APPLICATION OF BAYLIS-HILLMAN METHODOLOGY IN THE CONSTRUCTION OF COMPLEX HETEROCYCLIC TARGETS

THESIS

Submitted in fulfilment of the requirements

For the degree

DOCTOR OF PHILOSOPHY

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ABSTRACT

Baylis-Hillman reactions using various aromatic aldehydes, activated alkenes and catalysts have been used to: - access an extensive range of poly-heterocyclic products; explore chemoselectivity; and optimise reaction efficiency.

Chromone-3-carbaldehydes and chromone-2-carbaldehydes, prepared *via* Vielsmeier-Haack and Kostanecki-Robinson methodology, respectively, have been used as Baylis-Hillman substrates with four different catalysts, *viz*., 1,4-diazabicyclo[2.2.2]octane (DABCO), 3-hydroxyquinuclidine (3-HQ), imidazole and N',N',N',N'-tetramethylpropanediamine (TMPDA), and with methyl vinyl ketone (MVK), methyl acrylate, cyclic enones (2-cyclohexen-1-one, 2-cyclopenten-1-one and chromones) as activated alkenes. Reactions of the chromone-3-carbaldehydes with MVK afforded dimeric Baylis-Hillman adducts when catalyzed by DABCO but when the same reactions were repeated using 3-HQ as catalyst, the dimeric products were accompanied by tricyclic Baylis-Hillman adducts. Use of excess MVK, however, led to mixtures of the *normal* Baylis-Hillman adducts and the tricyclic adducts – interestingly, with the apparent absence of the dimeric products. While reactions of chromone-3-carbaldehydes with methyl acrylate afforded the normal Baylis-Hillman adducts, the chromone-2-carbaldehydes produced, instead, rearrangement products, consistent with an earlier, single observation.

Reactions of 2-nitrobenzaldehydes with cyclic enones using imidazole as catalyst afforded the normal Baylis-Hillman adducts, reductive cyclisation of the 2-cyclohexen-1-one and 2-cyclopenten-1-one adducts, using acetic acid and iron powder, afforded the corresponding quinoline derivatives.

Treatment of cyclic enones with pyridine-2-carbaldehydes and quinoline-2-carbaldehydes using TMPDA as catalyst generally gave the expected Baylis-Hillman adducts. However, indolizine derivatives were isolated directly from Baylis-Hillman reactions involving

pyridine-2-carbaldehydes and 2-cyclohexen-1-one. The remaining Baylis-Hillman adducts were cyclized to the corresponding indolizines by treatment with acetic anhydride both under reflux and under microwave-assisted conditions, the latter approach providing remarkably rapid and efficient access to the polycyclic products. Computer modelling studies have been conducted on selected polycyclic products at the Molecular Mechanics (MM), Quantum Mechanical (QM) and Density Functional (DFT) levels. The theoretical results have been used to calculate UV, IR and NMR absorption data, which have been compared, in turn, with the experimental spectroscopic data. Use has also been made of the MestreNova NMR prediction programme and, generally, good agreement has been observed between the predicted and experimental spectroscopic data

CONTENTS

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1. INTRODUCTION

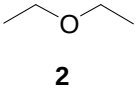
1.1 HETEROCYCLIC COMPOUNDS

1.1.1 General Overview

Heterocyclic compounds possess cyclic structures, made up of at least two different kinds of atoms in the ring. The most common types contain largely carbon atoms. Nitrogen, oxygen and sulphur are the most common heteroatoms.[1] Heterocyclic compounds are widely distributed in nature and are essential to life in many different ways. Most of the sugars and their derivatives, including vitamin C, exist largely in the form of five-membered (furan) or six-membered (pyran) rings with one oxygen atom as part of the ring system. Most members of the vitamin B group, such as vitamin B6, possess heterocyclic rings containing nitrogen. Even alkaloids, which are nitrogenous bases found in plants and many antibiotics, including penicillin, also contain heterocyclic ring systems. A large number of heterocyclic compounds, obtainable only by synthesis, have valuable properties as chemotherapeutic agents, dyestuffs and co-polymers.[1]

Heterocyclic compounds can be aliphatic or aromatic in character, depending on their electronic constitution. Generally, aliphatic heterocyclic compounds are chemically similar to their acyclic aliphatic analogues, *e.g.*, tetrahydrofuran **1** and diethyl ether **2**. In a similar way, aromatic heterocyclic compounds have many properties resembling their aromatic carbocyclic analogues, *e.g.*, pyridine **3** and benzene **4**.[2]

1

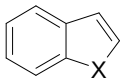


2

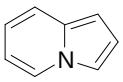
3

4

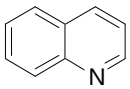
Generally, many well developed syntheses of the aromatic ring itself are known. A numbering convention for the atoms and substituents in simple heterocyclic rings starts from the heteroatom. The substituents are given lowest possible numbers and are cited in alphabetical order. When the heterocyclic ring contains more than one heteroatom, the order of preference for position 1 is oxygen, followed by suphur and then nitrogen.[1] A benzene ring may be fused onto heterocyclic systems in different positions resulting in different fused-ring structures. Depending on the nature of the heterocyclic ring, different fused analogues may be formed, as illustrated in compounds **5-11**.[1] In this study we have focused on fused heterocyclic compounds, in particular on indolizines **8**, quinolines **9** and chromones **11**.



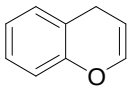
5: Indole (X = NH)
6: Benzofuran (X = O)
7: Benzothiophene (X =S)



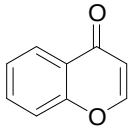
8: Indolizine



9: Quinoline



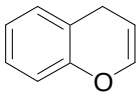
10: 4-*H*-benzopyran



11: Chromone

1.1.2 CHROMONES

The chemistry of chromones has been extensively reviewed.[3-5] The trivial name "chromones", first used by Bloch and Kostanecki in 1900,[4] was chosen to describe coloured, naturally occurring compounds known to contain the 4*H*-benzopyran moiety **10**. Chromones are benzanulated analogues of γ-pyrone **12**, which exhibit properties consistent with both canonical forms **12a** and **12b**; their systematic benzopyran nomenclature originates from pyran **13**.



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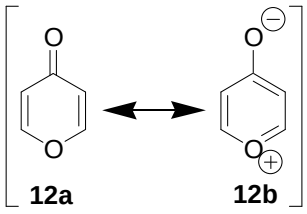
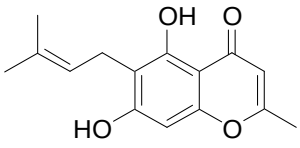


12a **12b**

13

1.1.2.1 Naturally occurring chromones

There is a large number of chromones that are found in plants that exhibit interesting biological activity.[3-6] Chromones have received resurgent interest from chemists due to their natural abundance in the flavonoid family, coupled with their pharmaceutical activity.[7-11] Flavonoids are phenylchromone derivatives that are present in plants. They have been shown to exhibit a wide variety of biological effects, including anti-cancer activity.[12] The majority of naturally occurring chromones contain alkoxy or hydroxy groups at C-5 and/or C-7, and a methyl group at C-2. The first of these compounds to be identified was peucenin **14**, which was isolated from the rhizome of the masterwort, *Peucedanum ostruthium*.[13] Eugenin **15**, the first alkoxychromone to be identified, was isolated from the wild clove, *Eugenia caryophyllata* (L.) Thunbg.[13]



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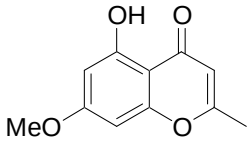

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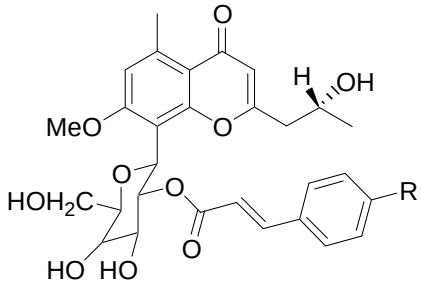
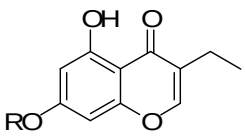


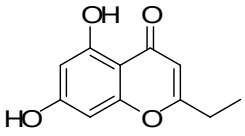
16a, R = H
16b, R = OH

Zhang *et al*.[14] have isolated and characterized other hydroxylated 2-methylchromones, *viz.*; isobiflorin and biflorin from *Euginia caryophyllata*, widely used in traditional Chinese medicine for the treatment of many diseases, such as disorders of the digestive system, bacterial and fungal infections and toothache.[14] Some chromone derivatives isolated from the *Pancratium maritimum*, which has been used as an ornamental plant, are 5,7-dihydroxy derivatives and exhibit characteristic UV absorption maxima.[15] The composition of Aloe leaf extracts has been extensively investigated.[16] 5-Methyl-chromome derivatives, isolated from the leaves of *Aloe vera*, have been extensively reviewed by Holzapfel *et al*.[17] and by Okumara *et al*.,[18-20] and some of these compounds inhibit tyrosine oxidation by mushroom tyrosinase. The two compounds responsible for

this inhibitory activity were shown to be isoaloeresin D (**16a**) and aloeresin E (**16b**), respectively.[18,19] Other alkylchromone derivatives include the 2- and 3-ethylchromone derivatives **17** and **18** isolated by Robeson *et al*.[21] from sweet pea, *Lanthyrus odoratus*, and the 5-methylchromone derivatives **19** isolated by Bittner *et al*.[22] from *Triptillion spinosum*.



17a; R = H
17b; R = Me



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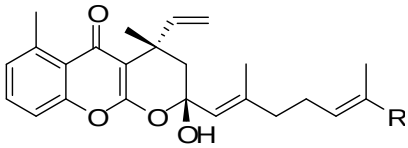
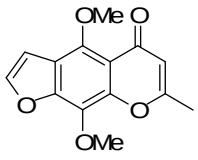


19a; R = Me
19b; R = CO_2Me
19c; R = CHO

Some of the most useful naturally occurring chromone derivatives include khellin **20**, a furochromone found in the fruits and seeds of *Ammi visnaga.*[23] Khellin was found to have vasodilator and smooth muscle relaxing properties, and was used to alleviate the symptoms of bronchial asthma.[23-25] Another class of naturally occurring chromones are the styrylchromone derivatives **21** isolated from the marine cyanophyte, *Hormothamnion enteromorphoides*.[26] These compounds were found to be potent cytotoxic agents to P388 lymphocytic leukemia and HL-60 human promyelocytic leukemia cell lines.[26] *Lachnum* is a rich source of biologically active metabolites and, recently, five new chromones from this genus have been isolated and characterized; some of these chromones have shown mild inhibition against the growth of *Mycobacterium tuberculosis.*[27] Aposphaerin A (**22A**) and B (**22B**) are potent antibiotics isolated from the endophytic fungus *Aposphaeria* spec. They contain the 2-vinylchromone system in their structure.[28]



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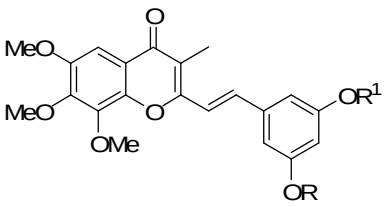
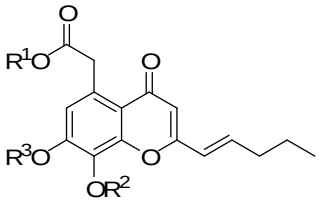


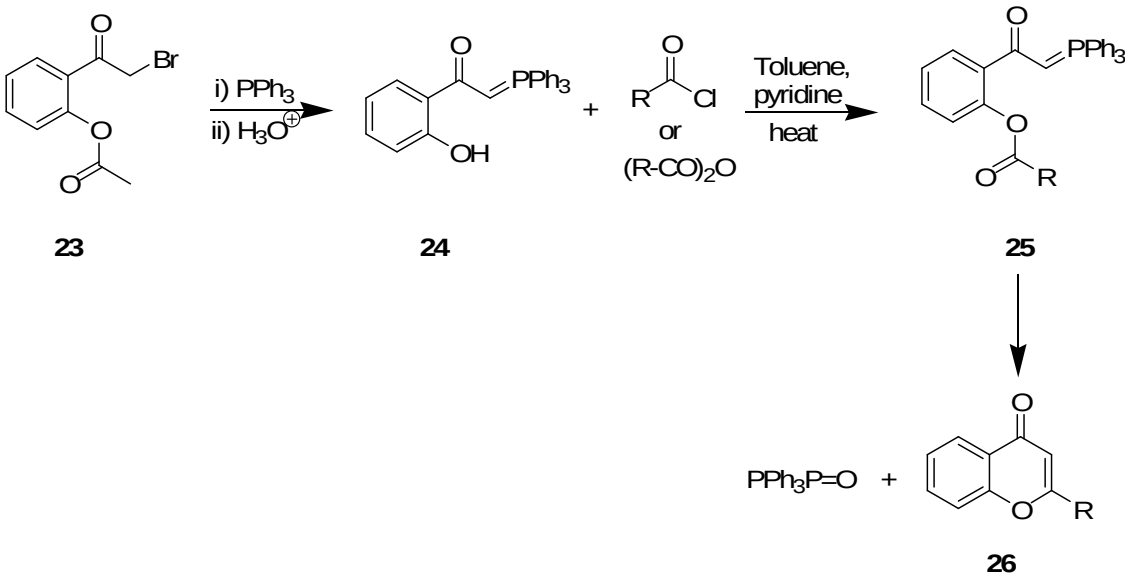
21a; R = R^1 = H
21b; R = R^1 = $COCH_3$



22a; R^1 = R^2 = OH, R^3 = Me
22b; R^1 = OEt, R^2 = R^3 = H

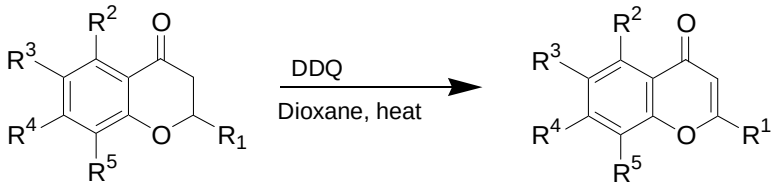
1.1.2.2 Synthesis of Chromones

The synthesis of chromones has been extensively reviewed,[29,30] and a complete survey is beyond the scope of this introduction. We shall, however, describe some of the simple methods used to synthesize chromones. One of these involves the use of *o*-hydroxyphenacylidinetriphenylphosphorane **24** under mild conditions. The phosphorane **24** is readily obtained from the reaction of triphenylphosphine with *o*-acetoxyphenacyl bromide **23**, followed by acid hydrolysis and treatment of the reaction mixture with sodium carbonate. Reaction of the phosphorane **24** with carboxylic acid chlorides or anhydrides in boiling toluene in the presence of pyridine gives an unstable phosphorane ester **25**, which undergoes spontaneous intramolecular cyclization to afford the chromones **26** (Scheme 1).[31]



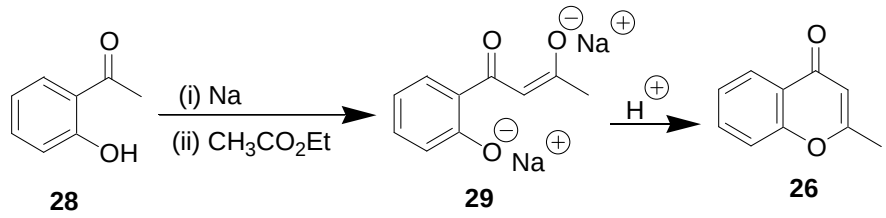
Scheme 1

Another method involves the efficient dehydrogenation of chromanones **27** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as a convenient oxidant (Scheme 2).[32] In the Kostanecki-Robinson strategy, *o*-hydroxyacetophenone **28** is condensed with an acylating agent to form a β-diketone derivative **29**, which spontaneously cyclizes to the chromone **26** on acidification (Scheme 3).[29].



27 **26**

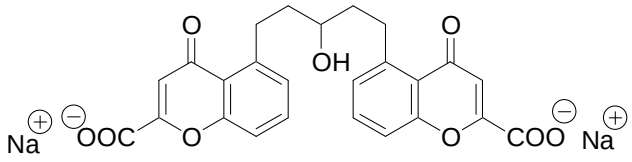
Scheme 2



28 **29** **26**

Scheme 3

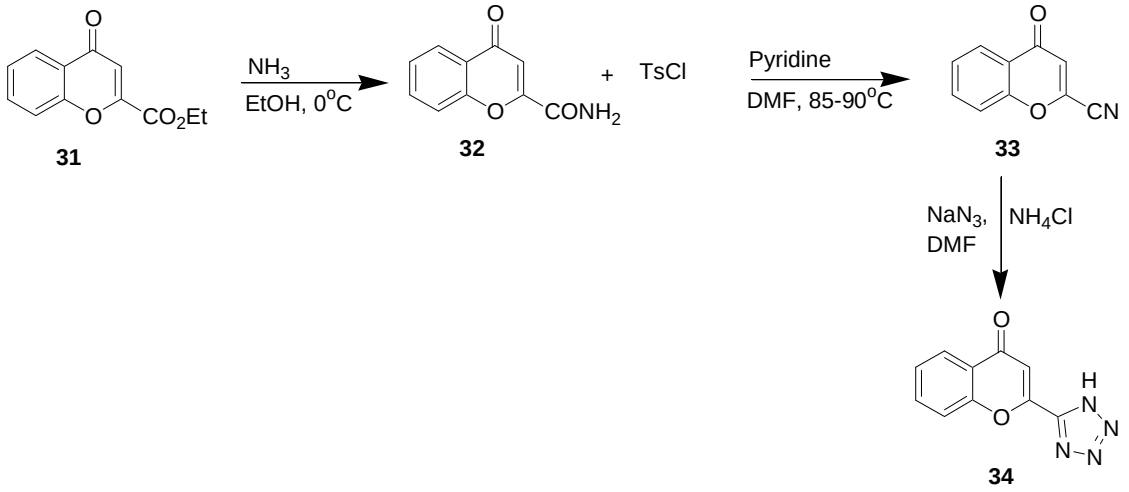
The discovery of naturally occurring medicinally useful chromones has prompted the synthesis of the chromone derivatives with pharmacological potential. One such compound, disodium cromoglycate [a sodium salt of 1,3-bis(2-carboxychroman-5-yloxy)-2-hydroxypropane] **30**, has attracted considerable interest. It was discovered that disodium cromoglycate **30** specifically inhibits the liberation of the mediators of anaphylaxis initiated by the interaction of antigens with regain-type antibodies.[33]



30

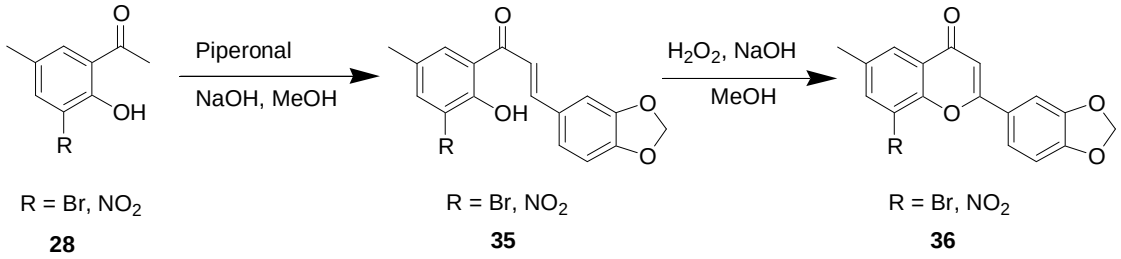
Disodium cromoglycate **30** was later introduced for the treatment of allergic asthma, and was reported to represent a new pharmacological approach to the treatment of this condition. It was also found to inhibit the release of histamine and slow-reacting substance of anaphylaxis (SRS-A) from sensitized human lung *in vitro*. In addition to

that, it was reported to prevent homologous passive cutaneous anaphylaxis (PCA) reactions in the rat.[34] The discovery of disodium cromoglycate led to a study of structural requirements for such biological activity, by Cairns *et al*.[34] The structure-activity relationship (SAR) studies attributed the biological activity to the position of attachment and length of the connecting link in the bis-chromone-2-carboxylic acids, as well as to the presence of atoms other than carbon in the linking chain.[34] Some chromones with acidic groups at C-2 or C-3 were found to inhibit the release of spasmogens, which usually follows antigen-antibody interaction. The majority of compounds examined contain a carboxyl group, replacement of which by a 5-tetrazolyl ring was shown to result in certain compounds with increased pharmacological activity (Scheme 4).[35,36] A further synthesis of chromones bearing a tetrazole ring linked to C-6 or C-8 through a methyleneoxy moiety has also been explored by Ellis *et al*.[37]



Scheme 4

Lee *et al*.[12] have reported the synthesis of flavonoids, for biological evaluation against cyclin-dependent kinase (CDK), and it was established that flavonoids with a hydroxyl group at C-3 were potent inhibitors of CDK2. The treatment of substituted 2-hydroxyacetophenones **28** with piperonal and NaOH in EtOH affords the chalcone derivatives **35**, which are converted to the 3-hydroxychromones **36** by treatment with NaOH and hydrogen peroxide (Scheme 5).[12]



R = Br, NO_2 **28**

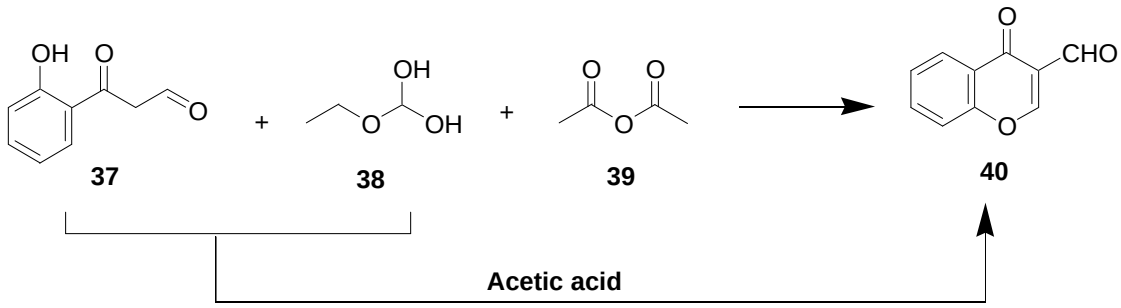
R = Br, NO_2 **35**

R = Br, NO_2 **36**

Scheme 5

1.1.2.3 Synthesis of Chromone-3-carbaldehydes

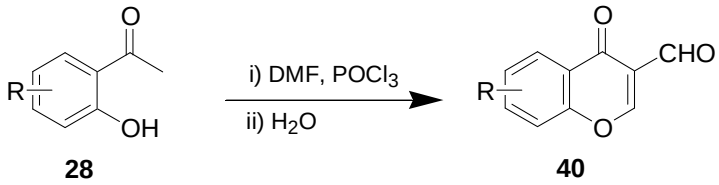
Among the different functionalized chromones, chromone-3-carbaldehyde **40** is unique, because of the large number of heterocycles obtainable from this system.[7] Several methods for the synthesis of chromone-3-carbaldehydes have been reported. These include the reaction 2-formyl-2'-hydroxyacetophenone **37** with ethyl orthoformate **38** in acetic anhydride **39** (Scheme 6),[38,39] in refluxing acetic acid,[7,38] in perchloric acid[7,40] or in a mixture of acetic-formic anhydride and sodium formate under mild conditions.[7,41]



Scheme 6

However, the most widely used method for the preparation of chromone-3-carbaldehydes **40** is the Vilsmeier-Haack reaction (Scheme 7). This involves the reaction between *o*-hydroxyacetophenone **28**, dimethylformamide and phosphorus oxychloride.[38] Ways of improving the Vielsmeier-Haack method have been reported. These include the

Vielsmeier-Haack reaction on a solid support, reported by Borrell *et al.*,[42] and the ultrasonically accelerated Vielsmeier-Haack reaction reported by Ali *et al.*[43]

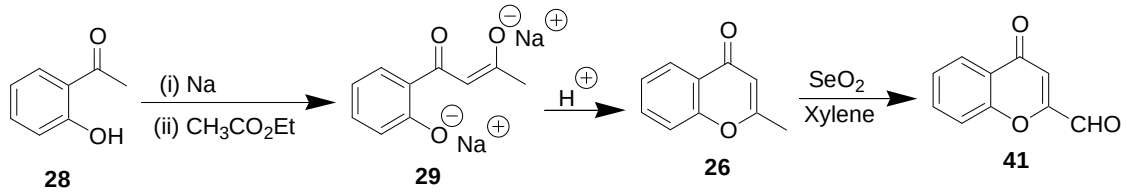


28 **40**

Scheme 7

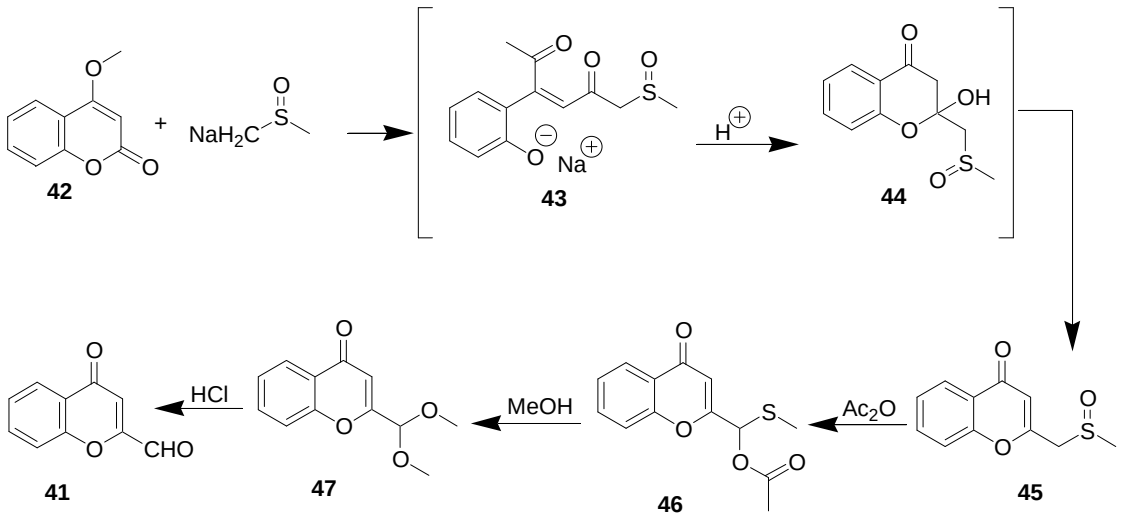
1.1.2.4 Synthesis of Chromone-2-carbaldehydes

Chromone-2-carbaldehyde **41** was first prepared *via* 2-methylchromone **26** by a three-step sequence involving 2-hydroxyacetophenone **28** as the starting material (Scheme 8).[44] Connor *et al.*[45] have reported a four-step synthesis, starting from 4-methoxycoumarin **42** (Scheme 9).[45]



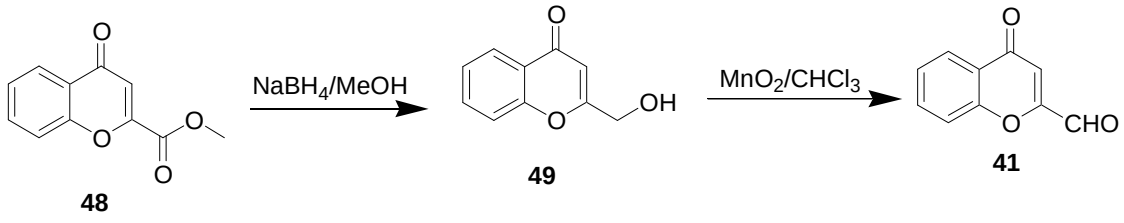
28 **29** **26** **41**

Scheme 8



Scheme 9

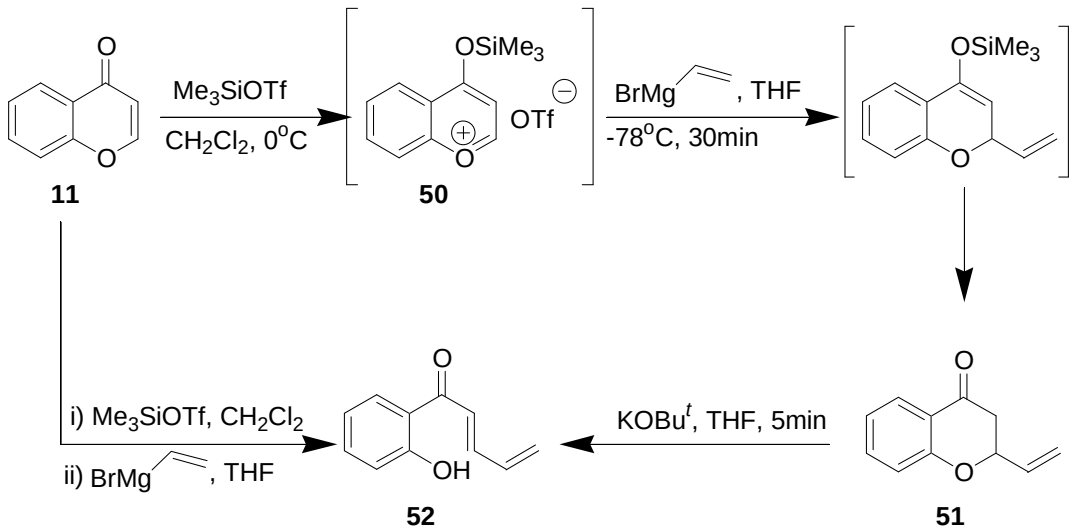
Earlier, chromone-2-carbaldehyde **41** was obtained from the oxidation of khellol **49** with manganese dioxide. Khellol is a 2-hydroxymethylchromone, which is obtained in a three-step synthesis from visnaginone benzyloxy acetate.[46] Payard *et al*.[47] have also reported the synthesis of chromone-2-carbaldehyde from methyl chromone-2-carboxylate **48**. This is achieved by selective reduction of the ester group with sodium borohydride, and the subsequent oxidation of the product by manganese dioxide to give the desired chromone-2-carbaldehyde **41** (Scheme 10).[47]



Scheme 10

1.1.2.5 Reactions of Chromones

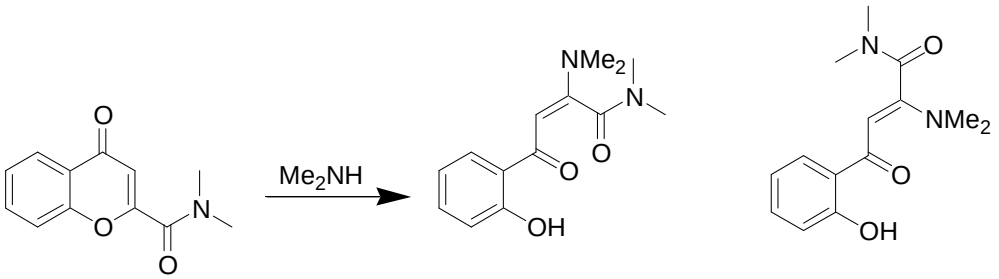
There are many reactions that chromones undergo. The majority of these reactions include nucleophilic attack at C-2 or C-4 of the chromone. Nucleophilic attack at C-2 affords conjugate addition products, and in some cases, ring-opening takes place at C-2. The ring-opening reaction of chromones usually affords products having either *E*- or *Z*-double bond configurations.[28,48] The treatment of chromones with Me_3SiOTf affords the benzopyrylium triflate **50** *in situ*, which is subsequently converted into 2-vinylchromanone **51** when treated with vinyl magnesium bromide at -78 ^oC. The biological activity of 2-vinylchromanones, as inhibitors of the growth of pathogenic and non-pathogenic microbes, is suspected to involve the ring-opening reaction of the labile arylallyl-ether moiety. Hence, treatment of the 2-vinylchromanone **51** with $KOBu^t$ affords 1-(2-hydroxyphenyl)penta-2,4-dien-1-one **52** *via* tandem ring-opening and *retro*-Michael reactions. It was also established that the treatment of chromones with Me_3SiOTf followed by vinyl magnesium bromide affords the open-chain 1-(2-hydroxyphenyl)penta-2,4-dien-1-one **52** directly (Scheme 11).[28]



Scheme 11

The ring-opening of chromones *via* C-2 nucleophilic attack prompted Davidson *et al.*[48] to investigate the possible implication of this molecular process in the biological activity of

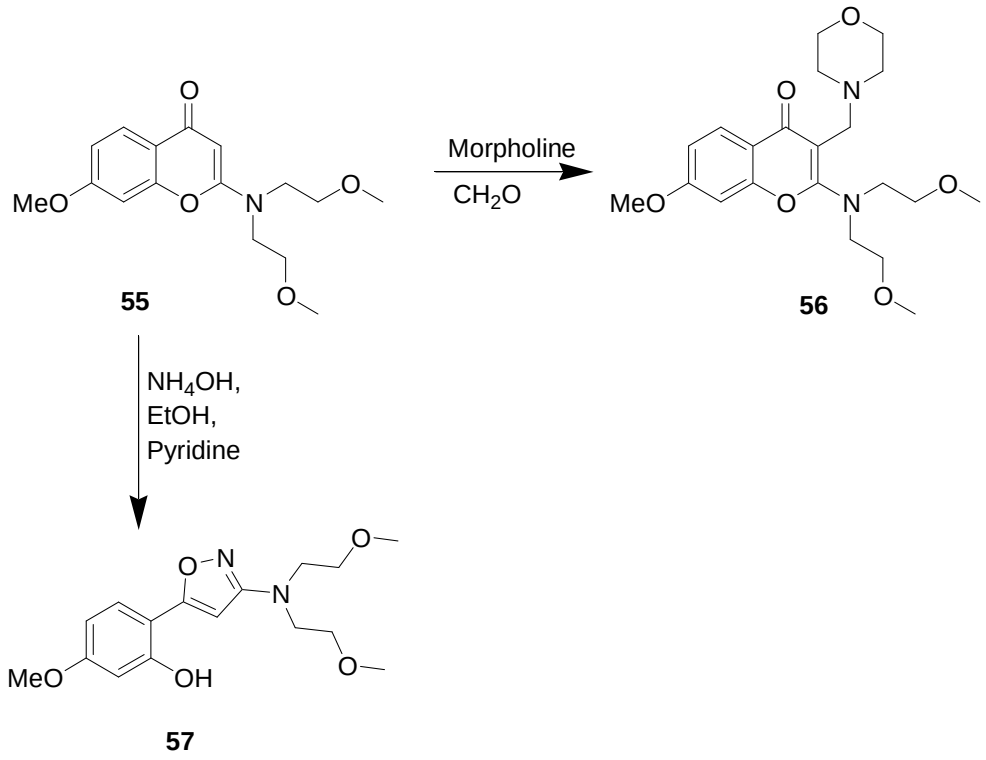
chromones. This was achieved by the treatment of *N*,*N*-dimethylchromone-2-carboxamide **53** with dimethylamine resulting in 2-(dimethylamino)-3-(2-hydroxybenzoyl)-*N*,*N*-dimethylacrylamide **54** (Scheme 12).[48]



53 **54a** **54b**

Scheme 12

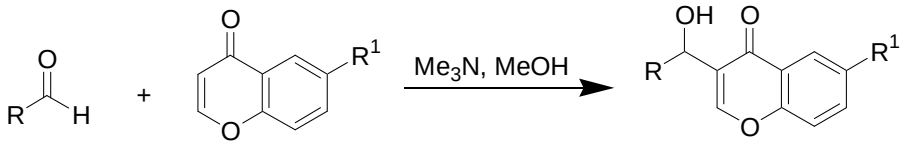
Treatment of 2-{bis(2-methoxyethyl)amino}chromone derivatives **55** with morpholine in the presence of 40% formaldehyde affords the Mannich bases **56** in good yield, while the treatment of the same aminochromone derivative **55** with hydroxylamine hydrochloride in ethanol and pyridine results in the opening of the chromone ring and the subsequent formation of the isoxazole ring **57** (Scheme 13).[49-51]



55 **56** **57**

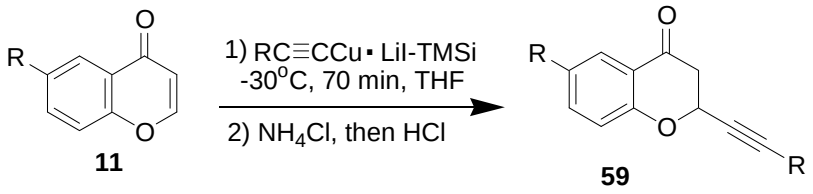
Scheme 13

Basavaiah *et al*.[52] reported the use of chromones **11** in Baylis-Hillman reactions, as activated alkenes. This involves the reaction of chromones with various aldehydes, catalyzed by trimethylamine in methanol (Scheme 14).[52] Eriksson *et al*.[53] reported the conjugate addition reaction of copper acetylides (together with TMSI and LiI) to chromones, to afford 2-[(trimethylsilyl)alkyl]-4-chromanone derivatives **59** in good to excellent yields (Scheme 15).[53] The reaction of chromones with *t*-butyldimethylsilyl triflate at 80 ^{o}C, readily affords 4-*t*-butyldimethylsiloxy-1-benzopyrylium triflate.[54]



11 **58**

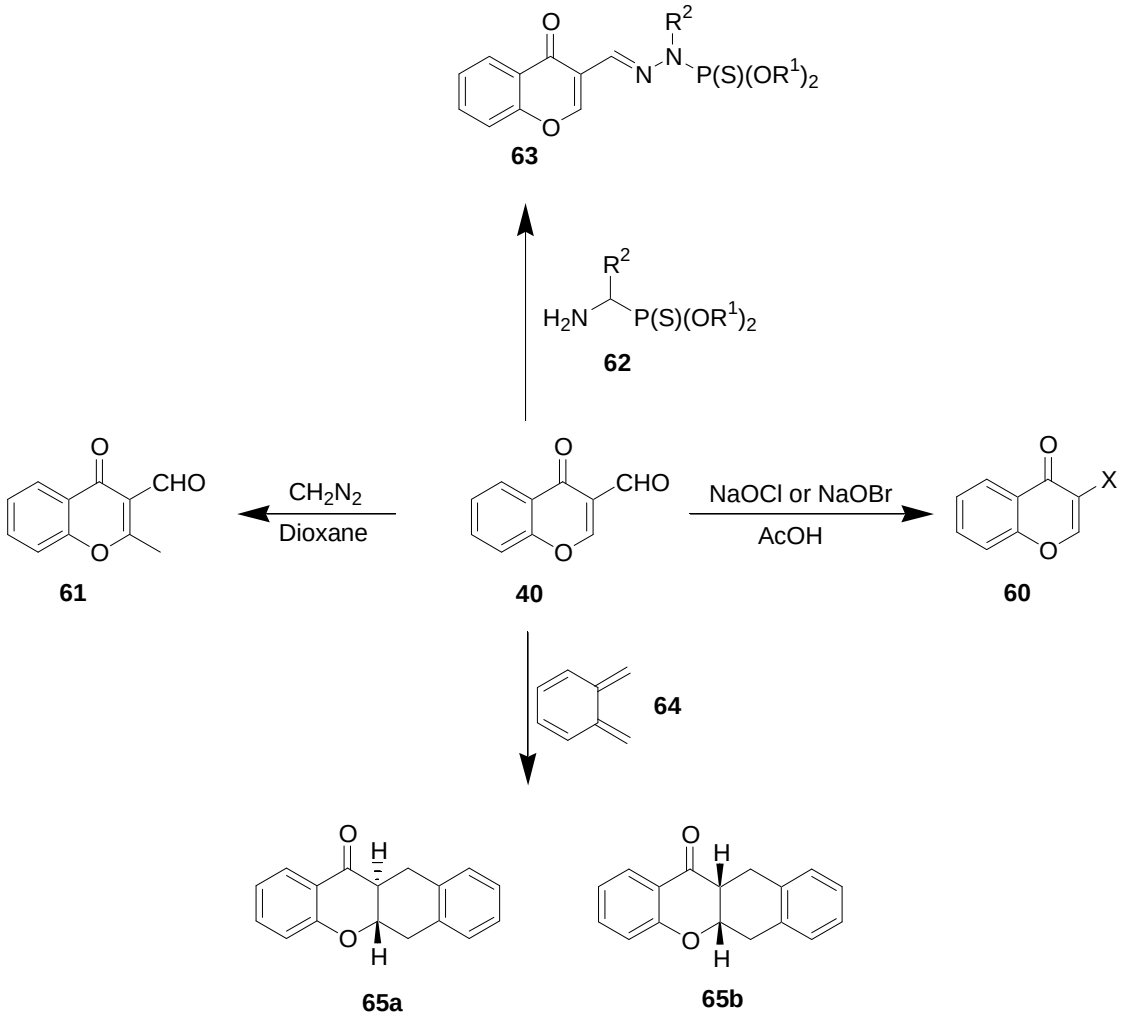
Scheme 14



Scheme 15

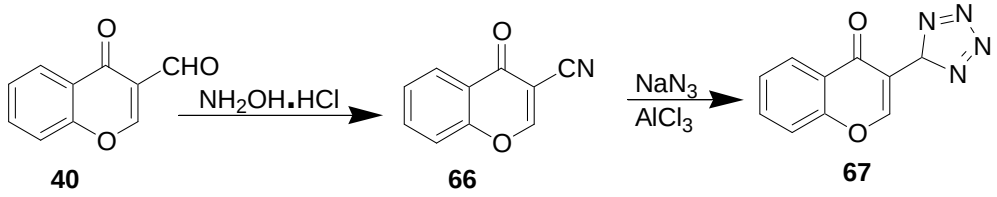
1.1.2.6 Reactions of Chromone-3-carbaldehydes

Much of the synthetic utility of chromone-3-carbaldehydes is derived from the reactivity of their electron-deficient centres at C-2, C-1' (CHO) and C-4, giving rise to products in which the chromone ring is retained or opened.[55] Chromone-3-carbaldehydes constitute the most studied class of chromones bearing an electron-withdrawing substituent at C-3.[56] Nohara *et al*.[57] reported the halogenation of chromone-3-carbaldehyde **40** at C-3, which involves the replacement of the aldehyde group. This is achieved by treating the chromone-3-carbaldehyde **40** with aqueous sodium hypochlorite or hypobromite in acetic acid affording 3-halogenochromone derivatives **60** (Scheme 16).[54] The reaction of chromone-3-carbaldehyde **40** with diazomethane affords 2-methylchromone-3-carbaldehyde **61** (Scheme 16).[57] Chromone-3-carbaldehydes can also be converted to Schiff's bases **63**, which are strong alkylating agents, by reaction with phosphorohydrazides **62** (Scheme 16).[58] They have also found application in Diels-Alder reactions with *ortho*-benzoquinodimethane **64**, forming the diastereomeric benzo[*b*]xanthones **65** following oxidation (Scheme 16).[56]



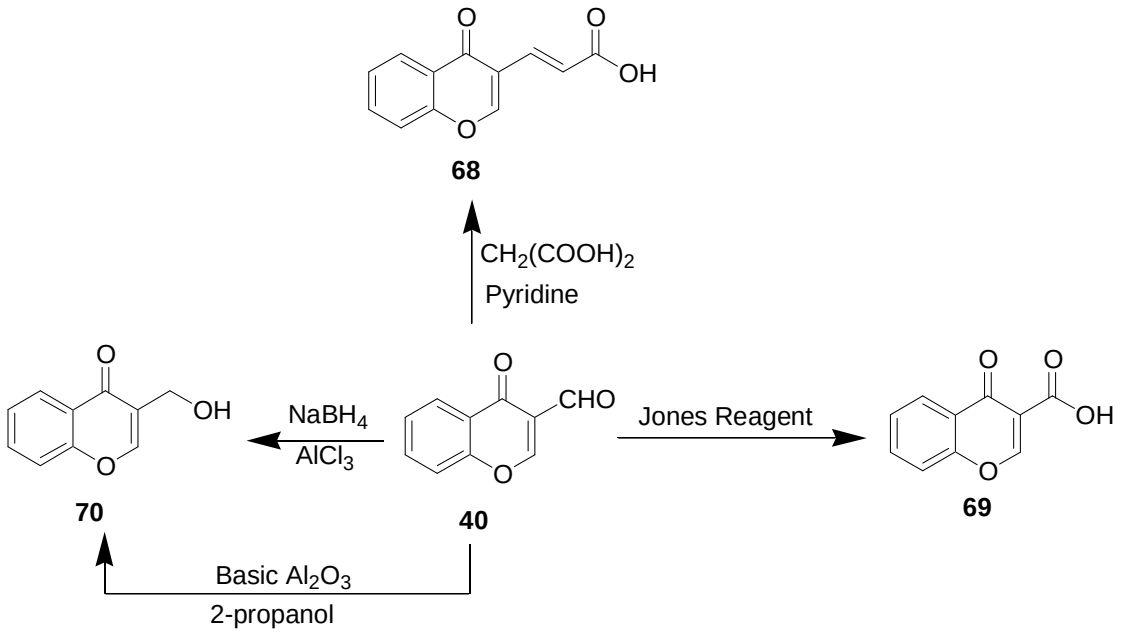
Scheme 16

Chromone-3-carbaldehydes can also be converted to 3-(1*H*-tetrazol-5-yl)chromones **67** *via* a carbonitrile derivative **66**. Thus, treatment of chromone-3-carbaldehyde **40** with hydroxylamine hydrochloride in 95% ethanol in the presence of HCl affords a 3-carbonitrile **66**, which is converted to the tetrazolo derivative **67** when treated with sodium azide in the presence of anhydrous aluminium chloride in THF (Scheme 17).[59]



Scheme 17

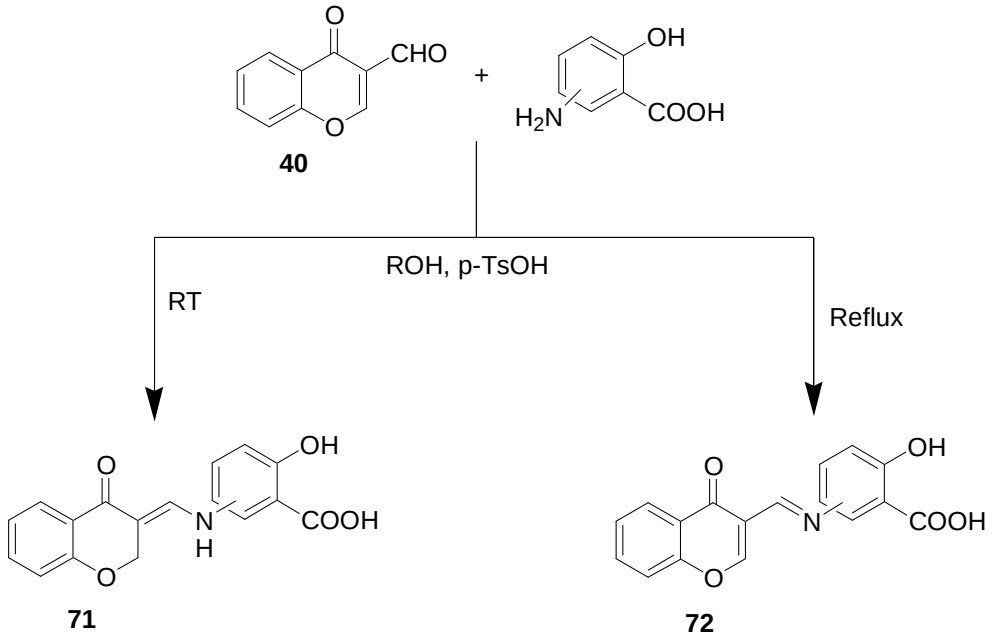
Chromone-3-carbaldehydes react with various α-amino acids and esters to give azomethine ylides and pyrroles under different conditions and can be converted to chromone-3-acrylic acids **68** when treated with malonic acid in pyridine (Scheme 18).[55,60] Other reactions include chromic acid oxidation with Jones reagent to give chromone-3-carboxylic acids **69**,[38] and reduction with sodium borohydride and aluminium chloride to give 3-hydroxymethylchromones **70**.[38] Treatment of chromone-3-carbaldehydes with basic alumina results in improved yields of 3-hydroxymethylchromones **70**.[61]



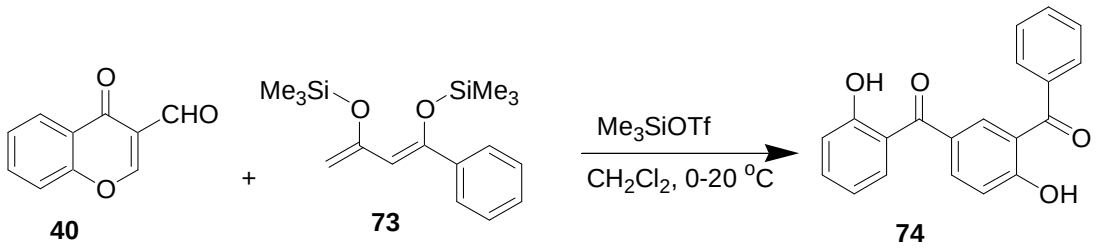
Scheme 18

The reaction of chromone-3-carbaldehydes **40** and aminosalicylic acid derivatives produces enamines **71** or imines **72** depending on the reaction conditions employed (Scheme 19),[62] while the benzophenone derivative **74** is obtained when chromone-3-carbaldehyde **40** is treated with the 1,3-bis(silyl enol ether) **73** in the presence of TMSOTf in a reaction called the domino "Michael-*retro*-Michael-aldol" reaction (Scheme 20).[63] Treatment of chromone-3-carbaldehydes **40** with excess quantities of the enol ethers **75a,b** yields the corresponding diastereomeric heterodiene cycloadducts **76a-d**, with the stereoselectivity illustrated in Scheme 21.[64,65] The reaction of chromone-3-carbaldehyde **40** with various diols affords chromone acetals **77** in good yields. These

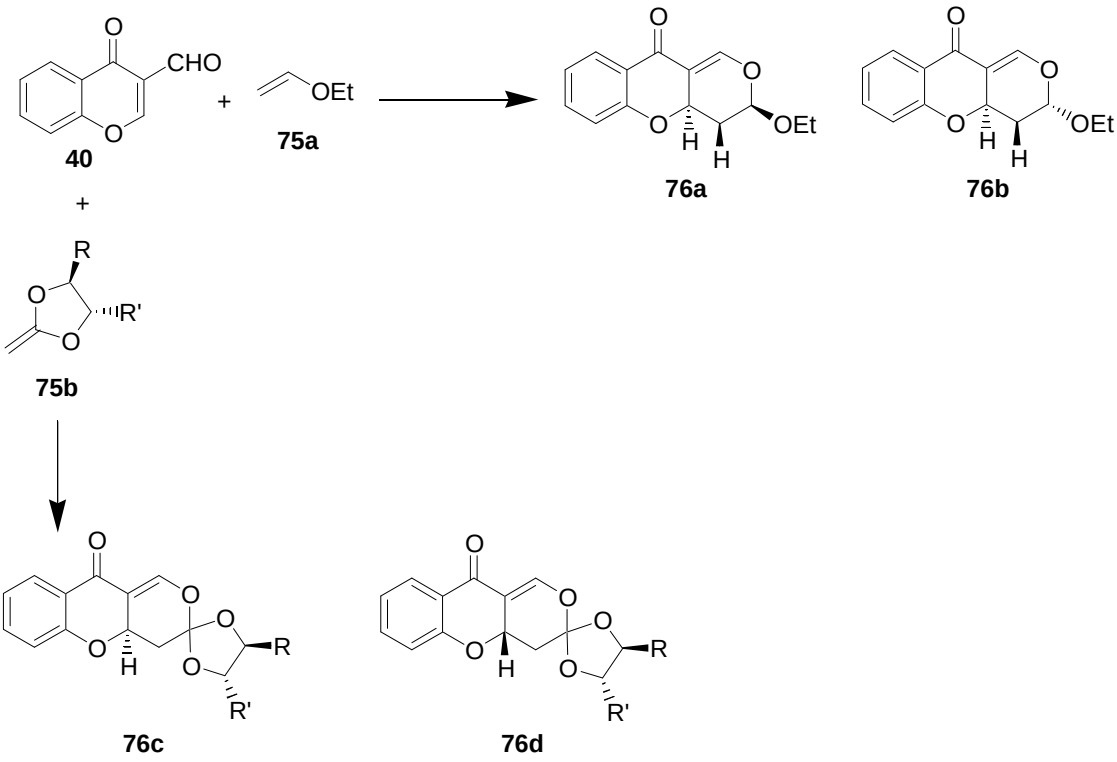
acetals **78** permit direct lithiation at C-2. Metallation is facilitated by :- i) ability of an acetal oxygen to coordinate with the metallating agent; and ii) the electron-withdrawing inductive effect of the heteroatom in the pyran ring which enhances the acidity of H-2. Thus, treatment of the acetal **77** with lithium 2,2,6,6-tetramethylpiperidine (LTMP) in THF at -78 ^{o}C affords the lithiated chromone derivative **78**, which, when quenched with various trapping reagents, yields the substituted chromone derivatives **79** (Scheme 22).[66]



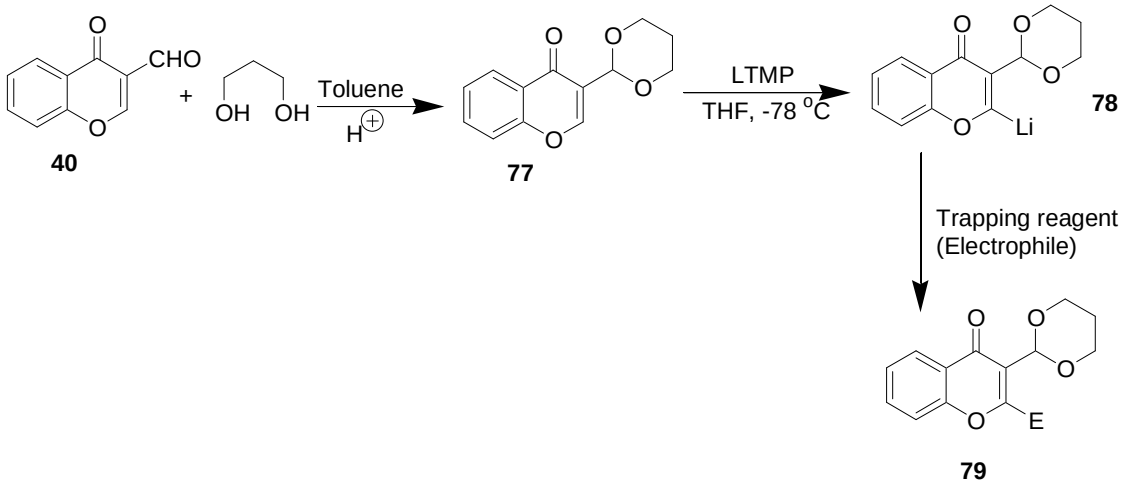
Scheme 19



Scheme 20



Scheme 21



Scheme 22

1.1.3 INDOLIZINES

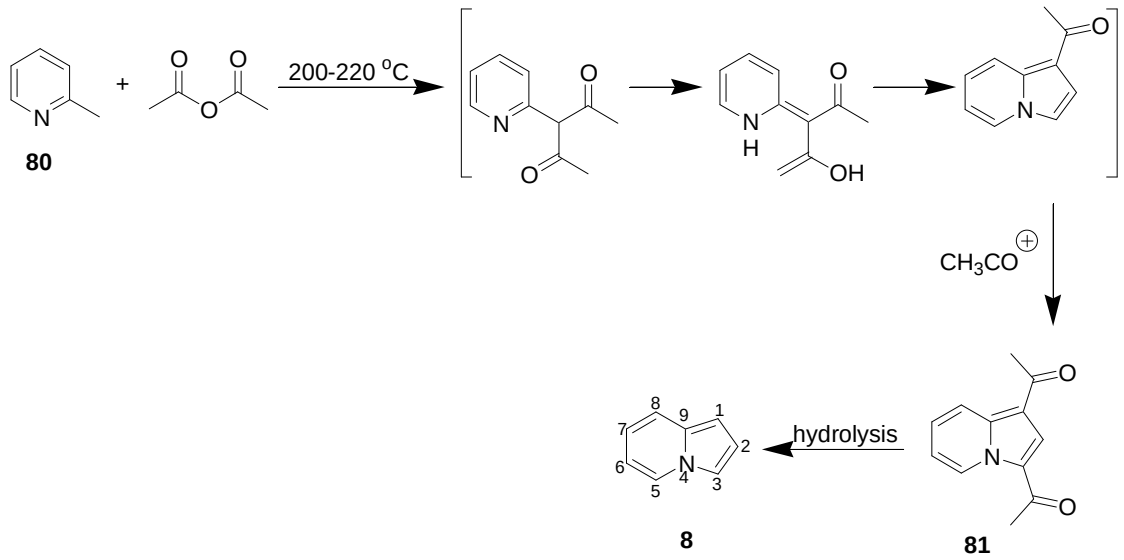
1.1.3.1 Historical Background

The history of indolizines dates back to 1890, when they were discovered by Angeli.[67] However, they were only first prepared in 1912 by Scholtz[68] from picoline and acetic anhydride. Indolizines have also been termed pyrrodine, pyrindole, 8-pyrrolopyridine, pyrrolo[1,2-*a*]pyridine or pyrrocoline. The generally accepted numbering system for indolizines **8** is shown below. Indolizines are weak bases which form salts with strong acids. They generated considerable interest after it was shown that they can be converted into cyclo[3.2.2]azines.[69-72] There have been three general approaches to the synthesis of indolizines, involving the formation of the five-membered ring moiety by intra- or intermolecular condensation, 1,3-dipolar cycloaddition or 1,5-dipolar cyclization.

1.1.3.2 Synthesis of Indolizines

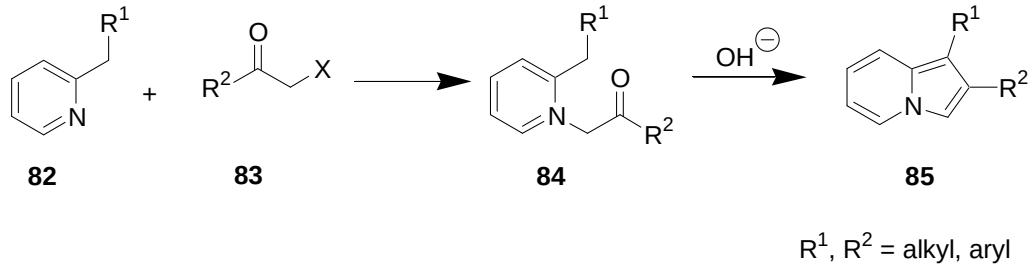
1.1.3.2.1 Synthesis of Indolizines via Condensation Reactions

Scholtz[68] reported that the reaction of 2-methylpyridine **80** and acetic anhydride at 200-220 ^{o}C yielded a "picolide", which on hydrolysis afforded indolizine **8**. The "picolide" was later shown to be 1,3-diacetylindolizine **81**. The pathway for the Scholtz reaction proposed by Tschitschibabin *et al*.[73] is outlined in Scheme 23.[73]



Scheme 23

The Scholtz reaction was used by Boekelheide *et al.*[74] to prepare 1-acetyl-5-methylindolizine, and was accepted as one of the general methods for preparing acylindolizines. Tschitschibabin[75] discovered an alternative method in 1927, which was considered of practical value for the preparation of 2-alkyl- or 2-arylindolizines **85**. This method involves ring-closure of quaternary pyridinium halides **84** and related compounds (Scheme 24). The limitation of the Tschitschibabin reaction is its failure to provide access to indolizines without substituents on the five-membered ring; however, modified Tschitschibabin reactions were reported later.[76]



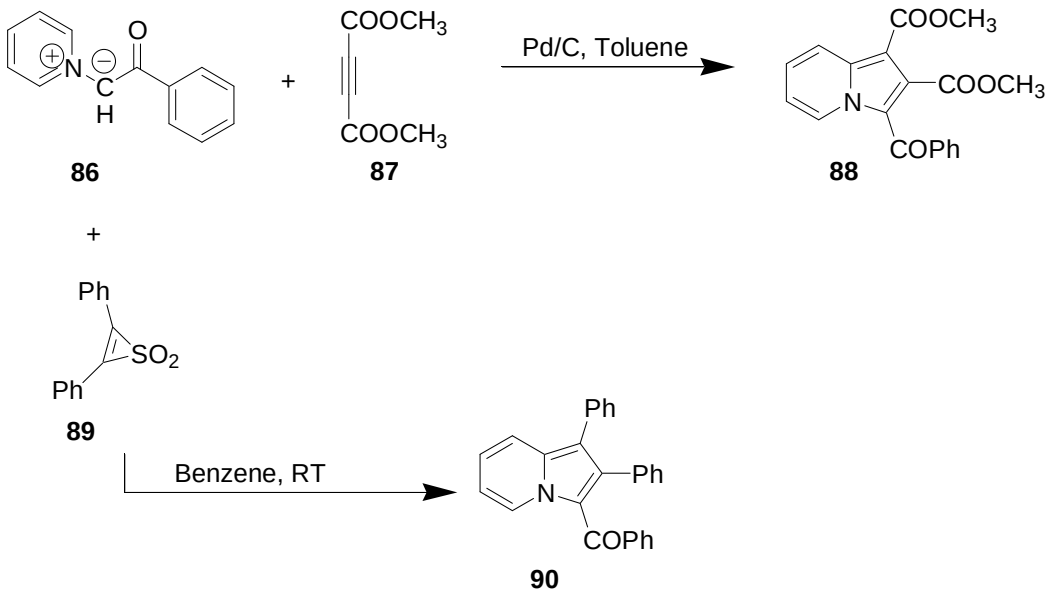
Scheme 24

A further method involves the cyclization of 3-(2-pyridyl)-1-propanols and their derivatives.[74] Amino groups were also found to be effective leaving groups when

displaced by nucleophilic attack of the heterocyclic nitrogen atom.[77-79] Indolizines can also be obtained from the reactions of heteroaromatic nitrogen compounds with acetylenic and olefinic compounds.[80-84]

1.1.3.2.2 Synthesis of Indolizines via 1,3-Dipolar Cycloaddition Reactions

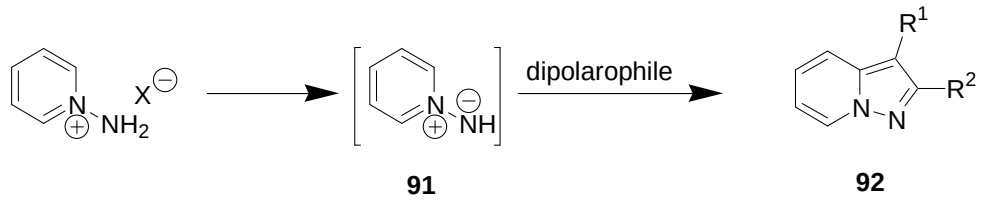
1,3-Dipolar cycloadditions are well documented as one of the most powerful methods for the synthesis of five-membered ring compounds.[85] This method has been applied in the synthesis of indolizines **88** by treating 1-phenacylpyridinium methylide **86** with dimethyl acetylenedicarboxylate **87** under dehydrogenating conditions (Scheme 25).[86] A major advantage of the 1,3-dipolar cycloaddition approach is the simple procedure which only requires two steps. However, substituents at positions 1, 2 and 3 are generally restricted to relatively small electron-withdrawing groups.[87]



Scheme 25

Diphenylthiirene *S,S*-dioxide **89** has been reported to behave like acetylenic compounds towards the pyridinium methylide **86**, affording the indolizine **90**.[88] 3-Azaindolizines **92** are obtained from the reaction of the *N*-iminopyridinium ylide **91** with acetylenic and

olefinic compounds, in a 1,3-dipolar cycloaddition reaction (Scheme 26). Indolizine derivatives can also be obtained by 1,3-dipolar cycloaddition reactions of 1,2-condensed aziridines, munchenones, munchenone imines and diazocyclopentadienes.[89]

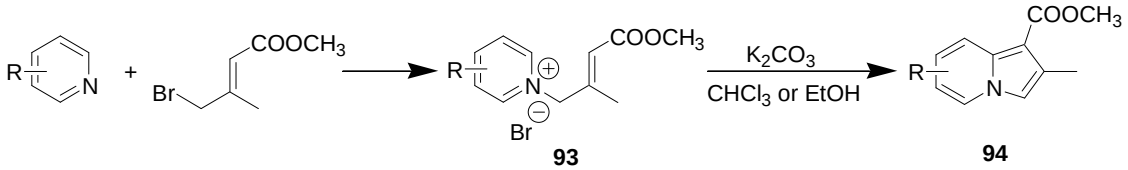


91 **92**

Scheme 26

1.1.3.2.3 Synthesis of Indolizines via 1,5-Dipolar Cyclizations

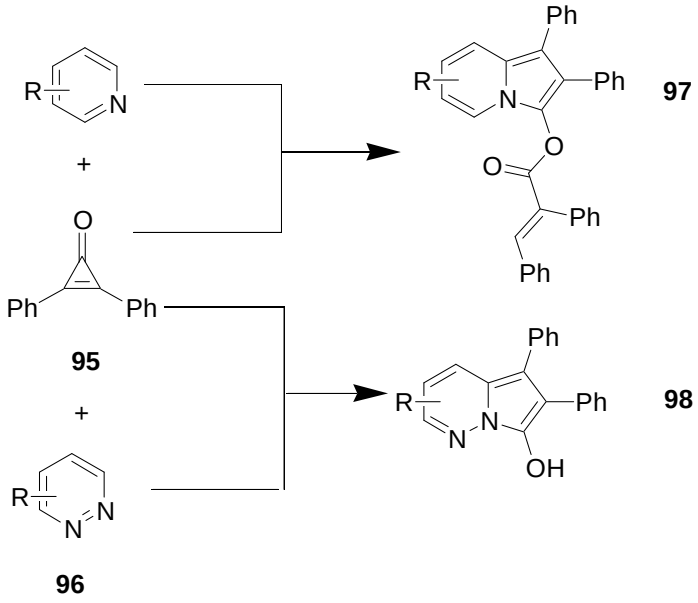
The synthesis of indolizines by 1,5-dipolar cyclization was first achieved in 1962,[90] in the preparation of an azaindolizine derivative, by reacting phenacylisoquinolinium bromide with hydroxylamine hydrochloride. Treatment of *N*-picrylmethylcycloimmonium ylide with a base affords benzoindolizine *via* elimination of nitrous acid, but this method is limited to the production of the benzo[*a*]- and naphtha[2,3-*b*]indolizine systems.[91] More intramolecular 1,5-dipolar cyclizations were described by Adamson *et al.*[92] and by Pratt *et al.*[93] They reported that treatment of *N*-allylpyridinium bromides **93** with potassium carbonate in ethanol or chloroform affords the indolizines **94** quite smoothly (Scheme 27).[94,95]



93 **94**

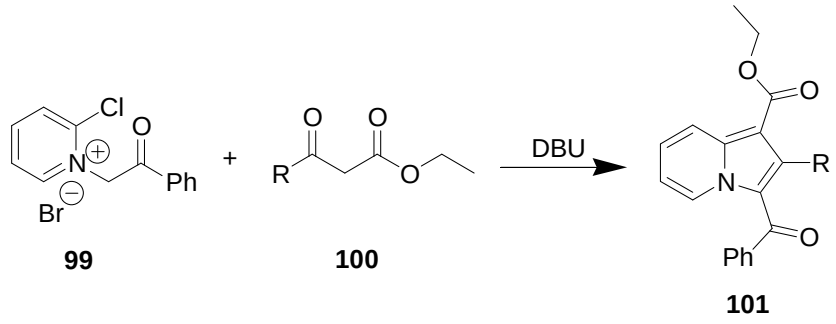
Scheme 27

Cyclopropenones **95** have been found to be useful in the synthesis of five- and six-membered heterocyclic compounds and, when treated with pyridines or diazabenzenes **96**, they yield indolizines **97** or azaindolizines **98**, respectively (Scheme 28).[94-100]



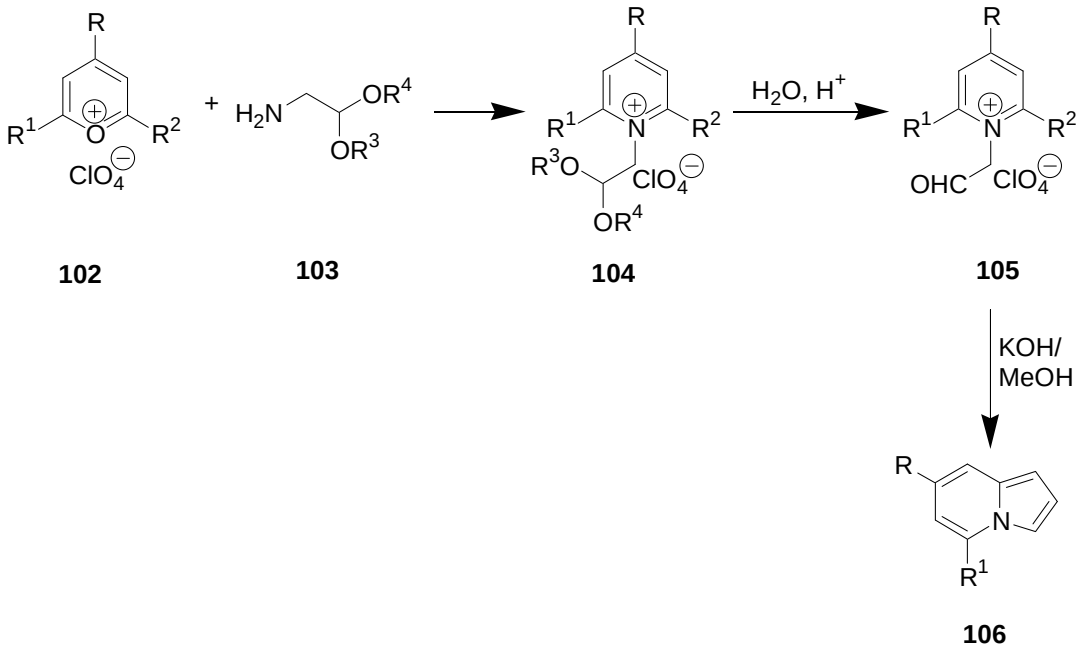
Scheme 28

1,2-Disubstituted indolizines **101** may be obtained from the reaction of 2-acetyl- or 2-benzoylpyridinium bromides with hydrazine hydrate.[101] The product yields are usually greater that in the Tschitschibabin reaction, with the reaction proceeding *via* a 1,5-diradical intermediate, which subsequently cyclizes to afford the indolizines.[85,101] Nugent *et al.*[102] have also reported the synthesis of 1,2,3-trisubstituted indolizines. Their procedure involves the 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU)-catalyzed reaction of halopyridinium salts **99** (obtained from the 2-halopyridine and an α-haloketone or ester) with ethyl acetoacetate **100** in acetonitrile (Scheme 29).[102]



Scheme 29

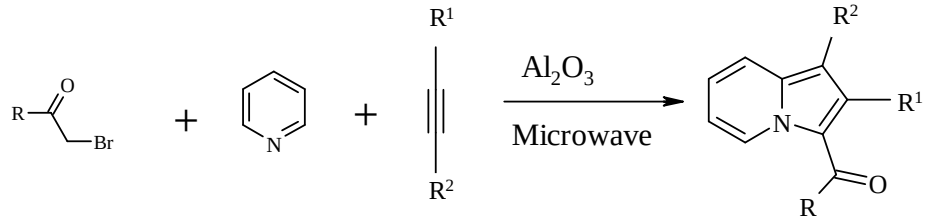
When pyrylium salts **102** are treated with aminoacetaldehyde dialkylacetals **103**, they produce pyridinium acetals **104**, which can be converted to pyridinium aldehydes **105** *via* acid hydrolysis.[103] Treatment of pyridinium aldehydes bearing alkyl groups at positions 2 and 6 with alkali hydroxides, readily affords the indolizines **106** (Scheme 30).[103]



102 **103** **104** **105** **106**

Scheme 30

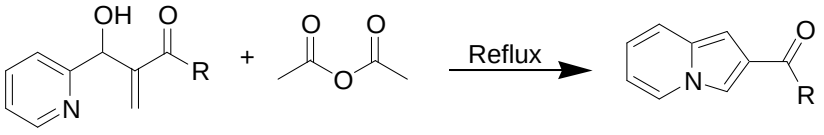
A combinatorial synthesis of indolizines on a solid support has been reported by Goff.[104] This approach involves a formal [3+2] cycloaddition of pyridinium ylides with electron-deficient alkenes.[104] A microwave-mediated, one-pot synthesis of indolizines **109** *via* a three-component reaction has been reported by Bora *et al.*[105] and involves reaction of a mixture of phenacyl bromide **107**, pyridine, substituted alkynes **108** and basic alumina (Scheme 31).[105]



107 **108** **109**

Scheme 31

Another route to indolizine synthesis has been reported by Bode *et al.*[106,107] This involves the treatment of selected Baylis-Hillman adducts **110** with acetic anhydride under reflux conditions (Scheme 32).[106,107] This is an interesting contribution to indolizine synthesis since it shows the versatility of the Baylis-Hillman adducts, as will be explained later. In addition it was the first application of the Baylis-Hillman reaction not only for the synthesis of indolizines but also other heterocyclic systems.



