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Microwave assisted regioselective synthesis of quinoline appended triazoles as potent anti-tubercular and antifungal agents *via* copper (I) catalyzed cycloaddition

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ABSTRACT

Quinolin-3-yl-methyl-1,2,3-triazolyl-1,2,4-triazol-3(4*H*)-ones 8j-v were synthesized by *click chemistry* as an ultimate tactic where [3 + 2] cycloaddition of azides with terminal alkynes has been evolved. Herein, we are inclined to divulge the implication and prevalence of $CuSO_4{\cdot}5H_2O$ and THF/water promoted [3 + 2] cycloaddition reactions. The foremost supremacy of this method are transitory reaction times, facile workup, excellent yields (88–92%) with exorbitant purity and regioselective single product formation both under conventional and microwave method. Docking studies illustrated strong binding interactions with enzyme InhA-D148G (PDB ID: 4DQU) by means of high C-score values. The anti-tubercular and antifungal screening of synthesized compounds proclaimed promising activity. The *in vitro* and *in silico* studies imply that these triazoles appended quinolines may acquire the ideal structural prerequisites for auxiliary expansion of novel therapeutic agents.

Tuberculosis (TB) is a treatable contagious lung disease caused by *Mycobacterium tuberculosis* (MTB), regardless of the accessibility of productive drugs, the disease causes tremendous number of deaths and remains the supreme cause of global deaths due to infectious diseases.[1] According to WHO 2020 report, an estimated ten million people contracted TB and around 1.2 million people died, including 0.208 million cases co-infected with HIV.[2] The prolonged treatment generally results in contravention of the treatment and therefore cause multidrug resistance tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) which are highly life threatening, extremely extortionate and complex to treat. The ever-increasing number of MDR-TB cases has caused immense concern as they contribute to an enhancement in deaths from TB and are habitually correlated with HIV infection. The existence of MDR-TB reflects a frailty in TB control, but this weakness can be treated with extended chemotherapy. With an extended treatment period, however, patients face an increased risk of toxicity and the treatment costs became several times higher than the typical treatment of TB.[11] This has created new challenges for the impediment, treatment and control of TB. Even with the availability of effective anti-TB drugs such as isoniazid and rifampicin, there is severe problem egress as MTB developed resistance against the first-line as well as the second-line drugs.[3] Therefore, there is an immense necessity to develop contemporary inhibitors that reduce the complexity and duration of the current therapeutic treatment as well as beneficially treat MDR and XDR tuberculosis.

Amidst innumerable *N*-heterocycles, quinolines and 1,2,3-triazoles are two essential classes of small heterocyclic molecules which have a wide range of chemotherapeutic demands. Quinolines and their analogs represent a fundamental class of organic molecules that have attracted significant attention from synthetic as well as medicinal chemists due to their existence in various natural products, displaying a broad range of physiological activities.[4] It is appealing to note that quinoline moiety is the core substructure in recently approved anti-TB drug, bedaquiline (TMC207), a diarylquinoline-based molecule.[5] Furthermore, some derivatives of an antimalarial drug mefloquine possess impressive antibacterial as well as anti-tubercular activity.[6] The quinoline-based antibiotics, ciprofloxacin and moxifloxacin also show promising anti-tubercular activity and are recommended by WHO as second-line anti-TB drugs.

The modern research in drug discovery has intended at introducing

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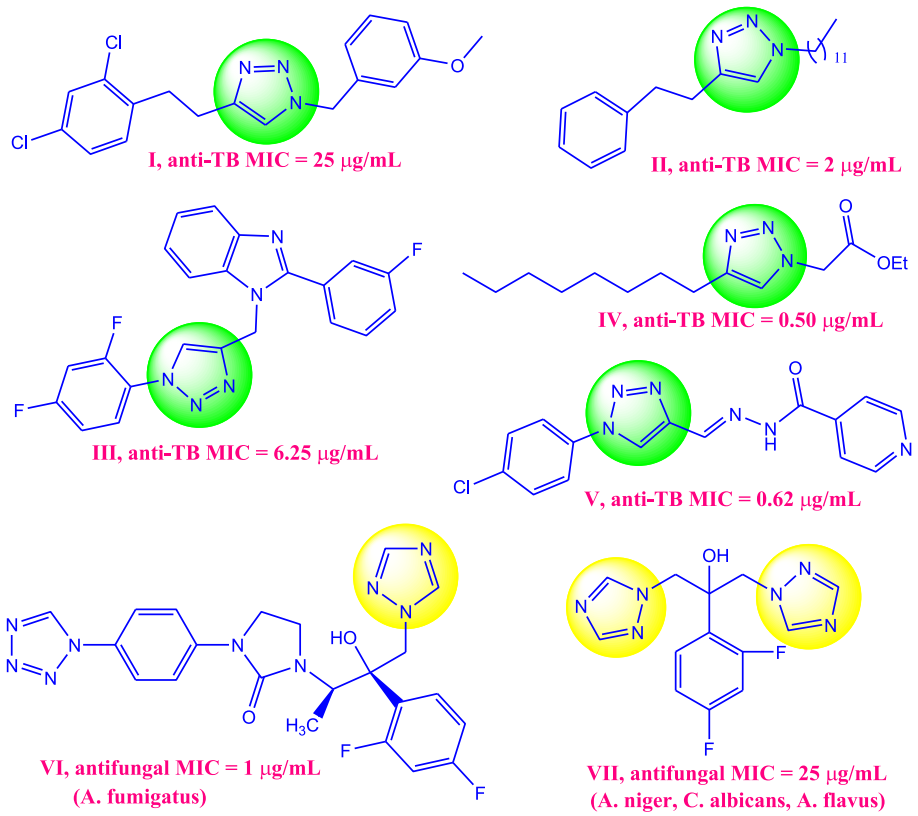


Fig. 1. 1,2,3-Triazoles and 1,2,4-Triazoles possessing anti-tubercular and antifungal activity.

the 1,2,3-triazole moiety as a connecting link between two or more pharmacophore. 1,2,3-Triazoles have gained much attention, as their fascinating physical and biological properties as well as their magnificent stability render them promising drug core structures. The 1,3-dipolar cycloaddition reaction of a 1,3-dipole to a dipolarophile (i.e. an acetylene or an alkyne) for the synthesis of five-membered heterocycles is a well-known transformation in synthetic organic chemistry.[7] The Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction has successfully fulfilled the requirement of "click chemistry" as prescribed by Sharpless and within a few years has become a premier component of synthetic organic chemistry.[8] Sharpless[9] and Meldal[10] have reported the dramatic rate enhancement (up to 10^7 times) and enhanced regioselectivity of the Huisgen 1,3- dipolar cycloaddition reaction of an organic azide and terminal acetylene to afford the 1,4-disubstituted-1,2,3-triazole in presence of Cu(I) catalyst.

