APPLICATION OF BAYLIS-HILLMAN METHODOLOGY IN THE SYNTHESIS OF HIV-1 ENZYME INHIBITORS

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MELODDY HLATINI MANYERUKE

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ABSTRACT

The application of Baylis-Hillman methodology has afforded access to a range of β-hydroxypropionate ester-AZT conjugates as potential dual-action HIV-1 IN/RT inhibitors. Two families comprising a total of nine β-hydroxypropionate ester-AZT conjugates were synthesised. The first family was accessed using *O*-benzylated salicylaldehydes and methyl acrylate and the second from unprotected salicylaldehydes using *tert*-butyl acrylate as the activated alkene. Spectroscopic methods were employed to fully characterize the compounds. Propargylation of the respective Baylis-Hillman adducts was achieved *via* conjugate addition of propargylamine. The resulting products were then employed in Cu(I)-catalysed "click" reactions with azidothymidine (AZT) to yield the desired β-hydroxypropionate ester-AZT conjugates.

Exploratory studies were also conducted to access 4-hydroxycoumarins from Baylis-Hillman derived adducts and to construct customized chiral Baylis-Hillman reaction sites. Many 4-hydroxycoumarins are known to exhibit a wide range of biological activities, and extending Baylis-Hillman methodology to access these systems is an important challenge. Two approaches were investigated. The first involved the formation of a 4-phthalimidocoumarin, aromatisation and hydrolysis of which was expected to lead to the 4-hydroxycoumarin target. The second, a variation of the first, involved the use of 4-(chrolomethyl)coumarin intermediates. Unfortunately, while various intermediates were prepared and characterised, neither approach led ultimately to the desired targets. *N*-substituted borneol-10-sulfonamides were constructed from camphor-10-sulfonyl chloride as chiral Baylis-Hillman reaction sites. In a preliminary study, however, none of the *N*-substituted borneol-10-sulfonamides exhibited Baylis-Hillman catalytic activity.

ACKNOWLEDGEMENTS

To the Creator and Original Scientist, my God and Father, who by his word has created everything seen and unseen and upholds all by the word of his power, be glory and thanks for his grace and love towards me and all his creation. He is omnipotent, lives forever, his dominion is an everlasting dominion and his kingdom is from generation to generation. He does according to his will among the inhabitants of the earth and none can stay his hand, or say to him, what doest thou. Nothing happens without him allowing it. He allowed me by his mercy to embark on and complete this work. So then it is not of him that willeth, nor of him that runneth, but of God that sheweth mercy (Rom. 9:16). May his name be praised.

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CONTENTS

1. INTRODUCTION

1.1. THE BAYLIS–HILLMAN REACTION

The formation of carbon-carbon bonds and functional group transformations constitute important challenges in organic chemistry research.[1,2] The Baylis-Hillman reaction is one of the recent carbon-carbon bond formation reactions and stands alongside other important reactions which include the Claisen rearrangements, Friedel-Crafts reaction, Diels-Alder reaction, Aldol reaction, Heck reaction and Reformatsky reaction.[1] Atom economy is a desirable feature in carbon-carbon forming reactions and is achieved in the Baylis-Hillman, Michael, Aldol and Diels-Alder reactions.[3] An efficient synthetic reaction needs to be not only atom economic but also when necessary, permit selective (regio-, stereo- and chemo-selective) transformations and efficient catalytic options.[1] The Baylis-Hillman reaction, while having both atom economy and functional group generation as its features, also has other desirable features, such as organocatalytic and aqueous media possibilities both of which are of environmental importance (green chemistry).[1,3] The Baylis-Hillman methodology is also attractive because the starting materials are often commercially available, large scale production is feasible, and the reaction proceeds under mild conditions.[2]

The methodology had its origins in work by different scientists in the sixties and seventies. In 1963 researchers[2,4] reported the tryalkylphosphine-catalysed dimerization of alkyl acrylates to give 2-methyleneglutarate derivatives, and this was followed in 1968 by the description by Morita and co-workers[4] of the reaction of aldehydes with acrylates or acrylonitrile using the catalyst tricyclohexylphosphine to produce 2-methylene-3-hydroxy alkanoates or alkylnitriles (using acrylonitrile). Baylis and Hillman in 1972 reported the production of highly functionalised molecules from the coupling of activated alkenes, α,β-unsaturated esters and ketones catalysed by tertiary amines, such as quinuclidine and 1,4-diazabicyclo[2.2.2]octane (DABCO) (**Figure 1**). The reaction came to be referred to as the Baylis-Hillman reaction and, subsequently, in recognition of Morita's contribution, also became known as the Morita-Baylis-Hillman (MBH) reaction.[2,4,5]

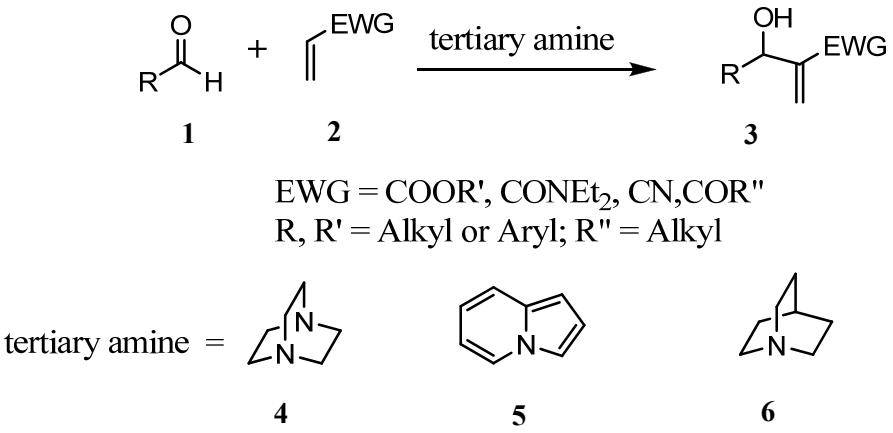


Figure 1. The Baylis-Hillman reaction, as identified in the original patent information.[5]

According to Wei and Shi the classical MBH reaction involves the formation of α-methylene-β-hydroxycarbonyl compounds by the combination of α,β-unsaturated carbonyl compounds with aldehydes under the influence of tertiary amine or phosphine as a catalyst.[2] It can be described as an atom-economic, carbon-carbon bond-forming reaction between activated alkenes at their α-position and carbon electrophiles in the presence of a catalyst or catalytic system to produce densely functionalized molecules referred to as Baylis-Hillman adducts.[3]

The main features of this reaction can be described as follows, first, it has three components (electrophiles, activated alkenes or alkynes, and catalysts) enabling a wide selection of substrates. When electrophiles are prochiral, a stereogenic centre is generated thus providing the asymmetric version of the reaction. The densely functionalised products (MBH adducts), which have three functional groups in close proximity to each other, are very useful synthons in the construction of various synthetic targets which include natural products. Intramolecular elaboration of the adducts can afford heterocyclic and carbocyclic compounds.[3-5] Interest in the reaction initially grew slowly only to grow exponentially in recent decades as its synthetic potential drew the attention of many synthetic organic chemists. In the process, the breadth of the three essential elements used in the reaction, *viz*., the activated olefin, catalyst and electrophile has also grown significantly.[6] The numerous publications on various aspects of the reaction are testimony to its phenomenal growth in recent years.[3]

1.1.1. Activated alkenes/alkynes, electrophiles and catalysts

Variations in the selection of the essential components, alkyne/alkene, electrophile and catalytic system has resulted in the generation of a large number of classes of highly functionalised adducts and the lure to create new classes of multi-functionalised molecules is driving research in this area.[4] Examples of alkenes and alkynes that have been used with success in the Baylis-Hillman methodology are illustrated in **Figure 2**.

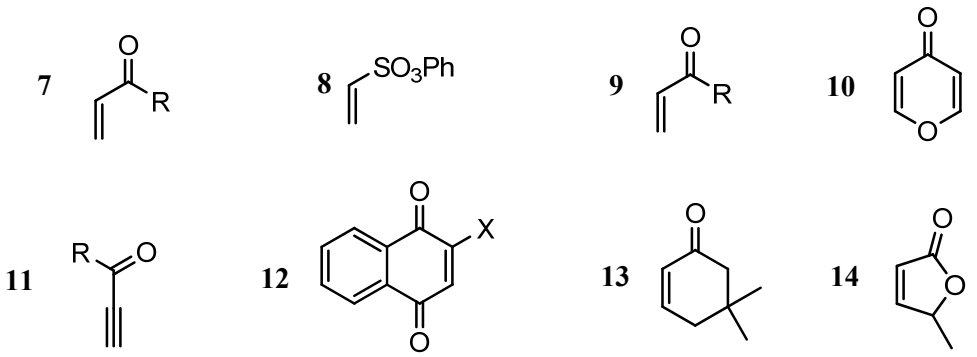


Figure 2. Activated, alkenes and alkynes used in the MBH reaction.[3,5]

Over the years a number of electrophiles have been used successfully including those illustrated in **Figure 3**.

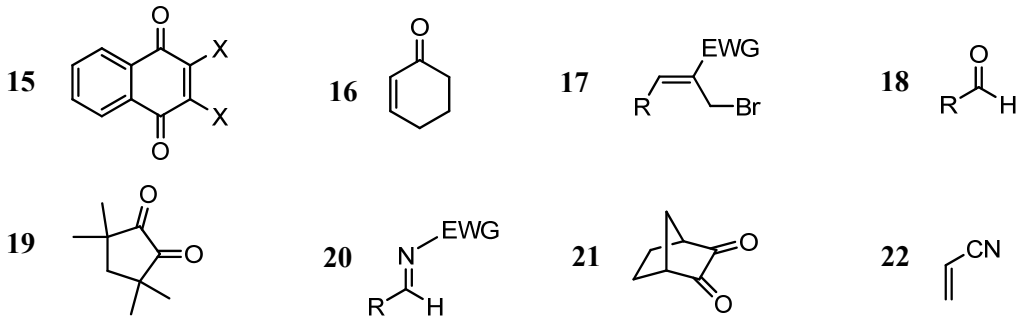


Figure 3. Elecrophiles used in the MBH reaction.[3,5]

Various catalysts have been employed in the Baylis-Hillman methodology with the prominent catalysts of choice being DABCO, 3-hydroxyquinuclidine and quinuclidine. **Figure 4** shows some molecules that have been used as catalysts.[1,5,7]

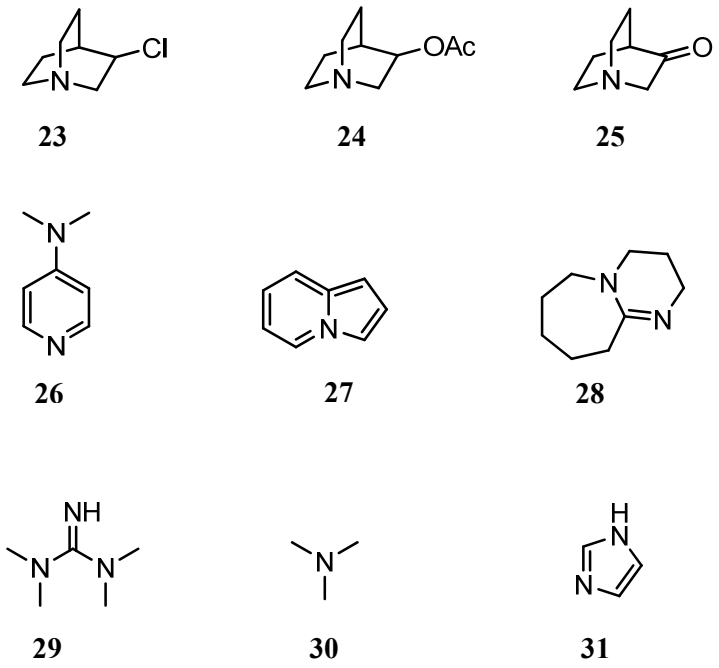


Figure 4 Catalysts used in the MBH reaction.[1,5,7]

1.1.2. Accelerating the Baylis-Hillman reaction

The Baylis-Hillman reaction however faces several drawbacks among which are slow reaction rate, low product yield, high concentration of the catalyst and the use of organic solvents that are hazardous.[8] The reaction may take days or weeks to reach completion, depending on reactivities of substrates used. However, its synthetic potential has stimulated investigations into modifications of the experimental protocols to mitigate the challenges and thus enhance the reaction rate and the yield of the Baylis-Hillman adducts.[6,8] Reported modifications include the use of more reactive activated olefins and electrophiles, new catalysts or catalytic systems, the use of excess catalyst, conducting the reaction under high pressure, the use of ultra sound, different solvent media, microwave irradiation, mechanical agitation.[1,6] Attention has been also given to facilitating intramolecular hydrogen bonding through having a hydroxyl group in the

substrate or catalyst, variations in the stoichiometry of the reactants and catalyst, additives and use of heterobimetallic complexes.[1,6,8,9] Most of the refinements, although helpful in increasing product yield and the reaction rate are limited to particular substrates.[8] The strategies which can be divided into chemical and physical methods with the former being more preferable as no specialised equipment is required.[10]

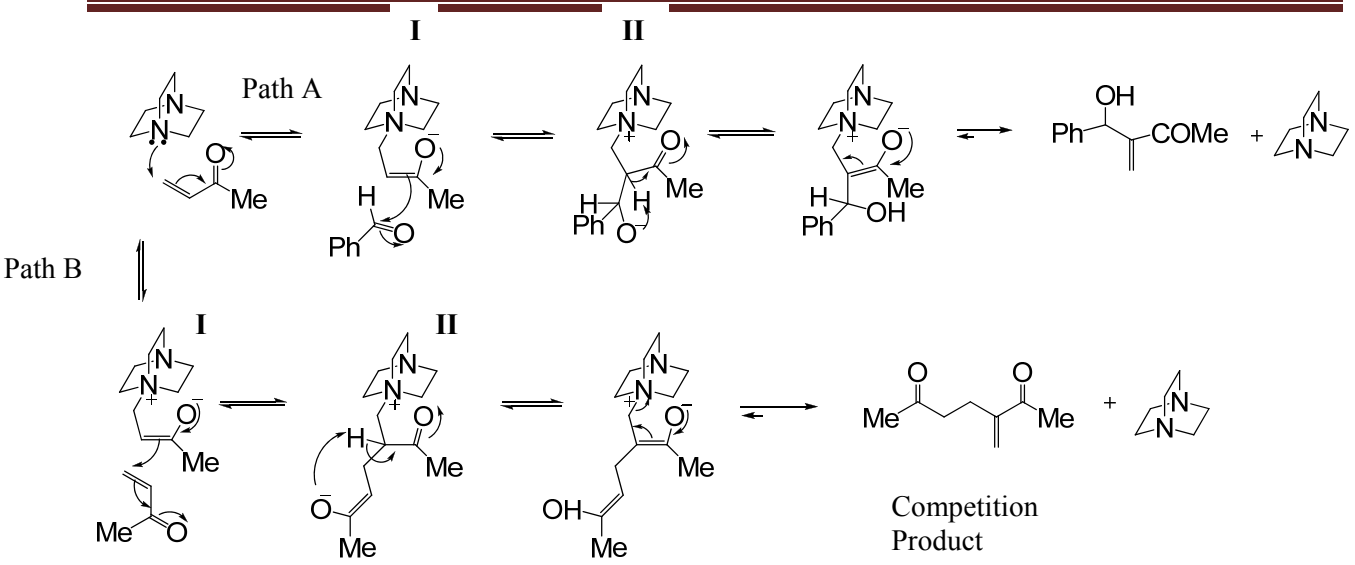
A solvent free method for rate acceleration and yield increase was developed by Saikia and Sarma.[6] Equimolar quantities of olefin and aldehyde were reacted in the presence of the catalyst, DABCO, at 20 mol% under neat conditions to afford high yields in a short time. They reported that their findings give further credence to mechanisms involving proton transfer in aprotic and protic solvents. Recently, Aravind and co-workers[8] studied the Baylis-Hillman Reaction in a PEG-200-DABCO medium under the influence of microwave energy and showed that the product yield was enhanced, the reaction time was much shorter and the catalyst concentration needed was only one tenth of that needed in a standard Baylis-Hillman reaction. Acke and Stevens[9] used a micro-reactor for the continuous production of Baylis-Hillman adducts in which the rate was approximately 30% faster than under batch conditions with comparable yields. The highest yield was achieved using a 1:1:3 molar ratio of 4-nitrobenzaldehyde, DABCO, and methyl acrylate in water/1,4-dioxane (1:1 v/v) at room temperature. Aggarwal *et al*.,[10] building on the well-reported fact that protic solvents accelerate the Baylis-Hillman used water or small amounts of formamide and $Yb(OTf)_3$ as solvent systems. Rate enhancements of up to 120% were achieved with methyl acrylate and benzaldehyde using $Yb(OTf)_3$ and formamide.

Cai and co-workers[11] found that the reaction rate of aromatic aldehydes and acrylonitrile or methyl acrylate was greatly enhanced in a homogenous water-organic solvent medium; moreover, higher yields were achieved at lower temperature. They found that the best catalysts were DMAP, DABCO, urotropine and Me_3N, while the solvent could be tetrahydrofuran, acetonitrile or 1,4-dioxane. In a similar investigation using aqueous-organic solvent systems conducted by de Souza *et al*.,[12] it was shown that water and organic solvents mixed at varying proportions gave good to high yields in shorter reaction times for certain aromatic aldehydes, acrylonitrile and methyl acrylate. The best system for the reaction with methyl acrylate was found to be DMSO-water (60:40) and for acrylonitrile, *tert*-butanol-water (60:40) with 100 % mol DABCO as the preferred catalyst. Yields of >98% in 30 minutes in the solvent-free Baylis-

Hillman reaction of *p*-nitrobenzaldehyde and methyl acrylate with DABCO as catalyst were achieved by Mark and Shumba[13] using mechanical agitation, called "high speed ball milling". Shang and co-workers[14] developed a new catalytic system, comprising a combination of $Sc(OTf)_3$ and 3-hydroxyquinuclidine, that accelerates the Baylis-Hillman reaction. They observed that the reaction was best conducted in DMF with 5 mol% of a 1:4 mixture of $Sc(OTf)_3$ and 3-hydroxyquiniclidine at 40 ^oC. Using a stoichiometric base catalyst and an aqueous medium, Yu and co-workers[15] converted a variety of aldehydes (aromatic and aliphatic) to their respective Baylis-Hillman adducts while Park and co-workers[16] described the use of octanol as an additive which greatly accelerated the Baylis-Hillman reaction, enabling the ready conversion of reactants into intended products. 1-1-Butyl-2,3-dimethylimidazolium hexafluorophosphate ([bdmim][PF_6]), a new, inert, ionic liquid has also been shown by Hsu and co-workers[17] to facilitate the Baylis-Hillman reaction with good to excellent yields.

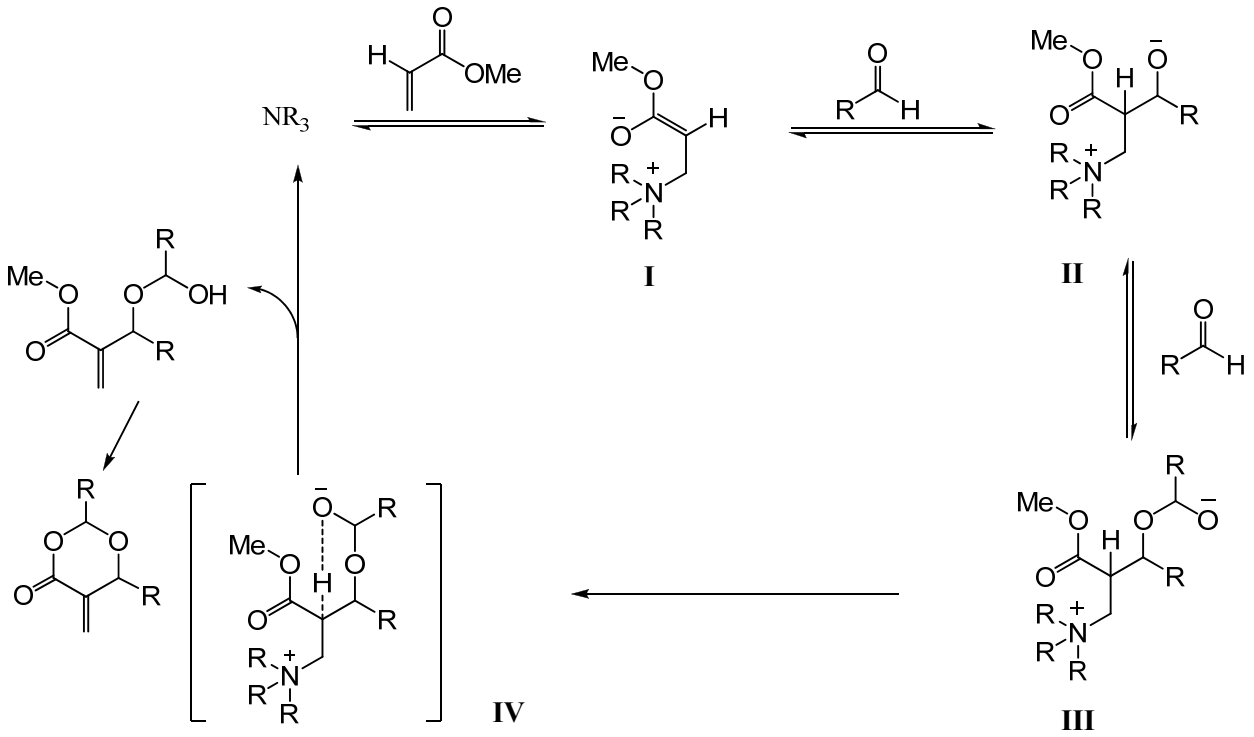
1.1.3. Mechanism

The wide variety of reactants, catalysts and reaction conditions reported for the Baylis-Hillman reactions has presented challenges in the elucidation of the mechanism.[3,4] Hoffmann was the first to propose a mechanism for the MBH and this was then refined through kinetic studies by Hill and Isaacs.[18] Bode and Kaye[19] undertook NMR-based kinetic studies which supported this mechanism, which is illustrated for the DABCO-catalysed coupling of methyl vinyl ketone (MVK) with benzaldehyde in **Scheme I** (Path A). This mechanism commences with the nucleophilic aza-michael addition of DABCO to MVK giving a zwitterionic enolate I which then reacts with benzaldehyde in an aldol-type reaction to produce zwitterion II which can undergo E2 or $E1_{CB}$ elimination to release DABCO following proton migration to provide the MBH adduct.[3] The rate determining step was taken to be the addition of enolate to the aldehyde.[2] Since MVK is highly reactive, a competition reaction may also occur in which a second molecule of MVK reacts with the zwitterion enolate I to afford the competition product on release of the catalyst (Path B).[1-3]



Scheme 1. Early mechanism proposed for the MBH reaction.[1]

Santos and co-workers[20] used electrospray ionisation mass and tandem mass spectrometry to probe the mechanism and successfully intercepted the catalytic cycle; they proposed intermediates and managed to characterise them. An achievement which provided evidence for the mechanism initially proposed by Isaacs and Hill.[18] More recently, in a re-evaluation of the MBH reaction mechanism by McQuade and co-workers[2] proton-transfer was proposed to be the rate determining step. They suggested that the MBH reaction mechanism is second-order with respect to aldehyde and that the proton-transfer step involved a six-membered hemi-acetal intermediate IV (**Scheme 2**), produced by reaction of the zwitterion III with a second molecule of aldehyde. However, Aggarwal and co-workers[2,18] suggested that the reaction was only second order in the initial stages before autocatalytic proton-transfer. **Scheme 2** details the mechanism proposed by McQuade and co-workers.[21] As before, an enolate is formed by the attack of DABCO on the activated alkene; the enolate then attacks an aldehyde molecule to form the second enolate III which then attacks a second aldehyde molecule leading to the formation of the hemi-acetal intermediate IV. Proton transfer of the α-hydrogen is considered rate determining and is followed by elimination of the catalyst to afford the MBH product.



Scheme 2. Later mechanistic proposal for the MBH reaction.[21]

Using rate and isotope data, Price and co-workers[22] demonstrated that the mechanism which involves a hemi-acetal intermediate was general for a wide variety of aryl aldehydes and valid in cases where additives, be they nonpolar, nonpolar/protic or polar aprotic, were used. They also concluded that the reaction was second-order in aldehyde and first-order in acrylate ester and DABCO. Amarante and co-workers[18] intercepted and structurally characterized new MBH intermediates using electrospray ionisation mass spectrometry and their findings supported the recent propositions by the McQuade and Aggarwal teams on the mechanism of the MBH reaction.

Robiette and co-workers[23] conducted a computational investigation of the MBH reaction mechanism that focused on an amine catalysed coupling of benzaldehyde and methyl acrylate. They looked at the mechanism under protic solvent-free conditions and how the mechanism and the RDS respond in the presence of alcohols. Their predictions in the absence of protic solvent were that deprotonation of the α-position was the rate determining step which occurred via a cyclic transition state. In the presence of an alcohol, a slightly lower energy pathway is provided, in which the alcohol operates as a shuttle in the transfer of the proton from carbon to oxygen.

1.2. APPLICATIONS OF THE BAYLIS-HILLMAN METHODOLOGY

The synthetic utility of the MBH adducts is due to the presence of at least three functional groups, *viz*., allylic, alcohol and ketone. Consequently, MBH adducts have been used as synthons in the synthesis of a many important cyclic and acyclic compounds, including drugs and natural products.[4,18,23] Cyclic compounds that have been accessed include coumarins, indolizines, indoles, indazoles, quinolones, chromones, chromenones, chromenes, naphthalenes and pyrazoles.[4,19,24] Based on the many chemical transformations of MBH adducts that have been reported, Lee and co-workers[24] have identified eight categories each of which is characterised by a particular key reaction; these categories and examples of the corresponding products are shown in **Table 1**.

Table 1: Categories of chemical transformations of MBH adducts and corresponding products.[24]

Category	**Examples of compounds synthesised**
1. Nucleophilic aromatic substitution	Naphthalenes, quinolines
2. Radical cyclisation	*Exo*-methylene tetrahydropyrans, tetrahyrofurans
3. Ring-closing metathesis	Pyrroles, cyclopentenes, lactones
4. Friedel-Crafts	Indene derivatives, 2-arylideneindan-1-ones
5. Halolactonisation	α-arylidene-γ-butryrolactones, 2,5-hydrofurans
6. Claisen rearrangement	4-Amino-2-benylideneindan-1-ones,3-benzyledene-3,4-dihydro-1*H*-quinoline-2-ones
7. Aldol condensation	3,4-Dihydro-2*H*-pyrans, *ortho*-hydroyacetophenones
8. Reductive cyclisation	γ-Lactams, quinolones, quinolines

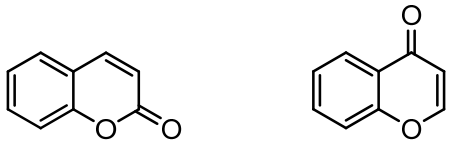
1.2.1. Bioactive molecules

Mehta and co-workers[25] reported a methodology which they used to access furofuranones, a class of compounds from MBH adducts, which were propargylated, converted to γ-butenolides and then into the targeted furo[3,2-*b*]furanones by an oxy-Michael addition reaction. These compounds exhibited bioactivity. Five important insect pheromones, (2*E*,4*S*)-2,4-dimethylhex-2-enoic acid, (+)-(*S*)-normanicone, (+)-(*S*)-manicone, (+)-dominicalure-I and (+)-dominicalure-II were synthesised by Das and co-workers.[26] from MBH adducts by application of stereoselective synthesis of trisubstituted olefins. While Junior and co-workers[27] synthesised over twenty antiparasitic MBH adducts using microwave irradiation. A diastereoselective approach was employed by Paioti and Coelho[28] for the total synthesis of the highly bioactive styryl lactones, (+/-)-leiocarpin A and (+/-)-goniodiol from a common intermediate that was accessed from a MBH adduct. Narender and co-wokers[29] synthesised six novel MBH adducts from substituted 2-chloronicotinaldehydes, which they screened for antimalarial activity and half of them were found to have substantial activity.

Novel highly functionalised MBH adducts of artemisinin, a well-known antimalarial agent were synthesised from 10-deoxoartemisinin aldehyde and tested for anticancer activity by Goswami and co-workers.[30] The artemisinin MBH adducts proved to be highly potent against cancer. Twenty 3-hydroxy-2-methylene-3-phenylpropionic acid MBH adducts were synthesised and tested for antimicrobial activity by Singh and Bhat.[31] Most of the derivatives showed potent antifungal and antibacterial activities. According to Limar and Vasconcellos[32] some simple MBH adducts have become a vital class of bioactive agents showing diverse activities such as antichagasic, antitumoral, antimalarial, leismanicidal and molluscicidal properties. Narender and co-workers[33] synthesised multisubstituted quinolones from MBH adducts obtained from 2-chloronicotinaldehydes and tested them for antimicrobial activity. They found the molecules to have significant antifungal and antibacterial activity, while Bhowmik and Batra[34] developed a novel MBH-mediated approach to the total synthesis of tamiflu (oseltamivir phosphate), an anti-influenza agent and to total synthesis of gabaculine, a neurotoxin.

1.3. COUMARINS

Coumarins are a large class of compounds which derive their name from *Coumarouna odorata Aube (Dipteryx odorata)*, the Tonka bean, from which coumarin, the simplest member was isolated in 1820.[35,36] These compounds are benzopyrones – compounds which contain a benzene ring fused to a pyrone ring which consist of two groups, the benzo-α-pyrones, to which coumarins belong, and the benzo-γ-pyrones (chromones) (**Figure 5**).[36]



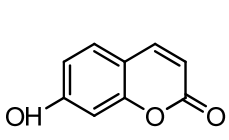
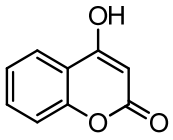
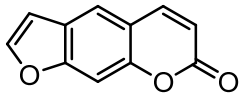
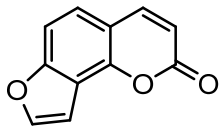
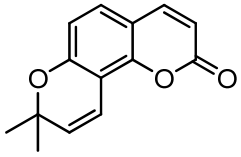
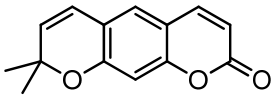
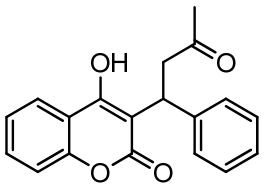
32 **33**

α-Benzopyrone (coumarin) γ-Benzopyrone (chromone)

Figure 5. Chemical structures of benzopyrone subgroups.[36]

Depending on the presence or absence of additional moieties, coumarins can be divided into simple coumarins, furanocoumarins, pyranocoumarins and pyrone-substituted coumarins.[36,37] The sub-groups and examples of each are shown in **Table 2** below. Other classifications recognize five groups, the simple, furano- and pyranocoumarins identified in **Table 2**, together with the bis- and triscoumarins and the coumarinolignan.[35] Coumarins occur in various plant families which include Fabiaceae, Apiaceae, Rutaceae, Solanaceae and Asteraceae, with the highest concentrations being found in fruits.[36,38] Some coumarins have been found in microorganisms, fungi and bacteria.[36,39] Toxic fungal natural products, aflatoxins have been isolated from *Aspergillus* species, while bacterial coumarins including coumermycin and novobiocin have been isolated from *Streptomyces*.[36] At least 1300 natural coumarins have been isolated, the large number arising from the different substitution patterns involving any of the six available sites on the coumarin nucleus.[40]

Table 2. Main coumarin subtypes and examples following Lacy and O' Kennedy.[36,37]

Classification	**Examples**
Simple Hydroxylated, alkoxylated or alkylated on benzene ring	  7-hydroxycoumarin 4-hyroxycoumarin
Furanocoumarins 5-membered furan ring attached to benzene ring. Linear or angular	  Psoralen Angelicin
Pyranocoumarins 6-membered ring attached to benzene ring Linear or angular	  Seselin Xanthyletin
Pyrone-substituted coumarins Substitution on pyrone ring, often at C-3 or C-4	 Warfarin

1.3.1. Uses of coumarins

Coumarins have diverse uses which range from medicinal to non–medicinal. Non–medicinal uses include the following, fluorescent dyes,[41] sun-screens, fluorescence indicators, laser dyes,[42] probes in non-biochemical heterogeneous inclusion systems, biochemical and biological systems,[43] electro-optical applications (in liquid crystalline polymers and in light and energy

harvesting and photo-active surfaces), fluorescent tags and in chiral stationary phases for HPLC[44], additives in perfumes, food and agrochemicals, and as intermediates in the synthesis of compounds such as chromones, fluorocoumarins and coumarones.[45,46] Coumarins also exhibit a wide spectrum of biological activities including anticoagulant, anthelmintic, anti-HIV, insecticidal, antimicrobial, anticancer, anti-inflammatory,[13] antioxidant, hepatoprotective, antiallergic, antiviral, and antithrombotics.[45-49] Pharmacological activities observed for various coumarins are shown in **Table 3**.

Table 3. Pharmacological activities of various coumarins.

Pharmacological activity	**Coumarin(s)**
1. Anticoagulant	Dicoumarol,[37] warfarin[36]
2. Antibacterial	Ammoresinol, novobiocin,[49] clorobiocin[36]
3. Anti-inflammatory	Coumarin, scoparone,[40] esculetin[49]
4. Antioxidant	Esculetin,[49] Umbelliferone, herniarin[39]
5. Anticancer	Scoparone,[39] esculetin,[36] osthole[49]
6. Antifungal	Osthole, psoralen[49]
7. Antihypertensive	Scoparone,[39] scopoletin[49]
8. Anti-HIV-1	Calanolide A and B,[48] michellamine B[50]
9. Immunostimulatory	Coumarin, 7-hdroxycoumarin[51]

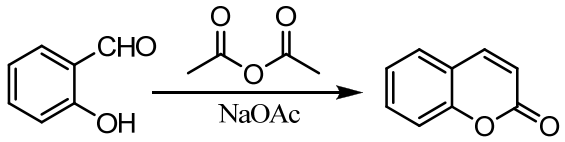
1.3.2. Synthesis of coumarins

The many applications of coumarins have made them attractive targets. Classical syntheses, such as the Pechmann, Wittig, Perkin, Knoevenagel, Reformatsky, Raschig and Claisen reactions,[45,46,52,53] have various drawbacks, including extreme reaction conditions, expensive

catalysts and waste challenges.[53,54] New approaches which address some of these challenges and which involve greener protocols have been developed.[45,53,55]

Perkin reaction

The Perkin condensation is perhaps, the simplest protocol for the synthesis of substituted coumarins.[56] The reaction was first reported by Perkin,[57] and involved heating salicylaldehyde with acetic anhydride and anhydrous sodium acetate (**Scheme 3**).



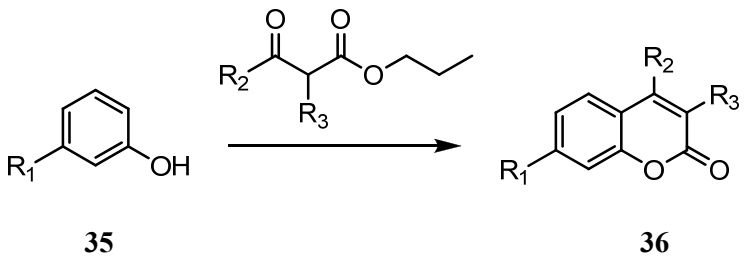
34 **32**

Scheme 3. The Perkin reaction.[35,57]

More generally, the Perkin synthesis can be described as the formation of coumarins by an aldol condensation of acid anhydrides and *ortho*-hydroxybenzaldehyde in the presence of an alkali salt of the acid.[35] The protocol has a narrow substrate scope and improvements have been reported involving use of anhydrous sodium fluoride as catalyst, use of a Mukaiyama esterification protocol and the mediation by propylphosphonic anhydride (T3P) acid.[35,56]

Pechmann Reaction

The Pechmann reaction, also known as the Pechmann condensation, is the most widely used method in the synthesis of coumarins due to its use of simple starting materials, *viz.*, β-ketoesters and phenols.[58,59] In the original reaction, Pechmann[57] synthesised a coumarin derivative by heating a mixture of phenol, malic acid and sulphuric acid. Generally, the reaction involves the condensation of phenols and β-ketoesters catalysed by acids (**Scheme 4**)[35] and can be considered to occur through three steps,[60] hydoxylalkylation, transesterification and dehydration. Acids such as H_2SO_4, HCl, $POCl_3$ and P_2O_5 have been reported as catalysts and have been used in large molar excess *e.g.* 5-fold for phosphorus pentoxide and 10-12-fold for sulphuric acid.[61] Use of excess acid catalyst is not environmentally attractive,[60] and the use of Amberlyst-15, Fitrol, Nafion resin/silica nanocomposites and H-BEA has been reported as improved alternatives.[35,60]



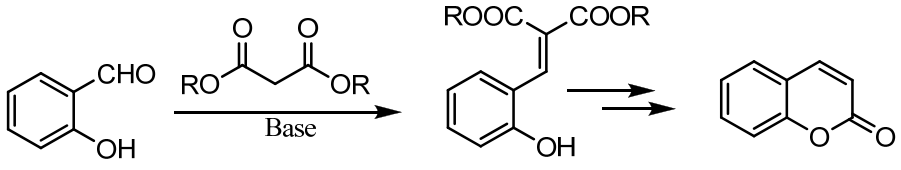
35 **36**

Scheme 4. The Pechmann reaction.[35]

Romanelli and co-workers[59] have synthesised coumarins by the Pechmann reaction using a Wells-Dawson heteropolyacid as a catalyst in a solvent-less protocol. The catalyst could be used again with no change in yields. Maheswara and co-workers[61] synthesised substituted coumarins in a Pechmann reaction invoving a heterogenous recyclable catalyst ($HClO_4.SiO_2$) in a solvent-free protocol. Other improvements to the Pechmann synthesis are use of Zeolite catalyst,[62] microwave assisted solvent-free synthesis[63] catalysed by $ZrOCl_2.8H_2O$, catalysis by 3-methyl-1-sulphonic acid, an imidazolium sulphate halogen-free recyclable acidic ionic liquid[58]. The use of titanium(IV) chloride under solvent-free conditions which was reported by Valizadeh and Shockravi[64] to afford products in higher yields than those obtained under standard conditions.

Knoevenagel Reaction

The condensation of aldehydes and active methylene compounds in the presence of amines or ammonia is known as the Knoevenagel reaction.[35] KnoevenageI first reported the solution phase synthesis of coumarins by the condensation of malonic acid with *ortho*-hydroxarylaldehydes in 1898, as illustrated in **Scheme 5**.



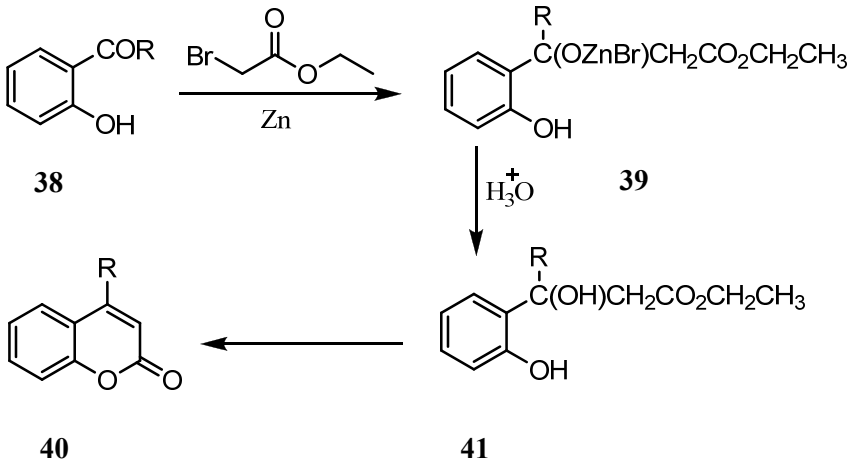
34 **37** **32**

Scheme 5. The Knoevenagel reaction. [35]

Phadtare and Shankarling[66] reported a protocol aimed at making the reaction greener. They synthesised coumarins using a biodegradable catalyst, choline chloride, in aqueous media and the catalyst could be reused several times without decrease in yield or activity. Prajapati and Gohain[67] used molecular iodine as a catalyst in a microwave irradiated version of the Knoevenagel condensation, obtaining coumarins in high yields.

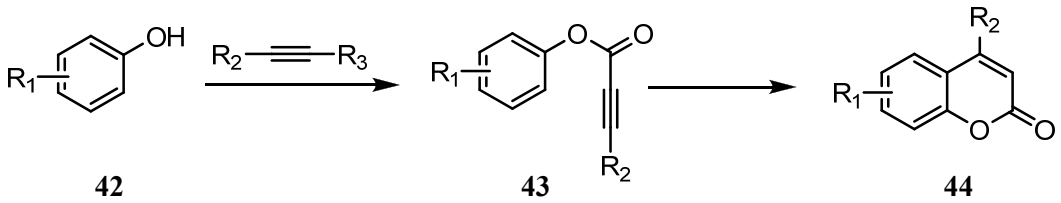
Reformatsky reaction

The reaction involves the condensation of ketones or aldehydes with organozinc compounds of α-halo esters yielding β-hydroxyesters, which undergo lactonisation to coumarins under appropriate conditions (**Scheme 6**).[35]



Scheme 6. The Reformatsky reaction.[35]

Improvements to the classic method have included the use of tellurium–triggered cyclisations and use of ultra sound.[68] Other less conventional methods have been developed for the synthesis of coumarins, *e.g.*, the stereo- and regioselective palladium-catalysed hydroarylation of functionalised alkynes with aryl halides (**Scheme 7**).[35] Van and co-workers[45] used ring-closing metathesis with Grubbs catalyst to synthesise coumarins from phenols while Gao and co-workers[69] reported a one-pot microwave assisted synthesis of coumarins under solvent-free conditions, using Meldrum's acid, phenol and Eaton's reagent.



