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Original article

New quinolin-4-yl-1,2,3-triazoles carrying amides, sulphonamides and amidopiperazines as potential antitubercular agents

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ABSTRACT

Three new series of quinoline-4-yl-1,2,3-triazoles carrying amides, sulphonamides and amidopiperazines were synthesized through multi-step reactions. The required intermediate, [1-(6-methoxy-2-methylquinolin-4-yl)-1*H*-1,2,3-triazol-4-yl]methanol **(2)** was prepared by treating 4-azido-6-methoxy-2-methylquinoline **(1)** with propargyl alcohol. Three different series of compounds were synthesized from this intermediate. All the newly synthesized compounds were characterized by spectral and elemental analyses. The structure of **2** was confirmed by X-ray crystallographic study. Further, the title compounds were evaluated for their *in vitro* anti-bacterial activity against five different bacterial strains and anti-mycobacterial activity against *Mycobacterium tuberculosis* H37Rv, *Mycobacterium smegmatis* (ATCC 19420) and *Mycobacterium fortuitum* (ATCC 19542). Title compounds, **6a**, **6d**, **6i**, **6j**, **7e**, **10a** and **10i** were found to be active against *Mycobacterium tuberculosis* H37Rv strain and could be lead molecules of interest.

1. Introduction

Tuberculosis (TB) is a lung infection caused mainly by *Mycobacterium tuberculosis* (Mtb). It is considered to be one of the most contagious and deadly diseases and is a major threat for public health. In combination with the HIV-1 infection tuberculosis is today amongst the biggest threat to the mankind. A large proportion of these new cases and deaths occur mostly in developing countries and the number of HIV-positive patients coinfected with Mtb is constantly rising [1]. As a result, the TB situation may become even worse with the spread of HIV-1 worldwide, emergence of multi-drug (isoniazid and rifampin) resistant (MDR-TB) and the extensively drug resistant (XDR-TB) strains.

It has been established that heterocyclic compounds play an important role in designing new class of structural entities for medicinal applications. Among pharmacologically important heterocyclic compounds, quinoline and its derivatives are significant because of their wide spectrum of biological activities and their presence in naturally occurring compounds. They have been shown to possess antimalarial [2–4], antibiotic [5,6], anticancer [7], anti-inflammatory [8], antihypertensive [9], tyrokinase PDGF-RTK inhibition [10] and anti-HIV [11,12] properties because of which a large number of currently available drugs contain quinoline nucleus as an important pharmacophore. Consequently, the quinoline skeleton is being chosen for the design of new bioactive molecules by a large number of researchers.

Over the past two decades, 1,2,3-triazole and its derivatives have attracted continued interest in the medicinal field owing to their varied biological activities such as anti-bacterial [13], antifungal [14], anti-allergic [15–17], anti-HIV [18], anticonvulsant [19], anti-inflammatory [20,21] and β -lactamase inhibition propeties [22].It is quite obvious that the favorable properties of 1,2,3-triazole ring like moderate dipole character, hydrogen bonding capability, rigidity and stability under *in vivo* conditions are responsible for their enhanced biological activities [23].

It is evident from the literature that quinoline-based compounds are known to exhibit excellent anti-TB properties [24–28]. Besides, some azole derivatives have also been shown to possess strong inhibitory activities *in vitro* and *in vivo* against *M. tuberculosis* strains [29]. Azoles may be regarded as a new class of effective antitubercular agents, which are reported to inhibit bacteria by blocking the biosynthesis of certain bacterial lipids and/or by additional mechanisms [30]. Among the azole derivatives,

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triazoles are also known to exhibit antimycobacterial properties [31]. An extensive literature survey reveals that till date enough efforts have not been made to combine quinoline and 1,2,3-triazoles moieties in a single molecular scaffold and to study its antitubercular activity. It has been established that more efficacious antimicrobial compounds can be designed by joining two or more biologically active heterocyclic systems together in a single molecular framework [32].

The limitations of the existing anti-TB drugs are many which include their drug resistance, the serious side effects, lack of efficacy and the treatment of resistant strains requires a prolongation of the therapy that employs more toxic drugs, increases the financial burden and thus making TB a vicious cycle. These factors necessitate the search for new antimycobacterial agents which are synthetically feasible, lacking side effects, and have physicochemical properties allowing oral administration. Therefore, it is inevitable to discover and develop new drugs for treatment of dreadful tuberculosis that has spread worldwide now.

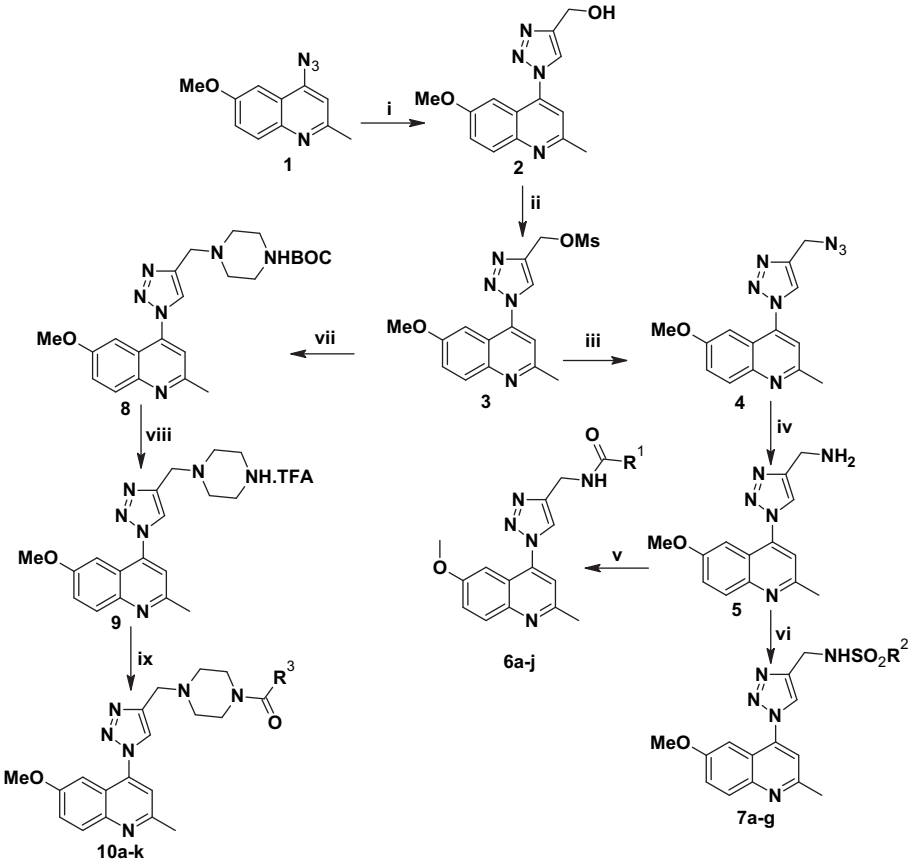
Against this background, and as a part of our continued research for new antitubercular agents, we have designed new bi-heterocyclic systems containing 1,2,3-triazole ring at position-4 of quinoline ring linked with interesting pharmocophores like amides, sulphonamides and amidopiperazine, hoping that new molecules would exhibit enhanced biological activity. In this communication, we herein report the synthesis of 1-[quinolin-4-yl)-1H-1,2,3-triazol-4-yl]methylamides (**6a**–**j**), 1-[1-(quinolin-4-yl)-1H-1,2,3-triazol-4-yl] methyl sulphonamides (**7a**–**g**), 4-[4-(piperazin-1-ylmethyl)-1H-1,2,3-triazol-1-yl]quinoline amides (**10a**–**k**) and evaluation of their *in vitro* anti-bacterial activity and antituberculosis activity. Further, single crystal X-ray study of compound **2** has been reported. It has been envisioned that these structural modifications could lead to a process of finding a molecule of interest for further exploration.

2. Results and discussion

2.1. Chemistry

The general synthesis of title compounds **6a**–**j, 7a**–**g** and **10a**–**k** is outlined in Scheme 1. The procedure for the synthesis of 4-azido-6-methoxy-2-methylquinoline (**1**) has been reported in our earlier work [33]. As mentioned in Scheme 1, the intermediate **2** was obtained by heating a mixture of 4-azido-6-methoxy-2-methylquinoline (**1**) and propargyl alcohol in dry THF/toluene (1:1) at 120 °C for 6 h. The intermediate **2** was then conveniently converted to its mesyl derivative **3**, which was further used as a key intermediate to obtain three different series of title compounds. The azide derivative **4** was obtained from the compound **3**, by treating it with sodium azide in DMF at 25 °C. It was further reduced with hydrogen under pressure using Pd/C as a catalyst to get 1-[1-(6-ethoxy-2-methylquinolin-4-yl)-1*H*-1,2,3-triazol-4-yl]methanamine (**5**) in good yield.

The title compounds, **6a**–**j** were synthesized by reacting the amine scaffold **5** with alkyl and substituted aryl acid chlorides, while the compounds **7a**–**g** were obtained by treating the compound **5** with substituted aryl sulfonyl chlorides at 0 °C in dichloromethane using pyridine as a base. In another reaction sequence the mesyl derivative **3** was treated with *tert*-butyl piperazine-1-carboxylate in acetonitrile to obtain an intermediate **8**, which was later converted to the intermediate **9** by treating it with trifluoroacetic acid in dichloromethane at 0 °C. The target



Scheme 1. 1-[1-(6-methoxy-2-methylquinolin-4-yl)-1*H*-1,2,3-triazol-4-yl]methanamine derivatives (i) Propargyl alcohol, THF/Toluene (1:1), 120 °C, 6 h (ii) MsCl, DCM, 25 °C, 2 h (iii) Sodium azide, DMF, 25–26 °C, 2 h (iv) Pd/C, MeOH, 2 h (v) R^1COCl, dichloromethane, pyridine, 0–25 °C, 1 h (vi) R^2SO_2Cl, pyridine, DCM, 0–25 °C, 1 h (vii) Piperazine-1-carboxylic acid tert-butyl ester, CH_3CN, 80 °C, 1 h (viii) TFA, dichloromethane, 0 °C and then 26–30 °C, 4 h (ix) dichloromethane, triethylamine, R^3COCl, 0 °C, 1 h.

