Design, development and evaluation of novel lead compounds as HIV-1 enzyme inhibitors

THESIS

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Abstract

This project has been concerned with the application of the Baylis-Hillman methodology to the synthesis of medicinally important diketo acid analogues (cinnamate ester-AZT conjugates and 3-hydroxy ester-AZT conjugates) as dual-action HIV-1 IN/RT inhibitors; and on exploratory studies in the preparation of 3-(amidomethyl)-(1*H*)-2-quinolones as PR inhibitors; and (1*H*)-2-quinolone-AZT conjugates as dual action IN/RT inhibitors. A series of Baylis-Hillman adducts has been prepared, typically in moderate to excellent yield, by reacting 2-nitrobenzaldehyde with methyl acrylate, ethyl acrylate and methyl vinyl ketone in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO). Subsequently, various transformations that include conjugate addition of primary and secondary amines to the α,ß-unsaturated moiety to obtain 2-(aminomethyl)-3-hydroxy-3-(2-nitrophenyl)propanoate derivatives, effective S_N2' substitution of the BH ß-hydroxy by a Vilsmeier-Haack *in situ*-generated chloride to afford Baylis-Hillman allyl chlorides, iron in acetic acid-catalyzed cyclisation to 3-acetoxymethyl-(1*H*)-2-quinolone derivatives were achieved.

Thus, using the Baylis-Hillman methodology, two nuanced classes of diketo acid analogues were constructed. These involved conjugating appropriate propargylamine derivatives with AZT using the 'click' reaction. In an exploratory study, the quinolone derivative, precisely 3-acetoxymethyl-(1*H*)-quinol-2-one, was transformed into 3-hydroxymethyl-(1*H*)-quinol-2-one using potassium carbonate in a mixture of methanol and water (1:1). Following successful hydrolysis, the resulting alcohol was transformed to the corresponding chloride, 3-chloromethyl-(1*H*)-quinol-2-one, using thionyl chloride. Subsequent nucleophilic substitution afforded 3-(aminomethyl)-(1*H*)-2-quinolone derivatives which were subsequently transformed to 3-(amidomethyl)-(1*H*)-2-quinolones; and 3-[(propargylamino)-methyl]-(1*H*)-quinol-2-one as precursors to quinolone-AZT derivatives. All compounds were characterized by NMR, IR, and where appropriate, high resolution MS.

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Finally, I dedicate this thesis to my late uncle Tlhanka Freddy Marutha.

“Morena boloka setshaba sa heso”

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1. Introduction

1.1. Human Immunodeficiency Virus

The Human Immunodeficiency Virus (HIV), the etiological agent of Acquired Immunodeficiency Syndrome (AIDS), is a member of the lentivirus genus *retroviridae* and exists in two strains, HIV-1 and HIV-2, the former being the deadly, dominant form that accounts for nearly 90% of global HIV/AIDS deaths.[1,2] This difference in transmission and virulence reflects the variety of HIV virus pathogenic potentials.[3]

HIV-1 has sub-strains that can be classified on the basis of viral sequence into four groups: the major group (M), the outlier group (O), and two new groups (N and P). The M group is responsible for more than 90% of HIV-1 infections worldwide and it comprises at least nine genetically distinct subtypes A, B, C, D, F, G, H, J, and K. Sometimes hybrid (mosaic) viruses arise which may not survive long. These exist as a combination of two of the above subtypes. However, those that infect more than one individual are known as "circulating recombinant forms" or CRFs.[1, 4, and 5]

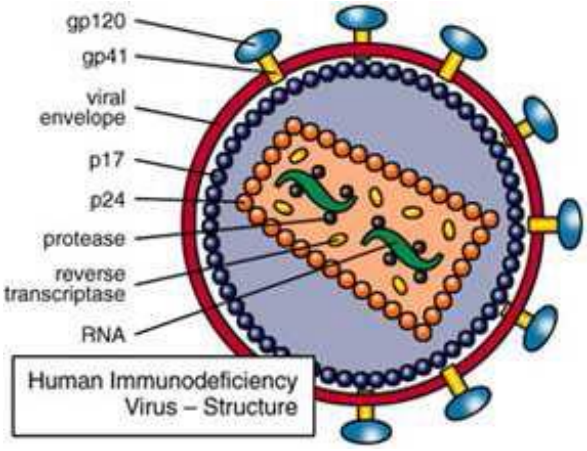


Figure 1. Structure of an HIV virion (Reproduced with permission) [6]

As illustrated in Figure 1, HIV is an enveloped retrovirus within which is enclosed two copies of the RNA genome which are reverse transcribed into DNA in the infected cell and then integrated within chromosomal DNA (cDNA). The integrated viral DNA is then transcribed into messenger RNA (mRNA), which is used in the direct synthesis of viral proteins after being carried out of

the cell nucleus into the cytoplasm. After assembly of viral proteins with the viral RNA's and other essential viral components, the new viral progeny acquires its envelope by budding at the cell surface and vacating the infected host cell.[2]

Invasion of the host cell is facilitated by glycoproteins, gp120 and gp41 in the viral envelope (Figure 2). The gp120 binds with high affinity to the cell surface molecule CD4 thereby drawing the virus to CD4 T cells and to dendritic cells and macrophages. Before fusion and entry into the cell, gp120 must also bind to co-receptors in the membrane of the host cell called chemokine receptors. Two chemokine receptors: CCR5, predominantly expressed on dendritic cells, macrophages, and CD4 T cells, and CXR4, expressed on activated T cells, are the major co-receptors for HIV. After binding of gp120 to receptors and co-receptors, the gp41 then causes fusion of the viral envelope and the plasma membrane of the cell, allowing the viral genome and associated viral proteins to enter the cytoplasm. [2, 5, 7]

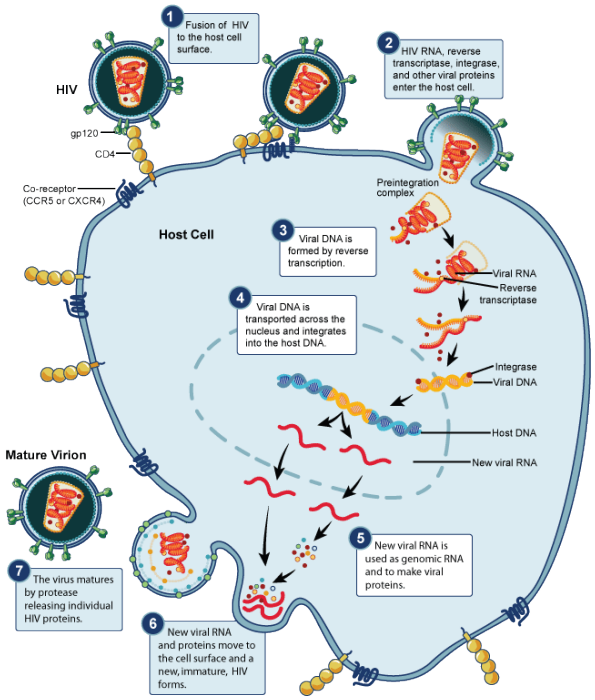


Figure 2. HIV replication cycle (Reproduced with permission).[8]

Epithelial cells that express chemokine receptors CXR4 and CCR5, heparan sulfate proteoglycan (HS), and galactosyl ceramide (GalCer) are HIV infection prone. Infection occurs as a result of HIV exposure to mucosal surfaces covered by two types of epithelial cell lining. In the human

body, the virus binds to CD4 presenting cells as well as to several types of antigen presenting cells. It is the infection of helper T cells (CD4+ cells) that results in clinical problems.[6] HIV infections generally occur through intimate contact of body fluids of an infected person with an uninfected person. The virus is transmitted through unprotected sexual intercourse, the use of contaminated needles in intravenous drug delivery, the therapeutic use of infected blood or blood products, and perinatal fluid exchange between a mother and her foetus.[1-7]

Most people infected with HIV eventually progress to AIDS. This is a condition in humans in which the immune system is compromised, leading to immune deficiency and leaving patients vulnerable to opportunistic infections from a variety of pathogens such as bacteria, fungi, and viruses.[2,4,10] Sufferers may live with the virus for an average of eight to ten years before progressing to AIDS. The progression period depends, to a great extent, on the HIV-1 subtype, with a longer latent period in subtype A than other subtypes. [3]

Genetic variations in the Human Leukocytes Antigen (HLA) type of the host may modify the disease outcome. HLA-B57 and HLA-B27 are associated with slower progression. Homozygosity of HLA class I expression is associated with more rapid disease progression, presumably because T cell response to infection is less diverse. A small proportion of people seroconvert, making antibodies against many HIV proteins, and do not seem to experience progression of the disease in that they do not exhibit immune deficiency characteristics, while still others, following HIV exposure, remain virus free.[3, 5]

1.2. HIV enzymes as potential therapeutic targets

Chemotherapeutic approaches to suppress replication of the HIV virus and defer the progression to AIDS have resulted in a profound reduction in morbidity and mortality as well as in the transmission of the virus, most notably in effective inhibition of mother-to-child transmission.[17] However, effectiveness of treatment varies according to individuals thereby requiring individualized regimens. Furthermore, the development of drug-resistant strains resulting from viral mutations also necessitates the need for ongoing research.[12, 13]

Replication of HIV-1 in host cells, like other retroviruses, depends on three essential viral enzymes: reverse transcriptase (RT), protease (PR) and integrase (IN). The HIV genome contains nine genes (Table 1) flanked by long terminal repeat (LTR) sequences which are required for the integration of the provirus into the host cell DNA and which contain binding sites for the gene regulatory proteins that control expression of the viral genes.[5,12,13]

Table 1. Components of the HIV-1 genome and their functions.[2,5,13]

Gene		**Gene function**
Gag	Group-specific antigen	Encodes structural proteins of the viral core
Pol	Polymerase	Encodes enzymes (protease, reverse transcriptase and integrase) involved in viral replication and integration
Env	Envelope	Encodes the viral envelope glycoproteins gp120 and gp41.
Tat	Transactivator	Encodes transcription of viral RNA from provirus
Rev	Regulator of viral expression	Encodes a regulator of expression of viral proteins
Nef	Negative-regulation factor	Induces, inhibits and down-regulates immunity
Vif	Viral infectivity	Provides defence against natural cellular immunity
Vpr	Viral protein R	Enhances viral production and release
Vpu	Viral protein U	Facilitates maturation of progeny viral particles and their efficient release

The three major genes *gag*, *pol* and *env* contain information needed for replication, and antiretroviral therapies (ART) developed so far have targeted the functions facilitated by these genes. HIV protease cleaves polyprotein translated from *gag* and *pol* mRNAs to generate the core proteins and enzymes of mature virions, whereas the *env*, encodeds a proteinwhich is cleaved by a host cell protease into gp120 and gp41, which are then assembled in the viral envelope as trimmers. Reverse transcriptase and protease have been particular targets for antiretroviral therapy (ART) and the use of combinations of inhibitors targeting these enzymes profoundly decreases the viral load for a prolonged period and defers progression to AIDS. [13-15]

The paramount need for the continuous development of antiretroviral drugs is largely influenced by mutations during viral replication that contribute to resistance to current ART, thus resulting in treatment failure. The introduction of highly active antiretroviral therapy (HAART) has improved disease prognosis and contained opportunistic diseases for patients who have adhered to treatment. HAART typically involves the use of two nucleoside reverse transcriptase inhibitors (NRTIs) plus either a protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI). HAART targets intracellular steps in the virus life cycle orchestrated by viral reverse transcriptase and protease. Health complications associated with HAART have prompted the development of novel antiretroviral agents that inhibit entry of the HIV into the target cell by preventing the binding of the host cell CD4 receptor with HIV envelope gp120 by blocking the chemokine receptors, and/or inhibiting fusion into the cell facilitated by gp41.[16,17]

1.2.1. ***HIV-1 protease***

HIV-1 protease is a homodimer comprising two 99 amino acid chains and belongs to the class of aspartic proteases characterized by the homology sequence Asp-Thr-Gly. It functions as a homodimer with a single C_2-symmetric active site which expands upon binding with the substrate. Each monomer's unit contributes an Asp-Thr-Gly sequence and contains an extended ß–sheet region, termed the "flap", that covers the substrate binding site which contains the critical aspartyl residues Asp-25 and Asp-25´ at the bottom of the cavity (Figure 4).[18, 19] HIV-1 PR is essential for the assembly and gathering of progeny virions as well as catalyzing cleavage

of viral polyprotein precursors into individual, mature proteins. Successful inactivation of the viral PR leads to the production of immature and non-infectious virus particles.

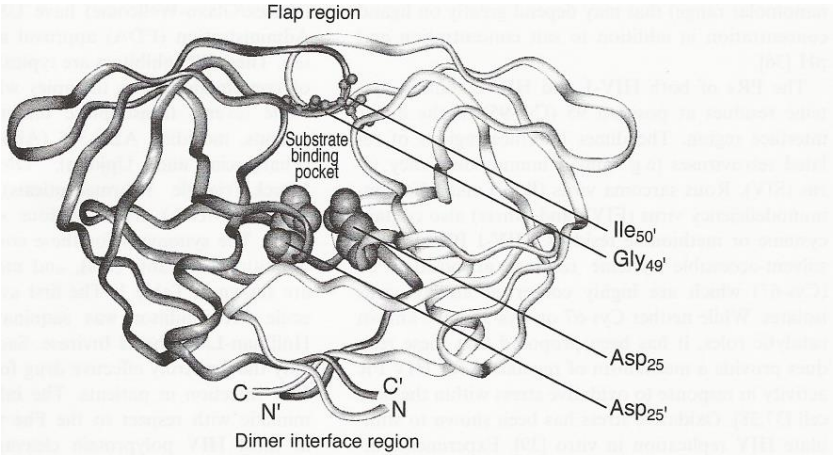


Figure 4. A schematic structure of HIV-1 protease (Reproduced with permission).[20]

HIV-1 PR catalysis relies on the presence of one protonated and one unprotonated aspartic residue, flanking a water molecule which serves as a catalytic nucleophile. The two aspartic residues together with water, facilitate cleavage of the polyprotein substrate in the protease cavity. [19,20]

The structurally equivalent hydrophobic binding sites on the protease enzyme are denoted S_1, S_2,……,S_n whereas P_1, P_2,……,P_n denote corresponding amino acid residues of the peptide substrate (Figure 5). The protease binding sites and amino acid peptide residues are counted relative to the scissile bond which cleaves during hydrolysis.[18-20]

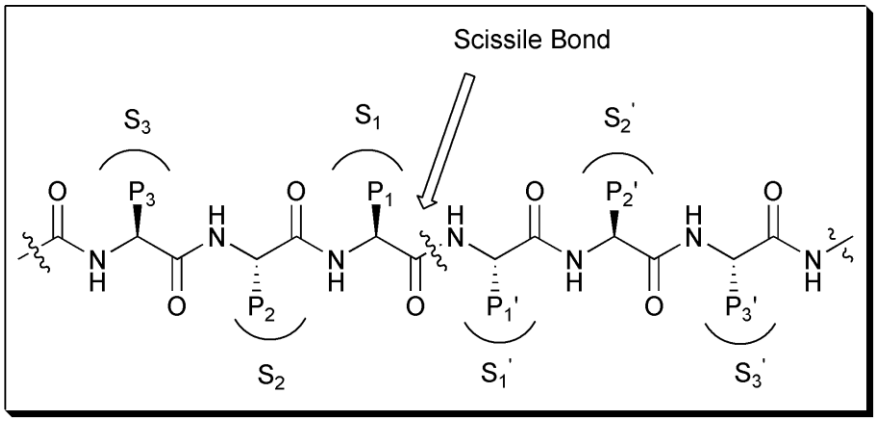


Figure 5. Standard nomenclature for HIV-PR (Reproduced with permission).[19]

1.2.2. *HIV-1 reverse transcriptase*

HIV-1 RT, a DNA polymerase enzyme,[18] plays a crucial role in the life-cycle of the virus, by transcribing the viral RNA to proviral DNA which is subsequently integrated into the host cell chromosome. Therapy against RT includes the use of non-nucleoside reverse transcriptase inhibitors (NNRTIs) and nucleoside reverse transcriptase inhibitors (NRTIs) that interfere with the capacity of RT polymerase to polymerize a DNA strand from either an RNA or DNA template.[20-22]

HIV-RT is an asymmetric heterodimer containing p66 (560 amino acids long) and p51 (440 amino acids long) domains that share a common amino terminus. The p66 domain is comprised of two spatially distinct domains, polymerase and RNase H as shown in Figure 6. The polymerase domains resemble a right-hand structure with fingers, palm and thumb subdomains. For replication to commence RT requires both a primer (host cell tRNA) and a template (viral RNA genome). The p66 unit of the heterodimer contains the active sites for both polymerase and RNase H activities whilst the p51 unit provides a structural support role. The replication process is outlined elsewhere.[23,24]

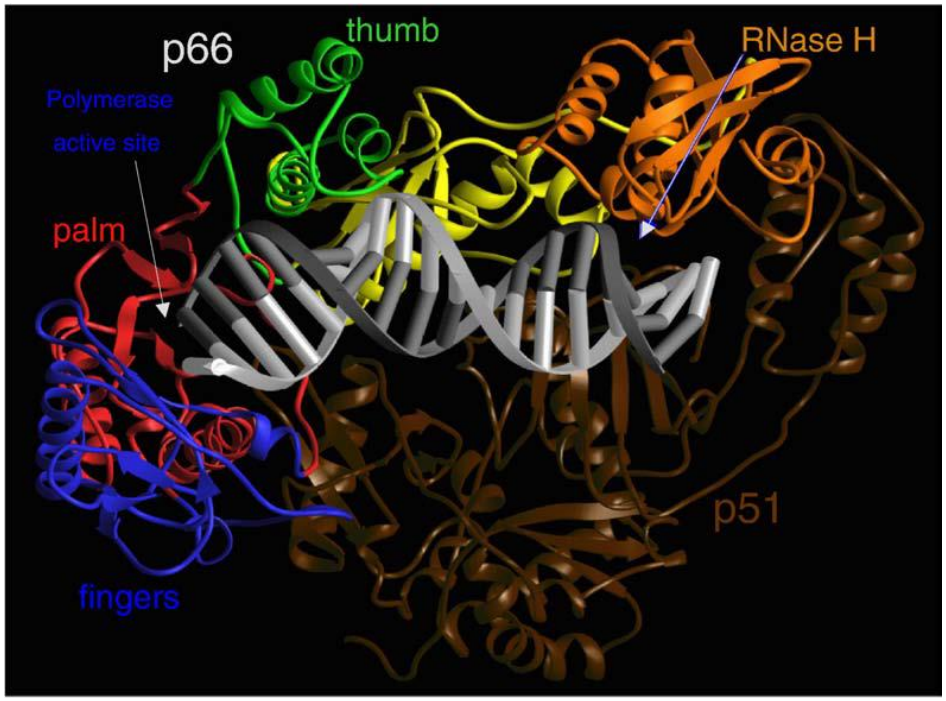


Figure 6. Ribbon representation of the X-ray crystallographic structure of HIV-1 RT (Reproduced with permission).[24]

1.2.3. *HIV-1 Integrase*

As illustrated in Figure 7, HIV-1 IN is a tridomain enzyme consisting of an *N*-terminal domain that expresses a His2.Cys2 motif that chelates zinc, a core domain that has catalytic triad enzymes (DDE) for enzymatic activities, and a *C*-terminal domain with an Src-homology3-like (SH3) fold for binding DNA non-specifically. The dimeric catalytic core domain contains the invariant acidic residues, Asp-64, Asp-116, and Glu-152, which are arranged in close proximity to coordinate the divalent Mg^{2+} metal and constitute the active site. The *N*-terminal domain of HIV-1 IN possesses the conserved pair of His and Cys residues in a motif that consists of alpha helices which can bind zinc. The *C*-terminal domain is responsible for non-specific binding to the DNA.[25]

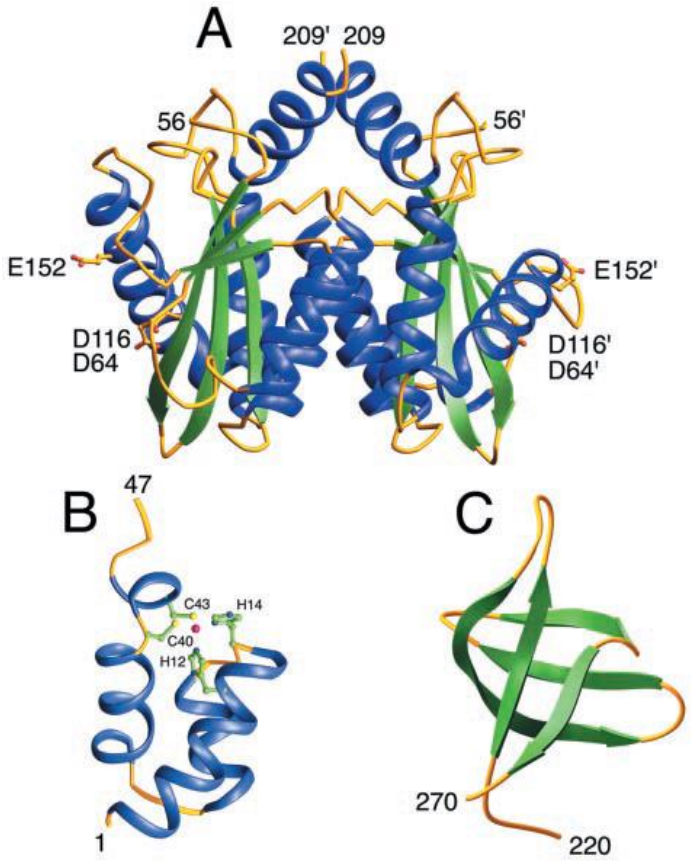


Figure 7. Structure of the tridomain HIV-1 integrase enzyme. A, the catalytic core domain; B, the *N*-terminal domain; C, the *C*-terminal domain (Reproduced with permission).[25]

HIV-1 IN is responsible for the irreversible insertion of the viral DNA into the target cell cytoplasm, maintainance of the HIV-1 genome in the infected cell, and efficient expression of viral proteins prior to replication. The process of DNA integration can be divided into three steps: (i) the assembly of the integrase on the viral DNA; (ii) endonucleolytic cleavage of the first two nucleotides from the 3´-terminal of the viral DNA; and (iii) strand transfer of recessed viral DNA to the host cell DNA.[26] All INIs (integrase inhibitors) have dual pharmacophores, one that is involved in a metal binding site which sequestrates the essential magnesium cofactors in the IN active site and the other, a hydrophobic group that selectively binds to certain complexes between the viral DNA and the integrase. The two pharmacophores are crucial for inhibition and selectivity, respectively.[1]

1.3. Social and economic impacts of HIV/AIDS.

Human Immunodeficiency Virus type 1 (HIV-1) and Acquired Immunodeficiency syndrome (AIDS) have cost the lives of millions of people around the globe thereby challenging the medical and scientific communities to develop antiretroviral drugs that directly target viral enzymes or processes essential for viral replication. Problems associated with patient non-compliance and the development of drug resistance led to the application of highly active antiretroviral therapy (HAART) which has resulted in a significant decline in the mortality and morbidity associated with HIV-1 infection. HAART comprises the use of a fixed dose combination of tablets containing at least two drugs that can be taken once daily. This therapy represents a complete ARV therapy and has become the primary treatment for first-time treatment takers.[27] Other developments aim to reform, improve and expand established therapeutic methods to attain greater potency. This entails, but is not limited to, patient medical records, pandemic assessments, monitoring or surveillance and evaluation. Such measures help to strengthen commitment, mobilize directly and indirectly affected parties, and inform interventions – scientific, medicinal, and social.[28]

These initiatives serve a crucial role in achieving the United Nations (UN) vision of zero new HIV infections and zero AIDS-related deaths as enshrined in the Millenium Development Goals (MDG). Antiretroviral therapy is estimated to have prevented 5.5 million deaths in low- and

middle-income countries from 1995 until 2012, reduced the risk of HIV transmission by up to 96%, reduced morbidity rate, and promoted social welfare. Africa, in particular the Sub-Saharan region, has the largest antiretroviral therapy programme with 7.6 million patients receiving the treatment (see Figure 8). Although recent World Health Organization (WHO) guidelines on HIV treatment have promoted access to life-saving treatment, shocking statistics still reveal that large populations, mostly in countries which cannot afford medication or where the medication is inaccessible due to social and economic factors, remain untreated. Therefore, considerable work remains to reach all who are eligible for treatment under the recent treatment framework.[29,30]

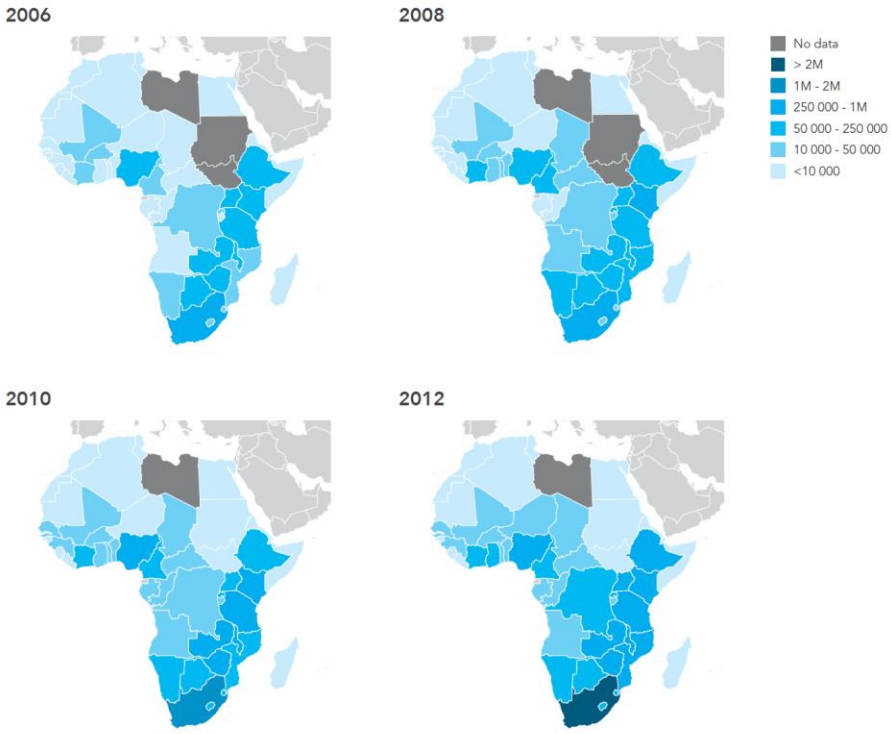


Figure 8. Number of people receiving antiretroviral therapy, 2006-2012 (Reproduced with permission).[31]

Despite ongoing efforts by governments, NGO's, and social organisations to address the impact of HIV/AIDS, the lack of effective regulation in the pricing of drugs by pharmaceutical industries remains a problem in accessing medication. High drug costs are attributed to the escalating costs of research and development and the lengthy approval protocols and requirements even though a number of financial incentives are being introduced by economically viable governments.

Recognizing the need for fast processing and efficient dissemination of AIDS therapy, drug development protocols were reformed to mitigate time and cost factors, but these drugs remain as some of the most expensive ever produced. In light of all the complex factors involved, price control cannot be envisioned easily as it has the potential (if not well premised) to affect drug innovation rate, funding to research and development, as well as the commitment and well-being of pharmaceutical companies.[30]

In the South African context, in addition to the well-known lack of political, which resulted in the delay of lifesaving ARV roll out to public health institutions, intellectual property rights monitored by the World Trade Organisation (WTO) protect pharmaceutical companies from the manufacture and importation of cheaper versions of drugs. The South African government had to roll out their first ARV program with an expensive and relatively outdated complex regimen in spite of a fixed dose therapy being available in India for a quarter of the price charged by big pharmaceutical companies.[32] Nonetheless, early ARV introduction at whatever cost, particularly for the prevention of mother-to-child treatment (PMTCT), ultimately saves money by reducing future HIV infections with the associated costs such as counseling, testing, and provision of life-long antiretroviral treatment for children born positive in the absence of this programme.[33]

Despite successful control in economically and politically stable areas, the HIV/AIDS epidemic continues to grow in less resourced areas and mainly affects poor people. Educational efforts to mitigate the spread represent a long-term approach, whilst medicinal and prophylactic approaches offer immediate intervention. It is therefore imperative to explore ways of reducing the costs of these critical drugs as well as developing new ones to address the ongoing challenges of resistance to established drugs.[29-31] An increasing number of countries have scaled up their HIV treatment and educational programmes. At the end of 2012, 9.7 million people had access to antiretroviral therapy in resource-limited areas out of a seemingly ambitious 2015 target of 15 million. [34]

According to De Clercq,[35] almost 40 antiretroviral compounds have been officially approved for HIV therapy; these include: (i) *nucleoside reverse transcriptase inhibitors (NRTIs)*: zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, and emtricitabine; (ii) *nucleotide reverse transcriptase inhibitors (NtRTIs)*: tenofovir and disoproxil fumarate; (iii) *non-nucleoside reverse transcriptase inhibitors (NNRTIs)*: nevirapine, delavirdine and efavirenz; and (iv)

protease inhibitors (PRIs): saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir (combined with ritonavir in a 4:1 ratio) and atazanavir; and the (v) *viral entry inhibitor*, enfuvirtide.

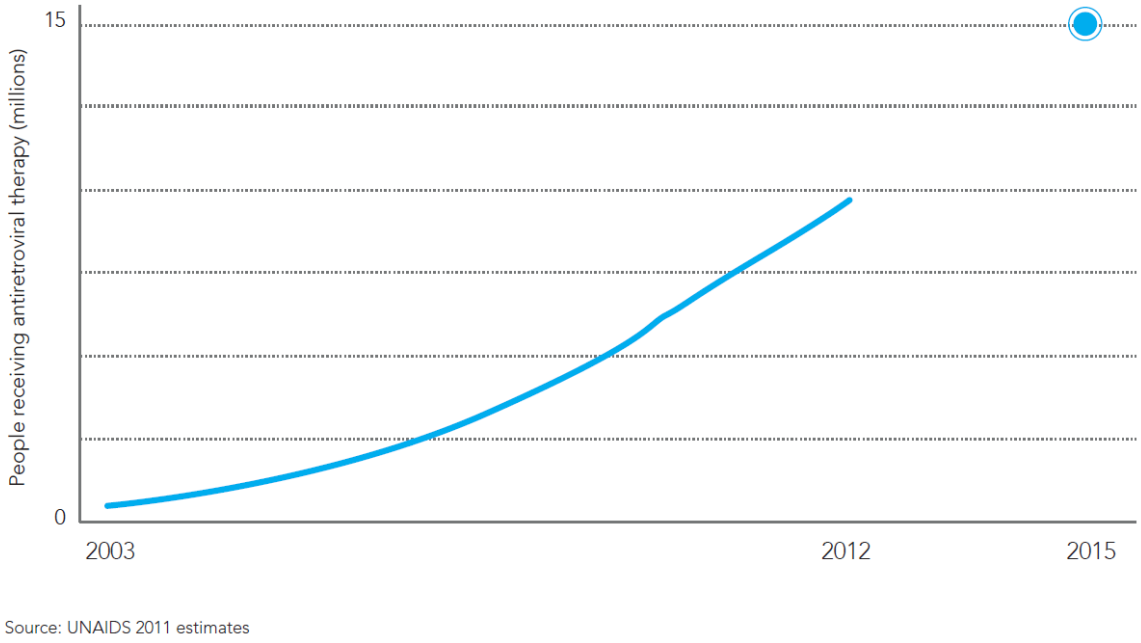


Figure 9. Graph representing number of people accessing HIV treatment in resource-limited areas (Reproduced with permission).[34]

HIV/AIDS affects a definable population subgroup because it is primarily transmitted through intimate contact with body fluids.[11] AIDS clinical symptoms include an aggressive form of *Karposi's sarcoma*, opportunistic *Pneumocystis carinii* pneumonia,[1] and persistent lymphadenopathy accompanied by a definitive and profound decrease in the level of the CD4 T cells. Following an HIV infection, the CD4 cell count decreases over time and cytotoxic CD8 cells (T8 cells) either remain constant or increase. A CD4 cell count < 200 cells/µL or a CD4 percentage to total lymphocytes of < 14 is a descriptive AIDS sign. [11]

HIV/AIDS impacts beyond the health of individuals to households, communities, and the development and growth of nations, many of which are in the Sub-Saharan region. The high rate of HIV infections and AIDS sufferers is a formidable challenge. Social factors such as economic, social, behavioral, medical care and application of research influence human health, life

expectancy, and the prevalence of disease. In response to HIV/AIDS, local and international governments have formulated strategic plans to mitigate this epidemic. This is evidenced by allocation of a significant fraction of their national budgets to health care, interventions to bridge health care disparities, determination to develop health care systems, expanded access to health care, promotion of a culture of novel research, and development of research institutions.[36-41]

Figure 10 illustrates global prevalence rates per region. It can be noted that the southern part of Sub-Saharan Africa, although consisting of only 9 countries, is the hardest hit region.

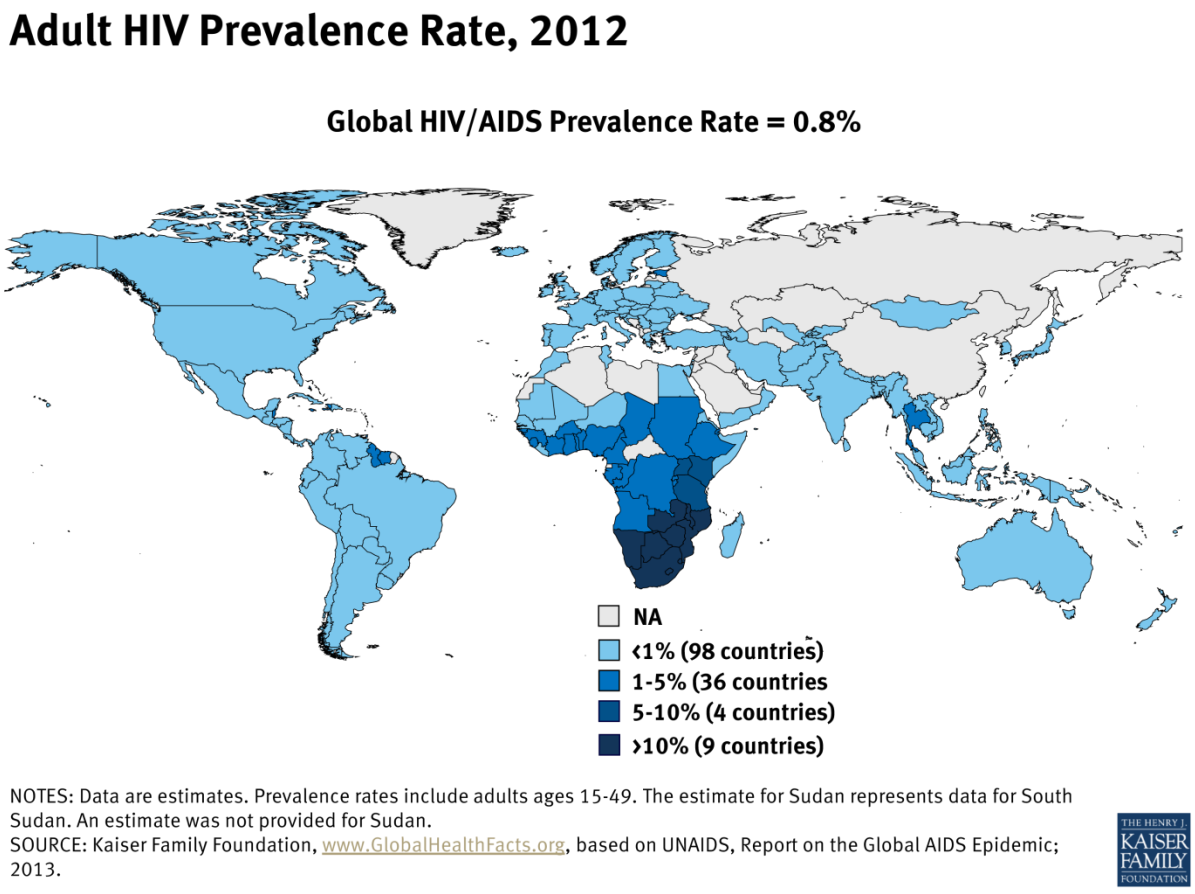


Figure 10. Global regional HIV adult prevalance rates (Reproduced with permission).[40]

It was estimated that two-thirds of the 35 million people living with HIV/AIDS reside in Sub-Saharan Africa with a rising majority in rural areas, impacting mainly economically-active adults, thus posing a serious health and social challenge.[37,38] International and local organizations

have committed to raising awareness of the urgent medical need in the Sub-Saharan African region.

This has led to a decline in the number of new HIV infections and AIDS related deaths, and an astonishing increase in the number of people receiving treatment in resource poor countries. As a result extensive attention is being focused on the rapid development and dissemination of medication. [39,40]

Out of the twenty-one highly communicable diseases identified by Benatar,[36] HIV/AIDS is by far the most significant causal agent of death across all age groups. He further argues that the failure to implement mother-to-child prevention therapy (MTCPT), despite the fact that it is among the most effective methods of preventing infection (after abstinence and prophylactic use), contributed to a high infection rate among children, the majority of whom die before adolescence.

Furthermore, in spite of being one of the best economies in Africa and competing globally, South Africa is among the countries most severely affected by the AIDS epidemic with the largest number of HIV infections (5.7 million) in the world by 2009.[41] Consequently, the reduction in the workforce, and the increase in mortality, morbidity and orphan rates have profoundly affected all aspects of society and development. Comprehensive and effective programmes formulated for the treatment and prevention of HIV infection have been hampered by the prevalence of high-risk sexual behavior largely influenced by drug and alcohol abuse, promiscuity, the expense of bottle-feeding over breast-feeding, extensive sexual abuse against children and women, a dearth of financial and human resources, adverse side-effects of antiretroviral drug therapy on poor and nutritionally deficient populations and drug resistance.[36]

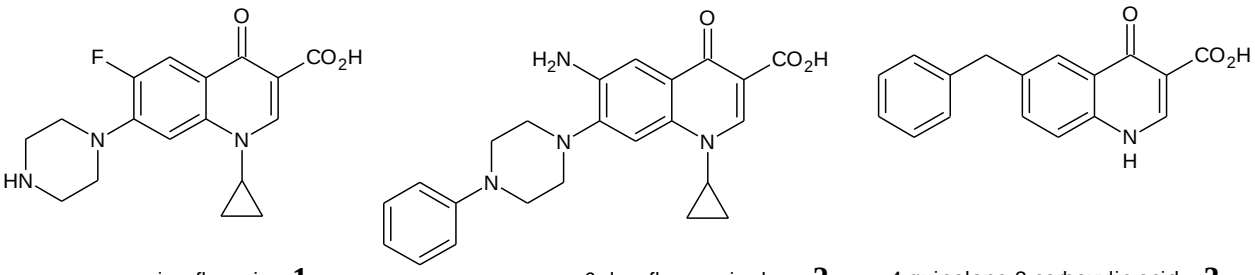
Biomedical intervention to address the epidemic must run concurrently with addressing other important endemic social challenges, such as extreme poverty, poor sanitation and nutrition, moral degeneration, and promiscuity. These factors influence the spread of HIV and ignorance of them will subject us to a circular race.[36,39,41.]

1.4. Quinoline and quinolone scaffolds in Human Immunodeficiency Virus drugs.

The development of antiretroviral drugs is a dynamic process which involves, on one hand, the identification and synthesis of molecular targets for chemotherapeutic intervention and, on the other, evaluation of the potency of these molecular targets relative to clinical counterparts. Various strategic trials which have been successfully pursued included several targets, *viz*, CD4 cells as the primary route for viral entry into the host cell, gp120 that facilitates viral absorption into the cell, CXCR4 and CCR5 as the co-receptors for viral entry, gp41, and the critical enzymes, HIV-1 reverse transcriptase (RT), integrase (IN) and protease (PR).[20-24,42]

From their classical use as antibacterial drugs, quinoline or quinolone-based natural products have progressed to playing a pivotal role in the search for a wide range of chemotherapeutics. Natural quinoline or quinolone-based products of the South American *Cinchona* species, *Rubiaceae,* Australian *Melicope* and *Rutaceae,* have *inter alia,* served as molecular models that motivated the development of quinoline or quinolone-based antimicrobial drugs.[42,43]

Quinoline and quinolone derivatives such as those displayed in Figure 11 have been used predominantly against urinary tract, gastrointestinal, respiratory, abdominal, skin, and soft tissue infections. They have also emerged as a significant class of anti-HIV drugs.[44-46]



ciprofloxacin **1** 6-desofluoroquinolone **2** 4-quinolone-3-carboxylic acid **3**

Figure 11. Representative examples of quinolone-based anti–HIV compounds.

Fluoroquinolone derivatives, *e.g.*, ciprofloxacin **1**, were the first generation of quinolone derivatives to be assessed against HIV and showed remarkable activity against chronically infected cells. Several fluoroquinolones displayed the potential to reduce Tumor Necrosis Factor-α (TNF-α), reduce activation of Nuclear Transcription Factor-kB (NF-kB), reduce LTR-driven gene expression, significantly reduce viral mRNA synthesis and inhibit cellular factors cooperating with the *tat* gene. Substitution of the fluoride with other functional groups, such as

amino, afforded more potent compounds which exhibited improved activity against chronically, acutely, and latently infected cells. These results represented useful leads for the development of new and effective AIDS chemotherapeutics.[45,47,48]

A significant number of drugs with a quinoline or quinolone motif have been developed as anti-HIV drugs, emphasizing the biological importance of quinolines and quinolones.[49] Their biological activities are well covered in medicinal journals and books, and several drugs containing quinoline or quinolone moieties have progressed to clinical use. These include: saquinavir **4** – the first HIV-1 PR inhibitor to be approved by the United States Food and Drug Administration (FDA);[50] styrylquinolines **5**, preliminarily identified as potential HIV-1 integrase inhibitors which exhibit no cytotoxicity at all; [49,51] and, most recently, elvitegravir **6** which bears a 4-quinolone core, emerged as one of the most potent antiretroviral drugs to date (Figure 12).[51]

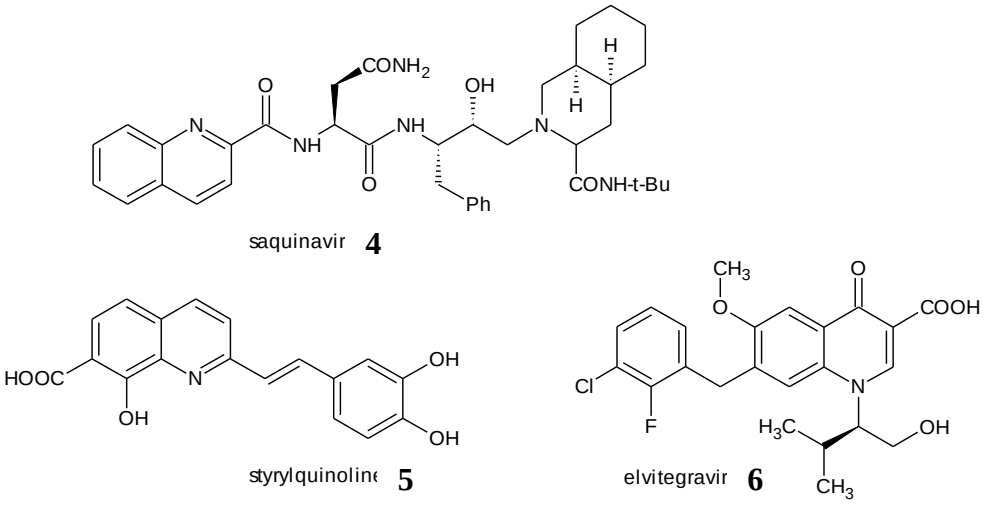
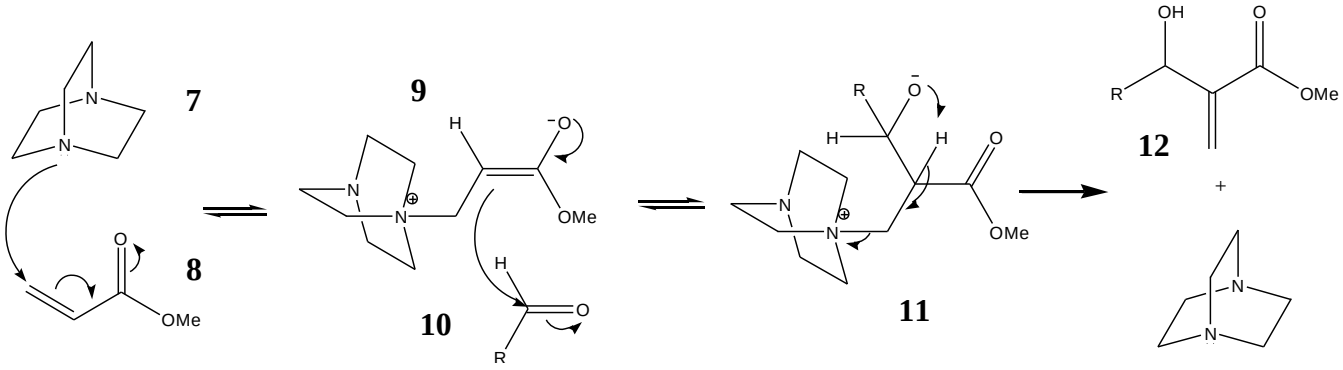


Figure 12. Clinically approved quinoline and quinolone-based antiretroviral drugs.

1.5. The Morita Baylis-Hillman reaction.

1.5.1. *Synthetic aspects*

Organic synthesis may be viewed as the construction of target molecules by forming carbon-carbon bonds between appropriate structural groups.[25] The Morita-Baylis-Hillman (MBH) reaction, sometimes referred to as the Baylis-Hillman (BH) reaction, is one of the most efficient, atom-economical carbon-carbon bond-forming transformations. It involves the reaction between an activated alkene (*e.g.* acrylic esters, acrylonitrile, vinyl ketones, vinyl sulfonate esters and vinyl phosphonates) and an aldehyde **10** in the presence of a nucleophilic catalyst, such as a phosphine or tertiary amine.[52,53] The reaction, first reported by Morita and co-workers in 1968, employed tricyclohexylphosphine as a catalyst, while a later, independent report by Baylis and Hillman in 1972, described the use of 1,4-diazabicyclo[2.2.2]octane (DABCO) **7** as a catalyst.[54] The BH reaction can be viewed as a three-step reaction involving successive aza-Michael, aldol, and elimination reactions in one pot (Scheme 1).



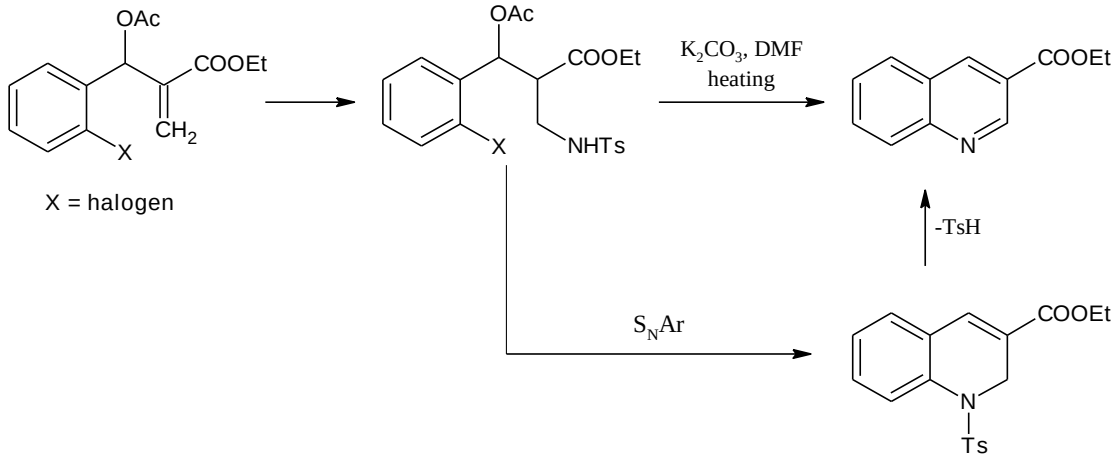
Scheme 1. Baylis–Hillman mechanism with DABCO **7** as a catalyst.[44]

The BH reaction affords a multifunctional adduct **12** with considerable potential for synthetic elaboration. Its synthetic potential has inspired a stream of research directed at enhancing the reaction rate and yield. Several reaction procedures and conditions that include variation of the catalyst, solvent media, pressure, ultrasound energy source, *etc.* have been explored. Recent revelations suggest the use of a mild base catalyst and an ionic liquid solvent to enhance the reaction rate.[44,55,56] Of late, the BH reaction has gained considerable attention because of the

multifunctional commutable adducts it affords and their application in a wide range of synthetic transformations into structurally complex and diverse medicinally important products.[56-59]

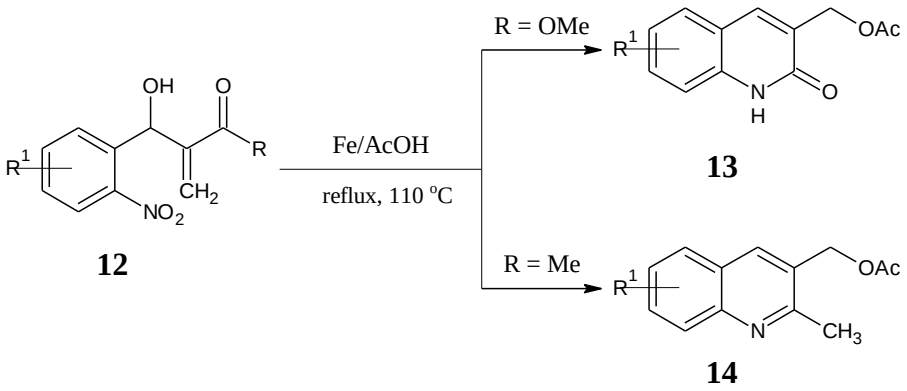
1.5.2. *Application of the Baylis–Hillman adducts in the synthesis of quinolones and quinolines*

Quinolines and quinolones are common motifs present in both natural and synthetic compounds,[60] and exhibit a range of bioactivities, such as antibacterial, antimalarial, antidiabetic, antiasthmatic, anti-inflammatory, antibiotic, antimicrobial, anticancer, and anti-HIV.[61-63] Owing to the biological importance of the quinoline and quinolone motifs, numerous syntheses have been developed. These include the classical Friedlander and the related Pfitzinger and von Niementowski reactions, in which use is made of *o*-aminobenzaldehydes. The relative inaccessibility of *o*-aminobenzaldehydes is a major limiting factor in the Friedlander methodology.[64] The first application of the BH methodology in the construction of benzannulated heterocycles, such as quinolines, quinoline *N*-oxides,[55] and 2-quinolones from 2-nitrobenzaldehydes were reported by our group.[33,65,66] Ka Young Lee *et al.*[67] subsequently reported the synthesis of 3-substituted quinolines through aromatic nucleophilic substitution (S_NAr), facilitated by the presence of the electron withdrawing conjugated ester moiety in BH adducts of *o*-halobenzaldehydes (Scheme 2).



