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SYNTHETIC AND SPECTROSCOPIC STUDIES OF 6-SUBSTITUTED CHROMONE DERIVATIVES

By

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Dedication

To my family, thank you for been so humble and patient. Your support brought me this far and I say thank you once again.

Declaration

I, Thata Golden Ramonetha, hereby declare that the dissertation for the Master of Science (Chemistry) degree at the University of Venda, hereby submitted by me, has not been submitted previously for a degree at this or any other university, that it is my own work in design and in execution, and that all reference material contained therein has been duly acknowledged.

Signature ……………………………………Date 03/05/2016

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Abstract

Chromones and chromone derivatives are naturally occurring compounds found in the plant kingdom; for example, baicalein was used as a diuretic and anti-allergic drug in ancient Chinese medicine. A range of chromone-2-carboxylic acids were synthesized from six substituted 2-hydroxyacetophenones. From these chromone-2-carboxylic acids, the acid chlorides were synthesized, from which chromone-2-carboxamide derivatives such as *N,N*-dimethylchromone-2-carboxamide, 1-[(6-bromochromon-2-yl)-carbonyl]-pyrrolidine, 1-[(6-chlorochromon-2-yl)-carbonyl]-pyrrolidine, 1-[(6-methoxychromon-2-yl)-carbonyl]-pyrrolidine, 1-[(6-bromochromo-2-yl)-carbonyl]-morpholine were also synthesized. The Suzuki cross-coupling reaction was also utilized, inserting a benzene ring in the chromone moiety of several chromone-2-carboxamides.

The compounds synthesized were purified either by flash chromatography or recrystallization using ethanol-water. The yields of chromone-2-carboxylic acids ranged from 85-90 %, those of the chromone-2-carboxamides ranged from 40-72 %, and for the Suzuki reaction the yields ranged from 40-55 %.

The compounds synthesized were analysed by ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy. The spectra of these compounds were as expected for the target compounds. The synthesized compounds were also analysed by FTIR spectroscopy for their functional groups, confirming the identities of the target compounds.

Keywords: *Chromones, synthesis, bioactivity, spectroscopy, flash chromatography.*

ACRONYMS AND ABBREVIATIONS

$CDCl_3$	**Deuterochloroform**
CH_2Cl_2	**Dichloromethane**
CH_3-	**Methyl**
CH_3O-	**Methoxy**
DMF	***N,N*-Dimethylformamide**
EtOAc	**Ethyl acetate**
EtOH	**Ethanol**
HCl	**Hydrochloric acid**
HIV	**Human Immunodeficiency Virus**
HPA	**Heteropoly acid**
H_2SO_4	**Sulphuric acid**
IR	**Infrared spectroscopy**
MS	**Mass spectrometry**
$NaOCH_2CH_3$	**Sodium ethoxide**
$NaOCH_3$	**Sodium methoxide**
NMR	**Nuclear magnetic resonance spectroscopy**
OH	**Hydroxyl**
$POCl_3$	**Phosphorus oxychloride**

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1.1 Physical and Spectroscopic Properties of Chromones

Most properties of chromones correlate with those of γ-pyrone and can be ascribed to the aliphatic dienone structure (**2**), although some properties, such as the lack of normal ketonic activity and the exceptional reactivity of the carbonyl oxygen, may be ascribed to essential π-electron delocalization consistent with the aromatic pyrylium betaine structure (**3**). Arndt was the first person to propose the electronic interaction of the ether oxygen with the carbonyl carbon.[5] According to the IUPAC nomenclature, chromone **1** is called 1,4-benzopyrone.[1,2] The great propensity of γ-pyrone and chromone to form salts with acids results from their observed basicity which has been rationalised in terms of the betaine structure (e.g. **3**).[7] Although the pK_a value of γ-pyrone (0.1) is comparable to nitrogen bases with very low basic strength, it is nevertheless remarkably high compared to other oxygen bases. The pK_a of chromone (2.0) is higher than that of γ-pyrone.[4]

The spectroscopic properties are rationalised in terms of the aliphatic dienone system (**2**). The IR carbonyl stretching frequency of chromone occurs at ca. 1660 cm^{-1}, the exact value depending on the solvent used.[8] This value is lower than the carbonyl stretching frequency of coumarin **8** (Figure 3; ν_{max} 1710 cm^{-1}) and IR spectroscopy may thus be used to differentiate chromones and coumarins. The UV spectra of chromone and its derivatives are characterised by four bands centred at 205, 225, 240 and 300 nm, the last two being major absorption bands. Solvent studies have shown that the shortest wavelength band is probably a $\pi \rightarrow \sigma^*$ transition involving the heteroatom lone-pair electron, while the three longer wavelength bands arise from $\pi \rightarrow \pi^*$ transitions. The latter bands are generally red-shifted by C-2 electron withdrawing groups or blue-shifted by a C-2 methyl group.[6]

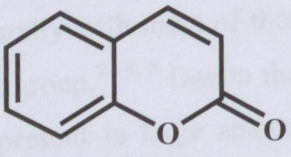

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Figure 3: Coumarin **8**

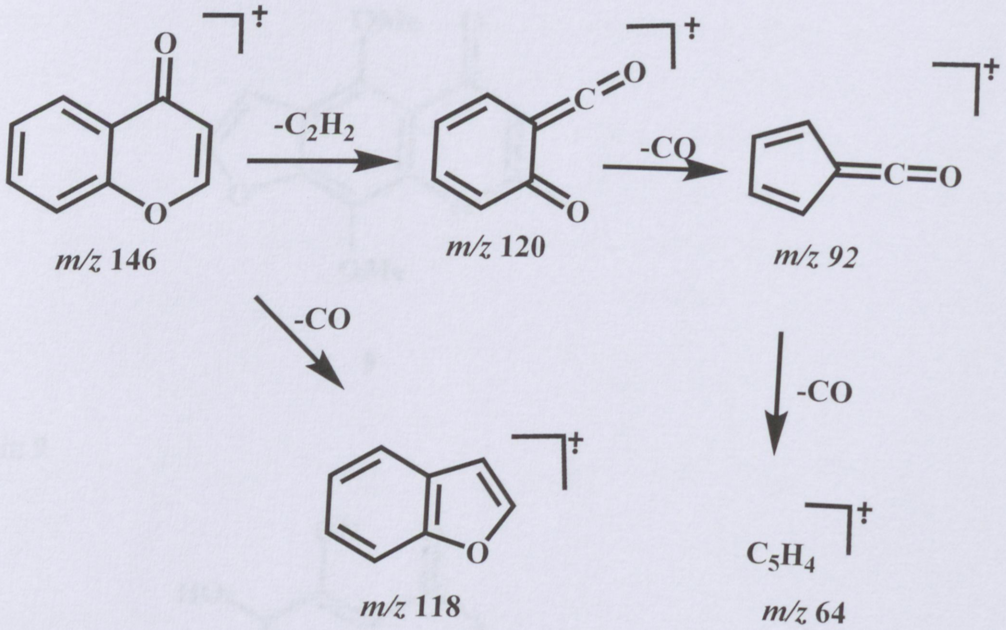
Studies of dipole moments and ^{1}H and ^{13}C NMR spectroscopy support the theory that some degree of aromaticity exists in chromones.[6] The π-electronic structure has been used to rationalize general chromone properties, with the γ-pyrone ring assuming the aliphatic dienone structure **2** rather than the pyrylium betaine structure **3**. The ^{1}H-NMR spectrum of chromone in $CDCl_3$ shows that 2-H and 3-H protons resonate at $\delta = 7.88$ and $\delta = 6.34$ ppm, respectively.[4] The values are nearly the same as the ones found in γ-pyrone (δ= 7.88 and 6.38 ppm, respectively), which shows that benzannulation has almost no effect on the ring current of the heterocyclic ring.[4]

In the ^{13}C-NMR spectrum of chromone, the carbonyl carbon (C-4) signal always resonates at low field (δ=177 ppm) and is nearly unaffected by substitution in the system. Substitution at C-2 or C-3 of the chromone nucleus, on the other hand, has a major effect on the chemical shifts of these carbon atoms. For example, substitution with either methyl or phenyl groups causes a downfield shift for the carbon to which they are attached, but an upfield shift for the adjacent carbon atoms.[4, 7] The infrared (IR) carbonyl stretching frequency for chromone is higher than that of γ-pyrone.

The mass spectrometric analysis of chromone yields a molecular ion that fragments *via* two routes involving either loss of carbon monoxide or ring cleavage by a retro-Diels-Alder (RDA) reaction (Scheme 1).[4]

1.2 Natural distribution and bioactivity of chromones

Chromones form one of the major classes of naturally occurring compounds, and interest in their chemistry continues to increase because they are very useful as biologically active agents.[4] There are many chromones that occur naturally with most of them containing a hydroxyl (OH) or an alkoxy (ROH, where R= CH_3, C_6H_5) group.[2, 4, 8] Due to their abundance in plants and their low toxicity, chromone derivatives are present in large amounts in the human diet. Some of the biological activities shown by chromone derivatives include anticancer,[9] neuroprotective,[10] anti-allergenic,[3,11] anti-fungal,[12] anti-microbial,[13] anti-viral,[14] anti-tubulin,[15] and anti-oxidant[3] properties; some are also tyrosine and protein kinase C inhibitors.[16]



Scheme 1: MS fragmentation of chromone

Many of these biological activities have resulted in the chromone ring system being regarded as a very useful structure in medicinal lead discovery.[17] A limited number of these chromones will be discussed which will illustrate their diversity of structure, location and biological or pharmacological activity.

Khellin **9** (Figure 4), a furochromone that was isolated from the fruits and seeds of *Ammi visnaga*, has been used in parts of the African continent for medical practices. It was found to induce the relaxation of muscles and cause an improvement or reduction of the symptoms of bronchial asthma.[18] The 2-aminochromones also exhibit biological activities. This chromone derivative is explained as an antiplatelet agent with enough power in treating unstable angina and other thrombolytic disorders.[19] These 2-aminochromones contain an alkoxy (e.g. methoxy (CH_3O)) or a hydroxyl (OH) group at C-7 and these structural features are said to be necessary for pharmacological activity.[18]

Koda *et al.* showed that the flavonoid baicalein **10** (Figure 5), which is part of the dried radix of *Scutellaria baicalensis* Gerog. was used as a diuretic and anti-allergic drug in ancient Chinese medicine. It has been reported to exhibit anti-allergic activity.[19, 20]

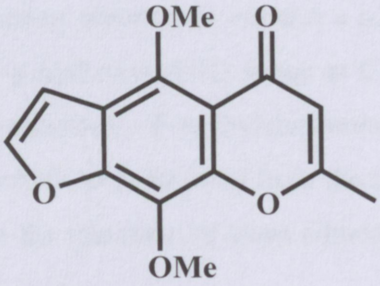


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Figure 4: Khellin **9**

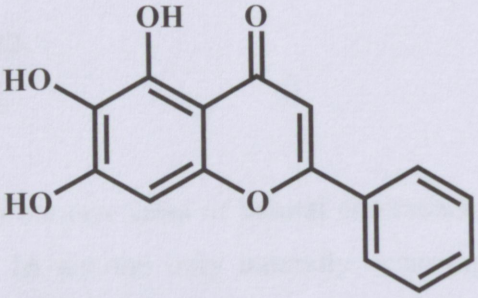

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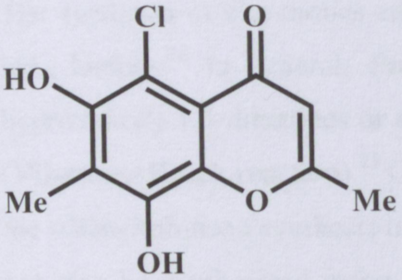
Figure 5: Baicalein **10**

Rupicolon **11**, which is a halogenated hydroxychromone, was isolated from the extracts of lichens, while the only natural chromone carboxylic acid, siphulin **12** (Figure 6), occurs in a Scandinavian lichen, *Siphula ceretites*.[2]



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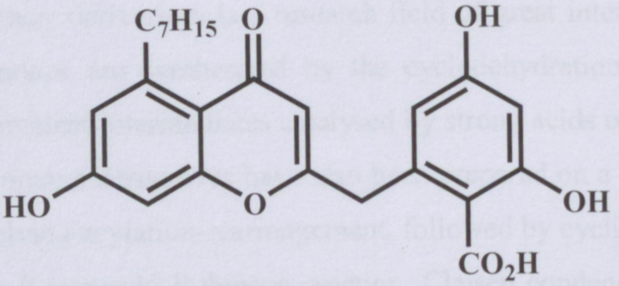

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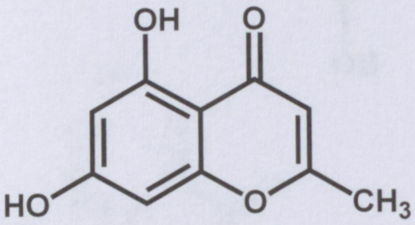
Figure 6: Rupicolin **11** and siphulin **12**

Some of these naturally occurring chromones contain a methyl (CH_3-) group at C-2, a phenyl (C_6H_5) group at C-2/C-3 and a hydroxyl (OH) group at C-5 and/or C-7 as shown in Figure 7. These chromones include 5,7-dihydroxy-2-methylchromone **12** and 5,6-dihydroxy-7-methoxy-2-methylchromone **13**, both of which were isolated from the bulb of *Pancratium biflorum* Roxb.[1,21] These compounds are used for the treatment of chest ailments and fungal diseases.[1,21]



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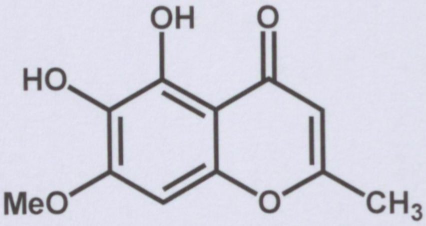

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Figure 7: 2-Methylchromones

2-Styrylchromones (Figure 8) are rare class of natural chromones. Hormothamnione **15** and 6-desmethoxyhormothamnione **16** are the only naturally occurring styrylchromones that were isolated from the marine cryptophyte *Chrysophaeum taylori*. Hormothamnione is exceptionally cytotoxic to P388 lymphocytic leukaemia and HL-60 promyelocytic leukaemia cell lines *in vitro* and appears to be a selective inhibitor of RNA synthesis. 6-Desmethoxyhormothamnione showed cytotoxicity to 9 KB cell lines.[22, 23]

1.3 General chromone syntheses

The synthesis of chromones and their derivatives is a research field of great interest and has a long history.[24] In general, chromones are synthesized by the cyclodehydration of 1-(*ortho*-hydroxyaryl)-1,3-diketones or equivalent intermediates catalysed by strong acids or strong bases (Vilsmeier-Haack reaction).[25] Chromone derivatives have also been prepared on a large scale by the Allan-Robinson synthesis involving acylation-rearrangement, followed by cyclization.[26] They can also be synthesized using the Kostanecki-Robinson reaction, Claisen condensation, Baker-Venkataraman rearrangement, acidic, basic, and/or microwave heating conditions of which are the most general synthetic methods.[27, 28] In the following discussion we will only restrict ourselves to four general methods.

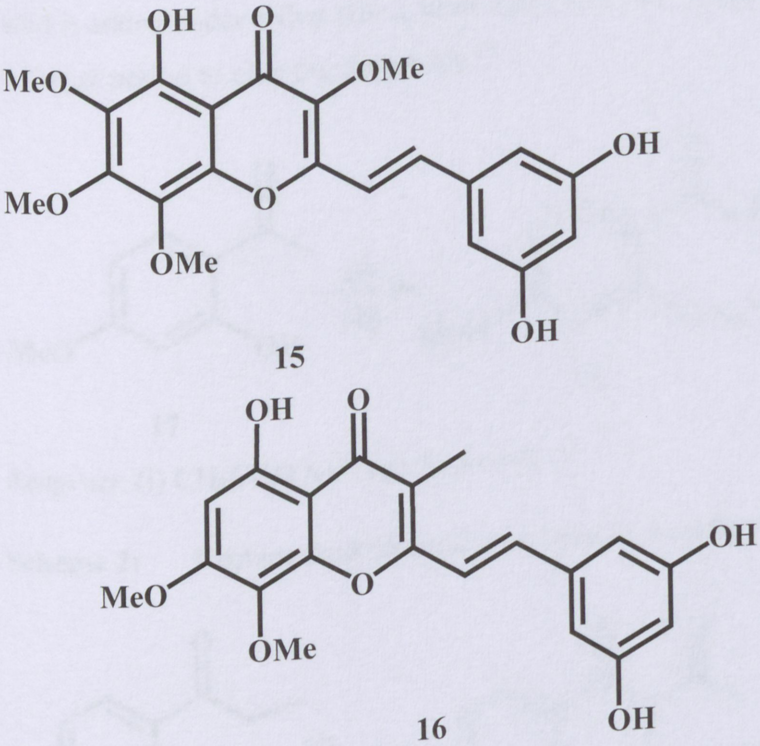


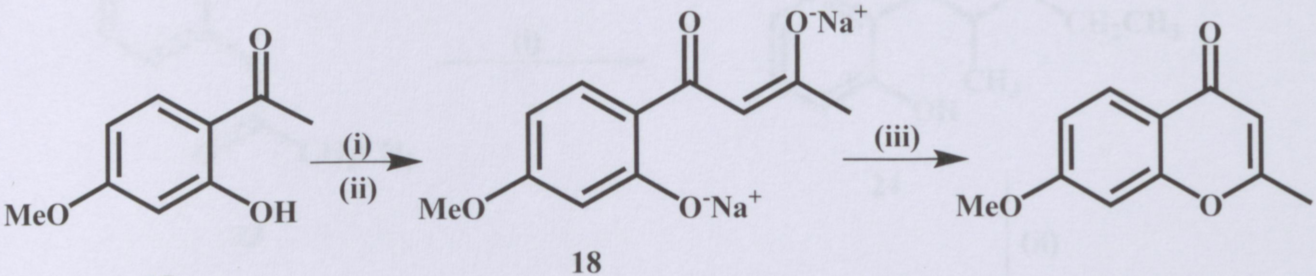
Figure 8: 2-Styrylchromones

1.3.1 Kostanecki-Robinson reaction

In the Kostanecki-Robinson reaction, chromones are formed from an alkoxy *ortho*-hydroxyaryl ketone and aliphatic acid anhydride in the presence of the corresponding aliphatic acid sodium salt, through *ortho*-acylation and aldol condensation.[29] 4-methoxy-2-hydroxyacetophenone **17** is condensed with an acylation agent to form an α,β-diketone derivative **18** which readily cyclizes to 7-methoxy-2-methylchromone **19** upon acidification as shown in Scheme 2.[17]

1.3.2 Claisen condensation with a carboxylic ester

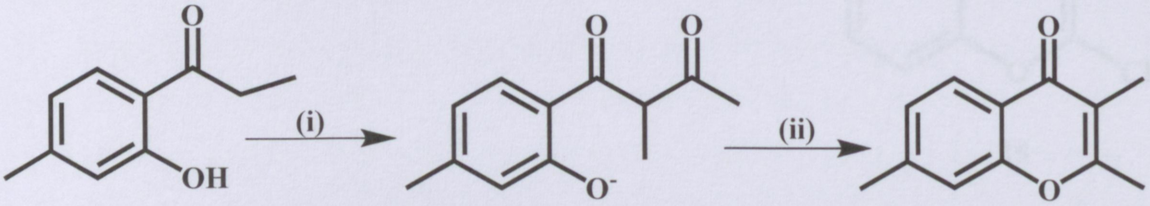
Claisen condensation is a carbon-carbon bond forming reaction that occurs between two esters or an ester and a carbonyl compound **20** in the presence of a strong base with a carboxylic ester in the presence of a strong base is one of the most frequently used methods when preparing chromones. The intermediate called 1,3-dioxophenol **21** is cyclized by heating in an acidic medium to give the 2-ethyl-3,7-dimethylchromone **22** as shown in Scheme 3. An excess of an acid is added under reflux (for a short time) or it can be allowed to stand at room temperature for a longer period to give the chromone.[29]



17 18 19

Reagents: (i) $CH_3COO^-Na^+$; (ii) Ac_2O (iii) H^+

Scheme 2: Kostanecki-Robinson: synthesis of 2-methyl-7-methoxychromone **19.**



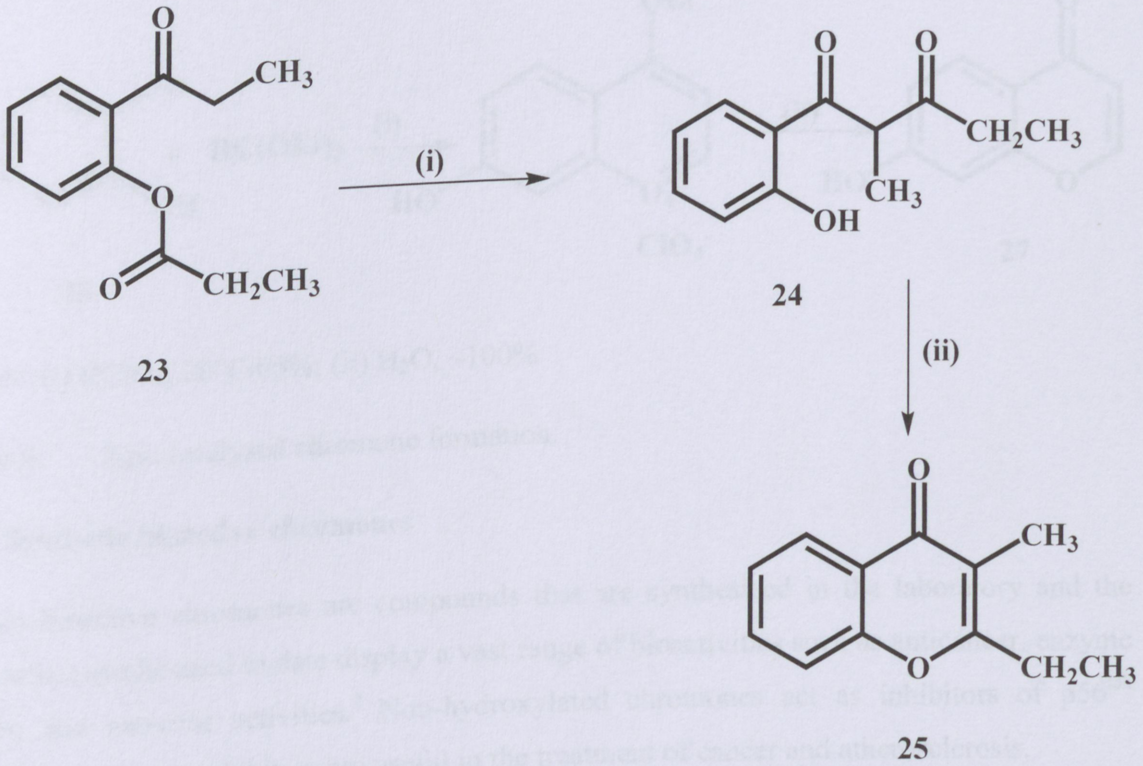
20 21 22

Reagents: (i) CH_3COOCH_3/base; (ii) H^+

Scheme 3: Claisen condensation to give 2,3,7-trimethylchromone **22**.

