); mp 97-98°C, UV λ_{max} (EtAc) nm (log ε) 274 (3.59);IR (KBr)υ_{max}: 3387 (N-H), 2983(C-H alkane), 1715 (C=O), 1255 (C-F), 1588 (C=C), 1187 (C-N), 1072, 1012, 741 cm^{-1};^{1}H NMR (CDCl$_3$, 600MHz) δ 7.96 (s, N-H), 7.22 (td, J = 7.92, 5.94 Hz, 1H, H-5"),7.07(d, J=7.68 Hz, 1H, H-6"), 7.02 (dt, J=9.50, 1.77 Hz, 1H, H-2"), 6.92 (td, J= 8.94, 2.34 Hz, 1H, H-4"), 4.42(s, 2H, H-7"), 4.31(q, J = 7.14 Hz, 4H, 2H-7/7'), 1.30(t, J=7.14 Hz, 6H, 3H-8/8'); ^{13}C NMR (CDCl$_3$, 150 MHz) δ 162.69(d,J_{CF}= 246.42 Hz, C-3"),159.44(2C, C-6/6'), 144.11 (C-2), 138.52 (d, J=7.40 Hz, C-1"), 130.27 (d, J=7.75 Hz, C-5"), 124.69 (d, J=3.19 Hz, C-6"), 115.93 (d, J= 22.01 Hz, C-2"), 114.89 (d, J=21.04 Hz, C-4"), 62.09 (2C, C-7/7'),37.58 (C-7"), 14.09 (2C, C-8/8'); ^{19}FNMR (CDCl$_3$, 376.5 MHz) δ. -112.22; EIMS (*m/z*, % rel. int.) 352 [M$^+$] (25), 307 (8), 278 (4), 234 (12), 206 (35), 109 (100);HRMS (*m/z*): 353.0961 M$^+$ + H (calculated for C$_{16}$H$_{17}$FN$_2$O$_4$S: 352.0893).

The C-4/5 ^{13}C NMR resonances could not be detected in the spectrum.

6b)*Diethyl 2-(4-fluorobenzylthio)-1H-imidazole-4,5-dicarboxylate*: Pale yellow sticky solid residue (85%yield); mp 99-101°C, UV λ_{max} (EtAc) nm (log ε) 280 (3.59); IR (KBr)υ_{max}: 3202 (N-H), 2984 (C-H alkane), 1709 (C=O), 1600 (C=C), 1256 (C-F), 1184 (C-N), 1070, 1012, 766 cm^{-1};^{1}H NMR (CDCl$_3$, 600MHz) δ 7.24 (dd, J = 8.04, 5.58 Hz, 2H, H-2"/6"),6.93 (t, J= 8.40 Hz, 2H, H-3"/5"), 4.34 (q,J= 7.14 Hz , 4H, 2H-7/7'), 4.32 (s, 2H, 2H-7"), 1.28 (t, J= 7.08 Hz, 6H, 3H-8/8');^{13}C NMR (CDCl$_3$, 150 MHz) δ163.01(2C, C-6/6') , 162.20 (d,J_{CF}= 248.20 Hz, C-4"), 144.39 (C-2), 132.36(d, J=3.28 Hz, C-1"), 131.61 (d, J=8.82 Hz, 2C, C-2"/6"),115.54 (d, J= 20.80 Hz, 2C, C-3"/5"),61.42(2C, C-7/7'), 36.82 (C-7"), 14.10(2C, C-

8/8') ; ^{19}FNMR (CDCl$_3$, 376.5 MHz) δ -115.40; EIMS (*m/z*, % rel. int.)   352 (20), 307 (5), 273 (3), 234 (7), 206 (13), 109 (100); HRMS (*m/z*): 353.0970 M$^+$ + H (calculated for C$_{16}$H$_{17}$FN$_2$O$_4$S: 352.0893).

6c)*Diethyl2-(3,4-difluorobenzylthio)-1H-imidazole-4,5-dicarboxylate:* Pale   yellow   solid residue (89% yield);mp 93-95°C;UV λ$_{max}$ (EtAc) nm (log ε) 273 (3.59); IR (KBr) υ$_{max}$: 3534 (N-H), 2985 (C-H alkane), 1719 (C=O), 1609 (C=C), 1288 (C-F), 1113 (C-N), 1078, 1008, 953, 778 cm^{-1};^{1}H NMR (CDCl$_3$, 600MHz)δ 7.22 (td, *J* = 7.43, 1.80 Hz, H-6"), 7.09 (m, H-2"), 7.02 (dd, *J*= 18.12, 8.28 Hz, H-5"), 5.86 (s, N-H),4.58 (s, 2H, 2H-7"), 4.35(q,*J*= 7.14 Hz, 4H, 2H-7/7'), 1.35 (t, *J*= 7.08 Hz, 6H, 3H-8/8');^{13}C NMR (CDCl$_3$, 150 MHz) δ 158.13 (2C, C-6/6'), 150.22($^\#$dd,*J*$_{CF}$= 248.31, 12.93 Hz, *C3"),150.05 ($^\#$dd,*J*$_{CF}$= 248.30, 12.08 Hz, *C4"),143.99 (C-2), 132.36 (d, *J*= 5.39 Hz, C-1"), 129.05 (2C, C-4/5), 125.46 (dd, *J*=6.51, 3.31 Hz, C-6"), 118.24 (d, *J*=17.74 Hz, **C-5"), 117.63 (d, *J*=17.47 Hz, **C-2"), 62.65 (2C, C-7/7'), 37.59 (C-7"), 14.08(2C, C-8/8') ; ^{19}FNMR (CDCl$_3$, 376.5 MHz) δ -137.93, -136.53; EIMS (*m/z*, % rel. int.) 370 [M$^+$] (21), 325 (6), 291 (3), 252(7), 224(24), 127 (100), HRMS (*m/z*): 371.0875 M$^+$ + H (calculated for C$_{16}$H$_{16}$F$_2$N$_2$O$_4$S: 370.0799).

*, ** Denote carbon resonances that may be interchangeable.

\# Denotes resonances that appear as a doublet of triplets since the resonances coincide with each other.

6d)*Diethyl 2-(perfluorobenzylthio)-1H-imidazole-4,5-dicarboxylate:* Light green solid residue (91% yield); mp 110-112°C; UV λ$_{max}$ (EtAc) nm (log ε) 270 (3.70); IR (KBr) υ$_{max}$: 3422 (N-H), 2988 (C-H alkane), 1706 (C=O), 1504 (C=C), 1196 (C-F), 1123 (C-N), 988, 963, 769 cm^{-1}; ^{1}H NMR (CDCl$_3$, 600MHz) δ 4.50 (s, N-H), 4.41 (s, 2H, 2H-7"), 4.25 (q, *J*= 7.10 Hz, 4H, 2H-7/7'), 1.26 (t, *J*=7.11 Hz, 6H, 3H-8/8');^{13}C NMR (CDCl$_3$, 150 MHz) δ

161.88 (2C, C-6/6'), 145.14 (d, J=247.99 Hz, 2C, C-3"/5"),142.14 (C-2), 137.46 (d, J=259.02 Hz,2C, C-2"/6"), 132.69 (*C-4"), 61.38 (2C, C-7/7'), 24.92 (C-7"), 14.40 (2C, C-8/8'); ^{19}FNMR (CDCl₃, 376.5 MHz) δ □-161.13 (2F), -153.41, 141.45 (2F); EIMS (*m/z*, % rel. int.) 424 (35), 378 (14), 350 (15), 306 (10), 278 (40), 181 (100); HRMS (*m/z*): 425.0591 M$^+$ + H (calculated for C₁₆H₁₃F₅N₂O₄S: 424.0516).

* The doublet could not be clearly seen in the ^{13}C NMR spectrum.

6e)*Diethyl2-(4-(trifluoromethyl)benzylthio)-1H-imidazole-4,5-dicarboxylate*: Pale yellow solid residue (92% yield); mp 68-70°C;UV λ$_{max}$ (EtOAc) nm (log ε) 278 (3.67); IR (KBr) υ$_{max}$: 3420 (N-H), 2985 (C-H alkane), 1722 (C=O), 1617 (C=C), 1321 (C-F), 1118 (C-N), 1065, 1018, 850, 765 cm^{-1};^{1}H NMR (CDCl₃, 400MHz) δ10.78 (s, N-H), 7.49 (d, *J*= 7.76 Hz, 2H, H-3"/5"), 7.41 (d, *J*= 8.0 Hz, 2H, H-2"/6"), 4.46 (s, 2H, 2H-7"), 4.33 (q, *J*= 7.11, 4H, 2H-7/7'), 1.33 (t, *J*=7.11 Hz, 6H, 3H-8/8');^{13}C NMR (CDCl₃, 100 MHz) δ 157.92 (2C, C-6/6'), 144.04 (C-2), 139.37 (C-1"), 129.57 (2C, C-2"/6"), 129.16 (d, *J* = 53.78 Hz, C-4"), 125.78 (2C, C-3"/5"), 125.18 (CF₃*), 62.74 (2C, 7/7'), 38.07 (C-7"), 14.07 (2C, C-8/8'); ^{19}FNMR (CDCl₃, 376.5 MHz) δ□ -62.64; EIMS (*m/z*, % rel. int.) 402 [M$^+$] (33), 357 (12), 328 (8), 284(13), 256 (48), 159 (100), 109 (16);HRMS (*m/z*): 403.0950 M$^+$ + H (calculated for C₁₇H₁₇F₃N₂O₄S: 402.0861).

* Quartet could not be observed.

6f)*Diethyl 2-(2,4-bis(trifluoromethyl)benzylthio)-1H-imidazole-4,5-dicarboxylate:* Off white solid residue (78% yield);mp 93-95°C;UV λ$_{max}$ (EtOAc) nm (log ε) 277 (3.68); IR (KBr) υ$_{max}$: 3229 (N-H), 2990 (C-H alkane), 1734 (C=O), 1280 (C-F), 1561 (C=C), 1110 (C-N), 1085, 1004, 772 cm^{-1};^{1}H NMR (CDCl₃, 600MHz) δ 10.26 (s, N-H), 7.86 (s, H-3"), 7.72 (d, *J*=8.10 Hz, H-5"), 7.68 (d, *J*= 8.20 Hz, H-6"), 4.62 (s, 2H, 2H-7"), 4.33* (q, *J*= 7.02 Hz,

2H, 2H-7), 4.40* (q, J= 7.02 Hz, 2H, 2H-7'), 1.34** (t, J=7.14 Hz, 3H, 3H-8), 1.39** (t, J=7.14 Hz, 3H, 3H-8');^{13}C NMR (CDCl$_3$, 150 MHz) δ160.63 (2C, C-6/6'), 143.52 (C-2), 139.98 (C-1"), 132.61 (C-6"), 130.44 (d, J = 33.42 Hz, C-2") , 129.25 (d, J = 31.62 Hz, C-4"), 129.05 (C-5"), 123.54 (C-3"), 123.43 (q, J = 272.55 Hz, 2"-CF$_3$), 123.17 (q, J = 270.67 Hz, 4"-CF$_3$), 61.88 (2C, C-7/7'), 33.41 (C-7"), 14.17 (2C, C-8/8'); ^{19}FNMR (CDCl$_3$, 376.5 MHz) δ☐-63.00, -59.77; EIMS (*m/z*, % rel. int.) 470 [M$^+$] (45), 425(16), 396 (12), 352(12), 324(100), 227 (80), 177 (22); HRMS (*m/z*): 471.0825 M$^+$ + H (calculated for C$_{18}$H$_{16}$F$_6$N$_2$O$_4$S: 470.0735).

*, ** Denote resonances that may be interchanged.

6g)*Diethyl2-(4-(trifluoromethoxy)benzylthio)-1H-imidazole-4,5-dicarboxylate:* Off white solid residue (91%yield); mp77-80°C; UV λ$_{max}$ (EtOAc) nm (log ε) 279 (3.62); IR (KBr) υ$_{max}$: 3464 (N-H), 2981 (C-H alkane), 1737 (C=O), 1596 (C=C), 1255 (C-F), 1150 (C-N), 1078, 1019, 858 cm^{-1};^{1}H NMR (CDCl$_3$, 600MHz) δ 7.85 (s, N-H), 7.35 (d, J= 8.46 Hz, 2H, H-2"/6"), 7.05(d, J=8.40 Hz, 2H, H-3"/5"), 4.55 (s, 2H, 2H-7"), 4.32(q, J= 7.14 Hz, 4H, 2H-7/7'), 1.31 (t, J=7.44 Hz, 6H, 3H-8/8');^{13}C NMR (CDCl$_3$, 150 MHz) δ 158.56 (2C, C-6/6'), 148.85 (C-4"), 144.18 (C-2), 134.25 (C-1"), 130.65 (2C, C-2"/6"), 129.38 (2C, C-4/5), 121.18 (2C, C-3"/5"), 120.23 (q*, J = 255.34 Hz, OCF$_3$), 62.45 (2C, C-7/7'), 37.88 (C-7"), 14.03 (2C, C-8/8'); ^{19}FNMR (CDCl$_3$, 376.5 MHz) δ☐ -57.89; EIMS (*m/z*, % rel. int.) 418 [M$^+$] (22), 373 (8), 339 (3), 300 (7), 272 (17), 175(100), 109(7); HRMS (*m/z*): 419.0893 M$^+$ + H (calculated for C$_{17}$H$_{17}$F$_3$N$_2$O$_5$S: 418.0810).

*The outer peaks of the quartet cannot be seen due to the reduced intensity of these peaks and the resonance overlaps with C-3"/5".

6h) *Diethyl 2-(4-nitrobenzylthio)-1H-imidazole-4,5-dicarboxylate*: Yellow solid residue (88% yield);mp 111-112°C;UV λ_{max} (EtOAc) nm (log ε) 274 (3.69); IR (KBr) υ_{max}: 3245 (N-H), 2984 (C-H alkane), 1734 (C=O), 1561 (C=C), 1519 (NO$_2$), 1478 (CH$_2$ bend), 1339, 1182, 1079 (C-N), 1013, 704 cm^{-1};^{1}H NMR (CDCl$_3$, 600MHz) δ 10.94 (s, N-H), 8.07 (d, *J*= 8.16 Hz, 2H, H-3"/5"), 7.44 (d, *J*= 8.16 Hz, 2H, H-2"/6"), 4.41 (s, 2H, H-7"), 4.33 (q, *J* = 6.72 Hz, 4H, 2H-7/7'), 1.32 (t, *J*=6.72 Hz, 6H, 3H-8/8'); ^{13}C NMR (CDCl$_3$, 150 MHz) δ162.61 (2C, C-6/6'), 147.29 (C-4"), 144.54 (C-2), 143.45 (C-1"),129.88 (2C, C-2"/6"), 127.65 (C-4/5), 123.82 (2C, C-3"/5"), 61.86(2C, C-7/7'), 36.43 (C-7"), 14.15 (2C, C-8/8'); LCMS* (*m/z*) 380 [M$^+$ + 1]; HRMS (*m/z*): 380.0906 M$^+$ + H (calculated for C$_{16}$H$_{17}$N$_3$O$_6$S: 379.0838).

* An EIMS of the compound could not be obtained.

6i) *Diethyl 2-(3-chlorobenzylthio)-1H-imidazole-4,5-dicarboxylate*: Off white sticky solid residue (70% yield); mp 107-109°C; UV λ_{max} (EtOAc) nm (log ε) 279 (3.37); IR (KBr) υ_{max}: 3334 (N-H), 2982 (C-H alkane), 1721 (C=O), 1597 (C=C), 1472 (CH$_2$ bend), 1077 (C-N), 1008, 687 (C-Clstretch) cm^{-1}; ^{1}H NMR (CDCl$_3$, 600MHz) δ 10.13 (s, N-H), 7.31 (s, H-2"), 7.20 (d, *J*= 7.26 Hz, 2H, H-4"/6"), 7.17 (t, *J*= 7.68 Hz, H-5"), 4.33 (s, 2H, H-7"), 4.35 (q, *J*=7.08 Hz, 4H, 2H-7/7'), 1.36 (t, *J*= 7.08 Hz, 6H, 3H-8/8');^{13}C NMR (CDCl$_3$, 150 MHz) δ161.97 (2C, C-6/6'), 143.71 (C-2), 138.71 (C-1"), 134.48 (C-3"), 129.97 (C-5"), 129.13 (C-2"), 128.01 (C-4"), 127.13 (C-6"), 61.87(2C, C-7/7'), 37.17 (C-7"), 14.17 (2C, C-8/8'); EIMS (*m/z*, % rel. int.) 368 [M$^+$] (27), 322 (8), 294 (6), 250(14), 222 (39), 125 (100), 89 (17); HRMS (*m/z*): 369.0681 M$^+$ + H (calculated for C$_{16}$H$_{17}$ClN$_2$O$_4$S: 368.0598).

2.1.6 X-Ray Crystallography

Single-crystal X-ray diffraction data were collected on a Bruker KAPPA APEX II DUO diffractometer using graphite-monochromated Mo-Kα radiation (χ = 0.71073 Å). Data

collection was carried out at 173(2) K. The temperature was controlled by an Oxford Cryostream cooling system (Oxford Cryostat). Cell refinement and data reduction were performed using the program SAINT. The data were scaled and an absorption correction performed using SADABS. The structure was solved by direct methods using SHELXS-97 and refined by full-matrix least-squares methods based on F^2 using SHELXL-97 and using the graphics interface program X-Seed. All non-hydrogen atoms were refined anisotropically and all hydrogen atoms could be found in the difference electron density maps but were placed in idealised positions and refined in riding models with U_{iso} set at 1.2 times those of their parent atoms and at a distance (C-H) of 0.95 Å. The structure was refined to a R factor of 0.0503.

2.2. In vitro antiplatelet aggregation assay

The use of experimental animals in this study was in accordance with the guidelines and care stipulated by the University of Zululandresearch animal ethics committee. Adult rats (~200g) (*Sprague-Dawley*) of either sex were collected from the Department of Biochemistry and Microbiology, University of Zululand.

The blood platelets were prepared following the method described by Tomita et al., (1983) and detailed by Mosa et al.(2011). A rat **(~200g)** was killed by a blow to the head. Blood was immediately collected from the abdominal aorta of the rat and was put in a centrifuge tube containing ADA (acid-dextrose-anticoagulant—0.085M trisodium citrate, 0.065 citric acid, 2% dextrose; 1 ml ADA: 5 ml blood). The blood was centrifuged (Eppendorf centrifuge 5804 R) at 1200 rpm for 15 min and at 2200 rpm for 3 min consecutively. Supernatant was collected and centrifuged at 3200 rpm for 15 min. The supernatant was discarded and the sediment (platelets) obtained was resuspended in 5 ml of washing buffer (pH 6.5—phosphate

buffer containing 0.113M NaCl, 5.5M glucose, 1mM EDTA). This was centrifuged at 3000 rpm for 15 min. The supernatant was discarded and the platelets were suspended in a smallvolume of a resuspending buffer (pH 7.4; containing 0.14 M NaCl, 15 mM Tris-HCl, 5 mM glucose). A 1:10 dilution of the platelets in the resuspending buffer was taken.The method previously described by Mekhfi et al., (2004) was adapted with some modifications to evaluate the antiplatelet aggregation activity of the compounds. The compounds were separately solubilized in dimethyl sulfoxide (DMSO) before being made up to the desired volume with 50 mM Tris–HCl buffer (pH 7.4; containing 7.5 mM ethylenediaminetetra-acetic acid (EDTA) and 175mM NaCl) to a final 1% DMSO concentration. The compounds were used at the final concentrations of 1, 3 and 10 mg/ml. The antiplatelet aggregation activity of the compounds wasseparately investigated on thrombin (5 U/ml) and ADP (5 mM) induced aggregation. The platelets (100 µl) were pre-incubated for 5 min with different concentrations of the compounds. The aggregation inducer (20 µl) was introduced to the mixture.

The 96-well microplate was used in the experiment and aggregation of the platelets was measured with the Biotek plate reader (ELx 808 UI, Biotek Instrument Supplies) using Gen5 software by following the change in absorbance at 415 nm. DMSO (1%) and aspirin were used as negative and positive controls, respectively. The experiment was done in triplicate and the mean slope (A) ± standard error of mean (SEM) reported.The inhibitory effect of the compounds on each parameter was calculated using the formula:

Inhibition (%) = $[(A_o − A_1)/A_o \times 100]$, where A_o is the mean slope of the control and $A_1$is the mean slope of the test compound.Estimated IC_{50} values were determined using a statistical package origin 6.1.

5.3. Results and discussion

In our synthetic design, we have chosen the imidazole-2-thione as the basic backbone of the molecules with diesters substituted across the double bond and a benzyl moiety covalently bonded to the sulfur atom with fluorine being present on this moiety. Thus, the molecules have fluorine, nitrogen and sulphur atoms incorporated in it, increasing its chances of reactivity. We have chosen benzyl moieties with mono-, di- and penta- fluoro groups as well as mono- and di- trifluoromethyl and the monotrifluoromethoxy groups as well as a nitro and chlorobenzyl moiety. The choice of the derivatives were governed by their availability as starting materials and our desire to investigate the effect that F, CF_3, OCF_3, NO_2 and Cl groups at the 3- and 4- positions have on reactivity. In the case of the 2,4-CF_3 derivative, this was chosen since the 3,4-CF_3 was not available. We aimed to explore the effect of the position of the different groups as well as the effect of di- and penta- fluoro substitution and di-trifluoromethyl substitution. The chloro group was chosen to compare whether the size and electronegativity of the halogen had an influence on reactivity and the nitro group chosen to compare the reactivity when a strongly electron withdrawing group was present.

The synthesis started with the esterification of glycine (**1**) with ethanol and thionyl chloride resulting in glycine ethyl ester hydrochloride (**2**), which was then formylated using ethyl formate in the presence of a triethylamine catalyst. The resultant *N*-formylglycine ethyl ester (**3**) was further reacted with sodium ethoxide and diethyl oxalate to produce the sodium 1,2-bis-ethoxycarbonyl-2-formylamino-ethenolate (**4**), which was directly converted to the carbamate with potassium thiocyanate and hydrochloric acid to produce the diethyl 2-mercapto-4,5-imidazoledicarboxylate (**5**), which was the intermediate that was reacted with the various substituted benzyl bromides with the basic sodium bicarbonate catalyst to form

the benzyl sulfanyl derivatives **6a-i**, which was studied for their antiplatelet activity. The scheme of the reaction is shown in Scheme 5-1.

The ^{1}H NMR spectra of the synthesised benzylthioimidazoles (**6a-i**) all showed aromatic resonances between δ_H 6.8 and 7.8 for the benzyl protons with the exception of **6d** (fluorinated at all positions on the aryl ring), a singlet for the benzylic protons at δ_H 4.3 to 4.6 and a quartet and triplet of the ester ethyl group at approximately δ_H 4.3 and 1.3 respectively with J = 7.0 Hz. The benzylic singlet of H-7" and the quartet of the methylene group (H-7 and H-7') appear close together in the ^{1}H NMR spectrum.

Scheme 5-1 The preparation of diethyl-2-(benzylthio)-2,3-dihydro-1H-imidazole-4,5-dicarboxylate derivatives in five steps (i) SOCl$_2$, -5°C, EtOH, reflux for 5-6 hrs (ii) ethyl formate and triethyl amine in EtOH, refluxed at 50-55°C for 24 hrs (iii) NaOEt , diethyl oxalate, left to stand for 24 hrs (iv) KSCN, HCl (v) NaHCO$_3$, DMF, substituted benzyl bromides, stirred at rt for 1.5 hrs.

Where fluorine was present on the aromatic ring, triplets of doublets and doublets of triplets were seen in the aromatic region due to coupling with both the fluorine and the hydrogen atoms. For example, **6a** shows triplets of doublets at δ_H 7.22 and δ_H 6.92 for H-5" and H-4" with J = 7.92 and 5.94, and 8.94 and 2.34 Hz respectively. A doublet of triplets can be seen for H-2" with J = 9.50 and 1.77 Hz. The H-6" proton, remotely situated from the fluorine atom, showed a doublet resonance with an observed $J_{5"/6"}$ of 7.68 Hz, however the peaks for this resonance was not as well resolved as that for H-5", resulting in the slight deviation in coupling constants. For benzyl rings which were *para* substituted, for example, **6e**, **g** and **h**, a pair of doublets were observed for these compounds with J being approximately 8.0 Hz. In the case of **6b**, the *para* fluorinated compound, H-2"/6" appears as a double doublet with J = 8.04 and 5.58 Hz and H-3"/5" appears as a triplet due to coupling with both the proton and fluorine atom, where the double doublet of H-3"/5" coalesces to produce a triplet with J = 8.40 Hz.

In the ^{13}C NMR spectrum, the ester carbonyl resonance (C-6/6') occurs at approximately δ 160 and the two equivalent ethyl methylene (C-7/7') and methyl (C-8/8') carbon resonances occur at approximately δ 61 and d 14 respectively. The benzylic carbon resonance (C-7") occurs at approximately δ 37. The imidazole carbon resonance (C-2) occurs at δ 144, with the other two resonances C-4 and C-5 only appearing in some spectra as a single resonance, probably because of the symmetry in the molecule at δ 129. These resonances were too weak to be detected in most of the spectra. The aromatic carbon resonances occur between δ 110-140. Where fluorine is substituted directly on the ring, the *ipso* carbon is split into a doublet with J_{C-F} = 246 Hz and the *ortho* and *meta* carbon resonances are also split into doublets with J being approximately 22 and 8 Hz respectively. In some cases *para* F-C coupling of J = 3

Hz can also be seen. For **6c**, the difluorinated compound, a double doublet for each of the *ipso* protons is seen at δ 150.22 and δ 150.05 respectively due to the two fluorine atoms being *ortho* to each other. This appears as a doublet of triplets due to coalescing of each of the double doublets. The CF_3 carbon resonances appear at δ 125 as a quartet with *J* being approximately 270 Hz. In some cases the quartet could not be clearly observed as in **6e** and in others, for example **6g**, the outer peaks of the quartet could not be seen due to the reduced intensity of these peaks, however, these are clearly seen in **6f**. In the pentafluoro compound (**6d**), the C-7″ benzylic carbon is more shielded than the others at δ 24.92, probably due to electron donation by the fluorine atoms.

In addition, the crystal structure of the parent compound, diethyl 2-mercapto-4,5-imidazoledicarboxylate(**5**) was determined and was shown to contain two molecules in the unit cell with a triclinic P_1 space group. The molecule was essentially planar with bond angles in the imidazole ring being between 122-125°, with only one of the bond angles between the ester group and the olefinic carbon and the nitrogen of the imidazole ring being 116°. The two ester groups point away from each other and extend out of the imidazole moiety like two functional arms. An ortep diagram of **5** is given in Figure 5-1.

Figure 5-1ORTEP diagram of diethyl 2-mercapto-4,5-imidazoledicarboxylate(**5**)

The synthesised compounds exhibited concentration and substituent dependent inhibitory activity of platelet aggregation induced by the two platelet agonists. Six of the ten synthesised compounds, including the carbazole intermediate (**5**), showed activity better than or comparable to aspirin (used as a standard) in the thrombin induced platelet aggregation assay (Table 5-1), while eight of the compounds showed either better or comparable activity to aspirin in the ADP-induced platelet aggregation (Table 5-2).

Table 5-1 Percentage inhibition of platelet aggregation at different concentrations of the compound on thrombin-induced platelet aggregation

No.	R	0.5 mg/ml	3.0 mg/ml	10.0 mg/ml	Estimated IC$_{50}$ (mM)
5	Carb	0.00 ± 1.91	58.1 ± 1.06	75.4 ± 0.95	11.18

6a	3-F	0.00 ± 0.87	0.00 ± 0.28	0.00 ± 0.25	ND
6b	4-F	0.00 ± 0.41	0.00 ± 0.98	0.00 ± 0.63	ND
6c	3,4-F	0.00 ± 0.62	51.8 ± 0.83	66.1 ± 0.64	7.99
6d	Penta-F	13.6 ± 0.85	65.9 ± 0.83	80.0 ± 0.84	5.28
6e	4-CF$_3$	0.00 ± 1.13	0.00 ± 0.21	0.00 ± 0.96	ND
6f	2,4-CF$_3$	0.00 ± 0.00	82.9 ± 0.94	84.2 ± 2.29	4.38
6g	4-OCF$_3$	0.00 ± 0.26	0.00 ± 1.14	27.1 ± 1.15	ND
6h	4-NO$_2$	57.2 ± 0.27	71.4 ± 0.83	76.8 ± 0.39	1.05
6i	3-Cl	55.8 ± 0.48	80.2 ± 0.99	84.3 ± 0.87	0.44
C*	Aspirin	30.5 ± 0.48	51.2 ± 0.47	66.3 ± 0.24	7.66

C* = aspirin; ND = not detected

Thrombin induced platelet aggregation assay

All the inactive compounds in the thrombin induced platelet aggregation assay were monosubsituted (3F (**6a**), 4F (**6b**), 4CF$_3$ (**6e**) and 4-OCF$_3$(**6g**)). The carbazole (**5**), together with the di and penta deriviatives (**6c-d** and **6f**) showed no or very little activity in the 0.5 mg/ml range, but their extrapolated estimatedIC$_{50}$ values were comparable to that of aspirin (Table 5-1). The best activity was displayed by the compounds with the 4-nitro (**6h**) and 3-chloro (**6i**) groups, which had estimatedIC$_{50}$ values of 0.40 and 0.44 mg/ml respectively. Furthermore, they were the only two compounds that showed appreciable activity at a low concentration of 0.5 mg/ml. Thus, electron withdrawing groups seemed to favour inhibition in the thrombin induced platelet aggregation assay. The fact that the monosubstituted fluoro atoms have no inhibitory effect could be due to their small size or the inability of the fluorine atom to co-ordinate to biological ligands as compared to chlorine. This however is overcome by phenyl groups with multiple fluorine atoms, as this shows an increase in activity.

Table 5-2 Percentage inhibition of platelet aggregation at different concentrations of the compound on ADP-induced platelet aggregation

No.	R	0.5 mg/ml	3.0 mg/ml	10.0 mg/ml	Estimated IC$_{50}$ (mM)
5	Carb	0.00 ± 0.90	0.00 ± 1.23	0.00 ± 0.53	ND
6a	3-F	0.00 ± 0.39	72.2 ± 0.46	74.8 ± 0.57	6.36
6b	4-F	68.7 ± 0.94	76.4 ± 0.19	86.6 ± 0.43	0.99
6c	3,4-F	0.00 ± 0.45	66.0 ± 1.08	82.3 ± 0.50	6.64
6d	Penta-F	0.00 ± 0.62	20.8 ± 0.31	35.8 ± 0.42	ND
6e	4-CF$_3$	0.00 ± 0.80	38.2 ± 0.51	53.8 ± 0.73	21.09
6f	2,4-CF$_3$	0.00 ± 0.85	0.00 ± 0.91	0.00 ± 0.69	ND
6g	4-OCF$_3$	14.1 ± 0.90	47.1 ± 1.19	50.9 ± 0.18	21.67
6h	4-NO$_2$	0.00 ± 0.33	0.00 ± 0.13	88.3 ± 1.73	18.57
6i	3-Cl	24.7 ± 1.03	46.6 ± 0.79	61.5 ± 0.53	12.90
C*		23.7 ± 0.90	45.3 ± 0.18	57.1 ± 1.15	32.86

C* = aspirin; ND = not detected

ADP-induced platelet aggregation assay

Compared to the thrombin induced platelet aggregation, the situation in this assay is quite different. Multiple fluorine atoms on the phenyl ring (**6d**) lead to loss of activity, whereas fluorine substitution at both the 3- and 3,4- positions (**6a** and **6c** respectively) lead to better activity than aspirin with Estimated IC$_{50}$ values of 2.24 and 2.46 mg/ml respectively (Table 5-1). The best activity is seen by the 4-fluorophenyl derivative (**6b**) which shows an Estimated IC$_{50}$ value of 0.35. The 3-chloro derivative (**6i**) also shows slightly better activity than aspirin Estimated IC$_{50}$ of 4.75 compared to 5.92 mg/ml) with the 4-CF$_3$ (**6e**), 4-OCF$_3$ (**6g**) and 4-NO$_2$ (**6h**) showing slightly weaker activity than aspirin with Estimated IC$_{50}$ values of 8.48, 9.06 and 7.04 mg/ml. Substitution of an additional CF$_3$ group at the 2-position as in **6f** results in loss of activity as was the case with the carbazole skeleton without any phenyl group attached to it. Thus, in this assay, small electron withdrawing groups such as fluorine substituted at the *para* position on the phenyl moiety results in the best activity. This activity

is reduced with larger electron withdrawing groups and electron donating groups and activity is reduced by further fluorinations on the phenyl ring.

Since the two platelet aggregation assays have different compounds showing the best activity and also have different compounds being inactive in the assays, there seems to be a different mechanism of platelet inhibition in both of these assays. However, three of the compounds, the 3,4-difluoro (**6c**), the 4-nitro (**6h**) and the 3-chloro (**6i**) have reasonable activity in both of the assays.

5.4. Conclusion:

Diethyl-2-(benzylsulfanyl)-1H-imidazole-4,5-dicarboxylate derivatives are easily prepared from glycine in a five step reaction involving activating glycine with *N*-formylation and transesterification, and then reacting this intermediate with diethyl oxalate followed by potassium cyanate and then the benzyl bromides. Different derivatives are active in each of the assays (thrombin induced and ADP-induced platelet aggregation assays), suggesting that different mechanisms are involved in each of the assays. The most active of the compounds in the thrombin induced assay are the 4-nitro (**6h**) and the 3-chloro (**6i**) derivatives whereas the most active compound in the ADP-induced assay is the 4-fluoro (**6b**) derivative. Three of the compounds, **6c**, **6h** and **6i**, the 3,4-difluoro, the 4-nitro and the 3-chloro derivatives have reasonable activity in both of the assays and could have potential as broad spectrum antiplatelet inhibitors. With the exception of **6c**, the fluoro derivatives were not as active as the nitro and chloro derivatives.

5.5. References

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Chapter 6. Crystal structures of three cinnamate esters and a fluoro-2-styrylchromone

6.1. 2-Acetylphenyl-(2*E*)-3-(4-fluorophenyl)-acrylate

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Abstract

In the title compound, $C_{17}H_{13}FO_3$, the dihedral angle between the aromatic rings is 70.34 (5). In the crystal, molecules are linked via pairs of bifurcated C—H…(O,O) hydrogen bonds,forming inversion dimers. These dimers are linked via C—H…O and C—H…F interactions, forming a three-dimensional structure.

Related literature

For the preparation, see: Pinto et al. (2000). For relatedstructures, see: Santos et al. (2009); Ren et al. (2006); Ren et al. (2006b). For bond-length data, see: Allen et al.(1987). The title compound is a core structure in variousnatural and pharmaceutically active compounds, displaying abroad spectrum of activity, see: Gomes et al. (2010).

Figure 6-1 Chemical structure of 2-Acetylphenyl-(2*E*)-3-(4-fluorophenyl)-acrylate

Table 6-1 Hydrogen-bond geometry (A˚, º).

Cg1 is the centroid of the C3–C8 ring.

D—H...A	D—H	H...A	D...A	D—H...A
C7—H7...F1i	0.95	2.52	3.2402(16)	132
C11—H11...O3ii	0.95	2.46	3.3369(16)	154
C13—H13...O3ii	0.95	2.45	3.3191(16)	153
C16—H16...O1iii	0.95	2.51	3.3590(17)	149
C6—H6...Cg1iv	0.95	2.99	3.818(1)	146

Symmetry codes: (i)x, -y+2, z-$\frac{1}{2}$ (ii)-x, -y+1, -z (iii)-x+$\frac{1}{2}$, y +$\frac{3}{2}$, -z +$\frac{1}{2}$ (iv)x,-y + 1, z-$\frac{1}{2}$.

