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A click chemistry approach for the synthesis of cyclic ureido tethered coumarinyl and 1-aza coumarinyl 1,2,3-triazoles as inhibitors of *Mycobacterium tuberculosis H37Rv* and their *in silico* studies

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ABSTRACT

Nucleoside bases like uracil, pharmacophoric triazoles and benzimidazolones have been used during the present study to design molecular matrices for antitubercular activity, employing Click Chemistry. Click triazoles **4/7/10** have been obtained by the reaction of 4-(Azidomethyl)-2*H*-chromen-2-ones/quinolin-2(1*H*)-ones **3** and propargyl ethers **2/6/9** derived from theophylline/6-methyl uracil/2-benzimidazolone respectively. In addition to spectral data structures have been confirmed by single crystal X-ray diffraction studies in case of uracil *bis* alkyne (**6**) and theophylline mono triazole (**4c**). Theophylline linked mono triazoles, **4(a-d)** and 6-methyl uracil linked *bis* triazoles, **7(a-e)** have been found to inhibit *Mycobacterium tuberculosis H37Rv* with MIC values in the range 55.62–115.62 μM. Benzimidazolone *bis* triazoles, **10(a-n)** showed better activity with MIC in the range 2.33–18.34 μM. Molecular modeling studies using Surflex-Dock algorithm supported our results.

1. Introduction

Tuberculosis (TB) continues to be a disease with one of the highest mortality rates. World Health Organization (WHO) has estimated 10 million cases in 2017 around the world and 1.6 million deaths among them.[1] There is no decrease in the mortality rates despite the availability of many clinically accepted drugs for the treatment of TB. A unique feature of the fatal pathogen *Mycobacterium tuberculosis* (Mtb) is its ability to combat TB drugs leading to multi drug resistant (MDR), extensively drug resistant (XDR) and totally drug resistant (TDR) tuberculosis. Drug resistant TB requires a long-term treatment using a combination of isoniazid, rifampicin, ethambutol and pyrazinamide. A number of review[2–4] and research articles[5–7] have emphasized the need for advanced therapeutic remedies and new drug regimens for TB.

Functionalized heterocycles have emerged as lead molecules in the chemotherapy of tuberculosis.[8] Heterocyclic moieties like quinolones,[9] pyrroles,[10] azoles,[11] pyridines,[12] and flavones[13] have been combined to obtain synergistic effects and have emerged as promising antitubercular agents with low MIC values.[14] Use of coumarins and 1,2,3-triazoles in combination with aryloxy,[15] alkylspacers[16] and benzimidazole[17] (Fig. 1A) has emerged as a powerful approach in designing anti-TB agents. Biodegradation of coumarins leads to *in situ* generation of carboxylic and phenolic –OH groups[18] which facilitates penetration of drugs through the bacterial cell wall.[19] Potent anti-TB activity of triazoles can be ascribed to their ability to inhibit mycobacterial growth by blocking lipid biosynthesis and hydrogen bonding interaction at the active site of enzymes viz. DprE1 (decaprenylphosphoryl-*b*-D-ribose-20-epimerase) and InhA (NADH dependent trans enoyl-acyl-carrier-protein reductase), which enhances the bioavailability of the molecule.[20]

Cyclic urea and ureides have been identified as pharmacophores in a number of bioactive compounds.[21–23] Further, they have been reported to exhibit a wide range of biological activities, such as antimicrobial,[24] antitubercular,[25] antitumor,[26] anti-HIV[27] and antidiabetic.[28] They have also been reported to be NK_1 antagonists,[29] Chk_1 inhibitors[30] and calcium selective fluoroionophores.[31] Coumarinyl theophylline[32] (Fig. 1B) and amidyl theophylline[33] have been reported to exhibit promising anti-TB activity. Among the uracil derivatives[34,35] *N*-cyclopentenyl uracil[36] (Fig. 1C) inhibited the growth of Mtb at a higher concentration. During last decade, a variety of nucleoside analogues have been reported to target thymidylate synthase (ThyX), thymidine monophosphate kinase (TMPKmt), adenosine kinase (ADK) and purine nucleoside phosphorylase which are the enzymes involved in nucleoside

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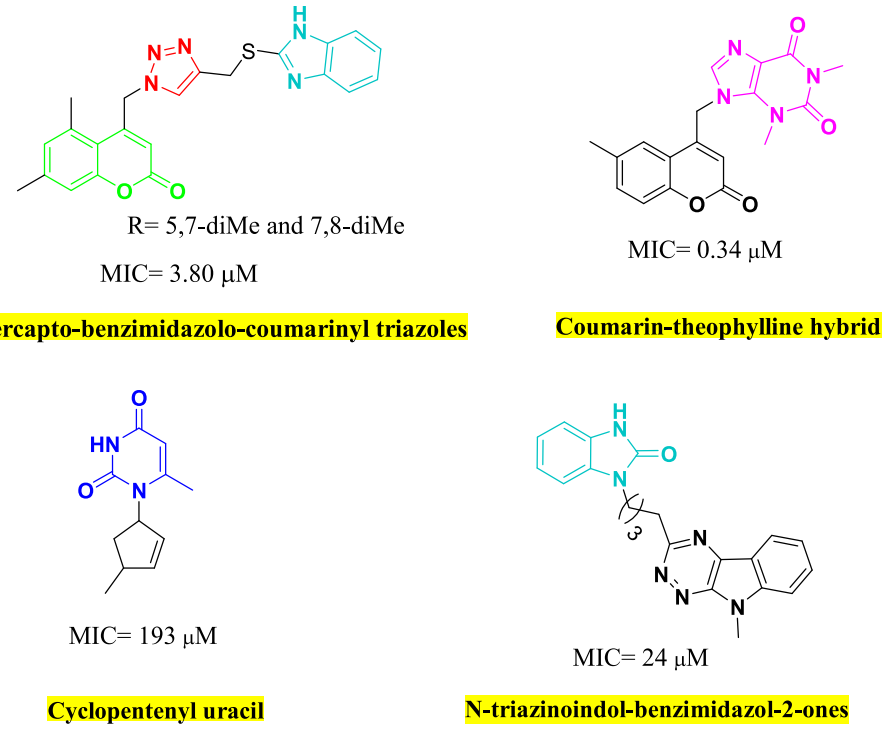


Fig. 1. Present study related anti-tubercular agents.

salvage pathway.[37] Nucleoside salvage pathway utilizes number of enzymes, whose structural and functional features are different for Mtb compared to humans.[38] *N*-triazinoindol-benzimidazol-2-ones were reported as Mtb inhibitors in which the cell wall enzyme RmlC (dTDP-6-deoxy-D-*xylo*-4-hexulose 3′,5′-epimerase) was targeted[39] (Fig. 1D). Penetration of drugs through Mtb cell wall is very difficult since it is made up of saturated long chain mycolic acids. Hence, targeting RmlC will be a key factor in development of anti-TB drugs.

