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**UTILIZATION OF THE BAYLIS-HILLMAN AND RELATED
REACTIONS IN ANTIPARASITIC DRUG DISCOVERY**

By

NONTOBEKO MABIZELA

A thesis presented for the degree of

MASTERS OF SCIENCE

In the Department of Chemistry

UNIVERSITY OF CAPE TOWN



Supervisor:

Assoc. Prof Kelly Chibale

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DECLARATION

I declare that “Utilization of the Baylis-Hillman and related reactions in antiparasitic drug discovery” is my own work and that all sources I have used or quoted have been indicated and acknowledged by means of complete reference.

Signed by candidate

Nontobeko Mabizela

University of Cape Town

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ABSTRACT

Baylis-Hillman adducts and compounds containing quinoline moieties have been previously utilized extensively in the search for antiparasitic agents. Work in this dissertation describes a series of compounds based on the Baylis-Hillman and the related three-component aza Baylis-Hillman reactions synthesised for biological evaluation as potential inhibitors of two parasitic cysteine proteases (cruzain and Falcipain-2) and as antiparasitic agents. The utilization of polymer-supported bases in the Baylis-Hillman reaction is described. The use of ultrasound in combination with Lewis acids is also described in an attempt to improve the reaction rate.

Of the different compounds synthesized and tested, 2-[quinolin-4-yl-(toluene-4-sulfonylamino)-methyl]-acrylic acid tert-butyl ester showed the most promise as a potential antitrypanosomal agent. On the other hand the corresponding Baylis-Hillman adducts were less effective.

ABBREVIATIONS

Anal.	Analytical
Ar	aryl
Aq	aqueous
ATP	adenosine 5 'triphosphate
B-H	Baylis-Hillman
BEMP	(2- <i>tert</i> -Butylimino-3-ethyl-1,1-dimethyl-2 λ^5 - [1,3,2]diazaphosphinan-2-yl)-diethyl-amine
br	broad (in NMR)
<i>t</i> -Bu	<i>tert</i> -butyl
°C	degrees Celcius
Calc.	calculated
CDCl ₃	deutero chloroform
CNS	central nervous system
CO ₂	carbon dioxide
CQ	chloroquine
d	doublet (in NMR)
dd	doublets of doublets(in NMR)
DABCO	1,4-diazabicyclo-2, 2, 2, -octane
DBU	1,8-diazabicyclo (5.4.0) undec-7-ene
DMAP	4-Dimethylaminopyridine
DMF	<i>N, N</i> -dimethylformamide

DMF	<i>N, N</i> -dimethylformamide
DMSO	dimethylsulphoxide
DNA	deoxyribonucleic acid
δ	chemical shift in parts per million downfield from tetramethylsilane
dt	doublets of triplets (in NMR)
ED ₅₀	effective dose required to inhibit 50% of parasitic growth
EI	electron impact (in mass spectrometry)
Et	ethyl
Et ₃ N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
FAB	fast atomic bombardment
g	gram (s)
h	hour (s)
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hunig's base	Diisopropylethylamine
Hz	hertz
IC ₅₀	inhibitory concentration to inhibit 50% of enzyme activity
IR	infrared
<i>J</i>	coupling constant (in NMR)
K ₂ CO ₃	potassium carbonate

μ	micro (10^{-6})
m	multiplet (in NMR),
MDR	multidrug resistance
MeOH	methanol
MgSO ₄	magnesium sulphate
MHz	megahertz
min	minute (s)
ml	milliliter
mol	mole (s)
mol.dm ⁻³	moles per litre
mp	melting point
<i>m/z</i>	mass to charge ratio (in mass spectra)
Na ₂ SO ₄	sodium sulphate
NMR	nuclear magnetic resonance
Nu	nucleophile
<i>o</i>	ortho
<i>p</i>	para
<i>P.</i>	<i>plasmodium</i>
Ph	phenyl
PS	polymer supported
PS-EDC	polymer-supported 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
P-TBD	1, 5, 7- triazabicyclo [4.4.0] dec-5-ene

q	quartet (in NMR)
R_f	retention factor
RNA	ribonucleic acid
rt	room temperature
s	singlet (in NMR)
s	second (s)
SiO ₂	silicon oxide (silica gel)
t	triplet (in NMR)
td	triplets of doublets (in NMR)
<i>tert</i>	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
WHO	world health organization

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CHAPTER 1

INTRODUCTION TO DISEASES

1.1 MALARIA

1.1.1 Introduction

Malaria is a serious, sometimes fatal disease caused by a parasite. It is one of the 10 most prevalent and deadly diseases in the world. The World Health Organization estimates that 300 to 500 million clinical cases occur every year with over 1.2 to 2.7 million deaths^[1]. 90% of these occur in sub-Saharan Africa, 800 to 1000 cases of malaria are reported in Australia each year and about 1,200 cases of malaria are diagnosed in the United States each year. It is a parasitic disease spread by the bite of anopheles mosquito, which is active between dusk and dawn. There are four kinds of malaria parasites that can infect humans: *Plasmodium falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. *P. falciparum* is the most serious and prevalent. The principal symptoms of *P. falciparum* malaria include fever and flu-like illness, shaking chills, headache, muscle aches, tiredness and sweats but it can also present as a respiratory or gastrointestinal illness. Nausea, vomiting, and diarrhea may also occur. Malaria may cause anaemia and jaundice (yellow coloring of the skin and eyes) because of the loss of red blood cells. Infection with one type of malarial, *P. falciparum*, if not promptly treated, may cause kidney failure, seizures, mental confusion, coma, and death. For most people, symptoms begin 10 days to 4 weeks after infection, although a person may feel ill as early as 8 days or up to 1 year later. Two kinds of malaria, *P. vivax* and *P. ovale*, can relapse; some parasites can rest in the liver for several months up to 4 years after a person is bitten by an infected mosquito. When these parasites come out of hibernation and begin invading red blood cells, the person will become sick.

In addition the available antimalarial drugs are losing efficacy because the malaria parasite has developed resistance to most existing antimalarials. Chloroquine is an exceptionally safe antimalarial and has been used widely for more than 40 years. However, its value has been compromised by the emergence of chloroquine resistant *P. falciparum*^[2]. Therefore there is an urgent need for the development of alternative drugs.

1.1.2 Life cycle of Plasmodium^[2]

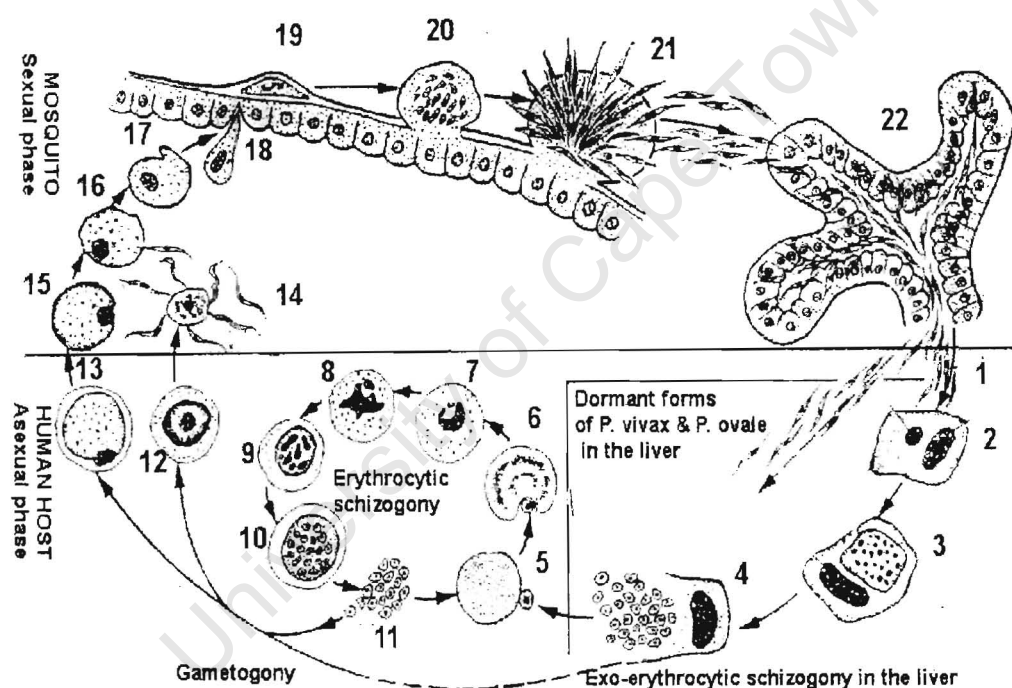


Figure 1.

The parasite undergoes a development stage in the female anophelid species, which requires a blood meal to mature her eggs. She bites a human and injects material from her salivary glands, which contains primitive malarial parasites called sporozoites, before feeding. These sporozoites circulate in the blood for a short time and then

settle in the liver where they enter the parenchymal cells and multiply; this stage is known as pre-erythrocytic schizogony. After about 12 days there may be many thousands of young parasites known as merozoites in one liver cell (hepatic parenchyma cell), the cell ruptures and the free merozoites enter red blood cells. In the case of *P. vivax*, and *P. ovale* the liver cycle continues and requires a course of primaquine to eliminate it. *P. falciparum* on the other hand does not have a continuing liver cycle.

In the red blood cells the parasites develop into two forms, a sexual and an asexual cycle. The sexual cycle produces male and female gametocytes, which circulate in the blood and are taken up by a female mosquito when taking a blood meal. The male and female gametocytes fuse in the mosquito's stomach and form oocysts in the wall of the stomach. These oocysts develop over a period of days and contain large numbers of sporozoites, which move to the salivary glands and are ready to be injected into man when the mosquito next takes a meal. In the asexual cycle the developing parasites form schizonts in the red blood cells, which contain many merozoites, the infected red cells rupture and release a batch of young parasites, merozoites, which invade new red cells^[3]. In *P. vivax*, *P. ovale* and probably *P. malariae*, all stages of development subsequent to the liver cycle can be observed in the peripheral blood. However, in the case of *P. falciparum* only ring forms and gametocytes are usually present in the peripheral blood. Developing forms appear to stick in the blood vessels of the large organs such as the brain and restrict the blood flow with serious consequences.

In falciparum malaria the parasites multiply very rapidly and may occupy 30% or more of the red blood cells causing a very significant level of haemolysis. One reason

for this is that *P. falciparum* invades red cells of all ages whereas *P. vivax* and *P. ovale* prefer younger red cells, while *P. malariae* seeks mature red cells.

1.1.3 History of malaria chemotherapy

Malaria chemotherapy began in the 17th century after a patient took a remedy made from the cinchona tree bark. Quinine has been used for more than three centuries and until the 1930's it was the only effective agent for the treatment of malaria. It is one of the four main alkaloids found in the bark of the Cinchona tree and is the only drug which over a long period of time has remained largely effective for treating the disease. It is now only used for treating severe falciparum malaria partly because of undesirable side effects. In Africa in the 1930's and 40's it was known for people to take quinine when they thought they had "a touch of malaria" and the association of repeated infections with falciparum malaria and inadequate treatment with quinine, resulted in the development in some of acute massive intravascular haemolysis and haemoglobinuria i.e. black water fever.

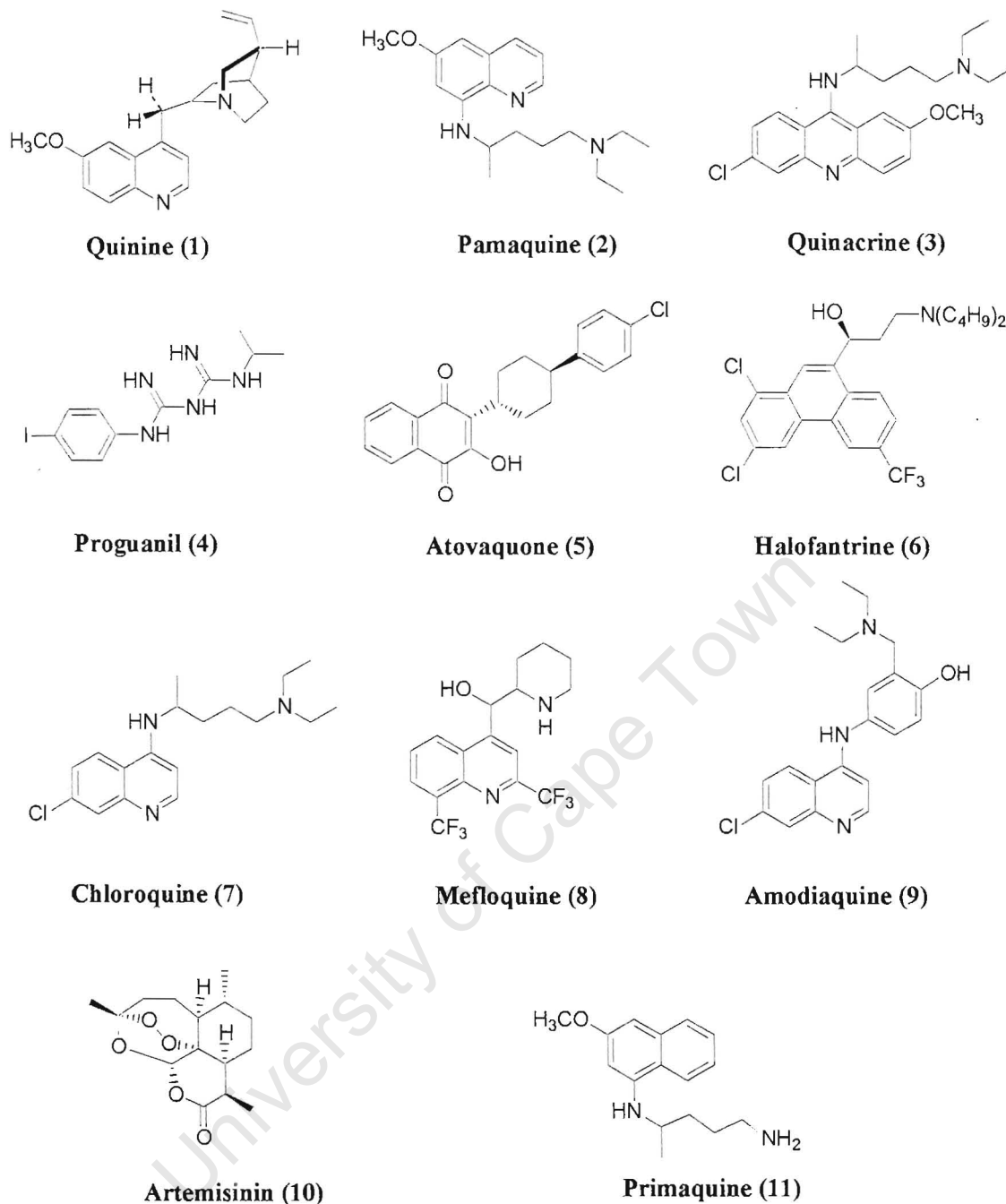


Figure 2. Chemical structures of some antimalarial agents.

Although Pamaquine **2** was developed as the first 8-aminoquinoline that proved to be the first compound capable of preventing relapse in vivax malaria in 1925, quinacrine (mepacrine) **3** was the first effective compound to be developed against falciparum malaria in 1932. The drug became so popular that it wasn't possible to have enough supply, therefore the shortfall as well as the side effects led to intensification of efforts for developing synthetic quinine analogues as antimalarials.

Also known as chloroquinadine is proguanil **4** ^[2]. This drug falls into the biguanide class of the antimalarials and was first synthesized in 1946. The drug is a folate antagonist and destroys the malaria parasite by binding to the enzyme dihydrofolate reductase in much the same way as pyrimethamine. It is still used as a prophylactic in some countries. In 1998 a new drug combination was released in Australia called Malarone. This is a combination of proguanil **4** and atovaquone **5**. Atovaquone **5** became available in 1992 and was used with success for the treatment of *pneumocystis carinii*. When combined with proguanil **4** there is a synergistic effect and the combination is at the present time very effective. The drug combination has undergone several large clinical trials and has been found to be 95% effective in otherwise drug resistant falciparum malaria. Halofantrine **6** is another drug, which belongs to the class of compounds called phenanthrene-methanols and is not related to quinine. It is an effective antimalarial introduced in 1980s, but due to its short half-life of 1 to 2 days, is not suitable for use as a prophylactic. Unfortunately resistant forms are increasingly being reported and there is some concern about side effects.

Chloroquine ^[4] **7** is a very effective 4-amino-quinoline both for treatment and prophylaxis. It was first used in the 1940s shortly after the Second World War and was effective in curing all forms of malaria; with few side effects when taken in the dose prescribed for malaria and it was low in cost. Unfortunately most strains of

falciparum malaria are now resistant to chloroquine and more recently chloroquine resistant vivax malaria has also been reported. In case of generalized psoriasis, chloroquine and other chloroquine-like drugs, including primaquine, quinidine and proguanil **3** should be avoided.

If Mefloquine **8** is to be used to combat malaria it is probably best to start the treatment 4 weeks before entering a malarious area as it takes this long to build up to satisfactory blood levels. It is a readily tolerated antimalarial drug active against both the sensitive and the resistant strain of *P. falciparum*. Because of its relation to quinine the two drugs must not be used together. There has been a report of various undesirable side effects including acute brain syndrome. Doxycycline is an alternative to mefloquine for short-term treatment.

A Mannich base derivative, amodiaquine **9**, introduced into the field in the late 1950s, has been shown to be a superior alternative to CQ in the areas of high CQ resistance [5]. Unfortunately in the mid-1980s, the use of amodiaquine declined abruptly following initial reports of agranulocytosis and hepatitis when the drug was used.

Artemisinin [6] **10** is derived from a Chinese herbal remedy and covers a group of products. The two most widely used are artesunate and artemether. While they are widely used in South East Asia they are not licensed in much of the so-called "western world". A high rate of treatment failures has been reported and it is now being combined with mefloquine for the treatment of falciparum malaria [7].

Primaquine **11** is the only available drug for the treatment and clearing of *Plasmodia* from the liver and is thus used in the cure for *P. vivax* and *P. ovale*. However toxic effects include mild anaemia, cyanosis and haemolysis [5].

1.2 American Trypanosomiasis

1.2.1 Introduction

American Trypanosomiasis otherwise known, as Chagas' disease is a parasitic disease caused by kinetoplastid protozoan parasite *Trypanosoma cruzi*. It is responsible for the deaths of millions of people in Latin America^[8]. It represents a serious problem for public health, as there are currently no satisfactory methods of immune prophylaxis or chemotherapy. The life cycle starts when an infected insect vector takes a blood meal and releases trypomastigotes in its faeces near the site of the bite wound. Trypomastigotes enter the host through the wound or through intact mucosal membranes, such as the conjunctiva. Inside the host, the trypomastigotes invade cells and differentiate into amastigotes. Amastigotes are released infecting new cells and some transforming into trypomastigotes and remain in the blood stream. The vector becomes infected when it ingests amastigotes or trypomastigote in a blood meal. The parasite reproduces asexually in the vectors gut becoming infective metacyclic trypomastigote in the midgut.

1.2.2 Chemotherapy

There is a continuous interest in the development of new specific chemotherapeutic approaches for American trypanosomiasis. The main drug in use is Nifurtimox^[9] **12** but it has undesirable side effects and is inefficient in treating the chronic state of the disease^[8]. It only affects total parasite clearance in 50% of the patients. Among the most promising new approaches are sterol biosynthesis inhibitors (SBI) exemplified by Ruvucunazole **13**. Ruvuconazole **13** is a very potent and specific anti- *T. cruzi* agent *in vitro* but its *in vivo* activity is limited, probably due to its unfavourable pharmacokinetic properties^[10]. However, these results do not necessarily rule out the

potential utility of ruvuconazole in the treatment of *T. cruzi* infections.