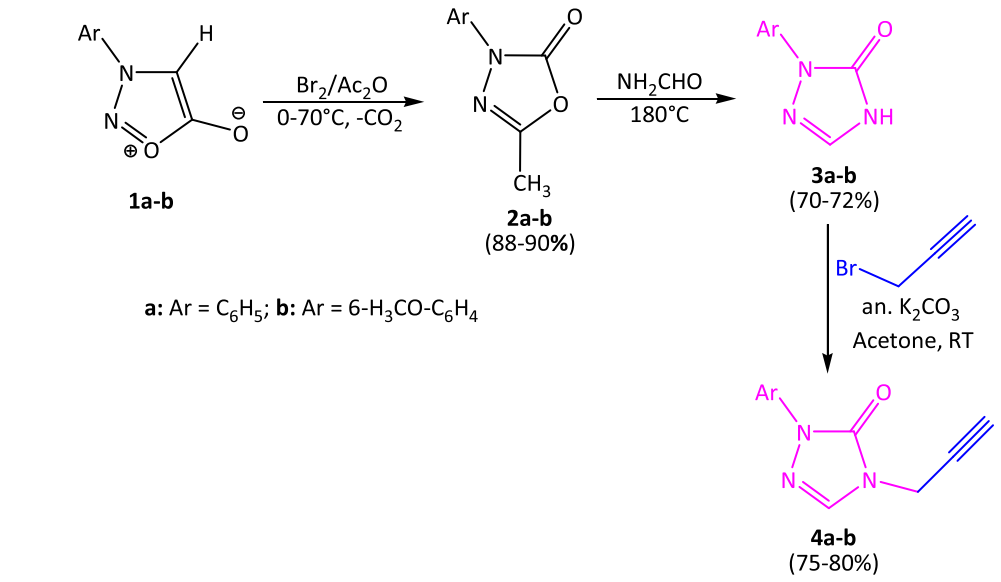
In recent times, 1,2,3-triazoles have been a vital class of compounds because of their wide range of biological applications together with anti-tubercular,[11] antibacterial, anti-allergic, anti-HIV,[12] anti-fungal,[13] α-glycosidase inhibitor[14] and anti-tubercular[15] activities. Baltas and co-workers[16] reported the 1,4-disubstituted 1,2,3-triazole derivatives (I and II) (Fig. 1) exhibiting good inhibitory activities against MTB H37Rv. In a similar way, benzimidazole clubbed 1,2,3-triazoles with fluorine (III) series of H37Rv strain inhibitors have been reported.[17] The 1,2,3-triazole based compounds (IV) are active against various pathogenic and opportunistic *Mycobacteria* including *M.avium* and MTB.[18] Recently, a 1,2,3-triazole based isoniazid derivative (V) has shown to possess anti-tubercular activity against MTB H37Rv. The well known antifungal drugs TAK-456 (VI) and fluconazole (VII) are also compiled of triazole entity as well (Fig. 1).

Considerable attention is attracted by 1,2,4-triazoles which are among pharmacologically vital heterocyclic compounds due to their captivating biological activities. Hence, for a more direct path, we choose to prepare 1,2,4-triazole using *N*-arylsydnone which belongs to mesoionic class of compounds. *N*-Arylsydnone act as functional and novel precursor for the synthesis of diverse biologically functional heterocycles *viz.*, pyrazoles, 1,3,4-oxadiazoles, phenyl indazoles, pyrazolines, and tetrazines *via* 1,3-dipolar cycloaddition and addition elimination reactions.[19]

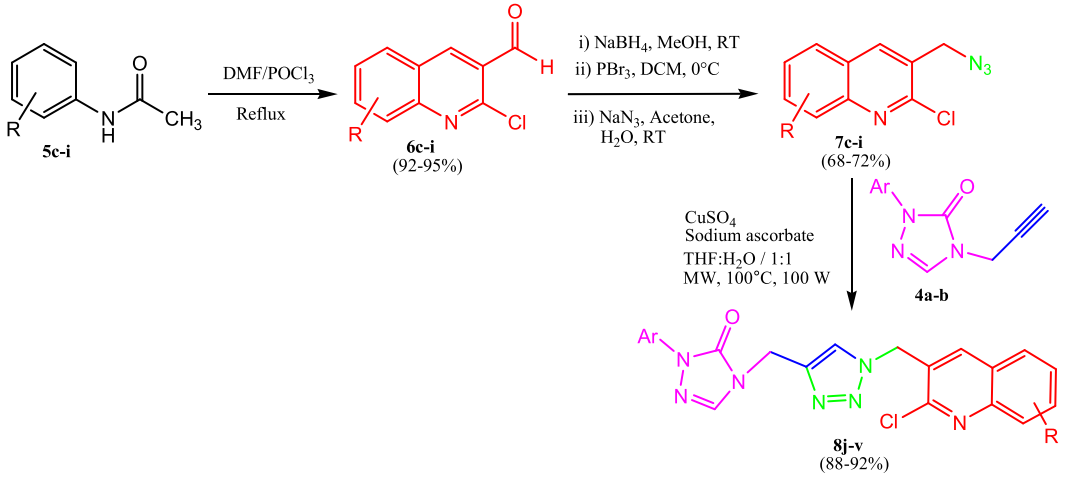
Microwave irradiation has been used efficiently to escalate diverse chemical reactions. Often, a few minutes of microwave irradiation are adequate for reactions that conventionally require several hours for accomplishment. The attributes of Microwave Assisted Organic Synthesis (MAOS) is the fabulous acceleration perceived in numerous reactions with consequences that cannot be reproduced by conventional heating. Due to the certainty that it is more eco-friendly, Microwave synthesis is deemed as a significant approach towards green chemistry.[20]

To designate the complications of escalating resistance, grievous side effects of a few anti-TB drugs, prolonged treatment, incompatibility of anti-retroviral therapies for contemporary TB regimen, research activities to build up novel anti-TB agents with intense efficacy have become a hasty priority. Numerous studies targeting the mycobacterial cell wall and predominantly the biosynthesis of mycolic acid have been publicized. *InhA* also known as *Enoy Acyl Carrier Protein Reductase* (Mtb ENR) is a vital enzyme of mycolic acid biosynthesis pathway. In the synthesis of type II fatty acids which are essential for the formation of the mycobacterial cell wall, this pathway is implicated and is therefore considered to be a good target. The major advantage of this target is that it is present in the mycobacterium but is missing in human. Furthermore, *InhA* has been acknowledged as the molecular target of the frontline anti-tubercular drugs isoniazid and ethionamide (ETA).[21]