110 **111**

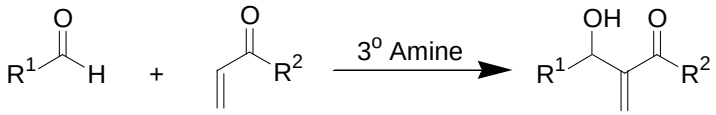
Scheme 32

1.1.3.3 Biological Activity of Indolizines

Many biologically active compounds possess an indole nucleus in their structure. The similarity between the indole and indolizine nuclei prompted speculation that indolizine analogues of certain biologically active indoles could have similar or even better biological activity.[108] A range of indolizine derivatives were therefore synthesized and structure-activity relationship studies carried out to understand which groups enhance biological activity. Harrel *et al.*[108-110] reported Mannich bases derived from indolizines as central nervous system depressants. Indolizine derivatives possessing activities against 5-hydroxytryptamine, histamine and acetylcholine were reported by Antonini *et al*.,[111] and by Cingolani *et al.*[112,113] Gubin *et al.*[114] have reported 1-sulfonylindolizine derivatives as potent calcium channel blockers, with comparable activity to that of other known calcium antagonists, *viz.*, verapamil and *cis*-(+)-diltiazen.[114] Recently, Gundersen *et al*.[115] have reported some indolizine derivatives with antibacterial activity against *Mycobacterium tuberculosis*.[115]

1.2 THE BAYLIS-HILLMAN REACTION

The Baylis-Hillman reaction (or Morita-Baylis-Hillman reaction, as it is sometimes called) dates back to 1968, when Morita *et al*.[116] described the reaction of various aldehydes with acrylic compounds catalyzed by tricyclohexylphosphine.[116] It was then later reported by Baylis and Hillman in 1972 in the patent literature,[117] who used tertiary amine catalysts to effect carbon-carbon bond forming reactions. The reaction typically involves the coupling of α,β-unsaturated carbonyl systems **113** with aldehydes **112** in the presence of a tertiary amine catalyst to afford adducts **114** containing a chiral centre (Scheme 33). Baylis and Hillman used cyclic tertiary amines such as 1,4-diazabicyclo[2.2.2.]octane (DABCO) and quinuclidine as catalysts in their original work.



112 **113** **114**

Scheme 33

Baylis-Hillman adducts are versatile intermediates which allow further functional group manipulation. A major drawback of the Baylis-Hillman (B-H) reaction, however, is its generally slow rate, with reactions taking days, or even weeks to afford the desired Baylis-Hillman adducts. Due to this drawback, numerous attempts, both chemical and physical, have been made to enhance the rate of the reaction.[118] Some of these methods have resulted in remarkable reaction rate increases, and in some cases, permitted previously unreactive species to react. Chemical methods are often more attractive than physical methods because they do not require any specialized equipment.[118] The chemical methods employed involve variation of the catalyst and variation of the solvent, including use of water (a green solvent).[118,119] The physical methods employed involve elevated temperatures, elevated pressures, microwave and ultrasound radiation.[120-122] The aim is to establish reaction conditions that are applicable to a wide range of substrates.

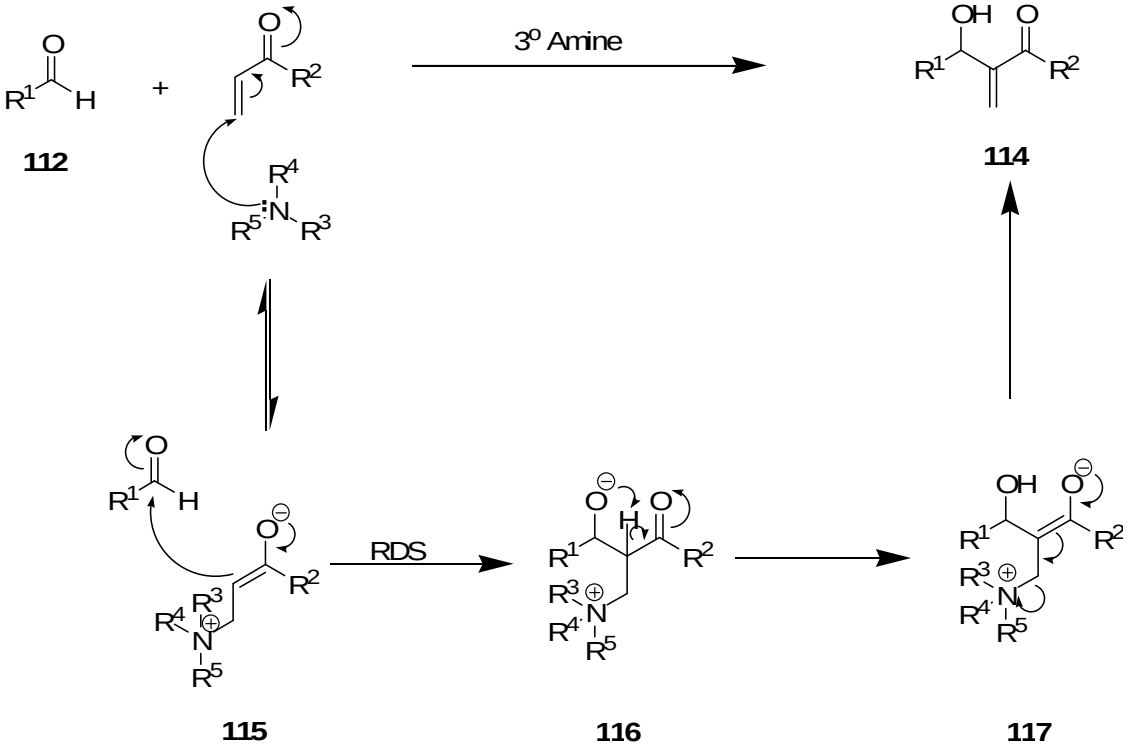
In the Baylis-Hillman reaction, addition of a zwitterionic enolate **115** to the aldehyde is believed to be the rate-determining step (Scheme 34). Hence, increasing the amount of the enolate or activation of the aldehyde is expected to result in increased reaction rates. It is believed that, since the Baylis-Hillman reaction involves charged transition states and intermediates, it should be accelerated by the use of polar solvents, *via* intermolecular charge-dipole interactions.[123] Among the reported methods for rate enhancement, the use of water as a solvent or co-solvent is well documented.[119,123-125] Yu *et al.*[123] have reported the use of water and dioxane as co-solvents in the Baylis-Hillman reaction of both aliphatic and aromatic aldehydes with activated alkenes. They observed improved reaction rates and product yields, suggesting that water stabilizes the transition states or intermediates.[123] Aggarwal *et al.*[124] investigated the actual role played by water in the rate acceleration of the Baylis-Hillman reaction. This was done by employing "salting-in" (CsI) and "salting out" (LiCl) agents, which would show whether rate acceleration in water was caused by hydrophobic effects. Their results showed that such effects played no role in enhancing the reaction rate, as both "salting-in" and "salting-out" agents caused an increase in reaction rate. Hence they concluded that the dominant factor was hydrogen-bonding.[124] As alluded to earlier, the best conditions are those that can be applied over a wide range of substrates. Sulpholane was found to provide improved reaction rates and product yields for a wide range of aldehydes and Michael acceptors.[126]

DABCO was initially known as the traditional catalyst for the Baylis-Hillman reaction. However, other catalysts were discovered, among them 3-hydroxyquinuclidine, which was reported to enhance the rate significantly,[127] and DBU which has been reported to increase the reaction rate by up to 50-fold.[118] DBU has a relatively high pKa and is also sterically hindered. Generally, steric hindrance results in low reaction rates or no reaction at all. However, in the case of DBU, it seems that amine basicity is more important than steric hindrance. In order to investigate the correlation between reaction rate and pKa, a range of quinuclidine-based catalysts were investigated by Aggarwal *et al.*[128] From their analysis, they concluded that there is a broad correlation between the reaction rate and the pKa of the quinuclidine-based catalyst. The fastest rate was observed with the

quinuclidine catalyst with the highest pKa, and the lowest rate with the quinuclidine catalyst with the lowest pKa.[128] Co-catalysts have also been explored, with the aim of enhancing the reaction rate. Maher *et al.*,[129] for example, have reported the use of the hydrogen-bonding bis-aryl ureas as good co-catalysts in a DABCO-catalyzed Baylis-Hillman reaction.[129]

1.2.1 The Baylis-Hillman Mechanism

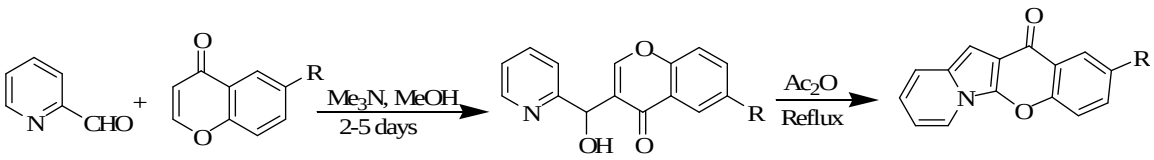
The generally accepted mechanism of the Baylis-Hillman reaction is illustrated in Scheme 34. The reaction appears to be initiated by the conjugate addition of the tertiary amine catalyst to the activated alkene **113** to afford the zwitterionic enolate **115**, which then attacks the carbonyl carbon of the aldehyde **112** in an aldol-type reaction to afford another zwitterion **116**, in what is generally believed to be the rate-determining step (RDS). The final product **114** is obtained by rapid proton transfer and subsequent elimination of the catalyst.[130]



Scheme 34

1.2.2 The Baylis-Hillman Reaction in the Synthesis of Heterocyclic Systems

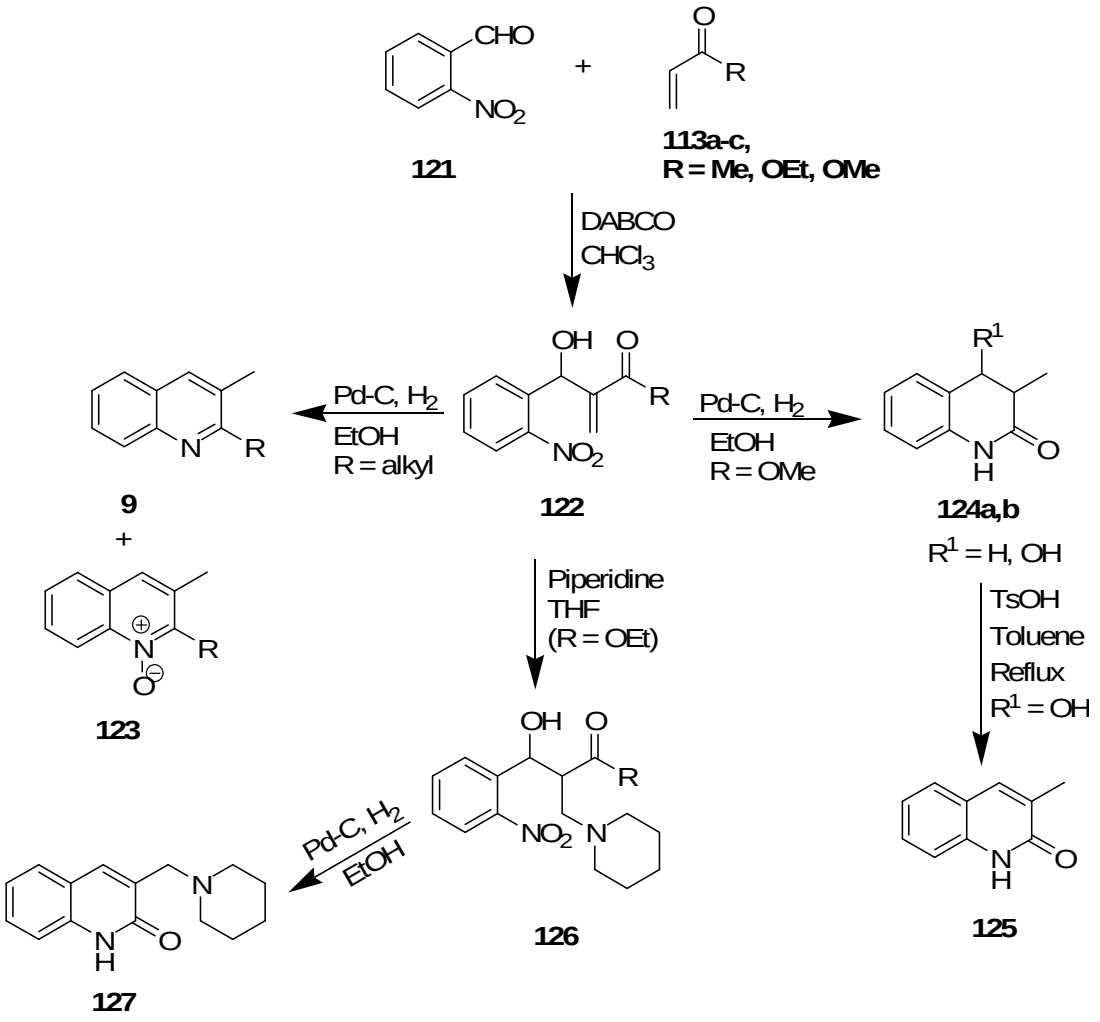
Baylis-Hillman adducts have been shown to be useful and versatile synthons for the construction of heterocyclic systems. The preparation of indolizines from Baylis-Hillman adducts has already been mentioned (Scheme 32).[106,107] Following this report, Basavaiah *et al*.[131] reported the synthesis of indolizines *via* the same method, but using cyclic enones *i.e*., chromones as Michael acceptors to obtain the polycyclic systems **120** (Scheme 35).[131]



118 **11** **119** **120**

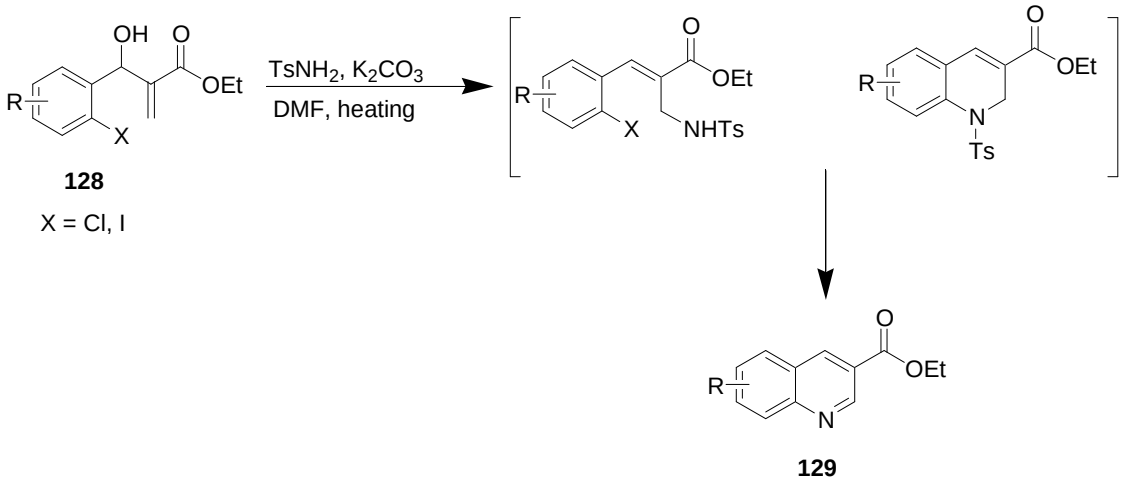
Scheme 35

The first application of Baylis-Hillman methodology to the synthesis of quinolines **9** was reported by our group in 1998.[132] This involved the treatment of 2-nitrobenzaldehyde **121** with methyl vinyl ketone **113a**, methyl acrylate **113b** or ethyl acrylate **113c** in the presence of DABCO at, or below, room temperature to give the corresponding Baylis-Hillman adducts **122** in moderate to good yields. Catalytic hydrogenation of the Baylis-Hillman adducts afforded quinolines **9** and quinoline *N*-oxides **123**, 3-methyl-2-oxo-1,2,3,4-tetrahydroquinoline **124a** and 4-hydroxy-3-methyl-2-oxo-1,2,3,4-tetrahydroquinoline **124b**. The dehydration of the 4-hydroxy analogue **124b** afforded 3-methyl-2-quinolinone **125**. Treatment of the ethyl ester **122** with piperidine led to the conjugate addition product **126**, subsequent catalytic hydrogenation of which gave the 2-quinolinone **127** (Scheme 36). [132]



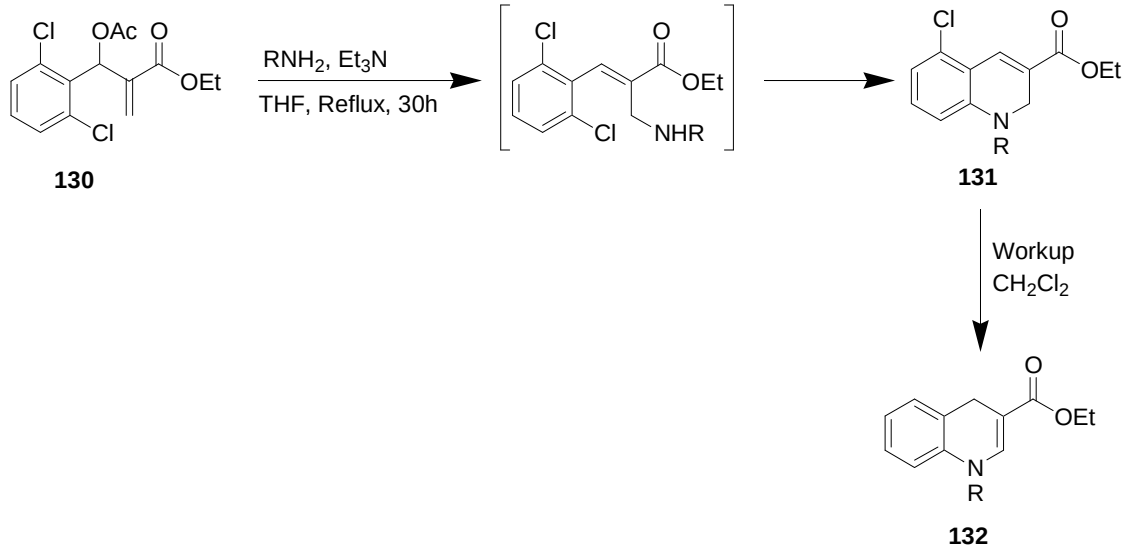
Scheme 36

Numerous attempts to use the Baylis-Hillman reaction in the preparation of quinoline derivatives **9** have since followed. These include the transformation of Baylis-Hillman adducts derived from *o*-halobenzaldehyde *N*-tosylimines **128** into the corresponding quinolines **129**. This is achieved by the treatment of Baylis-Hillman adducts **128** with tosylamide and potassium carbonate in DMF to afford the desired quinoline **129** (Scheme 37).[133,134]



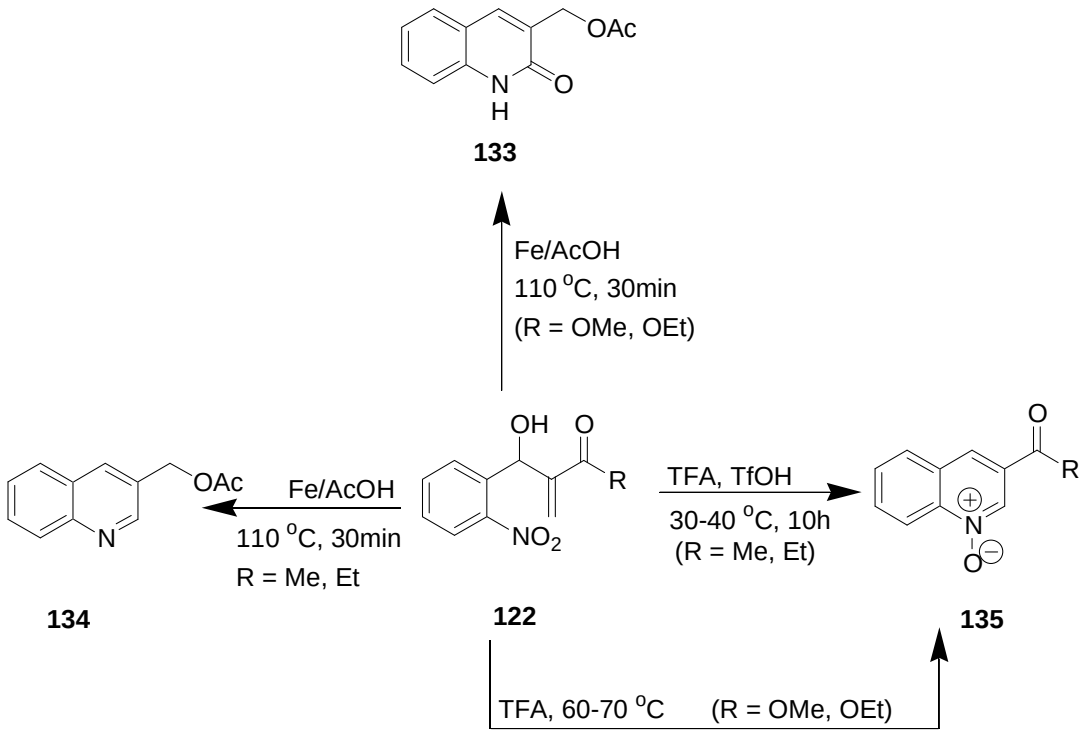
Scheme 37

Kim *et al.*[135] have also reported the synthesis of *N*-substituted 1,4-dihydroquinoline derivatives **132** from Baylis-Hillman acetates **130**. This is achieved by treating Baylis-Hillman acetates **130** with benzylamine or cyclohexylamine affording 1,2-dihydroquinoline derivatives **131**, which are subsequently isomerized into 1,4-dihydroquinoline derivatives **132** (Scheme 38).[135]



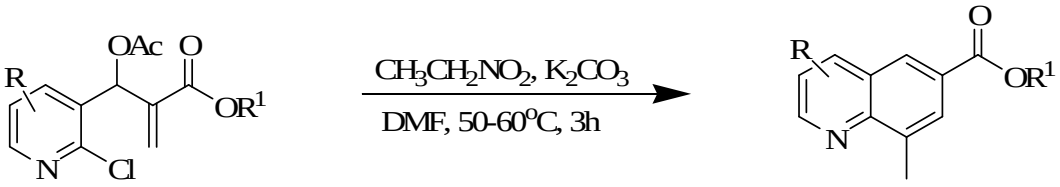
Scheme 38

Basavaiah *et al.*[136] reported the conversion of Baylis-Hillman adducts **122** derived from 2-nitrobenzaldehyde **121** and alkyl acrylates **113** and alkyl vinyl ketones **113** to quinol-2-ones **133** and quinolines **134**, respectively. This was achieved by treating the respective Baylis-Hillman adducts with acetic acid and iron powder at 110 ^{o}C for 30 minutes (Scheme 39).[136] Lee *et al.*[137] reported the synthesis of 3-substituted-4-hydroxyquinoline *N*-oxides **135** from Baylis-Hillman adducts **122** derived from 2-nitrobenzaldehyde by treating the Baylis-Hillman adducts **122** with trifluoroacetic acid (TFA) and triflic acid at 30-40 ^{o}C for 10 hours (Scheme 39).[137] A similar reaction was described by Amarante *et al.*,[138] however, using only trifluoroacetic acid (TFA) at 60-70 ^{o}C.



Scheme 39

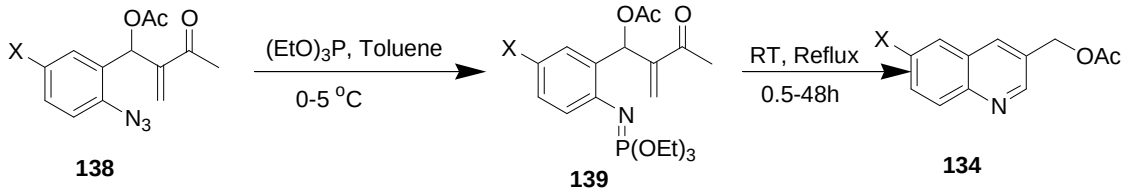
The treatment of Baylis-Hillman acetates **136**, derived from 2-chloronicotinaldehydes, with nitroethane and potassium carbonate in DMF at 50-60 ^{o}C for 3-4 hours affords the quinolines **137** in good to excellent yields (Scheme 40).[139]



136 **137**

Scheme 40

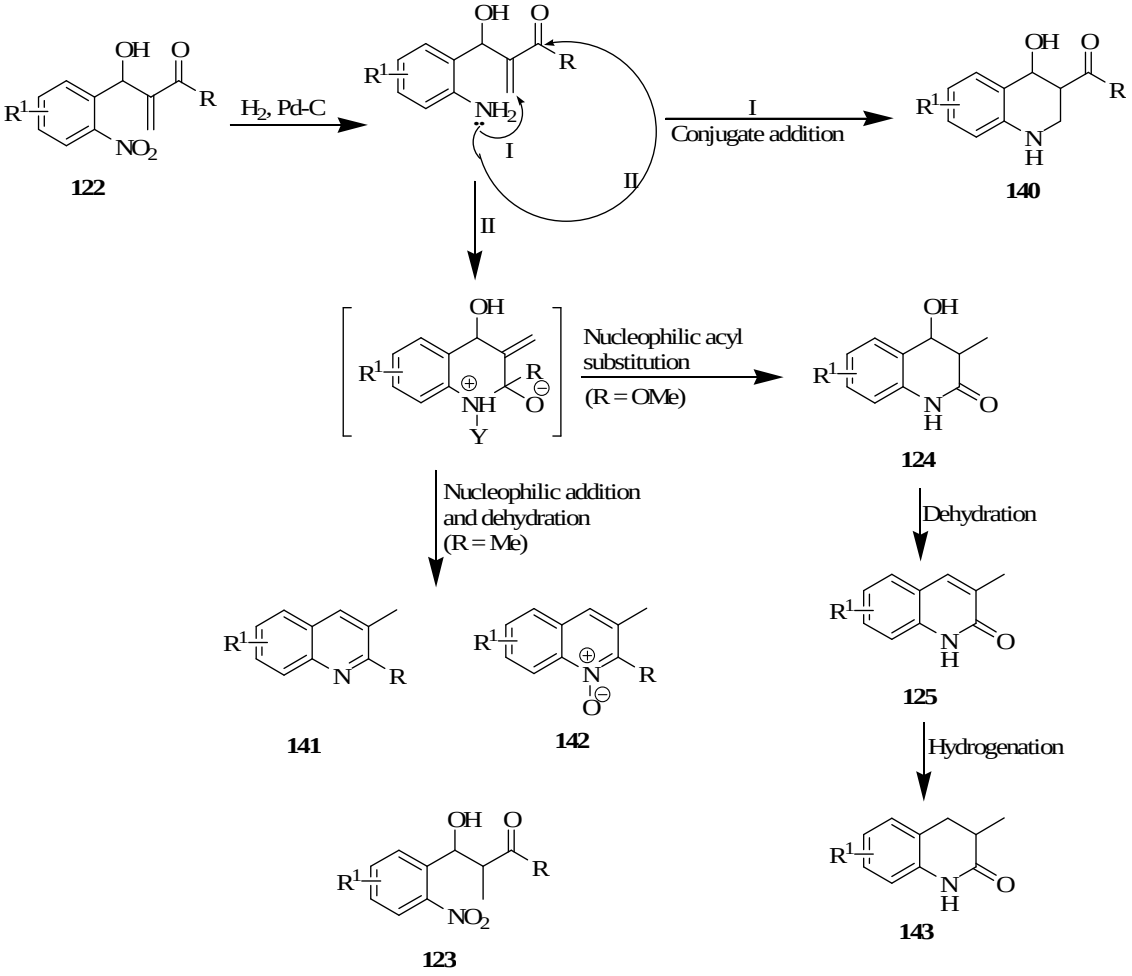
The synthesis of 3-acetoxymethylquinolines **134** from Baylis-Hillman adducts **138**, formed by the reaction of 2-azidobenzaldehyde and methyl vinyl ketone, has been described by Yi *et al.*[140] This involves the treatment of the Baylis-Hillman acetates **138** with $(EtO)_3P$ in toluene, initially at 0-5 ^oC for 30 minutes, and then at reflux for up to 48 hours (Scheme 41).[140]



138 **139** **134**

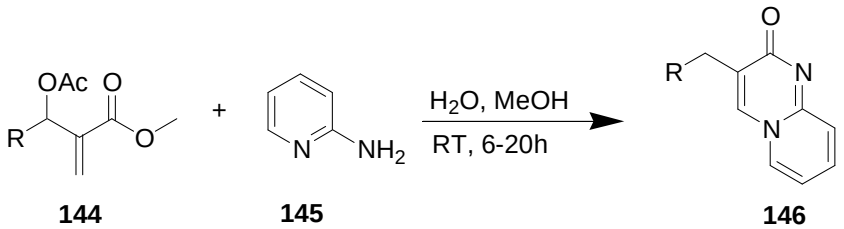
Scheme 41

Further research in our group,[141] on the synthesis of quinoline derivatives from Baylis-Hillman adducts has been reported. Variation of the reducing systems and the activated alkenes was found to afford various quinoline derivatives depending on the cyclization path (Scheme 42).



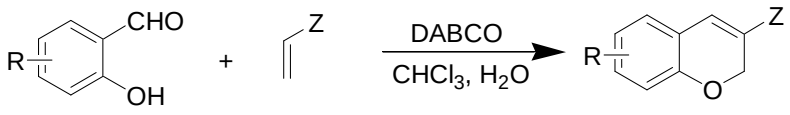
Scheme 42

Basavaiah *et al.*[142] further demonstrated the versatility of the Baylis-Hillman reaction by converting Baylis-Hillman acetates **144** into the substituted fused pyrimidine derivatives **146** in a one-pot reaction. This was achieved by treating the Baylis-Hillman acetates **144** with 2-aminopyridine **145** under mild and "green" conditions (Scheme 43).[142]



Scheme 43

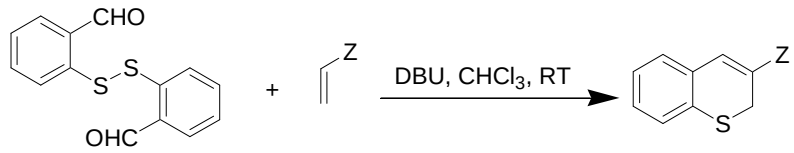
Baylis-Hillman methodology is also applicable in the synthesis of 3-substituted 2*H*-chromenes **148**. This has been achieved, in our group, by the DABCO-catalyzed reaction of salicylaldehydes **147** with various Michael acceptors in a heterogeneous mixture of chloroform and water (Scheme 44).[143,144]



147 **148** Z = COR^1, R^1 = Me, Et, Ph, H
Z = SO_2Ph, SO_3Ph, CN

Scheme 44

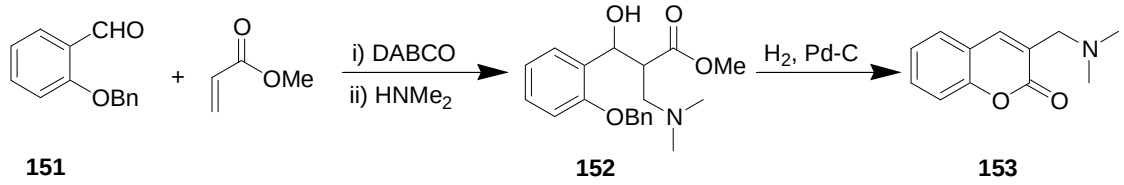
3-Substituted thiochromenes (2*H*-1-benzothiopyrans) **150** can also be conveniently accessed in one step *via* the Baylis-Hillman reaction, as was first demonstrated in our group in 2001.[145] This was achieved by the DBU-catalyzed reaction of 2,2'-dithiodibenzaldehyde **149** with various Michael acceptors in chloroform (Scheme 45).[145]



149 **150** Z = COR, CO_2R, CN, SO_2Ph, SO_3Ph
R = Me, Et

Scheme 45

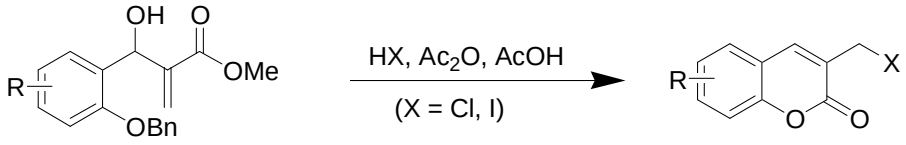
Coumarins **153**, another class of heterocyclic compounds found in plants, can also be synthesized using the Baylis-Hillman reaction. Drewes *et al.*[146] reported the three-step synthesis of substituted coumarins illustrated in Scheme 46. Treatment of the adducts **152** derived from *o*-benzylated salicylaldehyde **151** with dimethylamine affords the conjugate-addition product **152**, which cyclizes to give the coumarin derivative **153** on catalytic hydrogenation (Scheme 46).[146]



151 **152** **153**

Scheme 46

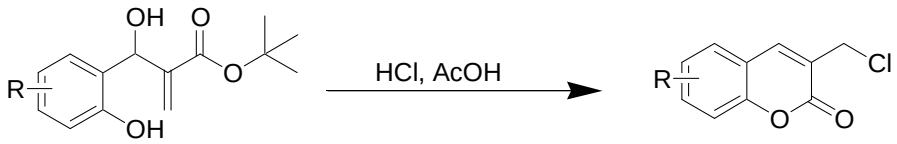
In our group,[147] more convenient methods for synthesizing coumarins **155** were later reported. The first report described the reaction of *o*-benzylated Baylis-Hillman adducts **154** with halogen acid (HI or HCl) in acetic acid and acetic anhydride, the deprotection and cyclisation steps occurring *in situ* (Scheme 47).[147]



154 **155**

Scheme 47

In a further improvement, it was found that treatment of Baylis-Hillman adducts **156**, derived from salicylaldehydes and tert-butyl acrylate, with HCl in acetic acid under refluxing conditions afforded the coumarin derivatives **155**. It should be noted that, in this method, the hydroxyl group of the salicylaldehyde need not be protected (Scheme 48).[148]

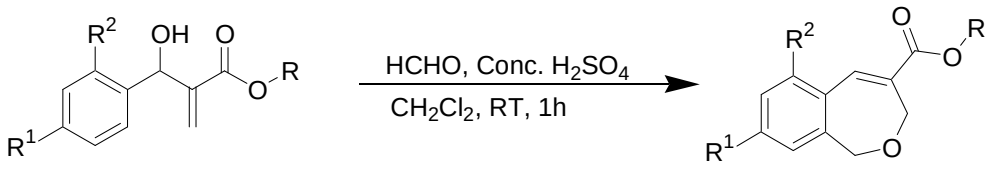


156 **155**

Scheme 48

Benzoxepines **158** exhibit interesting medicinal properties, and simple methods for the synthesis of these compounds are desirable. Basavaiah *et al.*[149] have reported a simple

one-pot synthesis of benzoxepine derivatives **158**, involving the formation of C-O and C-C bonds through Prins-type and Friedel-Crafts reactions of the Baylis-Hillman adducts **157** (Scheme 49).[149]



157 **158**

Scheme 49

1.3 PREVIOUS WORK DONE IN THE GROUP

In addition to developing the synthetic methodologies described in the preceding section, attention has also been given to physical organic studies of various heterocyclic systems. Infrared studies of substituted chromone-2-carboxylate esters revealed carbonyl band doubling, which was solvent-, substituent- and temperature-dependent and which was explained in terms of rotameric equilibria between *syn-s-trans* and *anti-s-trans* forms.[150] Substituted chromone-2-carboxamides have been prepared,[151] and dynamic NMR studies of these compounds revealed a temperature-dependant splitting of the *N*-alkyl ^{1}H- and ^{13}C-NMR signals, which was attributed to internal rotation of the amide group.[151]

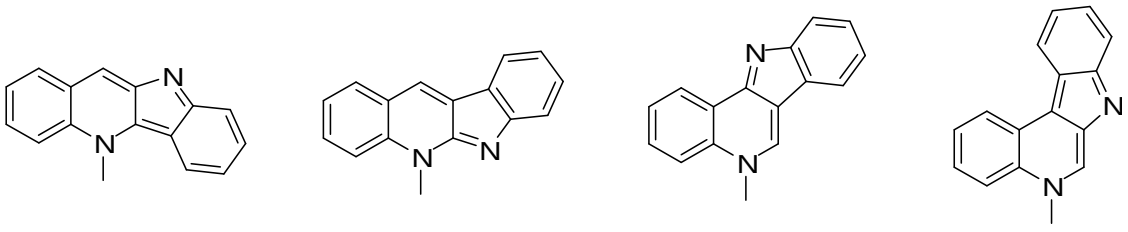
The susceptibility of chromone derivatives to ring-opening *via* nucleophilic attack at C-2 has been illustrated by the amine-mediated ring-opening of substituted chromone-2-carboxamides[48,152] and a kinetic-mechanistic study demonstrated the influence of substituents on the ring-opening process. Mass spectrometric analysis of the ring-opened, polyfunctional acrylamide derivatives permitted elucidation of their major fragmentation patterns,[153] while dynamic NMR analysis of rotational isomerism in these systems permitted the calculation of internal rotational barriers.[154] Dynamic ^{1}H NMR spectroscopy was used to explore the influence of substituents on the internal rotation of

the amino group in 2-(*N*,*N*-dialkylamino)chromones;[155] nitrogen lone-pair delocalization was presumed to inhibit rotation about the N-(CO) bond. The influence of various substituents on the electron density at C-2 and on the acidity of a series of 2-carboxychromones has also been investigated.[156-158] Chromone derivatives have been used in the construction of ritonavir analogues as potential HIV-1 protease inhibitors,[159] and chromone-3-carbaldehydes have been employed as Baylis-Hillman substrates, affording unprecedented dimeric substrates.[160]

The thermal cyclization of the Baylis-Hillman adducts to indolizines was presumed to follow an addition elimination sequence, a process which is clearly facilitated by the conversion of the hydroxyl function into a better leaving group, the acetate. In addition to this, the enhanced electrophilicity of the vinyl system faciltates intramolecular conjugate addition. Dynamic NMR analysis was used to characterize the indolizines.[107]

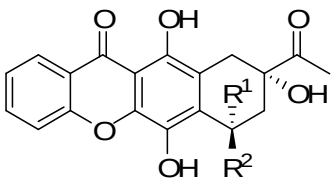
1.4 AIMS OF THE PRESENT STUDY

A number of polyheterocyclic compounds are biologically active. Some of the compounds are found in plants, while some are synthetic analogues. The roots of the plant, *Cryptolepis sanguinolenta* contain some polycyclic alkaloids with interesting antiplasmodial activity. These are the cryptolepine (5-methyl-5*H*-indolo[3,2-*b*]quinoline) **A**, neocryptolepine (5-methyl-5*H*-indolo[2,3-*b*]quinoline) **B** and isocryptolepine (5-methyl-5*H*-indolo[3,2-*c*]quinoline) **C**.[161,162] Their synthetic analogue, called isoneocryptolepine (5-methyl-5*H*-indolo[2,3-*c*]quinoline) **D**,[163-167] was found to be two times less active than **A** against the K1 strain of *Plasmodium falciparum* (chloroquine-resistant strain of the malaria parasite). However, it was found to be four times less cytotoxic, therefore having a much better selectivity index than **A**, making it a better lead compound for further validation of indoloquinolines as potential antiplasmodial drugs. The mechanism of action of **D** is similar to that of chloroquine, that is, the inhibition of the haeme detoxification process.[166,167]

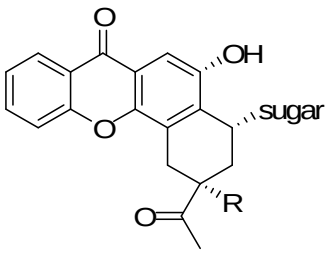


A **B** **C** **D**

Another class of compounds that are abundant in natural products are the xanthone derivatives,[168,169] and they possess interesting biological activities. These include inhibition of the monoamineoxygenase enzymes (MAO-A and MAO-B),[168,169] anti-inflammatory, anti-oxidant, anti-ulcer,[170,171] bronchodilatory in the treatment of asthma[172] and anti-tumor activities.[173,174] Polycyclic synthetic xanthone derivatives **E**, **F** and **G** below were reported to be cytotoxic *in vitro* against a human breast cancer MCF-7 cell line[175] and against leukaemia L1220 cells.[176,177]

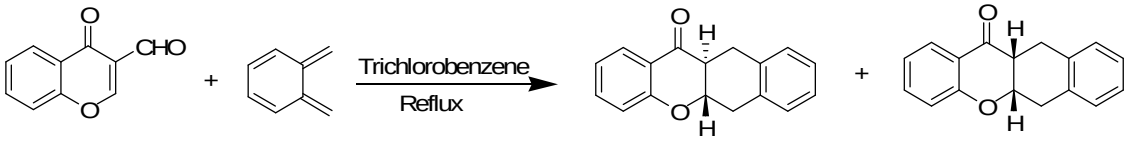


E_1; R^1 = OH, R^2 = H
E_2; R^1 = H, R^2 = OH
F; R^1 = sugar, R^2 = H



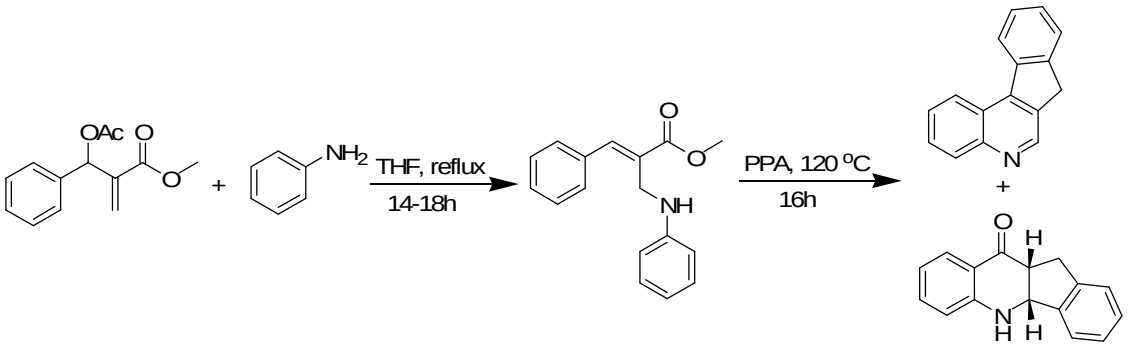
G_1; R = H
G_2; R = OH

Sandulache *et al.*[178] reported a method for the synthesis of benzo[*b*]xanthones from chromone-3-carbaldehydes as dienophiles and the highly reactive diene, *ortho*-benzoquinodimethane, *via* a Diels-Alder reaction (Scheme 50).



Scheme 50

Indenoquinoline derivatives are another class of polycyclic compounds possessing a wide range of biological activities. These include 5-HT-receptor binding,[179] anti-inflammatory,[180] anti-tumor,[181] of steroid reductase inhibitory, [182] acetylcholinesterase inhibitory[183] and antimalarial activities.[184] Lee *et al.*[185] have reported the synthesis of indenoquinoline derivatives from Baylis-Hillman acetates (Scheme 51), again showing the versatility of the Baylis-Hillman reaction in the synthesis of biologically active polycyclic compounds.



Scheme 51

The present study has focused on the application of Baylis-Hillman methodology in the construction of polyheterocyclic targets. Particular emphasis has been placed on exploring the effects of varying the catalytic systems and the use of microwave-assisted reactions. The research has included the following specific objectives:

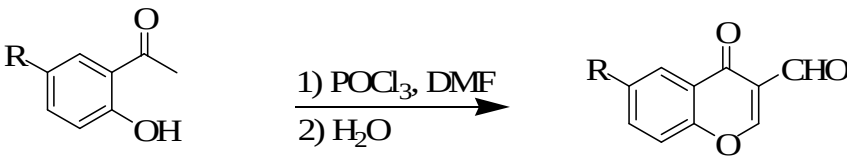
1. The synthesis of substituted chromone-2- and -3-carbaldehydes and their use as substrates in Baylis-Hillman reactions using methyl acrylate and methyl vinyl ketone as activated alkenes.
2. Baylis-Hillman reactions involving 2-nitrobenzaldehyes and cyclic enones, with a view to synthesizing polycyclic quinoline derivatives.
3. Baylis-Hillman reactions involving pyridine-2-carbaldehyde and quinoline-2-carbaldehyde with cyclic enones, and subsequent conversion of the products to polycyclic indolizine derivatives.
4. Absorption and fluorescence studies of selected polycyclic indolizine systems.
5. Computational studies to explore correlations between theoretical and experimental spectroscopic data.

2. DISCUSSION

The discussion covers:- the preparation of chromone-3- and chromone-2-carbaldehydes as Baylis-Hillman substrates (Sections 2.1 and 2.3, respectively); reactions involving chromone-3-carbaldehydes (Section 2.2); reactions involving chromone-2-carbaldehydes (Section 2.4); Baylis-Hillman reactions involving cyclic enones (Section 2.5); synthesis of quinoline derivatives (Section 2.5.2); synthesis of polycyclic indolizine derivatives (Section 2.5.3) and spectroscopic studies of selected polycyclic indolizine derivatives (Sections 2.6, 2.7 and 2.8).

2.1 Preparation of Chromone-3-carbaldehydes

The series of substituted chromone-3-carbaldehydes **40a-e** were prepared as Baylis-Hillman precursors using the Vielsmeier-Haack reaction. This was achieved by treating the corresponding *o*-hydroxyacetophenones **28a-e** with phosphorus oxychloride in dry DMF at -20 ^{o}C (Scheme 50).[186] The mechanism of the Vielsmeier-Haack reaction involves double bond formylation of the acetophenone enolate **160** by the Vielsmeier-Haack "complex" **159(i-iii)**, obtained from the *in situ* reaction of phosphorus oxychloride and DMF, with tautomers **159(ii)** and **159(iii)** being the predominant structures (Scheme 51).[187] This is followed by hydrolysis to afford the crude chromone-3-carbaldehydes **40a-e**, in a one-pot reaction. Recrystallisation of the crude products from acetone afforded the pure chromone-3-carbaldehydes **40a-e** in 30-72% yields (Table 1).

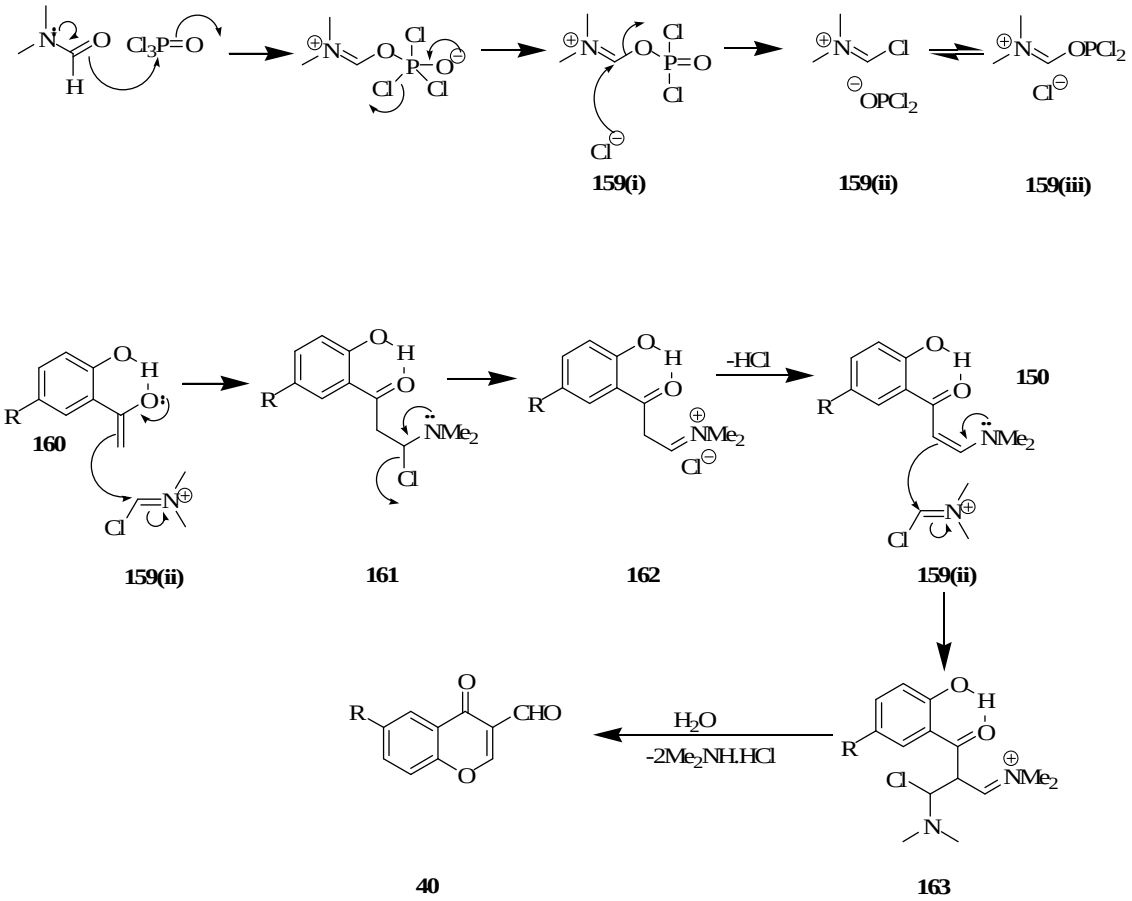


28a-e **40a-e**

Scheme 50

Table 1. Comparative yields of purified chromones-3-carbaldehydes **40a-e**.

Acetophenone	Product	R	Yield (%)
28a	**40a**	H	63
28b	**40b**	Br	72
28c	**40c**	Cl	70
28d	**40d**	F	30
28e	**40e**	OMe	35



Scheme 51

The products were fully characterized by spectroscopic (IR, MS, ^{1}H and ^{13}C NMR) analysis. Figures 1 and 2 show the ^{1}H and ^{13}C NMR spectra of chromone-3-carbaldehyde **40a**, respectively. The ^{1}H NMR spectrum (Figure 1) of the parent system, chromone-3-carbaldehyde **40a**, reveals an overlapping triplet and doublet at *ca* 7.5 ppm corresponding

to the 6- and 8-methine protons, a singlet at 8.52 ppm corresponding to the 2-methine proton and a singlet at 10.36 ppm corresponding to the formyl proton. The ^{13}C NMR spectrum (Figure 2) reveals 10 carbon signals, with the 2-methine carbon resonating at 160.5 ppm and the carbonyl carbon signals resonating at 176.0 and 188.5 ppm.

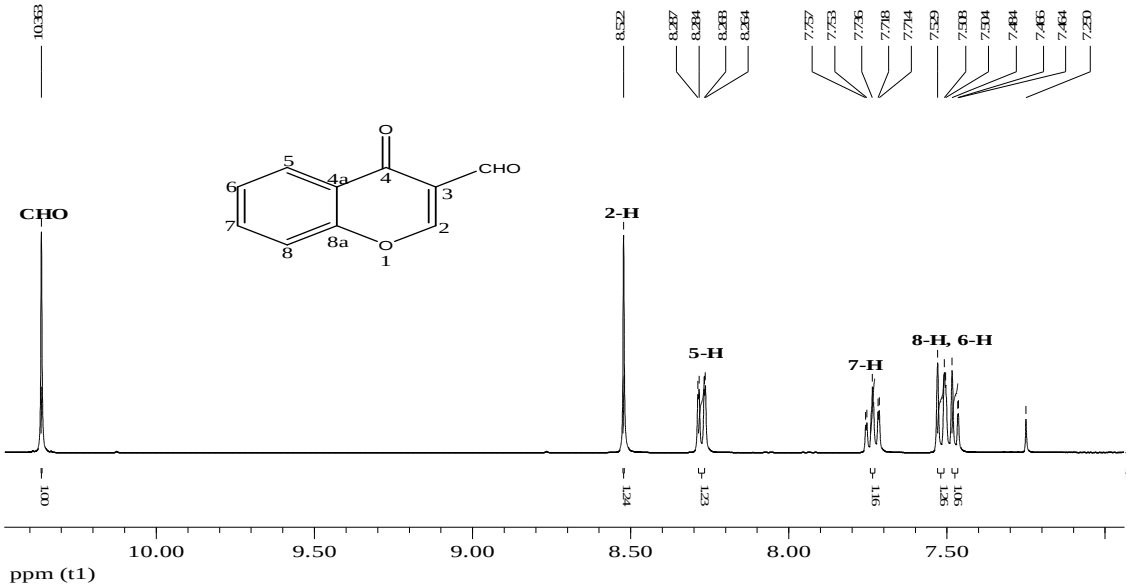


Figure 1. 400 MHz ^{1}H NMR spectrum of chromone-3-carbaldehyde **40a** in $CDCl_3$.

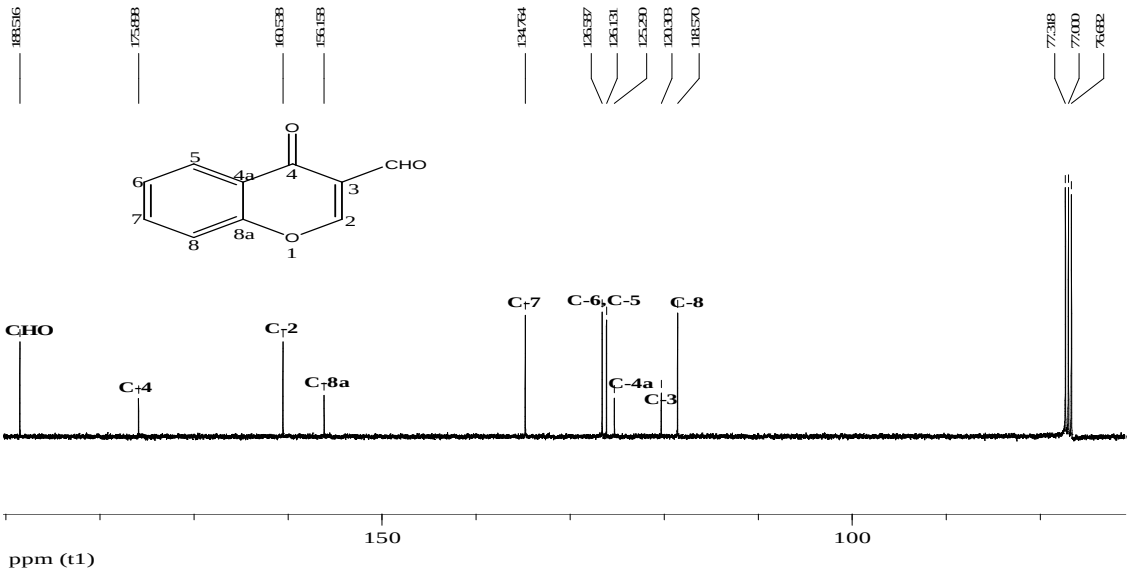


Figure 2. 100 MHz ^{13}C NMR spectrum of chromone-3-carbaldehyde **40a** in $CDCl_3$.

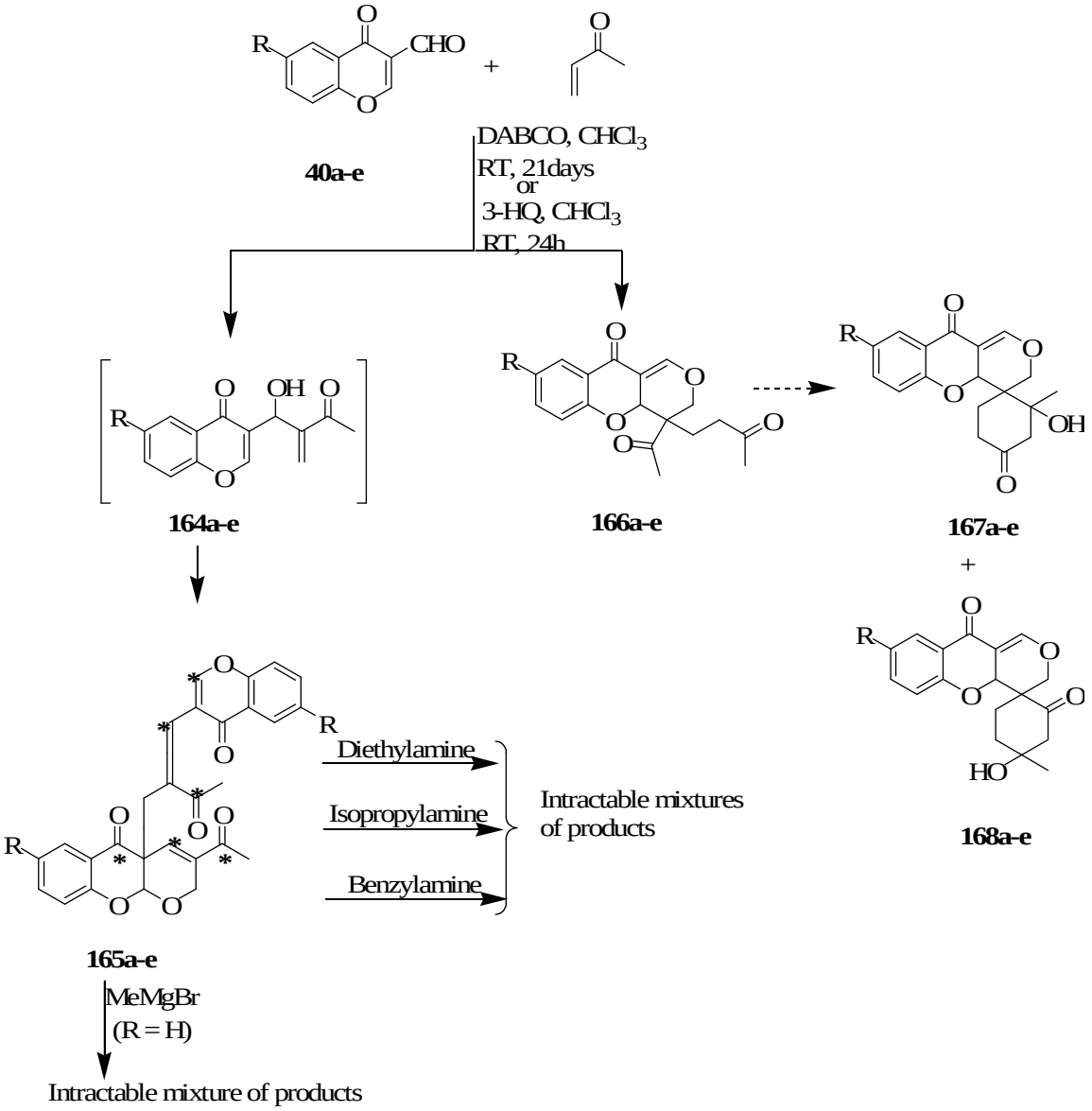
2.2 Baylis-Hillman reactions involving chromone-3-carbaldehydes

2.2.1 Reactions of chromone-3-carbaldehydes with methyl vinyl ketone

The series of chromone-3-carbaldehydes **40a-e** were reacted with methyl vinyl ketone using DABCO as catalyst in chloroform for 21 days (Scheme 52). Work-up and chromatography of the crude products afforded the chromone dimers **165a-e** (24 to 49%; Table 2). None of the Baylis-Hillman products **164a-e** were isolated from these reactions and it was assumed that they had been converted, in each case, to the corresponding chromone dimers **165a-e**. The reactions were repeated using 3-hydroxyquinuclidine as catalyst for 24 hours (Scheme 52). Work-up and chromatography of the crude products afforded the chromone dimers **165a-e** in significantly improved yields (34 to 72%; Table 2) and the tricyclic products **166a-d** (4 to 12%, Table 3), which were recently isolated by Molefe.[196] It was hoped that, in the present study, these products could be elaborated further, as indicated in Scheme 52, to afford the spiro derivatives **167** and **168**.

Table 2. Isolated yields of chromone dimers **165a-e** using DABCO and 3-HQ.

Aldehyde	Chromone dimer	R	Yield (%) Using DABCO	Yield (%) Using 3-HQ
40a	**165a**	H	49	72
40b	**165b**	Br	24	47
40c	**165c**	Cl	39	66
40d	**165d**	F	25	34
40e	**165e**	OMe	30	46

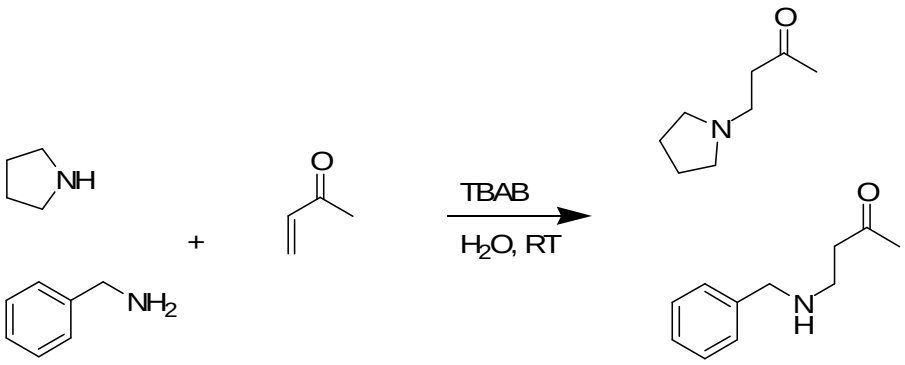

40a-e
DABCO, CHCl3
RT, 21days
or
3-HQ, CHCl3
RT, 24h
164a-e
166a-e
167a-e
168a-e
165a-e
Diethylamine
Isopropylamine
Benzylamine
Intractable mixtures of products
MeMgBr
(R = H)
Intractable mixture of products

Scheme 52

Table 3. Initial isolated yields of tricyclic adducts **166a-d**.

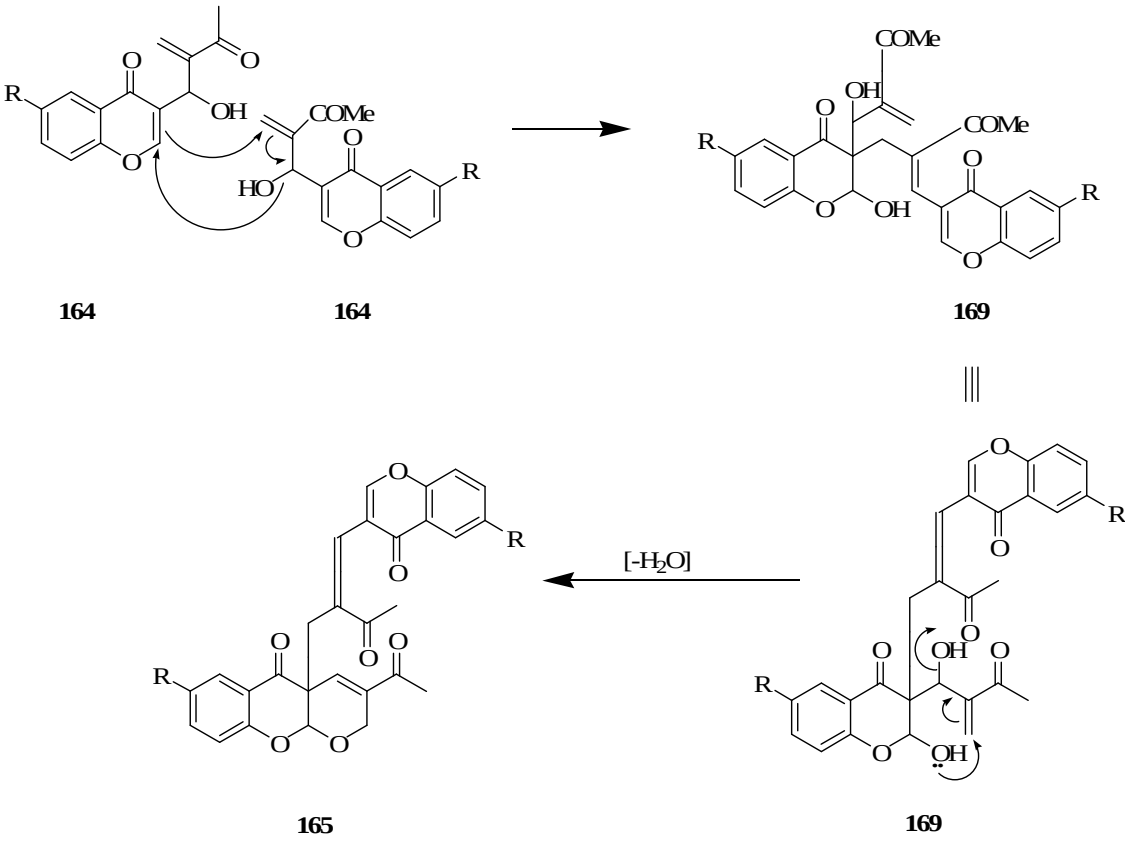
Aldehyde	Tricyclic adduct	R	Yield (%) Using 3-HQ
40a	**166a$_1$**	H	12
40a	**166a$_2$**	H	4
40b	**166b**	Br	7
40c	**166c**	Cl	5
40d	**166d**	OMe	

Methyl vinyl ketone was treated, as a model substrate, with amines (pyrrolidine and benzylamine) using tetrabutylammonium bromide (TBAB) as catalyst in water to afford conjugate addition products as reported by Xu *et al.*[195] and illustrated below in Scheme 53. The chromone dimers **165a-e** were also treated with pyrrolidine under the same conditions, but, due to poor solubility of the chromone dimers in water, no reaction was observed by TLC monitoring. The chromone dimers were then treated with various amines (benzylamine, isopropylamine and diethylamine) under neat conditions at room temperature affording intractable mixtures of products (Scheme 52). The chromone dimers **165a-e** were also treated with methyl magnesium bromide, with the intention of exploring regioselectivity of nucleophilic attack at the various electrophilic sites [*] (Scheme 52). However, seemingly intractable mixtures of products were also obtained. Chromatography of the mixtures using both flash and HPLC methods generally failed to afford pure products.



