Synthesis and *in vitro* biological evaluation of 2,3-substituted quinoline derivatives

Thesis

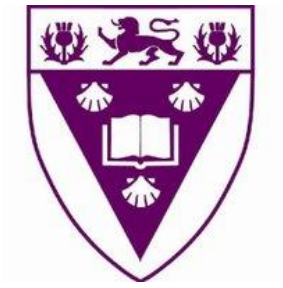
submitted in fulfilment of the

requirements for the degree of

Master of Science (Chemistry)

of

Rhodes University



by

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Abstract

The urgent need for new systemic pharmacological entities prompted us to report a library of 2,3-substituted quinoline derivatives. Considering the ubiquity of quinoline-containing compounds in pharmacologically active small molecules, synthesized 2,3-substituted quinoline derivatives were *in vitro* biologically evaluated for their potential antitubercular, antimalarial and antitrypanosomal activities.

Quinoline scaffold was achieved by the Vilsmeier-Haack methodology, affording synthetically useful chloro and formyl substituents on C-2 and C-3 respectively. These two substituents acted as handles in expanding the chemical space around the quinoline ring. Target compounds were synthesized in six to seven steps, employing conventional synthetic organic protocols adapted from various literature. The final compounds were accessed in moderate to good yields. The structural identity of each compound was confirmed by common spectroscopic techniques. Aryl quinoline carboxamide derivatives **3.113 – 3.126** were isolated as rotamers, hence, Variable-Temperature Nuclear Magnetic Resonance (VT-NMR) was employed in resolving ^{1}H splitting. At elevated temperature (~328 K); *N*-methylene carbons were not visible on ^{13}C NMR due to signal line broadening effects. The presence of these nuclei in such cases was, however, supported by 2-dimensional NMR and high-resolution MS data.

Most of the compounds achieved in this study displayed promising antimalarial activity against chloroquine-sensitive 3D7 strain of *Plasmodium falciparum* compared to antitrypanosomal activity against *Trypanosoma brucei brucei* 427 strain. In particular, compounds **3.80** and **3.108** showed superior activity against chloroquine-sensitive 3D7 *P. falciparum* strain with IC_{50} values < 1 µM. More importantly, most of the compounds were non-toxic as determined by HeLa cells, indicating their selectivity towards the parasites. Exploring the space provided on the quinoline scaffold revealed that methoxy incorporation on C-2 is very critical in

enhancing antimalarial activity of this class of quinoline compounds. The preliminary SAR of compounds **3.57 – 3.72** showed that compounds containing the 3-cinnamate exhibited enhanced antimalarial activity compared to 2 and 4-cinnamates. Finally, benzamide compounds **3.113 − 3.126** showed poor activity against *Mycobacterium tuberculosis* H37Rv strain with only compounds **3.113**, **3.117 – 3.120** and **3.126** showing appreciable MIC_{90} values in the range of 40 – 85 µM.

Dedication

Dedicated to my late mother, Teresa Bokosi

Acknowledgements

First and foremost, I would like to thank God for the life, strength, knowledge and opportunity that He accorded me to be able to pursue this research study.

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Table of Contents

List of abbreviations

AcOH	Acetic acid
Ac_2O	Acetic anhydride
AIDS	Acquired immunodeficiency syndrome
aq.	Aqueous
ATP	Adenosine triphosphate
bs	Broad singlet
^{13}C NMR	Carbon-13 Nuclear Magnetic Resonance
°C	Degrees Celsius
Calcd	Calculated
conc.	Concentrated
COSY	Correlation spectroscopy
CQ	Chloroquine
δ	Chemical Shift
d	Doublet
DCM	Dichloromethane
dt	Doublet of triplets
ddd	Doublet of doublet of doublets
DEPT-135	Distortionless Enhancement by Polarization Transfer-135
DMAP	*N*,*N*-Dimethylpyridin-4-amine

DMF	*N, N*-dimethyl formamide
DMSO	Dimethyl sulfoxide
eq	Equivalent
ESI	Electrospray Ionisation
EtOAc	Ethyl acetate
EtOH	Ethanol
g	Gram
h	Hour
HIV	Human immunodeficiency virus
^{1}H NMR	Hydrogen-1 Nuclear Magnetic Resonance
HMBC	Heteronuclear Multiple Bond Correlation
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear Single Quantum Correlation
HTS	High throughput screening
IC_{50}	50% Inhibitory Concentration
IC_{90}	90% Inhibitory Concentration
IR	Infra-red spectroscopy
J	Coupling constant
K	Kelvin
lit	Literature

m	Multiplet
Me	Methyl
MeOH	Methanol
mg	Milligram
MHz	Megahertz
MIC	Minimum inhibitory concentration
min	Minute
ml	Millilitre
mmol	Millimolar
mol	Moles
M.p.	Melting point
m/z	Mass-to-charge ratio
M^+	Molecular ion
nM	Nanomolar
NMR	Nuclear Magnetic Resonance
pLDH	Plasmodial lactate dehydrogenase
ppm	Parts per million
Py	Pyridinyl
r.t	Room temperature
s	Singlet

SAR	Structure-activity relationship
sat	Saturated
t	Triplet
td	Triplet of doublets
TB	Tuberculosis
TEA	Triethylamine
TLC	Thin layer chromatography
μg	Microgram
μL	Microlitre
μM	Micromolar
WHO	World Health Organization

Chapter One

Introduction and literature review

1.1. General overview: Tuberculosis

Tuberculosis (TB) is one of the oldest infectious diseases claiming scores of human lives worldwide. As detailed in the World Health Organization (WHO) annual Global Tuberculosis Report 2018, an estimated 10.0 million people developed TB disease[1]. Despite a decrease in global TB mortality, 1.6 million people died from TB in 2017[1]. Tuberculosis is caused by a type of bacterium called *Mycobacterium tuberculosis*, which is carried in airborne particles called droplet nuclei, of 1–5 microns in diameter which are transmitted when a person with untreated active TB releases them through coughing, sneezing, shout or sing[2] . Low-income and middle-income countries account for more than 95% of the active cases of TB in the world where its effects on health, the micro and macroeconomy and society itself are too large to estimate [1, 3, 4].

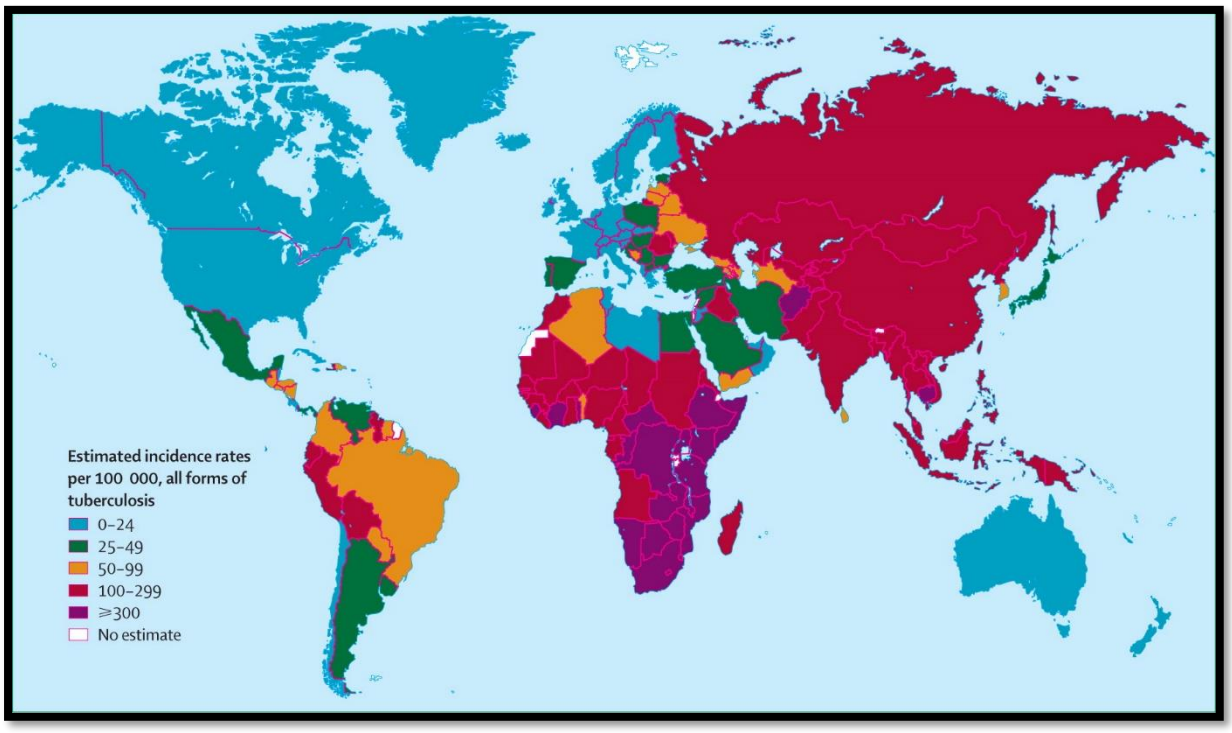


Figure 1.1: World distribution of tuberculosis[5]. Reproduced by permission.

1.1.1 Mycobacterial species

More than 20 mycobacterial species are known to cause disease in humans. *Mycobacterial* species includes *M. tuberculosis, M. bovis, M. bovis* BCG (the vaccine strain), *M. microti, M. africanum, M. caprae, M. canettii*, *M. pinnipedii*, *M. caprae, M. canettii* and *M. pinnipedii*[3, 6-8]. However, *M. tuberculosis* is by far the most important human pathogen[3].

1.1.2 Latent tuberculosis

Latent tuberculosis is a clinical state in which a person has immunologic evidence of TB but lacks symptoms and signs of the disease[9]. The *Mycobacteria* remain viable within the host, but the individual is asymptomatic and non-infectious. However, if the host's immune system is unable to contain the *Mycobacteria*, the organism will have an opportunity to progress to an active, symptomatic infection[10]. Hence, the risk of developing active TB following latent is dependent on many factors, especially the immunological status of the infected host[11]. In terms of diagnosis, there are two tests that are available for identification of latent tuberculosis infection namely; the tuberculin skin test (TST) and the interferon gamma (IFN-γ) release assay (IGRA). It has been shown that both TST and IGRA are acceptable but are imperfect tests[12, 13].

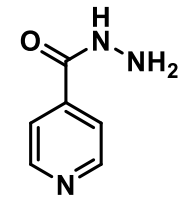
1.1.3 Tuberculosis vaccination

The only licensed vaccine against TB, Bacille Calmette-Guérin (BCG), was developed more than 100 years ago[14]. While BCG does confer consistent protection against disseminated disease[15], there is a clear need for a vaccine that is more effective than the BCG vaccine, in particular to reduce the risk of infection with *M. tuberculosis* and the risk of progression from infection to active TB disease in adults. There are nearly 12 TB vaccine candidates in various phases of clinical trials[1, 14, 16, 17]. An effective new TB vaccine would save millions of lives as the international community pushes progress towards ending the global TB epidemic by 2030

as part of the Sustainable Development Goals (SDGs)[14]. Although there is hope from these new candidates in the pipeline, it is unlikely that a new TB vaccine will be available in the immediate future[1].

1.1.4 Current tuberculosis chemotherapy

World Health Organization (WHO) recommended a standard chemotherapy of TB which include six-month regimen of four first-line anti TB-drugs that form the core of treatment[18] *viz*, isoniazid **1.10**, rifampicin **1.11**, pyrazinamide **1.12** and ethambutol **1.13**. Streptomycin **1.14** is also regarded as first line TB drug. The treatment comprises of a two month course of all four drugs followed by four months course of isoniazid and rifampicin[19]. This long course of duration often leads to poor patient adherence[20].



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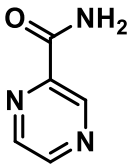

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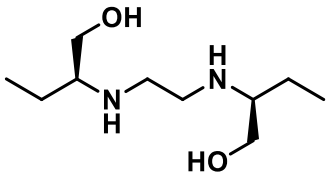

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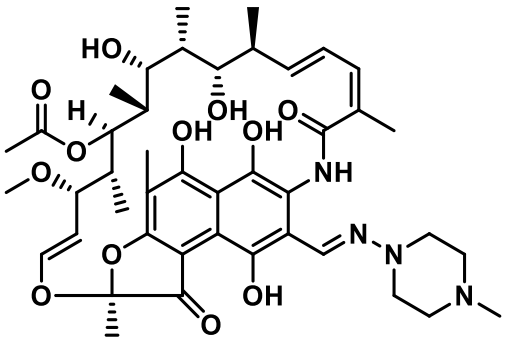

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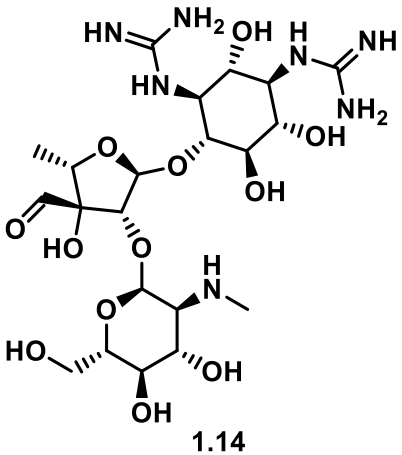

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1.1.5 Drug Resistance and Human Immunodeficiency Virus synergism

Despite the availability of these drugs, a significant challenge in the fight against TB is the emergence and rising cases of Multi-Drug Resistant TB (MDR-TB)[21]. Multidrug-resistant TB (MDR-TB) is defined as TB that is resistant to isoniazid and rifampicin. Globally, 160 684 cases of Multi-Drug-/Rifampicin- Resistant (MDR/RR) TB were detected in 2017 (a small increase from 153119 in 2016)[1]. Of these, a total of 139 114 people (87%) were enrolled on treatment with a second-line regimen, up from 129 689 in 2016[1]. Multi Drug Resistant-TB is much more difficult to treat than fully susceptible disease, requiring expensive second-line drugs for at least eighteen months compared with cheaper first-line drugs for only six months[22]. A few number of people with MDR-TB, develop extensively drug-resistant TB (XDR-TB). Extensively drug-resistant -TB is defined as MDR-TB with additional resistance to any fluoroquinolones and to at least one of three injectable agents (kanamycin, amikacin, or capreomycin)[23]. Drug resistance to *M. tuberculosis* results from spontaneous and random mutations in the bacterial chromosome that result in reduced susceptibility to specific agents[24]. More recently, a more worrying situation has emerged with the description of *M. tuberculosis* strains that have been found resistant to all antibiotics that are available for treatment, a situation labelled as totally drug resistant (TDR)-TB or extremely drug resistant (XXDR) in India and Iran[21, 25, 26]. Human Immunodeficiency Virus (HIV) co-infection is also contributing to large escalations in the incidence of TB in countries most heavily affected by Acquired Immuno Deficiency Syndrome (AIDS), notably sub-Saharan Africa[27]. Infection with HIV is the most powerful known risk factor predisposing for *M. tuberculosis* infection and progression to active disease, which increases the risk of latent TB reactivation 20-fold[28]. Thus, *M. tuberculosis* and HIV act in synergy, accelerating the decline of immunological functions[28,29]

1.2 General overview: Malaria

Malaria represents one of the notable causes of death worldwide, despite decades of strategic interventions aimed at reducing incidence and related mortality. The infectious disease has a predominant prevalence in the tropical and subtropical regions, mainly comprising the most significant proportion of disease burdened developing countries. According to the World Malaria Report 2018, around 219 million people were affected by malaria in 2017, with an estimated 435 000 deaths[30]. Over 80% of these deaths occur in sub-Saharan Africa, and children less than 5 years of age and pregnant women are the most vulnerable groups affected by malaria[30-32].

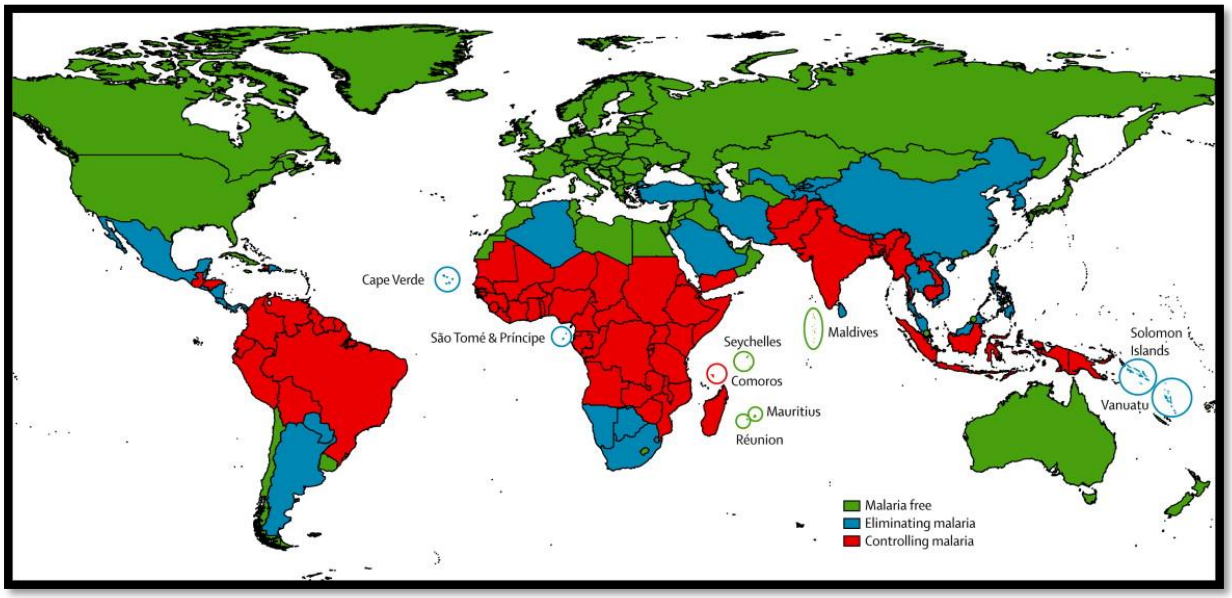


Figure 1.2: World distribution of Malaria[33].

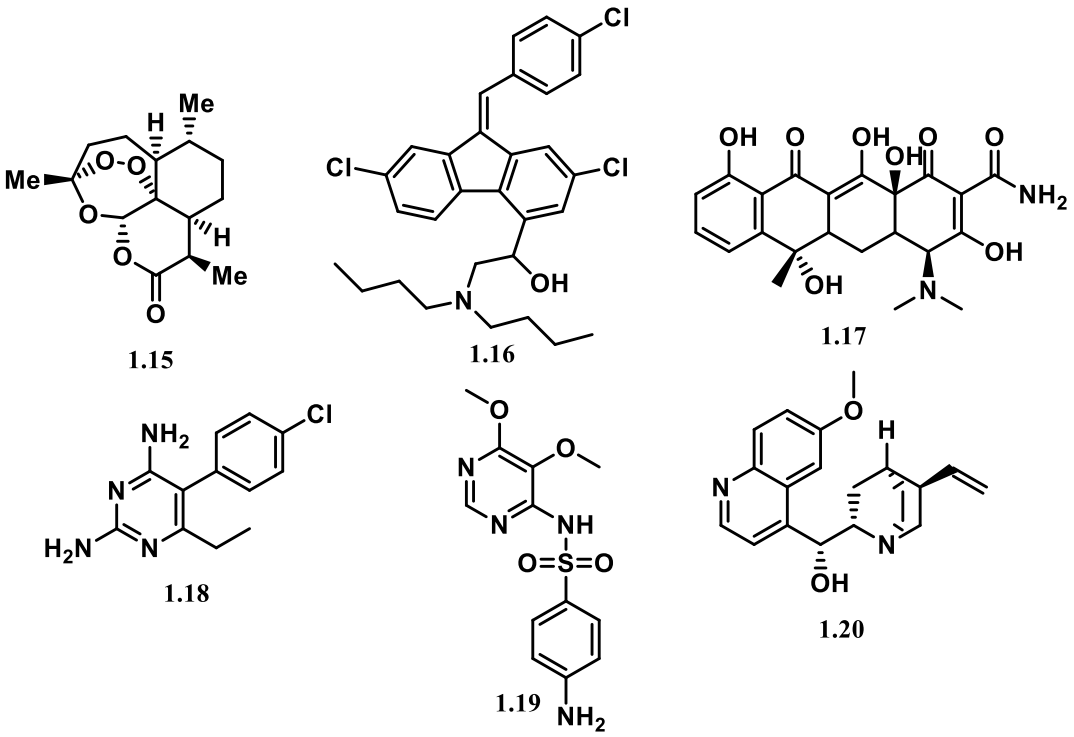
1.2.1 Malaria species

Malaria is caused by single-celled protozoan, *Plasmodium*, that enters the blood stream as a consequence of a bite by an infected mosquito (Anopheles). The four major species of *Plasmodium* traditionally recognized as responsible of human malaria include: *P. falciparum, P. malaria, P. ovale and P. vivax*. A plasmodium species of simian origin *P. knowlesi*, has also

been reported to be infectious to humans albeit with milder virulence[34, 35]. However, *P. falciparum* is responsible for the majority of malaria deaths globally and is the most documented species in sub-Saharan Africa.

1.2.2 Malaria Chemotherapy

To date, chemotherapy still remains an important tool in combating malaria infections in endemic sub-Saharan African region[36]. Representative examples of traditional antimalarial chemotherapeutics include artemisinin **1.15** and its derivatives, lumefantrine **1.16**, tetracycline **1.17**, Pyrimethamine **1.18**, sulfadoxine **1.19** and quinine **1.20**; an example of quinoline-containing antimalarial drugs.



1.15 1.16 1.17

1.18 1.19 1.20

1.2.3 Malaria Vaccination

Malaria vaccines have long been a research priority hence more than thirty *P. falciparum* malaria vaccine candidates are at either advanced preclinical or clinical stages of evaluation. However, Mosquirix™ (RTS,S/AS01), a malaria vaccine[37, 38], is the only prospect

recommended by WHO for pilot introduction in selected areas of three African countries in young children through routine immunization programmes beginning April 2019[39].

1.2.4 Malaria Drug Resistance

Plasmodium falciparum has developed resistance to nearly all the currently available antimalarial drugs. Hence, the use of two antimalarials simultaneously, especially when the antimalarials have different mechanisms of action, has shown potential for inhibiting the development of resistance to either of the components[40, 41]. This is evidenced in Artemisinin-based combination therapies (ACTs), deemed the best anti-malarial drugs available nowadays[42], however, the choice of ACT is based on the outcome of therapeutic efficacy studies against local strains of *P. falciparum* malaria[43].

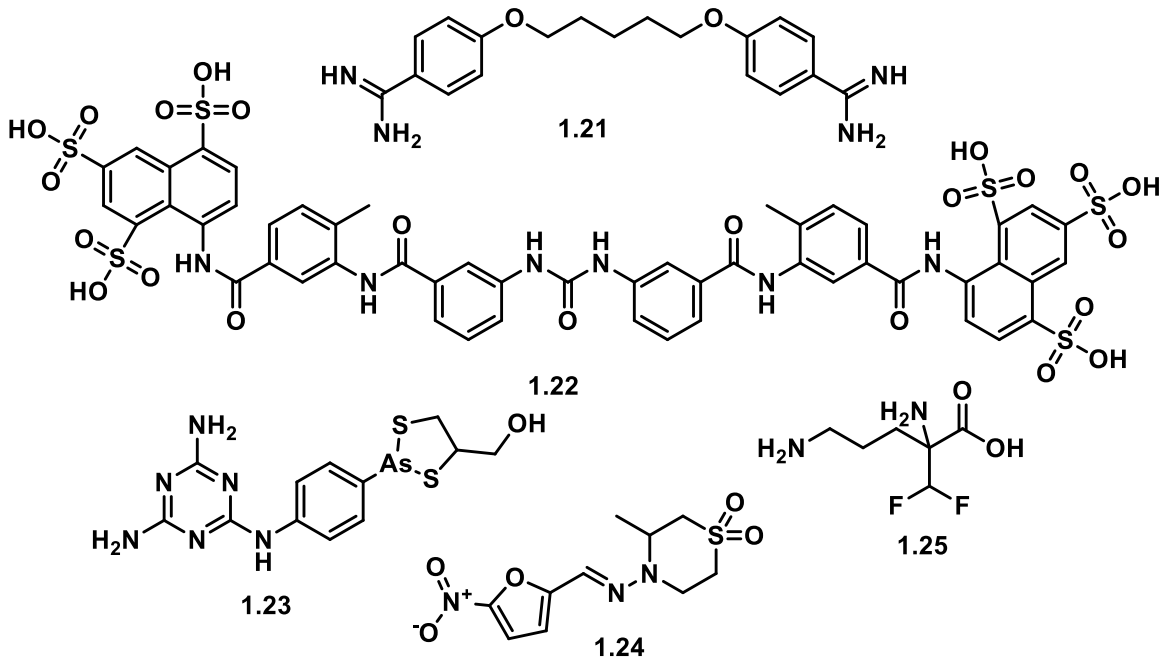
1.3 General overview: Human African Trypanosomiasis

Human African trypanosomiasis (HAT) or sleeping sickness is caused by infection of two trypanosome sub-species transmitted by tsetse flies, *Trypanosoma brucei (T.b) gambiense* in Western and Central Africa and the less common *Trypanosoma brucei.(T.b) rhodesiense*, most prevalent in the Eastern and Southern Africa[44, 45]. It is reported that *T.b. gambiense* causes more than 95% of all HAT cases[46]. Human African trypanosomiasis is endemic in 36 sub-Saharan Africa countries with about 80 million people at risk[47]. Approximately 1446 new cases were reported in 2017, which is the lowest level since the start of systematic global data-collection 80 years ago[48, 49]. Although far less people are affected by HAT, it is fatal if left untreated[50].

1.3.1 Human African trypanosomiasis chemotherapy

Human African trypanosomiasis chemotherapy has major disadvantages that limit more widespread use in the endemic regions of sub-Saharan Africa. For instance, Pentamidine **1.21**, and suramin **1.22** are limited by their effectiveness against the only first stage of *T. b. gambiense* and

T. b. rhodesiense, respectively[51]. Second stage drug; melarsoprol **1.23**, is toxic[51, 52] and has increasing treatment failures while Nifurtimox **1.24** - eflornithine **1.25** combination therapy (introduced in 2009) is expensive, laborious to administer, and lacks efficacy against *T. b. rhodesiense*[53]. Currently, there is no vaccine available for treatment of this disease[50, 54-56].



1.4 Rationale for searching for new drugs

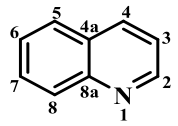
Despite impressive headway taken towards TB, malaria and HAT eradication, challenges are still innumerable. Currently, there are no approved vaccines for older age groups against these pathogens. Treatment success rates remain too low in the high-burden countries due to poor management and patient noncompliance among others[4]. The situation has been further exacerbated by the emergence and spread of drug-resistant parasites[57-60] which is curbing the effectiveness of the current drugs. Therefore, as one way to fight these pathogens, it is imperative for researchers to develop novel, fast acting and more efficacious antitubercular, antimalarial and antitrypanosomal agents, preferably, those compounds with new mechanisms of action to replace the existing regimens.

Chapter Two

Quinolines: Chemistry and their use in drug discovery

2.1 Quinolines: General introduction

Quinoline (**2.1a**) has a chemical formula of C_9H_7N and a molecular weight of 129.16. It is a weak tertiary heterocyclic base with log P value of 2.04, acidic pK_b of 4.85 and a basic pK_a of 9.5[61]. It is a hygroscopic, yellowish oily liquid, slightly soluble in water, soluble in alcohol, ether and many other organic solvents[62]. Structurally, it comprises a fused ring of benzene and pyridine, with the nitrogen atom next to the benzene ring. When nitrogen atom occupies the second position, it is called isoquinoline (**2.1b**).



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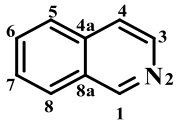


2.1b

Quinoline undergoes both electrophilic and nucleophilic substitution reactions. The pyridine ring in quinoline is electron deficient particularly on C-2 and C-4 which makes it susceptible to nucleophilic attack, whilst the hydrophobic benzene ring is susceptible to electrophilic attack, making quinoline a very interesting motif for various chemical modifications as shown by its canonical structures in **Figure 2.1**.

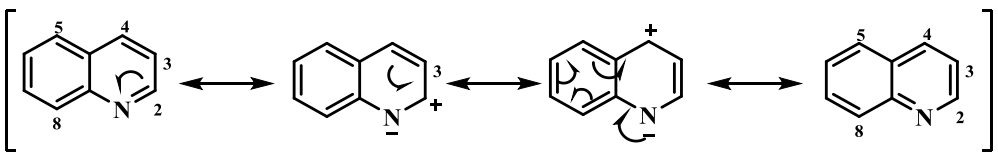


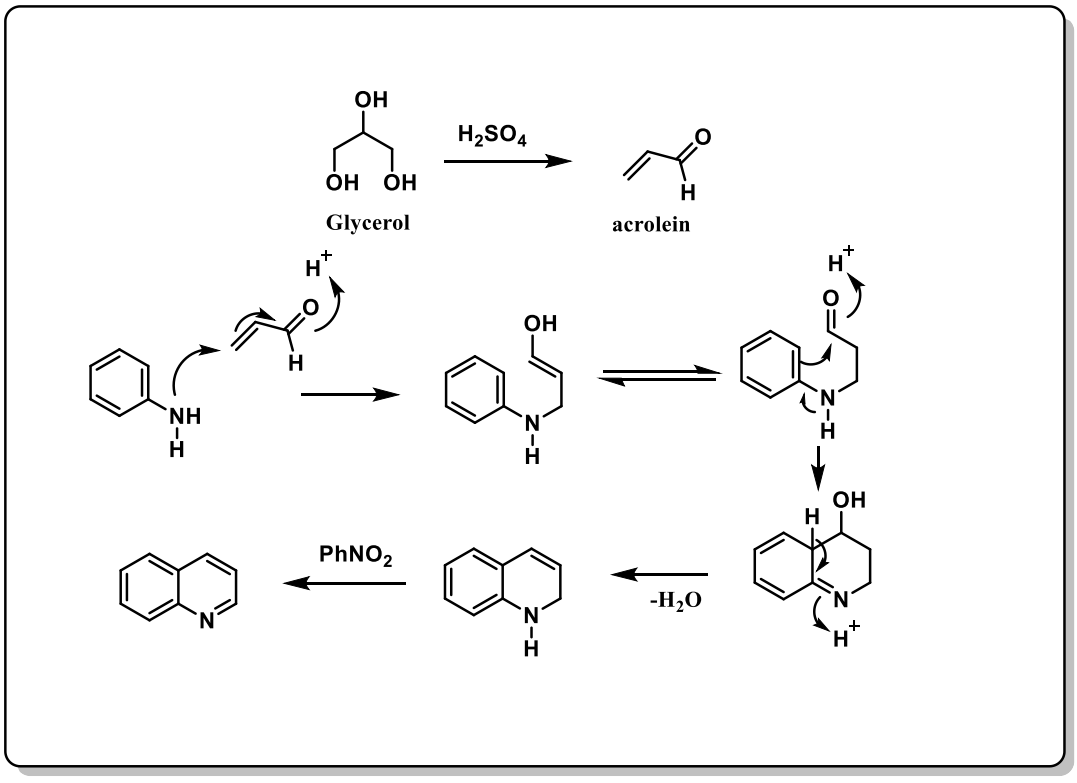
Figure 2.1 Canonical structures of quinoline.

2.2 Classical synthetic routes of quinolines

Quinoline structural motif is readily accessible through several classical synthetic routes[63]. Some of the well-known classical methods include Skraup synthesis, Doebner-Miller synthesis, Combes synthesis, Pfitzinger synthesis, Friedlander synthesis and Meth-Cohn synthesis. Harsh reaction conditions and poor yields associated with these synthetic approaches has led to modifications and slight alterations in the methods[64]. Below is a synopsis of these representative classical methods for synthesising quinoline and the corresponding compounds.

2.2.1 The Skraup synthetic method of quinolines[65]

This synthesis involves gently heating a mixture of anilines (with a free ortho position), glycerol, sulfuric acid and an oxidising agent (**Scheme 2.1**).

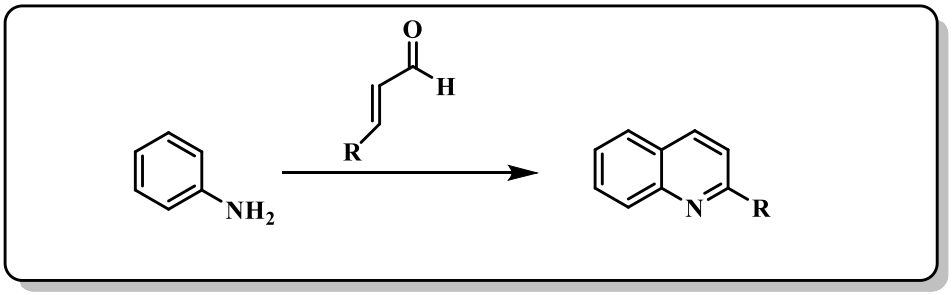


Scheme 2.1 Skraup quinoline synthesis.

The reaction is believed to proceed *via* acid-catalysed elimination of water molecules from glycerol to afford acrolein, followed by conjugate addition of acrolein to aniline to give the anilinopropanal intermediate. Acid-catalysed intramolecular electrophilic addition followed by protonation and dehydration give rise to the dihydroquinoline, which is further oxidized to the final product quinoline.

2.2.2 The Döebner-Miller synthetic method of quinolines[63]

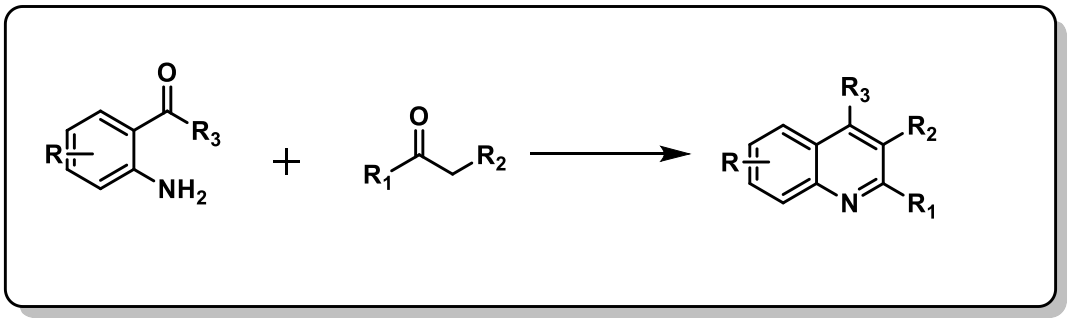
The Döebner-Von Miller synthetic method is similar to that of Skraup. In this synthesis, glycerol is replaced by two aldehyde molecules, which form α, β-unsaturated aldehyde by acid-catalyzed aldol condensation. The treatment of the α,β-unsaturated aldehyde with an aniline results in the formation of quinolines.



Scheme 2.2 Döebner-Miller quinoline synthesis.

2.2.3 The Friedländer synthetic method of quinolines[66]

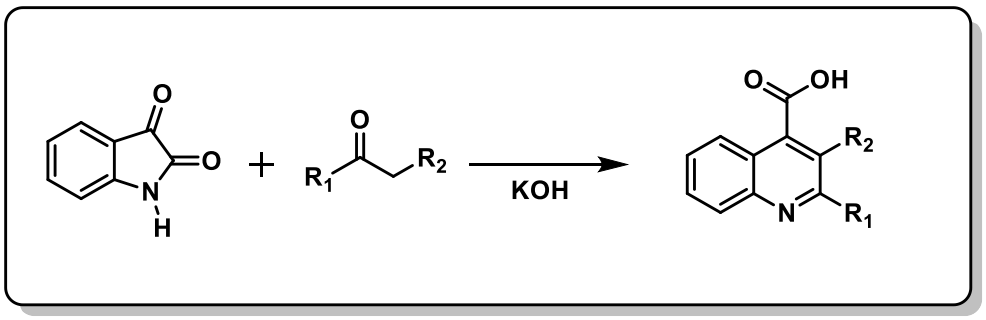
The Friedländer reaction is a base- or acid-promoted condensation of an aromatic 2-amino-substituted carbonyl compound (aldehyde, ketone, or an equivalent thereof) with an appropriately substituted ketone containing a reactive α-methylene group followed by cyclodehydration to produce a quinoline derivative (**Scheme 2.3**)**.** Friedländer annulations are generally carried out either by refluxing an aqueous or alcoholic solution of the reactants in the presence of a base or acid[66].



Scheme 2.3 Friedländer quinoline synthesis.

2.2.4 Pfitzinger synthetic method of quinolines[67]

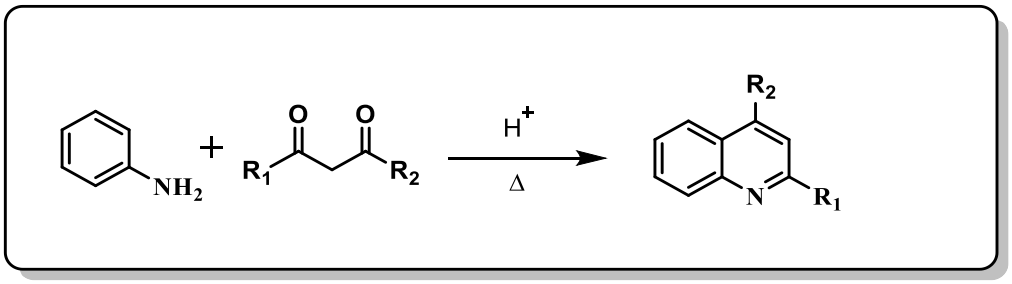
Pfitzinger reaction can be considered as an extension of the Friedländer synthesis as it uses an isatic acid or isatin under strong basic conditions such as sodium hydroxide or potassium hydroxide and an α-methylene ketone for condensation to form a 4-quinolinecarboxylic acid (**Scheme 2.4**).



Scheme 2.4 Pfitzinger quinoline synthesis.

2.2.5 Combes synthetic method of quinolines[68]

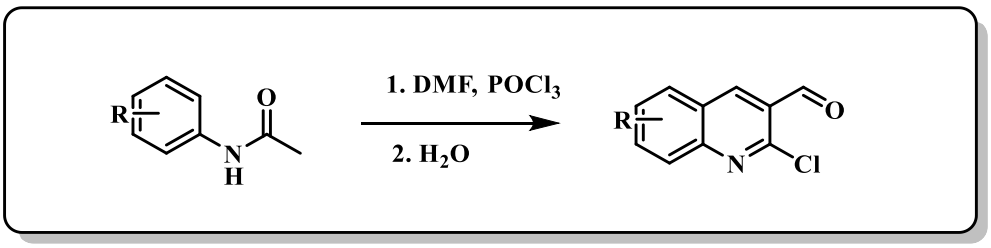
Combes synthesis is an acid catalysed condensation of anilines, which involves the nucleophilic addition of aniline to the carbonyl group of the β-diketones to form enamine intermediate followed by electrophilic aromatic annulations to yield the 2,4-substituted quinoline backbone.



Scheme 2.5 Combes quinoline synthesis.

2.2.6 Meth-Cohn synthetic method of quinolines[69]

This synthetic approach involves the conversion of acetanilides into 2-chloroquinoline-3-carbaldehydes using the Vilsmeier reagent, an iminium salt formed from the reaction of DMF with acid chlorides such as phosphorus oxychloride. This adduct is one of the most commonly used reagents for the introduction of an aldehydic group into aromatic compounds and olefins.



Scheme 2.6 Meth-Cohn quinoline synthesis.

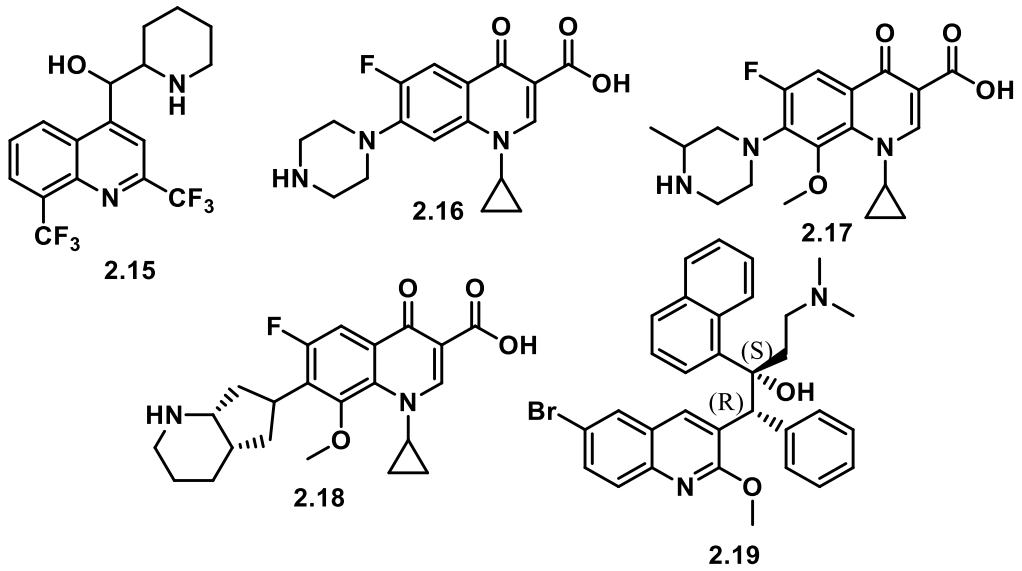
The chemistry of 2-chloroquinoline-3-carbaldehydes has received considerable attention recently, owing to their versatility due to the presence of chlorine on C-2 and formyl group on C-3 which act as handles in the construction of a variety of bioactive compounds[70-72]. The derivatives of 2-chloroquinoline-3-carbaldeydes have been reported to display a broad spectrum of pharmacological activities including antitubercular[29], antibacterial[73], antimalarial[74], antitrypanosomal[75], anticancer[76, 77], antifungal[78], and ant-HIV[79] activities. In this research study, we adopted this synthetic approach due to its high yields affordability and very

simplistic reaction work up. Below, we will discuss the diversity of 2,3-substituted quinolines in medicinal chemistry through a selection of examples which have been reported in literature.

2.3 Medicinal chemistry and biological activity of 2,3-substituted quinoline and quinolone containing compounds

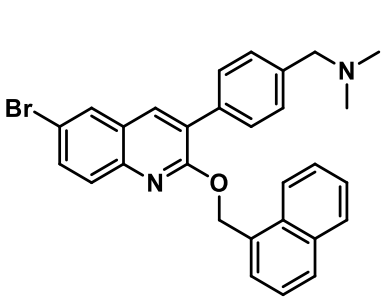
2.3.1 Antitubercular activity

The quinoline nucleus is an important unit in heterocyclic compounds found in many synthetic and natural products with antitubercular activity. Quinoline based mefloquine **2.15** is known for its antimalarial activity and its analogues have been shown to display sub-micromolar anti-TB activity[29, 80-84]. Fluoroquinolones, such as ciprofloxacin **2.16**, gatifloxacin **2.17** and moxifloxacin **2.18** are known promising agents for the treatment of TB though suffer from drug resistance[85].

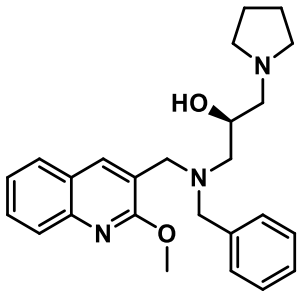


Bedaquiline (BQ), **2.19,** a lead compound of the diarylquinoline series, potently inhibits both drug-sensitive and drug resistant *M. tuberculosis in vitro* with minimum inhibitory concentration (MIC) value of 0.06 µg/mL[86]. It has a remarkably long elimination half-life in plasma due to a combination of prolonged plasma half-life, high tissue penetration and long

half-life in tissues[87]. The drug targets the proton pump of the adenosine triphosphate (ATP) synthase. Inhibition of this ATP synthase function leads to ATP depletion and imbalance in pH homeostasis, both contributing to decreased survival[88, 89]. However, there have been several cases of resistance to bedaquiline[90-92]. Efforts to improve the antitubercular activity of BQ through structural modifications and hybridisation have been extensive. In the quest for inhibitors active against *M. tuberculosis* H37Rv, He *et al.*[93, 94] synthesised a library of compounds with the aim of simplifying the chemical synthesis of bedaquiline and working towards new alternative leads. The high throughput screening (HTS) campaign led to the identification of compound **2.20**, which displayed potential *in vitro* antitubercular activity against *M. tuberculosis* H37Rv with an MIC_{90} value of 0.87 µM.



2.20



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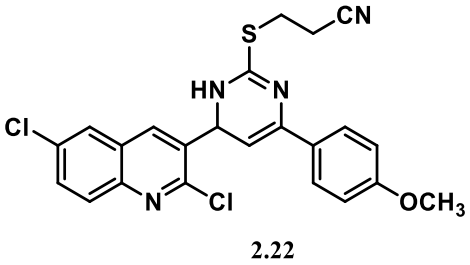
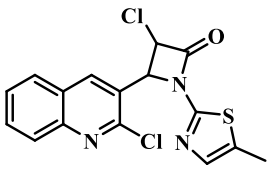


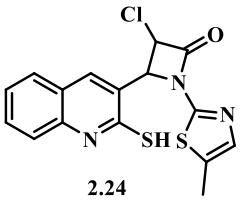
2.22

In an effort to identify new chemical entities, a novel series of arylquinoline derivatives were synthesised as potential anti-tubercular agents by Jain *et al.*[95]. In their study, crucial pharmacophoric features of bedaquiline and the three-dimensional geometry were retained. The synthesised compounds showed encouraging activities with IC_{50} values ranging from 5.18 − 138.5 µM with compound **2.21** emerging as the most active compound. Trivedi *et al.*[96] prepared a series of 3-((6-(2,6-dichloroquinolin-3-yl)-4-aryl-1,6-dihydro-pyrimidin-2-yl)thio)propanenitriles and evaluated their molecular properties prediction and drug-likeness model score by Molinspiration property calculation toolkit and MolSoft software, respectively. Compound **2.22** gave the maximum drug-likeness model score of 0.42. These compounds were

also screened for their *in vitro* antitubercular activity against *M. tuberculosis* H37Rv and compound **2.22** showed superior activity with MIC value of 0.20 μg/mL. Quinoline-based azetidinone and thiazolidinone analogues were prepared and screened against *M. tuberculosis* H37Rv by Mistry and Jauhari[97]. Preliminary *in vitro* antitubercular activity results indicated that compounds **2.23** – **2.26** were the most active against *M. tuberculosis* H37Rv strain.



2.23



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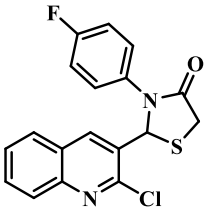
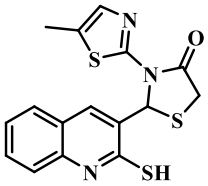
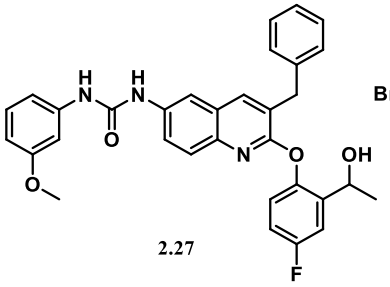


2.25

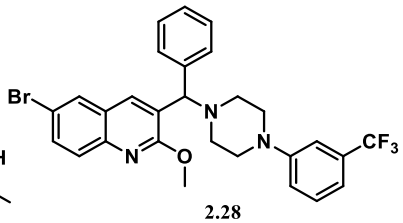


2.26

As part of an on-going SAR study around diarylquinoline class of compounds, Upadyayaya *et al*[98] synthesised derivatives of 3-benzyl-6-bromo-2-methoxy-quinolines and amides of 2-[(6-bromo-2-methoxy-quinolin-3-yl)-phenyl-methyl]-malonic acid monomethyl ester. It was found that the antitubercular activity of compounds **2.27** and **2.28** were comparable to the standard drug isoniazid.



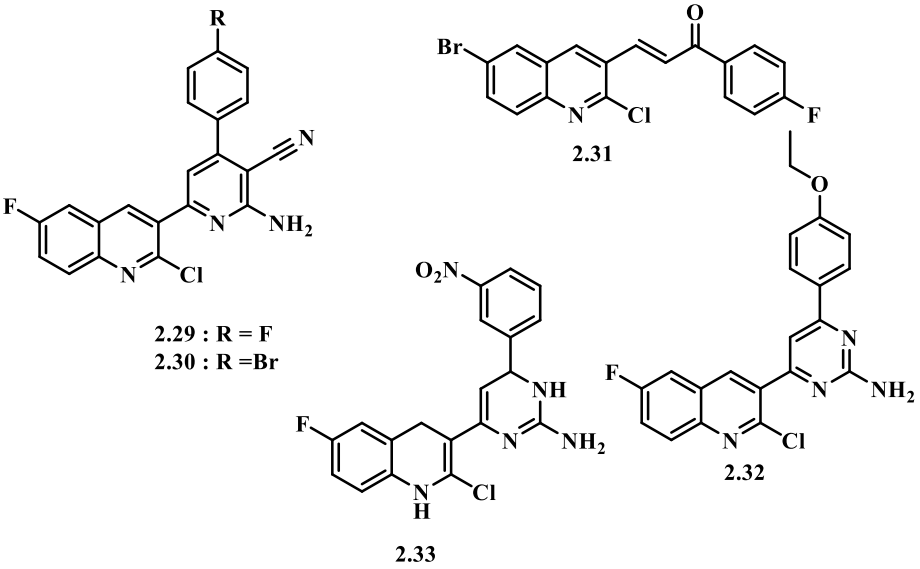
2.27



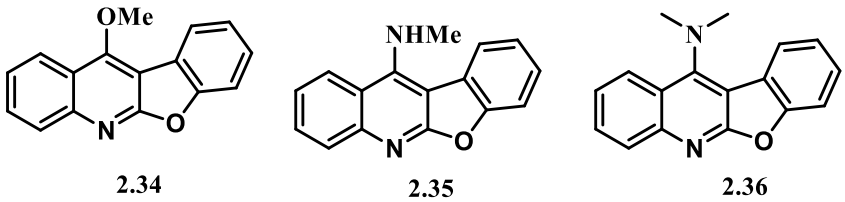
2.28

A series of substituted quinolinyl chalcones, quinolinyl pyrimidines and pyridines were synthesised and evaluated for their anti-TB activity *in vitro* against *M. tuberculosis* H37Rv by

Coutinho *et al.*[99]. Compounds **2.29** and **2.30** were found to be the most active of the series while analogues **2.31, 2.32** and **2.33** exhibited promising activity and inhibited the growth of *M. tuberculosis* by 99%, 97% and 99%, respectively, at a concentration of 6.25 μg/mL.