Comment

The title compound (*E*)-2-acetylphenyl-3-(4-fluorophenyl)-acrylate was obtained as an intermediate en route to thesynthesis of 4′-fluoro-2-styrylchromone and easily converts to the 2-hydroxyphenyl pentadienone with DMSO in thepresence of a strong base (Santos *et al.*, 2009). It was synthesized according to the procedure by Pinto *et al.* (2000) withmodification. The title compound is a core structure in various natural and pharmaceutically active compounds,displaying a broad spectrum of activity (Gomes *et al.*, 2010).

In the molecule of the title compound (Figure 6-1and Figure 6-2), the two aromatic rings (ring 1: C3—C4—C5—C6—C7—C8; ring 2:C12—C13—C14—C15—C16—C17 are almost perpendicular to each other with a dihedral angle of 70.34 (5)°.The torsion angle C9—

C10—C11—C12 is -178.8 (1)°, indicating a *trans* configuration of the double bond. All bondlengths and angles are within normal ranges (Allen *et al.*,1987). In the crytsal packing, ring 1 adopts a parallel offsetarrangement with itself of the neighbouring molecule with a centroidal distance of 4.125 (1) A. The crystal is furtherstablized by a number of weak hydrogen bonds with the type C—H…*X* (*X* = O or F) and C—H…π (Table 6-1).

Experimental

Phosphorous oxychloride (15.6 mmol) was added to a solution of 2-hydroxyacetophenone (12.0 mmol) and 4-fluorocinnamic acid (15.6 mmol) in dry pyridine. The solution was stirred at 60‑70 °C for 3 h, and then poured into ice and waterand the reaction mixture acidified with hydrochloric acid (pH 3‑4). The obtained solid was removed by filtration anddissolved in ethyl acetate (100 ml) and purified by silica gel column chromatography using a 7:3 mixture of ethylacetate:n-hexane as the eluent. The solvent was evaporated to dryness and the residue recrystallized from ethanol,resulting in the title compound with a 72% yield and am.p of 80‑82°C.IR (KBr) υ_{max} (cm^{-1}): 1729 (C=O), 1670 (C=O), 1624 (C=C), 1590, 1446, 1221 (C−F), 1202, 1159, 1050. ^{1}H NMR(CDCl$_3$, 400 MHz): δ7.84 (d, *J* = 15.96 Hz, 1H, Hβ), 7.81 (dd, *J* = 8.00,1.60 Hz, 1H), 7.58 (dd, *J* = 8.60, 5.42, 2H), 7.53 (td, *J* = 8.00, 1.52 Hz, 1H), 7.33 (td, *J* = 8.00, 0.72 Hz, 1H), 7.17 (dd, *J* = 8.00, 0.72 Hz, 1H), 7.09 (t, *J* = 8.60 Hz,2H), 6.58 (d, *J* = 15.96 Hz, 1H, Hα), 2.54 (s, 3H, CH$_3$). ^{13}C NMR (CDCl$_3$, 100 MHz): δ197.78 (C=O), 165.14 (C=O), 164.25 (d, J_{CF} = 250.70 Hz), 149.07, 145.99, 133.36, 131.30, 130.43 (d, *J* = 8.37 Hz, 2C), 130.32 (d, J_{CF} = 3.55 Hz), 130.15, 126.10, 123.78,116.58 (d, *J* = 2.37 Hz), 116.20 (d, J_{CF} = 21.85 Hz, 2C), 29.71 (CH$_3$). ^{19}F NMR (CDCl$_3$, 376.5 MHz): δ -108.54. EIMS (probe) 70 eV (*m/z*, *rel*.int.) 284 (M$^+$) (21), 149 (100), 121 (25), 101 (20).

Refinement

All non-hydrogen atoms were refined anisotropically. All hydrogen atoms could be found in the difference electrondensity maps but were finally placed in idealized positions refining in riding models with Uiso set at 1.2 or 1.5 times Ueqof their parent atoms.

Computing details

Data collection: *COLLECT* program (Nonius, 2000); cell refinement: *DENZO-SMN* (Otwinowski& Minor, 1997); datareduction: *DENZO-SMN* (Otwinowski& Minor, 1997); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3* (Farrugia, 2012);software used to prepare material for publication: *WinGX*(Farrugia, 2012).

Figure 6-2*ORTEP* diagram showing the molecular structure of the titled compound with atomic labelling scheme. Non-H atoms are drawn with 50% probability displacement ellipsoids and H atoms are shown as open circles.

Special details

Geometry. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the fullcovariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles andtorsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry.An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

Refinement. Refinement of $F2$ against ALL reflections. The weighted R-factor $wR$and goodness of fit S are based on $F2$,conventional$R$-factors R are based on F, with F set to zero for negative $F2$. The threshold expression of $F2 > \sigma(F2)$ is usedonly for calculating R-factors(gt) *etc.* and is not relevant to the choice of reflections for refinement. R-factors based on $F2$ are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

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6.2. (*E*)-2-Acetyl-4-fluoro-phenyl 3-(4-fluorophenyl)-acrylate

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Abstract

The title compound, $C_{17}H_{12}F_2O_3$, crystallizes with two planar molecules in the asymmetric unit.The title molecule has the packing 4 molecules in a unicell.The molecule confirmation is stabilized by O—H intra-molecular hydrogen-bond inter-action with a distance of 2.677Å.

Related literature

For the preparation, see: Pinto et al. (2000). For related structures, see: Santos et al. (2009); Ren, et al. (2006a); Renet al. (2006b). For bond-length data, see: Allen et al.(1987). The title compound is a core structure in various natural and pharmaceutically active compounds, displaying abroad spectrum of activity, see: Gomes et al. (2010).

Figure 6-3 Chemical structure of (*E*)-2-Acetyl-4-fluorophenyl 3-(4-fluorophenyl)-acrylate

Table 6-2 Hydrogen-bond geometry (Å, °)

D----H…..A	D - H	H…A	D…A	D - H…A
C1*A*—H1*A*2*B*⋯O1*B*	0.98	2.51	3.314(3)	139
C4*B*—H4*B*⋯O1*B*[ii]	0.95	2.40	2.734(3)	101
C10A—H10A⋯O3B[i]	0.95	2.46	3.407(2)	172
C10B—H10B⋯O3A[i]	0.95	2.54	3.484(2)	174
C11A—H11A⋯O2A	0.95	2.39	2.750(2)	102
C11B—H11B⋯O1A[iii]	0.95	2.58	3.484(2)	159
C11B—H11B⋯O2B	0.95	2.40	2.759(2)	102
C13A—H13A⋯O3B[i]	0.95	2.52	3.455(3)	170
C13B—H13B⋯O3A[i]	0.95	2.55	3.499(3)	177

Symmetry codes (i)-x, 1-y, 2-z (ii)-x, 2-y, 1-z (iii)1+x, y, z

Comment

The title compound (*E*)-2-acetyl-4-fluorophenyl-3-(4-fluorophenyl)-acrylate was obtained as an intermediate en route to the synthesis of the corresponding 2-styrylchromone.It was synthesized according to the procedure by Pinto *et al.* (2000)with modification. The title compound is a core structure in various natural and pharmaceutically active compounds, displaying a broad spectrum of activity (Gomes *et al.*, 2010).

In the molecule of the title compound (Figure 6-3 and Figure 6-4), the two aromatic rings (ring 1: C3—C4—C5—C6—C7—C8; ring 2: C12—C13—C14—C15—C16—C17 are almost perpendicular to each other with a dihedral angle of 110.24 (16)°. The torsion angle C9—C10—C11—C12 is -176.94 (1)°, indicating a *trans* configuration of the double bond. All bond lengths and angles are within normal ranges (Allen *et al.*,1987). In the crystal packing, ring 1 adopts a parallel offset arrangement with itself of the neighbouring molecule with centroidal distance of 4.600 (1) Å. The crystal is further stabilized by a number of weak hydrogen bonds (Table 6-2) with the type C—H···X (X = O or F).

Experimental

Phosphorous oxychloride (15.6 mmol) was added to a solution of 4-fluoro-2-hydroxyacetophenone (12.0 mmol) and 4'-fluoro cinnamic acid (15.6 mmol) in dry pyridine. The solution was stirred at 60–70°C for 3 h, and then poured into ice and water and the reaction mixture acidified with hydrochloric acid (pH 3–4). The obtained solid was removed by filtration and dissolved in ethyl acetate (100 ml) and purified by silica gel column chromatography using a 7:3 mixture of ethyl acetate:n-hexane as the eluent. The solvent was evaporated to dryness and the residue recrystallized from ethanol, resulting in the title compound with a 68% yield and m.p of 60–62°C.IR (KBr) u_{max}: 1724 (C=O), 1679 (C=O), 1361 (C—O), 1225 (C—F), 1143 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.87 (dd, J = 8.75, 6.34 Hz, 1H), 7.84 (d, J = 15.96 Hz, 1H, Hβ), 7.58 (dd, J = 8.72, 5.40 Hz, 2H), 7.10 (d, J = 8.60 Hz, 2H), 7.03 (td, J = 8.75, 2.45 Hz, 1H), 6.92 (dd, J = 8.90, 2.45 Hz, 1H), 6.56 (d, J = 15.96 Hz, 1H, Hα), 2.53 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 196.11 (C=O), 165.11 (C=O), 164.99 (d, J_{CF} = 254.07 Hz), 164.35 (d, J_{CF} = 250.95 Hz), 150.99, 146.55, 132.20 (d, J = 10.14 Hz), 130.47 (d, J = 8.47 Hz, 2C), 130.17 (d, J = 3.0 Hz), 127.62 (d, J = 3.51 Hz), 116.26 (d, J = 21.94 Hz, 2C), 116.11 (d, J = 2.24 Hz), 113.34 (d, J = 21.20 Hz), 111.70 (d, J=

23.99 Hz), 29.73 (CH$_3$); ^{19}F NMR (CDCl$_3$, 376.5 MHz) δ -103.81, -103.17; EIMS (probe) 70 eV (*m/z*, rel. int.) 302 M$^+$ (3), 149 (100), 121 (92), 101 (75); calculated molecular mass: 302.27.

Refinement

All non-hydrogen atoms were refined anisotropically. All hydrogen atoms could be found in the difference electron density maps but were finally placed in idealized positions refining in riding models with *U*iso set at 1.2 or 1.5 times *U*eq of their parent atoms.

Computing details

Data collection: *SAINT* (7.60a, Bruker AXS Inc., Madison, WI, USA, 2006); cell refinement: *SAINT* (7.60a, Bruker AXS Inc., Madison, WI, USA, 2006); data reduction: *SAINT* (7.60a, Bruker AXS Inc., Madison, WI, USA, 2006); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *X-SEED* (Barbour, 2001); software used to prepare material for publication: *SHELXL97* (Sheldrick, 2001).

Figure 6-4 Mercury diagram showing the molecular structure of the titled compound with atomic labelling scheme.

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2$ sigma (F^2) is used only for calculating R-factors (gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R- factors based on ALL data will be even larger.

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6.3. (E)-2-acetylphenyl-3-(4-methoxyphenyl)-acrylate

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Abstract

The structure of (*E*)-2-acetyl-phenyl- 3-(4-methoxyphenyl)acrylate, $C_{18}H_{16}O_4$, at 173 K has orthorhombic (Pbca) symmetry. In the crystal packing, the title compound has eight molecules in one unit cell.

Related literature

For the preparation, see: Pinto et al. (2000). For related structures, see: Santos et al. (2009); Ren et al. (2006a); Ren et al. (2006b). For bond-length data, see: Allen et al.(1987). The title compound is a core structure in various natural and pharmaceutically active compounds, displaying abroad spectrum of activity, see: Gomes et al. (2010).

Figure 6-5 Chemical structure of (E)-2-acetylphenyl-3-(4-methoxyphenyl)acrylate.

Comment

The title compound (*E*)-2-acetylphenyl-3-(4-methoxyphenyl)acrylate was obtained as an intermediate en route to the synthesis of the corresponding 2-styrylchromone.It was synthesized according to the procedure by Pinto et al. (2000) with modification. The title compound is a core structure in various natural and pharmaceutically active compounds, displaying a broad spectrum of activity (Gomes et al., 2010).

In the molecule of the title compound (Figure 6-5 and Figure 6-6), the two aromatic rings (ring 1: C3—C4—C5—C6—C7—C8; ring 2: C12—C13—C14—C15—C16—C17 are almost perpendicular to each other. The torsion angle C9—C10—C11—C12 is -176.84 (1)°, indicating a *trans* configuration of the double bond. All bond lengths and angles are within normal ranges (Allen et al., 1987). In the crytsal packing, ring 1 adopts a perpendicular offset arrangement with itself of the neighbouring molecule with a centroidal distance of 4.056 (1) Å.

Experimental

Phosphorous oxychloride (15.6 mmol) was added to a solution of 2-hydroxyacetophenone (12.0 mmol) and 4'-methoxy cinnamic acid (15.6 mmol) in dry pyridine. The solution was stirred at 60–70°C for 3 h, and then poured into ice and water and the reaction mixture

acidified with hydrochloric acid (pH 3–4). The obtained solid was removed by filtration and dissolved in ethyl acetate (100 ml) and purified by silica gel column chromatography using a 7:3 mixture of ethyl acetate: n-hexane as the eluent. The solvent was evaporated to dryness and the residue recrystallized from ethanol, resulting in the title compound with a 91% yield and a m.p of 97–99°C.IR (KBr) υ_{max}: 1711 (C=O), 1680 (C=O), 1600 (C=C), 1509, 1581, 1246, 1189 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.83 (d, J =15.92 Hz, 1H), 7.80 (dd, J = 8.04, 1.55 Hz, 1H), 7.53 (d, J = 8.72 Hz, 2H), 7.51 (td, J = 7.55, 1.55 Hz, 1H), 7.31 (td, J = 8.04, 0.76 Hz, 1H), 7.17 (d, J = 8.00 Hz, 1H), 6.91 (d, J = 8.72, 2H), 6.52 (d, J = 15.92 Hz, 1H), 3.84 (s, 3H, OCH$_3$), 2.54 (s, 3H, CH$_3$); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 197.90 (C=O), 165.53 (C=O), 161.91, 149.28, 147.15, 133.26, 131.54, 130.23 (2C), 130.04, 126.78, 125.95, 123.81, 114.45 (2C), 114.10, 55.43, 29.92; EIMS (probe) 70 eV (*m/z*, rel. int.) 296 M$^+$ (7), 161 (100), 133 (49), 118 (16), 90 (15), 77 (16); calculated molecular mass: 296.10.

Refinement

All non-hydrogen atoms were refined anisotropically. All hydrogen atoms could be found in the difference electron density maps but were finally placed in idealized positions refining in riding models with *U*iso set at 1.2 or 1.5 times *U*eq of their parent atoms.

Computing details

Data collection: *COLLECT* program (Nonius et al., 2000); cell refinement: *DENZO-SMN*(Otwinowski & Minor et al., 1997); datareduction: *DENZO-SMN* (Otwinowski & Minor et al.,1997); program(s) used to solve structure: *SHELXS97* (Sheldrick et al., 2008);program(s) used to refine structure: *SHELXL97* (Sheldrick et al., 2008); molecular graphics: *ORTEP-3* (Farrugia et al., 2012);software used to prepare material for publication: *WinGX* (Farrugia et al., 2012).

Figure 6-6 *ORTEP* diagram showing the molecular structure of the titled compound with atomic labelling scheme. Non-H atoms are drawn with 50% probability displacement ellipsoids and H atoms are shown as open circles.

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are takeninto account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2$ sigma (F^2) is used only for calculating R-

factors (gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R- factors based on ALL data will be even larger.

Acknowledgements

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6.4.   2'-Fluoro-2-styrylchromone

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Abstract

The title compound, $C_{17}H_{11}FO_2$, has a packing of 4 molecules in a unit cell. The dihedral angle between the benzene rings is 98.04 (5)°.The torsion angle C1—C7—C8—C9 is -179.67°, indicating a *trans* configuration of the double bond. All bond lengths and angles are within normal ranges (Allen *et al.*,1987).

Related literature

For the preparation, see: Pinto et al. (2000). For related structures, see: Santos et al. (2009); Conti et al., (2005); Ren et al. (2006a); Renet al. (2006b). For bond-length data, see: Allen et al.(1987). The title compound is a core structure in various natural and pharmaceutically active compounds, displaying abroad spectrum of activity, see: Gomes et al. (2010).

Figure 6-7 Chemical structure of 2'-fluoro-2-styrylchromone

Comment

In the title compound (Figure 6-7 and Figure 6-8), the molecule is almost planar with the bond angles between 113 and 124°. The compound crystallizes with four planar molecules in the symmetric unit and contains four molecules per unit cell. The molecular conformation is stabilized by a C-F distance of 1.366 Å and a C=O distance of 1.237Å. This planarity of the molecule makes it very suitable to fit into enzyme pockets of substrates allowing for greater interaction between the molecule and enzyme.

The title compound 2'-fluro-2-styrylchromone was synthesized according to the procedure by Pinto *et al.* (2000) with modification. It is a core structure in various natural and pharmaceutically active compounds and was screened for its anti-bacterial activity using Gram-positive bacteria (*Staphylococcus aureus*, *scuii* and *xylosus* and *Bacillus subtilis*) and Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia*). The compounds were most effective against *B. subtilis* (ATCC 6633) followed by *E. coli* (ATCC 25922) and *S. aureus* (ATCC 29212). The compound showed best activity from a small library of mono and difluoro 2-styrylchromones, against the *B.subtilis* strains among all tested bacteria. This could therefore indicate that the activity of the 2-styrylchromones increase with increased fluorine substitution on the phenyl ring.

Experimental

The title compound was synthesized in a three step reaction in accordance with Silva *et al.* (2000) with modification.

Step-1: Phosphorous oxychloride (15.6 mmol) was added to a solution of the appropriate 2-hydroxyacetophenone (12.0 mmol) and the 2-fluoro cinnamic acid (15.6 mmol) in dry pyridine. The solution was stirred at 60–70°C for 3h, and then poured into ice and water, and the reaction mixture acidified with hydrochloric acid (pH 3-4). The obtained solid was removed by filtration and dissolved in ethyl acetate (100 ml) and purified by silica gel column chromatography using a 7:3 mixture of ethyl acetate:*n*-hexane as the eluent. The solvent was evaporated to dryness and the residue recrystallised from ethanol, resulting in *2-(2'-fluorocinnamoyloxy)acetophenone.*

Step-2: Potassium hydroxide powder (0.05 mmol, 2.8 g) was added to a solution of 2-cinnamoyloxy)acetophenone (10 mmol) in dimethyl sulfoxide (15 ml). The solution was stirred at room temperature until complete disappearance of the starting material, which was monitored by TLC. A typical reaction time was 2h. The solution was then poured into ice water and HCl and the pH adjusted to 5. The obtained solid was removed by filtration, dissolved in ethyl acetate (150 ml) and purified by silica gel chromatography using ethyl acetate :*n*-hexane (7:3) as the eluent. The solvent was evaporated to dryness and the residue recrystallised from ethanol, resulting in *3-hydroxy-1-(2-hydroxyphenyl)-5-(2-fluorophenyl)-2,4-pentadien-1-one* .

Step-3: *p*-Toluene-sulfonic acid (3.42 mmol) was added to a solution of the appropriate *3-hydroxy-1-(2-hydroxyphenyl)-5-(2-fluorophenyl)-2,4-pentadien-1-one* (6.5 mmol) in dimethyl sulfoxide (20 ml). The reaction mixture was heated at 90°C for 2h, and then poured into ice and water and stirred for 10 min. The obtained solid was removed by filtration, dissolved in chloroform (100 ml) and washed with a 20% aqueous solution of sodium thiosulphate. The

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solvent was evaporated to dryness and the residue was purified by silica gel chromatography, using chloroform:*n*-hexane (7:3) as the eluent, to produce2'-fluro-2-styrylchromone, a light yellow solid residue (68% yield); mp 150-152°C. UV λ_{max} (CH$_3$OH) nm (log ε): 325 (3.37); IR (KBr) υ_{max}: 1682 (C=O), 1625, 1589 (C—C), 1562, 1464, 1391 (C—F), 1125, 968 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.17 (dd, *J* = 7.94, 1.56 Hz, 1H), 7.72 (d, *J* = 16.24 Hz, 1H, Hβ), 7.66 (ddd, *J* = 8.56, 7.20, 1.56 Hz, 1H), 7.59 (td, *J* = 7.60, 1.50 Hz, 1H), 7.53 (d, *J* = 8.28 Hz, 1H), 7.37 (td, *J* = 7.92, 0.80 Hz, 1H) , 7.32 (m, 1H), 7.17 (t, *J* = 7.92 Hz, 1H), 7.11 (ddd, *J* = 9.20, 8.20, 2.36 Hz, 1H), 6.87 (d, *J* = 16.24 Hz, 1H, Hα), 6.32 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 178.48 (C=O), 161.47, 161.17 (d, J_{CF} = 253.27 Hz, C2'), 156.02, 133.88, 131.25 (d, *J* = 8.67 Hz), 129.47 (d, *J* = 3.10 Hz, Cβ), 128.39 (d, *J* = 2.72 Hz), 125.69, 125.05, 124.56 (d, *J* = 3.57 Hz), 124.13, 123.09 (d, *J* = 11.68 Hz), 122.67 (d, *J* = 6.51 Hz, Cα), 117.93, 116.23 (d, *J* = 21.81 Hz), 111.21; ^{19}F NMR (CDCl$_3$, 376.5 MHz) δ -115.39; EIMS (*m/z*, rel. int.) 265 (M$^+$-1) (100), 237 (12), 207 (20), 146 (36), 92 (25); HRMS (*m/z*) M$^+$ 266.0733 (calculated for C$_{17}$H$_{11}$FO$_2$: 266.0743).

Refinement

All non-hydrogen atoms were refined anisotropically. All hydrogen atoms could be found in the difference electron density maps but were finally placed in idealized positions refining in riding models with *U*iso set at 1.2 or 1.5 times *U*eq of their parent atoms.

Computing details

Data collection: *COLLECT* program (Nonius et al., 2000); cell refinement: *DENZO-SMN* (Otwinowski & Minor et al., 1997); data reduction: *DENZO-SMN* (Otwinowski & Minor et al., 1997); program(s) used to solve structure: *SHELXS97* (Sheldrick et al., 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick et al., 2008); molecular graphics: *ORTEP-3*

(Farrugia et al., 2012); software used to prepare material for publication: *WinGX* (Farrugia et al., 2012).

Figure 6-8   Mercury diagram showing the molecular structure of the titled compound with atomic labelling scheme.

Special details

Refinement.Refinement of F^2 against ALL reflections.   The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2$ sigma (F^2) is used only for calculating R-factors (gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually

in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Acknowledgements

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Chapter 7. Conclusion

7.1. The 2-styrylchromones

A series of ten fluorinated and methoxylated 2-styrylchromoneswere prepared in three steps based on the Baker-Venkataraman rearrangement and screened for anti-bacterial activity. Six of the ten compounds were novel. None of thesecompounds were reported to exhibit antibacterial activity prior to this study. Their antibacterial activity was carried out using Gram-positive bacteria (three species of *Staphylococcus,S. aureus,S.scuii* and *S.xylosus*andone *Bacillus*species, *B. subtilis*) and Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia*). The compounds were most effective against the Gram positive bacteria, *B. subtilis* followed by *S. aureus* and a single strain of the Gram negative *E. coli* (ATCC 25922). Difluorination on the phenyl ring was shown to enhance antibacterial activity and fluorine substitution at the 6-position was shown to be best for antibacterial activity. In comparison to tetracycline, the activity indices of the fluorinated styrylchromones ranged from 0.50 to 0.75 against *B. subtilis*. The compounds may not be able to act as antibacterials alone, but may be able to enhance the antibacterial action of other antibiotic compounds by acting synergistically with them.

In addition, the 3-hydroxy-2,4-pentadien-1-one intermediates were tested for their antioxidant activity by the 2,2-diphenyl-1-pycryl-hydrazyl (DPPH) radical scavenging assay and Ferric Reducing Power assay (FRAP) since these compounds contained a free hydroxyl group at the 3-position.The prepared library of compounds were ideal to assess whether or not the deactivating fluorine atoms on the phenyl ring were better at promoting hydrogen or electron transfer to free radicals than the activating methoxylated derivatives. All the methoxylated analogues showed better activity thanthe fluorinated analogues and comparable to that of ascorbic acid.

The crystal structures of two of the 2-styrylchromones, the 2'-fluoro-2-styrylchromone and the 6-fluoro-2-styrylchromone show the geometry and absolute structure of the molecules so that all the 2-styrylchromone structures could be fashioned around this. Suitable crystals for X-Ray analysis were also obtained for three of the cinnamate esters and their absolute structures were also determined by X-Ray crystallography to study the dihedral angles and geometry of the different functional groups. It was found that the two aromatic rings were almost perpendicular to each other and during the transformation of the cinnamate ester to the 2-styrylchromone, the molecule becomes almost planar.

In addition a complete NMR study of all the intermediates and target molecules are also presented here to provide a basis for identification of similar derivatives. The unambiguous assignments of the protons and carbon atoms are provided as well as intricate couplings between fluorine and hydrogen as well as fluorine and carbon. NMR assignments were made with the aid of HSQC and HMBC data as well as the coupling constants of the different proton and carbon resonances.

Limitations and future work

1) The yields of some of the 2-styrylchromones, in particular **A5b** (62%), **A5e** (45%) and **A5i** (55%) were comparatively low compared to the other styrylchromones with yields of between 70 and 90%. The methodology will need to be modified in order to optimize these yields.

2) 2-Styrylchromones with fluorination at multiple sites on the aromatic rings as well as other positions on the skeleton such as the Δ^2 double bond and the α,β double bond linking the chromone skeleton to the phenyl ring. This can be followed by QSAR and computational studies to enable further modification and drug design.

3) Only a few strains of Gram positive and Gram negative bacteria were tested against. Other strains of bacteria can be used to determine the antibacterial activity of the compounds against them and thereby determine whether or not the compounds have a broader spectrum of antibiotic activity.

4) Other biological activities on the new compounds could be investigated, for example antirihnovirus, anticancer and anti-HIV activity in which related compounds have shown to be active against.

4) All synthesized 2-styryl chromone compounds can be transformed into

1) dienes using Diels-Alder reactions;

2) pyrazolines with the reaction of diazomethane;

3) 1,2,3-triazoles by bromination followed by reaction with sodium azide.

Further computational and biological activity of these analogues can also be carried out to determine whether or not these derivatives can provide leads to be developed into drugs against pathogenic and other disorders for example, antibacterial, anti-cancer and anti-HIV drugs.

7.2.   The 2-thioimidazole dicarboxylates

Seven fluorinated derivatives of diethyl-2-(benzylthio)-2,3-dihydro-1H-imidazole-4,5-dicarboxylate (**a-g**) as well as a nitro and chloro derivative (**h-i**) were prepared in five steps from glycine, ethyl formate, diethyl oxalate, potassium thiocyanate and substituted benzyl bromides. The synthesized compounds exhibited concentration dependent anti-platelet aggregation activity on both the thrombin and ADP induced platelet aggregation. The 4-nitro and 4-fluoro compounds exhibited the highest activity from the compounds tested, with estimated IC_{50} values of 0.40 and 0.35mg/mL for the thrombin-induced and ADP-induced

platelet aggregation, respectively, and further modifications to the structures of these compounds may lead to better anti-platelet aggregation activity.

In addition, the crystal structure of 2-mercapto-4,5-imidazoledicarboxylate is presented to provide an insight into the structural geometry of the molecule.

Limitations and future work

1) The library of fluorinated analogues synthesised is rather limit and more fluorinated and other halides analogues ofdiethyl-2-(benzylthio)-2,3-dihydro-1H-imidazole-4,5-dicarboxylateswould need to be synthesized to provide a more comprehensive study of the anti-platelet activity of these types of compounds. This can also be followed by QSAR and computational studies to enable further modification and drug design.

2) Other types of antiplatelet aggregation such as epinephrineinduced platelet aggregation can also be used to provide a more comprehensive study on the antiplatelet activity.

4) Other types of biological activities could also be investigated for example antibacterial, anti-fungal, anticancer, anti-HIV activity.

5) The substitution of benzyl halides in the 2-mercapto-4,5-imidazoledicarboxylate at the sulphur and nitrogen atoms with the reaction of 2 moles of benzyl halides can also be carried out. These synthesized compounds can be screened for biological assays such as antibacterial, anti-fungal, anticancer, anti-HIV activity and anti-TB in addition to anti-platelet activity.

In general, the work described here provides a platform for structural elucidation and biological activity of two classes of compounds, the 2-styrylchromones and 2-thioimidazoles. Other projects and ideas can be generated from this work for future studies.

Appendix-1

A1-1 X-ray Crystallographic data of 6-fluoro-2-styrylchromone discussed in Chapter 2

Crystal data

$C_{17}H_{11}FO_2$	$F(000) = 1104$
$M_r = 266.26$	$D_x = 1.388$ Mg m^{-3}
Monoclinic, $C2/c$	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$a = 28.505$ (3) Å	Cell parameters from 9566 reflections
$b = 5.6688$ (6) Å	$\theta = 1.5–28.3°$
$c = 16.4254$ (16) Å	$\mu = 0.10$ mm^{-1}
$\beta = 106.189$ (2)°	$T = 173$ K
$V = 2548.9$ (5) Å^3	Plate, yellow
$Z = 8$	$0.29 \times 0.12 \times 0.04$ mm

Data collection

Bruker Kappa Duo Apex II Diffractometer	3158 independent reflections
Radiation source: fine-focus sealed tube	2023 reflections with $I > 2\sigma(I)$
graphite	$R_{int} = 0.042$
0.5° ϕ scans and ω scans	$\theta_{max} = 28.3°$, $\theta_{min} = 1.5°$
Absorption correction: multi-scan *SADABS* (Sheldrick, 1997)	$h = -38 \rightarrow 30$
$T_{min} = 0.972$, $T_{max} = 0.996$	$k = -7 \rightarrow 7$
9566 measured reflections	$l = -21 \rightarrow 21$

Refinement

Refinement on F^2	Primary atom site location: structure-invariant direct methods
Least-squares matrix: full	Secondary atom site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.044$	Hydrogen site location: inferred from neighbouring sites
$wR(F^2) = 0.112$	H-atom parameters constrained
$S = 1.03$	$w = 1/[\sigma^2(F_o^2) + (0.0479P)^2 + 0.4765P]$ where $P = (F_o^2 + 2F_c^2)/3$
3158 reflections	$(\Delta/\sigma)_{max} < 0.001$
181 parameters	$\Delta\rho_{max} = 0.25$ e Å^{-3}
0 restraints	$\Delta\rho_{min} = -0.22$ e Å^{-3}

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($Å^2$)

	x	y	z	$U_{iso}*/U_{eq}$
F1	0.19366 (4)	0.82319 (19)	0.54681 (7)	0.0519 (3)
O1	0.06955 (4)	0.18317 (19)	0.55091 (7)	0.0342 (3)
O2	0.01028 (4)	0.61778 (17)	0.34986 (7)	0.0297 (3)
C1	0.05660 (5)	0.6599 (3)	0.40109 (10)	0.0265 (3)
C2	0.08052 (6)	0.8553 (3)	0.38023 (10)	0.0306 (4)
H2	0.0651	0.9503	0.3326	0.037*
C3	0.12675 (6)	0.9085 (3)	0.42960 (11)	0.0326 (4)
H3	0.1438	1.0409	0.4167	0.039*
C4	0.14798 (6)	0.7659 (3)	0.49835 (11)	0.0329 (4)
C5	0.12538 (5)	0.5722 (3)	0.51941 (10)	0.0308 (4)
H5	0.1412	0.4777	0.5669	0.037*
C6	0.07855 (5)	0.5164 (3)	0.46957 (9)	0.0259 (3)
C7	0.05199 (5)	0.3101 (3)	0.48845 (10)	0.0269 (3)
C8	0.00474 (5)	0.2732 (3)	0.42952 (10)	0.0280 (3)
H8	-0.0135	0.1379	0.4361	0.034*
C9	-0.01448 (5)	0.4231 (3)	0.36549 (10)	0.0273 (3)
C10	-0.06285 (6)	0.4126 (3)	0.30549 (10)	0.0302 (4)
H10	-0.0717	0.5343	0.2643	0.036*
C11	-0.09557 (6)	0.2443 (3)	0.30442 (10)	0.0304 (4)
H11	-0.0861	0.1220	0.3453	0.036*
C12	-0.14486 (5)	0.2297 (3)	0.24620 (10)	0.0275 (3)
C13	-0.17421 (6)	0.0354 (3)	0.25122 (11)	0.0347 (4)
H13	-0.1624	-0.0808	0.2937	0.042*
C14	-0.22019 (6)	0.0106 (3)	0.19511 (11)	0.0405 (4)
H14	-0.2396	-0.1230	0.1989	0.049*
C15	-0.23795 (6)	0.1789 (3)	0.13365 (12)	0.0388 (4)
H15	-0.2694	0.1604	0.0947	0.047*
C16	-0.20992 (6)	0.3747 (3)	0.12883 (11)	0.0367 (4)
H16	-0.2224	0.4919	0.0871	0.044*
C17	-0.16400 (6)	0.4009 (3)	0.18424 (10)	0.0319 (4)
H17	-0.1451	0.5364	0.1804	0.038*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
F1	0.0329 (6)	0.0591 (7)	0.0561 (7)	-0.0176 (5)	0.0000 (5)	0.0023 (6)
O1	0.0361 (7)	0.0309 (6)	0.0326 (6)	-0.0006 (5)	0.0047 (5)	0.0067 (5)
O2	0.0273 (6)	0.0302 (6)	0.0300 (6)	-0.0038 (4)	0.0053 (5)	0.0043 (5)
C1	0.0243 (8)	0.0282 (8)	0.0284 (8)	-0.0017 (6)	0.0094 (6)	-0.0041 (6)
C2	0.0341 (9)	0.0274 (8)	0.0323 (9)	0.0000 (7)	0.0128 (7)	0.0006 (7)
C3	0.0337 (9)	0.0298 (8)	0.0382 (9)	-0.0062 (7)	0.0164 (7)	-0.0037 (7)
C4	0.0250 (8)	0.0378 (9)	0.0353 (9)	-0.0053 (7)	0.0073 (7)	-0.0055 (7)
C5	0.0271 (8)	0.0340 (8)	0.0306 (9)	0.0006 (7)	0.0070 (7)	0.0010 (7)
C6	0.0252 (8)	0.0264 (8)	0.0279 (8)	0.0011 (6)	0.0104 (6)	-0.0016 (6)
C7	0.0288 (8)	0.0247 (7)	0.0282 (8)	0.0011 (6)	0.0093 (7)	-0.0007 (6)
C8	0.0284 (8)	0.0244 (7)	0.0312 (8)	-0.0039 (6)	0.0083 (7)	-0.0001 (6)
C9	0.0286 (8)	0.0266 (8)	0.0273 (8)	-0.0032 (6)	0.0089 (7)	-0.0013 (6)
C10	0.0324 (9)	0.0318 (8)	0.0258 (8)	0.0000 (7)	0.0070 (7)	0.0024 (7)
C11	0.0328 (9)	0.0288 (8)	0.0277 (8)	-0.0002 (7)	0.0055 (7)	0.0005 (7)
C12	0.0283 (8)	0.0276 (8)	0.0269 (8)	-0.0008 (6)	0.0079 (6)	-0.0040 (6)
C13	0.0398 (10)	0.0303 (8)	0.0338 (9)	-0.0050 (7)	0.0101 (7)	0.0024 (7)
C14	0.0372 (10)	0.0379 (10)	0.0464 (11)	-0.0131 (8)	0.0115 (8)	-0.0064 (8)
C15	0.0230 (8)	0.0463 (10)	0.0427 (10)	-0.0025 (7)	0.0022 (7)	-0.0078 (8)
C16	0.0296 (9)	0.0351 (9)	0.0423 (10)	0.0054 (7)	0.0048 (8)	0.0042 (8)
C17	0.0271 (8)	0.0272 (8)	0.0397 (10)	-0.0004 (6)	0.0066 (7)	0.0012 (7)

Geometric parameters (Å, º)