Scheme 53

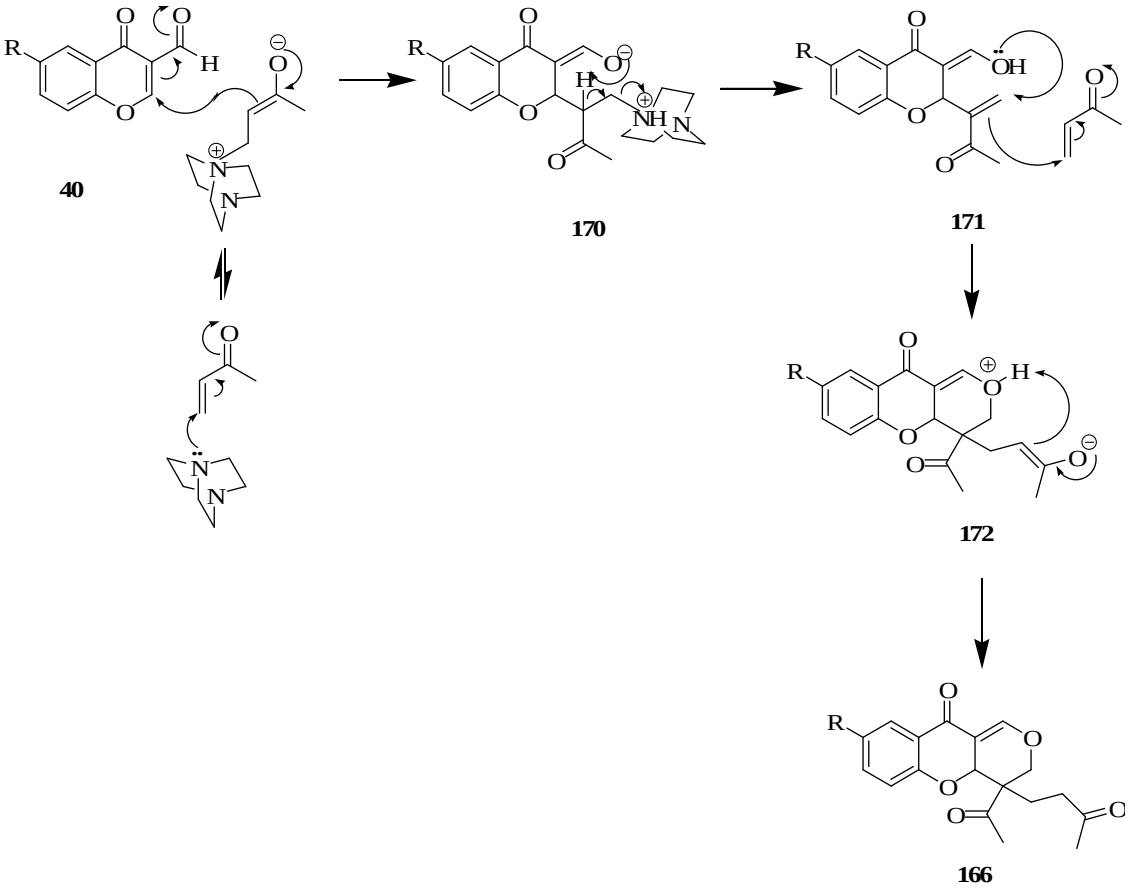
The chromone dimers, first isolated by Sabbagh,[159] are presumed to form *via* the mechanistic sequence outlined in Scheme 54. This involves an intermolecular reaction between two Baylis-Hillman adducts **164** to give the intermediate **169**. Attack of the hemi-acetal hydroxyl oxygen on the α,β-unsaturated carbonyl moiety then results in intramolecular cyclization *via* an S_N2' or conjugate addition-elimination process to afford the chromone dimer **165**.



Scheme 54

The tricyclic products **166a-e** had been obtained by Molefe[196] using 3-hydroxyquinuclidine as catalyst and their formation has been rationalized as shown in Scheme 55. The zwitterionic enolate, formed from the reaction of the catalyst and methyl vinyl ketone, attacks the chromone-3-carbaldehyde **40** at position 2, instead of attacking the aldehyde's carbonyl carbon, to afford the intermediate **170**. This shows the susceptibility of C-2 to nucleophilic attack. Proton transfer, followed by elimination of

the catalyst produces the intermediate **171**. Cyclization *via* an intramolecular conjugate addition and a tandem intermolecular Michael reaction then affords the tricyclic products **166a-d**.



Scheme 55

The chromone dimers **165a-e** were fully characterized by spectroscopic (IR, MS, ^{1}H and ^{13}C and 2-dimensional NMR) analysis. The ^{1}H NMR spectrum (Figure 3) of the chromone dimer **165a** reveals two singlets at 2.28 and 2.42 ppm corresponding to the 12- and 16-methyl groups, a singlet at 3.22 ppm corresponding to the 13-methylene protons, a pair of doublets at *ca* 4.5 ppm corresponding to the diastereotopic 2-methylene protons, a singlet at 5.00 ppm corresponding to the 9a proton and a singlet at 7.17 ppm corresponding to the 4-methine proton. The ^{13}C NMR spectrum (Figure 4) reveals 28 carbon signals. The C-16 and C-12 methyl groups resonate at 25.3 and 25.8 ppm,

respectively, the C-13 and C-2 methylene carbons resonate at 25.9 and 65.9 ppm respectively, the C-4a quarternary carbon at 50.1 ppm and the C-9a methine carbon at 99.8 ppm. The data from DEPT135, COSY, HSQC and HMBC spectra were used to facilitate the assignment of the signals.

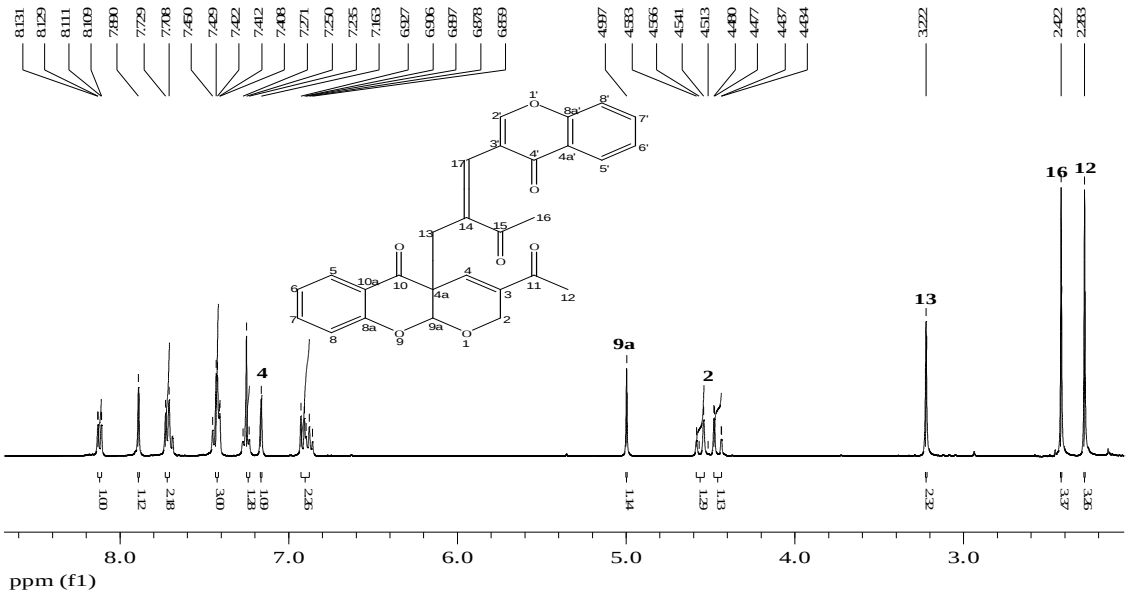


Figure 3. 400 MHz ^{1}H NMR spectrum of chromone dimer **165a** in $CDCl_3$.

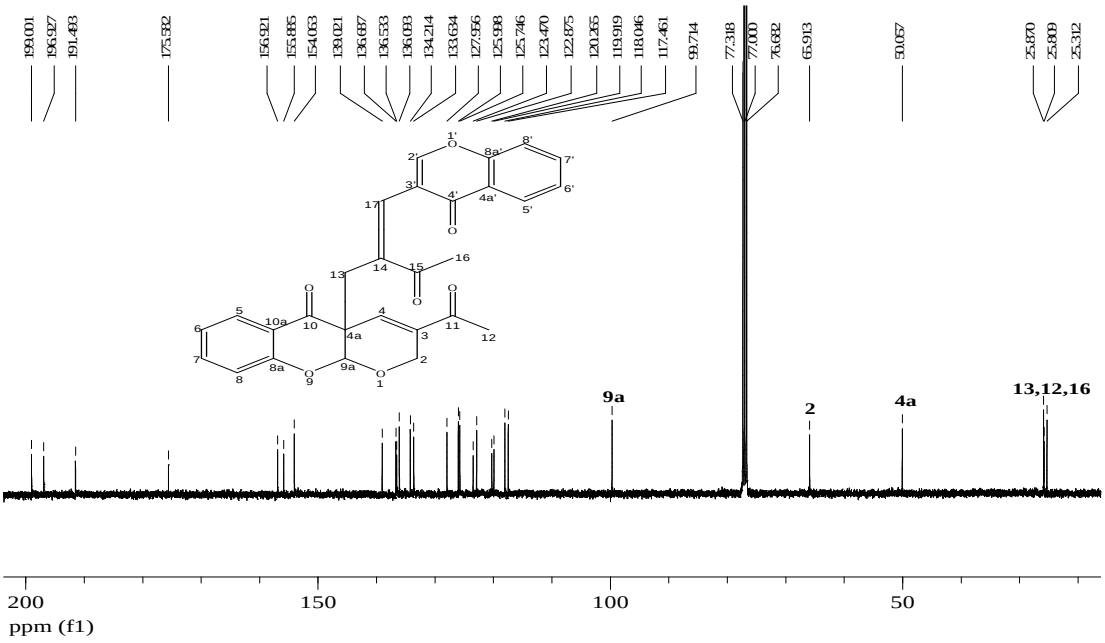


Figure 4. 100 MHz ^{13}C NMR spectrum of chromone dimer **165a** in $CDCl_3$.

Semi-preparative HPLC of the parent tricyclic product **166a** (R = H) afforded two fractions, shown, for the first time, to be diastereomeric products **166a$_1$** and **166a$_2$** arising from the presence of the two stereogenic centres (C-8a and C-9). The ^{1}H NMR spectrum (Figure 5) of the tricyclic adduct **166a$_1$** shows two multiplets at 2.02 and 2.19 ppm corresponding to the diastereotopic 13-methylene protons, two singlets at 2.06 and 2.37 ppm corresponding to the 16- and 12-methyl groups respectively, two multiplets at 2.40 and 2.54 ppm corresponding to the diastereotopic 14-methylene protons, a doublet of doublets at *ca* 4.67 ppm corresponding to the 10-methylene protons, a singlet at 5.12 ppm corresponding to the 8a-methine proton and a triplet at 7.28 ppm corresponding to the 2-methine proton which couples with the 10-methylene protons.

The ^{1}H NMR spectrum (Figure 6) of the tricyclic diastereomer **166a$_2$** (the second fraction from semi-preparative HPLC) illustrates the similarities and differences from the ^{1}H NMR spectrum of the diastereomer **166a$_1$** (Figure 5). The triplet at 2.18 ppm corresponds to the 13-methylene protons, the two singlets at 2.11 and 2.29 ppm to the 16- and 12-methyl groups respectively, the triplet at 2.56 ppm to the 14-methylene protons, the pair of doublets at *ca* 4.5 ppm to the 10-methylene protons, the singlet at 5.40 ppm to the 8a-methine proton and the broad singlet at 6.67 ppm to the 2-methine proton. The COSY spectra of the diastereomeric products (Figures 7 and 8) reveal the long range couplings (marked X) between the 2-methine proton and the diastereotopic 10-methylene protons for the two diastereotopic tricyclic products **166a$_1$** and **166a$_2$**, respectively.

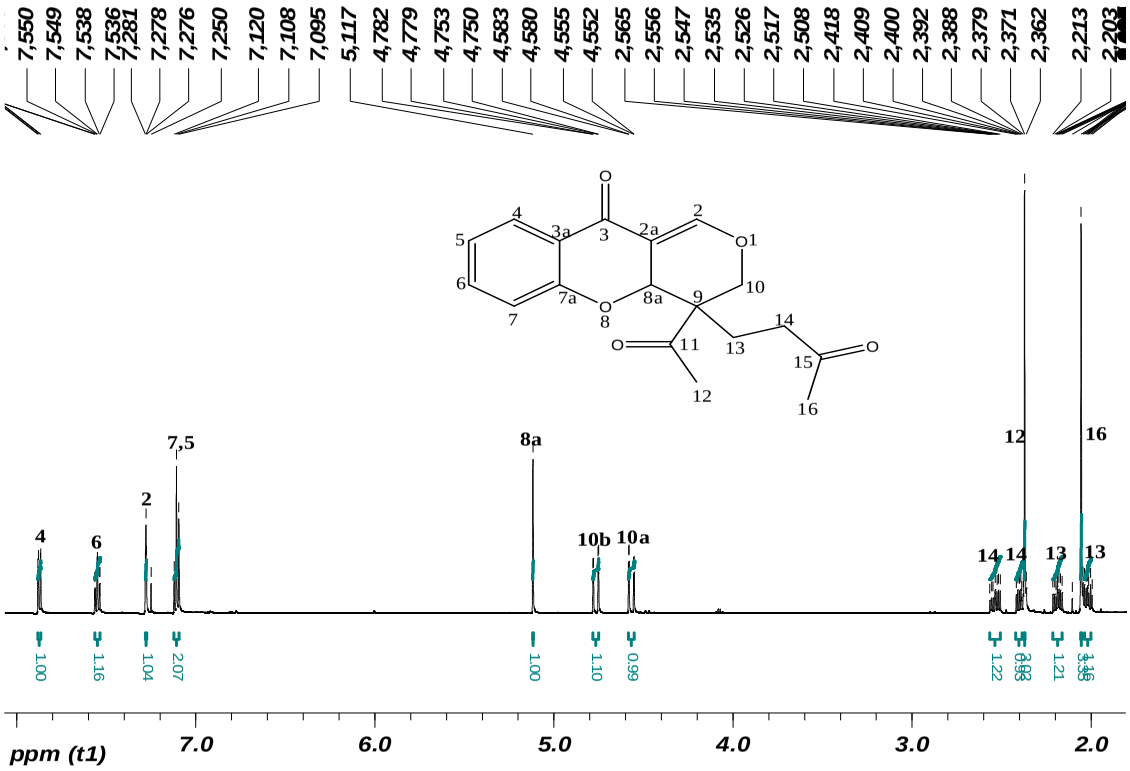


Figure 5. 600 MHz ^{1}H NMR spectrum of the tricyclic adduct **166a$_1$** in $CDCl_3$.

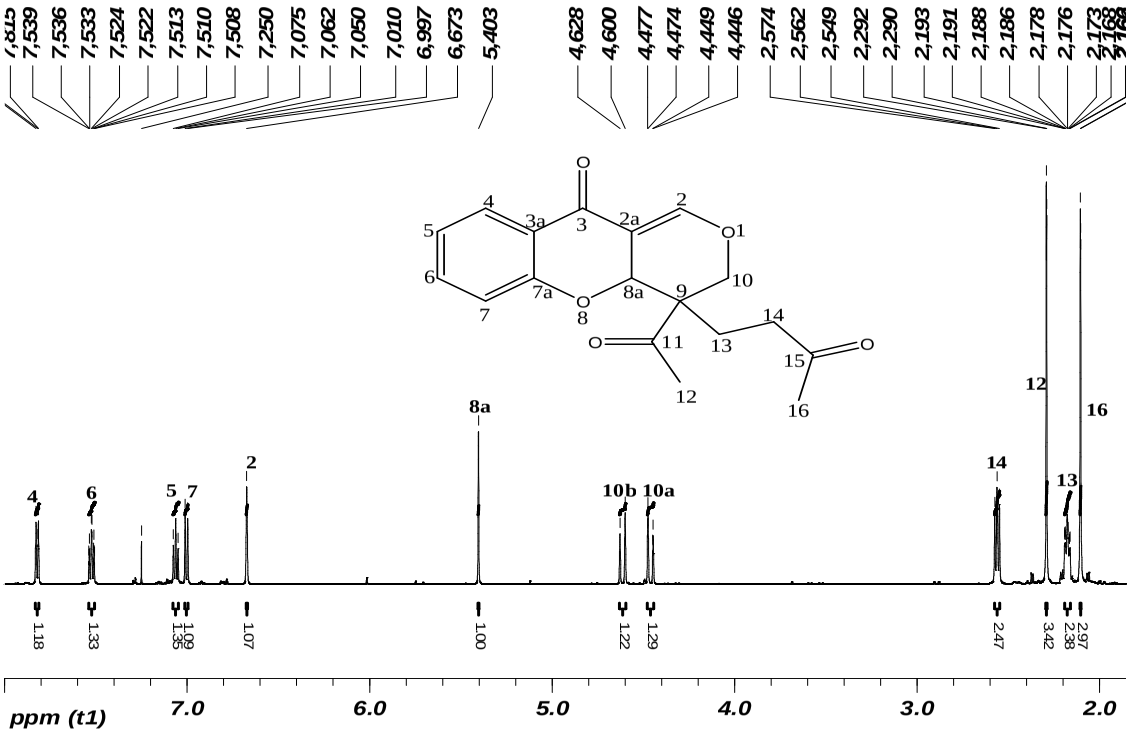


Figure 6. 600 MHz ^{1}H NMR spectrum of the tricyclic adduct **166a$_2$** in $CDCl_3$.

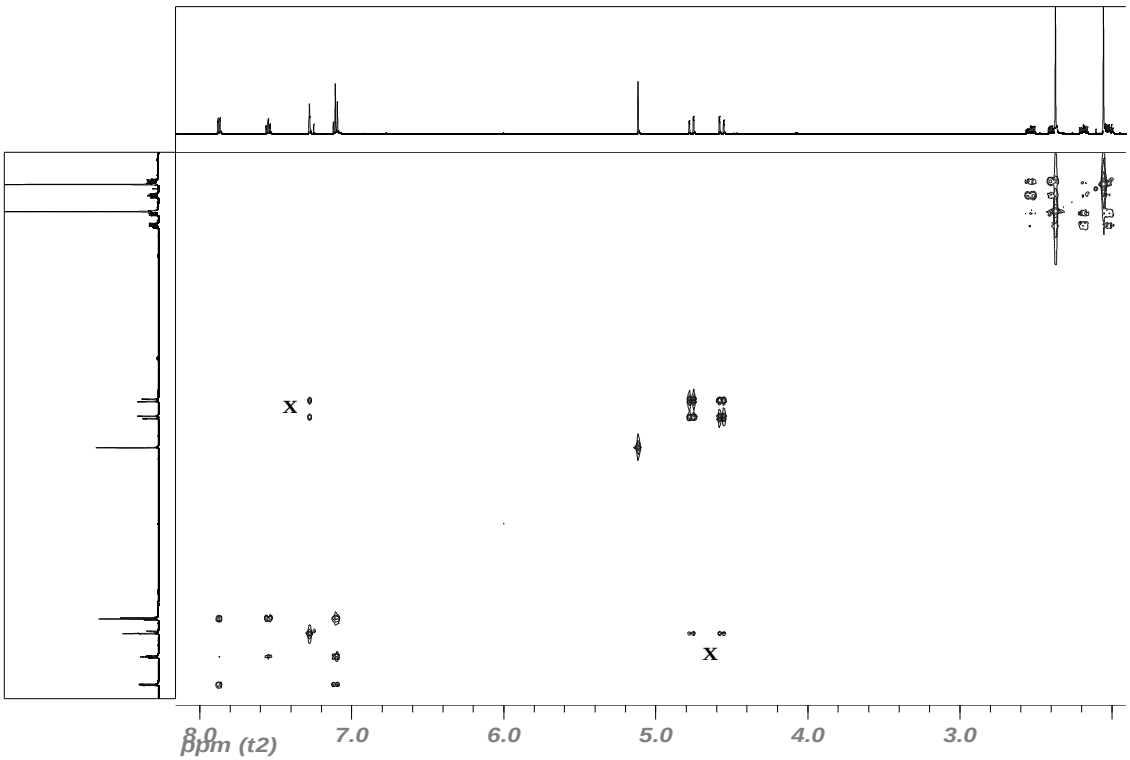


Figure 7. COSY spectrum of the tricyclic adduct **166a$_1$** in $CDCl_3$.

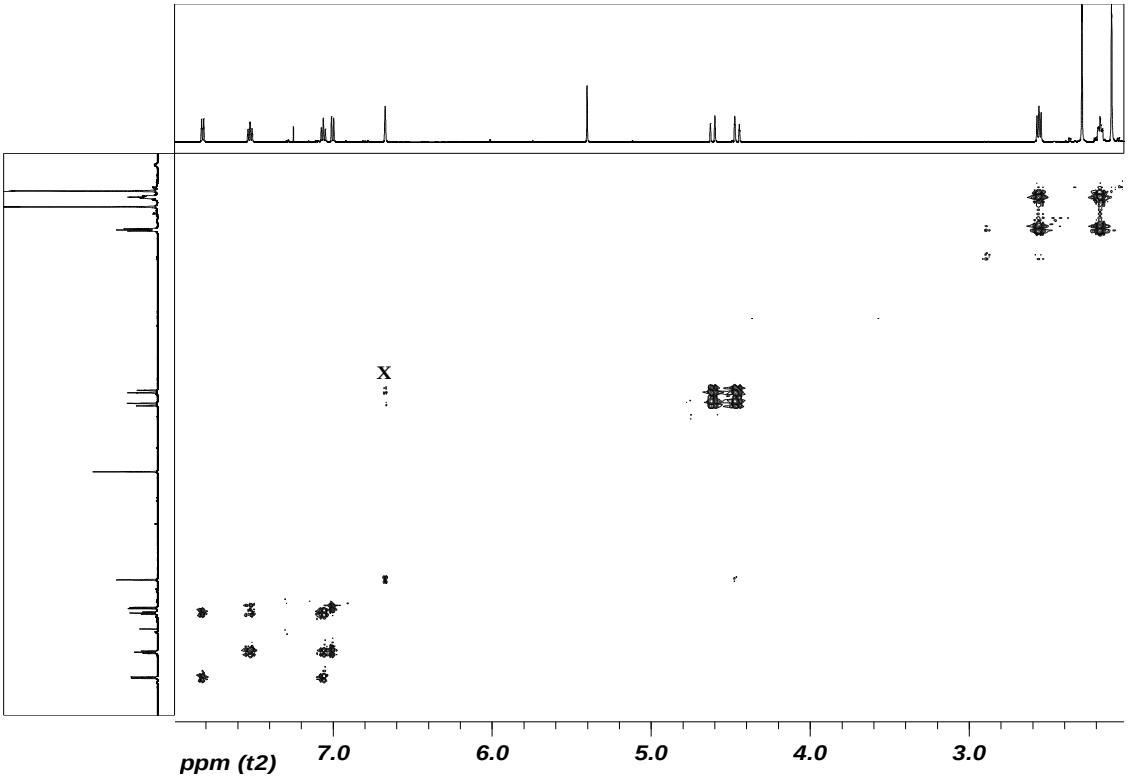


Figure 8. COSY spectrum of tricyclic the adduct **166a$_2$** in $CDCl_3$.

The high resolution mass spectra (Figures 9 and 10) of the two diastereomeric tricyclic products **166a$_1$** and **166a$_2$** reveal molecular ion peaks at *m/z* = 314.11478 and *m/z* = 314.11486 respectively, confirming their common atomic composition.

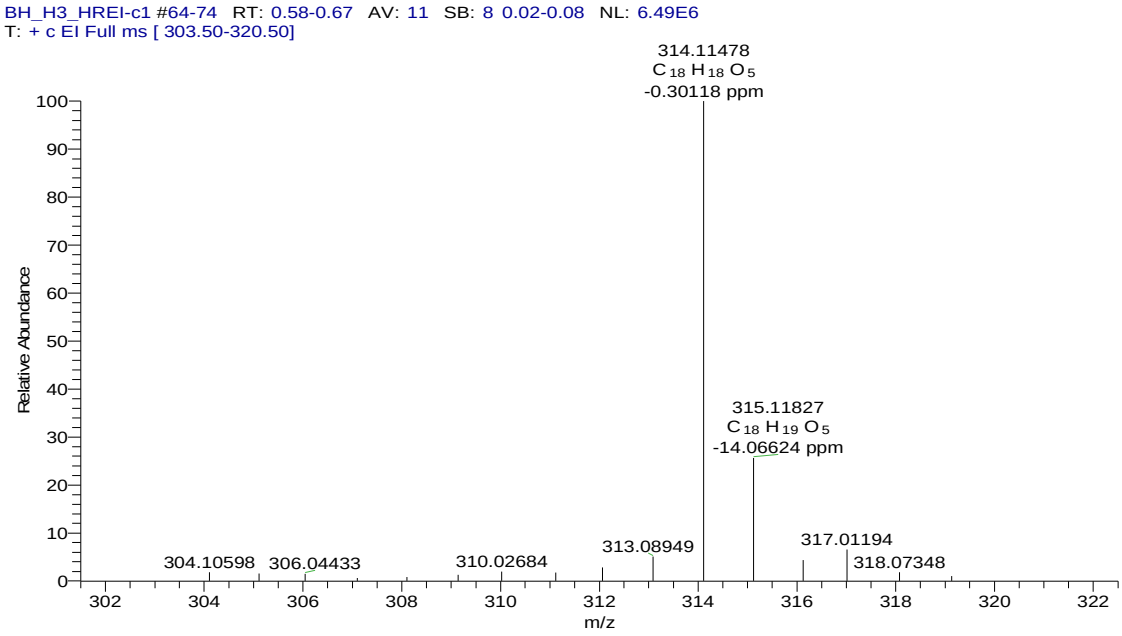


Figure 9. HREI Mass spectrum of the tricyclic adduct **166a$_1$**.

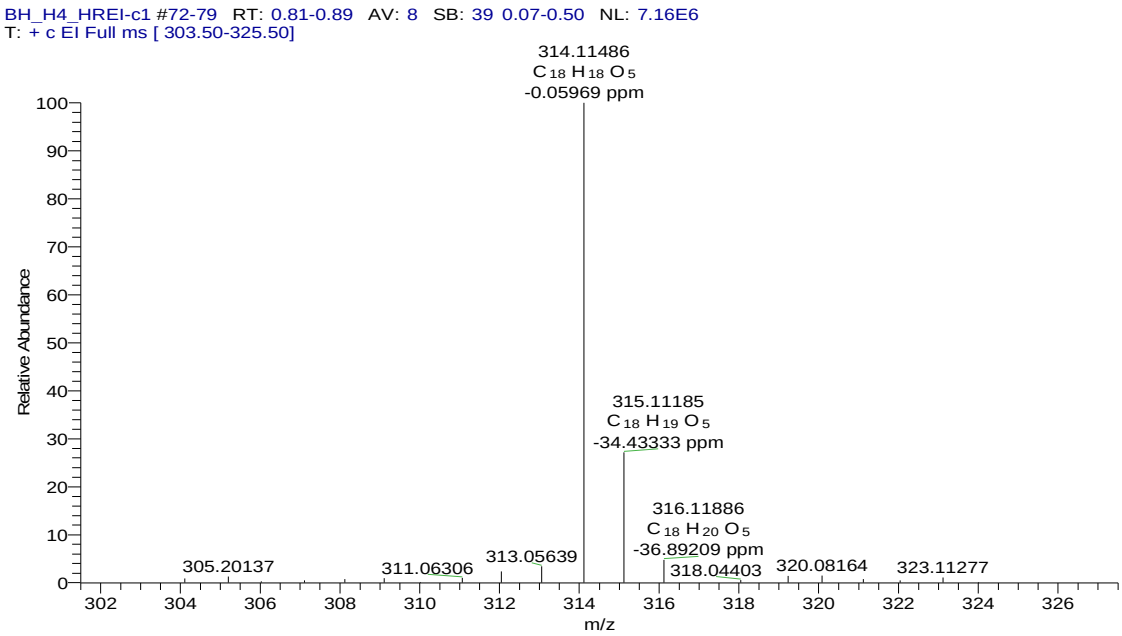


Figure 10. HREI Mass spectrum of the tricyclic adduct **166a$_2$**.

The ^{13}C NMR spectrum (Figure 11) of the tricyclic product **166a$_1$** reveals 18 carbon signals. The C-13 methylene nucleus resonates at 24.8 ppm, the C-12 and C-16 methyl nuclei at 25.4 and 30.0 ppm, the C-14 methylene nucleus at 37.7 ppm, the quartenary carbon C-9 at 49.1 ppm, the C-10 methylene nucleus at 65.8 ppm, the C-8a methine carbon at 99.9 ppm, the vinylic carbon C-2 at 135.3 ppm and the three carbonyl carbons at 192.5, 196.5 and 206.6 ppm. The DEPT135 spectrum (Figure 12) confirms the presence of three methylene carbons, C-13, C-14 and C-10, which resonate at 24.8, 37.7 and 65.8 ppm respectively. The HSQC and HMBC spectra (Figures 13 and 14) were used to assign the aromatic signals and also to confirm other signal assignments. Similar signal patterns were observed for the tricyclic adduct **166a$_2$**.

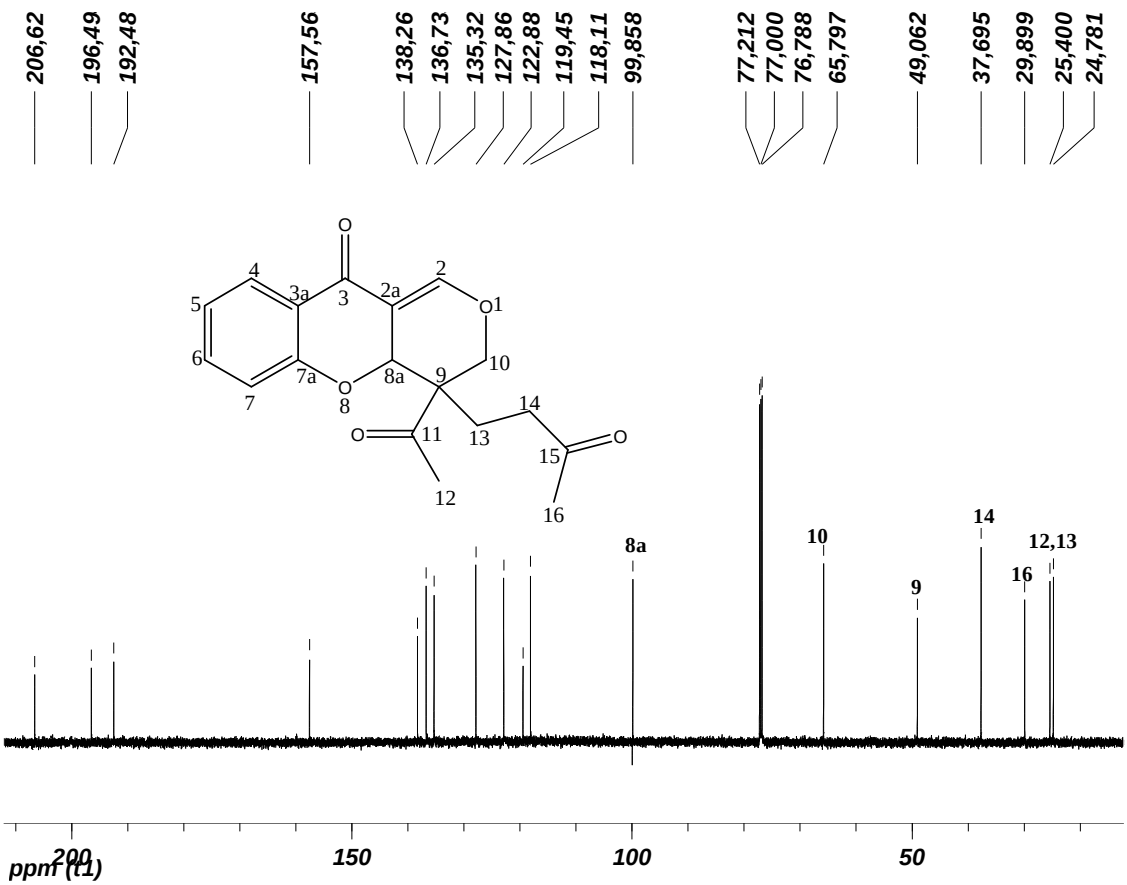


Figure 11. 150 MHz ^{13}C NMR spectrum of the tricyclic adduct **166a$_1$** in $CDCl_3$.

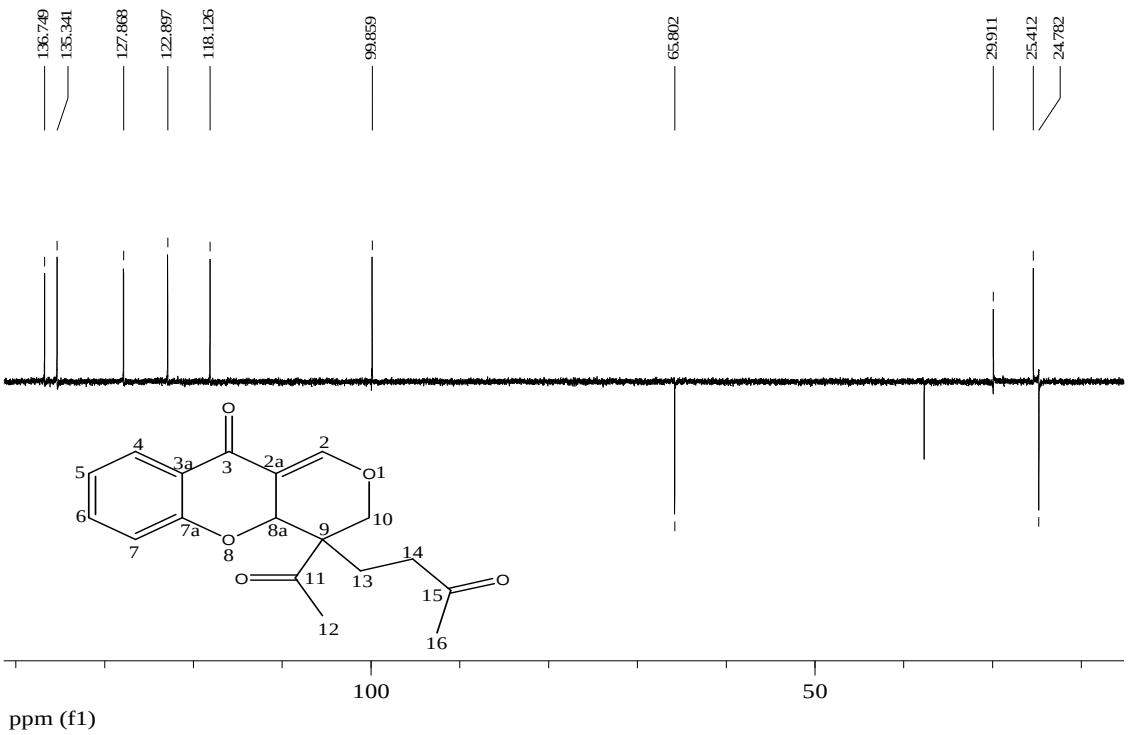


Figure 12. DEPT135 NMR spectrum of the tricyclic adduct **166a$_1$** in $CDCl_3$.

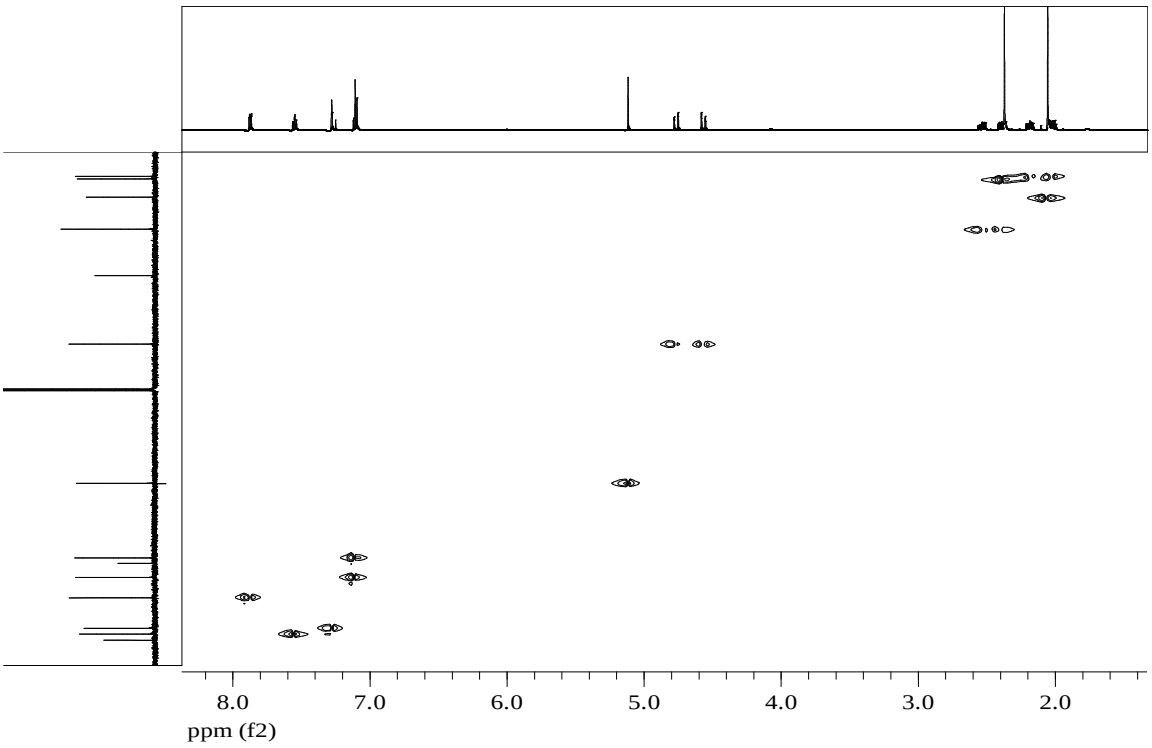


Figure 13. HSQC spectrum of the tricyclic adduct **166a$_1$** in $CDCl_3$.

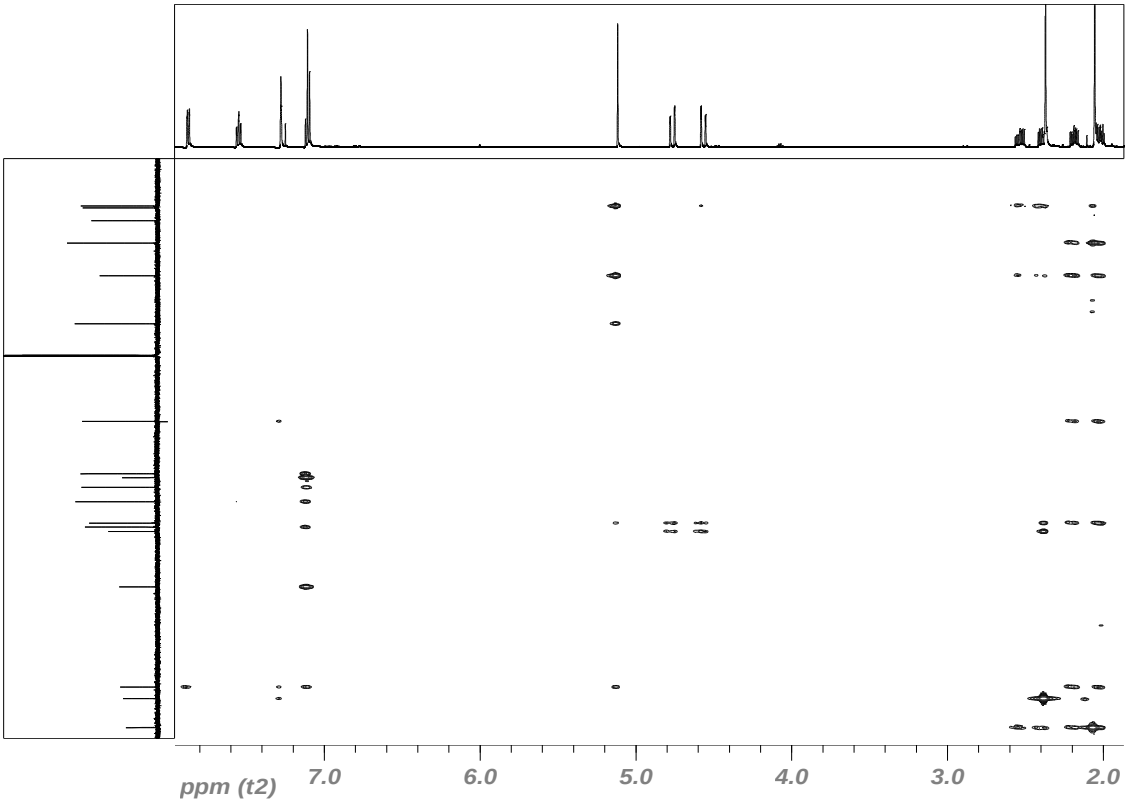


Figure 14. HMBC spectrum of the tricyclic adduct **166a$_1$** in $CDCl_3$.

The NOESY spectrum (Figure 15) of the parent tricyclic adduct **166a$_1$** reveals only the long-range coupling between the 2-methine proton and the 12-methyl group, marked with the rectangle, and the long-range coupling between the 8a-methine proton with one of the 10-methylene protons, marked with an oval shape. This spectrum does not provide enough information about the stereochemistry at the stereogenic centres C-8a and C-9.

On the other hand, the NOESY spectrum (Figure 16) of the parent diasteromeric tricyclic adduct **166a$_2$** reveals long-range coupling between the 8a-methine proton and the 13- and 14-methylene protons, marked with the rectangles. This interaction means that the 8a-methine and the 13- and 14-methylene protons are on the same side of the molecule, with the possible stereochemistry shown in Figure 17.

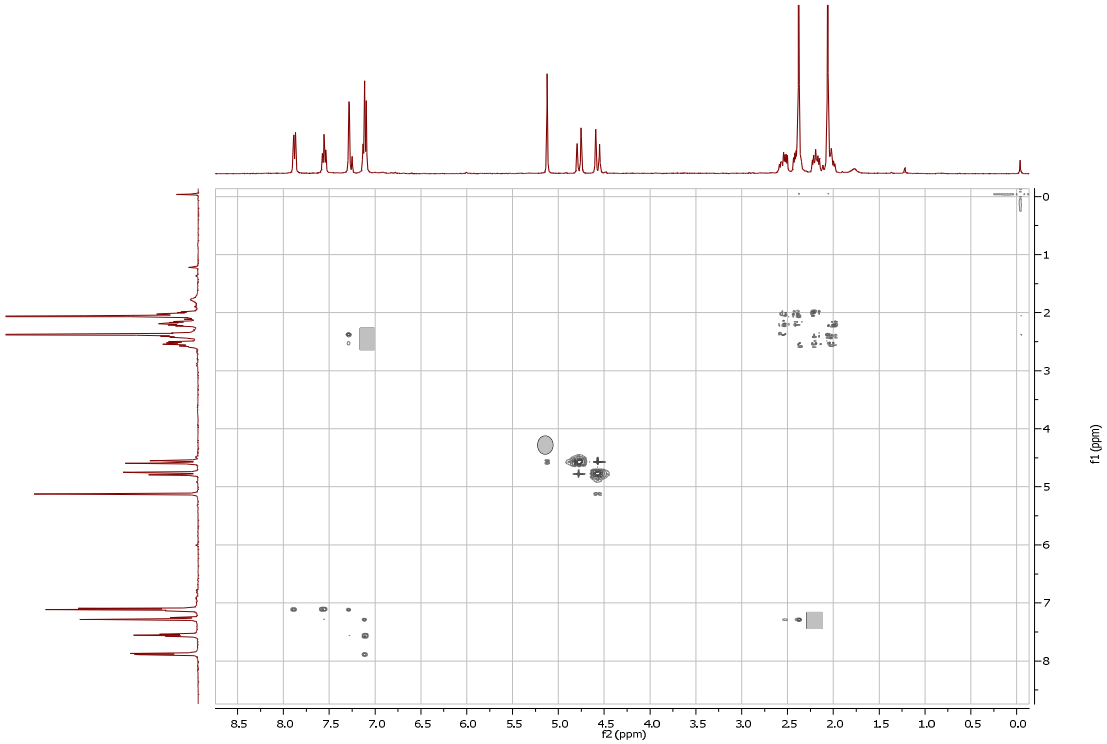


Figure 15. NOESY spectrum of the tricyclic adduct **166a$_1$** in $CDCl_3$.

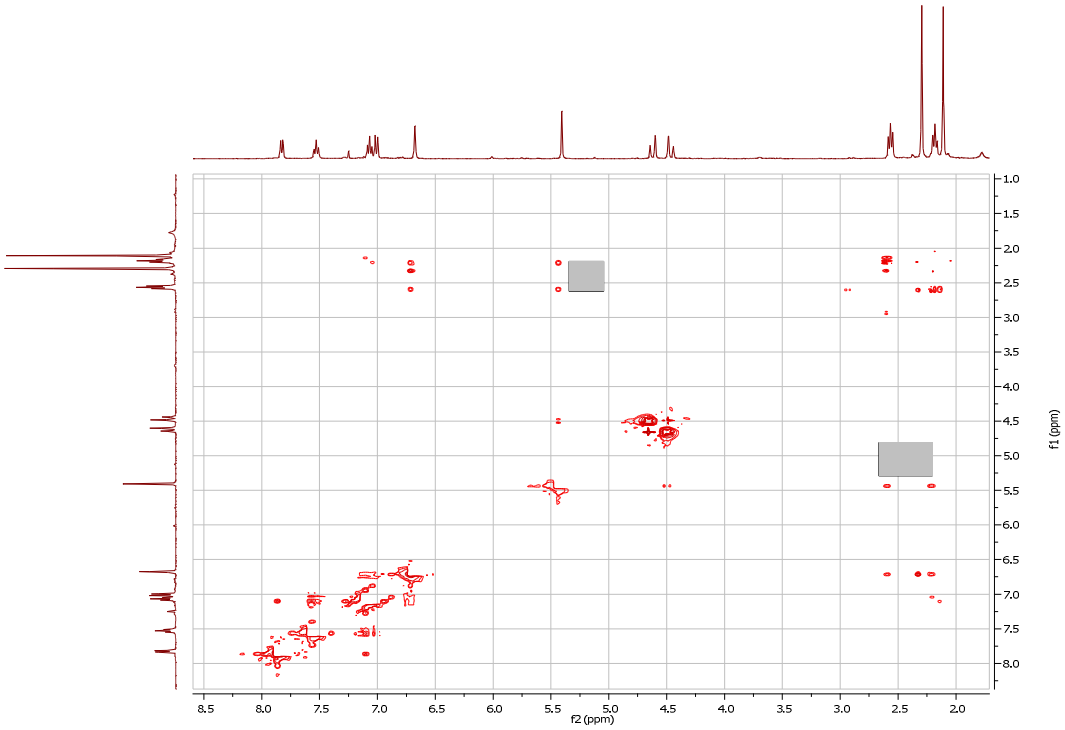


Figure 16. NOESY spectrum of the tricyclic adduct **166a$_2$** in $CDCl_3$.

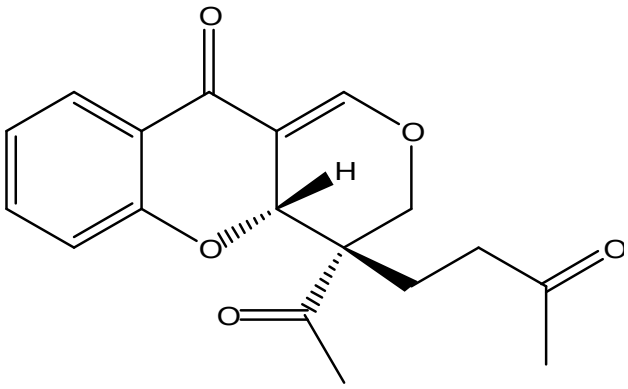


Figure 17. Possible stereochemistry of the tricyclic adduct **166a$_2$**.

Semi-preparative HPLC of the brominated and chlorinated analogues (**166b** and **166c**, respectively) afforded only one fraction in each one. The brominated analogue **166b** had similar ^{1}H NMR signal patterns to the parent system **166a$_1$**, whereas the chlorinated analogue **166c** had similar ^{1}H NMR signal patterns as the diastereomeric system **166a$_2$**.

The reaction was initially conducted using 3-hydroxyquinuclidine and 1.1 molar equivalents of MVK. Under these conditions, however, formation of the tricyclic products proved to be very inefficient (≤ 12% yield). The reactions were therefore repeated using:

i) Excess MVK (2.0 eq.), because the proposed mechanism (Scheme 54), indicates that two equivalents of MVK are involved in the reaction.

ii) 3-HQ, because it affords the products in shorter periods than DABCO.

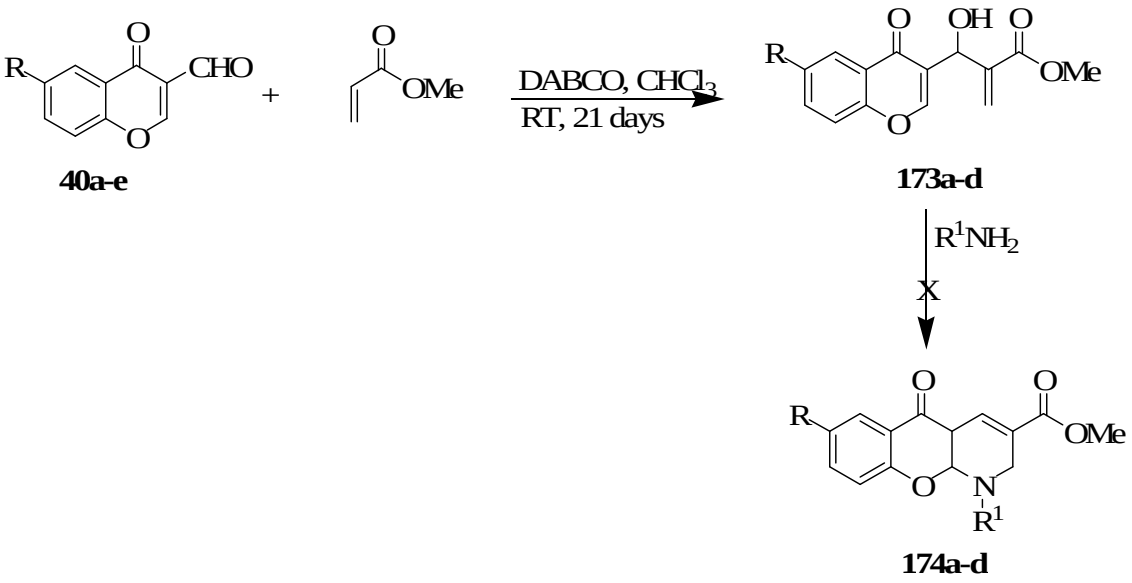
These changes were made in order to increase the yield of the tricyclic products, with the aim of cyclizing the acyclic ketones to afford spiro compounds **167** and **168** (Scheme 52). After stirring the reaction mixture at room temperature for 24 hours, followed by the usual work-up and flash chromatography, a mixture of the Baylis-Hillman adducts **164a-d** and the tricyclic products **166a-d** was isolated. Interestingly none of the chromone dimers **165-a-d** were isolated from these reactions (Scheme 52; Table 4). Cyclisation to spiro compounds will require (even) more efficient access to the tricyclic systems **166a-e**, hence it could be explored in future studies.

Table 4. Isolated yields of Baylis-Hillman adducts **164a-d** and tricyclic adducts **166a-d** using 3-HQ and 2 eq. of MVK

Product no.	R	164 [Yield (%)]	166 [Yield (%)]
166a$_1$	H	30	13
166b	Br	28	16
166c	Cl	23	11
166d	OMe	25	9

2.2.2 Reactions of chromone-3-carbaldehydes with methyl acrylate

The series of chromone-3-carbaldehydes **40a-d** were reacted with methyl acrylate using DABCO as a catalyst in chloroform for 21 days (Scheme 56, Table 5). Work-up and purification of the crude products using flash chromatography and HPLC afforded the Baylis-Hillman adducts **173a-d**. The Baylis-Hillman products were then treated with butylamine, in expectation of obtaining the tricyclic derivatives **174a-d**. However, the cyclic products **174a-d** were not isolated; instead intractable mixtures of products were obtained.



40a-e **173a-d** **174a-d**

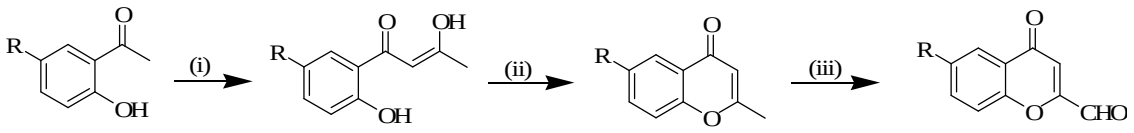
Scheme 56

Table 5. Isolated yields of Baylis-Hillman adducts **173a-d**.

Aldehyde	BH-adduct	R	Yield (%)
40a	**173a**	H	23
40b	**173b**	Br	20
40c	**173c**	Cl	15
40e	**173d**	OMe	19

2.3 Preparation of chromone-2-carbaldehydes

The chromone-2-carbaldehydes **177a-d** were synthesized *via* a three-step process starting from the corresponding 2-hydroxyacetophenones **28a-d**.[29,197-199] The first step involves treatment of each of the 2-hydroxyacetophenones with ethyl acetate and sodium ethoxide (generated *in situ* by reaction of sodium metal with dry ethanol) to afford the crude enolised β-diketo derivatives **175a-d**. Recrystallisation of the crude intermediates **175a-d** from petroleum ether (boiling range 60-80 ^{o}C) afforded the pure compounds in yields ranging from 60 to 97 %. On acidification, these intermediates cyclized spontaneously to the corresponding 2-methylchromones **176a-d**, which were recrystallised from hexane to afford the pure compounds in yields ranging from 33 to 77%. Oxidation of the 2-methylchromones with selenium dioxide in xylene afforded the crude chromone-2-carbaldehydes **177a-d**, which were purified using flash chromatography to afford the pure products in yields ranging from 10 to 45% (Scheme 57; Table 6).



28a-d **175a-d** **176a-d** **177a-d**

Scheme 57: Reagents and conditions (i) Ethyl acetate, Na metal, ethanol, reflux, 8h; (ii) Acetic acid, conc. H_2SO_4, reflux, 4h; (iii) SeO_2, xylene, reflux, 24 h.

Table 6. Isolated yields of β-diketo derivatives **175a-d**, 2-methylchromones **176a-d** and chromone-2-carbaldehydes **177a-d**.

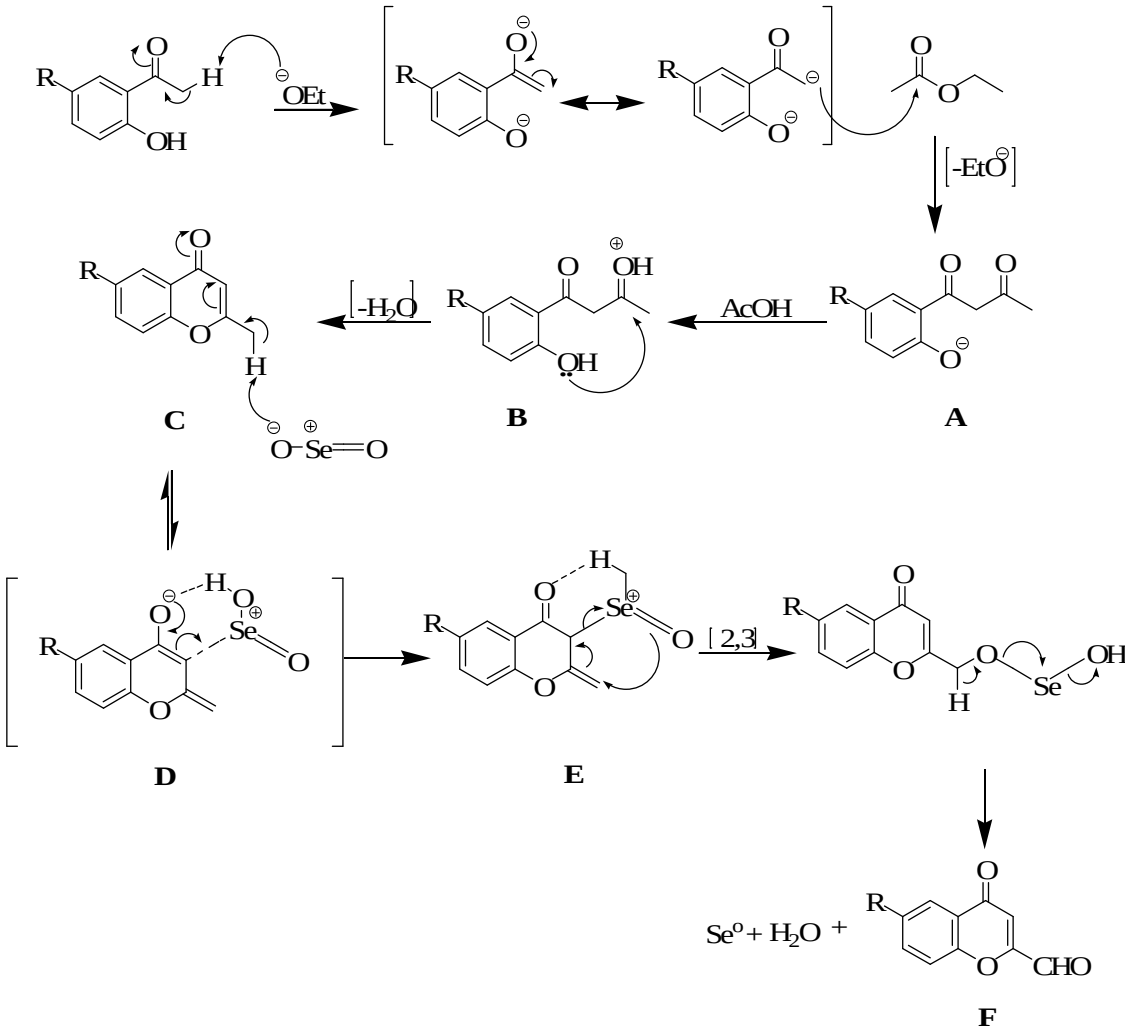
R	175a-d (Yield %)	176a-d (Yield %)	177a-d (Yield %)
H	70	33	21
Cl	60	77	45
OMe	97	54	10
Br	75	47	24

The probable mechanism for the synthesis of the chromone-2-carbaldehydes is illustrated in Scheme 58, and involves deprotonation of the methyl group of the acetophenone with sodium ethoxide, to afford a resonance-stabilized enolate, which then attacks the carbonyl carbon of ethyl acetate in a Claisen-Schmidt condensation sequence to afford the enolate intermediate **A**. Acid-catalysed cyclization and dehydration, leads to the 2-methylchromone **C**. The oxidation of 2-methylchromone **C** with selenium dioxide is considered to involve deprotonation of the methyl group to form a resonance-stabilized enolate **D**, which undergoes selenation at C-3 to afford intermediate **E**. A [2,3]-sigmatropic, followed by deselenation, finally the affords chromone-2-carbaldehyde **F**.[200-207]

The ^{1}H spectrum (Figure 18) of 6-methoxy-2-methylchromone **176c** reveals two singlets at 2.34 and 3.85 ppm corresponding to the 2-methyl and 6-methoxy groups, respectively, a singlet at 6.12 ppm corresponding to the 3-methine proton and the rest of the aromatic proton signals between 7.17 and 7.51 ppm. The ^{13}C spectrum (Figure 19) reveals 11 carbon signals, with the 2-methyl and 6-methoxy groups resonating at 20.5 and 55.8 ppm, respectively, and the carbonyl carbon resonating at 178.1 ppm.

The ^{1}H spectrum (Figure 20) of the oxidized analogue, 6-methoxychromone-2-carbaldhyde **177c**, reveals a singlet at 3.81 ppm corresponding to the 6-methoxy group, a singlet at 6.88 ppm corresponding to the 3-methine proton, and a singlet corresponding to the aldehyde proton at 9.78 ppm. The ^{13}C spectrum (Figure 21) again reveals 11 carbon

signals with the 6-methoxy carbon resonating at 56.0 ppm, 4-carbonyl carbon at 178.1 ppm and the aldehyde carbonyl carbon at 185.5 ppm.



Scheme 58

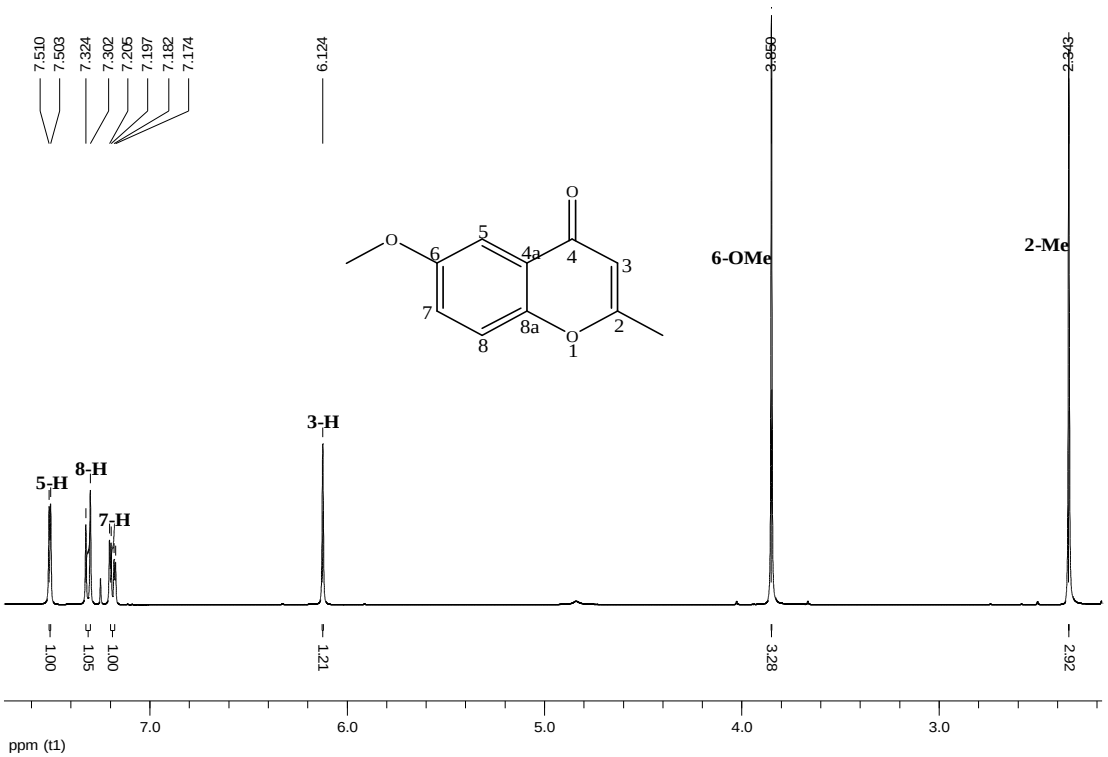


Figure 18. 400 MHz ^{1}H NMR spectrum of 6-methoxy-2-methylchromone **176c** in $CDCl_3$.

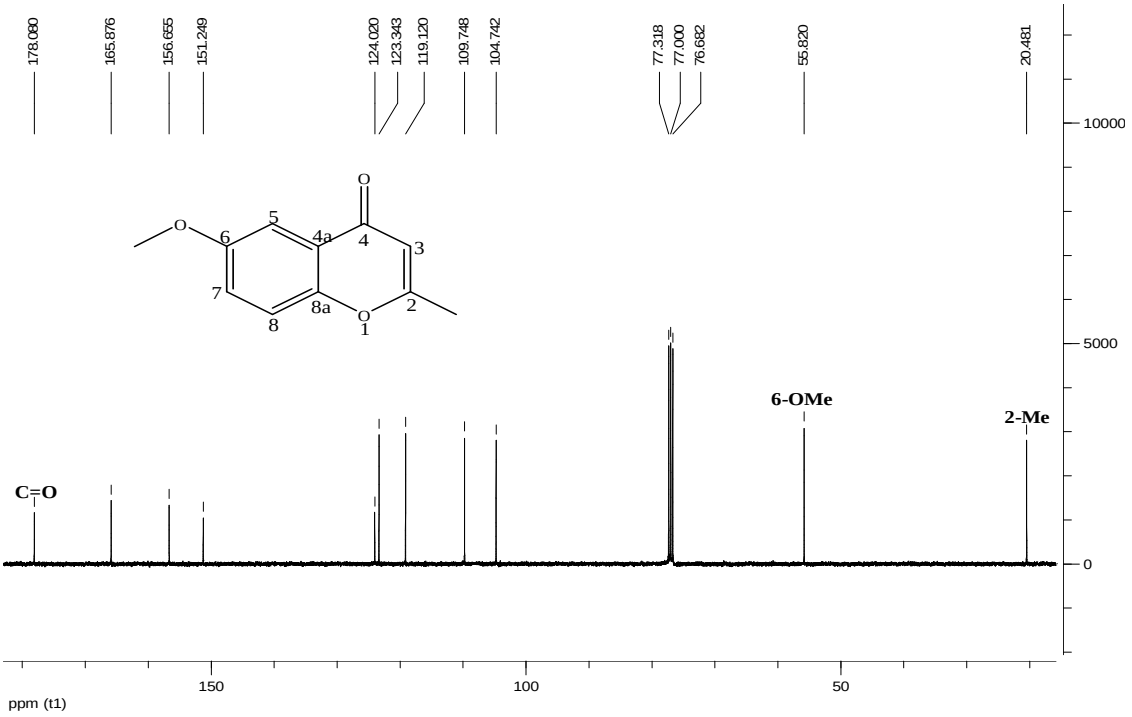


Figure 19. 100 MHz ^{13}C NMR spectrum of 6-methoxy-2-methylchromone **176c** in $CDCl_3$.

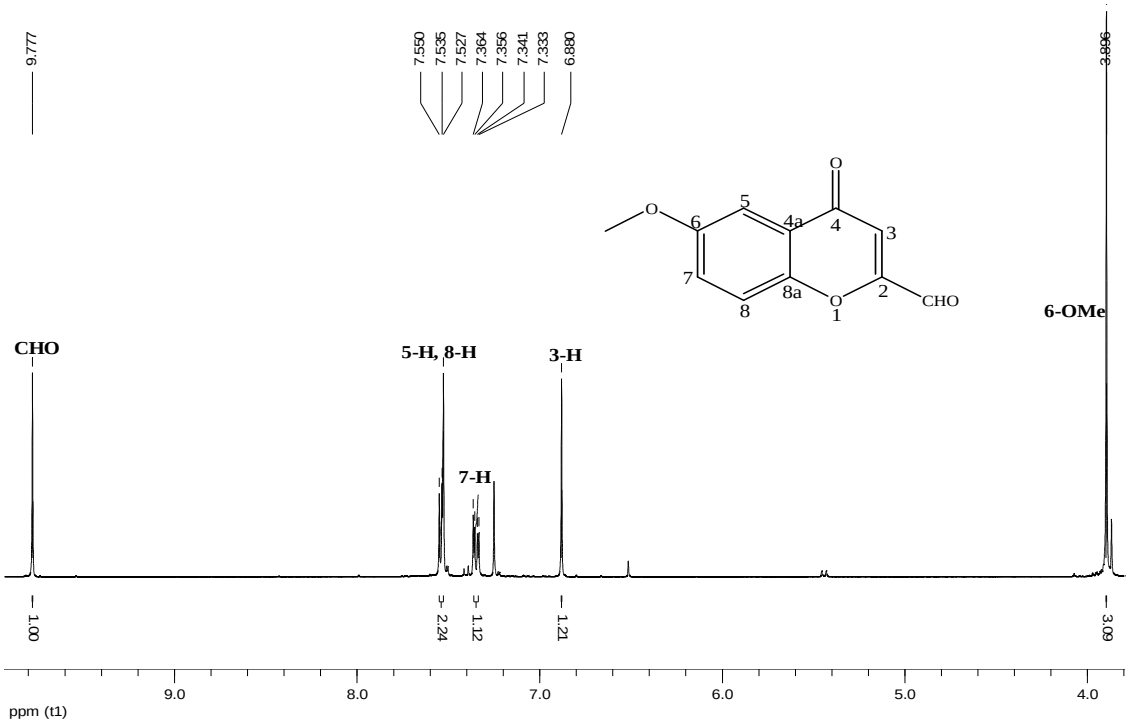


Figure 20. 400 MHz ^{1}H NMR spectrum of 6-methoxychromone-2-carbaldehyde **177c** in $CDCl_3$.

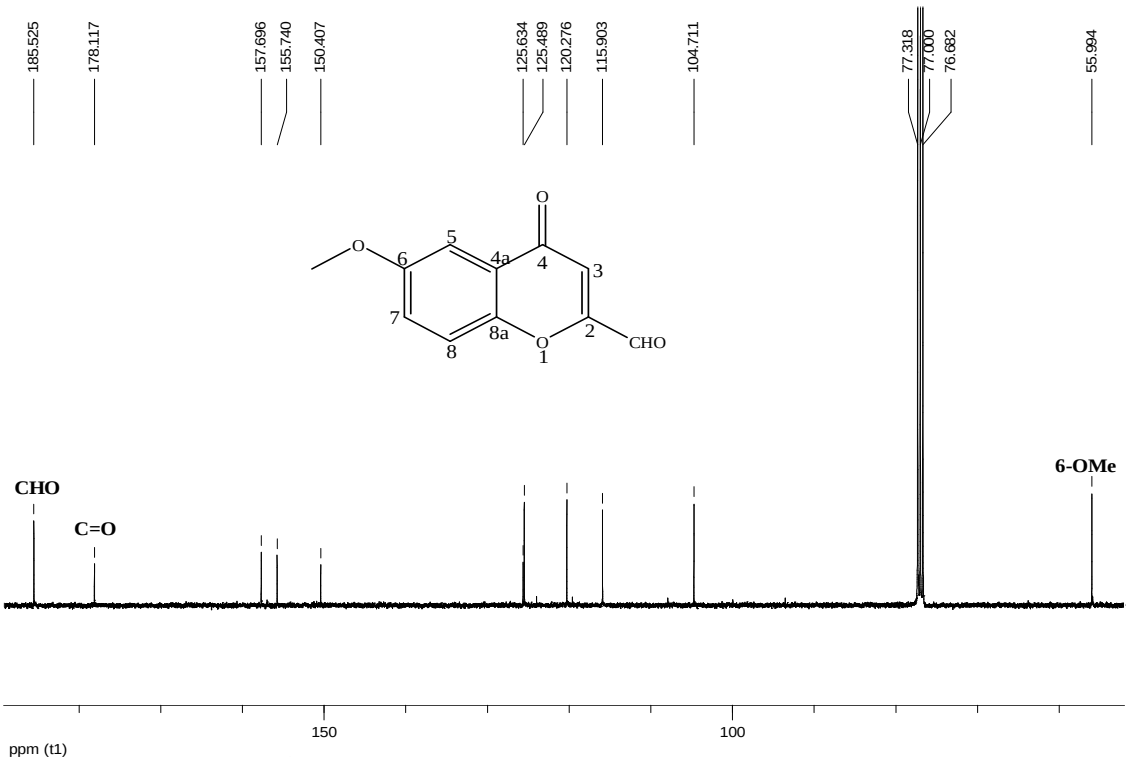
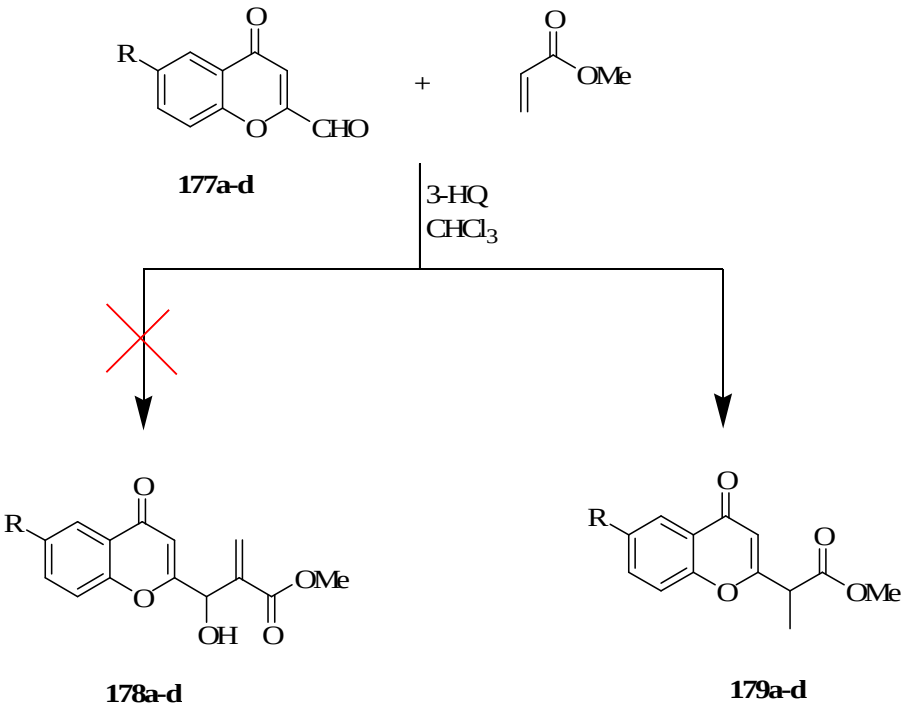


Figure 21. 100 MHz ^{13}C NMR spectrum of 6-methoxychromone-2-carbaldehyde **177c** in $CDCl_3$.

