APPLICATIONS OF THE BAYLIS-HILLMAN REACTION IN THE SYNTHESIS OF COUMARIN DERIVATIVES

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ABSTRACT

The reaction of specially prepared salicylaldehyde benzyl ethers with the activated alkenes, methyl acrylate or acrylonitrile, in the presence of the catalyst, DABCO, has afforded Baylis-Hillman products, which have been subjected to conjugate addition with either piperidine or benzylamine. Hydrogenolysis of these conjugate addition products in the presence of a palladium-on-carbon catalyst has been shown to afford the corresponding 3-substituted coumarins, while treatment of *O*-benzylated Baylis-Hillman adducts with HCl or HI afforded the corresponding 3-(halomethyl)coumarins directly, in up to 94%. The 3-(halomethyl)coumarins have also been obtained in excellent yields (up to 98%) and even more conveniently, by treating the unprotected Baylis-Hillman products with HCl in a mixture of AcOH and Ac_2O, obtained from *tert*-butyl acrylate and various salicylaldehydes. The generality of an established route to the synthesis of coumarins *via* an intramolecular Baylis-Hillman reaction, involving the use of salicylaldehyde acrylate esters in the presence of DABCO, has also been demonstrated.

Reactions between the 3-(halomethyl)coumarins and various nitrogen and carbon nucleophiles have been shown to proceed with a high degree of regioselectivity at the exocyclic allylic centre to afford 3-substituted coumarin products. The electron-impact mass spectra of selected coumarin derivatives have been investigated using high-resolution and B/E linked scan data. Fragmentation pathways have been proposed and fragmentation modes associated with different coumarin-containing analogues have been compared.

A series of coumarin-containing analogues of ritonavir (a clinically useful HIV-1 protease inhibitor) have been prepared and characterized. The synthetic approach has involved the coupling of coumarin derivatives with a hydroxyethylene dipeptide isostere to afford ritonavir analogues containing coumarin termini. An interactive docking procedure has been used to explore the docking of ritonavir and a coumarin-containing analogue into the enzyme active site.

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1. INTRODUCTION

1.1 Distribution, structure and nomenclature of coumarins

Coumarin and many of its derivatives occur naturally. The parent heterocycle, coumarin (Figure 1) was first isolated in 1920 by Vogel[1] from the fruit of *Dipteryx odorata Wild*. The common name, coumarin, comes from another plant *Coumarouna odorate*, in which it is found; the systematic name is 2*H*-1-benzopyran-2-one. [2, 3].

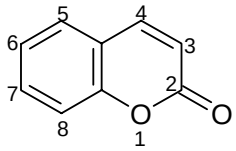


Figure 1. Structure of coumarin and atom numbering

Many compounds, which contain the coumarin moiety, exhibit useful and diverse biological activity and, in recent years, there has been a growing interest in their synthesis.[4] Some of these coumarin derivatives have been found to be useful in photochemotherapy, antitumor and anti-HIV therapy,[5,6] and as CNS-stimulants,[7] antibacterials,[8, 9] anticoagulants[10, 11] and dyes.[12]

Coumarins are widely distributed throughout the plant kingdom, with the vast majority carrying an oxygen substituent at the C-7 position. 7-Hydroxycoumarin (umbelliferone) is often regarded as the parent (in a structural and biogenetic sense) of a large number of structurally more complex coumarins.[2] Coumarins occur as secondary metabolites in the seeds, roots and leaves of many plant species; their function is far from clear, although suggestions include plant growth regulators, fungistats, bacteriostats and , even, waste products.[13]

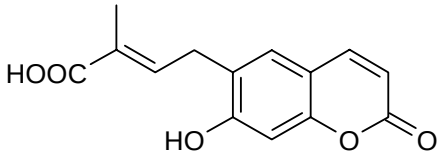
Synthetic coumarins are widely used as aroma chemicals because of their odour strength, tenacity, stability to alkali and relatively cheap price; applications include use as a sweetener and fixative (in perfume); fragrance enhancers (for natural essential oils); blenders (in soaps and detergents); aroma enhancers (in tobacco); and for imparting pleasant odours to industrial products.[3]

1.2. Naturally occurring coumarins

Most reviews classify coumarins according to whether particular compounds are simple coumarins or derivatives of linear or angular furanocoumarins or pyranocoumarins. Murray *et al.*[2] used a biogenetically related approach based upon the number of nuclear oxygen atoms in classifying coumarin-containing compounds – an approach which will be used in this survey of naturally occurring coumarins. Unfortunately, many natural coumarins have been assigned botanically derived names, with many ending with the suffixes, "–ol" or "–one".

1.2.1. 7-Oxygenated coumarins

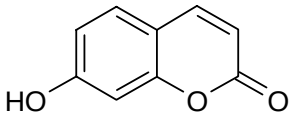
Two new coumarins have been isolated from the root of *Peucedanum ostruthium(L) Koch*, which has been used since ancient times in folk medicine against various diseases. One of these coumarins is the 7-hydroxycoumarin **2**; this type of prenylated coumarin, containing a free carboxyl group, has only been found in one other species, *viz*., *Evodia vitiflora*.[14]



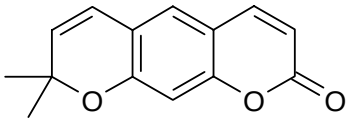
6-(3-carboxybut-2-enyl)-7-hydroxycoumarin **2**

The isolation of five coumarins from the root and bark of *Pleiospermium alatum*, a medicinal plant growing in Sri Lanka and India was reported by Bandara *et al.*[15] These coumarins are all 7-oxygenated systems and exemplify simple coumarins (**3**) as well as linear (**4**) and angular pyranocoumarin (**5**) types. Seselin **5** displays significant antifungal activity against *Cladosporium cladosporioides.*[15] Numerous 7-alkoxy-coumarins (e.g. compounds **6a-d**) have been isolated from various plants, including:- *Pamburus missionis,*[16] *Clausena anisata,*[17] *Murraya exotica,*[18] *Pteryxia terebinthina (Hook),*[19] *Aster praealtus,*[20] *Coleonema album,*[21] *Musineon divaricatum,*[22]

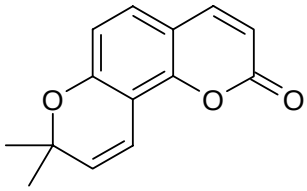
Micomelum minutum,[23a, b] and *Boronia algida.*[24]



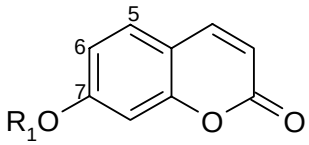
Umbelliferone **3**



Xanthyletin **4**



Seselin **5**



6a-d

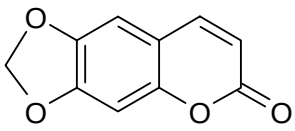
	R	Ref.
6a	$CH_2CH_2CH=C(CH_3)CH_2(C_5H_5O_2)$	17
6b	$CH_2CH=C(CH_3)CH_2CH(OH)CH=C(CH_3)_2$	17
6c	$CH_2CH_2CH(CH_3)C(=CH_2)CH_2CH_2CH(OH)C(OH)(CH_3)_2$	20
6d	$CH_2CH_2CH=C(CH_3)_2$	21

1.2.2. Dioxygenated coumarins

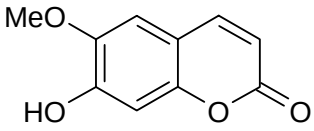
Common di-oxygenation patterns include the 5,7-; 6,7-; and 7,8-arrangements.

1.2.2.1. 6,7-Dioxygenated coumarins

Ayapin (6,7-methylenedioxycoumarin) **7** and scopoletin (6-methoxy-7-hydroxy-coumarin) **8** are simple 6,7-dioxygenated coumarin derivatives; they have been described as phytolexins and are known to have inhibitory activity against microorganisms. Cabello-Hurtado *et al.*[25] undertook a study of the role and biosynthesis of the coumarins in *Helianthus spp.*, and were able to demonstrate the presence of scopoletin **8** and ayapin **7** in *Helianthus tuberosus,* their differential accumulation in response to treatment with chemical elicitors like $CuCl_2$ or sucrose.



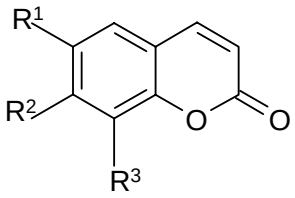
Ayapin **7**



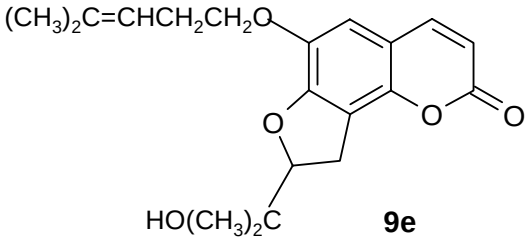
Scopoletin **8**

Highest and earliest accumulation of both coumarins was measured after copper treatment. These results contradict the previous data obtained by Tai and Robeson,[26a,b] which suggested that in *Helianthus tuberosus,* scopoletin **8** is not the precursor of ayapin **7** and that both compounds are synthesised by the tuber of *Helianthus tuberosus* after wounding or treatment with a chemical elicitor.

Examples of other types of 6,7-dioxygenated coumarins include compounds **9a-e**, obtained from the aerial parts of plant species such as:- *Pterocaulon virgatunm,*[27]*Angelica dahurica,*[28] *Diosma acmaeophylla,*[29] *Ruta angustifolia,*[30] *Ticorea longiflora,*[31] *Chorilaena quercifolia*[32] and *Pterocaulon polystachium.*[33]



9a-d

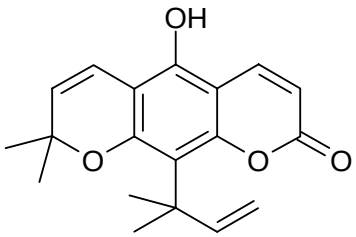


9e

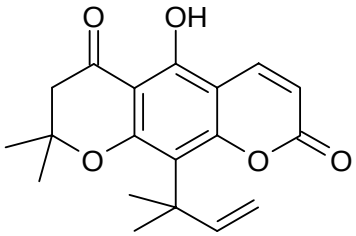
	R^1	R^2	R^3
9a	OCH_3	$OCH_2CHOHC(CH_3)=CH_2$	H
9b	OH	OCH_3	H
9c	OCH_3	OCH_3	H
9d	OCH_3	OCH_3	$CH_2CH_2CH=C(CH_3)_2$

1.2.2.2 5,7-Dioxygenated coumarins

Huang *et al*. [34] reported the isolation of 5,7-dioxygenated coumarins which include: -nordentatin **10**, shown to be a strong antibacterial compound; two new pyrano-coumarins, claucavatin-A **11** and claucavatin-B (as well as carbazole alkaloids) from the root bark of *Clausena excavata* used as a folk medicine in the treatment of snake bite and as a detoxification agent.

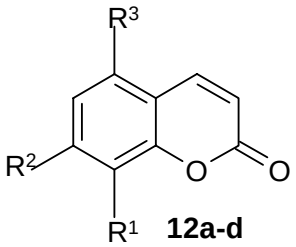


Nordentatin **10**



Claucavatin-A **11**

Other 5,7-dioxygenated coumarins, such as compounds **12a-d** have been found in the aerial parts of various plants species, including *Eriostemon myoporoides,*[35] *Seseli sibiricum,*[36] *Murraya paniculate,*[37a,b] *Eriostemon brucei and E.brucei subspecies cinereus*[38] and *Dorstenia brasiliensis.*[39]

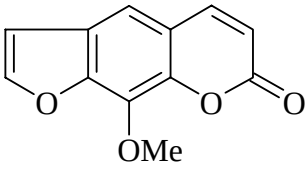


12a-d

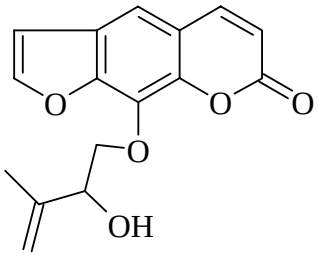
	R^1	R^2	R^3
12a	$CH_2C(CH_3)_2COOH$	OCH_3	OCH_3
12b	$CH_2C(CH_3)_2COOCH_3$	OCH_3	OCH_3
12c	$(CH_2)_2CH=C(CH_3)(CH_2)_2CH=C(CH_3)_2$	OH	OH
12d	H	$OCH_2CH=C(CH_3)_2$	OH

1.2.2.3 7,8-Dioxygenated coumarins

Ceska *et al.*[40a] reported the isolation of furocoumarins in low yields from the cultivated species, *Daucus carota*, using a combination of ultrasensitive bioassay and HPLC techniques. One of these furocoumarins was the 7,8-dioxygenated derivative, 8-methoxypsoralen **13**. Furocoumarins have been shown to be potent photosensitizers,[40b] and to exhibit photomutagenic and photocytotoxic properties. As part of the ongoing phytochemical and chemotaxonomic study of members of the *Cusparieae*, Muller *et al.*[41] isolated from the genus, *Metrodorea nigra*, a number of known coumarins, including compound **14**.

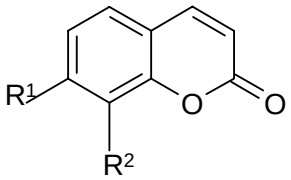


8-methoxypsoralen **13**



Isogospherol **14**

Other 7,8-dioxygenated coumarins, such as compounds **15a-c,** have been found in the aerial parts of various plants species, *viz.*, *Zanthoxylum schinifolium,*[42a,b] *Boenninghausenia albiflora*[43] and *Metodorea flavida.*[44]



15a-c

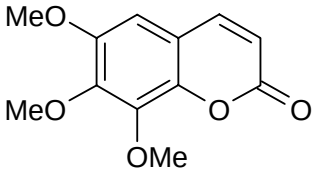
	R^1	R^2
15a	$OCH_2CH=C(CH_3)(CH_2)_2CH(OH)C(CH_3)=CH_2$	OCH_3
15b	$OCH_2CH=C(CH_3)CH_2CH=CHC(CH_3)_2OH$	OCH_3
15c	$OCH_2CH=C(CH_3)(CH_2)_2CH=C(CH_3)_2$	OCH_3

1.2.3. Trioxygenated coumarins

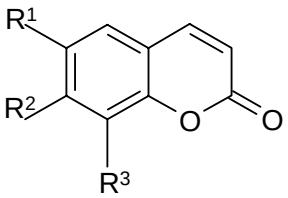
Coumarins in this group are classified into three basic categories, *viz.*, 6,7,8-; 5,7,8-; and 5,6,7-trioxygenated coumarins.

1.2.3.1. 6,7,8-Trioxygenated coumarins

Del Castillo *et al.* [30] isolated from the aerial parts of *Ruta angustifolia*, a new natural coumarin, augustifolin, two other coumarins, scoparone and 6,7,8-trimethoxy-coumarin **16** and the alkaloid, graveolin. Previous studies on *Pelargonium reniforme* Curt revealed the presence of various coumarins and tannins. *Pelargonium species,*[45] indigenous to certain areas of Southern Africa, are used as an antidiarrhoic and a general remedy for the treatment of colds and infection of the lungs in folk medicine, and have been shown to contain a number of highly oxygenated coumarins, including compounds **17a-f**. Other plant species containing 6,7,8-trioxygenated coumarins include:- *Imaptiens balsamine* root cultures,[46] *Agathosma pubarula*,[47] and *Metrodorea flavida*.[44]



6,7,8-trimethoxycoumarin **16**

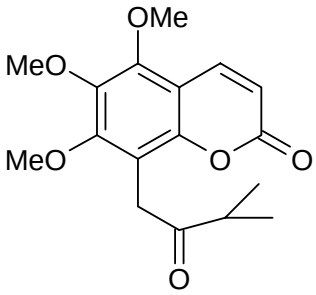


17a-f

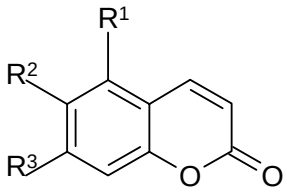
	R^1	R^2	R^3
17a	OH	OH	OCH_3
17b	OH	OH	OH
17c	OCH_3	OH	OCH_3
17d	OCH_3	$OCH_2CH=C(CH_3)_2$	OH
17e	OCH_3	OH	OH
17f	OCH_3	$OCH_2CH=C(CH_3)_2$	OCH_3

1.2.3.2. 5,6,7 Trioxygenated coumarins

Tian-Shung Wu[37] obtained from the leaves of *Murraya paniculata* var. omphalocarpa, ten coumarins of which two, murrayanone **18** and murraculatin, were new, the former being a 5,6,7-trioxygenated coumarin. Compounds **19a-e** are examples of some naturally occurring 5,6,7-trioxygenated coumarins, which have been isolated from the following plant species (each of which has been shown to contain biologically active principles):- *Drummondita hassellii* and *D. calida,*[48] *Pelargonium siddoides,*[45] *Simsia cronquistii,*[49] *Pterocaulon balansea* and *P. lanatum,*[50] and *Pterocaulon polystachium.*[33]



Murrayanone **18**



19a-e

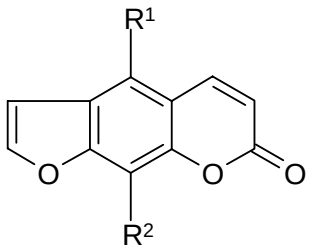
	R^1	R^2	R^3
19a	OCH_3	OCH_3	OH
19b	OCH_3	OCH_3	$OCOCH_3$
19c	OCH_3	OCH_3	OCH_3
19d	OCH_3	$OCH_2CH=C(CH_3)_2$	$OCH_2CH=C(CH_3)_2$
19e	OCH_3	OH	$OCH_2CH=C(CH_3)_2$

1.2.3.3 5,7,8-Trioxygenated coumarins

The structural elucidation and antimicrobial activities of certain 5,7,8-trioxygenated coumarins obtained from the dried root of the medicinal plant, *Angelica dehurica* (Umbelliferae), have been reported.[28] Nielsen and Lemmich[51] have tentatively assigned the stereochemistry of *byakangelicine* and *byakangelis* on the basis of optical rotation data; these compounds are among the major constituents of *Umbelliferum*.

The genus *Phebalium* Vent occurs throughout Australia, including Tasmania, and in the northern island of New Zealand. It is divided into four sections, Phebalium (*ca* 20 taxa), Eriostemoides (three taxa), Gonioclados (two taxa) and Leionema (*ca* 20 taxa). Phytochemical studies carried out on the aerial parts of 15 taxa (14 species and two subspecies) of Phebalium (Rutaceae) resulted in the isolation of no less than 34 coumarins of which twenty-eight were new to the genus and seven appeared to be novel natural products. The distribution of these coumarins has been reviewed and their chemotaxonomy discussed.[52]

Compounds **20a-f** are examples of the 5,7,8-trioxygenated coumarins isolated from *Ruta graveolens,*[53] *Phebalium* (Rutaceae)[52] and *Pterocaulon vigatum .L.*[50]

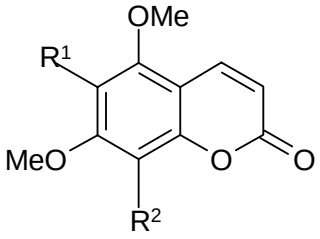


20a-f

	R^1	R^2
20a	$OCH_2CH(OH)C(CH_3)_2OH$	$OCH_2CH(OH)C(CH_3)_2OH$
20b	OCH_3	$OCH_2CH=C(CH_3)_2$
20c	OCH_3	$OCH_2CH(OH)C(CH_3)_2OH$
20d	OCH_3	OCH_3
20e	OH	OCH_3
20f	OCH_3	$OCH_2CHOC(CH_3)_2$

1.2.4. Tetraoxygenated coumarins

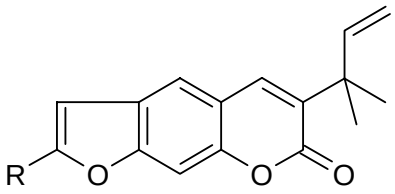
Coumarins in this class are oxygenated at positions 5,6,7 and 8, but are not as common as those in the other classes. Examples of this type of coumarin are the 6,8-dihydroxy-5,7-dimethoxycoumarin **21a** and the 5,6,7,8-tetramethoxycoumarin **21b** isolated from *Pelargonium sidoides* by Kolodziej and co-worker in their search for biologically active compounds in this species.[45]



21a: $R^1 = R^2 = OH$
21b: $R^1 = R^2 = OCH_3$

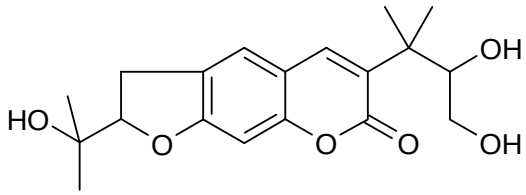
1.2.5. 3-Substituted coumarins

Most coumarins in this category are furanocoumarins, a great number of which have been isolated from plant species, such as *Ruta graveolens, Ruta pinnata, Helietta longifoliata* and *Ruta chalepensis L*. Joshi and Gawad reported the occurrence of a number of coumarins in the root of *Clausena indica* Oliv, including chalepensin **22a** and chalepin **22b**.[54]



22a: R = H
22b: R = $C(CH_3)_2OH$

Tillequin *et al.*[17] have reported the isolation, structural elucidation and biogenesis of some 21 coumarins from the leaves, stem-bark and roots of the plant, *Clausena anisata*, growing in Ngaoundere and Oku in the Cameroon. Two of the compounds isolated were the 3-substituted coumarins **23** and **24**. 3-substituted coumarins have also been isolated from *Amyis simplicifolia Karst,*[55] *Ruta graveolens,*[53] *Boenninghausenia albifola,*[56] *Chloroxylon swietenia DC,*[57] *Clausena excavata*[34] and *Amyris balsamifera.*[58]



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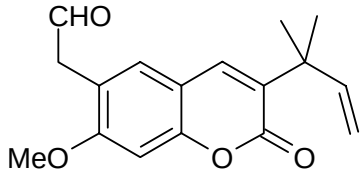
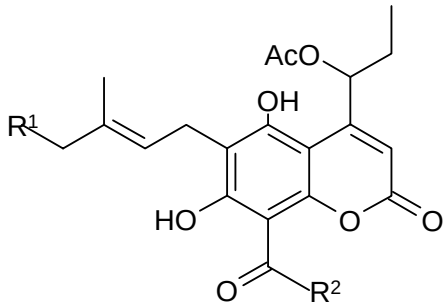


24

1.2.6. 4-Substituted coumarins

Good examples of this type of coumarin are the Mammea coumarins, which have been isolated from *Mammea americana, M. africana, Mesua ferrea* and *M. thwaitesii*. Important members of the group are the 4-(1-acetoxypropyl) coumarins **25a-e** all of which exhibit insecticidal properties. Another group of coumarins belonging to this class are the seshadrins isolated from *Dalbergia volubilis* and 3',5-dihydroxy-4',7-dimethoxy-4-phenylcoumarin isolated from *Exostema caribaeum*.[59] The synthesis of these compounds has been investigated by Bose and Banerji in continuation of their work on 4-phenylcoumarins.[60] 4-Substituted coumarins have also been isolated from *Mammea longifolia,*[61] *Mesua racemose,*[62] *Kielmeyera reticulata*[63] and *phyllum teysmannii.*[64]



25a-e

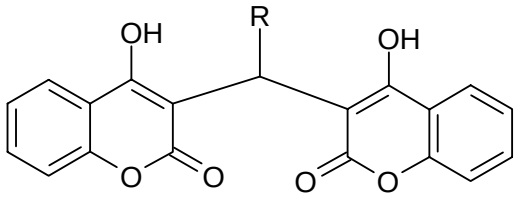
	R^1	R^2
a	H	$CH_2CH_2CH_3$
b	H	$CH(CH_3)CH_2CH_3$
c	H	$CH_2CH_2CH_2CH_3$
d	H	$CH(CH_3)_2$
e	$CH_2CH=C(CH_3)_2$	$CH(CH_3)CH_2CH_3$

1.3. Biologically active coumarins

The coumarins have been the subject of extensive studies because of their interesting biological activities and have, in fact, been used as therapeutic agents for the treatment of various diseases. Coumarins show quite diverse biological activities, including anticoagulant, antiallergic, vascodilatory, anthelmintic, diuretic, insecticidal and antibiotic properties.[1,8]

1.3.1. Anticoagulant compounds

The anticoagulant properties of dicoumarol **26a**, [3,3-methylene-bis(4-hydroxy coumarin)], isolated from spoiled sweet clover hay, were discovered in 1941.[1] This discovery led to the synthesis of a series of coumarin derivatives (*e.g* **26b,c**) with anticoagulant properties.[1] Dicoumarol **26a**, which can be readily synthesized by condensing 4-hydroxycoumarin with formaldehyde,[65a] has been identified as the cause of sweet clover disease in cattle.[65b] This compound has also been used in medicine to reduce blood-clotting in patients suffering from cardiovascular disease.[65b]

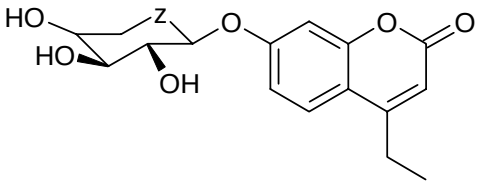


26a-c

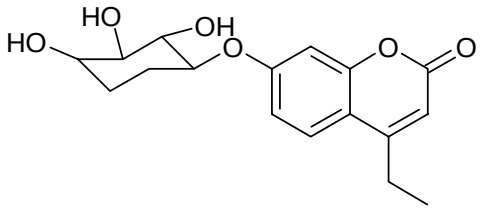
	R	
26a	H	Dicoumarol
26b	CH_3	Pentrombon
26c	COOEt	Tromexan

The anticoagulant properties of such 4-hydroxycoumarins are due to their ability to inhibit the synthesis of the coagulant factor, vitamin K_1, in the liver. The process of clotting involves polymerisation and cross linking of a soluble serum protein, prothrombin, into a hard insoluble polypeptide known as fibrin.[66] Warfarin, 4-(4-hydroxycoumarin-3-yl)-4-phenylbutan-2-one, is perhaps the best known anticoagulant. It is widely used as a rodenticide, and for the treatment of various thromboembolic diseases.[67-68]

Coumarin glycosides show significant potential as oral antithrombotic agents. For example, iliparcil **27a**, a xyloside has been reported to exhibit interesting antithrombotic activity, limited, however by its ready hydrolysis *in vivo*. In order to increase the bioavailability of iliparcil, the enantiomeric analogues, (+)-**27b** and (-)-**27c**, were prepared, the laevorotatory enantiomer being found to be the more active as an oral antithrombotic agent in rats.[69]



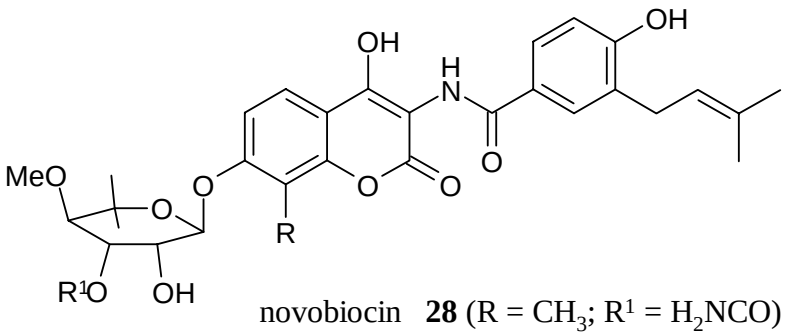
27a (Z = S)
(+)-**27b** (Z = CH_2)



(-)-**27c**

1.3.2. Antibiotic and antibacterial coumarins

Novobiocin **28**, chlorobiocin **29** and related synthetic analogues, are coumarin derivatives which possess both antibiotic and broad-spectrum, Gram-positive antibacterial properties. Musicki *et al.*[70-73] studied the structure-activity relationships of a series of coumarin bases as DNA gyrase inhibitors. The results of their work led to stereoselective synthesis of 5-monoalkyl- and 5,5-dialkyl-substituted noviose derivatives from L-arabinose, and the development of two series of DNA gyrase inhibitors, in which the coumarin moiety is replaced by isothiochroman-2,2-dioxide and 1,2-benzooxathiin-2,2-dioxide moieties.



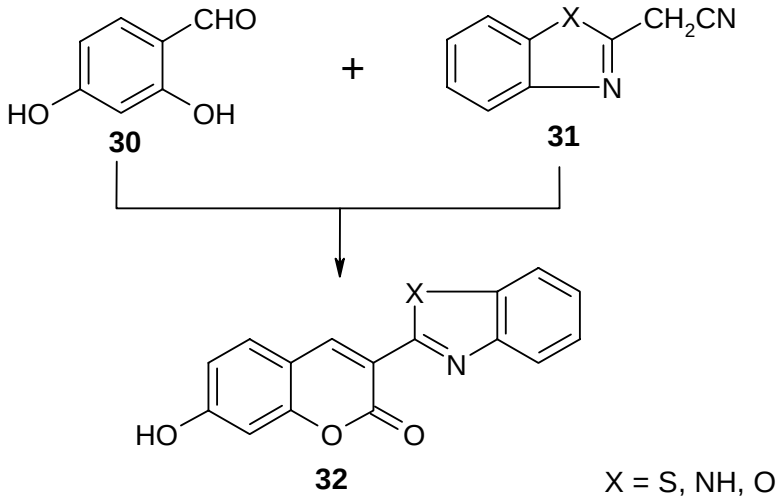
novobiocin **28** (R = CH_3; R^1 = H_2NCO)
chlorobiocin **29** (R = Cl ; R^1 = C_6H_9N)

Novobiocin and chlorobiocin are naturally occurring antibacterials, which have been isolated from certain *Streptomyces* species.[74] However, their toxicity and poor pharmacokinetic properties have prevented their use as antibiotics. Chatreaux *et al.*[74] prepared analogues of the antibiotic novobiocin, containing highly functionalised coumarin structures and exhibiting improved pharmacological and pharmacokinetic properties.

The coumarin-based antibiotics possess a 3-amino-4-hydroxycoumarin moiety and a substituted deoxysugar (noviose), which constitute a common core essential for biological activity. Kinetic and structural studies have shown that the coumarin-based antibiotics are competitive inhibitors of ATP binding to the gyrase B subunit, while labelling studies have established that the substituted coumarin moiety is biosynthesised from L-tyrosine and the deoxysugar from D-glucose.[75]

1.3.3. Biologically active fluorescent and photostable coumarins

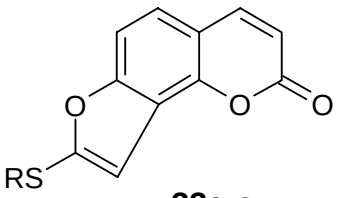
3-Substituted 7-hydroxycoumarins have been shown to act as photostable laser dyes that emit in the blue-green region of the visible spectrum. The emission range increases when the 3-substituent is a heterocyclic moiety,[76] and Abdallah *et al.*[77] have reported the synthesis 15 new 3-substituted 7-hydroxycoumarins [*e.g.* compounds **32**(X = S, NH, O)] designed to extend the tunability range and maximise output. This work was based on the assumption that the introduction of biologically active heterocycles at position-3 could lead to physiologically active fluorescent compounds of biological interest.[78-79]



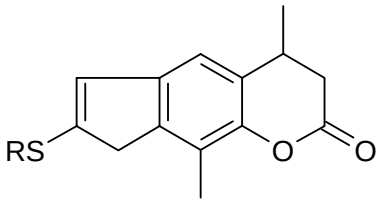
The fluorescence properties of coumarin derivatives depend on their substituents, which influence the degree of intramolecular charge transfer from 6- and /or 7-electron-donating substituents to the electron-accepting coumarin ring. 7-Hydroxy-coumarin, for example, is strongly fluorescent and finds use in several applications.[80,82] Yamana *et al.* [83] have reported the introduction of a 2'-coumarin-labelled nucleoside as a fluorescence energy transfer (FRET) donor in DNA duplexes to facilitate the analysis of DNA structures in solution. Coumarins are also widely used as flash-pumpable laser dyes or for photographic purposes because their triplet excited state is achieved in high yield. Beley *et al.*[12] combined tridentate ligands, such

as 2,2',6',2''-terpyridines or cyclometallating analogues, such as 6-phenyl-2,2'-bipyridine, with 2,4-diarylchromeno[3,4-*c*]pyridin-5-ones to obtain new fused-ring ligands with enhanced spectral absorption.

A new method for the synthesis of furocoumarin *via* base-catalysed ring cleavage and subsequent furan ring closure of 6(8)-(1,2,3-thiadiazol-4-yl)-7-hydroxycoumarin has been used to obtained the angelicin and psoralen derivatives **33a-c** and **34a-b,** respectively. Furocoumarin itself has a wide range of applications, such as reaction with DNA following excitation with long wavelength UV light, in the treatment of skin diseases and in molecular biology as a reagent for the investigation of nucleic acid structure and function.[84]



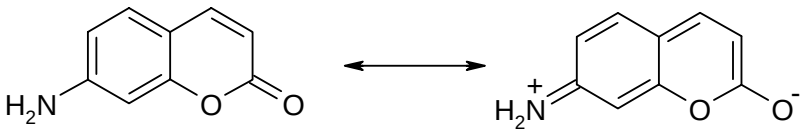
33a-c



34a-b

	R
a	methyl
b	*n*-hexadecyl
c	*p*-fluorobenzyl

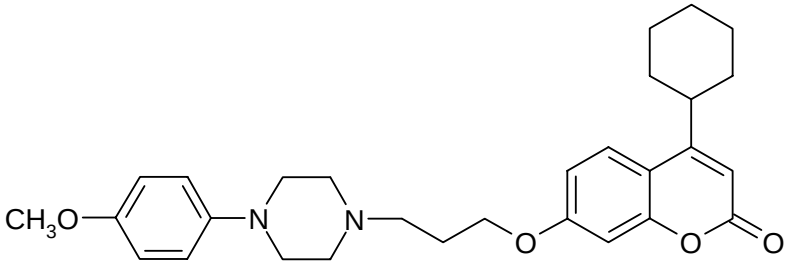
The 7-aminocoumarins comprise an important class of laser dyes, their dipole moment in the excited state (*e.g* **36**) is greater than in the ground state (*e.g* **35**) and, consequently, they exhibit larger Stokes shifts.[67]



35 **36**

1.3.4. Potential antipsychotic compounds

In an effort to gather further data about the structural factors which determine serotonergic and dopaminergic affinity and selectivity, Fall *et al.*[85-86] investigated how the substitution-pattern affects the pharmacological profile of arylpiperazinecoumarin derivatives which have high affinity for dopamine and serotonin. A series of compounds containing a bulky lipophilic group, such as cyclohexyl, at position 4 (*e.g.* compound **37**) were prepared. Dopamine (DA) and serotonin (5-HT) receptors are implicated in various psychiatric and neurological disorders, and research has shown that the *N*-arylpiperidine fragment is important for CNS-activity, especially dopaminergic and serotonergic activity.



Arylpiperazinopropyloxycoumarin **37**

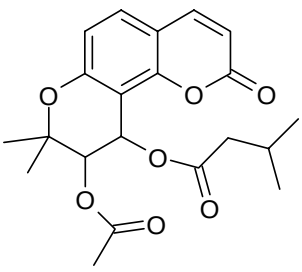
A series of potential antipsychotic compounds containing a furocoumarin moiety linked to various arylpiperazine or piperidine groups have been synthesised, and many of them have been shown to exhibit high affinity for the dopamine–D_1 and D_2, α_1-adrenergic and serotonin 5-HT_2 receptors *in vitro*. Many of the compounds also show antipsychotic activity in mice and in rats.[87]

1.3.5. Anti-HIV compounds

The human immunodeficiency virus type 1 (HIV-1) belongs to a subfamily of retroviruses, *Lenti virinae*, and is the etiologic agent of the acquired immunodeficiency syndrome (AIDS). Among the HIV-enzymes, three have been targetted for therapeutic development, *viz.*, reverse transcriptase, protease and integrase. HIV-1 is a retrovirus and contains 3 genes, known as the gag, pol and env

genes. The integration of HIV-DNA into the genomic DNA of the host cell is carried out by the integrases, while the protease acts like a "pair of molecular scissors" cleaving the viral gag-pol precursor proteins. Four HIV-1 protease inhibitors have been approved for the treatment of AIDS; these are saquinavir, ritonavir, indinavir and nelfinavir.[88-90]

Takeuchi *et al.*[91] reported the synthesis of 42 khellactone derivatives by introducing additional substituents at positions 3, 4, 5, and 6 of the coumarin nucleus. Their investigation was prompted by the isolation of the suksdorfin **38** from *Lomatium uksdorfii*. 3',4'-Di-*O*-(-)-camphanoyl-(+)-*cis*-khellactone (DCK) **39**, one of the khellactones synthesised, is a potent inhibitor of HIV-1 replication- even more potent than AZT. The results indicated that an *R*-configuration and di-*O*-(-)-camphanoyl substitution at each of the 3'- and 4'-positions are very important for anti-HIV activity. Results obtained when this drug was used in combination with other anti-HIV compounds suggest that its mode of action does not involve inhibition of the HIV reverse transcriptase (RT), making it possible to use it in combination with RT inhibitors.



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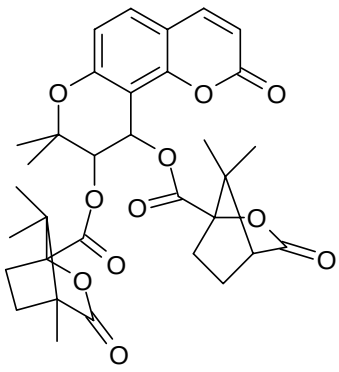

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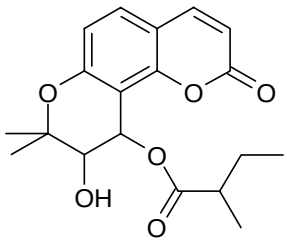
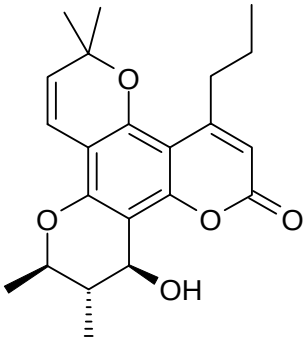


40

In an attempt to discover more potent and selective anti-HIV compounds, Kuo-Hsiung Lee *et al.*[92] investigated the synthesis and anti-HIV activity of dihydroseselins (*e.g.* compound **40**) as analogues of DCK **39**. In their review of reverse transcriptase inhibitors of natural origin, Konig *et al.*[93] have shown that HIV-1-RT

inhibitors have been isolated from many different structural classes, *viz*., coumarins,[94] flavonoids, tannins, alkaloids, lignans, terpenes, naphtho- and anthraquinones and polysaccharides.

Coumarins isolated from *Calophyllum* genus (Guttiferae) with either an alkyl or a phenyl group at the 4-position of the coumarin nucleus possess anti-HIV-1 activity, and structural modifications indicated that the stereochemistry of the 2,3-dimethyl-4-chromanol ring present in such molecules plays an important role in such activity.[95] Calanolides-A **41** and -B **42** are among a series of coumarins recently isolated from species of *Calophyllum;* both compounds strongly inhibited the *in vitro* replication and cytopathicity of HIV-1.[96, 97]



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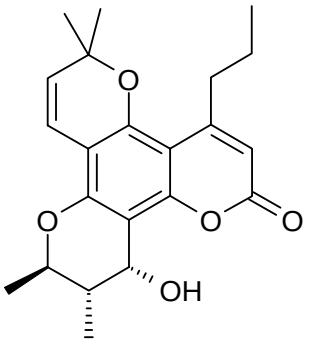
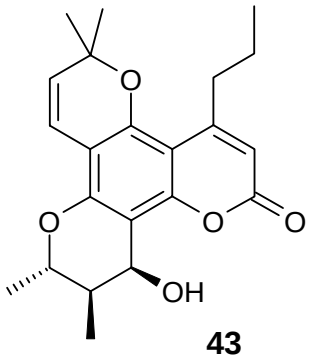


42

Fuller *et al*.[97] undertook both chemical and biological studies of the latex exuded from trees of the genus *Calophyllum* in an effort to identify an adequate and sustainable natural source of calanolide-A, an anti-HIV drug. In their finding, calanolide-A not presence in latex, instead a related coumarin, costatolide **43**, was abundant in latex of *Calophyllum teymannii var.inophylloide* and is currently being evaluated as a possible alternative to calanolide-A for drug development. Cardellina *et al*.[98] reported methods for the chiral resolution of (+)-calanolide-A **41** and (-)-calanolide-A **44** from synthetic (±)-calanolide-A, and (+)-calanolide-B **42** and (-)-calanolide-B (**43**, costatolide) from a racemic mixture isolated from *Calophyllum lanigerium.*



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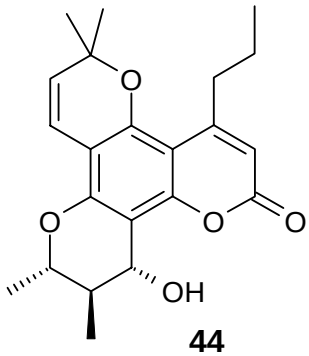
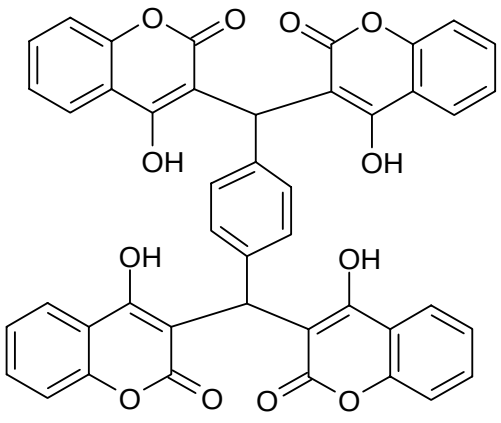


44

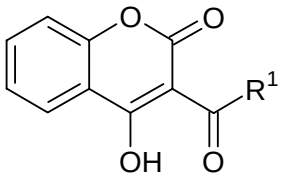
Recent reports have shown that the presence of multiple aromatic rings contributes to good inhibitory potency for HIV-1 integrase inhibitors.[99a] Burke and co-workers,[99b] in an effort to develop new inhibitors, carried out studies on certain coumarin-based analogues using the coumarin derivative **45** as a model. The high HIV-1 integrase inhibitory potency of these compounds was attributed to the presence of several planes of symmetry which allow multiple orientations. The results show that affinity is affected by the position of the central phenylene linker and the points of attachment of the coumarin units.



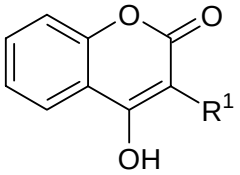
45

Talele and Kulkarni [100] have reported the design and synthesis of a novel series of nonpeptidic HIV-1 protease inhibitors that interact with the S1, S1′ and S2 binding sites of HIV-1 protease; they have also reported X-ray crystal structures of peptide

and nonpeptide-derived inhibitors and developed an interactive docking procedure. The results obtained from the interactive docking suggest that 4-hydroxycoumarin-3-yl phenyl ketones **46a-e** and their analogues **47a-b** should be effective HIV-1 protease inhibitors.



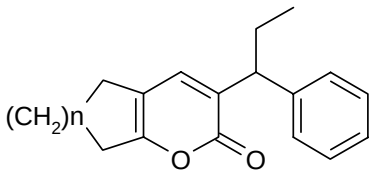
46a-e



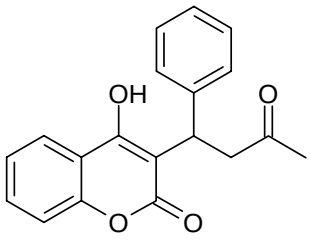
47a-b

Compound	R^1
46a	styryl
46b	4-methoxystyryl
46c	4-fluorostyryl
46d	4-chlorostyryl
46e	4-hydroxy-3-methoxystyryl
47a	3-(α-ethylbenzyl)-
47b	3-phenoxypropyl

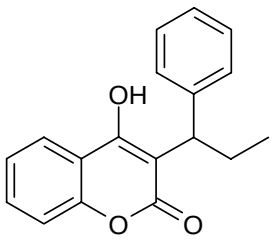
Attention has been given to low molecular weight, non-peptidic compounds, in which the benzene ring of the coumarin moiety is replaced by conformationally flexible cycloalkyl rings of various sizes.[101] The resulting products **48** exhibited an increase in enzyme binding affinity, with the cycloalkyl ring folding into the S1 pocket of the protease. Crystal structures of the cylcoalkyl derivatives have shown that the cyclooctyl ring is better able to fill the S1 region than the cycloheptyl ring.[101]



48 (n = 1,2.3,4, and 6)



49



50

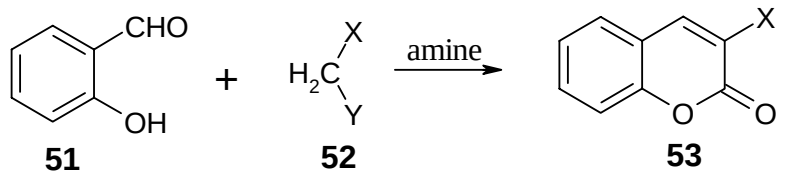
Thaisrivongs *et al.* [102, 103] have reported the screening of 5000 dissimilar compounds from the Upjohn collection for HIV-1 protease inhibitory activity. The 4-hydroxycoumarin **49** (warfarin) was identified as a weak inhibitor (IC_{50} ≈30μM); recently, 4-hydroxybenzopyran-2-ones (warfarin and derivatives) and 4-hydroxy-pyran-2-one have been reported as competitive inhibitors of HIV protease.[102] Based on these findings, compounds with similar structures were screened from the Upjohn collection and phenprocoumon **50** was found to have significant inhibitory (K_i =1 μM) and antiviral activity (ED_{50}= 100-300μM). Both warfarin and phenoprocoumon exhibit high bioavailabilty and low clearance in humans and, therefore, are promising lead structures for the discovery of new orally bioavailable, non-peptidic HIV protease inhibitors.

1.4. Methods of coumarin synthesis

Many synthetic routes to the couumarins have been developed. These include use of the Pechmann, Claisen, Perkin, Knoevenagel, Reformatsky and Wittig reactions, to mention but a few.

1.4.1 Knoevenagel condensation

The Knoevenagel reaction involves the condensation of benzaldehydes with activated methylene compounds in the presence of an amine, and is used to overcome the inherent difficulties associated with the synthesis of coumarins *via* the Perkin reaction. In order to obtain coumarin rather than the usual cinnamic acid, a 2-hydroxy substitutent must be present in the aromatic aldehyde and the conditions for the Knoevenagel reaction are less severe than those required for the Perkin reaction. Various coumarins have been prepared *via* Knoevenagel condensation of salicylaldehyde with activated methylene compounds as illustrated in Scheme 1.[67]



51 **52** **53**

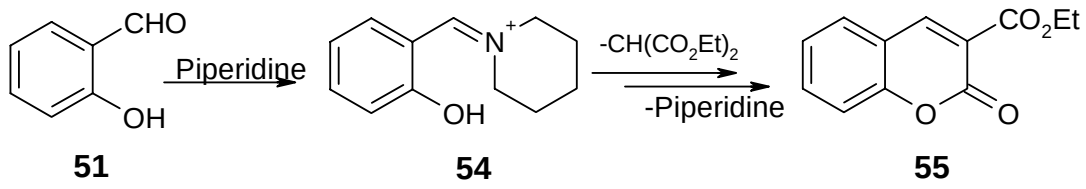
X = CO_2H, CO_2Et, $CONH_2$, CN

Y = CO_2H, CO_2Et, CN

Scheme 1

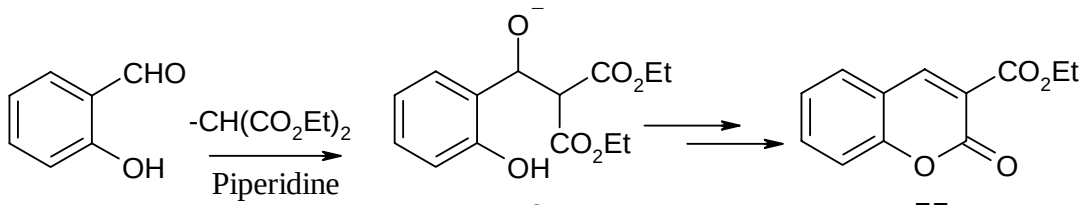
Two different mechanisms have been proposed for the above Knoevenagel reaction.[104] In the first (Scheme 2), formation of an imine or iminium salt **54** with the amine (*e.g* piperidine) is followed by reaction with the enolate of the active methylene compound, elimination of the amine and intramolecular ring closure to give the coumarin **55**. The second proposal involves attack by the carbanion, produced by deprotonation of the active methylene compound by the amine, on the

carbonyl group to give the intermediate **56**. Proton transfer, ring-closure *via* acyl substitution and dehydration then gives the coumarin **55**.



51 **54** **55**

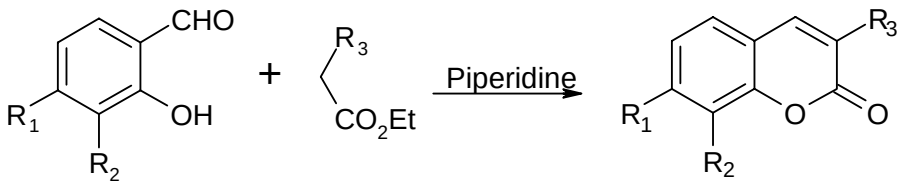
Scheme 2



51 **56** **55**

Scheme 3

Bogdal.[13] has shown that, under microwave irradiation, the Knoevenagel condensation can be successfully applied to the synthesis of a number of coumarins with yields up of 94%. This reaction involves the condensation of salicylaldehydes **57** with carboxylic esters in the presence of piperidine under solvent-free conditions (Scheme 4).



57 **58** **59**

R_1 = H, Et_2N R_3 = CO_2Et, COMe, CN, p-$C_6H_4NO_2$

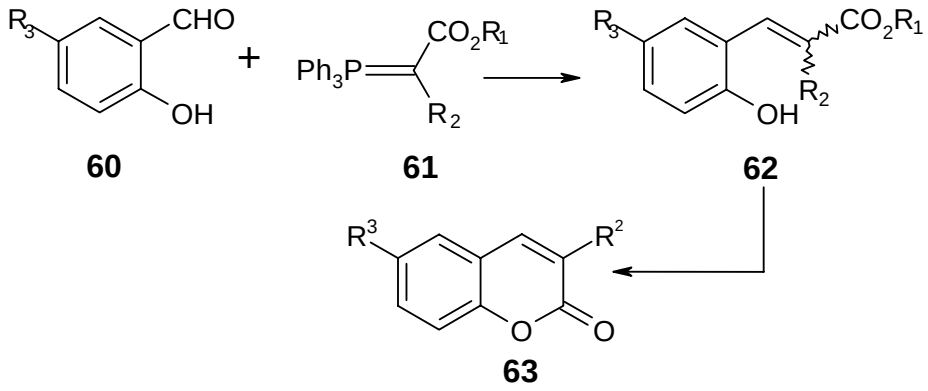
R_2 = H, OMe

Scheme 4

A procedure for preparing coumarin-3-carboxylic acids in up to 80% yield by reacting malononitrile with an aldehyde or ketone in the presence of piperidine, has been reported.[105] An attempt to extend this methodology to the synthesis of 4-phenyl derivatives by reacting 2,4-dihydroxybenzophenone with malononitrile, diethyl malonate or malonic acid in the presence of piperidine resulted in the formation of the decarboxylated analogue.[105]

1.4.2. Wittig reaction

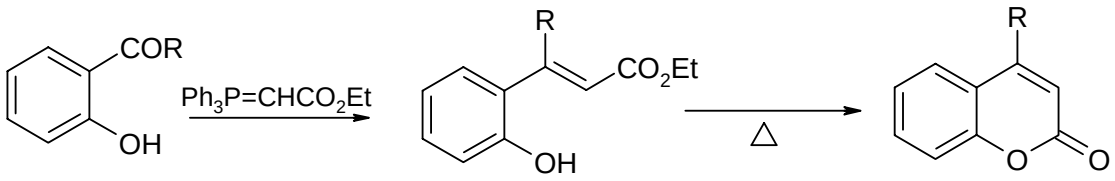
Mali and Yadav[106,107] developed a preparation of coumarins *via* Wittig olefination-cyclisation of 3-(2-hydroxyaryl)propenoic esters (Scheme 5). Cyclization under olefination conditions depends on formation of the *Z*-alkene intermediate **62**, and concomitant formation of the *E*-alkenes is often a problem. This difficulty may be addressed by heating the reaction mixture, or by photochemical isomerization, but these methods suffer from variable yields, inconvenient work-up, or both.[108] In an attempt to solve these problems, McNab and co-workers[108,109] showed that the cyclization takes places in consistently high yield when the isolated 3-(2-hydroxyaryl)propenoic esters **62** are subjected to flash vacuum pyrolysis (FVP). While the *E*-configuration of the double bond precludes cyclization, the barrier to isomerization is overcome by the high-temperature.



$R_1 = CH_3, CH_2CH_3$ $R_2 = H, CH_3$ $R_3 = H, Cl, NO_2$

Scheme 5

The synthesis of coumarins by condensing *o*-hydroxybenzaldehydes or *o*-hydroxyacetophenones **64** with the stable phosphorane, (ethoxycarbonylmethylene)-triphenylphosphorane has also been reported (Scheme 6).[106,67,110] Uriarte *et al.*[85] have also made use of the Wittig reaction in the synthesis of potential antipsychotic compounds containing the coumarin moiety by subjecting keto diphenols to a Wittig reaction with (ethoxycarbonylmethylene)triphenylphosphorane to give the expected 7-ethoxycoumarin in rather poor yield (24%) and 7-hydroxycoumarin in 70% yield.

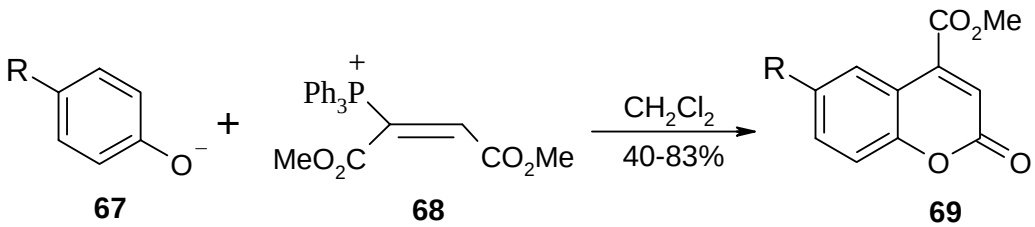


64 **65** **66**

R = Me, H

Scheme 6

A new and efficient route to the synthesis of 4-carboxymethylcoumarins **69** (Scheme 7), based on an aromatic electrophilic substitution reaction between the conjugate base of a substituted phenol and the betaine formed by the addition of triphenylphospine to dimethyl acetylenedicarboxylate (DMAD) has also been reported.[111] This method complements older established methods and offers significant advantages for the synthesis of coumarins having acid-sensitive functional groups.



67 **68** **69**

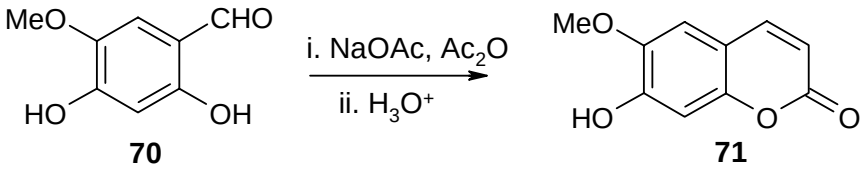
R = CH_3, *t*-Bu, OCH_3, $COCH_3$, NO_2

Scheme 7

Highly functionalised heterocycles are key components of many natural and synthetic compounds of pharmaceutical or agrochemical relevance. Loffler *et al*.[112] reported a one-pot synthesis of coumarins based on the reaction of salicylic esters with a cumulated phosphorus ylide. This reaction is considered to take place *via* an addition /Wittig olefination / Claisen rearrangement sequence, and the cascade can be controlled by varying the temperature.