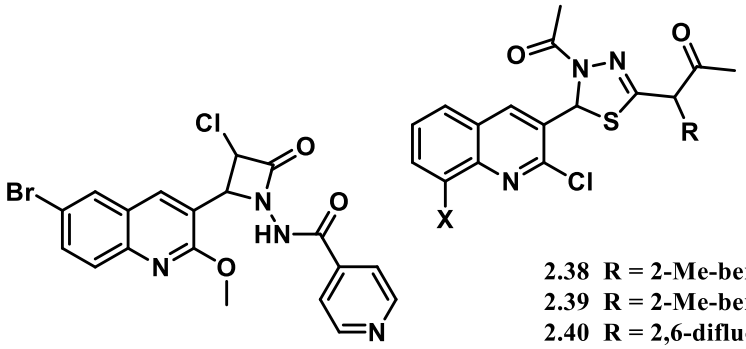
Early 2010, Yang *et. al.*[100] synthesised a library of compounds of benzofuro[2,3-*b*]quinoline derivatives as potential anti-TB agents with low cytotoxicity. Among the tested compounds, **2.34 – 2.36** were highly active against *M. tuberculosis* H37Rv strain with MIC values of < 0.20 μg/mL and very low cytotoxicity against Vero cell with IC_{50} values of > 30.0 μg/mL.



2.3.2 Antibacterial activity

The scourge of bacterial infections and rising cases of drug resistance against clinically approved drugs has prompted an urgent search for new chemical scaffolds. Recently, Joshi *et al.*[101] reported the synthesis of a new series of Schiff base and azetidinone derivatives of quinoline. In some derivatives, chlorine atom on the second position of quinoline scaffold was

replaced by the methoxy group, with the aim to establish the importance of methoxy substituent for biological activity. The synthesised analogues were evaluated for *in vitro* antibacterial activity against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli* and *Vibrio cholera*. Out of the compounds synthesised, compound **2.37** was found to be the most active against all the bacterial strains as compared to the standard drugs ciprofloxacin and norfloxacin used.



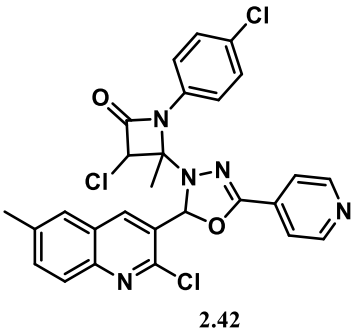
2.37

2.38 R = 2-Me-benzene X = Cl
2.39 R = 2-Me-benzene X = H
2.40 R = 2,6-difluorobenzene X = H
2.41 R = 4-Me-benzene X = H

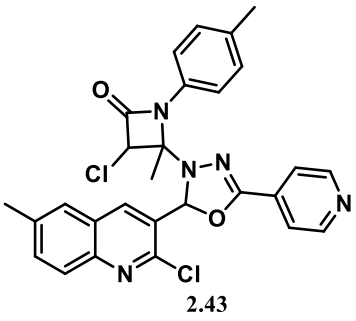
In an attempt to discover new antibacterial agents, Bhat *et al.*[102] developed a new class of 3-(1,3,4-thiadiazol-2-yl)quinoline derivatives. The antibacterial potential of the synthesised Maderivatives was evaluated using tube dilution technique against Gram negative (*Salmonella typhimurium* and *E. coli*) and Gram-positive (*Streptococcus pyogenes* and *S. aureus*) bacterial strains. Among the synthesized derivatives, compounds **2.38** and **2.39** exhibited good activity against *S. aureus* and compounds **2.40** and **2.41** were found to be most potent against *S. pyogenes*. The antibacterial activity results for these compounds were almost equal to the standard drug amoxicillin.

Endeavouring to find new pharmacologically active molecules, Desai *et al.*[103] synthesised a novel class of azetidinones. Synthesized compounds were screened for their *in vitro* antibacterial potential against *E. coli, P. aeruginosa, S. aureus, S. pyogenes, C. albicans, A. niger* and *A. clavatus* by broth dilution method. Among the series, 3-chloro-1-(4-chlorophenyl)-4-(2-(2-chloro-6-methylquinolin-3-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2*H*)-

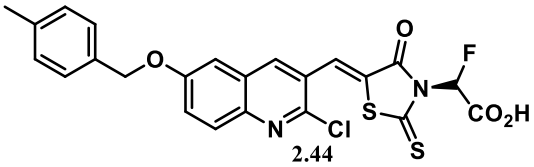
yl)-4-methylazetidin-2-one **2.42** and 3-chloro-4-(2-(2-chloro-6-methylquinolin-3-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2*H*)-yl)-4-methyl-1-*p*-tolylazetidin-2-one **2.43** showed excellent antibacterial activity comparable to a standard drug ampicillin.



2.42

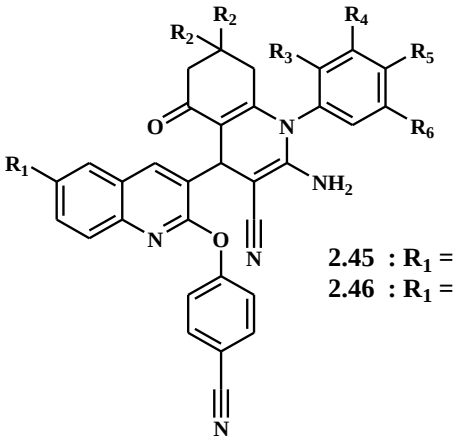


2.43



2.44

Guo *et al.*[104] synthesised a new series of quinoline derivatives, which were obtained from 6-hydroxy-3,4-dihydroquinolin-2(1*H*)-one treated by 1-(chloromethyl)-4-methylbenzene. These compounds were evaluated for their antimicrobial potential against *S. aureus* and *E. coli* bacterial strains. Among the tested compounds, compound **2.44** exhibited potential antibacterial activity comparable to standard drugs (norfloxacin, oxacillin, gatifloxacin, and moxifloxacin). Kathrotiya *et al.*[105] reported a novel set of *β*-aryloxyquinoline-based *N*-arylquinoline analogues and their *in vitro* antibacterial potential against Gram-positive; *B. subtilis, C. tetani, S. pneumonia* and Gram-negative bacterial; *E. coli, S. typhimurium, V. cholerae*.

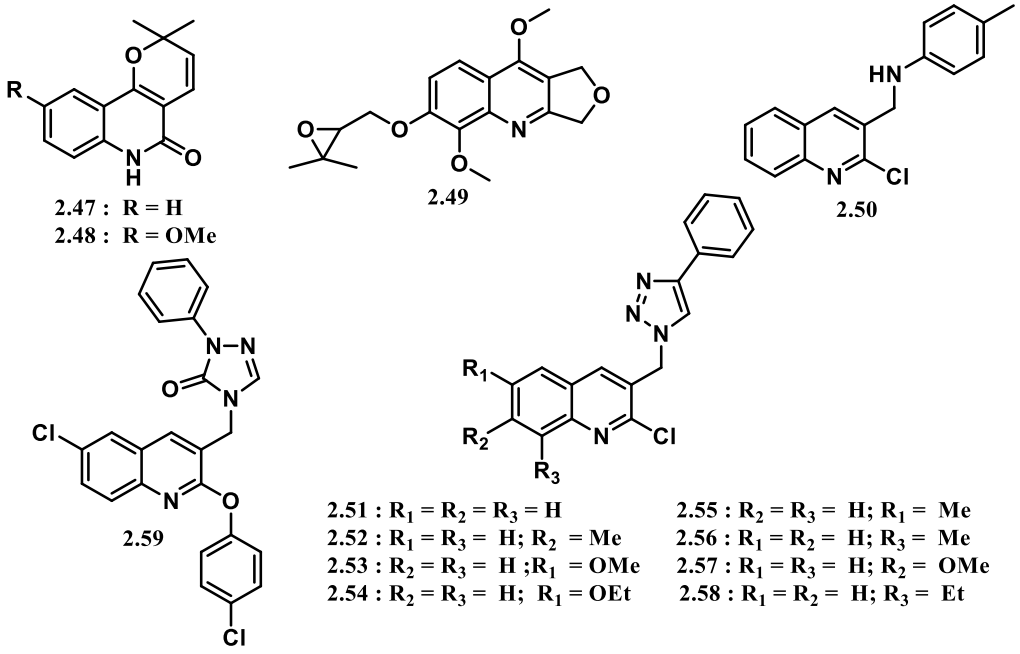


2.45 : R_1 = Cl, R_2 = H, R_3 = R_5 = R_6 = H, R_4 = H
2.46 : R_1 = CH_3, R_2 = CH_3, R_3 = R_5 = R_6 =F, R_4 = CF_3

Compounds **2.45** and **2.46** displayed highest antibacterial activity against gram negative bacteria in comparison with ampicillin, ciprofloxacin, norfloxacin, chloramphenicol, griseofulvin, and nystatin as reference drugs.

2.3.3 Antifungal activity

The spread of multidrug-resistant strains of fungi and the reduced number of drugs available have made it necessary to search for new classes of antifungal compounds that inhibit resistant mechanisms[106]. Cantrell *et al.*[107] isolated and identified alkaloids **2.47** – **2.49** from *Haplophyllum sieversii*, which showed remarkable *in vitro* antifungal activities against *Phomopsis. obscurans, Colletotrichum. gloeosporioides, Colletotrichum. fragariae, Colletotrichum acutatum* and *Fusarium. oxysporum*.

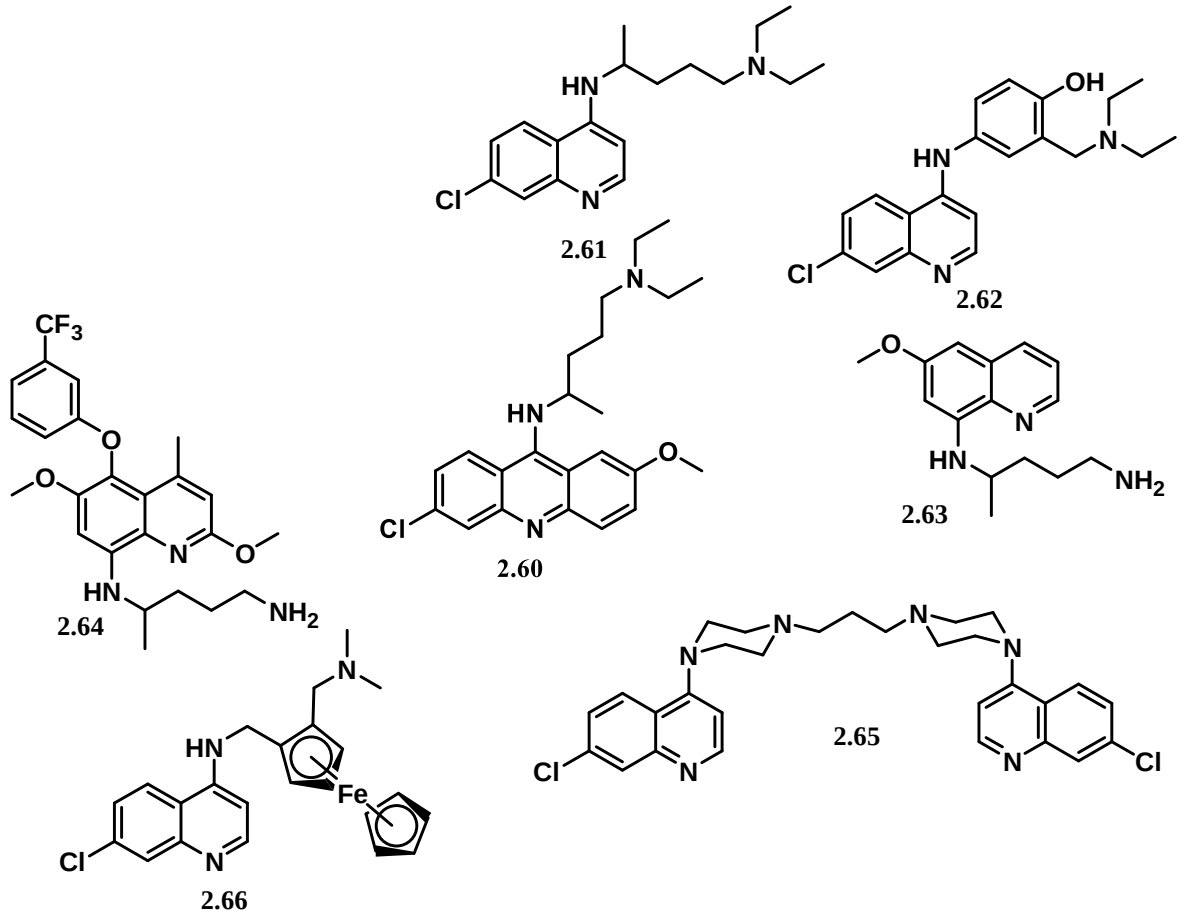


Kumar *et al*.[108] developed secondary amines containing 2-chloroquinoline and evaluated them for their *in vitro* antifungal activity against *Aspergillus. niger*, *Aspergillus. flavus*, *Monascus purpureus* and *Penicillium citrinum*. Of the synthesised compounds, **2.50** was more active against *A. niger* MTCC 281 and *A. flavus* MTCC 277 strains whereas less active against *M. purpureus* MTCC 369 and *P. citrinum* NCIM 768 strains. Kategaonka *et al*.[109] synthesised a library of new 2-chloro-3-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)quinoline derivatives and evaluated their antifungal activities. All the compounds **2.51 – 2.58** demonstrated potential inhibition against all the fungal strains tested. A screening campaign by Somagond *et al*.[94, 110] for fungicidal compounds resulted in the identification of **2.59**, quinoline containing a 1,2,4-triazole moiety which was very active against *A. fumigatus* and *C. albicans*.

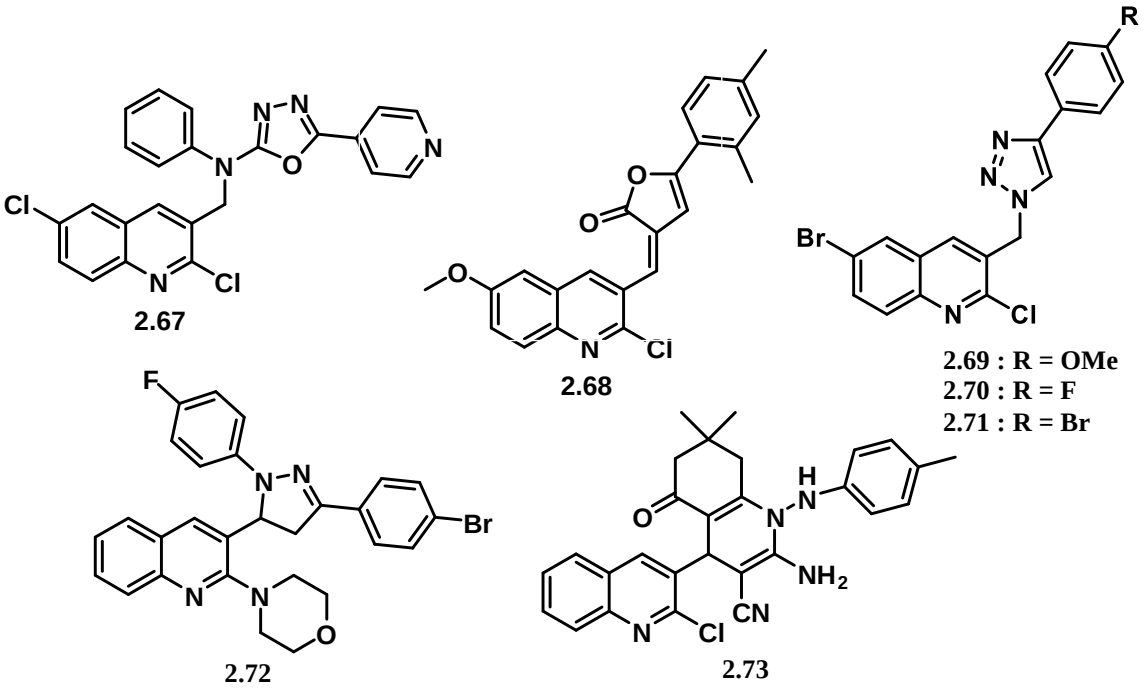
2.3.4 Antimalarial activity

Malaria remains one of the greatest health challenges confronting humankind, and the search for better drugs, both in terms of efficacy and cost, is a global health imperative. Historically, quinolines are by far the most important group of anti-malarials[111]. Quinoline-containing antimalarials, such as quinine **1.20**, mefloquine **2.15**, Quinacrine **2.60**, chloroquine **2.61**,

amodiaquine **2.62**, primaquine **2.63**, tafenoquine **2.64**, piperaquine **2.65** and ferroquine **2.66** have been mainstays of chemotherapy against malaria.

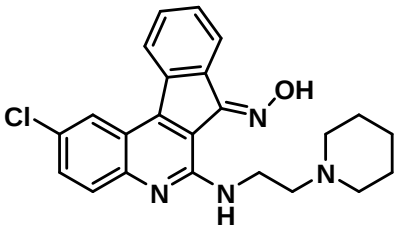


Although the number of fatalities due to malaria have been substantially reduced, the emergence of drug resistance to most of the available antimalarials poses a threat[112]. To overcome the drug resistance, numerous efforts have been undertaken to modify the launched antimalarials in an attempt to discover entirely novel structures[113]. In an effort to discover new antimalarial agents, Ladani *et al.*[114] synthesised a library of 2-chloroquinoline clubbed with 1,3,4-oxadiazole motifs. These compounds displayed excellent activity against the *P. falciparum* strain compared to quinine. Encouragingly, compound **2.67** was found to have a significant IC_{50} value of 0.089 μM against the *P. falciparum* chloroquine sensitive 3D7 strain.

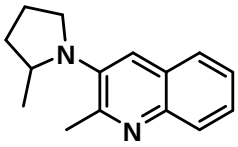


Recently, Akhter *et al.*[115] synthesised 3-[(2-chloroquinolin-3-yl) methylene]-5- phenylfuran-2(3*H*)-one derivatives and evaluated their antimalarial activity. The most potent of the tested compounds, **2.68**, showed an IC_{50} value of 0.50 µM against *P. falciparum.* The falcipain-2 was identified as potential target for these compounds by *in silico* studies. The docking studies of synthesised compounds on falcipain-2 revealed vital interactions and binding conformation. Parthasaradhi *et al.*[116] synthesised a series of novel 6-bromo-2-chloro-3- (4-phenyl-[1,2,3] triazol-1-ylmethyl)-quinoline and its derivatives. From the screened compounds, **2.69** had IC_{50} value of 5.09 µM, **2.70** IC_{50} value of 3.25µ M and **2.71** IC_{50} value of 2.13 µM against W2 strain of *P. falciparum*. Karad *et al.*[117] synthesised a series of novel morpholinoquinoline based conjugates with pyrazoline moiety under microwave reaction conditions and evaluated preliminary *in vitro* antimalarial activity against *P. falciparum*. The *in vitro* analysis revealed that compound **2.72** had a higher IC_{50} value of 0.015 µM as compared to chloroquine 0.062 µM. *N*-arylamino biquinoline derivatives were synthesised and evaluated for their antimalarial activity against chloroquine-sensitive (3D7) strain of *P. falciparum* by Patel and colleagues[118]. The compounds were evaluated in *vitro* for their activity against the inhibition growth of *P.*

falciparum. Some of them showed antimalarial activity with IC_{50} values as low as 0.005 – 0.009 μg/mL. The most active compound of the *N*-aryaminobiquinoline derivatives, **2.73** had superior antimalarial activity compared to chloroquine. Barteselli *et al*.[119] designed a new class of indenoquinoline compounds and evaluated their *in vitro* antiplasmodial activity against chloroquine-sensitive D10 and 3D7 strains and chloroquine-resistant W-2 strain of *P. falciparum*. Out of the synthesised derivatives, 2-chloro-6-(2-(piperidin-1-yl) ethylamino)-7*H*-indeno[2,1-*c*] quinolin-7-one oxime **2.74** showed potential antimalarial activity having low micromolar activity against *P. falciparum* strains and low resistance index compared to chloroquine as a standard. Vandekerckhove *et al*.[120] reported synthesis of a novel class of (hydroxyalkylamino)quinoline derivatives via cyclization of diallylaminoquinolines and 4-chloro-*N*-quinolinylbutanamides and their *in vitro* antiplasmodial potential against a chloroquine-sensitive strain of *P. falciparum* (NF54) and chloroquine-resistant strain of *P. falciparum* (Dd2) using parasite lactate dehydrogenase assay. Among the prepared derivatives, 2-methyl-3-(2-methylpyrrolidin-1-yl) quinoline **2.75** was found to be the most potent antimalarial agent, having low micromolar activity against NF54 and Dd2 strains of malaria parasite *P. falciparum* compared with artesunate as standard.



2.74

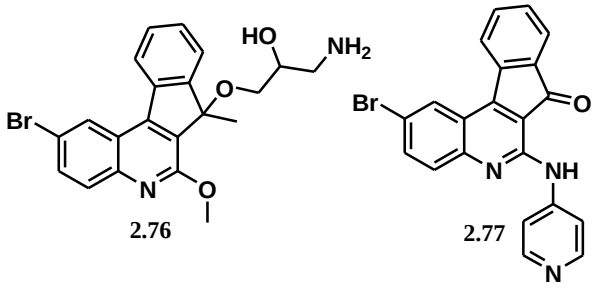


2.75

2.3.5 Antitrypanosomal activity

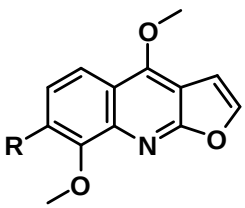
Despite recent advances in drug research, finding a safe, effective and easy to use chemotherapy for HAT remains a challenging task[51]. Inspired by quinoline scaffold,

Chattopadhyaya and co-workers[121] identified new lead compounds based indenoquinolines with variable side chains from their HTS as antiprotozoal agents. Compounds **2.76** and **2.77** represent those that inhibited very strongly *in vitro* the growth of the *T. cruzi* and *T. brucei* with IC_{50} value of < 0.25 μM. These compounds showed a superior activity compared to that of nifurtimox.

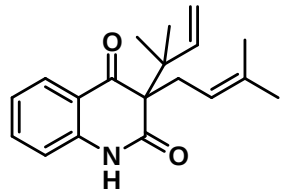


2.3.6 Anti-HIV activity

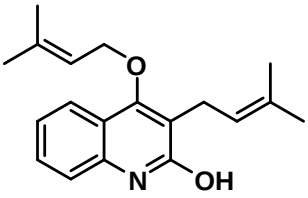
Natural products are an important source of new drug candidates[122]. γ-Fagarine **2.78** and haplopine **2.79** are furoquinoline class of alkaloids isolated from root bark of *Zanthoxylum ailanthoides*. γ-Fagarine has been reported to possess potent anti-HIV activity with EC_{50} and therapeutic index (TI) values of <0.44 μM and >231, respectively. Haplopine, which has a hydroxy (-OH) group at C-7 position, showed EC_{50} and TI values of 2.58 μM and 36.7, respectively[123]. The natural product compound **2.80** isolated from *H. tuberculatum* exhibit anti-HIV activity against HIV-1 in cultured human lymphoblastoid CEM-SS cells (EC_{50} 1.64 μM, IC_{50} 26.9 μM).



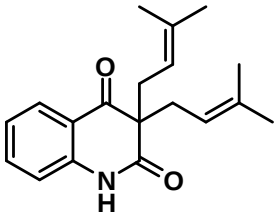
2.78 : R = H
2.79 : R = OH



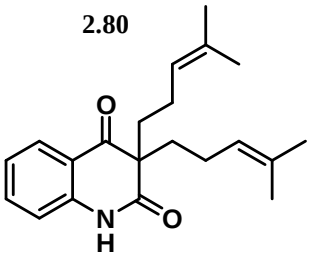
2.80



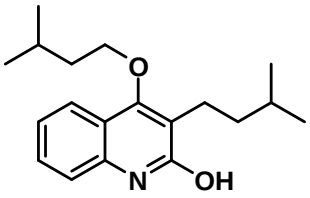
2.81



2.82

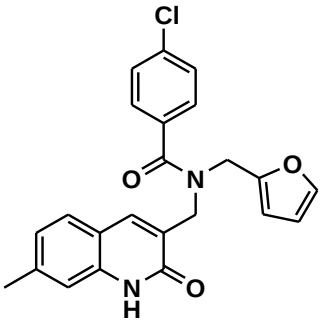


2.83



2.84

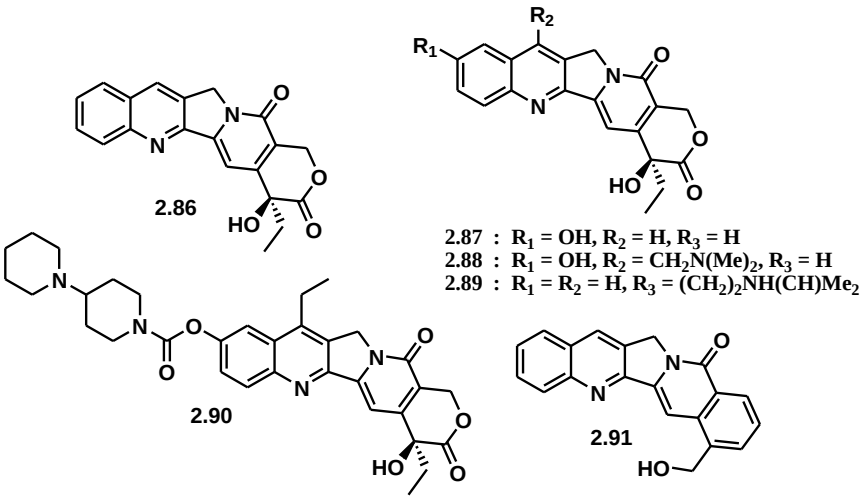
Motivated by natural products **2.80** and **2.81**, Bhutani and coworkers[124] reported synthesis of 47 alkylated derivatives of quinoline 2,4-diol and anti-HIV activity in human CD4+ T cell line CEM-GFP, infected with HIV-1 NL4-3. Compounds **2.82** – **2.84** were the most active with IC_{50} values in the range of 2.35 – 3.89 μM. Compound **2.82** was found to be more potent than lead molecule **2.80**. Inspired by the broad biological activity of quinolines, Debnath and co-workers[125] identified benzo-fused benzamidazoles and 3-(amidomethyl)-2-quinolones as anti-HIV agents. Synthesised compounds were designed specifically to bind to the *C*-terminal domain of the HIV-1 capsid. Of the synthesised compounds, **2.85** was identified as the most active compound with IC_{50} value of 1.06 μM.



2.85

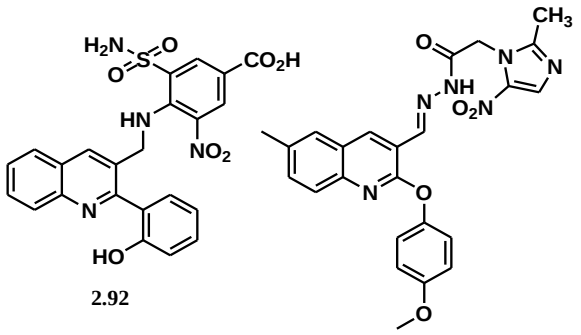
2.3.7 Anticancer activity

Quinoline derivatives fused with various heterocycles have displayed potent anticancer activity targeting different sites like topoisomerase I, telomerase, farnasyl transferase Src tyrosine kinase, protein kinase CK-II etc[126-129]. Camptothecin **2.86** extracted from Chinese plant, bark and stem of *Camptotheca acuminate* as a natural alkaloid inhibits the growth of tumor cells[130] although the use of camptothecin systemically is very limited due to its significant toxicity[131]. Camptothecin has been a target by many research groups due to its impressive biological activity. Topotecan **2.87**, belotecan **2.88** and irinotecan **2.89**, synthetic analogues of **2.86** have showed potency as antitumor agents[71, 132-134]. Compounds **2.90** and **2.91** are synthetic antitumor agents motivated by natural product **2.86**[135].



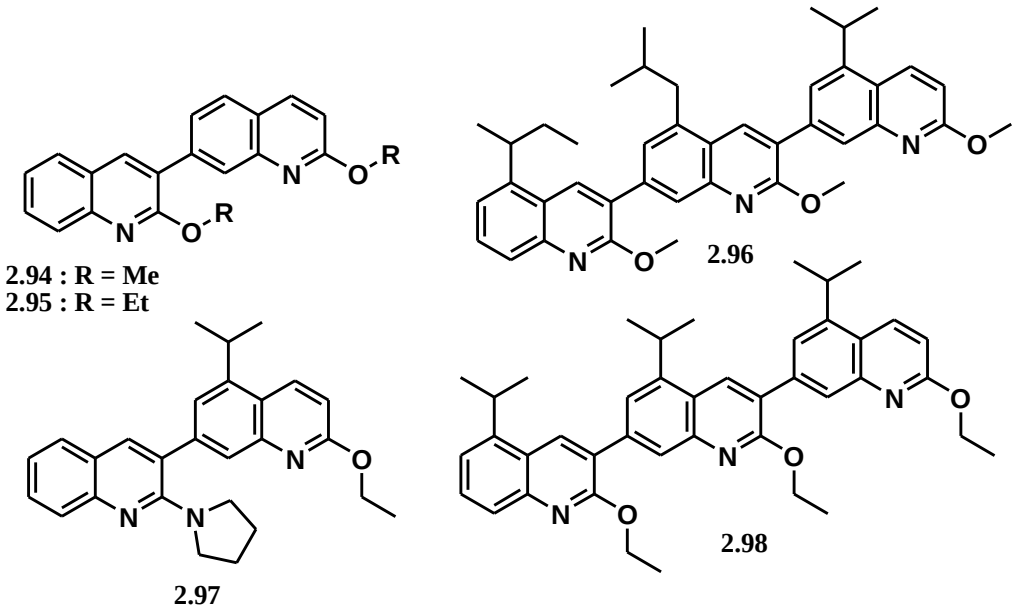
Mulakayala *et al.*[136] synthesised 6*H*-1-benzopyrano[4,3-*b*] quinolin-6-ones derivatives. These compounds were evaluated for their antiproliferative properties *in vitro* against four cancer cell lines; human chronic myeloid leukemia cells (K562), human colon carcinoma cells (Colo-205), breast cancer cells (MDA-MB 231) and human neuroblastoma cells (IMR32). Compound **2.92** showed 61% inhibition at 10 mM concentration indicating intrinsic anticancer properties of this compound. Makawana *et al.*[137] reported compound **2.93**, which showed effective

antiproliferative activity with an IC_{50} value of 0.12 ± 0.05 μM as epidermal growth factor receptor (EGFR) inhibitor.



2.92 **2.93**

Broch *et al*.[138] described the synthesis of di- and trimeric quinoline derivatives as well as their *in vitro* antiproliferative activities toward a human fibroblast primary culture and two human solid cancer cell lines (MCF-7 and PA1). All the synthesized compounds **2.94 – 2.98** were slightly active toward PA 1 and MCF-7 cell lines.



2.94 : R = Me
2.95 : R = Et

2.96

2.97

2.98

2.4 Aim and objectives

Aim:

The present study seeks to investigate the structure-activity relationships (SARs) of 2,3-substituted quinoline as a template for the preparation of novel potential antitubercular, antimalarial and antitrypanosomal agents.

Objectives:

- The synthesis and full characterisation of envisaged 2,3-substituted quinoline based derivatives as bioactive small molecules.
- *In vitro* preliminary pharmacological evaluation of 2,3-substituted quinoline based derivatives for activity against H37Rv strain of *M. tuberculosis*, 3D7 strain of *P. falciparum* and nagana *T. b. brucei* 427 strain.

Chapter Three

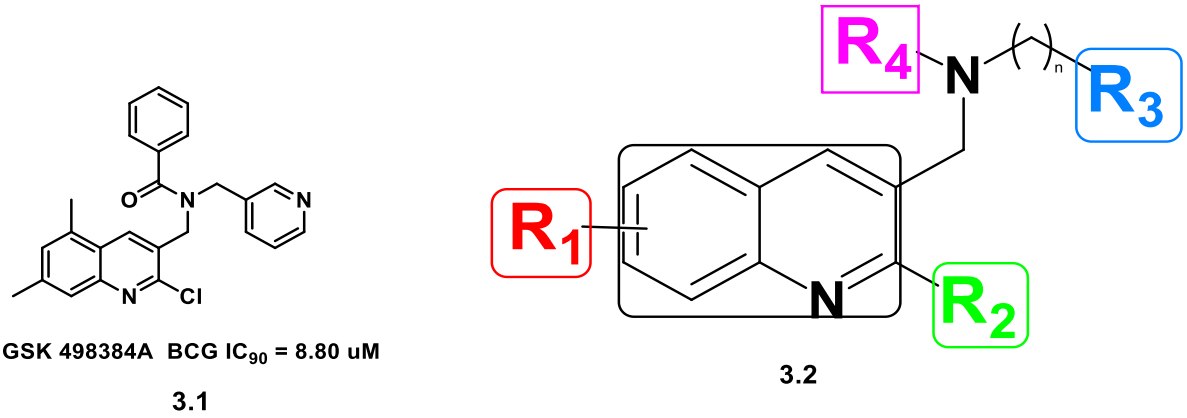
Synthesis and characterisation of 2,3-substituted quinoline derivatives

3.1 Introduction

This chapter describes the synthesis and characterisation of novel series of quinoline based compounds as antitubercular, antimalarial and antitrypanosomal agents. Two routes were developed to access final desired compounds using simple and cheap conventional synthetic methods. Final target compounds were fully characterised using common analytical techniques such as IR, NMR, MS and M.p.

3.2 Rationale for the synthesis of 2,3-substituted quinoline derivatives

In an effort to find new antimalarial drugs, in 2010 GlaxoSmithKline (GSK)[139] together with others[140, 141] published >10 000 compounds as starting points to rapidly identify promising compounds to be converted into antimalarial and antitubercular drugs. The released datasets served to encourage participations in lead-generation activities. In this study, we intended to expand the SAR of compound **3.1**[142] (**Figure 3.1**) in an effort to develop novel quinoline-based compounds with envisaged antitubercular, antimalarial and antitrypanosomal activity. Thus, the proposed project focused on the synthesis of small molecules (**3.2**) containing a quinoline framework with beneficial biological effects.



GSK 498384A BCG IC_{90} = 8.80 uM

3.1

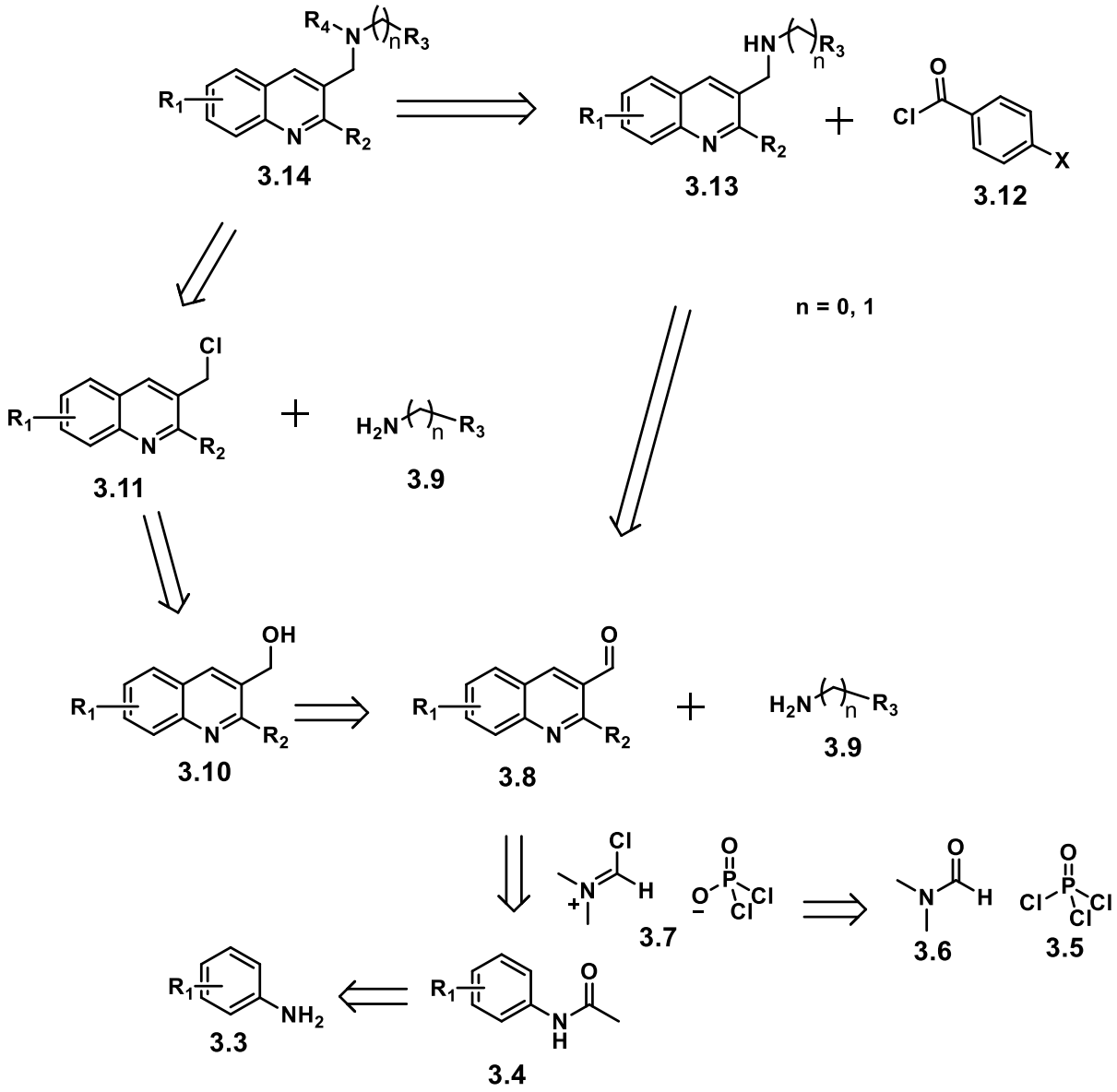
3.2

Figure 3.1: Proposed chemical modifications of GSK 498384A (**3.1**) as part of a wider SAR as depicted in **3.2**. It encapsulates the blueprint design of target compounds bearing quinoline scaffold highlighted in black rectangle. R_1, R_2, R_3 and R_4 represent the proposed regions for structural alterations.

3.3 Results and discussions

3.3.1 Retrosynthetic analysis of target compounds

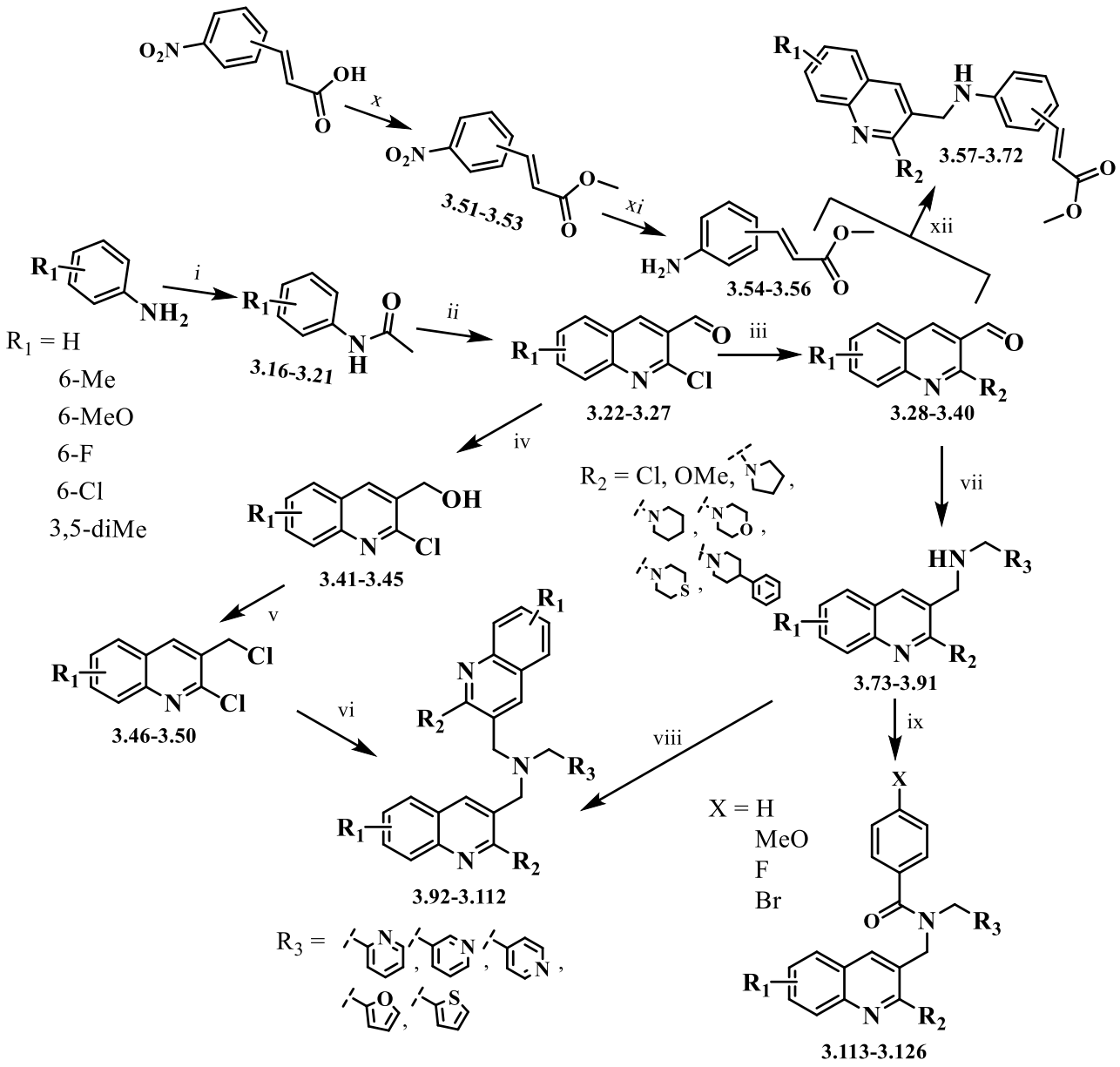
Scheme 3.1 illustrates the retrosynthetic analysis of target compounds. R_4–N bond disconnection leads to the secondary amine intermediates **3.13** and acid chloride **3.12** or chloromethyl quinolines **3.11** and aromatic primary amines **3.9**. The C–N bond cleavage of the amine intermediates **3.13** allows the access of the formyl quinolines **3.8** or chloromethylquinolines **3.11** and the aromatic primary amines **3.9**. Quinolines **3.8** are afforded from a Vilsmeier – Haack reaction of acetamides **3.4** that are directly synthesised from commercially available anilines **3.3**.



Scheme 3.1: Retrosynthesis of proposed quinoline based compounds.

3.3.2 Reaction scheme for the synthesis of quinoline derivatives

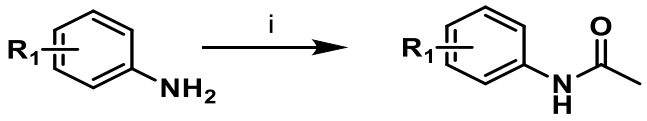
Overall synthetic route for the synthesis of quinoline based derivatives complementary to the retrosynthetic analysis presented in **scheme 3.1** is shown in **scheme 3.2** below. On exploratory studies, 6-methoxy bis quinoline derivative was demethylated using boron tribromide in DCM.



Scheme 3.2. Overall synthetic route for the synthesis of quinoline derivatives. *Reagents and conditions*: (i) Ac_2O, DCM, r.t, 30 min; (ii) DMF – $POCl_3$, 80 ^oC, 5 – 18 h; (iii) MeOH/KOH or DMF, K_2CO_3, saturated cyclic amines, reflux, 2.5 – 10 h ; (iv) MeOH, $NaBH_4$, r.t, 30 min; (v) DCM, $SOCl_2$, 50 ^oC, 3 – 4 h; (vi) aromatic primary amines, EtOH, TEA (cat), reflux, 36 – 48 h, MeOH/NaH, r.t, 70 °C, 36 h; (vii) Aromatic primary amines, EtOH, AcOH (cat), reflux, 12 h, $NaBH_4$, 0 ^oC to r.t, 6 h; (viii) 3-(chloromethyl)quinolines, EtOH, TEA, 78°C, 12 – 18 h; (ix) 4-substituted benzoyl chlorides, DCM, TEA, DMAP(cat), 0 ^oC, 12 h; (x) MeOH, H_2SO_4 (cat), 65 ^oC, 3 h; (xi) Zn, NH_4Cl, MeOH, r.t, 3 h; (xii) MeOH, AcOH (cat), 60 °C, 12 h, $NaCNBH_3$, 0°C to r.t, 12 h.

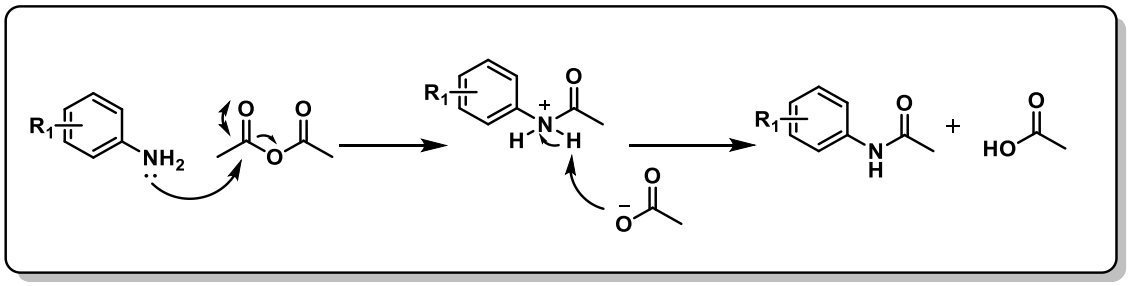
3.3.3 Synthesis of acetanilides

Having rationalised the retrosynthetic and synthetic route maps to achieving target compounds, the first step was to synthesise *N*-phenylacetamides (**Scheme 3.2**). We used commercially available anilines **3.15 a−f** and acetic anhydride in the preparation of the desired *N*-phenylacetamides as reported by many research groups[143-146].



3.15a	: R = H	**3.16** : R = H	98%
3.15b	: R = 4-Me	**3.17** : R = 4-Me	97%
3.15c	: R = 4-OMe	**3.18** : R = 4-OMe	97%
3.15d	: R = 4-F	**3.19** : R = 4-F	98%
3.15e	: R = 4-Cl	**3.20** : R = 4-Cl	97%
3.15f	: R = 3,5-diMe	**3.21** : R = 3,5-diMe	96%

Scheme 3.3 *Reagents and conditions*: (i) Ac_2O, DCM, r.t, 30 min.



Scheme 3.4: Proposed mechanism of acetylation.

The product is formed by nucleophilic substitution reaction where the aniline is the nucleophile and the acetyl group of the acetic anhydride is the electrophile. Compounds **3.16 − 3.21** were obtained in 96 – 98% yield after recrystallisation from water.

3.3.3.1 Spectroscopic characterisation of acetanilides

The successful acetylation of anilines was confirmed by proton (^{1}H) and carbon-13 nuclear magnetic resonance spectroscopy techniques. The signals observed for all the acetanilides

correlated with the ones reported in literature[69]. For example, the spectrum of compound **3.16** is shown in **Figure 3.2**. For ^{1}H NMR, chemically equivalent methyl protons of the -$COCH_3$- group integrating for three resonated at 2.14 ppm, whilst the -CONH- signal integrating for one appeared downfield as a broad signal at 7.95 ppm. The ^{13}C-NMR spectrum showed the characteristic signals of the methyl group of -$COCH_3$- at 24.4 ppm and the carbonyl carbon at 168.9 ppm, which further confirmed successful acetylation of the anilines.