42 **43** **44**

Scheme 7. Palladium-catalysed synthesis of coumarins.[35]

1.3.3. 4-Hydroxycoumarins

There has been a great deal of interest in 4-hydroxycoumarins (2*H*-1-benzopyran-2-ones) arising from their photodynamic and numerous pharmacological activities, which include: anti-inflammatory, anti-arthritic, antibacterial, anti-cancer, anti-coagulant and anti-viral.[70,71] The discovery of dicoumarol as the agent responsible for a haemorrhagic disease in cattle fed on sweet clover hay, that had begun to ferment, stimulated the study of 4-hydroxycoumarins and led to the development of warfarin (**Figure 6**), as a rodenticide and of 4-hydroxycoumarin (4-HC) analogues as therapeutics for thromboses, rheumatic heart defects, embolisms, stenocardia, angina, myocardial infarcts and thrombophlebitis.[72,73,74] Typified by warfarin which was introduced into clinical practice more than 50 years ago, 4-hydroxycoumarins have become the mainstay of oral anticoagulant therapy for various thromboembolic health conditions.[75] These compounds are antagonists of vitamin K and target vitamin K epoxide reductase, inhibiting its reduction to dihydrovitamin K and resulting in the regulation of blood coagulation.[70,72] The 4-hydroxycoumarin anticoagulants have in common an enolic benzopyran structure (**Figure 6**) which appears to be a requirement for vitamin K.[75]

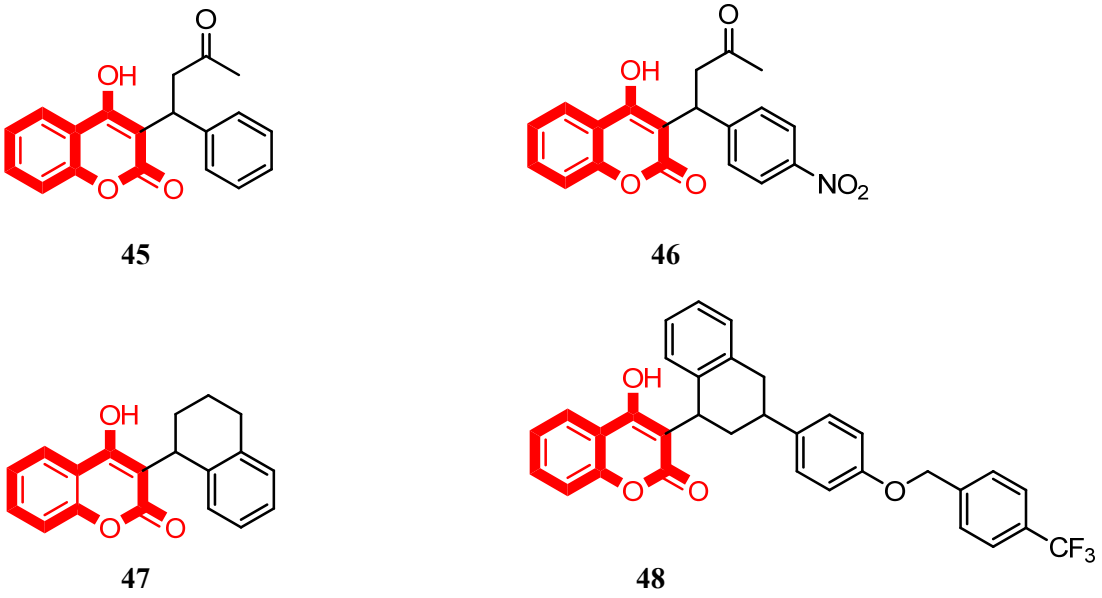
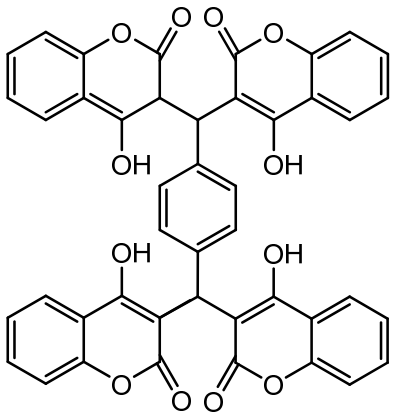


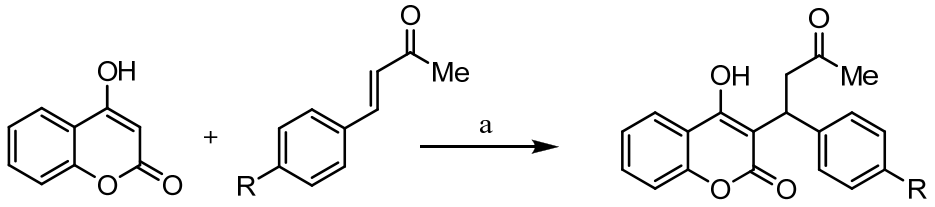
Figure 6. 4-Hydroxycoumarin coagulants.[70,75]

Derivatives of 4-hydroxycoumarin have also provided alternative non-catechol-containing HIV-1 integrase inhibitors of high inhibitory potency, examples of which are coumermycin and the tetrameric compound shown in **Figure 7**.[76] Mazumder and co-workers[77] investigated the latter compound and found it to show anti-viral, anti-integrase and anti-protease activity. A number of other synthetic approaches to 4-hydroxycoumarin derivatives been reported in literature. Danchev and co-workers,[70] for example, condensed of 4-hydroxycoumarin with substituted aromatic aldehydes or unsaturated ketones (**Scheme 8**).



49

Figure 7. Tetramer NSC 158393.[76,77]



50 **51** **52**

R = H, Halogen, Nitro (a): pyridine, NaOH, EtOH

Scheme 8[78]

Swenson's group[79] reported a synthesis of 4-hydroxycoumarin derivatives from benzyl malonic acid and phenol. Varying the conditions they were able to synthesise 3-(*p*-azido-, *p*-amino- and nitobenzyl)-4-hydroxycoumarins. Dezelic and Trkovnik[80] used a modified form of the Pauly-Lockemann method to convert 2-acetoxy-5-bromo-benzoate to 4-hydroxy-6-bromocoumarin.

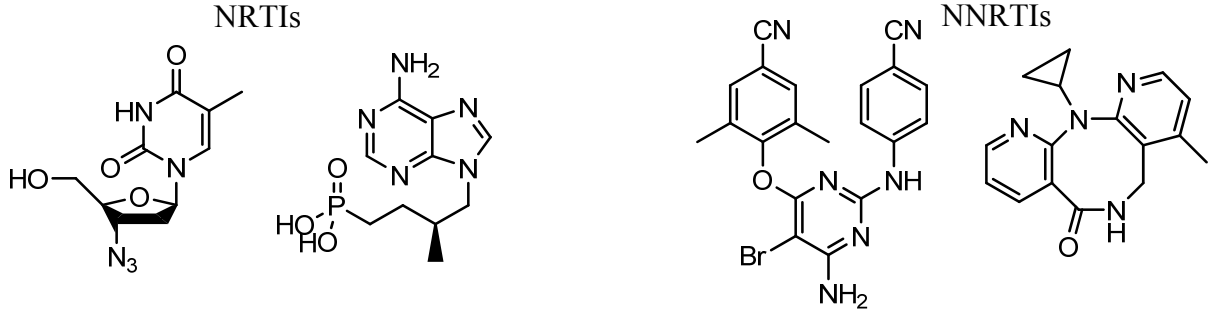
1.4. HIV-1 ENZYMES INHIBITION

The human immunodeficiency virus type-1 (HIV-1) has been identified as the causative agent of the acquired immunodeficiency syndrome (AIDS).[81] Despite the development and discovery of a number of chemotherapeutic agents, AIDS remains a significant health-threat worldwide. Therapeutic agents of the nucleoside (*e.g.*, AZT, D4T, and DDC) and non-nucleoside HIV reverse transcriptase (RT) inhibitors and protease (PR) inhibitors have been used and, at times, in combination therapy. However, toxicity and the emergence of drug resistance present serious challenges.[48] The development of drug resistance is compounded by the HIV's high rate of mutation; hence the need for new drugs with novel structural features and inhibition mechanisms.[50] Steps in the HIV replicative cycle present themselves as targets for chemotherapeutic intervention and these steps include: adsorption of the virus on the host cell membrane; fusion of the viral case with host cell membrane; viral nucleocaspid uncoating; reverse transcription of viral RNA to proviral DNA; integration of the proviral DNA into the cellular genome; replication of DNA; and transcription of proviral DNA to RNA.[48]

1.4.1. Reverse Transcriptase Inhibition

The reverse transcription of genetic material is a critical step unique to retroviruses, of which the HIV is one.[50] A retrovirus is a single stranded RNA virus which uses DNA polymerase (RT) to make double stranded DNA which can insert itself into the host cell DNA. Inhibition of this critical step in viral replication offers an attractive target in the treatment of AIDS.[82] Nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are the two main categories of HIV-1 RT inhibitors, and over 50 structural classes of such inhibitors have been described.[83]

NRTIs are analogues of deoxynucleosides which lack an OH group on the 3` carbon of the deoxyribose moiety but contain a 5`-OH group which can be triphosphorylated by host cell kinases thus permitting them to be mistaken by RT as natural nucleotides.[84] The NRTIs incorporated into the growing viral DNA chain then function as chain terminators.[83] In contrast, NNRTIs do not need metabolic activation in the host cell and are exemplified by diverse hydrophobic molecules whose inhibitory activity depends on interaction with the non-nucleoside binding pocket-an allosteric site located 10 Å from the RT DNA polymerase active site.[82,84] The DNA synthesis is then stopped by the conformational change that results from the binding of the inhibitor at the allosteric site. **Figures 8** and **9** show some commercially available NRTIs and NNRTIs respectively.

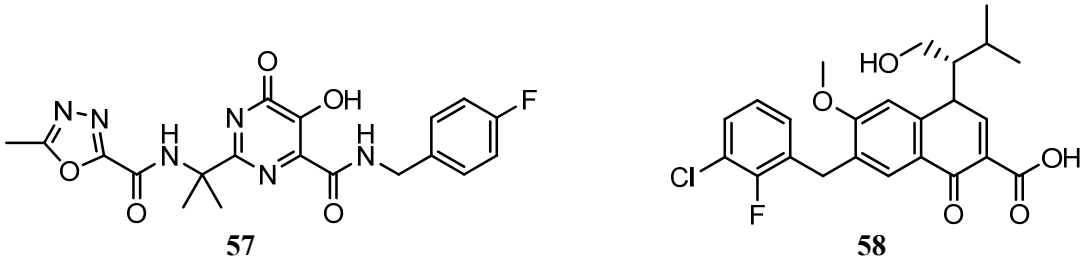


Figures 8. Some commercially available NRTIs[84] and NNRTIs.[83]

Natural products with HIV-1 RT inhibitory activity have been found in plants, micro-organisms and in marine organisms, while many synthetic compounds have also proved to be active RT inhibitors.[50]

1.4.2. Integrase Inhibition

HIV-1 integrase (IN), a pivotal enzyme for HIV-1 replication, facilitates insertion of viral DNA into the host cell genome.[85] The integration process has 3 steps, two of which are catalysed by IN, *viz*., 3`-processing, involving the step-wise removal of two nucleotides from each end of the reverse-transcribed viral DNA, followed by strand transfer in which the processed viral DNA is inserted into the host DNA.[86] The essential role IN plays in HIV-1 replication and its lack of a human counterpart have made it a good target for anti-AIDS therapeutics.[85,86] In 2007, Raltegravir (**Figure 9**) became the first IN inhibitor to be licenced.[81,87] In 2012, elvitegravir (**Figure 9**) became the second IN inhibitor to receive regulatory approval and, like raltegravir, is an integrase strand-transfer inhibitor (INSTI).[88]

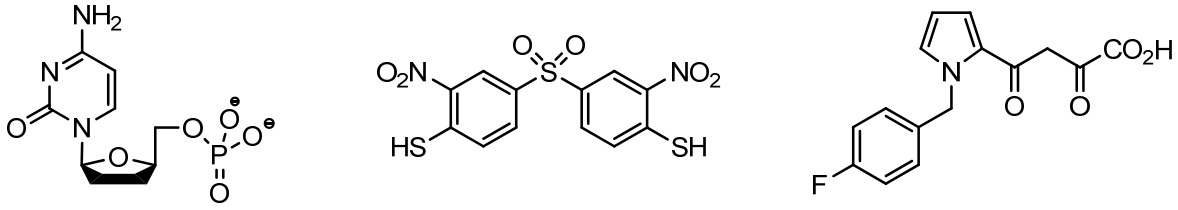


57 Raltegravir

58 Eltegravir

Figure 9. The first INSTIs to be approved.[81,88]

During the last 20 years, many diverse compounds, including peptides, mononucleotides, dinucleotides, oligonucleotides, quinolones, quinolone derivatives and hydroxylated aromatics have been reported as IN inhibitors some of which are illustrated in **Figure 10**.[81,89]



59 **60** **61**

Figure 10. Miscellaneous IN inhibitors.[89]

A class of IN inhibitors characterized by the presence aryl β-diketo acid (DKA) moiety (**Figure 11**) emerged in the late 1990s, having been discovered independently by scientists from Merk and Shionogi research laboratories.[90,91] The DKAs specifically inhibit the integration strand-transfer step and have been reported to be potent HIV-1 IN inhibitors *in vitro* and *in vivo*.[91] The DKA class of IN inhibitors has shown great promise, and various groups have used the DKA template to develop novel IN inhibitors and to explore how the DKA inhibitors function.[90,93]

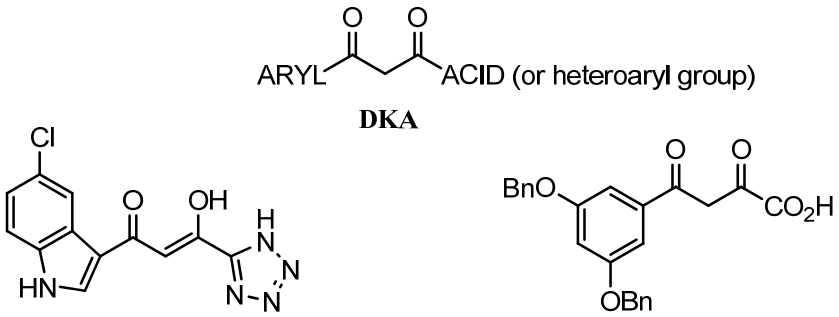


Figure 11. DKA moiety structure and 2 DKA IN inhibitors.

Burke and co-workers[90] used 5ClTEP, 1-(5-chloroindol-3-yl)-3-hydroxy-3-(2*H*-tetrazol-5-yl)propenone and L-708,906 as model DKA leads in a structure activity study. Davies and co-workers[92] studied the structure of a complex of the IN core domain with 5ClTEP. A novel class of IN inhibitors was discovered by Neamati and co-workers[93] through a 3-D pharmacophore-guided search. They generated a common-feature pharmacophore hypothesis based on bioisosteres of β-diketo acid IN inhibitors. The set was made up of 5ClTEP, S-1360 (the first IN inhibitor to undergo clinical trials) and two other analogues (**Figure 12**).

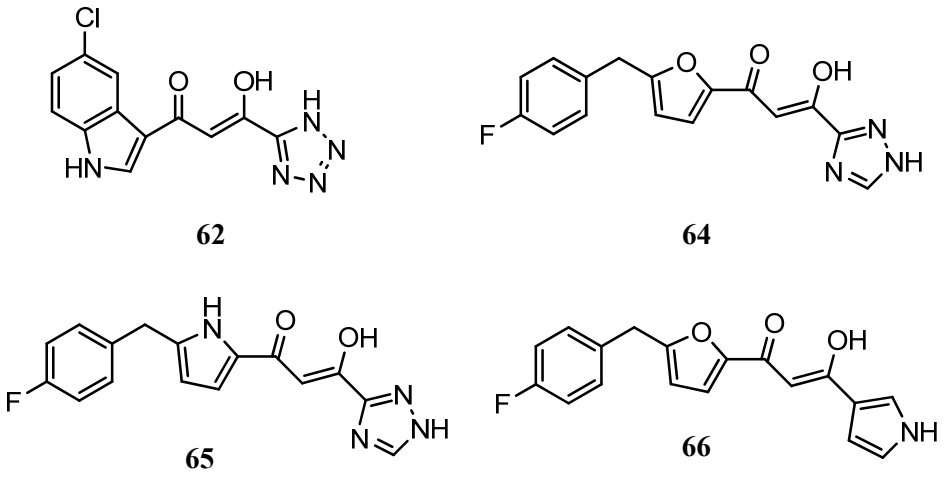
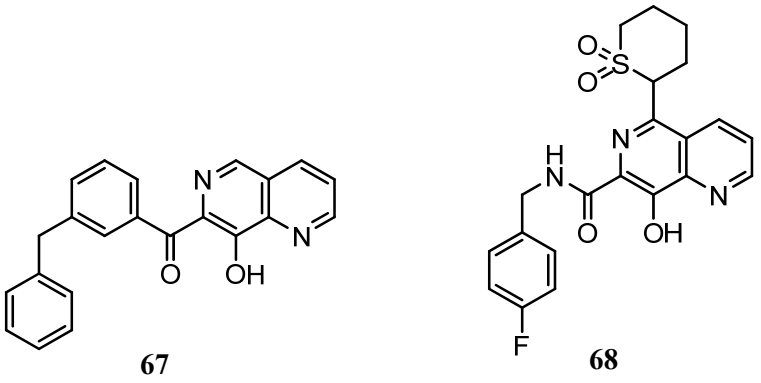


Figure 12. DKA **62** and bioisosteres **64-66**.[93]

The substitution of the 1,3-DKA moiety by 8-hydroxy- (1,6)naphthyridine resulted in a new family of DKA derivatives that are also IN strand-transfer inhibitors, exemplified by the naphthyridine compounds L-870,810 and L-870,812 (**Figure 13**).[91]



L-870,812 L-870,810

Figure 13. DKA derivatives.[91]

The DKA motif consisting of γ-ketone, enolizable α-ketone and carboxylic acid (or heteroaryl replacement) has been reported as necessary for the inhibitory activity of the DKAs whose common pharmacophore (or bioisostere) is illustrated in **Figure 14**.[94] Shinkai and co-workers[94] noted that the enolizable ketone at the α-postion of the DKAs is replaceable by a phenolic hydroxyl group suggesting that the α-enol form is the biologically active co-planar conformation and that the bioisoteres are three functional groups capable of adapting co-planar arrangement and mimicking the carboxyl oxygen, γ-ketone and α-enolizable ketone present in the DKA.

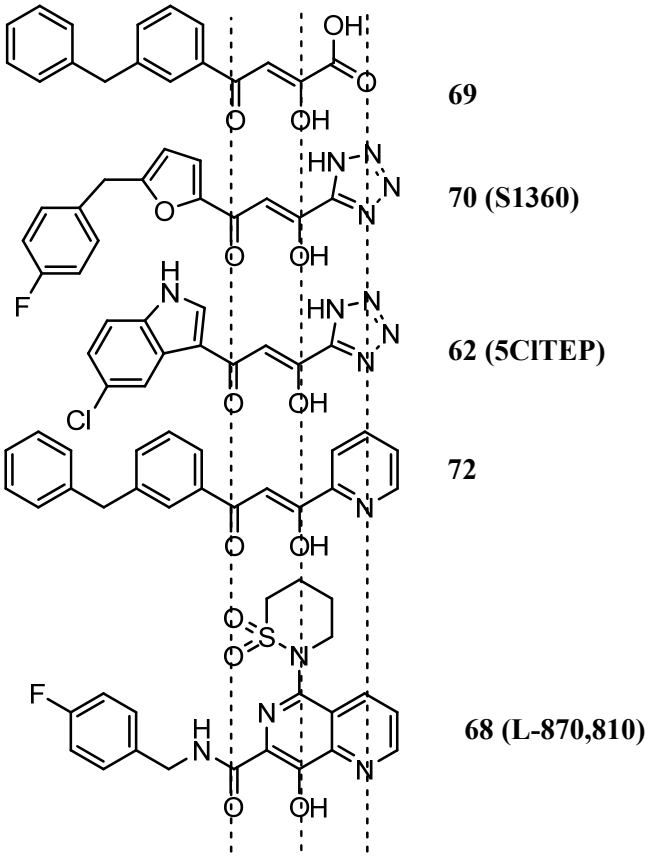


Figure 14. Alignment of DKAs and selected bioisosters,[94] illustrating their pharmacophoric similarities.

1.4.3. Dual action inhibition of HIV-1 enzymes

Highly active anti-retroviral therapy (HAART) has been used to lower the viral load in AIDS patients and improve their quality of life, but the efficacy of this therapy has been compromised by imperfect patient adherence to the complicated dosing, the toxicity of the drugs, viral rebound and the emergence of multi-drug resistance.[95] Using a single drug to inhibit two viral enzymes at the same time could lead to simplified dosing, and thus improved patient adherence, lower toxicity and reduced likelihood of drug resistance.[96] Morphy and Rankovic[97] proposed the concept of designing multifunctional ligands. They called ligands with specific multi-target roles, "*designed multiple ligands* (DMLs)" and categorized them as "*conjugates*", (for scaffolds linked by a linker), "*fused*", (directly coupled with no linker) and "*merged*" (for scaffolds integrated in a single structure and sharing common features). Vince and co-workers[95] coined the

term "*portmanteau inhibitor*" to describe the classification of inhibitors in which two scaffolds are merged into one but act at different sites in the viral life-cycle. There has been increasing recognition that molecules that can target more than one target at the same time can be used to treat a number of diseases in contrast with the "one molecule, one target and one disease approach" upon which drug discovery has been based until the beginning of the 21st century.[98] Interest in dual or multi-target ligands has also grown due to their generally simple pharmarcodynamic and pharmacokinetic properties in comparison with the combined application of several drugs; moreover such ligands often possess improved efficacy.[99]

Computer-aided design in drug development has obvious potential as it permits new lead compounds to be designed and they are evaluated for potential bioactivity before preparation of the compounds and their experimental biological assay.[100] Soliman and Moonsamy[96] designed compounds with potential as dual-action inhibitors against PR and RT. The pharmacophoric features of the compounds were based on the known PR and RT inhibitors, Darunavir and Zidovudine (**Figure 15**). Binding affinities of the dual acting compounds were found to be comparable to and, in some cases, higher than the reference drugs, with compound **74** (**Figure 16**) being the most active against both RT and IN.

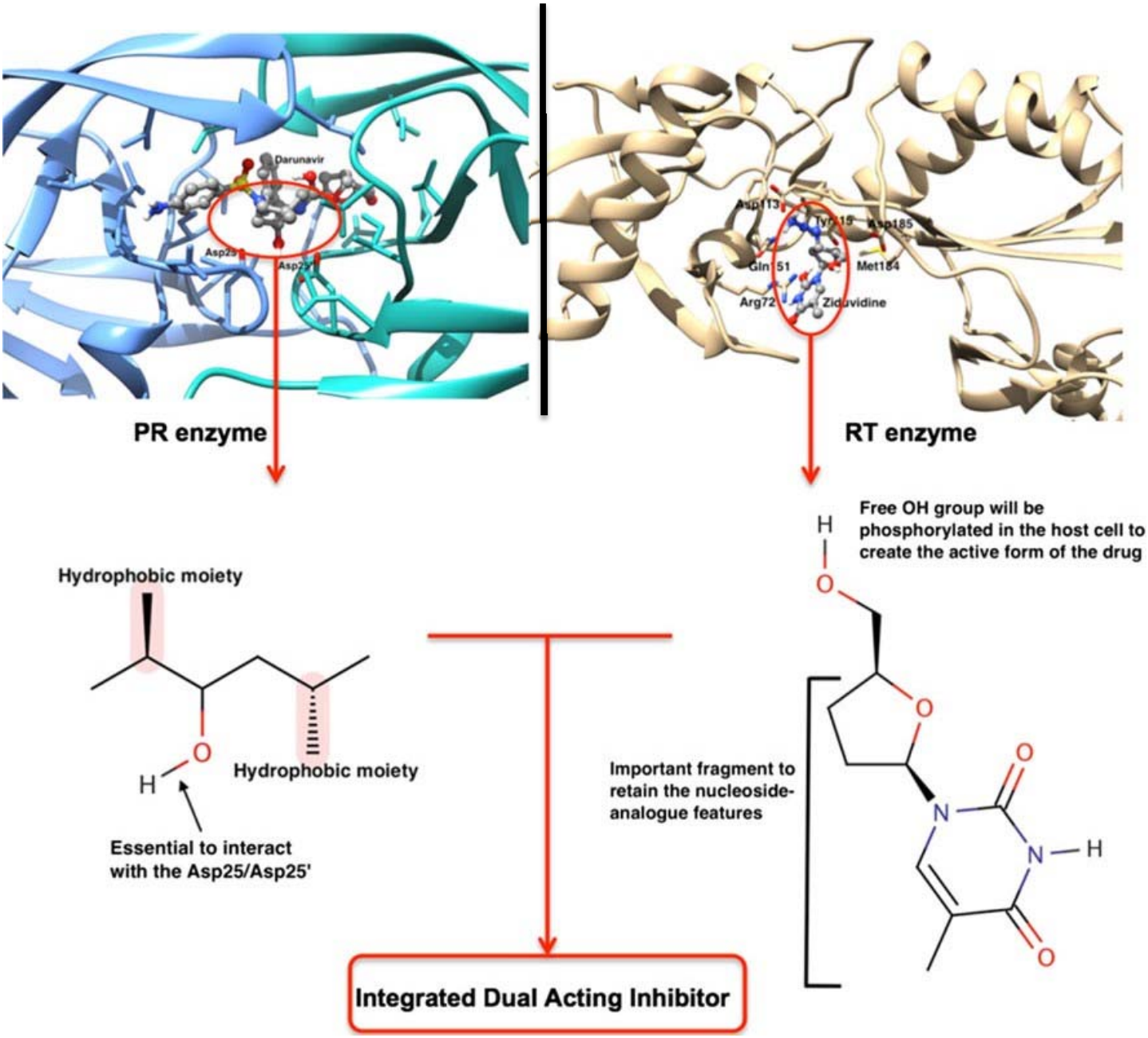


Figure 15. Darunavir-PR complex and Zidovudine-RT complex used to assign the pharmacophoric moieties (reproduced by permission).[96]

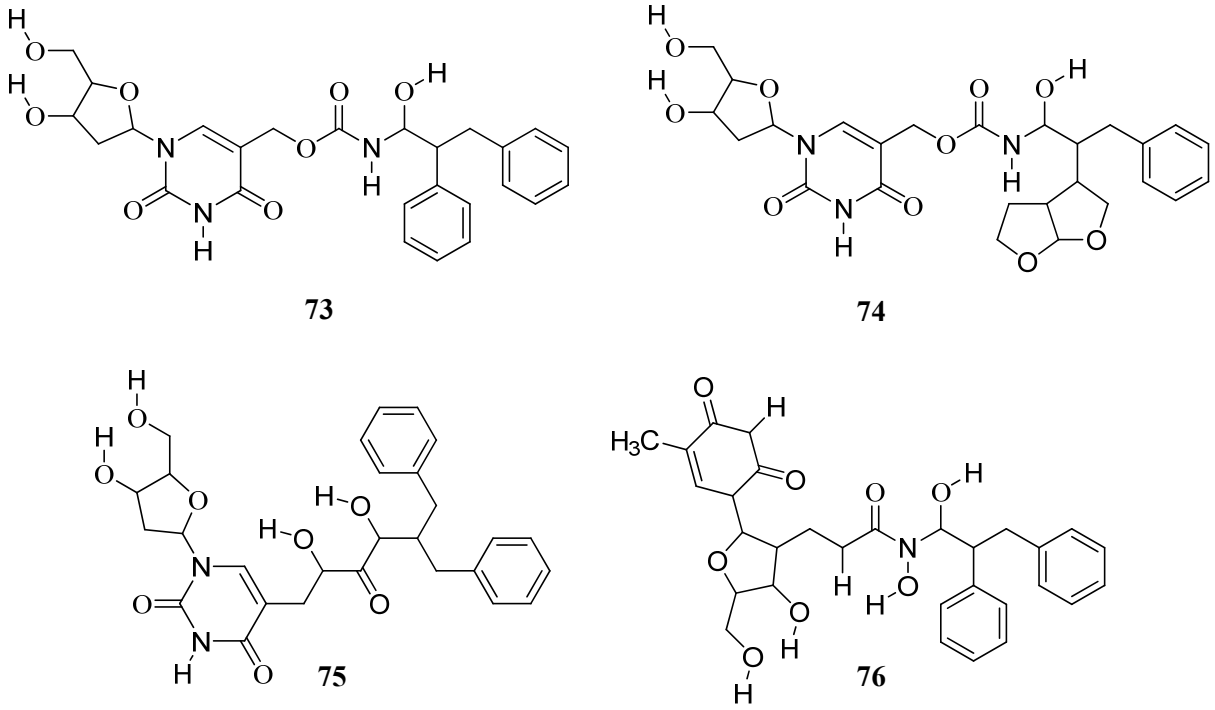


Figure 16. Potential dual-action inhibitors based on Darunavir and Zidovudine.[96]

Vince and co-workers[95] designed bi-functional inhibitors for IN and RT based on 1-[(2-hydroxyethoxy) methyl]-6-(phenylthio)thymine NNRTIs and DKA IN inhibitors. Biochemical studies of the compounds showed significant activity against IN and RT and low cytotoxicity. The best compound had an IC_{50} of 24 nM against RT, 4.4 μM against IN, and 10 nM against the HIV-1virus (**Figure 17**). The minimum requirement for IN binding is a double metal ion chelating moiety and a hydrophobic benzyl group; the incorporation of such a moiety into an NNRTI scaffold results in a potential IN/RT inhibitor as illustrated in **Figure 18**.[101]

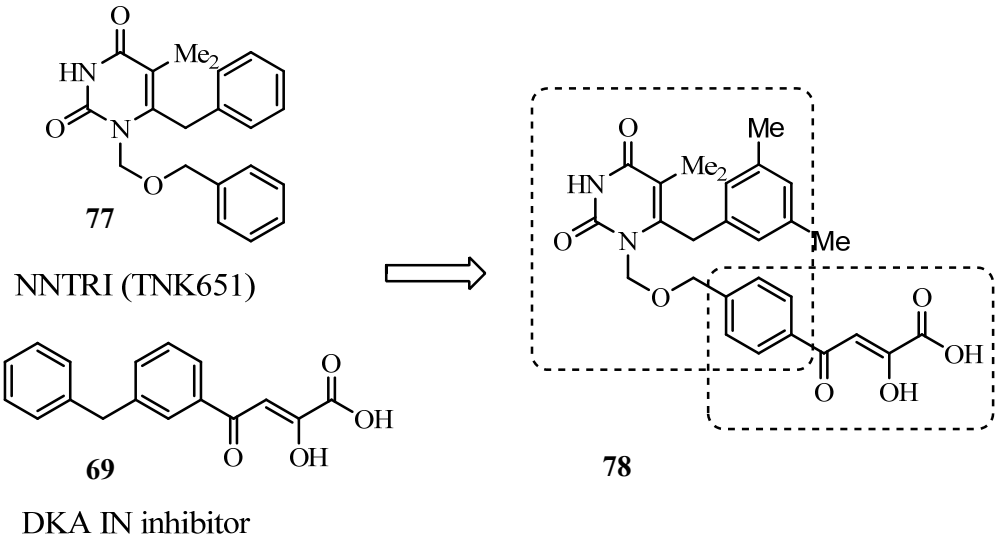


Figure 17. Portmanteu inhibitor based on RT and IN inhibitors.[95]

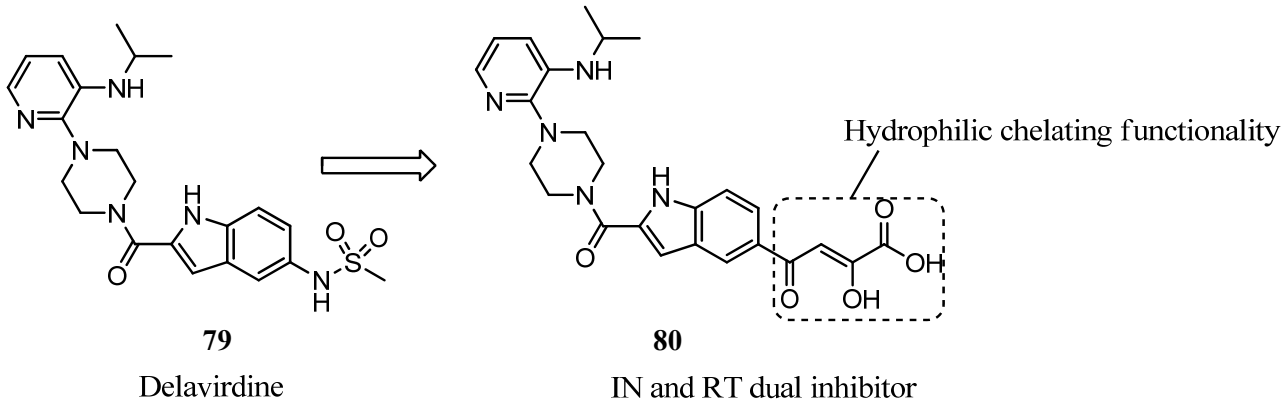


Figure 18. A dual IN/RT inhibitor based on incorporation of a hydrophilic chelating moiety in the delavirdine scaffold.[101]

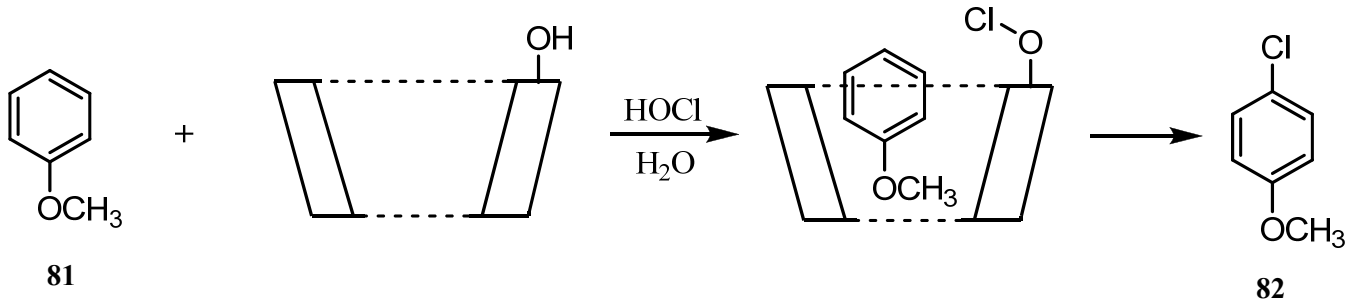
1.5. CUSTOMISED REACTION SITES

Nature has influenced the design of a number of inventions, among which is the aeroplane (based on the bird), submarine (fish), and microphone (eardrum). Researchers at SFU, British Columbia in 2008 developed a technology which uses specialised nano-optics for anti-counterfeiting of bank notes which replicates the shimmering iridescence of the Blue Morpho butterfly's wings which is due to reflection and fragmentation of light waves off nano-sized holes on the surfaces

of the butterfly's wings.[102] The shape of the Shinkansen Bullet train nose was inspired by the kingfisher's ability to dive into water with barely a ripple. The design, a 50 foot steel nose which resembles the bird's beak, resulted in reduced power use and increased speeds.[103] Such inspiration from nature known as Biomimicry or Biomimetics has resulted in the birth and development of Biomimetic Chemistry. Biomimetic Chemistry attempts to mimic natural enzymatic processes and reactions in order to improve organic chemistry.[104] Biomimetic Chemistry takes inspiration not blueprints from natural chemistry.[105]

Biochemical reactions are often superior to simple chemical reactions with respect to speed, conditions (normally mild conditions) and yield. Enzyme-controlled reactions are stereoselective, regioselective, and substrate specific; this among other things enables the formation of pure enantiomers from non-chiral precursors-quite attractive aspects to synthetic chemists.[106] The substrates are bound in well-defined geometries (enzyme-substrate complexes) where only certain substrates fit and particular points of the substrate can be attacked, hence the resultant substrate-, reaction- and stereoselectivity.[106,107,108] The stereocontrol has inspired the use of reagent-substrate complexes where a relatively rigid reagent directs attack to a specific part of the substrate.[106] Endeavours to mimic the attractive aspects of natural enzyme controlled reactions have led to the generation of artificial enzymes (catalysis by design),[108] customised active sites or engineered catalysts.

Cyclodextrins and recently, calixarenes, have found use in Biomimetic Chemistry especially in host-guest chemistry and enzyme mimics.[109] Other substances that have been explored in the mimicking of functions and structures of natural enzymes include metal complexes, polymers, supramolecules, porphyrins, nanozymes (nanomaterial-based artificial enzymes).[110] Simple cyclodextrins like α-cyclodextrins have been shown to act as catalysts, for example, in the chlorination of anisole (**Figure 19**).[111] The binding of anisole in the cavity provides regiocontrol leading to selective chlorination in the *para* position whereas, in the absence of the cyclodextrin, *ortho* and *para* positions are chlorinated.[108,111] The selective catalysis was also accompanied with a higher rate of reaction and different kinetics.[111] Substrates were also shown to be protected from reagents that could not be catalytically delivered by the cyclodextrin groups.