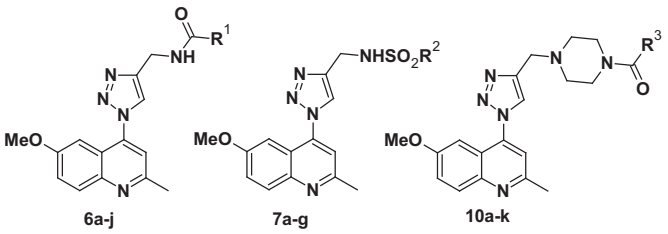
compounds **10a**–**k** were synthesized by reacting 6-methoxy-2-methyl-4-[4-(piperazin-1-ylmethyl)-1*H*-1,2,3-triazol-1-yl] quinoline.TFA salt (**9**) with alkyl and substituted aryl acid chlorides in presence of triethylamine in dichloromethane medium at 0 °C. The crude product was purified on a Biotage parallel column purifier using ethyl acetate/pet ether (4:1) to methanol (2–4%) in dichloromethane as eluant. The newly synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, LCMS and elemental analyses.

Formation of the intermediate **2** from azide intermediate **1** was confirmed by spectral studies. In its FTIR spectrum, a broad band was observed at 3595 cm^{-1} indicating the presence of OH group.-Further, its ^{1}H NMR spectrum showed a singlet at δ 8.66 ppm for an aromatic proton of the triazole ring. Also, a doublet was observed at δ 4.69 ppm accounting for the two methylene protons of 1,2,3-triazole-4yl methanol. The cyclization was further confirmed by its ^{13}C NMR spectrum, which showed two peaks at δ 116.98 and 150.27 ppm for the carbons belonging to triazole ring and side chain. Finally, the cyclization was established by its mass spectrum, wherein the compound **2** showed molecular ion peak at *m*/*z* 271 (M+1), confirming its molecular formula $C_{14}H_{14}N_4O_2$. This was further evidenced by a single crystal X-ray crystallographic analysis of the intermediate **2**.

Conversion of hydroxyl derivative **2** to mesylate compound **3** was confirmed by its ^{1}H NMR spectral study. In its ^{1}H NMR spectrum, methyl protons of mesylate group resonated at δ 3.32 ppm (OSO_2Me). Further, the formation of amine scaffold **5** from intermediate **4** was evidenced by its spectral data. Its FTIR spectrum showed a broad peak at 3425 cm^{-1} due to NH stretching. In its ^{1}H NMR spectrum, the appearance of a broad peak at δ 4.35 ppm indicates the presence of amine which disappeared on D_2O exchange. Finally its structure was confirmed by its mass spectrum, where it showed a molecular ion peak at m/z 270.13 (M+1) which corresponds to its molecular formula $C_{14}H_{15}N_5O$.

The formation of title compound **6a** was confirmed by spectral analysis. The ^{1}H NMR spectrum of compound **6a** showed a singlet

Table 1
Characterization and anti-bacterial screening data of compounds **6a**–**j**, **7a**–**g** and **10a**–**k**



Cpd[a]	$R^1/R^2/R^3$	Mol. For. M.Wt.	(%)[b]	clogP[c]	MIC(μg/mL)				
					S.a[d]	*S.p*[e]	*P.a*[f]	*K.p*[g]	*E.c*[h]
6a	Acetyl	$C_{16}H_{17}N_5O_2$311.33	90	1.70	0.4	0.2	0.2	0.1	0.1
6b	Cyclopropyl	$C_{18}H_{19}N_5O_2$337.37	87	2.42	0.4	0.4	1.6	0.2	0.4
6c	Cyclobutyl	$C_{19}H_{21}N_5O_2$351.40	80	2.84	1.6	0.8	0.8	1.6	1.6
6d	4-Fluoro benzoyl	$C_{21}H_{18}FN_5O_2$391.39	90	3.76	0.8	0.2	0.2	0.2	0.2
6e	2-Fluoro benzoyl	$C_{21}H_{18}FN_5O_2$391.39	50	3.76	0.8	0.2	0.4	0.2	0.4
6f	2-Chloro benzoyl	$C_{21}H_{18}ClN_5O_2$407.85	76	4.16	1.6	3.12	6.25	3.12	3.12
6g	4-Ethyl benzoyl	$C_{23}H_{23}N_5O_2$401.46	69	4.50	3.12	3.12	6.25	3.12	3.12
6h	4-Methyl benzoyl	$C_{22}H_{21}N_5O_2$387.43	92	4.09	1.6	0.8	6.25	3.12	3.12
6i	4-Methoxy benzoyl	$C_{22}H_{21}N_5O_3$403.43	87	3.47	0.8	0.4	0.4	0.1	0.1
6j	4-Trifluoro methylbenzoyl	$C_{22}H_{18}F_3N_5O_2$441.40	78	4.52	0.4	0.2	0.4	0.2	0.4
7a	4-Fluoro benzene	$C_{20}H_{18}FN_5O_3S$ 427.45	87	3.60	0.4	0.4	0.8	3.12	3.12
7b	2-Trifluoro methylbenzene	$C_{21}H_{18}F_3N_5O_3S$ 477.45	79	4.36	0.8	0.4	0.4	0.4	0.2
7c	3,4-Dichloro benzene	$C_{20}H_{17}Cl_2N_5O_3S$ 478.35	67	4.56	1.6	3.12	12.5	3.12	12.5
7d	4-Methyl benzene	$C_{21}H_{21}N_5O_3S$ 423.48	85	3.93	3.12	6.25	6.25	6.25	6.25
7e	4-Methoxy benzene	$C_{21}H_{21}N_5O_4S$ 439.48	96	3.31	6.25	1.6	1.6	1.6	3.12
7f	4-Ethyl benzene	$C_{22}H_{23}N_5O_3S$ 437.51	78	4.34	6.25	6.25	12.5	6.25	6.25
7g	Benzene	$C_{20}H_{19}N_5O_3S$ 409.46	86	3.44	12.5	6.25	6.25	6.25	6.25
10a	Acetyl	$C_{20}H_{24}N_6O_2$380.44	91	1.69	0.4	0.2	0.2	0.1	0.1
10b	Cyclopropyl	$C_{22}H_{26}N_6O_2$406.21	87	2.42	0.8	0.4	0.4	0.2	0.4
10c	Cyclobutyl	$C_{23}H_{28}N_6O_2$420.50	80	2.83	1.6	1.6	0.8	3.12	1.6
10d	4-Fluoro benzoyl	$C_{25}H_{25}FN_6O_2$460.50	90	3.75	0.8	0.4	1.6	0.8	0.8
10e	2-Fluoro benzoyl	$C_{25}H_{25}FN_6O_2$460.50	50	3.75	0.8	0.4	3.12	1.6	1.6
10f	2-Chloro benzoyl	$C_{25}H_{25}ClN_6O_2$476.95	76	4.15	3.12	3.12	3.12	3.12	6.25
10g	4-Ethyl benzoyl	$C_{27}H_{30}N_6O_2$470.56	69	4.50	6.25	6.25	6.25	3.12	3.12
10h	4-Methyl benzoyl	$C_{26}H_{28}N_6O_2$387.43	92	4.08	6.25	6.25	12.5	12.5	6.25
10i	4-Methoxy benzoyl	$C_{26}H_{28}N_6O_3$403.43	87	3.46	0.8	1.6	3.12	1.6	0.4
10j	Benzoyl	$C_{25}H_{26}N_6O_2$442.51	78	3.59	0.8	0.8	0.4	0.4	0.4
10k	3,4-Dichloro benzoyl	$C_{25}H_{24}Cl_2N_6O_2$511.40	65	4.71	6.25	0.8	0.8	0.8	3.12
CIP	Ciprofloxacin	–	–	–	1.0	0.4	0.4	0.05	0.05

[a] Compound.
[b] Isolated yield.
[c] CHEMDRAW 8.
[d] *Staphylococcus aureus* (ATCC-25923).
[e] *Streptococcus Pyogenes*.
[f] *Pseudomonas aeruginosa* (ATCC-27853).
[g] *Klebsiella pneumoniae*.
[h] *Escherichia coli* (ATCC-25922).

for three methyl protons of the acetyl group at δ 2.05 ppm whereas, the NH proton of the amide group resonated at δ 6.42 ppm. Furthermore, in its ^{13}C NMR spectrum the carbonyl carbon resonated at 174.81 ppm which confirms the presence of an amidic carbon. Its structure was further evidenced by its mass spectrum, where it showed a mass peak of 312.3 (M+1) which is matching to its molecular formula $C_{16}H_{17}N_5O_2$. The spectral data of all other intermediates and title compounds, **6a–j** and **7a–g** are given in experimental section.

Similarly, the formation of title compound **10h** was confirmed by its spectral data. In its ^{1}H NMR spectrum, three protons of the CH_3 group of 4-methylbenzoyl moiety were found to resonate at δ 2.43 ppm. The four protons of piperazine ring appeared at δ 2.58, while other four protons resonated at δ 3.38–3.41 and 3.65–3.68 ppm respectively. Its structure was further confirmed by its ^{13}C NMR spectrum, wherein it showed a peak at δ 169.73 ppm which corresponds to the carbonyl carbon of the amide. This was also evidenced by its FTIR spectrum where a strong band was seen at 1645 cm^{-1} that corresponds to the carbonyl group. Further, its structure was confirmed by its mass spectrum, which showed a base peak at 457.23 (M+1) matching with its molecular formula $C_{26}H_{28}N_6O_2$. The spectral data of the title compounds, **10a–k** are listed in experimental section. The characterization data and the anti-bacterial screening data of the title compounds are summarized in Table 1.

2.2. Biological activity

All the title compounds were screened for their *in vitro* antibacterial and antitubercular properties following standard methods.

