Application of the Baylis-Hillman Methodology in the Construction of Novel Heterocyclic Derivatives

THESIS

Submitted in fulfillment of the requirements for the degree
of

MASTER OF SCIENCE

of

Rhodes University

by

Dubekile Nyoni

B.Sc. Hons. (Midlands State University, Zimbabwe)

January 2008

ABSTRACT

Baylis-Hillman reactions of 2,2’-dithiodibenzaldehyde with the acyclic alkenes, methyl vinyl ketone (MVK) and methyl acrylate have afforded the thiochromene derivatives in moderate yields, and this approach has been extended to the use of the cyclic alkenes, 2-cyclohexenone and 2-cyclopentenone to afford the tricyclic analogues. In all cases, reduction of the disulphide link and intramolecular cyclisation occurred *in situ*, and a preliminary kinetic study of this reaction using the acyclic substrates MVK and methyl acrylate was undertaken with the aim of elucidating the mechanism involved. The results obtained showed that the consumption of both 2,2’-dithiodibenzaldehyde and MVK and/or methyl acrylate followed 1st-order kinetics during the initial stages of the reaction, but then deviated from 1st-order linearity. The reaction with methyl acrylate was much slower than with MVK, and the kinetic data indicates the mechanism to be more complex than anticipated.

Conjugate addition reactions of methyl acrylate-derived 2-nitrobenzaldehyde Baylis-Hillman adducts with the amines, piperidine and benzylamine, afforded a range of conjugate addition products as diastereomeric mixtures in excellent yield (80-100%). Catalytic hydrogenation of the conjugate addition products using a Pd-C catalyst in ethanol, has afforded the corresponding, novel 3-amino-2-quinolone derivatives in lower yield (22-37%).

The application of ^{13}C NMR prediction programmes to selected compounds synthesized in this study has revealed reasonable correlations between the experimental and predicted values.

ACKNOWLEDGEMENTS

Firstly, I would like to thank my supervisor Prof. P. T. Kaye for his guidance and support throughout the course of this project. The knowledge you imparted Prof., will forever be appreciated and working under your supervision has been a great and wonderful privilege.

I would also like to thank my co-supervisor, Dr. R. Klein for all the help and encouragement, for being a very good listener. Working under your supervision has been a wonderful experience.

My sincere thanks also go to Mr. A. Sonemann for collecting low-resolution mass spectrometric data, Martin Brits (University of the Witwatersrand) and Dr. Johan Jordaan (North-West University) for collecting high-resolution mass spectrometric data, and Ms. D. Molefe, Mr. K. Lobb, Mr. A. Soper and Mr. E. Lamprecht for help with kinetic experiments.

To the F22 research group, I really appreciate all your support. Babalwa and Mlu, your help in elucidating structures was greatly appreciated. To the entire Chemistry department at Rhodes, thank you. To my dear friends Antonia, Vongani and Saenna thank you so much for the encouragement.

A very special thank you to my family for always being there for me. To my late father, Mr. P.P. Nyoni (Mudhara PP), thank you for showing me the importance of education. To my mother, Mrs. F. P. Nyoni and aunt Mrs. O. Makuyana, your love, prayers and support kept me going when things were tough. Thank you.

Lastly I would like to thank the Midlands State University (Zimbabwe) and the NRF for financial support.

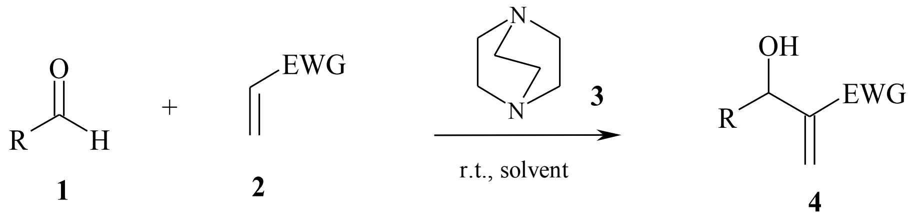
CONTENTS

1. INTRODUCTION

1.1 The Baylis-Hillman reaction

The Baylis-Hillman (BH) reaction or Morita-Baylis-Hillman (MBH), as it is sometimes known, involves the coupling of activated alkenes **2** with carbon electrophiles **1** in the presence of nucleophilic catalysts, such as 1,4-diazabicyclo[2.2.2]octane (DABCO) **3**.

This carbon-carbon bond forming reaction was first reported in 1972,[1] but its origins date back to 1968,[2] when Morita described the reaction of an aldehyde with acrylic compounds catalysed by tricyclohexylphosphine, which he called, “Carbinol addition”. However, the yields were very low. This reaction has of late become an essential and useful reaction for organic chemists, since it gives rise to highly functionalized molecules, which have proved to be valuable synthetic intermediates as shown by the numerous reviews on applications of the BH reaction.[3-16] The general outline of the BH reaction is as outlined in Scheme 1.



EWG= electron withdrawing group

Scheme 1

Over the years since its discovery, and especially during the last two decades, numerous advances have been made on the BH reaction, extending its application beyond the use of aldehydes and acrylates as reactants. The acrylate component has been substituted[3,11,15-17] by vinyl sulphoxides, vinyl sulphonates, allenic esters, alkyl vinyl ketones, vinyl phosphonates, acrylonitrile and acrolein. In addition to aldehydes, imines, tosylimines, α-ketoesters, fluoroesters and π-deficient olefins have been used. Baylis and Hillman reported the use of DABCO as their most successful catalyst in their patent[1] but, lately, various amine and phosphine catalysts[17-35] have been employed in this reaction; these include 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),[3,17,22,26] *N,N,N',N'*-tetramethyl-1,3-propanediamine (TMPDA),[22,24] imidazole,[23,27] quinuclidine,[29,30] 4-(dimethylamino)-pyridine (DMAP),[14,21,23] tetramethylguanidine (TMG)[26] (Fig. 1), trialkylphosphines[32,33,34] and diphenylmethylphosphine (PPh_2Me).[17] Each of these catalysts appear to work best with different substrates and under various conditions.

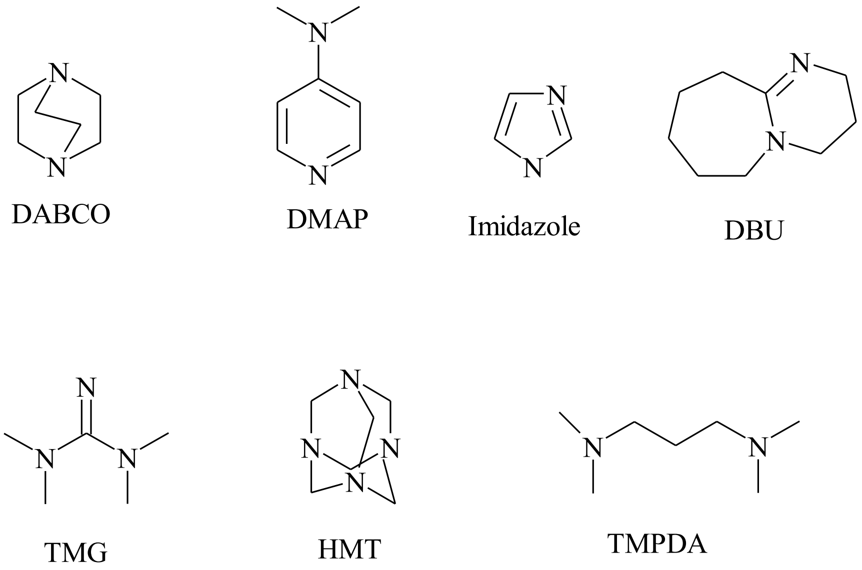
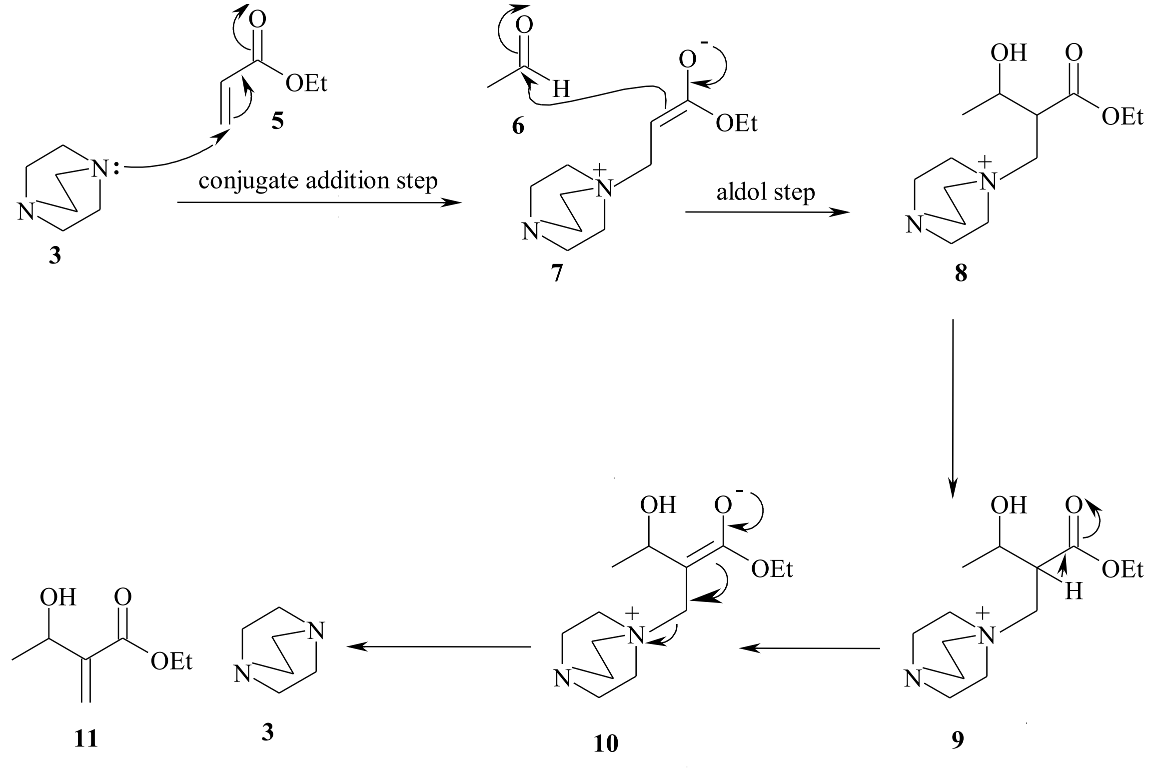


Figure 1. Tertiary amine catalysts used in the Baylis-Hillman reaction.

One of the major limitations of this reaction, however, is the slow reaction rates, with some reactions taking over a month to go to acceptable levels of completion. Many research groups have been working on rate acceleration, by manipulating catalysts,[17-20,22,23,24,26,27,28,31,] solvent systems[18,21,36-40] and using different substrates. Polar solvents such as chloroform,[3,6,15,16] THF,[11,24,36] dioxane,[4,14,28] methanol[22] and water/ aqueous mixtures,[18,21,27,36,39,41,42] have been used. Ionic Liquids (ILs) which are termed 'green solvents' because of their low vapour pressure, thermal stability and potential recyclability, have lately found application in BH chemistry as both solvents and catalysts.[10,37,43-46] Reports have also been made of solvent-free BH reactions.[47]

1.1.1 Mechanistic studies of the Baylis-Hillman reaction

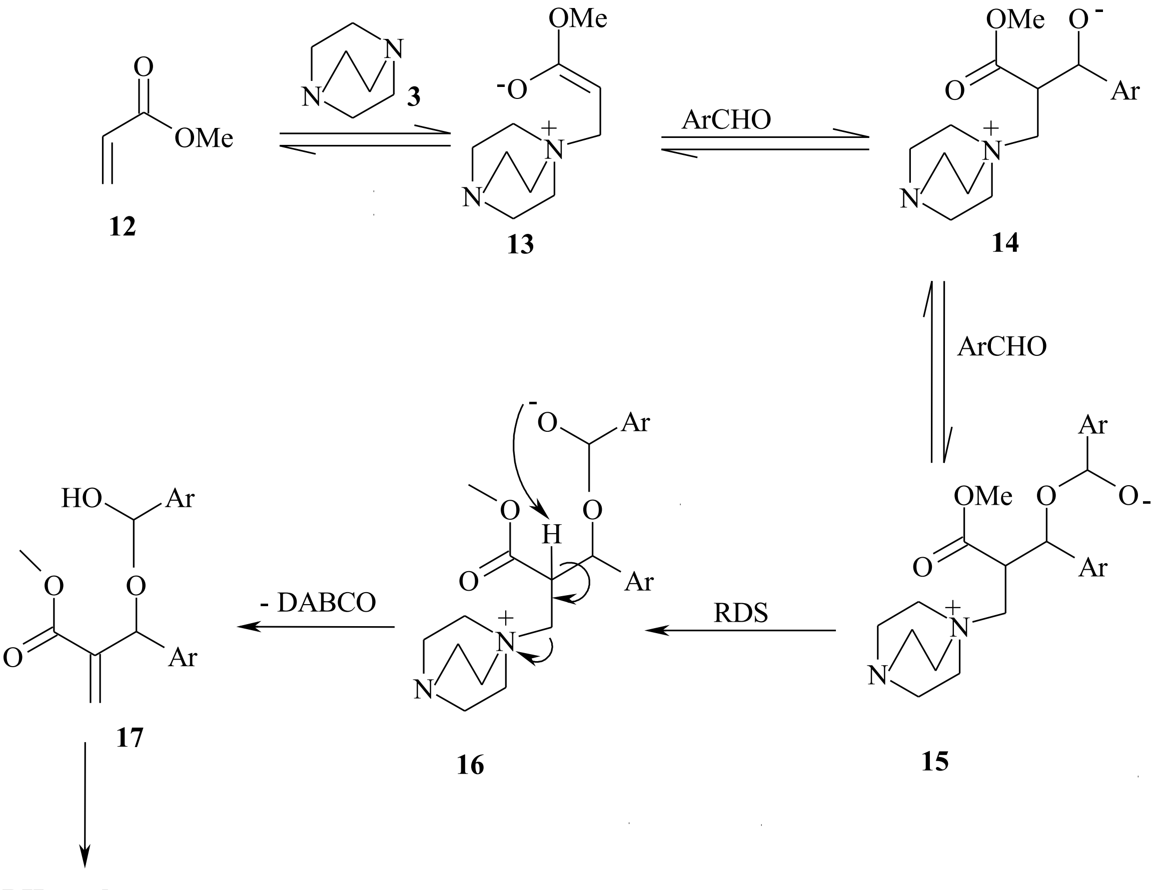
The generally accepted[1] mechanism for the BH reaction, outlined in Scheme 2, involves three main steps, the first being conjugate addition of the nucleophilic catalyst **3** to the activated alkene **5** to form a zwitterionic enolate **7**. This is followed by an aldol-type reaction between the zwitterionic adduct **7** and aldehyde **6**. Proton transfer and elimination of the catalyst from the adduct **10** then follows, yielding an α–methylene-β-hydroxy (BH) product **11**.



Scheme 2

The rate-determining step (RDS) was shown, by our group,[48] to involve reaction of the zwitterionic adduct **7** with the carbon electrophile (aldehyde) **6**, therefore the rate of this reaction can be enhanced by activating the carbon electrophile. Thus, pyridinecarbaldehydes tend to be more reactive than benzaldehydes. It should be noted that none of the zwitterionic intermediates (**7-10**) proposed in the mechanism have been isolated to date. Recently, McQuade and coworkers[49] suggested a new mechanism

(Scheme 3) involving 4th-order kinetics and based on initial rate data obtained from mass spectra for reactions in aprotic solvents. They found that the Baylis-Hillman rate determining step involved the transformation **15-16** and that the reaction is 2nd-order in aldehyde and 1st-order in each of DABCO and the acrylate ester.



Scheme 3

In a report focusing on the catalytic cycle, Caumul and Hailes[50] reported that the catalytic cycle and intermediates under acidic conditions are different to those under non-acidic conditions as outlined in Fig. 2. In acidic medium, protonation of the acrylate **19** is followed by conjugate addition of the amine, generated by deprotonation of the trialkylammonium ion **18** *in situ*. The enol **20** then attacks the protonated aldehyde **21** followed by elimination of the protonated amine **18** to give the BH product **23**. At pH 1, they reported that protonation of both the acrylate and aldehyde enhanced the reaction, and the zwitterionic enolate species was protonated, affording the cationic intermediate **20**. They suggested, from their findings, that reaction rates were reduced when sterically hindered bases were used, which due to steric hindrance in the intermediate **20** resulted in a shift in the equilibrium back to the starting materials.

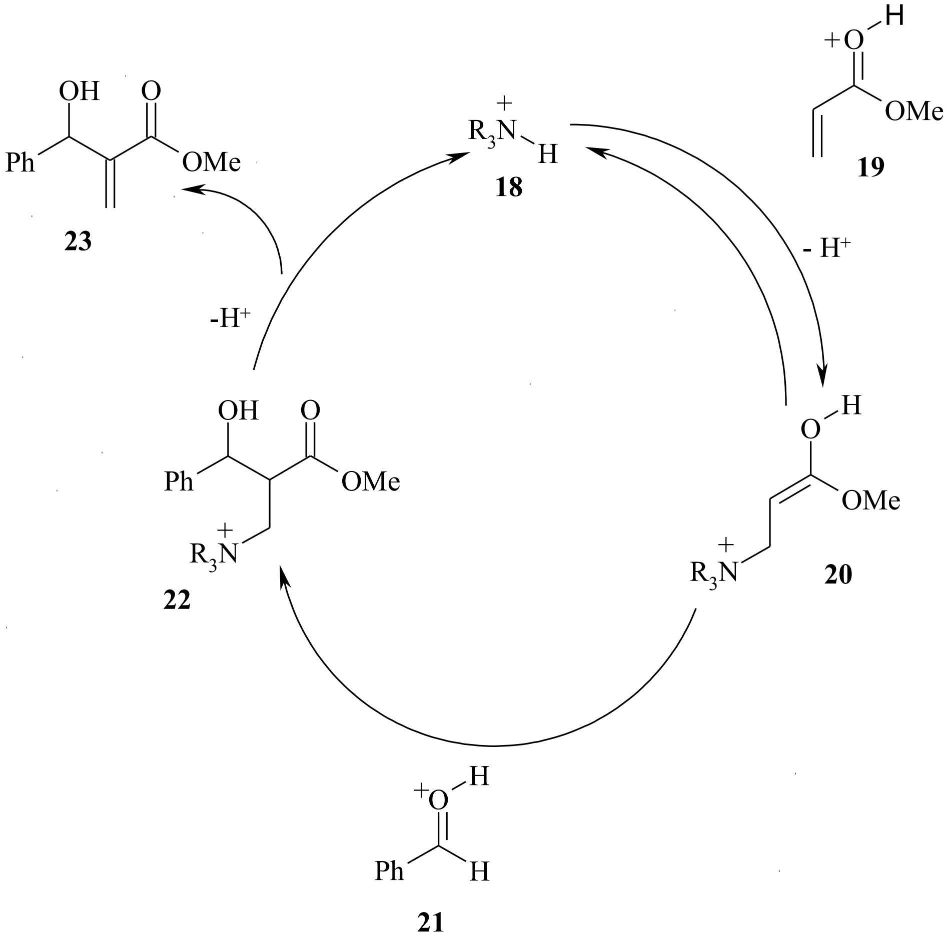


Figure 2. Catalytic cycle in acidic medium.

1.1.2 Effect of catalysts in the Baylis-Hillman reaction

Tertiary amines, such as DABCO, as well as phosphines have been used as catalysts in the BH reaction. DABCO, which is a relatively nucleophilic base, has so far been the catalyst of choice in most BH reactions. Over the last decade many research groups have looked at ways of improving the efficiency of DABCO as well the potential of other tertiary amines and phosphines as catalysts for the BH reaction.

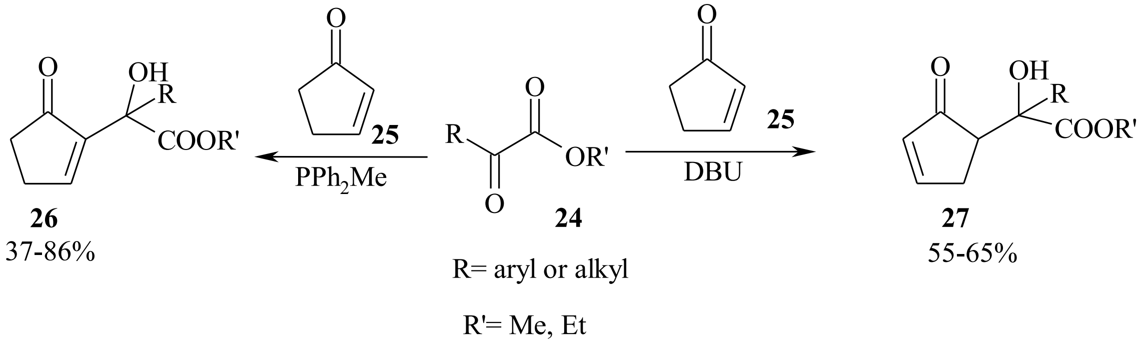
Yu *et al.*[18] confirmed that in a DABCO-catalysed reaction of an aldehyde with methyl acrylate, there is a competing side reaction between DABCO and methyl acrylate which reduces the effective available concentration of DABCO. Pre-incubation of 100 mol% DABCO with 3 equivalents of methyl acrylate in a 1:1 (v/v) mixture of dioxane and water, before addition of aldehyde, resulted in a 25-fold reduction in the initial rate of reaction and a 9-fold reduction in the yield of the final product. Addition of DABCO (100 mol%) at the same time as the substrate has been shown to obviate these problems.

DMAP, DABCO and urotropine (hexamethylene-tetraamine or HMT)[21] have each been used to catalyse the reaction of 4-nitrobenzaldehyde and methyl acrylate and in each case, resulted in very high yields (up to 96%) in a homogenous H_2O/1,4-dioxane medium. When the same reaction was repeated using triphenylphosphine as the catalyst, there was a reduction in the rate of reaction and the product was obtained in moderate yields. Trialkylphosphine nucleophilic catalysts have been used to effect cyclisation to give substituted cyclopentenes and cyclohexenes in 1,4-intramolecular BH addition reactions. The amines, DABCO, DBU, Et_2NH and DMAP, however, failed to catalyse the cyclisation.

HMT, a non-hygroscopic and stable reagent of low toxicity, has been reported[25] to be a cheap and convenient alternative catalyst in the BH reaction. HMT can be prepared by allowing a mixture of aqueous formalin and concentrated NH_3 solution to evaporate. It has been used to catalyse reactions between aromatic aldehydes and methyl acrylate or acrylonitrile.

The tertiary amine, DBU, has also found wide applications in the BH reaction and has been reported to accelerate BH reactions involving hindered enones such as 4,4-dimethylcyclopentenone and 4,4-dimethylcyclohexenone in methanol.[22] In our own research group, the synthesis of thiochromenes[3] *via* the BH reaction of 2,2’-dithiodibenzaldehyde was first attempted using DABCO as catalyst. When this failed to give any of the expected product, DABCO was then replaced by DBU, which afforded the desired thiochromenes (see Section 1.2.2, page 17).[3]

In another interesting observation involving the use of DBU and diphenylmethylphosphine (PPh_2Me), Shi and Zhang[17] found that these catalysts influenced the type of BH adduct formed. They described how the reaction of α-ketoesters with cyclopentenone, in the presence of either PPh_2Me or DBU, gave different functionalized tertiary alcohols (**26** and **27,** respectively; Scheme 4).



Scheme 4

Other catalysts such as TMPDA[24] and imidazole[23,27] have also been used in reactions involving cyclic enones with increased reaction rates being reported. Cyclic enones have been reported to exhibit slow reaction rates due to steric hindrance[24]. Leadbeater and van der Pol[26] have demonstrated that TMG is an effective catalyst for BH reactions with a variety of aldehydes, including simple aliphatic aldehydes. Another interesting development in catalysis for the BH reaction has been the introduction of ionic liquid-based tertiary amine catalysts,[28,29] and their use has been extended to the asymmetric version of the reaction.[30] Ionic liquid-based catalysts have the advantage of acting as both catalysts and solvents for the reaction; moreover, they can be recycled. Quinuclidine bound to ionic liquids has been shown to have very good catalytic activity.[29]

Use of co-catalyts with the traditional tertiary amine and phosphine catalysts has been reported,[31] and BH products have been obtained in yields of up to 98% using mild cooperative catalysts, *e.g.* tributylphosphine and phenols, such as (±)-1,1'-bis-2-naphthol (BINOL) in THF. Ikegami and Yoichi[31] had initially used 20mol% of DABCO in THF for 1h but failed to obtain any products, due, they suggested, to the fact that 1,1'-bis-2-naphthol (BINOL) functions as a Brønsted acid to activate the carbonyl group of the aldehyde and activated alkene.

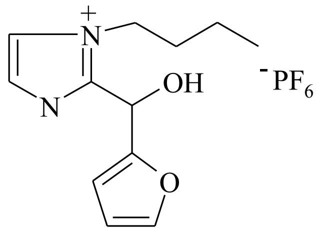
Scandium and lanthanide triflates[19] have been used as co-catalysts with DABCO while, Connon and Maher[20] have demonstrated that use of bis-aryl ureas as co-organocatalysts and hybrid catalysts with DABCO increase the efficiency of the reaction.

Polymer supported catalysts for the BH reaction have been reported. Toy and co-workers[33] used a range of polar polystyrene resins to support PPh_3, which then acts as a nucleophilic catalyst. Corma *et al*.[51] have reported a heterogenous BH reaction, in which 4-(*N*-benzyl-*N*-methylamino)pyridine bound to an insoluble polystyrene scaffold (PAP) served as a re-usable catalyst. By attaching a good, soluble catalyst to an insoluble support, a homogeneous process could thus be transformed into a heterogeneous process, improving product isolation at the end of the reaction.[51]

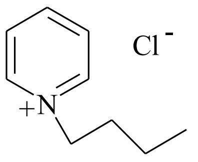
1.1.3 Effect of Solvents on the Baylis-Hillman reaction

The BH reaction proceeds in some cases without any solvent.[47] However, in cases where all the reactants are in solid form, a solvent is required. Polar solvents such as THF and CH_3CN have found widespread application in the BH reaction. As an environmental initiative, researchers have been exploring the potential of environmentally friendly solvents, such as ionic liquids (ILs)[10,37,43-46,52,53] and water,[36,38,41] as replacements for the volatile and flammable organic solvents commonly used. ILs are non-volatile, nonexplosive and thermally robust with a 3.0V electrochemical window; moreover, they can be recycled. The generally accepted BH mechanism (Scheme 2), involves separation of charge in the intermediate steps and, consequently, polar solvents such as THF and CH_3CN favour the reaction. ILs, being polar, were expected to promote the rate of reaction.

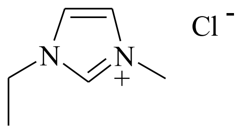
Rosa *et al.*[45] used the 1-butyl-3-methylimidazolium [bmim] cation-based IL [bmim][PF_6] in the BH reaction and observed a rate increase compared to the use of CH_3CN. The IL [bmim][PF_6] worked better with aromatic aldehydes than with aliphatic aldehydes. Another imidazolium-based IL, 1-butyl-2,3-dimethylimidazolium hexaflourophosphate [bdmim][PF_6] has been shown to be even more effective than [bmim][PF_6], giving moderate to excellent yields.[52] However, the chemical reactivity of [bmim][PF_6] in a BH reaction involving 2-furaldehyde has been noted by Hsu *et al.,*[52] who observed that the BH product was contaminated with the aldehyde-conjugated [bmim][PF_6] adduct **28** (Fig. 3), while the reaction in [bdmim][PF_6] gave the BH product without any of the corresponding aldehyde-conjugated IL adduct. Earlier, Aggarwal *et al.*[53] had shown that imidazolium-based ILs were not inert under mildly basic conditions, making them unsuitable as catalysts for the BH reaction due to their potential for deprotonation and subsequent direct addition to the aldehyde.



28



29



30

Figure 3

Chloroaluminate-based ILs [$AlCl_3$:MCl][44] where MCl is either, *N*-1-butylpyridinium chloride (BPC) **29** or 1-ethyl-3-methyl-*1H*-imidazolium chloride (EMIC) **30**, have been shown to accelerate BH reactions. It seems, based on yields, that [EMIC:$AlCl_3$] is a better IL compared to [BPC:$AlCl_3$]. Zhao *et al.*[37] have observed that the ILs, *N*-ethylpyridinium tetrafluoroborate ([EPy][BF_4] and *N*-butylpyridinium nitrate

([BuPy][NO_3], gave high yields when used as solvents in the BH reaction. Gong *et al.*[10] have also confirmed that [EPy][BF_4] serves as a good solvent for the BH reaction

Water has also been reported to be a very good solvent for the BH reaction.[36,38,41] Use of water as a reaction medium promotes the green chemistry concept as it eliminates the need for the conventional, highly volatile and flammable organic solvents.[42] Caumul and Hailes[50] reacted 2-nitrobenzaldehyde and methyl acrylate at 0ºC in aqueous medium (adjusted to pH 1 with concentrated HCl) using Me_3N or DBU as catalysts and obtained a 74% yield with Me_3N and 52% yield with DBU. Lubineau and co-workers[36] had discovered the rate acceleration of the BH reaction in water previously and had attributed it to stabilisation of the zwitterionic intermediate through hydrogen bonds.

Use of an aqueous/organic[6,21] homogeneous medium has also been shown to accelerate the BH reaction. Cai *et al.*[21] used aqueous methanol, ethanol, butanol, tetrahydrofuran, 1,4-dioxane or acrylonitrile to obtain good yields of BH products. Cyclic enones, which have been reported to be very unreactive substrates for the BH reaction, have been observed to react in a THF/H_2O homogenous medium with TMPDA as catalyst.[24]

Another solvent, sulpholane,[38,40] has found applications in the BH reaction. Sulpholane is an aprotic polar solvent, which appears to work best with DABCO as catalyst, giving good to excellent yields of BH adducts. Krishna *et al.*[38,40] have tried other aprotic solvents, such as *N*-methylpyrrolidinone (NMP) and *N*-methylmorpholine (NMM) for the BH reaction. When 4-nitrobenzaldehyde and ethyl acrylate were reacted in the presence of DABCO, both NMP and NMM worked well giving the respective BH adducts in excellent yields. Polyethyleneglycol (PEG)[54] has also been used as a solvent in the DABCO catalysed reaction of benzaldehyde and ethyl acrylate, the reaction being found to be complete within 2h and to afford the BH adduct in 92% yield. Treatment of benzaldehyde with a range of activated olefins in PEG gave very high yields of BH products. PEG can be recycled, which is a cost-saving advantage.

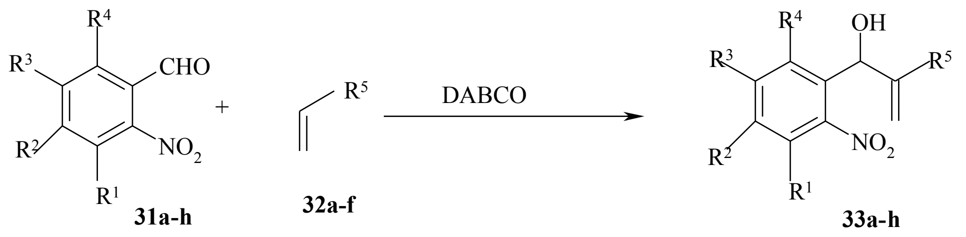
1.2 Applications of the Baylis-Hillman reaction

Baylis-Hillman products have found wide application in the construction of a range of heterocyclic systems including quinolines and quinolones,[5,8,11,12,13] chromenes,[6] thiochromenes,[3] coumarins[15,16] and indolizines,[55,56] many derivatives of which are biologically active.

1.2.1 Synthesis of Quinolines and Quinolones

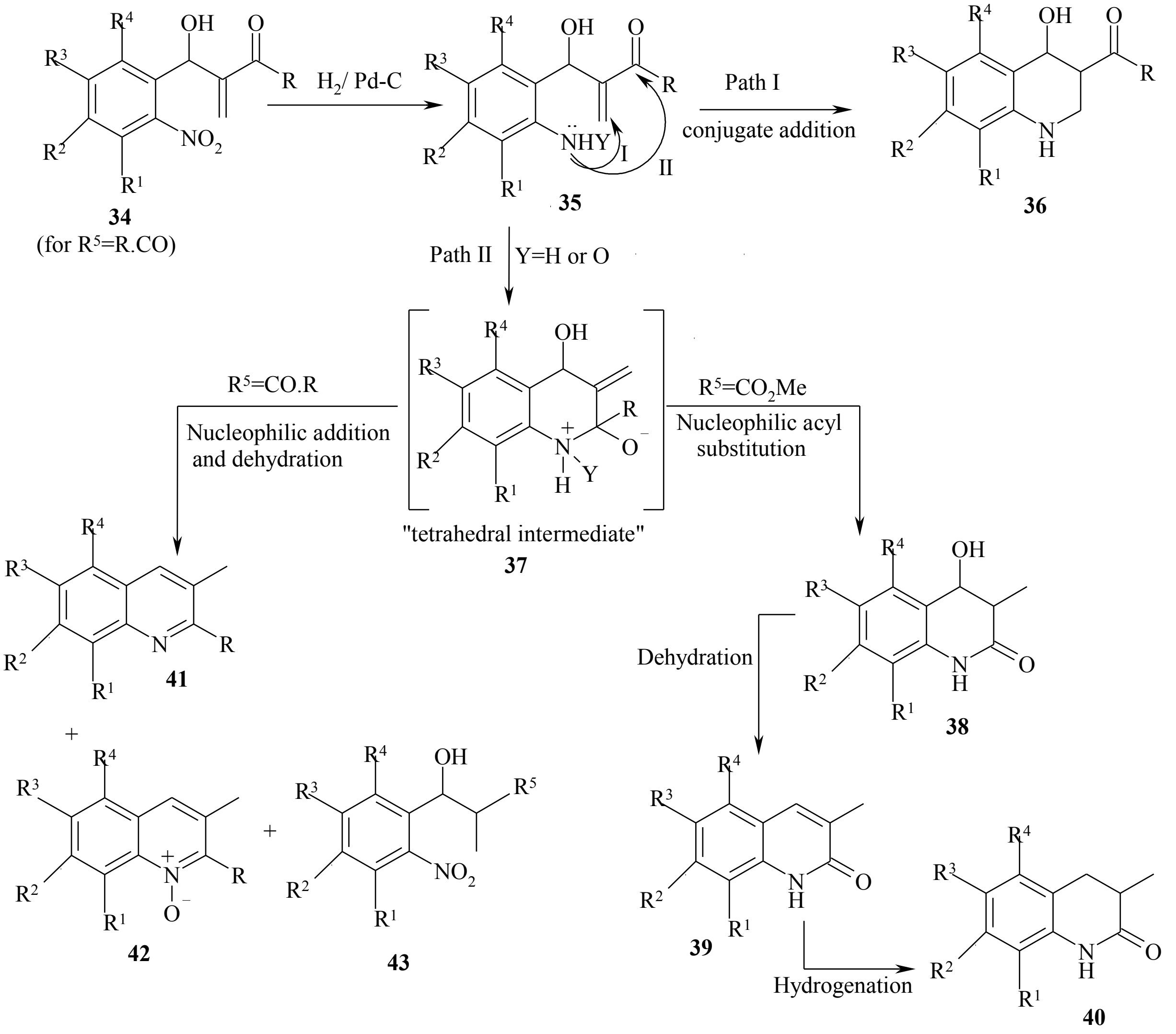
The BH approach to quinoline derivatives was initiated in our research group.[8,11] The approach involved the use of 2-nitrobenzaldehydes and a range of activated alkenes, such as MVK, methyl acrylate and ethyl acrylate in the presence of DABCO. 2-Aminobenzaldehydes, which are commonly used in quinoline syntheses are not easily accessible and hence the use of the easily accessible 2-nitrobenzaldehydes was a much more viable option. Kaye and co-workers [8,11] observed that catalytic hydrogenation of the BH adducts using a palladium-on-carbon catalyst (Scheme 5), afforded either quinolines **41** and quinoline-*N*-oxides **42** (when R^5= CO.R) or 2-quinolones 3**8-40** (when R^5= CO_2Me).

Following the initial communication by Kaye and co-workers,[11] numerous reports on the synthesis of quinoline derivatives *via* the BH reaction have been published. Kim and co-workers[5,13] have synthesised the 3-substituted 2-(1*H*)-quinolones **47a-c** and **48a-c**. Their approaches involved the use of zinc and trifluoroacetic acid (Scheme 6) and tin (II) chloride dihydrate (Scheme 7). The Zn/CF_3COOH route gave moderate to good yields of the 2-(1*H*)-quinolones, while moderate yields were obtained using $SnCl_2{\cdot}2H_2O$.