F1—C4	1.3626 (18)	C9—C10	1.455 (2)
O1—C7	1.2388 (17)	C10—C11	1.331 (2)
O2—C9	1.3722 (17)	C10—H10	0.9500
O2—C1	1.3742 (18)	C11—C12	1.465 (2)
C1—C6	1.388 (2)	C11—H11	0.9500
C1—C2	1.393 (2)	C12—C13	1.399 (2)
C2—C3	1.375 (2)	C12—C17	1.402 (2)
C2—H2	0.9500	C13—C14	1.383 (2)
C3—C4	1.383 (2)	C13—H13	0.9500
C3—H3	0.9500	C14—C15	1.379 (2)
C4—C5	1.366 (2)	C14—H14	0.9500
C5—C6	1.394 (2)	C15—C16	1.383 (2)
C5—H5	0.9500	C15—H15	0.9500

C6—C7	1.472 (2)	C16—C17	1.378 (2)
C7—C8	1.438 (2)	C16—H16	0.9500
C8—C9	1.345 (2)	C17—H17	0.9500
C8—H8	0.9500		
C9—O2—C1	118.79 (12)	C8—C9—C10	127.32 (14)
O2—C1—C6	122.25 (13)	O2—C9—C10	110.24 (13)
O2—C1—C2	116.11 (13)	C11—C10—C9	124.50 (15)
C6—C1—C2	121.64 (14)	C11—C10—H10	117.8
C3—C2—C1	118.96 (15)	C9—C10—H10	117.8
C3—C2—H2	120.5	C10—C11—C12	126.16 (15)
C1—C2—H2	120.5	C10—C11—H11	116.9
C2—C3—C4	118.84 (15)	C12—C11—H11	116.9
C2—C3—H3	120.6	C13—C12—C17	118.01 (14)
C4—C3—H3	120.6	C13—C12—C11	119.09 (14)
F1—C4—C5	119.01 (14)	C17—C12—C11	122.89 (14)
F1—C4—C3	117.83 (14)	C14—C13—C12	120.80 (15)
C5—C4—C3	123.15 (15)	C14—C13—H13	119.6
C4—C5—C6	118.42 (15)	C12—C13—H13	119.6
C4—C5—H5	120.8	C15—C14—C13	120.23 (15)
C6—C5—H5	120.8	C15—C14—H14	119.9
C1—C6—C5	118.97 (14)	C13—C14—H14	119.9
C1—C6—C7	119.61 (13)	C14—C15—C16	119.83 (15)
C5—C6—C7	121.41 (14)	C14—C15—H15	120.1
O1—C7—C8	124.01 (14)	C16—C15—H15	120.1
O1—C7—C6	121.54 (14)	C17—C16—C15	120.43 (16)
C8—C7—C6	114.45 (13)	C17—C16—H16	119.8
C9—C8—C7	122.38 (14)	C15—C16—H16	119.8
C9—C8—H8	118.8	C16—C17—C12	120.69 (15)
C7—C8—H8	118.8	C16—C17—H17	119.7
C8—C9—O2	122.41 (13)	C12—C17—H17	119.7
C9—O2—C1—C6	-2.0 (2)	O1—C7—C8—C9	175.63 (15)
C9—O2—C1—C2	177.80 (13)	C6—C7—C8—C9	-3.6 (2)
O2—C1—C2—C3	179.27 (14)	C7—C8—C9—O2	2.4 (2)
C6—C1—C2—C3	-0.9 (2)	C7—C8—C9—C10	-175.80 (15)
C1—C2—C3—C4	0.0 (2)	C1—O2—C9—C8	0.6 (2)
C2—C3—C4—F1	-179.45 (14)	C1—O2—C9—C10	179.04 (13)
C2—C3—C4—C5	0.6 (2)	C8—C9—C10—C11	-1.6 (3)
F1—C4—C5—C6	179.65 (14)	O2—C9—C10—C11	-179.98 (14)
C3—C4—C5—C6	-0.4 (2)	C9—C10—C11—C12	178.81 (15)

O2—C1—C6—C5	-179.09 (14)	C10—C11—C12—C13	177.46 (16)
C2—C1—C6—C5	1.1 (2)	C10—C11—C12—C17	-1.5 (3)
O2—C1—C6—C7	0.5 (2)	C17—C12—C13—C14	1.7 (2)
C2—C1—C6—C7	-179.26 (13)	C11—C12—C13—C14	-177.36 (15)
C4—C5—C6—C1	-0.4 (2)	C12—C13—C14—C15	-0.6 (3)
C4—C5—C6—C7	179.95 (14)	C13—C14—C15—C16	-0.8 (3)
C1—C6—C7—O1	-177.13 (14)	C14—C15—C16—C17	1.0 (3)
C5—C6—C7—O1	2.5 (2)	C15—C16—C17—C12	0.2 (3)
C1—C6—C7—C8	2.2 (2)	C13—C12—C17—C16	-1.5 (2)
C5—C6—C7—C8	-178.21 (14)	C11—C12—C17—C16	177.52 (16)

A1-2 X-ray crystallographic data of *diethyl 2-mercapto-4,5-imidazoledicarboxylate* discussed in Chapter 3

Crystal data

$C_9H_{12}N_2O_4S$	$Z = 2$
$M_r = 244.27$	$F(000) = 256$
Triclinic, $P\bar{1}$	$D_x = 1.455$ Mg m^{-3}
$a = 7.0493$ (11) Å	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$b = 8.7173$ (13) Å	Cell parameters from 4511 reflections
$c = 9.6955$ (14) Å	$\theta = 2.5–27.6°$
$\alpha = 79.246$ (3)°	$\mu = 0.29$ mm^{-1}
$\beta = 85.918$ (3)°	$T = 173$ K
$\gamma = 72.348$ (3)°	Block, yellow
$V = 557.71$ (14) Å^3	$0.12 \times 0.09 \times 0.04$ mm

Data collection

Bruker Kappa Duo Apex II Diffractometer	1804 reflections with $I > 2\sigma(I)$
Radiation source: fine-focus sealed tube	$R_{int} = 0.019$
graphite	$\theta_{max} = 27.6°$, $\theta_{min} = 2.5°$
0.5° ϕ scans and ω scans	$h = -9\rightarrow9$
4511 measured reflections	$k = -10\rightarrow11$
2536 independent reflections	$l = -12\rightarrow6$

Refinement

Refinement on F^2	Primary atom site location: structure-invariant direct methods
Least-squares matrix: full	Secondary atom site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.039$	Hydrogen site location: inferred from neighbouring sites
$wR(F^2) = 0.095$	H atoms treated by a mixture of independent and constrained refinement
$S = 1.01$	$w = 1/[\sigma^2(F_o^2) + (0.0445P)^2 + 0.0908P]$ where $P = (F_o^2 + 2F_c^2)/3$
2536 reflections	$(\Delta/\sigma)_{max} = 0.001$
155 parameters	$\Delta\rho_{max} = 0.29$ e Å^{-3}
2 restraints	$\Delta\rho_{min} = -0.29$ e Å^{-3}

Hydrogen-bond geometry (Å, °)

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O2^i	0.969(9)	1.861(11)	2.827(2)	175(2)
N2—H2···S1^{ii}	0.969(16)	2.325(16)	2.863(17)	171.4(14)

Symmetry codes: (i)1-x, 2-y,1-z (ii)1-x,1-y,2-z

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	y	z	U_{iso}*/U_{eq}
S1	0.37160 (8)	0.75878 (6)	0.93291 (5)	0.03030 (16)
O1	0.7302 (2)	0.64790 (16)	0.34320 (13)	0.0290 (3)
O2	0.6430 (2)	0.89175 (16)	0.41091 (14)	0.0339 (4)
O3	0.8677 (3)	0.33164 (17)	0.50149 (15)	0.0443 (4)
O4	0.7538 (2)	0.22686 (15)	0.70863 (14)	0.0309 (3)
N1	0.5218 (3)	0.76635 (19)	0.66774 (16)	0.0253 (4)
H1	0.472 (3)	0.8844 (4)	0.644 (3)	0.053 (7)*
N2	0.5817 (2)	0.52084 (18)	0.78242 (16)	0.0246 (4)
H2	0.589 (3)	0.4323 (19)	0.8609 (16)	0.047 (7)*
C1	0.8803 (3)	0.5941 (3)	0.1230 (2)	0.0371 (5)
H1A	1.0005	0.5267	0.1744	0.056*
H1B	0.9180	0.6424	0.0295	0.056*
H1C	0.7957	0.5259	0.1136	0.056*
C2	0.7690 (3)	0.7267 (2)	0.2012 (2)	0.0326 (5)
H2A	0.8490	0.8015	0.2052	0.039*
H2B	0.6421	0.7907	0.1541	0.039*
C3	0.6693 (3)	0.7456 (2)	0.4355 (2)	0.0251 (4)
C4	0.6260 (3)	0.6650 (2)	0.57731 (19)	0.0242 (4)
C5	0.4932 (3)	0.6795 (2)	0.79443 (19)	0.0237 (4)
C6	0.6649 (3)	0.5081 (2)	0.64964 (19)	0.0235 (4)
C7	0.7739 (3)	0.3490 (2)	0.6079 (2)	0.0274 (4)
C8	0.8552 (3)	0.0614 (2)	0.6809 (2)	0.0334 (5)
H8A	0.9982	0.0485	0.6599	0.040*
H8B	0.7953	0.0409	0.5995	0.040*
C9	0.8312 (4)	-0.0562 (3)	0.8103 (2)	0.0411 (6)
H9A	0.8951	-0.0372	0.8894	0.062*
H9B	0.8935	-0.1685	0.7944	0.062*
H9C	0.6891	-0.0399	0.8317	0.062*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
S1	0.0400 (3)	0.0221 (3)	0.0246 (3)	-0.0043 (2)	0.0043 (2)	-0.00341 (19)
O1	0.0423 (9)	0.0231 (7)	0.0204 (7)	-0.0089 (6)	0.0016 (6)	-0.0029 (5)
O2	0.0468 (10)	0.0184 (7)	0.0308 (8)	-0.0048 (6)	0.0084 (7)	-0.0019 (6)
O3	0.0597 (12)	0.0273 (8)	0.0348 (9)	-0.0010 (7)	0.0154 (8)	-0.0039 (7)
O4	0.0385 (9)	0.0173 (7)	0.0328 (8)	-0.0047 (6)	0.0075 (6)	-0.0034 (6)
N1	0.0324 (10)	0.0193 (8)	0.0220 (8)	-0.0057 (7)	0.0007 (7)	-0.0018 (7)
N2	0.0299 (10)	0.0175 (8)	0.0234 (8)	-0.0043 (7)	0.0010 (7)	-0.0009 (7)
C1	0.0405 (14)	0.0378 (12)	0.0318 (11)	-0.0088 (10)	0.0040 (10)	-0.0095 (9)
C2	0.0437 (14)	0.0300 (11)	0.0222 (10)	-0.0098 (10)	0.0016 (9)	-0.0023 (8)
C3	0.0254 (11)	0.0214 (10)	0.0259 (10)	-0.0045 (8)	-0.0010 (8)	-0.0021 (8)
C4	0.0281 (11)	0.0195 (9)	0.0240 (10)	-0.0058 (8)	0.0004 (8)	-0.0036 (7)
C5	0.0268 (11)	0.0196 (9)	0.0240 (10)	-0.0063 (8)	-0.0030 (8)	-0.0015 (8)
C6	0.0256 (11)	0.0204 (9)	0.0235 (9)	-0.0059 (8)	-0.0005 (8)	-0.0027 (8)
C7	0.0296 (12)	0.0226 (10)	0.0278 (10)	-0.0054 (8)	-0.0005 (8)	-0.0033 (8)
C8	0.0358 (13)	0.0205 (10)	0.0424 (12)	-0.0051 (9)	0.0025 (10)	-0.0087 (9)
C9	0.0481 (15)	0.0223 (11)	0.0489 (14)	-0.0072 (10)	-0.0032 (11)	-0.0007 (10)

Geometric parameters (Å, º)

S1—C5	1.6846 (19)	C1—H1A	0.9800
O1—C3	1.311 (2)	C1—H1B	0.9800
O1—C2	1.466 (2)	C1—H1C	0.9800
O2—C3	1.210 (2)	C2—H2A	0.9900
O3—C7	1.194 (2)	C2—H2B	0.9900
O4—C7	1.338 (2)	C3—C4	1.478 (3)
O4—C8	1.468 (2)	C4—C6	1.371 (2)
N1—C5	1.354 (2)	C6—C7	1.482 (3)
N1—C4	1.376 (2)	C8—C9	1.500 (3)
N1—H1	0.969 (2)	C8—H8A	0.9900
N2—C5	1.357 (2)	C8—H8B	0.9900
N2—C6	1.386 (2)	C9—H9A	0.9800
N2—H2	0.969 (2)	C9—H9B	0.9800
C1—C2	1.490 (3)	C9—H9C	0.9800
C3—O1—C2	115.53 (15)	C6—C4—C3	136.79 (17)
C7—O4—C8	115.51 (14)	N1—C4—C3	116.42 (16)

C5—N1—C4	111.18 (16)	N1—C5—N2	104.98 (16)
C5—N1—H1	124.0 (15)	N1—C5—S1	125.61 (14)
C4—N1—H1	124.8 (15)	N2—C5—S1	129.41 (14)
C5—N2—C6	111.05 (15)	C4—C6—N2	106.01 (16)
C5—N2—H2	122.0 (14)	C4—C6—C7	131.34 (17)
C6—N2—H2	126.9 (14)	N2—C6—C7	122.64 (16)
C2—C1—H1A	109.5	O3—C7—O4	124.86 (18)
C2—C1—H1B	109.5	O3—C7—C6	125.41 (18)
H1A—C1—H1B	109.5	O4—C7—C6	109.72 (16)
C2—C1—H1C	109.5	O4—C8—C9	107.26 (16)
H1A—C1—H1C	109.5	O4—C8—H8A	110.3
H1B—C1—H1C	109.5	C9—C8—H8A	110.3
O1—C2—C1	107.03 (16)	O4—C8—H8B	110.3
O1—C2—H2A	110.3	C9—C8—H8B	110.3
C1—C2—H2A	110.3	H8A—C8—H8B	108.5
O1—C2—H2B	110.3	C8—C9—H9A	109.5
C1—C2—H2B	110.3	C8—C9—H9B	109.5
H2A—C2—H2B	108.6	H9A—C9—H9B	109.5
O2—C3—O1	124.89 (18)	C8—C9—H9C	109.5
O2—C3—C4	120.18 (18)	H9A—C9—H9C	109.5
O1—C3—C4	114.91 (16)	H9B—C9—H9C	109.5
C6—C4—N1	106.78 (16)		
C3—O1—C2—C1	166.83 (18)	N1—C4—C6—N2	0.0 (2)
C2—O1—C3—O2	0.5 (3)	C3—C4—C6—N2	178.9 (2)
C2—O1—C3—C4	178.54 (17)	N1—C4—C6—C7	-178.9 (2)
C5—N1—C4—C6	-0.1 (2)	C3—C4—C6—C7	0.0 (4)
C5—N1—C4—C3	-179.22 (18)	C5—N2—C6—C4	0.0 (2)
O2—C3—C4—C6	-166.9 (2)	C5—N2—C6—C7	179.09 (18)
O1—C3—C4—C6	14.9 (4)	C8—O4—C7—O3	-0.8 (3)
O2—C3—C4—N1	11.9 (3)	C8—O4—C7—C6	-179.90 (17)
O1—C3—C4—N1	-166.28 (18)	C4—C6—C7—O3	8.0 (4)
C4—N1—C5—N2	0.1 (2)	N2—C6—C7—O3	-170.9 (2)
C4—N1—C5—S1	-179.75 (15)	C4—C6—C7—O4	-172.9 (2)
C6—N2—C5—N1	-0.1 (2)	N2—C6—C7—O4	8.3 (3)
C6—N2—C5—S1	179.76 (16)	C7—O4—C8—C9	174.81 (18)

A1-3 X Ray crystallographic data of 2-Acetylphenyl-(2*E*)-3-(4-fluorophenyl)acrylate discussed in Chapter 6, subchapter 6.1

Crystal data

$C_{17}H_{13}FO_3$	$F(000) = 1184$
$M_r = 284.27$	$D_x = 1.373$ Mg m^{-3}
Monoclinic, $C2/c$	Mo Ka radiation, l = 0.71073 Å
$a = 26.574$ (1) Å	Cell parameters from 6005 reflections
$b = 6.3883$ (3) Å	q = 3.1–27.5°
$c = 19.3304$ (6) Å	m = 0.10 mm^{-1}
b = 123.037 (2)°	$T = 173$ K
$V = 2751.01$ (19) Å^3	Plate, colourless
$Z = 8$	$0.26 \times 0.23 \times 0.09$ mm

Data collection

Nonius Kappa CCD diffractometer	2201 reflections with $I > 2\sigma(I)$
Radiation source: fine-focus sealed tube	$R_{int} = 0.021$
graphite	$\theta_{max} = 27.5°$, $\theta_{min} = 3.1°$
1.2° ϕ scans and ω scans	$h = -33 \rightarrow 34$
6005 measured reflections	$k = -8 \rightarrow 8$
3150 independent reflections	$l = -25 \rightarrow 24$

Refinement

Refinement on F^2	Primary atom site location: structure-invariant direct methods
Least-squares matrix: full	Secondary atom site location: difference Fourier map
$R[F^2 > 2s(F^2)] = 0.041$	Hydrogen site location: inferred from neighbouring sites
$wR(F^2) = 0.115$	H-atom parameters constrained
$S = 1.05$	$w = 1/[s^2(F_o^2) + (0.0612P)^2 + 0.6743P]$ where $P = (F_o^2 + 2F_c^2)/3$
3150 reflections	$(D/s)_{max} < 0.001$
191 parameters	$D\rho_{max} = 0.18$ e Å^{-3}
0 restraints	$D\rho_{min} = -0.20$ e Å^{-3}

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($\mathring{A}^2$)

	x	y	z	$U_{iso}*/U_{eq}$
F1	0.04188 (4)	1.49324 (13)	0.22111 (6)	0.0580 (3)
O1	0.26072 (5)	-0.02536 (18)	0.16114 (6)	0.0556 (3)
O2	0.16132 (4)	0.49823 (13)	0.02908 (6)	0.0379 (2)
O3	0.06857 (4)	0.41188 (17)	-0.00442 (7)	0.0522 (3)
C1	0.25590 (7)	0.3344 (3)	0.18081 (9)	0.0512 (4)
H1A	0.2225	0.3695	0.1867	0.077*
H1B	0.2633	0.4515	0.1548	0.077*
H1C	0.2921	0.3074	0.2354	0.077*
C2	0.24038 (6)	0.1439 (2)	0.12848 (8)	0.0377 (3)
C3	0.19990 (5)	0.1519 (2)	0.03588 (7)	0.0315 (3)
C4	0.19941 (6)	-0.0253 (2)	-0.00725 (8)	0.0369 (3)
H4	0.2241	-0.1415	0.0228	0.044*
C5	0.16398 (6)	-0.0351 (2)	-0.09234 (9)	0.0430 (4)
H5	0.1643	-0.1569	-0.1203	0.052*
C6	0.12814 (7)	0.1330 (2)	-0.13652 (8)	0.0447 (4)
H6	0.1039	0.1274	-0.1951	0.054*
C7	0.12732 (6)	0.3091 (2)	-0.09597 (8)	0.0418 (3)
H7	0.1026	0.4247	-0.1265	0.050*
C8	0.16273 (6)	0.3169 (2)	-0.01042 (8)	0.0327 (3)
C9	0.11003 (6)	0.5312 (2)	0.02865 (8)	0.0337 (3)
C10	0.11450 (6)	0.72268 (19)	0.07306 (8)	0.0339 (3)
H10	0.1496	0.8069	0.0972	0.041*
C11	0.06885 (6)	0.7778 (2)	0.07935 (8)	0.0346 (3)
H11	0.0355	0.6853	0.0548	0.042*
C12	0.06392 (6)	0.96377 (19)	0.11951 (7)	0.0321 (3)
C13	0.01102 (6)	0.9974 (2)	0.11673 (8)	0.0379 (3)
H13	-0.0204	0.8971	0.0906	0.045*
C14	0.00350 (6)	1.1745 (2)	0.15135 (8)	0.0418 (3)
H14	-0.0326	1.1971	0.1493	0.050*
C15	0.04946 (6)	1.3164 (2)	0.18860 (8)	0.0388 (3)
C16	0.10298 (6)	1.2888 (2)	0.19487 (8)	0.0385 (3)
H16	0.1344	1.3885	0.2226	0.046*
C17	0.10980 (6)	1.1118 (2)	0.15972 (8)	0.0360 (3)
H17	0.1464	1.0903	0.1629	0.043*

Atomic displacement parameters ($\mathring{A}^2$)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
F1	0.0663 (6)	0.0476 (5)	0.0611 (6)	-0.0033 (4)	0.0354 (5)	-0.0236 (4)
O1	0.0560 (7)	0.0582 (7)	0.0411 (6)	0.0116 (5)	0.0191 (5)	0.0104 (5)
O2	0.0366 (5)	0.0330 (5)	0.0456 (5)	-0.0029 (4)	0.0234 (4)	-0.0093 (4)
O3	0.0453 (6)	0.0485 (6)	0.0693 (7)	-0.0152 (5)	0.0354 (6)	-0.0258 (5)
C1	0.0492 (9)	0.0627 (10)	0.0346 (8)	-0.0076 (7)	0.0183 (7)	-0.0089 (7)
C2	0.0314 (7)	0.0486 (8)	0.0358 (7)	-0.0011 (6)	0.0201 (6)	-0.0001 (6)
C3	0.0303 (6)	0.0351 (7)	0.0331 (7)	-0.0026 (5)	0.0200 (5)	-0.0011 (5)
C4	0.0397 (7)	0.0348 (7)	0.0413 (8)	0.0037 (6)	0.0254 (6)	0.0013 (6)
C5	0.0512 (9)	0.0416 (8)	0.0440 (8)	-0.0030 (7)	0.0311 (7)	-0.0103 (7)
C6	0.0468 (8)	0.0541 (9)	0.0317 (7)	-0.0014 (7)	0.0205 (6)	-0.0045 (7)
C7	0.0437 (8)	0.0426 (8)	0.0361 (7)	0.0060 (6)	0.0199 (6)	0.0037 (6)
C8	0.0346 (7)	0.0305 (7)	0.0366 (7)	-0.0031 (5)	0.0217 (6)	-0.0039 (5)
C9	0.0348 (7)	0.0327 (7)	0.0334 (7)	0.0005 (6)	0.0183 (6)	0.0001 (5)
C10	0.0355 (7)	0.0296 (7)	0.0341 (7)	-0.0025 (5)	0.0174 (6)	-0.0019 (5)
C11	0.0352 (7)	0.0305 (7)	0.0344 (7)	-0.0032 (5)	0.0165 (6)	-0.0030 (5)
C12	0.0352 (7)	0.0295 (7)	0.0283 (6)	0.0002 (5)	0.0151 (5)	-0.0001 (5)
C13	0.0340 (7)	0.0377 (7)	0.0372 (7)	-0.0044 (6)	0.0164 (6)	-0.0086 (6)
C14	0.0366 (7)	0.0463 (8)	0.0408 (8)	0.0010 (6)	0.0199 (6)	-0.0080 (6)
C15	0.0492 (8)	0.0322 (7)	0.0313 (7)	0.0017 (6)	0.0196 (6)	-0.0063 (6)
C16	0.0424 (8)	0.0332 (7)	0.0343 (7)	-0.0080 (6)	0.0172 (6)	-0.0048 (6)
C17	0.0377 (7)	0.0338 (7)	0.0364 (7)	-0.0026 (6)	0.0201 (6)	-0.0015 (6)

Geometric parameters (Å, °)

F1—C15	1.3600 (15)	C7—C8	1.3878 (18)
O1—C2	1.2195 (17)	C7—H7	0.9500
O2—C9	1.3748 (16)	C9—C10	1.4614 (17)
O2—C8	1.3993 (15)	C10—C11	1.3310 (19)
O3—C9	1.1982 (16)	C10—H10	0.9500
C1—C2	1.490 (2)	C11—C12	1.4636 (17)
C1—H1A	0.9800	C11—H11	0.9500
C1—H1B	0.9800	C12—C13	1.3937 (18)
C1—H1C	0.9800	C12—C17	1.3972 (18)
C2—C3	1.5048 (19)	C13—C14	1.3835 (18)
C3—C8	1.3869 (18)	C13—H13	0.9500
C3—C4	1.4014 (18)	C14—C15	1.369 (2)
C4—C5	1.381 (2)	C14—H14	0.9500
C4—H4	0.9500	C15—C16	1.371 (2)

C5—C6	1.379 (2)	C16—C17	1.3814 (19)
C5—H5	0.9500	C16—H16	0.9500
C6—C7	1.378 (2)	C17—H17	0.9500
C6—H6	0.9500		
C9—O2—C8	116.42 (9)	O3—C9—O2	121.72 (12)
C2—C1—H1A	109.5	O3—C9—C10	127.06 (12)
C2—C1—H1B	109.5	O2—C9—C10	111.22 (11)
H1A—C1—H1B	109.5	C11—C10—C9	119.26 (12)
C2—C1—H1C	109.5	C11—C10—H10	120.4
H1A—C1—H1C	109.5	C9—C10—H10	120.4
H1B—C1—H1C	109.5	C10—C11—C12	127.80 (12)
O1—C2—C1	119.47 (12)	C10—C11—H11	116.1
O1—C2—C3	118.28 (12)	C12—C11—H11	116.1
C1—C2—C3	122.25 (12)	C13—C12—C17	118.24 (12)
C8—C3—C4	117.21 (11)	C13—C12—C11	119.00 (11)
C8—C3—C2	126.11 (11)	C17—C12—C11	122.76 (12)
C4—C3—C2	116.67 (11)	C14—C13—C12	121.07 (12)
C5—C4—C3	121.63 (13)	C14—C13—H13	119.5
C5—C4—H4	119.2	C12—C13—H13	119.5
C3—C4—H4	119.2	C15—C14—C13	118.25 (13)
C6—C5—C4	119.62 (13)	C15—C14—H14	120.9
C6—C5—H5	120.2	C13—C14—H14	120.9
C4—C5—H5	120.2	F1—C15—C14	118.60 (13)
C7—C6—C5	120.20 (12)	F1—C15—C16	118.28 (12)
C7—C6—H6	119.9	C14—C15—C16	123.12 (12)
C5—C6—H6	119.9	C15—C16—C17	118.02 (12)
C6—C7—C8	119.76 (13)	C15—C16—H16	121.0
C6—C7—H7	120.1	C17—C16—H16	121.0
C8—C7—H7	120.1	C16—C17—C12	121.26 (12)
C3—C8—C7	121.56 (12)	C16—C17—H17	119.4
C3—C8—O2	119.91 (11)	C12—C17—H17	119.4
C7—C8—O2	118.51 (11)		
O1—C2—C3—C8	164.97 (13)	C8—O2—C9—O3	-0.64 (18)
C1—C2—C3—C8	-14.7 (2)	C8—O2—C9—C10	178.87 (10)
O1—C2—C3—C4	-14.28 (18)	O3—C9—C10—C11	0.0 (2)
C1—C2—C3—C4	166.04 (12)	O2—C9—C10—C11	-179.43 (12)
C8—C3—C4—C5	0.71 (19)	C9—C10—C11—C12	-178.78 (11)
C2—C3—C4—C5	-179.97 (12)	C10—C11—C12—C13	177.62 (13)
C3—C4—C5—C6	0.1 (2)	C10—C11—C12—C17	-1.4 (2)

C4—C5—C6—C7	-0.5 (2)	C17—C12—C13—C14	1.26 (19)
C5—C6—C7—C8	0.0 (2)	C11—C12—C13—C14	-177.78 (12)
C4—C3—C8—C7	-1.21 (18)	C12—C13—C14—C15	0.0 (2)
C2—C3—C8—C7	179.54 (12)	C13—C14—C15—F1	178.52 (11)
C4—C3—C8—O2	-179.87 (11)	C13—C14—C15—C16	-1.6 (2)
C2—C3—C8—O2	0.88 (19)	F1—C15—C16—C17	-178.23 (11)
C6—C7—C8—C3	0.9 (2)	C14—C15—C16—C17	1.9 (2)
C6—C7—C8—O2	179.56 (12)	C15—C16—C17—C12	-0.56 (19)
C9—O2—C8—C3	-109.06 (13)	C13—C12—C17—C16	-0.95 (19)
C9—O2—C8—C7	72.24 (15)	C11—C12—C17—C16	178.05 (12)

Hydrogen-bond geometry (Å, °)

D—H⋯*A*	*D*—H	H⋯*A*	*D*⋯*A*	*D*—H⋯*A*
C1—H1*B*⋯O2	0.98	2.48	2.8245 (18)	100
C7—H7⋯F1[i]	0.95	2.52	3.2402 (16)	132
C11—H11⋯O3	0.95	2.50	2.8415 (16)	101
C11—H11⋯O3[ii]	0.95	2.46	3.3369 (16)	154
C13—H13⋯O3[ii]	0.95	2.45	3.3191 (16)	153
C16—H16⋯O1[iii]	0.95	2.51	3.3590 (17)	149
C6—H6⋯*Cg*1[iv]	0.95	2.99	3.818 (1)	146

Symmetry codes: (i) *x*, -*y*+2, *z*-1/2; (ii) -*x*, -*y*+1, -*z*; (iii) -*x*+1/2, *y*+3/2, -*z*+1/2; (iv) *x*, -*y*+1, *z*-1/2.

A1-4 X Ray crystallographic data of (*E*)-2-Acetyl-4-fluorophenyl-3-(4-fluorophenyl)acrylate

Crystal data

$C_{17}H_{12}F_2O_3$	$Z = 4$
$M_r = 302.27$	$F(000) = 624$
Triclinic, $P\overline{1}$	$D_x = 1.426$ Mg m^{-3}
$a = 7.6510\ (9)$ Å	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$b = 12.5610\ (14)$ Å	Cell parameters from 7877 reflections
$c = 15.4368\ (17)$ Å	$\theta = 1.7–25.7°$
$\alpha = 73.599\ (2)°$	$\mu = 0.12$ mm^{-1}
$\beta = 81.604\ (3)°$	$T = 173$ K
$\gamma = 88.124\ (3)°$	Needle, colourless
$V = 1407.9\ (3)$ Å^3	$0.29 \times 0.06 \times 0.05$ mm

Data collection

Bruker Kappa Duo Apex II Diffractometer	5294 independent reflections
Radiation source: fine-focus sealed tube	3362 reflections with $I > 2\square(I)$
graphite	$R_{int} = 0.019$
0.5° ϕ scans and ω scans	$\theta_{max} = 25.7°$, $\theta_{min} = 1.7°$
Absorption correction: multi-scan *SADABS* (Sheldrick, 1997)	$h = -9 \rightarrow 9$
$T_{min} = 0.968$, $T_{max} = 0.994$	$k = -15 \rightarrow 15$
7877 measured reflections	$l = -18 \rightarrow 17$

Refinement

Refinement on F^2	Primary atom site location: structure-invariant direct methods
Least-squares matrix: full	Secondary atom site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.042$	Hydrogen site location: inferred from neighbouring sites
$wR(F^2) = 0.114$	H-atom parameters constrained
$S = 0.96$	$w = 1/[\ \sigma^2(F_o^2) + (0.0608P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
5294 reflections	$(\Delta/\sigma)_{max} = 0.001$
399 parameters	$\Delta\rho_{max} = 0.21$ e Å^{-3}
0 restraints	$\Delta\rho_{min} = -0.24$ e Å^{-3}

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	y	z	$U_{iso}*/U_{eq}$
F1A	0.11548 (18)	0.53403 (10)	0.56787 (8)	0.0547 (4)
F2A	-0.01031 (19)	0.83163 (10)	1.30768 (8)	0.0568 (4)
O1A	-0.2165 (2)	0.87709 (12)	0.77866 (9)	0.0465 (4)
O2A	-0.00539 (17)	0.70018 (10)	0.80883 (8)	0.0295 (3)
O3A	-0.20253 (18)	0.55996 (11)	0.86357 (8)	0.0390 (4)
C1A	-0.1978 (3)	0.99574 (17)	0.62857 (14)	0.0464 (6)
H1A1	-0.2465	1.0502	0.6600	0.070*
H1A2	-0.2795	0.9851	0.5884	0.070*
H1A3	-0.0837	1.0227	0.5922	0.070*
C2A	-0.1727 (2)	0.88770 (16)	0.69741 (13)	0.0332 (5)
C3A	-0.0929 (2)	0.79367 (15)	0.66302 (12)	0.0285 (4)
C4A	-0.0905 (3)	0.79529 (17)	0.57163 (12)	0.0354 (5)
H4A	-0.1375	0.8575	0.5311	0.043*
C5A	-0.0214 (3)	0.70862 (18)	0.53913 (13)	0.0394 (5)
H5A	-0.0213	0.7105	0.4772	0.047*
C6A	0.0471 (3)	0.61982 (17)	0.59839 (13)	0.0369 (5)
C7A	0.0514 (3)	0.61431 (16)	0.68805 (13)	0.0344 (5)
H7A	0.1017	0.5525	0.7274	0.041*
C8A	-0.0195 (2)	0.70130 (15)	0.71936 (11)	0.0269 (4)
C9A	-0.1111 (2)	0.62836 (15)	0.87731 (12)	0.0268 (4)
C10A	-0.1016 (2)	0.64472 (15)	0.96679 (12)	0.0289 (4)
H10A	-0.1516	0.5890	1.0195	0.035*
C11A	-0.0273 (2)	0.73287 (15)	0.97889 (12)	0.0281 (4)
H11A	0.0272	0.7859	0.9256	0.034*
C12A	-0.0211 (2)	0.75625 (15)	1.06615 (12)	0.0278 (4)
C13A	-0.0902 (3)	0.68239 (16)	1.14934 (12)	0.0325 (5)
H13A	-0.1405	0.6139	1.1501	0.039*
C14A	-0.0864 (3)	0.70771 (17)	1.23050 (13)	0.0377 (5)
H14A	-0.1331	0.6574	1.2871	0.045*
C15A	-0.0132 (3)	0.80762 (17)	1.22748 (13)	0.0364 (5)
C16A	0.0565 (3)	0.88284 (16)	1.14777 (14)	0.0374 (5)
H16A	0.1056	0.9513	1.1479	0.045*
C17A	0.0529 (2)	0.85580 (16)	1.06695 (13)	0.0323 (4)
H17A	0.1020	0.9062	1.0109	0.039*
F1B	0.63202 (18)	0.51072 (10)	0.57600 (8)	0.0546 (4)

F2B	0.50720 (18)	0.83118 (10)	1.29099 (8)	0.0518 (3)
O1B	0.2986 (2)	0.96987 (12)	0.57913 (10)	0.0550 (4)
O2B	0.46287 (17)	0.71393 (10)	0.78960 (8)	0.0296 (3)
O3B	0.32306 (18)	0.54798 (11)	0.85217 (8)	0.0355 (3)
C1B	0.3017 (3)	0.92016 (17)	0.73712 (13)	0.0394 (5)
H1B1	0.2488	0.9935	0.7311	0.059*
H1B2	0.4131	0.9174	0.7619	0.059*
H1B3	0.2203	0.8632	0.7784	0.059*
C2B	0.3366 (3)	0.89925 (16)	0.64539 (13)	0.0336 (5)
C3B	0.4186 (2)	0.79314 (15)	0.63289 (12)	0.0280 (4)
C4B	0.4413 (3)	0.78131 (17)	0.54416 (13)	0.0361 (5)
H4B	0.4079	0.8408	0.4962	0.043*
C5B	0.5097 (3)	0.68733 (17)	0.52390 (13)	0.0398 (5)
H5B	0.5210	0.6804	0.4636	0.048*
C6B	0.5611 (3)	0.60369 (16)	0.59420 (13)	0.0367 (5)
C7B	0.5471 (3)	0.61009 (15)	0.68216 (12)	0.0317 (4)
H7B	0.5871	0.5515	0.7287	0.038*
C8B	0.4731 (2)	0.70444 (15)	0.70098 (11)	0.0264 (4)
C9B	0.3893 (2)	0.62852 (15)	0.86183 (12)	0.0276 (4)
C10B	0.3977 (2)	0.64876 (15)	0.94982 (12)	0.0295 (4)
H10B	0.3422	0.5959	1.0029	0.035*
C11B	0.4767 (2)	0.73519 (15)	0.96133 (12)	0.0288 (4)
H11B	0.5343	0.7869	0.9081	0.035*
C12B	0.4830 (2)	0.75797 (15)	1.04916 (12)	0.0283 (4)
C13B	0.4127 (3)	0.68483 (16)	1.13280 (12)	0.0314 (4)
H13B	0.3592	0.6172	1.1339	0.038*
C14B	0.4201 (3)	0.70989 (16)	1.21383 (13)	0.0356 (5)
H14B	0.3724	0.6602	1.2705	0.043*
C15B	0.4978 (3)	0.80800 (17)	1.21062 (13)	0.0357 (5)
C16B	0.5663 (3)	0.88258 (16)	1.13079 (13)	0.0357 (5)
H16B	0.6172	0.9506	1.1307	0.043*
C17B	0.5597 (3)	0.85643 (16)	1.04984 (13)	0.0325 (4)
H17B	0.6086	0.9069	0.9937	0.039*