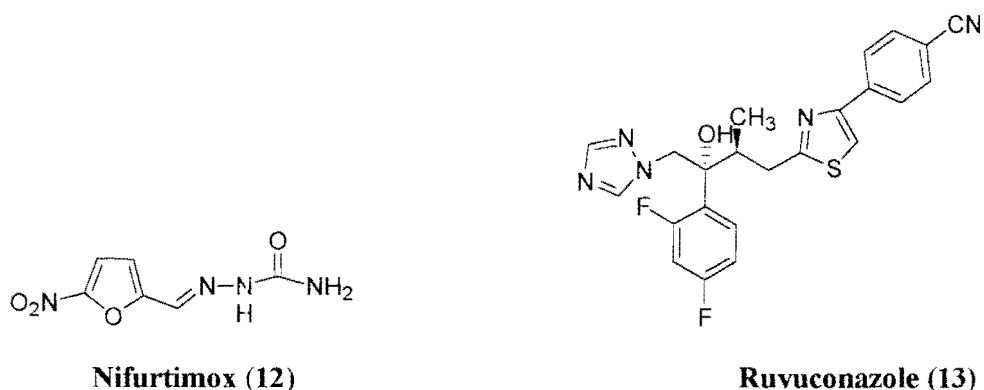


Figure 3. Chemical structures of drugs used in the treatment of Chagas disease.

1.3 Parasitic cysteine proteases

Cysteine proteases (CPs) exemplify common enzyme targets present in different parasites. They play numerous indispensable roles in the biology of parasitic organisms. Interest in CPs as targets for the development of antiparasitic chemotherapy derives from the recognition that they play a key role at various stages in the life cycle or pathogenicity of many parasites. Parasitic cysteine proteases inhibitors are generally compounds to which the thiol of the cysteine residue in the enzyme active site adds. The proposed general catalytic mechanism for the CPs, in which an active site thiol is utilised for hydrolysis, is shown in Figure 4. Histidine polarizes the enzyme cysteine thiol group of (Enz-Cys) allowing deprotonation even under nearly neutral to weakly acidic pH conditions. The resulting highly nucleophilic thiolate/imidazolium ion pair allows the thiolate anion to attack the carbonyl carbon of the scissile amide bond resulting in a tetrahedral intermediate. This is followed by acylation of the enzyme and the liberation of the first product. A second tetrahedral

intermediate is then formed *via* hydrolysis of the acyl-enzyme. The enzyme is regenerated following collapse of the second tetrahedral intermediate and product release.

As mentioned earlier parasites use cysteine proteases for important biological tasks.

Among such parasites are *T. cruzi*, *P. falciparum* and *Leishmania major*^[11-13].

Cruzain^[14] is the major cysteine protease of *T. cruzi*, which is essential for replication, and differentiation of the intracellular parasite. Cruzain thus represents an attractive chemotherapeutic target for treatment of Chagas' disease. Similarly Falcipain-2, a cysteine protease isolated from *P. falciparum*, has been shown to be involved in hemoglobin degradation, which appears to be necessary for the growth of the erythrocytic malaria parasite. The major cathepsin L and B-like protease of *Leishmania* is also of interest as a therapeutic target.

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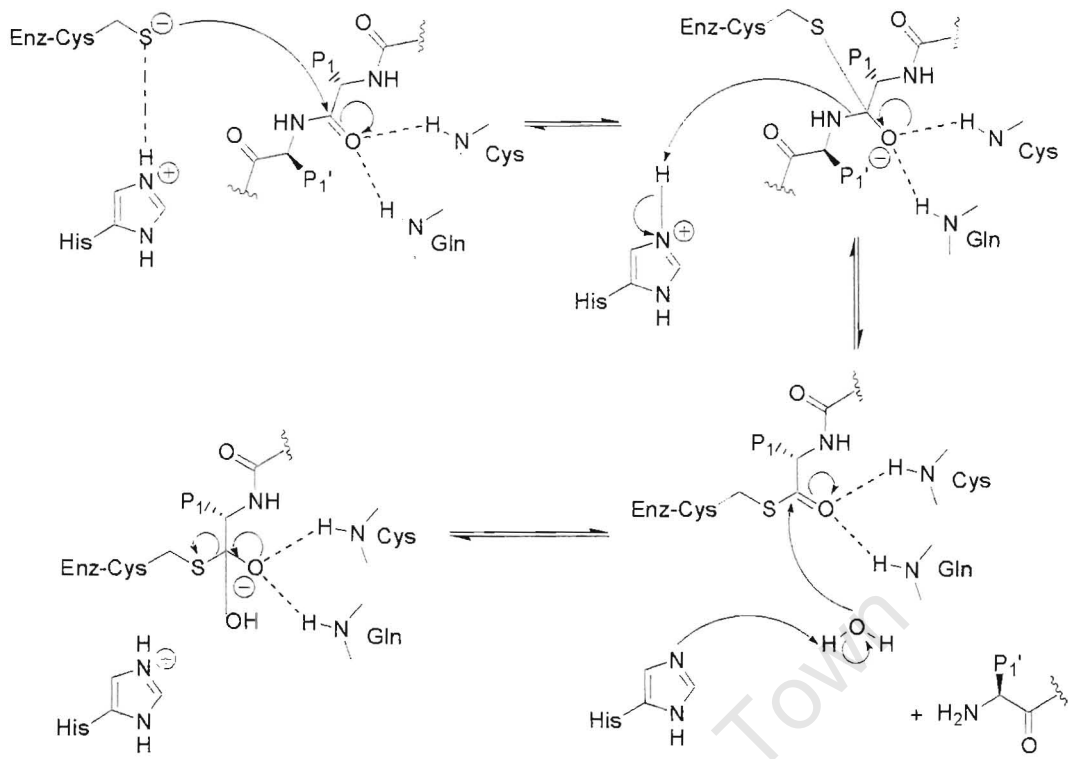


Figure 4. Catalytic mechanism of cysteine proteases.

CHAPTER 2

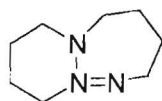
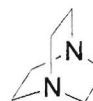
THE BAYLIS-HILLMAN REACTION

2.1 Introduction

The Baylis-Hillman (B-H) ^[15] reaction involves coupling an activated alkene with electrophiles (usually aldehydes) using a base (usually an amine) as a catalyst, Scheme 1.

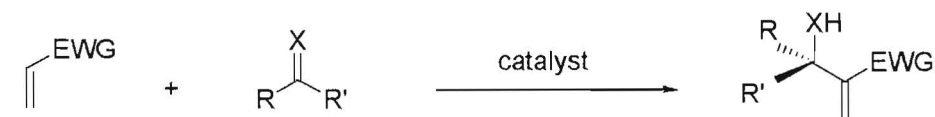
The B-H reaction is among the most economical and useful carbon-carbon bond forming reactions in organic synthesis. There are a number of different bases and catalyst systems used in this reaction. Amongst them are DMAP, 3-hydroxyquinidine, cinchonidine, PPh₃, quinidine and quinidine derivatives in aqueous THF ^{[16]-[17]}.

But the most frequently used catalysts are non-nucleophilic sterically-hindered tertiary amines like DBU **14**, or DABCO **15** ^[18]. Recently it has been shown that DBU is superior to DABCO by a factor of 50 as it produces a 50-fold increase in the rate of the reaction ^[18]. The key to the activity of DBU is thought to be the fact that the enolate is stabilized through conjugation, which increases its equilibrium concentration and results in enhanced rates.

**14****15**

There are a number of problems commonly associated with this reaction, most notably it's slow reaction rate, with some B-H reactions taking days or weeks to go to completion. Efforts to accelerate the reactions include the use of combinations of longer

reaction time, low-temperature techniques^[19] and the addition of Lewis acids^{[20]-[21]} such as lanthanide triflates or LiClO_4 and the use of ultrasound^{[20]-[21]}. These efforts even when successful in improving the rate of the Baylis-Hillman reaction are only applicable to a limited number of substrates.



EWG = CO_2R , CN

X = NR'', O

Scheme 1. The Baylis-Hillman reaction

The general accepted mechanism for the Baylis-Hillman reaction for an acrylate ester is illustrated in Figure 5.

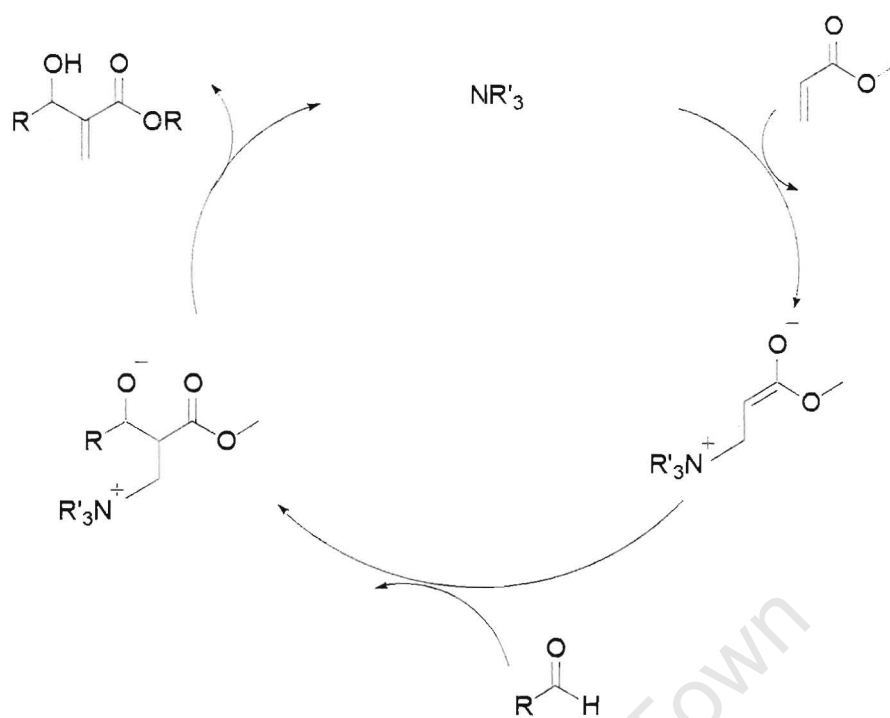
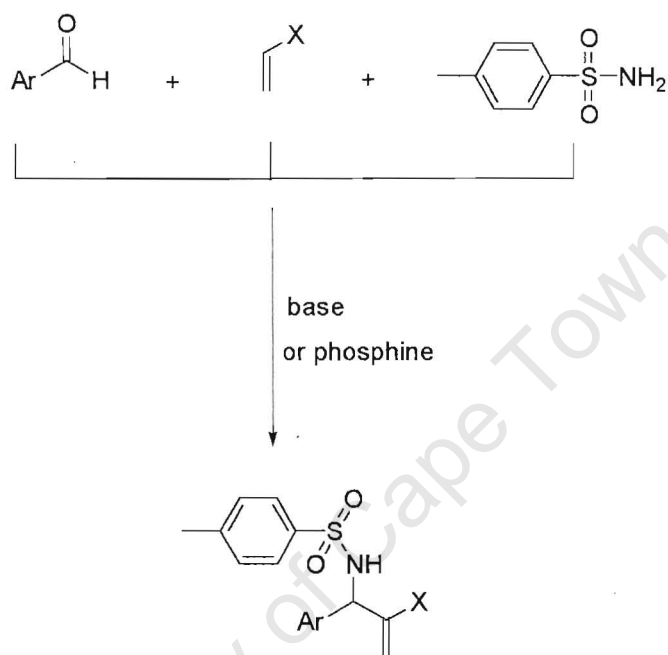


Figure 5. Mechanism for the Baylis Hillman reaction for an acrylate ester.

From the above mechanism, it is postulated that the nucleophilic 1,4-conjugate addition of the catalyst to the activated alkene affords an enolate, which then reacts with the electrophilic aldehyde to give the zwitterion. Elimination of the catalyst followed by protonation affords the B-H product with the catalyst being regenerated. Alternatively, an internal proton transfer may occur to give the resonance-stabilized zwitterions, which proceed to form the product by elimination.

A B-H reaction in which the product is a substituted sulfonamide derivative is an example of a three-component reaction often referred to as the aza-B-H^{[22]-[25]}. Scheme 2.



X = CN, CO₂R

Scheme 2. The aza Baylis-Hillman reaction

The mechanism for the aza-Baylis-Hillman reaction catalyzed by triphenylphosphine is roughly illustrated in Figure 6.

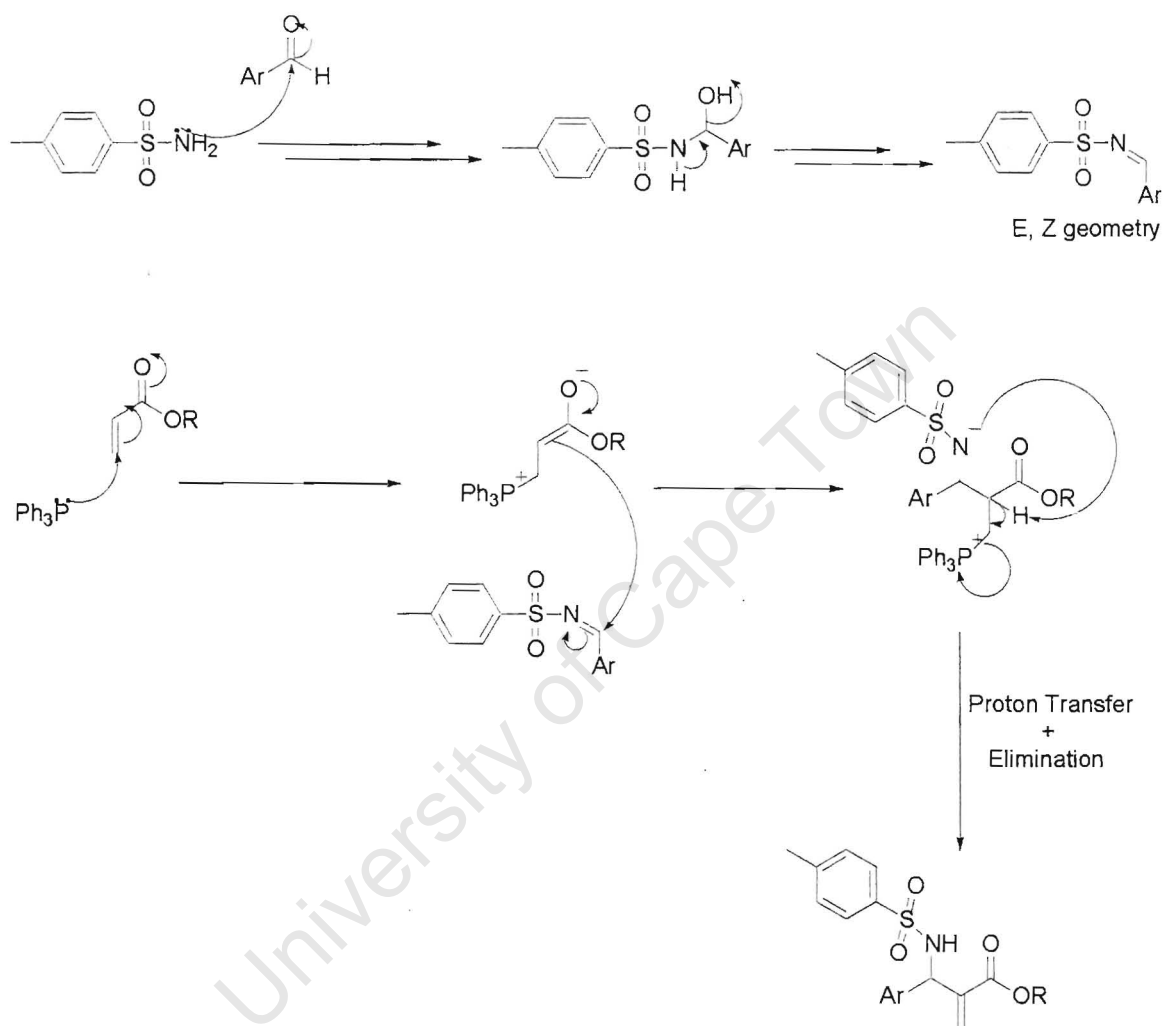
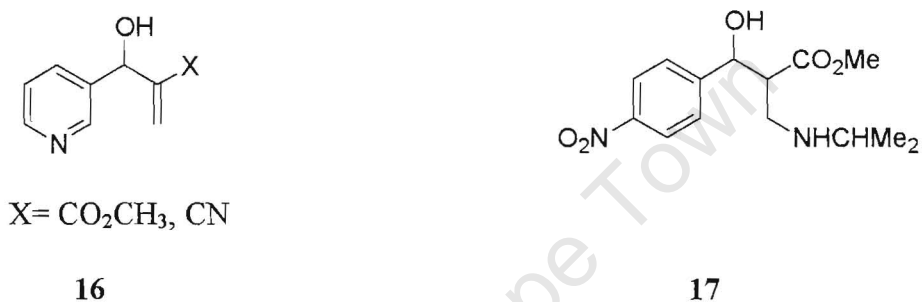


Figure 6. Mechanism of aza-B-H reaction catalyzed by triphenylphosphine.

2.2 Rationale behind utilization of B-H and aza B-H in antiparasitic drug discovery.

We reasoned that the B-H has potential application in drug discovery efforts against parasitic diseases for the following reasons:

- (i) There is literature precedent for B-H adducts and their derivatives as antimalarial agents ^[26]. These are exemplified by **16** and **17**.



- (ii) There is structural similarity between B-H adducts and antimalarial 4-quinoline methanols such as mefloquine. Figure 7.

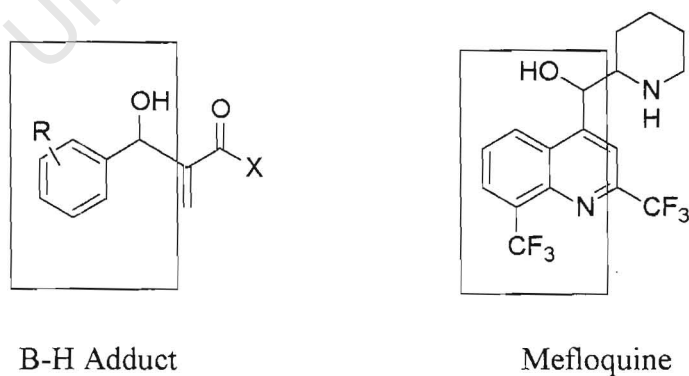


Figure 7.

- (iii) The presence of the α , β -unsaturated moiety in B-H adducts could render these potential inhibitors of cysteine proteases including cruzain and falcipain-2. B-H adducts could be envisaged to undergo 1,4-conjugate addition with the thiol (RSH) residue of the active site cysteine, Figure 8.

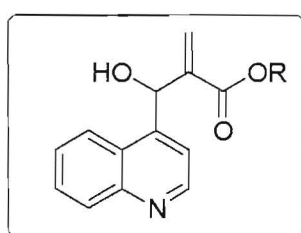


Figure 8.

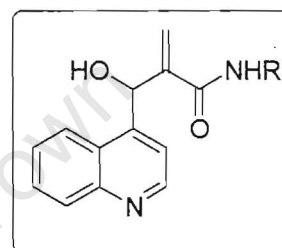
- (iv) The aza-B-H is a 3-component reaction, which could provide a powerful strategy for delineating structure-activity relationships. Furthermore, the antimalarial activity of aza-B-H adducts have not been reported to date.
- (v) Both the B-H and aza-B-H adducts are highly functionalised compounds which can further be chemically modified as part of structure-activity relationship studies.