1.3.3 The Baker-Venkataraman rearrangement

The Baker-Venkataraman rearrangement is the base-catalysed rearrangement of aromatic *ortho*-acyloxyketones such as **23** to give the aromatic diketones **24** (Scheme 4). The diketones are important synthetic intermediates that are widely used for the synthesis of chromones and other compounds. Beta-diketones can be cyclized, for example, to 2-ethyl-3-methylchromone **25** by treatment with bulky base, potassium *tert*-butoxide in DMSO as shown in Scheme 4.[29]

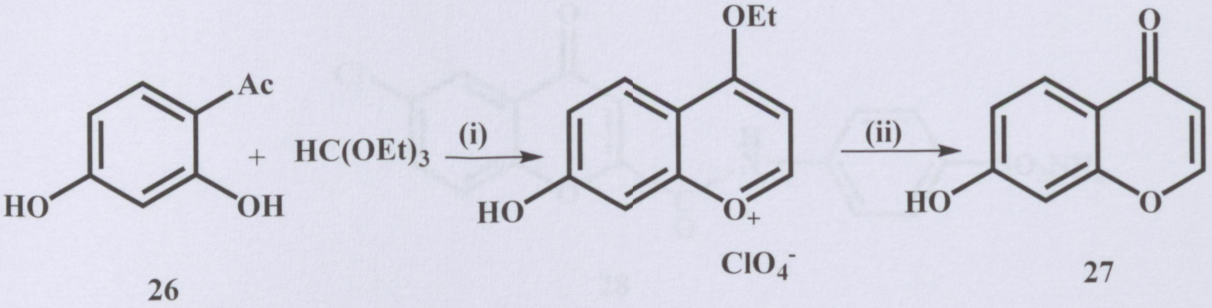


Reagents: (i) $C(CH_3)_3O^-K^+$/ DMSO, (ii) H^+

Scheme 4: Baker-Venkataraman rearrangement of *ortho*-acyloxyketone **23** and cyclization of a 1,3-diketone to 2-ethyl-3-methylchromone **25.**

1.3.4 Condensation under acidic conditions

Acids may act as catalysts in chromone ring closure, for example, perchloric acid ($HClO_4$), polyphosphoric acid (PPA), phosphorus oxychloride ($POCl_3$), hydrochloric acid (HCl), or sulphuric acid (H_2SO_4), can be used. $HClO_4$ was the first acid catalyst to be used for this reaction. For example, when a phenolic compound bearing an acyl side chain, such as **26**, is heated under reflux in perchloric acid, 7-hydroxychromone **27** is formed as shown in Scheme 5.[29]



Reagents: (i) $HClO_4$, 20°C/65%; (ii) H_2O, ~100%

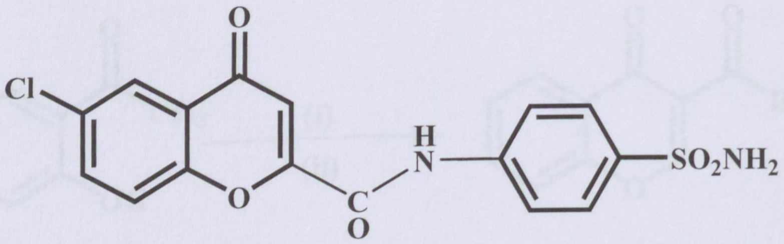
Scheme 5: Acid catalysed chromone formation.

1.3.5 Synthetic bioactive chromones

Synthetic bioactive chromones are compounds that are synthesized in the laboratory and the large number synthesized to date display a vast range of bioactivities such as anticancer, enzyme inhibitor, and antiviral activities.[2] Non-hydroxylated chromones act as inhibitors of $p56^{lck}$ tyrosine kinase. These inhibitors are useful in the treatment of cancer and atherosclerosis.

It has been shown that some chromone carboxamides constitute an effect on the central nervous system.[24] *N,N*-diethylchromone-2-carboxamide exhibits sedative and hypnotic activity. Several *N*-arylamides (Figure 9) exhibit analgesic properties; the sulphonamide **28** was found to be the most important arylamide to exhibit this activity. The amide **29** shows anti-histaminic activity and the *N*-arylchromone-3-carboxamides **30** show anti-bacterial activity.[24]

The substituted chromone-2- or 3-carboxamide **31** (Figure 10) has anti-inflammatory activity. The flavone was found to be the most important.[30]



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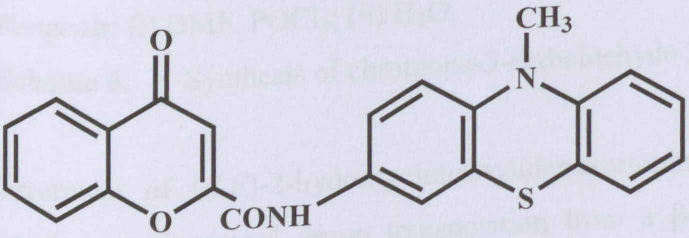

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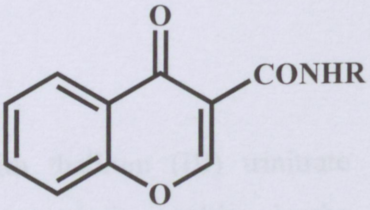

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Figure 9: Chromone carboxamides

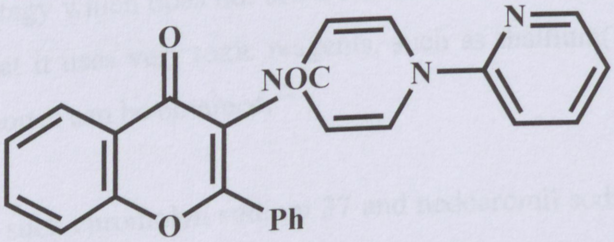

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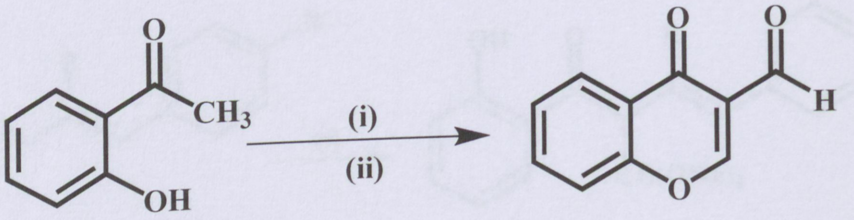
Figure 10: Chromone carboxamide derivative

Several synthetic chromones contain an aldehyde group at C-2 or C-3, for example, chromone-3-carbaldehyde **33,** which is prepared from *ortho*-hydroxyacetophenone **32** using DMF, $POCl_3$, and H_2O as shown in Scheme 6.[2]



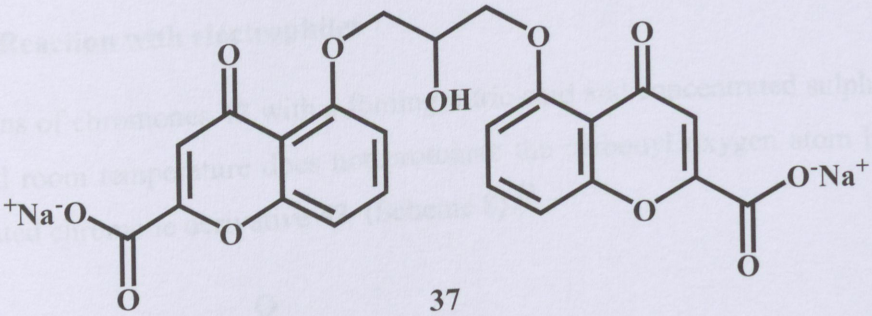
32 **33**

Reagents: (i) DMF, $POCl_3$; (ii) H_2O.

Scheme 6: Synthesis of chromone-3-carbaldehyde **33**

Treatment of (*E,E*)-2-hydroxycinnamylideneacetophenones **34** with thallium (III) trinitrate involves a cinnamoyl group transposition from a β-carbon to an α-carbon, resulting in the formation of intermediate 3-alkyl-4-aryl-1-(2-hydroxyphenyl)-2-dimethoxymethyl-3-buten-1-ones **35**. Treatment of acetals **35** with dilute hydrochloric acid gave the corresponding 3-styrylchromones **36** (Scheme 7). This method gave rise stereoselectively to the (*E*)-isomers and is the only known strategy which does not use a chromone as starting material. The reaction has some limitations in that it uses very toxic reagents, such as thallium(III) trinitrate, and only 3-(α,β-alkylstyryl)chromones can be obtained.[22]

Chromone derivatives such chromolyn sodium **37** and nedocromil sodium **38** (Figure 11) play a very useful part in preventing both early and late asthmatic responses to inhaled allergens, such as pollen, and reducing airway reactivity to a range of inhaled irritants, such as sulphur dioxide and cold air.[5] Many chromones have useful medicinal properties and some, like 8-allyl-2-styrylchromones **39**, are used as inhibitors for the growth of tumors.[37] Other chromone derivatives act as precursors for the formation of certain 8-acetic acid derivatives that have shown anticancer properties.[31]



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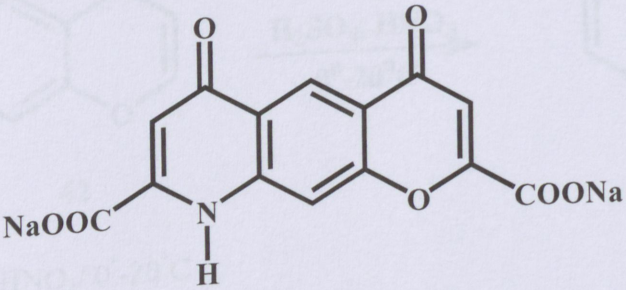

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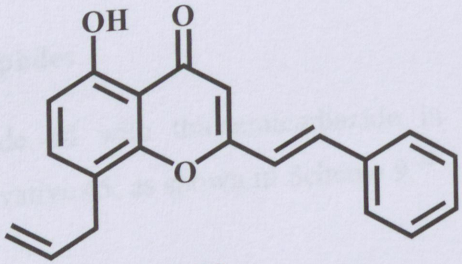

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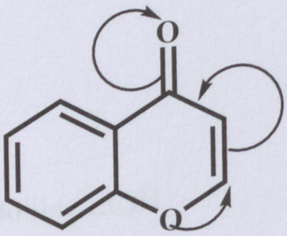
Figure 11 : Chromone derivatives with medicinal properties



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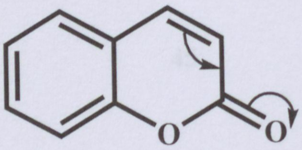

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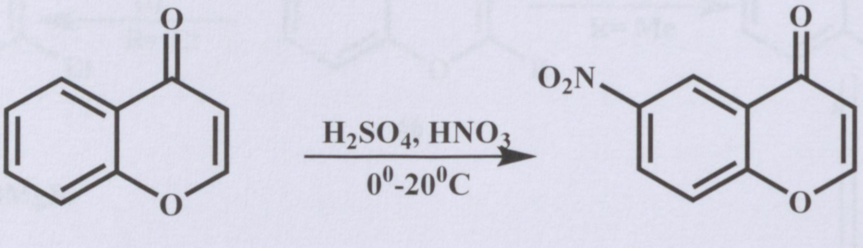
Figure 12: Chromone and coumarin

1.4.1 Reaction with electrophiles

Reactions of chromones **42** with a fuming nitric acid and concentrated sulphuric acid at between 0^0C and room temperature does not protonate the carbonyl oxygen atom but gives the 6-nitro substituted chromone derivative **43** (Scheme 8).[32]



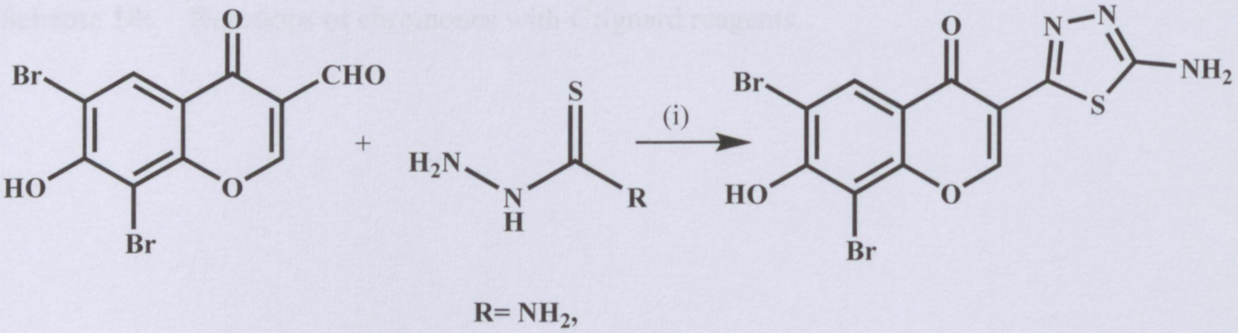
42 **43**

Reagents: H_2SO_4, HNO_3/ 0°-20°C

Scheme 8: Nitration of chromone.

1.4.2 Reaction with nucleophiles

Condensation of carbaldehyde **44** with thiosemicarbazide in boiling ethanol afforded the corresponding hydrazone derivative **45**, as shown in Scheme 9.[32]

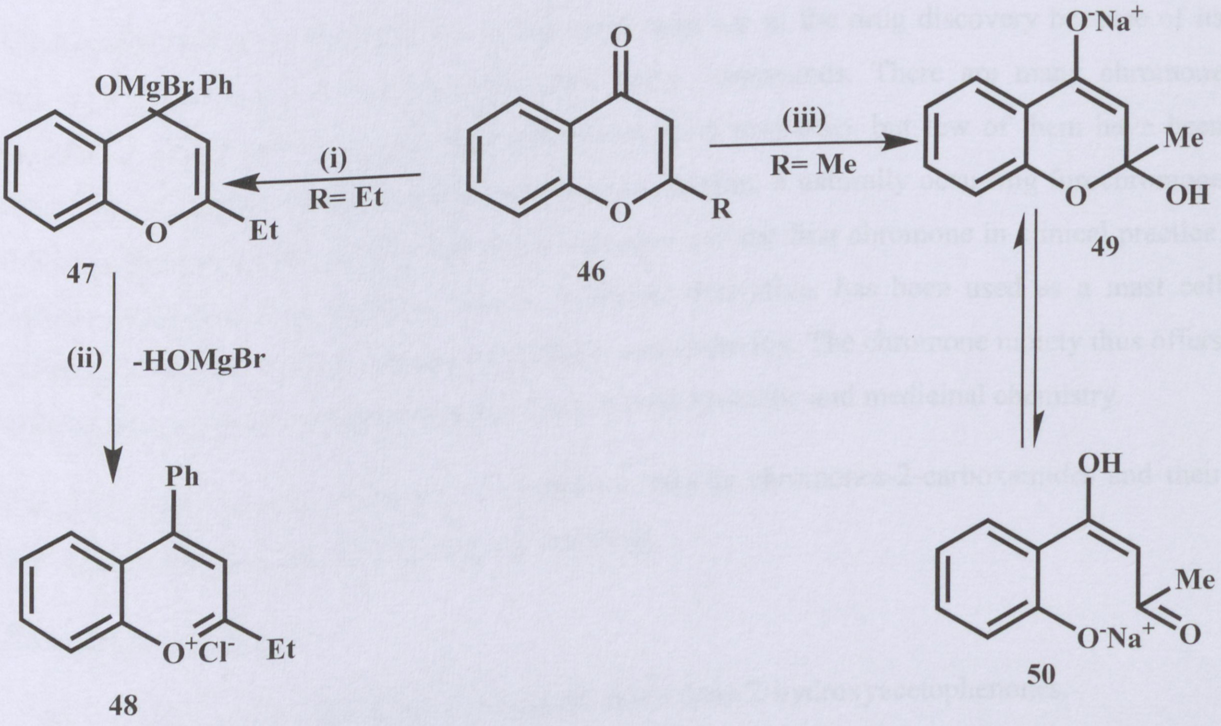


44 **45**

Reagents: (i) Boiling EtOH

Scheme 9: Condensation of chromone-3-carbaldehyde **45** with thiosemicarbazide.

Hard nucleophiles (such as Grignard reagents) may attack at the carbonyl carbon of compound **46** to give **47** of which upon acidification results in the final compound **48**, whereas softer ones such as hydroxide ions, attach at C2 by conjugative addition (e.g. **49**), and this may lead to ring opening (e.g. **50**) (Scheme 10).[32]



Reagents: (i) PhMgBr, Et_2O (ii) HCl/ 0°C (iii) NaOH aq

Scheme 10: Reactions of chromones with Grignard reagents.

Chapter 2

Problem Statement, Aims and Objectives

Chromones have been classified as an important structure in the drug discovery because of its use in a wide variety of pharmacologically active compounds. There are many chromone derivatives which are known for their pharmacological properties but few of them have been tested and successfully used as therapeutic agents. Khellin, a naturally occurring furochromone extracted from the seeds of the plant *Ammi visnaga,* was the first chromone in clinical practice. Sodium chromoglycate, which is also a chromone derivative, has been used as a mast cell stabilizer in allergic rhinitis, asthma and allergic conjunctivitis. The chromone moiety thus offers wide opportunity for new research endeavours in both synthetic and medicinal chemistry.

The aims of the present study are to synthesize various chromones-2-carboxamides and their derivatives and subject them to biological screening.

The objectives include:-

(i) Synthesis of chromone-2-carboxylic acids from 2-hydroxyacetophenones.
(ii) Synthesis of chromone-2-carboxamides from chromone-2-carbonyl chloride.
(iii) Microwave assisted ring-opening reaction of chromone-2-carboxamides.
(iv) Suzuki coupling reaction on 6-bromo-2-carboxamides
(v) Use of NMR, IR and MS to characterize compounds prepared.

Chapter 3

Results and Discussion

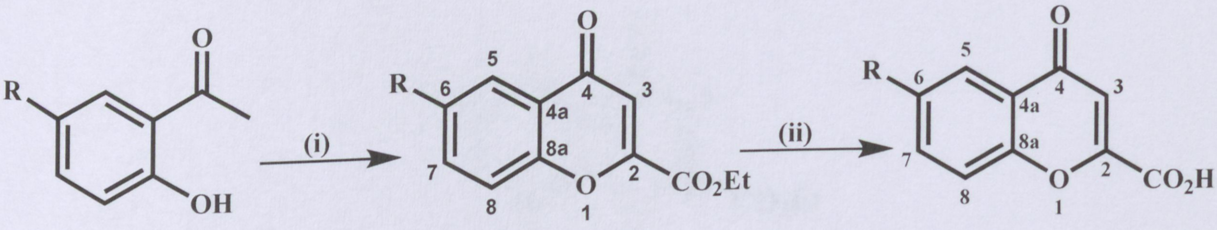
The substituted 2-hydroxyacetophenones were used as precursors for the preparation of chromone-2-caboxylic acids as shown in Scheme 11. These chromone-2-carboxylic acids were used as intermediates for the preparation of chromone-2-carboxamides as shown in Schemes 12-18. The 6-substituted bromochromone-2-carboxamide was further used for Suzuki cross-coupling reactions in section **3.3**.

3.1 Synthesis of chromone-2-carboxylic acids

Chromone-2-carboxylic acids **53a-53e** were synthesized as shown in the reaction Scheme 11. Claisen acylation of the 2-hydroxyacetophenones **51a-51e** and diethyl oxalate in the presence of sodium ethoxide which was generated in *situ*, followed by cyclization of the intermediates **52a-52e** and acid hydrolysis afforded the targeted compounds as described by Fitton and Smalley[33] and Bryan *et al*.[34] The ^{1}H NMR spectroscopy detected an ester intermediate, **52, 55, 58, 61, 64**. The chemical shift of the aromatic protons of the intermediates occur at low field (7.00-8.25 ppm), while the C-3 protons of the intermediate appear around (6.00-6.90 ppm). In all the reactions the crude intermediates were used without further purification.

The chromone-2-carboxylic acids **53a-53e** were also prepared using another method, using the 2-hydroxyacetophenones **51a-51e** and diethyl oxalate with sodium ethoxide, followed by sulphuric acid hydrolysis in one pot synthesis, as shown from reaction Scheme 12.[35] All the products were purified by recrystallization using hot ethanol-water solvents (ratio 80:20). The yields of these compounds were satisfactory compared with the literature ones (91-95%), ranging from 85 % to 90 %.

Although the melting points were different from the literature melting points the ^{1}H NMR and ^{13}C NMR indicates that the spectra are consistent with the structures of the compounds synthesised.

