2.1. Biological importance of quinolines

The quinoline ring system occurs in various natural products, especially in alkaloids [1] with interesting biological activities (Figure 2.1). Quinine, isolated as the active ingredient from the bark of Cinchona trees, is used in the treatment for malaria [2]. Chimamine alkaloids 
\( \text{viz.}, \) 4-methoxy-2-phenylquinoline, 2-(3,4-methylenedioxy phenylethyl)quinoline, cusparine, 2-(3,4-dimethoxyphenylethyl) quinoline, 4-methoxy-2-\(n\)-pentylquinoline, 2-\(n\)-propylquinoline and chimamine A, B and D, isolated from the bark of *Galipea longiflora* trees of the Rutaceae family, are found to treat leishmaniasis, a tropical disease in South America [3].

![Figure 2.1. Structure of naturally occurring quinoline alkaloids](image)

The quinoline derivatives exhibit various biological activities, including antimalarial [4], antiinflammatory [5], anticancer [6] including breast cancer [7], antibiotic [8], anti-HIV [9], potent liver X receptor agonist [10], potent nucleotide-mimicking competitive inhibitor of hepatitis C virus NS3 helicase [11], Pim-1 kinase [12] inhibitor and VEGFR-2 (vascular endothelial growth factor receptor-2) inhibitor [13].
2.2. Synthesis of quinoline derivatives

Many synthetic methods have been described for quinoline derivatives [14], which include Skraup, Doebner-von Miller, Pfitzinger, Conrad-Limpach, and Combes reactions. These protocols are described below.

Wu et al. [15] have used Skraup-Doebner-Von Miller method of quinoline synthesis when anilines 1 were condensed with γ-aryl-β, γ-unsaturated α-ketoesters 2 in refluxing TFA. This reaction involves 1,2-addition of anilines 1 to γ-aryl-β, γ-unsaturated α-ketoesters 2 to form Schiff’s base 3 followed by cyclization and then oxidation to afford the quinolines 5.

\[
\text{Phenyl} + \text{α,β-unsaturated carbonyl} \rightarrow \text{Schiff's base} \rightarrow \text{Cyclization} \rightarrow \text{Oxidation} \rightarrow \text{Quinoline}
\]

\[
\begin{align*}
1 & \quad + \quad 2 & \quad \xrightarrow{\text{TFA, reflux, 8-18 h}} & \quad \xrightarrow{42-83\%} & \quad 3 & \quad \rightarrow \quad 4 & \quad \rightarrow \quad [\text{O}] & \quad 5 \\
R & = & \text{H, Cl, F, OH, Me, OMe, NO}_2 & & R^1 & = & \text{C}_6\text{H}_5 & & 4\text{-ClC}_6\text{H}_4 & & 4\text{-MeC}_6\text{H}_4 & & 4\text{-OMeC}_6\text{H}_4 \\
R^2 & = & \text{CO}_2\text{Me, CO}_2\text{Et} & & R^3 & = & \text{C}_6\text{H}_5 & & 4\text{-ClC}_6\text{H}_4 & & 4\text{-MeC}_6\text{H}_4 & & 4\text{-OMeC}_6\text{H}_4
\end{align*}
\]

Perumal et al. [16] reported phosphotungstic acid as new catalyst for the synthesis of quinaldine 8a and lepidine 8b by using Doebner-Miller method. Reactions of aromatic amines 6 with α, β-unsaturated carbonyl compounds 7 via Michael addition, cyclization and aromatization by conventional heating or microwave irradiation were described to afford the corresponding quinolines 8 in high yields.

\[
\text{Aromatic amine} + \text{α,β-unsaturated carbonyl} \rightarrow \text{Michael addition} \rightarrow \text{Cyclization} \rightarrow \text{Aromatization} \rightarrow \text{Quinoline}
\]

\[
\begin{align*}
6 & \quad + \quad 7 & \quad \xrightarrow{\text{Phosphotungstic acid (aq)\quad toluene, 100 °C, 2 h\quad 75-89\%\quad or\quad Phosphotungstic acid,\quad SiO}_2\quad MW,\quad 10\text{-}15\text{ min\quad 79-94\%}} & \quad 8 \\
R^1 & = & \text{H, Br, Cl, OH, OMe, NO}_2 & & R^2 = & \text{H, Br, Cl, NO}_2 & & \text{8a:} & R^4 = & \text{Me}\quad \text{8b:} & R^5 = & \text{Me}
\end{align*}
\]

Musiol et al. [17] reported the synthesis of styryl quinolines 12 via condensation of anilines 9 with crotonaldehyde 10 in the presence of hydrochloric acid, followed by
microwave irradiation of the resulting quinoline 11 with aldehydes. Some of the synthesized compounds 12 exhibited the photosynthesis inhibiting activity.

Goswami et al. [18] reported a one-pot catalyst-free synthesis of functionalized quinolines 17 from the microwave assisted irradiation of aniline 13 and β-aryl vinyl ketone 14 to produce a Michael adduct 15 by subsequent cyclization and aromatization.

Ryabukhin et al. [19] described that the reaction of electron rich anilines 18 with 3-formylchromone 19 in the presence of TMSCl ensued the corresponding quinolines 20 in good yields.

Korivi et al. [20] developed an efficient and convenient Ni-catalyzed cyclization of 2-idoanilines 21 with alkynyl aryl ketones 22 to give 2,4-disubstituted quinolines 23.
They proposed that the reaction proceeded via formation of 2-aminochalcone on the basis of the regiochemistry of the product isolated.

\[
\begin{align*}
\text{R}^1 &= \text{H, Cl, Me, CF}_3; \text{R}^2 = \text{Me, Ph, Naphthyl}; \text{R}^3 = \text{n-Bu, Ph}
\end{align*}
\]

Cho et al. [21] reported a Pd-catalyzed approach to quinolines 26 from 2-iodoanilines 24 as a starting material. The reaction of 2-iodoaniline 24 with \(\alpha, \beta\)-unsaturated carbonyl compounds 25 catalyzed by Pd(OAc)\(_2\) and sodium acetate in DMF afforded the substituted quinolines 26 via Heck coupling and subsequent cyclization.

- R = H, C\(_6\)H\(_5\), Pr, Naphthyl; \(\text{R}^1 = \text{Me, C}_6\text{H}_{5\alpha}, \text{i-Pr, 4-OMeC}_6\text{H}_4; \text{R}^2 = \text{H, Me, CH}_2\text{C}_6\text{H}_5\)

Sakai et al. [22] described the first dimerization reaction between the identical molecules for the synthesis of quinolines 28. The 2-ethynyl anilines 27 undergo dimerization and intermolecular cyclization in the presence of InBr\(_3\) to yield the quinoline compounds 28.

- \(\text{R}^1 = \text{H, Me, F, CN, NO}_2; \text{R}^2 = \text{H, Me}\)

Croce et al. [23] transformed \(N\)-phenylsulfonyl-2-hydroxy-1,2,3,4-tetrahydroquinolines 31 to dihydroquinolines 32 in the presence of \(p\)-toluenesulphonic acid followed by deprotection under basic conditions to generate quinolines 33. The required \(N\)-phenylsulfonyl-2-hydroxy-1,2,3,4-tetrahydroquinolines 31 were obtained
from enolates of 1,3-dicarbonyl compounds 30 and \( N \)-(2-bromomethylphenyl)benzenesulfonamides 29 in highly stereoselective manner.

\[
\begin{align*}
&\text{SO}_2\text{Ph} \\
&\text{NH} \\
&\text{Br} \\
&R
\end{align*}
\]
\[
\begin{align*}
&\text{O} \\
&\text{R}^1 \\
&\text{R}^2 \\
&\text{NaH} \\
&\text{DMF}, \text{rt}, \text{60 }^\circ\text{C}
\end{align*}
\]

\[
\begin{align*}
&\text{SO}_2\text{Ph} \\
&\text{R} \\
&\text{COR}^2 \\
&\text{NaOH} \\
&\text{air} \\
&\text{dioxane}, \text{100 }^\circ\text{C}
\end{align*}
\]

\[
R = \text{H, Me, C}_6\text{H}_5; R^1 = \text{Me, C}_6\text{H}_5; R^2 = \text{Me, OMe}
\]

Savitha et al. [24] demonstrated that the formation of tetrahydroquinolines 37 could be achieved in one-pot by the reaction between anilines 34, hetero arylaldehydes 35 and \( N \)-vinylpyrrolidin-2-one 36 in the presence of CAN, in water or in aqueous acetonitrile. These conditions were mild and reactions were completed in a short reaction time affording good yields. The resulting tetrahydroquinolines 37 could be readily aromatized to quinolines 38 through CAN in acetonitrile under nitrogen atmosphere at 0 °C.