In view of our earlier reports on antitubercular activity of coumarinyl triazoles[15,17,19] and reports on corresponding theophyllines[32] as well as ability of benzimidazolones to inhibit enzyme RmlC,[39] it was thought of interest to design molecular hybrids with these pharmacophoric moieties, to achieve a synergistic effect. Present paper is an effort towards development of such hybrids of coumarin, triazole, pyrimidines and benzimidazolones through Click Chemistry. Alkynes derived from cyclic urea and ureides and azides derived from 4-bromomethyl coumarins/1-aza coumarins have been used to obtain coumarinyl mono/*bis*-1,2,3-triazoles of theophylline, uracil and benzimidazolone (Fig. 2). Structurally, this set include three essential pharmacophoric motifs, coumarin- 'cell wall penetrators', triazole- 'stable and interactive motif' and cyclic urea and ureides- 'Mtb biosynthesis inhibitors'.

2. Results and discussion

2.1. Chemistry

Coumarin linked 1,2,3-triazoles developed via 'Copper catalyzed Azide Alkyne Cycloaddition reaction (CuAAC)' have been reported from our lab[15,17,19] and same synthetic strategy has been applied here with few modifications. Dipolarophiles **2** and **9** have been synthesized by the reaction of theophylline and benzimidazol-2-one with propargyl bromide according to earlier reports[40,41] (Schemes 1 and 3). Another dipolarophile 6-methyl uracil *bis*-propargyl, **6** has been synthesized from 6-methyl uracil and propargyl bromide using tetra-butyl ammonium bromide (TBAB) and potassium carbonate in DMF (Scheme 2). Spectral data and single crystal X-ray studies of **6** confirmed *bis*-*N*-alkylation of 6-methyl uracil, **5**. The required dipolar azides for CuAAC reaction were obtained by a nucleophilic substitution reaction between sodium azide and 4-(bromomethyl)-2*H*-chromen-2-ones[42a]/quinolin-2(1*H*)-ones[42b] **3** in acetone/DMF at room temperature according to earlier reports.[15,17]

Cycloaddition reaction between dipolarophiles **2/6/9** and azides **3** was achieved using ascorbic acid and sodium carbonate along with copper sulfate in catalytic amounts in DMF/water, 1:1 (v/v) under reflux conditions. CuAAC being a highly regioselective reaction[43] afforded exclusively 1,4-disubstituted mono and *bis*-coumarinyl/1-aza coumarinyl triazoles **4(a-d)** and **7(a-e)** of cyclic ureides (**2** and **6** respectively), whereas *bis*-coumarinyl/1-aza coumarinyl triazoles **10(a-n)** of cyclic urea (**9**) in highly pure form.

Spectroscopic data of the synthesized triazoles **4(a-d)**, **7(a-e)** and **10(a-n)** confirmed their structures. Compound **4a** (X = O, R = 6-CH_3), theophylline coumarinyl triazole exhibited three carbonyl stretching bands at 1652 cm^{-1}, 1702 cm^{-1} and 1713 cm^{-1} in which first two bands are of theophylline carbonyl groups and third one due to lactone carbonyl stretching. ^{1}H NMR of **4a** (X = O, R = 6-CH_3) showed singlets at δ 8.26 and 8.24 ppm corresponding to C_5-H of triazole and C_8-H of theophylline respectively. C_3-H of coumarin resonated as a singlet at 5.74 ppm. Methylene protons linked to coumarin C_4 and cyclic ureide N_9 resonated as singlets at 5.93 and 5.60 ppm respectively. C_7-H and C_8-H of coumarin appeared as doublets with J_{ortho} = 8.4 Hz at 7.47 and 7.43 ppm respectively whereas C_5-H as a singlet at 7.61 ppm. Coumarin C_6-CH_3 protons resonated as a singlet at 2.35 ppm and two singlets at 3.20 and 3.41 ppm correspond to N-CH_3's protons. Further molecular ion peak in EI-MS at 433 *m/z* (50%) supported above results. Finally, the formation of cyclic theophylline mono-triazoles has been confirmed by single crystal X-ray diffraction studies of **4c** (CCDC No. 1911185). Fig. 3 depicts ORTEP of **4c** in which two molecules of **4c** have stacked one over the other.

Compound **7a** (X = O, R = 6-CH_3), 6-methyl uracil *bis*-coumarinyl triazole also exhibited three carbonyl stretching bands at 1661 cm^{-1}, 1707 cm^{-1} and 1727 cm^{-1} in which first two bands are of uracil moiety and third one due to lactone carbonyl stretching. ^{1}H NMR of **7a** (X = O, R = 6-CH_3) showed singlets at δ 8.26 and 8.12 ppm corresponding to C_5-H of both triazole rings. However C_5-H of uracil

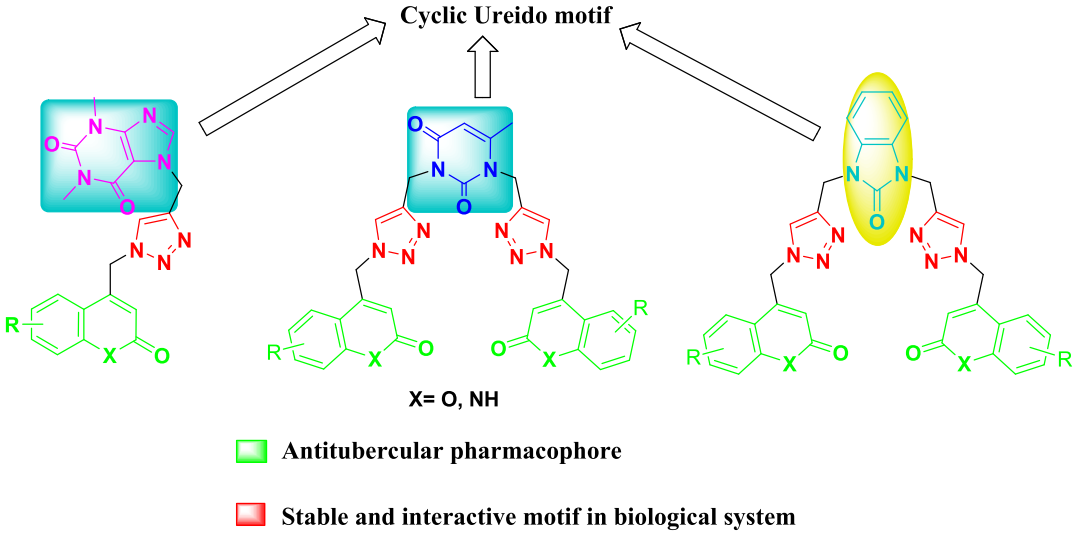


Fig. 2. Targeted Cyclic Ureido based coumarinyl-1,2,3-triazoles.