1.4.3. Perkin reaction

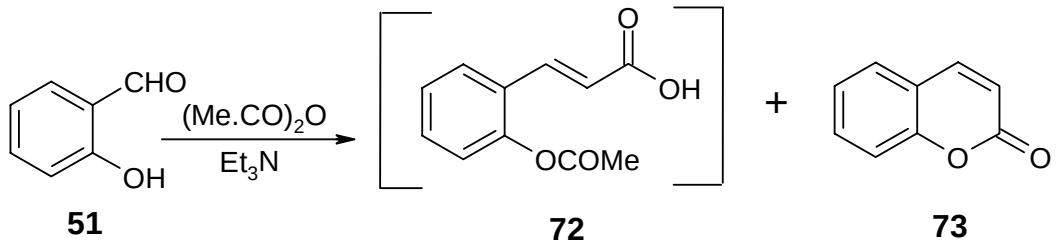
Perkin, in the mid-nineteenth century discovered the transformation now known as the Perkin reaction,[113] a reaction which involves heating an *O*-hydroxybenzaldehyde with acetic anhydride in the presence of sodium acetate at a high temperature (*ca*. 200^{o}C) to afford a *trans*-cinnamic acid. Optimum yields of coumarins are obtained when a 1:2 molar ratio of aldehyde to anhydride is used. Isomerization of the *trans*-cinnamic acid by irradiation or treatment with iodine followed by cyclization affords the coumarin **71** (Scheme 8).[114] The disadvantage of this approach is the generally poor yield of the coumarin obtained, due to the production of tarry materials under the severe reaction conditions of the Perkin synthesis. However, the obvious advantages is that the formation of isomeric chromones is not possible, as is the case with the Pechmann reaction.[67]



70 **71**

Scheme 8

Coumarin is also formed in the reaction of acetic anhydride and salicylaldehyde in the presence of trimethylamine as the base catalyst (Scheme 9).[115]



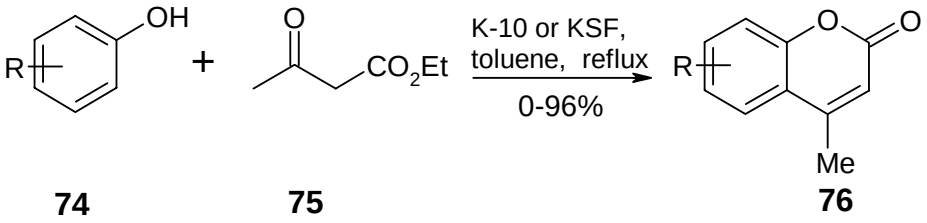
51 **72** **73**

Scheme 9

1.4.4. Pechmann reaction

The Pechmann reaction is a widely used method for preparing coumarins in good yield, it involves reacting a phenol with a β-oxo ester in the presence of a catalyst. The Pechmann reaction has been carried out using both homogeneous acid catalysts [such as sulphuric,[116a,b] hydrochloric, phosphoric and trifluoroacetic acids,[117] and with Lewis acids, such as zinc chloride,[118] iron (III) chloride, tin(IV) chloride, titanium chloride and aluminium chloride[119a]] and heterogeneous catalysts [such as cation-exchange resins, Nafion-H, zeolite-HBEA and other solid acids].[119b] Recently, microwave irradiation has also been applied to accelerate this reaction.[119c]

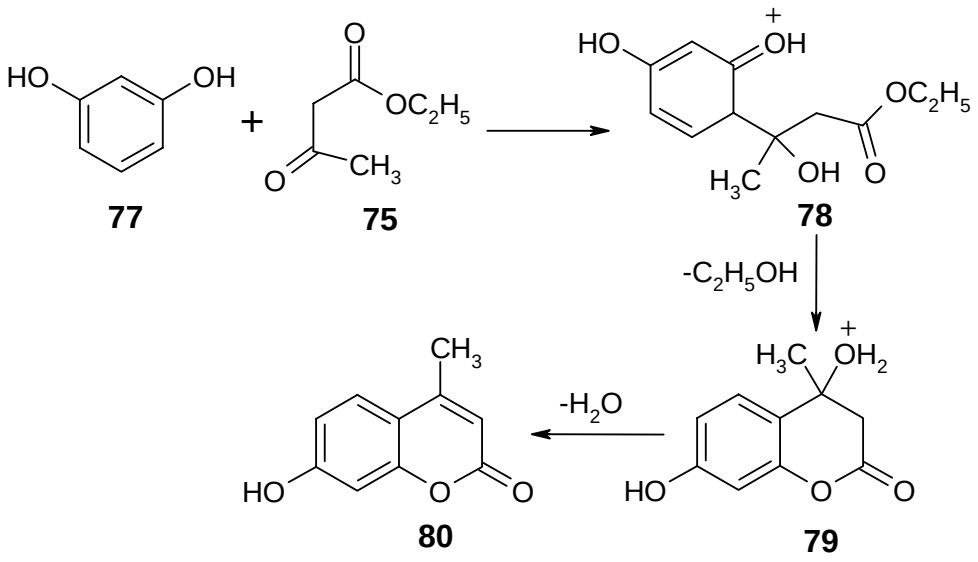
Zhan-Hui Zhang *et al.*[120] reported the synthesis of coumarins *via* the Pechmann reaction catalysed by montmorilonite K-10 or KSF in yields of up to 96% (Scheme 10). This procedure is environmentally friendly and inexpensive compared to previous methods. They reported that K-10 worked better than KSF in terms of reaction time and yield, and that the use of montmorilonite clays as heterogeneous catalysts is a viable alternative. Furthermore, this method has the advantages of easy separation of the product, minimal environmental effect and recyclability of the catalyst.



74 **75** **76**

Scheme 10

The use of the cation exchange resins, Zeokarb 225 and Amberlite IR.120, as condensing agents in the synthesis of hydroxycoumarins has also been reported.[121a] The main advantages of cation exchange resins are that they simplify the isolation of the product and tend to be relatively inexpensive. In order to obtain a maximum yield of the coumarin, between 20 and 40% of the resin by weight of the total reactants is used. The reaction is considered to involve the following steps:- (i) addition across the double bond of the enolic form of the β-keto ester; (ii) ring closure; and (iii) dehydration (Scheme 11).[121b]

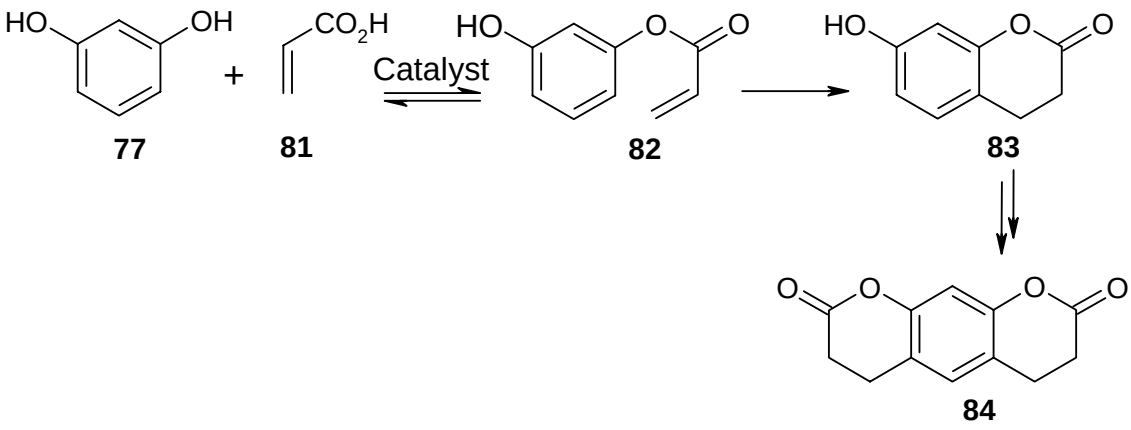


77 **75** **78** **79** **80**

Scheme 11

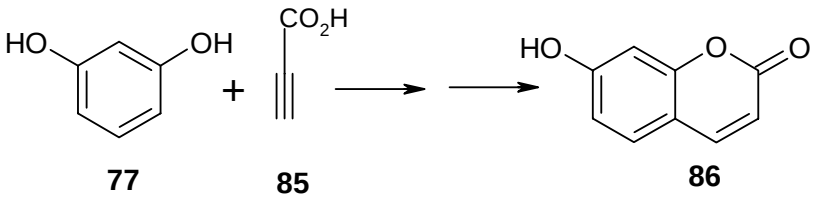
Bekkum *et al*.[122] have reported the synthesis of 7-hydroxycoumarin in *ca* 81% yield using a solid-acid catalysed reaction of phenols with carboxylic acids (or their esters).

Thus, equimolar amounts of resorcinol and acrylic acid, in the presence of zeolite H-beta [Si/Al =14] or Amberlyst-15, undergo esterification followed by ring closure (Scheme 12) to give both 7-hydroxy-3,4-dihydrocoumarin **83** (66%) and 3,4,6,7-tetrahydrobenzo[1,2-*b*:5,4-*b'*]dipyran-2,8-dione **84**. Another approach involves the reaction of resorcinol and propynoic acid in the presence of zeolite H-beta catalyst, at high temperature (150^{o}C) (Scheme 13). In a third approach, ethyl acetoacetate was reacted with resorcinol (Scheme 14) (Pechmann reaction) to afford 7-hydroxy-4-methylcoumarin **80**.



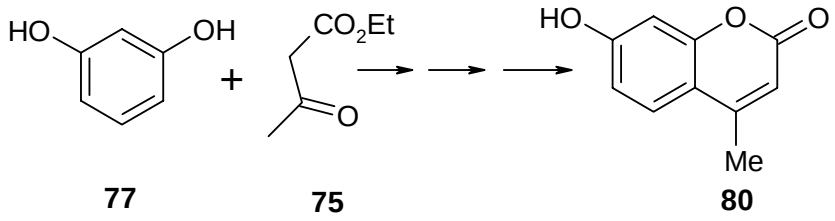
77 **81** **82** **83** **84**

Scheme 12



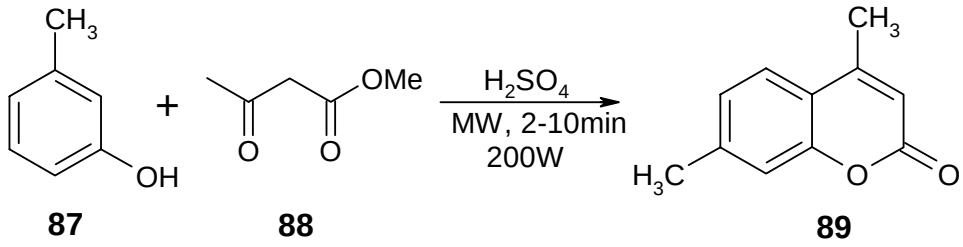
77 **85** **86**

Scheme 13



Scheme 14

Kad *et al*.[123] have reported the use of a microwave–assisted Pechmann reaction in the rapid and simple preparation of substituted coumarins, in yields of 72-82%, from substituted phenols and methyl acetoacetate in the presence of H_2SO_4 (Scheme 15). Comparison of their results with those obtained by classical methods at room temperature show a significient reduction in the reaction time for the microwave-assisted reaction, from several hours to a few minutes.

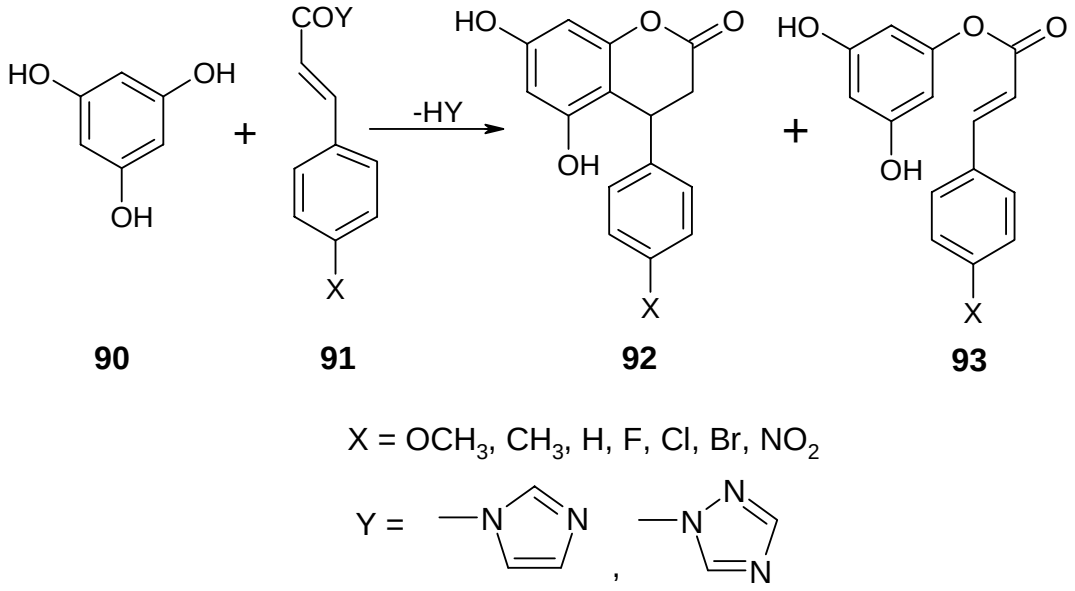


Scheme 15

1.4.5. Michael Reaction

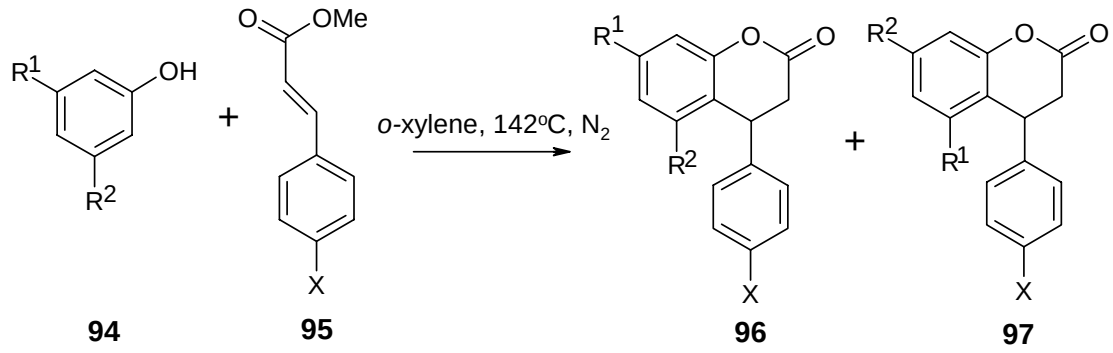
The simplest synthetic approach to 4-arylchroman-2-ones (useful precursors for 4-arylcoumarins) might be expected to involve the condensation of phenols with cinnamic acids (or alkyl cinnamates) in strongly acidic media, but this method afforded complex mixtures of reaction products.[124] Speranza *et al*.,[125] however, have reported a novel, mild procedure for the synthesis of 4-arylchroman-2-ones (and 1-arylbenzo[*f*]chroman-3-ones) *via* a Michael-type reaction of dihydric or trihydric phenols with *p*-substituted *N*-cinnamoylazoles in the presence of DBU (Scheme 16).

It was assumed that the mechanism of the reaction involves esterification followed by conjugate addition.



Scheme 16

Chroman-2-ones have been obtained in moderate to good yields by heating methyl (*E*)-cinnamates and phenols or naphthols in *o*-xylene under reflux in the absence of added catalyst.[125] Reaction conditions, such as temperature, solvent and substrate concentration proved to be critical in this synthesis which, depending on the substituents (R^1 and R^2), could afford isomeric products (Scheme 17; Table 1). The reaction was assumed to involve initial transesterification, followed by protonation of the ester function and intramolecular conjugate addition.[125]



Scheme 17

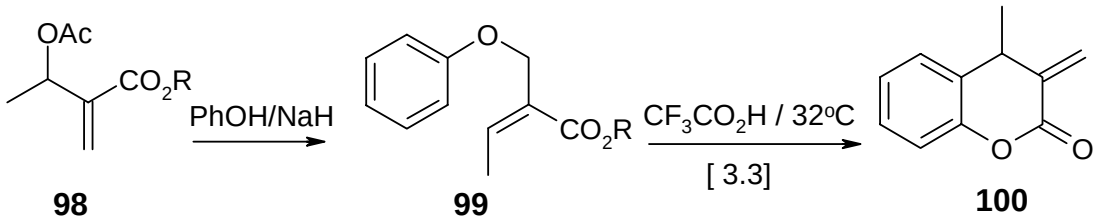
Table 1. Selected data for the condensation of phenols with methyl cinnamates.[125]

Product	R^1	R^2	X	Reaction time	Yield [a]/ %
96a	OH	H	OH	11hrs	52
96b	OH	H	OCH_3	10hrs	55
96c	OH	H	NMe_2	5hrs	60
96d (97d)[b]	OH	Me	NMe_2	7hrs	75 (2.5:1)[c]
96e	OH	OH	OH	2hrs	90
96f	OH	OH	OCH_3	3hrs	61
96g	OH	OH	NMe_2	1hr	70
96h (97d)[b]	OH	OMe	OH	13hrs	76 (2:1)[d]

[a] Isolated yield of pure product. [b] separation of the two isomers was performed by repeated flash chromatography. [c] Yield refers to the isomeric mixture. Regioisomer ratio (96d and 97d) determined by ^{1}H NMR analysis. [d] Unresolved mixture of the two isomers (96h and 97h).

1.4.6. Claisen rearrangement

Drewes *et al*.[126] reported the synthesis of 4-methyl-3-methylene-3,4-dihydrocoumarin **100** *via* the intramolecular Claisen-rearrangement of the aryl ether **99** in the presence of trifluoroacetic acid (Scheme 18). Such compounds had been synthesised previously by other routes, but Drewes' method is more efficient, because the precursor alkyl 3-acetoxy-2-methylene butanoate is readily prepared *via* acetylation of a Baylis-Hillman product and cyclization may be effected in the presence of trifluoroacetic acid to afford the coumarin **100** in 86% yield in a one-pot procedure.

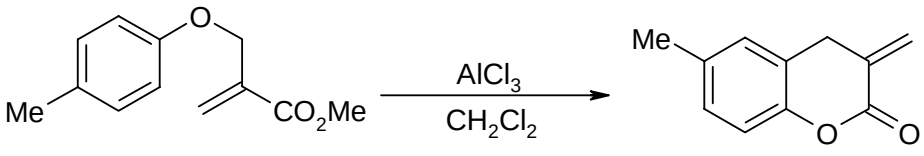


98 **99** **100**

R = alkyl

Scheme 18

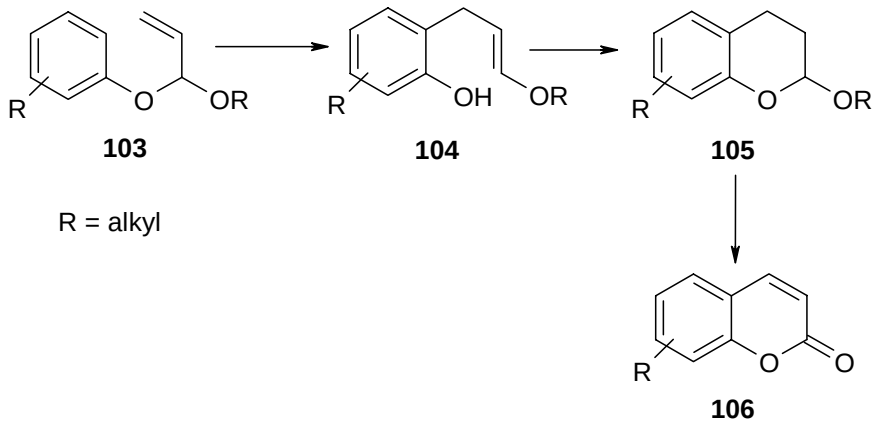
Previously, a similar approach to 3-methylenecoumarin was reported, which involves Lewis-acid catalysed Claisen rearrangement of an α-aryloxymethylacrylate ester **101** (Scheme 19).[127] A small amount of a dimer is also produced, which is assumed to form *via* an ene reaction of the highly reactive methylenecoumarin **102**.



101 **102**

Scheme 19

In an attempt to overcome the deficiencies and difficulties encountered with the Pechmann synthesis of coumarin derivatives Rapoport *et al.*[116a] developed a new application of the Claisen rearrangement using allyl or propargyl aryl ethers in which the allylic or propargylic α-carbon is oxygenated. This method has been applied in cases where formation of the coumarin could not be achieved using the Pechmann reaction. The approach is based on the rearrangement of the α-oxygenated allyl aryl ether **103** (Scheme 20). The intermediate alkoxychroman **105** is then oxidized to the corresponding coumarin.

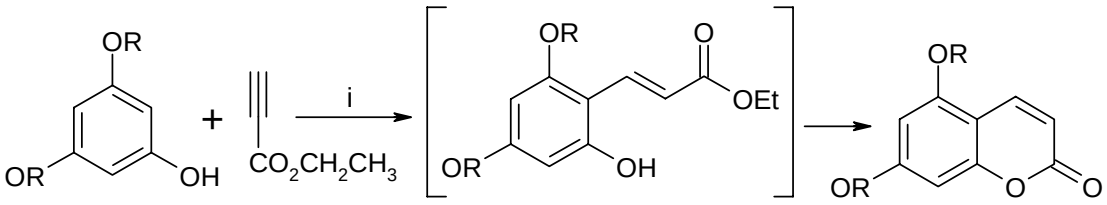


103 **104** **105** **106**

Scheme 20

1.4.7. Palladium-catalyzed addition

Trost and Toste, [128] in attempting to synthesize aflatoxin *via* a coumarin intermediate, explored a new reaction involving the use of a palladium(0) complex as catalyst system. This system is reported to effect:- cycloisomerization of enynes; reductive cyclization of enynes and diynes; and semi-hydrogenation of alkynes. Following the approach outlined in Scheme 21, they were able to synthesis, in yields of up to 88%, various coumarins which had proved inaccessible using methods like the Pechmann reaction. The mechanism for this reaction is considered to involve Pd(0) rather than Pd(+2). In formic acid palladium(II) acetate is reduced to Pd(0) which then catalyses the reaction. Although *cis*-addition initially affords the (*E*)-cinnamic ester **109**, the known ease of *E-Z* isomerization accounts for the isolation of coumarins rather than the (*E*)-cinnamates.

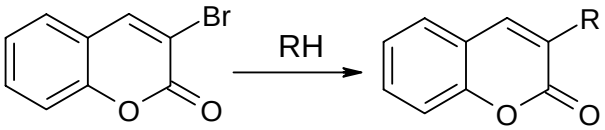


107 **108** **109** **110**

R = CH_3, H

Scheme 21 Reagents: i) HCOOH, 30% $Pd(OAc)_2$, 50% NaOAc at 50^oC

Mitra *et al*. [129] exploited the Heck reaction to synthesize 3-substituted coumarins. They reported the palladium-catalysed insertion of 3-bromocoumarin **111** into a number of alkenes and alkynes to form the 3-substituted coumarins **112a,b** in yields ranging from 48% to 91%.



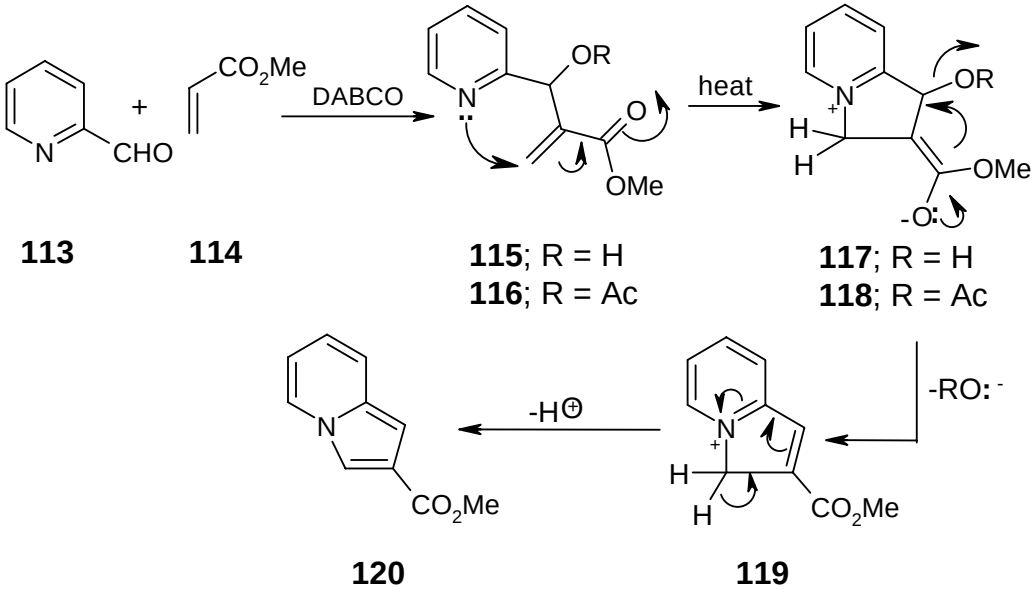
111 **112a-b**

	R
a	$-C(CH_3)=CHCO_2Me$
b	$-CH=CH(CH_3)_2OH$

Scheme 22 Reagents and conditions: Palladium(ll) acetate, tri-O-tolyphosphine, Triethylamine, 120^{o}C, 10h.

1.5. Previous work in the group and aims of the present investigation

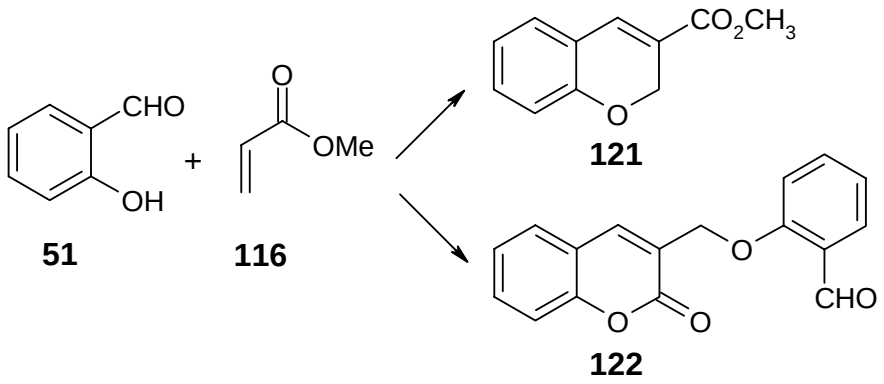
The Baylis-Hillman reaction has attracted the attention of organic chemists in recent years as it provides useful multifunctional molecules, which have been successfully employed as precursors in various synthetic processes. The application of this reaction in the synthesis of substituted indolizines *via* 1,4-diazabicyclo[2.2.2]octane (DABCO)-catalysed coupling of pyridine-2-carboxaldehydes and activated alkenes has been demonstrated by researchers in our group (Scheme 23).[130]



113 **114** **115**; R = H **116**; R = Ac **117**; R = H **118**; R = Ac **120** **119**

Scheme 23

Initial attempts to extend this methodology to the synthesis of the chromenes **121** Scheme 24) from salicylaldehyde precursors afforded an insoluble coumarin derivative **122** in low yield.[131] Subsequent studies aimed at optimising reaction conditions afforded the coumarin **122** in 50% yield, although, in general, chromene derivatives proved to be the most common products.[132a] Variation of the reaction conditions has permitted the chemoselective synthesis of chromenes[132b] and, in the present study, particular attention has been given to the preparation and reactions of the coumarin analogues



Scheme 24

The Baylis–Hillman approach has also been applied to the synthesis of quinoline derivatives **124-128** from *o*-nitrobenzaldehydes under mild conditions (Scheme 25)[133] and thiochromenes from 2,2-dithiodibenzaldehyde.[134]

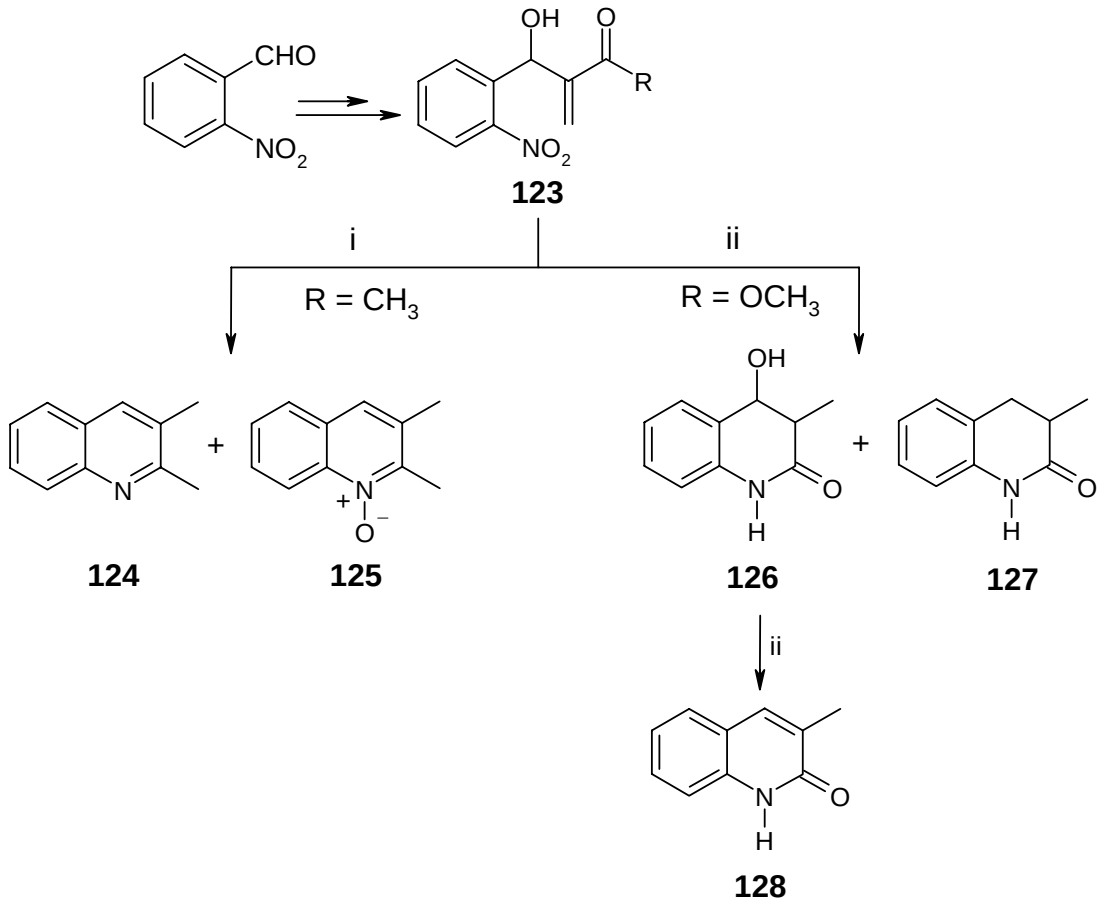
In a continuation of these investigations, the present study focused on the following objectives.

i) The use of salicylaldehyde derivatives in developing a chemoselective Baylis-Hillman approach to coumarin derivatives.

ii) An investigation of the reaction of the coumarin products with various nucleophiles.

iii) A study of the electron-impact (EI) mass fragmentation patterns exhibited by selected coumarin derivatives.

iv) The synthesis of coumarin-containing analogues of the HIV-1 protease inhibitor, ritonavir.



Scheme 25 Reagents and conditions: i) H_2, Pd-C, EtOH; ii) TsOH, toluene, reflux.

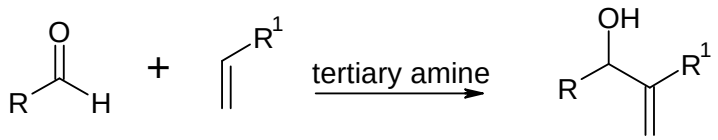
2. DISCUSSION

The discussion will focus mainly on the application of the Baylis-Hillman reaction in the synthesis of coumarin derivatives (Section 2.1). Attention will also be given to: - the regioselectivity of nucleophilic attack on various coumarin substrates (Section 2.2), the electron-impact (EI) mass fragmentation of coumarin derivatives (Section 2.3) and, finally, the synthesis of potential HIV-1 protease inhibitors containing coumarin moieties (Section 2.4).

2.1. APPLICATION OF THE BAYLIS-HILLMAN REACTION IN THE SYNTHESIS OF COUMARIN DERIVATIVES

2.1.1. The Baylis-Hillman reaction

The reaction involving a tertiary amine catalyst, such as 1,4-diazabicyclo[2.2.2]-octane (DABCO), an activated alkene and an aldehyde is widely referred to as the Baylis-Hillman or Morita-Baylis-Hillman reaction (Scheme 26). This important carbon-carbon bond-forming reaction, which typically affords multifunctional hydroxyalkyl derivatives **129**,[135] serves as a key step in the synthesis of several biologically active compounds.[135-142]

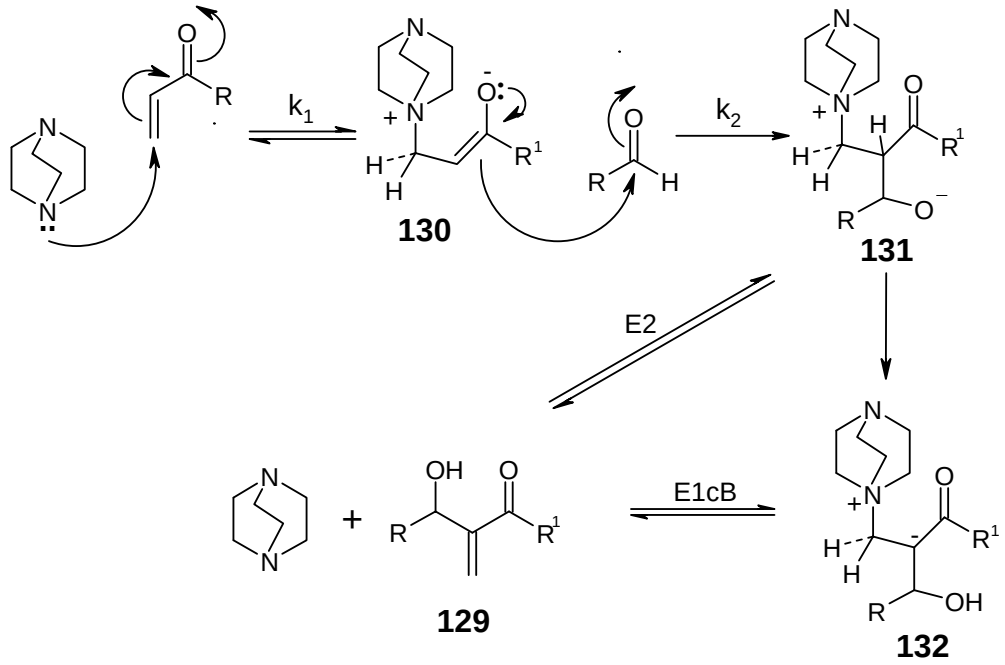


129

R^1 = COMe, CN, CO_2Et, *etc*.

Scheme 26

The reaction is considered to involve initial activation of the acrylate system *via* conjugate addition of the catalyst to afford the zwitterionic enolate **130** (Scheme 27). Formation of the second zwitterion **131**, *via* nucleophilic attack of the enolate **130** on the aldehyde is considered to be the rate determining step of the reaction.[143-144] Internal proton transfer may then afford a resonance-stabilized intermediate **132**, which can undergo E1cB elimination of the catalyst leading to the Baylis-Hillman

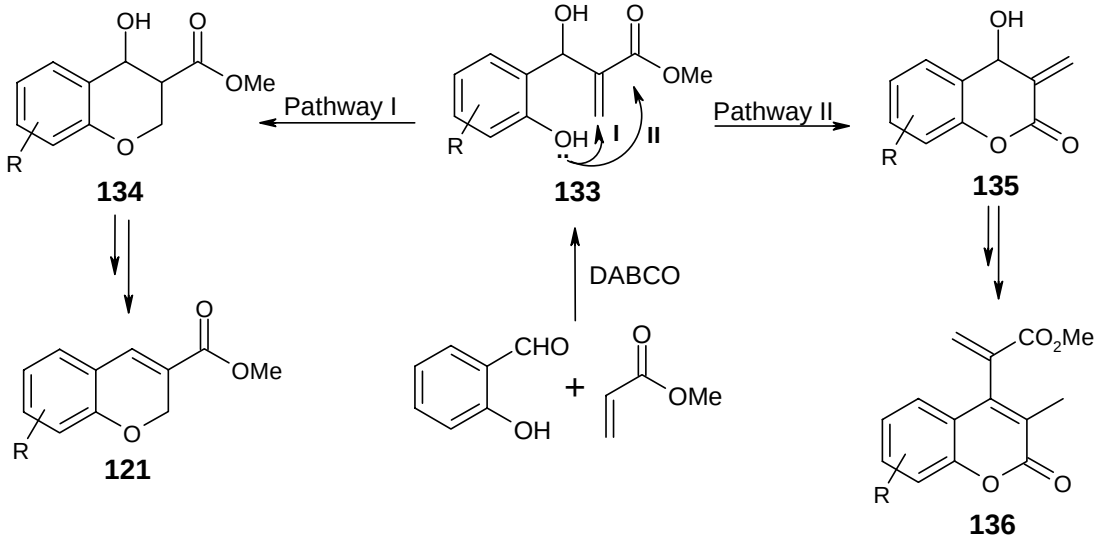


Scheme 27

product **129.** [145] Another possibility involves base-induced *anti*-E2 elimination of the catalyst and the H_α-proton, followed by protonation. An indication that both elimination pathways may operate is supported by a study of the solvent and pressure dependence of the reaction of benzaldehyde with crotononitrile.[146]

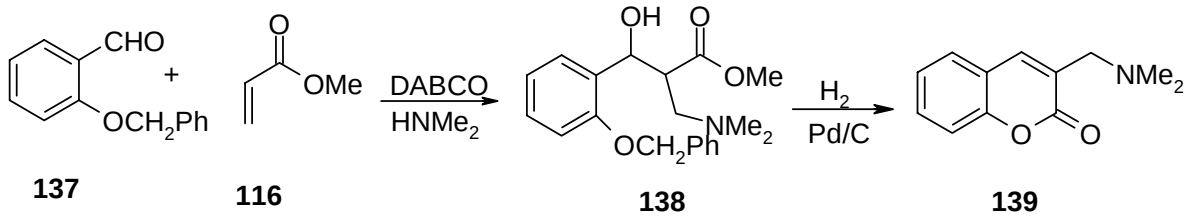
The Baylis-Hillman reaction, however, is not without drawbacks; prominent among these is the slow rate of the reaction.[147-148] Aggarwal *et al.*[149] reported the use of 1,8-diazabicyclo[5.4.0]undecene-7 (DBU) as a superior catalyst to accelerate Baylis-Hillman reactions. Other methods that have been reported to accelerate the Baylis-Hillman reaction include the following:- α-naphthyl acrylate as a Michael acceptor,[150] use of a Lewis acid as a co-catalyst,[151] mild co-operative catalysts[152] and indium-mediated allylation[153] to mention but a few. Morita *et al.*,[154] in reports which pre-date Baylis and Hillman's patent,[155] described the use of tertiary phosphines as a catalysts, while Kataoka *et al.*[156] recently reported the first "Chalcogeno-Baylis-Hillman" reaction in which the group 16 elements, sulfur and selenium, are used as catalysts in the presence of Lewis acids. Guigen Li *et al.*[157] have reported the use of $TiCl_4$ in Baylis-Hillman and Aldol reactions in the absence of a direct Lewis base.

In a previous investigation by Robinson,[158] the DABCO-catalysed Baylis-Hillman reaction between salicylaldehydes and methyl acrylate was observed to afford complex mixtures of chromene and coumarin derivatives (Scheme 28). It was assumed that the Baylis-Hillman product **133** is, in fact, formed but immediately undergoes cyclization *via* either conjugate addition (pathway I) to produce the chroman derivative **134**, or nucleophilic acyl substitution (pathway II) to afford the coumarin derivative **135**. Both products, **134** and **135,** then appear to undergo further reactions to give complex mixtures.



Scheme 28

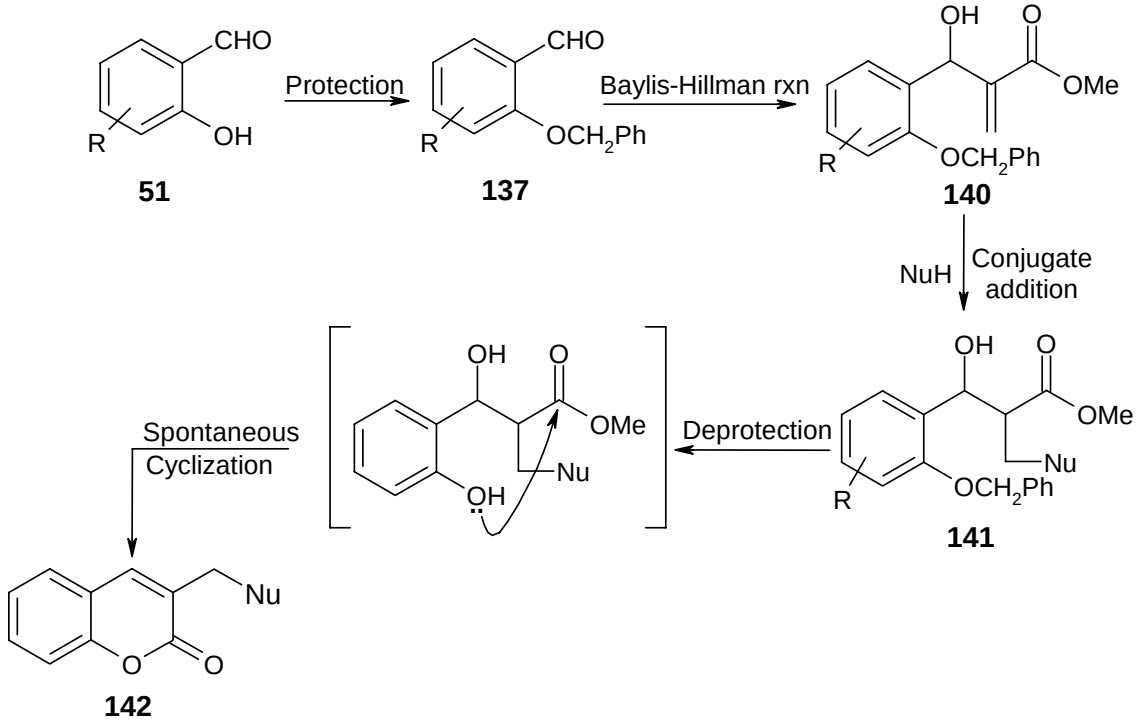
The use of *O*-acetylated and *O*-silylated salicylaldehydes was expected to inhibit cyclization and permit isolation of the Baylis-Hillman products.[158] However, the protecting groups chosen were not sufficiently stable. Drewes *et al.*[159] reported that



Scheme 29

salicylaldehyde benzyl ether **138** could be converted to the novel coumarin derivative **139** in an overall yield of 86% (Scheme 29). This was achieved by reacting the benzyl ether **137** with methyl acrylate **116** in the presence of DABCO, followed by conjugation addition of dimethylamine, debenzylation and spontaneous cyclisation.

The obvious stability of the benzyl protecting group under these conditions prompted us to use this general approach to prepare the coumarin derivatives required in the present investigation (Scheme 30). As will be seen later, however, other amines would be substituted for dimethylamine.

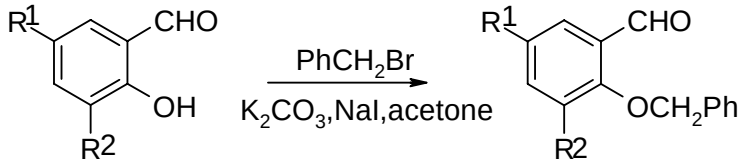


Scheme 30

2.1.2 Preparation of salicylaldehyde benzyl ethers

The value of the benzyl ether protecting group for alcohols has long been recognized, and this protecting group has been used in various reactions.[160] A protecting group needs to be efficiently introduced and later removed under mild conditions. The protecting group should also be inert towards reagents used in all the intermediate steps. The benzyl ether group was chosen to protect salicylaldehydes owing to its ease of formation, inherent stability and the variety of available deprotection methods, *viz*., 10% Pd/C in EtOH,[161] NaI-$BF_3.Et_2O$,[162] TMSI,[163] $SiCl_4$-NaI,[164] $AlCl_3$-$PhNMe_2$ in $CHCl_3$,[165] Ti (0),[166] to mention but a few.

Initial attempts to benzylate salicylaldehyde (using:- benzyl chloride and K_2CO_3 in acetone; benzyl chloride and NaH in toluene; or benzyl chloride and sodium ethoxide in ethanol) afforded the 2-benzyloxybenzaldehyde **137a** in a maximum yield of only (33%).



51a-f **137a-f**

	R^1	R^2	Yield / %
137a	H	H	74
137b	H	OMe	80
137c	H	OEt	70
137d	Cl	H	68
137e	Br	H	73
137f	Br	Br	66

Scheme 31

An alternative approach using benzyl bromide, K_2CO_3 and NaI in acetone, as outlined by Black,[167] was then adopted. The reaction is considered to involve a Finkelstein

reaction leading to the formation of sodium bromide and benzyl iodide, followed by an S_N2 reaction to afford the desired benzyl ether. Using this approach, the required benzyl ethers **137a-f** were prepared in up to 80% yield, as illustrated in Scheme 31.

The benzyl ethers **137a-f**, most of which are known, were fully characterized by elemental (high-resolution MS) and spectroscopic (IR and NMR) analysis. The ^{1}H NMR spectrum of 2-benzyloxy-5-chlorobenzaldehyde **137d,** a new compound, shows a two proton singlet at δ5.18 ppm, corresponding to the benzylic protons, and a one proton singlet at δ10.47 ppm, corresponding to the aldehydic proton (Figure 1a). The ^{13}C NMR spectrum (Figure 1b) reveals the benzylic carbon signal at δ71.0 ppm and the aldehydic carbonyl carbon at δ188.3 ppm; the correlations between the ^{1}H and ^{13}C NMR spectra were confirmed using the HETCOR data.

2.1.3. Synthesis of Baylis-Hillman products

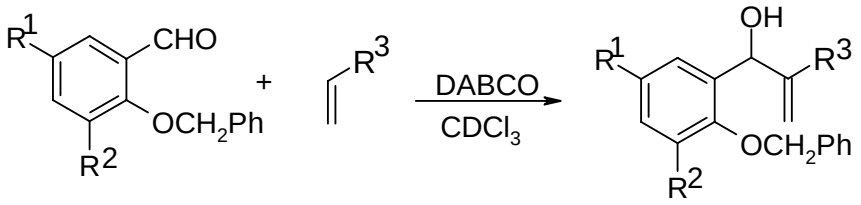
Careful attention was initially given to optimising the conditions for the Baylis-Hillman reaction of the salicylaldehyde benzyl ether **137a** (Scheme 32). The relative concentrations of the reactants, the solvent system and the reaction time were examined as indicated in Table **2.** After the reaction period indicated, the crude reaction mixture was analysed by ^{1}H NMR spectroscopy.

When the Baylis-Hillman reaction was carried out using a vigorously stirred mixture of $CDCl_3$ and D_2O as the solvent system, no trace of the Baylis-Hillman product **140a** was observed after six weeks at room temperature (entries 3 and 4). The highest yield of the product **140a** (95%) was obtained using 26.25 mmol of methyl acrylate to 2.63 mmol of DABCO in 0.25ml $CDCl_3$ (entry 7). The optimised conditions were then used for the reaction of the other benzylated salicylaldehydes **140b-f** to afford the corresponding Baylis-Hillman products in *isolated* yields ranging from 66 to 84% (Table 3).

(a)

(b)

Figure 1. **a**) 400 MHz ^{1}H NMR spectrum; and (**b**) 100 MHz p.n.d ^{13}C NMR spectrum of 2-benzyloxy-5-chlorobenzaldehyde **137d** in $CDCl_3$.



137 **116;** $R^3 = CO_2Me$ **140a-f;** $R^3 = CO_2Me$

143; $R^3 = CN$ **144a-e;** $R^3 = CN$

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

Scheme 32

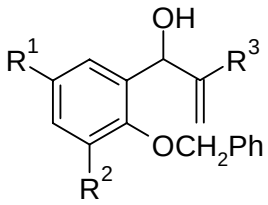
Table 2. Yield optimisation data for formation of the Baylis-Hillman product **140a**

Entry	Benzyl ether **137a** /mmol	Methyl acrylate /mmol	DABCO / mmol	Solvent [a] / ml	Time	Yield [b] / %
1	5.0	5.25	0.25	0.25	6wks	22
2	5.0	5.25	1	0.25	6wks	87
3	5.0	5.25	0.25	0.25 (0.25[c])	6wks	--
4	5.0	7.88	0.2	1 (1[c])	6wks	--
5	5.0	10.5	0.25	0.25	6wks	21
6	5.0	10.5	2.63	0.25	4wks	90
7	5.0	26.25	2.63	0.25	3wks	95

[a]Volume of $CDCl_3$ used. [b] Yield determined from ^1H NMR spectrum of the crude mixture.
[c] Volume of D_2O used together with $CDCl_3$.

The products were readily identified by ^{1}H and ^{13}C NMR spectroscopy, and the corresponding spectra for methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylene-propanoate **140a** is illustrated in Figure 2. The vinylic protons resonate as singlets at δ5.68 and δ6.28 ppm, the 3-methine proton as a singlet at δ5.93 ppm, the hydroxyl proton as a broad singlet at δ3.37 ppm and the methoxy methyl protons as a singlet at δ3.71 ppm (Figure 2a). The ^{13}C NMR spectrum (Figure 2b) reveals the vinylic methylene carbon signal at δ125.8 ppm, the HMQC (Figure 3) spectrum confirming attachment of the two methylene protons to the same carbon.

Table 3. Yields obtained for the Baylis-Hillman reactions of the benzyl ethers **137a-f** methyl acrylate or acrylonitrile.[a]



140a-f ; $R_3 = CO_2Me$
144a-e; $R_3 = CN$

	R^1	R^2	R^3	Yield [b]/ %
140a	H	H	CO_2Me	75
140b	H	OCH_3	CO_2Me	84
140c	H	OCH_2CH_3	CO_2Me	80
140d	Cl	H	CO_2Me	78
140e	Br	H	CO_2Me	84
140f	Br	Br	CO_2Me	66
144a	H	H	CN	55
144b	H	OCH_3	CN	61
144c	H	OCH_2CH_3	CN	91[c]
144d	Cl	H	CN	55
144e	Br	H	CN	51

[a] After a reaction time of 21 days. [b] Isolated yield. [c] After 7 days

(a)

(b)

Figure 2. **a**) 400 MHz ^{1}H NMR spectrum; and (**b**) 100 MHz p.n.d ^{13}C NMR spectrum of methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylene-propanoate **140a** in $CDCl_3$

Figure 3. The HMQC spectrum of methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanoate **140a** in $CDCl_3$

Application of the Baylis-Hillman methodology to the reaction of the salicylaldehyde benzyl ethers **137a-f** with other α,β-unsaturated systems, *viz*, acrylonitrile and methyl vinyl ketone was also explored. The order of reactivity of α,β-unsaturated systems ($XCH=CH_2$) has been shown to be: X = CHO > COMe > CN > CO_2R > $CONH_2$;[168] the presence of an electron-withdrawing group increases the electrophilicity of the alkene thus increasing the rate of formation of the enolate species **130** (Scheme 27).

The use of alternative activated alkenes has been explored by various groups. Thus, Basavaiah *et al.*[169] have reported the DABCO-catalysed synthesis of α-methylene-β-hydroxyalkanones in up to 73% yield by reacting methyl vinyl ketone with selected aldehydes in THF for 15 days. Villieras *et al*.[170] have reported the preparation of α-methylene-β-hydroxynitriles in up to 59% yield by treating selected aldehydes with acrylonitrile in the presence of DABCO. Normant *et al*.[171] have reported an extension of Baylis-Hillman methodology to include the use of vinyl sulfones as the activated alkenes; these reactions, however, were extremely slow, with reaction times extending to 11weeks. Perlmutter *et al*.[172] have recently shown that DABCO-catalysed reactions of aldehyde with aryl acrylates proceeds at significantly greater rates than with alkyl acrylates.

In the present study, treatment of the salicylaldehyde benzyl ether **137a** with methyl vinyl ketone (MVK) failed to afford the Baylis-Hillman product after 21 days under the previously optimised reaction conditions. However, replacement of MVK by acrylonitrile afforded the Baylis-Hillman product **144a** (Scheme 32) in 55% yield within 21 days (Table 3). The procedure was then extended to the preparation of the Baylis-Hillman products **144b-e,** compound **144c** being isolated in 91% yield after only 7 days. The acrylonitrile-derived products **144a-e** are all new and were fully characterized. The ^{1}H NMR spectrum of 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanenitrile **144a** reveals the 2'-vinylic proton singlets at δ5.93 and 5.96 ppm, the 3-methine proton singlet at δ5.54 ppm, and the hydroxyl proton singlet at δ3.08 ppm (Figure 4a). The ^{13}C NMR spectrum (Figure 4b) confirms the presence of the expected fifteen signals, with the 2"-methylene carbon resonating at δ129.7 ppm

and the nitrile carbon at δ155.9ppm. These assignments are supported by the HMQC, DEPT and COSY NMR data.

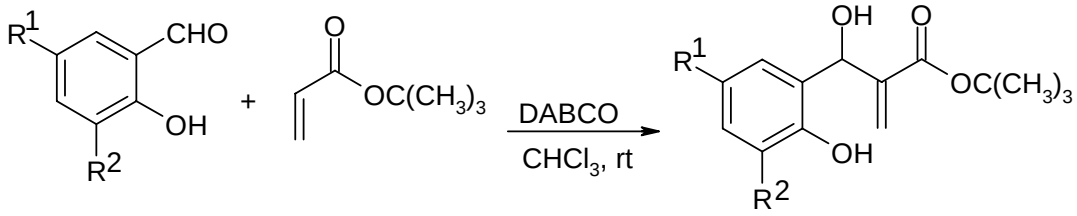
(a)

(b)

Figure 4. **a**) 400 MHz ^{1}H NMR spectrum; and (**b**) 100 MHz p.n.d ^{13}C NMR spectrum of 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropane-nitrile **144a** in $CDCl_3$.

2.1.4. Baylis-Hillman reactions between substituted salicylaldehydes and *tert*-butyl acrylate

In a cognate study directed towards the chemoselective synthesis of chromene derivatives, Nocanda[134] had observed that the use of *tert*-butyl acrylate as the activated alkene in a DABCO-catalysed reaction with salicylaldehyde afforded *tert*-butyl 3-hydroxy-3-(2-hydroxyphenyl)-2-methylenepropanoate **146a** in 49% yield after 7days. The isolation of the Baylis-Hillman product in this case was attributed to the electron-releasing inductive effect and the steric bulk of the *tert*-butyl group which serves to inhibit intramolecular cyclization (*via* conjugate addition or acyl substitution) to either chromene or coumarin derivatives. In the present study, this approach was extended to a range of salicylaldehyde precursors **51a-c, e-f** to obtain the *tert*-butyl esters **146a-c; e-f** (Scheme 33; Table 4), the intention being to explore the possibility of intramolecular cyclization *via* acyl substitution to afford coumarin derivatives.



51a-c, e-f **145** **146a-c, e-f**

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

Scheme 33

Table 4. Yields obtained for the reaction between salicyaldehydes **51a-c; e-f** and *tert*-butyl acrylate, **145** after 7days

	R^1	R^2	Yield %
146a	H	H	40
146b	H	OMe	57
146c	H	OEt	58
146e	Br	H	66
146f	Br	Br	44

The Baylis-Hillman products **146a-c, e-f** were fully characterized by both one- and two-dimensional NMR spectroscopy, and the ^{1}H NMR spectrum of compound **146e** (Figure 5a), which is typical of the series, reveals the two, characteristic vinylic proton signals at δ5.56 and 6.23 ppm, the 3-methine proton signal at δ5.63 ppm, the hydroxyl proton signal at δ4.26 ppm and the nine proton *tert*-butyl signal at δ1.51 ppm. In the corresponding ^{13}C NMR spectrum (Figure 5b), the *tert*-butyl methyl carbons resonate at δ28.0 ppm, the carbonyl carbon at δ166.7 ppm and the vinylic methylene carbon at δ127.2 ppm. The HMQC spectrum of compound **146e** (Figure 6) confirms attachment of the two vinylic protons to the same carbon.