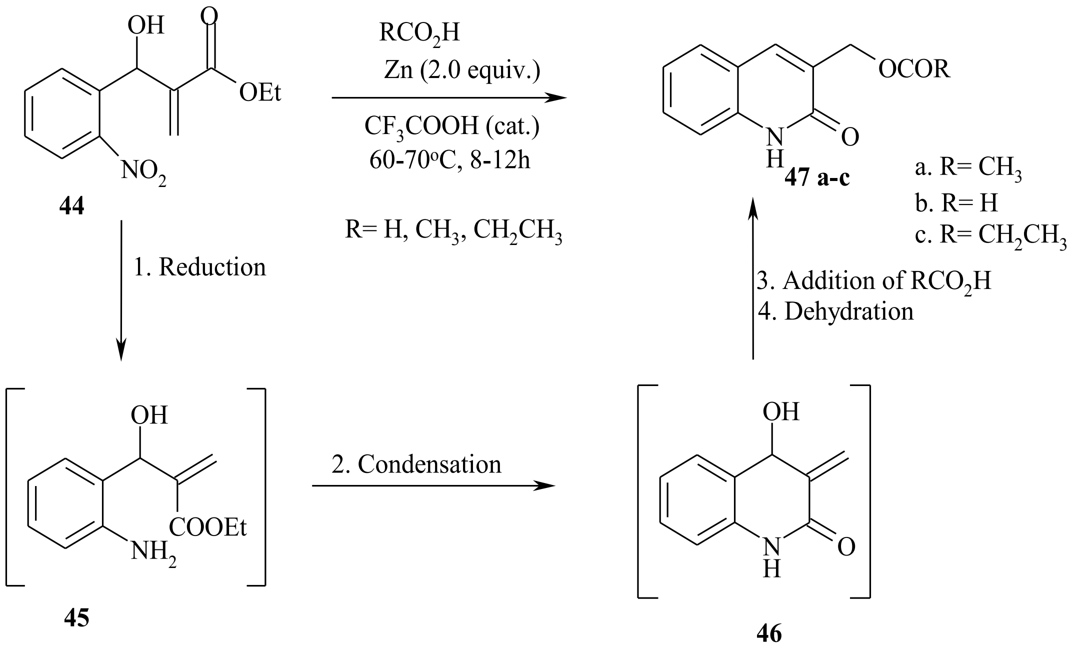


	R¹	R²	R³	R⁴
a	H	H	H	H
b	H	H	Cl	H
c	H	H	OH	H
d	OMe	H	H	H
e	H	H	H	Cl
f	H	OMe	OMe	H
g	H	-OCH$_2$O-		H
h	H	NO$_2$	H	H

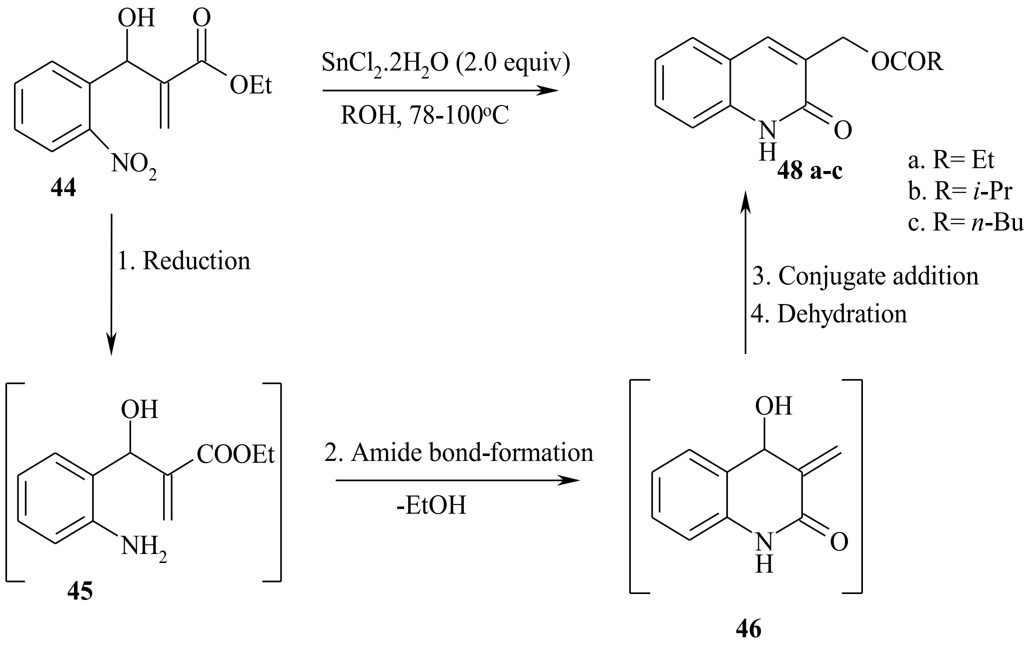
	R⁵
a	COMe
b	COEt
c	CO$_2$Me
d	CO$_2$Et
e	CN
f	SO$_2$Ph



Scheme 5[8]

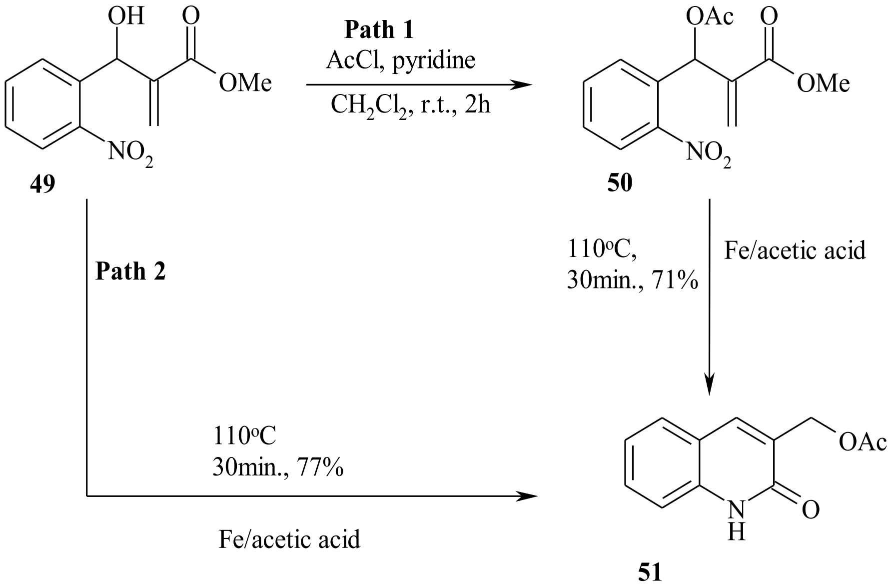


Scheme 6[13]



Scheme 7[5]

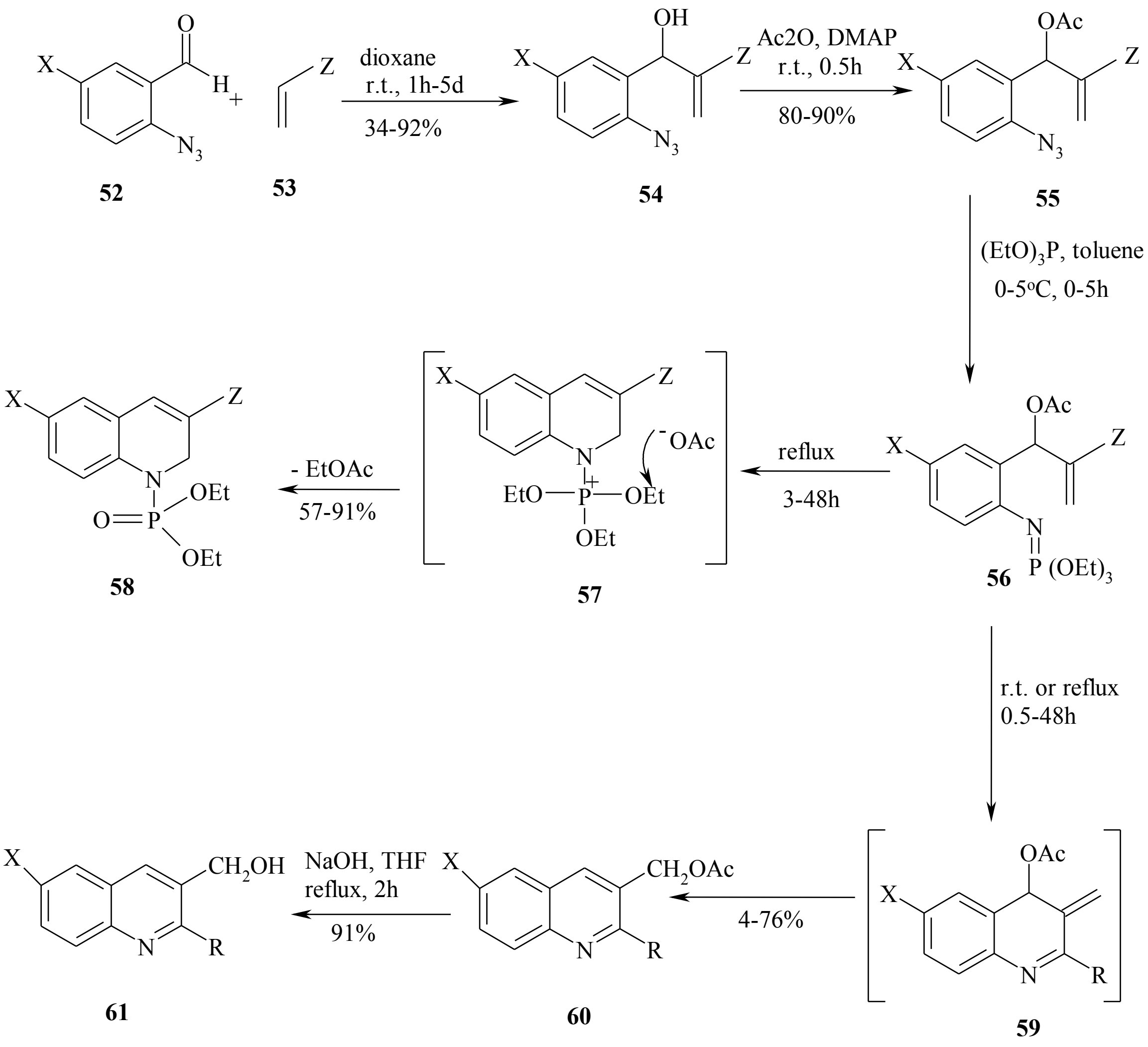
Basavaiah *et al.*,[12] on the other hand, began by acetylating the 2-nitrobenzaldehyde BH adduct **49** (Scheme 8; Path 1) to give compound **50**, and effecting cyclisation using Fe/acetic acid as a reducing system to give 3-acetoxymethyl-(1*H*)-quinolone **51** in 71% yield. Subsequently, they reduced the BH adduct directly using Fe/acetic acid at 110°C for 30 min. without prior acetylation (Scheme 8; Path 2), and obtained 3-acetoxymethyl-(1*H*)-quinolone **51** in 77% yield.



Scheme 8[12]

This methodology was extended to 2-nitrobenzaldehyde BH adducts derived from MVK[12] and provided access to 3-(acetoxymethyl)-2-methylquinoline in 63% yield.

Recently, Yi *et al.*[14] have reported the synthesis of 1-diethylphosphono-1,2-dihydroquinoline **58** and 3-(acetoxymethyl)quinoline **61** from 2-azidobenzaldehyde BH adducts derived from MVK, methyl acrylate and acrylonitrile (Scheme 9).

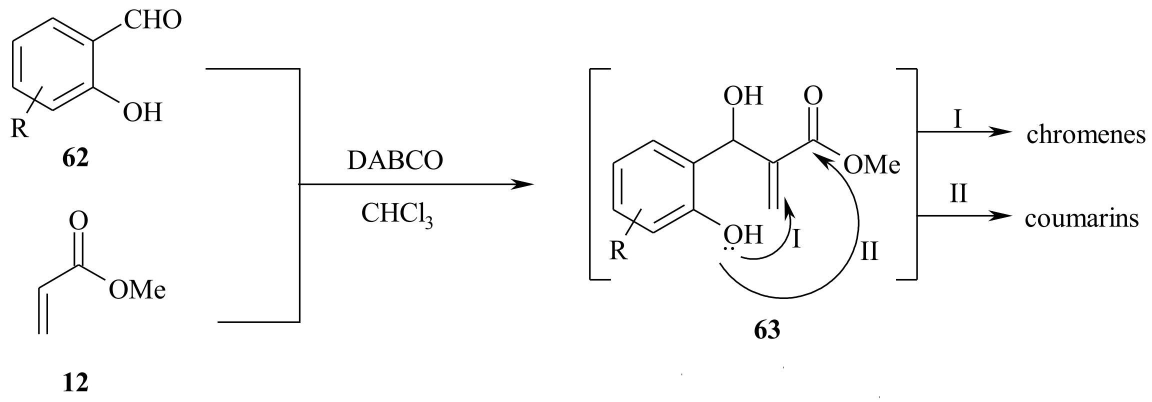


X= H, NO_2, OMe
Z= CO_2Me, COMe, CN
R= OMe, Me

Scheme 9[14]

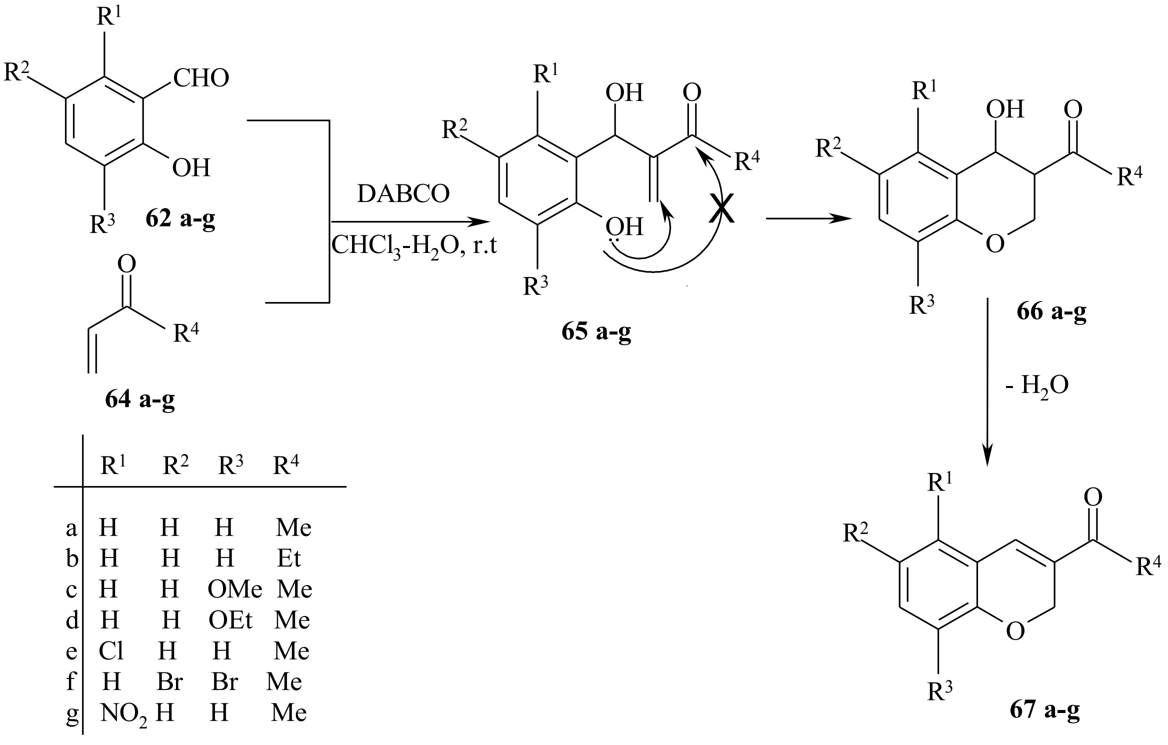
1.2.2 Synthesis of chromenes and thiochromenes

The construction of chromene systems has also been the subject of ongoing research in our group. Robinson[57,58] initially found that cyclisation of 2-hydroxybenzaldehyde BH adducts afforded mixtures of chromene and coumarin derivatives (Scheme 10). Path I, which involves conjugate addition to the vinylic bond, afforded chromenes, while path II, involving nucleophilic acyl attack at the carbonyl carbon of the ester group, afforded coumarin derivatives.



Scheme 10[6]

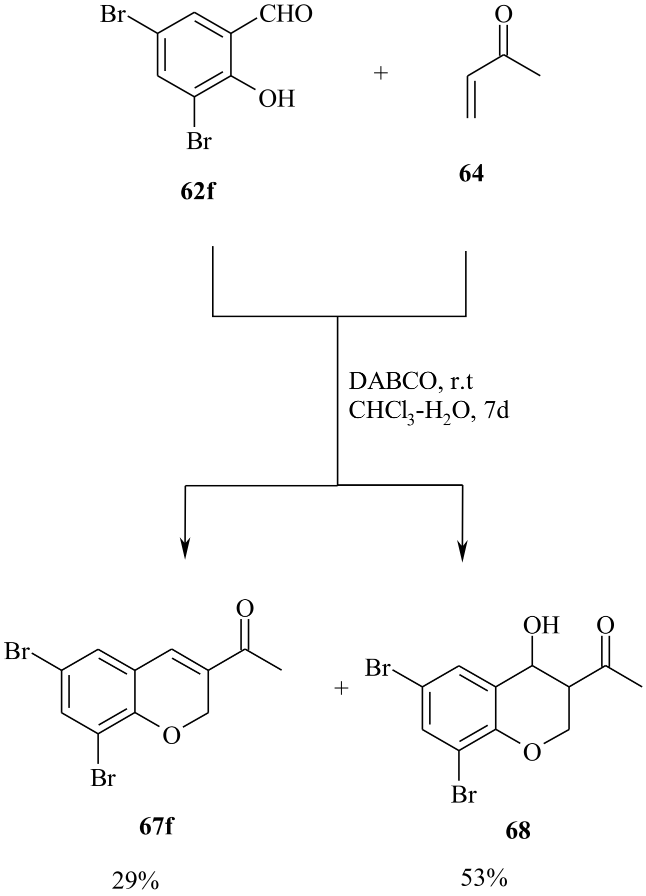
To obviate this problem of mixed product, the nucleophilic acyl substitution path (path II) was inhibited by replacing the acrylic esters with vinyl ketones (Scheme 11), an approach that gave the chromene derivatives **67a-g** in good yield.[6]



	R^1	R^2	R^3	R^4
a	H	H	H	Me
b	H	H	H	Et
c	H	H	OMe	Me
d	H	H	OEt	Me
e	Cl	H	H	Me
f	H	Br	Br	Me
g	NO_2	H	H	Me

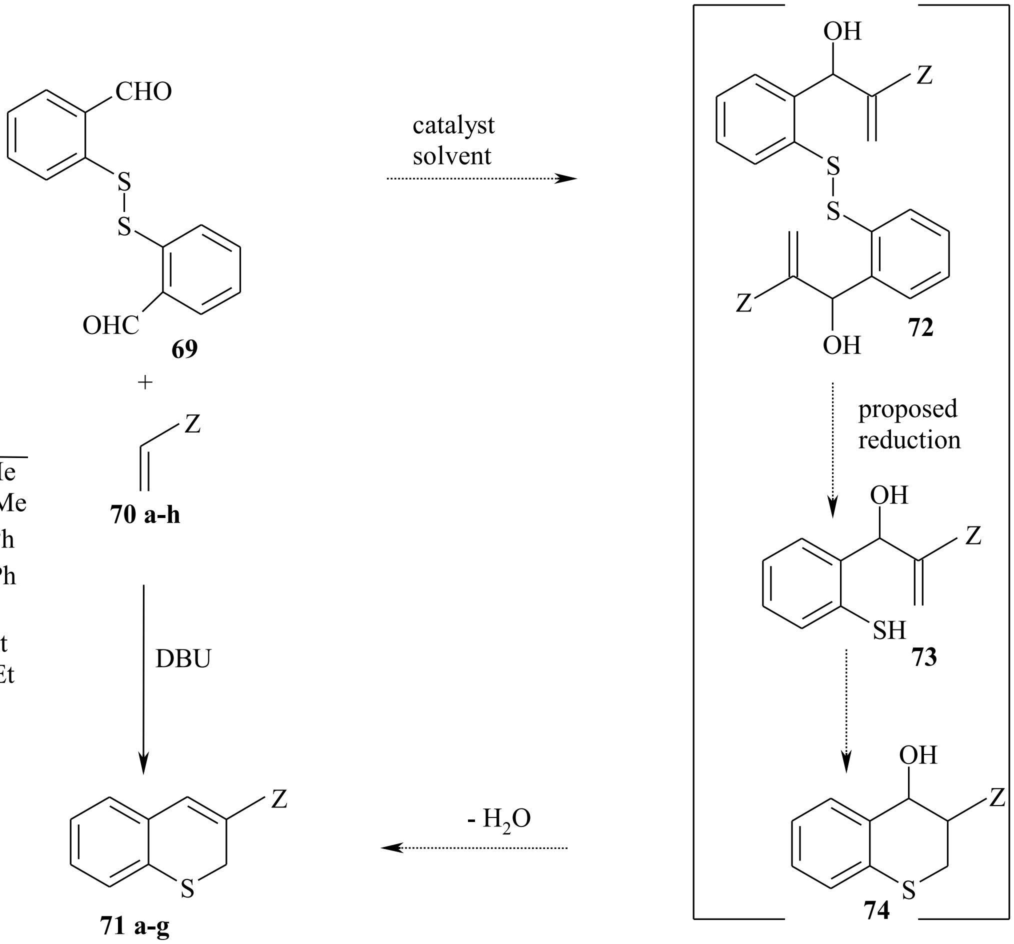
Scheme 11[6]

When MVK was reacted with 3,5-dibromo-2-hydroxybenzaldehyde **62f** in the presence of DABCO in $CHCl_3$/ H_2O at room temperature for 7days, a mixture of the chromanol **68** (53%) and the expected chromene **67f** (29%) were obtained (Scheme 12), a result consistent with the addition- elimination sequence proposed in Scheme 11.



Scheme 12[6]

This methodology was extended to the synthesis of sulphur containing analogues, *viz*., thiochromenes.[3] 2,2'-Dithiodibenzaldehyde **69** was reacted with MVK in the presence of DABCO, but this did not give the expected product. DBU was then used in place of DABCO, and remarkably the reaction proceeded to give the derived thiochromene **71a** directly (Scheme 13).



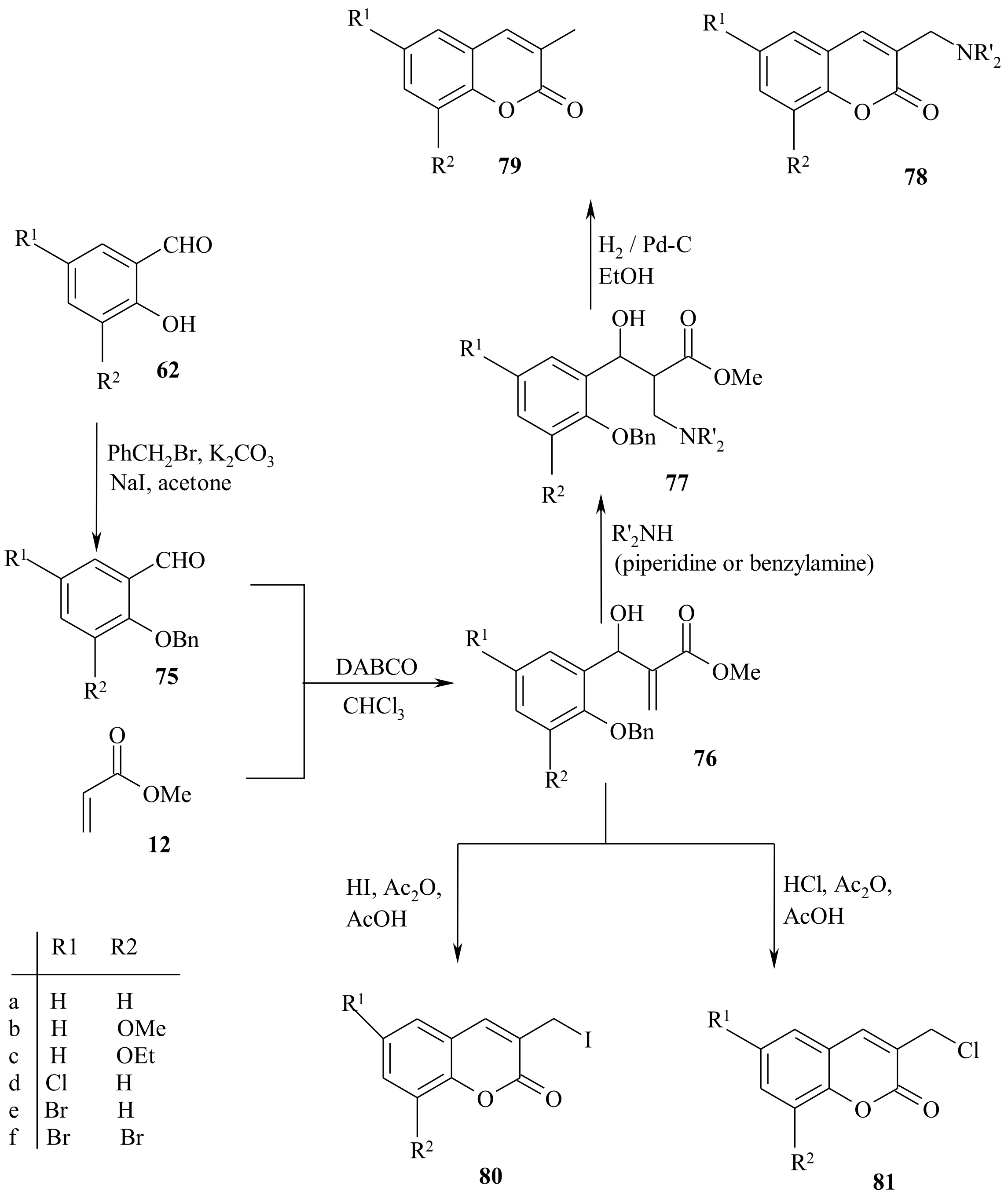
	Z
a	COMe
b	CO_2Me
c	SO_2Ph
d	SO_3Ph
e	CN
f	COEt
g	CO_2Et
h	CHO

Scheme 13[3]

The method was repeated with a range of activated alkenes **70a-h** to give the corresponding thiochromenes **71a-g**, rather than originally expected BH adducts **72**. The observed spontaneous reduction of the disulphide (**72-73**) and the cyclisation (**73-74**) and dehydration (**74-71**) raised questions concerning the mechanism involved in this particular BH reaction. A mechanism was proposed[3] which involved several steps and is given in Section 2.2.

1.2.3 Synthesis of coumarins

As indicated earlier, coumarins were initially obtained by Robinson[57,58] in mixtures with chromenes when 2-hydroxybenzaldehydes were reacted with ethyl acrylate in the presence of DABCO (Scheme 10), while Nocanda[6] succeeded in accessing chromenes selectively, there was still a need to control the regioselectivity of cyclisation to afford coumarins exclusively. Musa[15] began to achieve this by protecting the salicyaldehyde phenolic hydroxyl group as a benzyl ether, following an approach reported by Drewes *et al.*[59] Nucleophilic interception of the vinylic centre in the BH adducts **76** (Scheme 14) with either benzylamine or piperidine afforded the conjugate addition intermediates **77**. The last step involved deprotection of the phenolic oxygen *via* hydrogenolysis in the presence of 10% Pd/C catalyst, allowing acyl substitution and cyclisation to the 3-(aminomethyl)coumarins **78** as shown in Scheme 14.[15] In an alternative approach, halogen acids (HCl or HI) were used to effect deprotection and cyclisation to the 3-halomethyl analogues **80** and **81** in one pot.[15]

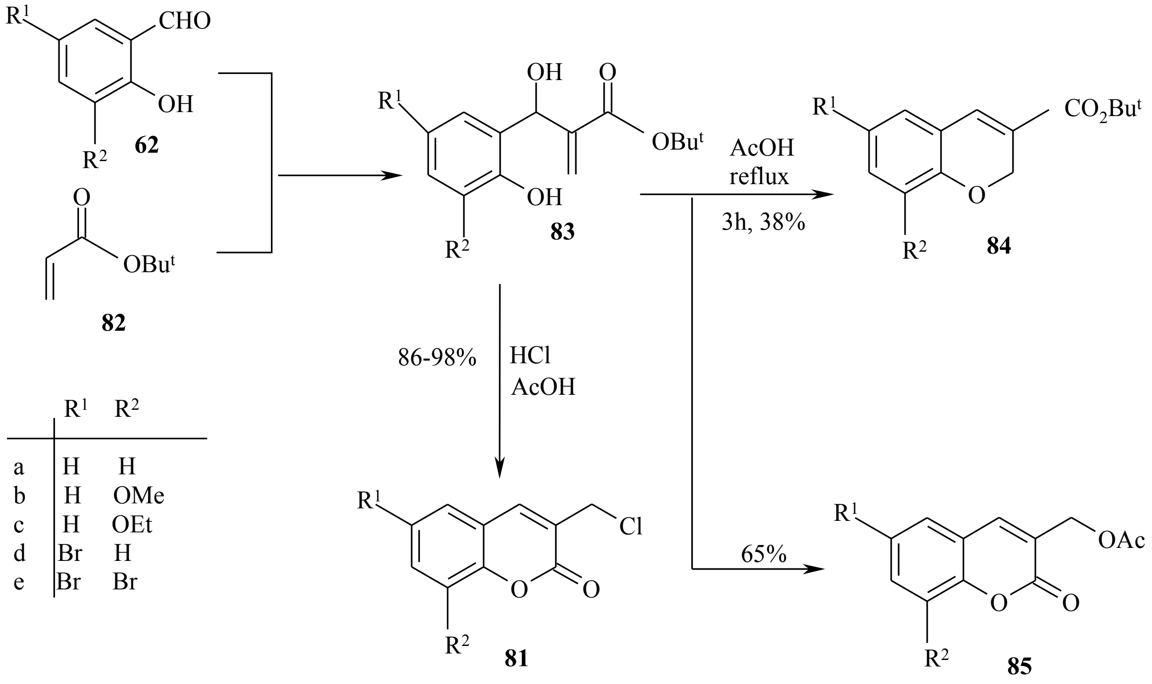


	R1	R2
a	H	H
b	H	OMe
c	H	OEt
d	Cl	H
e	Br	H
f	Br	Br

Scheme 14[15]

Having succeeded in preparing 3-(aminomethyl)- and 3-(chloromethyl)coumarins *via* direct cyclisation of protected BH adducts, Musa[16] explored formation of the coumarins *via* direct cyclisation of *unprotected* BH adducts. This was successfully achieved by reacting salicylaldehydes **62** with *t*-butyl acrylate **82** in the presence of DABCO (Scheme

15) to afford the stable and isolable BH products **83**. When these BH products were treated with HCl in acetic acid under reflux, the 3-(chloromethyl)coumarins **81** were obtained in high yield. Treatment of the BH products **83** with acetic acid alone, under reflux, afforded a mixture of the chromenes **84** and coumarins **85**.



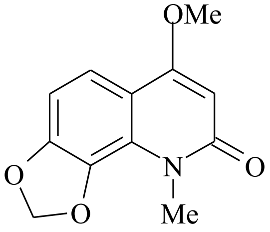
	R^1	R^2
a	H	H
b	H	OMe
c	H	OEt
d	Br	H
e	Br	Br

Scheme 15[16]

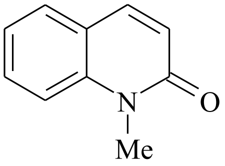
1.3 Naturally occurring and biologically active 2-quinolones

The 2-quinolone nucleus is present in a number of alkaloids extracted from various plants, animals and fungi which possess interesting physiological properties.[60] It is also found in medicinally important compounds, including antibiotics.[60]

Casimiroine **86** was extracted from the seeds of *Casimira edulis*, a medicinal and food plant of Mexico and Central America.[61] The plant was found to have anti-mutagenic activity, and this was attributed to the presence of casimiroine, which has also displayed promising chemopreventive activity against cancer by significantly inhibiting lesions induced by 7,12-dimethylbenz[a]anthracene (DMBA) in mouse mammary gland cultures.[61] Another methylquinolone, *N*-methylquinolin-2-one **87**,[61] has been isolated from Angostura bark *(Galipea. officinalis*) and has shown activity against *Mycobacterium tuberculosis*.

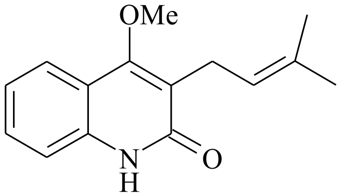


Casimiroine **86**

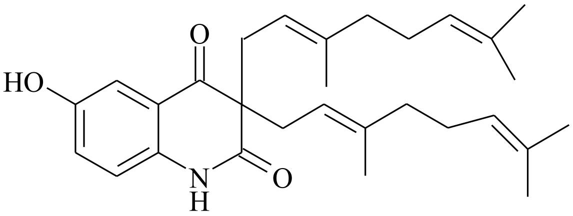


N-methylquinolin-2-one **87**

Atanin **88**, isolated from *Zanthoxylum integrifolium*,[61] has shown good inhibition of platelet aggregation *in vitro*, exhibiting a strong vaso-relaxing effect on the contraction of rat aorta induced by K^+ ions or norepinephrine. Another rare monoterpenoid quinolinone alkaloid, severibuxine **89**, was isolated from the Chinese plant, *Severinia buxifolia* (*Atlantia buxifolia*).[61] It is the first alkaloid to be isolated from this plant and has proved to be cytotoxic against P-388 murine leukemia and various other cell lines.

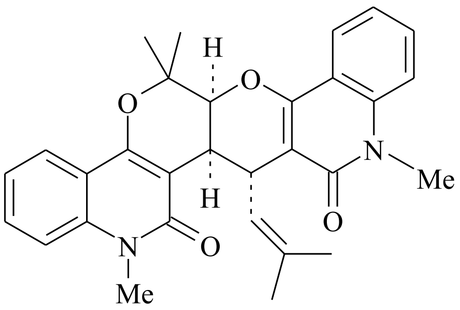


Atanine **88**

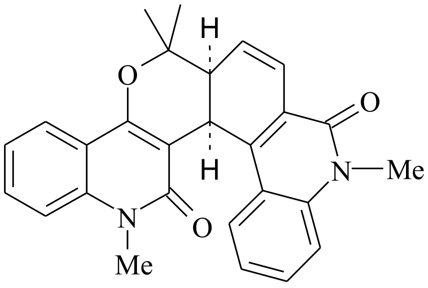


Severibuxine **89**

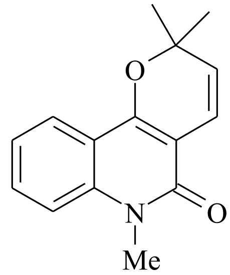
Compounds **90-92** were all isolated from the Vietnamese medicinal plant, *Melicope ptelefolia* (*Evodia lepta*). Two of them, melicobisquinolinone B **91**[61] and *N*-methylflindersine **92**,[61,62] inhibited mycelial growth of the fungus, *Cladosporium cucumerinum,* at nanomolar concentrations, whereas melicobisquinolinone A **90**[61] was inactive.



Melicobisquinolinone A **90**

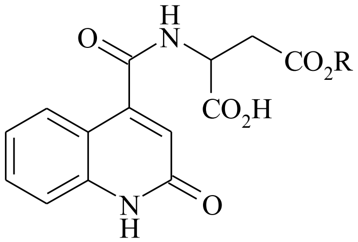


Melicobisquinolinone B **91**

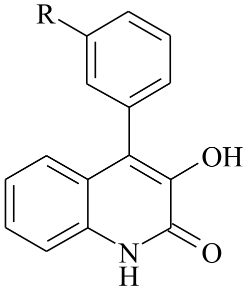


N-Methylflindersine **92**

Sterculine I **93** and sterculine II **94** have been isolated from the seeds of *Sterculia lychnophora*, a traditional Chinese drug, Pangdahai, used for the treatment of pharyngitis, tussis and constipation.[63] Viridicatin **95** and viridicatol **96** are two quinolone alkaloids that have been isolated from cultures of *Penicillium crustosum* and *Penicillium discolor,* respectively, grown on cheese agar.[63]

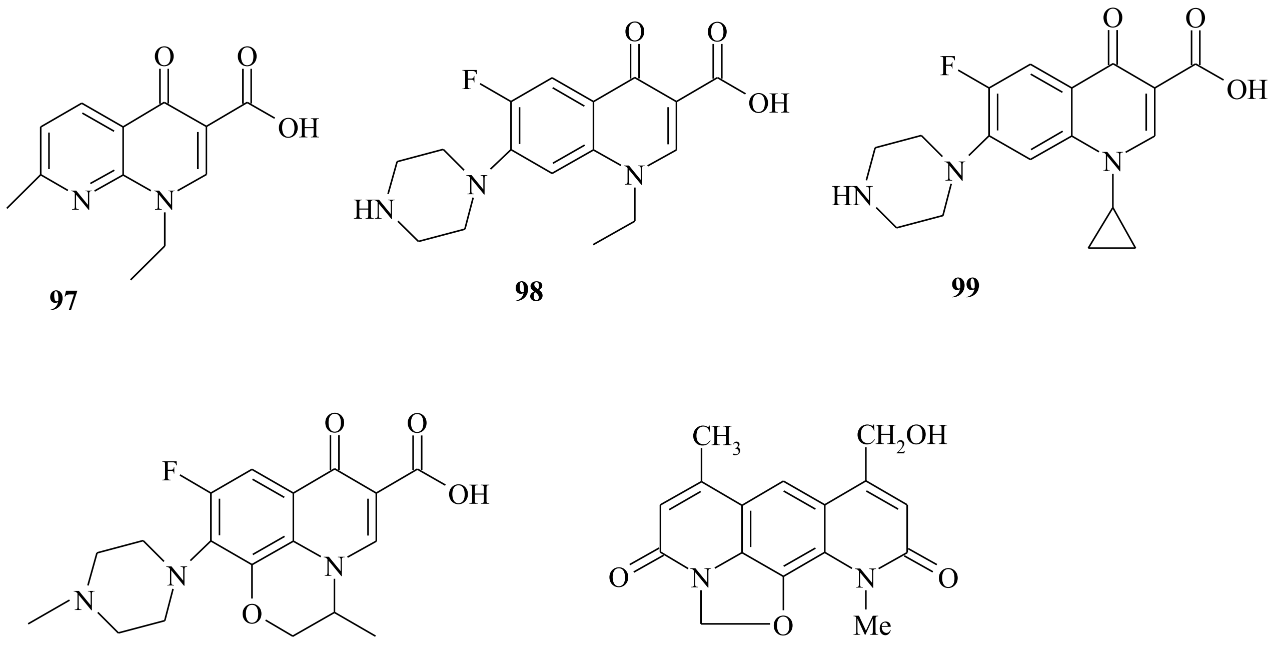


Sterculine I: R= *n*-Bu, **93**
II:R= Me, **94**



Viridicatin : R= H, **95**
Viridicatol : R= OH, **96**

A number of antibiotics, such as nalidixic acid **97,** norfloxacin **98**, ciprofloxacin **99** and ofloxacin **100**, contain the 4-quinolone nucleus. A fluorine atom at position-6 and a carbonyl group at position-4 are typical features of quinolone antibiotics in clinical use.



97 **98** **99**

100 **101**

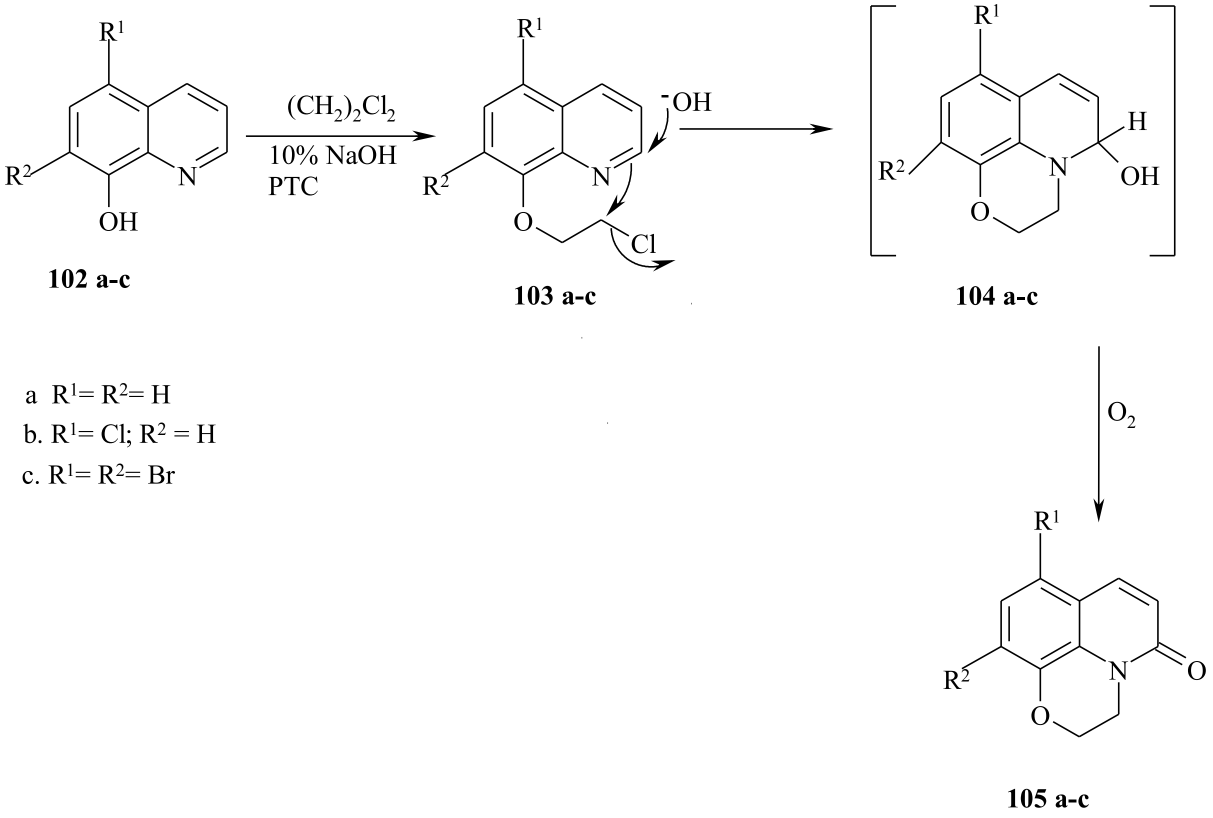
Figure 4. Quinolone antibacterials in clinical use.

These bacteriocidal quinolones and fluoroquinolones act by inhibiting the bacterial DNA gyrase or topoisomerase IV enzyme[64,65] and, by so doing, they inhibit DNA replication and transcription. 2-Quinolones which have the carbonyl group at position-2 have also become targets in drug discovery. Some 2-quinolones have been shown to exhibit antioxidative activity, nitric oxide production inhibitory activity, and cytotoxicity against human tumour cell lines; others are angiotensin II receptor antagonists, antiplatelet agents and antitumour agents.[66]

Nybomycin **101,** an antibacterial drug belonging to the 2-quinolone class of compounds, bears some structural resemblance to the 4-quinolone antibacterial drug, ofloxacin **100.**[65] Nybomycin **101** contains a fused 1,4-oxazolo ring system while ofloxacin **100** has a 1,4-

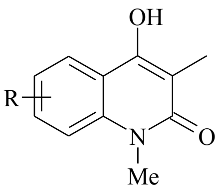
oxazino ring system; a common feature between these two compounds is the saturated hydrocarbon linkage between nitrogen and oxygen in these ring systems.

Sahu and co-workers[65] have reported a one-pot synthesis of 1,4-oxazino-2-quinolones **105a-c** from various 8-hydroxyquinoline analogues **102a-c** (Scheme 16) and their modification to derivatives of nybomycin **101**.

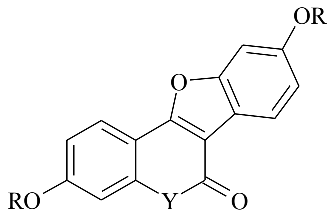


Scheme 16[65]

3-Aryl-4-hydroxy-2(1*H*)-quinolones **106** have been shown to be orally active and selective antagonists of the glycine site on the N-methyl D-aspartate (NMDA) receptor.[60] Coumestrol **107**, an estrogenic factor,[60] occurs naturally in forage crops, and non-steroidal estrogens with similar structures to coumesterol have been synthetically developed for the treatment of breast cancer. Kappe[60] has managed to synthesize aza-coumesterol derivatives by replacing the coumarin moiety with a 2-quinolone moiety, and some of these derivatives (*e.g.* **108)** have been found to exhibit activity against osteoporosis, a chronic disease of the skeleton which is characterized by bone fragility due to a reduction in bone mass.