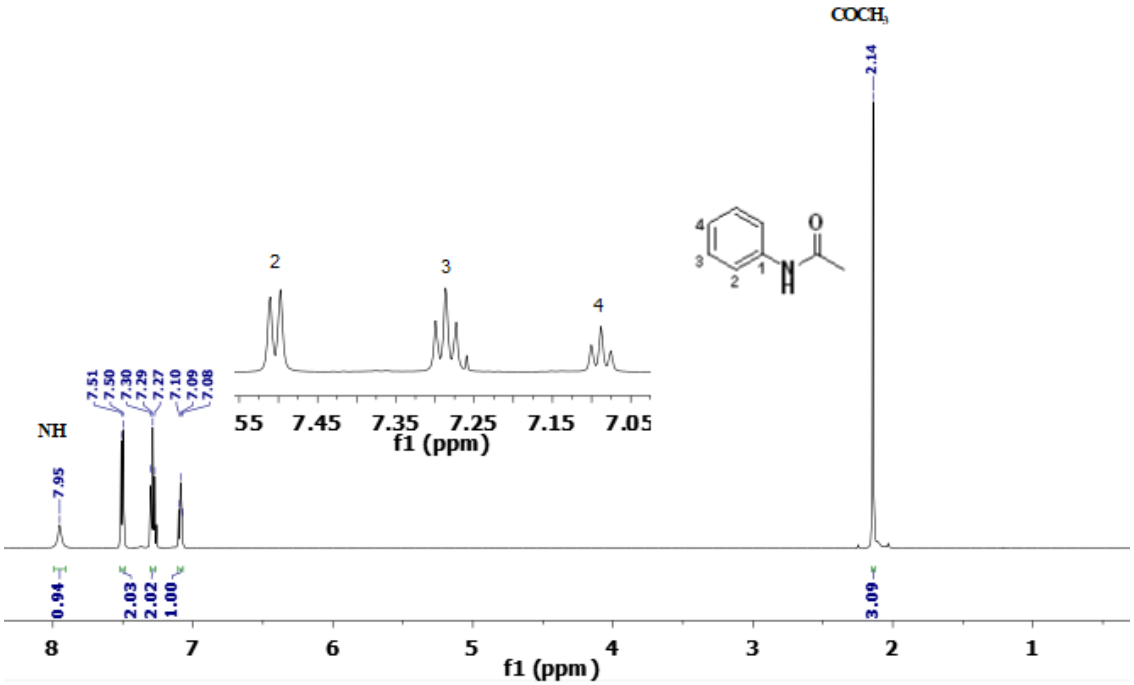
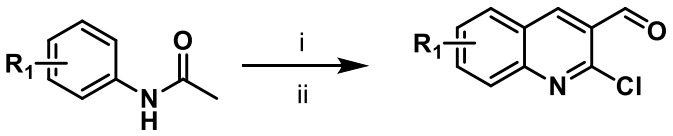


Figure 3.2: ^{1}H NMR spectrum (600 MHz, $CDCl_3$) for compound **3.16**.

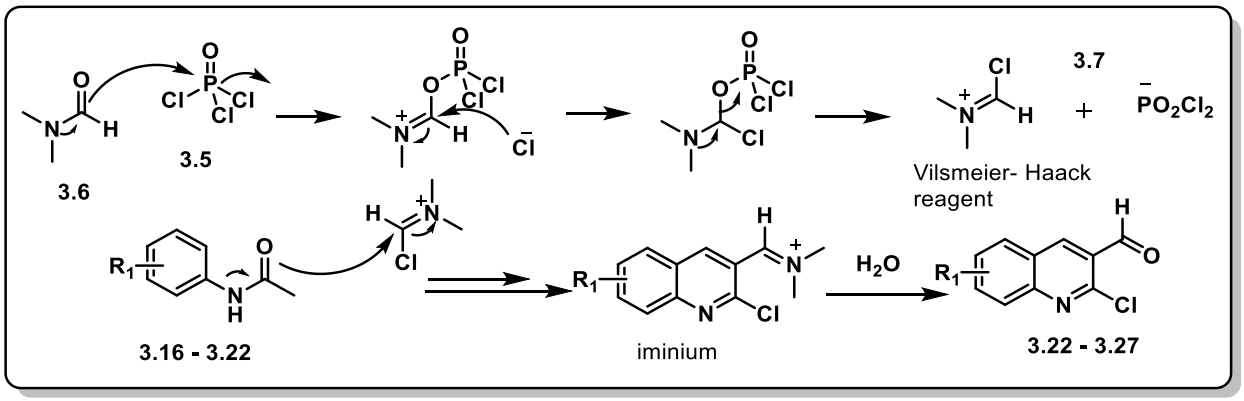
3.3.4 Synthesis of 2-chloroquinoline-3-carbaldehydes

The next step involved synthesis of the quinoline nucleus, which is the fundamental structural framework in our target compounds. We opted for Vilsmeier – Haack methodology since it affords quinoline scaffold with chloro and formyl substituents on C-2 and C-3, respectively. These substituents act as handles to expand the chemical space around the quinoline ring (**Scheme 3.5**).



3.22 : R = H 82%
3.23 : R = 6-Me 80%
3.24 : R = 6-OMe 62%
3.25 : R = 6-F 55%
3.26 : R = 6-Cl 36%
3.27 : R = 5,7-diMe 84%

Scheme 3.5 *Reagents and conditions*: (i) DMF – $POCl_3$, 90 °C, 5 – 24 h (ii) H_2O, 40 °C, 30 min.



Scheme 3.6. Proposed simple mechanism of quinoline synthesis.

Nucleophilic DMF (**3.6**) attacks $POCl_3$ **(3.5**) to form iminium Vilsmeier-Haack reagent salt (**3.7**) upon displacement of the oxygen and with a chlorine atom. The Vilsmeier-Haack reagent which is a highly reactive electrophile subsequently reacts with *N*-phenylacetamides to form the iminium intermediate that is hydrolysed to afford desired aldehydes **3.22 – 3.27**.

3.3.4.1 Spectroscopic characterisation of 2-chloroquinoline-3-carbaldehydes

The ^{1}H NMR spectrum of **3.22** in **Figure 3.3** shows all the expected signals. The spectrum reveals the disappearance of the -CONH- proton signal at 7.95 ppm and -$COCH_3$- protons at 2.14 ppm observed in the starting material **3.16**. The spectrum shows appearance of a new downfield singlet peak at 10.53 ppm integrating for one assignable to aldehydic proton. The

peak at 8.73 ppm indicates a new aromatic proton, which suggests successful cyclisation. In ^{13}C-NMR spectrum, the emergence of the prominent aldehydic carbonyl at 189.1 ppm and the disappearance of the acetyl group confirmed the successful synthesis of desired compounds.

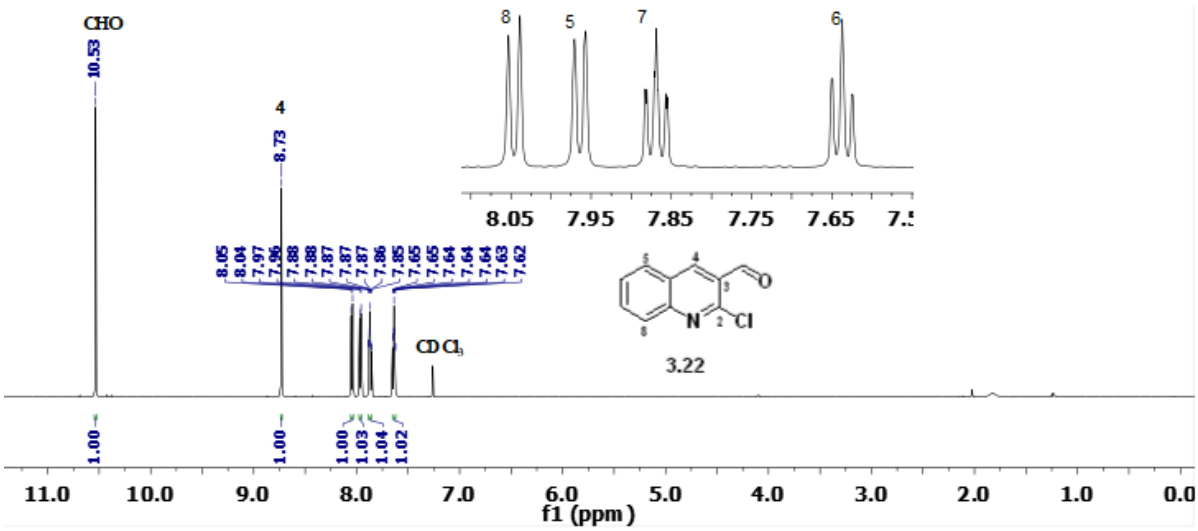
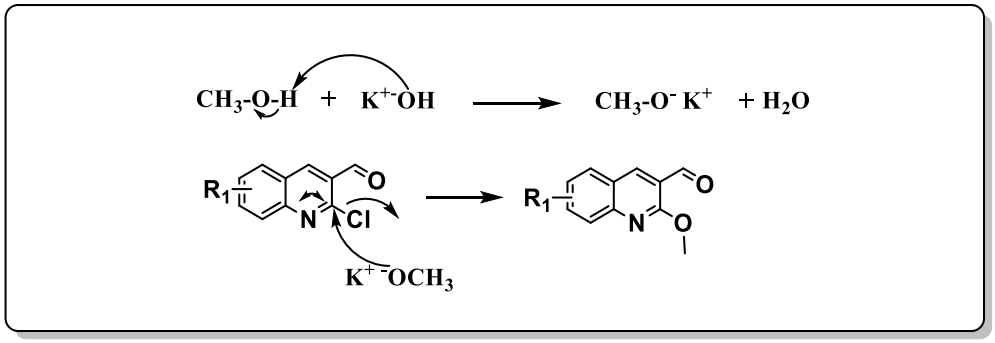


Figure 3.3: ^{1}H NMR spectrum (600 MHz, $CDCl_3$) for compound **3.22**.

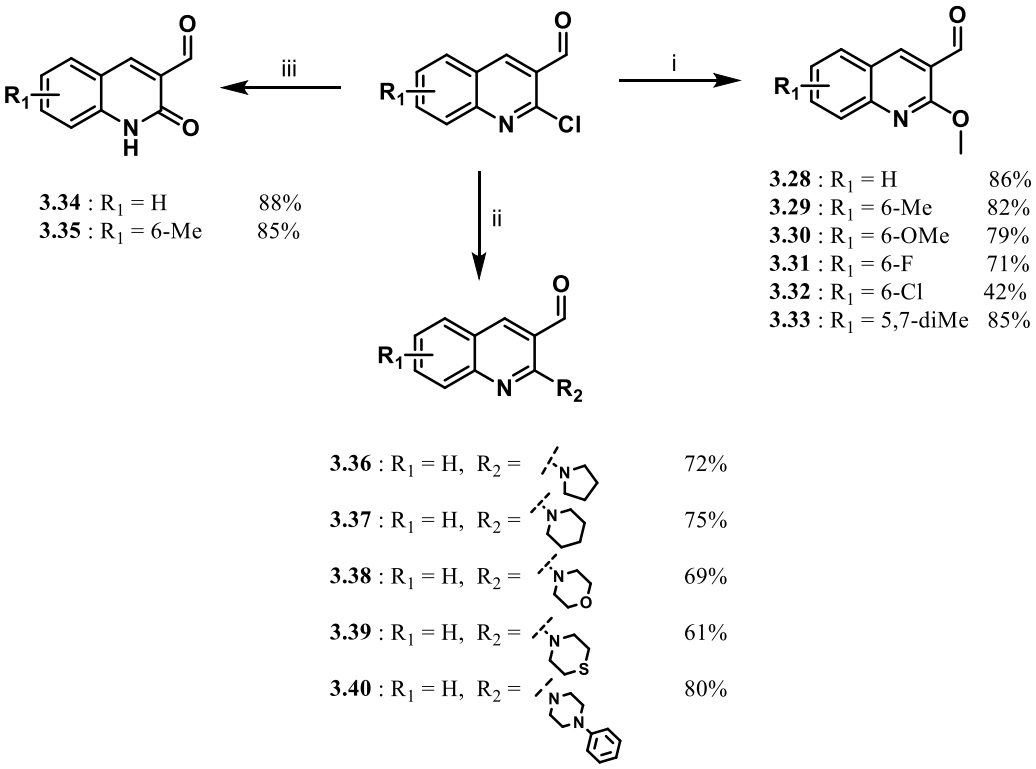
3.3.5 Synthesis of 2-substituted quinoline-3-carbaldehydes

After successfully synthesizing compounds **3.22 – 3.27**, we proceeded on to replacing chlorine atom on C-2 through nucleophilic substitution with methoxy group, or cyclic aliphatic amines. As can be rationalised from the resonance stabilized structures of quinoline from **Figure 2.1**, the positive charge is more localised on C-2 and C-4, making these positions more prone to nucleophilic attack. The presence of electron withdrawing chlorine atom on C-2 enhances the reactivity at this position. However, methanol is not a good nucleophile. Hence, KOH is used to abstract a fairly acidic proton from methanol to afford a good nucleophile methoxide ion which in turn attacks C-2 of quinoline scaffold (**Scheme 3.7**).



Scheme 3.7: Proposed mechanism of formation 2-methoxyquinoline-3-carbaldehydes **3.28 – 3.33**.

All the analogues **3.28 – 3.33** precipitated out upon addition of ice – cold water and then were collected by vacuum filtration. The dried crude products were recrystallized from DCM. For compounds **3.34 − 3.35** a solution of 2-chloroquinoline-3-carbaldehyde (1.00 mmol) in 70% aqueous acetic acid solution (10 mL) was heated at 90 °C for 10 h with stirring.



Scheme 3.8: *Reagents and conditions*: (i) MeOH/KOH, 60 °C, 2.5 – 6 h (ii) DMF/K_2CO_3, cyclic amine, 110 °C, 4 – 7 h (iii) 70% aqueous acetic acid, 90 °C, 10 h.

The solution was cooled to r.t and the precipitate formed were filtered, washed with water (10 mL) and air dried overnight to furnish needle-like crystals. Compounds **3.36 − 3.41** were prepared by mixing 2-chloroquinoline-3-carbaldehydes (10.0 mmol), an appropriate amine (11.7 mmol) and K_2CO_3 (11.7 mmol) in DMF (50 mL) and refluxed for 4–7 h while stirring. K_2CO_3 is used to abstract a proton from amines to afford good nucleophiles. After completion of the reaction (monitored by TLC), the mixture was cooled to r.t and poured into ice water under continuous stirring. The light-yellow precipitate for **3.37 − 3.40** were filtered and air dried for overnight. Compound **3.36** did not form a precipitate and was extracted using EtOAc (50 mL). The organic layer was successively washed with saturated brine (20 mL) and water (20 mL), dried ($MgSO_4$) and concentrated *in vacuo.* Purification of compounds **3.28 − 3.40** was done by column chromatography using $CHCl_3$–Hexane (1:1) mixture as the mobile phase.

3.3.5.1 Characterisation of 2-substituted quinoline-3-carbaldehydes

The structures of compounds **3.28 − 3.40** were confirmed by ^1H and ^{13}C NMR spectroscopy. **Figure 3.4** shows the ^1H NMR spectrum of compound **3.28**, a representative of the intermediates formed. ^1H NMR spectrum revealed one characteristic singlet at 4.18 ppm integrating for three, due to the chemically equivalent CH_3 protons from methoxy group that replaced chlorine atom. In ^{13}C NMR, there was an appearance of an extra signal observed at chemical shift 53.8 ppm corresponding to methoxy group inserted. The slight change in chemical shift of C-2 from 150.1 ppm for **3.22** to 161.2 ppm for **3.28** also confirmed successful nucleophilic substitution of a chlorine atom at C-2 due to the shielding effect of methoxy group.

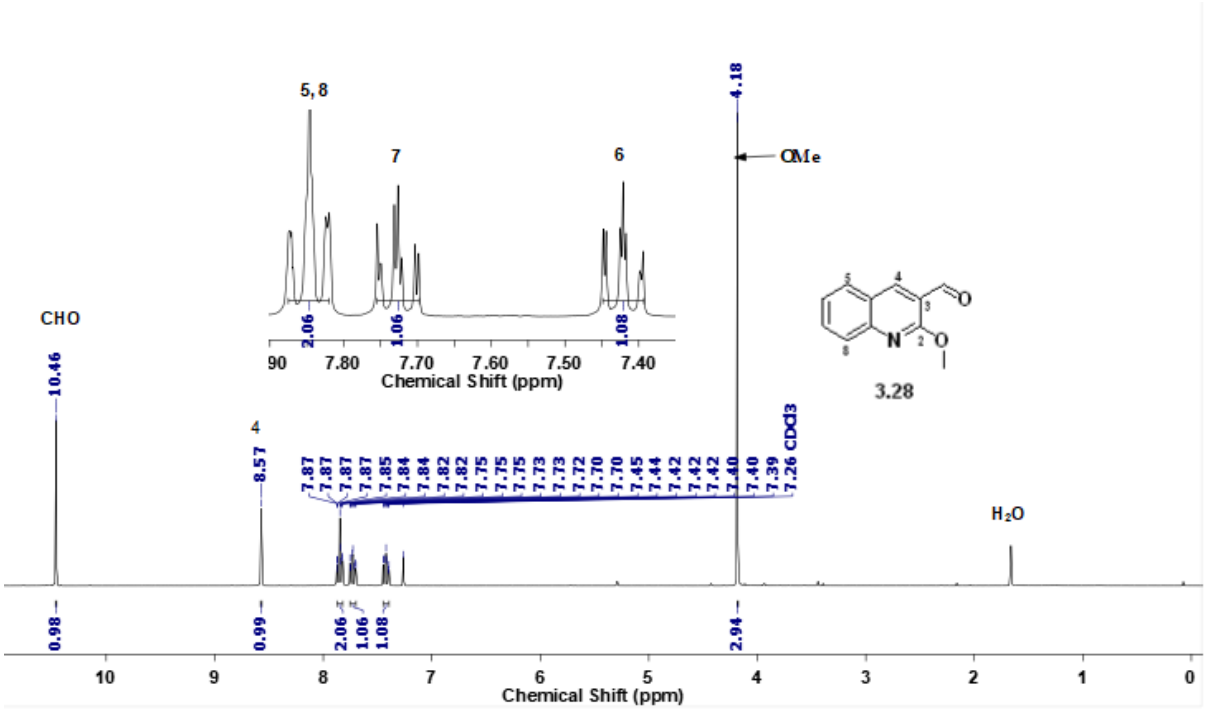
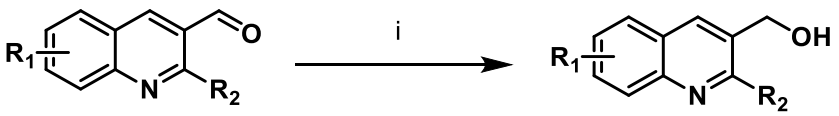


Figure 3.4: ^{1}H NMR spectrum (300 MHz, $CDCl_3$) for compound **3.28**.

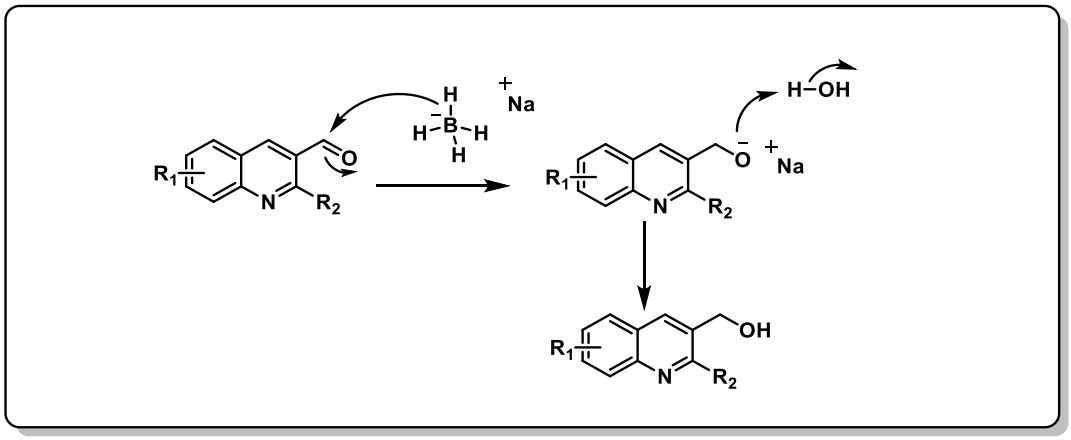
3.3.6 Synthesis of 3-(hydroxymethyl)quinolines

Sodium borohydride, a representative borohydride reagent is an effective and widely used reducing agent. The relatively low cost and ease with which it can be handled contribute to its popularity[147]. It is a reagent that transforms aldehydes and ketones to corresponding alcohols using methanol or ethanol as solvents (**Scheme 3.9**).



3.41 : R_1 = H, R_2 = Cl 94%
3.42 : R_1 = 6-Me, R_2 = Cl 90%
3.43 : R_1 = 6-OMe, R_2 = Cl 94%
3.44 : R_1 = 6-F, R_2 = Cl 88%
3.45 : R_1 = 5,7-diMe, R_2 = OMe 91%

Scheme 3.9: *Reagents and conditions*: (i) MeOH, $NaBH_4$, r.t, 30 min.



Scheme. 3.10: Proposed simplified mechanism for formation of **3.41 – 3.45**.

Sodium borohydride transfers a hydride ion to the carbonyl carbon forming a tetrahedral geometry. The Oxygen anion eventually abstracts a proton from water to form an alcohol. Thin layer chromatography confirmed the formation of a more polar compound and disappearance of the starting material. After reaction work up, alcohols were obtained in yields ranging from 88 – 94%.

3.3.6.1 Characterisation of 3-(hydroxymethyl)quinolines

The synthesised (hydroxymethyl)quinolines compounds **3.41−3.45** were confirmed by FT-IR, ^{1}H and ^{13}C NMR spectroscopic techniques. The representative ^{1}H NMR spectrum of the intermediates, compound **3.44** is shown in **Figure 3.5**. ^{1}H NMR revealed the anticipated disappearance of a more deshielded aldehydic proton. The emergence of the singlet OH signal integrating for one at 5.77 ppm and a new singlet peak integrating for two at chemical shift 4.69 ppm for CH_2 on C-3′ indicated the desired functional group conversion. In addition, the new CH_2 on C-3′ was split by OH to give doublets with *J*-coupling values in the range of 5.3 – 5.8 Hz for all analogues except **3.44**. ^{13}C NMR also corroborates the disappearance of a more deshielded aldehydic carbonyl. The appearance of a new CH_2 peak pointing down (negative) at 60.3 ppm on DEPT 135 experiment also confirmed successful conversion.

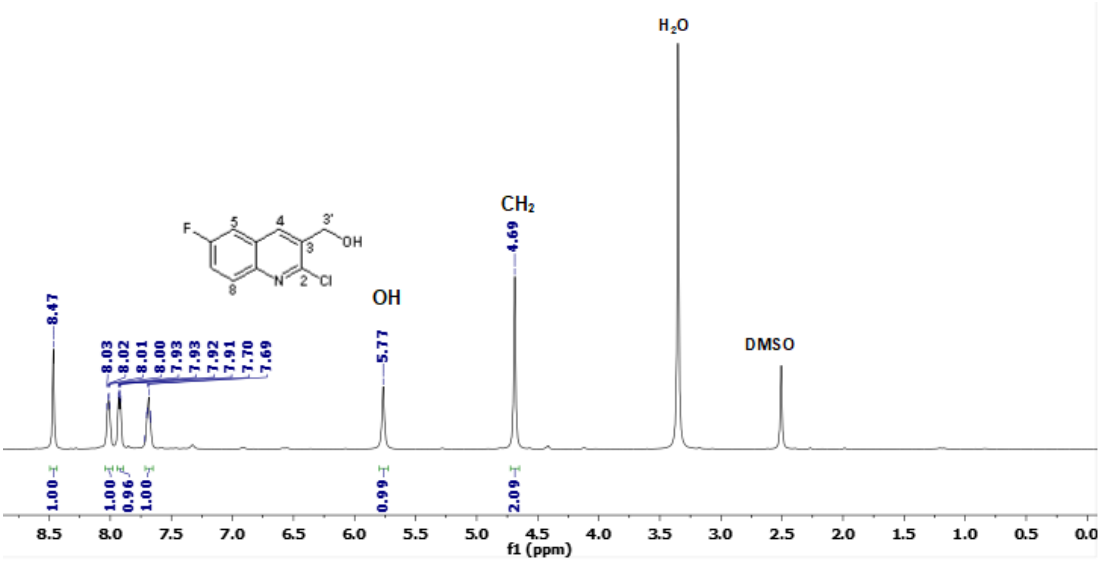
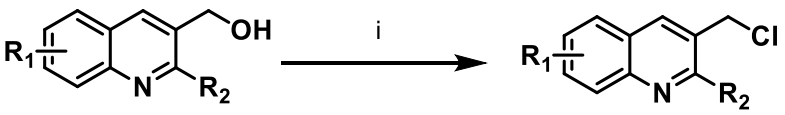


Figure 3.5: ^{1}H NMR spectrum (600 MHz, DMSO-*d6*) for compound **3.44**.

3.3.7 Synthesis of 3-(chloromethyl)quinolines

Conversion of quinoline alcohols **3.41 − 3.45** to corresponding quinoline chlorides **3.46 − 3.50** (**Scheme 3.11**) was crucial in that it provided substrates with a good leaving group which are susceptible to nucleophilic substitution. Many chlorinating agents have been reported in literature including phosphorus oxychloride ($POCl_3$), phosphorus pentachloride (PCl_5), thionyl chloride ($SOCl_2$), oxalyl chloride $(COCl)_2$, hydrogen chloride (HCl), etc[148].

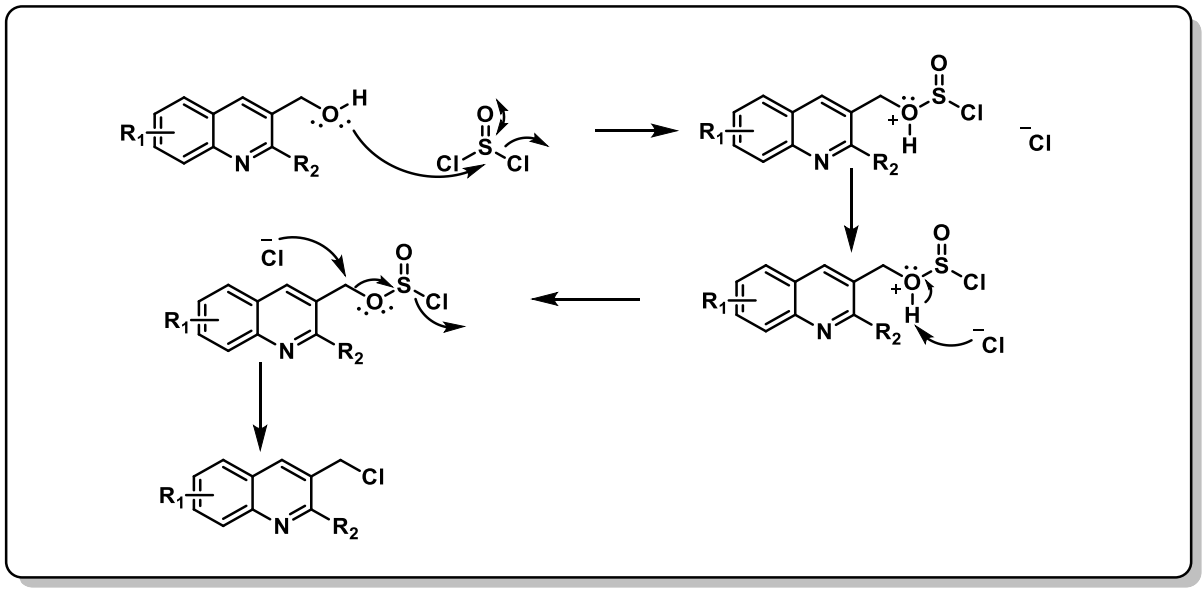


3.46 : R_1 = H, R_2 = Cl 90%
3.47 : R_1 = 6-Me, R_2 = Cl 88%
3.48 : R_1 = 6-OMe, R_2 = Cl 91%
3.49 : R_1 = 6-F, R_2 = Cl 79%
3.50 : R_1 = 5,7-diMe, R_2 = OMe 89%

Scheme 3.11: *Reagents and conditions*: (i) $SOCl_2$, DCM, 50 °C, 6 h.

In this research, $SOCl_2$ was used and afforded compounds **3.46 − 3.50** in good yields ranging from 79 – 91% (**Scheme 11**). The by-products formed in the reaction are SO_2 and HCl which are in gaseous form and easily escape into the atmosphere leaving behind pure products. This

reduces purification challenges. The nucleophilic oxygen atom of the alcohol displaces a chloride ion from thionyl chloride to form a protonated alkyl chlorosulfite intermediate (**Scheme 3.12**). Subsequent deprotonation of this intermediate by a base yields the alkyl chlorosulfite, an inorganic ester. Lastly, S_N2 reaction affords the chloromethyl quinolines **3.46 − 3.50**.



Scheme 3.12: Proposed mechanism of formation of 3-(chloromethyl)quinolines.

3.3.7.1 Spectroscopic characterisation of 3-(chloromethyl)quinolines

The formation of chlorinated compounds **3.46 − 3.50** was confirmed by FT-IR, ^{1}H NMR and ^{13}C NMR. Infrared spectra of the intermediates indicated the absence of OH band which is observed above 3000 cm^{-1}. The representative ^{1}H NMR spectrum of the compounds **3.47** is shown in **Figure 3.6**. The spectrum shows absence of OH group signal observed in the precursor compound **3.42**. Furthermore, CH_2Cl protons give rise to a singlet as they are not split by OH as was the case with compounds **3.41 − 3.45**. However, there was no major shift in ppm for CH_2Cl group as compared to the previous CH_2OH group.

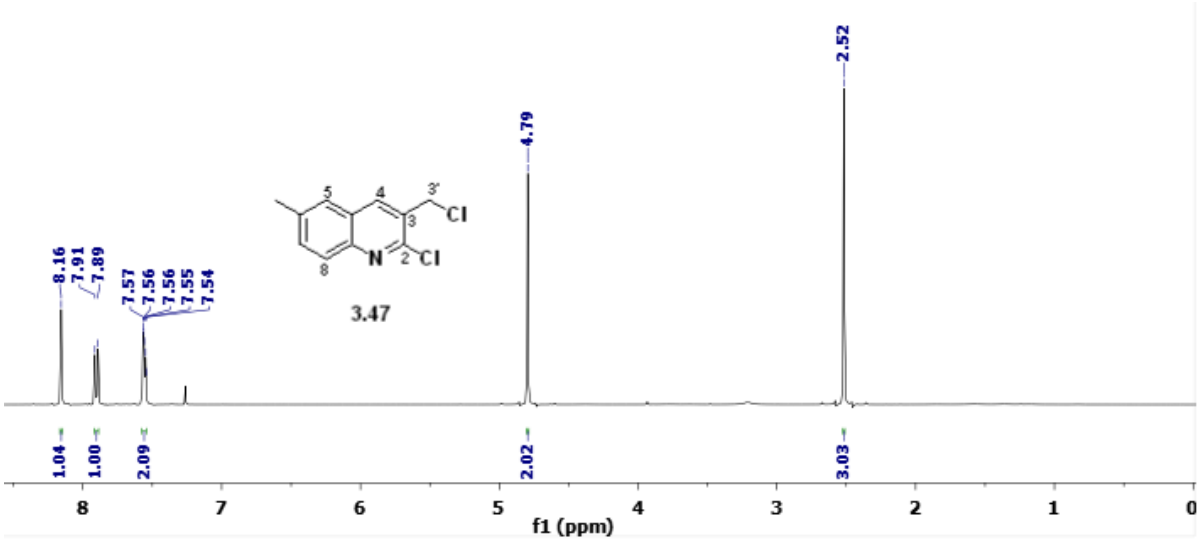
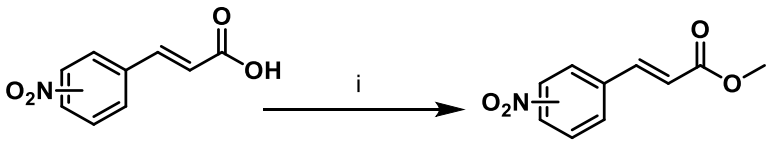


Figure 3.6: ^{1}H NMR spectrum (600 MHz, $CDCl_3$) for compound **3.47**.

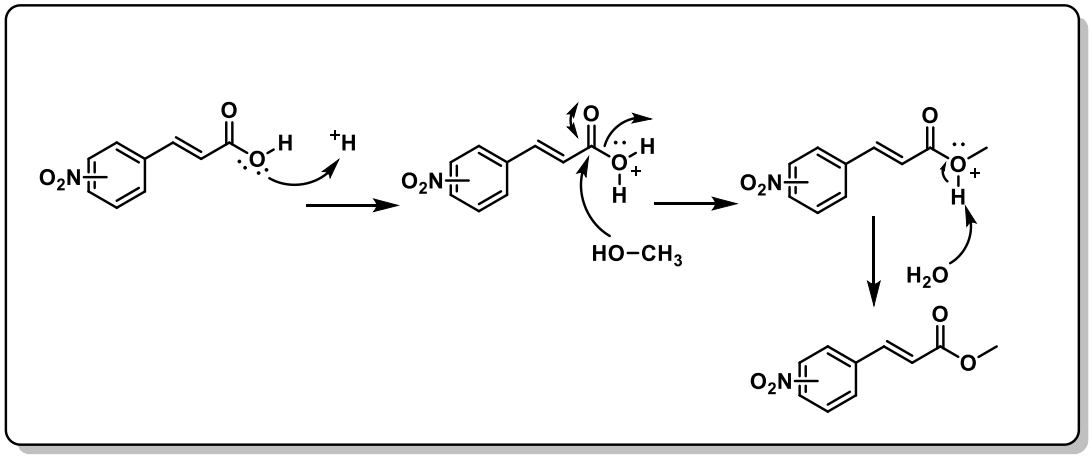
3.3.8 Synthesis of *trans* methyl nitrocinnamate

Trans nitro cinnamic acids underwent esterification with methanol which was treated with a few drops of conc. sulphuric acid catalyst (**Scheme 3.13**). The mixture was heated at reflux for 3 h, after which TLC showed disappearance of the starting material and a new less polar spot was observed. The reaction work up afforded *trans* methyl nitro cinnamate in very good yields ranging from 88 – 92%.



3.51 : *ortho*-NO_2 92%
3.52 : *meta*-NO_2, 98%
3.53 : *para*-NO_2, 88%

Scheme 3.13: *Reagents and conditions*: (i) MeOH, H_2SO_4 (cat), 65 °C, 3 h.



Scheme 3.14: Proposed mechanism of esterification.

3.3.8.1 Spectroscopic characterisation of *trans* methyl nitrocinnamate

The resulting esters **3.51 − 3.53** were characterised by ^{1}H and ^{13}C NMR spectroscopic techniques. The representative ^{1}H NMR spectrum of the compounds **3.51 − 3.53** shown in **Figure 3.7** revealed a characteristic methoxy substituent at chemical shift 3.82 ppm integrating for three protons.

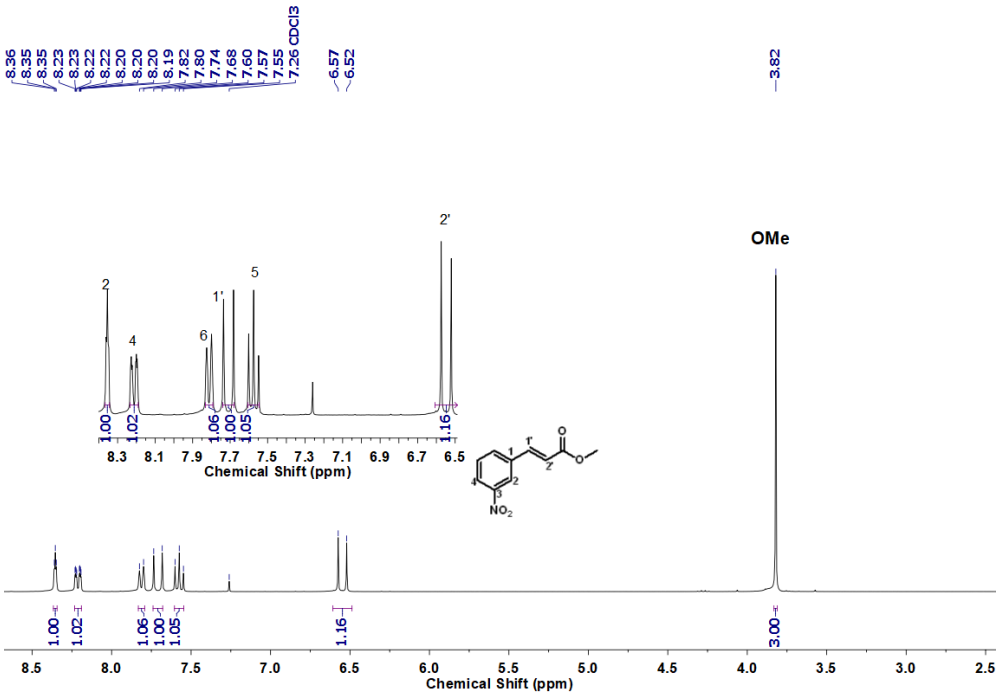
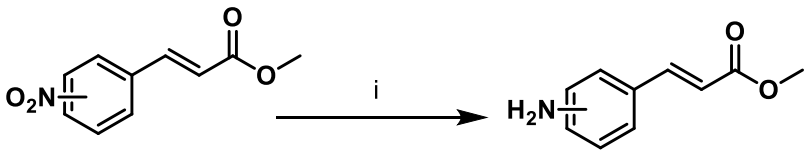


Figure 3.7: ^{1}H NMR spectrum (300 MHz, $CDCl_3$) for compound **3.52**.

Additionally, the spectrum showed the disappearance of the O-H proton signal observed for the *trans* cinnamic acid starting material. Furthermore, the spectrum revealed two doublets signals at chemical shifts 7.71 and 6.55 ppm with same *J* -coupling constant of 16.0 Hz attributed to H-1′ and H-2′ protons, respectively. The coupling constant suggest that both H-1′ and H-2′ maintained a *trans* geometry[149]. This data was again supported by ^{13}C NMR, which featured the diagnostic methoxy group signal resonating at chemical shift 52.0 ppm for **3.52**.

3.3.9 Synthesis of *trans* methyl aminocinnamate

The reduction of aromatic nitro compounds to corresponding anilines is one of the most important transformations in synthetic organic chemistry. Rapid and selective reduction of nitro compounds is important for the preparation of amino derivatives in the organic synthesis, particularly when a molecule has other reducible moieties[150-152]. Many methods have been reported in the literature for this reduction, including homogeneous and heterogeneous catalytic hydrogenation, reduction using metals[153]. The selective reduction of aromatic nitro compounds using iron and dilute acid, or stannous chloride[154] have been reported as efficient methods. However, recently zinc has been used in combination with acids/bases[155] and also with hydrogen donors[156] for the reduction of aromatic nitro compounds. Thus, treatment of **3.51 − 3.53** with zinc and hydrogen source NH_4Cl in MeOH yielded compounds **3.54 − 3.56** (**Scheme 3.15**) in more than 80% yields.



3.54 : *ortho*-NH_2 86%
3.55 : *meta*-NH_2, 82%
3.56 : *para*-NH_2, 80%

Scheme 3.15: *Reagents and conditions*: (i) Zn, NH_4Cl, MeOH, r.t, 3 h.

3.3.9.1 Spectroscopic characterisation of *trans* methyl aminocinnamate

To illustrate the successful reduction of the nitro compounds **3.51 − 3.53**, ^{1}H-NMR spectrum of compound **3.55** is presented (**Figure 3.8**). A new singlet peak resonating at chemical shift 3.75 ppm integrating for two protons is observed, which correlates to NH_2 following successful reduction. It is also observed that H-2 and H-4 are less deshielded as compared to H-2 and H-4 of the previous starting material **3.52** due to electron donating (NH_2) and withdrawing (NO_2) nature of the groups, which confirms the successful reduction of nitro group.

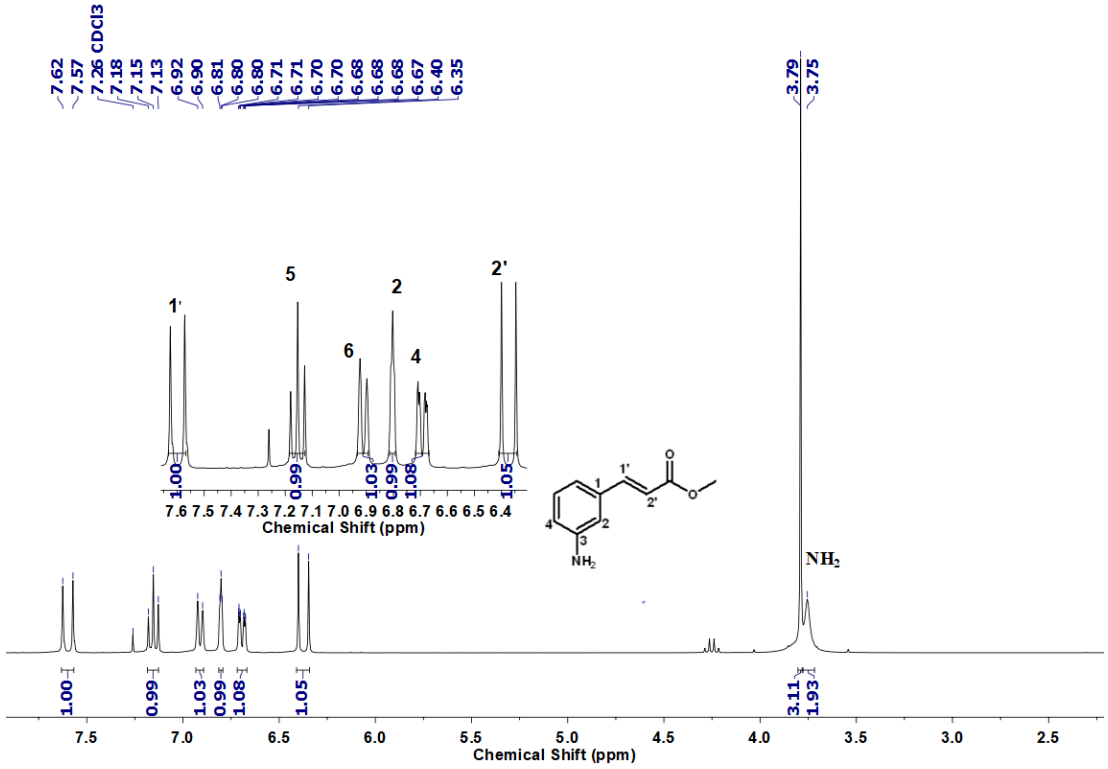
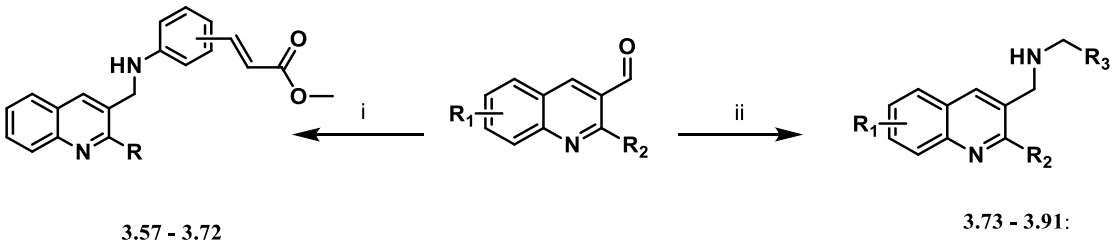


Figure 3.8: ^{1}H NMR spectrum (300 MHz, $CDCl_3$) for compound **3.55**.

3.3.10 Synthesis of quinolinyl amine derivatives 3.57 − 3.91

At this point, we endeavoured to employ an indirect reductive amination to synthesise secondary amine adducts. The reaction involved an *in-situ* formation of Schiff base intermediates by refluxing the aldehyde with relevant amines and subsequent borohydride reduction to obtain compounds **3.57 − 3.92** (**Scheme 3.16**). A Schiff base is a nitrogen analogue

of an aldehyde or ketone in which the C=O group is replaced by C=N group[157]. It is usually formed by condensation of an aldehyde or ketone with a primary amine. The first preparation of imines was reported in the 19th century by Hugo Schiff (1864).

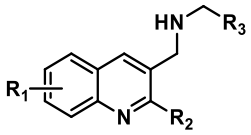


3.57 - 3.72 **3.73 - 3.91**:

Scheme 3.16: *Reagents and conditions*: (i) *trans* methyl aminocinnamate, MeOH, AcOH (cat), 60 °C, 12 h, $NaCNBH_3$, 0 →25 °C, 12 h (ii) Aromatic heterocyclic methyl amines, EtOH, AcOH (cat), 78 °C, 12 h, $NaBH_4$, r.t, 6 h.

For synthetic route (ii), quinoline-3-carbaldehyde was stirred in dry ethanol containing a catalytic amount of glacial acetic acid followed by addition of an appropriate amine drop wise after which the reaction mixture was heated at reflux overnight as reported by Jain *et al*[95]. The progress of the reaction was monitored by TLC and revealed that in all but 4-(aminomethyl)pyridine and 2-(aminomethyl)pyridine, both quinoline-3-carbaldehyde and primary heteroamine were completely consumed after refluxing for 12 h. There was no precipitation of the Schiff bases even though many imines tend to precipitate out[158-160]. The reaction was cooled to r.t and sodium borohydride added portion wise. When effervescence ceased, the mixture was let to stir for a further 6 h at r.t. Prominent more polar spot on TLC (EtOAc/Hexane 1:1) developed, presumably, our reduced Schiff base. The products were purified by silica gel column chromatography to give the desired compounds **3.73 – 3.91** in low to high yields (**Table 3.1**).

Table 3.1: Isolated quinolinyl amines **3.73 − 3.91** with corresponding yields.



Compound	R_1	R_2	R_3	Yield (%)
3.73	H	MeO		72
3.74	H	MeO		76
3.75	6-Me	MeO		75
3.76	5,7-diMe	MeO		71
3.77	6-MeO	MeO		84
3.78	6-F	MeO		45
3.79	H	MeO		34
3.80	5,7-diMe	MeO		57
3.81	H	Cl		51
3.82	H	MeO		70
3.83	6-Me	MeO		69
3.84	6-MeO	MeO		68
3.85	6-F	MeO		62
3.86	6-Cl	MeO		22
3.87	5,7-diMe	MeO		70
3.88	5,7-diMe	Cl		70
3.89	H	MeO		40
3.90	5,7-diMe	MeO		41
3.91	H	Cl		42

For synthetic route (i), sodium cyanoborohydride was used for the reduction of an imine *in situ* due to the co-presence of α, β unsaturated carbonyl group. The steric and electronic effects of cyano substituent greatly influences the reactivity of the borohydride ion[161]. Thus, sodium cyanoborohydride with its strongly electron withdrawing cyano group is a milder and more selective reducing agent than sodium borohydride[162].

3.3.10.1 Spectroscopic characterisation of quinolinyl amine derivatives 3.57 – 3.91

The structures of newly synthesised amines **3.57 – 3.91** were elucidated by combined use of IR, ^{1}H, C ^{13}NMR and DEPT-135 spectroscopic techniques. The N-H asymmetric sharp stretch around 3275 cm^{-1} was the characteristic one absorption band confirming the presence of a secondary amine. **Figure 3.9** shows the ^{1}H NMR spectrum of compound **3.82** as a representative for ^{1}H NMR of the reduced Schiff bases.

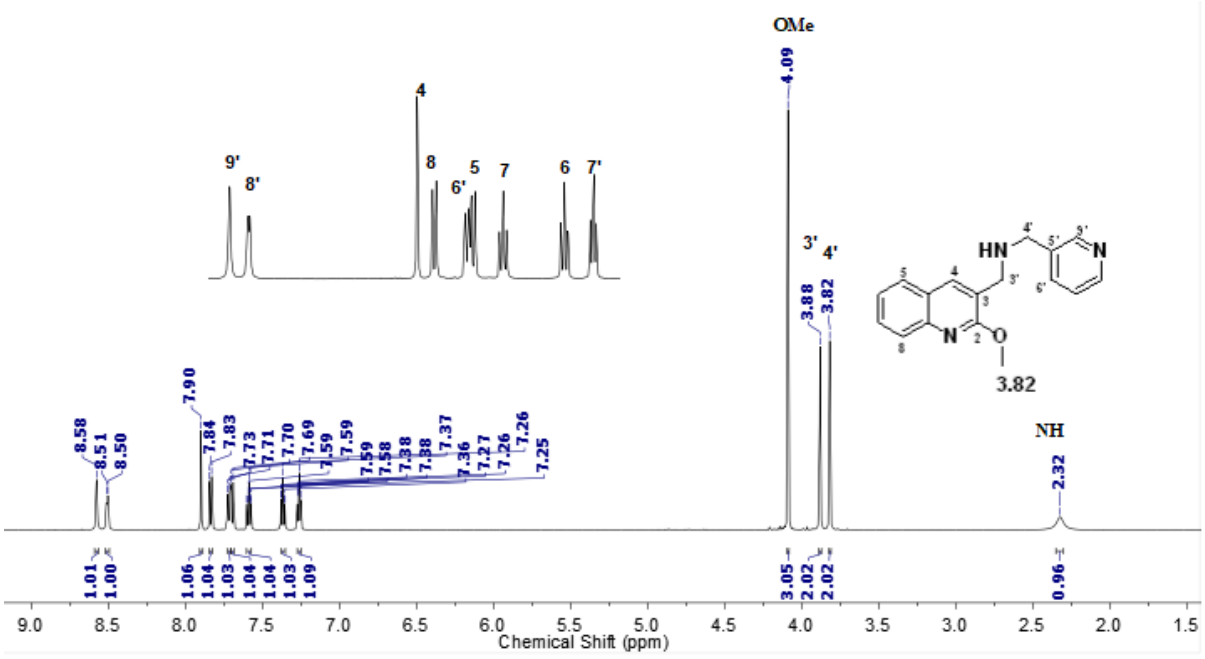
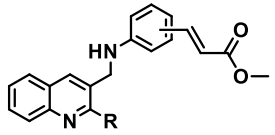
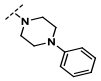
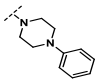


Figure 3.9: ^{1}H NMR spectrum (600 MHz, $CDCl_3$) for compound **3.82**.