(a)

(b)

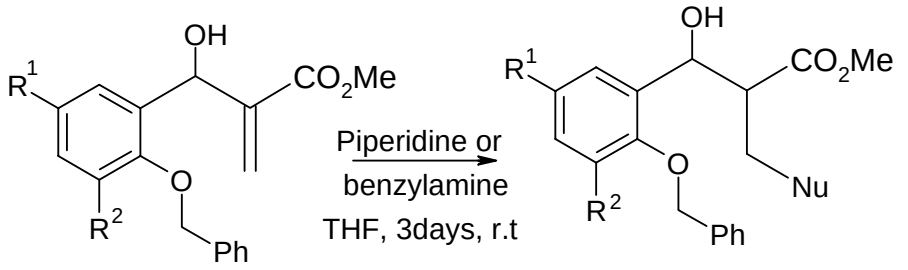
Figure 5. **a**) 400 MHz ^{1}H NMR spectrum; and (**b**) 100 MHz p.n.d ^{13}C NMR spectrum of *tert*-butyl 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-2-methylenepropanonate **146e** in $CDCl_3$.

Figure 6. The HMQC spectrum of *tert*-Butyl 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-2-methylenepropanonate **146e** in $CDCl_3$.

2.1.5. Conjugate addition to protected Baylis-Hillman products

The strategy (summarized in Scheme 30) to achieve the chemoselective synthesis of coumarin derivatives has involved :- i) the isolation of protected Baylis-Hillman products (discussed in the previous section); ii) conjugate addition to the α,β-unsaturated system to prevent cyclization to chromene *via* intramolecular attack at the vinylic centre; and iii) deprotection of the phenolic hydroxyl group to ensure cyclization *via* nucleophilic acyl substitution to afford the coumarin derivatives (Scheme 30). Having isolated the protected Baylis-Hillman products **140a-f** (and the non-protected *tert*-butyl esters **146a-c,e-f**), the next challenge was to explore the conjugate addition step.

Drewes *et al.*[159] have reported the use of dimethylamine as a nucleophile (Scheme 29), but we decided to explore conjugate addition using the less volatile nucleophiles, piperidine and benzylamine. It is known that both primary and secondary amines may attack α,β-unsaturated carbonyl compounds because the carbonyl group lowers the electron density at the beta-carbon of the double-bond, thereby permiting nucleophilic rather than electrophilic addition.[173] Reaction of the benzylated Baylis-Hillman



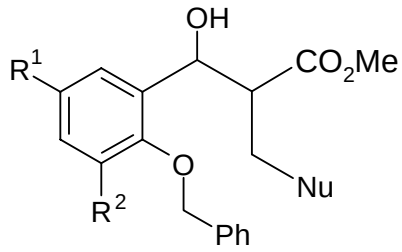
140a-f

147a-f (Nu =$PhCH_2NH$)
148a-f (Nu = piperidino)

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

Scheme 35

Table 5. Yields for conjugate addition of piperidine or benzylamine to the Baylis-Hillman products **140a-f**



147a-f (Nu = $PhCH_2NH$)
148a-f (Nu = Piperidino)

Compd.	R^1	R^2	Nucleophile	Isolated Yield / %
147a	H	H	Benzylamine	62
147b	H	OCH_3	Benzylamine	87
147c	H	OCH_2CH_3	Benzylamine	71
147d	Cl	H	Benzylamine	69
147e	Br	H	Benzylamine	63
147f	Br	Br	Benzylamine	71
148a	H	H	Piperidine	80
148b	H	OCH_3	Piperidine	55
148c	H	OCH_2CH_3	Piperidine	58
148d	Cl	H	Piperidine	63
148e	Br	H	Piperidine	62
148f	Br	Br	Piperidine	65

products **140a-f** when treated with piperidine or benzylamine as a nucleophile in THF at room temperature afforded the diastereomeric products **147a-f** and **148a-f** in yields ranging from 55 to 87% (Scheme 35; Table 5). The conjugate addition products **147a-f** and **148a-f** were fully characterized by elemental (high-resolution MS) and spectroscopic (MS, IR and NMR) analysis. The ^{1}H NMR spectrum of methyl 2-(benzylaminomethyl)-3-(2-benzyloxylphenyl)-3-hydroxypropanoate **147a** (Figure 7a) reveals a singlet at δ5.77 ppm corresponding to the 3-methine proton signal, and a

singlet at δ3.75 ppm corresponding to the methoxy protons signal. The pairs of benzylic protons resonate at δ5.13 and 3.67 ppm as a double doublet. The Dept-135 spectrum (Figure 7b) reveals the benzylic carbon signals at δ46.2 ppm and δ69.6 ppm. These assignments are confirmed by both HMQC (Figure 8) and COSY (Figure 9) NMR spectrum data.

(a)

(b)

Figure 7. **a**) 400 MHz ^{1}H NMR spectrum; and (**b**) DEPT-135 spectrum of methyl 2-(benzylaminomethyl)-3-(2-benzyloxylphenyl)-3-hydroxypropanoate **147a** in $CDCl_3$.

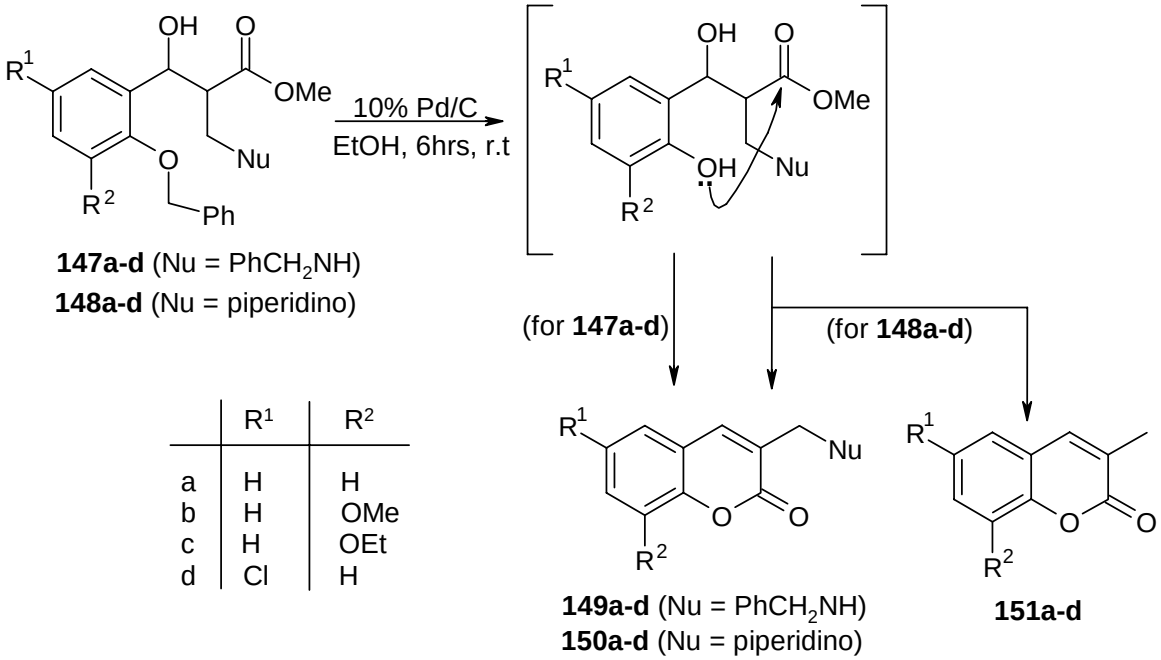
Figure 8. HMQC spectrum of methyl 2-(benzylaminomethyl)-3-(2-benzyloxy-phenyl)-3-hydroxypropanoate **147a** in $CDCl_3$.

Figure 9. COSY spectrum of methyl 2-(benzylaminomethyl)-3-(2-benzyloxy-phenyl)-3-hydroxypropanoate **147a** in $CDCl_3$.

2.1.6. Synthesis of 3-substituted coumarin derivarives

2.2.6.1. *Reductive deprotection and cyclization of conjugate addition products.*

In the next phase of our approach to coumarin derivatives, we explored catalytic hydrogenation under mild conditions to effect cleavage of the *O*-benzyl protecting group; spontaneous cyclization *via* intramolecular transesterification was then expected to afford the required coumarins. It is known that hydrogenolysis of benzylic oxygen bonds occurs readily,[174] and many catalysts have been used for this purpose. Palladium appears to be the preferred choice combining high hydrogenolysis activity with a low tendency to promote reduction of the aromatic ring.[175] It was therefore decided to use a 10% palladium-on-carbon catalyst. Selected conjugate addition products (**147a-d** and **148a-d**) were subjected to catalytic hydrogenoloysis in the presence of 10% palladium-on-carbon in ethanol at room temperature for 6 hours (Scheme 36). The benzylamino derivatives **147a-d** afforded the expected 3-substituted coumarins **149a-d**. The piperidino derivatives **148a-d**, however, in

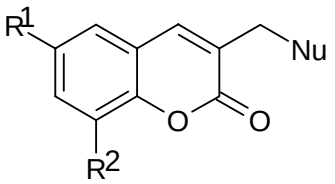


	R1	R2
a	H	H
b	H	OMe
c	H	OEt
d	Cl	H

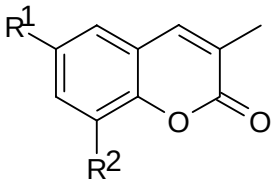
Scheme 36

addition to the expected 3-substituted coumarins **150a-d**, afforded the de-aminated products **151a-d**.

Table 6. Yields for the catalytic hydrogenolysis of selected conjugate addition products (Scheme 36)



149a-d (Nu = $PhCH_2NH$)
150a-d (Nu = piperidino)



151a-d

Compound	R^1	R^2	Isolated Yield / %
149a	H	H	53
149b	H	OCH_3	51
149c	H	OCH_2CH_3	66
149d	Cl	H	49
150a	H	H	51
150b	H	OCH_3	45
150c	H	OCH_2CH_3	49
150d	Cl	H	61
151a	H	H	20
151b	H	OCH_3	9.5
151c	H	OCH_2CH_3	14
151d	Cl	H	9

It is known that benzylic-oxgyen bonds undergo hydrogenolysis more readily than benzylic-nitrogen bonds, thus accounting for the formation of the expected 3-substituted coumarins **149a-d**. In the formation of the piperidino analogues **150a-d**, the *O*-benzyl protecting group was cleaved as expected, but the formation of the de-aminated coumarin derivatives **151a-d** was quite unexpected.

The 3-substituted coumarins **149a-d, 150a-d** and **151a-d** were fully characterized by elemental (high resolution MS) and spectroscopic (IR and NMR) analysis. The ^{1}H NMR spectrum of 8-methoxy-3-(piperidinomethyl)coumarin **150b** (Figure 10a) shows the piperidino proton signals at δ1.43, 1.65 and 2.24 ppm, and the methoxy proton singlet at δ3.93 ppm. The 1'-methylene protons resonate at δ3.42 ppm as a doublet (J =1.6 Hz) due to long-range allylic coupling with the vinylic 4-H nucleus which resonates at δ 7.77 ppm. This coupling relationship was confirmed by the COSY spectrum (Figure 11). The ^{13}C NMR spectrum (Figure 10b) reveals the piperidino carbon signals at δ 24.1, 26.0 ppm and 54.7 ppm, the 1'-methylene carbon signal at δ 56.9 ppm and a signal at δ56.2 ppm corresponding to the methoxy carbon. These assignments are supported by the HMQC and DEPT data. The ^{1}H NMR spectrum of 8-methoxy-3-methylcoumarin **151b** (Figure 12a) shows the methyl proton singlet resonating at δ 2.20 ppm, the methoxy proton singlet at δ 3.94 ppm and the vinylic 4-H proton singlet at δ 7.48 ppm. The ^{13}C NMR spectrum (Figure 12b) reveals the 1'-methyl carbon signal at δ 17.2 ppm and the methoxy carbon signal at δ 56.2 ppm These assignments are supported by the HMQC and DEPT data.

Possible explanations for the formation of compounds **151a-d** are outlined for compound **151a** in Scheme 37. In pathway I equilibration between the Baylis-Hillman product **140a** and the conjugate addition product **148a** could lead, during hydrogenolysis, to the formation of 4-hydroxy-3-methylenecoumarin **135** as a reaction intermediate. Further reduction and dehydration would then afford the de-aminated coumarin **151a**. The involvement of compound **135** was proposed by Bode *et al.*[176] as an intermediate in the formation of the novel coumarin derivative **122** (Scheme 24), while Robinson isolated compound **135** in 38% yield from the reaction of a disilylated Baylis-Hillman product.[158] A second possibility (pathway II) involves initial catalytic hydrogenolysis of compound **148a** followed by cyclization to the substituted coumarin **150a;** elimination of piperidine in the presence of the palladium-on-carbon catalyst then affords compound **151a.**

(a)

(b)

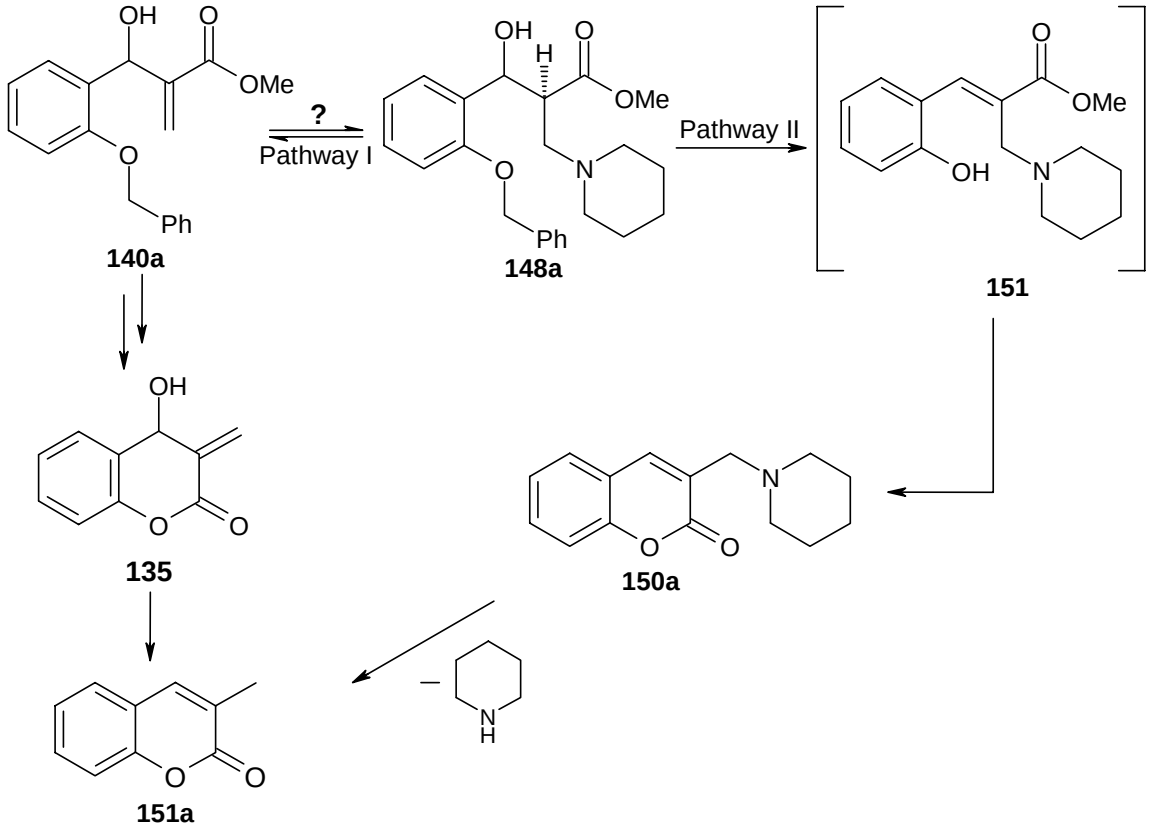
Figure 10. **a**) 400 MHz ^{1}H NMR spectrum; and (**b**) 100 MHz p.n.d ^{13}C NMR spectrum of 8-methoxy-3-(piperidinomethyl)coumarin **150b** in $CDCl_3$.

Figure 11. COSY spectrum of 8-methoxy-3-(piperidinomethyl)coumarin **150b** in $CDCl_3$.

(a)

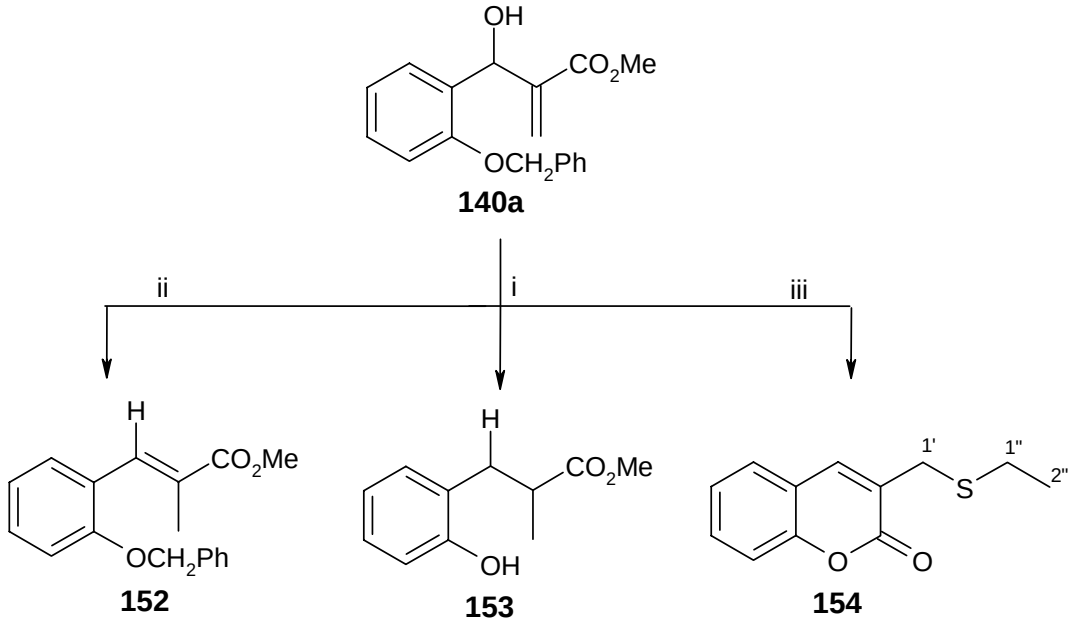
(b)

Figure 12. **a**) 400 MHz ^{1}H NMR spectrum; and (**b**) 100 MHz p.n.d ^{13}C NMR spectrum of 8-methoxy-3-methylcoumarin **151b** in $CDCl_3$



Scheme 37. Possible routes to the de-aminated product **151a**

In order to explore the possible formation of the de-aminated products **151a-d** *via* pathway I, debenzylation of the protected Baylis-Hillman product, methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanoate **140a** was investigated, using:- 10% palladium-on-carbon in ethanol;[177] a mixture of 10% palladium-on-carbon and 1,4-cyclohexadiene in ethanol;[178] and the combination of a hard acid and a soft nucleophile (Et_2O-BF_3 / EtSH) which has been used for the cleavage of the benzyl group.[179] Application of these methods, however afforded the respective products **152**, **153** and **154** (Scheme 38)



Scheme 38. Reagents: i) H_2, 10% Pd-C, EtOH , 6h; ii) 10% Pd-C, EtOH, 1,4-cyclohexadiene, 2h; iii) EtSH, Et_2O-BF_3, 40min.

The structures of these reduction products (**152-154**) were fully elucidated using both one- and two-dimensionial NMR spectroscopy. The ^{1}H NMR spectrum of 3-(ethylsulfanylmethyl)coumarin **154** (Figure 13a), reveals the 1"-CH_2 signal as a quartet at δ2.61 ppm, and the 2"-CH_3 signal as a triplet at δ1.30 ppm. The ^{13}C NMR spectrum (Figure 13b) reveals the corresponding 2"-methyl carbon signal at δ14.4 ppm, and the 1"- and 1'-methylene carbon signals at δ26.3 ppm and δ30.8 ppm respectively. These assignments are supported by the HMQC, DEPT and COSY NMR data.

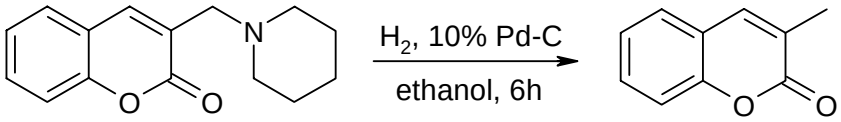
Heck *et al.*[180] have reported the catalytic hydrogenolysis of an allylic piperidino system using triethylammonium formate and a palladium catalyst. Although an attempt to extend this methodology to the synthesis of 3-methylcoumarin **151a** *via* hydrogenolysis of 3-(piperidinomethyl)coumarin **150a** using 10% palladium-on-carbon, HCOOH and Et_3N proved unsuccessful, elimination of piperidine did occur

(a)

(b)

Figure 13. **a**) 400 MHz ^{1}H NMR spectrum; **b**) 100 MHz p.n.d ^{13}C NMR spectrum of 3-(ethylsulfanylmethyl)coumarin **154** in $CDCl_3$.

during hydrogenolysis in the presence of 10% palladium-on-carbon catalyst to afford 3-methylcoumarin **151a** as a sole product in 92% yield (Scheme 39). We therefore presume that the de-aminated coumarins **151a-d** are, in fact, produced *via in situ* elimination of piperidine from the respective precursors **150a-d** (Scheme 36).

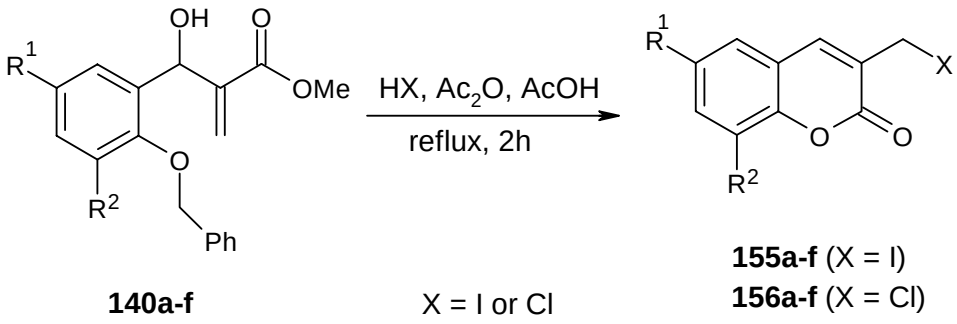


150a **151a**

Scheme 39

2.1.6.2. *Acid-catalysed deprotection and cyclization of the* O*-benzylated Baylis Hillman products*

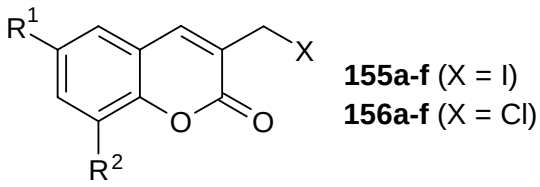
Ethers are known to be cleaved by heating with concentrated hydriodic acid or hydrobromic acid under quite vigorous conditions.[181-182] Uriarte *et al.*[85] reported the used of hydriodic acid in the demethylation and cyclization of ethyl 3-cyclohexyl-3-hydroxy-3-(2,5-dimethoxyphenyl)-2-propenoate to afford 4-cyclohexyl-6-hydroxy-coumarin in yields of up to 68%. The benzylated Baylis-Hillman products **140a-f** were therefore treated with hydriodic acid in a mixture of acetic acid and acetic anhydride at reflux temperature (Scheme 40), and the 3-(iodomethyl)coumarins **155a-f** were isolated in yields ranging from 61 to 85% (Table 7). Hydriodic acid, however , is expensive and difficult to handle and, consequently, it was decided to explore the use of concentrated hydrochloric acid as alternative reagent. This, in fact, afforded the 3-(chloromethyl)coumarins **156a-f** in even better yields (up to 94%)!



Scheme 40

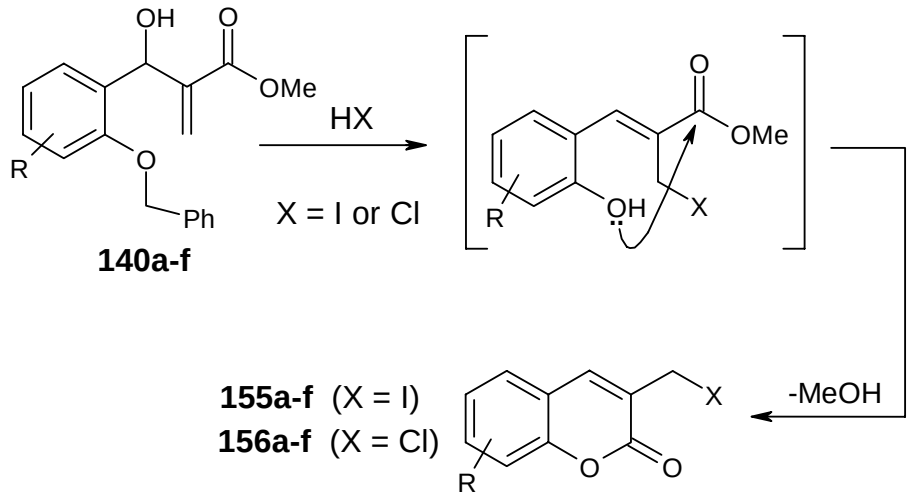
The formation of the novel 3-(halomethyl)coumarins is presumed to involve conjugate addition of the halogen acid to the α,β-unsaturated ester moiety and acid-catalysed dehydration (or S_N' displacement of OH by X), cleavage of the benzyl ether and finally cylization, as outlined in Scheme 41. The advantages of this approach compared to the general method outlined in Scheme 28 are as follows :- no need for prior conjugate addition of nucleophile, convenient deprotection and cyclization, all in one pot and in high yield.

Table 7. Yields obtained for 3-halomethylcoumarins **155a-f** and **156a-f**



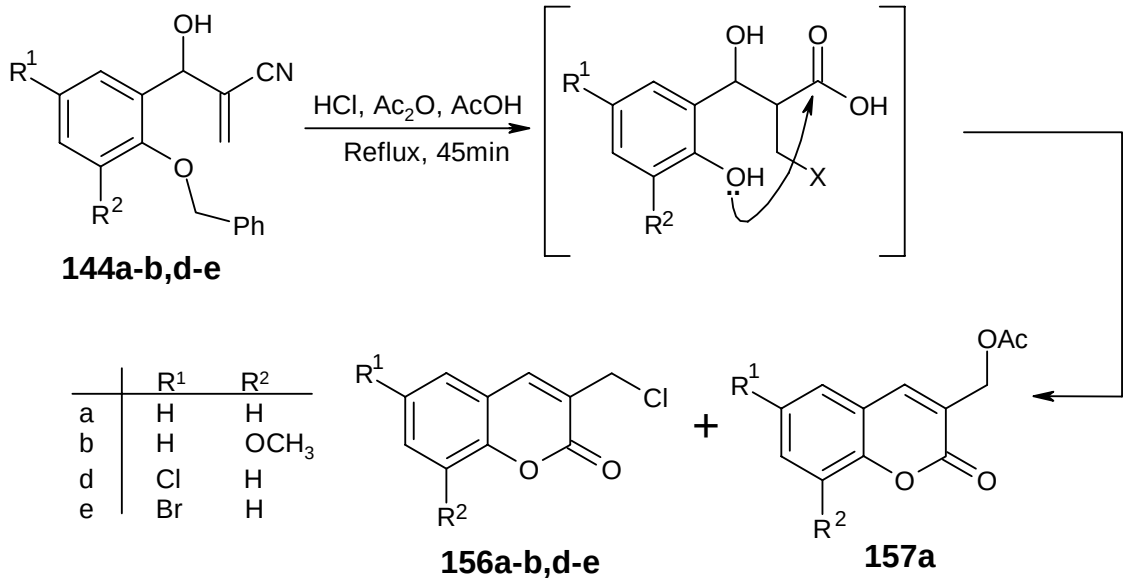
155a-f (X = I)
156a-f (X = Cl)

Substrate	R^1	R^2	**155** Yield / %	**156** Yield / %
140a	H	H	66	80
140b	H	OCH_3	62	87
140c	H	OCH_2CH_3	61	94
140d	Cl	H	85	94
140e	Br	H	61	81
140f	Br	Br	61	90



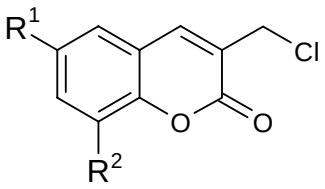
Scheme 41. Proposed steps in the formation of the 3-(halomethyl)coumarins **155a-f** and **156a-f** (reflecting S_N' displacement of OH).

It was decided to extend this procedure (Scheme 40) to the protected Baylis-Hillman adducts **144**, which contain an α,β-unsaturated nitrile moiety. Nitriles are generally hydrolysed by acid to either carboxylic acids or amides with the former being the more common product. It was hoped that hydrolysis of the nitrile function would be followed by intramolecular acyl substitution to afford the coumarin in one pot. The Baylis-Hillman adducts **144a-b,d-e** were therefore treated with hydrochloric acid in a mixture of acetic acid and acetic anhydride at reflux temperature for 45 min, to afford the 3-(chloromethyl)coumarin derivatives **156a-b,d-e** in up to 87% yield; in one case, 3-(acetoxymethyl)coumarin **157a** was also isolated in 14% yield (Scheme 42; Table 8).

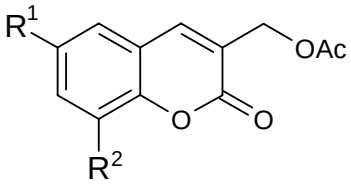


Scheme 42

Table 8. Data for the reaction of the benzylated Baylis-Hillman nitriles **144a-b,d-e** (Scheme 42).



156a-b,d-e



157a

Substrate	R^1	R^2	**156** Yield / %	**157** Yield / %
144a	H	H	75%	14%
144b	H	OCH_3	69%	0
144d	Cl	H	87%	0
144e	Br	H	75%	0

The ^{1}H NMR spectrum of 3-(chloromethyl)-8-ethoxycoumarin **156c** reveals (on expansion) the characteristic 1'-methylene proton signal at δ 4.55 ppm as a doublet (*J* = 0.8 Hz) due to long-range allylic coupling with the vinylic 4-H nucleus (Figure 14a). Although, the 4-H nucleus appears to resonate as a singlet at δ7.85 ppm, the allylic coupling relationship was confirmed by the COSY spectrum (Figure 15). The ^{13}C NMR spectrum (Figure 14b) shows the 1'-methylene carbon signal at δ 41.0 ppm, the ethoxy methylene carbon signal at δ 65.1 ppm and the methyl carbon signal at δ14.7 ppm. Assignment of the carbon signals is supported by the DEPT and HMQC spectra. The ^{1}H NMR spectrum of the 3-(acetoxymethyl)coumarin **157a** reveals the characteristic acetyl proton signal at δ 2.15 ppm and the methylene proton singlet at δ 5.06 ppm (Figure 16a). The ^{13}C NMR specrum (Figure 16b) shows the acetyl carbon signal at δ 20.9 ppm and the methylene carbon at δ 61.2 ppm.

(a)

(b)

Figure 14. **a)** 400 MHz ^{1}H NMR spectrum; **b)** 100 MHz p.n.d ^{13}C NMR spectrum of 3-(chloromethyl)-8-ethoxycoumarin **156c** in $CDCl_3$.

Figure 15. 400MHz COSY spectrum of 3-(chloromethyl)-8-ethoxycoumarin **156c** in $CDCl_3$.

(a)

(b)

Figure 16. **a)** 400 MHz ^{1}H NMR spectrum; **b)** 100 MHz p.n.d ^{13}C NMR spectrum of 3-(acetoxymethyl)coumarin **157a** in $CDCl_3$.

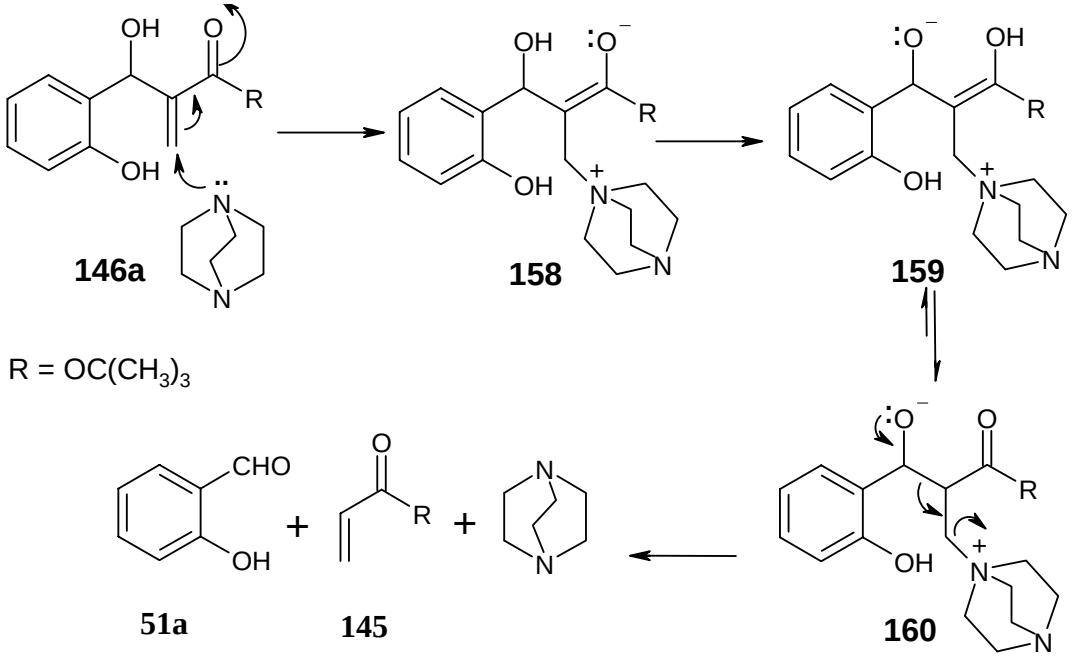
2.1.6.3. *Synthesis of coumarin derivatives via direct cyclization of unprotected Baylis-Hillman products*

In the previous section, treatment of the *O*-benzylated Baylis-Hillman products **140a-f** and **144a-e** with hydriodic or hydrochloric acid (in acetic acid and acetic anhydride) was shown to afford the corresponding 3-(halomethyl)coumarins **155a-f** and **156a-f** in yields of up to 94%, without needing to protect the double bond by conjugate addition of an amine. In an approach to the synthesis of coumarins, which was to prove even more convenient, attention was given to the cyclization of the completely unprotected Baylis-Hillman *tert*-butyl esters **146**. (The electron-releasing inductive effect and steric bulk of the *tert*-butyl group in these compounds appear to inhibit spontaneous cyclization *via* acyl substitution to coumarin derivatives, or *via* conjugate addition to chromenes.)

Reaction of *tert*-butyl 3-hydroxy-3-(2-hydroxyphenyl)-2-methylenepropanoate **146a** with DABCO in $CDCl_3$ might have been expected to permit cyclization to a chroman system *via* intramolecular displacement of DABCO from intermediates, such as **158** or

Figure 17. 400 MHz ^{1}H NMR spectrum of a crude mixture resulting from the reaction of *tert*-butyl 3-hydroxy-3-(2-hydroxyphenyl)-2-methylene propanoate **146a** with DABCO in $CDCl_3$.

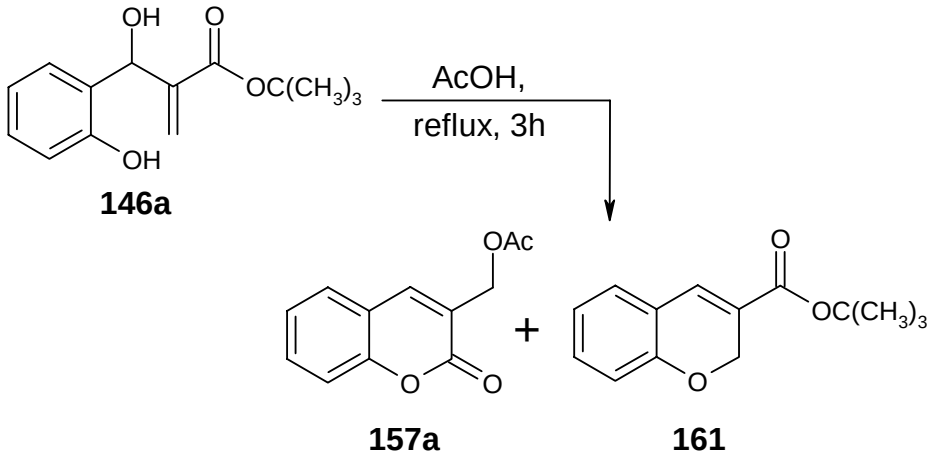
159 (Scheme 43). In the event, the reaction led to the formation of the precursors, *tert*-butyl acrylate **145** and salicyaldehyde **51a,** as determined by ^{1}H NMR analysis of the crude mixture. The ^{1}H NMR spectrum (Figure 17) revealed the *tert*-butyl and vinylic proton signals corresponding to *tert*-butyl acrylate and a one proton signal at δ 9.89 ppm, corresponding to the aldehydic proton of salicyaldehyde. This observation is consistent with previous reports,[183-184] which suggested that the overall Baylis-Hillman reaction was reversible, and is also in agreement with the result obtained from a parallel study in our group directed at the preparation of chromene derivatives.[132b] A tentative mechanistic sequence for the process, outlined in Scheme 43, involves conjugate addition by DABCO to the Baylis-Hillman ester **146a** to afford the zwitterionic enolate **158**, which undergoes proton transfer to form an enol **159**; tautomerization to the keto form **160** and, finally, elimination of DABCO to afford salicylaldehyde and *tert*-butyl acrylate.



Scheme 43

However, when a solution of the Baylis-Hillman *tert*-butyl ester **146a** in acetic acid was heated under reflux, cyclization occurred to give 3-(acetoxymethyl)coumarin **157a** in 40% yield and the chromene ester **161** in 24% yield (Scheme 44). This result clearly supports the assumption that both coumarins and chromenes may be obtained

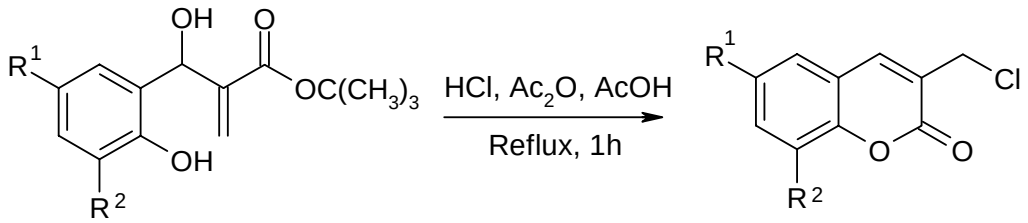
via cyclization of salicylaldehyde-derived Baylis-Hillman products as outlined in Scheme 28.



146a **157a** **161**

Scheme 44

In order to ensure regioselective cyclization *via* intramolecular acyl substitution to the coumarins, we decided to explore the use of hydrochloric acid in acetic acid. Treatment of *tert*-butyl 3-hydroxy-3-(2-hydroxyphenyl)-2-methylenepropanoate **146a** with hydrochloric acid in acetic acid gave the 3-(chloromethyl)coumarin **156a** in 98% yield after 1 hour (Scheme 45). Surprisingly, use of hydriodic acid instead of hydrochloric acid resulted in the formation of the 3-iodomethyl analogue **155a** in only 10% yield. The advantages of this method of preparing 3-substituted coumarins are clearly evident in that it obviates the need to :- i) protect the salicylaldehyde hydroxyl group as the *O*-benzyl ether; ii) block access to chromenes by conjugate addition of an amine to the Baylis-Hillman product; and iii) debenzylate the ether to permit cyclization. Moreover, the procedure is simple, rapid and affords the coumarin products in excellent yield (Table 9).



146a-c, e,f **156a-c, e,f**

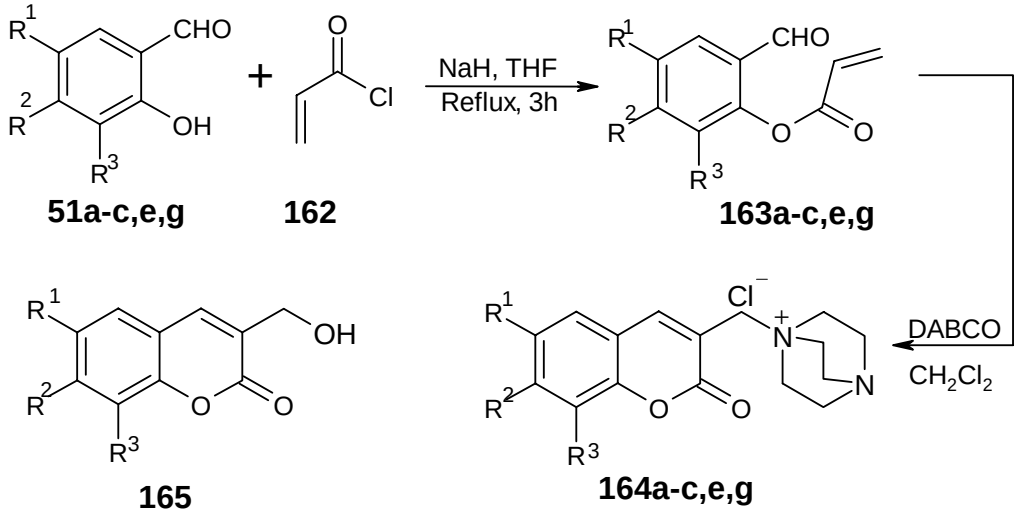
Scheme 45

Table 9. Yields for the acid-catalysed cyclization of the Baylis-Hillman *tert*-butyl esters **146a-c,e,f**.

Compound	R^1	R^2	Isolated Yield / %
156a	H	H	98
156b	H	OMe	97
156c	H	OEt	90
156e	Br	H	95
156f	Br	Br	95

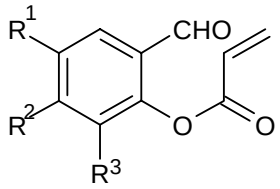
2.1.7. Intramolecular Baylis-Hillman reaction.

The aim in this approach was to synthesize coumarin derivatives *via* an intramolecular Baylis-Hillman reaction, in which both the electrophilic and activated alkene moieties are present and suitably located in the same molecule. Recently, Drewes *et al.*[159] reported an intramolecular Baylis-Hillman reaction of the acrylate ester of salicylaldehyde in the presence of DABCO to afford the crystalline quaternary ammonium salt **164a** in 81% yield, together with 3-(hydroxymethyl)coumarin **165** in only 10% yield (Scheme 46). In the present study, the generality of the methodology outlined by Drewes *et al.*[159] was investigated as an alternative route to the synthesis of substituted coumarins. A range of salicylaldehyde acrylate esters **163a-c,e,g** were prepared by treating acryloychloride in THF with the phenoxide ions generated from the salicylaldehydes **51**. Reaction of the resulting acrylate esters **163a-c,e,g** with DABCO in CH_2Cl_2 afforded the quaternary salts **164a-c,e,g** in moderate to excellent yields (Table 10); there was, however, no evidence of the formation of the corresponding 3-(hydroxymethyl)coumarins viz., **165**.

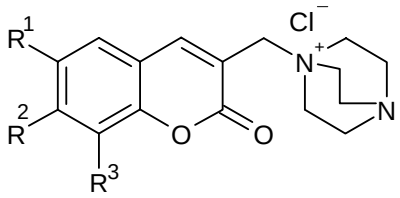


Scheme 46

Table 11. Yields for the salicylaldehyde acrylate esters **163a-c,e,g** and **164a-c,e,g** (Scheme 46).



163a-c,e,g



164a-c,e,g

Compound	R^1	R^2	R^3	Isolated yield / %
163a	H	H	H	83
163b	H	H	OMe	87
163c	H	H	OEt	89
163e	Br	H	H	86
163g	H	NO_2	H	99
164a	H	H	H	61 (78[a])
164b	H	H	OMe	54
164c	H	H	OEt	52
164e	Br	H	H	59
164g	H	NO_2	H	70

[a] Yield reported by Drewes *et al.* (Ref. 159)

The ^{1}H NMR spectrum of the 7-nitro derivative **164g** (Figure 18a) reveals broad signals corresponding to the DABCO protons at δ 3.00 and 3.43 ppm, while the methylene protons resonate as a singlet at δ 4.43 ppm. The ^{13}C NMR spectrum (Figure 18b) shows the methylene carbon signal at δ 61.0 ppm, the assignment of all ^{13}C signals being supported by the DEPT spectra (Figure 19). The downfield shifts of the methylene proton and carbon signal is due to the ionic charge in the molecule.

(a)

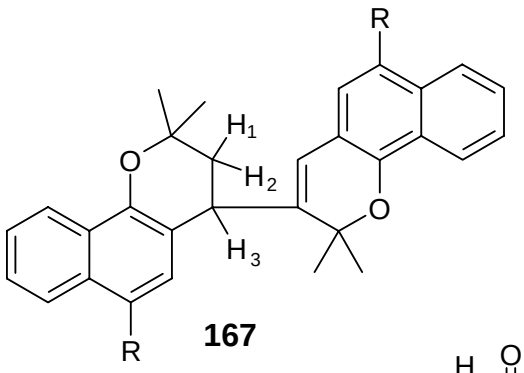
(b)

Figure 18. **a**) 400 MHz ^{1}H NMR spectrum; and (**b**) 100 MHz p.n.d ^{13}C NMR spectrum of 7-nitro derivative **164g** in DMSO-d_6.

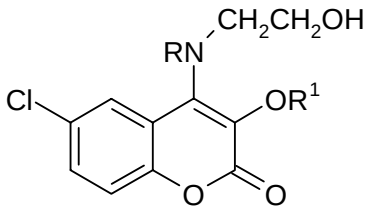
Figure 19. HMQC NMR spectrum of 7-nitro derivative **164g** in DMSO-d_6.

2.2. REGIOSELECTIVITY OF NUCLEOPHILIC ATTACK ON VARIOUS COUMARIN SUBSTRATES.

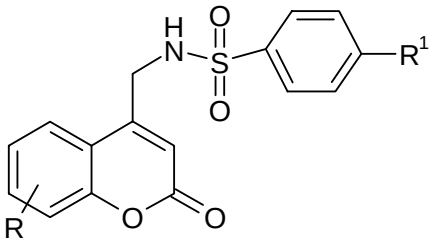
Having prepared a range of coumarin substrates, their reaction with various nucleophilic reagents could be studied. A number of unusual examples of nucleophilic attack on the coumarin systems have been reported. Newman and Dalton[185] rationalized the formation of the 3-alkoxy derivatives **166** from their 3-chloro precursors in terms of an internal Michael addition involving the ω-hydroxy group, nucleophilic displacement of the chlorine at C-3 and finally, a reverse Michael reaction. Livingstone *et al.*[186] have reported the formation of dimeric coumarin derivatives **167** following reaction of 2,2-dimethyl-2*H*-naphtho[1,2-*b*]pyrans with methylmagnesium iodide and treatment with acid.



167



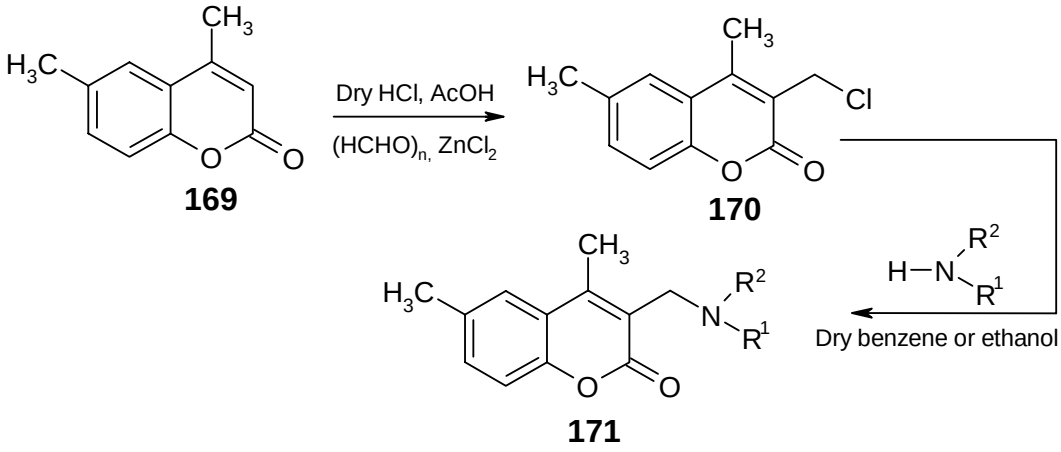
166



168

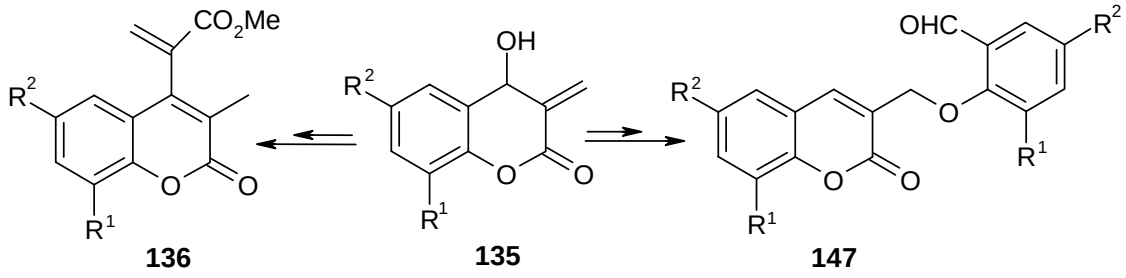
Amino-substituted coumarins have been reported to possess CNS stimulant activity,[187] and are present in many antimalarial and antimicrobial agents. Research on Mannich bases of 7-hydroxy-4-phenylcoumarin[188] and 7-ethoxy-4-methylcoumarin[189] has revealed that the biological activity of the coumarin system may be enhanced by the presence of an amino group. Raju *et al.*[190] have reported the synthesis of 3-aminomethyl- and 3-(picolylaminomethyl)coumarins *via* nucleophilic substitution of

of the 3-(chloromethyl)coumarin **170** (Scheme 47) with a view to evaluating their antibacterial activity. Patil *et al.*[191] have prepared a range of coumarin sulphonamides **168** *via* the corresponding 4-(bromomethyl)coumarin.



Scheme 47

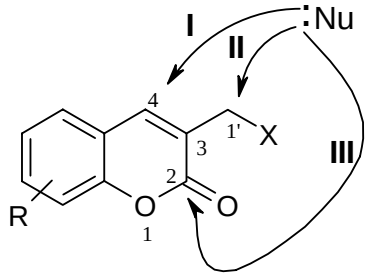
In our own group, Robinson[158] isolated various coumarin derivatives from Baylis-Hillman reactions of salicylaldehyde precursors, the formation of which has been attributed to *in situ* attack by nucleophiles present in the reaction mixture on coumarin intermediates of type **135** (Scheme 48).



Scheme 48

In principle, a nucleophile might be expected to attack a coumarin substrate of the type **155, 156** or **164** at any of the electrophilic centres, C-2, C-4 or C-1', as illustrated in Figure **20**. Allylic halides commonly undergo nucleophilic displacement with (S_N';

path I) or without (S_N; path II) rearrangement,[192] resulting in the formation of two types of product, rearranged and normal, while esters typically undergo nucleophilic acyl substitution (path III).



155 (X = I)
156 (X = Cl)
164 (X = $DABCO^+$)

I Conjugate addition or allylic (S_N') displacement of X.

II Direct (S_N) displacement of X.

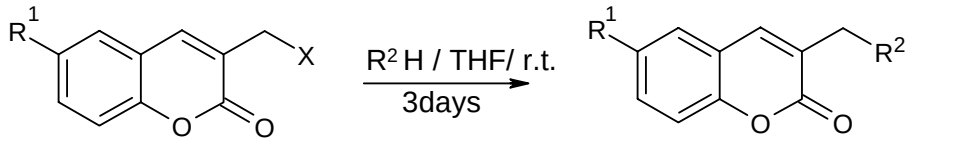
III Nucleophilic acyl substitution (ring opening) or nucleophilic addition.

Figure 20. Possible modes of nucleophilic attack on coumarin derivatives

In the present study, we have explored the regioselectivity of nucleophilic attack on the 3-(halomethyl)coumarins **155** and **156** and the DABCO-derived quaternary ammonium compounds **164**. Various nucleophilic reagents have been used, *viz*., piperidine, benzylamine, Grignard reagents and the enolates of both malonic ester and ethyl acetoacetate.

2.2.1. Reaction with nitrogen nucleophiles

The 3-(iodomethyl)coumarins **155a,e** were treated with piperidine in THF at room temperature for 3days, to afford the corresponding 3-(piperidinomethyl)coumarins, **149a,e** (Scheme 49) in moderate to excellent yield (Table 11). The use of benzylamine instead of piperidine afforded the 3-(benzylaminomethyl)coumarin **142a** in 57% yield. Since none of the rearranged products were detected, it seems that, in the cases examined, the reaction proceeds exclusively *via* direct nucleophilic substitution at the allylic centre, C-1/ (Path II; Fig. 20). The quaternary DABCO salt **164a** reacted similarly with piperidine to afford the substituted product **149a** (42%). The lower yields observed with the DABCO salt **164a,** in comparison with the iodo analogues, are probably due to its poor solubility in THF.



155a,e
164a

R 2 H = benzylamine, piperidine

149a (R^2 = $PhCH_2NH$)
150a,e (R^2 = piperidino)

Scheme 49

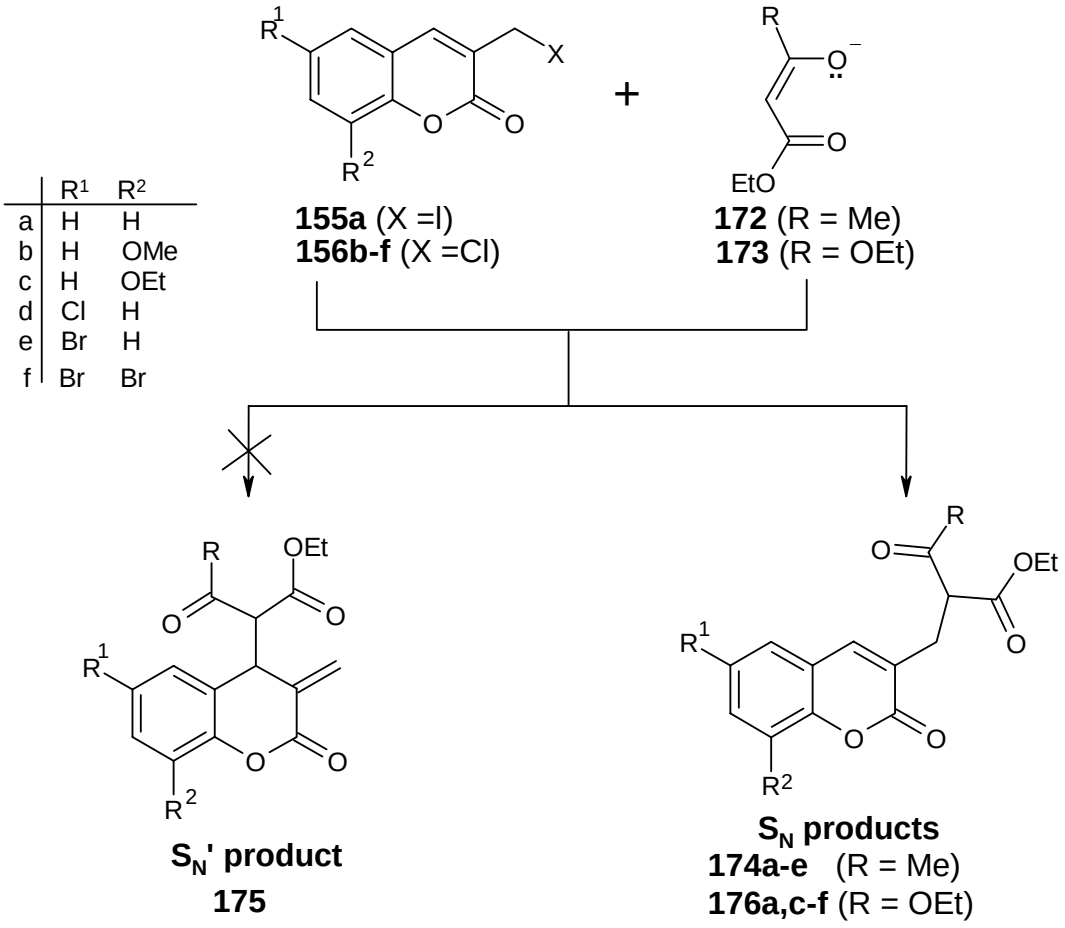
Table 11. Results obtained from the reaction of benzylamine and piperidine with coumarin substrates.