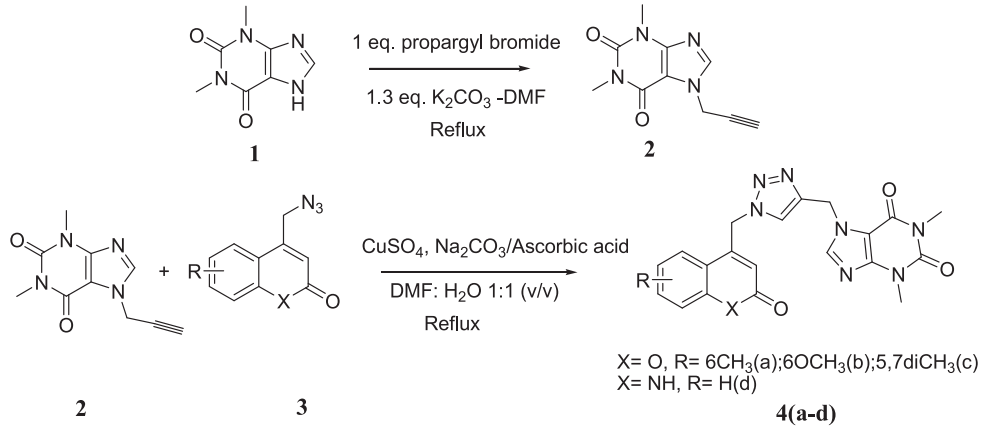
appeared as a singlet at 5.80 ppm. C_3-H and C_5-H of two coumarin rings resonated as two pairs of singlets at 5.737–5.730 ppm and 7.65–7.64 ppm respectively. Methylene protons linked to coumarin C_4 and uracil N_1/N_3, also resonated as two pairs of singlets at 5.92–5.89 ppm and 5.11–5.06 ppm respectively. C_7-H and C_8-H of coumarin appeared as two pairs of doublets with $J = 8.8$ Hz at 7.476–7.479 and 7.327–7.329 ppm respectively. C_6-CH_3 protons of coumarin resonated as two singlets at 2.37–2.36 ppm whereas singlet at 2.41 ppm corresponds to C_6-CH_3 protons of uracil moiety. Further molecular ion peak in EI-MS at 632 *m/z* (12%) for compound **7a** confirmed the formation of uracil *bis*-coumarinyl triazole. ^{1}H NMR of **7a** exhibited duplicates for all the signals excluding two signals at 2.41 and 5.80 ppm, which is due to the unsymmetrical nature of the molecule.

Compound **10a** (X = O, R = 6-CH_3), benzimidazol-2-one *bis*-coumarinyl triazole exhibited two carbonyl stretching bands at 1693 cm^{-1} and 1724 cm^{-1} due to cyclic urea and lactone carbonyl stretchings respectively. ^{1}H NMR of **10a** (X = O, R = 6-CH_3) showed singlets at δ 8.24 and 5.72 ppm corresponding to C_5-H of triazole and C_3-H of coumarin respectively. Methylene protons linked to coumarin C_4 and benzimidazol-2-one N_1/N_3 resonated as singlets at 5.87 and 5.13 ppm respectively. C_7-H and C_8-H of coumarin appeared as doublets with $J = 8.4$ Hz at 7.43 and 7.29 ppm respectively whereas C_5-H as a singlet at 7.57 ppm. Two doublet of doublets with $J = 6$ and 3.2 Hz at 7.15 and 6.98 ppm correspond to aromatic protons of benzimidazol-2-one moiety. Coumarin C_6-CH_3 protons resonated as a singlet at 2.30 ppm. Further (M + H) peak observed at 641 *m/z* (65%) in positive mode ESI of compound **10a** confirmed the formation of benzimidazol-2-one *bis*-coumarinyl triazole. All the signals of coumarin and triazole ring have shown double integration in ^{1}H NMR of **10a**, which is due to symmetrical nature of the molecule.

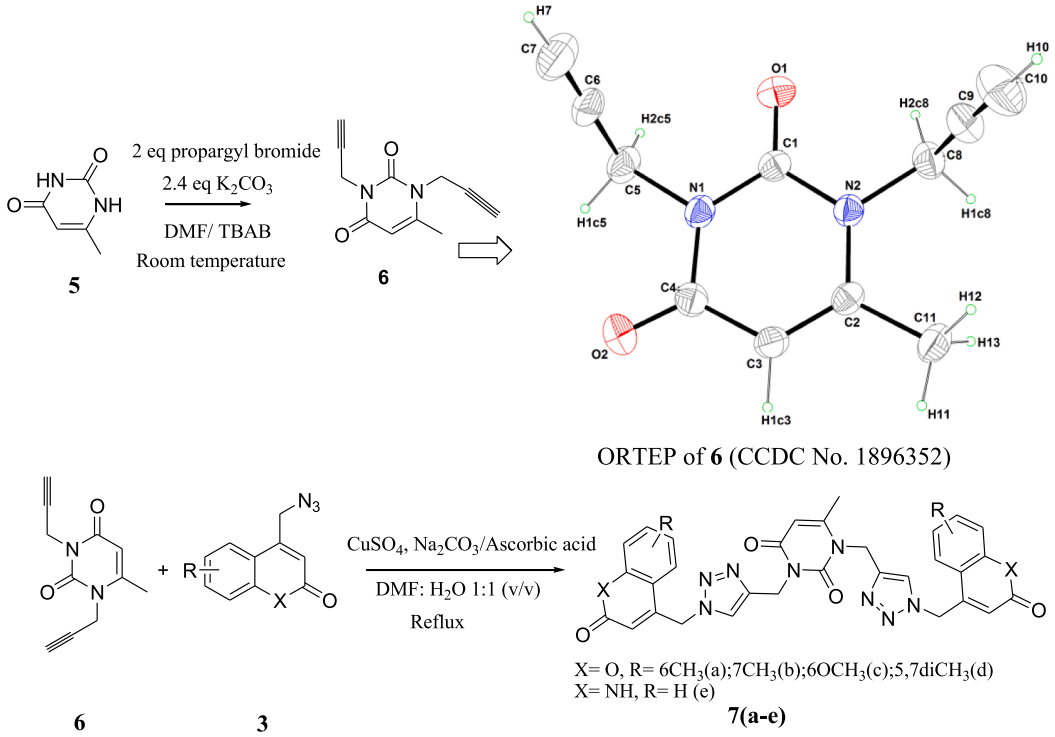
2.2. *Mycobacterium tuberculosis H37Rv inhibition*

All the synthesized compounds were tested for *Mycobacterium tuberculosis* strain *H37Rv* inhibition using microplate Alamar Blue assay (MABA).[44] Theophylline mono-triazole compounds, **4(a-d)** and 6-methyl uracil *bis*-triazole compounds, **7(a-e)** have exhibited moderate inhibition of *M. tuberculosis H37Rv*, with minimum inhibitory concentration (MIC) in the range 55.62–115.62 μM (Table 1). Benzimidazolone *bis*-triazoles, **10(a-n)** have inhibited *M. tuberculosis H37Rv* with MIC 2.35–18.34 μM (Table 1). Twelve compounds (**10a**, **10b**, **10c**, **10d**, **10f**, **10g**, **10h**, **10i**, **10j**, **10l**, **10m** and **10n**) among fourteen synthesized benzimidazolone *bis*-triazoles have shown MIC values in the range 2.35–8.76 μM, which is less than that of Ciprofloxacin, a standard drug used whose MIC was 9.43 μM. Compound **10k** was as active as Streptomycin (MIC = 10.74 μM). Compound **10e** showed considerable inhibition with MIC 18.25 μM less than that of Pyrazinamide.