\[
\begin{align*}
&\text{R} \\
&\text{NH}_2 \\
&\text{R}^1\text{-CHO} \\
&\text{N=O} \\
&\text{5 mol\% CAN} \\
&\text{H}_2\text{O or ac}_3\text{MeCN rt, 30-50 min}
\end{align*}
\]

\[
\begin{align*}
&\text{R} \\
&\text{N=O} \\
&\text{R}^1 \\
&\text{MeCN, 0 °C, 20 min}
\end{align*}
\]

Kikuchi et al. [25] reported the synthesis of 2,3-disubstituted quinoline 42 bearing an ester group at 3-position by the reaction of aniline 39, aldehydes 40 and ethyl propionate 41 in the presence of Ga(OTf)\(_3\) in refluxing ethanol. During this endeavour they investigated catalytic influence of several Lewis acids including Yb(OTf)\(_3\), InBr\(_3\), AlCl\(_3\), BF\(_3\)·OEt\(_2\), Ga(OTf)\(_3\), In(OTf)\(_3\), Sc(OTf)\(_3\) and discovered that Ga(OTf)\(_3\) and Sc(OTf)\(_3\) were most effective. In contrast to the ortho- or meta- substituted anilines, the para- substituted anilines gave better yields of the envisaged quinolines.
2.3. Friedlander reaction

Friedlander reaction for quinoline was originally described by Friedlander in 1882 and has been accepted to be one of the most convenient routes to this scaffold. This transformation comprises of a base or acid-promoted condensation of an aromatic 2-amino-substituted carbonyl compound with an appropriately substituted carbonyl derivative containing a reactive α-methylene group and subsequent cyclodehydration.

2.3.1. Base catalysed-Friedlander reactions

Kalai et al. [26] reported the synthesis of paramagnetic quinolines 45 from the reaction of 4-oxo-TEMPO 43 with 2-amino benzaldehyde 44 in the presence of sodium methoxide-mediated reaction.

Haddadin et al. [27] reported an efficient Friedlander reaction under basic condition between 2-aminobenzaldehydes 46 and appropriate cyclic (Z)-2-benzylidenethietan-3-one 47 in the presence of 10% potassium hydroxide in ethanol giving (Z)-2-benzyliden-2H-thieto[3,2-b]quinolines 48a-c.
2.3.2. Acid catalysed-Friedlander reactions

Wang et al. [28] described a highly efficient procedure for the synthesis of substituted quinolines \( 51 \) by the Friedlander reaction of 2-aminoarylketone or 2-aminoarylaldehyde \( 49 \) with carbonyl compounds \( 50 \) in the presence of hydrochloric acid utilizing water as the solvent.

\[
\begin{align*}
\text{R} &= \text{H, 2,4-(Br)2; } \text{R}^1 = \text{H, Me, 4F-C}_6\text{H}_4; \text{R}^2 = \text{CO}_2\text{Et, COMe; R}^3 = \text{Me} \\
\text{R}^4 = \text{H, 5-Cl; R}^2 = \text{CH}_3, \text{C}_6\text{H}_5; \text{R}^3 = \text{CH}_3; \text{R}^4 = \text{COCH}_3, \text{COOEt, COOCH(CH}_3)_2
\end{align*}
\]

Selvam et al. [29] reported the reaction of 2-amino aromatic ketones \( 49 \) with \( \alpha \)-methylenec containing ketones \( 50 \) in the presence of potassium bisulphate in aqueous ethanol at reflux to furnish 2,3,4-substituted quinolines \( 52 \).

Balamurugan et al. [30] described the synthesis of a series of 2,9-diaryl-2,3-dihydrothieno[3,2-b]quinolines \( 54 \) from the reaction of 5-aryldihydro-3(2H)-thiophenones \( 53 \) with 2-aminobenzophenones \( 49 \) in the presence of trifluoroacetic acid under solvent-free microwave irradiation at 100 °C.

\[
\begin{align*}
\text{Ar} &= \text{C}_6\text{H}_5, p-\text{MeC}_6\text{H}_4, p-\text{ClC}_6\text{H}_4, p-\text{FC}_6\text{H}_4, 1-\text{Naphthyl; R} = \text{H, Cl}
\end{align*}
\]

2.3.3. Lewis-acid catalysed-Friedlander reactions

In recent times several Lewis-acids have been successfully employed for performing the Friedlander reaction. Stannous chloride, \( \text{SnCl}_2\cdot2\text{H}_2\text{O} \), served as a suitable catalyst.
to initiate the reaction between the 2-aminoarylketones 49 with different carbonyl compounds 55 at room temperature yielding the corresponding 2,3,4-substituted quinolines 56 [31].

\[
\begin{array}{c}
\text{Ph}\quad \text{Cl} \quad \text{O} \\
\text{N} \quad \text{H}_2 \\
\text{Cl} \quad \text{O} \\
\begin{array}{c}
49 \\
55 \\
56 \\
\end{array}
\end{array}
\begin{array}{c}
\text{SnCl}_2\cdot 2\text{H}_2\text{O} \\
\text{neat, rt} \\
15-140 \text{ min} \\
92-98\% \\
R = \text{Me}, R^1 = \text{OEt}, R & R^1 = -\text{CH}_2\text{C(Me)}_2\text{CH}_{2-}
\end{array}
\]

Bose et al. [32] demonstrated that CeCl\textsubscript{3}·7H\textsubscript{2}O can act as a reusable catalyst for the synthesis of quinolines 57 via the Friedlander annulation of 2-aminoarylketones 49 with different carbonyl compounds 50.

\[
\begin{array}{c}
\text{Cl} \quad \text{O} \\
\text{N} \quad \text{H}_2 \\
\begin{array}{c}
49 \\
50 \\
57 \\
\end{array}
\end{array}
\begin{array}{c}
\text{CeCl}_3\cdot 7\text{H}_2\text{O} \\
\text{MeCN, rt, 1.5-5 h} \\
65-95\% \\
R = \text{Me}, C_6\text{H}_5; R^1 = \text{Me}; R^2 = \text{Me}, \text{CO}_2\text{Et}, \text{CO}_2\text{Me}, \text{COMe}
\end{array}
\]

De et al. [33] reported Y(OTf)\textsubscript{3} as a very efficient Lewis acid catalyst for synthesis of quinolines 58 from the Friedlander reaction of 2-aminoarylketones 49 with different carbonyl compounds 50.

\[
\begin{array}{c}
\text{O} \\
\text{N} \quad \text{H}_2 \\
\begin{array}{c}
49 \\
50 \\
58 \\
\end{array}
\end{array}
\begin{array}{c}
\text{Y(OTf)}_3 \\
\text{MeCN, rt, 4-6 h} \\
76-92\% \\
R = \text{H}, 4\text{-Cl}; R^1 = \text{Me}, C_6\text{H}_5; R^2 = \text{CO}_2\text{Et}, \text{COEt}, \text{COMe}; R^3 = \text{Me}
\end{array}
\]

Zolfigol et al. [34] optimized the Friedlander annulation between 2-aminoarylketones and ketones or \(\beta\)-diketones with several Lewis acids \textit{viz.}, Al(HSO\textsubscript{4})\textsubscript{3}, FeCl\textsubscript{3}·6H\textsubscript{2}O, Fe(NO\textsubscript{3})\textsubscript{3}·9H\textsubscript{2}O, Bi(NO\textsubscript{3})\textsubscript{3}, Cr(NO\textsubscript{3})\textsubscript{3}·9H\textsubscript{2}O, Ni(NO\textsubscript{3})\textsubscript{3}·6H\textsubscript{2}O, Zr(NO\textsubscript{3})\textsubscript{4} and Zr(HSO\textsubscript{4})\textsubscript{4}. It was observed that Zr(NO\textsubscript{3})\textsubscript{4} and Zr(HSO\textsubscript{4})\textsubscript{4} in H\textsubscript{2}O gave the desired poly substituted quinolines in excellent yields. Moreover, various Lewis acids such as FeCl\textsubscript{3} [35], NaAuCl\textsubscript{4}.2H\textsubscript{2}O [36], Nd(NO\textsubscript{3})\textsubscript{3}.6H\textsubscript{2}O [37], Sc[(O\textsubscript{3}SOC\textsubscript{12}H\textsubscript{25})\textsubscript{3}] [38], ZnCl\textsubscript{2},BiCl\textsubscript{3}, silverphosphotate [39] and zirconium tetra(dodecyl sulfate) (Zr(DS)\textsubscript{4})
[40] have been shown to be effective catalysts for Friedlander annulation affording substituted quinoline ring systems.

2.4. Applications of Friedlander reaction

In this section, we highlight the applications of Friedlander reaction for the synthesis of the quinoline moiety embedded in the structures of a number of significant natural or non natural products with important biological properties. For example, Mizuno et al. [41] reported a convenient synthesis of the quinoline base of the antirheumatic drug TAK-603 64 utilizing the Friedlander reaction as the key step. The hydrochloride salt form of the amino derivative 61 provides sufficient acidity to act as catalyst in the reaction to afford the desired quinoline unit 62. Subsequently, they developed a convenient and efficient method for the generation of different metabolites of TAK-603 64 in high yields [42].