All the aromatic and aliphatic protons were accounted for and most importantly, the disappearance of the downfield aldehydic proton signal observed from the starting material **3.28** and the appearance of a singlet methylene group at chemical shift 3.88 ppm. A broad singlet signal at chemical shift 2.32 ppm which is diagnostic of the aliphatic NH group confirmed the identity of **3.82**. The ^{13}C NMR spectrum presented all the expected fourteen aromatic carbon signals. The new aliphatic C-3′ confirmed the successful formation of our desired compounds. Confidently, DEPT-135 cemented the formation of the desired secondary amine by showing a peak pointing down (negative) resonating at 48.3 ppm corresponding to methylene C-3′ in addition to methylene C-4′ resonating at 50.3 ppm.

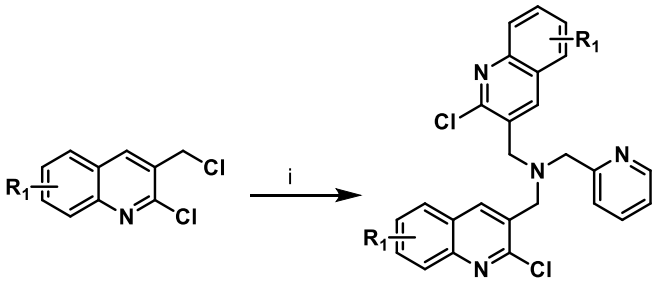
Table 3.2: Yields of isolated quinolinyl cinnamate amines **3.57 – 3.72**.



Compound	Position of acrylate	R	Yield (%)	Compound	Position of acrylate	R	Yield (%)
3.57	*meta*		70	**3.65**	*para*		40
3.58	"	OH	66	**3.66**	"		32
3.59	"		35	**3.67**	"		35
3.60	"		57	**3.68**	*ortho*		61
3.61	"		70	**3.69**	"		52
3.62	"		45	**3.70**	"		65
3.63	*para*		31	**3.71**	"		38
3.64	"		35	**3.72**	"		75

3.3.11 Synthesis of *bis* 2-chloroquinoline derivatives 3.92 – 3.95

An attempt to synthesise symmetrical *bis* 2-chloroquinolines **3.92 – 3.95** in one pot was successful only when the amine was 2-(aminomethyl)pyridine in very good yields. The other amines; 3-(aminomethyl)pyridine, 4-(aminomethyl)pyridine, 2-thiophenylamine and furfurylamine did not proceed *in situ* to form proposed tertiary amines, as they only gave the secondary amine intermediates. Compounds **3.46 – 3.49** were reacted with 2-(aminomethyl)pyridine in absolute EtOH followed by TEA at reflux temperature for 36 – 48 h, after which purification was achieved using column chromatography [on silica gel; elution with hexane/EtOAc 2:1)]. The yields ranging from 35 − 84% were reported with **3.93** having an outstanding percent yield. There was no trace of product formed due to nucleophilic substitution of chlorine on C-2 of the quinoline by 2-(aminomethyl)pyridine nucleophile probably due to the fact that C-2 is sterically hindered.



3.46 : R_1 = H,
3.47 : R_1 = 6-Me,
3.48 : R_1 = 6-OMe,
3.49 : R_1 = 6-F,

3.92 : R_1 = H, 78%
3.93 : R_1 = 6-Me, 84%
3.94 : R_1 = 6-OMe, 52%
3.95 : R_1 = 6-F, 35%

Scheme 3.17: *Reagents and conditions*: (i) 2-(aminomethyl)pyridine, EtOH, TEA, 78 °C, 36 – 48 h.

3.3.11.1 Spectroscopic characterisation of *bis* 2-chloroquinoline compounds 3.92 – 3.95

The structures of newly synthesized tertiary amines were elucidated by combined use of FT-IR, 1D NMR, 2D NMR and HRMS and M.p. Using compound **3.92** as an example, ^{1}H NMR spectrum of **3.92** is shown in **Figure 3.10**. Infrared confirmed the formation of a tertiary amine

by the disappearance of N-H band which normally appears above 3100 cm^{-1} on the spectrum. In the ^{1}H NMR spectrum of intermediate **3.46**, a sharp singlet at chemical shift 4.82 ppm arising due to CH_2Cl function was observed. However, this signal underwent slight upfield shift in compounds **3.92 – 3.95** to chemical shift values ranging from 4.04 – 4.07 ppm. This diamagnetic shift may be attributed to weak electron withdrawing effect of N as compared to Cl. Furthermore, in ^{13}C NMR spectra, CH_2Cl carbon resonated at chemical shift 43.2 ppm which underwent slight paramagnetic shift in compounds **3.92 – 3.95** to chemical shift values in the region 56.1 – 56.5 ppm. The mass spectrometry data of compounds **3.92 – 3.95** showed intense signals at *m/z*: 459.1142 (**3.92**), 487.1459 (**3.93**) 519.1348 (**3.94**), and 495.0952(**3.95**), which were consistent with their pseudo molecular ions $[M+H]^+$. These observations confirmed the successful substitution of chloromethyl group with amine in the targeted compounds (**3.92 – 3.95**)

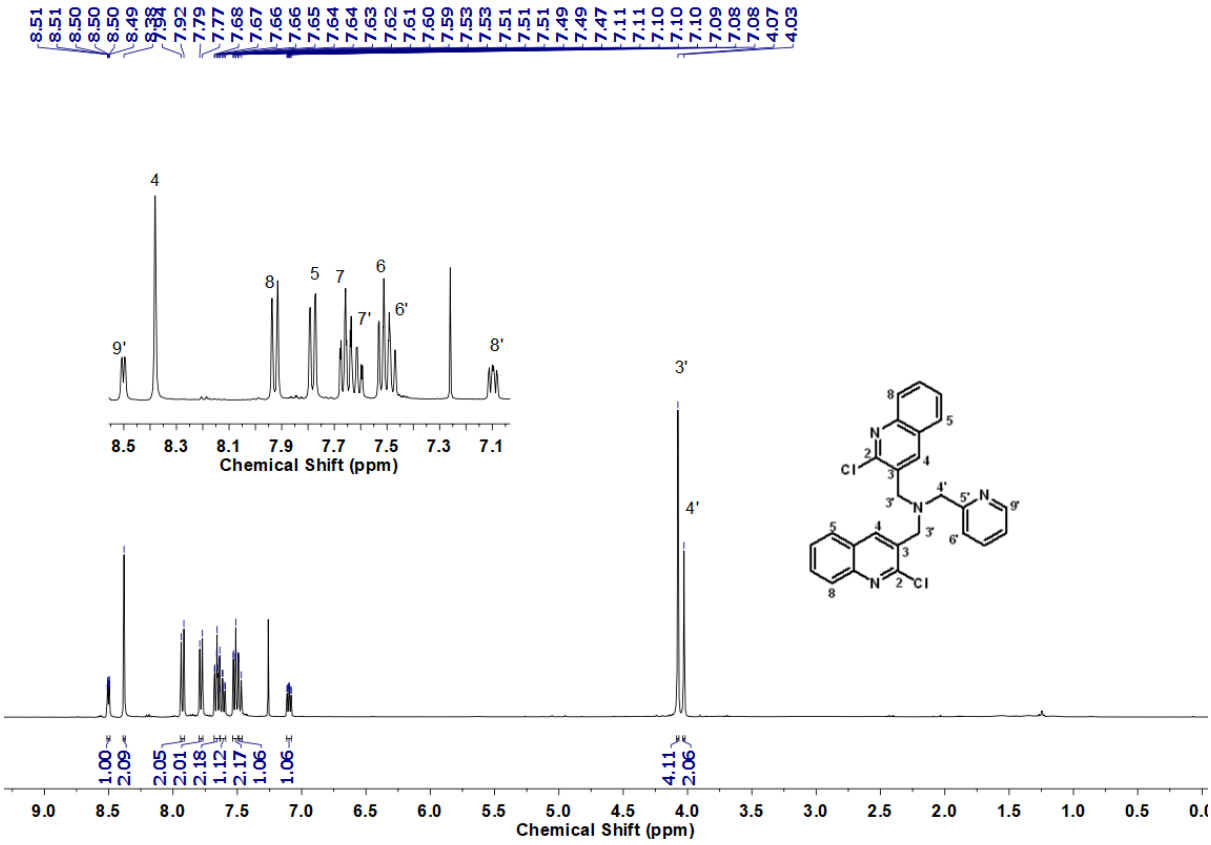
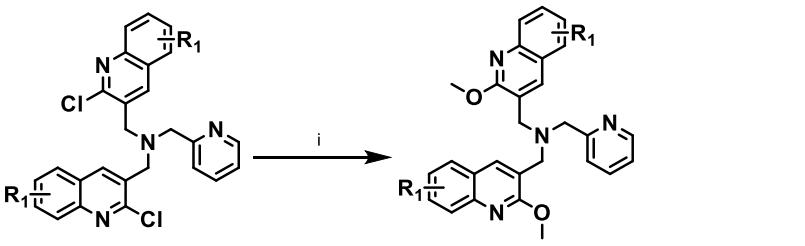


Figure 3.10:^{1}H NMR spectrum (600 MHz, $CDCl_3$) for compound **3.92**.

3.3.12 Synthesis of *bis* 2-methoxyquinoline derivatives 3.96 – 3.99

A similar method to that described for nucleophilic substitution of chlorine atom by a methoxy group in section **3.3.4.** was used to prepare compounds **3.96 – 3.99**, which were obtained in yields ranging from 55 – 72%. However, NaOH was replaced by NaH to avoid formation of water molecules in the reaction vessel.



3.92 : R_1 = H,
3.93 : R_1 = 6-Me,
3.94 : R_1 = 6-OMe,
3.95 : R_1 = 6-F,

3.96 : R_1 = H, 55%
3.97 : R_1 = 6-Me, 68%
3.98 : R_1 = 6-OMe, 58%
3.99 : R_1 = 6-F, 72%

Scheme 3.18: *Reagents and conditions*: (i) MeOH/NaH, 70 °C, 36 h.

3.3.12.1 Spectroscopic characterisation of *bis* 2-methoxyquinoline derivatives 3.96 – 3.99

To illustrate the successful formation of our methoxylated compounds, ^{1}H-NMR spectrum of compound **3.98** is shown below (**Figure 3.11**). Methoxylation was indicated by the appearance of a new singlet peak integrating for six protons at chemical shift 3.83 ppm, which correlates to nucleophilic substitution of chlorine atom by a methoxy group. Furthermore, the ^{13}C NMR spectrum showed a new characteristic signal of the methoxy at 53.5 ppm after successful displacement of the Cl group. The slight change in chemical shift of C-2 from 148.2 ppm for **3.94** to 159.4 ppm for **3.98** also confirmed successful nucleophilic substitution of chlorine atom on C-2.

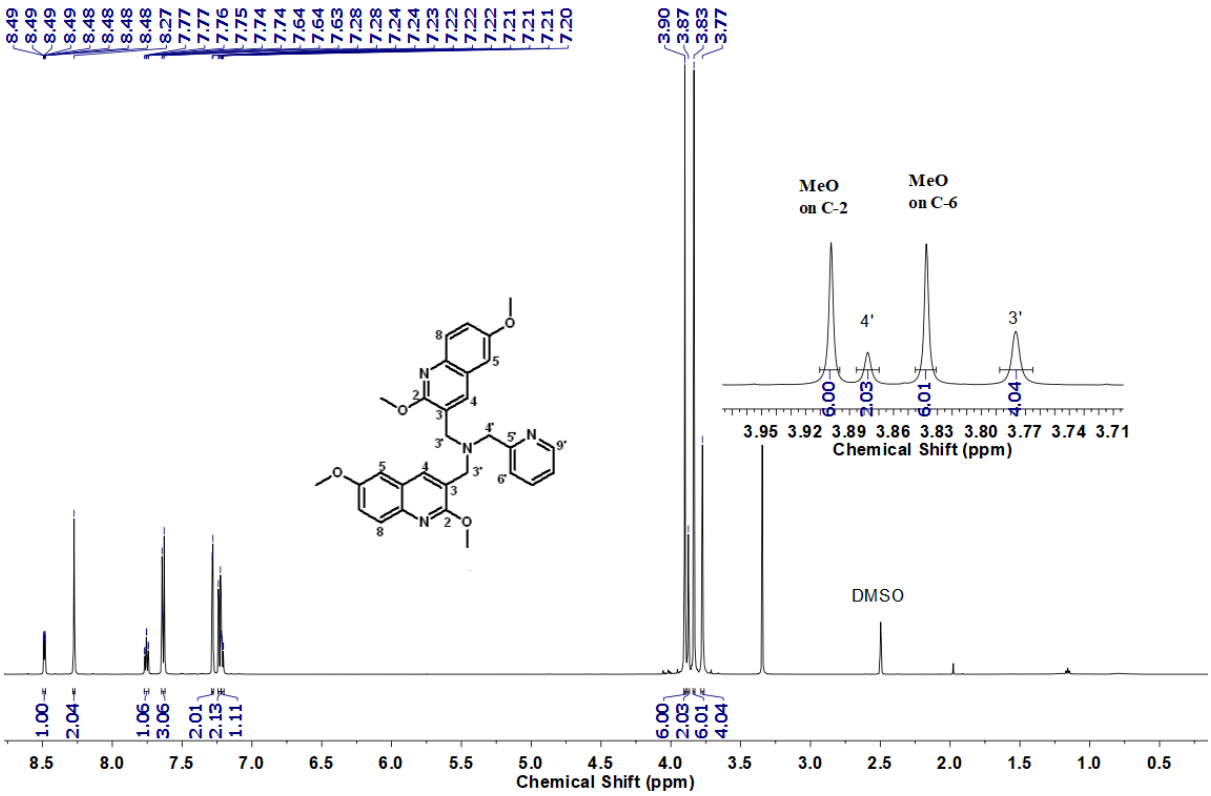
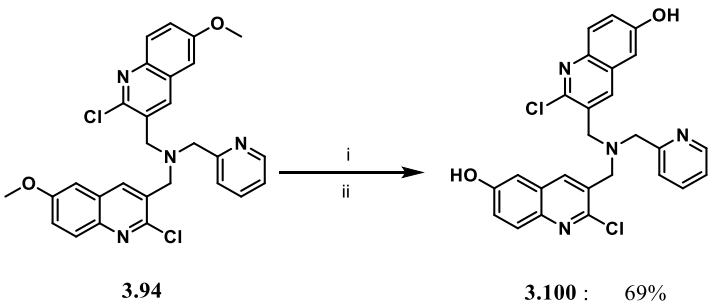


Figure 3.11:[1]H NMR spectrum (600 MHz, DMSO-*d6*) for compound **3.98**.

3.3.13 Synthesis of demethylated compound 3.100

After successfully synthesising compound **3.94** in section **3.3.10**, we attempted to demethylate the methoxy group on C-6 of the quinoline ring by treating it with boron tribromide in DCM at -78 °C under nitrogen gas atmosphere. Boron tribromide (BBr_3) is a relatively mild reagent for effectively cleaving phenolic methyl ethers[163]. Reaction work up afforded the demethylated adduct in yield of 69% after column chromatography.



Scheme 3.19: Reagents and conditions: (i) BBr_3 1M in DCM, -78 °C, N_2 (g), 30 min (ii) r.t, N_2 (g), 3 h.

3.3.13.1 Spectroscopic characterisation of demethylated compound 3.100

Compound **3.100** was characterised using FT-IR, ^{1}H NMR and ^{13}C NMR. In the IR spectrum, the hydroxyl band appears in the range 3230 – 3200 cm^{-1}. ^{1}H NMR shows all twelve aromatic proton signals in the aromatic region. However, appearance of the prominent new downfield singlet integrating for two at chemical shift 10.12 ppm indicated the presence of an OH group. On performing the deuterium wash experiment, the signal corresponding to OH resonating around chemical shift 10.12 ppm in $CDCl_3$ disappeared. This resulted from the fact that the hydrogen carried is exchangeable and was presumably exchanged for deuterium atoms (from D_2O) which are not visible in NMR. ^{13}C NMR confirms the disappearance of the methoxy group signal resonating at 55.6 ppm in **3.94**. Finally, HMBC experiment conducted showed multiple bond correlation between the formed OH proton with C-6, C-5 and C-7.

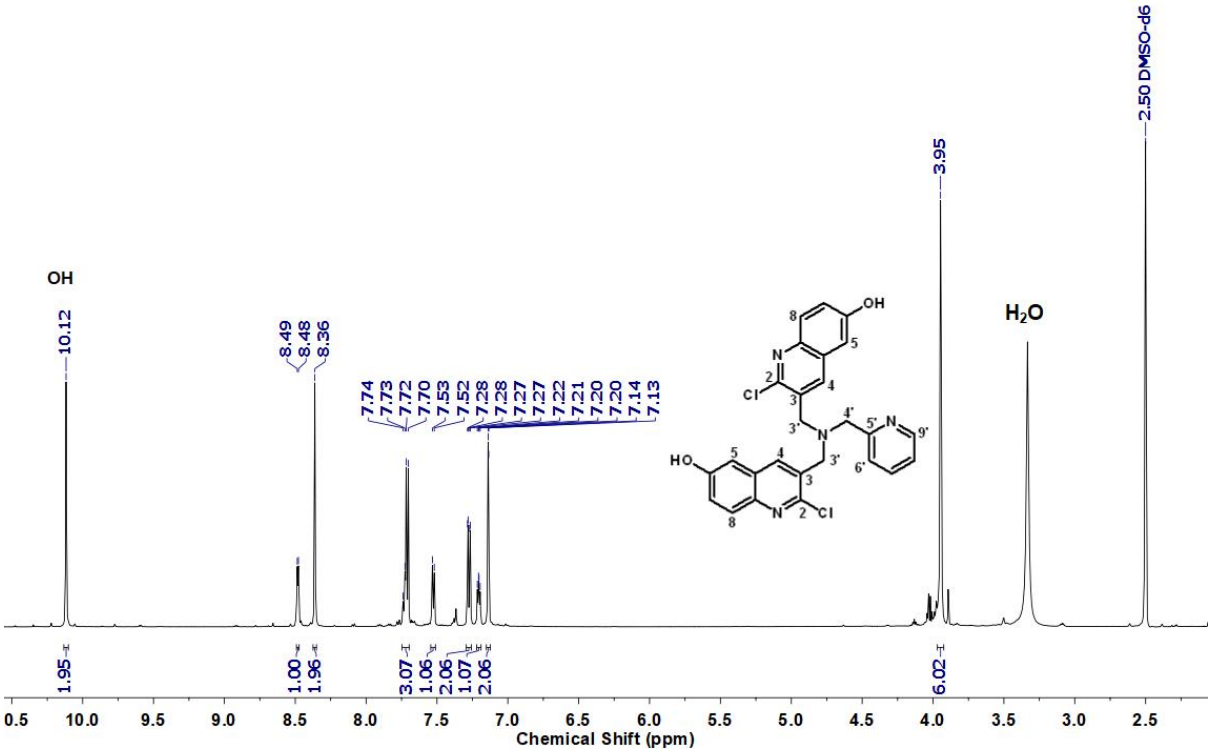
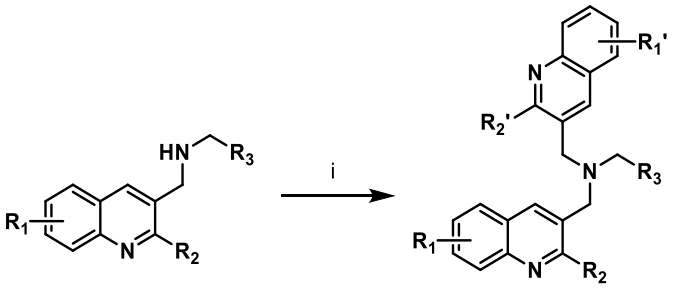


Figure 3.12:^{1}H NMR spectrum (600 MHz, DMSO-*d6*) for compound **3.100**.

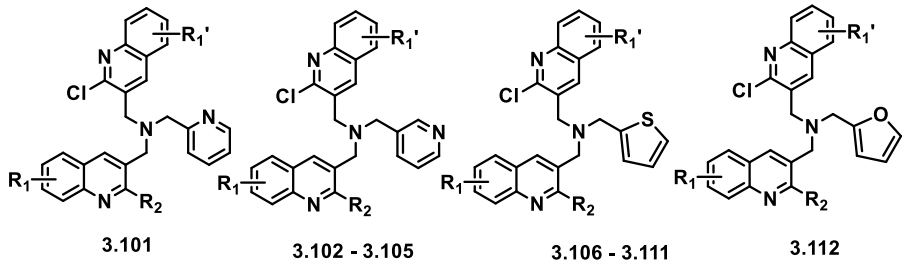
3.3.14 Synthesis of *bis* quinoline derivatives 3.101 – 3.112

For those compounds that did not form *in situ*, the approach was to run the chloro-amine coupling of relevant secondary amines **3.73 – 3.91** with relevant chloromethylquinolines **3.46 – 3.50**, via nucleophilic substitution using ethanol and TEA[114] as shown in **Scheme 3.19**. Various amines **3.73 − 3.91** were dissolved in ethanol and treated with TEA at 78 °C for 5 min. Respective (chloromethyl)quinolines **3.46 – 3.50** were added portion wise and the reaction mixture allowed to heat under reflux for 12 – 18 h while monitoring the reaction progress by TLC. Reaction work-up and subsequent purification by silica gel chromatography afforded the desired tertiary amines in low to high yields ranging from 17 − 82% (**Table 3.3**).



Scheme 3.20: *Reagents and conditions*: (i) 3-(Chloromethyl)quinolines, EtOH, TEA, 78 °C, 12 – 18 h.

Table 3.3: Isolated yields and M.p of target compounds.**3.101 – 3.112**.



Compound	R	R_2	$R_{1'}$	Yield (%)	M.p °C
3.101	H	MeO	H	65	85 – 87
3.102	H	MeO	6-Me	65	130 – 131
3.103	6-F	MeO	6-Me	54	139 – 140
3.104	5,7-diMe	Me	6-Me	19	-
3.105	5,7-diMe	Cl	6-Me	17	-
3.106	6-Me	MeO	6-Me	60	107 – 109
3.107	6-Me	MeO	6-MeO	82	141 – 142
3.108	6-MeO	MeO	6-Me	79	137 – 138
3.109	6-F	MeO	6-Me	65	190 – 192
3.110	5,7-diMe	MeO	6-Me	81	84 – 86
3.111	5,7-diMe	MeO	6-MeO	59	79 – 80
3.112	H	MeO	6-Me	71	-

- Viscous liquid

3.3.14.1 Spectroscopic characterisation of *bis* quinoline derivatives 3.101 − 3.112

Compounds **3.101 − 3.112**, were characterised by common spectroscopic techniques. Successful nucleophilic substitution was indicated by the disappearance of the sharp bands in the IR spectra of products, which often appeared at *v* 3364 – 3221 cm^{-1} for the secondary amines intermediates (**3.73 − 3.91**). This indicated that N-H group was no longer present in the products. ^{1}H-NMR spectra of all compounds show the presence of new aromatic protons after introduction of various substituted chloromethylquinolines. For example, ^{1}H-NMR spectrum of **3.107** in **Figure 3.13,** eleven aromatic protons are presented with expected multiplicity. The full structural elucidation of each compound was carried out using 2D NMR spectroscopic data sets consisting of COSY, HSQC and HMBC experiments. In addition, high resolution mass spectral data confirmed the formation of these compounds.

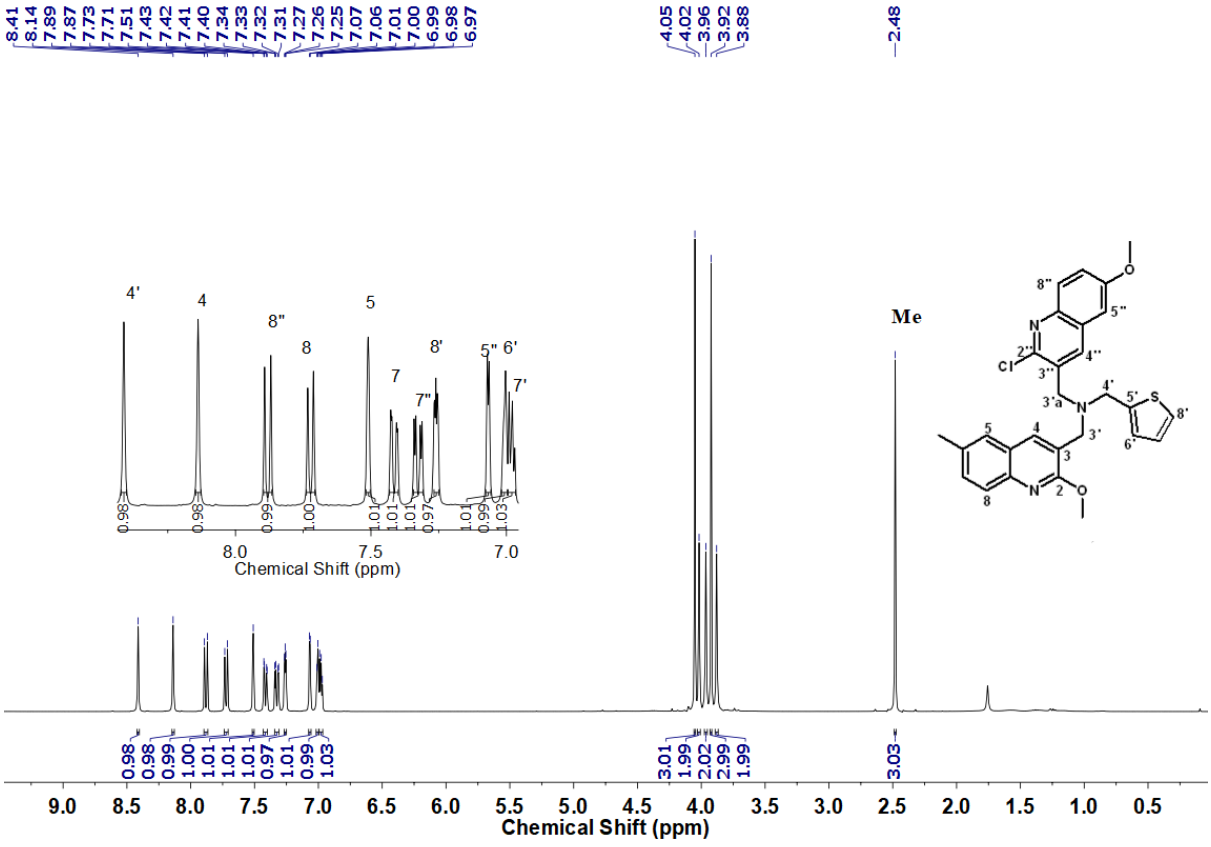
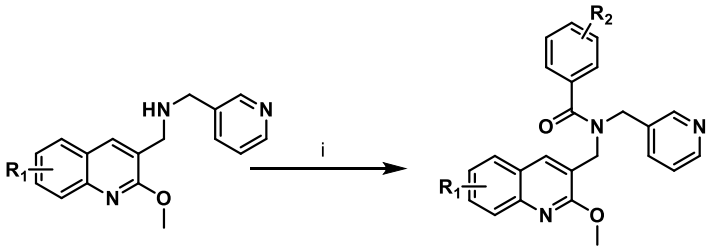


Figure 3.13: ^{1}H NMR spectrum (600 MHz, $CDCl_3$) for compound **3.107**.

3.3.15 Synthesis of benzamide derivatives 3.113 – 3.126

Having been successful in synthesising *bis* quinoline systems, the last attempt was to explore the use of **3.73 – 3.91** precursor compounds in the synthesis of carboxamide derivatives. Amide bond constitutes a fundamental functional group in organic and biological chemistry[164]. Amide bonds are found in many drugs, natural products, and polymers. It is reported that more than 25% of all drugs contain at least one amide bond[165]. Reaction between acyl chloride and amine is one of the easiest methods of amide bond formation. An additional base is usually required to trap the formed HCl and avoid the conversion of the amine into its unreactive HCl salt. These couplings are usually performed in inert dry solvents, in the presence of a non-nucleophilic tertiary amine i.e. TEA, normally accelerated with a catalytic amount of DMAP[166]. Nevertheless, the disadvantages of using acyl halides include their readily hydrolysis, racemisation and the exothermic nature of their reaction with amines as well as difficulties in purification[167].

The preparation of tertiary amides as shown in **Scheme 3.21** involved *N*-acylation of the secondary amines **3.73 – 3.91** with different 4-substituted benzoyl chlorides. Besides hit molecule GSK498384A, this class of compounds is also greatly inspired by the work of Debnath and co-workers[125] who reported the synthesis of 4-chloro-*N*-(furan-2-ylmethyl)-*N*-((6-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl) benzamide as an inhibitor targeted to the HIV-1 capsid. Thus, compounds **3.73** – **3.91** in DCM at 0 °C treated with TEA and DMAP were reacted with excess relevant benzoyl chlorides in a stoppered round bottomed flask. The TLC showed a new single spot (no other unidentifiable spots on plate). The products were purified by using column chromatography and obtained as solids in 41 – 74% yields (**Table 3.4**).



Scheme 3.21: *Reagents and conditions*: (i) Benzoyl chloride, DCM, TEA, DMAP (cat), 0 °C, 12 h.

3.3.15.1 Spectroscopic characterisation of benzamide derivatives 3.113 − 3.126

The structures of the synthesised benzamide derivatives were confirmed by FT-IR, ^{1}H and ^{13}C NMR spectroscopy as well as HRMS. For instance, the IR spectrum of compound **3.113** revealed the presence of a broad intense band in the range 1628 – 1617 cm^{-1} assignable to the -C=O- of the amide unit. The NMR spectra of benzamide compounds were complicated to analyse at 298 K because of signal broadening giving rise to unresolved multiplicities. The tendency of benzamides to form rotamers due to hindered rotation about the C–N bond of the amide[168] results in complicated spectra. This arises from delocalisation of the nitrogen lone pair of electrons leading to stabilisation of the planar rotamers I and II[169] as shown in **Figure 3.14**

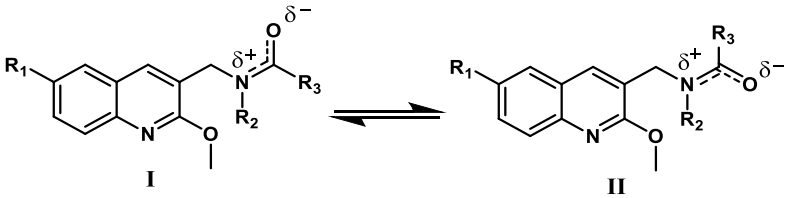
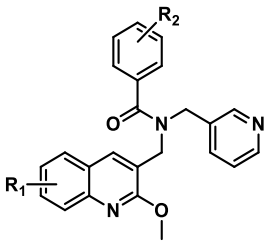


Figure 3.14 Rotameric options for the benzamide derivatives.

Table 3.4: Isolated yields, M.p and HRMS values of benzamide compounds.



Compound	R_1	R_2	Yield (%)	M.p. (°c)	$[M + H]^+$
3.113	6-OMe	4-Br	47	107 – 109	492.0927
3.114	6-MeO	H	70	148 – 150	414.1816
3.115	6-MeO	4-OMe	64	99 – 101	444.1920
3.116	6-MeO	4-F	51	106 – 108	432.1719
3.117	6-Me	4Br	42	114 – 116	476.0972
3.118	6-Me	4-F	49	139 – 141	416.1779
3.119	6-Me	H	72	136 – 138	398.1878
3.120	6-F	4-Br	46	143 – 145	480.0733
3.121	6-F	4-F	43	109 – 111	420.1525
3.122	6-F	4-MeO	41	129 – 131	432.1721
3.123	6-F	H	69	127 – 129	402.1619
3.124	H	H	71	147 – 149	384.1714
3.125	H	4-OMe	65	142 – 144	414.1813
3.126	H	4-F	55	122 – 124	402.1623

The rotamers obtained were not separable on silica gel column chromatography. Organic chemists often responded to this problem by conducting variable-temperature (VT) NMR experiments, changing NMR solvents, or adding complexing agents[170]. In this study, Variable temperature (VT) NMR was the preferred method for studying the equilibration of the rotamers due to absence of a variety different deuterated NMR solvents and complexing agents. At r.t we observed multiple peaks with broad signals and complex splitting while at higher temperatures the spectrum simplifies as the equivalent peaks are averaged out.

The ^{1}H-NMR spectrum of compound **3.113** shown below (**Figure 3.15**) reveals expected aromatic signals integrating for twelve, methylene protons (from H - 3′ and H - 4′) integrating for four and two methoxy groups integrating for six protons. However, the splitting pattern is complex and difficult to interpret at 298 K. Signals of H-3′ and H-4′ overlap and give rise to a multiplet at chemical shift ranging from 4.70 – 4.51 ppm. Gradual increase of temperature from 298 K to 318 K resolves the overlapping methylene protons into two distinct singlet peaks integrating for two protons independently. Signal overlap is also observed in aromatic protons which is resolved by the gradual temperature increase. When temperature gets enough high, signal duplication turns to merge at coalescence temperature, which results from the fast exchange of the two rotamers.

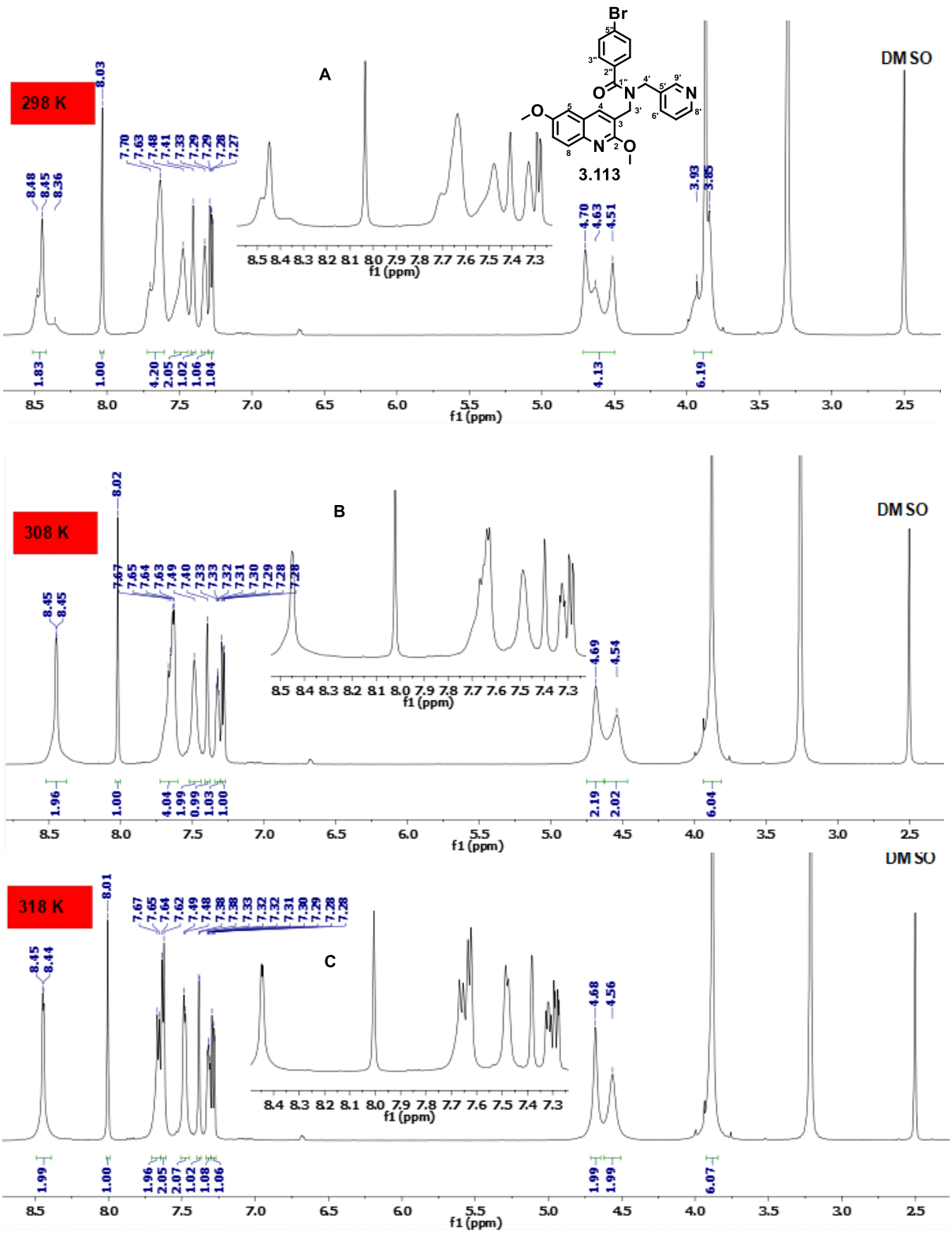


Figure 3.15: ^{1}H NMR spectrum (600 MHz, DMSO-$_{d6}$) of benzamide derivative **3.113** at (A) 298 K, (B) 308 K and (C). 318 K

^{13}C NMR shows expected aromatic carbon peaks for all aryl quinoline carboxamide compounds both at r.t and elevated temperature. Interestingly, at r.t the two *N*-methylene groups show four signals (two intense and two weak signals) confirming the presence of rotamers. Increasing the temperature of the NMR probe to 328 K made *N*-methylene signals cease to be clearly visible. The apparent absence of expected two ^{13}C NMR *N*-methylene signals in most of the compound spectra are attributed to site-exchange line-broadening effects[171]. The presence of these nuclei in such cases is, however, supported by the HRMS data and by other 2D experiments. The HRMS using Electron Spray Ionisation (ESI+) shown in **Figure 3.16** reveals the molecular ion peak at *m/z* 492.0927 which is consistent with the proposed chemical structure of **3.113**.

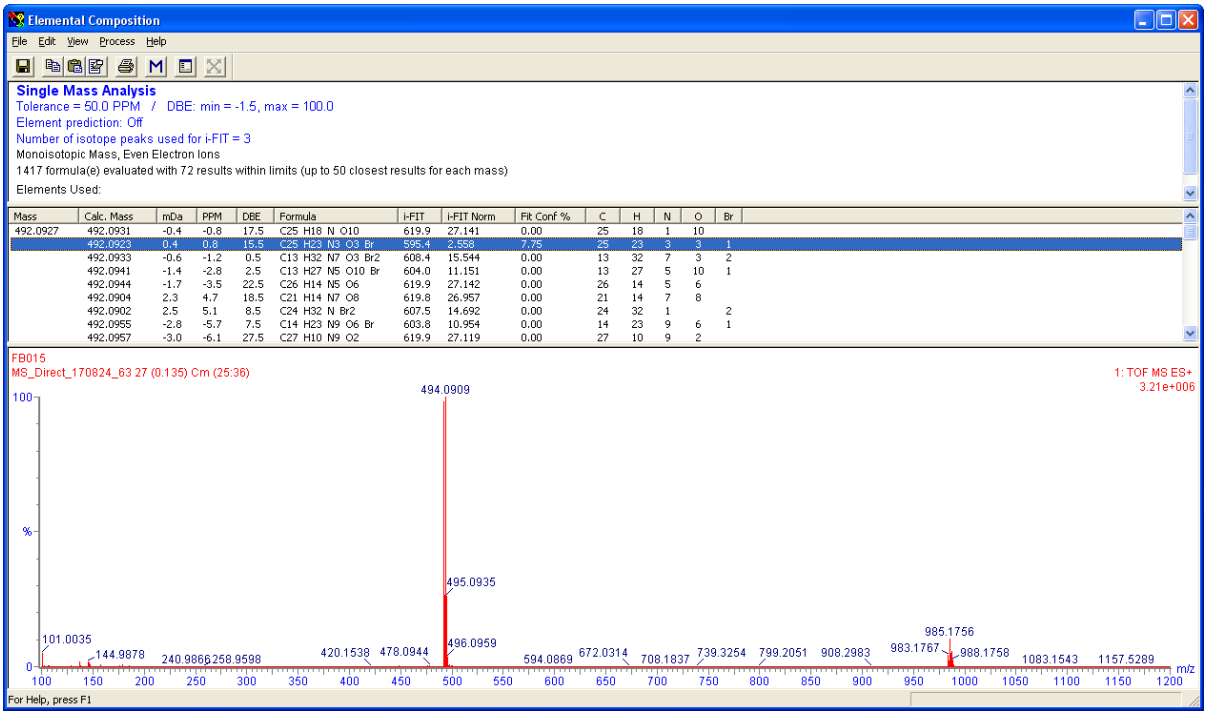


Figure 3.16: HRMS spectrum of benzamide derivative **3.113**.

Chapter Four

In vitro biological evaluation of 2,3-substituted quinoline derivatives

4.1 Introduction

This research was pursued to investigate new quinoline based compounds as potential antitubercular, antimalarial and antitrypanosomal agents. Herein, the synthesised compounds were screened in a broth microdilution assay against *M. tuberculosis* H37Rv using rifampicin as a standard to establish their antitubercular potential. Considering the importance of quinoline scaffold in compounds for treatment of protozoan parasitic diseases, the compounds investigated in this study were also cross-screened for their potential activity against *P. falciparum* and nagana *T.b. brucei*, causative agents for malaria and animal African trypanosomiasis. Target compounds were evaluated *in vitro* against 3D7; - the chloroquine sensitive (CQS) strain of *P. falciparum*, with chloroquine (CQ) included as the control drug. Antitrypanosomal activity of the compounds was evaluated against *T. b. brucei* 427 strain using pentamidine (PMD) as a positive control. The cytotoxicity potential of target compounds was assessed against HeLa (human cervix adenocarcinoma) cells and emetine was used as standard. Antimalarial and antitrypanosomal activities are expressed as IC_{50}, which is the minimum concentration of a compound necessary to cause 50% inhibition of growth. Antitubercular activity is reported as MIC_{90}, which is the minimum concentration required to inhibit tubercular growth by 90%. The biological screening assays were conducted in collaboration with the following laboratories: 1) Centre for Chemico- and Biomedicinal Research (CCBR)/Biochemistry and Microbiology Department, Rhodes University – Professor Heinrich Hoppe; 2) SAMRC/NHLS/UCT Molecular Mycobacteriology Research Unit, Department of Pathology, University of Cape Town – Associate Professor Digby Warner.

4.2 Biological results and discussion

4.2.1 *In vitro* antimalarial and antitrypanosomal activities of quinolinyl secondary amines 3.57 − 3.91

Compounds **3.57 – 3.72** were first screened *in vitro* against human HeLa cells at a single point concentration of 20 μM in duplicates prior to conducting other assays to investigate potential cytotoxicity effects. Compounds exhibiting <50% cell viability were considered to pose cytotoxicity risk, while compounds exhibiting >50% cell viability were considered to pose low cytotoxicity risk[172]. Similarly, antimalarial and antitrypanosomal screening of these two series also commenced with the single-concentration screening to determine parasite percent viability. **Figure 4.1** shows percent viability assessments of the 3D7 Chloroquine sensitive strain of *P. falciparum, T. b. brucei* 427 strain and HeLa cells at 20 μM.

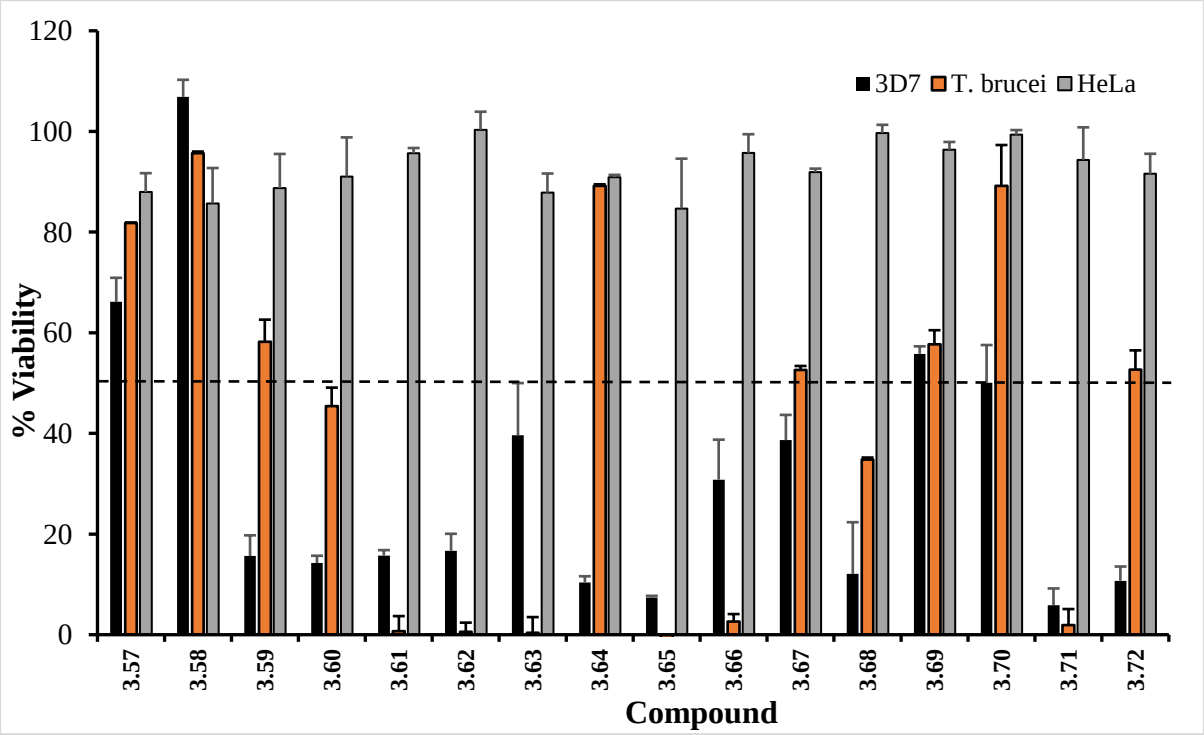
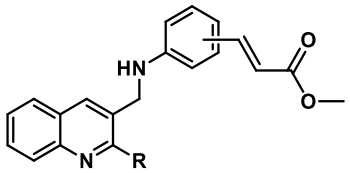


Figure 4.1: *In vitro* antimalarial, antitrypanosomal and cytotoxicity (HeLa) data for compounds **3.57 – 3.72** expressed as percentage viability.

From **Figure 4.1**, all compounds in this series showed no significant decrease in percent viability of the HeLa cells (>80%) during a 24 h incubation, confirming that the observed activities are specific to the protozoan parasites. Compounds **3.59 – 3.68**, **3.71** and **3.72** on the other hand, exhibited significant growth inhibition and the percentage viability of *P. falciparum* 3D7 strain for each compound was below 50% at 20 μM. Compounds **3.60 –3.63**, **3.65 – 3.66**, **3.68** and **3.71** exhibited below 50% growth inhibition of trypanosome parasites at 20 μM. The IC_{50} values of compounds that exhibited plasmodial/trypanosome percent viability values of < 50% were determined.

Table 4.1: *In vitro* antimalarial, antitrypanosomal and ClogP data for **3.57** − **3.72**.



Compound	Position of acrylate	R	IC_{50} (μM)	IC_{50} (μg/ml)	*C*logP[a]
			3D7	*T. b. brucei*	
3.59	*meta*	pyrrolidin-1-yl	9.11	ND	4.2
3.60	"	piperidin-1-yl	1.39	21.1	4.7
3.61	"	morpholino	3.10	16.9	3.3
3.62	"	thiomorpholino	3.09	12.3	4.1
3.63	*para*	pyrrolidin-1-yl	26.3	13.1	4.1
3.64	"	piperidin-1-yl	7.01	ND	4.7
3.65	"	morpholino	16.6	ND	3.3
3.66	"	thiomorpholino	16.7	5.60	4.1
3.67	"	4-phenylpiperazin-1-yl	1.78	ND	5.3
3.68	*ortho*	methoxy	21.0	12.9	4.6
3.71	"	thiomorpholino	7.46	4.50	4.1
3.72	"	4-phenylpiperazin-1-yl	8.32	ND	5.3
CQ			0.016	-	-
PMD			-	0.017	-

[a]ChemBioDraw Ultra 14.0 used to generate *C*logP. CQ: Chloroquine. PMD: Pentamidine

Based on the single concentration screening data, the IC_{50} values for antimalarial were determined for compounds **3.59 – 3.68**, **3.71** and **3.72** and antitrypanosomal for compounds **3.60 – 3.63**, **3.65 – 3.66**, **3.68** and **3.71** (**Table 4.1**). Twelve analogues, **3.59 – 3.68, 3.71** and **3.72** exhibit favourable antiplasmodial activity against the 3D7 strain, whereas seven analogues in the series, **3.60 – 3.63, 3.66, 3,68** and **3.71** possess promising antitrypanosomal activity against the nagana 427 strain. Highest antiplasmodial activity is observed for analogue **3.60** with an IC_{50} value of 1.39 µM whereas **3.71** shows the highest antitrypanosomal activity with an IC_{50} value of 4.50 µg/ml. This data suggest that 3-cinnamate moiety is more favourable for antiplasmodial activity compared to the 2-cinnamate and 4-cinnmate as deduced from the IC_{50} values of **3.59** (9.11 µM), **3.60** (1.39 µM), **3.61** (3.10 µM) and **3.62** (3.09 µM) which are all < 10 µM. The next set of results are for quinolinyl secondary amines **3.73 – 3.91** synthesised. The percent viability data for the antimalarial and cytotoxicity of compounds **3.73 – 3.91** is presented in **Figure 4.2**.

