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Original article

Synthesis of 3-heteroarylthioquinoline derivatives and their *in vitro* antituberculosis and cytotoxicity studies

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ABSTRACT

A series of 3-heteroarylthioquinoline derivatives has been synthesized by the Friedlander annulation of 2-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]-1-aryl-1-ethanone/2-(1,3-benzothiazol-2-ylsulfanyl)-1-aryl-1-ethanone/1-aryl-2-[(2-phenyl-2*H*-1,2,3,4-tetraazol-5-yl)sulfanyl]-1-ethanone with 2-aminobenzophenone in good yields using $YbCl_3$ as the catalyst. These compounds have been screened for their *in vitro* activity against *Mycobacterium tuberculosis* H37Rv (MTB) and among the 21 compounds screened, 2-[2-(4-bromophenyl)-4-phenyl-3-quinolyl]sulfanyl-5-methyl-1,3,4-thiadiazole (**5d**) and 2-[2-(4-chlorophenyl)-4-phenyl-3-quinolyl]sulfanyl-5-methyl-1,3,4-thiadiazole (**5c**) were found to be the most active compounds with MIC of 3.2 and 3.5 μM respectively against MTB. The cytotoxic effects against mouse fibroblasts (NIH 3T3) *in vitro* were evaluated for **5c** and **5d**, which displayed no toxic effects ($IC_{50} > 1000$ μM) against the mouse fibroblast cell line NIH 3T3.

1. Introduction

Tuberculosis (TB) is an infectious disease caused by different species of mycobacterium. The statistics shows that around 32% of the world's population is infected by Mycobacterium tuberculosis, the main causal agent of TB and today more people die from tuberculosis than ever before [1,2]. TB continues to be a major cause of death among HIV-positive individuals [3]. Currently, the six to nine month multidrug protocol used in the treatment of TB is highly effective with drug-susceptible TB, but poor patient compliance promotes development of drug resistance [4]. Although the existing method of curing is very effective against TB, the length of treatment, the toxicity and the potential for drug–drug interactions are factors that highlight the need for new anti-tubercular drugs [5,6]. In addition, *Mycobacterium tuberculosis* (MTB) is resistant to some of the first and second line drugs [7]. Therefore, effective new drugs [8] and strategies [9] are essential to treat the TB bacilli.

As a privileged fragment, quinoline is a common structural motif found in many natural products with remarkable pharmacological properties [10]. Members of this family have wide applications in medicinal chemistry, being used as antimalarial [11], anti-inflammatory [12], anticancer [13], anti-breast cancer [14], antibiotic [15] and for anti-HIV activities [16]. Ciprofloxacin and moxifloxacin (Fig. 1) are promising agents for the treatment of TB [17] having quinoline moiety. Quinoline based mefloquine (Fig. 2) is known for anti-tubercular activity [18–21] and its analogs have displayed moderate [22] to submicromolar [23] anti-TB activity. Diarylquinoline TMC207 was targeted to the proton pump of *Mycobacterium tuberculosis* ATP synthase and found to have inhibited mycobacterial growth effectively [24]. As mefloquine and TMC207 (Fig. 2) both target ATP synthase, it is anticipated that synthesis of new types of molecules incorporating the molecular features of both mefloquine and TMC207 with quinoline substructure might produce a new hit against *M. tuberculosis*. Thus, in continuation to our exploration for new anti-tubercular agents [25], we planned to synthesize three series of 3-heteroarylthioquinolines (**5**–**7**), having some structural similarities with mefloquine and TMC207 (Fig. 2).

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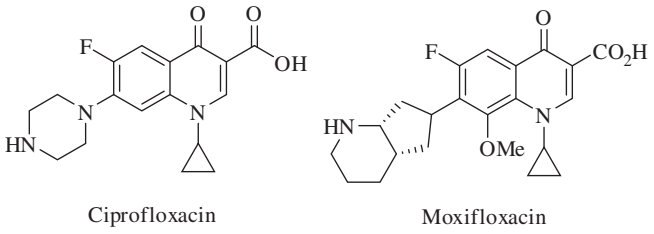


Fig. 1. Chemical structures of anti-TB drugs.

2. Results and discussion

2.1. Chemistry

In the present investigation, the Friedlander annulation reactions of aminobenzophenone **1** with different ketones, *viz*. 2-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]-1-aryl-1-ethanone **2**, 2-(1,3-benzothiazol-2-ylsulfanyl)-1-aryl-1-ethanone **3** and 1-aryl-2-[(2-phenyl-2*H*-1,2,3,4-tetraazol-5-yl)sulfanyl]-1-ethanone **4** were carried out in acetonitrile in the presence of $YbCl_3$ as Lewis acid catalyst at 80 °C for 1 h. The reaction has led to 2-aryl-4-phenyl-3-quinolyl (5-methyl-1,3,4-thiadiazol-2-yl)sulfides **5a**–**g**, 1,3-benzothiazol-2-yl [2-aryl-4-phenyl-3-quinolyl]sulphides **6a**–**g** and 2-aryl-4-phenyl-3-[(2-phenyl-2*H*-1,2,3,4-tetraazol-5-yl)sulfanyl]quinoline **7a**–**g** respectively (Table 1; Scheme 1). Though several acid catalysts such as Bronsted acids, Lewis acids and ionic liquids have been employed for Friedlander reactions [26], 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 different catalysts tried, ytterbium (III) chloride ($YbCl_3$) is found to be the best for the generation of **5**, **6** and **7**. To the best of our knowledge, $YbCl_3$ has not been used as a catalyst for Friedlander reaction and is now found to be more effective than other Lewis acids investigated.