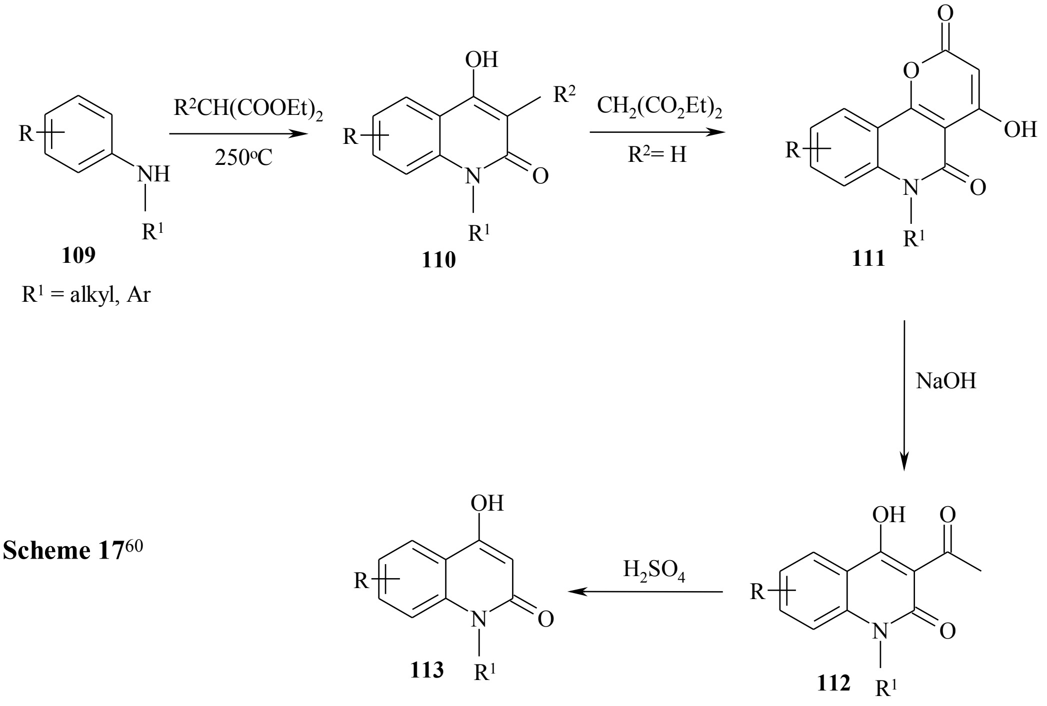


106

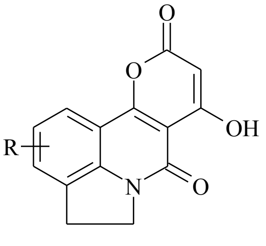


107 Y= O ; R= H
108 Y= NH ; R= CO.NMe$_2$

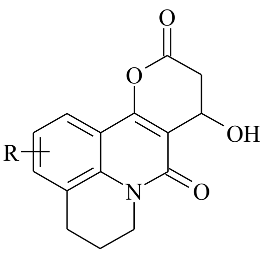
The synthetic pathway used by Kappe[60] is outlined in Scheme 17. When anilines or anilino derivatives **109** are fused with substituted dialkyl malonates in a 1:1 ratio in the absence of solvent at high temperatures (≥ 250ºC), 3-substituted-4-hydroxy-2-quinolones **110** are obtained in good yields.



Scheme 17[60]



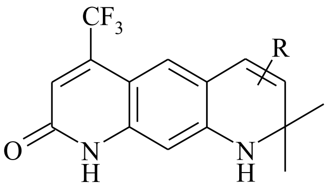
114



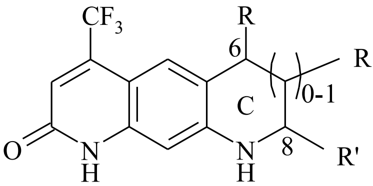
115

If 2 equivalents of unsubstituted diethyl malonate are used, then the tricyclic products **111** are formed. Use of cyclic anilines, such as indoline and tetrahydroquinoline, leads to tetracyclic products, such as **114** and **115**.

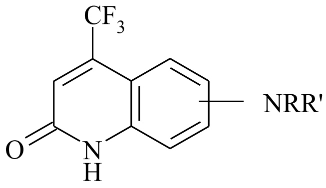
Zhi and co-workers[67] have successfully developed androgen receptor (AR) agonists of type **117**, based on an early linear tricyclic quinoline pharmacore **116** (Fig. 5). They[67] found that the bis(alkyl) groups at position-8 were responsible for the AR antagonist activity, while small alkyl groups on a saturated C-ring exhibited AR agonist activity.



116



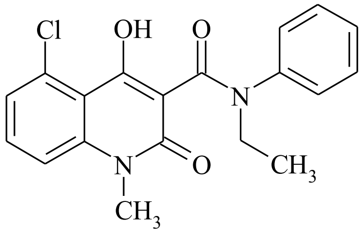
117



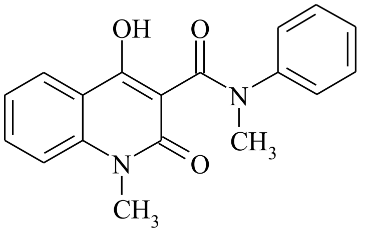
118

Figure 5.[67] Non-steroidal AR modulators: (116) AR antagonists; (117) AR agonists; and (118) new compounds.

5-Chloro-*N*-ethyl-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-*N*-phenyl-3-quinoline-carboxamide (laquinimod) **119**,[68] which was developed by Active Biotech research has successfully undergone a clinical phase II trial for the treatment of multiple sclerosis (MS), an auto-immune disease that affects the central nervous system. Roquinimex **120** was used as the lead compound in the research programme.

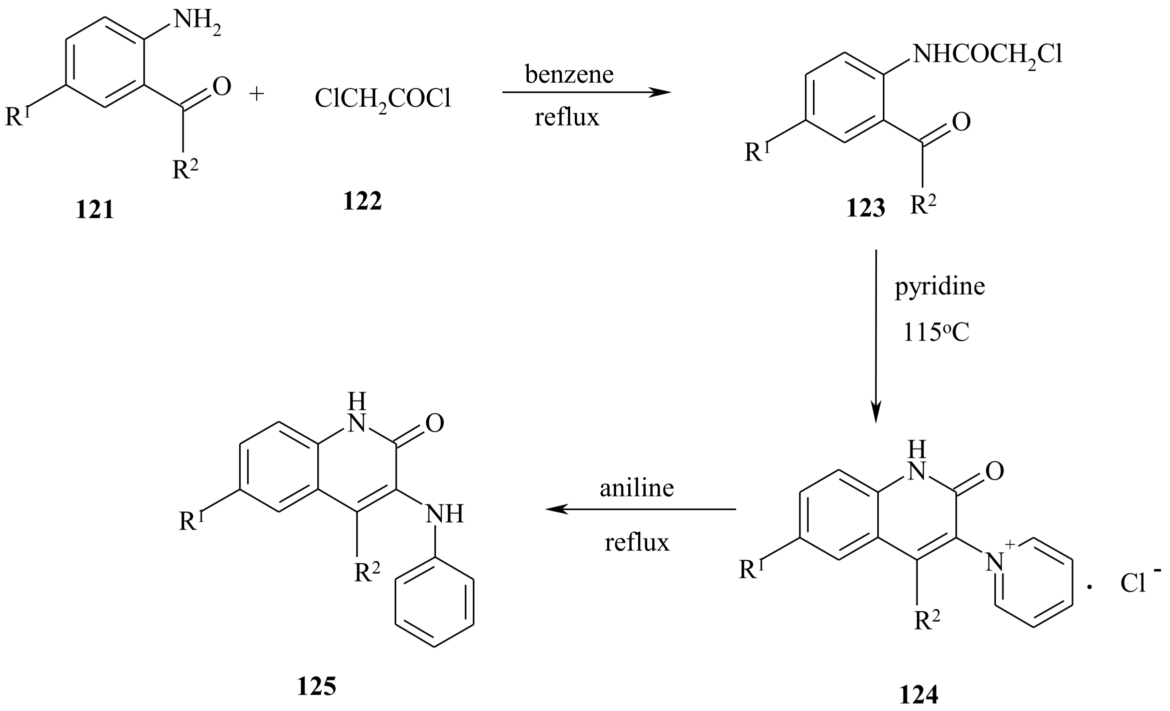


Laquinimod **119**



Roquinimex **120**

Quinoline compounds have been used for decades as antimalarials, and Asis *et al.*[69] have explored the anti-malarial potential of 3-amino-2-quinolones, and have reported a procedure for their synthesis (Scheme 18).

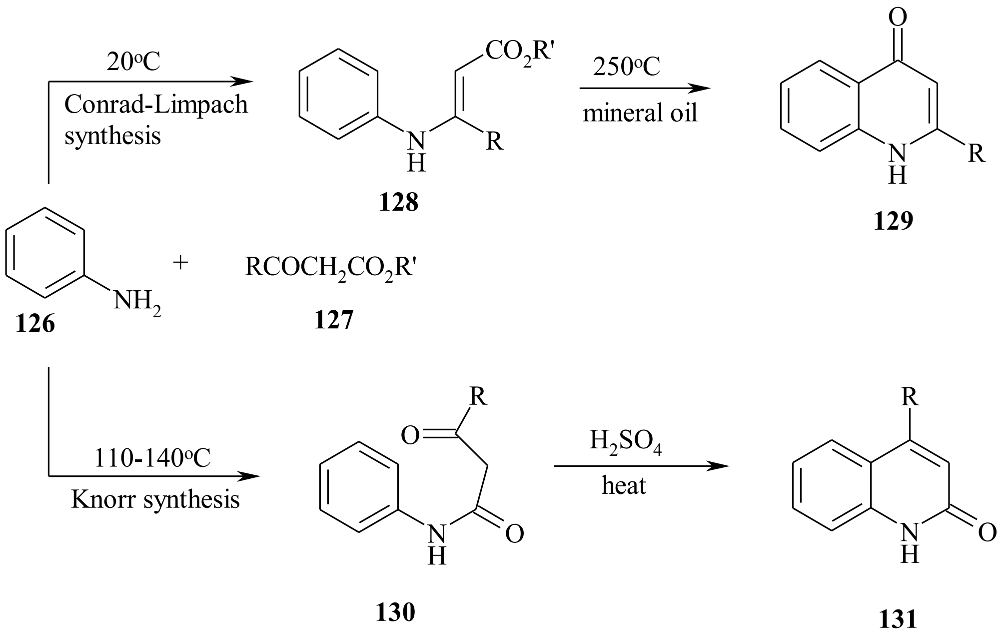


a : R^1= Cl, R^2= C_6H_5
b : R^1= H, R^2= CH_3

Scheme 18[69]

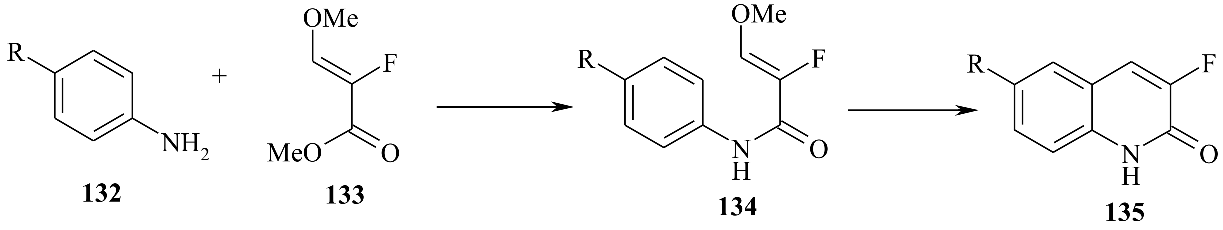
As indicated above, the 2-quinolone nucleus can be transformed into a wide range of biologically active compounds, and various synthetic methods have been developed to access 2-quinolone derivatives. These methods include:- the acid-catalysed cyclisation of acyl-acetoanilides (the Knorr synthesis; Scheme 19),[70] which is probably the most general method; microwave-enhanced synthesis;[66] cyclisation of *o*-amino-functionalised benzoylacetates; palladium-catalysed amidation of *o*-carbonyl-substituted aryl halides; palladium-catalysed carbonylative annulation of terminal alkynes;[71] and cyclisation of cinnamanilides.

The reaction between aniline and *β*-keto-esters under different reaction conditions gives different products, as outlined in Scheme 19.[70,72,73] At low temperature (20°C), the amino group condenses with the more reactive ketone carbonyl of the *β*-keto-ester in a kinetically-controlled reaction to give a *β*-aminoacrylic ester **128**, which cyclises by heating to give 4-quinolones **129** in a reaction known as the Conrad-Limpach synthesis. However, under thermodynamically-controlled conditions (110-140ºC), a more stable anilide **130** is formed, which undergoes ring closure on heating to give 2-quinolones **131**, and this is known as the Knorr synthesis.[70,72,73]



Scheme 19

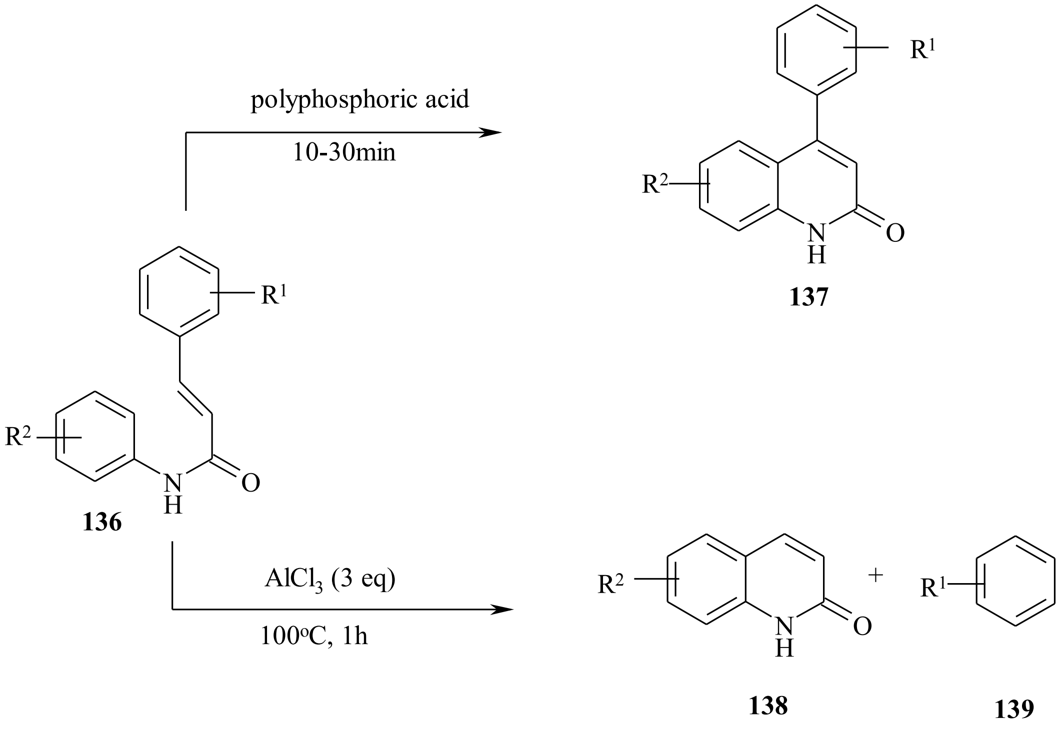
In a modified Knorr type reaction, Mavers *et al.*[74] synthesised 3-fluoro-2-quinolones **135** from *p*-substituted anilines in quantitative yields (Scheme 20). When *o*-substituted anilines were used, they also gave the 3-fluoro-2-quinolones in quantitative yields, but *m*-substituted anilines gave mixtures of regioisomers.



R= F_3C, F, H_3CO

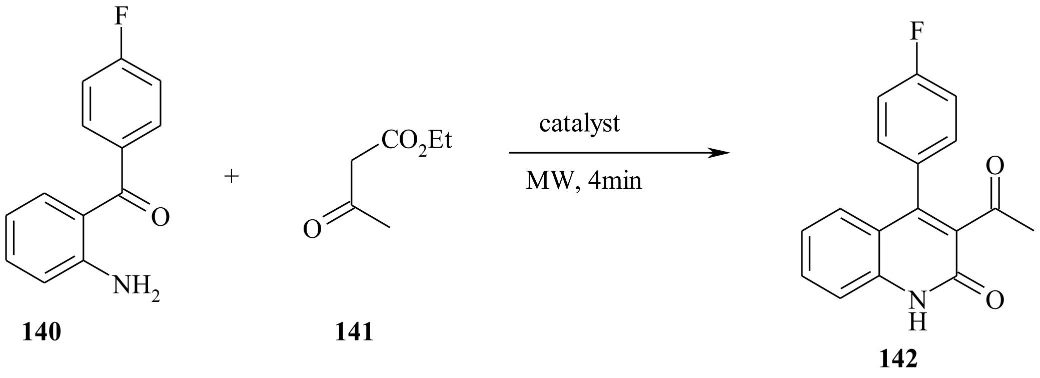
Scheme 20[74]

Heating cinnamanilides in the presence of polyphosphoric acid results in the formation of 4-aryl-3,4-dihydro-2-quinolones **137** (Scheme 21).[70] *Para*-substituents (R^1) on the aryl ring promote ring closure whereas *o*-substituents hinder ring closure. An electron-withdrawing group in the benzannulated ring may prevent ring closure, while strongly electron-releasing groups may cause loss of the aryl group if the reaction temperature is not kept as low as possible. When heated with $AlCl_3$, cinnamanilides afford 2-quinolones **138** with loss of the aryl group **139**.[70]



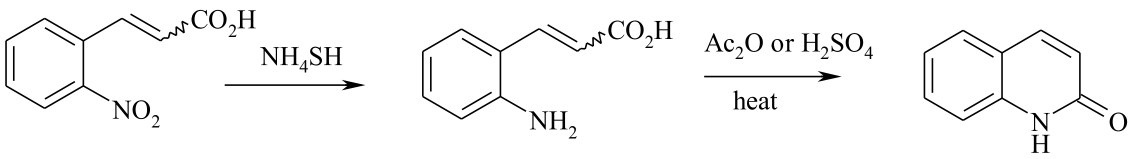
Scheme 21

Recently Jia *et al.*[66] have synthesized compounds closely related in structure to the 4-aryl-3,4-dihydro-2-quinolones **137**. They reacted 2-amino-4'-fluorobenzophenone **140** with ethyl acetoacetate **141** under microwave conditions, using $CuSO_4{\cdot}5H_2O$, CuCl, $CuCl_2{\cdot}2H_2O$ and $CeCl_3{\cdot}7H_2O$ as catalysts, to obtain the 2-quinolones **142** in moderate yields; $CeCl_3{\cdot}7\ H_2O$ was the best catalyst.



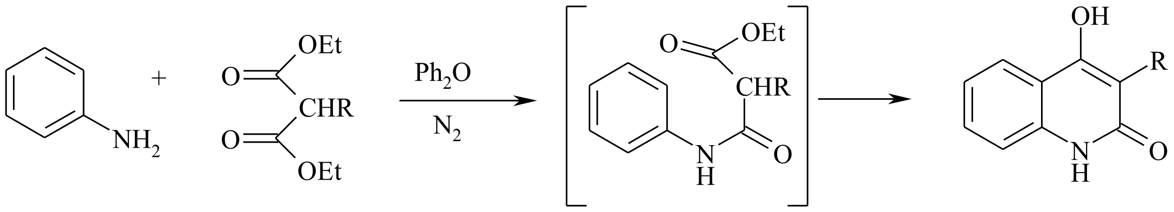
Scheme 22

Ortho-amino-allo-cinnamic acid **144** readily undergoes ring-closure to afford 2-quinolones **145** (Scheme 23). In the Coombes synthesis, aniline **126** is reacted with substituted malonic esters **146** in diphenyl ether under nitrogen to afford 3-substituted-4-hydroxyl-2-quinolones **148** *via* an acyl substitution reaction (Scheme 24).[70,75] 2-quinolones **151** have also been synthesized by carbonylative annulation of terminal alkynes,[71] using a Pd catalyst as illustrated in Scheme 25.



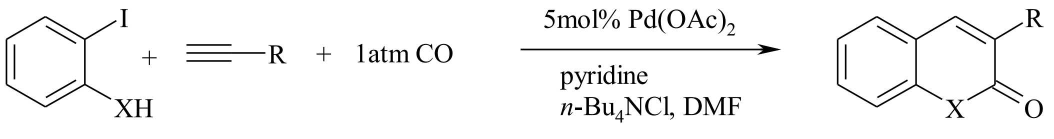
143 **144** **145**

Scheme 23



126 **146** **147** **148**

Scheme 24



149 **150** **151**

X=O, NCO_2Et

X=O, NH

Scheme 25

1.4 Aims of the present study

The formation of C-C bonds is a fundamental process in organic chemistry and the Baylis-Hillman reaction has proved to be useful in this regard. The BH reaction affords multifunctional adducts which serve as intermediates for the target compounds which constitute the focus of the present study.

More specifically, attention has been given to the following:

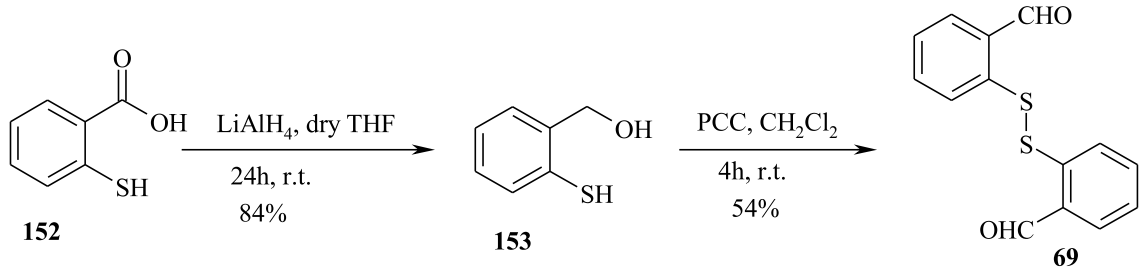
1. The synthesis of thiochromenes using the BH reaction.
2. A preliminary kinetic study of the formation of these thiochromenes.
3. The synthesis of 2-nitrobenzaldehyde BH adducts and their elaboration to 3-amino-2-quinolones.
4. The application of ^{13}C NMR chemical shift prediction programmes to selected products.

2. RESULTS and DISCUSSION

The discussion which follows will focus mainly on applications of the Baylis-Hillman (BH) methodology in the synthesis of 2*H*-1-benzothiopyrans (thiochromenes) and 2-quinolones. Attention will be given to:- i) the synthesis of thiochromenes and a preliminary kinetic study of their formation (Sections 2.1 and 2.2); ii) the synthesis of 2-nitrobenzaldehyde BH adducts and their reduction to quinoline derivatives (Sections 2.3.1 and 2.3.2); iii) conjugate addition reactions of these BH adducts with piperidine and benzylamine (Section 2.3.3); and iv) catalytic hydrogenation of the conjugate addition products to afford 2-quinolone derivatives (Section 2.3.4).

2.1 Synthesis of 2*H*-1-Benzothiopyrans

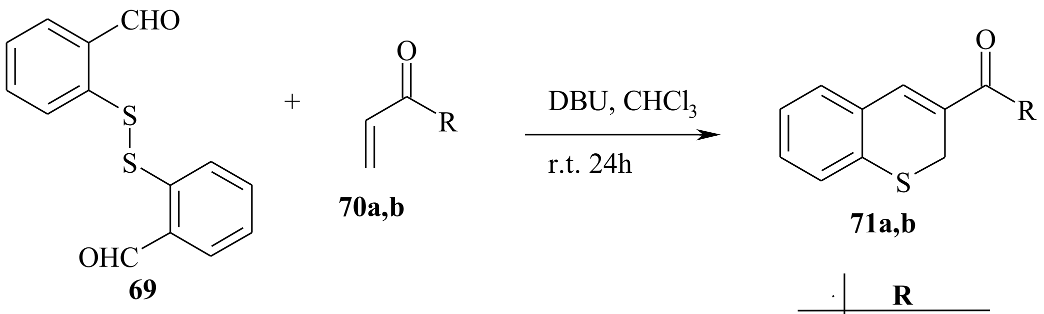
The synthesis of thiochromenes required the precursor, 2,2'-dithiodibenzaldehyde **69**, which was then used as the carbon electrophile in the BH reaction. The procedure reported by Arnoldi and Carrughi,[76] which involves lithium aluminium hydride ($LiAlH_4$) reduction of 2-mercaptobenzoic acid **152**, was followed to give 2-mercaptobenzyl alcohol **153** in 84% yield. Controlled oxidation of the alcohol **153** using pyridinium chlorochromate (PCC), as reported by Kasmai and Mischke,[77] gave the required precursor, 2,2'-dithiodibenzaldehyde **69** in 54% yield (Scheme 26).



Scheme 26

2.1.1 Synthesis of thiochromene derivatives using the BH reaction.

With the intention of extending earlier work,[3,78] 2,2'-dithiodibenzaldehyde **69** was treated with the activated alkenes, MVK **70a** and methyl acrylate **70b**, in model BH reactions using DBU as the catalyst. The reaction proceeded, as expected, to give the corresponding thiochromenes **71a,b**, which were isolated in 53 and 48% yield, respectively (Scheme 27). The formation of both products was confirmed by 1- and 2-dimensional NMR analysis. In the ^{1}H NMR spectrum of the methyl ester **71b** (Figure 6), the methyl proton resonates at 3.83 ppm while the 2-methylene signal is at 3.73 ppm.



	R
a	Me
b	OMe

Scheme 27

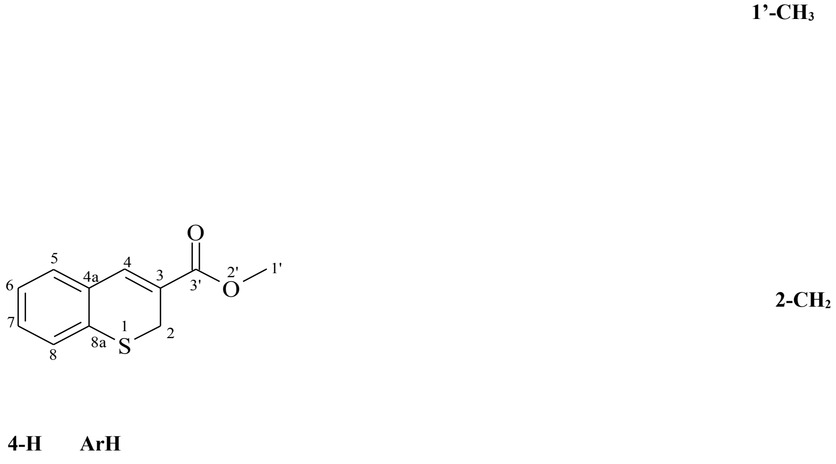
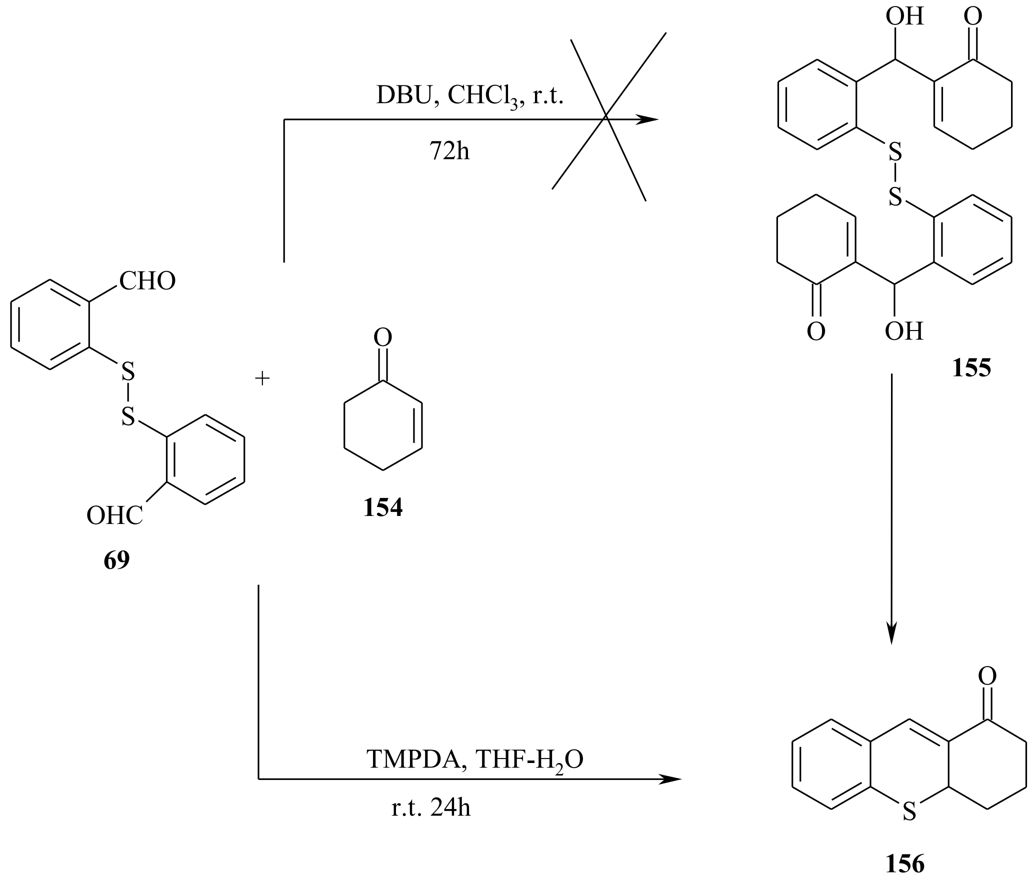


Figure 6. 400MHz ^{1}H NMR spectrum of **71b** in $CDCl_3$

2.1.2 Reaction of 2,2'-dithiodibenzaldehyde 69 with cyclic ketones.

Attention was then given to the use of cyclic ketones, such as 2-cyclohexenone **154** and 2-cyclopentenone **157** as activated alkenes – substrates that had not been used in the previous study. Successful application of these cyclic enones would lead to the formation of thioxanthone derivatives, examples of which have been identified as potential anti-cancer drugs.[79-81] The standard synthesis of the xanthone skeleton, however, requires multistep procedures involving benzophenone or diaryl ether intermediates and harsh reaction conditions.[82] The successful application of cyclic enones in the BH synthesis of thiochromenes was expected to provide a much simpler route to the thioxanthone skeleton under ambient conditions.

Initially the same reaction conditions used for acyclic activated alkenes were used for the reaction with 2-cyclohexenone **154**. These involved using chloroform as solvent, DBU as catalyst and reacting at room temperature. The reaction was monitored using TLC and after 24 hours the starting material seemed to have disappeared. ^{1}H NMR analysis of the crude product, however, failed to show any of the expected product **156** or the presumed precursor **155** (Scheme 28). Cyclic ketones have been reported to exhibit very slow reaction rates under BH conditions, and often no reaction is observed at all.[24] Several catalysts and solvent systems have been explored in an effort to accelerate the reaction rates of cyclic enones. Luo *et al.*[23] used imidazole in an aqueous THF medium, while Kim and co-workers[24] used TMPDA in aqueous THF and both groups managed to achieve rate acceleration in BH reactions involving cyclic enones.



Scheme 28

Following the method reported by Kim and co-workers,[24] the reaction of 2,2'-dithiodibenzaldehyde **69** and 2-cyclohexenone **154** was repeated using TMPDA as catalyst in place of DBU and aqueous THF in place of chloroform. Under these conditions, 2,3,4,4a-tetrahydrothioxanthen-1-one **156** was obtained in 20% yield (Scheme 28). Formation of compound **156** was confirmed by 1- and 2-D NMR, IR and High Resolution Mass Spectrometry (HRMS).

The ^{1}H NMR spectrum of compound **156** (Fig. 7), revealed splitting of the 2-H, 3-H and 4-H signals, which can be attributed to both vicinal coupling and geminal coupling between diastereotopic protons – the latter arising from the chiral centre at C-4a. The proton at the chiral centre, 4a-H, resonates at 4.28 ppm and is a multiplet as expected. The corresponding chiral carbon (C-4a) resonates at 38.3 ppm in the ^{13}C NMR spectrum (Fig. 8), with the carbonyl carbon resonating at 197.3 ppm. The DEPT-135 spectrum

(Fig. 9) confirms the presence of the three methylene carbons, C-2, C-3 and C-4. Vicinal coupling of the 4a-H proton with both diastereotopic 4-H protons is evident in the COSY spectrum (Fig. 10). The HSQC spectrum of compound **156** (Fig. 11) confirms that the 4a-H proton is attached to C-4a, and also reveals that there is indeed splitting of the diastereotopic methylene proton signals attached to carbons 2, 3 and 4. The structure of compound **156** was further confirmed by the HMBC spectrum (Fig. 12), which shows the connectivity between C-4a and C-6 and also the connectivity between the carbonyl carbon and C-10 as expected.

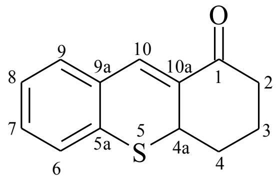


Figure 7. 600MHz ^{1}H NMR spectrum of **156** in $CDCl_3$

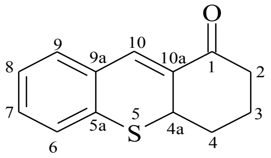


Figure 8. 150MHz ^{13}C NMR spectrum of compound **156** in $CDCl_3$.

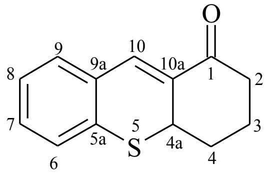


Figure 9. 150MHz DEPT-135 NMR spectrum of compound **156** in $CDCl_3$

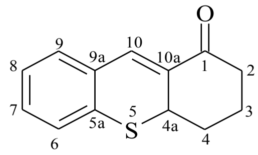


Figure 10. COSY NMR spectrum of compound **156** in $CDCl_3$.

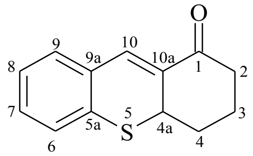


Figure 11. HSQC NMR spectrum of compound **156** in $CDCl_3$**.**

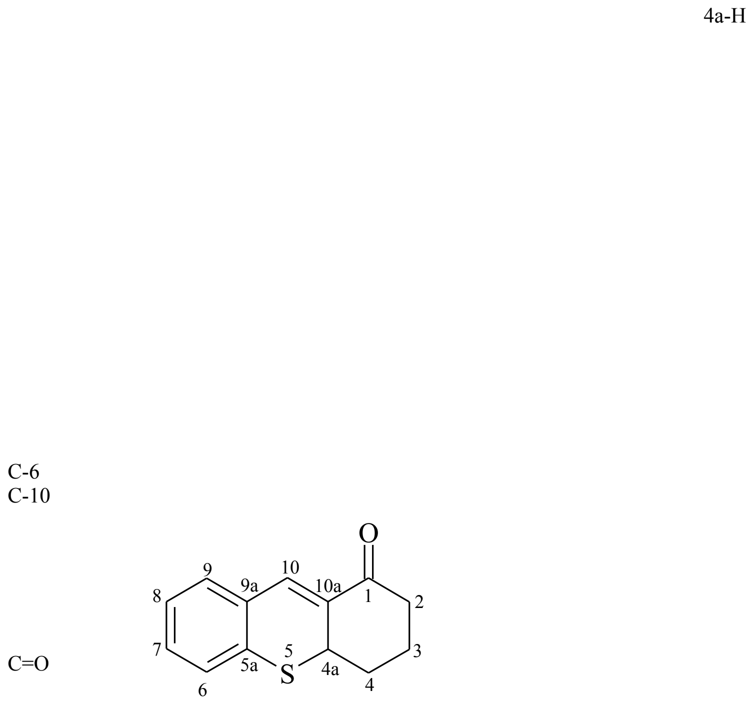
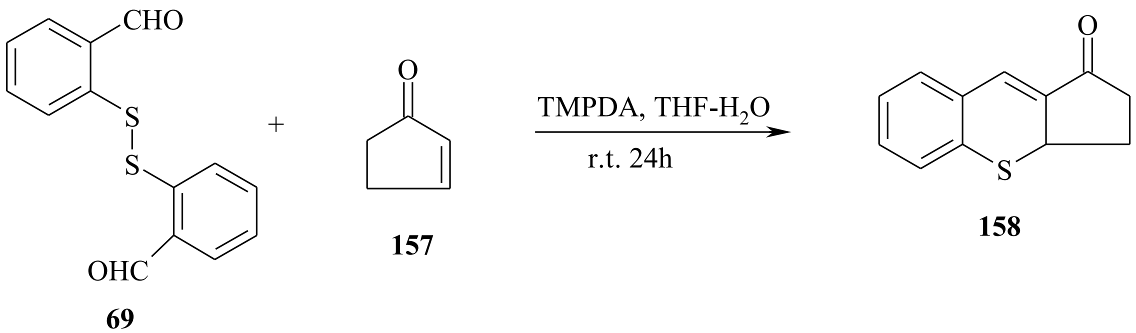


Figure 12. HMBC NMR spectrum of compound **156** in $CDCl_3$.

The procedure for the synthesis of compound **156** was repeated using 2-cyclopentenone **157** in place of 2-cyclohexenone **154** (Scheme 29). Purification of the crude product proved rather difficult, affording the impure product **158** in 39% yield. NMR, IR and low resolution mass spectrometry were then used to confirm the presence of compound **158**. A C=O stretching band at 1725cm^{-1}, characteristic of a carbonyl attached to a ring system, and a base peak at *m*/*z* 202 in the low resolution mass spectrum, corresponding to the molecular ion of compound **158**, was evidence that we had managed to synthesise compound **158**.