In connection with the expansion of new active molecules against MTB, a small focused array of 1,2,3-triazole integrated molecules have been competently equipped by *click chemistry*. We were persuaded to design green and novel quinolinyl-1,2,3-triazolyl-1,2,4-triazol-3(*4H*)-ones 8j-v from biologically active starting materials in minimal steps with favorable overall yield. Herein, we are inclined towards reporting the most expedient synthesis of 1,4-disubstituted-1,2,3-triazoles both



Scheme 1. Synthesis of acetylenic dipolarophile 4a-b.



c: R = H; **d:** R = 6-Br; **e:** R = 6-Cl; **f:** R = 7-Cl; **g:** R = 6-CH_3; **h:** R = 8-CH_3; **i:** R = 7-OCH_3; **j:** Ar = C_6H_5, R = H; **k:** Ar = C_6H_5, R = 6-Br; **l:** Ar = C_6H_5, R = 6-Cl; **m:** Ar = C_6H_5, R = 7-Cl; **n:** Ar = C_6H_5, R = 6-CH_3; **o:** Ar = C_6H_5, R = 8-CH_3; **p:** Ar = C_6H_5, R = 7-OCH_3; **q:** Ar = 4-OCH_3-C_6H_4, R = H; **r:** Ar = 4-OCH_3-C_6H_4, R = 6-Br; **s:** Ar = 4-OCH_3-C_6H_4, R = 6-Cl; **t:** Ar = 4-OCH_3-C_6H_4, R = 7-Cl; **u:** Ar = 4-OCH_3-C_6H_4, R = 6-CH_3; **v:** Ar = 4-OCH_3-C_6H_4, R = 8-CH_3;

Scheme 2. Synthesis of quinolinyl-1,2,3-triazolyl-1,2,4-triazol-3(*4H*)-one 8j-v.

conventionally as well as microwave irradiation and their anti-tubercular, antifungal activity and molecular docking study.

Results and discussion

The current study explores the most commodious green approach for the synthesis of regioselective quinolinyl-1,2,3-triazolyl-1,2,4-triazol-3(*4H*)-one 8j-v with excellent yields and purity in shorter duration (Scheme 2). 2-Chloro-6/7/8-substituted-quinoline-3-carbaldehyde 6c-i was synthesized by *Vilsmeier-Haack reaction* which further was reduced using $NaBH_4$ to the corresponding alcohol which later gave 3-(bromomethyl)-2-chloro-6/7/8-substituted quinoline when treated with phosphorous tribromide in DCM. The corresponding dipolar azide 7c-i was obtained by treating 3-(bromomethyl)-2-chloro-6/7/8-substituted quinoline with sodium azide in aqueous acetone at room temperature. This was accompanied by azide-alkyne cycloaddition of the acetylenic dipolarophiles 4a-b (Scheme 1) and 3-azidomethyl quinolines 7c-i, for

Table 1
Optimization of reaction conditions for the compound 8j.

Entry	$CuSO_4{\cdot}H_2O$ (mol%)	Solvent	Time (h)	Yield (%)
1	0	DMF	24	0
2	2	DMF	18	24
3	2	DMSO	14	32
4	5	*t*-butanol	24	0
5	10	*t*-butanol:H_2O (1:1)	15	65
6	10	*t*-butanol:H_2O (1:2)	12	63
7	10	THF:H_2O (1:1)	4	65
8	15	THF:H_2O (2:1)	4	70
9	15	THF:H_2O (1:2)	3	68
10	15	THF:H_2O (1:1)	1	80
11	15	*t*-butanol:H_2O (1:2)	7	68
12	15	PEG-400	8	70
13	15	*t*-butanol:H_2O (2:1)	7	63
14	20	THF:H_2O (1:1)	1	80
15	20	PEG-400	5	72

Table 2
Synthesized compounds (8j-v) and their yields.

Products 8j-v	Ar	R	Conventional		Microwave	
			Time (h)	Yield (%)	Time (min)	Yield (%)
8j	C_6H_5	H	4	80	3	92
8k	C_6H_5	6-Br	5	75	3	90
8l	C_6H_5	6-Cl	6	79	3	91
8m	C_6H_5	7-Cl	4	75	5	88
8n	C_6H_5	6-CH_3	5	74	3	89
8o	C_6H_5	8-CH_3	4	79	3	90
8p	C_6H_5	7-OCH_3	5	80	4	88
8q	4-H_3CO-C_6H_4	H	6	80	5	91
8r	4-H_3CO-C_6H_4	6-Br	4	81	4	88
8s	4-H_3CO-C_6H_4	6-Cl	5	78	3	92
8t	4-H_3CO-C_6H_4	7-Cl	6	77	5	91
8u	4-H_3CO-C_6H_4	6-CH_3	4	79	4	90
8v	4-H_3CO-C_6H_4	8-CH_3	5	80	4	90

which we have optimized the reaction conditions with miscellaneous catalytic amount of $CuSO_4{\cdot}5H_2O$ in various solvents as cited in Table 1.

For the optimization of the yields, miscellaneous prerequisite conditions have been implemented for the emergence of final compounds (Table 1). The presence of $CuSO_4{\cdot}5H_2O$ was evident as no product formation was discerned in its deprivation (Table 1, entry 1). An additional array of reaction mixture was enabled to stir at customary room temperature within the occupancy of sodium ascorbate and $CuSO_4{\cdot}5H_2O$ in DMF and the reaction was accomplished with poor yield (Table 1, entry 2). No product emergence was noticed, when dry *t*-butanol was used as the solvent (Table 1, entry 4). Evidently, an overabundance of water was fruitful to this method. Moreover, the reason could be that it is going to advance the emulsification of 4a-b in this reaction system. It was discerned eventually that the reaction proceeded more proficiently when the reaction was carried out in the existence of $CuSO_4{\cdot}5H_2O$ (15 mmol) in THF:H_2O in 1:1 ratio at room temperature provoking outstanding yield of the cycloaddition product. On that account, kneading use of these optimal reaction conditions, product 8j was secluded with 80% of yield (Table 1, entry 10). Ultimately, we explored indistinguishable reaction in diverse catalyst ratios and solvent systems such as dimethyl sulfoxide (DMSO) (Table 1, entry 3), THF/H_2O (2:1) (Table 1, entry 8), THF/H_2O (1:2) (Table 1, entry 9), *t*-butanol/Water (1:1) (Table 1, entry 5), *t*-butanol/water (1:2) (Table 1, entry 6, 11), *t*-butanol/water (2:1) (Table 1, entry 13), PEG-400 (Table 1, entry 12, 15). Earlier divulged reaction conditions with various solvents, resulted in the product with moderate yields by means of prolonged time. The use of only 15 mol% $CuSO_4{\cdot}5H_2O$ is generous to thrust the reaction to progress further and elevated quantities of the catalyst did not enhance the yields to any eminent expanse (Table 1, entry 14). This composition of catalyst and the solvent were used for the synthesis of title compounds under microwave irradiation method which exerted the enhanced yields (88–92%) instantaneously (3–5 min). At this precise moment, we comprehend the significance and the preponderance of $CuSO_4{\cdot}5H_2O$ and THF/water promoted [3+2] cycloaddition reactions.