The structures of the 3-heteroarylthioquinolines **5**, **6** and **7** were established from ^1H, ^{13}C and 2D NMR spectroscopic data as illustrated for a representative example, **6e**. In the ^1H NMR spectrum of **6e**, the *p*-OMe substituted aryl ring H-3″ proton showed 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 contours with carbon signals at 132.6, and 159.8 ppm ascribable to C-1″ and C-4″ respectively (Fig. 3). Further, H-2″ showed 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 appeared as doublet of doublet of doublet at 7.79 ppm with $J = 8.4$, 6.0 and 2.4 Hz, which

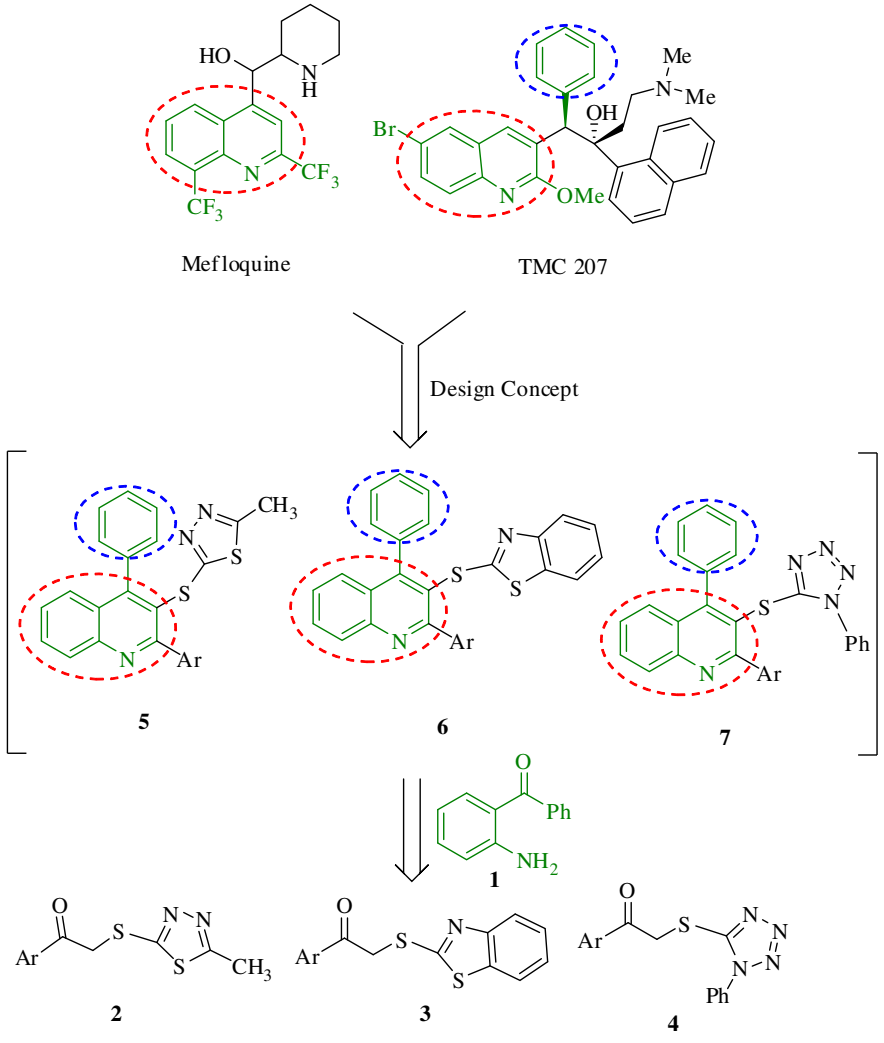


Fig. 2. Design of quinoline series based on mefloquine and TMC207.

Table 1
Yield and *Mycobacterium tuberculosis* H37Rv (MTB) activities of quinoline derivatives **5**–**7**.