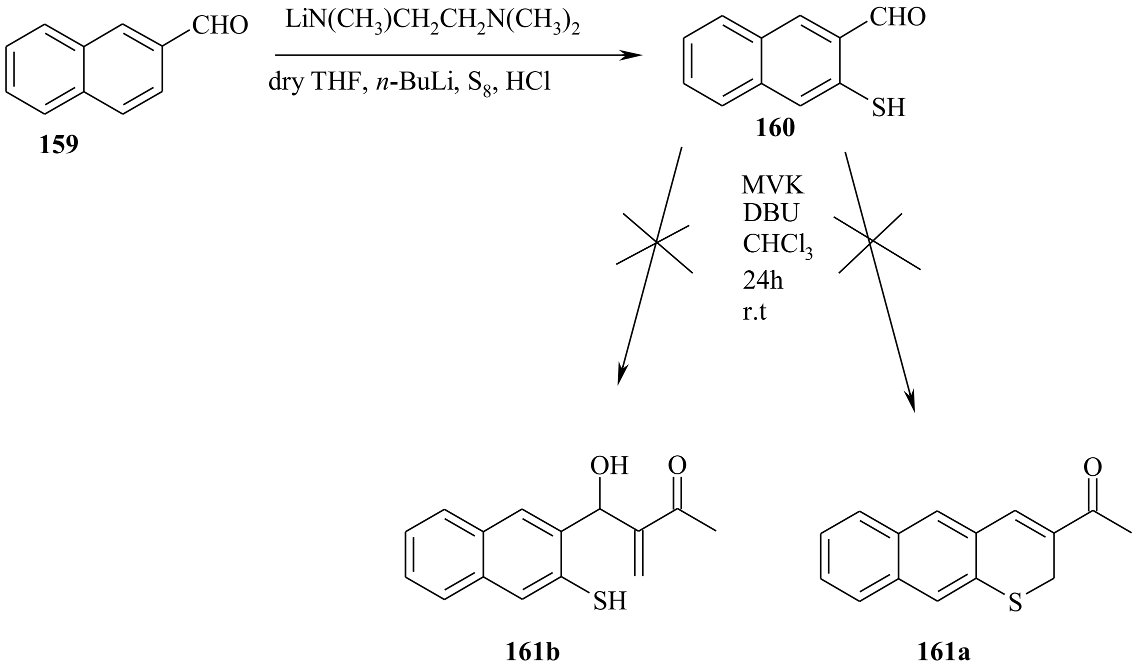


69

Scheme 29

2.1.3 Extending the thiochromene system by use of a bicyclic aldehyde precursor.

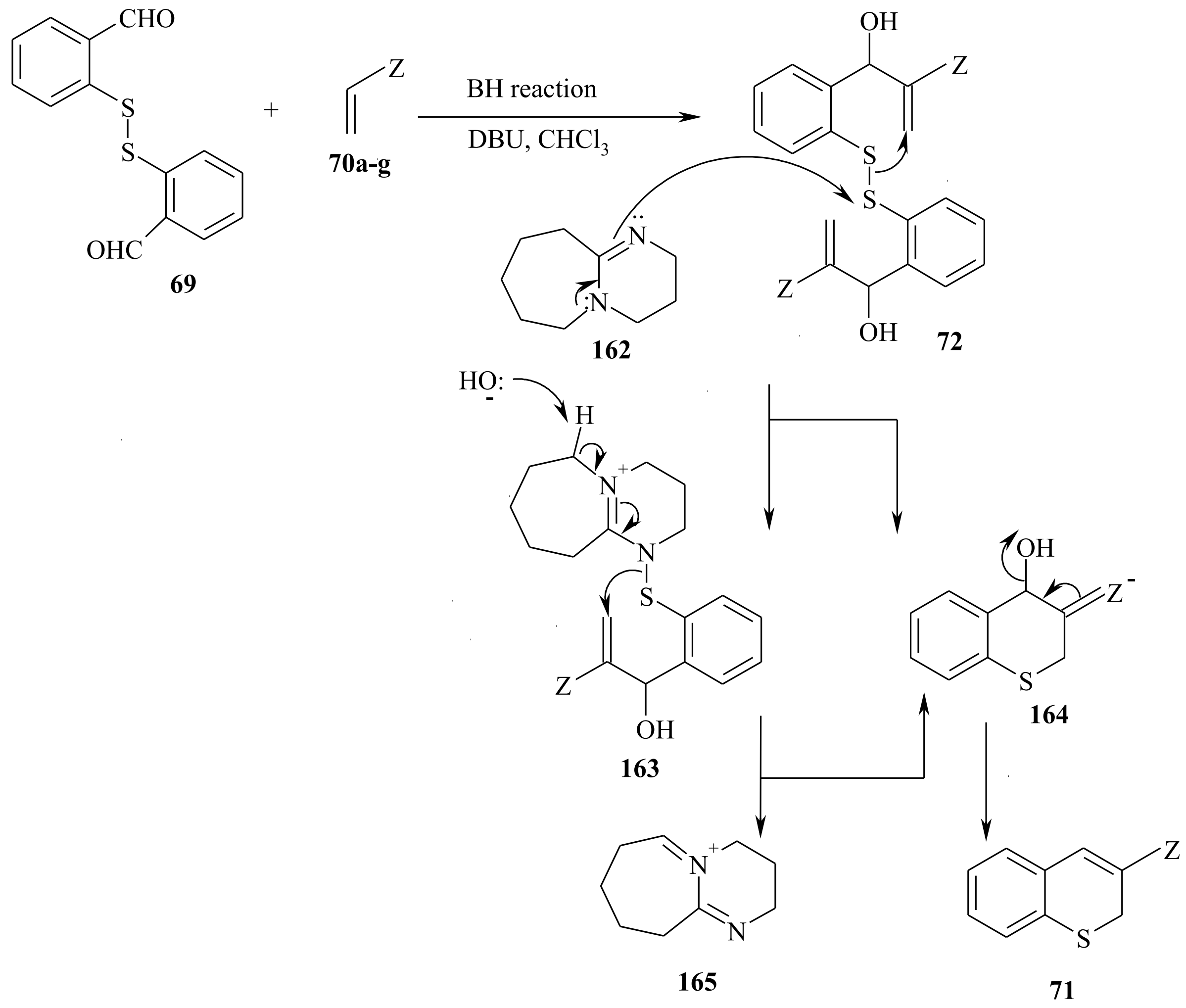
Having had success in extending the thiochromene system, by use of cyclic enones, it was decided to explore the use of a bicylic aldehyde precursor, as another route to extending the thiochromene system. Pardoe and co-workers[83] reported a procedure for the synthesis of various 2-mercaptobenzaldehydes, which involves the use of sulphur as an electrophile to quench *ortho*-lithiated intermediates, affording aryl thiols at low temperatures of -20 and -40°C. Using their approach, we attempted to synthesise 2-mercaptonaphthaldehyde **160** as a precursor for the BH reaction, to replace 2,2'-dithiodibenzaldehyde **69**. As illustrated in Scheme 30, 2-naphthaldehyde **159** was reacted with butyl lithium (2.5M in hexane) and *N,N,N'*-trimethyl-1,2-ethylenediamine in dry THF at -20°C for 24h, after which the mixture was cooled to -40°C and treated with sulphur, and stirred for a further 3h. Quenching of the mixture with 2M-HCl followed by aqueous workup, afforded a pale pink oil, with a very strong unpleasant smell, characteristic of thiols, which we assumed to be compound **160**. Due to the unstable nature of compounds such as **160 (**as reported by Pardoe and co-workers[83]), compound **160** was used immediately in the BH reaction without any purification. In a BH reaction, 2-mercaptonaphthaldehyde **160** was reacted with MVK and DBU in chloroform (Scheme 30). However, ^{1}H NMR analysis of the crude product did not show any signals corresponding to either of the two possible products **161a** and **161b.**



Scheme 30

2.2 Preliminary kinetic study of the Baylis-Hillman synthesis of thiochromenes.

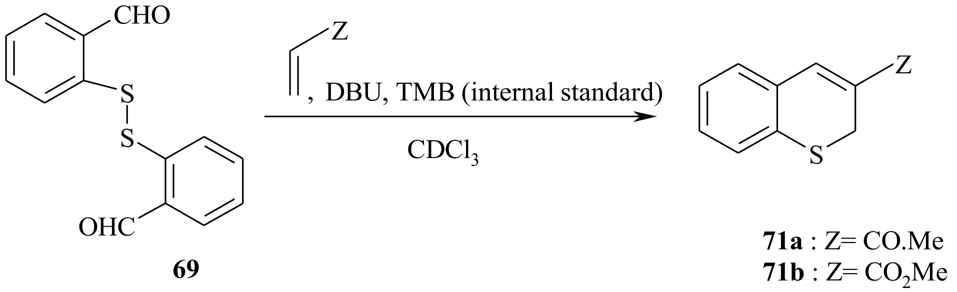
In the initial report,[3] a mechanism was proposed for the synthesis of thiochromenes *via* the BH methodology. The proposed mechanism which accounts for the observed *in situ* reduction of the disulphide **72** is outlined in Scheme 31. It was suggested that nucleophilic fission of the BH disulphide **72** by DBU or hydroxide ion (eliminated in turn from intermediate **164**) was responsible for the reductive cleavage of the sulphur species **72**, while elimination of the catalyst and cyclisation of intermediate **163** was facilitated by the nucleophilicity of the sulphur species. In the proposed mechanism, the catalyst DBU **162** is not regenerated; an iminium ion **165** is formed instead.



Scheme 31[3]

2.2.1 Kinetic Studies

Preliminary kinetic studies aimed at understanding the formation of the thiochromenes **71** as well as the thioxanthones **156** and **158**, were carried out. However, despite the attention given in this study to this reaction, its mechanism is still far from being understood. The progress of the reaction was monitored using ^{1}H NMR integral ratios of selected signals corresponding to 2,2'-dithiodibenzaldehyde **69**, MVK **70a** and DBU **162**, against those of the internal standard, 1,3,5-trimethoxybenzene (TMB) which formed part of the reaction mixture. Kinetic runs were carried out in $CDCl_3$, which was purified prior to use according to a literature procedure,[84] in which $CDCl_3$ is passed through neutral alumina and crushed 4Å molecular sieves under N_2 to remove any hydrochloric acid that may have formed. All kinetic runs were carried out in 1ml graduated NMR tubes.



Scheme 32

Following Scheme 32, reactant mixtures were initially prepared in a molar ratio of 1:3:0.7 (dialdehyde **69**: MVK: DBU). A $CDCl_3$ solution of aldehyde **69**, MVK and TMB was prepared in a 3ml volumetric flask. A known volume of this solution was then transferred into a graduated NMR tube, into which DBU was added. This approach gave problems in that it appeared from the ^1H NMR spectra that the aldehyde signal, which appears at 10.22 ppm, had disappeared within the first 10 minutes of the reaction. This implied that the reaction was probably occurring too fast as a result of the high DBU concentration, which seemed unlikely given the typically slow reaction rates of BH reactions. Another possibility was that DBU was masking the aldehyde. It was then decided to attempt the reaction without any catalyst, but results obtained after 18h showed that nothing at all had happened, emphasizing the need for a catalyst particularly in this case, where DBU is envisioned to be taking part in a series of intermediate steps leading to the formation of the thiochromenes **71** (Scheme 31).

A different approach was then adopted, which was aimed at slowing down the reaction to enable the progress to be followed, as well as obtaining accurate, reproducible data. This approach involved the use of a 5-decimal point balance in weighing out all the substrates. For the first duplicate kinetic runs (Experiments 1a and 1b), using this approach, molar ratios of 1:2.4:1 (aldehyde: MVK: DBU) were used. Two stock solutions, **A** and **B**, were prepared in 1ml volumetric flasks. Stock solution **A** contained, 2,2'-dithiodibenzaldehyde

69, MVK and TMB in $CDCl_3$, while stock solution **B** contained DBU in $CDCl_3$. Using a 250μl syringe, equal volumes of solutions **A** and **B** were transferred into a graduated 1ml NMR tube. The reaction was run on a 400MHz NMR spectrometer, with 5min intervals between spectra. Duplicate runs were carried out, and Table 1 shows the ratios of the reactants as well as the initial concentrations in the different experiments/kinetic runs. Experiments 4a and 4b were carried out using methyl acrylate in place of MVK. A stacked ^1H NMR plot (Fig. 13) shows the progress of the reaction for Experiment 1a with the aldehyde signal at 10.22 ppm disappearing rapidly.

Table 1. Ratios of reactants and their initial concentrations.

Experiment	Ratio of reactants ArCHO:MVK:DBU:TMB	Initial[ArCHO] /molL^{-1}	Initial[MVK] /molL^{-1}	Initial[DBU] /molL^{-1}	Initial[TMB] /molL^{-1}
1a	1: 2.4: 1: 0.4	0.20	0.49	0.21	0.08
1b	1: 2.4: 1: 0.4	0.20	0.49	0.21	0.08
2a	1: 5: 1: 0.4	0.20	1.05	0.20	0.07
2b	1: 5: 1: 0.4	0.20	1.05	0.20	0.07
3a	1: 10: 2: 0.7	0.11	1.05	0.20	0.07
3b	1: 10: 2: 0.7	0.11	1.05	0.20	0.07
4a‡	1:5.5:1:0.4	0.60	3.30	0.62	0.24
4b‡	1:5.5:1:0.4	0.60	3.30	0.62	0.24

---

‡ Experiments 4a and 4b were carried out using methyl acrylate in place of MVK.

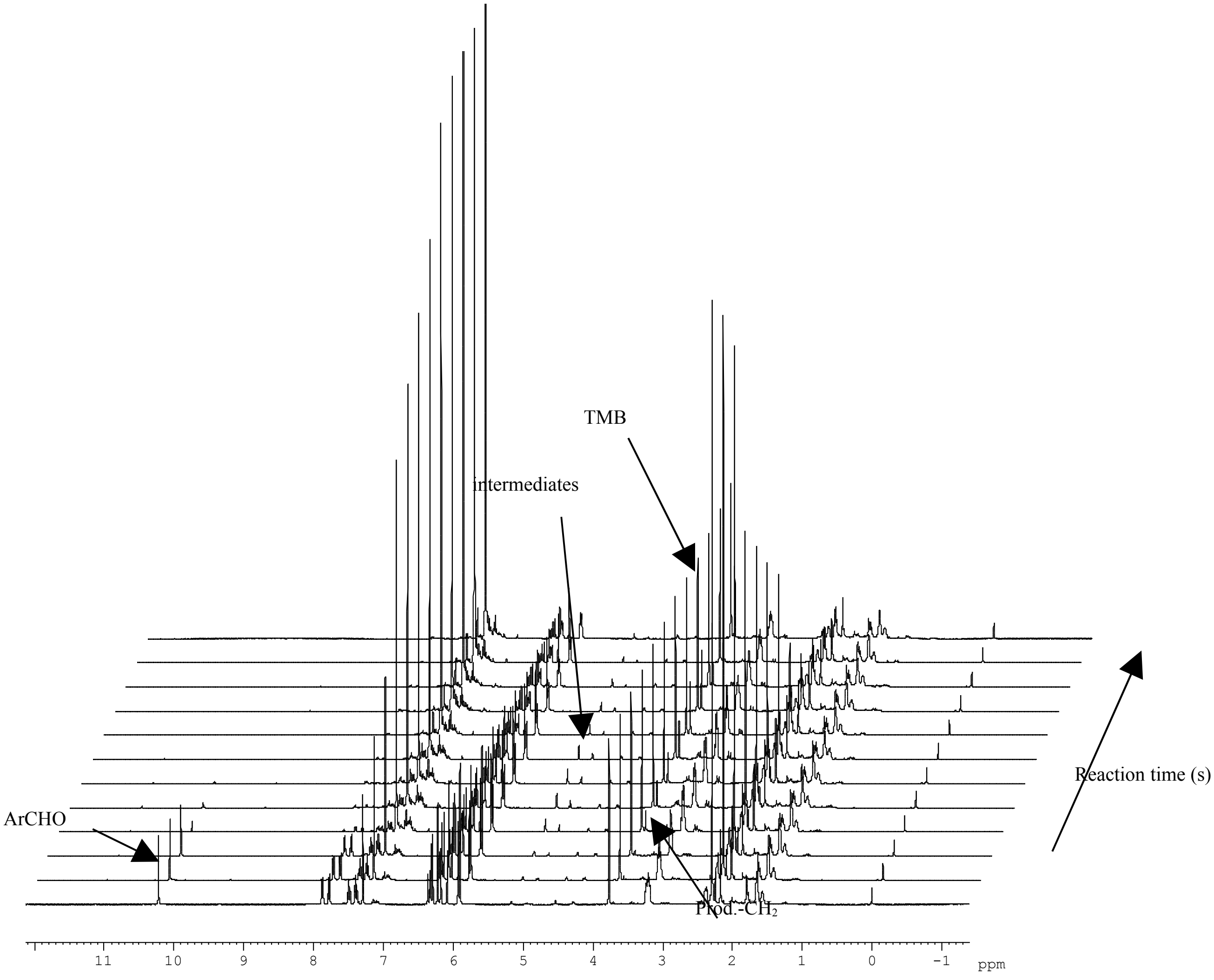


Figure 13. Stacked plot of ^{1}H NMR spectra for Experiment 1a (reaction with MVK).

At *ca.* 5.0 ppm there are 2 signals, which are not part of the starting reactants, that appear to increase in intensity and then decrease as the reaction progresses, indicating the possibility of formation of one or more intermediates. As mentioned earlier (Section 1.1.1), the proposed intermediates for the accepted BH mechanism (Scheme 2; Section 1.1.1), have not been isolated to date owing to their transient nature. In this study, isolation of any intermediates formed was not attempted. The appearance of a signal at *ca.* 3.7 ppm corresponding to the methylene signal of compound **71a**, is evident in the stacked plot (Fig. 13). The standard TMB signal at 3.73 ppm remains constant throught the reaction as expected. The ^{1}H NMR integral data were used to determine the rate of appearance of product or the rate of disappearance of the reactants. Using the formula below, integral data were converted to concentrations.

$$\left\{ \left(\frac{\text{Integral}}{\text{No. of protons}} \right) \div \left(\frac{\text{TMB integral}}{9} \right) \right\} \times \left[\text{TMB} \right]$$

Figure 14 shows a graph of concentration *versus* time for Experiment 1a. From the graph, the decrease in concentration of 2,2'-dithiodibenzaldehyde **69** as well as that of MVK is evident. Product formation is also evident, although the shape of its graph seems to suggest a reaction involving autocatalysis, which cannot be ruled out given the complexity of the reaction and the experimental results obtained. However, there appears to be little or no change in the concentration of DBU. The data for each run was corrected for a zero-time error.

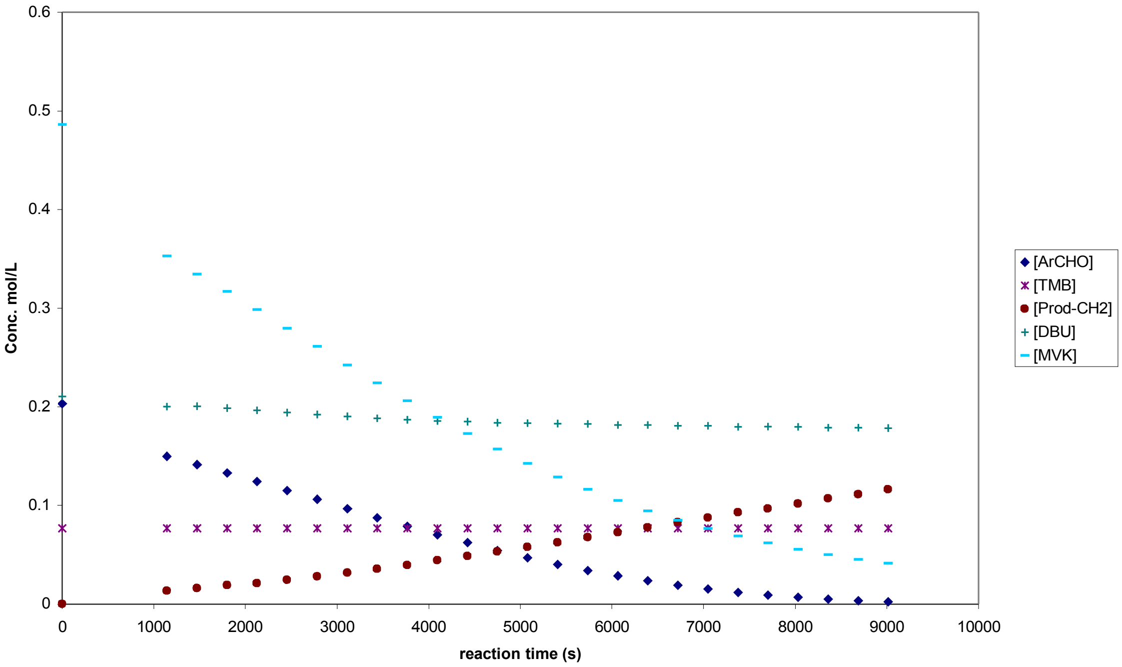


Figure 14. Plot of concentration *vs* time for Experiment 1a.

For the next set of duplicate runs (Experiments 2a and 2b), the MVK molar concentration was doubled, while the dialdehyde and DBU were maintained constant, *i.e* dialdehyde **69**:MVK:DBU::1:5:1. The concentration of the dialdehyde was observed to decrease more rapidly as its concentration had dropped to zero after only 3100s, compared to about 8000s in Experiment 1.

The molar concentration of 2,2'-dithiodibenzaldehyde **69**, was then reduced by half (i.e dialdehyde **69**:MVK:DBU::0.5:5:2; (Experiments 3a and 3b). A rapid decrease in the MVK concentration was observed, relative to that observed in Experiment 1, while there was no significant change in the rate of consumption of the aldehyde, and the curve for the formation of the product again exhibits a sigmoidal shape characteristic of autocatalysis.

Experiments 4a and 4b were carried out using methyl acrylate as the activated alkene, replacing MVK. Molar ratios equivalent to those used for Experiments 2a and 2b were used. Results obtained showed that the reaction was much slower compared to the one with MVK. Fig. 15 shows the rate of consumption of the reactants and it is evident that after more than 35000s the dialdehyde **69** had not been fully consumed. Drewes *et al.*[85] had earlier observed this slow reactivity of methyl acrylate and their results showed that MVK reacted 10-45 times faster than methyl acrylate.

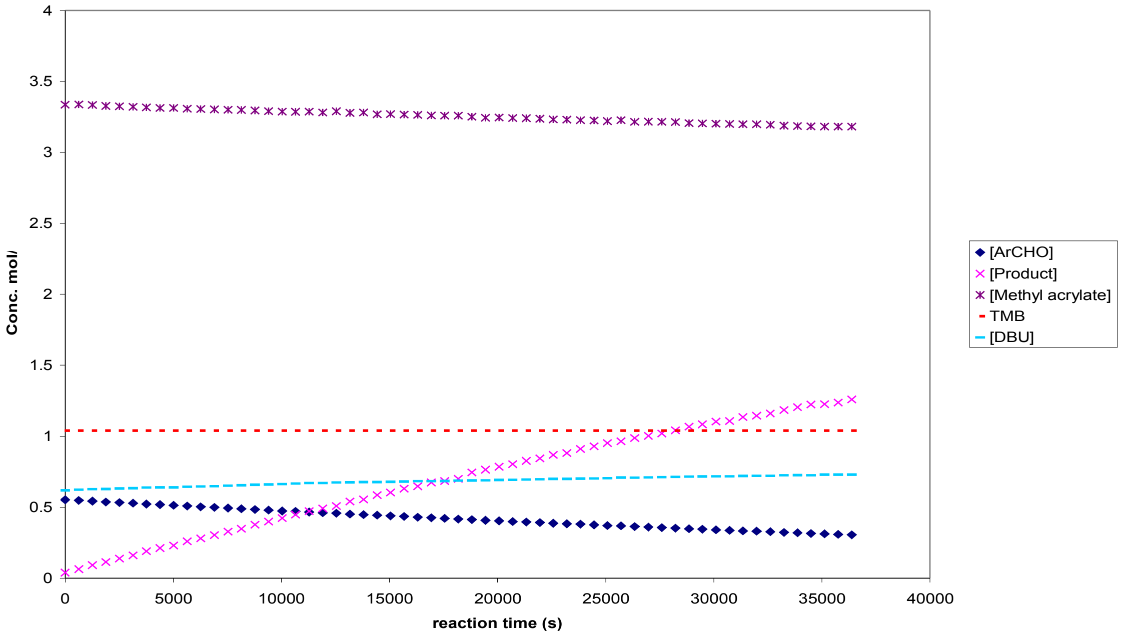


Figure 15. Plot of concentration *vs* time for Experiment 4b

Plots of ln[substrate] against time for each of the reactants, the dialdehyde **69**, MVK and DBU, failed to afford straight lines. In fact, none of the graphs obtained for all duplicate kinetic runs at different concentrations, appeared to follow either 1st- or 2nd-order kinetics (*e.g.*, Figs. 16-18). These observations indicated that the mechanism for the reaction under study was probably more complex than anticipated.

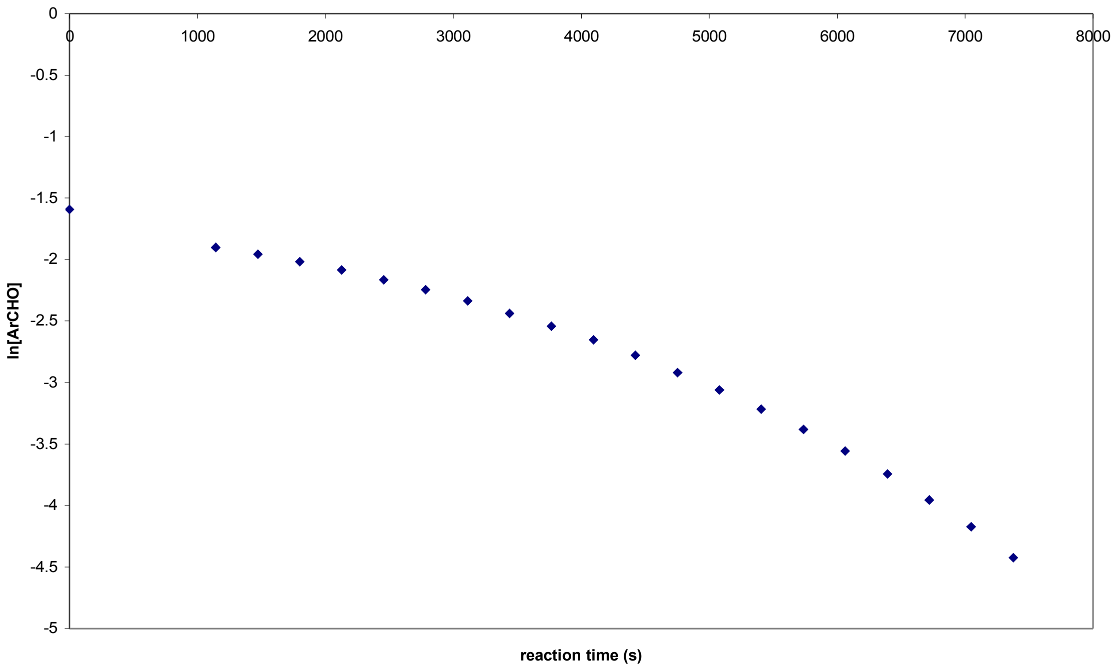


Figure 16. Plot of ln[aldehyde **69**] *vs* time for the consumption of the dialdehyde **69** in Experiment 1a.

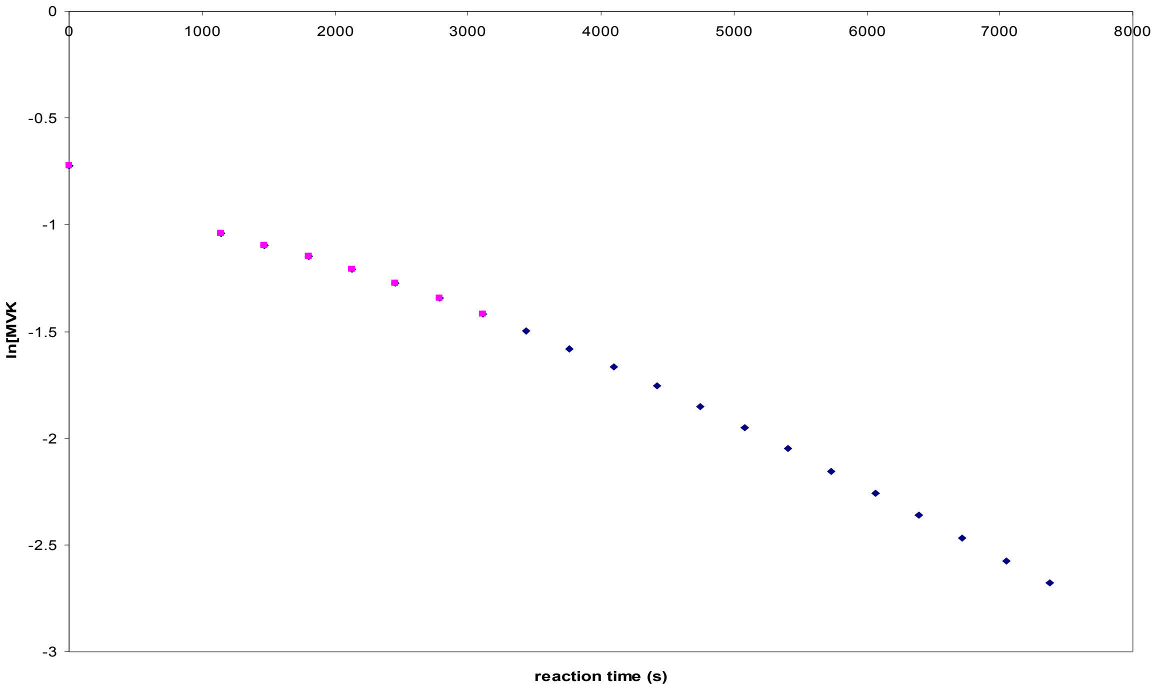


Figure 17. Plot of ln[MVK] *vs* time for the consumption of MVK in Experiment 1a.

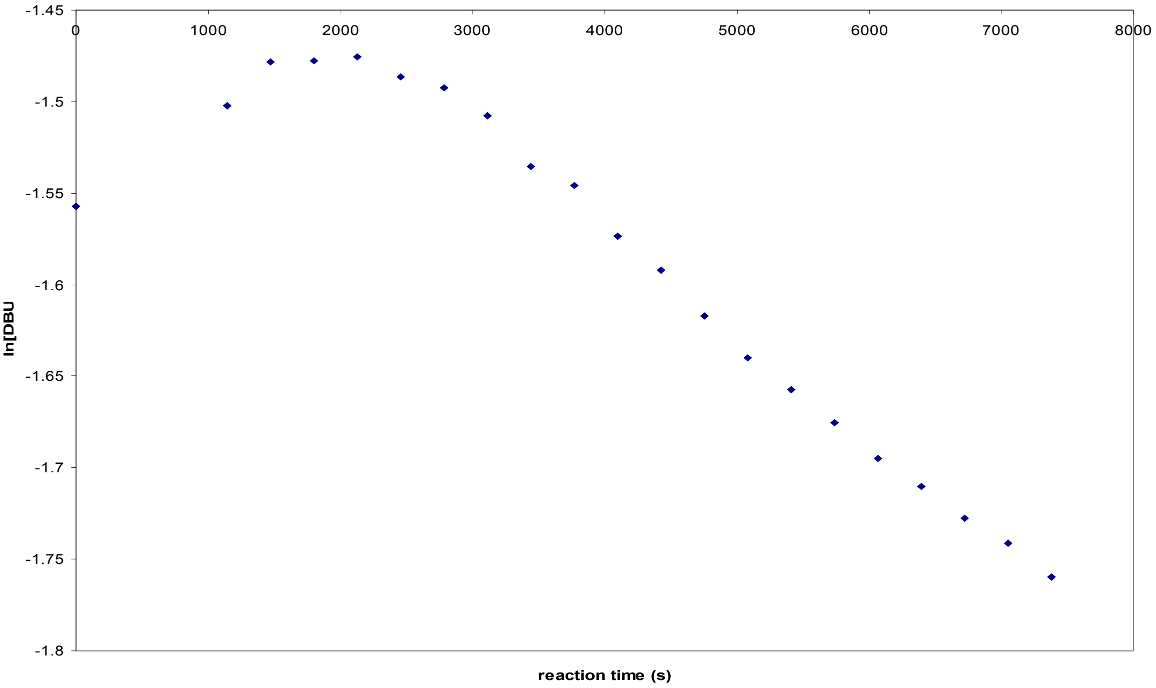


Figure 18. Plot of ln[DBU] *vs* time for the consumption of DBU in Experiment 1a.

It seems, however, that in the early stages of the reaction (*ca*. 4000s for Experiment 1), both the dialdehyde **69** and MVK obey 1st-order kinetics. A plot of the data for both the dialdehyde **69** and MVK over the initial 4000s (Experiment 1), 2000s (Experiment 2) and 3000s (Experiment 3) gave almost linear plots for all the three experiments; examples are shown in Figs. 19 and 20. The reaction with methyl acrylate (Experiments 4a and 4b) gave a linear plot in the dialdehyde for the initial 4000s Fig. 21.

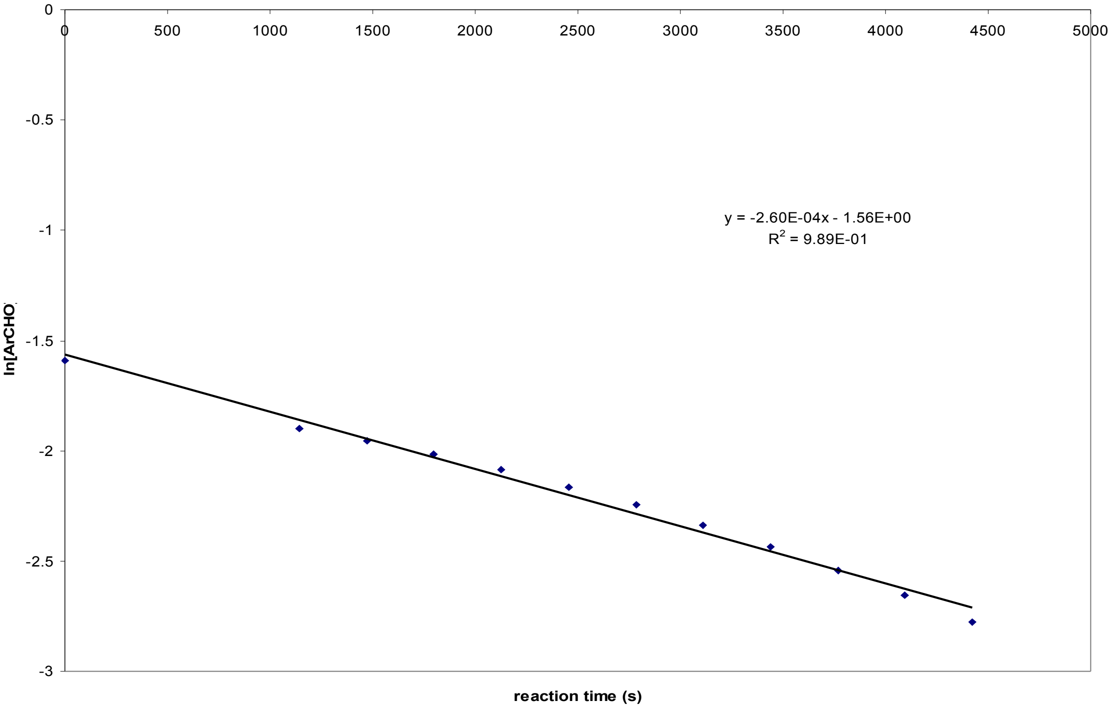


Figure 19. 1st-Order plot for the consumption of the dialdehyde **69** for the first 4500s from Experiment 1a.

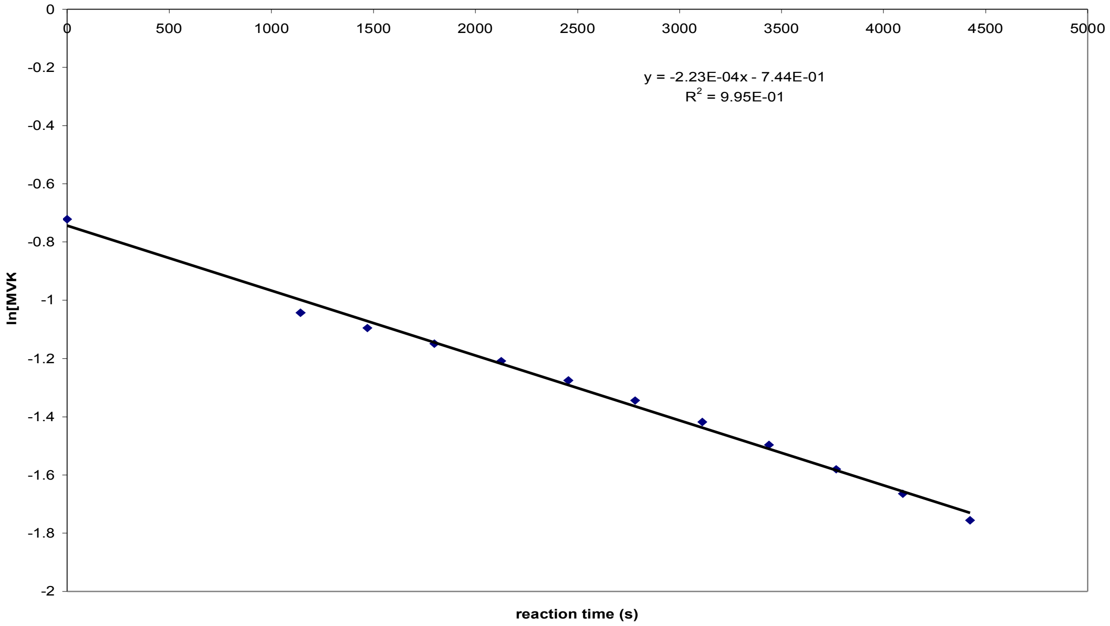


Figure 20. 1st-Order plot for the consumption of MVK for the first 4500s from Experiment 1a.

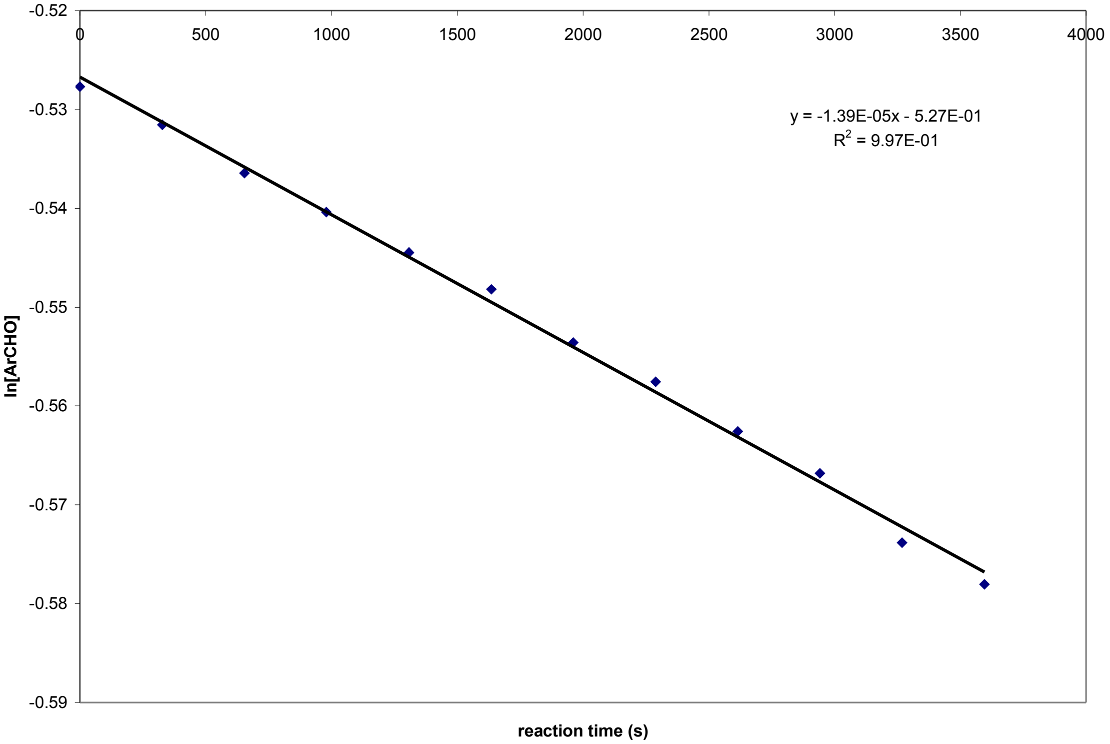


Figure 21. 1st-order plot for the consumption of dialdehyde **69** for the initial 4000s from Experiment 4a.

The observed deviation from linearity after *ca.* 4000s (Experiment 1) and 2000s and 3000s respectively for Experiments 2 and 3 could indicate the operation of competing reactions. Similar plots were obtained for Experiments 2 and 3 and the rate constants were calculated for the consumption of the dialdehyde **69** and MVK during the initial stages. Table 2 summarises the observed kinetic data and shows the reproducibility of the results in the duplicate runs *e.g.* Experiments 1a and 1b:

Table 2. Summary of the 1st-order kinetic data for BH reactions of the dialdehyde **69** and the activated alkenes MVK and methyl acrylate (Scheme 32).

Experiment	Initial [ArCHO]	Initial [MVK]	$-k_{ArCHO}$ x10^{-4} /s^{-1}	$-k_{MVK}$ x10^{-4} /s^{-1}	$-k_{methylacrylate}$ x10^{-4}/s^{-1}
1a **1b**	0.20 0.20	0.49 0.49	2.60 2.52	2.23 2.45	
2a **2b**	0.20 0.20	1.05 1.05	4.28 4.12	2.04 2.14	
3a **3b**	0.11 0.11	1.05 1.05	4.21 3.80	1.95 2.30	
4a **4b**	0.60 0.60	3.30 3.30	0.14 0.15		0.015 0.017

From the observed kinetic data the following conclusions can be drawn:

i) The rate of consumption of the aldehyde **69** is affected significantly by the concentration of MVK but not *vice versa* (Experiments 1 and 2, Table 2).

ii) The reaction with MVK is much faster than with methyl acrylate (Experiments 2 and 4, Table 2), a result that had earlier been observed by Drewes *et al.*[85] The slow reactivity of methyl acrylate in comparison to MVK can be attributed to the reduced electrophilicity of the terminal vinylic centre due to the net electron–releasing effect of the methoxy oxygen.

iii) The overall reaction is more complex than originally anticipated.

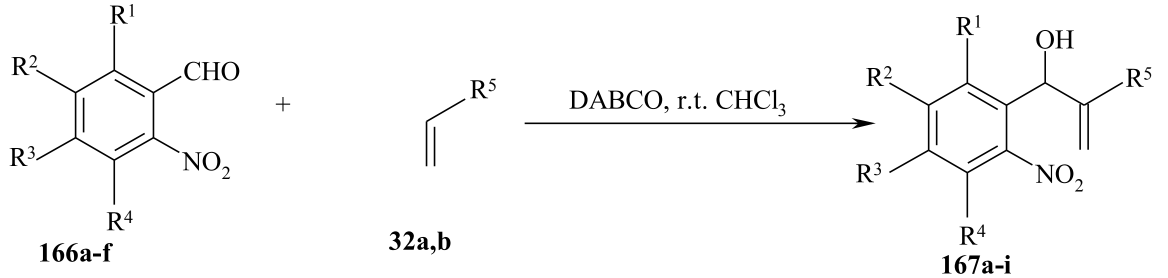
A detailed investigation of this reaction will form part of a proposed PhD programme.

2.3 Application of the Baylis-Hillman reaction in the synthesis of 2-quinolone derivatives.

2.3.1 Synthesis of 2-nitrobenzaldehyde BH adducts

This research is a continuation of work previously initiated in our group,[11] but this study focuses more on the methyl acrylate-derived 2-nitrobenzaldehyde BH adducts, which have been shown to afford the 2-quinolone nucleus on cyclisation,[8,11,12,86] rather than quinoline derivatives, as mentioned earlier (Section 1.2.1). 2-aminobenzaldehydes, which are common precursors in quinoline syntheses are relatively inaccessible, and thus the use of 2-nitrobenzaldehydes is a much simpler approach to the quinoline nucleus.

A range of substituted 2-nitrobenzaldehydes **166a-f**, were reacted with the activated alkenes **32a,b** under standard BH reaction conditions with DABCO as catalyst and $CHCl_3$ as solvent (Scheme 33).