2.4 Baylis-Hillman reactions involving chromone-2-carbaldehydes

2.4.1 Reactions of chromone-2-carbaldehydes with methyl acrylate

The series of chromone-2-carbaldehydes **177a-d** were reacted with methyl acrylate using 3-hydroxyquinuclidine as catalyst in a minimal volume of chloroform at room temperature for 24 hours. Purification of the crude products using flash chromatography afforded the interesting products **179a-d** in yields ranging from 13% to 35% (Scheme 59; Table 7). None of the expected Baylis-Hillman adducts **178a-d** were isolated. In an earlier study, Molefe[196] had obtained the 6-methoxy substituted system alone and the intention in the present study was to confirm the reproducibility of this unexpected transformation and demonstrate its applicability to a range of substrates.

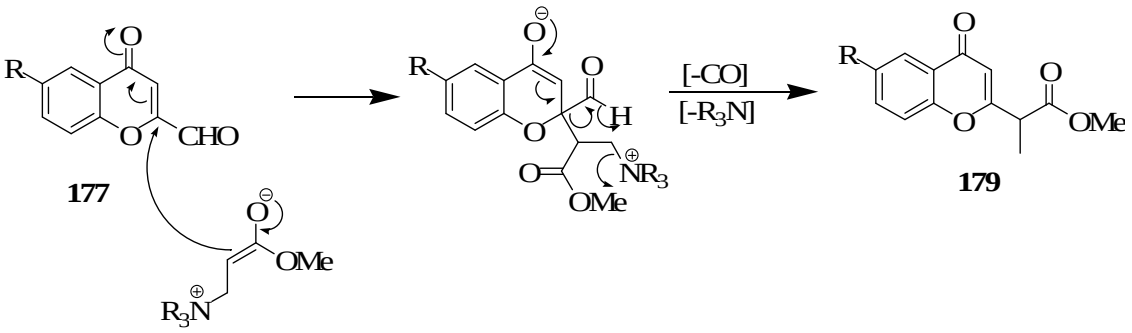


Scheme 59

Table 7. Isolated yields of products **179a-d**

Aldehyde	R	Product	Yield
177a	**H**	**179a**	13
177b	**Cl**	**17ab**	19
177c	**OMe**	**179c**	35
177d	**Br**	**179d**	30

A possible mechanism for the formation of products **179a-d** is shown in Scheme 60. This involves displacement of the aldehyde group at position 2. The zwitterionic enolate, formed from reaction of the tertiary amine catalyst with methyl acrylate, attacks the electrophilic centre C-2 of the chromone instead of the aldehyde carbonyl carbon, and the rearrangement which involves loss of CO and the tertiary amine catalyst affords the products **179a-d**.



Scheme 60

2.5 Baylis-Hillman reactions involving cyclic enones

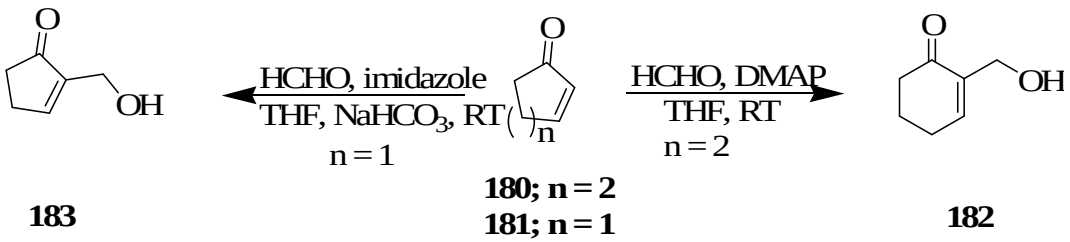
Applications of cyclic enones in Baylis-Hillman reactions were also investigated. The traditional catalyst, DABCO, in these reactions, has been found to be inefficient,[188,189] as has the use of 3-hydroxyquinuclidine. The reason for this lack of catalytic activity can be attributed to steric factors in the cyclic enones and the rigidity of the catalysts (DABCO and 3-HQ). When comparing the steric effects in reactions involving MVK and cyclic enones, it should be noted that MVK has two hydrogen atoms at the β-carbon of the α,β-unsaturated ketone, whereas the cyclic enones have one hydrogen atom and a methylene group (CH_2), making them relatively inaccessible for nucleophilic attack by tertiary amine catalysts.[188,189]

This has led to the investigation of better and more effective reaction conditions, most of which involve the use of catalysts other than DABCO, and the use of certain additives to facilitate the reaction. The use of $TiCl_4$ as a catalyst has been reported by Li *et al*.,[190] by Patra *et al*.[191] and by Basavaiah *et al*.[192] Other catalysts that have been reported include 4-(dimethylamino)pyridine (DMAP) in aqueous solution,[188] imidazole in aqueous solution[193,194,208,209] sodium methoxide,[210] trimethylamine[211] and *N,N,N',N'*-tetramethyl-1,3-propanediamine (TMPDA).[212] In the present study, cyclic enones have been reacted with 2-nitrobenzaldehydes, pyridine-2- and quinoline-2-carbaldehydes and chromone-3-carbaldehydes under various Baylis-Hillman conditions.

2.5.1 Reactions of cyclic enones with 2-nitrobenzaldehydes and their conversion to quinoline derivatives

In these reactions, a number of catalysts and reaction conditions have been explored. In model reactions, 2-cyclohexen-1-one **180** and 2-cyclopenten-1-one **181** were reacted, as reported,[153] with aqueous formaldehyde using DMAP as catalyst in THF for 12 hours (Scheme 61). While work-up and chromatography afforded 2-(hydroxymethyl)cyclohex-

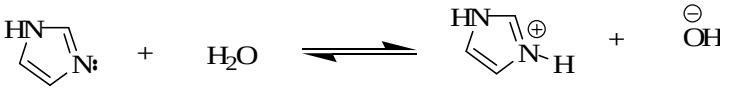
2-enone **182** in 38%, only a trace quantity of 2-(hydroxymethyl)cyclopent-2-enone **183** was obtained under these conditions. The catalytic activity of DMAP was further investigated using a wide range of aldehydes, and cyclic enones. However, reaction of benzaldehydes with 2-cyclohexen-1-one, using DMAP as catalyst in THF-water (1:1) for 12 hours, afforded only trace amounts of the desired Baylis-Hillman adducts. Even after extended reaction periods of *ca* 36 to 48 hours, the product yields were still very poor, and it was clear that the DMAP-THF-water reaction conditions were not generally applicable to a broad spectrum of substrates.



183 **180; n = 2** **181; n = 1** **182**

Scheme 61

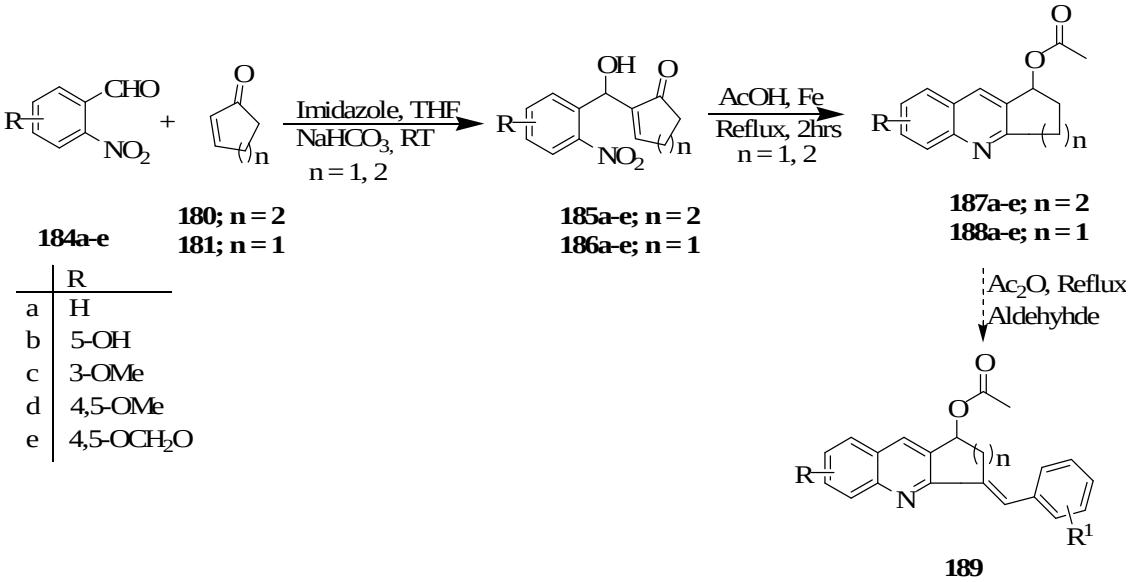
The poor results obtained using DMAP as catalyst prompted the investigation of a different catalyst, which could be used for a wider range of substrates. Reaction of 2-cyclopenten-1-one **181** with aqueous formaldehyde for 36 hours, using imidazole as catalyst in a mixture of THF and aqueous 1M $NaHCO_3$, following a procedure reported by Luo *et al.*[208] afforded 2-(hydroxymethyl)cyclopent-2-enone **183** in 75% yield, after work-up and flash chromatography (Scheme 61). The use of water in Baylis-Hillman reactions has been reported to enhance the reaction rate.[118,119,124] In aqueous reaction conditions, imidazole undergoes a proton transfer with water as illustrated in Scheme 62. However, in basic aqueous conditions it is believed that protonation of imidazole is depressed, thus leaving neutral imidazole to catalyze the reaction, *i.e.*, the basicity of the medium is likely to be important for rate enhancement. This conclusion is reflected in the observed dependence of reaction rate on the pH of the reaction.[208]



Scheme 62

The promising catalytic activity of imidazole in this reaction led to the use of this catalyst in reactions of a series of 2-nitrobenzaldehydes **184a-e** with both 2-cyclohexen-1-one **180** and 2-cyclopenten-1-one **181** in THF-aqueous 1M $NaHCO_3$. The Baylis-Hillman adducts **185a-e** and **186a-e** were obtained in yields ranging from 39% to 100%, after work-up and flash chromatography (Scheme 63, Table 8). These conditions clearly proved to be effective for these particular substrates. The Baylis-Hillman adducts **185a-e** and **186a-e** were then transformed into the corresponding quinoline derivatives **187a-e** and **188a-e** by treating them with acetic acid and iron powder under reflux for 2 hours (Scheme 63), following a reported methodology by Basavaiah *et al.*[136] In their approach, Baylis-Hillman adducts, derived from 2-nitrobenzaldehydes and methyl vinyl ketone and methyl acrylate, were converted to quinoline derivatives. 2-Styrylquinoline derivatives have exhibited potential as HIV-1 intergrase inhibitors,[213] and it was hoped that the styrylquinoline derivatives **189** might be prepared as possible HIV-1 intergrase inhibitors. Unfortunately, the product yields of the quinoline derivatives **187** and **188** were generally low, except for two cases (**187c** and **188a**), and their conversion to the styrylquinoline derivatives was not pursued.

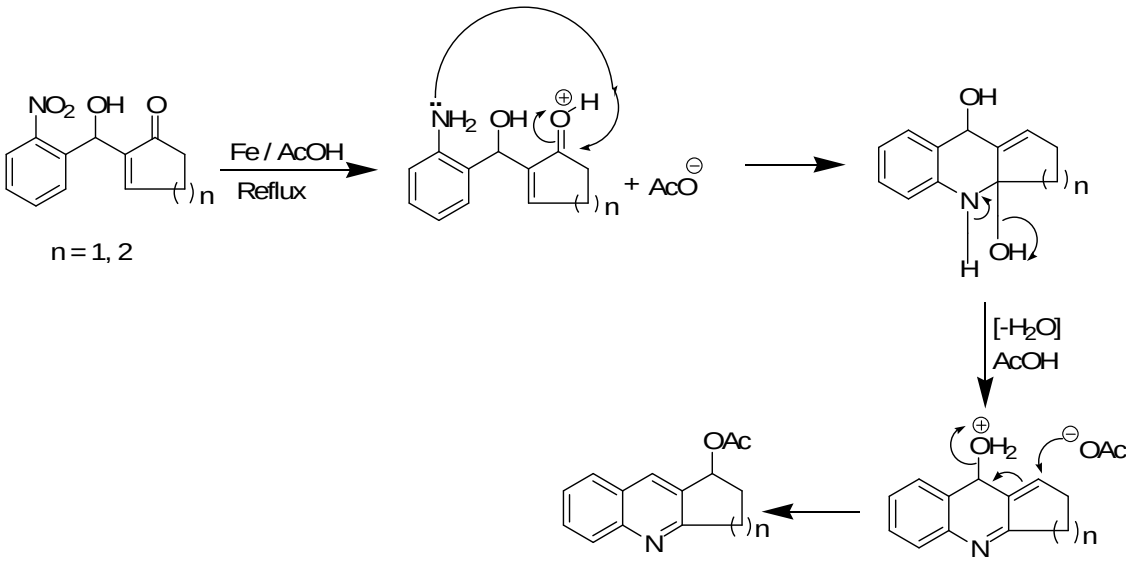
The mechanism proposed for the formation of the quinoline derivatives **187** and **188** is shown in Scheme 64.[136] Reduction of the nitro group to an amine and protonation of the carbonyl group permits cyclization and dehydration *via* nucleophilic addition to the carbonyl group. Acid-catalysed allylic displacement of OH by acetate, then affords the quinoline derivative.[136]



Scheme 63

Table 8. Isolated yields of Baylis-Hillman adducts **185a-e**, **186a-e** and quinoline derivatives **187a-e**.

Aldehyde (184)	R	185 (Yield %)	186 (Yield %)	187 (Yield %)	188 (Yield %)
a	H	66	61	26	71
b	5-OH	79	76	5	18
c	3-OMe	85	98	71	37
d	4,5-OMe	100	97	37	38
e	4,5-OCH_2O	70	97	44	42



Scheme 64

The products **185-188** were all fully characterized by spectroscopic (IR, MS, ^{1}H and ^{13}C NMR) analysis. The ^{1}H NMR spectrum (Figure 22) of the Baylis-Hillman adduct **185a**, derived from 2-nitrobenzaldehyde and 2-cyclohexen-1-one, reveals three multiplets at 1.98, 2.34 and 2.44 ppm corresponding to the 5-, 4-, and 6-methylene protons respectively, a singlet at 6.17 ppm corresponding to the 2" proton, a triplet at 6.61 ppm corresponding to the 3-methine proton and signals for the aromatic protons between 7.42 and 7.90 ppm. The ^{13}C NMR spectrum (Figure 23) reveals 13 carbon signals. The 5, 4- and 6-methylene carbons resonate at 22.4, 25.7 and 38.2 ppm, respectively; the asymmetric carbon 2" resonates at 67.2 ppm, while the aromatic carbons resonate between 124.4 and 148.1 ppm and the carbonyl carbon at 199.7 ppm.

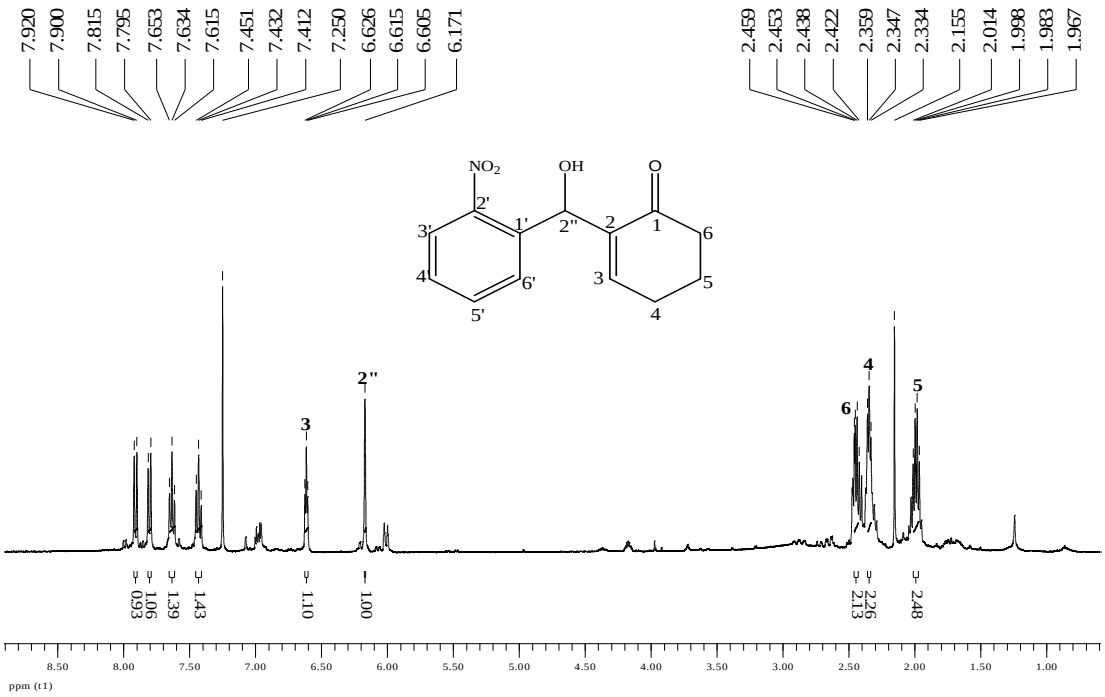


Figure 22. 400 MHz ^{1}H NMR spectrum of Baylis-Hillman adduct **185a** in $CDCl_3$.

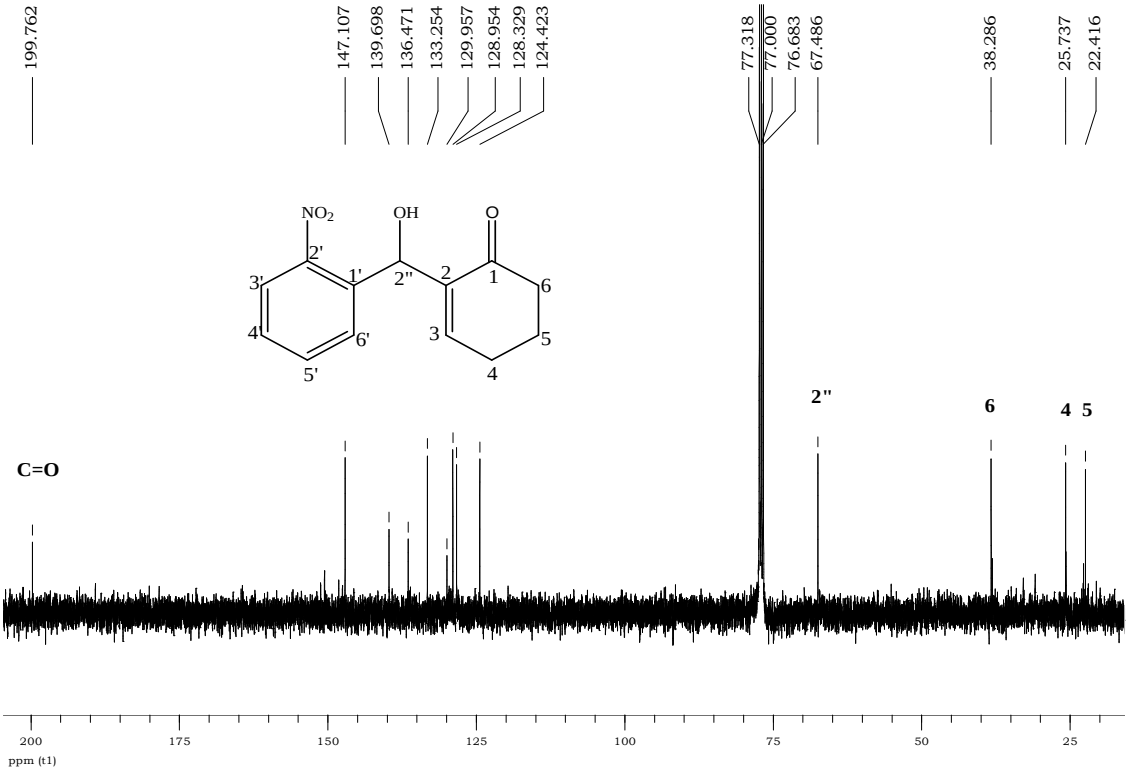


Figure 23. 100 MHz ^{13}C NMR spectrum of Baylis-Hillman adduct **185a** in $CDCl_3$.

The ^{1}H NMR spectrum (Figure 24) of the quinoline derivative **188b** reveals a singlet at 2.08 ppm corresponding to the acetyl methyl group, two multiplets at 2.23 and 2.55 ppm corresponding to the 2-methylene protons, two multiplets at 3.08 and 3.33 ppm to the 3-methylene protons, a multiplet at 6.27 ppm to the 1-methine proton at the chiral centre, a singlet at 8.05 pm to the 4'-methine proton and the remaining aromatic protons between 7.18 and 7.93 ppm. The ^{13}C NMR spectrum (Figure 25) reveals 14 carbon signals. The acetyl methyl group resonates at 21.2 ppm, the 2- and 3-methylene carbons at 30.7 and 31.3 ppm, respectively, the asymmetric carbon, C-1 at 75.7 ppm, the carbonyl group at 171.3 ppm and the rest of the aromatic carbons between 110.0 and 163.0 ppm. The COSY spectrum (Figure 26) was also used to facilitate the assignment of the proton signals. It reveals long range interaction between the 1-methine proton at the chiral centre and the 4'-methine proton, marked X. The HSQC (Figure 27) was also used to facilitate the assignment of the signals. It clearly confirms the signal assignments made in the proton and carbon spectra. The protons resonating at 2.23 and 2.55 ppm are shown to belong to the same carbon (C-2) at 30.7 ppm, the protons at 3.08 and 3.33 ppm both belong to the same carbon (C-3) at 31.3 ppm. The chiral carbon C-1 at 75.7 ppm, corresponds to the 1-methine proton at 6.27 ppm.

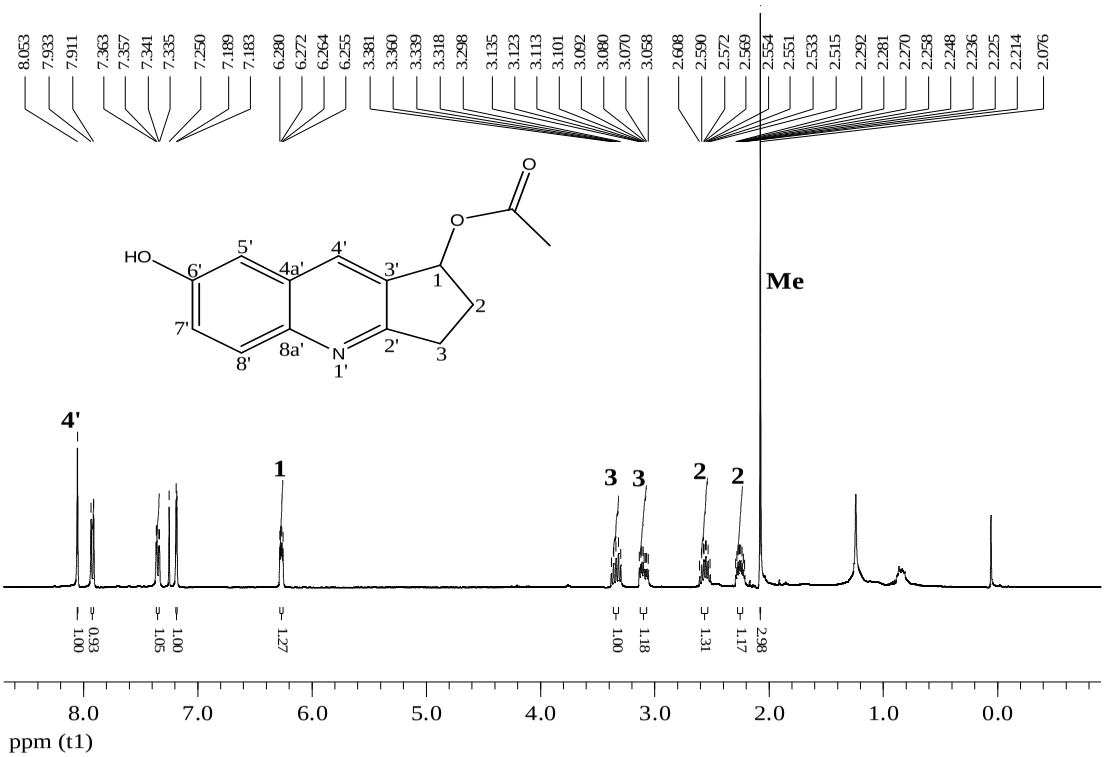


Figure 24. 400 MHz ^{1}H NMR spectrum of the quinoline derivative **188b** in $CDCl_3$.

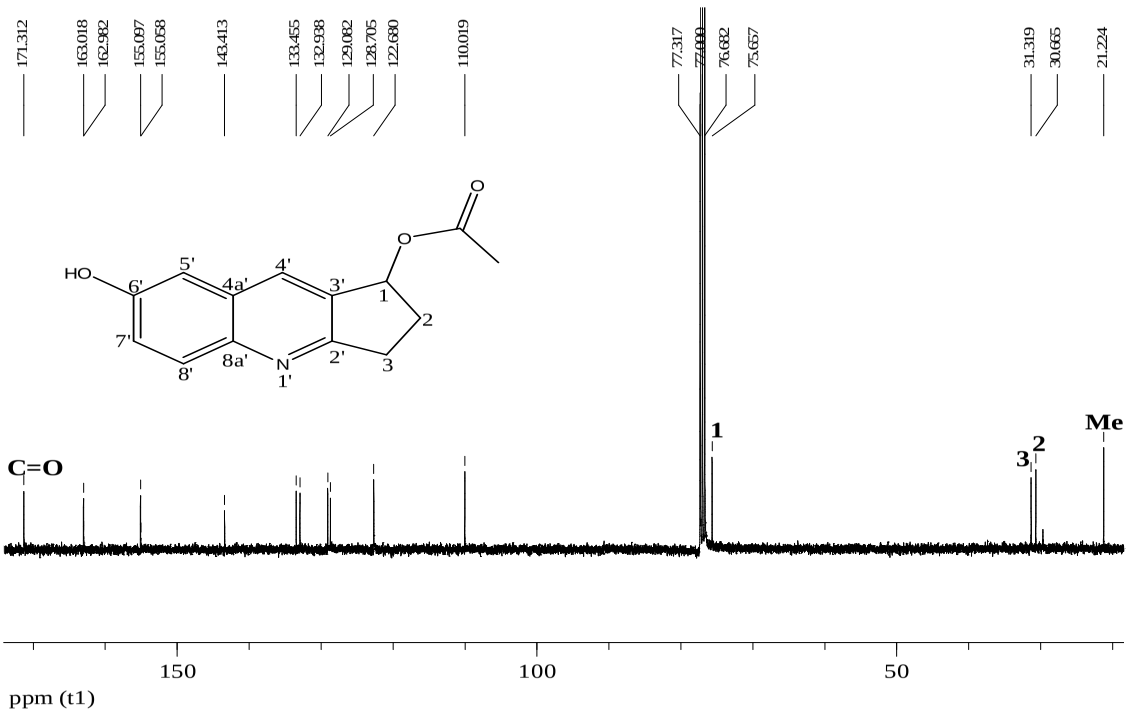


Figure 25. 100 MHz ^{13}C NMR spectrum of the quinoline derivative **188b** in $CDCl_3$.

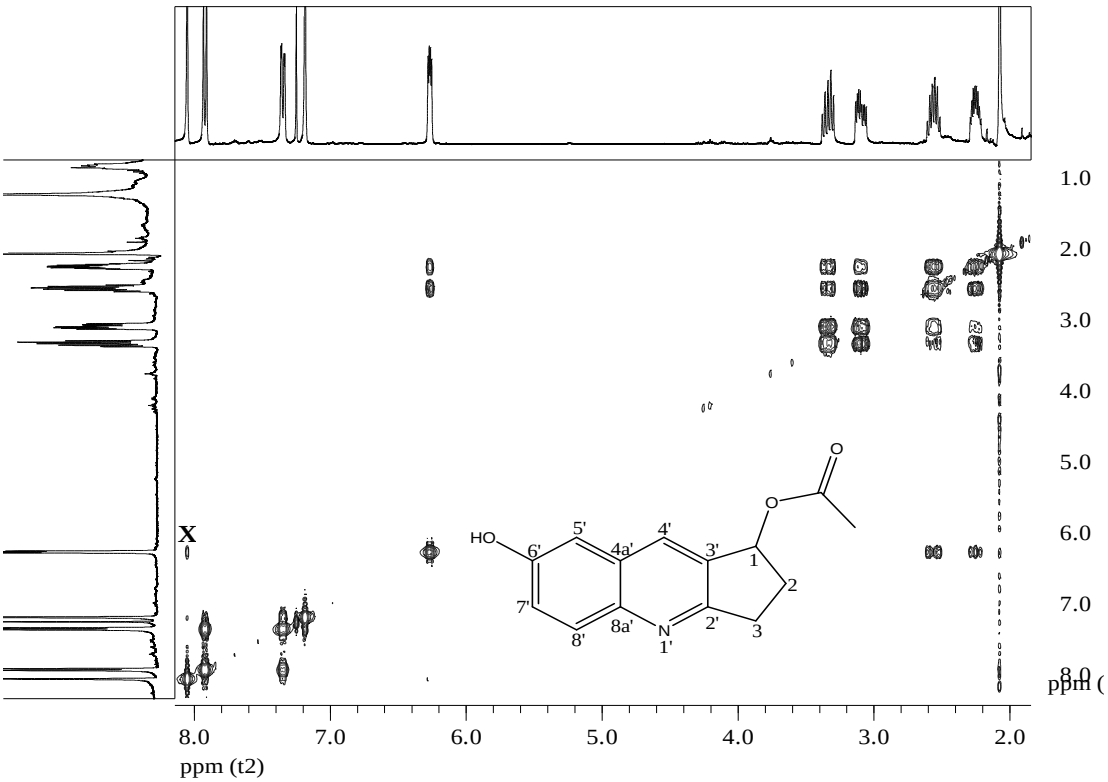


Figure 26. COSY spectrum of the quinoline derivative **188b** in $CDCl_3$.

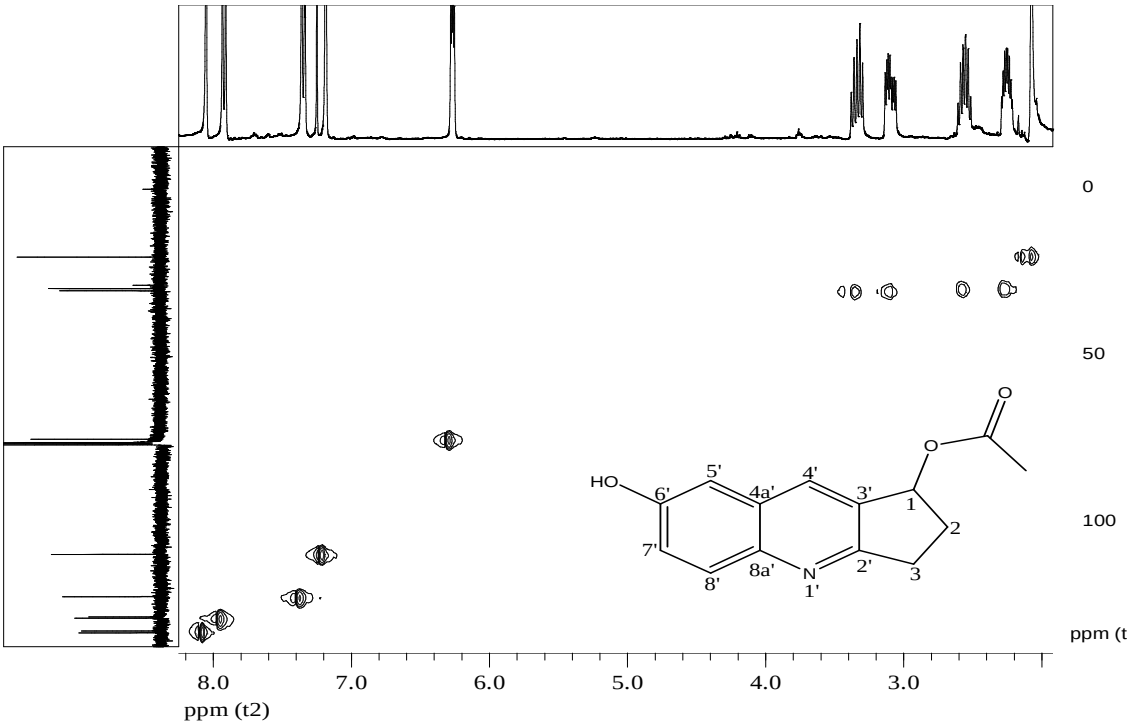
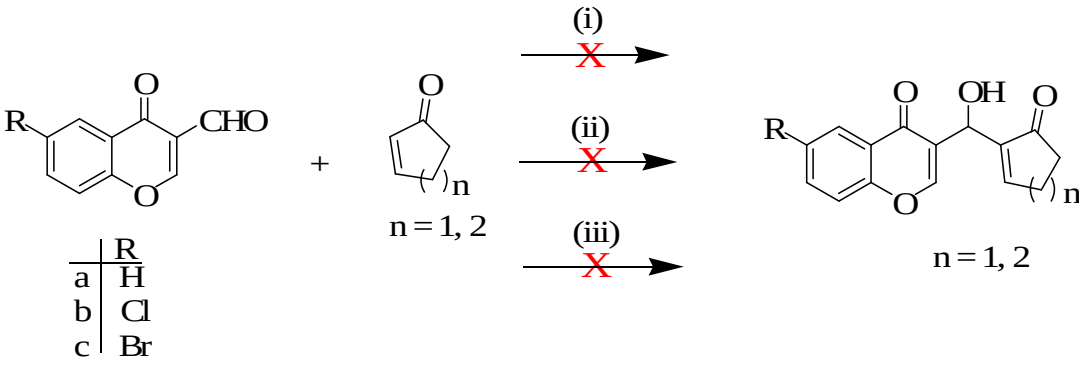


Figure 27. HSQC spectrum of the quinoline derivative **188b** in $CDCl_3$.

2.5.2 Reactions of cyclic enones with chromone-3-carbaldehydes

A series of chromone-3-carbaldehydes were reacted with 2-cyclohexen-1-one and 2-cyclopenten-1-one using imidazole as a catalyst in THF-aqueous 1M-$NaHCO_3$ (1:4 [$^v/_v$]) (Scheme 65). After 7 days of stirring at room temperature both starting materials were recovered unconsumed. The volume of the aqueous solution used in this reaction was greater than that of THF, and it was assumed that the lack of reactivity was due to poor solubility of the chromone-3-carbaldehydes in the solvent system. The reaction conditions were then altered, and the reaction was conducted using TMPDA as catalyst and THF-water (1:1 [$^v/_v$]) as solvent. However, even after 7-10 days of stirring, no product was isolated after work-up, and the starting materials were again recovered unconsumed. It was then presumed that the poor solubility of the chromone-3-carbaldehydes in THF could be the reason for the lack of reaction. The solvent system was then changed to chloroform-water and the reactions were repeated using TMPDA as catalyst. Again, however, after days of stirring the starting materials remained unchanged, although there was a colour change from colourless to red during the course of the reaction. (A similar pattern was also observed with the attempted Baylis-Hillman reactions involving chromone-3-carbaldehydes and chromones, in an attempt to synthesize bis-chromone Baylis-Hillman adducts.)



Scheme 65. **Reagents and conditions**: (i) Imidazole, THF-$NaHCO_3$; (ii) TMPDA, THF-H_2O; (iii) TMPDA, $CHCl_3$-H_2O.

From these observations it was clear that solubility alone was not the problem, and there were other factors inhibiting the reaction. Luo *et al.*[208] and Lee *et al.*[212] have reported that imidazole and TMPDA are good catalysts for Baylis-Hillman reactions involving cyclic enones. We have also shown that, even in reactions that involve chromones as the activated alkenes, these catalysts are effective (See Section 2.5.4). Chromone-3-carbaldehydes are susceptible to nucleophilic attack at three centres, *viz.*, C-2, the formyl carbon and C-4, and it is possible that TMPDA and imidazole might attack the chromone-3-carbaldehydes at C-2 in a conjugate-addition sequence thus decreasing the electrophilicity of the aldehydic carbon, and inhibiting the Baylis-Hillman reaction from taking place as illustrated in Figure 28. Nucleophilic attack at position 2 has also been illustrated by the formation of the interesting tricyclic Baylis-Hillman adduct 166 (Section 2.2.1, Scheme 55).

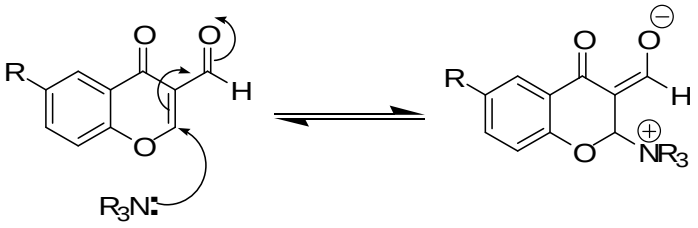


Figure 28

2.5.3 Reactions of cyclic enones with pyridine-2-carbaldehydes and quinoline-2-carbaldehyde

The encouraging results we obtained using imidazole under basic aqueous conditions, following the reported procedure by Luo *et al.*,[208] led us to use these conditions in reactions of 2-cyclohexen-1-one **180** and 2-cyclopenten-1-one **181** with pyridine-2-carbaldehyde **190**, 6-methylpyridine-2-carbaldehyde **191** and quinoline-2-carbaldehyde **200** with the expectation of converting the products to the polycyclic indolizine derivatives **196-199** (Scheme 66). In the event, work-up and flash chromatography

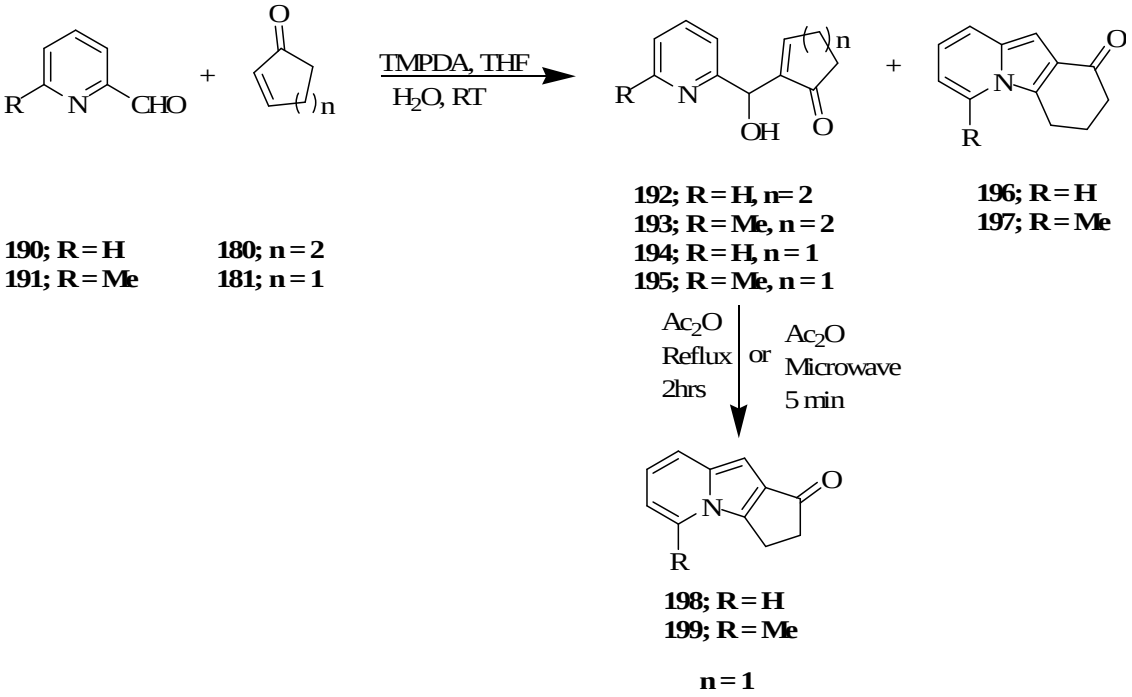
afforded the desired Baylis-Hillman products **192-195**, **201** and **202** in poor to moderate yields (Table 9).

In an alternative approach, reported by Lee *et al.*,[212] we reacted 2-cyclohexen-1-one **180** and 2-cyclopenten-1-one **181** with pyridine-2-carbaldehyde **190**, 6-methylpyridine-2-carbaldehyde **191** and quinoline-2-carbaldehyde **200** using TMPDA as catalyst in a THF-water (1:1[$^{v}/_{v}$]) solution. Work-up and purification afforded the desired Baylis-Hillman adducts **192-195**, **201** and **202** in moderate to good yields (Scheme 66, Table 9). In addition to these Baylis-Hillman adducts, the cyclized indolizine derivatives **196** and **197** were also isolated in 32 and 39% yield, respectively. When the Baylis-Hillman adducts **194**, **195**, **201** and **202** were treated with acetic anhydride under reflux for two hours the indolizine derivatives **198** and **199** were obtained in and 22 and 28% yield, respectively, while **203** and **204** were only obtained in trace amounts (Table 10). It should be noted that the indolizine derivatives **196** and **197** were isolated from the Baylis-Hillman reaction, but no cyclized products were isolated in the Baylis-Hillman reactions involving 2-cyclopenten-1-one **181**.

Microwave synthesis represents a major breakthrough in synthetic chemistry methodology, a dramatic change in the way chemical synthesis is performed. Conventional heating, known to be less efficient and time-consuming, has been recognized to be creatively limiting. Microwave synthesis provides more time to expand scientific creativity, test new theories and develop new processes. Instead of spending hours or even days to synthesize a single compound, now we can perform the same reaction in minutes. Microwave synthesis can be effectively applied to a wide range of reactions, increasing reaction rates, improving yields and purity. In addition, microwave synthesis creates completely new possibilities in performing chemical transformations. Microwaves transfer energy directly to the reactive species, thus promoting transformations that are not possible using conventional heating. Energy is applied directly to the reactants, whilst bulk heating is minimized by use of simultaneous cooling.

A microwave is a form of electromagnetic energy that falls at the lower end frequency of the electromagnetic spectrum. Microwave energy consists of an electric field and a magnetic field, with the former transferring energy to heat the substance. Traditionally, synthesis has been achieved through conductive heating with an external heat source, whereby heat is driven to the substance by first passing it through the walls of the reaction vessels to reach the solvent and the reactants. This is a slow and less efficient process as it depends on the thermal conductivity of the various materials that must be penetrated. Microwave heating, on the other hand, is a very different process, where microwaves couple directly with the molecules in the reaction mixture, leading to a rapid rise in temperature.[214] Microwave synthesis has been applied over a wide range of reactions, which include acetyl hydrolysis,[215] ester hydrolysis,[216] esterification,[217] the Baylis-Hillman reaction[218] and the Diels-Alder reaction.[219,220]

Consequently, this methodology was explored in the cyclisation of cyclic enone- and chromone-derived Baylis-Hillman adducts to afford the corresponding indolizine derivatives. When Baylis-Hillman adducts **194**, **195**, **201** and **202** were treated with acetic anhydride in a microwave reactor for 5 minutes the corresponding indolizine derivatives **198** and **199** were obtained in 49 and 58%, respectively, while indolizine derivatives **203** and **204** were still only obtained in trace amounts (Table 10).



190; R = H
191; R = Me

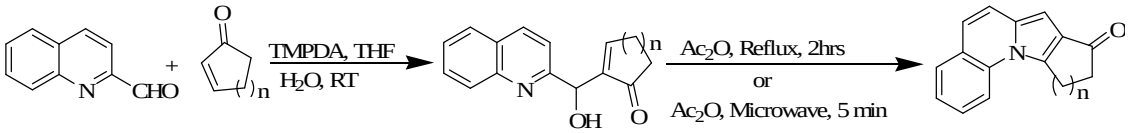
180; n = 2
181; n = 1

192; R = H, n= 2
193; R = Me, n = 2
194; R = H, n = 1
195; R = Me, n = 1

196; R = H
197; R = Me

198; R = H
199; R = Me

n = 1



200

180; n = 2
181; n = 1

201; n = 2
202; n = 1

203; n = 2
204; n = 1

Scheme 66

Table 9. Isolated yields of Baylis-Hillman adducts **192-195, 201 and 202**.

Aldehyde	R	Enone (n = 1, 2)	B-H adduct	Yield (%) using imidazole	Yield (%) using TMPDA
190	**H**	**2**	**192**	23	40
191	**Me**	**2**	**193**	28	43
190	**H**	**1**	**194**	34	77
191	**Me**	**1**	**195**	30	56
200	**-**	**2**	**201**	24	40
200	**-**	**1**	**202**	27	44

Table 10. Isolated yields of indolizine derivatives **196-199**, **203** and **204** obtained under reflux and under microwave-assisted conditions.

Indolizine	Yield (%) [RT, in water]	Yield (%) [under reflux]	Yield (%) [under microwave]
196	32	-	-
197	39	-	-
198	-	22	49
199	-	28	58
203	-	trace	trace
204	-	trace	trace

As mentioned earlier, DABCO is a poor catalyst for Baylis-Hillman reactions involving cyclic enones,[153,154] and it has been suggested that the increased reaction rates observed when using TMPDA as a catalyst may be attributed to a number of factors, *viz*:[212]

i) the presence of two equivalents of Lewis base sites (as in DABCO);

ii) flexibility and relatively little steric hindrance and flexibility around the nitrogen atom; and

iii) the stabilizing effect of the zwitterionic intermediates by intramolecular ion-dipole interaction, as shown in Figure 29 below.

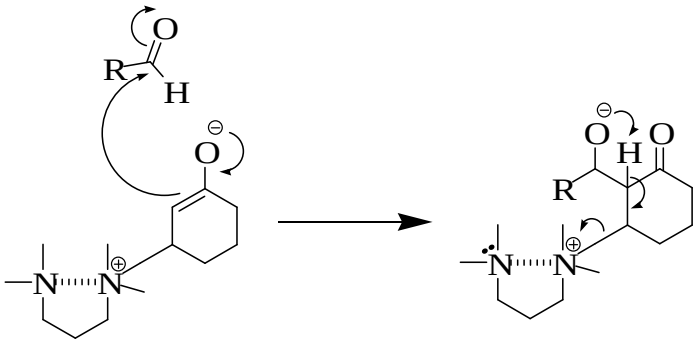


Figure 29

The ^{1}H NMR spectrum (Figure 30) of the Baylis-Hillman adduct **194** derived from pyridine-2-carbaldehyde and 2-cyclopenten-1-one reveals two multiplets at *ca* 2.4 and 2.6 ppm corresponding to the 4- and 5-methylene protons, respectively, a broad singlet at 5.05 ppm corresponding to the hydroxyl group (OH), a singlet at 5.56 ppm corresponding to the 2”-proton, a triplet at 7.17 ppm corresponding to the 3-methine proton and the rest of the aromatic protons between 7.46 and 8.49 ppm. The ^{13}C NMR spectrum (Figure 31) reveals the expected 11 carbon signals. The 4- and 5-methylene carbons resonate at 26.6 and 35.3 ppm respectively and the asymmetric carbon C-2” resonates at 68.2 ppm; the vinylic and aromatic carbons resonate between 121 and 160 ppm, while the carbonyl carbon resonates at 208.8 ppm. Similar patterns were observed in the spectra of the Baylis-Hillman adduct **195** derived from 6-methylpyridine-2-carbaldehyde and 2-cyclopenten-1-one.

The ^{1}H NMR spectrum (Figure 32) of the corresponding indolizine derivative **198** reveals two multiplets at *ca* 3.0 and 3.1 ppm corresponding to the 3- and 2-methylene protons, respectively, and a singlet at 6.50 ppm corresponding to the 1’-methine proton. The ^{13}C NMR spectrum (Figure 33) reveals the expected 11 carbon signals, with the 3- and 2-methylene carbons resonating at 19.8 and 41.2 ppm respectively, the 1’-methine carbon at 91.9 ppm, the vinylic and aromatic carbons resonate between 111.8 and 147.7 ppm and the carbonyl carbon at 198.6 ppm.

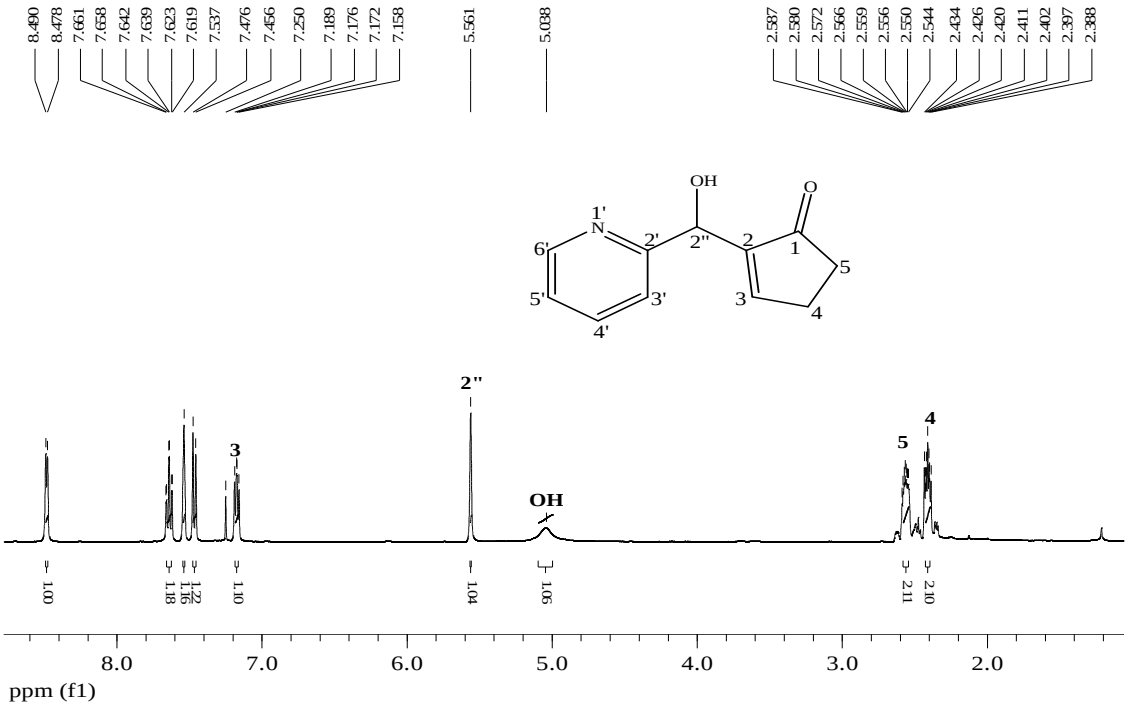


Figure 30. 400 MHz ^{1}H NMR spectrum of Baylis-Hillman adduct **194** in $CDCl_3$.

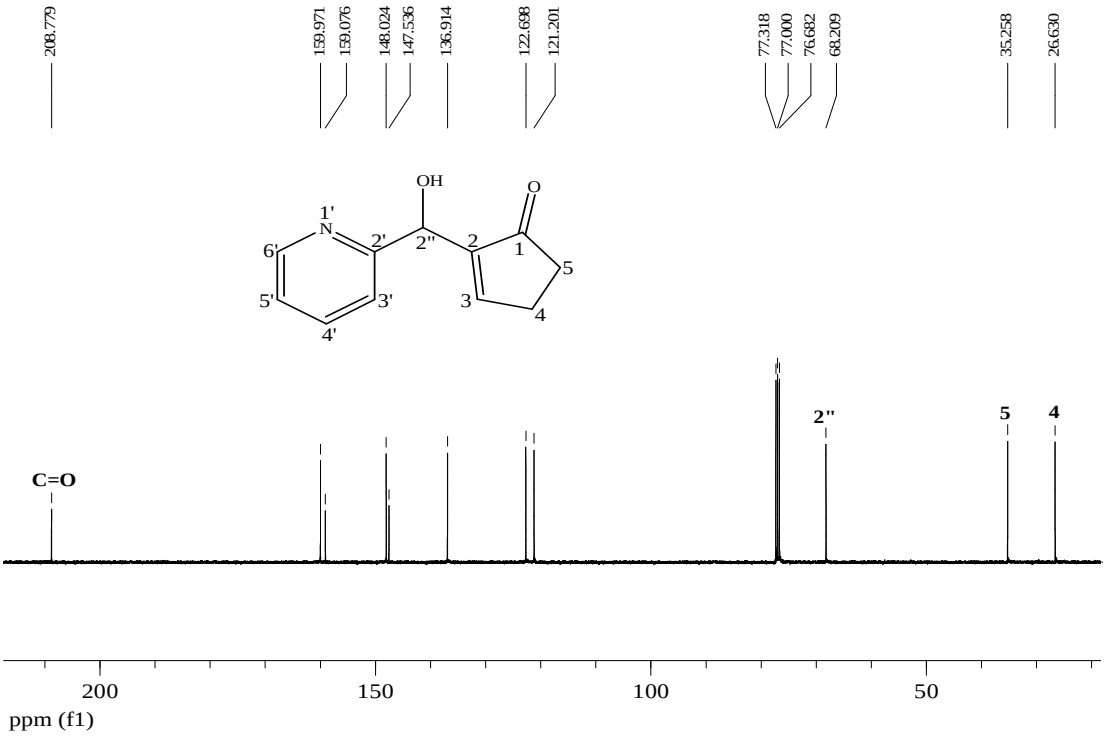


Figure 31. 100 MHz ^{13}C NMR spectrum of Baylis-Hillman adduct **194** in $CDCl_3$.

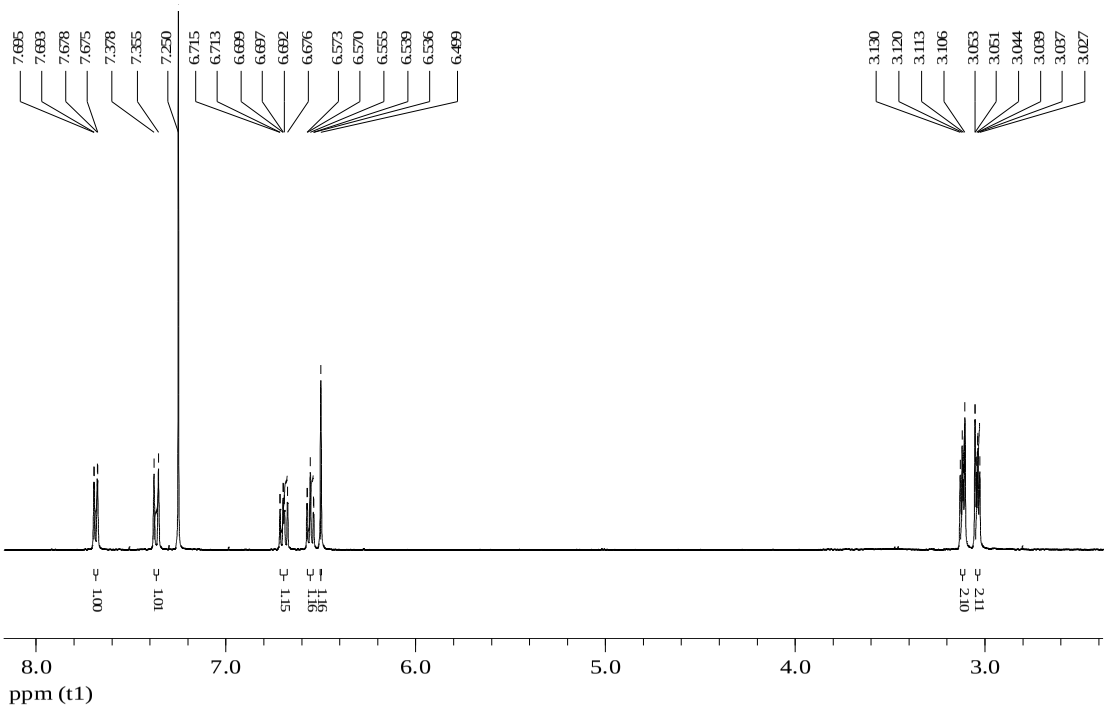


Figure 32. 400 MHz ^{1}H NMR spectrum of the indolizine derivative **198** in $CDCl_3$.

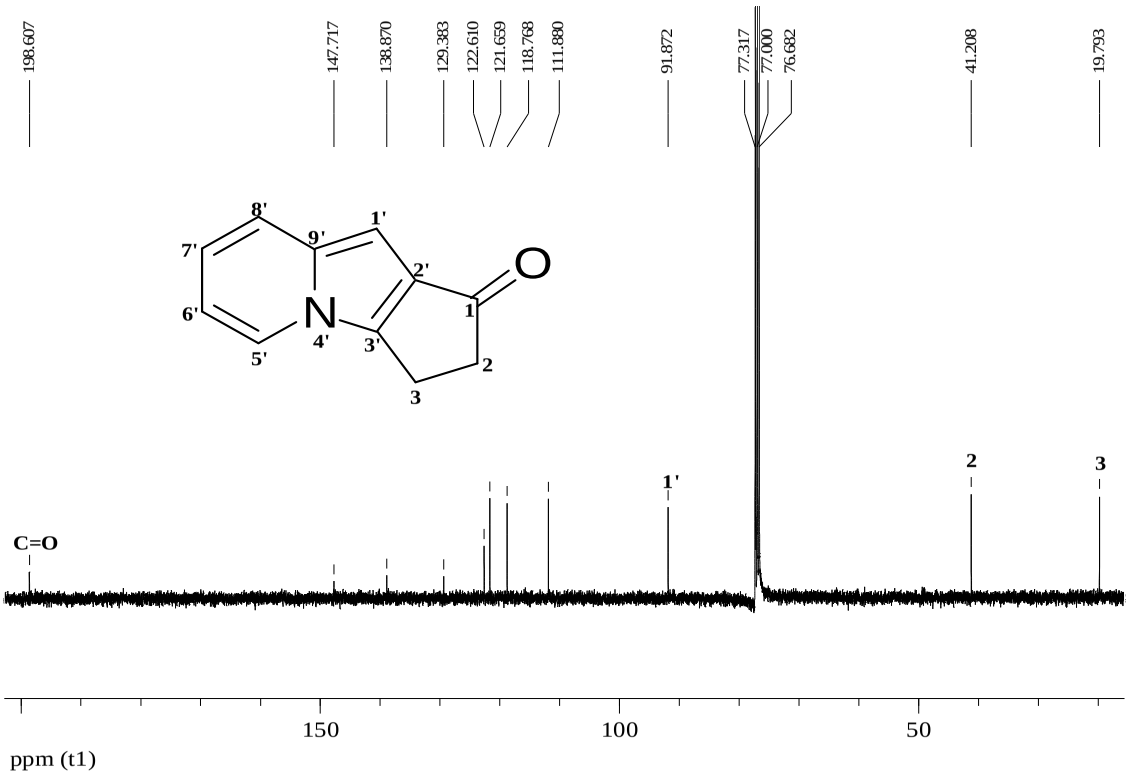


Figure 33. 100 MHz ^{13}C NMR spectrum of the indolizine derivative **198** in $CDCl_3$.

The Baylis-Hillman reaction between pyridine-2-carbaldehydes and 2-cyclohexen-1-one afforded two products after purification by flash chromatography- the expected Baylis-Hillman products **192** and **193** and the corresponding indolizine derivatives **196** and **197** produced *in situ* cyclisation.

The ^{1}H NMR spectrum (Figure 34) of the first fraction isolated from the reaction of pyridine-2-carbaldehyde with 2-cyclohexen-1-one confirmed the formation of the indolizine derivative **196** revealing a multiplet at 2.30 ppm corresponding to the 3-methylene protons, a triplet at 2.62 ppm corresponding to the 2-methylene protons, a triplet at 2.96 ppm corresponding to the 4-methylene protons, two triplets at 6.56 and 6.66 ppm corresponding to the 6'- and 7'-methine protons respectively, a singlet at 6.75 ppm corresponding to the 1'-methine proton and two doublets at 7.36 and 7.64 ppm corresponding to the 5'- and 8'-methine protons respectively. The ^{13}C NMR spectrum (Figure 35) reveals the expected 12 carbon signals. The C-4, C-3 and C-2 methylene carbons resonate at 21.0, 23.6 and 38.6 ppm, respectively, the C-1' methine carbon resonates at 95.4 ppm, the aromatic carbons between 112.2 and 132.9 ppm and the carbonyl carbon resonates at 196.1 ppm. The COSY spectrum (Figure 36) was used to assign all the signals, and from this NMR data it was clear that this particular fraction is that of the cyclized Baylis-Hillman adduct, the indolizine derivative **196**, since no singlet is observed at *ca* 5.6 ppm corresponding to the 2"-methine proton. In addition no interaction is observed in the COSY spectrum (Figure 36) between the vinylic protons and the methylene protons, as would be the case in Baylis-Hillman adducts. A similar NMR signal pattern was observed for the indolizine derivative **197** obtained from the Baylis-Hillman reaction involving 6-methylpyridine-2-carbaldehyde and 2-cyclohexen-1-one.

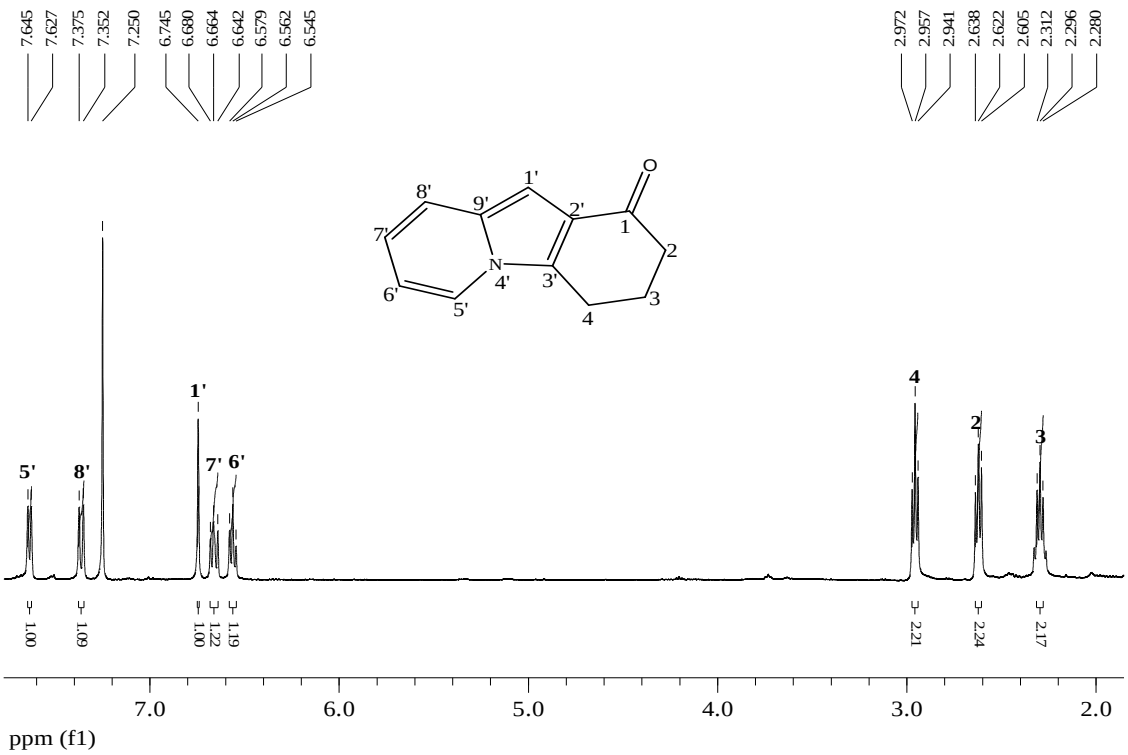


Figure 34. 400 MHz ^{1}H NMR spectrum of the indolizine derivative **196** in $CDCl_3$.

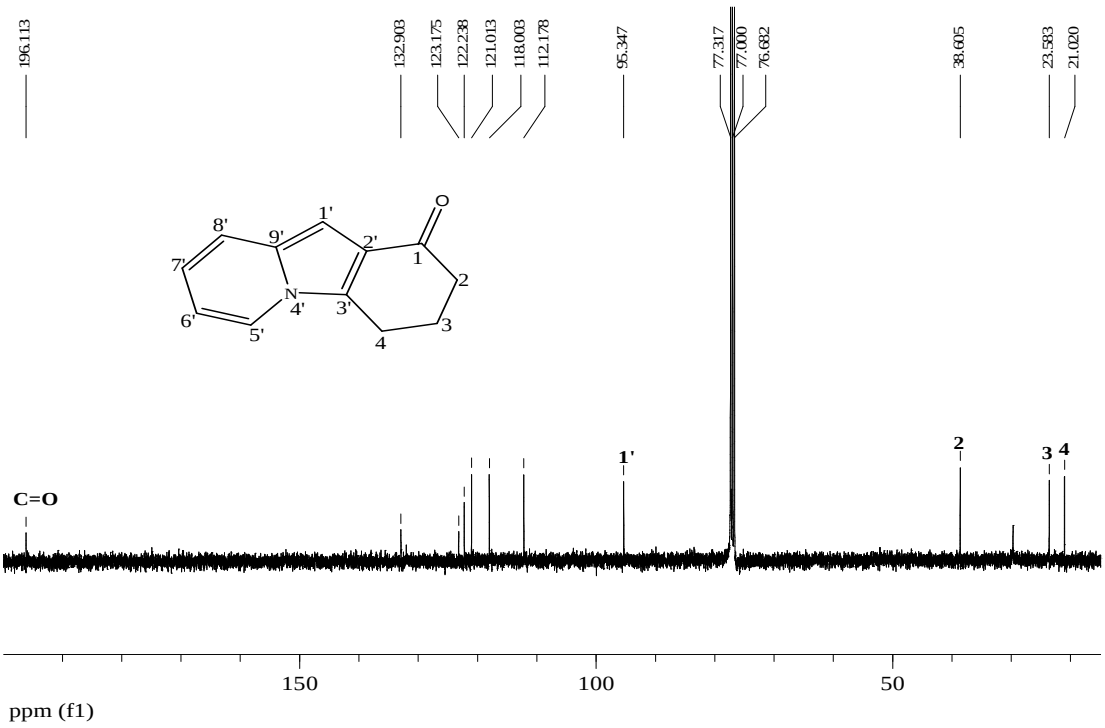


Figure 35. 100 MHz ^{13}C NMR spectrum of the indolizine derivative **196** in $CDCl_3$.

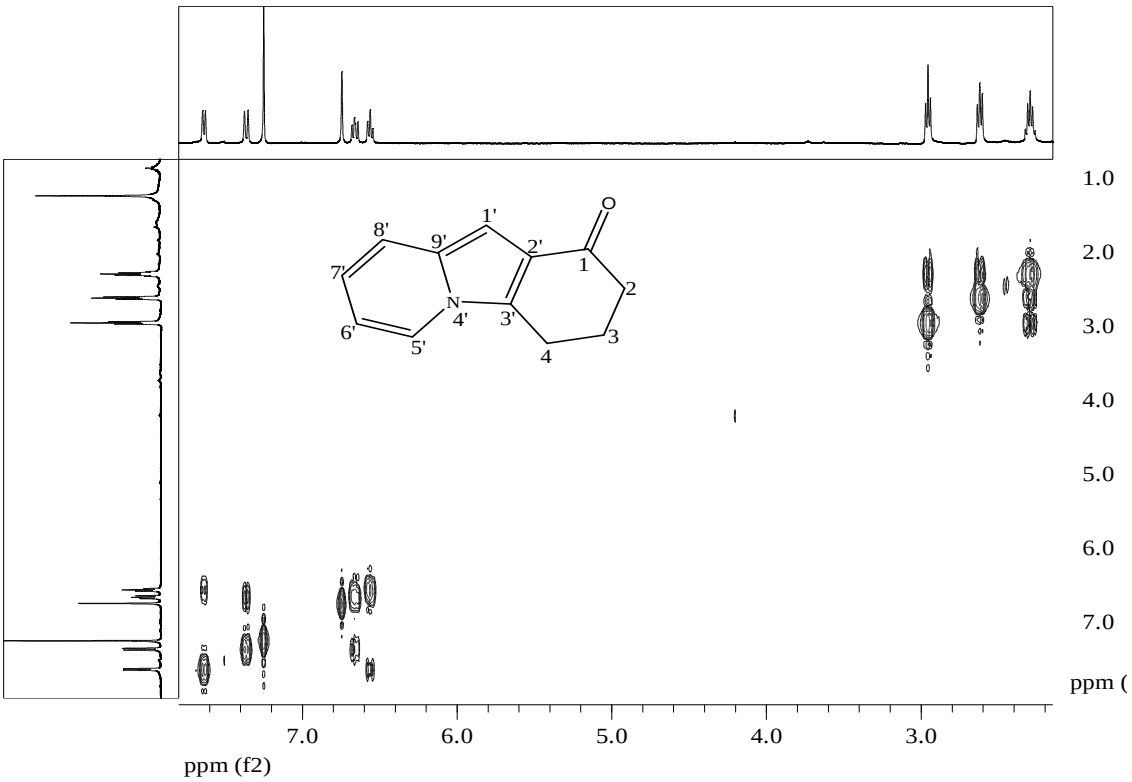


Figure 36. COSY spectrum of the indolizine derivative **196** in $CDCl_3$.