Entry	Compd.	Ar	Reaction Time (h)	Yield (%)[a]	mp (°C)	MTB (MIC) (μM)
1	**5a**	C_6H_5	1	84	159–160	30.4
2	**5b**	4-MeC_6H_4	1	82	190–191	29.4
3	**5c**	4-ClC_6H_4	1	90	192–193	3.5
4	**5d**	4-BrC_6H_4	1	81	193–194	3.2
5	**5e**	4-$MeOC_6H_4$	1	86	190–191	28.3
6	**5f**	2-Naphthyl	1	80	150–151	13.5
7	**5g**	4-PhC_6H_4	1	82	182–183	6.4
8	**6a**	C_6H_5	1	85	142–143	55.9
9	**6b**	4-MeC_6H_4	1.5	83	144–145	54.3
10	**6c**	4-ClC_6H_4	1.5	80	152–153	12.9
11	**6d**	4-BrC_6H_4	1.5	83	154–155	5.9
12	**6e**	4-$MeOC_6H_4$	1.5	80	162–163	>52.4
13	**6f**	2-Naphthyl	1.5	79	165–166	50.3
14	**6g**	4-PhC_6H_4	1.5	81	242–243	47.2
15	**7a**	C_6H_5	2	85	161–162	54.6
16	**7b**	4-MeC_6H_4	2	79	143–144	53.0
17	**7c**	4-ClC_6H_4	2	81	142–143	50.8
18	**7d**	4-BrC_6H_4	2	83	180–181	23.3
19	**7e**	4-$MeOC_6H_4$	2	84	148–149	51.2
20	**7f**	2-Naphthyl	2	78	120–121	49.2
21	**7g**	4-PhC_6H_4	2	86	173–174	46.8
	Isoniazid					0.4
	Rifampicin					0.1
	Ciprofloxacin					4.7
	Ethambutol					7.6

[a] After purification by column chromatography.

showed 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 contours with C-6 at 127.3 ppm and C-8a at 148.2 ppm. The doublet of H-8 proton also showed 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 show: (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 shows H, H-COSY correlation with multiplet at 7.16–7.22 ppm, which is assigned to H-6′ proton. The H-6′ proton is further showed C, H-COSY correlation with carbon signal at 124.0 ppm and HMBC correlations with C-7′a at 135.3 ppm. The structure of the quinolines **5**–**7** was further confirmed by a single crystal X-ray crystallographic study of **6f** (Fig. 4) [27].

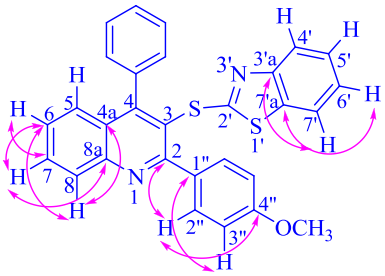


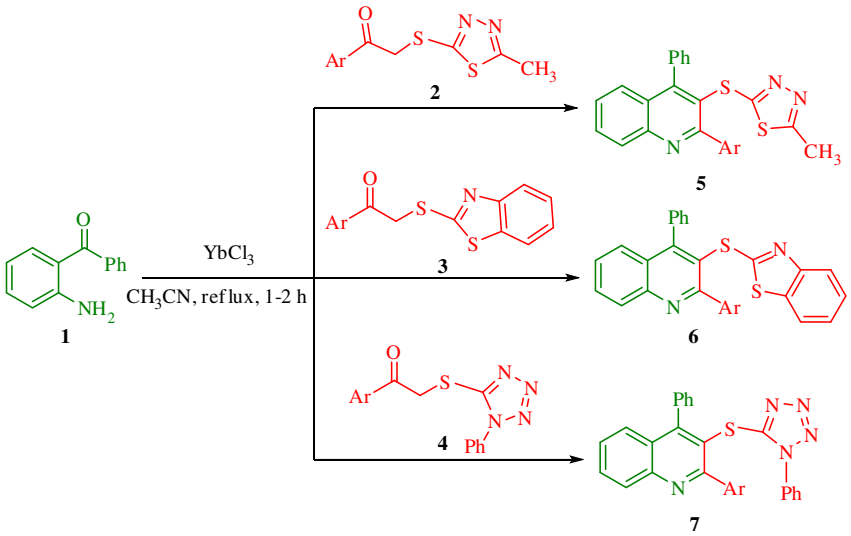
Fig. 3. Selected HMBCs of **6e**.

2.2. Pharmacology

2.2.1. Anti-tubercular activity

All the newly synthesized compounds were screened for their *in vitro* antimycobacterial activity against MTB in Middle brook 7H11 agar medium supplemented with OADC by agar dilution method similar to that recommended by the National Committee for Clinical Laboratory Standards for the determination of MIC in duplicate [28]. 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 1.

In the first phase of screening against MTB, all the 3-heteroarylthioquinoline derivatives **5**–**7** showed good *in vitro* activity against MTB with MIC ranging from 3.2 to 55.9 μM. Four compounds (**5c**, **5d**, **5g** and **6d**) 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 **5c** (MIC: 3.5 μM) and **5d** (MIC: 3.2 μM) were found to be more potent against MTB. The other two series of quinolines **6a**–**g** and **7a**–**g**, however, were less potent than rifampicin, isoniazid, ciprofloxacin and ethambutol. 2-[2-(4-Bromophenyl)-4-phenyl-3-quinolyl]sulfanyl-5-methyl-1,3,4-thiadiazole (**5d**) 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-



Scheme 1. Synthesis of quinoline derivatives **5**–**7**.