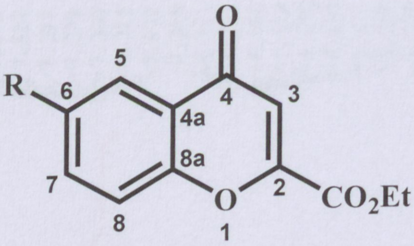


51 **52** **53**

2-hydroxy-acetophen-one	R	Ethyl chromone-2-carboxylate	Yield (%)	Chromone-2-carboxylic acid	% Yield	m.p. °C	Lit. m.p.°C [35]
51		52		53			
a	H	a	93	a	90	231-249	250-251
b	Br	b	91	b	92	208-213	265
c	Cl	c	89	c	92	179-188	267-269
d	CH_3O	d	90	d	92	299-303	268
e	F	e	88	e	91	239-248	257-259

Reagents: (i) NaOEt-EtOH/N_2, $(CO_2Et)_2$, (ii) AcOH-HCl (2:1), heat(2hrs)

Scheme 11: Synthesis of chromone-2-carboxylates and chromone-2-carboxylic acids.



R= H= 52a
Br= 52b
Cl= 52c
MeO= 52d
F= 52e

Table 1: ^{13}C NMR chemical shift values (ppm) of **52a-52e** in $CDCl_3$ (at 100MHz).

Nucleus	**52a**	**52b**	**52c**	**52d**	**52e**
CO_2Et	160.4	160.1	160.2	160.5	161.1
C-2	156.0	154.7	154.2	157.5	160.3
C-3	116.8	120.7	120.5	113.7	113.8
C-4	178.8	177.4	177.2	178.5	177.7
C-4a	125.7	125.6	125.1	125.0	125.6
C-5	126.0	128.3	131.9	104.5	110.7
C-6	124.2	119.5	125.2	152.1	158.6
C-7	134.9	137.7	134.96	125.2	123.2
C-8	114.6	114.6	114.5	120.3	121.1
C-8a	152.4	152.4	152.4	150.9	152.2
CH_2	63.2	63.2	63.2	63.0	63.2
CH_3	14.1	14.1	14.1	14.1	14.1
OCH_3	-	-	-	55.9	-

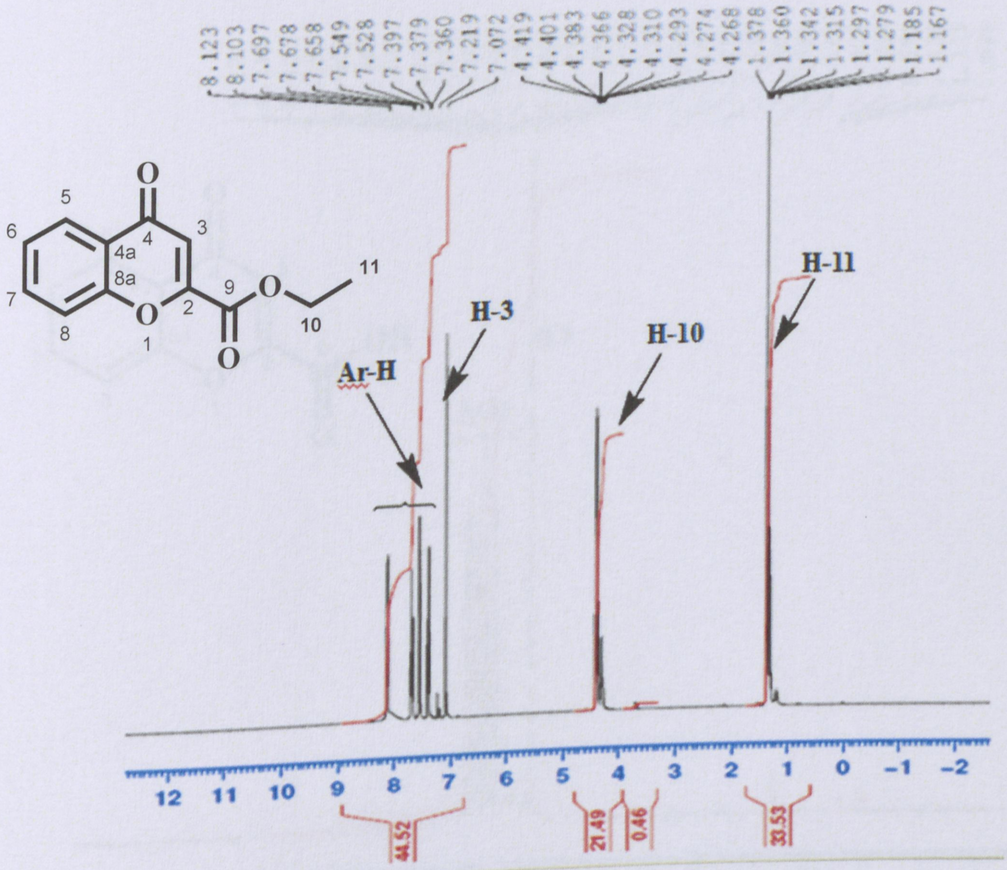


Figure 13: ^{1}H NMR spectrum of Ethyl chromone-2-carboxylate **52** in DMSO-*d*$_6$.

Table 2: ^{13}C NMR chemical shift values (ppm) of **53a-53e** in DMSO (at 100MHz).

Nucleus	**53a**	**53b**	**53c**	**53d**	**53e**
COOH	161.9	161.7	161.9	161.9	161.7
C-2	155.8	154.9	155.8	157.4	158.5
C-3	119.2	122.0	119.2	120.9	123.9
C-4	178.0	177.4	178.0	177.8	177.6
C-4a	125.3	125.5	124.1	124.8	125.4
C-5	126.4	127.4	126.6	105.0	110.9
C-6	124.1	119.0	125.3	153.4	160.9
C-7	135.5	138,3	135.7	124.9	122.3
C-8	113.9	113.6	113.9	112.9	113.0
C-8a	153.6	154.9	153.7	150.6	152.4
OCH_3	-	-	-	56.2	-

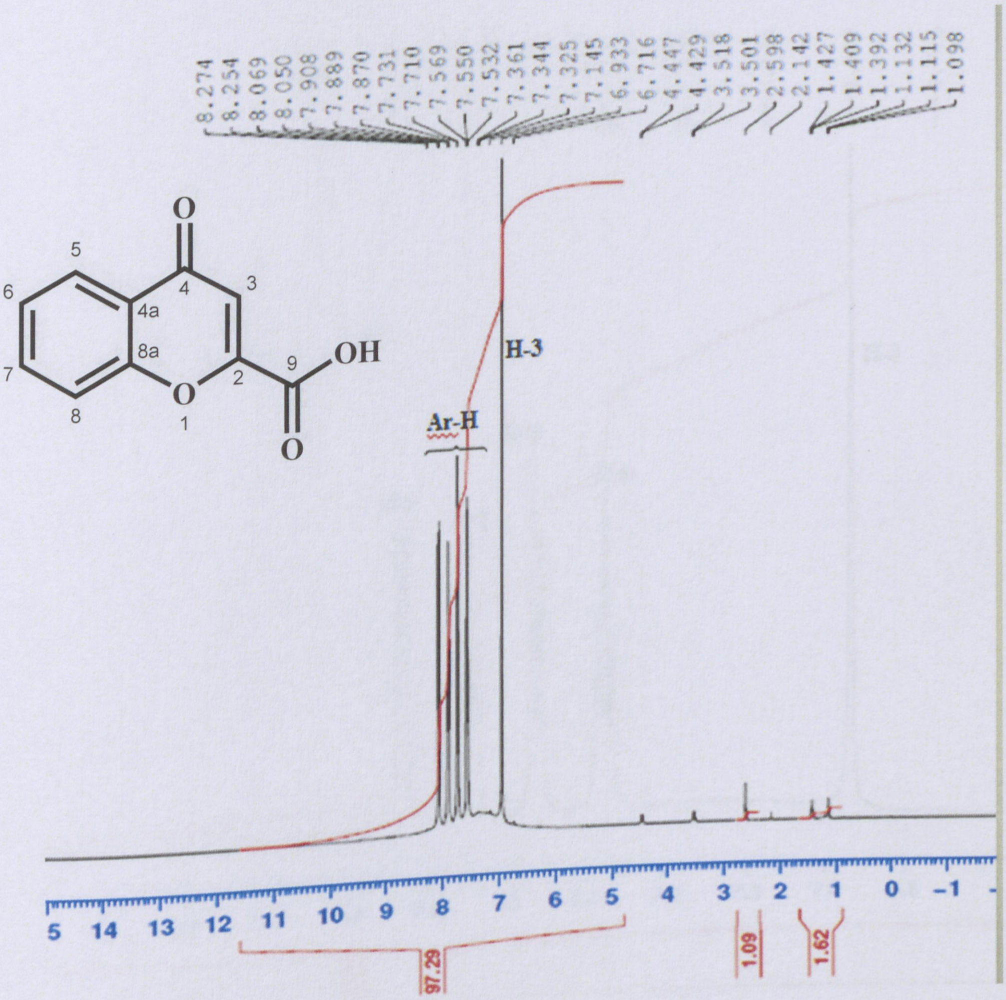


Figure 14: ^{1}H NMR spectrum of chromone-2-carboxylic acid **53a** in DMSO-d_6.

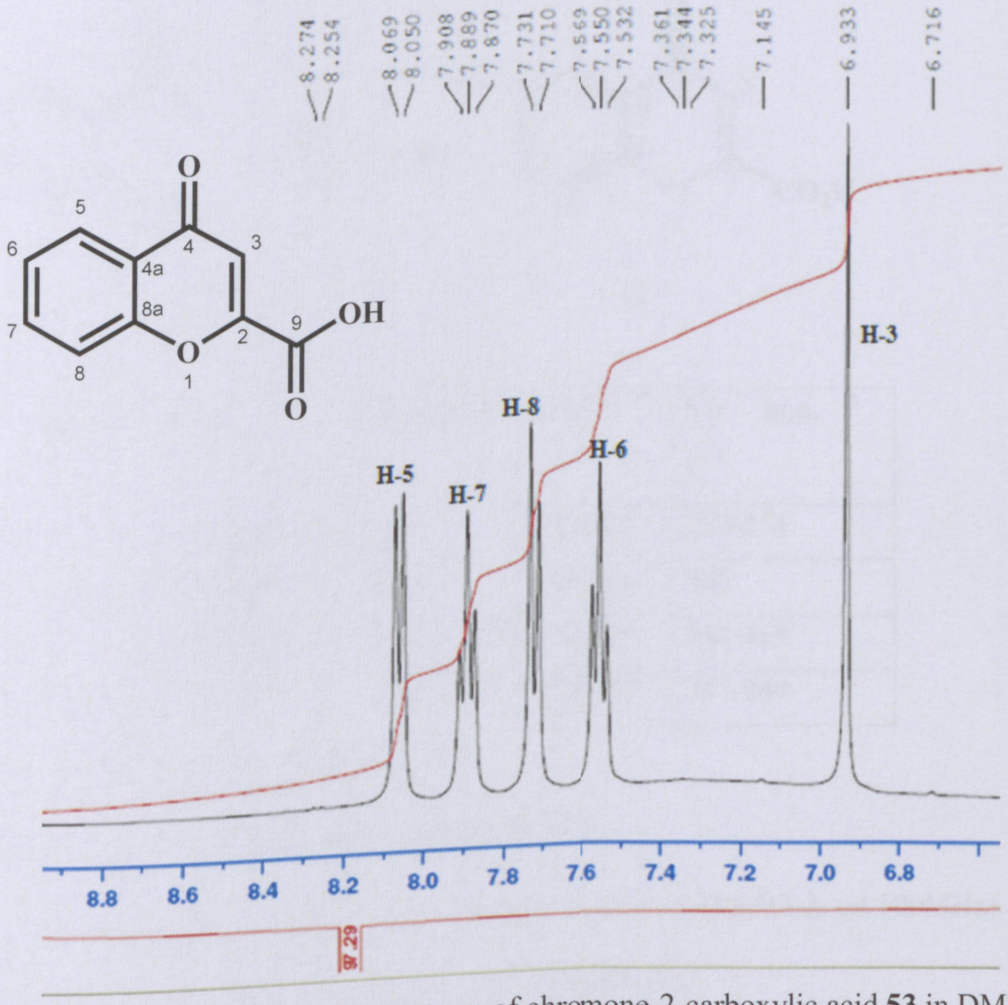
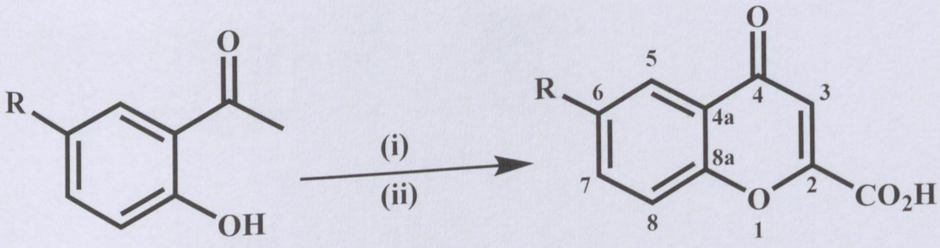


Figure 14a: Expansion of ^{1}H NMR spectrum of chromone-2-carboxylic acid **53** in DMSO-d_6.



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53

53	**R**	**% Yield**	**m.p. °C [35]**	**Lit. m.p. °C[35]**
A	**H**	**88**	**228-231**	**250-251**
B	**Br**	**90**	**147-153**	**265**
C	**Cl**	**88**	**179-183**	**267-269**
E	**F**	**85**	**173-177**	**257-259**

Reagents: (i) NaOEt-EtOH (ii) H_2SO_4, heat

Scheme 12: Synthesis of chromone-2-carboxylic acids.

Table 3: ^{13}C NMR chemical shift values (ppm) of **53a-53c** in DMSO-d_6 (at 100MHz).

Nucleus	**53a** (R=H)	**53b** (R=Br)	**53c** (R=Cl)
COOH	161.9	160.2	161.6
C-2	155.8	154.7	154.5
C-3	119.3	120.7	121.9
C-4	178.0	177.1	177.1
C-4a	125.4	125.6	124.3
C-5	126.5	128.3	131.0
C-6	124.2	119.5	125.2
C-7	135.6	137.7	135.5
C-8	113.9	114.7	113.8
C-8a	153.7	152.4	152.9

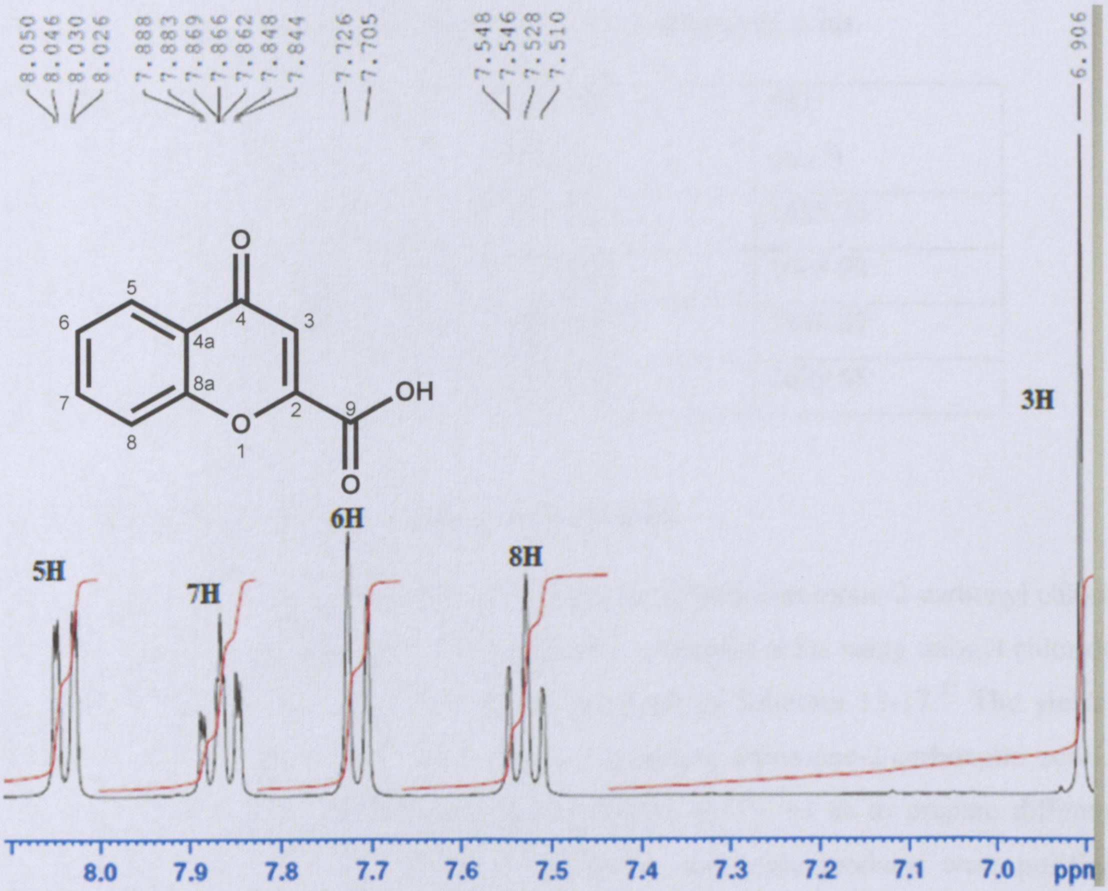


Figure 15: ^{1}H NMR spectrum of chromone-2-carboxylic acid **53a** in DMSO-d_6.

The ^{1}H NMR spectra of the chromone-2-carboxylic acids is characterised by the vinyl proton (3-H) singlet at ca 6.89 ppm (Table 4). C-6 substituents produce small variations in the (3-H) chemical shift, as shown in **Table 4**. The IR carbonyl absorption bands (*ca* 1732 cm^{-1}) of chromone-2-carboxylic acids are well separated from the ketone carbonyl absorption bands occurring at *ca* 1648 cm^{-1}.

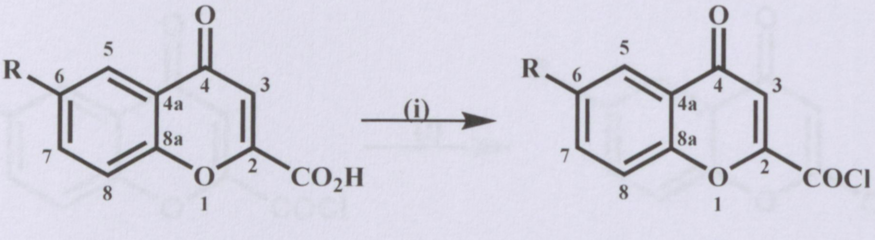
TABLE 4: Selected spectral data for chromone-2-carboxylic acids.

Chromone-2-carboxylic acid	3-H (ppm)	COOH (cm^{-1})	CO (cm^{-1})
53a	6.91	1732.61	1625.76
53b	6.94	1731.27	1648.92
53c	6.97	1726.82	1649.47
53d	6.85	1721.15	1629.68

3.2 Preparation of Chromone-2-carboxamides

The chromone-2-carboxamides **55a-o** were prepared from chromone-2-carbonyl chlorides **54a-e**, which in turn, were prepared from chromone-2-carboxylic acids using thionyl chloride and *N,N*-dimethylformamide in 1,2-dichloroethane as shown in Schemes 13-17.[37] The yields of all the carboxamide were calculated from the corresponding chromone-2-carboxylic acids. Different types of amines were used together with pyridine at 0°C so as to prepare different types of chromone-2-carboxamides.[38] In all the reactions, the crude products were purified by flash chromatography using a mixture of ethyl acetate and hexane (4:2 ratio) as the eluent.

Synthesis of chromone-2-carbonyl chloride.



53 **54**

TABLE 5: Synthesized chromone-2-carbonyl chlorides.

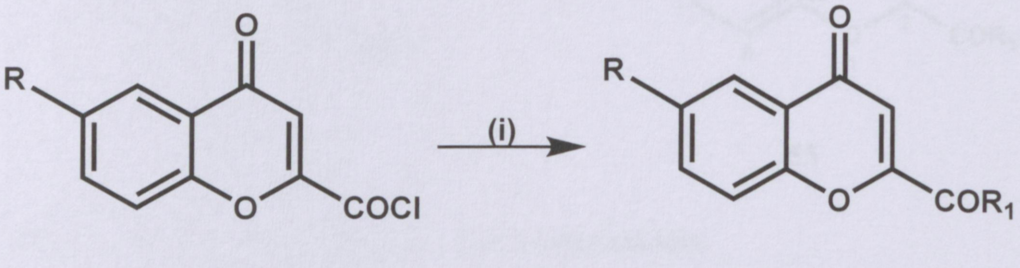
53	R_1	54	Percentage yield (%)
A	H	A	95
B	Br	B	92
C	Cl	C	92
D	MeO	D	93
E	F	E	89

These compounds were immediately used due to their high reactivity.

Reagents:(i) $SOCl_2$, DMF, $ClCH_2CH_2Cl$, heat

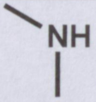
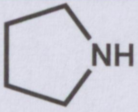
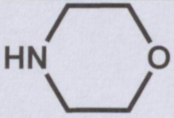
Scheme 13: Synthesis of substituted chromone-2-carbonyl chlorides.

Synthesis of chromone-2-carboxamide.

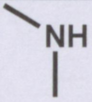
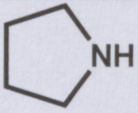
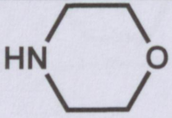


54 **55**

TABLE 6: Synthesized substituted chromone-2-carboxamides.

55	**R**	**R_1**	**% Yield**
A	**H**		**72**
B	**H**		**55**
C	**H**		**41**

Reagents:(i) Pyridine, 0°, **R_1= (Defined in the table below)**

R_1		
		

Scheme 14: Synthesis of substituted chromone-2-carboxamides.