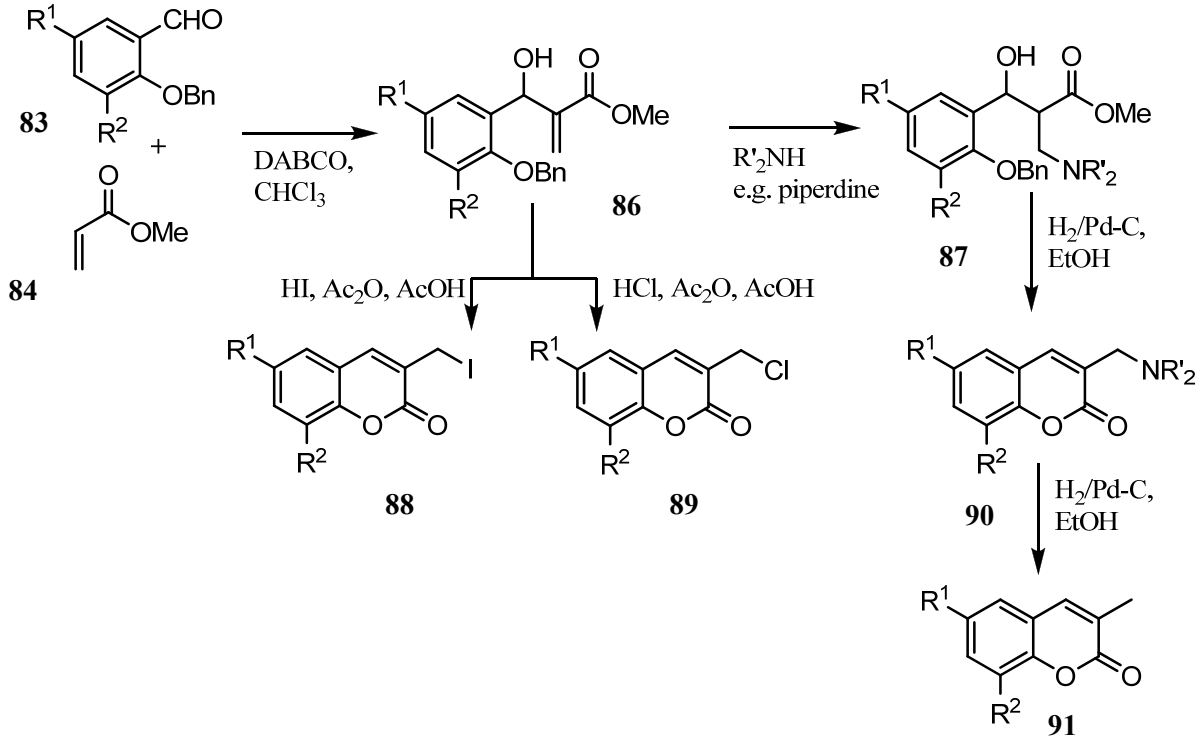
81 **82**

Figure 19. Cyclodextrin-catalysed chlorination of anisole.[111]

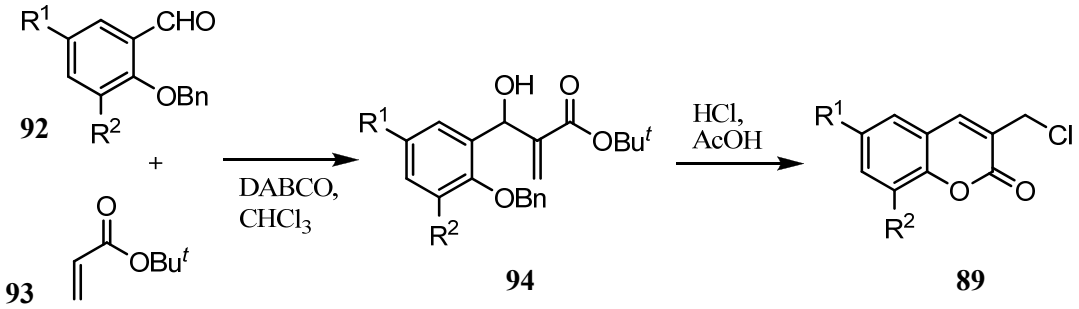
Active sites can also be made using molecular imprinting. In this approach selective binding sites are made by using a molecular template.[112] The target molecule or its derivative is used as a template for imprinting cross-linked polymers. Removal of the template after polymerisation exposes binding sites that are complementary in the position of functional groups, size and shape then affords a substrate-selective polymer.[112,113] The molecular recognition capacity shown by the imprinting effect has been attributed to the production of a shape-selective cavity that is complementary to the template and the prior-arrangement of functional groups in the polymer by the template.[114] To organise the functional monomers around the template, interactions such as covalent, non-covalent, electrostatic and metal ion coordination can be used.[115] The molecular imprinting technology first appeared 80 years ago and the material used then was silica gel.[116]

1.6. PREVIOUS WORK DONE IN THE GROUP

The Baylis-Hillman reaction has been applied in our group in the synthesis of various heterocyclic compounds, which include chromenes, coumarins, indolizines, quinolones and thiochromenes.[117] Several approaches have been used to access coumarin derivatives from Baylis-Hillman adducts. In one approach *O*-benzylated 2-hydroxybenzaldehydes are used as starting material with methyl acrylate as the activated alkene and cyclisation being achieved through either acid catalysis or hydrogenation using Pd-C catalyst (**Scheme 9**).[118] In a more direct approach, use of *tert*-butyl acrylate as the activated alkene, acid-catalysed cyclisation of unprotected Baylis-Hillman adducts affords coumarin derivatives (**Scheme 10**).[119]

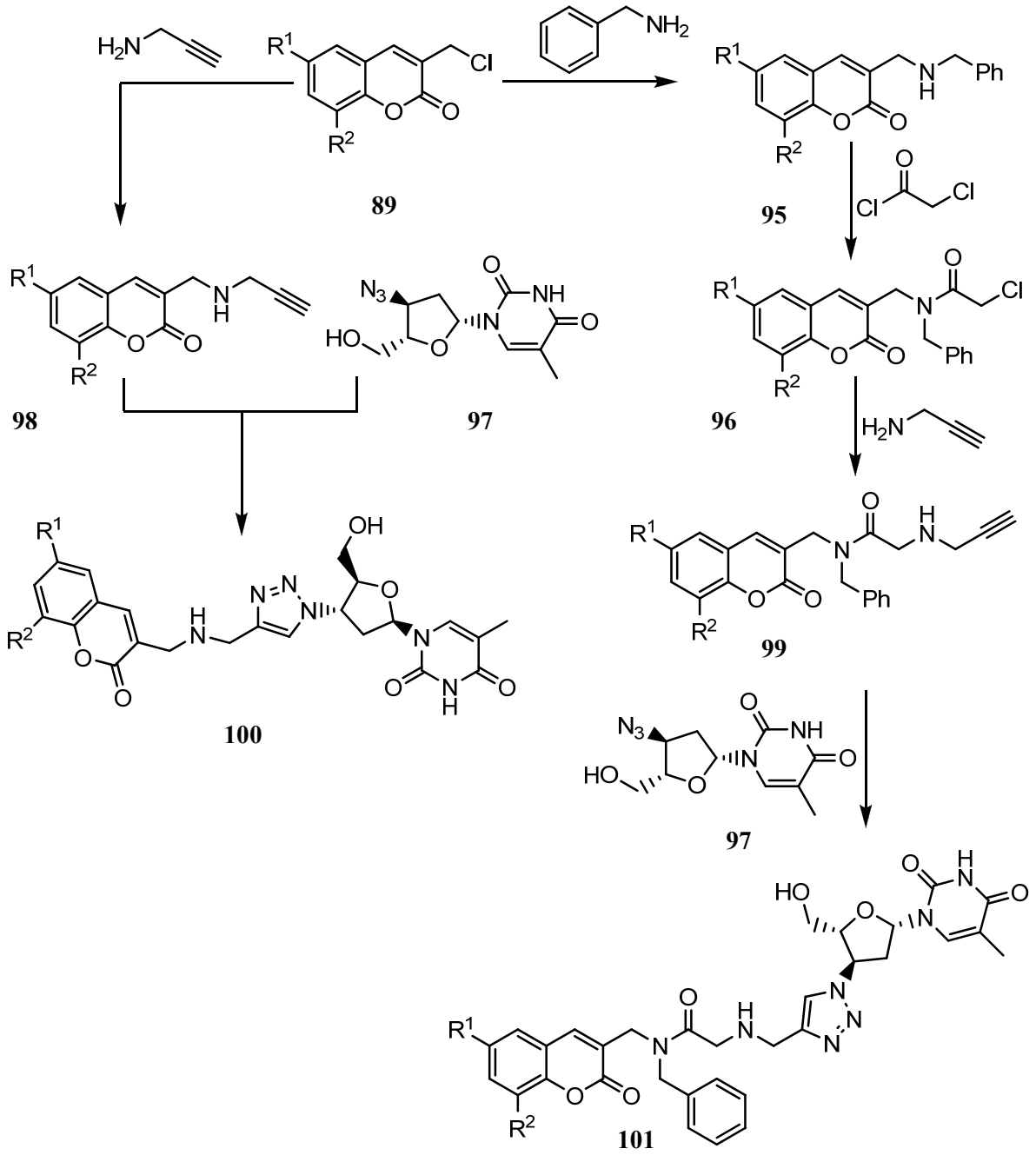


Scheme 9. Coumarin derivatives from protected 2-hydroxybenzaldehydes.[118]



Scheme 10. Coumarin derivatives from unprotected 2-hydroxybenzaldehydes.[119]

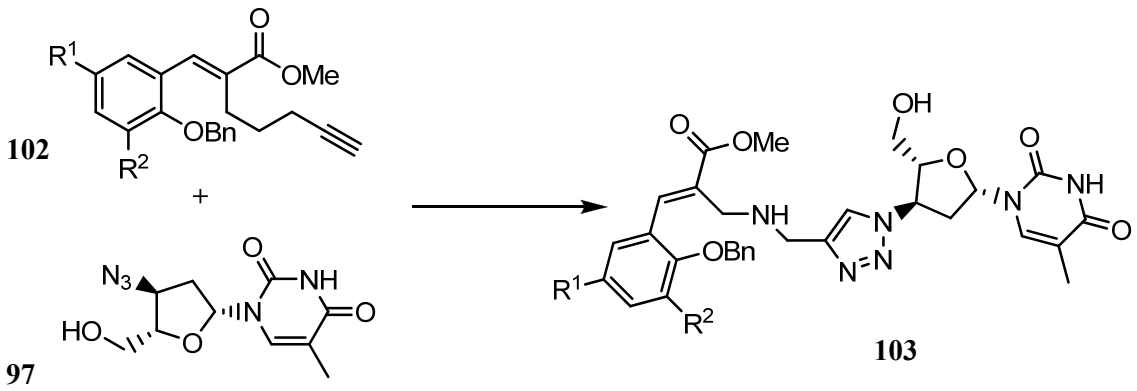
Coumarin derivatives, accessed from Baylis-Hillman adducts, have been explored as potential dual-action HIV-1 protease and reverse transcriptase inhibitors as part of our research involving applications of Baylis-Hillman methodology in the synthesis of more complex molecular targets.[120] Click chemistry was used to couple azidothymidine, an RT inhibitor, with Baylis-Hillman-derived coumarin derivatives to access potential HIV-1 PR/RT inhibitors (**Scheme 11**).[120,121] The conjugates, both *N*-benzylated and non-benzylated, were evaluated for their HIV-1 RT and PR inhibition potential using enzyme-inhibition assays, computer modelling and saturation difference NMR techniques.[121]



Scheme 11. Synthesis of coumarin-AZT conjugates.

Cinnamate ester-AZT conjugates have been synthesized from *O*-benzylated 2-hydroxybenzaldehydes (**Scheme 12**),[122] while other investigations involving Baylis-Hillman-derived heterocycles with medicinal potential have included the synthesis of hydroxyethylene dipeptide isosteres containing coumarin, chromene, thiochromene and chromone moieties as

analogues of ritonavir, a PR inhibitor.[123,124] Research has also focussed on kinetic and mechanistic studies of the Baylis-Hillman and related reactions.[125,126]



Scheme 12. Synthesis of cinnamate ester-AZT conjugates.

1.7. AIMS OF THE CURRENT INVESTIGATION

The present study continues our emphasis on applications of Baylis-Hillman methodology in synthesis and was expected to involve the following objectives:

1. Synthesis of benzylated and non-benzylated Baylis-Hillman adducts and their use in the synthesis of cinnamate esters that are analogous to DKAs as potential dual-action HIV-1 RT/IN inhibitors

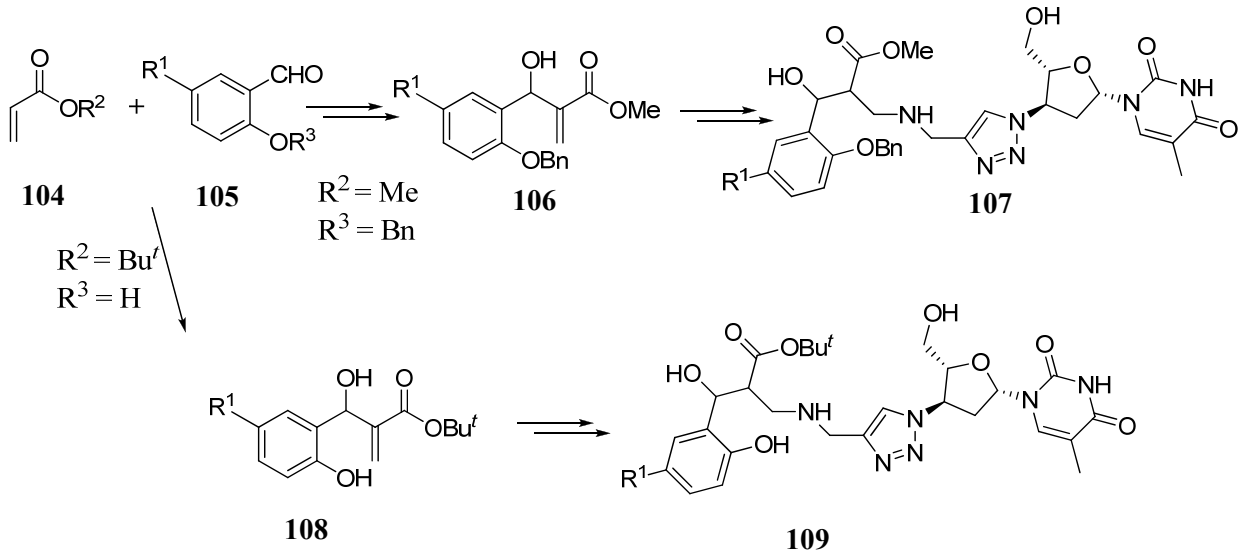
2. Synthesis of customised camphor-based Baylis-Hillman reaction sites.

3. Evaluation of the customised reaction sites as Baylis-Hillman reaction catalysts.

4. Synthesis of analogues of 4-hydroxycoumarin using Baylis-Hillman methodology.

2. RESULTS AND DISCUSSION

This discussion will cover applications of Baylis-Hillman methodology in the synthesis of β-hydroxypropionate ester-AZT conjugates as potential dual-action HIV-1 IN/RT inhibitors (Section **2.1**) and in exploratory studies on accessing 4-hydroxycoumarins (Section **2.2**) and on the construction of customised chiral Baylis-Hillman reaction sites (Section **2.3**). Overall reaction plans to access the ester-AZT conjugates are shown in **Scheme 13.**



Scheme 13. Reaction plans for β-hydroxy ester-AZT conjugates.

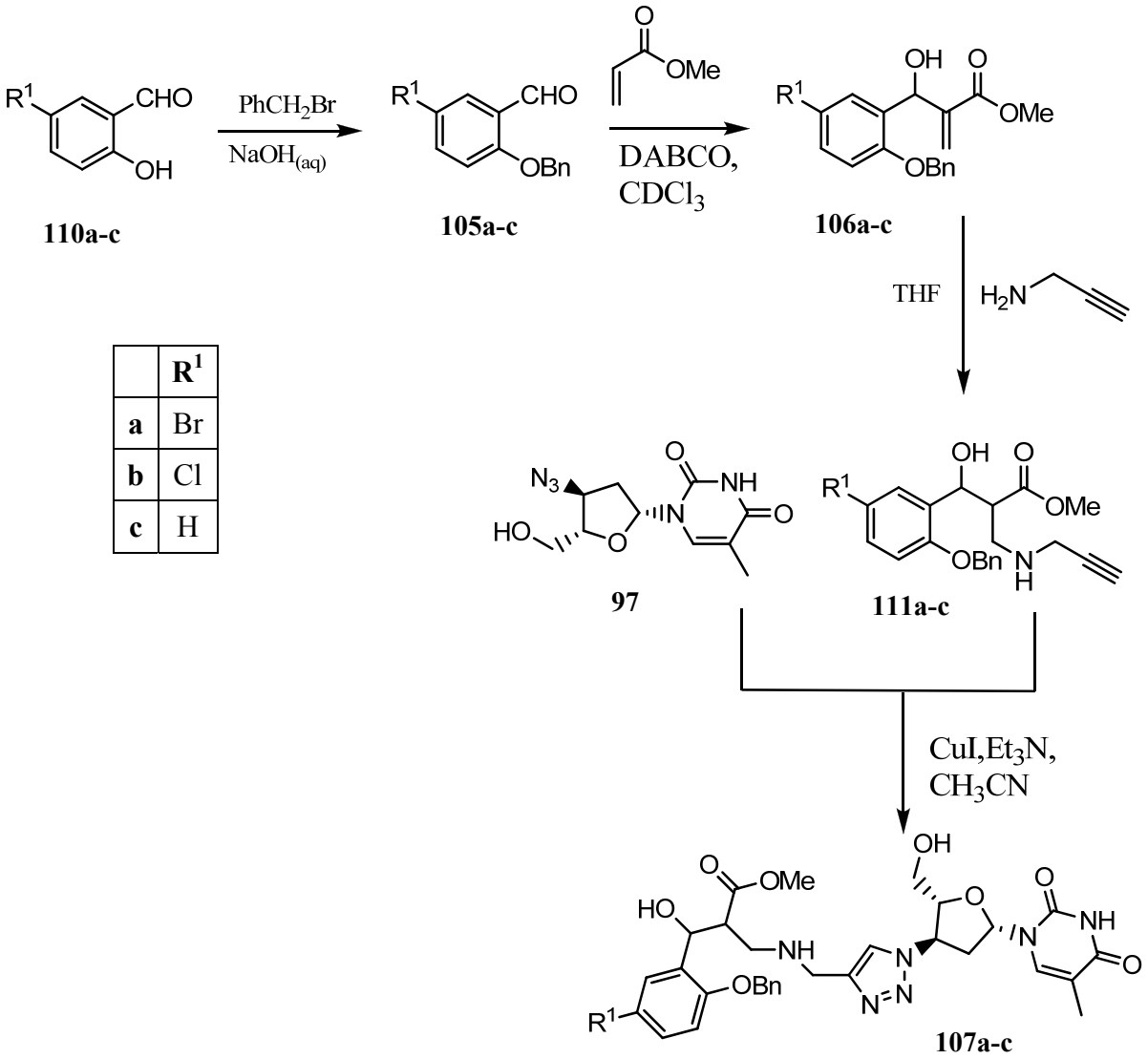
2.1. SYNTHESIS OF β-HYDROXYPROPIONATE ESTER-AZT CONJUGATES

AZT is an established RT inhibitor and DKAs are known IN inhibitors as mentioned earlier. β-hydroxy ester derivatives are analogues of the DKAs and, consequently, may be expected to have anti-IN activity. It was hoped that joining AZT and β-hydroxy ester moieties would result in the formation of molecules which might act as dual-action inhibitors of HIV-1 RT and IN.

2.1.1. Synthesis of β-hydroxy ester-AZT conjugates from *O*-benzylated salicylaldehydes

The pathway used involved several steps, *viz*., i) the benzylation of the 2-hydroxybenzaldehydes **110a-c** (**Scheme 14**); ii) a Baylis-Hillman reaction between each of the *O*-benzylated salicylaldehydes **105a-c** and methyl acrylate; iii) conjugate addition of propargylamine to the

Baylis-Hillman adducts **106a-c**; and, finally, iv) the click reaction of the propargyl derivatives **111a-c** with AZT. Baylis-Hillman reactions of 2-hydroxybenzaldehydes with methyl (or ethyl) acrylate are known to result in the spontaneous formation of complex mixtures of 2-chromene and coumarin derivatives.[118] Benzylation of the 2-hydroxy group, however, permits isolation and controlled elaboration of the *O*-benzylated adducts.[118]



	R[1]
a	Br
b	Cl
c	H

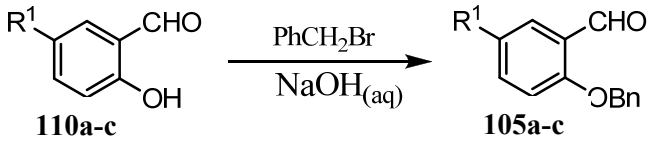
110a-c **105a-c** **106a-c**

Scheme 14. Synthesis of β-hydroxypropionate ester-AZT conjugates **107a-c** from the *O*-benzylated salicylaldehydes **105a-c**.

Benzylation was achieved in yields of 65-87% by heating the compounds **110a-c** with benzyl bromide and $NaOH_{(aq)}$ under reflux for 30 minutes (**Table 4**). An alternative approach to the

benzyl ethers, in which the salicylaldehydes are reacted with benzyl bromide under reflux in the presence of K_2CO_3 and KI for 12 hours, was initially employed but then abandoned due to the generally lower yields (the maximum yield achieved with this approach was 54%). The ^{1}H NMR spectrum for compound **105a** shows the benzylic proton singlet at 5.18 ppm, the aldehydic proton singlet at 10.46 ppm and the expected aromatic proton signals between 6.9 and 8.0 ppm (**Figure 20**). In the ^{13}C NMR spectrum, the signals at 70.8 ppm and 188.3 ppm correspond to the benzylic and aldehydic carbons, respectively, while the remaining ten signals correspond to the aromatic carbons (**Figure 21**).

Table 4. Yields of 2-(benzyloxy)benzaldehydes **105a-c.**



110a-c **105a-c**

Compound	R^1	Isolated Yields (%)
105a	Br	87
105b	Cl	81
105c	H	65

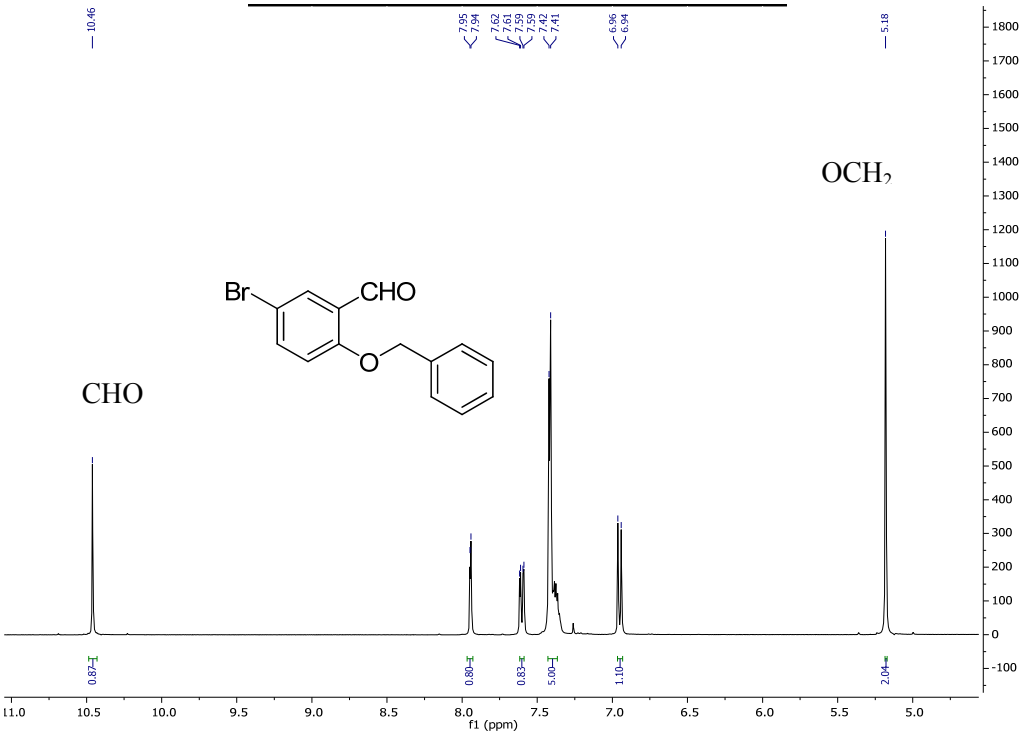


Figure 21. 400 MHz ^{1}H NMR spectrum of compound **105a** in $CDCl_3$.

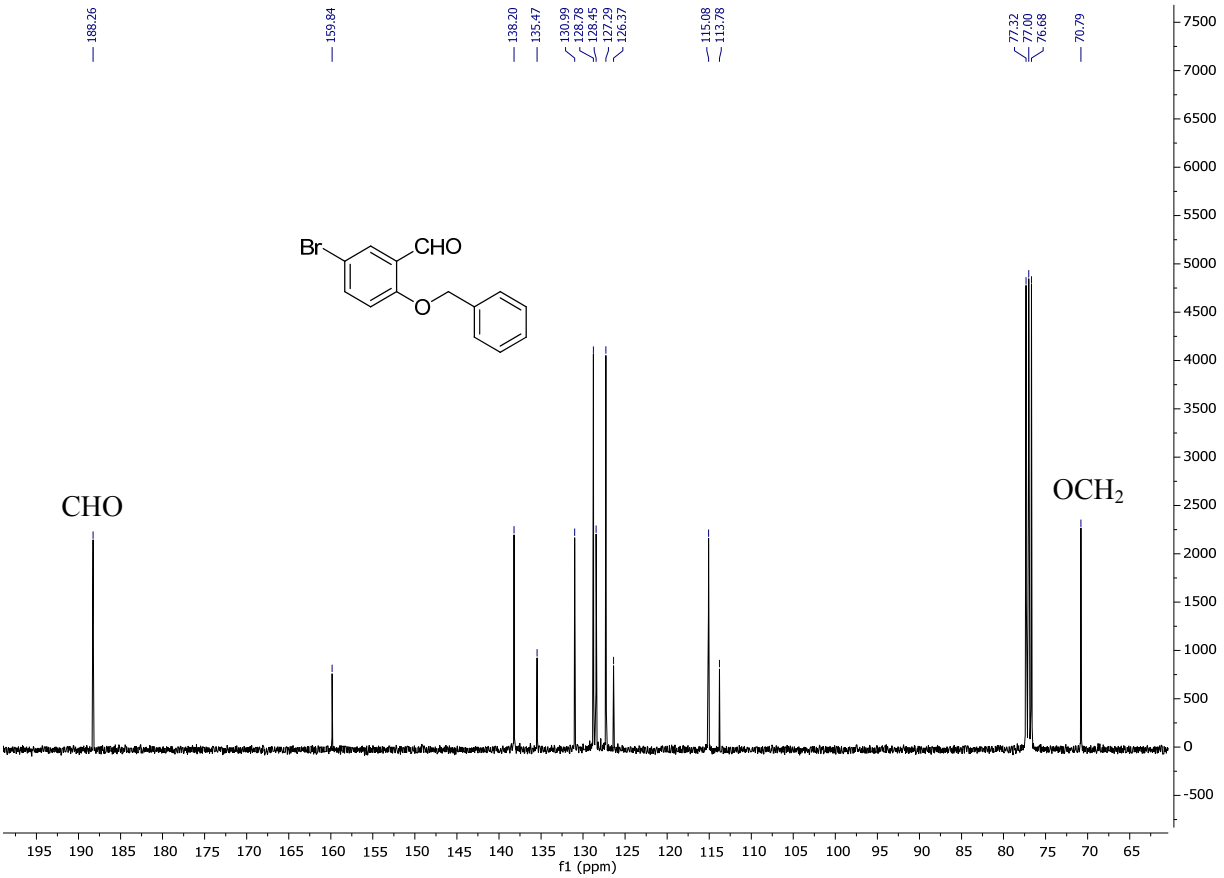


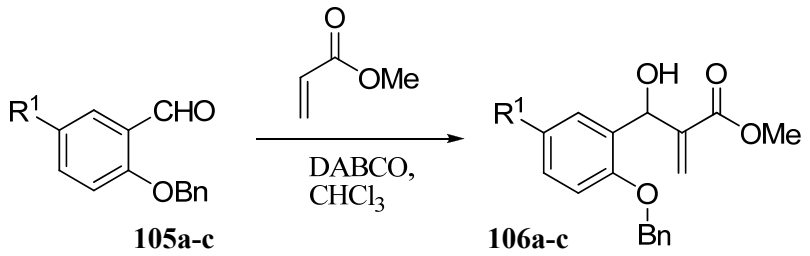
Figure 22. 100 MHz ^{13}C NMR spectrum of compound **105a** in $CDCl_3$.

2.1.2. Baylis-Hillman reaction of the *O*-benzylated salicylaldehyde 105a-c with methyl acrylate

The salicylaldehyde benzyl ethers **105a-c** were then reacted with methyl acrylate in DABCO-catalysed Baylis-Hillman reactions with $CHCl_3$ as solvent. The reactions were allowed to run for 21 days with stirring at room temperature. Work-up afforded the Baylis-Hillman adducts in yields ranging from 54 to 64% (**Table 5**). The ^{1}H NMR spectrum of methyl 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-methylenepropanoate **106a** (**Figure 23**) shows the methyl proton signal as a singlet at 3.74 ppm, the benzylic protons resonating as a singlet at 5.05 ppm and the 3-methine proton at 5.89 ppm. The vinylic proton signals appear as singlets at 5.66 ppm and at 6.30 ppm (characteristic of these protons in Baylis-Hillman adducts, exhibiting no germinal coupling). The DEPT 135 NMR spectrum (**Figure 24**) shows the methyl, 3-methine and benzylic

carbons resonating at 52.0, 67.7 and 70.4 ppm respectively. The methylene signal at 126.5 ppm confirms attachment of the two vinylic protons on the same carbon (C-3`).

Table 5. Yields of methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanoates **106a-c.**



Compound	R^1	Isolated Yields (%)
106a	Br	54
106b	Cl	61
106c	H	64

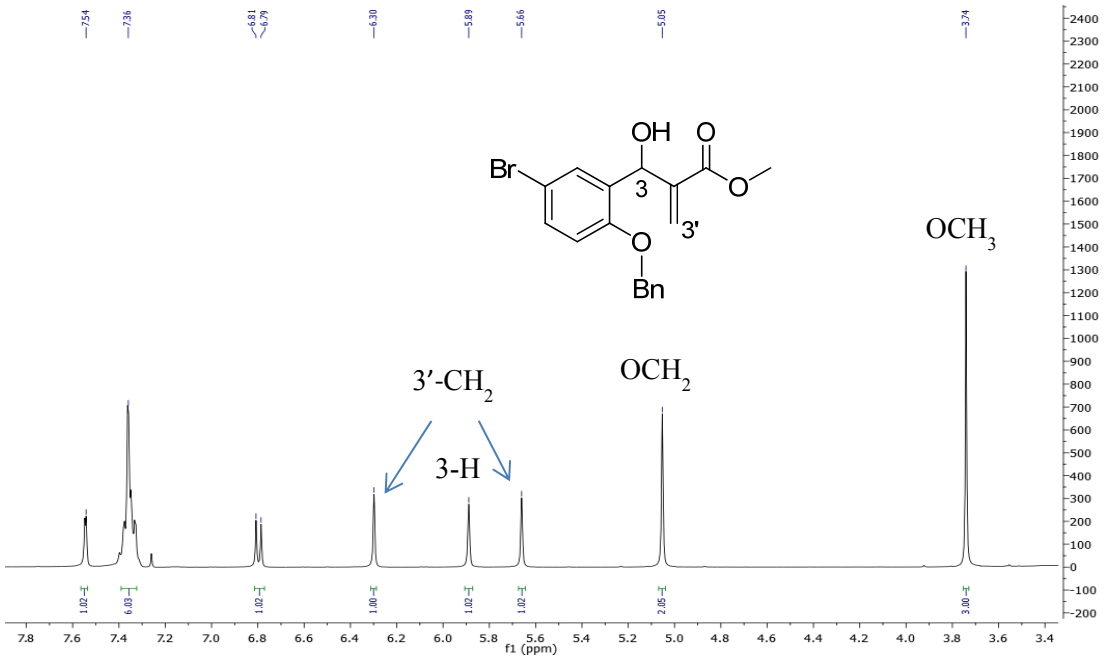


Figure 23. 400 ^{1}H NMR spectrum of compound **106a** in $CDCl_3$.

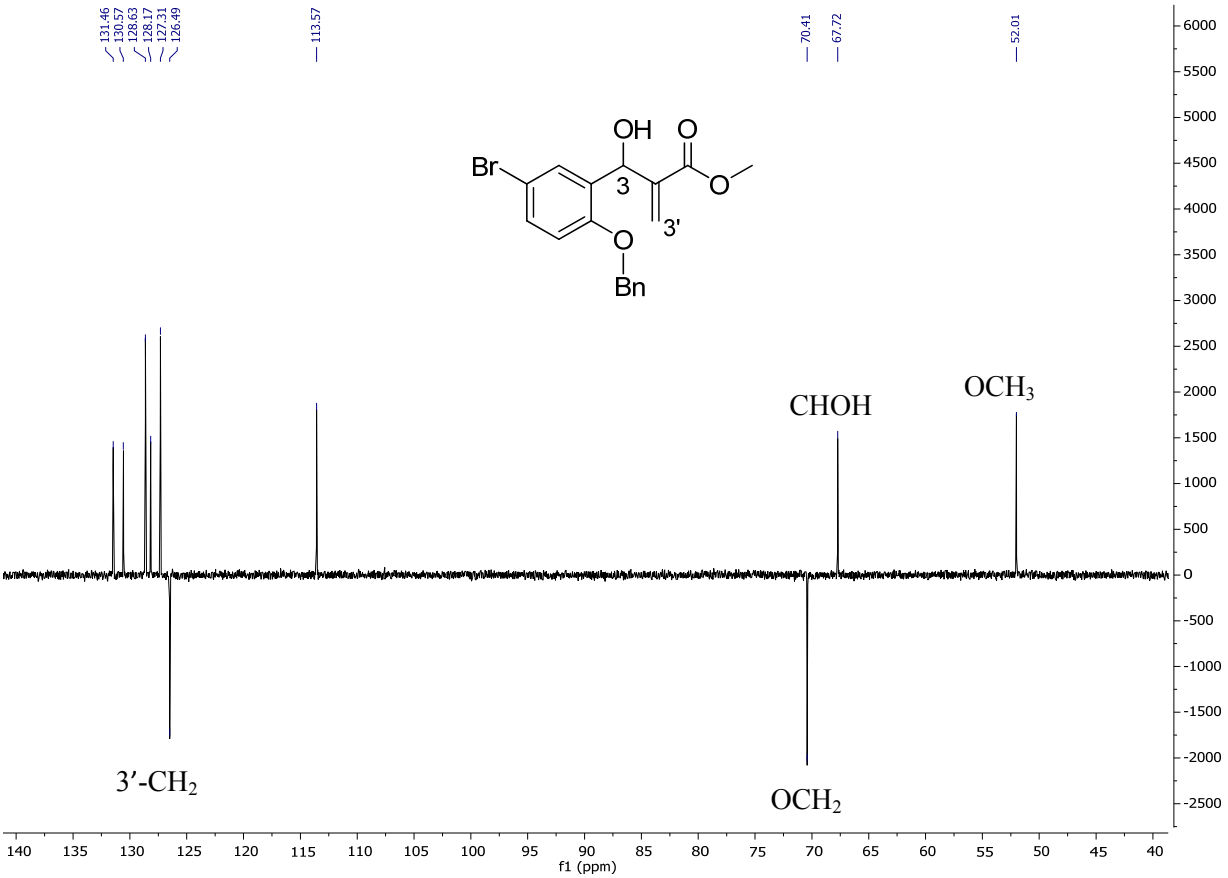


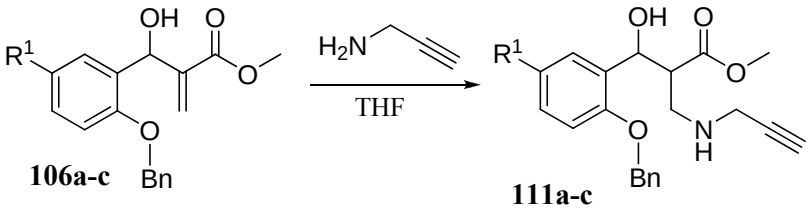
Figure 24. DEPT 135 NMR spectrum of compound **106a** in $CDCl_3$.

2.1.3. Synthesis of 3`-propargylamino derivatives 111a-c

The Baylis-Hillman adducts **106a-c** were then reacted with propargylamine in dry THF. In each case, the reaction mixture was stirred at room temperature for 3 days. The propargyl moiety enables the subsequent click reaction with AZT. Flash chromatography following work-up afforded the products **111a-c** in yields of up to 97% (**Table 6**). Further purification using preparative layer chromatography (PLC) instead of flash chromatography permitted the isolation of diastereomers in the cases of the 5-bromophenyl (**111a**) and the benzyloxyphenyl (**111c**) derivatives. Due to the presence of the stereogenic centres in componds **106a-c**, 4 stereoisomeric products are expected in each case, i.e. 2 diastereisomeric pairs of enantiomers. The ^{1}H NMR spectrum of one of the diastereomeric pairs of enantiomers **111a** shows the benzylic proton signal at about 5.07 ppm and the methylene proton signals NCH_2C and $CHCH_2$ proton signals at

about 2.88 and 3.11 ppm respectively (**Figure 25).** The DEPT 135 NMR spectrum (**Figure 26**) shows the methylene carbons, NCH_2C, $CHCH_2$ and OCH_2 resonating at 38.2, 48.4 and 71.6 ppm respectively. Interestingly the DEPT spectrum also reveals two quaternary carbon signals at 72.4 and 80.6 ppm which suggests that the quaternary acetylenic carbon also bore a proton. The appearance of the quaternary alkyne carbon signal in the DEPT 135 spectrum is, in fact, due to the large $^2J_{C,H}$ coupling.

Table 6. Yields of propargyl amino derivatives **a-c.**



Compound	R^1	Isolated Yields (%)
111a	Br	84
111b	Cl	97
111c	H	76

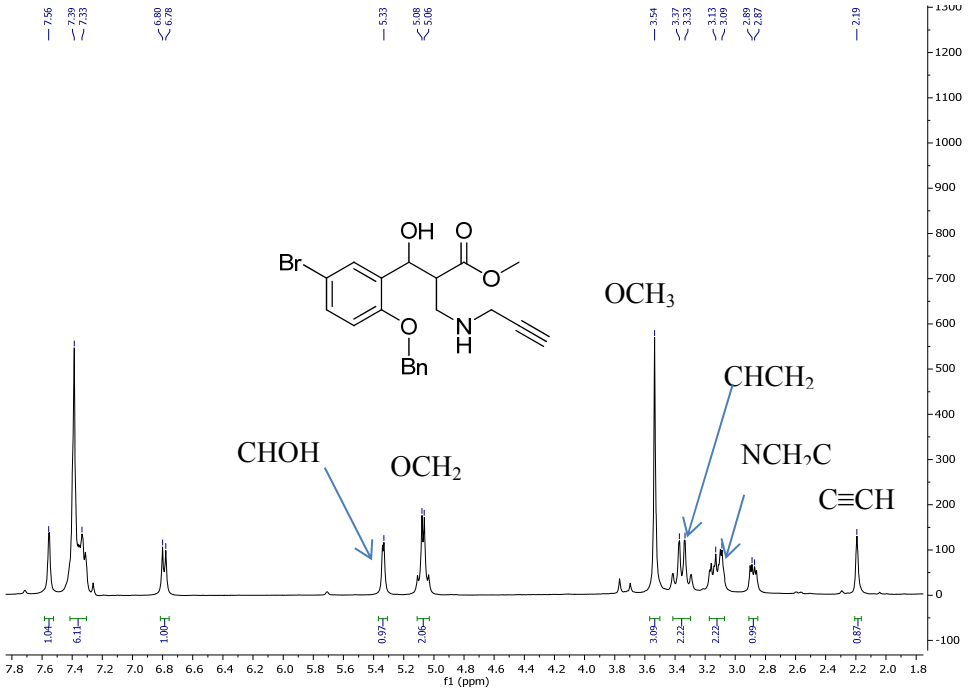


Figure 25. 400 MHz ^{1}H NMR spectrum of compound **111a** in CD_3OD.

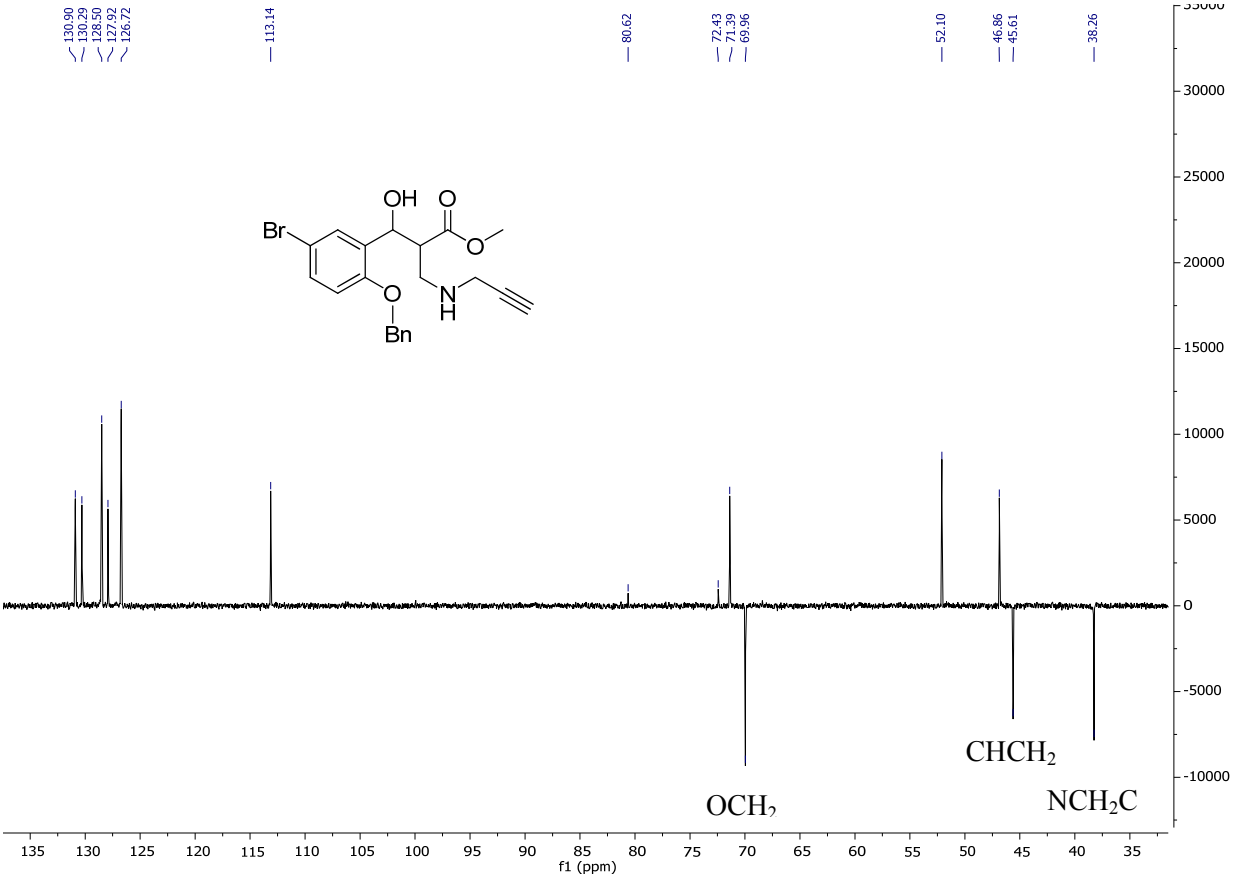


Figure 26. DEPT 135 NMR spectrum of compound **111a** in CD_3OD.

The diastereomeric ratios (based on the isolated yields) for compounds **111a** and **111c** were 56:44 and 60:40, respectively. The relative chemical shifts of the carbon signals for the diastereomers of **111a** are shown in the corresponding ^{13}C and DEPT 135 spectra (**Figures 27** and **28**). The spectra reveal similar signal patterns in each case but the chemical shifts are different, confirming the diasteromeric relationship between the isomers.