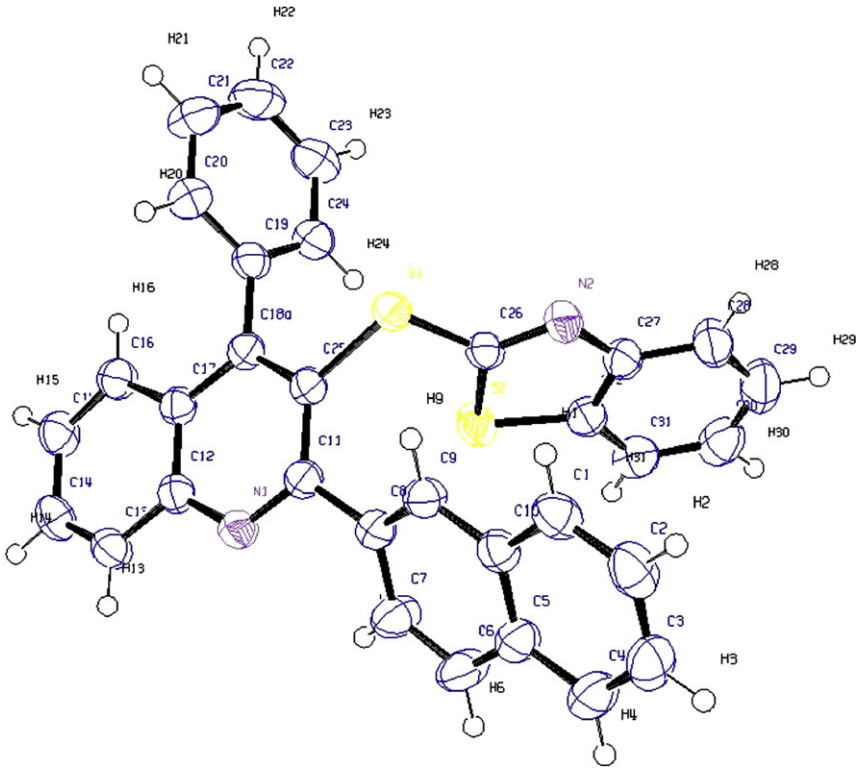


Fig. 4. ORTEP diagram of **6f**.

thiadiazole (**5c**), was also found to be more active with MIC of 3.5 μM against MTB and is 1.34 and 2.17 times more potent than ciprofloxacin and ethambutol respectively.

With respect to structure-MTB activity relationship, the data in Table 1 show that the substituents present in the 3-position of quinoline ring has a profound effect on the activity of **5**–**7**, the order of activity, in general, being 2-methyl-1,3,4-thiadiazole > benzo[*d*] thiazole > 2-phenyl-2*H*-tetrazole as revealed by the comparison of MIC data of compounds **5**–**7**. It is clear that quinolines with sulfur heterocyclic unit at position 3 are found to be more active than quinolines having a heterocycle with four nitrogen atoms at this position. Among the aryl groups in the series of compound **5**, the order of activity is 4-BrC_6H_4 > 4-ClC_6H_4 > 4-PhC_6H_4 > 2-naphthyl > 4-$MeOC_6H_4$ > 4-MeC_6H_4 > C_6H_5. In **5** and **6**, the presence of halogens in the aryl ring enhances the antimycobacterial activity as seen from the MIC values of **5c** (MIC: 3.5 μM), **5d** (MIC: 3.2 μM), **6d** (MIC: 5.9 μM) (Table 1).

2.2.2. Cytotoxicity

The cytotoxicity of the compounds **5c** and **5d** were studied *in vitro* using NIH 3T3 mouse embryonic fibroblasts cell line (NIH 3T3) by MTT assay [29]. MTT is a yellow colored 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 percentage cell viability was decreased with increasing the concentration of the both **5c** and **5d** (Fig. 5). However, the half maximal inhibitory concentration (IC_{50}) value determined by Graph Pad Prism software was found to be >1000 μM for both **5c** (1263 μM) and **5d** (2050 μM). This indicates that the synthesized compounds **5c** and **5d** are not toxic to the normal fibroblasts (NIH 3T3).

3. Conclusions

In conclusion, a simple and efficient procedure for the synthesis of novel 3-heteroarylthioquinoline derivatives in excellent yields has been developed using Friedlander annulation in the presence of $YbCl_3$ as a catalyst. These quinolines displayed good *in vitro* antimycobacterial activity against MTB. Both **5c** and **5d** did not produce any cytotoxicity on NIH 3T3 cells and showed the IC_{50} value of >1000 μM. This lack of cytotoxic potential of compounds **5c** and **5d**

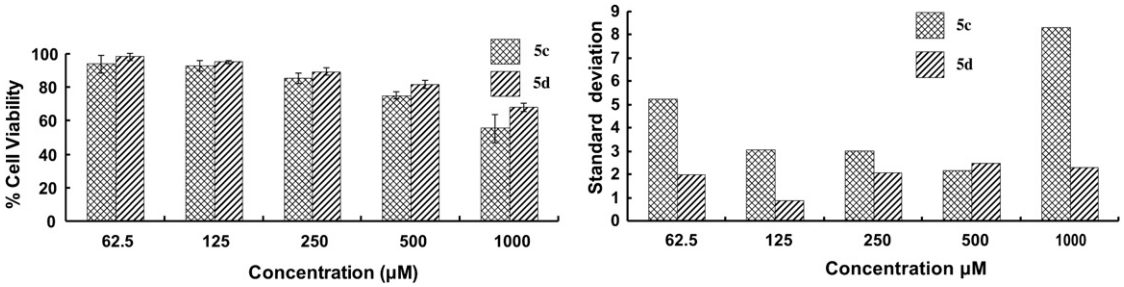


Fig. 5. Comparison of cytotoxicity on NIH 3T3 cells for compounds **5c** and **5d**.

are of great significance for their possible use in the treatment of MTB other than cancer.