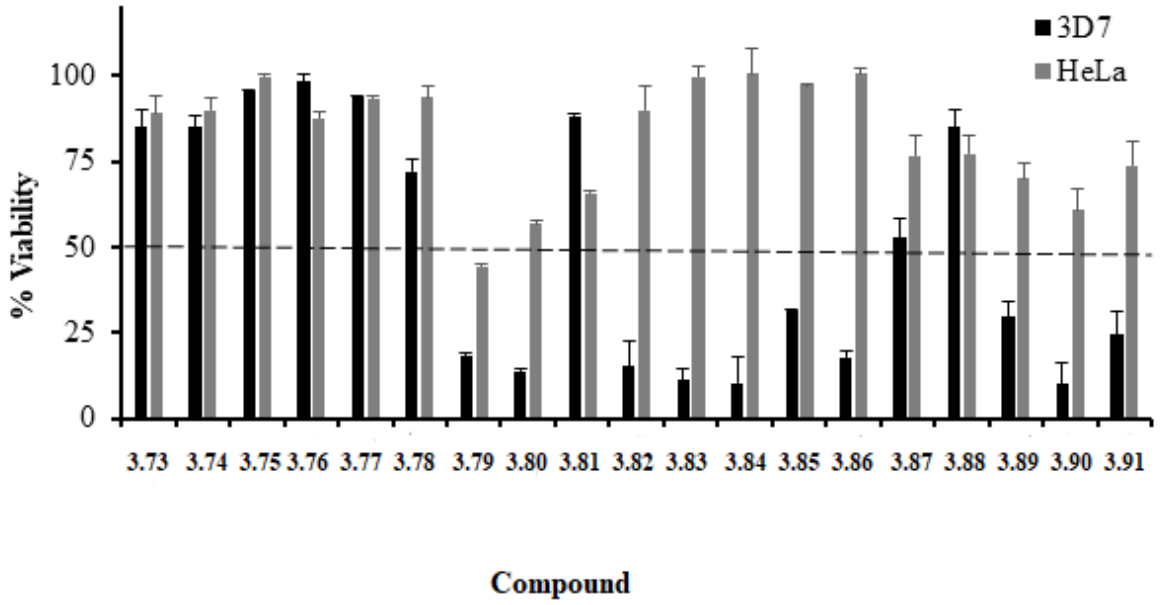
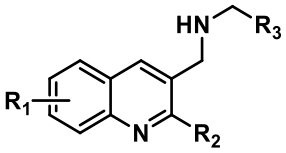


Figure 4.2: *In vitro* antimalarial and cytotoxicity (HeLa) data for compounds **3.73 – 3.91** expressed as percentage viabilitiy**.**

The single-point concentration evaluation of these compounds **3.73 – 3.91**, reveal that compounds **3.79 − 3.80**, **3.82 – 3.86**, and **3.89 – 3.91** were effective and reduced the parasite viability to below 50% at the concentration of 20 µM (**Figure 4.2**). Although compound **3.79** showed percent *P. falciparum* viability of <50%, it is coupled with significant cytotoxicity as it exhibited <50% HeLa cell viability.

Table 4.2: *In vitro* antimalarial activity expressed as IC_{50} and ClogP of **3.73 – 3.91**.



Compound	R_1	R_2	R_3	IC_{50} (µM)	ClogP[a]
				3D7	
3.79	H	OMe	2-Py	1.40	1.9
3.80	5,7-diMe	OMe	2-Py	0.23	2.9
3.82	H	OMe	3-Py	13.4	1.9
3.83	6-Me	OMe	3-Py	13.4	2.4
3.84	6-OMe	OMe	3-Py	12.8	2.2
3.85	6-F	OMe	3-Py	17.9	2.1
3.86	6-Cl	OMe	3-Py	16.8	2.6
3.89	H	OMe	4-Py	2.10	1.9
3.90	5,7-diMe	OMe	4-Py	12.0	2.9
3.91	H	Cl	4-Py	2.30	1.9
CQ	-	-	-	0.023	-

[a]ChemBioDraw Ultra 14.0 used to generate ClogP. CQ: Chloroquine

The bioassay results from **Table 4.2** reveal several interesting features:

(i) Most of quinolinyl secondary amines displayed encouraging *P. falciparum* activity with IC_{50} values in the range 0.20 – 18 μM, and compound **3.80** identified as hit compound (IC_{50} < 1 μM).

(ii) Incorporation of pyridinyl group clubbed with a methoxy group at position C-2 of quinoline appeared to increase inhibitory activity against the 3D7 strain of *P. falciparum* parasite.

(iii) With methoxy group at position C-2 of the quinoline, the order of antiplasmodial activity against 3D7 strain of *P. falciparum* for pyridinyl moiety is 2-pyridinyl (**3.79 − 3.80**) > 4-pyridinyl (**3.82 − 3.86**) >>3-pyridinyl (**3.89 − 3.91**).

(iv) Substitution of the pyridinyl moiety with 2-thiophenyl and 2-furanyl groups resulted in reduced activity against the *P. falciparum* strain.

4.2.2 *In vitro* antiplasmodial activity of *bis*-quinolinyl-based compounds 3.92 − 3.112

With the primary objective of improving the activity of the hit compound **3.80** (**Table 4.2**), we explored the effects of converting the free N-H group in compounds **3.73 − 3.91** by incorporating the second quinoline motif to form tertiary amine analogues **3.92 – 3.100** and **3.101 – 3.112** referred to as *bis*-quinoline derivatives. The preliminary cell viability results of all the synthesized target compounds are summarised in **Figure 4.3**.

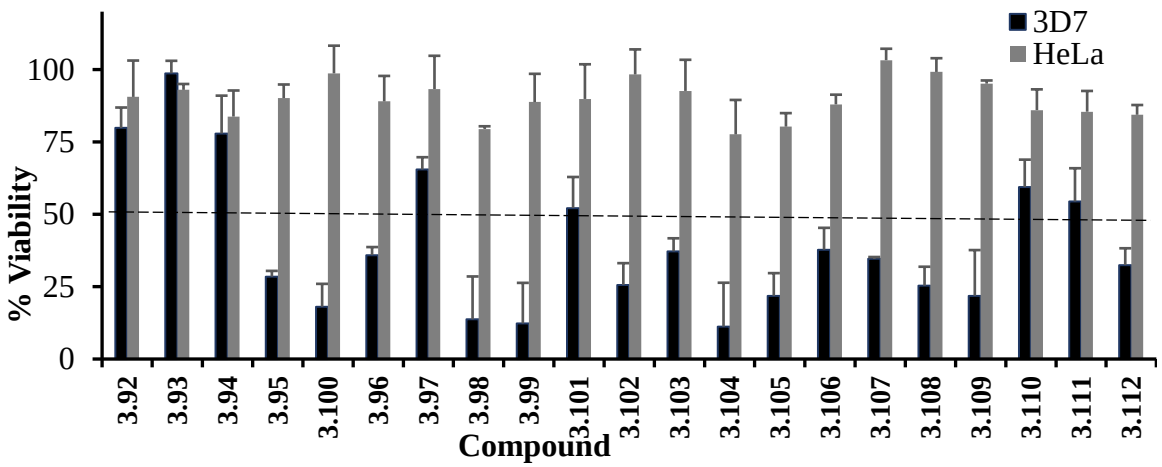
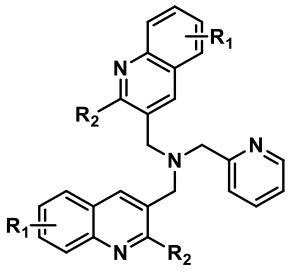


Figure 4.3: *In vitro* antimalarial and cytotoxicity activity expressed as percentage viabilities of **3.92 − 3.112**.

All target compounds showed no cytotoxicity against the HeLa cells at concentration 20 µM, and in most cases >85% HeLa cell viability was often observed (**Figure 4.3**). In terms of antiplasmodial potency, compounds **3.95**, **3.96**, **3.98**, **3.99**, **3.100**, **3.102 − 3109** and **3.112** demonstrated a percentage *P. falciparum* viability of <50% at the concentration of 20 µM. These results underline the intrinsic anti-malarial property of the compounds containing the bis quinoline motif, and the series was later put forward for further dose-response analysis and ultimate IC_{50} determination. The IC_{50} values of these compounds are presented in **Tables 4.3** and **4.4**.

Table 4.3: *In vitro* antimalarial activity expressed as IC_{50} and ClogP of *bis*-quinolines.

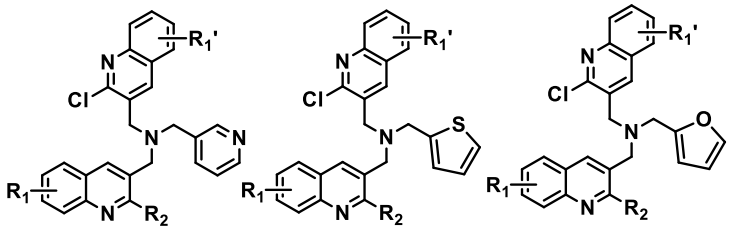


Compound	R_1	R_2	IC_{50} µM/(3D7)	*C*logP[a]
3.95	6-F	Cl	9.80	5.6
3.96	H	OMe	3.50	5.3
3.98	6-OMe	OMe	3.40	5.9
3.99	5,7-diMe	OMe	2.80	7.3
3.100	6-OH	Cl	2.50	5.4
CQ	-		0.023	-

[a]ChemBioDraw Ultra 14.0 used to generate ClogP. CQ: Chloroquine

From **Table 4.3**, compounds **3.95** and **3.100** showed favourable activity against the 3D7 strain with IC_{50} values of 9.8 and 2.5 µM, respectively. Note that, a simple structural modification at position C-2 of the quinoline with the methoxy group led to analogues **3.96**, **3.98** and **3.99**, showing superior antiplasmodial activity as compared to the precursor compounds **3.92, 3.93** and **3.94** respectively, which were ineffective (showed > 50% percent viability) at the single point screening concentration of 20 µM. This data suggest that a methoxy moiety on the position C-2 enhances antiplasmodial activity than chlorine atom for this sub-series. With the second position of quinoline seemingly favouring methoxy substituent for improved antimalarial activity, the next step was to expand the SAR of the *bis*-quinolines series with methoxy group at position C-2 and incorporating 3-pyridinyl and other five-membered heterocyclic systems. The *in vitro* biological data is presented in **Table 4.4.**

Table 4.4: *In vitro* antimalarial activity and *C*logP of *bis*-quinolines **3.102–3.112**.



Compound	R_1	R_2	$R_{1'}$	IC_{50} µM/(3D7)	*C*logP[a]
3.102	H	MeO	6-Me	9.8	5.8
3.103	6-F	MeO	6-Me	9.6	6.0
3.104	3,5-DiMe	MeO	6-Me	12.3	6.8
3.105	3,5-DiMe	Cl	6-Me	7.6	6.8
3.106	6-Me	MeO	6-Me	12.6	7.4
3.107	6-Me	MeO	6-MeO	13.4	7.2
3.108	6-MeO	MeO	6-Me	0.93	7.2
3.109	6-F	MeO	6-Me	11.3	7.1
3.112	H	MeO	6-Me	22.8	6.5
CQ	-	-	-	0.023	-

[a]ChemBioDraw Ultra 14.0 used to generate ClogP. CQ: Chloroquine

From **Table 4.4**, all compounds containing 3-pyridinyl moiety in combination with the methoxy group at position C-2 showed promising antimalarial activity with IC_{50} values in the range 7.6 – 12.3 µM. Compound **3.108**, bearing a 2-thiophenyl moiety emerged as the most active compound with IC_{50} value of 0.93 µM. However, looking closely at compound **3.108** presented in **Table 4.4** shows that methoxy substituent is on position C-6 of the quinoline core. This is not totally surprising given that several clinically used quinoline antimalarials including quinine, primaquine and tafenoquine bear a methoxy group at the same position. In fact, this structural similarity could allude to potential antimalarial mechanism of action of the synthesized compounds. It is worth noting that despite compounds having almost similar *C*logP

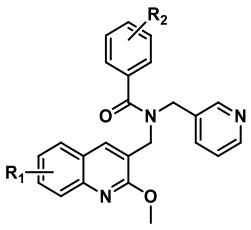
values, a simple modification of the chemical structure at position C-6 of the quinoline motif resulted in a big antiplasmodial activity variation among compounds as seen in compounds **3.106**, **3.108** and **3.109** by > 10-fold.

4.2.3 *In vitro* biological activities of aryl quinoline carboxamide compounds

Inspired by compound **3.80** (**Table 4.2**), the next set of compounds involved the incorporation of amide bond to form arylquinolinecarboxamides **3.113 – 3.126**, with the aim of evaluating the influence of the amide bond on the biological activity. Regrettably, most of these compounds were insoluble in DMSO and as such they were screened for their biological activity as suspensions which could have affected the bioassay results generated[173]. **Table 4.5** shows a summary of biological data of arylquinolinecarboxamide derivatives. At the single point concentration of 20 µM, only **3.119** reduced the percentage of malaria parasite viability to below 25%. None of the other compounds in this series were active and often the percentage parasite viability >60% was often observed. Subsequently, compound **3.119** was evaluated further for dose-response analysis to determine the corresponding IC_{50} value, which exhibited promising IC_{50} value of 1.27 µM against the 3D7 strain of *P. falciparum*. Similarly, compound **3.117** was the only member of this series that showed moderate activity against *T. b. brucei* with an IC_{50} value of 23.6 µM, while the rest of the other compounds were inactive.

The arylquinolinecarboxamide derivatives were evaluated for their potential antitubercular activity using the H37Rv strain of *M. tuberculosis*. Except compounds **3.113**, **3.117 – 3.120** and **3.126** which showed modest antitubercular activity with MIC_{90} values in the range of 40 – 80 µM, none of the compounds (**Table 4.5**) were active and majority showed poor activity at the maximum tested concentration MIC_{90} > 125 µM.

Table 4.5: *In vitro* antitubercular and ClogP of aryl quinoline carboxamides **3.113 – 3.126**.



Compound	R_1	R_2	MIC_{90}/µM	*C*logP[a]
			H37Rv	
3.113	6-MeO	4-Br	55.14	5.0
3.114	6-MeO	H	>125	4.0
3.115	6-MeO	4-OMe	>125	4.3
3.116	6-MeO	4-F	>125	4.3
3.117	6-Me	4Br	40.33	5.2
3.118	6-Me	4-F	62.50	4.5
3.119	6-Me	H	84.19	4.3
3.120	6-F	4-Br	50.14	4.9
3.121	6-F	4-F	>125	4.2
3.122	6-F	4-MeO	>125	4.2
3.123	6-F	H	>125	3.9
3.124	H	H	>125	3.8
3.125	H	4-OMe	>125	4.0
3.126	H	4-F	67.27	4.0
RMP			0.075	

[a]ChemBioDraw Ultra 14.0 used to generate ClogP. RMP: Rifampicin

As illustrated by data presented in **Table 4.5** above, it is observed that the structural variation around the quinoline ring on position 6 (R_1) and/or the functionalization of the benzoyl scaffold (R_2) influenced the antitubercular activity. Structure-activity relationship analysis of this series suggested that a methyl group at position 6 of the quinoline nucleus promoted antitubercular activity better than hydrogen, methoxy and fluoro groups. This was evident when comparing compounds **3.117** (MIC_{90}; 40.33 µM), **3.118** (MIC_{90}; 62.50 µM) and **3.119** (MIC_{90}; 84.19 µM)

all bearing a 6-methyl substituent on quinoline ring. With hydrogen on position 6, only **3.126**, methoxy only **3.113** and fluoro only **3.120** showed appreciable activity with MIC_{90} values of 67.27, 55.14, 50.14 μM respectively. Furthermore, incorporating bromine substituent on position 4′ of the benzoyl moiety as observed in compounds **3.117** (MIC_{90}; 40.33 μM), **3.113** (MIC_{90}; 55.14 μM) and **3.120** (MIC_{90}; 50.14 μM), significantly improved antitubercular activity than the other groups. It is however important to note that compound **3.117** (MIC_{90}; 40.33 μM), bearing both the favoured 6-methyl group on quinoline ring and bromine group on position 4′ of the benzoyl moiety emerged as the most active compound in the series as anticipated.

4.3 Conclusions

This research described *in vitro* biological activity of synthesized series of 2,3-substituted quinoline derivatives as potential antimalarial, antitrypanosomal and antitubercular agents. For secondary quinolinyl amines series, compounds **3.80** and **3.108** were identified as hit compounds with IC_{50} values of 0.23 μM and 0.93 μM against the 3D7 strain of *P. falciparum* respectively. On the other hand, in the arylquinolinecarboxamides derivatives **3.113 – 3.126**, only **3.119** showed appreciable antimalarial activity with an IC_{50} value of 1.27 μM against *P. falciparum* 3D7 strain and unfortunately, the rest of the other compounds from this series were inactive. Compound **3.117** was the only active analogue against *T. b. brucei* with an IC_{50} value of 23.6 μM. The arylquinolinecarboxamide series was also screened for potential antitubercular activity using *M. tuberculosis* H37Rv strain. Only a handful of compounds showed modest activity with MIC_{90} values in the range of 40 – 80 μM. Majority of the compounds in this series showed no activity against *M. tuberculosis* H37Rv strain. In this study, the data revealed that substitution of Cl group by methoxy moiety at C-2 of the quinoline scaffold is critical for biological activity of this class of 2,3-substituted quinolines. Due to time limitations, compounds **3.57 – 3.72**, **3.73 − 3.91** and **3.92 – 3.112** had just been submitted for antitubercular assays at the time of this thesis compilation.

Chapter Five

Experimental section

5.1 General Methods

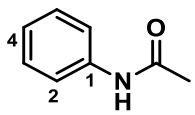
All chemicals and bulk solvents used in this study were sourced from Sigma-Aldrich (Pty) Ltd. and/or Merck (Pty) Ltd. and used without further purification. The progress of the reactions was monitored using analytical thin layer chromatography (TLC), performed on precoated silica gel plates (60 F254) from Merck. The plates were visualised under ultraviolet (UV 254 or 366 nm) light, or in iodine flask. Where necessary, crude compounds were purified by column chromatography using silica gel 60 Å, 70 – 230 mesh (0.068 – 0.2 mm) from Merck.

The ^{1}H, ^{13}C NMR and 2D NMR spectra were recorded on Bruker Biospin 300, Avance II 400 or Avance II 600 MHz spectrometers at r.t, unless stated otherwise. The samples were analysed in deuterated solvents, DMSO-d_6 with chemical shifts 2.5 ppm in ^{1}H NMR and 39.5 ppm in ^{13}C NMR and $CDCl_3$-*d* with chemical shifts 7.26 ppm in ^{1}H NMR and 77.2 ppm in ^{13}C NMR. The spectra were processed using MestReNova version 11.0 software. The chemical shifts were recorded in parts per million (ppm) and the *J*-coupling constants in Herts (Hz). The abbreviations used to describe signal multiplicities were: s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, t = triplet, td = triplet of doublets and m = multiplet. For Liquid chromatography–mass spectrometry (LC–MS) data, Bruker compact qTOF instrument was employed and processed using MZmine software. The high-resolution mass spectra (HRMS) were recorded on a Waters Synapt G2 Mass Spectrometer using electron spray ionization in the positive ionization mode (ESI+), and the IR spectra were recorded on PerkinElmer 100 FT-IR Spectrometer in the mid-IR range (640 – 4000 cm^{-1}). Lastly, melting points were determined using Stuart melting point apparatus SMP30 and were reported as obtained.

5.1.1 General procedure for synthesis of *N*-phenylacetamides (3.16 − 3.21)[174]

A 50 mL round bottom flask was charged with aniline (5.0 mmol), 20 mL of DCM and Ac_2O (6.0 mmol). The resultant reaction mixture was stirred at r.t for 30 min. After reaction completion as indicated by TLC, the mixture was washed with a saturated solution of Na_2CO_3, the organic layer dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude was recrystallised from water to obtain the desired *N*-phenylacetamide in good yields (96 – 98%).

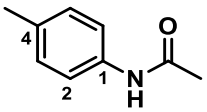
_N_-phenylacetamide (3.16)



3.16

White solid. Yield = 98%; M.p.: 111–113 ^oC (Lit.[175] 113–115 ^oC); ^1H NMR (300 MHz, $CDCl_3$): δ_H = 7.61 (1H, s, NH), 7.50 (2H, d, *J* = 7.8 Hz, H-2), 7.30 (2H, t, *J* = 7.8 Hz, H-3), 7.09 (1H, t, *J* = 7.6 Hz, H-4), 2.16 (3H, s, $C\underline{H_3}C=O$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 168.6, 137.9, 129.0, 124.3, 120.0, 24.5.

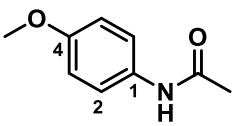
_N_-(4-Methylphenyl)acetamide (3.17)



3.17

White solid. Yield = 97%; M.p.: 141−143 ^oC (Lit.[176] 149–151 ^oC); ^1H NMR (300 MHz, $CDCl_3$): δ_H = 7.59 (1H, s, NH), 7.37 (2H, d, *J* = 8.4 Hz, H-2), 7.10 (2H, d, *J* = 8.4 Hz, H-3), 2.30 (3H, s, CH_3), 2.14 (3H, s, $C\underline{H_3}C=O$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 168.5, 135.4, 133.9, 129.4, 120.2, 24.4, 20.9.

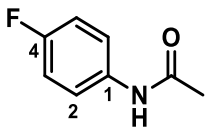
_N_-(4-Methoxyphenyl)acetamide (3.18)



3.18

White solid. Yield = 97%; M.p.: 129−131 ^oC (Lit.[177] 128–130 ^oC); ^1H NMR (300 MHz, $CDCl_3$): δ_H = 7.62 (1H, s, NH), 7.43 – 7.33 (2H, m, H-2), 6.88 – 6.78 (2H, m, H-3), 3.77 (3H, s, OCH_3), 2.13 (3H, s, $C\underline{H_3}C=O$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 168.6, 156.4, 131.0, 122.0, 114.1, 55.5, 24.3.

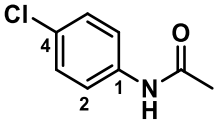
***N*-(4-Fluorophenyl)acetamide (3.19)**



3.19

White solid. Yield = 96%; M.p.: 148−150 °C (Lit.[178] 153–155 °C); ^{1}H NMR (400 MHz, Acetone-d_6): δ_H = 9.03 (1H, s, NH), 7.48 – 7.44 (2H, m, H-2), 6.88 – 6.83 (2H, m, H-3), 1.88 (3H, s, C$\underline{H_3}$C=O); ^{13}C NMR (100 MHz, Acetone-d_6): δ_C = 168.0, 158.5 (d, $J_{F.C}$ = 239.9 Hz), 135.9 (d, $J_{F.C}$ = 2.6 Hz), 120.8 (d, $J_{F.C}$ = 7.7 Hz), 115.0 (d, $J_{F.C}$ = 22.4 Hz), 23.2.

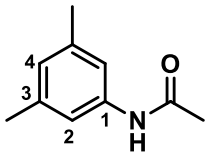
***N*-(4-Chlorophenyl)acetamide (3.20)**



3.20

White solid. Yield = 97%; M.p.:171−173 °C (Lit.[179] 176–178 °C); ^{1}H NMR (400 MHz, Acetone-d_6): δ_H = 9.10 (1H, s, NH), 7.52 – 7.49 (2H, m, H-2), 7.15 – 7.12 (2H, m, H-3), 1.92 (3H, s, C$\underline{H_3}$C=O); ^{13}C NMR (100 MHz, Acetone-d_6): δ_C = 168.1, 138.5, 128.5, 127.3, 120.5, 23.4.

***N*-(3,5-dimethylphenyl)acetamide (3.21)**



3.21

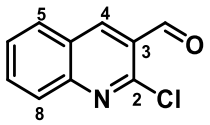
Yellow solid. Yield = 96%; M.p.: 135−137 °C (Lit.[180] 141–142 °C); ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.50 (1H, s, NH), 7.13 (2H, s, H-2), 6.74 (1H, s, H-4), 2.27 (6H, s, CH_3), 2.14 (3H, s, $COCH_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 168.8, 138.6, 137.9, 126.0, 117.9, 24.5, 21.3.

5.1.2 General procedure for synthesis of 2-chloroquinoline-3-carbaldehydes (3.22 − 3.27)[69]

A round bottom flask charged with *N*, *N*-dimethylformamide (7.0 mol) was placed on an ice bath and the temperature kept at 0 – 5 °C. To this flask, phosphorus oxychloride (12.0 mol) was added dropwise and the reaction mixture was stirred for 1 h at 0 – 5 °C. The appropriate *N*-phenylacetamide (1.0 mol) was then added and stirred for a further 30 min followed by heating under reflux for 5 – 24 h under N_2(g) atmosphere. After the reaction was completed

(TLC monitoring), the mixture was poured into 200 g of crushed ice under constant stirring. The precipitate obtained was vacuum filtered, washed with water (2 × 30 mL), air-dried and recrystallized from EtOAc to give the relevant compounds **3.22 − 3.27** in 36 – 84% yield.

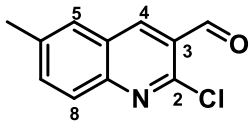
2-Chloroquinoline-3-carbaldehyde (3.22)



3.22

Yellow solid. Yield = 82%; M.p.: 143–145 °C (Lit.[69] 148–159 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 10.55 (1H, s, CHO), 8.74 (1H, s, H-4), 8.06 (1H, d, *J* = 8.5 Hz, H-5), 7.97 (1H, d, *J* = 8.2 Hz, H-8), 7.90- 7.85 (1H, m, H-6), 7.67 – 7.62 (1H, m, H-7); ^{13}H NMR (75 MHz, $CDCl_3$): δ_C = 189.1, 150.1, 149.6, 140.3, 133.6, 129.7, 128.6, 128.1, 126.5, 126.4.

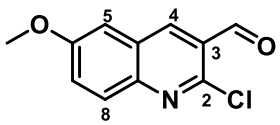
2-Chloro-6-methylquinoline-3-carbaldehyde (3.23)



3.23

Yellow solid. Yield = 80%; M.p.: 119–121 °C (Lit.[69] 124–125 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 10.54 (1H, s, CHO), 8.65 (1H, s, H-4), 7.95 (1H, d, *J* = 8.4 Hz, H-8), 7.72 – 7.68 (2H, m, H-5, H-7), 2.56 (3H, s, CH_3); ^{13} C NMR (75 MHz, $CDCl_3$): δ_C = 189.3, 149.3, 148.2, 139.5, 138.4, 135.9, 128.4, 128.2, 126.6, 126.3, 21.6.

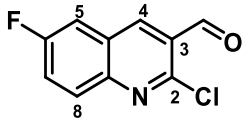
2-Chloro-6-methoxyquinoline-3-carbaldehyde (3.24)



3.24

Yellow solid. Yield = 62%; M.p.: 144–146 °C (Lit.[69] 145.5–146.6 °C); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H = 10.35 (1H, s, CHO), 8.79 (1H, s, H-4), 7.92 (1H, d, *J* = 9.1 Hz, H-8), 7.64 (1H, d, *J* = 2.9 Hz, H-5), 7.59 (1H, dd, *J* = 9.1, 2.9 Hz, H-7), 3.91 (3H, s, OCH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C = 190.0, 158.7, 146.8, 145.1, 140.2, 129.6, 128.1, 126.8, 126.6, 108.1, 56.3.

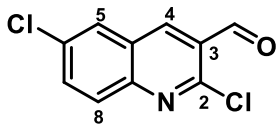
2-Chloro-6-fluoroquinoline-3-carbaldehyde (3.25)



3.25

Yellow solid. Yield = 55%; M.p.: 123–125 ^{o}C (Lit.[181] 71 ^{o}C); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 10.49 (1H, s, CHO), 8.63 (1H, s, H-4), 8.01 (1H, dd, J = 9.2, 5.1 Hz, H-8), 7.62 – 7.51 (2H, m, H-5, H-7); ^{13} C NMR (75 MHz, $CDCl_3$): δ_C = 188.9, 161.0 (d, $J_{F.C}$ = 252.0 Hz), 149.4 (d, $J_{F.C}$ = 2.9 Hz), 146.7, 139.5 (d, $J_{F.C}$ = 5.8 Hz), 131.2 (d, $J_{F.C}$ = 9.2 Hz), 127.3 (d, $J_{F.C}$ = 10.3 Hz), 126.9, 123.8 (d, $J_{F.C}$ = 26.1 Hz), 112.6 (d, $J_{F.C}$ = 22.1 Hz).

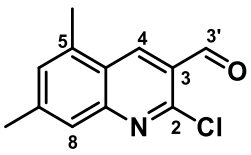
2,6-Dichloroquinoline-3-carbaldehyde (3.26)



3.26

Yellow solid. Yield = 36%; M.p.: 177–179 ^{o}C (Lit.[69] 190.5–191.5 ^{o}C); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 10.55 (1H, s, CHO), 8.66 (1H, s, H-4), 8.01 (1H, d, J = 9.0 Hz, H-8), 7.96 (1H, d, J = 2.2 Hz, H-5), 7.80 (1H, dd, J = 9.0, 2.2 Hz, H-7); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 188.8, 150.3, 147.9, 139.2, 134.4, 134.1, 130.1, 128.1, 127.2, 127.1.

2-Chloro-5,7-dimethylquinoline-3-carbaldehyde (3.27)



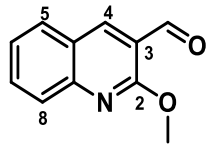
3.27

Yellow solid. Yield = 84%; M.p.: 131–133 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 10.53 (1H, s, CHO), 8.83 (1H, s, H-4), 7.66 (1H, s, H-6), 7.29 (1H, s, H-8), 2.71 (3H, s, CH_3), 2.55 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 189.4, 150.5, 150.1, 144.9, 137.0, 136.6, 130.9, 125.9, 124.9, 124.3, 22.2, 18.6.

5.1.3 General procedure for the synthesis of 2-methoxyquinoline-3-carbaldehydes (3.28 – 3.33)[182]

To a solution of KOH (75.7 mmol) in 100 mL of MeOH was added the corresponding 2-chloro-3-quinolinecarboxaldehyde (52.2 mmol) with constant stirring. The mixture was heated under reflux for 2.5 – 6 h and then cooled to r.t. The product was precipitated out by adding water (300 mL) and then collected by vacuum filtration. The dried crude was recrystalised from DCM to afford compounds **3.28 − 3.33** in yields ranging from 42 – 89%.

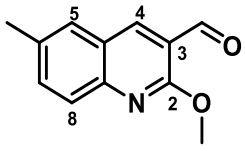
2-Methoxyquinoline-3-carbaldehyde (3.28)



3.28

Yellow solid. Yield = 89%; M.p.: 96–98 °C (Lit.[182] 92–93 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 10.46 (1H, s, CHO), 8.57 (1H, s, H-4), 7.88 – 7.82 (2H, m, H-5, H-8), 7.75 – 7.70 (1H, m, H-6), 7.45 – 7.39 (1H, m, H-7), 4.18 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 189.3, 161.2, 149.0, 140.0, 132.5, 129.7, 127.3, 125.0, 124.4, 120.1, 53.8.

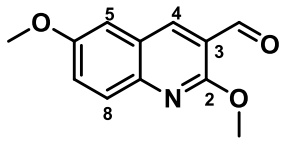
2-Methoxy-6-methylquinoline-3-carbaldehyde (3.29)



3.29

Yellow solid. Yield = 82%; M.p.: 87−89 °C (Lit.[101] 94–96°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 10.47 (1H, s, CHO), 8.50 (1H, s, H-4), 7.77 (1H, d, *J* = 8.5 Hz, H-8), 7.60 (1H, d, *J* = 2.0 Hz, H-5), 7.57 (1H, dd, *J* = 8.5, 2.0 Hz, H-7), 4.18 (3H, s, OCH_3), 2.51 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 189.5, 160.9, 147.4, 139.4 (2C), 134.7, 128.6, 127.0, 124.4, 120.0, 53.7, 21.2.

2, 6-Dimethoxyquinoline-3-carbaldehyde (3.30)

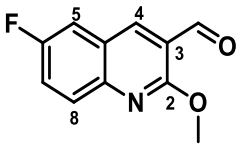


3.30

Yellow solid. Yield = 78%; M.p.: 148–150 °C (Lit.[183] 122–124 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 10.47 (1H, s, CHO), 8.49 (1H, s, H-4), 7.78 (1H, d, *J* = 9.2 Hz, H-8), 7.40 (1H, dd, *J* = 9.2, 2.9 Hz, H-7), 7.12

(1H, d, J = 2.9 Hz, H-5), 4.16 (3H, s, OCH_3), 3.92 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 189.5, 160.1, 156.6, 144.7, 138.6, 128.6, 125.0, 124.8, 120.0, 107.3, 55.6, 53.7.

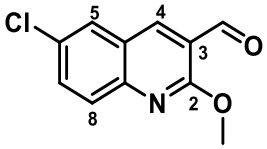
6-Fluoro-2-methoxyquinoline-3-carbaldehyde (3.31)



3.31

Yellow solid. Yield = 71%; M.p.: 117–119 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ_H = 10.39 (1H, s, CHO), 8.43 (1H, s, H-4), 7.78 (1H, dd, J = 9.0, 5.1 Hz, H-8), 7.45 – 7.37 (2H, m, H-5, H-7), 4.10 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 189.1, 160.8 (d, $J_{F.C}$ = 1.9 Hz), 159.3 (d, $J_{F.C}$ = 246.4 Hz), 145.8 (d, $J_{F.C}$ = 0.9 Hz), 139.1 (d, $J_{F.C}$ = 5.1 Hz), 129.4 (d, $J_{F.C}$ = 8.7 Hz), 124.7 (d, $J_{F.C}$ = 9.7 Hz), 122.2 (d, $J_{F.C}$ = 25.1 Hz), 120.6, 112.7 (d, $J_{F.C}$ = 21.0 Hz), 53.9.

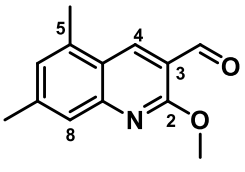
6-Chloro-2-methoxyquinoline-3-carbaldehyde (3.32)



3.32

Yellow solid. Yield = 42%; M.p.: 141–143 ^oC (Lit.[101] 145–147 ^oC); ^1H NMR (300 MHz, $CDCl_3$): δ_H = 10.45 (1H, s, CHO), 8.48 (1H, s, H-4), 7.81 (1H, d, J = 9.0 Hz, H-8), 7.79 (1H, d, J = 2.8 Hz, H-5), 7.65 (1H, dd, J = 9.0, 2.8 Hz, H-7), 4.18 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 188.9, 161.4, 147.3, 138.8, 133.1, 130.5, 128.8, 128.1, 125.0, 120.7, 54.0.

2-Methoxy-5,7-dimethylquinoline-3-carbaldehyde (3.33)



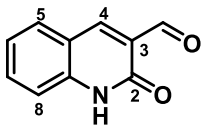
3.33

Yellow solid. Yield = 85%; M.p.: 98–100 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ_H = 10.42 (1H, s, CHO), 8.65 (1H, s, H-4), 7.48 (1H, s, H-6), 7.06 (1H, s, H-8), 4.15 (3H, s, OCH_3), 2.62 (3H, s, CH_3), 2.48 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 189.4, 161.2, 149.8, 143.4, 136.9, 136.2, 127.9, 124.8, 121.8, 118.4, 53.6, 22.1, 18.7.

5.1.4 General synthesis of 2-oxo-1,2-dihydroquinoline-3-carbaldehydes[184]

A solution of an appropriate 2-chloroquinoline-3-carbaldehyde (1.00 mmol) in 70% aqueous AcOH solution (10 mL) was heated at 95 °C for 10 h with stirring. The progress of the reaction was monitored by TLC. The solution was cooled to r.t and the precipitate formed was filtered, washed with water (10 mL) and air dried overnight to furnish needle-like crystals of **3.34** and **3.35** in yields of 88% and 85% respectively.

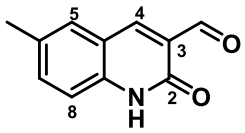
2-Oxo-1, 2-dihydroquinoline-3-carbaldehyde (3.34)



3.34

Yellow solid. Yield = 88%; M.p.: 309–311 ^{o}C (Lit.[184] 303−305 ^{o}C); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H = 12.21 (1H, bs, CONH), 10.24 (1H, s, CHO), 8.50 (1H, s, H-4), 7.92 − 7.90 (1H, m, H-5), 7.71 – 7.61 (1H, m, H-8), 7.37 − 7.34.(1H, m, H-6), 7.29 – 7.20 (1H, m, H-7); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C = 190.2, 172.4, 142.9, 141.6, 134.1, 131.4, 126.1, 123.1, 118.6, 115.9.

6-Methyl-2-oxo-1, 2-dihydroquinoline-3-carbaldehyde (3.35)



3.35

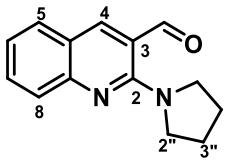
Yellow solid: Yield = 85%; M.p.: 228−230 °C (Lit.[125] 201–202 ^{o}C); ^{1}H NMR (400 MHz, DMSO): δ_H = 12.09 (1H, bs, CONH), 10.21 (1H, s, CHO), 8.40 (1H, s, H-4), 7.71 (1H, s, H-5), 7.48 (1H, d, J = 8.5 Hz, H-5), 7.24 (1H, d J = 8.5, Hz, H-7), 2.36 (3H, s, CH_3); ^{13}C NMR (100 MHz, DMSO): δ_C = 190.3, 170.8, 143.5, 138.9, 134.0, 129.0, 128.2, 123.5, 122.1, 118.2, 21.3.

5.1.5 General procedure for the synthesis of 2-aminoquinoline-3-carbaldehydes[117]

A mixture of 2-chloroquinoline-3-carbaldehyde (10.0 mmol), an appropriate amine (11.7 mmol) and K_2CO_3 (11.7 mmol) in DMF (50 mL) was heated under reflux for 7 h while stirring. After completion of the reaction (monitored by TLC), the mixture was cooled to r.t and poured

into ice water under continuous stirring. The light-yellow precipitate for **3.37 − 3.40** were filtered and air dried for overnight. Compound **3.36** did not form a precipitate and was extracted using EtOAC (50 mL). The organic layer was washed with brine (20 mL) and water (20 mL), dried ($MgSO_4$) and concentrated *in vacuo.* Purification of the compounds was done by silica gel column chromatography using $CHCl_3$ – Hexane (1:1) mixture as the mobile phase. Compounds **3.36 − 3.40** were obtained in 61 – 80% yield using this method.

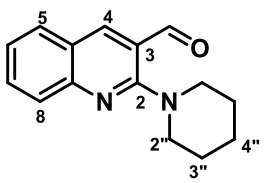
2-(Pyrrolidin-1-yl)quinoline-3-carbaldehyde (3.36)



3.36

Brown viscous liquid. Yield = 72%; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 10.18 (1H, s, CHO), 8.38 (1H, s, H-4), 7.72 − 7.71 (1H, m, H-5), 7.70 – 7.68 (1H, m, H-8), 7.64 – 7.58 (1H, m, H-6), 7.24 − 7.18 (1H, m, H-7), 3.66 – 361 (4H, m, H-2″), 2.00 – 1.95 (4H, m, H-3″); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 189.8, 154.7, 150.2, 143.7, 132.6, 129.1, 126.6, 122.6, 122.3, 120.7, 50.9, 25.7.

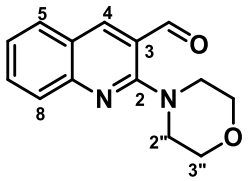
2-(Piperidin-1-yl)quinoline-3-carbaldehyde (3.37)



3.37

Yellow solid. Yield = 75%; M.p.:74–76 ^{o}C (Lit.[185] 84–84 ^{o}C); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 10.07 (1H, s, CHO), 8.38 (1H, s, H-4), 7.73 (1H, d, *J* = 8.6 Hz, H-5), 7.70 – 7.67 (1H, m, H-8), 7.61 − 7.56 (1H, m H-6), 7.29 − 7.23 (1H, m, H-7), 3.39 – 3.34 (4H, m, H-2″), 1.73 – 1.67 (4H, m, H-3″), 1.64 − 1.58 (2H, m, H-4″); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 190.6, 160.3, 149.4, 141.1, 132.2, 129.3, 127.5, 124.4, 123.9, 122.4, 52.6, 26.0, 24.5.

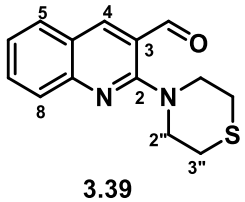
2-Morpholinoquinoline-3-carbaldehyde (3.38)



3.38

Yellow solid. Yield = 69%; M.p.: 96–98 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 10.18 (1H, s, CHO), 8.50 (1H, s, H-4), 7.85 – 7.79 (2H, m, H-5, H-8), 7.74 – 7.68 (1H, m, H-6), 7.42 – 7.36 (1H, m, H-7), 3.94 – 3.90 (4H, m, H-3″), 3.50 – 3.47 (4H, m, H-2″); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 190.0, 158.8, 149.3, 143.2, 132.6, 129.5, 127.6, 124.9, 124.2, 122.1, 66.9, 51.5.

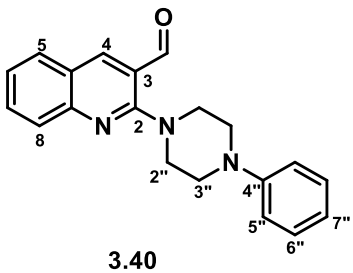
2-Thiomorpholinoquinoline-3-carbaldehyde (3.39)



3.39

Yellow solid. Yield = 61%; M.p.: 142–144 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 10.12 (1H, s, CHO), 8.48 (1H, s, H-4), 7.82 (1H, d, *J* = 8.5 Hz, H-5), 7.79 (1H, d, *J* = 8.3 Hz, H-8), 7.72 – 7.67 (1H, m, H-6), 7.40 – 7.36 (1H, m, H-7), 3.79 – 3.77 (4H, m, H-2″), 2.88 – 2.84 (4H, m, H-3″); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 190.0, 159.4, 149.2, 142.8, 132.6, 129.3, 127.6, 124.9, 124.1, 122.2, 53.5, 27.5.

2-(4-Phenylpiperazin-1-yl)quinoline-3-carbaldehyde (3.40)



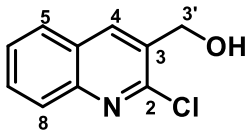
3.40

Yellow solid. Yield = 80%; M.p.: 139–141 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 10.23 (1H, s, CHO), 8.52 (1H, s, H-4), 7.87 (1H, d, *J* = 8.5 Hz, H-5), 7.81 (1H, d, *J* = 8.0 Hz, H-8), 7.74 – 7.70 (1H, m, H-6), 7.40 (1H, t, *J* = 7.4 Hz, H-7), 7.33 – 7.29 (2H, m, H-6″), 7.01 (2H, d, *J* = 8.2 Hz, H-5″), 6.91 (1H, t, *J* = 7.3 Hz, H-7″), 3.69 – 3.65 (4H, m, H-3″), 3.44 – 3.40 (4H, m, H-2″); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 190.2, 157.0, 151.2, 149.3, 142.7, 132.6, 129.3, 129.2, 127.6, 124.8, 124.1, 122.2, 120.0, 116.3, 51.1, 49.2.

5.1.6 General procedure for the synthesis of 3-(hydroxymethyl)quinolines[108]

To a solution of quinoline-3-carbaldehydes (1.0 eq) in absolute methanol (10 mL), solid sodium borohydride (1.2 eq) was added portion wise over a period of 30 min with constant stirring at r.t. The solvent was evaporated under reduced pressure and the resultant crude triturated with water to form crystalline solid, which was filtered, washed with water (10 mL) and air dried. The crude product was recrystallized from methanol to afford desired compounds in good yields (88 – 94%).

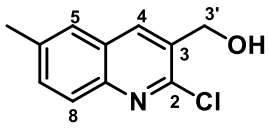
(2-Chloroquinolin-3-yl)methanol (3.41)



3.41

Yellow solid. Yield = 94%; M.p.: 166–168 ^{o}C (Lit.[186] 162−163 ^{o}C); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H = 8.45 (1H, s, H-4), 8.06 (1H, d, J = 8.1 Hz, H-8), 7.94 (1H, d, J = 8.9 Hz, H-5), 7.78 – 7.76 (1H, m, H-7), 7.66 – 7.60 (1H, m, H-6), 5.74 (1H, t, J = 5.5 Hz, OH), 4.69 (2H, dd, J = 5.5, 1.1 Hz, H-3′); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C = 148.9, 146.5, 136.3, 134.4, 130.6, 128.4, 127.9, 127.7, 127.6, 60.4.

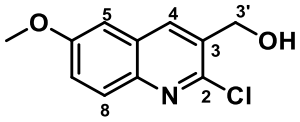
(2-Chloro-6-methylquinolin-3-yl)methanol (3.42)



3.42

Yellow solid. Yield = 90%; M.p.: 126–128 ^{o}C (Lit.[187] 124−125 ^{o}C); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.86 (1H, s, H-4), 7.74 (1H, d, J = 8.5 Hz, H-8), 7.46 (1H, d, J = 1.9 Hz, H-5), 7.43 (1H, dd, J = 8.5, 1.9 Hz, H-7), 4.74 (2H, d, J = 5.3 Hz, H-3′), 2.48 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 148.5, 144.2, 135.2, 133.8, 131.2, 126.6 (2C), 125.2, 124.7, 61.34, 21.3.

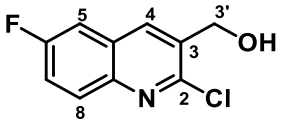
(2-Chloro-6-methoxyquinolin-3-yl)methanol (3.43)



3.43

Yellow solid. Yield = 94%; M.p.: 143–145 °C (Lit.[187] 129−131 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.16 (1H, s, H-4), 7.89 (1H, d, *J* = 9.2 Hz, H-8), 7.35 (1H, dd, *J* = 9.2, 2.6 Hz, H-7), 7.06 (1H, d, *J* = 2.6 Hz, H-5), 4.90 (2H, d, *J* = 5.5 Hz, H-3′), 3.91 (3H, s, $OC\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δc = 158.2, 146.4, 142.8, 135.1, 132.6, 129.5, 128.4, 122.8, 105.2, 62.0, 55.6.

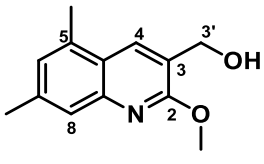
(2-Chloro-6-fluoroquinolin-3-yl)methanol (3.44)



3.44

Yellow solid. Yield = 88%; M.p.: 132–134 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ_H = 8.47 (1H, s, H-4), 8.04 – 7.99 (1H, m, H-8), 7.93 – 7.92 (1H, m, H-7), 7.70 – 7.67 (1H, m, H-5), 5.77 (1H, s, OH), 4.69 (2H, s, H-3′); ^{13}C NMR (150 MHz, DMSO-d_6): δ_C = 160.5 (d, $J_{F.C}$ = 245.6 Hz), 148.3 (d, $J_{F.C}$ = 2.4 Hz), 143.6, 135.8 (d, $J_{F.C}$ = 5.3 Hz), 135.4, 130.8 (d, $J_{F.C}$ = 10.4 Hz), 128.5 (d, $J_{F.C}$ = 10.8 Hz), 120.5 (d, $J_{F.C}$ = 25.6 Hz), 111.7 (d, $J_{F.C}$ = 22.3 Hz), 60.3.

(2-Methoxy-5,7-dimethylquinolin-3-yl)methanol (3.45)



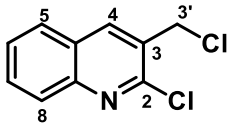
3.45

Yellow solid. Yield = 91%; M.p.: 133–135 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.08 (1H, s, H-4), 7.51 (1H, s, H-6), 7.06 (1H, s, H-8), 4.77 (2H, d, *J* = 5.8 Hz, H-3′), 4.11 (3H, s, OCH_3), 2.60 (3H, s, CH_3), 2.47 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 160.1, 146.6, 139.3, 134.2, 132.4, 127.2, 124.6, 123.0, 122.3, 61.7, 53.4, 21.7, 18.8.

5.1.7 General procedure for the synthesis of 3-(chloromethyl)quinolines[114]

To a solution of 3-(hydroxymethyl)quinolines (10.0 mmol) in dry DCM, thionyl chloride (13.0 mmol) was added and the reaction mixture was allowed to heat under reflux for 6 h. After reaction completion as indicated by TLC, the mixture was diluted with DCM, and the excess thionyl chloride quenched by cautious addition of water. The organic layer was successively washed with saturated $NaHCO_3$ (20 mL) and water (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude product which was recrystallized from methanol.