The ^{1}H NMR spectrum (Figure 37) of the Baylis-Hillman adduct **192**, isolated as the second fraction reveals a multiplet at *ca* 2.00 ppm corresponding to the 5-methylene protons, a multiplet at *ca* 2.4 ppm corresponding to the 4- and 6-methylene protons, a broad singlet at 4.85 ppm corresponding to the hydroxyl group (OH), a singlet at 5.66 ppm corresponding to the 2"-methine proton, a triplet at 7.02 ppm corresponding to the 3-methine proton and the aromatic protons resonating between 7.15 and 8.50 ppm. The ^{13}C NMR spectrum (Figure 38) reveals the expected 12 carbon signals. The C-5, C-4 and C-6 methylene carbons resonate at 22.5, 25.8 and 38.5 ppm, respectively, the C-2" asymmetric carbon resonates at 70.2 ppm, while the aromatic carbons resonate between 121.3 and 160.2 ppm and the carbonyl carbon at 199.5 ppm. A similar pattern was observed in the Baylis-Hillman adduct **193** derived from 6-methylpyridine-2-carbaldehyde and 2-cyclohexen-1-one.

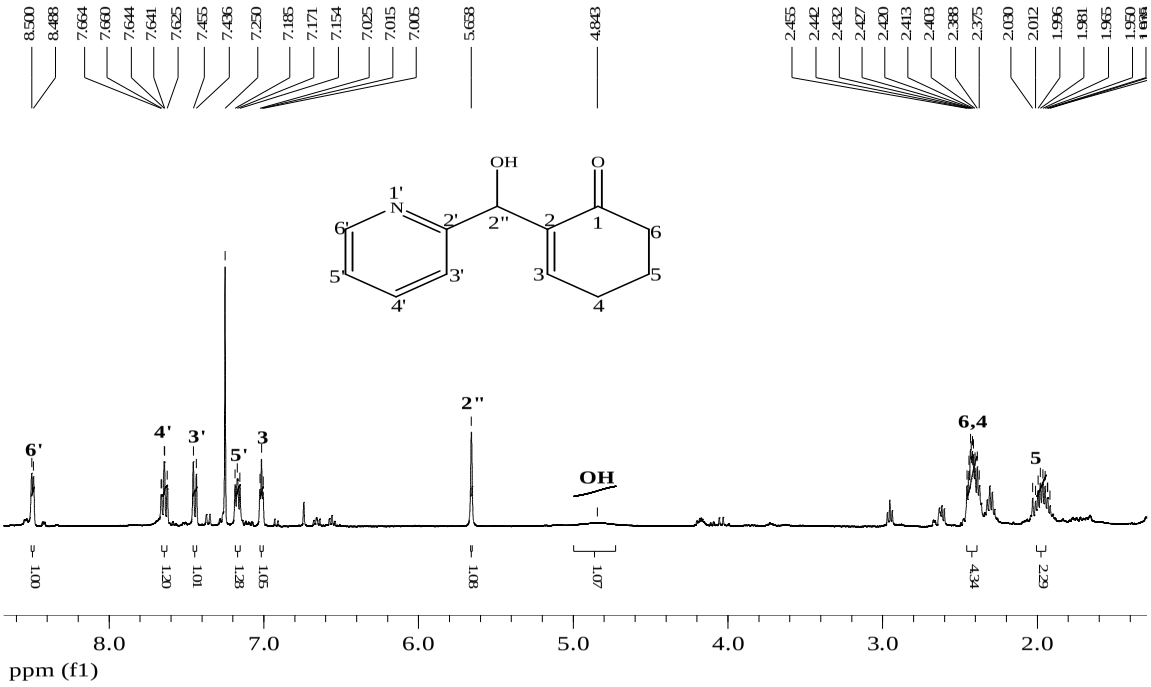


Figure 37. 400 MHz ^{1}H NMR spectrum of Baylis-Hillman adduct **192** in $CDCl_3$.

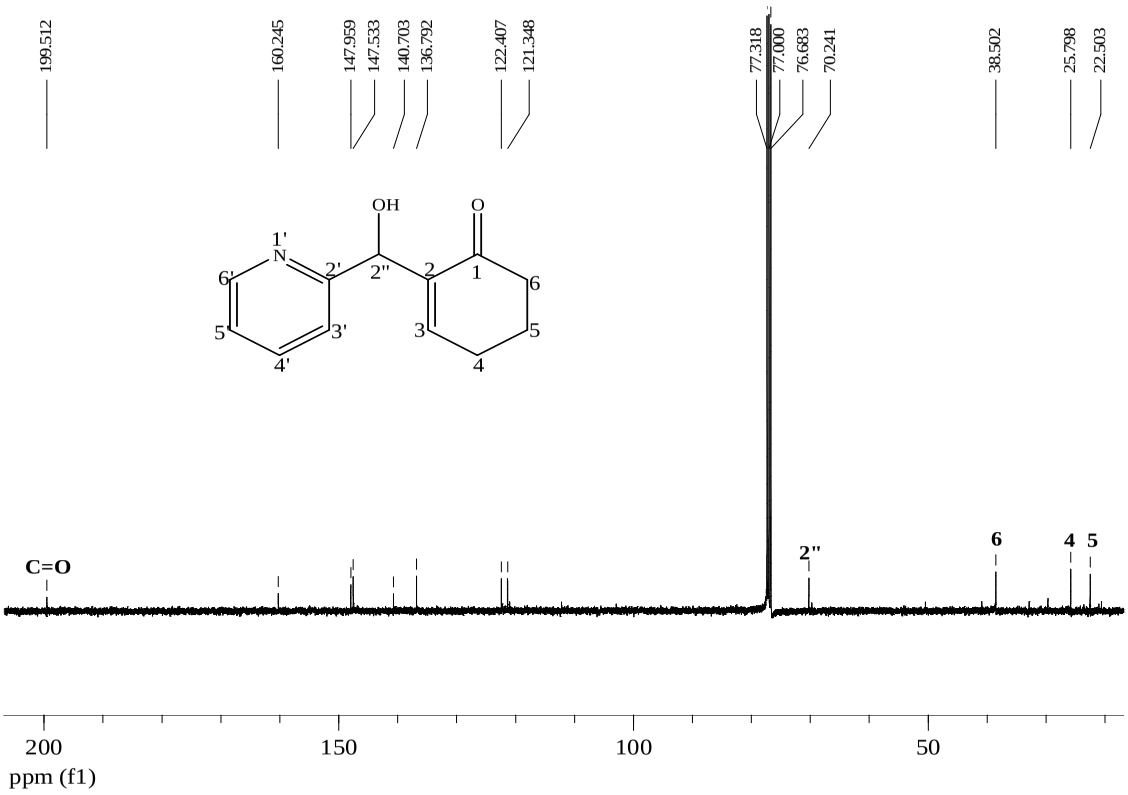
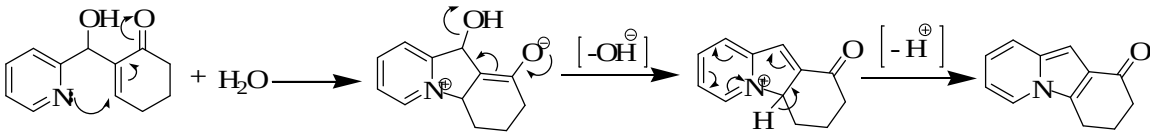


Figure 38. 100 MHz ^{13}C NMR spectrum of Baylis-Hillman adduct **192** in $CDCl_3$.

As indicated above, water enhances the rate of the Baylis-Hillman reaction[212] and it was used for that purpose in these reactions. The synthesis of indolizine derivatives from Baylis-Hillman adducts derived from pyridine-2-carbaldehydes involves the treatment of the Baylis-Hillman adducts with acetic anhydride under reflux for two hours. Water not only enhanced the rate of the reaction between pyridine-2-carbaldehydes and 2-cyclohexen-1-one, but also facilitated the *in situ* conversion of the Baylis-Hillman adducts **192** and **193** to the corresponding indolizine derivatives **196** and **197**. However, the *in situ* cyclisation step was not observed for the Baylis-Hillman reaction involving the pyridine-2-carbaldehydes and 2-cyclopenten-1-one (Scheme 66). It is not certain why the cyclisation of the Baylis-Hillman adducts to the corresponding indolizine derivatives is only limited to the reactions involving 2-cyclohexen-1-one, but the angle-strain effects might well inhibit *in situ* cyclisation of the 2-cyclopenten-1-one analogues. The mechanism for the formation of the indolizine derivatives **196** and **197** is presumed to follow the sequence illustrated in Scheme 67. The aqueous medium may be expected to stabilize the ionic species involved and thus facilitate the cyclization of the Baylis-Hillman adduct to the corresponding indolizine derivative.

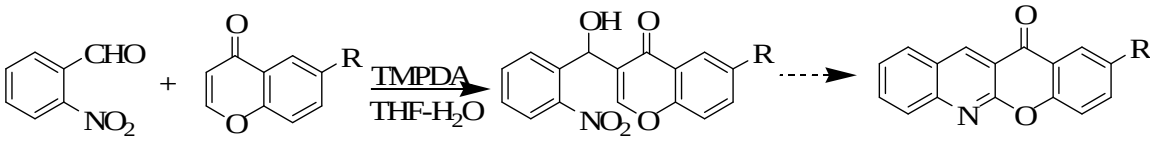


Scheme 67.

2.5.4 Reactions with chromones as cyclic enones

A series of chromone derivatives were also reacted with pyridine-2-carbaldehyde and 6-methylpyridine-2-carbaldehyde, using imidazole as catalyst in THF-aqueous 1M $NaHCO_3$ for 36 hours, but with disappointing results. Only small traces of the chromone-derived products were observed on the TLC plate; starting materials were largely unconsumed. It was expected that these chromone-derived Baylis-Hillman adducts would be converted to the corresponding polycyclic indolizine derivatives **210** and **211**, referred to as benzofluorenones . However, it should be noted that the largely aqueous solvent mixture results in poor solubility of the chromone derivatives and, hence, little or no reaction takes place even over prolonged periods. When starting materials and reagents were dissolved in THF, the addition of aqueous $NaHCO_3$ resulted in the precipitation of the chromone derivatives, thus inhibiting reaction.

However, when 2-nitrobenzaldehyde **184a** and was reacted with the chromones **205a** and **205b** using TMPDA as catalyst in a THF-water (1:1[v/v]) solution, the Baylis-Hillman adducts **206a** and **206b** were obtained in yields of 32% and 48%, respectively, (Scheme 68, Table 11). These Baylis-Hillman adducts **206a** and **206b** are potential starting materials for the synthesis of the fused quinoline-chromone systems **207a** and **207b**. However, due to time constraints, the last step could not be carried out (Scheme 67).



184a **205a; R = H** **205b; R = Cl** **206a; R = H** **206b; R = Cl** **207a; R = H** **207b; R = Cl**

Scheme 68

Table 11. Isolated yields for the Baylis-Hillman adducts **206a** and **206b**.

Product	R	Yield (%)
206a	**H**	32
206b	**Cl**	48

The ^{1}H NMR spectrum (Figure 39) of the Baylis-Hillman adduct **206a** reveals a singlet at 6.50 ppm corresponding to the 2”-methine proton on the chiral carbon, a singlet at 7.77 ppm corresponding to the 2-methine proton and the aromatic protons between 7.39 and 8.19 ppm. The ^{13}C NMR spectrum (Figure 40) reveals the expected 16 carbon signals. The distinct and significant signals at 66.3 and 177.9 ppm correspond to the chiral carbon (C-2”) and the carbonyl carbon, respectively. The remaining carbon atoms resonate between 118.2 and 156.3 ppm.

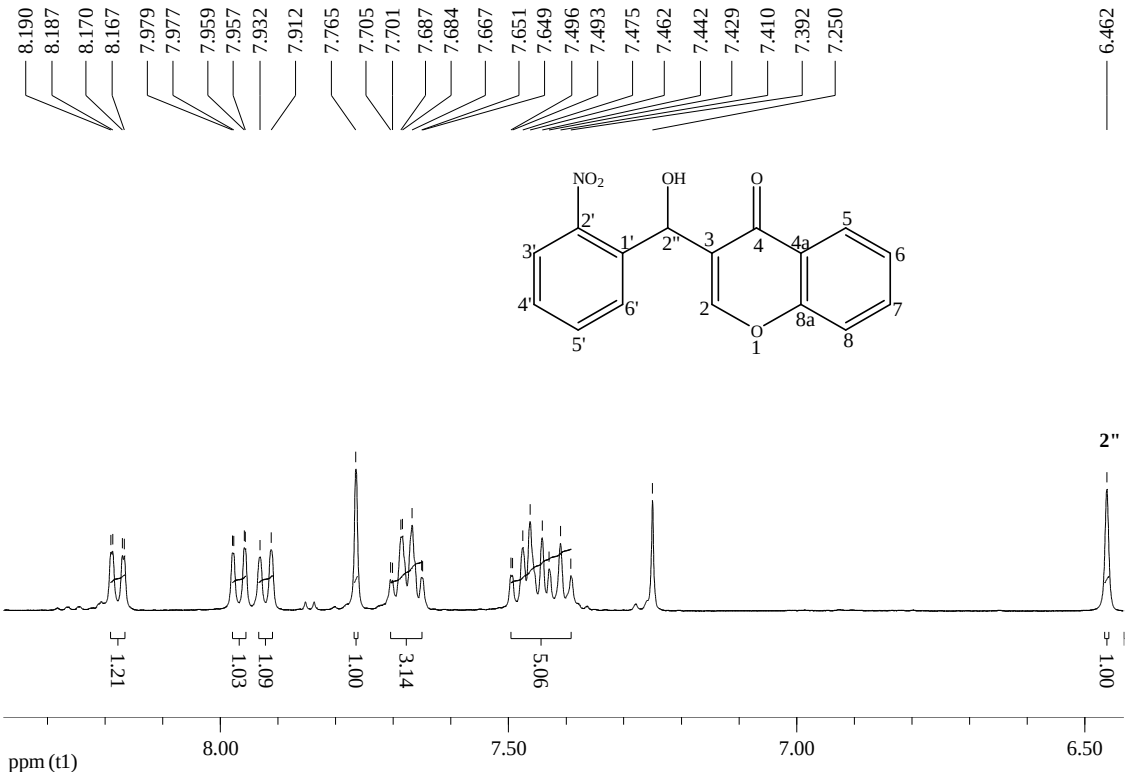


Figure 39. 400 MHz ^{1}H NMR spectrum of Baylis-Hillman adduct **205a** in $CDCl_3$.

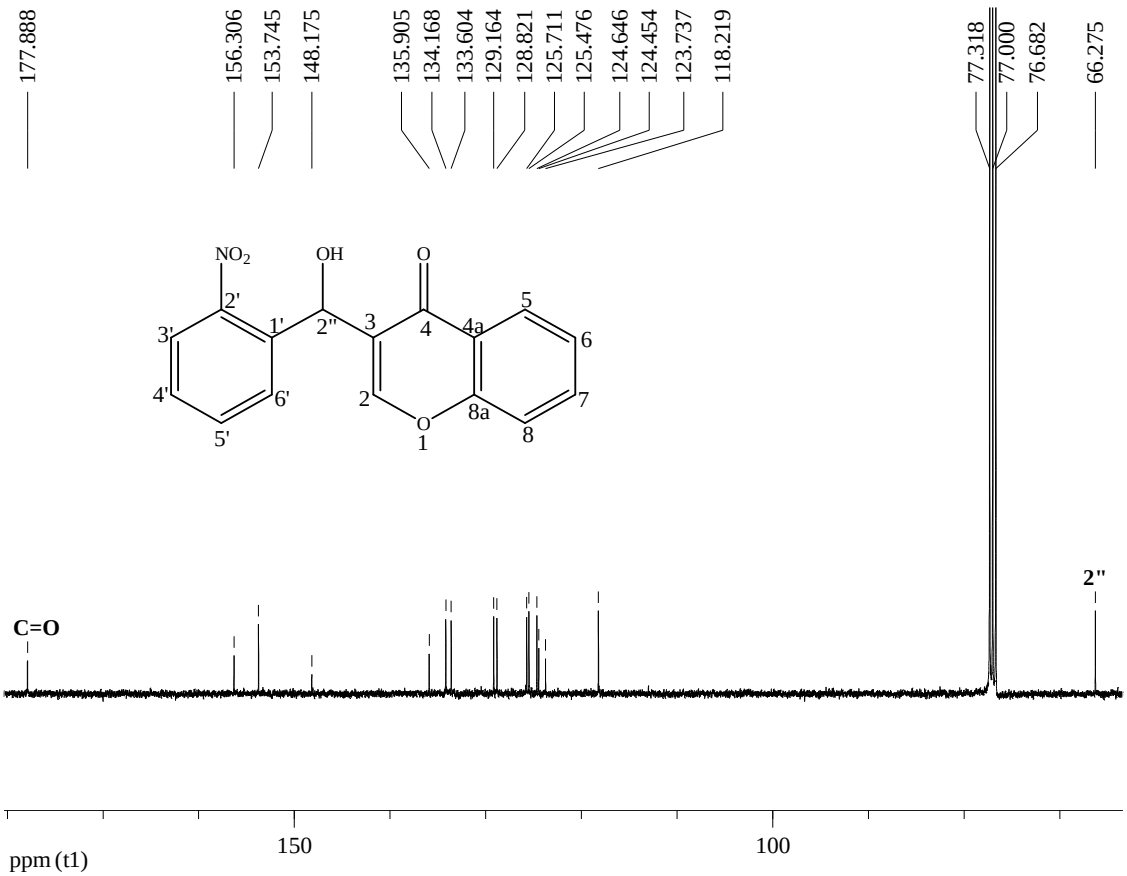
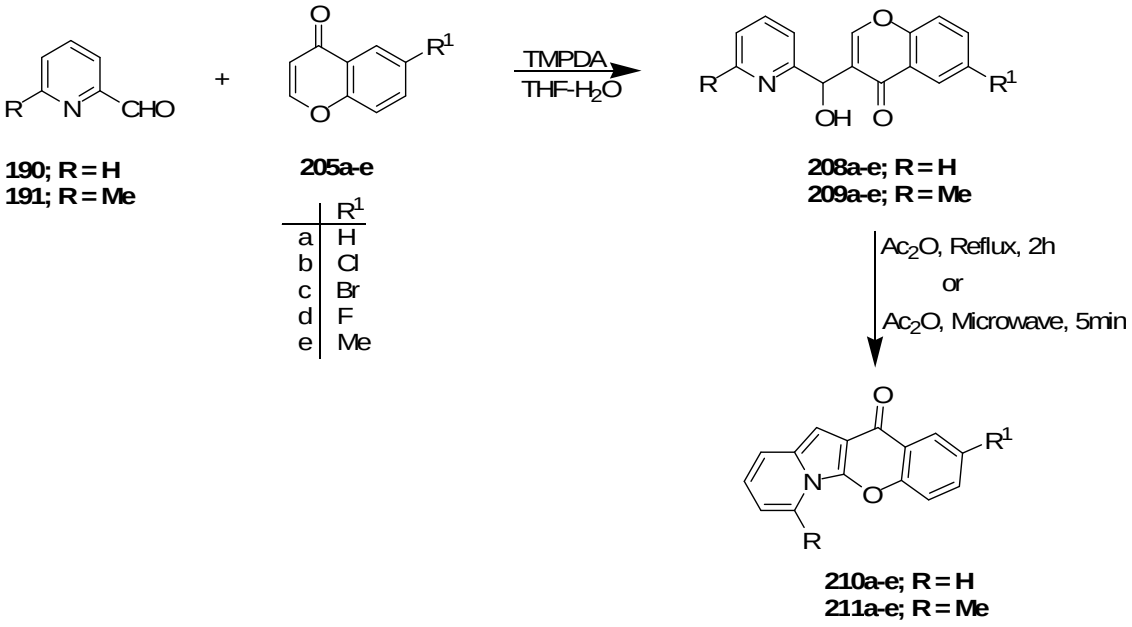


Figure 40. 100 MHz ^{13}C NMR spectrum of Baylis-Hillman adduct **205a** in $CDCl_3$.

Given the success of the TMPDA/THF-water system in these reactions, the series of chromones **205a-e** were similarly reacted with pyridine-2-carbaldehyde **190**, 6-methylpyridine-2-carbaldehyde **191** and quinoline-2-carbaldehyde **212**. Work-up and purification afforded the desired Baylis-Hillman adducts **208a-e**, **209a-e** and **213a-e** in good to excellent yields (Schemes 69, Table 12). The Baylis-Hillman adducts **208a-e**, **209a-e** and **213a-e** were then treated with acetic anhydride under reflux for 2 hours to afford the corresponding indolizine derivatives **210a-e**, **211a-e** and **214a-e** in moderate to good yields (Scheme 70, Table 13).

The cyclisation reactions were repeated in a microwave reactor for 5 minutes affording the indolizine derivatives **210a-e**, **211a-e** and **214a-e** in good to excellent yields (Scheme 70, Table 13). It should be noted that the indolizine derivatives prepared in the microwave reactor were cleaner and very bright in colour; in addition, the product yields

were, in all cases, better than those obtained under reflux. The microwave-assisted approach thus provides a definite improvement in terms of time, yield and purity for the synthesis of these indolizine derivatives.



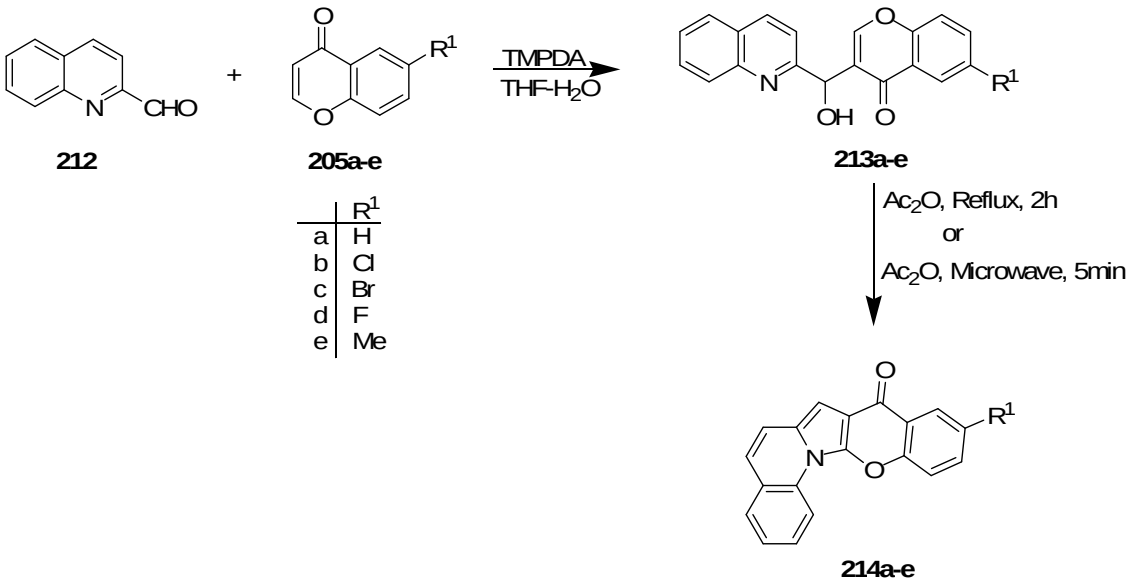
190; R = H
191; R = Me

205a-e

	R^1
a	H
b	Cl
c	Br
d	F
e	Me

208a-e; R = H
209a-e; R = Me

210a-e; R = H
211a-e; R = Me



212

205a-e

	R^1
a	H
b	Cl
c	Br
d	F
e	Me

213a-e

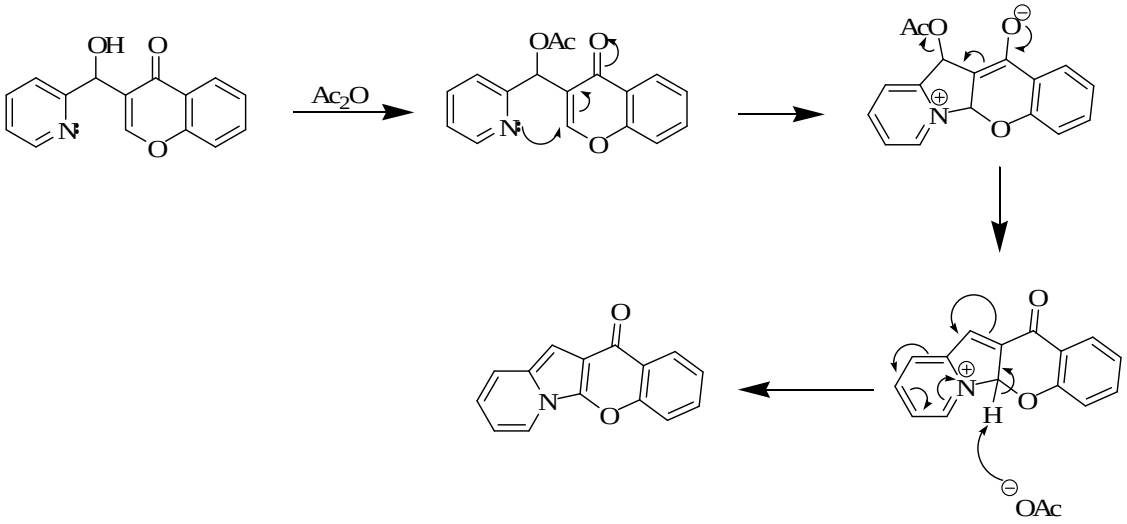
214a-e

Scheme 69

Table 12. Isolated yields of Baylis-Hillman adducts **208, 209** and **213**

Product	R	R^1	Yield (%)
208a	**H**	**H**	64
208b	**H**	**Cl**	58
208c	**H**	**Br**	80
208d	**H**	**F**	83
208e	**H**	**Me**	68
209a	**Me**	**H**	81
209b	**Me**	**Cl**	40
209c	**Me**	**Br**	62
209d	**Me**	**F**	42
209e	**Me**	**Me**	39
213a	**-**	**H**	68
213b	**-**	**Cl**	62
213c	**-**	**Br**	65
213d	**-**	**F**	56
213e	**-**	**Me**	67

A mechanism for the formation of indolizines from Baylis-Hillman adducts has been proposed by our group,[106,107] and is illustrated in Scheme 70. Acetylation of the hydroxide group, makes it a better leaving group compared to the hydroxide ion as in Scheme 67. Nucleophilic attack by the pyridyl nitrogen on the α,β-unsaturated system, in a conjugate addition elimination sequence is followed by rearrangement to afford the indolizine derivative.



Scheme 70

Table 13. Isolated yields of indolizine derivatives **210**, **211** and **214** obtained under reflux and under microwave-assisted conditions.

Product	**R**	**R^1**	**Yield (%) Reflux (2hrs)**	**Yield (%) Microwave (5min)**
210a	**H**	**H**	61	90
210b	**H**	**Cl**	56	74
210c	**H**	**Br**	44	52
210d	**H**	**F**	46	58
210e	**H**	**Me**	44	58
211a	**Me**	**H**	30	65
211b	**Me**	**Cl**	38	63
211c	**Me**	**Br**	53	80
211d	**Me**	**F**	42	48
211e	**Me**	**Me**	34	46
214a	-	**H**	38	50
214b	-	**Cl**	42	58
214c	-	**Br**	54	70
214d	-	**F**	39	53
214e	-	**Me**	36	57

All of the products detailed in Scheme 69 and Tables 12 and 13 were fully characterized, and the NMR data is illustrated by the following examples. The ^{1}H NMR spectrum (Figure 41) of the Baylis-Hillman adduct **208d**, derived from pyridine-2-carbaldehyde and 6-fluorochromone reveals a singlet at 5.99 ppm corresponding to the 2"-methine proton on the asymmetric carbon, a singlet at 8.08 ppm corresponding to the 2-methine proton and the remaining aromatic protons between 7.18 and 8.51 ppm. The ^{13}C NMR spectrum (Figure 42) reveals the expected 15 carbon signals. The asymmetric carbon C-2" resonates at 68.3 ppm, while the remaining aromatic carbons resonate between 110.6 and 160.7 ppm, with the carbonyl carbon resonating at 176.7 ppm. The ^{1}H NMR spectrum (Figure 43) of the Baylis-Hillman adduct **213d**, derived from quinoline-2-carbaldehyde and 6-fluorochromone reveals a singlet at 6.23 ppm corresponding to the 2"-methine proton while the aromatic protons resonate between 7.35 and 8.13 ppm. The ^{13}C NMR spectrum (Figure 44) reveals 19 carbon signals consistent with structure **213d**. The asymmetric carbon C-2" resonates at 67.5 ppm, the remaining aromatic carbons between 110.5 and 159.7 ppm and the carbonyl carbon at 176.6 ppm.

The indolizine products were all similarly characterized. The ^{1}H NMR spectrum (Figure 45) of the 5-ring indolizine derivative **211c**, for example reveals a singlet at 2.96 ppm corresponding to the methyl group, a singlet at 6.80 ppm to the 1-methine proton with the rest of the aromatic protons resonating between 6.27 and 8.53 ppm. The ^{13}C NMR spectrum (Figure 46) reveals, as expected, 16 carbon signals, with the methyl group resonating at 20.2 ppm, the 1-methine carbon at 91.7 ppm, the rest of the aromatic carbons between 109.8 and 152.8 ppm and the carbonyl at 173.5 ppm.

The ^{1}H NMR spectrum (Figure 47) of the 6-ring indolizine derivative **214a** reveals all the protons resonating in the aromatic region. In particular, the 1-methine proton resonates at 6.94 ppm as a singlet. The ^{13}C NMR spectrum (Figure 48) reveals 19 carbon signals. Again here the asymmetric carbon C-2" of the parent Baylis-Hillman adduct disappears and it is replaced by the 1-methine carbon which resonates at 95.2 ppm and the carbonyl carbon resonates at 174.2 ppm.

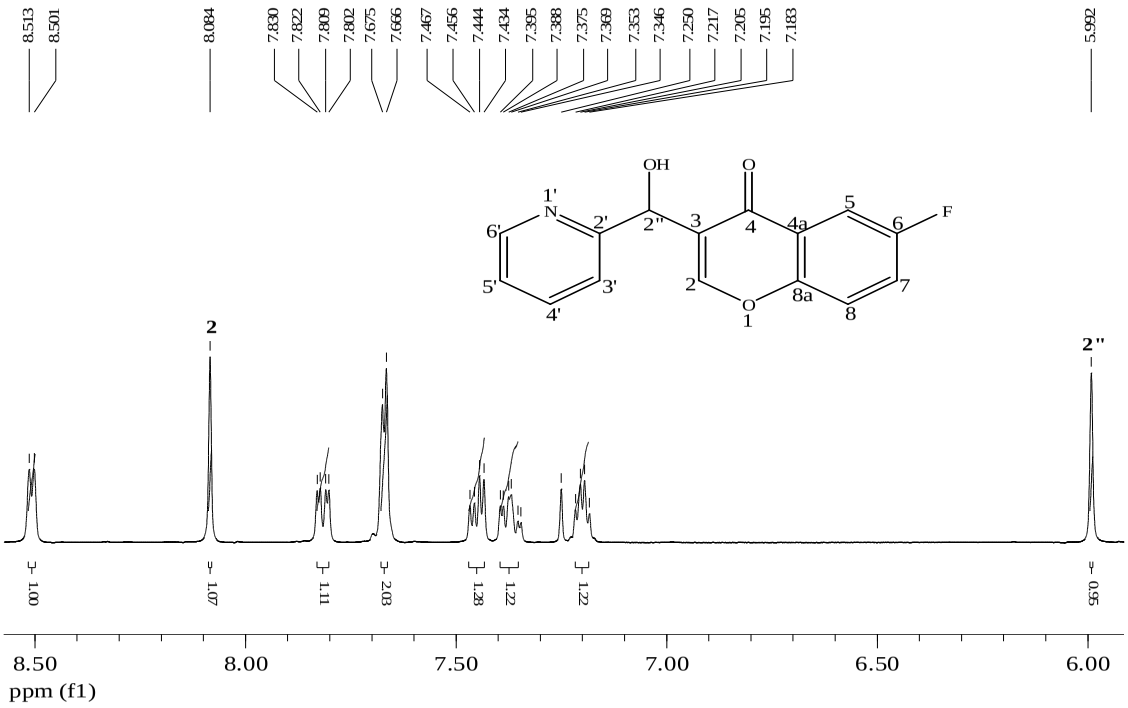


Figure 41. 400 MHz ^{1}H NMR spectrum of Baylis-Hillman adduct **208d** in $CDCl_3$.

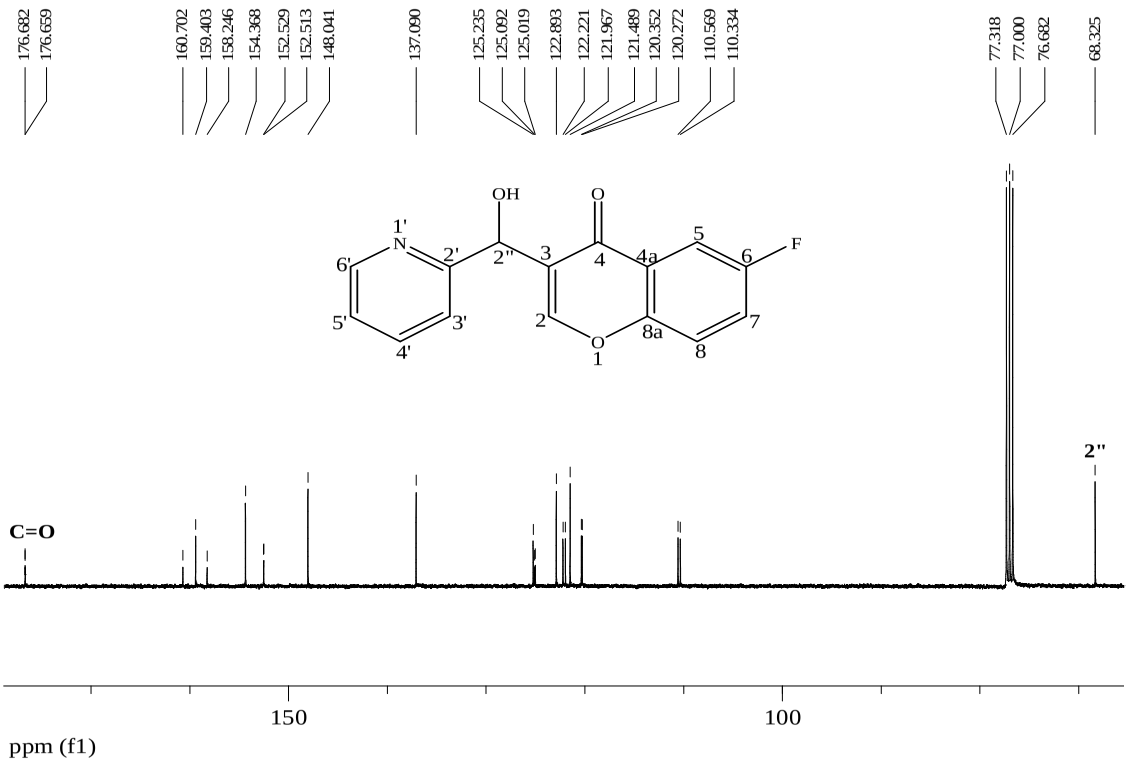


Figure 42. 100 MHz ^{13}C NMR spectrum of Baylis-Hillman adduct **208d** in $CDCl_3$.

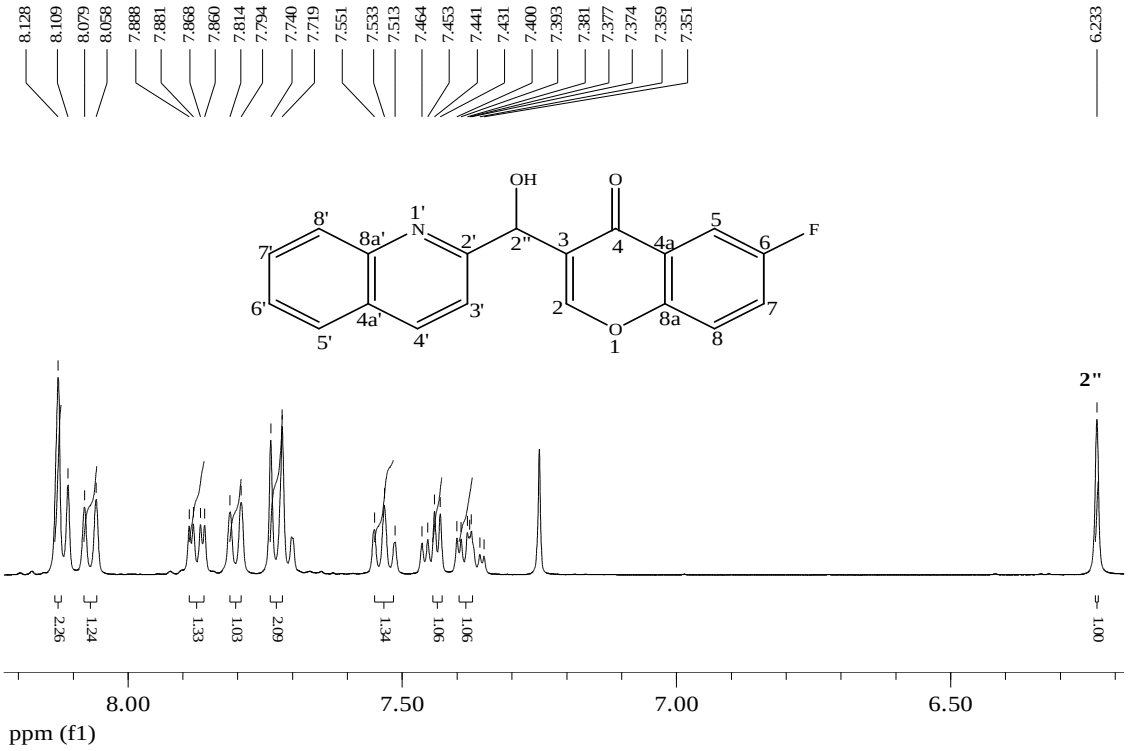


Figure 43. 400 MHz ^{1}H NMR spectrum of Baylis-Hillman adduct **213d** in $CDCl_3$.

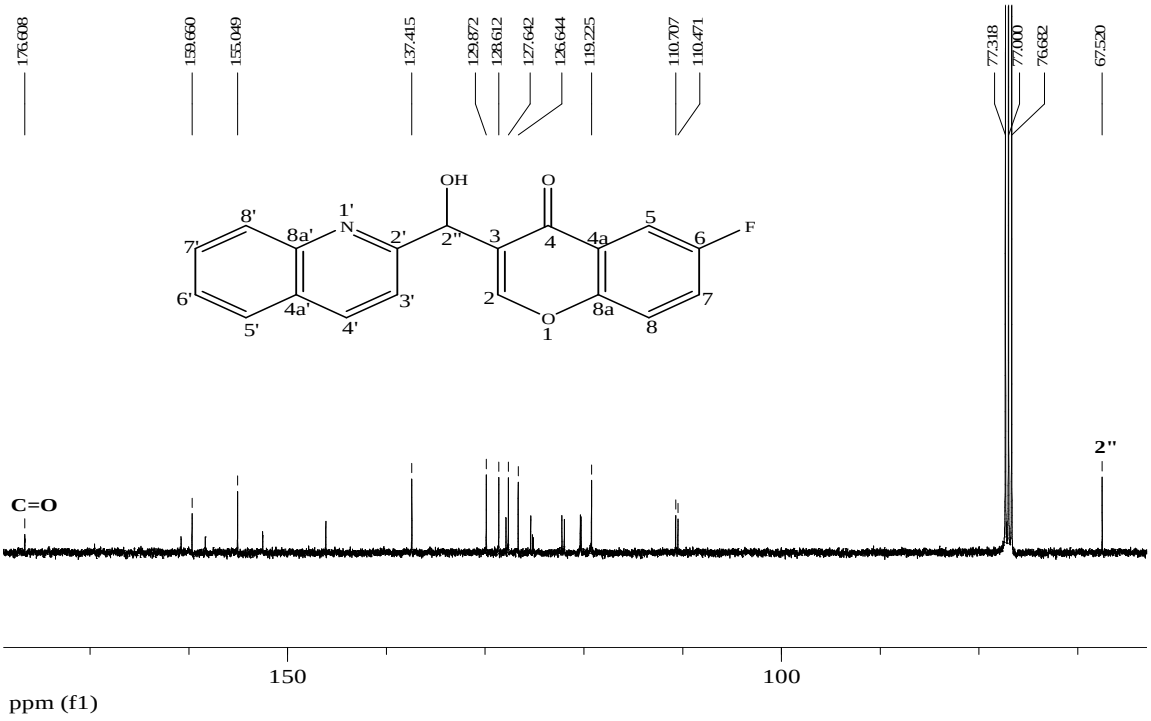


Figure 44. 100 MHz ^{13}C NMR spectrum of Baylis-Hillman adduct **213d** in $CDCl_3$.

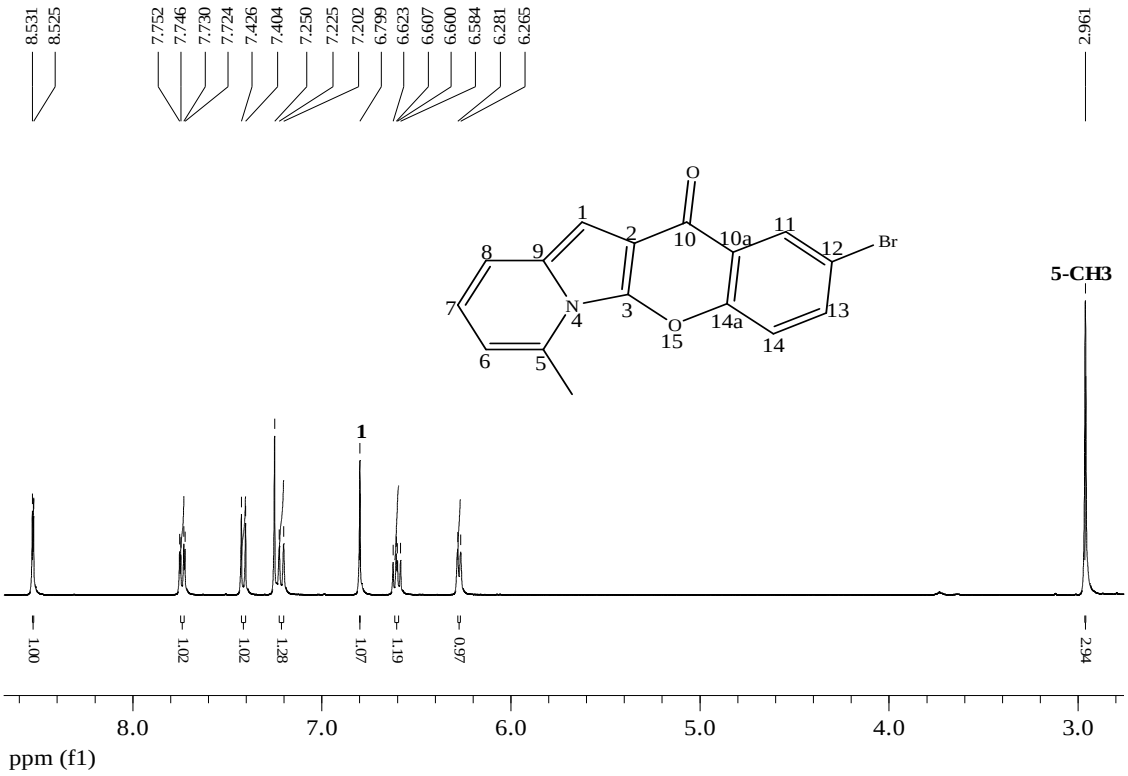


Figure 45. 400 MHz ^{1}H NMR spectrum of the indolizine derivative **211c** in $CDCl_3$.

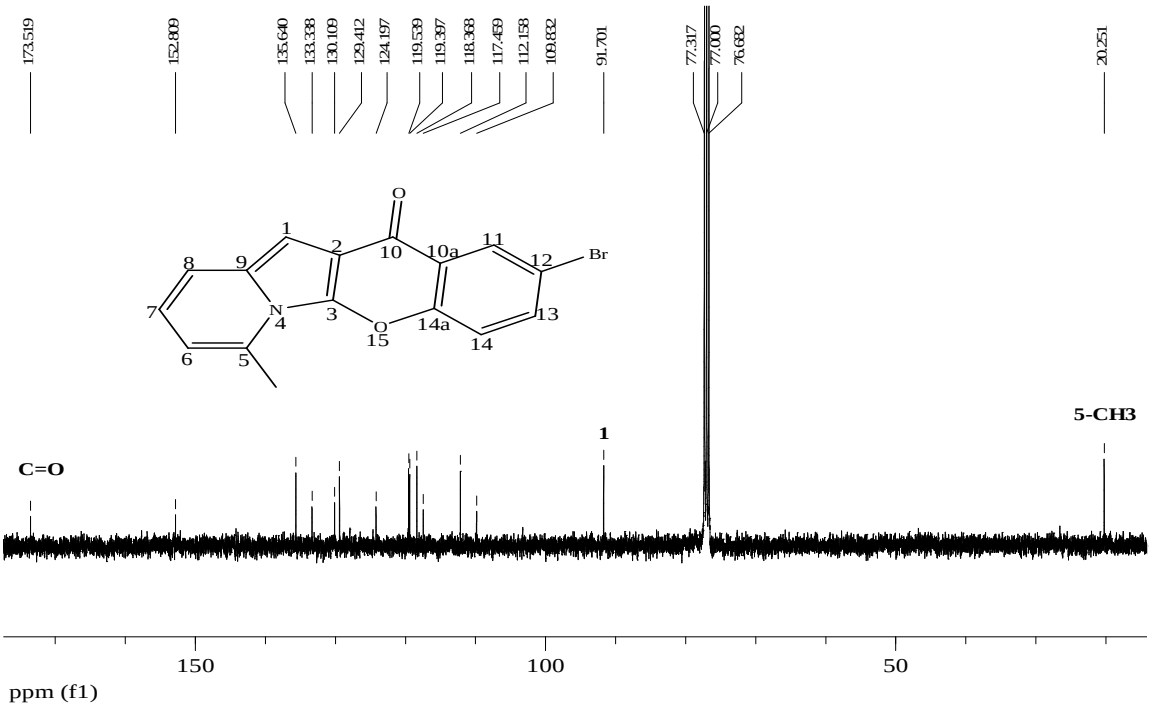


Figure 46. 100 MHz ^{13}C NMR spectrum of the indolizine derivative **211c** in $CDCl_3$.

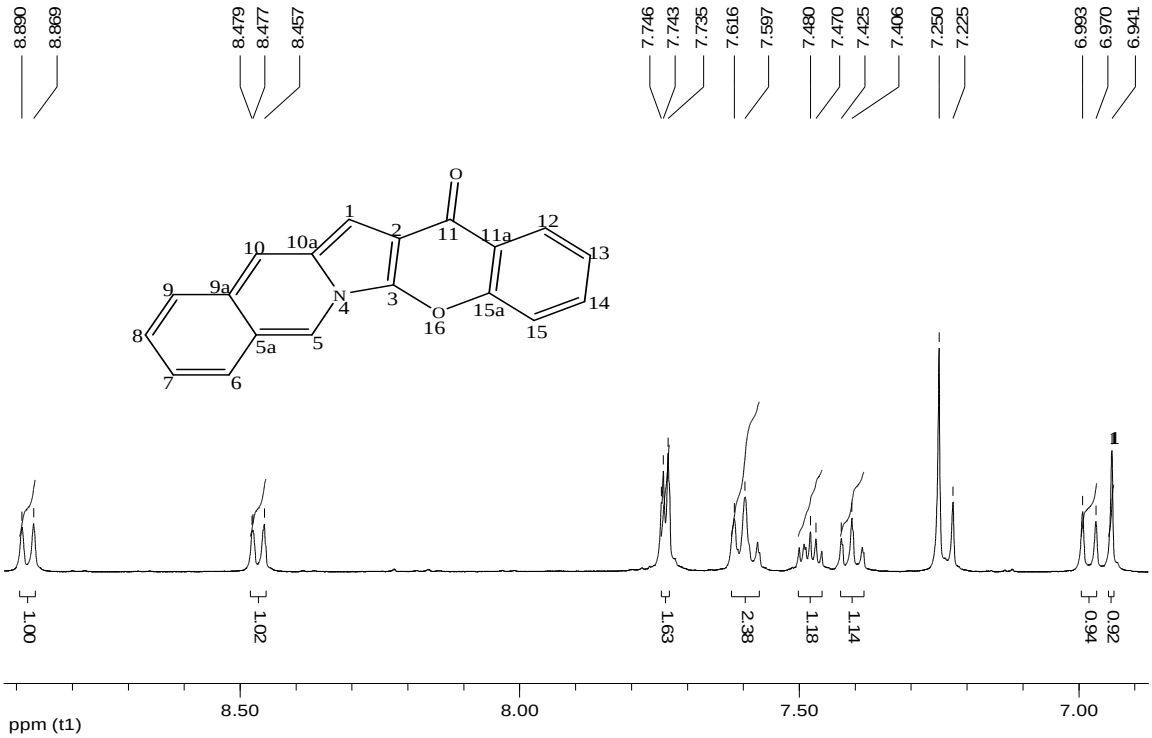


Figure 47. 400 MHz ^{1}H NMR spectrum of the indolizine derivative **214a** in $CDCl_3$.

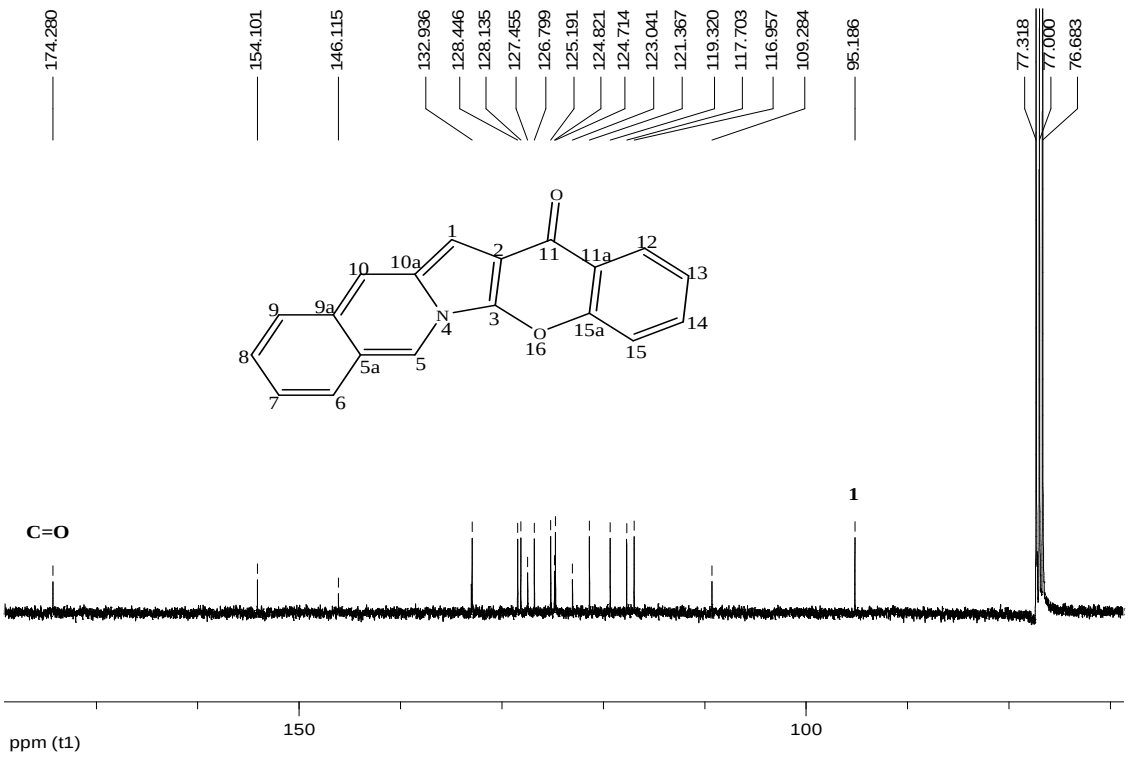


Figure 48. 100 MHz ^{13}C NMR spectrum of the indolizinederivative **214a** in $CDCl_3$.

2.6 Comparison of calculated *vs* experimental ^{1}H and ^{13}C NMR spectra, for selected indolizine derivatives and Baylis-Hillman adducts

NMR chemical shifts are an important tool in characterizing molecular systems and structures and the use of NMR spectral predictions can be useful in supporting structural assignments. In this section we consider the application of two different NMR prediction approaches, *viz*., the Gaussian '03 GIAO method and MestreNova, each of which can be very useful. The data obtained from these NMR prediction/calculation methods is then compared with the experimental NMR data. The assignment of the experimental signals was supported, in all cases by DEPT-135 and 2-D NMR data.

Gaussian '03 includes a facility for predicting magnetic properties, including NMR shielding tensors and chemical shifts. These magnetic properties are calculated from first principles, as the mixed second derivative of the energy with respect to an applied magnetic field and the nuclear magnetic moment. As a result, they can produce high accuracy results for the entire range of molecular systems studied experimentally *via* NMR techniques. Gaussian '03 can give accurate predictions of magnetic properties for all types of molecular systems. It also has the ability to predict chemical shifts for atoms other than hydrogen and carbon. NMR properties can be computed as part of a systematic and self-consistent study of a molecule. However, it cannot give nuclear multiplicities, such as doublets, triplets and so on for the proton spectra. All reported Gaussian '03 chemical shifts were computed at the gauge invariant atomic orbital (GIAO) B3LYP/6-311G+(2d,p) level, with respect to TMS. When using the GIAO method, the programme computes absolute nuclear chemical shieldings (σ_{abs}) for hydrogen and carbon nuclei, which cannot be measured directly. They can only be converted to a chemical shift scale using a reference $\delta_{calc.} = \sigma_{ref} - \sigma_{abs}$. Tetramethylsilane (TMS) is accepted as a reference for both ^{13}C and ^{1}H NMR data, and the calculated absolute shieldings for ^{13}C (182.4656 ppm) and for ^{1}H (31.8821 ppm) are used to refer σ_{abs} to the chemical shift scale.

On the other hand, MestreNova not only gives accurate predictions, as does Gaussian ’03, but it also provides multiplicities, such as doublets, triplets and so on, for the proton spectra. Therefore, these prediction tools, together with experimental data, provide powerful methods for NMR studies of complex molecules.

The chemical shifts obtained from the two NMR prediction tools, *viz*., Gaussian ’03 and MestreNova, are tabulated and compared to the experimental chemical shifts for both the ^{1}H and ^{13}C nuclei. NMR predictions for the selected compounds, **166a**, **187a**, **196, 210a** and **214a**, were carried out and the results are shown below.

Figure 49 depicts the modelled structure of compound **196** at its minimum energy, using the Gaussian ’03 method, together with its line structure. Tables 14 and 15 show the experimental and calculated chemical shifts for the ^{1}H and ^{13}C spectra, respectively, for compound **196**. The differences between experimental and calculated NMR values are given in parentheses. There is a generally good match between proton chemical shifts for both the predicted and experimental data shown in Table 14. However, there are differences in the multiplicities of the 2-, 3- and 4-methylene protons, and in the predicted spectra (Table 14), each of the six methylene protons resonates at a slightly different chemical shift values, as if each pair of protons are diastereotopic. However, the experimental spectrum shows each pair of methylene protons resonating as a triplet. Clearly, the calculated spectra are based on a single energy-minimised conformation in which the cyclohexenone ring is puckered. The conformational flip barrier is expected to be low and the puckered conformations interconvert rapidly, with the experimental data reflecting time-averaged chemical shifts which correlate closely with the averaged predicted values using both Gaussian and MestreNova data. The ^{13}C chemical shifts for both predictive and experimental data correspond reasonably well, the largest difference being 8.3 ppm (Table 15).

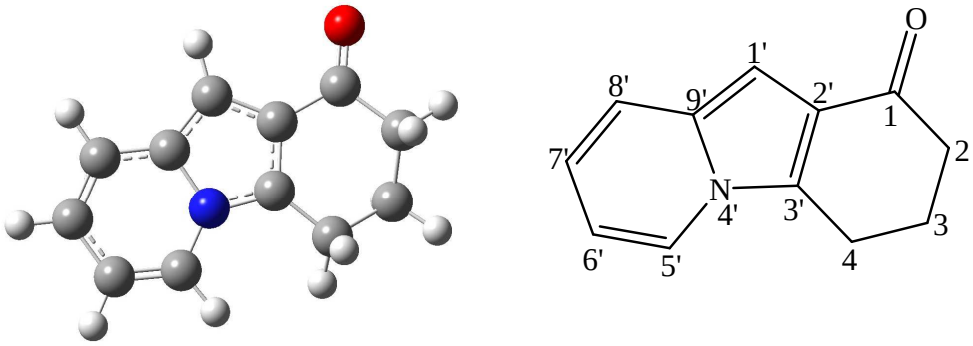


Figure 49. The Gaussian modelled structure of compound **196** together with its numbered line structure.

Table 14. Calculated *vs* experimental ^{1}H chemical shifts for compound **196** in ppm.

H	Experimental	Calculated (Gaussian)	Calculated (MestreNova)
2a	2.62	2.62 (0)	2.86 (0.24)
2b	2.62	2.54 (0.08)	2.58 (0.04)
3a	2.30	2.38 (0.08)	2.38 (0.08)
3b	2.30	2.23 (0.07)	2.16 (0.14)
4a	2.96	2.98 (0.02)	2.95 (0.01)
4b	2.96	3.00 (0.04)	3.03 (0.07)
1'	6.75	7.19 (0.44)	7.40 (0.65)
5'	7.64	7.81 (0.17)	7.54 (0.10)
6'	6.56	6.74 (0.18)	7.13 (0.57)
7'	6.66	6.85 (0.19)	6.70 (0.04)
8'	7.36	7.67 (0.31)	7.42 (0.06)

Table 15. Calculated *vs* experimental ^{13}C chemical shifts for compound **196** in ppm.

C	Experimental	Calculated (Gaussian)	Calculated (MestreNova)
1	196.1	199.8 (3.7)	192.4 (3.7)
2	38.6	42.8 (4.2)	37.8 (0.8)
3	23.6	28.4 (4.8)	23.5 (0.1)
4	21.0	25.2 (4.2)	22.8 (1.8)
1'	95.4	102.3 (6.9)	99.3 (3.9)
2'	123.2	131.5 (8.3)	130.0(6.8)
3'	132.0	134.6 (2.6)	133.9 (1.9)
5'	122.2	126.3 (4.1)	127.6 (5.4)
6'	112.2	117.6 (5.4)	116.1 (3.9)
7'	118.0	120.9 (2.9)	118.0 (0)
8'	121.0	127.2 (6.2)	124.0 (3)
9'	132.9	140.5 (7.6)	134.9 (2)

Figure 50 shows the modelled structure of compound **210a** at its minimum energy, using the Gaussian '03 method, together with its line structure, while Tables 16 and 17 show the experimental and calculated chemical shifts for the ^{1}H and ^{13}C spectra, respectively. The correlation between experimental and calculated values using Gaussian '03 is, in some cases, poor with the prediction for H-15 being almost 1 ppm too high. The difference between the experimental and MestreNova values for H-15 is much smaller (0.06 ppm), but the predicted values for H-6 and H-7 are > 0.7 ppm larger than the experimental values. There is a generally better matching of the experimental and calculated ^{13}C-NMR data, but the Gaussian '03 value for C-3 is 35.8 ppm downfield of the experimental signal (Table 17). On the other hand, C-1 and C-13 resonate downfield of the MestreNova predicted signals.

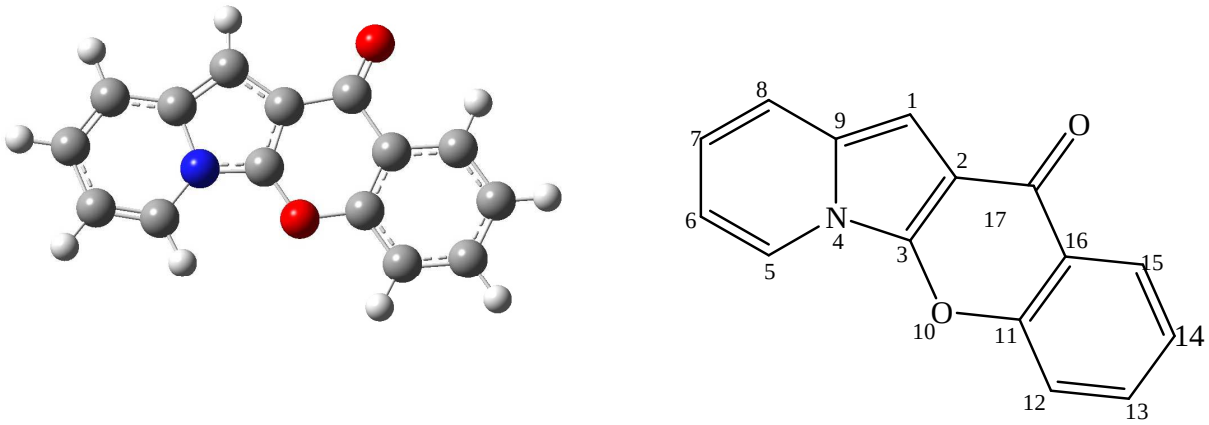


Figure 50. The Gaussian modelled structure of compound **210a**, together with its numbered line structure.

Table16. Calculated *vs* experimental ^{1}H chemical shifts for compound **210a** in ppm.

H	Experimental	Calculated (Gaussian)	Calculated (MestreNova)
1	6.84	7.25 (0.41)	7.04 (0.2)
5	8.45	8.27 (0.18)	8.34 (0.11)
6	6.60	6.83 (0.23)	7.32 (0.72)
7	6.70	6.92 (0.22)	7.46 (0.76)
8	7.60	7.69 (0.09)	7.63 (0.03)
12	7.39	7.83 (0.44)	7.59 (0.2)
13	7.70	7.88 (0.18)	7.67 (0.03))
14	7.44	7.71 (0.27)	7.57 (0.13)
15	8.04	8.99 (0.95)	7.98 (0.06)

Table 17. Calculated *vs* experimental ^{13}C chemical shifts for compound **210a** in ppm.

C	Experimental	Calculated (Gaussian)	Calculated (MestreNova)
1	91.1	98.2 (7.1)	108.2 (17.1)
2	123.3	118.0 (5.3)	123.5 (0.2)
3	109.3	145.1 (35.8)	115.2 (5.9)
5	124.4	124.4 (0)	124.0 (0.4)
6	111.7	116.7 (5)	116.1 (4.4)
7	117.4	122.0 (4.6)	117.2 (0.2)
8	118.8	126.5 (7.7)	118.0 (0.8)
9	133.0	134.5 (1.5)	133.2 (0.2)
11	154.1	161.8 (7.7)	155.2 (1.1)
12	120.1	121.4 (1.3)	118.4 (1.7)
13	133.0	137.3 (4.3)	150.8 (17.8)
14	120.7	128.4 (7.7)	118.7 (2)
15	127.1	134.7 (7.6)	124.9 (2.2)
16	128.0	130.6 (2.6)	127.4 (0.6)
17	175.0	179.2 (4.2)	173.9 (1.1)

Figure 51 shows the Gaussian modelled structure of compound **214a** at its minimum energy, together with its line structure, and Tables 18 and 19 summarize the experimental and calculated chemical shifts for the ^{1}H and ^{13}C spectra, respectively. While some of the experimental ^{1}H NMR chemical shift values correlate well with the predicted values, significant discrepancies are apparent for H-6, -11 and -16, using both prediction approaches. In the case of H-19, however, the MestreNova value is close to the experimental value whereas the Gaussian value varies by 1.43 ppm.

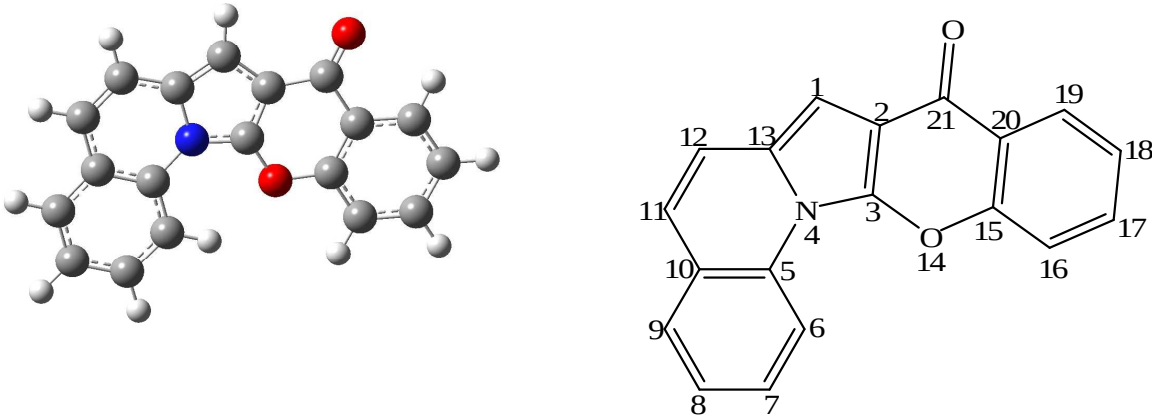


Figure 51. The Gaussian modelled structure of compound **214a** together with its numbered line structure.

Table18. Calculated *vs* experimental ^{1}H chemical shifts for compound **214a** in ppm.

H	Experimental	Calculated (Gaussian)	Calculated (MestreNova)
1	6.94	7.28 (0.34)	7.38 (0.44)
6	8.88	9.54 (0.66)	8.27 (0.61)
7	7.75	7.89 (0.14)	7.91 (0.16)
8	7.58	7.72 (0.14)	7.62 (0.04)
9	7.60	7.91 (0.31)	7.67 (0.07)
11	8.48	7.26 (1.22)	8.00 (0.48)
12	7.41	7.51 (0.1)	7.57 (0.16)
16	6.98	7.95 (0.97)	7.40 (0.42)
17	7.49	7.96 (0.47)	7.60 (0.11)
18	7.22	7.73 (0.51)	7.54 (0.32)
19	7.62	9.05 (1.43)	7.77 (0.15)

Table 19. Calculated *vs* experimental ^{13}C chemical shifts for compound **214a** in ppm.

C	Experimental	Calculated (Gaussian)	Calculated (MestreNova)
1	95.2	102.4 (7.2)	91.4 (3.8)
2	116.9	117.0 (0.1)	110.7 (6.2)
3	109.3	151.5 (42.2)	155.2 (45.9)
5	132.9	140.5 (7.6)	132.8 (0.1)
6	125.2	122.3 (2.9)	124.7 (0.5)
7	125.2	132.1 (6.9)	124.9 (0.3)
8	124.7	129.1 (4.4)	121.6 (3.1)
9	124.8	133.3 (8.5)	122.1 (2.7)
10	127.4	132.2 (4.8)	128.8 (1.4)
11	128.4	125.2 (3.2)	131.8 (3.4)
12	117.7	124.8 (7.1)	118.0 (0.3)
13	146.1	133.5 (12.6)	133.2 (12.9)
15	154.1	162.0 (7.9)	168.4 (14.3)
16	119.3	121.0 (1.7)	118.7 (0.6)
17	128.1	137.0 (8.9)	129.9 (1.8)
18	121.4	129.0 (7.6)	119.2 (2.2)
19	126.8	134.1 (7.3)	127.4 (0.6)
20	123.0	130.1 (7.1)	119.4 (3.6)
21	174.3	178.1 (3.8)	173.9 (0.4)

Figure 52 illustrates the Gaussian modelled structure of compound **187a** at its minimum energy, together with its line structure. Tables 20 and 21 summarize the experimental and calculated chemical shifts for the ^{1}H and ^{13}C spectra, respectively. The Gaussian '03 predictions for the signals for H-1, -3 and -8 differ significantly from the experimental values. The cyclohexane ring is puckered rendering the 2-, 3- and 4-methylene protons diastereotopic in the modeled conformation. However, rapid (on the NMR time-scale) conformational flipping results in time-averaged signals for each of the methylene groups

in the experimental spectrum. Rotation of the acetyl methyl group similarly results in a time-averaged singlet, rather than the three singlets predicted Gaussian. The MestreNova ^{1}H and ^{13}C predicted data generally correspond more closely to the experimental NMR spectra, than the Gaussian data (Table 21). Several experimental signals exhibit chemical shifts which differ significantly from the Gaussian '03 data, *e.g.* C-2', C-4a' and C-8a'.