4. Experimental

4.1. General methods

All melting points reported in this work were measured in open capillaries. The ^1H 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 δ 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. The antimycobial studies were carried out at Birla Institute of Technology & Science-Pilani, Hyderabad Campus, while the cytotoxic studies at K M C H College of Pharmacy, Coimbatore.

4.2. General procedure for quinoline derivatives (**5**–**7**)

A mixture of equimolar amount of 2-aminobenzophenone **1** (100 mol %, 2.3 mmol) and ketone **2**/**3**/**4** (100 mol%, 2.3 mmol) [30] 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 through silica gel column (10% ethyl acetate in petroleum ether) to afford the pure product **5**–**7**. Full characterization data for all the compounds (**5**–**7**) are given below.

4.2.1. 2,4-Diphenyl-3-quinolyl (5-methyl-1,3,4-thiadiazol-2-yl) sulphide (**5a**)

Isolated as colorless solid; ^1H NMR (300 MHz, $CDCl_3$) δ_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, $CDCl_3$) δ_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 $C_{24}H_{17}N_3S_2$: C, 70.04; H, 4.16; N, 10.21%. Found C, 69.99; H, 4.12; N, 10.26%.

4.2.2. 2-(4-Methylphenyl)-4-phenyl-3-quinolyl(5-methyl-1,3,4-thiadiazol-2-yl)sulfide (**5b**)

Isolated as colorless solid; ^1H NMR (300 MHz, $CDCl_3$) δ_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, $CDCl_3$) δ_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 $C_{25}H_{19}N_3S_2$: C, 70.56; H, 4.50; N, 9.87%. Found C, 70.50; H, 4.55; N, 9.92%.

4.2.3. 2-[2-(4-Chlorophenyl)-4-phenyl-3-quinolyl]sulfanyl-5-methyl-1,3,4-thiadiazole (**5c**)

Isolated as colorless solid; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 2.60 (s, 3H, CH_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, $CDCl_3$) δ_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 $C_{24}H_{16}Cl\ N_3S_2$: C, 64.63; H, 3.62; N, 9.42%. Found C, 64.59; H, 3.67; N, 9.46%.

4.2.4. 2-[2-(4-Bromophenyl)-4-phenyl-3-quinolyl]sulfanyl-5-methyl-1,3,4-thiadiazole (**5d**)

Isolated as colorless solid; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 2.59 (s, 3H, CH_3), 7.32 (dd, 2H, $J = 6.0$, 1.5 Hz, Ar–H), 7.46–7.52 (m, 9H, Ar–H), 7.76–7.82 (m, 1H, Ar–H), 8.19 (d, 1H, $J = 8.4$ Hz, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_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 $C_{24}H_{16}BrN_3S_2$: C, 58.78; H, 3.29; N, 8.57%. Found C, 58.74; H, 3.34; N, 8.61%.

4.2.5. 2-[2-(4-Methoxyphenyl)-4-phenyl-3-quinolyl]sulfanyl-5-methyl-1,3,4-thiadiazole (**5e**)

Isolated as colorless solid; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 2.57 (s, 3H, CH_3), 3.83, (s, 3H, OCH_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, $CDCl_3$) δ_C: 15.6, 55.3, 113.3, 122.9, 127.0, 127.1, 127.2, 128.2, 128.4, 129.1, 129.5, 130.7, 131.0, 132.6, 136.7, 147.9, 155.6, 159.9, 161.4, 165.1, 165.9. Anal. Calcd for $C_{25}H_{19}N_3OS_2$: C, 68.00; H, 4.34; N, 9.52%. Found C, 67.94; H, 4.39; N, 9.59%.

4.2.6. 2-Methyl-5-[2-(2-naphthyl)-4-phenyl-3-quinolyl]sulfanyl-1,3,4-thiadiazole (**5f**)

Isolated as colorless solid; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 2.46 (s, 3H, CH_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, $CDCl_3$) δ_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, 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 $C_{28}H_{19}N_3S_2$: C, 72.86; H, 4.15; N, 9.10%. Found C, 72.79; H, 4.22; N, 9.16%.

4.2.7. 2-(2-(Biphenyl-4-yl)-4-phenylquinolin-3-ylthio)-5-methyl-1,3,4-thiadiazole (**5g**)

Isolated as colorless solid; ^1H NMR (300 MHz, $CDCl_3$) δ_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, $CDCl_3$) δ_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 $C_{30}H_{21}N_3S_2$: C, 73.89; H, 4.34; N, 8.62%. Found C, 73.83; H, 4.41; N, 8.67%.