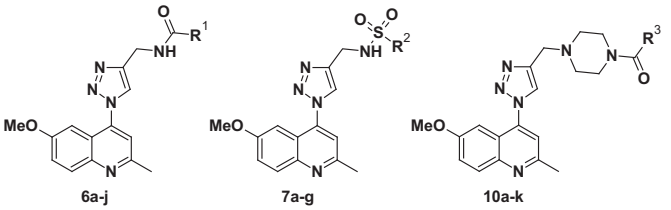
2.2.1. Antibacterial study

Antibacterial activity of title compounds were investigated against five different bacterial strains, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae and Escherichia coli* using ciprofloxacin as reference, by serial dilution method. Table 1 summarizes the anti-bacterial screening results (MIC μg/mL) of tested compounds in comparison with that of the standard.

2.2.2. Antitubercular study

Based on the promising results from the anti-bacterial screening, title compounds were further tested for their both preliminary and second level *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv, *Mycobacterium smegmatis* (ATCC 19420) and *Mycobacterium fortuitum* (ATCC 19542) using isoniazid (INH) and rifampicin (RIF) as standards. The results of preliminary and second level antimycobacterial screening of the tested compounds are tabulated in Table 2.

Table 2
Preliminary and second level *in vitro* antimycobacterial screening data of the title compounds, **6a-j, 7a-g and 10a-k**.



Cpd[a]	Preliminary *in vitro* screening results; MIC(μg/mL)				Second level screening results; MIC(μg/mL)		
	MTB[b]	MS[c]	MF[d]	%[e]	MTB	MS	MF
6a	1	10	10	95	0.625	10	10
6b	1	100	100	90	1.25	–	–
6c	10	100	100	85	10	–	–
6d	1	10	100	90	0.625	10	–
6e	1	100	100	90	1.25	–	–
6f	10	100	100	80	10	–	–
6g	100	100	100	80	–	–	–
6h	100	100	100	–	–	–	–
6i	1	10	10	95	0.625	5	10
6j	1	10	10	95	0.625	10	5
7a	1	100	100	85	1.25	–	–
7b	1	100	10	90	1.25	–	10
7c	100	100	100	–	–	–	–
7d	10	100	100	85	10	–	–
7e	1	10	10	90	0.625	10	10
7f	100	100	100	–	–	–	–
7g	100	100	100	–	–	–	–
10a	1	10	100	95	0.625	10	–
10b	10	100	100	90	5	–	–
10c	10	100	100	90	10	–	–
10d	1	1	10	90	1.25	1.25	10
10e	1	10	100	90	1.25	5	–
10f	100	100	100	–	10	–	–
10g	100	100	100	–	–	–	–
10h	100	100	100	–	–	–	–
10i	1	10	10	90	0.625	5	10
10j	10	100	100	85	10	–	–
10k	10	100	100	85	5	–	–
INH[f]	0.7	50	12.5	95	0.7	50	12.5
RIF[g]	0.5	1.5	1.5	95	0.5	1.5	1.5

[a] Compound.
[b] *Mycobacterium tuberculosis* H37Rv.
[c] *Mycobacterium smegmatis* (ATCC 19420).
[d] *Mycobacterium fortuitum* (ATCC 19542).
[e] Percentage of inhibition against *M. tuberculosis H37Rv*.
[f] Isoniazid.
[g] Rifampicin, '–' Not detected.

Table 3
Crystal data and measurement details for compound **2**.

Crystal data	
Empirical formula	$C_{14}H_{14}N_4O_2$
Formula weight	270.29
Crystal system	Triclinic
Crystal dimension	0.18 mm × 0.18 mm × 0.16 mm
Space group	P1
a(Å)	8.0203(5)
	8.0203(5)
	8.0203(5)
b(Å)	9.6239(6)
c(Å)	10.3396(7)
Volume (Å^3)	661.21(7)
Angle α, β, γ	101.995(4), 110.072(3), 109.012(3)
Z	2
Crystal density, g/cm^3	1.358
F_{000}	284
μ (mm^{-1})	0.095
Absorption coefficient	0.09
Temperature (T)	296(2)
Radiation wavelength	0.71073
Radiation type	MoKα
Radiation source	Fine-focus sealed tube
Radiation monochromator	Graphite
h_{min}	−11
h_{max}	11
k_{min}	−13
k_{max}	13
l_{min}	−14
l_{max}	14
Reflns (Fo)	3917
Structure refinement	SHELXL-97

2.3. X-ray crystallographic study of compound **2**

The X-ray crystallographic analysis of the intermediate **2** was carried out on a colorless plate crystal, with approximate dimensions 0.18 mm × 0.18 mm × 0.16 mm, grown from the slow evaporation of a dilute ethanol solution at room temperature. The crystal structure solution was worked out by full matrix least-squares method using SHELXL97. All the atoms were located in different Fourier maps and refined isotropically, using a riding model and all the projections were generated using ORTEP. The details of the crystal data and refinement are shown in Table 3. Also the single crystal image for compound **2** is given in Fig. 1.

2.4. Biological results

The anti-bacterial screening data of compounds **6a**–**j**, **7a**–**g** and **13a**–**k** displayed promising activities against all the tested bacterial strains at MIC 0.1–12.5 μg/mL concentrations. From the screening results, it has been observed that **6a**, **6d**–**e**, **6i**–**j**, **7b** and **10a**–**b** are the active compounds against all the three Gram positive bacterial strains, viz. *S. aureus*, *S. pyogenes*, *P. aeruginosa* at 0.2–0.8 μg/mL concentrations whereas the compounds **6b**, **7a** and **10d**–**e** are active against *S. aureus and S. pyogenes* at 0.4–0.8 μg/mL concentrations. Similarly, the compounds **6a**, **6i** and **10a** displayed substantial activity at 0.1 μg/mL concentrations against *K. pneumoniae and E. coli* strains whereas **6b**, **6d**–**e**, **6j** and **10b** is active at 0.2 μg/mL against *K. pneumoniae.* On similar lines, the compounds **6b**, **6d**–**e**, **6j**, **7b**, **10b** and **10i**–**j** exhibited promising activity against *E. coli* at 0.2–0.4 μg/mL concentrations.

The active compounds, **6a**, **6d**, **6e**, **6i**–**j**, **7b** and **10a**–**b** which showed promising activity against all the Gram positive bacterial strains comprised of important pharmacophoric groups like acetyl, fluoro, methoxy, trifluoromethyl, cyclopropyl groups in their structures are responsible for substantial activity.

The newly synthesized title compounds were further screened against three different TB strains. Initially the compounds were tested at 1, 10 and 100 μg/mL concentrations. The compounds, **6a**–**f**, **6i**–**j**, **7a**–**b**, **7d**–**e**, **10a**–**e** and **10i**–**k** are active at 1 and 10 μg/mL concentrations. These compounds were further taken for second level screening with concentration ranging from 0.3125 to 5 μg/mL. In the second level testing, the compounds **6a**, **6d** and **6i** showed promising activity against *M. tuberculosis H37Rv* at 0.625 μg/mL. In addition the title compounds **6a**, **6d** and **6i**–**j** are active against *M. smegmatis* at 5 and 10 μg/mL and also **6a** and **6i**–**j** are the active compounds against *M. fortuitum* between 5 and 10 μg/mL and showed significant activity than the reference compound isoniazid (MIC = 0.7 μg/mL against *Mycobacterium tuberculosis* H37Rv, 50 μg/mL against *Mycobacterium smegmatis* and 12.5 μg/mL against *Mycobacterium fortuitum).* Among the sulfonamide derivatives (**7a**–**g**), **7e** displayed promising activity at 0.625 μg/mL against *Mycobacterium tuberculosis* H37Rv and active at 10 μg/mL against *M. smegmatis* and *M. fortuitum*.

Among the amidopiperazines (**10a**–**k**), the compounds **10a** and **10i** showed substantial activity at 0.625 μg/mL against *Mycobacterium tuberculosis* H37Rv. Further the compounds **10a**, **10d**–**e** and **10i** were more potent than isoniazid against *M. smegmatis*. Furthermore, the compound **10d** showed significant activity at 1.25 μg/mL in comparison to rifampicin (RIF) whose MIC value is 1.5 μg/mL against *M. smegmatis*. Similarly the compounds **10d** and **10i** showed activity at 10 μg/mL against *M. fortuitum.*

The promising antitubercular activity of **6a**, **6d**, **6i**–**j** and **7e** is mainly due to the presence of amide derivatives carrying simple pharmacophoric groups like acetyl, fluoro, methoxy and trifluoromethyl. Similarly the significant activity of **10a**, **10d**–**e** and **10i** can be attributed to the amidopiperazines carrying pharmacophoric groups like acetyl, fluoro, methoxy groups in the title molecules. It is well known from the literature that the presence of these groups imparts a variety of properties including steric, electronic properties, enhanced binding interactions, metabolic stability, changes in physical properties and selective reactivities [34,35].

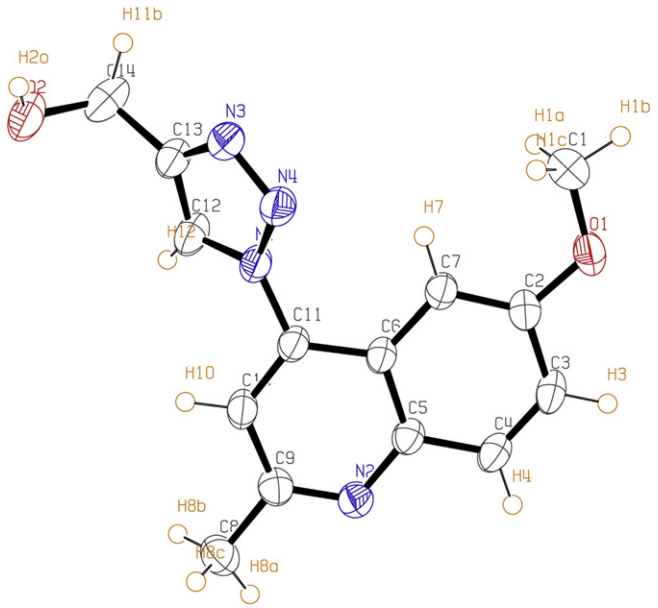


Fig. 1. ORTEP diagram showing the X-ray crystal structure of compound **2**.