These considerations led to the design of compounds **18-53** for exploratory studies against the parasitic cysteine proteases, falcipain-2 and cruzain as well as the parasites themselves.

Incorporation of a quinoline moiety (Class 1 and 2) was expected to increase accumulation of the compound in the acidic food vacuole of the malaria parasite.



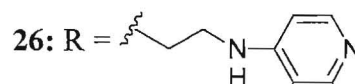
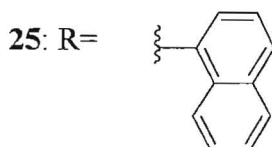
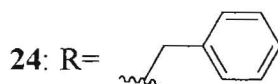
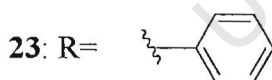
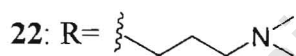
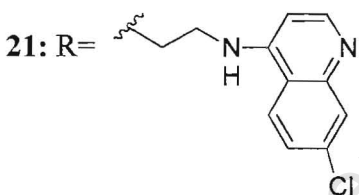
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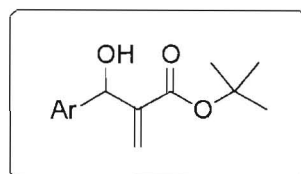
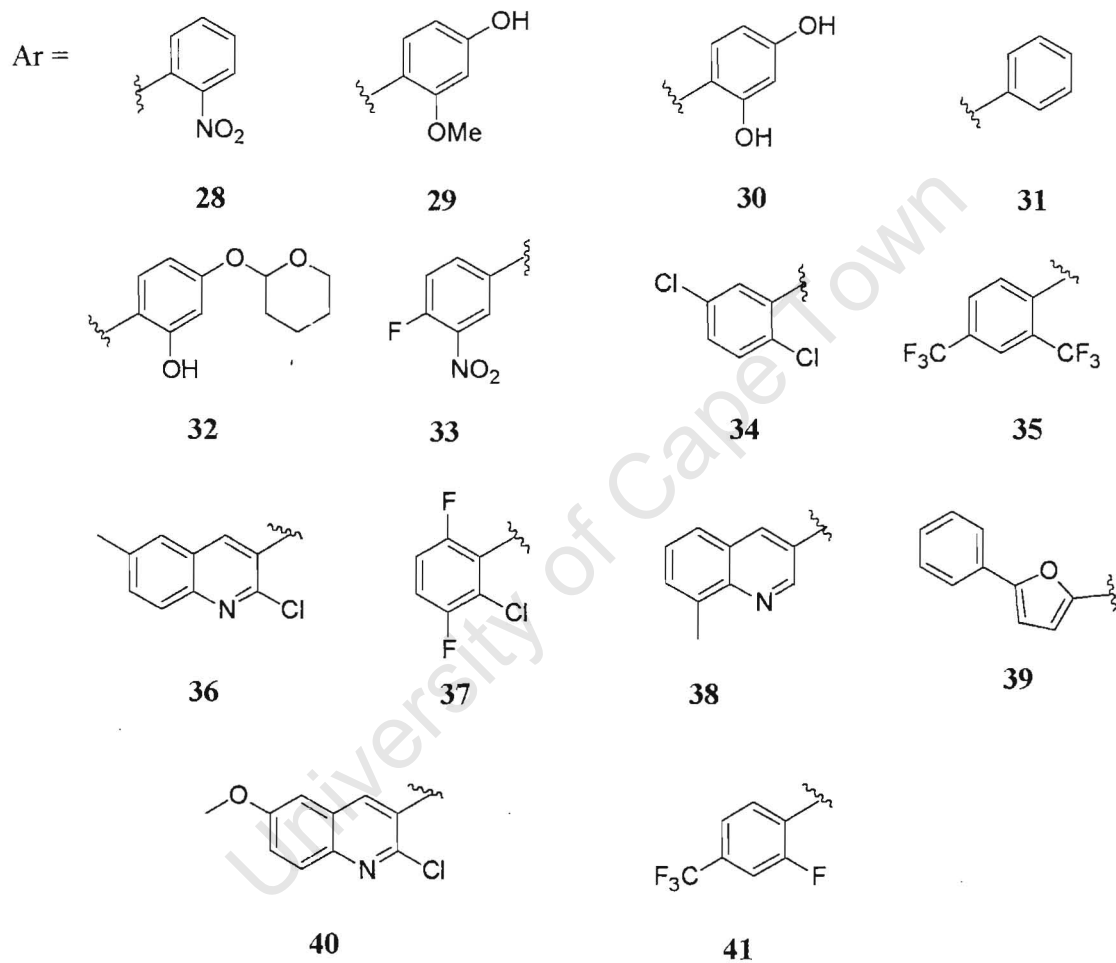
Class 2

18: R= t-Bu **19:** R= H,

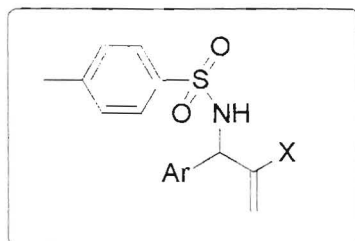
20: R= Methyl



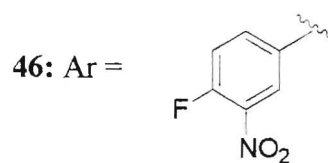
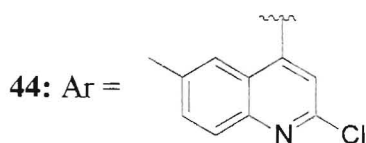
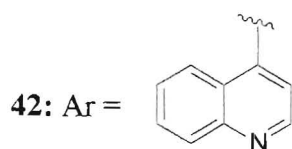
Class 3 compounds were designed in order to explore the effect of different substituents on the biological activity.

**Class 3**

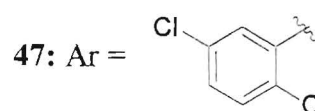
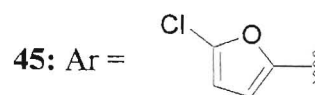
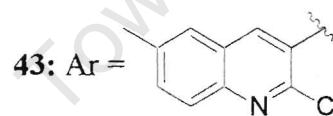
Class 4 compounds are aza-B-H adducts in which the alkene activating group is varied between the nitrile and ester.



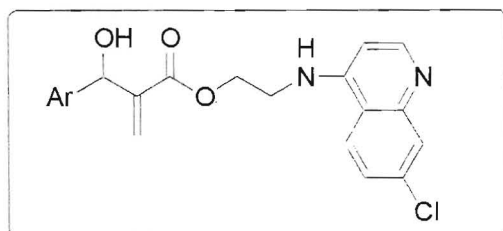
X = *t*-Butyloxycarbonyl



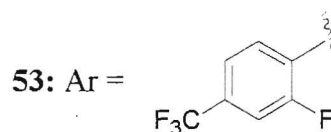
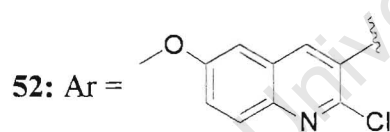
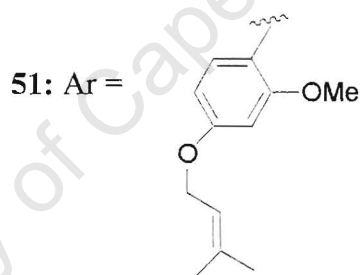
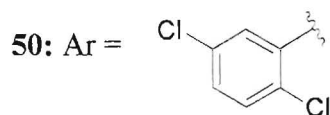
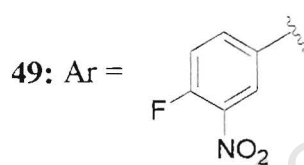
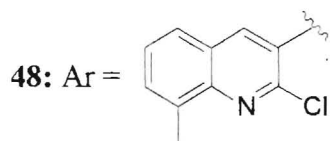
X = CN



Class 5 compounds were designed in order to explore the effect of incorporating a quinoline moiety as part of the acrylate substrate with a view to maximizing antimalarial activity.



Class 5



CHAPTER 3

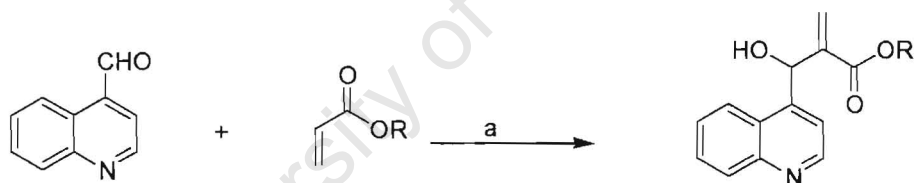
RESULTS AND DISCUSSION

3.1 Chemistry

3.1.1 Synthesis of target compounds

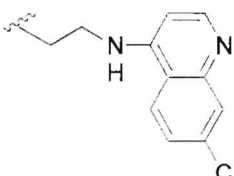

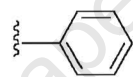
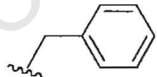
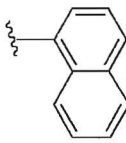
3.1.1.1 Synthesis of class 1 compounds

These compounds were synthesised by stirring a mixture of 4-quinoline-carbaldehyde and the acrylate in DBU at room temperature for 23hrs. The product mixtures were purified by column chromatography affording B-H adducts in moderate to high yields, Table 1. Compounds, which were synthesized in this way, were identified by the characteristic set of signals in the ^1H NMR spectrum. The key ^1H NMR diagnostic signals are that of the two-proton singlet for the terminal methylenic protons at $\sim \delta$ 6.60 ppm, and the doublet for the hydroxyl group at $\sim \delta$ 2.00 ppm.



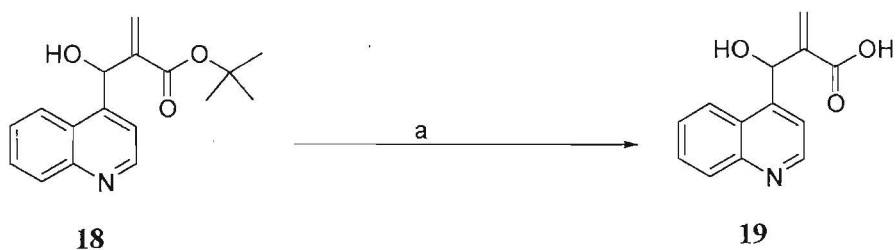
Scheme 3. Reagents and conditions: (a) 5 equiv. acrylate, DBU

Table 1. Table showing substituents (R) from B-H adducts and their synthetic yields

Entries	Compound	R	Product Yield %
1	18	^t Bu	48
2	21		89
3	22		80
4	23		15
5	24		26
6	25		10

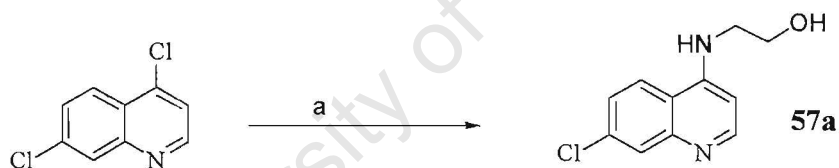
3.1.1.2 Synthesis of Class 2 compounds

Compound **19** was synthesized by deprotection of the *tert*-butyl ester **18**. The reaction was carried out using a 1:1 mixture of TFA and CH₂Cl₂ at 25 °C. TLC analysis showed the reaction was complete after 30 min. The product was isolated in 97% yield, Scheme 4.

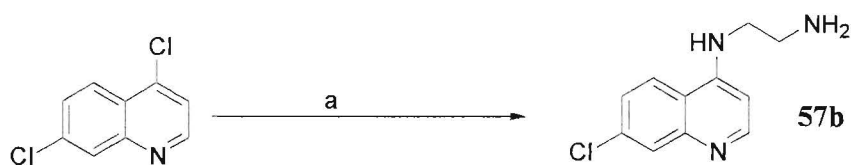


Scheme 4. Reagents and conditions: (a) 1 equiv. of TFA, CH_2Cl_2 , 25 °C, 15 min, 97%.

The ethanolamine and ethylene diamine-derived quinoline alcohol **57a** and amine **57b**, intermediates (Scheme 5&6) required for the synthesis of the corresponding acrylates and amides respectively, were prepared by reacting the amine precursor with 4,7-dichloroquinoline as described in the literature ^[26]. Work-up of the reaction and extraction with EtOAc followed by purification (by column chromatography) afforded the products, both as white powders, in a yield in the range of 80-92%.

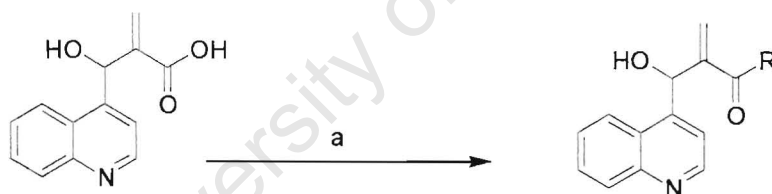


Scheme 5. Reagent and conditions: 20 equiv. Ethanolamine, 80-140 °C, 5h, 92%




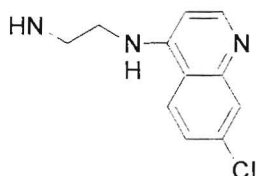
Scheme 6. Reagents and conditions: 4.5 equiv. ethylenediamine, 80-140 °C, 5h, 78%

A facile preparation of compounds **27** and **26** using commercially available PS-EDC was found to be a convenient route for coupling of amines with the carboxylic acid [27]. PS-EDC is a polymer-supported activating agent, which works on the same principle as dicyclohexyl carbodimide (DCC). Activation of the carboxyl moiety results in the immobilization of the acid onto the polymer surface of PS-EDC. Reaction of this activated polymer-bound carboxyl with amines results in the displacement of the PS-EDC with concomitant release of the product. An initial attempt was made to convert the carboxylic acid to the corresponding acid chloride followed by reacting with the amine [26]. Results using this method were unsatisfactory and hence the application of PS-EDC. The polymer-assisted synthesis using this supported coupling agent has various advantages including the ease of separation of the supported species from a reaction mixture by filtration and washing (Scheme 7). Table 2 summarizes the chemical yields.



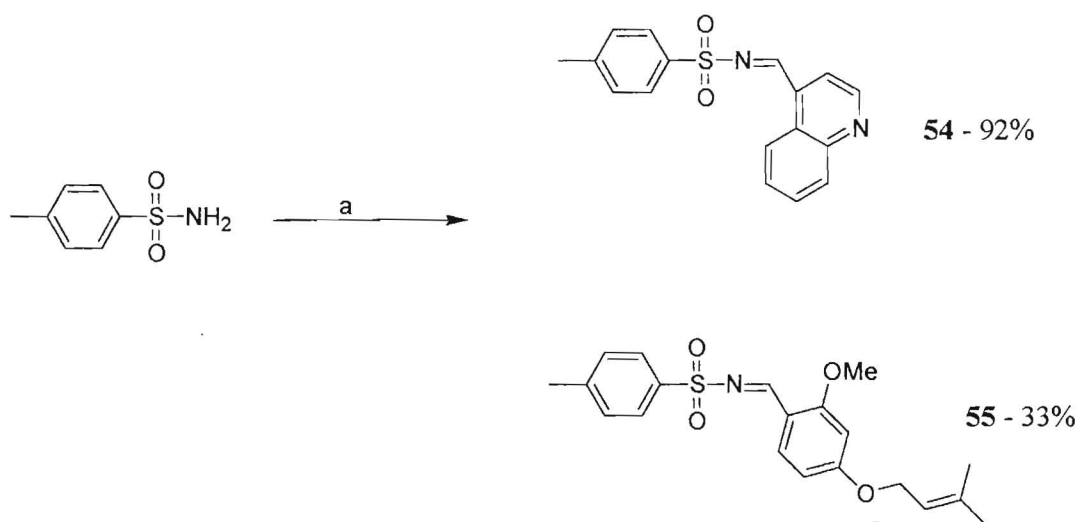
Scheme 7. Reagents and conditions: (a) 1 equiv. of amine, 2.5 equiv. of PS-EDC, CHCl_3

Table 2. Table showing substituents (R) from the product and their synthetic yields

Entries	Compound	R	Product Yield %
1	27		65
2	26		69

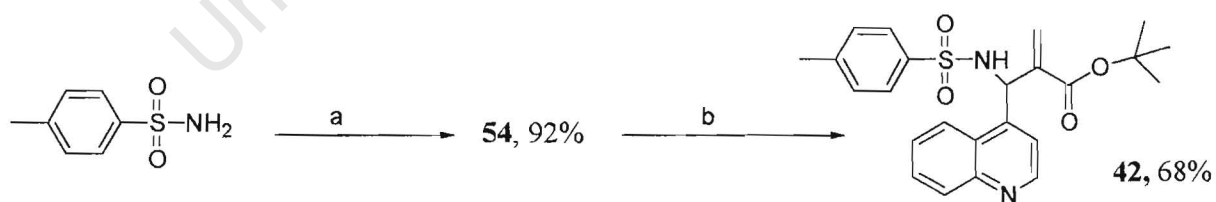
3.1.1.3 Synthesis of Class 4 compounds

The synthesis of compounds **54** and **55** was first carried out by reacting commercially available *p*-toluenesulfonamide with an aldehyde in the presence of acetic acid in catalytic amount and methanol as a solvent to form the corresponding sulfonylimine, Scheme 8. The ¹H NMR of the product showed only traces of impurities and therefore, further purification was unnecessary.



Scheme 8. Reagents and conditions: (a) 1 equiv. of aldehyde, MeOH, 50-70 °C, 17hrs.

A mixture of sulfonylimine, acrylate and DABCO was stirred at room temperature for 16hrs yielding a substituted sulfonamide derivative **42**. Purification was done by column chromatography.



Scheme 9. Reagents and conditions: (a) 1 equiv. of aldehyde, MeOH, Acetic acid, 50-70 °C, 17hrs. (b) 5 equiv. *t*-Buyl acrylate, DABCO.

Alternatively, a one-pot protocol was adapted, involving the reaction of arylaldehydes (1 equiv.), acrylic acid 2-(7-chloro-quinolin-4-ylamino)-acrylic acid ethyl ester/ acrylonitrile (3 equiv.), in the presence of *p*-toluenesulfonamide and triphenylphosphine in 2-propanol as a solvent^[28]. Scheme 10. Table 3.



Scheme 10. Reagents and conditions: 1 equiv. of Arylaldehyde, 5 equiv. of ester/ acrylonitrile, 1 equiv. of *p*-toluenesulfonamide, 0.005 equiv. of PPh₃ and 2-propanol.

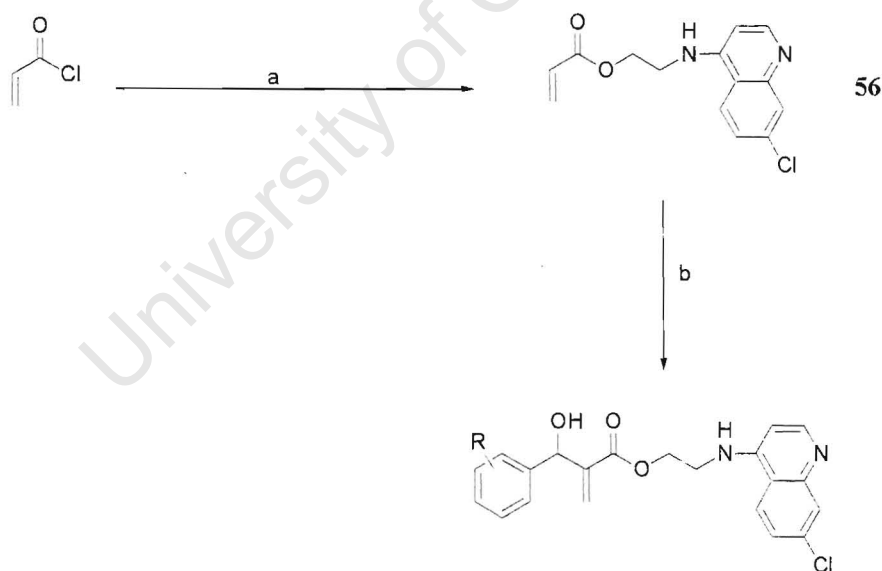
Table 3.