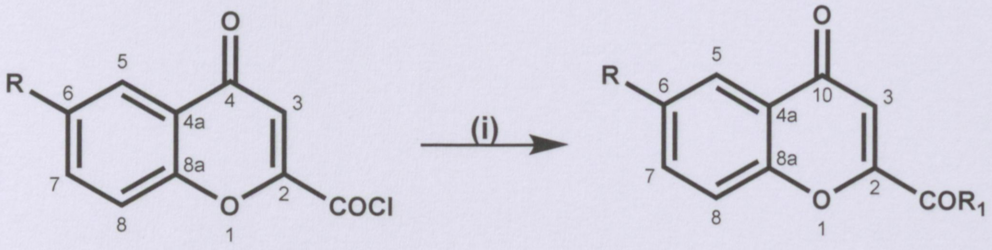


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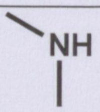
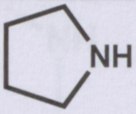
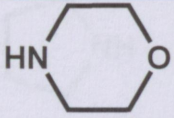
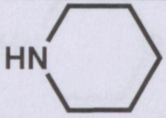
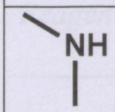
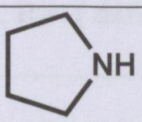
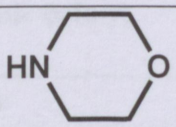
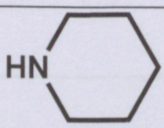
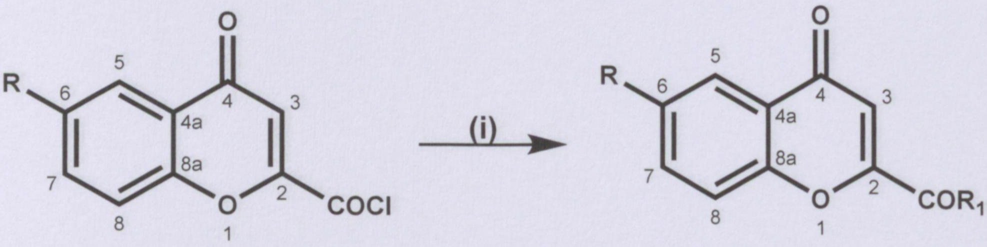
TABLE 7: Synthesized substituted chromone-2-carboxamides.

56	R	R₁	% Yield
D	**Br**		**78**
E	**Br**		**77**
F	**Br**		**45**
G	**Br**		**48**

Reagents:(i) Pyridine, 0°, **R_1= (defined in the table below)**

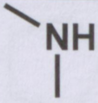
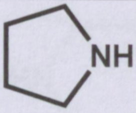
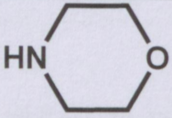
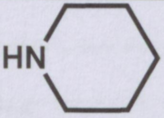
R₁			
			

Scheme 15: Synthesis of substituted chromone-2-carboxamides.

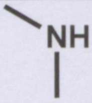
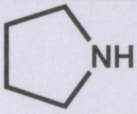
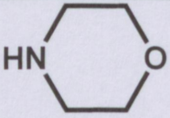
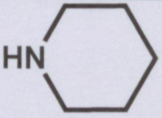


54 **55**

TABLE 8: Synthesized 5-Chloro substituted chromone-2-carboxamides.

Chromone-2-carboxamide	**R**	**R_1**	**% Yield**
H	**Cl**		**43**
I	**Cl**		**46**
J	**Cl**		**41**
K	**Cl**		**55**

Reagents:(i) Pyridine, 0°, **R_1= (defined in the table below)**

R_1			
			

Scheme 16: Synthesis of 5-chloro substituted chromone-2-carboxamides.

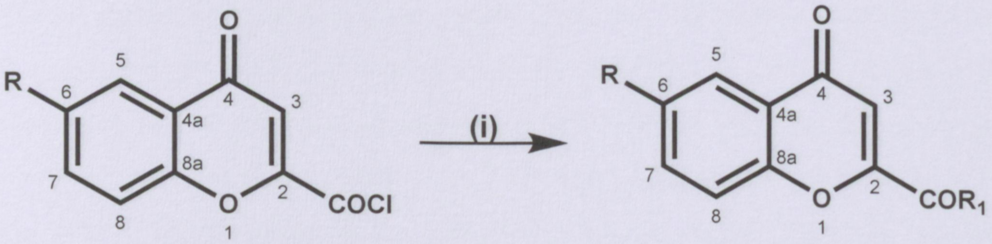


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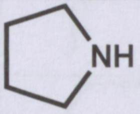
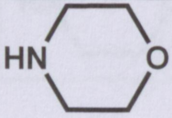
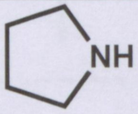
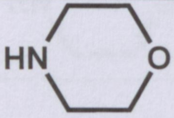
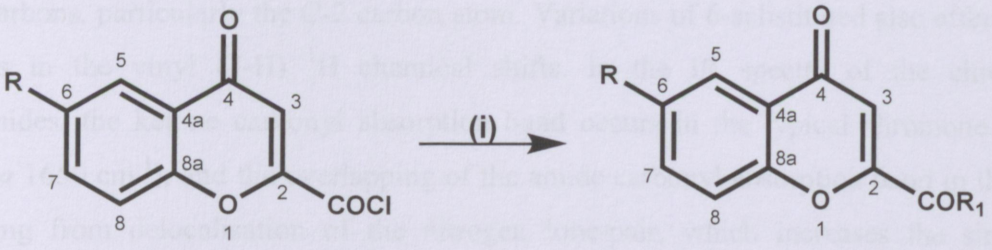
TABLE 9: Synthesized 5-methoxy substituted chromone-2-carboxamides.

Chromone-2-carboxamide	**R**	**R_1**	**% Yield**
L	**MeO**		**66**
M	**MeO**		**69**

Reagents: (i) Pyridine, 0°, **R_1= (defined in the table below)**

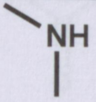
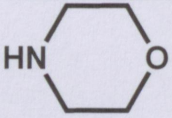
R_1	
	

Scheme 17: Synthesis of 5-methoxy substituted chromone-2-carboxamides.

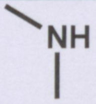
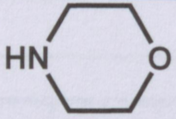


54 **55**

TABLE 10: Synthesized 5-fluoro substituted chromone-2-carboxamides.

Chromone-2-carboxamides	**R**	**R$_1$**	**% Yield**
N	**F**		**47**
O	**F**		**38**

Reagents:(i) Pyridine, 0°, **R$_1$= (defined in the table below)**

R$_1$	
	

Scheme 18: Synthesis of 5-fluoro substituted chromone-2-carboxamides.

The ^{1}H NMR spectra of the chromone-2-carboxamide **55a-o** are characterised by the vinyl proton (3-H) singlet at *ca* 6.52 ppm. The splitting of *N*-alkyl signals that is seen at room temperature in the **55a**, **55d**, **55h** NMR spectra reflects slow site-exchange of the *N*-alkyl substituents. The C-6 substituents produce wide variations in the C-6 ^{13}C chemical shifts relative to the parent chromone-2-carboxamide **55**. This effect slowly decreases with distance from the pyrone carbons, particularly the C-2 carbon atom. Variations of 6-substituted also effected small variations in the vinyl (3-H) ^{1}H chemical shifts. In the IR spectra of the chromone-2-carboxamides, the ketone carbonyl absorption band occurs in the typical chromone carbonyl region (*ca* 1650 cm^{-1}), and the overlapping of the amide carbonyl absorption band in this region is resulting from delocalisation of the nitrogen lone-pair, which increases the single-bond character of the amide carbonyl.

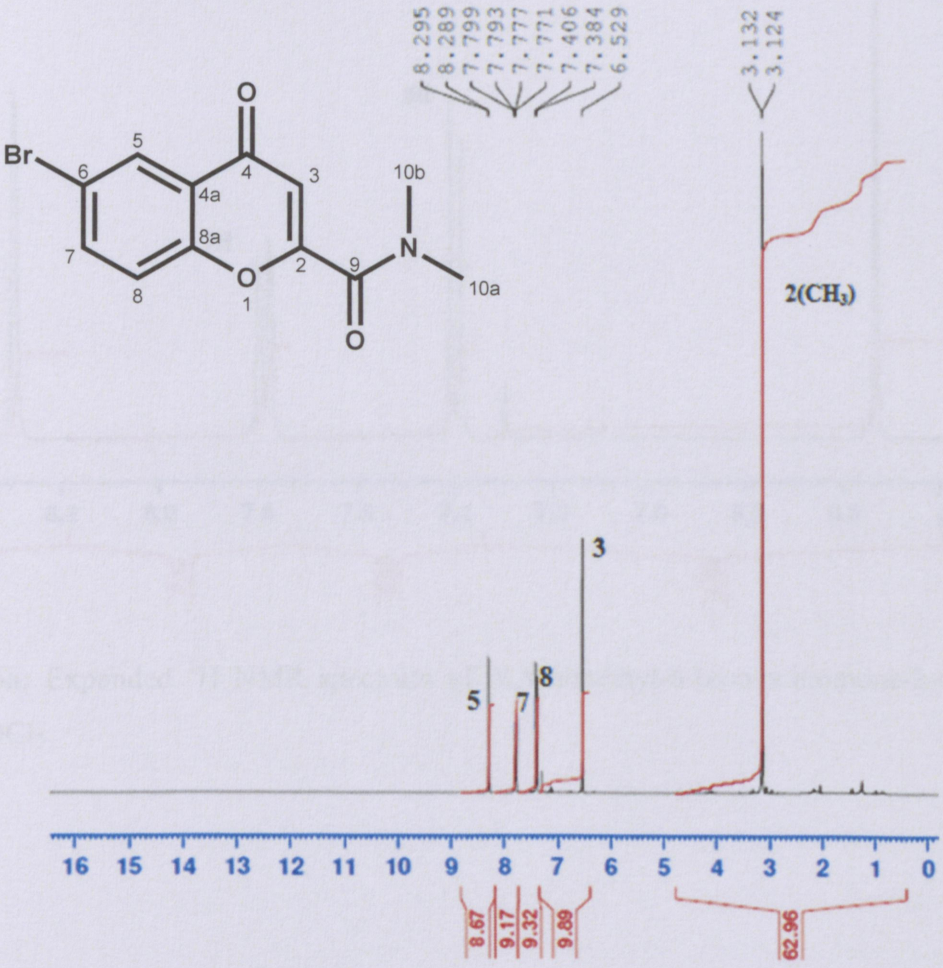


Figure 16: ^{1}H NMR spectrum of *N,N*-dimethyl-6-bromochromone-2-carboxamide **55d** in CDCl$_3$.

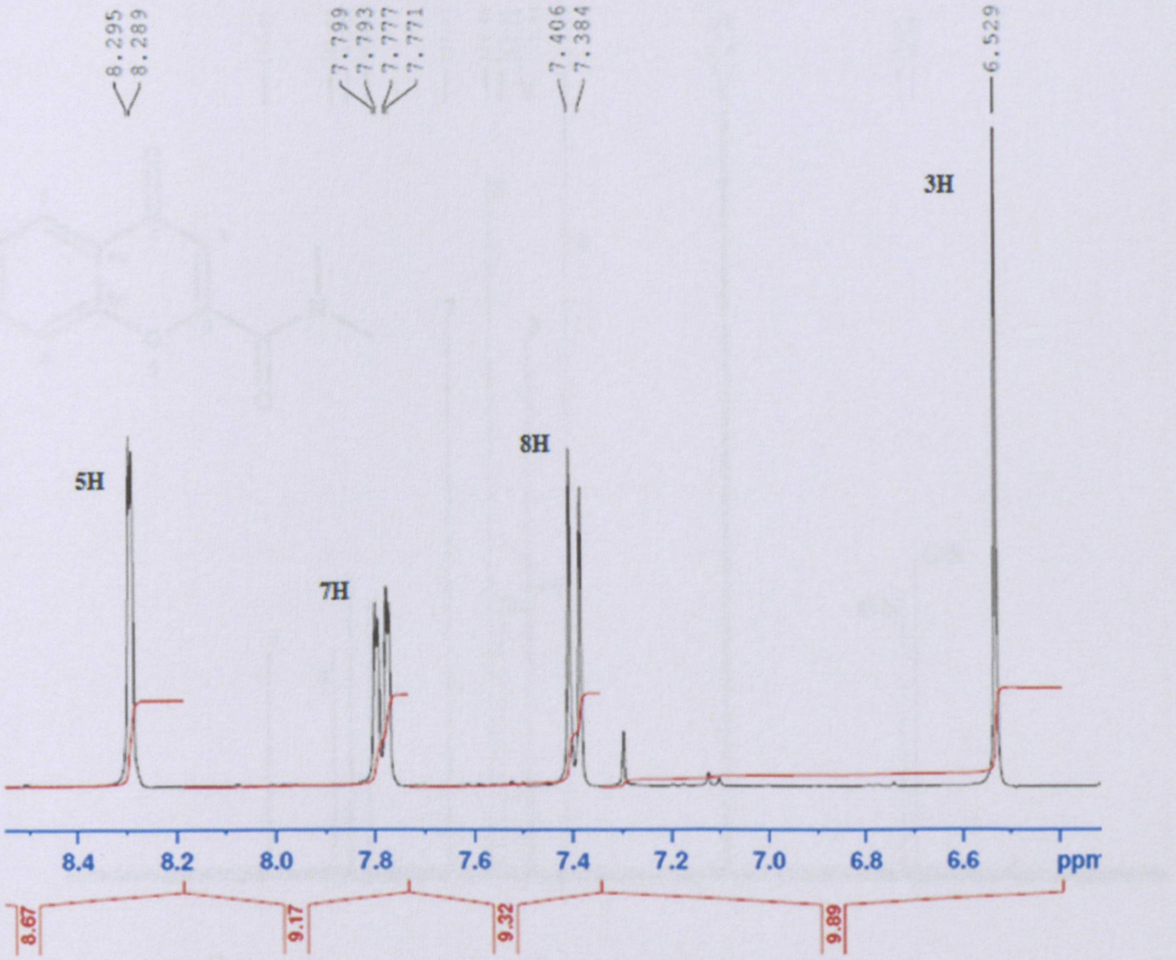


Figure 16a: Expanded ^{1}H NMR spectrum of *N,N*-dimethyl-6-bromochromone-2-carboxamide **55d** in $CDCl_3$.

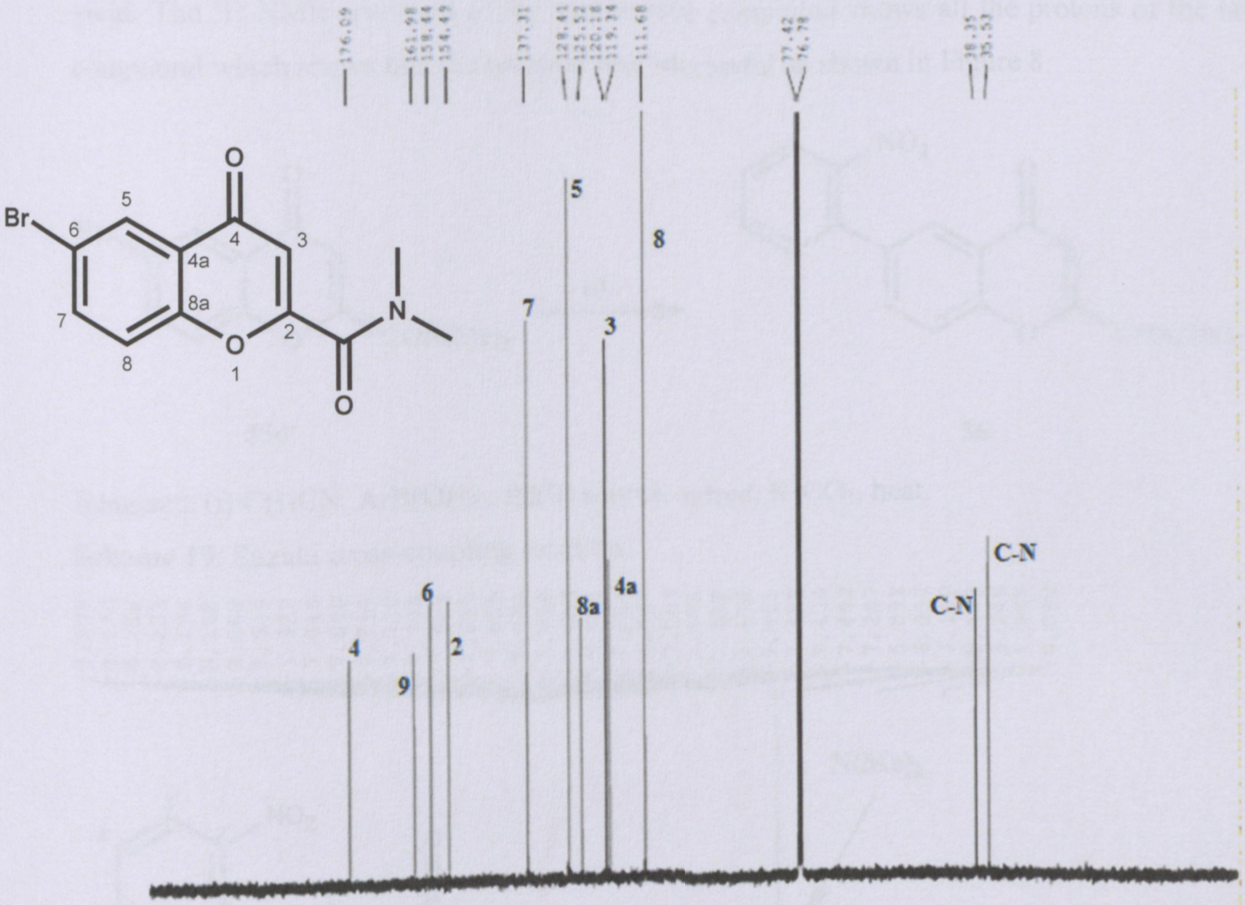
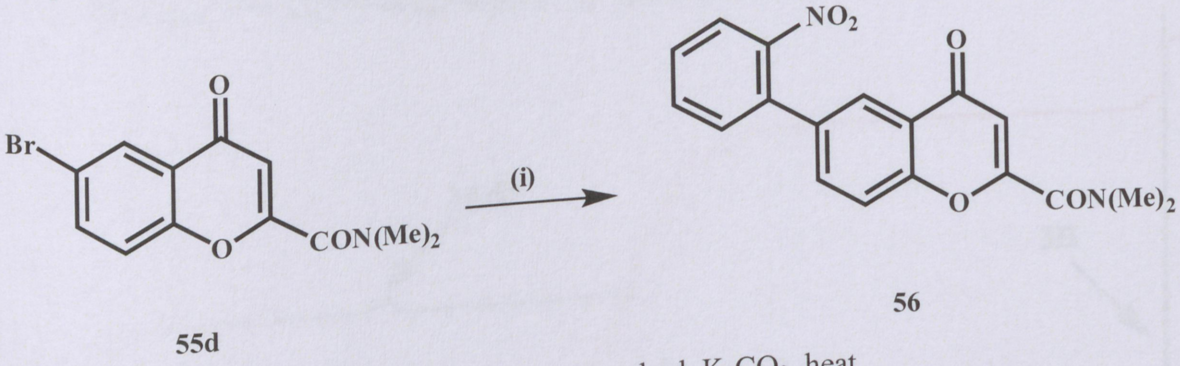


Figure 17: The ^{13}C NMR spectrum of *N,N*-dimethyl-6-bromochromone-2-carboxamide **55d** in $CDCl_3$.

3.3 Suzuki cross-coupling reactions

In our quest to synthesize novel compounds which might have enhanced biological activity, we decided to extend our studies to metal coupling reaction and investigated the Suzuki reactions (Scheme 19). The Suzuki cross-coupling reactions were done using the 6-bromochromone-2-carboxamides **55d**. This compound **55d** was dissolved in acetonitrile, substituted phenylboronic acids, tetrakis(triphenyl phosphine)palladium(0) and anhydrous potassium carbonate were added and the reaction was done under nitrogen gas as shown in scheme **22**. The compounds were purified by column chromatography using ethyl acetate as the running solvent. The yield of the compound **56** was 40 % on average and further research needs to be conducted to optimize the yield. The ^{1}H NMR spectrum of the synthesised compound shows all the protons of the target compound which shows that the reaction was successful as shown in Figure 8.



Reagents: (i) CH_3CN, $ArB(OH)_2$, Pd(0) source, anhyd. K_2CO_3, heat.