3. Conclusion

In our present research work we have accomplished the synthesis of twenty eight new derivatives of quinoline-4-yl-1,2,3-triazoles carrying amides, sulphonamide and piperazine moieties. The new chemical entities were characterized by spectral and elemental analyses. The title compounds were tested for their *in vitro* anti-bacterial properties against five different bacterial strains, viz., ATCC-25922 *Escherichia coli*, ATCC-25923 *Staphylococcus aureus*, ATCC-27853 *Pseudomonas aeruginosa*, clinical isolate of *Klebsiella pneumoniae* and *S. Pyogenes* and also antimycobacterial activity against three different strains, viz. *M. tuberculosis H37Rv*, *M. smegmatis* and *M. fortuitum*. Among the tested compounds, **6a**, **6d**, **6i**, **6j**, **7e**, **10a** and **10i** showed significant antitubercular activity when compared to isoniazid. The substantial activity of these compounds may be attributed to the important pharmacophoric groups present in the molecule, viz., acetyl, methoxy, trifluoromethyl and fluoro group. Further, **6a**, **6i**, **6j**, **7e** and **10i** were active against all the three mycobacterial strains and were more potent than the isoniazid. In summary these compounds from our present research work could be lead molecules of interest.

4. Experimental

4.1. General

Melting points were determined using Buchi B-540 by open capillary and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Shimadzu FTIR 157 spectrophotometer. Final compound purifications were carried out using Quad biotage Flash purifier (A Dyax Corp. Company). All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 (300.12 MHz), Bruker BioSpin Corp.,

Germany, using TMS (tetra methyl silane) as an internal standard. All chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane. The mass spectra were recorded either on Single quadrapole mass or XCT Ion trap spectrometer operating at 70 eV. The mass spectra of a few were recorded on a 410 Prostar binary PDA detector (Varian Inc, USA). Elemental analysis was performed on Flash EA 1112 Thermo Electron Corporation CHNSO analyzer. The homogeneity of the compounds was monitored by thin layer chromatography (TLC) on silica gel 40 F254 (Merck, Darmstadt, Germany) coated on aluminum plates, visualized by UV light and $KMnO_4$ solution. Starting materials were purchased from Aldrich Chemical Company or Spectrochem Chemical Company and used without further purification. All solvents were of analytical grade and freshly distilled prior to use.

4.2. Procedure for the preparation of [1-(6-methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl]methanol (**2**)

A mixture of 4-azido-6-methoxy-2-methylquinoline (**1**) (10 g, 0.046 mol), propargyl alcohol (12.89 g, 0.23 mol) in dry THF/toluene (10 vol, 1:1) was heated to 120 °C and the reaction was maintained for 6 h. The reaction mass was concentrated under reduced pressure and purified by flash chromatography over silica gel (230–400 mesh) using 3–6% methanol in dichloromethane as eluant to obtain a yellow color solid (7.57 g, 60%). m.p. 195.8–196.1 °C; IR (KBr,cm^{-1}) ν_{max}: 3595 (OH), 1498 (CH), 1210 (CO), 1140 (C–N); ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.70 (s, 3H, CH_3), 3.81 (s, 3H, CH_3), 4.69 (d, 2H, J = 5.4Hz, CH_2), 5.40 (m, 1H, OH), 7.20 (d, 1H, J = 2.7Hz, ArH), 7.51 (dd, 1H, J = 9.3Hz, ArH), 7.65 (s, 1H, ArH), 8.01 (d, 1H, J = 9.3Hz, ArH), 8.66 (s, 1H, ArH); ^{13}C δ ppm ($CDCl_3$-75 MHz) = 23.48, 53.60, 56.60, 106.96, 112.18, 116.98, 121.30, 129.75, 133.19, 144.93, 150.27, 155.90, 162.73; LC/MS (ESI-MS) m/z 271.11 (M+1). Anal. Calcd for $C_{14}H_{14}N_4O_2$; C, 62.21; H, 5.22; N, 20.73; Found; C, 62.27; H, 5.31; N, 20.68.

4.3. Procedure for the preparation of [1-(6-methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl]methyl methanesulfonate (**3**)

To a cooled solution of [1-(6-methoxy-2-methylquinolin-4-yl)-1*H*-1,2,3-triazol-4-yl] methanol (**2**) (6 g, 22.0 mmol) in dichloromethane (60 mL), triethylamine (5.61 g, 55 mmol) was added methane sulfonyl chloride (3.02 g, 26.4 mmol) drop wise. The reaction mass was stirred at 25 °C for 1 h. The reaction completion was monitored by TLC. When the reaction was complete, the mass was diluted with methylene chloride, washed with water, brine solution, dried over anhydrous sodium sulfatesulfate and concentrated under reduced pressure to afford an off white color solid (7.11 g, 92%). ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.71 (s, 3H, CH_3), 3.32 (s, 3H, OSO_2Me), 3.80 (s, 3H, OCH_3), 5.53 (s, 2H, CH_2), 7.10 (d, 1H, J = 2.7Hz, ArH), 7.52 (dd, 1H, J = 9.3Hz, ArH), 7.71(s, 1H, ArH), 8.01 (d, 1H, J = 9.3Hz, ArH), 9.01 (s, 1H, ArH); LC/MS (ESI-MS) m/z 349.09 (M+1).

4.4. Procedure for the preparation of 4-[4-(azidomethyl)-1H-1,2,3-triazol-1-yl]-6- methoxy-2-methylquinoline (**4**)

A mixture of [1-(6-methoxy-2-methylquinolin-4-yl)-1*H*-1,2,3-triazol-4-yl] methyl methanesulfonate (**3**) (4 g, 11.0 mmol), sodium azide (1.49 g, 22.0 mmol) in dry DMF (50 mL) was stirred at 25 °C for 2 h. The reaction completion was monitored by TLC. After the completion of the reaction, it was quenched with ice cold water. The off white color solid obtained was filtered, washed with water and vacuum dried (2.98 g, 88%). m.p. 218–219.2 (decomp); IR (KBr,cm^{-1}) ν_{max}: 2925 (CH), 1210 (CO), 1140 (C–N); ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.80 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.69 (s, 3H, CH_2), 7.09 (d, 1H, J = 3Hz, ArH), 7.37 (s, 1H, ArH), 7.45 (dd, 1H, J = 9.3Hz, ArH), 8.03 (s, 1H, ArH), 8.05 (d, 1H, J = 9.3Hz, ArH); LC/MS (ESI-MS) m/z 296.12 (M+1). Anal. Calcd for $C_{14}H_{14}N_4O_2$; C, 62.21; H, 5.22; N, 20.73; Found; C, 62.27; H, 5.31; N, 20.68.

4.5. Procedure for the preparation of 1-[1-(6-methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl]methanamine (**5**)

To a solution of 4-[4-(azidomethyl)-1*H*-1,2,3-triazol-1-yl]-6-methoxy-2-methylquinoline (**4**) (3 g, 10.0 mmol) in methanol (40 mL) was added Pd/C (0.3 g). The reaction mass carried out under H_2 pressure. The catalyst was filtered and the filtrate was concentrated under reduced pressure to get a pale yellow color viscous liquid (Yield-86%). IR (KBr,cm^{-1}) ν_{max}: 3425 (NH), 1498 (CH), 1210 (CO), 1140 (C–N); ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.80 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.20 (t, 2H, J = 5.3Hz, CH_2), 4.35 (br, 2H, NH_2) 7.09 (d, 1H, J = 3.0 Hz, ArH), 7.37 (s, 1H, ArH), 7.45 (dd, 1H, J = 9.3Hz, ArH), 8.03 (s, 1H, ArH), 8.06 (d, 1H, J = 9.3Hz, ArH); LC/MS (ESI-MS) m/z 270.13 (M+1). Anal. Calcd for $C_{14}H_{14}N_4O_2$; C, 62.44; H, 5.61; N, 26.01; Found; C, 62.52; H, 5.72; N, 26.06.

4.6. General procedure for the preparation of 1-[1-(6-methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl]methylamide series (**6a–j**)

Pyridine (0.146 g, 1.85 mmol) was added to a solution of 1-[1-(6-methoxy-2-methylquinolin-4-yl)-1*H*-1,2,3-triazol-4-yl] methanamine (**5**) (0.2 g, 0.74 mmol) in dichloromethane (4 mL) followed by corresponding acid chlorides (0.74 mmol) at 0 °C. The reaction completion was monitored by TLC and the reaction was completed. The reaction mass was concentrated under reduced pressure. The crude product was purified on a Biotage parallel column purifier using solvent ethyl acetate: petroleum ether (4:1) to methanol (2–3%) in dichloromethane as eluant.

The characterization data including spectral data for the final compounds, **6a–j** are given below.

4.6.1. N-((1-(6-methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl)methyl) acetamide (**6a**)

Appearance: white solid; m.p. 155.7–156 °C; IR (KBr,cm^{-1}) ν_{max}: 3480 (NH), 1630 (C=O), 1210 (C–O), 1140 (C–N); ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.05 (s, 3H, CH_3), 2.79 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.66 (d, 2H, J = 5.7Hz, CH_2), 6.42 (br, 1H, NH), 7.16 (d, 1H, J = 2.7Hz, ArH), 7.35 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 8.02 (s, 1H, ArH), 8.06 (d, 1H, J = 9.3Hz, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 22.80, 23.48, 30.63, 56.60, 107.18, 112.10, 117.02, 119.75, 121.30, 129.75, 135.82, 141.10, 145.20, 156.12, 162.73, 174.81; MS: (ESI, m/z, %): 312 (M+1, 45), 284 (7), 225 (18), 173 (10), 95 (33), 70 (67), 56 (100); Anal. Calcd for $C_{16}H_{17}N_5O_2$; C, 61.72; H, 5.50; N, 22.49; Found; C, 61.79; H, 5.61; N, 22.44.