Nourry et al. [43] described the total synthesis of natural product, Lavendamycin analogs 74 using Friedlander annulation. Condensation of 2-aminobenzaldehyde 66 with methylacetoacetate in the presence of piperidine afforded 2-methyl-quinoline-3-carboxylic acid methyl ester 67. Reduction of the ester followed by protection with the silyl group and oxidation with SeO₂ afforded the aldehyde. Pictet-Spengler reaction of the resulting aldehyde with tryptophan methyl ester in p-xylene on reflux and subsequent desilylation furnished the desired hydroxylester 70. Compound 70 upon treatment with Dess Martin periodinane (DMP) in pyridine furnished the product 71 via oxidation and intramolecular cyclization. Their attempt to prepare the deoxygenated compound through reduction with BH₃·THF afforded 73.
Perzy na et al. [44] reported the synthesis of benzo(5,6)pyrrolizino[1,2-b]quinoline 77 as a cytotoxic agent by Friedlander reaction of 2-acyl anilines 75 with pyrroloindoles 76 using pyridinium p-toluenesulfonate (PPTS) in n-BuOH.

Yu et al. [45] reported the synthesis of camptothecin-A 79 via Friedlander synthesis of 2-aminobenzaldehyde 66 with ketone 78 under thermal conditions.
Dallavalle et al. [46] reported the synthesis of substituted luotonin-A like compound 82 by the Friedlander reaction of 2-aminobenzaldehyde 80 with the ketone 81 in the presence of p-toluenesulphonic acid in toluene.
2.5. Synthesis of quinoline derivatives 87-89 - The present work

In the present investigation, initially the reaction of 2-aminobenzophenone 83 (100 mol%) with 1-(4-chlorophenyl)-2-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]-1-ethanone 84c (100 mol%) was investigated at 80 °C. After a period of 5 h under reflux with acetonitrile in presence of AlCl3 (100 mol%), the reaction afforded 2-[2-(4-chlorophenyl)-4-phenyl-3-quinolyl]sulfanyl-5-methyl-1,3,4-thiadiazole 87c in 75% yield (Entry 1, Table 2.1).

![Scheme 2.1. Synthesis of quinoline derivatives 87-89](image)

Inspired by this result, the efficacy of various Lewis acids such as AlCl3, ZnCl2, SnCl2.6H2O, FeCl3, BiCl3, YbCl3 and Yb(OTf)3 (Table 2.1) were tested for the model reaction under the above conditions. Though several acid catalysts such as Bronsted acids, Lewis acids and ionic liquid have been employed for Friedlander reactions, [28-41] some of these procedures are complicated by harsh reaction conditions, use of harmful organic solvents, low yields and difficulties in the work-up procedures. Among the catalysts screened (Table 2.1), YbCl3 showed 90% isolated yield for 87c. Over the past few years, ytterbium (III) chloride is emerging as a powerful nontoxic, inexpensive and eco-friendly, readily available, economical lanthanide Lewis acid catalyst for various organic transformations [47].
Table 2.1. Lewis acid screening for the synthesis of 87c in acetonitrile

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Mol%</th>
<th>Time (h)</th>
<th>Yield of 87c (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AlCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>100</td>
<td>5</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>ZnCl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>100</td>
<td>5</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>FeCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>100</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>SnCl&lt;sub&gt;2.6H2O&lt;/sub&gt;</td>
<td>50</td>
<td>5</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>BiCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>25</td>
<td>3</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>Yb(OTf)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>25</td>
<td>3</td>
<td>78</td>
</tr>
<tr>
<td>7</td>
<td>YbCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>25</td>
<td>1</td>
<td>90</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield after purification by column chromatography.

After the optimized conditions (Table 2.1), the scope of the reaction was examined in detail. As shown in Scheme 1, the Friedlander annulation reactions of aminobenzophenone 83 with different ketones, viz. 2-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]-1-phenyl-1-ethanone 84, 2-(1,3-benzothiazol-2-ylsulfanyl)-1-phenyl-1-ethanone 85 and 1-phenyl-2-[2-phenyl-2H-1,2,3,4-tetraazol-5-yl)sulfanyl]-1-ethanone 86 were carried out in acetonitrile in the presence of YbCl<sub>3</sub> under heating conditions for 1 h. Typically, a mixture of ketones 84-86, aminobenzophenone 83 and YbCl<sub>3</sub> in (1:1:0.25) ratio was refluxed at 80 °C for 1-2 h. The reaction has led to 2-aryl-4-phenyl-3-quinolyl (5-methyl-1,3,4-thiadiazol-2-yl)sulfides 87a-g, 1,3-benzothiazol-2-yl[2-aryl-4-phenyl-3-quinolyl] sulphones 88a-g and 2-aryl-4-phenyl-3-[(2-phenyl-2H-1,2,3,4-tetraazol-5-yl)sulfanyl]quinoline 89a-g respectively (Table 2.2). To the best of our knowledge, YbCl<sub>3</sub> has not been used in effecting Friedlander reaction and it is found to be effective than other Lewis acids investigated.
The structure of 2-aryl-4-phenyl-3-quinolyl(5-methyl-1,3,4-thiadiazol-2-yl)sulfides were established from $^1$H and $^{13}$C NMR spectra for a representative example 87c. In the proton NMR, the singlet at 2.60 ppm corresponds to methyl group. The thirteen aromatic protons appear from 7.30 to 8.21 ppm. The carbon signal of methyl group appears at 15.6 ppm (Figure 2.2 to 2.4).

### Table 2.2. Yield and melting points of derivatives 87-89

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compd.</th>
<th>Ar</th>
<th>Reaction Time (h)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>87a</td>
<td>C$_6$H$_5$</td>
<td>1.0</td>
<td>84</td>
<td>159–160</td>
</tr>
<tr>
<td>2</td>
<td>87b</td>
<td>4-MeC$_6$H$_4$</td>
<td>1.0</td>
<td>82</td>
<td>190–191</td>
</tr>
<tr>
<td>3</td>
<td>87c</td>
<td>4-ClC$_6$H$_4$</td>
<td>1.0</td>
<td>90</td>
<td>192–193</td>
</tr>
<tr>
<td>4</td>
<td>87d</td>
<td>4-BrC$_6$H$_4$</td>
<td>1.0</td>
<td>81</td>
<td>193–194</td>
</tr>
<tr>
<td>5</td>
<td>87e</td>
<td>4-MeOC$_6$H$_4$</td>
<td>1.0</td>
<td>86</td>
<td>190–191</td>
</tr>
<tr>
<td>6</td>
<td>87f</td>
<td>2-Naphthyl</td>
<td>1.0</td>
<td>80</td>
<td>150–151</td>
</tr>
<tr>
<td>7</td>
<td>87g</td>
<td>4-PhC$_6$H$_4$</td>
<td>1.0</td>
<td>82</td>
<td>182–183</td>
</tr>
<tr>
<td>8</td>
<td>88a</td>
<td>C$_6$H$_5$</td>
<td>1.0</td>
<td>85</td>
<td>142–143</td>
</tr>
<tr>
<td>9</td>
<td>88b</td>
<td>4-MeC$_6$H$_4$</td>
<td>1.5</td>
<td>83</td>
<td>144–145</td>
</tr>
<tr>
<td>10</td>
<td>88c</td>
<td>4-ClC$_6$H$_4$</td>
<td>1.5</td>
<td>80</td>
<td>152–153</td>
</tr>
<tr>
<td>11</td>
<td>88d</td>
<td>4-BrC$_6$H$_4$</td>
<td>1.5</td>
<td>83</td>
<td>154–155</td>
</tr>
<tr>
<td>12</td>
<td>88e</td>
<td>4-MeOC$_6$H$_4$</td>
<td>1.5</td>
<td>80</td>
<td>162–163</td>
</tr>
<tr>
<td>13</td>
<td>88f</td>
<td>2-Naphthyl</td>
<td>1.5</td>
<td>79</td>
<td>165–166</td>
</tr>
<tr>
<td>14</td>
<td>88g</td>
<td>4-PhC$_6$H$_4$</td>
<td>1.5</td>
<td>81</td>
<td>242–243</td>
</tr>
<tr>
<td>15</td>
<td>89a</td>
<td>C$_6$H$_5$</td>
<td>2.0</td>
<td>85</td>
<td>161–162</td>
</tr>
<tr>
<td>16</td>
<td>89b</td>
<td>4-MeC$_6$H$_4$</td>
<td>2.0</td>
<td>79</td>
<td>143–144</td>
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<tr>
<td>17</td>
<td>89c</td>
<td>4-ClC$_6$H$_4$</td>
<td>2.0</td>
<td>81</td>
<td>142–143</td>
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<tr>
<td>18</td>
<td>89d</td>
<td>4-BrC$_6$H$_4$</td>
<td>2.0</td>
<td>83</td>
<td>180–181</td>
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<tr>
<td>19</td>
<td>89e</td>
<td>4-MeOC$_6$H$_4$</td>
<td>2.0</td>
<td>84</td>
<td>148–149</td>
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<tr>
<td>20</td>
<td>89f</td>
<td>2-Naphthyl</td>
<td>2.0</td>
<td>78</td>
<td>120–121</td>
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<tr>
<td>21</td>
<td>89g</td>
<td>4-PhC$_6$H$_4$</td>
<td>2.0</td>
<td>86</td>
<td>173–174</td>
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</table>