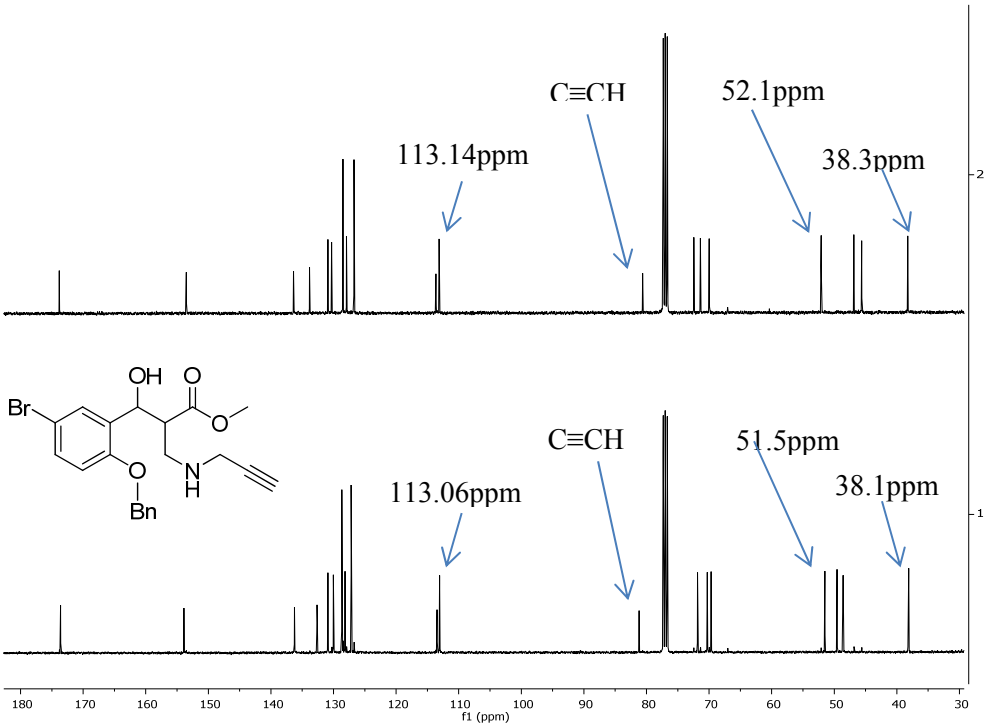


Figure 27. 100 MHz ^{13}C NMR spectra of diastereomers **111a$_1$** and **111a$_2$** in $CDCl_3$.

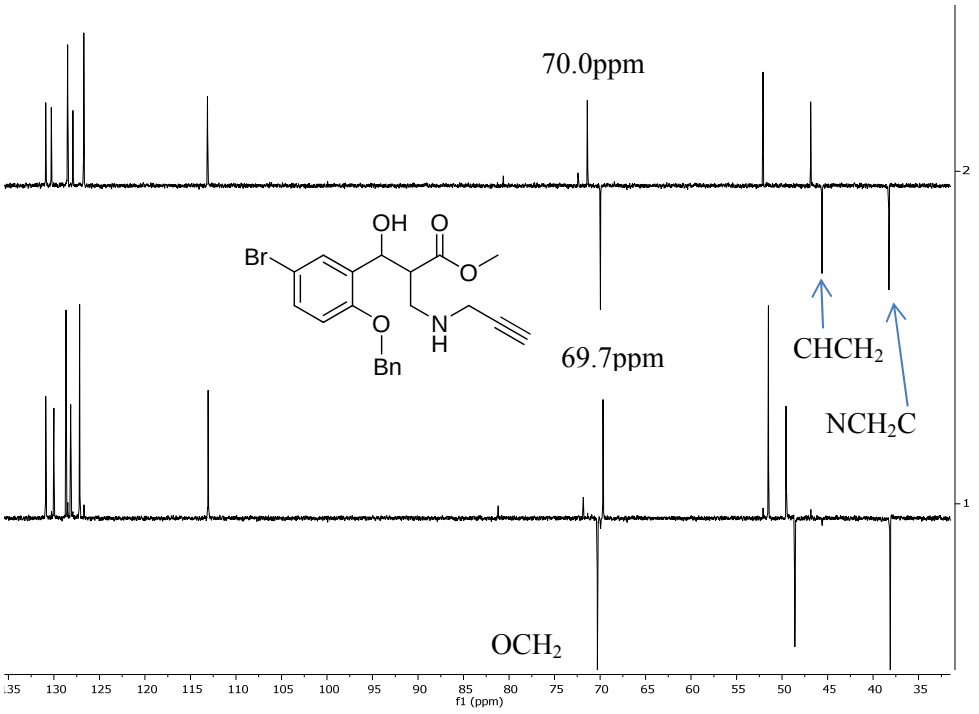
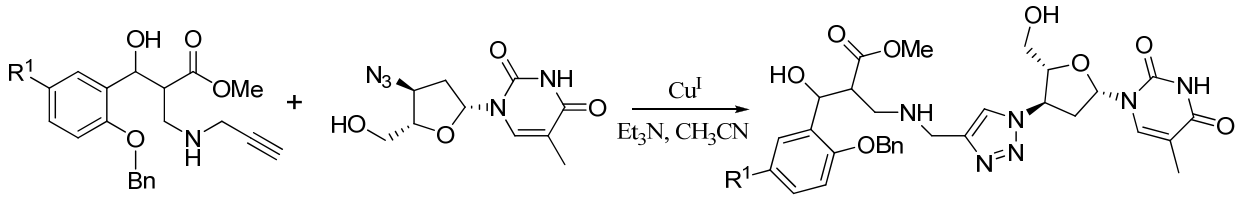


Figure 28. DEPT 135 NMR spectra of diastereomers **111a$_1$** and **111a$_2$** in $CDCl_3$.

2.1.4. Click reaction of propargylamino derivatives 111a-c

The propargyl derivatives **111a-c** were reacted with AZT in CH_3CN in the presence of a Cu^I catalyst and Et_3N (**Scheme 26**). The term 'click reaction' or, alternatively, 'click chemistry' originates from Sharpless and co-workers[127] who, inspired by nature's ability to synthesize from small units the three main families of macromolecules (polynucleotides, polypeptides and polysaccharides), endeavored to use heteroatom links (C-X-C) to join small units in the generation of products and coined the approach 'click chemistry'. Click chemistry facilitates faster drug lead discovery and optimization.[128] The click reaction binds two molecular building blocks under mild conditions in high-yielding, selective and facile reactions.[129] Common examples of these C-heteroatom bond-forming reactions include cycloadditions of unsaturated species, *e.g.*, 1,3-dipolar cycloaddition and Diels-Alder reactions, nucleophilic substitution and additions to C-C multiple bonds, *e.g.*, aziridination and epoxidation.[127]

The Cu^I-catalysed azide/alkyne cycloaddition (CuAAC) is the most widely used click reaction. It can be performed using Cu^I from various sources or Cu^I pre-catalysts, which include use of a Cu^{II} salt together with sodium ascorbate as a reducing agent, or a Cu^I compound such as CuBr together with an amine ligand or a base and a reducing agent (sodium ascorbate) to prevent aerobic oxidation to Cu^{II}.[129] Reported at the same time by two groups, Medal (Denmark)[130] and Fokin and Sharpless (US),[130] the CuAAC exclusively transforms organic azides and terminal alkynes into the corresponding 1,4-disubstituted 1,2,3-triazoles ─ unlike the uncatalysed reaction which needs higher temperatures and yields mixtures of 1,4- and 1,5-triazole regioisomers.[130] The reaction has been found to offer a straight-forward way of connecting building blocks having various functional groups, has proved to be dependable and offers high levels of compatibility between reactants.[128,130] In our group, two approaches have been used in CuAAC, Cu^{II} together with sodium ascorbate as reducing agent and CuI with Et_3N. In the present investigation, CuI and Et_3N were used (**Scheme 15**).



Scheme 15. Click reaction of propargylamino derivatives **111a-c** with AZT.

Table 7. Yields of hydroxy ester-AZT conjugates **107a-c.**

Compound	R^1	Isolated Yields (%)
$107a_1$*	Br	72
$107a_2$*	Br	36
107b	Cl	92
$107c_1$	H	55

* Diastereomers

The yields ranged from 36-92%. The click reaction was conducted with each of the two diastereomeric propargylamino ester derivatives **$111a_1$** and **$111a_2$** with yields for the major and minor diastereomers being 72% and 36%, respectively. For the propargylamino derivative **111c** only the major isomer, **$111c_1$** was used in the click reaction. The DEPT 135 NMR spectrum (**Figure 29**) shows the various methyl, methylene and methine signals for compound **107b** with the expected five methylene signals for CH_2CHN, CH_2NCH_2CH, CH_2OH and $ArOCH_2$ at 39.0, 44.5, 48.8, 62.1 and 71.5 ppm, respectively. The HSQC spectrum (**Figure 30**) clearly shows three of the methylene signals highlighted in the DEPT 135 NMR spectrum. Of particular interest are the correlations between the CH_2CHN methylene carbon (resonating at 39.0 ppm) with the corresponding methylene protons which resonate separately at 2.68 and 2.79 ppm, reflecting their inherent diastereotopicity. The correlations between the CH_2OH methylene carbon (resonating at 62.1 ppm) and its corresponding methylene protons at 3.75 and 3.84 ppm reveal the same pattern.

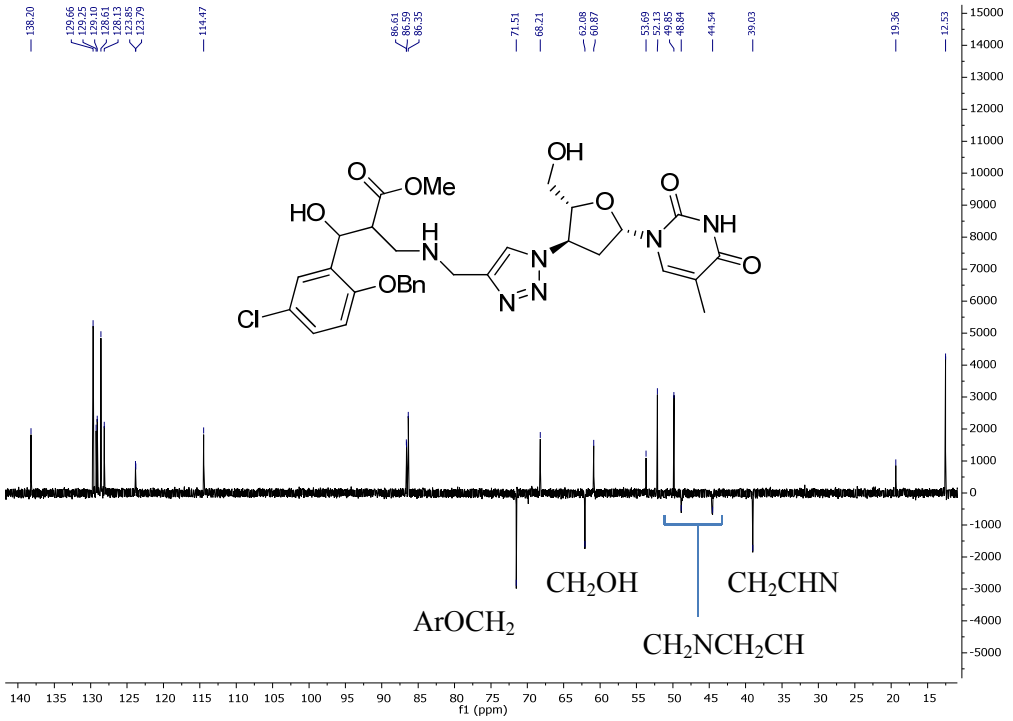


Figure 29. DEPT 135 NMR spectrum of compound **107b** in CD_3OD.

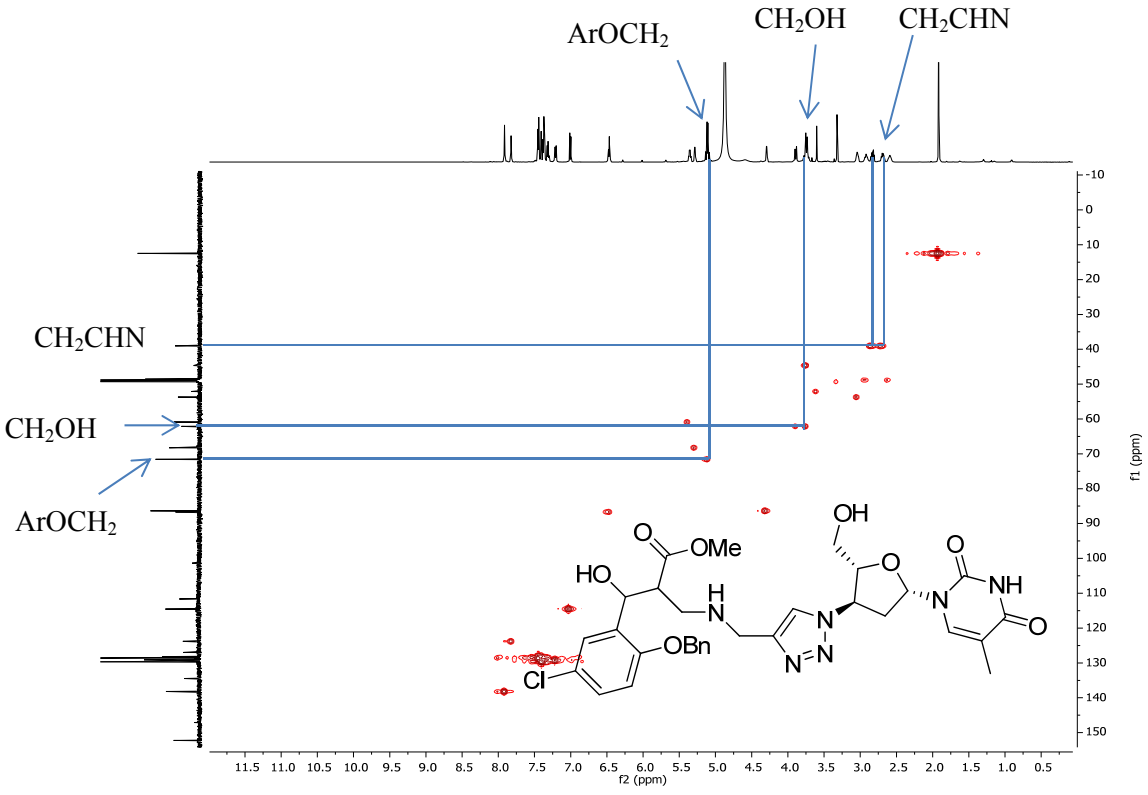
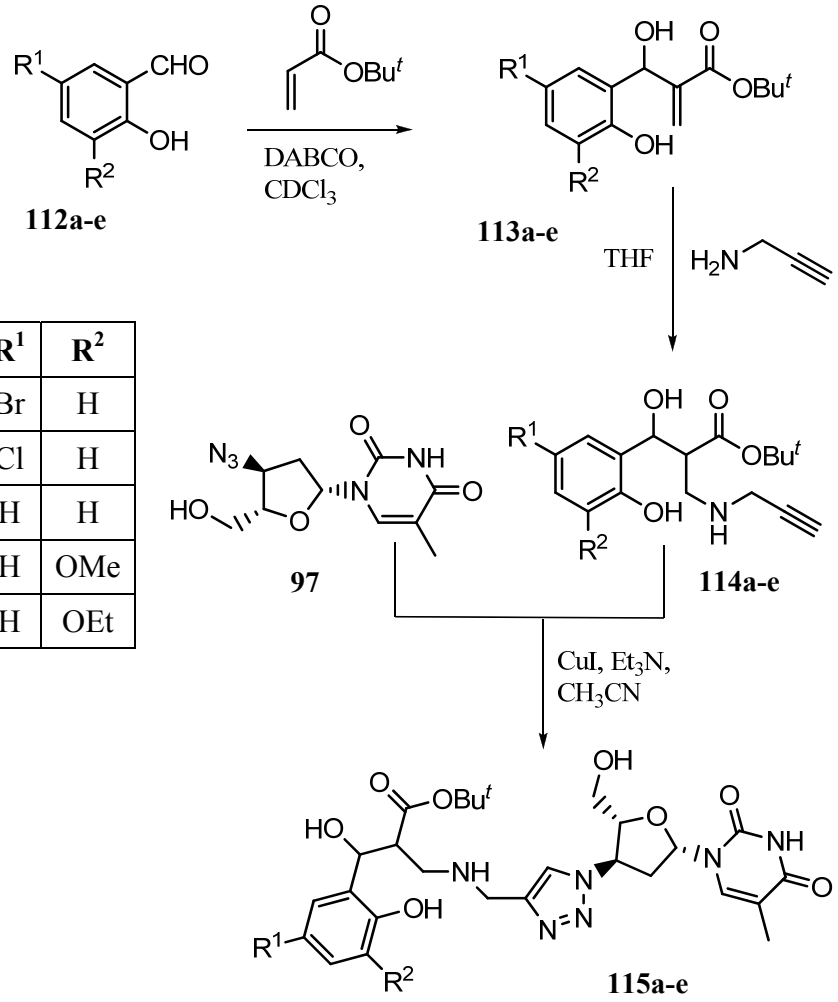


Figure 30. HSQC spectrum of compound **107b** in CD_3OD.

2.1.5. Synthesis of β-hydroxypropionate ester-AZT conjugates from unprotected salicylaldehydes

Unlike their methyl ester analogues, Baylis-Hillman adducts derived from reactions between *tert*-butyl acrylate and salicylaldehydes are stable and isolable. Consequently, they can be used as substrates in subsequent reactions without the danger of uncontrolled cyclisation and without the need to benzylate the phenolic group in the salicylaldehyde precursors. In this study, five different salicylaldehydes were used. The general reaction pathway to the β-hydroxy ester-AZT conjugates is shown in **Scheme 16**.



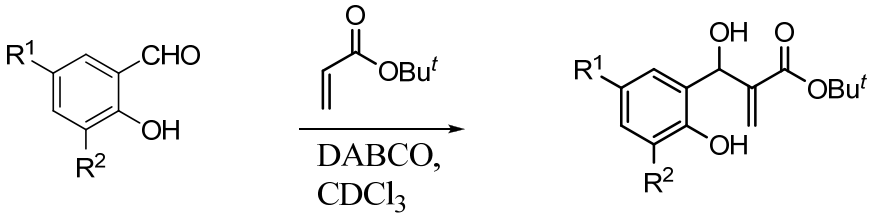
Compound	R^1	R^2
115a	Br	H
115b	Cl	H
115c	H	H
115d	H	OMe
115e	H	OEt

Scheme 16. Synthesis of of β-hydroxy ester-AZT conjugates from non-benzylated salicylaldehydes.

2.1.6. Baylis-Hillman reactions with *tert*-butyl acrylate

The salicylaldehydes **112a-e** were reacted with *tert*-butyl acrylate in DABCO-catalysed Baylis-Hillman reactions using $CHCl_3$ as solvent. The reactions were allowed to run for 7-21 days with stirring at room temperature. The bromo- and chlorosalicylaldehyde products **113a** and **113b** had formed significantly after 4 days but the reactions were allowed to run for 7 days to enhance the yield. Work-up afforded the Baylis-Hillman adducts in yields ranging from 21 to 69% after chromatography (**Table 8**). The methoxy- and ethoxy-substituted salicylaldehyde adduct yields were particularly low. Further study aimed at improving the yields is an avenue that may be pursued. The ^{1}H NMR spectrum (**Figure 31**) of *tert*-butyl 3-(5-chloro-2-hydroxyphenyl)-3-hydroxy-2-methylenepropanoate, **113b**, which is representative for the series, shows the *tert*-butyl singlet at 1.31 ppm. The vinylic proton signals appear as singlets at 5.64 and 6.05 ppm with the upfield signal overlapping with the 4-methine proton signal. The three aromatic proton signals appear between 6.7 and 7.1 ppm. The DEPT 135 NMR spectrum shows the *tert*-butyl methyl carbon signal at 27.6 ppm, the 4-methine carbon signal at 64.6 ppm and the vinylic CH_2 carbon signal at 123.1 ppm (**Figure 32**).

Table 8. Yields of the *tert*-butyl adducts **113a-e.**



112a-e **113a-e**

Compound	R^1	R^2	Isolated yields (%)
113a	Br	H	69
113b	Cl	H	54
113c	H	H	36
113d	H	OMe	26
113e	H	OEt	21

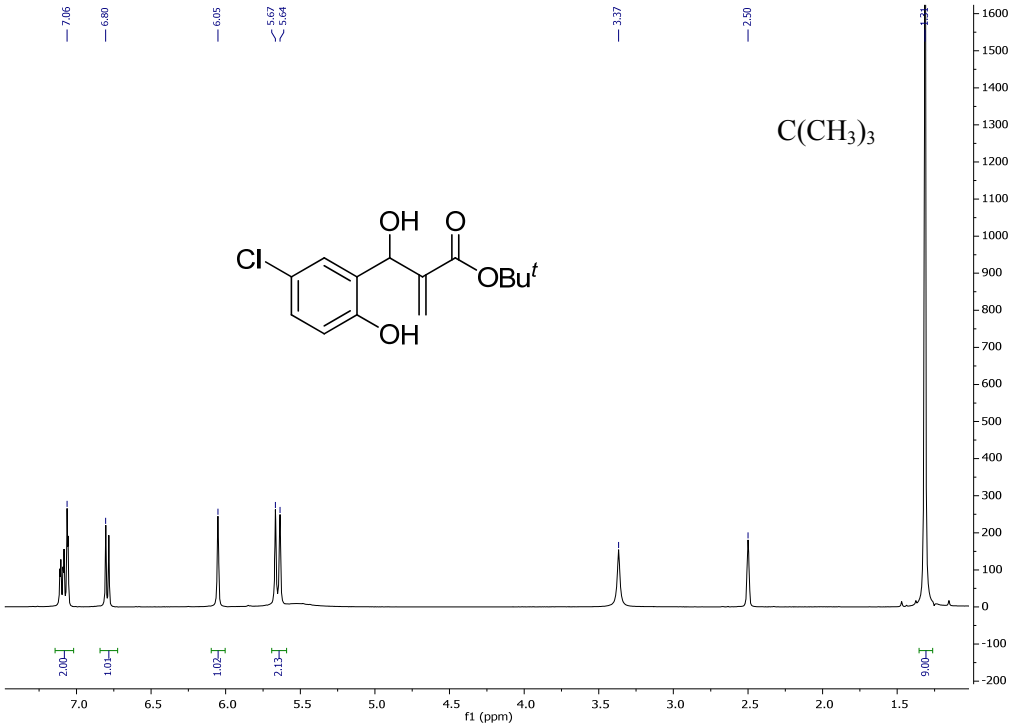


Figure 31. 400 MHz ^{1}H NMR spectrum of compound **113b** in DMSO-d_6.

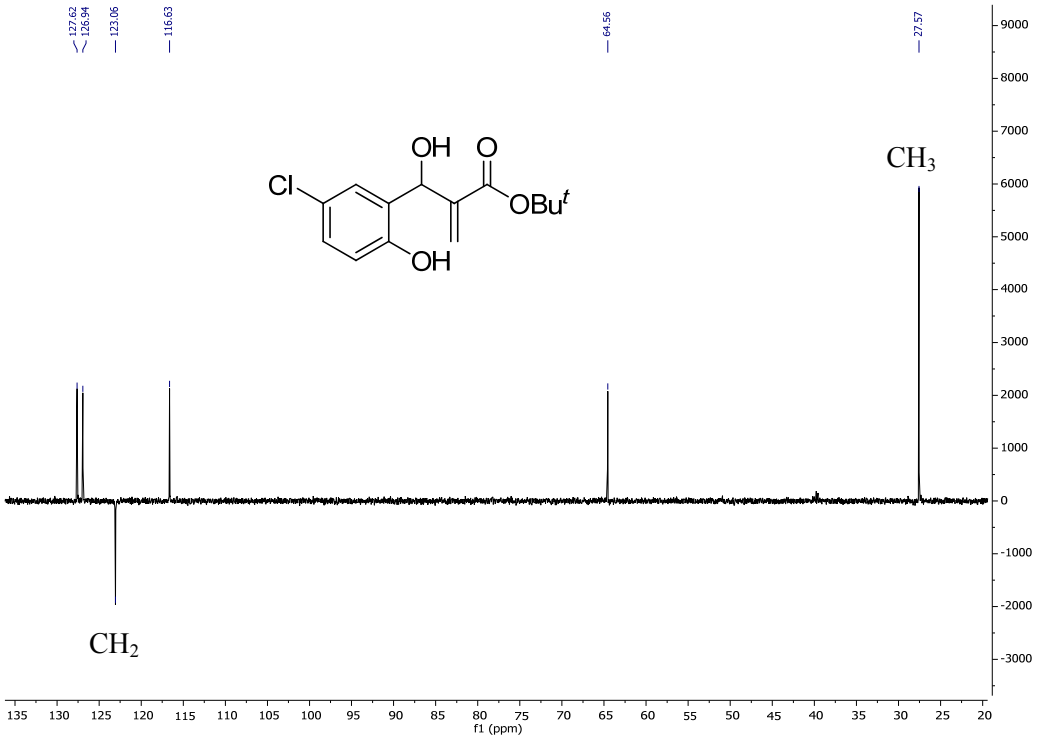
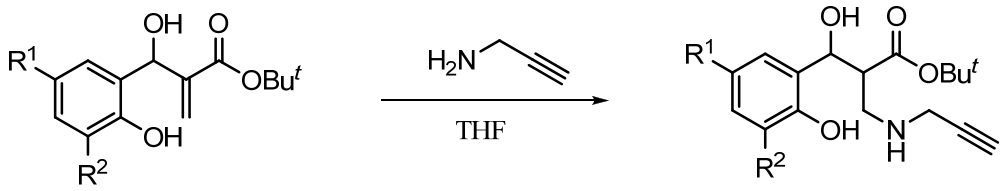


Figure 32. DEPT 135 NMR spectrum of compound **113b** in DMSO-d_6.

2.1.7. Synthesis of propargylamino derivatives 114a-e

A similar method to that described for the *O*-benzylated adducts in Section **2.1.3** was used to prepare compounds **114a-e** in yields ranging from 46 to 84% (**Table 9**). The ^{1}H NMR spectrum of compound **114b** confirms the formation of the propargylamino products (**Figure 33**). The absence of the vinylic proton signals of the precursor and the presence of the signals at 2.57, 3.35 and 5.21 ppm corresponding to C≡CH, CH_2C≡CH and C*H*OH, respectively confirm the formation of the propargylamino product. The DEPT 135 spectrum (**Figure 34**) shows the two expected methylene carbon signals, an intense *tert*-butyl methyl signal and three aromatic methine carbon signals consistent with the expected product. The DEPT 135 spectrum also shows a signal at 82 ppm for the quaternary alkyne carbon signal as discussed for the *O*-benzylated propargyl compounds (Section **2.1.3.**) The propargyl products, as described earlier, carry the propargyl moiety which enables the subsequent click reaction with AZT.

Table 9. Yields of propargylamino derivatives **114a-e.**



113a-e **114a-e**

Compound	R^1	R^2	Isolated yields (%)
114a	Br	H	77
114b	Cl	H	84
114c	H	H	57
114d	H	OMe	67
114e	H	OEt	46

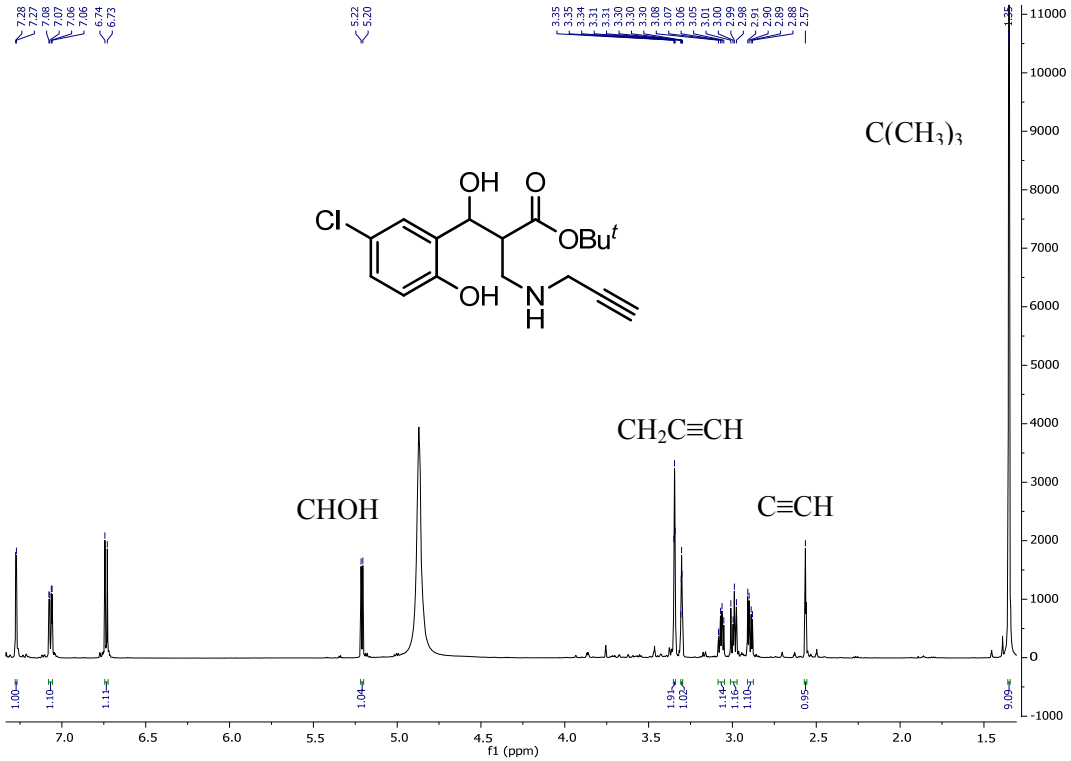


Figure 33. 600 MHz ^{1}H NMR spectrum of compound **114b** in CD_3OD.

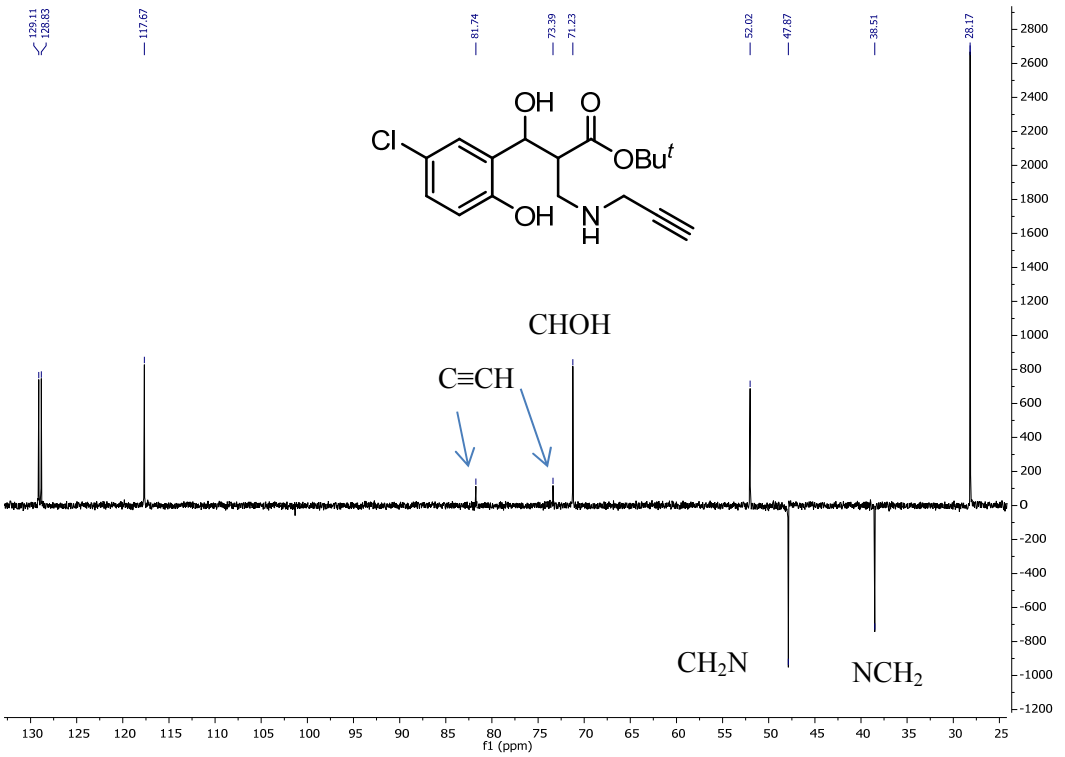
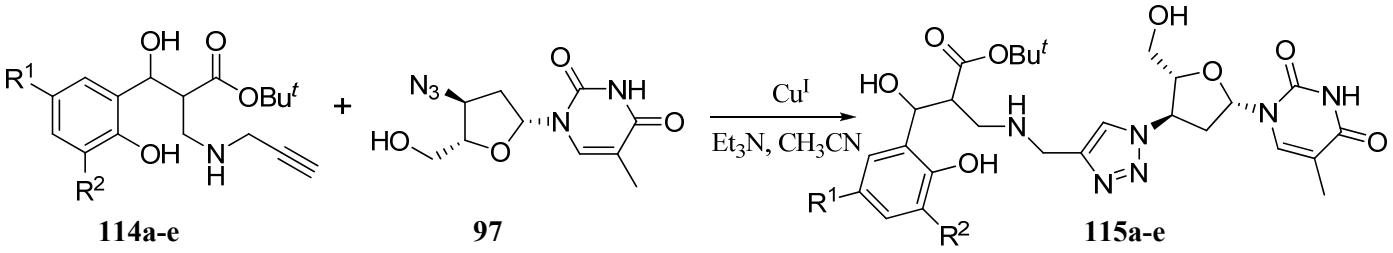


Figure 34. DEPT 135 NMR spectrum of compound **114b** CD_3OD.

2.1.8. Click reactions of the propargylamino derivatives 114a-e

The propargyl derivatives **114a-e** were reacted with AZT in CH_3CN in the presence of a Cu^I catalyst and Et_3N (**Scheme 27**). The reaction mixtures were allowed to stir at room temperature for 48 hours after which purification was achieved using column chromatography [on silica gel; elution with hexane − EtOAc (2:1)] except for the methoxy substituted derivative **115d**, for which the purification described for the benzylated derivatives was used and which afforded better yields. Time constraints prevented the use of the better yielding purification method for the rest of the non-benzylated derivatives. The yields ranged from 10 to 66% with **115d** having an outstandingly high yield when compared to the rest which are all below 20% (**Table 10**). The ^{13}C NMR spectrum of **115b** reveals the *tert*-butyl methyl carbon signal at 12.5, the *tert*-butyl quartenary carbon signal at 82.2 and the ester carbonyl signal at 173.5 ppm (**Figure 35**). The spectrum also shows the expected number of carbon signals. The DEPT 135 spectrum (**Figure 36**) shows the 4 expected methylene carbon signals, the upfield AZT methyl signal, the intense *tert*-butyl methyl carbon signal and 5 aromatic methine carbon signals consistent with the expected product.



Scheme 17. Click reaction of propargylamino derivatives **114a-e** with AZT.

Table 10. Yields of propargylhydroxy ester-AZT conjugate **115a-e.**

Compound	R^1	R^2	Isolated yields (%)
115a	Br	H	13
115b	Cl	H	14
115c	H	H	16
115d	H	OMe	66
115e	H	OEt	10

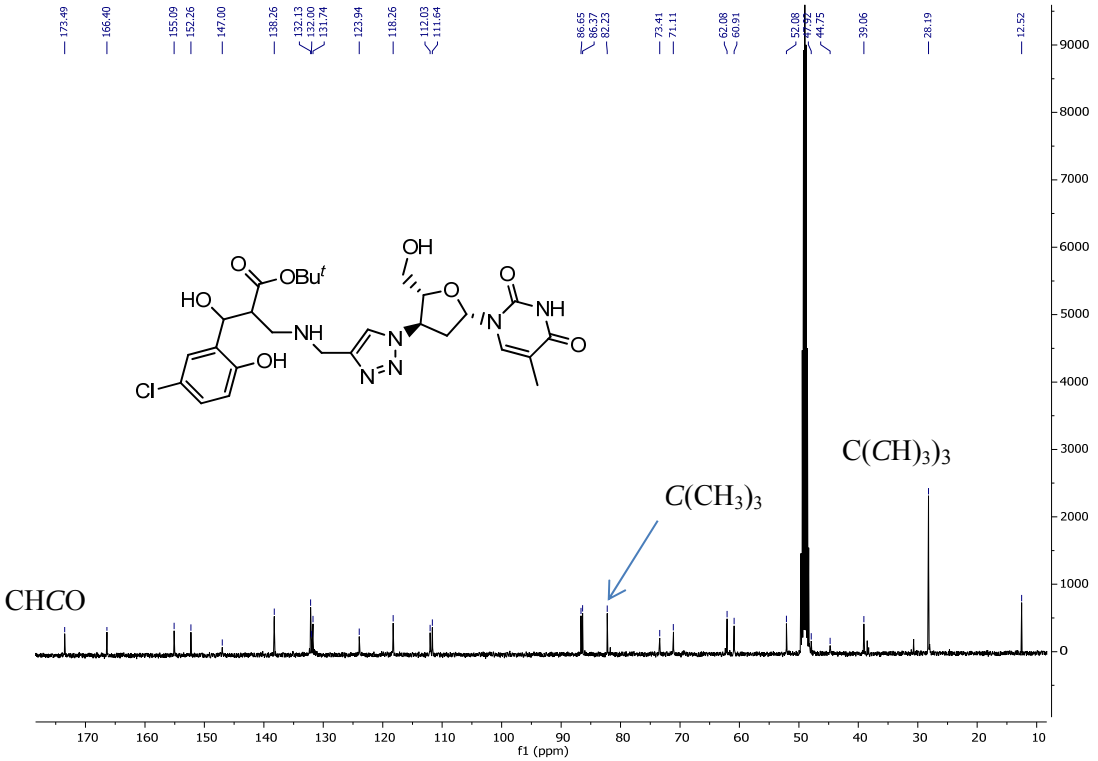


Figure 35. 100 MHz ^{13}C NMR spectrum of isomers of compound **115b** in CD_3OD.

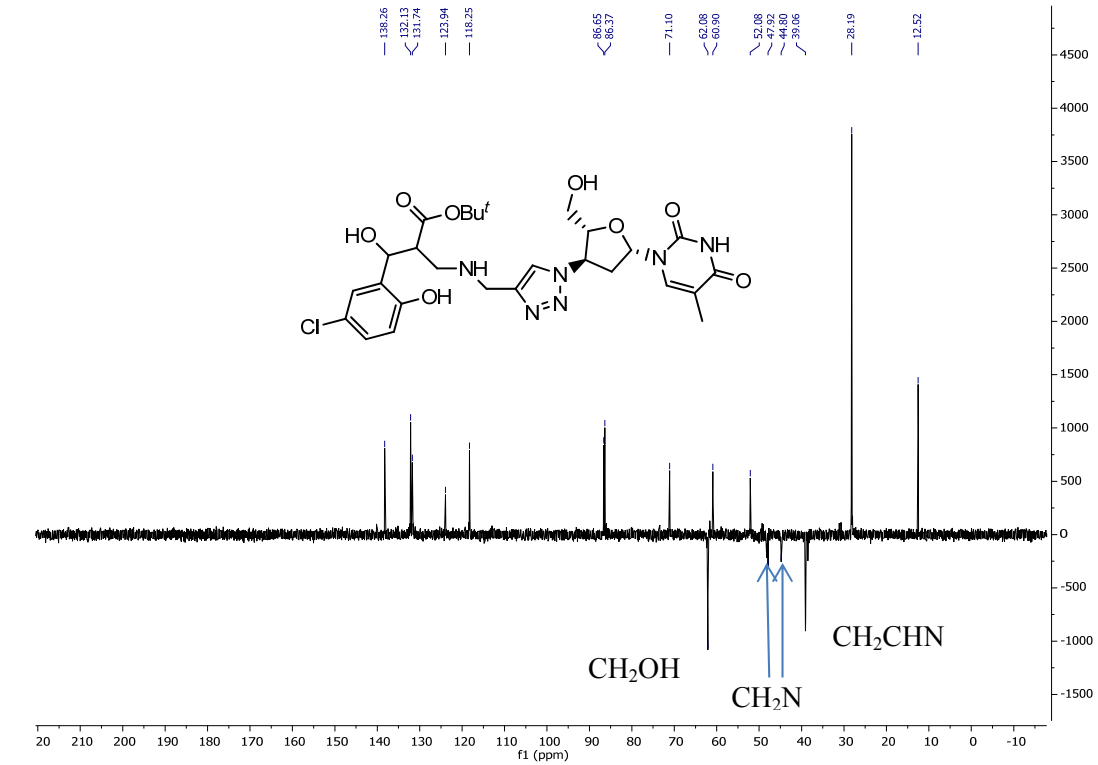
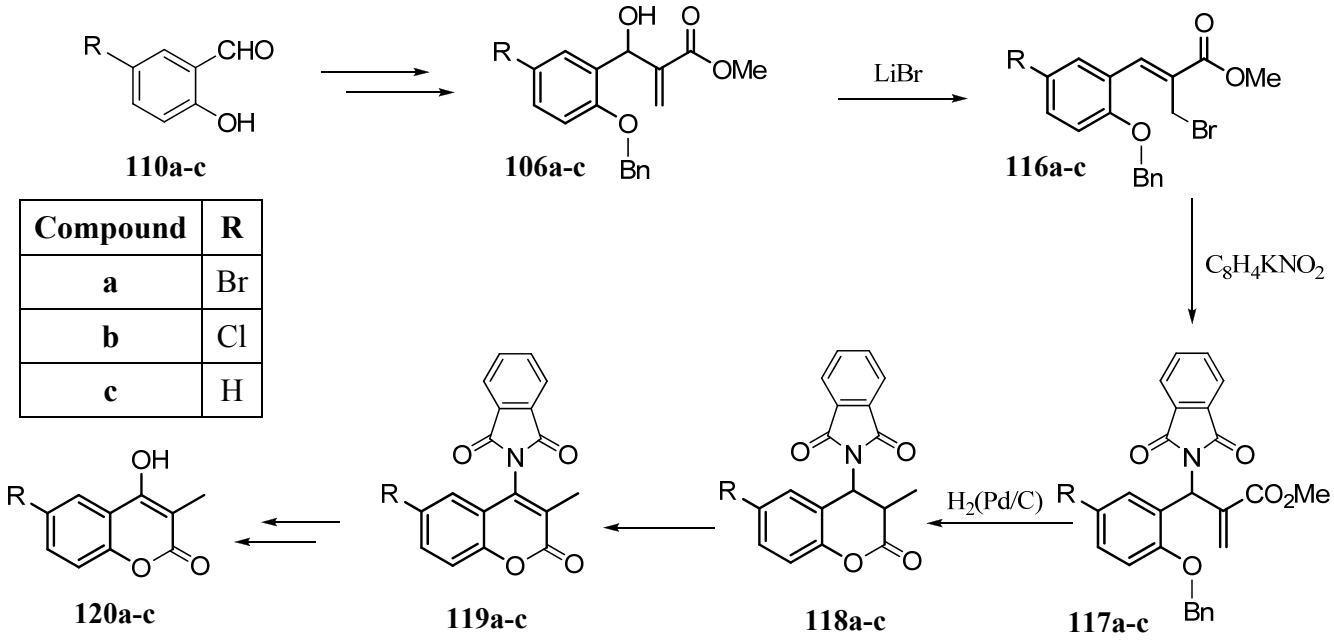


Figure 36. DEPT 135 NMR spectrum of compound **115b** in CD_3OD.