Atomic displacement parameters ($\mathring{A}^2$)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
F1A	0.0733 (9)	0.0569 (8)	0.0419 (7)	0.0081 (7)	-0.0027 (6)	-0.0304 (6)
F2A	0.0896	0.0532 (8)	0.0374 (7)	-0.0025 (7)	-0.0174 (7)	-0.0239 (6)

	(10)					
O1A	0.0573 (10)	0.0445 (9)	0.0327 (8)	0.0062 (7)	0.0052 (7)	-0.0094 (7)
O2A	0.0369 (8)	0.0308 (7)	0.0198 (6)	-0.0077 (6)	-0.0041 (5)	-0.0048 (5)
O3A	0.0499 (9)	0.0396 (8)	0.0284 (7)	-0.0167 (7)	0.0001 (6)	-0.0120 (6)
C1A	0.0616 (15)	0.0348 (12)	0.0415 (13)	0.0020 (11)	-0.0122 (11)	-0.0062 (10)
C2A	0.0291 (11)	0.0366 (12)	0.0335 (11)	-0.0028 (9)	-0.0037 (9)	-0.0092 (9)
C3A	0.0277 (10)	0.0315 (10)	0.0244 (10)	-0.0066 (8)	-0.0008 (8)	-0.0055 (8)
C4A	0.0352 (11)	0.0428 (12)	0.0240 (10)	-0.0068 (9)	-0.0040 (8)	-0.0017 (9)
C5A	0.0446 (13)	0.0539 (14)	0.0205 (10)	-0.0070 (10)	-0.0017 (9)	-0.0124 (10)
C6A	0.0397 (12)	0.0429 (12)	0.0313 (11)	-0.0025 (10)	0.0005 (9)	-0.0182 (10)
C7A	0.0392 (12)	0.0355 (11)	0.0286 (10)	-0.0038 (9)	-0.0048 (9)	-0.0083 (9)
C8A	0.0298 (10)	0.0322 (11)	0.0184 (9)	-0.0062 (8)	-0.0018 (7)	-0.0068 (8)
C9A	0.0280 (10)	0.0253 (10)	0.0253 (10)	-0.0006 (8)	-0.0015 (8)	-0.0050 (8)
C10A	0.0330 (11)	0.0302 (10)	0.0209 (9)	-0.0018 (8)	-0.0007 (8)	-0.0045 (8)
C11A	0.0308 (10)	0.0279 (10)	0.0237 (9)	0.0010 (8)	-0.0020 (8)	-0.0050 (8)
C12A	0.0290 (10)	0.0269 (10)	0.0280 (10)	0.0023 (8)	-0.0060 (8)	-0.0081 (8)
C13A	0.0426 (12)	0.0299 (11)	0.0266 (10)	-0.0015 (9)	-0.0072 (9)	-0.0091 (8)
C14A	0.0505 (13)	0.0356 (12)	0.0268 (10)	-0.0010 (10)	-0.0050 (9)	-0.0086 (9)
C15A	0.0489 (13)	0.0412 (12)	0.0265 (11)	0.0064 (10)	-0.0127 (9)	-0.0180 (9)
C16A	0.0428 (13)	0.0307 (11)	0.0438 (12)	0.0001 (9)	-0.0120 (10)	-0.0158 (10)
C17A	0.0344 (11)	0.0302 (11)	0.0325 (11)	0.0008 (9)	-0.0053 (8)	-0.0089 (8)
F1B	0.0825 (10)	0.0453 (8)	0.0404 (7)	0.0142 (7)	-0.0021 (7)	-0.0239 (6)
F2B	0.0790 (9)	0.0516 (8)	0.0336 (7)	-0.0002 (7)	-0.0119 (6)	-0.0240 (6)
O1B	0.0816 (12)	0.0420 (9)	0.0398 (9)	0.0172 (8)	-0.0173 (8)	-0.0064 (7)
O2B	0.0409 (8)	0.0281 (7)	0.0211 (6)	-0.0042 (6)	-0.0051 (6)	-0.0082 (5)

O3B	0.0467 (9)	0.0322 (8)	0.0278 (7)	-0.0115 (6)	-0.0032 (6)	-0.0084 (6)
C1B	0.0500 (13)	0.0316 (11)	0.0391 (12)	0.0031 (10)	-0.0059 (10)	-0.0145 (9)
C2B	0.0343 (11)	0.0300 (11)	0.0356 (11)	-0.0053 (9)	-0.0073 (9)	-0.0062 (9)
C3B	0.0302 (10)	0.0285 (10)	0.0254 (10)	-0.0051 (8)	-0.0037 (8)	-0.0070 (8)
C4B	0.0406 (12)	0.0395 (12)	0.0260 (10)	-0.0029 (10)	-0.0063 (9)	-0.0048 (9)
C5B	0.0531 (14)	0.0461 (13)	0.0236 (10)	-0.0016 (10)	-0.0052 (9)	-0.0150 (9)
C6B	0.0450 (13)	0.0318 (11)	0.0350 (11)	0.0013 (9)	-0.0013 (9)	-0.0147 (9)
C7B	0.0380 (11)	0.0301 (11)	0.0267 (10)	-0.0019 (9)	-0.0052 (8)	-0.0067 (8)
C8B	0.0300 (10)	0.0281 (10)	0.0225 (9)	-0.0065 (8)	-0.0018 (8)	-0.0096 (8)
C9B	0.0287 (10)	0.0282 (10)	0.0240 (10)	0.0013 (8)	-0.0030 (8)	-0.0047 (8)
C10B	0.0334 (11)	0.0313 (11)	0.0231 (10)	-0.0005 (9)	-0.0038 (8)	-0.0066 (8)
C11B	0.0290 (10)	0.0297 (11)	0.0269 (10)	0.0020 (8)	-0.0036 (8)	-0.0072 (8)
C12B	0.0301 (10)	0.0281 (10)	0.0276 (10)	0.0039 (8)	-0.0056 (8)	-0.0093 (8)
C13B	0.0373 (11)	0.0299 (11)	0.0305 (10)	0.0025 (9)	-0.0084 (8)	-0.0124 (8)
C14B	0.0450 (13)	0.0324 (11)	0.0285 (11)	0.0039 (9)	-0.0043 (9)	-0.0079 (9)
C15B	0.0474 (13)	0.0387 (12)	0.0275 (10)	0.0080 (10)	-0.0101 (9)	-0.0183 (9)
C16B	0.0438 (13)	0.0316 (11)	0.0372 (11)	-0.0001 (9)	-0.0097 (10)	-0.0163 (9)
C17B	0.0352 (11)	0.0306 (11)	0.0318 (11)	0.0019 (9)	-0.0039 (8)	-0.0097 (8)

Geometric parameters (Å, º)

F1A—C6A	1.355 (2)	F1B—C6B	1.355 (2)
F2A—C15A	1.358 (2)	F2B—C15B	1.364 (2)
O1A—C2A	1.220 (2)	O1B—C2B	1.214 (2)
O2A—C9A	1.358 (2)	O2B—C9B	1.375 (2)
O2A—C8A	1.397 (2)	O2B—C8B	1.397 (2)
O3A—C9A	1.207 (2)	O3B—C9B	1.201 (2)

C1A—C2A	1.495 (3)	C1B—C2B	1.497 (3)
C1A—H1A1	0.9800	C1B—H1B1	0.9800
C1A—H1A2	0.9800	C1B—H1B2	0.9800
C1A—H1A3	0.9800	C1B—H1B3	0.9800
C2A—C3A	1.504 (3)	C2B—C3B	1.504 (3)
C3A—C8A	1.396 (3)	C3B—C8B	1.399 (2)
C3A—C4A	1.403 (2)	C3B—C4B	1.404 (3)
C4A—C5A	1.382 (3)	C4B—C5B	1.373 (3)
C4A—H4A	0.9500	C4B—H4B	0.9500
C5A—C6A	1.372 (3)	C5B—C6B	1.375 (3)
C5A—H5A	0.9500	C5B—H5B	0.9500
C6A—C7A	1.371 (3)	C6B—C7B	1.371 (3)
C7A—C8A	1.380 (3)	C7B—C8B	1.383 (3)
C7A—H7A	0.9500	C7B—H7B	0.9500
C9A—C10A	1.465 (2)	C9B—C10B	1.461 (2)
C10A—C11A	1.332 (3)	C10B—C11B	1.326 (3)
C10A—H10A	0.9500	C10B—H10B	0.9500
C11A—C12A	1.465 (2)	C11B—C12B	1.470 (2)
C11A—H11A	0.9500	C11B—H11B	0.9500
C12A—C17A	1.394 (3)	C12B—C17B	1.389 (3)
C12A—C13A	1.397 (2)	C12B—C13B	1.400 (3)
C13A—C14A	1.381 (3)	C13B—C14B	1.383 (3)
C13A—H13A	0.9500	C13B—H13B	0.9500
C14A—C15A	1.377 (3)	C14B—C15B	1.371 (3)
C14A—H14A	0.9500	C14B—H14B	0.9500
C15A—C16A	1.370 (3)	C15B—C16B	1.365 (3)
C16A—C17A	1.387 (3)	C16B—C17B	1.387 (3)
C16A—H16A	0.9500	C16B—H16B	0.9500
C17A—H17A	0.9500	C17B—H17B	0.9500
C9A—O2A—C8A	117.63 (14)	C9B—O2B—C8B	119.28 (14)
C2A—C1A—H1A1	109.5	C2B—C1B—H1B1	109.5
C2A—C1A—H1A2	109.5	C2B—C1B—H1B2	109.5
H1A1—C1A—H1A2	109.5	H1B1—C1B—H1B2	109.5
C2A—C1A—H1A3	109.5	C2B—C1B—H1B3	109.5
H1A1—C1A—H1A3	109.5	H1B1—C1B—H1B3	109.5
H1A2—C1A—H1A3	109.5	H1B2—C1B—H1B3	109.5
O1A—C2A—C1A	120.50 (18)	O1B—C2B—C1B	119.29 (19)
O1A—C2A—C3A	121.66 (17)	O1B—C2B—C3B	118.99 (18)
C1A—C2A—C3A	117.84 (17)	C1B—C2B—C3B	121.72 (17)

C8A—C3A—C4A	116.93 (17)	C8B—C3B—C4B	116.63 (17)
C8A—C3A—C2A	122.40 (16)	C8B—C3B—C2B	126.54 (16)
C4A—C3A—C2A	120.66 (17)	C4B—C3B—C2B	116.83 (17)
C5A—C4A—C3A	121.59 (19)	C5B—C4B—C3B	122.72 (18)
C5A—C4A—H4A	119.2	C5B—C4B—H4B	118.6
C3A—C4A—H4A	119.2	C3B—C4B—H4B	118.6
C6A—C5A—C4A	118.47 (18)	C4B—C5B—C6B	117.43 (18)
C6A—C5A—H5A	120.8	C4B—C5B—H5B	121.3
C4A—C5A—H5A	120.8	C6B—C5B—H5B	121.3
F1A—C6A—C7A	117.96 (19)	F1B—C6B—C7B	117.93 (18)
F1A—C6A—C5A	119.38 (18)	F1B—C6B—C5B	118.78 (17)
C7A—C6A—C5A	122.65 (19)	C7B—C6B—C5B	123.28 (19)
C6A—C7A—C8A	117.98 (19)	C6B—C7B—C8B	117.96 (18)
C6A—C7A—H7A	121.0	C6B—C7B—H7B	121.0
C8A—C7A—H7A	121.0	C8B—C7B—H7B	121.0
C7A—C8A—C3A	122.35 (17)	C7B—C8B—O2B	118.74 (16)
C7A—C8A—O2A	118.51 (16)	C7B—C8B—C3B	121.94 (16)
C3A—C8A—O2A	118.97 (16)	O2B—C8B—C3B	119.20 (16)
O3A—C9A—O2A	122.24 (16)	O3B—C9B—O2B	122.89 (16)
O3A—C9A—C10A	125.13 (17)	O3B—C9B—C10B	124.69 (17)
O2A—C9A—C10A	112.63 (16)	O2B—C9B—C10B	112.40 (16)
C11A—C10A—C9A	124.06 (17)	C11B—C10B—C9B	125.09 (17)
C11A—C10A—H10A	118.0	C11B—C10B—H10B	117.5
C9A—C10A—H10A	118.0	C9B—C10B—H10B	117.5
C10A—C11A—C12A	126.50 (17)	C10B—C11B—C12B	125.74 (17)
C10A—C11A—H11A	116.7	C10B—C11B—H11B	117.1
C12A—C11A—H11A	116.7	C12B—C11B—H11B	117.1
C17A—C12A—C13A	118.45 (17)	C17B—C12B—C13B	118.22 (17)
C17A—C12A—C11A	119.53 (16)	C17B—C12B—C11B	119.13 (17)
C13A—C12A—C11A	122.01 (17)	C13B—C12B—C11B	122.64 (17)
C14A—C13A—C12A	120.80 (18)	C14B—C13B—C12B	120.78 (18)
C14A—C13A—H13A	119.6	C14B—C13B—H13B	119.6
C12A—C13A—H13A	119.6	C12B—C13B—H13B	119.6
C15A—C14A—C13A	118.46 (18)	C15B—C14B—C13B	118.60 (18)
C15A—C14A—H14A	120.8	C15B—C14B—H14B	120.7
C13A—C14A—H14A	120.8	C13B—C14B—H14B	120.7
F2A—C15A—C16A	119.04 (18)	F2B—C15B—C16B	118.99 (18)
F2A—C15A—C14A	117.92 (17)	F2B—C15B—C14B	118.19 (18)
C16A—C15A—C14A	123.04 (18)	C16B—C15B—C14B	122.82 (18)

C15A—C16A—C17A	117.81 (18)	C15B—C16B—C17B	118.24 (18)
C15A—C16A—H16A	121.1	C15B—C16B—H16B	120.9
C17A—C16A—H16A	121.1	C17B—C16B—H16B	120.9
C16A—C17A—C12A	121.44 (18)	C16B—C17B—C12B	121.33 (18)
C16A—C17A—H17A	119.3	C16B—C17B—H17B	119.3
C12A—C17A—H17A	119.3	C12B—C17B—H17B	119.3
O1A—C2A—C3A—C8A	-18.2 (3)	O1B—C2B—C3B—C8B	178.79 (18)
C1A—C2A—C3A—C8A	162.02 (17)	C1B—C2B—C3B—C8B	-0.8 (3)
O1A—C2A—C3A—C4A	161.39 (19)	O1B—C2B—C3B—C4B	-1.9 (3)
C1A—C2A—C3A—C4A	-18.4 (3)	C1B—C2B—C3B—C4B	178.46 (18)
C8A—C3A—C4A—C5A	1.1 (3)	C8B—C3B—C4B—C5B	1.3 (3)
C2A—C3A—C4A—C5A	-178.53 (18)	C2B—C3B—C4B—C5B	-178.04 (18)
C3A—C4A—C5A—C6A	-0.4 (3)	C3B—C4B—C5B—C6B	-1.6 (3)
C4A—C5A—C6A—F1A	180.00 (17)	C4B—C5B—C6B—F1B	-178.85 (18)
C4A—C5A—C6A—C7A	-0.7 (3)	C4B—C5B—C6B—C7B	0.0 (3)
F1A—C6A—C7A—C8A	-179.50 (17)	F1B—C6B—C7B—C8B	-179.33 (17)
C5A—C6A—C7A—C8A	1.2 (3)	C5B—C6B—C7B—C8B	1.8 (3)
C6A—C7A—C8A—C3A	-0.6 (3)	C6B—C7B—C8B—O2B	-178.01 (17)
C6A—C7A—C8A—O2A	-175.83 (17)	C6B—C7B—C8B—C3B	-2.1 (3)
C4A—C3A—C8A—C7A	-0.5 (3)	C9B—O2B—C8B—C7B	-51.3 (2)
C2A—C3A—C8A—C7A	179.03 (17)	C9B—O2B—C8B—C3B	132.62 (17)
C4A—C3A—C8A—O2A	174.70 (16)	C4B—C3B—C8B—C7B	0.6 (3)
C2A—C3A—C8A—O2A	-5.7 (3)	C2B—C3B—C8B—C7B	179.89 (18)
C9A—O2A—C8A—C7A	-74.0 (2)	C4B—C3B—C8B—O2B	176.51 (16)
C9A—O2A—C8A—C3A	110.55 (19)	C2B—C3B—C8B—O2B	-4.2 (3)
C8A—O2A—C9A—O3A	7.0 (3)	C8B—O2B—C9B—O3B	-4.6 (3)
C8A—O2A—C9A—C10A	-172.49 (15)	C8B—O2B—C9B—C10B	176.77 (15)
O3A—C9A—C10A—C11A	-166.69 (19)	O3B—C9B—C10B—C11B	177.12 (19)
O2A—C9A—C10A—C11A	12.8 (3)	O2B—C9B—C10B—C11B	-4.2 (3)
C9A—C10A—C11A—C12A	176.92 (18)	C9B—C10B—C11B—C12B	178.60 (18)
C10A—C11A—C12A—C17A	-176.24 (19)	C10B—C11B—C12B—C17B	-175.23 (18)
C10A—C11A—C12A—C13A	2.7 (3)	C10B—C11B—C12B—C13B	4.0 (3)
C17A—C12A—C13A—C14A	0.4 (3)	C17B—C12B—C13B—C14B	-0.3 (3)
C11A—C12A—C13A—C14A	-178.47 (19)	C11B—C12B—C13B—C14B	-179.46 (18)
C12A—C13A—C14A—C15A	0.2 (3)	C12B—C13B—C14B—C15B	0.0 (3)
C13A—C14A—C15A—F2A	179.92 (18)	C13B—C14B—C15B—F2B	-178.91 (18)
C13A—C14A—C15A—C16A	-0.2 (3)	C13B—C14B—C15B—C16B	0.8 (3)
F2A—C15A—C16A—C17A	179.56 (17)	F2B—C15B—C16B—C17B	178.38 (17)
C14A—C15A—C16A—C17A	-0.3 (3)	C14B—C15B—C16B—C17B	-1.3 (3)

C15A—C16A—C17A—C12A	0.9 (3)	C15B—C16B—C17B—C12B	1.0 (3)
C13A—C12A—C17A—C16A	-1.0 (3)	C13B—C12B—C17B—C16B	-0.3 (3)
C11A—C12A—C17A—C16A	177.96 (18)	C11B—C12B—C17B—C16B	178.93 (18)

A1-5   X Ray crystallographic data of (*E*)-2-acetylphenyl-3-(4-methoxyphenyl)acrylate

Crystal data

$C_{18}H_{16}O_4$	D_x = 1.328 Mg m^{-3}
M_r = 296.31	Mo Kρradiation, λ = 0.71073 Å
Orthorhombic, Pbca	Cell parameters from 25075 reflections
a = 7.7165 (2) Å	θ = 3.0–28.3°
b = 14.2736 (3) Å	μ= 0.09 mm^{-1}
c = 26.9200 (6) Å	T = 173 K
V = 2965.03 (12) Å^3	Block, colourless
Z = 8	0.53 × 0.42 × 0.27 mm
F(000) = 1248	

Data collection

Bruker Kappa Duo Apex II Diffractometer	3677 independent reflections
Radiation source: fine-focus sealed tube	3217 reflections with I > 2$\square$(I)
graphite	R_{int} = 0.029
0.5° ϕ scans and ω scans	θ_{max} = 28.3°, θ_{min} = 3.0°
Absorption correction: multi-scan SADABS (Sheldrick, 1997)	h = -10→10
T_{min} = 0.952, T_{max} = 0.975	k = -19→18
25075 measured reflections	l = -35→27

Refinement

Refinement on F^2	Primary atom site location: structure-invariant direct methods
Least-squares matrix: full	Secondary atom site location: difference Fourier map
R[F^2 > 2σ(F^2)] = 0.037	Hydrogen site location: inferred from neighbouring sites
wR(F^2) = 0.098	H-atom parameters constrained
S = 1.02	w = 1/[$\sigma^2(F_o^2)$ + $(0.049P)^2$ + 1.0541P] where P = $(F_o^2 + 2F_c^2)$/3
3677 reflections	$(\Delta/\sigma)_{max}$ < 0.001
201 parameters	$\Delta\rho_{max}$ = 0.34 e Å^{-3}
0 restraints	$\Delta\rho_{min}$ = -0.17 e Å^{-3}

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($Å^2$)

	x	y	z	U_{iso}*/U_{eq}
O1	0.45244 (11)	0.49905 (6)	0.17391 (3)	0.0320 (2)
O2	0.31420 (10)	0.36157 (5)	0.11532 (3)	0.02206 (17)
O3	0.08890 (11)	0.40232 (6)	0.16382 (3)	0.02668 (18)
O4	0.08027 (12)	0.79216 (6)	-0.08812 (3)	0.0316 (2)
C1	0.70962 (15)	0.45828 (8)	0.21663 (4)	0.0268 (2)
H1A	0.7392	0.5243	0.2113	0.040*
H1B	0.8004	0.4185	0.2024	0.040*
H1C	0.7001	0.4461	0.2523	0.040*
C2	0.54008 (13)	0.43694 (7)	0.19193 (4)	0.0199 (2)
C3	0.48195 (13)	0.33652 (7)	0.19053 (4)	0.0182 (2)
C4	0.53877 (14)	0.27337 (7)	0.22689 (4)	0.0209 (2)
H4	0.6162	0.2942	0.2520	0.025*
C5	0.48361 (15)	0.18071 (7)	0.22675 (4)	0.0235 (2)
H5	0.5215	0.1390	0.2520	0.028*
C6	0.37317 (15)	0.14911 (7)	0.18966 (4)	0.0244 (2)
H6	0.3365	0.0856	0.1894	0.029*
C7	0.31599 (14)	0.21011 (7)	0.15289 (4)	0.0224 (2)
H7	0.2412	0.1885	0.1273	0.027*
C8	0.36909 (13)	0.30272 (7)	0.15393 (4)	0.0189 (2)
C9	0.17167 (14)	0.41441 (7)	0.12636 (4)	0.0201 (2)
C10	0.13112 (14)	0.48570 (7)	0.08915 (4)	0.0224 (2)
H10	0.0347	0.5253	0.0956	0.027*
C11	0.21787 (14)	0.49999 (8)	0.04699 (4)	0.0228 (2)
H11	0.3106	0.4585	0.0396	0.027*
C12	0.18128 (14)	0.57483 (7)	0.01116 (4)	0.0219 (2)
C13	0.26580 (14)	0.57645 (8)	-0.03460 (4)	0.0233 (2)
H13	0.3456	0.5279	-0.0424	0.028*
C14	0.23633 (14)	0.64739 (8)	-0.06925 (4)	0.0234 (2)
H14	0.2952	0.6471	-0.1002	0.028*
C15	0.11985 (14)	0.71846 (8)	-0.05791 (4)	0.0232 (2)
C16	0.03313 (16)	0.71780 (8)	-0.01233 (4)	0.0284 (2)
H16	-0.0471	0.7661	-0.0046	0.034*
C17	0.06367 (16)	0.64736 (8)	0.02136 (4)	0.0273 (2)
H17	0.0039	0.6478	0.0522	0.033*
C18	0.16381 (17)	0.79671 (9)	-0.13536 (4)	0.0323 (3)
H18A	0.2895	0.8005	-0.1306	0.048*

H18B	0.1236	0.8523	-0.1533	0.048*
H18C	0.1357	0.7404	-0.1546	0.048*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0287 (4)	0.0192 (4)	0.0482 (5)	0.0000 (3)	-0.0077 (4)	0.0055 (3)
O2	0.0245 (4)	0.0243 (4)	0.0173 (3)	0.0045 (3)	0.0001 (3)	0.0035 (3)
O3	0.0249 (4)	0.0304 (4)	0.0247 (4)	0.0038 (3)	0.0033 (3)	0.0055 (3)
O4	0.0373 (5)	0.0314 (4)	0.0262 (4)	0.0107 (4)	0.0059 (3)	0.0111 (3)
C1	0.0255 (5)	0.0235 (5)	0.0313 (5)	-0.0027 (4)	-0.0040 (4)	-0.0026 (4)
C2	0.0207 (5)	0.0187 (4)	0.0201 (4)	-0.0002 (4)	0.0028 (4)	-0.0005 (4)
C3	0.0179 (4)	0.0172 (4)	0.0194 (4)	0.0014 (4)	0.0023 (4)	0.0002 (3)
C4	0.0218 (5)	0.0214 (5)	0.0195 (5)	0.0023 (4)	-0.0010 (4)	0.0001 (4)
C5	0.0278 (5)	0.0203 (5)	0.0225 (5)	0.0036 (4)	0.0016 (4)	0.0042 (4)
C6	0.0284 (5)	0.0170 (5)	0.0277 (5)	-0.0010 (4)	0.0037 (4)	0.0004 (4)
C7	0.0228 (5)	0.0223 (5)	0.0220 (5)	-0.0011 (4)	-0.0003 (4)	-0.0028 (4)
C8	0.0195 (5)	0.0201 (5)	0.0171 (4)	0.0028 (4)	0.0022 (4)	0.0020 (3)
C9	0.0199 (5)	0.0203 (5)	0.0201 (5)	-0.0008 (4)	-0.0036 (4)	-0.0003 (4)
C10	0.0224 (5)	0.0224 (5)	0.0223 (5)	0.0028 (4)	-0.0038 (4)	0.0017 (4)
C11	0.0226 (5)	0.0229 (5)	0.0229 (5)	0.0017 (4)	-0.0039 (4)	0.0019 (4)
C12	0.0227 (5)	0.0226 (5)	0.0204 (5)	-0.0002 (4)	-0.0027 (4)	0.0026 (4)
C13	0.0217 (5)	0.0243 (5)	0.0240 (5)	0.0026 (4)	-0.0003 (4)	0.0012 (4)
C14	0.0230 (5)	0.0278 (5)	0.0195 (5)	0.0003 (4)	0.0020 (4)	0.0028 (4)
C15	0.0249 (5)	0.0236 (5)	0.0210 (5)	0.0010 (4)	-0.0016 (4)	0.0040 (4)
C16	0.0332 (6)	0.0273 (5)	0.0246 (5)	0.0094 (5)	0.0045 (4)	0.0026 (4)
C17	0.0331 (6)	0.0288 (5)	0.0200 (5)	0.0051 (5)	0.0044 (4)	0.0028 (4)
C18	0.0354 (6)	0.0347 (6)	0.0268 (6)	0.0044 (5)	0.0053 (5)	0.0121 (5)

Geometric parameters (Å, º)

O1—C2	1.2160 (13)	C7—H7	0.9500
O2—C9	1.3662 (13)	C9—C10	1.4618 (14)
O2—C8	1.4018 (12)	C10—C11	1.3334 (15)
O3—C9	1.2060 (13)	C10—H10	0.9500
O4—C15	1.3644 (13)	C11—C12	1.4667 (14)
O4—C18	1.4271 (14)	C11—H11	0.9500
C1—C2	1.4988 (15)	C12—C13	1.3941 (14)
C1—H1A	0.9800	C12—C17	1.4038 (15)

C1—H1B	0.9800	C13—C14	1.3954 (14)
C1—H1C	0.9800	C13—H13	0.9500
C2—C3	1.5023 (14)	C14—C15	1.3893 (15)
C3—C8	1.4008 (14)	C14—H14	0.9500
C3—C4	1.4010 (14)	C15—C16	1.3976 (15)
C4—C5	1.3895 (15)	C16—C17	1.3744 (15)
C4—H4	0.9500	C16—H16	0.9500
C5—C6	1.3880 (16)	C17—H17	0.9500
C5—H5	0.9500	C18—H18A	0.9800
C6—C7	1.3902 (15)	C18—H18B	0.9800
C6—H6	0.9500	C18—H18C	0.9800
C7—C8	1.3843 (14)		
C9—O2—C8	114.38 (8)	O2—C9—C10	114.05 (9)
C15—O4—C18	117.72 (9)	C11—C10—C9	125.61 (10)
C2—C1—H1A	109.5	C11—C10—H10	117.2
C2—C1—H1B	109.5	C9—C10—H10	117.2
H1A—C1—H1B	109.5	C10—C11—C12	125.07 (10)
C2—C1—H1C	109.5	C10—C11—H11	117.5
H1A—C1—H1C	109.5	C12—C11—H11	117.5
H1B—C1—H1C	109.5	C13—C12—C17	117.58 (10)
O1—C2—C1	120.95 (10)	C13—C12—C11	120.21 (10)
O1—C2—C3	121.30 (9)	C17—C12—C11	122.20 (10)
C1—C2—C3	117.75 (9)	C12—C13—C14	121.77 (10)
C8—C3—C4	117.67 (9)	C12—C13—H13	119.1
C8—C3—C2	122.13 (9)	C14—C13—H13	119.1
C4—C3—C2	120.19 (9)	C15—C14—C13	119.24 (10)
C5—C4—C3	120.98 (10)	C15—C14—H14	120.4
C5—C4—H4	119.5	C13—C14—H14	120.4
C3—C4—H4	119.5	O4—C15—C14	125.22 (10)
C6—C5—C4	119.96 (9)	O4—C15—C16	114.92 (10)
C6—C5—H5	120.0	C14—C15—C16	119.85 (10)
C4—C5—H5	120.0	C17—C16—C15	120.14 (10)
C5—C6—C7	120.23 (10)	C17—C16—H16	119.9
C5—C6—H6	119.9	C15—C16—H16	119.9
C7—C6—H6	119.9	C16—C17—C12	121.42 (10)
C8—C7—C6	119.33 (10)	C16—C17—H17	119.3

C8—C7—H7	120.3	C12—C17—H17	119.3
C6—C7—H7	120.3	O4—C18—H18A	109.5
C7—C8—C3	121.81 (9)	O4—C18—H18B	109.5
C7—C8—O2	117.89 (9)	H18A—C18—H18B	109.5
C3—C8—O2	120.20 (9)	O4—C18—H18C	109.5
O3—C9—O2	121.95 (9)	H18A—C18—H18C	109.5
O3—C9—C10	124.00 (10)	H18B—C18—H18C	109.5
O1—C2—C3—C8	25.77 (15)	C8—O2—C9—C10	171.05 (9)
C1—C2—C3—C8	-154.62 (10)	O3—C9—C10—C11	-178.81 (11)
O1—C2—C3—C4	-153.44 (11)	O2—C9—C10—C11	1.47 (16)
C1—C2—C3—C4	26.18 (14)	C9—C10—C11—C12	-176.73 (10)
C8—C3—C4—C5	-0.54 (15)	C10—C11—C12—C13	-172.04 (11)
C2—C3—C4—C5	178.70 (9)	C10—C11—C12—C17	8.79 (17)
C3—C4—C5—C6	1.23 (16)	C17—C12—C13—C14	0.28 (16)
C4—C5—C6—C7	-0.67 (16)	C11—C12—C13—C14	-178.93 (10)
C5—C6—C7—C8	-0.57 (16)	C12—C13—C14—C15	0.07 (17)
C6—C7—C8—C3	1.29 (16)	C18—O4—C15—C14	0.47 (17)
C6—C7—C8—O2	177.74 (9)	C18—O4—C15—C16	-179.69 (11)
C4—C3—C8—C7	-0.73 (15)	C13—C14—C15—O4	179.43 (11)
C2—C3—C8—C7	-179.96 (9)	C13—C14—C15—C16	-0.41 (17)
C4—C3—C8—O2	-177.11 (9)	O4—C15—C16—C17	-179.46 (11)
C2—C3—C8—O2	3.67 (14)	C14—C15—C16—C17	0.39 (18)
C9—O2—C8—C7	97.15 (11)	C15—C16—C17—C12	-0.02 (19)
C9—O2—C8—C3	-86.34 (11)	C13—C12—C17—C16	-0.31 (17)
C8—O2—C9—O3	-8.68 (14)	C11—C12—C17—C16	178.89 (11)

A1-6   X Ray crystallographic data of 2'-Fluro-2-styrylchromone

Crystal data

$C_{17}H_{11}FO_2$	$F(000) = 552$
$M_r = 266.26$	$D_x = 1.395$ Mg m^{-3}
Monoclinic, $P2_1/c$	Mo $K\rho$ radiation, $\lambda = 0.71073$ Å
$a = 13.0965$ (16) Å	Cell parameters from 6596 reflections
$b = 4.9113$ (5) Å	$\theta = 1.6–28.4°$
$c = 19.736$ (2) Å	$\mu = 0.10$ mm^{-1}
$\beta = 93.140$ (3)°	$T = 173$ K
$V = 1267.5$ (2) Å^3	Needle, colourless
$Z = 4$	$0.23 \times 0.03 \times 0.03$ mm

Data collection

Bruker Kappa Duo Apex II Diffractometer	1657 reflections with $I > 2\square(I)$
Radiation source: fine-focus sealed tube	$R_{int} = 0.048$
graphite	$\theta_{max} = 28.4°$, $\theta_{min} = 1.6°$
0.5° ϕ scans and ω scans	$h = -15 \rightarrow 17$
6596 measured reflections	$k = -6 \rightarrow 5$
3169 independent reflections	$l = -26 \rightarrow 23$

Refinement

Refinement on F^2	Secondary atom site location: difference Fourier map
Least-squares matrix: full	Hydrogen site location: inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)] = 0.050$	H-atom parameters constrained
$wR(F^2) = 0.118$	$w = 1/[\sigma^2(F_o^2) + (0.0473P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$S = 0.98$	$(\Delta/\lambda)_{max} < 0.001$
3169 reflections	$\Delta\rho_{max} = 0.26$ e Å^{-3}
182 parameters	$\Delta\rho_{min} = -0.19$ e Å^{-3}
0 restraints	Extinction correction: *SHELXL*, Fc$^* = $kFc[1+0.001xFc$^2\lambda^3$/sin(2$\theta$)]$^{-1/4}$
Primary atom site location: structure-invariant direct methods	Extinction coefficient: 0.0045 (13)