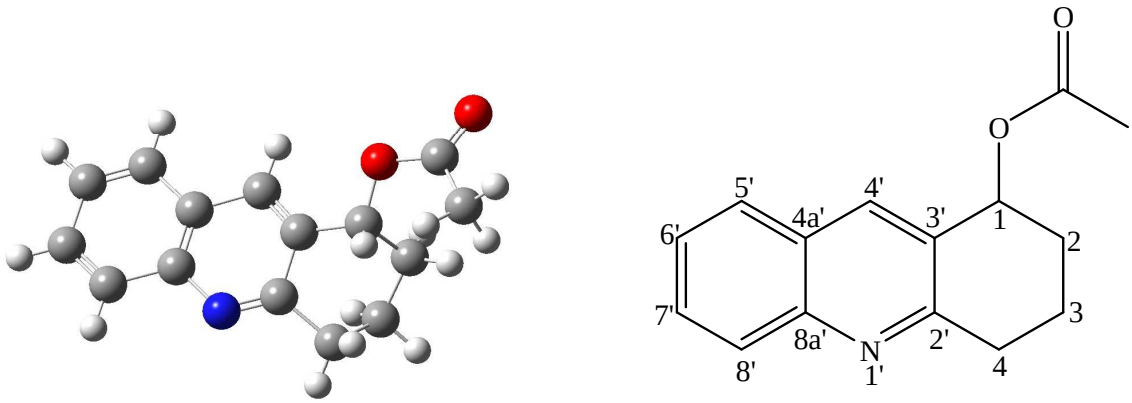


Figure 52. The Gaussian modelled structure of compound **187a**, together with its numbered line structure.

Table 20. Calculated *vs* experimental ^{1}H chemical shifts for compound **187a** in ppm.

H	Experimental	Calculated (Gaussian)	Calculated (MestreNova)
Me(a)	2.11	2.33 (0.22)	2.20 (0.09)
Me(b)	2.11	2.64 (0.53)	2.20 (0.09)
Me(c)	2.11	1.97 (0.14)	2.20 (0.09)
1	6.19	5.09 (1.1)	6.20 (0.01)
2a	2.00	2.46 (0.46)	1.61 (0.39)
2b	2.00	1.08 (0.92)	1.49 (0.51)
3a	3.24	1.38 (1.86)	3.33 (0.09)
3b	3.08	0.50 (2.58)	3.00 (0.08)
4a	2.18	2.42 (0.24)	2.40 (0.22)
4b	2.08	2.17 (0.09)	2.02 (0.06)
4'	8.11	7.99 (0.12)	8.23 (0.12)
5'	7.76	7.86 (0.1)	7.92 (0.16)
6'	7.47	7.57 (0.1)	7.47 (0)
7'	7.67	7.70 (0.03)	7.50 (0.17)
8'	7.99	9.08 (1.09)	8.19 (0.2)

Table 21. Calculated *vs* experimental ^{13}C chemical shifts for compound **187a** in ppm.

C	Experimental	Calculated (Gaussian)	Calculated (Mestrenova)
Me	18.6	23.7 (5.1)	21.2 (2.6)
1	69.9	77.9 (8)	63.9 (6)
2	32.9	31.1 (1.8)	31.8 (1.1)
3	21.4	24.8 (3.4)	22.7 (1.3)
4	28.8	34.8 (6)	30.1 (1.3)
2'	158.6	174.7 (16.1)	160.1 (1.5)
3'	128.8	142.0 (13.2)	129.9 (1.1)
4'	136.9	134.5 (2.4)	134.2 (2.7)
4a'	126.9	143.2 (16.3)	127.9 (1)
5'	125.9	139.3 (13.4)	125.5 (0.4)
6'	127.8	138.1 (10.3)	128.0 (0.2)
7'	128.3	139.4 (11.1)	128.4 (0.1)
8'	129.9	141.2 (11.3)	132.9 (3)
8a'	147.6	165.2 (17.6)	139.8 (7.8)
C=O	170.7	199.7 (29)	170.4 (0.3)

While the predicted NMR data correlate reasonably well with the experimental data for many nuclei in the compounds examined above, it is apparent that, in some cases, significant deviations are observed. The introduction of solvent corrections to the calculated data might well improve the correlation with the experimental data and such refinement is now being explored. Consequently, caution should be exercised in the use of predictive methods. In the following example, attention has been given to the use of the predictive methods in differentiating diastereomeric products.

Figure 53 is the Gaussian modelled structure of the tricyclic Baylis-Hillman compound **166a** at its minimum energy, using Gaussian '03 method, together with its line structure. Tables 22 and 23 show the experimental and calculated chemical shifts for the ^{1}H and ^{13}C

spectra, respectively, for compounds **166a$_1$** and **166a$_2$**. Unfortunately, there are a number of significant variations between the experimental and predicted ^{1}H and ^{13}C values for diastereomers and it is evident that unambiguous assignment of the structure using the predicted data is not possible in this case. The proton NMR data from the MestreNova programme is consistent with the diastereomeric isomer **166a$_2$**.

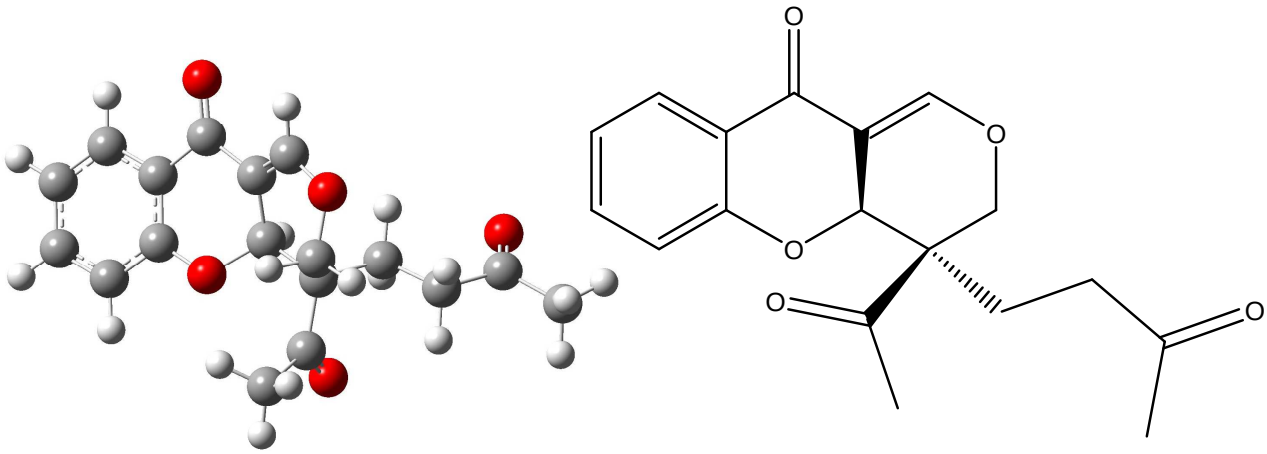


Figure 53. The Gaussian modelled structure of compound **166a$_2$** and its numbered line structure.

Table 22. Calculated *vs* experimental ^{1}H chemical shifts for the diastereomeric compounds **166a$_1$** and **166a$_2$** in ppm.

H	Experimental (166a$_1$)	Experimental (166a$_2$)	Calculated (MestreNova) for 166a
2	7.28	6.67	7.70
4	7.87	7.82	7.92
5	7.09	7.06	7.49
6	7.55	7.52	7.59
7	7.12	7.00	7.55
8a	5.12	5.40	5.55
10a	4.57	4.45	3.92
10b	4.77	4.61	4.66
12	2.36	2.29	2.42
13a	2.40	2.56	2.57
13b	2.53	2.56	2.57
14a	2.01	2.18	2.34
14b	2.18	2.18	2.34
16	2.06	2.11	2.18

Table 23. Calculated *vs* experimental ^{13}C chemical shifts for the diastereomeric compounds **166a$_1$** and **166a$_2$** in ppm.

C	Experimental (166a$_1$)	Experimental (166a$_2$)	Calculated (Mestrenova) for 166a (racemic)
2	136.7	137.1	134.5
2a	119.5	119.2	118.3
3	192.5	193.1	165.4
3a	138.3	138.0	134.5
4	122.9	122.6	122.8
5	127.9	127.2	126.8
6	135.3	135.9	126.8
7	118.1	118.2	118.2
7a	157.6	157.6	158.0
8a	99.9	99.4	73.8
9	49.1	49.7	53.3
10	65.8	62.5	72.6
11	206.6	206.5	175.7
12	29.9	29.9	28.6
13	24.8	25.2	21.0
14	37.7	37.7	38.7
15	196.5	196.3	165.4
16	25.4	27.7	28.4

2.7 Comparison of calculated *vs* experimental UV spectra, for selected indolizine derivatives

The polycyclic compounds prepared in this study were expected to exhibit interesting UV absorption and fluorescent properties. Consequently, it was decided to calculate the electronic transitions for selected systems and compare their experimental spectra with the theoretical data. The use of density functional theory (DFT) has become a very popular computational method for the calculation of a number of molecular properties. It has good computational efficiency and, as such, has been applied to inorganic and organometallic complexes.[221-225] The time-dependent generalization of DFT (TDDFT) offers a rigorous route to calculate the dynamic response to charge density.[226-228] The reliability of the TDDFT approach in obtaining accurate predictions of excitation energies is well documented.[229-231]

Preliminary UV spectral calculations of selected compounds, *i.e.*, **210a** and **214a**, were conducted using the Gaussian '03 programme.[232] The geometry optimization was carried out using the B3LYP functional, while the electronic spectra were calculated with the TDDFT method.[233] These calculation results are compared with the experimental data. In addition to these, experimental UV spectral measurements were conducted on the other compounds in the series, in order to establish the nature of any substituent effects.

The spin-allowed singlet transitions for compound **210a** were calculated with the TDDFT method, and are listed in Table 24. These are compared with the experimental results obtained for compound **210a**. Figure 54 shows the calculated UV spectrum of compound **210a**, while Figures 56 and 57 are the experimental UV spectra of compounds **210a** and **210d**, respectively. The calculated spectrum of compound **210a** shows some important bands at 399.81, 270.59, 263.12, 247.32, 244.43, 228.58, 228.56, 220.92 and 212.13 nm (Table 24, column 4; Figure 54), with the electronic transitions shown in parentheses (Table 24, column 2). Compound **210a** has 61 occupied molecular orbitals; orbital 61 is the highest occupied molecular orbital (HOMO) and 62 is the lowest unoccupied

molecular orbital (LUMO). The transition with the highest oscillator strength (*f* = 0.4197, entry 4,) is at 247.32 nm and it is from the HOMO to the LUMO + 3, with the orbital energy diagram shown in Figure 55 (the atomic orbital contributions to the corresponding molecular orbitals are illustrated alongside). The first experimental band at 416.34 nm is ascribed to the calculated transition at 399.81 nm, the experimental band at 272.96 nm to the calculated transition at 270.59 nm, the experimental band at 262.96 nm to the calculated transition at 263.12 and the last experimental band at 250.65 nm to the calculated transition at 247.32 nm with the highest oscillator strength (*f* = 0.4197, entry 4), with E = 5.0131 eV and this transition is illustrated in Figure 55. The HOMO-LUMO gap is at 399.81 nm, with oscillator strength (*f* = 0.0613, entry 1), with E = 3.1011 eV. Figures 56 and 57 are the experimental UV spectra for compounds **210a** and **210d**, respectively. The low intensity bands calculated to be present in the region 244-228 nm presumably lie beneath the major experimental band at 247nm, while the calculated bands at 220.92 and 212.13 nm probably lie just beyond the experimental limits of the instrument. These UV spectra are similar to each other, which shows that substituents have very little effect on the UV absorption of these compounds. A similar UV absorption pattern was observed with the rest of the compounds in this series, with only slight differences, *viz*., small red shifts in the bands for the substituted systems (see Table 25). Figure 58 is the emission spectrum of compound **210a** at 260 nm, and a similar pattern was again observed for the other compounds in this series.

Table 24. Calculated electronic transitions for compound **210a** with the TDDFT method *vs* experimental transitions.

Entry #	**Important configurations**	**E (eV)**	**λ (nm)**	***f***	**Experimental (λ [nm])**
1	61-62 (H→L)	3.1011	399.81	0.0613	416.34
2	59-62 (H-2→L)	4.5820	270.59	0.1904	272.96
3	58-62 (H-3→L)	4.7121	263.12	0.1594	262.96
4	61-65 (H→L+3)	5.0131	247.32	0.4197	250.93
5	57-62 (H-4→L)	5.0725	244.43	0.0466	
6	61-66 (H→L+4)	5.4241	228.58	0.0466	

7	60-64 (H-1→L+2)	5.4246	228.56	0.0001	
8	59-64 (H-2→L+2)	5.6121	220.92	0.1106	
9	59-64 (H-2→L+2)	5.8401	212.13	0.2502	

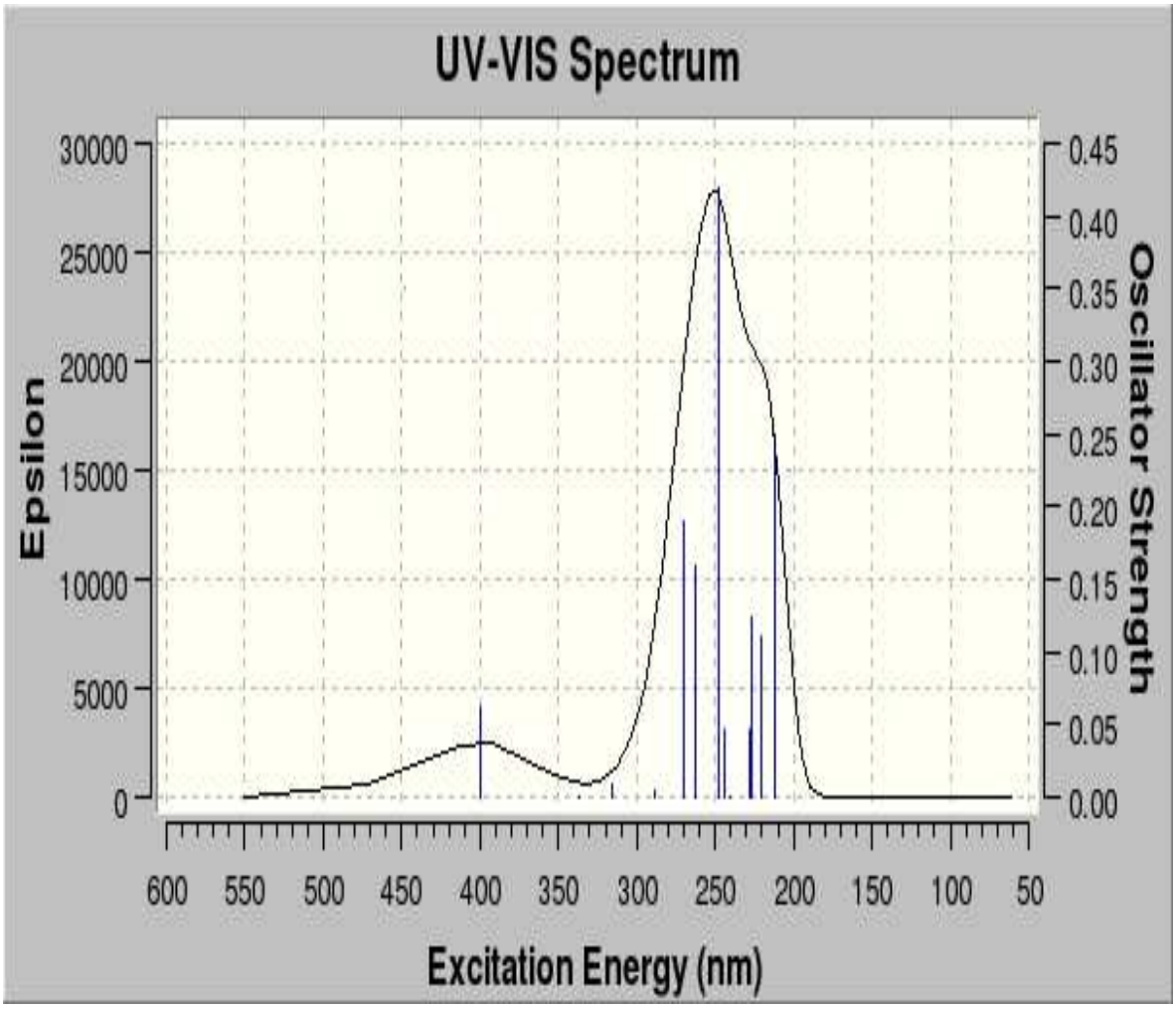


Figure 54. Predicted UV spectrum of compound **210a** using Gaussian ’03.

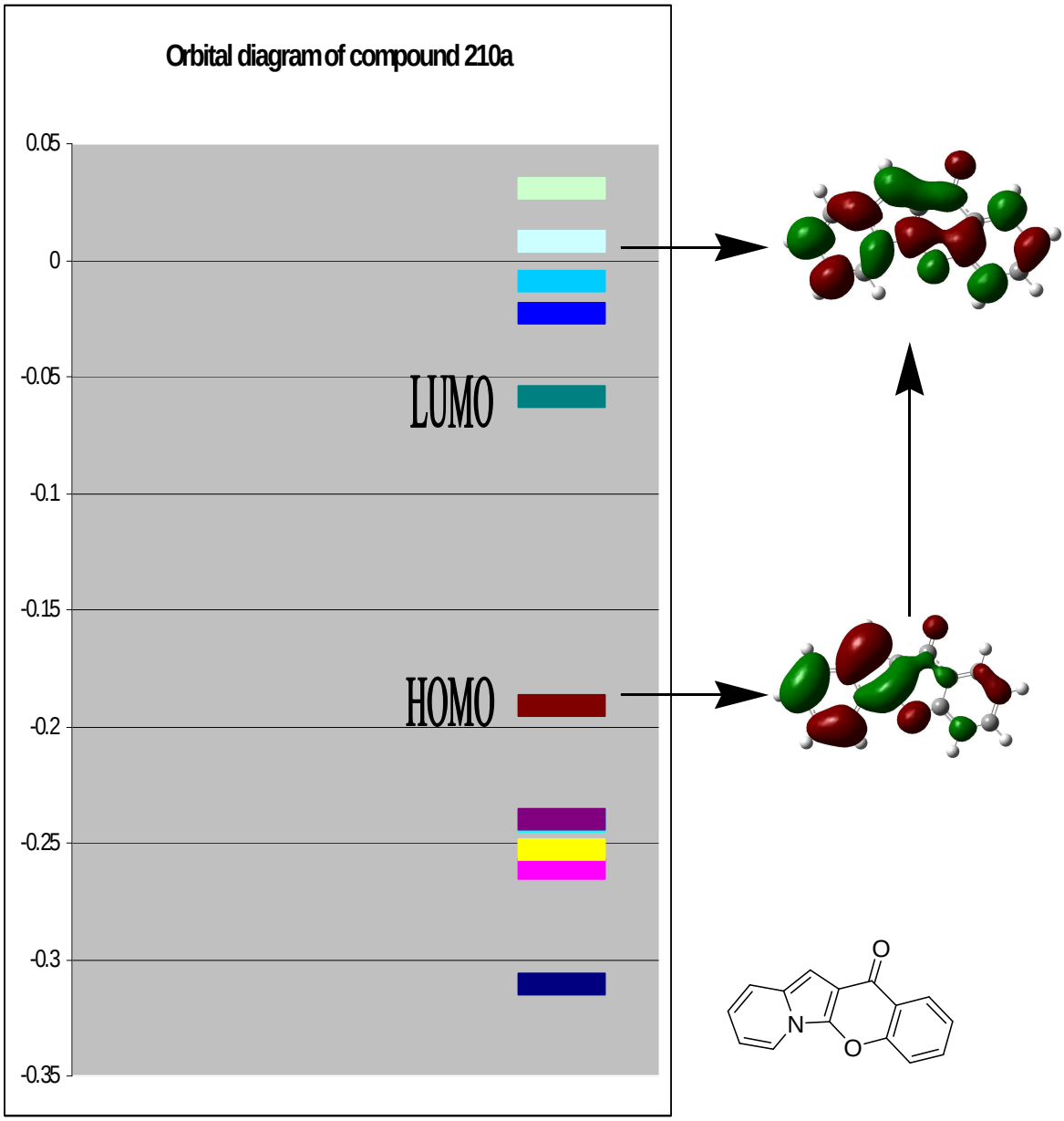


Figure 55. Orbital diagram of compound **210a**, showing the transition at 247.32 nm from HOMO to LUMO + 3 and the atomic orbital contributions to molecular orbitals involved.

Table 25: Comparative UV absorption maxima for compounds **210a, c-e** in chloroform.

R = H (Compound 210a)	**R = Br (Compound 210c)**	**R = F (Compound 210d)**	**R = Me (Compound 210e)**
416.34 nm	426.06 nm	426.06 nm	435.07 nm
272.96 nm	282.96 nm	292.03 nm	292.03 nm
262.96 nm	272.96 nm	282.03 nm	282.03 nm
250.93 nm	260.93 nm	270.93 nm	270.93 nm

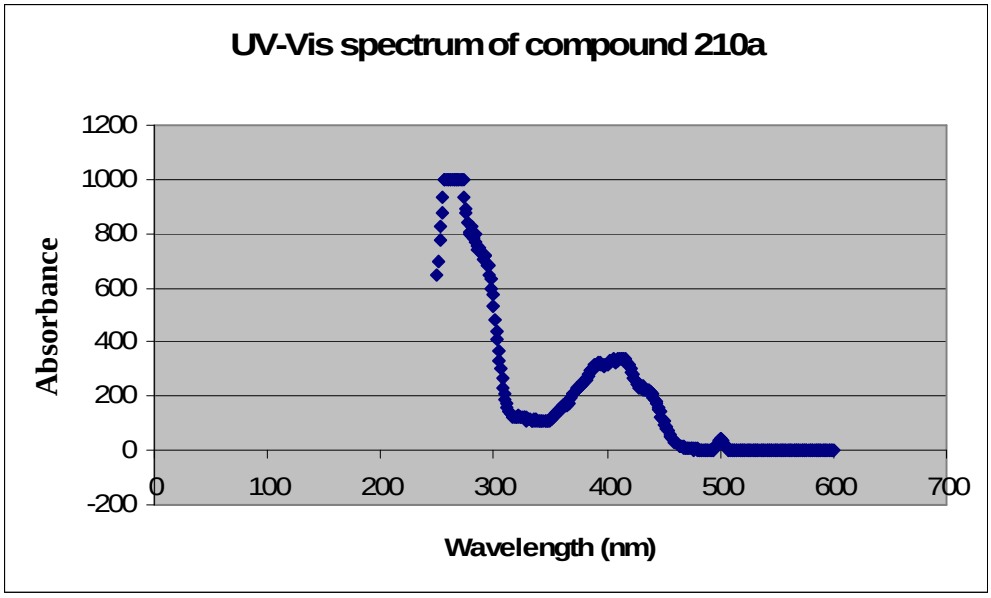


Figure 56. Experimental UV spectrum of compound **210a**, in chloroform.

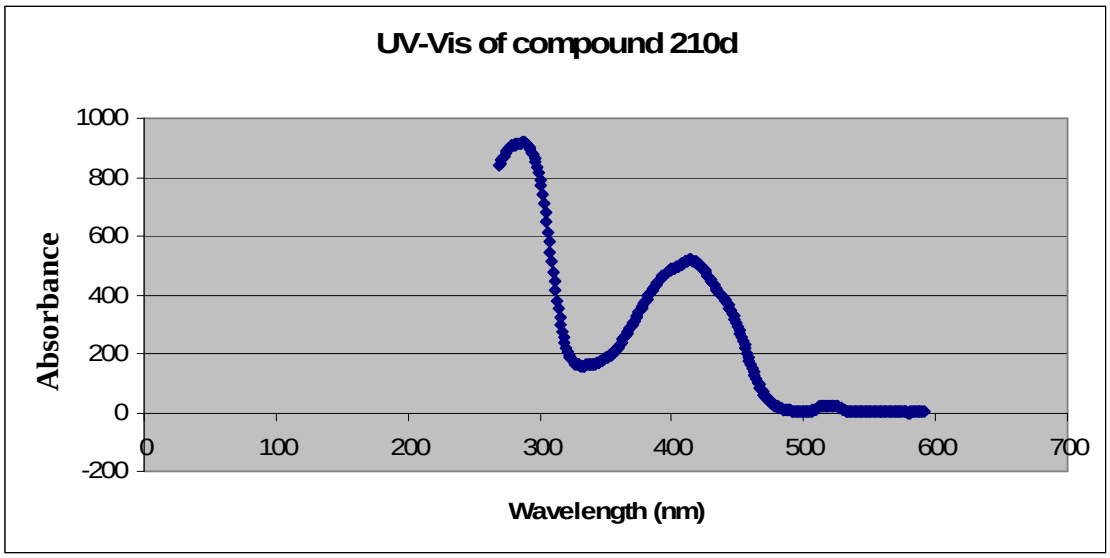


Figure 57. Experimental UV spectrum of compound **210d**, in chloroform.

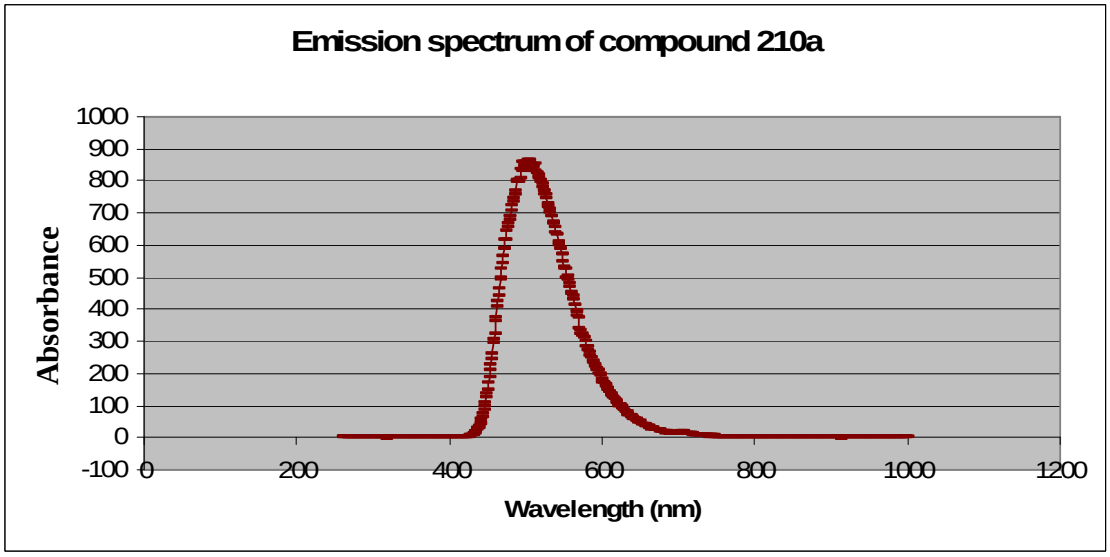


Figure 58. Experimental emission spectrum of compound **210a** at 260 nm, in chloroform.

Figure 59 shows the calculated UV spectrum of compound **214a**, while Figures 61 and 62 are the experimental UV spectra for compounds **214a** and **214d**, respectively. The calculated spectrum of compound **214a** shows important bands at 382.42, 327.10, 310.46, 281.60, 273.49, 257.49, 245.17, 243.42, 237.04, 232.98 and 230.11 nm (Table 26, column 4; Figure 58), with the electronic transitions shown in parentheses (Table 26,

column 2). Compound **214a** has 74 occupied molecular orbitals; orbital 74 is the highest occupied molecular orbital (HOMO) and 75 is the lowest unoccupied molecular orbital (LUMO). The transition with the highest oscillator strength (f = 0.4135, entry 4) is at 281.60 nm and it corresponds to a transition from HOMO -1 to LUMO, with the orbital energy diagram shown in Figure 60. The HOMO-LUMO transition is at 382.43 nm, with an oscillator strength f = 0.1575. The first experimental band at 391.97 nm is ascribed to the calculated transition at 382.43 nm, the experimental band at 344.91 nm to the calculated transition at 327.10 nm, experimental band at 317.96nm to the calculated transition at 310.46 nm, the experimental band at 290.49 nm to the calculated transition at 281.60 nm with the highest oscillator strength (f = 0.4135, entry 4) and the last experimental band at 274.06 nm to the calculated transition at 273.49 nm - transition shown in Figure 59. Figures 61 and 62 are the experimental UV spectra for compounds **214a** and **214d**, respectively. In this series of compounds the UV spectra are again similar to each other (see Table 27), which shows that substituents have very little effect on the overall UV absorption of these compounds. Figure 63 is the emission spectrum of compound **214a** at 260 nm, and a similar pattern was again observed for the other compounds in this series. In fact, in this series, the absorption maxima are almost identical

Table 26. Calculated electronic transitions for compound **214a** with the TDDFT method

Entry #	**Important configurations**	**E (eV)**	**λ (nm)**	***f***	**Experimental (λ [nm])**
1	74-75 (H→L)	3.2420	382.43	0.1575	391.97
2	74-76 (H→L+1)	3.7904	327.10	0.0694	344.91
3	74-77 (H→L+2)	3.9936	310.46	0.0051	317.96
4	73-75 (H-1→L)	4.4028	281.60	0.4135	290.49
5	74-78 (H→L+3)	4.5334	273.49	0.0295	274.06
6	73-76 (H-1→L+1)	4.8151	257.49	0.0833	
7	69-75 (H-5→L)	5.0571	245.17	0.0403	
8	70-75 (H-4→L)	5.0935	243.42	0.0211	
9	71-76 (H-3→L+1)	5.2305	237.04	0.0234	

10	74-78 (H→L+3)	5.3216	232.98	0.0891	
11	74-79 (H→L+4)	5.3881	230.11	0.2777	

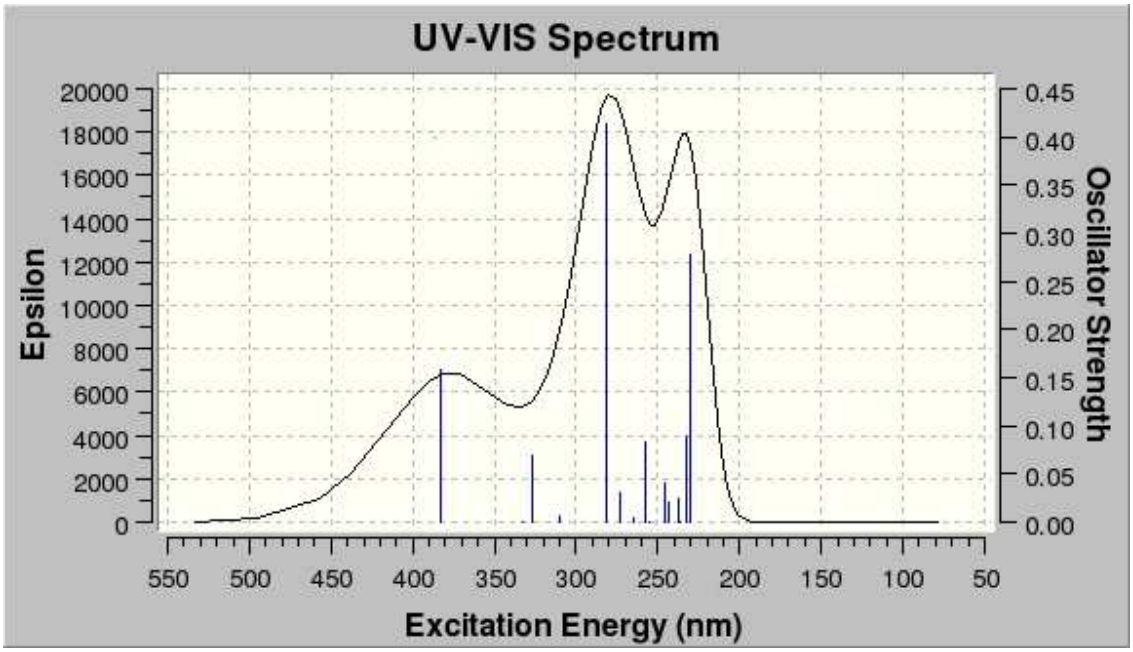
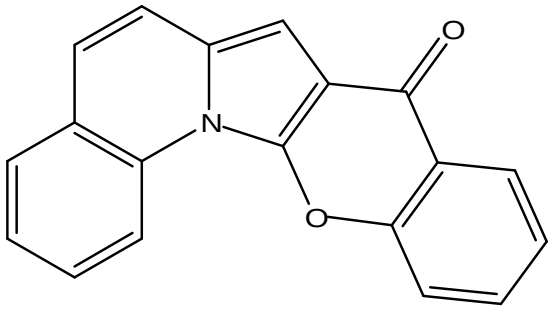


Figure 59. Predicted UV spectrum of compound **214a** using Gaussian ’03.



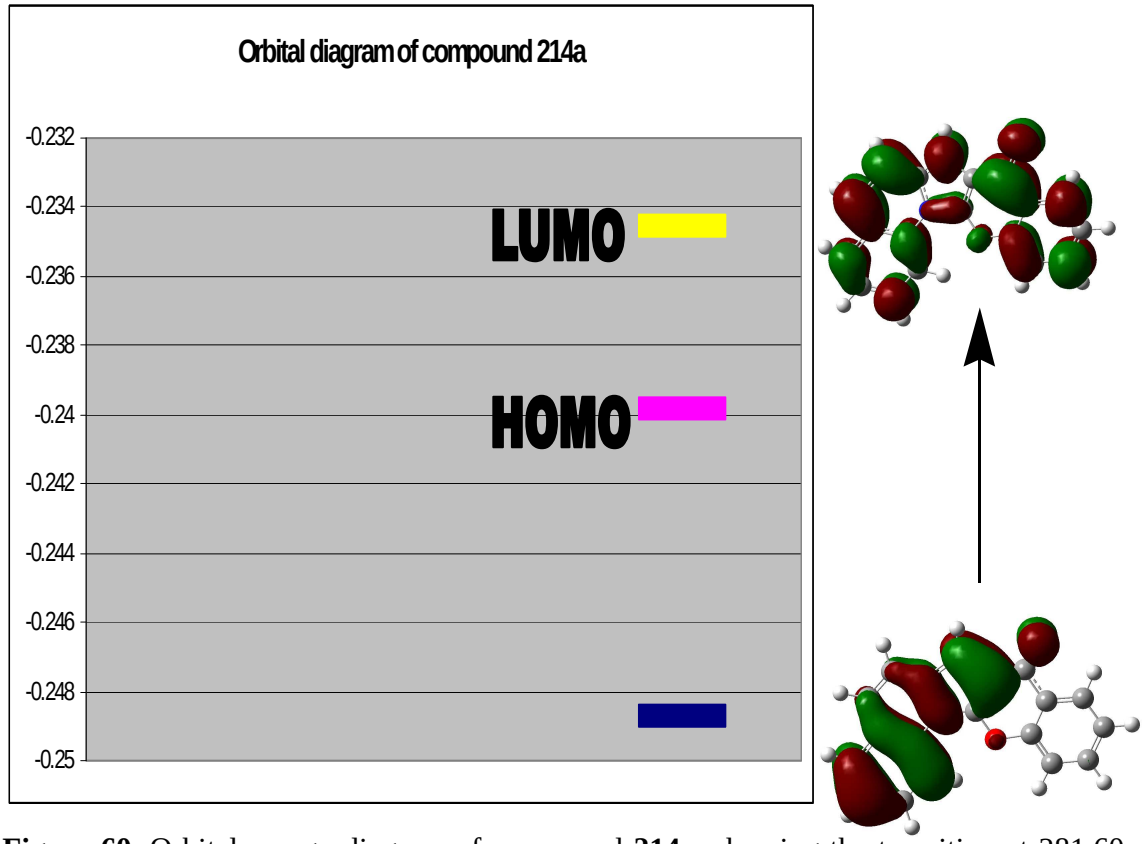


Figure 60. Orbital energy diagram of compound **214a**, showing the transition at 281.60 nm and the atomic orbital contributions to the molecular orbitals involved.

Table 27: Comparative UV absorption maxima for the series **214a, c, d** in chloroform

R = H (Compound 214a)	R = Br (Compound 214c)	R = F (Compound 214d)
391.97 nm	391.96 nm	387.07 nm
344.91 nm	345.07 nm	345.07 nm
317.96 nm	317.96 nm	317.96 nm
290.49 nm	291.07 nm	290.93 nm
274.06 nm	274.06 nm	274.06 nm

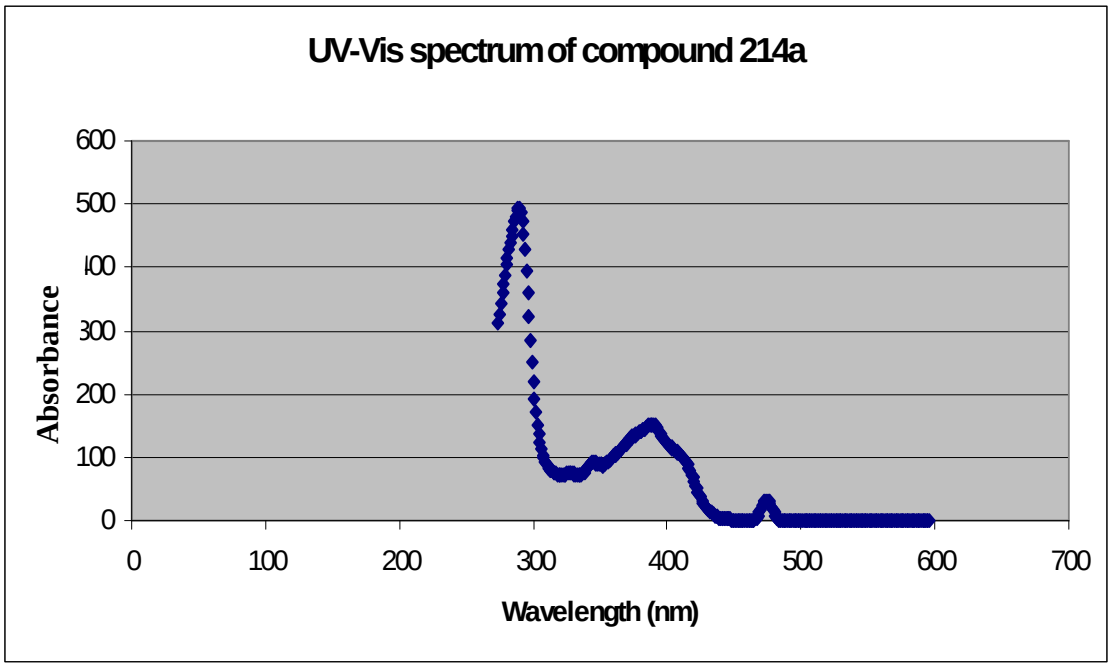


Figure 61. Experimental UV spectrum of compound **214a**, in chloroform.

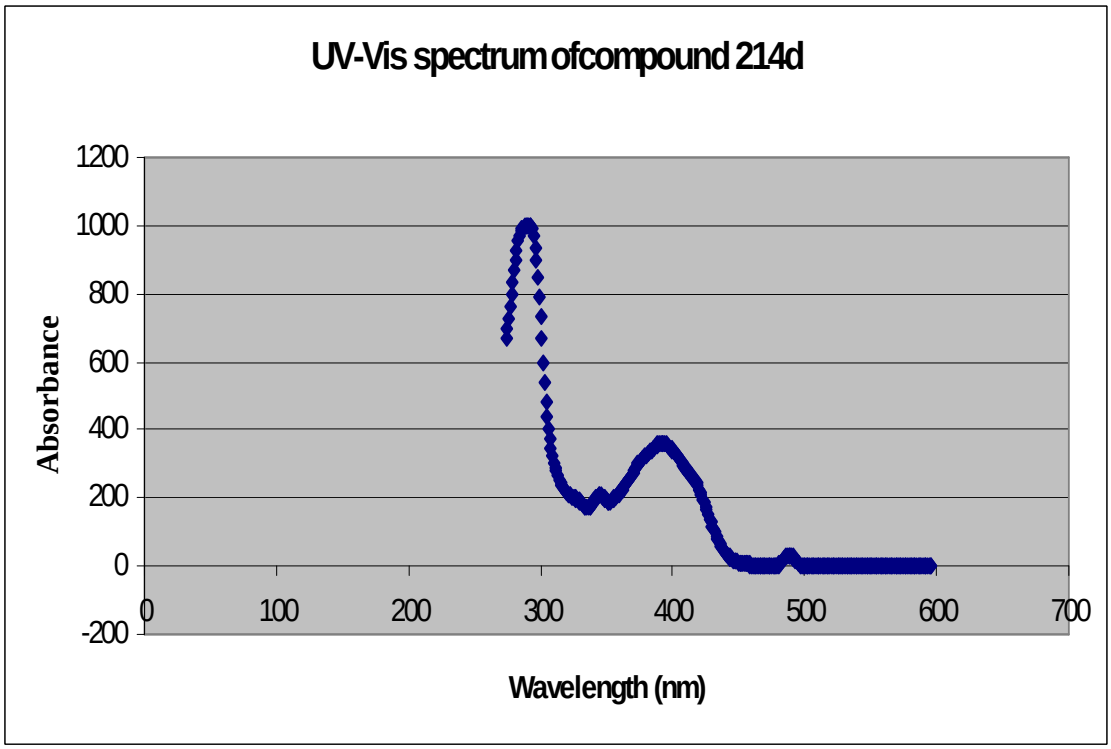


Figure 62. Experimental UV spectrum of compound **214d**, in chloroform.

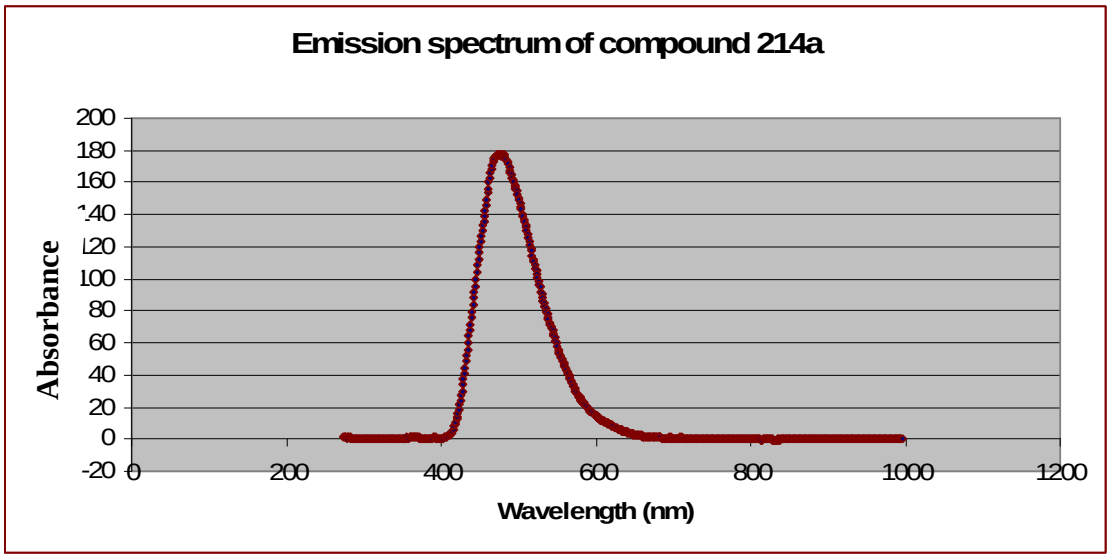


Figure 63. Experimental emission spectrum of compound **214a** at 260 nm, in chloroform.

2.8 CONCLUSIONS

This study has been concerned with the use of Baylis-Hillman methodology in the construction of poly-heterocyclic products, and particular attention has been given to the effects of varying the reactants, the catalysts and the reaction conditions. Chromone-3- and -2-carbaldehydes, pyridinecarbaldehydes and 2-nitrobenzaldehydes have all been used as substrates, together with methyl vinyl ketone (MVK), methyl acrylate, cyclic enones (2-cyclohexen-1-one, 2-cyclopenten-1-one and chromones) as activated alkenes, and 1,4-diazabicyclo[2.2.2]octane (DABCO), 3-hydroxyquinuclidine (3-HQ), imidazole and N',N',N',N'-tetramethylpropanediamine (TMPDA) as catalysts.

The chromone-3-carbaldehydes were successfully prepared using Vielsmeier-Haack methodology in yields ranging between 30 and 72%, while chromone-2-carbaldehydes were obtained from Kostanecki-Robinson reactions in somewhat lower yields ranging from 10 to 45%. Baylis-Hillman reactions of these chromone-3- and 2-carbaldehydes were conducted using the four different catalysts {1,4-diazabicyclo[2.2.2]octane (DABCO), 3-hydroxyquinuclidine (3-HQ), imidazole and N',N',N',N'-tetramethylpropanediamine (TMPDA)} and the five different activated alkene systems [methyl vinyl ketone (MVK), methyl acrylate, 2-cyclohexen-1-one, 2-cyclopenten-1-one and chromones]. The reactions between the chromone-3-carbaldehydes and MVK afforded dimeric products in poor to moderate yields when catalysed by DABCO whereas, when the reaction was catalysed by 3-HQ, the dimeric products were isolated in improved yields in a shorter period, together with tricyclic products.

The normal Baylis-Hillman adducts, isolated from reactions of chromone-3-carbaldehydes with methyl acrylate using DABCO as a catalyst, were also treated with primary amines in expectation of obtaining tricyclic derivatives; however, intractable mixtures of products were again obtained. Reactions involving chromone-3-carbaldehydes with cyclic enones 2-cyclohexene-1-one, 2-cyclopenten-1-one and chromones) using imidazole or TMPDA as catalysts under different solvent conditions, failed to yield any of the expected products. Instead, the starting materials were recovered unconsumed – an observation attributed to the susceptibility of chromone-3-

carbaldehydes to nucleophilic attack at C-2 by the catalyst, thus decreasing the electrophilicity of the aldehydic group and inhibiting the Baylis-Hillman reaction. Similarly, when chromone-2-carbaldehydes were treated with cyclic enones using different catalysts (imidazole and TMPDA), the starting materials were obtained unconsumed.

Use of chromone-2-carbaldehydes as substrates in the presence of methyl acrylate, afforded, albeit in very low yields, interesting rearrangement products, thus confirming formation of a single analogue in a previous study in our group.

The reactions between 2-nitrobenzaldehydes and the cyclic enones, however, afforded normal Baylis-Hillman adducts, and subsequent reductive cyclization of the adducts derived from cyclohexen-1-one and cyclopent-1-one afforded the corresponding quinoline derivatives in yields ranging from 5-71%.

Reactions involving pyridine-2-carbaldehydes and quinoline-2-carbaldehydes with cyclic enones catalyzed by TMPDA typically afforded the expected Baylis-Hillman adducts in good yields. The Baylis-Hillman adducts were cyclized to the corresponding indolizine derivatives by treating them with acetic anhydride under reflux or microwave assisted conditions. The microwave-assisted reactions afforded the indolizine derivatives in much shorter time with improved yields and purity. Interestingly, the reactions between pyridine-2-carbaldehydes and 2-cyclohexen-1-one afforded the cyclized indolizine derivatives directly – a phenomenon not observed with reactions involving 2-cyclopenten-1-one.

When comparing the catalysts used for the Baylis-Hillman reactions carried out in this study, 3-hydroxyquinuclidine was found to be superior to DABCO in reactions involving chromone-3-carbaldehydes and MVK. On the other hand, imidazole was found to be suitable for reactions involving 2-nitrobenzaldehydes and cyclic enones, while TMPDA was found to be good for reactions involving pyridine-2-carbaldehydes and quinoline-2-carbaldehydes with cyclic enones.

Computational studies were carried out on selected compounds at the QM and DFT levels using the Gaussian ’03 programme. The theoretical models were used to calculate NMR and UV spectroscopic properties. The calculated and experimental NMR data were, in many cases, in good agreement, and generally correlated well with the ^{1}H and ^{13}C values predicted using the MestraNova programme. The calculated UV absorption data generally correlated well with the experimental spectra, and it was apparent that substituted compounds in a series had very similar properties, showing that, in the cases examined, the substituents have little effect on the absorption spectra.

From our studies, it is apparent that the Baylis-Hillman reaction permits access to a remarkable variety of poly-heterocyclic scaffolds, which are capable, in turn, of further structural elaboration. Future research in this area is expected to involve the following.

- Optimisation of the yields of the tricyclic Baylis-Hillman products, in order to explore their cyclization to novel spiro compounds.
- Extension of the promising microwave-assisted approach to the construction of complex poly-heterocyclic systems.
- Re-examination of the reactions of the Baylis-Hillman dimers to explore the regioselectivity of nucleophilic attack at various electrophilic centres and to characterize the fragmentation products.
- Screening of selected systems for antibacterial and other biological activity.

3. Experimental

3.1 General

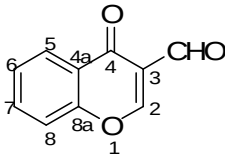
^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 400 and 600 MHz spectrometers at 303K, and were calibrated using the solvent signals; coupling constants are given in Hertz (Hz). Melting points were determined using a Kofler hot-stage apparatus, and are uncorrected. IR spectra were recorded on a Perkin Elmer Spectrum 2000 FT-IR spectrometer. Low-resolution mass spectra were recorded on a Finnigan GCQ spectrometer (Rhodes University) and high-resolution mass spectra were recorded on a VG70-SEQ double-focusing magnetic sector instrument (University of the Witwatersrand Mass Spectrometry Unit).

Flash Chromatography was carried out using Merck silica gel 60 [230-240 mesh (particle size 0.040-0.063 mm)] and preparative layer chromatography was conducted using silica gel 60 PF_{254}. Thin layer chromatography (TLC) was carried out on pre-coated Merck silica gel F_{254} plates, visualization being achieved by inspection under UV light (254nm) or following exposure to iodine.

N,*N*-Dimethylformamide (DMF) was pre-dried and distilled from 3Å molecular sieves under reduced pressure. Ethanol was dried by reaction with magnesium turnings and iodine and then distilled from the resulting magnesium alkoxide under nitrogen.

3.2 Baylis-Hillman reactions involving chromone-3-carbaldehydes

3.2.1 Synthesis of chromone-3-carbaldehydes



Chromone-3-carbaldehyde 40a. A solution of 2-hydroxyacetophenone (6.80 g, 50 mmol) in dry DMF (50 mL) was stirred under nitrogen at -20 ^{o}C for 5 min. $POCl_3$ (18.7 mL, 200 mmol) was then added drop-wise maintaining the temperature at -20 ^{o}C. The reaction mixture was stirred for a further 30 min. and then allowed to warm to room temperature. After stirring overnight it was poured into ice-water (75 mL), and the resulting slurry was left to stand to enhance precipitation. The precipitate was filtered off, washed successively with water and ethanol and recrystallized from acetone to afford, as a white crystalline solid, chromone-3-carbaldehyde **40a** (5.46 g, 63%), m.p. 153-154 ^{o}C (lit.,[159] 152-153 ^{o}C); ν_{max} (KBr)/cm^{-1} 1649 and 1690 (2x C=O); δ_H (400 MHz; $CDCl_3$) 7.51 (1H, t, *J* 8.0 Hz, 6-H), 7.56 (1H, d, *J* 8.8 Hz, 8-H), 7.78 (1H, ddd, *J* 1.6, 7.2 and 8.6 Hz, 7-H), 8.33 (1H, dd, *J* 1.6 and 8.0 Hz, 5-H), 8.57 (1H, s, 2-H) and 10.41 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 118.6 (C-8), 120.8 (C-3), 125.8 (C-4a), 126.6 (C-5), 127.1 (C-6), 135.2 (C-7), 156.6 (C-8a), 161.0 (C-2), 178.4 (C-4) and 189.0 (CHO); *m/z* 174 (**M**$^{+}$, 6%) and 146 (100).

6-Bromochromone-3-carbaldehyde 40b. The method used for the preparation of chromone-3-carbaldehyde **40a** was followed, using 5-bromo-2-hydroxyacetophenone (5.00 g, 23.3 mmol). Work-up and recrystallisation from acetone afforded, as a yellow crystalline solid, 6-bromochromone-3-carbaldehyde **40b** (4.23 g, 72%), m.p. 187-189 ^{o}C (lit,[159,160,196] 186-188 ^{o}C); ν_{max} (KBr)/cm^{-1} 1655 and 1699 (2x C=O); δ_H (400 MHz; $CDCl_3$) 7.43 (1H, d, *J* 8.8 Hz, 8-H), 7.82 (1H, dd, *J* 2.4 and 8.8 Hz, 7-H), 8.38 (1H, d, *J*

2.4 Hz, 5-H), 8.53 (1H, s, 2-H) and 10.33 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 120.3 (C-6), 120.4 (C-3), 120.5 (C-8), 126.6 (C-4a), 128.8 (C-5), 137.8 (C-7), 154.9 (C-8a), 160.6 (C-2), 174.6 (C-4), and 188.0 (CHO). *m/z* 252 (**M**$^+$, 4%) and 226 (100).

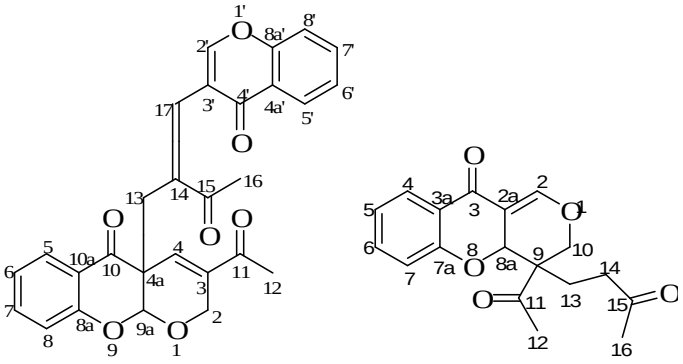
6-Chlorochromone-3-carbaldehyde 40c. The method used for the preparation of chromone-3-carbaldehyde **40a** was followed, using 5-chloro-2-hydroxyacetophenone (5.00 g, 29.3 mmol). Work-up and recrystallisation from acetone afforded, as a yellow crystalline solid, 6-chlorochromone-3-carbaldehyde **40c** (7.23 g, 70%), m.p. 165-167 ^oC (lit.,[159] 166-168 ^oC); ν_{max} (KBr)/cm^{-1} 1655 and 1695 (2x C=O); δ_H (400 MHz; $CDCl_3$) 7.49 (1H, d, *J* 9.2 Hz, 8-H), 7.68 (1H, dd, *J* 2.4 and 8.8 Hz, 7-H), 8.23 (1H, d, *J* 2.4 Hz, 5-H), 8.52 (1H, s, 2-H) and 10.34 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 120.3 (C-3), 120.3 (C-8), 125.6 (C-5), 126.3 (C-4a), 132.8 (C-6), 135.0 (C-7), 154.5 (C-8a), 160.6 (C-2), 174.8 (C-4) and 188.0 (CHO). *m/z* 208 (**M**$^+$, 4%) and 180 (100).

6-Fluorochromone-3-carbaldehyde 40d. The method used for the preparation of chromone-3-carbaldehyde **40a** was followed, using 5-fluoro-2-hydroxyacetophenone (3.00 g, 19.5 mmol). Work-up and recrystallisation from acetone afforded, as an off-white crystalline solid, 6-fluorochromone-3-carbaldehyde **40d** (1.13g; 30%), m.p. 157-159 ^oC (lit.,[159] 156-158 ^oC); ν_{max} (KBr)/cm^{-1} 1695 and 1702 (2x C=O); δ_H (400 MHz, $CDCl_3$) 7.47 (1H, m, 7-H), 7.56 (1H, m, 8-H), 7.92 (1H, dd, *J* 2.8 and 7.8 Hz, 5-H), 8.54 (1H, s, 2-H) and 10.35 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 111.4 (C-5), 119.6 (C-4a), 120.9 (C-8), 123.1 (C-7), 126.6 (C-6), 126.7 (C-3), 152.3 (C-8a), 160.7 (C-2), 175.2 (C-4) and 188.2 (CHO). *m/z* 192 (**M**$^+$, 4%) and 164 (100).

6-Methoxychromone-3-carbaldehyde. **40e**. The method used for the preparation of chromone-3-carbaldehyde **40a** was followed, using 5-methoxy-2-hydroxyacetophenone (3.00 g, 18.1 mmol). Work-up and recrystallisation from acetone afforded, as an off-white crystalline solid, 6-methoxychromone-3-carbaldehyde **40e** (1.80 g; 35%), m.p. 164-

165 ^{o}C (lit.,[159] 164-166 ^{o}C); ν_{max} (KBr)/cm^{-1} 1656 and 1702 (2x C=O); δ_H (400 MHz; $CDCl_3$) 3.91 (3H,s, OCH_3), 7.30 (1H, dd, *J* 2.8 and 9.2 Hz, 7-H), 7.45 (1H, d, *J* 8.8 Hz, 8-H), 7.63 (1H, d, 3.2 Hz, 5-H), 8.51 (1H, s, 2-H) and 10.39 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 56.1 (OCH_3), 105.5 (C-5), 119.6 (C-3), 120.0 (C-8), 124.4 (C-7), 126.1 (C-4a), 151.0 (C-8a), 158.0 (C-6), 160.2 (C-2), 175.8 (C-4) and 188.7 (CHO). *m/z* 204 (**M**$^{+}$, 1%) and 176 (100).

3.2.2 Reactions of chromone-3-carbaldehydes with methyl vinyl ketone



The chromone dimer 165a and **9-[11-acetyl-(15-oxo-butyl)-10-dihydro-3*H*-pyrano(9,2*a*)]chromen-3-one 166a**. Chromone-3-carbaldehyde **40a** (1.00 g, 5.75 mmol) was dissolved in $CHCl_3$ (7.0 mL). Methyl vinyl ketone (0.84 g, 6.3 mmol) and DABCO (0.20 g, 1.8 mmol) were added, and the resulting mixture was stirred at room temperature for three weeks with TLC monitoring. The reaction mixture was concentrated *in vacuo* and ethyl acetate added to the crude product, producing a yellow precipitate. The yellow precipitate was filtered off by suction and washed with ethyl acetate to afford, as an off-white solid, the chromone dimer **165a** (0.65 g, 72 %), m.p. 193-195 ^{o}C (lit.,[196] 193-194 ^{o}C); ν_{max} (KBr)/cm^{-1} 1606, 1642, 1665 and 1695 (4x C=O); δ_H (400 MHz; $CDCl_3$) 2.28 (3H, s, 12-H), 2.42 (3H, s, 16-H), 3.22 (2H, s, 13-H), 4.51-4.59 (2H, m, 2-Ha and 2-Hb), 5.00 (1H, s, 9-Ha), 6.86-6.93 (2H, m, 5-H and 6-H), 7.16 (1H, s, 4-H), 7.26 (1H, m, 8-H), 7.40-7.45 (3H, m, 17-H, 7'-H and 8'-H), 7.69-7.73 (2H, m, 6'-H and 7-H), 7.89 (1H, s,

2'-H), and 8.12 (1H, dd, *J* 1.2 Hz and 7.8 Hz, 5'-H); δ_C (100 MHz; $CDCl_3$) 25.3 (C-12 and C-16), 25.9 (C-13), 50.1 (C-4a), 65.9 (C-2), 99.8 (C-9a), 117.5 (C-5), 118.1 (C-7'), 120.0 (C-10a), 120.3 (C-4a'), 122.9 (C-6), 123.5 (C-8a'), 125.8 (C-8'), 126.0 (C-5'), 128.0 (C-7), 133.6 (C-17), 134.2 (C-6'), 136.1 (C-8), 136.6 (C-3),136.7 (C-4), 139.1 (C-14), 154.1 (C-2'), 155.9 (C-3'), 157.0 (C-8a), 175.6 (C-4'), 191.5 (C-10), 196.9 (C-11) and 199.0 (C-15); *m/z* 470 ($\mathbf{M}^+$, 8%) and 427 (100%).

9-[11-Acetyl-(15-oxo-butyl)-10-dihydro-3*H*-pyrano(9,2*a*)]chromen-3-one 166a. The filtrate from the above reaction was concentrated *in vacuo*, purified by flash chromatography [on silica; elution with hexane-EtOAc (1:2)] to give a mixture of products, which was subjected to HPLC [elution with hexane-EtOAc (1:3)] to give two fractions as viscous oils.

Fraction 1. **9-[11-acetyl-(15-oxo-butyl)-10-dihydro-3*H*-pyrano (9,2*a*)]chromen-3-one** as a yellow viscous oil **$\mathbf{166a_1}$** (12%), (Found: $\mathbf{M}^+$ 314.11478. Calc. for $C_{18}H_{18}O_5$, M: 314.11543.); δ_H (600 MHz, $CDCl_3$) 2.01 (1H, m, 14-H), 2.18 (1H, m, 14-H), 2.06 (3H, s, 16-CH_3), 2.36 (3H, s, 12-CH_3), 2.40 (1H, m, 13-H), 2.53 (1H, m, 13-H), 4.57 (1H, dd, *J* 1.8 and 16.8 Hz, 10-Ha), 4.77 (1H, dd, *J* 1.8 and 17.4 Hz, 10-Hb), 5.12 (1H, s, 8a-H), 7.09-7.12 (2H, m, 5-H and 7-H), 7.28 (1H, s, 2-H), 7.55 (1H, td, *J* 1.2 and 7.8 Hz, 6-H), and 7.87 (1H, dd, *J* 1.8 and 7.8 Hz, 4-H); δ_C (100 MHz; $CDCl_3$) 24.8 (C-13), 25.4 (C-16), 29.9 (C-12), 37.7 (C-14), 49.1 (C-9), 65.8 (C-10), 99.9 (C-8a), 118.1 (C-7), 119.5 (C-2a), 122.9 (C-4), 127.9 (C-5), 135.3 (C-6), 136.7 (C-2), 138.3 (C-3a), 157.6 (C-7a), 192.5 (3-C=O), 196.5 (15-C=O) and 206.6 (11-C=O); *m/z* 193 (100%), 151 (15%), 136 (22%) and 121 (12%).

Fraction 2. **Diastereoisomeric *9-[11-acetyl-(15-oxo-butyl)-10-dihydro-3*H-*pyrano(9,2a)]chromen-3-one*** **$\mathbf{166a_2}$** as a colourless viscous oil (4%); (Found: $\mathbf{M}^+$ 314.11486. Calc. for $C_{18}H_{18}O_5$, M 314.11543.), δ_H (600 MHz, $CDCl_3$) 2.11 (3H, s, 16-CH_3), 2.18 (2H, t, *J* 7.8 Hz, 14-Ha,b), 2.29 (3H, s, 12-CH_3), 2.56 (2H, t, *J* 7.8 Hz, 13-Ha,b), 4.45 (1H, dd, *J* 1.8 and 15.6 Hz, 10-Ha), 4.61 (1H, dd, *J* 1.2 and 15.6 Hz, 10-Hb), 5.40 (1H, s, 8a-H), 6.67 (1H, s, 2-H), 7.00 (1H, d, *J* 8.4 Hz, 7-H), 7.06 (1H, t, *J* 7.8 Hz,

5H), 7.52 (1H, td, *J* 1.8 and 8.4 Hz, 6-H) and 7.82 (1H, dt, *J* 1.8 and 7.8 Hz, 4-H); δ_C (100 MHz; $CDCl_3$) 25.2 (C-13), 27.7 (C-16), 29.9 (C-12), 37.7 (C-14), 49.7 (C-9), 62.5 (C-10), 99.4 (C-8a), 118.2 (C-7), 119.2 (C-2a), 122.6 (C-4), 127.2 (C-5), 135.9 (C-6), 137.1 (C-2), 138.0 (C-3a), 157.6 (C-7a), 193.1 (3-C=O), 196.3 (15-C=O) and 206.5 (11-C=O); *m/z* 193 (100%), 151 (15%), 136 (22%) and 121 (12%).

6-bromo-substituted chromone dimer 165b and **9-[11-acetyl-(15-oxo-butyl)-10-dihydro-3*H*-pyrano (9,2*a*)]-5-bromochromen-3-one 166b.** The method used for the preparation of the chromone dimer **165a** was followed, using 6-bromochromone-3-carbaldehyde **40b** (3.00 g, 11.9 mmol). Work-up afforded as a cream solid, 6-bromo-substituted chromone dimer.**165b** (1.74 g; 47 %), m.p. 223-224 ^oC (lit.,[196] 222-224 ^oC); ν_{max} (KBr)/cm^{-1} 1600, 1670, 1675 and 1710 (4x C=O); δ_H (400 MHz; $CDCl_3$) 2.31 (3H, s, 12-H), 2.43 (3H, s, 16-H), 3.14 (2H, s, 13-H), 4.55 (2H, dd, *J* 17.2 and 17.2 Hz, 2-Ha and 2-Hb), 4.98 (1H, s, 9a-H), 6.77 (1H, d, *J* 8.8 Hz, 8-H), 7.28 (1H, m, 7-H), 7.11 (1H, s, 4-H), 7.33-7.37 (2H, m, 7'-H and 17-H), 7.78-7.82 (2H, m, 5-H and 8'-H), 7.87 (1H, s, 2'-H) and 8.27 (1H, d, *J* 2.4 Hz, 5'-H); δ_C (100 MHz; $CDCl_3$) 25.4 (C-12 and C-16), 25.9 (C-13), 50.0 (C-4a), 66.0 (C-2), 99.8 (C-9a), 115.9 (C-6), 119.4 (C-8), 120.0 (C-3' and C-6'), 120.4 (C-8'), 121.2 (C-10a), 124.6 (C-4a'), 128.7 (C-5), 130.4 (C-17), 133.3 (C-5'), 136.2 (C-7), 136.5 (C-3), 137.3 (C-4), 138.8 (C-7'), 139.4 (C-14), 154.1 (C-2'), 154.5 (C-8a'), 155.9 (C-8a), 174.1 (C-4'), 190.3 (C-11), 196.9 (C-15) and 198.9 (C-10); *m/z* 628 ($\mathbf{M}^+$, 9%) and 585 (100%).

9-[11-acetyl-(15-oxo-butyl)-10-dihydro-3*H*-pyrano(9,2*a*)]-5-bromochromen-3-one 166b. The filtrate from the above reaction was concentrated *in vacuo*, purified by flash chromatography [on silica; elution with hexane-EtOAc (1:2)] afforded a mixture of products, which was subjected to HPLC [elution with hexane-EtOAc (1:3)] to give as a brown viscous oil 9-[11-acetyl-(15-oxo-butyl)-10-dihydro-3H-pyrano(9,2a)]-5-bromochromen-3-one **166b**, [Found: $\mathbf{M}^+$ 394.02412 (^{81}Br) and $\mathbf{M}^+$ 392.02570 (^{79}Br). Calc. for $C_{18}H_{17}BrO_5$, M 393.22858 (^{81}Br) and M 392.02594 (^{79}Br).]; δ_H (400 MHz,

$CDCl_3$) 2.04 (1H, m, 14-H), 2.09 (3H, s, 16-CH_3), 2.20 (1H, m, 14-H), 2.39 (3H, s, 12-CH_3), 2.42 (1H, m, 13-H), 2.52 (1H, m, 13-H), 4.59 (1H, d, *J* 17.2 Hz, 10-Ha), 4.80 (1H, d, *J* 17.2 Hz, 10-Hb), 5.12 (1H, s, 8a-H), 7.04 (1H, d, *J* 8.8 Hz, 7-H), 7.26 (1H, s, 2-H), 7.65 (1H, dd, *J* 2.4 and 8.8 Hz, 6-H) and 8.01 (1H, d, *J* 2.4 Hz, 4-H); δ_C (100 MHz; $CDCl_3$) 24.7 (C-13), 25.5 (C-16), 30.0 (C-12), 37.6 (C-14), 49.0 (C-9), 66.0 (C-10), 100.0 (C-8a), 115.8 (C-2a), 120.2 (C-7), 120.8 (C-4), 130.3 (C-6), 134.8 (C-2), 138.4 (C-3a), 139.4 (C-5), 156.5 (C-7a), 191.4 (C-3), 196.5 (C-15) and 206.5 (C-11); *m/z* 323(6%), 199 (8%), 193 (100%), 151 (32%) and 136(52%).

6-chloro-substituted chromone dimer 165c and ***9-[11-acetyl-(15-oxo-butyl)-10-dihydro-3*H*-pyrano (9,2*a*)]-5-chlorochromen-3-one 166c*** The method used for the preparation of the chromone dimer **165a** was followed, using 6-chlorochromone-3-carbaldehyde **40c** (1.00 g, 4.80 mmol). Work-up afforded as a cream solid, 6-chloro-substituted chromone dimer **165c** (0.85 g, 66%), m.p. 112-114 ^oC (lit.,[196] 113-115 ^oC); ν_{max} (KBr)/cm^{-1} 1655, 1678. 1684 and 1702 (4x C=O); δ_H (400 MHz; $CDCl_3$) 2.29 (3H, s, 12-H), 2.43 (3H, s, 16-H), 3.19 (2H, s, 13-H), 4.54 (2H, dd, *J* 17.2 and 17.6 Hz, 2-Ha and 2-Hb), 4.98 (1H, s, 9a-H), 6.85 (1H, d, *J* 8.8 Hz, 8-H), 7.10 (1H, s, 4-H), 7.15 (1H, dd, *J* 2.4 and 8.8 Hz, 7-H), 7.36 (1H, s, 17-H), 7.40 (1H, d, *J* 8.8 Hz, 8'-H), 7.63-7.67 (2H, m, 5-H and 7'-H), 7.86 (1H, s, 2'-H) and 8.09 (1H, d, *J* 2.4 Hz, 5'-H); δ_C (100 MHz; $CDCl_3$) 25.3 (C-12 and C-16), 25.9 (C-13), 50.0 (C-4a), 66.0 (C-2), 99.9 (C-9a), 119.8 (C-8'), 120.3 (C-3'), 120.8 (C-10a), 124.3 (C-6), 125.5 (C-4a'), 127.3 (C-6'), 128.6 (C-5), 131.9 (C-5'), 133.3 (C-17), 134.6 (C-7), 136.0 (C-7'), 136.1 (C-3), 136.6 (C-4), 139.4 (C-14), 154.1 (C-2'), 154.1 (C-8a'), 155.4 (C-8a), 174.3 (C-4'), 190.4 (C-11), 196.8 (C-15), 198.8 (C-10); *m/z* 538 ($\mathbf{M}^+$, 14%) and 495 (100%).