Taking into account the aforesaid provisions, an array of structurally conflicting novel quinolinyl-1,2,3-triazolyl-1,2,4-triazol-3(4*H*)-one derivatives 8j-v were synthesized in adequate yields (88–92%) and represented in Table 2.

Surflex-Dock was used to probe the featured intermolecular interactions amid the ligand and the target protein. Docking studies furnish a fair idea related to drug-receptor interactions. Three-dimensional structure information on the target protein was captured from the PDB entry 4DQU. Processing of the protein comprised the deletion of the ligand and the solvent molecules as well as the inclusion of hydrogen atoms. In order to rationalize the biological results of our compounds, molecular docking studies with the enoyl acyl carrier protein reductase (InhA) of *M. tuberculosis* were performed. This objective is present only in the mycobacterium and acknowledged as the molecular target of the frontline anti-tubercular drugs. All the inhibitors were docked into the active site of enzyme InhA-D148G (PDB ID: 4DQU) as portrayed in Fig. 2. The inferred binding energies of the compounds are tabularized in Table 3. The compound 8n makes two hydrogen bonding interactions at the vital site of the enzyme (PDB ID: 4DQU) as portrayed in the Fig. 3A-B, bonding interaction raised from 2nd nitrogen atom of triazole ring with hydrogen of ILE21 (-N——H-ILE21, 2.12 Å) and oxygen atom of carbonyl group present on the 3rd position of triazole ring crafts a bonding interaction with hydrogen of ILE194 (-C═O——H-ILE194, 1.99 Å). The remaining docking portrays are provided in electronic supplementary information. As emphasized in the Fig. 4A–C, the compound 8r makes two hydrogen bonding interactions at the active site of the enzyme (PDB ID: 4DQU), bonding interaction raised from 2nd nitrogen atom of triazole ring with hydrogen of ILE21 (-N——H-ILE21,

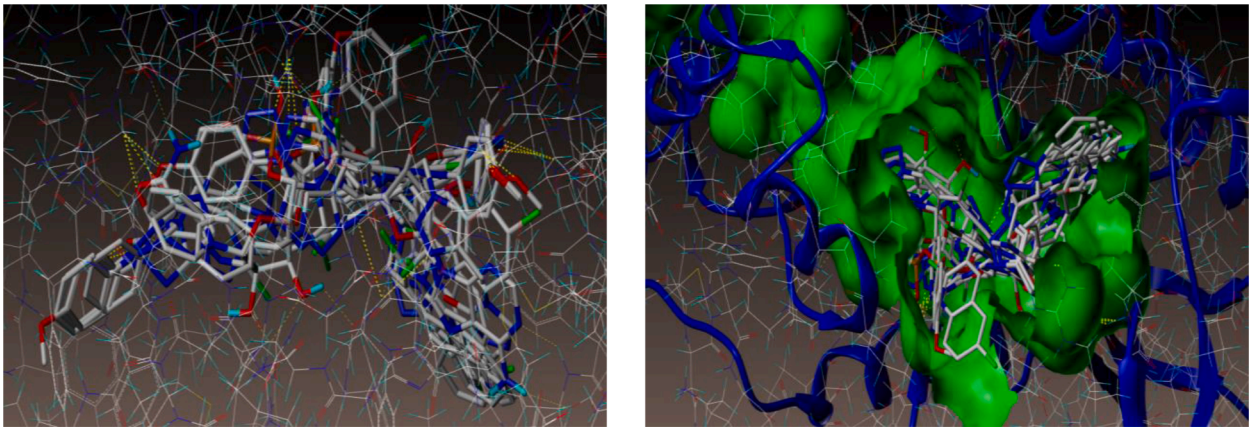


Fig. 2. Binding mode of all the compounds at the active site of the enzyme InhA-D148G (PDB ID: 4DQU).

Table 3
Surflex docking score (kcal/mol) of the title compounds 8j-v on enzyme (PDB ID: 4DQU).

Entry No.	C Score[a]	Crash Score[b]	Polar Score[c]	D Score[d]	PMF Score[e]	G Score[f]	Chem Score[g]	Amino acid involved inH-bond
4DQU_ligand	7.75	−1.15	5.90	−1259.86	−86.99	−334.65	−20.41	–
8j	6.58	−1.41	0.87	−123.135	−2.577	−241.755	−31.308	ILE21
8k	6.65	−1.03	0.01	−144.864	5.896	−255.643	−29.712	–
8l	5.47	−1.10	1.88	−131.442	−24.804	−207.341	−30.912	GLY96
8m	5.37	−2.41	0.21	−128.149	−11.300	−269.945	−25.338	GLY96
8n	7.77	−0.68	2.47	−131.123	−13.083	−218.531	−34.241	ILE21, ILE194
8o	6.49	−0.72	1.18	−114.824	2.852	−214.792	−28.891	THR196
8p	7.91	−1.10	1.41	−135.707	−31.539	−251.691	−35.334	THR196, TYR158
8q	7.57	−2.84	0.96	−165.417	−27.279	−312.274	−39.375	GLY14
8r	6.69	−1.04	1.64	−120.606	5.097	−220.268	−25.655	ILE21, ILE194
8s	6.29	−1.40	1.15	−141.606	−25.267	−242.446	−30.594	ILE194
8t	5.33	−2.95	1.53	−125.070	−70.960	−291.639	−36.366	ARG43, PHE41
8u	8.98	−3.19	1.01	−161.357	−16.595	−329.923	−36.240	GLY14, ASP42
8v	8.64	−3.63	0.98	−162.859	−25.550	−348.613	−37.191	ASP42, GLY14
Isoniazid	3.58	−0.87	4.25	−50.863	−1.345	−100.434	−18.170	–

[a] CScore (Consensus Score) integrates a number of popular scoring functions for ranking the affinity of ligands bound to the active site of a receptor and reports the output of total score.
[b] Crash-score revealing the inappropriate penetration into the binding site. Crash scores close to 0 are favorable. Negative numbers indicate penetration.
[c] Polar score indicating the contribution of the polar interactions to the total score. The polar score may be useful for excluding docking results that make no hydrogen bonds.
[d] D-score for charge and van der Waals interactions between the protein and the ligand.
[e] PMF-score indicating the Helmholtz free energies of interactions for protein–ligand atom pairs (Potential of Mean Force, PMF).
[f] G-score showing energy of hydrogen bonding in the complex (i.e., ligand–protein).
[g] Chem-score points for H-bonding, lipophilic contact, and rotational entropy, along with an intercept term.