Scheme 2. Synthesis of quinoline derivatives through nucleophilic aromatic substitution (S_NAr).[67]

This project has focused, partly, on the synthesis of 3-substituted quinolines and quinolones (Figure 13) from *o*-nitrobenzaldehyde-derived BH adducts employing a facile method developed by Basaviah *et al.*[58] to obtain 3-acetoxymethyl-(1*H*)-2-quinolone **13** and 3-acetoxymethyl-2-methylquinoline **14** from appropriate BH adducts. However, the latter system **14** was not explored further due to low yields. Lee and Kim reported a similar synthesis using zinc in acetic acid in the presence of a catalytic amount of trifluoroacetic acid.[68]



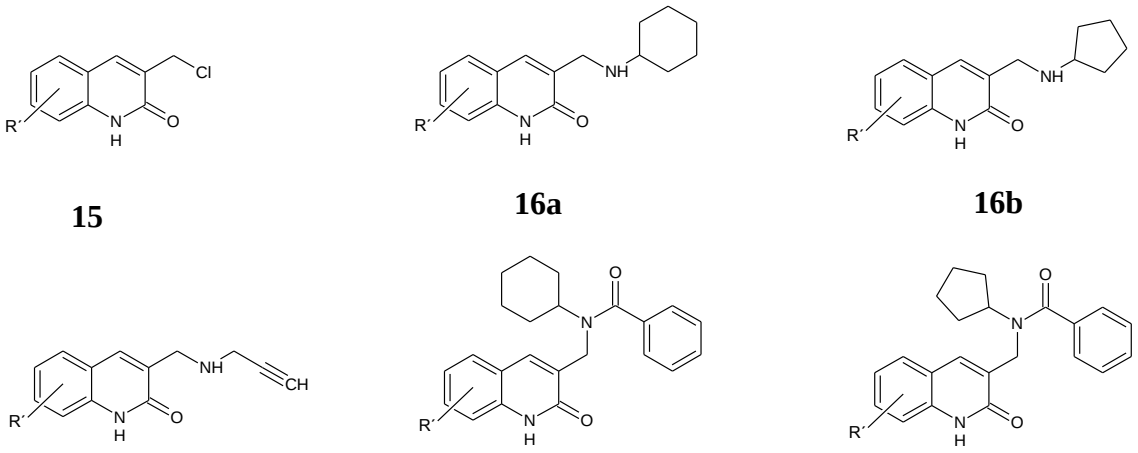
Scheme 3. Facile synthesis of quinoline and quinolone derivatives from BH adduct.

Over the past years since the discovery of quinoline and quinolone motifs as key ingredients in traditional medicine and synthetic drugs, enormous medicinal progress has been achieved. Eventual success in using quinoline in numerous therapeutics is attributed to indigenous knowledge systems as well as progressive research scholarship in order to bring about the transformations that the medicinal chemistry community needs to heal and prevent disease. Medicinal research attempts to provide solutions and insights which ultimately mitigate the strength of a disease – as has been the case in the developments achieved in anti-HIV therapy. It addresses matters of epidemiology, etiology, drug development, and potency. Although there have been successful developments, the quest for a permanent and effective anti-HIV therapy remains a global challenge and continues to spur research.[69]

Rational drug design involves the use of computational, crystallographic, bioassay, and NMR methods.[70,71] Some computational approaches have been used to probe the binding of various inhibitors of HIV-1 PR. These methods range from simple molecular docking to free energy perturbation methods using molecular dynamics. According to Wlodarwer and Vodrasek,[44]

molecular dynamics calculations have been used for studying enzyme dynamics and the influence of certain mutations on structure and stability. On the other hand, novel NMR-based screening shows great promise in drug discovery over the conventional bioassay-based screening. NMR analysis can provide 3D ligand/receptor structures, conformations of enzyme-bound ligands and locate binding sites of the ligand. In conjunction with crystallographic data, enzyme-inhibitor interactions in a dynamic state can thus be mapped out.[36,69] STD NMR, one of the most sensitive and versatile ligand-observed NMR screening methods, can be used to detect ligands with binding affinities typically in the micromolar to millimolar range. Although STD NMR has the ability to detect high-affinity ligands which undergo minimal chemical exchange on the NMR time scale, detection can also be achieved through ligand-observed NMR experiments.[50,70-72]

The Baylis-Hillman reaction, used as the starting point of this project, provides multifunctional adducts which, in turn, can serve as precursors for the synthesis of heterocyclic systems, in particular quinoline and quinolone derivatives (Figure13).



15 **16a** **16b**

17 **18a** **18b**

Figure 13. Targeted, biologically important 3-substituted 2-quinolone derivatives.

Aminoquinolones represent useful leads for the development of effective drugs against HIV/AIDS both in the chronic and acute stages.[30] Studies conducted by Cecchetti *et al.*[73] suggested the potential of 6-amino-4-quinolones (Figure 14) as anti-HIV compounds, particularly as integrase inhibitors. They revealed that bulky substituents at the N-1 and C-8

positions as well as alkylation of the amino group compromised the compound's efficiency. This revelation highlights the importance of an amino group. On the other hand, efficiency improved with the presence of a critical functional group at the C-3 position, a small polar substituent at C-7 and a small substituent at N-1. Requirements for small substituents at C-8 satisfy steric restriction assessments for facile RNA-quinolone interaction. It is well established that this type of quinolone rapidly inhibits HIV-1 replication. The size of the substituent at the C-7 position does not affect the drug potency.[73,46]

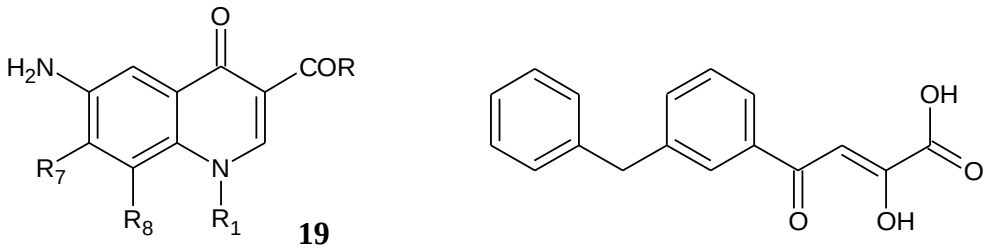


Figure 14. General representations of the 6-amino-4-quinolones **19** and diketo compound assessed.[46,47,73]

The 4-quinolone scaffold is readily synthesised on a large scale and is characterized by well-established biochemical properties. Exploration of this class of compounds has enjoyed considerable attention and has afforded improved anti-HIV agents that effectively reduce the rate of viral replication for a prolonged period. [11, 74, 75]

The use of reverse transcriptase and protease inhibitors in antiretroviral chemotherapy has faced serious challenges in the form of virus mutations leading to resistance and their failure to eradicate the virus completely or achieve complete suppression. Consequently, antiretroviral chemotherapy has been directed at the development of integrase inhibitors. By 2006,[47] only the diketo acid class of compounds (Figure 14) was at an advanced stage of development. It was later reported that antibiotics containing the quinolone motif exhibited improved integrase inhibition activities. As a result more attention has been directed to the development of quinolone-based drugs, [75] in particular the 4-quinolone carboxylic acid class of compounds as a viable alternative to the diketo acids.[47,73] Quinolone-based IN inhibitors display specificity for

strand transfer catalysis of the enzyme thereby blocking essential viral integration into the host cell nuclear DNA, a prime step in viral infection.[9]

1.6. Previous work in our group and aims of the current study.

Our research group has been involved in exploring applications of Baylis-Hillman methodology in the synthesis of indolizines **20**, thiochromenes **21**, and coumarins **22**, quinolines **23** and **25**, and quinolones **24**. In addition, attention has been given to the synthesis of Baylis-Hillman-derived ritonavir analogues **26**, and coumarin-AZT analogues **27** as potential dual-action HIV-1 PR/RT inhibitors, respectively (Figure 15). [2,36,44,49,51]

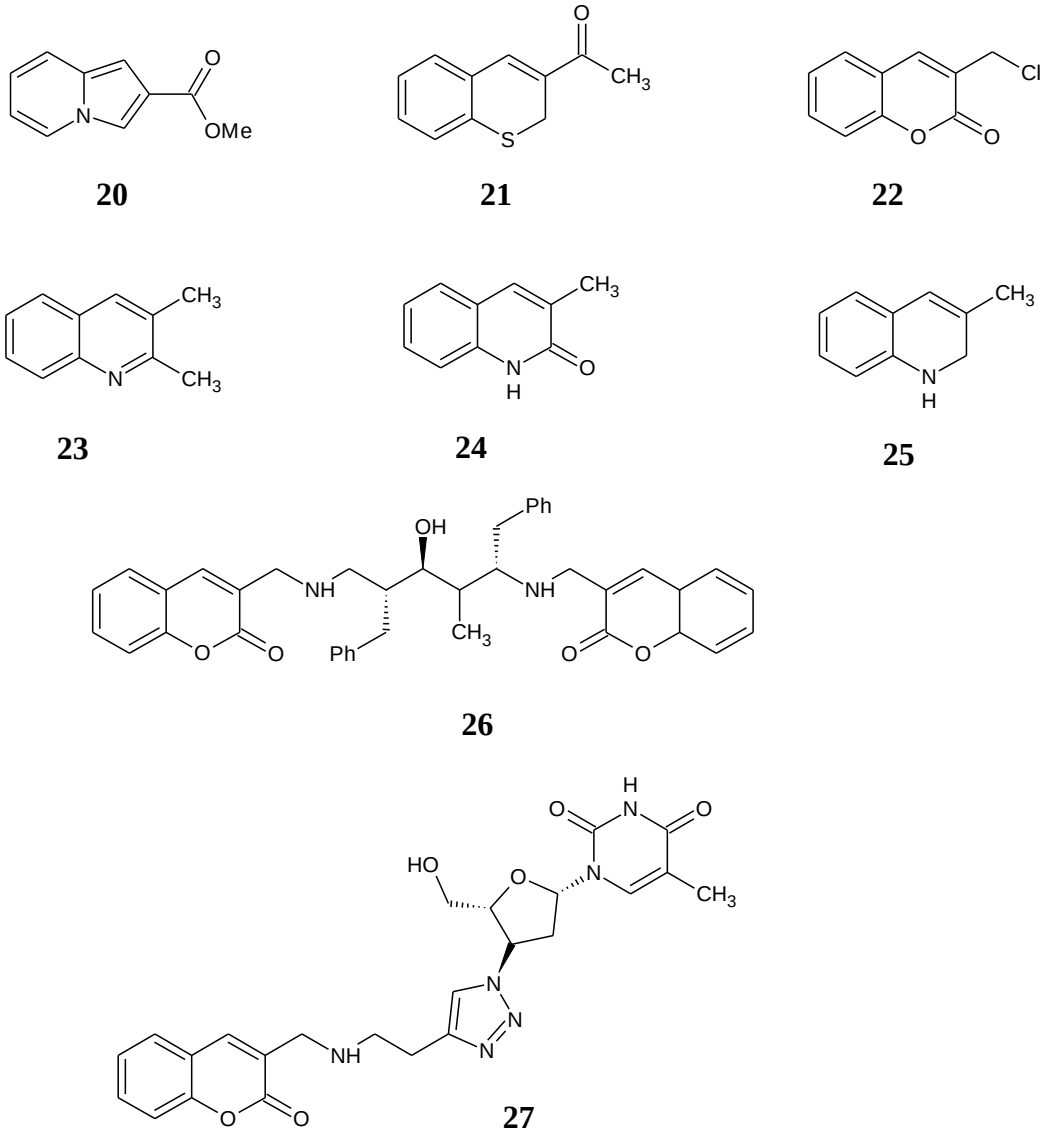


Figure 15

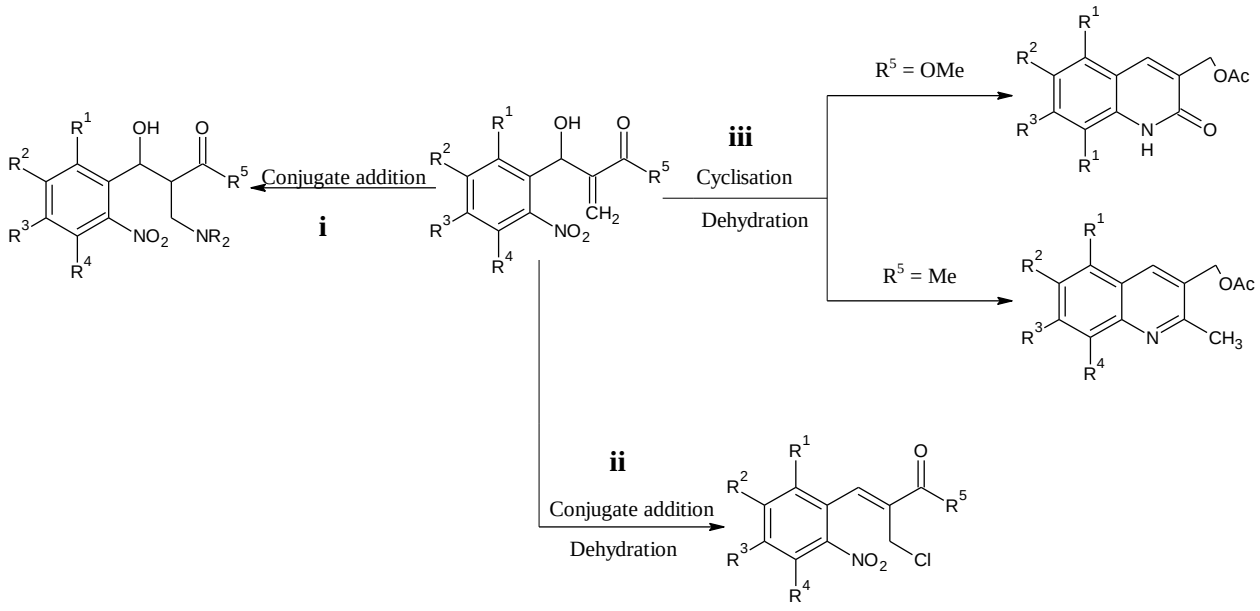
The benefits of currently available HIV drugs are likely to be short-term due to the constant viral mutations resulting in the development of resistance. There is thus an ongoing need to develop novel chemotherapeutic agents with new mechanisms of action in order to address these problems.[65,74] Moreover, evaluation of such compounds ideally requires computer modeling to determine possible ligand-enzyme interactions followed by bioassays in conjunction with some analytical tools such as STD NMR. This requires appropriate facilities and reliable methods to obtain accurate analyses. At the end, there must be a critical assessment of the evidence derived from experiments.

Consequently, the objectives of this project include the following:

1. Synthesis of a series of Baylis-Hillman adducts as quinoline or quinolone scaffolds using 2-nitrobenzaldehydes and methyl acrylate or MVK in the presence of DABCO.
2. Synthesis of cinnamate allyl chlorides as intermediates for subsequent nucleophilic substitution reactions.
3. Development of quinolone derivatives to access 3-(cycloalkylamino)methylquinolones and, subsequently, 3-amidomethyl-2-quinolones as potential HIV-1 PR inhibitors.
4. Application of click chemistry in the construction of cinnamate ester-AZT, 3-hydroxy ester-AZT or quinolone-AZT conjugates as potential dual–action HIV-1 IN/RT inhibitors.
5. Preliminary *in vitro* evaluation of selected products.

2. Results and discussion

The development of new methodologies for the construction of carbon-carbon bonds and functional group transformations incorporating atom economy and selectivity constitute core principles in the advancement of synthetic organic chemistry. The ongoing demand for new medicinal compounds requires economical, efficient and facile synthetic methods with high selectivity. The Baylis-Hillman reaction satisfies these requirements permitting facile access to cyclic and acyclic molecules that previously seemed very tedious and time consuming to synthesize.[77,78] This project was aimed at addressing the demand for medicinally important acyclic and cyclic molecules using the Baylis-Hillman methodology. Scheme 4 outlines the application of the Baylis-Hillman reaction to yield intermediates with potential for synthetic elaboration.

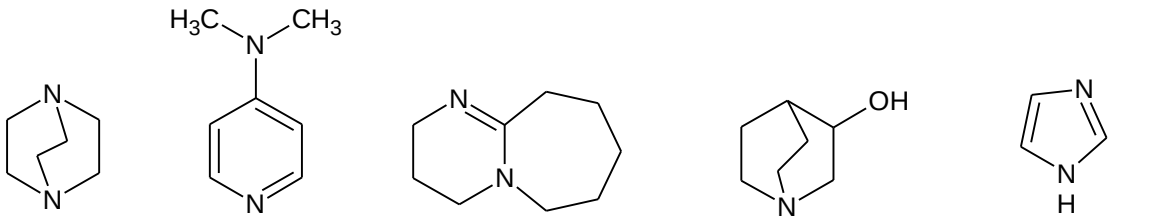


Scheme 4. "Roadmap" of transformations of the Baylis-Hillman adducts.

In line with identified objectives, the discussion focuses on the application of Baylis-Hillman methodology in the construction of diketo acid (DKA) analogues: cinnamate ester-AZT conjugates and 3-hydroxy ester-AZT conjugates as dual-action HIV-1 IN/RT inhibitors; and on exploratory studies on the preparation of 3-(amidomethyl)-(1*H*)-2-quinolones as PR inhibitors; and (1*H*)-2-quinolone-AZT conjugates as dual action IN/RT inhibitors.

2.1. Preparation of Baylis-Hillman adducts

The Morita-Baylis-Hillman reaction, sometimes referred to as the Baylis-Hillman reaction, is named after scientists A.B. Baylis, M.E.D. Hillman and K. Morita. It allows direct synthesis of highly versatile, α-methylene-ß-hydroxycarbonyl adducts, from the base catalyzed reaction of α,ß-unsaturated carbonyl compounds with aldehydes.[79] It is used to couple activated alkenes and aldehydes in the presence of an unhindered nucleophilic tertiary catalyst, most commonly: 1,4-diazabicyclo[2.2.2]octane (DABCO) **7**, 4-dimethylaminopyridine (DMAP) **28**, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) **29**, 3-hydroxyquinuclidine (3-HQ) **30** and imidazole **31** (Scheme 5).



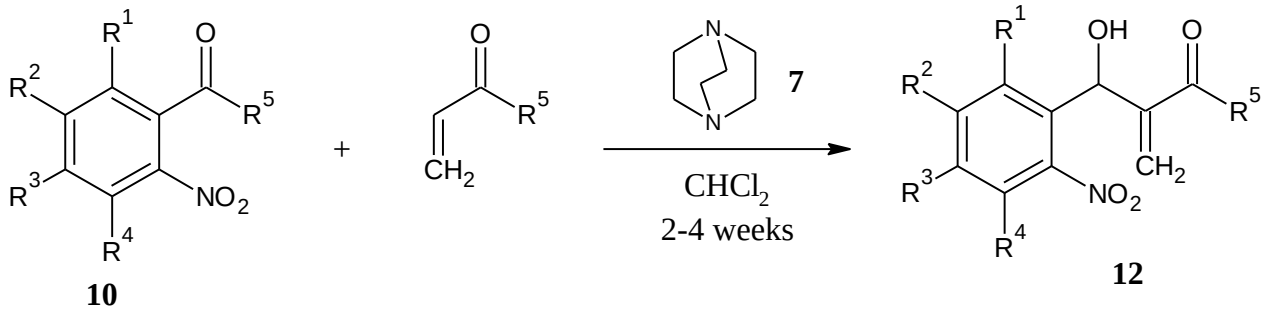
DABCO DMAP DBU 3-HQ Imidazole

7 **28** **29** **30** **31**

Scheme 5

The aldehydes used for the Baylis-Hillman reaction in this study were the 2-nitrobenzaldehydes **10a-i** (Scheme 6) with methyl vinyl ketone (MVK) **32** and methyl acrylate **8** employed as activated alkenes to afford functionally diverse BH adducts **12a-i** in yields of 4-85 % as shown in Table 2. All BH reactions were run at room temperature and atmospheric pressure in chloroform using DABCO **7** as catalyst for at least 2 to 8 weeks depending on the substrate used. The yields of the Baylis-Hillman products obtained after chromatographic purification varied substantially, with lower yields observed for compounds **12b**, **12e**, **12h**, and **12i**. The low yields obtained for adducts **12e** (4%) and **12b** (35%) may be attributed to reduction of the electrophilicity of the reactive aldehyde precursor as a result of the presence of additional electron-releasing ring substituents. The rate and efficiency of the Baylis-Hillman reaction, particularly for low yielding substrates, was significantly improved in later reactions when minimal solvent was used. The amount of DABCO **7** was increased as well as the amount of

methyl acrylate. Employment of microwave-assisted reactions failed to improve yields and increasing reaction temperature resulted in polymerization.



R^1 = H

R^2 = H, OCH_3, Cl, OH, or OCH_2O

R^3 = H, Cl, or OCH_2O

R^4 = H or OMe

R^5 = OCH_3, OCH_2CH_3, or CH_3

See Table 2 for substitution patterns

Scheme 6. General representation of Baylis-Hillman reactions undertaken in this study.

Table 2. Summary of the Baylis-Hillman adducts **12**.

Entries	R^1	R^2	R^3	R^4	R^5	% Yield
a	H	H	H	H	OCH_3	76
b	H	OCH_2O		H	OCH_3	38
c	H	Cl	H	H	OCH_3	83
d	H	H	H	Cl	OCH_3	79
e	H	OCH_3	OCH_3	H	OCH_3	4
f	H	OCH_3	H	H	OCH_3	85
g	H	H	OCH_3	H	OCH_3	79
h	H	H	H	H	OCH_2CH_3	35
i	H	H	H	H	CH_3	35

All of the Baylis-Hillman adducts **12a-i** were fully characterized by NMR and IR analysis and, in some cases, by high-resolution mass spectrometric (MS) analysis. In the ^{1}H-NMR spectrum, the Baylis-Hillman product is generally characterized by the presence of three signals (typically singlets) between *ca.* 5.5 and 6.5 ppm corresponding to the 3-methine proton and the two methylene protons, while characteristic ^{13}C-NMR signals include the methine C-3 signal at *ca.* 67 ppm, the methylene signal at *ca.* 126 ppm and the carbonyl carbon signal at *ca.* 166 ppm. The former are clearly evident in the ^{1}H-NMR spectrum of the BH product **12a** (Figure 16); thus two vinylic protons resonate at 5.73 ppm and 6.37 ppm, and the methine proton at 6.20 ppm. Furthermore, the OH signal resonates as a broad singlet at 3.39 ppm. The methoxy singlet as well as the four aromatic proton signals are also clearly evident.

The ^{13}C-NMR spectrum (Figure 17) shows the expected 11 carbon signals with the ester carbonyl carbon at 166.4 ppm. The DEPT 135 (Figure 18) in conjunction with ^{13}C-NMR spectrum permits identification of the characteristic methylene signal at 126.5 ppm and the methine (C-3) signal at 67.8 ppm. Three more quartenary carbon and four aromatic carbon signals as well as the methoxy carbon signal are also evident. The presence of the OH, aromatic C-H, and the C=O functional groups are confirmed in the IR (Figure 19) by the bands at 3445, 2985 and 1707 cm^{-1}, respectively.

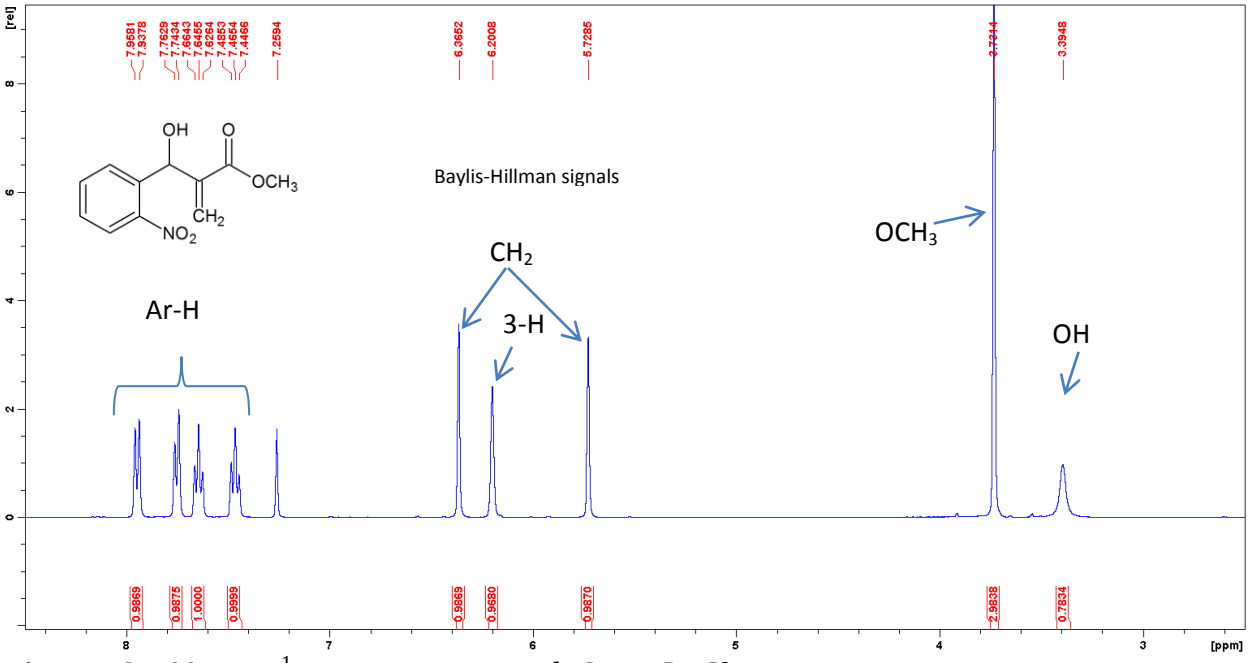


Figure 16. 400 MHz ^{1}H-NMR spectrum of **12a** in $CDCl_3$.

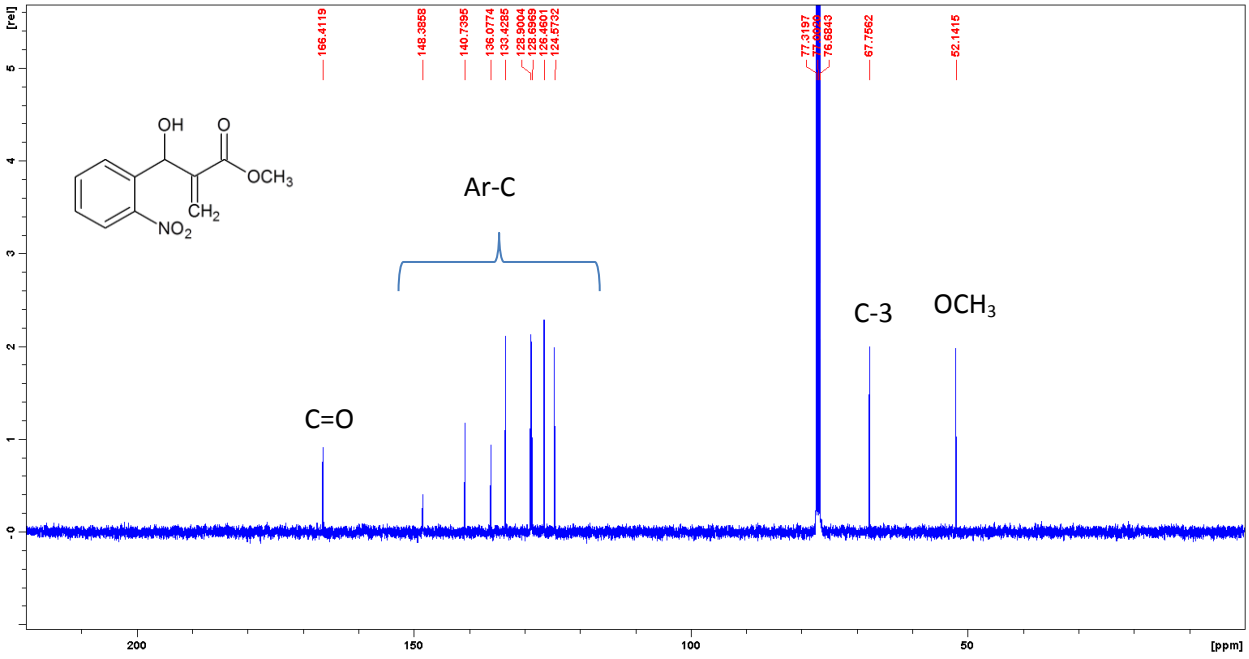


Figure 17. 100 MHz ^{13}C-NMR spectrum of **12a** in $CDCl_3$.

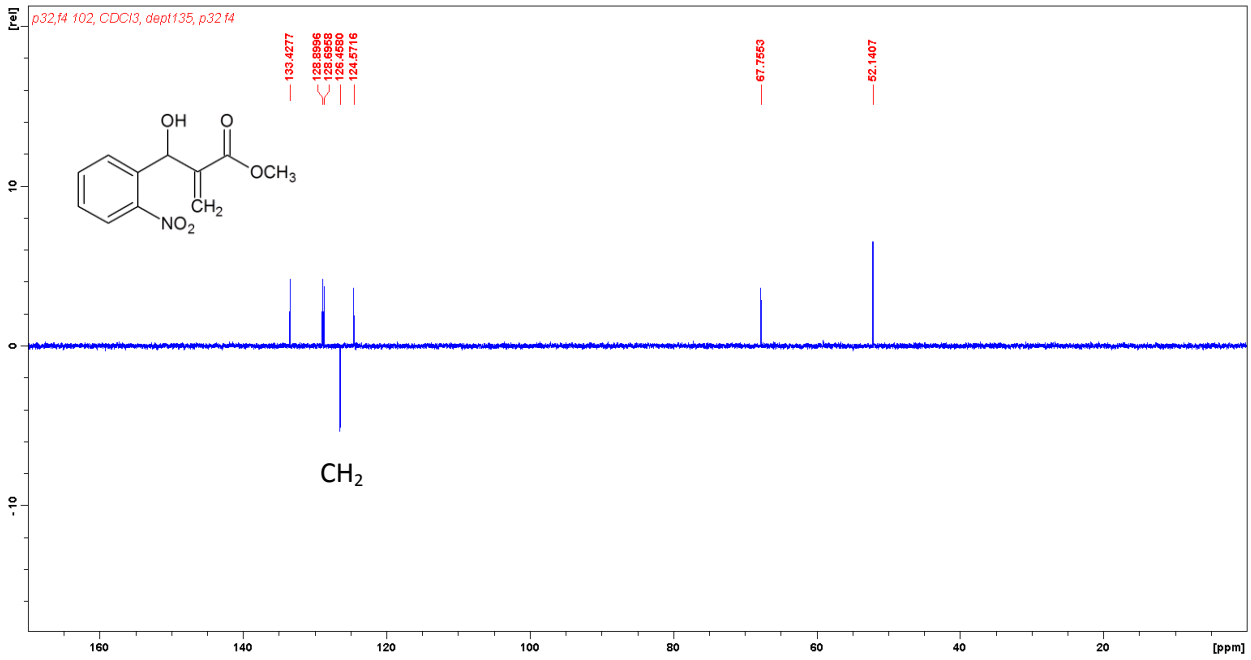


Figure 18. DEPT 135 NMR spectrum of **12a** in $CDCl_3$.

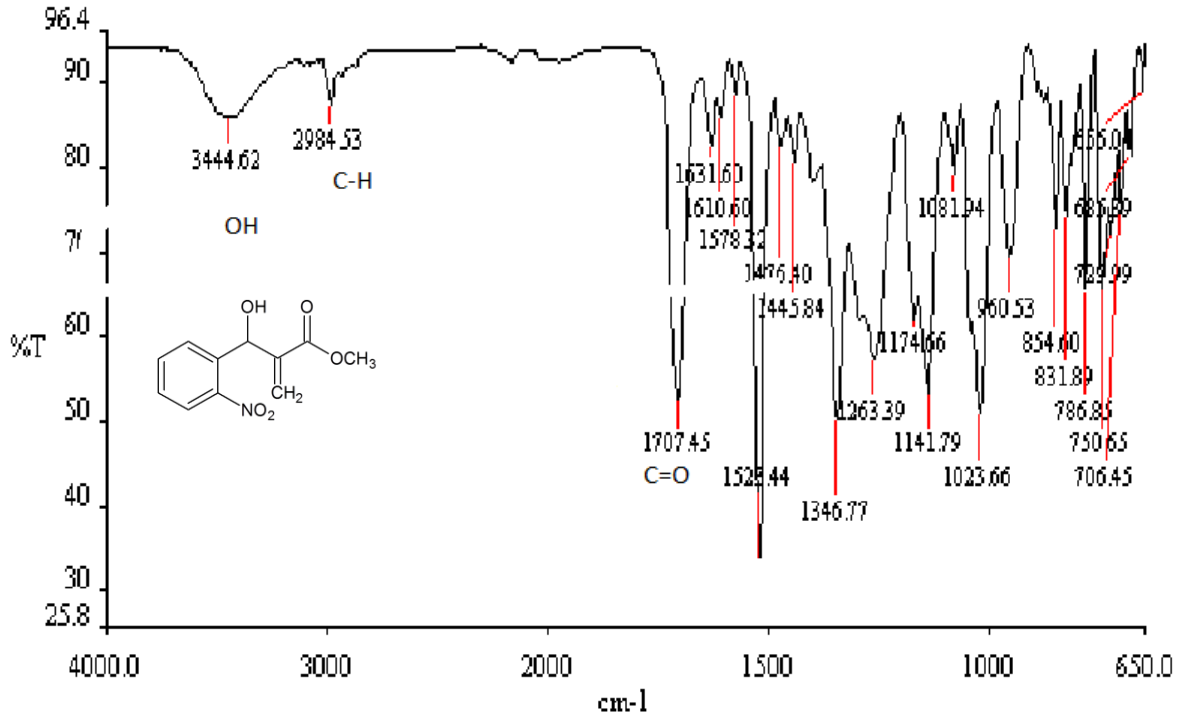


Figure 19. IR spectrum of methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **12a**.

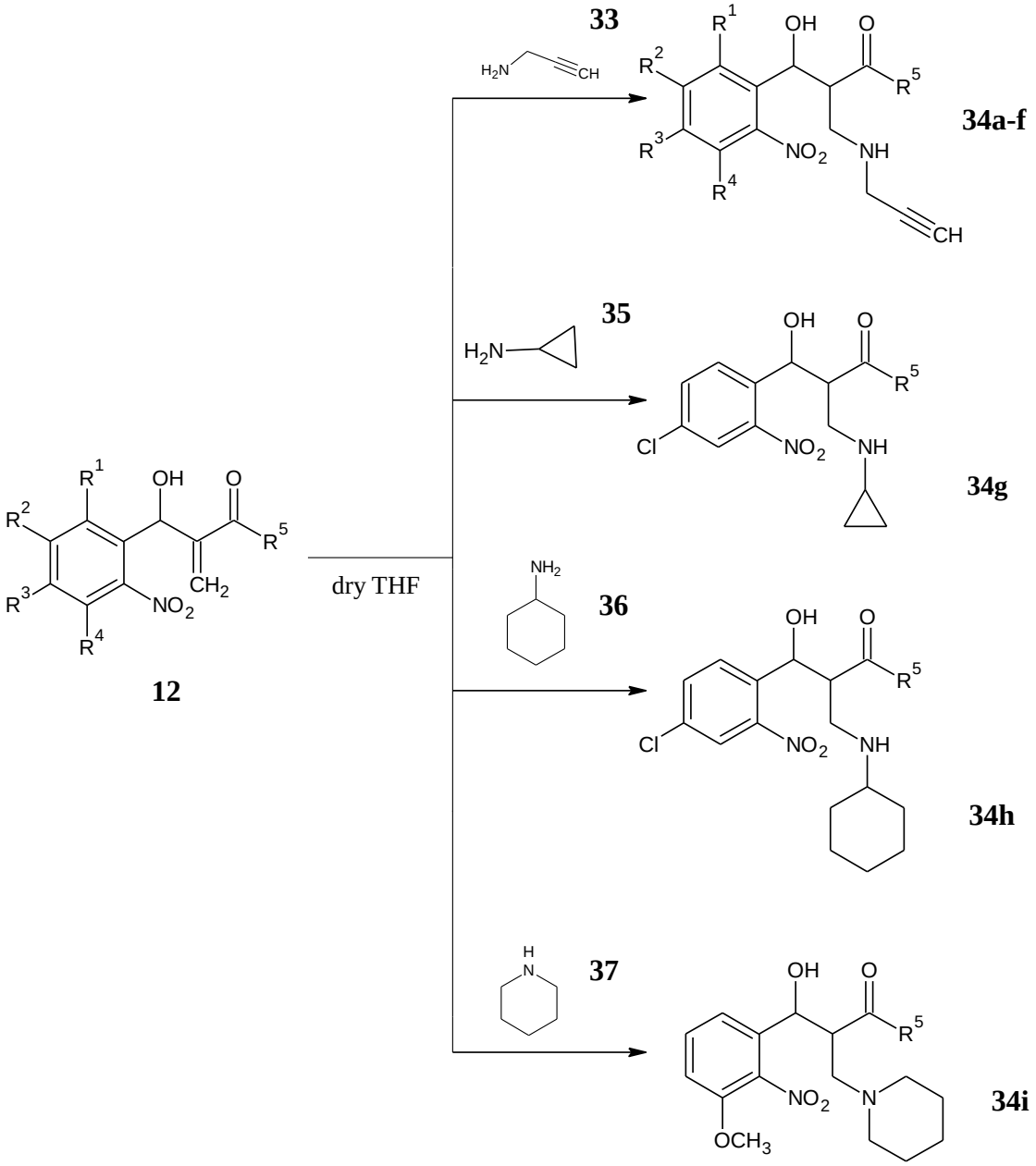
With the Baylis-Hillman adducts **12a-i** in hand, various transformations could be achieved including: **(i)** conjugate addition of primary and secondary amines to the α,ß-unsaturated moiety to obtain 2-(aminomethyl)-3-hydroxy-3-(2-nitrophenyl)propanoate derivatives, **(ii)** effective S_N2' substitution of the BH ß-hydroxy by a Vilsmeier-Haack *in situ*-generated chloride to afford Baylis-Hillman allyl chlorides, and **(iii)** iron in acetic acid-catalyzed cyclisation to yield 3-acetoxymethyl-(1*H*)-2-quinolone derivatives. Cyclisation of the BH adducts and subsequent reactions is discussed in the exploratory studies outlined in Section 2.3.

2.2. Preparation of diketo acid analogues as potential dual-action HIV-1 IN/RT inhibitors.

2.2.1. *Conjugate addition reaction of the Baylis-Hillman ester adducts*.

Following the framework outlined in Scheme 7, the first pathway involved conjugate addition of the primary amine, propargylamine **33**, to a series of α,ß-unsaturated ester adducts **12** to afford compounds **34a-f**. Cyclopropylamine **35**, cyclohexylamine **36,** and the secondary amine, piperidine **37** were used to afford the corresponding adducts **34g**, **34h** and **34i** (Scheme 7). A typical reaction involved treating 1 eq. of an adduct **12** with 1.2 eq. of an amine, except for cyclopropylamine **35** and cyclohexylamine **36** which were used in greater excess.

The reactions were generally conducted at room temperature in anhydrous THF and the reaction progress was monitored by TLC. In cases where the amine was used as both the solvent and reactant, the reaction did not take place. After completion, the reaction mixtures were concentrated *in vacuo* and the crude products purified by column chromatography. The piperidine, cyclohexylamine and cyclopropylamine adducts proved to be easier to purify than the propargylamine adducts. All products (Table 3) were obtained as pairs of diastereomers, arising from the presence of two stereogenic centres – an inherent stereogenic centre at the ß-carbon and a new stereogenic center at the α-carbon relative to the ester carbonyl group. 3-Methoxy-substituted derivatives were more reactive and gave products in high yields as shown in Table 3. All products were characterized by NMR and IR spectroscopy, but attention was not directed at resolution of the diastereomers.



Scheme 7. Conjugate addition of amines to Baylis-Hillman adducts.

In the ^{1}H NMR spectrum of methyl 3-hydroxy-2-[(propargylamino)methyl]-3-(2-nitrophenyl)-propanoate **34a**, two one-proton signals appear at 5.74 and 5.97 ppm due to the 3-methine proton for each (enantiomeric) pair of diastereomers, the integral ratio of 1:1.3 corresponds to the diastereomeric ratio. The presence of eight aromatic proton signals (two multiplets and four doublets) is also evidence of a pair of diastereomers (Figure 20).

Table 3. Percentage yield of compounds **34a-i**

Entries	R^1	R^2	R^3	R^4	R^5	% Yield
a	H	H	H	H	OCH_3	66
b	H	H	H	H	OCH_2CH_3	63
c	H	H	H	OCH_3	OCH_3	83
d	H	H	H	OCH_3	OCH_2CH_3	87
e	H	OCH_3	OCH_3	H	OCH_2CH_3	20
f	H	OCH_2O		H	OCH_2CH_3	60
g	H	H	Cl	H	OCH_3	45
h	H	H	Cl	H	OCH_3	35
i	H	H	H	OCH_3	OCH_3	78

The complexity of the spectrum in the high field region is also indicative of the presence of diastereomers. HSQC analysis reveals that the two triplet signals between 2.2 and 2.3 ppm belong to the alkyne proton of the propargylamine (7-H) and their multiplicity reflects long range coupling with the aminomethylene protons. Furthermore, the DEPT 135 spectrum shows two pairs of methylene signals, one for C-5 at 38.2 and 38.4 ppm, and another for C-4 at 46.1 and 49.6 ppm. The doubling of these and other signals in the ^{13}C and DEPT 135 spectra are consistent with the presence of diastereomers.

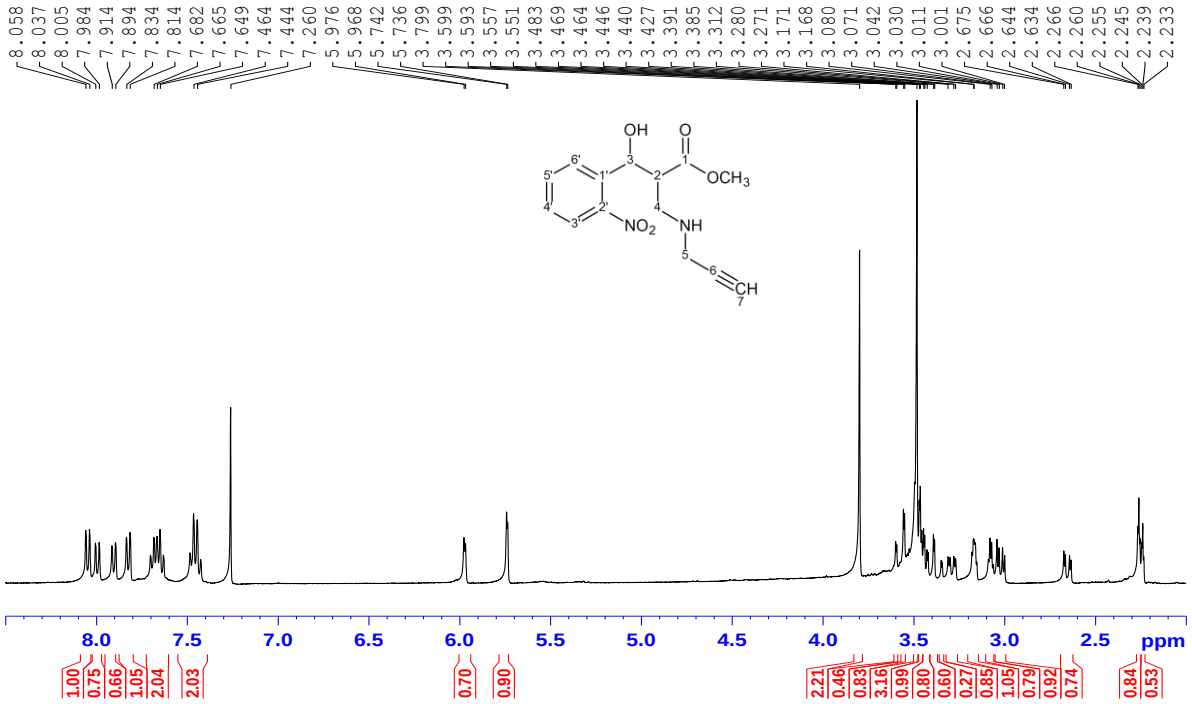


Figure 20. 400 MHz ^{1}H-NMR spectrum of methyl 3-hydroxy-3-(2-nitrophenyl)-2-[(propargylamino)methyl]propanoate **34a** in $CDCl_3$.

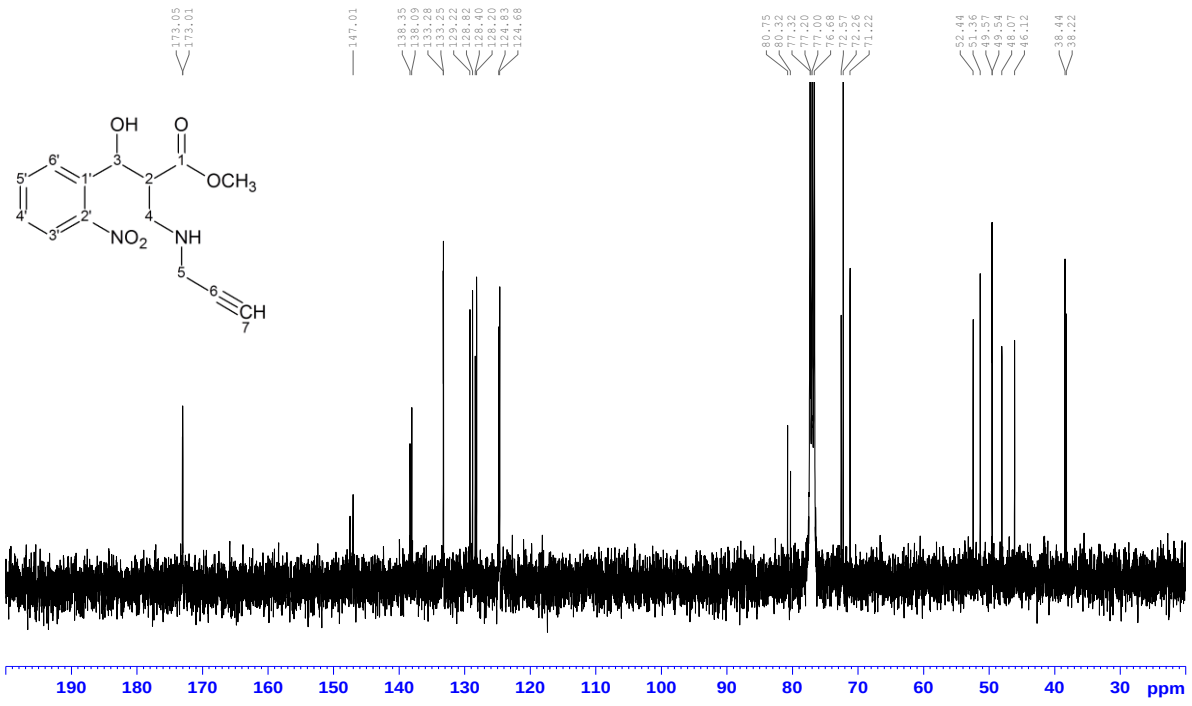


Figure 21. 100 MHz ^{13}C NMR spectrum of **34a** in $CDCl_3$.