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($\mathring{A}^2$)

	x	y	z	U_{iso}*/U_{eq}
F1	0.11364 (9)	1.4331 (3)	0.42702 (7)	0.0456 (4)
O1	0.20328 (10)	0.8161 (3)	0.25042 (7)	0.0298 (4)
O2	0.41846 (10)	0.3760 (3)	0.15406 (8)	0.0404 (4)
C1	0.28604 (14)	1.4138 (4)	0.39919 (10)	0.0258 (5)
C2	0.21127 (15)	1.5275 (4)	0.43779 (10)	0.0295 (5)
C3	0.22903 (17)	1.7248 (4)	0.48598 (11)	0.0348 (5)
H3	0.1748	1.7959	0.5107	0.042*
C4	0.32823 (17)	1.8178 (4)	0.49767 (11)	0.0357 (5)
H4	0.3428	1.9548	0.5308	0.043*
C5	0.40641 (16)	1.7112 (4)	0.46114 (11)	0.0348 (5)
H5	0.4745	1.7747	0.4694	0.042*
C6	0.38559 (15)	1.5138 (4)	0.41297 (10)	0.0316 (5)
H6	0.4400	1.4429	0.3883	0.038*
C7	0.26046 (15)	1.2081 (4)	0.34762 (10)	0.0278 (5)
H7	0.1902	1.1793	0.3353	0.033*
C8	0.32877 (15)	1.0576 (4)	0.31657 (10)	0.0278 (5)
H8	0.3989	1.0871	0.3294	0.033*
C9	0.30567 (14)	0.8534 (4)	0.26507 (10)	0.0269 (5)
C10	0.37750 (15)	0.7116 (4)	0.23420 (10)	0.0286 (5)
H10	0.4474	0.7473	0.2465	0.034*
C11	0.35339 (15)	0.5077 (4)	0.18327 (10)	0.0288 (5)
C12	0.24286 (14)	0.4687 (4)	0.16872 (10)	0.0248 (4)
C13	0.20474 (15)	0.2754 (4)	0.12143 (10)	0.0300 (5)
H13	0.2510	0.1640	0.0984	0.036*
C14	0.10117 (16)	0.2454 (4)	0.10802 (11)	0.0355 (5)
H14	0.0761	0.1145	0.0758	0.043*
C15	0.03324 (16)	0.4082 (4)	0.14197 (12)	0.0397 (6)
H15	-0.0382	0.3884	0.1322	0.048*
C16	0.06783 (15)	0.5964 (4)	0.18916 (11)	0.0348 (5)
H16	0.0212	0.7054	0.2125	0.042*
C17	0.17267 (15)	0.6241 (4)	0.20213 (10)	0.0272 (5)

Atomic displacement parameters ($\mathring{A}^2$)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
F1	0.0289 (7)	0.0480 (8)	0.0602 (9)	-0.0013 (6)	0.0042 (6)	-0.0085 (7)

O1	0.0240 (7)	0.0317 (8)	0.0333 (8)	-0.0004 (6)	-0.0001 (6)	-0.0064 (7)
O2	0.0283 (8)	0.0500 (10)	0.0431 (9)	0.0038 (7)	0.0031 (7)	-0.0126 (8)
C1	0.0302 (11)	0.0218 (10)	0.0250 (11)	0.0008 (8)	-0.0024 (8)	0.0046 (9)
C2	0.0256 (11)	0.0297 (12)	0.0327 (12)	-0.0004 (9)	-0.0020 (9)	0.0058 (10)
C3	0.0432 (13)	0.0293 (12)	0.0327 (13)	0.0030 (10)	0.0086 (10)	-0.0017 (10)
C4	0.0525 (15)	0.0289 (12)	0.0254 (12)	-0.0042 (10)	-0.0007 (10)	-0.0022 (10)
C5	0.0336 (12)	0.0339 (12)	0.0361 (13)	-0.0037 (9)	-0.0053 (10)	-0.0038 (10)
C6	0.0287 (12)	0.0336 (12)	0.0324 (12)	-0.0003 (9)	0.0012 (9)	-0.0004 (10)
C7	0.0266 (11)	0.0266 (11)	0.0298 (11)	-0.0041 (9)	-0.0030 (8)	0.0022 (9)
C8	0.0280 (11)	0.0276 (11)	0.0272 (11)	-0.0029 (9)	-0.0028 (8)	0.0023 (9)
C9	0.0232 (10)	0.0276 (11)	0.0296 (11)	-0.0029 (8)	0.0000 (8)	0.0036 (9)
C10	0.0249 (11)	0.0317 (11)	0.0291 (12)	-0.0042 (9)	-0.0005 (9)	0.0012 (9)
C11	0.0265 (11)	0.0307 (12)	0.0293 (12)	0.0020 (9)	0.0023 (9)	0.0038 (10)
C12	0.0249 (10)	0.0253 (10)	0.0243 (11)	-0.0004 (8)	0.0020 (8)	0.0037 (9)
C13	0.0340 (12)	0.0283 (11)	0.0280 (12)	-0.0008 (9)	0.0033 (9)	-0.0011 (9)
C14	0.0348 (13)	0.0336 (12)	0.0379 (13)	-0.0066 (10)	-0.0014 (10)	-0.0061 (10)
C15	0.0260 (11)	0.0416 (14)	0.0510 (15)	-0.0018 (10)	-0.0023 (10)	-0.0088 (12)
C16	0.0253 (11)	0.0343 (12)	0.0448 (14)	0.0009 (9)	0.0025 (10)	-0.0079 (10)
C17	0.0290 (11)	0.0258 (11)	0.0269 (11)	-0.0018 (9)	0.0017 (9)	-0.0006 (9)

Geometric parameters (Å, °)

F1—C2	1.366 (2)	C8—C9	1.448 (3)
O1—C9	1.369 (2)	C8—H8	0.9500
O1—C17	1.384 (2)	C9—C10	1.343 (3)
O2—C11	1.237 (2)	C10—C11	1.442 (3)
C1—C2	1.390 (3)	C10—H10	0.9500
C1—C6	1.406 (3)	C11—C12	1.473 (3)
C1—C7	1.460 (3)	C12—C17	1.389 (3)
C2—C3	1.369 (3)	C12—C13	1.404 (3)
C3—C4	1.385 (3)	C13—C14	1.376 (3)
C3—H3	0.9500	C13—H13	0.9500
C4—C5	1.387 (3)	C14—C15	1.395 (3)
C4—H4	0.9500	C14—H14	0.9500
C5—C6	1.375 (3)	C15—C16	1.371 (3)
C5—H5	0.9500	C15—H15	0.9500
C6—H6	0.9500	C16—C17	1.390 (3)
C7—C8	1.335 (3)	C16—H16	0.9500
C7—H7	0.9500		

C9—O1—C17	118.68 (15)	C10—C9—C8	123.57 (18)
C2—C1—C6	115.30 (18)	O1—C9—C8	113.93 (17)
C2—C1—C7	121.23 (18)	C9—C10—C11	122.99 (18)
C6—C1—C7	123.47 (19)	C9—C10—H10	118.5
F1—C2—C3	118.06 (18)	C11—C10—H10	118.5
F1—C2—C1	117.38 (18)	O2—C11—C10	123.91 (18)
C3—C2—C1	124.56 (19)	O2—C11—C12	122.41 (18)
C2—C3—C4	118.1 (2)	C10—C11—C12	113.68 (17)
C2—C3—H3	120.9	C17—C12—C13	117.83 (17)
C4—C3—H3	120.9	C17—C12—C11	120.34 (18)
C3—C4—C5	120.1 (2)	C13—C12—C11	121.83 (18)
C3—C4—H4	119.9	C14—C13—C12	120.75 (19)
C5—C4—H4	119.9	C14—C13—H13	119.6
C6—C5—C4	120.1 (2)	C12—C13—H13	119.6
C6—C5—H5	119.9	C13—C14—C15	119.6 (2)
C4—C5—H5	119.9	C13—C14—H14	120.2
C5—C6—C1	121.8 (2)	C15—C14—H14	120.2
C5—C6—H6	119.1	C16—C15—C14	121.13 (19)
C1—C6—H6	119.1	C16—C15—H15	119.4
C8—C7—C1	124.71 (18)	C14—C15—H15	119.4
C8—C7—H7	117.6	C15—C16—C17	118.51 (19)
C1—C7—H7	117.6	C15—C16—H16	120.7
C7—C8—C9	125.90 (19)	C17—C16—H16	120.7
C7—C8—H8	117.1	O1—C17—C12	121.81 (17)
C9—C8—H8	117.1	O1—C17—C16	116.06 (17)
C10—C9—O1	122.50 (18)	C12—C17—C16	122.13 (19)
C6—C1—C2—F1	-178.85 (16)	C9—C10—C11—O2	179.6 (2)
C7—C1—C2—F1	2.0 (3)	C9—C10—C11—C12	-0.4 (3)
C6—C1—C2—C3	0.5 (3)	O2—C11—C12—C17	-179.08 (19)
C7—C1—C2—C3	-178.62 (18)	C10—C11—C12—C17	0.9 (2)
F1—C2—C3—C4	179.05 (18)	O2—C11—C12—C13	1.1 (3)
C1—C2—C3—C4	-0.3 (3)	C10—C11—C12—C13	-178.86 (18)
C2—C3—C4—C5	-0.1 (3)	C17—C12—C13—C14	1.1 (3)
C3—C4—C5—C6	0.3 (3)	C11—C12—C13—C14	-179.08 (18)
C4—C5—C6—C1	-0.1 (3)	C12—C13—C14—C15	-0.2 (3)
C2—C1—C6—C5	-0.3 (3)	C13—C14—C15—C16	-0.7 (3)
C7—C1—C6—C5	178.82 (19)	C14—C15—C16—C17	0.7 (3)
C2—C1—C7—C8	-168.4 (2)	C9—O1—C17—C12	0.3 (3)
C6—C1—C7—C8	12.5 (3)	C9—O1—C17—C16	-179.66 (17)

C1—C7—C8—C9	-179.67 (18)	C13—C12—C17—O1	178.85 (17)
C17—O1—C9—C10	0.3 (3)	C11—C12—C17—O1	-0.9 (3)
C17—O1—C9—C8	-179.59 (16)	C13—C12—C17—C16	-1.2 (3)
C7—C8—C9—C10	178.4 (2)	C11—C12—C17—C16	179.04 (18)
C7—C8—C9—O1	-1.8 (3)	C15—C16—C17—O1	-179.73 (19)
O1—C9—C10—C11	-0.2 (3)	C15—C16—C17—C12	0.3 (3)
C8—C9—C10—C11	179.63 (18)		

Hydrogen-bond geometry (Å, °)

D—H···A	D—H	H···A	D···A	D—H···A
C7—H7···O1	0.95	2.46	2.791(2)	100

2-F 1st step proton in CDCL3

7.4024
7.3982
7.3885
7.3864
7.3695
7.3676
7.3508
7.3486
7.2771
7.2407
7.2317
7.2300
7.2221
7.2117
7.2098
7.2043
7.1801
7.1787
7.1567
7.1541
7.1324
7.1310
6.8265
6.7859

2.5926

A-3a

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

0.9544
0.9794
2.1348
2.0819
2.0029
1.0884
0.9592
3.0000

8   7   6   5   4   3   [ppm]

^{1}H NMR Spectrum of 2-(2'-Fluorocinnamoyloxy) acetophenone (A-3a)

2-F 1st step proton in CDCL3

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

A-3a

Peak labels (ppm): 8.0260, 7.9855, 7.8306, 7.8267, 7.8110, 7.8070, 7.6171, 7.6132, 7.5981, 7.5944, 7.5793, 7.5753, 7.5697, 7.5654, 7.5499, 7.5465, 7.5308, 7.5267, 7.4133, 7.4042, 7.3989, 7.3792, 7.3743, 7.3652, 7.3610, 7.3513, 7.3492, 7.3323, 7.3304, 7.3136, 7.3114, 7.2399, 7.2035, 7.1945, 7.1928, 7.1849, 7.1745, 7.1726, 7.1671, 7.1429, 7.1415, 7.1195, 7.1169, 7.0952, 7.0938, 6.7893, 6.7487

Integration values: 0.9595, 0.9841, 2.1459, 2.1026, 1.8559, 1.1063, 0.9799

Expanded ^{1}H NMR Spectrum of 2-(2'-Fluorocinnamoyloxy) acetophenone (A-3a)

2-F 1st step 13C in CDCL3

A-3a

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

^{13}C NMR Spectrum of 2-(2'-Fluorocinnamoyloxy) acetophenone (A-3a)

2-F 1st step 13C in CDCL3

Expanded ^{13}C NMR Spectrum of 2-(2'-Fluorocinnamoyloxy) acetophenone (A-3a)

2-F 1st step F-19 in CDCL3

A-3a

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

—-113.5796

0   - 50   - 100   - 150   - 200   [ppm]

^{19}F NMR Spectrum of 2-(2'-Fluorocinnamoyloxy) acetophenone (A-3a)

COSY Spectrum of 2-(2'-Fluorocinnamoyloxy) acetophenone (A-3a)

HSQC Spectrum of 2-(2'-Fluorocinnamoyloxy) acetophenone (A-3a)

HMBC Spectrum of 2-(2'-Fluorocinnamoyloxy) acetophenone (A-3a)

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

NOESY Spectrum of 2-(2'-Fluorocinnamoyloxy) acetophenone (A-3a)

IR Spectrum of 2-(2'-Fluorocinnamoyloxy) acetophenone (A-3a)

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

A-3a

c:\pel_data\spectra\asif ir data\2-f 1st step

Peak labels: 1682.41, 1627.88, 1483.51, 1456.02, 1423.42, 1312.06, 1284.80, 1227.00, 1146.87, 1091.45, 986.91, 928.61, 875.97, 796.68, 753.74, 694.71, 593.66, 566.98, 502.99, 483.38, 454.36

MS Spectrum of 2-(2'-Fluorocinnamoyloxy) acetophenone (A-3a)

3-F 1st step proton in cdcl3

7.3188
7.3166
7.2940
7.2892
7.2698
7.2637
7.2401
7.1858
7.1841
7.1658
7.1639
7.1347
7.1304
7.1252
7.1141
7.1083
7.0968
7.0905
7.0846
6.6698
6.6300

2.5506

A-3b

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

1.9443
1.0258
2.9703
1.0169
0.9866
0.9902
0.9715
3.0000

^{1}H NMR Spectrum of 2-(3'-Fluorocinnamoyloxy) acetophenone (A-3b)

Expanded ^{1}H NMR Spectrum of 2-(3'-Fluorocinnamoyloxy) acetophenone (A-3b)

13C NMR Spectrum of 2-(3'-Fluorocinnamoyloxy) acetophenone (A-3b)

3-F 1st 13C in CDCL3

Expanded 13C NMR Spectrum of 2-(3'-Fluorocinnamoyloxy) acetophenone (A-3b)

3-F 1s step F19 in cdcl3

−−112.2725

A-3b

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

^{19}F NMR Spectrum of 2-(3'-Fluorocinnamoyloxy) acetophenone (A-3b)

May20-2012-NK-Asif 13 1 /opt/topspin NK

3-F 1s step COESY in cdcl3

A-3b

Chemical Formula: C$_{17}$H$_{13}$FO$_3$
Exact Mass: 284.0849

COSY Spectrum of 2-(3'-Fluorocinnamoyloxy) acetophenone (A-3b)

HSQC Spectrum of 2-(3'-Fluorocinnamoyloxy) acetophenone (A-3b)

HMBC Spectrum of 2-(3'-Fluorocinnamoyloxy) acetophenone (A-3b)

A-3b

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

3-F 1s step NOESY in cdcl3

A-3b

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

NOESY Spectrum of 2-(3'-Fluorocinnamoyloxy) acetophenone (A-3b)

IR Spectrum of 2-(3'-Fluorocinnamoyloxy) acetophenone (A-3b)

c:\pel_data\spectra\asif ir data\3-f 1st step.s[

File   : C:\MSDCHEM\1\DATA\ASIF DATA\NEW DATA\ASIF\3-F\3-F1ST.D
Operator   : Mehbub
Acquired   : 16 Jun 2011 13:52   using AcqMethod NATURAL
Instrument :   Instrumen
Sample Name: 3-F 1st step sample
Misc Info   :
Vial Number: 1

MS Spectrum of 2-(3'-Fluorocinnamoyloxy) acetophenone (A-3b)

Scan 1880 (20.136 min): 3-F1ST.D

A-3b

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

4-F 1st step proton sample in CDCL3

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

Expanded ^{1}H NMR Spectrum of 2-(4'-Fluorocinnamoyloxy) acetophenone (A-3c)

4-F 1st step 13C sample in CDC13

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

Peaks: 197.7862; 165.5080, 165.1454, 163.0010; 149.0755, 145.9950, 133.3677, 131.3059, 130.4323, 130.3486, 130.3155, 130.1540, 126.1052, 123.7827, 116.6004, 116.5767, 116.3128, 116.0943; 29.7168

^{13}C NMR Spectrum of 2-(4'-Fluorocinnamoyloxy) acetophenone (A-3c)

4-F 1st step 13C sample in CDCl3

A-3c

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

Peak labels: 197.7862, 165.5080, 165.1454, 163.0010, 149.0755, 145.9950, 133.3677, 131.3059, 130.4323, 130.3486, 130.3155, 130.1540, 126.1052, 123.7827, 116.6004, 116.5767, 116.3128, 116.0943

ppm axis: 180, 160, 140, 120 [ppm]

Expanded ^{13}C NMR Spectrum of 2-(4'-Fluorocinnamoyloxy) acetophenone (A-3c)

4-F 1st step F-19 sample in CDCL3

−108.5428

A-3c

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

0   − 50   − 100   − 150   − 200   [ppm]

^{19}F NMR Spectrum of 2-(4'-Fluorocinnamoyloxy) acetophenone (A-3c)

IR Spectrum of 2-(4'-Fluorocinnamoyloxy) acetophenone (A-3c)

c:\pel_data\spectra\asif ir data\4-f

File   : C:\MSDCHEM\1\DATA\ASIF DATA\ASIF\4F1ST.D
Operator : ASIF
Acquired : 8 Jun 2011 14:20   using AcqMethod NATURAL
Instrument : Instrumen
Sample Name: 4-F 1st step
Misc Info :
Vial Number: 1

Abundance

Scan 1906 (20.275 min): 4F1ST.D

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

A-3c

320000
310000
300000
290000
280000
270000
260000
250000
240000
230000
220000
210000
200000
190000
180000
170000
160000
150000
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0

43
51
63
75
83
92
101
109
121
136
149
157 165
175
183
196
207 215 225 233
241
256
269
284

m/z--> 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300 30

MS Spectrum of 2-(4'-Fluorocinnamoyloxy) acetophenone (A-3c)

3,5-F 1st step proton in CDCl3

Peak list: 7.8310, 7.8270, 7.8114, 7.8075, 7.7726, 7.7327, 7.5725, 7.5683, 7.5529, 7.5493, 7.5338, 7.5295, 7.3607, 7.3588, 7.3418, 7.3400, 7.3230, 7.3211, 7.2355, 7.1761, 7.1745, 7.1545, 7.1088, 7.0964, 7.0916, 7.0766, 7.0718, 7.0598, 6.8817, 6.8759, 6.8704, 6.8600, 6.8543, 6.8486, 6.8382, 6.8327, 6.8270, 6.6581, 6.6183

2.5439

Structure label: A-3d

Chemical Formula: $C_{17}H_{12}F_2O_3$
Exact Mass: 302.0755

Integration values: 0.0243, 1.0072, 1.0237, 1.8650, 0.9794, 1.0000, 3.0047

15   10   5   0   [ppm]

^{1}H NMR Spectrum of 2-(3',5'-Difluorocinnamoyloxy) acetophenone (A-3d)

3,5-F 1st step proton in CDCl3

Expanded ^{1}H NMR Spectrum of 2-(3',5'-Difluorocinnamoyloxy) acetophenone (A- 3d)

3,5-F 1st step ~~proton~~ in CDCl3

13C

197.6052

164.5834
164.4653
162.0070
148.8653
144.4991
144.4710
144.4425
137.3682
137.2738
137.1784
133.4716
131.0076
130.2845
126.2697
123.7476
119.7252
111.1564
111.0846
110.9684
110.8973
110.1788
105.9244
105.6722

29.5164

Chemical Formula: $C_{17}H_{12}F_2O_3$
Exact Mass: 302.0755

A-3d

C-1
C=O
3"
2'
β
1"
1
4
6'
5'
3'
α
2" 6"
C-4"
C-2

200   150   100   50   0   [ppm]

^{13}C NMR Spectrum of 2-(3',5'-Difluorocinnamoyloxy) acetophenone (A-3d)

3,5-F 1st step proton in CDCl3

¹³C

Chemical Formula: $C_{17}H_{12}F_2O_3$
Exact Mass: 302.0755

Peak labels: 197.6052; 164.5834; 164.4653; 162.0070; 148.8653; 144.4991; 144.4710; 144.4425; 137.3682; 137.2738; 137.1784; 133.4716; 131.0076; 130.2845; 126.2697; 123.7476; 119.7252; 111.1564; 111.0846; 110.9684; 110.8973; 106.1788; 105.9244; 105.6722

Expanded ¹³C NMR Spectrum of 2-(3',5'-Difluorocinnamoyloxy) acetophenone (A-3d)

Jul28-2011-NK-Asif 22 1 C:\Bruker\TOPSPIN guest

3,5-F 1st step proton in CDCl3

144.4991
144.4710
144.4425

β

3,5-F 1st step proton in CDCl3

Jul28-2011-NK-Asif 22 1 C:\Bruker\TOPSPIN guest

3,5-F 1st step proton in CDCl3

3,5-F 1st step F-19 in CDC13

Chemical Formula: $C_{17}H_{12}F_2O_3$
Exact Mass: 302.0755

A-3d

−108.7580

−95 −100 −105 −110 −115 −120 [ppm]

^{19}F NMR Spectrum of 2-(3',5'-Difluorocinnamoyloxy) acetophenone (A-3d)

COSY Spectrum of 2-(3',5'-Difluorocinnamoyloxy) acetophenone (A-3d)

HSQC Spectrum of 2-(3',5'-Difluorocinnamoyloxy) acetophenone (A-3d)

HMBC Spectrum of 2-(3',5'-Difluorocinnamoyloxy) acetophenone (A-3d)

A-3d

Chemical Formula: $C_{17}H_{12}F_2O_3$
Exact Mass: 302.0755

3,5-1st step noesy in CDCL3

α/6"

3'/4'

5'/6'

NOESY Spectrum of 2-(3',5'-Difluorocinnamoyloxy) acetophenone (A-3d)

A-3d

Chemical Formula: $C_{17}H_{12}F_2O_3$

Exact Mass: 302.0755

Chemical Formula: $C_{17}H_{12}F_2O_3$
Exact Mass: 302.0755

A-3d

IR Spectrum of 2-(3',5'-Difluorocinnamoyloxy) acetophenone (A-3d)

c:\pei_data\spectra\asif ir data\3,5-f 1st

Abundance

Scan 1825 (19.583 min): 35-F1.D

620000
600000
580000
560000
540000
520000
500000
480000
460000
440000
420000
400000
380000
360000
340000
320000
300000
280000
260000
240000
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0

m/z--> 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300 310 320 32

43
53
63
77
87
99
108
119
131
139
148
157
167
183
193
201
214
230
243
258
274
287
302
311 320

Chemical Formula: $C_{17}H_{12}F_2O_3$
Exact Mass: 302.0755

A-3d

MS Spectrum of 2-(3',5'-Difluorocinnamoyloxy) acetophenone (A-3d)

4,4-F 1st step proton in CDC13

7.8833
7.8680
7.8614
7.8456
7.8286
7.5984
7.5937
7.5849
7.5766
7.5683
7.5633
7.2401
7.1256
7.1213
7.1041
7.0826
7.0765
7.0604
7.0544
7.0403
7.0384
7.0345
7.0193
7.0131
6.9423
6.9362
6.9199
6.9137
6.5851
6.5453

2.5326

A-3e

Chemical Formula: $C_{17}H_{12}F_2O_3$
Exact Mass: 302.0755

1.9468   1.9207   3.1596 0.9169   0.9508   3.0000

10   8   6   4   [ppm]

^{1}H NMR Spectrum of 4-fluoro-2-(4'-Fluorocinnamoyloxy) acetophenone (A-3e)

4-F 1st step proton sample in CDCL3

7.5626
7.5577
7.5472
7.5439
7.5278
7.5239
7.3489
7.3303
7.3117
7.3098
7.2390
7.1822
7.1621
7.1178
7.0964
7.0749

6.6009
6.5610

2.5489

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

A-3c

β 6'

4'
2''/6''

5'

3'

3''/5''

α

2

2.0758

3.3200

1.0661

1.0181
2.1772

1.0422

3.0000

8   7   6   5   4   3   [ppm]

^{1}H NMR Spectrum of 2-(4'-Fluorocinnamoyloxy) acetophenone (A-3c)

4,4-F 1st step proton in CDCl3

7.8833
7.8680
7.8614
7.8456
7.8286

7.5984
7.5937
7.5849
7.5766
7.5683
7.5633

7.2401

7.1256
7.1213
7.1041
7.0826
7.0765
7.0604
7.0544
7.0403
7.0384
7.0345
7.0193
7.0131
7.0131

6.9423
6.9362
6.9199
6.9137

6.5851
6.5453

β 6'

2'' 6''

3'' 5''

5'

3'

α

1.9468

1.9207

3.1596

0.9169

0.9508

A-3e

Chemical Formula: C$_{17}$H$_{12}$F$_2$O$_3$
Exact Mass: 302.0755

Expanded ^{1}H NMR Spectrum of 4-fluoro-2-(4'-Fluorocinnamoyloxy) acetophenone

(A-3e)

4,4-F 1st 13C in CDCL3

Chemical Formula: $C_{17}H_{12}F_2O_3$
Exact Mass: 302.0755

A-3e

^{13}C NMR Spectrum of 4-fluoro-2-(4'-Fluorocinnamoyloxy) acetophenone (A-3e)

4,4-F 1st 13C in CDCL3

166.2539
165.6128
164.6614
163.7132
163.1033

150.9590
150.8468

146.5559
145.5276

132.2614
132.1595
130.5219
130.4368
130.2812
130.1965
130.1621
127.6479
127.6119

116.3710
116.2681
116.1520
116.1124
116.0902
113.4606
113.2487
111.8313
111.5919

[*1e6]

A-3e

Chemical Formula: C₁₇H₁₂F₂O₃

$Chemical\ Formula:\ C_{17}H_{12}F_2O_3$

Exact Mass: 302.0755

2″/6″

α

3″/5″

6′

1″

β

1′

2′

5′

3′

4′

C=O

4″

Expanded ¹³C NMR Spectrum 4-fluoro-2-(4'-Fluorocinnamoyloxy) acetophenone (A-3e)

4,4-F 1st step proton in CDC13

−103.7921
−103.8125
−103.8330
−108.1720

A-3e

Chemical Formula: $C_{17}H_{12}F_2O_3$
Exact Mass: 302.0755

[rel]

0   − 50   − 100   − 150   − 200   [ppm]

^{19}F NMR Spectrum of 4-fluoro-2-(4'-Fluorocinnamoyloxy) acetophenone (A-3e)

COSY Spectrum of 4-fluoro-2-(4'-Fluorocinnamoyloxy) acetophenone (A-3e)

HSQC Spectrum of 4-fluoro-2-(4'-Fluorocinnamoyloxy) acetophenone (A-3e)

HMBC Spectrum of 4-fluoro-2-(4'-Fluorocinnamoyloxy) acetophenone (A-3e)

NOESY Spectrum of 4-fluoro-2-(4'-Fluorocinnamoyloxy) acetophenone (A-3e)

c:\pel_data\spectra\asif ir data\4,4-f 1st   IR Spectrum of 4-fluoro-2-(4'-Fluorocinnamoyloxy) acetophenone (A-3e)

File   : C:\MSDCHEM\1\DATA\ASIF DATA\NEW DATA\ASIF\44-F\4F4F1ST.D
Operator   : Mehbub
Acquired   : 17 Jun 2011 16:35   using AcqMethod NATURAL
Instrument :   Instrumen
Sample Name: 4F4F 1st step sample
Misc Info :
Vial Number: 1

Scan 1866 (20.016 min): 4F4F1ST.D

A-3e

Chemical Formula: $C_{17}H_{12}F_2O_3$
Exact Mass: 302.0755

4-F acetophenone 1st step proton in CDCL3

7.9347
7.9093
7.8821
7.8689
7.8603
7.8444
7.5964
7.5916
7.5824
7.5727
7.4230
7.4181
7.4099
7.4059
7.3957
7.2399
7.0551
7.0489
7.0351
7.0333
7.0292
7.0140
7.0078
6.9481
6.9420
6.9256
6.9194
6.6597
6.6198

2.5325

A-3f

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

β
6' 2" 6"
3",4",5"
2
α

1.2535
1.4999
1.5027
1.7020
2.1637
0.9862
0.9589
1.0000
2.6318

8   7   6   5   4   3   [ppm]

^{1}H NMR Spectrum of 4-fluoro-2-cinnamoyloxy acetophenone (A-3f)

4-F acetophenone 1st step proton in CDCL3

A-3f

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

Expanded ^{1}H NMR Spectrum of 4-fluoro-2-cinnamoyloxy acetophenone (A-3f)

4-F acetophenone 1st step 13C in CDCL3

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

^{13}C NMR Spectrum of 4-fluoro-2-cinnamoyloxy acetophenone (A-3f)

4-F acetophenone 1st step 13C in CDCL3

Expanded ^{13}C NMR Spectrum of 4-fluoro-2-cinnamoyloxy acetophenone (A-3f)

4-F acetophenone 1st step F-19 in CDCL3

-103.9176

A-3f

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

0   - 50   - 100   - 150   - 200   [ppm]

^{19}F NMR Spectrum of 4-fluoro-2-cinnamoyloxy acetophenone (A-3f)

IR Spectrum of 4-fluoro-2-cinnamoyloxy acetophenone (A-3f)

c:\pel_data\spectra\asif ir data\4-f acetophenone 1st

MS Spectrum of 4-fluoro-2-cinnamoyloxy acetophenone (A-3f)

File   : C:\MSDCHEM\1\DATA\ASIF DATA\ASIF\4FACE1.D
Operator : ASIF
Acquired : 10 Jun 2011 13:38   using AcqMethod NATURAL
Instrument : Instrumen
Sample Name: 4-F acetophenone 1st step sample
Misc Info :
Vial Number: 1

Scan 1860 (19.965 min): 4FACE1.D

Abundance

A-3f
Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

5-F Acetophenone 1st step in CDCL3

7.5100
7.5024
7.4882
7.4808
7.4220
7.4177
7.4086
7.3935
7.3855
7.3770
7.2606
7.2530
7.2375
7.2203
7.2127
7.1716
7.1600
7.1494
7.1379
6.6590
6.6190

2.5363

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

A-3g

β

2''6''

3'

3''5''4''

4'

6'

α

X

1.0266
1.9797
1.1937
3.3004
0.9493
0.9549
3.0000

^{1}H NMR Spectrum of 5-fluoro-2-cinnamoyloxy acetophenone (A-3g)

5-F Acetophenone 1st step in CDCL3

7.9025
7.8625

7.5890
7.5794
7.5704
7.5100
7.5024
7.4882
7.4808
7.4220
7.4177
7.4086
7.3935
7.3855
7.3770

7.2606
7.2530
7.2375
7.2203
7.2127
7.1716
7.1600
7.1494
7.1379

6.6590
6.6190

A-3g

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

β

2''6''

3'

3'5''4''

4'

6'

α

1.0266

1.9797

1.1937

3.3004

0.9493

0.9549

7.8   7.6   7.4   7.2   7.0   6.8   6.6   [ppm]

Expanded ^{1}H NMR Spectrum of 5-fluoro-2-cinnamoyloxy acetophenone (A-3g)

5-F Acetophenone 13C 1st step in CDCL3

165.2339
161.1366
158.6843
147.8014
145.0542
133.9000
132.6662
132.6041
131.0496
130.6709
129.0457
129.0590
128.9852
128.4852
128.3005
125.4824
125.4032
120.2110
119.9784
116.6181
116.4133
116.3771
77.3320
77.2177
77.0141
76.6972
29.7881

A-3g

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

C2

^{13}C NMR Spectrum of 5-fluoro-2-cinnamoyloxy acetophenone (A-3g)

Expanded ^{13}C NMR Spectrum of 5-fluoro-2-cinnamoyloxy acetophenone (A-3g)

S-F Acetophenone F19 1st step in CDCL3

-115.3515
-115.3638

A-3g

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

− 90   − 100   − 110   − 120   − 130   [ppm]

[rel]

^{19}F NMR Spectrum of 5-fluoro-2-cinnamoyloxy acetophenone (A-3g)

COSY Spectrum of 5-fluoro-2-cinnamoyloxy acetophenone (A-3g)

5-F Acetophenone HSQC 1st step in CDCL3

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

A-3g

F1 [ppm]

F2 [ppm]

HSQC Spectrum of 5-fluoro-2-cinnamoyloxy acetophenone (A-3g)

HMBC Spectrum of 5-fluoro-2-cinnamoyloxy acetophenone (A-3g)

NOESY Spectrum of 5-fluoro-2-cinnamoyloxy acetophenone (A-3g)

IR Spectrum of 5-fluoro-2-cinnamoyloxy acetophenone (A-3g)

A-3g

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

c:\pel_data\spectra\asif ir data\5-f acetophenone

File   : C:\MSDCHEM\1\DATA\ASIF DATA\NEW DATA\ASIF\5-F ACETOPHENONE\5-FACE1.D
Operator   : Mehbub
Acquired   : 19 Jul 2011   12:37   using AcqMethod NATURAL
Instrument :   Instrumen
Sample Name: 5-F acetophenone 1 st step sample
Misc Info :
Vial Number: 1

MS Spectrum of 5-fluoro-2-cinnamoyloxy acetophenone (A-3g)

Scan 3545 (34.359 min): 5-FACE1.D

A-3g

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

4-OMe 1st step proton sample in CDC13

Chemical Formula: $C_{18}H_{16}O_4$
Exact Mass: 296.1049

A-3h

^{1}H NMR Spectrum of 2-(4'-methoxycinnamoyloxy) acetophenone (A-3h)

Expanded ^{1}H NMR Spectrum of 2-(4'-methoxycinnamoyloxy) acetophenone (A-3h)

4-OMe 1st step 13C sample in CDC13

Chemical Formula: $C_{18}H_{16}O_4$
Exact Mass: 296.1049

Peak labels: 197.9039, 165.5390, 161.9100, 149.2879, 147.1512, 133.2679, 131.5400, 130.2287, 130.0441, 126.7868, 125.9523, 123.8104, 114.4802, 114.1079, 55.4345, 29.9275

Handwritten assignments: 3''5'', 2''6'', β, 4', 6', 5', 3', α, OMe, c-2, c-1, c=0, 4'', 2', 2'

200 150 100 50 [ppm]

^{13}C NMR Spectrum of 2-(4'-methoxycinnamoyloxy) acetophenone (A-3h)

COSY Spectrum of 2-(4'-methoxycinnamoyloxy) acetophenone (A-3h)

4-OMe 1st hsqc in CDCl3

A-3h

Chemical Formula: $C_{18}H_{16}O_4$
Exact Mass: 296.1049

HSQC Spectrum of 2-(4'-methoxycinnamoyloxy) acetophenone (A-3h)

HMBC Spectrum of 2-(4'-methoxycinnamoyloxy) acetophenone (A-3h)

A-3h

Chemical Formula: $C_{18}H_{16}O_4$
Exact Mass: 296.1049

NOESY Spectrum of 2-(4'-methoxycinnamoyloxy) acetophenone (A-3h)

IR Spectrum of 2-(4'-methoxycinnamoyloxy) acetophenone (A-3h)

c:\pel_data\spectra\4-ome 1st step.sp - 4-OMe

Chemical Formula: $C_{18}H_{16}O_4$
Exact Mass: 296.1049

A-3h

Labeled peaks: 1711.59, 1680.54, 1600.27, 1508.99, 1419.36, 1245.92, 1168.32, 1136.77, 1072.23, 1029.89, 969.28, 923.97, 824.57, 768.51, 608.58, 556.17, 513.03

MS Spectrum of 2-(4'-methoxycinnamoyloxy) acetophenone (A-3h)

3,4-OMe 1st step proton in CDCl3

7.5383
7.5224
7.5186
7.3399
7.3382
7.3194
7.3023
7.3004
7.2401
7.1810
7.1756
7.1706
7.1618
7.1604
7.1548
7.1500
7.1094
7.1049
6.8902
6.8696
6.5430
6.5035

3.9179

2.5543

OMe x 2

β δ'

4'

5' 3''6'' 2''

5''

α'

Chemical Formula: $C_{19}H_{18}O_5$
Exact Mass: 326.1154

A-3i

1.9715

1.0127

0.9829

2.0132
1.0129

1.0283

0.9853

6.5886

3.0000

8   7   6   5   4   3   [ppm]

^{1}H NMR Spectrum of 2-(3',4'-methoxycinnamoyloxy) acetophenone (A-3i)