Entries	Compound #	Aldehyde	X	Product yield (%)
1	43, 44		CO ₂ ^t Bu / CN	66 / 53
2	46		CO ₂ ^t Bu	72
3	47		CN	63
4	45		CN	48

It was found that a one-pot three component aza-Baylis-Hillman reaction of arylaldehydes, acrylonitrile/ester and *p*-toluenesulfonamide can be achieved using PPh_3 in isopropanol. Yields ranging from 48-72% were obtained using variously substituted arylaldehyde. Better yields were obtained when *tert*-butyl acrylate was used (entry 1).

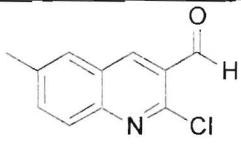
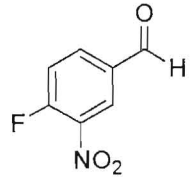
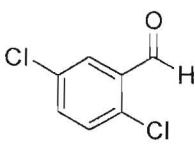
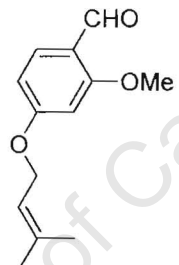
3.1.1.4 Synthesis of Class 5 compounds

The starting point for the synthesis of Class 5 compounds was the preparation of the acrylic ester **56** from the corresponding alcohol and acryloyl chloride in the presence of Et_3N using CH_2Cl_2 as a solvent^[29]. Acrylate **56** was then treated with respective aldehydes in the presence of DBU to give compounds **48-53** in highly variable yields. The variable yields were due to incompleteness of the reaction.



Scheme 11. Reagents and Conditions: (a) 1 equiv 2-(7-Chloro-quinolin-4-ylamino)-ethanol, Et_3N , CH_2Cl_2 , 60min, 37%, (b) arylaldehyde, DBU

Table 4.

Compound #	Aldehyde	Product yield (%)
48	 <chem>Cc1ccc2nc(Cl)c(C=O)cc2c1</chem>	67
49	 <chem>O=Cc1ccc(F)c([N+](=O)[O-])c1</chem>	92
50	 <chem>O=Cc1cc(Cl)cc(Cl)c1</chem>	82
51	 <chem>CC(=C)COc1ccc(C=O)c(OC)c1</chem>	69

3.1.2 Support Bound reagents as potential catalysts for the B-H reaction

When using an amine catalyst, one of the major drawbacks of the B-H reaction is the extra aqueous work-up step required at the end to remove the amine from the reaction. It is desirable to avoid this step by using support-bound catalysts ^[30] such as those based on BEMP (**58**), PTBD (**59**), Hunigs base (**60**), DMAP (**61**), and KF-Al₂O₃, which can be conveniently removed by filtration. There have been previous unsuccessful attempts at using polymer-bound phosphorus-based catalysts ^[31].

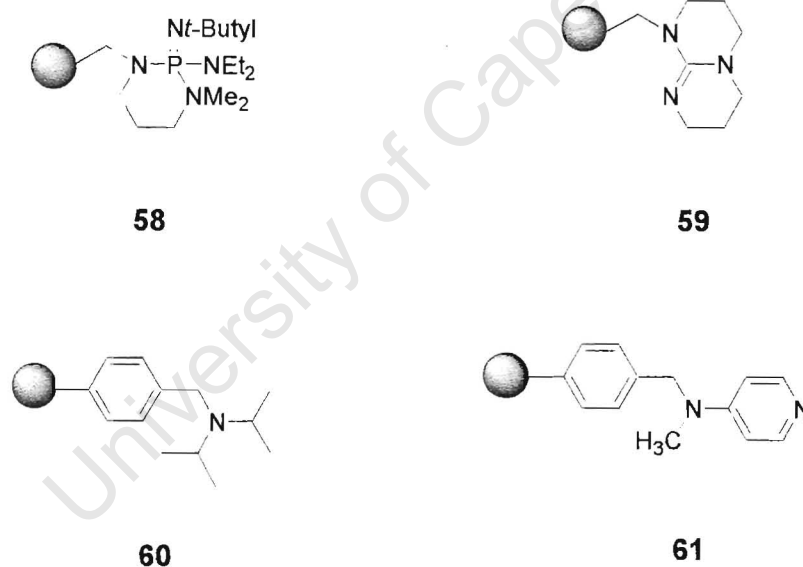
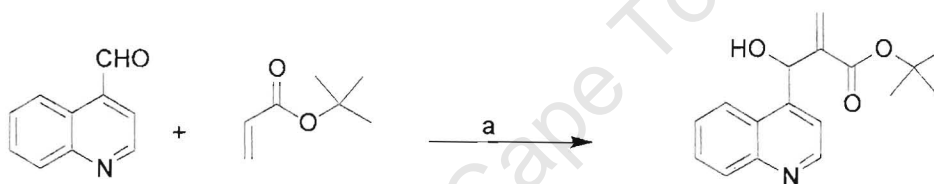


Figure 9. Polymer supported bases

For exploratory studies BEMP (**58**) was chosen, even though it is strongly basic and non-nucleophilic, because it has been used extensively in various contexts ^[31]. PTBD bears resemblance to DBU, a guanidine base used in B-H reaction ^[32]. Polymer-

supported Hunigs base is a tertiary amine resembling triethylamine, which has also been successfully used in B-H reactions ^[33]. On the other hand PS-DMAP is a nucleophilic base chosen due to literature precedence concerning the use of DMAP in B-H reaction ^{[34]-[35]}. KF-Al₂O₃ was chosen because it has been reported to be useful in catalysing Michael addition and other reactions ^{[36]-[37]}.

The results of catalyst screening are summarized in Tables 5-9. Initial catalyst screening experiments were performed using 4-quinoline-carbaldehyde with *tert*-butyl acrylate in acetonitrile as a solvent ^[38]. The results are presented in Table 5.

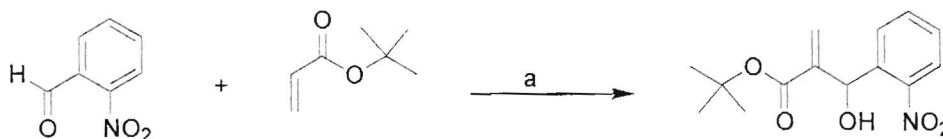


Scheme 3. Reagents and conditions: (a) 1 equiv. of aldehyde, 5 equiv. *t*-Butyl acrylate, and 1 equiv. of catalyst

Table 5. Screening of support bound catalysts for activity in the Baylis-Hillman reaction.

Entries	Catalyst	Reaction time (hrs)	Mol. Ratio	
			Aldehyde: acrylate: catalyst	Product Yield (%)
1	58	16	1 : 3 : 1	51
2	59	16	1 : 3 : 1	47
3	KF-Al ₂ O ₃	16	1 : 3 : 1	40
4	60	16	1 : 10 : 1	0
5	61	16	1 : 10 : 1	0

In this preliminary study BEMP was surprisingly found catalyze the reaction. However, one significant drawback in the BEMP-mediated reaction was the undesired formation of a self-aldol condensation by-product from the initial aldehyde^[19]. No by-products were observed in the case of PTBD and KF-Al₂O₃, which also showed catalytic activity. Coupled with the low cost, KF-Al₂O₃ was selected for further studies along with BEMP, which was available in large quantities. Results are presented in Tables 6-9. No reactions were observed in the case of PS-DMAP and PS-Hunigs base.



Scheme 13. Reagents and conditions: (a) 1 equiv. of 2-nitro-benzaldehyde 5 equiv. *t*-Butyl acrylate, DBU

Table 6. Optimisation of catalyst loading and reaction time.

Entries	Catalyst	Reaction time	Mol. Ratio ^a	Product Yield %
1	58	16	1 : 1 : 0.1	23
2	58	16	1 : 1 : 0.3	33
3	58	16	1 : 1 : 0.5	47
4	58	16	1 : 1 : 1	51
5	58	16	1 : 1 : 3	54
6	58	16	1 : 3 : 1	65
7	58	16	1 : 10 : 1	69
8	KF-Al ₂ O ₃	23	1 : 1 : 0.5	35
9	KF-Al ₂ O ₃	23	1 : 1 : 1	38
10	KF-Al ₂ O ₃	23	1 : 1 : 3	40
11	KF-Al ₂ O ₃	18	1 : 3 : 1	55
12	KF-Al ₂ O ₃	18	1 : 10 : 1	57

a : ratio of aldehyde: acrylate: catalyst

In the case of BEMP and KF-Al₂O₃, decreasing the catalyst loading from 1 to

0.1 mol. ratio resulted in the reduction of the product yield when the acrylate is kept at 1 equivalence (see entries 1, 2, 3 and 8).

In an attempt to eliminate by-product formation in the BEMP-catalyzed reaction, the effect of varying temperatures on the product yield was studied ^[16]. The reaction was performed at varying temperatures for 16 h. Results are presented in Table 7.

Table 7. Optimisation of reaction temperature.

Entries	Catalyst	Mol. Ratio	Time	Temperature (°C)	Product Yield
1	58	1 : 3: 1	16	0	30
2	58	1 : 3: 1	16	25	65
3	58	1 : 3: 1	16	40	54
4	KF-Al ₂ O ₃	1 : 3: 1	16	25	53
5	KF-Al ₂ O ₃	1 : 3: 1	16	40	49

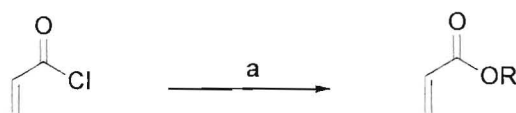
It was noted that the optimum yields of product (65% and 53%) were obtained when the reaction was performed at room temperature and a reaction time of 16 hrs (entry 2 and 4, Table 7).

Next the effect of solvent using a common aldehyde, *o*-nitrobenzaldehyde in *t*-Butyl acrylate and BEMP was studied. The results are shown in Table 8. From this brief study, acetonitrile and dichloromethane emerged as suitable solvents (entries 1 and 2), Surprisingly, little to no product was obtained when tetrahydrofuran and isopropanol solvents, which are more polar than dichloromethane were used.

Table 8. Assessment of the effect of solvent on the reaction.

Entries	Solvent	Catalyst	Product Yield %
1	Acetonitrile (anhydrous)	58 /KF-Al ₂ O ₃	64 / 45
2	Dichloromethane (distilled)	KF-Al ₂ O ₃	53
3	Tetrahydrofuran (anhydrous)	58 /KF-Al ₂ O ₃	No reaction
4	Isopropanol	58 /KF-Al ₂ O ₃	34 / no reaction
5	1,2-dichloroethane	58	No reaction

Studies aimed at optimizing reaction conditions by investigating the effects of changing the acrylate^[39] on the yields of the reaction were also undertaken. Structural variants of acrylates may provide stereo or stereoelectronic effect to stabilize the oxy anion intermediate and subsequently accelerate the reaction. Results are presented in Table 9. Prior to this study the necessary acrylates had to be synthesised in appropriate cases. Most acrylates were synthesized directly from commercially available acryloyl chloride and the corresponding alcohols. The results of the reactions of various acrylates are presented in Table 9.



Scheme 14. Reagents and conditions: (a) 1 equiv. of acryloyl chloride, 1 equiv. Alcohol, Et₃N, CH₂Cl₂, 37-64 %

Table 9. Effect of the nature of acrylate

Entries	R	Catalyst	Ratio	Yield (%)
1	Me	58	1 : 3 : 1	60
2	Me	KF-Al ₂ O ₃	1 : 3 : 1	46
3	<i>tert</i> -Bu	58	1 : 3 : 1	65
4	<i>tert</i> -Bu	KF-Al ₂ O ₃	1 : 3 : 1	51
5	Ph	58	1 : 3 : 1	25
6	Bn	58	1 : 3 : 1	36
7	1-naphthyl	58	1 : 3 : 1	20

Overall the yields obtained in these reactions were poor to moderate. With **58** as catalyst, the best yields were obtained with *tert*-butyl and methyl acrylates (entries 3 and 1), with yields in case of phenyl, benzyl and 1-naphthyl acrylates somewhat poorer. The *tert*-butyl and methyl acrylates also contributed to moderately good yields when KF-AL₂O₃ was used as catalyst (entries 2 and 4).

At this point, ultrasound was considered as an option for accelerating the reaction. It has been reported that the use of La(OTf)₃ as a co-catalyst and ultrasound provides up to a 40 fold increase over the use of DABCO alone^{[40]-[42]}, especially when aromatic aldehydes are used as electrophiles^[43]. The effect caused by ultrasound is due to the cavitation effect, which transfers a huge amount of energy, which can effectively

contribute to produce an acceleration of the reaction rate. Table 10, shows the results obtained by efforts to accelerate the reaction using ultrasound.

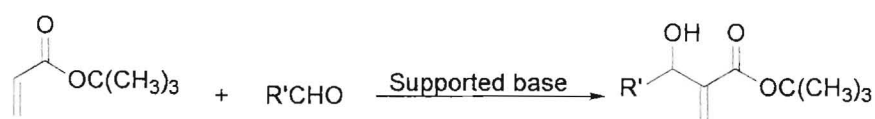
Table 10. Effect of the ultrasound

Entries	Condition	Ratio ^a	Reaction time (hrs)	Co-catalyst	Yield (%)
1	Ultrasound	1 : 3 : 1	6	-	39
2	Ultrasound	1 : 3 : 1	6	LiClO ₄	41
3	Stirring	1 : 3 : 1	6	LiClO ₄	43
4	Shaking	1 : 3 : 1	6	-	-

a : ratio of aldehyde: acrylate: catalyst

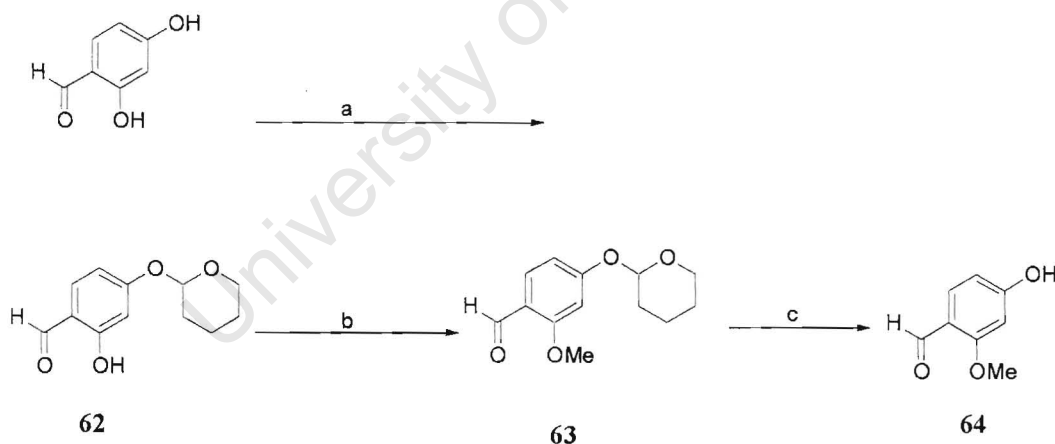
All reactions were carried out with the ultrasonic bath temperature carefully monitored between 35-40 °C. The reaction was TLC monitored after each hour. In order to compare all the reactions under the same experimental conditions, the reaction was stopped after 6 h. The presence of co-catalyst LiClO₄ appears to not affect the yield of the reaction when ultrasound is used or when the reaction is stirred (entries 1-3). In the absence of co-catalyst LiClO₄, shaking is ineffective in promoting reaction whereas the use of ultrasound does result in the moderate yields of product.

3.1.2.1 Synthesis of class 3 compounds



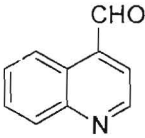
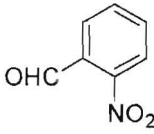
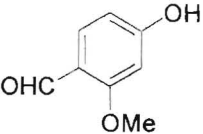
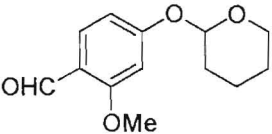
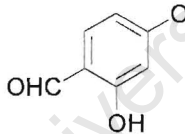
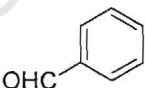
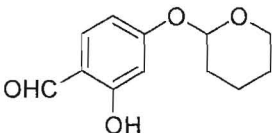
Scheme 16.

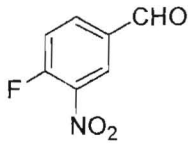
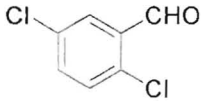
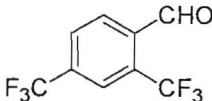
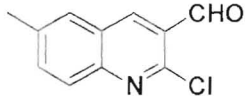

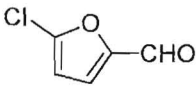
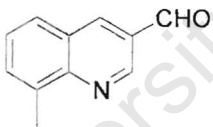
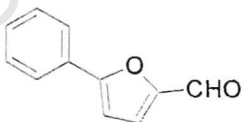
In order to further determine the scope and limitation of the B-H reaction catalysed by BEMP and $\text{KF-Al}_2\text{O}_3$, the reaction was extended to other aromatic aldehydes under optimum conditions ^{[46]-[47]}. These results are presented in Table 11. 4-quinoline carbaldehyde and 2-nitrobenzaldehyde are included in the table for comparison purposes. Most of these aldehydes were commercially available from sigma-aldrich except for aldehydes **62**, **63** and **64**, which were synthesised as shown in Scheme 15. A solution of 2,4-dihydroxybenzaldehyde, pyridinium *p*-toluenesulfonate and 3,4-dihydro-2*H*-pyran in dry DCM was stirred for 48hrs at room temperature ^[48]. The reaction mixture was washed with 1 M sodium carbonate and concentrated to give **62**. Compound **63** was synthesised by suspending **62**, NaOH and CH_3I in DMSO and stirring at room temperature for 1hr. Removal of the THP protecting group from **63** using 4 M HCl afforded **64**.

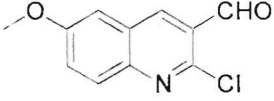
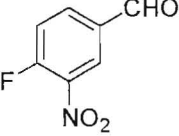
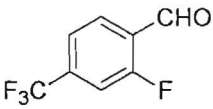
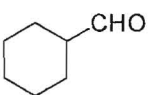
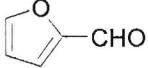
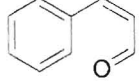
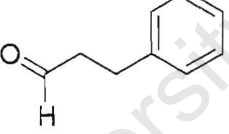


Scheme 15. Reagents and conditions: (a) 3,4-Dihydro-2*H*-pyran, CH_2Cl_2 , RT, 96% ; (b) CH_3I , NaOH, DMSO, 70% ; (c) 4M HCl, EtOH, 89%.

Table 11. Baylis-Hillman reaction of *tert*-butyl acrylate with different aldehydes catalysed by support-bound bases.