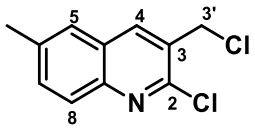
2-Chloro-3-(chloromethyl)quinoline (3.46)



3.46

Yellow solid. Yield = 90%; M.p.: 116−117 °C (Lit.[188] 116 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.07 (1H, s, H-4), 7.86 (1H, d, *J* = 8.4 Hz, H-8), 7.73 (1H, d, *J* = 8.0 Hz, H-5), 7.67 – 7.61 (1H, m, H-7), 7.43 – 7.37 (1H, m, H-6), 4.82 (2H, s, H-3′); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 159.7, 146.4, 138.1, 129.9, 127.6, 127.0, 125.0, 124.4, 121.7, 43.5.

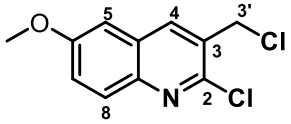
2-Chloro-3-(chloromethyl)-6-methylquinoline (3.47)



3.47

Yellow solid. Yield = 88%; M.p.: 96–98 °C (Lit.[188] 140 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.18 (1H, s, H-4), 7.93 (1H, d, *J* = 9.1 Hz, H-8), 7.60 – 7.56 (2H, m, H-5, H-7), 4.82 (2H, s, H-3′), 2.54 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 148.7, 145.7, 138.2, 137.7, 133.3, 129.0, 127.8, 127.2, 126.5, 43.2, 21.6.

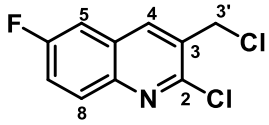
2-Chloro-3-(chloromethyl)-6-methoxyquinoline (3.48)



3.48

Yellow solid. Yield = 91%; M.p.: 113–115 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.15 (1H, s, H-4), 7.90 (1H, d, *J* = 9.2 Hz, H-8), 7.37 (1H, dd, *J* = 9.2, 2.8 Hz, H-7), 7.06 (1H, d, *J* = 2.8 Hz, H-5), 4.80 (2H, s, H-3′), 3.91 (3H, s, OC<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 158.5, 146.9, 143.3, 137.5, 129.6, 129.2, 128.3, 123.7, 105.1, 55.7, 43.2.

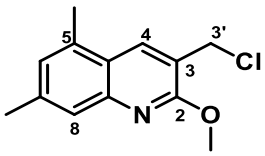
2-Chloro-3-(chloromethyl)-6-fluoroquinoline (3.49)



3.49

Yellow solid. Yield = 79%; M.p.: 102–104 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.24 (1H, s, H-4), 8.02 (1H, dd, *J* = 9.2, 5.2 Hz, H-8), 7.51 (1H, td, *J* = 9.0, 2.7 Hz, H-7), 7.45 (1H, dd, *J* = 8.5, 2.7 Hz, H-5), 4.82 (2H, s, H-3′); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 160.9 (d, $J_{F.C}$ = 250.1 Hz), 149.0 (d, $J_{F.C}$ = 3.0 Hz), 144.3, 137.9 (d, $J_{F.C}$ = 5.4 Hz), 130.8 (d, $J_{F.C}$ = 9.2 Hz), 130.1, 127.9 (d, $J_{F.C}$ = 10.2 Hz), 121.2 (d, $J_{F.C}$ = 25.7 Hz), 110.9 (d, $J_{F.C}$ = 22.2 Hz), 42.9.

3-(Chloromethyl)-2-methoxy-5,7-dimethylquinoline (3.50)



3.50

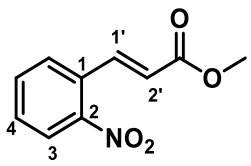
Yellow solid. Yield = 89%; M.p.: 101–103 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.07 (1H, s, H-4), 7.52 (1H, s, H-6), 7.06 (1H, s, H-8), 4.80 (CH_2, s H-3′), 4.11 (3H, s, OCH_3), 2.60 (3H, s, CH_3), 2.48 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 160.1, 146.5, 139.2, 134.2, 132.3, 127.2, 124.6, 123.0, 122.3, 61.5, 53.4, 21.7, 18.8.

5.1.8 General procedure for the esterification of nitro cinnamic acids [189]

To a solution of *trans* nitrocinnamic acid (16.0 mmol) in methanol (100 mL), a few drops of conc. H_2SO_4 were added and the mixture heated under reflux for 3 h. After cooling to r.t,

methanol was evaporated *in vacuo*. The resultant residue dissolved in EtOAc, followed by washing with saturated aqueous $NaHCO_3$ solution (20 mL) and then with water (20 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to afford the relevant methyl *trans* nitrocinnamate.

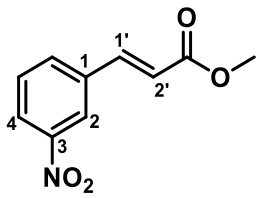
Methyl (*E*)-3-(2-nitrophenyl)acrylate (3.51)



3.51

Yellow solid. Yield = 92%; M.p.: 68–70 ^{o}C (Lit.[190] 72 ^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.10 (1H, d, *J* = 15.9 Hz, H-1′), 8.03 (1H, d, *J* = 7.5 Hz, H-3), 7.70 – 7.63 (2H, m, H-5, H-6), 7.56 – 7.53 (1H, m, H-4), 6.37 (1H, d, *J* = 15.9 Hz, H-2′), 3.83 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 166.5, 148.6, 140.4, 133.9, 130.9, 130.7, 129.4, 125.2, 123.1, 52.3.

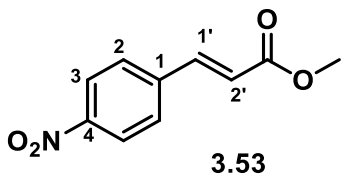
Methyl (*E*)-3-(3-nitrophenyl)acrylate (3.52)



3.52

Yellow solid. Yield = 98%; M.p.: 126–128 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.35 (1H, t, *J* = 1.9 Hz, H-2), 8.21 (1H, ddd, *J* = 8.0, 2.0, 0.9 Hz, H-4), 7.81 (1H, d, *J* = 7.9 Hz, H-6), 7.71 (1H, d, *J* = 16.0 Hz, H-1′), 7.57 (1H, t, *J* = 8.0 Hz, H-5), 6.55 (1H, d, *J* = 16.0 Hz, H-2′), 3.82 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 166.5, 148.7, 141.9, 136.1, 133.6, 130.0, 124.5, 122.4, 121.0, 52.0.

Methyl (*E*)-3-(4-nitrophenyl)acrylate (3.53)



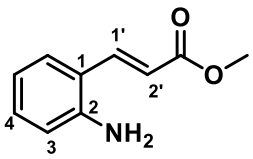
3.53

Yellow solid. Yield = 88%; M.p.: 139–141 ^{o}C (Lit.[191] 132–133 ^{o}C); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.23 (2H, d, *J* = 8.8 Hz, H-3), 7.74 – 7.64 (3H, m, H-2, H-1′), 6.55 (1H, d, *J* = 16.0 Hz, H-2′), 3.82 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 166.4, 148.5, 141.9, 140.5, 128.6, 124.1, 122.0, 52.1.

5.1.9 General procedure for the synthesis of methyl *trans* aminocinnamates[192]

To a solution of respective methyl *trans* nitrocinnamate (12.1 mmol) in methanol (100 mL), activated Zn powder (96.7 mmol) and NH_4Cl (26.2 mmol) were added at 0 °C and the reaction mixture was heated under reflux for 12 h. The resulting mixture was filtered through Celite 545 and evaporated *in vacuo* to give concentrated crude product. The concentrated product was poured into EtOAc (100 mL) and sonicated for 10 min. The insoluble matter was filtered off and the filtrate was washed with saturated $NaHCO_3$ (20 mL), dried ($MgSO_4$), evaporated *in vacuo* to give the desired compound.

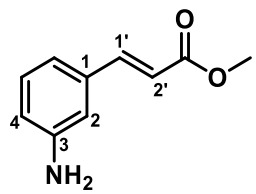
Methyl (*E*)-3-(2-aminophenyl)acrylate (3.54)



3.54

Yellow solid. Yield = 86%; M.p.: 64–66 °C (Lit.[193] 64–65 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.86 (1H, d, *J* = 15.7 Hz, H-1′), 7.40 (1H, d, *J* = 7.5 Hz, H-6), 7.23 – 7.16 (1H, m, H-5), 6.82 – 6.76 (1H, m, H-4), 6.73 (1H, d, *J* = 7.8 Hz, H-3), 6.38 (1H, d, *J* = 15.8 Hz, H-2′), 3.83 – 3.81 (5H, m, NH_2 overlapping with OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 167.8, 145.7, 140.4, 131.4, 128.1, 119.9, 119.0, 117.7, 116.8, 51.7.

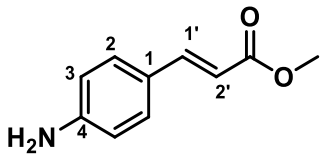
Methyl (*E*)-3-(3-aminophenyl)acrylate (3.55)



3.55

Yellow solid. Yield = 82%; M.p.: 79–81 °C (Lit.[100] 80–82 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.60 (1H, d, *J* = 16.0 Hz, H-1′), 7.15 (1H, t, *J* = 7.9 Hz, H-5), 6.91 (1H, d, *J* = 7.8 Hz, H-6), 6.81 – 6.79 (1H, m, H-2), 6.69 (1H, ddd, *J* = 8.0, 2.2, 0.8 Hz, H-4), 6.37 (1H, d, *J* = 16.0 Hz, H-2′), 3.79 (3H, s, OCH_3), 3.75 (2H, s, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 167.5, 146.7, 145.3, 135.4, 129.8, 118.6, 117.6, 117.1, 114.1, 51.7.

Methyl (*E*)-3-(4-aminophenyl)acrylate (3.56)



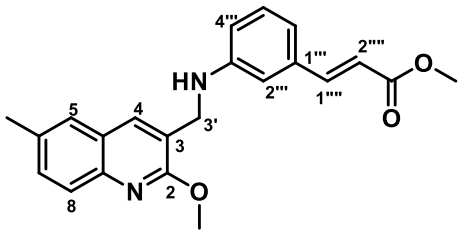
3.56

Yellow solid. Yield = 80%; M.p.: 136–138 °C (Lit.[194] 128–129 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.60 (1H, d, *J* = 15.9 Hz, H-1′), 7.35 – 7.31 (2H, m, H-2), 6.65 – 6.60 (2H, m, H-3), 6.23 (1H, d, *J* = 15.9 Hz, H-2′), 3.98 (2H, s, NH_2), 3.77 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 168.2, 148.9, 145.2, 129.9, 124.6, 114.8, 113.2, 51.4.

5.1.10 General procedure for the synthesis of methyl (*E*)-quinolinyl methyl amino phenyl acrylates[195]

To a solution of methyl amino cinnamate (0.50 mmol) and quinoline-3-carbaldehyde (0.50 mmol) in methanol (10 mL), a few drops of glacial AcOH were added and the resultant reaction mixture heated under reflux for 12 h. After 12 h elapsed, the reaction mixture was cooled to 0 °C in an ice bath and sodium cyanoborohydride (1.0 mmol) was portion wise added over a period of 10 min. The reaction mixture was stirred at r.t. overnight. The solvent was evaporated *in vacuo* and the residue dispersed in water (10 mL) and extracted with EtOAc (2 × 20 mL). The organic layers were combined and washed with brine (25 mL) and dried ($MgSO_4$). The solvent was removed in *vacuo* and the crude product was purified by silica gel column chromatography (EtOAc/hexane 1:1) to give the desired compounds.

Methyl-(*E*)-3-(3-(((2-methoxy-6-methylquinolin-3-yl)methyl)amino)phenyl)acrylate (3.57)

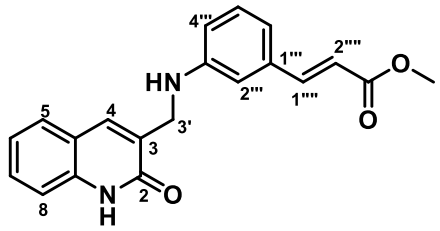


3.57

Yellow solid. Yield = 70%; M.p: 120–122 °C; ν_{max}/cm^{-1} 3347 (N-H), 1713 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.81 (1H, s, H-4), 7.75 (1H, d, *J* = 9.0 Hz, H-8), 7.60 (1H, d, *J* = 16.0 Hz, H-1′′′′), 7.43- 7.41 (2H, m, H-5, H-

7), 7.17 (1H, t, *J* = 7.8 Hz, H-5‴), 6.89 (1H, d, *J* = 7.8 Hz, H-6‴), 6.77 (1H, s, H-2‴), 6.66 (1H, dd, *J* = 8.0, 2.0 Hz, H-4‴), 6.36 (1H, d, *J* = 16.0 Hz, H-2⁗), 4.42 (2H, s, H-3′), 4.39 (1H, s, NH), 4.13 (3H, s, OCH_3), 3.79 (3H, s, $OCOCH_3$), 2.45 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 167.6, 160.0, 148.2, 145.5, 144.0, 135.4, 135.19, 133.7, 131.1, 129.7, 126.6, 126.5, 125.2, 122.6, 117.6, 117.5, 115.1, 112.3, 53.5, 51.7, 43.3, 21.3; HRMS (ESI): *m/z* calcd for $C_{22}H_{23}N_2O_3$ $[M+H]^+$: 363.1709, found 363.1707.

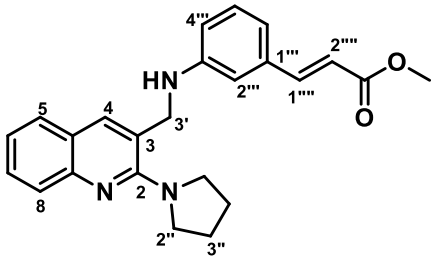
Methyl-(*E*)-3-(3-(((2-oxo-1,2-dihydroquinolin-3-yl)methyl)amino)phenyl)acrylate (3.58)



3.58

White crystalline solid. Yield = 66%; M.p: 212–214 °C; ν_{max}/cm^{-1} 3387 (N-H), 1739 (C=O); ^1H NMR (600 MHz, DMSO-d_6): δ_H = 11.89 (1H, bs, CONH), 7.76 (1H, s, H-4), 7.59 (1H, d, *J* = 7.4 Hz, H-8), 7.52 (1H, d, *J* = 16.0 Hz, H-1⁗), 7.45 (1H, t, *J* = 6.8 Hz, H-5‴), 7.32 (1H, d, *J* = 7.8 Hz, H-5), 7.15 – 7.11 (2H, m, H-6, H-7), 6.80 – 6.88 (2H, m, H-2‴, H-6‴), 6.68 (1H, d, *J* = 7.6 Hz, H-4‴), 6.47 (1H, d, *J* = 16.0 Hz, H-2⁗), 6.27 (1H, bs, CH_2NH), 4.21 (2H, s, H-3′), 3.70 (3H, s, OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6): δ_C = 167.2, 162.2, 149.4, 146.0, 138.30, 135.5, 135.0, 131.3, 130.1, 130.0, 128.0, 122.3, 119.6, 117.4, 116.8, 115.4, 115.3, 111.8, 51.9, 42.2; HRMS (ESI): *m/z* calcd for $C_{20}H_{19}N_2O_3$ $[M+H]^+$: 335.1396, found 335.1399.

Methyl-(*E*)-3-(3-(((2-(pyrrolidin-1-yl)quinolin-3-yl)methyl)amino)phenyl)acrylate (3.59)

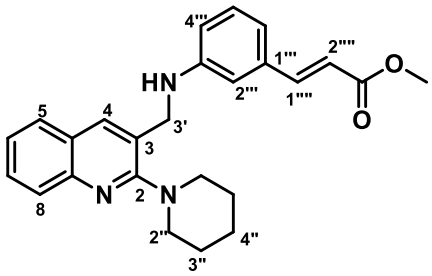


3.59

Yellow solid. Yield = 35%; M.p: 99–101 °C; ν_{max}/cm^{-1} 3337 (N-H), 1712 (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ_H = 7.85 (1H, s, H-4), 7.75 (1H, d, *J* = 8.3 Hz, H-5), 7.62 (1H, d, *J* = 16.0 Hz, H-1⁗), 7.54 – 7.52 (2H, m, H-6, H-8), 7.22 – 7.17 (2H, m, H-5‴, H-7), 6.92 (1H, d, *J* = 7.5 Hz, H-6‴),

6.77 (1H, s, H-2‴), 6.65 (1H, dd, *J* = 8.0, 1.9 Hz, H-4‴), 6.39 (1H, d, *J* = 16.0 Hz, H-2‴″), 4.42 (2H, s, H-3′), 3.79 (3H, s, OCH_3), 3.73 – 3.70 (4H, m, H-2″), 1.99 – 1.93 (4H, m, H-3″); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 166.5, 155.9, 147.0, 144.3, 136.7, 134.4, 128.8, 128.3, 126.0, 125.2, 122.6, 121.5, 121.1, 116.7, 116.5, 113.9, 112.8, 110.9, 50.6, 48.7, 45.7, 24.6; HRMS (ESI): *m/z* calcd for $C_{24}H_{26}N_3O_2$ $[M+H]^+$: 388.2025, found 388.2023.

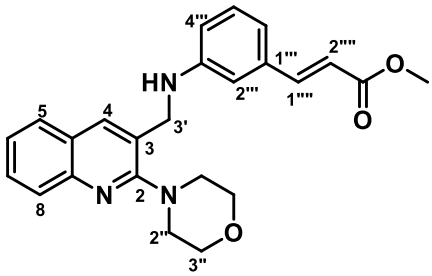
Methyl-(*E*)-3-(3-(((2-(piperidin-1-yl)quinolin-3-yl)methyl)amino)phenyl)acrylate (3.60)



3.60

Yellow solid. Yield = 57%; M.p: 104–106 °C; ν_{max}/cm^{-1} 3426 (N-H), 1724 (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ_H = 8.03 (1H, s, H-4), 7.90 (1H, d, *J* = 8.4 Hz, H-5), 7.64 – 7.55 (3H, m, H-8, H-6, H-1‴″), 7.35 – 7.31 (1H, m, H-7), 7.17 (1H, t, *J* = 7.8 Hz, H-5‴), 6.89 (1H, d, *J* = 7.6 Hz, H-6‴), 6.76 (1H, s, H-2‴), 6.65 (1H, dd, *J* = 8.0, 1.9 Hz, H-4‴), 6.37 (1H, d, *J* = 16.0 Hz, H-2‴″), 4.73 (1H, s, NH), 4.44 (2H, s, H-3′), 3.79 (3H, s, OCH_3), 3.30 – 3.25 (4H, m, H-2″), 1.81 – 1.76 (4H, m, H-3″), 1.70 – 1.65 (2H, m, H-4″); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 167.6, 161.2, 148.4, 146.5, 145.5, 136.6, 135.4, 129.8, 129.0, 127.5, 127.1, 126.7, 125.5, 124.4, 117.8, 117.5, 115.1, 112.0, 51.7 (2C), 44.7, 26.4, 24.6; HRMS (ESI): *m/z* calcd for $C_{25}H_{28}N_3O_2$ $[M+H]^+$: 402.2182, found 402.2180.

Methyl-(*E*)-3-(3-(((2-morpholinoquinolin-3-yl)methyl)amino)phenyl)acrylate (3.61)

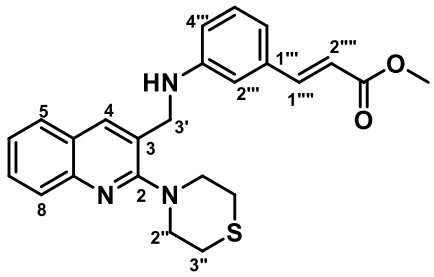


3.61

Brown solid. Yield = 70%; M.p: 131–133 °C; ν_{max}/cm^{-1} 3395 (N-H), 1696 (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ_H = 8.09 (1H, s, H-4), 7.90 (1H, d, *J* = 8.4 Hz, H-5), 7.66 (1H, d, *J* = 8.0 Hz, H-8), 7.63 – 7.58 (2H, m, H-6, H-1‴″), 7.39 – 7.35 (1H, m, H-7), 7.18 (1H, t, *J* = 7.9 Hz, H-5‴), 6.91

(1H, d, *J* = 7.5 Hz, H-6‴), 6.76 (1H, s, H-2‴), 6.65 (1H, dd, *J* = 8.0, 1.9 Hz, H-4‴), 6.36 (1H, d, *J* = 16.0 Hz, H-2⁗), 4.58 (1H, s, NH), 4.45 (2H, s, H-3′), 3.93 – 3.90 (4H, m, H-3″), 3.79 (3H, s, OCH_3), 3.38 – 3.34 (4H, m, H-2″); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 167.5, 159.9, 148.1, 146.5, 145.3, 137.2, 135.4, 129.9, 129.3, 127.7, 127.2, 126.0, 125.7, 124.8, 118.0, 117.6, 115.1, 111.9, 67.2, 51.7, 50.9, 44.7; HRMS (ESI): *m/z* calcd for $C_{24}H_{26}N_3O_3$ $[M+H]^+$: 404.1974, found 404.1974.

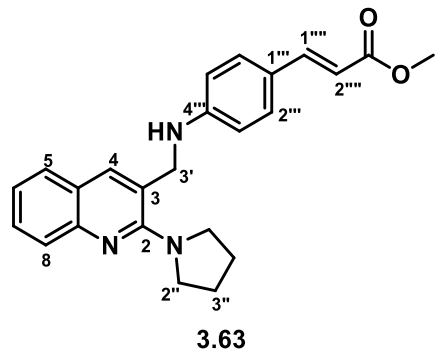
Methyl-(*E*)-3-(3-(((2-thiomorpholinoquinolin-3-yl)methyl)amino)phenyl)acrylate (3.62)



3.62

Brown solid. Yield = 45%; M.p: 73–75 °C; ν_{max}/cm^{-1} 3418 (N-H), 1704 (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ_H = 8.08 (1H, s, H-4), 7.90 (1H, d, *J* = 8.4 Hz, H-5), 7.65 (1H, d, *J* = 8.3 Hz, H-8), 7.63 – 7.56 (2H, m, H-6, H-1⁗), 7.37 (1H, t, *J* = 7.5 Hz, H-7), 7.18 (1H, t, *J* = 7.8 Hz, H-5‴), 6.90 (1H, d, *J* = 7.4 Hz, H-6‴), 6.74 (1H, s, H-2‴), 6.64 (1H, dd, *J* = 8.1, 2.0 Hz, H-4‴), 6.35 (1H, d, *J* = 16.0 Hz, H-2⁗), 4.52 (1H, s, NH), 4.42 (2H, s, H-3′), 3.78 (3H, s, OCH_3), 3.63 − 3.60 (4H, m, H-2″), 2.88 – 2.85 (4H, m, H-3″); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 167.5, 160.7, 148.1, 146.4, 145.3, 137.0, 135.4, 129.9, 129.3, 127.7, 127.2, 126.3, 125.7, 124.8, 118.0, 117.6, 115.1, 111.9, 52.9, 51.7, 44.5, 28.0; HRMS (ESI): *m/z* calcd for $C_{24}H_{26}N_3O_2S$ $[M+H]^+$: 420.1746, found 420.1745.

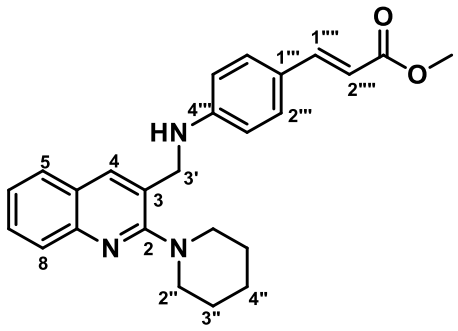
Methyl-(*E*)-3-(4-(((2-(pyrrolidin-1-yl)quinolin-3-yl)methyl)amino)phenyl)acrylate (3.63)



3.63

Yellow solid. Yield = 31%; M.p: 96–98 °C; ν_{max}/cm^{-1} 3423 (N-H), 1707 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.88 (1H, s, H-4), 7.61 (1H, d, *J* = 15.9 Hz, H-1‴), 7.57 – 7.51 (3H, m, H-8, H-5, H-7), 7.38 (2H, d, *J* = 8.5 Hz, H-2‴), 7.22 (1H, t, *J* = 7.4 Hz, H-6), 6.60 (2H, d, *J* = 8.6 Hz, H-3‴), 6.22 (1H, d, *J* = 15.9 Hz, H-2‴'), 4.48 (2H, s, H-3′), 3.78 (3H, s, OCH_3), 3.73 – 3.71 (4H, m, H-2″), 1.98 – 196 (4H, m, H-3″); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 168.2, 161.2, 149.4, 145.1, 144.4, 134.0, 132.8, 130.0, 129.6, 127.0, 124.1, 122.7, 121.8, 112.9, 112.7, 111.9, 51.5, 49.8, 46.4, 25.7; HRMS (ESI): *m/z* calcd for $C_{24}H_{26}N_3O_2$ $[M+H]^+$: 388.2025; found 388.2031.

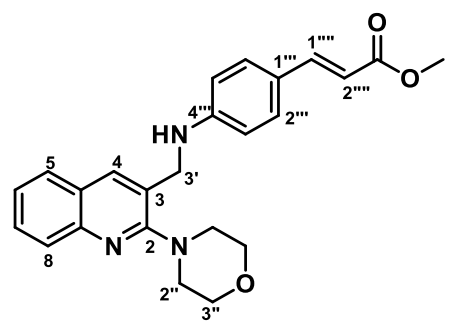
Methyl-(*E*)-3-(4-(((2-(piperidin-1-yl)quinolin-3-yl)methyl)amino)phenyl)acrylate (3.64)



3.64

Yellow solid. Yield = 35%; M.p: 146–148 °C; ν_{max}/cm^{-1} 3422 (N-H), 1704 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.00 (1H, s, H-4), 7.89 (1H, d, *J* = 8.2 Hz, H-8), 7.63 (1H, d, *J* = 8.0 Hz, H-5), 7.61 – 7.56 (2H, m, H-7, H-1‴), 7.37 – 7.32 (3H, m, H-6, H-2‴), 6.60 (2H, d, *J* = 8.6 Hz, H-3‴), 6.21 (1H, d, *J* = 15.9 Hz, H-2‴'), 4.96 (1H, s, NH), 4.48 (2H, s, H-3′), 3.77 (3H, s, OCH_3), 3.29 – 3.23 (4H, m, H-2″), 1.78 – 1.76 (4H, m, H-3″), 1.69 – 1.63 (2H, m, H-4″); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 168.2, 161.1, 149.8, 146.5, 145.2, 136.6, 132.9, 130.0, 129.2, 127.5, 127.1, 126.2, 125.4, 124.5, 123.9, 112.8, 51.6, 51.4, 44.6, 26.4, 24.5; HRMS (ESI): *m/z* calcd for $C_{25}H_{28}N_3O_2$ $[M+H]^+$: 402.2182; found 402.2181.

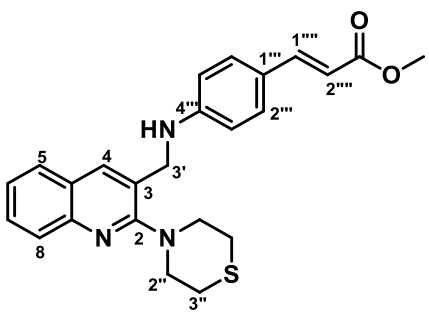
Methyl-(*E*)-3-(4-(((2-morpholinoquinolin-3-yl)methyl)amino)phenyl)acrylate (3.65)



3.65

Yellow solid. Yield = 40%; M.p: 147–149 °C; ν_{max}/cm^{-1} 3422 (N-H), 1708 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.05 (1H, s, H-4), 7.91 (1H, d, *J* = 8.0 Hz, H-8), 7.66 (1H, d, *J* = 8.0 Hz, H-5), 7.63 – 7.57 (2H, m, H-7, H-1‴), 7.39 − 7.35 (3H, m, H-6, H-2‴), 6.59 (2H, d, *J* = 8.5 Hz, H-3‴), 6.22 (1H, d, *J* = 15.9 Hz, H-2‴'), 4.83 (1H, s, NH), 4.48 (2H, s, H-3′), 3.92 – 3.89 (4H, m, H-3″), 3.77 (3H, s, OCH_3), 3.36 – 3.33 (4H, m, H-2″); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 168.1, 159.7, 149.5, 146.1, 145.0, 137.2, 132.9, 130.0, 129.5, 127.6, 127.2, 125.6, 124.9, 124.2, 113.0, 112.8, 67.1, 51.5, 50.8, 44.5; HRMS (ESI): *m/z* calcd for $C_{24}H_{26}N_3O_3$ $[M+H]^+$:404.1974; found 404.1975.

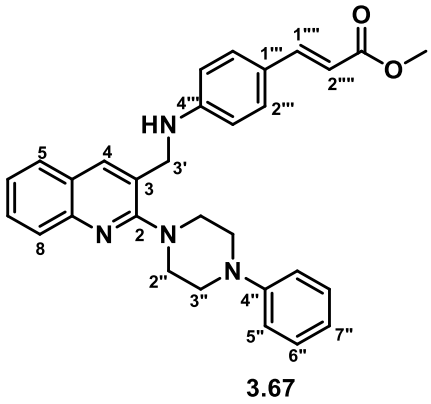
Methyl-(*E*)-3-(4-(((2-thiomorpholinoquinolin-3-yl)methyl)amino)phenyl)acrylate (3.66)



3.66

Yellow solid. Yield = 32%; M.p: 94–98 °C; ν_{max}/cm^{-1} 3379 (N-H), 1685 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.96 (1H, s, H-4), 7.83 (1H, d, *J* = 8.3 Hz, H-8), 7.57 (1H, d, *J* = 8.2 Hz, H-5), 7.54 – 7.49 (2H, m, H-7, H-1‴), 7.29 – 7.27 (3H, m, H-6, H-2‴), 6.50 (2H, d, *J* = 8.5 Hz, H-3‴), 6.13 (1H, d, *J* = 15.9 Hz, H-2‴'), 4.70 (1H, s, NH), 4.37 (2H, s, H-3′), 3.68 (3H, s, OCH_3), 3.54 – 3.50 (4H, m, H-2″), 2.79 – 2.77 (4H, m, H-3″); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 168.1, 160.4, 149.6, 145.0, 144.4, 136.1, 132.6, 130.0, 129.9, 127.6, 127.2, 126.0, 125.6, 125.0, 124.2, 112.8, 52.9, 51.5, 44.3, 28.0; HRMS (ESI): *m/z* calcd for $C_{24}H_{26}N_3O_2S$ $[M+H]^+$: 420.1746; found 420.1742.

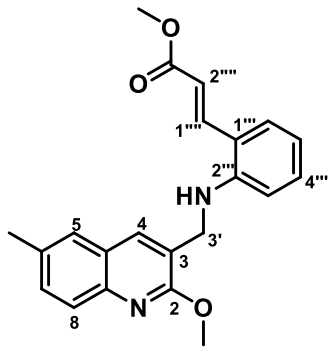
Methyl-(*E*)-3-(4-(((2-(4-phenylpiperazin-1-yl)quinolin-3-yl)methyl)amino)phenyl) acrylate (3.67)



3.67

Yellow solid. Yield = 35%; M.p: 160–162 °C; ν_{max}/cm^{-1} 3426 (N-H), 1704 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.06 (1H, s, H-4), 7.93 (1H, d, *J* = 8.0 Hz, H-8), 7.67 (1H, d, *J* = 8.0 Hz, H-5), 7.64 – 7.59 (2H, m, H-1′′′′, H-7), 7.40 – 7.36 (3H, m, H-5, H-2′′′), 7.31 (2H, t, *J* = 7.9 Hz, H-6′′), 7.01 (2H, d, *J* = 8.2 Hz, H-5′′), 6.90 (1H, t, *J* = 7.3 Hz, H-7′′), 6.61 (2H, d, *J* = 8.5 Hz, H-3′′′), 6.23 (1H, d, *J* = 15.9 Hz, H-2′′′′), 4.87 – 4.84 (1H, m, NH), 4.52 (2H, d, *J* = 3.9 Hz, H-3′), 3.78 (3H, s, OCH_3), 3.55 – 3.51 (4H, m, H-3′′), 3.42 – 3.39 (4H, m, H-2′′); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 168.2, 159.8, 151.2, 149.6, 146.5, 145.1, 137.0, 130.0, 129.4, 129.2, 127.7, 127.2, 125.7, 125.6, 124.9, 124.1, 120.0, 116.2, 112.9, 112.8, 51.5, 50.3, 49.4, 44.5; HRMS (ESI): *m/z* calcd for $C_{30}H_{31}N_4O_2$ $[M+H]^+$: 479.2447, found 479.2439.

Methyl-(*E*)-3-(2-(((2-methoxy-6-methylquinolin-3-yl)methyl)amino)phenyl)acrylate (3.68)

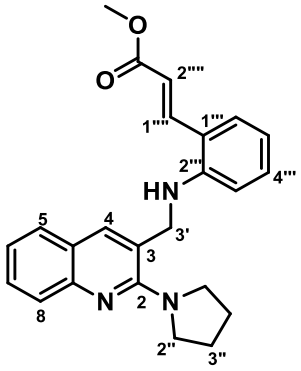


3.68

Yellow solid. Yield = 61%; M.p: 106–108 °C; ν_{max}/cm^{-1} 3426 (N-H), 1716 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.94 (1H, d, *J* = 15.7 Hz, H-1′′′′), 7.79 (1H, s, H-4), 7.75 (1H, d, *J* = 9.0 Hz, H-8), 7.43 – 7.41 (2H, m, H-5, H-6′′′), 7.40 (1H, dd, *J* = 7.8, 1.3 Hz, H-7), 7.19 – 7.16 (1H, m, H-4′′′), 6.72 (1H, t, *J* = 7.5 Hz, H-5′′′), 6.61 (1H, d, *J* = 8.2 Hz, H-3′′′), 6.41 (1H, d, *J* = 15.7 Hz, H-2′′′′), 4.74 (1H, s, NH), 4.48 (2H, s, H-3′), 4.14 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 2.45 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 167.7, 159.9, 146.3, 144.0, 140.3, 135.2, 133.7,

131.6, 131.1, 128.3, 126.6, 126.5, 125.2, 122.4, 120.2, 118.1, 117.8, 112.2, 53.5, 51.7, 43.4, 21.3; HRMS (ESI): *m/z* calcd for $C_{22}H_{23}N_2O_3$ $[M+H]^+$: 363.1709, found 363.1707.

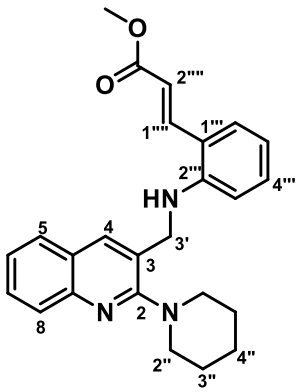
Methyl-(*E*)-3-(2-(((2-(pyrrolidin-1-yl)quinolin-3-yl)methyl)amino)phenyl)acrylate (3.69)



3.69

Yellow solid. Yield = 52%; M.p: 98–100 °C; ν_{max}/cm^{-1} 3341 (N-H), 1704 (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ_H = 7.89 (1H, s, H-4), 7.86 (1H, d, *J* = 15.9 Hz, H-1′′′′), 7.77 (1H, d, *J* = 8.4 Hz, H-5), 7.57 (1H, d, *J* = 8.1 Hz, H-8), 7.56 – 7.51 (1H, m, H-6), 7.40 (1H, dd, *J* = 8.0, 0.96 Hz, H-6′′′), 7.25 – 7.20 (2H, m, H-7, H-4′′′), 6.76 (1H, t, *J* = 7.5 Hz, H-5′′′), 6.60 (1H, d, *J* = 8.2 Hz, H-3′′′), 6.38 (1H, d, *J* = 15.7 Hz, H-2′′′′), 4.66 (1H, s, NH), 4.48 (2H, d, *J* = 4.5 Hz, H-3′), 3.79 (3H, s, OCH_3), 3.71 – 3.68 (4H, m, H-2′′), 1.99 – 1.95 (4H, m, H-3′′); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 167.6, 157.2, 147.0, 146.1, 140.2, 137.5, 131.7, 129.4, 128.4, 127.1, 126.5, 123.8, 122.7, 122.1, 120.2, 118.3, 117.9, 111.7, 51.7, 49.7, 46.8, 25.7; HRMS (ESI): *m/z* calcd for $C_{24}H_{26}N_3O_2$ $[M+H]^+$: 388.2025, found 388.2025.

Methyl-(*E*)-3-(2-(((2-(piperidin-1-yl)quinolin-3-yl)methyl)amino)phenyl)acrylate (3.70)

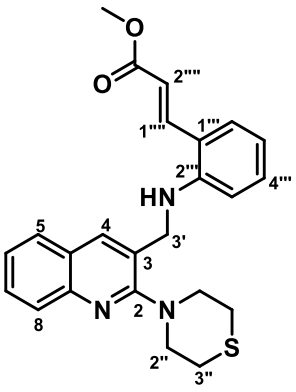


3.70

Yellow solid. Yield = 65%; M.p: 111–113 °C; ν_{max}/cm^{-1} 3368 (N-H), 1708 (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ_H = 7.93 (1H, s, H-4), 7.84 (1H, d, *J* = 15.8 Hz, H-1′′′′), 7.80 (1H, d, *J* = 8.5 Hz, H-5), 7.56 (1H, d, *J* = 7.9 Hz, H-8), 7.51 – 7.47 (1H, m, H-6), 7.31 (1H, dd, *J* = 7.7, 1.1 Hz, H-6′′′), 7.28 – 7.23 (1H, m, H-7), 7.14 – 7.09 (1H, m, H-4′′′), 6.64 (1H, t, *J* = 7.5 Hz, H-5′′′), 6.51 (1H, d, *J* = 8.2 Hz, H-3′′′), 6.31 (1H, d, *J* = 15.7 Hz, H-2′′′′), 5.08 (1H, s, NH), 4.42 (2H, s, H-3′), 3.71 (3H, s, OCH_3), 3.20 – 3.16 (4H, m, H-2′′), 1.70 – 1.66 (4H, m, H-3′′), 1.59 – 1.54 (2H,

m, H-4′′); ^{13}C NMR (100 MHz, $CDCl_3$):δ_C = 167.7, 161.1, 146.6, 146.4, 140.3, 136.6, 131.7, 129.1, 128.3, 127.5, 127.2, 126.3, 125.5, 124.5, 120.2, 118.1, 117.8, 111.8, 51.7, 51.6, 45.2, 26.3, 24.6; HRMS (ESI): *m/z* calcd for $C_{25}H_{28}N_3O_2$ $[M+H]^+$: 402.2182, found 402.2178.

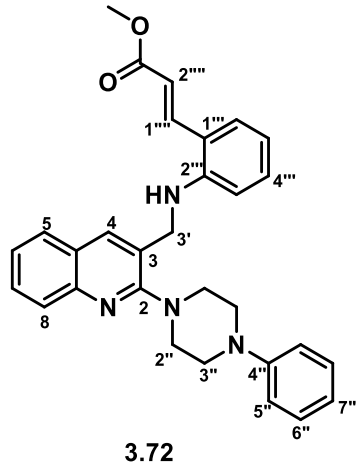
Methyl-(*E*)-3-(2-(((2-thiomorpholinoquinolin-3-yl)methyl)amino)phenyl)acrylate (3.71)



3.71

Yellow solid. Yield = 38%; M.p: 117–119 °C; ν_{max}/cm^{-1} 3399 (N-H), 1696 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.96 (1H, s, H-4), 7.85 – 7.80 (2H, m, H-5, H-1′′′′), 7.57 (1H, d, *J* = 7.7 Hz, H-8), 7.52 (1H, t, *J* = 7.7 Hz, H-6), 7.32 (1H, d, *J* = 7.7 Hz, H-6′′′), 7.29 (1H, t, *J* = 7.5 Hz, H-7), 7.12 (1H, t, *J* = 7.7 Hz, H-4′′′), 6.66 (1H, t, *J* = 7.5 Hz, H-5′′′), 6.47 (1H, d, *J* = 8.3 Hz, H-3′′′), 6.32 (1H, d, *J* = 15.7 Hz, H-2′′′′), 4.88 (1H, s, NH), 4.39 (2H, s, H-3′), 3.71 (3H, s, OCH_3), 3.54 – 3.50 (4H, m, H-2′′), 2.78 – 2.75 (4H, m, H-3′′); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 167.7, 160.6, 146.4, 146.2, 140.1, 137.0, 131.7, 129.3, 128.3, 127.7, 127.2, 126.0, 125.7, 124.9, 120.2, 118.3, 118.0, 111.7, 52.8, 51.7, 44.9, 27.9; HRMS (ESI): *m/z* calcd for $C_{24}H_{26}N_3O_2S$ $[M+H]^+$:420.1746, found 420.1745.

Methyl-(*E*)-3-(2-(((2-(4-phenylpiperazin-1-yl)quinolin-3-yl)methyl)amino)phenyl) acrylate (3.72)



3.72

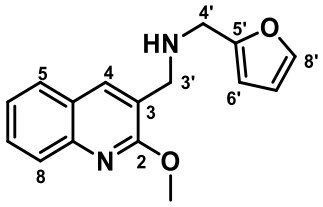
Pale yellow solid. Yield = 75%; M.p:122–124°C; ν_{max}/cm^{-1} 3445 (N-H), 1904 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.09 (1H, s, H-4), 7.97 – 7.90 (2H, m, H-5, H-1′′′′), 7.69 (1H, d, *J* = 7.9 Hz, H-8), 7.63 (1H, t, *J* = 7.6 Hz, H-6), 7.42 − 7.38 (2H, m, H-7, H-6′′′), 7.30 (2H, t, *J* = 7.8 Hz, H-6′′), 7.23 (1H, t, *J* = 7.7 Hz, H-4′′′), 7.00 (2H, d, *J* = 8.1 Hz, H-5′′), 6.90 (1H, t, *J* =

7.2 Hz, H-7″), 6.76 (1H, t, *J* = 7.4 Hz, H-5‴), 6.61 (1H, d, *J* = 8.2 Hz, H-3‴), 6.39 (1H, d, *J* = 15.7 Hz, H-2‴′), 5.07 (1H, s, NH), 4.55 (2H, s, H-3′), 3.77 (3H, s, OCH_3), 3.56 – 3.53 (4H, m, H-3″), 3.43 – 3.38 (4H, m, H-2″); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 167.6, 159.7, 151.3, 146.3, 146.2, 140.2, 137.4, 131.7, 129.5, 129.2, 128.3, 127.5, 127.3, 125.7, 125.6, 124.9, 120.3, 120.0, 118.4, 118.1, 116.2, 111.7, 51.7, 50.3, 49.4, 45.2; HRMS (ESI): *m/z* calcd for $C_{30}H_{31}N_4O_2$ $[M+H]^+$: 479.2447, found 479.2449.

5.1.11 General procedure for the synthesis of quinolinyl methanamines[95]

Quinoline-3-carbaldehydes (compounds **3.28 − 3.33**, **3.35)** (8.0 mmol) were dissolved in ethanol (20 mL) containing catalytic amount of glacial AcOH (45 µL, 0.8 mmol). The appropriate amine (8.4 mmol) was added dropwise after which the reaction mixture was heated under reflux overnight, cooled to 0 °C after which sodium borohydride (16.0 mmol) was added in small portions over a period of 30 min. After the effervescence ceased, the reaction was stirred at r.t for 6 h. Water (50 mL) was added and ethanol evaporated *in vacuo*. The aqueous solution was extracted with DCM (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc:Hexane, 5:3) to obtain desired products.

1-(Furan-2-yl)-*N*-((2-methoxyquinolin-3-yl)methyl)methanamine (3.73)

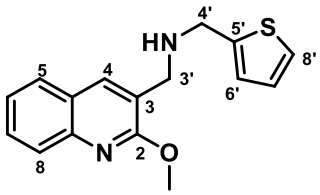


3.73

Tan viscous liquid. Yield = 72%; ν_{max}/cm^{-1}: 3337 (N-H); ^1H NMR (300 MHz, $CDCl_3$) δ_H = 7.93 (1H, s, H-4), 7.84 (1H, d, *J* = 8.4 Hz, H-8), 7.70 (1H, dd, *J* = 8.0, 1.2 Hz, H-5), 7.61 − 7.56 (1H, m, H-6), 7.39 − 7.34 (2H, m, H-7, H-8′), 6.32 (1H, dd, *J* = 3.1, 1.9 Hz, H-7′), 6.22 – 6.20 (1H, m, H-6′), 4.10 (3H, s, OCH_3), 3.90 (2H, s, H-4′), 3.83 (2H, s, H-3′), 2.05 (1H,

s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 160.8, 153.7, 145.8, 141.9, 136.7, 129.0, 127.2, 126.9, 125.3, 124.1, 123.8, 110.1, 107.0, 53.5, 48.1, 45.5; LC-MS (ESI): *m/z* calcd for $C_{16}H_{17}N_2O_2$ $[M+H]^+$: 269.1290, found 269.1350.

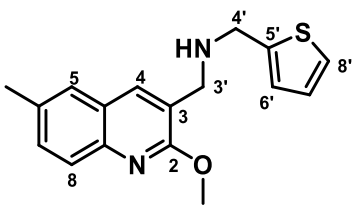
1-(2-Methoxyquinolin-3-yl)-*N*-(thiophen-2-ylmethyl)methanamine (3.74)



3.74

Yellow viscous liquid. Yield = 76%; ν_{max}/cm^{-1} 3282 (N-H); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.93 (1H, s, H-4), 7.85 (1H, d, *J* = 8.4 Hz, H-8), 7.71 (1H, d, *J* = 7.9 Hz, H-5), 7.62 – 7.58 (1H, m, H-6), 7.40 – 7.36 (1H, m, H-7), 7.24 (1H, dd, *J* = 5.0, 1.1 Hz, H-8′), 6.99 – 6.96 (1H, m, H-7′), 6.95 – 6.94 (1H, m, H-6′), 4.10 (3H, s, OCH_3), 4.02 (2H, s, H-3′), 3.94 (2H, s, H-4′), 2.15 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 160.8, 145.8, 143.9, 136.6, 129.0, 127.2, 126.9, 126.7, 125.3, 125.0, 124.6, 124.1, 123.7, 53.6, 48.0, 47.5; LC-MS (ESI): *m/z* calcd for $C_{16}H_{17}N_2OS$ $[M+H]^+$: 285.1062, found 285.1111.

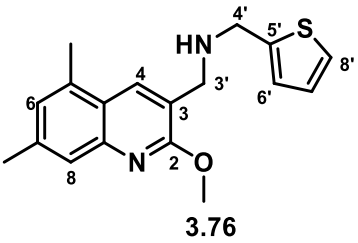
1-(2-Methoxy-6-methylquinolin-3-yl)-*N*-(thiophen-2-ylmethyl)methanamine (3.75)



3.75

Yellow solid. Yield = 75%; M.p: 52–55 °C; ν_{max}/cm^{-1} 3309 (N-H); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.75 (1H, s, H-4), 7.66 (1H, d, *J* = 8.5 Hz, H-8), 7.39 (1H, d, *J* = 1.8 Hz , H-5), 7.34 (1H, dd, *J* = 8.5, 1.8 Hz, H-7), 7.16 (1H, dd, *J* = 5.0, 1.1 Hz, H-8′), 6.89 (1H, dd, *J* = 5.0, 3.5 Hz, H-7′), 6.86 (1H, d, *J* = 3.5 Hz, H-6′), 4.00 (3H, s, OCH_3), 3.92 (2H, s, H-3′), 3.83 (2H, s, H-4′), 2.40 (3H, s, CH_3), 2.09 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 160.4, 144.1, 144.0, 136.5, 133.7, 131.1, 126.7, 126.6, 126.4, 125.2, 125.0, 124.6, 123.5, 53.5, 48.1, 47.5, 21.4; LC-MS (ESI): *m/z* calcd for $C_{17}H_{19}N_2OS$ $[M+H]^+$: 299.1218, found 299.1272.

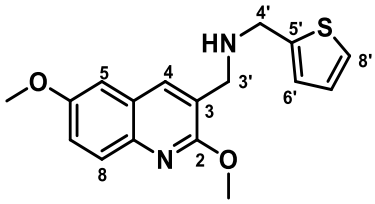
1-(2-Methoxy-5,7-dimethylquinolin-3-yl)-*N*-(thiophen-2-ylmethyl)methanamine (3.76)



3.76

Pale yellow solid. Yield = 71%; M.p: 83–85 °C; ν_{max}/cm^{-1} 3298 (N-H); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.03 (1H, s, H-4), 7.52 (1H, s, H-6), 7.25 (1H, dd, *J* = 5.0, 1.3 Hz, H-8′), 7.06 (1H, s, H-8), 6.98 (1H, dd, *J* = 5.0, 3.5 Hz, H-7′), 6.96 – 6.94 (1H, m, H-6′), 4.09 (3H, s, OCH_3), 4.02 – 4.00 (2H, m, H-3′), 3.94 (2H, s, H-4′), 2.61 (3H, s, CH_3), 2.48 (3H, s, CH_3), 2.14 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 160.7, 146.4, 144.2, 138.9, 133.0, 133.5, 127.0, 126.6, 124.9, 124.6, 124.5, 122.3, 121.9, 53.4, 48.4, 47.5, 21.7, 18.8; LC-MS (ESI): *m/z* calcd for $C_{18}H_{21}N_2OS$ $[M+H]^+$: 313.1375, found 313.1483.