2.2. EXPLORATORY STUDIES ON ACCESSING 4-HYDROXYCOUMARINS

In Section **1.3.3.** the importance of 4-hydroxycoumarins as bioactive compounds with a wide range of activities was discussed. In this study, several approaches were explored to access these important compounds. Two of the approaches are shown in **Schemes 18** and **19**.

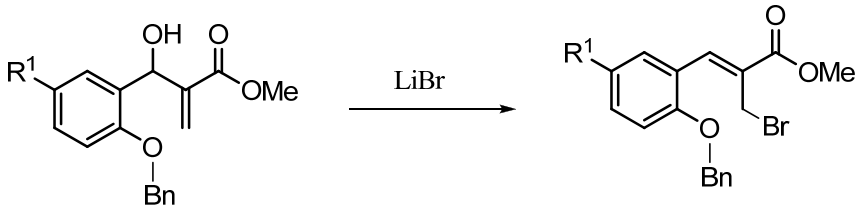


Scheme 18. Proposed route to 4-hydroxycoumarins *via* cinnamate ester derivatives.

2.2.1. Cinnamate ester route to 4-hydroxycoumarins

The 2-(bromomethyl) cinnamate ester derivatives were formed in yields of up to 86% (**Table 11**) by reacting the Baylis-Hillman adducts **106a-c** with LiBr in conc. H_2SO_4. The ^1H NMR spectrum of compound **116a** shows the methyl, 2-bromomethylene and benzylic proton signals at 3.87, 4.33 and 5.12 ppm, respectively (**Figure 37**). The vinylic proton signals for the precursor are absent in the product and the new vinylic proton signal appears downfield at 7.96 ppm. The DEPT 135 spectrum (**Figure 38**) shows the expected two methylene carbon signals at 26.6 and 70.6 ppm and the expected seven aromatic and vinylic methine carbon signals.

Table 11. Yields of cinnamate ester derivatives **116a-c.**



106a-c **116a-c**

Compound	R	Isolated Yields (%)
116a	Br	86
116b	Cl	84
116c	H	55

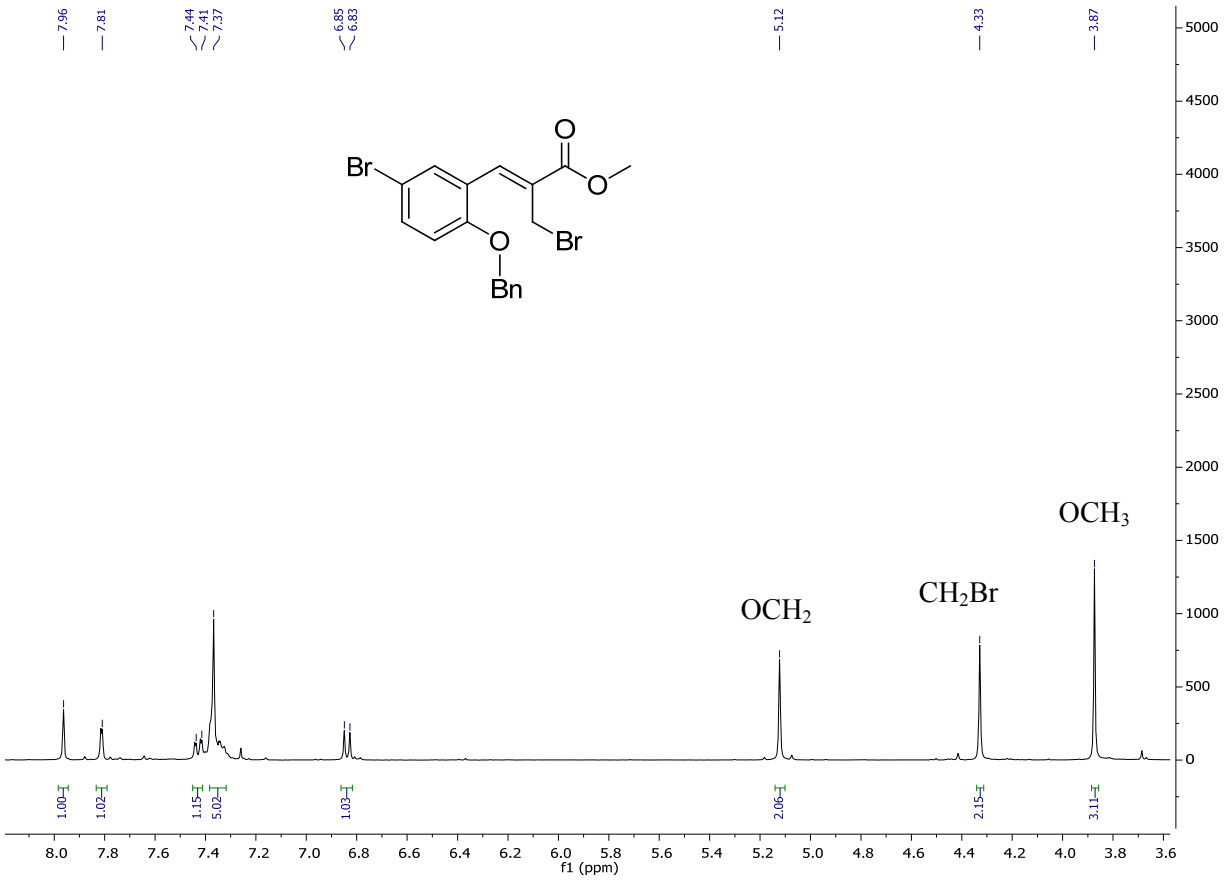


Figure 37. 400 MHz ^{1}H NMR spectrum of compound **116a** in $CDCl_3$.

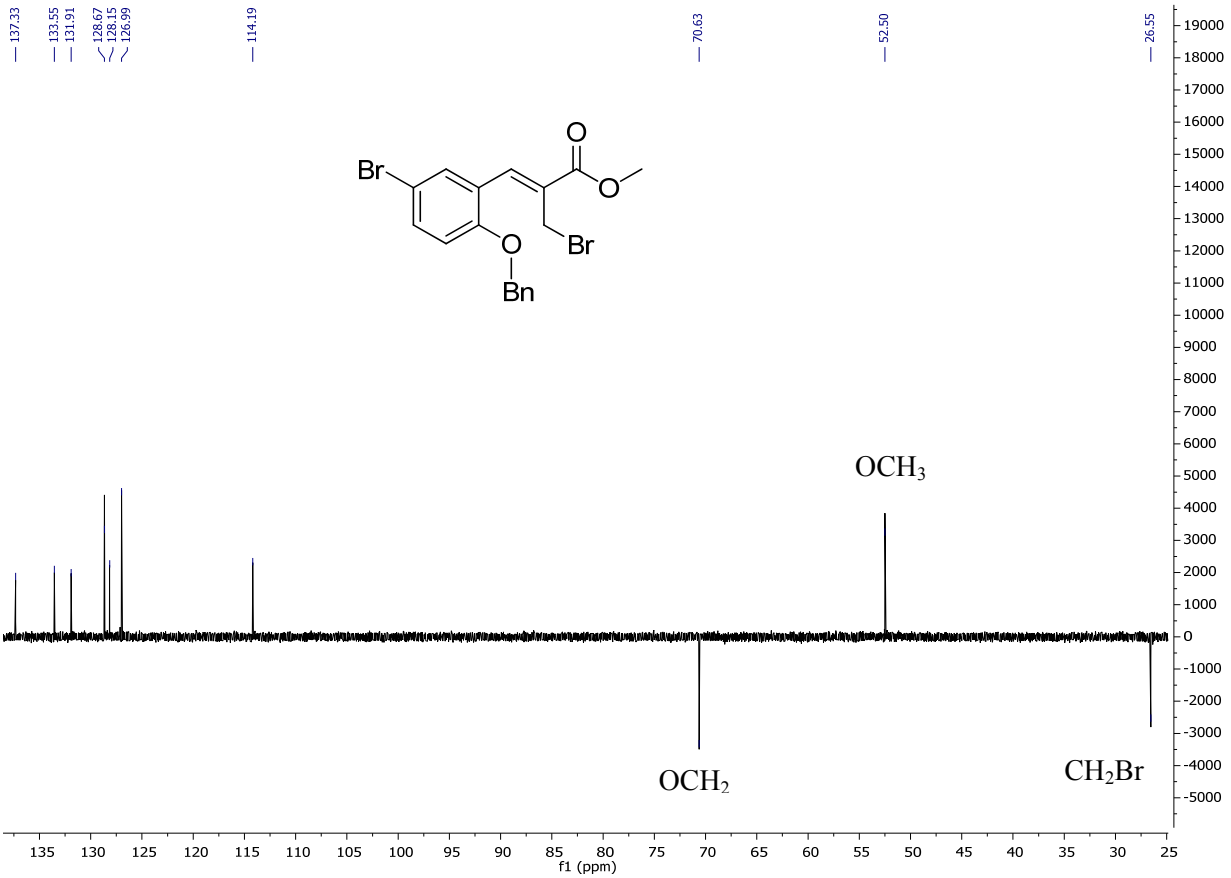
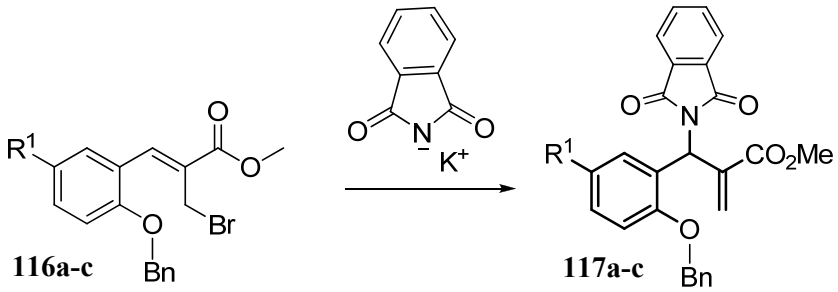


Figure 38. DEPT 135 NMR spectrum of compound **116a** in $CDCl_3$.

Following preliminary studies in our group, the brominated cinnamate ester derivatives **116a-c** were then reacted with potassium phthalimide affording the phthalimido-systems **117a-c**. The phthalimido-ester derivatives were obtained in yields of up to 86% after purification by column chromatography (**Table 12**). The ^{1}H NMR spectrum of compound **117a** reveals the methyl and benzylic proton signals as singlets at 3.69 and 5.04 ppm, respectively (**Figure 39**). The vinylic proton signals appear as singlets at 5.68 and 6.56 ppm. The DEPT 135 spectrum shows the methyl and the benzylic and vinylic methylene carbons resonating at 52.2, 70.3 and 129.1 ppm, respectively (**Figure 40**). The eight aromatic methine carbon signals appear as expected. Cyclisation of these adducts **117** using hydrogen and a Pd/C catalyst was expected to afford the phthalimido-coumarin systems **118a-c** with the phthalimide moiety at position 4. It was hoped that aromatisation, followed by hydrolysis would provide access to 4-aminocoumarin systems and subsequently 4-hydroxycoumarin systems. Attempts to synthesise the 4-

phthalimidocoumarin with both the 5-bromo- and 5-chloro precursors proved unsuccessful. No attempt was done for the unsubstituted precursor.

Table 12. Yields of phthalimido-ester derivatives **117a-c.**



Compound	R^1	Isolated Yields (%)
117a	Br	84
117b	Cl	79
117c	H	86

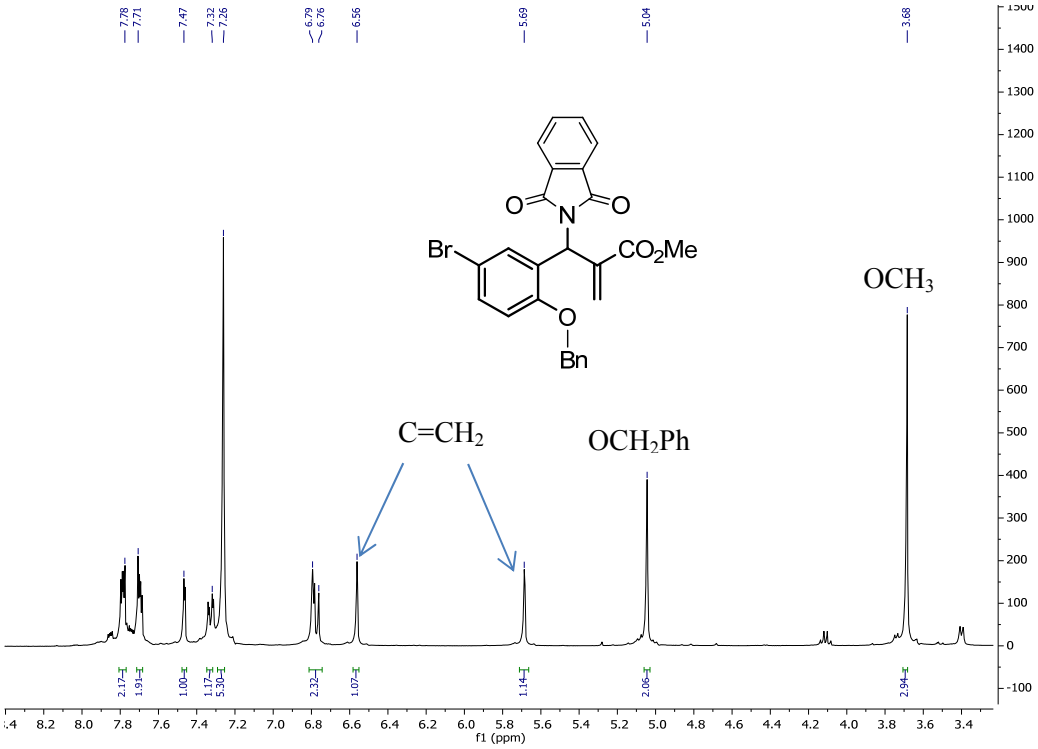


Figure 39. 400 MHz ^{1}H NMR spectrum of compound **117a** in $CDCl_3$.

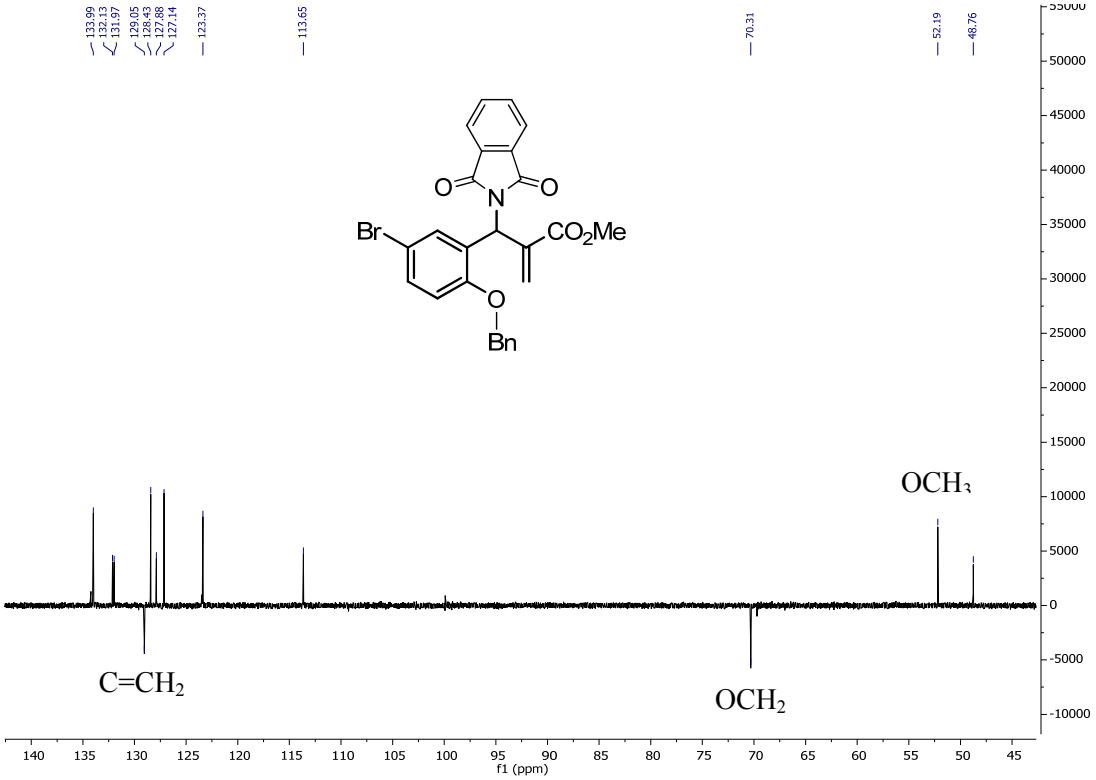
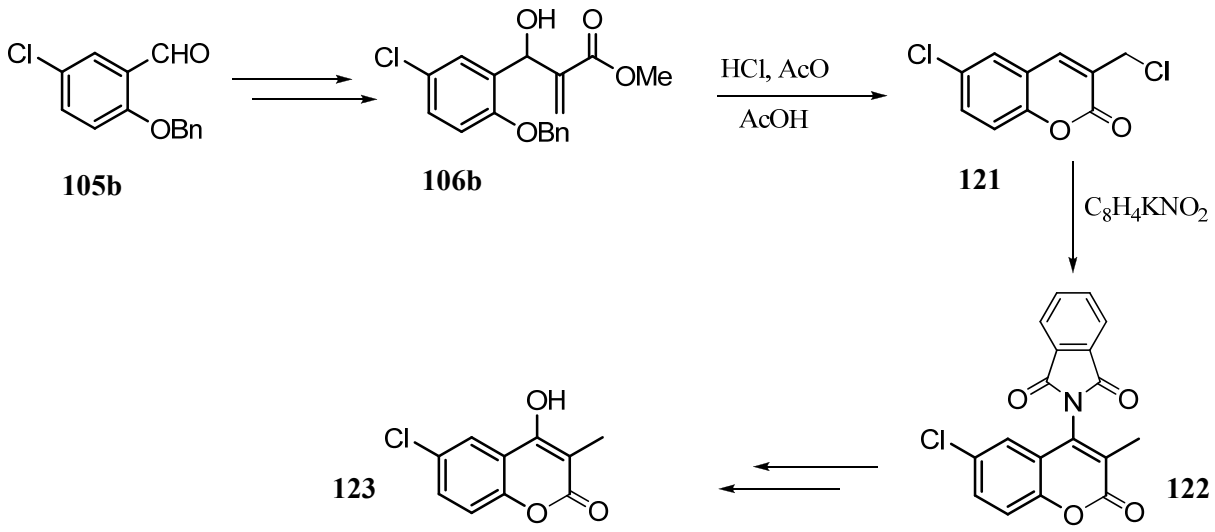


Figure 40. DEPT 135 NMR spectrum of compound **117a** in $CDCl_3$.

2.2.2. 3-(Chloromethyl)coumarin route to 4-hydroxycoumarin

In another approach, acid-catalysed cyclisation of the Baylis-Hillman adduct afforded the 3-(chloromethyl)coumarin which was then reacted with potassium phthalimide in the hope of attaching the phthalimide moiety at position 4. Aromatisation, followed by hydrolysis of the 4-phthalimidocoumarin, was then expected to provide access to aminocoumarin systems and subsequently 4-hydroxycoumarin systems. The acid-catalyzed cyclisation of *O*-benzylated Baylis-Hillman adducts is considered to involve initial conjugate addition of HCl thus inhibiting attack at the resulting tetrahedral chloromethylene centre (necessary for chromene formation) and favouring the formation of coumarins.[118] Methyl 3-(2-benzyloxy-5-chlorophenyl)-3-hydroxy-2-methylpropanoate **106b** was consequently cyclised to the corresponding coumarin derivative **121** using HCl, AcOH and Ac_2O (**Scheme 19**).



Scheme 19. Proposed route to 4-hydroxycoumarin *via* acid catalyzed coumarin synthesis.

The resulting coumarin **121** was then reacted with potassium phthalimide in the hope of forming the 4-phthalimido-coumarin *via* allylic (S_N`) substitution; aromatisation and hydrolysis was then expected to provide access to 4-aminocoumarin systems and, subsequently, the desired 4-hydroxycoumarin products. The yield of the 3-(chloromethyl)coumarin **121** was 80%. The ^{1}H NMR spectrum of compound **121** reveals the methylene protons resonating as a singlet at 4.52 ppm and the 4-methine proton as a singlet at 7.80 ppm (**Figure 41**). The ^{13}C NMR (**Figure 42**) spectrum shows the expected 10 carbon signals and the DEPT 135 spectrum shows the expected aromatic methine carbon signals (**Figure 43**) and the methylene carbon signal at 40.8 ppm.

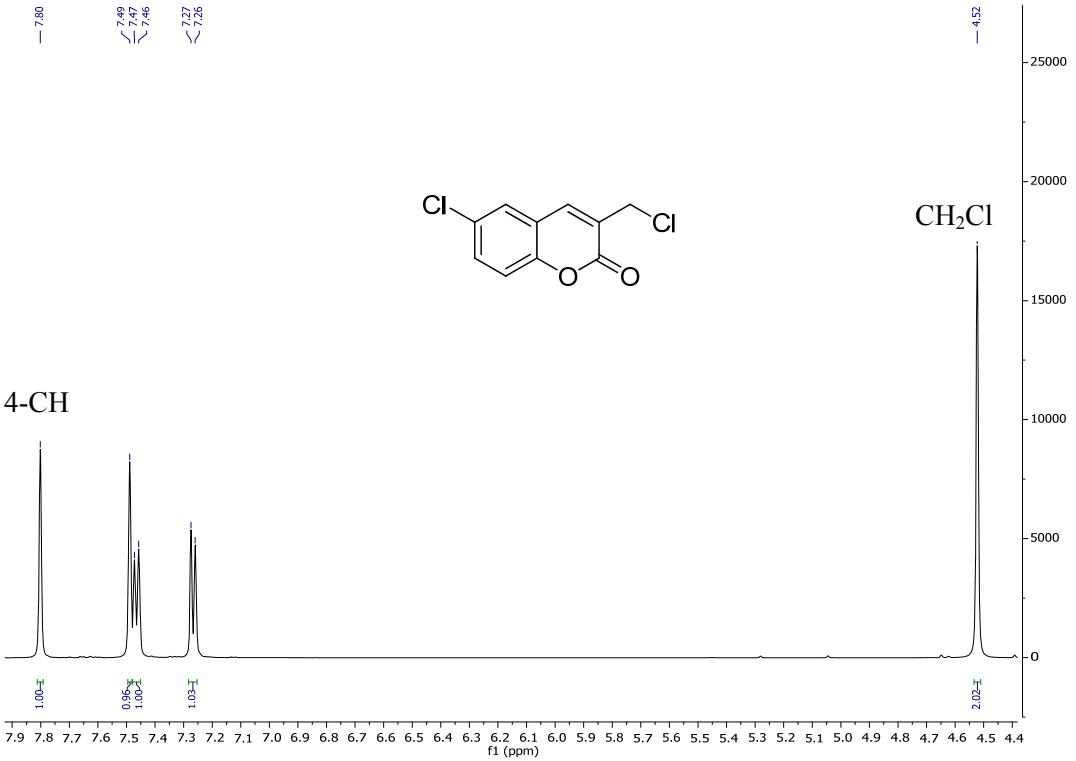


Figure 41. 600 MHz ^{1}H NMR spectrum of compound **121** in $CDCl_3$.

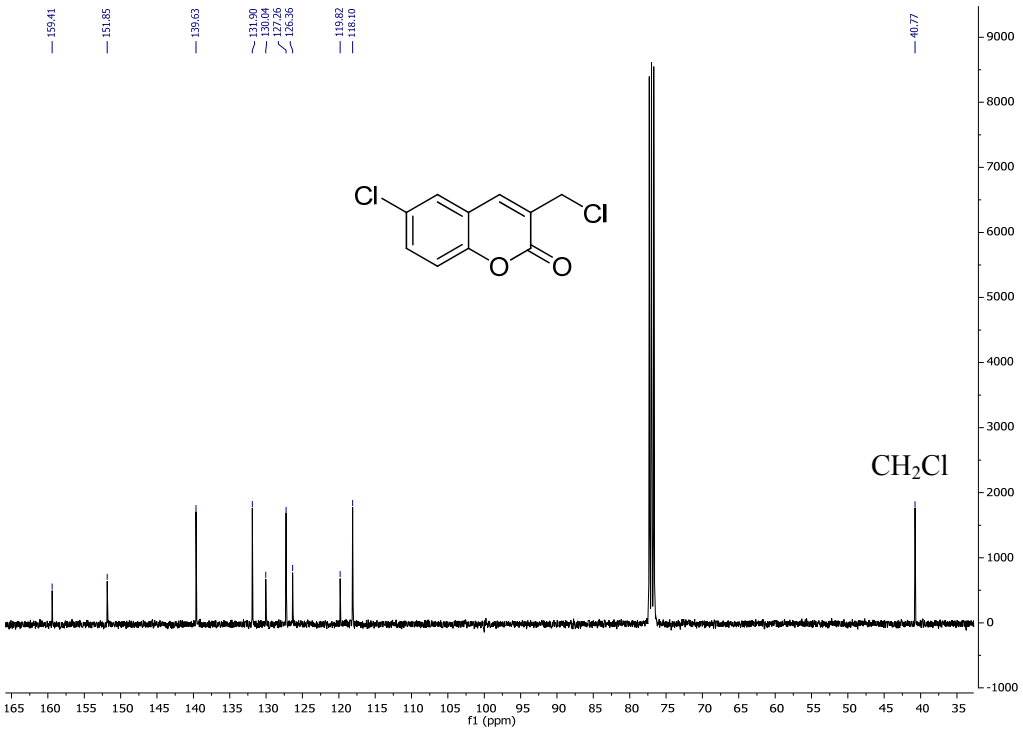


Figure 42. 100 MHz ^{13}C NMR spectrum of compound **121** in $CDCl_3$.

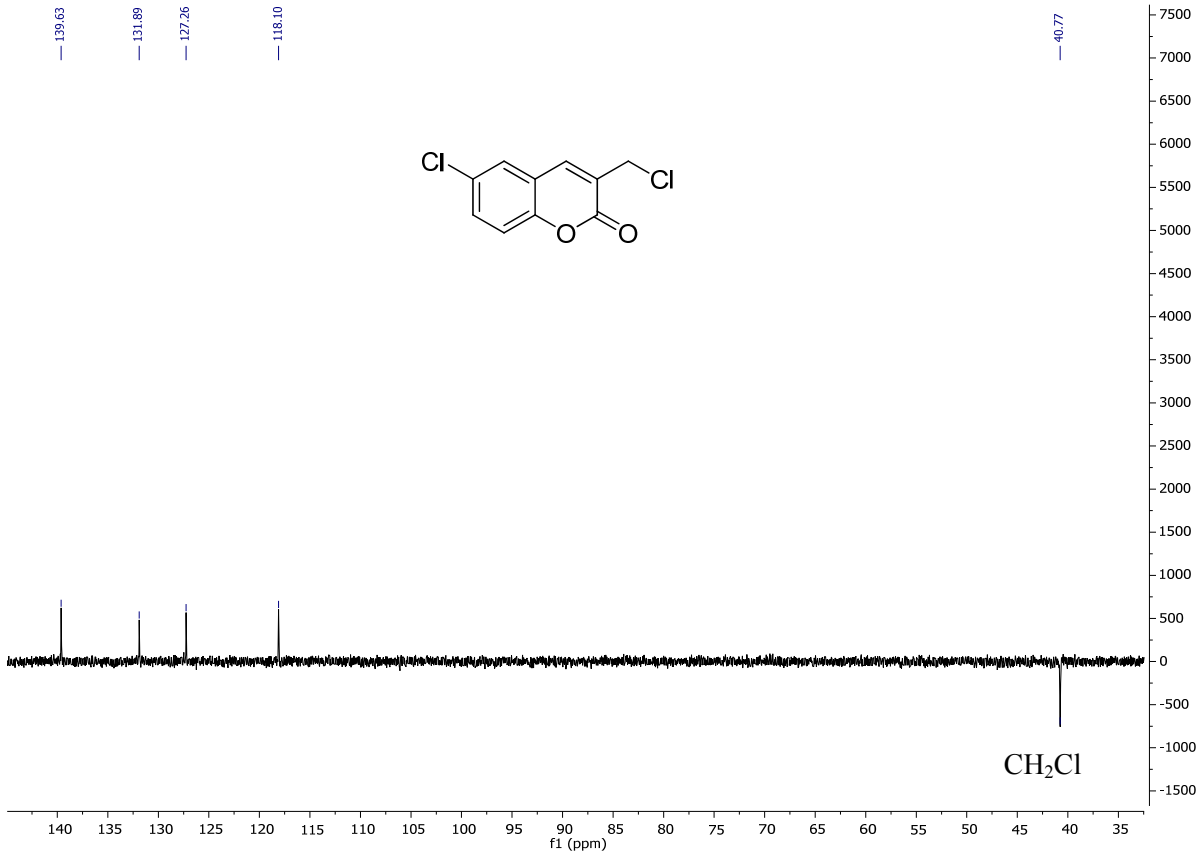
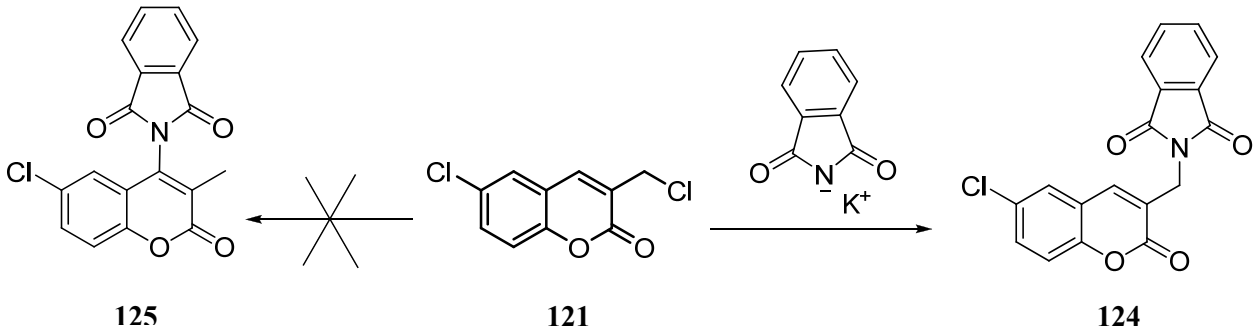


Figure 43. DEPT 135 NMR spectrum of compound **121** in $CDCl_3$.

Unfortunately, the desired $S_N`$ displacement of chloride by potassium phthalimide was not successful, and direct S_N displacement occurred instead (**Scheme 20**), as confirmed by NMR and high resolution mass spectrometry data. Thus, the ^1H NMR spectrum of the product **124** in CD_2Cl_2 (**Figure 44**) shows the methylene protons resonating as a singlet at 4.78 ppm and the expected aromatic methine proton signals. The presence of the methylene ^1H and ^{13}C signals confirm the formation of compound **124**; the desired product **125** has no methylene group. Time constraints precluded further research on access to the desired 4-hydroxycoumarins using Baylis-Hillman methodology − a challenge which will enjoy future attention. The ^{13}C NMR spectrum in CD_2Cl_2 reveals 14 signals accounting for all 14 of the expected carbons (**Figure 45**). In the DEPT 135 spectrum the six aromatic methine carbon signals are quite apparent (**Figure 46**).



Scheme 20. Reaction of compound **121** with potassium phthalimide.

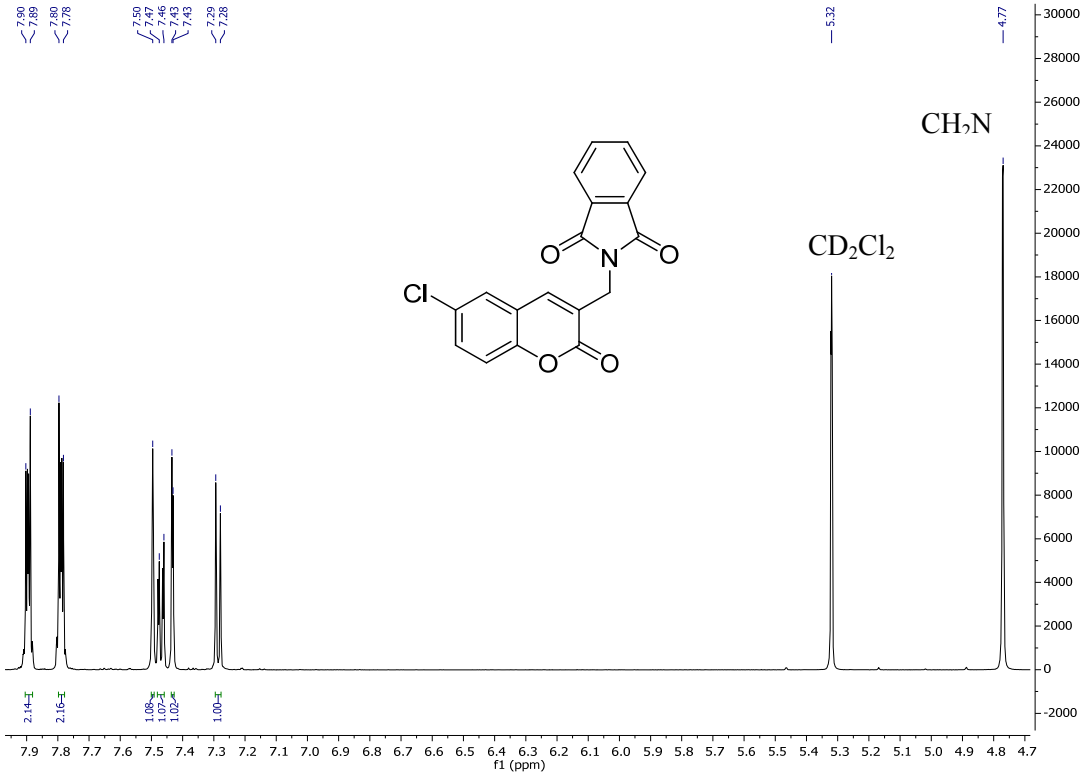


Figure 44. 600 MHz ^{1}H NMR spectrum of compound **124** in CD_2Cl_2.

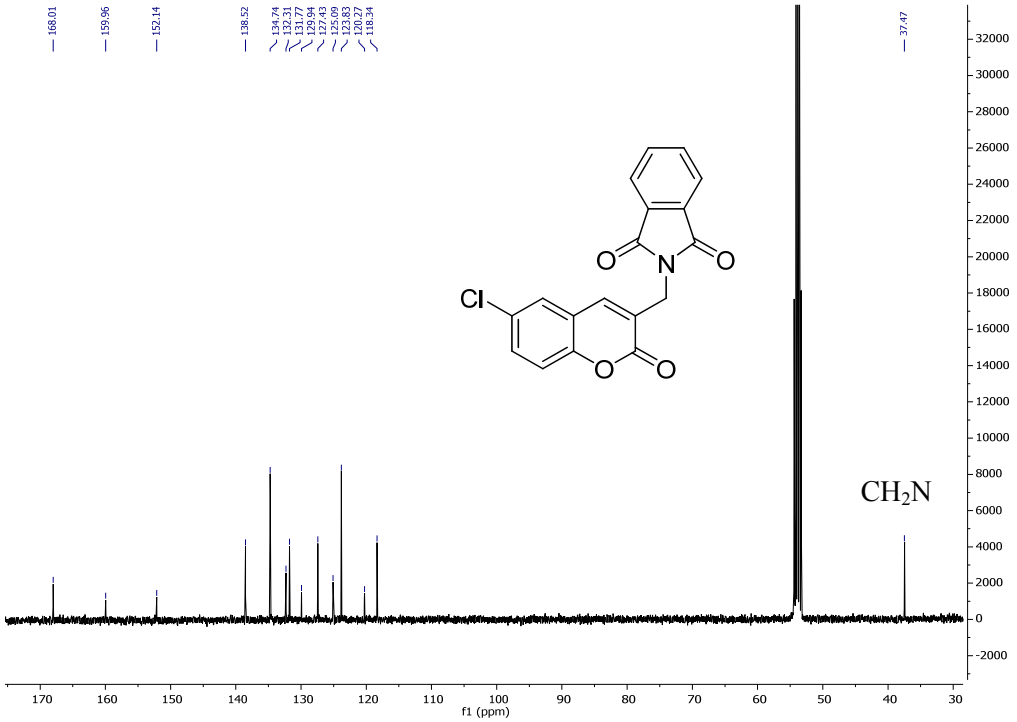


Figure 45. 100 MHz ^{13}C NMR spectrum of compound **124** in CD_2Cl_2.

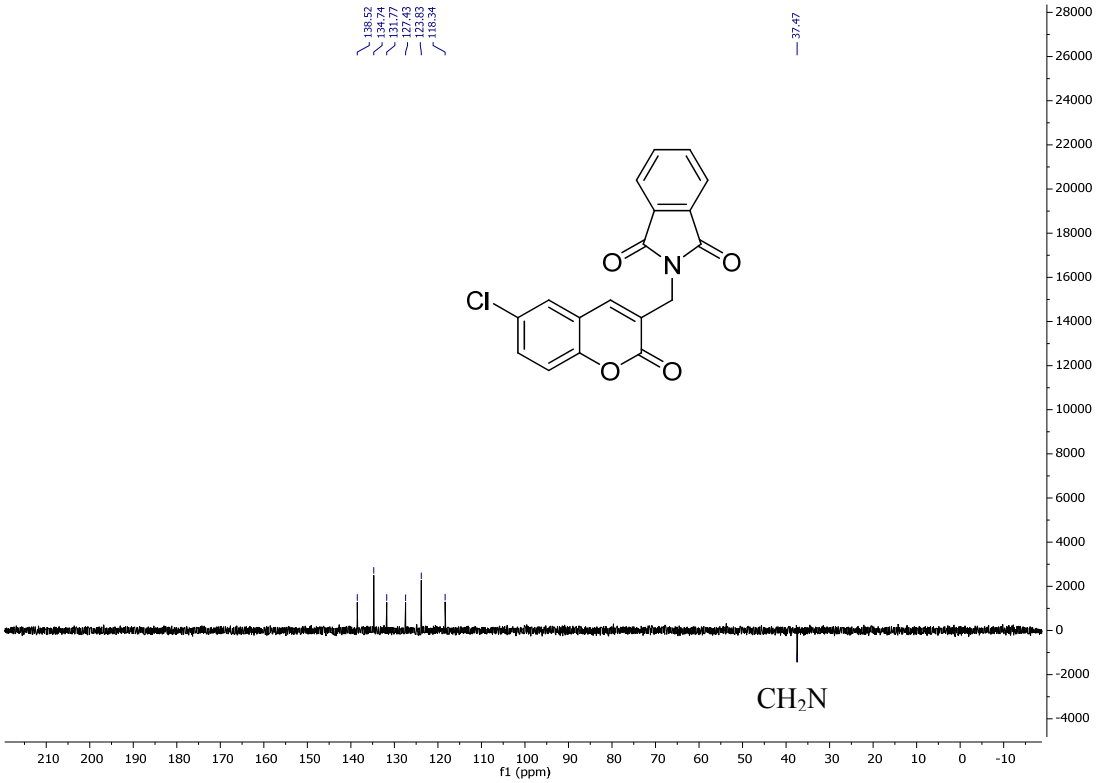
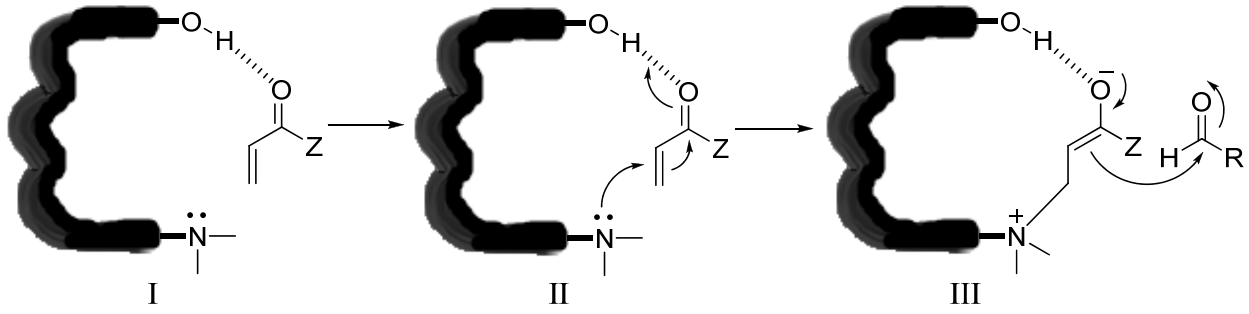


Figure 46. DEPT 135 NMR spectrum of compound **124** in CD_2Cl_2.