9-[11-acetyl-(15-oxo-butyl)-10-dihydro-3*H*-pyrano(9,2*a*)]-5-chlorochromen-3-one 166c: The filtrate from the above reaction was concentrated *in vacuo*, purified by flash chromatography [on silica; elution with hexane-EtOAc (1:2)] afforded a mixture of products, which was subjected to HPLC [elution with hexane-EtOAc (1:3)] to give as a

colourless viscous oil (Calc. for $C_{18}H_{17}ClO_5$; *m/z* 348.07645. Found *m/z* 348.07590 M^+); *9-[11-acetyl-(15-oxo-butyl)-10-dihydro-3*H*-pyrano(9,2*a*)]-5-chlorochromen-3-one* ***166c***, δ_H (400 MHz, $CDCl_3$) 2.03 (3H, s, 16-H). 2.20 (2H, t, J 8.4 Hz, 14-H), 2.32 (3H, s, 12-CH3), 2.57 (2H, t, J 8.0 Hz, 13-H), 4.48 (1H, dd, J 1.6 and 16.8 Hz, 10-Ha), 4.63 (1H, dd, 0.8 and 17.2 Hz, 10-Hb), 5.41 (1H, s, 8a-H), 6.66 (1H, s, 2-H), 7.00 (1H, J 8.8 Hz, 7-H), 7.48 (1H, dd, J 2.8 and 8.8 Hz, 6-H), 7.80 (1H, d, J 2.8 Hz, 4-H). δ_C (100 MHz; $CDCl_3$) 25.3 (C-16), 27.6 (C-13), 31.9 (C-12), 37.6 (C-14), 49.7 (C-9), 62.8 (C-10), 99.7 (C-8a), 120.0 (C-2a), 120.1 (C-7), 126.6 (C-4), 128.4 (C-6), 135.4 (C-2), 136.9 (C-3a), 138.3 (C-5), 156.1 (C-7a), 192.3 (C-3), 196.3 (C-15), 206.4 (C-11); *m/z* 277 (14%), 235 (9%), 193 (100%), 151 (44%) and 136 (71%).

6-fluoro-substituted chromone dimer 165d. The method used for the preparation of the chromone dimer **165a** was followed, using 6-fluorochromone-3-carbaldehyde **40d** (2.00 g, 10.42 mmol). Work-up afforded as a cream solid, 6-fluoro-substituted chromone dimer **165d** (0.89 g, 34%), m.p. 230-232 ^oC (lit.,[196] 230-231 ^oC); ν_{max} (KBr)/cm^{-1} 1675, 1683, 1698 and 1717 (4x C=O); δ_H (400 MHz; $CDCl_3$) 2.28 (3H, s, 12-H), 2.43 (3H, s, 16-H), 3.20 (2H, dd, *J* 13.6 and 14.0 Hz, 2x 13-H), 4.52 (2H, dd, *J* 16.8 and 17.2 Hz, 2-Ha and 2-Hb), 4.98 (1H, s, 9a-H), 6.92 (1H, d, *J* 4.0 Hz, 5-H), 6.99 (1H, m, 7-H), 7.10 (1H, s, 4-H), 7.35 (1H, d, *J* 7.6 Hz, 8-H), 7.40 (1H, s, 17-H),7.44-7.47 (2H, m, 5'-H and 7'-H), 7.76 (1H, d, *J* 8.8 Hz, 8'-H) and 7.89 (1H, s, 2'-H), δ_C (100 MHz; $CDCl_3$) 25.3 (C-12), 25.8 (C-16),25.9 (C-13), 49.9 (C-4a), 66.0 (C-2), 110.7 (C-9a), 119.2 (C-8), 119.7 (C-3'), 120.3 (C-5), 122.5 (C-5'), 122.8 (C-8'), 123.5 (C-10a), 123.8 (C-4a'), 133.4 (C-7), 136.0 (C-7'),136.7 (C-17), 139.3 (C-4), 152.0 (C-3), 153.1 (C-14), 154.2 (C-2'), 158.6 (C-6), 159.0 (C-8a),161.0 (C-6'), 174.8 (C-4'), 190.7 (C-11), 196.8 (C-15) and 198.8 (C-10).; *m/z* 506 (**M^+**, 7%) and 463 (100%).

6-methoxy-substituted chromone dimer 165e. The method used for the preparation of the chromone dimer **165a** was followed, using 6-methoxychromone-3-carbaldehyde **40e** (1.50 g, 7.4 mmol). Work-up afforded as a cream solid, 6-methoxy-substituted chromone

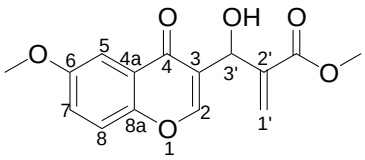
dimer **165e** (0.70 g, 30%), m.p. 203-204 ^{o}C (lit.,[196] 203-205 ^{o}C); ν_{max} (KBr)/cm^{-1} 1655, 1674, 1677 and 1701 (4x C=O); δ_H (400 MHz; $CDCl_3$) 2.33 (3H, s, 12-H), 2.45 (3H, s, 16-H), 3.22 (2H, dd, *J* 13.6 and 14.0 Hz, 13-Ha and 13-Hb), 3.72 (3H, s, 6-OCH_3), 3.92 (3H, s, 6'-OCH_3), 4.55 (2H, dd, *J* 17.2 and 17.2 Hz, 2x 2-H), 4.95 (1H, s, 9a-H), 6.69 (1H, dd, *J* 2.8 and 9.0 Hz, 7-H), 6.76 (1H, d, *J* 9.2 Hz, 8-H), 7.08 (1H, d, *J* 2.8, 5-H), 7.17 (1H, s, 4-H), 7.28 (1H, dd, *J* 3.2 and 9.2 Hz, 7'-H), 7.34 (1H, d, *J* 9.2 Hz, 8'-H), 7.42 (1H, s, 17-H), 7.44 (1H, d, *J* 3.2, 5'-H) and 7.86 (1H, s, 2'-H); δ_C (100 MHz; $CDCl_3$) 25.4 (C-12), 25.9 (C-13 and C-16), 50.1 (C-4a), 55.5 (6'-OCH3), 55.9 (6-OCH3), 66.9 (C-2), 99.7 (C-9a), 105.0 (C-5), 108.1 (C-8), 118.5 (C-6'), 119.2 (C-8'), 119.3 (C-7), 119.8 (C-3'),124.0 (C-7'), 124.1 (C-4a'), 125.1 (C-10a), 133.9 (C-17), 136.0 (C-3), 137.3 (C-4), 139.0 (C-14), 150.6 (C-2'), 151.4 (C-8a'), 153.8 (C-8a), 154.7 (C-6), 157.2 (C-6'), 175.3 (C-4'), 191.4 (C-11), 197.1 (C-15) and 199.2 (C-10).; *m/z* 530 (**M**$^{+}$, 21%) and 487 (100%).

3.2.2.1 Attempted reactions of chromone dimer 165a with various amines and Grignard reagents

The chromone dimer **165a** was treated with various amines such as benzylamine, isopropylamine, glycine ethyl ester, pyrrolidine and diethylamine. Work-up followed by flash chromatography afforded a mixture of products which was subjected to HPLC [elution with hexane-EtOAc (1:2)] to give an intractable mixture of products, with some of them appearing to be fragments of the expected products as observed from their mass spectra.

The chromone dimer **165a** was treated with methyl magnesium bromide at -78 ^{o}C. Work-up followed by flash chromatography afforded an intractable mixture of products.

3.2.3 Reactions of chromone-3-carbaldehydes with methyl acrylate

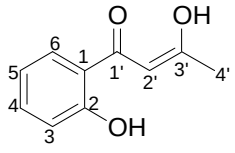


6-Methoxy-3-[3-hydroxy-2-(methoxycarbonyl)-1-propen-3-yl]chromone 173e. The method used for the preparation of the chromone dimer **165a** was followed, using 6-methoxychromone-3-carbaldehyde **40e** (0.20 g; 0.98 mmol) and methyl acrylate. Work-up followed by flash chromatography [on silica gel; elution with hexane-EtOAc(1:1), and HPLC on Partisil 10, elution with hexane-EtOAc (1:1)], afforded as a yellow oil, 6-methoxy-3-[3-hydroxy-2-9methoxycarbonyl)-1-propen-3-yl]chromone **173e** . δ_H (400 MHz; $CDCl_3$) 3.73 (3H, s, $COOCH_3$), 3.87 (3H, s, 6-OCH_3), 4.72 (1H, br s, OH), 5.60 (1H, s, 3'-H), 6.15 (1H, s, 1'-H), 6.43 (1H, s, 1-'H), 7.27 (1H, dd, *J* 2.2 and 9.2 Hz, 7-H),7.40 (1H, d, *J* 9.2 Hz, 8-H), 7.52 (1H, d, *J* 3.2 Hz, 5-H) and 8.03 (1H, s, 2-H); δ_C (100 MHz; $CDCl_3$) 52.0 ($COOCH_3$), 55.9 (6-OCH3), 67.8 (C-3'), 104.3 (C-5), 119.6 (C-8), 121.9 (C-3), 124.3 (C-7), 124.5 (C-4a), 126.6 (C-1'), 139.5 (C-2'), 151.1 (C-8a), 154.1 (C-2), 157.0 (C-6), 166.5 ($COOCH_3$) and 177.8 (C-4).

6-Bromo-3-[3-hydroxy-2-(methoxycarbonyl)-1-propen-3-yl]chromone 173b. The method used for the preparation the chromone dimer **165a** was followed, using 6-bromochromone-3-carbaldehyde **40b** (0.20 g; 0.79 mmol) and methyl acrylate. Work-up followed by chromatography [on silica gel; elution with hexane-EtOAc(1:1), followed by HPLC on Partisil 10, elution with hexane-EtOAc(1:1)], afforded as a yellow solid, 6-bromo-3-[3-hydroxy-2-9methoxycarbonyl)-1-propen-3-yl]chromone **173b**, mp 114-116 ^oC (lit.,[196] 114-116 ^oC); δ_H (400 MHz; $CDCl_3$) 3.74 (3H, s, $COOCH_3$), 4.43 (1H, d, *J* 8.0, OH), 5.60 (1H, d, *J* 7.2 Hz, 3'-H), 6.13 (1H, s, 1'-H), 6.43 (1H, s, 1'-H), 7.37 (1H, d, *J* 8.8 Hz, 8-H), 7.75 (1H, dd, *J* 2.4 and 8.8Hz, 7-H), 8.05 (1H, s, 2-H) and 8.29 (1H, d, *J* 2.4 Hz, 5-H); (100 MHz; $CDCl_3$) 52.0 (OCH_3), 67.6 (C-3'), 118.8 (C-8), 120.2 (C-6), 123.1 (C-3), 125.1 (C-4a), 127.0 (C-5), 128.2 (C-1'), 137.0 (C-5), 139.0 (C-7), 154.5 (C-2), 155.0 (C-8a), 166.5 (CO.O) and 176.5 (C=O).

3.3 Baylis-Hillman reactions involving chromone-2-carbaldehydes

3.3.1 Synthesis of 1-(2-Hydroxyphenyl)-1,3-butanediones



1-(2-Hydroxyphenyl)-1,3-butanedione 175a. A solution of 2-hydroxyacetophenone (10.00 mL, 83.1 mmol) in dry ethyl acetate (35.0 mL, 358 mmol) was added drop-wise to a stirred suspension of sodium ethoxide [generated *in situ* by adding sodium metal (8.00 g, 348 mmol) to dry ethanol (40.0 mL)]. The resulting yellow mixture was boiled gently under reflux for *ca* 8 hours until a thick yellow slurry was formed. After cooling to room temperature, the mixture was poured into diethyl ether (200 mL) and allowed to stand for 1 hour to enhance precipitation. The resulting precipitate was filtered off, washed with diethyl ether and dissolved in ice-cold water (100 mL). The solution was acidified with acetic acid and the resulting precipitate was filtered off and recrystallized from petroleum ether (boiling range 60-80 ^{o}C) to afford, as a yellow solid, 1-(2-hydroxyphenyl)-1,3-butanedione **175a** (10.31 g, 70%), δ_H (400 MHz; $CDCl_3$) 2.14 (3H, s, 4'-CH_3), 6.17 (1H, s, 2'-H), 6.86 (1H, t, *J* 8.0 Hz, 5-H), 6.96 (1H, d, *J* 8.0 Hz, 3-H), 7.43 (1H, t, *J* 8.8 Hz, 4-H), 7.62 (1H, d, *J* 8.0 Hz, 6-H), 12.06 (1H, s, 2-OH) and 14.96 (1H, s, 3'-OH); δ_C (100 MHz; $CDCl_3$) 22.7 (4'-CH_3), 95.4 (C-2'), 118.4 (C-1), 118.7 (C-5), 119.0 (C-3), 128.5 (C-6), 135.7 (C-4), 162.5 (C-2), 182.9 (C-3') and 195.4 (C=O).

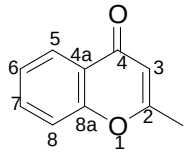
1-(5-Chroro-2-hydroxyphenyl)-1,3-butanedione 175b. The experimental procedure employed in the synthesis of 1-(2-hydroxyphenyl)-1,3-butanedione **175a** was followed, using 5-chloro-2-hydroxyacetophenone (5.00 g, 29 mmol). Work-up afforded as a greenish-yellow solid, 1-(5-Chroro-2-hydroxyphenyl)-1,3-butanedione **175b** (3.74 g, 60%). δ_H (400 MHz; $CDCl_3$) 2.16 (3H, s, 4'-CH_3), 6.11 (1H, s, 2'-H), 6.91 (1H, d, *J* 9.2

Hz, 3-H), 7.36 (1H, dd, *J* 2.4 and 8.8 Hz, 4-H), 7.57 (1H, d, *J* 2.4 Hz, 6-H), 11.96 (1H, s, 2-OH) and 14.87 (1H, s, 3'-OH); δ_C (100 MHz; $CDCl_3$) 22.8 (4'-CH_3), 95.4 (C-2'), 119.1 (C-3), 120.2 (C-1), 123.7 (C-5), 127.7 (C-6), 135.4 (C-4), 160.9 (C-2), 184.0 (C-3') and 194.1 (C=O).

1-(5-Methoxy-2-hydroxyphenyl)-1,3-butanedione 175c The experimental procedure employed in the synthesis of 1-(2-hydroxyphenyl)-1,3-butanedione **175a** was followed, using 5-methoxy-2-hydroxyacetophenone (10.0 g, 60 mmol). Work-up afforded as a greenish-yellow solid, 1-(5-methoxy-2-hydroxyphenyl)-1,3-butanedione **175c** (12.20 g, 97%). δ_H (400 MHz; $CDCl_3$) 2.14 (3H, s, 4'-CH_3), 3.78 (3H, s, 5-O CH_3), 6.10 (1H, s, 2'-H), 6.90 (1H, d, *J* 9.6 Hz, 3-H), 7.06 (1H, dd, *J* 2.8 and 9.6 Hz, 4-H), 7.32 (1H, d, *J* 3.2 Hz, 6-H), 11.62 (1H, s, 2-OH) and 15.05 (1H, s, 3'-OH); δ_C (100 MHz; $CDCl_3$) 22.8 (4'-CH_3), 56.0 (5-O CH_3), 95.4 (C-2'), 107.2 (C-1), 111.5 (C-6), 119.4 (C-3), 123.3 (C-4), 151.9 (C-2), 156.8 (C-5), 183.2 (C-3') and194.9 (C=O).

1-(5-Bromo-2-hydroxyphenyl)-1,3-butanedione 175d The experimental procedure employed in the synthesis of 1-(2-hydroxyphenyl)-1,3-butanedione **175a** was followed, using 5-bromo-2-hydroxyacetophenone (5.00 g, 23 mmol). Work-up afforded as a greenish-yellow solid, 1-(5-bromo-2-hydroxyphenyl)-1,3-butanedione **175d** (4.46 g, 75%). δ_H (400 MHz; $CDCl_3$) 2.16 (3H, s, 4'-CH_3), 6.10 (1H, s, 2'-H), 6.85 (1H, d, *J* 8.8 Hz, 3-H), 7.48 (1H, dd, *J* 2.4 and 8.8 Hz, 4-H), 7.70 (1H, d, *J* 2.0 Hz, 6-H), 12.04 (1H, s, 2-OH) and 14.86 (1H, s, 3'-OH); δ_C (100 MHz; $CDCl_3$) 22.8 (4'-CH_3), 95.4 (C-2'), 119.7 (C-5), 120.6 (C-3), 130.7 (C-1), 138.2 (C-6), 161.4 (C-4), 176.8 (C-2), 184.0 (C-3') and 194.0 (C=O).

3.3.2 Synthesis of 2-methylchromones



2-Methylchromone 176a. A stirred solution of 1-(2-hydroxyphenyl)-1,3-butanedione **175a** (10.0 g, 56 mmol), glacial acetic acid (51 mL) and sulphuric acid (2.0 mL) was boiled gently under reflux for *ca* 4 hours. The resulting, hot, red solution was poured into ice-cold water (255 mL) and basified with 10% aq. sodium bicarbonate. The resulting precipitate was filtered off, washed with ice-cold water and recrystallized from hexane to afford as yellow solid, 2-methylchromone **176a** (2.96 g, 33%), m.p. 68-70 ^{o}C (lit.,[196] 69-70 ^{o}C); ν_{max} (KBr)/cm^{-1} 1655 (C=O); δ_H (400 MHz; $CDCl_3$) 2.36 (3H, s, 2-CH_3), 6.15 (1H, s, 3-H), 7.33-7.40 (2H, m, 6- and 8-H), 7.62 (1H, t, *J* 8.0 Hz, 7-H) and 8.16 (1H, d, *J* 7.6 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 20.6 (2-CH_3), 110.5 (C-3), 117.7 (C-8), 123.5 (C-4a), 124.9 (C-6), 125.6 (C-5), 133.4 (C-7), 156.4 (C-8a), 166.1 (C-2), and 178.2 (C=O). *m/z* 160 (**M**$^+$, 100%).

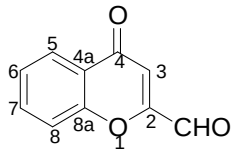
6-Chroro-2-methylchromone 176b. The experimental method used to synthesize 2-methylchromone **176a** was followed using 1-(5-chloro-2-hydroxyphenyl)-1,3-butanedione **175b** (2.00 g, 10 mmol). Work-up afforded as a yellow fluffy solid, 6-chloro-2-methylchromone **176b** (1.41 g, 77%), m.p. 112-114 ^{o}C (lit.,[196] 112-114 ^{o}C); ν_{max} (KBr)/cm^{-1} 1674 (C=O); δ_H (400 MHz; $CDCl_3$) 2.37 (3H, s, 2-CH_3), 6.15 (1H, s, 3-H), 7.35 (1H, d, *J* 8.8 Hz, 8-H), 7.55 (1H, dd, *J* 2.4 and 8.8 Hz, 7-H) and 8.11 (1H, d, *J* 2.4 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 20.6 (2-CH_3), 110.5 (C-3), 119.5 (C-5), 124.5 (C-6), 125.1 (C-7), 130.8 (C-4a), 133.6 (C-8), 154.7 (C-8a), 166.4 (C-2) and 176.9 (C=O). *m/z* 194 (**M**$^+$, 100%).

6-Methoxy-2-methylchromone 176c. The experimental method used to synthesize 2-methylchromone **176a** was followed using 1-(5-methoxy-2-hydroxyphenyl)-1,3-butanedione **175c** (9.2 g, 44 mmol). Work-up afforded as a green solid, 6-methoxy-2-

methylchromone **176c** (4.57 g, 54%), m.p. 105-106 ^{o}C (lit,[196] 107-108 ^{o}C); ν_{max} (KBr)/cm^{-1} 1675 (C=O); δ_H (400 MHz; $CDCl_3$) 2.34 (3H, s, 2-CH_3), 3.85 (3H, s, 6-OCH_3), 6.12 (1H, s, 3-H), 7.20 (1H, dd, *J* 2.8 and 8.8 Hz, 7-H), 7.31 (1H, d, *J* 8.8 Hz, 8-H) and 7.50 (1H, d, *J* 2.8 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 20.5 (2-CH_3), 55.8 (6-OCH_3), 104.7 (C-5), 109.8 (C-3), 119.1 (C-7), 123.3 (C-8), 124.0 (C-4a), 151.2 (C-8a), 156.7 (C-6), 165.9 (C-2) and 178.1 (C=O). *m/z* 190 (**M**$^{+}$, 100%).

6-Bromo-2-methylchromone 176d. The experimental method used to synthesize 2-methylchromone **176a** was followed using 1-(5-bromo-2-hydroxyphenyl)-1,3-butanedione **175d** (4.0 g, 16 mmol). Work-up afforded as a green solid, 6-bromo-2-methylchromone **176d** (1.8 g, 47%), m.p. 118-120 ^{o}C (lit.,[196] 118-120 ^{o}C); ν_{max} (KBr)/cm^{-1} 1677 (C=O); δ_H (400 MHz; $CDCl_3$) 2.37 (3H, s, 2-CH_3), 6.16 (1H, s, 3-H), 7.29 (1H, d, *J* 8.8 Hz, 8-H), 7.70 (1H, dd, *J* 2.4 and 8.8 Hz, 7-H) and 8.27 (1H, d, *J* 2.4 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 20.6 (2-CH_3), 110.6 (C-3), 118.3 (C-6), 119.7 (C-8), 124.8 (C-4a), 128.2 (C-5), 136.4 (C-7), 155.2 (C-8a), 166.5 (C-2) and 176.8 (C=O). *m/z* 239 (**M**$^{+}$, 100%).

3.3.3 Synthesis of Chromone-2-carbaldehydes



Chromone-2-carbaldehyde 177a. A solution of 2-methylchromone **176a** (2.50 g, 15.62 mmol) and selenium dioxide (8.66 g, 78.1 mmol) in xylene (52 mL) was stirred under reflux for 24 hrs. The hot solution was filtered and washed with hot xylene. The xylene was removed *in vacuo* and the crude product was purified by flash chromatography (on silica gel; elution with chloroform) to afford, as a brown solid, chromone-2-carbaldehyde **177a** (0.56 g, 21%), m.p. 160-162 ^{o}C (lit.,[196] 160-163 ^{o}C); ν_{max} (KBr)/cm^{-1} 1664 and 1699 (2x C=O); δ_H (400 MHz; $CDCl_3$) 6.88 (1H, s, 3-H), 7.44 (1H,

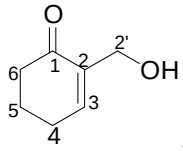
td, *J* 1.6 and 8.0 Hz, 6-H), 7.58 (1H, d, *J* 8.4 Hz, 8-H), 7.74 (1H, td, *J* 1.6 and 8.4 Hz, 7-H), 8.17 (1H, dd, *J* 1.6 and 8.0 Hz, 5-H) and 9.77 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 116.9 (C-8), 118.8 (C-3), 124.8 (C-4a), 125.9 (C-6), 126.1 (C-5), 135.2 (C-7), 156.0 (C-8a), 178.3 (C-2), 185.5 (C-4) and 207.0 (CHO). *m/z* 174 ($\mathbf{M}^+$, 100%).

6-Chlorochromone-2-carbaldehyde 177b. The experimental procedure employed for the preparation of chromone-2-carbaldehyde **177a** was followed using 6-chloro-2-methylchromone **176b** (1.40 g, 6.73 mmol) and selenium dioxide (3.73 g, 33.7 mmol). Flash chromatography (on silica gel; elution with chloroform) afforded, as a brown solid, 6-chlorochromone-2-carbaldehyde **177b** (0.68 g, 45%), m.p. 162-164 ^oC (lit.,[196] 162-164 ^oC); ν_{max} (KBr)/cm^{-1} 1674 and 1717 (2x C=O); δ_H (400 MHz; $CDCl_3$) 6.88 (1H, s, 3-H), 7.37 (1H, d, *J* 8.8 Hz, 8-H), 7.66 (1H, dd, *J* 2.4 and 8.8 Hz, 7-H), 8.05 (1H, d, *J* 2.4 Hz, 5-H) and 9.74 (1H, s, CHO). δ_C (100 MHz; $CDCl_3$) 116.4 (C-3), 120.5 (C-5), 124.8 (C-7), 125.4 (C-6), 132.2 (C-4a), 135.4 (C-8), 153.8 (C-8a), 156.0 (C-2), 177.2 (C-4) and 185.1 (CHO). *m/z* 208 ($\mathbf{M}^+$, 100%).

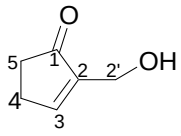
6-Methoxychromone-2-carbaldehyde 177c. The experimental procedure employed for the preparation of chromone-2-carbaldehyde **177a** was followed using 6-methoxy-2-methylchromone **176c** (4.0 g, 21 mmol) and selenium dioxide (11.68 g, 105 mmol). Flash chromatography [on silica gel; elution with chloroform] afforded as a brown solid, 6-methoxychromone-2-carbaldehyde **177c** (0.39 g, 10%), m.p. 174-176 ^oC (lit.,[196] 174-176 ^oC); ν_{max} (KBr)/cm^{-1} 1678 and 1718 (2x C=O); δ_H (400 MHz; $CDCl_3$) 3.90 (3H, s, 6-OCH_3), 6.88 (1H, s, 3-H), 7.35 (1H, dd, *J* 3.2 and 9.2 Hz, 7-H), 7.52-7.55 (2H, m, 5-H and 8-H) and 9.78 (1H, s, CHO). δ_C (100 MHz; $CDCl_3$) 56.0 (6-OMe), 104.7 (C-5), 115.9 (C-8), 120.3 (C-7), 125.5 (C-3), 125.6 (C-4a), 150.4 (C-8a), 155.7 (C-6), 157.7 (C-2), 178.1 (C-4) and 185.5 (CHO). *m/z* 204 ($\mathbf{M}^+$, 100%).

6-Bromochromone-2-carbaldehyde 177d. The experimental procedure employed for the preparation of chromone-2-carbaldehyde **177a** was followed using 6-bromo-2-methylchromone **176d** (1.50 g, 6.28 mmol) and selenium dioxide (3.48 g, 31.4 mmol). Flash chromatography [on silica gel; elution with chloroform] afforded as a brown solid, 6-bromochromone-2-carbaldehyde **177d** (0.39 g, 24%), m.p. 170-172 ^{o}C (lit.,[196] 170-172 ^{o}C); ν_{max} (KBr)/cm^{-1} 1675 and 1717 (2x C=O); δ_H (400 MHz; $CDCl_3$) 6.92 (1H, s, 3-H), 7.51 (1H, d, *J* 8.8 Hz, 8-H), 7.85 (1H, dd, *J* 2.4 and 8.8 Hz, 7-H), 8.32 (1H, d, *J* 2.4 Hz, 5-H) and 9.78 (1H, s, CHO), δ_C (100 MHz; $CDCl_3$) 116.8 (C-3), 119.8 (C-5), 120.7 (C-7), 126.0 (C-6), 128.6 (C-8), 138.2 (C-4a), 154.4 (C-8a), 156.0 (C-2), 177.0 (C=O), 185.0 (CHO) and 185.1 (CHO). *m/z* 254 (**M**$^{+}$, 100%).

3.4 Reactions of cyclic enones with formaldehyde

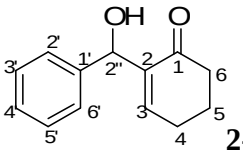


2-(Hydroxymethyl)cyclohex-2-enone 182. A solution of 2-cyclohexenone (7.00 mL; 72.5 mmol), aqueous formaldehyde (4.00 mL; 145 mmol) and DMAP (0.90 g; 7.3 mmol) in THF (5.0 mL) was stirred at room temperature overnight. The resulting mixture was then acidified with 1.50 N HCl and extracted with CH_2Cl_2 (5x 100 mL). The organic extracts were successively washed with aqueous $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4. The solvent was evaporated *in vacuo*, and the crude product purified by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] to afford, as a yellow oil, 2-(hydroxymethyl)cyclohex-2-enone **182** (3.07 g; 38%). δ_H (400 MHz; $CDCl_3$) 1.79-1.86 (2H, m, 5-H), 2.21-2.27 (4H, m, 4-H and 6-H), 3.42 (1H, t, *J* 5.2 Hz, OH), 4.04 (2H, d, *J* 3.2 Hz, 2'-H) and 6.82 (1H, t, *J* 4.0 Hz, 3-H); δ_C (100 MHz; $CDCl_3$) 22.3 (C-5), 25.2 (C-4), 37.8 (C-6), 60.2 (C-2'), 137.9 (C-3), 146.2 (C-2) and 199.8 (C=O). *m/z* 126 (**M**$^{+}$, 100%).



2-(Hydroxymethyl)cyclopent-2-enone 183 To a stirred solution of formaldehyde (0.20 mL, 6.7 mmol) and imidazole (0.45 g, 6.7 mmol) in THF (7.0 mL) and 1 M aq. $NaHCO_3$ (27 mL) was added 2-cyclopenten-1-one (1.00 mL, 10.0 mmol.). The reaction mixture was stirred for 36 hours at room temperature and then quenched with 1 N HCl and extracted with ethyl acetate (4x 100 mL). The organic extracts were dried over anhydrous Na_2SO_4, the solvent was evaporated *in vacuo*, and the crude product was purified by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] to afford as brown solid, 2-(hydroxymethyl)cyclopent-2-enone **183** (0.56 g, 75%); m.p. 76-78 ^oC (lit.,[193] 71-72 ^oC); δ_H (400 MHz; $CDCl_3$) 2.44 (2H, m, 4-H), 2.63 (2H, m, 5-H), 4.36 (2H, s, 2'-H) and 7.51 (1H, t, *J* 1.4 Hz, 3-H); δ_C (100 MHz; $CDCl_3$) 26.8 (C-4), 35.0 (C-5), 57.7 (C-2'), 144.9 (C-2), 158.8 (C-3), 209.8 (C=O). *m/z* 113 ($\mathbf{M}^+$, 100%).

3.5 Reactions of cyclic enones with benzaldehydes



2-[Hydroxy(2-nitrophenyl)methyl]cyclohex-2-enone 185a. The method used for the preparation of 2-(hydroxymethyl)cyclopent-2-enone **183** was followed, using 2-nitrobenzaldehyde (0.20 g, 1.3 mmol) and 2-cyclohexen-1-one (0.26 mL, 2.7 mmol). Work-up, followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded, as a light brown viscous oil, 2-[hydroxy(2-nitrophenyl)methyl]cyclohex-2-enone **185a** (0.22 g, 66%); δ_H (400 MHz; $CDCl_3$) 1.98 (2H, m, 5-H), 2.34 (2H, m, 4-H), 2.44 (2H, m, 6-H), 3.44 (1H, s, OH), 6.16 (1H, s, 2"-H), 6.61 (1H, t, *J* 4.0 Hz, 3-H), 7.42 (1H, td, *J* 1.6 Hz and 8.4 Hz, 5'-H), 7.62 (1H, td, *J* 1.6 Hz and 8.0 Hz, 4'-H), 7.78 (1H, dd, *J* 1.2 Hz and 8.0 Hz, 6'-H) and 7.90 (1H, dd, *J* 1.2 Hz and 8.0 Hz, 3'-H); δ_C (100 MHz; $CDCl_3$) 22.4 (C-5), 25.7 (C-4), 38.2 (C-6), 67.2 (C-2"), 124.4 (C-3'), 128.3 (C-4'), 128.9 (C-6'), 133.2 (C-3), 136.6 (C-1'), 139.8 (C-2),

147.1 (C-5'), 148.1 (C-2') and 199.7 (C=O). Calc. for $C_{13}H_{13}NO_4$; *m/z* 247.24666. *m/z* 247(**M**$^+$, 100%).

2-[Hydroxy(5-hydroxy-2-nitrophenyl)methyl]cyclohex-2-enone 185b. The method used for the preparation of 2-(hydroxymethyl)cyclopent-2-enone **183** was followed, using 3-methoxy-2-nitrobenzaldehyde (0.22 g, 1.0 mmol) and 2-cyclohexen-1-one (0.20 g, 0.20 mL, 2.1 mmol). Work-up, followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded, as a light brown viscous oil, 2-[hydroxy(5-hydroxy-2-nitrophenyl)methyl]cyclohex-2-enone **185b** (0.22 g, 79%); δ_H (400 MHz; $CDCl_3$) 1.96 (2H, m, 5-H), 2.28-2.51 (4H, o/m, 4-H and 6-H), 6.36 (1H, s, 2"-H), 6.56 (1H, t, *J* 4.4 Hz, 3-H), 6.80 (1H, dd, *J* 2.8 and 9.2 Hz, 4'-H), 7.36 (1H, d, *J* 2.4 Hz, 6'-H) and 8.02 (1H, d, *J* 8.8 Hz, 3'-H); δ_C (100 MHz; $CDCl_3$) 22.3 (C-5), 25.8 (C-4), 38.1 (C-6), 67.2 (C-2"), 115.1 (C-6'), 115.2 (C-4'), 128.3 (C-3'), 139.7 (C-3), 140.1 (C-1'), 148.2 (C-2 and C-2'), 161.5 (C-5') and 200.7 (C=O). *m/z* 263 (**M**$^+$, 100%).

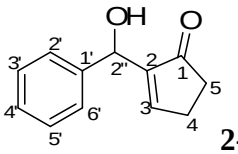
2-[Hydroxy(3-methoxy-2-nitrophenyl)methyl]cyclohex-2-enone 185c. The method used for the preparation of 2-(hydroxymethyl)cyclopent-2-enone **183** was followed, using 3-methoxy-2-nitrobenzaldehyde (0.19 g, 1.0 mmol) and 2-cyclohexen-1-one (0.20 mL, 2.1 mmol). Work-up, followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded, as a light brown viscous oil, 2-[hydroxy(3-methoxy-2-nitrophenyl)methyl]cyclohex-2-enone **185c** (0.24 g, 85%); δ_H (400 MHz; $CDCl_3$) 2.00 (2H, m, 5-H), 2.36-2.44 (4H, m, 4-H and 6-H), 3.87 (3H, s, OCH_3), 5.60 (1H, s, 2"-H), 6.74 (1H, t, *J* 4.4 Hz, 3-H), 6.97 (1H, d, *J* 8.4 Hz, 4'-H), 7.22 (1H, d, *J* 8.0 Hz, 6'-H) and 7.43 (1H, t, *J* 8.4 Hz, 5'-H); δ_C (100 MHz; $CDCl_3$) 22.2 (C-5'), 25.8 (C-4), 38.3 (C-6), 56.5 (OCH_3), 68.8 (C-2"), 111.7 (C-4'), 119.4 (C-6'), 131.0 (C-2' and C-3), 134.6 (C-1'), 138.3 (C-2), 148.8 (C-5'), 150.7 (C-3') and 200.2 (C=O). *m/z* 277 (**M**$^+$, 100%).

2-[Hydroxy(4,5-dimethoxy-2-nitrophenyl)methyl]cyclohex-2-enone 185d. The method used for the preparation of 2-(hydroxymethyl)cyclopent-2-enone **183** was followed, using 3-methoxy-2-nitrobenzaldehyde (0.22 g, 1.0 mmol) and 2-cyclohexen-1-one (0.20 mL, 2.1 mmol). Work-up, afforded as a light brown viscous oil, 2-[hydroxy(4,5-dimethoxy-2-nitrophenyl)methyl]cyclohex-2-enone **185d** (0.32 g, 100%). δ_H (400 MHz; $CDCl_3$) 2.00 (2H, m, 5-H), 2.29-2.52 (4H, o/m, 4-H and 6-H), 3.94 (3H, s, 5-OCH_3), 3.99 (3H, s, 4-OCH_3), 6.31 (1H, s, 2"-H), 6.42 (1H, t, *J* 4.0 Hz, 3-H), 7.34 (1H, s, 6'-H) and 7.64 (1H, s, 3'-H); δ_C (100 MHz; $CDCl_3$) 22.4 (C-5), 25.7 (C-4), 38.3 (C-6), 56.3 (5-OCH_3), 56.4 (4-OCH_3), 67.4 (C-2"), 107.9 (C-3'), 110.1 (C-6'), 131.8 (C-1'), 140.3 (C-3), 146.4 (C-2 and C-2'), 147.8 (C-4'), 153.5 (C-5') and 200.2 (C=O). *m/z* 307 ($\mathbf{M}^+$, 100%).

2-[Hydroxy(6-nitrobenzo[1,3]dioxol-5-yl)methyl]cyclohex-2-enone 185e. The method used for the preparation of 2-(hydroxymethyl)cyclopent-2-enone **183** was followed, using 6-nitropiperonal (0.20 g, 1.0 mmol) and 2-cyclohexen-1-one (0.20 mL, 2.1 mmol). Work-up, followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded, as a light brown viscous oil, 2-[hydroxy(6-nitrobenzo[1,3]dioxol-5-yl)methyl]cyclohex-2-enone **185e** (0.21 g, 70%); δ_H (400 MHz; $CDCl_3$) 1.98 (2H, m, 5-H), 2.33-2.49 (4H, o/m, 4-H and 6-H), 6.11 (2H, s, OCH_2O), 6.18 (1H, s, 2"-H), 6.59 (1H, t, *J* 4.4 Hz, 3-H), 7.23 (1H, s, 6'-H) and 7.50 (1H, s, 3'-H); δ_C (100 MHz; $CDCl_3$) 22.4 (C-5), 25.7 (C-4), 38.3 (C-6), 67.3 (C-2"), 103.0 (OCH_2O), 105.4 (C-3'), 107.9 (C-1' and C-6'), 134.2 (C-2'), 139.8 (C-2), 146.7 (C-3), 147.1 (C-4'), 152.2 (C-5') and 199.9 (C=O). *m/z* 291 ($\mathbf{M}^+$, 100%).

2-[Hydroxy(4-nitro-phenyl)methyl]cyclohex-2-enone The method used for the preparation of 2-(hydroxymethyl)cyclopent-2-enone **183** was followed, using 4-nitrobenzaldehyde (0.78 g, 5.2 mmol) and 2-cyclohexen-1-one (1.00 mL, 10.4 mmol). Work-up, followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded, as a yellow oil, 2-[hydroxy(4-nitrophenyl)methyl]cyclohex-2-enone (0.57

g, 45%). δ_H (400 MHz; $CDCl_3$) 1.87 (2H, m, 5-H), 2.27-2.32 (4H, o/m, 4-H and 6-H), 5.52 (1H, s, 2”-H), 6.85 (1H, t, *J* 3.8 Hz, 3-H), 7.43 (2H, d, *J* 8.0 Hz, 2-H and 6’-H) and 7.99 (2H, d, *J* 7.6 Hz, 3’-H and 5’-H); δ_C (100 MHz; $CDCl_3$) 22.4 (C-5), 25.8 (C-4), 38.4 (C-6), 72.1 (C-2”), 123.5 (C-3’ and C-5’), 127.1 (C-2’ and C-6’), 140.2 (C-2), 148.1 (C-3), 149.3 (C-1’ and C-4’) and 200.0 (C=O). *m/z* 247 (**M**$^+$, 100%).



2-(Hydroxybenzyl)cyclopent-2-enone. The method used for the preparation of 2-(hydroxymethyl)cyclopent-2-enone **183** was followed, using benzaldehyde (1.00 mL, 9.85 mmol). Work-up, followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded as a brown solid, 2-(hydroxybenzyl)cyclopent-2-enone (0.71 g, 39%); m.p. 83-85 ^oC (lit.,[208] 84-86 ^oC); δ_H (400 MHz; $CDCl_3$) 2.10 (2H, m, 4-H), 2.29 (2H, t, *J* 3.6 Hz, 5-H), 4.44 (1H, s, OH), 5.33 (1H, s, 2”-H), 7.07 (1H, m, 3-H) and 7.12-7.23 (5H, series of multiplets, Ar-H); δ_C (100 MHz; $CDCl_3$) 26.6 (C-4), 35.3 (C-5), 70.0 (C-2”), 126.3 (C-2’ and C-6’), 127.9 (C-4’), 128.5 (C-3’ and C-5’), 141.3 (C-3), 147.7 (C-1’), 159.3 (C-2) and 209.6 (C=O). *m/z* 187 (**M**$^+$, 100%).

2-[Hydroxy(2-nitrophenyl)methyl]cyclopent-2-enone 186a. The method used for the preparation of 2-(hydroxymethyl)cyclopent-2-enone **183** was followed, using 2-nitrobenzaldehyde (0.20 g, 1.3 mmol). Work-up, followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded, as a brown viscous oil, 2-[hydroxy(2-nitrophenyl)methyl]cyclopent-2-enone **186a** (0.20 g, 61%). δ_H (400 MHz; $CDCl_3$) 2.45 (2H, m, 4’-H), 2.54 (2H, m, 5’-H), 4.50 (1H, s, OH), 6.14 (1H, s, 2”-H), 7.20 (1H, m, 3’-H), 7.44 (1H, t, *J* 7.6 Hz, 5-H), 7.65 (1H, t, *J* 7.6 Hz, 4-H), 7.84 (1H, d, *J* 8.0 Hz, 6-H) and 7.94 (1H, d, *J* 8.0 Hz, 3-H); δ_C (100 MHz; $CDCl_3$) 26.7 (C-4’), 35.0 (C-5’), 65.2 (C-2”), 124.5 (C-6), 128.5 (C-4), 128.8 (C-3’), 133.6 (C-5), 136.5 (C-1), 145.7 (C-2’), 159.9 (C-2) and 209.3 (C=O). *m/z* 233 (**M**$^+$, 100%).

2-[Hydroxy(5-hydroxy-2-nitrophenyl)methyl]cyclopent-2-enone 186b. The method used for the preparation of 2-(hydroxymethyl)cyclopent-2-enone **183** was followed, using 5-hydroxy-2-nitrobenzaldehyde (0.20 g, 1.2 mmol). Work-up, followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded, as a brown viscous oil, 2-[hydroxy(5-hydroxy-2-nitrophenyl)methyl]cyclopent-2-enone **186b** (0.39 g, 76%); δ_H (400 MHz; DMSO) 2.32 (2H, m, 4-H), 2.46 (2H, m, 5-H), 5.85 (1H, s, 2"-OH), 5.95 (1H, s, 2"-H), 6.80 (1H, dd, *J* 2.8 and 9.2 Hz, 4'-H), 7.12 (1H, t, *J* 2.4 Hz, 3-H), 7.23 (1H, d, *J* 2.8 Hz, 6'-H), 7.95 (1H, d, *J* 8.8 Hz, 3'-H) and 10.88 (1H, s, 5-OH); δ_C (100 MHz; DMSO-$_{d6}$) 25.9 (C-4), 34.4 (C-5), 61.8 (C-2"), 114.4 (C-6'), 114.7 (C-4'), 127.7 (C-3'), 138.4 (C-3), 142.4 (C-1'), 147.3 (C-2'), 158.7 (C-2), 162.5 (C-5') and 206.6 (C=O). *m/z* 249 (**M**$^+$, 100%).

2-[(3-Methoxy-2-nitrophenyl)hydroxymethyl]cyclopent-2-enone 186c. The method used for the preparation of 2-(hydroxymethyl)cyclopent-2-enone **183** was followed, using 3-methoxy-2-nitrobenzaldehyde (0.22 g, 1.2 mmol). Work-up followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded as a brown viscous oil, 2-[(3-methoxy-2-nitrophenyl)hydroxymethyl]cyclopent-2-enone **186c** (0.31 g, 98%). δ_H (400 MHz; $CDCl_3$) 2.33 (2H, m, 4-H), 2.47 (2H, m, 5-H), 3.91 (3H, s, OCH_3), 5.97 (1H, s, 2"-H), 6.97 (1H, d, *J* 8.4 Hz, 4'-H), 7.15 (1H, t, *J* 1.2 Hz, 3-H), 7.22 (1H, d, *J* 8.0 Hz, 6'-H) and 7.43 (1H, t, *J* 8.4 Hz, 5'-H), (100 MHz; $CDCl_3$) 25.8 (C-4), 35.5 (C-5), 56.5 (OCH_3), 62.3 (C-2"), 111.6 (C-4'), 119.6 (C-6'), 129.8 (C-2' and C-3), 134.5 (C-1'), 138.2 (C-2), 149.2 (C-5'), 150.3 (C-3') and 200.0 (C=O).

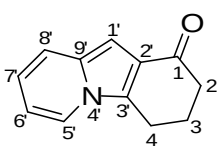
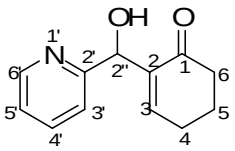
2-[(4,5-Dimethoxy-2nitrophenyl)hydroxymethyl]cyclopent-2-enone 186d. The method used for the preparation of 2-(hydroxymethyl)cyclopent-2-enone **183** was followed, using 4,5-dimethoxy-2-nitrobenzaldehyde (0.25 g, 1.2 mmol). Work-up followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded as a brown viscous oil, 2-[(4,5-dimethoxy-2nitrophenyl)hydroxymethyl]cyclopent-2-enone **186d** (0.34 g, 97%). δ_H (400 MHz;

$CDCl_3$) 2.43-2.50 (4H, m, 4-H and 5-H), 3.95 (3H, s, 5-OMe), 3.99 (3H, s, 4-OMe), 6.28 (1H, s, 2"-H), 7.11 (1H, t, *J* 1.2 Hz, 3-H), 7.37 (1H, s, 6'-H) and 7.64 (1H, s, 3'-H). δ_C (100 MHz; $CDCl_3$) 26.6 (C-4), 35.2 (C-5), 56.4 (4-OMe), 56.5 (5-OMe), 65.5 (C-2"), 107.8 (C-3'), 109.9 (C-6'), 132.0 (C-1'), 145.8 (C-3), 148.00 (C-2'), 153.8 (C-2), 158.2 (C-4'), 159.6 (C-5') and 209.9 (C=O). *m/z* 293 (**M**$^+$, 100%).

2-[Hydroxy(6-nitrobenzo[1,3]dioxol-5-yl)-methyl]-cyclopent-2-enone 186e. The method used for the preparation of 2-(hydroxymethyl)cyclopent-2-enone **183** was followed, using 3,4-dioxomethylen-6-nitrobenzaldehyde (0.23 g, 1.2 mmol). Work-up, followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded, as a brown viscous oil, 2-[hydroxy(6-nitrobenzo[1,3]dioxol-5-yl)-methyl]-cyclopent-2-enone **186e** (0.31 g, 97%); δ_H (400 MHz; $CDCl_3$) 2.44 (2H, m, 4-H), 2.48 (2H, m, 5-H), 6.12 (2H, s, OCH_2O), 6.16 (1H, s, 2"-H), 7.22 (1H, t, *J* 2.4 Hz, 3-H), 7.26 (1H, s, 6'-H) and 7.52 (1H, s, 3'-H); δ_C (100 MHz; $CDCl_3$) 26.5 (C-4), 35.1 (C-5), 65.6 (C-2"), 103.1 (OCH_2O), 105.3 (C-3'), 107.7 (C-6'), 134.3 (C-3), 145.6 (C-1'), 147.3 (C-2'), 152.5 (C-2), 158.2 (C-4'), 159.8 (C-5') and 209.8 (C=O). *m/z* 233 (**M**$^+$, 100%).

2-[Hydroxy(4-nitrophenyl)methyl]cyclopent-2-enone. The method used for the preparation of 2-(hydroxymethyl)cyclopent-2-enone **183** was followed, using 4-nitrobenzaldehyde (1.21 g, 8.00 mmol). Work-up, followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded, as a light brown solid, 2-[hydroxy(4-nitrophenyl)methyl]cyclopent-2-enone (0.97 g, 52%); m.p. 142-143 ^oC (lit,[208,209,212] 143-144 ^oC); δ_H (400 MHz; $CDCl_3$) 2.46 (2H, m, 4-H), 2.61 (2H, m, 5-H), 3.64 (1H, s, OH), 5.66 (1H, s, 2"-H), 7.27 (1H, m, 3-H), 7.55-7.58 (2H, m, 2'-H and 6'-H) and 8.20-8.24 (2H, m, 3'-H and 5'-H), δ_C (100 MHz; $CDCl_3$) 26.8 (C-4), 35.1 (C-5), 69.0 (C-2"), 123.7 (C-3' and C-5'), 127.1 (C-1' and C-6'), 146.7 (C-3), 147.5 (C-2), 148.5 (C-1'), 159.7 (C-4') and 209.2 (C=O). *m/z* 233 (**M**$^+$, 100%).

3.6 Reactions of cyclic enones with pyridine-2-carbaldehydes and quinoline-2-carbaldehydes

3,4-Dihydro-2*H*-pyrido[1,2-*a*]indol-1-one 195 and **2-[Hydroxy(pyridin-2-yl)methyl]cyclohex-2-enone 191**. The method for the preparation 2-[hydroxy(pyridin-2-yl)methyl]cyclopent-2-enone was followed, using pyridine-2-carbaldehyde (0.25 mL, 2.6 mmol) and 2-cyclohexene-1-one (2.0 eq.). Work-up, followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded two fractions, as green viscous oils.

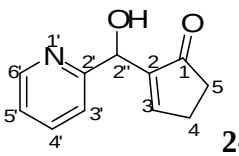
Fraction 1: 3,4-dihydro-2*H*-pyrido[1,2-*a*]indol-1-one 196 (0.15 g, 32 %), ν_{max} (Nujol)/cm^{-1} 1713 (C=O); δ_H (400 MHz; $CDCl_3$) 2.28 (2H, m, 3-H), 2.61 (2H, t, *J* 6.0 Hz, 2-H), 2.95 (2H, t, *J* 6.4 Hz, 4-H), 6.55 (1H, t, *J* 7.2 Hz, 6'-H), 6.65 (1H, t, *J* 9.2 Hz, 7'-H), 6.74 (1H, s, 1'-H), 7.35 (1H, d, *J* 9.2 Hz, 8'-H) and 7.63 (1H, d, *J* 7.2 Hz, 5'-H); δ_C (100 MHz; $CDCl_3$) 21.0 (C-4), 23.6 (C-3), 38.6 (C-2), 95.4 (C-1'), 112.2 (C-6'), 118.0 (C-7'), 121.0 (C-8'), 122.2 (C-5'), 123.2 (C-2'), 132.0 (C-3'), 132.9 (C-9') and 196.0 (C=O). Calc. for $C_{12}H_{11}NO$; *m/z* 185 (**M**$^+$, 100%).

Fraction 2: 2-[Hydroxy(pyridin-2-yl)methyl]cyclohex-2-enone 192, (0.21 g, 40%) ν_{max} (Nujol)/cm^{-1} 1713 (C=O), 3371 (OH); δ_H (400 MHz; $CDCl_3$) 1.98 (2H, m, 5-H), 2.36-2.46 (4H, o/m, 6- and 4-H), 4.85 (1H, br s, OH), 5.66 (1H, s, 2"-H), 7.02 (1H, t, *J* 4.0 Hz, 3-H), 7.17 (1H, t, *J* 5.6 Hz, 5'-H), 7.44 (1H, d, *J* 7.6Hz, 3'-H), 7.64 (1H, t, *J* 7.6 Hz, 4'-H) and 8.49 (1H, d, *J* 4.8 Hz, 6'-H); δ_C (100 MHz; $CDCl_3$) 22.5 (C-5), 25.8 (C-4), 38.5 (C-6), 70.2 (C-2"), 121.3 (C-5'), 122.4 (C-3'), 136.8 (C-3), 140.7 (C-2), 147.5 (C-4'), 148.0 (C-6'), 160.2 (C-2') and 199.5 (C=O). *m/z* 203 (**M**$^+$, 100%).

6-Methyl-3,4-dihydro-2*H*-pyrido[1,2-*a*]indol-1-one 197 and **2-[Hydroxy(6-methylpyridin-2-yl)methyl]cyclohex-2-enone 193**. The method for the preparation 2-(hydroxy-pyridin-2-yl-methyl-cyclopent-2-enone was followed using 6-methylpyridine-2-carbaldehyde (0.31 g, 2.6 mmol) and 2-cyclohexen-1-one (2.0 eq.). Work-up, followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded, two fractions as brown viscous oils.

Fraction 1: **6-methyl-3,4-dihydro-2*H*-pyrido[1,2-*a*]indol-1-one 196** (0.17 g, 32%), δ_H (400 MHz; $CDCl_3$) 2.22 (2H, q, *J* 6.4 Hz, 3-H), 2.55 (2H, t, *J* 6.4 Hz, 2-H), 2.78 (3H, s, 5-CH_3), 3.55 (2H, t, *J* 6.0 Hz, 4-H), 6.19 (1H, d, *J* 6.8 Hz, 6'-H), 6.49 (1H, t, *J* 6.4 Hz, 7'-H), 6.75 (1H, s, 1'-H) and 7.18 (1H, d, *J* 8.8 Hz, 8'-H); δ_C (100 MHz; $CDCl_3$) 21.7 (5-CH_3), 24.5 (C-4), 25.8 (C-3), 37.9 (C-2), 96.7 (C-1'), 113.4 (C-6'), 118.2 (C-8'), 119.3 (C-7'), 124.2 (C-2'), 133.4 (C-3'), 134.8 (C-5'), 135.0 (C-9') and 196.5 (C=O). *m/z* 199 (**M**$^+$, 100%).

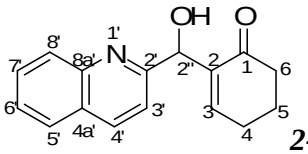
Fraction 2: Baylis-Hillman adduct; **2-[Hydroxy(6-methylpyridin-2-yl)methyl]cyclohex-2-enone 192** (0.22 g, 39%), δ_H (400 MHz; $CDCl_3$) 1.95 (2H, m, 5-H), 2.35 (2H, m, 4-H), 2.42 (2H, m, 6-H), 2.50 (3H, s, 6-CH_3), 5.23 (1H, br s, OH), 5.65 (1H, s, 2"-H), 6.96-7.00 (2H, m, 5'-H and 3-H), 7.15 (1H, d, *J* 8.0 Hz, 3'-H) and 7.49 (1H, t, *J* 7.6 Hz, 4'-H); δ_C (100 MHz; $CDCl_3$) 22.5 (6-CH_3), 24.1 (C-5), 25.7 (C-4), 38.4 (C-6), 69.0 (C-2"), 118.1 (C-5'), 121.8 (C-3'), 137.0 (C-3), 141.0 (C-2), 147.3 (C-4'), 156.6 (C-6'), 159.1 (C-2') and 199.3 (C=O). *m/z* 217 (**M**$^+$, 100%).



2-[Hydroxy(pyridin-2-yl)methyl]cyclopent-2-enone 193. A solution of pyridine-2-carbaldehyde (0.30 mL, 3.2 mmol) and 2-cyclopenten-1-one (0.50 mL, 6.3 mmol) in THF (2.4 mL) was stirred at room temperature. To this was added TMPDA (0.50 mL, 3.2 mmol) and water (0.5 mL), and the resulting red solution was stirred at room temperature for 36 hrs. The solution was extracted with ethyl acetate and purified

by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] to afford, as a light brown viscous oil, 2-[hydroxy(pyridin-2-yl)methyl]cyclopent-2-enone **193**. (0.46 g, 77%). δ_H (400 MHz; $CDCl_3$) 2.45 (2H, m, 4-H), 2.59 (2H, m, 5-H), 7.20 (1H, m, 3-H), 7.48 (1H, t, *J* 7.6 Hz, 5'-H), 7.56 (1H, d, *J* 7.2 Hz, 3'-H), 7.66 (1H, td, *J* 1.6 Hz and 7.6 Hz, 4'-H) and 8.52 (1H, d, *J* 4.8 Hz, 6'-H); δ_C (100 MHz; $CDCl_3$) 26.7 (C-4), 35.4 (C-5), 68.3 (C-2"), 121.3 (C-5'), 122.8 (C-3'), 137.0 (C-3), 147.7 (C-4'), 148.1 (C-2), 159.1(C-6'), 159.9 (C-2') and 208.8 (C=O). Calc. for $C_{11}H_{11}NO_2$; *m/z* 190 ($\mathbf{M}^+$, 100%).

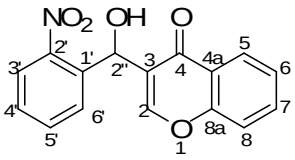
2-[Hydroxy(6-methylpyridin-2-yl)methyl]cyclopent-2-enone 194. The method for the preparation 2-[hydroxy(pyridin-2-yl)methyl]cyclopent-2-enone **193** was followed using 6-methylpyridine-2-carbaldehyde (0.31 g, 2.6 mmol). Work-up, followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded, as a brown viscous oil, 2-[hydroxy(6-methylpyridin-2-yl)methyl]cyclopent-2-enone **194**. (0.30 g, 56 %); ν_{max} (Nujol)/cm^{-1} 1704 (C=O), 3371 (OH); δ_H (400 MHz; $CDCl_3$) 2.41 (2H, m, 4-H), 2.50 (3H, s, CH_3), 2.54 (2H, m, 5-H), 7.01 (1H, t, *J* 7.2 Hz, 3-H), 7.21 (1H, d, *J* 7.6 Hz, 5'-H), and 7.49-7.53 (2H, m, 3'-H and 4'-H), δ_C (100 MHz; $CDCl_3$) 24.1 (6-CH_3), 26.6 (C-4), 35.3 (C-5), 67.6 (C-2"), 118.0 (C-5'), 122.2 (C-3'), 137.2 (C-3), 147.9 (C-2), 156.8 (C-6'), 158.0 (C-2'), 159.9 (C-4') and 208.7 (C=O). *m/z* 205 ($\mathbf{M}^+$, 100%).



2-[Hydroxy(quinolin-2-yl)methyl]cyclohex-2-enone 200. The method for the preparation 2-[hydroxy(pyridin-2-yl)methyl]cyclopent-2-enone **193** was followed using quinoline-2-carbaldehyde (0.10 g, 0.64 mmol) and 2-cyclohexene-1-one (2.0 eq.). Work-up, followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded, as brown viscous oils, *2-[hydroxy(quinolin-2-yl)methyl]cyclohex-2-enone* ***200*** (0.072 g, 44%), ν_{max} (Nujol)/cm^{-1} 1717 (C=O), 3367 (OH); δ_H (400 MHz; $CDCl_3$) 1.97 (2H, m, 5-H), 2.28 (2H, m, 4-H), 2.45 (2H, m, 6-H), 5.90 (1H, s, 2"-H), 7.07 (1H, t, *J* 4.0 Hz, 3-H), 7.47 (1H, d, *J* 8.4 Hz, 3'-H), 7.52 (1H, t, *J* 8.0 Hz, 6'-H), 7.70 (1H,

t, *J* 8.4 Hz, 7'-H), 7.80 (1H, d, *J* 8.4 Hz, 5'-H), 8.05 (1H, d, *J* 8.4 Hz, 8'-H) and 8.09 (1H, d, *J* 8.8 Hz, 4'-H); δ_C (100 MHz; $CDCl_3$) 22.5 (C-5), 25.9 (C-4), 38.5 (C-6), 69.1 (C-2"), 119.2 (C-3'), 126.4 (C-6'), 127.6 (C-5'), 127.7 (C-4a'), 128.7 (C-8'), 129.7 (C-7'), 137.0 (C-3), 140.9 (C-2), 146.2 (C-8a'), 148.2 (C-4'), 160.4 (C-2') and 199.2 (C=O). *m/z* 253 ($\mathbf{M}^+$, 100%).

3.7 Reactions of chromones with 2-nitrobenzaldehydes

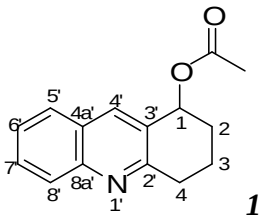


3-[Hydroxy(2-nitrophenyl)methyl]chromone 205a. The method for the preparation 2-[hydroxy(pyridin-2-yl)methyl]cyclopent-2-enone **193** was followed using 2-nitrobenzaldehyde (0.16 g; 1.1 mmol) and chromone (0.30 g; 2.1 mmol). Work-up, followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded, as a brown solid, 3-[hydroxy(2-nitrophenyl)methyl]chromone **205a** (0.11 g, 32%), m.p. 168-170 ^oC (lit.,[192] 168-169 ^oC); δ_H (400 MHz; $CDCl_3$) 4.53 (1H, s, OH), 6.46 (1H, s, 2"-H), 7.38-7.49 (4H, m, 4'-H, 5'-H, 6-H and 7-H), 7.68 (1H, d, *J* 6.8 Hz, 8-H), 7.76 (1H, s, 2-H), 7.92 (1H, d, *J* 7.6 Hz, 6'-H), 7.96 (1H, d, *J* 8.0 Hz, 5-H) and 8.17 (1H, d, *J* 8.0 Hz, 3'-H); δ_C (100 MHz; $CDCl_3$) 66.3 (C-2"),118.2 (C-8), 123.8 (C-3), 124.5 (C-4a), 124.6 (C-6), 125.5 (C-3'), 125.7 (C-6'), 128.8 (C-4'), 129.2 (C-5), 133.6 (C-5'), 134.1 (C-7), 135.9 (C-1'), 148.2 (C-2'), 153.7 (C-2), 156.3 (C-8a) and 177.9 (C=O). *m/z* 297 ($\mathbf{M}^+$, 100%).

6-Chloro-3-[hydroxyl(2-nitrophenyl)methyl]chromone 205b. The method described for the preparation 2-[hydroxy(pyridin-2-yl)methyl]cyclopent-2-enone **193** was followed using 2-nitrobenzaldehyde (0.16 g; 1.1 mmol) and 6-chlorochromone (0.40 g; 2.1 mmol). Work-up, followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded, as a brown solid, 6-chloro-3-[hydroxyl(2-nitrophenyl)methyl]chromone

205b (0.17 g, 48%); m.p. 208-210 ^{o}C (lit.,[192] 209-211 ^{o}C) δ_H (400 MHz; $CDCl_3$) 4.33 (1H, br s, OH), 6.45 (1H, s, 2"-H), 7.42 (1H, d, *J* 8.8 Hz, 8-H), 7.49 (1H, td, *J* 1.2 Hz and 8.4 Hz, 4'-H), 7.61 (1H, dd, *J* 2.8 Hz and 8.8 Hz, 7-H), 7.68 (1H, td, *J* 1.2 Hz and 7.6 Hz, 5'-H), 7.77 (1H, s, 2'-H), 7.89 (1H, dd, *J* 1.2 Hz and 8.0 Hz, 6'-H), 7.98 (1H, dd, *J* 1.2 Hz and 8.0 Hz, 3'-H) and 8.14 (1H, d, *J* 2.4 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 66.1 (C-2"), 120.0 (C-8), 124.7 (C-3), 125.2 (C-6' and C-3'), 129.0 (C-4'), 129.1 (C-5), 131.5 (C-6), 133.7 (C-5'), 134.4 (C-7), 135.7 (C-1'), 153.9 (C-2' and C-2), 154.7 (C-8a) and 176.6 (C=O). *m/z* 331 ($\mathbf{M}^+$, 100%).

3.8 Synthesis of quinoline derivatives



1-Acetoxy-1,2,3,4-tetrahydroacridine **187a**. To a stirred solution of 2-[hydroxy-(2-nitro-phenyl)-methyl]-cyclohex-2-enone (0.10 g, 0.41 mmol) in acetic acid (2.00 mL) at 120 ^{o}C, was added iron powder (0.14 g, 2.43 mmol). The brown solution was further stirred at 120 ^{o}C for 2hrs, cooled to room temperature. Acetic acid was removed on a rotavapor, and ethyl acetate added to the crude mixture, stirred for 2-5 minutes. It was then filtered to remove iron powder, and the filtrate concentrated on a rotavapor. Flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded as a brown viscous oil, *1-acetoxy-1,2,3,4-tetrahydroacridine* **187a** (0.0254 g, 26%). δ_H (400 MHz; $CDCl_3$) 2.00 (2H, m, 2-H), 2.08 (1H, m, 4-H), 2.11 (3H, s, CH_3), 2.18 (1H, m, 4-H), 3.08 (1H, m, 3-H), 3.24 (1H, m, 3-H), 6.19 (1H, t, *J* 4.4 Hz, 1-H), 7.47 (1H, t, *J* 7.6 Hz, 6'-H), 7.67 (1H, t, *J* 8.0 Hz, 7'-H), 7.76 (1H, d, *J* 8.0 Hz, 5'-H), 7.99 (1H, d, *J* 8.8 Hz, 8'-H) and 8.11 (1H, s, 4'-H); δ_C (100 MHz; $CDCl_3$) 18.6 (CH_3), 21.4 (C-3), 28.8 (C-4), 32.9 (C-2), 69.9 (C-1), 125.9 (C-5'), 126.9 (C-4a'), 127.8 (C-6'), 128.3 (C-7'), 128.8 (C-3'), 129.9 (C-8'), 136.9 (C-4'), 147.6 (C-8 a'), 158.6 (C-2') and 170.7 (C=O).

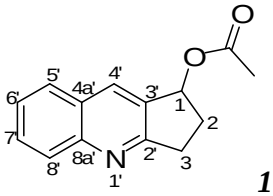
6-Hydroxy-1,2,3,4-tetrahydroacridin-1-yl acetate **187b**. The experimental method employed for the synthesis of 1-acetoxy-1,2,3,4-tetrahydroacridine was followed using 2-[hydroxy-(5-hydroxy-2-nitro-phenyl)-methyl]-cyclohex-2-enone (0.10 g, 0.38 mmol). Work-up followed by flash chromatography [on silica gel; elution with hexane-EtOAc (2:1)] afforded as a brown viscous oil, acetic acid 7-*hydroxy-1,2,3,4-tetrahydroacridin-1-yl acetate* **187b** (5.1 mg, 5%). δ_H (400 MHz; $CDCl_3$) 1.92-1.95 (2H, m, 2-H), 2.01-2.07 (2H, m, 4-H), 2.10 (3H, s, CH_3), 3.02-3.08 (1H, m, 3-H), 3.18-3.24 (1H, m, 3-H), 6.16 (1H, t, *J* 4.8 Hz, 1-H), 7.12 (1H, d, *J* 2.0 Hz, 5'-H), 7.30 (1H, dd, *J* 2.0 and 9.2 Hz, 7'-H), 7.86 (1H, d, *J* 9.2 Hz, 8'-H) and 7.98 (1H, s, 4'-H); δ_C (100 MHz; $CDCl_3$) 18.4 (CH_3), 21.4 (C-3), 28.7 (C-4), 31.6 (C-2), 69.8 (C-1), 109.0 (C-5'), 123.3 (C-7'), 128.4 (C-4a'), 128.5 (C-8'), 129.1 (C-4'), 136.4 (C-3'), 142.1 (C-8a'), 155.2 (C-6'), 155.22 (C-2') and 170.9 (C=O).

8-Methoxy-1,2,3,4-tetrahydroacridin-1-yl acetate **187c**. The experimental method employed for the synthesis of 1-acetoxy-1,2,3,4-tetrahydroacridine was followed using 2-[hydroxy-(3-methoxy-2-nitro-phenyl)-methyl]-cyclohex-2-enone (0.10 g, 0.36 mmol). Work-up followed by flash chromatography [on silica gel; elution with hexane-EtOAc (2:1)] afforded as a brown viscous oil, *5-methoxy-1,2,3,4-tetrahydroacridin-1-yl acetate* **187c**. (69.3 mg, 71%). δ_H (400 MHz; $CDCl_3$) 1.94-2.04 (3H, m, 2-H and 3-H), 2.06 (3H, s, $OCOCH_3$), 2.08-2.15 (1H, m, 2-H), 3.10-3.18 (1H, m, 4-H), 3.28-3.35 (1H, m, 4-H), 4.05 (3H, s, OMe), 6.17 (1H, t, *J* 5.2 Hz, 1-H), 7.00 (1H, dd, *J* 0.8 and 7.2 Hz, 7'-H), 7.32-7.40 (2H, m, 5'-H and 6'-H) and 8.07 (1H, s, 4'-H). δ_C (100 MHz; $CDCl_3$) 18.7 (CH_3), 21.4 (C-3), 28.8 (C-4), 33.1 (C-2), 56.0 (8-OMe), 69.9 (C-1), 107.8 (C-7'), 119.6 (C-5'), 126.0 (C-6' and C-4a'), 128.0 (C-3'), 129.4 (C-8a'), 136.8 (C-4'), 154.5 (C-8'), 157.7 (C-2') and 170.7 (C=O).

6,7-Dimethoxy-1,2,3,4-tetrahydroacridin-1-yl acetate **187d**. The experimental method employed for the synthesis of 1-acetoxy-1,2,3,4-tetrahydroacridine was followed using 2-[hydroxy-(4,5-dimethoxy-2-nitro-phenyl)-methyl]-cyclohex-2-enone (0.10 g, 0.33

mmol). Work-up followed by flash chromatography [on silica gel; elution with hexane-EtOAc (2:1)] afforded as a brown viscous oil, *6,7-dimethoxy-1,2,3,4-tetrahydroacridin-1-yl acetate* **187d** (0.036 g, 37%); δ_H (400 MHz; $CDCl_3$) 1.95-2.00 (2H, m, 2-H), 2.04-2.07 (2H, m, 3-H), 2.10 (3H, s, $OCOCH_3$), 2.97-3.05 (1H, m, 4-H), 3.13-3.20 (1H, m, 4-H), 3.98 (3H, s, 7-OMe), 4.00 (3H, s, 6-OMe), 6.16 (1H, t, *J* 4.4 Hz, 1-H), 7.00 (1H, s, 5'-H), 7.33 (1H, s, 8'-H) and 7.96 (1H, s, 4'-H); δ_C (100 MHz; $CDCl_3$) 18.7 (CH_3), 21.5 (C-3), 29.7 (C-4), 32.5 (C-2), 56.0 (7-OMe), 56.1 (6-OMe), 70.0 (C-1), 105.0 (C-5'), 106.9 (C-8'), 122.4 (C-4a'), 126.8 (C-3'), 135.4 (C-4'), 144.7 (C-8a'), 149.4 (C-6'), 153.0 (C-7'), 156.0 (C-2') and 170.8 (C=O).