Expanded ^{1}H NMR Spectrum of 2-(3',4'-methoxycinnamoyloxy) acetophenone (A- 3i)

^{13}C NMR Spectrum of 2-(3',4'-methoxycinnamoyloxy) acetophenone (A-3i)

COSY Spectrum of 2-(3',4'-methoxycinnamoyloxy) acetophenone (A-3i)

HSQC Spectrum of 2-(3',4'-methoxycinnamoyloxy) acetophenone (A-3i)

HMBC Spectrum of 2-(3',4'-methoxycinnamoyloxy) acetophenone (A-3i)

NOESY Spectrum of 2-(3',4'-methoxycinnamoyloxy) acetophenone (A-3i)

IR Spectrum of 2-(3',4'-methoxycinnamoyloxy) acetophenone (A-3i)

File   : C:\MSDCHEM\1\DATA\ASIF DATA\ASIF\34OME1.D
Operator   : ASIF
Acquired   : 8 Jun 2011 12:05   using AcqMethod NATURAL
Instrument   : Instrumen
Sample Name : 3,4OMe 1st step
Misc Info   :
Vial Number : 1

Abundance

Scan 2810 (27.997 min): 34OME1.D

MS Spectrum of 2-(3',4'-methoxycinnamoyloxy) acetophenone (A-3i)

A-3i

Chemical Formula: $C_{19}H_{18}O_5$
Exact Mass: 326.1154

3,4 Metheyledioxy 1st step proton in CDCL3

Chemical Formula: $C_{18}H_{14}O_5$
Exact Mass: 310.0841

^{1}H NMR Spectrum of 2-(3',4'-methylenedioxycinnamoyloxy) acetophenone (A-3j)

3,4 Metheyledioxy 1st step proton in CDCL3

Expanded ^{1}H NMR Spectrum of 2-(3',4'-methylenedioxycinnamoyloxy) acetophenone (A-3j)

3,4 Metheyledioxy 1st step 13C in CDCL3

197.8473

165.3987

150.1723
149.2166
148.4784
147.1169
133.2886
131.4732
130.0672
128.4926
125.9910
125.1837
123.7948

114.6064

108.6462
106.7048

101.7039

29.8656

A-3j

Chemical Formula: $C_{18}H_{14}O_5$
Exact Mass: 310.0841

^{13}C NMR Spectrum of 2-(3',4'-methylenedioxycinnamoyloxy) acetophenone (A-3j)

IR Spectrum of 2-(3',4'-methylenedioxycinnamoyloxy) acetophenone (A-3j)

Chemical Formula: $C_{18}H_{14}O_5$
Exact Mass: 310.0841

A-3j

c:\pel_data\spectra\3,4- methelendioxy 1st st·

MS Spectrum of 2-(3',4'-methylenedioxycinnamoyloxy) acetophenone (A-3j)

2-F 2nd step in cdcl3

14.5563

12.1765

7.7534
7.7134
7.7025
7.6991
7.6823
7.6790
7.5618
7.5581
7.5426
7.5391
7.5238
7.5201
7.4606
7.4570
7.4394
7.4217
7.4182
7.4400
7.3381
7.2400
7.1825
7.1637
7.1449
7.1265
7.1034
7.0990
7.0976
7.0770
6.9833
6.9637
6.9620
6.9060
6.9043
6.8857
6.8675
6.8654
6.7249
6.6849
6.3248

A-4a

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

3 OH

2' OH

3 OH

0.9095

1.0000

1.9693
3.616
0.9670
1.2398
1.3681
0.9930
0.9465

0.9628

14   12   10   8   6 [ppm]

^{1}H NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(2-fluorophenyl)-2,4-
pentadien-1-one (A-4a)

Expanded ¹H NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(2-fluorophenyl)-2,4-pentadien-1-one (A-4a)

2-F 2nd step 13C in cdcl3

196.4792
174.0275
162.6392
160.1490
139.2694
136.1851
132.6856
132.1667
131.3807
129.2750
128.5633
124.9006
124.8116
124.5002
124.1953
123.1953
123.0619
119.0508
118.7690
116.4039
116.1963
97.4169

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

A-4a

200   150   100   50   0   [ppm]

^{13}C NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(2-fluorophenyl)-2,4-pentadien-1-one (A-4a)

2-F 2nd step 13C in cdcl3

Expanded ^{13}C NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(2-fluorophenyl)-2,4-pentadien-1-one (A-4a)

2-F 2nd step F-19 in cdcl3

−114.1812

^{19}F NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(2-fluorophenyl)-2,4-pentadien-1-one (A-4a)

COSY Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(2-fluorophenyl)-2,4-pentadien-

1-one (A-4a)

NOESY Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(2-fluorophenyl)-2,4-pentadien-

1-one (A-4a)

HSQC Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(2-fluorophenyl)-2,4-pentadien-

1-one (A-4a)

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

A-4a

c:\pel_data\spectra\asif ir data\2 nd step samp

IR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(2-fluorophenyl)-2,4-pentadien-1-one (A-4a)

Peak labels: 2833.72, 2601.40, 1913.20, 1680.39, 1626.73, 1581.00, 1483.60, 1456.28, 1417.42, 1325.17, 1311.80, 1283.34, 1227.20, 1186.34, 1148.16, 1091.05, 1033.40, 987.32, 971.62, 927.42, 874.72, 796.01, 753.06, 742.03, 693.58, 593.17, 566.86, 537.19, 502.43, 482.95, 453.18

Axis labels: %T, cm-1

File : C:\MSDCHEM\1\DATA\ASIF DATA\NEW DATA\ASIF\2-F REPEATE\2-F2ND.D
Operator : Mehbub
Acquired : 21 Jun 2011 13:46 using AcqMethod NATURAL
Instrument : Instrumen
Sample Name: 2-F Second step sample
Misc Info :
Vial Number: 1

Scan 2206 (22.921 min): 2-F2ND.D

A-4a
Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

MS Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(2-fluorophenyl)-2,4-pentadien-1-one (A-4a)

3-F 2nd step proton in CDcl3

14.5458

12.1498
7.6974
7.6938
7.6772
7.6736
7.6079
7.5685
7.4689
7.4650
7.4475
7.4300
7.4261
7.3714
7.3664
7.3521
7.3466
7.3325
7.3125
7.2930
7.0833
7.0791
7.0621
7.0583
7.0444
7.0418
7.0381
7.0357
7.0282
6.9900
6.9882
6.9764
6.9686
6.9671
6.9126
6.9104
6.8927
6.8749
6.8726
6.5877
6.5482
6.5389
6.3215

A-4b

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

2'-OH

2

3-OH

1.0313

1.1023

1.1515
2.6000
1.1093
1.0962
1.0991

14   12   10   8   6   4   [ppm]

¹H NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3-fluorophenyl)-2,4-pentadien-1-one (A-4b)

3-F 2nd step proton in CDcl3

7.6974
7.6938
7.6772
7.6736
7.6079
7.5685
7.4689
7.4650
7.4475
7.4300
7.4261
7.3714
7.3664
7.3521
7.3466
7.3325
7.3124
7.2930
7.0833
7.0791
7.0621
7.0583
7.0444
7.0418
7.0381
7.0357
7.0282
6.9900
6.9882
6.9764
6.9686
6.9671
6.9126
6.9104
6.8927
6.8749
6.8726
6.5877
6.5482
6.5389
6.3215

A-4b

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

1.0680
1.1515
1.0882
2.6000
1.2746
1.0644
1.1093
1.0962
1.0991

Expanded ^{1}H NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3-
fluorophenyl)-2,4-pentadien-1-one (A-4b)

3-F 2nd step F-19 in CDcl3

−−112.3253

A-4b

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

0   - 50   - 100   - 150   - 200   [ppm]

^{19}F NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3-fluorophenyl)-2,4-
pentadien-1-one (A-4b)

3-F 2nd step carbon in CDcl3

196.4115

173.7269

164.8733
162.7726

138.3824
136.0718
130.5703
128.6263
124.0692
123.5129
119.0842
118.8488
117.0089
116.7949
114.1634
113.9494

98.0496

A-4b

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

200   150   100   50   0   [ppm]

^{13}C NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3-fluorophenyl)-2,4-
pentadien-1-one (A-4b)

3-F 2nd step carbon in CDcl3

Peak labels: 196.2501, 173.6374, 164.3415, 162.6863, 138.3337, 138.3050, 136.0072, 130.5427, 130.4606, 128.5357, 124.0736, 124.0457, 123.5151, 119.0892, 119.0069, 118.8182, 116.9888, 116.7745, 114.1540, 113.9365, 97.4427

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

A-4b

180   160   140   120   100   [ppm]

Expanded ^{13}C NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3-fluorophenyl)-2,4-pentadien-1-one (A-4b)

COSY Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3-fluorophenyl)-2,4-pentadien-1-one (A-4b)

3-F 2nd step E19 in cdcl3

NoESY

NOESY Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3-fluorophenyl)-2,4-pentadien-1-one (A-4b)

A-4b

Chemical Formula: $C_{17}H_{13}FO_3$

Exact Mass: 284.0849

HSQC Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3-fluorophenyl)-2,4-pentadien-

1-one (A-4b)

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3-F 2nd step HMBC in cdcl3

HMBC Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3-fluorophenyl)-2,4-pentadien-

1-one (A-4b)

A-4b

Chemical Formula: $C_{17}H_{13}FO_3$

Exact Mass: 284.0849

IR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3-fluorophenyl)-2,4-pentadien-1-one (A-4b)

c:\pel_data\spectra\asif ir data\2 nd step s⸱

Scan 4048 (38.655 min): 3-F2ND.D

A-4b

Chemical Formula: $C_{17}H_{13}FO_3$

Exact Mass: 284.0849

MS Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3-fluorophenyl)-2,4-pentadien-1-one (A-4b)

4-F 2nd step proton in CDCl3

— 14.6241

— 12.1765

7.7287
7.6897
7.6875
7.6702
7.6665
7.6223
7.5829
7.5466
7.5406
7.5332
7.5250
7.5170
7.5113
7.5042
7.4604
7.4566
7.4423
7.4390
7.4358
7.4215
7.4178
7.1041
7.0990
7.0826
7.0777
7.0661
7.0611
7.0556
6.9858
6.9837
6.9648
6.9627
6.9051
6.9026
6.8849
6.8672
6.8649
6.5169
6.4774
6.2970

A-4c

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

2^1-OH

3-OH

$3''5''$

$2''6''$

$6'3'$

$4'$

$3'5'$

4

2

0.8312

0.7020

0.8976

0.3000
0.8953

0.8882
0.9002

14   12   10   8   6   [ppm]

^{1}H NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(4-fluorophenyl)-2,4-pentadien-1-one (A-4c)

4-F 2nd step proton in CDCl3

7.6665
7.6223
7.5829
7.5466
7.5406
7.5332
7.5250
7.5170
7.5113
7.5042
7.4604
7.4566
7.4423
7.4390
7.4358
7.4215
7.4178

7.1041
7.0990
7.0826
7.0777
7.0661
7.0611
7.0556
6.9858
6.9837
6.9648
6.9627
6.9051
6.9026
6.8849
6.8672
6.8649

6.5169
6.4774

6.2970

A-4c

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

6'
5
2"6"
4'
3"5"
3'
5'
4
2

1.0123
0.9014
2.3293
0.8976
2.3000
0.8785
0.8953
0.8882
0.9002

7.6 7.4 7.2 7.0 6.8 6.6 6.4 [ppm]

Expanded ^{1}H NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(4-fluorophenyl)-2,4-pentadien-1-one (A-4c)

4-F 2nd step F19 in CDCl3

A-4c

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

−109.5534

0   − 50   − 100   − 150   − 200   [ppm]

^{19}F NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(4-fluorophenyl)-2,4-
pentadien-1-one (A-4c)

4-F 2nd step F19 in CDCl3

196.0378
174.2514
165.0298
162.6467
138.5355
135.8757
131.2734
130.2371
129.8523
129.7711
128.4773
121.8872
119.0446
118.7924
116.2591
116.0420
96.9899

A-4c

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

^{13}C NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(4-fluorophenyl)-2,4-
pentadien-1-one (A-4c)

4-F 2nd step F19 in CDCl3

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

A-4c

196.0378
174.2514
165.0298
162.6467
138.5355
135.8757
131.2734
130.2371
129.8523
129.7711
128.4773
121.8872
119.0446
118.7924
116.2591
116.0420
96.9899

180   160   140   120   100 [ppm]

Expanded ^{13}C NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(4-fluorophenyl)-2,4-pentadien-1-one (A-4c)

COSY Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(4-fluorophenyl)-2,4-pentadien-

1-one (A-4c)

NOESY Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(4-fluorophenyl)-2,4-pentadien-1-one (A-4c)

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4-F 2nd step NOESY in CDCl3

Chemical Formula: C$_{17}$H$_{13}$FO$_3$
Exact Mass: 284.0849

A-4c

HSQC Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(4-fluorophenyl)-2,4-pentadien-

1-one (A-4c)

4-F 2nd step HMBC exapanded spectra in CDCl3

Chemical Formula: C$_{17}$H$_{13}$FO$_3$
Exact Mass: 284.0849

A-4c

HMBC Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(4-fluorophenyl)-2,4-pentadien-

1-one (A-4c)

89.9

85

80
1888.99

75

70
1683.27

65

2824.79

60

55

50

1056.38
%T   45
1033.62

1096.41   864.25   697.60   432.47
40
652.38

1329.52
1627.41   1412.84   1268.72   1129.10   638.40   561.78
35
966.98   411.51

1434.13
1598.77   1296.99   1185.85   952.66   786.63   683.81
30
515.83

1552.56   1234.86   484.26
25
1156.39   505.05   473.16

1572.36
20

1489.00

15
825.65   744.73

OH

A-4c

Chemical Formula: C₁₇H₁₃FO₃
10
Exact Mass: 284.0849

4.0
4000.0   3000   2000   1500   1000   500   380.0

cm-1

c:\pel_data\spectra\asif ir data\2 nd step   **IR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(4-fluorophenyl)-2,4-pentadien-1-**
one (A-4c)

File   : C:\MSDCHEM\1\DATA\ASIF DATA\ASIF\4F2ND.D
Operator : ASIF
Acquired : 8 Jun 2011 14:56   using AcqMethod NATURAL
Instrument : Instrumen
Sample Name: 4-F 2nd step
Misc Info :
Vial Number: 1

Abundance

Scan 2202 (22.887 min): 4F2ND.D

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

A-4c

MS Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(4-fluorophenyl)-2,4-pentadien-
1-one (A-4c)

3,5-F 2nd step proton in CDcl3

−14.4633

−12.1062

7.6912
7.6877
7.6710
7.6674
7.5317
7.4923
7.4762
7.4724
7.4577
7.4549
7.4373
7.4335
7.2400
7.0533
7.0485
7.0331
7.0283
7.0163
6.9924
6.9910
6.9723
6.9707
6.9164
6.9142
6.8964
6.8786
6.8765
6.8334
6.8275
6.8114
6.8059
6.8002
6.7896
6.7841
6.5750
6.5356
6.3296

A-4d

Chemical Formula: $C_{17}H_{12}F_2O_3$
Exact Mass: 302.0755

3OH

2'OH

2

6' 5' 5' 2"|6" 4" 4

1.0000

1.0538

1.0225
1.2087

0.581
0.529
1.2975

1.1192

1.0069

14   12   10   8   [ppm]

^{1}H NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3, 5-difluorophenyl)-2,4-pentadien-1-one (A-4d)

3,5 2nd step 1H in CDCl3

7.6905
7.6869
7.6703
7.6667
7.5306
7.4912
7.4758
7.4721
7.4545
7.4514
7.4369
7.4332
7.2403
7.0528
7.0479
7.0323
7.0275
6.9926
6.9907
6.9715
6.9696
6.9696
6.9165
6.9142
6.8963
6.8785
6.8757
6.8273
6.8111
6.8054
6.8000
6.7837
6.5742
6.5349
6.3288

A-4d

Chemical Formula: $C_{17}H_{12}F_2O_3$
Exact Mass: 302.0755

6'
5
4'
2'6''
3'
5'
4''
4

1.0870
1.0425
1.0078
2.1269
1.1030
1.1744
1.3686
1.1417
1.0111

7.5
7.0
6.5
[ppm]

Expanded ^{1}H NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3, 5-difluorophenyl)-2,4-pentadien-1-one (A-4d)

3,5 2nd step F19 in CDCL3

196.4266

172.8414
164.5917
164.4651
162.7395
162.1148
161.9883

138.3979
138.3032
138.2072
136.9734
136.1752
128.5652
124.8036
119.1460
118.9477
118.8560
110.6111
110.5404
110.4255
110.3554
105.3276
105.0741
104.8208
97.8950

77.3303
77.2162
77.0126
76.6952

A-4d

Chemical Formula: $C_{17}H_{12}F_2O_3$
Exact Mass: 302.0755

1
3
2'
3''/5''
1''5
4'
6'
4
5'3'
1''
2''6''
4''
2

200   150   100   50   0   [ppm]

^{13}C NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3,5-difluorophenyl)-2,4-
pentadien-1-one (A-4d)

44-F 2nd step F19 in   cdcl3

−−100.642(

−−109.574(

Chemical Formula: $C_{17}H_{12}F_2O_3$
Exact Mass: 302.0755

A-4d

^{19}F NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3, 5-difluorophenyl)-2,4-pentadien-1-one (A-4d)

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3,5 2nd step [illegible] in CDCL3
COESY

A-4d

Chemical Formula: $C_{17}H_{12}F_2O_3$
Exact Mass: 302.0755

COSY Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3, 5-difluorophenyl)-2,4-

pentadien-1-one (A-4d)

NOESY Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3, 5-difluorophenyl)-2,4-

pentadien-1-one (A-4d)

HSQC Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3, 5-difluorophenyl)-2,4-

pentadien-1-one (A-4d)

HMBC Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3, 5-difluorophenyl)-2,4-

pentadien-1-one (A-4d)

A-4d

Chemical Formula: $C_{17}H_{12}F_2O_3$
Exact Mass: 302.0755

A-4d

Chemical Formula: $C_{17}H_{12}F_2O_3$
Exact Mass: 302.0755

%T

cm-1

1583.39
1489.09
1428.99 1293.18
1341.05
1181.30
1119.89
982.13
962.33
843.37
800.04
745.87
680.79
590.37
563.95
509.16

c:\pel_data\spectra\asif ir data\2 nd step sampl IR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3, 5-difluorophenyl)-2,4-pentadien-1-one (A-4d)

File   : C:\MSDCHEM\1\DATA\ASIF DATA\ASIF\35FSEC.D
Operator : ASIF
Acquired : 10 Jun 2011 16:07   using AcqMethod NATURAL
Instrument : Instrumen
Sample Name: 3,5-F second step sample
Misc Info :
Vial Number: 1

Scan 2081 (21.853 min): 35FSEC.D

Abundance

m/z--> 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440

39 51 65 77 93 107 121 139 151 167 180 194 207 219 232 255 267 285 302 319 337 355 367 380 396 410 424 439 452

Chemical Formula: $C_{17}H_{12}F_2O_3$
Exact Mass: 302.0755

A-4d

MS Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3, 5-difluorophenyl)-2,4-pentadien-1-one (A-4d)

44-F 2nd step 1H in cdcl3

^{1}H NMR Spectrum of 3-Hydroxy-1-(4-fluoro-2-hydroxyphenyl)-5-(4-fluorophenyl)-
2,4-pentadien-1-one (A-4e)

44-F 2nd step 1H in cdcl3

Expanded ¹H NMR Spectrum of 3-Hydroxy-1-(4-fluoro-2-hydroxyphenyl)-5-(4-fluorophenyl)-2,4-pentadien-1-one (A-4e)

44F 2nd step in cdcl3
probe=5mmBBOz/av600

—194.8721

—174.2085

166.4012
165.0970
165.0037
162.9884

—138.7305

130.7124
130.6337
129.8750
129.8216

—121.7072

116.2522
116.1065

107.4051
107.2554
105.3827
105.2262

—96.7787

A-4e

Chemical Formula: $C_{17}H_{12}F_2O_3$
Exact Mass: 302.0755

200   180   160   140   120   100   80   60 [ppm]

^{13}C NMR Spectrum of 3-Hydroxy-1-(4-fluoro-2-hydroxyphenyl)-5-(4-fluorophenyl)-
2,4-pentadien-1-one (A-4e)

44-F 2nd 13C in cdcl3

Chemical Formula: $C_{17}H_{12}F_2O_3$
Exact Mass: 302.0755

Expanded ^{13}C NMR Spectrum of 3-Hydroxy-1-(4-fluoro-2-hydroxyphenyl)-5-(4-fluorophenyl)-2,4-pentadien-1-one (A-4e)

COSY Spectrum of 3-Hydroxy-1-(4-fluoro-2-hydroxyphenyl)-5-(4-fluorophenyl)-2,4-

pentadien-1-one (A-4e)

44-F 2nd NOESY in cdcl3

NOESY Spectrum of 3-Hydroxy-1-(4-fluoro-2-hydroxyphenyl)-5-(4-fluorophenyl)-2,4-pentadien-1-one (A-4e)

A-4e

Chemical Formula: $C_{17}H_{12}F_2O_3$

Exact Mass: 302.0755

44-F 2nd HSQC in cdcl3

F1 [ppm]

2

3'

5'

3"5"

4

2" 6"

6'

5

6' 5 2"6" 3"5" 3' 5' 4 2

100

110

120

130

140

8.0   7.5   7.0   6.5   6.0   F2 [ppm]

F 3' 2' OH

4'

5'

6'

1' 1 2 3 4 1" 5

O   OH   5

5" 4"-F

6"

3"

2"

A-4e

Chemical Formula: $C_{17}H_{12}F_2O_3$
Exact Mass: 302.0755

HSQC Spectrum of 3-Hydroxy-1-(4-fluoro-2-hydroxyphenyl)-5-(4-fluorophenyl)-2,4-

pentadien-1-one (A-4e)

IR Spectrum of 3-Hydroxy-1-(4-fluoro-2-hydroxyphenyl)-5-(4-fluorophenyl)-2,4-pentadien-1-one (A-4e)

14.4833

12.5557

7.7006
7.6899
7.6857
7.6751
7.6571
7.6307
7.5496
7.5473
7.5365
7.3945
7.3819
7.3785
6.6627
6.6585
6.6454
6.6413
6.6069
6.6027
6.5875
6.5845
6.5581
6.2117

F 3' 2' OH
4' 1' 1 2 3 4 5'' 6'' 4''
5' 6' OH 5 1'' 3''
O OH 2''

A-4f

Chemical Formula: C$_{17}$H$_{13}$FO$_3$
Exact Mass: 284.0849

2

4''

3''5''

2''6''

5

1

6

2'OH

3'5'

4

3OH

1.0810

1.0000

0.8775
1.6283
2.1952

0.8713

0.8470

14   12   10   8   [ppm]

^{1}H NMR Spectrum of 3-Hydroxy-1-(4-fluoro-2-hydroxyphenyl)-5-(phenyl)-2,4-
pentadien-1-one (A-4f)

7.7006
7.6899
7.6857
7.6751
7.6571
7.6307

7.5496
7.5473
7.5365

7.3945
7.3819
7.3785

6.6627
6.6585
6.6454
6.6413
6.6069
6.6027
6.5875
6.5845
6.5581

6.2117

A-4f

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

6'
5
2" 6"
3" 4" 5"
3'
5'
4
2

1.0148
0.8775
1.6283
2.1952
0.8366
0.9103
0.8713
0.8470

7.6   7.4   7.2   7.0   6.8   6.6   6.4   [ppm]

Expanded ^{1}H NMR Spectrum of 3-Hydroxy-1-(4-fluoro-2-hydroxyphenyl)-5-(phenyl)-2,4-pentadien-1-one (A-4f)

4-F aceto 2nd step 13C in CDCL3

194.8598
174.4233
166.3733
165.0813
164.9875
140.0970
134.9261
130.7202
130.6426
130.1801
128.9989
128.0290
121.9797
115.9591
107.3757
107.2236
105.3562
105.2023
96.7801

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

A-4f

^{13}C NMR Spectrum of 3-Hydroxy-1-(4-fluoro-2-hydroxyphenyl)-5-(phenyl)-2,4-pentadien-1-one (A-4f)

Asif 94 1 /opt/topspin NK

4-F aceto 2nd step HSQC

A-4f

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

Asif 92 1 /opt/topspin NK

6' 5 2"6" 3"4"5" 3' 5' 4

4-F aceto 2nd step proton COESY

2

4
5'
3'

4|5

3"4"5" / 2"6"6" 3"5"4"
2"6"

5
6'

2"6"" / 3"4"5"

4|5

A-4f

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

8.0

6.5   F2 [ppm]

F1 [ppm]

6.5

7.0

7.5

8.0

4-F aceto 2nd step in cdcl3 HMBCGP

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

A-4f

IR Spectrum of 3-Hydroxy-1-(4-fluoro-2-hydroxyphenyl)-5-(phenyl)-2,4-pentadien-1-one (A-4f)

c:\pel_data\spectra\4-f second st

Abundance

Scan 2143 (22.382 min): 4FACE2.D

Chemical Formula: $C_{17}H_{13}FO_3$

Exact Mass: 284.0849

A-4f

MS Spectrum of 3-Hydroxy-1-(4-fluoro-2-hydroxyphenyl)-5-(phenyl)-2,4-pentadien-1-one (A-4f)

5-Acetophenone 2nd step proton in CDCL3

¹H NMR Spectrum of 3-Hydroxy-1-(5-fluoro-2-hydroxyphenyl)-5-phenyl-2,4-pentadien-1-one (A-4g)

Expanded ^{1}H NMR Spectrum of 3-Hydroxy-1-(5-fluoro-2-hydroxyphenyl)-5-phenyl-
2,4-pentadien-1-one (A-4g)

5-Acetophenone 2nd step C13 in CDCL3

^{13}C NMR Spectrum of 3-Hydroxy-1-(5-fluoro-2-hydroxyphenyl)-5-phenyl-2,4-pentadien-1-one (A-4g)

5-Acetophenone 2nd step C13 in CDCL3

194.8413
194.8136
175.2394
158.7255
156.3085
153.9406
140.5853
134.8439
134.4329
130.3056
129.0244
128.9610
128.5852
128.1063
123.3098
123.0760
121.8610
119.9994
119.9258
118.7607
118.6957
113.5805
113.3452
96.8113

A-4g

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

3"/5"

2"/6"

5

4"

1"

4'

3'

1'

6'

2

3

2'

5'

1

180   160   140   120   [ppm]

COSY Spectrum of 3-Hydroxy-1-(5-fluoro-2-hydroxyphenyl)-5-phenyl-2,4-pentadien-1-one (A-4g)

Jun10-2012-NK-Asif 14 1 /opt/topspin NK

5- Aceto 2nd step COESY in cdcl3

A-4g
Chemical Formula: C₁₇H₁₃FO₃
Exact Mass: 284.0849

NOESY Spectrum of 3-Hydroxy-1-(5-fluoro-2-hydroxyphenyl)-5-phenyl-2,4-pentadien-1-one (A-4g)

A-4g

Chemical Formula: $C_{17}H_{13}FO_3$

Exact Mass: 284.0849

HSQC Spectrum of 3-Hydroxy-1-(5-fluoro-2-hydroxyphenyl)-5-phenyl-2,4-pentadien-1-

one (A-4g)

HMBC Spectrum of 3-Hydroxy-1-(5-fluoro-2-hydroxyphenyl)-5-phenyl-2,4-pentadien-

1-one (A-4g)

5- Aceto 2nd step F19 in cdcl3

A-4g

Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

−−124.330(

IR Spectrum of 3-Hydroxy-1-(5-fluoro-2-hydroxyphenyl)-5-phenyl-2,4-pentadien-1-one (A-4g)

c:\pel_data\spectra\asif ir data\2 nd step

File   : C:\MSDCHEM\1\DATA\ASIF DATA\NEW DATA\ASIF\5-F ACETOPHENONE\5-FACE2.D
Operator   : Mehbub
Acquired   : 16 Jul 2011 16:25   using AcqMethod NATURAL
Instrument :   Instrumen
Sample Name: 5-F acetophenone 2nd step sample
Misc Info :
Vial Number: 1

MS Spectrum of 3-Hydroxy-1-(5-fluoro-2-hydroxyphenyl)-5-phenyl-2,4-pentadien-1-one (A-4g)

Scan 2163 (22.553 min): 5-FACE2.D

A-4g
Chemical Formula: $C_{17}H_{13}FO_3$
Exact Mass: 284.0849

4-OMe 2nd step proton in CDCL3

¹H NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(4-methoxyphenyl)-2,4-pentadien-1-one (A-4h)

Expanded ^{1}H NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(4-methoxyphenyl)-2,4-pentadien-1-one (A-4h)

4-OMe 2nd step proton in CDCL3

Peaks (ppm):
-195.3273
-174.9070
-162.2490
-161.4491
-161.0972
-146.2647
-139.4988
-135.3354
-129.7727
-129.4461
-128.1313
-127.4816
-119.4117
-118.8526
-118.6939
-118.4428
-114.2634
-114.1992
-114.1308
-114.0006
-96.1376
-55.1495

A-4h

Chemical Formula: $C_{18}H_{16}O_4$
Exact Mass: 296.1049

Peak assignments: C-1, C-3, C-2', C-4'', C-5, 4', 1'', 6', 4, 5', 3', 2''6'', 3''5'', C-2, OMe, X

150   100   50   [ppm]

^{13}C NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(4-methoxyphenyl)-2,4-Pentadien-1-one (A-4h)

COSY Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(4-methoxyphenyl)-2,4-

pentadien-1-one (A-4h)

HSQC Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(4-methoxyphenyl)-2,4-pentadien-1-one (A-4h)

HMBC Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(4-methoxyphenyl)-2,4-

pentadien-1-one (A-4h)

NOESY Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(4-methoxyphenyl)-2,4-pentadien-1-one (A-4h)

IR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(4-methoxyphenyl)-2,4-pentadien-1-one (A-4h)

File   : C:\MSDCHEM\1\DATA\ASIF DATA\4OME2ND.D
Operator : ASIF
Acquired : 7 Jun 2011   15:20   using AcqMethod NATURAL
Instrument : Instrumen
Sample Name: 4OMe 2 nd step
Misc Info :
Vial Number: 1

Abundance

Scan 2369 (24.230 min): 4OME2ND.D

17000

16000

15000

14000

13000

12000

11000

10000

9000

8000

7000

6000

5000

4000

3000

2000

1000

0

m/z--> 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350

44
53
63
77
90
103
118
133
147
161
178 191
207
221
237 253 267
281
296
313 327 341
355

Chemical Formula: $C_{18}H_{16}O_4$
Exact Mass: 296.1049

A-4h

MS Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(4-methoxyphenyl)-2,4-
pentadien-1-one (A-4h)

3,4-OMe 2nd step proton in CDCl3

Chemical Formula: $C_{19}H_{18}O_5$
Exact Mass: 326.1154

14.7138

12.2366

7.6901
7.6867
7.6699
7.6664
7.6160
7.5768
7.4251
7.4075
7.2400
7.1467
7.1420
7.1259
7.1213
7.0661
7.0615
6.9785
6.9767
6.9574
6.9556
6.8863
6.8712
6.8654
6.8534
6.8513
6.4715
6.4323
6.2888

3.9551
3.9279
3.9191
3.9123
3.9029

3-OH

2'-OH

OMe

1.0298

1.0000

1.0685
1.0275
2.2252

1.0271
0.9795

6.1636

14   12   10   8   6   4   [ppm]

^{1}H NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3,4-dimethoxyphenyl)-2,4-
pentadien-1-one (A-4i)

3,4-OMe 2nd step proton in CDCl3

Expanded ^{1}H NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3,4-dimethoxyphenyl)-2,4-pentadien-1-one (A-4i)

3,4-OMe 2nd step C13 in CDC13

Chemical Formula: $C_{19}H_{18}O_5$
Exact Mass: 326.1154

^{13}C NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3, 4-dimethoxyphenyl)-
2,4-pentadien-1-one (A-4i)

Jul09-2011-NK-Asif 13 1 /opt/topspin NK

COSY Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3,4-dimethoxyphenyl)-2,4-pentadien-1-one (A-4i)

3,4-OMe 2nd step COESY in CDCl3

A-4i

Chemical Formula: $C_{19}H_{18}O_5$

Exact Mass: 326.1154

HSQC Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3,4-dimethoxyphenyl)-2,4-

pentadien-1-one (A-4i)

HMBC Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3,4-dimethoxyphenyl)-2,4-pentadien-1-one (A-4i)

NOESY Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3,4-dimethoxyphenyl)-2,4-pentadien-1-one (A-4i)

IR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3,4-dimethoxyphenyl)-2,4-pentadien-1-one (A-4i)

Abundance

Scan 2805 (27.955 min): 34OME2.D

m/z-->

18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000

44
63
77
91
105
119 133
148
163
176
191
207
221 238 251
267
281
294 309
326
341 355
377 392
412 429 45

Chemical Formula: $C_{19}H_{18}O_5$
Exact Mass: 326.1154

A-4i

3,4 Methylendioxy 2nd step proton in cdcl3

14.6881

12.2187

7.6814
7.6784
7.6614
7.6583
7.5739
7.5348
7.4461
7.4425
7.4251
7.4076
7.4039
7.2399
7.0507
7.0340
7.0141
7.0110
6.9747
6.9549
6.9535
6.8959
6.8761
6.8576
6.8263
6.8063
6.4179
6.3788
6.2625
6.0034
5.9851

Chemical Formula: $C_{18}H_{14}O_5$
Exact Mass: 310.0841

A-4j

CH2

3

2'

1.0000

0.9364

1.1070
1.1579
1.1070

1.1344

1.0722
1.0105

2.3908

14   12   10   8   6   [ppm]

^{1}H NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3,4-
methelenedioxyphenyl)-2,4-pentadien-1-one (A-4j)

Jul11-2011-NK-Asif 20 1 /opt/topspin NK

3,4 Methylendioxy 2nd step proton in cdcl3

7.6814
7.6784
7.6614
7.6583
7.5739
7.5348
7.4461
7.4425
7.4251
7.4076
7.4039
7.2399
7.0507
7.0340
7.0141
7.0110
6.9747
6.9549
6.9535
6.8959
6.8761
6.8576
6.8263
6.8063
6.4179
6.3788
6.2625
6.0034
5.9851

CH2

Chemical Formula: $C_{18}H_{14}O_5$
Exact Mass: 310.0841

A-4j

1.1070
1.1579
1.1070
2.2397
1.0764
1.1146
1.1344
1.0722
1.0105
2.3908

7.5   7.0   6.5   6.0   [ppm]

Expanded ^{1}H NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3,4-methelenedioxyphenyl)-2,4-pentadien-1-one (A-4j)

Jul11-2011-NK-Asif 21 1 /opt/topspin NK

3,4 Methylendioxy 2nd step 13C in cdcl3

Chemical Formula: $C_{18}H_{14}O_5$
Exact Mass: 310.0841

Peaks (ppm): 195.6958, 174.8383, 162.5541, 149.5748, 148.4755, 139.7319, 135.6846, 129.5065, 128.4277, 124.5626, 120.1397, 119.0965, 118.9947, 118.7331, 108.7094, 106.6363, 106.3108, 101.6126, 96.6127

^{13}C NMR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3,4-methelenedioxyphenyl)-2,4-pentadien-1-one (A-4j)

COSY Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3,4-methelenedioxyphenyl)-

2,4-pentadien-1-one (A-4j)

NOESY Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3,4-methelenedioxyphenyl)-2,4-pentadien-1-one (A-4j)

HMBC Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3,4-methelenedioxyphenyl)-

2,4-pentadien-1-one (A-4j)

HSQC Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3,4-methelenedioxyphenyl)-

2,4-pentadien-1-one (A-4j)

86.6
80
75
70
65
60
55
50
%T 45
40
35
30
25
20
15
10
6.0

2901.06

1693.77

1621.80
1602.66

1566.69

1484.47
1446.80

1239.66

1171.51

1294.93

1103.04

977.65

1035.90

925.92

844.28

807.02

720.65

514.25

495.08

419.56

4000.0   3000   2000   1500   1000   500   380.0

cm-1

3' 2' OH
4'
5'   1'   1   2   3   4
6'   5
O   OH

5'' 4'' O
6''   7''
1''   O
2'' 3''