Scheme 19: Suzuki cross-coupling reaction

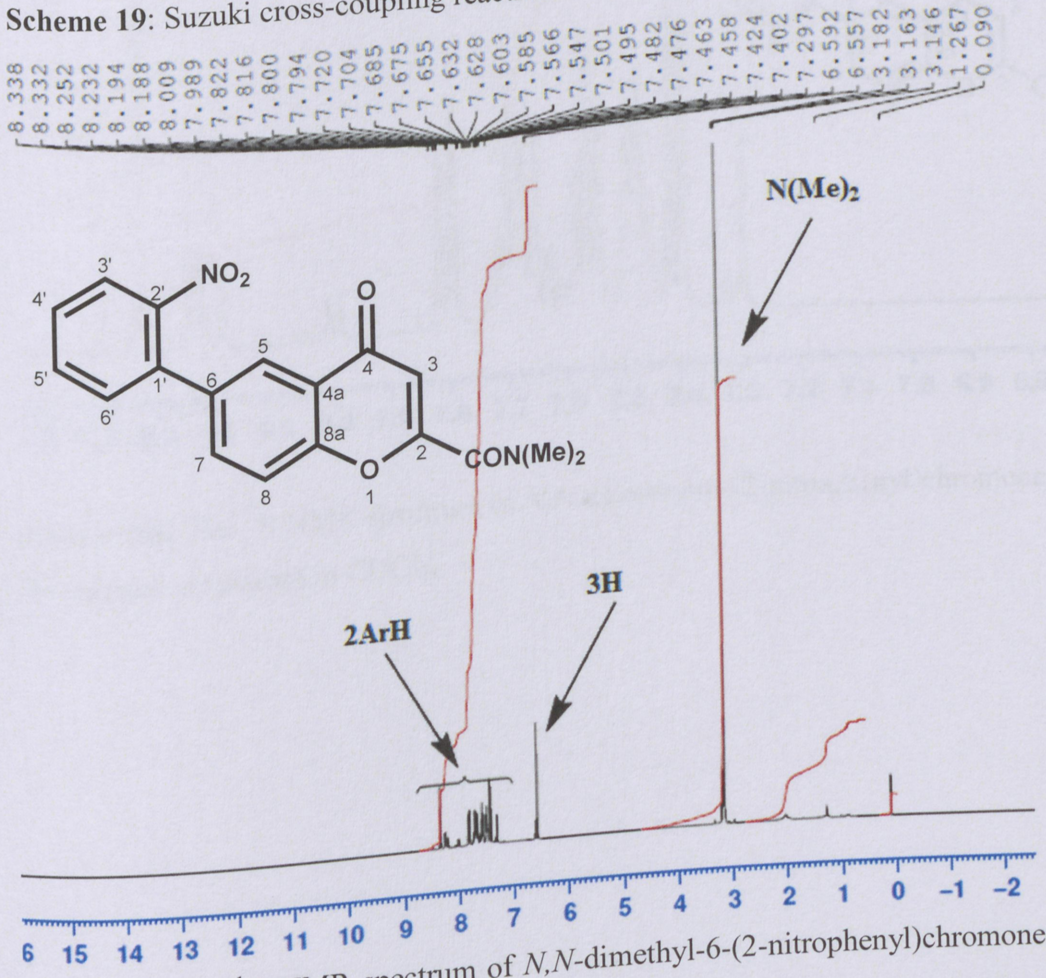


Figure 18: The ^{1}H NMR spectrum of *N,N*-dimethyl-6-(2-nitrophenyl)chromone-2-carboxamide **56** in $CDCl_3$.

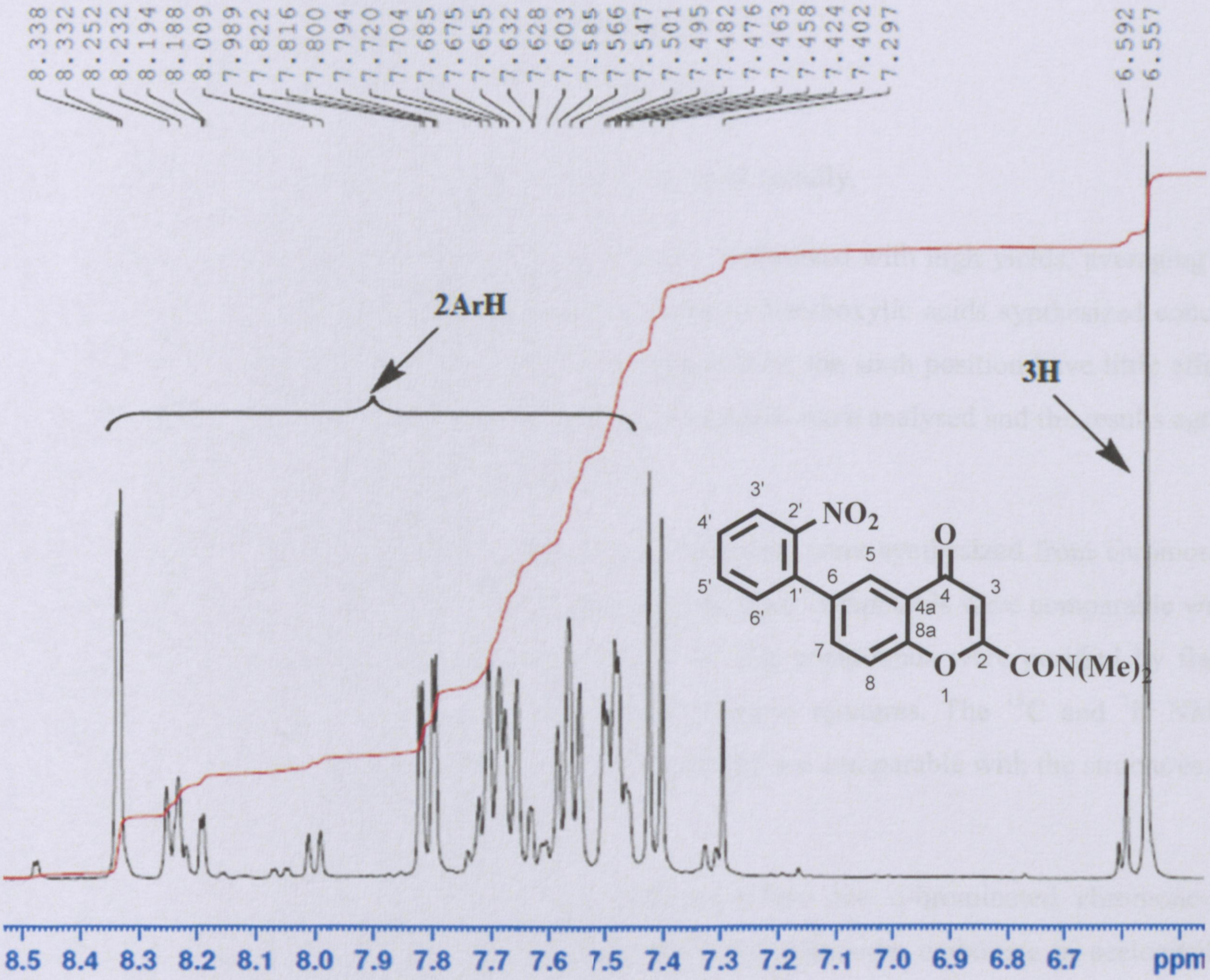


Figure 18a: The ^{1}H NMR spectrum of *N,N*-dimethyl-6-(2-nitrophenyl)chromone-2-carboxamide **56** (expanded version) in $CDCl_3$.

Chapter 4

Conclusions

Various chromone derivatives have been synthesized successfully.

The 6-substituted chromone-2-carboxylic acids were synthesized with high yields, averaging to 92 %. The ^1H and C-13 NMR spectra of the chromone-2-carboxylic acids synthesized concur with the literature ones, which show that the substituents on the sixth position have little effect on both rings. In addition, the IR spectra of these compounds were analysed and the results agree with the structures of the synthesized compounds.

The chromone-2-carboxamides, including novel compounds, were synthesized from chromone-2-carbonyl chlorides and the yields of previously synthesized compounds were comparable with those reported in literature with a range of 48-71 %. The compounds were purified by flash column chromatography using ethyl acetate and/or hexane mixtures. The ^{13}C and ^1H NMR spectra of the chromone-2-carboxamide were analysed and are comparable with the structures of these compounds.

The Suzuki coupling reactions were also explored where the 6-brominated chromone-2-carboxamides were subjected to a palladium catalyst and potassium carbonate in acetonitrile. These novel compounds were characterized by ^1H and ^{13}C NMR spectroscopy. The results obtained confirm that Suzuki reaction was successful but the purified products still requires CHN analysis to confirm the structure of these compounds.

Future studies will include:

- Mass spectroscopic analysis of chromone -2-carboxamides.
- Further investigation on Suzuki cross-coupling reactions and other metal coupling reactions.
- Bioactivity studies of chromone-2-carboxamides.
- Microwave-assisted ring opening of chromone-2-carboxamides.
- Bioactivity studies of chromone-2-carboxamides

Chapter 5

Experimental

5.1 General conditions

The melting points were determined on a BÜCHI Melting Point B-540 and are uncorrected. NMR spectra were recorded on a Bruker AMX 400, from $CDCl_3$ or DMSO-d_6 solutions generally using residual non-deuterated solvent as internal standard. The ^{13}C spectra were interpreted using DEPT spectra and the normal ^{13}C spectra with the same frequencies. IR spectra were recorded on a FTIR BRUKER ALPHA-P spectrophotometer.

Flash chromatography was performed on Merck Silica gel 60 [particle size 0.040-0.063 mm (230-400 mesh)]. Thin layer chromatography was performed on MN ALUGRAM Xtra SIL G/UV_{254} TLC plates. The plates were analysed by inspection under UV, using a CM-10 Fluorescence Spectroanalysis cabinet.

5.2 Preparation of chromone derivatives

***Ethyl chromone-2-carboxylate* 52a**.[40] – NaOEt was generated in situ by adding Na metal (1.60 g, 69.5 mmol) to dry EtOH (30 ml) under nitrogen gas. A warm solution of 2-hydroxyacetophenone (3.76 g, 17.5 mmol) and diethyl oxalate (13.05 ml, 97 mmol) was added into NaOEt solution. The reaction mixture was gently boiled and stirred under reflux for 40 minutes (until it becomes thick yellow and slurry). The reaction mixture was allowed to cool to room temperature and poured into Et_2O (73 ml) (acidity was checked using pH indicator). The solid was extracted with Et_2O (3x 60 ml), the extracts were combined, dried over anhydrous $MgSO_4$ and evaporated to yield crude ethyl chromone-2-carboxylate **52a** (4.3 g, 93 %) [δ_H (400 MHz: $CDCl_3$-d_1) 1.34 (3H, t, *CH_3*), 4.38 (2H, q, *CH_2*CH_3), 7.07 (1H, s, *CH*) 7.38 (1H, t, *J* = 8.8, 8H) 7.53 (1H.d, *J* = 8.4 Hz, 6H) 7.68 (1H, t, *J* = 7.6 Hz, 7H) 8.10 (1H, d, *J* = 8 Hz, 5H)], [δ_C (100 MHz: $CDCl_3$-d_1) 14.1 (*CH_3*) 63.2 (*CH_2*-CH_3) 156.0 (C-2) 116.8 (C-3) 178.8 (C-4) 125.7 (C-4a) 126.0 (C-5) 124.25 (C-6) 134.9 (C-7) 114.6 (C-8) 160.4 (CO_2Et)], which was used without further purification.

***Ethyl 6-bromochromone-2-carboxylate* 52b**.[40] The experimental procedure employed for the synthesis of ethyl chromone-2-carboxylate was followed, using 5-bromo-2-hydroxyacetophenone (3.76 g, 17.5 mmol), diethyl oxalate (13.05 ml, 97 mmol), Na metal (1.60 g, 69.5 mmol) and dry EtOH (30ml). Work-up afforded a solid shown, by NMR spectroscopy, to give ethyl 6-bromochromone-2-carboxylate **59** [δ_H (400 MHz: CDCl$_3$-d_1) 1.30 (3H, t, CH_3), 4.40 (2H, q, CH_2CH$_3$), 7.03 (1H, s, CH), 7.41 (1H, d, J = 8.8 Hz, 8H) 7.72 (1H, dd, J = 2 Hz, 7H) 8.20 (1H, d, J = 1.6 Hz, 5H)], [δ_C (100 MHz: CDCl$_3$-d_1) 14.1 (CH_3-CH$_2$), 63.2 (CH$_3$-CH_2), 154.7 (C-2), 120.7 (C-3), 177.4 (C-4), 125.6 (C-4a), 128.3 (C-5), 119.5 (C-6), 137.7 (C-7), 114.6 (C-8), 152.4 (C-8a), 160.1 (CO$_2$Et)], which was used without further purification.

***Ethyl 6-chlorochromone-2-carboxylate* 52c**.[40] The experimental procedure employed for the synthesis of ethyl chromone-2-carboxylate was followed, using 5-chloro-2-hydroxyacetophenone (3.76 g, 17.5 mmol), diethyl oxalate (13.05 ml, 97 mmol), Na metal (1.60 g, 69.5 mmol) and dry EtOH (30 ml). Work-up afforded a solid shown, by NMR spectroscopy, to comprise a mixture of ethyl 6-chlorochromone-2-carboxylate **52c** [δ_H (400 MHz: CDCl$_3$-d_1) 1.32 (3H, t, CH_3), 4.36 (2H, q, CH_2CH$_3$), 7.02 (1H, s, CH), 7.48 (1H, d, J = 8.8 Hz, 8H) 7.58 (1H, dd, J = 2 & 2.4 Hz, 7H) 8.03 (1H, s, 5H)], [δc (100 MHz: CDCl$_3$-d_1) 14.1 (CH$_2$$CH_3$), 63.2 ($CH_2CH_3$), 154.2 (C-2), 120.5 (C-3), 177.2 (C-4) 125.1 (C-4a), 131.9 (C-5), 125.2 (C-6) 134.9 (C-7), 114.5 (C-8), 152.4 (C-8a), 160.2 (CO$_2$Et)], which was used without further purification.

***Ethyl 6-methoxychromone-2-carboxylate* 52d**.[40] The experimental procedure employed for the synthesis of ethyl chromone-2-carboxylate was followed, using 5-methoxy-2-hydroxyacetophenone (3.76 g, 17.5mmol), diethyl oxalate (13.05 ml, 97mmol), Na metal (1.60g, 69.5mmol) and dry EtOH (30ml). Work-up afforded a crude ethyl 6-methoxychromone-2-carboxylate **75** [δ_H (400 MHz: DMSO-d_6) 1.31 (3H, t, CH_3), 3.83 (3H, s, CH_3O), 4.30 (2H, q, CH_2CH$_3$), 7.21 (1H, s, CH) 7.05 (1H, s, 5H) 7.25 (1H, t, J = 6.4 Hz, 8H) 7.46 (1H, t, J = 11.2 Hz, 7H)], [δ_H (100 MHz: DMSO-d_6) 14.1 (CH_3-CH$_2$), 63.0 (CH$_3$-CH_2), 55.9 (CH$_3$-O,) 157.5 (C-2), 113.7 (C-3), 178.5 (C-4), 125.0 (C-4a), 104.5 (C-5), 152.1 (C-6),125.2 (C-7), 120.3 (C-8), 150.9 (C-8a), 160.5 (CO$_2$Et)].

Ethyl 6-fluorochromone-2-carboxylate **52e**.[40] The experimental procedure employed for the synthesis of ethyl ethyl chromone-2-carboxylate was followed, using 5-methoxy-2-hydroxyacetophenone (3.76 g, 17.5mmol), diethyl oxalate (13.05 ml, 97mmol), Na metal (1.60g, 69.5mmol) and dry EtOH (30ml). Work-up afforded a crude ethyl 6-fluorochromone-2-carboxylate **64** [δ_H (400 MHz: DMSO-d_6) 1.34 (3H, t, CH_3), 4.37 (2H, q, CH_2CH_3), 7.02 (1H, s, *CH*), 7.37 (1H,m, J = 2.8 Hz, 2.8 Hz, 8H) 7.54(1H, *dd*, J = 4 Hz, 4 Hz, 7H) 7.71 (1H, *dd*, J = 2.8 Hz, 2.8 Hz, 5H). [δ_H (100 MHz: DMSO-d_6) 14.1 (CH_3-CH_2), 63.0 (CH_3-CH_2), 160.3 (C-2), 113.8 (C-3), 177.7 (C-4), 125.6 (C-4a), 110.7 (C-5), 158.6 (C-6),123.2 (C-7), 121.1 (C-8), 152.2 (C-8a), 160.1 (CO_2Et)].

Chromone-2-carboxylic acid (53a)

Method 1[40]: A mixture of ethyl chromone-2-carboxylate **52a**, concentrated HCl (15 ml) and AcOH (30 ml) was boiled gently under reflux for 1.5 hr. The mixture was cooled, H_2O (50 ml) was added and the precipitate was filtered to afford chromone-2-carboxylic acid (5.36 g, 90 %), (m.p. 221-231°C), [δ_H (400 MHz: DMSO) 6.91 (1H,s, CH=C), 7.51-8.05 (4H, m, ArH)], [δ_C (100 MHz: DMSO-d_6) 113.93 (C-3), 119.28 (C-8), 124.16 (C-4a), 125.35 (C-6), 126.46 (C-5), 135.57 (C-7), 153.47 (C-8a), 155.00 (C-2), 161.05 (COOH), 178.04 (C-4)], ν_{max} /cm^{-1} 3420.69 (OH, CO_2H), 1732.61 (C=O, CO_2H), 1613.96 (CO, C-4).[40]

Method 2[42]: A mixture of 2-hydroxyacetophenone (3.00 g, 22.02 mmol) and diethyl oxalate (7.5 ml, 55.2 mmol) was added to sodium (1.50 g, 6.53 mmol) in absolute ethanol (EtOH) (30 ml). The mixture was heated at 50^{0}C for 3 hrs, cooled, added to 25% sulphuric acid (H_2SO_4) (25 ml) and heated under reflux for 1.5 hr. After the reaction mixture was cooled, an insoluble solid was collected. The resulting solid was recrystallized from aqueous ethanol (EtOH:H_2O, 80:20) to give chromone-2-carboxylic acid (3.80 g, 88 %).[42]

***6-Bromochromone-2-carboxylic acid* 53b.** The experimental procedure employed for the synthesis of chromone-2-carboxylic acid (**method 1)** was followed, using a mixture of Ethyl 4-(5-bromo-2-hydroxyphenyl)-2,4-dioxobutanoate and ethyl 6-bromo-2-hydroxychromanone-2-carboxylate, concentrated HCl (15 ml) and AcOH (30 ml), then boiled gently under reflux for 1.5 hr. Work-up afforded 6-bromochromone-2-carboxylic acid (4.30 g, 92 %), mp 147-156°C, [δ_H

(400 MHz: DMSO-d_6) 6.97 (1H, s, CH=C), 7.71-8.01 (3H, m, ArH)], [δ_C (100 MHz) 114.7 (C-8), 120.7 (C-3), 119.5 (C-6), 125.6 (C-4a), 137.7 (C-7), 152.4 (C-8a), 154.70 (C-2), 160.20 (COOH), 177.10 (C-4)], ν_{max}/ cm^{-1} 3442.14 (OH, CO_2H), 1728.08 (C=O, CO_2H), 1620.36 (C=O, C-4).

6-Bromochromone-2-carboxylic acid **53b.** The experimental procedure for the synthesis of chromone-2-carboxylic acid **(method 1)** was followed, using a mixture of 6-bromo-2-hydroxyacetophenone (3.00 g, 22.02 mmol) and diethyl oxalate (7.5ml, 55.2 mmol), then added to sodium (1.50 g, 6.53 mmol) in absolute ethanol (EtOH) (30 ml). Work-up afforded 6-bromochromone-2-carboxylic acid (3.20 g, 90 %), mp 145-153°C, [δ_H (400 MHz: DMSO-d_6) 6.97 (1H, s, 3H), 8.11 (1H, d, *J*= 2.4 Hz, 5H) 7.72 (1H, d, *J*= 9.2 Hz, 8H) 8.01, dd, *J*= 2.4 Hz, 8H)], [δ_C (100 MHz) 113.6 (C-8), 122.0 (C-3), 119.0 (C-6), 125.5 (C-4a), 138.3 (C-7), 153.9 (C-8a), 154.9 (C-2), 161.7 (COOH), 177.4 (C-4)], ν_{max}/ cm^{-1} 3459.22 (OH, CO_2H), 1731.27 (C=O, CO_2H), 1620.68 (C=O, C-4).

6-Chlorochromone-2-carboxylic acid **53c.** The experimental procedure employed for the synthesis of chromone-2-carboxylic acid (**method 1)** was followed, using a mixture of 6-chlorochromone-2-carboxlate, concentrated HCl (15 ml) and AcOH (30 ml), then boiled gently under reflux for 1.5 hr. Work-up afforded 6-chlorochromone-2-carboxylic acid (4.65 g, 92 %), m.p. (179-188°C), [δ_H (400 MHz: DMSO-d_6) 6.95 (1H, s, 3H), 8.10 (1H, d, *J*= 2.4 Hz, 5H) 7.72 (1H, d, *J*= 9.2 Hz, 8H) 8.01 (1H, dd, *J*= 2.4, 9.2 Hz, 7H)], [δ_C (100 MHz) 113.9 (C-8), 119.2 (C-3), 125.3 (C-6), 124.1 (C-4a), 135.7 (C-7), 153.7 (C-8a), 155.8 (C-2), 161.9 (COOH), 178.0 (C-4)], ν_{max}/ cm^{-1} 3385.77 (OH, CO_2H), 1726.82 (C=O, CO_2H), 1649.47 (C=O,C-4).

6-Methoxychromone-2-carboxylic acid **53d.** The experimental procedure employed for the synthesis of chromone-2-carboxylic acid (**method 1)** was followed, using a mixture of ethyl 4-(5-methoxy-2-hydroxyphenyl)-2,4-dioxobutanoate, concentrated HCl (15 ml) and AcOH (30 ml), then boiled gently under reflux for 1.5 hr. Work-up afforded 6-methoxychromone-2-carboxylic acid (4.30 g, 92 %), m.p. (299-303°C) [δ_H (400 MHz: DMSO-d_6) 3.87 (3H, s, CH_3O), 6.89 (1H, s, 3H), 7.45 (1H, d, *J*= 2.1 Hz, 7H) 7.69 (1H, d, *J*= 8.8 Hz, 8H), 7.40 (1H, d, *J*= 2.1 Hz, 5H)], [δ_C (100 MHz: DMSO-d_6) 56.22 (CH_3-O,) 121.0 (C4a), 125.0 (C-3), 113.0 (C-8), 124.9 (C-7), 105.0 (C-5), 153.5 (C-6), 150.7 (C-8a), 161.4 (C-2), 157.5 (COOH), 177.8 (C-4)], ν_{max}/ cm^{-1} 3383.97 (OH, CO_2H), 1721.15 (C=O, CO_2H), 1629.68 (C=O, C-4).