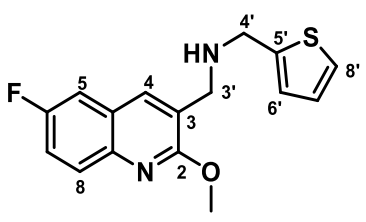
1-(2,6-Dimethoxyquinolin-3-yl)-*N*-(thiophen-2-ylmethyl)methanamine (3.77)



3.77

Pale yellow solid. Yield = 84%; M.p: 49–50 °C; ν_{max}/cm^{-1}: 3302 (N-H); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.84 (1H, s, H-4), 7.74 (1H, d, *J* = 9.1 Hz, H-8), 7.26 – 7.22 (2H, m, H-7, H-8′), 7.03 (1H, d, *J* = 2.8 Hz, H-5), 6.97 – 6.93 (2H, m, H-6′, H-7′), 4.06 (3H, s, OCH_3), 4.00 (2H, s, H-3′), 3.91 (2H, s, H-4′), 3.89 (3H, s, OCH_3), 2.07 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 159.5, 156.1, 144.0, 141.2, 136.0, 128.2, 126.7, 125.8, 125.0, 124.5, 123.8, 120.5, 106.1, 55.5, 53.4, 48.1, 47.5; LC-MS (ESI): *m/z* calcd for $C_{17}H_{19}N_2O_2S$ $[M+H]^+$: 315.1167, found 315.1235.

1-(6-Fluoro-2-methoxyquinolin-3-yl)-*N*-(thiophen-2-ylmethyl)methanamine (3.78)

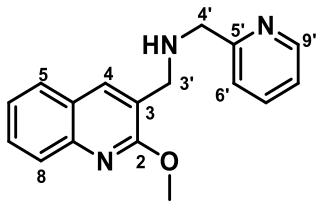


3.78

Pale yellow solid. Yield = 45%; M.p: 68–70°C; ν_{max}/cm^{-1} 3290 (N-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.88 (1H, s, H-4), 7.84 – 7.79 (1H, m, H-8), 7.38 – 7.32 (2H, m, H-5, H-7), 7.24 (1H, dd, *J* = 4.9, 1.3 Hz, H-8′), 6.99 – 6.93 (2H, m, H-6′, H-7′), 4.08

(3H, s, OCH_3), 4.02 (2H, s, H-3′), 3.93 (2H, s, H-4′), 2.05 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 160.4 (d, $J_{F.C}$ = 2.0 Hz), 159.1 (d, $J_{F.C}$ = 243.5 Hz), 143.9, 142.5 (d, $J_{F.C}$ = 1.25 Hz), 135.9 (d, $J_{F.C}$ = 1.6 Hz), 135.8 (d, $J_{F.C}$ = 1.4 Hz), 128.9 (d, $J_{F.C}$ = 8.8 Hz), 126.7, 125.7 (d, $J_{F.C}$ = 9.6 Hz), 124.9, 124.5, 118.3 (d, $J_{F.C}$ = 25.0 Hz), 110.7 (d, $J_{F.C}$ = 22.3 Hz), 53.6, 47.9, 47.7; LC-MS (ESI): *m/z* calcd for $C_{16}H_{16}FN_2OS$ $[M+H]^+$: 303.0967, found 303.1022.

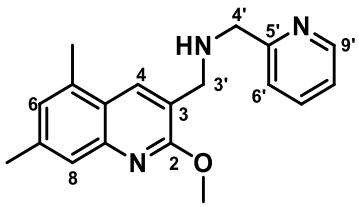
1-(2-Methoxyquinolin-3-yl)-*N*-(pyridin-2-ylmethyl)methanamine (3.79)



3.79

Dark brown viscous liquid. Yield = 34%; ν_{max}/cm^{-1} 3364 (N-H); ^1H NMR (400 MHz, $CDCl_3$): δ_H = 8.55 – 8.54 (1H, m, H-9′), 8.04 (1H, s, H-4), 7.82 (1H, d, *J* = 8.3 Hz, H-8), 7.70 (1H, d, *J* = 8.3 Hz, H-5), 7.64 (1H, td, *J* = 7.7, 1.8 Hz, H-7′), 7.61 – 7.56 (1H, m, H-6), 7.38 – 7.34 (2H, m, H-7, H-6′), 7.19 – 7.16 (1H, m, H-8′), 4.10 (3H, s, OCH_3), 4.06 (2H, s, H-4′), 4.05 (2H, s, H-3′); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 160.5, 157.5, 149.3, 146.0, 137.7, 136.7, 129.3, 127.4, 126.9, 125.2, 124.2, 122.5, 122.4, 121.8, 53.7, 53.4, 48.1; LC-MS (ESI): *m/z* calcd for $C_{17}H_{18}N_3O$ $[M+H]^+$: 280.1450, found 280.1516.

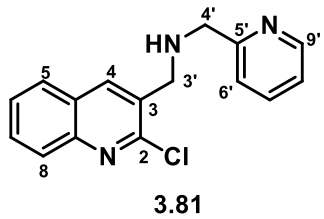
1-(2-Methoxy-5,7-dimethylquinolin-3-yl)-*N*-(pyridin-2-ylmethyl)methanamine (3.80)



3.80

Pale yellow viscous liquid. Yield = 57%; ν_{max}/cm^{-1} 3310 (N-H); ^1H NMR (600 MHz, $CDCl_3$): δ_H = 8.55 – 8.54 (1H, m, H-9′), 8.06 (1H, s, H-4), 7.63 (1H, td, *J* = 7.7, 1.7 Hz, H-7′), 7.48 (1H, s, H-6), 7.34 (1H, d, *J* = 7.7 Hz, H-6′), 7.17 – 7.14 (1H, m, H-8′), 7.03 (1H, s, H-8), 4.07 (3H, s, OCH_3), 3.98 (2H, s, H-4′), 3.94 (2H, s, H-3′), 2.74 (1H, s, NH), 2.59 (3H, s, CH_3), 2.45 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C = 160.6, 159.4, 149.3, 146.3, 138.9, 136.5, 134.0, 133.4, 127.0, 124.5 (2C), 122.3, 122.1, 121.9, 54.5, 53.4, 48.8, 21.7, 18.9; LC-MS (ESI): *m/z* calcd for $C_{19}H_{22}N_3O$ $[M+H]^+$: 308.1763, found 308.1855.

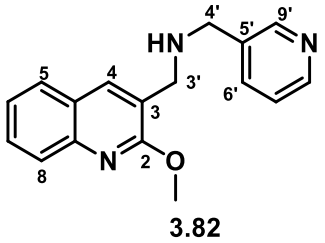
1-(2-Chloroquinolin-3-yl)-*N*-(pyridin-2-ylmethyl)methanamine (3.81)



3.81

Brown crystalline solid. Yield = 51%; M.p: 44–45 °C; ν_{max}/cm^{-1} 3221 (N-H); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.58 – 8.55 (1H, m, H-9′), 8.27 (1H, s, H-4), 7.98 (1H, d, *J* = 8.5 Hz, H-8), 7.80 (1H, d, *J* = 8.2 Hz, H-5), 7.70 – 7.66 (1H, m, H-6), 7.66 – 7.62 (1H, m, H-7′), 7.55 – 7.51 (1H, m, H-7), 7.33 (1H, d, *J* = 7.8 Hz, H-6′), 7.18 – 7.15 (1H, m, H-8′), 4.09 – 4.08 (2H, m, H-4′), 4.02 (2H, s, H-3′), 2.84 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 158.8, 150.6, 149.4, 146.8, 137.5, 136.6, 131.4, 130.1, 128.2, 127.4 (2C), 127.1, 122.4, 122.2, 54.3, 50.2; LC-MS (ESI): *m/z* calcd for $C_{16}H_{15}ClN_3$ $[M+H]^+$: 284.0955, found 284.1068.

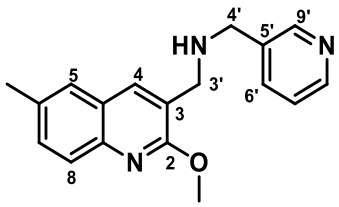
1-(2-Methoxyquinolin-3-yl)-*N*-(pyridin-3-ylmethyl)methanamine (3.82)



3.82

Yellow crystalline solid. Yield = 70%; M.p: 48–51 °C; ν_{max}/cm^{-1} 3275 (N-H); ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.58 – 8.57 (1H, m, H-9′), 8.51 (1H, d, *J* = 4.0 Hz, H-8′), 7.90 (1H, s, H-4), 7.84 (1H, d, *J* = 8.3 Hz, H-8), 7.72 (1H, d, *J* = 7.8 Hz, H-6′), 7.70 (1H, d, *J* = 7.4 Hz, H-5), 7.60 – 7.57 (1H, m, H-6), 7.38 – 7.35 (1H, m, H-7), 7.28 – 7.25 (1H, m, H-7′), 4.09 (3H, s, OCH_3), 3.88 (2H, s, H-3′), 3.82 (2H, s, H-4′), 2.32 (1H, s, NH); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 160.7, 149.8, 148.6, 145.8, 136.8, 135.9, 135.4, 129.1, 127.2, 126.9, 125.2, 124.2, 123.6, 123.5, 53.6, 50.3, 48.3; LC-MS (ESI): *m/z* calcd for $C_{17}H_{18}N_3O$ $[M+H]^+$: 280.1450, found 280.1475.

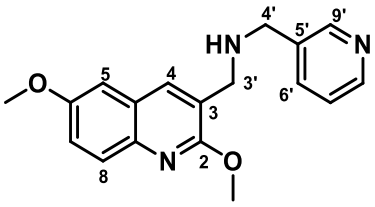
1-(2-Methoxy-6-methylquinolin-3-yl)-*N*-(pyridin-3-ylmethyl)methanamine (3.83)



3.83

White crystalline solid. Yield = 69%; M.p: 70–72°C; ν_{max}/cm^{-1} 3270.8 (N-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.58 – 8.57 (1H, m, H-9′), 8.51 (1H, dd, *J* = 4.8, 1.6 Hz, H-8′), 7.81 (1H, s, H-4), 7.75 – 7.70 (2H, m, H-8, H-6′), 7.47 (1H, s, H-5), 7.42 (1H, dd, *J* = 8.5, 1.8 Hz, H-7), 7.33 – 7.21 (1H, m, H-7′), 4.08 (3H, s, OCH_3), 3.87 (2H, d, *J* = 0.7 Hz, H-3′), 3.81 (2H, s, H-4′), 2.48 (3H, s, CH_3), 2.02 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 160.3, 149.7, 148.5, 144.1, 136.4 (2C), 135.9, 135.5, 133.8, 131.1, 126.6, 126.4, 125.2, 123.5, 53.5, 50.2, 48.5, 21.4; LC-MS (ESI): *m/z* calcd for $C_{18}H_{20}N_3O$ $[M+H]^+$: 294.1606, found 294.1631.

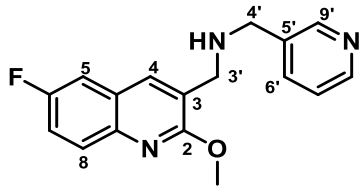
1-(2,6-Dimethoxyquinolin-3-yl)-*N*-(pyridin-3-ylmethyl)methanamine (3.84)



3.84

White crystalline solid. Yield = 68%; M.p: 95–96 °C; ν_{max}/cm^{-1} 3252 (N-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.58 (1H, d, *J* = 1.6 Hz, H-9′), 8.51 (1H, dd, *J* = 4.8, 1.6 Hz, H-8′), 7.82 (1H, s, H-4), 7.76 – 7.70 (2H, m, H-8, H-6′), 7.30 – 7.27 (1H, m, H-7′), 7.26 – 7.23 (1H, m, H-7), 7.04 (1H, d, *J* = 2.8 Hz, H-5), 4.06 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.87 (2H, d, *J* = 0.7 Hz, H-3′), 3.82 (2H, s, H-4′), 2.12 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 159.4, 156.2, 149.8, 148.5, 141.1, 136.0 (2C), 135.5, 128.2, 125.8, 123.8, 123.5, 120.6, 106.0, 55.5, 53.5, 50.2, 48.4; LC-MS (ESI): *m/z* calcd for $C_{18}H_{20}N_3O_2$ $[M+H]^+$: 310.1556, found 310.1586.

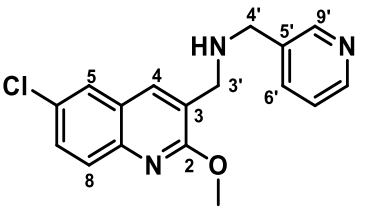
1-(6-Fluoro-2-methoxyquinolin-3-yl)-*N*-(pyridin-3-ylmethyl)methanamine (3.85)



3.85

White crystalline solid. Yield = 62%; M.p: 110–112 °C; ν_{max}/cm^{-1}: 3240 (N-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.58 (1H, d, *J* = 1.6 Hz, H-9′), 8.51 (1H, dd, *J* = 4.8, 1.6 Hz, H-8′), 7.86 (1H, s, H-4), 7.84 – 7.78 (1H, m, H-8), 7.74 – 7.69 (1H, m, H-6′), 7.38 – 7.30 (2H, m, H-5, H-7), 7.30 – 7.25 (1H, m, H-7′), 4.07 (3H, s, OCH_3), 3.88 (2H, d, *J* = 0.8 Hz, H-3′), 3.83 (2H, s, H-4′), 1.99 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 160.4 (d, $J_{F.C}$ = 2.0 Hz), 159.1 (d, $J_{F.C}$ = 243.5 Hz), 143.9, 142.5 (d, $J_{F.C}$ = 0.9 Hz), 135.9 (2C), 135.4 (d, $J_{F.C}$ = 1.4 Hz), 128.6 (d, $J_{F.C}$ = 8.8 Hz), 126.7, 125.7 (d, $J_{F.C}$ = 9.6 Hz), 124.9, 124.5, 118.3 (d, $J_{F.C}$ = 25.0 Hz), 110.7 (d, $J_{F.C}$ = 22.3 Hz), 53.5 (d, $J_{F.C}$ = 3.0 Hz), 47.9, 47.7; LC-MS (ESI): *m/z* calcd for $C_{17}H_{17}FN_3O$ $[M+H]^+$: 298.1356, found 298.1390.

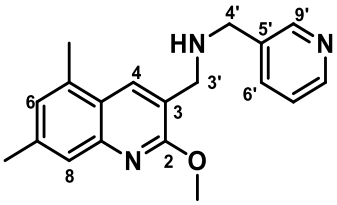
1-(6-Chloro-2-methoxyquinolin-3-yl)-*N*-(pyridin-3-ylmethyl)methanamine (3.86)



3.86

Yellow crystalline solid. Yield = 22%; M.p: 113–116 °C; ν_{max}/cm^{-1}: 3252 (N-H); ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.58 (1H, s, H-9′), 8.51 (1H, d, *J* = 3.8 Hz, H-8′), 7.83 (1H, s, H-4), 7.75 (1H, d, *J* = 8.9 Hz, H-8), 7.72 (1H, d, *J* = 8.0 Hz, H-6′), 7.67 (1H, d, *J* = 2.3 Hz, H-5), 7.51 (1H, dd, *J* = 8.9, 2.3 Hz, H-7), 7.28 – 7.26 (1H, m, H-7′), 4.07 (3H, s, OCH_3), 3.87 (2H, s, H-3′), 3.83 (2H, s, H-4′), 2.50 (1H, s, NH); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 160.9, 149.7, 148.6, 144.2, 135.9, 135.7, 135.3, 129.7, 129.5, 128.4, 126.0, 125.9, 124.8, 123.5, 53.7, 50.4, 48.1; LC-MS (ESI): *m/z* calcd for $C_{17}H_{17}ClN_3O$ $[M+H]^+$: 314.1060, found 314.1109.

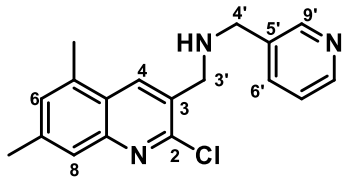
1-(2-Methoxy-5,7-dimethylquinolin-3-yl)-*N*-(pyridin-3-ylmethyl)methanamine (3.87)



3.87

White crystalline solid. Yield = 70%; M.p: 73–75 °C; ν_{max}/cm^{-1}: 3321 (N-H); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.57 (1H, d, *J* = 1.8 Hz, H-9′), 8.50 (1H, dd, *J* = 4.8, 1.8 Hz, H-8′), 7.99 (1H, s, H-4), 7.72 – 7.69 (1H, m, H-6′), 7.50 (1H, s, H-6), 7.29 – 7.21 (1H, m, H-7′), 7.04 (1H, s, H-8), 4.07 (3H, s, OCH_3), 3.88 (2H, s, H-3′), 3.81 (2H, s, H-4′), 2.58 (3H, s, CH_3), 2.45 (3H, s, CH_3), 2.19 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 160.6, 149.7, 148.5, 146.4, 139.0, 135.9, 135.5, 133.9, 133.5, 127.1, 124.6, 123.4, 122.3, 121.8, 53.4, 50.3, 48.8, 21.7, 18.8; LC-MS (ESI): *m/z* calcd for $C_{19}H_{22}N_3O$ $[M+H]^+$: 308.1763, found 308.1859.

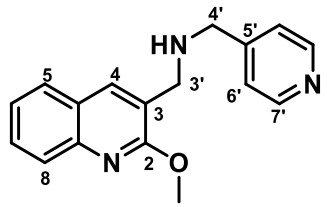
1-(2-Chloro-5,7-dimethylquinolin-3-yl)-*N*-(pyridin-3-ylmethyl)methanamine (3.88)



3.88

Yellow solid. Yield = 70%; M.p: 84–85 °C; ν_{max}/cm^{-1}: 3321 (N-H); ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.60 (1H, d, *J* = 1.4 Hz, H-9′), 8.51 (1H, dd, *J* = 4.8, 1.4 Hz, H-8′), 8.23 (1H, s, H-4), 7.74 (1H, d, *J* = 7.8 Hz, H-6′), 7.60 (1H, s, H-6), 7.28 (1H, dd, *J* = 7.8, 4.8 Hz, H-7′), 7.20 (1H, s, H-8), 4.01 (2H, s, H-3′), 3.88 (2H, s, H-4′), 2.62 (3H, s, CH_3), 2.48 (3H, s, CH_3), 2.35 (1H, s, NH); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 150.1, 149.8, 148.8, 147.6, 140.5, 136.0, 135.0, 134.5, 134.2, 130.1, 129.4, 125.4, 124.7, 123.6, 50.5, 50.4, 21.9, 18.8; LC-MS (ESI): *m/z* calcd for $C_{18}H_{19}ClN_3$ $[M+H]^+$: 312.1268, found 312.1392.

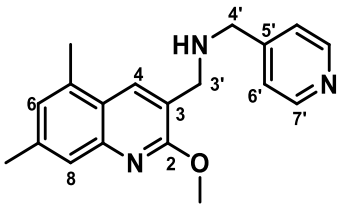
1-(2-Methoxyquinolin-3-yl)-*N*-(pyridin-4-ylmethyl)methanamine (3.89)



3.89

Yellow viscous liquid. Yield = 40%; ν_{max}/cm^{-1}: 3325 (N-H); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.55 (2H, d, *J* = 5.6 Hz, H-7′), 7.90 (1H, s, H-4), 7.84 (1H, d, *J* = 8.3 Hz, H-8), 7.69 (1H, d, *J* = 8.3 Hz, H-5), 7.61 – 7.57 (1H, m, H-7), 7.37 (1H, t, *J* = 7.1 Hz, H-6), 7.31 (2H, d, *J* = 5.6 Hz, H-6′), 4.09 (3H, s, OCH_3), 3.89 (2H, s, H-3′), 3.83 (2H, s, H-4′), 2.86 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 160.7, 149.8, 148.9, 145.9, 137.0, 129.2, 127.2, 126.9, 125.2, 124.2, 123.2, 123.1, 53.6, 51.5, 48.2; LC-MS (ESI): *m/z* calcd for $C_{17}H_{18}N_3O$ $[M+H]^+$: 280.1450, found 280.1523.

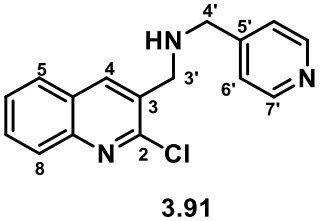
1-(2-Methoxy-5,7-dimethylquinolin-3-yl)-*N*-(pyridin-4-ylmethyl)methanamine (3.90)



3.90

Yellow viscous liquid. Yield = 41%; ν_{max}/cm^{-1}: 3305.6 (N-H); ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.55 (2H, d, *J* = 5.8 Hz, H-7′), 7.98 (1H, s, H-4), 7.50 (1H, s, H-6), 7.30 (2H, d, *J* = 5.8 Hz, H-6′), 7.05 (1H, s, H-8), 4.08 (3H, s, OCH_3), 3.88 (2H, s, H-3′), 3.82 (2H, s, H-4′), 2.59 (3H, s, CH_3), 2.46 (3H, s, CH_3), 2.16 (1H, s, NH); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 160.6, 149.8, 149.3, 146.5, 139.1, 133.9, 133.6, 127.1, 124.6, 123.1, 122.3, 121.8, 53.4, 51.6, 48.8, 21.7, 18.8; LC-MS (ESI): *m/z* calcd for $C_{19}H_{22}N_3O$ $[M+H]^+$: 308.1763, found 308.1853.

1-(2-Chloroquinolin-3-yl)-*N*-(pyridin-4-ylmethyl)methanamine (3.91)



3.91

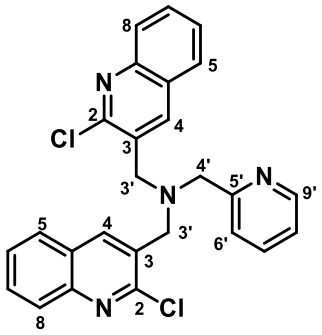
Yellow solid. Yield = 41%; M.p: 63–64 °C; ν_{max}/cm^{-1}: 3282 (N-H); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.57 – 8.55 (2H, m, H-7′), 8.19 (1H, s, H-4), 8.00 (1H, d, *J* = 8.5 Hz, H-8), 7.81 (1H, d, *J* = 8.2 Hz, H-5), 7.73 – 7.68 (1H, m, H-7), 7.57 – 7.53 (1H, m, H-6), 7.33 (2H,

d, *J* = 6.0 Hz, H-6′), 4.04 (2H, s, H-3′), 3.90 (2H, s, H-4′), 2.59 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 150.5, 149.9, 148.6, 146.9, 137.7, 130.9, 130.3, 128.2, 127.4, 127.3, 123.0 (2C), 51.8, 50.2; LC-MS (ESI): *m/z* calcd for $C_{16}H_{15}ClN_3$ $[M+H]^+$: 284.0955, found 284.1068.

5.1.12 General procedure for the synthesis of *bis*-2-chloroquinolinyl derivatives[108]

Respective 2-chloro-3-(chloromethyl)quinolines (5.00 mmol) were dissolved in 10 mL of absolute ethanol followed by 2-(aminomethyl)pyridine (2.5 mmol) along with 1 mL of TEA and the mixture heated under reflux for 24 – 36 h. After completion of the reaction (TLC), the solvent was removed under reduced pressure. The crude product was dissolved in EtOAc, washed successively with brine (20 mL) and water (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The solid mass obtained was purified by silica gel column chromatography (EtOAc/Hexane: 1:1) to obtain the desired compounds.

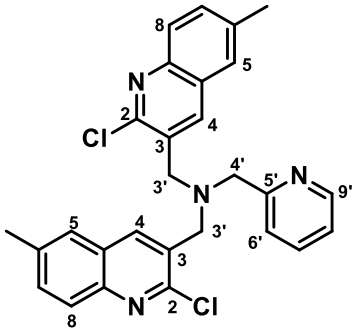
1-(2-Chloroquinolin-3-yl)-*N*-((2-chloroquinolin-3-yl)methyl)-*N*-(pyridin-2-ylmethyl)methanamine (3.92)



3.92

Brown crystalline solid. Yield = 78%; M.p: 102–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.51 – 8.49 (1H, m, H-9′), 8.38 (2H, s, H-4), 7.93 (2H, d, *J* = 8.5 Hz, H-8), 7.78 (2H, d, *J* = 7.5 Hz, H-5), 7.68 – 7.64 (2H, m, H-6), 7.61 (1H, td, *J* = 7.7, 1.0 Hz, H-7′), 7.53 – 7.49 (2H, m, H-7), 7.48 (1H, d, *J* = 8.0 Hz, H-6′), 7.10 (1H, ddd, *J* = 7.4, 4.9, 1.0 Hz, H-8′), 4.07 (4H, s, H-3′), 4.03 (2H, s, H-4′); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 158.3, 150.8, 148.8, 146.8, 138.6, 136.8, 130.3, 130.2, 128.1, 127.5, 127.1 (2C), 123.2, 122.4, 60.4, 56.3; HRMS (ESI): *m/z* calcd for $C_{26}H_{21}N_4Cl_2$ $[M+H]^+$: 459.1143, found 459.1142.

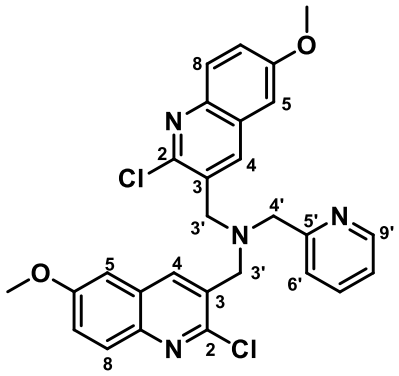
1-(2-Chloro-6-methylquinolin-3-yl)-*N*-((2-chloro-6-methylquinolin-3-yl)methyl)-*N*-(pyridin-2-ylmethyl)methanamine (3.93)



3.93

Brown solid. Yield = 84%; M.p: 150–152 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.47 (1H, d, *J* = 3.8 Hz, H-9′), 8.29 (2H, s, H-4), 7.81 (2H, d, *J* = 8.5 Hz, H-8), 7.66 (1H, t, *J* = 7.4 Hz, H-7′), 7.55 – 7.52 (3H, m, H-5, H-6′), 7.48 (2H, d, *J* = 8.5 Hz, H-7), 7.14 – 7.10 (1H, m, H-8′), 4.07 – 4.02 (6H, m, H-3′, H-4′), 2.49 (6H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 158.1, 149.9, 147.8, 145.4, 138.1, 137.6, 137.1, 132.5, 128.0, 127.7, 127.2, 126.4, 123.5, 122.5, 59.7, 56.4, 21.6; HRMS (ESI): *m/z* calcd for $C_{28}H_{25}N_4Cl_2$ $[M+H]^+$: 487.1456, found 487.1459.

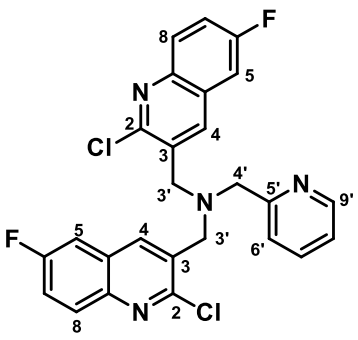
1-(2-Chloro-6-methoxyquinolin-3-yl)-*N*-((2-chloro-6-methoxyquinolin-3-yl)methyl)-*N*-(pyridin-2-ylmethyl)methanamine (3.94)



3.94

Brown solid. Yield = 52%; M.p: 177–178 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.52 – 8.50 (1H, m, H-9′), 8.23 (2H, s, H-4), 7.82 (2H, d, *J* = 9.2 Hz, H-8), 7.62 (1H, td, *J* = 7.7, 1.7 Hz, H-7′), 7.48 (1H, d, *J* = 7.7 Hz, H-6′), 7.30 (2H, dd, *J* = 9.2, 2.8 Hz, H-7), 7.12 – 7.09 (1H, m, H-8′), 7.01 (2H, d, *J* = 2.8 Hz, H-5), 4.04 (4H, s, H-3′), 4.02 (2H, s, H-4′), 3.90 (6H, s, OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 158.3, 158.2, 148.7, 148.2, 142.8, 137.5, 136.8, 130.4, 129.5, 128.3, 123.3, 122.9, 122.3, 105.0, 60.3, 56.2, 55.6; HRMS (ESI): *m/z* calcd for $C_{28}H_{25}N_4Cl_2O_2$ $[M+H]^+$: 519.1355, found 519.1348.

1-(2-Chloro-6-fluoroquinolin-3-yl)-*N*-((2-chloro-6-fluoroquinolin-3-yl)methyl)-*N*-(pyridin-2-ylmethyl)methanamine (3.95)



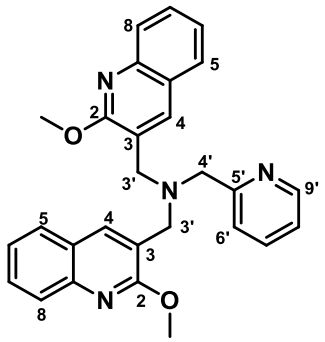
3.95

Brown solid. Yield = 35%; M.p: 141–143 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.53 (1H, ddd, *J* = 4.8, 1.8, 1.0 Hz, H-9′), 8.33 (2H, s, H-4), 7.90 (2H, dd, *J* = 8.8, 5.2 Hz, H-8), 7.63 (1H, td, *J* = 7.7, 1.8 Hz, H-7′), 7.46 – 7.37 (5H, m, H-5, H-7, H-6′), 7.12 (1H, ddd, *J* = 7.4, 4.9, 1.0 Hz, H-8′), 4.05 (4H, s, H-3′), 4.01 (2H, s, H-4′); ^{13}C NMR (75 MHz, $CDCl_3$): δc = 160.6 (d, $J_{F.C}$ = 249.3 Hz), 158.0, 150.1 (d, $J_{F.C}$ = 3.0 Hz), 149.0, 143.7, 137.7 (d, $J_{F.C}$ = 5.4 Hz), 136.8, 131.3, 130.6 (d, $J_{F.C}$ = 9.3 Hz), 127.8 (d, $J_{F.C}$ = 9.9 Hz), 123.2, 122.4, 120.4 (d, $J_{F.C}$ = 25.8 Hz), 110.7 (d, $J_{F.C}$ = 21.5 Hz), 60.5, 56.1; HRMS (ESI): *m/z* calcd for $C_{26}H_{19}N_4Cl_2F_2$ $[M+H]^+$: 495.0955, found 495.0952.

5.1.13 General procedure for the synthesis of *bis*-2-methoxyquinolinyl derivatives[196]

150.0 mg (3.75 mmol) of sodium hydride (60% in mineral oil) was added to methanol (5 mL) and the mixture stirred for 15 min at r.t. To this suspension, respective bis-2-chloroquinolinyl derivative (0.190 mmol) was added and the reaction mixture heated at 70 ^{o}C for 36 h. The reaction was quenched by addition of water (10 mL). The product was extracted with EtOAc (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc: Hexane 1:1) to yield desired compounds.

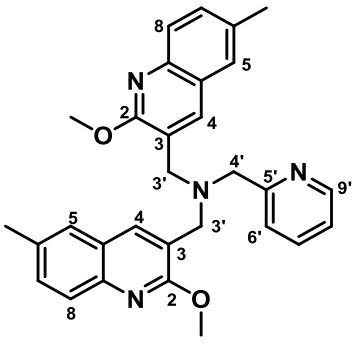
1-(2-Methoxyquinolin-3-yl)-*N*-((2-methoxyquinolin-3-yl)methyl)-*N*-(pyridin-2-ylmethyl)methanamine (3.96)



3.96

Brown solid. Yield = 55%; M.p: 95–97 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.53 (1H, d, *J* = 4.3 Hz, H-9′), 8.26 (2H, s, H-4), 7.83 (2H, d, *J* = 8.3 Hz, H-8), 7.72 (2H, d, *J* = 7.9 Hz, H-5), 7.64 − 7.63 (2H, m, H-6′, H-7′), 7.58 (2H, t, *J* = 7.5 Hz, H-7), 7.36 (2H, t, *J* = 7.4 Hz, H-6), 7.14 – 7.11 (1H, m, H-8′), 4.06 (6H, s, OCH_3), 4.01 (2H, s, H-4′), 3.90 (4H, s, H-3′); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 160.8, 158.8, 149.0, 145.7, 137.2, 136.6, 129.1, 127.4, 126.8 (2C), 125.3, 124.0, 122.4, 122.1, 60.4, 53.4, 53.1; HRMS (ESI): *m/z* calcd for $C_{28}H_{27}N_4O_2$ $[M+H]^+$: 451.2134, found 451.2121.

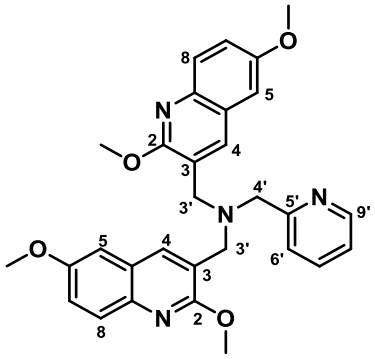
1-(2-Methoxy-6-methylquinolin-3-yl)-*N*-((2-methoxy-6-methylquinolin-3-yl)methyl)-*N*-(pyridin-2-ylmethyl)methanamine (3.97)



3.97

Brown solid. Yield = 68%; M.p: 119–121 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 8.50 – 8.48 (1H, m, H-9′), 8.27 (2H, s, H-4), 7.76 (1H, td, *J* = 7.7, 1.7 Hz, H-7′), 7.65 – 7.60 (5H, m, H-7, H-8, H-6′), 7.42 (2H, dd, *J* = 8.5, 1.9 Hz, H-5), 7.22 (1H, ddd, *J* = 7.2, 4.7, 0.9 Hz, H-8′), 3.92 (6H, s, OCH_3), 3.86 (2H, s, H-4′), 3.78 (4H, s, H-3′), 2.42 (6H, s, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 160.4, 159.6, 149.2, 143.7, 137.0, 136.9, 133.6, 131.4, 127.0, 126.6, 125.4, 123.3, 122.9, 122.6, 60.3, 53.6, 52.6, 21.3; HRMS (ESI): *m/z* calcd for $C_{30}H_{31}N_4O_2$ $[M+H]^+$: 479.2447, found 479.2445.

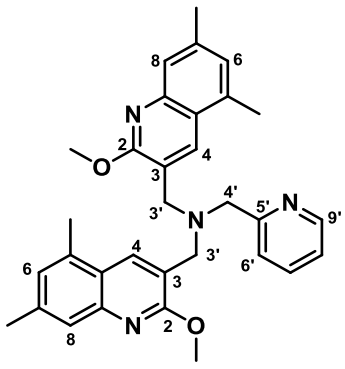
1-(2,6-Dimethoxyquinolin-3-yl)-*N*-((2,6-dimethoxyquinolin-3-yl)methyl)-*N*-(pyridin-2-ylmethyl)methanamine (3.98)



3.98

Brown solid. Yield = 58%; M.p: 65–67 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ_H = 8.50 – 8.48 (1H, m, H-9′), 8.28 (2H, s, H-4), 7.76 (1H, td, *J* = 7.7, 1.8 Hz, H-7′), 7.65 – 7.63 (3H, m, H-8, H-6′), 7.28 (2H, d, *J* = 2.8 Hz, H-5), 7.23 (2H, dd, *J* = 9.0, 2.8 Hz, H-7), 7.22 – 7.20 (1H, m, H-8′), 3.90 (6H, s, OCH_3), 3.88 (2H, s, H-4′), 3.84 (6H, s, OCH_3), 3.78 (4H, s, H-3′); ^{13}C NMR (150 MHz, DMSO-d_6): δ_C = 159.6, 159.4, 156.1, 149.2, 140.7, 137.0, 136.9, 128.1, 126.1, 123.4, 122.9, 122.6, 120.9, 107.0, 60.4, 55.8, 53.5, 52.6; HRMS (ESI): *m/z* calcd for $C_{30}H_{31}N_4O_4$ $[M+H]^+$: 511.2345, found 511.2344.

1-(2-Methoxy-5,7-dimethylquinolin-3-yl)-*N*-((2-methoxy-5,7-dimethylquinolin-3-yl)methyl)-*N*-(pyridin-2-ylmethyl)methanamine (3.99)

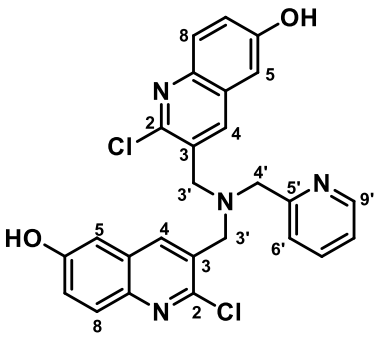


3.99

Brown solid. Yield = 72%; M.p: 113–114 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.54 − 8.53 (1H, m, H-9′), 8.46 (2H, s, H-4), 7.69 (1H, d, *J* = 7.6 Hz, H-6′), 7.64 (1H, td, *J* = 7.6, 1.7 Hz, H-7′), 7.48 (2H, s, H-6), 7.14 – 7.12 (1H, m, H-8′), 7.01 (2H, s, H-8), 4.03 (6H, s, OCH_3), 3.99 (2H, bs, H-4′), 3.91 (4H, bs, H-3′), 2.54 (6H, s, CH_3), 2.45 (6H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C =160.7, 159.4, 149.1, 146.2, 138.7, 136.4, 133.7, 133.1, 126.7, 124.5 (2C), 122.4, 122.2, 122.0, 60.8, 53.2, 53.0, 21.7, 18.7; HRMS (ESI): *m/z* calcd for $C_{32}H_{35}N_4O_2$ $[M+H]^+$: 507.2760, found 507.2762.

5.1.14 Synthesis of 1-(2-chloro-6-hydoxyquinolin-3-yl)-*N*-((2-chloro-6-hydroxyquinolin-3-yl)methyl)-*N*-(pyridin-2-ylmethyl)methanamine[197]

To a solution of compound **3.94** (50 mg, 0.100 mmol) in DCM (1 mL) at −78 °C under N_2(g) atmosphere, boron tribromide (0.16 mL 1M solution in DCM, 2.4 mmol) was added dropwise using a syringe and the reaction mixture was stirred for 30 min at −78 °C. The reaction mixture was allowed to warm to r.t and stirred for a further 3 h. After the 3 h had elapsed, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (2 mL) and the product extracted with EtOAc (2 × 5 mL). The organic layers were combined, washed with brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexane: 1:2) to yield compound **3.100**.



3.100

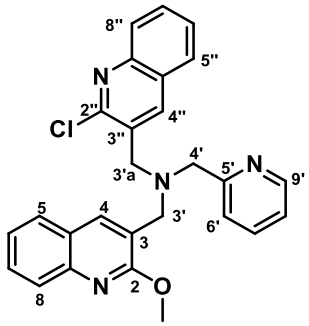
Tan solid. Yield = 69%; M.p: 184–185 °C; ν_{max}/cm^{-1}: 3206 (O-H); ^{1}H NMR (600 MHz, DMSO-d_6): δ_H = 10.12 (2H, s, OH), 8.48 (1H, d, *J* = 4.8 Hz, H-9′), 8.36 (2H, s, H-4), 7.74 – 7.70 (3H, m, H-8, H-7′), 7.53 (1H, d, *J* = 7.8 Hz, H-6′), 7.27 (2H, dd, *J* = 9.0, 2.5 Hz, H-7), 7.22 – 7.20 (1H, m, H-8′), 7.14 (2H, d, *J* = 2.5 Hz, H-5), 3.96 – 3.93 (6H, m, H-3′, H-4′); ^{13}C NMR (150 MHz, DMSO-d_6): δ_C = 158.8, 156.5, 149.2, 147.3, 141.6, 137.7, 136.9, 130.6, 129.4, 128.8, 123.7, 123.0, 122.7, 108.8, 60.2, 55.7; HRMS (ESI): *m/z* calcd for $C_{26}H_{21}N_4O_2Cl_2$ $[M+H]^+$: 491.1042, found 491.1039.

5.1.15 General procedure for the synthesis of 2-chloroquinolinyl-2-methoxyquinolinyl derivatives[108]

Respective 2-chloro-3-(chloromethyl)quinoline (5.00 mmol) was dissolved in 20 mL of absolute ethanol followed by addition of equimolar amount of quinolinyl-*N*-(pyridinylmethyl)

methanamine (5.00 mmol) and 1 mL of TEA. The reaction mixture was heated under reflux for 12 – 16 h. After completion of the reaction (TLC), the solvent was removed under reduced pressure. The dried mass was dissolved in EtOAc, successively washed with brine (20 mL) and water (20 mL), dried (Na_2SO_4) and concentrated in *vacuo*. The solid mass obtained was purified by silica gel column chromatography (EtOAc: Hexane 1:1) to obtain the desired compounds.

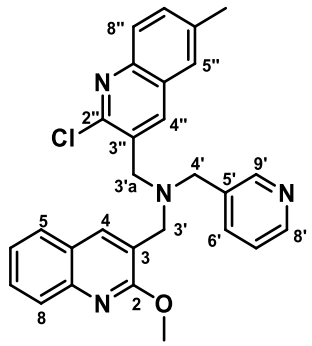
1-(2-Chloroquinolin-3-yl)-*N*-((2-methoxyquinolin-3-yl)methyl)-*N*-(pyridin-2-ylmethyl)methanamine (3.101)



3.101

Brown solid. Yield = 65%; M.p: 85–87 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.51 (1H, d, *J* = 4.2 Hz, H-9′), 8.48 (1H, s, H-4″), 8.16 (1H, s, H-4), 7.98 (1H, d, *J* = 8.4 Hz, H-8″), 7.83 – 7.77 (2H, m, H-8, H-7′), 7.72 – 7.70 (1H, m, H-6′), 7.68 – 7.66 (1H, m, H-5″), 7.64 – 7.61 (1H, m, H-5), 7.59 – 7.56 (2H, m, H-6, H-6″), 7.53 (1H, t, *J* = 7.5 Hz, H-7″), 7.35 (1H, t, *J* = 6.1 Hz, H-7), 7.11 (1H, dd, *J* = 7.6, 5.1 Hz, H-8′), 4.07 – 4.05 (5H, m, H-4′, OCH_3), 4.03 (2H, s, H-3a′), 3.96 (2H, s, H-3′); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 160.9, 158.9, 150.9, 148.8, 146.8, 145.8, 138.2, 137.8, 136.8, 130.8, 130.2, 129.2, 128.2, 127.5, 127.3 (2C), 127.0, 126.8, 125.1, 124.1, 122.8, 122.3, 122.2, 60.3, 55.9, 53.5, 53.3; HRMS (ESI): *m/z* calcd for $C_{27}H_{24}N_4OCl$ $[M+H]^+$: 455.1639, found 455.1641.

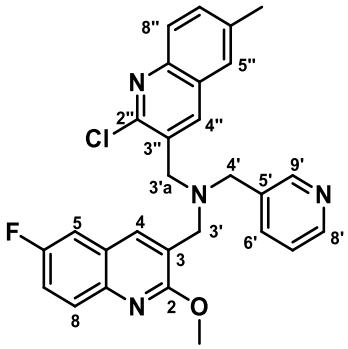
1-(2-Chloro-6-methylquinolin-3-yl)-*N*-((2-methoxyquinolin-3-yl)methyl)-*N*-(pyridin-3-ylmethyl)methanamine (3.102)



3.102

Brown solid. Yield = 65%; M.p: 130–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.72 (1H, s, H-9′), 8.49 (1H, d, *J* = 4.0 Hz, H-8′), 8.30 (1H, s, H-4″), 8.09 (1H, s, H-4), 7.86 (1H, d, *J* = 8.6 Hz, H-8″), 7.81 (1H, d, *J* = 8.3 Hz, H-5), 7.76 (1H, d, *J* = 7.8 Hz, H-6′), 7.71 (1H, d, *J* = 7.9 Hz, H-8), 7.60 – 7.56 (1H, m, H-6), 7.55 (1H, d, *J* = 1.7 Hz, H-5″), 7.50 (1H, dd, *J* = 8.6, 1.7 Hz, H-7″), 7.38 – 7.34 (1H, m, H-7), 7.25 − 7.23 (1H, m, H-7′), 4.06 (3H, s, OCH_3), 3.91 (2H, s, CH_2, H-3′a), 3.83 (2H, s, CH_2, H-3′), 3.80 (2H, s, CH_2, H-4′), 2.51 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C =160.8, 150.0, 149.8, 148.7, 145.8, 145.4, 137.4 , 137.3, 137.1, 136.3, 134.3, 132.4, 130.6, 129.2, 127.9, 127.3 (2C), 126.9, 126.3, 125.1, 124.1, 123.4, 122.4, 56.3, 55.4, 53.5, 52.7, 21.6; HRMS (ESI): *m/z* calcd for $C_{28}H_{26}N_4OCl$ $[M+H]^+$: 469.1795, found 469.1794.

1-(2-Chloro-6-methylquinolin-3-yl)-*N*-((6-fluoro-2-methoxyquinolin-3-yl)methyl)-*N*-(pyridin-3-ylmethyl)methanamine (3.103)

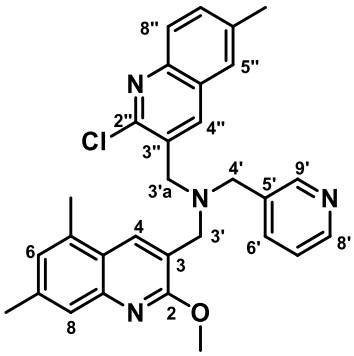


3.103

Brown solid. Yield = 54%; M.p: 139–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.71 (1H, s, H-9′), 8.49 (1H, d, *J* = 3.8 Hz, H-8′), 8.27 (1H, s, H-4″), 8.02 (1H, s, H-4), 7.85 (1H, d, *J* = 8.6 Hz, H-8″), 7.78 – 7.74 (2H, m, H-8, H-6′), 7.54 (1H, d, *J* = 1.7 Hz, H-5″), 7.50 (1H, dd, *J* = 8.6, 1.7 Hz, H-7″), 7.35 – 7.29 (2H, m, H-5, H-7), 7.28 – 7.24 (1H, m, H-7′), 4.02 (3H,

s, OCH_3), 3.91 (2H, s, CH_2, H-3′a), 3.82 (2H, s, CH_2, H-3′), 3.80 (2H, s, CH_2, H-4′), 2.51 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 160.3, 159.1 (d, $J_{F.C}$ = 241.1 Hz), 149.9, 149.8, 148.7, 145.4, 142.6, 137.3, 137.2, 136.5 (d, $J_{F.C}$ = 4.6 Hz), 136.4, 134.2, 132.5, 130.4, 128.9 (d, $J_{F.C}$ = 8.8 Hz), 127.9, 127.3, 126.3, 125.4 (d, $J_{F.C}$ = 9.6 Hz), 123.6, 123.5, 118.6 (d, $J_{F.C}$ = 25.0 Hz), 110.8 (d, $J_{F.C}$ = 21.8 Hz), 56.4, 55.5, 53.5, 52.6, 21.6; HRMS (ESI): *m/z* calcd for $C_{28}H_{25}N_4OFCl$ $[M+H]^+$: 487.1701, found 487.1695.

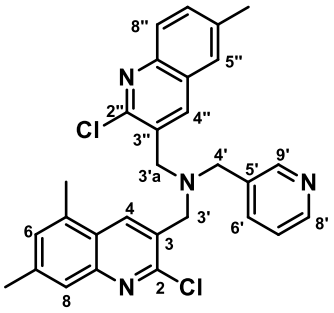
1-(2-Chloro-6-methylquinolin-3-yl)-*N*-((2-methoxy-5,7-dimethylquinolin-3-yl)methyl)-*N*-(pyridin-3-ylmethyl)methanamine (3.104)



3.104

Brown viscous liquid. Yield = 19%; ^1H NMR (400 MHz, $CDCl_3$): δ_H = 8.72 (1H, bs, H-9′), 8.49 (1H, bs, H-8′), 8.31 (1H, s, H-4″), 8.20 (1H, s, H-4), 7.86 (1H, d, *J* = 8.6 Hz, H-8″), 7.76 (1H, d, *J* = 7.8 Hz, H-6′), 7.53 (1H, d, *J* = 1.6 Hz, H-5″), 7.50 (1H, dd, *J* = 8.6, 1.6 Hz, H-7″), 7.46 (1H, s, H-6), 7.27 – 7.24 (1H, m, H-7′), 7.03 (1H, s, H-8), 4.04 (3H, s, OCH_3), 3.91 (2H, s, CH_2, H-3′a), 3.84 (2H, s, CH_2, H-3′), 3.81 (2H, s, CH_2, H-4′), 2.58 (3H, s, CH_3), 2.51 (3H, s, CH_3), 2.44 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 160.6, 150.0, 149.8, 148.6, 146.4, 145.3, 139.3, 137.3, 137.1, 136.3, 134.5, 134.0, 133.8, 132.4, 130.7, 127.8, 127.3, 127.1, 126.2, 124.5, 123.4, 122.2, 120.5, 56.3, 55.4, 53.3, 52.8, 21.7, 21.6, 18.8; HRMS (ESI): *m/z* calcd for $C_{30}H_{30}N_4OCl$ $[M+H]^+$: 497.2108, found 497.2108.