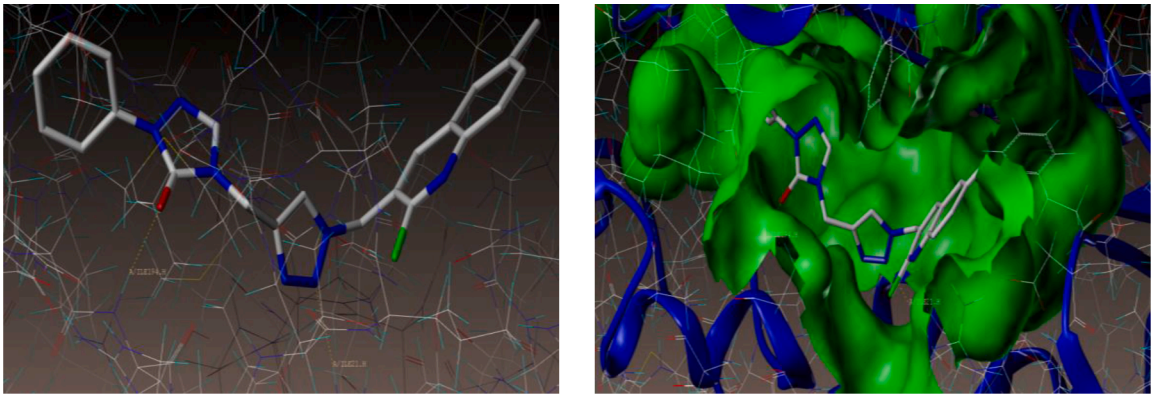


Fig. 3. Binding interaction of compound 8n at the active site of the enzyme InhA-D148G (PDB: 4DQU).

2.45 Å) and oxygen atom of methoxy group present on the phenyl ring makes a bonding interaction with hydrogen of ILE194 (-O——H-ILE194, 2.08 Å). As portrayed in Fig. 5(A–C), the 4DQU_ligand manifested nine H-bonding interactions (Amino acids; SER20, ILE21, THR196, ILE194, GLY96, ILE95, LYS165, VAL165, ASP64). Standard Isoniazid has shown six bonding interactions at the active site of the enzyme (PDB ID: 4DQU) (Amino acids; ALA22, SER20, ILE21, GLY14, SER94, LYS165). Interestingly, most of the newly synthesized compounds have shown same interactions with the amino acids GLY14, ASP42, THR196, ILE21, ILE194, GLY96 as that of 4DQU_ligand and isoniazid. Hence, from these studies, we can corroborate the experimental findings, which suggest that the title compounds act by inhibiting the InhA enzyme. The docked view of isoniazid has been represented in Fig. 6(A–C). Fig. 7(A and B) personifies the hydrophobic and hydrophilic amino acids encompassing to the studied compounds 8n and 8r.

The comparative molecular docking study of synthesized compounds and 4DQU_ligand emphasizes that the synthesized compounds manifested high C-score value. 4DQU_ligand Cscore value is 7.75 whereas four compounds 8n, 8p, 8u and 8v have higher C-score values than the 4DQU_ligand. The synthesized compounds bind to the enzyme in equivalent manner as that of 4DQU_ligand. Thus, the compounds unveiled the resemblance in the genesis of H-bond with the standard drug isoniazid and 4DQU_ligand especially with respect to the residues ILE21 and ILE194 amino acid residues.

In vitro anti-tubercular activity

The synthesized compounds were screened for their anti-tubercular efficacy against *M. tuberculosis* H37Rv (ATCC-27294) using the standard Microplate Alamar Blue Assay (MABA) with standard drug isoniazid. The results were compared with ciprofloxacin and pyrazinamide. All the compounds were tested against *M. tuberculosis* H37Rv at diverse concentrations ranging from 0.20 μg/ml to100 μg/ml. The MIC of the tested compounds divulged in Table 4, revealed that most of the newly synthesized compounds proclaimed lower MIC values ranging from 1.60 μg/ml to 25 μg/ml against *M. tuberculosis* H37Rv strain.

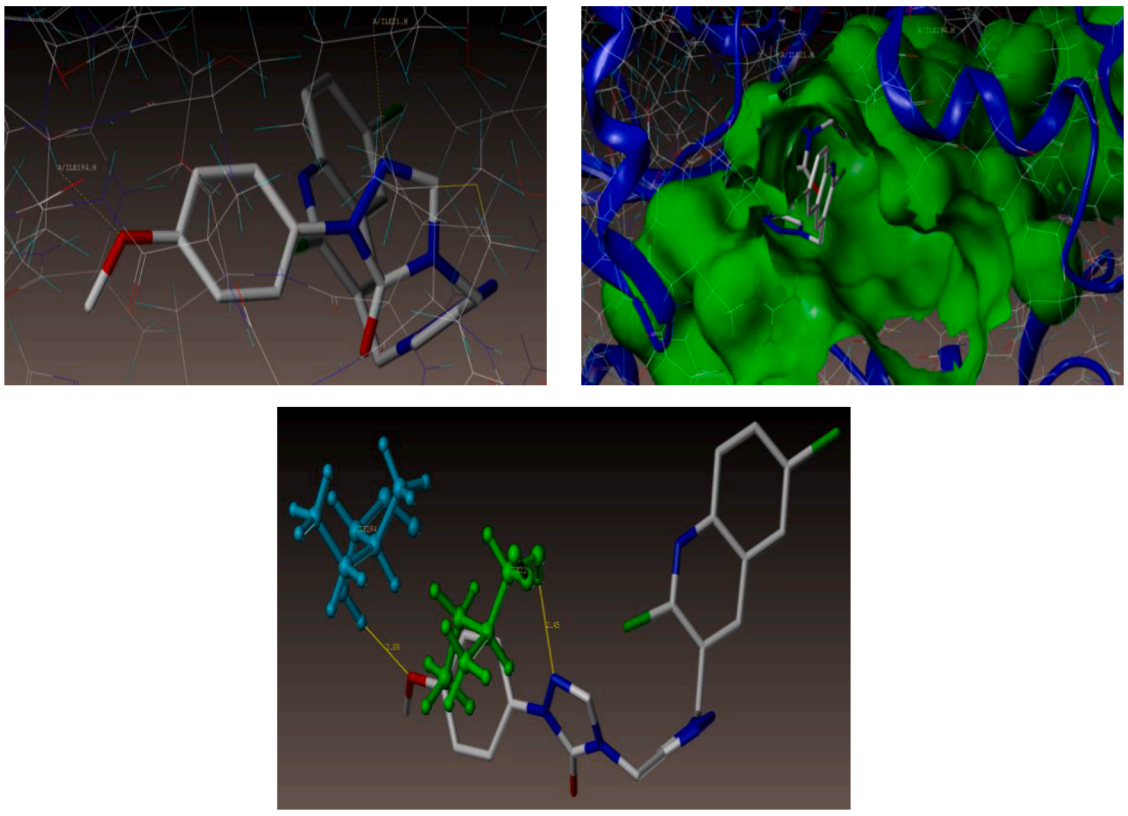


Fig. 4. Interaction of compound 8r at the vital site of the enzyme PDB: 4DQU.