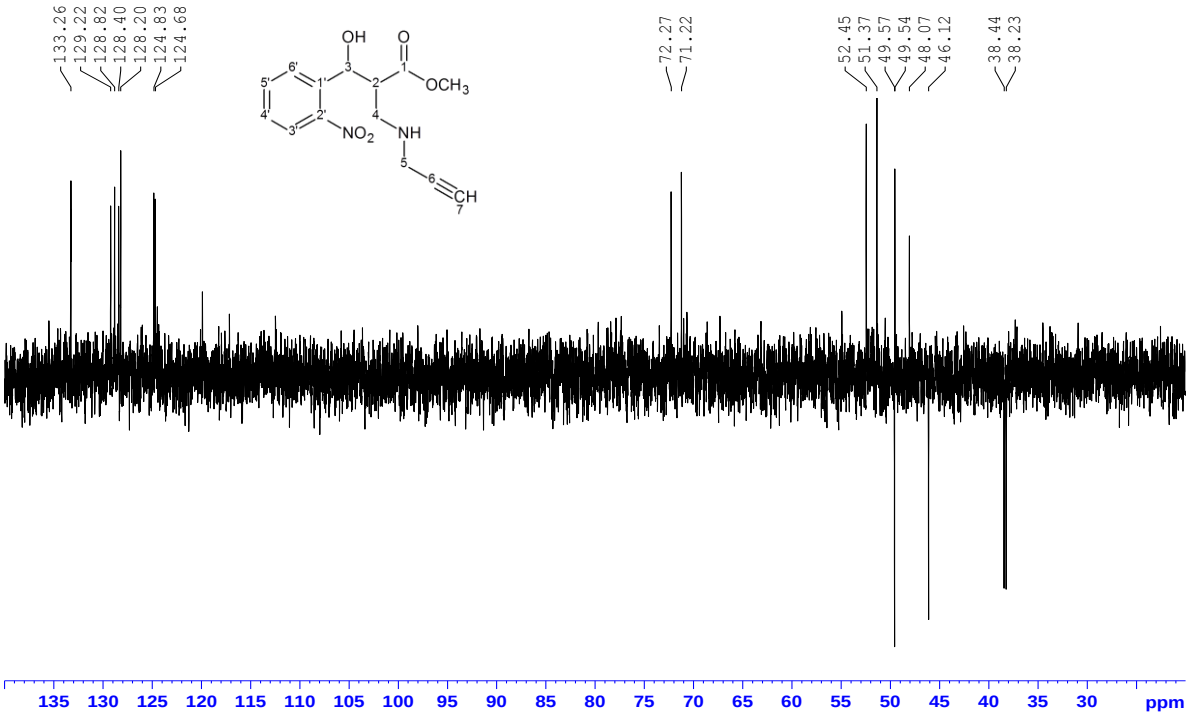


Figure 22. DEPT 135 NMR spectrum of **34a** in $CDCl_3$.

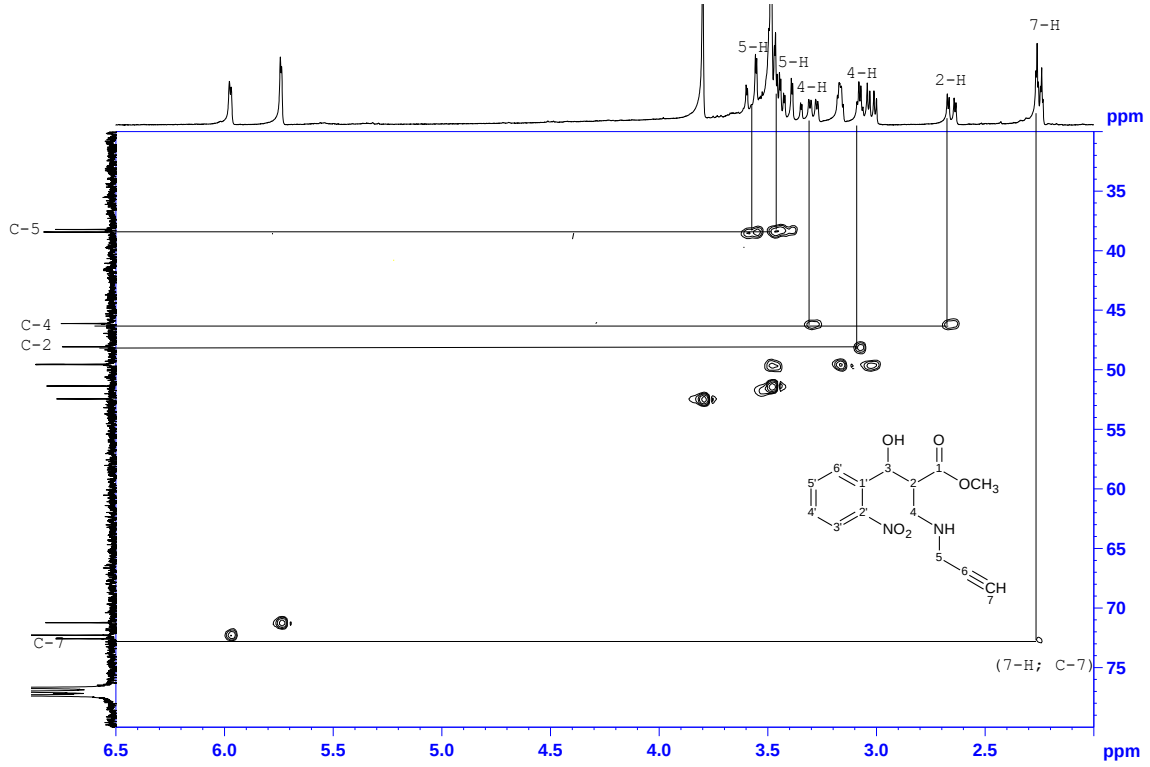


Figure 23. HSQC spectrum of **34a** in $CDCl_3$.

The DEPT 135 **(**Figure 24) spectrum of the diastereomeric 3-cyclopropylamino analogue **34g** reveals the aminomethylene signals at 47.6 and 49.1 ppm, cyclopropyl methylene signals upfield at *ca.* 6.2 ppm and aromatic methine carbon signals which are consistent with successful synthesis of compound **34g**. While compound **34i** was obtained in 78% yield, the cyclopropylamino and cyclohexylamino analogues were obtained in 45 and 35% yield, respectively. Differences in reactivity could be attributed to nuances in the electronic properties of the Baylis-Hillman adducts used. The mass spectrum of compound **34h** (Figure 25) obtained by electrospray ionisation mass spectrometry (ESI-MS) contains a protonated molecular ion $[M+H\ (^{35}Cl)]^+$ peak at m/z 371.1372 as the base peak and MH^+ (^{37}Cl) peak at m/z 373.1374. The fragment ion peak at m/z 353.1264 corresponds to an odd electron fragment ion resulting from dehydration.

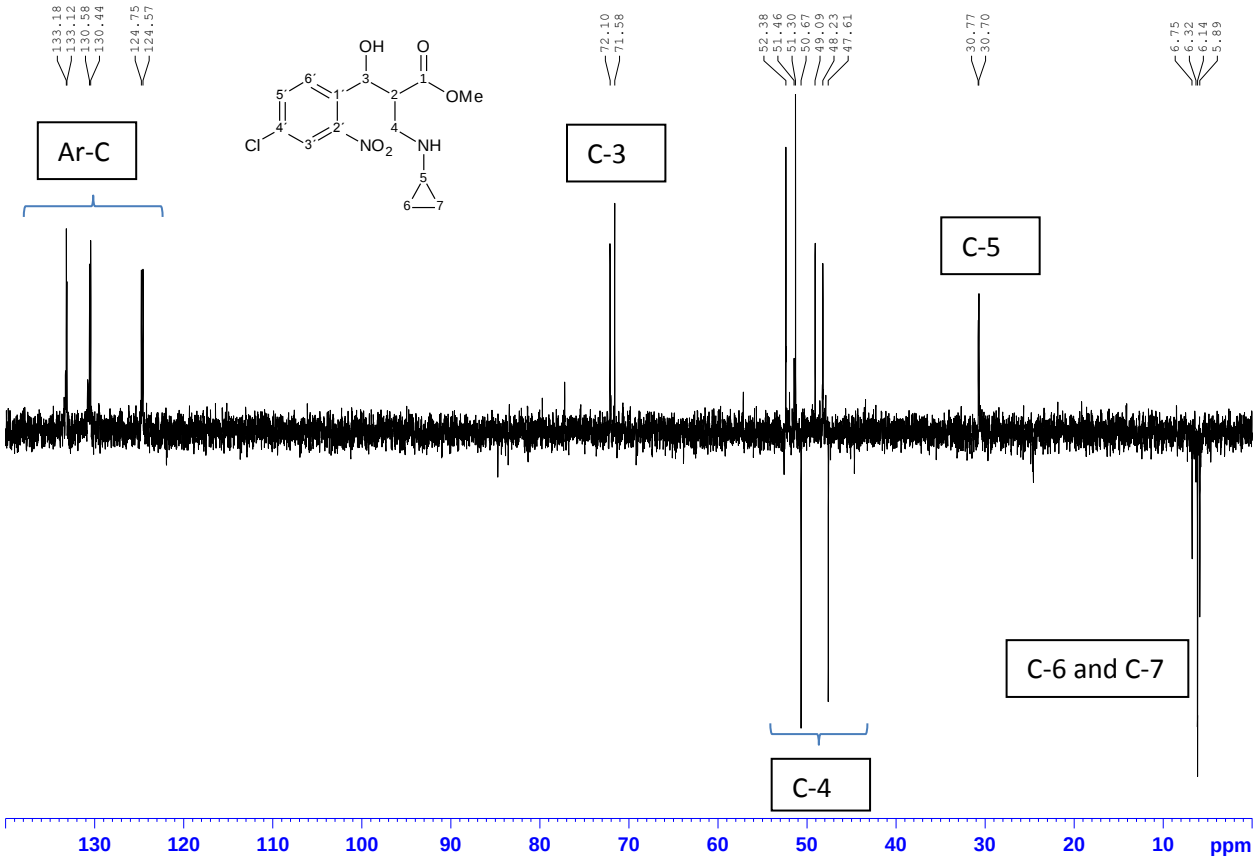


Figure 24. DEPT 135 NMR spectum of **34g** in $CDCl_3$.

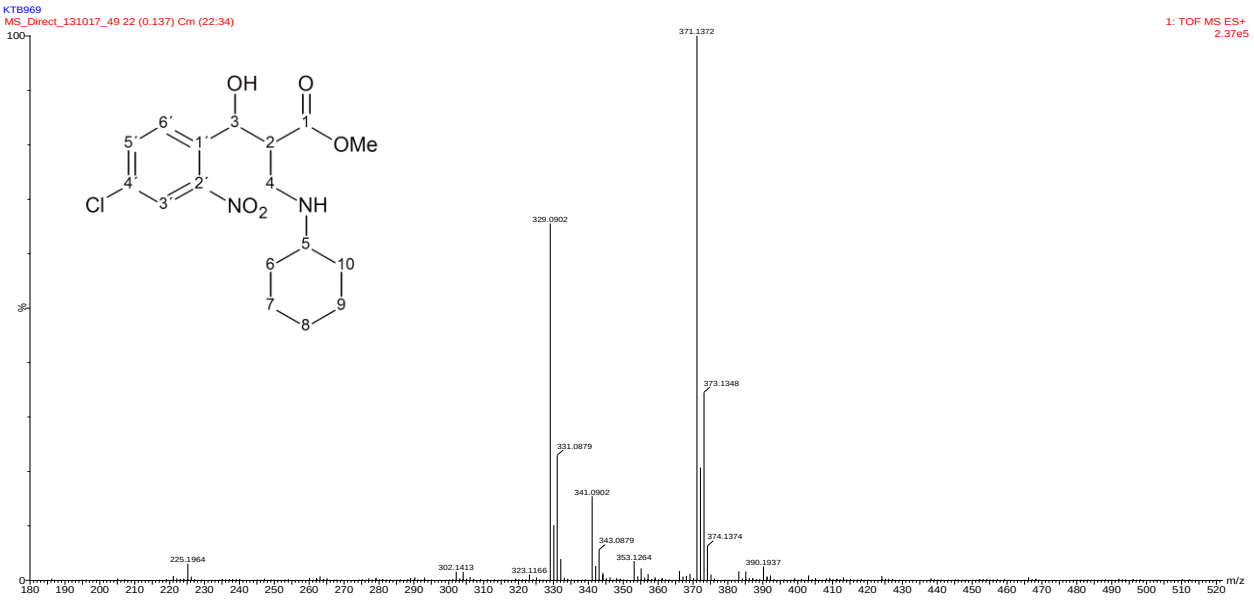
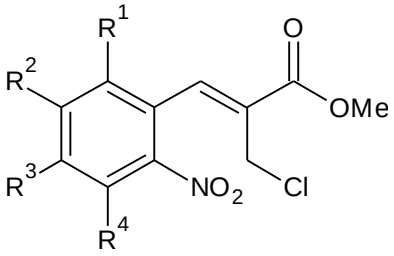


Figure 25. HRMS spectrum of methyl 3-(5-chloro-2-nitrophenyl)-2-[(cyclohexylamino)methyl]-3-hydroxypropanoate **34h** using electrospray ionisation.

2.2.1. *Synthesis of Baylis-Hillman-derived allyl chlorides.*

The Vilsmeier-Haack reagent is a versatile, efficient, economical, and mild reagent with the capability of executing a wide variety of chemical transformations. It enjoys application in formylation, esterification, cycloaddition, and ring annulation reactions, and as an activating agent for the conversion of alcohols to alkyl chlorides.[80,81] In respect of this project, the Vilsmeier-Haack reagent was successfully used for the chlorination/dehydration of Baylis-Hillman adducts **12**, to afford the allyl chloride esters **15a-h** (Scheme 4). The reaction progress was monitored by TLC after which work-up and chromatography afforded the allyl chlorides **15a-h** in moderate to excellent yields (Table 4).

Table 4. Yields of α-(chloromethyl)cinnamate esters **15a-h** from the Baylis-Hillman adducts **12**.

Chloromethyl cinnamate esters		R^1	R^2	R^3	R^4	% Yield
	**a**	H	H	H	H	65
	b	H	OCH_2O		H	37
	c	H	Cl	H	H	47
	d	H	H	Cl	H	86
	e	H	OCH_3	OCH_3	H	-
	f	H	OCH_3	H	H	52
	g	H	H	H	OCH_3	45
	h	H	OH	H	H	-

In the synthesis of the α-(chloromethyl)cinnamate esters **15a-h**, disappearance of the three characteristic Baylis-Hillman ^{1}H NMR signals between 5.5 and 6.5 ppm is expected as well as disappearance of the vinylic methylene signal at *ca.* 126 ppm in ^{13}C NMR spectrum. Furthermore, disappearance of the ß-hydroxy group is also expected to be evident from the IR spectrum of the resulting cinnamate ester, and all of the IR spectra obtained for these products satisfied this expectation. The ^{1}H NMR spectrum of the α-(chloromethyl)cinnamate ester **15a** (Figure 26) clearly depicts the methyl ester singlet at 3.48 ppm, followed by the methylene singlet at 3.82 ppm. Instead of four aromatic protons in the aromatic region, five proton signals are observed, the additional vinylic proton (3-H) confirming the formation of the cinnamate

ester. The absence of the Baylis-Hillman methylene signal at *ca.* 126 ppm in the DEPT 135 NMR spectrum also provides evidence that cinnamate esters were formed.

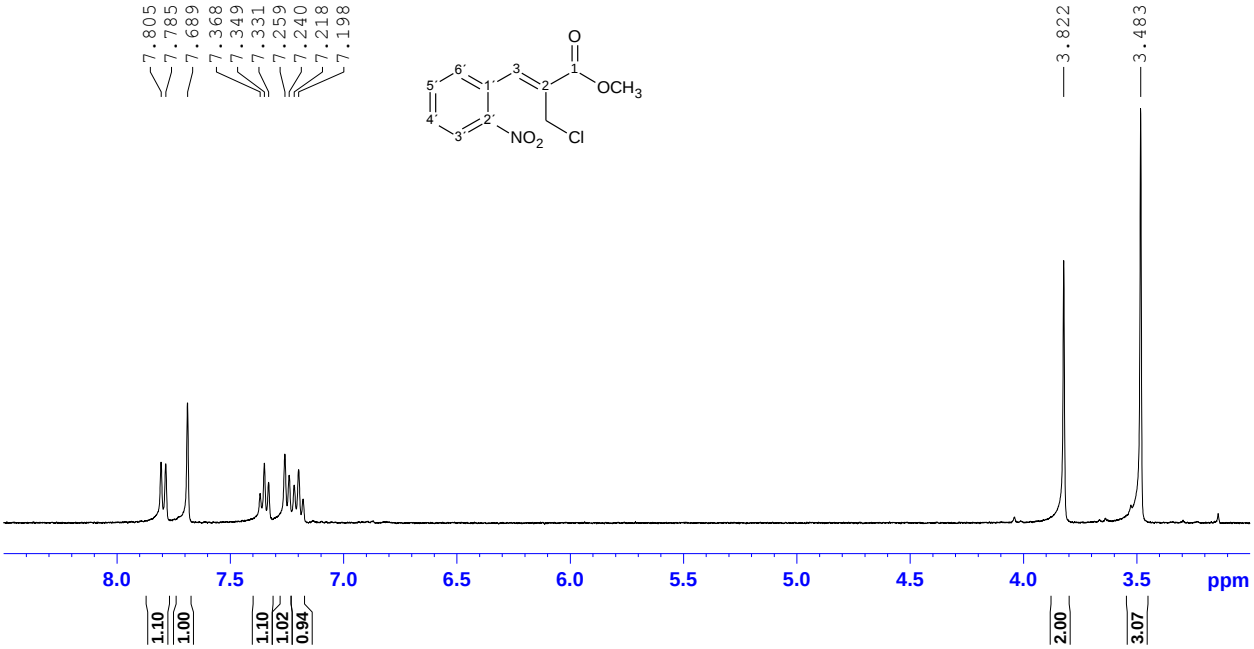
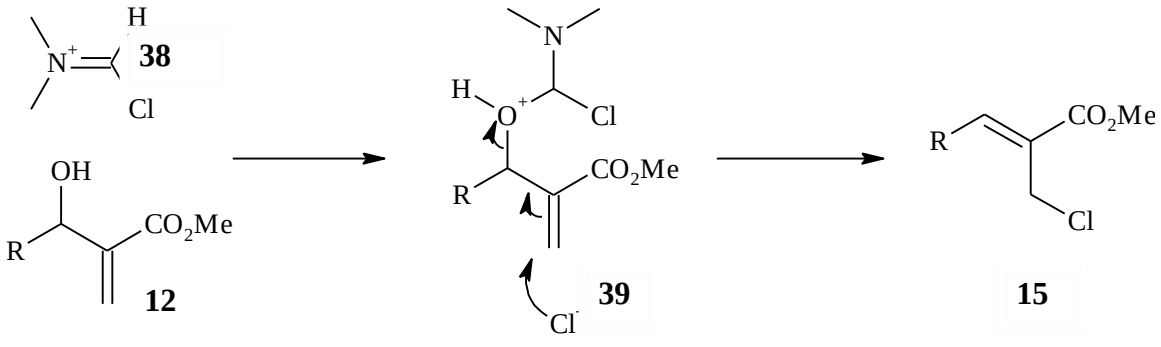


Figure 26. 400 MHz ^{1}H-NMR spectrum of methyl 2-(chloromethyl)-3-(2-nitrophenyl)-propenoate **15a** in $CDCl_3$.

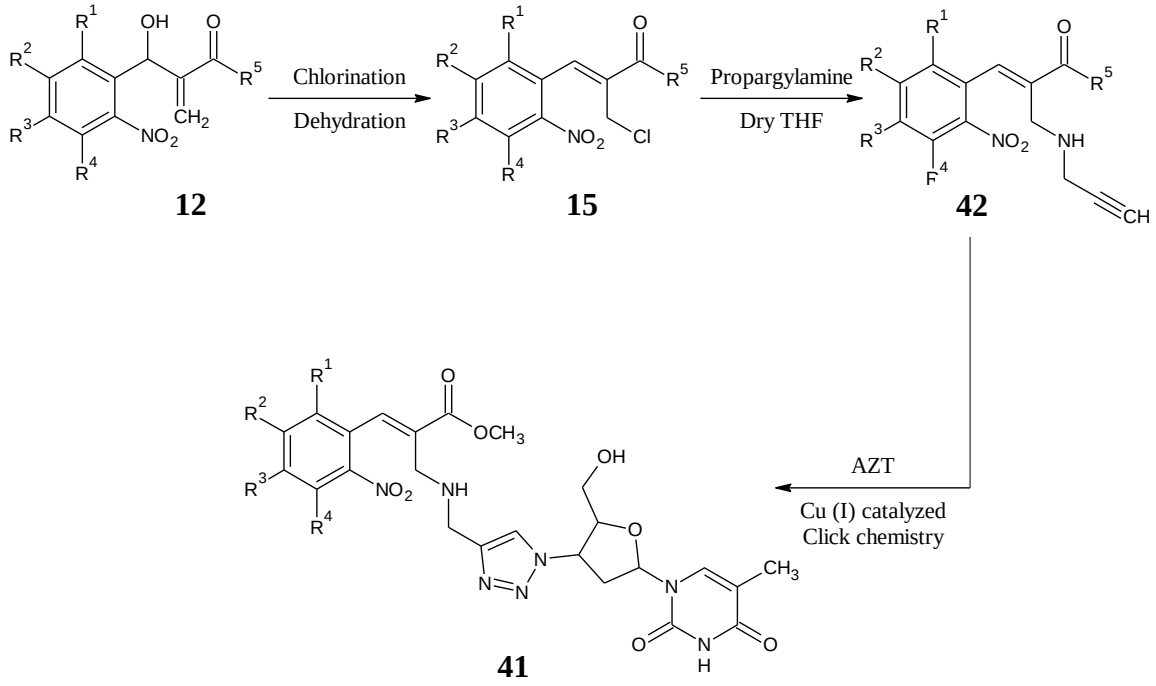
The Vilsmeier-Haack chloromethyleneiminium salt, generated by treatment of *N*,*N*-dimethylformamide (DMF) and phosphorous oxychloride ($POCl_3$) in dichloromethane (CH_2Cl_2) at room temperature is the reagent responsible for the chlorination of Baylis-Hillman adduct **12**. It has been proposed that the ß-hydroxy group is activated by complexing with the imine carbon followed by allylic attack of the chloride anion with consequent displacement of the activated hydroxyl group.



Scheme 8. Possible mechanism for the synthesis of allyl chlorides.[82]

2.2.2. *Propargylation of the α-(chloromethyl)cinnamate esters*

Ultimately, the α-(chloromethyl)cinnamate esters **15a-h** would be linked with 3´-azido-3´-deoxythymidine (AZT) in the construction of dual-action HIV-1 reverse transcriptase/integrase inhibitors **40** and **41**. Prior to linking the cinnamate esters with AZT, the α-(chloromethyl)cinnamate esters **15** were first treated with propargylamine **33** to afford the substitution products **42** subsequent to which the "click" reaction was expected to afford the cinnamate ester-AZT conjugates **41**. The same methodology would be used to link AZT with BH adducts **34a-f** to obtain the DKA analogues **40**.



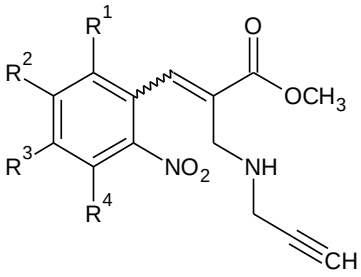
12 **15** **42** **41**

Scheme 9

Following the approach outlined in Scheme 9, the α-(chloromethyl)cinnamate esters **15** were treated with propargylamine using a method applied in the synthesis of the ß-hydroxy analogues **34a-f**. The reaction progress was monitored in each case with TLC. After completion the reaction mixture was concentrated *in vacuo* and the crude product purified by chromatography to afford the propargylamine adduct **42** in generally moderate to excellent yield, as illustrated in Table 5. Formation of the desired products involved direct (S_N) displacement of the chloride anion by propargylamine. Contrary to expectation, no products associated with allylic ($S_N´$)

displacement were obtained. Operation of an S_N' reaction would involve propargylamine attacking at the ß position of the propenoate in adduct **15** thereby displacing the chloride anion and forming an α-methylene moiety. Compound **42b** and **42g** were obtained in sufficient purity as not to require chromatography.

Table 5. Percentage yield of α-propargylaminomethyl cinnamate esters **42**.

α-propargylaminomethyl cinnamate esters		R^1	R^2	R^3	R^4	Yield/ %
	**a**	H	H	H	H	33
	b	H	OCH_2O		H	-
	c	H	Cl	H	H	96
	d	H	H	Cl	H	76
	e	H	OCH_3	H	H	52
	f	H	H	H	OCH_3	60
	g	H	OH	H	H	-

The ^{1}H NMR spectrum of the propargylamino product methyl 3-(3-methoxy-2-nitrophenyl)-2-[(propargylamino)methyl]propenoate **42f** shows the two expected methoxy protons at 3.81 and 3.92 ppm, and the two *N*-methylene proton signals at 3.40 and 3.55 ppm (Figure 27). Significant features in the ^{13}C NMR spectrum of **42f** (Figure 28) include the two methylene, five quaternary and four aromatic methine signals, as well as the terminal and quaternary alkyne carbon signals. Interestingly, in the case of the parent system **42a**, the yield was low (33%) and the NMR spectra indicated the presence of both (E)- and (Z)-diastereomers. In all other cases, only a single geometric isomer was observed.

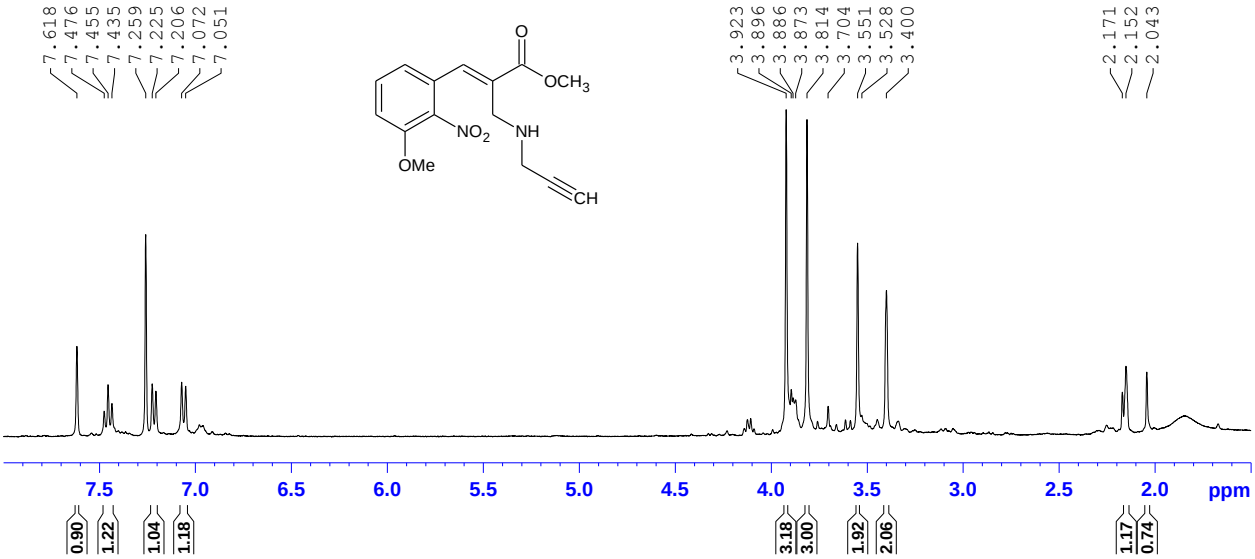


Figure 27. 400 MHz ^{1}H NMR spectrum of methyl 3-(3-methoxy-2-nitrophenyl)-2-[(propargyl-amino)methyl]propenoate **42f** in $CDCl_3$.

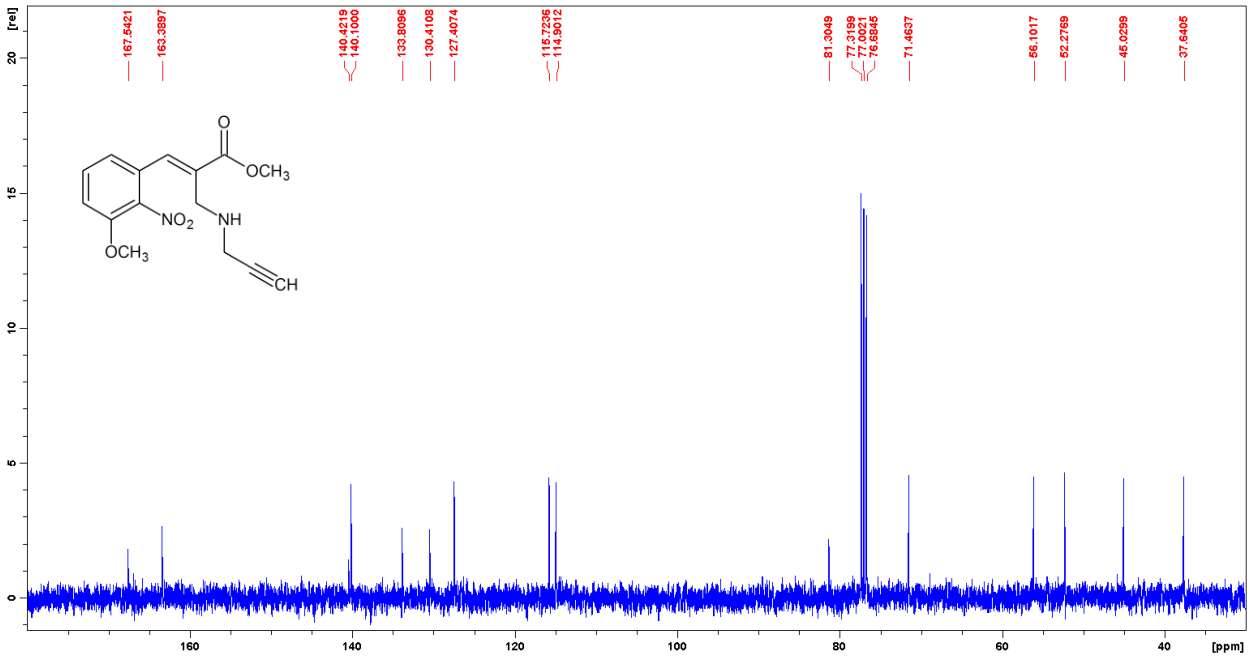


Figure 28. 100 MHz ^{13}C NMR spectrum of methyl 3-(3-methoxy-2-nitrophenyl)-2-[(propargyl-amino)methyl]propenoate **42f** in $CDCl_3$.

2.2.3. *Synthesis of diketo acid analogues: 3-hydroxy ester-AZT and cinnamate ester-AZT conjugates*.

AZT has been used clinically as an HIV-1 RT inhibitor.[29] Part of the aim in this research was to develop dual-action HIV-1 RT/IN inhibitors by conjugating AZT with BH adducts. Using BH methodology, feasible routes to two nuanced classes of BH-AZT conjugates were followed.[18,29] Introduction of the propargyl group to the 3-hydroxy ester **12** or allyl chloride **15** facilitates linkage to the AZT *via* a 'click' reaction. The 'click' reaction involves a 1,3-dipolar Huisgen cycloaddition between the terminal alkyne and an organic azide group giving 1,4-disubstituted triazoles under Cu(I) catalysis. The Cu(I) salt is generated *in situ* through the reduction of a stable Cu(II) salt such as $CuSO_4.5H_2O$ with sodium ascorbate.

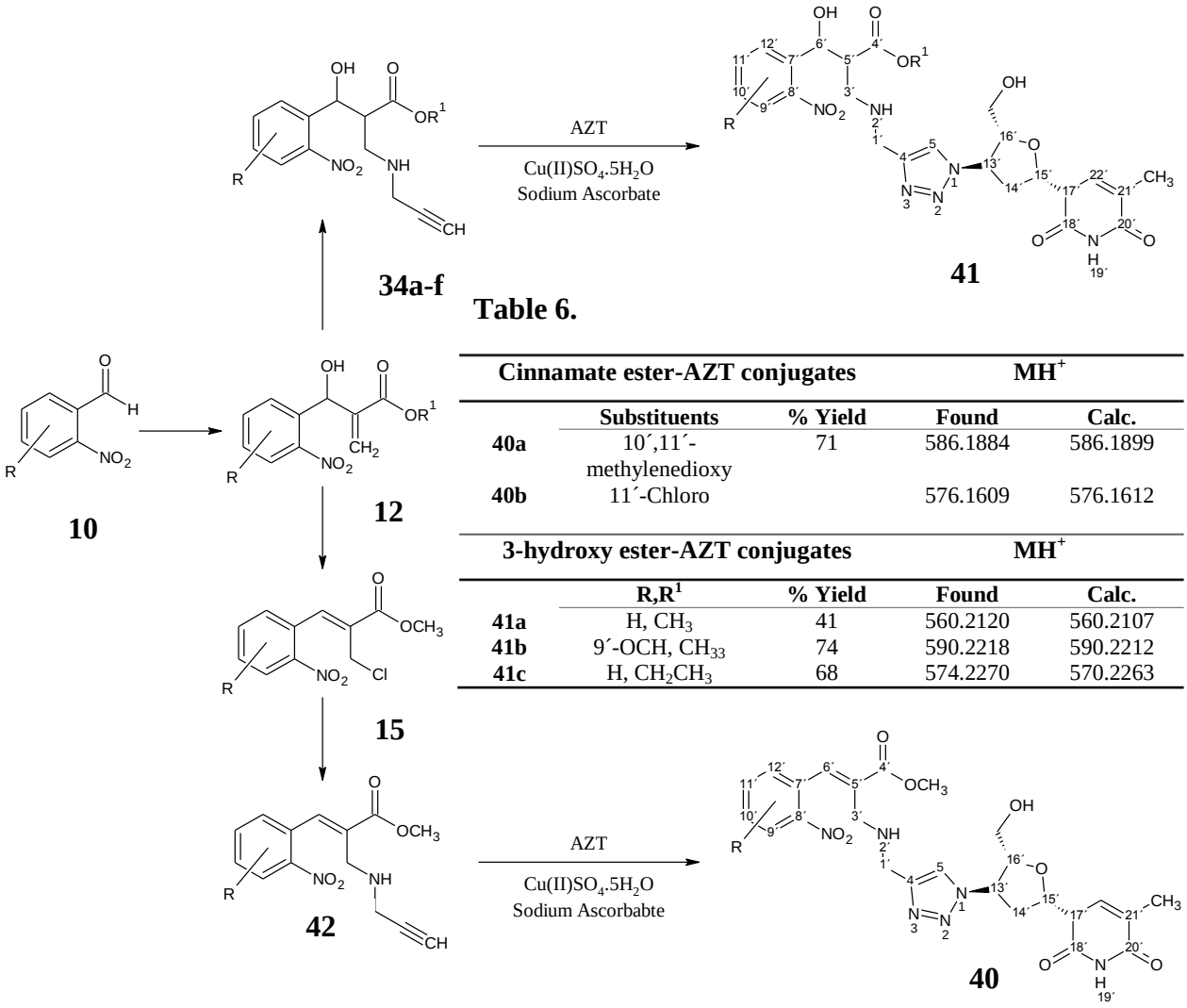


Table 6.

Cinnamate ester-AZT conjugates			MH^+	
	Substituents	**% Yield**	**Found**	**Calc.**
40a	10´,11´-methylenedioxy	71	586.1884	586.1899
40b	11´-Chloro		576.1609	576.1612

3-hydroxy ester-AZT conjugates			MH^+	
	R,R^1	**% Yield**	**Found**	**Calc.**
41a	H, CH_3	41	560.2120	560.2107
41b	9´-OCH, CH_{33}	74	590.2218	590.2212
41c	H, CH_2CH_3	68	574.2270	570.2263

Scheme 10. Pathway to DKA analogues.

The method adopted, which has been employed previously in our research group, involved dissolving propargylamine derivatives (1 eq.) in THF/H_2O (1:1) and then adding AZT (1.2 eq), a catalytic amount of copper(II) sulphate pentahydrate (5%) and sodium ascorbate. The reaction mixture was stirred at room temperature and reaction progress monitored with TLC. After completion, work-up and column chromatography afforded the corresponding products **40** or **41** depending on the substrate used.

The 3-hydroxy ester products were characterized using high resolution MS, NMR and IR analysis. Due to the molecular complexity and the presence of a number of stereogenic centres, NMR analysis proved to be somewhat challenging. The ^{1}H NMR spectrum (Figure 30) of **41a** reveals a singlet at 1.84 ppm corresponding to the AZT methyl protons; the diastereotopic 14-methylene protons of the furanose ring resonate at 2.66 and 2.82 ppm, respectively, as multiplets, the methoxy protons at 3.54 ppm, the six aromatic protons between 7.0 and 8.0 ppm and the 16´-methine proton at 4.42 ppm. The ^{13}C NMR spectrum (Figure 31) reveals the absence of the substrate terminal alkyne carbon signals and the presence of three carbonyl carbons, two from AZT and one from the ester moiety between 160 and 180 ppm and the AZT and ester methyl carbons at 12.6 and 52.4 ppm, respectively. The appearance of four methylene signals in the DEPT 135 (Figure 32) also supports formation of the product. The HSQC spectrum (Figure 33) shows the 13´/15´-methine signals, 14´-methylene signals and the AZT methyl signals. Confirmation of the molecular formula of compound **41b** is provided by the molecular ion peak at m/z 590.2218 in the high-resolution mass spectrum.

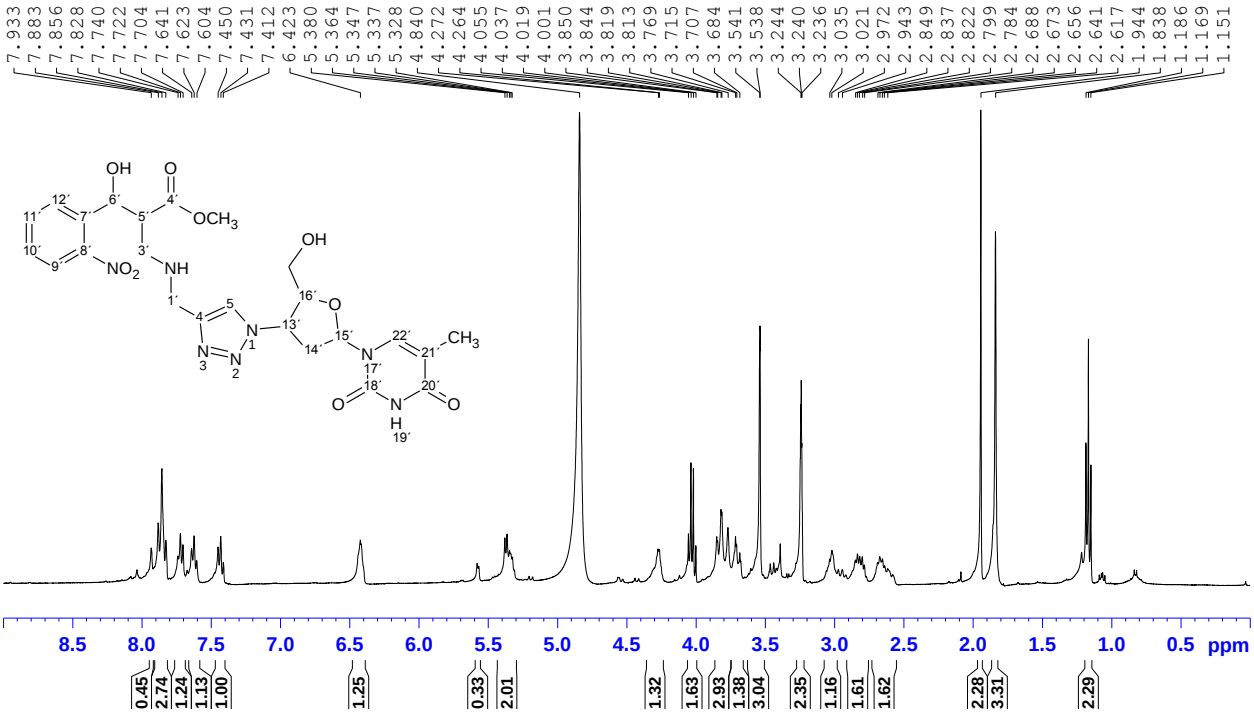


Figure 30. 400 MHz ^{1}H NMR spectrum of **41a** in methanol-d_4.

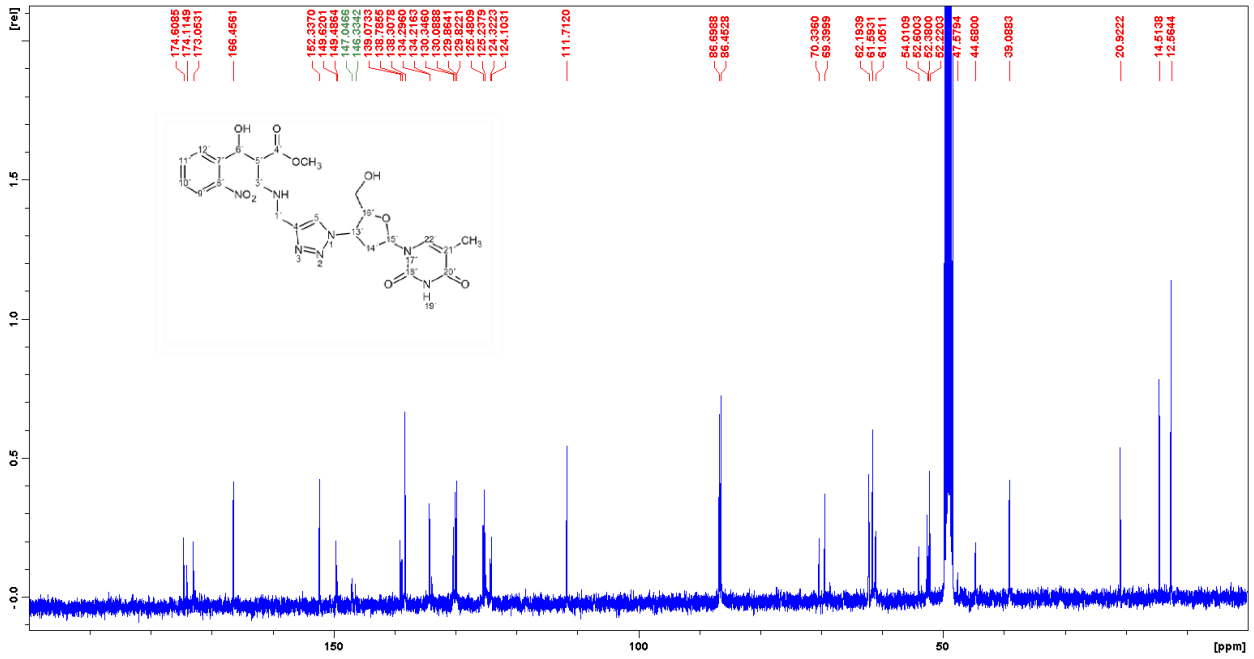


Figure 31. 100 MHz ^{13}C NMR spectrum of **41a** in methanol-d_4.

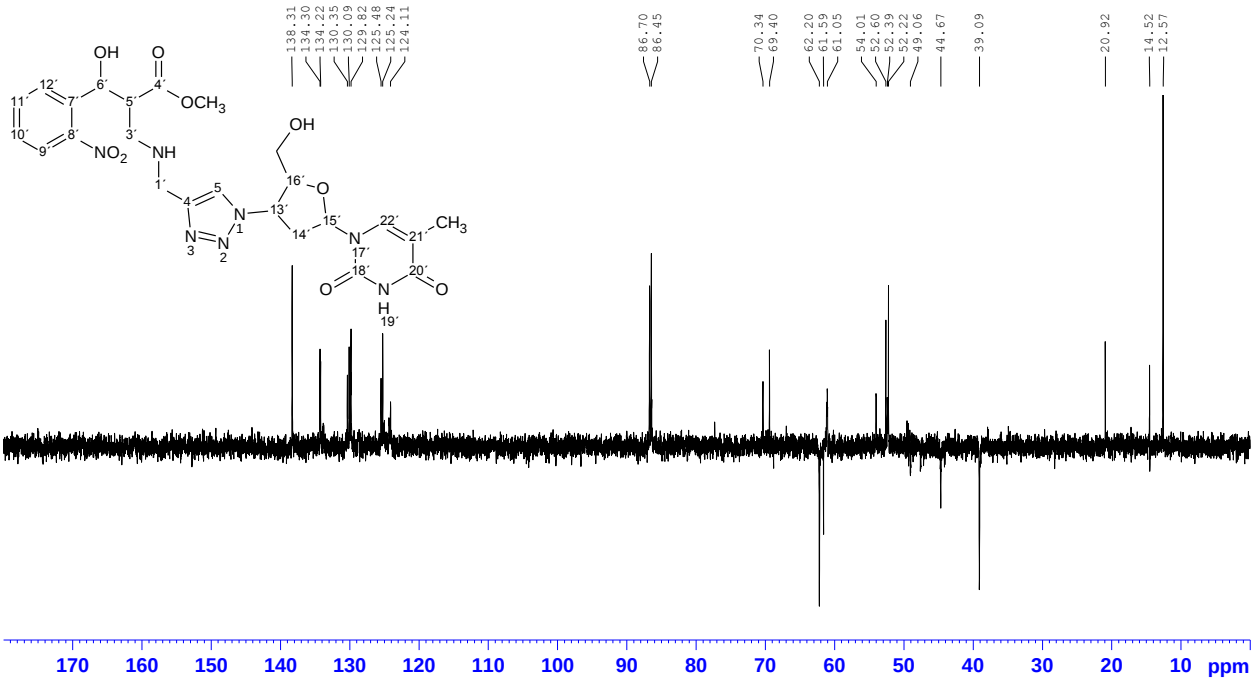


Figure 32. DEPT 135 NMR spectrum of **41a** in methanol-d_4.

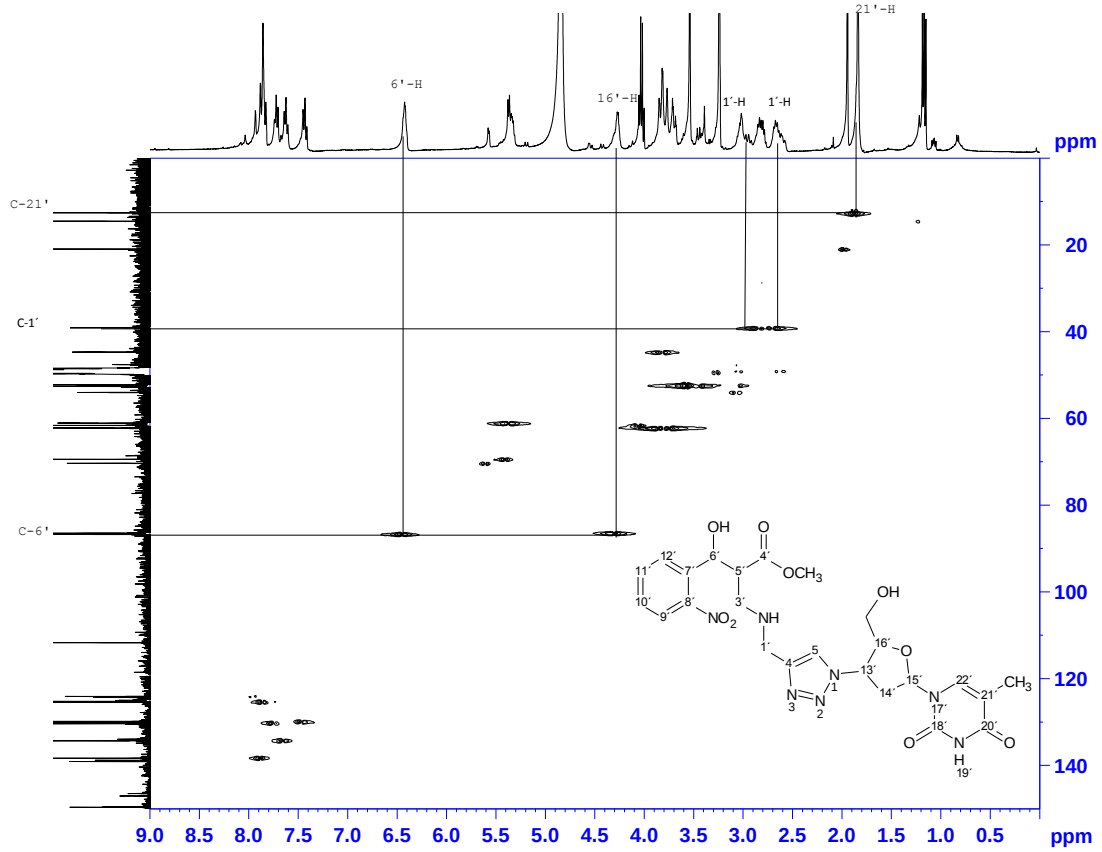


Figure 33. HSQC spectrum of **41a** in methanol-d_4.

The IR spectrum of the 3-hydroxy ester-AZT conjugate **41b (**obtained in 74% yield) also showed the expected OH band at *ca.* 3332 cm^{-1} and the C=O peak at *ca.* 1683 cm^{-1} whilst the HRMS data showed the corresponding molecular ion peaks (Figure 34).