Entries	Aldehyde	Catalyst	Ratio	Product yield (%)
1		58 /KF-Al ₂ O ₃	1 : 3 : 1	51 / 48
2		58 /KF-Al ₂ O ₃	1 : 3 : 1	65 / 53
3		58	1 : 3 : 1	63
4		58	1 : 3 : 1	0
5		58	1 : 3 : 1	65
6		58	1 : 3 : 1	53
7		58	1 : 3 : 1	57

Entries	Aldehyde	Catalyst	Ratio	Product yield (%)
8		58 /KF-Al ₂ O ₃	1 : 3 : 1	60 / 41
9		58 /KF-Al ₂ O ₃	1 : 3 : 1	63 / 45
10		58 /KF-Al ₂ O ₃	1 : 3 : 1	65
11		58	1 : 3 : 1	45
12		KF-Al ₂ O ₃	1 : 3 : 1	46
13		KF-Al ₂ O ₃	1 : 3 : 1	32
14		58 /KF-Al ₂ O ₃	1 : 3 : 1	56 / 52
15		58 /KF-Al ₂ O ₃	1 : 3 : 1	46 / 41

Entries	Aldehyde	Catalyst	Ratio	Product yield (%)
16		58/KF-Al ₂ O ₃	1 : 3 : 1	40 / 23
17		58/KF-Al ₂ O ₃	1 : 3 : 1	58 / 41
18		58/KF-Al ₂ O ₃	1 : 3 : 1	63 / 50
19		58	1 : 3 : 1	15
20		58	1 : 3 : 1	26
21		58	1 : 3 : 1	10
22		KF-Al ₂ O ₃	1 : 3 : 1	47

Many aromatic aldehydes and branched aliphatic aldehydes are reluctant to serve as substrates, the major drawback being the slowness of the reaction. However in this study the main emphasis was given to aromatic aldehydes. The investigation involved aldehydes without any substituents on the aromatic ring, substituents with electron donating groups (entries 3, 4 and 5) and substituents with electron-withdrawing groups (entries 2, 8, 9, 10, 11 and 12). As shown in Table 11, both aliphatic (entries 19-22) and aromatic aldehydes (entries 1-18 & 23) were converted to their corresponding B-H products in yield range 10-65 %. However, it is not clear which substitution pattern on the aromatic ring could be successfully used to achieve better yields. For aliphatic aldehydes a dramatic decrease in the yield was observed.

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CHAPTER 4

BIOLOGICAL RESULTS AND DISCUSSION

4.1 Activity of selected compounds against cruzain and *T. cruzi*

The data in Table 12 shows the activity of selected derivatives (Figure 10) with respect to inhibition of the enzyme cruzain.

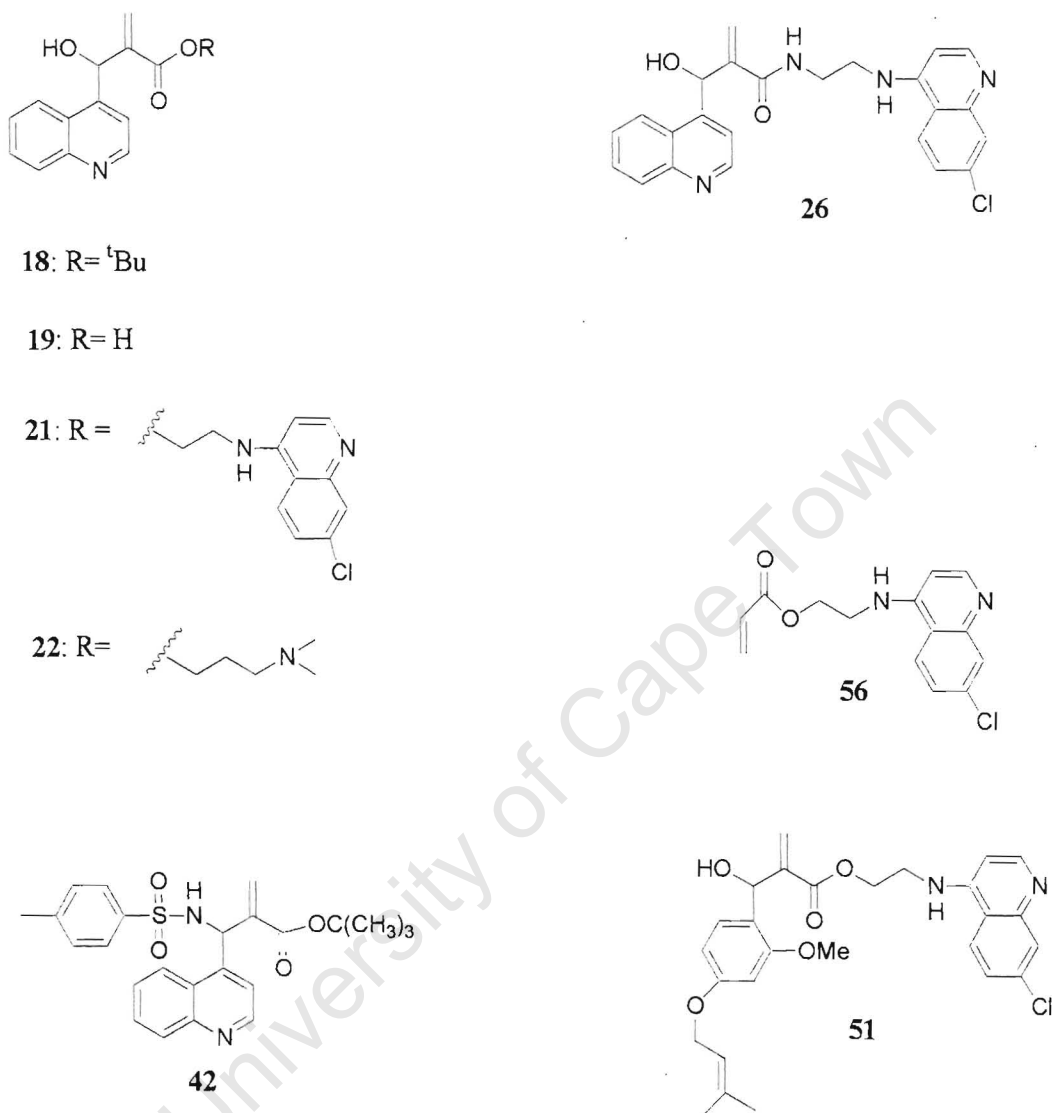
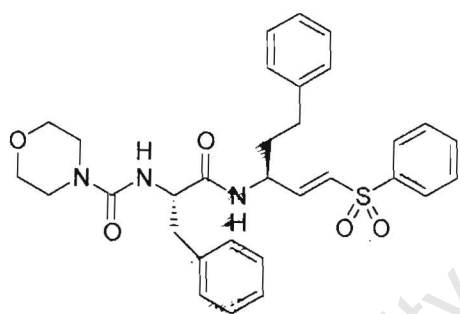
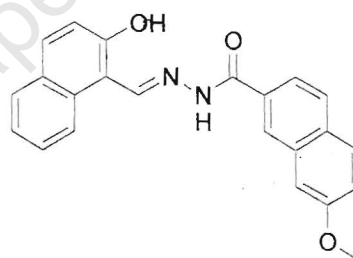


Figure 10. Chemical structures of B-H adducts and quinoline derivatives

The assays were performed at the University of California San Francisco, USA. All of the compounds were tested against 4nM cruzain by incubating them with the enzyme for 5 minutes and then adding substrate. Three concentrations of each inhibitor were tested: 10, 1 and 0.1 μ M. The IC₅₀, which is defined as the concentration of inhibitor decreasing substrate hydrolysis by 50%, was determined. The results are shown in Table 12. The data for standard control drugs **K777**, a vinyl sulfone and **K1102** an acyl hydrazine is included partly for comparison purposes. Figure 11. However, since the controls belong to two totally different aforementioned classes of compounds, they cannot be compared directly with the compounds in Table 12, which are Baylis-Hillman adducts. Their inclusion mainly serves the purpose of confirming the reproducibility of the assay over a time period.



Vinyl Sulfone (K777)



Acyl Hydrazide (K1102)

Figure 11.

Table 12. Inhibition of cruzain.

Entries	Compound	IC ₅₀ , μM
1	K1102	0.002-0.01
2	K777	0.07-0.3
3	18	>>10
4	19	>>10
5	21	>>10
6	22	>>10
7	26	>>10
8	42	2.8
9	51	>>10
10	56	>>10

As seen from Table 12 there is no evidence that the compounds were acting against cruzain except for compound **42** (Entry 8), which showed an IC₅₀ value of 2.8 μM. Based on the activity of compound **42**, future work should further include the synthesis of aza-B-H adducts with substrates varied between different acrylates, aldehydes and sulfonamides.

4.1.1 *T. cruzi* in culture

T. cruzi survival or death within the oxidative environment generated by activated macrophages depends on the capacity of the parasite to cope against the cytotoxic potential of the compound being tested. Figure 12 shows activity of selected compounds in culture.

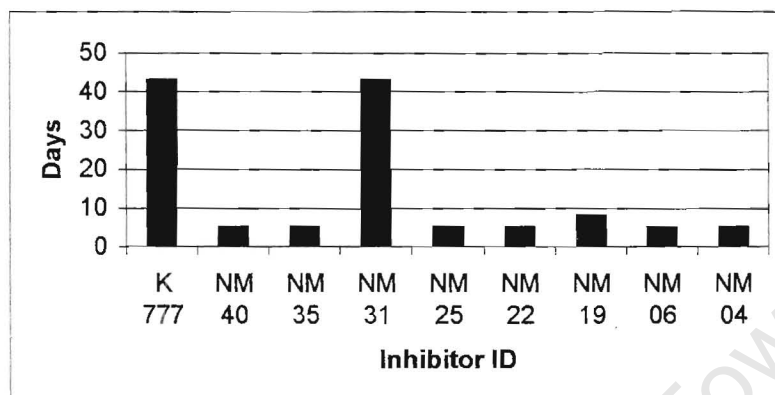


Figure 12.

Inhibitor ID	NM 40	NM 35	NM 31	NM 25	NM 22	NM 19	NM 06	NM 04
Compound	22	26	42	57	21	56	19	18

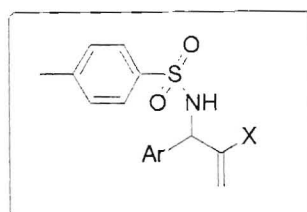
T. cruzi-infected mammalian cells treated with 42 survived more than 40 days in culture as compared to 5 days for their untreated counterparts at a concentration of 5 μ M. This concentration is even lower than that for the control (K777) that is normally used at 10 μ M.

Since K777 is a potent inhibitor of cruzain, and *T. cruzi*-infected cells survive more than 40 days when treated with this compound, the cell culture data obtained with 42

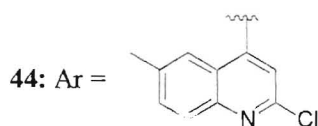
suggests cruzain may not be the primary target for **42**. The cell culture activity involves complicated factors. Compounds that are potent inhibitors of cruzain in vitro are not necessarily active in cell culture. Compounds must be able to cross the macrophage's cell membrane and cross the parasite's cytoplasm in sufficient quantity to significantly inhibit cruzain without killing the host cell. In view of this, compound **42** may possess the requisite transport properties to reach its targets, including cruzain.

4.2 Activity of selected compounds against Falcipain-2, W2 and *Trypanosoma brucei*.

A series of compounds (Figure 13) was tested against falcipain-2 and W2, a chloroquine resistant strain of *P. falciparum*, the causative agent of malaria. Activity of the compounds against cultured malaria parasite was determined and their IC₅₀ values reported in Table 13. Selected compounds were also screened for inhibition of *Trypanosoma brucei*, the causative agent of African sleeping sickness. The 50% effective dose value (ED₅₀), i.e. the inhibitor concentration necessary to reduce the growth rate of the cells by 50%, was determined. The results are also shown in Table 13.



X = *t*-Butyl acrylate



X = CN

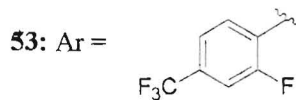
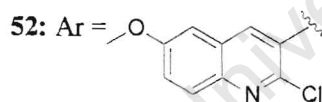
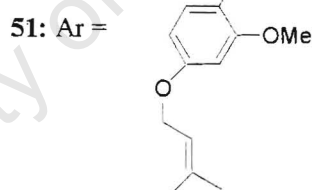
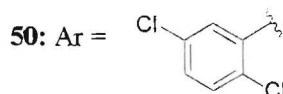
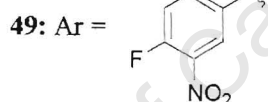
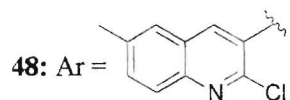
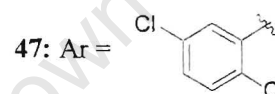
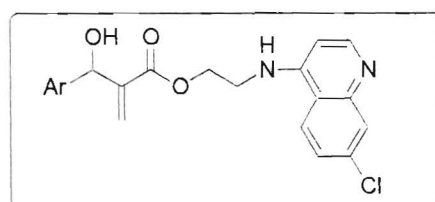
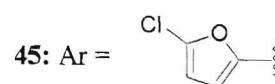
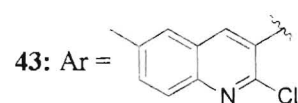


Figure 13.

Table 13. Activity against chloroquine resistant strain (W2), Falcipain-2 and *T. brucei*.

Entries	Compound	W2 IC ₅₀ (μM)	Falcipain-2 IC ₅₀ (μM)	<i>T. brucei</i> ED ₅₀ (μM)
1	18	>10000	>10	ND
2	19	>10000	>10	ND
3	21	0.197	>10	ND
4	22	>10000	>10	ND
5	26	>10000	>10	ND
6	27	ND ^a	ND	ND
7	56	>1000	>10	ND
8	42	>1000	2	ND
9	44	ND	ND	3
10	43	ND	ND	>10
11	45	2.417	ND	>10
12	47	ND	ND	>10
13	49	ND	ND	>10
14	50	1.597	ND	4
15	51	0.171	>10	ND
16	52	1.597	>10	>10
17	53	ND	ND	>10

^a Not determined

As shown in the table only compounds **21**, **45**, **50**, **51** and **52** generally showed activity (albeit modest) against the W2 strain. With the exception of **42**, compounds did not have an effect against falcipain-2, at the cut-off concentration of 10 μM . Lack of correlation between the antimalarial activity of **21**, **51** and **52** and inhibition of falcipain-2 suggests that falcipain-2 is not the target. The food vacuole abnormality that should accompany toxicity due to falcipain-2 inhibition was not seen even at high concentration. Antimalarial activity is probably due to inhibition of other unknown targets. When tested against *T. brucei*, compounds **44** and **50** exhibited ED_{50} values of <10 , whilst the ED_{50} values of other compounds were greater than 10 μM , suggesting these two compounds to be moderately active.

Due to factors beyond our control, some compounds were not tested within the time frame of the project.

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4.3 CONCLUSION

The potential use of KF-Al₂O₃, PTBD and BEMP as support-bound catalysts for the B-H reaction was demonstrate. For most cases moderate yields were obtained. Further studies are required in order to improve the reaction rate and chemical yields.

2-[quinolin-4-yl-(toluene-4-sulfonylamino)-methyl]-acrylic acid *tert*-butyl ester, **42** showed the most promising result as a potential antitrypanosomal agent and forms a basis for the synthesis of other aza- B-H adducts, with the substrates being varied between different acrylates, aldehydes and sulfonamides as part of structure-activity relationship studies. including the synthesis and biological evaluation of the respective enantiomers. The activity of **44** and **50** against *rhodesain*, the cysteine protease from *T. brucei*, was not tested. This would have enabled a correlation to be made between the antiparasitic activity and inhibition of *rhodesain*. The activity of some of the B-H and aza B-H should also be tested against *rhodesain*.

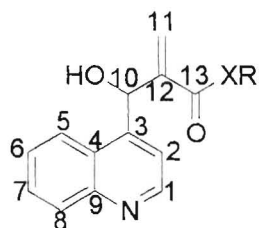
CHAPTER 5

5.1 General

All reactions were monitored by TLC on 25 aluminium sheets silica gel 60 F₂₅₄ (MERCK) and visualised under ultraviolet light (254 nm) and either sprayed with anisaldehyde spray (freshly prepared from a 2.5% solution of p-methoxybenzaldehyde (20 cm³) and 18M sulphuric acid (1cm³) or cerium (IV) ammonium sulphate in 8M sulphuric acid, followed by heating at 200 °C. Column chromatography was carried out using silica gel 60 (0.063- 0.200mm).

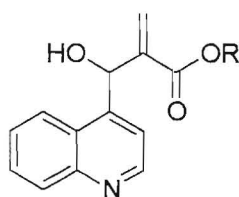
Melting points were taken on a Fischer-John hot stage microscope melting point apparatus and are uncorrected. The IR spectra were obtained using a Mattson Instrument Satellite FTIR spectrometer (potassium bromide disks and plastic films). The ¹H NMR spectra were recorded on either a Varian VXR-200 at 200MHz, Varian Mercury 300MHz or Varian Unity spectrometer (400MHz) and chemical shifts (δ) are in ppm relative to internal tetramethylsilane (TMS). ¹³C NMR spectra were recorded on the same instruments operating at 50, 75, 100 MHz respectively. Elemental analyses were performed using a Fisons EA 1108 CH-N instrument. Mass spectra were recorded on a VG micromass 16F spectrometer operating at 70eV with an accelerating voltage of 4kV. Others were determined using VG-70E spectrometer at the Cape Technikon.

The following numbering system was used to assign aromatic protons in the proton nuclear magnetic resonance spectra of compounds based on quinoline moieties.



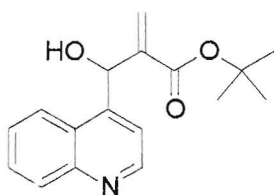
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5.2 General method for the preparation of targets 18, 21, 23, 24 and 25



A mixture of 4-quinoline-carbaldehyde (3mmol), ester (0.66ml) and DBU (0.45ml) was stirred at room temperature for 16h. The reaction mixture was purified by column chromatography yielding an *ester*.

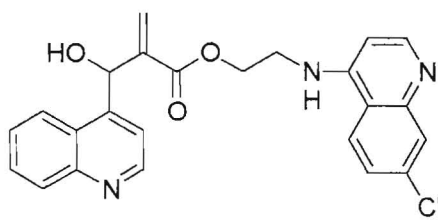
Esters used: *t*-Butyl acrylate (0.5125g, 3mmol), Acrylic acid 2-(7-chloro-quinolin-4-ylamino)-ethyl ester (0.0853g, 0.3mmol), Acrylic acid phenyl ester (0.1g, 0.63mmol), Acrylic acid benzyl ester (0.1g, 0.63mmol), Acrylic acid naphthalen-1-yl ester (0.1g, 0.63mmol).



2-(Hydroxy-quinolin-4-yl-methyl)-acrylic acid tert-butyl ester.

18

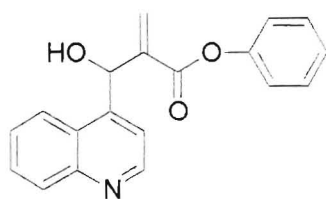
Yield (0.45g, 50%) as white crystals; R_f 0.20 (3:7, EtOAc: Hexane); mp 120-130 °C; IR (CHCl_3) ν_{max} 3611, 3018, 2410, 1707 cm^{-1} ; δ_{H} (300MHz; CDCl_3) 8.31 (1H, d, $J=8.4$, H-1), 8.16 (1H, d, $J=6.5$, H-8), 7.93 (1H, d, $J=6.3$, H-5), 7.60 (1H, m, H-7), 7.58 (1H, t, $J=6.3$, H-6), 7.24 (1H, d, $J=8.2$, H-2), 6.65 (2H, s, $\text{C}=\text{CH}_2$, H-11), 5.41 (1H, d, $J=9.4$, CHOH , H-10), 2.04 (1H, d, $J=9.2$, OH), 1.47 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_{C} (75.45 MHz) 162.2, 150.4, 148.7, 145.4, 137.2, 130.3, 129.1, 127.0, 126.7, 123.7, 118.4, 76.6 and 28.03; LRMS (EI) m/z 285 (M^+); $\text{C}_{17}\text{H}_{19}\text{NO}_3$ requires 285.34; Calc. for C, 70.31; H, 7.01; N, 5.12; Found, C, 71.55; H, 6.64; N; 4.71.