Substrate	R^1	X	R^2H: Nucleophile	Product	Yield of product / %
155a	H	I	Benzylamine	**149a**	57
155a	H	I	Piperidine	**150a**	82
155e	Br	I	Piperidine	**150e**	55
155e	Br	I	Benzylamine	**149e**	88
164a	H	DABCO [a]	Piperidine	**150a**	42

[a] As the quaternary ammonium chloride.

2.2.2. Reaction with enolate nucleophiles

The regioselectivity of attack by the enolate anions derived from ethyl acetoacetate and diethyl malonate (**172** and **173**, respectively) were investigated using 3-(halomethyl)coumarin substrates (Scheme 50). The enolate anions were generated by treating ethyl acetoacetate, or diethyl malonate, with sodium ethoxide in ethanol. The 3-(halomethyl)coumarins were then added under nitrogen to afford the S_N products **174** and **176** (Table 12).



Scheme 50

The coumarin derivatives **174a-e** and **176a,c-f** were fully characterized by one- and two-dimensional NMR and high-resolution mass spectrometric analysis. The ^{1}H NMR spectrum of the compound **174a** (Figure 21a) reveals the characteristic 4'-vinylic signals at δ 7.59 ppm, while the ^{13}C NMR spectrum (Figure 21b) exhibits the expected 16 signals (expansion reveals that the signal at *ca* δ 30.0 ppm is due to two overlapping signals). Assignment of the carbon signals is supported by the DEPT, HMQC and COSY (Figure 22) spectra.

Table 12 : Results from the reaction of the enolates with 3-(iodomethyl)coumarin **155a** and the 3-(chloromethyl)coumarins **156b-f** (Scheme 50).

Substract	R^1	R^2	Enolate anion	Products	
				No.	Yield / %
155a	H	H	A	**174a**	41
156b	H	OMe	A	**174b**	42
156c	H	OEt	A	**174c**	42
156d	Cl	H	A	**174d**	41
156e	Br	H	A	**174e**	42
155a	H	H	B	**176a**	47
156c	H	OEt	B	**176c**	50
156d	Cl	H	B	**176d**	61
156e	Br	H	B	**176e**	45
156f	Br	Br	B	**176f**	42

"A" represents sodium enolate of ethyl acetoacetate. "B" represents sodium enolate of malonic ester.

(a)

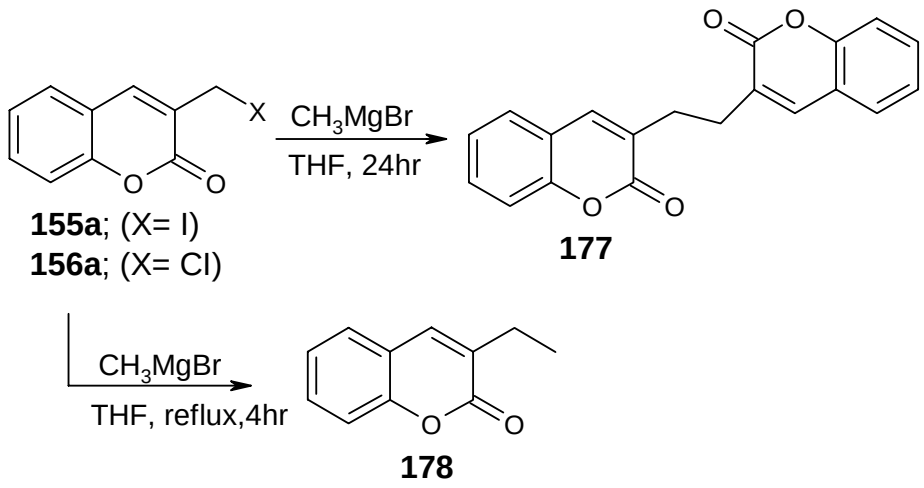
(b)

Figure 21 **a**) 100 MHz ^{1}H NMR spectrum; and (**b**) 100 MHz p.n.d ^{13}C NMR spectrum of the S_N product **174a** in $CDCl_3$.

Figure 22 COSY NMR spectrum of the S_N product **174a** in $CDCl_3$.

2.2.3. Reaction with Grignard reagents

Coumarins, on treatment with Grignard reagents typically undergo initial addition at the carbonyl carbon, C-2. When 3-(iodomethyl)coumarin **155a** was treated with methyl magnesium bromide in THF, a symmetrical dimer **177** was obtained in 94% yield (Scheme 51), but attempts to reproduce this result under the same conditions were unsuccessful. The formation of dimer **177** may be rationalized in terms of initial metal-halogen exchange between one molecule of compound **155a** and CH_3MgBr. The coumaryl Grignard reagent then displaces the iodine from the second molecule of the coumarin **155a**.



Scheme 51

In an alternative method, reaction of 3-(chloromethyl)coumarin **156** with methyl magnesium bromide in refluxing THF (Scheme 51) afforded the 3-ethylcoumarin **178** (29%), which was fully characterized. The ^{1}H NMR spectrum (Figure 23a) reveals the methyl triplet at δ 1.25 ppm, and the methylene quartet at δ 2.60 ppm. The ^{13}C NMR spectrum (Figure 23b) reveals the methyl and methylene carbon signals at δ 12.4 and δ 23.9 ppm, respectively, and the requisite number of eleven carbon signals. It is thus apparent that for all the systems examined (Section 2.2.1-3), substitution occurs at the exocyclic 1'-carbon.

(a)

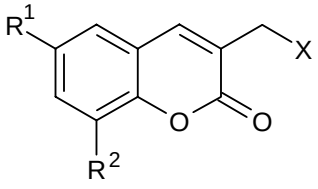
(b)

Figure 23 **a**) 100 MHz ^{1}H NMR spectrum; and (**b**) 100 MHz p.n.d ^{13}C NMR spectrum of 3-ethylcoumarin **178** in $CDCl_3$.

2.3. MASS SPECTROMETRIC STUDIES OF 3-SUBSTITUTED COUMARINS

Coumarin, itself generally exhibits a relatively highly abundant molecular ion (*m/z* 146) under mass spectral conditions, which loses carbon monoxide to give a benzofuran radical cation (*m/z* 118),[193] while 4-hydroxycoumarins favour a retro-Diels-Alder fragmentation. The mass spectra of many methyl-substituted coumarins have been investigated.[193] For example, 4-methylcoumarin fragments *via* the loss of carbon monoxide to give a 3-methylbenzofuran radical cation, subsequent loss of a hydrogen atom giving a benzopyrylium species (*m/z* 131).[193] Loss of a methyl radical from the benzofuran radical cation derived from 7-methoxy-4-methylcoumarin has been confirmed by deuterium-labelling experiments,[193] while naturally occurring coumarins bearing large alkyl side chains typically exhibit cleavage of the side chain prior to elimination of carbon monoxide.

Here, we report the results of an electron-impact (EI) mass spectrometric study of selected 3-substituted coumarins. The major fragmentation patterns exhibited by compounds **149a-e** and **150a-e** were investigated using high-resolution and B/E linked scan data. The EI mass spectra for 3-(benzylaminomethyl)coumarin **149a** and 3-(piperidinomethyl)coumarin **150a** are illustrated in Figure 24, and the proposed mass fragmentation pathways are outlined in Schemes 52 and 53, respectively.



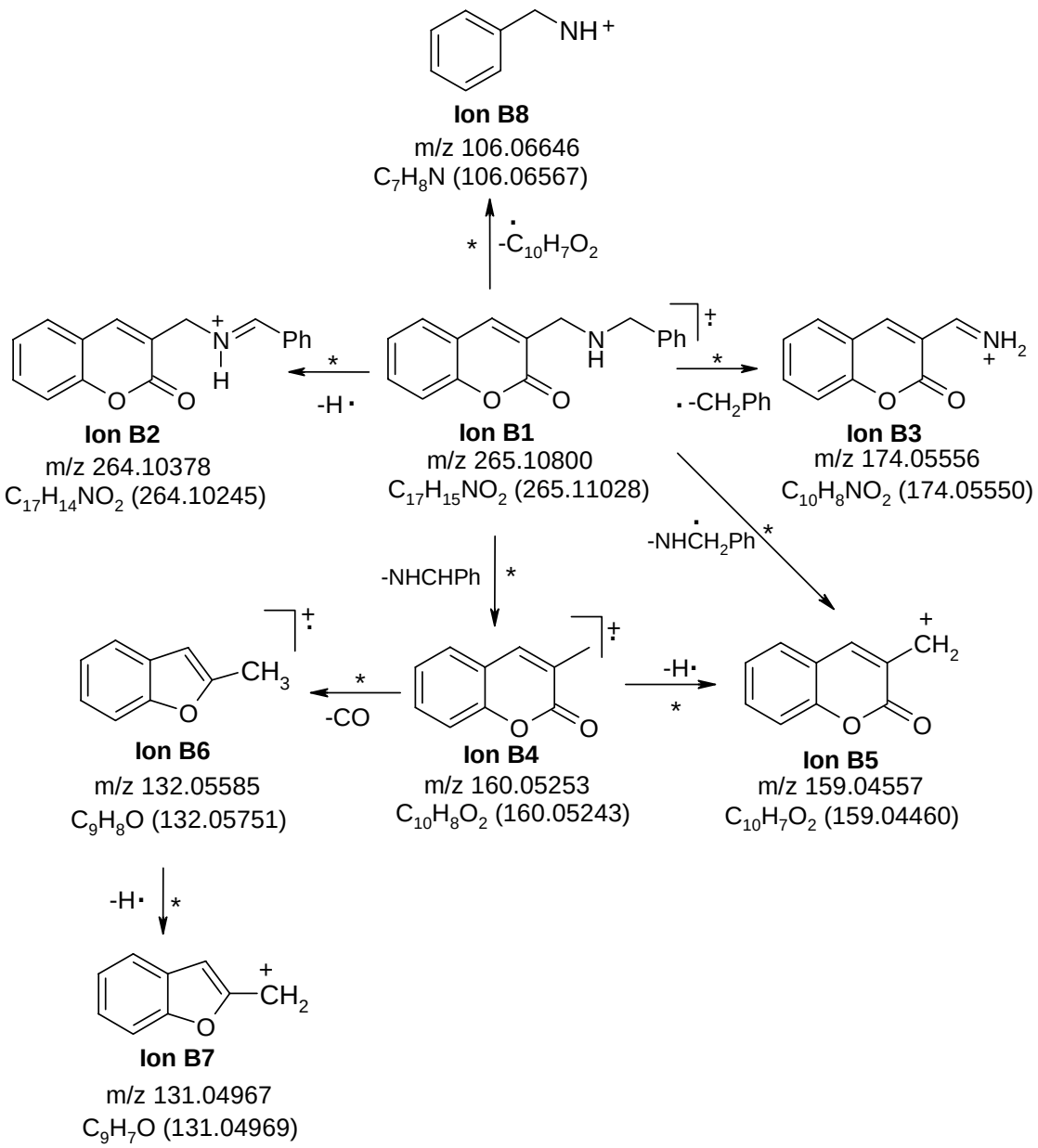
149a-e; (X = $PhCH_2NH$)
150a-e; (X = piperidino)

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

(a)

(b)

Figure 24. High-resolution EI mass spectra of:- a) 3-(benzylaminomethyl)coumarin **149a;** and b) 3-(piperidinomethyl)coumarin **150a.**

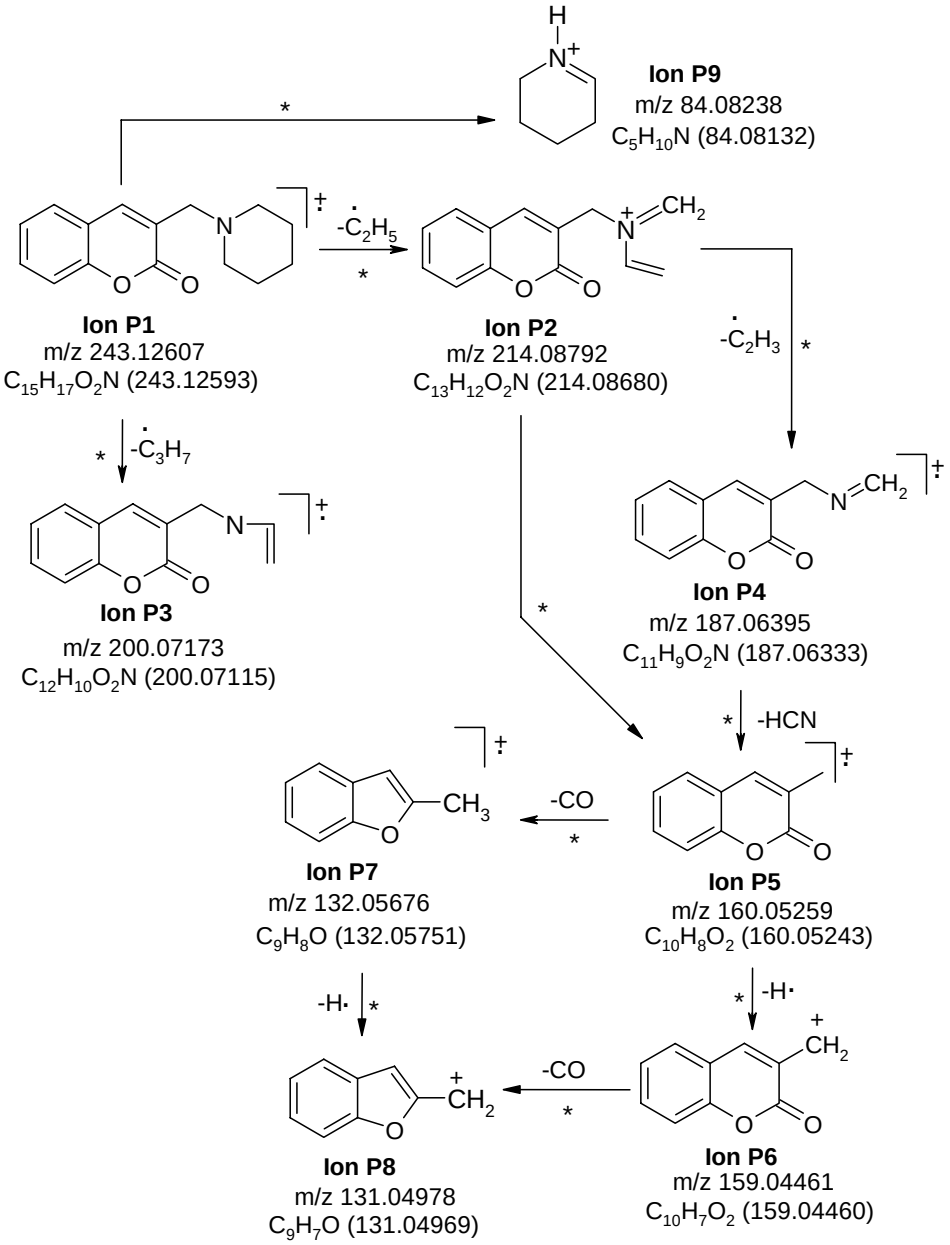


Scheme 52 . Proposed EI mass fragmentation pathways for 3-(benzylaminomethyl)-coumarin **149a**. High-resolution data (*m/z*) are followed, in parentheses, by calculated formula masses; an asterisk indicates a pathway supported by the B/E linked scan data. The prefix "B" indicates 3-(benzylamino-methyl)coumarin ion types.

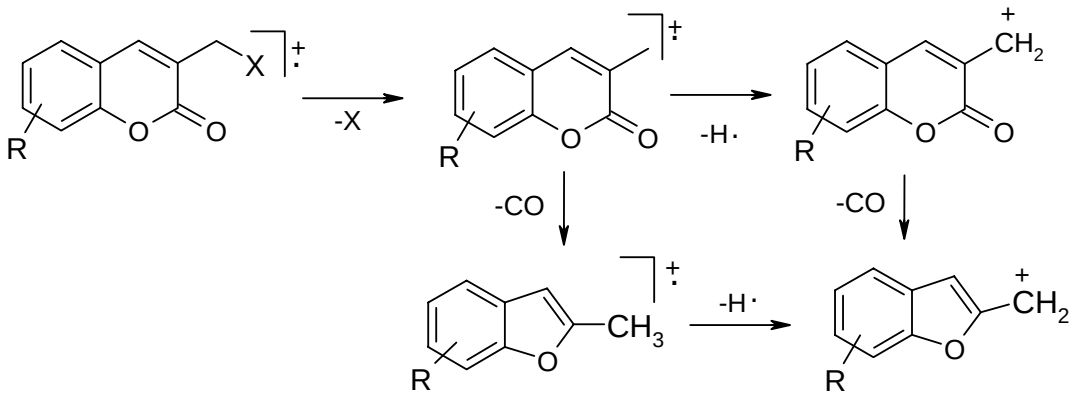
The fragmentation of the molecular ion **B1** (*m/z* 265) from compound **149a** (Scheme 52) involves the loss of :- i) a hydrogen atom to give the resonance-stabilized cation **B2** (*m/z* 264); ii) a benzyl radical to give the resonance-stabilized cation **B3** (*m/z* 174) ; and iii) benzylimine or a benzylamino radical to afford fragments **B4** (*m/z* 160) or **B5** (*m/z* 159), respectively. Successive loss of carbon monoxide and a hydrogen atom from the odd-electron species **B4** then affords the 2-methylbenzofuran radical cation **B6** (*m/z* 132) and the resonance-stabilized cation **B7** (*m/z* 131). It is apparent from the linked scan data that the benzylamino cation **B8**, which is responsibile for the base peak at *m/z* 106, is formed by direct fragmentation of the molecular ion **B1.**

In the case of compound **150a,** fragmentation of the molecular ion **P1** (*m/z* 243) (Scheme 53) *via* loss of an ethyl or propyl radical affords ions **P2** (*m/z* 214) or **P3** (*m/z* 200), respectively, reflecting known fragmentations in the piperidine system.[194-195] Loss of an ethylene radical from the ion **P2** accounts for the formation of the odd-electron species **P4** (*m/z* 187); subsequent elimination of hydrogen cyanide affords ion **P5** (*m/z* 160), which then undergoes sequential loss of carbon monoxide and a hydrogen radical to afford the benzofuran fragments **P7** (*m/z* 132) and **P8** (*m/z* 131), respectively. The cation **P6** (*m/z* 159) is formed *via* loss of a hydrogen atom from ion **P5**. All of these fragmentations are supported by the linked scan data, which also support direct fragmentation of the molecular ion **P1** to afford the piperidinyl cation **P9** responsible for the base peak at *m/z* 84.

Not surprisingly, the mass fragmentation patterns observed for componds **149a** and **150a** (Schemes 52 and 53) are very similar and the common fragmentation modes are illustrated in Scheme 54.



Scheme 53 . Proposed EI mass fragmentation pathways for 3-(piperidinomethyl)-coumarin **150a**. High-resolution data (*m/z*) are followed, in parentheses, by calculated formula masses; an asterisk indicates a pathway supported by linked scan data. The prefix "P" indicates 3-(piperidinomethyl)-coumarin ion types.



Scheme 54. Fragmentations common to the 3-substituted coumarins **149a** and **150a**.

M/z values and relative intensities of peaks observed in the mass spectra of the 3-(benzylaminomethyl)coumarins **149a-e**, sorted according to ion types **B1-B8** (Scheme 52), are summarized in Table 13. Table 14 similarily summarises the peaks observed in the mass spectra of the 3-(piperidinomethyl)coumarins **150a-e** which correspond to ion types **P1-P9** (Scheme 53). The mass spectra and high-resolution data for compounds **149b-e** and **150b-e** are detailed in the experimental section.

Table 13. Ion Types **B1-B8** observed in the mass spectra of the **149a-e**.

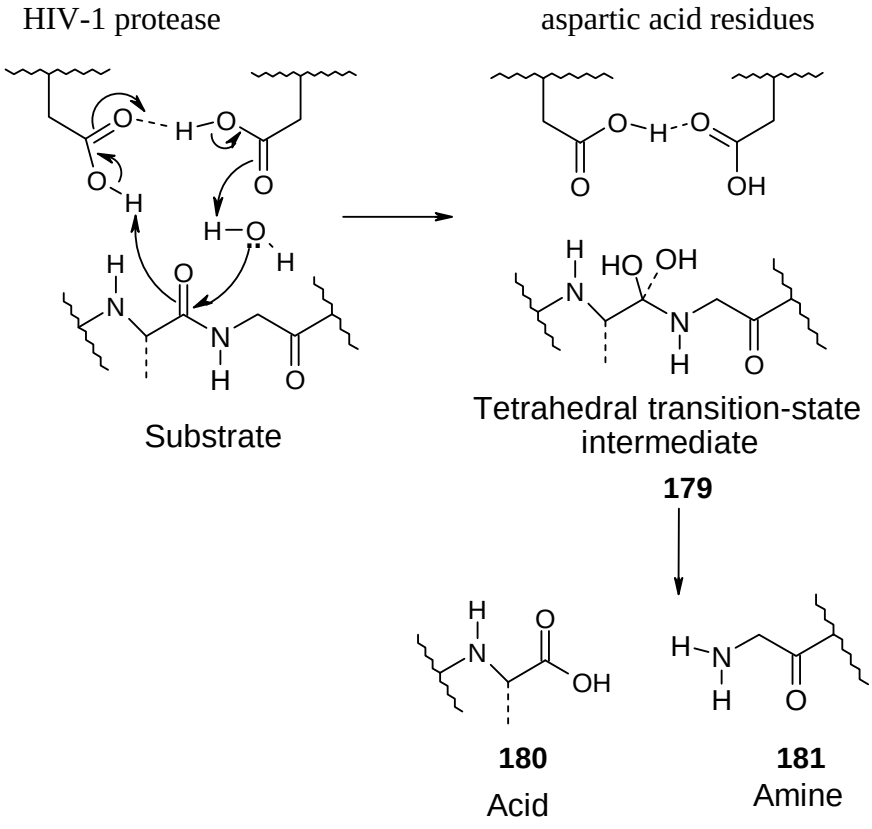
Compd	**B1**	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**
149a	265 (0.3)	264 (0.8)	174 (37)	160 (7)	159 (10)	132 (0.3)	131 (7)	106 (100)
149b	295 (0.3)	294 (0.7)	204 (36)	190 (8)	189 (9)	162 (1.7)	161 (0.3)	106 (100)
149c	309 (0.6)	308 (14)	218 (59)	204 (6)	203 (12)	176 (13)	175 (3)	106 (100)
149d	299 (0.4)	298 (0.8)	208 (32)	195 (3.3)	196 (2.3)	166 (3.1)	165 (8)	106 (100)
149e	344 (2)	343 (42)	252 (72)	238 (17)	237 (19)	210 (7.2)	209 (17)	106 (100)

Table 14. Ion Types **P1-P9** observed in the mass spectra of the **150a-e**.

Compd	**P1**	**P2**	**P3**	**P4**	**P 5**	**P6**	**P7**	**P8**	**P9**
150a	243 (7)	214 (4.5)	200 (8)	187 (2)	160 (11)	159 (8)	132 (3)	131 (5)	84 (100)
150b	273 (17)	244 (3)	230 (20)	217 (4)	190 (34)	189 (17)	162 (4)	131 (0.2)	84 (100)
150c	287 (19)	258 (3)	244 (2)	231 (3)	204 (18)	203 (13)	176 (21)	175 (3.5)	84 (100)
150d	277 (11)	248 (3)	234 (15)	221 (3)	160 (2.5)	159 (2.2)	166 (4.6)	165 (11)	84 (100)
150e	321 (8)	292 (2)	278 (11)	265 (2)	238 (14)	237 (9)	----	209 (7)	84 (100)

2.4. HIV-1 PROTEASE INHIBITORS

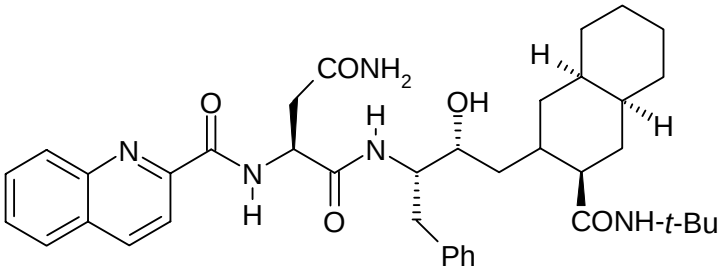
HIV-1 protease is an enzyme, which cleaves peptides. It is a symmetrical dimer consisting of two 99 amino acid monomers, each of which contributes an aspartic acid residue at the active site.[196-197] HIV-1 protease functions as a "pair of molecular scissors" which cleave gag and pol precursor proteins to produce viral structural proteins as shown in Scheme 55. Numerous HIV-1 protease inhibitors have been designed with the incorporation of non-hydrolysable groups which mimic the natural, polypeptide substrates.[198]



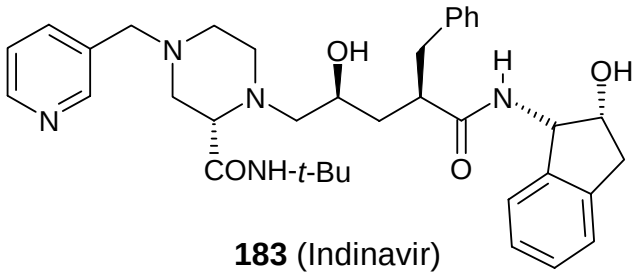
Scheme 55

The cleavage mechanism (Scheme 55) is considered to involve the delivery of a water molecule to the substrate cleavage site by the two aspartic acid residues. The resulting "tetrahedral transition-state intermediate" **179** collapses to give *C*-terminal acid (**180**) and *N*-terminal amine (**181**) fragments, which can then be used by the virus for

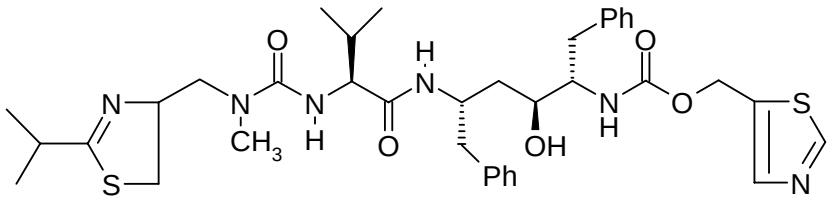
structural purposes.[199] Inhibition of this cycle affords virions which are immature and non-infectious.[200-201] The protease enzyme has been an attractive target for antiviral therapy, and there are currently four approved HIV-1 protease inhibitors for the treatment of AIDS, *viz*., saquinavir **182**, indinavir **183**, ritonavir **184** and nelfinavir **185.**



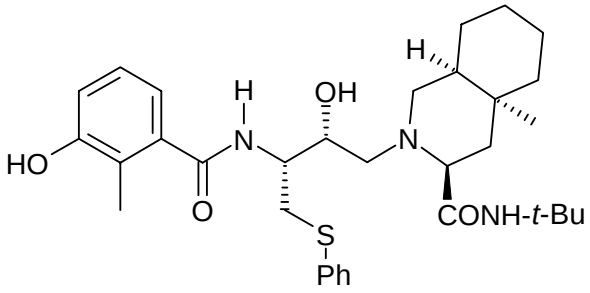
182 (Saquinavir)



183 (Indinavir)

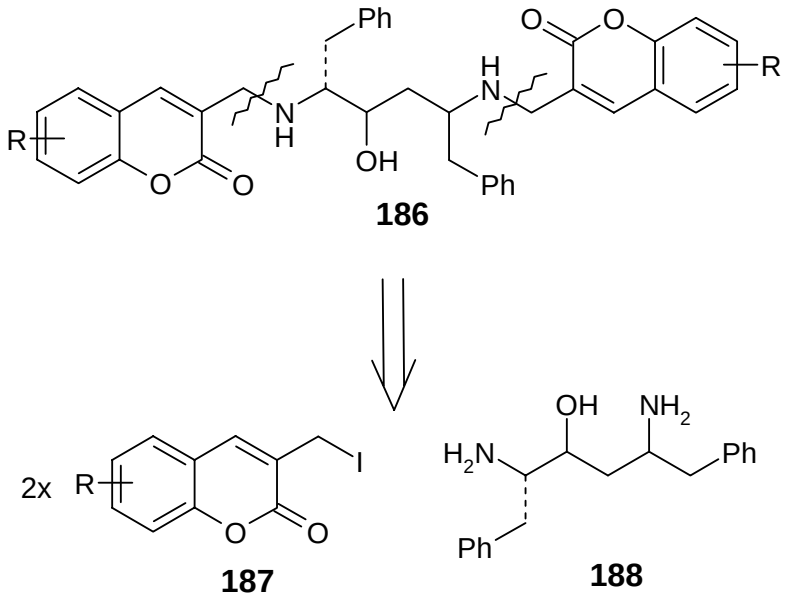


184 (Ritonavir)



185 (Nelfinavir)

In our study, the aim has been to synthesise ritonavir analogues **186**, which contain coumarin moieties at the termini of a common "backbone". Ritonavir and its clinically useful analogues contain a hydroxyethylene dipeptide "backbone", and our strategy, therefore, was to synthesise the diamine **188**, which could then be coupled to 3-halomethylcoumarins to afford the required ritonavir analogues as illustrated in the retrosynthetic analysis (Scheme 56).



186

187

188

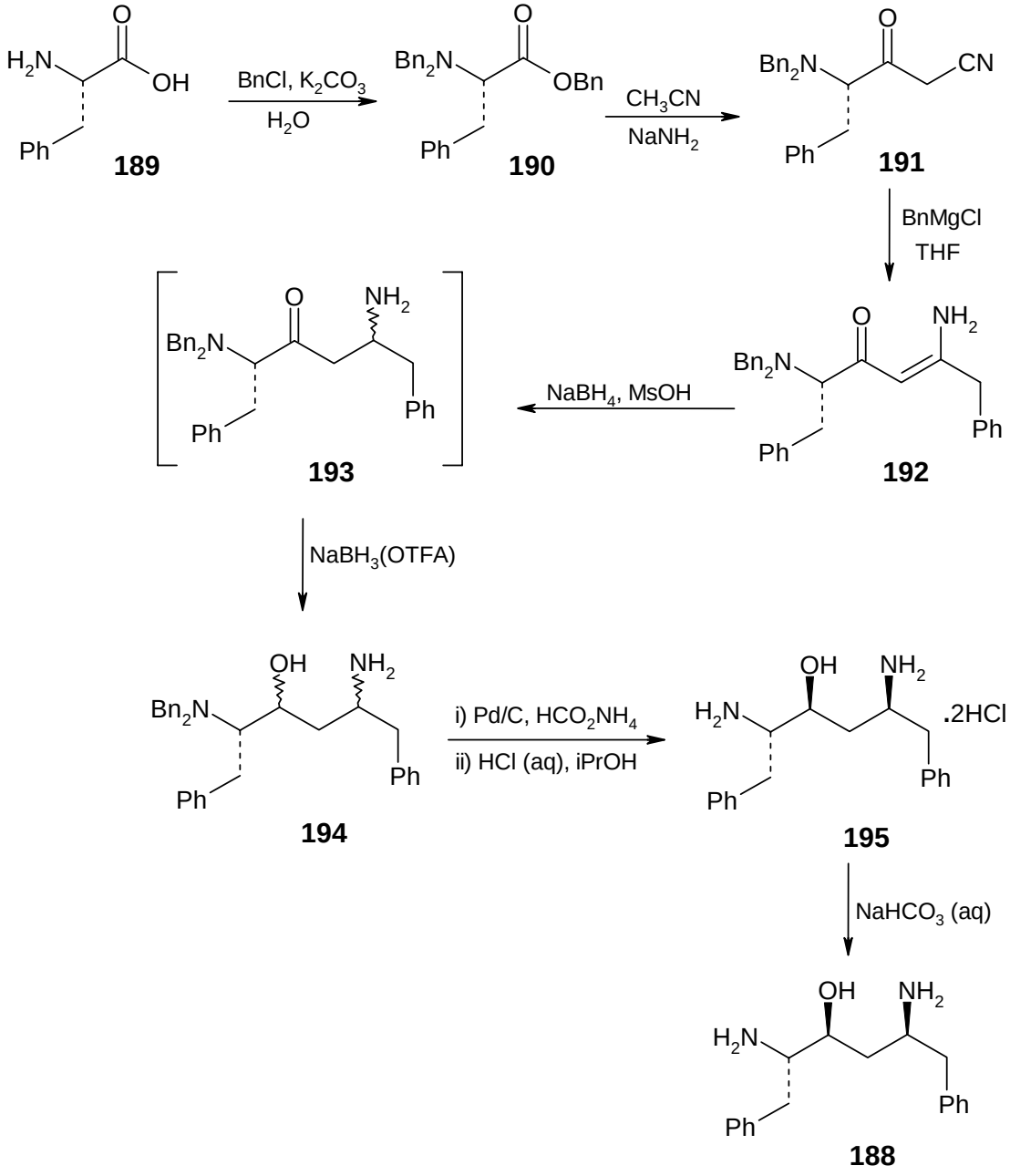
Scheme 56

2.4.1. Synthesis of the diamine "backbone".

The diamine **188,** required as the "backbone" for the novel ritonavir analogues, was synthesized using the methodology reported by Stuk *et al.*[202] (Scheme 57). This approach required the protection of the amino group of the precursor, L-phenylalanine **189,** as the *N*,*N*-dibenzyl derivative. Reaction of L-phenylalanine with benzyl chloride under basic conditions gave the tribenzylated derivative **190**, which was then treated with the acetonitrile-derived anion in THF at -40^{o}C to afford the cyanomethylketone product **191**; the temperature and the addition of the reagent have to be carefully controlled to minimize racemization. Reaction of intermediate **191** with 3 equivalents of benzyl magnesium chloride gave the enaminone **192** which, on reduction with sodium borohydride in the presence of methanesulphonic acid, afforded the intermediate ketone **193**. Further reduction using $NaBH_3$(OTFA), followed by debenzylation (with 5% palladium-on-carbon catalyst in the presence of ammonium formate) and treatment with concentrated HCl gave the hydrochloride salt **195.** Conversion to the required free diamine **188** was achieved by neutralising with saturated aqueous sodium carbonate. Compounds **188-195** were all fully characterized and the ^{1}H NMR and ^{13}C NMR spectroscopic data were shown to be consistent with those reported by Stuk *et al.*[202]

2.4.2. Synthesis of coumarin-containing ritonavir analogues .

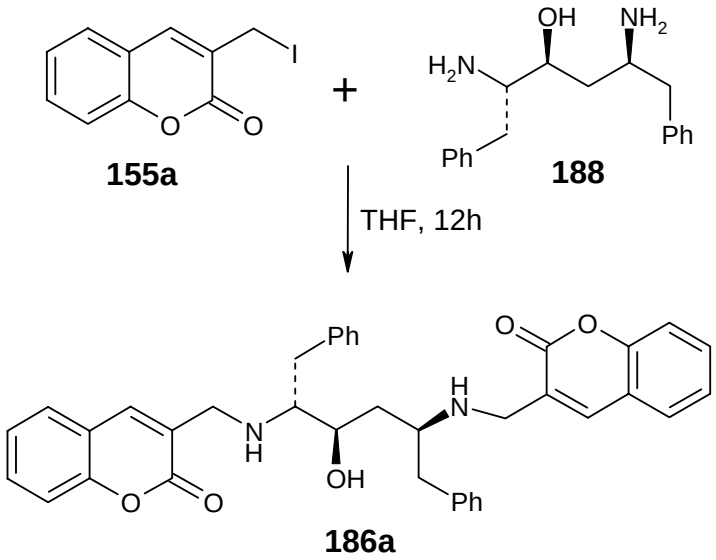
We had previously explored the reaction of 3-(halomethyl)coumarins with nitrogen nucleophiles, v*iz*., benzylamine and piperidine (Scheme 49), with success and an extension of this methodology to the diamine **188** was expected to afford the ritonavir analogue **186a** (Scheme 58). Treatment of the diamine **188** with 3-(iodomethyl)-coumarin **155a** in THF for *ca* 8h, in fact, afforded the required product **186** in 25% yield (Scheme 58). Purification of compound **186a** using preparative layer chromatography, however, proved to be difficult. Nevertheless, purified material was obtained and fully characterized.



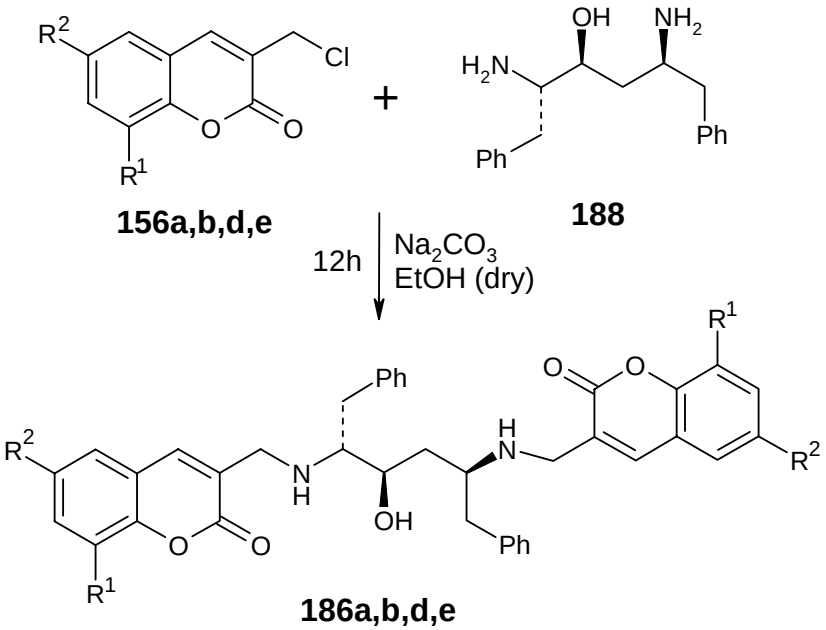
Scheme 57

An alternative method was then explored, which involved boiling a mixture of 3-(iodomethyl)coumarin **155a**, diamine **188** and $NaHCO_3$ in acetone, under reflux for *ca 2*h, to give the required product **186a** in only 13% yield. In a third approach, a mixture of 3-(chloromethyl)coumarin **156a**, the diamine **188** and Na_2CO_3 in ethanol was stirred for *ca* 76h; work-up afforded the required product **186a** in 50% yield, and

this method was then used to prepare the substituted analogues **186b,d** and **e** in yields ranging from 53to 71% (Scheme 59; Table 15).



Scheme 58



Scheme 59

In a final attempt to optimise the yield further, the quaternary ammonium salt **164a** was used as the substrate instead of a 3-(halomethyl)coumarin. Remarkably, when the salt **164a** was stirred together with the diamine **188** in ethanol at room temperature, the ritonavir analogue **186a** was isolated in 85% yield!

Table 15. Yield of the novel analogues of ritonavir containing coumarin moieties **186a,b,d,e** (Scheme 59).

	R^1	R^2	Isolated Yield / %
186a	H	H	50 (85) [a]
186b	OCH_3	H	53
186d	H	Br	71
186e	H	Cl	63

[a] Using the coumaryl quaternary ammonium salt **164a**

The novel ritonavir analogues 1**86a,b,d,e** were all characterized using high-resolution MS and one- and two-dimensional NMR analysis. The ^{1}H NMR spectrum of compound **186d** (illustrated in Figure 25) reveals the 3-methine proton multiplet at *ca* 3.95 ppm, the 5-methine signal at 3.10 ppm, the 4-methylene multiplet at 1.64 ppm and the diastereotopic amino methylene signals at 3.65 and 3.71 ppm. The ^{13}C NMR spectrum (Figure 26a) shows the three methine carbons resonating at 72.9 ppm (C-3), 63.5 ppm (C-2) and 59.7 (C-5), while the five methylene carbons resonate at 36.6 and 37.1 (2x $NHCH_2$), 40.7 (C-1), 45.8 (C-4) and 46.7 (C-8). The methylene and the methine carbon signal assignments were confirmed using the DEPT spectrum (Figure 26b).

2.4.3. Molecular modelling studies of a ritonavir analogue

The application of molecular modelling and X-ray crystallographic techniques has led to the synthesis of several highly potent HIV-1 protease inhibitors.[202] In this study, docking of the coumarin-containing ritonavir analogue **186a** into the active site of the HIV-1 protease enzyme[203] was explored using an interactive docking procedure.[100]

Figure 25. 400 MHz ^{1}H NMR spectrum of (2*S*,3*S*,5*S*)-3-hydroxy-2,5-bis[(6-bromo-2-oxo-2*H*-chromen-3-yl)methylamino]-1,6-diphenylhexane **186d** in $CDCl_3$.

(a)

(b)

Figure 26. **a**)100 MHz ^{13}C NMR spectrum; and (**b**) DEPT spectrum of spectrum of (2*S*,3*S*,5*S*)-3-hydroxy-2,5-bis[(6-bromo-2-oxo-2*H*-chromen-3-yl)-methylamino]-1,6-diphenylhexane **186d** in $CDCl_3$.

It was hoped that the hydroxyl group and lactone oxygens of compound **186a** might be suitably located to hydrogen bond with structural water molecules or amino acid residues in the receptor cavity, thereby enhancing its binding to HIV-1 protease. A three-dimensional model of the synthetic ritonavir analogue **186a** was built using the MSI Cerius^2 platform on an SG-O2 computer. The X-ray structure of the HIV-1 protease enzyme containing ritonavir (Figure 27), as determined by Kempf *et al.*,[204] was down-loaded from the Cambridge Crystallographic Data Base. Energy minimization of compound **186a** was achieved using the Universial Force Field; the resulting structure was then used for the docking procedure. Removal of ritonavir from the enzyme structure exposed the receptor cavity of the enzyme (Figure 28). Using the LIGAND-FIT module, the synthetic analogue **186a** was docked interactively into the enzyme active site. The conformer exhibiting the best fit (as shown in Figure 29) was examined for possible hydrogen-bonding interactions with the enzyme active site. The potential hydrogen-bonding interactions between the compound **186a** and the enzyme receptor in the presence of structural water molecules is illustrated in Figure 30. It is apparent that hydrogen-bonding interaction may be possible between:- i) a structural water molecule and both the 3-hydroxyl group and an amine nitrogen atom (inter-atomic separations of 3.484 and 2.377 Å, respectively); and ii) the isoleucine 50B residue and the second amino nitogen of compound **186a** (2.630Å)

Having successfully synthesised the ritonavir analogues **186a,b,d** and **e**, and having demonstrated the ability of the parent system **186a** to fit within the receptor cavity, the next phase of the programme is to submit the synthetic analogues for biological testing.

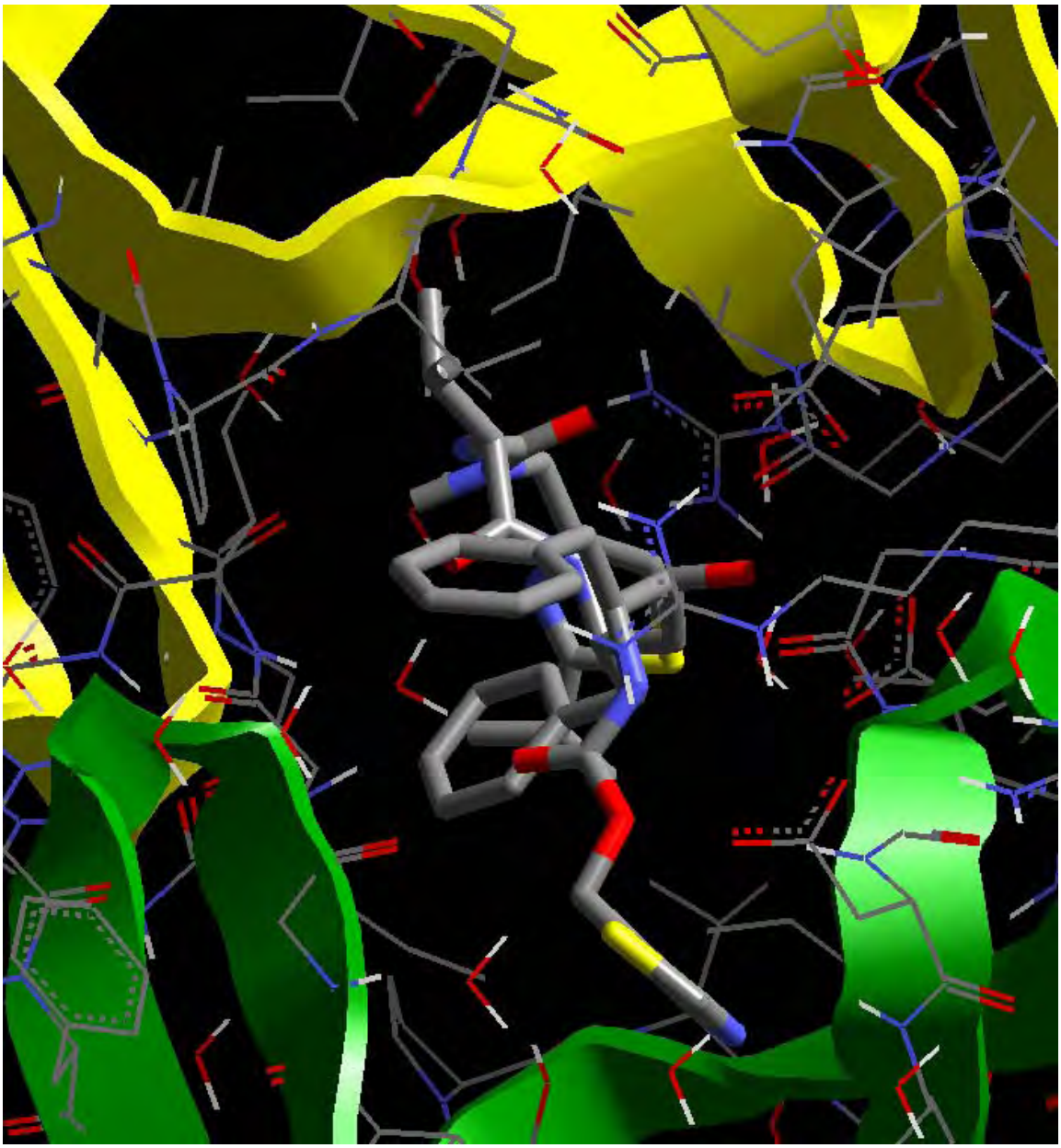


Figure 27. X-Ray Diffraction structure of HIV-1 protease showing ritonavir in the enzyme binding cavity, as determined by Kempf.[204]

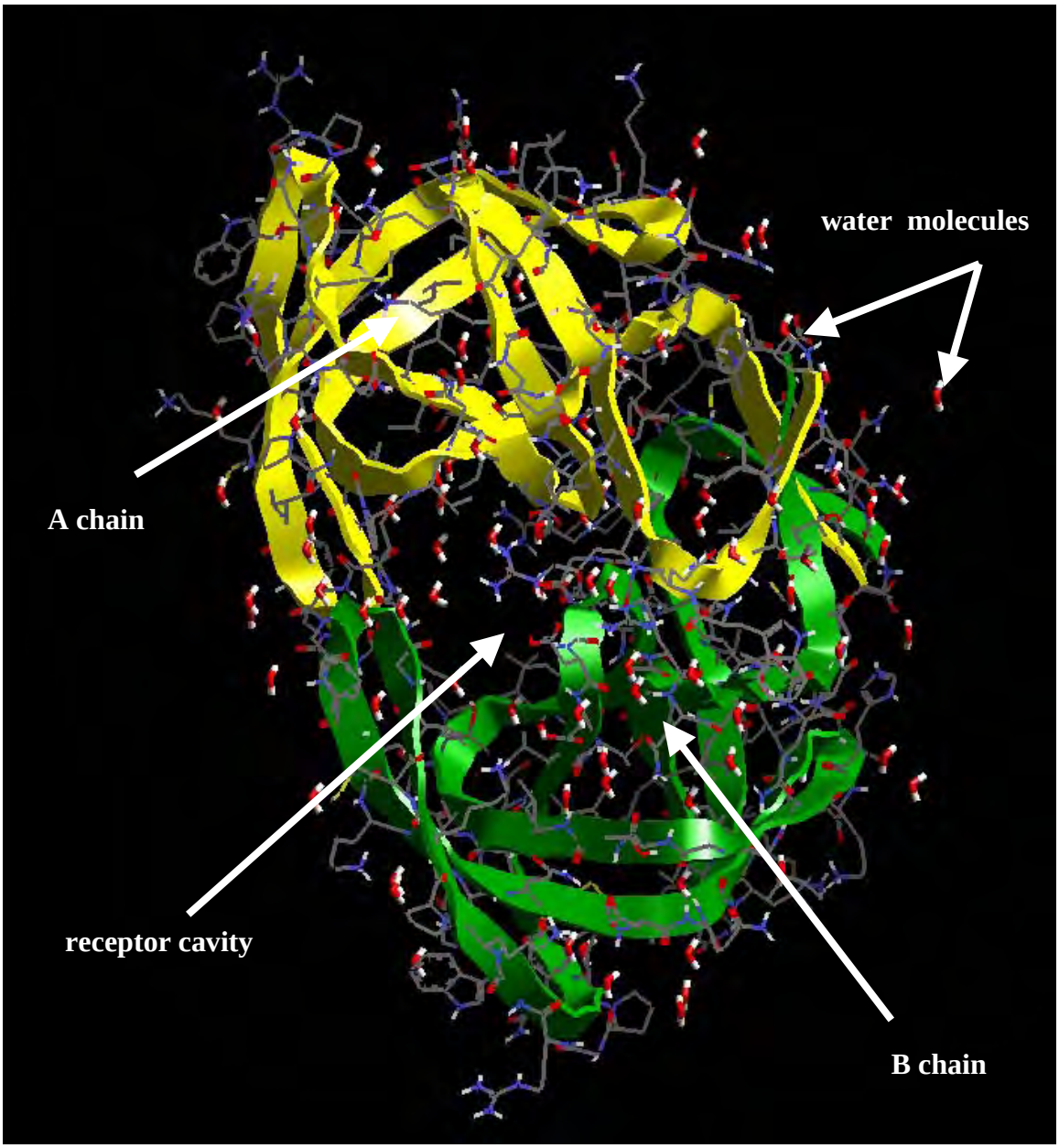


Figure 28. Active Site of the HIV-I protease enzyme from the X-ray structure reported by Kempf *et al.* [204]

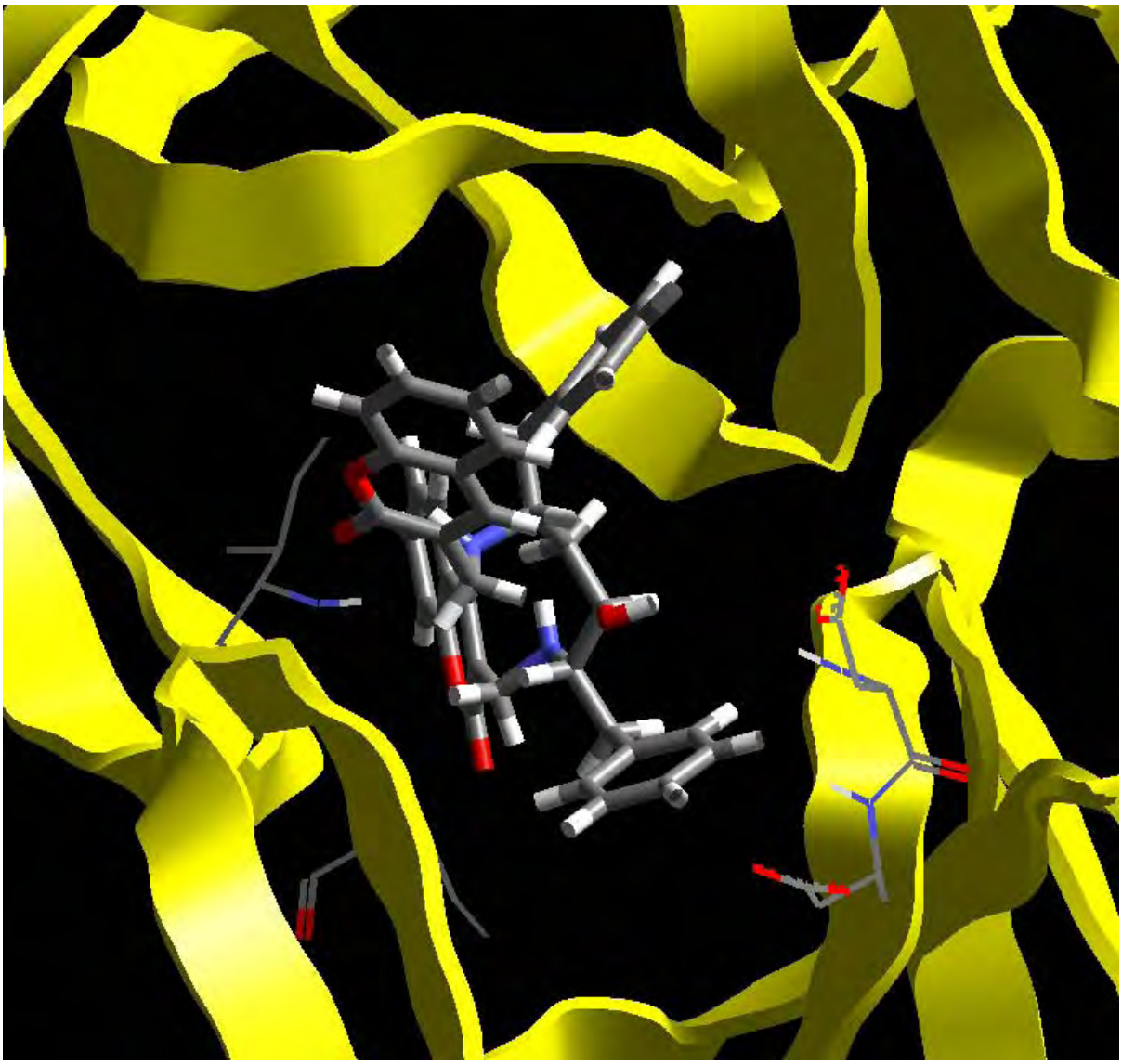


Figure 29. The “bestfit” conformation of the synthetic inhibitor **186a** (R, R’, R”= H) in the active site of the HIV-1 protease enzyme.

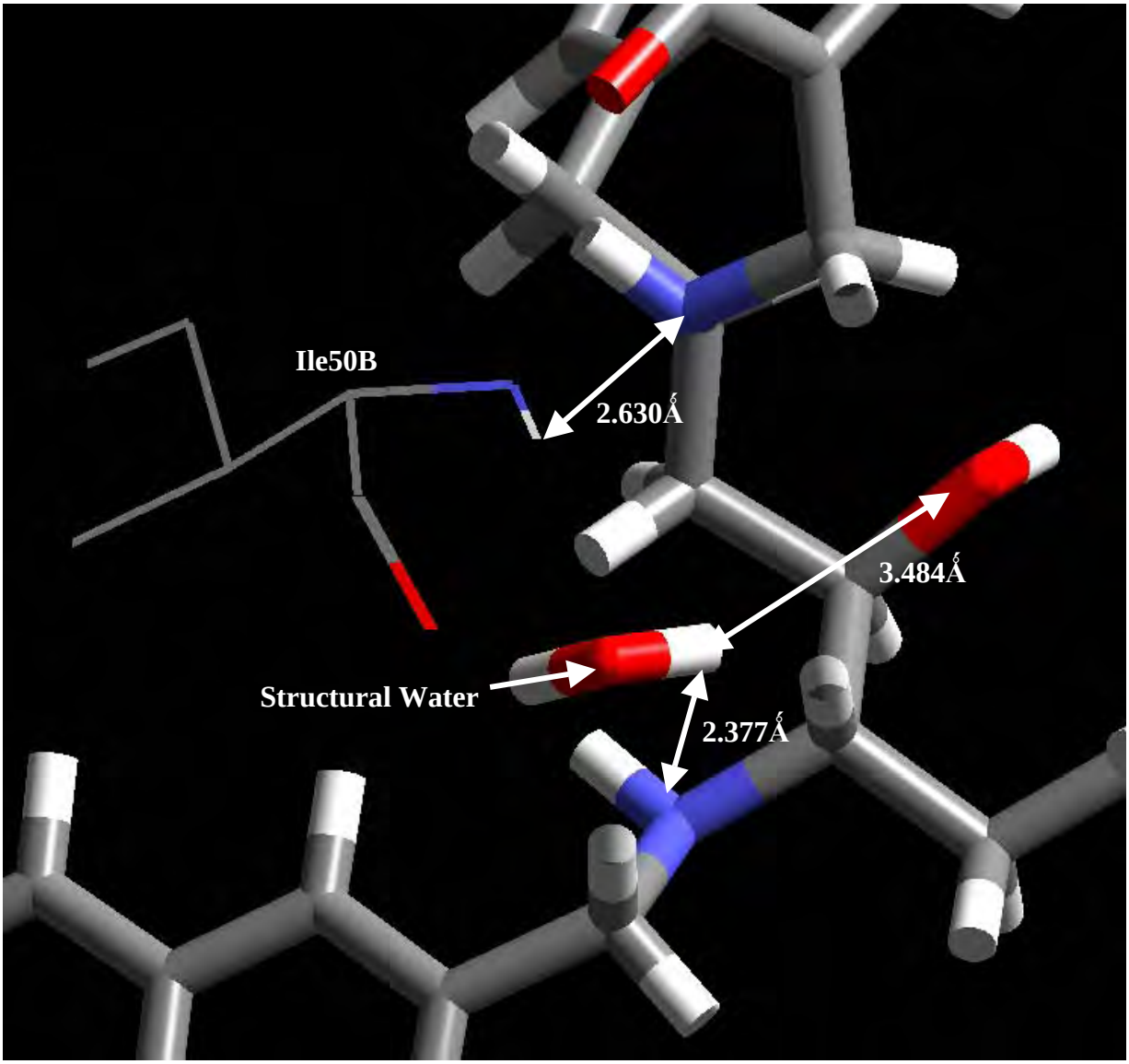


Figure 30. The possible hydrogen-bnding interactions between the synthetic inhibitor **186a** and HIV-1 protease enzyme receptor.