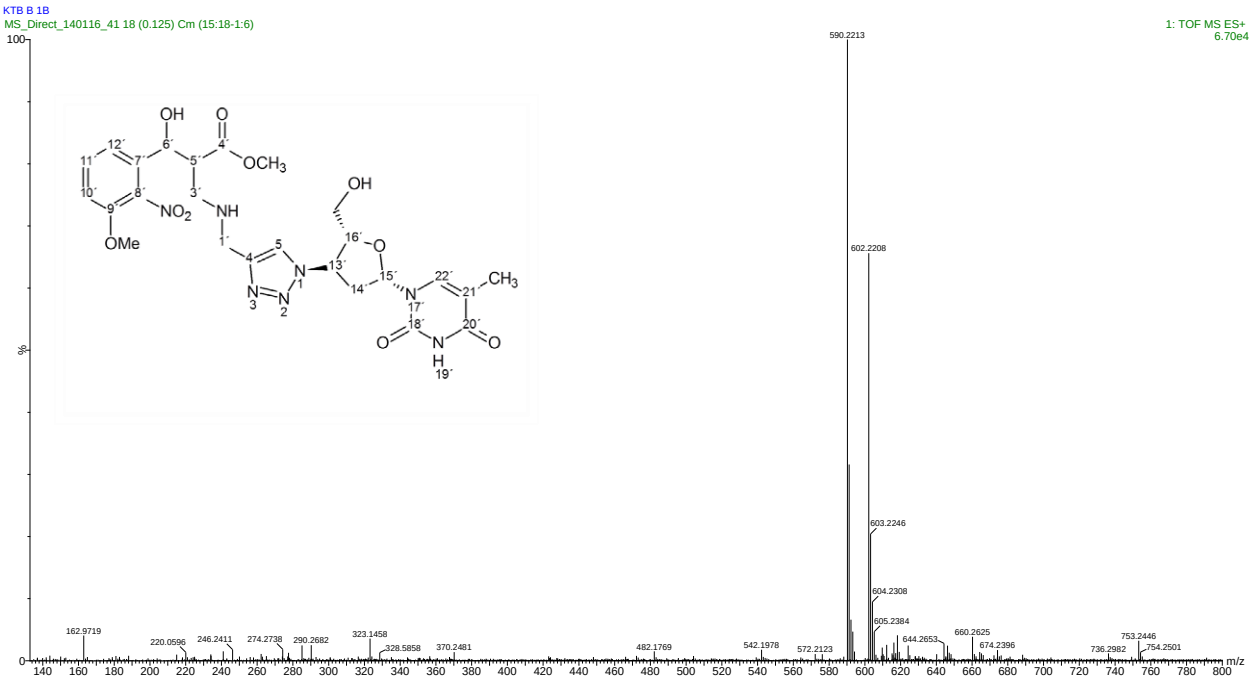


Figure 34. ESI-MS spectrum of 3-hydroxy ester-AZT conjugate **41b**.

Whilst the NMR data indicate the possible presence of minor contaminants, the formation of the desired diastereotopic cinnamate ester-AZT conjugate **40a** was confirmed**.** Thus, the ^{1}H NMR spectrum (Figure 35) reveals the AZT and ester methyl protons at 1.84 and 3.76 ppm, a multiplet at 2.33 ppm corresponds to the 14´-methylene protons, and methylenedioxy protons were observed at 6.15 ppm. The diastereotopic methylene protons adjacent to the alcohol group on the furanose ring are split and resonate at 3.69 and 3.84 ppm. The ^{13}C NMR spectrum (Figure 36) shows the carbonyl carbon signals at 166.4 and 168.9 and the DEPT 135 NMR spectrum (Figure 37) reveals the five expected methylene signals.

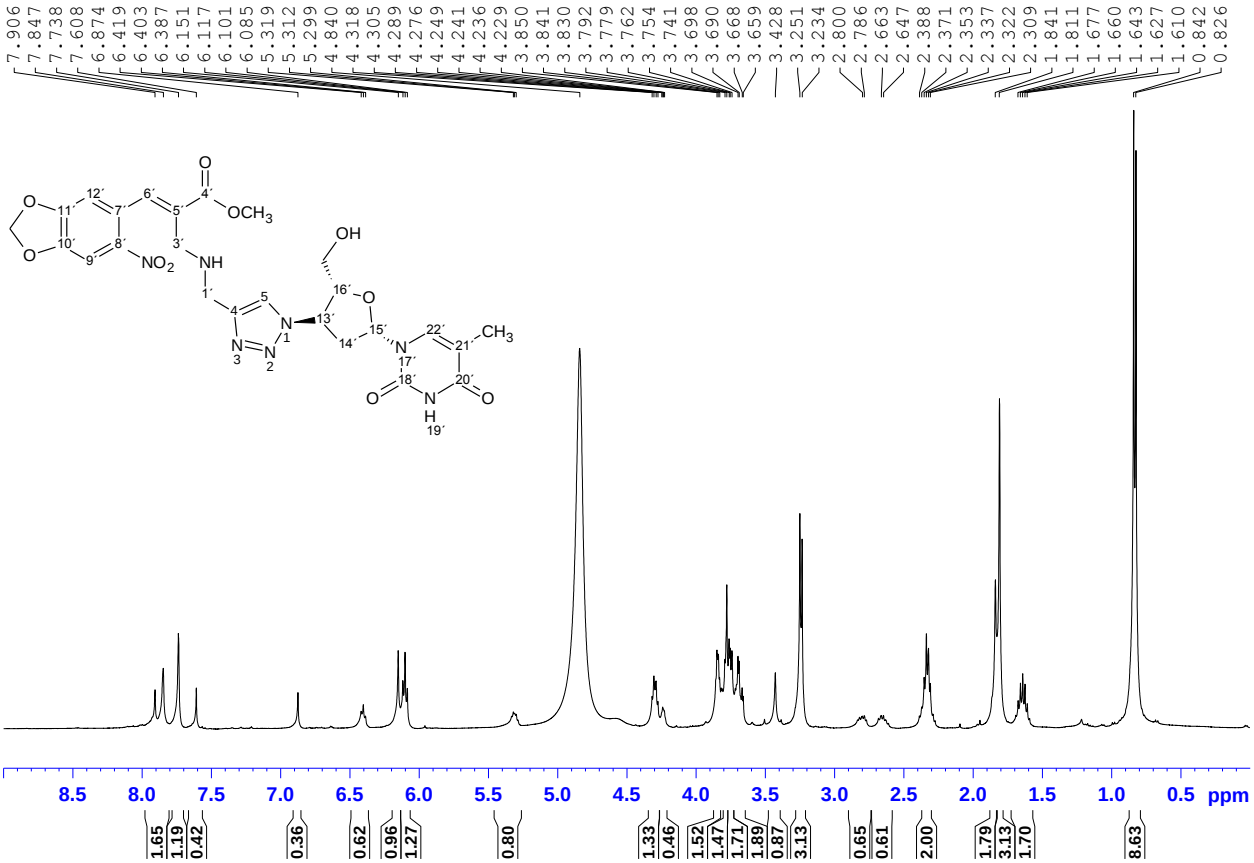


Figure 35. 400 MHz ^{1}H NMR spectrum of **40a** in methanol-d_4.

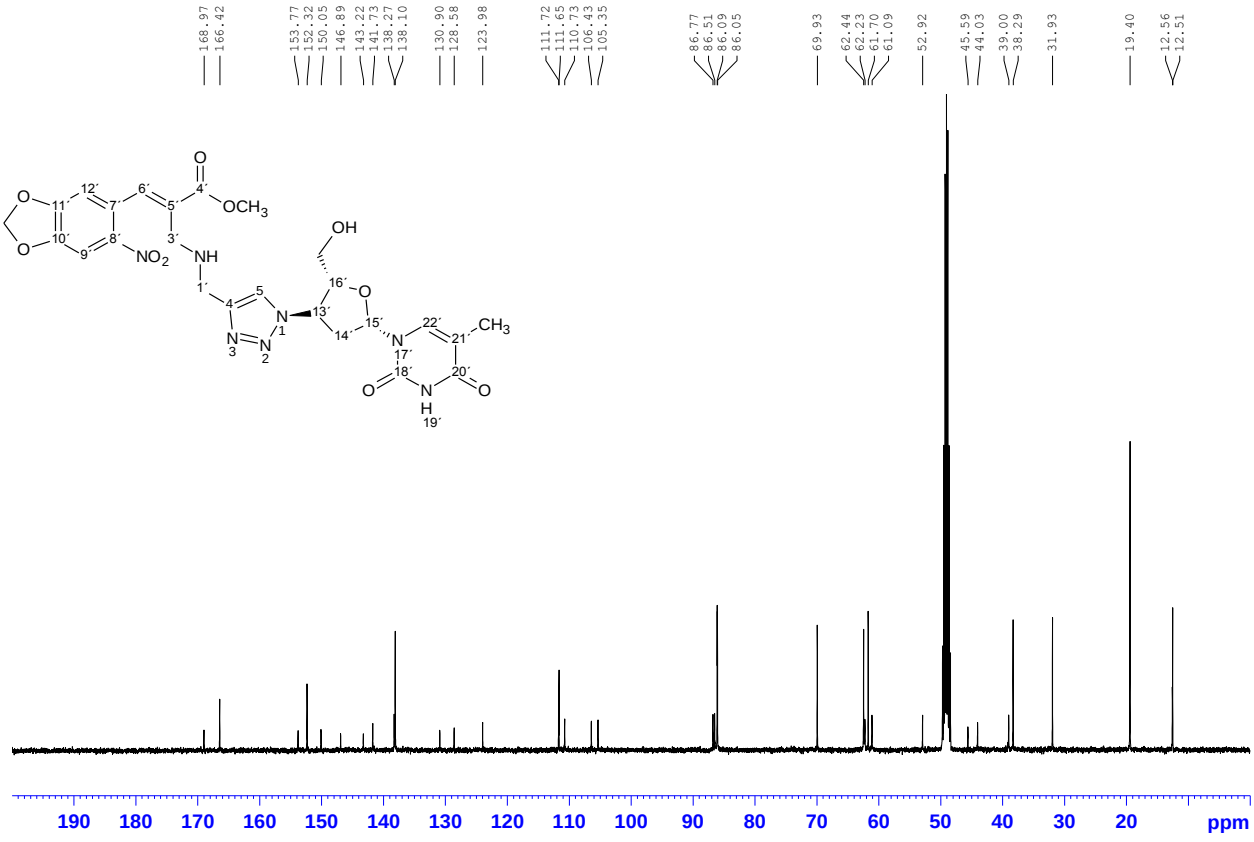


Figure 36. 100 MHz ^{13}C NMR spectrum of **40a** in methanol-d_4.

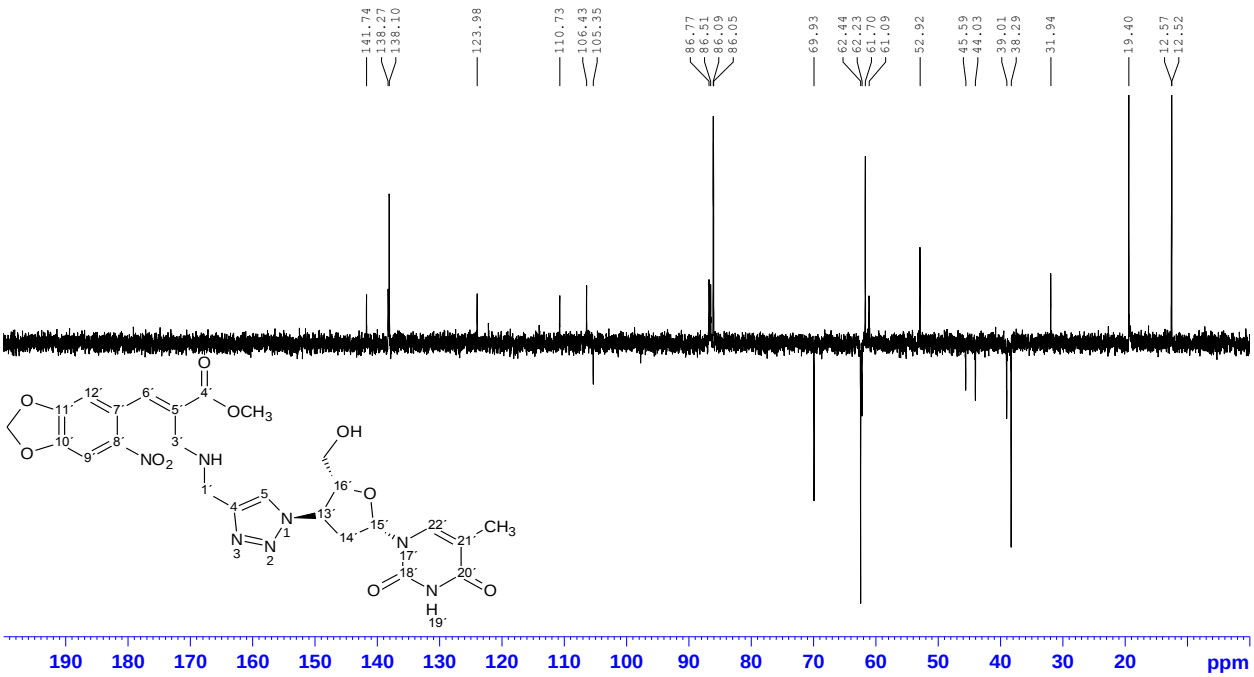
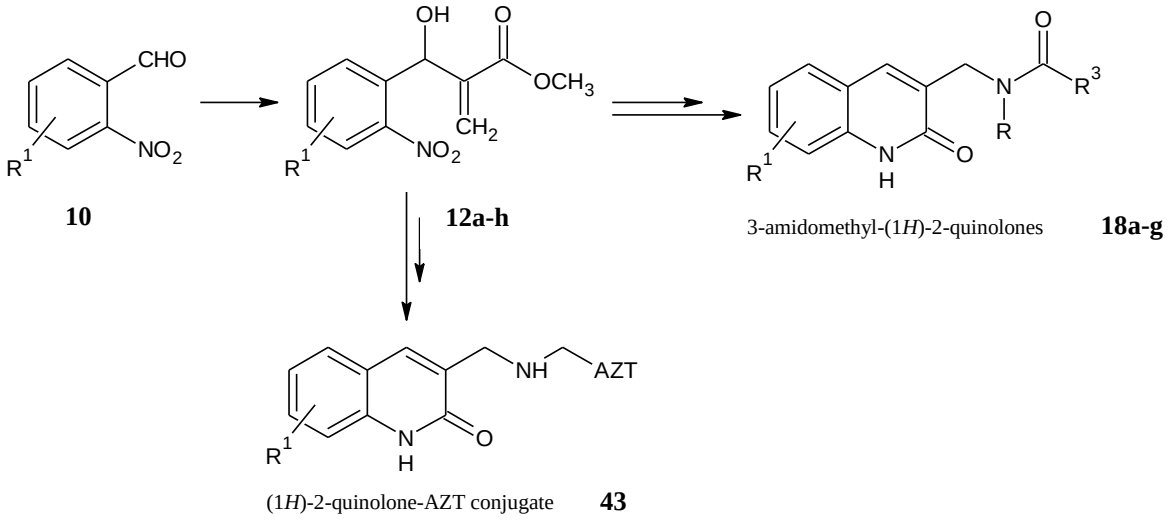


Figure 37. DEPT-135 NMR spectrum of **40a** in methanol-d_4.

Although time constraints have prevented extension of the range of AZT conjugates, synthetic access to both series of compounds of cinnamate ester-AZT conjugates **40** and 3-hydroxy ester-AZT conjugates **41** has clearly been established. Ongoing research in this area will permit the preparation of further analogues, followed by HPLC purification and evaluation of their HIV-1 IN and RT inhibiting potential.

2.3. Exploratory studies

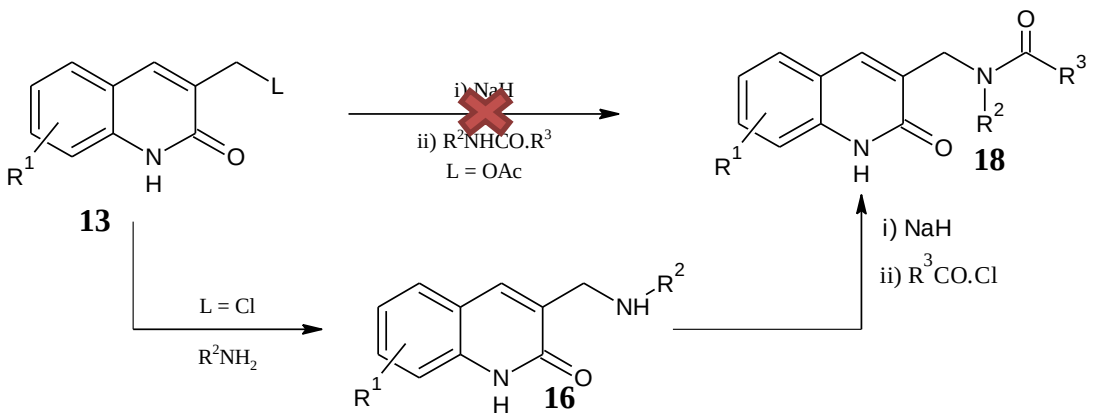
Parallel, exploratory studies using the 2-nitrobenzaldehyde derivatives **10** described in the previous sections were also undertaken. These will be described in sections 2.3.1 to 2.3.3. In addition, these studies included research into the synthesis of:- i) 3-amidomethyl-(1*H*)-2-quinolones (Section 2.3.4) and ii) (1*H*)-2-quinolone-AZT conjugates (Section 2.3.5).



10 **12a-h** 3-amidomethyl-(1*H*)-2-quinolones **18a-g**

(1*H*)-2-quinolone-AZT conjugate **43**

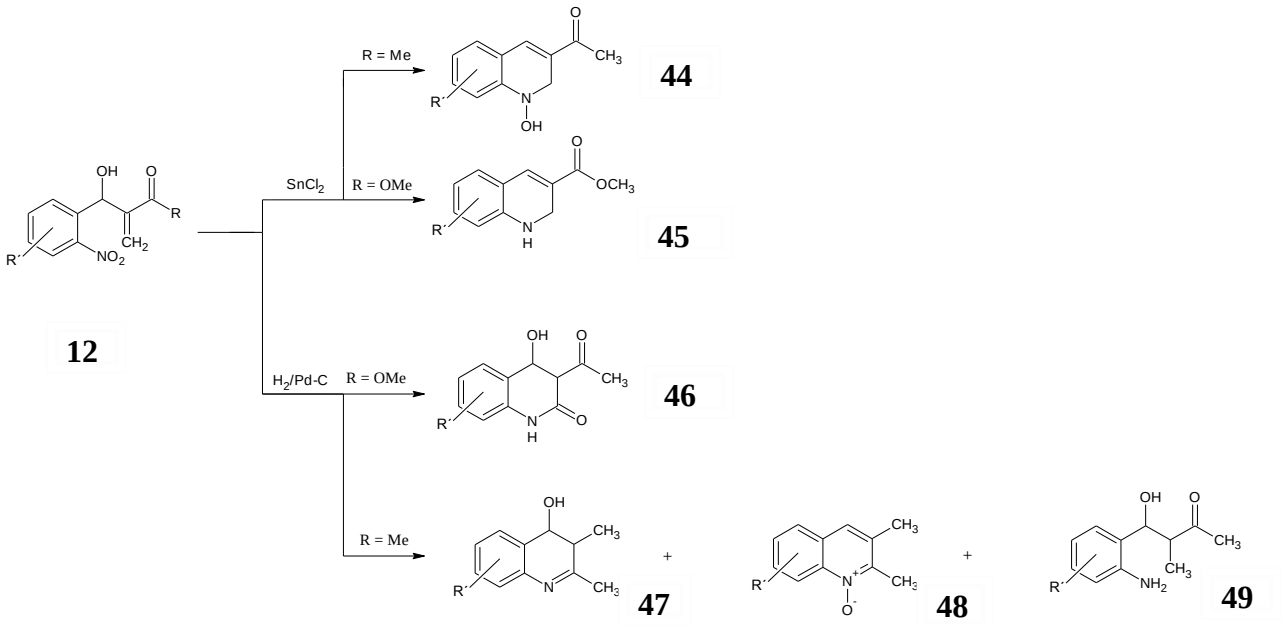
Scheme 11. Targets in exploratory studies.



Scheme 12. Approach to the targeted 3-amidomethyl-(1*H*)-2-quinolones.

2.3.1. *Conversion of Baylis-Hillman adducts to 3-aminomethyl-2-quinolones.*

As indicated earlier, our group has been involved in seminal application of BH methodology in the construction of various quinolone derivatives (see Scheme 13). Consequently, MINTEK research, exploring the development of 3-amidomethyl-(1*H*)-2-quinolones, sought our assistance in establishing access to these compounds.



Scheme 13. Synthesis of quinoline and quinolone derivatives through aryl nitro reduction using Pd on C or stannous chloride ($SnCl_2$).[65,66,76]

2.3.1.1. Synthesis of 3-substituted 2-quinolones.

The first step required reductive cyclisation of the BH adducts to afford 2-quinolones containing suitable substituents at C-3. Several methods of reducing the nitro group have been examined, including catalytic hydrogenation using 10 % palladium on carbon catalyst in EtOH; reduction using stannous chloride dihydrate;[51,66] and, most recently, use of an iron in acetic acid system.[58] Using the former two methods, intramolecular cyclisation took place either *via* conjugate addition or nucleophilic attack at the carbonyl carbon giving a mixture of products **44**-**49**. In addition, early cyclisation yielded quinolone-*N*-oxides **48** (Scheme 13).[66]

However, application of the iron in acetic acid system provided the 3-acetoxymethyl-(1*H*)-2-quinolones **13a-h** from adducts **12a-h** in excellent yields of up to 99% (Table 7). Thus, cyclisation was achieved by reducing the nitro group with catalytic iron powder in acetic acid under reflux at 110 °C. The reaction was monitored by TLC, which showed formation of a product after 30 minutes; and was allowed to run for 12 hours to maximize yield. Work-up and column chromatography gave the desired products. In many cases, NMR analysis of the crude quinolones **13a-h** indicated that the products were clean enough to be used directly in the subsequent reaction.

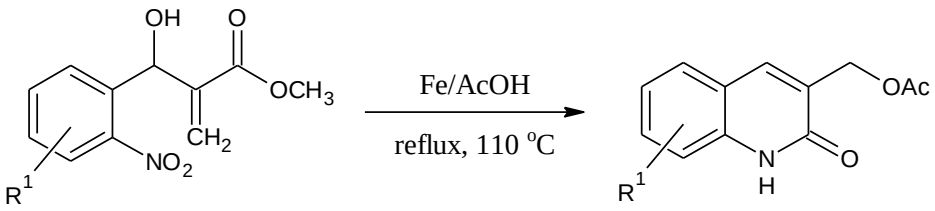


Figure 38. Preparation of 3-acetoxymethyl-(1*H*)-2-quinolones **13a-h**.

Table 7. Percentage yield of cyclized adducts **13a-h**.

3-acetoxymethyl-(1*H*)-2-quinolone	R^1	% Yield
13a	H	91
13b	6,7-methylenedioxy	62
13c	6-chloro	81
13d	7-chloro	86
13e	6,7-dimethoxy	71
13f	6-methoxy	99
13g	7-methoxy	63
13h	7-hydroxy	38

The ^{1}H NMR spectrum of **13a** (Figure 39) shows all the expected signals including the characteristic 4-methine proton singlet at 7.88 ppm, the methylene singlet at 5.23 ppm and the acetate CH_3 singlet at 2.19 ppm. All aromatic protons are observed in the aromatic region: two doublets and two triplets. A broad singlet at 12.22 ppm corresponds to the N-H proton. The ^{13}C NMR spectrum (Figure 40) shows the expected 12 carbon signals including the amide carbonyl at 163.1 ppm and acetate carbonyl at 170.9 ppm and the methylene carbon at 61.4 ppm verifying that cyclisation had been achieved successfully. The reaction involves selective acyl substitution and, therefore, no mixtures of products were obtained.

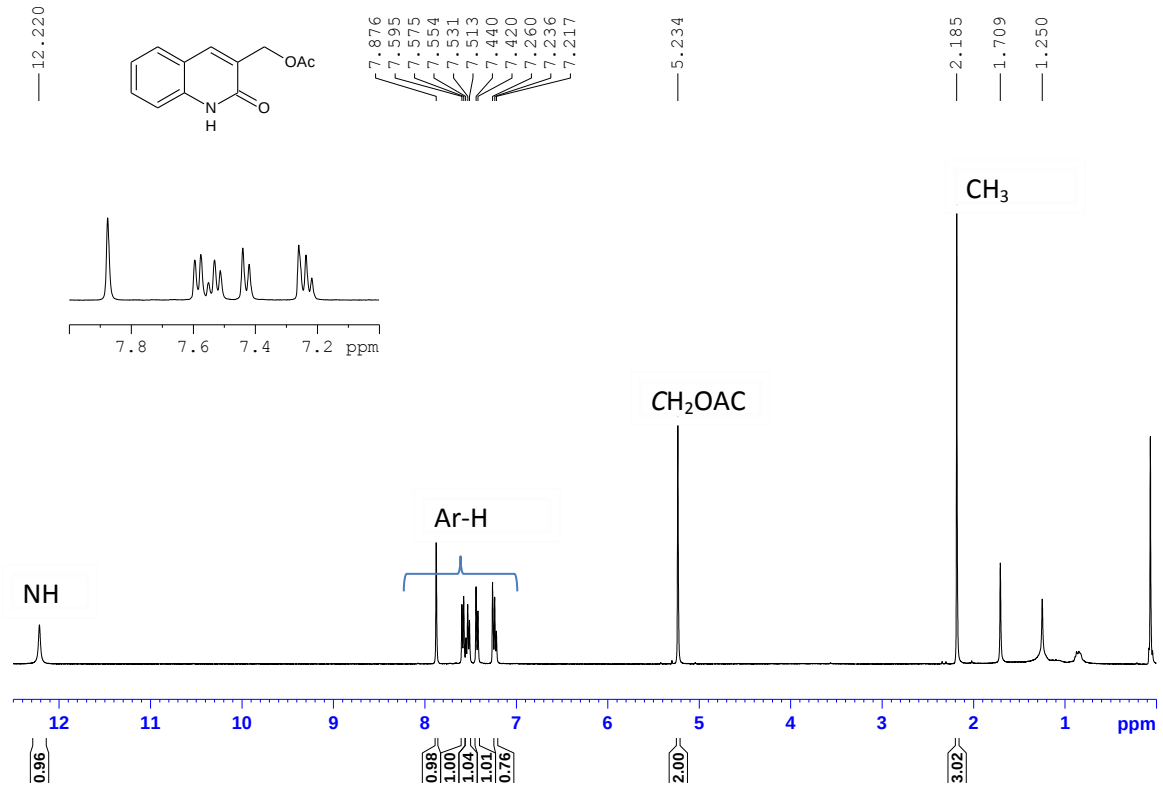


Figure 39. 400 MHz ^{1}H NMR spectrum of 3-acetoxymethyl-(*1H*)-quinol-2-one **13a** in $CDCl_3$.

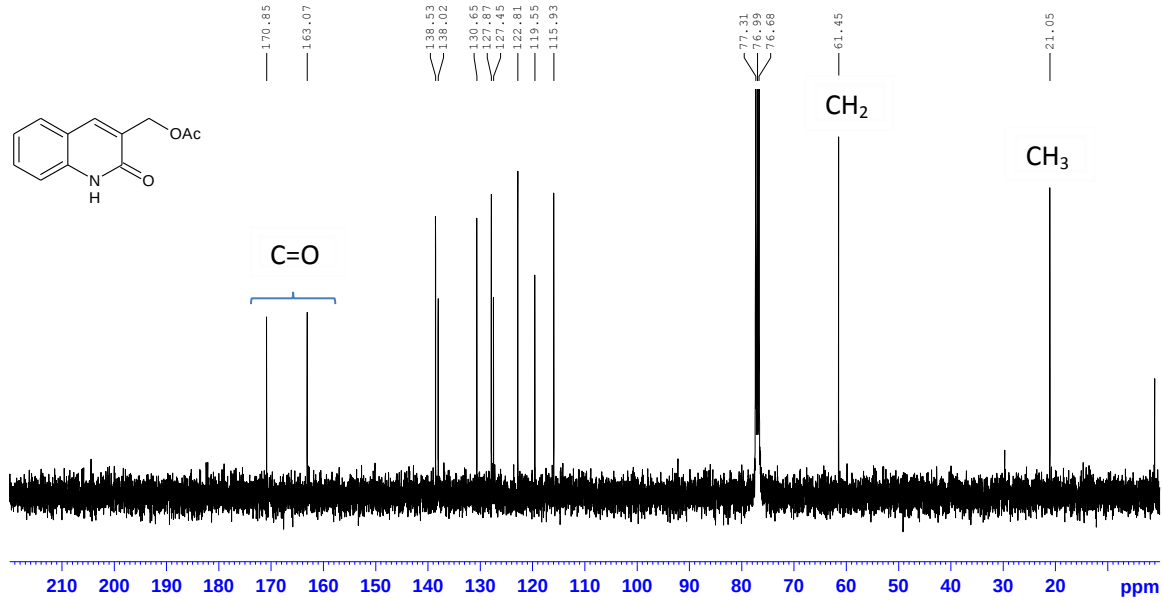
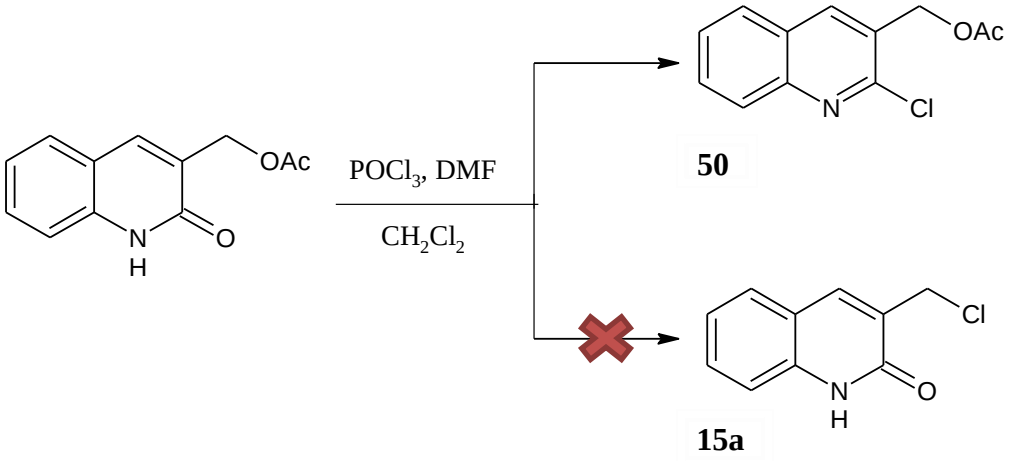


Figure 40. 100 MHz ^{13}C NMR spectrum of 3-acetoxymethyl-(*1H*)-quinol-2-one **13a** in $CDCl_3$.

On the assumption that the acetate group would serve as a good leaving group, a series of nucleophilic substitution reactions with a variety of nucleophiles was attempted. Both base and

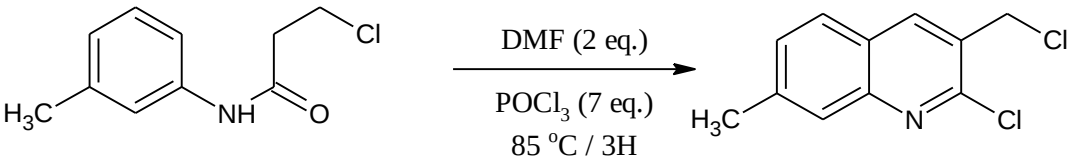
acid catalyzed substitution of the acetate by propargylamine, aniline or piperidine in either dry methanol or THF did not succeed. Elaboration of the quinolone derivatives *via* substitution of the acetate presented enormous challenges and was not successful until functional group interconversion was considered followed by nucleophilic substitution.



Scheme 14. Vilsmeier-Haack attempted synthesis of 3-(chloromethyl)-(1*H*)-2-quinolone **15a**.

In an attempt to generate the 3-chloromethyl derivatives **15a**, the 3-(acetoxymethyl)-(1*H*)-2-quinolone **13a** was reacted with the Vilsmeier-Haack reagent. However, the 2-chloroquinoline **50** was obtained instead of the expected 3-chloromethyl derivative **15a** (Scheme 14). The reaction of the quinolone **13a** and the Vilsmeier-Haack reagent was conducted in a stoppered flask at room temperature and was monitored by TLC. After 48 hours TLC showed the appearance of a product, and work-up and column chromatography afforded a cream solid, which was identified as 3-acetoxymethyl-2-chloroquinoline **50**. The ^{1}H NMR spectrum (Figure 41) of the resulting product resembles that of the reactant, 3-acetoxymethyl-(1*H*)-2-quinolone **13a**. All five aromatic proton signals are present, as are the methylene proton and the acetate methyl proton signals. There is however, a difference in the aromatic proton pattern (Figure 39) indicating that a change had occurred. In the ^{13}C NMR spectrum, only one carbonyl signal (at 170.5 ppm) is observed and this corresponds to the acetate carbonyl carbon and a new quaternary carbon signal appearing at 149.6 ppm is evidence that a new C-Cl bond has been formed in place of C=O.

This finding is similar to results reported by Calvin *et al.*[83] in which chloroethyl anilide **51** was treated with the Vilsmeier-Haack reagent to give 2-chloro-3-chloromethylquinoline **52** (Scheme 15).



51 **52**

Scheme 15.

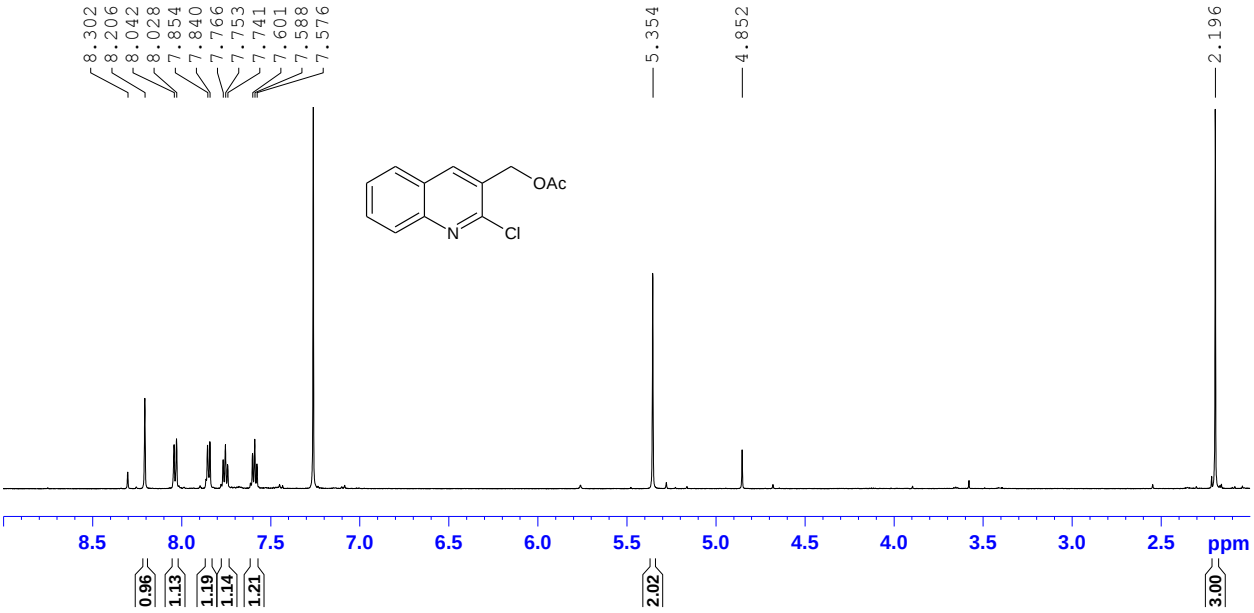


Figure 41. 400 MHz ^{1}H NMR spectrum of 3-acetoxymethyl-2-chloroquinoline **50** in $CDCl_3$.

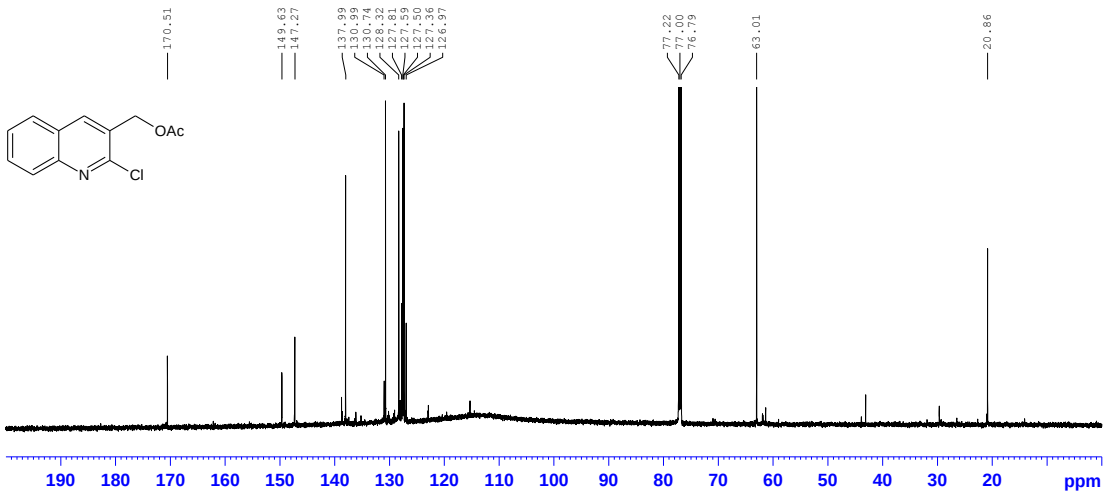
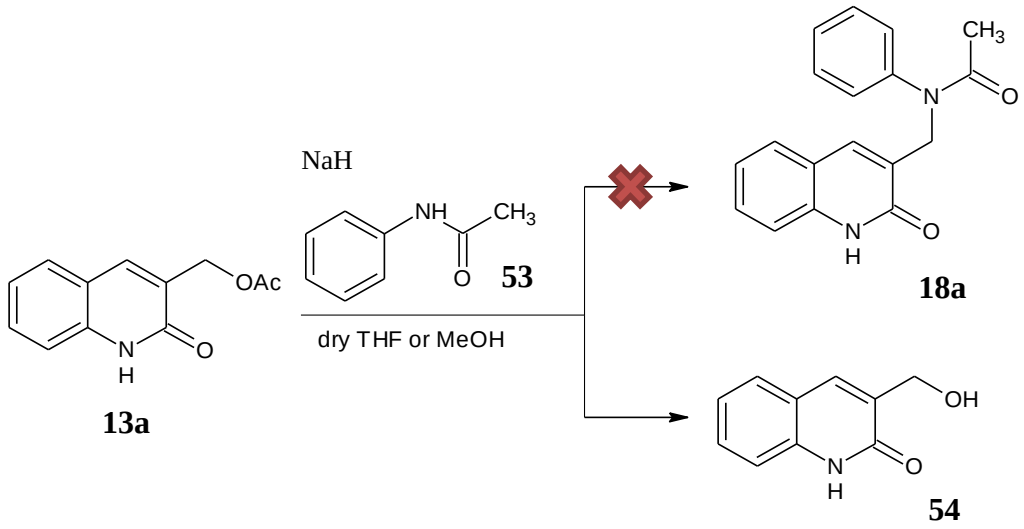


Figure 42. 100 MHz ^{13}C NMR spectrum of 3-acetoxymethyl-2-chloro-quinoline **50** in $CDCl_3$.

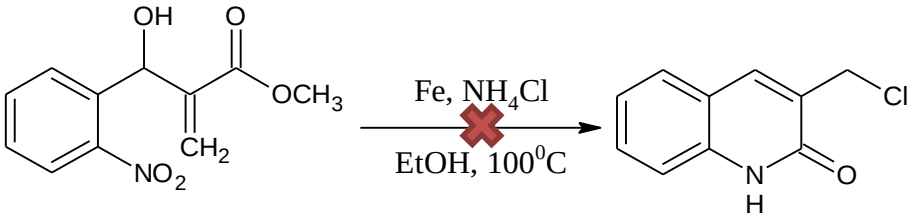
Towards our goal of substituting an amide moiety in the place of acetate, a solution of acetanilide anion (generated by addition of hexane-washed sodium hydride in dry THF to the acetanilide **53** under argon) was added to a solution of the acetate **13a**. The formation of the anion was monitored by TLC at regular intervals, and it was observed that the colour of the milky white ester suspension changed gradually to cream and, eventually, to orange, suggesting the formation of the acetanilide. In another attempt, an amide anion was added dropwise to the acetate solution. In neither approach was the desired product obtained, but purification of the crude product afforded the hydrolyzed adduct, 3-(hydroxymethyl)-(1*H*)-2-quinolone **54a**, the ^{1}H NMR spectrum of which is illustrated in Figure 48.



Scheme 16. Attempted synthesis of 3-[(amido)methyl]-(1*H*)-2-quinolone **18a**.

Failure to obtain the desired amide product **18a** led us to explore other avenues to 3-substituted quinolones using better leaving groups than acetate. These attempts included the following:

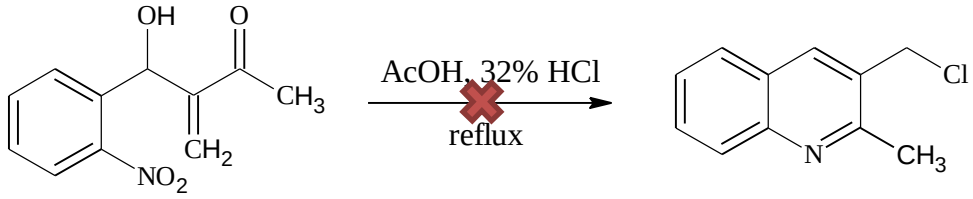
Reductive cyclisation of the BH adduct using iron powder and ammonium chloride in ethanol under reflux at 100 ^0C (Scheme 17). Thus, a solution of methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **12a** and ammonium chloride in ethanol was stirred under reflux and electrolytic iron powder was added. NMR analysis of the crude product showed that some changes had occurred but work-up and purification presented particular challenges and the approach was abandoned.



12a **15a**

Scheme 17.

Conjugate addition of HCl and acid-catalysed cyclisation (Scheme 18). This involved adding 32% HCl (3 mL) to a solution of 3-hydroxy-2-methylene-3-(2-nitrophenyl)butan-2-one **12i** in acetic acid (10 mL) and then refluxing for 12 hours, after which the solution was cooled to room temperature, poured into ice-cold water and stirred. The crude product was extracted but analysis showed this attempt to be unsuccessful.

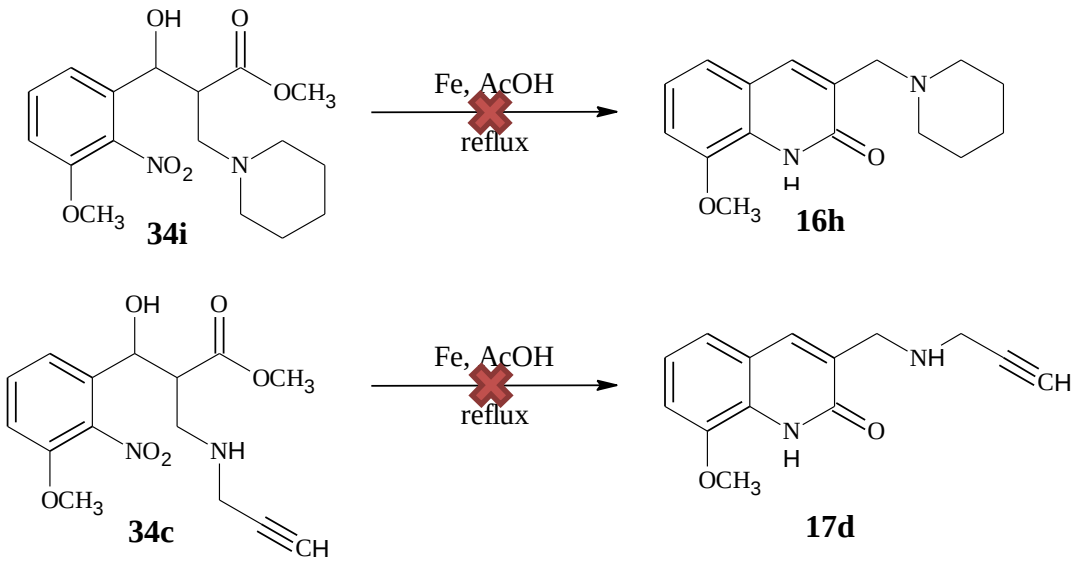


12i **55**

Scheme 18.

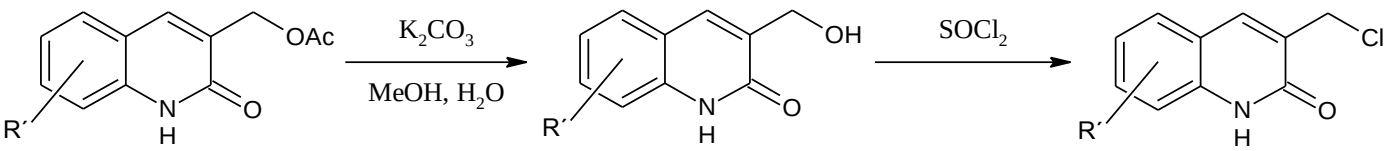
Reductive cyclisation of 2-[(alkylamino)methyl]-3-hydroxy-3-(2-nitrophenyl)propanoate esters (Scheme 19). Thus, compound **34i** was treated with iron in acetic acid, but the 3-acetoxy-(1*H*)-2-

quinolone **13** was obtained. Reaction of the 3-[(propargylamino)methyl] analogue **34c** similarly afforded the corresponding 2-quinolone in negligible yield.



Scheme 19

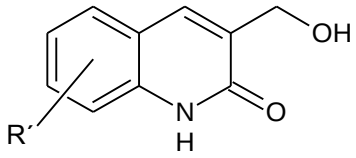
The discovery that the acetate group could be transformed into a hydroxyl group using anhydrous potassium carbonate in methanol with a few drops of water and that the resulting alcohol could be chlorinated provided a breakthrough.[58] However, functional group interconversion from acetate to hydroxyl often required addition of extra water at times when the reaction was not proceeding and, therefore, an improved and more effective method involved carrying out the reaction in a solvent mixture of methanol : water (1:1). The latter method dramatically improved the reaction and complete conversion occurred, permitting successful hydrolysis of crude acetates. Following the strategic plan outlined in the following Scheme, the corresponding 3-hydroxymethyl-(1*H*)-2-quinolones **54a-h** were obtained from the acetates **13a-h**, generally in good yield (Table 8).



Scheme 20

All reactions were conducted at room temperature and reaction progress was monitored by TLC. Use of the improved methodology enhanced the yield of **54a** from 63 to 87 %. Compounds **54f** and **54g** were obtained from hydrolysis of the corresponding crude acetates – hence their low yields. Compound **54h** was characterised with IR prior to subsequent reaction with $SOCl_2$.

Table 8. Yields of 3-hydroxymethyl-(1*H*)-2-quinolones

3-hydroxymethyl-(*1H*)-quinol-2-ones		R´	% Yield
	**54a**	H	87
	54b	6,7-methylenedioxy	79
	54c	6-chloro	83
	54d	7-chloro	85
	54e	6,7-dimethoxy	-
	54f	6-methoxy	56
	54g	7-methoxy	34
	54h	7-hydroxy	-

In the overlaid IR spectra (Figure 43) of 3-acetoxymethyl-(1*H*)-2-quinolone **13a** (blue; top) and 3-hydroxymethyl-(1*H*)-2-quinolone **54a** (black; bottom), significant functional group transformations are shown. The latter spectrum shows appearance of the OH group at 3367 cm^{-1}, the disappearance of the acetate carbonyl group at 1732 cm^{-1}, with the amide carbonyl group at 1648 cm^{-1} remaining unchanged, denoting that functional group interconversion of acetate to hydroxyl had been successfully achieved.

The ^{1}H NMR spectrum of **54a** shows five aromatic proton signals in the aromatic region and an NH proton signal at 11.81 ppm; the methylene protons resonate at 4.40 ppm whereas the OH proton resonates at 5.25 ppm (Figure 44). A significant shift of the methylene proton signals from *ca.* 5.2 ppm in the acetate to 4.4 ppm in the alcohol derivatives signifies that the transformation was successful. The ^{13}C NMR spectrum of **54a** showed a C=O signal at 161.6 ppm and methylene signal at 58.9 ppm. The HRMS shows an $[M+H]^+$ peak at 176.0714, an $[M+Na]^+$ peak at 199.0530, and the base peak at 158.0607 corresponding to a fragment resulting from dehydration.

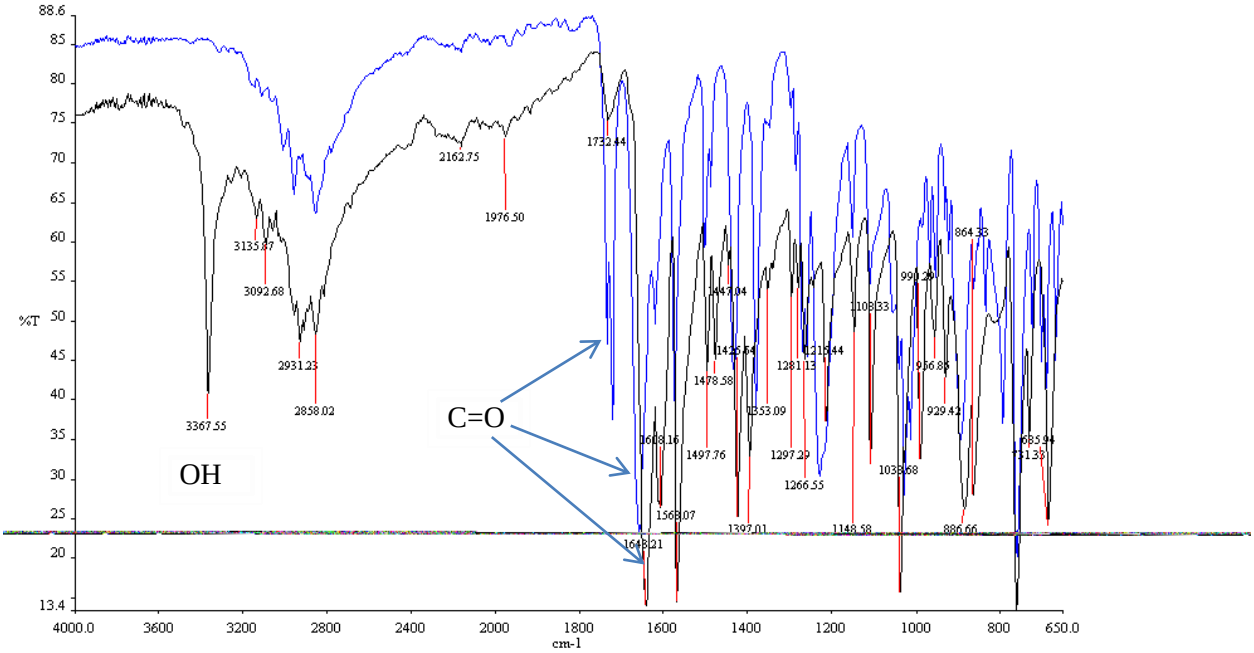


Figure 43. IR Spectra of 3-acetoxymethyl-(1*H*)-2-quinolone **13a** (blue; top) and 3-hydroxy-methyl-(1*H*)-2-quinolone **54a** (black; bottom).