A-4j

Chemical Formula: $C_{18}H_{14}O_5$
Exact Mass: 310.0841

IR Spectrum of 3-Hydroxy-1-(2-hydroxyphenyl)-5-(3,4-methelenedioxyphenyl)-2,4-pentadien-1-one (A-4j)

File   : C:\MSDCHEM\1\DATA\ASIF DATA\NEW DATA\ASIF\3,4METHYLENDIOXY\34METH2.D
Operator : Mehbub
Acquired : 16 Jun 2011 14:40   using AcqMethod NATURAL
Instrument : Instrumen
Sample Name: 3,4 methylendioxy 2nd step sample
Misc Info :
Vial Number: 1

Abundance

Scan 2612 (26.389 min): 34METH2.D

Chemical Formula: $C_{18}H_{14}O_5$
Exact Mass: 310.0841

A-4j

m/z-->

2-F 3rd step(Purified) In CDCl3

A-5a

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

8.1761

7.7239
7.6689
7.5967
7.5323
7.3754
7.3283
7.2403
7.1791
7.1132
6.8714
6.3252

0.9619

1.0315
1.0255
1.0325
0.9787
1.1387
0.9310
1.0431
1.0393
0.9913
1.0237

8.0   7.5   7.0   6.5   [ppm]

^{1}H NMR Spectrum of 2'-Fluro-2-styrylchromone (A-5a)

2-F 3rd step(Purified) C13 In CDCl3

A-5a

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

Peak labels:
178.4897

162.4112
161.4243
159.8978
156.0104

133.8233
131.2560
131.1693
129.4014
128.3381
125.6961
125.0679
124.5491
124.1323
123.1556
123.0395
122.7041
122.6394
117.9602
116.3586
116.1405
111.1637

^{13}C NMR Spectrum of 2'-Fluro-2-styrylchromone (A-5a)

2-F 3rd step(Purified) C13 In CDC13

178.4616

162.4386
161.4790
159.9053

156.0286

133.8801
131.2542
129.4779
128.3967
125.6936
125.0371
124.5737
124.1103
123.1063
122.6430

117.9319
116.2328

111.2128

A-5a

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

180   170   160   150   140   130   120   [ppm]

Expanded ^{13}C NMR Spectrum of 2'-Fluro-2-styrylchromone (A-5a)

COSY Spectrum of 2'-Fluro-2-styrylchromone (A-5a)

A-5a

Chemical Formula: $C_{17}H_{11}FO_2$

Exact Mass: 266.0743

HSQC Spectrum of 2'-Fluro-2-styrylchromone (A-5a)

Sep11-2011-NK-Asif 17 1 /opt/topspin NK

2-F 3rd step(Purified) HMBC In CDCl3

HMBC Spectrum of 2'-Fluro-2-styrylchromone (A-5a)

A-5a

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

Sep11-2011-NK-Asif 15 1 C:\Bruker\TOPSPIN guest

2-F 3rd step(Purified) NOESY In CDC13

NOESY Spectrum of 2'-Fluro-2-styrylchromone (A-5a)

A-5a

Chemical Formula: $C_{17}H_{11}FO_2$

Exact Mass: 266.0743

2-F 3rd step(Purified) F-19 In CDCl3

-115.3975

A-5a

Chemical Formula: $C_{17}H_{11}FO_2$

Exact Mass: 266.0743

1.0000

| 0 | - 50 | - 100 | - 150 | - 200 | [ppm] |

^{19}F NMR Spectrum of 2'-Fluro-2-styrylchromone (A-5a)

Peak List

No.	Abscissa	Ordinate	Type
1	325.22	0.3542	Peak

Chemical Formula: $C_{17}H_{11}FO_2$

Exact Mass: 266.0743

A-5a

325.22 0.35423

UV Spectrum of 2'-Fluro-2-styrylchromone (A-5a)

nm

IR Spectrum of 2'-Fluro-2-styrylchromone (A-5a)

Abundance

Scan 2248 (23.197 min): 2-FFINAL.D

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

A-5a

MS Spectrum of 2'-Fluro-2-styrylchromone (A-5a)

2-FSC (sample 3) – formula should be C17H11F1O2 btw

MM2-FSC_12033016361G #36   RT: 1.28   AV: 1   NL: 5.34E6
T: + c EI Full ms [89.50-400.50]

Relative Abundance

92.10
119.09
120.08
125.10
146.11
170.12
173.10
207.13
209.15
218.15
237.15
249.15
265.16
266.16
268.17
267.17
307.29
341.12
355.20

MM2-FSC_12033016385O-c1 #28-34   RT: 0.56-0.68   AV: 7   NL: 2.72E6
T: + c EI Full ms [249.50-270.50]

Relative Abundance

262.9973
264.0601
265.0654

266.0733
C$_{17}$H$_{11}$O$_{2}$F$_{1}$
-1.8524 ppm

267.0353
268.0400
269.0860

m/z

A-5a

Chemical Formula: C$_{17}$H$_{11}$FO$_{2}$
Exact Mass: 266.0743

HRMS Spectrum of 2'-Fluro-2-styrylchromone (A-5a)

29 October 2012

3-F 3rd step 1H in cdcl3

[*1e6]

8.1943
8.1910
8.1745
8.1712

7.6973
7.6932
7.6758
7.6585
7.6543
7.5724
7.5296
7.5070
7.4041
7.4023
7.3844
7.3667
7.3620
7.3484
7.2763
7.2515
7.2402

7.0821
7.0668
7.0620
7.0495
7.0440

6.7906
6.7506

6.3446

A-5b

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

0.9226

1.0873

2.0014

3.0053

1.1447

1.1566

1.0000

0.9401

8.0   7.5   7.0   6.5   [ppm]

^{1}H NMR Spectrum of 3'-Fluro-2-styrylchromone (A-5b)

3-F 3rd step 13C in cdcl3

178.5067

164.3780
161.9232
161.2217
156.0073

137.3199
137.2420
135.5858
135.5583
133.8962
130.5840
130.5015
125.7637
125.1419
124.0971
123.6251
123.5986
121.6692
117.8729
116.8056
116.5910
114.1026
113.8840
111.1500

77.3403
77.2253
77.0224
76.7054

5'

6'

4'

3'

F

β

1'

α

2

3

8

9

7

6

5

10

O

O

A-5b

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

4

3'

2

9

β

1'

7

5'

5

6

α

10
6

8

4'

2'

3

200   150   100   50   [ppm]

[*1e6]

20

15

10

5

0

^{13}C NMR Spectrum of 3'-Fluro-2-styrylchromone (A-5b)

Expanded ^{13}C NMR Spectrum of 3'-Fluro-2-styrylchromone (A-5b)

3-F 3rd step 1H in cdcl3

−112.4141
−112.4285

A-5b

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

^{19}F NMR Spectrum of 3'-Fluro-2-styrylchromone (A-5b)

HSQC Spectrum of 3'-Fluro-2-styrylchromone (A-5b)

COSY Spectrum of 3'-Fluro-2-styrylchromone (A-5b)

A-5b

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

HMBC Spectrum of 3'-Fluro-2-styrylchromone (A-5b)

NOESY Spectrum of 3'-Fluro-2-styrylchromone (A-5b)

Peak List

Spectrum: 3-F-R
Comment:
Threshold: 0.1000
Abscissa units: nm
Ordinate units: A

No.	Abscissa	Ordinate	Type
1	325.09	0.3427	Peak

A-5b

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

325.09,0.34272

nm

UV Spectrum of 3'-Fluro-2-styrylchromone (A-5b)

IR Spectrum of 3'-Fluro-2-styrylchromone (A-5b)

c:\pel_data\spectra\asif ir data\final step sample ir

Inset structure labels: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, O, β, α, 1', 2', 3', 4', 5', 6', F

A-5b
Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

Peak labels (cm⁻¹):
1694.35, 1631.80, 1622.76, 1611.98, 1579.74, 1562.65, 1487.44, 1464.94, 1443.87, 1435.00, 1421.87, 1389.12, 1336.54, 1318.73, 1298.68, 1272.35, 1247.35, 1222.09, 1178.65, 1164.26, 1147.00, 1140.86, 1122.64, 1074.20, 1026.11, 999.00, 968.12, 941.46, 879.74, 857.41, 775.58, 758.00, 752.00, 732.00, 699.59, 686.60, 674.21, 646.23, 622.88, 588.13, 581.00, 552.90, 543.23, 502.75, 482.13, 447.14, 434.77, 318.22

MS Spectrum of 3'-Fluro-2-styrylchromone (A-5b)

HRMS Spectrum of 3'-Fluro-2-styrylchromone (A-5b)

29 October 2012

^{1}H NMR Spectrum of 4'–fluoro-2-styrylchromone (A-5c)

4-F 3rd step 13C in DMSO

177.1371

164.0913
161.6853

155.4327

135.3506
134.3355
131.6038
131.5716
130.0641
129.9636
125.3423
123.4219
120.4182
118.2270
116.1342
115.9127

110.0284

A-5c

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

180   160   140   120   100   [ppm]

^{13}C NMR Spectrum of 4'–fluoro-2-styrylchromone (A-5c)

−−110.726;

A-5c

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

0   − 50   − 100   − 150   − 200   [ppm]

^{19}F NMR Spectrum of 4'–fluoro-2-styrylchromone (A-5c)

COSY Spectrum of 4'–fluoro-2-styrylchromone (A-5c)

HSQC Spectrum of 4'-fluoro-2-styrylchromone (A-5c)

HMBC Spectrum of 4'–fluoro-2-styrylchromone (A-5c)

A-5c

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

NOESY Spectrum of 4'–fluoro-2-styrylchromone (A-5c)

Peak List

Spectrum: 4-F-R
Comment:
Threshold: 0.1000
Abscissa units: nm
Ordinate units: A

No.	Abscissa	Ordinate	Type
1	328.27	0.3705	Peak

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

A-5c

328.27,0.37047

A

nm

UV Spectrum of 4'-fluoro-2-styrylchromone (A-5c)

IR Spectrum of 4'–fluoro-2-styrylchromone (A-5c)

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

A-5c

c:\pel_data\spectra\asif ir data\final step

MS Spectrum of 4'-fluoro-2-styrylchromone (A-5c)

Scan 2280 (23.470 min): 4FFINAL.D

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

A-5c

MM 4-FSC (sample 5)

MM4-FSC_120330170242 #41-45   RT: 1.57-1.73   AV: 5   NL: 1.07E6
T: + c EI Full ms [89.50-450.50]

MM4-FSC_120401192435-c1 #29   RT: 0.57   AV: 1   NL: 1.61E5
T: + c EI Full ms [249.50-270.50]

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

A-5c

HRMS Spectrum of 4'–fluoro-2-styrylchromone (A-5c)

5

^{1}H NMR Spectrum of 3',5'-difluoro-2-styrylchromone (A-5d)

3-F 3rd step C13 in cdcl3

178.3750

164.5248
162.1753
162.0466
160.5978

155.9725

138.2813

134.3229
133.9950

125.7967
125.2335
124.1176
122.9808

117.8722

111.7096
110.4139
110.3417
110.2292
110.1573
105.2144
104.9603
104.7065

77.3294
77.2160
77.0120
76.6943

A-5d

Chemical Formula: $C_{17}H_{10}F_2O_2$
Exact Mass: 284.0649

^{13}C NMR Spectrum of 3',5'-difluoro-2-styrylchromone (A-5d)

3-F 3rd step F-19 in cdcl3

--108.992:

A-5d

Chemical Formula: C$_{17}$H$_{10}$F$_2$O$_2$
Exact Mass: 284.0649

30 [rel]

25

20

15

10

5

0

0   − 50   − 100   − 150   − 200   [ppm]

^{19}F NMR Spectrum of 3',5'-difluoro-2-styrylchromone (A-5d)

COSY Spectrum of 3',5'-difluoro-2-styrylchromone (A-5d)

HSQC Spectrum of 3',5'-difluoro-2-styrylchromone (A-5d)

May28-2012-NK-Asif 17 1 /opt/topspin NK

3-F 3rd step HMBC in cdcl3

A-5d

Chemical Formula: $C_{17}H_{10}F_2O_2$

Exact Mass: 284.0649

HMBC Spectrum of 3',5'-difluoro-2-styrylchromone (A-5d)

NOESY Spectrum of 3',5'-difluoro-2-styrylchromone (A-5d)

Chemical Formula: $C_{17}H_{10}F_2O_2$
Exact Mass: 284.0649

Peak List

No.	Abscissa	Ordinate	Type
1	322.82	0.4776	Peak

A-5d
Chemical Formula: $C_{17}H_{10}F_2O_2$
Exact Mass: 284.0649

322.82,0.47764

A

nm

UV Spectrum of 3',5'-difluoro-2-styrylchromone (A-5d)

IR Spectrum of 3',5'-difluoro-2-styrylchromone (A-5d)

File   : C:\MSDCHEM\1\DATA\ASIF DATA\ASIF\35F3RD\35F3RD.D
Operator   : ASIF
Acquired   : 12 Jun 2011 14:01   using AcqMethod NATURAL
Instrument : Instrumen
Sample Name : 3,5-F final step sample
Misc Info   :
Vial Number : 1

Scan 2124 (22.220 min): 35F3RD.D

Abundance

m/z-->

A-5d

Chemical Formula: $C_{17}H_{10}F_2O_2$

Exact Mass: 284.0649

MS Spectrum of 3',5'-difluoro-2-styrylchromone (A-5d)

3,5-difluoroSc (sample 1)

MM_12030131337 #38 RT: 1.36 AV: 1 NL: 1.18E5
T: + c EI Full ms [89.50-400.50]

Relative Abundance

164.06
175.16
177.18
189.18
191.19
203.19
217.21
219.22
231.22
232.22
263.06
267.07
268.08
283.06
284.07
285.07
287.28
301.29
328.39

MM_12030145853-c1 #66-91 RT: 0.96-1.33 AV: 26 NL: 1.07E6
T: + c EI Full ms [279.50-295.50]

Relative Abundance

280.3078
281.9991
283.0552
284.0633
C$_{17}$H$_{10}$O$_2$F$_2$
-3.5637 ppm
285.0635
C$_{17}$H$_{11}$O$_2$F$_2$
-30.2390 ppm
286.0201
289.0654
290.9867
293.9853

m/z

A-5d
Chemical Formula: C$_{17}$H$_{10}$F$_2$O$_2$
Exact Mass: 284.0649

HRMS Spectrum of 3',5'-difluoro-2-styrylchromone (A-5d)

4,4-F 3rd step proton in CDCL3(Purified)

8.2114
8.1955
8.1893
8.1733

7.5746
7.5696
7.5610
7.5535
7.5446
7.5395
7.5141

7.2184
7.2124
7.1957
7.1898
7.1353
7.1290
7.1256
7.1138
7.1042
7.0930
7.0869
7.0825

6.7017
6.6616

6.2846

A-5e
Chemical Formula: $C_{17}H_{10}F_2O_2$
Exact Mass: 284.0649

0.9939
3.2025
1.0334
3.0921
1.0846
1.0000

8.0   7.5   7.0   6.5   6.0   [ppm]

^{1}H NMR Spectrum of 7,4'-difluro-2-styrylchromone (A-5e)

4,4-F 3rd step 13C in CDCL3(Purified)

A-5e

Chemical Formula: $C_{17}H_{10}F_2O_2$

Exact Mass: 284.0649

^{13}C NMR Spectrum of 7,4'-difluro-2-styrylchromone (A-5e)

4,4-F 3rd step F19 in CDCL3(Purified)

A-5e
Chemical Formula: $C_{17}H_{10}F_2O_2$
Exact Mass: 284.0649

−102.9616
−109.8963

0   − 50   − 100   − 150   − 200   [ppm]

^{19}F NMR Spectrum of 7,4'-difluro-2-styrylchromone (A-5e)

COSY Spectrum of 7,4'-difluro-2-styrylchromone (A-5e)

Aug07-2011-NK-Asif 15 1 C:\Bruker\TOPSPIN guest

4,4-F 3rd step COESY in CDCL3(Purified)

A-5e

Chemical Formula: $C_{17}H_{10}F_2O_2$

Exact Mass: 284.0649

HSQC Spectrum of 7,4'-difluro-2-styrylchromone (A-5e)

NOESY Spectrum of 7,4'-difluro-2-styrylchromone (A-5e)

A-5e
Chemical Formula: $C_{17}H_{10}F_2O_2$
Exact Mass: 284.0649

Peak List

Spectrum: 44-F-R
Comment:
Threshold: 0.1000
Abscissa units: nm
Ordinate units: A

No. Abscissa Ordinate Type
─────────────────────────────────
1   327.00   0.5211   Peak

A-5e
Chemical Formula: $C_{17}H_{10}F_2O_2$
Exact Mass: 284.0649

327.00,0.52108

A

UV Spectrum of 7,4'-difluro-2-styrylchromone (A-5e)

nm

IR Spectrum of 7,4'-difluro-2-styrylchromone (A-5e)

A-5e
Chemical Formula: $C_{17}H_{10}F_2O_2$
Exact Mass: 284.0649

c:\pel_data\spectra\asif ir data\final step sample ir\4,4 -f

7,4-FSC (sample 2)

samp2-c1 #64-99 RT: 0.93-1.45 AV: 36 NL: 1.47E5
T: + c EI Full ms [279.50-295.50]

Relative Abundance

283.0575

284.0642
C$_{17}$H$_{10}$O$_{2}$F$_{2}$
-0.3266 ppm

285.1073
C$_{17}$H$_{11}$O$_{2}$F$_{2}$
123.1582 ppm

m/z

A-5e
Chemical Formula: C$_{17}$H$_{10}$F$_{2}$O$_{2}$
Exact Mass: 284.0649

HRMS Spectrum of 7,4'-difluro-2-styrylchromone (A-5e)

29 October 2012

4-F aceto 3rd pure 1H in cdcl3

8.2119
8.1960
8.1898
8.1740

7.5959
7.5826
7.5790
7.5624
7.5588
7.4302
7.4144
7.3957
7.3918
7.3745
7.2297
7.2237
7.2069
7.2010
7.1333
7.1272
7.1120
7.1064
7.0907
7.0848

6.7866
6.7463

6.2973

A-5f
Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

1.0000

3.2433

3.1366

1.0609

1.0350

1.0510

1.0025

8.0   7.5   7.0   6.5   [ppm]

^{1}H NMR Spectrum of 7-fluoro-2-styrylchromone (A-5f)

4-F aceto 3rd Pure 13C in cdcl3

A-5f

Chemical Formula: $C_{17}H_{11}FO_2$

Exact Mass: 266.0743

177.4816
164.4861
162.0173
157.0842
156.9505
137.1937
134.8867
130.0087
129.0536
128.2515
128.1451
127.7284
121.0054
119.8956
113.8106
113.5850
110.6218
104.7644
104.5105

13C NMR Spectrum of 7-fluoro-2-styrylchromone (A-5f)

4-F aceto 3rd Pure F19 in cdcl3

−103.0301
−103.0484

A-5f

Chemical Formula: $C_{17}H_{11}FO_2$

Exact Mass: 266.0743

^{19}F NMR Spectrum of 7-fluoro-2-styrylchromone (A-5f)

COSY Spectrum of 7-fluoro-2-styrylchromone (A-5f)

A-5f

Chemical Formula: $C_{17}H_{11}FO_2$

Exact Mass: 266.0743

HSQC Spectrum of 7-fluoro-2-styrylchromone (A-5f)

NOESY Spectrum of 7-fluoro-2-styrylchromone (A-5f)

A-5f
Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

Peak List

No.	Abscissa	Ordinate	Type
1	312.97	0.3436	Peak

A-5f

Chemical Formula: $C_{17}H_{11}FO_2$

Exact Mass: 266.0743

312.97 0.34362

nm

UV Spectrum of 7-fluoro-2-styrylchromone (A-5f)

IR Spectrum of 7-fluoro-2-styrylchromone (A-5f)

A-5f

Chemical Formula: $C_{17}H_{11}FO_2$

Exact Mass: 266.0743

c:\pel_data\spectra\asif ir data\final step sample ir\4-facetophenol

MS Spectrum of 7-fluoro-2-styrylchromone (A-5f)

File   : C:\MSDCHEM\1\DATA\ASIF DATA\ASIF\4FACE3.D
Operator   : ASIF
Acquired   : 10 Jun 2011 14:58   using AcqMethod NATURAL
Instrument : Instrumen
Sample Name: 4-F acetophenone final step sample
Misc Info :
Vial Number: 1

Scan 2169 (22.604 min): 4FACE3.D

A-5f

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

MM 4-Faceto-SC (sample 6)

MM4-FacetoSC_120401192636 #43-49   RT: 1.18-1.35   AV: 7   NL: 7.70E6
T: + c EI Full ms [89.50-270.50]

Relative Abundance

MM4-FacetoSC_120401195435-c1 #125   RT: 2.49   AV: 1   NL: 1.57E5
T: + c EI Full ms [249.50-270.50]

Relative Abundance

m/z

262.9969

265.0681

266.0730
$C_{17}H_{11}O_2F_1$
-2.8077 ppm

266.9858

A-5f

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

HRMS Spectrum of 7-fluoro-2-styrylchromone (A-5f)

29 October 2012

5-F acetophenone 3rd step proton in CDCL3

7.8340
7.8262
7.8135
7.8057

7.6149
7.5751
7.5632
7.5439
7.5335
7.5211
7.5108

7.3941
7.3921

7.2399

6.7975
6.7573

6.3121

A-5g

Chemical Formula: C$_{17}$H$_{11}$FO$_2$
Exact Mass: 266.0743

5'

2'6'
β

8

7
3'5'4'

×

α

H-3

0.9683

3.2338

1.1129

4.0649

1.0654

1.0000

7.5

7.0

6.5

[ppm]

^{1}H NMR Spectrum of 6-Fluoro-2-styrylchromone (A-5g)

5-F acetophenone 3rd step proton in CDCL3

177.6340
177.6112
161.9959
160.7281
158.2772
152.2055
137.3569
134.8859
130.0234
129.0532
128.8940
128.7848
128.2410
127.7363
125.3579
125.2858
121.9176
121.6663
120.0362
119.9308
119.8522
110.8157
110.5815
109.8950

A-5g

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

^{13}C NMR Spectrum of 6-Fluoro-2-styrylchromone (A-5g)

5-F acetophenone 3rd step proton in CDCL3

A-5g

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

-115.519(
-115.529(

^{19}F NMR Spectrum of 6-Fluoro-2-styrylchromone (A-5g)

COSY Spectrum of 6-Fluoro-2-styrylchromone (A-5g)

HSQC Spectrum of 6-Fluoro-2-styrylchromone (A-5g)

HMBC Spectrum of 6-Fluoro-2-styrylchromone (A-5g)

Jul27-2011-NK-Asif 15 1 /opt/topspin NK

5-F acetophenone 3rd step NOESY in CDCL3

A-5g

Chemical Formula: $C_{17}H_{11}FO_2$

Exact Mass: 266.0743

NOESY Spectrum of 6-Fluoro-2-styrylchromone (A-5g)

Peak List

Spectrum: 5-FACE-R
Comment:
Threshold: 0.1000
Abscissa units: nm
Ordinate units: A

No.	Abscissa	Ordinate	Type
1	329.81	0.4479	Peak

A-5g

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

UV Spectrum of 6-Fluoro-2-styrylchromone (A-5g)

329.81,0.44787

IR Spectrum of 6-Fluoro-2-styrylchromone (A-5g)

Inset label:

A-5g

Chemical Formula: $C_{17}H_{11}FO_2$
Exact Mass: 266.0743

Ring/position labels on structure: 8, 9, 1, O, 7, 6, F, 5, 10, 4, 3, 2, α, β, 1', 2', 3', 4', 5', 6'

Axis labels: %T, cm-1

Y-axis values: 95.9, 90, 85, 80, 75, 70, 65, 60, 55, 50, 45, 40, 35, 30, 25.0

X-axis values: 4000.0, 3000, 2000, 1500, 1000, 500, 380.0

Peak labels:
1710.44
1627.83
1594.63
1577.78
1567.26
1477.99
1446.42
1378.07
1329.77
1284.37
1271.51
1245.89
1234.92
1206.24
1172.35
1120.99
1076.23
1065.11
1027.50
1007.82
998.72
966.66
931.59
901.31
885.83
869.39
828.11
818.76
795.78
787.12
769.92
751.89
723.81
710.74
685.29
620.79
611.98
564.44
544.89
536.79
515.77
488.76
464.27
438.65
401.00
394.75

c:\pei_data\spectra\asif ir data\final step sample ir\5-face

File   : C:\MSDCHEM\1\DATA\ASIF DATA\NEW DATA\ASIF\5-F ACETOPHENONE\5-FACE3D.D
Operator   : Mehbub
Acquired   : 17 Jul 2011   14:33   using AcqMethod NATURAL
Instrument   :   Instrumen
Sample Name: 5-F acetophenone 3rd step sample
Misc Info   :
Vial Number: 1

Scan 2229 (23.117 min): 5-FACE3D.D

MS Spectrum of 6-Fluoro-2-styrylchromone (A-5g)

^{1}H NMR Spectrum of 4'-Methoxy-2-styrylchromone (A-5h)

Expanded ^{1}H NMR Spectrum of 4'-Methoxy-2-styrylchromone (A-5h)

4-OMe 3rd step 13C in CDCl3

A-5h

Chemical Formula: $C_{18}H_{14}O_3$
Exact Mass: 278.0943

Peak labels (left to right): 178.4846; 162.2552; 161.1153; 156.0324; 146.3515; 138.7647; 136.6578; 133.6015; 130.9491; 130.0141; 129.2964; 127.8057; 125.6955; 125.0075; 124.9123; 124.1560; 117.9084; 117.7962; 114.4863; 114.3953; 113.4904; 111.5948; 109.9478; 55.4274

^{13}C NMR Spectrum of 4'-Methoxy-2-styrylchromone (A-5h)

4-OMe 3rd step 13C in CDCl3

A-5h

Chemical Formula: $C_{18}H_{14}O_3$
Exact Mass: 278.0943

Expanded ^{13}C NMR Spectrum of 4'-Methoxy-2-styrylchromone (A-5h)

Aug09-2011-NK-Asif 24 1 /opt/topspin NK

4-OMe 3rd step COESY in CDCl3

COSY Spectrum of 4'-Methoxy-2-styrylchromone (A-5h)

A-5h

Chemical Formula: $C_{18}H_{14}O_3$

Exact Mass: 278.0943

HSQC Spectrum of 4'-Methoxy-2-styrylchromone (A-5h)

HMBC Spectrum of 4'-Methoxy-2-styrylchromone (A-5h)

NOESY Spectrum of 4'-Methoxy-2-styrylchromone (A-5h)

A-5h

Chemical Formula: $C_{18}H_{14}O_3$

Exact Mass: 278.0943

Peak List

No.	Abscissa	Ordinate	Type
1	354.00	0.3115	Peak

Chemical Formula: $C_{18}H_{14}O_3$
Exact Mass: 278.0943

A-5h

354.00,0.31152

UV Spectrum of 4'-Methoxy-2-styrylchromone (A-5h)

IR Spectrum of 4'-Methoxy-2-styrylchromone (A-5h)

c:\pel_data\spectra\asif ir data\final step sample ir\4-

Abundance

Scan 2388 (24.393 min): 4OME3RD.D

m/z-->

Chemical Formula: $C_{18}H_{14}O_3$
Exact Mass: 278.0943

A-5h

MS Spectrum of 4'-Methoxy-2-styrylchromone (A-5h)

Expanded ^{1}H NMR Spectrum of 3',4'-Dimethoxy-2-styrylchromone (A-5i)

3,4-OMe 3rd step proton

7.8362
7.8319
7.8147
7.8114
7.7973
7.7930
7.7140
7.6936
7.6792
7.6390
7.4924
7.4907
7.4728
7.4550
7.3688
7.3645
7.2857
7.2812
7.2650
7.2605
7.1316
7.0915
7.0466
7.0384
7.0174

—6.4078

3.8356
3.8044

A-5i

Chemical Formula: $C_{19}H_{16}O_4$
Exact Mass: 308.1049

OMe

5'   4'   OMe

6'

β   1'   2'   3'   OMe

8   9   1

7   2   α

6   4   3

5   10

O

OMe

5   7   α β   6   c   6'   α   5'

3

0.9179
0.8951
1.7940
1.0626
0.8796
0.9903
0.8702
0.9800

1.0000

6.5675

8   7   6   5   4   3   [ppm]

^{1}H NMR Spectrum of 3',4'-Dimethoxy-2-styrylchromone (A-5i)

3,4-OMe 3rd step 13C

A-5i

Chemical Formula: $C_{19}H_{16}O_4$
Exact Mass: 308.1049

^{13}C NMR Spectrum of 3',4'-Dimethoxy-2-styrylchromone (A-5i)

COSY Spectrum of 3',4'-Dimethoxy-2-styrylchromone (A-5i)

A-5i

Chemical Formula: $C_{19}H_{16}O_4$

Exact Mass: 308.1049

HSQC Spectrum of 3',4'-Dimethoxy-2-styrylchromone (A-5i)

NOESY Spectrum of 3',4'-Dimethoxy-2-styrylchromone (A-5i)

Peak List

No.	Abscissa	Ordinate	Type
1	367.66	0.2493	Peak

Chemical Formula: $C_{19}H_{16}O_4$
Exact Mass: 308.1049

A-5i

367.66,0.24933

UV Spectrum 3',4'-Dimethoxy-2-styrylchromone (A-5i)

IR Spectrum of 3',4'-Dimethoxy-2-styrylchromone (A-5i)

c:\pel_data\spectra\asif ir data\final step sample ir\3,4-om

A-5i
Chemical Formula: $C_{19}H_{16}O_4$
Exact Mass: 308.1049

MS Spectrum of 3',4'-Dimethoxy-2-styrylchromone (A-5i)

8.1815
8.1688

7.6696
7.6680
7.6558
7.6439
7.6423
7.5208
7.5078
7.4941
7.3827
7.3701
7.3577
7.2403
7.0862
7.0545
7.0411
6.8390
6.8257
6.6099
6.5834
6.2801
6.0101

A-5j

Chemical Formula: $C_{18}H_{12}O_4$
Exact Mass: 292.0736

0.9677
1.0500
1.9938
1.0650
0.9919
1.0250
0.9838
1.0163
0.9707
2.0000

8.0   7.5   7.0   6.5   6.0   5.5 [ppm]

^{1}H NMR Spectrum of 3',4'-Methylenedioxy-2-styrylchromone (A-5j)

3,4 OCH2O 3rd step 13C in CDCL3

178.4558

161.9893

156.0100

149.3225
148.5281

136.6701
133.6512
129.5309
125.7014
124.9514
124.1420
123.9158
118.3512
117.8029

110.1763
108.6950
106.1514

101.6037

A-5j

Chemical Formula: $C_{18}H_{12}O_4$
Exact Mass: 292.0736

1

2

9

4 3'

β 7

1' 5 6 6'

7 8

3 5 2'

CH2

150

100

50

[ppm]

^{13}C NMR Spectrum of 3',4'-Methylenedioxy-2-styrylchromone (A-5j)

3,4 OCH2O 3rd step 13C in CDCL3

A-5j

Chemical Formula: $C_{18}H_{12}O_4$
Exact Mass: 292.0736

Expanded ^{13}C NMR Spectrum of 3',4'-Methylenedioxy-2-styrylchromone (A-5j)

COSY Spectrum of 3',4'-Methylenedioxy-2-styrylchromone (A-5j)

A-5j

Chemical Formula: $C_{18}H_{12}O_4$

Exact Mass: 292.0736

HSQC Spectrum of 3',4'-Methylenedioxy-2-styrylchromone (A-5j)

HMBC Spectrum of 3',4'-Methylenedioxy-2-styrylchromone (A-5j)

A-5j

Chemical Formula: $C_{18}H_{12}O_4$
Exact Mass: 292.0736

Peak List

Spectrum: 34-DIM-R
Comment:
Threshold: 0.1000
Abscissa units: nm
Ordinate units: A

No.	Abscissa	Ordinate	Type
1	329.12	0.3473	Peak

Chemical Formula: $C_{18}H_{12}O_4$
Exact Mass: 292.0736

A-5j

329.12 0.34726

UV Spectrum 3',4'-Methylenedioxy-2-styrylchromone (A-5j)

IR Spectrum of 3',4'-Methylenedioxy-2-styrylchromone (A-5j)

c:\pel_data\spectra\asif ir data\final step sample ir\3,'

Scan 2624 (26.491 min): 34METH3.D

MS Spectrum of 3',4'-Methylenedioxy-2-styrylchromone (A-5j)

G-Salt 1H NMR in DMSO
4.18 (q, J=7.38 Hz, 2H)
3.74 (s, 2H)
1.22 (t, J=7.18 Hz, 3H)
8.50 (s, 1H,N-H)

[*1e6]

— 8.5073

— 4.1888
— 3.7472
— 2.4977
— 1.2239

B-2

Chemical Formula: $C_4H_{10}ClNO_2$
Exact Mass: 139.0400

$Cl^{-+}H_3N$ ... OEt

1.3889

1.9860
2.0598

3.0000

15   10   5   0   [ppm]

^{1}H NMR Spectrum of glycine ethyl ester hydrochloride (B-2)

G-Salt 1H NMR in DMSO

^{13}C NMR Spectrum of glycine ethyl ester hydrochloride (B-2)

Sep21-2012-NK-Asif 11 1 /opt/topspin NK

G-Salt 1H NMR in DMSO

39.4518

CH₂

—8.1950

—7.2400

4.1899
4.1794
4.1778
4.1682
4.1663
4.1557
4.1540
4.0225
4.0137

3.0854
3.0731
3.0607
3.0486

1.2504
1.2392
1.2266

[*1e6]

B-3
Chemical Formula: C₅H₉NO₃
Exact Mass: 131.0582

0.8739

2.0880
2.0124

0.8489

3.1000

8   6   4   2   [ppm]

¹H NMR Spectrum of *N*-formylglycine ethyl ester (B-3)

4.1899
4.1794
4.1778
4.1682
4.1663
4.1557
4.1540

4.0225
4.0137

3.0854
3.0731
3.0607
3.0486

B-3
Chemical Formula: $C_5H_9NO_3$
Exact Mass: 131.0582

2.0880

2.0124

0.8489

Expanded ^{1}H NMR Spectrum of glycine ethyl ester hydrochloride (B-2)

B-5

Chemical Formula: $C_9H_{12}N_2O_4S$
Exact Mass: 244.0518

−13.1932

4.2736
4.2616
4.2500
4.2380

−2.5000

1.2789
1.2668
1.2552

1.9100

4.2381

6.2386

[*1e6]

[ppm]

^{1}H NMR Spectrum of 2-mercapto-4,5-imidazoledicarboxylate (B-5)

4.2736
4.2616
4.2500
4.2380

B-5
Chemical Formula: $C_9H_{12}N_2O_4S$
Exact Mass: 244.0518

4.2381

Expanded ^{1}H NMR Spectrum of 2-mercapto-4,5-imidazoledicarboxylate (B-5)

B-5
Chemical Formula: $C_9H_{12}N_2O_4S$
Exact Mass: 244.0518

Expanded ^{1}H NMR Spectrum of 2-mercapto-4,5-imidazoledicarboxylate (B-5)

Asif 31 1 /opt/topspin NK

carboxylate-1 in dmso-d6

Expanded ¹H NMR Spectrum of 2-mercapto-4,5-imidazoledicarboxylate (B-5)

carboxylate-1 in dmso-d6

164.2142
157.7104
123.3730
62.0459
14.2803

100 [*1e6]

80

60

40

20

0

O

7

8

6

O

5

1
H
N

2

S

8'

6'

4

N
H
3

7'

O

B-5

Chemical Formula: $C_9H_{12}N_2O_4S$

Exact Mass: 244.0518

200　　150　　100　　50　　0　[ppm]

^{13}C NMR Spectrum of 2-mercapto-4,5-imidazoledicarboxylate (B-5)

File   :C:\msdchem\1\data\Asif2012\CARBOXYLATE NMR.D
Operator : ANITA
Acquired : 28 Mar 2012 11:41   using AcqMethod NATPRODUCTS MANUAL INJ SPLIT.M
Instrument : 5973N
Sample Name: 2UL
Misc Info :
Vial Number: 1

Abundance

Scan 2059 (19.143 min): CARBOXYLATE NMR.D\data.ms

244.1

70.1

124.0

170.1

200.0

281.1 310.8 341.1 383.3 415.1 445.4 476.1 505.2   559.4   607.5 637.5 678.6

m/z-->

145000
140000
135000
130000
125000
120000
115000
110000
105000
100000
95000
90000
85000
80000
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0

Chemical Formula: C$_9$H$_{12}$N$_2$O$_4$S
Exact Mass: 244.0518

B-5

MS Spectrum of 2-mercapto-4,5-imidazoledicarboxylate (B-5)

Abs.