<sup>a</sup>Yield after isolation through column
Figure 2.2. $^1$H NMR Spectrum of 87c (CDCl$_3$)

Figure 2.3. $^1$H NMR Spectrum of 87c (expanded)
The structures of 1,3-benzothiazol-2-yl[2-aryl-4-phenyl-3-quinolyl] sulphides 88 were deduced from $^1$H, $^{13}$C and 2D NMR spectroscopic data as illustrated for a representative example 88e. In the $^1$H NMR spectrum of 88e, the $p$-OMe substituted aryl ring H-3'' proton shows doublet at 6.84 ppm with $J = 9.0$ Hz, which shows (i) H,H-COSY correlation with the doublet at 7.66 ppm ($J = 9.0$ Hz), [H-2'' protons], (ii) C,H-COSY correlation with the signal at 113.2 ppm assignable to C-3'' and (iii) HMBC with carbon signals at 132.6, and 159.8 ppm ascribable to C-1'' and C-4'' respectively (Figure 2.5).

Further, H-2'' shows C,H-COSY correlation with the signal at 130.8 ppm and HMBC correlations with carbon signals at 159.8 and 162.2 ppm confirming the latter signals.
as C-4” and quinoline ring C-2 carbon respectively. The quinoline H-7 proton appears as doublet of doublet of doublet at 7.79 ppm with $J = 8.4, 6.0$ and 2.4 Hz, which shows H,H-COSY correlation with doublet at 8.25 ppm ($J = 8.4$ Hz, H-8), C,H-COSY correlation with the signal at 131.1 ppm and HMBC with C-6 at 127.3 ppm and C-8a at 148.2 ppm. The doublet of H-8 proton also shows C, H-COSY correlation with C-8 at 129.6 ppm and HMB correlations with *ipso* C-4a at 127.2 ppm and C-6 at 127.3 ppm. The H-7’ proton of benzo[d]thiazole ring appears as doublet at 7.57 ppm ($J = 8.1$ Hz) and shows: (i) C,H-COSY correlation with the signal at 120.7 ppm due to C-7' and (ii) HMBC connections with *ipso* C-3'a at 153.4 ppm. This H-7’ proton exhibits H,H-COSY correlation with multiplet at 7.16-7.22 ppm, which is assignable to H-6'. The H-6' proton further gives C,H-COSY correlation with carbon signal at 124.0 ppm and HMBC with C-7'a at 135.3 ppm (Figure 2.6 to 2.15).

**Figure 2.6. $^1$H NMR Spectrum of 88e (CDCl$_3$)**
Results and discussion

Figure 2.7. $^1$H NMR Spectrum of 88e (expanded)

Figure 2.8. $^{13}$C NMR Spectrum of 88e (CDCl$_3$)
Chapter-2

Results and discussion

Figure 2.9. DEPT - 135 Spectrum of 88e (CDCl₃)

Figure 2.10. H,H - COSY Spectrum of 88e
Chapter 2

Results and discussion

Figure 2.11. H,H - COSY Spectrum of 88e (expanded)

Figure 2.12. HMBC Spectrum of 88e (CDCl₃)
Figure 2.13. HMBC Spectrum of 88e (expanded)

Figure 2.14. C,H - COSY Spectrum of 88e (CDCl₃)
The structure of the quinoline 88 is further confirmed by single crystal X-ray crystallographic study of 88f (Figure 2.16).

The structure of 2-aryl-4-phenyl-3-[(2-phenyl-2H-1,2,3,4-tetraazol-5-yl)sulfanyl] quino- lines were established from $^1$H and $^{13}$C NMR spectra for a representative example 87c. In the proton NMR, the singlet at 2.35 ppm corresponds to methyl group and the remaining eighteen aromatic protons appear from 6.94 to 8.22 ppm. The carbon signal of methyl group appears at 21.2 ppm (Figure 2.17 to 2.19).
Figure 2.17. $^1$H NMR Spectrum of 89b (CDCl$_3$)

Figure 2.18. $^1$H NMR Spectrum of 89b (expanded)
A plausible mechanism for the formation of the quinoline derivatives 87-89 is proposed (Scheme 2.2). The condensation of 2-aminobenzophenone 83 and ketones 84-86 promoted by YbCl3 catalyst affords the imine 90, which tautomerises to furnish the enamine 91, whose subsequent annulation affords the quinoline derivatives 87-89.
2.6 Anti-tubercular activity

All the newly synthesized compounds are screened for their in vitro antimycobacterial activity against MTB in Middlebrook 7H11 agar medium supplemented with OADC by agar dilution method, similar to the method recommended by the National Committee for Clinical Laboratory Standards for the determination of MIC in duplicate [49]. The MTB clinical isolate was resistant to isoniazid, rifampicin, ethambutol, and ciprofloxacin. The MIC is defined as the minimum concentration of compounds required to inhibit 99% of bacterial growth. The MIC values of the synthesized compounds determined at 7.4 pH, along with that of standard drugs are listed in Table 2.3.

In the first phase of screening against MTB, all the quinoline derivatives 87-89 showed good in vitro activity against MTB with MIC ranging from 3.2 to 55.9 μM. Four compounds (87c, 87d, 87g and 88d) inhibited MTB with MIC less than 6.5 μM and were more potent than the first line anti-TB drug, ethambutol (MIC: 7.6 μM). When compared to ciprofloxacin (MIC: 4.7 μM), two compounds 87c (MIC: 3.5 μM) and 87d (MIC: 3.2 μM) were found to be more potent against MTB. The other two series of quinolines 88a-g and 89a-g, however, were less potent than rifampicin, isoniazid, ciprofloxacin and ethambutol. Compound, 2-[2-(4-bromophenyl)-4-phenyl-3-quinolyl]sulfanyl-5-methyl-1,3,4-thiadiazole (87d) displayed the maximum potency with MIC of 3.2 μM being 1.47 and 2.38 times more potent than ciprofloxacin and ethambutol respectively. Another compound, 2-[2-(4-chlorophenyl)-4-phenyl-3-quinolyl]sulfanyl-5-methyl-1,3,4-thiadizole (87c) was also found to be more active with MIC of 3.5 μM against MTB and was 1.34 and 2.17 times more potent than ciprofloxacin and ethambutol respectively. With respect to structure-MTB activity relationship, the data in Table 2.3 show that the substituents present in the 3-position of quinoline ring has a profound effect on the activity of 87-89, the order of activity, in general, being 2-methyl-1,3,4-thiadiazole > benzo[d]thiazole > 2-phenyl-2H-tetrazole as revealed by the comparison of MIC data of compounds 87-89 (Figure 2.20).
## Results and discussion