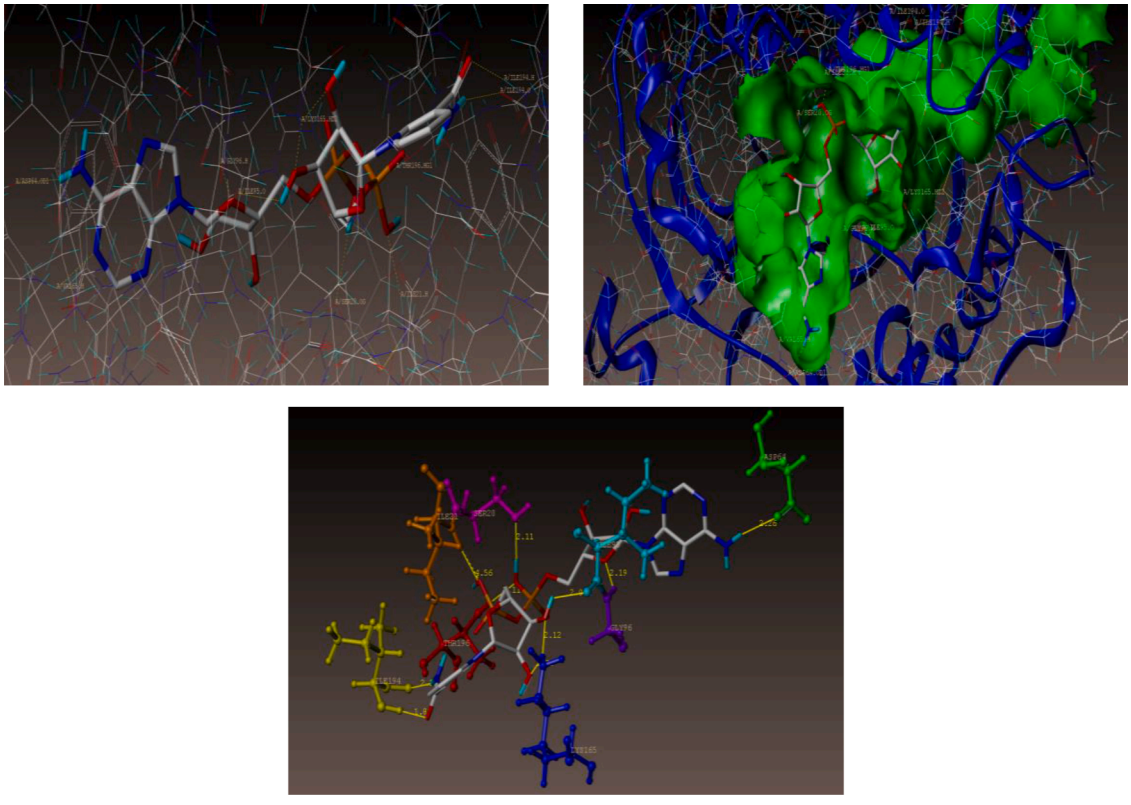


Fig. 5. Interacting sort of compound 4DQU_ligand at the vital site of the enzyme PDB: 4DQU.

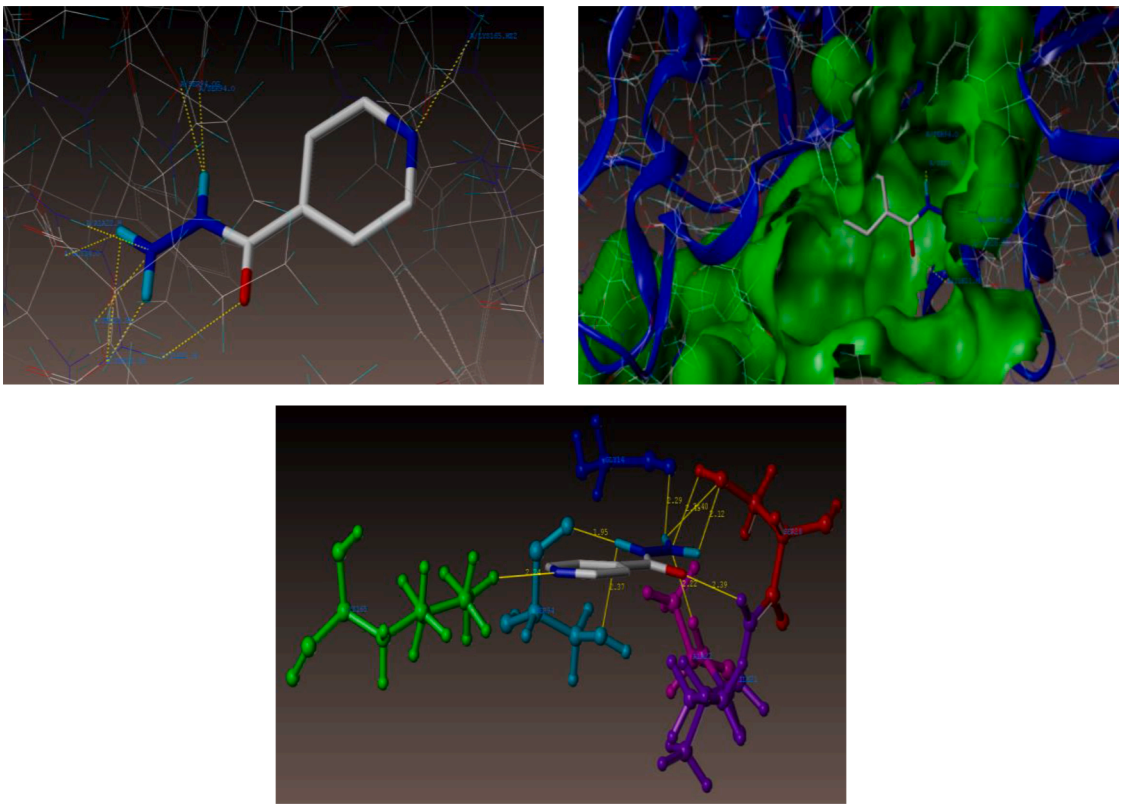


Fig. 6. Docked view of Isoniazid at the active spot of the enzyme PDB: 4DQU.