4.2.8. 1,3-Benzothiazol-2-yl(2,4-diphenyl-3-quinolyl)sulphide (**6a**)

Isolated as colorless solid; ^1H NMR (300 MHz, $CDCl_3$) δ_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, $CDCl_3$) δ_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 $C_{28}H_{18}N_2S_2$: C, 75.30; H, 4.06; N, 6.27%. Found C, 75.22; H, 4.12; N, 6.32%.

4.2.9. 1,3-Benzothiazol-2-yl[2-(4-methylphenyl)-4-phenyl-3-quinolyl]sulphide (**6b**)

Isolated as colorless solid; ^1H NMR (300 MHz, $CDCl_3$) δ_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, $CDCl_3$) δ_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 $C_{29}H_{20}N_2S_2$: C, 75.62; H, 4.38; N, 6.08%. Found C, 75.56; H, 4.46; N, 6.13%.

*4.2.10. 1,3-Benzothiazol-2-yl[2-(4-chlorophenyl)-4-phenyl-3-quinolyl]sulphide (**6c**)*

Isolated as colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ_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, $CDCl_3$) δ_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 $C_{28}H_{17}ClN_2S_2$: C, 69.91; H, 3.56; N, 5.82%. Found C, 69.85; H, 3.61; N, 5.89%.

*4.2.11. 1,3-Benzothiazol-2-yl[2-(4-bromophenyl)-4-phenyl-3-quinolyl]sulphide (**6d**)*

Isolated as colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ_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, $CDCl_3$) δ_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 $C_{28}H_{17}BrN_2S_2$: C, 66.40; H, 3.26; N, 5.33%. Found C, 66.33; H, 3.32; N, 5.39%.

*4.2.12. 2-[2-(4-Methoxyphenyl)-4-phenyl-3-quinolyl]sulfanyl-1,3-benzothiazole (**6e**)*

Isolated as colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ_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), 7.28–7.41 (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, $CDCl_3$) δ_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 $C_{29}H_{20}N_2OS_2$: C, 73.08; H, 4.43; N, 5.88%. Found C, 72.99; H, 4.49; N, 5.95%.

*4.2.13. 1,3-Benzothiazol-2-yl[2-(5,8-dihydro-2-naphthalenyl)-4-phenyl-3-quinolyl]sulphide (**6f**)*

Isolated as colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ_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, $CDCl_3$) δ_C: 120.6, 121.7, 122.5, 124.1, 125.9 (2C), 126.3, 126.8, 127.2, 127.3, 127.5 (2C), 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 $C_{32}H_{20}N_2S_2$: C, 77.39; H, 4.06; N, 5.64%. Found C, 77.32; H, 4.13; N, 5.70%.

*4.2.14. 2-(2-(Biphenyl-4-yl)-4-phenylquinolin-3-ylthio)benzo[d]thiazole (**6g**)*

Isolated as colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ_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, $CDCl_3$) δ_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 $C_{34}H_{22}N_2S_2$: C, 78.13; H, 4.24; N, 5.36%. Found C, 78.05; H, 4.30; N, 5.43%.

*4.2.15. 2,4-Diphenyl-3-[(1-phenyl-1H-1,2,3,4-tetrazol-5-yl) sulfanyl]quinoline (**7a**)*

Isolated as colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ_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, $CDCl_3$) δ_C: 120.1, 123.9, 127.0, 127.3, 127.4, 127.8, 128.2, 128.4, 128.5, 128.8, 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 $C_{28}H_{19}N_5S$: C, 73.50; H, 4.19; N, 15.31%. Found C, 73.42; H, 4.24; N, 15.38%.

*4.2.16. 2-(4-Methylphenyl)-4-phenyl-3-[(1-phenyl-1H-1,2,3,4-tetraazol-5-yl)sulfanyl]quinoline (**7b**)*

Isolated as colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.35 (s, 3H, CH_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 (ddd, 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, $CDCl_3$) δ_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 $C_{29}H_{21}N_5S$: C, 73.86; H, 4.49; N, 14.85%. Found C, 73.79; H, 4.56; N, 14.93%.

*4.2.17. 2-(4-Chlorophenyl)-4-phenyl-3-[(1-phenyl-1H-1,2,3,4-tetraazol-5-yl)sulfanyl]quinoline (**7c**)*

Isolated as colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ_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, Ar–H), 8.2 (d, 1H, J = 8.4 Hz, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 120.2, 123.7, 123.9, 127.1, 127.6, 128.1, 128.4, 128.7, 129.0, 129.4, 129.7, 130.1, 130.3, 131.5, 132.9, 134.7, 136.5, 138.5, 147.9, 153.6, 155.9, 160.6. Anal. Calcd for $C_{28}H_{18}ClN_5S$: C, 68.35; H, 3.69; N, 14.23%. Found C, 68.26; H, 3.76; N, 14.28%.