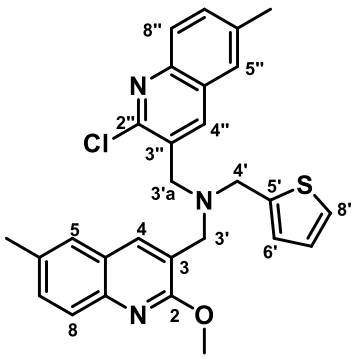
1-(2-Chloro-5,7-dimethylquinolin-3-yl)-*N*-((2-chloro-6-methylquinolin-3-yl)methyl)-*N*-(pyridin-3-ylmethyl)methanamine (3.105)



3.105

Brown viscous liquid. Yield = 17%; ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.75 (1H, bs, H-9′), 8.50 (1H, bs, H-8′), 8.36 (1H, s, H-4″), 8.18 (1H, s, H-4), 7.87 (1H, d, *J* = 7.6 Hz, H-7′), 7.80 (1H, d, *J* = 8.5 Hz, H-8″), 7.54 – 7.52 (2H, m, H-5″, H-6), 7.49 (1H, dd, *J* = 8.6, 1.3 Hz, H-7″), 7.36 – 7.32 (1H, m, H-7′), 7.17 (1H, s, H-8), 3.97 (2H, s, CH_2, H-3′a), 3.96 (2H, s, CH_2, H-3′), 3.88 (2H, s, CH_2, H-4′), 2.60 (3H, s, CH_3), 2.50 (3H, s, CH_3), 2.45 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 150.1, 149.6, 148.6, 147.6, 147.4, 145.4, 140.7, 138.0, 137.9, 137.4, 135.1, 134.8, 134.0, 132.6, 130.0, 129.9, 128.3, 127.8, 127.1, 126.2, 125.3, 124.6, 124.0, 56.8, 56.1, 56.0, 21.9, 21.6, 18.7; HRMS (ESI): *m/z* calcd for $C_{29}H_{27}N_4Cl_2$ $[M+H]^+$: 501.1613, found 501.1617.

1-(2-Chloro-6-methylquinolin-3-yl)-*N*-((2-methoxy-6-methylquinolin-3-yl)methyl)-*N*-(thiophen-2-ylmethyl)methanamine (3.106)

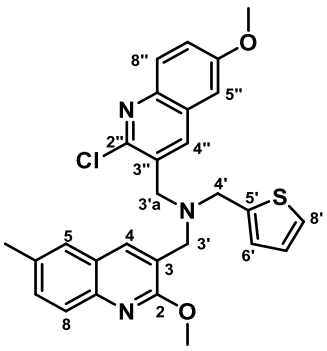


3.106

Brown solid. Yield = 60%; M.p: 107–109 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.46 (1H, s, H-4″), 8.16 (1H, s, H-4), 7.88 (1H, d, *J* = 8.6 Hz, H-8″), 7.73 (1H, d, *J* = 8.5 Hz, H-8), 7.59 (1H, bs, H-5″), 7.52 – 7.50 (2H, m, H-5, H-7″), 7.42 (1H, dd, *J* = 8.5, 1.8 Hz, H-7), 7.27 (1H, dd, *J* = 5.4, 0.66 Hz, H-8′), 7.00 (1H, d, *J* = 2.7 Hz, H-6′), 6.98 (1H, dd, *J* = 5.0, 3.5 Hz, H-7′), 4.05 (3H, s, OCH_3), 4.01 (2H, s, CH_2, H-4′), 3.97 (2H, s, CH_2, H-3a′), 3.87 (2H, s, CH_2, H-3′), 2.52 (3H, s, CH_3), 2.49 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C

= 160.4, 149.7, 145.3, 144.0, 142.7, 136.9 (2C), 136.2, 133.6, 132.2, 131.1, 131.0, 127.8, 127.5, 126.7, 126.6, 126.5 (2C), 125.8, 125.3, 124.9, 122.6, 54.8, 53.4, 53.3, 52.1, 21.6, 21.3; HRMS (ESI): *m/z* calcd for $C_{28}H_{27}N_3OSCl$ $[M+H]^+$: 488.1563, found 488.1566.

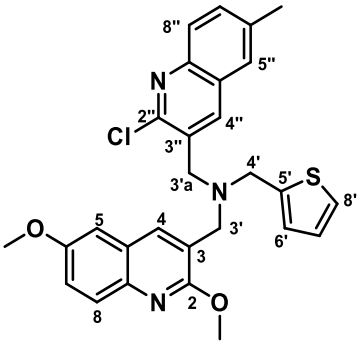
1-(2-Chloro-6-methoxyquinolin-3-yl)-*N*-((2-methoxy-6-methylquinolin-3-yl)methyl)-*N*-(thiophen-2-ylmethyl)methanamine (3.107)



3.107

Brown solid. Yield = 82%; M.p: 141–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.41 (1H, s, H-4″), 8.14 (1H, s, H-4), 7.88 (1H, d, *J* = 9.2 Hz, H-8″), 7.72 (1H, d, *J* = 8.5 Hz, H-8), 7.51 (1H, d, *J* = 1.6 Hz, H-5), 7.41 (1H, dd, *J* = 8.5, 1.6 Hz, H-7), 7.33 (1H, dd, *J* = 9.2, 2.7 Hz, H-7″), 7.27 – 7.25 (1H, m, H-8′), 7.07 (1H, d, *J* = 2.7 Hz, H-5″), 7.00 (1H, d, *J* = 2.8 Hz, H-6′), 6.99 – 6.97 (1H, m, H-7′), 4.05 (3H, s, OCH_3), 4.02 (2H s, CH_2, H-4′), 3.96 (2H, s, CH_2, H-3a′), 3.92 (3H, s, OCH_3), 3.88 (2H s, CH_2, H-3′), 2.48 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 160.4, 158.1, 148.0, 144.0, 142.7, 136.3 (2C), 133.6, 131.3, 131.1, 129.6, 128.6, 126.7, 126.6, 126.5, 125.8, 125.2, 124.9, 122.6 (2C), 105.2 (2C), 55.7, 54.8, 53.4 (2C), 52.1, 21.3; HRMS (ESI): *m/z* calcd for $C_{28}H_{27}N_3O_2SCl$ $[M+H]^+$: 504.1513, found 504.1520.

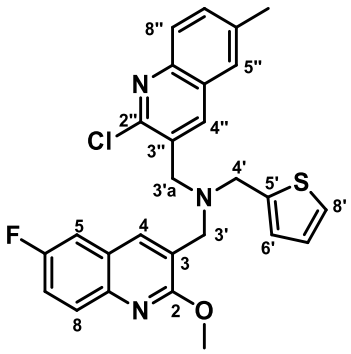
1-(2-Chloro-6-methylquinolin-3-yl)-*N*-((2,6-dimethoxyquinolin-3-yl)methyl)-*N*-(thiophen-2-ylmethyl)methanamine (3.108)



3.108

Brown solid. Yield = 79%; M.p: 137–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.43 (1H, s, H-4″), 8.12 (1H, s, H-4), 7.87 (1H, d, *J* = 8.6 Hz, H-8″), 7.73 (1H, d, *J* = 9.1 Hz, H-8), 7.58 (1H, d, *J* = 1.8 Hz, H-5″), 7.50 (1H, dd, *J* = 8.6, 1.8 Hz, H-7″), 7.26 − 7.22 (2H, m, H-7, H-8′), 7.06 (1H, d, *J* = 2.8 Hz, H-5), 7.00 (1H, d, *J* = 2.6 Hz, H-6′), 6.97 (1H, dd, *J* = 4.9, 3.5 Hz, H-7′), 4.03 (3H, s, OCH_3), 4.01 (2H, s, CH_2, H-4′), 3.96 (2H, s, CH_2, H-3a′), 3.90 (3H, s, OCH_3), 3.87 (2H, s, CH_2, H-3′), 2.51 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 159.5, 156.1, 149.8, 145.3, 142.6, 141.1, 136.9 (2C), 135.9, 132.2, 131.0, 128.2, 127.8, 127.5, 126.7, 126.4, 125.9 (2C), 124.9, 122.9, 120.6, 106.2, 55.6, 54.9, 53.3, 52.1, 21.6; HRMS (ESI): *m/z* calcd for $C_{28}H_{27}N_3O_2SCl$ $[M+H]^+$: 504.1513, found 504.1514.

1-(2-Chloro-6-methylquinolin-3-yl)-*N*-((6-fluoro-2-methoxyquinolin-3-yl) methyl)-*N*-(thiophen-2-ylmethyl)methanamine (3.109)

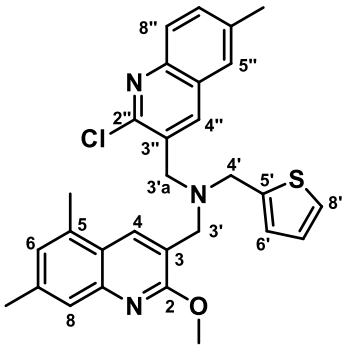


3.109

Brown solid. Yield = 65%; M.p: 190–192 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.42 (1H, s, H-4″), 8.18 (1H, s, H-4), 7.87 (1H, d, *J* = 8.6 Hz, H-8″), 7.78 (1H, dd, *J* = 9.0, 5.2 Hz, H-8), 7.58 (1H, d, *J* = 1.6 Hz, H-5″), 7.51 (1H, dd, *J* = 8.6, 1.6 Hz, H-7″), 7.38 – 7.30 (2H, m, H-5, H-7), 7.27 − 7.25 (1H, m, H-8′), 7.01 − 7.00 (1H, m, H-6′), 6.99 – 6.96 (1H, m, H-7′), 4.04 (3H, s, OCH_3), 4.01 (2H, s, CH_2, H-4′), 3.97 (2H, s, CH_2, H-3′a), 3.87 (2H, s, CH_2, H-3′), 2.52 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 160.3, 159.1 (d, $J_{F.C}$ = 244 Hz), 149.7, 145.3, 142.4, 137.1, 136.9, 135.8 (d, $J_{F.C}$ = 4.6 Hz), 132.3, 130.8, 128.8 (d, $J_{F.C}$ = 8.8 Hz),

127.8 (2C), 127.5, 126.8, 126.4, 125.9, 125.7 (d, $J_{F.C}$ = 9.6 Hz), 125.0, 124.0, 118.4 (d, $J_{F.C}$ = 24.8 Hz), 110.8 (d, $J_{F\,C}$ = 21.7 Hz), 55.0, 53.5, 53.4, 52.0, 21.6; HRMS (ESI): *m/z* calcd for $C_{27}H_{24}N_3OFSCl$ $[M+H]^+$: 492.1313, found 492.1311.

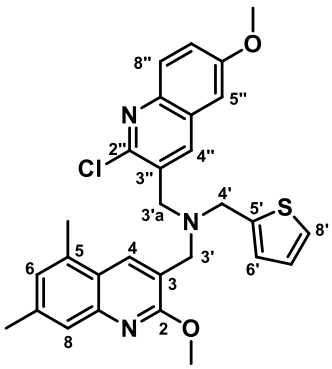
1-(2-Chloro-6-methylquinolin-3-yl)-*N*-((2-methoxy-5,7-dimethylquinolin-3-yl)methyl)-*N*-(thiophen-2-ylmethyl)methanamine (3.110)



3.110

Brown solid. Yield = 81%; M.p: 84–86 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.47 (1H, s, H-4″), 8.42 (1H, s, H-4), 7.87 (1H, d, *J* = 8.6 Hz, H-8″), 7.55 (1H, d, *J* = 1.8 Hz, H-5″), 7.50 (1H, dd, *J* = 8.6, 1.8 Hz, H-7″), 7.48 (1H, s, H-6), 7.26 – 7.25 (1H, m, H-8′), 7.05 (1H, s, H-8), 7.01 – 7.00 (1H, m, H-6′), 6.97 (1H, dd, *J* = 5.0, 3.5 Hz, H-7′), 4.05 (3H, s, OCH_3), 4.02 (2H, s, CH_2, H-4′), 3.98 (2H, s, CH_2, H-3′a), 3.89 (2H, s, CH_2, H-3′), 2.63 (3H, s, CH_3), 2.51 (3H, s, CH_3), 2.46 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 160.6, 149.7, 146.2, 145.3, 142.9, 139.0, 137.0 (2C), 134.0 (2C), 132.2, 131.1, 127.8, 127.5, 127.0, 126.7, 126.3 , 125.8, 124.9, 124.5, 122.4, 121.0, 54.9, 53.4, 53.3, 52.2, 21.7, 21.6, 18.9; HRMS (ESI): *m/z* calcd for $C_{29}H_{29}N_3OSCl$ $[M+H]^+$: 502.1720, found 502.1725.

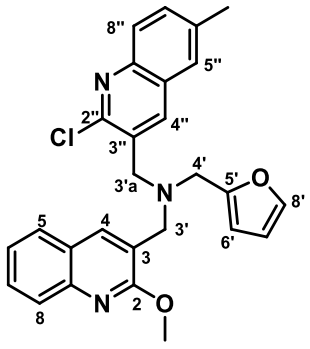
1-(2-Chloro-6-methoxyquinolin-3-yl)-*N*-((2-methoxy-5,7-dimethylquinolin-3-yl)methyl)-*N*-(thiophen-2-ylmethyl)methanamine (3.111)



3.111

Brown solid. Yield = 59%; M.p: 79–80 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.43 (1H, s, H-4″), 8.39 (1H, s, H-4), 7.87 (1H, d, *J* = 9.2 Hz, H-8″), 7.48 (1H, s, H-6), 7.32 (1H, dd, *J* = 9.2, 2.8 Hz, H-7″), 7.26 – 7.25 (1H, m, H-8′), 7.04 – 7.03 (2H, m, H-5″, H-8), 7.01 (1H, d, *J* = 2.7 Hz, H-6′), 6.97 (1H, dd, *J* = 5.0, 3.5 Hz, H-7′), 4.05 (3H, s, OCH_3), 4.03 (2H, s, CH_2, H-4′), 3.97 (2H, s, CH_2, H-3′a), 3.91 (3H, s, OCH_3), 3.89 (2H, s, CH_2, H-3′), 2.62 (3H, s, CH_3), 2.46 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 160.6, 158.1, 148.0, 146.2, 142.7 (2C), 139.0, 136.4, 133.9, 133.5, 131.4, 129.6, 128.5, 127.0, 126.7, 125.8, 125.0, 124.5, 122.5, 122.4, 120.9, 105.0, 55.6, 54.9, 53.5, 53.3, 52.2, 21.7, 18.9; HRMS (ESI): *m/z* calcd for $C_{29}H_{29}N_3O_2SCl$ $[M+H]^+$: 518.1669, found 518.1671.

1-(2-Chloro-6-methylquinolin-3-yl)-*N*-(furan-2-ylmethyl)-*N*-((2-methoxyquinolin-3-yl) methyl)methanamine (3.112)



3.112

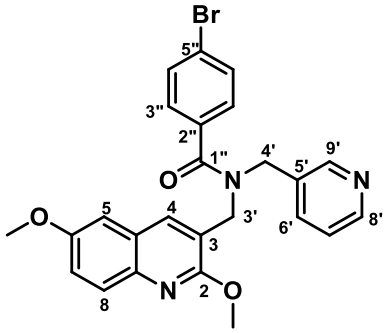
Brown viscous liquid. Yield = 71%; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.35 (1H, s, H-4″), 8.20 (1H, s, H-4), 7.88 (1H, d, *J* = 8.6 Hz, H-8″), 7.82 (1H, d, *J* = 8.4 Hz, H-5), 7.73 (1H, d, *J* = 7.4 Hz, H-8), 7.60 – 7.55 (2H, m, H-6, H-5″), 7.50 (1H, d, *J* = 8.7 Hz, H-7″), 7.44 (1H, s, H-8′), 7.36 (1H, t, *J* = 7.5 Hz, H-7), 6.35 – 6.33 (1H, m, H-6′), 6.29 – 6.27 (1H, m, H-7′), 4.05 (3H,

s, OCH_3), 3.98 (2H, s, CH_2, H-3′a), 3.87 (2H, s, CH_2, H-3′), 3.82 (2H, s, CH_2, H-4′), 2.51 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 160.9, 152.2, 150.0, 145.7, 145.3, 142.3, 137.2, 136.9, 132.2, 131.0, 129.0, 127.8 (2C), 127.5, 127.4, 126.8, 126.4, 125.3, 124.0, 123.0, 110.2, 109.0, 55.2, 53.5, 52.0, 50.3, 21.6; HRMS (ESI): *m/z* calcd for $C_{27}H_{25}N_3O_2Cl$ $[M+H]^+$: 458.1635, found 458.1634.

5.1.16 General procedure for the synthesis of 2-methoxyquinolinylbenzamide derivaties[198]

Suitable amine (**3.73 − 3.91**) (10.0 eq), TEA (20.0 eq) and DMAP (1.0 eq) were dissolved in 10 mL of DCM. The Flask was cooled to 0 °C in an ice bath and corresponding 4-substituted benzoyl chloride (20.0 eq) was added dropwise over a period of 2 min. The reaction mixture was warmed to r.t. and stirred for overnight under N_2(g) atmosphere. The reaction was quenched by water (5 mL) and extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc: Hexane 2:8) to yield desired benzamides.

4-Bromo-*N*-((2,6-dimethoxyquinolin-3-yl)methyl)-*N*-(pyridin-3-ylmethyl)benzamide (3.113)

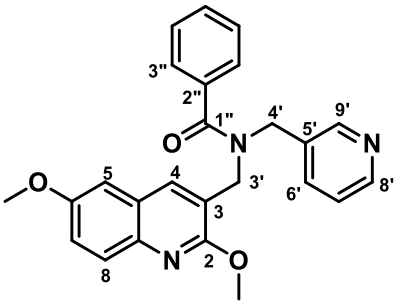


3.113

White crystalline solid. Yield = 47%; M.p: 107–109 °C; ν_{max}/cm^{-1} 1621 (C=O); ^1H NMR (600 MHz, DMSO-d_6 at **328 K**): δ_H = 8.46 − 8.44 (2H, m, overlapping H-8′ and H-9′), 8.00 (1H, s, H-4), 7.68 – 7.66 (2H, m, H-8, H-6′), 7.63 (2H, d, *J* = 7.9 Hz, H-3″), 7.48 (2H, d, *J* = 7.3 Hz, H-4″), 7.38 (1H, d, *J* = 2.0 Hz, H-5), 7.31 (1H, dd, *J* = 7.5, 4.9 Hz, H-7′), 7.28 (1H,

dd, *J* = 9.0, 2.7 Hz, H-7), 4.68 (2H, s, CH_2, H-3′), 4.56 (2H, s, CH_2, H-4′), 3.93 − 3.86 (6H, m, 2 × OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6 at **328 K**) δ_C = 171.0, 158.8, 156.4, 149.3, 148.9, 141.0, 136.3, 135.8, 131.9, 129.2, 128.1, 126.1 (2C), 123.9, 123.5, 121.3, 121.0 (2C), 107.5, 56.0, 53.5; HRMS (ESI): *m/z* calcd for $C_{25}H_{23}N_3O_3Br$ $[M+H]^+$: 492.0931, found 492.0927.

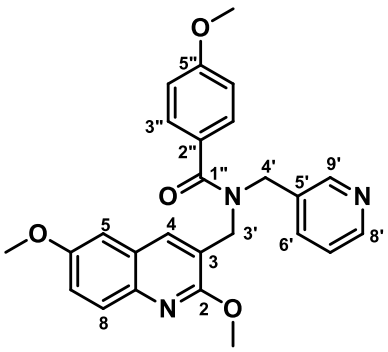
_N_-((2,6-Dimethoxyquinolin-3-yl)methyl)-_N_-(pyridin-3-ylmethyl)benzamide (3.114)



3.114

White crystalline solid. Yield = 70%; M.p: 148–150 °C; ν_{max}/cm^{-1} 1628 (C=O); ^1H NMR (600 MHz, DMSO-d_6 at **328 K**): δ_H = 8.47 – 8.44 (2H, m, overlapping H-8′ and H-9′), 8.04 (1H, s, H-4), 7.67 – 6.66 (2H, m, H-6′, H-8), 7.52 (2H, bs, H-3″), 7.47 – 7.41 (4H, m, H-5, H-4″ H-5″), 7.34 (1H, dd, *J* = 7.8, 4.8 Hz, H-7′), 7.29 (1H, dd, *J* = 9.0, 2.9 Hz, H-7), 4.70 (2H, s, CH_2, H-3′), 4.56 (2H, s, CH_2, H-4′), 3.91 – 3.87 (6H, m, 2 × OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6 at **328 K**): δ_C = 172.0, 158.7, 156.3, 149.3, 148.9, 140.9, 136.6, 136.0, 135.5, 133.3, 130.1, 128.9, 128.1, 127.0, 126.1, 124.0, 121.3, 121.2, 107.4, 55.9, 53.6; HRMS (ESI): *m/z* calcd for $C_{25}H_{24}N_3O_3$ $[M+H]^+$: 414.1818, found 414.1816.

_N_-((2,6-Dimethoxyquinolin-3-yl)methyl)-4-methoxy-_N_-(pyridin-3-ylmethyl)benzamide (3.115)

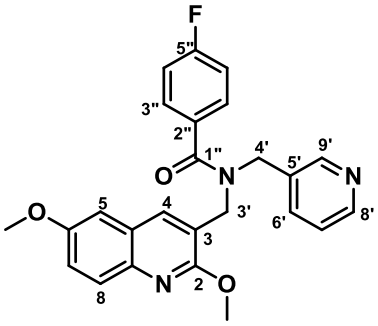


3.115

White crystalline solid. Yield = 64%; M.p: 99–101 °C; ν_{max}/cm^{-1} 1613.0 (C=O); ^1H NMR (600 MHz, DMSO-d_6 at **328 K**): δ_H = 8.46 – 8.43 (2H, m, overlapping H-8′ and H-9′), 8.04 (1H, s, H-4), 7.69 – 7.66 (2H, m, H-6′, H-8), 7.49 (2H, d, *J* = 6.3 Hz, H-3″), 7.42 (1H, d, *J* = 2.6 Hz, H-5), 7.34 (1H, dd, *J* = 7.4, 4.9 Hz, H-7′), 7.28 (1H, dd, *J* = 9.0, 2.6 Hz, H-7), 6.97

(2H, d, *J* = 7.7 Hz, H-4″), 4.69 (2H, s, CH_2, H-3′), 4.57 (2H, s, CH_2, H-4′), 3.89 – 3.85 (6H, m, 2 × OCH_3), 3.76 (3H, s, OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6 at **328 K**): δ_C = 171.9, 160.8, 158.7, 156.3, 154.8, 149.4, 148.9, 140.9, 135.7, 133.5, 129.0, 128.5, 128.1, 126.1, 124.0, 121.4, 121.3, 114.2, 107.3, 55.9, 55.7, 53.6; HRMS (ESI): *m/z* calcd for $C_{26}H_{26}N_3O_4$ $[M+H]^+$: 444.1923, found 444.1920.

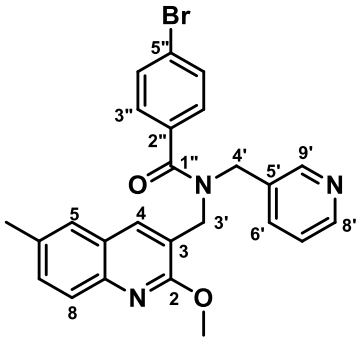
_N_-((2,6-Dimethoxyquinolin-3-yl)methyl)-4-fluoro-_N_-(pyridin-3-ylmethyl)benzamide (3.116)



3.116

White crystalline solid. Yield = 51%; M.p: 106–108 °C; ν_{max}/cm^{-1} 1632 (C=O); ^{1}H NMR (600 MHz, DMSO-d_6 at **328 K**): δ_H = 8.47 − 8.44 (2H, m, overlapping H-8′ and H-9′), 8.03 (1H, s, H-4), 7.68 – 7.67 (2H, m, H-6′, H-8), 7.63 – 7.58 (2H, m, H-3″), 7.40 (1H, s, H-5), 7.35 – 7.32 (1H, m, H-7′), 7.30 (1H, d, *J* = 9.0 Hz, H-7), 7.26 (2H, t, *J* = 8.3 Hz, H-4″), 4.70 (2H, s, CH_2, H-3′), 4.59 (2H, s, CH_2, H-4′), 3.91 – 3.89 (6H, m, 2 × OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6 at **328 K**): δ_C = 171.1, 163.1 (d, $J_{F.C}$ = 246.6 Hz), 158.8, 156.4, 149.3, 148.9, 141.0, 136.1, 135.6, 133.3, 133.0 (d, $J_{F.C}$ = 3.4 Hz), 129.6 (d, $J_{F.C}$ = 8.1 Hz), 128.1, 126.1, 123.9, 121.3, 121.1, 115.9 (d, $J_{F.C}$ = 21.9 Hz), 107.5, 56.0, 53.5; HRMS (ESI): *m/z* calcd for $C_{25}H_{23}N_3O_3F$ $[M+H]^+$: 432.1723, found 432.1719.

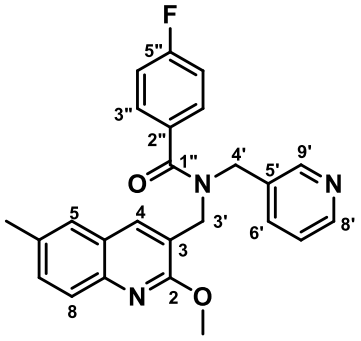
4-Bromo-*N*-((2-methoxy-6-methylquinolin-3-yl)methyl)-*N*-(pyridin-3-ylmethyl) benzamide (3.117)



3.117

White solid. Yield = 42%; M.p: 114–116 °C; ν_{max}/cm^{-1} 1621 (C=O); ^{1}H NMR (600 MHz, DMSO-d_6 at **308 K**): δ_H = 8.46 − 8.44 (2H, m, overlapping H-8′ and H-9′), 7.98 (1H, s, H-4), 7.70 – 7.62 (5H, m, H-6′, H-5, H-8, H-3″), 7.50 – 7.47 (3H, m, H-7, H-4″), 7.34 – 7.30 (1H, m, H-7′), 4.68 (2H, s, CH_2, H-3′), 4.56 (2H, s, CH_2, H-4′), 3.90 (3H, s, OCH_3), 2.46 (3H, s, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6 at **308 K**): δ_C = 171.0, 159.6, 149.3, 148.9, 144.0, 135.7, 135.2, 133.9, 131.9, 129.3, 129.2, 127.2, 127.1, 126.6, 125.2, 123.9, 123.5, 121.0, 120.7, 53.6, 46.6, 44.0, 21.3; HRMS (ESI): *m/z* calcd for $C_{25}H_{23}N_3O_2Br$ $[M+H]^+$: 476.0974, found 476.0972.

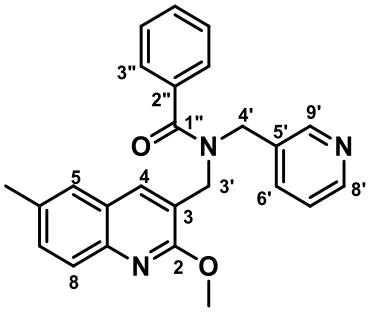
4-Fluoro-*N*-((2-methoxy-6-methylquinolin-3-yl) methyl)-*N*-(pyridin-3-ylmethyl) benzamide (3.118)



3.118

Off white solid. Yield = 49%; M.p: 139–141 °C; ν_{max}/cm^{-1} 1632 (C=O); ^{1}H NMR (600 MHz, DMSO-d_6 at **308 K**): δ_H = 8.47 − 8.44 (2H, m, overlapping H-8′ and H-9′), 7.99 (1H, s, H-4), 7.71 – 7.63 (3H, m, H-6′, H-5, H-8), 7.63 – 7.58 (2H, m, H-3″), 7.48 (1H, dd, *J* = 8.5, 1.7 Hz, H-7), 7.32 (1H, dd, *J* = 7.6, 4.9 Hz, H-7′), 7.26 (2H, t, *J* = 8.6 Hz, H-4″), 4.68 (2H, s, CH_2, H-3′), 4.59 (2H, s, CH_2, H-4′), 3.91 (3H, s, OCH_3), 2.46 (3H, s, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6 at **308 K**): δ_C = 171.1, 163.1 (d, $J_{F.C}$ = 246.9 Hz), 159.7, 149.3, 148.8, 144.0, 136.5, 135.6, 133.9, 133.4, 133.0 (d, $J_{F.C}$ = 3.2 Hz), 131.8, 129.6 (d, $J_{F.C}$ = 8.6 Hz), 127.2, 126.6, 125.2, 123.9, 120.9, 115.9 (d, $J_{F.C}$ = 21.7 Hz), 53.6, 49.0, 46.6, 21.3; HRMS (ESI): *m/z* calcd for $C_{25}H_{23}N_3O_2F$ $[M+H]^+$: 416.1774, found 416.1779.

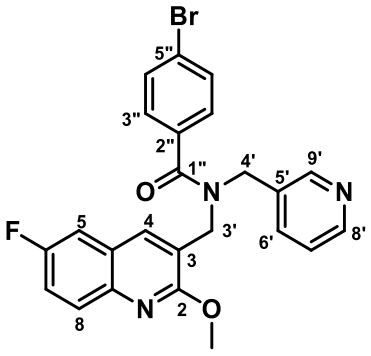
***N*-((2-Methoxy-6-methylquinolin-3-yl) methyl)-*N*-(pyridin-3-ylmethyl)benzamide (3.119)**



3.119

White crystalline solid. Yield = 72%; M.p: 136–138 °C; ν_{max}/cm^{-1} 1621 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.56 − 8.51 (2H, m, overlapping H-8′ and H-9′), 7.76 − 7.72 (3H, m, H-4, H-8, H-6′), 7.51 (1H, s, H-5), 7.49 – 7.44 (3H, m, H-3″, H-5″), 7.42 − 7.37 (3H, m, H-7, H-4″), 7.31 – 7.26 (1H, m, H-7′), 4.78 (2H, s, CH_2, H-3′), 4.52 (2H, s, CH_2, H-4′), 3.97 (3H, s, OCH_3), 2.51 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 172.8, 159.6, 149.5, 149.1, 144.3, 136.1, 135.7, 135.3, 134.6, 134.1, 132.8, 131.7, 130.0, 128.6, 126.7, 126.5, 124.9, 123.7, 120.3, 53.4, 48.1, 45.7, 21.3; HRMS (ESI): *m/z* calcd for $C_{25}H_{24}N_3O_2$ $[M+H]^+$: 398.1869, found 398.1878.

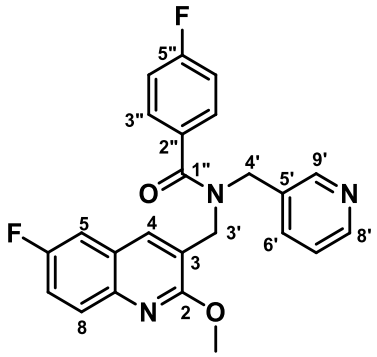
4-Bromo-*N*-((6-fluoro-2-methoxyquinolin-3-yl)methyl)-*N*-(pyridin-3-ylmethyl) benzamide (3.120)



3.120

White crystalline solid. Yield = 46%; M.p: 143–145 °C; ν_{max}/cm^{-1}: 1636 (C=O); ^{1}H NMR (600 MHz, DMSO-d_6 at **328 K**): δ_H = 8.45 − 8.43 (2H, m, overlapping H-8′ and H-9′), 8.11 (1H, s, H-4), 7.81 – 7.48 (8H, m, H-6′, H-8, H-3″, H-5, H-7, H-4″), 7.35 – 7.28 (1H, m, H-7′), 4.69 (2H, s, CH_2, H-3′), 4.57 (2H, s, CH_2, H-4′), 3.91 (3H, s, OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6 at **328 K**): δ_C = 171.1 , 159.8, 158.9 (d, $J_{F\,C}$ = 241.6 Hz), 149.5, 148.9, 142.6, 136.6, 135.7, 133.4, 131.9, 129.2, 129.1 (d, $J_{F.C}$ = 9.0 Hz), 125.8 (d, $J_{F.C}$ = 8.7 Hz), 125.1, 123.9, 123.5, 122.1, 119.2 (d, $J_{F.C}$ = 21.8 Hz), 111.7 (d, $J_{F.C}$ = 22.1 Hz), 53.8, 48.8, 46.4; HRMS (ESI): *m/z* calcd for $C_{24}H_{20}N_3O_2FBr$ $[M+H]^+$: 480.0723, found 480.0733.

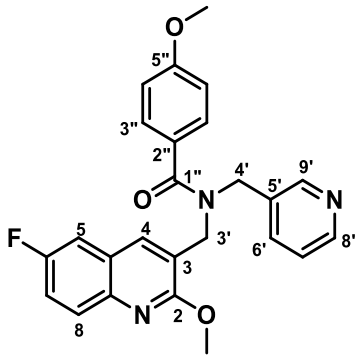
4-Fluoro-*N*-((6-fluoro-2-methoxyquinolin-3-yl)methyl)-*N*-(pyridin-3-ylmethyl) benzamide (3.121)



3.121

White crystalline solid. Yield = 43%; M.p: 109–111 °C; ν_{max}/cm^{-1} 1625 (C=O); ^{1}H NMR (600 MHz, DMSO-d_6 at **328 K**): δ_H = 8.46 − 8.42 (2H, m, overlapping H-8′ and H-9′), 8.11 (1H, s, H-4), 7.79 (1H, dd, *J* = 8.8, 5.3 Hz, H-8), 7.74 (1H, dd, *J* = 7.6, 2.0 Hz, H-5), 7.67 (1H, bs, H-6′), 7.63 – 7.58 (2H, m, H-3″), 7.52 (1H, td, *J* = 8.8, 2.9 Hz, H-7), 7.31 (1H, dd, *J* = 7.6, 4.8 Hz, H-7′), 7.26 (2H, t, *J* = 8.7 Hz, H-4″), 4.70 (2H, s, CH_2, H-3′), 4.61 (2H, s, CH_2, H-4′), 3.93 (3H, s, OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6 at **328 K**): δ_C = 171.2, 163.1 (d, $J_{F.C}$ = 247.1 Hz), 159.9 , 159.0 (d, $J_{F.C}$ = 241.6 Hz), 149.3, 148.9, 142.6, 136.4, 135.6, 133.3, 132.9 (d, $J_{F.C}$ = 3.2 Hz), 129.6 (d, $J_{F.C}$ = 8.5 Hz), 129.1 (d, $J_{F.C}$ = 9.0 Hz), 125.8 (d, $J_{F.C}$ = 9.8 Hz), 123.9, 122.3, 119.2 (d, $J_{F.C}$ = 24.8 Hz), 115.9 (d, $J_{F.C}$ = 21.8 Hz), 111.7 (d, $J_{F.C}$ = 22.2 Hz), 54.8, 53.8; HRMS (ESI): *m/z* calcd for $C_{24}H_{20}N_3O_2F_2$ $[M+H]^+$: 420.1524, found 420.1525.

***N*-((6-Fluoro-2-methoxyquinolin-3-yl)methyl)-4-methoxy-*N*-(pyridin-3-ylmethyl) benzamide (3.122)**

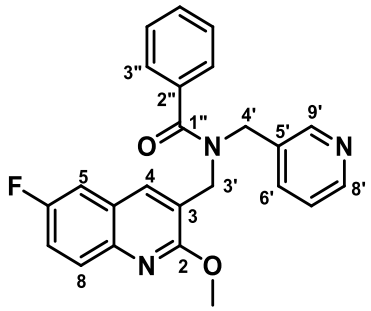


3.122

White crystalline solid. Yield = 41%; M.p: 129–131 °C; ν_{max}/cm^{-1} 1617 (C=O); ^{1}H NMR (600 MHz, DMSO-d_6 at **328 K**): δ_H = 8.46 − 8.42 (2H, m, overlapping H-8′ and H-9′), 8.09 (1H, s, H-4), 7.79 (1H, dd, *J* = 9.1, 5.3 Hz, H-8), 7.74 (1H, dd, *J* = 9.4, 2.7 Hz, H-5), 7.66 (1H, d, *J* = 7.3 Hz, H-6′), 7.52 (1H, td, *J* = 9.1, 3.0 Hz, H-7), 7.48 (2H, d, *J* = 8.5 Hz, H-3″), 7.31 (1H, dd, *J* = 7.7, 4.8 Hz, H-7′), 6.97 (2H, d, *J* = 8.5 Hz, H-4″), 4.69 (2H, s, CH_2, H-3′), 4.60 (2H, s, CH_2, H-4′), 3.93 (3H, s, OCH_3), 3.77 (3H, s, OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6

at **328 K**): δ_C = 171.9, 160.8, 159.9, 159.0 (d, $J_{F.C}$ = 241.6 Hz), 149.3, 148.9, 142.6, 136.2, 135.6, 133.5, 129.1 (d, $J_{F.C}$ = 8.9 Hz), 129.0, 128.5, 125.9 (d, $J_{F.C}$ = 10.3 Hz), 123.9, 122.5, 119.1 (d, $J_{F.C}$ = 25.1 Hz), 114.3, 111.7 (d, $J_{F.C}$ = 22.2 Hz), 55.7, 53.8; HRMS (ESI): *m/z* calcd for $C_{25}H_{23}N_3O_3F$ $[M+H]^+$: 432.1723, found 432.1721.

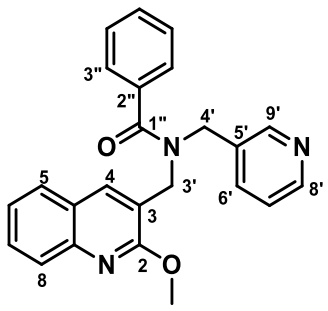
***N*-((6-Fluoro-2-methoxyquinolin-3-yl)methyl)-*N*-(pyridin-3-ylmethyl)benzamide (3.123)**



3.123

White crystalline solid. Yield = 69%; M.p: 127–129 °C; ν_{max}/cm^{-1}: 1636 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.55 – 8.33 (2H, m, Overlapping H-8′ and H-9′), 7.88 (1H, s, H-4), 7.74 (1H, dd, *J* = 8.8, 5.2 Hz, H-8), 7.59 (1H, bs, H-6′), 7.46 – 7.25 (7H, m, H-5, H-7, H-3″, H-4″, H-5″), 7.25 – 7.19 (1H, m, H-7′), 4.70 (2H, s, CH_2, H-3′), 4.50 (2H, s, CH_2, H-4′), 3.90 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 172.2, 159.5, 159.2 (d, $J_{F.C}$ = 242.9 Hz), 149.5, 149.2, 142.8, 136.1, 135.5, 134.9, 132.5, 130.1, 129.0 (d, $J_{F.C}$ = 7.6 Hz), 128.6, 126.7, 125.3 (d, $J_{F.C}$ = 5.2 Hz), 123.7, 121.6, 119.1 (d, $J_{F.C}$ = 23.4 Hz), 110.8 (d, $J_{F.C}$ = 22.4 Hz), 53.6, 48.1, 45.8; HRMS (ESI): *m/z* calcd for $C_{24}H_{21}N_3O_2F$ $[M+H]^+$: 402.1618, found 402.1619.

***N*-((2-Methoxyquinolin-3-yl)methyl)-*N*-(pyridin-3-ylmethyl)benzamide (3.124)**

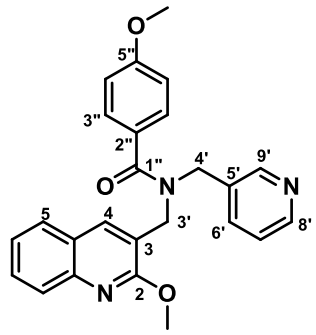


3.124

White crystalline solid. Yield = 71%; M.p: 147–149 °C; ν_{max}/cm^{-1} 1626 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.51 – 8.33 (2H, m, overlapping H-8′ and H-9′), 7.94 (1H, s, H-4), 7.77 (1H, d, *J* = 8.4 Hz, H-8), 7.75 – 7.63 (2H, m, H-5, H-6′), 7.56 (1H, t, *J* = 7.4 Hz, H-5″), 7.42 – 7.38 (2H, m, H-3″), 7.33 − 7.30 (4H, m, H-6, H-7, H-4″), 7.22 (1H, dd, *J* = 7.7, 4.9 Hz, H-7′), 4.72 (2H, s, CH_2, H-3′), 4.49 (2H, s, CH_2, H-4′), 3.95 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 172.9, 159.9, 149.6, 149.1, 146.0, 138.1,

136.1, 135.7, 132.8, 130.1, 129.7, 128.6, 127.3, 127.0, 126.7, 124.9, 124.6, 123.7, 120.5, 53.6, 48.1, 45.7; HRMS (ESI): *m/z* calcd for $C_{24}H_{22}N_3O_2$ $[M+H]^+$: 384.1712, found 384.1714.

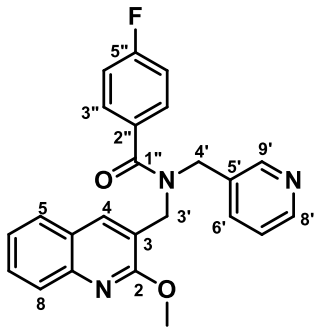
4-Methoxy-*N*-((2-methoxyquinolin-3-yl)methyl)-*N*-(pyridin-3-ylmethyl)benzamide (3.125)



3.125

White crystalline solid. Yield = 65%; M.p: 142–144 °C; ν_{max}/cm^{-1}: 1625 (C=O); ^{1}H NMR (600 MHz, DMSO-d_6 at **328 K**): δ_H = 8.46 − 8.42 (2H, m, overlapping H-8′ and H-9′), 8.10 (1H, s, H-4), 7.93 (1H, d, *J* = 7.8 Hz, H-8), 7.76 (1H, d, *J* = 8.3 Hz, H-5), 7.68 (1H, bs, H-6′), 7.66 – 7.64 (1H, m, H-7), 7.50 (2H, d, *J* = 8.1 Hz, H-3″), 7.46 – 7.43 (1H, m, H-6), 7.33 (1H, dd, *J* = 7.5, 4.9 Hz, H-7′), 6.97 (2H, d, *J* = 8.1 Hz, H-4″), 4.71 (2H, s, CH_2, H-3′), 4.61 (2H, s, CH_2, H-4′), 3.93 (3H, s, OCH_3), 3.77 (3H, s, OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6 at **328 K**): δ_C = 171.9, 160.8, 160.2, 149.3, 148.8, 145.6, 136.7, 135.5, 133.5, 130.0, 129.0, 128.5, 128.2, 126.8, 125.3, 124.7, 124.0, 121.3, 114.2, 55.7, 53.8; HRMS (ESI): *m/z* calcd for $C_{25}H_{24}N_3O_3$ $[M+H]^+$: 414.1818, found 414.1813.

4-Fluoro-*N*-((2-methoxyquinolin-3-yl)methyl)-*N*-(pyridin-3-ylmethyl) benzamide (3.126)



3.126

White crystalline solid. Yield = 55%; M.p: 122–124 °C; ν_{max}/cm^{-1}: 1628 (C=O); ^{1}H NMR (600 MHz, DMSO-d_6 at **328 K**): δ_H = 8.46 − 8.42 (2H, m, overlapping H-8′ and H-9′), 8.10 (1H, s, H-4), 7.93 (1H, d, *J* = 7.9 Hz, H-8), 7.76 (1H, d, *J* = 8.1 Hz, H-5), 7.68 (1H, bs, H-6′), 7.66 – 7.64 (1H, m, H-7), 7.62 – 7.59 (2H, m, H-3″), 7.46 – 7.43 (1H, m, H-6), 7.32 (1H, dd, *J* = 7.6, 4.9 Hz, H-7′), 7.26 (2H, t, *J* = 8.7 Hz, H-4″), 4.70 (2H, s, CH_2, H-3′), 4.60 (2H, s, CH_2, H-4′), 3.93 (3H, s, OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6 at **328 K**): δ_C = 171.1, 163.1 (d, $J_{F.C}$ = 246.9 Hz), 160.2, 149.3,

148.9, 145.7, 137.1, 135.6, 133.4, 133.0 (d, $J_{F.C}$ = 3.3 Hz), 129.9, 129.7 (d, $J_{F.C}$ = 8.6 Hz), 128.2, 126.8, 125.3, 124.7, 123.9, 121.1, 115.9 (d, $J_{F.C}$ = 21.5 Hz), 53.7; HRMS (ESI): *m/z* calcd for $C_{24}H_{21}N_3O_2F$ $[M+H]^+$: 402.1618, found 402.1623.

5.2 Procedures for growth inhibition assays

5.2.1 HeLa cell cytotoxicity assay

HeLa cells (Cellonex) were cultured in DMEM medium (Lonza) supplemented with 10% fetal calf serum and antibiotics (penicillin/streptomycin/amphotericin B) at 37 °C in a 5% CO_2 incubator. Cells were plated in 96-well plates at a cell density of 2×10^4 cells/well and grown overnight. Serial dilutions of test compounds were incubated with the cells for an additional 24 h and cell viability in the wells assessed by adding 20 µL resazurin toxicology reagent (Sigma-Aldrich) for an additional 2-4 h. Fluorescence readings (excitation 560 nm, emission 590 nm) obtained for the individual wells were converted to % cell viability relative to the average readings obtained from untreated control wells. Plots of % cell viability vs. log[compound] were used to determine IC_{50} values by non-linear regression using GraphPad Prism (v. 5.02).

5.2.2 *In vitro* antimalarial assay

The 3D7 strain of *P.falciparum* was routinely cultured in medium consisting of RPMI1640 containing 25 mM Hepes (Lonza), supplemented with 0.5% (w/v) Albumax II (ThermoScientific), 22 mM glucose, 0.65 mM hypoxanthine, 0.05 mg/mL gentamicin and 2-4% (v/v) human erythrocytes. Cultures were maintained at 37 °C under an atmosphere of 5% CO_2, 5% O_2, 90% N_2. To assess antiplasmodial activity, three-fold serial dilutions of test compounds in culture medium were added to parasite cultures (adjusted to 2% parasitaemia, 1% haematocrit) in 96-well plates and incubated for 48 h. Duplicate wells per compound concentration were used. Plasmodial lactate dehydrogenase (pLDH) enzyme activity in the individual wells was determined by removing 20 µL of the parasite cultures and mixing it with 125 µL colorimetric substrate solution containing 0.18 M L-lactic acid, 0.13 mM acetylpyridine adenine dinucleotide, 0.39 mM nitrotetrazolium blue chloride, 0.048 mM

phenazineethosulphate and 0.16% (v/v) Triton X-100 in 44 mM Tris buffer (pH 9). Color development was monitored by measuring absorbance at 620 nm in a Spectramax M3 plate reader (Molecular Devices). Absorbance values were converted to % parasite viability relative to untreated control cultures and plotted against log[compound] to derive IC_{50} values by non-linear regression using GraphPad Prism (v. 5.02) software.

5.2.3 *In vitro* antitrypanosomal assay

Trypanosoma brucei brucei 427 trypomastigotes were cultured in IMDM medium (Lonza) supplemented with 10% fetal calf serum, HMI-9 supplement, hypoxanthine and penicillin/streptomycin at 37 °C in a 5% CO_2 incubator. Serial dilutions of test compounds were incubated with the parasites in 96-well plates for 24 h and residual parasite viability in the wells determined by adding 20 μL resazurin toxicology reagent (Sigma-Aldrich) and incubating for an additional 2 − 4 h. Reduction of resazurin to resorufin by viable parasites was assessed by fluorescence readings (excitation 560 nm, emission 590 nm) in a Spectramax M3 plate reader. Fluorescence readings were converted to % parasite viability relative to the average readings obtained from untreated control wells. IC_{50} values were determined by plotting % viability vs. log[compound] and performing non-linear regression using GraphPad Prism (v. 5.02) software.

5.2.4 *In vitro* antitubercular assay

The minimum inhibitory concentration (MIC) was determined using the standard broth micro dilution method, where a 10 mL culture of *M.tuberculosis* pMSp12:GFP[199], was grown to an optical density (OD600) of 0.6–0.7. The media used were: (i) Gaste-Fe (glycerol-alanine-salts) medium pH 6.6, supplemented with 0.05% Tween-80 and 1% Glycerol, and (ii) 7H9 supplemented with 10% Albumin Dextrose Catalase supplement (ADC), 0.05% Tween-80[200,

[201]. Cultures grown in Gaste-Fe were diluted 1:100 and cultures grown in 7H9 ADC were diluted 1:500, prior to inoculation of the MIC assay. The compounds to be tested were reconstituted to a concentration of 10 mM in DMSO. Two-fold serial dilutions of the test compound were prepared across a 96-well micro titre plate, after which, 50 µL of the diluted *M. tuberculosis* cultures were added to each well in the serial dilution. The plate layout was a modification of the method previously described[202]. Assay controls used were a minimum growth control (Rifampicin at 2 × MIC) and a maximum growth control (5% DMSO). The micro titre plates were sealed in a secondary container and incubated at 37 °C with 5% CO_2 and humidification. Relative fluorescence (excitation 485 nM; emission 520 nM) was measured using a plate reader (FLUOstar OPTIMA, BMG LABTECH, Ortenberg, Germany), at day 7 and day 14. The raw fluorescence data were achieved and analysed using the CDD Vault from Collaborative Drug Discovery, in which, data were normalized to the minimum and maximum inhibition controls to generate a dose response curve (% inhibition), using the Levenberg-Marquardt (Burlingame, CA, USA, www.collaborativedrug.com) damped least squares method, from which the MIC_{90} was calculated. The lowest concentration of drug that inhibits growth of more than 90% of the bacterial population was considered the MIC_{90}.

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