2.5 Conclusions

An earlier investigation had revealed that the Baylis-Hillman reaction between salicylaldehyde and methyl acrylate resulted in the formation of complex mixtures of chromene and coumarin derivatives, and no less than eight distinct product types, including both coumarins and chromenes, had been isolated.

The present study was aimed at developing the Baylis-Hillman methodology to ensure regioselective intramolecular acyl substitution to afford coumarins chemoselectively. Initally, the synthesis of coumarins was achieved using protecting group strategies. Specially prepared *O*-benzylated salicylaldehydes were reacted with activated alkenes to give the corresponding Baylis-Hillman products in 51-91% yield. Subsequent conjugate addition reactions of the Baylis-Hillman products with the amines, benzylamine and piperidine, afforded diastereomeric adducts which, following catalytic hydrogenolysis, cyclized spontaneously to give the 3-substituted coumarins in up to 67% yield; 3-methylcoumarins were also isolated as minor products. The formation of the 3-methylcoumarins under these conditions was examined and found to be due to cleavage of the conjugate addition products during catalytic hydrogenolysis.

The *O-b*enzylated Baylis-Hillman products were successfully cyclized, under acid-catalysed conditions using HI or HCl, to give the 3-(halomethyl)coumarins in up to 94% yield, thus eliminating the amine conjugate addition step. This process appears to involve removal of the benzyl ester protecting group, conjugate addition of the halo acid to the α,β-unsatuarated ester moiety and spontaneous cyclization. It was found that use of HCl gave better yields then HI. The use of *completely unprotected* Baylis-Hillman products, prepared from *tert*-butyl acrylate and various salicylaldehydes afforded the 3-(chloromethyl)coumarins in even better yields (up to 98%), the advantage of this method being the elimination of protecting groups altogether. An alternative approach to 3-substituted coumarins *via* intramolecular DABCO-catalysed Baylis-Hillman reactions of salicylaldehyde acrylate esters was also explored, affording coumarin-derived quaternary salts in up to 70% yield. An electron-impact

(EI) mass spectrometric study of selected 3-substituted coumarins, using high-resolution and B/E linked scan data, has revealed certain common fragmentation modes.

Regioselectivity studies involving substitution reactions of 3-(halomethyl)coumarins with various carbon and nitrogen nucleophiles and the enolate-derived anions of ethyl acetoacetate and diethyl malonate have been undertaken. The results indicated the exclusive formation of S_N-type (rather than S_N') products in up to 61% yield, with substitution occuring at the exocyclic allylic centre in each case.

Four ritonavir analogues containing coumarin moieties have been synthesized by treating a specially prepared, hydroxyethylene dipeptide isostere with several coumarin derivatives in the presence of base. Use of a DABCO-derived quaternary ammonium salt instead of a (halomethyl)coumarin gave the required product under mild conditions in 85% yield – an approach which clearly provides convenient and efficient access to these complex systems.

It is apparent that the various aims of the project have been successfully addressed. Future research in this area is expected to include the following

1) Use of carbon nucleophiles, such as butyllithium and Grignard reagents, to further explore the regioselectivity of nucleophilic attack on the coumarin system.
2) Biological testing of the ritonavir analogues.
3) Further work on the interactive docking procedure, as a means of investigating the hydrogen-bonding interactions between the synthetic ritonavir analogues and the HIV1-protease enzyme receptor.

3. EXPERIMENTAL

3.1. General

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. NMR spectra were run on Bruker AMX400 or AVANCE 400mHz spectrometers at 303^{o}K. Spectra recorded in $CDCl_3$ were calibrated using the solvent signals at 7.25 ppm for ^{1}H and 77.0 for ^{13}C, while ^{1}H NMR spectra run in CD_3OD were calibrated using the solvent signal at 3.31 ppm. IR spectra were recorded on a Perkin-Elmer FT-IR Spectrum 2000 spectrometer. Low-resolution mass spectra were obtained on a Finnegan Mat GCQ mass spectrometer using the electron impact (EI) ionisation mode, and high-resolution mass spectra on a VG 70-SEQ double focusing magnetic sector spectrometer (Cape Technikon Mass Spectrometry Unit).

Flash chromatography was carried out using Merck Silica gel 60 [particle size 0.040-0.063 mm (230-400 mesh)], while preparative layer chromatography was effected on glass plates coated with Merck silica gel 60 PF_{254}. Thin layer chromatography (TLC) was performed using precoated Merck silica gel F_{254} plates, with visualization of the components by inspection under UV light (254/365 nm) and /or by exposure to iodine vapour.

Solvents were dried under dry N_2 using the procedures described by Perrin and Armarego.[205] Thus, THF was dried over sodium wire and distilled using benzophenone as an indicator, dichloromethane was distilled from CaH_2, methanol was distilled from magnesium methoxide (generated *in situ* by reacting methanol with magnesium turnings in the presence of iodine) and acetone was distilled from and stored over 3A molecular sieves.

3.2. Preparative procedures

3.2.1. Preparation of salicylaldehyde benzyl ethers

2-Benzyloxybenzaldehyde 137a

To a mixture of salicylaldehyde (6.3g, 52mmol), benzyl bromide (6.2ml, 52mmol), anhydrous K_2CO_3 (42.8g, 0.31mol) and NaI (46.5g, 0.31mol) was added distilled acetone (100ml), and the mixture was boiled under reflux for 12h. Water (50ml) was then added and the aqueous layer extracted with $CHCl_3$ (2x100ml). The combined extracts were washed with brine and dried (anhyd. Na_2SO_4), filtered and concentrated *in vacuo* to give a dark brown oil. Crystallization from hexane afforded, as yellow crystals, 2-benzyloxybenzaldehyde **137a** (8.63g, 79%), m.p. 42-44^oC (lit.,[206] cites as oil) (Found: $\mathbf{M}^+$, 212.08396. Calc. for $C_{14}H_{12}O_2$ *M*, 212.08373); γ_{max}(KBr)/cm^{-1} 1685 (C=O); δ_H (400 MHz; $CDCl_3$) 5.19 (2H, s, OCH_2Ph), 7.06 (2H, d, *J* 8.0Hz, ArH), 7.33-7.55 (6H, series of multiplets, Ar-H), 7.86 (1H, d, *J* 8.0Hz, Ar-H) and 10.57 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 70.5 (OCH_2Ph), 113.0, 121.0, 125.2, 127.3, 128.3, 128.4, 128.7, 135.8, 136.1 and 161.0 (Ar-C) and 189.7 (C=O); *m/z* 212 (M^+, 6.1%) and 91 (100).

2-Benzyloxy-3-methoxybenzaldehyde 137b

The procedure described for the synthesis of 2-benzyloxybenzaldehyde **137a** was followed, using 3-methoxysalicylaldehyde (4.76g, 31mmol), benzyl bromide (3.72ml, 31.3mmol), anhydrous K_2CO_3 (26g, 0.19mol) and NaI (28.2g, 0.19mol) in distilled acetone (100ml). Work-up afforded, as a white solid, 2-benzyloxy-3-methoxybenzaldehyde **137b** (6.80g, 89%), m.p. 38-40^oC (from hexane) (lit.,[207] 45^oC) (Found: $\mathbf{M}^+$, 242.09476. Calc. for $C_{15}H_{14}O_3$ *M*, 242.09429); γ_{max} (KBr)/cm^{-1} 1695 (C=O); δ_H (400 MHz; $CDCl_3$) 3.94 (3H, s, OCH_3), 5.17 (2H, s, OCH_2Ph), 7.10-7.18 (2H, series of multiplets, Ar-H), 7.32-7.39 (6H, series of overlapping signals, Ar-H) and 10.24 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 56.1 (OCH_3), 76.3 (OCH_2Ph), 118.1, 119.1, 124.2, 128.5, 128.6, 128.7, 130.4, 136.4, 151.1 and 153.1 (Ar-C) and 190.2

(C=O); *m/z* 242 (M^+, 7.2%) and 213 (100).

2-Benzyloxy-3-ethoxybenzaldehyde 137c

The procedure described for the synthesis of 2-benzyloxybenzaldehyde **137a** was followed, using 3-ethoxysalicylaldehyde (5.2g, 31mmol), benzyl bromide (3.72ml, 31.3mmol), anhydrous K_2CO_3 (26g, 0.19mol) and NaI (28.2g, 0.19mol) in distilled acetone (100ml). Work-up afforded, as a pale orange powder, 2-benzyloxy-3-ethoxybenzaldehyde **137c** (6.84g, 85%), m.p. 36-38^{o}C (from hexane) (lit.,[208] 39-40^{o}C) (Found: $\mathbf{M}^+$, 256.10841. Calc. for $C_{16}H_{16}O_3$ *M*, 256.10994); γ_{max} (KBr)/cm^{-1} 1688 (C=O); δ_H (400 MHz; $CDCl_3$) 1.51 (3H, t, *J* 7.2Hz, CH_3), 4.15 (2H, q, *J* 7.2Hz, OCH_2CH_3), 5.19 (2H, s, OCH_2Ph), 7.09-7.40 (8H, series of overlapping signals, Ar-H) and 10.26 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 14.9 (CH_3), 64.7 (OCH_2CH_3), 76.2 (OCH_2Ph), 119.0, 119.1, 124.2 128.5, 128.6, 128.7, 130.3, 136.5, 151.3 and 152.3 (Ar-C) and 190.3 (C=O); *m/z* 256 (M^+, 11.1%) and 227 (100).

2-Benzyloxy-5-chlorobenzaldehyde 137d

The procedure described for the synthesis of 2-benzyloxybenzaldehyde **137a** was followed, using 5-chlorosalicylaldehyde (4.9g, 31mmol), benzyl bromide (3.72ml, 31.3mmol), anhydrous K_2CO_3 (26g, 0.19mol) and NaI (28.2g, 0.19mol) in distilled acetone (100ml). Work-up afforded, as pale yellow crystals, *2-benzyloxy-5-chlorobenzaldehyde* **137d** (5.15g, 67%), m.p. 70-72^{o}C (from hexane) (Found: $\mathbf{M}^+$, 246.04567. $C_{14}H_{11}O_2{}^{35}Cl$ requires *M*, 246.04476); γ_{max} (KBr)/cm^{-1} 1680 (C=O); δ_H (400 MHz; $CDCl_3$) 5.18 (2H, s, OCH_2Ph), 7.00 (1H, d, *J* 8.8Hz, Ar-H), 7.34-7.42 (5H, series of multiplets, Ar-H), 7.45 (1H, dd, *J* 2.4Hz and *J* 8.8Hz, Ar-H), 7.79 (1H, d, *J* 2.4Hz, ArH) and 10.47 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 71.0 (OCH_2Ph), 114.8, 126.2, 126.8, 127.3, 128.0, 128.5, 128.8, 135.3, 135.6 and 159.4 (Ar-C) and 188.3 (C=O); *m/z* 246 [M^+ (^{35}Cl), 9.6%] and 91 (100).

2-Benzyloxy-5-bromobenzaldehyde 137e

The procedure described for the synthesis of 2-benzyloxybenzaldehyde **137a** was followed, using 5-bromosalicylaldehyde (9.14g, 31mmol), benzyl bromide (3.72ml, 31.3mmol), anhydrous K_2CO_3 (26g, 0.19mol) and NaI (28.2g, 0.19mol) in distilled acetone (100ml). Work-up afforded, as light yellow crystals, 2-benzyloxy-5-bromobenzaldehyde **137e** (6.43g, 71%), m.p. 72-74^{o}C (from hexane) (lit.,[209] 73-74^{o}C) (Found: $\mathbf{M^+}$**,** 289.99356. Calc. for $C_{14}H_{11}O_2{}^{79}Br$ *M*, 289.99424); γ_{max} (KBr)/cm^{-1} 1682 (C=O); δ_H (400 MHz; $CDCl_3$) 5.18 (2H, s, OCH_2Ph), 6.95 (1H, d, *J* 8.8Hz, Ar-H), 7.32-7.43 (5H, series of multiplets, Ar-H), 7.59 (1H, dd, *J* 2.8Hz and *J* 8.8Hz, Ar-H), 7.94 (1H, d, *J* 2.8Hz, Ar-H) and 10.45 (1H, s ,CHO); δ_C (100 MHz: $CDCl_3$) 70.9 (OCH_2Ph), 113.9, 115.2, 126.5, 127.3, 128.5, 128.8, 131.1, 135.5, 138.2 and 159.9 (ArC) and 188.2 (C=O); *m/z* 290 [M^+ (^{79}Br), 11.6%] and 91 (100).

2-Benzyloxy-3,5-dibromobenzaldehyde 137f

The procedure described for the synthesis of 2-benzyloxybenzaldehyde **137a** was followed, using 3,5-dibromosalicylaldehyde (8.76g, 31.3mmol), benzyl bromide (3.72ml, 31.3mmol), anhydrous K_2CO_3 (26g, 0.19mol) and NaI (28.2g, 0.19mol) in distilled acetone (100ml). Work-up afforded, as white crystals, 2-benzyloxy-3,5-dibromobenzaldehyde **137f** (7.6, 66%), m.p. 100-102^{o}C (from hexane) (lit.,[209] 109.5-110^{o}C) (Found: $\mathbf{M^+}$, 367.90452. Calc. for $C_{14}H_{10}O_2{}^{79}Br_2$ *M*, 367.90475); γ_{max} (KBr)/ cm^{-1} 1695 (C=O); δ_H (400 MHz; $CDCl_3$) 5.12 (2H, s, OCH_2Ph), 7.38 (5H, s, Ar-H), 7.85 (1H, d, *J* 2.4Hz, Ar-H), 7.97 (1H, d, *J* 2.4Hz, Ar-H) and 9.96 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 78.0 (OCH_2Ph), 118.3, 119.5, 128.8, 128.9, 129.2, 132.8, 134.7, 134.9, 157.4 and 141.4 (Ar-C) and 187.5 (C=O); *m/z* 368 [M^+ ($^{79}Br_2$), 5.5%] and 91 (100).

3.2.2. Preparation of Baylis-Hillman products

The reaction between 2-benzyloxybenzaldehyde **137a** and methyl acrylate in the presence of DABCO to give the Baylis-Hillman product **140a** was studied in detail by varying the experimental parameters in order to determine the optimum conditions. The reaction was monitored using ^{1}H NMR spectroscopy and the results are discussed in Section 2.1.3 (p. 47).

3.2.2.1. Optimisation Studies of Baylis-Hillman reaction

Experiment 1

A mixture of 2-benzyloxybenzaldehyde **137a** (1.06g, 5mmol), methyl acrylate (0.50ml, 5.3mmol) and DABCO (28mg, 0.25mmol) in $CDCl_3$ (0.25ml) was stirred in a stoppered reaction flask for five weeks to give the Baylis-Hillman product, methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanoate **140a** (*ca* 22%), as determ - ined by ^{1}H NMR analysis of the crude reaction mixture.

Experiment 2

A mixture of 2-benzyloxybenzaldehyde **137a** (1.06g, 5mmol), methyl acrylate (0.50ml, 5.3mmol) and DABCO (112mg, 1mmol) in $CDCl_3$ (0.25ml) was stirred in a stoppered reaction flask for six weeks to give the Baylis-Hillman product, methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanoate **140a** (*ca* 87%), as determin- ed by ^{1}H NMR analysis of the crude reaction mixture.

Experiment 3

A mixture of 2-benzyloxybenzaldehyde **137a** (1.06g, 5mmol), methyl acrylate (0.50ml, 5.3mmol) and DABCO (28mg, 0.25mmol) in $CDCl_3$ (0.25ml) and D_2O (0.25ml) was stirred in a stoppered reaction flask for six weeks with no evidence of the formation of the expected Baylis-Hillman product, methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanoate **140a**, as determined by ^{1}H NMR analysis of the crude reaction mixture.

Experiment 4

A mixture of 2-benzyloxybenzaldehyde **137a** (1.06g, 5mmol), methyl acrylate (0.71ml, 7.9mmol) and DABCO (22.4mg, 0.2mmol) in $CDCl_3$ (1ml) and D_2O (1ml) was stirred in a stoppered reaction flask for six weeks with no evidence of the formation of the expected Baylis-Hillman product, methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanoate **140a**, as determined by ^1H NMR analysis of the crude reaction mixture.

Experiment 5

A mixture of 2-benzyloxybenzaldehyde **137a** (1.06g, 5mmol), methyl acrylate (*ca* 1.0ml, 10mmol) and DABCO (28mg, 0.25mmol) in $CDCl_3$ (0.25ml) was stirred in a stoppered reaction flask for six weeks to give the Baylis-Hillman product, methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanoate **140a** (*ca* 21%), as determined by ^1H NMR analysis of the crude reaction mixture.

Experiment 6

A mixture of 2-benzyloxybenzaldehyde **137a** (1.06g, 5mmol), methyl acrylate (*ca* 1.0ml, 10.5mmol) and DABCO (294mg, 2.63mmol) in $CDCl_3$ (0.25ml) was stirred in a stoppered reaction flask for four weeks to give the Baylis-Hillman product, methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanoate **140a** (*ca* 90%), as determined by ^1H NMR analysis of the crude reaction mixture.

Experiment 7

A mixture of 2-benzyloxybenzaldehyde **137a** (1.06g, 5mmol), methyl acrylate (2.37ml, 26.3mmol) and DABCO (294mg, 2.63mmol) in $CDCl_3$ (0.25ml) was stirred in a stoppered reaction flask for three weeks to give the Baylis-Hillman product, methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanoate **140a** (*ca* 95%), as determined by ^1H NMR analysis of the crude reaction mixture.

3.2.2.2. Preparation of O-benzylated Baylis-Hillman products

Methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanoate 140a

A mixture of 2-benzyloxybenzaldehyde **137a** (1.06g, 5.0mmol), methyl acrylate (1.0ml, 11mmol) and DABCO (294mg, 2.63mmol) in $CDCl_3$ (0.25ml) was stirred in a stoppered reaction flask for three weeks. The mixture was concentrated *in vacuo* to give a brown oil, which was purified by flash column chromatography [elution with hexane-EtOAc (3:1)] to afford starting material 2-benzyloxybenzaldehyde **137a** (0.16g, 11%) and, as a pale yellow oil,[159] methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanoate **140a** (1.12g, 75%) (Found, $\mathbf{M}^+$ 298.12046. Calc. for $C_{18}H_{18}0_4$ *M*, 298.12051); γ_{max} (thin film)/cm^{-1} 3501 (OH) and 1728 (C=O); δ_H (400 MHz; $CDCl_3$) 3.37 (1H, br s, OH), 3.71 (3H, s, OCH_3), 5.08 (2H, s, OCH_2Ph), 5.68 and 6.28 (2H, 2xs, $C=CH_2$), 5.93 (1H, s, *CH*OH), 6.92-7.38 (9H, series of overlapping multiplets, Ar-H); δ_C (100 MHz; $CDCl_3$) 51.9 (OCH_3), 68.6 (CHOH), 70.3 (OCH_2), 111.9, 121.1, 125.8, 127.4, 127.8, 128.0, 128.6 128.9, 129.6, 136.7, 141.4 and 155.8 ($C=CH_2$ and Ar-C) and 167.0 (C=O); *m/z* 298 (M^+, 1.5%) and 175 (100).

Methyl 3-(2-benzyloxy-3-methoxyphenyl)-3-hydroxy-2-methylenepropanoate 140b

The procedure described for the synthesis of methyl 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-methylenepropanonate **140e** was followed, using 2-benzyloxy-3-methoxybenzaldehyde **137b** (1.21g, 5.0mmol), methyl acrylate (2.37ml, 26.3mmol) and DABCO (294mg, 2.63mmol) in $CDCl_3$ (0.25ml). Work-up afforded the starting material, 2-benzyloxy-3-methoxybenzaldehyde **137b** (0.24g, 15%) and, as a pale yellow oil, *methyl 3-(2-benzyloxy-3-methoxyphenyl)-3-hydroxy-2-methylene-propanoate* **140b** (1.34g, 84%) (Found: $\mathbf{M}^+$, 328.13079. $C_{19}H_{20}O_5$ requires *M*, 328.13107); γ_{max} (thin film)/cm^{-1} 3501(OH) and 1728 (C=O); δ_H (400 MHz; $CDCl_3$) 2.88 (1H, d, *J* 5.2Hz, OH), 3.69 and 3.89 (6H, 2xs, $2xOCH_3$), 5.07 (2H, s, OCH_2), 5.71 and 6.27 (2H, 2xs, $C=CH_2$), 5.86 (1H, d, *J* 5.2Hz, *CH*OH), 6.89-7.45 (8H, series of multiplets, Ar-H); δ_C (100 MHz; $CDCl_3$) 51.8 and 55.8 ($2xOCH_3$), 67.7 (CHOH), 74.7 (OCH_2), 112.1, 119.4, 124.1, 125.8, 128.0, 128.2, 128.4, 135.1, 137.6, 141.7,

145.3 and 152.5 (C=CH_2 and Ar-C) and 166.8 (C=O); *m/z* 328 (M^+, 9.7%) and 205 (100).

Methyl 3-(2-benzyloxy-3-ethoxyphenyl)-3-hydroxy-2-methylenepropanoate 140c

The procedure described for the synthesis of methyl 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-methylenepropanonate **140e** was followed, using 2-benzyloxy-3-ethoxy benzaldehyde **137c** (1.28g, 5.0mmol), methyl acrylate (2.37ml, 26.3mmol) and DABCO (294mg, 2.63mmol) in $CDCl_3$ (0.25ml). Work-up afforded the starting material, 2-benzyloxy-3-ethoxybenzaldehyde **137c** (10mg, 0.6%) and, as a pale yellow oil, m*ethyl 3-(2-benzyloxy-3-ethoxyphenyl)-3-hydroxy-2-methylenepropanoate* **140c** (1.37g, 80%) (Found: $\mathbf{M}^+$, 342.14677. $C_{20}H_{22}O_5$ requires *M*, 342.14672); γ_{max} (thin film)/cm^{-1} 3484 (OH) and 1719 (C=O); δ_H (400 MHz; $CDCl_3$) 1.47 (3H, t, *J* 7Hz, CH_3), 2.93 (1H, d, *J* 5.2Hz, OH), 3.69 (3H, s, OCH_3), 4.10 (2H, q, *J* 6.8Hz, OCH_2CH_3), 5.10 (2H, s, OCH_2Ph), 5.72 and 6.28 (2H, 2xs, C=CH_2) 5.87 (1H, d, *J* 5.2Hz, *CH*OH), 6.89-7.46 (8H, series of multiplets, Ar-H); δ_C (100 MHz; $CDCl_3$) 15.0 (OCH_2CH_3), 51.8 (OCH_3), 64.3 (OCH_2CH_3), 68.0 (CHOH), 74.7 (OCH_2Ph), 125.8 (C=CH_2), 113.2, 119.4, 124.1,0 128.0, 128.42, 128.35, 135.2, 137.7, 141.7, 145.5 and 151.9 (*C*=CH_2 and Ar-C) and 166.9 (C=O); *m/z* 342 (M^+, 15.6%) and 219 (100).

Methyl 3-(2-benzyloxy-3-chlorophenyl)-3-hydroxy-2-methylenepropanoate 140d

The procedure described for the synthesis of methyl 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-methylenepropanonate **140e** was followed, using 2-benzyloxy-5-chlorobenzaldehyde **137d** (1.23g, 5.0mmol), methyl acrylate (2.37ml, 26.3mmol) and DABCO (294mg, 2.63mmol) in $CDCl_3$ (0.25ml). Work-up afforded the starting material, 2-benzyloxy-5-chlorobenzaldehyde **137d** (60mg, 3.6%) and, as pale a yellow oil, *methyl 3-(2-benzyloxy-3-chlorophenyl)-3-hydroxy-2-methylenepropanoate* **140d** (1.29g, 78%) (Found: $\mathbf{M}^+$**,** 332.08243. $C_{18}H_{17}O_4{}^{35}Cl$ requires *M*, 332.08154); γ_{max} (thin film)/cm^{-1} 3479 (OH) and 1715 (C=O); δ_H (400 MHz; $CDCl_3$) 3.32 (1H, br s, OH), 3.73 (3H, s, OCH_3), 5.05 (2H, s, OCH_2Ph), 5.66 and 6.29 (2H, 2xs, C=CH_2),

5.88 (1H, s, *CH*OH), 6.84 (1H, d, *J* 8.8Hz, Ar-H), 7.17-7.40 (7H, series of multiplets, Ar-H); δ_C (100 MHz; $CDCl_3$) 52.0 (OCH_3), 67.8 (CHOH), 70.5 (OCH_2Ph), 126.4 (C=*C*H_2), 113.1, 126.2, 127.3, 127.8, 128.2, 128.5, 128.6, 131.5, 136.3, 140.7 and 154.2 (C=CH_2 and Ar-C) and 166.9 (C=O); *m/z* 332 [M^+(^{35}Cl), 5.7%] and 209 (100).

Methyl 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-methylenepropanoate 140e

A mixture of 2-benzyloxy-5-bromobenzaldehyde **137e** (1.46g, 5.0mmol), methyl acrylate (2.37ml, 26.3mmol) and DABCO (294mg, 2.63mmol) in $CDCl_3$ (0.25ml) was stirred in a stoppered reaction flask for three weeks. Work-up afforded the starting material, 2-benzyloxy-5-bromobenzaldehyde **137e** (80mg, 4.2%) and, as pale yellow crystals, *methyl 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-methylenepropanonate* **140e** (1.58g, 84%), m.p. 114-116^{o}C (Found: **M**$^+$, 376.02870. $C_{18}H_{17}O_4{}^{79}Br$ requires *M*, 376.03102); γ_{max} (KBr)/cm^{-1} 3217 (OH) and 1716 (C=O); δ_H (400 MHz; $CDCl_3$) 3.32 (1H, br s, OH), 3.72 (3H, s, OCH_3), 5.04 (2H, s, OCH_2Ph), 5.65 and 6.28 (2H, 2xs, C=CH_2), 5.88 (1H, s, *CH*OH), 6.78 (1H, d, *J* 8.4Hz, Ar-H), 7.30-7.39 (6H, series of multiplets, Ar-H) and 7.54 (1H, d, *J* 2.4Hz, ArH); δ_C (100 MHz; $CDCl_3$) 52.0 (OCH_3), 67.7 (CHOH), 70.5 (OCH_2Ph), 113.5, 113.7, 126.4, 127.3, 128.2 128.6, 130.6, 131.5, 131.9, 136.2, 140.8 and 154.7 (C=CH_2 and Ar-C) and 166.9 (C=O); *m/z* 376 [M^+(^{79}Br), 11.5%) and 255 (100).

Methyl 3-(2-benzyloxy-3,5-dibromophenyl)-3-hydroxy-2-methylenepropanoate 140f

The procedure described for the synthesis of methyl 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-methylenepropanonate **140e** was followed, using 2-benzyloxy-3,5-dibromobenzaldehyde **137f** (1.85g, 5.0mmol), methyl acrylate (2.37ml, 26.3mmol) and DABCO (294mg, 2.63mmol) in $CDCl_3$ (0.25ml). Work-up afforded the starting material, 2-benzyloxy-3,5-dibromobenzaldehyde **137f** (50mg, 2.2%) and, as a pale yellow oil, *methyl 3-(2-benzyloxy-3,5-dibromophenyl)-3-hydroxy-2-methylene-propanoate* **140f** (1.50g, 66%) (Found: M^+, 453.94193. $C_{18}H_{16}O_4{}^{79}Br_2$ requires *M*, 453.94153); γ_{max} (thin film)/cm^{-1} 3501 (OH) and 1732 (C=O); δ_H (400 MHz; $CDCl_3$)

2.84 (1H, br s, OH) 3.69 (3H, s, OCH_3), 5.05 and 5.09 (2H, 2xd, *J* 10.8Hz, OCH_2Ph), 5.76 and 6.35 (2H, 2xs, $C=CH_2$), 5.81 (1H, d, *J* 3.2Hz, *CH*OH), 7.35-7.48 (6H, series of multiplets, ArH); δ_C (100 MHz; $CDCl_3$) 52.1 (OCH_3), 67.3 (CHOH), 75.5 (OCH_2Ph), 126.6 ($C=CH_2$), 117.7, 118.3, 128.2, 128.5, 128.6, 130.2, 135.6, 136.3, 138.5, 140.5 and 152.5 ($C=CH_2$ and Ar-C) and 166.4 (C=O); *m/z* 454 [M^+($^{79}Br_2$), 1.9%] and 333 (100).

3-(2-Benzyloxyphenyl)-3-hydroxy-2-methylenepropanenitrile 144a

A mixture of 2-benzyloxybenzaldehyde **137a** (1.06g, 5.0mmol), acrylonitrile (1.72ml, 26.3mmol) and DABCO (294mg, 2.63mmol) in $CDCl_3$ (0.25ml) was stirred in a stoppered reaction flask for 21 days.The mixture was concentrated *in vacuo* to give a dark brown oil (1.67g), which was purified using flash chromatography [elution with hexane-EtOAc (3:1)] to afford, as a pale yellow oil, *3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanenitrile* **144a** (0.73g, 55%) (Found: $\mathbf{M}^+$, 265.11071. $C_{17}H_{15}NO_2$ requires *M*, 265.11028); γ_{max} (thin film)/cm^{-1} 3432 (OH) and 2217(CN); δ_H (400 MHz; $CDCl_3$) 3.08 (1H, br s, OH), 5.08 and 5.10 (2H, t, *J* 12Hz, OCH_2Ph), 5.54 (1H, s, *CH*OH), 5.93 and 5.96 (2H, 2xd, *J* 1.6Hz and *J* 0.4Hz, $C=CH_2$), 6.97-7.42 (9H, series of overlapping signals, ArH); δ_C (100 MHz; $CDCl_3$) 70.5 (OCH_2Ph), 70.6 (CHOH), 129.7 ($C=CH_2$), 112.2, 117.1, 121.5, 125.8, 127.4, 127.6, 128.0, 128.3, 128.7, 130.0 and 136.2 ($C=CH_2$ and Ar-C) and 155.9 (CN); *m/z* 265 (M^+, 27.6%) and 91 (100).

3-(2-Benzyloxy-3-methoxyphenyl)-3-hydroxy-2-methylenepropanenitrile 144b

The procedure described for the synthesis of 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanenitrile **144a** was followed, using 2-benzyloxy-3-methoxy-benzaldehyde (1.21g, 5.0mmol), acrylonitrile (1.72ml, 26.3mmol) and DABCO (294mg, 2.63mmol) in $CDCl_3$ (0.25ml). Work-up afforded, as a pale yellow oil, *3-(2-benzyloxy-3-methoxyphenyl)-3-hydroxy-2-methylenepropanenitrile* **144b** (0.90g, 61%) (Found: $\mathbf{M}^+$, 295.12122. $C_{18}H_{17}NO_3$ requires *M*, 295.12084); γ_{max} (thin film)/cm^{-1} 3432 (OH) and 2227(CN); δ_H (400 MHz; $CDCl_3$) 2.77 (1H, d, *J* 5.6Hz, OH), 3.90

(3H, s, OCH_3), 5.06 and 5.14 (2H, 2xd, *J* 11.2Hz, OCH_2Ph), 5.43 (1H, d, *J* 5.6Hz, *CH*OH), 5.89 and 5.92 (2H, 2xd, J1.6Hz, $C=CH_2$), 6.93-7.42 (8H, series of overlapping signals, ArH); δ_C (100 MHz, $CDCl_3$) 55.8 (OCH_3), 69.6 (CHOH) 74.9 (OCH_2Ph), 128.9 ($C=CH_2$), 113.0, 117.1, 119.4, 124.6, 125.8, 128.2, 128.3, 128.5, 133.0, 137.2 and 145.2 ($C=CH_2$ and Ar-C) and 152.5 (CN); *m/z* 295 (M^+, 35.2%) and 187 (100).

3-(2-Benzyloxy-3-ethoxyphenyl)-3-hydroxy-2-methylenepropanenitrile 144c

The procedure described for the synthesis of 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanenitrile **144a** was followed, using 2-benzyloxy-3-ethoxy-benzaldehyde (1.28g, 5.0mmol), acrylonitrile (1.72ml, 26.3mmol) and DABCO (294mg, 2.63mmol) in $CDCl_3$ (0.25ml). Work-up afforded, as a pale yellow oil, *3-(2-benzyloxy-3-ethoxyphenyl)-3-hydroxy-2-methylenepropanenitrile* **144c** (1.40g, 91%) (Found: $\mathbf{M}^+$, 309.13738. $C_{19}H_{19}NO_3$ requires *M*, 309.13649); γ_{max} (thin film)/cm^{-1} 3443 (OH) and 2228 (CN); δ_H (400 MHz; $CDCl_3$) 1.47 (3H, t, *J* 7Hz, CH_3), 2.80 (1H, br s, OH), 4.12 (2H, q, *J* 6.8Hz, OCH_2CH_3), 5.08 and 5.17 (2H, 2xd, *J* 10.8Hz, OCH_2Ph), 5.43 (1H, br s, *CH*OH), 5.90 and 5.93 (2H, 2xd, *J*1.2Hz, $C=CH_2$), 6.91-7.42 (8H, series of overlapping signals, ArH); δ_C (100 MHz; $CDCl_3$) 14.9 (CH_3), 64.2 (OCH_2CH_3), 74.9 (OCH_2Ph), 69.8 (CHOH), 129.8 ($C=CH_2$), 114.1, 117.1, 119.4, 124.6, 125.8, 128.3, 128.5, 131.2, 133.0, 137.2 and 145.2 ($C=CH_2$ and Ar-C) and 152.5 (CN); *m/z* 309 (M^+, 5.9%) and 201 (100).

3-(2-Benzyloxy-3-chlorophenyl)-3-hydroxy-2-methylenepropanenitrile 144d

The procedure described for the synthesis of 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanenitrile **144a** was followed, using 2-benzyloxy-5-chlorobenz-aldehyde (1.23g, 5.0mmol), acrylonitrile (1.72ml, 26.3mmol) and DABCO (294mg, 2.63mmol) in $CDCl_3$ (0.25ml). Work-up afforded, as a pale yellow oil, 3-*(2-benzyloxy-3-chlorophenyl)-3-hydroxy-2-methylenepropanenitrile* **144d** (0.82g, 55%) (Found: $\mathbf{M}^+$, 299.07235. $C_{17}H_{14}NO_2{}^{35}Cl$ requires *M*, 299.07131); γ_{max} (thin film)/cm^{-1} 3397 (OH) and 2220 (CN); δ_H (400 MHz; $CDCl_3$) 2.88 (1H, d, *J* 6.0Hz, OH), 5.05

and 5.08 (2H, 2xd, *J* 11.6Hz, OCH_2Ph), 5.54 (1H, d, *J* 6.0Hz, *CH*OH), 5.94 and 5.98 (2H, 2xd, *J*1.6Hz, $C=CH_2$), 6.84 (1H, d, *J* 8.8Hz, ArH), 7.24-7.40 (7H, series of multiplets, ArH); δ_C (100 MHz; $CDCl_3$) 69.6 (CHOH), 70.9 (OCH_2Ph), 130.3 ($C=CH_2$), 113.5, 116.8, 125.2, 126.6, 127.6, 127.8, 128.5, 128.8, 129.2, 129.6 and 135.8 ($C=CH_2$ and Ar-C) and 154.3 (CN); *m/z* 299 [M^+(^{35}Cl), 18.1%] and 91 (100).

3-(2-Benzyloxy-5-bromophenyl)-3-hydroxy-2-methylenepropanenitrile 144e

The procedure described for the synthesis of 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanenitrile **144a** was followed, using 2-benzyloxy-5-bromo-benzaldehyde (1.46g, 5.0mmol), acrylonitrile (1.72ml, 26.3mmol) and DABCO (294mg, 2.63mmol) in $CDCl_3$ (0.25ml). Work-up afforded, as pale yellow crystals, *3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-methylenepropanenitrile* **144e** (0.88g, 51%), m.p. 80-82^{o}C (Found: $\mathbf{M}^+$, 343.01884. $C_{17}H_{14}NO_2{}^{79}Br$ requires *M*, 343.02079); γ_{max} (KBr)/cm^{-1} 3413 (OH) and 2231 (CN); δ_H (400 MHz; $CDCl_3$) 2.83 (1H, d, *J* 6.0Hz, OH), 5.05 and 5.08 (2H, 2xd, *J* 11.6Hz, OCH_2Ph), 5.54 (1H, d, *J* 4.8Hz, *CH*OH), 5.96 and 5.98 (2H, 2xd, *J* 1.2Hz, $C=CH_2$), 6.86 (1H, d, *J* 8.8Hz, ArH), 7.35-7.42 (6H, series of overlapping signals, ArH) and 7.52 (1H, d, *J* 2.4Hz, ArH); δ_C (100 MHz; $CDCl_3$) 69.5 (CHOH), 70.8 (OCH_2Ph), 130.3 ($C=CH_2$), 113.8, 113.9, 116.8, 125.2, 127.6, 128.5, 128.8, 129.6, 130.7, 132.6 and 135.7 ($C=CH_2$ and Ar-C) and 154.8 (CN); *m/z* 342 [M^+(^{79}Br), 13.2%) and 92 (100).

3.2.2.3. Baylis-Hillman reactions of salicylaldehyde and tert*-butyl acrylate*

***tert*-Butyl 3-hydroxy-3-(2-hydroxyphenyl)-2-methylenepropanoate 146a**

A mixture of salicylaldehyde (1.0ml, 9.6mmol), *tert*-butyl acrylate (2.1ml, 14mmol) and DABCO (0.86g, 7.7mmol) in $CDCl_3$ (3ml) was stirred in a stoppered reaction flask for 14 days. The mixture was concentrated *in vacuo* to give dark brown oil, which was purified using flash chromatography [elution with hexane-EtOAc (4:1)] to afford, *tert*-butyl 3-hydroxy-3-(2-hydroxyphenyl)-2-methylenepropanoate **146a** (0.95g, 40%) as a colorless oil which later crystalised, m.p.108-110^{o}C (lit.,[134] 104-

106°C) (Found: **M**$^+$, 250.11914. Calc. for $C_{14}H_{18}O_4$ *M*, 250.12051); γ_{max} (KBr)/cm^{-1} 3361 (OH) and 1693 (C=O); δ_H (400 MHz; $CDCl_3$) 1.51 [9H, s, $C(CH_3)_3$], 4.29 (1H, d, *J* 3.6Hz, OH), 5.48 and 6.23 (2H, 2xs, $C=CH_2$), 5.69 (1H, d, *J* 2.4Hz, *CH*OH), 6.85-7.20 (4H, series of multiplets, ArH), 8.09 (1H, s, ArOH); δ_C (100 MHz, $CDCl_3$) 28.1 [$C(CH_3)_3$], 74.0 (CHOH), 82.7 [$C(CH_3)_3$], 127.0 ($C=CH_2$), 117.6, 119.8, 125.8, 124.1, 127.8, 129.6 and 140.8 ($C=CH_2$ and Ar-C) and 156.1 (C=O); *m/z* 250 (M$^+$, 1.2%) and 131 (100).

tert-Butyl 3-hydroxy- 3-(2-hydroxy-3-methoxyphenyl)-2-methylenepropanoate 146b

The procedure described for the synthesis of *tert*-butyl 3-hydroxy-3-(2-hydroxyphenyl)-2-methylenepropanoate **146a** was followed, using 3-methoxy salicylaldehyde (1.52g, 9.6mmol), *tert*-butyl acrylate (2.1ml, 14mmol) and DABCO (0.86mg, 7.7mmol) in $CDCl_3$ (3ml). Work-up afforded, as a pale yellow oil, tert-*butyl 3-hydroxy-3-(2-hydroxy-3-methoxyphenyl)-2-methylenepropanoate* **146b** (1.53g, 57%) (Found: **M**$^+$, 280.13073. $C_{15}H_{20}O_5$ requires *M*, 280.13107); γ_{max} (thin film)/cm^{-1} 3412 (OH) and 1714 (C=O); δ_H (400 MHz; $CDCl_3$) 1.45 [9H, s, $C(CH_3)_3$], 3.68 (1H, d, *J* 4.0Hz, OH), 3.91 (3H, s, OCH_3), 5.64 and 6.22 (2H, 2xs, $C=CH_2$), 5.81 (1H, d, *J* 2.8Hz, *CH*OH), 6.61 (1H, s, ArOH) and 6.82 (3H, s, ArH); δ_C (100 MHz; $CDCl_3$) 28.0 [$C(CH_3)_3$], 56.0 (OCH_3), 69.9 (CHOH), 81.7 [$C(CH_3)_3$], 125.4 ($C=CH_2$), 110.5, 119.6, 119.7, 126.3, 142.0, 143.8, and 147.1($C=CH_2$ and Ar-C) and 166.2 (C=O); *m/z* 280 (M$^+$, 8.2%) and 161 (100).

tert-Butyl 3-hydroxy-3-(3-ethoxy-2-hydroxyphenyl)-2-methylenepropanoate 146c

The procedure described for the synthesis of *tert*-butyl 3-hydroxy-3-(2-hydroxyphenyl)-2-methylenepropanoate **146a** was followed, using 3-ethoxy salicylaldehyde (1.66g, 9.6mmol), *tert*-butyl acrylate (2.1ml, 14mmol) and DABCO (0.86g, 7.7mmol) in $CDCl_3$ (3ml). Work-up afforded, as a pale yellow oil, tert-*butyl 3-hydroxy-3-(3-ethoxy-2-hydroxyphenyl)-2-methylenepropanoate* **146c** (1.65g, 58%) (Found: **M**$^+$, 294.14688. $C_{16}H_{22}O_5$ requires *M*, 294.14672); γ_{max} (thin film)/cm^{-1} 3383 (OH) and

1714 (C=O); δ_H (400 MHz; $CDCl_3$) 1.43 [12H, overlapping s and t, $C(CH_3)_3$ and OCH_2CH_3], 3.63 (1H, d, *J* 5.2Hz, CHO*H*), 4.09 (2H, q, *J* 7.2Hz, OCH_2CH_3), 5.66 and 6.21 (2H, 2xs, $C=CH_2$), 5.82 (1H, d, *J* 4.0Hz, *CH*OH), 6.45 (1H, s, ArOH) and 6.83 (3H, series of overlapping signals, ArH); δ_C (100 MHz; $CDCl_3$) 14.8 (CH_2CH_3), 28.0 [$C(CH_3)_3$], 64.5 (OCH_2CH_3), 69.4 (CHOH), 81.5 [$C(CH_3)_3$], 111.3, 119.5, 119.6, 125.1, 126.6, 142.2, 143.6 and 146.1($C=CH_2$ and Ar-C) and 166.1 (C=O); *m/z* 294 (M^+, 18.2%) and 220 (100).

tert-Butyl 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-2-methylenepropanoate 146e

The procedure described for the synthesis of *tert*-butyl 3-hydroxy-3-(2-hydroxyphenyl)-2-methylenepropanoate **146a** was followed, using 5-bromosalicylaldehyde (1.93g, 9.6mmol), *tert*-butyl acrylate (2.1ml, 14mmol) and DABCO (0.86g, 7.7mmol) in $CDCl_3$ (3ml) and stirring for 3 days. The reaction mixture was filtered through a layer of silica gel. Crystallization from $CHCl_3$ afforded, as white crystals, tert-*butyl 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-2-methylenepropanoate* **146e** (2.07g, 66%), m.p. 186-188^{o}C (Found: **M**$^+$, 328.03063. $C_{14}H_{17}O_4{}^{79}Br$ require *M*, 328.03102); γ_{max} (KBr)/cm^{-1} 3298 (OH), and 1686 (C=O); δ_H (400 MHz, $CDCl_3$) 1.51 [9H, s, $C(CH_3)_3$], 4.26 (1H, br s, OH), 5.56 and 6.23 (2H, 2xs, $C=CH_2$), 5.63 (1H, s, *CH*OH), 6.80 (1H, d, *J* 8.8Hz, ArH), 7.09 (1H, d, *J* 8.4Hz, ArH), 7.29 (1H, dd, *J* 8.8 and *J* 2.0Hz, ArH) and 8.18 (1H, br s, ArOH); δ_C (100 MHz, $CDCl_3$) 28.0 [$C(CH_3)_3$], 72.9 (CHOH), 83.0 [$C(CH_3)_3$], 111.8, 119.5, 126.5, 127.2, 130.3, 132.2, 140.3 and 155.1 ($C=CH_2$ and Ar-C) and 166.7 (C=O); *m/z* 328 [$M^+(^{79}Br)$, 3.7%] and 211 (100).

tert-Butyl 3-(3,5-dibromo-2-hydroxyphenyl)-3-hydroxy-2-methylenepropanoate 146f

The procedure described for the synthesis of *tert*-butyl 3-hydroxy-3-(2-hydroxyphenyl)-2-methylenepropanoate **146a** was followed, using 3,5-dibromo-salicylaldehyde (2.69g, 9.6mmol), *tert*-butyl acrylate (7.68ml, 52.5mmol) and DABCO (0.86g, 7.7mmol) in $CDCl_3$ (3ml) and stirring for 3 days. The reaction mixture was filtered through a layer of silica gel. Crystallization from $CHCl_3$

afforded, as white crystals, *tert-butyl 3-(3,5-dibromo-2-hydroxyphenyl)-3-hydroxy-2-methylenepropanoate* **146f** (1.70g, 44%) m.p. 186-188^{o}C; (Found: **M**$^{+}$**,** 405.94240. $C_{14}H_{16}O_4{}^{79}Br_2$ require *M*, 405.94153); δ_H (400 MHz, $CDCl_3$) 1.48 [9H, s, $C(CH_3)_3$], 4.24 (1H, br s, OH), 5.62 and 6.26 (2H, 2xs, $C=CH_2$), 5.67 (1H, s, *CH*OH), 7.16 (1H, d, *J* 2.0Hz, ArH), 7.56 (1H, d, *J* 2.0Hz, ArH) and 8.12 (1H, br s, ArOH); δ_C (100 MHz, $CDCl_3$) 28.0 [$C(CH_3)_3$], 71.5 (CHOH), 82.9 [$C(CH_3)_3$], 112.0, 112.1, 127.0, 128.4, 129.7, 134.4, 140.3 and 151.0 ($C=CH_2$ and Ar-C) and 166.3 (C=O).

3.2.3. Reaction of nitrogen nucleophiles with Baylis-Hillman products

3.2.3.1. Conjugate addition reactions with benzylamine

Methyl 2-(benzylaminomethyl)-3-(2-benzyloxyphenyl)-3-hydroxypropanoate 147a

A mixture of methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanoate **140a** (0.6g, 2mmol), benzylamine (0.22ml, 2mmol) in methanol (4ml) was stirred in a stoppered reaction flask for 3 days. Excess benzylamine was evaporated *in vacuo* to give a yellow oil (0.80g), which was purified by preparative layer chromatography [elution with hexane-MeOH-EtOAc (2:0.1:1)] to afford *methyl 3-(2-benzylamino-methyl)-3-(2-benzyloxyphenyl)-3-hydroxypropanoate* **147a** (0.50g, 62%) as pale yellow crystals, m.p. 94-96^{0}C (Found: **MH**$^{+}$, 406.201633. $C_{25}H_{28}NO_4$ requires *M+1*, 406.201834); γ_{max} (KBr)/cm^{-1} 3308 (OH) and 1720 (C=O); δ_H (400 MHz; $CDCl_3$) 2.54 (1H, dd, *J* 12Hz and *J* 3.2Hz, CH_ANHCH$_2$Ph), 3.06-3.13 (2H, series of overlapping signals, CHCH_BNHCH$_2$Ph), 3.64 and 3.69 (2H, 2xd, *J* 12.8Hz, NHCH_2Ph), 3.75 (3H, s, OCH_3), 5.13 (2H, 2xd, *J* 12.2Hz, OCH_2Ph), 5.77 (1H, m, *CH*OH), 6.91 and 6.95 (2H, 2xd, *J* 8.4Hz and *J* 7.6Hz, ArH) and 7.20-7.47 (12H, series of overlapping signals, Ar-H); δ_C (100 MHz; $CDCl_3$) 46.2 (CH_2NHCH_2Ph), 47.4 ($CHCO_2CH_3$), 51.9 (OCH_3), 54.2 ($CH_2NH_2CH_2Ph$), 69.6 (OCH_2Ph), 71.8 (CHOH), 111.3, 120.9, 126.8, 127.0, 127.2, 127.7, 128.1, 128.37, 128.42, 128.5, 131.7, 137.0, 139.1 and 154.5 (Ar-C) and 174.2 (C=O); *m/z* 405 (M^+, 0.1%) and 91 (100).

Methyl 2-(benzylaminomethyl)-3-(2-benzyloxy-3-methoxyphenyl)-3-hydroxy-propanoate 147b

The procedure described for the synthesis of methyl 2-(benzylaminomethyl)-3-(2-benzyloxyphenyl)-3-hydroxypropanoate **147a** was followed, using 3-(2-benzyloxy-3-methoxyphenyl)-3-hydroxy-2-methylenepropanoate **140a** (0.66g, 2mmol), benzylamine (0.22ml, 2mmol) in methanol (4ml). Work-up and chromatography afforded m*ethyl 2-(benzylaminomethyl)-3-(2-benzyloxy-3-methoxyphenyl)-3-hydroxypropanoate* **147b** (0.76g, 87%) as a pale yellow oil, (Found: **MH**$^+$, 436.212314. $C_{26}H_{30}O_5N$ requires *M+1*, 436.212398); γ_{max} (thin film)/cm^{-1} 3325 (OH) and 1732 (C=O); δ_H (400 MHz; $CDCl_3$) 2.48 (1H, dd, *J* 12.4 and *J* 3.2Hz, *CH*$_A$NHCH$_2$Ph), 3.04-3.12 (2H, series of overlapping signals, C*H*C*H*$_B$NHCH$_2$Ph), 3.65 (2H, s, CH$_2$NHC*H*$_2$Ph), 3.73 and 3.90 (6H, 2xs, OCH_3), 4.89 and 5.22 (2H, 2xd, *J* 10.8Hz, OCH_2Ph), 5.65 (1H, m, *CH*OH) and 6.89-7.53 (13H, series of multiplets, ArH); δ_C (100 MHz; $CDCl_3$) 46.1 (*C*H$_2$NHCH$_2$Ph), 48.1 (*C*HCO$_2$CH$_3$), 51.8 and 55.7 (2xOCH$_3$), 54.1 (CH$_2$NH$_2$*C*H$_2$Ph), 72.1 (CHOH), 74.5 (OCH$_2$Ph), 111.2, 118.8, 123.9, 127.1, 127.9, 128.19, 128.24, 128.3, 128.4, 137.1, 137.5, 139.0, 143.8 and 152.3 (Ar-C) and 173.8 (C=O); *m/z* 436 (MH$^+$, 17.3%) and 120 (100).

Methyl 2-(benzylaminomethyl)-3-(2-benzyloxy-3-ethoxyphenyl)-3-hydroxypropanoate 147c

The procedure described for the synthesis of methyl 2-(benzylaminomethyl)-3-(2-benzyloxyphenyl)-3-hydroxypropanoate **147a** was followed, using 3-(2-benzyloxy-3-ethoxyphenyl)-3-hydroxy-2-methylenepropanoate **140c** (0.68g, 2mmol), benzylamine (0.22ml, 2mmol) in methanol (4ml). Work-up and chromatography afforded *methyl 2-(benzylaminomethyl)-3-(2-benzyloxy-3-ethoxyphenyl)-3-hydroxypropanoate* **147c** (0.64g, 71%) as a pale yellow oil, (Found: **MH**$^+$, 450.228102. $C_{27}H_{32}O_5N$. requires *M+1*, 450.228048); γ_{max} (thin film)/cm^{-1} 3323 (OH) and 1733 (C=O); δ_H (400 MHz; $CDCl_3$) 1.49 (3H, t, *J* 7.0Hz, OCH$_2$C*H*$_3$), 2.47 (1H, m, C*H*$_A$NHCH$_2$Ph), 3.06-3.10 (2H, m, C*H*C*H*$_B$NHCH$_2$Ph), 3.64 (2H, s, CH$_2$NHC*H*$_2$Ph), 3.72 (3H, s, OCH_3), 4.10 (2H, q, *J* 6.8Hz, OC*H*$_2$CH$_3$), 4.89 and 5.24 (2H, 2xd, *J* 10.4Hz, OCH_2Ph), 5.64 (1H, s, C*H*OH) and 6.87-7.52 (13H, series of multiplets, ArH); δ_C (100 MHz; $CDCl_3$) 15.0

(OCH_2CH_3), 46.1 ($CH_2NH_2CH_2Ph$), 48.1 ($CHCO_2CH_3$), 51.9 (OCH_3), 54.1 (NH_2CH_2Ph), 64.1 (OCH_2CH_3), 72.2 (CHOH), 74.5 (OCH_2Ph), 112.2, 118.7, 123.9, 127.2, 128.0, 128.28, 128.31, 128.46, 128.50, 137.2, 137.7, 139.1, 143.9 and 151.7 (Ar-C) and 174.0 (C=O); *m/z* 450 (MH^+, 6.9%) and 91 (100).

Methyl 2-(benzylaminomethyl)-3-(2-benzyloxy-5-chlorophenyl)-3-hydroxypropanoate 147d

The procedure described for the synthesis of methyl 2-(benzylaminomethyl)-3-(2-benzyloxyphenyl)-3-hydroxypropanoate **147a** was followed, using 3-(2-benzyloxy-3-chlorophenyl)-3-hydroxy-2-methylenepropanoate **140d** (0.67g, 2mmol), benzylamine (0.22ml, 2mmol) in methanol (4ml). Work-up and chromatography afforded, as a yellow solid, *methyl 2-(benzylaminomethyl)-3-(2-benzyloxy-5-chlorophenyl)-3-hydroxypropanoate* **147d** (0.61g, 69%), m.p. 68-70^{o}C (Found: **MH**$^+$, 440.162907. $C_{25}H_{27}NO_4{}^{35}Cl$, requires: *M+1*, 440.162861); γ_{max} (KBr)/cm^{-1} 3298 (OH) and 1732 (C=O); δ_H (400 MHz; $CDCl_3$) 2.51 (1H, m, CH_ANHCH$_2$Ph), 3.05 (1H, m, C*H*CH$_2$NH), 3.14 (1H, m, CH_BNHCH$_2$Ph), 3.68 (2H, s, CH$_2$NHCH_2Ph), 3.74 (3H, s, OCH_3), 5.06 (2H, 2xd, *J* 12.0Hz, OCH_2Ph), 5.72 (1H, d, *J* 2.4Hz, C*H*OH) and 6.83-7.51 (13H, series of multiplets, ArH); δ_C (100 MHz; $CDCl_3$) 46.3 (CH_2NHCH_2Ph), 47.0 ($CHCO_2CH_3$), 52.0 (OCH_3), 54.2 ($CH_2NH_2CH_2Ph$), 70.0 (OCH_2Ph), 71.5 (CHOH), 112.7, 126.3, 126.8, 127.3, 127.4, 127.8, 127.9, 128.2, 128.5, 128.6, 133.8, 136.5, 138.7 and 153.0 (Ar-C) and 173.8 (C=O); *m/z* 440 [$MH^+(^{35}Cl)$, 1.8%] and 91 (100).