Hydroxy-quinolin-4-yl-methyl)-acrylic acid 2-(7-

chloro-quinolin-4-ylamino)-ethyl ester. 21

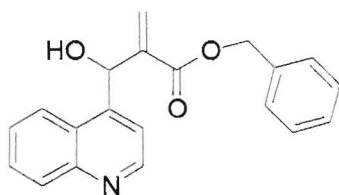
The residue was evaporated giving the product *ester*. Yield (0.073g, 89%) as brown gum; R_f 0.13 (0.5: 9.5 MeOH: CH_2Cl_2); δ_{H} (300MHz, CDCl_3) 8.35 (2H, m, H-1 and H-1), 8.25 (1H, d, $J=8.5$, H-8), 8.22 (2H, m, H-5 and H-8), 8.16 (1H, m, H-7), 7.95 (2H, m, H-5 and H-6), 7.93 (1H, d, $J=8.2$), 7.44 (1H, m, H-2 and H-6), 6.65 (2H, s, $\text{C}=\text{CH}_2$, H-11), 5.19 (1H, d, $J=10.2$, CHOH , H-10), 4.20, (1H, t, $J=11.4$, NH), 3.90 (2H, t, $J=11.0$, OCH_2), 3.32 (2H, q, $J=11.2$, CH_2NH), 2.08 (1H, d, $J=10.8$, OH); δ_{C} (75.45 MHz) 165.2, 157.2, 149.1, 148.1, 145.7, 145.3, 132.8, 131.7, 130.6, 129.7, 128.7, 126.4, 124.2, 124.0, 122.8, 118.5, 118.0, 117.6, 84.0, 72.5 and 69.0; LRMS (EI) m/z 434; $\text{C}_{24}\text{H}_{20}\text{N}_3\text{O}_3\text{Cl}$ requires 433,89; Calc. for C, 56.44; H, 4.65; Cl, 8.17; N, 9.68; Found C, 56.55, H, 4.65, N, 10.76.



2-(Hydroxy-quinolin-4-yl-methyl)-acrylic acid phenyl ester.

23

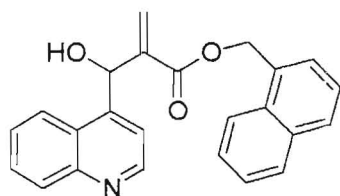
Yield (0.032g, 16%) as brown oil. R_f 0.1 (4:6 EtOAc: Hexane); δ_H (300MHz, $CDCl_3$), 8.25 (1H, d, $J=1.0$, H-1), 8.10 (1H, d, $J=4.6$, H-8), 7.88 (1H, d, $J=4.8$, H-5), 7.71 (1H, m, H-7), 7.53 (1H, t, $J=4.4$, H-6), 7.30 (1H, d, $J=1.2$, H-2), 7.11 (2H, dd, $J=2.6$ and 9.2, Ar), 7.09 (3H, m, Ar), 6.56 (2H, s, $C=CH_2$, H-11), 6.20 (1H, m, $CHOH$, H-10), 2.3 (1H, m, OH); δ_C (75.45 MHz) 161.0, 142.1, 140.9, 140.6, 140.4, 128.6, 128.5, 128.2, 128.0, 71.2; HRMS (EI) m/z 305, $C_{19}H_{15}NO_3$ requires 305.33.



2-(Hydroxy-quinolin-4-yl-methyl)-acrylic acid benzyl ester. 24

ester. 24

Yield (0.051g, 26%) as yellow oil; R_f 0.1 (4: 6 EtOAc: Hexane); δ_H (300MHz; $CDCl_3$) 9.12 (1H, d, $J=8.2$, H-1), 8.50 (1H, d, $J=4.0$, H-8), 8.42 (1H, d, $J=4.0$, H-5), 8.01 (1H, m, H-7), 7.95 (1H, t, $J=4.2$, H-6), 7.88 (1H, d, $J=8.5$, H-2), 7.65 (5H, m, Ar), 6.40 (2H, s, $C=CH_2$, H-11), 5.80 (2H, s, OCH_2), 5.19 (1H, d, $J=11.5$, $CHOH$, H-10), 2.20 (1H, d, $J=11.4$, OH); δ_C (75.45 MHz) 165.2, 148.7, 145.4, 145.3, 142.1, 129.1, 128.8, 128.7, 128.5, 128.1, 125.6, 124.2, 124.1, 123.9, 78.1, 75.4; LRMS (EI) m/z 318; $C_{20}H_{17}NO_3$ requires 319.35.



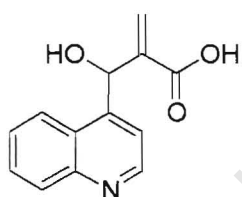
2-(Hydroxy-quinolin-4-yl-methyl)-acrylic acid naphthalen-

1-ylmethyl ester. 25

Yield (0.0048g, 10%) as brown oil; R_f 0.3 (4: 6 EtOAc: Hexane); δ_H (300MHz; CDCl₃) 8.84 (1H, d, $J=6.5$, H-1), 8.73 (1H, d, $J=5.4$, H-8), 8.01 (2H, m, H-5 and Ar), 7.78 (5H, m, Ar), 7.63 (2H, m, H-7), 7.52 (1H, d, $J=6.5$, H-2), 7.50 (1H, t, $J=5.3$), 7.48 (1H, m, Ar), 6.68 (2H, s, C=CH₂, H-11), 5.48 (2H, s, OCH₂), 5.46 (1H, d, $J=11.6$, CHOH, H-10), 2.48 (1H, d, $J=11.4$, OH); δ_C (75.45 MHz) 165.4, 152.3, 150.1, 149.6, 149.5, 135.3, 135.2, 129.0, 128.8, 128.7, 128.5, 128.4, 128.1, 127.6, 127.4, 119.4, 119.1 and 72.3; HRMS (EI) m/z 369.38741 ; C₂₄H₁₉NO₃ requires 369.41

5.3 Procedure for the preparation of target compounds 22, 26 and 27

5.3.1 Preparation procedure of an acid

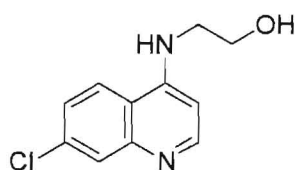


2-(Hydroxy-quinolin-4-yl-methyl)-acrylic acid. 19

Trifluoroacetic acid (1 equiv.) was added to 2-(Hydroxy-quinolin-4-yl-methyl)-acrylic acid methyl ester (4 mmol) in CH₂Cl₂. The reaction mixture was stirred at room temperature with TLC monitoring after 15min. After completion, the solvent was evaporated off and excess TFA removed by co-evaporation with cyclohexane to yield an acid that is dark brown solid (0.27g, 90%); R_f 0.1 (1:9 MeOH: CH₂Cl₂); mp 120-125°C;

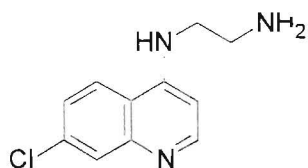
IR (CHCl₃) ν_{\max} 3850, 3742, 2799, 1740 cm⁻¹; δ_{H} (300MHz, CDCl₃), 9.15 (1H, s, OHC(O)), 8.33 (1H, d, $J=3.0$, H-1), 8.31 (1H, d, $J=5.4$, H-8), 8.04 (1H, d, $J=5.2$, H-5), 7.8 (1H, m, H-7), 7.58(1H, t, $J=5.5$, H-6), 7.83 (1H, d, $J=3.2$, H-2), 6.56 (2H, s, C=CH₂, H-11), 5.61 (1H, d, $J=11.7$, CHOH, H-10), 2.25 (1H, d, $J=11.3$, OH); δ_{C} (75.45 MHz) 167.9, 148.3, 144.1, 133.5, 129.5, 128.6, 126.5, 69.0 and 50.0; LRMS (EI) m/z 229 (M⁺); C₁₃H₁₁NO₃ requires 229.07.

5.3.2 Procedures for the starting materials



2-(7-Chloro-quinolin-4-ylamino)- ethanol. 57a

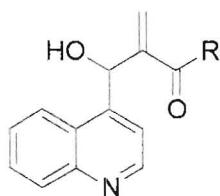
A mixture of 4,7-dichloroquinoline (1.987g, 10 mmol), alcohol (20 equiv.), Et₃N (0.3 equiv.) and K₂CO₃ was heated for 1h at 80 °C with stirring. It was then heated at 135-140 °C for 4 h with continuous stirring to drive the reaction to completion, and thereafter cooled to room temperature. The reaction was left at room temperature for 2 hrs to crystallize out of the solution. The product was recrystallised in methanol giving an alcohol (0.88g, 41%) as white powder. R_f (1:9 MeOH: CH₂Cl₂) 0.13; mp 206-208; IR (Nujol) ν_{\max} 3618, 3029, 1534, 1392 cm⁻¹; δ_{H} (400MHz; CD₃OD) 8.04 (1H, d, $J=4.0$, H-1), 7.98 (1H, m, H-8), 7.71 (1H, d, $J=3.6$, H-5), 7.39 (1H, d, $J=3.2$, H-6), 7.24 (1H, d, $J=4.3$, H-2), 4.02 (1H, t, $J=9.8$, NH), 3.70 (2H, q, $J=9.2$, CH₂NH), 3.50 (2H, m, CH₂OH), 2.15 (1H, m, OH); δ_{C} (75.45 MHz, CDCl₃) 151.4, 149.5, 149.0, 134.6, 128.1 and 64.5; LRMS (FAB) m/z 221.7; C₁₁H₁₁ClN₂O requires 222.06



N-(7-Chloro-quinolin-4-yl)-ethane-1,2- diamine. 57b

A mixture of 4.7 Dichloroquinoline (10mmol) and ethylenediamine (4ml) was heated for 1h at 80 °C with stirring. It was then heated at 135-140 °C for 4 hrs with continuous stirring to drive the reaction to completion, and there after cooled to room temperature. NaOH (1N, 20ml) was added followed by heating to 40 °C for 10min. Thereafter ethyl acetate (125ml) was added followed by warming to 35 °C for 1h and cooling to room temperature. The organic layer was separated from the aqueous phase, washed with water and was dried over sodium sulfate (anhydrous) and the solvent was evaporated off to obtain off white crystals (1.709g, 77%). mp 124-127 °C; R_f 0.34 (1:9 MeOH: CH₂Cl₂); δ_H (400MHz; CD₃OD) 8.19 (1H, d, $J=5.4$, H-1), 7.88 (1H, m, H-8), 7.49 (1H, d, $J=6.2$, H-5), 7.20 (1H, d, $J=5.1$, H-2), 7.16 (1H, d, $J=6.0$, H-6), 4.6 (1H, t, $J=9.6$, NH), 3.32 (2H, q, $J=10.5$, NHCH₂), 3.1 (2H, m, CH₂NH₂), 2.4 (2H, m, NH₂); δ_C (75.45 MHz, CDCl₃) 151.6, 151.2, 148.5, 135.2, 126.4, 124.9, 123.2, 117.7, 98.6, 53.6, 44.6, 39.5; C₁₁H₁₂ClN₃ requires; Calc. for C, 59.60; H, 5.46; Cl, 15.99; N, 18.95 Found C, 59.30, H, 5.46, N, 18.88.

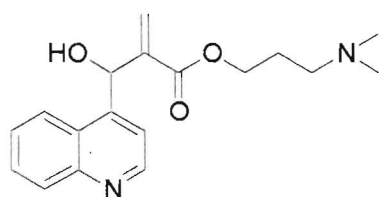
5.3.3 General procedure for preparation of 22 and 26



To a suspension of PS-EDC (1.2mmol) in chloroform (10ml) amine/alcohol (0.45mmol) and acid (0.54mmol) were added. After the reaction was shaken overnight at room temperature, the mixture was filtered. The resin was washed with chloroform (3 x 8ml), and the combined filtrate was evaporated to dryness. The crude was purified using column chromatography.

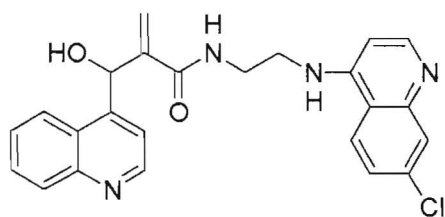
Alcohol used: 3-Dimethylamino-propan-1-ol (0.2g, 0.87mmol)

Amines used: N1-(7-Chloro-quinolin-4-yl)-ethane-1,2-diamine (0.1g, 0.45mmol)



2-(Hydroxy-quinolin-4-yl-methyl)-acrylic acid 3-dimethylamino-propyl ester. 22

Yield (0.22g, 80%) as brown oil; R_f 0.17 (2:8 MeOH: CH_2Cl_2); δ_H (300MHz, CDCl_3) 8.85 (2H, m, H-1 and H-8), 8.16 (1H, d, $J=2.0$, H-5), 8.15 (1H, m, H-7), 7.65 (1H, t, $J=2.3$, H-6), 7.62 (1H, m, H-2), 6.20 (2H, s, $\text{C}=\text{CH}_2$, H-11), 5.45 (1H, m, CHOH , H-10), 4.27 (2H, t, $J=12.5$, OCH_2), 2.93 (2H, t, $J=12.3$, CH_2N), 2.65 (6H, s, $\text{N}(\text{CH}_3)_2$), 2.15 (1H, m, OH), 1.4 (2H, m, CH_2); δ_C (75.45 MHz) 167.0, 150.3, 150.1, 144.7, 130.0, 129.6, 129.1, 128.9, 127.5, 126.7, 126.3, 123.8, 119.0, 77.2, 68.2, 58.7, 43.0 and 29.6; LRMS (EI) m/z 314; $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_3$ requires 314.38; Calc. for C, 68.77; H, 7.05; N, 8.91; Found C, 67.98; H, 7.01; N, 8.50.

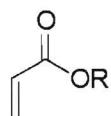


N-[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-2-

(hydroxy-quinolin-4-yl-methyl)-acrylamide. 26

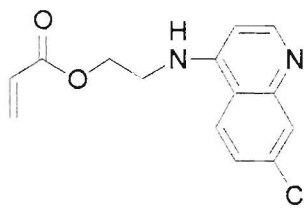
Yield (0.083g, 43%) as yellow oil. R_f 0.45 (2:8 MeOH: CH_2Cl_2); δ_{H} (300MHz, CDCl_3) 8.50 (2H,m, H-1 and H-1), 8.2 (1H, d, $J=9.3$, NHC(O)), 8.01 (4H, m, H-8, H-8, H-5 and H-5), 7.95 (4H, m, H-2, H-6 and H-2 and H-2), 6.25 (2H, s, $\text{C}=\text{CH}_2$, H-11), 5.64 (1H, d, $J=13.9$, CHOH , H-10), 4.25 (1H, m, NH-Ar), 3.48 (2H, t, $J=9.9$, NHCH_2), 3.17 (2H, q, $J=9.6$, CH_2NH), 2.19 (1H, d, $J=14.0$, OH); δ_{C} (75.45 MHz) 166.0, 154.6, 149.2, 145.3, 145.1, 144.9, 144.7, 144.3, 129.7, 126.8, 125.4, 125.2, 119.8, 119.7, 119.4, 115.4, 77.42, 38.89 and 33.25; LRMS (EI) m/z 433; $\text{C}_{24}\text{H}_{21}\text{ClN}_4\text{O}_2$ requires 432.90.

5.4 General procedure for the preparation of ester acrylates 56



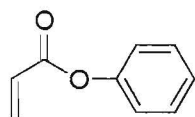
A solution of acryloyl chloride (1.9 mmol) in CH_2Cl_2 (5ml) was cooled in an ice bath. Alcohol (4.6 mmol) was added to the cold solution, and then a solution of redistilled Et_3N (0.5ml) in CH_2Cl_2 (1.25ml) was added dropwise and stirred for 1 hr. The product was purified by column chromatography and an *ester* was obtained.

Alcohols used: 2-(7-Chloro-quinolin-4-ylamino)-ethanol, Phenol, Phenyl-methanol and Naphthalen-1-ol



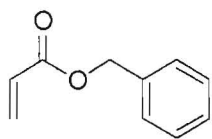
Acrylic acid 2-(7-chloro-quinolin-4-ylamine)-ethyl ester. 56

Yield (1.320g, 37%) as yellow powder; R_f 0.35 (1:9 MeOH: CH₂Cl₂); mp 78-79 °C; IR (CHCl₃) ν_{\max} 1721, 1514 cm⁻¹; δ_H (400MHz, CDCl₃) 8.96 (1H, d, $J=4.4$, H-1), 8.18 (1H, s, H-8), 7.71 (2H, m, H-6 and H-5), 7.31 (1H, d, $J=4.5$, H-2), 6.40 (2H, d, $J=9.2$, CH=CH₂, H-11), 6.25 (1H, t, $J=9.0$, CH=CH₂), 4.40 (2H, d, $J=14.1$, OCH₂), 4.00 (1H, t, $J=13.9$, NH), 3.56 (2H, q, $J=14.2$, CH₂NH); δ_C (75 MHz) 165.5, 152.0, 150.3, 147.1, 131.4, 131.2, 129.1, 127.4, 124.1, 120.9, 63.4, 62.3, 48.6, 30.9; LRMS (EI) m/z 276 (M)⁺, C₁₄H₁₃ClN₂O₂ requires 276.72, Calc. for C, 60.77; H, 4.74; Cl, 12.81; N, 10.12; Found C, 61.32; H, 4.21; N 7.87.



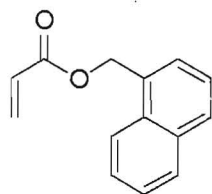
Acrylic acid phenyl ester.

Yield (0.3139g, 50%) as white powder; R_f 0.37 (1:9 MeOH: CH₂Cl₂); mp 56-59 °C; δ_H (300MHz; CDCl₃) 7.33 (2H, m, Ar), 7.28 (3H, m, Ar), 6.03 (1H, t, $J=10.2$, CH=CH₂), 5.98 (2H, d, $J=10.7$, CH=CH₂); δ_C (75.45 MHz) 165.0, 135.9, 131.0, 128.5, 128.3, 128.2, 128.1; HRMS (EI) m/z 148.05247 (M⁺); C₉H₈O₂ requires 148.05.



Acrylic acid benzyl ester.

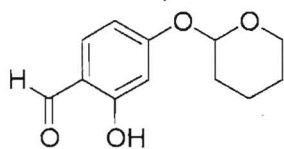
Yield (0.42g, 56%) as yellow powder; R_f 0.35 (3:7 EtOAc: Hexane); mp 68-70 °C R_f 0.38 (1:9 MeOH: CH_2Cl_2); δ_{H} (300MHz; CDCl_3) 7.40 (5H, m, Ar), 6.48 (1H, t, $J=11.7$, $\text{CH}=\text{CH}_2$), 6.22 (2H, d, $J=11.6$, $\text{CH}=\text{CH}_2$), 5.21(2H, s, OCH_2); δ_{C} (75.45 MHz) 165.9, 135.9, 131.0, 128.5, 128.0, 76.7, HRMS (EI) m/z 162.06829 (M^+); $\text{C}_{10}\text{H}_{10}\text{O}_2$ requires 162.06.