*4.2.18. 2-(4-Bromophenyl)-4-phenyl-3-[(1-phenyl-1H-1,2,3,4-tetraazol-5-yl)sulfanyl]quinoline (**7d**)*

Isolated as colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 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, 7.50, Ar–H), 7.73 (dd, 1H, J = 9.0, 2.4 Hz, Ar–H), 8.12 (d, 1H, J = 9.0 Hz, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 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 $C_{28}H_{18}BrN_5S$: C, 62.69; H, 3.38; N, 13.06%. Found C, 62.63; H, 3.45; N, 13.12%.

*4.2.19. 2-(4-Methoxyphenyl)-4-phenyl-3-[(1-phenyl-1H-1,2,3,4-tetraazol-5-yl)sulfanyl]quinoline (**7e**)*

Isolated as colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.77 (s, 3H, OCH_3), 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 55.2, 113.3, 120.3, 123.8, 126.9, 127.1, 127.2, 128.2, 128.5, 128.9, 129.2, 129.4, 129.6, 130.3, 131.1, 132.6, 132.9, 136.6, 147.9, 153.7, 155.6, 159.7, 161.4. Anal. Calcd for $C_{29}H_{21}N_5OS$: C, 71.44; H, 4.34; N, 14.36%. Found C, 71.50; H, 4.40; N, 14.45%.

*4.2.20. 2-(5,8-Dihydro-2-naphthalenyl)-4-phenyl-3-[(1-phenyl-1H-1,2,3,4-tetraazol-5-yl)sulfanyl]quinoline (**7f**)*

Isolated as colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 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 $C_{32}H_{21}N_5S$: C, 75.72; H, 4.17; N, 13.80%. Found C, 75.65; H, 4.22; N, 13.87%.

*4.2.21. 2-(Biphenyl-4-yl)-4-phenyl-3-(1-phenyl-1H-tetrazol-5-ylthio)quinoline (**7g**)*

Isolated as colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 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, $CDCl_3$) δ_C: 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 $C_{34}H_{23}N_5S$: C, 76.52; H, 4.34; N, 13.12%. Found C, 76.44; H, 4.40; N, 13.19%.

4.3. Anti-tubercular activity

Ten fold serial dilutions of each test compounds **5a**–**g**, **6a**–**g** and **7a**–**g** were incorporated into Middle brook 7H11 agar medium with OADC Growth Supplement. Inoculum of *M. tuberculosis* H37Rv were prepared from fresh Middle brook 7H11 agar slants with OADC Growth Supplement adjusted to 1 mg/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 μL 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 °C, and final readings were recorded after 28 days. The minimum inhibitory concentration (MIC) is defined as the minimum concentration of compound required to give complete inhibition of bacterial growth.

4.4. Cytotoxicity

The NIH 3T3 mouse embryonic fibroblasts line (NIH 3T3) was obtained from National Center 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 °C, 5% CO_2, 95% air and 100% relative humidity. Maintenance cultures were passaged weekly, and the culture medium was changed twice a week.

The monolayer cells were detached with trypsin-ethylenediaminetetraacetic acid to make single cell suspensions and viable cells were counted using a hemocytometer and diluted with medium with 5% FBS to give final density of 1 x 10^5 cells/mL. One hundred microliters 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 °C, 5% CO_2, 95% air and 100% relative humidity. After 24 h, the cells were treated with serial concentrations of the compounds **5c** and **5d**. They were initially dissolved in neat dimethylsulfoxide (DMSO) and further diluted in serum free medium to produce various concentrations. One hundred microliters 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% CO_2, 95% air and 100% relative humidity for 48 h. The medium containing without samples were served as control. Triplicate was maintained for all concentrations. After 48 h, the cells in each well were quantified by MTT assay [29]. Briefly, 15 μl of MTT (5 mg/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:

$$\%\ \text{Cell viability} = [\text{A}]\text{Test}/[\text{A}]\text{Control} \times 100$$

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Appendix. Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.ejmech.2011.07.046.