4.6.2. N-((1-(6-methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl)methyl)cyclopro panecarboxamide (**6b**)

Appearance: off white solid; m.p. 168.4–169.1 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 0.98 (m, 2H, CH_2), 1.01 (m, 2H, CH_2), 1.45 (m, 1H, CH), 2.77 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.66 (d, 2H, J = 5.7Hz, CH_2), 6.71(br, 1H, NH), 7.16 (d, 1H, J = 2.7Hz, ArH), 7.35 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 8.03 (s, 1H, ArH), 8.06 (d, 1H, J = 9.3Hz, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 7.17, 20.61, 23.48, 31.64, 56.60, 107.18, 112.10, 117.02, 121.30, 121.34, 129.75, 134.53, 141.10, 144.37, 156.12, 162.73, 178.61; LC/MS (ESI-MS) m/z 338.16 (M+1). Anal. Calcd for $C_{18}H_{19}N_5O_2$; C, 64.08; H, 5.68; N, 20.76; Found; C, 64.17; H, 5.73; N, 20.73.

*4.6.3. N-((1-(6-methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl)methyl)cyclo butanecarboxamide (**6c**)*

Appearance: Pale yellow solid; m.p. 183.6–184 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 1.01–1.2 (m, 2H, CH_2), 1.36–1.48 (m, 4H, CH_2), 1.98 (m, 1H, CH), 2.77 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.66 (d, 2H, J = 5.7Hz, CH_2), 7.01 (br, 1H, NH), 7.16 (d, 1H, J = 2.7Hz, ArH), 7.35 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 8.03 (s,1H, ArH), 8.06 (d, 1H, J = 9.3Hz, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 17.60, 23.48, 25.11, 31.64, 38.48, 56.60, 107.18, 112.10, 117.02, 121.30, 121.34, 129.75, 134.53, 141.10, 144.37, 156.12, 162.73, 177.88; LC/MS(ESI-MS) *m*/*z* 352.17(M+1).

*4.6.4. -Fluoro-N-((1-(6-methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl)methyl) benzamide (**6d**)*

Appearance: white solid; m.p. 201.4–202 °C; ^{1}H NMR($CDCl_3$-300 MHz) δ 2.79 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 4.86 (d, 2H, J = 5.7Hz, CH_2), 7.11–7.16 (m, 2H, ArH), 7.17 (d, 1H, J = 2.7Hz, ArH), 7.35 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 7.70–7.72 (m, 2H, ArH), 8.03 (d, 1H, J = 9.3Hz, ArH), 8.16 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 23.48, 31.55, 56.60, 107.18, 112.10, 113.90, 114.60, 117.02, 118.39, 121.30, 126.93, 127.10, 129.75, 133.13, 136.95, 141.10, 149.74, 156.12, 159.97, 162.73, 166.47, 168.28; MS: (ESI, *m*/*z*, %): 392 (M+1, 38), 364 (9), 225 (19), 167 (13), 149 (80), 84 (30), 70 (57), 56 (94).

*4.6.5. 2-Fluoro-N-((1-(6-methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl)methyl) benzamide (**6e**)*

Appearance: off white solid; m.p. 210–210.8 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.77 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.92 (d, 2H, J = 5.7Hz, CH_2), 7.17 (d, 1H, J = 2.7Hz, ArH) 7.26–7.32 (m, 2H, ArH), 7.35 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 7.47–7.55 (m, 2H, ArH), 8.03 (d, 1H, J = 9.3Hz, ArH), 8.09–8.12 (m, 1H, NH), 8.17 (s, 1H, ArH); LC/MS (ESI-MS) *m*/*z* 392.15(M+1).

*4.6.6. 2-Chloro-N-((1-(6-methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl)methyl) benzamide (**6f**)*

Appearance: white color solid; m.p. 148.7–149.1 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.78 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.66 (d, 2H, J = 5.7Hz, CH_2), 7.12 (m, 1H, ArH), 7.16 (d, 1H, J = 2.7Hz, ArH), 7.32 (m, 1H, Ar), 7.35 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 7.55 (m, 2H, ArH), 8.0 (br, 1H, NH), 8.03 (d, 1H, J = 9.3Hz, ArH), 8.16 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 23.48, 31.55, 56.60, 107.18, 112.10, 117.02, 118.39, 121.30, 125.40, 126.10, 128.60, 129.75, 132.23, 133.27, 134.40, 136.95, 141.10, 149.74, 156.12, 162.73, 166.73; LC/MS (ESI-MS) *m*/*z* 408.3 (M+1).

*4.6.7. 4-Ethyl-N-((1-(6-methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl)methyl) benzamide (**6g**)*

Appearance: pale yellow solid; m.p. 208.7–209.3 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 1.2 (t, 3H, J = 7.2Hz, CH_3), 2.2 (q, 2H, J = 7.2Hz, CH_2), 2.78 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.86 (d, 2H, J = 5.7Hz, CH_2), 7.15 (d, 2H, J = 8.0Hz, ArH), 7.16 (d, 1H, J = 2.7Hz, ArH), 7.23 (d, 2H, J = 8.0Hz, ArH), 7.35 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 8.03 (d, 1H, J = 9.3Hz, ArH), 8.16 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 14.60, 23.48, 27.90, 31.55, 56.60, 107.18, 112.10, 117.02, 118.39, 121.30, 127.49, 127.67, 129.75, 135.85, 136.95, 141.10, 149.42,149.74, 156.12, 162.73, 168.28; LC/MS (ESI-MS) *m*/*z* 402.19 (M+1).

*4.6.8. N-((1-(6-methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl)methyl)-4- methylbenzamide (**6h**)*

Appearance: off white solid; m.p. 200–200.9 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.33 (s, 1H, CH_3), 2.78 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.86 (d, 2H, J = 5.7Hz, CH_2), 7.15 (d, 2H, J = 8.0Hz, ArH), 7.16 (d, 1H, J = 2.7Hz, ArH), 7.23 (d, 2H, J = 8.0Hz, ArH), 7.35 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 8.03 (d, 1H, J = 9.3Hz, ArH), 8.16 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 20.90, 23.48, 27.90, 31.55, 56.60, 107.18, 112.10, 117.02, 118.39, 121.30, 125.27, 126.72, 129.75, 135.85, 136.95, 141.10, 149.42, 149.74, 156.12, 162.73, 168.28; LC/MS(ESI-MS) *m*/*z* 388.17 (M+1).

*4.6.9. 4-Methoxy-N-((1-(6-methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl)methyl) benzamide (**6i**)*

Appearance: white solid; m.p. 216–216.9 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.78 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.86 (d, 2H, J = 5.7Hz, CH_2), 7.08 (d, 2H, J = 8.0Hz, ArH), 7.16 (d, 1H, J = 2.7Hz, ArH), 7.23 (d, 2H, J = 8.0Hz, ArH), 7.35 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 8.03 (d, 1H, J = 9.3Hz, ArH), 8.16 (s, 1H, ArH); LC/MS (ESI-MS) *m*/*z* 404.17 (M+1).

*4.6.10. N-[1-(6-Methoxy-2-methyl-quinolin-4-yl)-1H- [1,2,3] triazol-4-ylmethyl]-4- trifluoromethyl-benzamide (**6j**)*

Appearance: yellow color gummy solid; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.78 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.86 (d, 2H, J = 5.7Hz, CH_2), 7.16 (d, 1H, J = 2.7Hz, ArH), 7.35 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 7.80 (m, 2H, ArH) 8.03 (d, 1H, J = 9.3Hz, ArH), 8.05 (m, 2H, -ArH), 8.16 (s, 1H, ArH); LC/MS (ESI-MS) *m*/*z* 442.14 (M+1).

*4.7. General procedure for the preparation of 1-[1-(6-Methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl] methyl sulphonamide series (**7a**–**g**)*

To a cooled solution of 1-[1-(6-Methoxy-2-methylquinolin-4-yl)-1*H*-1,2,3-triazol-4-yl] methanamine (**5**) (0.2 g, 0.74 mmol) in dichloromethane (4 mL) was added pyridine (0.146 g, 1.85 mmol) followed by corresponding sulfonyl chlorides (0.74 mmol) at 0 °C. The reaction completion was monitored by TLC. After the reaction was complete, the solvent was evaporated under reduced pressure. The crude product was purified on a Biotage parallel column purifier using ethyl acetate: petroleum ether (4:1) to methanol (2–4%) in dichloromethane as eluant. The characterization and spectral data for the title compounds **7a-g** are given below.

*4.7.1. 4-Fluoro-N-[1-(6-methoxy-2-methyl-quinolin-4-yl)-1H-[1,2,3]triazol-4-methyl]- benzenesulfonamide (**7a**)*

Appearance: pale yellow solid; m.p. 232.9–233.4 °C; ^{1}H ($CDCl_3$-300 MHz) δ 2.79 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 4.86 (d, 2H, J = 5.7Hz, CH_2), 7.17 (d, 1H, J = 2.7Hz, ArH), 7.26–7.30 (m, 2H, ArH), 7.35 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 7.65–7.72 (m, 2H, ArH), 8.03 (d, 1H, J = 9.3Hz, ArH), 8.16 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 23.48, 49.11, 56.60, 107.18, 112.10, 115.20, 115.91, 117.02, 119.53, 121.30, 128.17, 128.34, 129.75, 133.70, 139.61, 140.73, 141.10, 156.12, 162.73, 168.91; LC/MS (ESI-MS) *m*/*z* 428.11 (M+1).

*4.7.2. N-[1-(6-methoxy-2-methyl-quinolin-4-yl)-1H- [1,2,3]triazol-4-ylmethyl]-2-trifluoro methyl-benzenesulfonamide (**7b**)*

Appearance: white solid; m.p. 213.8 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.78 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.86 (d, 2H, J = 5.7Hz, CH_2), 7.08–7.15 (m, 2H, ArH), 7.16 (d, 1H, J = 2.7Hz, ArH), 7.35 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 7.54–7.62 (m, 4H, ArH),8.03 (d, 1H, J = 9.3Hz, ArH), 8.16 (s, 1H, ArH); LC/MS (ESI-MS) *m*/*z* 478.11 (M+1).