Acrylic acid naphthalen-1-yl ester.

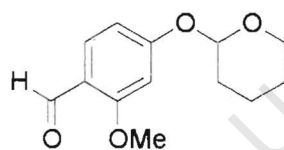
(0.430g, 64%) as yellow oil; R_f 0.32 (1:9 MeOH: CH_2Cl_2), δ_{H} (300MHz; CDCl_3) 7.86 (1H, d, $J=5.4$, Ar); 7.48 (5H, m, Ar); 7.26 (1H, d, $J=5.2$, Ar), 6.42 (2H, d, $J=13.2$, $\text{CH}=\text{CH}_2$), 6.03 (1H, t, $J=13.5$, $\text{CH}=\text{CH}_2$), 5.92 (2H, s, OCH_2); δ_{C} (75.45 MHz) 164.8, 148.5, 134.0, 132.7, 131.6, 129.5, 128.1, 127.9, 126.7, 125.8, 121.2, 118.63; HRMS (EI) m/z 212.06799 (M^+); $\text{C}_{14}\text{H}_{12}\text{O}_2$ requires 212.06; Calc. for C, 78.77; H, 5.09; Found C, 78.67, H 5.35.

5.5 General procedure for the preparation of aldehyde. 62, 63 and 64.



2-Hydroxy-4-(tetrahydro-pyran-2-yloxy)-benzaldehyde ^[47] . **62**

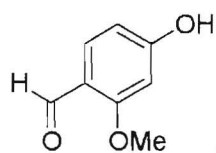
A solution of 2,4-dihydroxybenzaldehyde (14.48 mmol), pyridium *p*-toluenesulfonate (0.58 mmol) and 3,4-dihydro-2H-pyran (23.17 mmol) in dry DCM (20 ml) was stirred for 48 hrs at room temperature. The reaction mixture was extracted with dichloromethane and the organic phases were washed with 1M sodium carbonate (20 ml) and concentrated under reduced pressure to give **62** (3.224g, 96 %) as pale yellow oil. R_f 0.2 (3: 7 MeOH: CH₂Cl₂); δ_H (400MHz; CDCl₃) 11.34 (1H, s, HC(O)), 7.34 (1H, m, Ar), 6.66 (2H, m, Ar), 5.45 (1H, s, Ar-OH), 3.60 (2H, t, $J=11.5$, OCH₂), 1.82 (2H, t, $J=11.8$ CH₂), 1.65 (4H, m, 2CH₂); δ_C (75.45 MHz) 194.5, 164.4, 164.1, 135.2, 115.7, 109.4, 103.7, 96.2, 62.9, 62.1, 30.6 and 29.9.



2-Methoxy-4-(tetrahydro-pyran-2-yloxy)-benzaldehyde ^[47] . **63**

62 (9.6 mmol), NaOH (20.1 mmol) and CH₃I were suspended in DMSO (15 ml), stirred for 1hr at room temperature and then added to water (60 ml). The reaction mixture was extracted with DCM (3 X 100ml) and the combined organic phases were washed with water and concentrated in vacuum to give **63** (2.385g, 70%) as light brown oil. R_f 0.32 (3:

7 MeOH: CH₂Cl₂); δ_{H} (400MHz; CDCl₃) 11.34 (1H, s, HC(O)), 7.34 (1H, m, Ar), 6.66 (2H, m, Ar), 5.45 (1H, t, $J=11.6$, OCH₂), 3.69 (3H, s, OCH₃), 3.60 (2H, t, $J=11.2$, CH₂), 1.65 (4H, m, 2CH₂); δ_{C} (75.45 MHz) 194.5, 163.2, 163.1, 135.2, 115.7, 109.4, 103.7, 96.2, 62.9, 62.1, 56.4, 30.6 and 30.2.



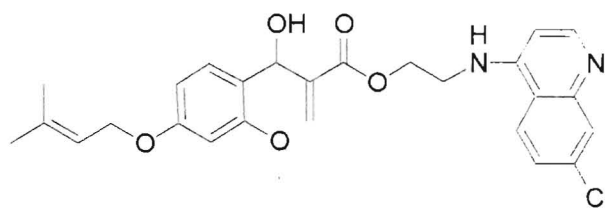
4-Hydroxy-2-methoxy-benzaldehyde ^[47]. **64**

To a stirred solution of **63** (5.5 mmol) in ethanol (20 ml), 4M HCl (6 ml) was added. The resulting mixture was stirred for 15 min and then added to water (60 ml). The reaction mixture was extracted with EtOAc (3 X 100ml), washed with brine (100 ml) and concentrated to give a residue, which was recrystallized from toluene to afford **64** (1.130g, 0.89%) as pale green powder. R_f 0.15 (3: 7 MeOH: CH₂Cl₂); δ_{H} (400MHz; CDCl₃) 10.1 (1H, s, HC(O)), 7.65 (1H, m, Ar), 6.47 (2H, m, Ar), 4.78 (1H, s, OH), 3.88 (3H, s, OCH₃); δ_{C} (75.45 MHz) 188.6, 165.9, 164.8, 158.1, 130.5, 127.9, 117.7 and 54.9.

5.6 General procedure for the preparation of **48**, **49**, **50**, **51**, **52** and **53**.

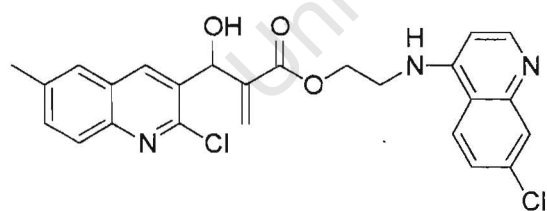
Arylaldehydes (1 equiv.), acrylic ester (3 equiv.) in DBU (1 equiv.) were stirred at room temperature for 16 hrs. The product mixture was purified by column chromatography.

Aldehydes used: 2-Methoxy-4-(3-methyl-but-2-enyloxy)-benzaldehyde, 2-Chloro-6-methyl-quinoline-3-carbaldehyde, 2,5-Dichloro-benzaldehyde, 2-Chloro-6-methoxy-quinoline-3-carbaldehyde, 4-Fluoro-3-nitro-benzaldehyde.



2-{Hydroxy-[2-methoxy-4-(3-methylbut-2-enyloxy)-phenyl]-methyl}-acrylic acid 2-(7-chloro-quinolin-4-ylamino)-ethyl ester. 51

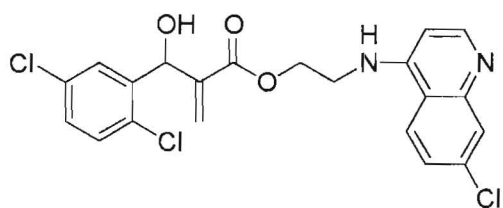
Yield (0.123g, 69%) brown oil; R_f 0.1 (1:9 MeOH: CH_2Cl_2); δ_{H} (300MHz, CDCl_3) 9.0 (1H, d, $J=2.7$, H-1), 8.7 (1H, s, H-8), 8.5 (2H, m, H-5 and H-6), 7.97 (1H, d, $J=2.6$, H-2), 7.81 (1H, m, Ar), 6.45 (2H, m, Ar), 6.11 (2H, s, $\text{C}=\text{CH}_2$), 5.45 (1H, m, CHOH), 5.25 (1H, d, $J=10.2$, $\text{CH}=\text{C}$), 4.60 (2H, t, $J=10.5$, CH_2O), 4.25 (2H, t, $J=9.4$, OCH_2), 4.12 (1H, t, $J=9.5$, NH), 3.63 (3H, s, OCH_3), 3.38 (2H, m, CH_2NH), 2.2 (1H, m, OH), 1.80 (6H, s, $\text{C}=(\text{CH}_3)_2$); δ_{C} (75.45 MHz) 165.5, 160.2, 158.4, 156.8, 148.8, 143.8, 138.6, 134.2, 128.5, 125.2, 123.0, 122.8, 122.4, 98.5, 68.8, 68.2, 65.4, 54.3, 26.2 and 20.0; HRMS (FAB) m/z 496.18 HR; $\text{C}_{27}\text{H}_{29}\text{ClN}_2\text{O}_5$ requires 496.98.



2-[(2-Chloro-6-methyl-quinolin-3-yl)-hydroxy-methyl]-acrylic acid 2-(7-chloro-quinolin-4-ylamino)-ethyl ester. 48

Yield (1.420g, 67%) as; δ_{H} (400MHz, CDCl_3) 8.48 (1H, d, $J=6.0$, H-1), 8.10 (2H, m, H-5 and H-8), 7.92 (1H, d, $J=6.2$, H-8), 7.88 (2H, m, H-5 and H-3), 7.43 (1H, d, $J=6.0$, H-7), 7.20 (1H, d, $J=6.1$, H-2), 6.20 (2H, s, $\text{C}=\text{CH}_2$, H-11), 5.29 (1H, m, CHOH , H-10), 4.22

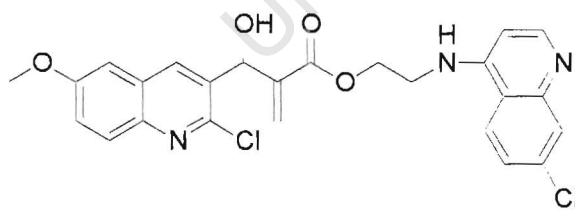
(2H, t, $J=10.2$, OCH_2), 4.20 (2H, q, $J=10.4$, CH_2NH), 4.0 (1H, m, NH), 2.54 (3H, s, CH_3), 2.0 (1H, s, OH); δ_{C} (75.45 MHz) 145.9, 143.2, 143.0, 138.4, 138.3, 138.0, 128.2, 128.0, 126.4, 126.3, 126.3, 123.8, 123.4, 123.0, 122.2, 121.4, 69.4, 55.6, 21.0; $\text{C}_{25}\text{H}_{21}\text{Cl}_2\text{N}_3\text{O}_3$ requires 482.36.



2-[(2,5-Dichloro-phenyl)-hydroxy-methyl]-

acrylic acid 2-(7-chloro-quinolin-4-ylamino)-ethyl ester. 50

Yield (2.501g, 82 %) as; δ_{H} (400MHz, CDCl_3) 8.60 (1H, d, $J=6.2$, H-1), 8.39 (1H, m, H-8), 8.28 (1H, d, $J=6.3$, H-5), 8.23 (1H, d, $J=6.1$, H-6), 8.18 (1H, d, $J=6.3$, H-2), 7.23 (3H, m, Ar), 6.11 (1H, s, $\text{C}=\text{CHH}$, H-11), 5.98 (1H, s, $\text{C}=\text{CHH}$, H-11), 5.70 (1H, d, $J=9.3$, CHOH , H-10), 4.11 (2H, t, $J=11.2$, OCH_2), 4.0 (1H, t, $J=11.7$, NH), 3.93 (2H, m, CH_2NH), 2.34 (1H, d, $J=9.4$, OH); δ_{C} (75.45 MHz) 165.5, 159.6, 156.8, 153.3, 148.7, 148.6, 147.9, 145.5, 140.6, 129.7, 129.6, 129.4, 125.1, 122.1, 120.6, 119.7, 118.6, 118.5, 71.6, 56.6; $\text{C}_{21}\text{H}_{17}\text{Cl}_3\text{N}_2\text{O}_3$ requires 451.73.

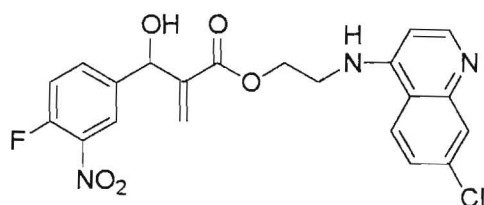


2-[(2-Chloro-6-methoxy-quinolin-3-yl)-

hydroxy-methyl]-acrylic acid 2-(7-chloro-quinolin-4-ylamino)-ethyl ester. 52

Yield (1.150g, 64%) as. R_f 0.25 (1:9 MeOH: CH_2Cl_2); δ_{H} (300MHz; CDCl_3) 8.98 (1H, d, $J=4.4$, H-1), 8.21 (1H, m, H-8), 7.73 (4H, m, H-8, H-5, H-5 and H-3), 7.45 (2H, m, H-7 and H-6), 7.33 (1H, d, $J=4.4$, H-2), 6.41 (2H, s, CH_2CH , H-11), 5.45 (1H, d, $J=11.4$,

CHOH, H-10), 4.4 (2H, m, OCH₂), 4.2 (2H, q, *J*=13.5, CH₂NH), 4.0 (1H, t, *J*=13.8, NH), 3.8 (3H, s, OCH₃), 2.0 (1H, d, *J*=11.1, OH); δ_C (75.45 MHz) 165.1, 159.0, 155.5, 150.1, 150.0, 149.8, 142.8, 136.4, 134.7, 131.4, 130.0, 128.5, 122.3, 121.8, 121.6, 68.6, 66.7, 54.7 and 54.0; HRMS (FAB) *m/z* 498; C₂₅H₂₁Cl₂N₃O₄ requires 498.36.

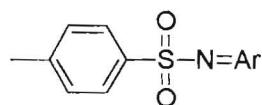


2-[(4-Fluoro-3-nitro-phenyl)-hydroxy-methyl]-

acrylic acid 2-(7-chloro-quinolin-4-ylamino)-ethyl ester. 49

Yield (2.43g, 92%) as; δ_H (400MHz; CDCl₃) 8.96 (1H, *J*=4.4, H-1), 8.18 (1H, m, H-8), 7.82 (1H, d, *J*=5.4, H-5), 7.80 (1H, t, *J*=5.6, H-6), 7.40 (1H, d, *J*=4.3, H-2), 7.45 (2H, m, Ar), 7.32 (1H, td, 0.4 and 9.1, Ar), 6.42 (2H, m, C=CH₂, H-11), 5.27 (1H, m, CHOH, H-10), 4.40 (2H, t, *J*=9.4, OCH₂), 4.0 (1H, m, NH), 3.6 (2H, q, *J*=9.7, CH₂NH), 2.16 (1H, m, OH); δ_C (75.45 MHz) 165.1, 152.2, 143.8, 141.6, 140.0, 131.5, 130.0, 129.9, 129.4, 129.3, 127.8, 127.6, 126.6, 124.6, 121.1, 106.3, 62.5, 58.4, 48.8, 29.8 and 21.7; C₂₁H₁₇ClFN₃O₅ requires 445.83.

5.7 Synthesis of sulphonyl amines 54 and 55

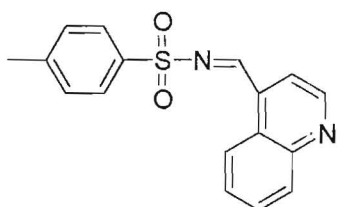


General procedure for the preparation of sulphonyl imines

Toluene-4-sulfonamide (3.8mmol) and 4-quinoline-carboxaldehyde (3.2mmol) were dissolved in MeOH (6.3ml). Acetic acid (0.5ml) was added and the reaction mixture was

stirred at 50-70 °C for 17 h. To the reaction mixture chloroform (~10ml) was added followed by water. The organic layer was separated and the solvent evaporated off.

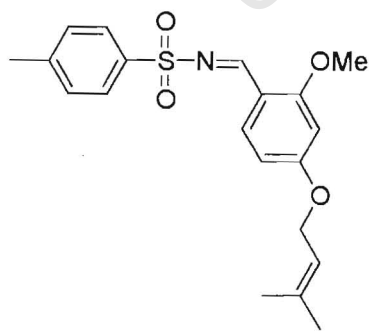
Aldehydes used: Quinoline-4-carboxaldehyde (0.130g, 0.76mmol) and 2-Methoxy-4-(3-methyl-but-2-enyloxy)-benzaldehyde (0.08g).



4-methyl-N-(quinolin-4-ylmethylene) benzenesulfonamide.

54

Sulfonamide product obtained as a brown solid (0.56g, 92%) as off-white crystals. IR ν_{\max} (CHCl₃) 2410, 1343, 1046 cm⁻¹; R_f 0.33 (3:7 EtOAc: Hexane); δ_H (400MHz, CDCl₃) 9.20 (1H, s, N=CH), 9.15 (1H, d, $J=7.4$, H-1), 9.09 (1H, d, $J=8.3$, H-8), 8.89 (1H, d, $J=6.4$, H-5), 8.65 (1H, m, H-7), 8.6 (1H, t, $J=8.5$, H-6), 8.22 (1H, d, $J=7.3$, H-2) 7.50 (2H, d, $J=6.0$, Ar), 7.34 (2H, d, $J=8.2$, Ar), 2.36 (3H, s, CH₃); δ_C (75.45MHz) 173.7, 160.1, 148.2, 138.4, 138.5, 130.2, 129.2, 128.5, 127.6, 126.4, 28.9; LRMS (EI) m/z 310.0; C₁₈H₁₅NO₂S requires 309.9; Calc. for C, 65.79; H, 4.55; N, 9.03; S, 10.33; Found 64.12, H, 5.04, N, 9.08.



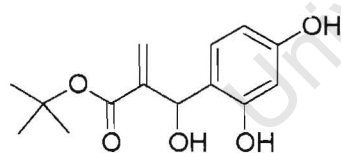
N-[2-Methoxy-4-(3-methyl-but-2-enyloxy)]-4-methyl-

benzenesulfonamide. 55

Yield (0.026g, 33%); R_f 0.32 (3:7 EtOAc: Hexane); δ_H (3.00MHz, $CDCl_3$) 8.21 (1H, s, N=CH), 7.82 (2H, dd, $J=9.4$ and 2.0), 7.33 (2H, t, $J=8.0$), 7.27 (1H, m), 6.46 (2H, m), 5.26 (1H, t, $J=11.6$, C=CH), 4.81 (2H, d, $J=11.8$, OCH₂), 3.88 (3H, s, OCH₃), 2.42 (3H, s, CH₃), 1.76 (6H, s, C(CH₃)₂); δ_C (75.45MHz) 188.3, 165.5, 163.6, 139.2, 130.7, 129.7, 129.6, 127.7, 126.5, 119.0, 106.3, 99.82, 98.68, 76.59, 65.20, 55.58, 21.48 and 18.22. LRMS (EI) m/z 373; C₂₀H₂₃NO₄S requires 373.47, C, 64.32; H, 6.21; N, 3.75; S, 8.59, Found C, 64.75, H, 6.66, N, 3.33.

5.8 General procedure for BH reaction

A mixture of Aldehyde (0.3mmol), *tert*-butyl acrylate/ methyl acrylate (0.66ml) and acetonitrile/ DCM/ isopropanol was stirred at room temperature in the presence of either **58**, **59**, **60**, **61**, DBU, DABCO or KF-Al₂O₃ as catalyst. The reaction was ended after the allotted time by filtering with dichloromethane. The crude product was purified by column chromatography using ethyl acetate and hexane as the eluting solvent yielding an ester.

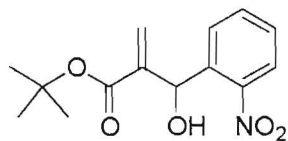


2-[(2,4-Dihydroxy-phenyl)-hydroxy-methyl]-acrylic acid

tert-butyl ester. 30

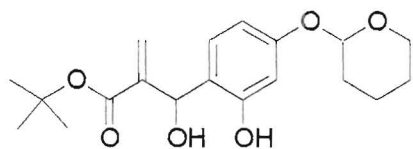
Yield (0.122g, 65%) as brown oil; R_f 0.35 (3: 7 EtOAc: Hexane); δ_H (200MHz; $CDCl_3$) 7.44 (1H, d, $J=2.4$, Ar), 6.53 (1H, m, Ar), 6.41 (1H, d, $J=2.3$, Ar), 6.39 (2H, s, C=CH₂, H-11), 5.20 (1H, d, $J=10.2$, CHOH, H-10), 4.90 (2H, s, 2OH), 2.40 (1H, d, $J=10.3$, OH),

1.48 (9H, s, OC(CH₃)); δ_C (75.45MHz) 167.0, 160.2, 158.5, 129.6, 129.5, 129.3, 129.0, 84.0, 66.2, 29.4; HRMS (EI) m/z 266; C₁₄H₁₈O₅ requires 266.29.