***6-Fluorochromone-2-carboxylic acid* 53d.** The experimental procedure for the synthesis of chromone-2-carboxylic acid **(method 1)** was followed, using a mixture of 6-fluoro-2-hydroxyacetophenone (3.00 g, 22.02 mmol) and diethyl oxalate (7.5 ml, 55.2 mmol), then added to sodium (1.50 g, 6.53 mmol) in absolute ethanol (EtOH) (30 ml). Work-up afforded 6-chlorochromone-2-carboxylic acid (3.90 g, 85 %), m.p. (173-182°C). [δ_H (400 MHz: DMSO-d_6) 6.92 (1H, s, 3H) 7.84 (1H, dd, *J*= 4.4, 4 Hz, 5H), 7.78 (1H, dd, *J*= 4.4, 3.2 Hz, 7H) 7.74 (1H, m, 8H) [δ_C (100 MHz) 110.9 (C-5) 113.0 (C-8), 123.9 (C-3), 160.9 (C-6), 125.4 (C-4a), 122.3 (C-7), 113.0 (C-8a), 158.5 (C-2), 161.7 (COOH), 177.6 (C-4)].

***Chromone-2-carbonyl chloride* 54a.**[44] Thionyl chloride (0.77 ml, 10.6 mmol) was added to a suspension of chromone-2-carboxylic acid (1.52 g, 8 mmol) in dry 1,2-dichloroethane (12 ml) and dry *N,N*-dimethylformamide (0.16 ml, 1,2 mmol) [A pre-weighed 100 ml round-bottom flask was used]. The resulting mixture was heated under reflux for 2 hrs. The reaction was monitored by TLC (calcium chloride and nitrogen gas were used). The reaction mixture was allowed to cool to room temperature. The solvent was removed under vacuum. The vacuum pressure was broken and dry 1.2-dichloroethane (15 ml) was added and removed under vacuum to afford the crude chromone-2-carbonyl chloride (1.59 g, 95 %).[44] [δ_H (400 MHz: DMSO-d_6) 6.97 (1H, s, 3H) 8.10 (1H, d, *J*= 3.2 5H) 7.92 (1H, t, *J*= 7.6 Hz, 6H), 7.78 (1H, d, *J*= 8.4 Hz, 8H) 7.58 (1H, t, *J*= 7.6 7H)] [δ_C (100 MHz) 113.9 (C-8), 125.4 (C-5) 126.6 (C-3), 119.4 (C-6), 125.4 (C-4a), 124.1 (C-7), 135.7 (C-8a), 161.8 (C-2), 155.9 (COCl), 178.2 (C-4)].

***6-Bromochromone-2-carbonyl chloride* 54b.** The experimental procedure employed for the synthesis of chromone-2-carbonyl chloride was followed, using thionyl chloride (0.77 ml, 10.6 mmol) which was added to a suspension of 6-bromochromone-2-carboxylic acid (1.52 g, 8 mmol) in dry 1,2-dichloroethane (12 ml) and dry *N,N*-dimethylformamide (0.16 ml, 1.2 mmol). Work-up afforded 6-bromochromone-2-carbonyl chloride (2.21 g, 92 %) [δ_H (400 MHz: DMSO-d_6) 6.96 (1H, s, 3H) 8.12 (1H, d, *J*= 2.4 Hz, 5H), 8.02 (1H, dd, *J*= 2.4 Hz, 7H) 7.74 (1H, d, *J*= 9.2 8H)] [δ_C (100 MHz) 113.9 (C-8), 127.5 (C-5) 125.7 (C-3), 119.0 (C-6), 122.1 (C-4a), 138.2 (C-7), 154.2 (C-8a), 161.6 (C-2), 154.9 (COCl), 177.0 (C-4)].

***6-Chlorochromone-2-carbonyl chloride* 54c.** The experimental procedure employed for the synthesis of chromone-2-carbonyl chloride was followed, using thionyl chloride (0.77 ml, 10.6 mmol) which was added to a suspension of 6-chlorochromone-2-carboxylic acid (1.79, 8 mmol) in dry 1,2-dichloroethane (12 ml) and dry *N,N*-dimethylformamide (0.16ml, 1.2 mmol). Work-up afforded 6-chlorochromone-2-carbonyl chloride (1.79 g, 92 %) [δ_H (400 MHz: DMSO-d_6) 6.96 (1H, s, 3H) 8.12 (1H, d, *J*= 2.4 Hz, 5H), 8.02 (1H, dd, *J*= 2.4 Hz, 7H) 7.74 (1H, d, *J*= 9.2 8H)] [δ_C (100 MHz) 113.6 (C-8), 126.5 (C-5) 125.7 (C-3), 119.3 (C-6), 123.2 (C-4a), 139.4 (C-7), 155.1 (C-8a), 161.9 (C-2), 155.7 (COCl), 178.0 (C-4)].

***6-Methoxychromone-2-carbonyl chloride* 54d.** The experimental procedure employed for the synthesis of chromone-2-carbonyl chloride was followed, using thionyl chloride (0.77 ml, 10.6 mmol) which was added to a suspension of 6-methoxychromone-2-carboxylic acid (1.76 g, 8 mmol) in dry 1,2-dichloroethane (12 ml) and dry *N,N*-dimethylformamide (0.16 ml, 1.2 mmol). Work-up afforded 6-methoxychromone-2-carbonyl chloride (1.70 g, 89 %) [δ_H (400 MHz: DMSO-d_6) 3.84 (3H, s, CH_3O), 6.85 (1H, s, 3H), 7.62 (1H, d, *J*= 9.2 Hz, 7H) 7.40 (1H, d, *J*= 9.2 Hz, 8H, 7.31 (1H, s, 5H)], [δ_C (100 MHz: DMSO-d_6) 56.22 (CH_3-O,) 104.96 (C4a), 112.9 (C-3), 120.9 (C-8), 124.8 (C-7), 124.9 (C-5), 150.6 (C-6), 153.4 (C-8a), 157.4 (C-2), 161.9 (COOH), 177.8 (C-4)].

***6-Ffluorochromone-2-carbonyl chloride* 54e.** The experimental procedure employed for the synthesis of chromone-2-carbonyl chloride was followed, using thionyl chloride (0.77 ml, 10.6 mmol) which was added to a suspension of 6-fluorochromone-2-carboxylic acid (1.67 g, 8 mmol) in dry 1,2-dichloroethane (12 ml) and dry *N,N*-dimethylformamide (0.16 ml, 1.2 mmol). Work-up afforded 6-fluorochromone-2-carbonyl chloride (1.69 g, 93 %) [δ_H (400 MHz: DMSO-d_6) 6.96 (1H, s, 3H) 8.12 (1H, d, *J*= 2.4 Hz, 5H), 8.02 (1H, dd, *J*= 2.4 Hz, 7H) 7.74 (1H, d, *J*= 9.2 8H)] [δ_C (100 MHz) 113.9 (C-8), 127.5 (C-5) 125.7 (C-3), 119.0 (C-6), 122.1 (C-4a), 138.2 (C-7), 154.2 (C-8a), 161.6 (C-2), 154.9 (COCl), 177.0 (C-4)].

***N,N-Dimethyl-Chromone-2-carboxamide* 55a.**[38] A stirred suspension of the crude chromone-2-carbonyl chloride (1.67 g, 8 mmol) was cooled in dry pyridine (20 ml) in ice for 30 minutes. Slurry of dimethylammonium chloride (1.30 g, 16 mmol) in dry pyridine (5 ml) was added drop-wise. The reaction mixture was stirred for 3 hrs in an ice-bath and 21 hrs at room temperature. The resulting reaction mixture was poured in 2M HCl (200 ml), cooled in ice for 30 minutes and extracted with EtOAc (4x 75 ml). The EtOAc extracts were combined and sequentially washed with 5% $NaHCO_3$ (2x 100 ml) and saturated aqueous NaCl (100 ml). The extract was dried over anhydrous $MgSO_4$, the solvent was evaporated to get the crude chromone-2-carboxamide. The product was purified by flash chromatography using EtOAc: hexane (4:2) as eluent (1.25 g, 72 %). ν_{max}/ cm^{-1} 1730.07 (C=O, CON), 1604.55 (C=O, C-4).[46] [δ_H (400 MHz: DMSO-d_6) 3.13 (6H, s, NMe$_2$) 6.59 (1H, s, 3H) 7.53 (1H, t, *J*= 7.6 Hz) 6H) 7.69 (1H, d, *J*= 8.4 Hz, 8H) 7.84 (1H, t, *J*= 7.6 Hz, 7H) 8.05 (1H, d, *J*= 8.0 Hz, 5H)], [δ_H (400 MHz: DMSO-d_6) 35.5 (N(CH$_3$)$_2$) 119.1 (C-8), 127.5 (C-5) 111.2 (C-3), 124.1 (C-6), 125.4 (C-4a), 135.2 (C-7), 155.9 (C-8a), 158.1 (C-2), 160.7 (CON), 177.1 (C-4)].

***1-[(Chromon-2-yl)-carbonyl]-pyrrolidine* 55b.**[38] The experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide **55** was followed, using pyrrolidine (1.5 ml, 18 mmol) in dry pyridine (5 ml). Work-up afforded the crude product which was purified by flash chromatography using EtOAc:hexane (4:2) as the running solvent (1.07 g, 55 %), m.p (165-170°C), [δ_H (400 MHz: CDCl$_3$) 1.88-1.99 (4H, m, CH$_2$*CH$_2$CH$_2$*CH$_2$), 3.27-3.44 (4H, m, N(CH$_2$-)$_2$), 5.76 (1H, s, 3H), 7.93(1H, dd, *J*= 1.2 Hz, 5H) 7.36 (1H, t, *J*= 1.2 Hz) 6.86 (1H, d, *J*= 1.2 Hz) 6.81 (1H,dd, *J*= 2.4 Hz)], [δ_C (100 MHz: CDCl$_3$) 22.4 (N-C-CH$_2$), 23.6 (N-C-**C**H$_2$), 47.5 (N-C), 47.7 (N-C), 88.9 (C-3), 113.7 (C-8), 117.0 (C-4a), 124.6 (C-5), 124.9 (C-6), 132.0 (C-7), 152.6 (C-8a), 161.5 (C-2), 164.8 (OCN), 188.8 (C-4)], ν_{max}/ cm^{-1} 1738.52 (C=O, CON), 1612.94 (C=O, C-4).

***1-[(Chromon-2-yl)-carbonyl]-morpholine* 55c.**[38] The experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide **55a** was followed, using morpholine (1.31 ml, 18mmol) in dry pyridine (5ml). Work-up afforded the crude product which was purified by flash chromatography using EtOAc:hexane (4:2) as the running solvent (0.83 g, 41 %) m.p. (61-69°C) [δ_H (400 MHz: CDCl$_3$) 1.17-1.21 (4H, d, N(CH$_2$)$_2$) 2.10 (4H, s, O(CH$_2$)$_2$) 7.05 (1H, s, CH=C) 8.06 (1H, d, *J*= 8 Hz, 5H) 7.85 (1H, t, *J*= 7.6 Hz, 7H) 7.70 (1H, d, *J*= 8.4 Hz, 8H) 7.53 (1H, t, *J*= 7.6 Hz)], [δ_C (100 MHz: CDCl$_3$), 47.4 (N-C), 42.6 (N-C), 66.6 (C-**C**-O), 66.2 (C-**C**-O), 111.3 (C-3), 119.1 (C4a), 124.2 (C-8), 125.4 (C-6), 126.5 (C-7), 135.2 (C-5), 158.1 (C8a), 155.9 (C-2), 160.7 (O**C**N), 177.1 (C-4)].

***N,N-Dimethyl-6-bromochromone-2-carboxamide* 55d.**[38] The experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide **55a** was followed, using a crude 6-bromochromone-2-carbonyl chloride (2.30 g, 8 mmol). Work-up afforded the crude product which was purified by flash chromatography using EtOAc: hexane (4:2) as the eluent (1.87 g, 78 %), m.p. (103-112°C), [δ_H (400 MHz: DMSO-d_6) 3.14 (6H, s, ((CH$_3$)$_2$N), 6.54 (1H, s, CH=C), 7.46-8.16 (3H, m, ArH)], [δ_C (100 MHz: DMSO-d_6) 35.3 (C-N), 38.3 (C-N), 111.6 (C-3), 119.3 (C-4a), 120.1 (C-8), 125.5 (C-6), 128.4 (C-5), 137.3 (C-7), 154.4 (C-8a), 158.4 (C-2), 161.9 (OCN), 176.0 (C-4)], ν_{max}/ cm^{-1} 1732.76 (C=O, CON), 1637.18 (C=O, C-4).

1-[(6-BromoChromon-2-yl)-carbonyl]-pyrrolidine **55e.**[38] The experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide **55a** was followed, using a crude 6-bromochromone-2-carbonyl chloride (2.30 g, 8 mmol) and pyrrolidine (1.5 ml, 18 mmol) in dry pyridine (5 ml). Work-up afforded the crude product which was purified by flash chromatography using EtOAc:hexane (4:2) as the eluent (1.98 g, 77 %), m.p. (109-116°C), [δ_H (400 MHz: CDCl$_3$) 1.10-2.02 (4H, m, CH$_2$CH$_2$), 3.32-3.47 (4H, m, N(CH$_2$)$_2$), 6.72 (1H, s, CH=C), 7.31 (1H, *dd, J 8.8* Hz, 8H), 7.66 (1H, *ddd, J* 4 Hz, *2.68*H), 8.22 (1H, *d, J 4,* 5H)], [δ_C (100 MHz: CDCl$_3$) 23.4 (C-CH$_2$), 23.6 (C-**C**H$_2$), 61.4 (N-C), 88.5 (C-3), 113.6 (C-8), 118.4 (C-4a), 119.7 (C-7), 124.5 (C-6), 127.2 (C-5), 151.3 (C-8a), 153.6 (C-2), 160.2 (O**C**N), 176.07 (C-4)], ν_{max}/ cm^{-1} 1729.89 (C=O, CON) 1649.58 (C=O, C-4).

1-[6-Bromo(Chromon-2-yl)-carbonyl]-morpholine **55f.**[38] The experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide **55a** was followed, using a crude 6-bromochromone-2-carbonyl chloride (2.30 g, 8 mmol) and morpholine (1.31 ml, 18 mmol) in dry pyridine (5 ml). Work-up afforded the crude product which was purified by flash chromatography using EtOAc:hexane (4:2) as the eluent (1.20 g, 45 %), (127-134°C), [δ_H (400 MHz: CDCl$_3$), 1.36 (4H, m, N(CH$_2$)$_2$), 4.38 (4H, m, O(CH$_2$)$_2$) 7.04 (1H, s, CH=C), 7.43 (1H, *d, J 8.8,* 8H), 7.72 (1H, *dd, J 2.4* Hz, *J* 2.8 Hz 7H), 8.21 (1H, *d, J* 4, 5H)], [δ_C (100 MHz: CDCl$_3$), 21.4 (N-C), 28.1 (N-C), 42.3 (C-**C**-O), 42.3 (C-**C**-O), 111.7 (C-3), 117.8 (C4a), 119.4 (C-8), 124.5 (C-6), 127.6 (C-7), 136.3 (C-5), 151.3 (C8a), 153.8 (C-2), 159.1 (O**C**N), 177.2 (C-4)], ν_{max}/ cm^{-1} 1733.55 (C=O, CON), 1647.24 (C=O, C-4).

1-[(6-Bromochromon-2-yl)-carbonyl]-piperidine **55g.**[38] The experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide **55a** was followed, using a crude 6-bromochromone-2-carbonyl chloride (2.30 g, 8 mmol) and piperidine (1.51 ml, 18 mmol) in dry pyridine (5 ml). Work-up afforded the crude product which was purified by flash chromatography using EtOAc: hexane (4:2) as the eluent (0.984 g, 48 %), m.p. (139-149°C), [δ_H (400 MHz: CDCl$_3$) 1.16-1.37 (2H, m, CH$_2$*CH$_2$*CH$_2$), 1.61-1.80 (4H, m, *CH$_2$*CH$_2$*CH$_2$*), 3.12 (4H, t, N(CH$_2$)$_2$), 6.97 (1H, s, CH=C), 7.41 (1H, *dd, j* 8.8 Hz,8H), 7.66 (1H, *dddd, J* 4 Hz, 7H), 8.18

(1H, *dd, J* 4.4 Hz, 5H)], [δ_C (100 MHz: $CDCl_3$) 21.4 (C-C-**C**H_2), 28.1 (C-**C**H_2-C), 28.3 (C-**C**H_2), 46.0 (N-C), 46.0 (N-C), 108.5 (C-8), 11.3 (C-3), 117.7 (C-4a), 119.7 (C-7), 124.46 (C-6), 127.3 (C-5), 151.4 (C-8a) 159.2 (C-2), 163.7 (O**C**N), 177.5 (C-4)], ν_{max}/ cm^{-1} 1730.22 (C=O, CON), 1649.27 (C=O, C-4).

N,N-Dimethyl-6-chlorochromone-2-carboxamide **55h.**[38] The experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide **55a** was followed, using a crude 6-chlorochromone-2-carbonyl chloride (1.94 g, 8 mmol) and dimethylammonium chloride (1.30 g, 16 mmol). Work-up afforded the crude product which was purified by flash chromatography using EtOAc: hexane (4:2) as the eluent (0.83 g, 43 %), m.p. (119-125°C), [δ_H (400 MHz: $CDCl_3$) 3.06-3.07 (6H, d, $N(CH_3)_2$), 6.46 (1H, s, *CH*=C), 7.38 (1H, *d, J* 8 Hz, 8H), 7.57 (1H, *dd, j* 2.4 Hz, 7H)], [δ_C (100 MHz: $CDCl_3$) 35.5 (N-CH_3), 38.4 (N-CH_3), 111.6 (C-3), 120.0 (C-8), 125.1 (C-4a), 125.2 (C-7), 131.8 (C-6), 134.6 (C-5), 154.0 (C-8a), 158.4 (C-2), 161.9 (CN), 176.3 (C-4)], ν_{max}/ cm^{-1} 1732.00 (C=O, CON), 1642.66 (C=O, C-4).

1-[(6-ChloroChromon-2-yl)-carbonyl]-pyrrolidine **55i.**[38] The experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide **55a** was followed, using a crude 6-chlorochromone-2-carbonyl chloride (1.94 g, 8 mmol) and pyrrolidine (1.5 ml, 18 mmol) in dry pyridine (5 ml). Work-up afforded the crude product which was purified by flash chromatography using EtOAc: hexane (4:2) as the eluent (0.897 g, 46 %), m.p. (131-139°C), [δ_H (400 MHz: $CDCl_3$) 1.88-1.99 (4H, m, CH_2*CH_2CH_2*CH_2), 3.30-3.45 (4H, m, $N(CH_2)_2$), 5.50 (1H, s, CH=C), 6.77 (1H, *d, J* 8 Hz, 8H), 7.18 (1H, *dd, j* 4 Hz, 8H), 7.54 (1H, *d, J* 4 Hz, 5H)], [δ_C (100 MHz: $CDCl_3$) 23.6 (NC-**C**H_2), 24.3 (NC-**C**H_2), 47.8 (N-C), 47.94 (N-C), 88.5 (C-3), 120.0 (C-8), 121.3 (C-4a), 122.5 (C-7), 128.5 (C-5), 134.3 (C-6), 155.1 (C-8a), 161.2 (C-2), 165.03 (OCN), 187.79 (C-4)], ν_{max}/ cm^{-1} 1741.88 (C=O, CON), 1609.33 (C=O, CON).

1-[(6-Chloro-Chromon-2-yl)-carbonyl]-morpholine **55j.**[38] The experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide **55a** was followed, using a crude 6-chlorochromone-2-carbonyl chloride (1.94 g, 8 mmol) and morpholine (1.31 ml, 18 mmol) in dry pyridine (5 ml). Work-up afforded the crude product which was purified by flash chromatography using EtOAc: hexane (4:2) as the eluent (1.28 g, 41 %), m.p. (127-134°C), [δ_C (100 MHz: $CDCl_3$) 14.08 (N-C), 14.34 (N-C), 62.35 (CH_2-O), 63.31 (CH_2O), 114.14 (C-8), 120.01 (C-4a), 121.92 (C-3), 124.42 (C-7), 131.18 (C-6), 135.64 (C-5), 152.99 (C-8a), 154.47 (C-2), 160.25 (OCN), 176.86 (C-4)], ν_{max}/ cm^{-1} 1735.96 (C=O, CON), 1645.18 (C=O, C-4).

1-[(6-CholoroChromon-2-yl)-carbonyl]-piperidine **55k.**[38] The experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide **55a** was followed, using a crude 6-chlorochromone-2-carbonyl chloride (1.94 g, 8 mmol) and piperidine (1.51 ml, 18 mmol) in dry pyridine (5 ml). Work-up afforded the crude product which was purified by flash chromatography using EtOAc: hexane (4:2) as the eluent (1.13 g, 55 %), m.p. (121-128°C). [δ_C (100 MHz: $CDCl_3$) 21.43 (C-C-**C**H_2) 28.12 (C-**C**H_2-C), 28.66 (C-**C**H_2-), 43.56 ($N(CH_2)_2$), 111.48 (C-8), 119.53 (C-3), 123.92 (C-7), 124.14 ((C-4a), 130.20 (C-6), 133.65 (C-5), 151.37 (C-8a), 153.22 (C-2), 159.18 (OCN), 176.20 (C-4)

1-[(6-Methoxychromon-2-yl)-carbonyl]-pyrrolidine **55l.**[38] The experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide **55a** was followed, using a crude 6-methoxychromone-2-carbonyl chloride (1.91 g, 8 mmol) and pyrrolidine (1.5 ml, 18 mmol) in dry pyridine (5 ml). Work-up afforded the crude product which was purified by flash chromatography using EtOAc: hexane (4:2) as the eluent (1.44 g, 66 %), m.p. (178-186°C), [δ_H (400 MHz: $CDCl_3$) 1.18 (1H, s, CH_3O), 1.81-1.84 (4H, m, CH_2*CH_2CH_2*CH_2), 3.25-3.35 (4H, m, $N(CH_2)_2$), 5.53 (1H, s, CH=C), 6.77 (1H, *d*, *J* 8.8, 7H), 6.89 (1H, *dd*, *J* 3.2 Hz, *J* 2.8 Hz 8H), 7.12 (1H, *d*, *J* 3.2 Hz, 5H)], [δ_C (100 MHz: $CDCl_3$) 24.78 (NC-CH_2), 25.36 (NC-**C**H_2), 45.34 (N-C), 47.20 (N-C), 56.15 (CH_3-O), 88.90 (C-3), 112.94 (C-8), 118.70 (C-7), 120.26 (C-5), 120.43 (C-4a), 151.13 (C-6), 156.96 (C-8a), 157.03 (C-2), 165.39 (OCN), 189.44 (C-4)], ν_{max}/ cm^{-1} 1724.68 (C=O, CON), 1640.93 (C=O, C-4).