6,7-Dioxol-methylene-1,2,3,4-tetrahydroacridin-1-yl acetate **187e**. The experimental method employed for the synthesis of 1-acetoxy-1,2,3,4-tetrahydroacridine was followed using 2-[hydroxy(6,7-dioxol-methylene-2-nitrophenyl)-methyl]cyclohex-2-enone (0.10 g, 0.34 mmol). Work-up followed by flash chromatography [on silica gel; elution with hexane-EtOAc (2:1)] afforded as a brown viscous oil, *6,7-dioxol-methylene-1,2,3,4-tetrahydroacridin-1-yl acetate* **187e** (0.043 g, 44%); δ_H (400 MHz; $CDCl_3$) 1.93-2.01 (2H, m, 3-H), 2.05-2.08 (2H, m, 3-H), 2.13 (3H, s, $OCOCH_3$), 2.95-3.03 (1H, m, 4-H), 3.12-3.18 (1H, m, 4-H), 6.11 (2H, s, OCH_2O), 6.16 (1H, t, *J* 4.4 Hz, 1-H), 7.26 (1H, s, 5'-H), 7.52 (1H, s, 8'-H) and 7.98 (1H, s, 4'-H), δ_C (100 MHz; $CDCl_3$) 18.6 (CH_3), 21.3 (C-3), 28.7 (C-4), 32.7 (C-2), 70.0 (C-1), 102.0 (O-CH_2-O), 104.1 (C-8'), 105.4 (C-5'), 124.3 (C-4a'), 132.1 (C-3'), 133.0 (C-4'), 146.5 (C-8a'), 147.8 (C-6'), 151.3 (C-7'), 163.5 (C-2'), 171.3 (C=O).



1-Acetoxy-1,2,3,-trihydroacridine The experimental method employed for the synthesis of 1-acetoxy-1,2,3,4-tetrahydroacridine was followed using 2-[hydroxy(2-nitrophenyl)-methyl]cyclopent-2-enone (0.10 g, 0.43 mmol). Work-up

followed by flash chromatography [on silica gel; elution with hexane-EtOAc (2:1)] afforded as a brown viscous oil, *1-acetoxy-1,2,3,-trihydroacridine* (0.074 g, 71%), δ_H (400 MHz; $CDCl_3$) 2.08 (3H, s, CH_3), 2.26 (1H, m, 2-H), 2.58 (1H, m, 2-H), 3.12 (1H, m, 3-H), 3.37 (1H, m, 3-H), 6.30 (1H, m, 1-H), 7.49 (1H, t, *J* 7.8 Hz, 6'-H), 7.69 (1H, t, *J* 8.0 Hz, 7'-H), 7.80 (1H, d, *J* 8.0 Hz, 5'-H), 8.03 (1H, d, *J* 8.4 Hz, 8'-H) and 8.18 (1H, s, 4'-H), δ_C (100 MHz; $CDCl_3$) 21.2 (CH_3), 30.6 (C-3), 32.1 (C-2), 75.7 (C-1), 125.9 (C-6'), 127.1 (C-4a'), 128.4 (C-5'), 128.6 (C-7'), 129.8 (C-8'), 132.9 (C-3'), 133.6 (C-4'), 148.9 (C-8a'), 166.2 (C-2') and 171.0 (C=O).

6-Hydroxy-1,2,3,-trihydroacridin-1-yl acetate The experimental method employed for the synthesis of 1-acetoxy-1,2,3,4-tetrahydroacridine was followed using 2-[hydroxy(5-hydroxy-2-nitrophenyl)-methyl]cyclopent-2-enone (0.15 g, 0.60 mmol). Work-up followed by flash chromatography [on silica gel; elution with hexane-EtOAc (2:1)] afforded as a brown viscous oil, *6-hydroxy-1,2,3,-trihydroacridin-1-yl acetate* (0.026 g, 18%), δ_H (400 MHz; $CDCl_3$) 2.07 (3H, s, CH_3), 2.23 (1H, m, 2-H), 2.55 (1H, m, 2-H), 3.08 (1H, m, 3-H), 3.33 (1H, m, 3-H), 6.26 (1H, m, 1-H), 7.17 (1H, d, *J* 2.4 Hz, 5'-H), 7.35 (1H, dd, *J* 2.4 and 8.8 Hz, 7'-H), 7.91 (1H, d, *J* 9.2 Hz, 8'-H) and 8.04 (1H, s, 4'-H), δ_C (100 MHz; $CDCl_3$) 22.6 (CH_3), 30.7 (C-3), 31.5 (C-2), 75.6 (C-1), 109.9 (C-5'), 122.7 (C-7'), 128.7 (C-4a'), 129.1 (C-8'), 132.8 (C-4'), 133.4 (C-3'), 143.5 (C-8a'), 155.2 (C-6'), 163.0 (C-2') and 171.2 (C=O).

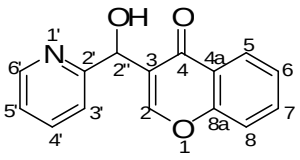
6,7-Dimethoxy-1,2,3-trihydroacridin-1-yl acetate. The experimental method employed for the synthesis of 1-acetoxy-1,2,3,4-tetrahydroacridine was followed using 2-[hydroxy(6,7-dimethoxy-2-nitrophenyl)-methyl]cyclopent-2-enone (0.15 g, 0.51 mmol). Work-up followed by flash chromatography [on silica gel; elution with hexane-EtOAc (2:1)] afforded as a brown viscous oil, *6,7-dimethoxy-1,2,3-trihydroacridin-1-yl acetate* (0.056 g, 38%), δ_H (400 MHz; $CDCl_3$), 1.82 (1H, m, 2-H), 2.02 (3H, s, CH_3), 2.20 (1H, m, 2-H), 3.02 (1H, m, 3-H), 3.27 (1H, m, 3-H), 3.93 (3H, s, 7-OMe), 3.96 (3H, s, 6-OMe), 6.22 (1H, m, 1-H), 7.00 (1H, s, 5'-H), 7.37 (1H, s, 8'-H) and 8.02 (1H, s, 4'-H), δ_C

(100 MHz; $CDCl_3$) 21.2 (CH_3), 30.5 (C-3), 31.6 (C-2), 75.9 (C-1), 105.7 (C-5'), 107.0 (C-8'), 122.4 (C-4a'), 131.0 (C-3'), 132.2 (C-4'), 145.5 (C-8a'), 149.2 (C-6'), 152.7 (C-7'), 163.5 (C-2') and 171.0 (C=O).

8-Methoxy-1,2,3-trihydroacridin-1-yl acetate. The experimental method employed for the synthesis of 1-acetoxy-1,2,3,4-tetrahydroacridine was followed using 2-[hydroxy(3-methoxy-methylene-2-nitrophenyl)-methyl]cyclopent-2-enone (0.09 g, 0.34 mmol). Work-up followed by flash chromatography [on silica gel; elution with hexane-EtOAc (2:1)] afforded as a brown viscous oil, *8-methoxy-1,2,3-trihydroacridin-1-yl acetate* (0.032 g, 37%), δ_H (400 MHz; $CDCl_3$), 1.84 (1H, m, 2-H), 2.04 (3H, s, CH_3), 2.18 (1H, m, 2-H), 3.04 (1H, m, 3-H), 3.30 (1H, m, 3-H), 4.07 (3H, s, 8-OMe), 6.23 (1H, m, 1-H), 7.02 (1H, dd, *J* 0.8 and 7.2 Hz, 7'-H), 7.33-7.42 (2H, m, 5'-H and 6'-H) and 8.05 (1H, s, 4'-H), δ_C (100 MHz; $CDCl_3$) 21.4 (CH_3), 31.1 (C-3), 31.7 (C-2), 56.0 (8-OMe), 75.7 (C-1), 108.2 (C-7'), 120.1 (C-5'), 125.8 (C-6' and C-4a'), 127.7 (C-3'), 129.4 (C-8a'), 137.2 (C-4'), 154.5 (C-8'), 157.6 (C-2') and 170.7 (C=O).

6,7-Dioxol-methylene-1,2,3-trihydroacridin-1-yl acetate. The experimental method employed for the synthesis of 1-acetoxy-1,2,3,4-tetrahydroacridine was followed using 2-[hydroxy(6,7-dioxol-methylene-2-nitrophenyl)-methyl]cyclopent-2-enone (0.15 g, 0.54 mmol). Work-up followed by flash chromatography [on silica gel; elution with hexane-EtOAc (2:1)] afforded as a brown viscous oil, *6,7-Dioxol-methylene-1,2,3-trihydroacridin-1-yl acetate* (0.062 g, 42%), δ_H (400 MHz; $CDCl_3$) 1.84 (1H, m, 2-H), 2.03 (3H, s, CH_3), 2.20 (1H, m, 2-H), 3.07 (1H, m, 3-H), 3.29 (1H, m, 3-H), 6.08 (2H, s, O-CH_2-O), 6.23 (1H, m, 1-H), 7.03 (1H, s, 8'-H), 7.51 (1H, s, 5'-H), 8.00 (1H, s, 4'-H), δ_C (100 MHz; $CDCl_3$) 21.2 (CH_3), 30.6 (C-3), 31.7 (C-2), 75.9 (C-1), 101.8 (O-CH_2-O), 103.4 (C-8'), 105.1 (C-5'), 124.1 (C-4a'), 131.3 (C-3'), 132.9 (C-4'), 146.9 (C-8a'), 147.4 (C-6'), 151.1 (C-7'), 163.7 (C-2'), 171.1 (C=O).

3.9. Reactions of chromones with pyridine-2-carbaldehydes



3-[Hydroxy(pyridn-2-yl)methyl]chromone 207a. The method for the preparation 2-[hydroxy(pyridin-2-y**i**l)methyl]cyclopent-2-enone **193** was followed using pyridine-2-carbaldehyde (0.56 g, 0.50 mL, 5.26 mmol) and chromone (1.54 g, 10.51 mmol). Work-up followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded as a brown solid, 3-[hydroxy(pyridin-2-yl)methyl]chromone **207a** (0.85 g, 64%), m.p. 87-89 ^{o}C (lit.,[192] 82-84 ^{o}C); δ_H (400 MHz; $CDCl_3$) 7.38 (1H, t, *J* 7.6 Hz, 6-H), 7.44 (1H, d, *J* 8.4 Hz, 8-H), 7.62- 7.68 (4H, m, 4'-H, 5-H, 5'-H and 7-H), 8.06 (1H, s, 2-H), 8.20 (1H, d, *J* 8.0 Hz, 3'-H) and 8.51 (1H, d, *J* 4.8 Hz, 6'-H); δ_C (100 MHz; $CDCl_3$) 68.68 (C-7'), 118.2 (C-8), 122.8 (C-3), 124.0 (C-3'), 125.2 (C-4a), 125.7 (C-6), 125.8 (C-5), 133.8 (C-7), 137.0 (C-4'), 148.0 (C-2), 154.1 (C-6'), 156.3 (C-8a), 159.8 (C-2') and 177.5 (C=O). *m/z* 254 ($\mathbf{M}^+$, 100%).

6-Chloro-3-[hydroxy(pyridin-2-yl)methyl]chromone **207b**. The method for the preparation 2-[hydroxy(pyridin-2-yl)methyl]cyclopent-2-enone **193** was followed using pyridine-2-carbaldehyde (0.15 g, 0.13 mL, 1.38 mmol) and 6-chlorochromone (0.50 g, 2.77 mmol). Work-up followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded as a cream solid, *6-chloro-3-[hydroxy(pyridin-2-yl)methyl]chromone* **207b** (0.46 g, 58 %), m.p. 114-116 ^{o}C; ν_{max} (Nujol)/cm^{-1} 1643 (C=O) and 3552 (br OH); δ_H (400 MHz; $CDCl_3$) 5.22 (1H, s, OH), 5.99 (1H, s, 2"-H), 7.20 (1H, dd, *J* 4.4 Hz and 8.8 Hz, 5'-H), 7.40 (1H, d, *J* 8.8 Hz, 3'-H), 7.59 (1H, dd, *J* 2.4 Hz and 8.8 Hz, 7-H), 7.66-7.70 (2H, m, 4'-H and 8-H), 8.07 (1H, s, 2-H), 8.16 (1H, d, *J* 2.4 Hz, 5-H) and 8.51 (1H, d, *J* 4.8 Hz, 6'-H); δ_C (100 MHz; $CDCl_3$) 68.3 (C-2"), 119.9 (C-5), 121.5 (C-5'), 122.9 (C-3'), 124.9 (C-3), 125.2 (C-7), 126.1 (C-4a), 131.2 (C-6), 134.0 (C-8), 137.1 (C-4'), 148.1 (C-2), 154.3 (C-6'), 154.7 (C-2'), 159.4 (C-8a) and 176.3 (C=O). *m/z* 287 ($\mathbf{M}^+$, 100%).

6-Bromo-3-[hydroxy(pyridin-2-yl)methyl]chromone **207c**. The method for the preparation 2-[hydroxy(pyridin-2-yl)methyl]cyclopent-2-enone **193** was followed using pyridine-2-carbaldehyde (0.56 g, 0.50 mL, 5.26 mmol) and 6-bromochromone (1.30 g, 5.78 mmol). Work-up followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded as a cream crystalline solid, *6-bromo-3-[hydroxy(pyridin-2-yl)methyl]chromone* **207c** (1.40 g, 80%), m.p. 80-83 ^{o}C; ν_{max} (Nujol)/cm^{-1} 1634 (C=O) and 3363 (br OH); δ_H (400 MHz; $CDCl_3$) 4.87 (1H, s, OH), 5.99 (1H, s, 2"-H), 7.22 (1H, m, 5'-H), 7.33 (1H, d, *J* 9.2 Hz, 8-H), 7.66-7.70 (2H, m, 4'-H and 3'-H), 7.72 (1H, dd, *J* 2.4 Hz and 8.8 Hz, 7-H), 8.08 (1H, s, 2-H), 8.31 (1H, d, *J* 2.4 Hz, 5-H) and 8.50 (1H, d, *J* 4.8 Hz, 6'-H); δ_C (100 MHz; $CDCl_3$) 68.3 (C-2"), 118.7 (C-6), 120.1 (C-8), 121.5 (C-5'), 122.9 (C-3'), 125.2 (C-3), 126.1 (C-4a), 128.3 (C-5), 136.8 (C-4'), 137.1 (C-7), 148.1 (C-2), 154.3 (C-6'), 155.1 (C-8a), 159.3 (C-2') and 176.1 (C=O). *m/z* 330 (**M**$^+$, 100%).

6-Fluoro-3-[hydroxyl(pyridin-2-yl)methyl]chromone **207d**. The method for the preparation 2-[hydroxy(pyridin-2-yl)methyl]cyclopent-2-enone **193** was followed using pyridine-2-carbaldehyde (0.56 g, 0.50 mL, 5.26 mmol) and 6-fluorochromone (0.95 g, 5.78 mmol). Work-up followed by flash chromatography afforded as a cream solid, *6-fluoro-3-[hydroxyl(pyridin-2-yl)methyl]chromone* **207d** (1.18 g, 83%), m.p. 136-138 ^{o}C; ν_{max} (Nujol)/cm^{-1} 1632 (C=O) and 3372 (br OH); δ_H (400 MHz; $CDCl_3$) 7.20 (1H, d, *J* 8.0 Hz, 8-H), 7.37 (1H, m, 7-H), 7.45 (1H, dd, *J* 4.4 and 9.2 Hz, 5'-H), 7.66-7.70 (2H, m, 3'-H and 5-H), 7.82 (1H, dd, *J* 2.8 and 8.4 Hz, 4'-H), 8.08 (1H, s, 2-H) and 8.51 (1H, d, *J* 4.8 Hz, 6'-H); δ_C (100 MHz; $CDCl_3$) 68.3 (C-2"), 120.3 (C-5), 121.5 (C-5'), 122.0 (C-8), 122.2 (C-3), 122.9 (C-7), 125.2 (C-4a), 137.1 (C-3'), 148.0 (C-4'), 152.5 (C-8a), 154.4 (C-2), 158.2 (C-2'), 159.4 (C-6'), 160.7 (C-6) and 176.7 (C=O). *m/z* 271 (**M**$^+$, 100%).

6-Methyl-3-[hydroxy(pyridin-2-yl)methyl]chromone **207e**. The method for the preparation 2-[hydroxy(pyridin-2-yl)methyl]cyclopent-2-enone **193** was followed using pyridine-2-carbaldehyde (0.56 g, 0.50 mL, 5.26 mmol) and 6-methylchromone (0.93 g, 5.78 mmol). Work-up followed by flash chromatography [on silica gel; elution with

hexane-EtOAc (1:1)] afforded as a cream crystalline solid, 6-methyl-3-[hydroxy(pyridin-2-yl)methyl]chromone **207e** (0.96 g, 68%), m.p. 88-90 ^{o}C (lit.,[192] 90 ^{o}C); ν_{max} (Nujol)/cm^{-1} 1633 (C=O) and 3380 (br OH); δ_H (400 MHz; $CDCl_3$) 2.42 (3H, s, 6'-CH_3), 5.32 (1H, br s, OH), 5.99 (1H, s, 2"-H), 7.17-7.20 (1H, m, 5'-H), 7.33 (1H, d, *J* 8.4 Hz, 8-H), 7.45 (1H, dd, *J* 2.4 Hz and 8.4 Hz, 7-H), 7.64-7.70 (2H, m, 4'-H and 3'-H), 7.97 (1H, s, 2-H), 8.03 (1H, s, 5-H) and 8.50 (1H, d, *J* 4.8 Hz, 6'-H); δ_C (100 MHz; $CDCl_3$) 20.9 (CH_3), 68.8 (C-2"), 117.9 (C-8), 121.4 (C-5'), 122.7 (C-3'), 123.6 (C-3), 124.9 (C-5), 125.5 (C-4a), 135.1 (C-7), 135.2 (C-6), 137.0 (C-4'), 148.0 (C-2), 154.0 (C-6'), 154.6 (C-8a), 159.8 (C-2') and 177.6 (C=O). *m/z* 267 ($\mathbf{M}^+$, 100%).

3-[Hydroxy(6-methylpyridin-2-yl)methyl]chromone **208a**. The method for the preparation 2-[hydroxy(pyridin-2-yl)methyl]cyclopent-2-enone **193** was followed using 6-methylpyridine-2-carbaldehyde (0.17 g, 1.42 mmol) and chromone (0.40 g, 2.83 mmol). Work-up followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded as a cream solid, *3-[hydroxy(6-methylpyridin-2-yl)methyl]chromone* **208a** (0.30 g, 81%), m.p. 98-100 ^{o}C; ν_{max} (Nujol)/cm^{-1} 1645 (C=O) and 3367 (br OH); δ_H (400 MHz; $CDCl_3$) 2.52 (3H, s, 6-CH_3), 5.99 (1H, s, 2"-H), 7.02 (1H, d, *J* 7.6 Hz, 8-H), 7.35-7.44 (3H, m, 5-H, 5'-H and 6-H), 7.52 (1H, t, *J* 7.6 Hz, 7-H), 7.62 (1H, td, *J* 1.6 Hz and 8.4 Hz, 4'-H), 8.04 (1H, s, 2-H) and 8.20 (1H, dd, *J* 1.6 Hz and 8.0 Hz, 3'-H); δ_C (100 MHz; $CDCl_3$) 24.2 (6-CH_3), 67.8 (C-2"), 118.1 (C-5'), 118.3 (C-3'), 122.3 (C-8), 124.0 (C-3), 125.1 (C-6), 125.7 (C-5), 126.1 (C-4a), 133.7 (C-7), 137.3 (C-4'), 154.2 (C-2), 156.2 (C-6'), 156.8 (C-2'), 158.6 (C-8a) and 177.4 (C=O). *m/z* 267 ($\mathbf{M}^+$, 100%).

6-Chloro-3-[hydroxy(6-methylpyridin-2-yl)methyl]chromone **208b**. The method for the preparation 2-[hydroxy(pyridin-2-yl)methyl]cyclopent-2-enone **193** was followed using 6-methylpyridine-2-carbaldehyde (0.17 g, 1.42 mmol) and 6-chlorochromone (0.51 g, 2.83 mmol). Work-up followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded as a cream solid, *6-chloro-3-[hydroxy(6-methylpyridin-2-*

yl)methyl]chromone **208b** (0.18 g, 40%), m.p. 127-130 ^{o}C; ν_{max} (Nujol)/cm^{-1} 1645 (C=O) and 3376 (br OH); δ_H (400 MHz; $CDCl_3$) 2.54 (3H, s, 6-CH_3), 5.53 (1H, s, OH), 5.99 (1H, s, 2"-H), 7.05 (1H, d, *J* 7.2 Hz, 7-H), 7.38-7.43 (2H, m, 3'-H and 5'-H), 7.53 (1H, d, *J* 7.6 Hz, 8-H), 7.58 (1H, t, *J* 8.8 Hz, 4'-H), 8.05 (1H, s, 2-H) and 8.17 (1H, d, *J* 1.2 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 24.2 (6-CH_3), 67.4 (C-2"), 118.4 (C-5'),119.9 (C-3'), 122.4 (C-8), 125.0 (C-3), 125.2 (C-5), 126.4 (C-4a), 131.2 (C-6), 133.9 (C-7), 137.4 (C-4'), 154.4 (C-2), 154.6 (C-8a), 156.9 (C-6'), 158.3 (C-2') and 176.2 (C=O). *m/z* 301 (**M**$^{+}$, 100%).

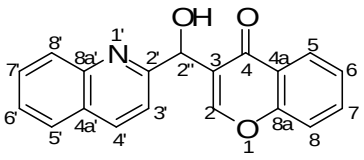
6-Bromo-3-[hydroxy(6-methylpyridin-2-yl)methyl]chromone **208c**. The method for the preparation 2-[hydroxy(pyridin-2-yl)methyl]cyclopent-2-enone was **193** followed using 6-methylpyridine-2-carbaldehyde (0.20 g, 1.65 mmol) and 6-bromochromone (0.41 g, 1.82 mmol). Work-up followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded as a cream solid, *6-bromo-3-[hydroxy(6-methylpyridin-2-yl)methyl]chromone* **208c** (0.35 g, 62%), m.p. 123-126 ^{o}C; ν_{max} (Nujol)/cm^{-1} 1647 (C=O) and 3358 (br OH); δ_H (400 MHz; $CDCl_3$) 2.53 (3H, s, CH_3). 5.56 (1H, s, OH), 5.99 (1H, s, 2"-H), 7.04 (1H, d, *J* 7.2 Hz, 5'-H), 7.33 (1H, d, *J* 8.8 Hz, 8-H), 7.41 (1H, d, *J* 8.0 Hz, 3'-H), 7.54 (1H, t, *J* 7.6 Hz, 4'-H), 7.71 (1H, dd, *J* 2.4 Hz and 8.8 Hz, 7-H), 8.06 (1H, s, 2-H) and 8.33 (1H, d, *J* 2.4 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 24.2 (CH_3), 67.4 (C-2"), 118.4 (C-8), 118.6 (C-6), 120.1 (C-5'), 122.4 (C-3'), 125.3 (C-3), 126.4 (C-4a), 128.4 (C-5), 136.7 (C-4'), 137.4 (C-7), 154.4 (C-2), 155.0 (C-8a), 156.9 (C-2'), 158.2 (C-6') and 176.1 (C=O). *m/z* 345 (**M**$^{+}$, 100%).

6-Fluoro-3-[Hydroxy(6-methylpyridin-2-yl)methyl]chromone **208d**. The method for the preparation 2-[hydroxy(pyridin-2-yl)methyl]cyclopent-2-enone **193** was followed using 6-methylpyridine-2-carbaldehyde (0.20 g, 1.65 mmol) and 6-fluorochromone (0.30 g, 1.82 mmol). Work-up followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded as a cream solid, *6-fluoro-3-[hydroxy(6-methylpyridin-2-yl)methyl]chromone* **208d** (0.20 g, 42%), m.p. 128-130 ^{o}C; ν_{max} (Nujol)/cm^{-1} 1638 (C=O)

and 3371 (br OH); δ_H (400 MHz; $CDCl_3$) 2.54 (3H, s, 6-CH_3), 6.00 (1H, s, 2”-H), 7.04 (1H, d, *J* 7.6 Hz, 5’-H), 7.36-7.46 (3H, m, 3’-H, 5-H and 8-H), 7.54 (1H, t, *J* 7.6 Hz, 4’-H), 7.84 (1H, dd, *J* 3.6 and 8.4 Hz, 7-H) and 8.06 (1H, s, 2-H), δ_C (100 MHz; $CDCl_3$) 24.2 (6-CH_3), 67.5 (C-2”), 110.7 (C-5), 118.4 (C-5’), 120.2 (C-8), 120.3 (C-3), 121.8 (C-7), 122.1 (C-4a), 122.4 (C-3’), 125.7 (C-4’), 137.4 (C-8a), 154.5 (C-2), 155.4 (C-2’), 156.9 (C-6’), 158.4 (C-6) and 176.6 (C=O). *m/z* 285 (**M**$^+$, 100%).

6-Methyl-3-[Hydroxy(6-methylpyridin-2-yl)methyl]chromone **208e**. The method for the preparation 2-[hydroxy(pyridin-2-yl)methyl]cyclopent-2-enone **193** was followed using 6-methylpyridine-2-carbaldehyde (0.20 g, 1.65 mmol) and 6-methylchromone (0.30 g, 1.82 mmol). Work-up followed by flash chromatography [on silica gel; elution with hexane-EtOAc (1:1)] afforded as a cream solid, *6-methyl-3-[hydroxy(6-methylpyridin-2-yl)methyl]chromone* **208e** (0.18 g, 39%), m.p. 134-136 ^oC; ν_{max} (Nujol)/cm^{-1} 1647 (C=O) and 3371 (br OH); δ_H (400 MHz; $CDCl_3$) 2.43 (3H, s, 6’-CH_3), 2.54 (3H, s, 6-CH_3), 5.57 (1H, d, *J* 5.2 Hz, OH), 6.00 (1H, d, *J* 5.2 Hz, 2”-H), 7.03 (1H, d, *J* 7.2 Hz, 5’-H), 7.33 (1H, d, *J* 8.8 Hz, 8-H), 7.43-7.47 (2H, m, 5-H and 7-H), 7.53 (1H, t, *J* 7.6 Hz, 4’-H) and 7.99-8.01 (2H, m, 2-H and 3’-H); δ_C (100 MHz; $CDCl_3$) 20.9 (6’-CH_3), 24.2 (6-CH_3), 67.8 (C-2”), 117.9 (C-8), 118.3 (C-5’), 122.2 (C-3’), 123.7 (C-3), 125.0 (C-5), 125.9 (C-4a), 135.0 (C-7), 135.1 (C-6), 137.3 (C-4’), 154.1 (C-2), 154.6 (C-8a), 156.8 (C-6’), 158.7 (C-2’) and 177.5 (C=O). *m/z* 281 (**M**$^+$, 100%).

3.10 Reactions of chromones with quinoline-2-carbaldehydes



3-[Hydroxy(quinolin-2-yl)methyl]chromone **212a**. The method for the preparation 2-[hydroxy(pyridin-2-yl)methyl]cyclopent-2-enone **193** was followed using quinoline-2-carbaldehyde (0.40 g, 2.46 mmol) and chromone (0.30 g, 2.05 mmol). Work-up followed by flash chromatography afforded as a cream solid, *3-[hydroxy(quinolin-2-yl)methyl]chromone* **212a** (0.42 g, 68%), m.p. 168-170 ^{o}C; (Found: $\mathbf{M}^{+}$ 303.08898. Calc. for $C_{19}H_{13}NO_3$, M: 303.08954). ν_{max} (Nujol)/cm^{-1} 1649 (C=O) and 3358 (br OH); δ_H (600 MHz, $CDCl_3$) 5.90 (s, 1H, OH), 6.24 (s, 1H, 2”-H), 7.40 (td, 1H, *J* 1.2 Hz and 8.4 Hz, 6’-H), 7.42 (d, 1H, *J* 8.4 Hz, 5’-H), 7.52 (td, 1H, *J* 1.2 Hz and 8.4 Hz, 6-H), 7.65 (td, 1H, *J* 1.2 Hz and 8.4 Hz, 7’-H), 7.71 (td, 1H, *J* 1.8 Hz and 8.4 Hz, 7-H), 7.75 (d, 1H, *J* 9.0 Hz, 3’-H), 7.79 (d, 1H, *J* 8.4 Hz, 5-H), 8.07 (d, 1H, *J* 8.4 Hz, 8-H), 8.10-8.12 (m, 2H, 3-H and 4’-H) and 8.25 (dd, 1H, *J* 1.8 Hz and 8.4 Hz, 8’-H); δ_C (100 MHz, $CDCl_3$) 67.78 (C-2”), 118.17 (C-8), 119.31 (C-3’), 124.08 (C-3), 125.25 (C-6), 125.80 (C-6’), 125.94 (C-4a), 126.56 (C-5’), 127.62 (C-8’), 127.87 (C-4a’), 128.67 (C-7’), 129.78 (C-5), 133.74 (C-4’), 137.30 (C-7), 146.21 (C-8a’), 154.79 (C-2), 156.30 (C-2’), 159.99 (C-8a) and 177.36 (C=O); *m/z* 303 ($\mathbf{M}^{+}$, 22%), 227 (7%), 209 (12%), 181 (23%), 153 (30%) and 130 (100%).

6-Chloro-3-[hydroxyl(quinolin-2-yl)methyl]chromone **212b**. The method for the preparation 2-[hydroxy(pyridin-2-yl)methyl]cyclopent-2-enone **193** was followed using quinoline-2-carbaldehyde (0.30 g, 2.46 mmol) and 6-chlorochromone (0.37 g, 2.05 mmol). Work-up followed by flash chromatography afforded as a cream solid, *6-chloro-3-[hydroxyl(quinolin-2-yl)methyl]chromone* **212b** (0.43 g, 62%), m.p. 150-153 ^{o}C; (Found: $\mathbf{M}^{+}$: 337.05003. Calc. for $C_{19}H_{12}ClNO_3$; M: 337.05057). ν_{max} (Nujol)/cm^{-1} 1649 (C=O) and 3376 (br OH); δ_H (600 MHz; $CDCl_3$) 6.23 (1H, s, 2”-H), 7.39 (1H, d, *J* 9.0 Hz, 8-H),7.52 (1H, td, *J* 0.6 Hz and 7.8 Hz, 6’-H), 7.59 (1H, dd, *J* 2.4 Hz and 9.0 Hz, 7-

H), 7.70-7.74 (2H, m, 3'-H and 7'-H), 7.80 (1H, d, *J* 8.4 Hz, 5'-H), 8.06 (1H, d, *J* 9.0 Hz, 4'-H), 8.11-8.14 (2H, m, 2-H and 8'-H) and 8.20 (1H, d, *J* 2.4 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 67.5 (C-2"), 119.3 (C-8), 119.9 (C-3'), 125.1 (C-3), 125.2 (C-6'), 126.2 (C-4a'), 126.7 (C-5'), 127.6 (C-8'), 127.9 (C-4a), 128.6 (C-7'), 129.9 (C-5), 131.3 (C-6), 134.00 (C-4'), 137.4 (C-7), 146.2 (C-8a'), 154.6 (C-2'), 155.0 (C-2), 159.6 (C-8a) and 176.2 (C=O); *m/z* 337 ($\mathbf{M}^+$, 11%), 209 (7%), 181 (13%), 153 (19%) and 130 (100%).

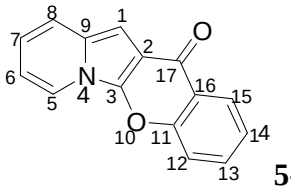
6-Bromo-3-[hydroxyl(quinolin-2-yl)methyl]chromone **212c.** The method for the preparation 2-[hydroxy(pyridin-2-yl)methyl]cyclopent-2-enone **193** was followed using quinoline-2-carbaldehyde (0.20 g, 1.27 mmol) and 6-bromochromone (0.24 g, 1.06 mmol). Work-up followed by flash chromatography afforded as a cream solid, *6-bromo-3-[hydroxyl(quinolin-2-yl)methyl]chromone* **212c** (0.26 g, 65%), m.p. 152-154 ^oC; [Found $\mathbf{M}^+$: 382.99632 (^{81}Br) and 380.99927 (^{79}Br). Calc. for $C_{19}H_{12}BrNO_3$; M 382.20752 (^{81}Br) and 381.0006 (^{79}Br)]. ν_{max} (Nujol)/cm^{-1} 1643 (C=O) and 3363 (br OH); δ_H (600 MHz; $CDCl_3$) 5.91 (1H, br s, OH), 6.23 (1H, s, 2"-H), 7.32 (1H, d, *J* 8.8 Hz, 8-H), 7.53 (1H, m, 7-H), 7.70-7.74 (3H, m, 2-H, 6'-H and 7'-H), 7.80 (1H, d, *J* 8.0 Hz, 3'-H), 8.06 (1H, d, *J* 8.4 Hz, 5'-H), 8.11-8.14 (2H, m, 4'-H and 8'-H) and 8.37 (1H, d, *J* 2.4 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 67.5 (C-2"), 118.9 (C-6), 119.3 (C-8), 120.1 (C-3), 125.4 (C-4a), 126.3 (C-4a'), 126.7 (C-6'), 127.6 (C-5'), 127.9 (C-4a), 128.5 (C-8'), 128.6 (C-7'), 129.9 (C-5), 136.7 (C-4'), 137.4 (C-7), 146.2 (C-8a'), 155.0 (C-2), 155.1 (C-8a), 159.6 (C-2') and 176.0 (C=O); *m/z* 383 ($\mathbf{M}^+$, 7%), 209 (7%), 181 (13%), 153 (16%) and 130 (100%).

6-Fluoro-3-[hydroxyl(quinolin-2-yl)methyl]chromone **212d**. The method for the preparation 2-[hydroxy(pyridin-2-yl)methyl]cyclopent-2-enone **193** was followed using quinoline-2-carbaldehyde (0.20 g, 1.27 mmol) and 6-fluorochromone (0.17 g, 1.06 mmol). Work-up followed by flash chromatography afforded as a cream solid, *6-fluoro-3-[hydroxyl(quinolin-2-yl)methyl]chromone* **212d** (0.20 g, 56%), m.p. 136-138 ^oC; (Found: $\mathbf{M}^+$: 321.07932. Calc. for $C_{19}H_{12}FNO_3$; M: 321.08012). ν_{max} (Nujol)/cm^{-1} 1643

(C=O) and 3363 (br OH); δ_H (400 MHz; $CDCl_3$) 6.23 (1H, s, 2”-H), 7.37 (1H, d, *J* 7.6 Hz, 8-H), 7.44 (1H, d, *J* 4.0 Hz, 5-H), 7.54 (1H, td, *J* 1.2 and 8.0 Hz, 6’-H), 7.70-7.75 (3H, m, 2-H, 3’-H and 7’-H), 7.80 (1H, d, *J* 8.0 Hz, 8’-H), 7.88 (1H, dd, *J* 3.2 and 8.4 Hz, 7-H), 8.07 (1H, d, *J* 8.8 Hz, 5’-H) and 8.11-8.14 (2H, m, 4’-H and 8’-H); δ_C (100 MHz; $CDCl_3$) 67.5 (C-2”), 119.2 (C-8), 120.4 (C-5), 122.0 (C-7),122.2 (C-3’), 125.2 (C-3), 125.4 (C-4a’), 126.6 (C-6’), 127.6 (C-5’), 127.9 (C-4a), 128.6 (C-8’), 129.9 (C-7’), 137.4 (C-4’), 146.1 (C-8a), 152.5 (C-8a’), 158.3 (C-6), 155.1 (C-2), 159.7 (C-2’) and 176.6 (C=O); *m/z* 321($\mathbf{M}^+$, 15%), 209 (3%), 181 (12%), 153 (17%) and 130 (100%).

6-Methyl-3-[hydroxyl(quinolin-2-yl)methyl]chromone **212e**. The method for the preparation 2-[hydroxy(pyridin-2-yl)methyl]cyclopent-2-enone **193** was followed using quinoline-2-carbaldehyde (0.20 g, 1.3 mmol) and 6-methylchromone (0.17 g, 1.1 mmol). Work-up followed by flash chromatography afforded as a cream solid, *6-methyl-3-[hydroxyl(quinolin-2-yl)methyl]chromone* **212e** (0.22 g, 67 %), m.p. 183-186 ^oC; δ_H (400 MHz; $CDCl_3$) 2.42 (3H, s, 6-Me), 5.25 (1H, br s, OH), 6.32 (1H, s, 2”-H), 7.46 (1H, d, *J* 8.4 Hz, 8-H), 7.74-7.87 (3H, m, 2-H, 3’-H and 7-H), 7.91-7.96 (2H, m, 5-H and 6’-H), 8.16 (1H, t, *J* 8.4 Hz, 7’-H), 8.24-8.30 (2H, m, 4’-H and 5’-H), 8.38 (1H, d, *J* 8.4 Hz, 8’-H), δ_C (100 MHz; $CDCl_3$) 20.9 (6-Me), 62.2 (C-2”), 117.9 (C-8), 121.0 (C-3), 125.0(C-3’), 127.5 (C-6’), 127.8 (C-4a), 128.5 (C-4a’), 129.1 (C-5’), 129.3 (C-8’), 130.2 (C-5), 130.6 (C-6), 131.0 (C-4’)135.0(C-7), 146.0 (C-8a’), 147.5 (C-2), 155.3 (C-8a), 164.4 (C-2’), 177.9 (C=O).

3.11 Synthesis of polycyclic indolizine derivatives



5-Oxo-4a-aza-benzo[b]fluoren-10-one 209a. **Method 1**. 3-[hydroxy(pyridin-2-yl)methyl]chromone (0.35 g, 1.4 mmol) and acetic anhydride (1.3 mL, 13.89 mmol) were stirred at 150 ^{o}C under reflux for 1h. The resulting green reaction solution was cooled to room temperature forming a green precipitate which was subsequently filtered off to afford as a green solid, 5-oxo-4a-aza-benzo[b]fluoren-10-one (0.20 g, 61%).

Method 2: The 3-[hydroxy(pyridin-2-yl)methyl]chromone (0.20 g, 1.39 mmol) and acetic anhydride were stirred at 150 ^{o}C in a microwave reactor for 5 min. The resulting green reaction solution was cooled to room temperature forming a green precipitate which was subsequently filtered off to afford as a green solid, 5-oxo-4*a*-aza-benzo[*b*]fluoren-10-one **209a** (0.30 g, 90%), m.p. 178-180 ^{o}C (lit.,[192] 170-172 ^{o}C); (Found: $\mathbf{M}^{+}$: 235.06276. Calc. for $C_{15}H_9NO_2$; M: 235.06333). ν_{max} (KBr)/cm^{-1} 1209 (C-N), 1660 (C=C), 1719 (C=O) and 3077 (C-H); δ_H (400 MHz; $CDCl_3$) 6.61 (1H, t, *J* 7.2 Hz, 6-H), 6.70 (1H, t, *J* 9.2 Hz, 7-H), 6.84 (1H, s, 1-H), 7.39 (1H, d, *J* 9.6 Hz, 12-H), 7.44 (1H, td, *J* 1.2 Hz and 8.0 Hz, 14-H), 7.60 (1H, d, *J* 8.0 Hz, 8-H), 7.70 (1H, td, *J* 1.6 Hz and 8.4 Hz, 13-H), 8.04 (1H, dd, *J* 1.2 Hz and 7.2 Hz, 15-H) and 8.45 (1H, dd, *J* 1.6 Hz and 8.0 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 91.2 (C-1), 109.3 (C-3), 111.7 (C-6), 117.4 (C-7), 118.8 (C-8), 120.1 (C-12), 120.7 (C-14), 123.3 (C-2), 124.4 (C-5), 127.1 (C-15), 128.0 (C-16), 133.0 (C-9 and C-13), 154.1 (C-11) and 175.0 (C=O); *m/z* 235 ($\mathbf{M}^{+}$, 100%), 207 (28%) and 179 (56%).

***8-Chloro-5-Oxo-4*a*-aza-benzo[*b*]fluoren-10-one* 209b**. The procedure (methods 1 and 2) for the preparation of the indolizine, 5-oxo-4*a*-aza-benzo[*b*]fluoren-10-one **209a** was followed using 6-chloro-3-[hydroxy(pyridin-2-yl)methyl]chromone (0.35 g, 1.22 mmol).

Work up afforded as a green solid, *8-chloro-5-oxo-4a-aza-benzo[b]fluoren-10-one* **209b** (**Method 1**: 0.18 g, 56%), (**Method 2**: 0.24 g, 74%), m.p. 198-200 ^{o}C; (Found: $\mathbf{M}^{+}$: 269.02382. Calc. for $C_{15}H_8ClNO_2$; M: 269.02436). ν_{max} (KBr)/cm^{-1} 1207 (C-N), 1605 (C=C), 1704 (C=O) and 3064 (C-H); δ_H (400 MHz; $CDCl_3$) 6.61 (1H, t, *J* 7.2Hz, 7-H), 6.72 (1H, t, *J* 9.2 Hz, 6-H), 6.81 (1H, s,1-H), 7.38 (1H, d, *J* 9.2 Hz, 12-H), 7.54 (1H, d, *J* 8.8 Hz, 8-H), 7.62 (1H, dd, *J* 2.8 Hz and 8.8 Hz, 13-H), 8.01 (1H, d, *J* 7.2 Hz, 5-H) and 8.39 (1H, d, *J* 2.8 Hz, 15-H); δ_C (100 MHz; $CDCl_3$) 91.2 (C-1), 109.1 (C-3), 112.0 (C-6), 119.0 (C-7), 119.1 (C-8), 120.0 (C-12), 120.7 (C-5), 124.32 (C-2), 126.5 (C-15), 128.3 (C-16), 130.2 (C-14), 133.0 (C-9 and C-13), 152.3 (C-11) and 173.6 (C=O), *m/z* 269 ($\mathbf{M}^{+}$, 100%), 241 (40%), 213 (56%) and 178 (40%).

8-Bromo-5-Oxo-4a-aza-benzo[b]fluoren-10-one **209c**. The procedure (methods 1 and 2) for the preparation of the indolizine, 5-oxo-4*a*-aza-benzo[*b*]fluoren-10-one **209a** was followed using 6-bromo-3-[hydroxy(6-methylpyridin-2-yl)methyl]chromone (0.20 g, 0.60 mmol). Work up afforded as a green solid, *8-bromo-5-oxo-4a-aza-benzo[b]fluoren-10-one* **209c** (**Method 1**: 0.083 g, 44%), (**Method 2**: 0.098 g, 52%), m.p. 202-203 ^{o}C; [Found: $\mathbf{M}^{+}$: 314.97223 (^{81}Br) and $\mathbf{M}^{+}$: 312.97384 (^{79}Br). Calc. for $C_{15}H_8BrNO_2$; M: 314.13356 (^{81}Br) and 312.97328 (^{79}Br)]. ν_{max} (KBr)/cm^{-1} 1207 (C-N), 1647 (C=C), 1719 (C=O) and 3063 (C-H);δ_H (400 MHz; $CDCl_3$) 6.62 (1H, t, *J* 6.4 Hz, 6-H), 6.72 (1H, t, *J* 6.4 Hz, 7-H), 6.81 (1H, s, 1-H), 7.37 (1H, d, *J* 9.2 Hz, 12-H), 7.50 (1H, d, *J* 8.8 Hz, 8-H), 7.76 (1H, dd, *J* 2.4 and 8.8 Hz, 13-H), 8.00 (1H, dd, *J* 0.8 and 7.2 Hz, 5-H) and 8.54 (1H, d, *J* 2.4 Hz, 15-H); δ_C (100 MHz; $CDCl_3$) 91.2 (C-1), 109.0 (C-3), 111.9 (C-6), 117.6 (C-2), 119.1 (C-7), 119.3 (C-8), 120.0 (C-12), 120.6 (*C*-5), 124.6 (C-14), 128.2 (C-16), 129.5 (C-15), 135.7 (C-13), 140.7 (C-9), 152.7 (C-11) and 173.4 (C=O); m/z 313 ($\mathbf{M}^{+}$, 100%), 285 (38%), 257 (54%), 206 (41%) and 178 (100%).

8-Fluoro-5-Oxo-4a-aza-benzo[b]fluoren-10-one **209d**. The procedure (methods 1 and 2) for the preparation of the indolizine, 5-oxo-4*a*-aza-benzo[*b*]fluoren-10-one **209a** was followed using 6-fluoro-3-[hydroxy(6-methylpyridin-2-yl)methyl]chromone (0.15 g, 0.54

mmol). Work up afforded as a green solid, *8-fluoro-5-oxo-4a-aza-benzo[b]fluoren-10-one* **209d** (**Method 1**, 0.062g, 46%), (**Method 2**; 0.078 g, 58%), m.p. 196-198 ^{o}C; (Found: $\mathbf{M}^{+}$: 253.05337. Calc. for $C_{15}H_8FNO_2$; M: 253.05391). ν_{max} (KBr)/cm^{-1} 1207 (C-N), 1660 (C=C), 1702 (C=O) and 3107 (C-H); δ_H (400 MHz; $CDCl_3$) 6.62 (1H, t, *J* 6.4 Hz, 6-H), 6.72 (1H, t, *J* 6.4 Hz, 7-H), 6.82 (1H, s, 1-H), 7.38-7.44 (2H, m, 12- and 15-H), 7.60 (1H, dd, *J* 4.0 and 9.2 Hz, 13-H), 8.02 (1H, d, *J* 7.2 Hz, 8-H) and 8.09 (1H, dd, *J* 3.2 and 8.4 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 90.9 (C-1), 111.8 (C-6), 112.1 (C-2), 119.1 (C-3), 119.2 (C-7), 120.0 (C-15), 120.6 (C-8), 120.7 (C-13), 120.9 (C-12), 124.4 (C-16), 128.2 (C-5), 141.0 (C-11), 150.0 (C-9), 157.8 (C-3), 160.3 (C-14) and 173.9 (C=O); *m/z* 253 ($\mathbf{M}^{+}$, 100%), 225 (37%) and197 (56%).

8-Methyl-5-Oxo-4a-aza-benzo[b]fluoren-10-one 209e. The procedure (methods 1 and 2) for the preparation of the indolizine, 5-oxo-4*a*-aza-benzo[*b*]fluoren-10-one **209a** was followed using 6-methyl-3-[hydroxy(6-methylpyridin-2-yl)methyl]chromone (0.28 g, 1.05 mmol). Work up afforded as a green solid, 8-methyl-5-oxo-4*a*-aza-benzo[*b*]fluoren-10-one **209e**, (**Method 1**: 0.11 g, 44%), (**Method 2**: 0.15 g, 58%), m.p. 93-95 ^{o}C (lit.,[192] 94-96 ^{o}C); (Found: $\mathbf{M}^{+}$: 249.07847. Calc. for $C_{16}H_{11}NO_2$; M: 249.07898).; ν_{max} (KBr)/cm^{-1} 1207 (C-N), 1652 (C=C), 1737 (C=O) and 3116 (C-H); δ_H (400 MHz; $CDCl_3$) 2.49 (3H, s, CH_3), 6.59 (1H, td, *J* 0.8 and 7.2 Hz, 7-H), 6.69 (1H, m, 6-H), 6.83 (1H, s, 1-H), 7.38 (1H, d, *J* 9.2 Hz, 12-H), 7.50-7.53 (2H, m, 8-H and 13-H), 8.02 (1H, dd, *J* 0.8 and 7.2 Hz, 5-H) and 8.23 (1H, s, 15-H); δ_C (100 MHz; $CDCl_3$) 20.9 (14-CH_3), 91.1 (C-1), 109.2 (C-6), 111.5 (C-2 and C-3), 117.1 (C-7), 118.7 (C-8), 120.1 (C-12), 120.7 (C-16), 122.9 (C-5), 126.4 (C-15), 127.9 (C-9), 134.1 (C-14), 141.0 (C-13), 152.3 (C-11) and 175.1 (C=O); *m/z* 249 ($\mathbf{M}^{+}$, 100%), 221 (34%) and193 (46%).

4-Methyl-5-oxa-4*a*-aza-benzo[*b*]fluoren-10-one **210a**. The procedure (methods 1 and 2) for the preparation of the indolizine, 5-oxo-4*a*-aza-benzo[*b*]fluoren-10-one **209a** was followed using 3-[hydroxy-(6-methyl-pyridin-2-yl)-methyl]-chromone (0.12 g, 0.45 mmol). Work up afforded as a green solid, *4-methyl-5-oxa-4a-aza-benzo[b]fluoren-10-*

one **210a**, (**Method 1**: 0.033 g, 30%), (**Method 2**: 0.072 g, 65%), m.p. 183-187 ^{o}C; δ_H (400 MHz; $CDCl_3$) 2.93 (3H, s, 5-CH_3), 6.31 (1H, d, *J* 6.4 Hz, 6-H), 6.58 (1H, t, *J* 6.4 Hz, 7-H), 6.76 (1H, s, 1-H), 7.19 (1H, d, *J* 9.2 Hz, 12-H), 7.43 (1H, d, *J* 8.8 Hz, 8-H) and 7.74 (1H, dd, *J* 2.4 and 8.8 Hz, 13-H), δ_C (100 MHz; $CDCl_3$) 20.3 (5-CH_3), 91.2 (C-1), 109.0 (C-3), 112.4 (C-6), 117.2 (C-7), 118.6 (C-8), 120.0 (C-12), 120.8 (C-14), 123.5 (C-2), 127.3 (C-15), 127.8 (C-16), 130.4 (C-5), 133.0 (C-9), 133.6 (C-13), 154.5 (C-11) and 174.8 (C=O).

8-Chloro-4-methyl-5-oxa-4*a*-aza-benzo[*b*]fluoren-10-one **210b**. The procedure (methods 1 and 2) for the preparation of the indolizine, 5-oxo-4*a*-aza-benzo[*b*]fluoren-10-one **209a** was followed using 6-chloro-3-[hydroxy(6-methylpyridin-2-yl)methyl]chromone (0.10 g, 0.33 mmol). Work up afforded as a green solid, *8-chloro-4-methyl-5-oxa-4a-aza-benzo[b]fluoren-10-one* **210b**, (**Method 1**: 0.036 g, 38%), (**Method 2**, 0.060 g, 63%), m.p. 169-172 ^{o}C; δ_H (400 MHz; $CDCl_3$) 2.96 (3H, s, 5-CH_3), 6.27 (1H, d, *J* 6.4 Hz, 6-H), 6.60 (1H, t, *J* 6.4 Hz, 7-H), 6.80 (1H, s, 1-H), 7.38 (1H, d, *J* 9.2 Hz, 12-H), 7.54 (1H, d, *J* 8.8 Hz, 8-H), 7.62 (1H, dd, *J* 2.8 Hz and 8.8 Hz, 13-H) and 8.39 (1H, d, *J* 2.8 Hz, 15-H), δ_C (100 MHz; $CDCl_3$) 20.3 (5-CH_3), 91.5 (C-1), 112.5 (C-6), 119.0 (C-7), 119.6 (C-8), 120.4 (C-12), 124.5 (C-2), 126.6 (C-15), 128.2 (C-16), 129.8 (C-5),130.4 (C-14), 133.0 (C-13), 143.3 (C-9), 152.3 (C-11) and 174.5 (C=O).

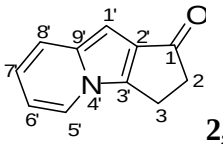
8-Bromo-4-methyl-5-oxa-4*a*-aza-benzo[*b*]fluoren-10-one **210c**. The procedure (methods 1 and 2) for the preparation of the indolizine, 5-oxo-4*a*-aza-benzo[*b*]fluoren-10-one **209a** was followed using 6-bromo-3-[hydroxy-(6-methyl-pyridin-2-yl)-methyl]-chromone (0.08 g, 0.23 mmol). Work up afforded as a green solid, *8-bromo-4-methyl-5-oxa-4a-aza-benzo[b]fluoren-10-one* **210c** (**Method 1**: 0.05, 53%), (**Method 2**: 0.061 g, 80%), m.p. 223-225 ^{o}C; [Found: $\mathbf{M}^+$: 328.98666 (^{81}Br) and $\mathbf{M}^+$: 326.98890 (^{79}Br). Calc. for $C_{16}H_{10}BrNO_2$; M: 328.16014 (^{81}Br) and M: 326.98949 (^{79}Br)]. ν_{max} (KBr)/cm^{-1} 1207 (C-N), 1647 (C=C), 1719 (C=O) and 3064 (C-H); δ_H (400 MHz; $CDCl_3$) 2.96 (3H, s, 5-CH_3), 6.27 (1H, d, *J* 6.4 Hz, 6-H), 6.60 (1H, t, *J* 6.4 Hz, 7-H), 6.80 (1H, s, 1-H), 7.21

(1H, d, *J* 9.2 Hz, 12-H), 7.41 (1H, d, *J* 8.8 Hz, 8-H), 7.74 (1H, dd, *J* 2.4 and 8.8 Hz, 13-H) and 8.53 (1H, d, *J* 2.4 Hz, 15-H); δ_C (100 MHz; $CDCl_3$) 20.3 (5-CH_3), 91.6 (C-1), 109.8 (C-3), 112.1 (C-6), 117.4 (C-14), 118.3 (C-2), 119.4 (C-8), 119.6 (C-7), 124.1 (C-16), 129.4 (C-12), 130.1 (C-5),133.3 (C-15), 135.6 (C-13), 142.8 (C-9), 152.8 (C-11), 152.8 (C-11) and 173.5 (C=O). *m/z* 327 (**M**$^+$, 100%), 299 (39%), 271 (54%), 220 (34%), 192 (66%) and 165 (28%).

8-Fluoro-4-methyl-5-oxa-4*a*-aza-benzo[*b*]fluoren-10-one **210d**. The procedure (methods 1 and 2) for the preparation of the indolizine, 5-oxo-4*a*-aza-benzo[*b*]fluoren-10-one **209a** was followed using 6-fluoro-3-[hydroxy-(6-methyl-pyridin-2-yl)-methyl]-chromone (0.05 g, 0.18 mmol). Work up afforded as a green solid, *8-fluoro-4-methyl-5-oxa-4a-aza-benzo[b]fluoren-10-one* **210d** (**Method 1**: 0.020 g, 42%), (**Method 2**: 0.023 g, 48%), m.p. 208-210 ^oC; (Found:**M**$^+$: 267.06900. Calc. for $C_{16}H_{10}FNO_2$; M: 267.06956); ν_{max} (KBr)/cm^{-1} 1202 (C-N), 1654 (C=C), 1735 (C=O) and 3068 (C-H); δ_H (400 MHz; $CDCl_3$) 2.99 (3H, s, 5-CH3), 6.27 (1H, d, *J* 6.4 Hz, 6-H), 6.60 (1H, t, *J* 6.4 Hz, 7-H), 6.82 (1H, s, 1-H), 7.23 (1H, d, *J* 2.8 Hz, 15-H), 7.41 (1H, m, 12-H), 7.54 (1H, dd, *J* 4.0 and 8.8 Hz, 8-H) and 8.08 (1H, dd, *J* 3.2 and 8.4 Hz, 13-H); δ_C (100 MHz; $CDCl_3$) 20.3 (5-CH_3), 91.3 (C-1), 111.5 (C-3), 111.8 (C-2), 112.0 (C-6), 118.3 (C-7), 119.3 (C-8), 119.5 (C-15), 120.6 (C-13), 120.9 (C-12), 123.9 (C-16), 130.0 (C-5), 133.4 (C-9), 160.2 (C-11), 167.2 (C-14) and 174.0 (C=O); *m/z* 267 (**M**$^+$, 100%), 239 (36%), and 211(56%).

5,8-Dimethyl-5-oxa-4*a*-aza-benzo[*b*]fluoren-10-one **210e**. The procedure (methods 1 and 2) for the preparation of the indolizine, 5-oxo-4*a*-aza-benzo[*b*]fluoren-10-one **209a** was followed using 6-methyl-3-[hydroxy-(6-methyl-pyridin-2-yl)-methyl]-chromone (0.05 g, 0.18 mmol). Work up afforded as a green solid, *5,8-dimethyl-5-oxa-4a-aza-benzo[b]fluoren-10-one* **210e** (**Method 1**: 0.033 g, 34%), (**Method 2**: 0.044 g, 46%), m.p. 225-226 ^oC; (Found: **M**$^+$: 263.09403. Calc. for $C_{17}H_{13}NO_2$; M: 263.09463); ν_{max} (KBr)/cm^{-1} 1207 (C-N), 1647 (C=C), 1748 (C=O), 3138 (C-H); δ_H (400 MHz; $CDCl_3$)

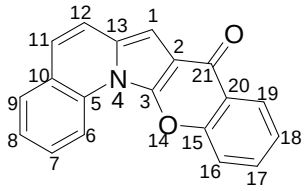
2.49 (3H, s, 14-CH_3). 2.98 (3H, s, 5-CH_3), 6.24 (1H, d, *J* 6.4 Hz, 6-H), 6.58 (1H, t, *J* 6.4 Hz, 7-H), 6.83 (1H, s, 1-H), 7.22 (1H, d, *J* 9.6 Hz, 12-H), 7.43 (1H, d, *J* 8.4 Hz, 8-H), 7.49 (1H, dd, *J* 2.4 and 8.8 Hz, 13-H) and 8.22 (1H, d, *J* 1.6 Hz, 15-H); δ_C (100 MHz; $CDCl_3$) 20.3 (5-CH_3), 20.9 (14-CH_3), 91.5 (C-1), 109.9 (C-6), 111.7 (C-2 and C-3), 117.3 (C-8), 118.3 (C-7), 119.1 (C-12), 122.3 (C-16), 126.2 (C-15), 129.7 (C-5), 133.4 (C-9), 134.0 (C-13), 143.1 (C-14), 152.3 (C-11) and 175.2 (C=O); *m/z* 263 (**M**$^+$, 100%), 235 (38%) and 207 (59%).



2,3-Dihydro-3*b*-aza-cyclopenta[*a*]inden-1-one The procedure for the preparation of the indolizine (methods 1 and 2), 5-oxo-4*a*-aza-benzo[*b*]fluoren-10-one **209a** was followed using 2-(hydroxy-pyridin-2-yl-methyl-cyclopent-2-enone (0.1 g, 0.53 mmol). Work up followed by chromatography afforded as a green viscous oil, 2,3-dihydro-3*b*-aza-cyclopenta[*a*]inden-1-one (**Method 1**, 0.02 g, 22%), (**Method 2**, 0.05 g, 49%) ν_{max} (Nujol)/cm^{-1} 1713 (C=O); δ_H (400 MHz; $CDCl_3$) 3.04 (2H, m, 1-H), 3.12 (2H, m, 2-H), 6.50 (1H, s, 1'-H), 6.70 (1H, td, *J* 0.8 and 9.2 Hz, 7'-H), 7.37 (1H, d, *J* 9.2 Hz, 8'-H) and 7.68 (1H, dd, *J* 1.2 and 7.2 Hz, 5'-H); δ_C (100 MHz; $CDCl_3$) 19.8 (C-2), 41.2 (C-1), 91.9 (C-1'), 111.9 (C-6'), 118.8 (C-7'), 121.7 (C-8'), 122.6 (C-5'), 129.4 (C-2'), 138.9 (C-3'), 147.7 (C-9') and 198.6 (C=O). *m/z* 171 (**M**$^+$, 100%).

5-Methyl-2,3-dihydro-3*b*-aza-cyclopenta[*a*]inden-1-one The procedure for the preparation of the indolizine (methods 1 and 2), 5-oxo-4*a*-aza-benzo[*b*]fluoren-10-one **209a** was followed using 2-[hydroxy(6-methylpyridin-2-yl)methyl]cyclopent-2-enone **194** (0.1 g, 0.49 mmol). Work up followed by chromatography afforded as a green viscous oil, 2,3-dihydro-3*b*-aza-cyclopenta[*a*]inden-1-one (**Method 1**, 0.026 g, 28%), (**Method 2**, 0.053 g, 58%) ν_{max} (Nujol)/cm^{-1} 1713 (C=O); δ_H (400 MHz; $CDCl_3$) 2.76 (3H, s, 5'-Me), 3.06 (2H, m, 1-H), 3.14 (2H, m, 2-H), 6.21 (1H, d, *J* 6.8 Hz, 6'-H), 6.51 (1H, t, *J* 6.4 Hz, 7'-H), 6.74 (1H, s, 1'-H) and 7.19 (1H, d, *J* 8.8 Hz, 8'-H); δ_C (100 MHz;

$CDCl_3$) 20.3 (C-2), 21.9 (5-Me), 41.4 (C-1), 97.1 (C-1'), 113.6 (C-6'), 118.5 (C-8'), 118.9 (C-7'), 123.8 (C-2'), 133.3 (C-3'), 134.6 (C-5'), 135.3 (C-9') and 196.7 (C=O).



13-Oxa-13*b-*aza-dibenzo[*b,g*]fluoren-8-one **213a**. The procedure (methods 1 and 2) for the preparation of the indolizine, 5-oxo-4*a*-aza-benzo[*b*]fluoren-10-one **209a** was followed using 3-(hydroxy-quinolin-2-yl-methyl)-chromone (0.10 g, 0.33 mmol). Work-up afforded as a green solid, *13-oxa-13b-aza-dibenzo[b,g]fluoren-8-one* **213a** (**Method 1**: 0.036 g, 38%), (**Method 2**: 0.047 g, 50%), m.p. 197-200 ^{o}C; (Found: $\mathbf{M}^{+}$: 285.07845. Calc. for $C_{19}H_{11}NO_2$; M: 285.07898). ν_{max} (KBr)/cm^{-1} 1209 (C-N), 1649 (C=C), 1735 (C=O), 3059 (C-H); δ_H (400 MHz; $CDCl_3$) 6.94 (1H, s, 1-H), 6.98 (1H, d, *J* 9.2 Hz, 16-H), 7.22 (1H, m, 18-H), 7.41 (1H, t, *J* 7.6 Hz, 12-H), 7.49 (1H, m, 17-H), 7.58-7.62 (3H, m, 8-H, 9-H and 19-H), 7.75 (1H, m, 7-H), 8.48 (1H, d, *J* 8.0 Hz, 11-H) and 8.88 (1H, d, *J* 8.4 Hz, 6-H); δ_C (100 MHz; $CDCl_3$) 95.2 (C-1), 109.3 (C-3), 116.9 (C-2), 117.7 (C-12), 119.3 (C-16), 121.4 (C-18), 123.0 (C-20), 124.7 (C-8), 124.8 (C-9), 125.2 (C-6 and C-7), 126.8 (C-19), 127.4 (C-10), 128.1 (C-17), 128.4 (C-11), 132.9 (C-5), 146.1 (C-13), 154.1 (C-15) and 174.3 (C=O); *m/z* 285 ($\mathbf{M}^{+}$, 100%), 257 (52%) and 229 (73%).

10-Chloro-13-oxa-13*b-*aza-dibenzo[*b,g*]fluoren-8-one **213b** The procedure Methods 1 and 2) for the preparation of the indolizine, 5-oxo-4*a*-aza-benzo[*b*]fluoren-10-one **209a** was followed using 6-chloro-3-(hydroxy-quinolin-2-yl-methyl)-chromone (0.06 g, 0.18 mmol). Work up afforded as a green solid, *10-chloro-13-oxa-13b-aza-dibenzo[b,g]fluoren-8-one* **213b** (**Method 1**: 0.024 g, 42%), (**Method 2**: 0.033 g, 58%), m.p. 219-220 ^{o}C; (Found: $\mathbf{M}^{+}$:319.03949. Calc. for $C_{19}H_{10}ClNO_2$; M: 319.04001). ν_{max} (KBr)/cm^{-1} 1204 (C-N), 1652 (C=C), 1737 (C=O), 3064 (C-H); δ_H (400 MHz; $CDCl_3$) 6.87 (1H, s, 1-H), 6.95 (1H, d, *J* 9.2 Hz, 17-H), 7.17 (1H, d, *J* 9.6 Hz, 16-H), 7.39 (1H, t,

J 7.6 Hz, 8-H), 7.53-7.63 (5H, m, 7-H, 9-H, 11-H, 12-H and 19-H) and 8.73 (1H, d, *J* 8.4 Hz, 6-H); δ_C (100 MHz; $CDCl_3$) 95.1 (C-1), 109.1 (C-3), 116.8 (C-2), 119.1 (C-12), 119.2 (C-16), 121.7 (C-8), 124.0 (C-9), 124.7 (C-20), 125.3 (C-10), 126.2 (C-6), 127.7 (C-7), 128.2 (C-18), 128.5 (C-19), 130.6 (C-17), 132.9 (C-5 and C-11), 145.9 (C-13), 152.2 (C-15) and 172.8 (C=O); *m/z* 319 (**M**$^+$, 100%), 291 (48%), 263 (61%) and 228 (43%).

***10-Bromo-13-oxa-13*b-*aza-dibenzo[*b,g*]fluoren-8-one* 213c**. The procedure (methods 1 and 2) for the preparation of the indolizine, 5-oxo-4*a*-aza-benzo[*b*]fluoren-10-one **209a** was followed using 6-bromo-3-(hydroxy-quinolin-2-yl-methyl)-chromone (0.10 g, 0.26 mmol). Work up afforded as a green solid, *10-bromo-13-oxa-13b-aza-dibenzo[b,g]fluoren-8-one* **213c** (**Method 1**: 0.051 g, 54%), (**Method 2**: 0.066 g, 70%), m.p. 236-238 ^oC; [Found: **M**$^+$: 364.98791 (^{81}Br) and **M**$^+$: 362.98892 (^{79}Br). Calc. for $C_{19}H_{10}BrNO_2$; M: 364.19224 (^{81}Br) and M: 362.98949 (^{79}Br)]. ν_{max} (KBr)/cm^{-1} 1207 (C-N), 1652 (C=C), 1770 (C=O), 3085 (C-H); δ_H (400 MHz; $CDCl_3$) 6.92 (1H, s, 1-H), 7.00 (1H, d, *J* 9.6 Hz, 16-H), 7.23 (1H, m, 12-H), 7.43 (1H, t, *J* 7.6 Hz, 8-H), 7.56-7.64 (3H, m, 7-H, 9-H and 11-H), 7.81 (1H, dd, *J* 2.4 and 8.8 Hz, 17-H), 8.57 (1H, d, *J* 2.4 Hz, 19-H) and 8.82 (1H, d, *J* 8.8 Hz, 6-H); δ_C (100 MHz; $CDCl_3$) 95.1 (C-1), 109.1 (C-3), 114.8 (C-2), 116.9 (C-18), 117.2 (C-12), 118.0 (C-16), 119.1 (C-8), 119.4 (C-9), 121.7 (C-10), 124.8 (C-20), 125.4 (C-7), 127.7 (C-6), 128.2 (C-19), 128.5 (C-11), 129.3 (C-17), 132.7 (C-5), 135.7 (C-13), 152.7 (C-15) and 172.7 (C=O); *m/z* 363 (**M**$^+$, 100%), 335(49%), 305 (49%), 256 (40%) and 228 (93%).

***10-Fluoro-13-oxa-13*b-*aza-dibenzo[*b,g*]fluoren-8-one* 213d** The procedure (methods 1 and 2) for the preparation of the indolizine, 5-oxo-4*a*-aza-benzo[*b*]fluoren-10-one **209a** was followed using 6-fluoro-3-(hydroxy-quinolin-2-yl-methyl)-chromone (0.10 g, 0.31 mmol). Work up afforded as a green solid, *10-fluoro-13-oxa-13b-aza-dibenzo[b,g]fluoren-8-one* **213d** (**Method 1**: 0.037 g, 39%), (**Method 2**: 0.050 g, 53%), m.p. 220-222 ^oC; (Found: M^+: 303.06898. Calc. for $C_{19}H_{10}FNO_2$; M: 303.06956). ν_{max}

(KBr)/cm^{-1} 1207 (C-N), 1647 (C=C), 1748 (C=O), 3138 (C-H); δ_H (400 MHz; $CDCl_3$) 6.94 (1H, s, 1-H), 7.01 (1H, d, *J* 9.2 Hz, 16-H), 7.23 (1H, m, 17-H), 7.43-7.48 (2H, d, 12-H, 19-H), 7.59-7.64 (2H, m, 7-H and 8-H), 7.77 (1H, dd, *J* 4.0 and 8.8 Hz, 9-H) and 8.85 (1H, d, *J* 8.4 Hz, 6-H); δ_C (100 MHz; $CDCl_3$) 95.0 (C-1), 111.7 (C-3), 111.9 (C-2), 116.9 (C-19), 119.2 (C-12), 120.8 (C-16), 121.1 (C-15), 121.8 (C-8), 124.8 (C-9), 125.4 (C-7), 127.9 (C-20), 128.2 (C-6), 128.5 (C-11), 132.8 (C-10), 146.3 (C-5), 150.0 (C-13), 158.0 (C-15), 160.5 (C-18) and 177.5 (C=O); *m/z* 303 ($\mathbf{M}^+$, 100%), 275 (50%) and 247 (82%).

***10-Methyl-13-oxa-13*b-*aza-dibenzo[*b,g*]fluoren-8-one* 213e**. The procedure (methods 1 and 2) for the preparation of the indolizine, 5-oxo-4*a*-aza-benzo[*b*]fluoren-10-one **209a** was followed using 6-methyl-3-(hydroxy-quinolin-2-yl-methyl)-chromone (0.10 g, 0.32 mmol). Work up afforded as a green solid, *10-methyl-13-oxa-13*b-*aza-dibenzo[*b,g*]fluoren-8-one* **213e** (**Method 1**: 0.034 g, 36%), (**Method 2**: 0.054 g, 57%), m.p. 203-205 ^oC; δ_H (400 MHz; $CDCl_3$) 2.49 (3H, s, 18-CH_3), 6.90 (1H, s, 1-H), 7.01 (1H, d, *J* 9.2 Hz, 16-H), 7.38 (1H, d, *J* 7.6 Hz, 12-H), 7.49-7.58 (4H, m, 17-H, 8-H, 9-H and 19-H), 7.71 (1H, m, 7-H), 8.50 (1H, d, *J* 8.0 Hz, 11-H) 8.84 (1H, d, *J* 8.4 Hz, 6-H); δ_C (100 MHz; $CDCl_3$) 21.2 (18-CH_3), 95.5 (C-1), 109.7 (C-3), 117.2 (C-2), 118.2 (C-12), 119.4 (C-16), 121.3 (C-18), 122.8 (C-20), 124.5 (C-8), 124.8 (C-9), 125.2 (C-7), 126.5 (C-19), 127.3 (C-10), 127.8 (C-6), 128.3 (C-17), 128.8(C-11), 133.2 (C-5), 134.1 (C-14), 146.4 (C-13), 154.3 (C-15) and 174.6 (C=O).

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