Methyl 2-(benzylaminomethyl)-3-(2-benzyloxy-5-bromophenyl)-3-hydroxy propanoate 147e

The procedure described for the synthesis of methyl 2-(benzylaminomethyl)-3-(2-benzyloxyphenyl)-3-hydroxypropanoate **147a** was followed, using 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-methylenepropanoate **140e** (0.60g, 2mmol), benzylamine (0.22ml, 2mmol) in methanol (4ml). Work-up and chromatography afforded *methyl 2-*

(benzylaminomethyl)-3-(2-benzyloxy-5-bromophenyl)-3-hydroxypropanoate **147e** (0.61g, 63%) as a yellow oil, (Found: **MH**$^+$, 484.112392. $C_{25}H_{26}NO_4{}^{79}Br$ requires *M+1*, 484.112345); γ_{max} (thin film)/cm^{-1} 3324 (OH) and 1732.3 (C=O); δ_H (400 MHz; $CDCl_3$) 2.53 (1H, m, *CH*$_A$NHCH$_2$Ph), 3.07 (1H, m, *CH*CH$_2$NHCH$_2$Ph), 3.16 (1H, ddd, *J* 1.6Hz, *J* 2.0Hz and *J* 8.0Hz, C*H*$_B$NHCH$_2$Ph), 3.69 (2H, 2xd, *J* 13.4, CH$_2$NHC*H*$_2$Ph), 3.75 (3H, s, OCH$_3$), 5.08 (2H, 2xd, *J* 11.8, OCH$_2$Ph), 5.74 (1H, s, C*H*OH), 6.80 (1H, d, *J* 8.8Hz, ArH), 7.27-7.44 (11H, series of multiplets, ArH) and 7.69 (1H, d, *J* 2.0Hz, ArH); δ_C (100 MHz; $CDCl_3$) 46.3 (*C*H$_2$NHCH$_2$Ph), 47.0 (*C*HCO$_2$CH$_3$), 52.0 (OCH$_3$), 54.2 (CH$_2$NH$_2$*C*H$_2$Ph), 69.9 (OCH$_2$Ph), 71.3 (CHOH), 113.2, 113.6, 126.9, 127.3, 127.9, 128.1, 128.4, 128.5, 130.1, 130.8, 134.1, 136.3, 138.7 and 153.5 (Ar-C) and 173.7 (C=O); *m/z* 484 [MH$^+$(^{79}Br), 3.0%] and 121 (100).

Methyl 2-(benzylaminomethyl)-3-(2-benzyloxy-3,5-dibromophenyl)-3-hydroxy propanoate 147f

The procedure described for the synthesis of methyl 2-(benzylaminomethyl)-3-(2-benzyloxyphenyl)-3-hydroxypropanoate **147a** was followed, using 3-(2-benzyloxy-3,5-dibromophenyl)-3-hydroxy-2-methylenepropanoate **140f** (0.91g, 2mmol), benzylamine (0.22ml, 2mmol) in methanol (4ml). Work-up and chromatography afforded *methyl 2-(benzylaminomethyl)-3-(2-benzyloxy-3,5-dibromophenyl)-3-hydroxy propanoate*, **147f** (0.80g, 71%) as a yellow oil, (Found: **MH**$^+$, 562.122773. $C_{25}H_{26}NO_4{}^{79}Br_2$, requires: *M+1*, 562.022856); γ_{max} (thin film)/cm^{-1} 3419 (OH) and 1747 (C=O); δ_H (400 MHz; $CDCl_3$) 2.43 (1H, dd, *J* 12.4Hz, C*H*$_A$NHCH$_2$Ph), 3.02 (1H, m, C*H*CH$_2$NH), 3.14 (1H, dd, *J* 12.4Hz and *J* 12.8Hz, CH$_B$NHCH$_2$Ph), 3.60 (2H, s, CH$_2$NHC*H*$_2$Ph), 3.70 (3H, s, OCH$_3$), 4.81 and 5.15 (2H, 2xd, *J* 10.0Hz, OCH$_2$Ph), 5.59 (1H, d, *J* 2.8Hz, *CH*OH) and 7.27-7.57 (12H, series of multiplets, ArH); δ_C (100 MHz; $CDCl_3$) 46.3 (*C*H$_2$NHCH$_2$Ph), 47.7 (*C*HCO$_2$CH$_3$), 52.1 (OCH$_3$), 54.2 (CH$_2$NH$_2$*C*H$_2$Ph), 72.1 (CHOH), 75.2 (OCH$_2$Ph), 117.9, 118.3, 127.6, 128.3, 128.48, 128.54, 128.6, 128.7, 130.0, 134.8, 136.1, 138.2, 140.6 and 151.3 (Ar-C) and 173.1 (C=O); *m/z* 562 [M$^+$(^{79}Br$_2$), 1.2%] and 91 (100).

3.2.3.2. Conjugate addition reactions with piperidine

Methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-(piperidinomethyl)propanoate 148a

A mixture of methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanoate **140a** (0.56g, 2mmol) and piperidine (0.50ml) in THF (5ml) was stirred in a stoppered reaction flask for 3 days. Excess piperidine was evaporated *in vacuo* to give a yellow oil (0.77g), which was purified by preparative layer chromatography [elution with $CHCl_3$-EtOAc (3:1)] to afford *methyl* 3-(*2-benzyloxyphenyl)-3-hydroxy-2-(piperidinomethyl)propanoate* **148a** (0.61g, 80%) as pale yellow crystals, m.p. 102-104^oC (Found: $\mathbf{M}^+$**,** 383.21036. $C_{23}H_{29}NO_4$ requires *M*, 383.20966); γ_{max} (KBr)/$_{CM}^{-1}$ 3145 (OH) and 1722 (C=O); δ_H (400 MHz; $CDCl_3$) 1.43 (2H, m, C*H*$_2$CH$_2$CH$_2$N), 1.58 (4H, m, C*H*$_2$C*H*$_2$N), 2.41 and 2.51 (4H, 2x br s, C*H*$_2$C*H*$_2$N), 2.69 (1H, d, *J* 9.2Hz, C*H*$_A$NHCH$_2$Ph), 3.00 (1H, t, *J* 11.2Hz, C*H*CH$_2$NH), 3.26 (1H, m, C*H*$_B$NHCH$_2$Ph), 3.40 (3H, s, OCH_3), 5.05 and 5.10 (2H, 2xd, *J* 12.0Hz, OCH_2Ph), 5.38 (1H, d, *J* 8.0Hz, *CH*OH), 6.90 (1H, d, *J* 8.4Hz, ArH), 6.94 (1H, t, *J* 7.2Hz, ArH) and 7.18-7.37 (7H, series of multiplets, ArH); δ_C (100 MHz; $CDCl_3$) 23.9, 25.8 and 54.8 (*C*H$_2$*C*H$_2$*C*H$_2$N), 47.3 (*C*HCO$_2$CH$_3$), 51.5 (OCH_3), 60.0 (CH$_2$N*C*H$_2$), 70.3 (OCH_2Ph), 72.9 (CHOH), 112.1, 121.0, 127.3, 127.7, 128.41, 128.43, 128.7, 130.7, 137.2 and 155.9 (Ar-C) and 172.6 (C=O); *m/z* 383 (M^+, 1.0%) and 91 (100).

Methyl 3-(2-benzyloxy-3-methoxyphenyl)-3-hydroxy-2(piperidinomethyl)propanoate 148b

The procedure described for the synthesis of methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-(piperidinomethyl)propanoate **148a** was followed, using 3-(2-benzyloxy-3-methoxyphenyl)-3-hydroxy-2-methylenepropanoate **140b** (0.66g, 2mmol) and piperidine (0.50ml) in THF (5ml). Work-up and chromatography afforded, as a pale yellow oil, *methyl 3-(2-benzyloxy-3-methoxyphenyl)-3-hydroxy-2-(piperidinomethyl)-propanoate* **148b** (0.46g, 55%) (Found: $\mathbf{M}^+$, 413.22071. $C_{24}H_{31}NO_5$ requires *M*, 413.22022); γ_{max} (thin film)/cm^{-1} 3366 (OH) and 1732 (C=O); δ_H (400 MHz; $CDCl_3$) 1.42 (2H, m, C*H*$_2$CH$_2$CH$_2$N), 1.57 (4H, m, C*H*$_2$CH$_2$N), 2.37 and 2.53 (4H, 2x br s,

CH_2CH_2N), 2.64 (1H, d, *J* 12Hz, $CHCH_ANCH_2$), 2.96 (1H, t, *J* 10.8, $CHCH_BNCH_2$), 3.21 (1H, m, $CHCO_2CH_3$), 3.40 and 3.88 (6H, 2xs, OCH_3), 4.97 and 5.13 (2H, 2xd, *J* 10.8Hz, OCH_2Ph), 5.31 (1H, d, *J* 8.4Hz, CHOH), 6.85 (1H, dd, *J* 7.2Hz and *J* 7.2Hz, Ar-H), 7.02-7.38 (5H, series of multiplets, Ar-H) and 7.52 (2H, d, *J* 7.2Hz, Ar-H); δ_C (100 MHz; $CDCl_3$) 23.9, 25.9 and 54.7 ($CH_2CH_2CH_2N$), 47.5 ($CHCO_2CH_3$), 51.5 and 55.8 ($2xOCH_3$), 60.4 ($CHCH_2N$), 73.3 (CHOH), 74.8 (OCH_2Ph), 111.8, 120.2, 124.0, 127.6, 127.9, 128.2, 136.0, 138.2, 145.7 and 152.7 (Ar-C) and 172.4 (C=O); *m/z* 413 (M^+, 1.3%) and 99 (100).

Methyl 3-(2-benzyloxy-3-ethoxyphenyl)-3-hydroxy-2-(piperidinomethyl)prop - anoate 148c

The procedure described for the synthesis of methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-(piperidinomethyl)propanoate **148a** was followed, using 3-(2-benzyloxy-3-ethoxyphenyl)-3-hydroxy-2-methylenepropanoate **140c** (0.69g, 2mmol) and piperidine (0.50ml) in THF (5ml). Work-up and chromatography afforded, as a pale yellow oil, *methyl 3-(2-benzyloxy-3-ethoxyphenyl)-3-hydroxy-2-(piperidinomethyl)-propanoate* **148c** (0.50g , 58%) (Found: $\mathbf{M}^+$, 427.23545. $C_{25}H_{33}NO_5$ requires *M*, 427.23587); γ_{max} (thin film)/cm^{-1} 3419 (OH) and 1731 (C=O); δ_H (400 MHz; $CDCl_3$) 1.47 (5H, overlapping signals, OCH_2CH_3 and $CH_2CH_2CH_2N$), 1.54 (4H, m, $CH_2CH_2CH_2N$), 2.37 (2H, br s, $CH_2CH_2CH_2N$), 2.53 (2H, m, $CH_2CH_2NCH_2$), 2.64 and 2.99 (2H, dd, *J* 3.6Hz and *J* 9.6Hz, $CHCH_2N$), 3.21 (1H, m, $CHCO_2CH_3$), 3.40 (3H, s, OCH_3), 4.06 (2H, q, *J 7.2*Hz, OCH_2CH_3), 4.98 and 5.13 (2H, 2xd, *J* 10.8Hz, OCH_2Ph), 5.30 (1H, d, *J* 8.0Hz, CHOH) and 6.84-7.53 (8H, series of multiplets, Ar-H); δ_C (100 MHz; $CDCl_3$) 15.0 (OCH_2CH_3), 23.9, 25.9 and 54.7 ($CH_2CH_2CH_2N$), 47.4 ($CHCO_2CH_3$), 51.5 (OCH_3), 60.3 (CH_2N), 64.2 (OCH_2CH_3), 73.4 (CHOH), 74.8 (OCH_2Ph), 113.0, 120.1, 123.9, 127.6, 128.1, 128.2, 136.1, 138.3, 146.0 and 152.0 (Ar-C) and 172.5 (C=O); *m/z* 427 (M^+, 1.2%) and 99 (100).

Methyl 3-(2-benzyloxy-5-chlorophenyl)-3-hydroxy-2-(piperidinomethyl)propan - oate 148d

The procedure described for the synthesis of methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-(piperidinomethyl)propanoate **148a** was followed, using 3-(2-benzyloxy-5-chlorophenyl)-3-hydroxy-2-methylenepropanoate **140d** (0.67g, 2mmol) and piperidine (0.50ml) in THF (5ml). Work-up and chromatography afforded, as a pale yellow oil, *methyl 3-(2-benzyloxy-5-chlorophenyl)-3-hydroxy-2-(piperidinomethyl)propanoate* **148d** (0,67g, 63%) (Found: $\mathbf{M}^+$, 417.17090. $C_{23}H_{28}NO_4{}^{35}Cl$ requires *M*, 417.17069); γ_{max} (thin film)/cm^{-1} 3347 (OH) and 1714 (C=O); δ_H (400 MHz; $CDCl_3$) 1.43 (2H, m, C*H*$_2$CH$_2$CH$_2$N), 1.58 (4H, m, C*H*$_2$CH$_2$N), 2.40 and 2.52 (4H, 2x br s, CH$_2$C*H*$_2$N), 2.64 and 2.99 (2H, 2xdd, *J* 12.8Hz and *J* 12.6Hz, CHC*H*$_2$N), 3.11 (1H, m, C*H*CO$_2$CH$_3$), 3.42 (3H, s, OCH$_3$), 5.04 (2H, 2x d, *J* 11.8Hz , OCH$_2$Ph), 5.41 (1H, d, *J* 7.6Hz, C*H*OH), 6.81(1H, d, *J* 8.8Hz, Ar-H) and 7.13-7.46 (7H, series of multiplets, Ar-H); δ_C (100 MHz; $CDCl_3$) 23.9, 25.9 and 54.8 (CH$_2$CH$_2$CH$_2$N), 47.3 (*C*HCO$_2$CH$_3$), 51.5 (OCH$_3$), 59.9 (CH*C*H$_2$N), 70.5 (OCH$_2$Ph), 71.9 (CHOH), 113.2, 126.1, 127.2, 127.9, 128.2, 128.4, 128.5, 132.8, 136.7 and 154.3 (Ar-C) and 172.2 (C=O); *m/z* 417 [$M^+(Cl^{35})$, 1.2%] and 98 (100).

Methyl 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-(piperidinomethyl)propanoate 148e

The procedure described for the synthesis of methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-(piperidinomethyl)propanoate **148a** was followed, using methyl 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-methylenepropanoate **140e** (0.75g,2mmol) and piperidine (0.50ml) in THF (5ml). Work-up and chromatography afforded, as a pale yellow oil, *methyl 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-(piperidinomethyl) propanoate* **148e** (0.60g, 62%) (Found: $\mathbf{M}^+$, 461.12015. $C_{23}H_{28}NO_4{}^{79}Br$ requires *M*, 461.12017); γ_{max} (thin film)/cm^{-1} 3419 (OH) and 1732 (C=O); δ_H (400 MHz; $CDCl_3$) 1.43 (2H, m, C*H*$_2$CH$_2$CH$_2$N), 1.57 (4H, m, C*H*$_2$CH$_2$N), 2.39-2.51 (4H, 2x br s, CH$_2$C*H*$_2$N), 2.64 (1H, m, CHC*H*$_A$N), 2.99 (1H, t, *J* 10.8Hz, CHC*H*$_B$N), 3.10 (1H, m, C*H*CO$_2$CH$_3$), 3.42 (3H, s, OCH$_3$), 5.03 (2H, 2xd, *J* 11.8Hz, OCH$_2$Ph), 5.41 (1H, d, *J* 7.6Hz, C*H*OH), 6.75 (1H, d, *J* 8.4Hz, Ar-H), 7.27-7.42 (6H,

series of overlapping signals, Ar-H) and 7.53 (1H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 23.9, 25.8 and 54.7 ($CH_2CH_2CH_2N$), 47.3 ($CHCO_2CH_3$), 51.5 (OCH_3), 59.8 ($CHCH_2N$), 70.4 (OCH_2Ph), 71.8 (CHOH), 113.4, 113.6, 127.1, 127.9, 128.5, 131.15, 131.17, 133.2, 136.6 and 154.7 (Ar-C) and 172.1 (C=O); *m/z* 461 [$M^+(^{79}Br)$, 3.4%] and 99 (100).

Methyl 3-(2-benzyloxy-3,5-dibromophenyl)-3-hydroxy-2-(piperidinomethyl)-propanoate 148f

The procedure described for the synthesis of methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-(piperidinomethyl)propanoate **148a** was followed, using 3-(2-benzyloxy-3,5-dibromophenyl)-3-hydroxy-2-methylenepropanoate **140f** (0.91g, 2mmol) and piperidine (0.50ml) in THF (5ml). Work-up and chromatography afforded, as a pale yellow oil, *methyl 3-(2-benzyloxy-3,5-dibromophenyl)-3-hydroxy-2-(piperidino-methyl)propanoate* **148f** (0.73g, 65%) (Found: $\mathbf{M}^+$, 539.02614. $C_{23}H_{27}NO_4{}^{79}Br_2$ requires *M*, 539.03068); γ_{max} (thin film)/cm^{-1} 3412 (OH) and 1732 (C=O); δ_H (400 MHz; $CDCl_3$) 1.44 (2H, m, $CH_2CH_2CH_2N$), 1.56 (4H, m, CH_2CH_2N), 2.38 and 2.56 (4H, 2x br s, CH_2CH_2N), 2.63 (1H, d, *J* 10.8Hz, $CHCH_AN$), 3.02 (2H, series of multiplets, $CHCH_BN$ and $CHCO_2CH_3$), 3.42 (3H, s, OCH_3), 4.91 and 5.12 (2H, 2xd, *J* 10.4Hz, OCH_2Ph), 5.24 (1H, d, *J* 8.0Hz, CHOH), 7.33-7.53 (5H, series of multiplets, Ar-H), 7.59 (1H, d, *J* 2.0Hz, Ar-H) and 7.65 (1H, d, *J* 2.4Hz, Ar-H); δ_C (100 MHz; $CDCl_3$) 23.8, 25.8 and 54.8 ($CH_2CH_2CH_2N$), 47.3 ($CHCO_2CH_3$), 51.8 (OCH_3), 60.4 ($CHCH_2N$), 73.1 (CHOH), 75.5 (OCH_2Ph), 117.6, 118.4, 127.9, 128.1, 128.4, 130.9, 135.1, 136.9, 139.6 and 152.8 (Ar-C) and 171.5 (C=O); *m/z* 539 [$M^+(^{79}Br_2)$, 0.4%] and 99 (100).

3.2.4. Synthesis of coumarins *via* conjugate addition products

3-(Benzylaminomethyl)coumarin 149a

A mixture of methyl 2-(benzylaminomethyl)-3-(2-benzyloxyphenyl)-3-hydroxy-propanoate **147a** (490mg, 1.21mmol) and pre-equilibriated 10% Pd-C catalyst (84mg) in 95% EtOH (6.7ml) was hydrogenated at room temperature and atmospheric pressure. Hydrogen absorption ceased after the uptake of one equivalent of hydrogen. The mixture was filtered and the solvent removed *in vacuo* to give the crude mixture (360mg), as a pale yellow oil, which was purified using preparative layer chromatography [elution with $CHCl_3$-EtOAc (3:1)] to afford, as a pale yellow solid, *3-(benzylaminomethyl)coumarin* **149a** (170mg, 53%), m.p. 70-74^oC (Found: $\mathbf{M}^+$, 265.10796. $C_{17}H_{15}O_2N$ requires *M*, 265.11028); γ_{max} (KBr)/cm^{-1} 3323 (N-H) and 1713 (C=O); δ_H (400 MHz; $CDCl_3$) 1.98 (1H, br s, NH), 3.76 (2H, d, *J* 1.2Hz, 1'-CH_2), 3.86 (2H, s, CH_2Ph), 7.23-7.51 (9H, series of overlapping signals, Ar-H) and 7.72 (1H, s, 4-H);† δ_C (100 MHz; $CDCl_3$) 48.3 and 53.2 (2xCH_2), 116.4, 119.2, 124.3, 127.0, 127.4, 127.5, 128.1, 128.4, 130.9, 139.1, 139.7 and 153.1 (ArC) and 161.4 (C=O); *m/z* 265 (M^+, 0.9%) and 174 (100).

3-(Benzylaminomethyl)-8-methoxycoumarin 149b

The procedure described for the synthesis of 3-(benzylaminomethyl)coumarin **149a** was followed, using methyl 2-(benzylaminomethyl)-3-(2-benzyloxy-3-methoxy-phenyl)-3-hydroxypropanoate **147b** (550mg, 1.26mmol) and pre-equilibriated 10% Pd-C catalyst (84mg) in absolute EtOH (6.7ml). Work-up and chromatography afforded, as a pale yellow oil, *3-(benzylaminomethyl)-8-methoxycoumarin* **149b** (0.19g, 51%) (Found: $\mathbf{M}^+$, 295.11855. $C_{18}H_{17}O_3N$ requires *M*, 295.12084); γ_{max} (KBr)/cm^{-1} 3394 (N-H) and 1714 (C=O); δ_H (400 MHz; $CDCl_3$) 1.88 (1H, br s, NH), 3.76 (2H, d, *J* 1.2Hz, 1'-CH_2), 3.84 (2H, s, CH_2Ph), 3.95 (3H, s, OCH_3), 7.04 (2H, d, *J* 8.0Hz, Ar-H), 7.17-7.36 (6H, series of multiplets, Ar-H) and 7.69 (1H, s, 4-H);†

†coupling to the 1'CH_2 group is evident in the COSY spectrum.

δ_C (100 MHz; $CDCl_3$) 48.4 and 53.2 ($2xCH_2$), 56.3 (OCH_3), 113.0, 119.1, 120.0, 124.3, 127.1, 127.7, 128.2, 128.5, 139.3, 139.7, 142.9 and 147.1 (Ar-C) and 160.9 (C=O); *m/z* (FAB) 296 (MH^+, 100%).

3-(Benzylaminomethyl)-8-ethoxycoumarin 149c

The procedure described for the synthesis of 3-(benzylaminomethyl)coumarin **149a** was followed, using methyl 2-(benzylaminomethyl)-3-(2-benzyloxy-3-ethoxy-phenyl)-3-hydroxypropanoate **147c** (550mg, 1.22mmol) and pre-equilibriated 10% Pd-C catalyst (84mg) in absolute EtOH (6.7ml). Work-up and chromatography afforded, as a pale yellow solid *3-(benzylaminomethyl)-8-ethoxycoumarin* **149c** (250mg, 66%), m.p. 98-102^{o}C (Found: $\mathbf{M}^+$, 309.13649. $C_{19}H_{19}NO_3$ requires *M*, 309.13649); γ_{max}(KBr)/cm^{-1} 3300 (N-H) and 1712 (C=O); δ_H (400MHz; $CDCl_3$) 1.49 (3H, t, *J* 6.8Hz, $OCH_2\mathit{CH_3}$), 2.00 (1H, br s, NH), 3.76 (2H, d, *J* 0.8Hz, 1'-CH_2), 3.84 (2H, s, CH_2Ph), 4.20 (2H, q, *J* 6.8Hz, $O\mathit{CH_2}CH_3$), 7.01-7.36 (8H, series of multiplets, Ar-H) and 7.68 (1H, d, *J* 0.8Hz, 4-H);† δ_C (100 MHz; $CDCl_3$) 14.7 ($OCH_2\mathit{C}H_3$), 48.4 and 53.2 ($2xCH_2N$), 64.9 ($O\mathit{C}H_2CH_3$), 114.3, 119.0, 120.0, 124.2, 127.0, 127.5, 128.1, 128.4, 139.3, 139.8, 143.1 and 146.4 (Ar-C) and 161.0 (C=O); *m/z* (FAB) 310 (MH^+, 100%).

3-(Benzylaminomethyl)-6-chlorocoumarin 149d

The procedure described for the synthesis of 3-(benzylaminomethyl)coumarin **149a** was followed, using methyl 2-(benzylaminomethyl)-3-(2-benzyloxy-5-chloro-phenyl)-3-hydroxypropanoate **147d** (540mg, 1.23mmol) and pre-equilibriated 10% Pd-C catalyst (84mg) in absolute EtOH (6.7ml). Work-up and chromatography afforded, as a yellow solid, *3-(benzylaminomethyl)-6-chlorocoumarin* **149d** (180mg, 49%), m.p. 106-110^{o}C (Found: $\mathbf{M}^+$, 298.06348. $C_{17}H_{13}O_3NCl^{35}$ requires *M-1*, 298.06348); γ_{max} (KBr)/cm^{-1} 3322 (N-H) and 1719 (C=O); δ_H (400 MHz; $CDCl_3$) 1.82 (1H, br s, NH), 3.75 (2H, d, *J* 0.6Hz, 1'-CH_2), 3.85 (2H, s, CH_2Ph), 7.23-7.45 (8H, series of multiplets, Ar-H) and 7.69 (1H, s, 4-H);† δ_C (100 MHz; $CDCl_3$) 48.1 and

53.7 (2xCH_2N), 117.8, 120.3, 126.7, 127.1, 128.0, 128.4, 128.8, 129.5, 130.8, 137.7, 139.6 and 151.4 (Ar-C) and 160.7 (C=O); *m/z* 298 [MH^+ (Cl^{35}), 96.1%] and 91 (100).

3-(Piperidinomethyl)coumarin 150a and 3-methylcoumarin 151a

A mixture of methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-(piperidinomethyl)-propanoate **148a** (466mg, 1.22mmol) and pre-equilibriated 10% Pd-C catalyst (84mg) in absolute EtOH (6.7ml) was hydrogenated at room temperature and atmospheric pressure for 6h. The resulting mixture was filtered and the solvent removed *in vacuo* to give a pale yellow oil (380mg), which was purified by preparative layer chromatography [elution with $CHCl_3$-EtOAc (3:1)] to afford the following two products:-

i) ***3-(piperidinomethyl)coumarin*** **150a,** as a brown solid (150mg, 51%), m.p. 66-68°C (Found: $\mathbf{M}^+$, 243.12588. $C_{15}H_{17}O_2N$ requires *M*, 243.12593); γ_{max} (KBr)/ cm^{-1} 1723 (C=O); δ_H (400 MHz; $CDCl_3$) 1.46 (2H, m, C*H*$_2$$CH_2CH_2N$), 1.59 (4H, m, C*H*$_2$$CH_2N$), 2.48 (4H, br s, CH_2C*H*$_2$N), 3.42 (2H, d, *J* 0.4Hz, 1'-CH_2), 7.23-7.49 (4H, series of multiplets, ArH) and 7.78 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$) 24.1, 25.9 and 54.7 ($CH_2CH_2CH_2N$), 56.9 (1'-CH_2), 116.3, 119.3, 124.2, 126.0, 127.5, 130.7, 139.4 and 152.9 (Ar-C) and 161.6 (C=O); *m/z* 243 (M^+, 62.9%) and 200 (100); and

ii) ***3-methylcoumarin*** **151a,** as a pale yellow solid (40mg, 20%), m.p. 92-94°C (lit.,[210] 90-92°C) (Found: M^+, 160.05272. $C_{10}H_8O_2$ requires: *M*, 160.05243); γ_{max} (KBr)/cm^{-1} 1707 (C=O); δ_H (400 MHz; $CDCl_3$) 2.22 (3H, s, CH_3), 7.23-7.48 (4H, multiplets, Ar-H) and 7.52 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$) 17.1 (CH_3), 116.4, 119.5, 124.2, 125.7, 126.9, 130.4, 139.2, 153.2 and 162.2 (Ar-C); *m/z* 160 (M^+, 82.1%) and 131(100).

8-Methoxy-3-(piperidinomethyl)coumarin 150b and 8-methoxy-3-methyl coumarin 151b

The procedure described for the synthesis of 3-(piperidinomethyl)coumarin **150a** and 3-methylcoumarin **151a** was followed, using methyl 3-(2-benzyloxy-3-methoxy-phenyl)-3-hydroxy-2-(piperidinomethyl)propanoate **148b** (503mg, 1.22mmol) and

pre-equilibriated 10% Pd-C catalyst (84mg) in absolute EtOH (6.7ml). Work-up and chromatography afforded:-

i) ***8-methoxy-3-(piperidinomethyl)coumarin*** **150b,** as a pale yellow oil (150mg, 45%) (Found: $\mathbf{M}^+$, 273.13684. $C_{16}H_{19}O_3N$ requires *M*, 273.13649); γ_{max} (thin film)/cm^{-1} 1714 (C=O); δ_H (400 MHz; $CDCl_3$) 1.45 (2H, m, C*H*$_2$$CH_2CH_2N$), 1.60 (4H, m, C*H*$_2$$CH_2N$), 2.47 (4H, t. *J* 7.2Hz, CH_2C*H*$_2$N), 3.42 (2H, d, *J* 1.6Hz, 1'-CH_2), 3.93 (3H, s, OCH_3), 7.02 (1H, d, *J* 8.8Hz, ArH), 7.06 (1H, d, *J* 7.6Hz, ArH), 7.18 (1H, t, *J* 7.8Hz, ArH) and 7.77 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$) 24.1, 26.0 and 54.7 ($CH_2CH_2CH_2N$), 56.2 (OCH_3), 56.9 (1'-CH_2), 112.7, 119.1, 120.1, 124.1, 126.3, 139.7, 142.7 and 147.0 (Ar-C) and 161.1 (C=O); *m/z* 273 (M^+, 91.2%) and 230 (100); and

ii) ***8-methoxy-3-methylcoumarin*** **151b,** as a grey solid (22mg, 9.5%), m.p. 68- 72^{o}C (Found: $\mathbf{M}^+$, 190.06299. $C_{11}H_{10}O_3$ requires *M*, 190.06299); γ_{max} (KBr)/cm^{-1} 1716 (C=O); δ_H (400 MHz; $CDCl_3$) 2.20 (3H, s, CH_3), 3.94 (3H, s, OCH_3), 7.01 (2H, t, *J* 8.4Hz, ArH), 7.18 (1H, t, *J* 8.0Hz, ArH) and 7.48 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$) 17.2 (CH_3), 56.2 (OCH_3), 112.4, 118.4, 120.2, 124.1, 126.1, 139.3, 142.9 and 147.0 (ArC) and 161.6 (C=O); *m/z* 190 (M^+, 100%).

8-Ethoxy-3-(piperidinomethyl)coumarin 150c and 8-ethoxy-3-methylcoumarin 151c

The procedure described for the synthesis of 3-(piperidinomethyl)coumarin **150a** and 3-methylcoumarin **151a** was followed, using methyl 3-(2-benzyloxy-3-ethoxyphenyl)-3-hydroxy-2-(piperidinomethyl)propanoate **148c** (520mg, 1.22 mmol) and pre-equilibriated 10% Pd-C catalyst (84mg) in absolute EtOH (6.7ml). Work-up and chromatography afforded:-

i) ***8-ethoxy-3-(piperidinomethyl)coumarin*** **150c**, as a pale yellow oil (170mg, 49%) (Found: $\mathbf{M}^+$, 287.15293. $C_{17}H_{21}O_3N$ requires *M*, 287.15214); γ_{max} (thin film)/cm^{-1} 1731 (C=O); δ_H (400 MHz; $CDCl_3$) 1.47 (5H, m, OCH_2C*H*$_3$ and C*H*$_2$$CH_2CH_2N$), 1.62 (4H, m, C*H*$_2$$CH_2N$), 2.49 (4H, t, *J* 4.8Hz, CH_2C*H*$_2$N), 3.45 (2H, s, 1'-CH_2), 4.17 (2H, q, *J* 7.0Hz, OC*H*$_2$$CH_3$), 7.02 and 7.05 (2H, 2x d, *J* 8Hz and *J* 7.6Hz, ArH), 7.17 (1H,

t, *J* 8Hz, ArH) and 7.77 (1H, s, 4-H); δ_C (100 MHz, $CDCl_3$) 14.8 (OCH_2CH_3), 24.2, 26.0 and 54.7 ($CH_2CH_2CH_2N$), 56.9 (1'-CH_2), 65.0 (OCH_2CH_3), 114.3, 119.1, 120.3, 124.1, 126.3, 139.8, 143.1 and 146.4 (Ar-C) and 161.3 (C=O); *m/z* 287 (74.4%) and 176 (100); and

ii) ***8-ethoxy-3-methylcoumarin*** **151c**, as a pale yellow oil (35mg, 14%) (Found: $\mathbf{M}^+$, 204.07884. $C_{12}H_{12}O_3$ requires *M*, 204.07864); γ_{max} (thin film)/cm^{-1} 1714 (C=O); δ_H (400 MHz; $CDCl_3$) 1.47 (3H, t, *J* 7.0Hz, CH_2CH_3), 2.19 (3H, d, *J* 1.2Hz, 3-CH_3), 4.16 (2H, q, *J* 6.8Hz, OCH_2CH_3), 6.95 and 6.98 (2H, 2xdd, *J* 1.2Hz and *J* 8.0Hz, ArH), 7.15 (1H, t, *J* 8.0Hz, ArH) and 7.47 (1H, d, *J* 1.2Hz, ArH); δ_C (100 MHz; $CDCl_3$) 14.7 (OCH_2CH_3), 17.1 (3-CH_3), 64.8 (OCH_2CH_3), 113.7, 118.4, 120.3, 124.0, 125.9, 139.4, 143.1 and 146.3 (Ar-C) and 161.8 (C=O); *m/z* 204 (M^+, 59.1%) and 176 (100).

6-Chloro-3-(piperidinomethyl)coumarin 150d and 6-chloro-3-methylcoumarin 151d

The procedure described for the synthesis of 3-(piperidinomethyl)coumarin **150a** and 3-methylcoumarin **151a** was followed, using methyl 3-(2-benzyloxy-5-chlorophenyl)-3-hydroxy-2-(piperidinomethyl)propanoate **148d** (508mg, 1.22mmol) and pre-equilibriated 10% Pd-C catalyst (84mg) in absolute EtOH (6.7ml). Work-up and chromatography afforded:-

i) ***6-chloro-3-(piperidinomethyl)coumarin*** **150d,** as a pale yellow solid (205mg, 61%), m.p. 116-118^oC (Found: $\mathbf{M}^+$, 277.08708. $C_{15}H_{16}O_2N^{35}Cl$ requires *M*, 277.08696); γ_{max}(KBr)/cm^{-1} 1724 (C=O); δ_H (400 MHz; $CDCl_3$) 1.47 (2H, m, $CH_2CH_2CH_2N$), 1.63 (4H, m, CH_2CH_2N), 2.48 (4H, t, *J* 4.8Hz, CH_2CH_2N), 3.42 (2H, d, *J* 1.6Hz, 1'-CH_2), 7.26 (1H, t, *J* 4.6Hz, ArH), 7.40 and 7.42 (1H, 2x d, *J* 2.4 Hz and *J* 2.8Hz, ArH), 7.48 (1H, d, *J* 2.4Hz, ArH) and 7.72 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$) 24.2, 26.1 and 54.8 ($CH_2CH_2CH_2N$), 57.0 (1'-CH_2), 117.8, 120.6, 126.9, 127.8, 129.5, 130.7, 138.0 and 151.4 (ArC) and 161.0 (C=O); *m/z* 277 [M^+ (^{35}Cl), 52.3%) and 234 (100); and

ii) 6-chloro-3-methylcoumarin 151d, as a pale yellow solid (22mg, 9%), m.p. 70-72^oC (lit.,[210] 158-160^oC) (Found: $\mathbf{M}^+$, 194.01329. Calc. for $C_{10}H_7O_2{}^{35}Cl$ *M*, 194.01346); γ_{max} (KBr)/cm^{-1} 1707 (C=O); δ_H (400 MHz; $CDCl_3$) 2.21 (3H, s, CH_3)

and 7.22-7.42 (4H, series of multiplets, Ar-H); δ_C (100 MHz; $CDCl_3$) 17.3 (CH_3), 117.9, 120.6, 126.2, 127.3, 126.5, 130.4, 137.9 and 151.6 (Ar-C) and 161.6 (C=O); *m/z* 194 [M^+ (^{35}Cl), 100%].

Investigation of the preparation of 3-methylcoumarin 151a from 3-(piperidino-methyl)coumarin 150a

Method 1

A solution of 3-(piperidinomethyl)coumarin **150a** (20mg, 0.08mmol) in CD_3OD (0.5ml) in an NMR tube was examined regularly by ^1H NMR analysis over a period of 43 days, with no evidence of the formation of the 3-methylcoumarin.. Evaporation of the solvent afforded a crude product, which was purified by preparative layer chromatography [elution with $CHCl_3$-EtOAc (3:1)] to give the starting material, 3-(piperidinomethyl)coumarin **150a**.

Method 2

Conc. HCl (1drop) was added to a solution of 3-(piperidinomethyl)coumarin **150a** (20mg, 0.08mmol) in CD_3OD (0.5ml) in an NMR tube and the solution was analysed regularly for several days by ^1H NMR spectroscopy, with no evidence of the formation of 3-methylcoumarin **151a**. Evaporation of the solvent afforded a crude product, which was purified by preparative layer chromatography [elution with $CHCl_3$-EtOAc (3:1)] to give the starting material, 3-(piperidinomethyl)coumarin **150a**.

Method 3

To a mixture of 3-(piperidinomethyl)coumarin **150a** (260mg, 0.5mmol), formic acid (0.12ml) and Et_3N (0.6ml) was added pre-equilibriated 10% Pd-C catalyst (1.2mg), and the resulting mixture was stirred under a reflux condenser for 72h at 25^{o}C. The mixture was filtered and the solvent removed *in vacuo* to give a crude product (70mg), which was purified by preparative layer chromatography [elution with $CHCl_3$-EtOAc (3:1)] to afford the starting material, 3-(piperidinomethyl)coumarin **150a**.

Method 4

A mixture of 3-(piperidinomethyl)coumarin **150a** (150mg, 0.61mmol) and pre-equilibriated 10% Pd-C catalyst (42mg) in absolute EtOH (4ml) was hydrogenated at room temperature and atmospheric pressure for 6h. The resulting mixture was filtered and the solvent removed *in vacuo* to give 3-methylcoumarin **151a** (90mg, 92%), as a pale yellow solid.

3.2.5. Miscellaneous reactions

6-Bromo-3-methylcoumarin 151e

The procedure (method 1) described for the synthesis of 3-(iodomethyl)coumarin **155a** was followed, using conc. HI (10ml) and methyl 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-methylenepropanoate **140e** (0.46g, 1.0mmol) in a mixture of AcOH (5ml) and Ac_2O (5ml). Work-up afforded, as a yellow solid, *6-bromo-3-methylcoumarin* **150e** (0.16g, 65%), m.p. 152-154^oC (Found: $\mathbf{M}^+$, 237.96430. $C_{10}H_70_2{}^{79}Br$ require *M*, 237.96294); γ_{max} (KBr)/cm^{-1} 1728 (C=O); δ_H (400 MHz; $CDCl_3$) 2.21 (3H, d, *J* 1.2Hz, CH_3), 7.19 (1H, dd, *J* 2.2Hz and *J* 7.2Hz, Ar-H), 7.42 (1H, d, *J* 0.8Hz, Ar-H) and 7.53 (2H, dd, *J* 2.4Hz and *J* 2.0Hz, Ar-H); δ_C (100 MHz; $CDCl_3$) 17.2 (CH_3), 116.8, 118.17, 118.2, 121.1, 127.3, 129.2, 133.2, 137.7 (Ar-C) and 152.1 (C=O); *m/z* 238 [M^+(^{79}Br), 0.3%] and 92 (100).

Methyl 3-(2-benzyloxyphenyl)-2-methylpropenoate 152

A solution of methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanoate **140a** (0.30g, 1mmol) in ethanol (4ml) was stirred under N_2, in a two-necked round - bottomed flask, immersed in a water bath at 25^oC. Pre-equilibrated 10% Pd/ C catalyst (84mg) was then added, followed by 1,4–cyclohexadiene (0.94ml, 10mmol). The mixture boiled under reflux for 2h and then filtered through celite. The solid residue was washed with ethanol (*ca* 5ml), and the filtrate and the washings were combined and evaporated *in vacuo* to afford a crude residue (0.25g), which was purified using preparative layer chromatography [elution with hexane-EtOAc (3:1)] to afford, as a

yellow oil, *methyl 3-(2-benzyloxyphenyl)-2-methylpropenoate* **152** (50mg, 18%) (Found: $\mathbf{M}^+$, 282.12610. $C_{18}H_{18}O_3$ requires *M*, 282.12559); γ_{max} (thin film)/cm^{-1} 1711 (C=O); δ_H (400 MHz; $CDCl_3$) 2.08/2.12‡(3H, 2xd, *J* 1.6Hz and *J* 1.6Hz, CH_3C=C), 3.59/3.82‡(3H, 2xs, OCH_3), 5.10/5.14‡ (2H, 2xs, OCH_2Ph), 6.90-7.44 (9H, series of multiplets, Ar-H) and 7.95 (1H, br s, Ar-H); δ_C (100 MHz; $CDCl_3$) 14.2/21.3‡ (CH_3), 51.3/51.9†(OCH_3), 70.2 (OCH_2Ph), 112.5, 120.5, 127.0, 127.8, 128.5, 129.0, 129.7, 130.3, 131.5, 135.0, 136.9 and 156.7 (Ar-C) and 169.1 (C=O); *m/z* 282 (M^+, 15%) and 92 (100).

Methyl 3-(2-hydroxyphenyl)-2-methylpropanoate 153

A mixture of methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanoate **140a** (0.36g, 1.2mmol) and pre-equilibriated 10% Pd-C catalyst (84mg) in absolute EtOH (6.7ml) was hydrogenated at room temperature and atmospheric pressure for 6h. The mixture was filtered and the solvent removed *in vacuo* to give a yellow oil (204mg), which was purified by flash chromatography [elution with hexane-EtOAc (3:1.5)], followed by extraction with acetone to afford, as a pale yellow oil, *methyl 3-(2-hydroxyphenyl)-2-methylpropanoate* **153** (186mg, 80%) (Found: $\mathbf{M}^+$, 194.09567. $C_{11}H_{14}O_3$ requires *M*, 194.09429); γ_{max} (thin films)/cm^{-1} 3396 (0H) and 1709 (C=O); δ_H (400 MHz; $CDCl_3$) 1.26 (3H, d, *J* 7.2Hz, 2-CH_3), 2.70 (1H, dd, *J* 4.8 and 13.6Hz, CH_AH), 2.86 (1H, m, $CHCH_3$), 3.01 (1H, dd, *J* 8.8 and *J* 13.6 Hz, CH_BH), 3.65 (3H, s, OCH_3), 6.84 (2H, m, ArH), 6.92 (1H, br s, ArOH) and 7.05-7.11 (2H, m, ArH); δ_C (100 MHz; $CDCl_3$) 17.9 ($CHCH_3$), 33.5 (CH_2), 40.7 ($CHCH_3$), 52.1 (OCH_3), 116.8, 120.5, 125.8, 127.9, 131.2, 154.2 (Ar-C) and 178.7 (C=O); *m/z* 194 (M^+, 11.5%) and 162 (100).

‡ Chemical shift data reported in this format reflect the presence of geometric isomers.

3-(Ethylsulfanylmethyl)coumarin 154

To a solution of methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanoate **140a** (0.22g, 0.72mmol) in EtSH (2ml) was added $BF_3.Et_2O$ (1ml, 8mmol), and the resulting mixture was stirred at room temperature for 40min. The reaction mixture was then poured into water and extracted with diethyl ether. The combined organic fractions were washed with satd. brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford an oil (0.54g), which was purified using preparative layer chromatography [elution with hexane-EtOAc (3:1)] to afford, as a yellow solid, *3-(ethylsulfanylmethyl)coumarin* **154** (15mg, 10%), m.p. 68-72^oC (Found: $\mathbf{M}^+$, 220.05715. $C_{12}H_{12}O_2S$ requires *M*, 220.05580); γ_{max} (KBr)/cm^{-1} 1720 (C=O); δ_H (400 MHz; $CDCl_3$) 1.29 (3H, t, *J* 7.4Hz, $SCH_2C\mathit{H_3}$), 2.58 (2H, q, *J* 7.4Hz, $SC\mathit{H_2}CH_3$), 3.66 (2H, s, CH_2S), 7.27 (1H, d, *J* 7.6Hz, Ar-H), 7.33 (1H, d, *J* 8Hz, Ar-H), 7.48 (2H, t, *J* 8.0 Hz, Ar-H) and 7.71 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$) 14.4 ($SCH_2\mathit{C}H_3$), 26.3 and 30.8 ($\mathit{C}H_2S\mathit{C}H_2CH_3$) 116.6, 119.2, 124.4, 126.4, 127.5, 131.2, 139.4, 153.3 (Ar-C) and 161.0 (C=O); *m/z* (FAB) 220 (MH^+, 37%) and 160 (100).

3.2.5. Synthesis of coumarins *via* acid-catalysed reactions of *O*-benzylated Baylis-Hillman products

3-(Iodomethyl)coumarin 155a

Method 1

Conc. HI (10ml) was added to a solution of methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanoate **140a** (0.31g, 1.0mmol) in a mixture of AcOH (5ml) and Ac_2O (5ml). The mixture was boiled under reflux for 2h, allowed to cool to room temperature and then poured into ice-cooled water (10ml). Stirring for 30min (or more) gave a precipitate, which was filtered off and washed with hexane to afford, as a grey solid, *3-(iodomethyl)coumarin* **155a** (0.20g, 66%), m.p. 150-152^oC (Found: $\mathbf{M}^+$, 286.9554. $C_{10}H_80_2I$ requires *M*, 286.9569); γ_{max} (KBr)/cm^{-1} 1709 (C=O); δ_H (400

MHz; $CDCl_3$) 4.34 (2H, s, CH_2I), 7.22-7.52 (4H, series of doublets, Ar-H) and 7.81 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$) –1.6 (CH_2I), 116.7, 119.1, 124.7, 127.2, 127.6, 131.9, 140.4 and 153.5 (Ar-C) and 159.7 (C=O); *m/z* 287 (M^+, 0.21%) and 159 (100).

Method 2

Conc. HI (2ml) was added to a solution of *tert*-butyl 3-hydroxy-3-(2-hydroxyphenyl)-2-methylenepropanoate **146a** (52mg, 0.21mmol) in a mixture of AcOH (1ml) and Ac_2O (1ml). The mixture was boiled under reflux for 2h, allowed to cool to room temperature and then poured into ice-cooled water (5ml). Stirring for 30min (or more) gave a precipitate, which was filtered off and washed with hexane to afford, as a pink solid, 3-iodomethylcoumarin **155a** (10mg, 17%).

3-(Iodomethyl)-8-methoxycoumarin 155b

The procedure (method 1) described for the synthesis of 3-(iodomethyl)coumarin **155a** was followed, using conc. HI (10ml) and methyl 3-(2-benzyloxy-3-methoxyphenyl)-3-hydroxy-2-methylenepropanoate **140b** (0.34g, 1.0mmol) in a mixture of AcOH (5ml) and Ac_2O (5ml). Work-up afforded, as a light yellow solid, *3-(iodomethyl)-8-methoxycoumarin* **155b** (0.20g, 62%), m.p. 184-186^{o}C (Found: $\mathbf{M}^+$, 315.95968. $C_{11}H_90_3I$ requires *M*, 315.95965); γ_{max} (KBr)/cm^{-1} 1718 (C=O); δ_H (400 MHz; $CDCl_3$) 3.94 (3H, s, OCH_3), 4.34 (2H, s, CH_2I), 7.06 (2H, overlapping doublets, Ar-H), 7.18 (1H, t, *J* 8Hz, Ar-H) and 7.78 (1H, s, 4-H). δ_C (100 MHz; $CDCl_3$) –1.7 (CH_21), 56.3 (OCH_3), 113.8, 119.1, 119.8, 124.6, 127.6, 134.6, 140.6 and 143.0 (Ar-C) and 159.2 (C=O); *m/z* 316 (M^+, 0.1%) and 189 (100).

8-Ethoxy-3-(iodomethyl)coumarin 155c

The procedure (method 1) described for the synthesis of 3-(iodomethyl)coumarin **155a** was followed, using conc. HI (10ml) and methyl 3-(2-benzyloxy-3-ethoxyphenyl)-3-hydroxy-2-methylenepropanoate **140c** (0.35g, 1.0mmol) in a mixture of AcOH (5ml) and Ac_2O (5ml). Work-up afforded, as a brown solid, *8-ethoxy-3-(iodomethyl)coumarin* **155c** (0.21g, 61%), m.p. 120-122^{o}C (Found: $\mathbf{M}^+$, 329.97490.

$C_{12}H_{11}0_3I$ requires *M*, 329.97530); γ_{max} (KBr)/cm^{-1} 1714 (C=O); δ_H (400 MHz; $CDCl_3$) 1.49 (3H, t, *J* 7.0Hz, CH_3), 4.20 (2H, q, *J* 6.8Hz, OCH_2CH_3), 4.37 (2H, s, CH_2I), 7.07 (2H, overlapping doublets, Ar-H), 7.18 (1H, t, *J* 7.8Hz, ArH) and 7.80 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$) –1.5 (CH_2I), 14.7 (OCH_2CH_3), 65.0 (OCH_2CH_3), 115.0, 119.1, 119.9, 124.6, 127.4, 140.7, 143.4 and 146.26 (Ar-C) and 159.4 (C=O); *m/z* 329 (M^+, 0.2%) and 203 (100).

6-Chloro-3-(iodomethyl)coumarin 155d

The procedure (method 1) described for the synthesis of 3-(iodomethyl)coumarin **155a** was followed, using conc. HI (10ml) and methyl 3-(2-benzyloxy-5-chlorophenyl)-3-hydroxy-2-methylenepropanoate **140d** (0.34g, 1.0mmol) in a mixture of AcOH (5ml) and Ac_2O (5ml). Work-up afforded, as a yellow solid, *6-chloro-3-(iodomethyl)coumarin* **155d** (0.28g, 85%), m.p. 188-190°C (Found: (**M**+Na)$^+$, 342.8979. $C_{10}H_60_2I^{35}ClNa$ requires *M*+Na, 342.8998); γ_{max} (KBr)/cm^{-1} 1747 (C=O); δ_H (400 MHz; $CDCl_3$) 4.35 (2H, s, CH_2I), 7.29-7.48 (3H, series of multiplets, Ar-H) and 7.75 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$) –2.3 (CH_21), 118.2, 120.1, 126.9, 128.7, 130.0, 131.7, 140.0, 151.9 and 159.1 (Ar-C and C=O); *m/z* 321 [M^+(^{35}Cl), 0.1%] and 193 (100).

6-Bromo-3-(iodomethyl)coumarin 155e

The procedure (method 1) described for the synthesis of 3-(iodomethyl)coumarin **155a** was followed, using conc. HI (10ml) and methyl 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-methylenepropanoate **140e** (0.37g, 1.0mmol) in a mixture of AcOH (5ml) and Ac_2O (5ml). Work-up afforded, as a grey solid, *6-bromo-3-(iodomethyl)coumarin* **155e** (0.23g, 61%), m.p. 148-150°C (Found: **M**$^+$, 364.86850. $C_{10}H_70_2I^{79}Br$ requires *M*, 364.86747); γ_{max} (KBr)/cm^{-1} 1722 (C=O); δ_H (400 MHz; $CDCl_3$) 4.35 (2H, s, CH_2I), 7.20-7.61 (3H, series of overlapping signals) and 7.74 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$) –2.4 (CH_2I), 117.3, 118.5, 120.6, 128.6, 130.0, 134.6, 138.9 and 152.3 (Ar-C) and 159.1 (C=O); m/z 365 [M^+(^{35}Cl), 0.3%] and 237 (100).

6,8-Dibromo-3-iodomethylcoumarin 155f

The procedure (method 1) described for the synthesis of 3-(iodomethyl)coumarin **155a** was followed, using conc. HI (10ml) and methyl 3-(2-benzyloxy-3,5-dibromophenyl)-3-hydroxy-2-methylenepropanoate **140f** (0.47g, 1.0mmol) in a mixture of AcOH (5ml) and Ac_2O (5ml). Work-up afforded, as a pink solid, *6,8-dibromo-3-(iodomethyl)coumarin* **155f** (0.28g, 61%), m.p. 208-210^{o}C (Found: **M**$^{+}$, 441.77080. $C_{10}H_5O_2I^{79}Br_2$ requires *M*, 441.77010); γ_{max} (KBr)/cm^{-1} 1747 (C=O); δ_H (400 MHz; $CDCl_3$) 4.36 (2H, s, CH_2I), 7.56 (1H, d, *J* 2.0Hz, Ar-H), 7.70 (1H, s, Ar-H) and 7.87 (1H, d, *J* 2.0Hz, Ar-H); δ_C (100 MHz; $CDCl_3$) –3.1 (CH_2I), 111.3, 117.2, 121.4, 129.2, 129.5, 137.3, 138.5, 149.3 and 158.2 (Ar-C and C=O); *m/z* 441 [M^{+}($^{79}Br_2$), 0.3%] and 305 (100).

3-(Chloromethyl)coumarin 156a

Method 1

Conc. HCl (10ml) was added to a solution of methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanoate **140a** (0.31g, 1.03mmol) in AcOH (5ml) and Ac_2O (5ml). The mixture was boiled under reflux for 2h, allowed to cool to room temperature and then poured into ice-cooled water (10ml). Stirring for 30min (or more) gave a precipitate, which was filtered off and washed with hexane to afford, as a purple solid, *3-(chloromethyl)coumarin* **156a** (0.16g, 80%), m.p. 108-110^{o}C (Found: **M**$^{+}$, 194.01346. $C_{10}H_7O_2{}^{35}Cl$ requires *M*, 194.01346); γ_{max} (KBr)/cm^{-1} 1713 (C=O); δ_H (400 MHz; $CDCl_3$) 4.55 (2H, s, CH_2Cl), 7.30-7.56 (4H, series of multiplets, ArH) and 7.88 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$) 41.0 (CH_2), 116.7, 118.8, 124.7, 125.0; 128.1, 132.0, 141.1 and 153.5 (Ar-C) and 160.1 (C=O); *m/z* 194 (M^{+}, 31.4%) and 159 (100).

Method 2

Conc. HCl (4ml) was added to a solution of *tert*-butyl 3-hydroxy-3-(2-hydroxyphenyl)-2-methylenepropanoate **146a** (0.51g, 2.1mmol) in AcOH (2ml). The mixture was boiled under reflux for 2h, allowed to cool to room temperature and then poured into ice-cooled water (10ml). Stirring for 30min (or more) gave a precipitate, which was filtered off and washed with hexane to afford, as a grey solid, 3-(chloromethyl)coumarin **156a** (0.39g, 98%).

Method 3

Conc. HCl (10ml) was added to a solution of 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanenitrile **144a** (0.27g, 1.0mmol) in AcOH (5ml) and Ac_2O (5ml). The mixture was boiled under reflux for *ca* 1h, allowed to cool to room temperature and then poured into ice-cooled water (10ml). Stirring for 30min (or more) gave a precipitate, which was filtered off and purified using preparative layer chromatography [elution $CHCl_3$-hexane (3:1)] to afford the following two products:-

i) 3-(chloromethyl)coumarin 156a (0.15g, 75%), as a pale yellow solid; and

ii) 3-(acetoxymethyl)coumarin 157a (30mg, 14%), as a pale yellow solid, m.p. 106-110^oC (Found: $\mathbf{M}^+$, 218.05797. $C_{12}H_{10}O_4$ requires *M*, 218.05791); δ_H (400 MHz; $CDCl_3$) 2.15 (3H, s, CH_3), 5.06 (2H, s, C*H*$_2$OAc), 7.29 (1H, d, *J* 7.6Hz, Ar-H), 7.33 (1H, d, *J* 8.4Hz, Ar-H), 7.54 (2H, series of multiplets, Ar-H) and 7.74 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$) 20.9 (CH_3), 61.2 (CH_2), 116.7, 118.7, 123.6, 124.7, 128.0, 131.8, 140.7 and 153.5 (Ar-C) and 160.3 and 170.5 (2x C=O); *m/z* 218 (M^+, 2%) and 175 (100).

3-(Chloromethyl)-8-methoxycoumarin 156b

Method 1

The procedure (method 1) described for the synthesis of 3-(chloromethyl)coumarin **156a** was followed, using conc. HCl (10ml) and a the solution of 3-(2-benzyloxy-3-methoxyphenyl)-3-hydroxy-2-methylenepropanoate **140b** (0.34g, 1.03mmol), in AcOH (5ml) and Ac_2O (5ml). Work-up afforded, as a pale pink solid,

3-(chloromethyl)-8-methoxycoumarin **156b** (0.20g, 87%), m.p. 146-148°C (Found: $\mathbf{M}^+$, 224.02470. $C_{11}H_9O_3{}^{35}Cl$ requires *M*, 224.02402); γ_{max} (KBr)/cm^{-1} 1720 (C=O); δ_H (400 MHz; $CDCl_3$) 3.99 (3H, s, OCH_3), 4.58 (2H, s, CH_2Cl), 7.13 (2H, 2xd, *J* 7.6Hz, Ar-H), 7.26 (1H, t, *J* 9.0Hz, Ar-H) and 7.89 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$) 41.0 (CH_2), 56.3 (OCH_3), 113.8, 119.4, 119.43, 124.6, 125.2, 141.2, 143.2 and 147.2 (Ar-C) and 159.6 (C=O); *m/z* 223 [$(M-H)^+$, 33.4%] and 189 (100).