1-[(6-methoxychromon-2-yl)-carbonyl]-morpholine **55m.**[38] The experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide **55a** was followed, using a crude 6-methoxychromone-2-carbonyl chloride (1.91 g, 8 mmol) and morpholine (1.31 ml, 18 mmol) in dry pyridine (5 ml). Work-up afforded the crude product which was purified by flash chromatography using EtOAc: hexane (4:2) as the eluent (1.60 g, 69 %), m.p. (140-146°C) [δ_H (400 MHz: $CDCl_3$), 1.95 (2H, s, NCH_2), 2.01 (2H, s, NCH_2), 3.04-3.05 (4H, d, $O(CH_2)_2$), 3.80 (3H,s, CH_3O), 6.44 (1H, s, CH=C), 7.19 (1H, *dd*, *J* 3.2 Hz, *J* 3.2 Hz 7H), 7.34 (1H, *d*, *J* 8.8 Hz, 8H), 7.44 (1H, *d*, *J* 3.2 Hz, 5H)], [δ_C (100 MHz: $CDCl_3$), 35.48 (CH_2-N), 37.39 (CH_2-N), 54.91 (CH_3-O), 75.91 (CH_2-O), 76.43 (CH_2O), 103.50 (C-8), 109.82 (C-3), 118.92 (C-7), 123.34 (C-5), 124.05 (C-4a), 149.41 (C-6), 156.33 (C-8a), 157.33 (C-2), 161.39 (OCN), 176.40 (C-4)], ν_{max}/ cm^{-1} 1739.48 (C=O, CON), 1635.97 (C=O, C-4).

***N,N-Dimethyl-6-fluorochromone-2-carboxamide* 55n.**[38] The experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide **55a** was followed, using a crude 6-fluorochromone-2-carbonyl chloride (1.81 g, 8 mmol) and dimethylammonium chloride (1.30 g, 16 mmol). Work-up afforded the crude product which was purified by flash chromatography using EtOAc: hexane (4:2) as the eluent (0.88 g, 47 %), m.p. (93-103°C).

***1-[(6-Fluorochromon-2-yl)-carbonyl]-morpholine* 55o.**[38] The experimental procedure employed for the synthesis of *N,N*-dimethylchromone-2-carboxamide **55a** was followed, using a crude 6-fluorochromone-2-carbonyl chloride (1.81 g, 8 mmol) and morpholine (1.31 ml, 18 mmol) in dry pyridine (5 ml). Work-up afforded the crude product which was purified by flash chromatography using EtOAc: hexane (4:2) as the eluent (0.84 g, 38 %), m.p. (156-165°C)

Suzuki cross-coupling reactions

***N,N-Dimethyl-6-(2-nitrophenyl)chromone-2-carboxamide* 56.**[39] *N,N*-dimethyl-6-bromochromone-2-carboxamide (0.22 g, 0.67 mmol) was dissolved in acetonitrile (CH_3CN) (23 ml). 2-Nitrophenylboronic acid (0.51 g, 3.03 mmol), $(PPh_3)_4Pd(0)$ (138 mg, 0.12 mmol), anhydrous K_2CO_3 (934 mg) were added and the reaction took place under argon gas. The mixture was stirred at 80°C for 6 hours. The reaction was monitored by TLC every 2 hours.

On completion, the reaction mixture was allowed to cool and diluted with H_2O (8 ml). The mixture was extracted with CH_2Cl_2 (5x 12 ml). The extracts were combined, washed with H_2O (10 ml), dried over anhydrous $MgSO_4$ and evaporated to afford the crude *N,N*-dimethyl-6-(2-nitrophenyl)chromone-2-carboxamide which was purified by column chromatography using ethyl acetate as the running solvent (0.093 g, 40 %), [δ_H (400 MHz: $CDCl_3$) 3.15 (6H, s, $N(Me)_2$), 6.56 (1H, s, CH=C), 7.30-8.34 (8H, m, Ar_2H)], [δ_C (100 MHz: $CDCl_3$) 35.58 (N-CH_3), 38.38 (N-CH_3), 111.70 (C-3), 119.38 (C-8), 120.19 (C-6’), 123.47 (C-4a), 125.54 (C-2’), 128.46 (C-4’), 128.47 (C-5’), 128.57 (C-6), 139.34 (C-7), 137.39 (C-6’), 154.52 (C8a), 158.42 (C-2), 162.02 (OCN)].

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Chapter 6

Appendices

6.1 Spectral data

Representative NMR Spectra

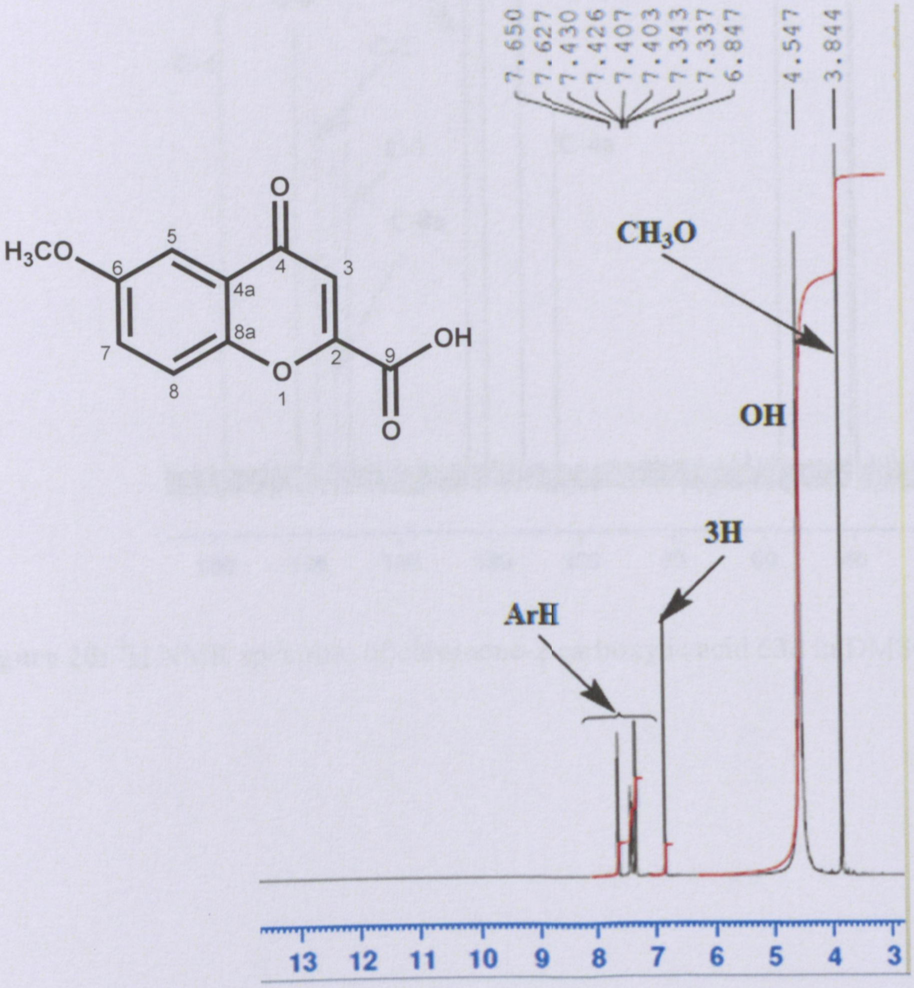


Figure 19: ^{1}H NMR spectrum of chromone-2-carboxylic acid **53d** in DMSO-*d*$_6$.

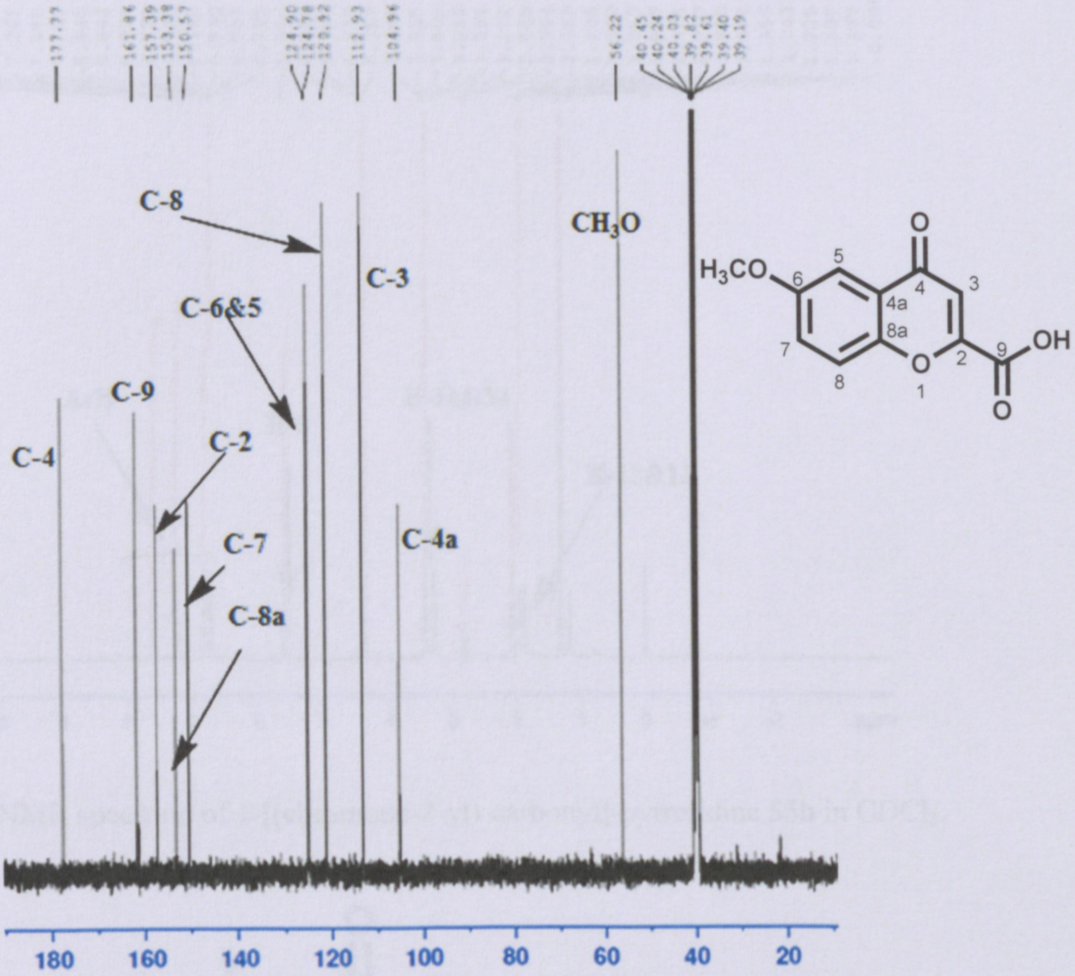


Figure 20: ^{1}H NMR spectrum of chromone-2-carboxylic acid **53d** in DMSO-d_6.

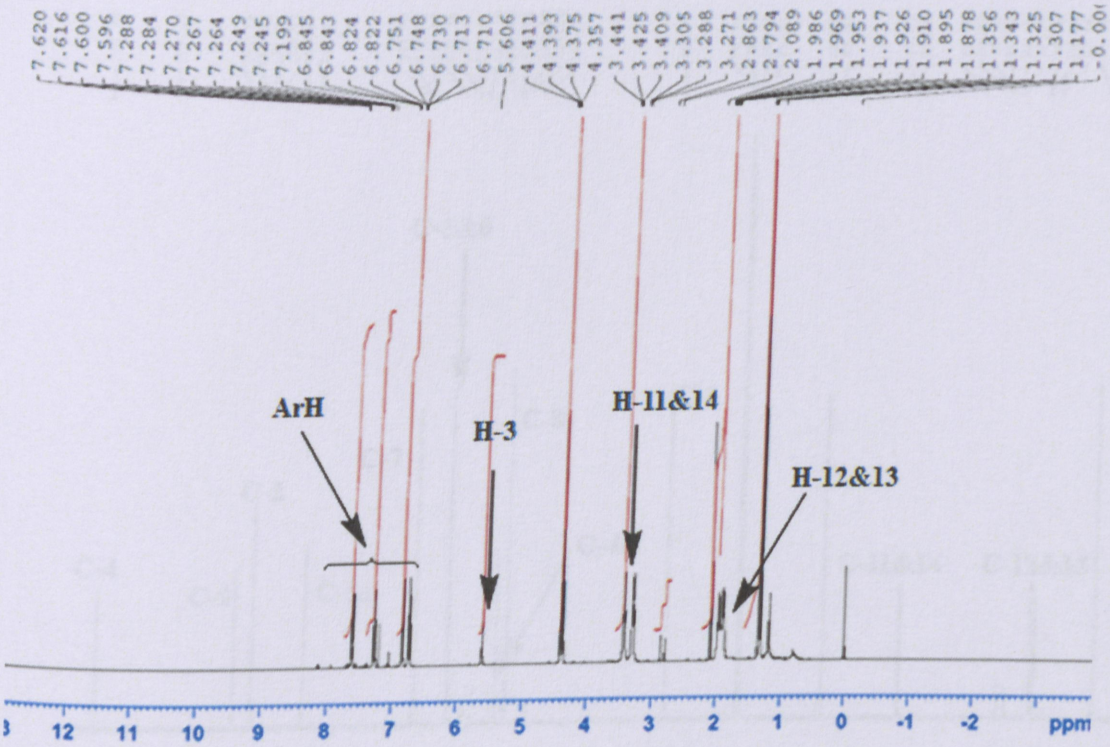
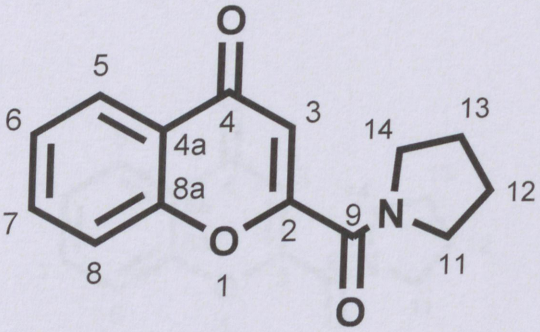


Figure 21: ^{1}H NMR spectrum of 1-[(chromone-2-yl)-carbonyl]-pyrrolidine **55b** in $CDCl_3$.



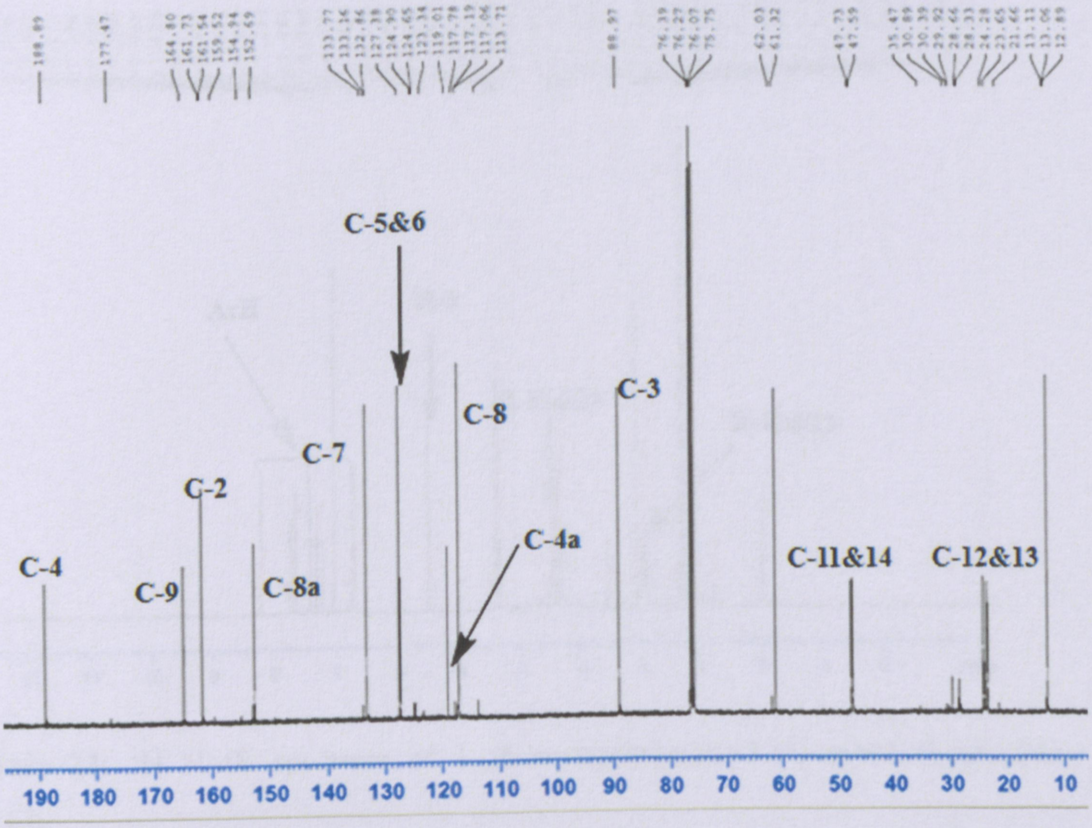
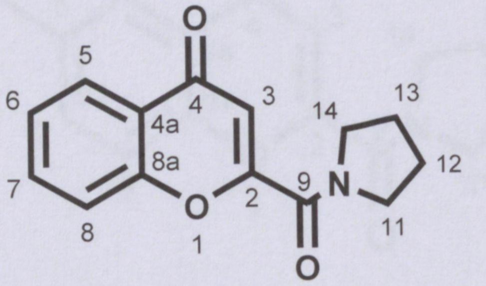


Figure 22: ^{13}C NMR spectrum of 1-[(chromone-2-yl)-carbonyl]-pyrrolidine **55b** in $CDCl_3$.



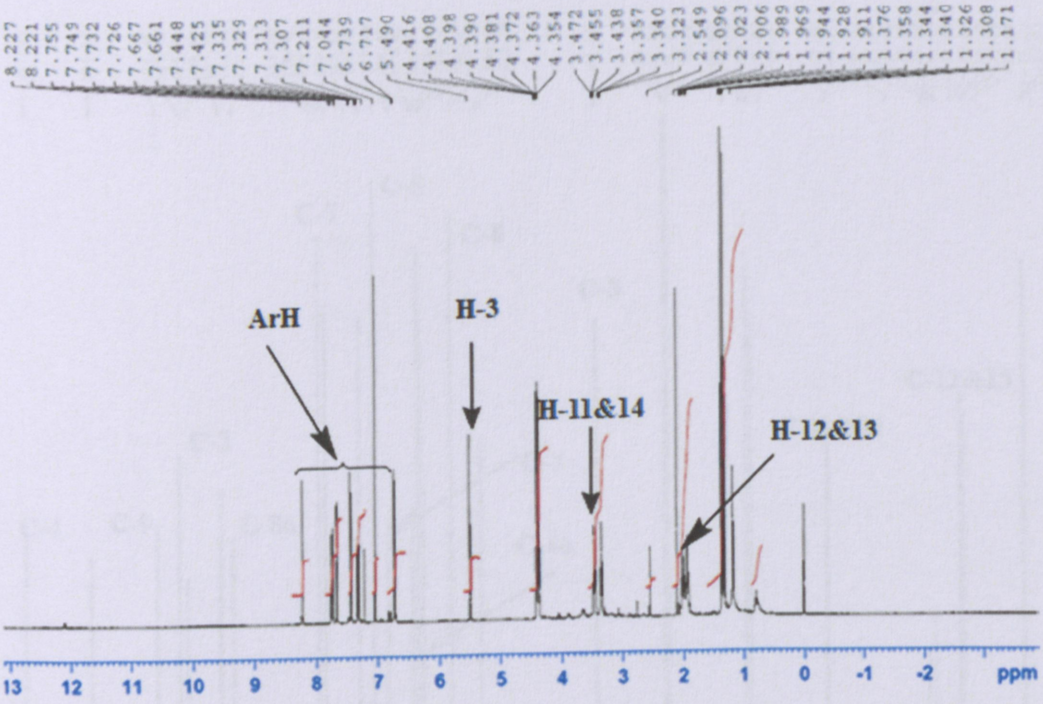
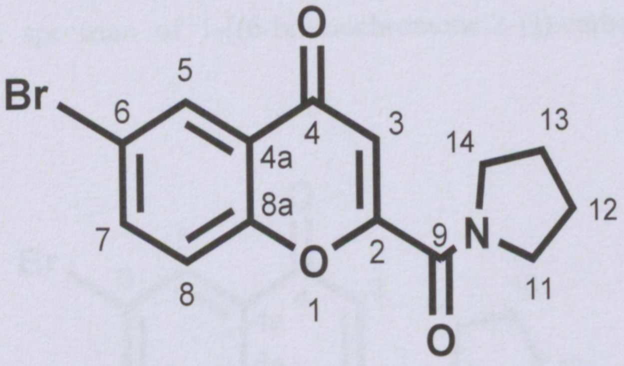


Figure 23: ^{1}H NMR spectrum of 1-[(6-bromochromone-2-yl)-carbonyl]-pyrrolidine **55e** in $CDCl_3$.