**Table 2.3.** Mycobacterium tuberculosis H37Rv (MTB) activities of quinoline derivatives 87-89

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compd.</th>
<th>Ar</th>
<th>MTB (MIC) (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>87a</td>
<td>C₆H₅</td>
<td>30.4</td>
</tr>
<tr>
<td>2</td>
<td>87b</td>
<td>4-MeC₆H₄</td>
<td>29.4</td>
</tr>
<tr>
<td>3</td>
<td>87c</td>
<td>4-ClC₆H₄</td>
<td>3.5</td>
</tr>
<tr>
<td>4</td>
<td>87d</td>
<td>4-BrC₆H₄</td>
<td>3.2</td>
</tr>
<tr>
<td>5</td>
<td>87e</td>
<td>4-MeOC₆H₄</td>
<td>28.3</td>
</tr>
<tr>
<td>6</td>
<td>87f</td>
<td>2-Naphthyl</td>
<td>13.5</td>
</tr>
<tr>
<td>7</td>
<td>87g</td>
<td>4-PhC₆H₄</td>
<td>6.4</td>
</tr>
<tr>
<td>8</td>
<td>88a</td>
<td>C₆H₅</td>
<td>55.9</td>
</tr>
<tr>
<td>9</td>
<td>88b</td>
<td>4-MeC₆H₄</td>
<td>54.3</td>
</tr>
<tr>
<td>10</td>
<td>88c</td>
<td>4-ClC₆H₄</td>
<td>12.9</td>
</tr>
<tr>
<td>11</td>
<td>88d</td>
<td>4-BrC₆H₄</td>
<td>5.9</td>
</tr>
<tr>
<td>12</td>
<td>88e</td>
<td>4-MeOC₆H₄</td>
<td>&gt;52.4</td>
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<tr>
<td>13</td>
<td>88f</td>
<td>2-Naphthyl</td>
<td>50.3</td>
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<td>14</td>
<td>88g</td>
<td>4-PhC₆H₄</td>
<td>47.2</td>
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<tr>
<td>15</td>
<td>89a</td>
<td>C₆H₅</td>
<td>54.6</td>
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<tr>
<td>16</td>
<td>89b</td>
<td>4-MeC₆H₄</td>
<td>53.0</td>
</tr>
<tr>
<td>17</td>
<td>89c</td>
<td>4-ClC₆H₄</td>
<td>50.8</td>
</tr>
<tr>
<td>18</td>
<td>89d</td>
<td>4-BrC₆H₄</td>
<td>23.3</td>
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<tr>
<td>19</td>
<td>89e</td>
<td>4-MeOC₆H₄</td>
<td>51.2</td>
</tr>
<tr>
<td>20</td>
<td>89f</td>
<td>2-Naphthyl</td>
<td>49.2</td>
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<tr>
<td>21</td>
<td>89g</td>
<td>4-PhC₆H₄</td>
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</table>

Isoniazid | 0.4  
Rifampicin | 0.1  
Ciprofloxacin | 4.7  
Ethambutol | 7.6  

Among the aryl groups in the series of compound 87, the order of activity is 4-BrC₆H₄ > 4-ClC₆H₄ > 4-PhC₆H₄ > 2-Naphthyl > 4-MeOC₆H₄ > 4-MeC₆H₄ > C₆H₅. In 87 and 88 bearing 2-methyl-1,3,4-thiadiazole and benzo[d]thiazole rings at 3-position of quinoline ring respectively, the presence of halogens in the aryl ring enhanced the antimycobacterial activity as seen from the MIC values of 87c (MIC: 3.5 µM), 87d (MIC: 3.2 µM), 88d (MIC: 5.9 µM) (Table 2.3).
2.7 Cytotoxicity

The cytotoxicity of the compounds 87c and 87d were studied in vitro using NIH 3T3 mouse embryonic fibroblasts cell line (NIH 3T3) by MTT assay [50]. MTT is a yellow coloured water soluble tetrazolium salt. A mitochondrial enzyme in living cells, succinate-dehydrogenase, cleaves the tetrazolium ring, converting the MTT to an insoluble purple formazan product that was read spectrophotometrically at 570 nm on the basis of linear absorbance to the number of living cells in culture. The MTT assay was validated using various concentrations of DMSO.

The dose-response graph (Figure 2.21) reveals that the % cell viability was decreased with increasing the concentration of both 87c and 87d. However, the half maximal inhibitory concentration (IC$_{50}$) value determined by GraphPad Prism software was found to be $>1000$ µM for both 87c and 87d. This indicates that the synthesized compounds 87c and 87d are not toxic to the normal fibroblasts (NIH 3T3).
2.8. Conclusion

In conclusion, a simple and efficient procedure for the synthesis of novel quinoline derivatives with 2-methyl-1,3,4-thiadiazole / benzo[d]thiazole / 2-phenyl-2H-tetrazole ring at 3-position linked by sulfur, in excellent yields has been developed using Friedlander annulation in the presence of YbCl₃ as a catalyst. All the synthesized compounds were characterized by NMR and crystal analysis. Among different acid catalysts screened, YbCl₃ is found to have excellent activity. YbCl₃ as a Lewis acid catalyst for Friedlander reaction is tested for the first time. The synthesized quinolines displayed good \textit{in vitro} antimycobacterial activity against MTB. Two of the most active compounds were tested for their cytotoxicity. Both \textbf{87c} and \textbf{87d} did not produce any toxicity on NIH 3T3 cells and showed the IC₅₀ value of >1000 µM. This lack of cytotoxic potential of compounds \textbf{87c} and \textbf{87d} are of great significance for their possible use in the treatment of MTB other than cancer.

\textbf{Figure 2.21}. Comparison of cytotoxicity on NIH 3T3 cells after 48 h of incubation with compounds \textbf{87c} and \textbf{87d} using the MTT assay.
2.9. Experimental section

2.9.1. General Methods

All the melting points reported in this work were measured in open capillaries. The $^1$H and $^{13}$C NMR spectra have been measured at 300 and 75 MHz respectively using Bruker 300 MHz (Avance) instrument in CDCl$_3$ using tetramethylsilane (TMS) as internal standard. Chemical shifts are reported as $\delta$ values (ppm). All one- and two-dimensional NMR spectra were obtained using standard Bruker software throughout. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer. Crystals suitable for X-ray crystallographic studies were obtained by crystallization from ethyl acetate.

2.9.2. General procedure for quinoline derivatives (87-89)

A mixture of equimolar amount of 2-aminobenzophenone 83 (100 mol%, 2.3 mmol) and ketone 84/85/86 (100 mol%, 2.3 mmol) [51] with YbCl$_3$ (25 mol%, 0.57 mmol) in acetonitrile (5 mL) was refluxed for 1-2 h. After completion of the reaction (monitored by TLC), the mixture was poured into ice water (200 mL) and the resulting crude solid was filtered and dried. The crude product was further purified by silica gel column chromatography (10% ethylacetate in petroleum ether) to afford the pure product 87-89. Full characterization data for all compounds (87-89) are given below.

2.9.2.1. 2,4-Diphenyl-3-quinolyl(5-methyl-1,3,4-thiadiazol-2-yl)sulphide (87a).

Isolated as colorless solid; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H: 2.58 (s, 3H, CH$_3$), 7.35-7.40 (m, 4H, Ar-H), 7.49-7.53 (m, 6H, Ar-H), 7.65 (brs, 2H, Ar-H), 7.82-7.84 (m, 1H, Ar-H), 8.48 (d, 1H, $J = 7.5$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C: 15.6, 123.0, 127.1, 127.3, 127.4, 127.8, 128.2, 128.5, 128.7, 128.9, 129.1, 129.2, 131.4, 136.3, 139.2, 146.9, 156.1, 161.5, 165.3 (2C). Anal. Calcd for C$_{24}$H$_{17}$N$_3$S$_2$: C, 70.04; H, 4.16; N, 10.21%. Found C, 69.97; H, 4.10; N, 10.28%.

2.9.2.2. 2-(4-Methylphenyl)-4-phenyl-3-quinolyl(5-methyl-1,3,4-thiadiazol-2-yl)sulfide (87b).

Isolated as colorless solid; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H: 2.38 (s, 3H, CH$_3$), 2.58 (s, 3H, CH$_3$), 7.19 (d, 2H, $J = 7.8$ Hz, Ar-H), 7.31-7.33 (m, 2H, Ar-H), 7.46-7.47 (m, 5H, Ar-H), 7.54 (d, 2H, $J = 7.8$ Hz, Ar-H), 7.75-7.80 (m, 1H, Ar-H), 8.21 (d, 1H, $J = 8.4$ Hz, Ar-H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C: 15.6, 21.3, 122.8,
127.0 (2C), 127.2, 128.1, 128.4, 128.5, 129.0, 129.1, 129.6, 131.0, 136.6, 137.3, 138.3, 147.8, 155.4, 161.9, 165.1, 165.9. Anal. Calcd for C_{25}H_{19}N_{3}S_{2}: C, 70.56; H, 4.50; N, 9.87%. Found C, 70.50; H, 4.57; N, 9.82%.

2.9.2.3. 2-[2-(4-Chlorophenyl)-4-phenyl-3-quinolyl]sulfanyl-5-methyl-1,3,4-thiadiazole (87c). Isolated as colorless solid; ^1^H NMR (300 MHz, CDCl\textsubscript{3}) δ\textsubscript{H}: 2.60 (s, 3H, CH\textsubscript{3}), 7.30-7.33 (m, 2H, Ar-H), 7.35 (d, 2H, J = 8.4 Hz, Ar-H), 7.43 -7.50 (m, 5H, Ar-H), 7.59 (d, 2H, J = 8.4 Hz, Ar-H), 7.80 (ddd, 1H, J = 8.4, 5.1 & 3.0 Hz, Ar-H), 8.19 (d, 1H, J = 8.4 Hz, Ar-H); ^13^C NMR (75 MHz, CDCl\textsubscript{3}) δ\textsubscript{C}: 15.6, 122.4, 127.1, 127.3, 127.4, 128.0, 128.2, 128.5, 129.1, 129.6, 130.6, 131.2, 134.6, 136.5, 138.7, 147.9, 155.6, 160.7, 165.2, 165.3. Anal. Calcd for C\textsubscript{24}H\textsubscript{16}ClN\textsubscript{3}S\textsubscript{2}: C, 64.63; H, 3.62; N, 9.42%. Found C, 64.57; H, 3.68; N, 9.49%.