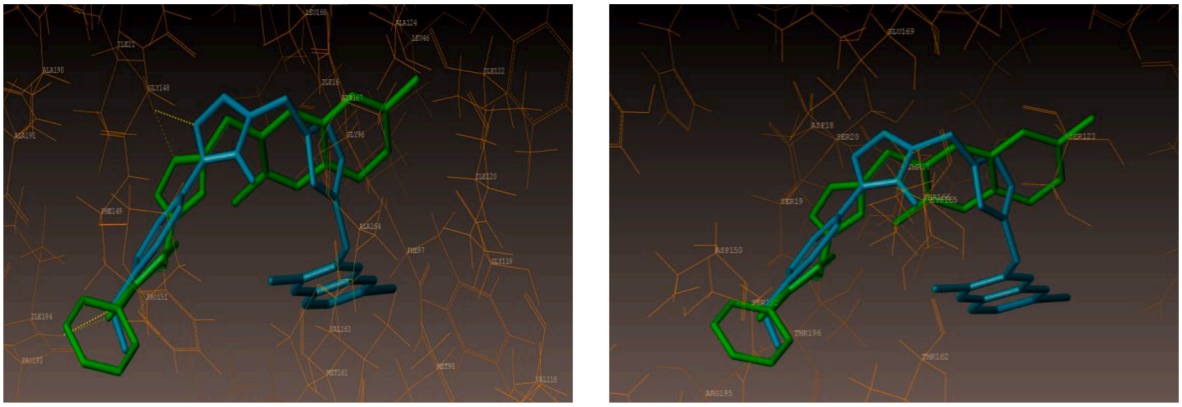


Fig. 7. A) Hydrophobic amino acids surrounded to compounds 8n (green colour) and 8r (cyan colour). B) Hydrophilic amino acids surrounded to compounds 8n and 8r.

The results manifested that compounds 8n (methyl at C_6 position of the quinoline), 8o (methyl at C_7 position of the quinoline), 8p (methoxy at C_6 position of the quinoline), 8s (chloro at C_6 position of the quinoline, 4-methoxy phenyl substitution at C_1 position of the 1,2,4-triazole), 8t (chloro at C_7 position of the quinoline, 4-methoxy phenyl substitution at C_1 position of the 1,2,4-triazole), 8u (methyl at C_6 position of the quinoline, 4-methoxy substitution at C_1 position of the 1,2,4-triazole), 8v (methyl at C_7 position of the quinoline, 4-methoxy at C_1 position of the 1,2,4-triazole) exhibited excellent activity with MICs ranging from 1.60 to 3.12 μg/ml in comparison with isoniazid having MIC of 1.60 μg/ml. Compounds 8j, 8k, 8l, 8m, 8q and 8r illustrated good to moderate activity with MIC of 6.25–25 μg/ml. The results also divulged that activating groups on quinoline and the phenyl ring attached to 1,2,4-triazole were perceived to enhance the anti-tubercular activity (*viz.*, 8n, 8o, 8p, 8s, 8t, 8u and 8v) with MICs 1.60–3.25 μg/ml.

The cytotoxicity studies were executed using MTT assay and imparted as IC_{50} (Table 4) for HEK293 (Normal human kidney cell line). The proportions between cytotoxicity and tubercular assessments facilitated the persistence of selectivity index (SI). According to *Tuberculosis Antimicrobial Acquisition and Coordinating Facility* (TAACF), new drugs must have a selective index equal or superior than 10, with MIC lower than 6.25 μg/ml and low cytotoxicity for further screening. In this

Table 4
In vitro anti-tubercular assessment of MIC (μg/ml) of title compounds 8j-v.

Entry	Ar	R	MIC(μg/ml)	IC_{50}(μg/ml)	SI
8j	C_6H_5	H	25	655.30	26.21
8k	C_6H_5	6-Br	25	1652.0	66.08
8l	C_6H_5	6-Cl	12.5	458.60	36.68
8m	C_6H_5	7-Cl	25	869.30	34.77
8n	C_6H_5	6-CH_3	3.12	477.50	153.04
8o	C_6H_5	8-CH_3	1.60	728.80	233.58
8p	C_6H_5	7-OCH_3	1.60	1008.0	630.00
8q	4-H_3CO-C_6H_4	H	12.5	958.40	76.67
8r	4-H_3CO-C_6H_4	6-Br	6.25	332.70	53.23
8s	4-H_3CO-C_6H_4	6-Cl	3.12	1062.0	340.38
8t	4-H_3CO-C_6H_4	7-Cl	3.12	1465.0	469.55
8u	4-H_3CO-C_6H_4	6-CH_3	1.60	615.20	384.50
8v	4-H_3CO-C_6H_4	8-CH_3	1.60	585.60	366.00
Isoniazid	–	–	1.60	–	–
Ciprofloxacin	–	–	3.12	–	–
Pyrazinamide	–	–	6.25	–	–

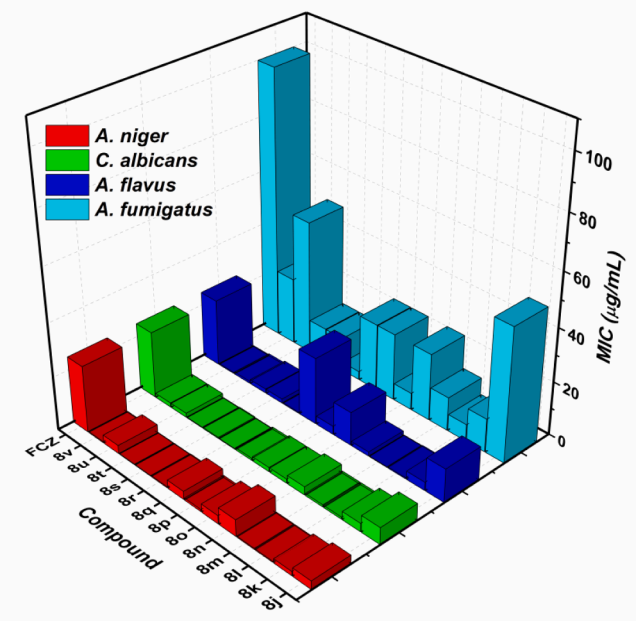


Fig. 8. *In vitro* antifungal results of the compounds 8j-v.

regard the compounds displayed acceptable safety and therapeutic index symbolized by their SI ranging from 26.21 to 630.

In vitro antifungal activity

The *in vitro* antifungal activity of the title compounds (8j-v) were tested against four different pathogenic fungal species viz., *A. niger, C. albicans, A. flavus* and *A. fumigatus.* Fluconazole the clinical antifungal drug was used as a reference. MICs (Minimum Inhibitory Concentrations in μg/ml) are summarized in Fig. 8.