*4.7.3. 3,4-Dichloro-N-[1-(6-methoxy-2-methyl-quinolin-4-yl)-1H-[1–3]triazol-4-ylmeth yl]-benzenesulfonamide (**7c**)*

Appearance: white solid; m.p. 217.3–217.8 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.78 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.66 (d, 2H, J = 5.7Hz, CH_2), 7.16 (d, 1H, J = 2.7Hz, ArH), 7.35 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 7.83–7.93 (m, 2H, ArH), 8.02 (s, 1H, ArH),

8.03 (d, 1H, J = 9.3Hz, ArH), 8.16 (s, 1H, ArH), 8.61 (t, 1H, J = 5.7Hz, NH); LCMS (ESI-MS) m/z 478.05 (M+1).

4.7.4. N-[1-(6-methoxy-2-methyl-quinolin-4-yl)-1H- [1,2,3]triazol-4-ylmethyl]-4-methyl-benzenesulfonamide (**7d**)

Appearance: pale yellow solid; m.p. 198.2–199.3 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.33 (s, 1H, CH_3), 2.78 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.86 (d, 2H, J = 5.7Hz, CH_2), 7.15 (d, 2H, J = 8.0Hz, ArH), 7.16 (d, 1H, J = 2.7Hz, ArH), 7.35 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 7.56 (d, 2H, J = 8.0Hz, ArH), 8.03 (d, 1H, J = 9.3Hz, ArH), 8.16 (s, 1H, ArH), 8.35 (t, 1H, J = 5.7Hz, NH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 21.60, 23.48, 49.11, 56.60, 107.18, 112.10, 117.02, 119.53, 121.30, 126.21, 128.08, 129.75, 133.70, 139.61, 141.10, 141.58, 145.38, 156.12, 162.73; LCMS (ESI-MS) m/z424.14 (M+1).

4.7.5. 4-Methoxy-N-[1-(6-methoxy-2-methyl-quinolin-4-yl)-1H-[1,2,3]triazol-4-ylmethyl]- benzenesulfonamide (**7e**)

Appearance: white solid; m.p. 256–256.7 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.78 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.86 (d, 2H, J = 5.7Hz, CH_2), 7.08 (d, 2H, J = 8.0Hz, ArH), 7.16 (d, 1H, J = 2.7Hz, ArH), 7.30 (d, 2H, J = 8.0Hz, ArH), 7.35 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 8.03 (d, 1H, J = 9.3Hz, ArH), 8.16 (s, 1H, ArH), 8.28 (t, 1H, J = 5.7Hz, NH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 23.48, 49.11, 55.50, 56.60, 107.18, 112.10, 114.38, 117.02, 119.53, 121.30, 124.40, 129.75, 133.70, 138.21, 139.61, 141.10, 156.12, 162.73, 162.89; LCMS(ESI-MS) m/z 440.13 (M+1).

4.7.6. 4-Ethyl-N-[1-(6-methoxy-2-methyl-quinolin-4-yl)-1H-[1,2,3]triazol-4-ylmethyl]-ben zenesulfonamide (**7f**)

Appearance: off white solid; m.p. 211–211.2 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 1.2 (t, 3H, J = 7.2Hz, CH_3), 2.2 (q, 2H, J = 7.2Hz, CH_2), 2.78 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.86 (d, 2H, J = 5.7Hz, CH_2), 7.15 (d, 2H, J = 8.0Hz, ArH), 7.16 (d, 1H, J = 2.7Hz, ArH), 7.32 (d, 2H, J = 8.0Hz, ArH), 7.35 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 8.03 (d, 1H, J = 9.3Hz, ArH), 8.16 (s, 1H, ArH), 8.38 (t, 1H, J = 5.7Hz, NH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 15.68, 23.48, 28.48, 49.11, 56.60, 107.18, 112.10, 117.02, 119.53, 121.30, 125.32, 129.75, 131.48, 133.70, 139.61, 141.10, 145.65, 147.07, 156.12, 162.73; LCMS (ESI-MS) m/z 438.15 (M+1).

4.7.7. N-[1-(6-methoxy-2-methyl-quinolin-4-yl)-1H- [1–3]triazol-4-ylmethyl]-benzene sulfonamide (**7g**)

Appearance: yellow gummy solid; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.79 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 4.20 (d, 2H, J = 5.7Hz, CH_2), 7.16 (d, 1H, J = 2.7Hz, ArH), 7.35 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3 Hz, ArH), 7.61–7.68 (m, 3H, ArH), 7.88–7.91 (m, 2H, ArH), 8.03 (d, 1H, J = 9.3Hz, ArH), 8.16 (s, 1H, ArH), 8.35 (t, 1H, J = 5.7Hz, NH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 23.48, 49.11, 56.60, 107.18, 112.10, 117.02, 119.53, 121.30, 124.93, 127.95, 129.75, 133.17, 133.70, 139.61, 141.10, 144.12, 156.12, 162.73; LCMS (ESI-MS) m/z = 410.12 (M+1).

4.8. Procedure for the preparation of tert-butyl 4–((1-(6-methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl)methyl)piperazine-1-carboxylate (**8**)

A mixture of [1-(6-methoxy-2-methylquinolin-4-yl)-1*H*-1,2,3-triazol-4-yl]methyl methane sulfonate (**3**) (8 g, 0.022 mol), *tert*-butyl piperazine-1-carboxylate (0.025 mol), potassium carbonate (6.33 g, 0.045 mol) in acetonitrile (100 mL) was heated to 80 °C for 1 h. The completion of reaction was monitored by TLC. After the reaction was complete, the mass was concentrated, diluted with ethyl acetate, washed with water, brine solution, dried over anhydrous sodium sulphate and finally concentrated under reduced pressure. The crude product was purified on a column chromatography using ethyl acetate/pet ether (4:1) as eluant to get a white solid (yield-94%). m.p. 140.2–141 °C; ^{1}H NMR ($CDCl_3$ -300 MHz) δ 1.45 (s, 9H, CH_3), 2.33 (s, 3H, CH_3), 2.53 (m, 4H, NCH_2), 2.58 (m, 4H, NCH_2), 3.86 (s, 3H, OCH_3), 3.88 (s, 2H, CH_2), 7.20 (d, 1H, J = 3.0Hz, ArH), 7.35 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 7.96 (s, 1H, ArH), 8.05 (s, 1H, J = 9.3Hz, ArH).

4.9. Procedure for the preparation of 6-methoxy-2-methyl-4-[4-(piperazin-1-ylmethyl)-1H-1,2,3-triazol-1-yl]quinoline (**9**)

To a solution of tert-butyl 4–((1-(6-methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl)methyl)piperazine-1-carboxylate **(8)** (7 g, 0.0159 mol) in DCM (70 mL) was added trifluoroacetic acid (15 mL) at 0 °C. The reaction mixture was stirred at 26–30 °C for 4 h. The reaction mixture was concentrated under reduced pressure to get **9** as a pale yellow gummy solid (7.2 g, 100%). ^{1}H NMR($CDCl_3$-300 MHz) δ 2.33 (s, 3H, CH_3), 2.46 (m, 4H, NCH_2), 2.51 (m, 4H, NCH_2), 3.86 (s, 3H, OMe), 3.88 (s, 2H, CH_2), 7.20 (d, 1H, J = 3Hz, ArH), 7.35 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 7.96 (s, 1H, ArH), 8.05 (d, 1H, J = 9.3Hz ArH).

4.10. General procedure for the preparation of 6-methoxy-2-methyl-4-[4-(piperazin-1-ylmethyl)-1H-1,2,3-triazol-1-yl]quinoline amide series (**10a–k**)

Triethylamine (0.139 g, 1.375 mmol) was added to a solution of 6-methoxy-2-methyl-4-[4-(piperazin-1-ylmethyl)-1*H*-1,2,3-triazol-1-yl]quinoline.TFA salt (**9**) (0.25 g, 0.55 mmol) in dry dichloromethane (6 mL) followed by the addition of different substituted acid chlorides (0.55 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for another 30 min. The reaction completion was monitored by TLC. After the completion of the reaction, the mass was concentrated under reduced pressure. The crude product was purified on a Biotage parallel column purifier using ethyl acetate: pet ether (4:1) to MeOH (3–5%) in dichloromethane. The characterization data for the title compounds **10a–k** are given below.

4.10.1. 1-{4-[1-(6-Methoxy-quinolin-4-yl)-1H- [1,2,3]triazol-4-ylmethyl]-piperazin-1-yl}- ethanone (**10a**)

Appearance: viscous liquid; IR (KBr,cm^{-1}) ν_{max}: 2925 (CH), 1645 (C=O), 1498 (CH), 1210 (C–O), 1140 (C–N); ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.10 (s, 3H, CH_3), 2.58 (t, 2H, J = 4.8Hz, NCH_2), 4.64 (t, 2H, J = 4.8Hz, NCH_2), 2.79 (s, 3H, CH_3), 3.52 (t, 2H, J = 4.8Hz, NCH_2), 3.67 (t, 2H, J = 4.8Hz, NCH_2), 3.86 (s, 3H, OCH_3), 3.88 (s, 2H, CH_2), 7.18 (d, 1H, J = 2.7Hz, ArH), 7.35 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 7.95 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3Hz, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 21.09, 23.48, 44.67, 46.61, 48.98, 56.01, 56.60, 107.18, 112.10, 117.02, 118.34, 121.30, 129.75, 134.27, 141.07, 141.10, 156.12, 162.73, 169.73; LC/MS (ESI-MS) m/z 381.2 (M+1).