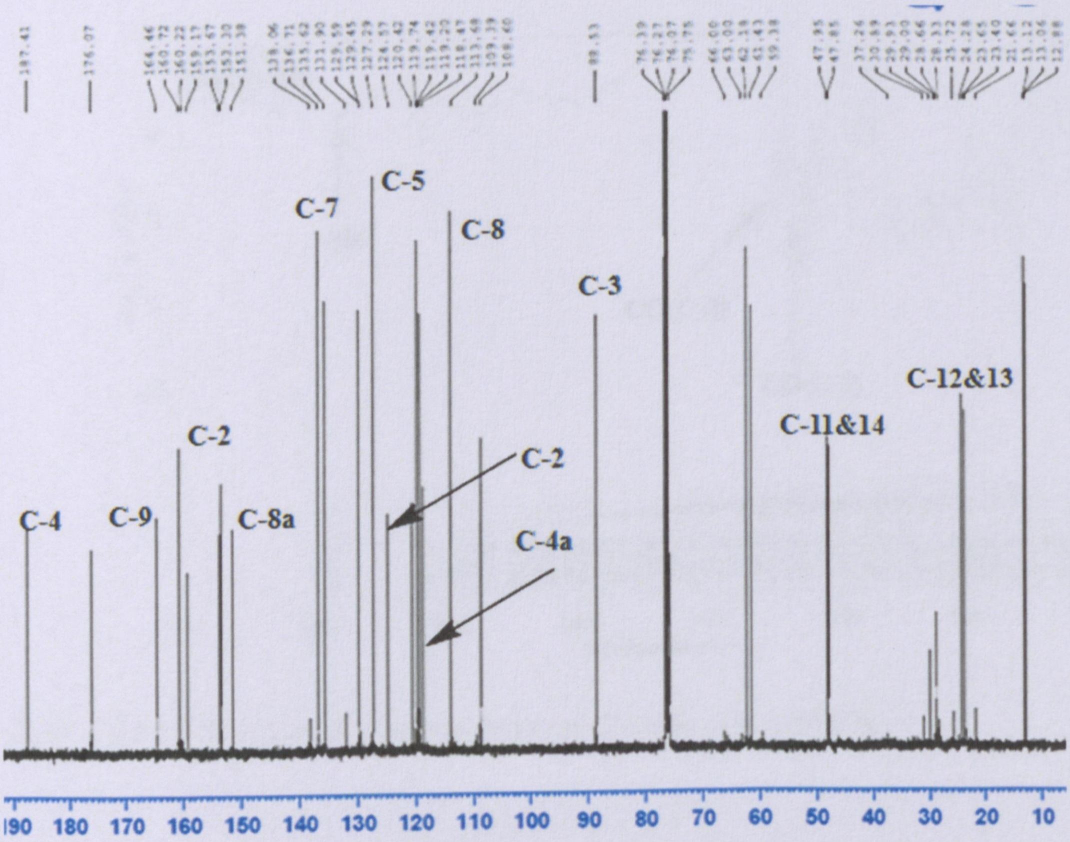
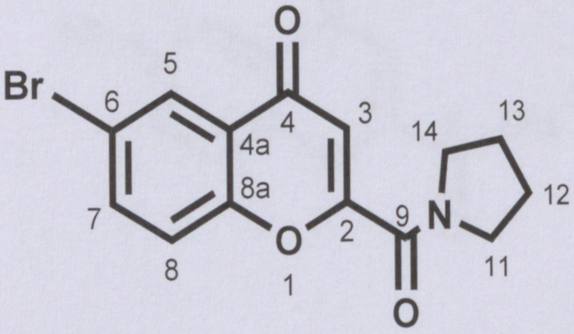


Figure 24: ^{13}C NMR spectrum of 1-[(6-bromochromone-2-yl)-carbonyl]-pyrrolidine **55e** in $CDCl_3$.



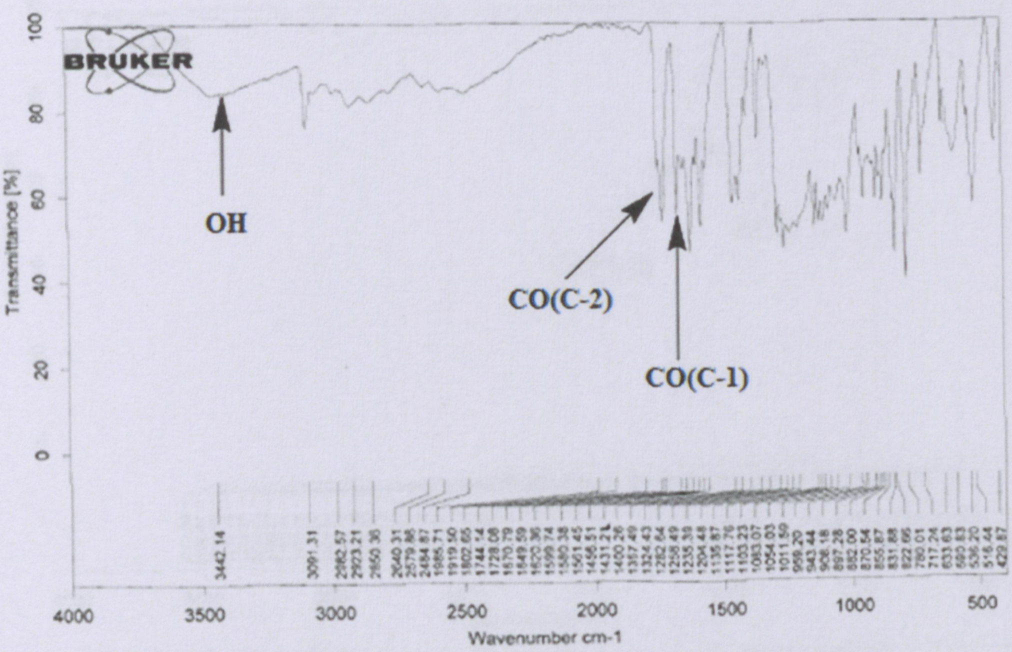
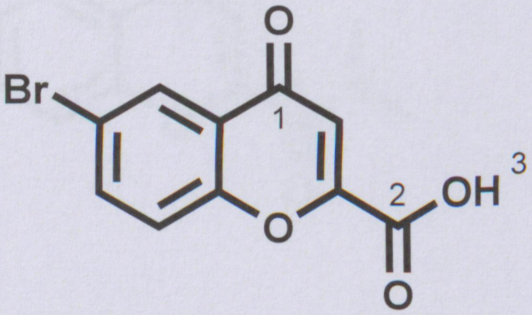


Figure 25: IR spectrum of 6-bromochromone-2-carboxylic acid **53b.**



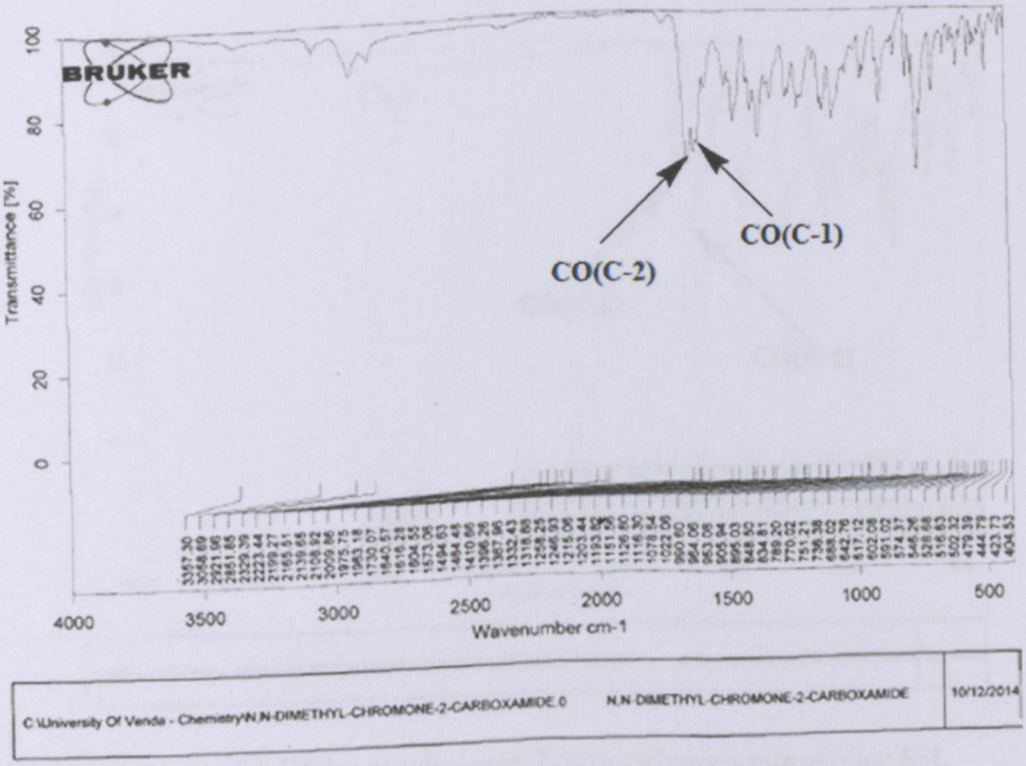
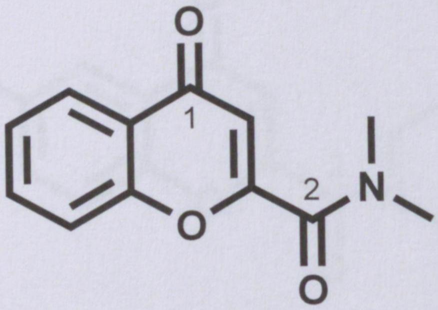


Figure 26: IR spectrum of *N,N*-dimethylchromone-2-carboxamide **55a.**



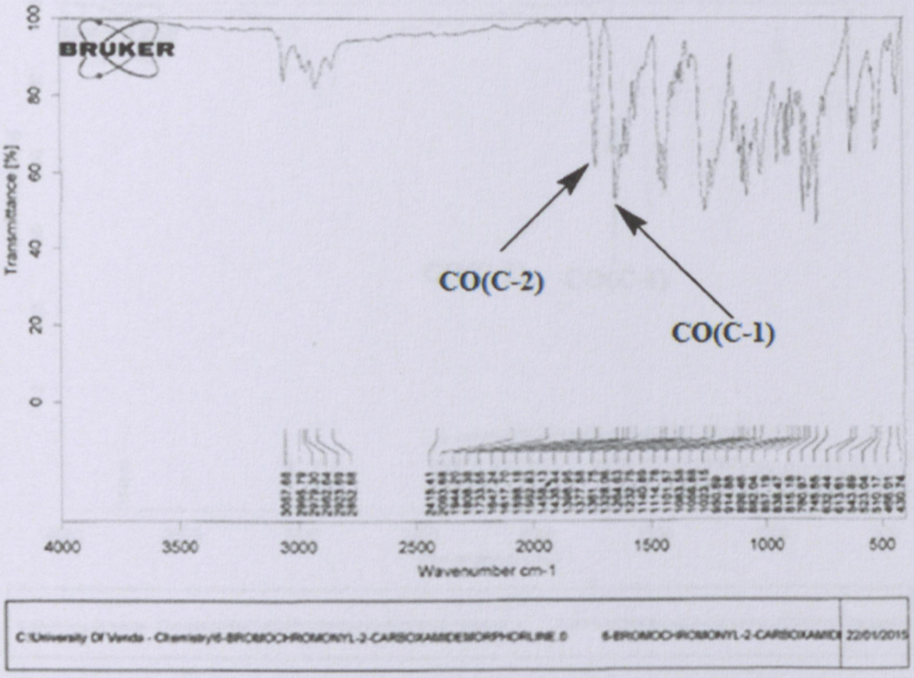
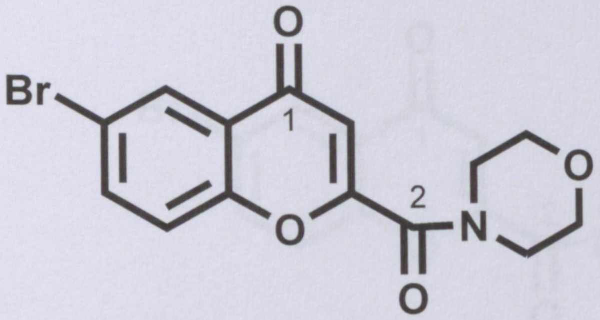


Figure 27: IR spectrum of 1-[(6-bromochromon-2-yl))-carbonyl]-morpholine **55f.**



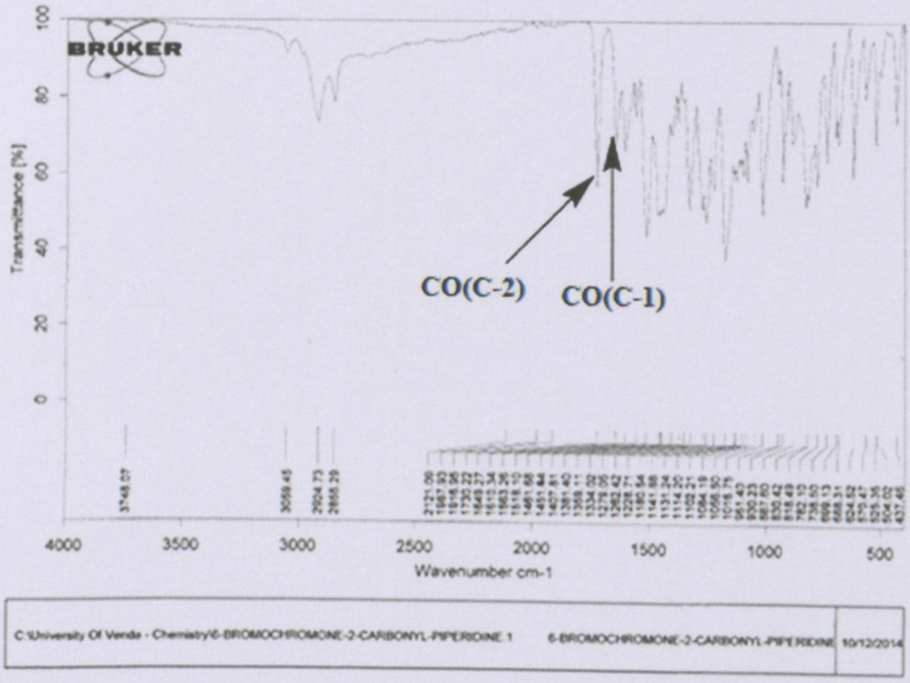
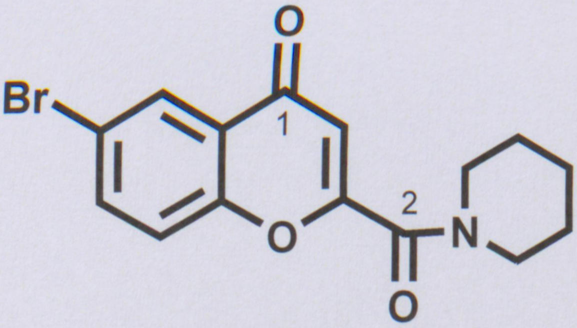
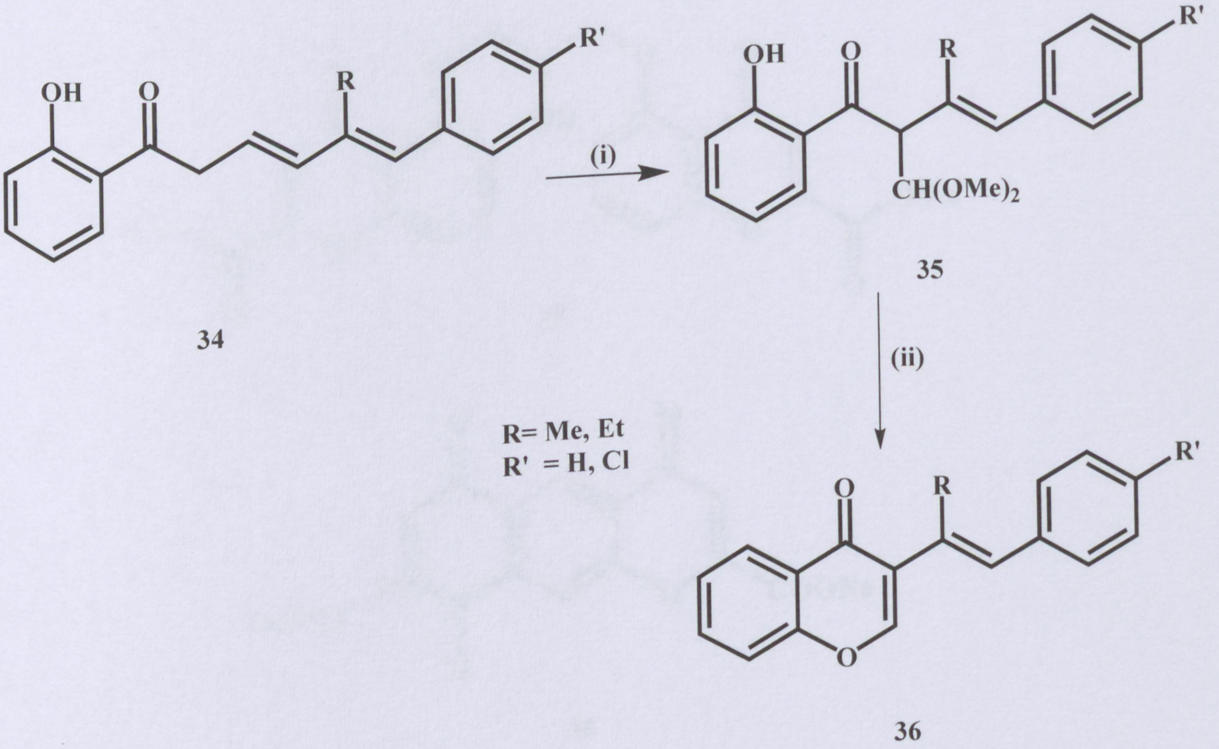


Figure 28: IR spectrum of 1-[(chromon-2-yl))-carbonyl]-piperidine **55g.**





Reagents: (i) Thallium(III) trinitrate; MeOH/trimethyl orthoformate at room temperature; (ii) HCl (aq)/reflux.

Scheme 7: Synthesis of 3-styrylchromones **36**

1.4 Reactions of Chromones

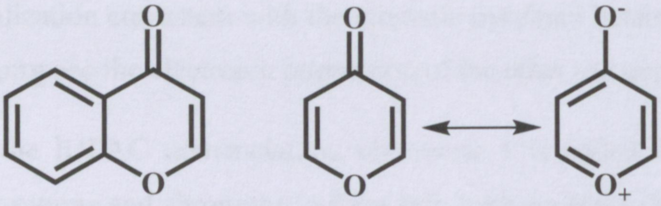
Chromones **40** are very much different from coumarins (benzopyran-2-ones) **41** in their chemistry (Figure 12) as its carbonyl group is conjugated with the oxygen atom through the double bond of the heterocycle. The benzene ring does not take part in the conjugation.[32]

Therefore this conjugation causes the chromone to be more basic, and it forms benzopyrylium salts when strong acids readily protonate the carbonyl oxygen atom.[32]

Chapter 1

Introduction: Chromone Chemistry

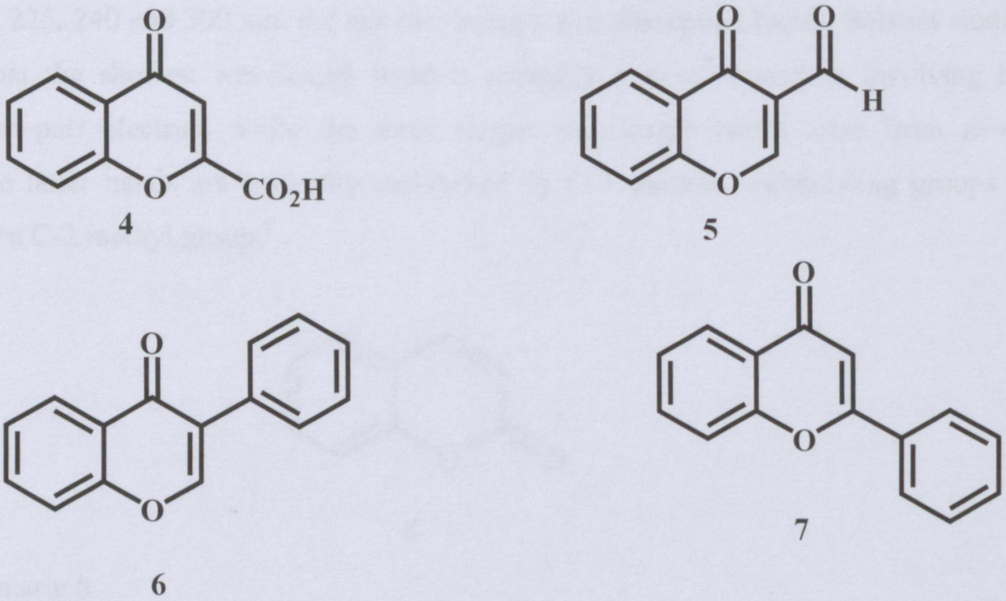
Chromones (such as **1**) belong to a family of heterocyclic compounds in which a benzene ring and a pyran-4-one (**2**) ring are fused together as shown in Figure 1.[1,2]



1 2 3

Figure 1: Chromone and pyran-4-one

There are several compound classes based on chromones and their derivatives such as chromone carboxylic acids **4**, chromone carbaldehyde **5**, flavones **6** and isoflavones **7** (Figure 2). Flavones (2-phenyl-4*H*-1-benzopyr-4-one) and isoflavones are chromone derivatives, which differ in location of the phenyl group. They belong to a major class of naturally occurring compounds called flavonoids,[3] mostly found in the plant kingdom, and are highly coloured; they therefore play an important role in the ecology of plants by making flowers and fruits attractive to insects.[4] The flavonoids are very useful as biologically active agents and some are used as drugs.[4]



4 5 6 7

Figure 2: Chromone derivatives