References

[1] D.A. Fidock, Nature 465 (2010) 297–298.
[2] T.S. Balganesh, P.M. Alzari, S.T. Cole, Trends Pharmacol. Sci. 29 (2008) 576–581.
[3] D.B. Young, M.D. Perkins, K. Duncan, C.E. Barry, J. Clin. Invest. 118 (2008) 1255–1265.
[4] A.M. Ginsberg, M. Spigelman, Nat. Med. 13 (2007) 290–294.
[5] C. Dye, B.G. Williams, Science 328 (2010) 856–861.
[6] W.J. Burman, Clin. Infect. Dis. 50 (2010) S165–S172.
[7] P. LoBue, Curr. Opin. Infect. Dis. 22 (2009) 167–173.
[8] Y. Zhang, K. Post-Martens, S. Denkin, Drug Discov. Today 11 (2006) 21–27.
[9] E.D. Brown, G.D. Wright, Chem. Rev. 105 (2005) 759–774.
[10] (a) M. Balasubramanian, J.G. Keay, in: A.R. Katritzky, C.W. Rees, E.F.V. Scriven (Eds.), Comprehensive Heterocyclic Chemistry II, vol. 5, Pergamon, New York, 1996, pp. 245–266;
(b) J.P. Michael, Nat. Prod. Rep. 14 (1997) 605–618.
[11] (a) A. Kumar, K. Srivastava, R. Kumar, S.K. Puri, P.M.S. Chauhan, Bioorg. Med. Chem. Lett. 20 (2010) 7059–7063;
(b) R. Arancibia, F. Dubar, B. Pradines, I. Forfar, D. Dive, A.H. Klahn, C. Biot, Bioorg. Med. Chem. 18 (2010) 8085–8091.
[12] P.A. Leatham, H.A. Bird, V. Wright, D. Seymour, A. Gordon, Eur. J. Rheumatol. Inflamm. 6 (1983) 209–211.
[13] W. A. Denny, W. R. Wilson, D. C. Ware, G. J. Atwell, J. B. Milbank, R. J. Stevenson. U.S. Patent 7064117 (2006).
[14] V.R. Solomon, C.H.H. Lee, Bioorg. Med. Chem. 18 (2010) 1563–1572.
[15] A. Mahamoud, J. Chevalier, A. Davin-Regli, J. Barbe, J.-M. Pages, Curr. Drug Targets 7 (2006) 843–847.
[16] (a) W.D. Wilson, M. Zhao, S.E. Patterson, R.L. Wydra, L. Janda, L. Strekowski, Med. Chem. Res. 2 (1992) 102–110;
(b) L. Strekowski, J.L. Mores, V.A. Honkan, A. Czarny, M.T. Cegla, S.E. Patterson, R.L. Wydra, R.F. Schinazi, J. Med. Chem. 34 (1991) 1739–1746.
[17] (a) Guidelines for the Management of Drug-Resistant Tuberculosis WHO/TB/96-210 (Rev.1). World Health Organization, Geneva, 1997;
(b) A.S. Ginsburg, J.H. Grosset, W.R. Bishai, Lancet Infect. Dis. 3 (2003) 432–442.
[18] S. Jayaprakash, Y. Iso, B. Wan, S.G. Franzblau, A.P. Kozikowski, Chem. Med. Chem. 1 (2006) 593–597.
[19] L.E. Bermudez, P. Kolonoski, M. Wu, P.A. Aralar, C.B. Inderlied, L.S. Young, Antimicrob. Agents Chemother. 43 (1999) 1870–1874.
[20] L.E. Bermudez, P. Kolonoski, L.E. Seitz, M. Petrofsky, R. Reynolds, M. Wu, L.S. Young, Antimicrob. Agents Chemother. 48 (2004) 3556–3558.
[21] L.E. Bermudez, P. Kolonoski, M. Petrofsky, M. Wu, C.B. Inderlied, L.S. Young, J. Infect. Dis. 187 (2003) 1977–1980.
[22] J. Mao, Y. Wang, B. Wan, A.P. Kozikowski, S.G. Franzblau, Chem. Med. Chem. 2 (2007) 1624–1630.
[23] M. Pieroni, A. Lilienkampf, B. Wan, Y. Wang, S.G. Franzblau, A.P. Kozikowski, J. Med. Chem. 52 (2009) 6287–6296.
[24] K. Andries, P. Verhasselt, J. Guillemont, W.H. Gohlmann, J. Neefs, J. Winkler, P. Timmerman, M. Zhu, E. Lee, P. Williams, D. Chaffoy, E. Huitric, S. Hoffner, E. Cambau, C. Pernot, N. Lounis, V. Jarlier, Science 307 (2005) 223–227.
[25] (a) R. Manikannan, S. Muthusubramanian, P. Yogeeswari, D. Sriram, Bioorg. Med. Chem. Lett. 20 (2010) 3352–3355;
(b) R. Manikannan, R. Venkatesan, S. Muthusubramanian, P. Yogeeswari, D. Sriram, Bioorg. Med. Chem. Lett. 20 (2010) 6920–6924.
[26] M. Barbero, S. Bazzi, S. Cadamuro, S. Dughera, Tetrahedron. Lett. 51 (2010) 2342–2344 references cited therein.
[27] Crystallographic data (excluding structure factors) for quinoline 6f in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 798947. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
[28] National Committee for Clinical Laboratory Standards, Antimycobacterial Susceptibility Testing for *Mycobacterium tuberculosis*, Proposed Standard M24-T. National Committee for Clinical Laboratory Standards, Villanova, PA, 1995.
[29] (a) T. Mosmann, J. Immunol. Methods 65 (1983) 55–63;
(b) A. Monks, D. Scudiero, P. Skehan, R. Shoemaker, K. Paull, D. Vistica, C. Hose, J. Langley, P. Cronise, A. Vaigro-Wolff, H. Campbell, J. Mayo, M. Boyd, J. Natl. Cancer Inst. 83 (1991) 757–766.
[30] (a) S. Saravanan, S. Muthusubramanian, S. Vasantha, S. Sivakoluthu, P. Raghavaiah, J. Sulfur Chem. 28 (2007) 181–199;
(b) L. Yimin, Z. Wei, QSAR Comb. Sci. 25 (2006) 728–731;
(c) L. Eberhard, R. Dieter, Z. Chem. 15 (1975) 351–352.