4.10.2. Cyclopropyl-{4-[1-(6-methoxy-quinolin-4-yl)-1H- [1,2,3] triazol-4-ylmethyl]-piperazin-1- yl}-methanone (**10b**)

Appearance: pale yellow solid; m.p. 120.1–120.3 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 0.98 (m, 2H, CH_2), 1.01 (m, 2H, CH_2), 1.45 (m, 1H, CH), 2.20 (s, 3H, CH_3), 2.56–2.66 (m, 4H, NCH_2), 2.79 (s, 3H, CH_3), 3.50–3.68 (m, 4H, NCH_2), 3.85 (s, 3H, OCH_3), 3.88 (s, 2H, CH_2), 7.18 (d, 1H, J = 2.7Hz, ArH), 7.35 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 7.95 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3Hz, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 7.40, 21.43, 23.48, 44.67, 46.61, 48.98, 56.01, 56.60, 107.18, 112.10, 117.02, 118.34, 121.30, 129.75, 134.27, 141.07, 141.10, 156.12, 162.73, 169.73; LC/MS (ESI-MS) m/z 406.22 (M+1).

*4.10.3. Cyclobutyl-{4-[1-(6-methoxy-quinolin-4-yl)-1H- [1,2,3] triazol-4-ylmethyl]-piperazin-1- yl}-methanone (**10c**)*

Appearance: yellow solid; m.p. 127.8–128 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.13–2.20 (m, 6H, CH_2), 2.57 (m, 4H, NCH_2), 2.79 (s, 3H, CH_3), 3.21–3.27 (m, 1H, CH), 3.38–3.41 (m, 2H, NCH_2), 3.65–3.68 (m, 2H, NCH_2), 3.85 (s, 3H, OCH_3), 3.86 (s, 2H, CH_2), 7.18 (d, 1H, J = 2.7Hz, ArH), 7.35 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 7.95 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3Hz, ArH); ^{13}C NMR ($CDCl_3$-75 MHz): δ 17.60, 23.48, 25.62, 40.98, 44.67, 46.61, 48.98, 56.01, 56.60, 107.18, 112.10, 117.02, 118.34, 121.30, 129.75, 134.27, 141.07, 141.10, 156.12, 162.73, 169.73; LC/MS (ESI-MS) m/z 421.23 (M^+).

*4.10.4. (4-Fluoro-phenyl)-{4-[1-(6-methoxy-quinolin-4-yl)-1H-[1,2,3]triazol-4-ylmethyl]- piperazin-1-yl}-methanone (**10d**)*

Appearance: off white solid; m.p. 135.3–136 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ2.57 (m, 4H, NCH_2), 2.79 (s, 3H, CH_3), 3.38–3.41 (m, 2H, NCH_2), 3.65–3.68 (m, 2H, NCH_2), 3.85 (s, 3H, OCH_3), 3.86 (s, 2H, CH_2), 7.18 (d, 1H, J = 2.7Hz, ArH), 7.26–7.30 (m, 2H, ArH), 7.35 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 7.65–7.72 (m, 2H, ArH), 7.95 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3Hz, ArH); LC/MS (ESI-MS) m/z 461.20 (M+1).

*4.10.5. (2-Fluoro-phenyl)-{4-[1-(6-methoxy-quinolin-4-yl)-1H-[1,2,3]triazol-4-ylmethyl]- piperazin-1-yl}-methanone (**10e**)*

Appearance: white solid; m.p. 111.2 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.62–2.74 (m, 4H, NCH_2), 2.77 (s, 3H, CH_3), 3.40 (m, 2H, NCH_2), 3.83 (s, 3H, OCH_3), 3.87 (m, 2H, NCH_2), 3.90 (s, 2H, CH_2), 7.05–7.22 (m, 3H, ArH), 7.33 (s, 1H, ArH), 7.36–7.38 (m, 2H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 7.95 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3Hz, ArH); LC/MS (ESI-MS) m/z 461.20 (M+1).

*4.10.6. (2-Chloro-phenyl)-{4-[1-(6-methoxy-quinolin-4-yl)-1H-[1,2,3]triazol-4-ylmethyl]- piperazin-1-yl}-methanone (**10f**)*

Appearance: tan colored solid; m.p. 123.3–124 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.55–2.74 (m, 4H, NCH_2), 2.79 (s, 3H, CH_3), 3.24–3.38 (m, 4H, NCH_2), 3.85 (s, 3H, OCH_3), 3.89 (s, 2H, CH_2), 7.18–7.31(m, 5H, ArH), 7.37 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 7.95 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3Hz, ArH); LC/MS (ESI-MS) m/z 477.18 (M+1).

*4.10.7. (4-Ethyl-phenyl)-{4-[1-(6-methoxy-quinolin-4-yl)-1H-[1,2,3]triazol-4-ylmethyl]- piperazin-1-yl}-methanone (**10g**)*

Appearance: off white solid; m.p. 124–124.6 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 1.2 (t, 3H, J = 7.2Hz, CH_3), 2.2 (q, 2H, J = 7.2Hz, CH_2), 2.58 (m, 4H, NCH_2), 2.79 (s, 3H, CH_3), 3.38–3.41 (m, 2H, NCH_2), 3.65–3.68 (m, 2H, NCH_2), 3.85 (s, 3H, OCH_3), 3.94 (s, 2H, CH_2), 7.08 (d, 2H, J = 8.0Hz, ArH), 7.18 (d, 1H, J = 2.7Hz, ArH), 7.23 (d, 2H, J = 8.0Hz, ArH), 7.37 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 7.95 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3Hz, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 14.60, 24.86, 27.90, 52.94, 55.60, 107.18, 112.10, 117.02, 118.34, 121.30, 125.75, 127.93, 129.75, 131.82, 134.27, 141.07, 141.10, 149.42, 156.12, 162.73, 169.73; LC/MS (ESI-MS) m/z 471.25 (M+1).

*4.10.8. {4-[1-(6-Methoxy-quinolin-4-yl)-1H- [1,2,3]triazol-4-ylmethyl]-piperazin-1-yl}-p-tolyl- methanone (**10h**)*

Appearance: yellow solid; m.p. 119.6 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.43 (s, 3H, CH_3), 2.58 (m, 4H, NCH_2), 2.79 (s, 3H, CH_3), 3.38–3.41 (m, 2H, NCH_2), 3.65–3.68 (m, 2H, NCH_2), 3.85 (s, 3H, OCH_3), 3.94 (s, 2H, CH_2), 7.15 (d, 2H, J = 8.0Hz, ArH), 7.18 (d, 1H, J = 2.7Hz, ArH), 7.23 (d, 2H, J = 8.0Hz, ArH), 7.37 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 7.95 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3Hz, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 21.3, 24.86, 52.94, 55.60, 107.18, 112.10, 117.02, 118.34, 121.30, 126.32, 128.83, 129.52, 129.75, 134.27, 140.06, 141.07, 141.10, 156.12, 162.73, 169.73; LC/MS (ESI-MS) m/z 457.23 (M+1).

*4.10.9. (4-Methoxy-phenyl)-{4-[1-(6-methoxy-quinolin-4-yl)-1H-[1,2,3]triazol-4-ylmethyl]- piperazin-1-yl}-methanone (**10i**)*

Appearance: yellow solid; m.p. 113.4 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.58 (m, 4H, NCH_2), 2.79 (s, 3H, CH_3), 3.38–3.41 (m, 2H, NCH_2), 3.65–3.68 (m, 2H, NCH_2), 3.72 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.94 (s, 2H, CH_2), 7.08 (d, 2H, J = 8.0Hz, ArH), 7.18 (d, 1H, J = 2.7Hz, ArH), 7.23 (d, 2H, J = 8.0Hz, ArH), 7.37 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 7.95 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3Hz, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 24.86, 52.94, 55.29, 55.60, 107.18, 112.10, 113.93, 117.02, 118.34, 121.30, 127.90, 128.41, 129.75, 134.27, 141.07, 141.10, 156.12, 160.54, 162.73, 169.73; LC/MS (ESI-MS) m/z 473.22 (M+1).

*4.10.10. {4-[1-(6-Methoxy-2-methyl-quinolin-4-yl)-1H- [1–3] triazol-4-ylmethyl]-piperazin-1- yl}-phenyl-methanone(**10j**)*

Appearance: pale yellow solid; m.p. 99.8–100.2 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.58 (m, 4H, NCH_2), 2.79 (s, 3H, CH_3), 3.38–3.41 (m, 2H, NCH_2), 3.65–3.68 (m, 2H, NCH_2), 3.85 (s, 3H, OCH_3), 3.94 (s, 2H, CH_2), 7.10 (m, 3H, ArH), 7.18 (d, 1H, J = 2.7Hz, ArH), 7.21–7.26 (m, 2H, ArH), 7.37 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 7.95 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3Hz, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 24.86, 52.94, 55.60, 107.18, 112.10, 117.02, 118.34, 128.17, 21.30, 126.49, 129.75, 130.03, 132.44, 134.27, 141.07, 141.10, 156.12, 162.73, 169.73; LC/MS (ESI-MS) m/z 443.21 (M+1).

*4.10.11. (3,4-Dichloro-phenyl)-{4-[1-(6-methoxy-quinolin-4-yl)-1H- [1,2,3]triazol-4- ylmethyl]-piperazin-1-yl}-methanone (**10k**)*

Appearance: tan color solid; m.p. 180.8–181 °C; ^{1}H NMR ($CDCl_3$-300 MHz) δ 2.55–2.74 (m, 4H, NCH_2), 2.79 (s, 3H, CH_3), 3.24–3.38 (m, 4H, NCH_2), 3.85 (s, 3H, OCH_3), 3.89 (s, 2H, CH_2), 7.18–7.31(m, 4H, ArH), 7.37 (s, 1H, ArH), 7.44 (dd, 1H, J = 9.3Hz, ArH), 7.95 (s, 1H, ArH), 8.03 (d, 1H, J = 9.3Hz, ArH); ^{13}C NMR ($CDCl_3$-75 MHz) δ 21.3, 24.86, 52.94, 55.60, 107.18, 112.10, 117.02, 118.34, 121.30, 126.72, 127.63, 129.75, 131.89, 133.98, 134.27, 134.89, 136.56, 141.07, 141.10, 156.12, 162.73, 169.73; LC/MS (ESI-MS) m/z 511.14 (M+1).