166a-f **32a,b** **167a-i**

	R^1	R^2	R^3	R^4
a	H	H	H	H
b	H	Cl	H	H
c	H	$-OCH_2O-$		H
d	H	H	H	OMe
e	Cl	H	H	H
f	H	H	NO_2	H

	R^5
a	COMe
b	CO_2Me

	R^1	R^2	R^3	R^4	R^5
a	H	H	H	H	COMe
b	H	Cl	H	H	COMe
c	H	$-OCH_2O-$		H	COMe
d	H	H	H	H	CO_2Me
e	H	H	H	OMe	CO_2Me
f	Cl	H	H	H	CO_2Me
g	H	$-OCH_2O-$		H	CO_2Me
h	H	H	NO_2	H	CO_2Me
i	H	Cl	H	H	CO_2Me

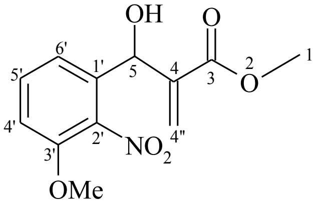
Scheme 33

Table 3. Table showing the yields of the BH products **167a-i** (Scheme 33)

Compound No.	Isolated yield %	M.p. / ºC
167a	75	80-82
167b	95	77-79
167c	60	97-99
167d	57	Oil
167e	65	108-109
167f	86	99-100
167g	15	121-123
167h	92	62-64
167i	Not isolated	-

The BH products **167a-h** were afforded in moderate to excellent yields (Table 3), the only exceptions being compounds **167g** and **167i**. Compound **167g** was isolated in 15% yield after 32days. Pakade[47] observed yield increases of some BH adducts when the alkene and catalyst were stirred together for a while prior to addition of the aldehyde. Using this approach, attempts to increase the yield of **167g** were carried out by stirring methyl acrylate and DABCO in $CHCl_3$ for 1h prior to the addition of the aldehyde, 4,5-methylenedioxy-2-nitrobenzaldehyde **166c**. According to the generally accepted BH mechanism illustrated in Scheme 2 (Section 1.1.1), the first step involves conjugate addition of the nucleophilic catalyst to the activated alkene. It was envisioned that reacting methyl acrylate and DABCO prior to aldehyde addition would facilitate this step. The reaction was monitored by TLC and after 21days it seemed there was still a lot of the starting material **166c** and very little product. The low yield obtained for compound **167g** was attributed to the less reactive methyl acrylate as compared to MVK, which gave the 4,5-methylenedioxy-BH adduct **167c** in 60% yield. The ^{1}H NMR spectrum of crude **167i** showed weak signals corresponding to the product, but attempts to isolate the product were not successful.

Compound **167e** was obtained as colourless crystals, which crystallized out of the reaction solution. BH products are characterized by two separate vinylic proton signals at *ca*. 6 ppm, which appear as singlets. The ^{1}H NMR spectrum of compound **167e** (Fig. 22), shows the vinylic proton signals at 5.86 and 6.41 ppm, with the methine proton resonating at 5.63 ppm. The ^{13}C NMR spectrum (Fig. 23) shows the carbonyl carbon signal at 166.1 ppm and the methine carbon at 68.3 ppm. The vinylic methylene carbon (C-4'') which is evident in the DEPT 135 spectrum (Fig. 24) resonates at 127.4 ppm.



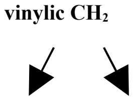


Figure 22. 400MHz ^1H NMR spectrum of compound **167e** in $CDCl_3$. (Structure numbered for convenience of signal assignment rather than systematically)

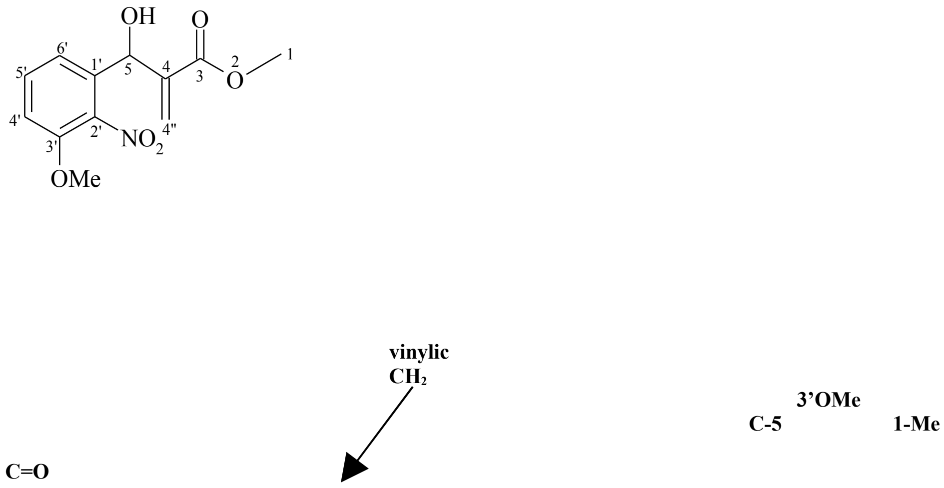


Figure 23. 100MHz ^{13}C NMR spectrum of compound **167e** in $CDCl_3$.

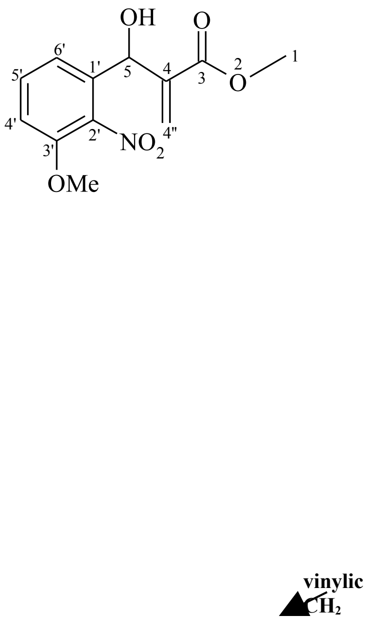
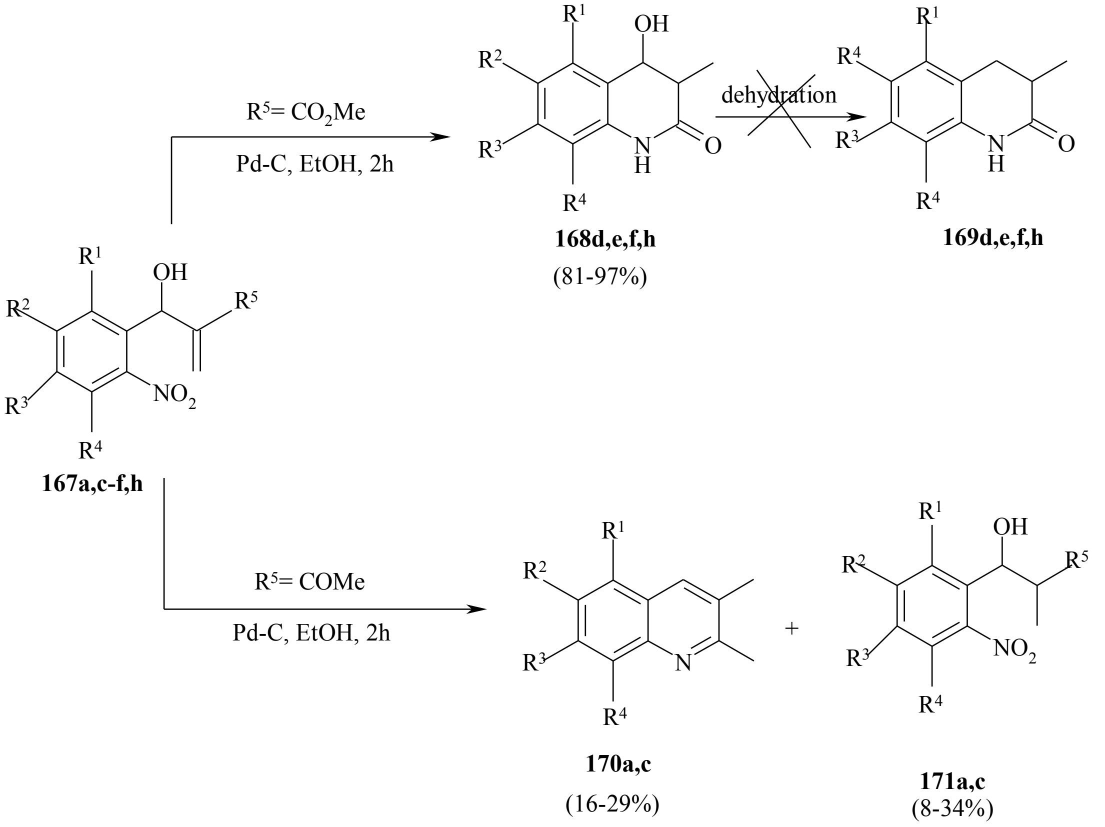


Figure 24. 100MHz DEPT-135 spectrum of compound 1**67e** in $CDCl_3$

2.3.2 Catalytic hydrogenation of the BH adducts

Catalytic hydrogenation of 2-nitrobenzaldehyde BH adducts, using a palladium-on-carbon (Pd-C) catalyst, as mentioned earlier (Section 1.2.1), results in reduction of the nitro group to the amine, with subsequent intramolecular cyclisation to the quinoline derivatives. The cyclisation as reported by Kaye and co-workers[8] was expected to follow two possible pathways (Scheme 5, Section 1.2.1). Path I involves conjugate addition to the vinylic carbon, affording 3-substituted-4-hydroxy-quinolines **35**. Path II involves nucleophilic attack on the carbonyl carbon, giving a tetrahedral intermediate **37**, and, depending on the nature of the activated alkene used, could afford either quinolines or 2-quinolones. MVK-derived BH adducts afforded quinolines **41**, quinoline-*N*-oxides **42** and nitro derivatives **43**, while the methyl acrylate-derived BH adducts afforded 2-quinolones (**38-40**). In the present study both MVK- and methyl acrylate-derived BH adducts were subjected to catalytic hydrogenation, using a Pd-C catalyst and ethanol as solvent (Scheme 34).



Scheme 34

The methyl acrylate-derived BH adducts **167d, e** and **f**, afforded the 4-hydroxy-3-methyl-2-quinolones **168d,e** and **f** in excellent yields of 87, 97 and 81%, respectively. Compound **167h**, however, gave the corresponding cyclised product **168h** in very low yield of 15%. Initially it was thought that the products obtained were the dehydrated products **169d,e,f** and **h**. However, the ^{1}H NMR spectrum of compound **168e** (Fig. 25) shows a doublet at 4.74 ppm which would not be expected for compound **169e**, as the 4-methylene protons would be diastereotopic and give rise to a pair of double of doublets. The ^{13}C NMR spectrum (Fig. 26), shows a signal resonating at 70.8 ppm, which was too far upfield for a methylene carbon (C-4, compound **169e**). The DEPT 135 spectrum (Fig. 27) did not show any methylene signal, which was further evidence that the compound was in fact **168e** and not **169e**. IR and 2D-NMR spectra were also used to elucidate the structure, an IR absorption band at 3366cm^{-1} indicated the presence of a hydroxyl group. The other BH adducts **167d,f** and **h** also gave the respective hydroxylated products **168d,f** and **h**. The MVK-derived BH adducts afforded the quinolines **170a** and **c** as well as the nitro derivatives **171a** and **c**; the yields, however, were quite low.

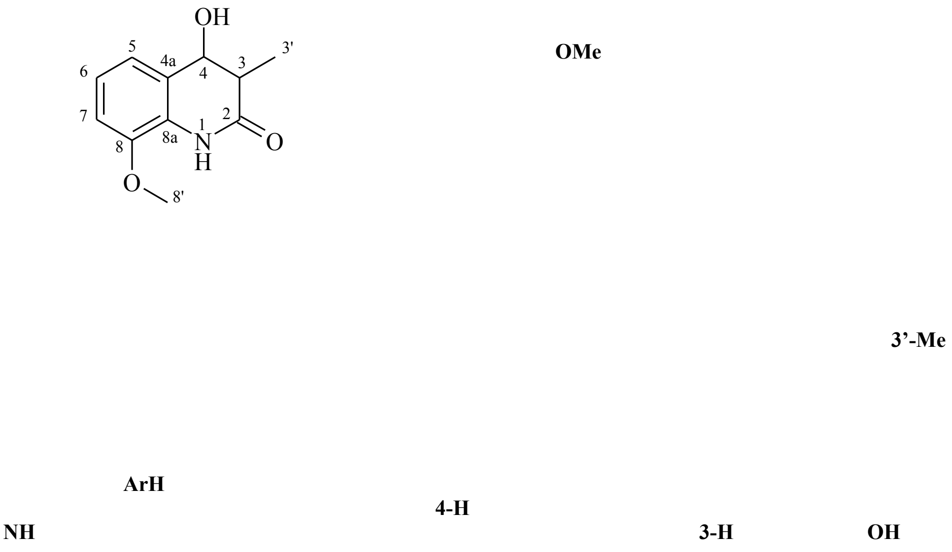


Figure 25. 600MHz ^{1}H NMR spectrum of compound **168e** in $CDCl_3$.

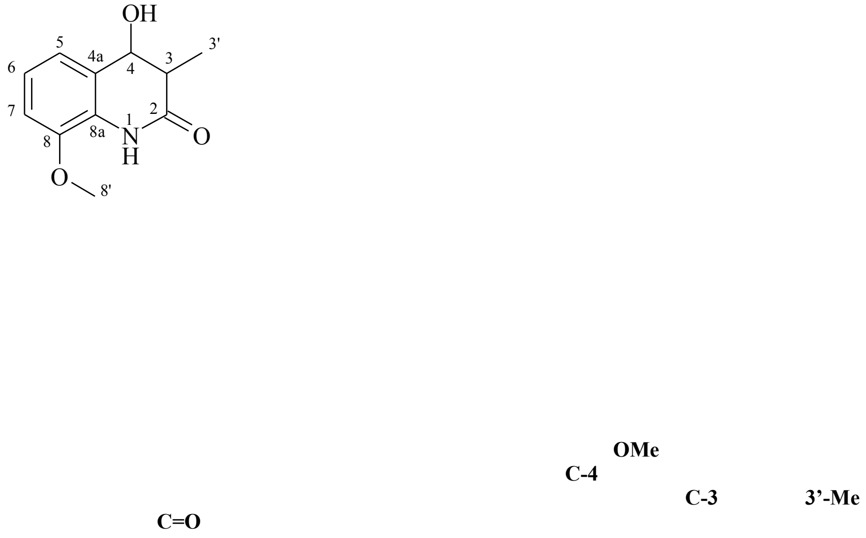


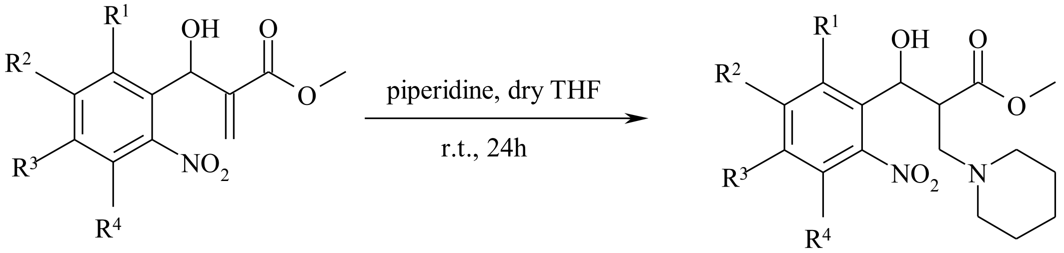
Figure 26. 150MHz ^{13}C NMR spectrum of compound **168e** in CDCl$_3$.

Figure 27. 150MHz DEPT-135 spectrum for compound **168e** in CDCl$_3$.

2.3.3 Reaction of Baylis-Hillman adducts with amines

2.3.3.1 Reaction of BH adducts with piperidine.

The series of methyl acrylate-derived 2-nitrobenzaldehyde BH adducts **167d,e,g** and **h**, were reacted with piperidine in dry THF for 24h (Scheme 35). Purification of the crude products using flash chromatography afforded the expected conjugate addition products **172d,e,g** and **h**, as diastereomeric mixtures in excellent yields as shown in Table 4, the only exception being **172h**, which was obtained in 32% yield. As expected the reaction of the chiral BH adducts with piperidine resulted in the formation of a new stereocenter at C-4. The composition of the diastereomeric products **172d,e,g** and **h** is given in Table 4, calculated from integrals of ^{13}C NMR signals of the major diastereomer relative to the minor diastereomer.



167d,e,g,h

172d,e,g,h

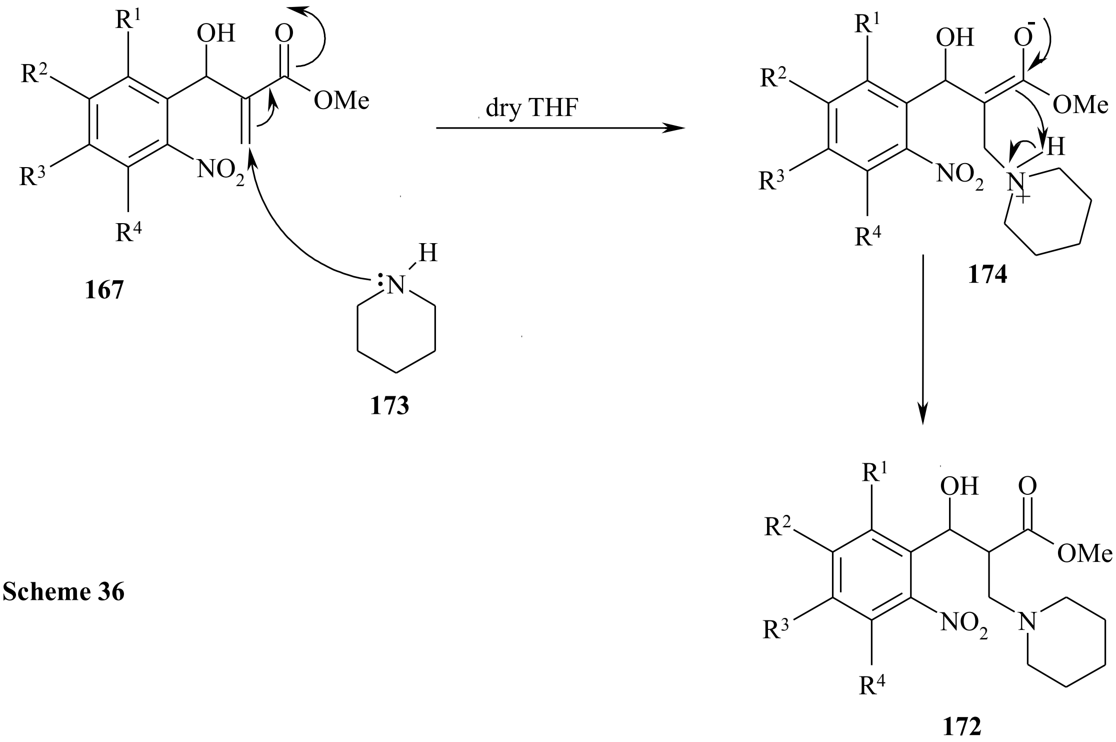
	R^1	R^2	R^3	R^4
d	H	H	H	H
e	H	H	H	OMe
g	H	-OCH$_2$O-		H
h	H	H	NO$_2$	H

Scheme 35

Table 4. Composition of diastereomeric products **172**.

Compound No.	Major diastereomer/ %	Minor diastereomer/ %	Overall Yield/ %
172d	88	12	84
172e	75	25	80
172g	91	9	100
172h	83	17	32

The mechanism for the formation of the diastereomeric products **172d,e,g** and **h** involves the conjugate addition of piperidine **173** to the vinylic carbon of the BH adduct **167** as illustrated in Scheme 36.



Scheme 36

The ^{1}H NMR spectrum (Fig. 28) of the diastereomeric mixture **172d** shows considerable splitting of signals, attributed to the presence of the two stereogenic centres at C-4 and C-5, as well the formation of mixtures of diastereoisomers. It is also evident that the vinylic proton signals characteristic of BH products, which appear *ca.* 6 ppm, have disappeared. The 4-H nucleus resonates as a double doublet of doublets (ddd) resonating at 3.17 ppm, with the corresponding carbon signal (Fig. 29) resonating at 51.8 ppm. Similar NMR patterns were exhibited by the analogous products **172e,g** and **h**. IR and HRMS data were used to further confirm the identity of the conjugate addition products **172d,e,g** and **h**.

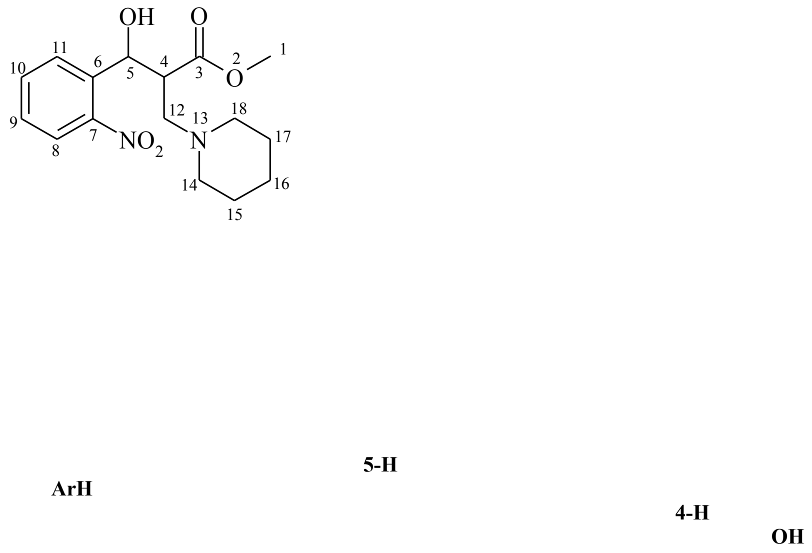


Figure 28. 600MHz ^{1}H NMR spectrum of the diastereomeric products **172d** in CDCl$_3$.

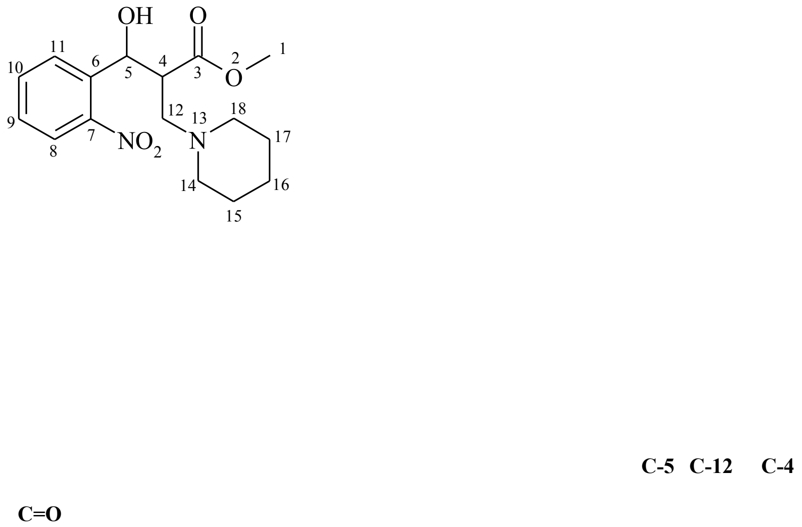
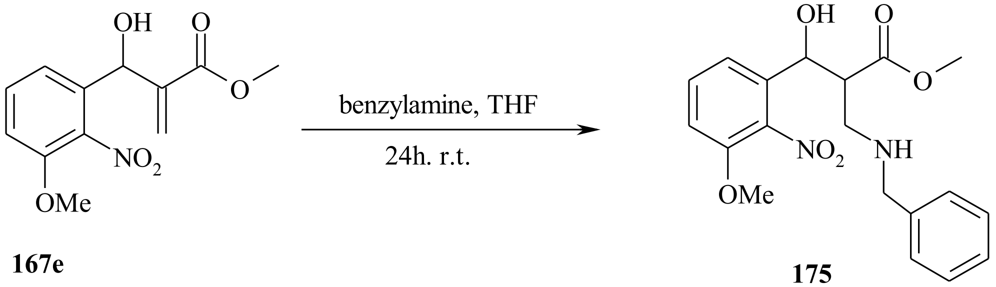


Figure 29. 150MHz ^{13}C NMR spectrum of the diastereomeric products **172d** in CDCl$_3$.

2.3.3.2 Reaction of BH adduct 168e with benzylamine.

The BH adduct **167e** was reacted with benzylamine in dry THF for 24h to afford the diastereomeric product **175** in 94% yield (Scheme 37). The ^1H NMR spectrum (Fig. 30), however, revealed two doublets *ca.* 5 ppm corresponding to the two methine (5-H_a and 5-H_b) protons of the diastereomers present in the mixture. The aromatic region shows overlapping signals corresponding to the two benzene rings. The ^{13}C NMR spectrum (Fig. 31) confirms the presence of diastereomers as evidenced by signals appearing in pairs, *e.g* two carbonyl signals at 172.5 and 172.9 ppm. From a comparison of relative ^1H integrals and ^{13}C signal intensities for corresponding nuclei; the diastereomeric excess was estimated to be 60%. Experimental data for the diastereomeric compounds **172d,e,g** and **h** as well as **175** (Section 3.3), were cited for the major diastereomer in each case.



Scheme 37

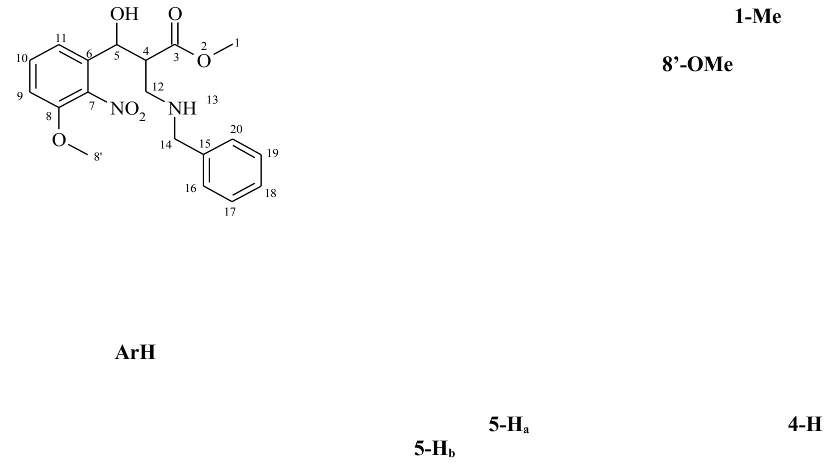


Figure 30. 600MHz ^{1}H NMR spectrum of compound **175** in CDCl$_3$ (5H$_a$ and 5H$_b$ refer to corresponding protons in the diastereomeric products).

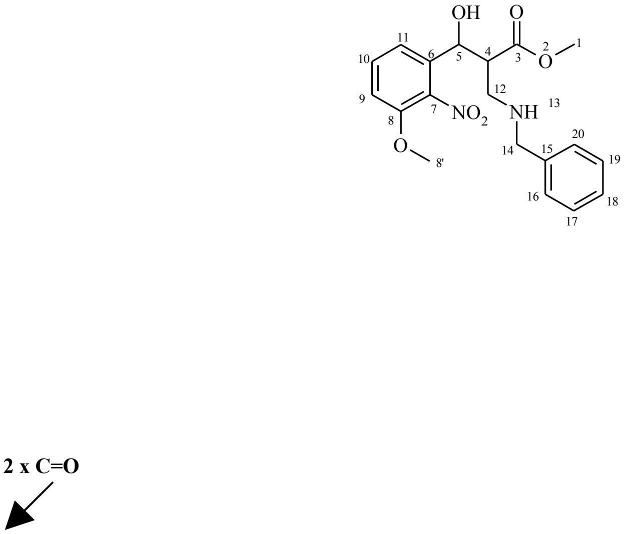
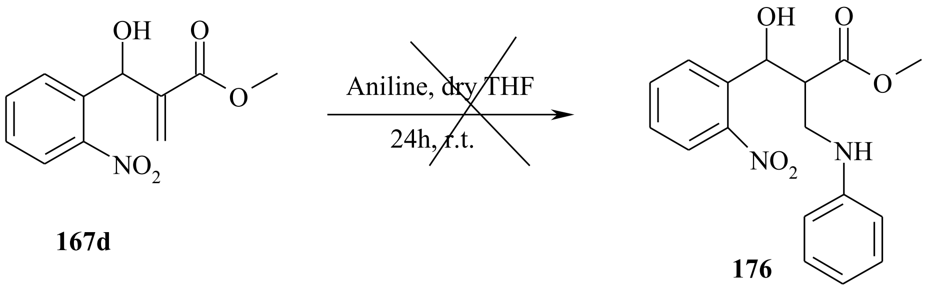


Figure 31. 150MHz ^{13}C NMR spectrum of compound **175** in CDCl$_3$.

2.3.3.3 Reaction of BH adduct 167d with aniline.

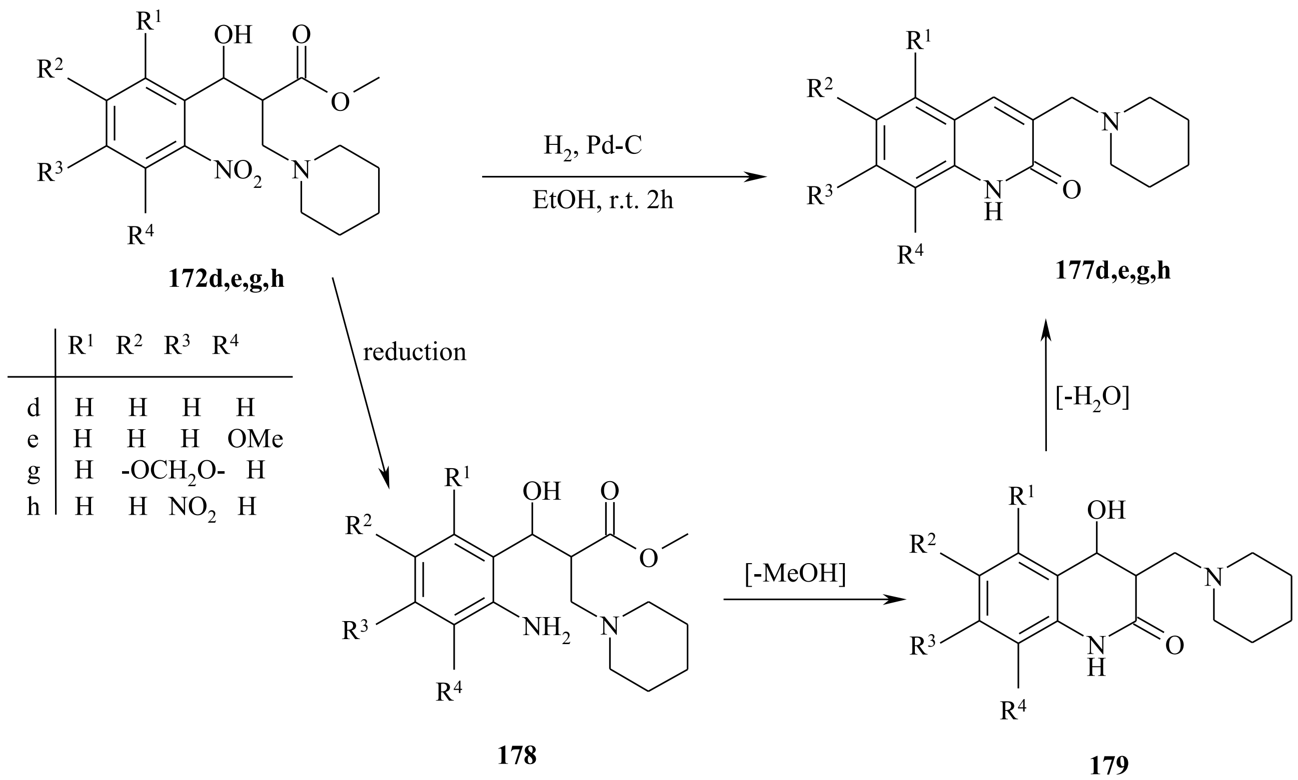
The conjugate addition reaction of BH adduct **167d** with aniline in THF failed to give the expected product **176** after 24h (Scheme 38). ^{1}H NMR analysis of the crude reaction mixture revealed that only starting material **167d** was present – a result attributed to the reduced nucleophilicity of the arylamino nitrogen.



Scheme 38

2.3.4 Catalytic hydrogenation of conjugate addition products.

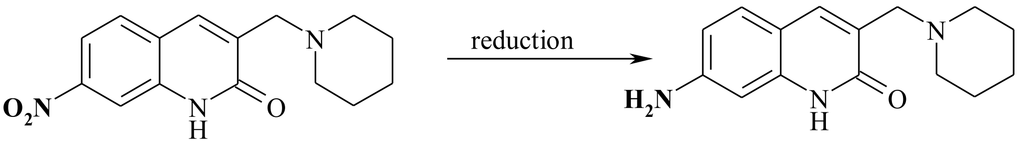
Compounds **172d,e,g** and **h** were subjected to catalytic hydrogenation using a Pd-C catalyst in ethanol (Scheme 39). Purification of the crude products by flash chromatography afforded the 3-amino-2-quinolones **177d,e,g** and **h** in low yields of 22, 36, 37 and 32%, respectively. Formation of these products involves reduction of the nitro group to the amine, followed by intramolecular cyclisation to the corresponding 2-quinolone. The cyclisation appears to occur *via* nucleophilic attack at the carbonyl carbon.



	R^1	R^2	R^3	R^4
d	H	H	H	H
e	H	H	H	OMe
g	H	$-OCH_2O-$		H
h	H	H	NO_2	H

Scheme 39

The 4-nitro-group in compound **172h** appeared to have been reduced to the amine during the reductive cyclisation, resulting in the formation of a 7-amino-substituted-2-quinolone **180** (Scheme 40) and not the expected 7-nitro-substituted-2-quinolone **177h**. Low resolution mass spectrometry showed a peak corresponding to the molecular ion of compound **180** and none corresponding to **177h**. The ^{1}H NMR spectrum of compound **177e** (Fig. 32) exhibits sharp signals in contrast to those exhibited by the conjugate addition products **172** (Fig. 28). This can be attributed to the disappearance of the two chiral centres in the substrate at C-4 and C-5. The amide proton in compound **177e** resonates at 9.13 ppm, while the carbonyl carbon resonates at 161.9 ppm (Fig. 33). To further elucidate the structures, 2D-NMR and HRMS data were used.



177h **180**

Scheme 40

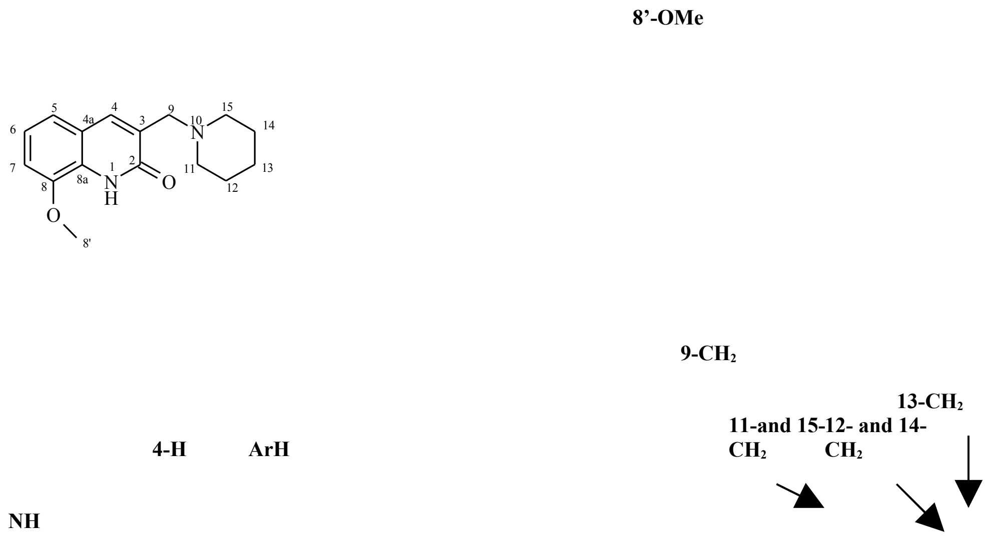


Figure 32. 600MHz ^{1}H NMR spectrum of compound **177e** in $CDCl_3$.

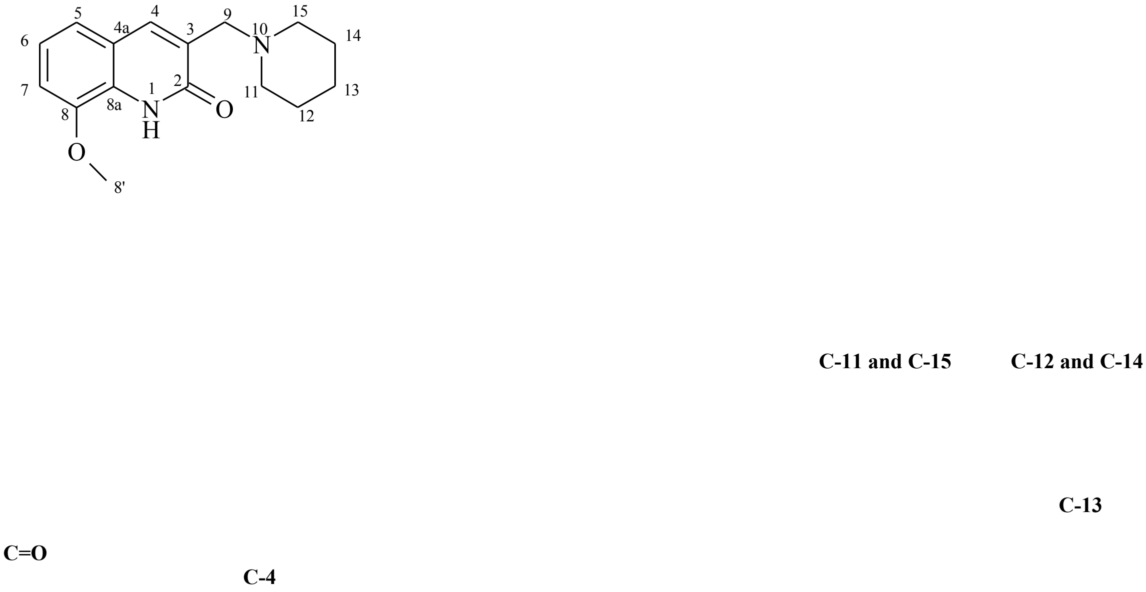


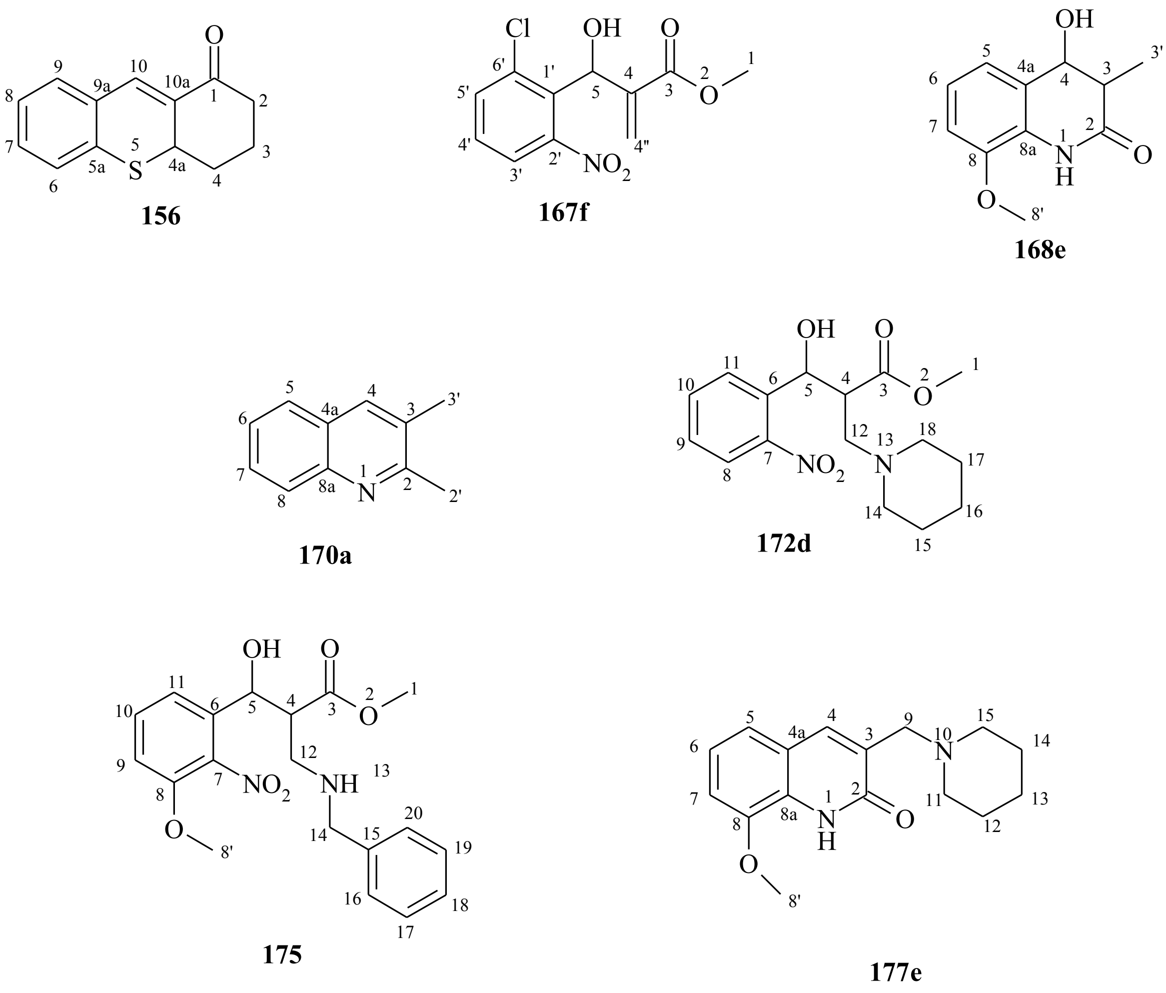
Figure 33. 150MHz ^{13}C NMR spectrum of compound **177e** in $CDCl_3$.