0.666
0.600
0.400
0.200
0.000
-0.061

250.00 300.00 350.00 400.00 450.00 500.00

nm.

2

1

No.	Wavelength nm.	Abs.
1	346.00	0.085
2	270.00	0.605

B-5

Chemical Formula: $C_9H_{12}N_2O_4S$

Exact Mass: 244.0518

3-F carb in cdcl3

B-6a

Chemical Formula: $C_{16}H_{17}FN_2O_4S$
Exact Mass: 352.0893

7.9800
7.2401
7.1873
7.1774
7.1642
7.1740
7.1608
7.1509
7.0432
7.0304
7.0080
7.0044
7.0014
6.9922
6.9885
6.9855
6.9805
6.8905
6.8896
6.8863
6.8855
6.8756
6.8718
6.8625
6.8615
6.8583
6.8574

4.4201
4.3249
4.3130

1.3057

^{1}H NMR Spectrum of Diethyl 2-(3-fluorobenzylthio)-1H-imidazole-4,5-dicarboxylate(B-6a)

3-F carb in cdcl3

Chemical Formula: $C_{16}H_{17}FN_2O_4S$
Exact Mass: 352.0893

Expanded ^{1}H NMR Spectrum of Diethyl 2-(3-fluorobenzylthio)-1H-imidazole-4,5-dicarboxylate(B-6a)

3-F carb in cdcl3

7.2279
7.2180
7.2147
7.2048
7.2014
7.1915

7.0838
7.0710
7.0486
7.0450
7.0420
7.0328
7.0291
7.0261

6.9311
6.9302
6.9270
6.9261
6.9162
6.9125
6.9031
6.9021
6.8989
6.8981

B-6a

Chemical Formula: $C_{16}H_{17}FN_2O_4S$
Exact Mass: 352.0893

5″

6″

2″

4″

1.0000

0.9466

0.9341

0.9013

7.4 7.2 7.0 6.8 6.6 [ppm]

Expanded ^{1}H NMR Spectrum of Diethyl 2-(3-fluorobenzylthio)-1H-imidazole-4,5-dicarboxylate(B-6a)

3-F carb 13C in cdcl3 11-4-12

163.5133
161.8801
159.4431

144.1156

138.5526
138.5035

130.3038
130.2524

124.7030
124.6818

116.0108
115.8649
114.9690
114.8295

62.0989

37.5844

14.0911

B-6a

Chemical Formula: $C_{16}H_{17}FN_2O_4S$
Exact Mass: 352.0893

8|8′

7|7′

3″

6|6′

2

1″

5″

6″

2″

4″

7″

[ppm]

160   140   120   100   80   60   40   20

^{13}C NMR Spectrum of Diethyl 2-(3-fluorobenzylthio)-1H-imidazole-4,5-dicarboxylate(B-6a)

3-F Final Carb F-19

−−112.2267

B-6a

Chemical Formula: $C_{16}H_{17}FN_2O_4S$
Exact Mass: 352.0893

¹⁹F NMR Spectrum of Diethyl 2-(3-fluorobenzylthio)-1H-imidazole-4,5-dicarboxylate(B-6a)

Abs.

0.989

0.500

0.000

-0.105

250.00   300.00   350.00   400.00   460.00   500.00

nm.

No.	Wavelength nm.	Abs.
1	274.00	0.898

B-6a

Chemical Formula: $C_{16}H_{17}FN_2O_4S$
Exact Mass: 352.0893

UV Spectrum of Diethyl 2-(3-fluorobenzylthio)-1H-imidazole-4,5-dicarboxylate(B-6a)

IR Spectrum of Diethyl 2-(3-fluorobenzylthio)-1H-imidazole-4,5-dicarboxylate(B-6a)

Chemical Formula: $C_{16}H_{17}FN_2O_4S$
Exact Mass: 352.0893

B-6a

c:\pel_data\spectra\asif ir data\carb\3-cl b

File   :C:\msdchem\1\data\Asif2012\Carboxylate compounds\3F-BB-FINAL
          (2).D
Operator :
Instrument : 5973N
Acquired : 5 Apr 2012 12:10   using AcqMethod NATPRODUCTS MANUAL INJ SPLIT.M
Sample Name: 3-F carb final
Misc Info :

Scan 2477 (22.201 min): 3F-BB-FINAL(2).D\data.ms

Chemical Formula: $C_{16}H_{17}FN_2O_4S$
Exact Mass: 352.0893

B-6a

Abundance

95000

90000

85000

80000

75000

70000

65000

60000

55000

50000

45000

40000

35000

30000

25000

20000

15000

10000

5000

0

57.1

109.1

139.0

174.1

206.1

234.1

278.1

307.1

352.1

399.5 429.1 461.9 503.2 550.1 593.5 625.0652.5 684.4

m/z--> 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500 520 540 560 580 600 620 640 660 680 700

MS Spectrum of Diethyl 2-(3-fluorobenzylthio)-1H-imidazole-4,5-dicarboxylate(B-6a)

Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
213 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   N: 0-5   O: 1-5   F: 1-5   S: 1-2
3-F 31 (0.511) Cm (1:31)
TOF MS ES+

7.10e+004

Minimum:		-1.5	50.0			
Maximum:	5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm) Formula
353.0961	353.0971	-1.0	-2.8	8.5	71.8	0.0	C16 H18 N2 O4 F S

Chemical Formula: $C_{16}H_{17}FN_2O_4S$
Exact Mass: 352.0893

B-6a

HRMS Spectrum of Diethyl 2-(3-fluorobenzylthio)-1H-imidazole-4,5-dicarboxylate(B-6a)

4-F carb

B-6b

Chemical Formula: $C_{16}H_{17}FN_2O_4S$
Exact Mass: 352.0893

7.2540
7.2447
7.2399
7.2313
6.9512
6.9372
6.9227

4.3689
4.3570
4.3452
4.3329
4.3256

1.3530
1.3412
1.3293

[*1e6]

2"/6"
3"/5"
7/7'
7"
8/8'

2.3603
2.0073
2.0852
6.0000

15   10   5   0   [ppm]

^{1}H NMR Spectrum of Diethyl 2-(4-fluorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6b)

4-F carb

4.3689
4.3570
4.3452
4.3329
4.3256

1.3530
1.3412
1.3293

[*1e6]

B-6b

Chemical Formula: $C_{16}H_{17}FN_2O_4S$
Exact Mass: 352.0893

7\7'

7"

8\8'

4.0644
2.0852

6.0000

4.0   3.5   3.0   2.5   2.0   1.5   [ppm]

Expanded ^{1}H NMR Spectrum of Diethyl 2-(4-fluorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6b)

4-F carb

Chemical Formula: $C_{16}H_{17}FN_2O_4S$
Exact Mass: 352.0893

B-6b

7.2540
7.2447
7.2399
7.2313

6.9512
6.9372
6.9227

2''/6''

3''/5''

2.3603

2.0073

7.8   7.6   7.4   7.2   7.0   6.8   [ppm]

Expanded ^{1}H NMR Spectrum of Diethyl 2-(4-fluorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6b)

4-F Barb in cdcl3

163.0178
161.3844
144.3992
132.3745
132.3527
130.6467
130.5882
115.6165
115.4786
61.8762
36.8218
14.1069

Chemical Formula: $C_{16}H_{17}FN_2O_4S$
Exact Mass: 352.0893

B-6b

2"/6"
3"/5"
8/8'
1"
7"
7/7'
6/6'
2
4"

150   100   50   0   [ppm]

^{13}C NMR Spectrum of Diethyl 2-(4-fluorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6b)

4-F Final Carb F-19

−−115.406

Chemical Formula: $C_{16}H_{17}FN_2O_4S$
Exact Mass: 352.0893

^{19}F NMR Spectrum of Diethyl 2-(4-fluorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6b)

UV Spectrum of Diethyl 2-(4-fluorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6b)

No	Wavelength nm.	Abs.
1	280.00	0.450

B-6b

Chemical Formula: $C_{16}H_{17}FN_2O_4S$
Exact Mass: 352.0893

4 F carb D.spc - Storage 122822

IR Spectrum of Diethyl 2-(4-fluorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6b)

c:\pel_data\spectra\asif ir data\carb\4-f

Scan 2499 (22.362 min): 4-F BENZYLBROMIDEFINAL(1).D\data.ms

Abundance

5400000

5200000

5000000

4800000

4600000

4400000

4200000

4000000

3800000

3600000

3400000

3200000

3000000

2800000

2600000

2400000

2200000

2000000

1800000

1600000

1400000

1200000

1000000

800000

600000

400000

200000

m/z--> 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500 520 540 560 580 600 620 640 660 680 700

70.1

109.1

139.1

170.0

206.1

234.1

273.1

307.1

352.1

380.2

418.1

461.0

489.1

534.9

565.3

597.8

636.9

668.4

699.0

B-6b

Chemical Formula: $C_{16}H_{17}FN_2O_4S$
Exact Mass: 352.0893

MS Spectrum of Diethyl 2-(4-fluorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6b)

Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
285 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   N: 0-5   O: 1-5   F: 1-5   S: 0-2
4-F3 (0.034) Cm (1:30)
TOF MS ES+

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
353.0970	353.0971	-0.1	-0.3	8.5	59.5	0.0	C16 H18 N2 O4 F S

| Minimum: | | | | -1.5 | | | |
| Maximum: | 5.0 | 5.0 | 50.0 | | | | |

Chemical Formula: $C_{16}H_{17}FN_2O_4S$
Exact Mass: 352.0893

B-6b

HRMS Spectrum of Diethyl 2-(4-fluorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6b)

3,4-F carb in 1H in cdcl3 3-4-2012

Chemical Formula: $C_{16}H_{16}F_2N_2O_4S$
Exact Mass: 370.0799

B-6c

7.2401
7.2328
7.2283
7.2241
7.2146
7.2116
7.1078
7.1047
7.0940
7.0422
7.0283
7.0119
6.9980

5.8739

4.5855
4.3689
4.3570

1.3582

^{1}H NMR Spectrum of Diethyl 2-(3,4-difluorobenzylthio)-1H-imidazole-4,5-dicarboxylate(B-6c)

3,4-F carb in 1H in cdcl3 3-4-2012

—4.5856

4.3808
4.3689
4.3571
4.3452

1.3701
1.3583
1.3465

B-6c

Chemical Formula: $C_{16}H_{16}F_2N_2O_4S$
Exact Mass: 370.0799

7''

7 7'

8 8'

1.9399

4.0152

6.0000

4.5 4.0 3.5 3.0 2.5 2.0 1.5 [ppm]

Expanded ^{1}H NMR Spectrum of Diethyl 2-(3,4-difluorobenzylthio)-1H-imidazole-4,5-dicarboxylate(B-6c)

3,4-F carb in 1H in cdcl3 3-4-2012

7.2402
7.2329
7.2283
7.2242
7.2146
7.2117
7.1078
7.1048
7.0941
7.0422
7.0284
7.0120
6.9980

—5.8684

B-6c

Chemical Formula: $C_{16}H_{16}F_2N_2O_4S$
Exact Mass: 370.0799

[*1e6]

20

15

10

5

0

6"

2"

5"

0.9842

1.0406

0.9874

0.9921

7.0

6.5

6.0

[ppm]

Expanded ^{1}H NMR Spectrum of Diethyl 2-(3,4-difluorobenzylthio)-1H-imidazole-4,5-dicarboxylate(B-6c)

7.2447
7.2402
7.2329
7.2283
7.2242
7.2146
7.2117

7.1078
7.1048
7.0941

7.0422
7.0284
7.0120
6.9980

B-6c

Chemical Formula: $C_{16}H_{16}F_2N_2O_4S$
Exact Mass: 370.0799

5"

5"

2"

0.9842

1.0406

0.9874

7.25   7.20   7.15   7.10   7.05   7.00   [ppm]

Expanded ^{1}H NMR Spectrum of Diethyl 2-(3,4-difluorobenzylthio)-1H-imidazole-4,5-dicarboxylate(B-6c)

3,4-F carb in cdcl3 3-4-2012

158.1399
151.3874
149.0033
143.9918
132.6242
129.1794
125.7346
118.2703
117.6468
71.3901
62.6591
37.6189
19.2691
14.1209

O
7
8
O
6
5
1
H
N
2
S
7''
8'
O
6'
4
N
3
1'
2'
6'
3'
5'
4'
F
F

B-6c

Chemical Formula: $C_{16}H_{16}F_2N_2O_4S$
Exact Mass: 370.0799

7|7'

8|8'

6|6'

2

3''4''

1''4'5''6''

5''2''

7''

200   150   100   50   0   [ppm]

^{13}C NMR Spectrum of Diethyl 2-(3,4-difluorobenzylthio)-1H-imidazole-4,5-dicarboxylate(B-6c)

Asif 41 1 C:\Bruker\TOPSPIN guest

3,4-F carb in cdcl3 3-4-2012

3,4-F Final Carb F-19

-136.537
-137.932

[*1e6]

B-6c

Chemical Formula: $C_{16}H_{16}F_2N_2O_4S$
Exact Mass: 370.0799

0   - 50   - 100   - 150   - 200   [ppm]

^{19}F NMR Spectrum of Diethyl 2-(3,4-difluorobenzylthio)-1H-imidazole-4,5-dicarboxylate(B-6c)

Abs.

3,4-Carb.spc - Storage 123248

nm.

No.	Wavelength nm.	Abs.
1	273.00	0.858

Chemical Formula: $C_{16}H_{16}F_2N_2O_4S$
Exact Mass: 370.0799

B-6c

UV Spectrum of Diethyl 2-(3,4-difluorobenzylthio)-1H-imidazole-4,5-dicarboxylate(B-6c)

IR Spectrum of Diethyl 2-(3,4-difluorobenzylthio)-1H-imidazole-4,5-dicarboxylate(B-6c)

c:\pel_data\spectra\as

Abundance

Scan 2468 (22.135 min): 2CF3-BB- FINAL.D\data.ms

127.1

224.1

252.1

291.1

325.1

370.1

70.1

97.1

157.0

188.1

398.1 429.0 460.8 488.8 522.6 551.1 584.2 627.3 662.4 697.4

m/z--> 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500 520 540 560 580 600 620 640 660 680 700

320000
300000
280000
260000
240000
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000

B-6c

Chemical Formula: $C_{16}H_{16}F_2N_2O_4S$
Exact Mass: 370.0799

MS Spectrum of Diethyl 2-(3,4-difluorobenzylthio)-1H-imidazole-4,5-dicarboxylate(B-6c)

Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
159 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   N: 0-5   O: 1-5   F: 2-5   S: 1-2
34-F 21 (0.342) Cm (1:31)
TOF MS ES+

Minimum:				-1.5		
Maximum:	5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
371.0875	371.0877	-0.2	-0.5	8.5	90.3	0.0	C16 H17 N2 O4 F2 S

Chemical Formula: $C_{16}H_{16}F_2N_2O_4S$
Exact Mass: 370.0799

B-6c

HRMS Spectrum of Diethyl 2-(3,4-difluorobenzylthio)-1H-imidazole-4,5-dicarboxylate(B-6c)

Asif 108 1 /opt/topspin NK

penta F in dmso

4.5060
4.4125
4.2692
4.2573
4.2455
4.2337

2.4999

1.2748
1.2629
1.2511

B-6d

Chemical Formula: $C_{16}H_{13}F_5N_2O_4S$
Exact Mass: 424.0516

7''

7/7'

8/8'

0.9661
2.0565
4.3263

6.0000

[*1e6]

[ppm]

^{1}H NMR Spectrum of Diethyl 2-(perfluorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6d)

Expanded ^{1}H NMR Spectrum of Diethyl 2-(perfluorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6d)

Expanded ^{1}H NMR Spectrum of Diethyl 2-(perfluorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6d)

penta F in dmso

2.4997

1.2745
1.2627
1.2508

B-6d

Chemical Formula: $C_{16}H_{13}F_5N_2O_4S$
Exact Mass: 424.0516

8|8'

6.0587

2.5   2.0   1.5   1.0   [ppm]

Expanded ^{1}H NMR Spectrum of Diethyl 2-(perfluorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6d)

^{13}C NMR Spectrum of Diethyl 2-(perfluorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6d)

penta F in dmso

Expanded ^{13}C NMR Spectrum of Diethyl 2-(perfluorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6d)

Penta-F Final Carb F-19

B-6d

Chemical Formula: $C_{16}H_{13}F_5N_2O_4S$
Exact Mass: 424.0516

—141.459₈

—153.413₈

—161.134₅

^{19}F NMR Spectrum of Diethyl 2-(perfluorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6d)

UV Spectrum of Diethyl 2-(perfluorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6d)

Penta-F carb.spc - Storage 1245/48

Abs.

0.665

0.600

0.400

0.200

0.000

-0.008

250.00   300.00   350.00   400.00   450.00   500.00

nm.

No.	Wavelength nm.	Abs.
1	270.00	0.601

B-6d

Chemical Formula: $C_{16}H_{13}F_5N_2O_4S$
Exact Mass: 424.0516

IR Spectrum of Diethyl 2-(perfluorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6d)

Scan 2306 (20.950 min): PENTA FLUORO BBFINAL.D\data.ms

Abundance

105000

100000

95000

90000

85000

80000

75000

70000

65000

60000

55000

50000

45000

40000

35000

30000

25000

20000

15000

10000

5000

0

60.1

97.0

125.0

153.1

181.0

211.0

243.1

278.0

306.0

350.1

378.0

424.1

452.3

503.1 536.8 564.2 592.2 622.1 655.5 684.3

m/z--> 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500 520 540 560 580 600 620 640 660 680 700

B-6d

Chemical Formula: $C_{16}H_{13}F_5N_2O_4S$
Exact Mass: 424.0516

MS Spectrum of Diethyl 2-(perfluorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6d)

Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
55 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 15-18 H: 10-15 N: 0-5 O: 1-5 F: 2-5 S: 1-1
penta-F 19 (0.307) Cm (1:31)
TOF MS ES+

3.17e+004

Minimum:				-1.5			
Maximum:	5.0	5.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
425.0591	425.0594	-0.3	-0.7	8.5	78.1	0.0	C16 H14 N2 O4 F5 S

Chemical Formula: C$_{16}$H$_{13}$F$_5$N$_2$O$_4$S
Exact Mass: 424.0516

B-6d

HRMS Spectrum of Diethyl 2-(perfluorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6d)

4-CF3 carb in cdcl3

^{1}H NMR Spectrum of Diethyl2-(4-(trifluoromethyl)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6e)

4-CF3 carb in cdcl3

Chemical Formula: $C_{17}H_{17}F_3N_2O_4S$
Exact Mass: 402.0861

— 10.7855

7.5006
7.4812
7.4289
7.4089

— 7.2400

B-6e

Expanded ^{1}H NMR Spectrum of Diethyl2-(4-(trifluoromethyl)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6e)

4-CF3 carb in cdcl3

Chemical Formula: $C_{17}H_{17}F_3N_2O_4S$
Exact Mass: 402.0861

B-6e

−4.4615

−4.3656
−4.3479
−4.3302
−4.3125

Expanded ^{1}H NMR Spectrum of Diethyl2-(4-(trifluoromethyl)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6e)

4-CF3

—157.9196

—144.0497
—139.4055
—129.5706
—129.4314
—128.9048
—125.8176
—125.7812

—62.7465

—38.0707

—14.0705

[*1e6]

Chemical Formula: C₁₇H₁₇F₃N₂O₄S
Exact Mass: 402.0861

$$\text{Chemical Formula: } C_{17}H_{17}F_3N_2O_4S$$
$$\text{Exact Mass: } 402.0861$$

B-6e

6|6' 2 1" 2"|6" 4" 9"|5" 7|7' 7" 8|8'

200   150   100   50   0   [ppm]

^{13}C NMR Spectrum of Diethyl2-(4-(trifluoromethyl)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6e)

Expanded ^{13}C NMR Spectrum of Diethyl2-(4-(trifluoromethyl)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6e)

4-CF3 carb in cdcl3

−62.6493

[*1e6]

B-6e

Chemical Formula: $C_{17}H_{17}F_3N_2O_4S$
Exact Mass: 402.0861

0   − 50   − 100   − 150   − 200 [ppm]

^{19}F NMR Spectrum of Diethyl2-(4-(trifluoromethyl)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6e)

UV Spectrum of Diethyl2-(4-(trifluoromethyl)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6e)

4-CF3 carb.spc - Storage 123740

Abs.

No.	Wavelength nm.	Abs.
1	278.00	0.594

B-6e

Chemical Formula: $C_{17}H_{17}F_3N_2O_4S$
Exact Mass: 402.0861

IR Spectrum of Diethyl2-(4-(trifluoromethyl)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6e)

Abundance

Scan 2424 (21.813 min): 4-CF3- CARB FINAL.D\data.ms

500000

480000

460000

440000

420000

400000

380000

360000

340000

320000

300000

280000

260000

240000

220000

200000

180000

160000

140000

120000

100000

80000

60000

40000

20000

m/z--> 0

70.0

109.1

159.1

189.0

224.1

256.1

284.1

328.1

357.1

402.1

430.0 475.1 525.0 561.0 591.7 622.1650.1678.4

40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500 520 540 560 580 600 620 640 660 680 700

Chemical Formula: $C_{17}H_{17}F_3N_2O_4S$
Exact Mass: 402.0861

B-6e

MS Spectrum of Diethyl2-(4-(trifluoromethyl)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6e)

Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
53 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   N: 0-5   O: 1-5   F: 2-5   S: 1-1
4-CF3 2 (0.017) Cm (1:31)
TOF MS ES+

1.59e+005

Minimum:			-1.5				
Maximum:	5.0	5.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
403.0950	403.0939	1.1	2.7	8.5	88.7	0.0	C17 H18 N2 O4 F3 S

Chemical Formula: $C_{17}H_{17}F_3N_2O_4S$
Exact Mass: 402.0861

B-6e

HRMS Spectrum of Diethyl2-(4-(trifluoromethyl)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6e)

¹H NMR Spectrum of Diethyl 2-(2,4-bis(trifluoromethyl)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6f)

Expanded ^{1}H NMR Spectrum of Diethyl 2-(2,4-bis(trifluoromethyl)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6f)

Expanded ^{1}H NMR Spectrum of Diethyl 2-(2,4-bis(trifluoromethyl)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6f)

2,4-CF3 carb

B-6f

Chemical Formula: $C_{18}H_{16}F_6N_2O_4S$
Exact Mass: 470.0735

— 10.2672

— 7.8671
7.7354
7.7219
7.6896
7.6761

— 7.2402

3''   5''   6''

0.9503

1.0218   1.0927   1.0598

10.0   9.5   9.0   8.5   8.0   7.5   [ppm]

Expanded ¹H NMR Spectrum of Diethyl 2-(2,4-bis(trifluoromethyl)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6f)

2,4-cF3 carb in cdcl3

¹³C NMR Spectrum of Diethyl 2-(2,4-bis(trifluoromethyl)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6f)

Expanded ^{13}C NMR Spectrum of Diethyl 2-(2,4-bis(trifluoromethyl)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6f)

2,4-CF3 Final Carb F-19

−59.7715
−63.0091

B-6f

Chemical Formula: $C_{18}H_{16}F_6N_2O_4S$
Exact Mass: 470.0735

^{19}F NMR Spectrum of Diethyl 2-(2,4-bis(trifluoromethyl)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6f)

UV Spectrum of Diethyl 2-(2,4-bis(trifluoromethyl))benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6f)

2,4-CF3 carb.spc - Storage 125227

Abs.

No.	Wavelength nm.	Abs.
1	277.00	0.619

B-6f

Chemical Formula: $C_{18}H_{16}F_6N_2O_4S$
Exact Mass: 470.0735

IR Spectrum of Diethyl 2-(2,4-bis(trifluoromethyl)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6f)

File : C:\msdchem\1\data\Asif2012\Carboxylate compounds\2CF3-BENZYL
BROMIDE-FINAL.D
Operator :
Instrument : 5973N
Acquired : 5 Apr 2012 14:46 using AcqMethod NATPRODUCTS MANUAL INJ SPLIT.M
Sample Name: ~~2-CF3~~ carb final
Misc Info : 2,4-bis CF3

Scan 2245 (20.504 min): 2CF3-BENZYLBROMIDE-FINAL.D\data.ms
324.1

Chemical Formula: $C_{18}H_{16}F_6N_2O_4S$
Exact Mass: 470.0735

B-6f

MS Spectrum of Diethyl 2-(2,4-bis(trifluoromethyl)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6f)

Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
95 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 16-20   H: 15-20   N: 1-5   O: 0-5   F: 5-10   S: 1-1
24-CF3 1 (0.017) Cm (1:29)
TOF MS ES+

Minimum:				-1.5	50.0								
Maximum:	5.0	5.0	50.0									
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula					
471.0825	471.0813	1.2	2.5	8.5	45.9	0.0	C18	H17	N2	O4	F6	S

Chemical Formula: $C_{18}H_{16}F_6N_2O_4S$
Exact Mass: 470.0735

B-6f

HRMS Spectrum of Diethyl 2-(2,4-bis(trifluoromethyl)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6f)

B-6g

Chemical Formula: $C_{17}H_{17}F_3N_2O_5S$
Exact Mass: 418.0810

−7.8500

7.3630
7.3490
7.2402
7.0644
7.0505

4.5575
4.3449
4.3330
4.3213
4.3092

1.3294
1.3170
1.3055

$7''$

$7|7'$

$8|8'$

$2''|6''$

$3''|5''$

1

0.9374

2.1267

0.9745

1.9330

3.9859

6.0000

8   6   4   2   0 [ppm]

^{1}H NMR Spectrum of Diethyl 2-(4-(trifluoromethoxy)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6g)

Expanded ^{1}H NMR Spectrum of Diethyl 2-(4-(trifluoromethoxy)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6g)

Expanded ^{1}H NMR Spectrum of Diethyl 2-(4-(trifluoromethoxy)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6g) .

o-cF3 carb in cdcl3

Chemical Formula: $C_{17}H_{17}F_3N_2O_5S$
Exact Mass: 418.0810

Peak labels: 158.5619, 148.8510, 144.1811, 134.2561, 130.6536, 130.5445, 129.3847, 121.1842, 119.4819, 77.2592, 76.8358, 62.4543, 37.6770, 14.0436

Assignments: 6/6', 4'', 2, 1'', 4/5, 2''/6'', 3''/5'', OCF3, 7/7', 7'', 8/8'

^{13}C NMR Spectrum of Diethyl 2-(4-(trifluoromethoxy)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6g)

--57.8974

B-6g

Chemical Formula: $C_{17}H_{17}F_3N_2O_5S$
Exact Mass: 418.0810

[*1e6]

800

600

400

200

0

0   − 50   − 100   − 150   − 200 [ppm]

^{19}F NMR Spectrum of Diethyl 2-(4-(trifluoromethoxy)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6g)

Abs.

0.447

0.400

0.200

0.000

-0.075

250.00　300.00　350.00　400.00　450.00　500.00

nm.

No.	Wavelength nm.	Abs.
1	279.00	0.404

B-6g

Chemical Formula: $C_{17}H_{17}F_3N_2O_5S$
Exact Mass: 418.0810

UV Spectrum of Diethyl 2-(4-(trifluoromethoxy)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6g)

IR Spectrum of Diethyl 2-(4-(trifluoromethoxy)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6g)

Chemical Formula: $C_{17}H_{17}F_3N_2O_5S$
Exact Mass: 418.0810

B-6g

c:\pel_data\spectra\asif ir data

File   : C:\msdchem\1\data\Asif2012\Carboxylate compounds\OCF3-BB-FIN
...   AL.D
Operator :
Instrument : 5973N
Acquired : 5 Apr 2012 14:15   using AcqMethod NATPRODUCTS MANUAL INJ SPLIT.M
Sample Name: methoxy CF3 carb final
Misc Info :

Abundance
5400000

Scan 2432 (21.872 min): OCF3-BB-FINAL.D\data.ms

5200000

5000000

4800000

4600000

4400000

4200000

4000000

3800000

3600000

3400000

3200000

3000000

2800000

2600000

2400000

2200000

2000000

1800000

1600000

1400000

1200000

1000000

800000

600000

400000

200000

69.1   109.1   142.0   175.1   205.0   243.1   272.1   300.1   339.1   373.1   418.2   446.2   489.0 519.2 549.4   593.1   630.8   673.2

m/z--> 0 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500 520 540 560 580 600 620 640 660 680 700

Chemical Formula: $C_{17}H_{17}F_3N_2O_5S$
Exact Mass: 418.0810

B-6g

MS Spectrum of Diethyl 2-(4-(trifluoromethoxy)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6g)

Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
49 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 15-19   H: 15-20   N: 0-5   O: 1-5   F: 2-5   S: 1-1
4-OCF3 2 (0.017) Cm (1:31)
TOF MS ES+

Minimum:				-1.5									
Maximum:		5.0	5.0	50.0									
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula						
419.0893	419.0889	0.4	1.0	8.5	76.7	0.0	C17	H18	N2	O5	F3	S	

Chemical Formula: $C_{17}H_{17}F_3N_2O_5S$
Exact Mass: 418.0810

B-6g

HRMS Spectrum of Diethyl 2-(4-(trifluoromethoxy)benzylthio)-1H-imidazole-4,5-dicarboxylate(B-6g)

1.29e+005

Asif 81 1 /opt/topspin NK
4-NO2 Carb in cdcl3

10.9489

8.0770
8.0643
7.4560
7.4424
7.2402

4.4108
4.3538
4.3422
4.3307
4.3184

1.3362
1.3251
1.3138

Chemical Formula: $C_{16}H_{17}N_3O_6S$
Exact Mass: 379.0838

B-6h

^{1}H NMR Spectrum of Diethyl 2-(4-nitrobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6h)

Expanded ^{1}H NMR Spectrum of Diethyl 2-(4-nitrobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6h)

4-NO2 Carb in cdcl3

[*1e6]

—1.3362
—1.3251
—1.3138

8| 5'

Chemical Formula: $C_{16}H_{17}N_3O_6S$
Exact Mass: 379.0838

B-6h

6.0000

1.4   1.3   1.2   [ppm]

Expanded ^{1}H NMR Spectrum of Diethyl 2-(4-nitrobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6h)

Expanded ^{1}H NMR Spectrum of Diethyl 2-(4-nitrobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6h)

4-NO2 Carb in cdcl3

—8.0770
—8.0643

—7.4560
—7.4424

—7.2402

3″/5″

2″/6″

2.1127

2.1176

[*1e6]

8.0   7.8   7.6   7.4   [ppm]

^{13}C NMR Spectrum of Diethyl 2-(4-nitrobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6h)

Abs.

No.   Wavelength nm.   Abs.

1   274.00   0.517

Chemical Formula: $C_{16}H_{17}N_3O_6S$
Exact Mass: 379.0838

B-6h

UV Spectrum of Diethyl 2-(4-nitrobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6h)

IR Spectrum of Diethyl 2-(4-nitrobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6h)

c:\pel_data\spectra\asif ir data\carb\4-n

Intens.
x10⁸
1.25
1.00
0.75
0.50
0.25
0.00

0.2   0.4   0.6   0.8   1.0   1.2   1.4   1.6   1.8   Time [min]

— 1000000.D: TIC +All MS

Intens.
x10⁶
3
2
1
0

250   500   750   1000   1250   1500   1750   2000   2250   2500   m/z

380.2

644.1   781.2

+MS, 0.0-0.4min #(2-16)

Chemical Formula: C₁₆H₁₇N₃O₆S
Exact Mass: 379.0838

B-6h

MS Spectrum of Diethyl 2-(4-nitrobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6h)

Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
20 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 16-20   H: 15-20   N: 1-5   O: 5-10   S: 1-1
4-NO2 2 (0.017) Cm (1:30)
TOF MS ES+

4.63e+003

Minimum:				-1.5			
Maximum:	5.0	5.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
380.0906	380.0916	-1.0	-2.6	9.5	56.8	0.0	C16 H18 N3 O6 S

B-6h

Chemical Formula: C₁₆H₁₇N₃O₆S
Exact Mass: 379.0838

HRMS Spectrum of Diethyl 2-(4-nitrobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6h)

3-Cl carb

7.3169
7.2397
7.2228
7.2082
7.1961
7.1831
7.1703
7.1587

4.3859
4.3744
4.3626
4.3507
4.3456
4.3335

1.3761
1.3643
1.3524

25 [*1e6]

20

15

10

5

0

Chemical Formula: $C_{16}H_{17}ClN_2O_4S$
Exact Mass: 368.0598

B-6i

2'|

7\7'| 7''

8/8''

0.8190
3.1855

1.9120

6.0000

8   6   4   2   [ppm]

^{1}H NMR Spectrum of Diethyl 2-(3-chlorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6i)

Expanded ^{1}H NMR Spectrum of Diethyl 2-(3-chlorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6i)

Expanded ^{1}H NMR Spectrum of Diethyl 2-(3-chlorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6i)

3-Cl carb

Expanded ^{1}H NMR Spectrum of Diethyl 2-(3-chlorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6i)

Asif 110 1 /opt/topspin NK

3-Cl carb

7.3169

7.2397
7.2228
7.2082
7.1961
7.1831
7.1703
7.1587

2″

4″/6″

5″

[*1e6]

10

8

6

4

2

0

7.4 7.3 7.2 7.1 [ppm]

3-Cl Final Step c13 purified

¹³C NMR Spectrum of Diethyl 2-(3-chlorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6i)

Abs.

No.	Wavelength nm.	Abs.
1	279.00	0.192

Chemical Formula: $C_{16}H_{17}ClN_2O_4S$

Exact Mass: 368.0598

B-6i

UV Spectrum of Diethyl 2-(3-chlorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6i)

IR Spectrum of Diethyl 2-(3-chlorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6i)

Chemical Formula: $C_{16}H_{17}ClN_2O_4S$
Exact Mass: 368.0598

B-6i

c:\pel_data\spectra\asif ir data\carl

Scan 2740 (24.125 min): 3-CL CARB FINAL.D\data.ms

Abundance

48000

46000

44000

42000

40000

38000

36000

34000

32000

30000

28000

26000

24000

22000

20000

18000

16000

14000

12000

10000

8000

6000

4000

2000

0

m/z--> 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500 520 540 560 580 600 620 640 660 680 700

60.1
89.1
125.1
155.1 188.0
222.0
250.1
294.0
322.1
368.1
401.3 429.4 470.3 504.2 533.1 561.1 611.8 639.1 668.4 698.4

Chemical Formula: $C_{16}H_{17}ClN_2O_4S$
Exact Mass: 368.0598

B-6i

MS Spectrum of Diethyl 2-(3-chlorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6i)

Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
148 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   N: 0-5   O: 0-5   S: 1-1   Cl: 0-5
3-Cl 4 (0.052) Cm (1:30)
TOF MS ES+

8.76e+004

Minimum: Maximum:				-1.5 50.0	5.0	5.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula		
369.0681	369.0676	0.5	1.4	8.5	104.7	0.0	C16 H18 N2 O4 S Cl		

Chemical Formula: $C_{16}H_{17}ClN_2O_4S$
Exact Mass: 368.0598

B-6i

HRMS Spectrum of Diethyl 2-(3-chlorobenzylthio)-1H-imidazole-4,5-dicarboxylate (B-6i)