Method 2

Conc. HCl (4ml) was added to a solution of *tert*-butyl 3-hydroxy-3-(2-hydroxy-3-methoxyphenyl)methylenepropanoate **146b** (0.58g, 2.1mmol) in AcOH (2ml). The mixture was boiled under reflux for 2hr, allowed to cool to room temperature and then poured into ice-cooled water (10ml). Stirring for 30min (or more) gave a precipitate, which was filtered off and washed with hexane to afford, as a grey solid, 3-(chloromethyl)-8-methoxycoumarin **156b** (0.45g, 97%).

Method 3

Conc. HCl (10ml) was added to a solution of 3-(2-benzyloxy-3-methoxyphenyl)-3-hydroxy-2-methylenepropanenitrile **144b** (0.30g, 1.0mmol) in AcOH (5ml) and Ac_2O (5ml). The mixture was boiled under reflux for *ca* 1h, allowed to cool to room temperature and then poured into ice-cooled water (10ml). Stirring for 30min (or more) gave a precipitate, which was filtered off and washed with hexane to afford, as a purple solid, 3-(chloromethyl)-8-methoxycoumarin **156b** (0.16g, 69%).

3-(Chloromethyl)-8-ethoxycoumarin 156c

Method 1

The procedure (method 1) described for the synthesis of 3-(chloromethyl)coumarin **156a** was followed, using conc. HCl (10ml) and a solution of methyl 3-(2-benzyloxy-3-ethoxyphenyl)-3-hydroxy-2-methylenepropanoate **140c** (0.35g, 1.0mmol) in AcOH (5ml) and Ac_2O (5ml). Work-up afforded, as a pale pink solid, *3-(chloromethyl)-8-ethoxycoumarin* **156c** (0.23g, 94%), m.p. 122-124°C (Found: $\mathbf{M}^+$, 238.03967. $C_{12}H_{11}O_3{}^{35}Cl$ requires *M*, 238.03967); γ_{max} (KBr)/cm^{-1} 1709 (C=O); δ_H (400 MHz;

$CDCl_3$) 1.49 (3H, t, *J* 7.0Hz, OCH_2CH_3), 4.18 (2H, q, *J* 7.0Hz, OCH_2CH_3), 4.55 (2H, d, *J* 0.8Hz, CH_2Cl), 7.08 (2H, d, *J* 7,2Hz, Ar-H), 7.20 (1H, t, *J* 8.0Hz, Ar-H) and 7.85 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$) 14.7 (OCH_2CH_3), 41.0 (CH_2), 55,1 (OCH_2CH_3), 115.2, 119.4, 119.6, 124.6, 125.1, 141.3, 143.4 and 146.5 (Ar-C) and 159.8 (C=O); *m/z* 238 (M^+, 28.5%) and 175 (100).

Method 2

Conc. HCl (4ml) was added to a solution of *tert*-butyl 3-hydroxy-3-(3-ethoxy-2-hydroxyphenyl)-2-methylenepropanoate **146c** (0.61g, 2.1mmol) in AcOH (2ml).The mixture was boiled under reflux for 2h, allowed to cool to room temperature and then poured into ice-cooled water (10ml). Stirring for 30min (or more) gave a precipitate, which was filtered off and washed with hexane to afford, as a grey solid, 3-(chloromethyl)-8-methoxycoumarin **156c** (0.45g, 90%).

6-Chloro-3-(chloromethyl)coumarin 156d

Method 1

The procedure (method 1) described for the synthesis of 3-(chloromethyl)coumarin **156a** was followed, using conc. HCl (15ml) and a solution of methyl 3-(2-benzyloxy-5-chlorophenyl)-3-hydroxy-2-methylenepropanoate **140d** (0.51g, 1.6mmol) in AcOH (7.5ml) and Ac_2O (7.5ml). Work-up afforded, as a pale pink solid, *6-chloro-3-(chloromethyl)coumarin* **156d** (0.33g, 94%), m.p. 112-114^oC (Found: $\mathbf{M}^+$, 227.97476. $C_{10}H_6O_2{}^{35}Cl_2$ requires *M*, 227.97448)); γ_{max} (KBr)/cm^{-1} 1729 (C=O); δ_H (400 MHz; $CDCl_3$) 4.54 (2H, s, CH_2Cl), 7.31 (1H, d, *J* 8.8Hz, Ar-H), 7.48 and 7.50 (2H, 2xd, *J* 2.3Hz, Ar-H) and 7.81 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$) 40.8 (CH_2), 118.1, 119.8, 126.3, 127.3, 130.0, 131.9, 139.7, 151.8 (Ar-C) and 159.5 (C=O); *m/z* 228 [M^+($^{35}Cl_2$), 23.2%] and 193 (100).

Method 2

Conc. HCl (20ml) was added to a solution of 3-(2-benzyloxy-5-chlorophenyl)-3-hydroxy-2-methylenepropanenitrile **144d** (0.93g, 3.1mmol) in AcOH (15ml) and Ac_2O (15ml). The mixture was boiled under reflux for *ca* 1h, allowed to cool to room temperature and then poured into ice-cooled water (*ca* 15ml). Stirring for 30min (or more) gave a precipitate, which was filtered off and washed with hexane to afford, as a purple solid, 6-chloro-3-(chloromethyl)coumarin **156d** (0.61g, 87%).

6-Bromo-3-(chloromethyl)coumarin 156e

Method 1

The procedure (method 1) described for the synthesis of 3-(chloromethyl)coumarin **156a** was followed, using conc. HCl (10ml) and a solution of methyl 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-methylenepropanoate **140e** (0.39g, 1.0mmol) in AcOH (5ml) and Ac_2O (5ml). Work-up afforded, as a pale pink solid, *6-bromo-3-(chloromethyl)coumarin* **156e** (0.22g, 81%), m.p. 116-118^oC (Found: $\mathbf{M}^+$, 271.92412. $C_{10}H_6O_2{}^{35}Cl^{79}Br$ requires *M*, 271.92397); γ_{max} (KBr)/cm^{-1} 1722 (C=O); δ_H (400 MHz; $CDCl_3$) 4.53 (2H, s, CH_2Cl), 7.24 (1H, d, *J* 8.8Hz, Ar-H), 7.62 (1H, dd, *J* 2.0Hz and *J* 8.8Hz, Ar-H), 7.66 (1H, d, *J* 2.0Hz, Ar-H) and 7.80 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$) 40.8 (CH_2), 117.3, 118.4, 120.3, 126.3, 130.3, 134.7, 139.6, 142.3 and 159.4 (ArC and C=O); *m/z* 271 [M^+($^{35}Cl^{79}Br$), 34.9%] and 237(100).

Method 2

Conc. HCl (4ml) was added to a solution of *tert*-butyl 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-2-methylenepropanoate **146e** (0.68g, 2.1mmol) in AcOH (2ml). The mixture was boiled under reflux for 2h, allowed to cool to room temperature and then poured into ice-cooled water (10ml). Stirring for 30min (or more) gave a precipitate, which was filtered off and washed with hexane to afford, as a grey solid, 6-bromo-3-(chloromethyl)coumarin **156e** (0.54g, 95%).

Method 3

Conc. HCl (10ml) was added to a solution of 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-methylenepropanenitrile **144e** (0.35g, 1.0mmol) in AcOH (5ml) and Ac_2O (5ml). The mixture was boiled under reflux for *ca* 1h, allowed to cool to room temperature and then poured into ice-cooled water (10ml). Stirring for 30min (or more) gave a precipitate, which was filtered off and washed with hexane to afford, as a purple solid, 6-bromo-3-(chloromethyl)coumarin **156e** (0.21g, 75%).

6,8-Dibromo-3-(chloromethyl)coumarin 156f

Method 1

The procedure (method 1) described for the synthesis of 3-(chloromethyl)coumarin **156a** was followed, using conc. HCl (15ml) and a solution of methyl 3-(2-benzyloxy-3,5-dibromophenyl)-3-hydroxy-2-methylenepropanoate **140f** (0.47g, 1.0mmol), in AcOH (7.5ml) and Ac_2O (7.5ml). Work-up afforded, as a pale pink solid, *6,8-dibromo-3-(chloromethyl)coumarin* **156f** (0.32g, 90%), m.p. 166-168^oC (Found $\mathbf{M}^+$, 349.83490. $C_{10}H_{15}O_2{}^{35}Cl^{79}Br_2$ requires *M*, 349.83448); γ_{max} (KBr)/cm^{-1} 1727 (C=O); δ_H (400 MHz; $CDCl_3$) 4.54 (2H, s, CH_2Cl), 7.67 (1H, d, *J* 2.0Hz, Ar-H), 7.78 (1H, s, Ar-H) and 7.88 (1H, d, *J* 2.0Hz, Ar-H); δ_C (100 MHz; $CDCl_3$) 40.5 (CH_2), 111.2, 117.3, 121.1, 127.1, 129.6, 137.5, 139.2 and 149.3 (Ar-C) and 158.48 (C=O); *m/z* 349 [M^+ ($^{35}Cl^{79}Br_2$), 51%) and 317 (100).

Method 2

Conc. HCl (4ml) was added to a solution of *tert*-butyl 3-(3,5-dibromo-2-hydroxyphenyl)-3-hydroxy-2-methylenepropanoate **140f** (0.84g, 2.1mmol) in AcOH (2ml). The mixture was boiled under reflux for 2h, allowed to cool to room temperature and then poured into ice-cooled water (10ml). Stirring for 30min (or more) gave a precipitate, which was filtered off and washed with hexane to afford, as a grey solid, 6,8-dibromo-3-(chloromethyl)coumarin **156f** (0.70, 95%).

3-(Acetoxymethyl)coumarin 157 and *tert*-butyl 2*H*-1-chromene-3-carboxylate 161

A mixture of *tert*-butyl 3-hydroxy-3-(2-hydroxyphenyl)-2-methylenepropanoate **146a** (0.14g, 0.57mmol) in AcOH (12ml) was boiled under reflux for 6h. Water (10ml) was added to the cooled solution and the resulting mixture was extracted with chloroform. The organic solution was dried over anhyd. Na_2SO_4, filtered and evaporated *in vacuo* to afford a yellow solid, which was purified using preparative layer chromatography [elution with $CHCl_3$-hexane (3:1)] to afford the following two products:-

i) **3-(acetoxymethyl)coumarin 157** (80mg, 40%), as a pale yellow solid; and

ii) ***3-tert*-butyl 2*H*-1-chromene-3-carboxylate 161,** as a pale yellow oil (50mg, 24%), (Found: $\mathbf{M}^+$, 232.11056. $C_{14}H_{16}O_3$ requires *M*, 232.10994); δ_H (400 MHz; $CDCl_3$) 1.53 [9H, s, $C(CH_3)_3$], 4.94 (2H, d, *J* 0.8Hz, CH_2), 6.82 (1H, d, *J* 8.0Hz, Ar-H), 6.90-7.20 (3H, series of multiplets, Ar-H) and 7.32 (1H, s, 4-H);† δ_C (100 MHz; $CDCl_3$) 28.1 [$C(CH_2)_3$], 64.6 (CH_2), 81.2 [$C(CH_2)_3$], 116.0, 121.3, 121.6, 124.3, 128.7, 131.6, 132.5 and 155.0 (Ar-C) and 163.9 (C=O); *m/z* 232 (M^+, 48%) and 131 (100).

3.2.7. Synthesis of coumarins *via* intramolecular Baylis-Hillman reactions

3.2.7.1 Preparation of salicylaldehyde acrylate esters

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2-Formylphenyl acrylate 163a [159]

To a suspension of NaH (50% dispersion in oil; 0.86g, 18mmol) in dry THF (15ml) under nitrogen was added salicylaldehyde (1.46ml, 13.7mmol) and the resulting mixture was boiled under reflux for 1h to generate the phenoxide ion. To the cooled solution, acryloyl chloride (1.45ml, 17.9mmol) in dry THF (15ml) was added dropwise, with stirring, and the reaction mixture was boiled under reflux for 3h. The reaction was quenched by the addition of water (20ml) and the resulting mixture extracted with diethyl ether. The organic layer was washed with satd. brine, dried over anhyd.

$MgSO_4$, and concentrated *in vacuo* to afford, as a yellow oil, 2-formylphenyl acrylate (2.0g, 83%) (Found: $\mathbf{M}^+$, 176.04764. Calc. for $C_{10}H_8O_3$ *M*, 176.04734); γ_{max} (KBr)/cm^{-1} 1747 (C=O); δ_H (400 MHz; $CDCl_3$) 6.09 and 6.66 (2H, 2xd, *J* 10.2Hz and *J* 17.2Hz, CH=*CH*$_2$), 6.37 (1H, dd, *J* 10.2Hz and 17.2Hz, C*H*=CH_2), 7.22 (1H, d, *J* 8.0Hz, ArH), 7.39 and 7.63 (2H, 2x t, *J* 7.4Hz and 7.6Hz, ArH), 7.90 (1H, d, *J* 7.6Hz, ArH) and 10.13 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 133.8 (CH=*C*H_2), 123.4, 126.5, 127.1, 128.1, 130.3, 135.3 and 151.8 (*C*H=CH_2 and Ar-C), 164.2 (C=O) and 188.4 (CHO); *m/z* 176 (M^+, 2.1%) and 121 (100).

2-Formyl-6-methoxyphenyl acrylate 163b

The procedure described for the synthesis of 2-formylphenyl acrylate **163a** was followed, using 3-methoxysalicylaldehyde (2.08g, 13.7mmol), NaH (50% dispersion in oil; 0.86g, 18mmol) in dry THF (15ml) and acryloyl chloride (1.45ml, 17.9mmol) in dry THF (15ml). Work-up afforded, as a yellow oil, *2-formyl-6-methoxyphenyl acrylate* **163b** (2.20g, 87%) (Found: $\mathbf{M}^+$, 206.05770. $C_{11}H_{10}O_4$ requires *M*, 206.05791); γ_{max}(KBr)/ cm^{-1} 1747 (C=O); δ_H (400 MHz; $CDCl_3$) 3.81 (3H, s, OCH_3), 6.06 and 6.64 (2H, 2xd, *J* 10.4 Hz and 17.2Hz, CH=C*H*$_2$), 6.37 (1H, dd, *J* 10.4 Hz and 17.2Hz, C*H*=CH_2), 7.19 (1H, d, *J* 8.4Hz, Ar-H), 7.29 (1H, t, *J* 8.0Hz, ArH), 7.44 (1H, d, *J* 8.0Hz, ArH) and 10.11 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 56.2 (OCH_3), 133.6 (CH=*C*H_2), 117.8, 120.5, 126.7, 126.8, 129.2, 141.6 and 151.6 (*C*H=CH_2 and Ar-C), 163.7 (C=O) and 188.4 (CHO); *m/z* 206 (M^+, 5%) and 151 (100).

6-Ethoxy-2-formylphenyl acrylate 163c

The procedure described for the synthesis of 2-formylphenyl acrylate **163a** was followed, using 3-ethoxysalicylaldehyde (2.78mmol, 13.7mmol), NaH (50% dispersion in oil; 0.86g, 18mmol) in dry THF (15ml) and acryloyl chloride (1.45ml, 17.9mmol) in dry THF (15ml). Work-up afforded, as a yellow oil, *6-ethoxy-2-formylphenyl acrylate* **163c** (2.67g, 89%) (Found: $\mathbf{M}^+$, 220.07389 $C_{12}H_{12}O_4$ requires *M*, 220.07356); γ_{max}(KBr) /cm^{-1} 1751 (C=O); δ_H (400 MHz; $CDCl_3$) 1.35 (3H, t, *J*

7.0Hz, OCH_2CH_3), 4.06 (2H, q, *J* 6.8Hz, OCH_2CH_3), 6.08 and 6.67 (2H, 2xd, *J* 8.0 Hz and *J* 7.8Hz, $CH=CH_2$), 6.39 (1H, dd, *J* 10.4 Hz and *J* 17.6Hz, $CH=CH_2$), 7.20 (1H, d, *J* 7.2Hz, Ar-H), 7.29 (1H, t, *J* 7.8Hz, ArH), 7.45 (1H, dd, *J* 7.6Hz and *J* 8.0Hz, ArH) and 10.14 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 14.6 (OCH_2CH_3), 64.9 (OCH_2CH_3), 133.4 ($CH=CH_2$), 118.9, 120.3, 126.7, 126.8, 129.3, 142.1 and 151.0 ($CH=CH_2$ and Ar-C), 163.7 (C=O) and 188.5 (CHO); *m/z* 220 (M^+, 41%) and 165 (100).

4-Bromo-2-formylphenyl acrylate 163e

The procedure described for the synthesis of 2-formylphenyl acrylate **163a** was followed, using 5-bromosalicylaldehyde (2.75ml, 13.7mmol), NaH (50% dispersion in oil; 0.86g, 18mmol) in dry THF (15ml) and acryloyl chloride (1.45ml, 17.9mmol) in dry THF (15ml). Work-up afforded, as white crystals, *4-bromo-2-formylphenyl acrylate* **163e** (3.01g, 86%), m.p. 70-72°C (from $CHCl_3$) (Found: $\mathbf{M}^+$, 253.95893 $C_{10}H_7O_3{}^{79}Br$ requires *M*, 253.95786); γ_{max}(KBr)/cm^{-1} 1751 (C=O); δ_H (400 MHz; $CDCl_3$) 6.12 (1H, dd, *J* 0.4Hz and *J* 10.4Hz, $CH=CH_A$), 6.67 (1H, dd, *J* 0.4Hz and *J* 17.2Hz, $CH=CH_B$), 6.36 (1H, dd, *J* 10.4Hz and *J* 17.2Hz, $CH=CH_2$), 7.14 (1H, d, *J* 8.4Hz, ArH), 7.73 (1H, dd, *J* 8.4Hz and *J* 2.4Hz, ArH), 8.01 (1H, d, *J* 2.4Hz, ArH) and 10.07 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 134.3 ($CH=CH_2$), 119.8, 125.2, 126.7, 129.3, 132.6, 138.0 and 150.8 ($CH=CH_2$ and Ar-C), 163.8 (C=O) and 186.9 (CHO); *m/z* 254 [M^+(^{79}Br), 7.2%] and 201 (100).

2-Formyl-5-nitrophenyl acrylate 163g

The procedure described for the synthesis of 2-formylphenyl acrylate **163a** was followed, using 4-nitrosalicylaldehyde (2.29mmol, 13.7mmol), NaH (50% dispersion in oil; 0.86g, 18mmol) in dry THF (15ml) and acryloyl chloride (1.45ml, 17.9mmol) in dry THF (15ml). Work-up afforded, as white soild, *2-formyl-5-nitrophenyl acrylate* **163g** (2.94g, 99%), m.p. 58-60°C (from $CHCl_3$) (Found: $\mathbf{M}^+$, 221.03189. $C_{10}H_7NO_5$ requires *M*, 221.03242); γ_{max}(KBr)/cm^{-1} 1747 (C=O); δ_H (400 MHz;

$CDCl_3$) 6.21 and 6.73 (2H, 2xd, *J* 10.8Hz, CH=C*H*$_2$), 6.40 (1H, dd, *J* 10.4 Hz and *J* 17.2Hz, *CH*=CH_2), 7.50 (1H, d, *J* 8.8Hz, ArH), 8.49 (1H, dd, *J* 2.4Hz and *J* 8.8Hz, ArH), 8.78 (1H, d, *J* 2.4Hz, ArH) and 10.20 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 135.3 (CH=*C*H_2), 124.8, 125.5, 126.3, 128.5, 129.5, 145.8 and 155.9 (*C*H=CH_2 and Ar-C), 163.1 (C=O) and 186.1 (CHO); *m/z* 221 (M^+, 7.2%) and 55 (100).

3.2.7.2. Preparation of coumarin-derived quaternary DABCO salts

Quaternary ammonium salt 164a[159]

To a solution of 2-formylphenyl acrylate **163a** (2g, 11mmol) dry dichloromethane (23ml) at –10^{o}C was added DABCO (1.27g, 11mmol), and the stirred solution was allowed to warm to room temperature over several hours. The resulting precipitate was filtered off, washed with dichloromethane and recrystallized from methanol and dichloromethane to afford, as a pale yellow solid, the quaternary ammonium salt **164a** (2.05g, 61%), m.p. <250^{o}C (dec.) (Found: **M**$^+$-HCl, 270.13662. Calc. for $C_{16}H_{18}O_2N_2$: *M-36*, 270.13683); γ_{max} (KBr)/cm^{-1} 1711 (C=O); δ_H (400 MHz; CD_3OD) 3.27 [6H, t, *J* 7.6Hz, $(CH_2)_3N$], 3.59 [6H, t, *J* 7.4Hz, $(CH_2)_3N^+$], 4.53 (2H, s, CH_2N^+), 7.48-7.86 (4H, series of multiplets, Ar-H) and 8.49 (1H, s, 4-H); δ_C (400 MHz; CD_3OD) 46.3 ($NCH_2CH_2N^+$), 53.87 ($^+NCH_2CH_2N$), 64.03 (CH_2N^+), 116.6, 117.7, 120.0, 126.4, 130.6, 135.1, 152.7 and 156.0 (Ar-C) and 163.0 (C=O); *m/z* 270 [(M^+-HCl), 9.3%] and 159 (100).

Quaternary ammonium salt 164b

The procedure described for the synthesis of the quaternary ammonium salt **164a** was followed, using DABCO (1.27g, 11mmol) and 2-formyl-6-methoxyphenyl acrylate **163b** (2.3g, 11mmol) in dry chloromethane (23ml) at –10^{o}C. Work-up and recrystallization from methanol and dichloromethane afforded, as a pale cream solid, *the quaternary ammonium salt* **164b** (2.01g, 54%), m.p. < 246^{o}C (dec.) (Found: **M**$^+$, 336.12394. $C_{17}H_{21}O_3N_2{}^{35}Cl$ requires *M*, 336.12407); γ_{max} (KBr)/cm^{-1} 1719 (C=O); δ_H

(400 MHz; DMSO-d_6) 3.24 [6H, t, *J* 7.2Hz, $(CH_2)_3N^+$], 3.56 [6H, t, *J* 7.2Hz, $(CH_2)_3N^+$], 4.03 (3H, s, OCH_3), 4.48 (2H, s, CH_2N^+), 7.42 (3H, series of overlapping signals, Ar-H) and 8.41 (1H, s, 4-H); δ_C (400 MHz; DMSO-d_6) 44.7 ($NCH_2CH_2N^+$), 51.6 ($^+NCH_2CH_2N$), 56.2 (OCH_3), 61.3 (CH_2N^+), 115.5, 115.9, 118.9, 120.2, 124.7, 143.2, 146.3 and 150.6 (Ar-C) and 160.5 (C=O); *m/z* 301 [(M^+-Cl), 2.1%] and 189 (100).

Quaternary ammonium salt 164c

The procedure described for the synthesis of the quaternary ammonium salt **164a** was followed, using DABCO (1.27g, 11mmol) and 6-ethoxy-2-formyphenyl acrylate **163c** (2.4g, 11mmol) in dry dichloromethane (23ml) at –10°C. Work-up and recrystallization from methanol and dichloromethane afforded, as a pale yellow solid, *the quaternary ammonium salt* **164c** (2.02g, 52%), m.p. <200°C (dec.) (Found: $\mathbf{M}^+$, 350.13995. $C_{18}H_{23}O_3N_2{}^{35}Cl$ requires *M*, 350.13972); γ_{max} (KBr)/cm^{-1} 1722 (C=O); δ_H (400 MHz; DMSO-d_6) 1.38 (3H, t, *J* 7.6Hz, OCH_2CH_3), 2.98 [6H, t, *J* 6.6Hz, $(CH_2)_3N^+$], 3.41 [6H, t, *J* 6.6Hz, $(CH_2)_3N^+$], 4.19 (2H, q, *J* 7.6Hz, OCH_2CH_3), 4.40 (2H, s, CH_2N^+), 7.30-7.36 (3H, series of overlapping signals, Ar-H) and 8.41 (1H, s, 4-H); δ_C (400 MHz; DMSO-d_6) 14.6 (OCH_2CH_3), 44.7 ($NCH_2CH_2N^+$), 51.6 ($^+NCH_2CH_2N$), 61.3 (CH_2N^+), 64.5 (OCH_2CH_3), 115.8, 116.3, 119.1, 120.2, 124.7, 143.3, 145.5 and 150.7 (Ar-C) and 160.6 (C=O); *m/z* 350 [M^+, 0.2%] and 175 (100).

Quaternary ammonium salt 164e

The procedure described for the synthesis of the quaternary ammonium salt **164a** was followed, using DABCO (1.27g, 11mmol) and 4-bromo-2-formylphenyl acrylate **163e** (2.8g, 11mmol) in dry dichloromethane (23ml) at –10°C. Work-up and recrystallization from methanol and dichloromethane afforded, as a pale cream solid, *the quaternary ammonium salt* **164e** (2.50g, 59%), m.p. < 252°C (dec.) (Found: $\mathbf{M}^+$, 384.02357. $C_{16}H_{18}O_2N_2{}^{35}Cl^{79}Br$ requires *M*, 384.02402); γ_{max} (KBr)/cm^{-1} 1727 (C=O); δ_H (400 MHz; DMSO-d_6) 3.03 [6H, t, *J* 7.0Hz, $(CH_2)_3N$], 3.43 [6H, t, *J*

7.0Hz, $(CH_2)_3N^+$], 4.42 (2H, s, CH_2N^+), 7.50 (1H, d, *J* 8.4Hz, Ar-H), 7.89 and 7.91 (2H, 2xd, *J* 2.4Hz and *J* 8.8Hz, Ar-H), 8.09 (1H, d, *J* 2.4Hz, Ar-H) and 8.35 (1H, s, 4-H); δ_C (400 MHz; DMSO-d_6) 44.7 ($NCH_2CH_2N^+$), 51.6 ($^+NCH_2CH_2N$), 61.1 (CH_2N^+), 116.2, 116.9, 118.4, 120.3, 131.2, 135.5, 149.0 and 152.9 (Ar-C) and 160.3 (C=O); *m/z* 348 [(M^+-HCl), 7.8%] and 237 (100).

Quaternary ammonium salt 164g

The procedure described for the synthesis of the quaternary ammonium salt **164a** was followed, using DABCO (1.27g, 11mmol) and 2-formyl-5-nitrophenyl acrylate **163g** (2.4g, 11mmol) in dry dichloromethane (23ml) at –10°C. Work-up and recrystallization from methanol and dichloromethane afforded, as a yellow solid, *the quaternary ammonium salt* **164g** (2.71g, 70%), m.p. < 210°C (dec.) (Found: $\mathbf{M}^+$, 351.09698. $C_{16}H_{18}O_4N_3{}^{35}Cl$ requires *M*, 351.09858); γ_{max} (KBr)/cm^{-1} 1726 (C=O); δ_H (400 MHz; DMSO-d_6) 3.00 [6H, br s, $(CH_2)_3N$], 3.43 [6H, br s, $(CH_2)_3N^+$], 4.43 (2H, s, CH_2N^+), 7.71 (1H, d, *J* 9.2Hz, Ar-H), 8.51 (1H, d, *J* 8.8Hz, Ar-H) and 8.76 (1H, s, 4-H); δ_C (400 MHz; DMSO-d_6) 44.7 ($NCH_2CH_2N^+$), 51.6 ($^+NCH_2CH_2N$), 61.0 (CH_2N^+), 117.7, 117.8, 118.7, 125.0, 127.6, 143.6, 149.3 and 157.4 (Ar-C) and 160.0 (C=O); *m/z* 316 [(M^+-Cl), 0.8%] and 204 (100).

3.3. Nucleophilic substitution reactions of coumarin derivatives

Reaction of 3-(iodomethyl)coumarin 155a with ethyl acetoacetate enolate

To a solution of sodium ethoxide [generated from sodium metal (18mg, 0.80mmol)] in dry ethanol (5ml) under N_2 was added ethyl acetoacetate (0.1ml), and the resulting mixture was heated to 50°C. 3-(Iodomethyl)coumarin **155a** (0.21g, 0.74mmol) was added and the resulting mixture boiled under reflux for 5h to afford a brown oil, which was purified using preparative layer chromatography [elution with hexane-EtOAc (3:1)] to afford, as a pale yellow solid, *ethyl 2-[(2-oxo-2*H*-chromen-3-yl)methyl]-3-oxobutanoate* **174a** (88mg, 41%), m.p. 62-66°C (Found: $\mathbf{M}^+$, 288.0996.

$C_{16}H_{16}O_5$ requires *M,* 288.09977); δ_H (400 MHz; $CDCl_3$) 1.17 (3H, t, *J* 7.2Hz, OCH_2CH_3), 2.25 (3H, s, $COCH_3$), 3.09 (2H, m, CH_2CH), 4.16 (3H, overlapping signals, OCH_2CH_3 and CH_2CH), 7.20-7.46 (4H, series of multiplets, Ar-H) and 7.59 (1H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 14.0 (OCH_2CH_3), 29.7 (CH_2CH), 29.8 ($COCH_3$), 57.1 (CH_2CH), 61.6 (OCH_2CH_3), 116.4, 119.2, 124.4, 125.5, 127.6, 131.1, 141.9 and 153.4 (Ar-C), 161.4, 168.7 and 202.0 (3x C=O); *m/z* 288 (M^+, 0.1%) and 221 (100).

Reaction of 3-(chloromethyl)-8-methoxycoumarin 156b with ethyl acetoacetate enolate

The procedure described for the synthesis of ethyl 2-[(2-oxo-2*H*-chromen-3 yl)methyl]-3-oxobutanoate **174a** was followed, using ethyl acetoacetate (0.2ml), sodium ethoxide (1.6mmol) in dry ethanol (10ml) and 3-(chloromethyl)-8-methoxycoumarin **156b** (0.33g, 1.5mmol). Work-up and chromatography afforded, as a yellow oil, *ethyl 2-[(8-methoxy-2-oxo-2*H*-chromen-3-yl)methyl]-3-oxobutanoate* **174b** (0.20g, 42%) (Found: $\mathbf{M}^+$, 318.11164. $C_{17}H_{18}O_6$ requires *M,* 318.11034); δ_H (400 MHz; $CDCl_3$) 1.18 (3H, t, *J* 7.0Hz, OCH_2CH_3), 2.26 (3H, s, $COCH_3$), 3.06 (2H, m, CH_2CH), 3.92 (3H, s, OCH_3), 4.13 (3H, series of overlapping signals, CH_2CH and OCH_2CH_3), 7.00 (2H, t, *J* 4.4Hz, Ar-H), 7.16 (1H, t, *J* 8.0Hz, Ar-H) and 7.58 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$) 14.0 (OCH_2CH_3), 29.7 (CH_2CH), 29.8 ($COCH_3$), 56.1 (OCH_3), 56.9 (CH_2CH), 61.5 (OCH_2CH_3), 113.0, 119.0, 120.0, 124.3, 125.6, 142.1, 142.9, and 146.9 (Ar-C), 160.9, 168.7 and 202.1 (3x C=O); *m/z* 318 (M^+, 0.9%) and 229 (100).

Reaction of 3-(chloromethyl)-8-ethoxycoumarin 156c with ethyl acetoacetate enolate

The procedure described for the synthesis of ethyl 2-[(2-oxo-2*H*-chromen-3 yl)methyl]-3-oxobutanoate **174a** was followed, using ethyl acetoacetate (0.2ml), sodium ethoxide (1.6mmol) in dry ethanol (10ml) and 3-(chloromethyl)-8-ethoxycoumarin **156c** (0.35g, 1.5mmol). Work-up and chromatography afforded, as a

pale yellow oil, *ethyl 2-[(8-ethoxy-2-oxo-2*H*-chromen-3-yl)methyl]-3-oxobutanoate* **174c** (0.21g, 42%) (Found: $\mathbf{M}^+$, 332.12539. $C_{18}H_{20}O_6$ requires *M*, 332.12599); δ_H (400 MHz; $CDCl_3$) 1.19 (3H, t, *J* 7.0Hz, OCH_2CH_3), 1.49 (3H, t, *J* 7.0Hz, OCH_2CH_3), 2.27 (3H, s, $COCH_3$), 3.04 (2H, m, CH_2CH), 4.14 (5H, series of overlapping signals, CH_2CH and 2xOCH_2CH_3), 7.00 (2H, m, Ar-H), 7.15 (1H, t, *J* 8.0Hz, Ar-H) and 7.59 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$) 14.0 and 14.7 (2xOCH_2CH_3), 29.8 (CH_2CH), 29.9 ($COCH_3$), 56.9 (CH_2CH), 61.6 and 64.8 (2xOCH_2CH_3), 114.2, 118.9, 119.9, 124.3, 125.5, 142.2, 143.2 and 146.3 (Ar-C), 161.1, 168.7 and 202.2 (3x C=O); *m/z* 332 (M^+, 1.1%) and 243 (100).

Reaction of 6-chloro-3-(chloromethyl)coumarin 156d with ethyl acetoacetate enolate

The procedure described for the synthesis of ethyl 2-[(2-oxo-2*H*-chromen-3 yl)methyl]-3-oxobutanoate **174a** was followed, using ethyl acetoacetate (0.2ml), sodium exthoxide (1.6mmol) in dry ethanol (10ml) and 6-chloro-3-(chloromethyl)-coumarin **156d** (0.34g, 1.5mmol). Work-up and chromatography afforded, as light yellow crystals, *ethyl 2-[(6-chloro-2-oxo-2*H*-chromen-3-yl)methyl]-3-oxobutanoate* **174d** (0.20g, 41%), m.p. 72-76^{o}C (Found: $\mathbf{M}^+$, 322.06132. $C_{16}H_{15}O_5{}^{35}Cl$ requires *M*, 322.06080); δ_H (400 MHz; $CDCl_3$) 1.19 (3H, t, *J* 7.0Hz, OCH_2CH_3), 2.23 (3H, s, $COCH_3$), 3.03 (2H, m, CH_2CH), 4.06 (1H, dd, *J* 6.8Hz and *J* 7.6Hz, CH_2CH), 4.16 (2H, m, OCH_2CH_3), 7.20-7.40 (3H, series of multiplets, Ar-H) and 7.54 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$) 14.0 (OCH_2CH_3), 29.6 (CH_2CH), 30.1 ($COCH_3$), 56.8 (CH_2CH), 61.6 (OCH_2CH_3), 117.8, 120.2, 126.76, 126.80, 129.7, 131.0, 140.6 and 151.6 (Ar-C), 160.8, 168.5 and 201.8 (3x C=O); *m/z* 322 (M^+, 0.7%) and 233 (100).

Reaction of 6-bromo-3-(chloromethyl)coumarin 156e with ethyl acetoacetate enolate

The procedure described for the synthesis of ethyl 2-[(2-oxo-2*H*-chromen-3 yl)methyl]-3-oxobutanoate **174a** was followed, using ethyl acetoacetate (0.2ml), sodium metal (36mg, 1.6mmol) in dry ethanol (10ml) and 6-bromo-3-(chloromethyl)coumarin **156e** (0.40g, 1.5mmol). Work-up and chromatography afforded, as light yellow crystals, *ethyl 2-[(6-bromo-2-oxo-2*H*-chromen-3-yl)methyl]-3-oxobutanoate* **174e** (0.23g, 42%), m.p. 108-110°C (Found: $\mathbf{M}^+$, 366.01084. $C_{16}H_{15}O_5{}^{79}Br$ requires *M*, 366.01028); δ_H (400 MHz; $CDCl_3$) 1.18 (3H, t, *J* 7.0Hz, OCH_2CH_3), 2.25 (3H, s, $COCH_3$), 3.01 (2H, m, CH_2CH), 4.04 (1H, t, *J* 7.2Hz, CH_2CH), 4.16 (2H, m, OCH_2CH_3), 7.14 (1H, d, *J* 8.4Hz, Ar-H) and 7.52 (3H, series of overlapping signals, Ar-H); δ_C (100 MHz; $CDCl_3$) 14.0 (OCH_2CH_3), 29.6 (CH_2CH), 30.2 ($COCH_3$), 56.8 (CH_2CH), 61.6 (OCH_2CH_3), 116.9, 118.1, 120.6, 126.7, 129.8, 133.8, 140.5 and 152.1 (Ar-C), 160.7, 168.5 and 201.7 (3x C=O); *m/z* 366 (M^+, 1.4%) and 279 (100).

Reaction of 3-(iodomethyl)coumarin 155a with diethyl malonate enolate

To a solution of sodium ethoxide [generated from sodium metal (18mg, 0.80mmol)] in dry ethanol (5ml) under N_2 was added diethyl malonate (0.1ml), and the resulting mixture was heated to 50°C. 3-(Iodomethyl)coumarin **155a** (0.21g, 0.74mmol) was added and the resulting mixture boiled under reflux for 5h to afford a brown oil, which was purified using preparative layer chromatography [elution with hexane-EtOAc (3:1)] to afford, as a pale yellow solid, *diethyl 2-[(2-oxo-2*H*-chromen-3-yl)methyl]propane-1,3-dioate* **176a** (0.11g, 47%), m.p. 66-70°C (Found: $\mathbf{M}^+$, 318.10974. $C_{17}H_{18}O_6$ requires *M*, 318.11034); δ_H (400 MHz; $CDCl_3$) 1.19 (6H, t, *J* 7.0Hz, 2x OCH_2CH_3), 3.11 (2H, d, *J* 7.6Hz, CH_2CH), 4.15 (4H, 2x q, *J* 2.8Hz, 2x OCH_2CH_3), 7.21-7.49 (4H, series of doublets, Ar-H) and 7.59 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$) 14.0 ($2xOCH_2CH_3$), 30.7 (CH_2CH), 49.9 (CH_2CH), 61.5 (2x OCH_2CH_3), 116.4, 119.1, 124.4, 125.3, 127.5, 131.2, 141.5 and 153.4 (Ar-C), 161.2 and 168.6 (2x C=O); *m/z* (FAB) 288 (MH^+, 22%) and 171 (100).

Reaction of 3-(chloromethyl)-8-ethoxycoumarin 156c with diethyl malonate enolate

The procedure described for the synthesis of diethyl 2-[(2-oxo-2*H*-chromen-3-yl)methyl]propane-1,3-dioate **176a** was followed, using diethyl malonate (0.21ml), sodium metal (1.6mmol) in dry ethanol (10ml) and 3-(chloromethyl)-8-ethoxycoumarin **156c** (0.33g, 1.5mmol). Work-up and chromatography afforded, as a yellow oil, *diethyl 2-[(8-ethoxy-2-oxo-2*H*-chromen-3-yl)methyl]propane-1,3-dioate* **176c** (0.27g, 50%) (Found: $\mathbf{M}^+$, 362.13673. $C_{19}H_{22}O_7$ requires *M*, 362.13655); δ_H (400 MHz; $CDCl_3$) 1.18 (6H, t, *J* 7.2Hz, 2x OCH_2CH_3), 1.46 (3H, t, *J* 7.2Hz, OCH_2CH_3), 3.10 (2H, d, *J* 8.0Hz, CH_2CH), 3.94 (1H, t, *J* 7.8Hz, CH_2CH), 4.08-4.17 (6H, series of overlapping signals, 3x OCH_2CH_3), 6.98 (2H, 2xd, *J* 7.8Hz, Ar-H), 7.13 (1H, t, *J* 8.0Hz, Ar-H) and 7.56 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$) 14.0 and 14.6 (2x OCH_2CH_3), 30.7 (CH_2CH), 49.7 (CH_2CH), 61.6 and 64.8 (2x OCH_2CH_3), 114.2, 118.8, 119.8, 124.2, 125.3, 147.1, 143.2 and 146.3 (Ar-C), 160.8 and 168.6 (2x C=O); *m/z* (FAB) 362 (M^+, 63%) and 270 (100).

Reaction of 6-chloro-3-(chloromethyl)coumarin 156d with diethyl malonate enolate

The procedure described for the synthesis of 2-[(2-oxo-2*H*-chromen-3-yl)methyl]-propane-1,3-dioate **176a** was followed, using diethyl malonate (0.2ml), sodium ethoxide (1.6mmol) in dry ethanol (10ml) and 6-chloro-3-(chloromethyl)coumarin **156d** (0.34g, 1.5mmol). Work-up and chromatography afforded, as light yellow crystals, *diethyl 2-[(6-chloro-2-oxo-2*H*-chromen-3-yl)methyl]propane-1,3-dioate* **176d** (0.32g, 61%), m.p. 100-104^{o}C (Found: $\mathbf{M}^+$, 352.07230. $C_{17}H_{17}O_6{}^{35}Cl$ requires *M*, 352.07137); δ_H (400 MHz; $CDCl_3$) 1.19 (6H, t, *J* 7.2Hz, 2x OCH_2CH_3), 3.10 (2H, d, *J* 7.6Hz, CH_2CH), 3.91 (1H, t, *J* 7.6Hz, CH_2CH), 4.15 (4H, 2x q, *J* 6.0Hz, 2x OCH_2CH_3), 7.21-7.42 (3H, series of multiplets, Ar-H) and 7.53 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$) 14.0 (2x OCH_2CH_3), 30.6 (CH_2CH), 49.7 (CH_2CH), 61.6 (2x

O*C*H_2CH_3), 117.9, 120.1, 126.6, 126.7, 129.6, 131.1, 140.2 and 151.7 (Ar-C), 160.6 and 168.4 (C=O); *m/z* (FAB) 352 (M^+, 29%) and 260 (100).

Reaction of 6-bromo-3-(chloromethyl)coumarin 156e with diethyl malonate enolate

The procedure described for the synthesis of 2-[(2-oxo-2*H*-chromen-3-yl)methyl]propane-1,3-dioate **174a** was followed, using diethyl malonate (0.2ml), sodium ethoxide (36mg, 1.6mmol) in dry ethanol (10ml) and 6-bromo-3-(chloromethyl)coumarin **156e** (0.40g, 1.5mmol). Work-up and chromatography afforded, as a pale yellow solid, *diethyl 2-[(6-bromo-2-oxo-2*H*-chromen-3-yl)methyl]-propane-1,3-dioate* **176e** (0.27g, 45%), m.p. 104-106°C (Found: **M**$^+$, 396.02156. $C_{17}H_{17}O_6{}^{79}Br$ requires *M*, 396.02085); δ_H (400 MHz; $CDCl_3$) 1.19 (6H, t, *J* 7.2Hz, 2x OCH$_2$C*H*$_3$), 3.10 (2H, d, *J* 7.6Hz, C*H*$_2$CH), 3.90 (1H, t, *J* 7.6Hz, CH$_2$C*H*), 4.13 (4H, 2x q, *J* 6.8Hz, 2x OC*H*$_2$CH$_3$), 7.16 (1H, d, *J* 9.2Hz, Ar-H) and 7.53 (3H, overlapping signals, Ar-H); δ_C (100 MHz; $CDCl_3$) 14.0 (2x OCH$_2$*C*H$_3$), 30.6 (*C*H$_2$CH), 49.6 (CH$_2$*C*H), 61.6 (2x O*C*H$_2$CH$_3$), 116.9, 118.1, 120.6, 126.5, 129.7, 133.9, 140.1 and 152.1 (Ar-C), 160.5 and 168.4 (C=O); *m/z* 396 [M^+(^{79}Br), 8.3%] and 307 (100).

Reaction of 6,8-dibromo-3-(chloromethyl)coumarin 156f with diethyl malonate enolate

The procedure described for the synthesis of 2-[(2-oxo-2*H*-chromen-3-yl)methyl]propane-1,3-dioate **174a** was followed, using diethyl malonate (0.2ml), sodium ethoxide (1.6mmol) in dry ethanol (10ml) and 6,8-dibromo-3-(chloromethyl)coumarin **156f** (0.65g, 1.5mmol). Work-up and chromatography afforded, as a pale yellow solid, *diethyl 2-[(6,8-dibromo-2-oxo-2*H*-chromen-3-yl)methyl]propane-1,3-dioate* **176f** (0.30g, 42%), m.p. 126-130°C (Found: **M**$^+$, 473.93159. $C_{17}H_{16}O_6{}^{79}Br_2$ requires *M*, 473.93136); δ_H (400 MHz; $CDCl_3$) 1.21 (6H, t, *J* 7.0Hz, 2x OCH$_2$C*H*$_3$), 3.12 (2H, d, *J* 7.6Hz, C*H*$_2$CH), 3.90 (1H, t, *J* 7.8Hz, CH$_2$C*H*),

4.16 (4H, 2x q, *J* 7.2Hz, 2x OC*H*$_2$CH$_3$), 7.50-7.53 (2H, series of overlapping signals, Ar-H) and 7.81 (1H, d, *J* 1.6Hz, Ar-H); δ_C (100 MHz; $CDCl_3$) 14.0 (2x OCH$_2$*C*H$_3$), 30.4 (*C*H$_2$CH), 49.6 (CH$_2$*C*H), 61.7 (2x O*C*H$_2$CH$_3$), 110.9, 116.9, 112.3, 127.4, 129.1, 136.7, 139.9 and 149.2 (Ar-C), 159.6 and 168.4 (C=O); *m/z* 473 [M^+($^{79}Br_2$), 0.4%] and 329 (100).

Reaction of 3-(iodomethyl)coumarin 155a with piperidine

Method 1

To a solution of 3-(iodomethyl)coumarin **155a** (0.11g, 0.40mmol) in THF (*ca* 2ml) was added piperidine (0.1ml), and the mixture was stirred at room temperature in a stoppered round-bottomed flask for 3d. The solvent was evaporated *in vacuo* to afford the crude product, which was purified using preparative layer chromatography [elution with $CHCl_3$-EtOAc (3:1)] to afford, as a brown solid, 3-(piperidinomethyl)coumarin **150a** (80mg, 82%).

Method 2

To a solution of the quaternary salt **164a** (0.11g, 0.40mmol) in THF (*ca 2*ml) was added piperidine (0.1ml), and the mixture was stirred at room temperature in a stoppered round-bottomed flask for 3d. The solvent was evaporated *in vacuo* to afford the crude product, which was purified using preparative layer chromatography [elution with $CHCl_3$-EtOAc (3:1)] to afford, as a brown solid, 3-(piperidinomethyl)coumarin **150a** (40mg, 42%).

Reaction of 6-bromo-3-(iodomethyl)coumarin 155e with piperidine

The procedure (method 1, above) described for the synthesis of 3-(piperidino-methyl)coumarin **150a** was followed, using piperidine (0.1ml) and 6-bromo-3-(iodomethyl)coumarin **155e** (0.15g, 0.40mmol) in THF (*ca* 2ml), and stirring the mixture at room temperature for 4h. Work-up and chromatography afforded, as a pale yellow solid, *6-bromo-3-(piperidinomethyl)coumarin* **150e** (70mg, 55%), m.p. 116-

118°C (Found: **M**$^+$, 321.03675. $C_{15}H_{16}NO_2{}^{79}Br$ requires *M*, 321.03644); δ_H (400 MHz; $CDCl_3$) 1.46 (2H, m, C*H*$_2$CH$_2$CH$_2$N), 1.60 (4H, m, C*H*$_2$CH$_2$N), 2.46 (4H, br s, CH$_2$C*H*$_2$N), 3.40 (2H, s, CH$_2$N), 7.17 (1H, d, *J* 8.8Hz, ArH), 7.52 (1H, dd, *J* 8.8Hz and *J* 1.6Hz, Ar-H), 7.61 (1H, d, *J* 1.6Hz, Ar-H) and 7.70 (1H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 24.0, 26.0 and 54.7 (CH$_2$CH$_2$CH$_2$N), 56.9 (CH$_2$N), 116.7, 118.1, 121.0, 127.6, 129.8, 133.4, 137.9 and 151.7 (Ar-C) and 160.8 (C=O); *m/z* 321 [M$^+$(^{79}Br) 42%] and 85 (100).

Reaction of 3-(iodomethyl)coumarin 155a with benzylamine

The procedure (method 1, p.170) described for the synthesis of 3-(piperidino-methyl)coumarin **150a** was followed, using benzylamine (0.11ml) and 3-(iodomethyl)coumarin **155a** (0.11g, 0.40mmol) in THF (*ca* 2ml), and stirring the mixture at room temperature for 4h. Work-up and chromatography afforded, as a yellow solid, 3-(benzylaminomethyl)coumarin **149a** (60mg, 57%).

Reaction of 6-bromo- 3-(iodomethyl)coumarin 155e with benzylamine

The procedure (method 1, p.170) described for the synthesis of 3-(piperidino-methyl)coumarin **150a** was followed, using benzylamine (0.11ml) and 6-bromo-3-(iodomethy)lcoumarin **155e** (0.15g, 0.40mmol) in THF (*ca* 2ml), and stirring the mixture for 4h. Work-up and chromatography afforded, as a yellow solid, *3-(benzylaminomethyl)-6-bromocoumarin* **149e** (120mg, 88%), m.p. 106-110°C (Found: **M**$^+$, 342.01166. $C_{17}H_{13}O_3N{}^{79}Br$ requires *M*, 342.01296); δ_H (400 MHz; $CDCl_3$) 2.0 (1H, br s, NH), 3.74 (2H, s, C*H*$_2$NHCH$_2$Ph), 3.84 (2H, s, CH$_2$NC*H*$_2$Ph), 7.21 (1H, d, *J* 8.8Hz, Ar-H), 7.25-7.6 (7H, series of overlapping signals, Ar-H) and 7.65 (1H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 48.2 and 53.2 (CH$_2$NCH$_2$), 116.9, 118.2, 120.8, 127.2, 128.1, 128.5, 128.9, 129.8, 133.7, 137.6, 139.6 and 152.2 (Ar-C) and 160.7 (C=O); *m/z* 342 [M$^+$(^{79}Br), 7.6%) and 252 (100).

Reaction of 3-(chloromethyl)coumarin 156a with methylmagnesium bromide

To a solution of 3-(chloromethyl)coumarin **156a** (0.16g, 0.80mmol) in THF (2ml) was added methyl magnesium bromide (2M solution in THF; 1.0mmol, 0.15ml), and the mixture was boiled under reflux for 4h. Water was then added and the aqueous layer extracted with $CHCl_3$. The combined extracts were washed with satd. brine and dried (anhyd. $NaSO_4$), filtered and concentrated *in vacuo* to afford the crude product, which was purified using preparative layer chromatography [elution with $CHCl_3$-EtOAc (3:1)] to afford, as a brown solid, *3-ethylcoumarin* **178** (40mg, 29%), m.p. 68-70^oC ; δ_H (400 MHz; $CDCl_3$) 1.25 (3H, t, *J* 7.6Hz, CH_2CH_3), 2.60 (2H, q, *J* 7.0Hz, CH_2CH_3), 7.22-7.26 (1H, m Ar-H), 7.30 (1H, d, *J* 8.0Hz, Ar-H) and 7.45 (3H, overlapping signals, Ar-H); δ_C (100 MHz; $CDCl_3$) 12.3 (CH_2CH_3), 23.9 (CH_2CH_3), 116.4, 119.6, 124.2, 127.1, 130.4, 131.3, 137.5 and 153.0 (Ar-C) and 161.8 (C=O); *m/z* 174 (M^+, 0.5%) and 159 (100).

Reaction of 3-(iodomethyl)coumarin 155a with methylmagnesium bromide

To a solution of 3-(iodomethyl)coumarin **155a** (0.23g, 0.8mmol) in THF (2ml) under N_2 was added methylmagnesium bromide (3M solution in diethyl ether; 0.12ml, 1.0mmol) at –10^oC, and the resulting mixture was stirred for 24h at room temperature to give a pale-yellow precipitate, which was filtered off, washed with hexane and dried *in vacuo* to afford, as a pale yellow solid, *1,2-bis(2-oxo-2*H*-chromen-3-yl)ethane* **177** (0.18g, 94%), m.p. 90^oC (Found: **M**$^+$, 318.09055. $C_{20}H_{14}O_4$ requires *M*, 318.08921); δ_H (400 MHz; $CDCl_3$) 2.96 (4H, s, CH_2), 7.24 (2H, s, Ar-H), 7.31 (2H, d, *J* 10.0Hz, Ar-H), 7.41-7.48 (4H, series of overlapping signals, Ar-H) and 7.57 (2H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 30.1 (CH_2), 116.9, 119.8, 124.8, 127.8, 128.6, 131.2, 140.2 and 153.3(Ar-C) and 162.1 (C=O); *m/z* 318 [M^+, 88%) and 159 (100).

3.4. Potential HIV-1 protease inhibitors

3.4.1. Preparation of the hydroxyethylene dipeptide isostere

(L)-*N*,*N*-Dibenzylphenylalanine benzyl ester 190 [211]

To a homogeneous solution of L-phenylalanine **189** (30g, 182mmol), K_2CO_3 (80g, 0.58mmol) and water (120ml) was added benzyl chloride (66ml, 0.58mmol). The solution was heated under reflux for 16h. Heptane (80ml) and water (60ml) were added to the cooled reaction mixture. The organic solution was separated, washed with water-methanol (2:1; 2x30ml) and concentrated in *vacuo* to afford, as a pale yellow oil (L)-*N*,*N*-dibenzylphenylalanine benzyl ester **190** (60.9g, 77%); γ_{max} (nujol mull/ cm^{-1}) 1732 (C=O); δ_H (400 MHz; $CDCl_3$) 3.04 and 3.17 (2H, 2xdd, *J* 8.0Hz and *J* 8.0Hz, CH_2), 3.57 (2H, d, *J* 14Hz, CH_2), 3.75 (1H, t, *J* 7.6Hz, CH), 3.96 (2H, d, *J* 14Hz, CH_2), 5.23 (2H, 2 xd, *J* 12.0Hz, CH_2), 7.03-7.42 (20H, m, ArH); δ_C (100 MHz; $CDCl_3$) 35.6 (CH_2), 54.3 (2x CH_2), 62.3 (CH), 66.0 (CH_2), 126.2, 126.9, 128.10, 128.13, 128.25, 128.34, 128.4, 128.5, 128.7, 129.3, 135.9, 138.0 and 139.2 (Ar-C) and 172.1 (C=O).

(4*S*)-4-Dibenzylamino-3-oxo-5-phenylpentanonitrile 191[211]

A solution of the crude benzyl ester **190** (60g, 138mmol) in dry THF (162ml) was cooled to –45°C under N_2. A separate flask was charged with sodium amide (95%; 12g, 297mmol) under N_2 followed by THF (134ml); the slurry was cooled to –45°C and CH_3CN (16.5ml, 330mmol) was added over 15min, and the resulting solution was then added to the ester solution over 15min. After stirring the mixture at –45°C for 2h, the reaction was quenched with 25% aqueous citric acid (285ml). The organic layer was separated, washed with 20% brine (285ml), filtered and concentrated *in vacuo*. The residue was crystallized from ethanol (denatured with toluene; 150ml) to afford (4*S*)-4-dibenzylamino-3-oxo-5-phenylpentanonitrile **191** as white crystals (33g, 65%), m.p. 132-134°C (lit.[211] 84-85°C) (Found: $\mathbf{M}^+$, 368.18799. Calc. for $C_{25}H_{24}N_2O$: M, 368.18886); δ_H (400 MHz, $CDCl_3$) 3.0 (1H, dd, *J* 3.2Hz and *J* 13.2Hz,

CH), 3.1 (1H, d, *J* 9.6Hz, CH), 3.21 (1H, dd, *J* 9.6Hz and *J* 13.5Hz, CH), 3.54 (1H, dd, *J* 3.2Hz and *J* 9.5Hz, CH), 3.59 (2H, d, *J* 13.2Hz, CH_2), 3.81 (2H, d, *J* 4.8Hz, CH_2), 3.89 (1H, d, *J* 11.2, CH) and 7.15-7.40 (15H, m , Ar-H); δ_C (100 MHz; $CDCl_3$) 28.5 (CH_2), 30.0 (CH_2), 54.8 (CH_2), 68.5 (CH), 113.8, 126.4, 127.8, 128.6, 128.8, 129.0, 129.5 and 138.1 (Ar-C) and 196.9 (C=O); *m/z* 368 (M+, 0.2%) and 300 (100)

(5*S*)-2-Amino-5-dibenzylamino-4-oxo-1,6-diphenylhex-2-ene 192 [211]

To a solution of nitrile **191** (35g, 95.3mmol) in dry THF (99ml) at 10°C was added a solution of benzylmagnesium chloride in dry THF (2.0M; 139ml, 278mmol). The solution was warmed to 25°C and stirred for 16h. The reaction mixture was cooled to 5°C and quenched by slow addition of 10% aqueous citric acid (510ml). The organic layer was separated and washed with saturated brine (331ml), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was crystallized from EtOH (denatured with toluene; 99ml) to afford (5*S*)-2-amino-5-dibenzylamino-4-oxo-1,6-diphenylhex-2-ene **192** as a white crystals (39.6g, 90%), m.p. 100-102°C (lit.[211] 101-102°C) (Found: $\mathbf{M}^+$, 460.25368. Calc. for $C_{32}H_{32}N_2O$: *M*, 460.25146); γ_{max} (nujol mull/ cm^{-1}) 1597 (C=O); δ_H (400 MHz; $CDCl_3$) 2.98 and 3.15 (2H, 2xdd, *J* 6.4Hz and *J* 8.0Hz, CH_2), 3.48 (3H, m, CH_2 and CH), 3.65 (2H, d, *J* 14Hz, CH_2), 3.80 (2H, d, *J* 14Hz, CH_2), 4.89 (1H, br s, NH), 5.10 (1H, s, CH), 7.11-7.41 (20H, m, Ar-H) and 9.81 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) 32.5 (CH_2), 42.3 (CH_2), 54.4 (CH_2), 66.6 (CH), 96.9, 125.6, 126.7, 127.3, 128.0, 128.1, 128.7, 128.9, 129.3, 129.5, 135.8, 140.1, 140.2 and 162.8 (Ar-C and CH=C) and 198.1 (C=O); *m/z* 460 (M^+, 0.2%) and 300 (100).