Lipophilicity of theophylline mono-triazoles, **4(a-d)** and 6-methyl uracil *bis*-trazoles, **7(a-c, e)** (Clog P: −0.007 to 1.121) was sufficiently lower than the benzimidazolone *bis*-triazoles, **10(a-n)** (Clog P: 0.428 to 4.482). Replacement of 6-methyl uracil with benzimidazolone,



Scheme 1. Synthesis of theophylline (cyclic ureide) coumarinyl triazoles.

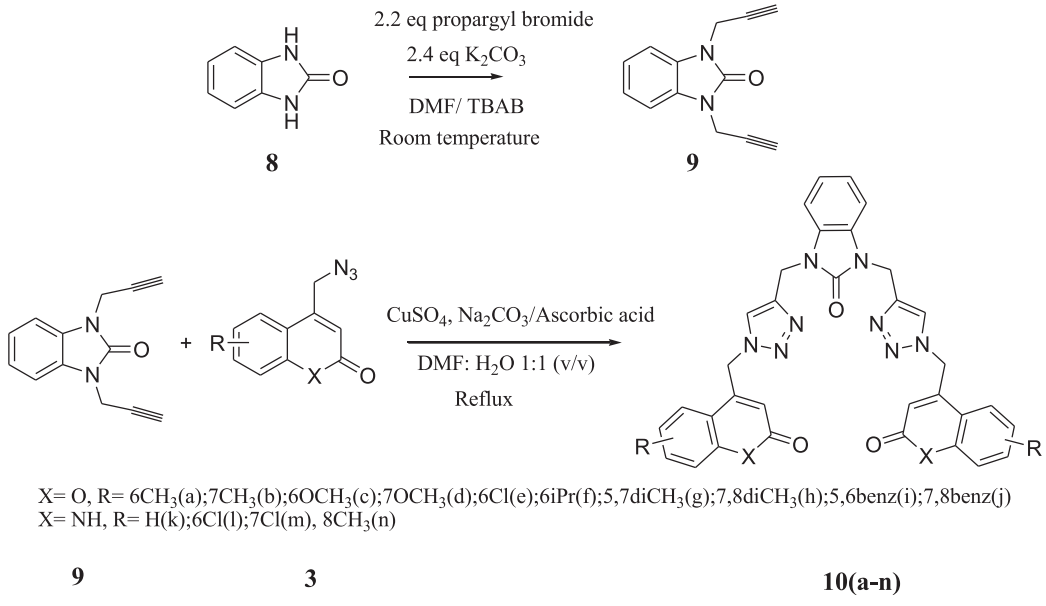


Scheme 2. Synthesis of 6-methyl uracil (cyclic ureide) *bis*-coumarinyl triazoles.

enhanced the lipophilicity of coumarinyl *bis*-triazoles, which in turn increased Mtb *H37Rv* inhibition. However, lipophilicity of one of the uracil *bis*-triazole, **7d** (Clog P: 2.119) was as high as that of benzimidazolone *bis*-triazoles **10(k-n)** (Clog P: 0.428 to 2.148). Here, increase in the lipophilicity of synthesized compound has not enhanced the ability of the drug molecules to inhibit *Mycobacterium tuberculosis H37Rv*. Further, molecular docking studies have been carried out to rationalize their behavior (see Section 3, below).

2.3. Cytotoxicity and stability of the synthesized compounds

We have found a good number of active anti-TB compounds (**10a**, **10b**, **10c**, **10d**, **10f**, **10g**, **10h**, **10i**, **10j**, **10l**, **10m** and **10n**) and the further step was to examine their toxicity where Human Embryonic kidney (HEK293) cells have been employed. From Table 1, tested compounds exhibited moderate to low levels of cytotoxicity with IC_{50} values of the human embryonic kidney cells in the range of 943–12294 μM, and none of 23 compounds exhibited any significant cytotoxic effects, suggesting huge potential for their *in vivo* use as anti-TB agents. Theophylline mono-triazoles, **4(a-d)** and 6-methyl uracil *bis*-triazoles, **7(a-e)** moderately inhibited HEK293 cell line with IC_{50} 10 to 100 folds higher than the respective MIC values for Mtb *H37Rv* inhibition. A second level of cytotoxicity was observed for benzimidazolone *bis*-triazoles with IC_{50} 100–10000 folds higher than respective Mtb *H37Rv* MIC values, which suggest that compounds **10a-10n** can act as new leads for the development of anti-TB drugs.



Scheme 3. Synthesis of cyclic urea (benzimidazol-2-one) *bis*-coumarinyl triazoles.