2.3. EXPLORATORY STUDIES ON THE CONSTRUCTION OF CHIRAL BAYLIS-HILLMAN CATALYSTS

The general aim in this area has been to design and construct engineered reaction scaffolds capable of catalysing specific reactions and acting as "synthetic enzymes". In this study, attention was given to such scaffolds capable of facilitating chiral Baylis-Hillman reactions. The scaffolds would have a cavity containing a hydroxyl group for hydrogen-bonding the activated alkene substrate and a nucleophilic tertiary amino group for conjugate addition to the activated alkene as illustrated in **Scheme 31**.



Scheme 31. Possible H-bonding interaction between the catalytic scaffold and the activated alkene in the 'reaction pocket' (I); subsequent reaction with a tethered nucleophile (II); and Baylis-Hillman type reaction with an aldehyde (III).

The intention was to construct borneol-10-sulfonamides such as compounds **126a-c** (**Figure 47**), starting from D-(+)-camphor sulfonyl chloride, to serve as chiral Baylis-Hillman catalytic systems.

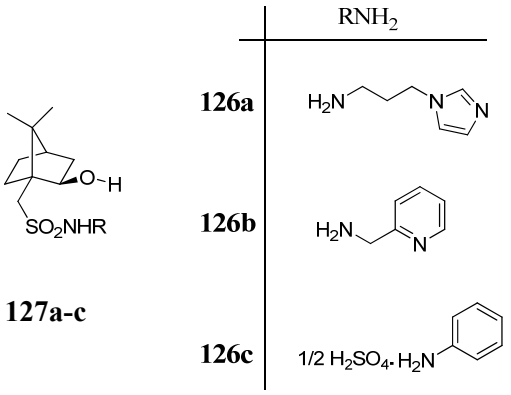
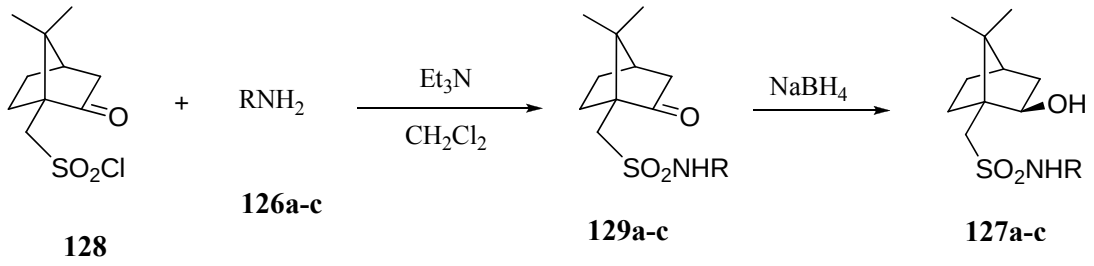


Figure 47. Proposed chiral scaffolds for catalysing chiral Baylis-Hillman reactions.

Access to these compounds involved reaction of campor-10-sulfonyl chloride **128** with the aromatic amines **126a-c** as illustrated in **Scheme 32**.



128 **126a-c** **129a-c** **127a-c**

Scheme 32. Proposed synthesis of customized sulfonamide catalysts **127a-c**.

The coupling of each of the three amines **126a-c** with camphor-10-sulfonyl chloride was expected to afford the camphor-10-sulfonamides **129a-c** (**Scheme 32**), reduction of which would afford the catalytic scaffolds **127a-c**. These systems would then be used in Baylis Hillman reactions with pyridine-4-carbaldehyde and methyl acrylate as Baylis-Hillman substrates and the reactions were to be monitored by ^{1}H NMR spectroscopy.

2.3.1. Synthesis of the sulfonamides 129a-c

Reaction of camphor-10-sulfonyl chloride **128** with *N*-(3-aminopropyl)imidazole **126a** using method A afforded the sulfonamide **129a** in a yield of 74%(**Table 13**). The ^{1}H NMR spectrum (**Figure 48**) of this compound reveals the methyl proton signals at 0.86 and 0.99 ppm, respectively. The three expected aromatic methine proton signals are present with the 16-H signal furthest downfield at 7.57 ppm. The ^{13}C NMR spectrum (**Figure 49**) shows the expected sixteen carbon signals with the C-1 and C-2 signals at 59.0 and 217.0 ppm, respectively. The DEPT 135 spectrum (**Figure 50**) reveals the 4-methine carbon signal at 42.6 ppm and the 7 expected methylene carbon signals at 26.3, 26.9, 31.5, 40.2, 42.9, 43.8 and 49.1 ppm.

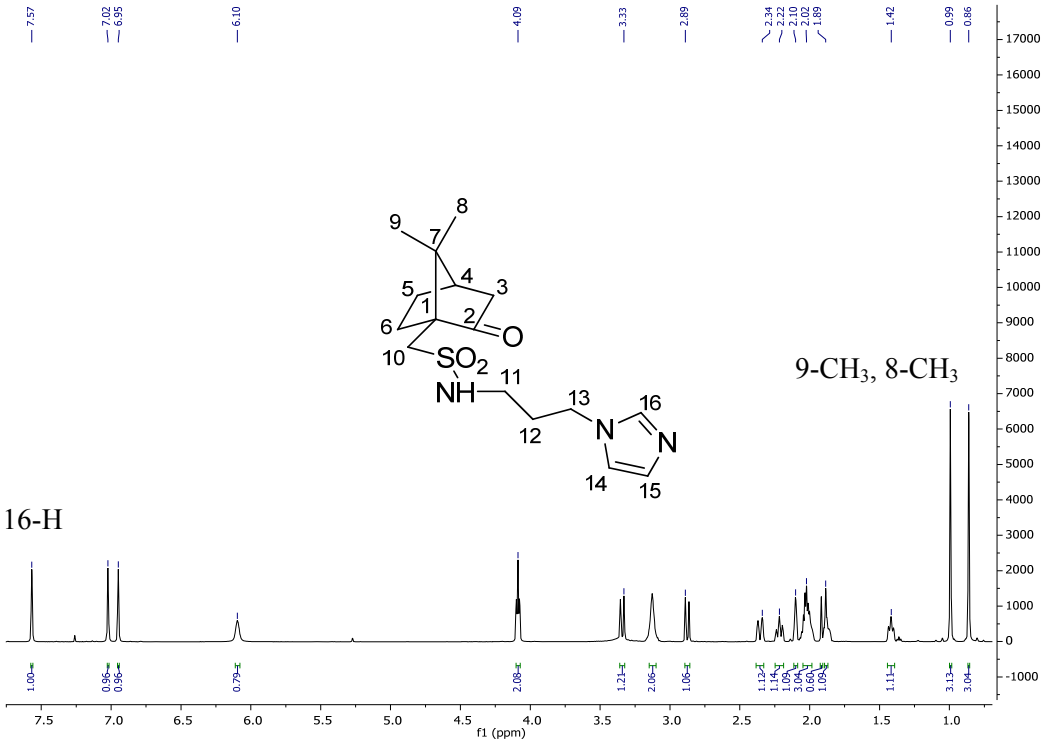


Figure 48. ^{1}H NMR spectrum of compound **129a** in $CDCl_3$.

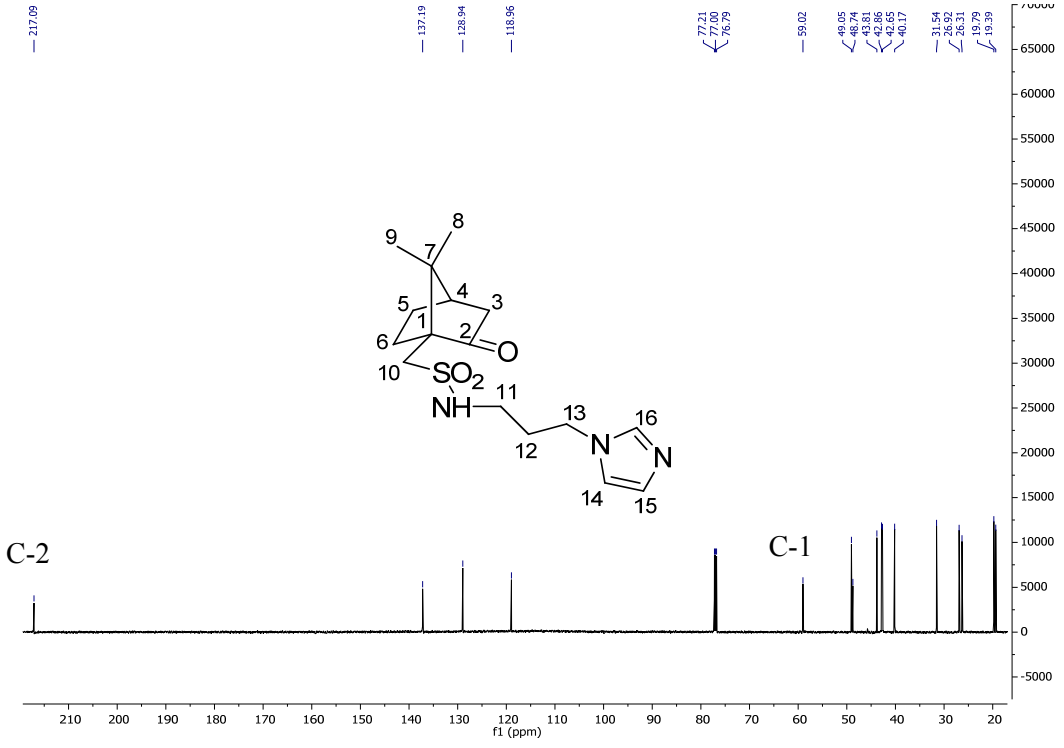


Figure 49. ^{13}C NMR spectrum of compound **129a** in $CDCl_3$.

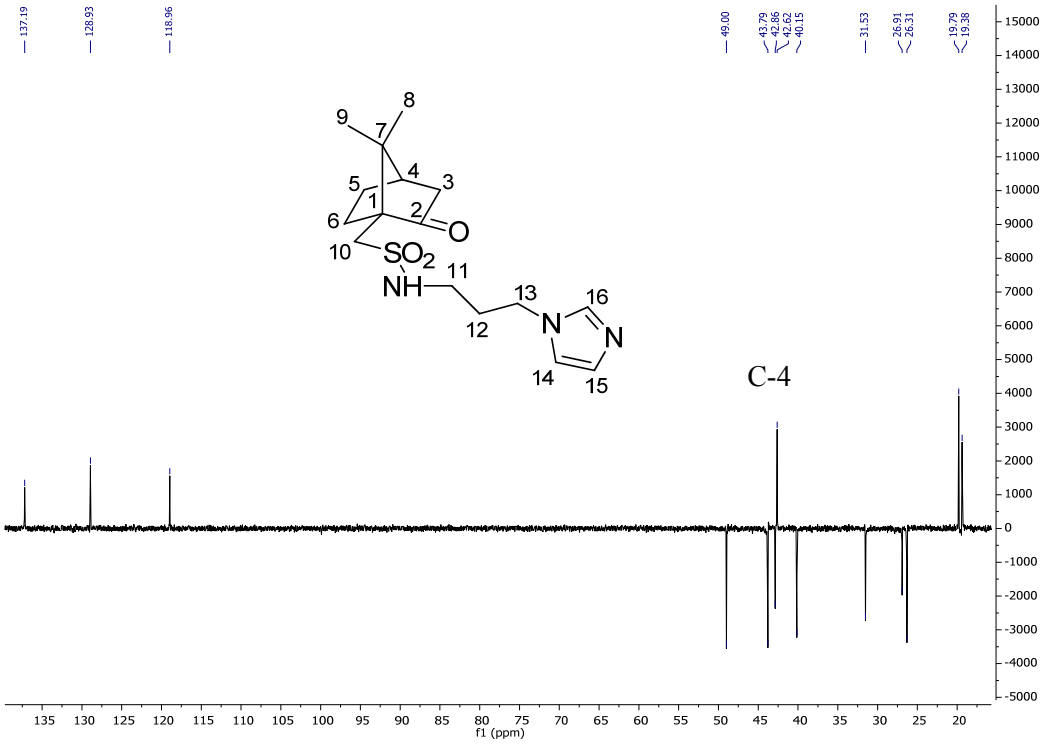
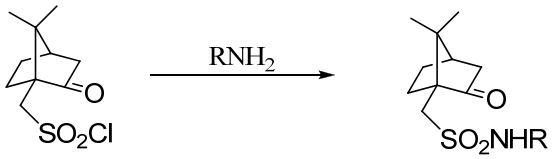


Figure 50. DEPT 135 NMR spectrum of compound **129a** in $CDCl_3$.

Table 13. Camphor-10-sulfonamides **164a-c.**



128 **129a-c**

Method A: Et_3N, CH_2Cl_2

Method B: KOH, DMAP, CH_3CN

Compound	RNH_2	Method	Yield (%)
129a	3-(imidazol-1-yl)propylamine	A	74
129b	2-picolylamine	A	89
129c	2-aminoimidazole.1/2 H_2SO_4	B	64

The camphor-10-sulfonamide **129b** was obtained in a yield of 89% (**Table 13**) using method A and was fully characterized. The DEPT 135 spectrum (**Figure 52**) reveals the 4-methine carbon signal at 42.6 ppm and the five expected methylene carbon signals at 26.2, 26.9, 42.7, 48.3 and 50.0 ppm, respectively. 2-Aminoimidazole **126c** was supplied as the hemi-sulfate salt and, consequently, required neutralization to release the nucleophilic amino group. This reaction was therefore conducted in CH_3CN using KOH as a base and DMAP as a nucleophilic acylation catalyst (method B). The desired camphor-10-sulfonamide **129c** was obtained in a yield of 64% (**Table 13**) and was also fully characterized. The DEPT 135 spectrum (**Figure 53**) reveals the 4-methine carbon signal at 44.0 ppm and the four expected methylene carbon signals at 25.7, 27.4, 43.6 and 48.3 ppm respectively.

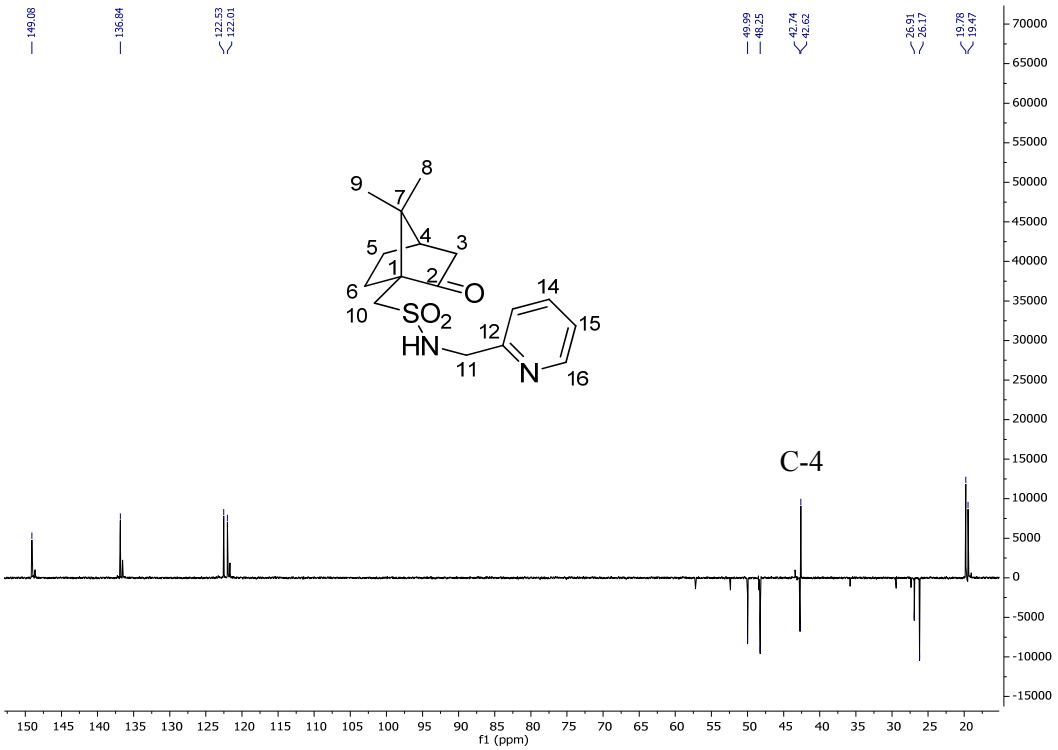


Figure 51. DEPT 135 NMR spectrum of compound **129b** in $CDCl_3$.

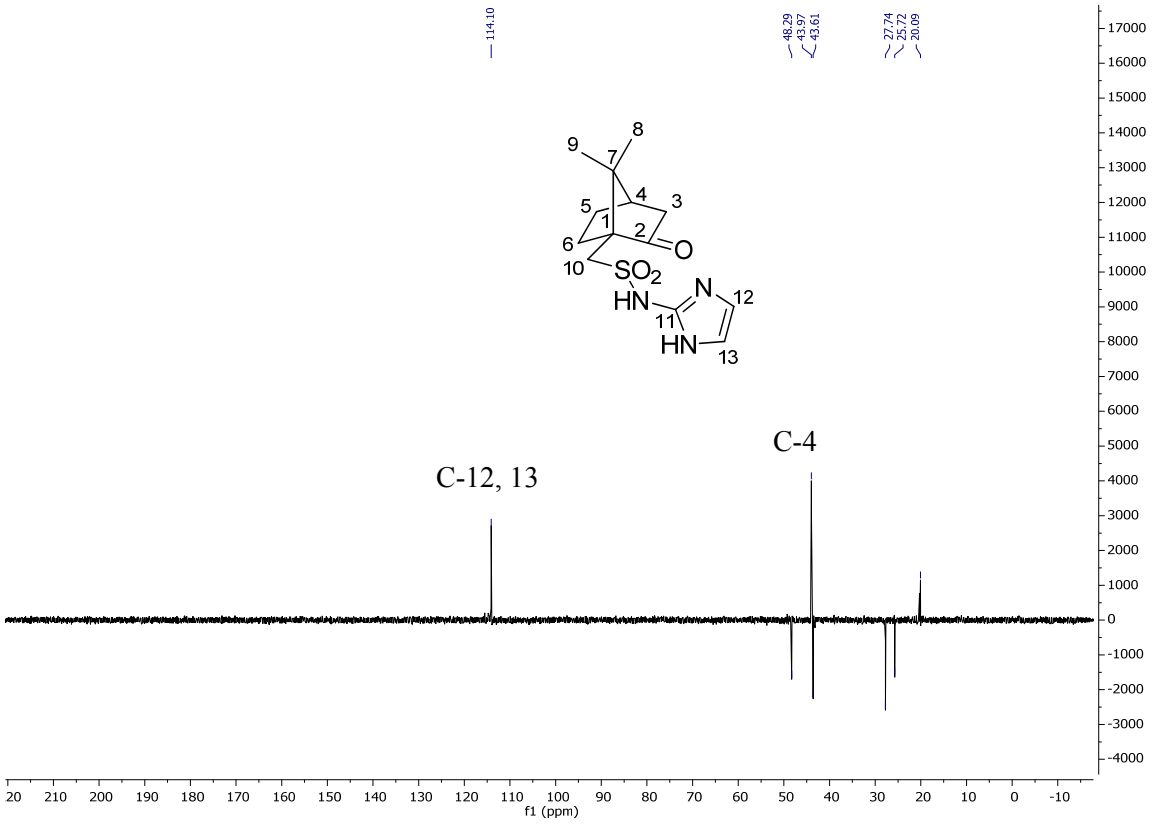
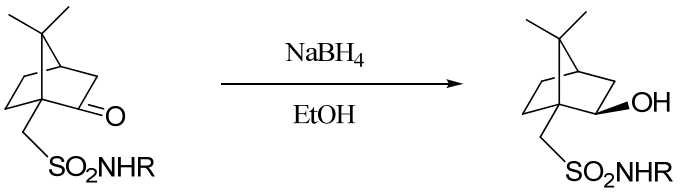


Figure 52. DEPT 135 NMR spectrum of compound **129c** in $CDCl_3$.

2.3.2. Synthesis of the bornyl-10-sulfonamides

The camphor-10-sulfonamides **129a** and **129b** were reduced under mild conditions using $NaBH_4$ to give the corresponding sulfonamide alcohols in excellent yields of 98 and 92%, respectively (**Table 14**). Both compounds were fully characterised. The ^{1}H NMR spectrum of the bornyl-10-sulfonamide **127a** shows the methyl proton singlets at 0.80 and 1.04 ppm, respectively (**Figure 54**) and the three aromatic methine signals are clearly evident. The ^{13}C NMR spectrum shows the expected 16 carbon signals with the C-1 and C-2 signals at 50.3 and 76.3 ppm, respectively (**Figure 55**); the C-2 signal, which appears at 217.1 in the ^{13}C NMR spectrum of the camphor precursor **129a,** is shifted upfield in spectrum of the alcohol **127a**. The formation of the 2-*exo*-alcohols in preference to the 2-*endo* diastereomers is attributed to the steric bulk of the 8-methyl group which inhibits *exo* attack by the hydride ion.[131]

Table 14. Bornyl-10-sulfonamides.



129a,b **127a,b**

Compound	RNH_2	Yield (%)
162a	3-(imidazol-1-yl)propylamine	98
162b	2-picolylamine	92

Preliminary evaluation of the efficacy of the bornyl-10-sulfonamide **127a** as a Baylis-Hillman catalyst in the reaction of pyridine-4-carbaldehyde with methyl acrylate failed to afford the desired adduct. Unfortunately, time constrains precluded further investigation at this stage.

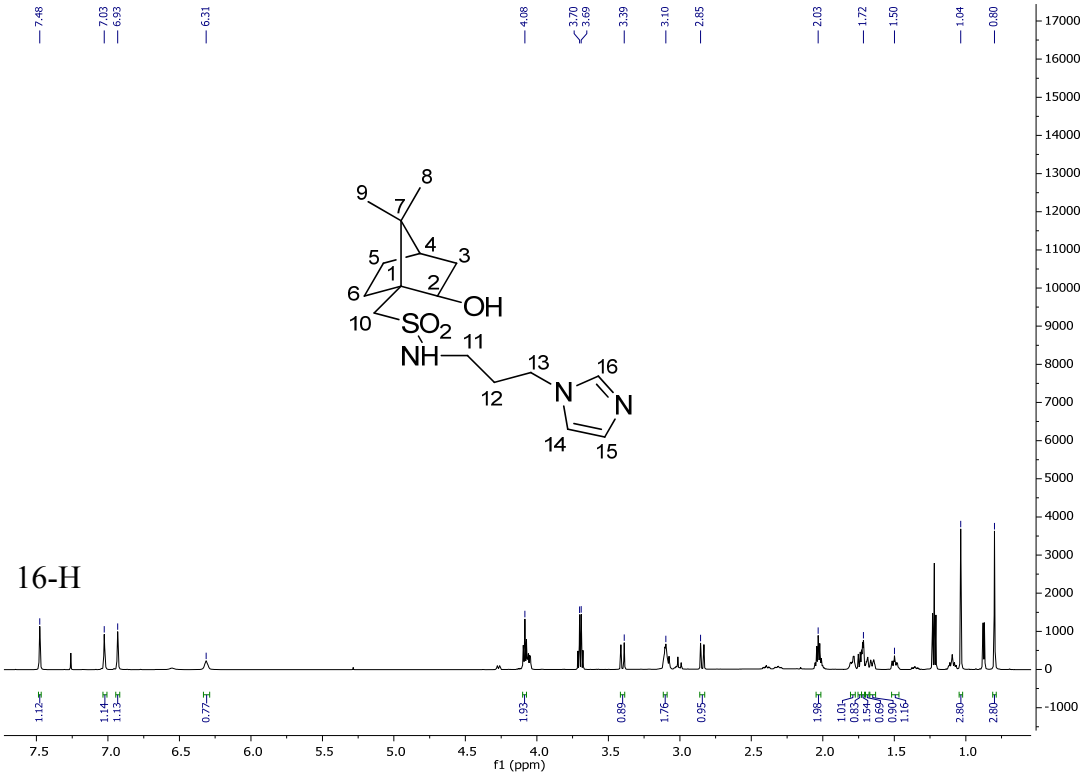


Figure 53. ^{1}H NMR spectrum of compound **127a** in $CDCl_3$.

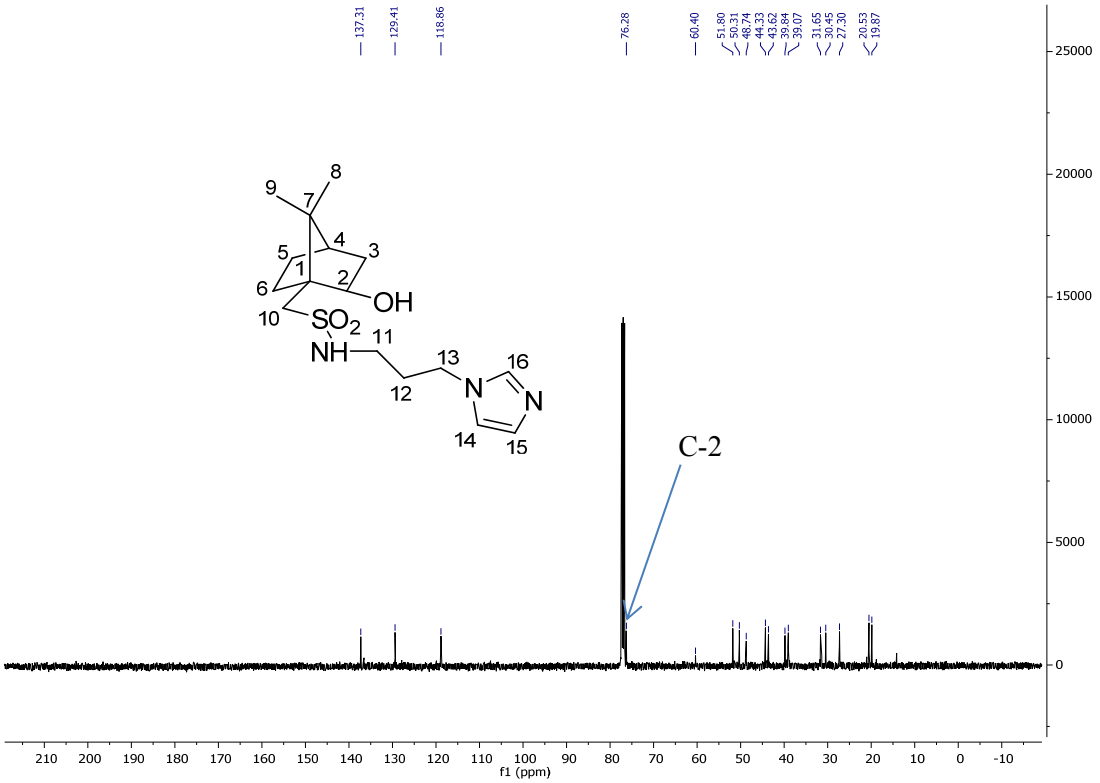


Figure 54. ^{13}C NMR spectrum of compound **127a** in $CDCl_3$.

2.4. CONCLUSIONS

This study has afforded opportunities for the application of Baylis-Hillman methodology in the synthesis of β-hydroxypropionate ester-AZT conjugates as potential dual-action HIV-1 IN/RT inhibitors, in which the AZT moiety serves as the RT inhibitor and the β-hydroxypropionate ester moiety serves as the IN inhibitor. The β-hydroxypropionate ester moiety is analogous to the DKAs which are known to inhibit HIV-1 IN. Nine β-hydroxypropionate ester-AZT conjugates were successfully synthesised from Baylis-Hillman propargylamino derivatives *via* 'click' chemistry cycloaddition with AZT. Of the nine conjugates prepared, four were derived from *O*-benzylated and five from non-benzylated salicylaldehyide Baylis-Hillman adducts. The protected β-hydroxypropionate ester-AZT conjugate yields ranged from 36 to 92% whereas those of the protected β-hydroxypropionate ester-AZT conjugates ranged from 10 to 60%.

Exploratory studies were also carried out to access 4-hydroxycoumarins from Baylis-Hillman derived adducts and to construct customised camphor-based chiral Baylis-Hillman reaction sites. Two qpproaches to the desired 4-hydroxycoumarins were explored, unfortunately without success in both cases. Two borneol-10-sulfonamides were constructed as chiral, Baylis-Hillman catalystic sites in several steps. Preliminary evaluation of these compounds as Baylis-Hillman catalysts however, revealed them to be inactive under the conditions employed.

Future work in these areas is expected to include the following objectives.

i) Optimisation of the yields of the β-hydroxypropionate ester-AZT conjugates from the non-protected salicylaldehydes.
ii) Evaluation of both classes of β-hydroxypropionate ester-AZT conjugates as potential dual-action HIV-1 IN/RT inhibitors using bioassay data and computer-simulated docking.
iii) Further investigation into accessing 4-hydroxycoumarins using Baylis-Hillman methodology.
iv) Use of computer-aided design to construct camphor-based customised chiral Baylis-Hillman catalysts.

3. EXPERIMENTAL

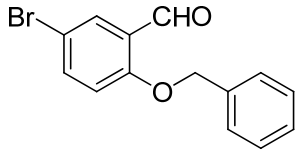
3.1. GENERAL

Reagents were used as supplied by Sigma-Aldrich without further purification. The drying of solvents was carried out following procedures described by Perrin and Armarego.[132] Thin layer chromatography was carried out on pre-coated Merck silica gel F254 plates, and viewed under UV light (254 / 365 nm) or following exposure to iodine. Flash chromatography was carried out using Merck silica gel 60 (particle size 0.040-0.063 mm) and preparative layer chromatography was conducted using Macherey-Nagel silica gel P / UV_{254}.

NMR spectra were recorded on Bruker AMX 400 MHz and Biospin 600 MHz spectrometers and were referenced using residual protonated solvent signals (δ_H: 7.26 ppm for $CDCl_3$, 5.32 ppm for CD_2Cl_2, 2.50 ppm for DMSO-d_6 and 3.31 ppm for CD_3OD; δ_C: 77.0 ppm for $CDCl_3$, 53.84 ppm for CD_2Cl_2, 39.5 ppm for DMSO-d_6, and 49.0 ppm for CD_3OD). High resolution mass spectra were recorded on a Waters API Q-TOF Ultima spectrometer (University of Stellenbosch, South Africa). IR spectra were recorded on a Perkin-Elmer FT-IR Spectrum 100 spectrometer (neat). Melting points were measured using a Reichert 281313 hot-stage apparatus, and are uncorrected.

3.2. PREPARATION OF *O*-BENZYLATED 3-HYDROXYPROPANAOATE ESTER-AZT CONJUGATES

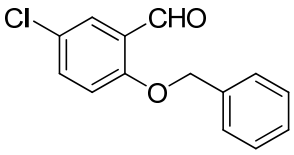
2-(Benzyloxy)-5-bromobenzaldehyde 105a



To 5-bromosalicylaldehyde (6.4 g, 32 mmol) in 10% NaOH (aq) (15 mL) was added benzyl bromide (3.8 ml, 32 mmol) and the mixture heated under reflux with stirring for 30 minutes. The mixture was cooled, water added (50 mL) and the solid which formed was filtered and washed thoroughly with water and dried. The solid was then crystallised from hexane and dried under vacuum to yield 2-(benzyloxy)-5-bromobenzaldehyde **105a** as a cream solid (8.1 g, 87 %), m.p. 73-74 ^oC (lit.[133] 73-74 ^oC); υ_{max}/cm^{-1} 1677 (C=O); δ_H (400 MHz; $CDCl_3$) 5.18 (2H, s, OCH_2Ph),

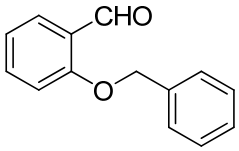
6.95 (1H, d, *J* = 9.0 Hz, ArH), 7.37-7.43 (5H, overlapping m, ArH), 7.60 (1H, dd, *J* = 8.9 and 2.7 Hz, ArH), 7.94 (1H, d, *J* = 2.6 Hz, ArH) and 10.46 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 70.8 (OCH_2Ph), 113.8, 115.1, 126.4, 127.3, 128.5, 128.8, 131.0, 135.5 and 138.2 (Ar-C), 159.8 [Ar(OBn)] and 188.3 (C=O).

2-(Benzyloxy)-5-Chlorobenzaldehyde 105b



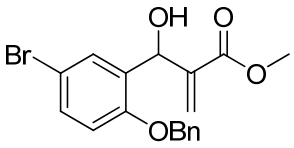
The procedure described for the synthesis of 2-(benzyloxy)-5-bromobenzaldehyde was employed using 5-chlorosalicylaldehyde (5 g, 32 mmol), 10% NaOH (aq) (15 mL), and benzyl bromide (3.8mL, 32 mmol). Work-up afforded 2-(benzyloxy)-5-chlorobenzaldehyde **105b** as a cream solid (6.4 g, 81 %), m.p.70-72 ^oC (lit.[134] 70-72 ^oC); υ_{max}/cm^{-1} 1678 (C=O); δ_H (400 MHz; $CDCl_3$) 5.18 (2H, s, OCH_2Ph), 6.95 (1H, d, *J* = 8.9 Hz, ArH), 7.36-7.43 (5H, overlapping m, ArH), 7.60 (1H, dd, *J* = 8.9 and 2.7 Hz, ArH), 7.94 (1H, d, *J* = 2.6 Hz, ArH) and 10.46 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 70.8 (OCH_2Ph), 113.8, 115.1, 126.4, 127.3, 128.5, 128.8, 131.0, 135.5 and 138.2 (Ar-C), 159.8 [Ar(OBn)] and 188.3 (C=O).

2-Benzyloxybenzaldehyde 105c[122]



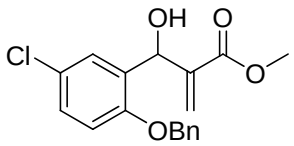
The procedure described for the synthesis of 2-(benzyloxy)-5-bromobenzaldehyde was employed using salicylaldehyde (3.4 mL, 32 mmol), 10% NaOH (aq) (15 mL), and benzyl bromide (3.8 mL, 32 mmol). Work-up afforded 2-benyloxybenzaldehyde **105c** as a brown gel (4.4 g, 65 %); υ_{max}/cm^{-1} 1678 (C=O); δ_H (400 MHz; $CDCl_3$) 5.20 (2H, s, OCH_2Ph),7.06 (1H, d, *J* = 8.0 Hz, ArH), 7.36-7.46 (5H, overlapping m, ArH), 7.54 (1H, td, *J* = 8.0 and 1.2 Hz, ArH), 7.87 (1H, dd, *J* = 7.7 and 1.8 Hz, ArH) and 10.57 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 70.4 (OCH_2Ph), 113.0, 121.0, 125.1, 127.2, 128.2, 128.4, 128.7, 135.9 and 136.0 (Ar-C), 151.0 [Ar(OBn)] and 189.7 (C=O).

Methyl 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-methylenepropanoate 106a



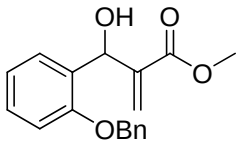
A mixture of 2-benzyloxy-5-bromobenzaldehyde **105a** (4.7 g, 16 mmol), methyl acrylate (2.9 mL, 32 mmol) and DABCO (0.45 g, 4 mmol) in $CHCl_3$ (10 mL) was stirred at room temperature for 21 days. The mixture was concentrated under vacuum and purified using column chromatography [elution with hexane-EtOAc (4:1)] to afford methyl 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-methylenepropanoate **106a** as a white solid (3.2 g, 54%), m.p. 76-77 ^oC(lit.[134] 114-116 ^oC); υ_{max}/cm^{-1} 3340 (OH) and 1719 (C=O); δ_H (400 MHz; $CDCl_3$) 3.74 (3H, s, OCH_3), 5.05 (2H, s, OCH_2Ph), 5.66 and 6.30 (2H, 2 x s, $C=CH_2$), 5.89 (1H, s, CHOH), 6.80 (1H, d, J = 8.7 Hz, ArH), 7.32-7.40 (6H, overlapping m, ArH) and 7.54 (1H, d, J = 2.5 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 52.0 (OCH_3), 67.7 (CHOH), 70.4 (OCH_2Ph), 126.5 ($C=\mathit{C}H_2$), 113.5, 113.6, 127.3, 128.2, 128.6, 130.6, 131.5, 131.8, 136.2, 140.6 and 154.6 ($\mathit{C}=CH_2$ and Ar-C) and 166.9 (C=O).

Methyl 3-(2-benzyloxy-5-chlorophenyl)-3-hydroxy-2-methylenepropanoate 106b



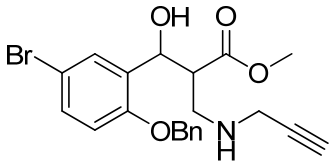
The procedure described for the synthesis of methyl 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-methylpropanoate **106a** was employed using 2-benzyloxy-5-chlorobenzaldehyde **105b** (4 g, 16 mmol), methylacrylate (2.9 mL, 32 mmol) and DABCO (0.45 g, 4 mmol) in $CHCl_3$ (10 mL). Work up afforded methyl 3-(2-benzyloxy-5-chlorophenyl)-3-hydroxy-2-methylenepropanoate **106b** as a white solid (3.2 g, 61%), m.p. 78-80 ^oC (lit.[118] reported as an oil); υ_{max}/cm^{-1} 3397 (OH) and 1712 (C=O); δ_H (400 MHz; $CDCl_3$) 3.74 (3H, s, OCH_3), 5.05 (2H, s, OCH_2Ph), 5.66 and 6.30 (2H, 2 x s, $C=CH_2$), 5.89 (1H, s, CHOH), 6.84 (1H, d, J = 8.7 Hz, ArH), 7.19 (1H, d, J = 8.77 Hz, ArH) and 7.31-7.42 (6H, overlapping m, ArH); δ_C (100 MHz; $CDCl_3$) 52.0 (OCH_3), 67.8 (CHOH), 70.5 (OCH_2Ph), 126.5 ($C=\mathit{C}H_2$), 113.1, 126.1, 127.3, 127.7, 128.0, 128.2, 128.6, 131.4, 136.2, 140.6 and 154.1 ($\mathit{C}=CH_2$ and Ar-C) and 166.9 (C=O).

***Methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylpropanoate 106c*[122]**



The procedure described for the synthesis of methyl 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-methylpropanoate **106a** was employed using 2-benzyloxybenzaldehyde **105c** (3.4 g, 16 mmol), methyl acrylate (2.9 mL, 32 mmol) and DABCO (0.45 g, 4 mmol) in $CHCl_3$ (10 mL). Work up afforded methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylpropanoate **106c** as a yellow oil (3.1 g, 64%); υ_{max}/cm^{-1} 3485 (OH) and 1716 (C=O); δ_H (400 MHz; $CDCl_3$) 3.46 (1H, br s, OH), 3.72 (3H, s, OCH_3), 5.09 (2H, s, OCH_2Ph), 5.70 and 6.30 (2H, 2 x s, $C=CH_2$), 5.94 (1H, s, CHOH), 6.92-7.02 (2H overlapping m, ArH) and 7.32-7.42 (6H overlapping m, ArH); δ_C (100 MHz; $CDCl_3$) 51.9 (OCH_3), 68.5 (CHOH), 70.1 (OCH_2Ph), 125.9 ($C=CH_2$), 111.8, 121.0, 127.3, 127.8, 128.0, 128.6, 128.8, 129.5, 136.6, 141.2 and 155.7 ($C=CH_2$ and Ar-C) and 167.0 (C=O).