2.9.2.4. 2-[2-(4-Bromophenyl)-4-phenyl-3-quinolyl]sulfanyl-5-methyl-1,3,4-thiadiazole (87d). Isolated as colorless solid; ^1^H NMR (300 MHz, CDCl\textsubscript{3}) δ\textsubscript{H}: 2.59 (s, 3H, CH\textsubscript{3}), 7.32 (dd, 2H, J = 6.0, 1.5 Hz, Ar-H), 7.46-7.52 (m, 9H, Ar-H), 8.19 (d, 1H, J = 8.4 Hz, Ar-H); ^13^C NMR (75 MHz, CDCl\textsubscript{3}) δ\textsubscript{C}: 15.6, 122.3, 122.9, 127.1, 127.3, 127.4, 128.2, 128.5, 129.1, 129.6, 130.9, 131.0, 131.2, 136.5, 139.2, 147.9, 155.7, 160.7, 165.2, 165.4. Anal. Calcd for C\textsubscript{24}H\textsubscript{16}BrN\textsubscript{3}S\textsubscript{2}: C, 58.78; H, 3.29; N, 8.57%. Found C, 58.71; H, 3.35; N, 8.63%.

2.9.2.5. 2-[2-(4-Methoxyphenyl)-4-phenyl-3-quinolyl]sulfanyl-5-methyl-1,3,4-thiadiazole (87e). Isolated as colorless solid; ^1^H NMR (300 MHz, CDCl\textsubscript{3}) δ\textsubscript{H}: 2.57 (s, 3H, CH\textsubscript{3}), 3.83, (s, 3H, OCH\textsubscript{3}), 6.91 (d, 2H, J = 8.4 Hz, Ar-H), 7.31-7.33 (m, 2H, Ar-H), 7.45-7.47 ( m, 5H, Ar-H), 7.63 (d, 2H, J = 8.4 Hz), 7.75-7.80 (m, 1H, Ar-H), 8.21 (d, 1H, J = 8.4 Hz, Ar-H); ^13^C NMR (75 MHz, CDCl\textsubscript{3}) δ\textsubscript{C}: 15.6, 123.2, 126.1, 126.5, 126.7, 127.1, 127.2, 127.4, 127.5, 127.6, 128.2, 128.4, 129.1, 129.5, 130.7, 131.0, 131.2, 136.7, 147.9, 155.6, 159.9, 161.4, 165.1, 165.9. Anal. Calcd for C\textsubscript{25}H\textsubscript{19}O\textsubscript{3}N\textsubscript{3}S\textsubscript{2}: C, 68.00; H, 4.34; N, 9.52%. Found C, 67.94; H, 4.39; N, 9.59%.

2.9.2.6. 2-Methyl-5-[2-(2-naphthyl)-4-phenyl-3-quinolyl]sulfanyl-1,3,4-thiadiazole (87f). Isolated as colorless solid; ^1^H NMR (300 MHz, CDCl\textsubscript{3}) δ\textsubscript{H}: 2.46 (s, 3H, CH\textsubscript{3}), 7.36-7.41 (m, 2H, Ar-H), 7.48-7.58 (m, 6H, Ar-H), 7.75-7.87 (m, 6H, Ar-H), 8.03 (s, 1H, Ar-H), 8.2 (d, 1H, J = 8.4 Hz, Ar-H); ^13^C NMR (75 MHz, CDCl\textsubscript{3}) δ\textsubscript{C}: 15.4, 123.2, 126.1, 126.5, 126.7, 127.1, 127.2, 127.4, 127.5, 127.6, 128.2, 128.4, 128.5, 128.8,
2.9.2.7. 2-(2-(Biphenyl-4-yl)-4-phenylquinolin-3-ylthio)-5-methyl-1,3,4-thiadiazole (87g). Isolated as colorless solid; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H: 2.57 (s, 3H, CH$_3$), 7.33-7.38 (m, 2H, Ar-H), 7.43-7.50 (m, 8H, Ar-H), 7.60 (d, 2H, $J = 8.1$ Hz, Ar-H), 7.61-7.63 (m, 2H, Ar-H), 7.72 (d, 2H, $J = 8.1$ Hz, Ar-H), 7.78 (ddd, 1H, $J = 8.4$, 5.1, 3.6 Hz, Ar-H), 8.24 (d, 1H, $J = 8.4$ Hz, Ar-H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C: 15.6, 122.8, 126.6 (2C), 127.1, 127.2, 127.4, 128.2, 128.5, 128.7, 129.0 (2C), 129.2, 129.7, 131.1, 136.6, 139.2, 140.7, 141.2, 147.9, 155.5, 161.6, 165.3, 165.7. Anal. Calcd for C$_{30}$H$_{21}$N$_3$S$_2$: C, 73.89; H, 4.34; N, 8.62%. Found C, 73.83; H, 4.41; N, 8.67%.

2.9.2.8. 1,3-Benzothiazol-2-yl(2,4-diphenyl-3-quinolyl)sulphide (88a). Isolated as colorless solid; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H: 7.21 (dt, 1H, $J = 7.4$, 0.9 Hz, Ar-H), 7.30-7.35 (m, 6H, Ar-H), 7.38-7.43 (m, 3H, Ar-H), 7.49-7.52 (m, 2H, Ar-H), 7.58 (d, 1H, $J = 7.8$ Hz, Ar-H), 7.62-7.67 (m, 2H, Ar-H), 7.69 (d, 1H, $J = 8.1$ Hz, Ar-H), 7.82 (ddd, 1H, $J = 8.4$, 5.7, 2.4 Hz, Ar-H), 8.27 (d, 1H, $J = 8.4$ Hz, Ar-H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C: 120.6, 121.6, 122.2, 123.9, 125.8, 127.1, 127.2, 127.3, 127.6 (2C), 128.0, 128.3, 128.9, 129.1, 129.6, 131.1, 135.2, 136.4, 140.0, 148.0, 153.2, 156.4, 162.6, 167.4. Anal. Calcd for C$_{28}$H$_{18}$N$_2$S$_2$: C, 75.30; H, 4.06; N, 6.27%. Found C, 75.22; H, 4.12; N, 6.32%.

2.9.2.9. 1,3-Benzothiazol-2-yl[2-(4-methylphenyl)-4-phenyl-3-quinolyl]sulphide (88b). Isolated as colorless solid; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H: 2.31 (s, 3H, CH$_3$), 7.12 (d, 2H, $J = 7.8$ Hz, Ar-H), 7.21 (t, 1H, $J = 7.8$ Hz, Ar-H), 7.30 -7.40 (m, 6H, Ar-H), 7.48-7.60 (m, 5H, Ar-H), 7.69 (d, 1H, $J = 7.8$ Hz, Ar-H), 7.81 (ddd, 1H, $J = 8.4$, 5.1, 2.4 Hz, Ar-H), 8.26 (d, 1H, $J = 8.4$ Hz, Ar-H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C: 21.3, 120.7, 121.7, 122.3, 124.0, 125.9, 127.0, 127.3, 128.1, 128.4, 128.5, 129.0 (2C), 129.2, 129.7, 131.2, 135.4, 136.6, 137.3, 138.3, 148.2, 153.4, 156.7, 162.8, 167.9. Anal. Calcd for C$_{29}$H$_{20}$N$_2$S$_2$: C, 75.62; H, 4.38; N, 6.08%. Found C, 75.56; H, 4.46; N, 6.13%. 

129.2, 129.7, 131.1, 132.9, 133.0, 136.7, 137.8, 147.9, 155.4, 161.8, 165.4, 165.5.

Anal. Calcd for C$_{28}$H$_{19}$N$_3$S$_2$: C, 72.86; H, 4.15; N, 9.10%. Found C, 72.79; H, 4.22; N, 9.16%.
2.9.2.10. **1,3-Benzothiazol-2-yl[2-(4-chlorophenyl)-4-phenyl-3-quinolyl]sulphide (88c)**. Isolated as colorless solid; $^1$H NMR (300 MHz, CDCl$_3$) $\delta_{H}$: 7.21 (t, 1H, $J = 7.5$ Hz, Ar-H), 7.25-7.35 (m, 5H, Ar-H), 7.38 -7.47 (m, 3H, Ar-H), 7.49-7.63 (m, 5H, Ar-H), 7.70 (d, 1H, $J = 8.1$ Hz, Ar-H), 7.79-7.84 (m, 1H, Ar-H), 8.23 (d, 1H, $J = 8.7$ Hz, Ar-H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta_{C}$: 120.7, 121.8, 122.0, 124.2, 126.0, 127.3, 127.4, 128.0, 128.2, 128.5, 129.0, 129.3, 129.6, 130.6, 131.4, 134.6, 135.2, 136.3, 138.5, 148.0, 153.2, 156.7, 161.4, 167.1. Anal. Calcd for C$_{28}$H$_{17}$ClN$_2$S$_2$: C, 69.91; H, 3.56; N, 5.82%. Found C, 69.85; H, 3.61; N, 5.89%.