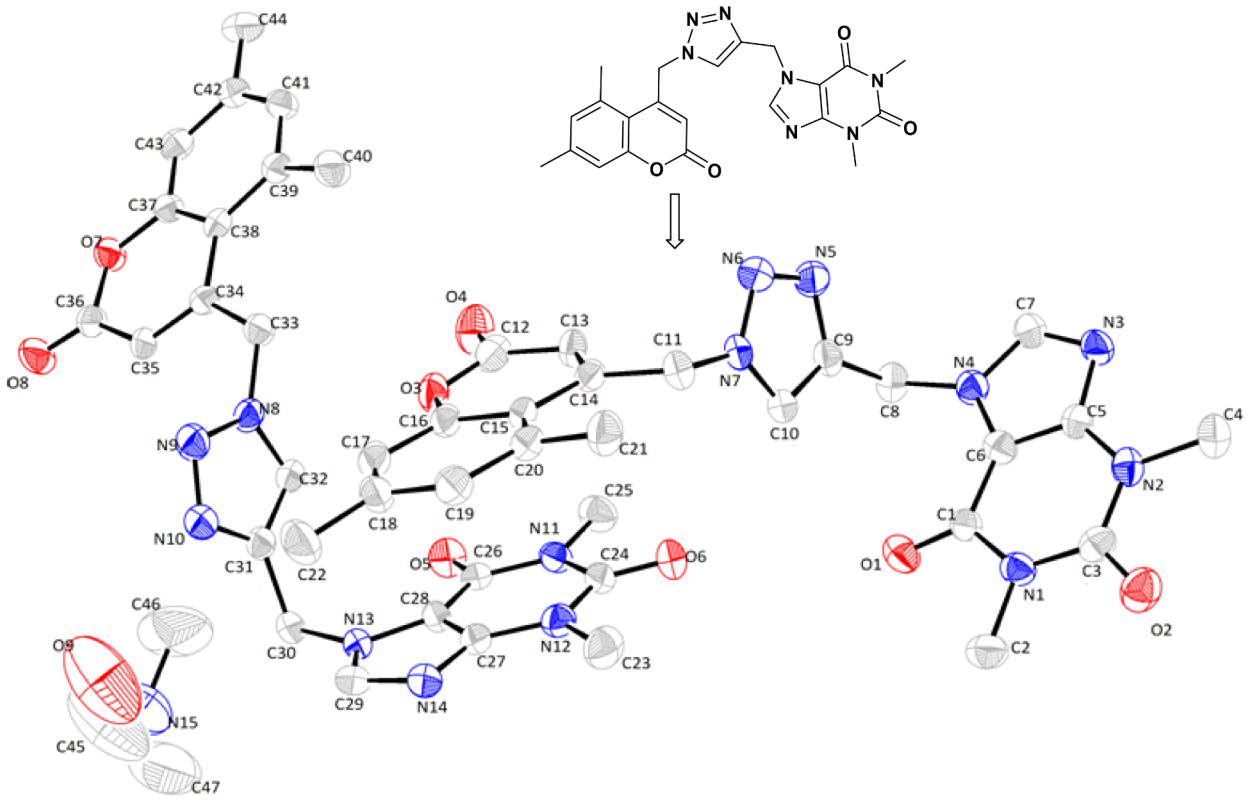


Fig. 3. ORTEP diagram of **4c** (two molecules stacked).

Table 1
Inhibition of *Mycobacterium tuberculosis H37Rv* by Theophylline, 6-methyl uracil and benzimidazolone coumarinyl/1-aza coumarinyl mono and *bis*-triazoles, **4(a-d)**, **7(a-e)** and **10a-n** and their cytotoxicity against the Human Embryonic kidney (HEK293) cells.

Compounds	X	R	MIC (μM)	Clog P[a]	Cytotoxicity IC_{50} (μM)
4a	O	6-CH_3	115.36	0.592	1109.77
4b	O	6-OCH_3	55.62	0.427	1376.65
4c	O	5,7-CH_3	111.17	1.091	ND
4d	NH	8-CH_3	115.62	−0.007	5041.90
7a	O	6-CH_3	79.07	1.121	1276.89
7b	O	7-CH_3	79.07	1.121	ND
7c	O	6-OCH_3	75.23	0.789	1521.55
7d	O	5,7-CH_3	75.67	2.119	ND
7e	NH	8-CH_3	79.28	−0.079	1152.60
10a	O	6-CH_3	2.49	2.626	3579.17
10b	O	7-CH_3	2.49	2.626	3521.42
10c	O	6-OCH_3	4.64	2.294	4121.01
10d	O	7-OCH_3	2.37	2.294	4617.55
10e	O	6-Cl	18.34	3.054	ND
10f	O	6-$CH(CH_3)_2$	2.49	4.482	3197.70
10g	O	5,7-CH_3	2.39	3.624	943.47
10h	O	7,8-CH_3	2.39	3.524	3429.04
10i	O	5,6-benzo	8.76	3.976	1133.42
10j	O	7,8-benzo	2.34	3.976	3126.09
10k	NH	H	10.23	0.428	ND
10l	NH	8-CH_3	2.50	1.426	4340.20
10m	NH	6-Cl	2.35	2.148	12294.15
10n	NH	7-Cl	2.35	2.148	4570.94
Pyrazinamide	–	–	25.38	−0.676	
Streptomycin	–	–	10.74	−4.278	
Ciprofloxacin	–	–	9.43	−1.146	

[a] Clog P values obtained from Chem-Office 2004 software: ND – Not determined.

Stability studies indicated that the samples were stable at room temperature. There was no significant change in the pattern of absorption and emission spectra of the compounds when observed in DMF and various buffers of pH 6–8 (supplementary Fig. S-1) over a period of 24 h. UV and fluorescence spectra of coumarinyl triazoles showed decrease in intensity when observed after 72 h in buffers. However, two characteristic absorption bands of coumarinyl triazoles around 290 and 320 nm and their emission bands[45] were unaltered in all the cases.

3. *In silico* studies

3.1. Molecular modeling

Molecular modeling has been used to predict the binding interaction of the compounds in the binding pocket of the enzymes. Molecular docking was carried out using Sybyl-X, version 2.0,[46] running on Intel® Core™ i3-2130 CPU@ 3.40 GHz processor using Windows 7 professional workstation. Surflex-Dock algorithm of sybyl-X 2.0 was used to dock designed compounds. The 3D crystal structures of enzymes *Mycobacterium tuberculosis H37Rv* InhA-D148G mutant (enoyl-[Acyl-Carrier-Protein] reductase) in complex with NADH and RmlC (dTDP-6-deoxy-D-*xylo*-4-hexulose 3′,5′-epimerase) with dTDP-rhamnose were downloaded from the Protein Data Bank with PDB entry codes 4DQU and 2IXC respectively and used for initial docking studies. Co-crystalized ligands (co-factors) were removed from the downloaded structures, water molecules were removed, essential H atoms were added, and side chains were fixed during protein preparation. Gasteigere-Huckel charges[47] were calculated for the ligand, while Amber 7FF02 were used for the protein. The model was then subjected to energy minimization following the gradient termination of the Powell method for 3000 iterations using Tripos force field with non-bonding cut off set at 9.0 and the dielectric constant set at 4.0. The binding of the synthesized compounds was also estimated using a variety of scoring functions that have been compiled into the single consensus score (C-Score).

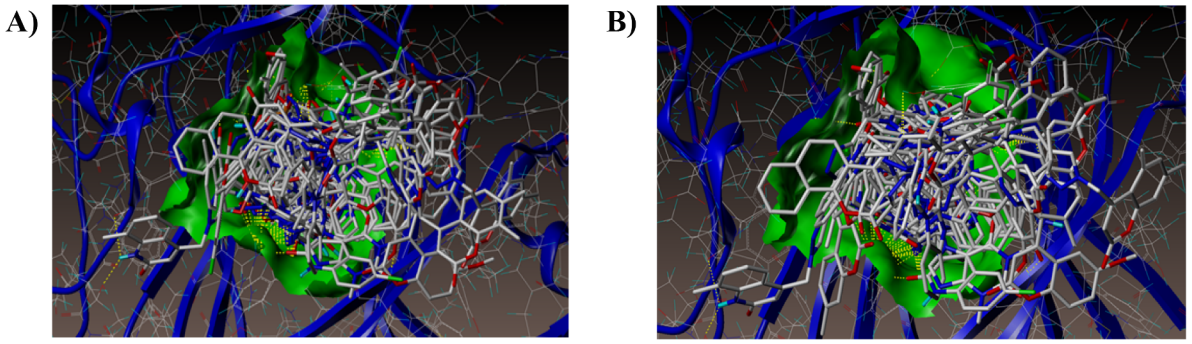


Fig. 4. Docked view of all the compounds at the active site of the enzymes PDB ID: 2IXC (A) and PDB ID: 4DQU (B).