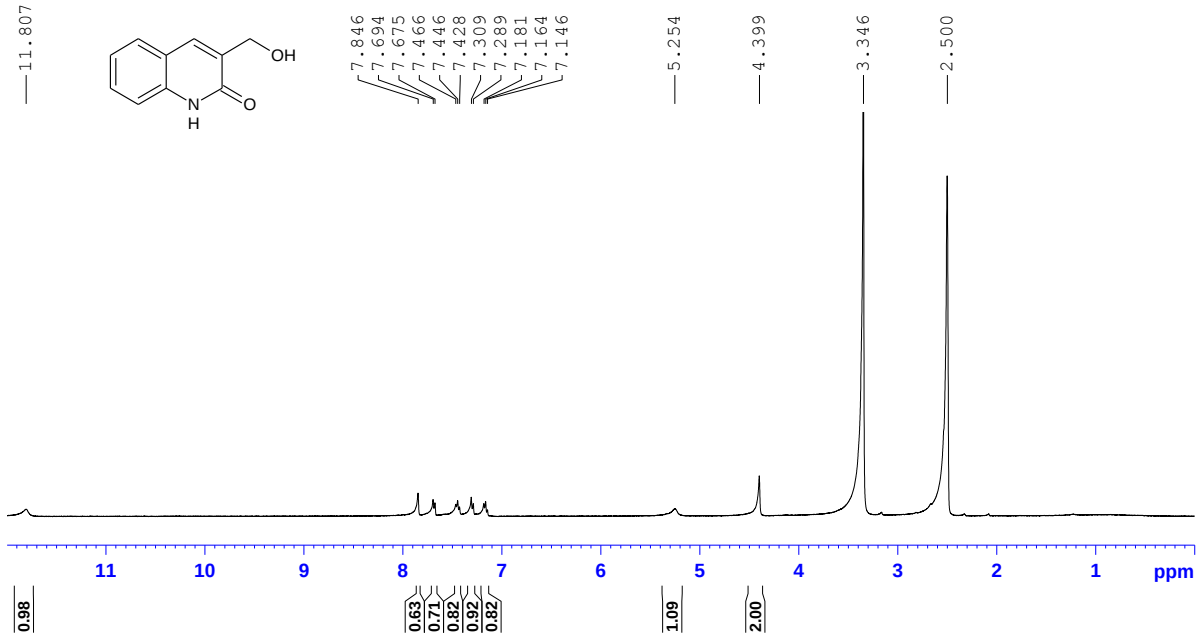


Figure 44. ^{1}H NMR spectrum of 3-hydroxymethyl-(1*H*)-2-quinolone **54a** in DMSO-d_6.

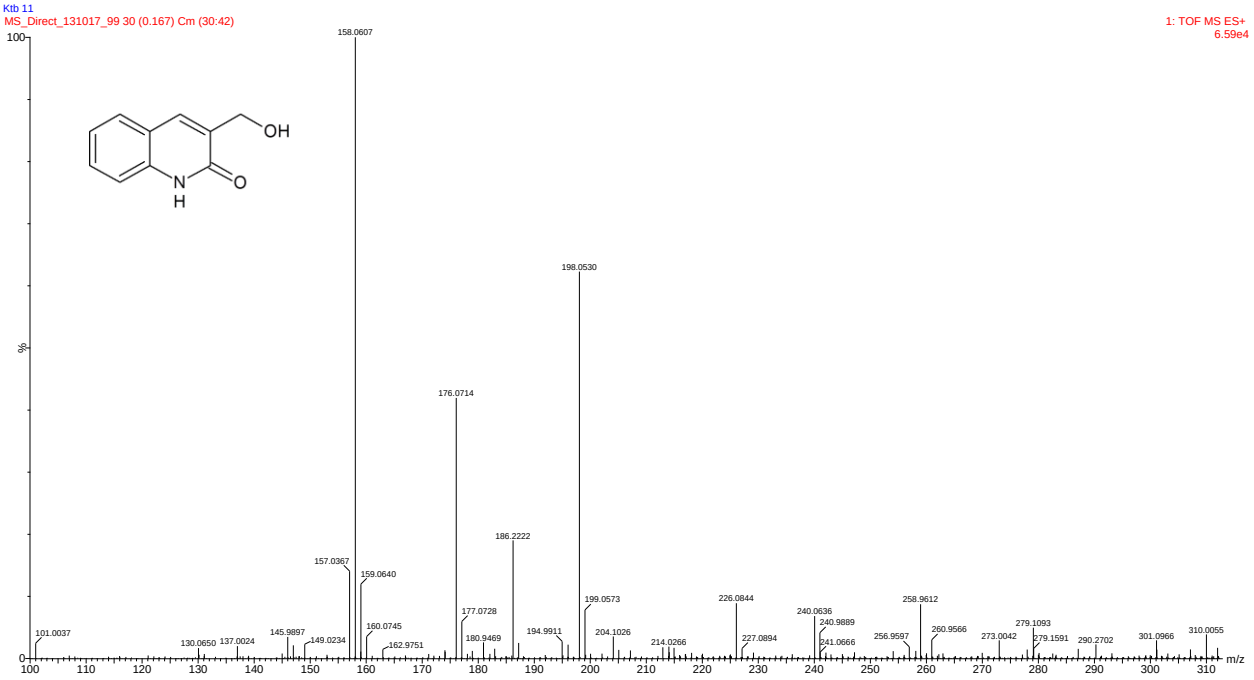
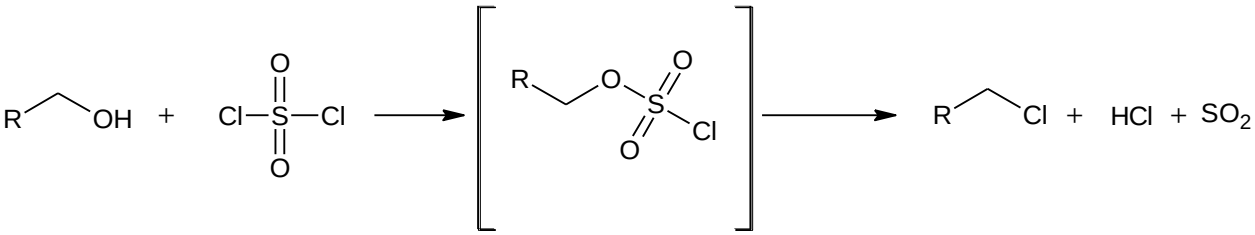


Figure 45. HRMS spectrum of 3-hydroxymethyl-(1*H*)-2-quinolone **54a** using an electrospray ionisation source.

2.3.2. *Synthesis of 3-chloromethyl-(1H)-2-quinolones*

Transformation of the alcohols **54** into the corresponding chlorides **15** was crucial in that it provided substrates with a good leaving group which are susceptible to nucleophilic substitution. A number of chlorination methods were explored, including use of the Vilsmeier-Haack reagent, phosphorus oxychloride and thionyl chloride.[84] The procedure based on the use of thionyl chloride gave the desired products in excellent yields without any by-product(s). *Caution must, however, be exercised when working with thionyl chloride as it is corrosive and reacts rapidly with moisture in the atmosphere.*

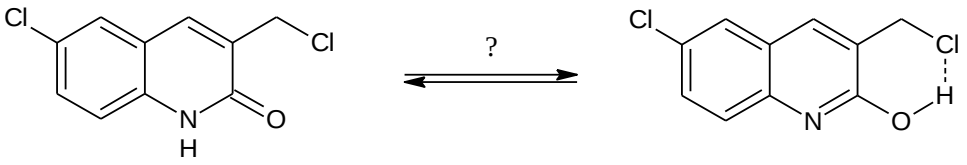
The nucleophilic alcohol oxygen atom is susceptible to attack by electrophiles thereby facilitating displacement. However, the hydroxyl group is itself a poor leaving group because it cannot adequately stabilise the resulting charge on the hydroxide ion. Therefore, the OH functional group needs to be modified to improve its role as a leaving group. The anion of a sulfonate ester is more stable than a hydroxide anion. Subsequent nucleophilic ipso-substitution proceeds by an internal nucleophilic substitution (S_Ni) mechanism (Scheme 21).



Scheme 21. The internal nucleophilic substitution (S_Ni) reaction mechanism: nucleophilic substitution of the hydroxyl group with chloride.[85] R = (1*H*)-2-quinolon-3-yl derivative.

The reactions between the alcohols **54** and thionyl chloride were also conducted under reflux in dry benzene for 12 hours. However, the yield was mediocre and some substrates did not dissolve in benzene. Analysis of the reaction mechanism suggested that benzene played a spectator role and it was decided that reaction could be conducted under solvent-free conditions; as a result the reaction time as well as the yields improved significantly.

The alcohols were stirred in excess thionyl chloride in a stoppered flask at room temperature (Scheme 20). After 30 minutes TLC showed complete chlorination after which the mixture was diluted with dichloromethane and left open in the fume hood for a few minutes to allow by-product gases to disperse. After concentration *in vacuo*, cool water was added to quench the residual thionyl chloride, filtered and air-dried to obtain the corresponding chlorinated products **15a-f**. However, alcohols **54e** and **54h** seemed not to have reacted under these conditions; hence, the chlorination was not successful. The chlorinated products **15** were obtained in yields ranging from 49 to 91 %. To our surprise, 3-(chloromethyl)-6-chloro-*(*1*H*)-2-quinolone **15c** was obtained as a pair of isomers in a ratio of 2:1 – as determined from the ^{1}H NMR integral data. It is thought that the isomers were, in fact, tautomers (Scheme 22)



Scheme 22. Proposed tautomerism in compound **15c**.

The ^{1}H NMR spectrum of 3-(chloromethyl)-(1*H*)-2-quinolone **15a** showed the methylene proton signal at 4.70 ppm, five aromatic proton signals between 7 and 8 ppm, and the NH proton at 11.80 ppm. The ^{13}C NMR and DEPT 135 NMR spectra revealed the methylene signal at 41.4 ppm, the carbonyl carbon signal at 162.6 ppm and all of the remaining eight carbon signals appear in the expected region of the ^{13}C NMR spectrum (Figure 46). In the IR spectrum (Figure 47) the amide carbonyl band appears at 1656 cm^{-1} and the precursor hydroxyl band at 3367 cm^{-1} has disappeared, verifying that the substitution was successful.

For compound **15c**, the ^{1}H NMR spectrum (Figure 48) shows two methylene proton signals resonating close to each other at 4.64 and 4.67 ppm, seven aromatic protons are observed in the aromatic region and two NH signals at 11.34 and 12.14 ppm. In the ^{13}C NMR spectrum, all ten expected signals appear in pairs.

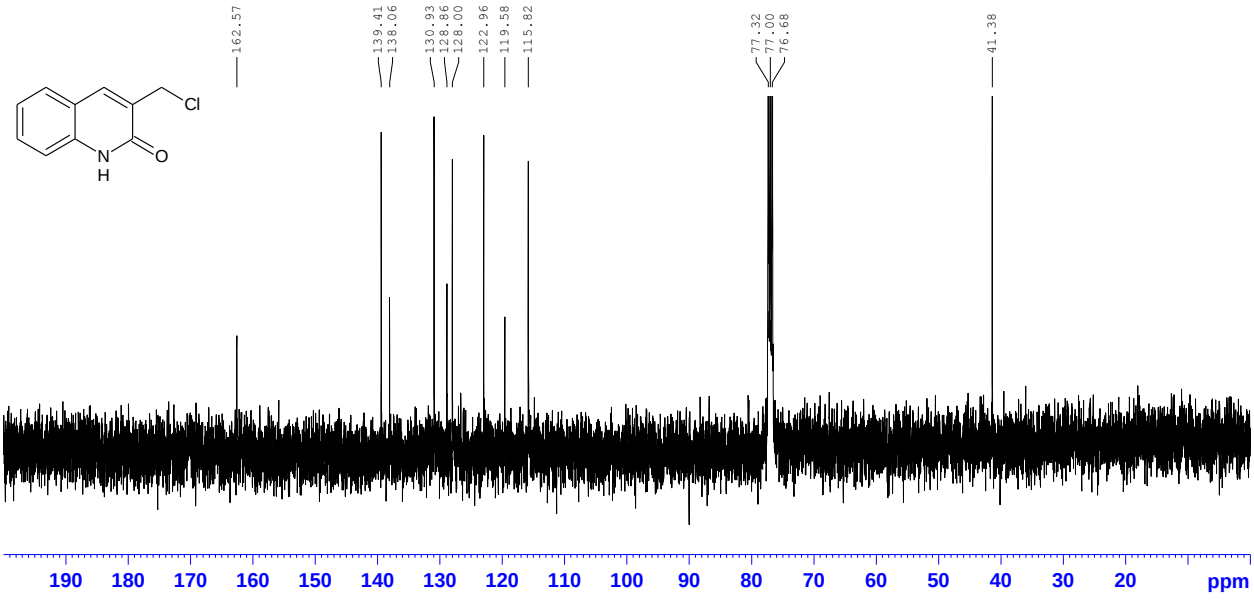


Figure 46. 100 MHz ^{13}C NMR spectrum of 3-(chloromethyl)-(1*H*)-2-quinolone **15a** in methanol-d_4.

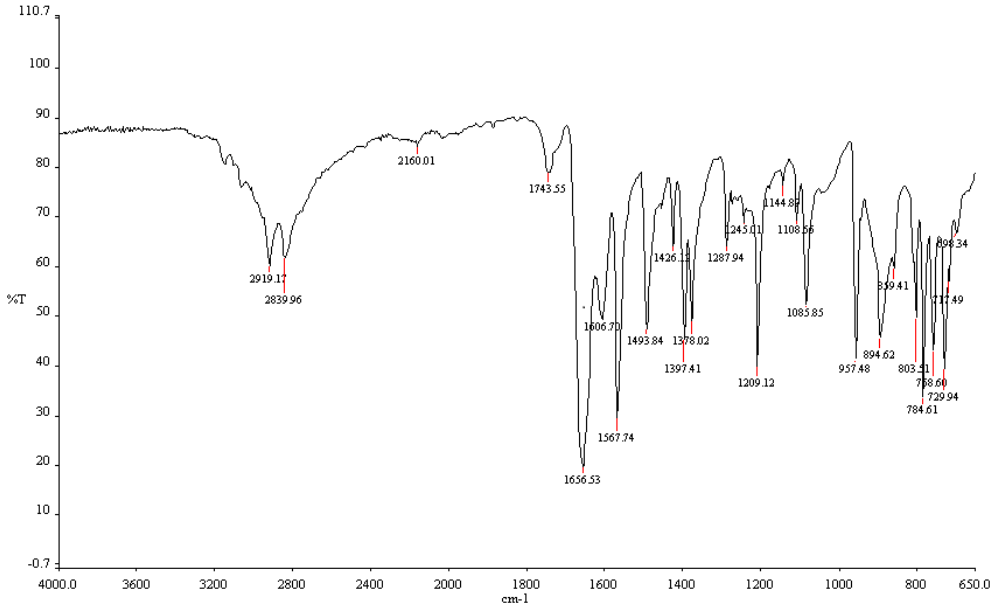


Figure 47. IR spectrum of 3-(chloromethyl)-(1*H*)-2-quinolone **15a**.

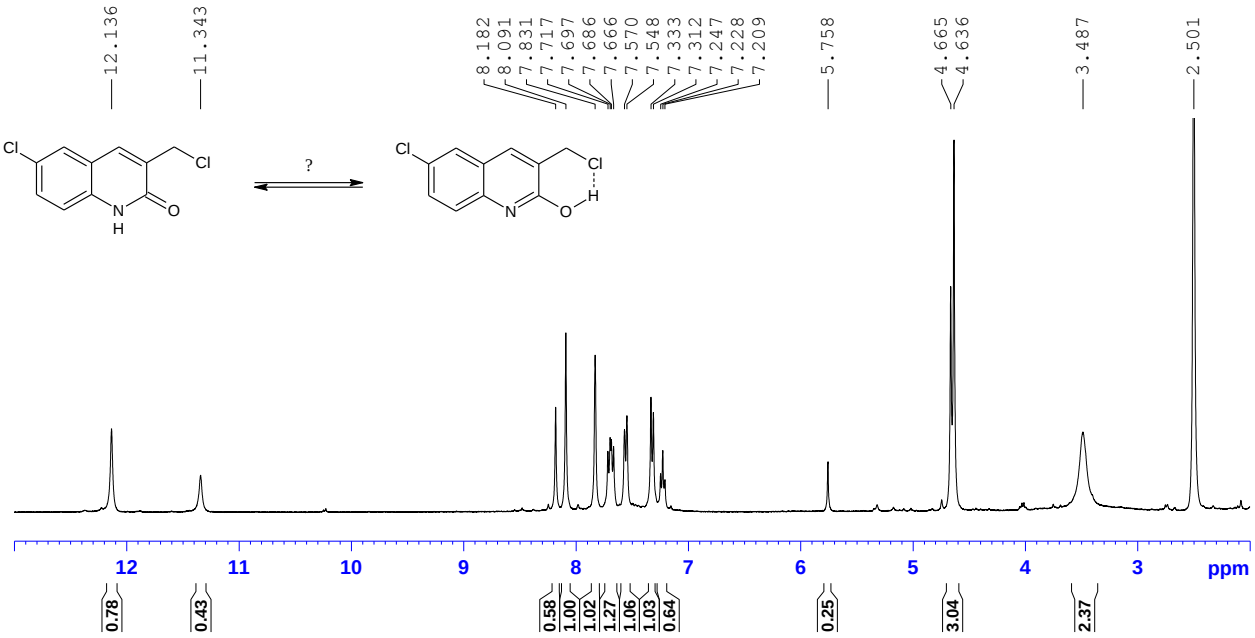


Figure 48. 400 MHz ^{1}H NMR spectrum of the tautomeric mixture of **15c** in DMSO-d_6.

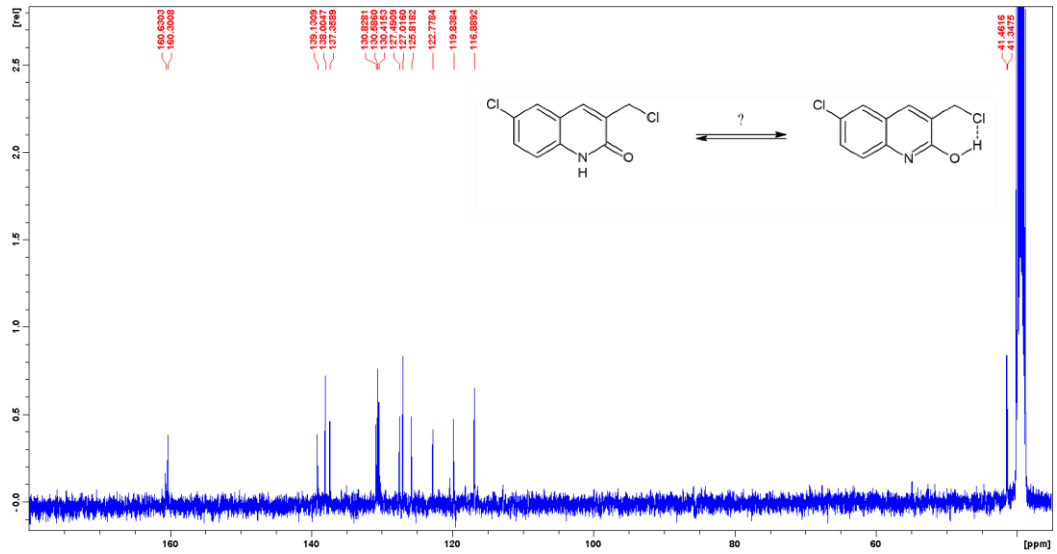
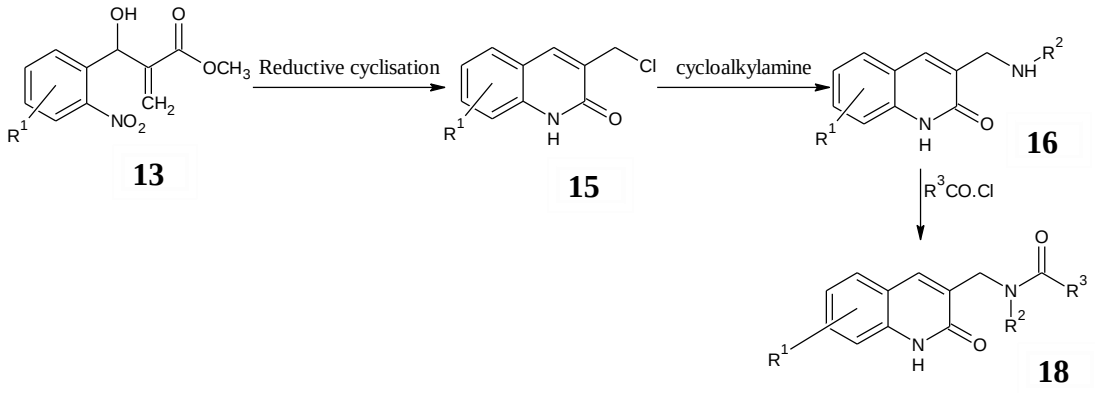


Figure 49. 400 MHz ^{13}C NMR spectrum of the tautomeric mixture of **15c** in DMSO-d_6.

2.3.3. *Nucleophilic substitution reaction of the allyl chlorides 15 with amines.*

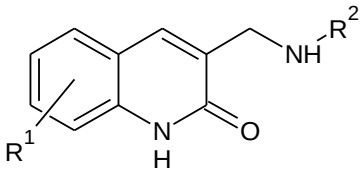
The synthesis of the potential anti-HIV quinoline-based compounds required reductive cyclisation of the BH adducts **12**, subsequent hydrolysis of the acetate derivatives **13**, chlorination, and nucleophilic substitution with appropriate amines leading to the 3-(cycloaminomethyl)-(1*H*)-2-quinolones **16a-f** and 3-(propargylaminomethyl)-(1*H*)-2-quinolones **17**. Synthesis of the 3-(aminomethyl)-(1*H*)-2-quinolones **16** and **17** are the penultimate steps towards the synthesis of the potential protease inhibitors **18** and the dual-action PR/RT inhibitors **43**.



Scheme 23

Following the approach outlined in Scheme 23, a trial reaction involving aniline and the allyl chloride **15d** was conducted in dry ethanol at room temperature; however, after 2 hours, TLC showed no change. The reaction mixture was then refluxed for 3 hours and TLC analysis showed formation of a product. The solution was concentrated but column chromatography of the crude product failed to offer the desired product. However, on reacting the allyl chlorides **15a-f** with excess primary cycloalkylamines in a stoppered flask with stirring at room temperature the reaction progressed to completion. The solution was concentrated and the product extracted with dichloromethane, dried over magnesium sulphate and filtered. The filtrate was concentrated and air-dried to give the desired products **16a-f** in good to excellent yields (up to 93 %; Table 9).

Table 9. Percentage yield of 3-[(cycloalkylamino)methyl]-(*1H*)-2-quinolones **16**.

3-(cycloalkylamino)methyl-(*1H*)quinolinones		R^1	R^2	% Yield
	**16a**	H	cyclohexyl	74
	16b	H	cyclopentyl	60
	16c	6-chloro	cyclohexyl	89
	16d	6-chloro	cyclopentyl	93
	16e	6-methoxy	cyclohexyl	65
	16f	8-methoxy	cyclopentyl	88

The 3-[(cycloalkylamino)methyl]-(*1H*)-2-quinolones **16a-f** were fully characterised. In the ^{1}H NMR spectrum (Figure 50) of compound **16a**, for example, all five quinolone proton signals are clearly evident in the aromatic region; the methylene signal shifted fron *ca.* 4.7 ppm (in the precursor allylic chloride **15a**) to 3.88 ppm, verifying that substitution had been successfully achieved. Signals in the high field region correspond to the cyclohexylamine protons.

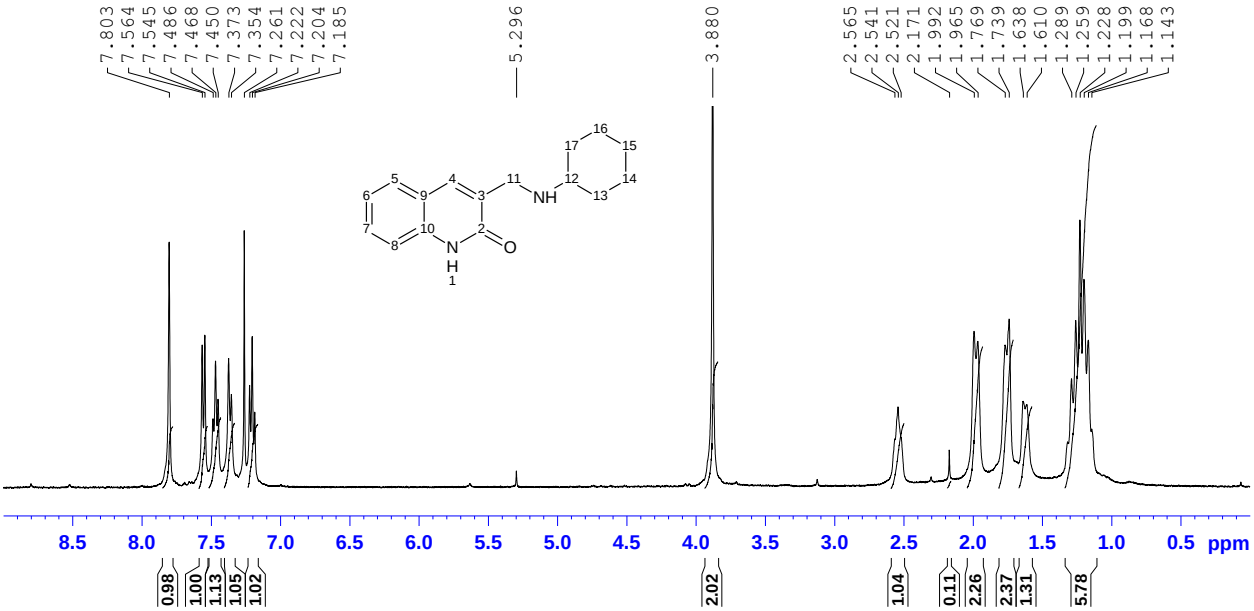


Figure 50. 400 MHz ^{1}H NMR spectrum of **16a** in $CDCl_3$.

The ^{13}C NMR spectrum (Figure 51) shows all of the expected thirteen carbon signals. In conjunction with the DEPT 135 NMR spectrum (Figure 52) it is apparent that the amide carbonyl carbon resonates at 164.0 ppm, the cyclohexylamine methine carbon (C-12) at 56.0 ppm, methylene signal (C-11) at 46.4 ppm, while the five cyclohexylamine methylene carbons resonate at 25.0, 26.1 and 33.5 ppm.

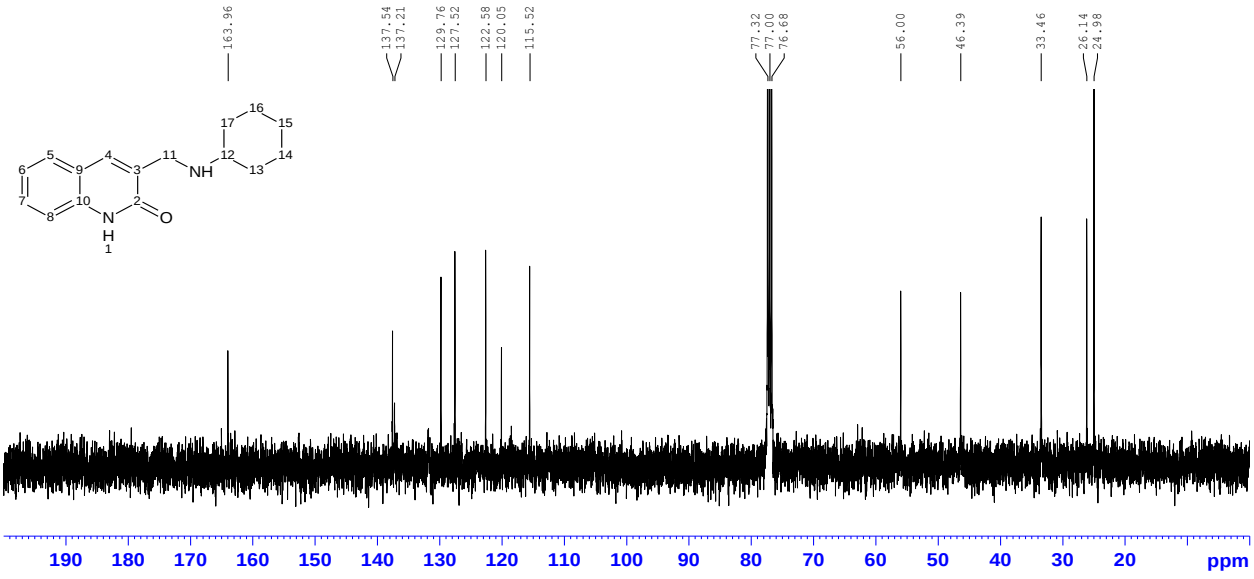


Figure 51. 100 MHz ^{13}C NMR spectrum of **16a** in $CDCl_3$.

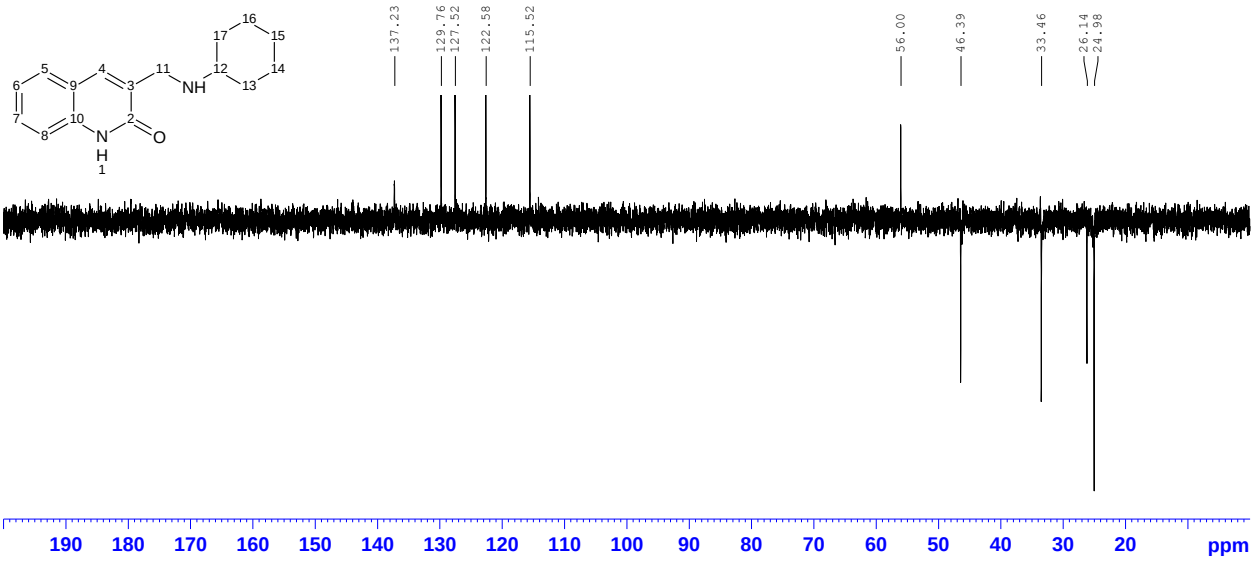


Figure 52. DEPT 135 NMR spectrum of **16a** in $CDCl_3$.

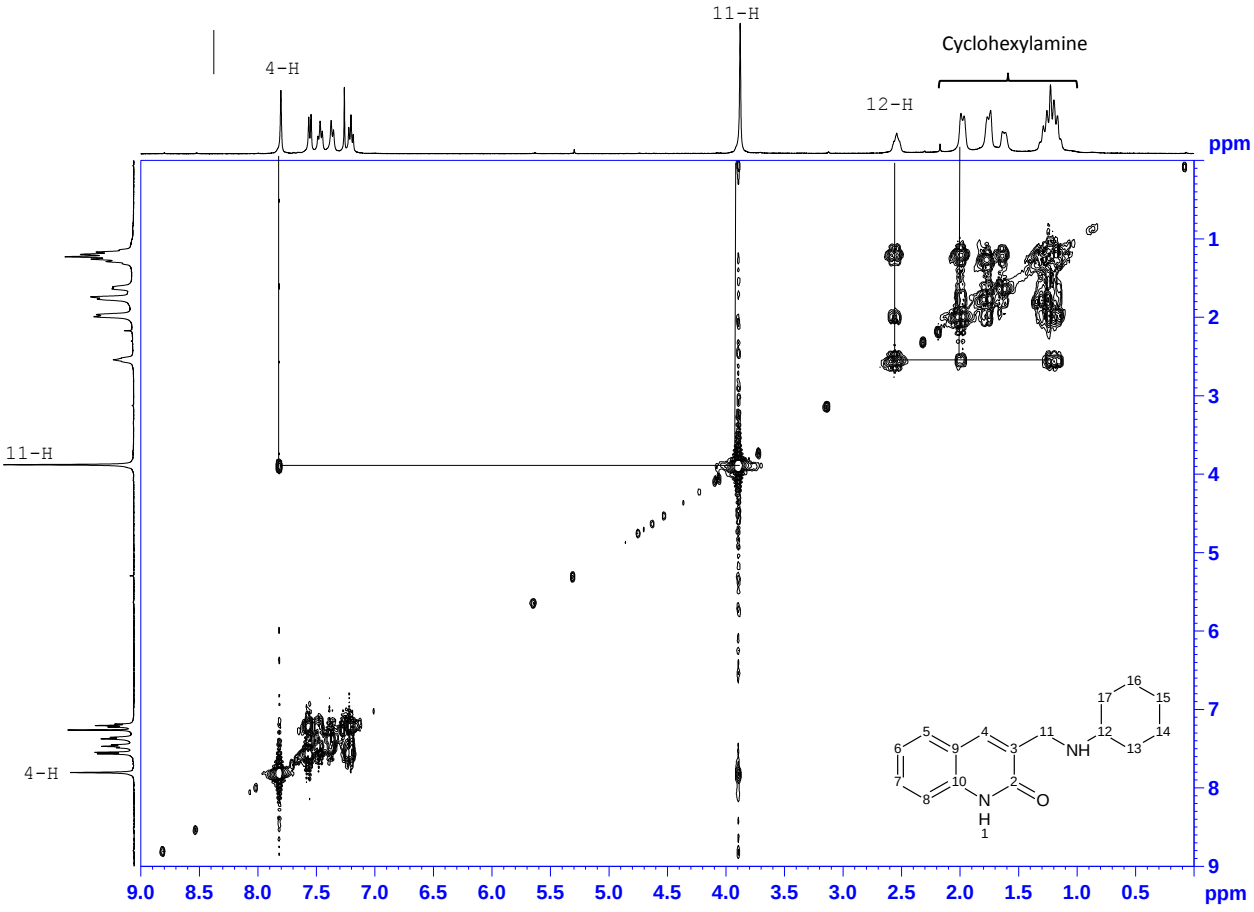


Figure 53. COSY spectrum of **16a** in $CDCl_3$.

In the COSY spectrum (Figure 53) it is apparent that the 2-methine proton responsible for the broad signal at 2.54 ppm couples with the pairs of diastereotopic protons of the adjacent methylene groups (13 and 14), which resonate at *ca.* 2.0 and 1.2 ppm. The allylic coupling between the 11-methylene protons and 4-methine proton is also clearly shown.

From the HSQC spectrum (Figure 54) the 11-methylene and 12-methine signals are clearly evident as are the correlations between the aromatic carbons and protons. As expected, the IR spectrum (Figure 55) shows the crucial NH band at 3294 cm^{-1} and the amide carbonyl (C=O) band at 1652 cm^{-1} confirming formation of the desired product.

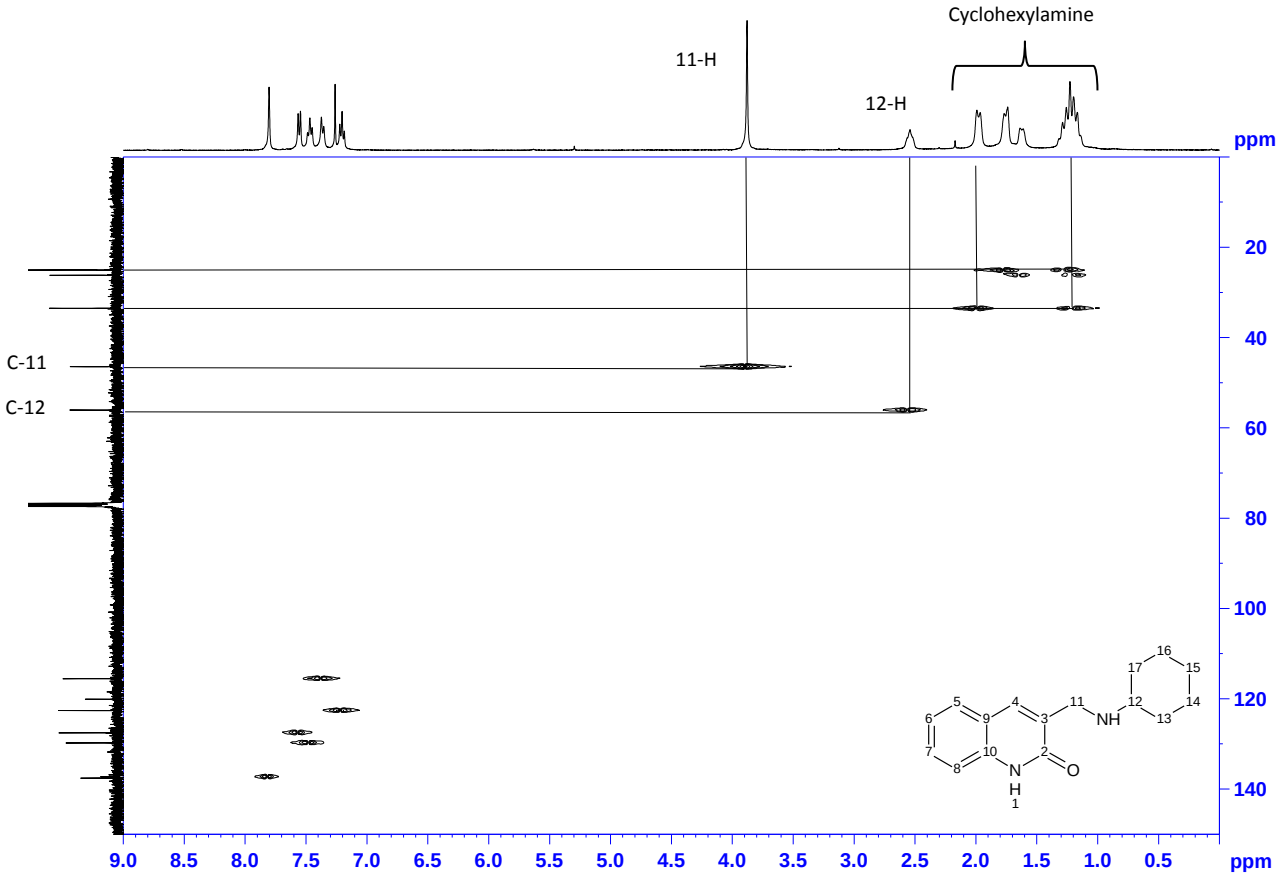


Figure 54. HSQC spectrum of **16a** in $CDCl_3$.

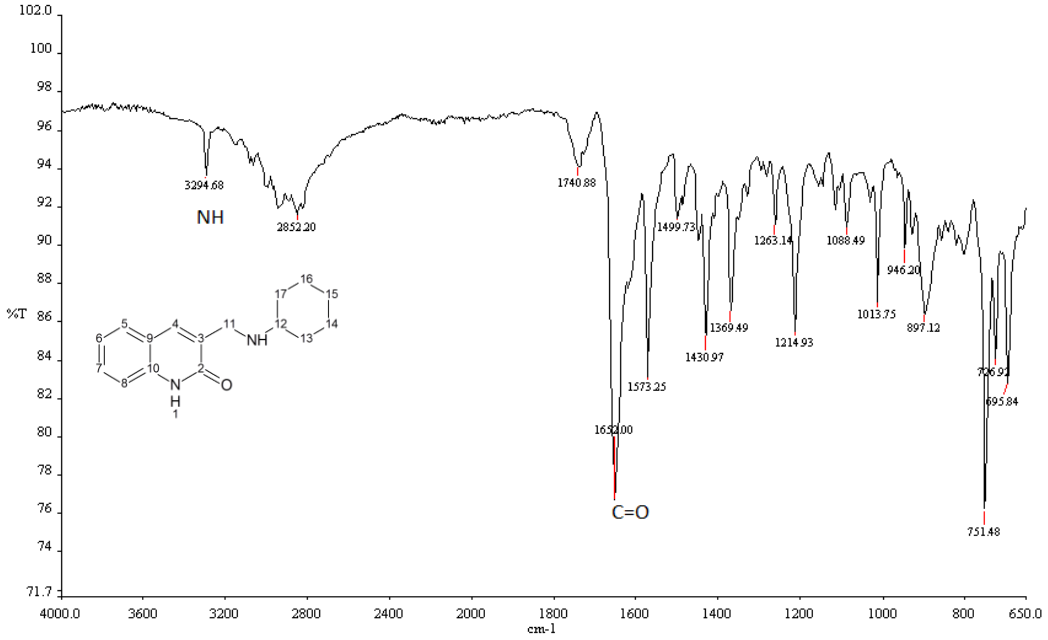


Figure 55. IR spectrum of **16a**.

The main challenge in the synthesis of 3-cyclopropylaminomethyl-(1*H*)-2-quinolone **16g** was the removal of unreacted cyclopropylamine. However, TLC and NMR analysis showed complete conversion to **16g** and the ESI-MS base peak at 215.1178 corresponds to the molecular ion (MH^+) peak of 3-[(cyclopropylamino)methyl]-(*1H*)-2-quinolone (Figure 56).

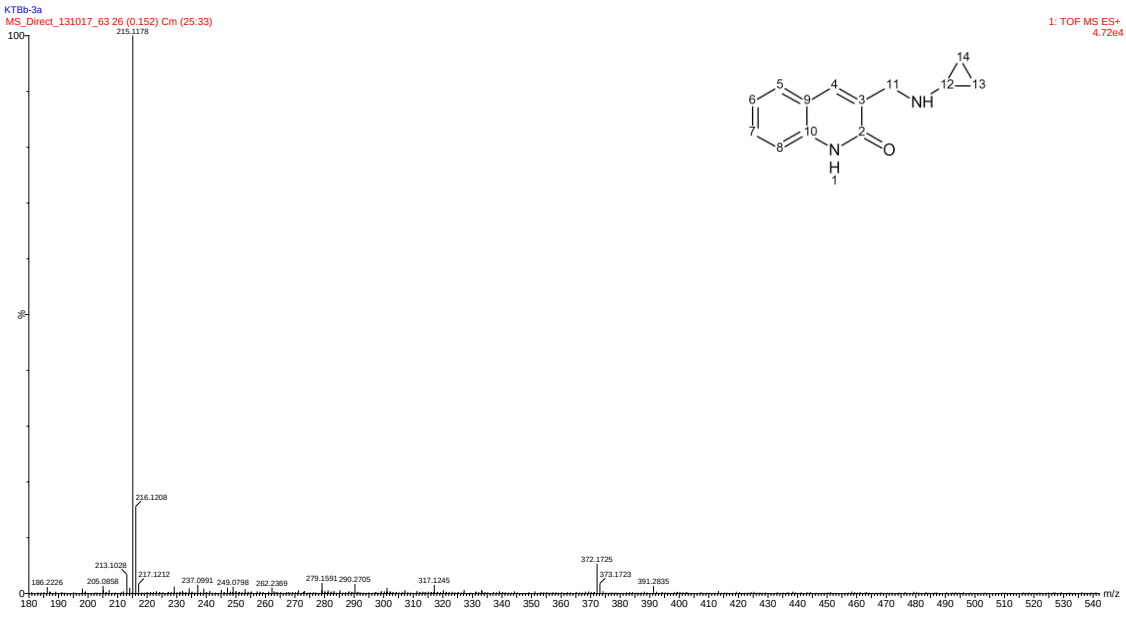
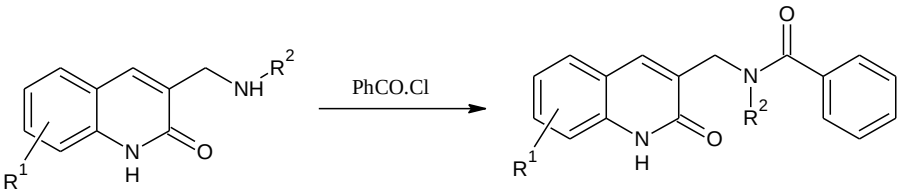


Figure 56. ESI-MS spectrum of **16g** using electrospray ionisation.

2.3.4. *Benzoylation of 3-(amino)methyl-(1H)-2-quinnolones.*

The neutral character, stability and hydrogen-bond accepting properties of the amide functional group makes it an important structural feature in medicinal chemistry.[86] Amide bond formation can be achieved from the condensation of an acyl halide with an amine producing HCl as a by-product. Disadvantages of the use of acyl halides include their ready hydrolysis, the exothermic nature of their reaction with amines as well as purification challenges.[87]

Having established access to the series of 3-(cycloalkylaminomethyl)-(1*H*)-2-quinolones **16a-f**, the final step in the preparation of the tertiary amides **18** (Scheme 23) involves acylation of the amines **16** using selected acyl halides ($R^3CO.Cl$). This approach was inspired by the synthesis of 2-[(chloroacetamido)methyl]coumarins previously achieved in our group by reacting 3-[(benzaylamino)methylcoumarins with chloroacetyl chloride.[88] Proof of concept in the aforementioned study was provided by the reaction of **16a-f** with benzoyl chloride to obtain compounds **18a-g** (Scheme 24).



16a-f **18a-g**

	R^1	R^2
a	H	cyclohexyl
b	H	cyclopentyl
c	6-chloro	cyclohexyl
d	6-methoxy	cyclopentyl
e	7-methoxy	cyclohexyl
f	8-methoxy	cyclopentyl

Scheme 24. Synthesis of 3-(amidomethyl)-(1*H*)-2-quinolones **18a-g**.

Thus, the 3-[(cycloalkylamino)methyl]-(1*H*)-2-quinolones **16a-f** were reacted with excess benzoyl chloride in a stoppered flask. Purification of the tertiary amides **18a-f**, however, proved to be particularly difficult, although spectroscopic analysis (NMR, IR and HRMS) provided evidence for the formation of the desired products. The ^{1}H NMR spectrum of compound **18b** (Figure 58) reveals signals in the aromatic region which integrate for the expected ten aromatic and vinylic protons and signals in the aliphatic region (*ca.* 0.6-2.0 ppm) which integrate for the the expected eight cyclopentyl methylene protons. The ^{13}C NMR spectrum (Figure 59) reveals two amide carbonyl carbon signals, the expected 14 aromatic carbon signals in the aromatic region, and the cyclopentyl methine and cyclopentyl methylene carbon signals. The IR spectrum

of compound **18a** (Figure 60) shows two amide carbonyl bands at 1636 and 1654 cm^{-1} and the HRMS confirmed successful synthesis of a series of amide compounds **18**.

The NMR spectra of compound **18b** (Figure 58) were complicated by the presence of rotamers due to hindered rotation about the C-N bond of the amide. This arises from delocalisation of the nitrogen lone pair of electrons leading to stabilization of the planar rotamers.[89]

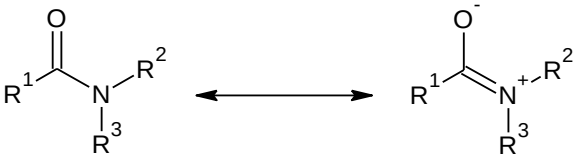


Figure 57. Resonance structures of amides.