2.4 Application of ^{13}C NMR chemical shift prediction programmes.

Three NMR chemical shift prediction methods were used to predict ^{13}C chemical shifts on selected compounds synthesized in this study. The MODGRAPH neural network and HOSE (hierarchically ordered spherical description of environment) methods[86] and the ChemWindow prediction option were used. Application of these prediction methods helped to confirm the chemical shift values that had been assigned, as well as permitting some assessment of the relevance of the different methods in this class of compounds.

Comparison of the experimental and predicted values for the selected compounds reveal generally good correlations, although in each case one or other method worked better. To obtain a clearer insight into the correlation between the experimental and predicted values, root mean square (RMS) values were calculated in each case. The smaller the RMS value, the smaller the deviation of experimental shift values from the predicted values and the better the correlation. From the RMS values in (Tables 5-11), it is evident that the ChemWindow prediction method provided the best correlations with the experimental data for compounds **156**, **167f**, **170a** and **175**. The MODGRAPH neural network also gave a good correlation for compound **167f** as well as compounds **168e** and **172d**. The HOSE method correlated best for compound **177e**.

The structure of compound **168e**, which was initially thought to contain a 4-methylene instead of the hydroxyl group was confirmed by the chemical shift of the C-4 which appeared further upfield *ca.* 70 ppm, than would a methylene carbon. All the prediction methods used confirmed this structure (Table 7).



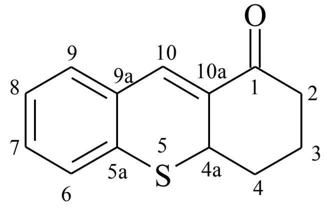
156 **167f** **168e**

170a **172d**

175 **177e**

Figure 34. Selected compounds used to correlate experimental ^{13}C NMR data with predicted data.

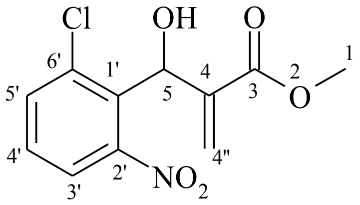
Table 5. Experimental (100MHz) and predicted ^{13}C NMR chemical shift data (δ/ppm) for 2,3,4,4a-tetrahydrothioxanthen-1-one **156** in CDCl$_3$.



Nucleus	**A**	**B**	**C**	**D**
C1	197.3	192.7	197.1	197.6
C2	39.2	38.5	36.6	39.5
C3	20.9	22.4	20.7	19.4
C4	28.4	28.9	31.7	32.7
C4a	38.3	41.4	41.4	42.1
C5a	135.4	138.4	130.7	133.3
C6	131.4	126.8	127.3	126.5
C7	126.7	129.1	125.5	127.9
C8	126.0	125.8	123.4	124.8
C9	130.2	129.4	127.3	126.4
C9a	130.5	133.0	122.4	133.0
C10	135.5	132.0	134.9	131.6
C10a	131.7	140.7	125.6	143.9
RMS values		2.1	7.5	2.0

A: Experimental data; **B**: Modgraph neural network predictions; **C**: Modgraph HOSE predictions; **D**: ChemWindow predictions.

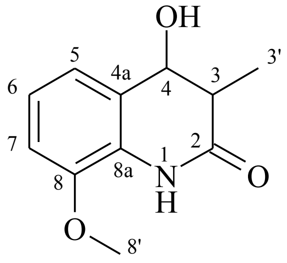
Table 6. Experimental (100MHz) and predicted ^{13}C NMR chemical shift data (δ/ppm) for the BH adduct methyl 3-(6-chloro-2-nitrophenyl)-3-hydroxy-2-methylenepropanoate **167f** in $CDCl_3$.



Nucleus	A	B	C	D
C1	52.1	52.1	51.8	50.8
C3	166.3	167.8	166.6	165.0
C4	151.4	141.8	137.1	144.6
C4’’	127.8	125.5	126.9	120.6
C5	68.9	71.4	77.0	66.1
C1’	131.7	138.2	134.3	134.3
C2’	135.6	151.2	143.6	149.6
C3’	129.3	122.5	120.7	121.8
C4’	122.8	129.7	128.5	128.1
C5’	133.3	131.9	124.9	135.1
C6’	138.0	135.7	135.2	134.5
RMS values		3.2	3.2	2.0

A: Experimental data; **B**: Modgraph neural network predictions; **C**: Modgraph HOSE predictions; **D**: ChemWindow predictions.

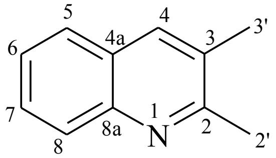
Table 7. Experimental (100MHz) and predicted ^{13}C NMR chemical shift data (δ/ppm) for 4-hydroxy-8-methoxy-3-methyl-3,4-dihydro-1*H*-quinolin-2-one **168e** in $CDCl_3$.



Nucleus	**A**	**B**	**C**	**D**
C2	171.1	173.9	179.8	177.2
C3	41.4	44.3	46.8	49.3
C4	**70.8**	**71.1**	**74.7**	**75.4**
C4a	123.0	122.3	134.3	134.0
C5	119.6	118.5	124.1	121.2
C6	125.8	123.2	129.3	124.2
C7	110.9	114.7	110.9	111.1
C8	145.9	145.2	147.9	153.0
C8a	125.9	127.8	116.2	126.6
C8’	55.9	56.8	55.9	56.0
C3’	10.4	12.7	14.6	8.9
RMS values		3.0	10.2	10.9

A: Experimental data; **B**: Modgraph neural network predictions; **C**: Modgraph HOSE predictions; **D**: ChemWindow predictions

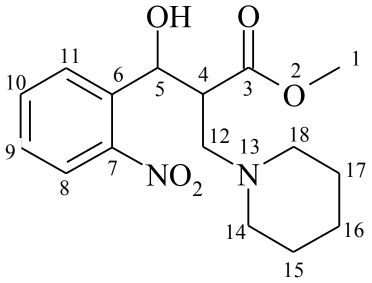
Table 8. Experimental (100MHz) and predicted ^{13}C NMR chemical shift data (δ/ppm) for 2,3-dimethylquinoline **170a** in $CDCl_3$.



Nucleus	**A**	**B**	**C**	**D**
C2	159.0	157.7	158.6	160.1
C3	130.0	129.6	129.7	129.2
C4	135.3	138.6	134.9	136.1
C4a	125.6	127.7	126.7	124.2
C5	126.7	127.0	126.6	126.5
C6	125.7	126.3	123.7	125.0
C7	128.2	129.5	128.0	127.9
C8	128.4	128.0	129.7	128.1
C8a	135.4	144.2	146.4	145.4
C2’	23.5	22.5	23.4	18.4
C3’	19.6	18.2	19.3	18.4
RMS values		3.6	2.8	0.5

A: Experimental data; **B**: Modgraph neural network predictions; **C**: Modgraph HOSE predictions; **D**: ChemWindow predictions.

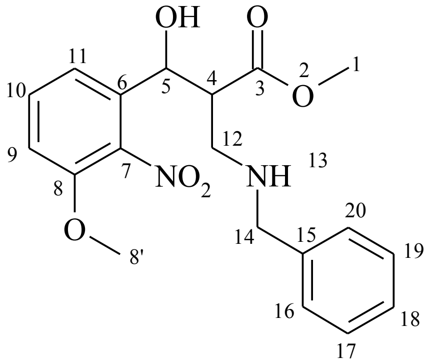
Table 9. Experimental (100MHz) and predicted ^{13}C NMR chemical shift data (δ/ppm) for methyl 3-hydroxy-3-(2-nitrophenyl)-2-[(piperidin-1-yl)methyl]propanoate **172d** in $CDCl_3$.



Nucleus	A	B	C	D
C1	51.8	52.2	51.9	50.7
C3	171.4	174.0	175.0	174.5
C4	48.4	52.5	41.5	48.3
C5	73.2	70.6	75.4	65.7
C6	136.6	141.7	134.3	136.2
C7	149.1	148.7	147.8	148.6
C8	124.0	123.5	124.0	122.7
C9	128.4	129.6	127.0	126.2
C10	132.3	133.1	126.2	133.7
C11	129.4	130.5	126.3	129.6
C12	60.8	56.1	50.5	51.1
C14	54.7	55.3	54.5	52.6
C15	25.8	24.6	26.0	27.6
C16	23.9	23.5	24.3	26.2
C17	25.8	24.6	26.0	27.6
C18	54.7	55.3	54.5	52.6
RMS values		1.4	6.3	4.1

A: Experimental data; **B**: Modgraph neural network predictions; **C**: Modgraph HOSE predictions; **D**: ChemWindow predictions.

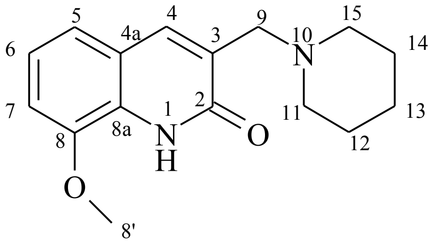
Table 10. Experimental (100MHz) and predicted ^{13}C NMR chemical shift data (δ/ppm) for methyl 2-[benzylaminomethyl]-3-hydroxy-3-(3-methoxy-2-nitrophenyl)propanoate **175** in $CDCl_3$.



Nucleus	A	B	C	D
C1	51.5	52.2	51.9	50.7
C3	172.9	173.8	175.0	174.5
C4	50.4	52.4	41.5	50.5
C5	71.1	71.2	75.4	65.7
C6	135.1	142.1	134.3	137.2
C7	139.0	142.5	144.1	134.2
C8	150.6	148.0	150.4	156.2
C8’	56.5	56.8	57.3	55.0
C9	111.6	114.8	115.7	111.8
C10	130.6	131.7	129.3	134.7
C11	119.1	120.9	126.3	121.9
C12	46.8	45.9	45.7	42.3
C14	53.9	53.6	52.4	55.0
C15	138.5	140.8	136.0	137.2
C16	128.1	127.6	129.4	128.1
C17	128.5	128.4	128.8	128.3
C18	127.2	126.6	127.7	126.8
C19	128.5	128.4	128.8	128.3
C20	128.1	127.6	129.4	128.1
RMS values		3.6	2.3	0.7

A: Experimental data; **B**: Modgraph neural network predictions; **C**: Modgraph HOSE predictions; **D**: ChemWindow predictions.

Table 11. Experimental (100MHz) and predicted ^{13}C NMR chemical shift data (δ/ppm) for 8-methoxy-3-[(piperidin-1-yl)methyl]-1*H*-quinolin-2-one **177e** in $CDCl_3$.



Nucleus	**A**	**B**	**C**	**D**
C2	161.9	164.6	162.8	163.1
C3	136.8	133.0	125.6	130.8
C4	131.3	128.9	127.6	133.2
C4a	119.4	123.1	116.5	127.8
C5	121.9	124.2	127.3	118.7
C6	120.3	123.6	126.3	125.0
C7	109.2	112.5	110.9	113.5
C8	145.3	145.2	147.9	153.8
C8a	127.5	128.4	129.2	124.1
C8’	56.8	56.8	55.9	56.0
C9	55.9	55.0	58.0	58.6
C11	54.9	54.1	54.6	52.3
C12	26.1	24.6	26.2	27.2
C13	24.3	23.5	24.4	26.2
C14	26.1	24.6	26.2	27.2
C15	54.9	54.1	54.6	52.3
RMS values		0.9	0.4	4.6

A: Experimental data; **B**: Modgraph neural network predictions; **C**: Modgraph HOSE predictions; **D**: ChemWindow predictions.

2.5 Conclusions

Earlier work in the group[3,78] had shown that Baylis-Hillman reactions of 2,2'-dithiodibenzaldehyde with a range of acyclic activated alkenes afforded the thiochromene derivatives directly rather than the expected BH adducts, raising mechanistic questions relating to their formation. In the present study, this approach was successfully extended to the use of the cyclic ketones, 2-cyclohexenone and 2-cyclopentenone, to give the tricyclic analogues directly. A preliminary kinetic study of this Baylis-Hillman reaction was carried out using the acyclic substrates, MVK and methyl acrylate, in an attempt to understand the mechanistic pathways involved in the spontaneous *in situ* reduction of the disulphide link and intramolecular cyclisation.[3] The kinetic data revealed the reaction to be even more complex than anticipated. First-order kinetic plots were obtained for the consumption of the dialdehyde and the activated alkenes during the initial stages of the reaction in all the experiments. As the reaction progressed, deviation from 1st-order linearity was observed suggesting the possibility of competing pathways. Not surprisingly, the reaction with methyl acrylate was observed to be much slower than with MVK.

Attention was also given to the synthesis of 2-nitrobenzaldehyde Baylis-Hillman adducts, particularly to the reaction of methyl acrylate with a series of substituted 2-nitrobenzaldehydes, shown in previous work[8,11,47,86] to afford 2-quinolones on cyclisation. Reaction of these Baylis-Hillman adducts with the amines, piperidine and benzylamine, gave the corresponding conjugate addition products as diastereomeric mixtures in excellent yield (80-100%), while the MVK-derived 2-nitrobenzaldehyde BH adducts failed to give the expected conjugate addition products. Catalytic hydrogenation of the diastereomeric products, using a Pd-C catalyst in ethanol afforded the 3-amino-2-quinolone derivatives in yields of between 22-37%.

Application of the ChemWindow, Modgraph neural network and HOSE (hierarchically ordered spherical description of environment) ^{13}C prediction programmes, to selected compounds synthesized in the study revealed good correlations between the predicted and experimental ^{13}C values.

While the immediate objectives of the present study have been addressed, future work in this area is expected to include the following:

i) A detailed kinetic and theoretical study of the BH synthesis of thiochromenes, in order to determine the mechanism.
ii) Yield optimisation of the polycyclic benzothiopyran derivatives.
iii) Reaction of 2,2'-dithiodibenzaldehyde with a range of substituted cyclic alkenes, to afford substituted thioxanthone derivatives, and the possible biological screening of these compounds.

3. EXPERIMENTAL

3.1 General

All reagents used in this study were used as supplied by the manufacturer. Solvents were dried according to literature procedures;[88] THF and Et_2O were dried over sodium wire and distilled from sodium using benzophenone as indicator, and CH_2Cl_2 was pre-dried over $CaCl_2$ and distilled from CaH_2.

Thin layer chromatography (TLC) was carried out using plastic plates, coated with Merck silica gel $60F_{254}$ and visualized under UV light (254/365nm) or, in cases where components were UV inactive, iodine vapour was used. Flash chromatography was performed using silica gel 60 (particle size 0.040-0.063nm)

NMR spectra were recorded on Bruker AMX 400 and Biospin 600 spectrometers in $CDCl_3$ and were calibrated using solvent signals (δ_H= 7.25ppm and δ_C= 77.0ppm). Low-resolution mass spectroscopy was conducted on a Finnigan-Mat GCQ mass spectrometer using electron ionisation (EI) mode, and high-resolution mass spectra were obtained by Martin Brits (University of Witwatersrand Mass Spectrometry Unit) and by Dr Johan Jordaan at North-West University (Potchefstroom campus). Infrared spectra were recorded on a Perkin Elmer FT-IR spectrum 2000 spectrometer using nujol mulls, and melting points were determined using a Reichert hot-stage apparatus, and are uncorrected.

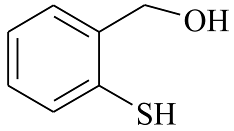
Structures have been numbered for convenience of signal assignment rather than systematically.

High-resolution mass spectrometry (HRMS) data for compounds **172d**, **172e**, **172g**, **172h**, **175**, **177d**, **177e**, **177g** and **180** was not available at the time of printing.

Table 12. List of compounds synthesized in this study.

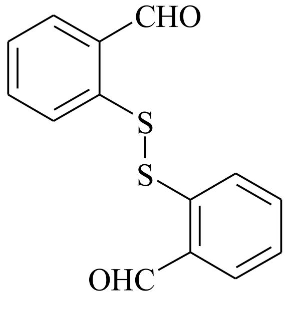
Compound Name and Number	**Page No.**
2-Mercaptobenzyl alcohol **153**	84
2,2’-dithiodibenzaldehyde **69**	84
3-Acetyl-2*H*-1-thiochromene **71a**	85
Methyl 2*H*-1-thiochromene-3-carboxylate **71b**	86
2,3,4,4a-Tetrahydrothioxanthen-1-one **156**	86
1-Oxocyclopenteno[2,3-b][2*H*]benzothiopyran **158**	87
4-Hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **167a**	98
4-(5-Chloro-2-nitrophenyl)-4-hydroxy-3-methylenebutan-2-one **167b**	98
4-Hydroxy-3-methylene-4-(4,5-methylenedioxy-2-nitrophenyl)butan-2-one **167c**	99
Methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **167d**	100
Methyl 3-hydroxy-2-methylene-3-(3-methoxy-2-nitrophenyl)propanoate **167e**	100
Methyl 3-(6-chloro-2-nitrophenyl)-3-hydroxy-2-methylenepropanoate **167f**	101
Methyl 3-hydroxy-2-methylene-3-(3,4-methylenedioxy-2-nitrophenyl)propanoate **167g**	102
Methyl 3-(2,4-dinitrophenyl)-3-hydroxy-2-methylenepropanoate **167h**	102
4-Hydroxy-3-methyl-3,4-dihydro-1*H*-quinolin-2-one **168d**	103
4-Hydroxy-8-methoxy-3-methyl-3,4-dihydro-1*H*-quinolin-2-one **168e**	104
5-Chloro-4-hydroxy-3-methyl-3,4-dihydro-1*H*-quinolin-2-one **168f**	105
4-Hydroxy-3-methyl-7-nitro-3,4-dihydro-1*H*-quinoli-2-one **168h**	105
2,3-dimethylquinoline **170a**	106
6,7-Methylenedioxy-2,3-dimethylquinoline **170c**	107
4-Hydroxy-3-methyl-4-(2-nitrophenyl)-butan-2-one **171a**	106
4-Hydroxy-3-methyl-4-(2-nitro-4,5-methylenedioxyphenyl)-butan-2-one **171c**	107
Methyl 3-hydroxy-3-(2-nitrophenyl)-2-[(piperidin-1-yl)methyl]propanoate **172d**	108
Methyl 3-hydroxy-3-(3-methoxy-2-nitrophenyl)-2-[(piperidin-1-yl)methyl]propanoate **172e**	109
Methyl 3-hydroxy-3-(3,4-methylenedioxy-2-nitrophenyl)-2-[(piperidin-1-yl)methyl]propanoate **172g**	109
Methyl 3-(2,4-dinitrophenyl)-3-hydroxy-2-[(piperidin-1-yl)methyl]propanoate **172h**	110
Methyl 2-[benzylaminomethyl]-3-hydroxy-3-(3-methoxy-2-nitrophenyl)propanoate **175**	111
3-[(Piperidin-1-yl)methyl]-1*H*-quinolin-2-one **177d**	113
8-Methoxy-3-[(piperidin-1-yl)methyl]-1*H*-quinolin-2-one **177e**	114
3-[(Piperidin-1-yl)methyl]-1*H*-[6,7]dioxoloquinolin-2-one **177g**	114
7-amino-3-[(piperidin-1-yl)methyl]-1*H*-quinolin-2-one **180**	115

3.2 Synthesis of thiochromene derivatives



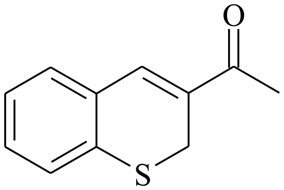
2-Mercarptobenzyl alcohol 153

A solution of 2-mercaptobenzoic acid (4.36g, 28.4mmol) in dry THF was added dropwise to a stirred slurry of lithium aluminium hydride (2.0g, 52mmol) in THF (80ml) under N_2, and the resulting mixture was stirred for 24h. EtOAc (10ml) and 10% sulphuric acid (40ml) were added dropwise. The resulting mixture was filtered and the aqueous layer extracted with EtOAc (2x 30ml). The combined organic layers were washed with saturated brine and dried over anhydrous Na_2SO_4, and the solvent was evaporated *in vacuo* to afford, as a light brown oil which crystallized after some time, 2-mercarptobenzyl alcohol **153** (3.28g, 84%); δ_H (400MHz; $CDCl_3$) 2.03 (1H, br s, OH) 3.67 (1H, s, SH), 4.72 (2H, s, CH_2), 7.16-7.18 (2H, overlapping multiplets, ArH) and 7.32-7.35 (2H, overlapping multiplets, ArH); δ_C (100MHz; $CDCl_3$) 64.4 (CH_2), 126.3 ,128.4, 128.6, 130.2, 131.4 and 138.8 (ArC).



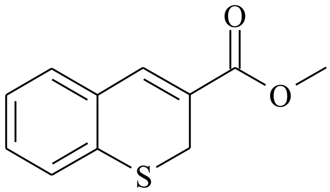
2,2'-Dithiodibenzaldehyde 69

In a 100ml round-bottomed flask, fitted with a reflux condenser, pyridinium chlorochromate (12.0g, 58mmol) was dispersed in dry, deoxygenated dichloromethane (45ml) under N_2. A solution of 2-mercaptobenzyl alcohol **153** (3.0g, 22mmol) in dry, deoxygenated dichloromethane (8.9ml) was added, *via* a syringe through a septum, to the stirred mixture. After stirring the reaction mixture for 4h at room temperature, dichloromethane (45ml) was added and the supernatant liquid was decanted from the black gum which had formed. The black gum was washed with dichloromethane (3 x 15ml) and dry diethyl ether (20ml) and the combined washings were passed through a florisil pad. The solvent was evaporated *in vacuo* and the residual solid was recrystallised from ethanol to afford 2,2'-dithiodibenzaldehyde **69** as white crystals (1.33g, 54%), m.p. 156-157°C (lit[78] 142-144°C,); δ_H (400MHz; $CDCl_3$) 7.38 (2H, t, *J*=7.37Hz, ArH), 7.48 (2H, t, *J*=7.62Hz, ArH), 7.77 (2H, d, *J*=8.02Hz, ArH), 7.85 (2H, d, J=7.44Hz, ArH) and 10.21 (2H, s, CHO); δ_C (100MHz; $CDCl_3$) 126.3, 126.7, 133.8, 134.3, 134.6, 140.0 (ArC) and 191.8 (C=O).



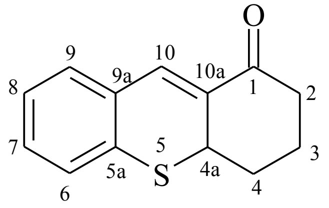
3-Acetyl-2*H*-1-thiochromene 71a

To a stirred solution of 2,2'-dithiodibenzaldehyde **69** (0.25g, 0.91mmol) and methyl vinyl ketone (0.22ml, 2.7mmol) in chloroform (1.0ml) under N_2, DBU (0.22ml, 1.5mmol) was slowly added and the reaction mixture was stirred vigorously in a stoppered flask under N_2 at room temperature for 24h. The resulting mixture was chromatographed [flash chromatography on silica; elution with EtOAc-hexane (2:3)] to afford, as a yellow oil, 3-acetyl-2*H*-1-thiochromene **71a** (0.18g, 53%), ν_{max}/cm^{-1} (nujol) 1653 (C=O); δ_H (400MHz; $CDCl_3$) 2.24 (3H, s, CH_3), 3.70 (2H, s, CH_2), 7.12-7.27 (4H, overlapping multiplets, ArH) and 7.38 (1H, s, 4-H); δ_C (100MHz; $CDCl_3$) 22.8 (CH_3), 25.3 (CH_2), 125.7, 127.3, 130.5, 130.8, 131.4, 131.5, 135.5 and 137.8 (ArC and C=CH) and 196.6 (C=O).



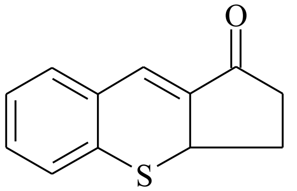
Methyl 2*H*-1-thiochromene-3-carboxylate 71b

To a stirred solution of 2,2’-dithiodibenzaldehyde **69** (0.25g, 0.91mmol) and methyl acrylate (0.24ml, 2.9mmol) in chloroform (1.0ml) under N_2, DBU (0.22ml, 1.5mmol) was slowly added and the reaction mixture was stirred vigorously in a stoppered flask under N_2 at room temperature for 24h. The resulting mixture was chromatographed [flash chromatography on silica; elution with EtOAc-hexane (2:3)] to afford, as a yellow oil, methyl 2*H*-1-thiochromene-3-carboxylate **71b** (0.15g, 48%); δ_H (400MHz; $CDCl_3$) 3.73 (2H, d, *J*=1.07Hz, CH_2), 3.83 (3H,s,CH_3), 7.08-7.27 (4H, m, ArH), 7.54 (1H, s, 4-H); δ_C (100MHz; $CDCl_3$) 24.0 (CH_2), 52.2 (CH_3), 123.0, 125.7, 127.1, 130.2, 130.6, 131.3, 134.0 and 137.3 (ArC and C=CH), and 166.3 (C=O).



2, 3, 4, 4a-Tetrahydrothioxanthen-1-one 156

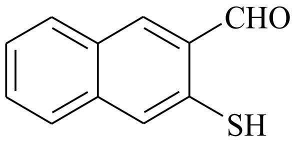
To a stirred solution of 2,2’-dithiodibenzaldehyde **69** (0.27g, 1mmol) in THF (0.8ml), 2-cyclohexenone (0.19ml, 2mmol) was added, followed by TMPDA (0.17ml, 1mmol); H_2O (0.8ml) was added last and the mixture was stirred for 72h at room temperature. Aqueous work up followed by flash chromatography [on silica; elution with hexane:ether:CH_2Cl_2 (4:1:1)] afforded, as an orange oil 2,3,4,4a-tetrahydrothioxanthen-1-one **156** (0.025g, 20%) (Found **M**: 216.060192. $C_{13}H_{12}SO$ requires: ***M***, 216.060887); ν_{max}/cm^{-1} (nujol) 1678 (C=O); δ_H (600MHz; $CDCl_3$) 1.75, 1.86, 2.12, 2.28 , 2.46 and 2.63 (6H, series of multiplets, 2-,3- and 4-CH_2), 4.28 (1H, m, 5-CH), 7.12 (1H, t, *J*=7.8, 8-ArH), 7.18 (1H, t, *J*=7.8, 7-ArH), 7.24 (1H, d, *J*=7.94Hz, 9-ArH), 7.28 (1H, d, *J*=7.2, 6-ArH), 7.52 (1H, d, *J*=1.8, 10-CH); δ_C (150MHz; $CDCl_3$) 20.9 (C-3), 28.4 (C-4), 38.3 (C-4a), 39.2 (C-2), 126.0 (C-8), 126.7 (C-7), 130.2 (C-9), 130.5 (C-9a), 131.4 (C-6), 131.7 (C-10a), 135.4 (C-5a), 135.5 (C-10) and 197.3 (C=O); *m/z* 216 (*M*: 100)



1-Oxocyclopenteno[2,3-*b*][2*H*]-benzothiopyran 158

The procedure described for the synthesis of compound **156** was followed, using 2,2'-dithiodibenzaldehyde **69** (0.27g, 1mmol), 2-cyclopentenone (0.17ml, 2mmol) and TMPDA (0.17ml, 1mmol) to afford as an orange oil, 1-oxocyclopenteno[2,3-*b*][2*H*]-benzothiopyran **158** (0.05g, 39%), Low-resolution mass spec.(Found M^+: 202; $C_{12}H_{10}OS$ requires 202.28)); ν_{max}/cm^{-1} (nujol) 1725 (C=O) δ_H (600MHz; $CDCl_3$) 1.66 (2H, m, 3-H), 2.30 and 2.36 (2H, m, 2-H), 2.69 (1H, m, 4-H) and 7.14-7.30 (5H, overlapping multiplets, ArH and C=CH). δ_C (150MHz; $CDCl_3$) 29.5 (C-3), 35.2 (C-2), 47.5 (C-4), 123.4 (C-8), 126.8 (C-6), 127.9 (C-10), 129.1 (C-7), 129.4 (C-9), 133.0 (C-9a), 138.4 (C-5a), 147.4 (C-10a) and 202.1 (C=O); *m/z* 202 (M^+: 80%).

Attempted synthesis of 3-mercapto-2-naphthaldehyde 160



To a solution of *N,N,N'*-trimethyl-1,2-ethylenediamine (1.4ml, 11mmol) in dry THF (40ml), was added butyllithium 2.5M in hexanes (4.2ml, 10.5mmol) at -20°C under argon, and the resulting mixture was stirred for 15min. 2-Naphthaldehyde **159** (1.56g, 10mmol) was added and the mixture was stirred at -20°C for 24h. The reaction was then cooled to -40°C and treated with sulphur (0.84g, 26mmol) and stirred for a further 3h at -20°C. The mixture was quenched with 2M-HCl and extracted with ethyl acetate. The combined extracts were washed with water followed by brine and dried over anhydrous $MgSO_4$. Evaporation of solvent *in vacuo* gave a pale pink oil (1.01g, 53%). ^{1}H NMR analysis of this showed the starting material **159** as well as new signals at 4.86 ppm and 5.29 ppm corresponding to product **160**.

3.3 Kinetic Study

All kinetic runs were carried out in $CDCl_3$ at 24°C (297K). The $CDCl_3$ was cleaned prior to use by passing it through neutral alumina and crushed 4Å molecular sieves in a dry Pasteur pipette under N_2.[75] All weighing for kinetic experiments was done on a Sartorius Micro electronic balance.

Preparation of stock solutions A and B

Stock solution **A** contained, 2,2'-dithiodibenzaldehyde **69**, MVK **70a** and 1,3,5-trimethoxybenzene (TMB) dissolved in $CDCl_3$ and stock solution **B** contained the catalyst DBU dissolved in $CDCl_3$. Solutions were made up to the mark in 1ml volumetric flasks. For the preparation of solution **A**, the required quantities of aldehyde **69**, and TMB were weighed into vials. MVK was weighed directly into a 1ml volumetric flask, into which aldehyde **69** and TMB were then added. $CDCl_3$ was added to dissolve the substrates and the solution was made up to the mark. For the preparation of solution **B**, DBU was weighed directly into a 1ml volumetric flask and the solution made up to the mark with $CDCl_3$. Duplicate runs were conducted using each set of prepared solutions. The results for one run in each case, are tabulated below for illustrative purposes.

Experiments 1a and 1b

Solution **A** was prepared using MVK (0.017g, 0.24mmol), 2,2'-dithiodibenzaldehyde **69** (0.027g, 0.10mmol) and TMB (0.006, 0.04mmol) and solution **B** using DBU (0.016g, 0.11mmol). Using a 250µl syringe, 250µl of each of solutions **A** and **B** was transferred into a 1ml graduated NMR tube. The NMR tube was shaken and timer was set to allow for zero-time correction between the times the reaction commenced and when the first spectrum was obtained on the NMR instrument. The interval time between successive spectra was set at 300s. The integral data was converted to concentration using the following equation:

$$\left\{ \left(\frac{\text{Integral}}{\text{No. of protons}}\right) \div \left(\frac{\text{TMB integral}}{9}\right) \right\} \;\mathrm{x}\; \left[\,\text{TMB}\,\right]$$

Table 13. Integral data for Experiment 1a

Expt. no.	**Time (s)**	**ArCHO**	**TMB**	**Prod. CH_2**	**MVK**	**DBU**
100	0	3.91422	9.02654	0.353618	13.8353	6.03142
101	328	3.72652	9.09901	0.426414	13.2272	6.07683
102	655	3.50684	9.10116	0.499638	12.5312	6.0285
103	982	3.29055	9.13157	0.559988	11.8459	6.03681
104	1309	3.02554	9.08374	0.641603	11.0343	5.96695
105	1636	2.85049	9.27273	0.749268	10.5147	6.09262
106	1964	2.58499	9.21652	0.849324	9.6992	6.03798
107	2291	2.34994	9.26857	0.956266	9.0278	6.01838
108	2618	2.11257	9.25325	1.0594	8.2812	6.00942
109	2945	1.92016	9.4079	1.20853	7.74101	6.07825
110	3272	1.68721	9.36428	1.31484	7.03424	6.0326
111	3599	1.47752	9.42843	1.45526	6.43097	6.03902
112	3927	1.27914	9.42179	1.57726	5.83385	6.01215
113	4254	1.09867	9.4553	1.71138	5.29015	6.02035
114	4581	0.928348	9.43404	1.84694	4.75768	6.00326
115	4908	0.788818	9.53707	2.0044	4.33805	6.04955
116	5239	0.645431	9.41067	2.1193	3.85752	5.96617
117	5566	0.529332	9.52102	2.28655	3.50702	6.00854
118	5893	0.419954	9.41121	2.38677	3.1189	5.92129
119	6220	0.329706	9.48049	2.55339	2.8281	5.92131
120	6550	0.250522	9.35133	2.62343	2.50997	5.8922
121	6878	0.188682	9.3995	2.76763	2.27031	5.90776
122	7205	0.134546	9.29045	2.87989	2.02797	5.81662
123	7533	0.095926	9.38135	3.02062	1.84453	5.87215
124	7861	0.064811	9.26186	3.11602	1.65926	5.79586

Prod.CH_2 is the methylene signal of the thiochromene **71**

Table 14. Concentration data for Experiment 1a

Expt. no.	Time(s)	[ArCHO]	[MVK]	[DBU]	[Prod.CH$_2$]	[TMB]
100	0	0.203499	0.486232	0.210746	0.000001	0.076687
101	1143	0.149644	0.3526231	0.230586	0.013519	0.076687
102	1471	0.141333	0.3344392	0.230472	0.016172	0.076687
103	1799	0.13297	0.3167666	0.228585	0.018945	0.076687
104	2127	0.124353	0.2984462	0.228138	0.021163	0.076687
105	2455	0.11494	0.2794625	0.226685	0.024375	0.076687
106	2783	0.106083	0.2608752	0.226742	0.027885	0.076687
107	3111	0.096789	0.2421098	0.226079	0.031801	0.076687
108	3439	0.087494	0.2240849	0.224079	0.035604	0.076687
109	3767	0.078786	0.2058934	0.224116	0.039509	0.076687
110	4095	0.070434	0.189299	0.222957	0.04433	0.076687
111	4423	0.062177	0.1728169	0.222313	0.048454	0.076687
112	4751	0.054079	0.1569208	0.221035	0.053264	0.076687
113	5079	0.046851	0.1424509	0.220207	0.05777	0.076687
114	5407	0.040098	0.1287171	0.219726	0.062461	0.076687
115	5735	0.033958	0.1160222	0.219596	0.06756	0.076687
116	6063	0.028543	0.1046461	0.218899	0.072528	0.076687
117	6391	0.023668	0.0943042	0.218781	0.077715	0.076687
118	6719	0.019186	0.0847419	0.217781	0.082877	0.076687
119	7047	0.015399	0.0762429	0.217123	0.087518	0.076687
120	7375	0.012001	0.068629	0.215537	0.092944	0.076687
121	7703	0.009245	0.0617502	0.21744	0.096812	0.076687
122	8031	0.006927	0.0555679	0.216897	0.10161	0.076687
123	8359	0.004998	0.050219	0.216057	0.106973	0.076687
124	8687	0.003529	0.0452339	0.216006	0.111113	0.076687
125	9015	0.002415	0.0412154	0.215951	0.116101	0.076687

Table 15. 1st-Order kinetics data for Experiment 1a.

Expt. no.	Time (s)	ln[ArCHO]	ln[MVK]	ln[DBU]
100	0	-1.59209	-0.72107	-1.5571
101	1143	-1.8995	-1.042356	-1.50236
102	1471	-1.95664	-1.095301	-1.47853
103	1799	-2.01763	-1.14959	-1.47772
104	2127	-2.08463	-1.209166	-1.47539
105	2455	-2.16335	-1.274889	-1.48631
106	2783	-2.24353	-1.343714	-1.49266
107	3111	-2.33522	-1.418363	-1.50761
108	3439	-2.43619	-1.49573	-1.53527
109	3767	-2.54102	-1.580399	-1.54557
110	4095	-2.65308	-1.664428	-1.57356
111	4423	-2.77777	-1.755522	-1.59223
112	4751	-2.91731	-1.852013	-1.61709
113	5079	-3.06078	-1.948757	-1.6398
114	5407	-3.21643	-2.050139	-1.65731
115	5735	-3.38263	-2.153975	-1.67527

116	6063	-3.55634	-2.257172	-1.69521
117	6391	-3.74363	-2.3612317	-1.7101
118	6719	-3.95357	-2.468144	-1.72786
119	7047	-4.17345	-2.57383	-1.74101
120	7375	-4.42277	-2.67904	-1.75992

Experiments 2a and 2b

The procedure described for Experiment 1 was followed, but doubling the concentration of MVK *i.e* MVK (0.036g, 0.52mmol), 2,2'-dithiodibenzaldehyde (0.027g, 0.10mmol), TMB (0.006g, 0.04mmol) and DBU (0.015g, 0.10mmol) were used.

Table 16. Integral data for Experiment 2a

Expt. no.	**Time (s)**	**ArCHO**	**MVK**	**DBU**	**TMB**	**Prod.CH$_2$**
100	0	3.68303	33.2387	6.70813	9.0009	0.261777
101	328	3.17723	31.1706	6.57479	8.94004	0.405608
102	655	2.64319	29.2151	6.4697	8.94217	0.568708
103	985	2.05224	26.9431	6.33252	8.88142	0.750057
104	1312	1.47945	24.7759	6.2144	8.86426	1.02581
105	1639	0.937604	22.2485	5.95786	8.65829	1.29185
106	1967	0.536734	20.214	5.89055	8.66658	1.643
107	2294	0.252046	18.1545	5.8531	8.55305	2.02168
108	2622	0.08578	16.3264	5.93844	8.63844	2.37503
109	2950	0.017482	14.2356	5.94794	8.47206	2.70089
110	3277	0.008704	12.8254	6.21262	8.58475	3.09452
111	3604	0.004933	10.8242	6.16661	8.46715	3.41844
112	3931	0.005553	9.41246	6.26558	8.5921	3.77532
113	4259	0.009795	8.23784	6.24319	8.4443	3.99821
114	4586	0.00971	7.37112	6.34368	8.57537	4.32448
115	4913	0.009477	6.53636	6.28514	8.45549	4.48287
116	5240	0.010078	5.92374	6.33006	8.53293	4.67351
117	5567	0.00696	5.29409	6.3151	8.50367	4.8212
118	5893	0.007852	4.87238	6.44483	8.63583	5.06346
119	6221	0.00826	4.42244	6.42313	8.65519	5.15619

Table 17. Concentration data for Experiment 2a.

Expt. no.	Time (s)	[Ar-CHO]	[MVK]	[DBU]	[TMB]	[Prod-CH_2]
100	0	0.20371	1.048138	0.201997	0.074499	0.00001
101	1181	0.137177	0.825335	0.083283	0.074499	0.00975
102	1509	0.119144	0.779252	0.082183	0.074499	0.01521
103	1837	0.099094	0.730191	0.080851	0.074499	0.021321
104	2165	0.077466	0.678012	0.079678	0.074499	0.028312
105	2493	0.055953	0.624682	0.078343	0.074499	0.038796
106	2821	0.036304	0.574303	0.076895	0.074499	0.05002
107	3149	0.020762	0.521287	0.075954	0.074499	0.063556
108	3477	0.009879	0.47439	0.076473	0.074499	0.079242
109	3805	0.003329	0.422403	0.076821	0.074499	0.092172
110	4133	0.000692	0.375542	0.078455	0.074499	0.106876
111	4461	0.00034	0.333899	0.08087	0.074499	0.120845
112	4789	0.000195	0.285713	0.081386	0.074499	0.135349
113	5117	0.000217	0.244836	0.08149	0.074499	0.147305
114	5445	0.000389	0.218033	0.08262	0.074499	0.158732
115	5773	0.00038	0.192111	0.082667	0.074499	0.169061
116	6101	0.000376	0.17277	0.083065	0.074499	0.177738
117	6429	0.000396	0.155156	0.082899	0.074499	0.183615
118	6757	0.000274	0.139142	0.082988	0.074499	0.190069
119	7085	0.000305	0.126098	0.083397	0.074499	0.196565
120	7413	0.00032	0.114198	0.08293	0.074499	0.199717

Table 18. 1st-Order kinetics data for Experiment 2a.