2.9.2.11. **1,3-Benzothiazol-2-yl[2-(4-bromophenyl)-4-phenyl-3-quinolyl]sulphide (88d)**. Isolated as colorless solid; $^1$H NMR (300 MHz, CDCl$_3$) $\delta_{H}$: 7.23 (t, 1H, $J = 7.5$ Hz, Ar-H), 7.32-7.34 (m, 2H, Ar-H), 7.37-7.44 (m, 6H, Ar-H), 7.51 -7.61 (m, 5H, Ar-H), 7.71 (d, 1H, $J = 8.1$ Hz, Ar-H), 7.82 (ddd, 1H, $J = 8.4$, 5.1, 2.4 Hz, Ar-H), 8.24 (d, 1H, $J = 8.4$ Hz, Ar-H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta_{C}$: 120.8, 121.8 (2C), 122.0, 123.0, 124.2, 126.0, 127.4, 127.5, 128.2, 128.6, 129.0, 129.7, 130.9 (2C), 131.4, 135.3, 136.4, 139.0, 148.1, 153.3, 156.8, 161.5, 167.1. Anal. Calcd for C$_{28}$H$_{17}$BrN$_2$S$_2$: C, 66.40; H, 3.26; N, 5.33%. Found C, 66.33; H, 3.32; N, 5.39%.

2.9.2.12. **2-[2-(4-Methoxyphenyl)-4-phenyl-3-quinolyl]sulfanyl-1,3-benzothiazole (88e)**. Isolated as colorless solid; $^1$H NMR (300 MHz, CDCl$_3$) $\delta_{H}$: 3.75 (s, 3H, OCH$_3$), 6.84 (d, 2H, $J = 9.0$ Hz, Ar-H), 7.16-7.22 (m, 1H, Ar-H), 7.16-7.34 (m, 6H, Ar-H), 7.46-7.51 (m, 2H, Ar-H), 7.57 (d, 1H, $J = 8.1$ Hz, Ar-H), 7.66 (d, 2H, $J = 9.0$ Hz, Ar-H), 7.67-7.71 (m, 1H, Ar-H), 7.79 (ddd, 1H, $J = 8.4$, 6.0, 2.4 Hz, Ar-H), 8.25 (d, 1H, $J = 8.4$ Hz, Ar-H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta_{C}$: 55.2, 113.2, 120.7, 121.7, 122.3, 124.0, 126.0, 127.0, 127.2, 127.3, 128.1, 128.4, 129.0, 129.6, 130.8, 131.1, 132.6, 135.3, 136.6, 148.2, 153.4, 156.7, 159.7, 162.2, 167.8. Anal. Calcd for C$_{29}$H$_{20}$N$_2$OS$_2$: C, 73.08; H, 4.43; N, 5.88%. Found C, 72.99; H, 4.49; N, 5.95%.

2.9.2.13. **1,3-Benzothiazol-2-yl[2-(5,8-dihydro-2-naphthalenyl)-4-phenyl-3-quinolyl] sulphide (88f)**. Isolated as colorless solid; $^1$H NMR (300 MHz, CDCl$_3$) $\delta_{H}$: 7.15 (dt, 1H, $J = 7.2$, 0.9 Hz, Ar-H), 7.26 (dt, 1H, $J = 7.5$, 1.2 Hz, Ar-H), 7.34 -7.45 (m, 7H, Ar-H), 7.48-7.55 (m, 3H, Ar-H), 7.61-7.69 (m, 2H, Ar-H), 7.75-7.83 (m, 4H, Ar-H), 8.11 (s, 1H, Ar-H), 8.29 (d, 1H, $J = 8.4$ Hz, Ar-H); $^{13}$C NMR (75 MHz,CDCl$_3$) $\delta_{C}$: 120.6, 121.7, 122.5, 124.1, 125.9 (2C), 126.3, 126.8, 127.2, 127.3, 127.5 (2C), 127.8, 128.2, 129.0, 129.6, 130.8, 131.1, 132.6, 135.3, 136.6, 148.2, 153.4, 156.7, 159.7, 162.2, 167.8. Anal. Calcd for C$_{29}$H$_{20}$N$_2$OS$_2$: C, 73.08; H, 4.43; N, 5.88%. Found C, 72.99; H, 4.49; N, 5.95%.
128.1 (2C), 128.3, 128.5, 128.9, 129.1, 129.7, 131.2, 132.7, 133.0, 135.3, 136.5, 137.6, 148.1, 153.2, 156.7, 162.6, 167.4. Anal. Calcd for C\textsubscript{32}H\textsubscript{20}N\textsubscript{2}S\textsubscript{2}: C, 77.39; H, 4.06; N, 5.64%. Found C, 77.32; H, 4.13; N, 5.70%.

2.9.2.14. 2-(2-(Biphenyl-4-yl)-4-phenylquinolin-3-ylthio)benzo[d]thiazole (88g). Isolated as colorless solid; $^1$H NMR (300 MHz, CDCl\textsubscript{3}) $\delta_H$: 7.21 (t, 1H, $J = 7.5$ Hz, Ar-H), 7.30 - 7.43 (m, 9H, Ar-H), 7.50-7.59 (m, 7H, Ar-H), 7.69 (d, 1H, $J = 8.1$ Hz, Ar-H), 7.78 (d, 2H, Ar-H), 7.79-7.85 (m, 1H, Ar-H), 8.32 (d, 1H, $J = 8.4$ Hz, Ar-H); $^{13}$C NMR (75 MHz, CDCl\textsubscript{3}) $\delta_C$: 120.7, 121.8, 122.3, 124.1, 126.0, 126.6, 127.1, 127.2, 127.3, 127.4, 127.5, 128.2, 128.5, 128.6, 129.1, 129.7 (2C), 131.2, 135.4, 136.5, 139.1, 140.7, 141.2, 148.2, 153.3, 156.6, 162.4, 167.6. Anal. Calcd for C\textsubscript{34}H\textsubscript{22}N\textsubscript{2}S\textsubscript{2}: C, 78.13; H, 4.24; N, 5.36%. Found C, 78.05; H, 4.30; N, 5.43%.

2.9.2.15. 2,4-Diphenyl-3-[(1-phenyl-1H-1,2,3,4-tetrazol-5-yl)sulfanyl]quinoline (89a). Isolated as colorless solid; $^1$H NMR (300 MHz, CDCl\textsubscript{3}) $\delta_H$: 6.96 ( d, 2H, $J = 7.5$ Hz, Ar-H), 7.33-7.41 (m, 7H, Ar-H), 7.43-7.50 (m, 6H, Ar-H), 7.55 (dd, 2H, $J = 7.1$, 2.0 Hz, Ar-H), 7.82 (ddd, 1H, $J = 8.4$, 5.7, 2.1 Hz, Ar-H), 8.26 (d, 1H, $J = 8.4$ Hz, Ar-H); $^{13}$C NMR (75 MHz, CDCl\textsubscript{3}) $\delta_C$: 120.1, 123.9, 127.0, 127.3, 127.4, 127.8, 128.2, 128.4, 128.5, 129.0, 129.2, 129.5, 130.0, 131.3, 132.8, 136.4, 140.0, 147.7, 153.7, 155.8, 161.7. Anal. Calcd for C\textsubscript{28}H\textsubscript{19}N\textsubscript{5}S: C, 73.50; H, 4.19; N, 15.31%. Found C, 73.42; H, 4.24; N, 15.38%.

2.9.2.16. 2-(4-Methylphenyl)-4-phenyl-3-[(1-phenyl-1H-1,2,3,4-tetraazol-5-yl)sulfanyl]quinoline (89b). Isolated as colorless solid; $^1$H NMR (300 MHz, CDCl\textsubscript{3}) $\delta_H$: 2.35 (s, 3H, CH\textsubscript{3}), 6.95 (dd, 2H, $J = 8.1$, 1.5, Ar-H), 7.12 (d, 2H, $J = 7.8$ Hz, Ar-H), 7.31-7.36 (m, 2H, Ar-H), 7.37-7.46 (m, 10 H, Ar-H), 7.77 (dd, 1H, $J = 8.4$, 5.1, 3.0 Hz, Ar-H), 8.2 (d, 1H, $J = 8.4$ Hz, Ar-H); $^{13}$C NMR (75 MHz, CDCl\textsubscript{3}) $\delta_C$: 21.2, 120.3, 123.9, 126.9, 127.2, 127.3, 128.2, 128.5, 128.6, 128.7, 129.0, 129.2, 129.6, 130.0, 131.1, 133.0, 136.6, 137.3, 138.2, 147.9, 153.8, 156.0, 161.9. Anal. Calcd for C\textsubscript{29}H\textsubscript{21}N\textsubscript{5}S: C, 73.86; H, 4.49; N, 14.85%. Found C, 73.79; H, 4.56; N, 14.93%.