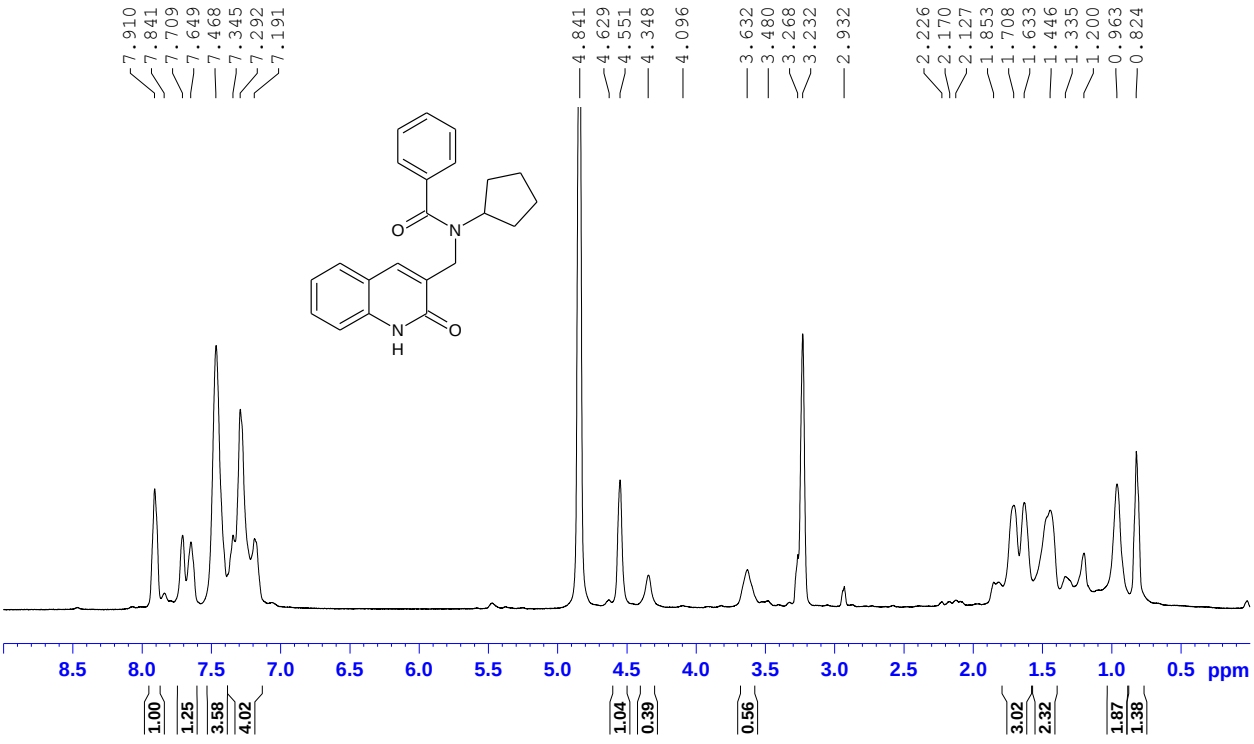


Figure 58. 400 MHz ^{1}H NMR spectrum of **18b** in methanol-d_4.

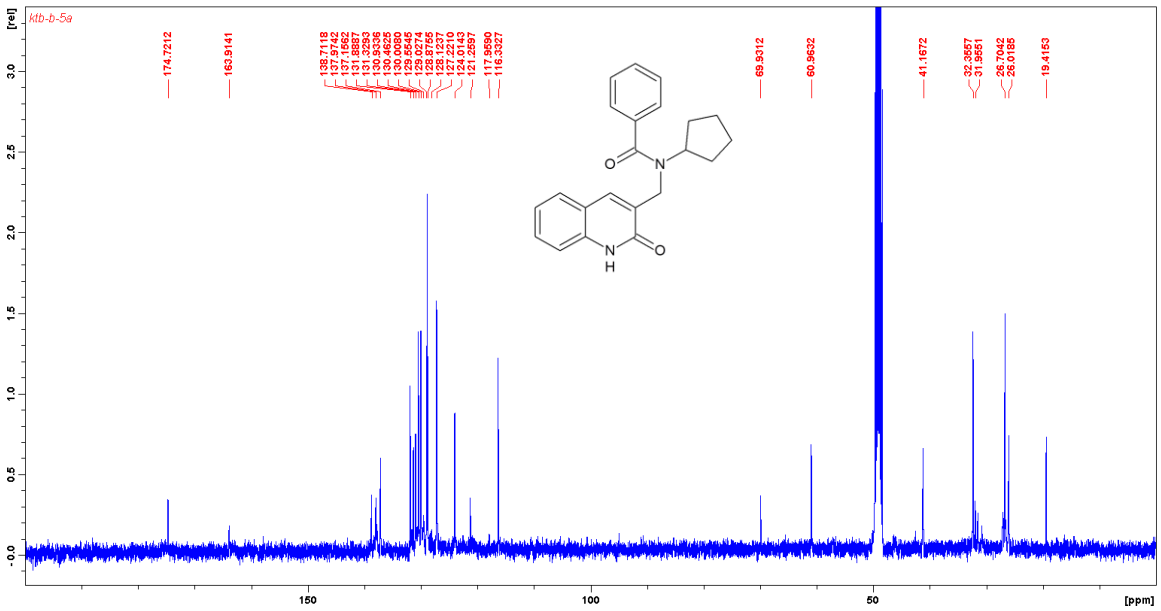


Figure 59. 100 MHz ^{13}C NMR spectrum of **18b** in methanol-d_4.

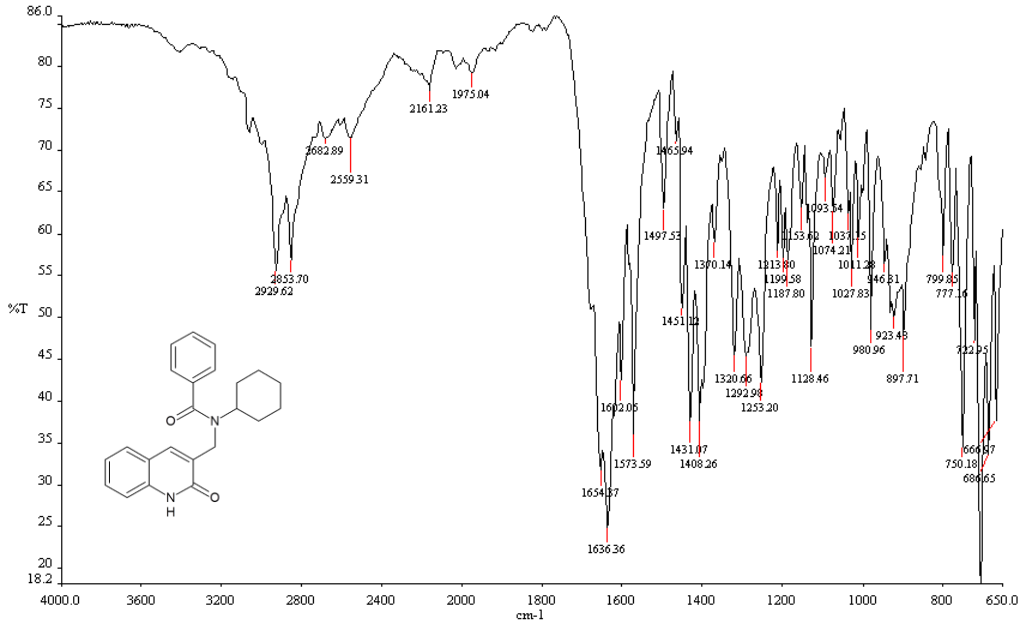
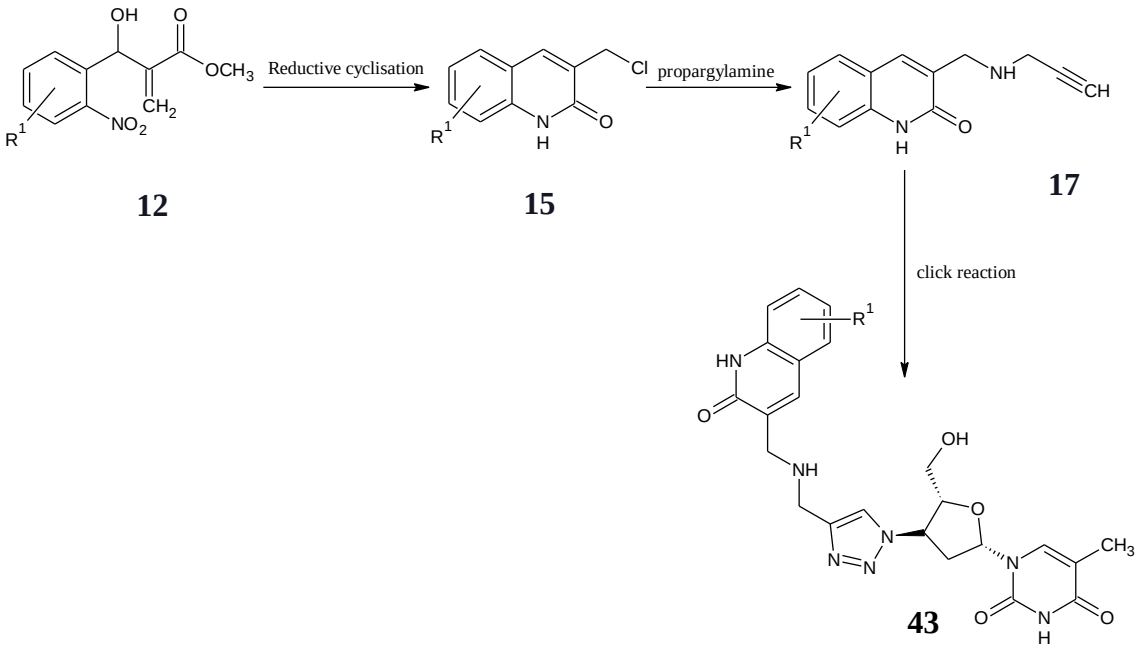


Figure 60. IR spectrum of **18a**.

2.3.5. *Synthesis of quinolone-AZT conjugates.*

For the synthesis of **17**, a corresponding substrate (1 eq.) in minimal dry THF was stirred in a stoppered flask at room temperature and an excess of propargylamine was then added. The reaction progress was monitored by TLC and after four days the solution was concentrated *in vacuo*. NMR analysis of the crude product confirmed the presence of the desired product and crude product was purified by preparative layer chromatography (PLC). NMR analysis of isolated products was inconclusive; however, mass spectra confirmed that the product was formed. In some cases solubility was not perfect and solutions were slightly warmed to dissolve substrates and the associated reaction rate was significantly slower than anticipated. An attempt to carry out propargylamination in solvent free conditions did not succeed. Therefore, improvements for this reaction may include use of dry protic or polar solvents. As a result, subsequent quinolone-AZT conjugates could not be synthesized.



Scheme 25.

The ^{13}C NMR spectrum of **17a** (Figure 61) shows the propargylamine methine and quaternary carbon signals at *ca.* 71.6 ppm and 81.7 ppm as well as the carbonyl signal at 163.71. The DEPT 135 (Figure 62) depicts all five expected aromatic carbon signals and the two propargylamine methylene signals are clearly shown at 37.5 and 48.1 ppm. Other peaks observed are evidence of contamination. However, after purification the resulting NMR data was messy and difficult to

interpret. Nonetheless, HRMS data for purified compound **17a** and **17b** showed the expected peaks. The m/z spectrum of **17a** shows the base peak at 213.1023 corresponding to the MH^+ ion peak. The ion peak at 205.0869 corresponds to a fragment ion resulting from dehydration, the peak at 187.1148 corresponds to a fragment ion resulting from elimination of ethyne, and a significant intense peak at 185.1086 corresponds to a fragmentation ion resulting from elimination of carbon monoxide (Scheme 26). A similar pattern is observed for **17b** (Figure 64), 7-chloro-3-[(propargylamino)methyl]-(1*H*)-2-quinolone **17c** and 8-methoxy-3-[(propargyl-amino)methyl]-(1*H*)-2-quinolone **17d.**

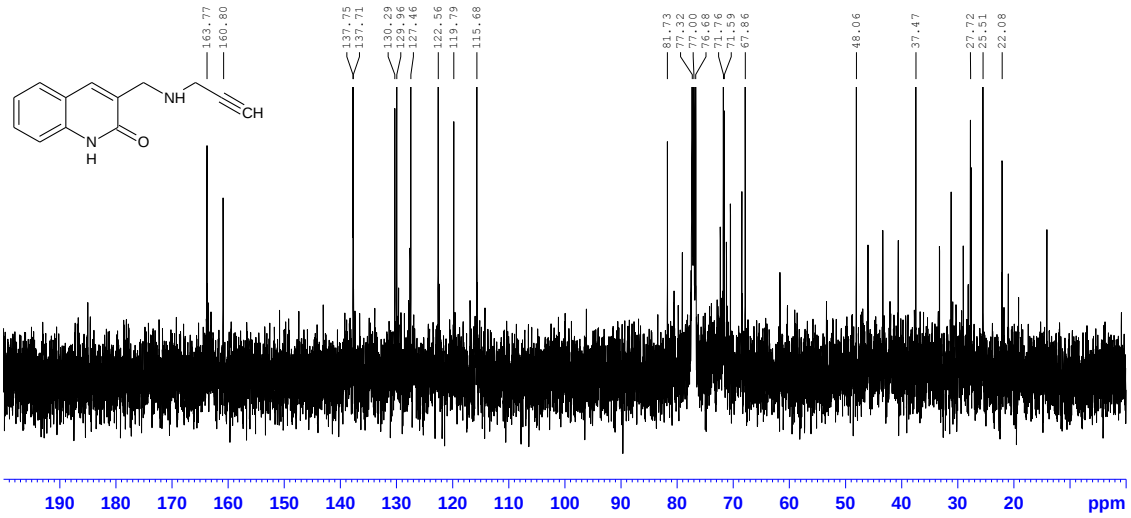


Figure 61. 100 MHz ^{13}C NMR spectrum of crude **17a**.

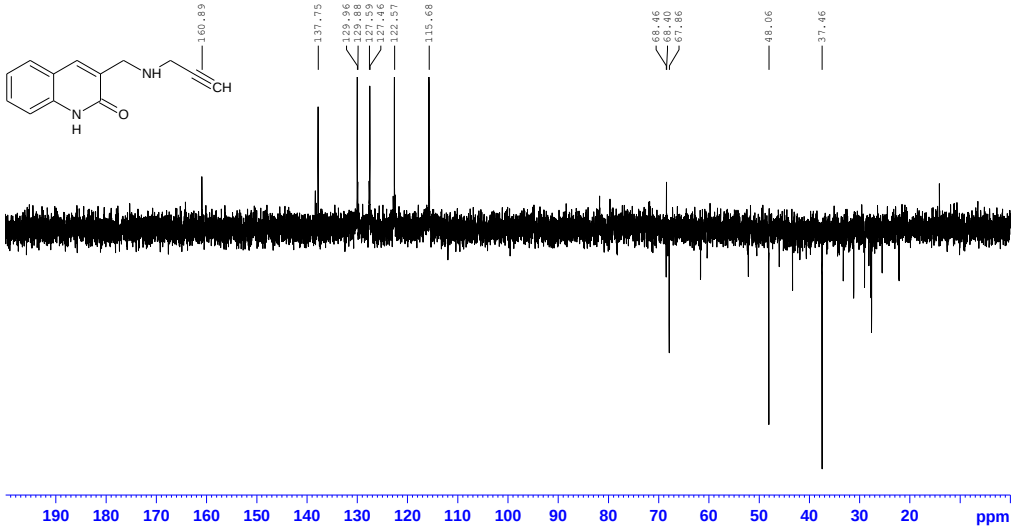
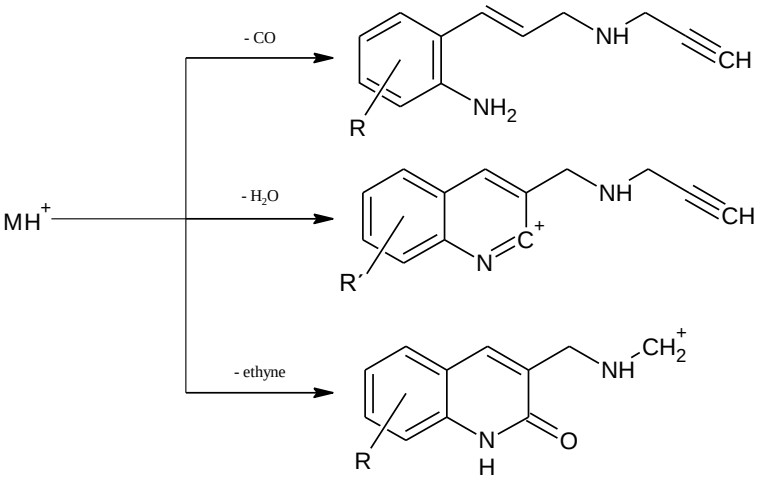


Figure 62. DEPT 135 NMR spectrum of crude **17a**.



Scheme 26. Fragmentation pattern for **17** in ESI sourced HRMS.

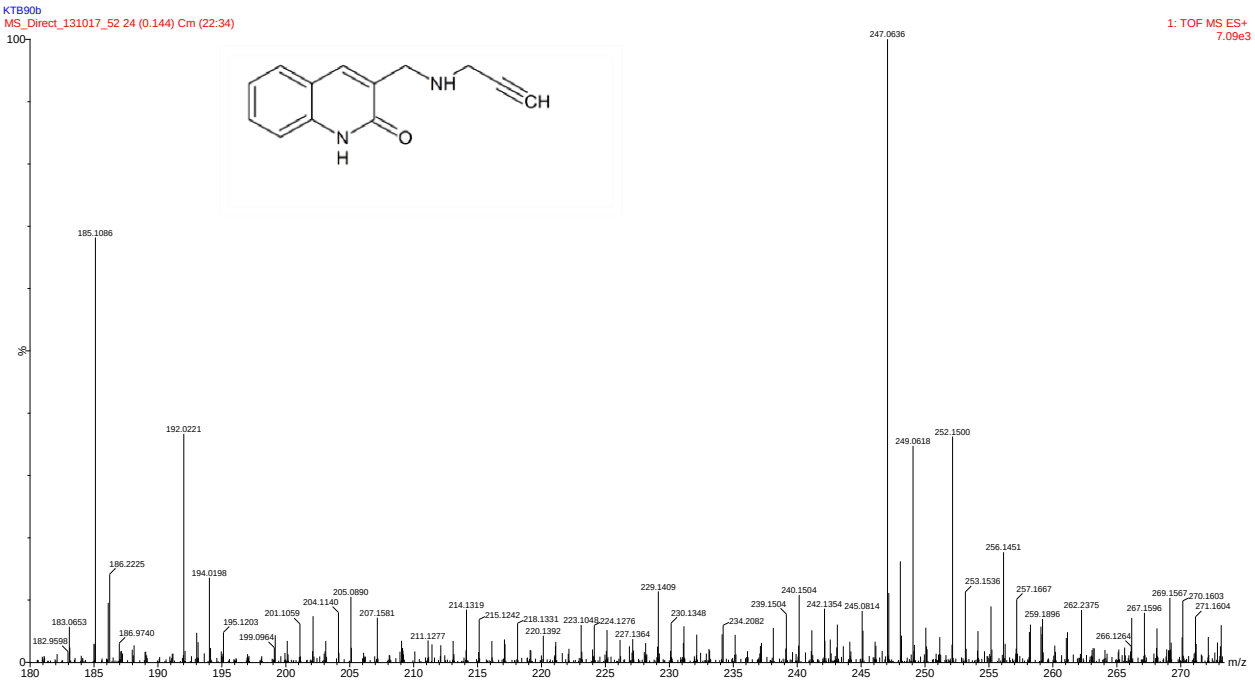


Figure 63. HRMS spectrum of 3-[(propargylamino)methyl]-(1*H*)-2-quinolone **17a** using electrospray ionisation positive mode.

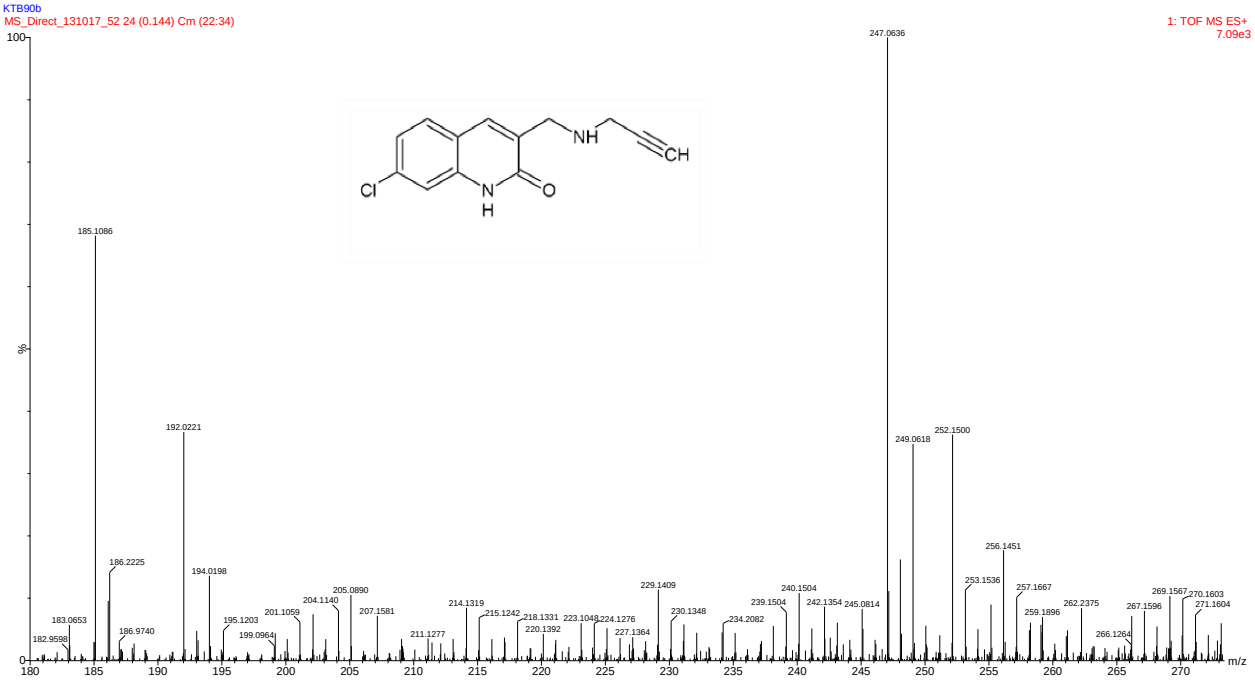


Figure 64. HRMS spectrum of 7-chloro-3-[(propargylamino)methyl]-(1*H*)-2-quinolone **17b** using electrospray ionisation positive mode.

Regarding preparation of 3-(amidomethyl)-(1*H*)-2-quinolones and quinolone-AZT conjugates, time constraints prevented optimisation of the purification methodology to access analytical samples necessary for full characterisation and bioassay purposes. Such optimisation will be addressed as part of further studies.

2.4. Conclusion

In this study, preparation of the functionally diverse Baylis-Hillman adducts from 2-nitrobenzaldehyde and methyl acrylate, ethyl acrylate or methyl vinyl ketone was achieved in yields ranging from 4 to 83%. Subsequently, using Baylis-Hillman derived 3-hydroxy esters and cinnamate esters, the Baylis-Hillman methodology was successfully employed in the construction of medicinally important diketo acid analogues (DKA): cinnamate ester-AZT conjugates and 3-hydroxy-AZT conjugates as potential dual-action HIV-1 IN/RT inhibitors. Furthermore, a series of 2-(aminomethyl)-3-hydroxy-3-(2-nitrophenyl)propanoate derivatives was successfully obtained by conjugate addition of primary and secondary amines to the α,β-unsaturated moiety of the Baylis-Hillman adduct, and Baylis-Hillman allyl chlorides were successfully attained by S_N2' substitution of the Baylis-Hillman hydroxyl group with a Vilsmeier-Haack generated chloride.

On the other hand, in exploratory studies, cyclisation of the Baylis-Hillman ester gave rise to 3-acetoxymethyl-(1*H*)-2-quinolone derivatives in excellent yields of up to 99% whilst MVK-derived BH ketones, specifically 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one, afforded 3-acetoxymethyl-2-methyl-(1*H*)-quinoline in 17% yield. Owing to excellent yields, the former was successfully elaborated to a series of novel 3-(cycloalkylaminomethyl)-(1*H*)-quinolones which are precursors to the targeted 3-(amidomethyl)-(1*H*)-quinolones, potential HIV-1 protease inhibitors and novel 3-[(propargylamino)methyl]-(1*H*)-2-quinolones which are precursors to the targeted quinolone-AZT conjugates, potential dual-action PR/RT inhibitors. Although time constraints prevented HPLC purification and analysis thereof, synthetic access to 3-(amidomethyl)-(1*H*)-quinolones and 3-[(propargylamino)methyl]-(1*H*)-2-quinolone compounds, and prospective quinolone-AZT conjugates, has clearly been established. The novel 3-(cycloalkylaminomethyl)-(1*H*)-quinolones and 3-(amidomethyl)-(1*H*)-quinolones were fully characterized by spectroscopy (IR, 1- and 2-D NMR) and high resolution MS.

3. Experimental

3.1. General

All chemical reagents were used as supplied by the manufacturer. Solvents were dried according to methods described by Perrin and Armarego[90] and Vogel[91]. Thin Layer Chromatography (TLC) was carried out using Merck Silicagel 60 PF_{254} plates and were viewed under ultraviolet (UV) light or visualized using iodine vapor, while column chromatography was carried out using Merck silica gel 60 and preparative layer chromatography was performed on pre-coated Merck silica gel F_{254} plates.

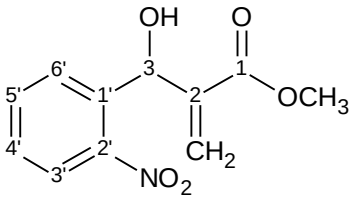
Melting points were determined using Reichert hot-stage apparatus and were uncorrected. High resolution mass spectra were obtained from a Waters Synapt G2 instrument (University of Stellenbosch). NMR spectra were recorded on Bruker 400 MHz AVANCE instrument and were calibrated using solvent signals [δ_H: 7.26 ppm for $CDCl_3$, 2.50 ppm for DMSO-d_6 and 3.31 ppm (quintuplet) for methanol-d_4; δ_C: 77.0 ppm for $CDCl_3$, 39.4 ppm for DMSO-d_6 and 49.05 for methanol-d_4]. IR spectra were recorded on a Perkin-Elmer FT-IR spectrometer 100.

3.2. Preparation of diketo acid analogues as potential dual-action HIV-1 IN/RT inhibitors.

3.2.1. Synthesis of Baylis Hillman adducts

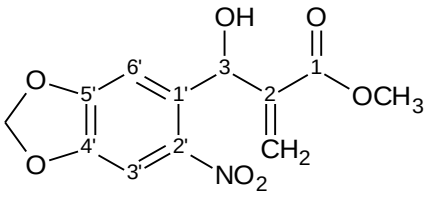
General procedure: To a solution of the 2-nitrobenzaldehyde derivative and methyl acrylate, ethyl acrylate or methyl vinyl ketone in $CHCl_3$, was added DABCO and the reaction mixture was stirred in a stoppered flask at room temperature. The reaction progress was monitored by TLC. The solvent and excess methyl acrylate, ethyl acrylate or methyl vinyl ketone were removed *in vacuo* and the crude product was purified by column chromatography.

Methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **12a**



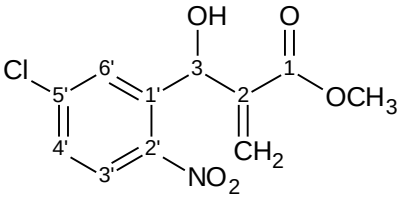
The general procedure, was followed using 2-nitrobenzaldehyde (2.50 g, 16.5 mmol), methyl acrylate (2.24 g, 24.8 mmol) and DABCO (92.8 mg, 0.8 mmol) in $CHCl_3$ (5 mL), and the reaction mixture was stirred in a stoppered flask at room temperature for 7 days. The crude product was purified by column chromatography on silica gel [elution with hexane:EtOAc (3:1)] to afford, as a brown gel, methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **12a** (1.28 g, 76%); ν_{max} (ATR)/cm^{-1} 3450 (OH) and 1729 (C=O); δ_H (400 MHz; $CDCl_3$) 3.39 (1H, s, OH), 3.73 (3H, s, OCH_3), 5.73 and 6.20 (2H, 2×s, $C=CH_2$), 6.36 (1H, s, 3-H), 7.46 (1H, t, *J* = 7.74 Hz, 4´-H), 7.65 (1H, t, *J* = 7.58 Hz, 5´-H), 7.75 (1H, d, J = 7.80, 6´-H), 7.94 (1H, d, J = 8.12, 3´-H); δ_c (100 MHz; $CDCl_3$) 52.0 (OCH_3), 67.5 (C-3), 124.4 (C-6´), 126.3 ($C=CH_2$), 128.7 (C-4´),128.9 C-5´), 129.0 (C-3´), 133.3(C-1´), 135.8 (C-2), 148.1 (C-2´) and 166.2 (C=O).

***Methyl 3-hydroxy-2-methylene -3-(4, 5-methylenedioxy-2-nitrophenyl)propanoate* 12b**



The general procedure was followed using 4,5-methylenedioxy-2-nitrobenzaldehyde (1.50 g, 7.70 mmol), methyl acrylate (0.73 g, 8.5 mmol) and DABCO (0.1 g, 0.9 mmol) in $CHCl_3$ (10 mL) and the reaction mixture was stirred in a stoppered flask at room temperature for a month. The crude product was purified by column chromatography on silica gel [elution with hexane:EtOAc (3:1)] to afford, as white crystals, methyl 3-hydroxy-2-methylene-3-(4, 5-methylenedioxy-2-nitrophenyl)propanoate **12b** (0.82 g, 38%), mp 121–124 ^{0}C (Lit.[37] 120-122 ^{0}C); (Found M-H: 280.0812. Calc. for $C_{12}H_{10}NO_7$: 280.0457); ν_{max} (ATR)/cm^{-1} 3487 (OH) and 1717 (C=O); δ_H (400 MHz; $CDCl_3$) 3.38 (1H, s, OH), 3.75 (3H, s, OCH_3), 5.69 and 6.18 (2H, 2 × s, C=CH_2), 6.11 (2H, s, OCH_2O),6.19 (1H,s 3-H), 7.16 (1H, s, 6´-H), 7.49 (1H, s, 3´-H); δ_c (100 MHz; $CDCl_3$) 52.2 (OCH_3), 67.6 (C-3), 103.0 (OCH_2O), 105.4 (C-6´), 107.7 (C-3´), 126.1 (C=*C*H_2), 133.7 (C-1´), 140.9 (C-2´), 142.1 (C-2),147.3 (C-5´), 152.1 (C-4´) and 166.5 (C=O).

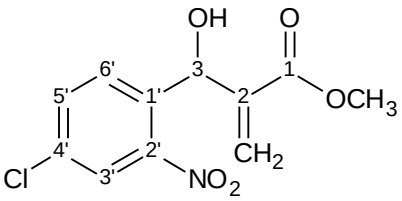
***Methyl 3-(5-chloro-2-nitrophenyl)-3-hydroxy-2-methylenepropanoate* 12c**



The general procedure was followed using 5-chloro-2-nitrobenzaldehyde (1.52 g, 8.3 mmol), methyl acrylate (1.07 g, 12.4 mmol) and DABCO (0.11 g, 0.91 mmol) in $CHCl_3$, and the reaction mixture was stirred in a stoppered flask at room temperature for several weeks. The crude product was purified by column chromatography on silica gel [elution with hexane:EtOAc (3:1)] to afford, as a brown solid, methyl 3-(5-chloro-2-nitrophenyl)-3-hydroxy-2-methylene-propanoate **12c** (1.87 g, 83%), mp 63–65 ^{0}C (Lit.[37] 64-66 ^{0}C); ν_{max} (ATR)/cm^{-1} 3471 (OH) and

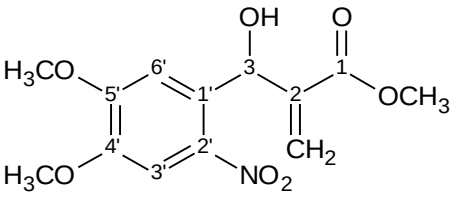
1717 (C=O); δ_H (400 MHz; $CDCl_3$) 3.73 (1H, s, OH), 3.77 (3H, s, OCH_3), 5.69 and 6.37 (2H, 2×s, C=CH_2), 6.23 (1H, s, 3-H), 7.44 (1H, d, *J* = 8.56 Hz, 4´-H), 7.77 (1H, s, 6´-H) and 7.94 (1H, d, *J* = 8.68 Hz, 3´-H); δ_c (100 MHz; $CDCl_3$) 52.3 (OCH_3), 67.5 (C-3), 126.2 (C-4´), 126.8 (C=*C*H_2), 128.8 (C-6´), 129.1 (C-3´), 138.5 (C-1´), 139.6 (C-5´), 140.3 (C–2) 145.8 (C-2´) and 163.3 (C=O).

Methyl 3-(4-chloro-2-nitrophenyl)-3-hydroxy-2-methylenepropanoate **12d**



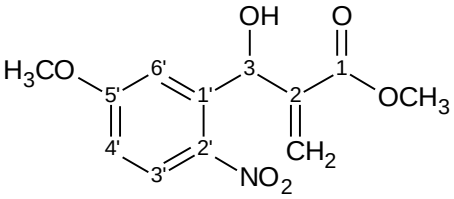
The general procedure was followed using 3-chloro-2-nitrobenzaldehyde (1.52 g, 8.3 mmol), methyl acrylate (1.07 g, 12.4 mmol) and DABCO (0.11 g, 0.91 mmol) in $CHCl_3$, and the reaction mixture was stirred in a stoppered flask at room temperature for six weeks. The crude product was purified by column chromatography on silica gel [elution with hexane:EtOAc (3:1)] to afford, as a yellow-brown solid, methyl 3-(4-chloro-2-nitrophenyl)-3-hydroxy-2-methylene-propanoate **12d** (1.78 g, 79%), mp 68-71 ^{0}C (Lit.[37] 78-80 ^{0}C); ν_{max} (ATR)/cm^{-1} 3477 (OH) and 1710 (C=O); δ_H (400 MHz; $CDCl_3$) 3.42 (1H, br s, OH), 3.74 (3H, s, OCH_3), 5.73 and 6.37 (2H, 2×s, C=CH_2), 6.16 (1H, s, 3-H), 7.61 (1H, d, *J* = 8.22 Hz, 5´-H), 7.72 (1H, d, *J* = 8.48 Hz, 6´-H) and 7.95 (1H, s, 3´-H); δ_c (100 MHz; $CDCl_3$) 52.3 (OCH_3), 67.4 (C-3), 124.6 (C-6´), 126.7 (C=*C*H_2), 130.3 (C-5´), 133.5 (C-8´), 134.5 (C-1´), 134.6 (C-2), 140.3 (C-2´) and 166.3 (C=O).

Methyl 3-hydroxy -3-(4, 5-dimethoxy-2-nitrophenyl)-2-methylenepropanoate **12e**



The general procedure was followed using 4,5-dimethoxy-2-nitrobenzaldehyde (1.50 g, 7.1 mmol), methyl acrylate (0.67 g, 7.8 mmol) and DABCO (0.1 g, 0.9 mmol) in $CHCl_3$ (5 mL) and the reaction mixture was stirred in a stoppered flask at room temperature for a month. The crude product was purified by column chromatography on silica gel [elution with hexane:EtOAc (3:1)] to afford, as a golden-brown solid, methyl 3-hydroxy-3-(4,5-dimethoxy-2-nitrophenyl)-2-methylenepropanoate **12e** (9.1 mg, 4%); ν_{max} (ATR)/cm^{-1} 3488 (OH) and 1737 (C=O); δ_H (400 MHz; $CDCl_3$) 3.75 (3H, s, OCH_3), 3.93 (3H, s, 4´-OCH_3), 3.96 (3H, s, 5´-OCH_3), 5.52 and 6.26 (2H, 2×s, C=CH_2), 6.28 (1H, s, 3-H), 7.24 (1H, s, 6´-H) and 7.60 (1H, s, 3´-H); δ_c (100 MHz; $CDCl_3$) 52.2 (OCH_3), 56.3 (4´-OCH_3), 56.4 (5´-OCH_3), 67.7 (C-3), 107.8 (C-6´), 109.9 (C-3´), 125.8 (C=*C*H_2), 131.3 (C-5´), 140.1 (C-4´), 141.2 (C-1´), 148.0 (C-2), 153.4 (C-2´) and 166.8 (C=O).

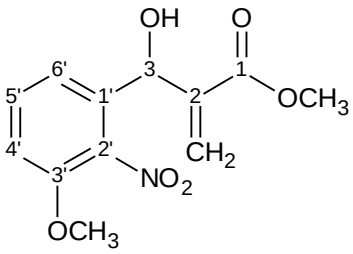
Methyl 3-hydroxy-3-(5-methoxy-2-nitrophenyl)-2-methylenepropanoate **12f**



The general procedure was followed, using 3-methoxy-2-nitrobenzaldehyde (0.50 g, 2.8 mmol), methyl acrylate (0.26 g, 3.1 mmol) and DABCO (72.5 mg, 0.65 mmol) in $CHCl_3$ (5 mL) and the reaction mixture was stirred in a stoppered flask at room temperature for 4 weeks. The crude product was purified by column chromatography on silica gel [elution with hexane:EtOAc (3:1)] to afford, as a light yellow crystals, methyl 3-hydroxy-(5-methoxy-2-nitrophenyl)-2-methylene propanoate **12f** (0.63 g, 85%), mp 68-72 ^{0}C (Lit.[37] 69-71 ^{0}C); ν_{max} (ATR)/cm^{-1} 3380 (OH) and

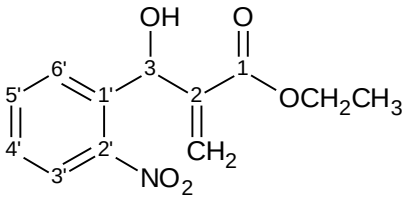
1721 (C=O); δ_H (400 MHz; $CDCl_3$) 3.53 (1H, br s, OH), 3.76 (3H, s, OCH_3), 3.90 (H, s, 5´-OCH_3), 5.58 and 6.31 (1H, 2×s, C=CH_2), 6.30 (1H, s, 3-H), 6.90 (1H, d, *J* = 9.00 Hz, 3´-H), 7.39 (1H, s, 6´-H), and 8.08 (1H, d, *J* = 9.08 Hz, 4´-H); δ_c (100 MHz; $CDCl_3$) 52.2 (OCH_3), 59.9 (5´-OCH_3), 67.9 (C-3), 113.3 (C-4´), 113.6 (C-6´), 126.2 (C=*C*H_2), 127.8 (C-3´), 139.4 (C-5´), 140.8 (C-1´), 141.0 (C-2), 163.7, (C-2´) and 166.7 (C=O).

Methyl 3-hydroxy-3-(3-methoxy-2-nitrophenyl)-2-methylenepropanoate **12g**



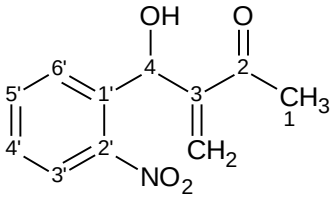
The general procedure was followed, using 3-methoxy-2-nitrobenzaldehyde (0.50 g, 2.8 mmol), methyl acrylate (0.26 g, 3.1 mmol) and DABCO (72.5 mg, 0.65 mmol) in $CHCl_3$ (5 mL) and the reaction mixture was stirred in a stoppered flask at room temperature for 2 weeks. The crude product was purified by column chromatography on silica gel [elution with hexane:EtOAc (3:1)] to afford, as a light yellow crystals, methyl 3-hydroxy-(3-methoxy-2-nitrophenyl)-2-methylene-propanoate **12g** (0.59 g, 79%), mp 109–112 ^{0}C (Lit.[37] 114-116 ^{0}C); ν_{max} (ATR)/cm^{-1} 3445 (OH) and 1708 (C=O); δ_H (400 MHz; $CDCl_3$) 3.70 (3H, s, OCH_3), 3.88 (3H, s, Ar-OCH_3), 3.94 (1H, s, OH), 5.64 and 5.86 (2H, 2×s, C=CH_2), 6.40 (1H, s, 3-H), 6.99 (1H, d, *J* = 8.24, 4´-H), 7.10 (1H, d, *J* = 9.00 Hz,6´-H) and 7.41 (1H, t, *J* = 8.10 Hz, 5´-H); δ_c (100 MHz; $CDCl_3$) 52.1 (OCH_3), 56.5 (Ar-OCH_3), 68.3 (C-3), 112.3 (C-4´), 119.4 (C-6´), 127.3 (C=*C*H_2), 131.3 (C-5´), 134.4 (C-1´), 139.7 (C-2 and C-3´), 150.9 (C-2´) and 166.1 (C=O).

Ethyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **12h**



The general procedure was followed, using 2-nitrobenzaldehyde (1.50 g, 9.9 mmol), ethyl acrylate (1.19 g, 11.9 mmol) and DABCO (0.56 g, 4.97 mmol) in $CHCl_3$ (5 mL) and the reaction mixture was stirred in a stoppered flask at room temperature for 7 days. The crude product was purified by column chromatography on silica gel [elution with hexane:EtOAc (3:1)] to afford, as a brown gel, ethyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate **12h** (1.28 g, 35%); ν_{max} (ATR)/cm^{-1} 3445 (OH) and 1707 (C=O); δ_H (400 MHz; $CDCl_3$) 1.21 (3H, t, *J* = 7.44 Hz, CH_3), 3.46 (1H, s, OH), 4.16 (2H, m, *J* = 8.12 Hz, OCH_2), 5.72 and 6.17 (2H, 2 × s, C=CH_2), 6.37 (1H, s, 3-H), 7.46 (1H, t, *J* = 7.74 Hz, 4`-H), 7.64 (1H, t, *J* = 7.58 Hz, 5´-H), 7.72 (1H, d, *J* = 7.84 Hz, 6´-H) and 7.94 (1H, d, *J* = 8.12 Hz, 3´-H); δ_c (100 MHz; $CDCl_3$) 14.0 (CH_3), 61.2 (OCH_2), 67.8 (C-3), 124.5 (C-6´), 126.2 (C=*C*H_2), 128.8 (C-4´ and C-5´), 133.4 (C-3´), 140.9 (C-2), 148.5 (C-2´) and 165.9 (C=O).

4-hydroxy-2-methylene-4-(2-nitrophenyl)butan-2-one **12i**



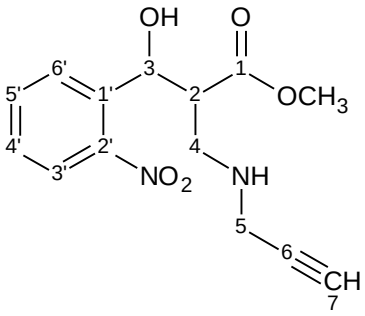
The general procedure was followed, using 2-nitrobenzaldehyde (2.50 g, 16.5 mmol), methyl vinyl ketone (2.24 g, 24.8 mmol) and DABCO (92.8 mg, 0·83 mmol) in $CHCl_3$ (5 mL) and the reaction mixture was stirred in a stoppered flask at room temperature for 7 days. The crude product was purified by column chromatography on silica gel [elution with hexane:EtOAc (3:1)] to afford, as a brown gel, 4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one **12i** (1.28 g, 35%); ν_{max} (ATR)/cm^{-1} 3460 (OH) and 1729 (C=O); δ_H (400 MHz; $CDCl_3$) 3.38 (1H, s, OH),

3.72 (3H, s, CH_3), 5.72 and 6.19 (2H, 2 × s, C=CH_2), 6.36 (1H, s, 4-H), 7.46 (1H, t, *J* = 7.74 Hz, 4´-H), 7.63 (1H, t, *J* = 7.58 Hz, 5´-H), 7.74 (1H, d, *J* = 7.84 Hz, 6´-H), and 7.79 (1H, d, J = 8.16, 3´-H); δ_c (100 MHz; $CDCl_3$) 52.2 (C-1), 67.6 (C-4), 124.6 (C-6´), 126.5 (C=*C*H_2), 128.7 (C-4´), 128.8 (C-5´), 133.5 (C-3´), 136.0 (C-1´), 140.6 (C-3), 148.2 (C-2`) and 166.4 (C=O).

3.2.2. Nucleophilic addition to Baylis-Hillman adducts.

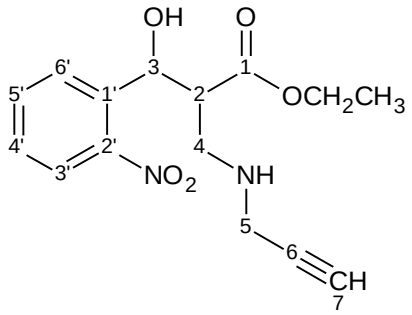
General procedure: The specified amine was added to a solution of the Baylis-Hillman adduct in dry THF and the reaction mixture was stirred in a stoppered flask at room temperature for periods which varied according to the reactants involved. The solution was then concentrated *in vacuo* and the crude mixture purified by flash chromatography to afford the desired product.

Methyl 3-hydroxy-3-(2-nitrophenyl)-2-(propargylamino)methylpropanoate **34a**



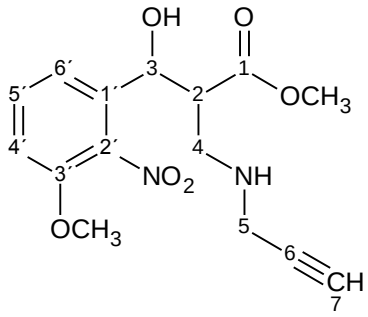
The general procedure was followed using methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)-propanoate (0.50 g, 2.1 mmol) and propargylamine (0.13 g, 2.3 mmol) in dry THF (5 mL) and the reaction was monitored with TLC [hexane:EtOAc (1:1)]. After 3 days, TLC showed the formation of a product. The reaction was allowed to run for a further 6 days after which the crude product was purified by column chromatography [elution with hexane:EtOAc (1:1)] to afford, as a red brown gel, a 1:1 diastereomeric mixture of methyl 3-hydroxy-3-(2-nitrophenyl)-2-(propargylamino)methylpropanoate **34a** (1.40 g, 66%); ν_{max} (ATR)/cm^{-1} 3459 (OH), 3292 (NH), and 1726 (C=O); δ_H (400 MHz; $CDCl_3$) 2.24 and 2.26 (2H, 2×t, *J* = 2.28 Hz, 7-H), 2.65 and 3.02 (2H, 2×dd, *J* = 3.40 Hz, 4-H), 3.08 and 3.17 (2H, 2×m, *J* = 2.64 Hz, 2-H), 3.29 (1H, d, *J* = 3.54 Hz, 4-H), 3.47 and 3.56 (2H, 2×d, *J* = 2.24 Hz, 5-H), 3.48 (3H, s, OCH_3), 3.60 (1H, dd, *J* = 2.65 Hz, OCH_3) and 3.80 (2H, s, OCH3), 5.97 (1H, d, *J* = 3.24 Hz, 3-H), 7.45 (2H, m, *J* = 8.04 Hz, 4´-H), 7.67 (2H, m, *J* = 7.72 Hz, 5´-H), 7.82 and 7.90 (2H, 2×d, *J* = 7.86 Hz, 3´-H), 7.99 and 8.05 (2H, 2×d, *J* = 8.14 Hz, 6´-H); δ_c (100 MHz; $CDCl_3$) 38.3 (C-5), 48.1 and 49.8 (C-2), 49.6 (C-4), 51.4 and 52.4 (OCH_3), 71.2 and 72.2 (C-3), 72.6 (C-7), 80.7 (C-6), 124.8 (C-6´), 128.3 (C-4´), 129.0 (C-3´), 133.3 (C-5´), 138.2 (C-1´), 147.0 (C-2´) and 173.0 (C=O).

Ethyl 3-hydroxy-3-(2-nitrophenyl)-2-[(propargylamino)methyl]propanoate **34b**



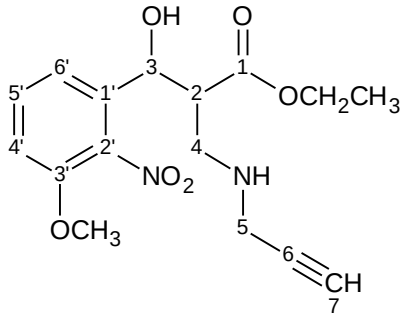
The general procedure was followed using ethyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate (0.35 g, 1.4 mmol) and propargylamine (92.6 mg, 1.7 mmol) in dry THF (5 mL) and the reaction was monitored with TLC [hexane:EtOAc (1:1)]. After 3 days, TLC showed the formation of a product. The reaction mixture was allowed to run for a further 6 days after which the crude product was purified by column chromatography on silica gel [elution with hexane:EtOAc (1:1)] to afford, as a brown gel, a 1:1 diastereomeric mixture of ethyl 3-hydroxy-3-(2-nitrophenyl)-2-[(propargylamino)methyl]propanoate **34b** (0.27 g, 63%); ν_{max} (ATR)/cm^{-1} 3292 (OH and NH) and 1724 (C=O); δ_H (400 MHz; $CDCl_3$) 0.97 and 1.29 (6H, 2×t, *J* = 7.11 Hz, *CH*$_3$), 2.24 and 2.26 (2H, 2×br s, 7-H), 2.67 and 3.28 (2H, 2×dd, *J* = 3.70 Hz, 4-H), 3.04 and 3.11 (2H, m, *J* =3.76 Hz, 2-H), 3.47 and 3.56 (2H, 2×d, *J* = 3.44 Hz, 5-H), 3.50 (2H, d, *J* = 3.24 Hz, 4-H), 3.94 and 4.23 (4H, 2×q, *J* = 6.43 Hz, O*CH*$_2$), 5.76 and 5.96 (2H, 2×d, *J* = 3.28 Hz, 3-H), 7.45 (2H, m, *J* = 7.39 Hz, 4´-H), 7.66 (2H, m, *J* = 7.46 Hz, 5´-H), 7.88 (2H, m, *J* = 7.17 Hz, 3´-H), 7.99 and 8.05 (2H, 2×d, *J* = 8.20 Hz, 6´-H) and 8.05 (1H, d, *J* = 8.14 Hz, 6´-H); δ_c (100 MHz; $CDCl_3$) 14.0 (*CH*$_3$), 38.4 (C-4), 46.3 (C-5), 48.2 and 49.3 (C-2), 49.7 (C-5), 60.6 and 61.4 (OCH_2), 71.4 (C-3), 72.3 (C-7), 80.6 (C-7), 124.8(C-6´), 128.2(C-4´), 129.2(C-3´), 133.3 (C-5´), 138.3 (C-1´), 147.6 (C-2´) and 173.6 (C=O).