The antifungal results revealed that all the compounds have exhibited excellent activity against the tested fungal strains. The synthesized compounds are proven to be better as compared with the marketed drug fluconazole. The compounds (8j-v) exhibited excellent activity against

A. niger with MIC values ranging from 0.20 to 6.25 μg/ml, *C. albicans* with MIC values ranging from 0.20 to 6.25 μg/ml, *A. flavus* with MIC values ranging from 0.20 to 12.50 μg/ml and *A. fumigatus* with MIC values ranging from 3.12 to 50 μg/ml in comparison with fluconazole.

In silico ADME prophecy

The measure of drug success is not only its superior productiveness but also an adequate ADME (absorption, distribution, metabolism, and excretion) portrait. Herein, we have computed molecular weight (MW), logarithm of partition coefficient (miLog P), number of hydrogen bond acceptors (*n*-ON), number of hydrogen bonds donors (*n*-OHNH), topological polar surface area (TPSA), number of rotatable bonds (*n*-ROTB), and Lipinski's rule of five[22] using Molinspiration online property calculation toolkit.[23] Absorption (% ABS) was calculated by: % ABS = 109 – (0.345 TPSA).[24] Drug-likeness model score (a collective property of physico-chemical properties, pharmacokinetics, and pharmacodynamics of a compound is represented by a numerical value) was figured by MolSoft software.[25]

The computational study of compounds 8j-v was performed to predict pharmacokinetic parameters, bioactivity and drug likeliness properties and is tabulated in Tables 5 and 6. The computational study reveals that compounds displayed a good % ABS (% absorption) ranging from 77.02 to 80.21%. Furthermore, all the synthesized compounds 8j-v obeyed the Lipinski's rule of five (miLog P $\leq$ 5). A molecule likely to be developed as an orally active drug aspirant should not be evidence for more than one violation of the following four criteria: miLog P (octanol–water partition coefficient) $\leq$ 5, molecular weight $\leq$500, number of hydrogen bond acceptors $\leq$10 and number of hydrogen bond donors $\leq$5.[26] The probability of a molecule to be potent will be greater for higher value of drug likeliness model score. Without exception all these compounds emerged having good potential for ultimate development as oral agents as they have obeyed the benchmark for orally active drugs.

In summary, a simple, efficient and green synthesis of novel quinolinyl-1,2,3-triazolyl-1,2,4-triazol-3(4*H*)-ones (8j-v) have been flourished. All the molecules were synthesized in modest to excessive yields under placid conditions. Both THF/water and $CuSO_4{\cdot}5H_2O$ are affordable and eco-friendly. The study revealed prominence of $CuSO_4{\cdot}5H_2O$ We comprehend the significance and the preponderance of $CuSO_4.5H_2O$ and THF/water promoted [3+2] cycloaddition reactions.

The newly synthesized compounds were screened for anti-tubercular and antifungal assay. The anti-TB results manifested that compounds 8n, 8o, 8p, 8s, 8t, 8u and 8v with MICs 1.60–3.25 μg/ml revealed excellent activity in comparison with the marketed drugs isoniazid (MIC 1.60 μg/ml) ciprofloxacin (MIC 3.12 μg/ml) and pyrazinamide (MIC 6.25 μg/ml). The compounds (8j-v) exhibited admirable antifungal activity against *A. niger* with MIC values ranging from 0.20 to 6.25 μg/ml, *C. albicans* with MIC values ranging from 0.20 to 6.25 μg/ml, *A. flavus* with MIC values ranging from 0.20 to 12.50 μg/ml and *A. fumigatus* with MIC values ranging from 3.12 to 50 μg/ml in comparison with fluconazole. The *in vitro* and *in silico* studies imply that these triazoles appended quinolines may acquire the ideal structural prerequisites for auxiliary expansion of novel therapeutic agents.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 5
Pharmacokinetic parameters of the compounds 8j-v.

Entry	MW	miLogP	TPSA	*n* Atoms	*n* ON	*n* OHNH	*n* Violation	*n* rotb	% ABS
8j	417.86	2.74	83.44	30	8	0	0	5	80.21
8k	496.76	3.53	83.44	31	8	0	0	5	80.21
8l	452.31	3.40	83.44	31	8	0	0	5	80.21
8m	452.31	3.40	83.44	31	8	0	0	5	80.21
8n	431.89	3.17	83.44	31	8	0	0	5	80.21
8o	431.89	3.14	83.44	31	8	0	0	5	80.21
8p	447.89	2.77	92.67	32	9	0	0	6	77.02
8q	447.89	2.80	92.67	32	9	0	0	6	77.02
8r	526.78	3.58	92.67	33	9	0	1	6	77.02
8s	482.33	3.45	92.67	33	9	0	0	6	77.02
8t	482.33	3.45	92.67	33	9	0	0	6	77.02
8u	461.91	3.22	92.67	33	9	0	0	6	77.02
8v	461.91	3.20	92.67	33	9	0	0	6	77.02

MW: Molecular weight, miLog P: Logarithm of partition coefficient, TPSA: Topological polar surface area, *n*-ON Acceptors: Number of hydrogen bond acceptors, *n*-OHNH donors: Number of hydrogen bonds donors, *n*-ROTB: Number of rotatable bonds, % ABS: Percentage absorption.

Table 6
Bioactivity and druglikeliness scores of compounds 8j-v.

Entry	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor	Drug likeliness
8j	0.28	−0.05	−0.01	−0.25	−0.10	0.08	0.02
8k	0.17	−0.14	−0.05	−0.37	−0.22	0.00	0.01
8l	0.27	−0.06	−0.02	−0.26	−0.11	0.06	0.29
8m	0.28	−0.03	−0.03	−0.26	−0.12	0.07	0.30
8n	0.23	−0.12	−0.06	−0.27	−0.15	0.02	0.00
8o	0.24	−0.15	−0.05	−0.24	−0.17	0.03	0.47
8p	0.23	−0.11	−0.01	−0.23	−0.15	0.04	0.08
8q	0.23	−0.11	−0.04	−0.25	−0.15	0.03	−0.04
8r	0.12	−0.20	−0.08	−0.35	−0.25	−0.04	−0.23
8 s	0.21	−0.12	−0.06	−0.25	−0.16	0.02	0.04
8 t	0.23	−0.08	−0.06	−0.25	−0.16	0.03	0.03
8u	0.18	−0.17	−0.08	−0.27	−0.19	−0.02	−0.29
8v	0.19	−0.19	−0.08	−0.24	−0.21	−0.01	0.29

GPCR-G-Protein-Coupled Receptors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2021.127984.

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