2.9.2.17. 2-(4-Chlorophenyl)-4-phenyl-3-[(1-phenyl-1H-1,2,3,4-tetraazol-5-yl)sulfanyl]quinoline (89c). Isolated as colorless solid; $^1$H NMR (300 MHz, CDCl\textsubscript{3}) $\delta_H$: 7.00 (dd, 2H, $J = 7.2$, 1.2 Hz, Ar-H), 7.26 (d, 2H, $J = 8.4$ Hz, Ar-H), 7.32 (dd, 2H, $J = 6.3$, 3.0 Hz, Ar-H), 7.38-7.53 (m, 10H, Ar-H), 7.81 (ddd, 1H, $J = 8.4$, 6.3, 2.1 Hz,
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2.9.2.18. 2-(4-Bromophenyl)-4-phenyl-3-[(1-phenyl-1H-1,2,3,4-tetraazol-5-yl)sulfanyl]quinoline (89d). Isolated as colorless solid; H NMR (300 MHz, CDCl3) δH: 7.00 (dd, 2H, J = 7.7, 2.0 Hz, Ar-H), 7.34 (d, 2H, J = 7.2 Hz, Ar-H), 7.39-7.40 (m, 12H, Ar-H), 7.73 (dd, 1H, J = 9.0, 2.4 Hz, Ar-H), 8.12 (d, 1H, J = 9.0 Hz, Ar-H); 13C NMR (75 MHz, CDCl3) δC: 121.5, 123.2, 123.8, 125.7, 128.1, 128.6, 128.9, 129.0, 129.4, 130.2, 130.5, 131.1, 131.3, 132.3, 132.7, 133.6, 135.7, 138.5, 146.3, 153.3, 154.9, 160.8. Anal. Calcd for C28H18BrN5S: C, 62.69; H, 3.38; N, 13.06%. Found C, 62.63; H, 3.45; N, 13.12%.

2.9.2.19. 2-(4-Methoxyphenyl)-4-phenyl-3-[(1-phenyl-1H-1,2,3,4-tetraazol-5-yl)sulfanyl]quinoline (89e). Isolated as colorless solid; H NMR (300 MHz, CDCl3) δH: 3.77 (s, 3H, OCH3), 6.81 (d, 2H, J = 9.0 Hz, Ar-H), 6.96 (dd, 2H, J = 7.8, 1.2 Hz, Ar-H), 7.27-7.30 (m, 2H, Ar-H), 7.34-7.43 (m, 8H, Ar-H), 7.50 (d, 2H, J = 9.0 Hz, Ar-H), 7.76 (ddd, 1H, J = 8.4, 5.1, 3.0 Hz, Ar-H), 8.2 (d, 1H, J = 8.4 Hz, Ar-H); 13C NMR (75 MHz, CDCl3) δC: 55.2, 113.3, 120.3, 123.8, 126.9, 127.1, 127.2, 128.2, 128.5, 128.9, 129.2, 129.4, 130.3, 131.1, 132.6, 132.9, 136.6, 147.9, 153.7, 155.6, 159.7, 161.4. Anal. Calcd for C29H21N5OS: C, 71.44; H, 4.34; N, 14.36%. Found C, 71.50; H, 4.40; N, 14.45%.

2.9.2.20. 2-(5,8-Dihydro-2-naphthalenyl)-4-phenyl-3-[(1-phenyl-1H-1,2,3,4-tetraazol-5-yl)sulfanyl]quinoline (89f). Isolated as colorless solid; H NMR (300 MHz, CDCl3) δH: 6.58 (d, 2H, J = 7.8 Hz, Ar-H), 7.13 (t, 2H, J = 8.1 Hz, Ar-H), 7.21-7.31 (m, 1H, Ar-H), 7.37-7.60 (m, 10H, Ar-H), 7.70-7.80 (m, 4H, Ar-H), 7.92 (s, 1H, Ar-H), 8.21 (d, 1H, J = 8.4 Hz, Ar-H); 13C NMR (75 MHz, CDCl3) δC: 120.7, 123.7, 126.3, 126.5, 126.6, 127.1, 127.4, 127.5 (2C), 127.6, 128.2, 128.3, 128.4, 128.6, 129.0, 129.1, 129.7, 129.8, 131.3, 132.6, 132.7, 133.0, 136.6, 137.4, 147.9, 153.8, 155.7, 161.8. Anal. Calcd for C32H21N5S: C, 75.72; H, 4.17; N, 13.80%. Found C, 75.65; H, 4.22; N, 13.87%.
2.9.2.21. 2-(Biphenyl-4-yl)-4-phenyl-3-(1-phenyl-1H-tetrazol-5-ylthio)quinoline (89g). Isolated as colorless solid; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 6.94 (d, 2H, \(J = 7.8\) Hz, Ar-H), 7.27-7.30 (m, 2H, Ar-H), 7.36-7.38 (m, 3H, Ar-H), 7.41-7.49 (m, 7H, Ar-H), 7.53-7.61 (m, 7H, Ar-H), 7.76-7.82 (m, 1H, Ar-H), 8.23 (d, \(J = 8.4\) Hz, Ar-H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 120.3, 123.9, 126.6, 127.0 (2C), 127.3, 127.4, 127.5, 128.3, 128.6, 128.8, 129.0, 129.2, 129.3, 129.7, 130.0, 131.3, 132.9, 136.6, 139.1, 140.4, 141.2, 147.9, 153.8, 155.7, 161.5. Anal. Calcd for C\(_{34}\)H\(_{23}\)N\(_5\)S: C, 76.52; H, 4.34; N, 13.12%. Found C, 76.44; H, 4.40; N, 13.19%.

2.9.3. Anti-tubercular activity

Ten fold serial dilutions of each test compounds 87a-g, 88a-g and 89a-g were incorporated into Middle brook 7H11 agar medium with OADC Growth Supplement. Inoculum of \(M.\) \(tuberculosis\) \(H_37Rv\) were prepared from fresh Middle brook 7H11 agar slants with OADC Growth Supplement adjusted to 1mg/mL (wet weight) in Tween 80 (0.05%) saline diluted to \(10^{-2}\) to give a concentration of approximately \(10^7\) cfu/mL. A 5 \(\mu\)L amount of bacterial suspension was spotted into 7H11 agar tubes containing 10-fold serial dilutions of drugs per mL. The tubes were incubated at 37 \(^{\circ}\)C, and final readings were recorded after 28 days. The minimum concentration of compound required to give complete inhibition of bacterial growth in each tube was determined as the MIC value for corresponding compound.

2.9.4. Cytotoxicity

The NIH 3T3 mouse embryonic fibroblasts (NIH 3T3) was obtained from National Centre for Cell Science (NCCS), Pune, and grown in Dulbeccos Modified Eagles Medium containing 10% fetal bovine serum (FBS). All the cells were maintained at 37 \(^{\circ}\)C, 5% CO\(_2\), 95% air and 100% relative humidity. Maintenance cultures were passage weekly, and the culture medium was changed twice a week.

The monolayer cells were detached with trypsin-ethylenediaminetetraacetic acid (EDTA) to make single cell suspensions and viable cells were counted using a hemocytometer and diluted the medium with 5% FBS to give final density of 1x10\(^5\) cells/ml. One hundred microlitres per well of cell suspension were seeded into 96-well plates at plating density of 10,000 cells/well and incubated to allow for cell attachment at 37 \(^{\circ}\)C, 5% CO\(_2\), 95% air and 100% relative humidity. After 24 h the
cells were treated with serial concentrations of the compounds 87c and 87d. They were initially dissolved in neat dimethylsulfoxide (DMSO) and further diluted in serum free medium to produce various concentrations. One hundred microlitres per well of each concentration was added to plates to obtain final concentrations of 1000, 500, 250, 125 and 63 µM. The final volume in each well was 200 µl and the plates were incubated at 37 °C, 5% CO₂, 95% air and 100% relative humidity for 48 h. The medium without samples was served as control. Triplicate was maintained for all concentrations. After 48 h the cells in each well was quantified by MTT assay. Briefly, 15µl of MTT (5mg/ml) in phosphate buffered saline (PBS) was added to each well and incubated at 37 °C for 4 h. The medium with MTT was then flicked off and the formed formazan crystals were solubilized in 100 µl of DMSO and then measured the absorbance at 570 nm using micro plate reader. The percentage cell viability was then calculated with respect to positive control as follows:

% cell viability = [A] Test / [A] control x 100


48. Crystallographic data (excluding structure factors) for 88f has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 798947.