Expt. no.	Time (s)	ln[ArCHO]	ln[MVK]	ln[DBU]
100	0	-1.59106	0.04702	-1.5995
101	1181	-1.98648	-0.19194	-1.96372
102	1509	-2.12742	-0.2494	-1.96236
103	1837	-2.31169	-0.31445	-1.96584
104	2165	-2.55792	-0.38859	-1.98142
105	2493	-2.88324	-0.47051	-1.99326
106	2821	-3.31583	-0.5546	-1.99283
107	3149	-3.87463	-0.65145	-2.00932
108	3477	-4.61734	-0.74573	-2.01258
109	3805	-5.70508	-0.8618	-2.01515
110	4133	-7.27592	-0.97938	-2.01397
111	4461	-7.98656	-1.09692	-2.01179

Experiments 3a and 3b

The procedure described for Experiment 1 was followed, doubling the concentration of MVK and halving that of aldehyde. MVK (0.072g, 1.04mmol), 2,2'-dithiodibenzaldehyde (0.014g, 0.05mmol), TMB (0.006g, 0.004mmol) and DBU (0.015g, 0.10mmol) were used.

Table 19. Integral data for Experiment 3b

Expt. no.	**Time (s)**	**ArCHO**	**MVK**	**DBU**	**TMB**	**Prod.CH$_2$**
100	0	1.70754	33.2371	7.29394	8.99736	0.187525
101	327	1.58132	32.7912	7.31078	9.09141	0.233181
102	654	1.42115	31.8576	7.30169	9.09791	0.214176
103	981	1.26475	30.9906	7.32315	9.07874	0.296107
104	1307	1.09018	30.0148	7.32273	9.10607	0.372325
105	1633	0.914643	28.9595	7.27898	9.03842	0.43365
106	1960	0.737773	27.6618	7.31379	9.03649	0.531192
107	2288	0.557517	26.4591	7.31356	9.07145	0.579006
108	2615	0.396922	25.1416	7.30687	9.09036	0.661384
109	2942	0.261536	23.8358	7.28041	9.0164	0.729599
110	3271	0.150649	22.5175	7.35059	9.07133	0.904884
111	3599	0.07634	21.2206	7.36196	9.09658	0.942495
112	3929	0.035922	19.7878	7.33326	9.0679	1.0543
113	4259	0.012901	18.4261	7.36588	9.10318	1.17811
114	4586	0.005458	17.2733	7.34947	9.10648	1.25167
115	4913	0.007774	15.9212	7.3553	9.13898	1.3802
116	5240	0.006337	14.7652	7.37973	9.1543	1.50483
117	5567	0.007483	13.8703	7.40456	9.13309	1.5468
118	5895	0.003038	13.1013	7.40521	9.15108	1.66727
119	6222	0.004463	11.9006	7.33309	9.11181	1.74432
120	6549	0.005055	11.0587	7.32667	9.07502	1.84423
121	6877	0.005689	10.6143	7.32767	9.12636	1.8799
122	7204	0.007427	10.0729	7.36899	9.11047	1.9489
123	7531	0.007391	9.24842	7.30612	9.09584	2.01824
124	7858	0.007294	8.63541	7.2988	9.07855	2.09292

Table 20. Concentration data for Experiment 3b

Expt. no.	**Time (s)**	**[ArCHO]**	**[MVK]**	**[DBU]**	**[TMB]**	**[Prod.CH$_2$]**
100	0	0.108026	1.128146	0.219205	0.080977	0.00001
101	997	0.069156	0.89741294	0.295408	0.080977	0.007595
102	1324	0.063382	0.87621441	0.293027	0.080977	0.009346
103	1651	0.056921	0.85065947	0.292454	0.080977	0.008578
104	1978	0.050764	0.82925622	0.293933	0.080977	0.011885
105	2305	0.043626	0.80073499	0.293034	0.080977	0.014899

106	2632	0.036875	0.77836423	0.293463	0.080977	0.017483
107	2959	0.029751	0.74364383	0.29493	0.080977	0.02142
108	3286	0.022395	0.70856988	0.293784	0.080977	0.023259
109	3613	0.015911	0.67188689	0.292904	0.080977	0.026512
110	3940	0.01057	0.64221564	0.294238	0.080977	0.029487
111	4267	0.006052	0.60302252	0.295275	0.080977	0.036349
112	4594	0.003058	0.5667139	0.294911	0.080977	0.037755
113	4921	0.001444	0.53012115	0.29469	0.080977	0.042368
114	5248	0.000516	0.49172764	0.294854	0.080977	0.047159
115	5575	0.000218	0.46079645	0.294091	0.080977	0.050086
116	5902	0.00031	0.42321631	0.293277	0.080977	0.055033
117	6229	0.000252	0.39183076	0.293759	0.080977	0.059902
118	6556	0.000299	0.3689372	0.295432	0.080977	0.061715
119	6883	0.000121	0.34779743	0.294877	0.080977	0.066391
120	7211	0.000178	0.31728428	0.293263	0.080977	0.069758
121	7538	0.000203	0.29603346	0.294195	0.080977	0.074053
122	7865	0.000227	0.28253879	0.29258	0.080977	0.075061
123	8192	0.000297	0.26859509	0.294743	0.080977	0.077951
124	8519	0.000296	0.24700687	0.292698	0.080977	0.080855
125	8846	0.000293	0.23107385	0.292961	0.080977	0.084006

Table 21. 1st-Order kinetics data for Experiment 3b.

Expt. no.	**Time (s)**	**ln[ArCHO]**	**ln[MVK]**	**ln[DBU]**
100	0	-2.22538	0.12058	-1.51775
101	997	-2.67139	-0.10824	-1.32322
102	1324	-2.75858	-0.132145	-1.32778
103	1651	-2.86609	-0.161744	-1.35623
104	1978	-2.98057	-0.187226	-1.31134
105	2305	-3.1321	-0.22222	-1.32574
106	2632	-3.30022	-0.25056	-1.3115
107	2959	-3.51489	-0.29619	-1.35998
108	3286	-3.79892	-0.34451	-1.37902
109	3613	-4.14074	-0.39767	-1.4313
110	3940	-4.54974	-0.44283	-1.41351
111	4267	-5.10737	-0.5058	-1.46108
112	4594	-5.79	-0.5679	-1.45588
113	4921	-6.54311	-0.63465	-1.47943
114	5248	-7.5694	-0.70983	-1.50307
115	5575	-8.43102	-0.7748	-1.48507

Experiments 4a and 4b

The procedure described for Experiment 1 was followed, with methyl acrylate as activated alkene replacing MVK. Methyl acrylate (0.041g, 0.52mmol), 2,2'-dithiodibenzaldehyde (0.028g, 0.10mmol), TMB (0.0063g, 0.04mmol) and DBU (0.016g, 0.10mmol). Interval time between successive spectra was set at 300s for Experiment 4a and 600s for Experiment 4b.

Table 22. Integral data for Experiment 4b

Expt. no.	Time (s)	ArCHO	Product	Methyl acrylate	TMB	DBU
100	0	1.06204	0.037605	3.211060047	12	3.56824
101	627	1.03867	0.059941	3.165620089	11.823	3.54486
102	1255	1.03326	0.086732	3.177550077	11.8808	3.58265
103	1882	1.0233	0.107963	3.172310114	11.8875	3.59423
104	2508	1.01972	0.132172	3.185800076	11.9472	3.63084
105	3136	0.994781	0.152245	3.133539915	11.7628	3.5835
106	3763	0.995942	0.181044	3.167710066	11.9048	3.64991
107	4390	0.975012	0.200107	3.119260073	11.7412	3.60528
108	5016	0.974053	0.218832	3.143889904	11.8341	3.63949
109	5645	0.960518	0.244777	3.126110077	11.7819	3.64695
110	6272	0.952883	0.265518	3.137109995	11.832	3.66953
111	6900	0.936582	0.284587	3.099750042	11.7016	3.64559
112	7526	0.92596	0.306709	3.093420029	11.684	3.661
113	8153	0.906069	0.321774	3.058130026	11.5555	3.63163
114	8780	0.904323	0.351911	3.078099966	11.6466	3.68242
115	9406	0.893063	0.371899	3.07013011	11.6302	3.68822
116	10033	0.883915	0.395276	3.068949938	11.6391	3.70959
117	10661	0.863026	0.410216	3.015980005	11.4443	3.66381
118	11291	0.862955	0.437265	3.046370029	11.553	3.71777
119	11918	0.849287	0.452541	3.023740053	11.4896	3.69827
120	12544	0.842056	0.468489	3.030139923	11.4845	3.72043
121	13171	0.823348	0.493836	2.995879889	11.3928	3.69657
122	13797	0.82524	0.511512	3.026819944	11.5012	3.74152
123	14424	0.805615	0.53195	2.971149921	11.3346	3.68741
124	15051	0.805855	0.554453	3.003629923	11.4533	3.73833
125	15677	0.793401	0.575157	2.982069969	11.3817	3.72272
126	16304	0.790028	0.594999	3.002199888	11.466	3.76353
127	16933	0.765237	0.607191	2.935060024	11.2257	3.68772
128	17560	0.766007	0.622528	2.967530012	11.3537	3.73829
129	18188	0.753011	0.633775	2.951889992	11.2932	3.72747
130	18816	0.749792	0.678172	2.961920023	11.3594	3.75783
131	19443	0.728269	0.682581	2.898560047	11.1388	3.69018
132	20071	0.726743	0.707462	2.924730062	11.2348	3.73846
133	20698	0.712137	0.716497	2.892790079	11.1262	3.70442

134	21324	0.715666	0.747563	2.932889938	11.2837	3.76862
135	21951	0.69514	0.749761	2.876189947	11.078	3.71019
136	22579	0.694121	0.778466	2.899369955	11.1828	3.75584
137	23205	0.681148	0.784292	2.873800039	11.0896	3.72963
138	23832	0.681731	0.815878	2.893029928	11.175	3.76938
139	24461	0.661587	0.818685	2.842420101	10.9897	3.71552
140	25088	0.6614	0.849161	2.874130011	11.1274	3.76772
141	25716	0.646147	0.847386	2.8364501	10.9573	3.73185
142	26342	0.644131	0.874991	2.848069906	11.0447	3.75792
143	26969	0.631639	0.879314	2.823600054	10.9451	3.73656
144	27596	0.632864	0.904658	2.855669975	11.0739	3.78922
145	28223	0.612738	0.906967	2.796979904	10.8521	3.7243
146	28849	0.614688	0.943481	2.832979918	11.0151	3.7881
147	29476	0.598524	0.93986	2.778739929	10.8144	3.72261
148	30103	0.594182	0.964128	2.798069954	10.8978	3.75803
149	30729	0.582632	0.958205	2.770420074	10.7919	3.72365
150	31356	0.580698	0.988615	2.785510063	10.8609	3.75726
151	31984	0.56829	0.985888	2.754309893	10.739	3.72049
152	32612	0.565816	1.00562	2.769049883	10.8075	3.7492
153	33242	0.556843	1.02423	2.756839991	10.7801	3.75295
154	33869	0.55684	1.05217	2.783250093	10.8908	3.80316
155	34497	0.540112	1.04984	2.732270002	10.7011	3.72747
156	35125	0.541509	1.0658	2.76534009	10.8353	3.80028
157	35753	0.531191	1.0647	2.738209963	10.7296	3.76066
158	36380	0.528647	1.09206	2.758630037	10.8132	3.79486

Table 23. Concentration data for Experiment 4b

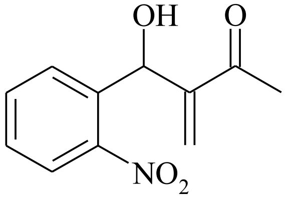
Expt. no.	Time (s)	[ArCHO]	[Product]	[Methyl acrylate]	TMB	[DBU]
100	0	0.551714	0.03907	3.336196059	1.03897	0.617883
101	627	0.547651	0.06321	3.33822411	1.03897	0.623024
102	1255	0.542149	0.091016	3.334502855	1.03897	0.626602
103	1882	0.53662	0.113232	3.327127906	1.03897	0.628273
104	2508	0.53207	0.13793	3.3245799	1.03897	0.631501
105	3136	0.527195	0.161368	3.321306032	1.03897	0.633038
106	3763	0.521514	0.189604	3.317475238	1.03897	0.637079
107	4390	0.517669	0.212488	3.312252739	1.03897	0.638057
108	5016	0.5131	0.230547	3.312199496	1.03897	0.639055
109	5645	0.508212	0.259024	3.30805943	1.03897	0.643202
110	6272	0.502037	0.279782	3.305643216	1.03897	0.644444
111	6900	0.498948	0.303217	3.30267476	1.03897	0.647375
112	7526	0.494032	0.32728	3.300895141	1.03897	0.65109
113	8153	0.488795	0.347174	3.29952625	1.03897	0.653049
114	8780	0.484037	0.376719	3.295095096	1.03897	0.657003
115	9406	0.478684	0.398678	3.291197674	1.03897	0.658966
116	10033	0.473419	0.423414	3.287416918	1.03897	0.662277
117	10661	0.470099	0.446897	3.285667558	1.03897	0.665238

118	11291	0.465637	0.471883	3.2875491	1.03897	0.668684
119	11918	0.460791	0.491063	3.281133648	1.03897	0.668847
120	12544	0.457071	0.508595	3.289538533	1.03897	0.673154
121	13171	0.450513	0.540426	3.27852346	1.03897	0.67422
122	13797	0.447292	0.554494	3.281163153	1.03897	0.675987
123	14424	0.443073	0.585125	3.26815567	1.03897	0.676003
124	15051	0.438612	0.603557	3.269641611	1.03897	0.678235
125	15677	0.43455	0.630034	3.266593516	1.03897	0.679652
126	16304	0.429522	0.646977	3.264465371	1.03897	0.682051
127	16933	0.424949	0.674367	3.259777253	1.03897	0.682618
128	17560	0.420581	0.683606	3.258682898	1.03897	0.684177
129	18188	0.41566	0.699685	3.258873862	1.03897	0.685852
130	18816	0.411472	0.744336	3.250890391	1.03897	0.687408
131	19443	0.407575	0.764012	3.244354429	1.03897	0.688402
132	20071	0.403246	0.785095	3.245673386	1.03897	0.69145
133	20698	0.398998	0.802882	3.24156289	1.03897	0.691841
134	21324	0.395379	0.826001	3.240623813	1.03897	0.694007
135	21951	0.39117	0.843812	3.236984237	1.03897	0.695934
136	22579	0.386936	0.867908	3.232491928	1.03897	0.697894
137	23205	0.382895	0.881752	3.230911515	1.03897	0.698848
138	23832	0.380294	0.910253	3.227674798	1.03897	0.700899
139	24461	0.37528	0.928785	3.224681308	1.03897	0.702533
140	25088	0.370531	0.951439	3.220305531	1.03897	0.703587
141	25716	0.367606	0.964189	3.227423612	1.03897	0.707707
142	26342	0.363559	0.98772	3.215001042	1.03897	0.707012
143	26969	0.359752	1.001633	3.216383596	1.03897	0.709391
144	27596	0.356258	1.018517	3.215080069	1.03897	0.711021
145	28223	0.351978	1.041986	3.213364032	1.03897	0.713122
146	28849	0.347873	1.067896	3.206560619	1.03897	0.714605
147	29476	0.345011	1.08354	3.203537912	1.03897	0.715284
148	30103	0.339887	1.103012	3.201135819	1.03897	0.716563
149	30729	0.336551	1.106993	3.200605225	1.03897	0.716975
150	31356	0.333303	1.134869	3.197593878	1.03897	0.718851
151	31984	0.329883	1.144585	3.197667705	1.03897	0.719895
152	32612	0.326366	1.160094	3.194404609	1.03897	0.720853
153	33242	0.322006	1.184566	3.188402639	1.03897	0.723408
154	33869	0.318732	1.20451	3.186227742	1.03897	0.725635
155	34497	0.314637	1.223148	3.183314602	1.03897	0.7238
156	35125	0.311544	1.226363	3.181939924	1.03897	0.728799
157	35753	0.308618	1.237166	3.181761339	1.03897	0.728306
158	36380	0.304766	1.259148	3.180706593	1.03897	0.729247

Table 24. 1st-Order kinetics data for Experiment 4b.

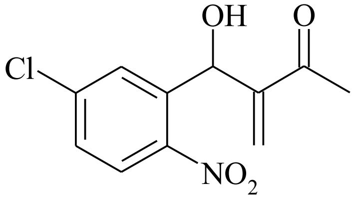
Expt. no.	Time (s)	ln[ArCHO]	ln[Macrylate]	ln[DBU]
100	0	-0.59473	1.2048	-0.481456
101	627	-0.60212	1.20543	-0.47317
102	1255	-0.61221	1.204324	-0.46744
103	1882	-0.62247	1.202109	-0.46478
104	2508	-0.63098	1.201343	-0.45966
105	3136	-0.64019	1.200358	-0.45722
106	3763	-0.65102	1.199204	-0.45086
107	4390	-0.65842	1.197629	-0.449328
108	5016	-0.66728	1.197612	-0.44776
109	5645	-0.67686	1.196362	-0.44196
110	6272	-0.68908	1.195631	-0.439367
111	6900	-0.69525	1.194332	-0.43483

3.4 Synthesis of 2-nitrobenzaldehyde BH adducts



4-Hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one 167a

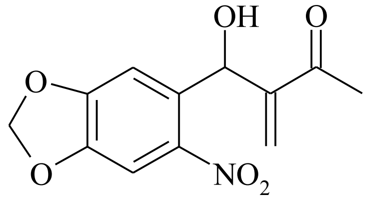
A solution of 2-nitrobenzaldehyde (10.0g, 66.0mmol), methyl vinyl ketone (6.99g, 99.0mmol), DABCO (0.37g, 3.3mmol) in $CHCl_3$ (2ml) was stirred in a stoppered flask at room temperature for 7 days. The solvent was evaporated from the resulting mixture *in vacuo,* and the crude product was purified by flash chromatography on silica [elution with EtOAc-hexane (1:3)] to afford, as yellow-brown crystals, 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **167a** (11.1g, 75%), m.p. 80-82°C (lit.[12] 94-95°C) (Found **M**$^+$: 221.06672. $C_{11}H_{11}NO_4$ requires *M*, 221.06881); ν_{max}/cm^{-1} (nujol) 3345 (OH) and 1665 (C=O); δ_H (400MHz; $CDCl_3$) 2.01 (1H, br s, OH), 2.35 (3H, s, CH_3), 5.77 and 6.15 (2H, 2 x s, CH_2), 6.20 (1H,d, *J*=4.4Hz, C*H*OH), 7.44 (1H, m, 4'-H), 7.63 (1H, m, 5'-H), 7.76 (1H, d, *J*=7.86Hz, 6'-H) and 7.95 (1H, dd, *J*=8.14Hz and 0.99Hz, 3'H); δ_C (100MHz; $CDCl_3$) 25.9 (C-1), 67.3 (C-4), 124.5 (C-3'), 126.4 (C=*C*H_2), 128.4 (C-4'), 128.8 (C-6'), 133.4 (C-5'), 136.5 (C-1'), 147.9 (C-2'), 148.9 (*C*=CH_2) and 199.6 (C-2); *m/z* 221 (**M**$^+$, 0.2%) and 43 (100).



4-(5-Chloro-2-nitrophenyl)-4-hydroxy-3-methylenebutan-2-one 167b

The procedure described for the synthesis of 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **167a** was followed, using 5-chloro-2-nitrobenzaldehyde

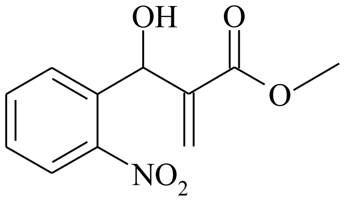
(1.00g, 5.4mmol), methyl vinyl ketone (0.68ml, 8.1mmol) and DABCO (0.03g, 0.27mmol) in $CHCl_3$ (0.6ml). The crude product was purified by flash chromatography on silica [elution with EtOAc-hexane (1:3)] to afford, as a reddish-brown oil which slowly crystallized, 4-(5-chloro-2-nitrophenyl)-4-hydroxy-3-methylenebutan-2-one **167b**. (1.4g, 95%), m.p. 77-79°C (lit.[47] 72-74°C) (Found: **$M-NO_2^+$** : 209.03621. $C_{11}H_{10}NO_4$ ^{35}Cl requires *M*-NO_2, 209.03693); ν_{max}/cm^{-1} (nujol) 3449 (OH) and 1692 (C=O); δ_H (400MHz; $CDCl_3$) 2.37 (3H, s, CH_3), 3.50 (1H, br s, OH), 5.76 and 6.15 (2H, 2x s, CH_2), 6.22 (1H, d, *J*=3.29Hz, C*H*OH), 7.41 (1H, dd, *J*=8.71Hz and 2.34Hz, 3'-H), 7.77 (1H, d, *J*= 2.30Hz, 6'-H) and 7.94 (1H, d, *J*=8.71Hz, 4'-H): δ_C (100MHz; $CDCl_3$) 25.9 (C-1), 67.2 (C-4), 126.2 (C-4'), 126.5 (C=*C*H_2), 128.6 (C-3'), 129.1 (C-1'), 138.7 (C-6'), 140.2 (C-2'), 146.1 (C-5'), 148.6 (*C*=CH_2) and 199.7 (C-2); *m/z* 255 [**M^+** (^{35}Cl); 13%] and 210 (100).



4-Hydroxy-3-methylene-4-(4,5-methylenedioxy-2-nitrophenyl)butan-2-one 167c

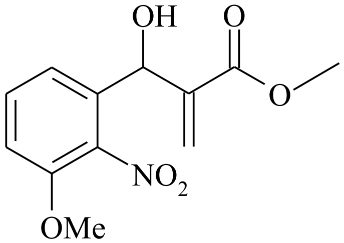
The procedure described for the synthesis of 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **167a** was followed, using, 4,5-methylenedioxy-2-nitrobenzaldehyde (3.06g, 15.6mmol), methyl vinyl ketone (2.7ml, 38.0mmol) and DABCO (0.11g, 1.0mmol) in $CHCl_3$ (0.4ml). The mixture was stirred in a stoppered flask at room temperature for 7 days. The solvent was evaporated from the resulting mixture *in vacuo,* and the crude product was purified by flash chromatography on silica [elution with EtOAc-hexane-$CHCl_3$ (1:1:3)] to afford, as reddish-yellow crystals, 4-hydroxy-3-methylene-4-(4,5-methylenedioxy-2-nitrophenyl)butan-2-one **167c** (2.5g, 60%); m.p. 97-99°C (lit[86] 100-103°C) (Found: **M^+**: 267.07429. $C_{12}H_{11}NO_6$ requires *M*, 267.18570); ν_{max}/cm^{-1} (nujol) 3466 (OH) and 1624 (C=O); δ_H (400MHz; $CDCl_3$) 2.43 (3H, s, CH_3), 3.60 (1H, br s, OH), 5.80 (1H, s ,C*H*OH), 6.16 (4H, overlapping signals, CH_2=C and OCH_2O), 7.31 (1H, s, 6'-H), 7.57 (1H, s, 3'-H); δ_C (100MHz; $CDCl_3$) 26.0 (C-1), 67.4 (C-4), 103.0 (O*C*H_2O), 105.5 (C-6'), 107.7 (C-3'), 126.0 (C=*C*H_2), 134.2 (C-1'), 147.1

(C=CH_2), 147.2 (C-5’), 149.1 (C-4’), 152.3 (C-2’) and 199.9 (C=O); *m/z* 266 (**M**$^+$, 0.9%) and 43 (100).



Methyl 3-hydroxy-2-methylene-3-(2- nitrophenyl)propanoate 167d

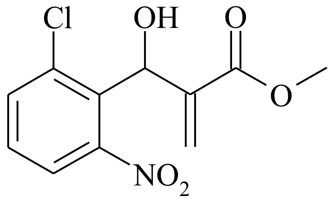
The procedure described for the synthesis of 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **167a** was followed, using 2-nitrobenzaldehyde (3.0g, 20mmol), methyl acrylate (2.7ml, 30mmol) and DABCO (0.11g, 1.0mmol) in $CHCl_3$ (0.6ml). The crude product was purified by flash chromatography on silica [elution with EtOAc-hexane (1:3) to afford as a light green oil, methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **167d** (2.85g, 57.3%) (Found: **M**$^+$-H_2O: 219.05329. $C_{11}H_{11}NO_5$ requires *M,* 219.05316); ν_{max}/cm^{-1} (nujol) 3471 (OH) and 1710 (C=O); δ_H (400MHz; $CDCl_3$) 3.45 (1H, br s, OH), 3.71 (3H, s, CH_3), 5.71 and 6.18 (2H, 2x s, CH_2), 6.35 (1H, s, C*H*OH), 7.45 (1H, t, *J*=7.74Hz, 4’-H), 7.63 (1H, t, *J*=7.61Hz, 5’-H), 7.74 (1H, d, *J*=7.81Hz, 6’-H) and 7.93 (1H, d, *J*=8.56, 3’-H); δ_C (100MHz; $CDCl_3$) 52.1 (OCH_3), 67.7 (CHOH), 124.6 (C=CH_2),126.4 (C=CH_2), 128.6 (C-3’), 128.9 (C-6’), 133.4 (C-4’), 136.1 (C-1’), 140.7 (C-5’), 148.3 (C-2’) and 166.4 (C=O); *m/z* 219 (**M**$^+$-H_2O, 11%) and 77 (100).



Methyl 3-hydroxy-2-methylene-3-(3-methoxy-2-nitrophenyl) propanoate 167e

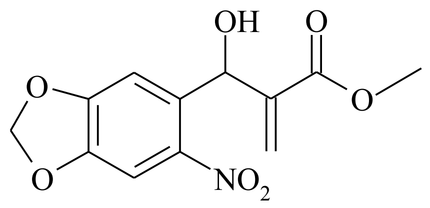
The procedure described for the synthesis of 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **167a** was followed, using 3-methoxy-2-nitrobenzaldehyde (0.5g, 3mmol), methyl acrylate (0.37ml, 4.2mmol) and DABCO (0.016g, 0.14mmol) in $CHCl_3$

(1ml). After 7 days, the solid was filtered off to give, as pure colourless crystals, *methyl 3-hydroxy-2-methylene-3-(3-methoxy-2-nitrophenyl)propanoate* **167e** (0.48g, 65%); m.p. 108-109°C; (Found: **M^+-NO_2**; 221.083260. $C_{12}H_{13}NO_6$ requires *M*, 221.081384); ν_{max}/cm^{-1} (nujol) 3485 (OH) and 1706 (C=O); δ_H (400MHz; $CDCl_3$) 3.25 (1H, br s, OH), 3.70 (3H, s, CH_3), 3.88 (3H, s, OCH_3), 5.62 (1H,s, C*H*OH), 5.86 and 6.41 (2H, 2x s, CH_2), 6.99 (1H, d, *J*=7.88Hz, 6'-H), 7.09 (1H, d, *J*=7.88Hz, 4'-H) and 7.41 (1H, t, *J*=8.15Hz, 5'H); δ_C (100MHz; $CDCl_3$) 52.1 (C-1), 56.5 (OCH_3), 68.3 (C-5), 112.2 (C-5'), 119.3 (C-6'), 127.4 (C-4''), 131.3 (C-4), 134.4 (C-1'), 139.6 (C-2'), 140.4 (C-4'), 150.9 (C-3') and 166.1 (C=O); *m/z* 221 (**M^+-NO_2**, 100%).



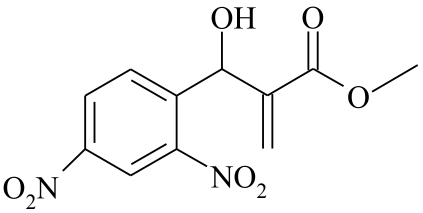
Methyl 3-(6-chloro-2-nitrophenyl)-3-hydroxy-2-methylenepropanoate 167f

The procedure described for the synthesis of 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **167a** was followed, using 6-chloro-2-nitrobenzaldehyde (0.50g, 2.7mmol), methyl acrylate (0.36ml, 4.1mmol) and DABCO (0.015g, 0.14mmol) in $CHCl_3$ (0.1ml). The crude product was purified by flash chromatography on silica [elution with EtOAc-hexane (1:3)] to afford, as a dark brown solid, *methyl 3-(6-chloro-2-nitrophenyl)-3-hydroxy-2-methylenepropanoate* **167f** (0.91g, 85.9%); m.p. 99-101°C; (**M^+-H_2O**; 252.989934. $C_{11}H_{10}ClNO_5$ requires *M*, 252.990376); ν_{max}/cm^{-1} (nujol) 3335 (OH) and 1704 (C=O); δ_H (400MHz; $CDCl_3$) 2.86 (1H,br s, OH), 3.73 (3H, s, CH_3), 5.73 (1H, s, C*H*OH), 6.17 and 6.44 (2H, 2 x s, CH_2), 7.38 (1H, t, *J*= 8.05Hz, 4'-H), 7.51 (1H, dd, *J*=8.02 and 0.94Hz, 5'-H) and 7.59 (1H, dd, *J*=8.02 and 1.13Hz, 3'-H); δ_C (100MHz; $CDCl_3$) 52.2 (C-1), 68.9 (C-4), 122.8 (C-4'), 127.8 (C=*C*H_2), 129.3 (C-3'), 131.7 (C-1'), 133.3 (C-5'), 135.6 (C-2'), 138 (C-6'), 151.4 (*C*=CH_2) and 166.3 (C=O); *m/z* 252 (**M^+-H_2O**, 23.4) and 55 (100).



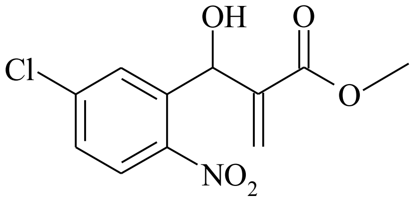
Methyl 3-hydroxy-2-methylene-3-(3,4-methylenedioxy-2-nitro-phenyl)propanoate 167g

The procedure described for the synthesis of 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **167a** was followed using 4,5-methylenedioxy-2-nitrobenzaldehyde (3.0g, 16mmol), methyl acrylate (2.7ml, 31mmol) and DABCO (0.11g, 1.0mmol) in $CHCl_3$ (0.4ml). The crude product was purified by flash chromatography on silica [elution with EtOAc-hexane-$CHCl_3$ (1:1:3)] to afford, as a pink-yellow solid, methyl 3-hydroxy-2-methylene-3-(3,4-methylenedioxy-2-nitrophenyl)propanoate **167g** (0.67g, 15.3%); m.p.121-123°C[89] (Found **M**$^+$: 281.052437. $C_{12}H_{11}NO_7$ requires *M*, 281.053552); ν_{max}/cm^{-1} (nujol) 3486 (OH) and 1706 (C=O); δ_H (400MHz; $CDCl_3$) 3.37 (1H, br s, OH), 3.74 (3H, s, CH_3), 5.69 and 6.33 (2H, 2 x s, CH_2), 6.11 (2H, s, C=CH_2), 6.17 (1H, d, *J*= 2.22Hz, C*H*OH), 7.16 (1H, s, ArH) and 7.49 (1H, s, ArH); δ_C (100MHz; $CDCl_3$) 52.2 (C-1), 67.8 (C-4), 103.0 (OCH_2O), 105.5 (C-6'), 107.7 (C-3'), 126.1 (C=*C*H_2), 133.6 (C-1'), 140.9 (*C*=CH_2), 142.2 (C-5'), 147.4 (C-4'), 152.2 (C-2') and 166.5 (C=O); *m/z* 281 (20.1).



Methyl 3-(2,4-dinitrophenyl)-3-hydroxy-2-methylenepropanoate 167h

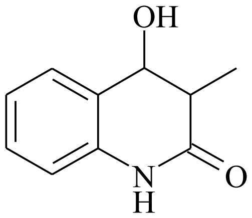
The procedure described for the synthesis of 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **167a** was followed using 2,4-dinitrobenzaldehyde (1.0g, 5.0mmol), methyl acrylate (0.69ml, 7.8mmol) and DABCO (0.03g, 0.27mmol) in $CHCl_3$ (1ml). The crude product was purified by flash chromatography on silica [elution with EtOAc-hexane-$CHCl_3$ (2:1:1)] to afford, as a green solid, methyl 3-(2,4-dinitrophenyl)-3-hydroxy-2-methylenepropanoate **167h** (1.32g, 92%), m.p. 62-64°C (lit.[86] 82-85°C) (Found **M**$^+$-H_2O: 264.03844. $C_{11}H_{10}N_2O_7$ requires M^+-H_2O, 264.038824); ν_{max}/cm^{-1} (nujol) 3449 (OH) and 1724 (C=O); δ_H (400MHz; $CDCl_3$) 2.96 (1H, br s, OH), 3.74 (3H, s, CH_3), 5.74 and 6.39 (2H, 2x s, CH_2), 6.29 (1H, s, C*H*OH), 8.03 (1H, d, *J*= 8.65Hz, 5'-H), 8.46 (1H, dd, *J*=8.66 and 2.25Hz, 6'-H) and 8.78 (1H, d, *J*=2.23Hz, 3'-H); δ_C (100MHz; $CDCl_3$) 52.4 (CH_3), 67.6 (CHOH), 120.0 (C-3'), 127.2 and 127.3 (C=CH_2), 130.7 (C-5'), 139.8 (C-6'), 146.8 (C-1'), 147.2 (C-2'), 148.1 (C-4') and 166.0 (C=O) ; *m/z* 264 (M^+- H_2O, 40%) and 59 (100).



Methyl 3-(5-chloro-2-nitrophenyl)-3-hydroxy-2-methylenepropanoate 167i

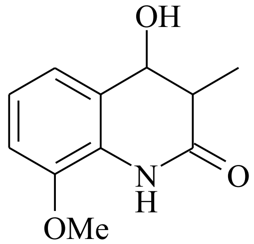
The procedure described for the synthesis of 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **167a** was followed, using 5-chloro-2-nitrobenzaldehyde (1.0g, 5.4mmol), methyl acrylate (1.6ml, 8.1mmol) and DABCO (0.03g, 0.27mmol) in $CHCl_3$ (0.2ml). After three weeks the reaction was stopped and it appeared from ^{1}H NMR of the crude product that there was very little of the expected product.

3.5 Catalytic Hydrogenation of BH adducts



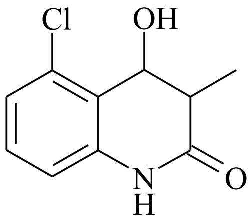
4-Hydroxy-3-methyl-3,4-dihydro-1*H*-quinolin-2-one 168d

To a solution of methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **167d** (1.09g, 4.50mmol) in ethanol (50ml) was added 10% Pd-C catalyst (0.16g), and the reaction mixture was stirred vigorously under hydrogen at atmospheric pressure for 1.5h. The solution was filtered and the solvent was evaporated from the filtrate *in vacuo*. The crude product was dissolved in CH_2Cl_2, dried over anyhdrous $MgSO_4$ and finally purified by flash chromatography on silica [elution with hexane-EtOAc (3:1)] to afford, as yellow-brown crystals, 4-hydroxy-3-methyl-3,4-dihydro-1*H*-quinolin-2-one **168d** (0.64g, 86.5%), m.p. 131-133°C; ν_{max}/cm^{-1} (nujol) 3423 (OH), 3064 (NH) and 1664 (C=O); δ_H (600MHz; $CDCl_3$) 1.27 (3H, d, CH_3), 2.28 (1H, m, 3-H), 5.44 (1H, d, *J*=6.19Hz, C*H*OH) 6.88 (1H, d, *J*=7.86Hz, Ar-H), 7.07 (1H, t, *J*=7.2Hz Ar-H), 7.26 (1H, d, *J*=7.74Hz, Ar-H), 7.96 (1H, t, *J*=8.32Hz, ArH) and 8.92 (1H, s, NH) ; δ_C (150MHz; $CDCl_3$) 13.3 (3-CH_3), 43.7 (C-3), 68.5 (C-4), 113.6 (C-7), 115.7 (C-6), 123.5 (C-4a), 124.5 (C-5), 126.4 (C-8), 140.9 (C-8a), 173.8 (C=O)



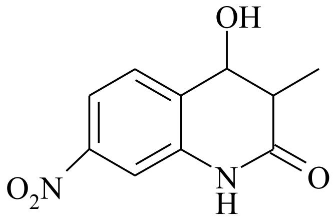
***4-Hydroxy-8-methoxy-3-methyl-3,4-dihydro-1*H*-quinolin-2-one* 168e**

The procedure described for the synthesis of compound **168d** was followed using the BH adduct **167e** (0.39g, 4.50mmol), ethanol (31ml) and 10% Pd-C catalyst (0.061g), to give as cream crystals, *4-hydroxy-8-methoxy-3-methyl-3,4-dihydro-1*H*-quinolin-2-one* **168e** (0.27g, 96.7%); m.p. 114-115°C; (Found **M**$^+$; 207.087343. $C_{11}H_{13}NO_3$ requires *M*, 207.086863); ν_{max}/cm^{-1} (nujol) 3366 (OH), 3088 (NH) and 1663 C=O); δ_H (600MHz; $CDCl_3$) 1.39 (3H, d, *J*=7.12Hz, 3'-CH_3), 1.64 (1H, br s, OH), 2.77 (1H, m, 3-H), 3.86 (3H, s, OCH_3), 4.74 (1H, d, *J*=3.65Hz, 4-H), 6.85 (1H, d, *J*= 8.73Hz, 7-H), 6.93 (1H, d, *J*=7.16Hz, 5-H), 7.01 (1H, m, 6-H) and 7.79 (1H, s, NH); δ_C (150MHz; $CDCl_3$) 10.4 (3'-CH_3), 41.4 (C-3), 55.9 (OCH_3), 70.8 (C-4), 111.0 (C-7), 119.6 (C-5), 123.0 (C-4a), 125.8 (C-6), 125.9 (C-8a), 145.9 (C-8) and 171.1 (C=O): *m/z* 207 (**M**$^+$, 100%).



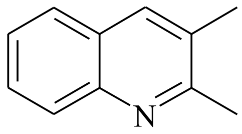
***5-Chloro-4-hydroxy-3-methyl-3,4-dihydro-1*H*-quinolin-2-one* 168f**

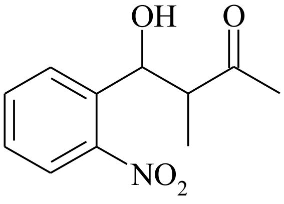
The procedure described for the synthesis of compound **168d** was followed using the BH adduct **167f** (0.42g, 4.50mmol), ethanol (35ml) and 10% Pd-C catalyst (0.071g), to afford, as a yellow-brown oil, *5-chloro-4-hydroxy-3-methyl-3,4-dihydro-1*H*-quinolin-2-one* **168f** (0.245g, 81%) (Found **M**: 211.057087. $C_{10}H_{11}ClNO_2$ requires *M*, 211.65); ν_{max}/cm^{-1} (nujol) 3374 (OH), 3060 (NH) and 1723 (C=O); δ_H (600MHz; $CDCl_3$) 1.39 (3H, t, *J*=7.85Hz, CH_3), 2.77 (1H, dd, *J*=10.27 and 6.93Hz, 3-H), 5.07 (1H, d, *J*=3.34Hz, C*H*OH), 6.79 (1H, d, *J*=7.91Hz, 8-H), 7.14 (1H, t, *J*=7.99Hz, 7-H), 7.30 (1H, d, *J*=8.18Hz, 6-H), 8.89 (1H, br s, OH) and 9.14 (1H, s, NH); δ_C (150MHz; $CDCl_3$) 22.1 (CH_3), 40.7 (C-3), 41.3 (C-4), 114.9 (C-8), 122.8 (C-4a), 124.5 (C-6), 130.3 (C-7), 133.5 (C-5), 139.2 (C-8a) and 172.6 (C=O); *m/z* 211 (**M**; 49%) and 154 (100).