Methyl 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate diastereomers 111a$_1$ and 111a$_2$

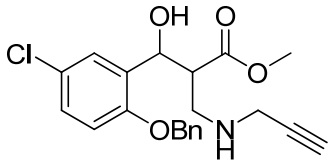


To a solution of methyl 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-methylenepropanoate **106a** (0.4 g, 1.1 mmol) in dry THF (1.5 mL) was added propargylamine (0.192 mL, 3 mmol) and the mixture stirred at r.t. for 3 days. The mixture was then concentrated under vacuum and chromatographed [PLC on silica gel; elution with hexane-EtOAc (2:1) to afford both diastereomers of *methyl 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-[(2propynylamino)methyl] propanoate. Diastereomer* ***111a$_1$*** as a cream solid (0.39 g, 84%), m.p. 78-82 ^oC; [HMRS: *m/z* calculated for $C_{21}H_{23}BrNO_4$ (MH^+) 432.0810. Found 432.0807]; υ_{max}/cm^{-1} 3283 (OH) and 1719 (C=O); δ_H (400 MHz; $CDCl_3$) 2.19 (1H, t, *J* = 2.5 Hz, C≡CH), 2.88 (1H, dd, *J* = 5.4 and 11.8 Hz, CHCO), 3.07-3.17 (2H, m, $CHCH_2$), 3.35 (2H, qd, *J* = 2.7 and 17.1 CH_2-C≡CH), 3.54 (3H, s, OCH_3), 5.03-5.12 (2H, m, OCH_2), 5.34 (1H, d, *J* = 4.2 Hz, C*H*OH), 6.79 (1H, d, *J* = 8.7 Hz, ArH), 7.29-7.46 (6H, overlapping m, ArH) and 7.55 (1H, d, *J* = 2.5 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 38.1 and 48.6 (NCH_2), 49.6 (*C*HCO), 51.5 (CH_3), 69.7 (CHOH), 70.3 (OCH_2) 71.8 and

81.2 (C≡CH), 113.1, 113.5, 127.2, 128.2, 128.7, 130.0, 130.9, 132.6, and 136.2 (Ar-C), 153.9 [ArC(OBn)] and 173.6 (C=O).

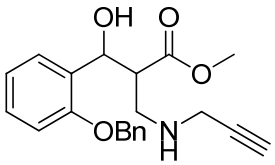
Diastereomer ***111a₂***, as cream solid (0.31 g, 66%) m.p. 68-70 ^{o}C; [HMRS: *m/z* calculated for $C_{21}H_{23}BrNO_4$ (MH^+) 432.0810. Found 432.0816]; υ_{max}/cm^{-1} 3336 (OH) and 1719 (C=O); δ_H (400 MHz; $CDCl_3$) 2.29 (1H, q, *J* = 2.9 and 3.4 Hz, C≡CH), 2.58 (1H, dd, *J* = 3.7 and 12.4 Hz, CHC*H*$_a$), 3.09 (1H, q, *J* = 3.4 Hz, CHCO), 3.20 (1H, dd, *J* = 3.2 and 12.5 Hz, CHC*H*$_b$), 3.37 (2H, qd, *J* = 2.6 and 17.0 C*H*$_2$-C≡CH), 3.76 (3H, s, OCH_3), 5.08 (2H, t, *J* = 5.7 Hz, OCH_2), 5.71 (1H, d, *J* = 3.1 Hz, C*H*OH), 6.80 (1H, d, *J* = 8.6 Hz, ArH), 7.27-7.48 (6H, overlapping m, ArH) and 7.72 (1H, d, *J* = 2.7 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 38.3 and 45.6 (NCH_2), 46.9 (*C*HCO), 52.1 (CH_3), 70.0 (OCH_2) 71.4 (CHOH), 72.4 and 80.6 (C≡CH), 113.1, 113.6, 126.7, 127.9, 128.5, 130.3, 130.9, 133.8, and 136.4 (Ar-C), 153.5 [ArC(OBn)] and 173.8 (C=O).

Methyl 3-(2-benzyloxy-5-chlorophenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate 111bas a mixture of diastereomers



The procedure described for the synthesis of methyl 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate **111a** was followed using 3-(2-benzyloxy-5-chlorophenyl)-3-hydroxy-2-methylenepropanoate **106b** (0.37, 1.1 mmol) in dry THF (1.5 mL) and propargylamine (0.192 mL, 3 mmol). Work-up afforded *methyl 3-(2-benzyloxy-5-chlorophenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate* **111b** as a cream solid (0.41 g, 97%), m.p. 88-92 ^{o}C; [HMRS: *m/z* calculated for $C_{21}H_{23}ClNO_4$ (MH^+) 388.1316. Found 388.1320]; υ_{max}/cm^{-1} 3460 (OH) and 1717 (C=O); δ_H (400 MHz; MeOD-d_4) 2.48 (1H, t, *J* = 2.6 Hz, C≡CH), 2.60-2.67 (1H, m, CHCO), 2.90-3.00 (2H, m, $CHCH_2$), 3.19 (2H, d, *J* = 2.6 Hz, C*H*$_2$-C≡CH),3.56 (3H, d, *J* = 4.3 Hz,OCH_3), 5.09 (2H, d, *J* = 2.7 Hz, OCH_2), 5.26 (1H, d, *J* = 6.1 Hz, C*H*OH), 6.99 (1H, d, *J* = 8.8 Hz, ArH), 7.19 (1H, dd, *J* = 2.8 and 8.7 Hz, ArH) and 7.29-7.50 (6H, overlapping m, ArH); δ_C (100 MHz; MeOD-d_4) 38.2 and 48.4 (NCH_2), 52.1 (*C*HCO), 53.6 (CH_3), 68.2 (C*H*OH), 71.6 (OCH_2), 73.4 and 81.8 (C≡CH), 114.4, 127.0, 128.2, 128.7, 129.1, 129.2, 129.7, 134.5 and 138.1 (Ar-C), 155.3 [Ar(OBn)] and 175.1 (C=O).

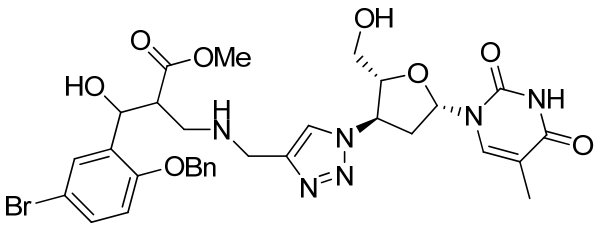
Methyl 3-(2-(benzyloxyphenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate diastereomers 111c$_1$ and 111c$_2$



The procedure described for the synthesis of methyl 3-(2-benyloxy-5-bromophenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate **111a** was followed using methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanoate **106c** (0.33, 1.1 mmol) in dry THF (1.5 mL) and propargylamine (0.192 mL, 3 mmol). Work-up afforded both diastereomers of *methyl 3-(2-(benzyloxy)phenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate.* *Diastereomer* ***111c$_1$*** as a yellow oil (0.30 g, 76%); [HMRS: *m/z* calculated for $C_{21}H_{24}NO_4$ (MH^+) 354.1705. Found 354.1695]; υ_{max}/cm^{-1} (C=O); δ_H (400 MHz; $CDCl_3$) 2.14-2,19 (1H, m, C≡CH), 2.90 (1H, dd, *J* = 6.6 and 12.0 Hz, CHC*H$_a$*), 3.01 (1H, dd, *J* = 4.7 and 12.1 Hz, CHC*H$_b$*), 3.14 (1H, t, *J* = 5.7 Hz, CHCO), 3.29-3.41 (2H, m, C*H$_2$* -C≡CH), 3.55 (3H, s, OCH_3), 5.06-5.14 (2H, m, OCH_2), 5.32 (1H, d, *J* = 5.3 Hz, C*H*OH), 6.90-7.02 (2H, m, ArH) and 7.30-7.45 (7H, overlapping m, ArH); δ_C (100 MHz; $CDCl_3$) 38.0 and 48.4 (NCH_2), 50.4 (*C*HCO), 51.5 (CH_3), 70.0 (OCH_2), 70.2 (CHOH), 71.6 and 81.4 (C≡CH), 111.4, 120.9, 127.16, 127.22, 128.0, 128.5, 128.6, 130.0 and 136.7 (Ar-C), 155.0 [ArC(OBn)] and 174.1 (C=O).

Diastereomer ***111c$_2$*** as a yellow oil; [HMRS: *m/z* calculated for $C_{21}H_{24}NO_4$ (MH^+) 354.1705. Found 354.1699]; υ_{max}/cm^{-1} (C=O); δ_H (400 MHz; $CDCl_3$) 2.18 (1H, m, C≡CH), 2.53 (1H, dd, *J* = 3.9 and 12.3 Hz, CHC*H$_a$*), 3.15 (1H, q, *J* = 3.5 Hz CHCO), 3.19-3.29 (2H, m, CHC*H$_b$* and C*H$_a$*-C≡CH), 3.41, 3.37-3.47 (1H, m, C*H$_b$*-C≡CH), 3.76 (3H, s, OCH_3), 5.07-5.16 (2H, m, OCH_2), 5.73 (1H, d, *J* = 3.5 Hz, C*H*OH), 6.94 (1H, d, *J* = 8.2 Hz, ArH), 7.04 (1H, t, *J* = 7.5 Hz, ArH), 7.23-7.49 (6H, overlapping m, ArH) and 7.54-7.58 (1H, m, ArH); δ_C (100 MHz; $CDCl_3$) 38.3 and 45.9 (NCH_2), 47.5 (*C*HCO), 52.0 (CH_3), 69.6 (OCH_2), 71.7 (CHOH), 72.1 and 80.8 (C≡CH), 111.4, 120.8, 126.7, 127.1, 127.7, 128.3, 128.4, 131.2 and 136.9 (Ar-C), 154.5 [ArC(OBn)] and 174.1 (C=O).

O-*Benzylated 3-hydroxypropanoate ester-AZT conjugate diastereomer 101a$_1$*



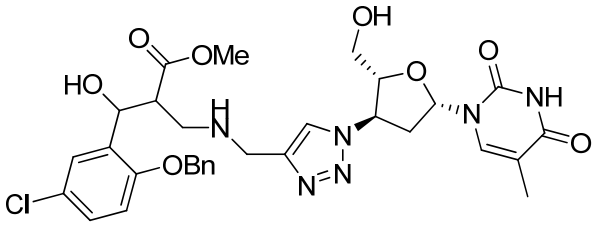
Methyl 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate **111a$_1$** (0.086 g, 0.2 mmol) was dissolved in CH_3CN (1 mL) and 3`-azidodeoxythymidine AZT (0.059 g, 0.22 mmol), Et_3N (33 μL) and CuI (0.0038 g) were added to the solution. The mixture was stirred for 48 hours then diluted with DCM (10 mL), washed with saturated aq. NH_4Cl solution (5 mL), followed by brine (5 mL), and dried over magnesium sulfate. The organic solution was concentrated under vacuum and the crude product purified by column chromatography [on silica gel; elution with EtOAc and then with EtOAc-methanol (1-4)] to afford O-*benzylated 3-hydroxypropanoate ester-AZT conjugate* ***101a*$_1$** as a pale yellow solid (0.1 g, 72%), m.p. 96-100 ^oC; [HMRS: *m/z* calculated for $C_{31}H_{36}BrN_6O_8$ (MH^+) 699.1778. Found 699.1805]; υ_{max}/cm^{-1} 1683 (C=O); δ_H (400 MHz; CD_3OD) 1.87 (3H, s, CH_3), 2.53 (1H, td, *J* = 4.8, 9.0 and 10.4 Hz, C*H*$_a$CHN), 2.60-2.70 (1H, m, CHC*H*$_a$N), 2.79 (1H, dd, *J* = 6.5 and 13.9 Hz, CHC*H*$_b$N), 2.87 (1H, t, *J* = 10.4 Hz, C*H*$_b$CHN), 2.95-3.01 (1H, m, CHCO), 3.55 (3H, s, OCH_3), 3.7 (3H, dq, *J* = 4.8, 6.0 and 11.4 Hz, CH_2OH and C*H*$_a$CN), 3.82-3.87 (1H, m, C*H*$_b$CN), 4.21-4.28 (1H, m, OCHC*H*N), 5.06 (2H, s, OCH_2Ph), 5.21-5.26 (1H, m, C*H*OH), 5.28-5.34 (1H, m, OC*H*CH_2OH), 6.42 (1H, t, *J* = 6.4 Hz, OCHN), 6.91 (1H, d, *J* = 8.8 Hz, ArH), 7.30 (4H, dt, *J* = 7.8 and 17.5 Hz, ArH), 7.40 (2H, d, *J* = 7.3 Hz, ArH), 7.49 (1H, d, *J* = 2.6 Hz, ArH), 7.78 (1H, s, ArH) and 7.88 (1H, s, ArH); δ_C (100 MHz; CD_3OD) 12.5 (CH_3Ar), 39.1 (*C*H_2CHN), 44.6 and 48.8 (CH_2N), 52.1 (OCH_3), 53.7 (CHCO), 60.9 (CHN), 62.1 (CH_2OH), 68.2 (CHOH), 71.5 (OCH_2Ph), 86.4 ($HOCH_2$*C*HO), 86.6 (NCHO), 111.7, 114.2, 115.0, 123.76, 123.83, 128.6, 129.1, 129.7, 131.1, 132.3, 134.9, 138.1, 138.2, 147.08, 147.13, 152.3, 155.8, 166.4 and 175.1 (Ar-C, C=C and C=O).

O-*Benzylated 3-hydroxypropanoate ester-AZT conjugate diastereomer 101a$_2$*

Methyl 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate **111a$_2$** (0.086 g, 0.2 mmol) was dissolved in CH_3CN (1 mL) and 3`-azidodeoxythymidine (0.059

g, 0.22 mmol), Et_3N (33 µL) and CuI (0.0038 g) were added to the solution. The mixture was stirred for 48 hours then diluted with DCM (10 mL), washed with saturated aq. NH_4Cl solution (5 mL), followed by brine (5 mL), and dried over magnesium sulfate. The organic solution was concentrated under vacuum and the crude product purified by column chromatography [on silica gel; elution with EtOAc and then with EtOAc-methanol (1-4)] to afford O-*benzylated 3-hydroxypropanoate ester-AZT conjugate diastereomer* ***101a₂*** as a pale yellow solid (0.05 g, 36%), m.p. 97-100 ^oC; [HMRS: *m/z* calculated for $C_{31}H_{36}BrN_6O_8$ (MH^+) 699.1778. Found 699.1786]; υ_{max}/cm^{-1} 1683 (C=O); δ_H (400 MHz; CD_3OD) 1.87 (3H, s, CH_3), 2.46 (1H, dt, *J* = 4.9, and 11.86 Hz, CH_aCHN), 2.63 (1H, td, J = 5.4, 10.1 and 11.2 Hz, CHCH_aN), 2.75 (1H, q, *J* = 6.0 and 6.7 Hz, CHCH_bN), 2.82 (1H, t, *J* = 11.4 Hz, CH_bCHN), 3.00-3.07 (1H, m, CHCO), 3.59 (3H, s, OCH_3), 3.65-3.70 (3H, m, CH_2OH and CH_aCN), 3.77-3.89 (1H, m, CH_bCN), 4.23 (1H, t, *J* = 4.2 Hz, OCHC*H*N), 5.05 (2H, s, OCH_2Ph), 5.27 (2H, t, *J* = 8.6 Hz, C*H*OH and OC*H*CH_2OH), 6.40 (1H, dt, *J* = 6.3 and 11.5 Hz, OCHN), 6.94 (2H, dt, *J* = 7.9 and 13.8 Hz, ArH), 7.14-7.43 (6H, overlapping m, ArH), 7.71 (1H, d, *J* = 7.8 Hz, ArH) and 7.87 (1H, s, ArH); δ_C (100 MHz; CD_3OD) 12.5 (CH_3Ar), 39.0 (*C*H_2CHN), 44.5 and 48.8 (CH_2N), 52.2 (OCH_3), 54.2 (CHCO), 60.9 (CHN), 62.1 (CH_2OH), 68.8 (CHOH), 71.2 (OCH_2Ph), 86.4 ($HOCH_2$*C*HO), 86.7 (NCHO), 111.7, 113.0, 122.0, 123.7, 128.3, 128.5, 129.0, 129.4, 129.6, 129.80, 129.84, 132.0, 138.2, 138.6, 147.1, 152.3, 156.8, 166.4 and 175.7 (Ar-C, C=C and C=O).

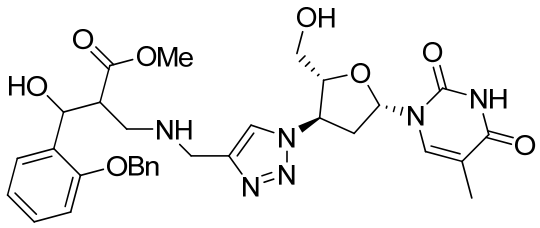
O-*Benzylated 3-hydroxypropanoate ester-AZT conjugate 101b*



The procedure described for the synthesis of **101a** was followed using methyl 3-(2-benzyloxy-5-chlorophenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate **111b** (0.16 g, 0.4 mmol), CH_3CN (1 mL) and 3`-azidodeoxythymidine (0.12 g, 0.44 mmol), Et_3N (67 µL) and CuI (0.008 g). Work-up afforded O-*benzylated 3-hydroxypropanoate ester-AZT conjugate* **101b** as a pale yellow solid (0.24 g, 92%), m.p. 86-90 ^oC; [HMRS: *m/z* calculated for $C_{31}H_{36}ClN_6O_8$ (MH^+) 655.2283. Found 655.2297]; υ_{max}/cm^{-1} (C=O); δ_H (400 MHz; CD_3OD) 1.86 (3H, s, CH_3), 2.53 (1H, p, *J* = 5.0 Hz, CH_aCHN), 2.58-2.70 (1H, m, CHCH_aN), 2.72-2.82 (1H, m, CHCH_bN), 2.87

(1H, t, *J* = 10.7 Hz, C*H*$_b$CHN), 2.95-3.03 (1H, m, CHCO), 3.54 (3H, s, OCH_3), 3.62-3.75 (3H, m, CH_2OH and C*H*$_a$CN), 3.84 (1H, dd, *J* = 2.9 and 12.2 Hz, C*H*$_b$CN), 4.24 (1H, dt, *J* = 3.2 and 6.3 Hz, OCHC*H*N), 5.05 (2H, s, OCH_2Ph), 5.23 (1H, dd, *J* = 2.0 and 6.8 Hz, C*H*OH), 5.30 (1H, dt, *J* = 5.4 and 9.9 Hz, OC*H*CH_2OH), 6.42 (1H, t, *J* = 6.4 Hz, OCHN), 6.95 (1H, d, *J* = 8.7 Hz, ArH), 7.15 (1H, dd, *J* = 2.8 and 8.9 Hz, ArH), 7.24-7.42 (6H, overlapping m, ArH), 7.40 (2H, d, *J* = 7.3 Hz, ArH), 7.78 (1H, d, *J* = 2.3 Hz, ArH) and 7.87 (1H, s, ArH); δ_C (100 MHz; CD_3OD) 12.5 (CH_3Ar), 39.0 (*C*H_2CHN), 44.5 and 48.8 (CH_2N), 52.1 (OCH_3), 53.7 (CHCO), 60.9 (CHN), 62.1 (CH_2OH), 68.2 (CHOH), 71.5 (OCH_2Ph), 86.4 ($HOCH_2$*C*HO), 86.6 (NCHO), 111.6, 114.5, 123.8, 123.9, 126.9, 128.1, 128.6, 129.1, 129.3, 129.7, 134.5, 138.1, 138.2, 147.0, 147.1, 152.2, 155.3, 166.4 and 175.1 (Ar-C, C=C and C=O).

O-*Benzylated 3-hydroxypropanoate ester-AZT conjugate 101c*

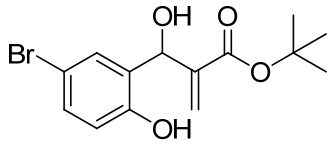


The procedure described for the synthesis of **101a** was followed using methyl 3-(2-(benzyloxyphenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate **111c** (0.071 g, 0.2 mmol), CH_3CN (1 mL) and 3`-azidodeoxythymidine (0.059 g, 0.22 mmol), Et_3N (33 μL) and CuI (0.0038 g). Work-up afforded O-*benzylated 3-hydroxypropanoate ester-AZT* conjugate ***101c*** as a pale yellow solid (0.069 g, 55%), m.p. 64-66 ^oC; [HMRS: *m/z* calculated for $C_{31}H_{37}N_6O_8$ (MH^+) 621.2673. Found 621.2683]; υ_{max}/cm^{-1} 1683 (C=O); δ_H (400 MHz; CD_3OD) 1.87 (3H, s, CH_3), 2.48 (1H, dd, *J* = 6.0 and 11.25 Hz, C*H*$_a$CHN), 2.63 (1H, td, *J* = 4.6 and 9.3 Hz, CHC*H*$_a$N), 2.77 (1H, dd, *J* = 6.4 and 13.9 Hz, CHC*H*$_b$N), 2.83 (1H, t, *J* = 11.0 Hz, C*H*$_b$CHN), 3.04 (1H, td, *J* = 4.6, 8.5 and 9.0 Hz, CHCO), 3.58 (3H, s, OCH_3), 3.68 (3H, t, *J* = 7.25 Hz, CH_2OH and C*H*$_a$CN), 3.80-3.86 (1H, m, C*H*$_b$CN), 4.19-4.26 (1H, m, OCHC*H*N), 5.07 (2H, s, OCH_2Ph), 5.29 (2H, d, *J* = 7.6 Hz, C*H*OH and OC*H*CH_2OH), 6.42 (1H, t, *J* = 6.4 Hz, OCHN), 6.96 (2H, p, *J* = 7.6 and 8.7 Hz, ArH), 7.18-7.44 (7H, overlapping m, ArH), 7.72 (1H, d, *J* = 7.6 Hz, ArH) and 7.87 (1H, s, ArH); δ_C (100 MHz; CD_3OD) 12.5 (CH_3Ar), 39.0 (*C*H_2CHN), 44.6

and 48.8 (CH_2N), 52.2 (OCH_3), 54.1 (CHCO), 60.8 (CHN), 62.1 (CH_2OH), 68.7 (CHOH), 71.1 (OCH_2Ph), 86.3 ($HOCH_2CHO$), 86.6 (NCHO), 111.7, 113.0, 122.0, 123.7, 123.8, 128.3, 128.5, 128.9, 129.6, 129.8, 132.0, 138.2, 138.6, 147.0, 147.1, 152.2, 156.8, 166.4 and 175.6 (Ar-C, C=C and C=O).

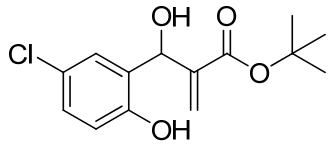
3.3. PREPARATION of NON-BENZYLATED 3-HYDROXYPROPANOATE ESTER-AZT CONJUGATES

tert-*Butyl 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-2-methylenepropanoate 113a*



A mixture of 5-bromosalicylaldehyde (8.2 g, 41 mmol), *tert*-butyl acrylate (9 mL, 60 mmol) and DABCO (3.4 g, 30 mmol) in $CHCl_3$ (12 mL) was stirred at room temperature for 7 days after which the crude product was filtered and washed with $CHCl_3$ to afford *tert*-butyl 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-2-methylenepropanoate **113a** as a white solid (9.3 g, 69%), m.p. 180-182 ^oC (lit.[119] 186-188 ^oC); υ_{max}/cm^{-1} 3290 (OH) and 1683 (C=O); δ_H (400 MHz; DMSO-d_6) 131 [9H, s, $C(CH_3)_3$], 5.64 (1H, s, C*H*OH), 5.66 and 6.05 (2H, 2 x s, $C=CH_2$), 6.75 (1H, d, J = 8.5 Hz, ArH), 7.17-7.24 (2H, overlapping m, ArH); δ_C (100 MHz; DMSO-d_6) 27.6 [$C(CH_3)_3$], 64.6 (CHOH), 80.1 [$C(CH_3)_3$], 109.7 and 117.2 (Ar-C), 123.1 ($C=CH_2$), 129.8, 130.5 and 132.0 (Ar-C), 144.9 ($C=CH_2$), 153.9 [ArC(OH)] and 165.0 (C=O).

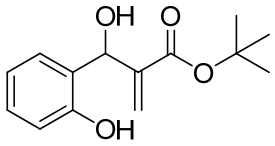
tert-*Butyl 3-(5-chloro-2-hydroxyphenyl)-3-hydroxy-2-methylenepropanoate 113b*



The procedure described for the synthesis of *tert*-butyl 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-2-methylenepropanoate **113a** was employed using 5-chlorosalicylaldehyde (6.4 g, 41 mmol), *tert*-butyl acrylate (9 mL, 60 mmol) and DABCO 93.4 g, 30 mmol) in $CHCl_3$ (12 mL). Work-up afforded *tert*-butyl 3-(5-chloro-2-hydroxyphenyl)-3-hydroxy-2-methylenepropanoate **113b** as a white solid (6.3 g, 54%), m.p. 166-168 ^oC (lit.[135] 185-187 ^oC); υ_{max}/cm^{-1} 3350 (OH)

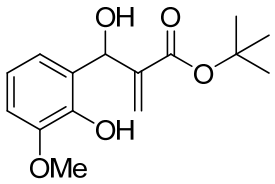
and 1683 (C=O); δ_H (400 MHz; DMSO-d_6) 131 [9H, s, $C(CH_3)_3$], 5.67 (1H, s, C*H*OH), 5.64 and 6.05 (2H, 2 x s, $C=CH_2$), 6.79 (1H, d, J = 8.5 Hz, ArH), 7.05-7.11 (2H, overlapping m, ArH); δ_C (100 MHz; DMSO-d_6) 27.6 [$C(CH_3)_3$], 64.6 (CHOH), 80.1 [$C(CH_3)_3$], 116.6 and 122.1 (Ar-C), 123.1 ($C=CH_2$), 126.9, 127.6 and 131.4 (Ar-C), 144.9 ($C=CH_2$), 153.4 [ArC(OH)] and 165.0 (C=O).

t*ert-*Butyl 3-hydroxy-3-(2-hydroxphenyl)-2-methylenepropanaoate 113c



A mixture of salicylaldehyde (4.3 mL, 41 mmol), *tert*-butyl acrylate (9 mL, 60 mmol) and DABCO (3.4 g, 30 mmol) in $CHCl_3$ (12 mL) was stirred at room temperature for 30 days after which the crude product was concentrated under vacuum and purified by column chromatography [on silica gel; elution with hexane-EtOAc (4:1)] to afford *tert*-butyl 3-hydroxy-3-(2-hydroxphenyl)-2-methylenepropanaoate **113c** as a white solid (3.7 g, 36%), m.p. 98-100 ^oC (lit.[119] 108-110 ^oC); υ_{max}/cm^{-1} 3350 (OH) and 1687 (C=O); δ_H (400 MHz; CD_3OD) 1.33 [9H, s, $C(CH_3)_3$], 5.76 and 6.17 (2H, 2 x s, $C=CH_2$) , 5.89 (1H, d, J = 3.7 Hz, C*H*OH), 6.75-6.78 (2H, m, ArH), 7.05-7.12 (2H, overlapping m, ArH); δ_C (100 MHz; CD_3OD) 28.13 [$C(CH_3)_3$], 67.85 (CHOH), 82.1 [$C(CH_3)_3$], 116.3 and 120.2 (Ar-C), 123.6 ($C=CH_2$), 128.6, 129.3 and 129.7 (Ar-C), 146.3 ($C=CH_2$), 156.3 [ArC(OH)] and 167.4 (C=O).

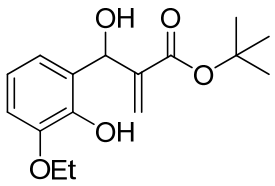
tert-*Butyl 3-hydroxy-3-(2-hydroxy-3-methoxyphenyl)-2-methylenepropanoate 113d*[122]



The procedure described for the synthesis of *tert*-butyl 3-hydroxy-3-(2-hydroxphenyl)-2-methylenepropanaoate **113c** was followed using 3-methoxysalicylaldehyde (6.2 g, 41 mmol), *tert*-butyl acrylate (9 mL, 60 mmol) and DABCO (3.4 g, 30 mmol) in $CHCl_3$ (12 mL). Work-up afforded *tert*-butyl 3-hydroxy-3-(2-hydroxy-3-methoxyphenyl)-2-methylenepropanoate **113d** as a yellow oil (3.0 g, 26%); υ_{max}/cm^{-1} 3428 (OH) and 1706 (C=O); δ_H (400 MHz; $CDCl_3$) 1.44

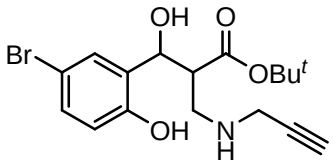
[9H, s, $C(CH_3)_3$], 5.65 and 6.22 (2H, 2 x s, $C=CH_2$), 3.85 (3H,s, OCH_3) 5.80 (1H, d, *J* = 4.9 Hz, C*H*OH), 6.80 (3H, d, *J* = 3.9 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 27.9 [$C(CH_3)_3$], 56.0 (OCH_3) 69.7 (CHOH), 81.7 [$C(CH_3)_3$], 110.4, 119.5 and 119.6 (Ar-C), 125.3 ($C=CH_2$), 126.3 (Ar-C), 141.9 ($C=CH_2$), 143.6 [ArC(OH)], 147.0 [ArC(OMe)] and 166.1 (C=O).

tert-*Butyl 3-(3-ethoxy-2-hydroxyphenyl)-3-hydroxy-2-methylenepropanoate 113e*[122]



The procedure described for the synthesis of *tert*-butyl 3-hydroxy-3-(2-hydroxphenyl)-2-methylenepropanaoate **113c** was followed using 3-methoxysalicylaldehyde (6.8 g, 41 mmol), *tert*-butyl acrylate (9 mL, 60 mmol) and DABCO (3.4 g, 30 mmol) in $CHCl_3$ (12 mL). Work up afforded *tert*-butyl 3-(3-ethoxy-2-hydroxyphenyl)-3-hydroxy-2-methylenepropanoate **113e** as a yellow oil (2.5 g, 21%); υ_{max}/cm^{-1} 3417 (OH) and 1699 (C=O); δ_H (400 MHz; $CDCl_3$) 1.34-1.48 [12H, m, overlapping s and t, $C(CH_3)_3$ and CH_2CH_3], 4.09 (2H, dt, *J* = 6.8 and 13.4 Hz, OCH_2CH_3), 5.66 and 6.21 (2H, 2 x s, $C=CH_2$) , 5.81 (1H, d, *J* = 5.2 Hz, *CH*OH), 6.80 (3H, overlapping m, ArH); δ_C (100 MHz; $CDCl_3$) 14.7 (CH_2CH_3), 27.9 [$C(CH_3)_3$], 64.8 (OCH_2CH_3) 69.3 (CHOH), 81.5 [$C(CH_3)_3$], 111.2, 119.2 and 119.5 (Ar-C), 125.1 ($C=CH_2$), 126.5 (Ar-C), 142.1 ($C=CH_2$), 143.6 [ArC(OH)], 146.0 [ArC(OEt)] and 166.0 (C=O).

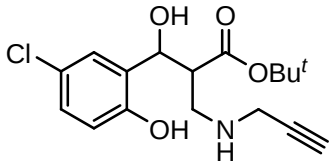
tert-*Butyl 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate 114a*



To a solution of *tert*-butyl 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-2-methylenepropanoate **113a** (0.72 g, 2.2 mmol) in dry THF (3 mL) was added propargylamine (0.3 mL, 4 mmol) and the mixture stirred at r.t. for 3 days. The mixture was then concentrated under vacuum and column chromatographed [on silica gel; elution with hexane-EtOAc (2:1) to afford *tert*-butyl 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate **114a** as a white solid (0.65 g, 77%), m.p. 136-138 ^oC (lit.[122] 136-138 ^oC); υ_{max}/cm^{-1} 3265 (OH) and 1729 (C=O);

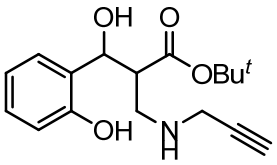
δ_H (400 MHz; CD_3OD) 1.32 [9H, s, $C(CH_3)_3$], 2.54 (1H, s, C≡CH), 2.85 (1H, s, CHCH_a), 2.95 (1H, d, J = 6.2 Hz, CHCH_b), 3.03 (1H, t, J = 6.2 Hz, CHCO), 3.30 (2H, d, J = 5.0 Hz, CH_2C≡CH), 5.16 (1H, d, J = 6.4 Hz, C*H*OH), 6.65 (1H, d, J = 6.7 Hz, ArH), 7.18 (1H, d, J = 8.7 Hz, ArH) and 7.37 (1H, d, J = 4.8 Hz, ArH); δ_C (100 MHz; CD_3OD), 28.2 [$C(CH_3)_3$], 38.5 and 47.9 (NCH_2), 52.1 (*C*HCO), 71.2 (*C*HOH), 73.4 and 81.8 (C≡CH), 82.2 [*C*$(CH_3)_3$], 112.0, 118.2, 131.8, 131.9 and 132.1 (Ar-C), 155.1 [ArC(OH)] and 173.5 (C=O).

tert-*Butyl 3-(5-chloro-2-hydroxyphenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate 114b*



The procedure for the synthesis of *tert*-butyl 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate **114a** was followed using *tert*-butyl 3-(5-chloro-2-hydroxyphenyl)-3-hydroxy-2-methylenepropanoate **113b** (0.63 g, 2.2 mmol), dry THF (3 mL), and propargylamine (0.3 mL, 4 mmol). Work-up afforded *tert*-butyl 3-(5-chloro-2-hydroxyphenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate **114b** as a white solid (0.63, 84%), m.p. 118-120 ^oC (lit.[122] 125-126 ^oC); υ_{max}/cm^{-1} 3464 (OH) and 1693 (C=O); δ_H (400 MHz; CD_3OD) 1.30 [9H, s, $C(CH_3)_3$], 2.52 (1H, s, C≡CH), 2.84 (1H, d, J = 6.8 Hz, CHCH_a), 2.94 (1H, s, CHCH_b), 3.02 (1H, t, J = 6.1 Hz, CHCO), 3.29 (2H, d, J = 4.9 Hz, CH_2C≡CH), 5.15 (1H, d, J = 7.1 Hz, C*H*OH), 6.7 (1H, t, J = 6.5 Hz, ArH), 7.02 (1H, tt, J = 2.9 and 5.9 Hz, ArH) and 7.23 (1H, t, J = 3.7 Hz, ArH); δ_C (100 MHz; CD_3OD), 28.2 [$C(CH_3)_3$], 38.5 and 47.9 (NCH_2), 52.0 (*C*HCO), 71.2 (*C*HOH), 73.4 and 81.7 (C≡CH), 82.2 [*C*$(CH_3)_3$], 117.7, 125.0, 128.8, 129.1 and 131.4 (Ar-C), 154.6 [ArC(OH)] and 173.5 (C=O).

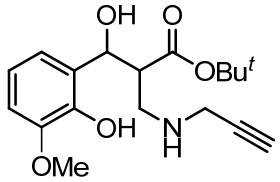
tert-*Butyl 3-hydroxy-3-(2-hydroxphenyl)-2-[(propynylamino)methyl]propanaoate 114c*



The procedure for the synthesis of *tert*-butyl 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate **114a** was followed using *tert*-butyl 3-hydroxy-3-(2-

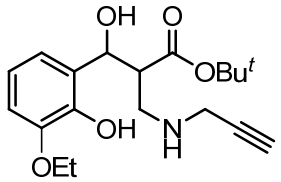
hydroxphenyl)-2-methylenepropanaoate **113c** (0.55 g, 2.2 mmol), dry THF (3 mL), and propargylamine (0.3 mL, 4 mmol). Work-up afforded *tert*-butyl 3-hydroxy-3-(2-hydroxphenyl)-2-[(propynylamino)methyl]propanaoate **114c** as a white solid (0.36 g, 57%), m.p. 66-68 ^{o}C (lit.[122] 68-70 ^{o}C); υ_{max}/cm^{-1} 3460 (OH) and 1710 (C=O); δ_H (400 MHz; CD_3OD) 1.29 [9H, s, $C(CH_3)_3$], 2.56 (1H, s, C≡CH), 2.90-3.00 (2H, m, CHCH_2), 3.09 (1H, t, *J* = 6.1 Hz, CHCO), 3.29 (2H, d, *J* =16.3 Hz, CH_2C≡CH), 5.16-5.23 (1H, m, C*H*OH), 6.8 (2H, dd, *J* = 5.32 and 14.7 Hz, ArH), 7.06 (1H, d, *J* = 6.1 Hz, ArH) and 7.31 (1H, d, *J* = 6.8 Hz, ArH); δ_C (100 MHz; CD_3OD), 28.2 [$C(CH_3)_3$], 38.5 and 48.2 (NCH_2), 52.2 (*C*HCO), 72.2 (*C*HOH), 73.5 and 81.6 (C≡CH), 82.1 [*C*$(CH_3)_3$], 116.3, 125.8, 129.0, 129.6 and 132.6 (Ar-C), 155.9 [ArC(OH)] and 173.7 (C=O).

tert-*Butyl 3-hydroxy-3-(2-hydroxy-3-methoxyphenyl)-2-[(2-propynylamino)methyl]propanoate 114d*



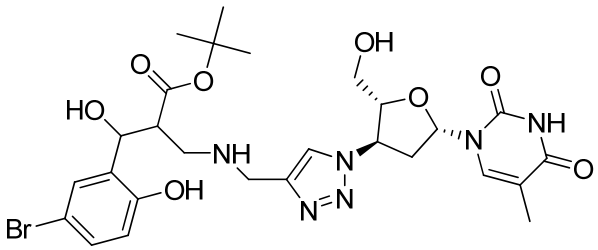
The procedure for the synthesis of *tert*-butyl 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate **114a** was followed using *tert*-butyl 3-hydroxy-3-(2-hydroxy-3-methoxyphenyl)-2-methylenepropanoate **113d** (0.62 g, 2.2 mmol), dry THF (3 mL), and propargylamine (0.3 mL, 4 mmol). Work-up afforded *tert*-butyl 3-hydroxy-3-(2-hydroxy-3-methoxyphenyl)-2-[(2-propynylamino)methyl]propanoate **114d** as a yellow oil (0.5 g, 67%); υ_{max}/cm^{-1} 3301 (OH) and 1715 (C=O); δ_H (400 MHz; CD_3OD) 1.30 [9H, s, $C(CH_3)_3$], 2.55 (1H, s, C≡CH), 2.94 (2H, qt, *J* = 6.3 and 12.9 Hz, CHCH_2), 3.04-3.10 (1H, m, CHCO), 3.26-3.33 (2H, m, CH_2C≡CH), 3.82 (3H, s, OCH_3), 5.28 (1H, s, C*H*OH), 6.77 (1H, d, *J* = 7.1 Hz, ArH), 6.83 (1H, d, *J* = 7.0 Hz, ArH) and 6.91 (1H, d, *J* = 7.3 Hz, ArH); δ_C (100 MHz; CD_3OD), 28.2 [$C(CH_3)_3$], 38.6 and 48.1 (NCH_2), 52.3 (*C*HCO), 56.5 (OCH3), 71.4 (*C*HOH), 73.4 and 81.8 (C≡CH), 82.0 [*C*$(CH_3)_3$], 111.5, 119.9, 120.8 and 129.5 (Ar-C), 144.8 and 148.7 [ArC(OH) and ArC(OMe)] and 173.7 (C=O).

tert-*Butyl 3-(3-ethoxy-2-hydroxyphenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate 114e*[122]



The procedure for the synthesis of *tert*-butyl 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate **114a** was followed *tert*-butyl 3-(3-ethoxy-2-hydroxyphenyl)-3-hydroxy-2-methylenepropanoate **113e** (0.65 g, 2.2 mmol), dry THF (3 mL), and propargylamine (0.3 mL, 4 mmol). Work up afforded *tert-butyl 3-(3-ethoxy-2-hydroxyphenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate* **114e** as a yellow oil (0.36 g, 46%); υ_{max}/cm^{-1} 3285 (OH) and 1714 (C=O); δ_H (400 MHz; CD_3OD) 1.31 [9H, s, $C(CH_3)_3$], 1.38 (3H,d, J = 6.2 Hz, OCH_2CH_3), 2.56 (1H, s, C≡CH), 2.94 (2H, dd, J = 6.7 and 12.7 Hz, $CHCH_2$), 3.08 (1H, t, J = 6.3 Hz, CHCO), 3.28-3.32 (2H, m, $CH_2C{\equiv}CH$), 4.06 (2H, t, J = 6.7 Hz, OCH_2), 5.27 (1H, s, CHOH), 6.75 (1H, d, J = 7.1 Hz, ArH), 6.81 (1H, d, J = 5.9 Hz, ArH) and 6.90 (1H, d, J = 6.3 Hz, ArH); δ_C (100 MHz; CD_3OD), 15.1 (OCH_2CH_3) 28.2 [$C(CH_3)_3$], 38.5 and 48.1 (NCH_2), 52.2 (CHCO),6 5.6 (OCH_2), 71.5 (CHOH), 73.4 and 81.7 (C≡CH), 82.0 [$C(CH_3)_3$], 112.8, 119.9, 120.8 and 129.5 (Ar-C), 145.0 and 147.8 [ArC(OH) and ArC(OEt)] and 173.7 (C=O).