3.2. Docking studies

N-Triazinoindol-benzimidazolones have been found to inhibit RmlC (dTDP-6-deoxy-D-*xylo*-4-hexopyranosid-4-ulose 3,5-epimerase), a TB cell wall biosynthetic enzyme.[38] Since benzimidazolone *bis*-coumarinyl triazoles exhibited excellent antitubercular activity against Mtb *H37Rv*, RmlC was considered as target. Triazoles have been reported as inhibitors of InhA-D148G mutant, a NADH-dependent enoyl-[Acyl-Carrier-Protein] reductase[7] and a study from our research group supports *bis*-triazoles interaction with InhA-D148G mutant.[15]

All the 23 inhibitors were docked into the active site of enzymes 2XIC and 4DQU (Fig. 4). The predicted binding energies of the compounds are listed in supplementary Table S-1 and Table S-2. The comparative molecular docking study of synthesized compounds with 2IXC and 4DQU ligand highlighted that the synthesized compounds exhibited high C-score value. 2IXC ligand showed C-score value of 6.93, whereas the twenty-one out of twenty-three compounds synthesized have higher C-score values. Similarly, C-score value of 4DQU ligand was found to be 7.75 whereas the twenty-one out of twenty-three triazole compounds have higher C-score values. In view of the high C score values and excellent activity exhibited by benzimidazolono-*bis*-coumarinyl triazoles **10h**, **10i**, **10j** and **10m** were further studied in detail for their binding interactions at the active site of the enzymes PDB: 2IXC and 4DQU.

Compound **10j** with excellent anti-TB activity and highest C-score value 9.97, showed five hydrogen bonding interactions at the active site of 2IXC, as depicted in the Figs. 5(A-D). Among five interactions two bonding interactions raised from 3rd nitrogen of triazole ring with hydrogen of ARG59 (−N···H−ARG59, 2.57 Å; 2.87 Å), 2nd nitrogen of triazole ring makes a bonding interaction with hydrogen of ARG59 (−N···H−ARG59, 1.92 Å), 2nd nitrogen of another triazole ring makes a bonding interaction with hydrogen of TYR138 (−N···H−TYR138, 2.55 Å) and oxygen atom of carbonyl group present on the 2nd position of coumarin ring makes a bonding interaction with hydrogen of LYS72 (−C═O···H−LYS72, 2.04 Å). Compound **10i**, regioisomer of **10j** with slightly low anti-TB activity have also shown five interactions at the active site of enzyme 2IXC (supplementary Fig. S-2). As depicted in Fig. 6(A) half part of the molecule **10i** was outside the active pocket of enzyme 2IXC and when docked view of **10i** and **10j** were superimposed with that of 2IXC ligand, the difference in the orientation of ligand and compounds **10i** and **10j** was clearly observed (Fig. 6A). However less active theophylline mono-triazole, **4d** and uracil *bis*-triazole, **7e** were oriented totally out of the plane of 2IXC ligand (Fig. 6B). The binding interaction of 2IXC ligand at active site showed eight bonding interactions and the docked view of the same has been depicted in supplementary Fig. S-2, in which ligand lies within the active pocket of enzyme 2IXC.

Compound **10h** having excellent anti-TB activity, showed six hydrogen bonding interactions at the active site of 4DQU, as depicted in the Figs. 7(A-D). Among six interactions two bonding interactions raised from second nitrogen of triazole ring with hydrogens of LYS165 and GLY96 (−N···H−LYS165, 2.74 Å; −N···H−GLY96, 2.74 Å), third nitrogen of triazole ring showed two more bonding interactions with hydrogens of LYS165 and GLY96 (−N···H−LYS165, 2.10 Å; −N····H−GLY96, 2.21 Å), oxygen of *δ*-lactone carbonyl group exhibited a bonding interaction with hydrogen of TYR158 (−C═O···H−TYR158, 1.94 Å) and oxygen of cyclic urea carbonyl group also showed hydrogen bonding interaction with hydrogen of GLY96 (−O···H−GLY96, 2.37 Å). Compound **10m** showed four hydrogen bonding interactions at the active site of the enzyme (PDB ID: 4DQU), as depicted in supplementary Fig. S-3(A-D).

As shown in Fig. 7B, compound **10h** lies well within the enzyme pocket. Fig. 8A indicates the superimposition of 2-benzimidazolone *bis*-triazoles **10h** and **10m** with ligand, in which both the compounds were found in plane with the ligand. However, less active theophylline mono-triazole, **4d** and uracil *bis*-triazole, **7e** oriented out of the plane of the ligand (Fig. 8B). And there were no H-bonding interactions from triazoles of **7e**, when observed at the active pocket of 4DQU (supplementary Fig. S-4). Supplementary Fig. s-5(a-b) represent the hydrophobic and hydrophilic amino acids surrounded to the compounds **10h** and **10m**.

In silico studies reveal that benzimidazolone *bis*-coumarinyl triazoles **10(a-n)**, were the most active compounds in the present study which inhibit InhA-D148G more efficiently than RmlC. Cyclic ureides (theophylline and uracil) in **4d** and **7e** have tethered the molecules in a non-interacting manner with 4DQU. A correlation between **NADH** (4DQU ligand) and the highly active compounds **10h** and **10m** has been observed. In turn, H-bonding interactions of triazole nitrogens emerged as a key factor in the antitubercular activity.