Methyl 3-hydroxy-3-(3-methoxy-2´-nitrophenyl)-2-[(propargylamino)methyl]propanoate **34c**



The general procedure was followed using methyl 3-hydroxy-2-methylene-3-(3-methoxy-2-nitrophenyl)propanoate (0.99 g, 3.71 mmol) and propargylamine (0.25 g, 4.45 mmol) in dry THF (5 mL) and the reaction was monitored with TLC. After 14 days, TLC showed the formation of a product and crude product was purified by column chromatography on silica gel [elution with hexane:EtOAc (1:1)] to afford, as a red brown gel, a 1:1 diastereomeric mixture of methyl 3-hydroxy-3-(3-methoxy-2-nitrophenyl)-2-[(propargylamino)methyl]propanoate **34c** (98.0 mg, 83%); ν_{max} (ATR)/cm^{-1} 3291 (OH and NH) and 1729 (C=O); δ_c (100 MHz; $CDCl_3$) 38.2 (5-CH_2), 46.5 and 49.0 (4-CH_2), 50.4 (C-2), 51.6 and 52.3 (OCH_3), 56.4 (3´-OCH_3), 70.7 (C-3), 72.6 (C-6), 80.8 (C-7), 111.7 (C-6´), 119.2 (C-5´), 130.7 (C-4´), 139.7 (C-3´), 150.5 (C-2´) and 173.0 (C=O).

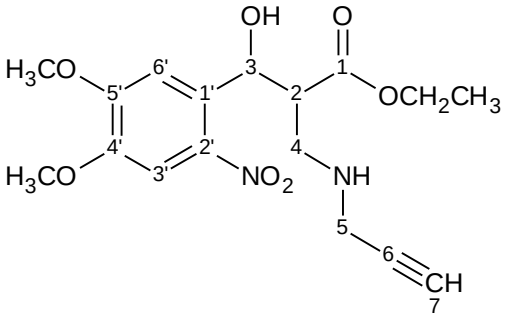
Ethyl 3-hydroxy-2-propargylaminomethyl-3-(3-methoxy-2-nitrophenyl)propanoate **34d**



The general procedure was followed using ethyl 3-hydroxy-2-methylene-3-(3-methoxy-2-nitrophenyl)propanoate (0.21 g, 0.80 mmol) and propargylamine (52.2 mg, 0.90 mmol) in dry THF (5 mL) and the reaction was monitored with TLC. After 3 days, TLC showed the formation

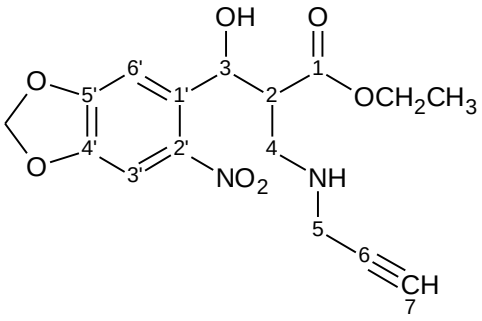
of a product. The reaction mixture was allowed to run for a further 6 days after which the crude product was purified by column chromatography on silica gel [elution with hexane:EtOAc (1:1)] to afford, as a brown gel, a 1:1 diastereomeric mixture of ethyl 3-hydroxy-3-(3-methoxy-2-nitrophenyl)-2-[(propargylamino)methyl]propanoate **34d** (0.22 g, 87%); ν_{max} (ATR)/cm^{-1} 3290 (OH and NH) and 1729 (C=O); δ_c (100 MHz, $CDCl_3$) δ_c (100 MHz; $CDCl_3$) 14.0 ($OCH_2\mathit{CH_3}$), 38.4 (C-4), 46.3 (C-5), 48.2 and 49.3 (C-2), 49.7 (C-5), 60.5 and 61.4 ($O\mathit{CH_2}CH_3$), 71.4 (C-3), 72.4 (C-7), 80.7 (C-7), (C-4´), 119.4 (C-6´), 127.3 ($C=CH_2$), 131.3 (C-5´), 134.4 (C-1´), 139.7 (C-2), 150.9 (C-2´), and 166.1 (C=O).

Ethyl 3-hydroxy-3-(4, 5-dimethoxy-2-nitrophenyl)-2-[(propargylamino)methyl]propanoate **34e**



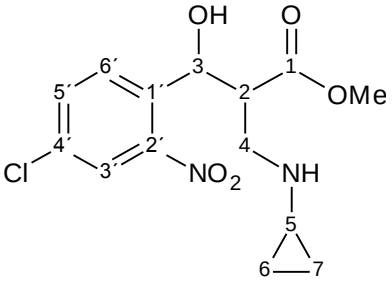
The general procedure was followed using ethyl 3-hydroxy-2-methylene-3-(4,5-dimethoxy-2-nitrophenyl)propanoate (91.0 mg, 0.30 mmol) and propargylamine (20.2 mg, 0.90 mmol) in dry THF (1 mL) and the reaction was monitored with TLC. After 3 days, TLC showed the formation of a product. The reaction mixture was allowed to run for a further 6 days after which the crude product was purified by PLC on silica gel [elution with hexane:EtOAc (1:1)] to afford as a brown gel, a diastereomeric mixture of ethyl 3-hydroxy-3-(4,5-dimethoxy-2-nitrophenyl)-2-[(propargylamino)methyl]propanoate **34e** (21.9 mg, 7%); ν_{max} (ATR)/cm^{-1} 3292 (OH and NH) and 1725 (C=O); δ_c (100 MHz; $CDCl_3$) 14.2 (CH_3), 38.3 (C-5), 48.1 and 49.8 (C-2), 49.6 (C-4), 56.3 (4´-OCH_3), 56.4 (5´-OCH_3), 60.5 and 61.4 (OCH_2), 71.2 and 72.2 (C-3), 72.6 (C-7), 80.7 (C-6), 107.8 (C-6´), 109.9 (C-3´), 131.3(C-5´),140.1 (C-4´),, 141.2 (C-1´), 153.4 (C-2´), and 166.8 (C=O).

Ethyl 3-hydroxy -3-(4, 5-methylenedioxy-2´-nitrophenyl) -2-propargylaminomethyl propanoate **34f**



The general procedure was followed using ethyl 3-hydroxy-2-methylene-3-(4,4-dimethoxy-2-nitrophenyl)propanoate (0.23 g, 0.80 mmol) and propargylamine (68.7 mg, 1.20 mmol) in dry THF (3 mL) and the reaction was monitored with TLC. After 3 days, TLC showed the formation of a product. The reaction mixture was allowed to run for a further 6 days after which the crude product was purified by column chromatography on silica gel [elution with hexane:EtOAc (1:1)] to afford, as a brown gel, a 1:1 diastereomeric mixture of ethyl 3-hydroxy-3-(4,5-methylene-dioxy-2-nitrophenyl)-2-[(propargylamino)methyl]propanoate **34f** (0.16 g, 60%); ν_{max} (ATR)/cm^{-1} 3287 (OH and NH) and 1721 (C=O); δ_c (100 MHz; $CDCl_3$) 14.0 (CH_3), 38.4 (C-4), 46.3 (C-5), 48.5 (C-2), 49.7 (C-5), 60.5 and 61.4 (OCH_2), 71.4 (C-3), 72.4 (C-7), 80.7 (C-7), 105.4 (C-6´), 107.7 (C-3´), 126.1 (OCH_2O), 133.7 (C-1´), 140.9 (C-2´), 147.3 (C-5´), 152.1 (C-4´), 166.5 (C=O).

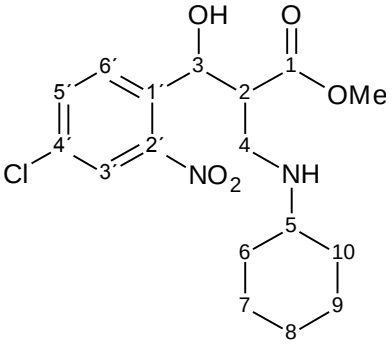
***Methyl 3-(4-chloro-2-nitrophenyl)-3-hydroxy-2-*[(*cyclopropylamino)methyl]propanoate** **34g**



An excess of cyclopropylamine was added to methyl 3-(4-chloro-2-nitrophenyl)-3-hydroxy-2-methylenepropanoate (89.1 mg, 0.33 mmol) and the solution was stirred in a stoppered flask at room temperature. The mixture was then concentrated *in vacuo* and crude product purified by

PLC [using silica gel; elution with hexane:EtOAc (2:1)] to afford, as a light brown gel, a 1:1 diastereomeric mixture of methyl 3-(4-chloro-2-nitrophenyl)-3-hydroxy-2-[(cyclopropylamino)-methyl]propanoate **34g** (47.9 mg, 45%); (Found M+H: 329.0902. Calc. for $C_{14}H_{18}ClN_2O_5$: 329.0905), ν_{max} (ATR)/cm^{-1} 1728 (C=O) and 3200 (NH); δ_H (400 MHz; $CDCl_3$) 0.38-0.84 (6 and 7–H), 2.05 and 2.20 (2H, 2×m, *J* = 3.44 Hz, 5-H), 2.78 and 3.25 (2H, 2×dd, *J* = 4.19 Hz, 4-H), 2.93 and 3.08 (2H, 2×m, *J* = 3.08 Hz, 2-H), 3.12 (1H, d, *J* = 4.08 Hz, 4-H), 3.47 and 3.74 (3H, 2×s, OCH_3), 3.49 (1H, s, 4-H), 5.64 (1H, s, 3-H) and 5.89 (1H, d, *J* = 3.92 Hz, 3-H), 7.61 (2H, m, *J* = 9.37 Hz, 6´-H), 7.78 (1H, m, *J* = 7.07, 5´-H), 7.95 and 8.04 (1H, 2×s, 3´-H); δ_c (100 MHz; $CDCl_3$) 5.9, 6.1, 6.8 (cyclopropylamine), 30.7 (C-5), 47.6 (4-CH_2), 48.2 and 49.1 (C-2), 50.7 (4-CH_2), 51.3 and 52.4 (OCH_3), 71.6 and 72.1 (C-3), 124.7 (C-3´), 130.5 (C-5´), 133.2 (C-6´), 137.0 (C–4´), 147.1(C–1´) and 147.8 (C–2´), and 172.6 (C=O).

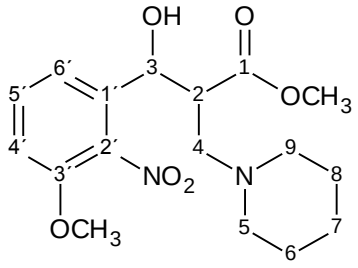
Methyl 3-(4´-chloro-2´-nitrophenyl)-2-cyclohexylaminomethyl-3-hydroxypropanoate **34h**



An excess of cyclohexylamine was added to methyl 3-hydroxy-3-(4-chloro-2-nitrophenyl)-2-methylenepropanoate (0.11 g, 0.40 mmol) and the mixture was stirred in a stoppered flask at room temperature. The mixture was then concentrated *in vacuo* and crude product purified by PLC [using silica gel; elution with hexane:EtOAc (2:1)] to afford, as a dark brown gel, a 1:1 diastereomeric mixture of methyl 2-(5-chloro-2-nitrophenyl)-3-hydroxy-2-[(cyclohexylamino)-methyl]propanoate **34h** (51.5 mg, 35%); (Found M+H: 371.1372. Calc. for $C_{17}H_{24}ClN_2O_5$: 371.1375), ν_{max} (ATR)/cm^{-1} 1727 (C=O); δ_c (100 MHz; $CDCl_3$) 24.9 (C-6 and C-10), 25.8 (C-8), 32.8 (C-7 and C-9), 44.8 and 47.5 (C-4), 48.3 and 48.9 (C-5), 51.3 (C-2), 52.4 (OCH_3), 71.2

and 72.2 (C-3), 124.7 (C-3´), 130.7 (C-5´), 133.5 (C-6´), 133.7 (C-4´), 137.5 (C-1´), 146.9 and 147.7 (C-2´) and 172.5 (C=O).

***Methyl 3-hydroxy-2-methyl-N-piperidine-3-(3´-methoxy-2´-nitrophenyl)propanoate* 34i**

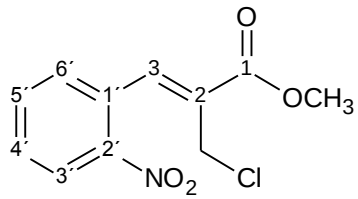


The general procedure was followed using an excess of cyclohexylamine and methyl 3-hydroxy-3-(3-methoxy-2-nitrophenyl)-2-methylenepropanoate (1.02 g, 3.81 mmol) in dry THF and the mixture was stirred in a stoppered flask at room temperature for a week. The mixture was then concentrated *in vacuo* and crude product purified on column chromatography [elution with hexane:EtOAc (2:1)] to afford, as a brown gel, a 1:1 diastereomeric mixture of methyl 3-hydroxy-3-(3-methoxy-2-nitrophenyl)-2-[(cyclohexylamino)methyl]propanoate **34i** (1.05 g, 78%) ;ν_{max} (ATR)/cm^{-1} 2938 (OH) and 1732 (C=O) ; δ_H (400 MHz; $CDCl_3$) 1.24, 1.45, 1.60, and 2.40 (10H, 5,6,7,8, and 9-H), 2.68 (2H, d, *J* = 12.75 Hz, 4-H), 3.00 and 3.30 (2H, 2×t, *J* = 11.38 Hz, 2-H), 3.48 (3H, s, OCH_3), 3.86 (3H, s, 3´-OCH_3), 5.08 (1H, d, *J* = 9.56 Hz, 3-H), 6.94 (2H, d, *J* = 8.04 Hz, 4´ and 6´-H), and 7.34 (1H, t, *J* = 8.12 Hz, 5´-H); δ_c (100 MHz; $CDCl_3$) 23.8 (7-CH_2), 25.7 (5, 6, 8, and 9-CH_2), 47.5 (C-2), 51.8 (OCH_3), 56.4 (3´-OCH_3), 61.0 (4-CH_2), 75.2 (C-3), 111.9 (C-6´), 120.0 (C-5´), 130.4 (C-4´), 140.3 (C-3´), 150.8 (C-2´) and 171.4 (C=O).

3.2.3. Synthesis of Baylis-Hillman-derived allyl chlorides.

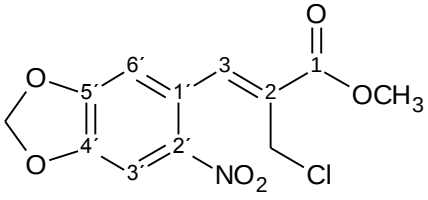
General procedure: An excess of phosphorus oxychloride ($POCl_3$) was added to DMF and the resulting mixture was stirred at room temperature for 15 minutes; CH_2Cl_2 was then added followed by a mixture of the Baylis-Hillman adduct (1 eq) in CH_2Cl_2, in one portion. The mixture was stirred at room temperature and monitored with TLC until completion. Water was added, and the organic phase separated and washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give the crude product. Purification by column chromatography [on silica gel; elution with hexane:EtOAc (2:1)] afforded the desired products.

Methyl 2-chloromethyl-3-(2-nitrophenyl)propenate **15a**



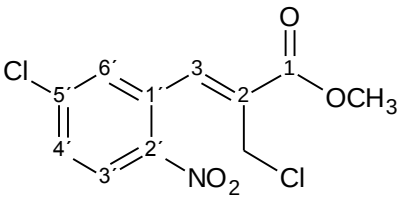
The general procedure was followed using $POCl_3$ (0.38 g, 2.5 mmol) in DMF (0.5 mL) , CH_2Cl_2 (5.0 mL) and a solution of methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate (0.19 g, 0.82 mmol) in CH_2Cl_2 (5.0 mL). Work up and column chromatography gave, as yellow crystals, methyl 2-chloromethyl-3-(2-nitrophenyl)propenoate **15a** (0.12 g, 65%); mp 60-61 ^{o}C (Lit. [37] 53-55 ^{0}C); ν_{max}(ATR)/cm^{-1} 1713 (C=O); δ_H (400 MHz; $CDCl_3$) 3.48 (3H, s, OCH_3), 3.82 (2H, s, CH_2Cl), 7.22 (1H, t, *J* = 7.76 Hz, 4´-H), 7.24 (1H, d, *J* = 7.52 Hz, 6´-H), 7.35 (1H, t, J = 7.52 Hz, 5´-H), 7.69 (1H, s, 3-H), and 7.79 (1H, d, J = 8.24 Hz, 3´-H).

Methyl 2-chloromethyl-3-(4, 5-methylenedioxy-2-nitrophenyl)propenate **15b**



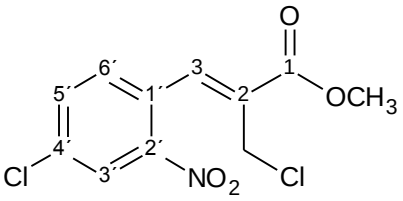
The general procedure was followed using $POCl_3$ (0.26 g, 1.7 mmol) in DMF (0.5 mL), CH_2Cl_2 (5.0 mL) and a solution of methyl 3-hydroxy-2-methylene-3-(4,5-methylenedioxy-2-nitrophenyl)propanoate (0.11 g, 0.39 mmol) in CH_2Cl_2 (7.0 mL). Work up and column chromatography gave, as yellow crystals, methyl 2-chloromethyl-3-(4,5-methylenedioxy-2-nitrophenyl)propenoate **15b** (43.4 mg, 37%); mp 88-91 (Lit[37] 197-199 ^{0}C); (Found M+H: 300.0260. Calc. for $C_{12}H_{11}ClNO_6$: 300.0275); ν_{max} (ATR)/cm^{-1} 1714 (C=O); δ_H (400 MHz; $CDCl_3$) 3.90 (3H, s, OCH_3), 4.26 (2H, s, CH_2Cl), 6.20 (2H, s, OCH_2O), 7.07 (1H, s, 6´-H), 7.71 (1H, s, 3´-H), and 8.04 (1H, s, 3-H).

Methyl 2-chloromethyl-3-(5-chloro-2-nitrophenyl)propenoate **15c**



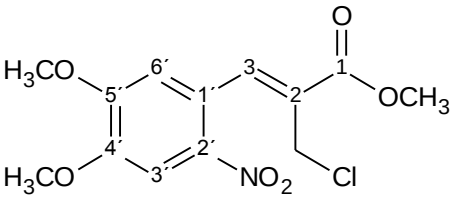
The general procedure was followed using $POCl_3$ (0.34 g, 2.2 mmol) in DMF (0.5 mL) , CH_2Cl_2 (5.0 mL) and a solution of methyl 3-(5-chloro-2-nitrophenyl)-3-hydroxy-2-methylenepropanoate (0.20 g, 0.74 mmol) in CH_2Cl_2 (6.0 mL). Work-up and column chromatography gave, as yellow crystals, methyl 2-chloromethyl-3-(5-chloro-2-nitrophenyl)propenoate **15c** (91 mg, 47%); mp 76-79 ^{o}C (Lit.[37] 74-76 ^{0}C); (Found M+H: 290.1000. Calc. for $C_{11}H_{10}ClNO4$: 289.9988); ν_{max} (ATR)/cm^{-1} 1707 (C=O); δ_H (400 MHz; $CDCl_3$) 3.55 (3H, s, OCH_3), 3.87 (2H, s, CH_2Cl), 7.21 (1H, d, *J* = 8.78 Hz, 4´-H), 7.30 (1H, s, 3-H), 7.68 (1H, s, 6´-H) and 7.83 (1H, d, *J* = 8.80 Hz, 3´-H); δ_c (100 MHz; $CDCl_3$) 38.2 (CH_2Cl), 52.8 (OCH_3), 126.7 (C-4´), 130.2 (C-6´), 130.5 (C-3´), 130.6 (C-1´), 132.0 (C-2), 139.0 (C-1), 140.7 (C-3), 145.6 (C-2´) and 165.4 (C=O).

Methyl 2-chloromethyl-3-(4-chloro-2-nitrophenyl)propenoate **15d**



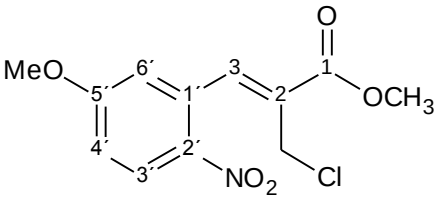
The general procedure was followed using $POCl_3$ (0.34 g, 2.2 mmol) in DMF (0.5 mL), CH_2Cl_2 (5.0 mL) and a solution of methyl 3-(4-chloro-2-nitrophenyl)-3-hydroxy-2-methylenepropanoate (0.20 g, 0.74 mmol) in CH_2Cl_2 (7.0 mL). Work-up and column chromatography gave, as yellow crystals, methyl 2-chloromethyl-3-(4-chloro-2-nitrophenyl)propenoate **15d** (0.17 g, 86%); mp 60-62 ^oC (Lit.[37] 60–62 ^0C); ν_{max} (ATR)/cm^{-1} 1717 (C=O); δ_H (400 MHz; $CDCl_3$) 3.91 (3H, s, OCH_3), 4.22 (2H, s, CH_2Cl), 7.65 (1H, d, *J* = 8.28 Hz, 6´-H), 7.74 (1H, d, *J* = 8.26 Hz, 5´-H), 8.03 (1H, s, 3´-H) and 8.22 (1H, s, 3-H).

Methyl 2-chloromethyl-3-(4, 5-dimethoxy-2-nitrophenyl)propenoate **15e**



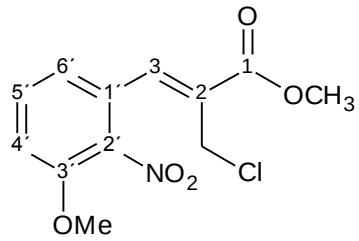
The general procedure was followed using $POCl_3$ in DMF (0.5 mL), CH_2Cl_2 (5.0 mL) and a solution of methyl 3-hydroxy-2-methylene-3-(4, 5-dimethoxy-2-nitrophenyl)propanoate (0.20 g, 0.74 mmol) in CH_2Cl_2 (7.0 mL). Work-up and column chromatography gave, as yellow crystals, methyl 2-chloromethyl-3-(4, 5-dimethoxy-2-nitrophenyl)propenoate **15e**; mp 137-140 ^0C (Lit.[37] 139-141 ^0C); (Found M-H: 314.0993. Calc. for $C_{13}H_{13}ClNO6$: 314.0431); ν_{max} (ATR)/cm^{-1} 1703 (C=O); δ_H (400 MHz; $CDCl_3$) 3.90 (3H, s, OCH_3), 3.99 (3H, s, 5´-OCH_3), 4.02 (3H, s, 4´-OCH_3), 4.30 (2H, s, CH_2Cl), 7.18 (1H, s, 6´–H), 7.78 (1H, s, 3´-H) and 8.01 (1H, s, 3-H); δ_c (100 MHz; $CDCl_3$) 39.3 (CH_2Cl), 52.6 (OCH_3), 56.5 and 56.8 (4´ and 5´-OCH_3), 108.1 (C-6´), 112.1 (C-3´), 124.7 (C-4´), 128.8 (C-6´), 140.1 (C-1´), 141.5 (C-3), 149.4 (C-2), 153.5 (C-2´) and 165.9 (C=O).

Methyl 2-chloromethyl-3-(5-methoxy-2-nitrophenyl)propenoate **15f**



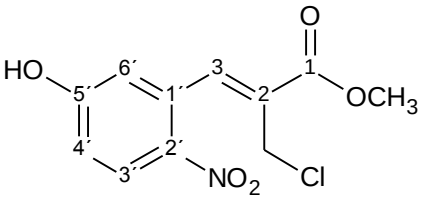
The general procedure was followed using $POCl_3$ (0.36 g, 2.3 mmol) in DMF (1.0 mL), CH_2Cl_2 (10.0 mL) and a solution of methyl 3-hydroxy-3-(5-methoxy-2-nitrophenyl)-2-methylene-propanoate (0.21 g, 0.78 mmol) in CH_2Cl_2 (5.0 ml). Work-up and column chromatography gave, as light yellow crystals, methyl 2-chloromethyl-3-(5-methoxy-2-nitrophenyl)propenoate **15f** (0.10 g, 52%); mp 98-100 ^oC (Lit.[37] 83-85 ^0C); ν_{max} (ATR)/cm^{-1} 1717 (C=O); δ_H (400 MHz; $CDCl_3$) 3.89 (3H, s, OCH_3), 3.94 (3H, s, 5´-OCH_3), 4.25 (2H, s, CH_2Cl), 7.01 (1H, d, *J* = 9.14 Hz, 4´-H), 7.12 (1H, s, 3-H), 8.13 (1H, s, 6´-H) and 8.22 (1H, d, *J* = 9.20 Hz, 3´-H).

Methyl 2-chloromethyl-3-(3-methoxy-2-nitrophenyl)propenoate **15g**



The general procedure was followed using $POCl_3$ (0.32 g, 2.1 mmol) in DMF (0.5 mL) , CH_2Cl_2 (5.0 mL) and a solution of methyl 3-hydroxy-3-(3-methoxy-2-nitrophenyl)-2-methylene-propanoate (0.11 g, 0.42 mmol) in CH_2Cl_2 (5.0 mL). Work-up and column chromatography gave, as light yellow crystals, methyl 2-chloromethyl-3-(3-methoxy-2-nitrophenyl)propenoate **15g** (48.0 mg, 45%); mp 92-94 ^oC (Lit.[37] 88-90 ^0C); ν_{max} (ATR)/cm^{-1} 1722 (C=O); δ_H (400 MHz; $CDCl_3$) 3.86 (3H, s, OCH_3), 3.94 (3H, s, 3´-OCH_3), 4.31 (2H, s, CH_2Cl), 7.12 (1H, d, *J* = 9.20 Hz, 4´-H), 7.25 (1H, d, *J* = 8.64 Hz, 6´-H), 7.53 (1H, t, *J* = 8.08, 5´-H) and 7.66 (1H, s, 3-H).

Methyl 2-chloromethyl-3-(5-hydroxy-2-nitrophenyl)propenoate **15h**

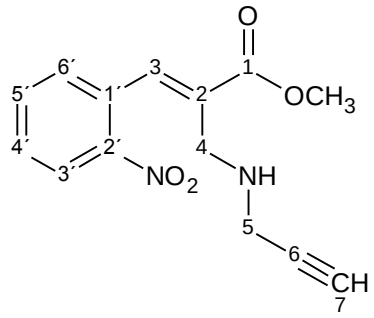


The general procedure was followed using $POCl_3$ (0.38 g, 2.5 mmol) in DMF (0.5 mL), CH_2Cl_2 (5.0 mL) and a solution of methyl 3-hydroxy-3-(5-hydroxy-2-nitrophenyl)-2-methylene-propanoate (0.21 g, 0.82 mmol) in CH_2Cl_2 (7.0 mL). Work-up and column chromatography gave, as yellow crystals, methyl 2-chloromethyl-3-(5-hydroxy-2-nitrophenyl)propenoate **15h**; ν_{max} (ATR)/cm^{-1} 3287 (Ar–OH) and 1599 (C=O); δ_H (400 MHz; $CDCl_3$) 3.87 (3H, s, OCH_3), 4.28 (2H, s, CH_2Cl), 6.93 (1H, d, J=2.44 Hz, 3´-H), 6.95 (1H, d, *J* = 9.06 Hz, 4´-H), 6.99 (1H, s, 6´-H), 8.08 (1H, s, OH) and 8.14 (1H, d, *J* = 9.08 Hz, 3´-H); δ_c (100 MHz; $CDCl_3$) 38.8 (CH_2Cl), 52.5 (OCH_3), 116.5 (C-4´), 116.7 (C-3´), 128.0 (C–6´), 128.5 (C-1´), 133.0 (C-5´), 141.8 (C-3), 162.0 (C-2´) and 166.0 (C=O).

3.2.4. Nucleophillic substitution of Baylis-Hillman-derived allyl chlorides.

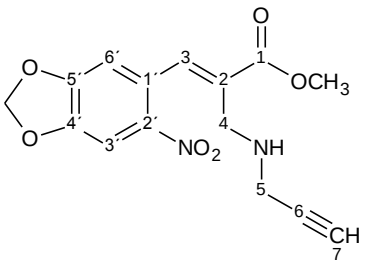
General procedure: Propargylamine (1.2 eq.) was added to a solution of the Baylis-Hillman-derived allyl chloride (1 eq.) in minimal dry THF and the mixture stirred in a stoppered flask at room temperature. The reaction was monitored by TLC. After completion, the solution was then concentrated *in vacuo* to give the crude product. Purification by column chromatography [on silica gel; eluting with hexane:EtOAc (2:1)] afforded the propargylamine derivatives.

***Methyl 3-(2-Nitrophenyl)-2-[(propargylamino)methyl]propenoate* 42a**



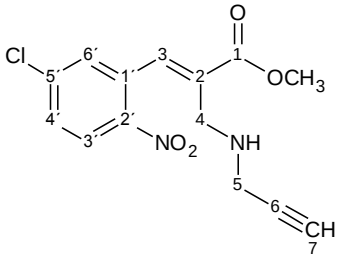
The general procedure was followed, using methyl 2-(chloromethyl)-3-(2-nitrophenyl)-propenoate (0.11 g, 0.42 mmol) and propargylamine in minimal dry THF. The solution was then concentrated *in vacuo* and the crude product purified by PLC [on silica gel; elution with hexane:EtOAc (2:1)] to afford, as a light brown gel, methyl 3-(2-nitrophenyl)-2-[(propargylamino)methyl]propenoate **42a** (39.7 mg, 33%); ν_{max} (ATR)/cm^{-1} 3294 (NH) and 1721 (C=O); δ_c (100 MHz; $CDCl_3$) 37.2 (C-5), 46.4 (C-4), 51.8 (OCH_3), 71.9 (C-7), 81.2 (C-6), 126.3 (C-6´), 128.6 (C-5´), 129.5 (C-4´), 131.5 (C-3), 132.1(C-1´), 137.7 (C-3´), 140.1 (C-2), 148.3(C-2´) and 167.3 (C=O).

***Methyl 3-(4, 5-Methylenedioxy-2-nitrophenyl)-2-[(propargylamino)methy]lpropenoate* 42b**



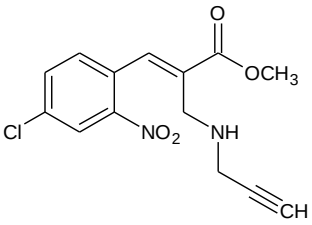
The general procedure was followed, using methyl 2-(chloromethyl)-3-(4,5-methylenedioxy-2-nitrophenyl)propenoate and propargylamine in dry THF. The solution was then concentrated *in vacuo* and the crude product purified on column chromatography [elution with hexane:EtOAc (2:1)] to afford, as a red brown gel, methyl 3-(4,5-methylenedioxy-nitrophenyl)-2-[(propargylamino)methyl]propenoate **42b**; (Found M-H: 317.0533, calc. for $C_{15}H_{13}N_2O_6$: 317.0773); ν_{max} (ATR)/cm^{-1} 3291 (NH) and 1710 (C=O); δ_H (400 MHz; $CDCl_3$) 2.16 (1H, s, NH), 3.34 (2H, s, 5-CH_2), 3.47 (2H, s, 4-CH_2), 3.82 (3H, OCH_3), 6.09 (1H, s, 7-H), 6.15 (2H, s, OCH_2O), 7.08 (1H, s, 6´-H), 7.64 (1H, s, 3´-H), and 7.97 (1H, s, 3-H); δ_c (100 MHz; $CDCl_3$) 37.5 (C-5), 44.8 (C-4), 52.2 (OCH_3), 71.5 (C-7), 81.2 (C-6), 102.9 (OCH_2O), 105.2 (C-5´), 110.2 (C-3´), 129.7 (C-1´), 130.2 (C-5´), 139.6 (C–3), 141.9 (C-3´), 148.2 (C-2), 152.0 (C-2´) and 167.5 (C=O).

***Methyl 3-(5-Chloro-2-nitrophenyl)-2-[(propargylamino)methyl]propenoate* 42c**



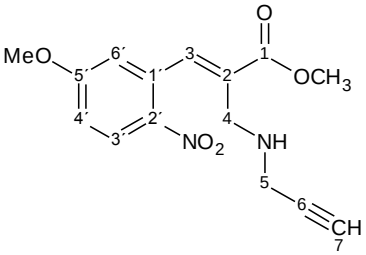
The general procedure was followed, using methyl 2-(chloromethyl)-3-(5-chloro-2-nitrophenyl)propenoate (78.6 mg, 0.27 mmol) and propargylamine (18.0 mg, 0.33 mmol) in minimal dry THF. The solution was then concentrated *in vacuo* and crude product purified by PLC [on silica gel; elution with hexane:EtOAc (2:1)] to afford, as a light brown gel, methyl 3-(5-chloro-2-nitrophenyl)-2-[(propargylamino)methyl]propenoate **42c** (83.2 mg, 96%); ν_{max} (ATR)/cm^{-1} 3292 (NH) and 1716 (C=O); δ_c (100 MHz; $CDCl_3$) 37.3 (C-5), 46.4 (C–4), 51.7 (OCH_3), 71.5 (C–7), 80.7 (C–6), 126.2 (C-6´), 128.5 (C-4´), 131.4 (C-3´), 131.9 (C-5´), 137.6 (C-3), 145.7 (C-1´), 148.2 (C-2), 167.1 (C-2´) and 173.0 (C=O).

***Methyl 3-(4-Chloro-2-nitrophenyl)-2-[(propargylamino)methy]lpropenoate* 42d**



The general procedure was followed, using methyl 2-chloromethyl-3-(4-chloro-2-nitrophenyl)propenoate (0.12 g, 0.42 mmol) and propargylamine (27.6 mg, 0.50 mmol) in dry THF. The solution was then concentrated *in vacuo* and the crude product purified by PLC [on silica gel; elution with hexane:EtOAc (2:1)] to afford, as a light brown gel, methyl 3-(4-chloro-2-nitrophenyl)-2-[(propargylamino)methyl]propenoate **42d** (97.8mg, 76%); ν_{max} (ATR)/cm^{-1} 3294 (NH) and 1697 (C=O); δ_H (400 MHz; $CDCl_3$) 2.98 (2H, s, 5-CH_2), 3.14 (2H, s, 4-CH_2), 3.30 (1H, br s, NH), 3.49 (OCH_3), 7.24 (1H, s, 3´-H), 7.31 (1H, d, *J* = 7.52 Hz, 6´-H), 7.70 (1H, s, 4-H) and 7.80 (1H, d, *J* = 8.08 Hz, 5´-H); δ_c (100 MHz; $CDCl_3$) 37.4 (C-5), 44.7 (C-4), 51.7 (OCH_3), 71.6 (C-7), 81.4 (C-6), 128.3 (C-4´), 129.5 (C-6´), 131.2 (C-5´), 132.8 (C-1´), 133.6 (C-3´), 139.1 (C-3), 147.5 (C-2), 167.5 (C-2´), and 173.5 (C=O).

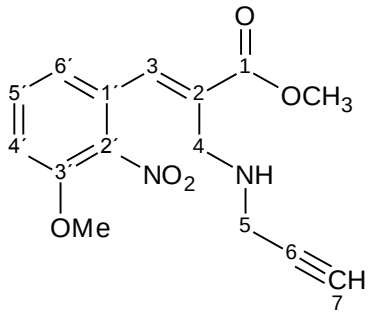
***Methyl 3-(5-Methoxy-2-nitrophenyl)-2-propargylaminomethylpropenoate* 42e**



The general procedure was followed, using methyl 2-(chloromethyl)-3-(5-methoxy-2-nitrophenyl)propenoate (89.4 mg, 0.32 mmol) and propargylamine (20.8 mg, 0.38 mmol) in minimal dry THF. The solution was then concentrated *in vacuo* and the crude product purified by PLC [on silica gel; elution with hexane:EtOAc (2:1)] to afford, as a light brown gel, methyl 3-(5-

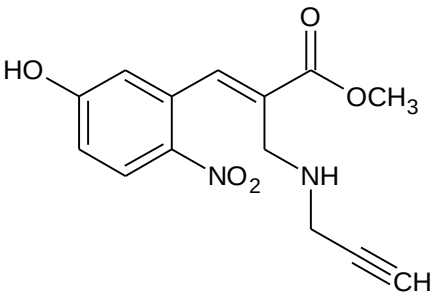
methoxy-2-nitrophenyl)-2-[(propargylamino)methyl]propenoate **42e** (50.0 mg, 52%); (Found M+H: 305.1135. Calc. for $C_{11}H_{17}N_2O_5$: 305.1138); ν_{max} (ATR)/cm^{-1} 3272 (NH) and 1714 (C=O); δ_H (400 MHz; $CDCl_3$) 2.02 (1H, s, 7–H), 2.06 (1H, s, NH), 3.35 (2H, s, 5-CH_2), 3.47 (2H, s, 4-CH_2), 3.84 (3H, s, OCH_3), 3.90 (3H, s, 5´-OCH_3), 6.96 (1H, d, *J* = 8.92 Hz, 4´-H), 7.14 (1H, s, 3-H), 8.08 (1H, s, 6´-H) and 8.19 (1H, d, *J* = 9.0 Hz, 3´-H); δ_c (100 MHz; $CDCl_3$) 37.6 (5-CH_2), 45.0 (4-CH_2), 52.3 (OCH_3), 56.1 (5´-OCH_3), 71.5 (C-6), 81.3 (C-7), 114.9 (C-6´), 115.7 (C-4´), 127.4 (C-3´),130.4 (C-1´), 133.8 (C-2), 140.1 (C-3), 140.4 (C-2´), 163.4 (C-5´) and 167.5 (C=O).

***Methyl 3-(3-Methoxy-2-nitrophenyl)-2-[(propargylamino)methyl]propenoate* 42f**



The general procedure was followed, using methyl 2-(chloromethyl)-3-(3-methoxy-2-nitrophenyl)propenoate (65.4 mg, 0.23 mmol) and propargylamine (15.2 mg, 0.28 mmol) in dry THF. The solution was then concentrated *in vacuo* and the crude product purified by PLC [on silica gel; elution with hexane:EtOAc (2:1)] to afford, as a light brown gel, methyl 3-(3-methoxy-2-nitrophenyl)-2-[(propargylamino)methyl]propenoate **42f** (47.5 mg, 69%); ν_{max} (ATR)/cm^{-1} 3292 (NH) and 1714 (C=O); δ_H (400 MHz; $CDCl_3$) 2.04 (1H, s, 7-H), 2.15 (1H, br s, NH), 3.40 (2H, s, 5-CH_2), 3.55 (2H, s, 4-CH_2), 3.81 (3H, s, OCH_3), 3.92 (3H, s, 3´-OCH_3), 7.06 (1H, d, *J* = 8.44 Hz, 4´-H), 7.22 (1H, d, *J* = 7.80 Hz, 5´-H), 7.46 (1H, t, *J* = 8.12 Hz, 5´-H) and 7.62 (1H, s, 3-H); δ_c (100 MHz; $CDCl_3$) 37.8 (5-CH_2), 45.1 (4-CH_2), 52.4 (OCH_3), 56.5 (3´-OCH_3), 71.7 (C-6), 81.4 (C-7), 112.9 (C-4´), 121.7 (C-5´), 127.9 (C-3´), 129.0 (C-1´), 131.2 (C-3), 134.6(C-2), 134.7 (C-6´), 151.2 (C–2´) and 167.3 (C=O).

***Methyl 3-(5-hydroxy-2-nitrophenyl)-2-[(propargylamino)methyl]propenoate* 42g**

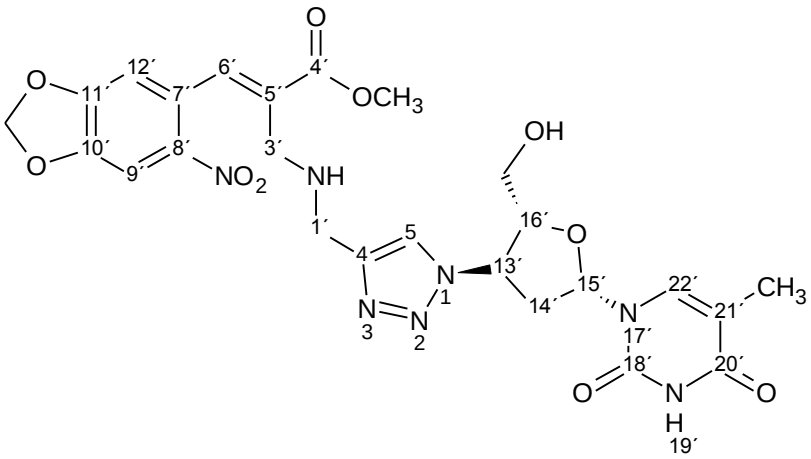


The general procedure was followed, using methyl 2-(chloromethyl)-3-(5-hydroxy-2-nitrophenyl)propenoate (55.6 mg) and propargylamine in dry THF. The solution was then concentrated *in vacuo* and a crystaline product obtained without purification, methyl 3-(5-hydroxy-2-nitrophenyl)-2-[(propargylamino)methyl]propenoate **42g**; ν_{max} (ATR)/cm^{-1} 3287 (NH and Ar–OH) and 1718 (C=O); δ_c (100 MHz; $CDCl_3$) 37.6 (5-CH_2), 45.0 (4-CH_2), 52.5 (OCH_3), 116.5 (C–4´), 116.7 (C–3´), 128.0 (C–6´), 128.5 (C–1´), 133.0 (C–5´), 141.8 (C–3), 162.0 (C–2´), and 166.0 (C=O).

3.2.5. Synthesis of cinnamate ester-AZT conjugates.

General procedure: Propargylamine derivative (1 eq), a catalytic amount of sodium ascorbate and copper sulphate pentahydrate were sequentially added to a solution of 3`-azido-3`-deoxythymidine (AZT) (1.2 eq.) in THF/H_2O (1:1). The mixture was stirred at room temperature for at least 24 hours and the reaction monitored by TLC. The mixture was then extracted with CH_2Cl_2, and the organic phase washed sequentially with H_2O and brine and then dried over anhydrous magnesium sulphate. The solution was concentrated *in vacuo* to give the crude product which was purified by column chromatography [on silica gel; elution with EtOAc followed by hexane:EtOAc (1:1) to afford an cinnamate ester-AZT conjugates.

***Cinnamate ester-AZT conjugate* 41a**



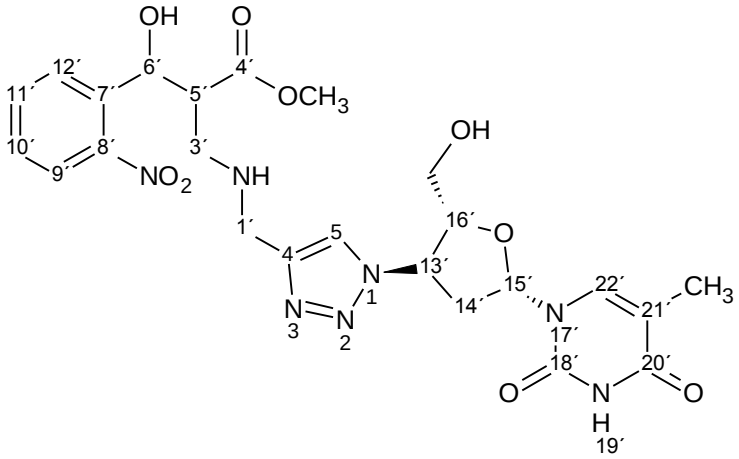
The general procedure was followed, using AZT (0.16 g, 0.60 mmol) in THF/H_2O (1:1) (10 mL), methyl 3-(4,5-methylenedioxy-nitrophenyl)-2-[(propargylamino)methyl]propenoate (0.31 g, 0.92 mmol), $CuSO_4.5H_2O$ (16.2 mg, 64.9 μmol) and sodium ascorbate (16.2 mg, 81.8 μmol). Work-up and column chromatography afforded, as a dark brown gel, the cinnamate ester conjugate **41a** (0.38g, 71%); (Found M+H: 586.1884. Calc. for $C_{25}H_{29}N_7O_{10}$:586.1899); ν_{max} (ATR)/cm^{-1} 3323 (OH) and 1687 (C=O); δ_H (400 MHz; methanol-d_4) 1.81 (3H, s, 21´–CH_3), 2.33 (2H, m, J = 5.96 Hz, 14´-H), 2.65 and 2.79 (2H, m, J = 5.66 Hz, 1´-H), 3.43 (1H, s, 1´-H), 3.69 (2H, d, J = 3.28 Hz, 1´-H and 3´-H), 3.76 (3H, t, J = 4.24 Hz, OCH_3), 3.77 (2H, t, J =5.48 Hz, 13´/15´-H), 3.84 (1H, m, J =3.28 Hz, 3´-H), 4.30 (1H, q, J = 4.19 Hz, 16´-H), 6.10 (1H, t, J = 6.36 Hz, 13´-H), 6.15 (2H, s, OCH_2O), 6.40 (1H, t, J = 6.38 Hz, 15´-H), 7.74 (1H, s,12´-H),

7.85 (1H, s, 9´-H) and 7.91 (1H, s, 6´-H); δ_c (100 MHz; methanol-d_4) 12.5 (21´-CH_3), 38.3 (C-14´), 39.0 and 44.8 (C-1´), 52.9 (OCH_3), 61.7 (C-16´), 62.4 (OCH_2O), 86.1 (C-15´/13´), 105.3 (OCH_2O), 106.4 (C-12´), 110.7 (C-9´), 111.7 (Ar-C), 124.0 (C-6´), 128.6 (Ar-C), 130.9 (Ar-C), 138.2 (C-22´ and C-7´), 141.7 (C-4), 143.2 (Ar-C), 146.9 (C-8´), 150.1 (Ar-C), 152.3 (C-20´), 153.8 (Ar-C), 166.4 (C-18´) and 167.0 (C=O).

3.2.6. Synthesis of 3-hydroxy ester-AZT conjugates and cinnamate ester-AZT conjugates.

General procedure: 3`-azido-3`-deoxythymidine (AZT) (1.2 eq.), a catalytic amount of sodium ascorbate and copper sulphate pentahydrate were sequentially added to a solution of the propargylamine derivative (1 eq) in THF/H_2O (1:1). The mixture was stirred at room temperature for at least 24 hours and the reaction monitored by TLC. The mixture was then extracted with CH_2Cl_2, and the organic phase washed sequentially with H_2O and brine and then dried over anhydrous magnesium sulphate. The solution was concentrated *in vacuo* to give the crude product which was purified by column chromatography [on silica gel; elution with hexane:EtOAc (1:2), followed by MeOH:EtOAc (2:3)] to afford the 3-hydroxy ester-AZT conjugates.