4.11. Antibacterial study

The newly synthesized title compounds were evaluated for their *in vitro* anti-bacterial activity against ATCC-25922 *Escherichia coli*, ATCC-25923 *Staphylococcus aureus*, ATCC-27853 *Pseudomonas aeruginosa*, clinical isolate of *Klebsiella pneumoniae* and *Streptococcus Pyogenes* bacterial strains by serial plate dilution method. The compounds were dissolved in 100% dimethyl sulfoxide (DMSO) and was diluted further (A two-fold serial dilutions) using Muller Hinton broth. Serial dilutions of the drug in Muller-Hinton broth were taken in tubes and their pH was adjusted to 7.2–7.4 using phosphate buffer. A standardized suspension of the test bacterium (as per the CLSI guidelines) was inoculated and incubated for 18–24 h at 37 °C [36]. The minimum inhibitory concentration (MIC) was noted by seeing the lowest concentration of the drug at which there was no visible growth. Activity of each compound was compared with ciprofloxacin as standard [37,38]. Minimum inhibitory concentrations (μg/mL) were determined for **6a**–**j**, **7a**–**g** and **10a**–**k** and the corresponding results are summarized in Table 1.

4.12. Antituberculosis study

The compounds were screened for their *in vitro* anti-mycobacterial activity against *M. tuberculosis H37Rv* ATCC 27294, and non-tubercular mycobacterial (NTM) species like *M. smegmatis* (MC2) ATCC 19420, and *M. fortuitum* ATCC 19542 by Resazurin Assay method [39] and their MIC values were determined. The standard drugs, viz. isoniazid (INH) and rifampicin (RIF) were used for comparison.

M. tuberculosis strains were grown in Middlebrook 7H9 broth (Difco BBL, Sparks, MD, USA) supplemented with 10% OADC Becton Dickinson, Sparks, MD, USA). The culture was diluted to McFarland 2 standard with the same medium. From this, 50 μL of this culture was added to 150 μL of fresh medium in 96 well microtitre plates. Stock solutions (2 mg/mL) of the test compounds were prepared in dimethyl formamide (DMF). The compounds were tested at 1, 10 and 100 μg/mL concentrations. Further the second level testing was carried out at concentrations 0.3125, 0.625, 1.25, 2.5, and 5 μg/mL. Control tubes had the same volumes of DMF without any substrate. Rifampicin (RIF) and isoniazid (INH) was used as the reference compounds. After incubation at 37 °C for 7 days, 20 μL of 0.01% Resazurin (Sigma, St. Louis. MO, USA) in water was added to each tube. Resazurin, a redox dye, is blue in the oxidized state and turns pink when reduced by the growth of viable cells. The control tubes showed a color change from blue to pink after 1 h at 37 °C. Compounds which prevented the change of color of the dye were considered to be inhibitory to *M. tuberculosis*.

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References

[1] J.T. Brooks, J.E. Kaplan, K.K. Holmes, C. Benson, A. Pau, H. Masur, Clin. Infect. Dis. 48 (2009) 609–611.
[2] M.P. LaMontagne, A.M.S. Markovac, M. Sami Khan, J. Med.Chem. 25 (1982) 964–968.
[3] M.P. LaMontagne, P. Blumbergs, R.E. Strube, J.Med.Chem. 25 (1982) 1094–1097.
[4] P. Nasveld, S. Kitchener, Trans. Royal Soc. Trop. Med. Hyg. 99 (2005) 2–5.
[5] A. Mahamoud, J. Chevalier, A. Davin-Regli, J. Barbe, Jean-Marie Pages, Curr. Drug Targets 7 (2006) 843–847.
[6] S. Eswaran, A.V. Adhikari, N.S. Shetty, Eur. J. Med. Chem. 44 (2009) 4637–4647.
[7] W.A. Denny, W.R. Wilson, D.C. Ware, G.J. Atwell, J.B. Milbank, R.J. Stevenson, U.S Patent (2006) 7064117.
[8] P.A. Leatham, H.A. Bird, V. Wright, D. Seymour, A. Gordon, Eur. J. Rheumatol.Inflamm 6 (1983) 209–211.
[9] N. Muruganantham, R. Sivakumar, N. Anbalagan, V. Gunasekaran, J.T. Leonard, Biol. Pharm. Bull. 27 (2004) 1683–1687.
[10] M.P. Maguire, K.R. Sheets, K. McVety, A.P. Spada, A. Zilberstein, J. Med. Chem. 37 (1994) 2129–2137.
[11] W.D. Wilson, M. Zhao, S.E. Patterson, R.L. Wydra, L. Janda, L. Strekowski, Med.Chem. Res. 2 (1992) 102–110.
[12] L. Strekowski, J.L. Mokrosz, V.A. Honkan, A. Czarny, M.T. Cegla, S.E. Patterson, R.L. Wydra, R.F. Schinazi, J. Med. Chem. 34 (1991) 1739–1746.
[13] D.R. Buckle, C.J.M. Rockell, J. Chem, Soc. Perkin Trans. 1 (1982) 627–630.
[14] D.R. Buckle, D.J. Outred, C.J.M. Rockell, H. Smith, B.A. Spicer, J. Med. Chem. 26 (1983) 251–254.
[15] D.R. Buckle, C.J.M. Rockell, H. Smith, B.A. Spicer, J. Med. Chem. 29 (1986) 2269–2277.
[16] M.J. Genin, D.A. Allwine, D.J. Anderson, M.R. Barbachyn, D.E. Emmert, S.A. Garmon, D.R. Graber, K.C. Grega, J.B. Hester, D.K. Hutchinson, J. Morris, R.J. Reischer, C.W. Ford, G.E. Zurenko, J.C. Hamel, R.D. Schaadt, D. Stapert, B.H. Yagi, J. Med. Chem. 43 (2000) 953–970.
[17] G.A. Nilkanth, S.P. Vandana, N.M. Nripendra, Awanit Kumar, K.S. Praveen, Aanchal Sharma, K.B. Manoj, Bioorg.Med.Chem.Lett. 19 (2009) 759–763.
[18] R. Alvarez, S. Velazquez, A. San-Felix, S. Aquaro, E. De Clercq, C.-F. Perno, A. Karlsson, J. Balzarini, M.J. Camarasa, J. Med. Chem. 37 (1994) 4185–4194.
[19] J.L. Kelley, C.S. Koble, R.G. Davis, E.W. McLean, F.E. Soroko, B.R. Cooper, J. Med. Chem. 38 (1995) 4131–4134.
[20] G. Biagi, G. Dell'Omodarme, M. Ferretti, I. Giorgi, O. Livi, V. Scartoni, Farmaco 45 (1990) 1181–1192.
[21] G. Biagi, O. Livi, V. Scartoni, A. Lucacchini, M.R. Mazzoni, Farmaco 41 (1986) 597–610.
[22] R.G. Micetich, S.N. Maiti, P. Spevak, T.W. Hall, S. Yamabe, N. Ishida, M. Tanaka, T. Yamazaki, A. Nakai, K. Ogawa, J. Med. Chem. 30 (1987) 1469–1474.
[23] H.C. Kolb, K.B. Sharpless, Drug Discov. Today 8 (2003) 1128–1137.
[24] D. Murugesan, S. Palaniappan, Y. Perumal, C. Arnab, N. Valakunja, S. Dharmarajan, Bioorg. Med. Chem. 16 (2008) 3408–3418.
[25] L. Annamaria, M. Jialin, W. Baojie, W. Yuehong, G.F. Scott, P.K. Alan, J. Med.Chem. 52 (2009) 2109–2118.
[26] J. Sarva, I. Yasuyoshi, W. Baojie, G.F. Scott, P.K. Alan, Chem. Med. Chem. 1 (2006) 593–597.
[27] N. Amit, M. Vikramdeep, M. Alpeshkumar, C. Evans, J. Rahul, Bioorg. Med. Chem. 15 (2007) 626–640.
[28] M. Dinakaran, P. Senthilkumar, P. Yogeeswari, A. China, V. Nagaraja, S. Dharmarajan, Int. J. Antimicrob. Agents 31 (2008) 337–344.
[29] D.R. Ashtekar, R. Costa-Perira, K. Hagrajan, M. Vishvamatham, A.D. Bhatt, W. Rittel, Antimicrob. Agents Chemother. 37 (1993) 183–186.
[30] M.R. Shiradkar, S.V. Bhandari, R.P. Kale, A. Laghate, A. Rathi, Asian J. Chem 18 (2006) 2700–2704.
[31] B.K. Singh, A.K. Yadav, B. Kumar, A.N. Gaikwad, S.K. Sinha, V. Chaturvedi, Carbohydr. Res. 343 (2008) 1153–1162.
[32] J. Xie, C.T. Seto, Bioorg. Med. Chem. 15 (2007) 458–473.
[33] K.D. Thomas, A.V. Adhikari, N.S. Shetty, Eur. J. Med.Chem. 45 (2010) 3803–3810.
[34] C.G. Wermuth, The Practice of Medicinal Chemistry, second edition, Elsevier, (Chapter 19), pp. 303–325.
[35] W.K. Hagmann, J. Med. Chem. 5 (2008) 4359–4369.
[36] M07-A8 Approved standard, Methods for Dilution Antimicrobial Susceptibility Tests for Bacterial that Grow Aerobically, eighth edition, vol. 29, (2009) pp. 1–10.
[37] C.H. Fenlon, M.H. Cynamon, Antimicrob. Agents Chemothe 29 (1986) 386–388.
[38] R. Davis, A. Markham, J.A. Balfour, Ciprofloxacin, an updated review of its pharmacology, therapeutic efficacy and tolerability, Drugs 51 (1996) 1019–1074.
[39] K.T. Neetu, S.T. Jaya, J. Antimicrob. Chemother. 60 (2007) 288–293.