In the present study we have reported three types of triazoles containing theophylline **4(a-d)**, 6-methyl uracil **7(a-e)** and benzimidazolone **10(a-n)**. Among the mono-triazoles **4(a-d)**, the 6-methoxy compound (**4b**) with MIC of 55.62 μM was the most active compound whereas, others were less active (Table 1). Uracil containing *bis*-triazoles exhibited MIC values in the range of 75–79 μM and their activity was not sensitive to the groups like $-CH_3$/$-OCH_3$. In the benzimidazolone containing *bis*-triazoles the activity has been found to be sensitive to the groups attached to coumarin ring. Compounds **10a** (**R** = 6-CH_3), **10b** (**R** = 7-CH_3) and **10d** (**R** = 6-CH_3) were most active compounds in this series with MIC values of 2.49, 2.49 and 2.37 μM. Introduction of an additional $-CH_3$ group as observed in **10g** and **10h** did inspire the activity. Among benzo substituted 7,8-benzo compound (**10j**) with MIC 2.34 μM was better inhibitor than the 5,6-benzo compound (**10i**) with MIC 8.76 μM. Among the carbostyril compounds **10k-10n** (X = NH), **10l** (R = 8-CH_3), **10m** (R = 6-Cl) and **10n** (R = 7-Cl) have MIC values of 2.50, 2.35 and 2.35 μM respectively, which shows that chloro substituent in the carbostyril has enhanced the activity compared to unsubstituted compound **10k** whose MIC value is 10.23 μM (Table 1). SAR depicted in Fig. 9 indicating all these effects.

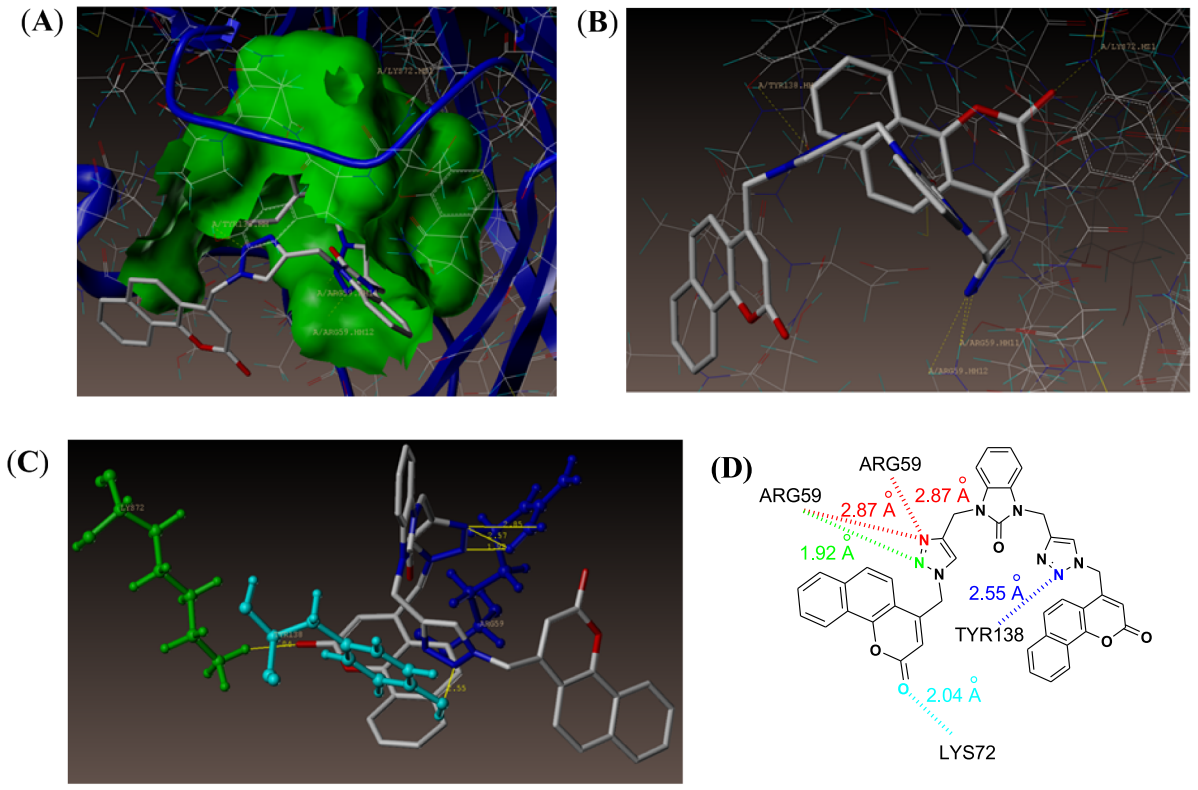


Fig. 5. Compound **10j** inside the proposed binding pocket of the enzyme RmlC (A), Docked mode of compound **10j** (B), 3D (C) and 2D (D) representation of docked view of compound **10j** at the active site of RmlC.

4. Conclusion

From the present study it can be concluded that two triazole units are necessary to achieve significant antitubercular activity as revealed by benzimidazolone *bis*-triazoles **10(a-n)** and most active compounds were **10h** and **10m**. Docking studies substantiated this observation which revealed an additional interaction of benzimidazolone oxygen. Theophylline mono triazoles, **4(a-d)** and *bis* triazoles from uracil, **7(a-e)** exhibited least and moderate activity respectively. Better activity of *bis*-triazoles **10(a-n)** is probably associated with the conformational flexibility which is relatively better than compounds **7(a-e)**.

5. Experimental section

5.1. Chemistry

Melting points were determined by open capillary method and are uncorrected. IR spectra (KBr disc) were recorded on a Nicolet-5700 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Jeol 400 and 100 MHz spectrometer using $CDCl_3$ and DMSO-d_6 as solvents. Chemical shifts are expressed in δ ppm. Mass spectra were recorded using Agilent-single Quartz GCMS and Watets model-Synapt G2-LCMS. Purity of the compound was checked by TLC. All the chemicals purchased were of analytical grade and unless otherwise stated they were used without further purification.

5.1.1. Procedure for the synthesis of 1,3-dimethyl-7-(prop-2-ynyl)-1H-purine-2,6(3H,7H)-dione (2)

Theophylline alkyne **2** was prepared according to literature method.[40] 2 g of theophylline **1** (11.1 mM) and 1.9 g of K_2CO_3 (14.4 mM) taken in 30 mL of DMF were stirred for 30 min at room temperature. Then 1.68 mL of propargyl bromide (22.2 mM) added to the reaction mixture and refluxed for 2 h. After completion of reaction as monitored by TLC, the reaction mixture was quenched in ice water

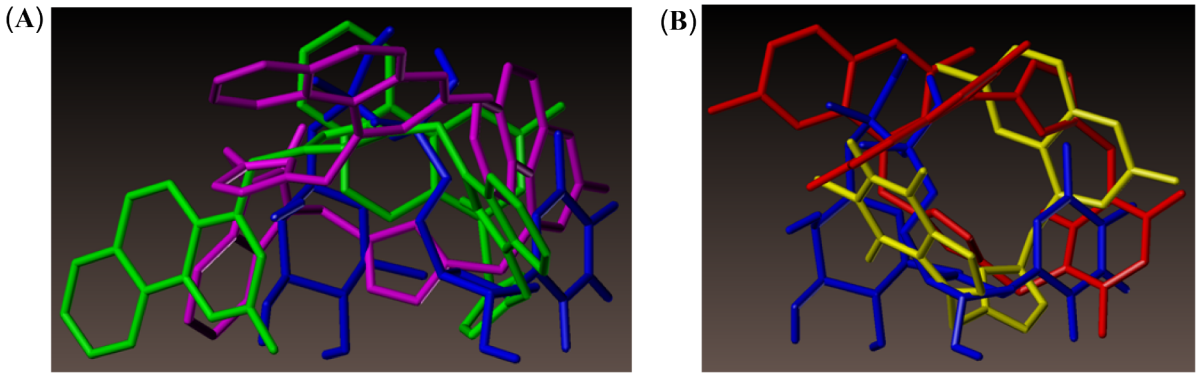


Fig. 6. Superimposition of compounds **10i** (Magenta colour) and **10j** (Green colour) (A) and compounds **4a** (Yellow colour) and **7a** (Red colour) (B) with RmlC ligand (Blue colour). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