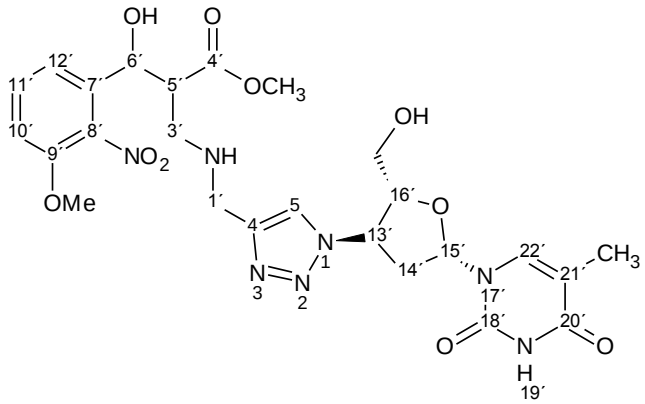
***3-hydroxy ester-AZT conjugate* 40a.**



The general procedure was followed, using methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate (1.20g, 0.68 mmol) in THF-H_2O (1:1; 10 mL), 3´-azido-3´-deoxythymidine (0.22 g, 0.81 mmol), sodium ascorbate (10.1 mg, 51.2 µmol) ,and copper sulphate pentahydrate (11.3 mg, 45.3. µmol). Work up and column chromatography afforded, as a red brown gel, a diastereomeric mixture of 3-hydroxy ester-AZT conjugates **40a** (0.15 g, 41%); (Found M+H: 560.2120. Calc. for $C_{24}H_{30}N_7O_9$: 560.2107); ν_{max} (ATR)/cm^{-1} 3298 (OH) and 1668 (C=O); δ_H (400 MHz; methanol-d_4) 1.84 (3H, s, 21´-H), 2.66 and (4H, m, *J* = 5.61 Hz, 14´-H), 3.02 (2H, m, *J* =5.96 Hz, 5´-H), 3.54 (3H, s, OCH_3), 3.70 (1H, m, *J* = 3.04 Hz, C*H*$_2$OH) and 3.82 (3H, t, *J* = 8.61 Hz, C*H*$_2$OH), 4.02 (2H, q, *J* = 5.35 Hz, 13´-H) and 5.32 (1H, m, J = 4.02,

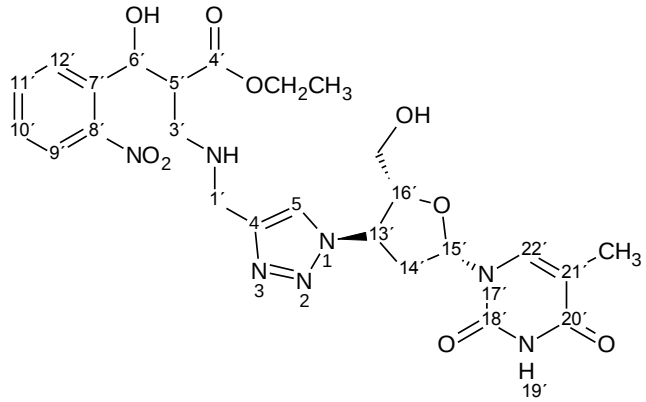
13´-H), 4.27 (1H, m, *J* = 3.16 Hz, 15´-H), 5.37 (1H, d, *J* = 6.20 Hz, 6´-H), 6.42 (1H, br s, 16´-H), 7.43 (1H, t, *J* = 7.70 Hz, 10´-H), 7.62 (1H, t, *J* = 7.50 Hz, 11´-H), 7.72 (1H, t, *J* = 7.20 Hz, 9´-H), and 7.86 (3H, t, *J* = 11.0 Hz, 4-H and 22´-H); δ_c (100 MHz; methanol-d_4) 12.6 (21´-CH_3), 39.1 (C-14´), 44.7 (C-3´), 52.2 and 52.4 (OCH_3), 52.6 (C-5´), 61.1 (C-16´), 61.6 (C-1´), 62.2 (CH_2OH), 69.4 (C-6´), 86.5 (C-13´/15´), 86.7(C-13´/15´), 111.7 (C-21´), 125.2 (C-12´),129.8 (C-10´), 130.1 (C-9´), 134.3 (C-11´), 138.3 (C-22´), 139.1 (C-7´), 146.3, 147.0 (C-8´) , 149.6 (C-4), 152.3 (C-20´), 166.5 (C-18´) and 173.1 (C=O).

***3-hydroxy ester-AZT conjugate* 40b.**



The general procedure was followed, using methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate (0.19 g, 0.58 mmol) in THF-H_2O (1:1; 10 mL), 3´-azido-3´-deoxythymidine (0.19 g, 0.70 mmol), sodium ascorbate (13.1 mg, 66.1 µmol) and copper sulphate pentahydrate (16.1 mg, 64.5 µmol). Work up and column chromatography afforded, as a red brown gel, a diastereomeric mixture of 3-hydroxy ester-AZT conjugates **40b** (0.25 g, 74%); (Found M+H: 590.2218. Calc. for $C_{25}H_{32}N_7O_{10}$: 590.2212); ν_{max} (ATR)/cm^{-1} 3332 (OH) and 1683 (C=O).

***3-hydroxy ester-AZT conjugate* 40c.**



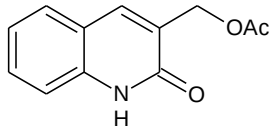
The general procedure was followed, using ethyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate (0.24 g, 0.71 mmol) in THF-H_2O (1:1; 10 mL), 3´-azido-3´-deoxythymidine (0.19 g, 0.71 mmol), sodium ascorbate (14.9 mg, 75.5 µmol) and copper sulphate pentahydrate (18.1 mg, 72.3 µmol). Work up and column chromatography afforded, as a red brown gel, a diastereomeric mixture of 3-hydroxy ester-AZT conjugates **40c** (0.28 g, 68%); (Found M+H: 574.2270. Calc. for $C_{25}H_{32}N_7O_9$: 574.2263); ν_{max} (ATR)/cm^{-1} 3297 (OH) and 1712 (C=O); δ_C (100 MHz; methanol-d_4) 12.6 (21´-CH_3), 14.3 (OCH_2CH_3), 39.1 (14´-CH_2), 47.9 (C-1´), 49.2 (C-3´), 52.4 and 53.5 (C-5´), 61.0 (C-16´), 61.6 (OCH_2CH_3), 62.2 (OCH_2OH), 69.4 (C-6´), 86.4 and 86.5 (C-13´/15´), 124.2 (C-4), 125.3 (C-12´), 129.8 (C-10´), 130.1 (C-9´), 134.3 (C-11´), 138.3 (C-21´), 139.1 (C-7´), 146.3, 147.0 (C-8´) , 149.6 (C-4), 152.3 (C-20´), 166.5 (C-18´), 173.1 (C=O).

3.3. Exploratory studies.

3.3.1. Cyclisation of Baylis-Hillman adducts.

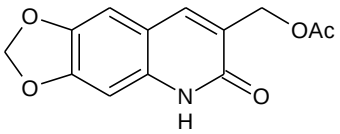
General procedure: Iron powder was added to a stirred solution of the Baylis-Hillman adduct in acetic acid at 110 ^{o}C with continued stirring. After 30 minutes, TLC showed the commencement of formation of a product and the reaction was allowed to run for 12 hours. The reaction mixture was then cooled to room temperature and the acetic acid removed *in vacuo*. Ethyl acetate was then added to the residues and the resulting mixture was stirred and filtered to remove the insoluble iron powder. The solid was washed with ethyl acetate and the washings were combined with the filtrate. The solvent was removed *in vacuo* and the crude product purified by column chromatography [on silica; elution with hexane:EtOAc (1:1)].

3-(Acetoxymethyl)-(1H)-2-quinolone **13a.**



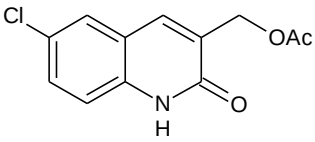
The general procedure was followed, using methyl 3-hydroxy-2-methylene-3-(2-nitrophenyl)propanoate (0.29 g, 1.2 mmol) and iron powder (0.31 g, 5.5 mmol) in acetic acid (10 mL) to afford, as white crystals, 3-(acetoxymethyl)-(1*H*)-2-quinolone **13a** (0.19 g, 91%), mp 181-183 ^{0}C (Lit.[40] 167-169); (Found M+H: 218.0861. Calc. for $C_{12}H_{12}NO_3$: 218.0817); ν_{max} (ATR)/cm^{-1} 1735 and 1723 (double band) and 1659 (C=O); δ_H (400 MHz; $CDCl_3$) 2.19 (3H, s, OAc), 5.23 (2H, s, CH_2OAc), 7.23 (1H, t, *J* = 8.54 Hz, 6-H), 7.43 (1H, d, *J* = 8.16 Hz, 5-H), 7.53 (1H, t, *J* = 8.34 Hz, 7-H), 7.59 (1H, d, *J* = 7.88 Hz, 8-H), 7.88 (1H, s, 4-H) and 12.22 (1H, s, NH); δ_c (100 MHz; $CDCl_3$) 21.1 (CH_3), 61.4 (C*H*$_2$OAc), 115.9 (C-5), 119.6 (C-9), 122.8 (C-6), 127.5 (C-7), 127.9 (C-3), 130.6 (C-8), 138.0 (C-10), 138.5 (C-4), 163.1 (C -2) and 170.9 (C=O).

3-(Acetoxymethyl)-6,7-methylenedioxy-(1H)-2-quinolone **13b.**



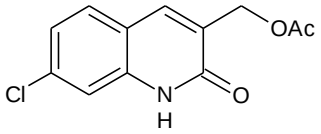
The general procedure was followed, using methyl 3-hydroxy-2-methylene-3-(4,5-methylenedioxy-2-nitrophenyl)propanoate (0.51 g, 1.8 mmol) and iron powder (0.41 g, 7.3 mmol) in acetic acid (15 mL) to afford, as white crystals, 3-(acetoxymethyl)-6,7-methylenedioxy-(1*H*)-2-quinolone **13b** (0.24 g, 62%), mp 191-193 ^{0}C (Lit.[49] 227-228 ^{0}C); ν_{max} (ATR)/cm^{-1} 1727 and 1659 (C=O); δ_H (400 MHz; $CDCl_3$) 2.15 (3H, s, CH_3), 5.17 (2H, s, CH_2OAc), 6.05 (2H, s, OCH_2O), 6.79 (1H, s, 5-H), 6..93 (1H, s, 8-H), 7.74 (1H, s 4-H) and 11.12 (NH); δ_c (100 MHz; $CDCl_3$) 20.7 (CH_3), 61.2 (CH_2OAc), 95.9 (C-8), 101.9 (OCH_2O), 105.1 (C-5), 114.5 (C-9), 128.9 (C-10), 134.9 (C-3), 139.5 (C-4), 144.8 (C-6), 151.2 (C-7), 163.3 C-2) and 170.8 (C=O).

3-(Acetoxymethyl)-6-chloro-(1H)-2-quinolone **13c**



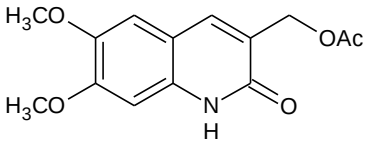
The general procedure was followed, using methyl 3-hydroxy-2-methylene-3-(5-chloro-2-nitrophenyl)propanoate (0.50 g, 1.9 mmol) and iron powder (0.49 g, 8.9 mmol) in acetic acid (10mL) to afford, as light yellow crystals, 3-(acetoxymethyl)-6-chloro-(1*H*)-2-quinolone **13c** (0.42 g, 81%), mp 218-222 ^{0}C (Lit.[49] 229-230 ^{0}C); (Found M+H: 252.0417. Calc. for $C_{12}H_{11}ClNO_3$: 252.6657); ν_{max} (ATR)/cm^{-1} 1739 and 1663 (C=O); δ_H (400 MHz; $CDCl_3$) 2.18 (3H, s, OAc), 5.21 (2H, s, CH_2OAc), 7.36 (1H, d, *J* = 8.72 Hz, 7-H), 7.47 (1H, d, *J* = 9.42 Hz, 8-H), 7.57 (1H, s, 5-H), 7.77 (1H, s, 4-H) and 12.35 (1H, br s, NH); δ_c (100 MHz; $CDCl_3$) 20.9 (CH_3), 61.2 (CH_2OAc), 117.3 (C-8) , 120.5 (C-10), 127.0 (C-9), 128.2 (C-5), 129.0 (C-7), 130.8 (C-3), 136.4 (C-6), 136.9 (C-4), 162.8 (C-2) and 170.6 (C=O).

3-(Acetoxymethyl)-7-chloro-(1H)-2-quinolone **13d**



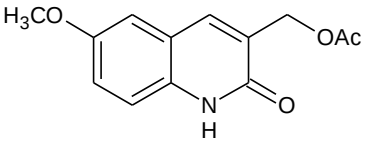
The general procedure was followed, using methyl 3-hydroxy-2-methylene-3-(4-chloro-2-nitrophenyl)propanoate (0.50 g, 1.9 mmol) and iron powder (0.49 g, 8.9 mmol) in acetic acid (10 mL) to afford, as white crystals, 3-(acetoxymethyl)-7-chloro-(1*H*)-2-quinolone **13d** (0.44 g, 86%); mp 161-163 ^{0}C, ν_{max} (ATR)/cm^{-1} 1736 and 1665 (C=O); δ_H (400 MHz; $CDCl_3$) 2.18 (3H, s, CH_3), 5.19 (2H, s, CH_2OAC), 7.20 (1H, d, *J* = 9.00 Hz, 5-H), 7.30 (1H, s, 8-H), 7.51 (1H, d, *J* = 8.44 Hz, 6-H), 7.80 (1H, s, 4-H) and 10.80 (1H, br s, NH); δ_c (100 MHz; $CDCl_3$) 21.0 (CH_3), 61.2 (CH_2OAc), 115.2 (C-5), 118.1 (C–9 and 10), 123.6 (C-6), 128.1 (C–3), 129.2 (C-8), 136.8 (C-7), 137.8 (C-4), 162.5 (C-2) and 170.7 (C=O).

3-(Acetoxymethyl)-6,7-dimethoxy-(1H)-2-quinolone **13e**



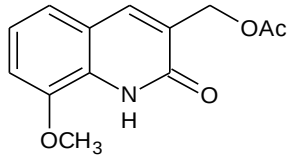
The general procedure was followed, using methyl 3-hydroxy-2-methylene-3-(4,5-dimethoxy-2-nitrophenyl)propanoate (0.20 g, 0.7 mmol) and iron powder (0.55 g, 3.6 mmol) in acetic acid (5 mL) to afford, as off-white crystals, 3-acetoxymethyl-6,7-dimethoxy-(1*H*)-2-quinolone **13e** (0.11 g, 71%), mp 184-187 ^{0}C (Lit.[40] 177-178 ^{0}C); ν_{max} (ATR)/cm^{-1} 1741 and 1654 (C=O); δ_H (400 MHz; DMSO-d_6) 2.10 (3H, s, CH_3), 3.78 and 3.80 (6H, 2×s, 2×Ar-OCH_3), 4.93 (2H, s, CH_2OAc), 6.85 (1H, s, 5-H), 7.22 (1H, s, 8-H), 7.80 (1H, s, 4-H) and 11.75 (1H, br s, NH); δ_c (100 MHz; DMSO-d_6) 20.8 (CH_3), 55.5 and 55.7 (6- and 7-OCH_3), 61.5 (CH_2OAc), 97.4 (C–5), 108.8 (C–8), 112.0 (C-9), 124.4 (C-6), 134.0 (C-7), 137.1 (C-4), 144.9 (C-3), 151.9 (C-10), 160.8 (C-2) and 170.3 (C=O).

3-(Acetoxymethyl)-6-methoxy-(1H)-2-quinolone **13f**



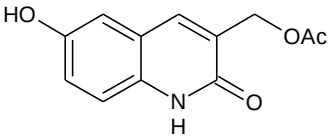
The general procedure was followed, using methyl 3-hydroxy-3-(5-methoxy-2-nitrophenyl)-2-methylenepropanoate (0.20 g, 0.7 mmol) and iron powder (0.19g, 3.5mmol) in acetic acid (5mL) to afford, as brown crystals, 3-(acetoxymethyl)-6-methoxy-(1*H*)-2-quinolone **13f** (0.18 g, 99%), mp 183-185 ^{0}C; ν_{max} (ATR)/cm^{-1} 1728 and 1654 (C=O); δ_H (400 MHz; $CDCl_3$) 2.18 (3H, s, CH_3), 3.86 (3H, s, 6-OCH_3), 5.22 (2H, s, CH_2OAc), 7.00 (1H, s, 5-H), 7.16 (1H, d, *J* = 8.72 Hz, 7-H), 7.34 (1H, d, *J* = 8.84 Hz, 8-H), 7.82 (1H, s, 4-H), and 12.02 (1H, br s, NH); δ_c (100 MHz; $CDCl_3$) 21.1 (CH_3), 55.6 (6-OCH_3), 61.5 (CH_2OAc), 108.8 (C-8), 117.2 (C-5), 120.1 (C-7), 120.3 (C-9), 125.6 (C-10), 127.8 (C-3), 138.1 (C-4), 155.2 (C-6), 162.6 (C-2) and 170.9 (C=O).

3-(Acetoxymethyl)-8-methoxy-(1H)-2-quinolone **13g**



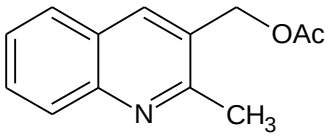
The general procedure was followed, using methyl 3-hydroxy-3-(3-methoxy-2-nitrophenyl)-2-methylenepropanoate (0.20 g, 0.8 mmol) and iron powder (0.26 g, 4.6 mmol) in acetic acid (10mL) to afford, as green crystals, 3-(acetoxymethyl)-8-methoxy-(1*H*)-2-quinolone **13g** (0.12 g, 63%), mp 191-193 (Lit.[49] 170-172 ^{0}C); ν_{max} (ATR)/cm^{-1} 1740 and 1647 (C=O); δ_H (400 MHz; DMSO-d_6) 2.12 (CH_3), 3.90 (3H, s, 8-OCH_3), 4.98 (2H, s, CH_2OAc), 7.14 (2H, d, J = 5.00 Hz, 5- and 7-H), 7.28 (1H, t, *J* = 9.00 Hz, 6-H), 7.88 (1H, s, 4-H) and 10.97 (1H, br s, NH); δ_c (100 MHz; DMSO-d_6) 20.6 (CH_3), 56.0 (8-OCH_3), 60.9 (CH_2OAc), 110.9 (C-5), 119.1 (C-6), 119.6 (C-9), 121.9 (C-7), 128.2 (C-10), 128.3 (C-3), 136.8 (C-4), 145.6 (C-8), 160.4 (C-2) and 170.1 (C=O).

3-Acetoxymethyl-6-hydroxy-(1*H*)-2-quinolone **13h**



The general procedure was followed, using methyl 3-hydroxy-3-(5-hydroxy-2-nitrophenyl)-2-methylenepropanoate (0.30 g, 1.2 mmol) and iron powder (0.40 g, 7.2 mmol) in acetic acid (10mL) to afford, as yellow crystals, 3-(acetoxymethyl)-6-hydroxy-(1*H*)-2-quinolone **13h** (97.4 mg, 38%), mp 157-159; ν_{max} (ATR)/cm^{-1} 3201 (OH), 1720 and 1606 (C=O); δ_H (400 MH; DMSO-d_6) 2.11 (3H, s, CH_3), 4.94 (2H, s, CH_2OAc), 7.00 (1H, s, 6-H), 7.17 (2H, d, J = 9.48 Hz, 7- and 8-H), 7.79 (1H, s, 4-H), 9.47 (1H, s, OH) and 11.75 (1H, s, NH); δ_c (100 MHz; DMSO-d_6) 20.8 (CH_3), 61.2 (CH_2OAc), 111.5 (C-5), 116.2 (C-8), 119.7 (C-9), 119.9 (C-7), 127.8 (C-3), 131.7 (C-10), 136.6 (C-4), 152.2 (C-6), 160.4 (C-2) and 170.3 (C=O).

3-(acetoxymethyl)-2-methylquinoline **14**

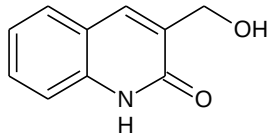


The general procedure was followed, using 3-hydroxy-2-methylene-3-(2-nitrophenyl)butanone (0.53 g, 2.4 mmol) and iron powder (0.50 g, 8.9 mmol) in acetic acid (10 mL) to afford, as brown crystals, 3-(acetoxymethyl)-2-methylquinoline **13i** (85.0 mg, 17%), mp 91-93 ^{0}C (Lit.[40] 94-95 ^{0}C); ν_{max} (ATR)/cm^{-1} 1735 (C=O); δ_H (400 MHz; $CDCl_3$) 2.14 (3H, s, CH_3), 2.76 (3H, s, Ar-CH_3), 5.28 (2H, s, CH_2OAc), 7.49 (1H, t, *J* = 7.44 Hz, 6-H), 7.68 (1H, t, *J* = 7.68 Hz, 7-H), 7.78 (1H, d, 8.00 Hz, 5-H), 8.01 (1H, d, *J* = 8.48 Hz, 8-H) and 8.07 (1H,s, 4-H).

3.3.2. Hydrolysis of 3-(Acetoxymethyl)-(1H)-2-quinolone derivatives.

General procedure: A mixture of 3-(acetoxymethyl)-(1*H*)-2-quinolone derivative (1 eq) and potassium carbonate (3 eq) in methanol-water (1:1) was stirred at room temperature for 24 hours after which TLC showed complete conversion the substrate. The reaction mixture was concentrated *in vacuo,* and the precipitate washed with dichloromethane. The filtrate and washings were dried with anhydrous $MgSO_4$, filtered, and then concentrated to give the 3-(hydroxymethyl)-(1*H*)-2-quinolone derivative.

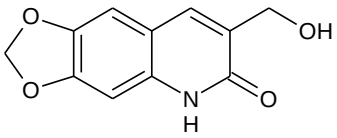
3-(Hydroxymethyl)-(1H)-2-quinolone **54a**



Method A: A mixture of 3-(acetoxymethyl)-(1*H*)-2-quinolone (0.13 g, 0.59 mmol) and potassium carbonate (0.25g, 1.8 mmol) in methanol containing few drops of water was stirred at room temperature for one hour. The reaction mixture was filtered and the precipitate washed with methanol (5 mL). The combined methanolic filtrate and washings were concentrated and the crude product was purified by column chromatography [on silica gel; elution with hexane:EtOAc (1:1)] to provide, as yellow crystals, 3-(hydroxymethyl)-(1*H*)-2-quinolone **54a** (65.0 mg, 63%), mp 208-210 ^{o}C (Lit.[40] 199-200 ^{0}C); (Found M+H: 176.0714. Calc. for $C_{12}H_{10}NO_2$: 176.0712); ν_{max} (ATR)/cm^{-1} 3368 (OH) and 1643 (C=O); δ_H (400 MHz; DMSO-d_6) 4.40 (2H, s, CH_2OH), 5.24 (1H, s, OH), 7.16 (1H, t, *J*=7.16 Hz, 6-H), 7.30 (1H, d, *J* = 8.05 Hz, 5-H), 7.45 (1H, t, *J* = 7.58 Hz, 7-H), 7.68 (1H, d, *J* = 7.48 Hz, 8-H), 7.85 (1H, s, 4-H) and 11.81 (1H, br s, 1-H); δ_c (100 MHz; DMSO-d_6) 58.9 (CH_2OH), 115.3 (C-5), 119.8 (C-9), 122.3 (C-6), 128.0 (C-7), 129.9 (C-3), 134.0 (C-8), 134.5 (C-10), 138.1(C-4) and 161.6 (C-2).

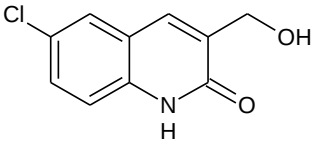
Method B: The general procedure was followed, using 3-acetoxymethyl-(1*H*)-quinol-2-one (0.64 g, 2.94 mmol) and potassium carbonate (1.23 g, 8.9 mmol) in methanol:water (1:1). Work-up afforded, as yellow crystals, 3-(hydroxymethyl)-(1*H*)-2-quinolone (0.45 g, 87%).

3-(Hydroxymethyl)-4,5-methylenedioxy-(1H)-2-quinolone **54b**



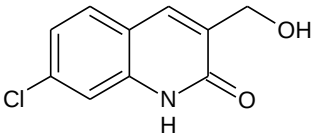
The general procedure was followed, using 3-(acetoxymethyl)-6,7-methylenedioxy-(1*H*)-2-quinolone (0.10 g, 0.40 mmol) and potassium carbonate (0.17 g, 1.2 mmol). Work-up afforded, as yellow crystals, 3-(hydroxymethyl)-6,7-methylenedioxy-(1*H*)-2-quinolone **54b** (69.6 mg, 79%), mp 188-190 ^{0}C; ν_{max} (ATR)/cm^{-1} 3149 (OH) and 1639 (C=O); δ_H (400 MHz; DMSO-d_6) 4.40 (2H, s, CH_2OH), 6.06 (2H, s, OCH_2O), 6.84 (1H, s, 5-H), 7.21 (1H, s, 8-H) and 7.72 (1H, s, 4-H).

3-Hydroxymethyl-6-chloro-(1H)-quinol-2-one **54c**



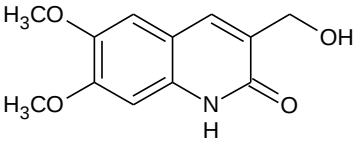
The general procedure was followed, using 3-(acetoxymethyl)-6-chloro-(1*H*)-2-quinolone (0.30 g, 1.1 mmol) and potassium carbonate (0.47 g, 3.4 mmol). Work-up afforded, as yellow crystals, 3-(hydroxymethyl)-6-chloro-(1*H*)-2-quinolone **54c** (0.20 g, 83%), mp 213-218 ^{0}C; ν_{max} (ATR)/cm^{-1} 3330 (OH) and 1644 (C=O); δ_H (400 MHz; $CDCl_3$) 4.66 (2H, s, CH_2OH), 7.14 (1H, d, J = 8.76 Hz, 7-H), 7.41 (1H, d, J = 8.68 Hz, 8-H), 7.51 (1H, s, 5-H), 7.64 (1H, s, 4-H) and 8.02 (1H, br s, 1-H); δ_C (100 MHz; $CDCl_3$) 58.8 (CH_2OH), 117.3 (C-8) , 120.5 (C-10), 127.0 (C-9), 128.2 (C-5), 129.0 (C-7), 130.8 (C-3), 136.4 (C-6), 136.9 (C-4) and 162.8 (C=O).

7-Chloro-3-(Hydroxymethyl)-(1H)-2-quinolone **54d**



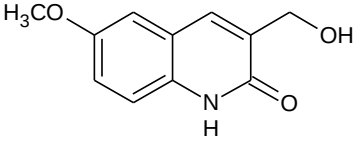
The general procedure was followed, using 3-(acetoxymethyl)-7-chloro–(1*H*)-2-quinolone (0.11 g, 0.39 mmol) and potassium carbonate (0.16 g, 1.2 mmol). Work-up afforded, as yellow crystals, 7-chloro-3-(hydroxymethyl)-(1*H*)-2-quinolone **54d** (68.6 mg, 85%), mp 209-212 ^{0}C; (Found M+H: 210.0314. Calc. for $C_{10}H_9ClNO_2$: 210.0322); ν_{max} (ATR)/cm^{-1} 3081 (OH) and 1622 (C=O); δ_H (400 Hz; DMSO-d_6) 4.38 (2H, s, CH_2OH), 7.03 (1H, d, *J* = 58.34 Hz, 5-H), 7.26 (1H, s, 8-H), 7.58 (1H, d, *J* = 8.36 Hz, 6-H) and 7.67 (1H, s, 4-H); δ_c (100 MHz; DMSO-d_6) 58.8 (CH_2OH), 114.6 (C-5), 118.9 (C-9), 122.5 (C-10), 127.4 (C-6), 29.9 (C-3), 133.5 (C-8), 134.1 (C-7), 135.8 (C-4) and 161.4 (C-2).

3-(Hydroxymethyl)-6,7-dimethoxy-(1H)-2-quinolone **54e**



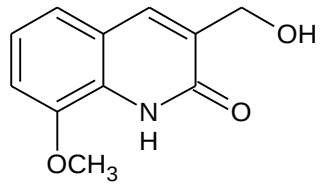
The general procedure was followed, using crude 3-acetoxymethyl-6,7-methylenedioxy-(1*H*)-2-quinolone and potassium carbonate. Work-up afforded, as yellow crystals, 3-hydroxymethyl-6,7-dimethxy-(1*H*)-2-quinolone **54e**, mp 215-217 ^{0}C; ν_{max} (ATR)/cm^{-1} 3087 (OH) and 1685 (C=O); δ_H (400 MHz; methanol-d_4) 3.79 and 3.90 (6H, 2×s, 6- and 7-OCH_3), 4.52 (2H, s, CH_2OH), 6.75 (1H, s, 5-H), 7.00 (1H, s, 8-H) and 7.85 (1H, s, 4-H).

3-(Hydroxymethyl)-6-methoxy-(1H)-2-quinolone **54f**



The general procedure was followed, using crude 3-(acetoxymethyl)-6-methoxy-(1*H*)-2-quinolone (synthesized from 0.52 g of the corresponding Baylis-Hillman adduct) and potassium carbonate (3 eq). Work up afforded, as yellow crystals, 3-(hydroxymethyl)-6-methoxy-(1*H*)-2-quinolone **54f** (0.23 g, 56%), mp 101-103 ^{0}C; (Found M+H: 206.0813. Calc. for $C_{11}H_{12}NO_3$: 206.0817), ν_{max} (ATR)/cm^{-1} 3345 (OH) and 1656 (C=O); δ_H (100 MHz; methanol-d_4) 3.79 (3H, Ar-OCH_3), 4.54 (2H, s, CH_2OH), 7.12 (2H, 7-and 8-H), 7.22 (1H, 5-H) and 7.89 (1H, 4-H); δ_c (100 MHz; methanol-d_4) 56.1 (Ar–OCH_3) , 60.4 (CH_2OH), 109.9 (C-8), 117.7 (C-5), 120.8 (C-9), 122.2 (C-7), 133.2 (C-10), 134.2 (C-3), 136.6 (C-4), 156.9 (C-6) and 163.4 (C-2).

3-Hydroxymethyl-8-methoxy-(1H)-2-quinolone **54g**

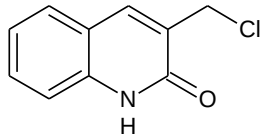


The general procedure was followed, using crude 3-acetoxymethyl-7-methoxy-(1*H*)-2-quinolone (synthesized from 0.56 g of the corresponding Baylis-Hillman adduct) and potassium carbonate (3 eq). Work-up afforded, as yellow crystals, 3-hydroxymethyl-7-methoxy-(1*H*)-2-quinolone **54g** (0.15 g, 34 %), mp 92-95 ^{0}C; (Found M+H: 206.0807. Calc. for $C_{11}H_{12}NO_3$: 206.0817); ν_{max} (ATR)/cm^{-1} 3340 (OH) and 1640 (C=O); δ_H (100 MHz; methanol-d_4) 3.25 (1H, OH), 4.54 (2H, CH_2OH), 7.05 (1H, 5-H), 7.14 (2H, 6 and 7-H) and 7.89 (1H, 4-H); δ_c (100 MHz; methanol-d_4) 56.6 (8-OCH_3), 60.3 (CH_2OH), 111.1 (C-5), 120.6 (C-6), 121.8 (C-9), 123.9 (C-7), 128.7 (C-10), 134.5 (C-3), 136.8 (C-4), 147.5 (C-8) and 163.5 (C-2).

3.3.3. Chlorination of 3-hydroxymethyl-(1H)-2-quinolone.

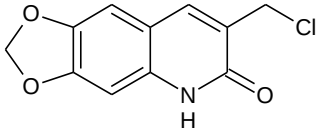
General procedure: An excess of thionyl chloride ($SOCl_2$) was added to the 3-(hydroxymethyl)-(1*H*)-2-quinolone derivative and the reaction mixture was stirred in a stoppered flask at room temperature. (*Caution: Thionyl chloride is very volatile and corrosive*.) After completion, the mixture was diluted with dichloromethane, and then excess thionyl chloride quenched with water. The organic layer was then dried and concentrated *in vacuo* to afford the 3-(chloromethyl)-(1*H*)-2-quinolone derivative **17**.

3-(Chloromethyl)-(1H)-2-quinolone **15a**



Method A: The general method was followed, using 3-(hydroxymethyl)-(1*H*)-2-quinolone (0.25 g, 1.4 mmol) to obtain, as white crystals, 3-(chloromethyl)-(1*H*)-2-quinolone **15a** (0.20 g, 91%), mp. 171-173 ^{0}C; (Found M+H: 194.0376. Calc. for $C_{10}H_9ClNO$: 194.0379); ν_{max} (ATR)/cm^{-1} 1656 (C=O); δ_H (400 MHz; $CDCl_3$) 4.71 (2H, s, CH_2Cl), 7.25 (1H, t, *J* = 7.76 Hz, 6-H) 7.41 (1H, d, *J* = 8.20 Hz, 5-H), 7.54 (1H,t, *J* = 7.60 Hz, 7-H), 7.60 (1H, d, *J* = 7.88 Hz, 8-H), 7.80 (1H, s, 4-H) and 11.80 (1H, br s, 1-H); δ_c (100 MHz; $CDCl_3$) 41.4 (CH_2Cl), 115.8 (C-5), 119.6 (C-9), 123.0 (C-6), 128.6 (C-7), 128.9 (C-3), 130.9 (C-8), 138.1(C-10), 139.4 (C-4) and 162.6 (C-2).

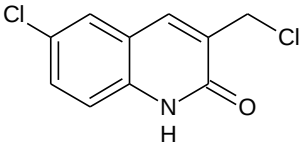
3-(Chloromethyl)-6,7-methylenedioxy-(1H)-2-quinolone **15b**



The general method was followed, using 3-(hydroxymethyl)-6,7-methylenedioxy-(1*H*)-2-quinolone (0.16 g, 0.72 mmol) to obtain, as brick red crystals, 3-chloromethyl-6,7-methylenedioxy-(1*H*)-2-quinolone **15b** (96.2 mg, 57%); mp 188-190 ^{0}C; ν_{max} (ATR)/cm^{-1} 1640 (C=O); δ_H (400 MHz; DMSO-d_6) 4.27 (2H, s, CH_2Cl), 6.07 (2H, s, OCH_2O), 6.81 (1H, s, 5-H),

7.21 (1H, s, 8-H), 7.72 (1H, s, 4-H), and 11.75 (1H, s, NH); δ_c (100 MHz; DMSO-d_6) 68.7 (CH_2Cl), 94.8 (C-8), 101.6 (OCH_2O), 105.2 (C-5), 113.2 (C-9), 126.8 (C-10), 134.7(C-3), 135.3 (C-4), 143.1(C-6), 149.5 (C-7) and 160.7 (C-2).

6-Chloro-3-(chloromethyl)-(1H)-2-quinolone **15c**



The general method was followed, using 6-chloro-3-(hydroxymethyl)-(1*H*)-2-quinolone (0.44 g, 2.1 mmol) to obtain, as light yellow crystals, an isomeric mixture of 3-chloromethyl-6-chloro-(*1H*)-quinol-2-one **17c** (0.30 g, 74 %); mp 182-185^{0}C; (Found M-H: 227.9973. Calc. for $C_{10}H_7Cl_2NO$: 228.0747); υ_{max} (ATR)/cm^{-1} 1654 (C=O).

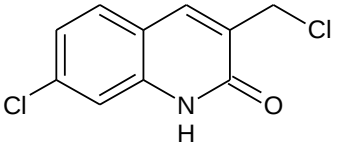
6-chloro-3-chloromethyl-(1H)-quinolone (67% isomer)

δ_H (400 MHz; DMSO-d_6) 4.64 (2H, s, CH_2Cl), 7.32 (1H, d, *J* = 8.60 Hz, 8-H), 7.56 (1H, d, *J* = 8.68 Hz, 7-H), 7.83 (1H, s, 5-H), 8.09 (1H, s, 4-H) and 12.14 (1H, s, NH); δ_c (100 MHz; DMSO-d_6) 41.6 (CH_2Cl), 116.9 (C-8), 119.8 (C-10), 125.8 (C-9), 127.0 (C-5), 134.4, 130.6 (C-7), 130.8 (C-3), 137.4 (C–6), 138.0 (C-4) and 160.3 (C=O).

3-chloromethyl-6-chloro-(1H)-quinol-2-one isomer (37% isomer)

δ_H (400 MHz; DMSO-d_6) 4.67 (2H, s, CH_2Cl), 7.23 (1H, t, *J* = 7.68 Hz, 8-H), 7.69 (2H, m, *J* = 6.82 Hz, 7-H and 5-H), 8.18 (1H, s, 4-H), and 11.34 (1H, s, NH); δ_c (100 MHz; DMSO-d_6) 41.5 (CH_2Cl), 119.8 (C-10), 122.8 (C-8), 125.8 (C-9), 127.5 (C-10), 130.6 (C-7), 130.8 (C-3), 137.4 (C-6), 139.1 (C-4) and 160.3 (C=O).

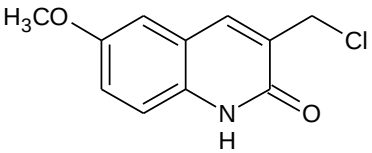
7-Chloro-3-(chloromethyl)-(1H)-2-quinolone **15d**



The general method was followed, using 7-chloro-3-(hydroxymethyl)-(1*H*)-2-quinolone (0.20 g, 0.96 mmol) to obtain, as a white powder, 7-chloro-3-(chloromethyl)-(1*H*)-2-quinolone **15d** (0.14 g, 79%), mp 208-210 ^{0}C; (Found M-H: 227.9976. Calc. for $C_{10}H_7Cl_2NO_3$: 228.0746); ν_{max} (ATR)/cm^{-1} ; δ_H (400 MHz; DMSO-d_6) 4.63 (2H, s, CH_2Cl), 7.25 (1H,d, J = 8.44 Hz, 5-H), 7.34 (1H, s, 8-H), 7.74 (1H, d, J = 8.48 Hz, 6-H) and 8.14 (1H, s, 4-H); δ_c (100 MHz; DMSO-d_6) 41.4 (CH_2Cl), 116.9 (C-5), 119.8 (C-9), 125.8 (C-10), 127.0 (C-6), 130.4 (C-3), 130.6 (C-8), 137.3 (C-7), 138.0 (C-4) and 160.3 (C-2).

Method B: To a stirred solution of 7-chloro-3-hydroxymethyl-(1H)-2-quinolone (0.20g) in dry benzene was added $SOCl_2$ (0.6ml), the reaction mixture was stirred under reflux for 2 days. The reaction mixture was diluted with CH_2Cl_2, sodium bicarbonate added, and the mixture filtered. The residue was washed with chloroform and filtrate concentrated *in vacuo* to obtain, as a yellow crystals, 7-chloro-3-chloromethyl-(1*H*)-2-quinolone. Crude NMR confirmed the formation of a product and prolonged time was require to enhance yield and removal of benzene presented challenges because of its high boiling point.

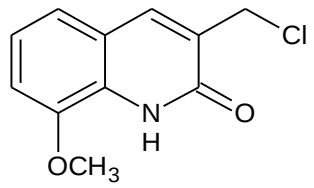
3-Chloromethyl-6-methoxy-(1H)-quinol-2-one **15e**



The general procedure was followed, using 3-(hydroxymethyl)-6-methoxy-(1*H*)-2-quinolone (0.23 g, 1.1 mmol) to obtain, as light yellow crystals, 3-(chloromethyl)-6-methoxy-(1*H*)-2-quinolone **15e** (0.10 g, 49%), mp 182-186 ^{0}C; (Found M+H: 224.0474. Calc. for $C_{11}H_{11}ClNO_2$: 224.0479); ν_{max} (ATR)/cm^{-1} 1662 (C=O); δ_H (400 MHz, DMSO-d_6) 3.78 (3H, Ar-OCH_3), 4.64 (2H, CH_2Cl), 7.20 (1H, Ar-H), 7.25 (2H, 2×Ar-H), 8.06 (1H, Ar-H), and 11.90 (1H, NH); δ_c

(100 MHz; DMSO-d_6) 41.4 (CH_2Cl), 55.03 (Ar–OCH_3), 108.9 (C-8), 115.9 (C-5), 118.9 (C-9), 119.7 (C-7), 129.0 (C-10), 132.8 (C-3), 138.5 (C-4), 153.8 (C-6) and 159.7 (C=O).

3-chloromethyl-8-methoxy-(1H)-quinol-2-one **15f**

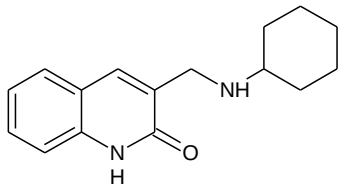


The general method was followed, using 3-(hydroxymethyl)-8-methoxy-(1*H*)-2-quinolone (0.14 g, 0.70 mmol) to obtain, as light yellow crystals, 3-(chloromethyl)-8-methoxy-(1*H*)-2-quinolone **15f** (0.12 g, 89%), mp 164-166 ^{0}C; (Found M+H: 224.0468. Calc. for $C_{11}H_{11}ClNO_2$: 224.0479); ν_{max} (ATR)/cm^{-1} 1645 (C=O); δ_H (400 MHz; $CDCl_3$) 4.01 (3H, s, 8-OCH_3), 4.70 (2H, CH_2Cl), 7.15 (1H, Ar-H), 7.36 (1H, Ar-H), 8.31 (1H, Ar-H), 8.58 (1H, Ar-H) and 12.25 (1H, NH); δ_c (100 MHz; $CDCl_3$) 39.9 (CH_2Cl), 56.8 (8-OCH_3), 111.5 (C-5), 119.6 (C-6), 121.5 (C-9), 122.8 (C-10), 125.6 (C-7), 126.7 (C-3), 142.5, 147.2 (C-8) and 160.8 (C=O).

3.3.4. Synthesis of 3-[(cycloalkylamino)methyl]-(1H)-2-quinolone.

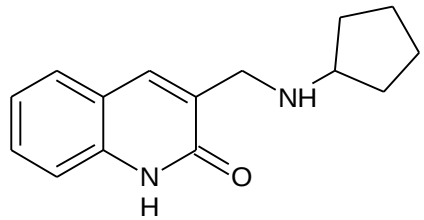
General procedure: A solution 3-chloromethyl-(*1H*)-quinol-2-one derivative and excess cycloalkylamine was stirred in a stoppered flask at room temperature and the reaction monitored with TLC [Hexane:EtOAc (2:1)] until completion. Water was added, and the organic phase extracted with dichloromethane. The organic layer was then dried over $MgSO_4$ and concentrated *in vacuo* to afford the desired product.

3-[(Cyclohexylamino)methyl]-(1H)-2-quinolone **16a**



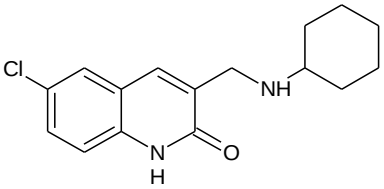
The general procedure was followed, using 3-(chloromethyl)-(1*H*)-2-quinolone (94.4 mg, 0.49 mmol) and cyclohexylamine to afford as brown solid, *3-[(cyclohexylamino)methyl]-(1H)-2-quinolone* **16a** (83.5 mg, 74%), mp 114-117 ^{0}C; (Found M+H: 257.1644. Calc. for $C_{16}H_{21}N_2O$: 257.1655); ν_{max} (ATR)/cm^{-1} 3290 (NH) and 1648 (C=O); δ_H (400 MHz; $CDCl_3$) 1.62 (1H, d, *J* =11.1 Hz,), 1.75 (2H, d, *J* = 12.1 Hz), 1.98 (2H, d, *J* = 10.9 Hz), 2.54 (1H, t, *J* = 8.92 Hz, 12-H), 3.88 (2H, s, CH_2), 7.20 (1H, t, *J* = 7.40 Hz, 7-H), 7.37 (1H, d, *J* = 7.8 Hz, 8-H), 7.47 (1H, t, *J* = 7.30 Hz, 6-H), 7.55 (1H, d, *J* = 7.7 Hz, 5-H), and 7.80 (1H, s, 4-H); δ_c (100 MHz; $CDCl_3$) 25.0 (C-14 and C-16), 26.1 (C-15), 33.5 (C-13 and C-17), 46.4 (C-11), 56.0 (C-12), 115.5 (C-8), 120.1 (C-10), 122.6 (C-7), 127.5 (C-5), 129.8 (C-6), 130.8 (C-9), 137.2 (C-4), 137.5 (C-3) and 164.0 (C=O).

3-[(Cyclopentylamino)methyl]-(1H)-2-quinolone **16b**



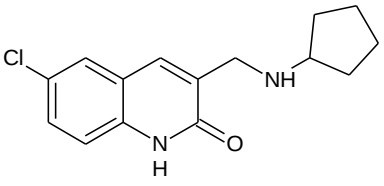
The general procedure was followed, using 3-(chloromethyl)-(1*H*)-2-quinolone (0.10 g, 0.52 mmol) and cyclopentylamine to afford as grey solid, *3-[(cyclopentylamino)methyl]-(1H)-2-quinolone* **16b** (76.6 mg, 60%), mp 109-112 ^{0}C; (Found M+H: 243.1483. Calc. for $C_{15}H_{19}N_2O_2$: 243.1498), ν_{max} (ATR)/cm^{-1} 3295 (NH) and 1652 (C=O); δ_H (400 MHz; methanol-d_4) 1.36 (2H, 13/16-H), 1.50 (2H, 15/17-H), 1.66 (2H, 15/17-H), 1.86 (2H, 13/16-H), 3.05 (1H, s, 12-H), 3.24 (2H, s, 11-H), 7.18 (1H, 7-H), 7.28 (1H, 8-H), 7.44 (1H, 6-H), 7.60 (1H, 5-H) and 7.86 (1H, s, 4-H); δ_c (100 MHz, methanol-d_4) 25.1 (C-14 and C-15), 33.5 (C-13 and C-16), 49.0 (C-11), 59.0 (C-12), 116.4 (C-8), 121.4 (C-10), 124.0 (C-7), 129.0 (C-5), 131.5(C-6), 137.4 (C-4), 139.2 (C-9), 139.7 (C-3) and 164.7 (C=O).

6-Chloro-3-[(cyclohexylamino)methyl]-(1H)-2-quinolone **16c**



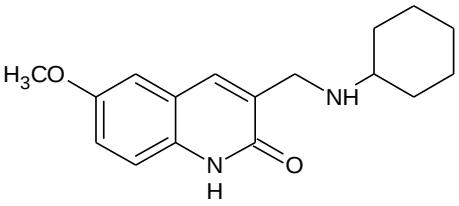
The general procedure was followed, using 6-chloro-3-(chloromethyl)-(1*H*)-2-quinolone (85.9 mg, 0.38 mmol) and cyclohexylamine to afford, as light brown crystals, *6-chloro-3-[(cyclohexylamino)methyl]-(1H)-2-quinolone* **16c** (60.2 mg, 89%), mp 151-155^{0}C; (Found M+H: 291.1258. Calc. for $C_{16}H_{20}ClN_2O$, M+H: 291.1266); ν_{max} (ATR)/cm^{-1} 3298 (NH) and 1651 (C=O); δ_c (100 MHz; $CDCl_3$) 24.9 and 25.0 (C-14 and C-16), 25.6 and 26.1(C-15), 33.3 and 36.7 (C-13 and C-17), 46.1 (C-11), 50.4 and 56.2 (C-12), 116.9, 121.1 , 122.7, 126.6, 127.8, 129.4, 129.9, 133.6, 136.0, 136.2 (Ar-C) and 163.6 (C=O.

6-Chloro-3-[(cyclopentylamino)methyl]-(1H)-2-quinolone **16d**



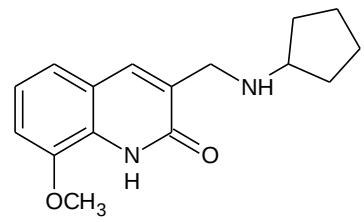
The general procedure was followed, using 6-chloro-3-(chloromethyl)-(1*H*)-2-quinolone (0.10 g, 0.45 mmol) and cyclopentylamine to afford, as grey crystals, *6-chloro-3-[(cyclopentylamino)-methyl]-(1H)-2-quinolone* **16d** (78.3 mg, 93%); mp 178-181 ^{0}C; (Found M+H: 277.1096. Calc. for $C_{15}H_{18}ClN_2O$: 277.1109); ν_{max} (ATR)/cm^{-1} 1650 (C=O); δ_c (100 MHz; $CDCl_3$) 24.1 (C-14 and C-15), 33.1 (C-13 and C-16), 47.8 (C-11), 117.0, 119.1, 120.8, 122.8, 126.5, 127.8, 129.4, 130.0, 133.7, 136.1, 136.5 (Ar-C) and 163.8 (C=O).

3-[(Cyclohexylamino)methyl]-6-methoxy-(1H)-2-quinolone **16e**



The general procedure was followed, using 3-(chloromethyl)-6-methoxy-(1*H*)-2-quinolone (0.10 g, 0.45 mmol) and cyclohexylamine to afford, as brown solid, *3-[(cyclohexylamino)methyl]-6-methoxy-(1H)-2-quinolone* **16e** (84.6 mg, 65%); mp 127-131^{0}C; (Found M+H: 287.1752. Calc. for $C_{17}H_{23}N_2O_2$: 287.1760); ν_{max} (ATR)/cm^{-1} 3289 (NH) and 1655 (C=O); δ_H (400 MHz; $CDCl_3$) 1.24-2.02 (13, 14, 15, and 16-H), 2.60 (1H, 12-H), 3.81 (2H, 11-H), 6.92 (1H, 8-H), 7.04 (1H, 7-H), 7.29 (1H,) and 7.80 (1H, 4-H); δ_c (100 MHz; $CDCl_3$) 24.9 (C-14 and C-16), 26.0 (C-15) and 33.0 (C-13 and C-17), 46.1 (C-11), 55.6 (6-OCH_3), 56.2 (C-12), 108.8 (C-5), 117.0 (C-6), 119.0(C-7), 119.4 (C-4), 120.5 (C-9), 132.3 (C-10), 155.0 (C-3) and 163.3 (C=O).

8-Methoxy-3-[(cyclopentylamino)methyl]-(1H)-2-quinolone **16f**



The general procedure was followed, using 3-(chloromethyl)-8-methoxy-(1*H*)-2-quinolone (0.10 g, 0.38 mmol) and cyclopentylamine to afford, as black crystals, *8-methoxy-3-cyclopentylaminomethyl-(1H)-quinolone* **16f** (74.5 mg, 88 %); mp 96-99 ^{0}C; (Found M+H: 273.1591. Calc. for $C_{16}H_{21}N_2O_2$: 273.1603); ν_{max} (ATR)/cm^{-1} 1645 (C=O); δ_H (400 MHz; $CDCl_3$) 1.39–1.97 (13, 14, 15, and 16–H), 3.12 (1H, 12–H), 6.91 (1H,), 7.10 (2H,) and 7.72 (1H,); δ_c (100 MHz; $CDCl_3$) 24.1 (C-14 and C-15), 33.0 (C-13 and C-16), 48.2 (C-11), 55.8 (8-OCH_3), 109.3 (C-5), 119.3 (C-6), 120.1 (C-9), 122.1 (C-7), 127.6 (C-10), 132.6 (C-3), 136.7 (C-4), 145.3 (C-8) and 161.9 (C=O).

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