(2*S*, 3*S*, 5*S*)-5-Amino-2-(dibenzylamino)-3-hydroxy-1,6-diphenylhexane 194 [211]

To a suspension of sodium borohydride (7.7g, 210mol) in dry THF (437ml) at –5°C, was added methanesulfonic acid (34ml, 525mmol), such that the temperature remained below 5°C. The reaction mixture was cooled to 0°C, and a solution of the enaminone **192** (39.6g, 86mmol) in THF (80ml) and *i*PrOH (46ml) was added, and the resulting mixture was stirred for 14h at 10°C. In a separate flask, a dispersion of sodium borohydride (13g, 343mmol) in THF (168ml) was cooled to 0°C, and

trifluoroacetic acid (33ml, 428mmol) was added slowly. The resulting mixture was stirred for 30min at 10°C and then added slowly to the enaminone solution maintaining the temperature below 15°C. The resulting mixture was stirred for 4h, cooled to 10°C, and quenched with 3M-NaOH (273ml). *tert*-Butyl methyl ether (315ml) was added and the organic layer was separated and washed with NaOH (33ml), 20% aqueous NH_4Cl (315ml) and 6% aqueous NaCl (2x 315ml). The organic solution was dried over Na_2SO_4 and concentrated *in vacuo* to afford a mixture of diastereomers **194** (40.3g).

(2*S*, 3*S*, 5*S*)-2,5-Diamino-3-hydroxy-1,6-diphenylhexane dihydrochloride 195 [211]

The diastereomeric mixture of the crude dibenzylamine **194** (40.3g, 86mmol), methanol (645ml), aqueous ammonium formate (27.4g in 46.3ml of water) and 5% palladium-on-carbon (50-60% water by weight; 8.0g) was heated under reflux for 6h. The cooled suspension was filtered through a bed of diatomaceous earth and the cake was washed with methanol (2x 300ml). The filtrate was concentrated *in vacuo* to afford an oil, which was dissolved in EtOAc (352ml) and washed with 4% aq.NaOH (402ml), 20% aqueous NaCl (390ml) and water (195ml). The organic layer was concentrated *in vacuo* and, to the residue, was added *i*PrOH (240ml) and conc. HCl (34ml). The resulting suspension was heated under reflux for 1h, cooled to 25°C and then stirred for 12h. The slurry was filtered and the cake washed with *i*PrOH to afford, as white crystals, the diamine dihydrochloride **195** (20g, 82%), m.p. 302-304°C (lit.[211] >300°C) (Found: $\mathbf{M}^+$-2Cl, 285.19812. Calc. for $C_{18}H_{25}N_2O$: *M*-70, 285.19669); δ_H (400 MHz; $CDCl_3$) 1.76 and 1.85 (2H, 2xm, CH_2), 2.91 (4H, m, 2xCH_2), 3.30 (1H, m, CH), 3.61 (1H, m, CH), 3.79 (1H, m, CH), 7.18-7.34 (10H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 36.8 (CH_2), 37.0 (CH_2), 40.0 (CH_2), 53.2 (CH), 58.6 (CH), 69.0 (CH), 128.60, 128.64, 130.20, 130.22, 130.5, 130.6, 136.7 and 136.9 (Ar-C).

(2*S*, *3S*, 5*S*)-2,5-Diamino-3-hydroxy-1,6-diphenylhexane 188[211]

A solution of the dihydrochloride salt **195** (0.50g, 1.4mmol) in water (2.0ml) was basified with a aqueous $NaHCO_3$ (monitored by pH indicator paper). The resulting solution was extracted with EtOAc. The combined extracts were dried over Na_2SO_4 and the solvent was evaporated *in vacuo* to afford (2*S*,3*S*,5*S*)-2,5-diamino-3-hydroxy-1,6-diphenylhexane **188** as a yellow oil (0.30g, 77%) (Found: $\mathbf{M}^+$-2Cl, 285.19599. Calc. for $C_{18}H_{25}N_2O$: *M*-70, 285.19669); δ_H (400 MHz; $CDCl_3$) 1.53 and 1.66 (2H, m, CH_2), 2.55-2.86 (5H, m, CH and 2x CH_2), 3.12 (1H, m, CH), 3.72 (1H, m, CH) and 7.12-7.32 (10H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 39.1 (CH_2), 41.2 (CH_2), 47.2 (CH_2), 54.0 (CH), 57.5 (CH), 74.4 (CH), 126.1, 126.5, 128.4, 128.6, 129.29, 129.30, 138.3 and 139.6 (ArC).

3.4.2. Preparation of coumarin containing ritonavir analogues

(2*S*,3*S*,5*S*)-3-Hydroxy-2,5-bis[(2-oxo-2*H*-chromen-3-yl)methylamino]-1,6-diphenylhexane 186a

Method 1

A mixture of 3-(iodomethyl)coumarin **155a** (0.11g, 0.4mmol) and (2*S*,3*S*,5*S*)-2,5-diamino-3-hydroxy-1,6-diphenylhexane **188** (0.14g, 0.50mmol) in THF (2ml) was stirred under N_2 at –45^{o}C for 8h. Evaporation of the solvent from the resulting mixture afforded a crude product (0.34g), which was purified by preparative layer chromatography [elution with EtOAc-MeOH (2.5:0.5)] to afford as a yellow oil, (2*S*, 3*S*,5*S*)-3-hydroxy-2,5-bis[(2-oxo-2*H*-chromen-3-yl)methylamino]-1,6-diphenyl-hexane **186a** (30mg, 25%).

Method 2

A mixture of 3-(iodomethyl)coumarin **155a** (0.11g, 0.4mmol), (2*S*,3*S*,5*S*)-2,5-diamino-3-hydroxy-1,6-diphenylhexane **188** (0.14g, 0.50mmol) and $NaHCO_3$ (0.2g) in acetone (5ml) was boiled under reflux for 2h. The resulting mixture was allowed to

cool and then filtered through a layer of silica. Evaporation of the filtrate *in vacuo* afforded a crude product (0.25g), which was purified by preparative layer chromatography [elution with hexane-EtOAc (2:3)] to afford, as a yellow oil, (2*S*,3*S*, 5*S*)-3-hydroxy-2,5-bis[(2-oxo-2*H*-chromen-3-yl)methylamino]-1,6-diphenylhexane **186a** (30mg, 13%)

Method 3

A mixture of 3-(chloromethyl)coumarin **156a** (0.16g, 0.8mmol), (2*S*,3*S*,5*S*)-2,5-diamino-3-hydroxy-1,6-diphenylhexane **188** (0.11g, 0.40mmol) and Na_2CO_3 (0.2g) in ethanol (3ml) was stirred for *ca.* 76h. The resulting mixture was filtered through a layer of silica and evaporation of the filtrate *in vacuo* afforded a crude product (0.18g), which was purified by preparative layer chromatography [elution with hexane-EtOAc (2:3)] to afford as a yellow oil, (*2*S,*3*S,*5*S*)-3-hydroxy-2,5-bis[(2-oxo-2*H*-chromen-3-yl)methylamino]-1,6-diphenylhexane* **186a** (60mg, 50%); (Found: $\mathbf{M}^+$, 600.26343. $C_{38}H_{36}N_2O_5$ require *M*, 600.26242); δ_H (400 MHz; $CDCl_3$) 1.68 (2H, m, CH_2), 2.65- 2.91 (4H, m, 2x CH_2), 3.01 (1H, dd, *J* 4.8Hz and *J* 13.2Hz, CH), 3.14 (1H, m, CH), 3.71 (4H, m, 2x CH_2), 4.01 (1H, d, *J* 14.8Hz, CH), 7.13-7.68 (20H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 36.0 (CH_2), 37.1(CH_2), 40.8(CH_2), 45.8 (CH_2), 46.8 (CH_2), 59.7 (CH), 63.5 (CH), 72.9 (CH), 117.8, 117.9, 120.1, 120.3, 126.2, 126.6, 126.9, 127.1, 128.1, 128.4, 128.6 129.0, 129.2, 129.3, 1295, 129.8, 130.8, 131.2, 137.5 137.8, 138.2, 139.2, 151.4 and 151.6 (Ar-C), 160.3 and 160.8 (C=O); *m/z* 597 [(M^+-2H), 0.8%] and 131 (100).

Method 4

A mixture of the quaternary salt **164a** (0.22g, 0.8mmol), (2*S*,3*S*,5*S*)-2,5-diamino-3-hydroxy-1,6-diphenylhexane **188** (0.11g, 0.40mmol) in ethanol (3ml) was stirred for *ca.* 76h. The resulting mixture was filtered through a layer of silica and evaporation of the filtrate *in vacuo* afforded, as a yellow oil, (2*S*,3*S*,5*S*)-3-hydroxy-2,5-bis[(2-oxo-2*H*-chromen-3-yl)methylamino]-3-hydroxy-1,6-diphenylhexane **186a** (0.10g, 85%).

(2*S*,3*S*,5*S*)-3-Hydroxy-2,5-bis[(8-methoxy-2-oxo-2*H*-chromen-3-yl)methylamino]-1,6-diphenylhexane 186b

A mixture of 8-methoxy-3-(chloromethyl)coumarin **156b** (0.18g, 0.8mmol), (2*S*,3*S*, 5*S*)-2,5-diamino-3-hydroxy-1,6-diphenylhexane **188** (0.11g, 0.40mmol) and Na_2CO_3 (0.2g) in ethanol (3ml) was stirred for *ca* 76h. The resulting mixture was filtered through a layer of silica, and evaporation of the filtrate *in vacuo* afforded a crude product (0.18g), which was purified by preparative layer chromatography [elution with EtOAc] to afford, as a yellow oil, *(2*S*,3*S*,5*S*)-3-hydroxy-2,5-bis[(8-methoxy-2-oxo-2*H*-chromen-3-yl)methylamino]-1,6-diphenylhexane* **186b** (70mg, 53%) (Found: **M**$^+$, 660.28558. $C_{40}H_{40}N_2O_7$ require *M*, 660.28355); δ_H (400 MHz; $CDCl_3$) 1.67 (2H, m, CH_2), 2.66-2.89 (4H, m, 2x CH_2), 2.98 (1H, m, CH), 3.13 (1H, m, CH), 3.71 (4H, m, 2x CH_2), 3.97 (7H, overlapping signals, CH and 2x CH_3), 6.96-7.66 (18H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 36.4 (CH_2), 37.0(CH_2), 40.6 (CH_2), 45.7 (CH_2), 46.8 (CH_2), 56.17 and 56.20 (2x CH_3), 59.7 (CH), 63.4 (CH), 72.9 (CH), 112.8, 113.2, 119.1, 119.2, 119.7, 120.0, 124.1, 124.3, 126.0, 126.5, 127.8, 126.9, 128.3, 128.6, 129.3, 129.4, 138.0, 138.8, 139.3, 139.6, 142.7, 142.8, 147.01 and 147.10 (Ar-C), 160.8 and 160.7 (C=O).

(2*S*,3*S*,5*S*)-3-Hydroxy-2,5-bis[(6-chloro-2-oxo-2*H*-chromen-3-yl)methylamino]-1,6-diphenylhexane 186d

A mixture of 6-chloro-3-(chloromethyl)coumarin **156d** (0.18g, 0.8mmol), (2*S*,3*S*,5*S*)-2,5-diamino-3-hydroxy-1,6-diphenylhexane **188** (0.11g, 0.40mmol) and Na_2CO_3 (0.2g) in ethanol (3ml) was stirred for *ca* 76h. The resulting mixture was filtered through a layer of silica, and evaporation of the filtrate *in vacuo* afforded a crude product (0.23g), which was purified by preparative layer chromatography [elution with EtOAc] to afford, as a yellow oil *(2*S*,3*S*,5*S*)-3-hydroxy-2,5-bis[(6-chloro-2-oxo-2*H*-chromen-3-yl)methylamino]-1,6-diphenylhexane* **186d** (95mg, 71%) (Found: **MH**$^+$, 669.19281. $C_{38}H_{35}{}^{35}Cl_2N_2O_5$ requires *M+1*, 669.19230); δ_H (400 MHz; $CDCl_3$) 1.63 (2H, m, CH_2), 2.76- 2.90 (3H, m, CH and CH_2), 2.94 and 2.97 (1H, dd, *J* 13.3 and *J* 4.8Hz, CH), 3.10 (1H, m, CH), 3.68 (4H, m, 2x CH_2), 3.96 (1H, d, *J* 15.2Hz, CH), 7.10-7.57 (19H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 36.5 (CH_2), 37.1

(CH_2), 40.7 (CH_2), 45.8 (CH_2), 46.8 (CH_2), 59.7 (CH), 63.5 (CH), 72.9 (CH), 117.8, 117.9, 120.1, 120.3, 126.2, 126.6, 126.9, 127.1, 128.1, 128.4, 128.7, 129.0, 129.2, 129.3, 1295, 129.8, 130.8, 131.2, 137.5, 137.8, 138.2, 139.2, 151.4 and 151.5 (Ar-C), 160.3 and 160.8 (C=O); *m/z* 668 (M^+, 1.1%) and 193 (100).

(2*S*,3*S*,5*S*)-3-Hydroxy-2,5-bis[(6-bromo-2-oxo-2*H*-chromen-3-yl)methylamino]-1,6-diphenylhexane 188e

A mixture of 6-bromo-3-(chloromethyl)coumarin **156e** (0.22g, 0.8mmol), (2*S*,3*S*,5*S*)-2,5-diamino-3-hydroxy-1,6-diphenylhexane **188** (0.11g, 0.40mmol) and Na_2CO_3 (0.2g) in ethanol (3ml) was stirred for *ca* 76h. The resulting mixture was filtered through a layer of silica, and evaporation of the filtrate *in vacuo* afforded a crude product (0.23g), which was purified by preparative layer chromatography [elution with EtOAc] to afford, as a yellow oil, *(2*S,*3*S,*5*S*)-3-hydroxy-2,5-bis[(6-bromo-2-oxo-2*H*-chromen-3-yl)methylamino]-1,6-diphenylhexane* **186e** (95mg, 63%) (Found: **(M+H)**, 757.0903. $C_{38}H_{35}{}^{79}Br_2N_2O_5$ require *M*, 757.09127); δ_H (400 MHz; $CDCl_3$) 1.64 (2H, m, CH_2), 2.74-2.89 (4H, m, 2x CH_2), 2.95 (1H, dd, *J* 8.4Hz and *J* 13.2Hz, CH), 3.10 (1H, m, CH), 3.68 (4H, m, 2x CH_2), 3.95 (1H, d, *J* 15.2Hz, CH), 7.07-7.53 (18H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 36.6 (CH_2), 37.1 (CH_2), 40.7 (CH_2), 45.8 (CH_2), 46.7 (CH_2), 59.7 (CH), 63.5 (CH), 72.9 (CH), 116.8, 117.0, 118.1, 118.2, 120.6, 120.8, 126.2, 126.6, 128.3, 128.4, 128.6, 129.1, 129.3, 129.4, 129.9, 130.0, 133.5, 134.0, 137.2, 137.89, 137.92, 139.3, 151.8 and 152.0 (Ar-H), 160.56 and 160.57 (2x C=O).

3.5. High-resolution mass spectrometric data

3-(Benzylaminomethyl)coumarin **149a**

Formula	**Observed Mass**	**Calculated Mass**
$C_{17}H_{15}NO_2$	265.10800	265.11028
$C_{17}H_{14}NO_2$	264.10378	264.10245
$C_{10}H_8NO_2$	174.05556	174.05550
$C_{10}H_8O_2$	160.05253	160.05243
$C_{10}H_7O_2$	159.04557	159.04460
C_9H_8O	132.05585	132.05751
C_9H_7O	131.04967	131.04969
C_9H_7	115.05437	115.05478
C_7H_8N	106.06646	106.06567

3-(Benzylaminomethyl)-8-methoxycoumarin **149b**

Formula	**Observed Mass**	**Calculated Mass**
$C_{18}H_{17}NO_3$	295.11889	295.12084
$C_{18}H_{16}NO_3$	294.11201	294.11302
$C_{11}H_{10}NO_3$	204.06667	204.06607
$C_{11}H_{10}O_3$	190.06200	190.06299
$C_{11}H_9O_3$	189.05356	189.05517
$C_{10}H_9O_2$	161.05823	161.06025
C_7H_8N	106.06572	106.06567

3-(Benzylaminomethyl)-8-ethoxycoumarin **149c**

Formula	**Observed Mass**	**Calculated Mass**
$C_{19}H_{19}NO_3$	309.13550	309.13649
$C_{19}H_{18}NO_3$	308.12906	308.12867
$C_{17}H_{13}NO_3$	279.09096	279.08954
$C_{12}H_{12}NO_3$	218,08219	218,08172
$C_{12}H_{12}O_3$	204.07760	204.07864
$C_{12}H_{11}O_3$	203.07136	203.07082
$C_{10}H_8NO_3$	190.05053	190.05042
$C_{10}H_8O_3$	176.04727	176.04734
$C_{10}H_7O_3$	175.04101	175.04220
C_7H_8N	106.06585	106.66567

3-(Benzylaminomethyl)-6-chlorocoumarin **149d**

Formula	**Observed Mass**	**Calculated Mass**
$C_{17}H_{13}NO_2{}^{35}Cl$	298.06312	298.06348
$C_{10}H_7NO_2{}^{35}Cl$	208.01637	208.01653
$C_{10}H_8NO_2$	174.05320	174.05550
$C_9H_7O{}^{35}Cl$	166.01672	166.01854
$C_9H_6O{}^{35}Cl$	165.01057	165.01072
$C_{10}H_7O_2$	159.04289	159.04460
$C_9H_6{}^{35}Cl$	149.01514	149.01580
C_9H_7O	131.04915	131.04969
C_7H_8N	106.06494	106.06567

3-(Benzylaminomethyl)-6-bromocoumarin **149e**

Formula	**Observed Mass**	**Calculated Mass**
$C_{17}H_{14}NO_2{}^{79}Br$	343.02410	343.02357
$C_{11}H_9O_2{}^{79}Br$	251.97943	251.07859
$C_{10}H_7O_2{}^{79}Br$	237.96097	237.96294
$C_{10}H_6O_2{}^{79}Br$	236.95387	236.95512
$C_9H_6O^{79}Br$	208.95883	208.96020
$C_{10}H_7NO_2$	173.04734	173.04768
C_9H_7NO	145.05268	145.05276
C_9H_7O	131.04870	131.04969
C_7H_8N	106.06559	106.06567

3-(Piperidinomethyl)coumarin **150a**

Formula	**Observed Mass**	**Calculated Mass**
$C_{15}H_{17}NO_2$	243.12507	243.12593
$C_{13}H_{12}NO_2$	214.08792	214.08680
$C_{12}H_{10}NO_2$	200.07173	200.07115
$C_{11}H_9NO_2$	187.06395	187.06333
$C_{10}H_8O_2$	160.05259	160.05243
$C_{10}H_7O_2$	159.04461	159.04460
C_9H_8O	132.05676	132.05751
C_9H_7O	131.04978	131.04969
C_9H_7	115.05417	115.05478
$C_5H_{10}N$	84.08238	84.08132

8-Methoxy-3-(piperidinomethyl)coumarin **150b**

Formula	Observed Mass	Calculated Mass
$C_{16}H_{19}NO_3$	273.13683	273.13649
$C_{14}H_{14}NO_3$	244.09818	244.09737
$C_{13}H_{12}NO_3$	230.08249	230.08172
$C_{12}H_{11}NO_3$	217.07386	217.07389
$C_{11}H_{10}O_3$	190.06355	190.06299
$C_{11}H_9O_3$	189.05593	189.05517
$C_{10}H_{10}O_2$	162.06678	162.06808
C_9H_7O	131.04899	131.04969
$C_5H_{10}N$	84.08116	84.08132

8-Ethoxy-3-(piperidinomethyl)coumarin **150c**

Formula	**Observed Mass**	**Calculated Mass**
$C_{17}H_{21}NO_3$	287.15264	287.15214
$C_{15}H_{16}NO_3$	258.11412	258.11302
$C_{14}H_{14}NO_3$	244.09787	244.09737
$C_{13}H_{13}NO_3$	231.08994	231.08954
$C_{12}H_{12}O_3$	204.07961	204.07864
$C_{12}H_{11}O_3$	203.07209	203.07082
$C_{10}H_{18}O_3$	176.04760	176.04734
$C_9H_7O_2$	147.04439	147.04460
C_9H_7O	131.04944	131.04969
$C_5H_{10}N$	84.08152	84.08132

6-Chloro-3-(piperidinomethyl)coumarin **150d**

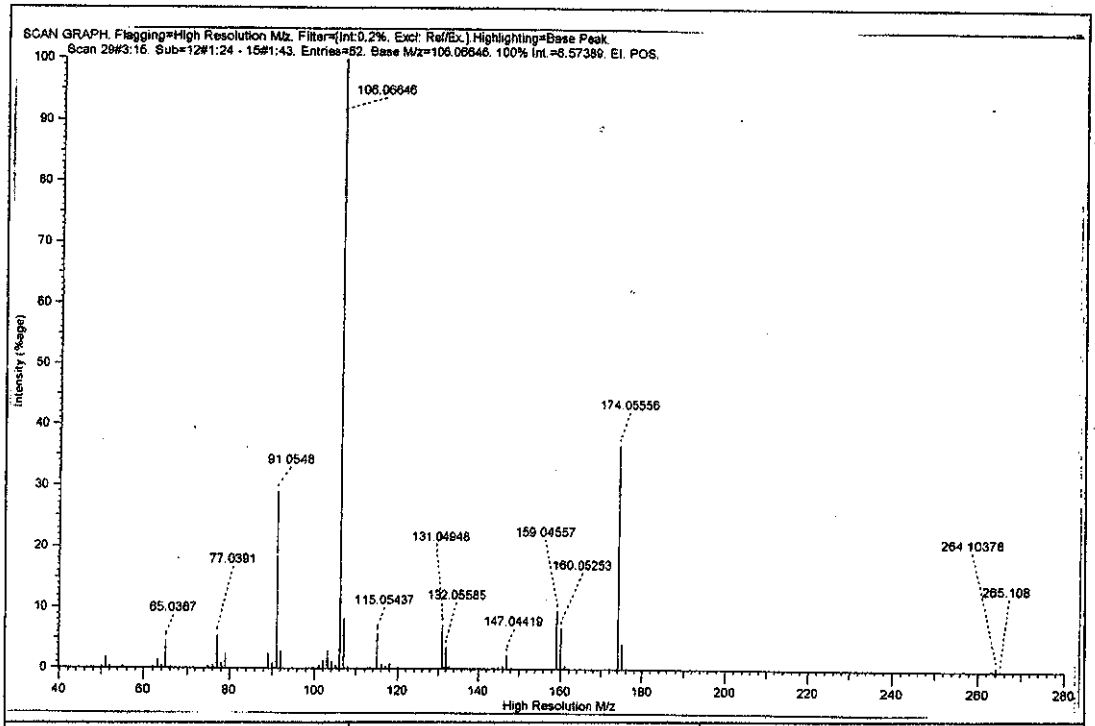
Formula	**Observed Mass**	**Calculated Mass**
$C_{15}H_{16}NO_2{}^{35}Cl$	277.08701	277.08696
$C_{13}H_{11}NO_2{}^{35}Cl$	248.04834	248.04783
$C_{12}H_9NO_2{}^{35}Cl$	234.03262	234.03218
$C_{11}H_8NO_2{}^{35}Cl$	221.02359	221.02436
$C_9H_5NO_2{}^{35}Cl$	193.99831	194.00088
$C_9H_6O^{35}Cl$	165.01029	165.01072
$C_5H_{10}N$	84.08143	84.08132

6-Bromo-3-(piperidinomethyl)coumarin **150e**

Formula	**Observed Mass**	**Calculated Mass**
$C_{15}H_{16}NO_2{}^{79}Br$	321.03543	321.03644
$C_{13}H_{11}NO_2{}^{79}Br$	291.99576	291.99731
$C_{12}H_9NO_2{}^{79}Br$	277.98160	277.98166
$C_{11}H_8NO_2{}^{79}Br$	264.97443	264.97384
$C_{11}H_7NO_2{}^{79}Br$	237.96336	237.96294
$C_{11}H_6NO_2{}^{79}Br$	236.955589	236.95512
$C_9H_6O^{79}Br$	208.95896	208.96020
$C_5H_{10}N$	84.08143	84.08132

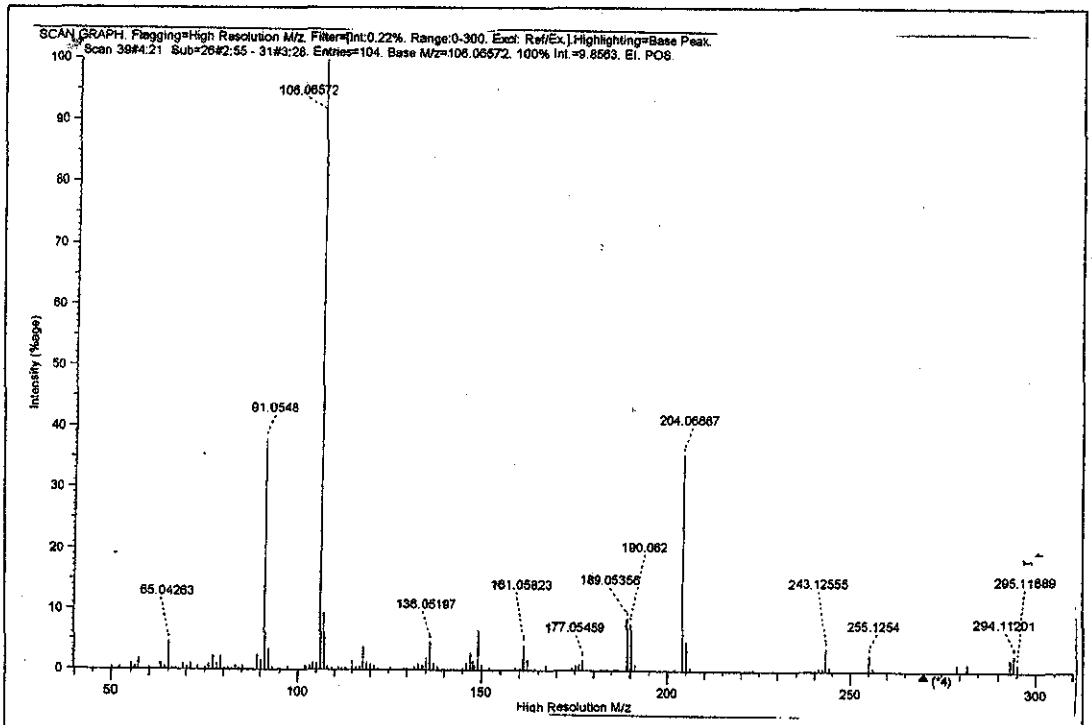
3.5. High-resolution mass spectrometric data

3-(Benzylaminomethyl)coumarin **149a**



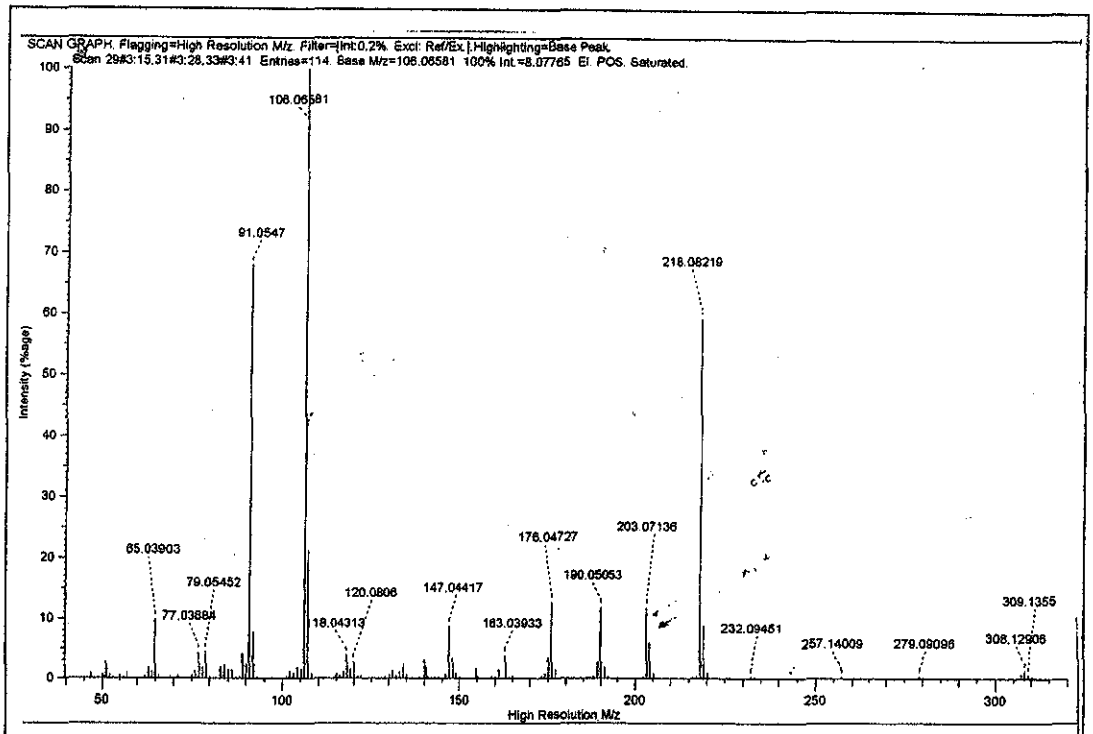
Formula	Observed Mass	Calculated Mass
$C_{17}H_{15}NO_2$	265.10800	265.11028
$C_{17}H_{14}NO_2$	264.10378	264.10245
$C_{10}H_8NO_2$	174.05556	174.05550
$C_{10}H_8O_2$	160.05253	160.05243
$C_{10}H_7O_2$	159.04557	159.04460
C_9H_8O	132.05585	132.05751
C_9H_7O	131.04967	131.04969
C_9H_7	115.05437	115.05478
C_7H_8N	106.06646	106.06567

3-(Benzylaminomethyl)-8-methoxycoumarin **149b**



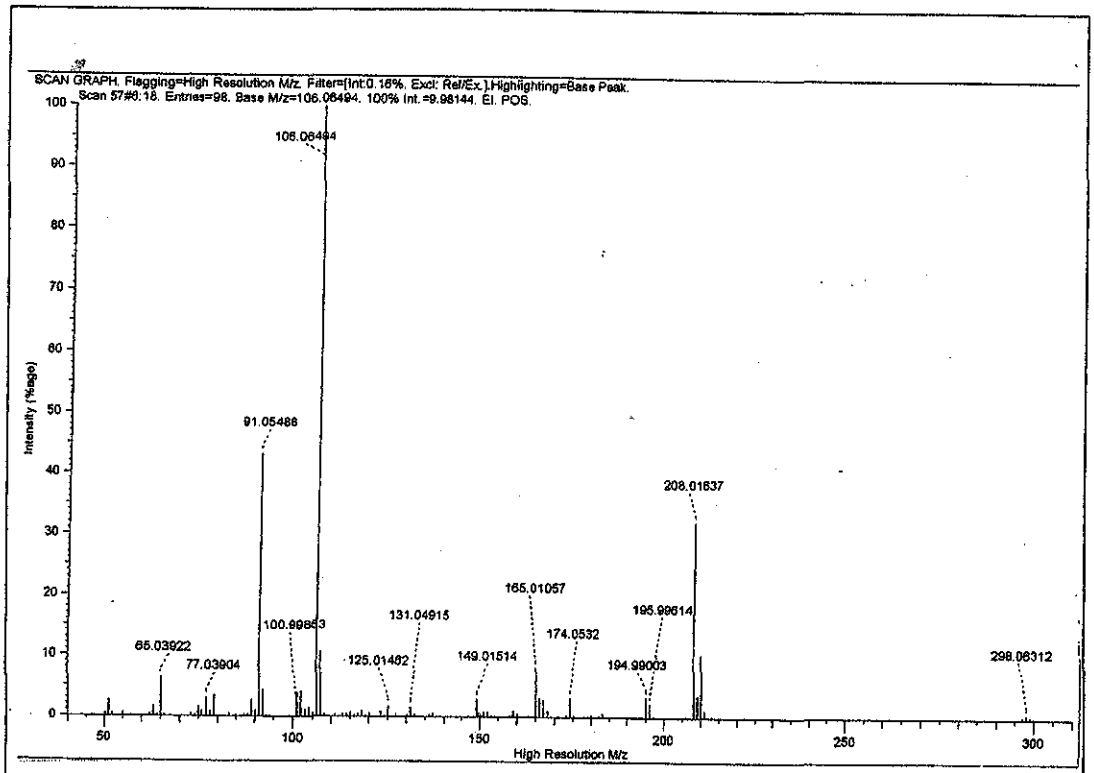
Formula	Observed Mass	Calculated Mass
$C_{18}H_{17}NO_3$	295.11889	295.12084
$C_{18}H_{16}NO_3$	294.11201	294.11302
$C_{11}H_{10}NO_3$	204.06667	204.06607
$C_{11}H_{10}O_3$	190.06200	190.06299
$C_{11}H_9O_3$	189.05356	189.05517
$C_{10}H_9O_2$	161.05823	161.06025
C_7H_8N	106.06572	106.06567

3-(Benzylaminomethyl)-8-ethoxycoumarin **149c**



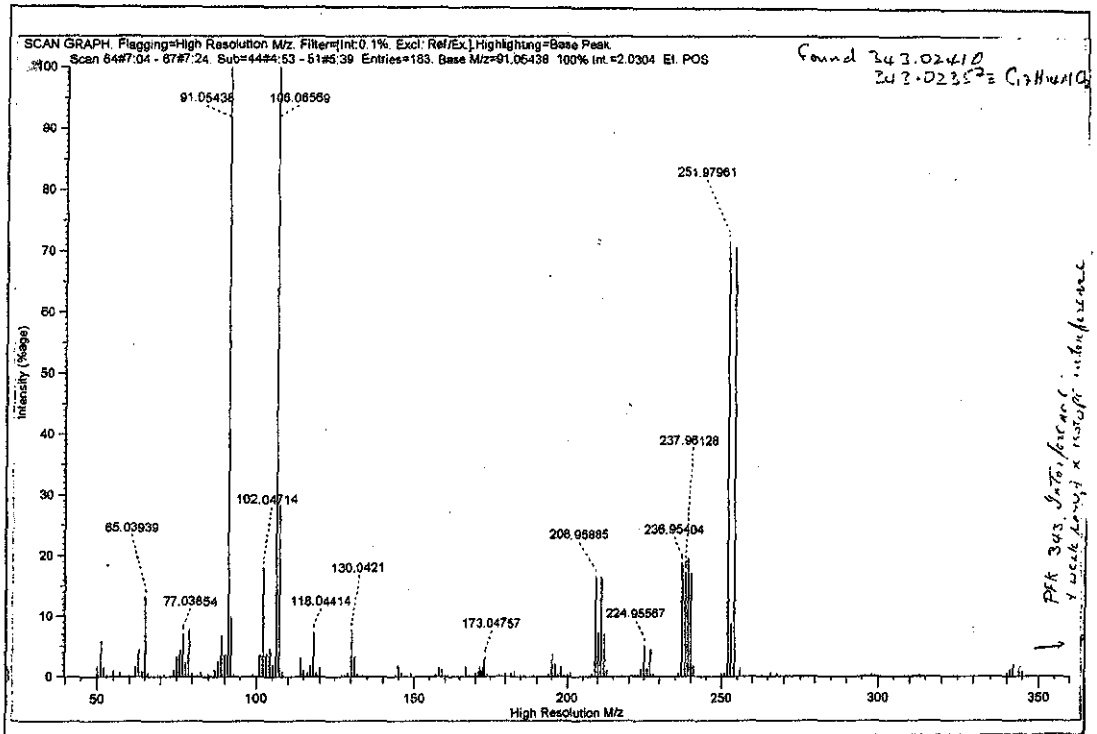
Formula	Observed Mass	Calculated Mass
$C_{19}H_{19}NO_3$	309.13550	309.13649
$C_{19}H_{18}NO_3$	308.12906	308.12867
$C_{17}H_{13}NO_3$	279.09096	279.08954
$C_{12}H_{12}NO_3$	218,08219	218,08172
$C_{12}H_{12}O_3$	204.07760	204.07864
$C_{12}H_{11}O_3$	203.07136	203.07082
$C_{10}H_8NO_3$	190.05053	190.05042
$C_{10}H_8O_3$	176.04727	176.04734
$C_{10}H_7O_3$	175.04101	175.04220
C_7H_8N	106.06585	106.66567

3-(Benzylaminomethyl)-6-chlorocoumarin **149d**



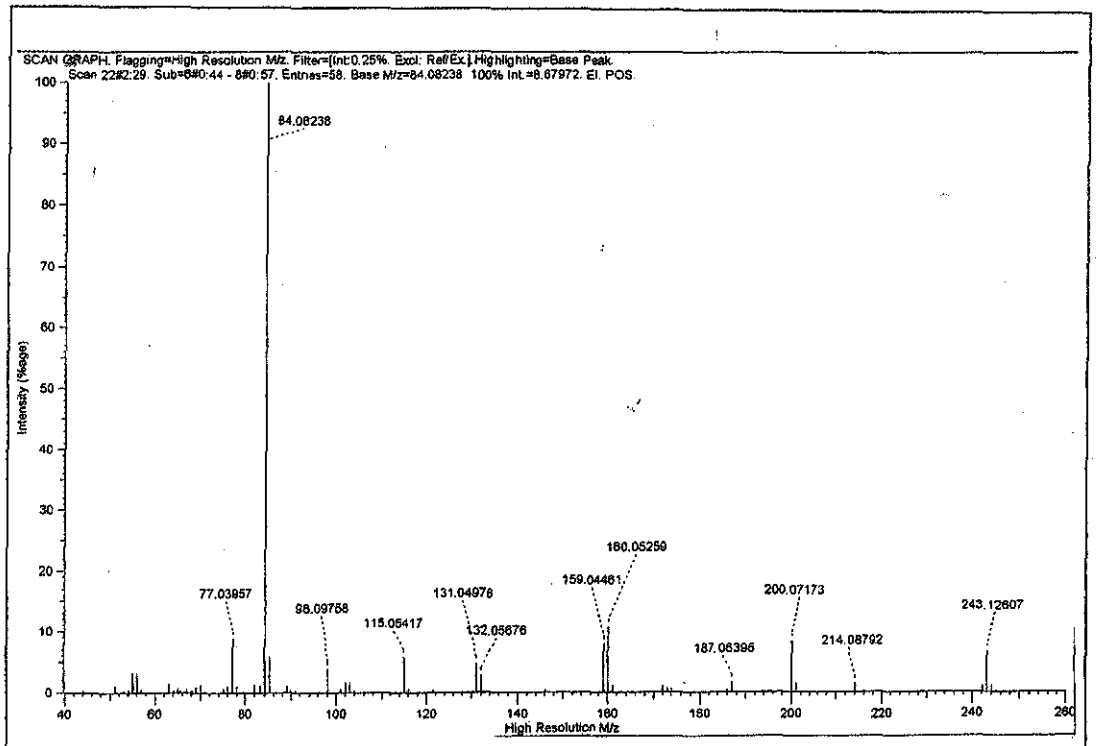
Formula	Observed Mass	Calculated Mass
$C_{17}H_{13}NO_2{}^{35}Cl$	298.06312	298.06348
$C_{10}H_7NO_2{}^{35}Cl$	208.01637	208.01653
$C_{10}H_8NO_2$	174.05320	174.05550
$C_9H_7O^{35}Cl$	166.01672	166.01854
$C_9H_6O^{35}Cl$	165.01057	165.01072
$C_{10}H_7O_2$	159.04289	159.04460
$C_9H_6{}^{35}Cl$	149.01514	149.01580
C_9H_7O	131.04915	131.04969
C_7H_8N	106.06494	106.06567

3-(Benzylaminomethyl)-6-bromocoumarin **149e**



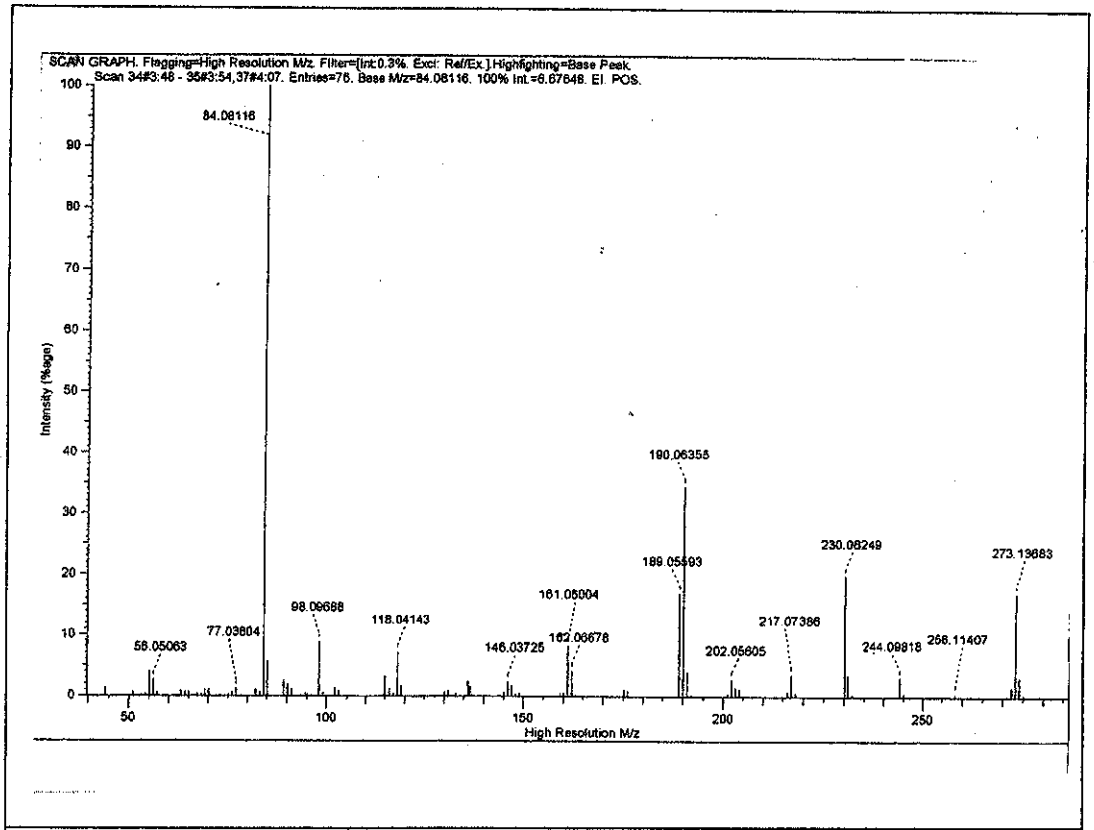
Formula	Observed Mass	Calculated Mass
$C_{17}H_{14}NO_2{}^{79}Br$	343.02410	343.02357
$C_{11}H_9O_2{}^{79}Br$	251.97943	251.07859
$C_{10}H_7O_2{}^{79}Br$	237.96097	237.96294
$C_{10}H_6O_2{}^{79}Br$	236.95387	236.95512
$C_9H_6O^{79}Br$	208.95883	208.96020
$C_{10}H_7NO_2$	173.04734	173.04768
C_9H_7NO	145.05268	145.05276
C_9H_7O	131.04870	131.04969
C_7H_8N	106.06559	106.06567

3-(Piperidinomethyl)coumarin **150a**



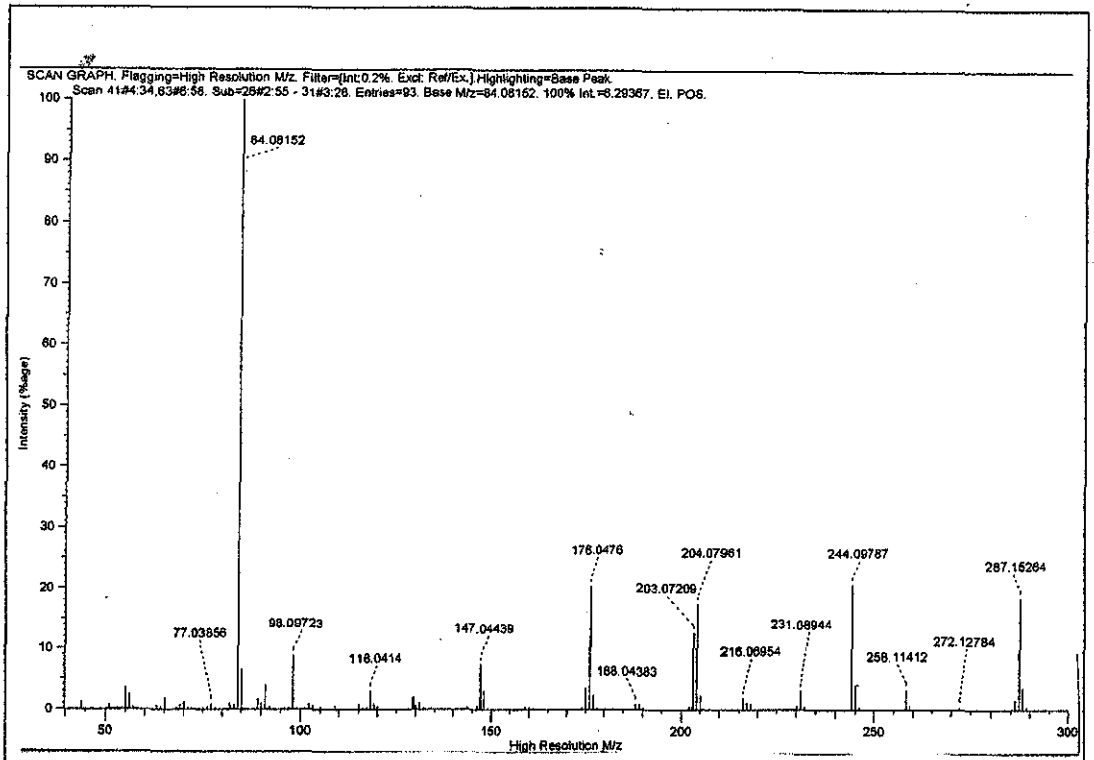
Formula	Observed Mass	Calculated Mass
$C_{15}H_{17}NO_2$	243.12507	243.12593
$C_{13}H_{12}NO_2$	214.08792	214.08680
$C_{12}H_{10}NO_2$	200.07173	200.07115
$C_{11}H_9NO_2$	187.06395	187.06333
$C_{10}H_8O_2$	160.05259	160.05243
$C_{10}H_7O_2$	159.04461	159.04460
C_9H_8O	132.05676	132.05751
C_9H_7O	131.04978	131.04969
C_9H_7	115.05417	115.05478
$C_5H_{10}N$	84.08238	84.08132

8-Methoxy-3-(piperidinomethyl)coumarin **150b**



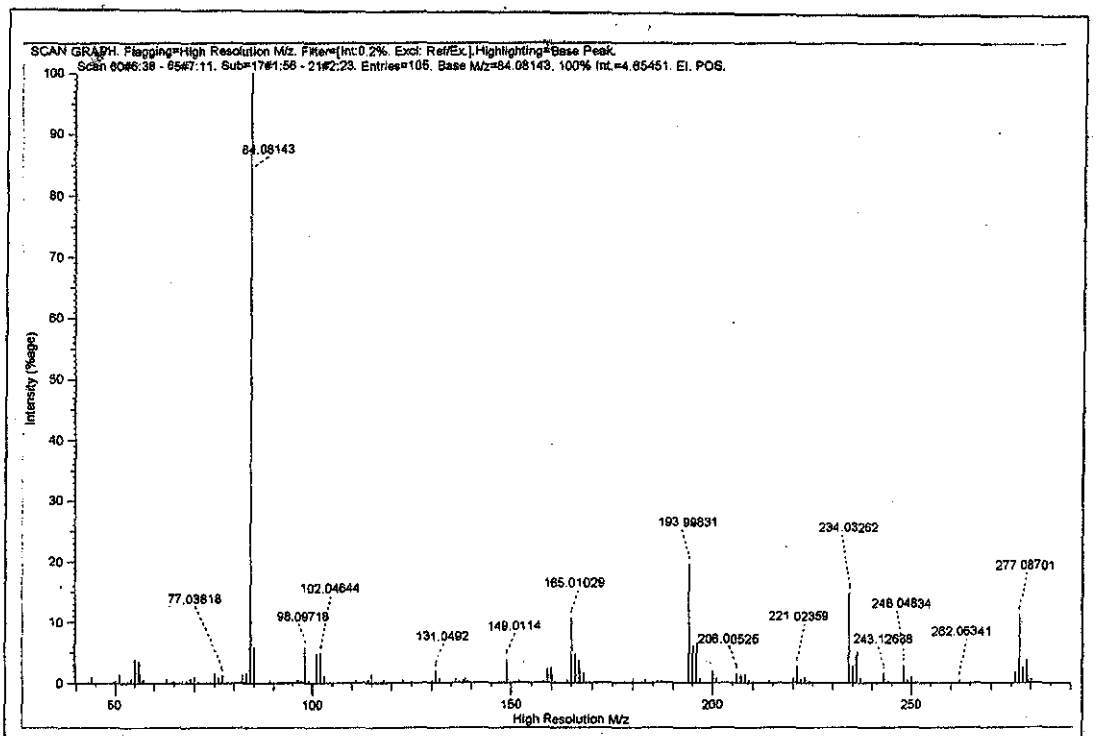
Formula	Observed Mass	Calculated Mass
$C_{16}H_{19}NO_3$	273.13683	273.13649
$C_{14}H_{14}NO_3$	244.09818	244.09737
$C_{13}H_{12}NO_3$	230.08249	230.08172
$C_{12}H_{11}NO_3$	217.07386	217.07389
$C_{11}H_{10}O_3$	190.06355	190.06299
$C_{11}H_9O_3$	189.05593	189.05517
$C_{10}H_{10}O_2$	162.06678	162.06808
C_9H_7O	131.04899	131.04969
$C_5H_{10}N$	84.08116	84.08132

8-Ethoxy-3-(piperidinomethyl)coumarin **150c**



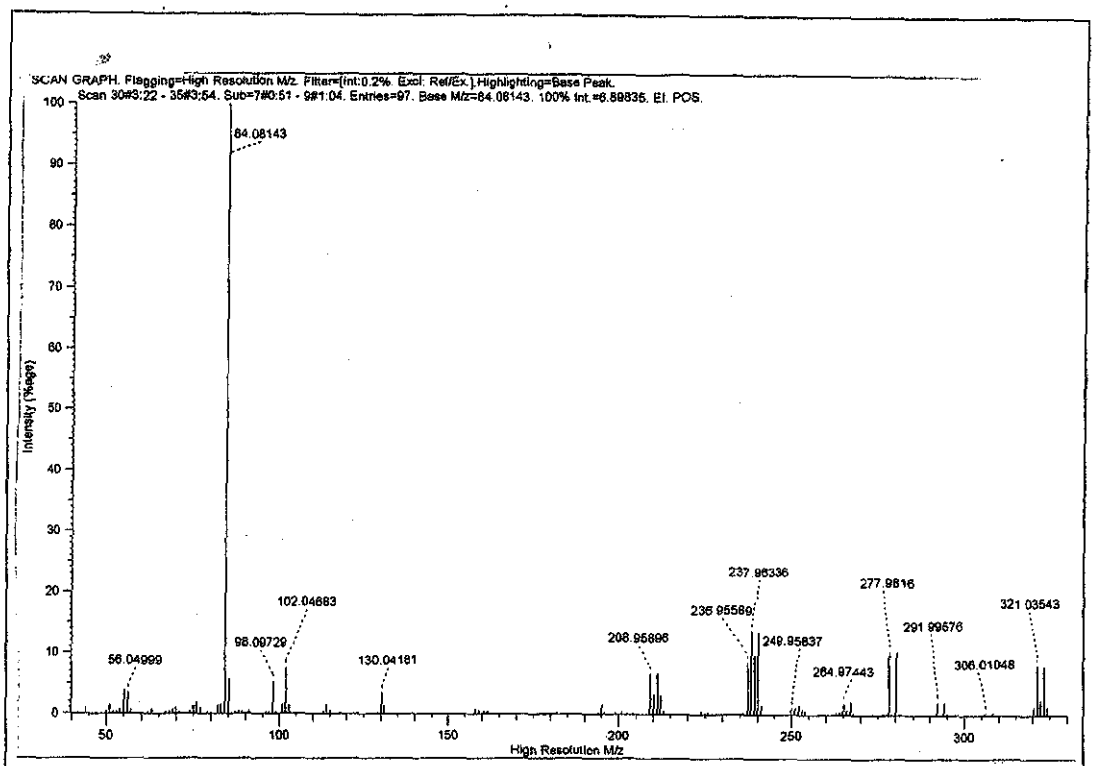
Formula	Observed Mass	Calculated Mass
$C_{17}H_{21}NO_3$	287.15264	287.15214
$C_{15}H_{16}NO_3$	258.11412	258.11302
$C_{14}H_{14}NO_3$	244.09787	244.09737
$C_{13}H_{13}NO_3$	231.08994	231.08954
$C_{12}H_{12}O_3$	204.07961	204.07864
$C_{12}H_{11}O_3$	203.07209	203.07082
$C_{10}H_{18}O_3$	176.04760	176.04734
$C_9H_7O_2$	147.04439	147.04460
C_9H_7O	131.04944	131.04969
$C_5H_{10}N$	84.08152	84.08132

6-Chloro-3-(piperidinomethyl)coumarin **150d**



Formula	Observed Mass	Calculated Mass
$C_{15}H_{16}NO_2{}^{35}Cl$	277.08701	277.08696
$C_{13}H_{11}NO_2{}^{35}Cl$	248.04834	248.04783
$C_{12}H_9NO_2{}^{35}Cl$	234.03262	234.03218
$C_{11}H_8NO_2{}^{35}Cl$	221.02359	221.02436
$C_9H_5NO_2{}^{35}Cl$	193.99831	194.00088
$C_9H_6O^{35}Cl$	165.01029	165.01072
$C_5H_{10}N$	84.08143	84.08132

6-Bromo-3-(piperidinomethyl)coumarin **150e**



Formula	Observed Mass	Calculated Mass
$C_{15}H_{16}NO_2{}^{79}Br$	321.03543	321.03644
$C_{13}H_{11}NO_2{}^{79}Br$	291.99576	291.99731
$C_{12}H_9NO_2{}^{79}Br$	277.98160	277.98166
$C_{11}H_8NO_2{}^{79}Br$	264.97443	264.97384
$C_{11}H_7NO_2{}^{79}Br$	237.96336	237.96294
$C_{11}H_6NO_2{}^{79}Br$	236.955589	236.95512
$C_9H_6O^{79}Br$	208.95896	208.96020
$C_5H_{10}N$	84.08143	84.08132

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