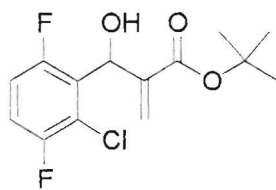
2-[Hydroxy-(2-nitro-phenyl)-methyl]-acrylic acid tert-butyl ester. 28

Yield (0.051g, 55%) as, R_f 0.35 (3: 7 EtOAC-Hex); IR ν_{max} 3452, 2932, 1709. 1528 cm⁻¹; δ_H (300MHz; CDCl₃) 8.31 (1H, m, Ar), 7.96 (2H, m, Ar), 7.55 (1H, m, Ar), 5.29 (2H, s, C=CH₂, H-11), 5.19 (1H, m, CHOH, H-10), 2.16 (1H, m, OH), 1.38 (9H, s, OC(CH₃)); δ_C (75.45MHz) 165.4, 147.2, 136.5, 133.6, 130.2, 129.5, 128.2, 128.0, 124.4, 73.7, 65.2 and 29.6; HRMS (EI) m/z 279.11 (M⁺); C₁₄H₁₇NO₅ requires 279.29.



2-{Hydroxy-[2-hydroxy-4-(tetrahydro-pyran-2-yloxy)-phenyl]-methyl}-acrylic acid tert-butyl ester. 32

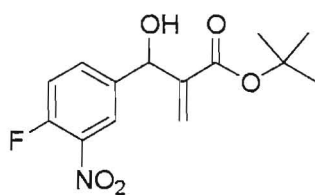
Yield (0.09g, 57%); R_f 0.36 (3:7 EtOAC-Hexane); δ_H (300MHz; CDCl₃) 7.45 (2H, m, Ar), 7.36 (1H, m, Ar), 6.67 (2H, m, C=CH, H-11), 5.10 (1H, s, Ar-OH), 4.96 (1H, d, $J=12.3$, CHOH, H-10), 3.60 (2H, t, $J=11.0$, OCH₂), 2.15 (1H, d, $J=12.7$, OH), 1.98 (1H, m, CH₂), 1.88 (4H, m, 2CH₂), 1.55 (9H, s, OC(CH₃)₃); δ_C (75.45MHz) 165.9, 160.2, 157.8, 145.6, 131.6, 127.6, 122.5, 117.4, 105.6, 79.3, 65.4, 30.1, 27.2, 21.2; 349; m/z C₁₉H₂₆O₆ requires 350.41.



2-[(2-Chloro-3,6-difluoro-phenyl)-hydroxy-methyl]-acrylic acid

tert-butyl ester. 37

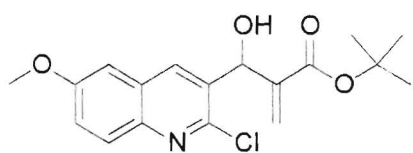
Yield (0.039g, 46%); R_f 0.38 (3:7 EtOAc-Hexane); δ_H (300MHz; $CDCl_3$) 7.25 (2H, m, Ar), 6.15 (1H, m, $C=CH_2$, H-11), 5.15 (1H, d, $J=14.8$, $CHOH$, H-10), 2.08 (1H, d, $J=14.6$, OH), 1.54 (9H, s, $OC(CH_3)_2$); δ_C (75.45MHz) 163.4, 160.1, 159.8, 148.2, 119.6, 118.7, 118.5, 63.4, 29.6; LRMS (EI) m/z 304 (M^+); $C_{14}H_{15}ClF_2O_3$ requires 304.7.



2-[(4-Fluoro-3-nitro-phenyl)-hydroxy-methyl]-acrylic acid

tert-butyl ester. 33

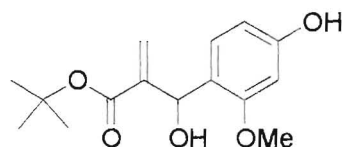
Yield (0.034g, 41%); R_f 0.25 (3:7 EtOAc: Hexane); δ_H (300MHz; $CDCl_3$) 8.60 (1H, m, Ar), 7.45 (2H, m, Ar), 6.20 (2H, m, $C=CH_2$, H-11), 5.46 (1H, d, $J=10.8$, $CHOH$, H-10), 2.14 (1H, d, $J=11.0$, OH), 1.45 (9H, s, $OC(CH_3)_3$); δ_C (75.45MHz) 187.9, 156.3, 137.8, 135.5, 135.4, 127.8, 124.7, 119.7, 74.4 and 29. LRMS (EI) m/z 297 (M^+); $C_{14}H_{16}FNO_5$ requires 297.28.



2-[(2-Chloro-6-methoxy-quinolin-3-yl)-hydroxy-

methyl]-acrylic acid tert-butyl ester. 40

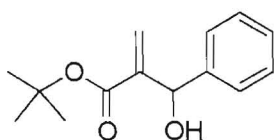
Yield (0.018g, 23 %); R_f 0.34 (3:7 EtOAc: Hexane); δ_H (300MHz; $CDCl_3$) 8.16 (1H, d, $J=1.3$, H-8), 7.87 (1H, m, H-5), 7.25 (1H, m, H-3) 7.15 (d, $J=1.2$, H-7), 6.65 (2H, s, C=CH₂, H-11), 5.45 (1H, d, $J=12.1$, CHOH, H-10), 3.92 (3H, s, OCH₃), 2.24 (1H, d, $J=12.3$, OH), 1.45 (9H, s, C(CH₃)₃); δ_C (75.45MHz) 165.6, 158.3, 143.0, 135.1, 134.8, 132.5, 129.6, 129.5, 128.4, 127.0, 123.1, 122.7, 105.2, 66.5, 62.5, 55.6, 49.8 and 29.67; HRMS (FAB m/z 350 (M^+); C₁₈H₂₀ClNO₄ requires 349.81; Calc. for C, 61.80; H, 5.76; Cl, 10.13; N, 4.00; Found C, 60.94; H, 5.45, N, 4.01.



2-[Hydroxy-(4-hydroxy-2-methoxy-phenyl)-methyl]-acrylic

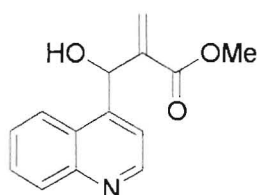
acid tert-butyl ester. 29

Yield (0.120g, 63%); R_f 0.25 (3:7 EtOAc: Hexane); δ_H (300MHz; $CDCl_3$) 7.70 (1H, m, Ar), 6.45 (2H, m, Ar), 5.90 (2H, m, C=CH₂, H-11), 5.19 (1H, d, $J=12.6$, CHOH, H-10), 3.84 (3H, s, OCH₃), 2.23 (1H, d, $J=12.8$, OH), 1.44 (9H, s, C(CH₃)₃); δ_C (75.45MHz) 165.4, 162.0, 154.8, 154.7, 154.2, 128.4, 128.0, 75.6, 63.4, 52.8 and 29; C₁₅H₂₀O₅ requires 280.32.



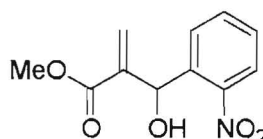
2-(Hydroxyphenyl-butyl)-acrylic acid tert-butyl ester. 31

Yield (0.11g, 53%) as off-white crystals; R_f 0.37 (3:7 EtOAc: Hexane); δ_H (200MHz; $CDCl_3$) 7.44 (5H, m, Ar), 6.01 (2H, s, $C=CH_2$, H-11), 5.44 (1H, m, $CHOH$, H-10), 2.22 (1H, m, OH), 1.48 (9H, s, $C(CH_3)_3$); δ_C (75.45MHz) 163.2, 150.9, 140.2, 128.9, 128.8, 128.7, 128.5, 122.4, 75.4, 72.1 and 29.0; LRMS (EI) m/z 220.1; $C_{14}H_{18}O_3$ requires 234.26.



2-(Hydroxy-quinolin-4-yl-methyl)-acrylic acid methyl ester. 20

Yield (0.021g, 50%) as brown oil; R_f 0.33 (3:7 EtOAc: Hexane); δ_H (300MHz, $CDCl_3$) 8.78 (1H, d, $J=2.4$, H-1), 8.56 (1H, d, $J=4.6$, H-8), 7.95 (1H, d, $J=4.8$, H-5), 7.88 (1H, m, H-7), 7.78 (1H, t, $J=4.5$, H-6), 7.56 (1H, d, $J=2.0$, H-2), 6.87 (2H, m, $C=CH_2$, H-11), 5.52 (1H, d, $J=13.2$, $CHOH$, H-10), 3.78 (3H, s, OCH_3), 2.56 (1H, d, $J=13.5$, OH); δ_C (75.45MHz) 166.0, 155.4, 154.3, 154.0, 136.7, 132.4, 132.0, 129.0, 128.6, 125.4, 123.2, 82.6 and 54.0; LRMS (EI) m/z 243; $C_{14}H_{13}NO_3$, requires 243.26.

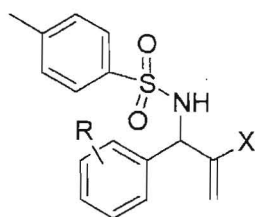


2-[Hydroxy-(2-nitro-phenyl)-methyl]-acrylic acid methyl ester

R_f 0.33 (3:7 EtOAc: Hexane); δ_H (300MHz, $CDCl_3$) 8.42 (1H, d, $J=4.5$, Ar), 7.82 (2H, m, Ar), 7.63 (1H, d, $J=4.2$, Ar), 5.58 (2H, s, $C=CH_2$, H-11), 5.10 (1H, m, $CHOH$, H-10),

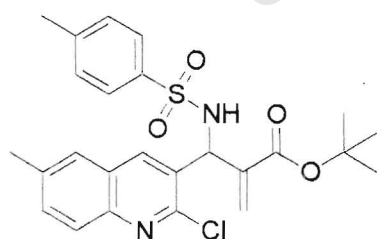
2.28 (1H, m, OH), 3.78 (3H, s, OCH₃); δ_c (75.45MHz) 164.7, 152.2, 150.3, 128.7, 128.3, 128.1, 128.0, 122.1, 72.5, 51.2.

5.9 Procedure for the preparation of compounds 32, 33, 50, 48, 49, 51 and 53.



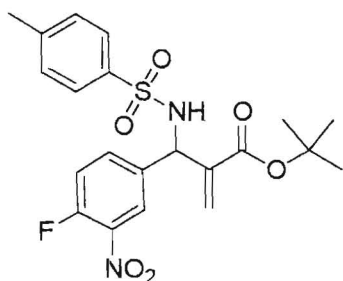
Method (a) for compound **50**: A mixture of *p*-toluenesulfonamide (0.76 mmol), aldehyde (0.64 mmol) in methanol and acetic acid was stirred at 65 °C for 17hrs giving a sulfonamide product, which after purification was reacted with *t*-Butyl acrylate in the presence of DABCO. The reaction mixture was stirred at room temperature for 16hrs. Purification by column chromatography.

Method (b) for compounds **42, 43, 44, 45, 46 and 47**: A mixture of sulfonamide, acrylate/ acrylonitrile in 2-propanol was stirred at room temperature for 16hrs yielding a substituted sulfonamide derivative. The purification was done by column chromatography.



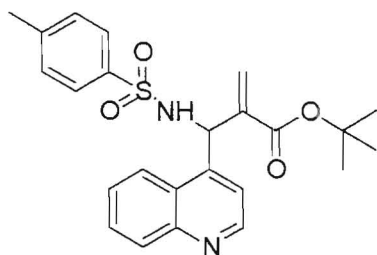
2-[(2-Chloro-6-methyl-quinolin-3-yl)-(toluene-4-sulfonylamino)-methyl]-acrylic acid tert-butyl ester. 44

Yield (0.755g, 66%) as off white oil; R_f 0.38 (3:7 EtOAc: Hexane); δ_H (300MHz; $CDCl_3$) 8.96 (1H, d, $J=4.8$, H-8), 8.17 (2H, m, H-3 and H-5), 7.80 (1H, d, $J=4.4$, H-7), 7.32 (2H, t, $J=4.4$, Ar), 7.27 (2H, d, $J=4.5$, Ar), 6.4 (2H, s, $C=CH_2$, H-11), 6.14 (1H, d, $J=12.3$, $CHNH$), 4.20 (1H, d, $J=12.0$, $NHCH$), 2.41 (6H, s, CH_3), 1.44 (9H, s, $C(CH_3)_3$); δ_C (75MHz) 165.7, 152.2, 150.3, 147.2, 143.5, 136.8, 131.5, 130.0, 127.7, 127.5, 126.5, 124.5, 124.2, 121.1, 77.1, 73.6, 62.4, 48.7, 29.6 and 21.6; HRMS (FAB) m/z 487 $C_{25}H_{27}ClN_2O_4S$ requires 487.04; Calc. for C, 60.40; H, 5.65; Cl, 6.86; N, 5.42; S, 6.20; Found C, 59.27; H, 5.56, N, 6.95.



2-[(4-Fluoro-3-nitro-phenyl)-(toluene-4-sulfonylamino)-methyl]-acrylic acid tert-butyl ester. 46

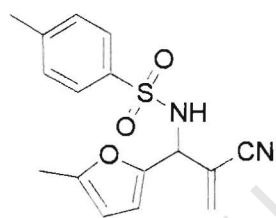
Yield (0.78g, 72%) as brown oil; R_f 0.22 (3:7 EtOAc: Hexane) δ_H (400MHz; $CDCl_3$) 8.01 (1H, d, $J=4.0$), 7.90 (2H, d, $J=4.2$), 7.80 (2H, d, $J=4.4$), 7.32 (2H, d, $J=4.1$), 6.42 (2H, s, $C=CH_2$), 5.27 (1H, m, $NHCH$), 2.43 (3H, s, CH_3), 2.16 (1H, m, NH), 1.60 (9H, s, $C(CH_3)_3$); δ_C (75.45MHz) 165.1, 152.2, 143.8, 141.6, 140.0, 131.5, 130.0, 129.9, 129.4, 129.3, 127.8, 127.6, 126.6, 124.6, 121.1, 106.3, 72.5, 48.8, 29.8 and 21.7; LRMS (FAB) m/z 450; $C_{22}H_{25}FN_2O_6S$ requires 450.13; Calc. for C, 54.99; H, 5.24; F, 3.95; N, 5.83; S, 6.67; Found C, 55.01; H, 5.34; N, 6.14.



2-[Quinolin-4-yl-(toluene-4-sulfonylamino)-methyl]-

acrylic acid tert-butyl ester. 42

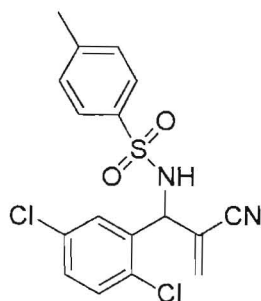
Yield (0.09g, 68%) as brown oil; R_f 0.33 (3:7 EtOAc: Hexane); δ_H (3.00MHz, $CDCl_3$) 8.98 (1H, d, $J=8.2$, H-1), 8.02 (1H, d, $J=4.0$, H-8), 7.86 (2H, m, Ar), 7.56 (1H, d, $J=4.0$, H-5), 7.46 (1H, m, H-7), 7.40 (1H, t, $J=4.2$, H-6), 7.22 (1H, d, $J=8.2$, H-2), 6.98 (2H, m, Ar), 6.01 (2H, s, $C=CH_2$, H-11), 5.6 (1H, d, $J=10.4$, NHCH), 2.48 (3H, s, CH_3), 2.12 (1H, d, $J=10.3$, NH), 1.45 (9H, s, $C(CH_3)_3$); δ_C (75.45MHz) 165.4, 158.2, 128.9, 128.7, 128.6, 128.5, 128.2, 122.7, 122.5, 122.0, 119.8, 119.4, 118.7, 84.2, 75.2, 48.1, 30.1, 20.8. LRMS (FAB) m/z 438; $C_{24}H_{26}N_2O_4S$ requires 438.16.



N-[1-(5-Chloro-furan-2-yl)-2-cyano-allyl]-4-methyl-

benzenesulfonamide. 45

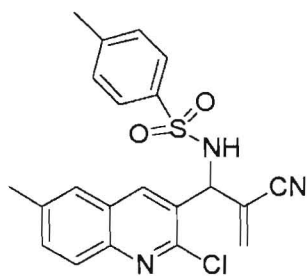
Yield (0.24, 48%) as yellow oil; R_f 0.32 (3:7 EtOAc: Hexane); δ_H (400MHz; $CDCl_3$) 7.82 (2H, d, $J=8.8$, Ar), 7.32 (2H, d, $J=8.6$, Ar), 6.2 (1H, s, $C=CH_2$), 6.0 (2H, m, fur), 4.82 (1H, m, NHCH), 2.42 (3H, s, Ar- CH_3), 2.16 (3H, s, fur- CH_3), 2.05 (1H, m, NH); δ_C (75.45MHz) 153.0, 143.7, 136.3, 130.4, 129.8, 126.5, 125.3, 109.1, 107.8, 60.1 and 21.6; LRMS (FAB) m/z 337; $C_{16}H_{16}ClN_2O_3S$ requires 336.79.



N-[2-Cyano-1-(2,5-dichloro-phenyl)-allyl]-4-methyl-

benzenesulfonamide. 47

Yield (0.23g, 63%) as white crystals; R_f 0.27 (3:7 EtOAc: Hexane); δ_H (400MHz; $CDCl_3$) 7.80 (2H, m), 7.43 (2H, m), 7.29 (1H, d, $J=7.5$), 7.09 (2H, d, $J=7.2$), 5.80 (2H, s, $C=CH_2$), 4.59 (1H, m, $NHCH$), 2.43 (3H, s, CH_3), 2.40 (1H, m, NH); δ_C (75.45MHz) 145.4, 144.4, 142.6, 135.7, 133.5, 132.7, 132.6, 129.8, 125.6, 120.2, 49.3, 21.3; LRMS (FAB) m/z 381 $C_{17}H_{14}Cl_2N_2O_2S$ requires 381.28



N-[1-(2-Chloro-6-methyl-quinolin-3-yl)-2-cyano-allyl]-4-

methyl-benzenesulfonamide. 43

Yield (0.529g, 53%) as white crystals; R_f 0.28 (3:7 EtOAc: Hexane); δ_H (400MHz; $CDCl_3$) 8.80 (1H, d, $J=8.0$, H-8), 8.78 (1H, m, H-5), 8.41 (1H, d, $J=8.2$, H-7), 8.32 (1H, m, H-3), 7.83 (2H, m, Ar), 7.64 (2H, m, Ar), 6.0 (2H, s, $C=CH_2$), 4.80 (1H, d, $J=13.5$, $NHCH$), 2.43 (9H, s, CH_3), 2.17 (1H, d, $J=13.4$, NH); δ_C (75.45 MHz) 156.7, 142.0, 140.8, 137.2, 135.4, 132.3, 131.6, 129.9, 129.7, 129.5, 123.4, 115.7, 41.2 and 21.4; LRMS (FAB) m/z 412 $C_{21}H_{18}ClN_2O_3S$ requires 411.91.

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