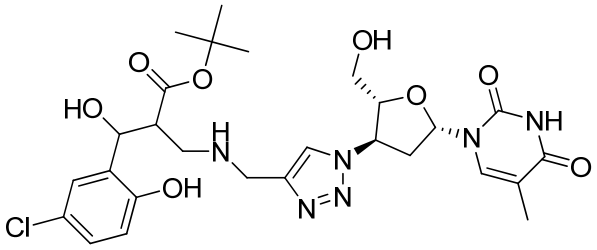
3-Hydroxypropanoate ester-AZT conjugate 115a



tert-Butyl 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate **114a** (0.15 g, 0.4 mmol) was dissolved in CH_3CN (2 mL) and 3`-azidodeoxythymidine (0.12 g, 0.44 mmol), Et_3N (67 µL) and CuI (0.008 g) were added to the solution. The mixture was stirred for 48 hours then diluted with DCM (10 mL), washed with saturated aq. NH_4Cl solution (5 mL), followed by brine (5 mL), and dried over magnesium sulfate. The organic solution was

concentrated under vacuum and the crude product purified by column chromatography [on silica gel; elution with hexane-EtOAc (2:1)] to afford *3-Hydroxypropanoate ester-AZT conjugate* ***115a*** as a pale yellow oil (0.32 g, 13%); [HMRS: *m/z* calculated for $C_{27}H_{36}BrN_6O_8$ (MH^+) 651.1778. Found 651.1790]; υ_{max}/cm^{-1} 1683 (C=O); δ_H (400 MHz; CD_3OD) 1.30 [9H, s, $C(CH_3)_3$], 1.86 (3H, s, CH_3), 2.68 (1H, dd, *J* = 7.1 and 13.7 Hz, C*H*$_a$CHN), 2.75-2.88 (2H, m, CHC*H*$_a$N and C*H*$_b$CHN), 2.89-2.95 (1H, m, CHC*H*$_b$N), 3.02 (1H, q, *J* = 11.36 and 14.7 Hz, CHCO), 3.73 and 3.79 (2H, s, C*H*$_2$CN), 3.86 (2H, d, *J* = 12.6 Hz, CH_2OH), 4.30 (1H, s, OCHC*H*N), 5.15 (1H, s, C*H*OH), 5.36 (1H, s, OC*H*CH_2OH), 6.44 (1H, q, *J* = 5.6 Hz, OCHN), 6.62-6.88 (1H, m, ArH), 7.12-7.20 (1H, m, ArH) 7.35 (1H, d, *J* = 10.0 Hz, ArH) 7.89 (2H, dd, *J* = 5.4 and 14.4 Hz, ArH); δ_C (100 MHz; CD_3OD) 12.5 (CH_3Ar), 28.2 [$C(CH_3)_3$], 39.1 (*C*H_2CHN), 44.8 and 48.0 (CH_2N), 52.0 (CHCO), 60.9 (CHN), 62.1 (CH_2OH), 71.1 (CHOH), 82.2 [*C*$(CH_3)_3$], 86.4 ($HOCH_2$*C*HO), 86.7 (NCHO), 111.6, 112.0, 118.2, 123.9, 131.7, 131.8, 132.0, 132.1, 138.3, 152.3, 155.1, 166.4 and 173.5 (Ar-C, C=C and C=O).

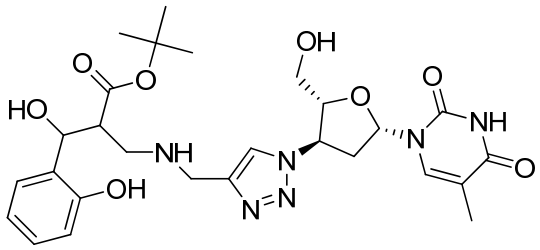
3-Hydroxypropanoate ester-AZT conjugate 115b



The procedure described for the synthesis of **115a** was followed using *tert*-butyl 3-(5-chloro-2-hydroxyphenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate **114b** (0.14 g, 0.4 mmol), CH_3CN (1 mL) and 3`-azidodeoxythymidine (0.12 g, 0.44 mmol), Et_3N (67 µL) and CuI (0.008 g). Work-up afforded *3-hydroxypropanoate ester-AZT conjugate* ***115b*** as a pale yellow solid (0.036 g, 14%), m.p. 100-102 ^oC; [HMRS: *m/z* calculated for $C_{27}H_{36}ClN_6O_8$ (MH^+) 607.0610. Found 607.1104]; υ_{max}/cm^{-1} 1683 (C=O); δ_H (400 MHz; CD_3OD) 1.29 [9H, s, $C(CH_3)_3$], 1.84 (3H, s, CH_3), 2.58-2.97 (4H, m, C*H*$_2$CHN, and CHC*H*$_2$N), 3.03 (1H, s, CHCO), 3.60-3.94 (4H, m, C*H*$_2$CN and CH_2OH), 4.29 (1H, s, OCHC*H*N), 5.15 (1H, s, C*H*OH), 5.36 (1H, s, OC*H*CH_2OH), 6.42 (1H, s, OCHN), 6.63 (1H, d, *J* = 8.3 Hz, ArH), 7.17 (1H, dd, *J* = 8.5 and 25.3 Hz, ArH) 7.33 (1H, s, ArH), 7.67-8.05 (2H, m, ArH); δ_C (100 MHz; CD_3OD) 12.5 (CH_3Ar), 28.2 [$C(CH_3)_3$], 39.1 (*C*H_2CHN), 44.8 and 48.2 (CH_2N), 52.0 (CHCO), 60.9 (CHN), 62.1

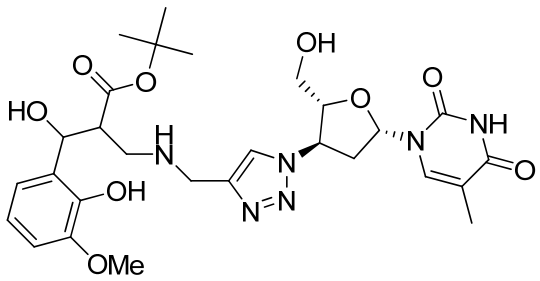
(CH_2OH), 71.1 (CHOH), 82.2 [$C(CH_3)_3$], 86.4 ($HOCH_2CHO$), 86.6 (NCHO), 111.6, 118.3, 119.3, 124.0, 131.7, 132.1, 135.1, 138.2, 140.1, 152.2, 155.1, 166.4 and 173.5 (Ar-C, C=C and C=O).

3-Hydroxypropanoate ester-AZT conjugate 115c



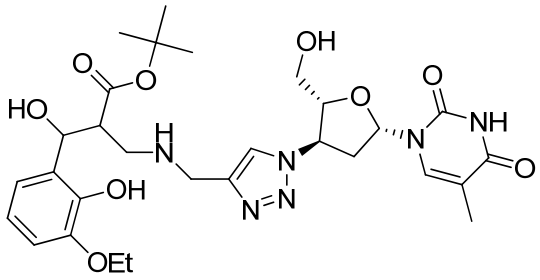
The procedure described for the synthesis of **115a** was followed using tert-butyl 3-hydroxy-3-(2-hydroxphenyl)-2-[(propynylamino)methyl]propanaoate **114c** (0.10 g, 0.4 mmol), CH_3CN (1 mL) and 3`-azidodeoxythymidine (0.12 g, 0.44 mmol), Et_3N (67 μL) and CuI (0.008 g). Work-up afforded *3-Hydroxypropanoate ester-AZT conjugate* ***115c*** as a pale yellow oil (0.030 g, 16%); [HMRS: *m/z* calculated for $C_{27}H_{36}N_6O_8$ (MH^+) 573.2673. Found 573.2676]; υ_{max}/cm^{-1} 1683 (C=O); δ_H (400 MHz; CD_3OD) 1.32 [9H, s, $C(CH_3)_3$], 1.86 (3H, s, CH_3), 2.67 (1H, td, *J* = 4.1 and 8.1 Hz, CH_aCHN), 2.82 (2H, dt, *J* = 6.1 and 12.5 Hz, CHCH_aN and CH_bCHN), 2.91 (1H, t, *J* = 9.8 Hz, CHCH_bN), 3.08 (1H, q, *J* = 6.1 Hz, CHCO), 3.73 (2H, s, CH_2CN), 3.88 (2H, s, CH_2OH), 4.23-4.34 (1H, m, OCHC*H*N), 5.27 (1H, dt, *J* = 5.3 and 10.2 Hz, C*H*OH), 5.33-5.39 (1H, m, OC*H*CH_2OH), 6.44 (1H, q, *J* = 6.5 Hz, OCHN), 7.30 (2H, dt, *J* = 3.2 and 7.4 Hz, ArH), 7.48-7.62 (2H, m, ArH), 7.84-7.94 (2H, m, ArH); δ_C (100 MHz; CD_3OD) 12.5 (CH_3Ar), 28.2 [$C(CH_3)_3$], 39.0 (CH_2CHN), 44.2 and 48.8 (CH_2N), 51.2 (CHCO), 61.0 (CHN), 62.1 (CH_2OH), 71.9 (CHOH), 82.4 [$C(CH_3)_3$], 86.4 ($HOCH_2CHO$), 86.6 (NCHO), 111.7, 117.2, 120.6, 125.9, 129.3, 132.6, 138.2, 142.0, 152.3, 154.6, 163.1, 166.4 and 173.5 (Ar-C, C=C and C=O).

3-Hydroxypropanoate ester-AZT conjugate 115d



The procedure described for the synthesis of **115a** was followed using tert-butyl 3-hydroxy-3-(2-hydroxy-3-methoxyphenyl)-2-[(2-propynylamino)methyl]propanoate **114d** (0.13 g, 0.4 mmol), CH_3CN (1 mL) and 3`-azidodeoxythymidine (0.12 g, 0.44 mmol), Et_3N (67 µL) and CuI (0.008 g). Work-up afforded *3-Hydroxypropanoate ester-AZT conjugate* **115d** as a pale yellow oil (0.16 g, 66%); [HMRS: *m/z* calculated for $C_{28}H_{39}N_6O_9$ (MH^+) 603.2779. Found 603.2783]; υ_{max}/cm^{-1} 1683 (C=O); δ_H (400 MHz; CD_3OD) 1.30 [9H, s, $C(CH_3)_3$], 1.87 (3H, s, CH_3), 2.69 (1H, td, *J* = 4.4 and 8.4 Hz, C*H*$_a$CHN), 2.77-2.85 (2H, m, CHC*H*$_a$N and C*H*$_b$CHN), 2.91 (1H, t, *J* = 9.8 Hz, CHC*H*$_b$N), 3.08 (1H, q, *J* = 6.1 Hz, CHCO), 3.73 and 3.85 (2H, s, C*H*$_2$CN), 3.76-3.84 (5H, s, OCH_3 and CH_2OH), 4.23-4.34 (1H, m, OCHC*H*N), 5.27 (1H, d, *J* = 6.1 Hz, C*H*OH), 5.33-5.39 (1H, m, OC*H*CH_2OH), 6.44 (1H, t, *J* = 6.4 Hz, OCHN), 6.71-6.88 (2H, m, ArH), 7.89 (2H, q, *J* = 5.4 Hz, ArH); δ_C (100 MHz; CD_3OD) 12.5 (CH_3Ar), 28.2 [C(*C*$H_3)_3$], 39.1 (*C*H_2CHN), 44.7 and 48.1 (CH_2N), 51.9 (CHCO), 56.6 (OCH_3), 60.9 (CHN), 62.1 (CH_2OH), 71.4 (CHOH), 82.1 [*C*$(CH_3)_3$], 86.4 ($HOCH_2$*C*HO), 86.7 (NCHO), 111.5, 111.7, 119.9, 120.6, 124.1, 129.5, 138.3, 144.7, 146.7, 148.7, 152.3, 166.4 and 173.8 (Ar-C, C=C and C=O).

3-Hydroxypropanoate ester-AZT conjugate 115e

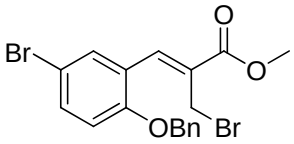


The procedure described for the synthesis of **115a** was followed using tert-butyl 3-(3-ethoxy-2-hydroxyphenyl)-3-hydroxy-2-[(2-propynylamino)methyl]propanoate **114e** (0.18 g, 0.4 mmol), CH_3CN (1 mL) and 3`-azidodeoxythymidine (0.12 g, 0.44 mmol), Et_3N (67 µL) and CuI (0.008 g). Work-up afforded *3-Hydroxypropanoate ester-AZT conjugate **115e*** as a pale yellow oil (0.30 g, 10%); [HMRS: *m/z* calculated for $C_{29}H_{41}N_6O_9$ (MH^+) 617.2935. Found 617.2956]; υ_{max}/cm^{-1} 1682 (C=O); δ_H (400 MHz; CD_3OD) 1.32 [9H, s, $C(CH_3)_3$], 1.35 (3H, t, *J* = 6.9 Hz, OCH_2CH_3), 1.86 (3H, s, CH_3), 2.68 (1H, ddd, *J* = 6.1, 8.6 and 14.3 Hz, C*H*$_a$CHN), 2.82 (2H, q, *J* = 4.5 and 5.5 Hz, CHC*H*$_a$N and C*H*$_b$CHN), 2.85-2.92 (1H, m, CHC*H*$_b$N), 3.07 (1H, td, *J* = 4.8 and 7.0 Hz, CHCO), 3.65-3.79 (2H, m, C*H*$_2$CN), 3.81-3.90 (2H, m, CH_2OH), 3.99-4.07 (2H, m, OC*H*$_2CH_3$), 4.30 (1H, dt, *J* = 3.0 and 5.7 Hz, OCHC*H*N), 5.25 (1H, d, *J* = 6.2 Hz, C*H*OH), 5.31-5.38 (1H, m,

OC*H*CH_2OH), 6.43 (1H, t, *J* = 6.4 Hz, OCHN), 6.71 (1H, t, *J* = 7.9 Hz, ArH), 6.79(1H, dd, *J* = 1.6 and 8.1 Hz, ArH), 6.84 (1H, dd, *J* = 1.6 and 7.7 Hz, ArH), 7.88 (2H, dd, *J* = 6.1 and 11.9 Hz, ArH); δ_C (100 MHz; CD_3OD) 12.5 (CH_3Ar), 15.1 (CH_2CH_3), 28.2 [$C(CH_3)_3$], 39.0 (CH_2CHN), 44.8 and 48.2 (CH_2N), 52.0 (CHCO), 60.9 (CHN), 62.1 (CH_2OH), 65.6 (OCH_2CH_3), 71.5 (CHOH), 82.0 [$C(CH_3)_3$], 86.4 ($HOCH_2CHO$), 86.7 (NCHO), 111.6, 112.7, 119.9, 120.6, 124.0, 129.6, 138.3, 144.9, 146.9, 147.8, 152.3, 166.4 and 173.8 (Ar-C, C=C and C=O).

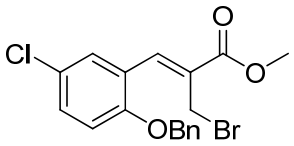
3.4. 4-SUBSTITUTED COUMARINS

Methyl (Z)-3-[2-(benzyloxy)-5-bromophenyl]-2-(bromomethyl)-2-propenoate 116a



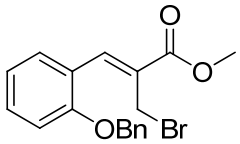
To a cooled mixture of methyl 3-(2-benzyloxy-5-bromophenyl)-3-hydroxy-2-methylenepropanoate **106a** (0.4 g, 1mmol) in acetonitrile (5 mL) was added conc. H_2SO_4 (1.5 mL) and LiBr (0.34 g, 4 mmol) and the mixture was stirred at 0 ^oC for 30 minutes and allowed to warm up to r.t. and then stirred further for 4 h. The mixture was then diluted in DCM, washed with water (15 mL), saturated aq. $NaHCO_3$ (15 mL) and brine (15 mL), dried over $MgSO_4$ and finally concentrated under vacuum and column chromatographed [on silica gel; elution with hexane-EtOAc (1:1)] affording methyl *(Z)*-3-[2-(benyloxy)-5-bromophenyl]-2-(bromomethyl)-2-propenoate **116a** as a yellow solid (0.4g, 86%), m.p. 87-90 ^oC (lit.[122] 90-91 ^oC); υ_{max}/cm^{-1} 1700 (C=O); δ_H (400 MHz; $CDCl_3$) 3.87 (3H, s, OCH_3), 4.33 (2H, s, CH_2Br), 5.12 (2H, s, OCH_2Ph), 6.84 (1H, d, *J* = 8.8 Hz, ArH), 7.31-7.44 (6H overlapping m, ArH), 7.81 (1H, d, *J* = 2.4 Hz, ArH), 7.96 (1H, s, 1`-H); δ_C (100 MHz; $CDCl_3$) 26.6 and 70.6 (CH_2), 52.5 (OCH_3), 113.2, 114.2, 125.8, 127.0, 128.2, 128.7, 129.6, 131.9, 133.6, 136.0 and 137.3 (C=CH and Ar-C), 156.0 [ArC(OBn)] and 166.0 (C=O).

Methyl (Z)-3-[2-(benzyloxy)-5-chlorophenyl]-2-(bromomethyl)-2-propenoate 116b



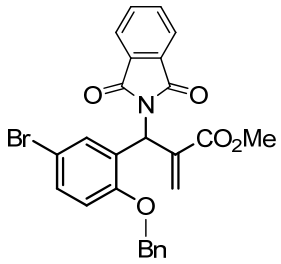
The procedure described for the synthesis of methyl (Z)-3-[2-(benzyloxy)-5-bromophenyl]-2-(bromomethyl)-2-propenoate **116a** was followed using methyl 3-(2-benzyloxy-5-chlorophenyl)-3-hybroxy-2-methylenepropanoate **106b** (0.33 g, 1 mmol), conc. H_2SO_4 (1.5 mL) and LiBr (0.34 g, 4 mmol) in acetonitrile (5 mL). Work-up afforded methyl *(Z)*-3-[2-(benyloxy)-5-chlorophenyl]-2-(bromomethyl)-2-propenoate **116b** as a yellow solid (0.4 g, 84%), m.p.76-78 ^oC (lit.[122] 80-81 ^oC); υ_{max}/cm^{-1} 1714 (C=O); δ_H (400 MHz; $CDCl_3$) 3.87 (3H, s, OCH_3), 4.33 (2H, s, CH_2Br), 5.12 (2H, s, OCH_2Ph), 6.89 (1H, d, *J* = 8.9 Hz, ArH), 7.28-7.39 (6H overlapping m, ArH), 7.68 (1H, d, *J* = 2.5 Hz, ArH), 7.97 (1H, s, 1`-H); δ_C (100 MHz; $CDCl_3$) 26.6 and 70.7 (CH_2), 52.5 (OCH_3), 113.8, 125.33, 126.0, 127.0, 128.2, 128.7, 129.6, 130.6, 137.4, 136.0 and 137.4 (C=CH and Ar-C), 155.5 [ArC(OBn)] and 166.3 (C=O).

Methyl (Z)-3-[2-(benzyloxy)phenyl]-2-(bromomethyl)-2-propenoate 116c[122]



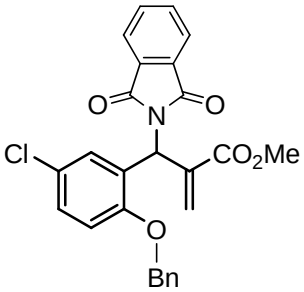
The procedure described for the synthesis of methyl (Z)-3-[2-(benyloxy)-5-bromophenyl]-2-(bromomethyl)-2-propenoate **116a** was followed using methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanoate **106c** (0.4 g, mmol), conc. H_2SO_4 91.5 mL) and LiBr (0.34 g, 4 mmol) in acetonitrile (5 mL). Work-up afforded methyl *(Z)*-3-[2-(benyloxy)phenyl]-2-(bromomethyl)-2-propenoate **116c** as a colourless gel (0.29g, 55%); υ_{max}/cm^{-1} 1712 (C=O); δ_H (400 MHz; $CDCl_3$) 3.87 (3H, s, OCH_3), 4.39 (2H, s, CH_2Br), 5.15 (2H, s, OCH_2Ph), 6.97 (1H, d, *J* = 8.3 Hz, ArH), 7.07 (1H, t, *J* = 7.4 Hz, ArH), 7.33-7.41 (6H overlapping m, ArH), 7.72 (1H, d, *J* = 7.5 Hz) and 8.11 (1H, s, 1`-H); δ_C (100 MHz; $CDCl_3$) 27.4 and 70.3 (CH_2), 52.3 (OCH_3), 112.5, 121.0, 123.9, 127.0, 128.4, 128.6, 129.6, 131.1, 136.5 and 138.9 (C=CH and Ar-C), 157.1 [ArC(OBn)] and 166.7 (C=O).

Methyl 3-[2-(benzyloxy)-5-bromophenyl]-3-phthalimido-2-methylenepropanoate 117a[122]



To a solution of methyl *(Z)*-3-[2-(benzyloxy)-5-bromophenyl]-2-(bromomethyl)-2-propenoate **116a** (0.25 g, 0.57 mmol) in CH_3CN (3 mL) was added DABCO (0.08 g, 0.7 mmol) and the mixture stirred for 30 minutes after which potassium phthalimide (0.12 g, 0.65 mmol) was added and the mixture stirred at r.t. for 2 days. The crude mixture was concentrated under vacuum and chromatographed [PLC on silica gel; elution with hexane-EtOAc (3:1) afforded methyl 3-[2-(benzyloxy)-5-bromophenyl]-3-phthalimido-2-methylenepropanoate **117a** as a cream gel (0.24 g, 84%); [HRMS: *m/z* calculated for $C_{26}H_{21}BrNO_5$ (MH^+) 506.0603. Found 506.0594]; υ_{max}/cm^{-1} 1709 (C=O); δ_H (400 MHz; $CDCl_3$) 3.69 (3H, s, OCH_3), 5.04 (2H, s, OCH_2PH), 5.68 and 6.56 (2H, 2 x s, $C=CH_2$), 6.77 (1H, d, *J* = 8.7 Hz, ArH) 6.79 (1H, s, CHN), 7.24-7.29 (5H, overlapping m, ArH), 7.33 (1H, dd, *J* = 2.6 and 8.7 Hz, ArH), 7.46 (1H, d, *J* = 2.5 hz, ArH), 7.70 (2H, dd, *J* = 3.0 and 5.5 Hz, ArH) and 7.79 (2H, dd, *J* = 3.0 and 5.5 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 48.8 (CHN),52.2 (OCH_3), 70.3 (CH_2), 113,0, 113.7, 123.4, 127.1, 127.7, 127.9, 128.4, 129.1, 132.0, 132.1, 134.0, 136.1 and 136.4 (C=CH and Ar-C),154.6 [ArC(OBn)], 165.8 and 167.8 (C=O).

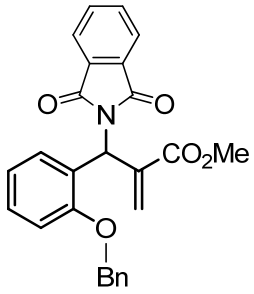
Methyl 3-[2-(benzyloxy)-5-chlorophenyl]-3-phthalimido-2-methylenepropanoate 117b



The procedure described for the synthesis of methyl 3-[2-(benzyloxy)-5-bromophenyl]-3-phthalimido-2-methylenepropanoate **117a** was followed using methyl *(Z)*-3-[2-(benyloxy)-5-chlorophenyl]-2-(bromomethyl)-2-propenoate **116b** (0.23 g, 0.57 mmol), CH_3CN (3 mL), DABCO (0.08 g, 0.7 mmol) and potassium phthalimide (0.12 g, 0.65 mmol). Work-up afforded

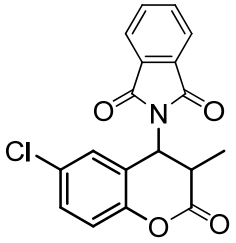
methyl 3-[2-(benzyloxy)-5-chlorophenyl]-3-phthalimido-2-methylenepropanoate **117b** as a cream gel (0.21 g, 79%); [HRMS: *m/z* calculated for $C_{26}H_{21}ClNO_5$ (MH^+) 462.1108. Found 462.1102]; υ_{max}/cm^{-1} 1710 (C=O); δ_H (400 MHz; $CDCl_3$) 3.69 (3H, s, OCH_3), 5.05 (2H, s, OCH_2PH), 5.69 and 6.57 (2H, 2 x s, $C=CH_2$), 6.80 (1H, s, CHN), 6.83 (1H,d, *J* = 8,7 Hz, ArH), 7.19 (!H, dd, *J* = 2.6 and 8.7 Hz, ArH) 7.25-7.28 (5H, overlapping m, ArH), 7.34 (1H, d, *J* = 2.6 Hz, ArH), 7.70 (2H, dd, *J* = 3.0 and 5.5 Hz, ArH) and 7.80 (2H, dd, *J* = 3.0 and 5.5 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 48.9 (CHN), 52.2 (OCH_3), 70.4 (CH_2), 113,2, 123.4, 125.7, 127.2, 127.3, 127.9, 128.4, 129.0, 129.3, 131.7, 134.0, 136.1 and 136.4 (C=CH and Ar-C), 154.2 [ArC(OBn)],165.8 and 167.8 (C=O).

Methyl 3-(2-benzyloxyphenyl)-3-phthalimido-2-methylenepropanoate 117c



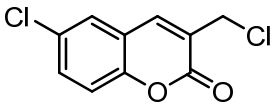
The procedure described for the synthesis of methyl 3-[2-(benzyloxy)-5-bromophenyl]-3-phthalimido-2-methylenepropanoate **117a** was followed using methyl *(Z)* 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylpropanoate **116c** (0.1 g, 0.28 mmol), CH_3CN (1.5 mL), DABCO (0.04 g, 0.35 mmol) and potassium phthalimide (0.06 g, 0.33 mmol). Work-up afforded methyl *3-(2-benzyloxyphenyl)-3-phthalimido-2-methylenepropanoate* **117c** as a cream oil (0.1 g, 86%); [HRMS: *m/z* calculated for $C_{26}H_{22}NO_5$ (MH^+) 428.1498. Found 428.1477]; υ_{max}/cm^{-1} 1708 (C=O); δ_H (400 MHz; $CDCl_3$) 3.66 (3H, s, OCH_3), 5.06 (2H, s, OCH_2PH), 5.65 and 6.53 (2H, 2 x s, $C=CH_2$), 6.85 (1H, s, CHN), 6.91 (2H, m, ArH) 7.19-7.29 (6H, overlapping m, ArH), 7.37 (1H, t, *J* = 6,3 Hz, ArH), 7.66 (2H, s, ArH) and 7.76 (2H, s, ArH) δ_C (100 MHz; $CDCl_3$) 49.2 (CHN),52.1 (OCH_3), 70.0 (CH_2), 111.9, 120.6, 123.3, 125.4, 127.2, 127.7, 128.4, 128.6, 129.2, 129.3, 131.8, 133.9, 136.7 and 137.0 (C=CH and Ar-C),155.6 [ArC(OBn)], 166.1 and 167.9 (C=O).

4-Phthalimido-3-methyl-3,4-dihydrocoumarin 118b



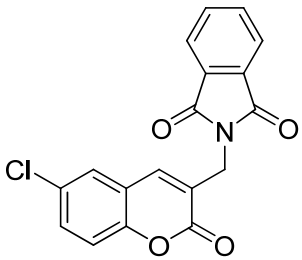
Methyl 3-[2-(benzyloxy)-5-chlorophenyl]-3-phthalimido-2-methylenepropanoate **117b** (0.2 g, 0.4 mmol) and pre-equilibrated 10% Pd/C catalyst (0.04 g) in absolute ethanol was hydrogenated at room temperature and atmospheric pressure. In a trial run, a very small quantity of the product was formed but in subsequent trials the desired product failed to form.

6-Chloro-3-(chloromethyl)coumarin 121



Conc. HCl (2.0 mL) was added to a solution of methyl 3-(2-benzyloxy-5-chlorophenyl)-3-hydroxy-2-methylenepropanoate **106b** (0.10, g, 0.2 mmol) in a mixture of AcOH (1.0 mL) and Ac_2O (1.0 mL). The mixture was boiled under reflux for 2h, allowed to cool to room temperature and then poured into ice-cooled water (5 mL). It was then stirred for ca. 30 min and the precipitate which formed was filtered off and washed with hexane to yield 6-chloro-3-(chloromethyl)coumarin **121** as a white solid (0.11 g, 80%), m.p. 100-102 ^{o}C (lit.[134] 111-114 ^{o}C); υ_{max}/cm^{-1} 1728 (C=O); δ_H (600 MHz; $CDCl_3$) 4.55 (2H, s, 1`-$CH_2$), 7.30 (1H, d, *J* = 8.7, ArH), 7.48-7.54 (2H, m, ArH) and 7.82 (1H, s, 4-H); $\delta_C$ (150 MHz; $CDCl_3$) 40.8 (C-1`), 118.1, 119.8, 126.4, 127.3, 130.1, 131.9, 139.6 and 151.9 (Ar-C) and 159.4 (C=O).

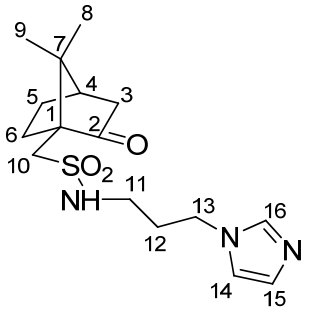
N-*[(6-Chlorocoumarin-3-yl)methyl]phthalimide 124*



6-Chloro-3-(chloromethyl)coumarin **121** (0.05 g, 0.22 mmol), was dissolved in CH_3CN and to the solution was added potassium phthalimide (0.05 g, 0.27 mmol) and the mixture stirred at room temperature for 2 days. The crude mixture was concentrated under vacuum and then water (3 mL) was added. The mixture was then filtered and the residue washed with water and dried yielding *N*-[(6-Chlorocoumarin-3-yl)methyl]phthalimide **124** as a white solid (0.06 g, 81%), m.p. 238-240 ^oC (lit.[122] 206-208 ^oC; [HRMS: *m/z* calculated for $C_{18}H_{11}ClNO_4$ (MH^+) 340.0377. Found 340.0379]; υ_{max}/cm^{-1} 1702 (C=O); δH (400 MHz; CD_2Cl_2) 4.77 (2H, s, NCH_2), 7.29 (1H, d, *J* = 8.8 Hz, ArH), 7.42-7.51 (3H, m, ArH), 7.79 (2H, s, ArH) and 7.90 (2H, s, ArH); δ_C (100 MHz; CD_2Cl_2) 37.5 (NCH_2), 118.3, 120.3, 123.8, 125.1, 127.4, 129.4, 131.8, 132.3, 134.7, 138.5 and 152.1 (Ar-C), 160.0 and 168.0 (C=O).

3.5. CUSTOMISED BAYLIS-HILLMAN CATALYSTS

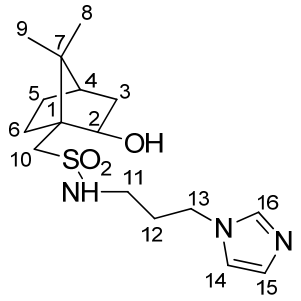
N-*[3-(1*H*-Imidazol-1-yl)propyl]-D-camphor-10=sulfonamide 129a*



A solution of camphor-10-sulfonyl chloride (2.5 g, 10 mmol), in dichloromethane (3 mL) was added dropwise to a stirred solution of 1-(3-aminopropyl)imidazole (1.2 mL, 10 mmol) and triethylamine (1.6 mL, 12 mmol) at 0 ^oC. After 20 minutes, the mixture was allowed to warm up to room temperature and then stirred for 6 hours. The resulting mixture was filtered to remove the precipitated salt; water (10 mL) was added to the filtrate and the organic layer extracted with dichloromethane (3 x 4 mL). The organic layer was washed with brine, dried with anhydrous magnesium sulfate and then concentrated under vacuum to produce a cream crystalline solid the *D-camphor-10-sulfonamide derivative* **129a** (2.49 g, 74%), m.p. 108-112 ^oC; [HRMS: *m/z* calculated for $C_{16}H_{26}N_3O_3S$ (MH^+) 340.1695. Found 340.1692]; υ_{max}/cm^{-1} 1742 (C=O); δ_H (600 MHz; $CDCl_3$) 0.86 and 0.99 (6H, 2 x s, 8- and 9-Me), 1.38-2.40 (9H, series of multiplets, 3-, 5-,

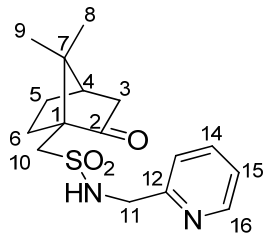
6- and 12-CH_2 and 4-H) 2.88 and 3.34 (2H, 2 x d, *J* = 15.1 Hz, 10-CH_2), 3.13 (2H, t, *J* = 5.8 Hz, 13-CH_2), 4.08 (2H, t, *J* = 4.0 Hz, 11-CH_2), 6.09 (IH, d, *J* = 6.4 Hz, NH), 6.95, 7.02 and 7.57 (3H, 3 x s, Ar-H); δ_C (150 MHz; $CDCl_3$) 19.4 and 19.8 (C-8 and C-9), 26.3 and 26.9 (C-5 and C-6) 31.5 (C-12), 40.2 (C-13), 42.6 (C-4), 42.9 (C-3), 43.8 (C-11), 48.7 (C-7), 49.1 (C-10), 59.0 (C-1), 119.0 (C-14), 128.9 (C-15), 137.2 (C-16) and 217.0 (C-2, C=O).

N-*[3-(1*H*-Imidazol-1-yl)propyl]-(*1*S)-exo-borneol-10-sulfonamide 127a*



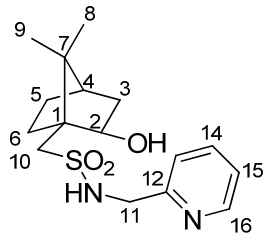
A solution of the camphor-10-sulphonamide **129a** (0.5 g, 1.5 mmol) in ethanol (2 mL) was added dropwise to a stirred solution of $NaBH_4$ (0.1 g, 2.7 mmol) in ethanol (4 mL) at 0 ^oC over 20 minutes. The mixture was allowed to warm to room temperature and stirred for 8 hours. Water (10 mL) was added and the organic layer extracted with dichloromethane (4 x 3 mL), washed with brine, filtered and concentrated under vacuum to produce the *bornyl sulfonamide derivative* as a colourless oil **127a** (0.49 g, 98%); [HMRS: *m/z* calculated for $C_{16}H_{28}N_3O_3S$ (MH^+) 342.1851. Found 342.1849]; υ_{max}/cm^{-1} 3550 (N-H); δ_H (600 MHz; $CDCl_3$) 0.80 and 1.04 (6H, 2 x s, 8- and 9-Me), 1.40-2.10 (9H, series of multiplets, 3-, 5-, 6- and 12-CH_2 and 4-H) 2.84 and 3.40 (2H, 2 x d, *J* = 13.7 Hz, 10-CH_2), 3.10 (2H, t, *J* = 5.8 Hz, 13-CH_2), 3.70 (1H, q, *J* = 7.0 Hz, 2-H), 4.08 (2H, t, *J* = 6.8 Hz, 11-CH_2), 6.31 (IH, s, NH), 6.93, 7.03 and 7.48 (3H, 3 x s, Ar-H); δ_C (150 MHz; $CDCL_3$) 19.9 and 20.5 (C-8 and C-9), 27.3 and 30.5 (C-5 and C-6) 31.7 (C-12), 39.1 (C-13), 39.8 (C-11), 43.6 (C-3), 44.3 (C-4), 48.7 (C-7), 50.3 (C-1), 51.8 (C-10), 76.3 (C-2,C-OH), 118.9 (C-14), 129.4 (C-15) and 137.3 (C-16).

N-*(2-Pyridylmethyl)-D-campor-10-sulfonamide 129b*



A solution of camphor-10-sulfonyl chloride (1.25 g, 5 mmol), in dichloromethane (3 mL) was added dropwise to a stirred solution of 2-picolyamine (0.52 mL, 5 mmol) and triethylamine (0.8 mL, 6 mmol) at 0 ^{o}C. After 20 minutes, the mixture was allowed to warm up to room temperature and then stirred for 6 hours. The resulting mixture was filtered to remove the precipitated salt. Water (10 mL) was added to the filtrate and the organic layer extracted with dichloromethane (3 x 4 mL). The organic layer was washed with brine, dried with anhydrous magnesium sulfate and then concentrated under vacuum to produce *N-(2-Pyridylmethyl)-D-campor-10-sulfonamide* **129b** as a brown oil (1.44 g, 89%); [HMRS: *m/z* calculated for $C_{16}H_{23}N_2O_3S$ (MH^+) 323.1429. Found 323.1430]; υ_{max}/cm^{-1} 1740 (C=O); δ_H (400 MHz; $CDCl_3$) 0.82 and 0.99 (6H, 2 x s, 8- and 9-Me), 1.38-2.40 (9H, series of multiplets, 3-, 5-, 6- and 11-CH_2 and 4-H) 2.91 and 3.46 (2H, 2 x d, *J* = 15.1 Hz, 10-CH_2), 4.47 (2H, q, *J* = 3.0 and 3.8 Hz, 11-CH_2), 6.29 (1H, t, *J* = 5.9 Hz, NH), 7.17 (1H, dt, J = 4.1 and 8.5 Hz, ArH) 7.36 (1H, d, *J* = 7.7 Hz, ArH) 7.66 (1H, td, *J* = 1.9 and 7.66 Hz, ArH) and 8.50 (1H, d, *J* = 5.2 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 19.5 and 19.8 (C-8 and C-9), 26.2 and 26.9 (C-5 and C-6) 42.6 (C-4), 42.7 (C-3), 48.3 (C-11), 48.5 (C-7), 50.0 (C-10), 59.0 (C-1), 122.0 (C-13), 122.5 (C-14), 136.8 (C-15), 149.1 (C-16), 156.1 (C-12) and 216.2 (C-2, C=O).

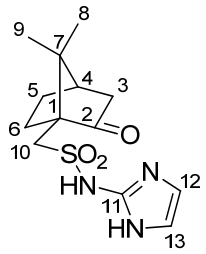
N-*Pyridin-2-ylmethyl)-(1S)-exo-borneol-10-sulfonamide 127b*



A solution of the camphor-10-sulfonamide **129b** (0.48 g, 1.5 mmol) in ethanol (2 mL) was added dropwise to a stirred solution of $NaBH_4$ (0.1 g, 2.7 mmol) in ethanol (4 mL) at 0 ^{o}C over 20

minutes. The mixture was allowed to warm to room temperature and stirred for 8 hours. Water (10 mL) was added and the organic layer extracted with dichloromethane (4 x 3 mL), washed with brine, filtered and concentrated under vacuum to produce, as a colourless oil, the borneol-10-sulfonamide **127b** (0.45g, 92%); υ_{max}/cm^{-1} 3560 (C=O); δ_H (400 MHz; $CDCl_3$) 0.74 and 0.99 (6H, 2 x s, 8- and 9-Me), 1.04-2.00 (9H, series of multiplets, 3-, 5-, 6- and 11-CH_2 and 4-H) 2.81 and 3.42 (2H, 2 x d, *J* = 13.9 Hz, 10-CH_2), 4.07 (1H, dd, *J* = 4.1 and 8.1 Hz, 2-H), 4.44 (2H, dd, *J* = 2.5 and 7.4 Hz, 11-CH_2), 5.29 (IH, s, NH), 7.23-7.32 (2H, m, ArH) 7.70 (1H, td, *J* =1.8 and 7.7 Hz, ArH) and 8.55 (1H, t, *J* = 5.0 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 19.8 and 20.5 (C-8 and C-9), 27.3 and 30.3 (C-5 and C-6) 39.2 (C-4), 44.3 (C-3), 47.8 (C-11), 48.7 (C-7), 50.3 (C-1), 52.3 (C-10), 76.0 (C-2), 122.2 (C-13), 122.9 (C-14), 137.2 (C-15), 149.2 (C-16) and 155.3 (C-12).

N-*(1*H-*imidazol-2-yl)-D-camhor-10-sulfonamide 129c*



A solution of camphor-10-sulfonyl chloride (2.5 g, 10 mmol), in acetonitrile (25 mL) was added dropwise under nitrogen to a stirred solution of 2-aminoimidazole sulfate (2.6 g, 10 mmol) and KOH (1.2 g, 20 mmol), DMAP (0.24 g, 2 mmol) in acetonitrile (25 mL) at 0 ^oC and the solution was stirred for 1 hr. Water (12.5 mL) was then added and the resulting mixture extracted with EtOAc (2 x 30 mL). The organic layer was dried over $MgSO_4$ and the solvent removed under vacuum to produce, as a brown oil, the camphor-10-sulfonamide **129c** (1.9 g, 64%); [HMRS: *m/z* calculated for $C_{13}H_{20}N_3O_3S$ (MH^+) 298.1225. Found 298.1224]; υ_{max}/cm^{-1} 1741 (C=O); δ_H (600 MHz; $CDCl_3$) 0.83 and 1.10 (6H, 2 x s, 8- and 9-Me), 1.38-3.40 (9H, series of multiplets, 3-, 5-, 6- and 10-CH_2 and 4-H), 6.77 (2H, d, *J* = 3.8 Hz, ArH); δ_C (150 MHz; $CDCl_3$) 20.1 and 20.3 (C-8 and C-9), 25.7 and 27.8 (C-5 and C-6) 43.6 (C-3), 44.0 (C-4), 48.3 (C-10), 48.9 (C-7), 59.5 (C-1), 114.1 (C-12 and 13), 148.8 (C-11) and 218.4 (C-2, C=O).

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