4-Hydroxy-3-methyl-7-nitro-3,4-dihydro-1*H*-quinolin-2-one 168h

The procedure described for the synthesis of **168d** was followed using the BH adduct **167h**, (0.29g, 4.50mmol), ethanol (25ml) and 10% Pd-C catalyst (0.05g). The reaction mixture was stirred vigorously under hydrogen at atmospheric pressure for 1.5h. The solvent was evaporated *in vacuo*, and the crude product was dissolved in CH_2Cl_2, dried (anyhdrous $MgSO_4$) and finally purified by flash chromatography on silica. ^{1}H NMR analysis of the chromatographed material revealed weak signals corresponding to the expected product, while low resolution mass spectrometry analysis of the impure product showed a peak at *m/z* 222 corresponding to the molecular ion of compound **168h.**



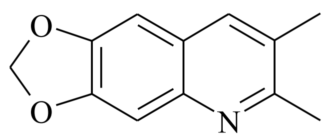


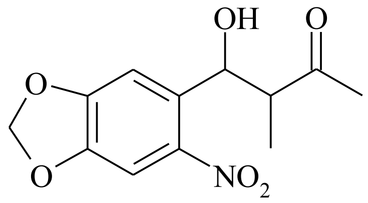
2,3-dimethylquinoline 170a and 4-hydroxy-3-methyl-4-(2-nitrophenyl)-butan-2-one 171a

The procedure described for the synthesis of compound **168d** was followed using the BH adduct **167a** (1.01g, 4.50mmol) in ethanol (50ml) and 10% Pd-C catalyst (0.16g), to afford two fractions:

Fraction 1. 2,3-Dimethylquinoline **170a** as light yellow crystals (0.15g, 16%), m.p. 65-68ºC (lit.[47] 69-70ºC) (Found **M**$^+$: 157.08826. $C_{11}H_{11}N$ requires *M*, 157.08915); ν_{max}/cm^{-1} (nujol) 1669 (N=C); δ_H (400MHz; $CDCl_3$) 2.45 (3H,s, 3-CH_3), 2.69 (3H, s, 2-CH_3), 7.44 (1H, t, *J*=7.42Hz, 6-H), 7.60 (1H, t, *J*=7.69Hz, 7-H), 7.70 (1H, d, *J*=8.12Hz, 5-H), 7.83 (1H, s, 4-H) and 7.98 (1H, d, *J*=8.47Hz, 8-H); δ_C (100MHz; $CDCl_3$) 19.6 (3-CH_3), 23.5 (2- CH_3), 125.6 (C-4a), 125.7 (C-6), 126.7 (C-5), 128.2 (C-7), 128.4 (C-8), 130.0 (C-3), 135.3 (C-4), 135.4 (C-8a) and 159.0 (C-2); *m/z* 157 (**M**$^+$, 100%).

Fraction 2. 4-Hydroxy-3-methyl-4-(2-nitrophenyl)butan-2-one **171a** as a brown oil (0.11g, 8.3%); ν_{max}/cm^{-1} (nujol) 3375 (OH) and 1722 (C=O); δ_H (400MHz; $CDCl_3$) 1.18 (3H, d, *J*=7.01Hz, CH_3CH), 2.12 (3H, s, CH_3CO), 3.02 (1H, m, 3-H), 4.33 (1H, t, *J*=7.02Hz, 4-H), 5.20 (1H, br s, OH), 7.48 (1H, t, *J*=7.0Hz, 5'-H), 7.61 (1H, t, *J*=7.2Hz, 4'-H), 7.77 (1H, d, *J*=8.15Hz, 3'-H) and 8.00 (1H, d, *J*= 8.15Hz, 6'-H); δ_C (100MHz; $CDCl_3$) 16.6 (CH_3CH), 27.8 (CH_3CO), 51.1 (C-3), 71.4 (C-4), 125.9 (C-5'), 129.0 (C-6'), 132.6 (C-3'), 136.1 (C-1'), 139.9 (C-2') and 213.5 (C=O).





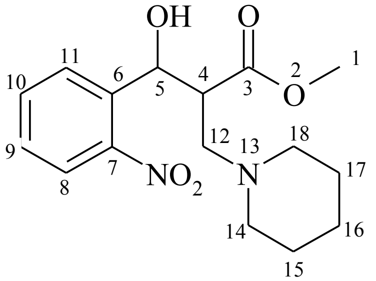
6,7-Methylenedioxy-2,3-dimethylquinoline 170c and 4-hydroxy-3-methyl-4-(2-nitro-4,5-methylenedioxyphenyl)-butan-2-one 171c

The procedure described for the synthesis of compound **170a** was followed, using the BH adduct **167c** (1.06g, 4.50mmol), ethanol (50ml) and 10% Pd-C catalyst (0.16g). The solvent was evaporated *in vacuo*, and the crude product was dissolved in CH_2Cl_2, dried (anyhd. $MgSO_4$) and finally purified by flash chromatography on silica [elution with hexane-EtOAc (3:1)] to afford two fractions.

Fraction 1. 6,7-Methylenedioxy-2,3-dimethylquinoline **170c** as yellow-brown crystals (0.23g, 29%), m.p. 149-151°C (lit.[47] 148-150°C) (Found, **M**$^+$: 203.07088. $C_{12}H_{11}NO_2$ requires *M*, 203.07082) ; ν_{max}/cm^{-1} (nujol) 1251 (N=C); δ_H (400MHz; $CDCl_3$) 2.35 (3H,s, 3-CH_3), 2.58 (3H, s, 2-CH_3), 6.03 (2H, s, CH_2), 6.92 (1H, s, 4-H), 7.26 (1H, s, 5-H) and 7.62 (1H, s, 8-H); δ_C (100MHz; $CDCl_3$) 12.9 (3-CH_3), 25.8 (2-CH_3), 136.9 (CH_2), 103.3 (C-4), 105.7 (C-5), 127.1 (C-8), 129.8 (C-4a), 136.9 (C-3), 138.1 (C-8a), 147.3 (C-6), 150.4 (C-7) and 198.9 (C-2); *m/z* 203 (**M**$^+$, 79%) and 43 (100).

Fraction 2. 4-Hydroxy-3-methyl-4-(2-nitro-4,5-methylenedioxyphenyl)butan-2-one **171c** as a brown oil, (0.36g, 33.7%); ν_{max}/cm^{-1} (nujol) 3435 (OH) and 1644 (C=O); δ_H (400MHz; $CDCl_3$) 1.13 (3H, d, *J*=7.01Hz, CH_3), 2.08 (3H, s, CH_3CO), 2.84 (1H, m, 3-H), 4.78 (1H, br s, OH), 5.91 (1H, s, 4-H), 6.03 (2H, s, CH_2), 6.93 (1H, s, 3'-H) and 7.60 (1H, s, 6'-H); δ_C (100MHz; $CDCl_3$) 13.5 ($\mathit{C}H_3CH$), 30.1 ($\mathit{C}H_3CO$), 52.3 (C-3), 70.3 (C-4), 102.3 (CH_2), 104.5 (C-6'), 134.4 (C-1'), 141.1 (C-2'), 106.8 (C-3'), 147.4 (C-4'), 151.2 (C-5') and 212.7 (C=O).

3.6 Reactions of methyl acrylate derived BH adducts with amines



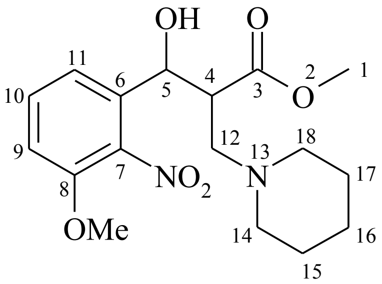
***Methyl 3-hydroxy-3-(2-nitrophenyl)-2-[(piperidin-1-yl)methyl]propanoate* 172d** †

A mixture of methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **167d** (0.54g, 2.3mmol), piperidine (0.5ml, 2mmol) and dry THF (5ml) was stirred in a stoppered flask for 24h. Excess piperidine was evaporated *in vacuo* and the residue was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (1:1)] to give, as a yellow crystalline solid, comprising a diastereomeric mixture (*ca*. 88% d.e.) of *methyl 3-hydroxy-3-(2-nitrophenyl)-2-[(piperidin-1-yl)methyl]propanoate* **172d** (0.61g, 84%) (Low-res APCI; Found $\mathbf{M}^+$: 323.283 requires $M_{,}$ 323.36); m.p. 76-78°C, ν_{max}/cm^{-1} (nujol) 3473 (OH) and 1714 (C=O); δ_H (600MHz; $CDCl_3$) 1.46 (2H, br s, 16-CH_2), 1.62 (4H, m, 15- and 17-CH_2), 2.42 (1H, br s, OH), 2.50 (4H, 2 x m, 14- and 18-CH_2), 2.80 and 3.03 (2H, 2 x m, 12-CH_2), 3.17 (1H, ddd, *J*=11.68, 8.85 and 3.14Hz, 4-CH_2), 3.46 (3H,s, CH_3), 5.55 (1H, d, *J*=8.83Hz, C*H*OH), 7.37 (1H, m, 9-H), 7.56 (1H, m, 11-H), 7.66 (1H, dd, *J*=7.86 and 1.14Hz, 10-H) and 7.71 (1H, dd, *J*=8.10 and 1.11Hz, 8-H); δ_C (150MHz; $CDCl_3$) 23.9 (C-16), 25.8 (C-15 and C-17), 48.4 (C-4), 51.8 (C-1), 54.7 (C-14 and C-18), 60.8 (C-12), 73.2 (C-5), 124.0 (C-8), 128.4 (C-9), 129.4 (C-11), 132.3 (C-10), 136.6 (C-6), 149.1 (C-7) and 171.4 (C=O); *m/z* 323 ($\mathbf{M}^+$, 100%)

---

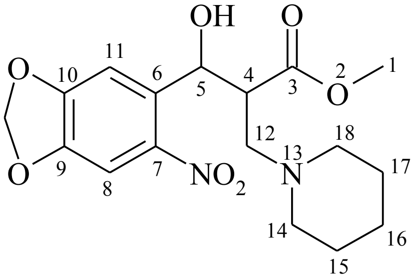
† NMR data cited for the major diastereomer according to indicated numbering.

Low-res APCI;- Low-resolution mass spectrometry using atmospheric pressure chemical ionization (APCI)



***Methyl 3-hydroxy-3-(3-methoxy-2-nitrophenyl)-2[(piperidin-1-yl)methyl] propanoate* 172e†**

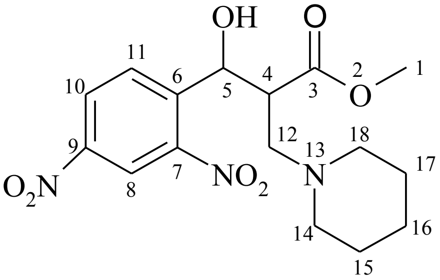
The procedure described for the synthesis of compound **172d** was followed ,using the BH adduct **167e** (0.51g, 1.9mmol), piperidine (0.5ml, 2mmol) and dry THF (5ml) to give as a brown oil, comprising a diastereomeric mixture (*ca.*75% d.e) of *methyl 3-hydroxy-3-(3-methoxy-2-nitrophenyl)-2[(piperidin-1-yl)methyl]propanoate* **172e** (0.54g, 80%) (Low-Res APCI; Found **M**$^+$: 353.210, $C_{17}H_{24}N_2O_6$ requires *M*, 353.38) ν_{max}/cm^{-1} (nujol) 3362 (OH) and 1743 (C=O); δ_H (600MHz; $CDCl_3$) 1.42 (2H, m, 16-CH_2), 1.63 (4H, m, 15- and 17-CH_2), 2.42 (4H, m, 14- and 18-CH_2), 2.70 and 3.00 (2H, dd and t, *J*=12.92 and 6.91Hz, *J*=12.26Hz, 12-CH_2), 3.31 (1H, ddd, *J*=12.15, 9.58 and 2.95Hz, 4-H), 3.47 (3H, s, OCH_3), 3.86 (3H, s, CH_3OCO), 5.07 (1H, d, *J*=9.52Hz, C*H*OH), 6.94 (2H, overlapping doublet, *J*=8.15Hz, 9-H and 11-H) and 7.33 (1H, t, *J*=8.11Hz, 10-H); δ_C (150MHz; $CDCl_3$) 23.9 (C-16), 25.7 (C-15 and C-17), 47.6 (C-4), 51.8 (C-1), 54.9 (C-14 and C-18), 56.4 (C-12), 61.1 (CH_3O), 75.3 (C-5), 111.9 (C-9), 120.1 (C-11), 130.4 (C-10), 130.7 (C-6), 135.0 (C-7), 150.9 (C-8) and 171.4 (C=O); *m/z* 353 (**M**$^+$, 100%).



***Methyl 3-hydroxy-3-(3,4-methylenedioxy-2-nitrophenyl)-2-[(piperidin-1-yl)methyl] propanoate* 172g†**

The procedure described for the synthesis of compound **172d** was followed, using the BH adduct **167g** (0.345g, 1.2mmol), piperidine (0.5ml, 2mmol) and dry THF (5ml) to give yellow-brown crystals comprising a diastereomeric mixture (*ca.* 91% d.e.) of *methyl 3-*

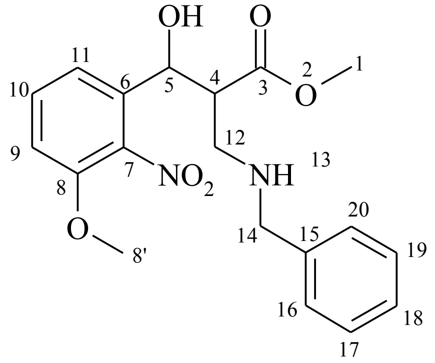
hydroxy-3-(3,4-methylenedioxy-2-nitrophenyl)-2-[(piperidin-1-yl)methyl]propanoate **172g** (0.448g, 99.7%); m.p.102-105°C (Low-Res. APCI; Found **M**$^+$ 367.267, $C_{17}H_{22}N_2O_7$ requires *M*, 367.37); ν_{max}/cm^{-1} (nujol) 3338 (OH) and 1713 (C=O); δ_H (600MHz; $CDCl_3$) 1.45 (2H, m, 16-CH_2), 1.58 (4H, m, 15- and 17-CH_2), 2.41 (1H, br s, OH), 2.66 (4H, m,14- and 18-CH_2), 2.73 and 3.04 (2H, dt, *J*=12.64 and *J*=10.31Hz, 12-CH_2), 2.93 (1H, m, 4-H), 3.49 (3H, s, OCH_3), 5.64 (1H, d, *J*=8.03Hz, C*H*OH), 6.07 (2H, s, OCH_2O), 7.18 (1H, s, 11-H) and 7.28 (1H, s, 8-H); δ_C (150MHz; $CDCl_3$) 23.8 (C-16), 25.8 (C-15 and C-17), 49.5 (C-4), 51.1 (OCH_3), 52.6 (C-14 and C-18), 71.4 (C-5), 101.0 (OCH_2O), 102.8 (C-8), 108.0 (C-11), 134.4 (C-6), 141.7 (C-7), 147.1 (C-9), 151.6 (C-10) and 171.2 (C=O); m/z 367 (**M**$^+$; 100%).



***Methyl 3-(2,4-dinitrophenyl)-3-hydroxy-2-[(piperidin-1-yl)methyl]propanoate* 172h†**

The procedure described for the synthesis of compound **172d** was followed, using the BH adduct **167h** (0.15g, 0.5mmol), piperidine (0.5ml, 2mmol) and dry THF (5ml) to give, as a brown oil, comprising a diastereomeric mixture (*ca*. 83% d.e.) of *methyl 3-(2,4-dinitrophenyl)-3-hydroxy-2-[(piperidin-1-yl)methyl]propanoate* **172h** (0.062g, 31.5%) (Low-res. APCI; Found **M**$^+$: 368.239, $C_{16}H_{21}N_3O_7$ requires *M*, 368.35); ν_{max}/cm^{-1} (nujol) 3317 (OH) and 1723 (C=O); δ_H (600MHz; $CDCl_3$) 1.48 (2H, m, 16-CH_2), 1.62 (4H, m, 15- and 17-CH_2), 2.54 (4H, m, 14- and 18-CH_2), 2.76 and 3.07 (2H, ddt, *J*=12.54, 1.96 and 12.04Hz, 12-CH_2), 3.30 (1H, m, 4-H), 3.50 (3H, s, OCH_3), 5.64 (1H, d, *J*=8.72Hz, C*H*OH), 7.92 (1H, d, *J*=8.59Hz, 11-H), 8.38 (1H, dd, *J*=8.54 and 1.48Hz, 10-H), 8.59 (1H, d, *J*=1.01Hz, 8-H); δ_C (150MHz; $CDCl_3$) 23.8 (C-16), 25.8 (C-15 and C-17), 47.9 (C-4), 52.1 (OCH_3), 54.7 (C-14 and C-18), 60.8 (C-12), 73.2 (C-5), 119.6 (C-8), 126.4

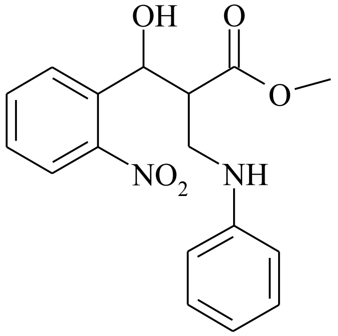
(C-10), 131.1 (C-11), 131.3 (C-9), 143.4 (C-6), 143.6 (C-7) and 170.9 (C=O); *m/z* 368 (**M**$^+$: 100%).



***Methyl 2-[benzylaminomethyl]-3-hydroxy-3-(3-methoxy-2-nitrophenyl)propanoate* 175†**

The procedure described for the synthesis of compound **172d** was followed, using the BH adduct **167e** (0.350g, 1.3mmol), benzylamine (0.5ml, 4.5mmol) and dry THF (5ml) to give a yellow oil comprising a diastereomeric mixture (*ca.* 60% d.e.) of *methyl 2-[benzylaminomethyl]-3-hydroxy-3-(3-methoxy-2-nitrophenyl)propanoate* **175** (0.463g, 94 %), (Found **M**$^+$**-NO**$_2$: 328.156965. $C_{19}H_{22}N_2O_6$ requires *M*, 328.154883); ν_{max}/cm^{-1} (nujol) 3598 (OH), 3304 (NH) and 1723 (C=O); δ_H (600MHz; CDCl$_3$) 2.75 (1H, dd, *J*=12.48 and 3.17Hz, NH), 2.73 and 3.15 (2H, m, 12-CH$_2$), 3.17 (1H, m, 4-H), 3.53 (3H, s, OCH$_3$), 3.78 (2H, m, 14-CH$_2$), 3.88 (3H, s, CH$_3$OCO), 5.12 (1H, d, *J*=3.84Hz, C*H*OH), 6.91 (2H, t, *J*=8.77Hz, ArH) and 7.24-7.34 (6H, overlapping multiplets, ArH); δ_C (150MHz; CDCl$_3$) 46.8 (C-12), 50.4 (C-4), 51.5 (C-1), 53.9 (C-14), 56.5 (C-8’), 71.1 (C-5), 111.6 (C-9), 119.1 (C-11), 127.2 (C-18), 128.1 (C-16 and C-20), 128.5 (C-17 and C-19), 130.6 (C-10), 135.1 (C-6), 138.5 (C-15), 139.0 (C-7), 150.6 (C-8) and 172.9 (C=O); *m/z* 328 (**M**$^+$**-NO2**, 58%) and 120 (100).

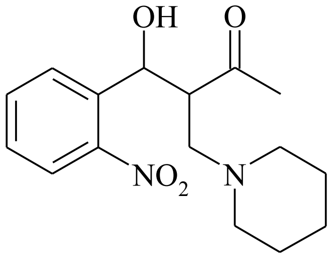
Attempted synthesis of methyl 3-hydroxy-3-(2-nitrophenyl)-2-phenylaminomethyl propanoate 176



The procedure described for the synthesis of compound **172d** was followed, using the methyl vinyl ketone-derived BH adduct **167d** (0.5g, 2.5mmol), aniline (0.5ml, 5.5mmol) and dry THF (5ml). Separation of the crude mixture afforded the starting material **167d** and aniline and no trace of the expected product.

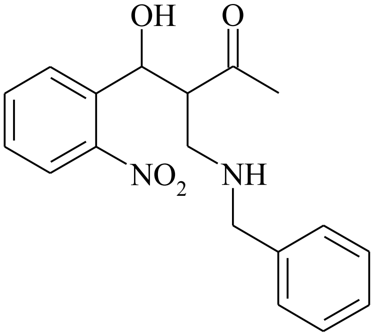
3.7 Reactions of methyl vinyl ketone derived BH adducts with amines

Attempted synthesis of 3-hydroxy-3-(2-nitrophenyl)-2-[(piperidin-1-yl)methyl]butanone



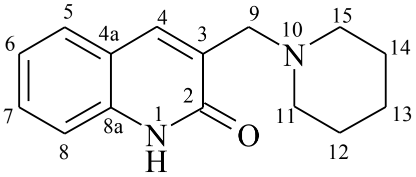
The procedure described for the synthesis of compound **172d** was followed, using the methyl vinyl ketone-derived BH adduct **167a** (0.5g, 2.5mmol), piperidine (0.5ml, 2mmol) and dry THF (5ml). Separation of the crude mixture gave several fractions, ^{1}H NMR analysis of which indicated that none of them corresponded to the expected product.

Attempted synthesis of 3-[benzylaminomethyl]-4-hydroxy-4-(2-nitrophenyl)butan-2-one.



The procedure described for the synthesis of compound **172d** was followed, using the methyl vinyl ketone-derived BH adduct **167a** (0.5g, 2.5mmol), benzylamine (0.5ml, 4.5mmol) and dry THF (5ml). Separation of the crude mixture gave several fractions, ^{1}H NMR analysis of which indicated that none of them corresponded to the expected product.

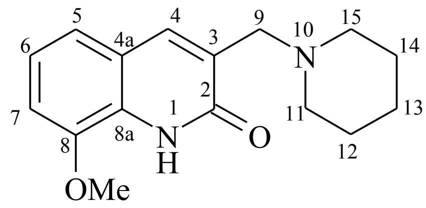
3.8 Catalytic hydrogenation of 2-nitropiperidine derivatives



3-[(Piperidin-1-yl)methyl]-1*H*-quinolin-2-one 177d

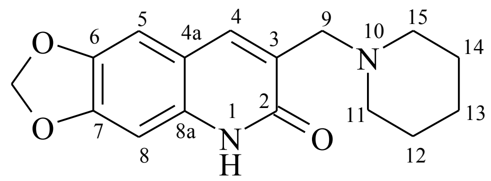
Compound **172d** (0.5g, 1.5mmol) was dissolved in ethanol (25ml), 10% Pd-C catalyst (0.08g) was added to the solution and the mixture was stirred vigorously under hydrogen at atmospheric pressure in a stoppered flask for 1.5h. The mixture was filtered, the solvent was evaporated *in vacuo,* and the solid residue was crystallised from ethyl acetate to give, as white crystals, 3-[(piperidin-1-yl)methyl]-1*H*-quinolin-2-one **177d** (0.083g, 22%), m.p. 220-222°C; (Low-res. APCI; Found **M**$^+$: 243.223. $C_{15}H_{18}N_2O$ requires *M*, 243.32); ν_{max}/cm^{-1} (nujol) 3138 (N-H) and 1650 (C=O); δ_H (600MHz; $CDCl_3$) 1.48 (2H, m, 13-CH_2), 1.64 (4H, m, 12- and 14-CH_2), 2.52 (4H, m, 11- and 15-CH_2), 3.56 (2H, s, 9-CH_2), 7.19 (1H, t, *J*=7.53Hz, 8-H), 7.28 (1H, d, *J*=8.15Hz, 6-H), 7.45 (1H, t, *J*=7.18Hz, 7-H), 7.57 (1H, d, *J*=7.70Hz, 4-H), 7.87 (1H, s, 5-H) and 10.80 (1H, br s, NH); δ_C

(150MHz; $CDCl_3$) 24.4 (C-13), 26.2 (C- 12 and C-14), 54.9 (C-11 and C-15), 56.8 (C-9), 115.3 (C-8), 120.2 (C-6), 122.4 (C-4a), 127.6 (C-4), 129.6 (C-5), 130.4 (C-7), 137.3 (C-3), 137.5 (C-8a) and 163.6 (C=O); *m/z* 243 (**M**$^+$: 100%).



8-Methoxy-3-[(piperidin-1-yl)methyl]-1**H*****-quinolin-2-one*** **177e**

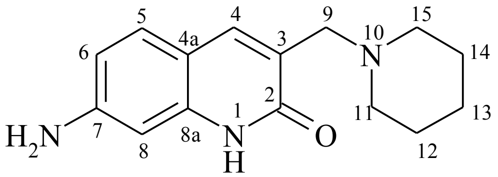
The procedure described for the synthesis of **177d** was followed, using compound **172e** (0.50g, 1.4mmol), ethanol (25ml) and 10% Pd-C (0.08g) to give, as light-yellow crystals, *8-methoxy-3-[(piperidin-1-yl)methyl]-1*H*-quinolin-2-one* **177e** (0.139g, 36%); m.p. 139-140ºC; (Low-res. APCI; Found **M**$^+$: 273.248. $C_{16}H_{20}N_2O_2$ requires *M*, 273.34); ν_{max}/cm^{-1} (nujol) 3130 (NH) and 1639 (C=O); δ_H (600MHz; $CDCl_3$) 1.46 (2H, m, 13-CH_2),1.62 (4H, m, x 12- and 14-CH_2), 2.50 (4H, m, 11- and 15-CH_2), 3.51 (2H, d, *J*=1.28Hz, 9-CH_2), 3.95 (3H, s, OCH_3), 6.91 (1H, dd, *J*=7.81Hz and 1.01 Hz, 7-H), 7.10 (1H, t, *J*=7.89Hz, 6-H), 7.16 (1H, dd, *J*=7.96Hz and 1.10Hz, 5-H), 7.82 (1H, s, 4-H) and 9.13 (1H, br s, NH); δ_C (150MHz; $CDCl_3$) 24.3 (C-13), 26.1 (C-12 and C- 14), 54.9 (C-11 and C-15), 55.9 (C-9), 56.8 (OCH_3), 109.2 (C-7), 119.4 (C-4a), 120.3 (C-6), 121.9 (C-5), 127.5 (C-8a), 131.3 (C-4), 136.8 (C-3), 145.3 (C-8) and 161.9 (C=O); *m/z* 273 (**M**$^+$: 100%).



3-[Piperidin-1-yl)methyl]-1**H*****-[6,7]dioxoloquinolin-2-one*** **177g**

The procedure described for the synthesis of **177d** was followed, using compound **172g** (0.5g, 1.4mmol), ethanol (25ml) and 10% Pd-C (0.08g) to give, as a yellow solid, *3-[piperidin-1-yl)methyl]-1*H*-[6,7]dioxoloquinolin-2-one* **177g** (0.144g, 36.9%); m.p. 192-

194°C (Low-res. APCI; Found **M**$^+$: 287.261. $C_{16}H_{18}N_2O_3$ requires *M*, 287.33); ν_{max}/cm^{-1} (nujol) 3321 (NH) and 1626 (C=O); δ_H (600MHz; $CDCl_3$) 1.24 and 2.53 (4H, series of multiplets, 11- and 15-CH_2), 1.46 (2H, br s, 13-CH_2), 1.62 (4H, m, 12-, 14-CH_2), 3.54 (2H, s, 9-CH_2), 6.02 (2H, s, OCH_2O), 6.85 (1H, s, 8-H), 6.92 (1H, s, 5-H), 6.96 (1H, s, NH) and 7.77 (1H, s, 4-H); δ_C (150MHz; $CDCl_3$) 24.2 (C-13), 25.9 (C-12, C-14), 54.6 (C-11 and C-15), 56.6 (C-9), 95.1 (C-8), 101.6 (OCH_2O), 101.8 (C-5), 105.0 (C-4a), 114.8 (C-8a), 126.4 (C-3), 130.0 (C-4), 144.2 (C-6), 150.1 (C-7) and 163.6 (C=O); *m/z* 287 (**M**$^+$; 100%).



***7-Amino-3-[(piperidin-1-yl)methyl]-1*H*-quinolin-2-one* 180**

The procedure described for the synthesis of compound **177d** was followed using compound **172h** (0.5g, 1.4mmol), ethanol (25ml) and 10% Pd-C (0.08g) to give, as a yellow-brown oil, *7-amino-3-[(piperidin-1-yl)methyl]-1*H*-quinolin-2-one*, **180** (0.11g, 32%) (Low-res. APCI: Found **M**$^+$: 258.299. $C_{15}H_{19}N_3O$ requires *M*, 258.332); ν_{max}/cm^{-1} (nujol) 3159 (NH) and 1593 (C=O); δ_H (600MHz; $CDCl_3$) 0.85 (2H, m, 13-CH_2), 1.57 (4H, 2 x m, 12- and 14-CH_2), 1.64 (4H, 2 x m, 11-H and 15-H), 3.52 (4H, overlapping multiplets, 2 x NH and 9-CH_2), 5.97 (1H, d, *J*=2.14Hz, 8-H), 5.99 (1H, d, *J*=2.16Hz, 6-H), 6.01 (1H, d, *J*=2.14Hz, 4-H), 6.88 (1H, d, *J*=8.17Hz, 5-H) and 7.98 (1H, br s, NH); δ_C (150MHz; $CDCl_3$) 24.7 (C-13), 26.2 (C-12 and C-14), 40.6 (C-11 and C-15), 46.8 (C-9), 101.9 (C-8), 104.4 (C-6), 110.4 (C-4a), 129.9 (C-4), 148.1 (C-5), 148.7 (C-3), 160.8 (C-8a), 163.5 (C-7) and 170.7 (C=O); m/z 258 (**M**$^+$; 28%) and 189 (100).

4. REFERENCES

1. Baylis, A.B.; Hillman, M.E.D. German Patent 2155113, 1972, *Chem. Abstr*. **1972**, 77, 34174q.
2. Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn*. **1968**, 41, 2815.
3. Kaye, P.T.; Nocanda, X.W. *Synthesis*, **2001**, 16, 2389-2392.
4. Lee, K.Y.; Lee, H.S.; Kim, J.N. *Bull. Korean Chem. Soc*. **2007**, 28(2), 333-335.
5. Lee, K.Y.; Kim, J.M.; Kim, J.N. *Bull. Korean Chem. Soc*. **2002**, 23(10), 1493-1495.
6. Kaye, P.T.; Nocanda, X.W. *J. Chem. Soc., Perkin Trans. 1*. **2002**, 1318-1323.
7. Brzezinski, L.J.; Rafel, S.; Leahy, J.W. *Tetrahedron*. **1997**, 53(48), 16423-16434.
8. Familoni, O.B.; Klaas, P.J.; Lobb, K.A.; Pakade, V.E.; Kaye, P.T. *Org. Biomol. Chem*., **2006**, 4, 3960-3965.
9. Basavaiah, D.; Reddy, R.J.; Rao, J.S. *Tetrahedron Lett.* **2006**, 47, 73-77.
10. Gong. H.; Cai. C-Q.; Yang. N-F.; Yang. L-N.; Zhang. J. and Fan. Q-H. *J Mol. Catal. A: Chem.* **2006**, 249, 236-239.
11. Familoni. O. B.; Kaye. P.T. and Klaas. P.J. *Chem. Commun*. **1998**, 2563-2564.
12. Basavaiah. D.; Reddy. R.M.; Kumaragurubaran. N. and Sharada. D.S. *Tetrahedron*. **2002**, 58, 3693-3697.
13. Lee. K.Y. and Kim. J.N. *Bull. Korean Chem. Soc*. **2002**, 23(7), 939-940.
14. Yi. H-W.; Park. H.W.; Song. Y.S. and Lee. K-J. *Synthesis*. **2006**, (12), 1953-1960.
15. Kaye. P.T. and Musa. M. A. *Synthesis*. **2002**, (18), 2701-2706.
16. Kaye. P. T.; Musa. M. A. and Nocanda. X. W. *Synthesis*. **2003**, (4), 531-534.
17. Shi. M.; and Zhang. W. *Tetrahedron*. **2005**, 61, 11887-11894.
18. Yu, C.; Liu, B.; Hu, L. *J. Org. Chem*. **2001**, 66, 5413-5418.
19. Aggarwal, V.K.; Mereu, A.; Tarver, G.J.; McCague, R. *J. Org. Chem.* **1998**, 63, 7183-7189.
20. Maher, D.J.; Connon, S.J. *Tetrahedron Lett*. **2004**, 45, 1301-1305.
21. Cai, J.; Zhou, Z.; Zhao, G.; Tang, C. *Org. Lett*. **2002**, 4(26), 4723-4725.

22. Luo, S.; Mi, X.; Hui, Xu.; Wang, P.G.and Cheng, J. *J. Org. Chem*. **2004**, 69, 8413-8422.
23. Luo, S.; Wang, P.G.; Cheng, J-P. *J. Org. Chem.* **2004**, 69, 555-558.
24. Lee, K.Y.; GowriSankar, S.; Kim, J.N. *Tetrahedron Lett*. **2004**, 45, 5485-5488.
25. de Souza, R.O.M.A.; Meireles, B.A.; Aguiar, L.C.S.; Vasconcellos, M.L.A.A. *Synthesis*. **2004**, (10), 1595-1600.
26. Leadbeater, N.E.; van der Pol, C. *J. Chem. Soc., Perkin Trans. 1*. **2001**, 2831-2835.
27. Luo, S.; Wang, P.G.; Cheng, J. *J. Org. Chem*. **2004**, 69, 555-558.
28. Lin, Y.; Lin, C.; Liu, C.and Tsai, T.Y.R. *Tetrahedron*. **2006**, 62, 872-877.
29. Mi, X.; Luo, S.; Cheng, J. *J. Org. Chem*. **2005**, 70, 2338-2341.
30. Balan, D.; Adolfsson, H. *Tetrahedron Lett*. **2003**, 44, 2521-2524.
31. Yamada, Y.M.A.; Ikegemi, S. *Tetrahedron Lett*. **2000**, 41, 2165-2169.
32. Frank. S.A.; Mergott. D.J and Roush. W.R. *J. Am. Chem. Soc*. **2002**, 124(11),
33. Zhao. L-J.; Kwong. C. K-W.; Shi. M. and Toy. P. H. Tetrahedron. 2005, 61, 12026-12032.
34. Rafel. S. and Leahy. J. W. *J. Org. Chem.* **1997**, 62, 1521-1522.
35. Yi. H-W.; Park. H.W.; Song. Y.S. and Lee. K-J. *Synthesis*. **2006**, (12), 1953-1960.
36. Auge. J.; Lubin. N. and Lubineau. A. *Tetrahedron Lett*. **1994**, 35(43), 7947-7948.
37. Zhao. S-H.; Zhang. H-R.; Feng. L-H.and Chen. Z-B. *J. Mol. Catal. A: Chem.* **2006**, 258, 251-256.
38. Krishna.P.R.; Manjuvani. A.; Kannan. V. and Sharma. G. V. M. *Tetrahedron Lett*, **2004**, 45, 1183-1185.
39. Aggarwal. V.K.; Dean. D.K.; Mereu. A. and Williams. R. *J. Org. Chem*. **2002**, 67, 510-514.
40. Krishna. P. R.; Manjuvani. A. and Sekha. E.R., http://www.arkat-usa.org/ark/journal/2005/I03_Rao/1203/1203.asp.
41. Yu. C.; Liu. B. and Hu. L. *J. Org. Chem*. **2001**, 66, 5413-5418.
42. Sa. M.M.; Ramos. M.D. and Fernandes. L. *Tetrahedron*. **2006**, 62, 11652-11656.
43. Pegot. B.; Vo-Thanh. G.; Cori. D. and Loupy. A. *Tetrahedron Lett*. **2004**, 45, 6425-6428.

44. Kumar. A. and Pawar. S. S. *Journal of Molecular Catalysis A: Chemical*, **2004**, 211, 43-47.
45. Rosa. J.N.; Afonso. C.A.M. and Santos. A. G. *Tetrahedron*. **2001**, 57, 4189-4193.
46. Durand. J.; Teuma. E. and Gomez. C. *R. Chimie*. **2007**, 152-177.
47. Pakade. V. E., MSc thesis, Rhodes University, 2006.
48. Bode, M. L., PhD thesis, Rhodes University, 1993.
49. Price, K.E.; Broadwater, S.J.; Jung, H.M.; McQuade, D.T. *Org. Lett*. **2005**, 7, 147.
50. Caumul. P. and Hailes. H.C. *Tetrahedron Lett*. **2005**, 46, 8125-8127.
51. Corma. A.; Garcia. H. and Levya. A. *Chem. Commun*., **2003**, 2806-2807.
52. Hsu. J-C.; Yen. Y-H.and Chu. Y-H. *Tetrahedron Lett*. **2004**, 45, 4673-4676.
53. Aggarwal, V. K.; Emme, I. and Mereu, A. *Chem. Commun*, **2002**, 1612-1613.
54. Chandrasekhar. S.; Narsihmulu. C.; Saritha. B. and Sultana. S. S. *Tetrahedron Lett*. **2004**, 45, 5865-5867.
55. Bode. M. L. and Kaye. P.T. *J. Chem. Soc. Perkin Trans. 1*. **1990**, 2612-2613.
56. Bode. M. L. and Kaye. P.T. *J. Chem. Soc. Perkin Trans. 1*. **1993**, 1809-1813.
57. Robinson, R. S., PhD thesis, Rhodes University, 1998.
58. Kaye, P. T. and Robinson, R, S. *Synth. Commun*. **1996**, 26, 2085.
59. Drewes, S. E.; Njamela, O.L; Emslie, N. D.; Ramesar, N. and Field, J. S. *Synth. Commun*. **1993**, 23, 2807.
60. Kappe. T. *IL Farmaco*. **1999**, 54, 309-315.
61. Michael. J. P. *Nat. Prod. Rep*. **2000**, 17, 603-620.
62. Abe. I.; Abe. T. ; Wanibuchi. K. and Noguchi. H. *Org. Lett*. **2006**, 8(26), 6063-6065.
63. Michael. J. P. *Nat. Prod. Rep.* **2004**, 21, 650-668.
64. Tanitame. A.; Oyamada. Y.; Ofuji. K.; Fujimoto. M.; Suzuki. K.; Ueda. T.; Terauchi. H.; Kawasaki. M.; Nagai. K.; Wachi. M. and Yamagishi. J. *Bioorg. Med. Chem*. **2004**, 12, 5515-5524.
65. Dutta. R.; Mandal. D.; Panda. N.; Mondal. N. B.; Banerjee. S.; Kumar. S.; Weber. M.; Luger. P. and Sahu. N. P. *Tetrahedron Lett*. **2004**, 45, 9361-9364.
66. Jia. C-S.; Dong. Y-W.; Tu. S-J.and Wang. G-W. *Tetrahedron*. **2007**, 63, 892-897.

67. van Oeveren. A.; Pio. B. A.; Tegley. C. M.; Higuchi. R. I.; Wu. M.; Jones. T. K.; Marschke. K. B.; Negro-Vilar. A. and Zhi. L. *Bioorg. Med. Chem. Lett.* **2007**, 17, 1523-1526.
68. Jansson. K.; Fristedt. T.; Svensson. B. and Jonsson. S. *J. Org. Chem.* **2006**, 71, 1658-1667
69. Asis. S. E.; Bruno. A. M.; Dominici. D.A.; Bollini. M. and Gaozza. C. H. *J. Heterocyclic Chem.* **2003**, 40, 107-112.
70. Joule. J. A. and Smith. G. F., *Heterocyclic Chemistry*, 2nd ed., Van Nostrand Reihold Co. Ltd, 1978, p. 82.
71. Kadnikov. D. V. and Larock. R. C. *J. Organomet. Chem.* **2003**, 687, 425-435.
72. Acheson. R. M., *Introduction to the Chemistry of Heterocyclic compounds*, 3rd ed. John Wiley & Sons, 1976, p. 299.
73. Palmer. M. H. "*Heterocyclic Compounds*", 1st ed., Edward Arnold Ltd., London, 1967.
74. Mavers. U.; Berruex. F. and Schlosser. M. *Tetrahedron*. **1996**, 52, 3223-3228.
75. Eiche, T. and Hauptman, S. *The Chemistry of Heterocycles*, Thieme, 1995, p.329.
76. Arnoldi, A. and Carughi, M., *Synthesis*, **1988**, 155.
77. Kasmai, H. S. and Mischke, S. G., *Synthesis*, **1989**, 763.
78. Nocanda, X. W., PhD Thesis, Rhodes University, 2001.
79. Varvaresou, A.; Tsotinis, A.; Papadaki-Valiraki, A. and Siatra-Papastaikoudi, Th. *Bioorg. Med. Chem. Lett.* **1996**, 6(7), 861-864.
80. Riahi, S.; Norouzi, P.; Moghaddam, A. B.; Ganjali, M. R.; Karimipour, G. R. and Sharghi, H. *Chem. Phys.* **2007**, 337, 33-38.
81. Kostakis, I.; Ghirtis, K.; Pouli, N.; Marakos, P.; Skaltsounis, A-L.; Leonce, S.; Caignard, D. H. and Attassi, G. *IL Farmaco*, **2000**, 55, 455-460.
82. Zhao, J and Larock, R. C, *Org. Lett.*, **2005**, 7(19), 4273-4275.
83. Gallagher, T., Pardoe, D. A and Porter, R. A., *Tetrahedron Lett.* **2000**, 41, 5415-5418.
84. Duggan, A., PhD Thesis, Rhodes University, 2006.
85. Drewes, S. E.; Freese, S. D.; Emslie, N. D. and Roos, G. H. P. *Synth. Commun.* **1988**, 18 (13), 1573-1580.

86. Klaas, P. J., MSc Thesis, Rhodes University, 2001.
87. Abraham, RJ, Robein, W, *"NMRPredict"*, Modgraph Consultants Ltd. Abraham, RJ, Mobli, M, www.spectroscopyeurope.com,16.
88. Perrin, D. D. and Armarego, W. L. F., *Purification of Laboratory Chemicals*, 3rd ed., Pergamon Press, Oxford, 1988.
89. Lee, K. Y; Kim, J. M. and Kim, J.N., *Tetrahedron*. **2003**, 59, 385-390.