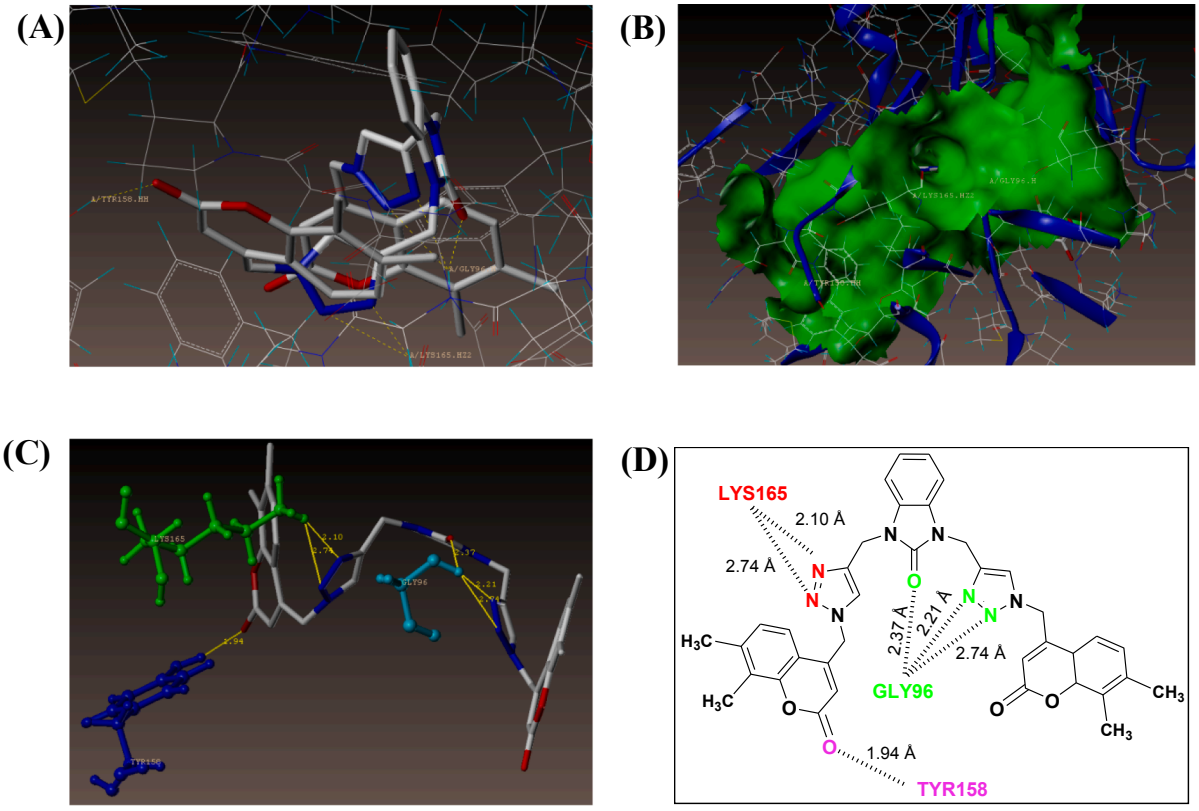


Fig. 7. Compound **10h** inside the proposed binding pocket of the enzyme InhAD148G (A), Docked mode of compound **10j** (B), 3D (C) and 2D (D) representation of docked view of compound **10h** at the active site of InhA-D148G.

and the separated solid was filtered and dried. 2.1 g of off-white compound **2** (M.P = 210–212 °C) was obtained and used for further reaction without any purification. IR (KBr): cm^{-1} 1651 and 1704 (theop C═O); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.83 (s, 1H, imid-H), 5.17 (d, 2H, J = 2.0 Hz, alkyne-CH_2), 3.60 (s, 3H, $-CH_3$), 3.41 (s, 3H, $-CH_3$), 2.60 (t, 1H, J = 2.0 Hz, alkyne-CH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 155.26, 149.12, 140.44, 133.74, 117.08, 76.56, 76.11, 36.47, 29.83, 28.00; MS (EI) *m/z*: Calcd. for $C_{10}H_{10}N_4O_2$-218.0804; Found: 218 [$M^{+\cdot}$].

*5.1.2. Procedure for the synthesis of 6-methyl-1,3-di(prop-2-ynyl) pyrimidine-2,4(1H,3H)-dione (**6**)*

To a stirred solution of 1 g of 6-methyl uracil **5** (7.9 mM), 2.32 g of potassium carbonate (16.2 mM) and 0.53 g of tetra-*n*-butyl ammonium bromide (1.05 mM) in 40 mL of DMF was added 1.42 mL of propargyl bromide (16.2 mM) drop wise. Reaction mixture was stirred at room temperature for about 12–14 h till the completion of reaction as indicated by TLC. Then the reaction mixture quenched in ice cold water and extracted using ethyl acetate (15 mL × 3). 1.2 g of light yellow compound **6** was obtained after evaporation of ethyl acetate under reduced pressure. White; Yield 84%; m.p: 124–126 °C; IR (KBr): cm^{-1} 1652 and 1702 (C═O), 2218 (C≡C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 5.68 (s, 1H, alkene-CH), 4.71 and 4.69 (d, 2H, J = 2 Hz, -alkyne-CH_2), 2.39 (s, 3H, $-CH_3$) 2.36 and 2.17 (t, 1H, J = 2 Hz, alkyne-CH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 160.86, 151.31, 151.06, 102.14, 78.01, 77.20, 73.40, 70.70, 34.18, 30.58, 19.51; EI-MS: MS (EI) *m/z*: Calcd. for $C_{11}H_{10}N_2O_2$-202.0742; Found: 202 [$M^{+\cdot}$ − 100%].

*5.1.3. Procedure for the synthesis of substituted 1,3-Bis(prop-2-ynyl)-1H-1,3-benzimidazol-2(3H)-one (**9**)*

Benzimidazolone *bis*-alkyne **9** was prepared according to literature method.[41] To a mixture of 0.5 g of 1*H*-benzimidazol-2(3*H*)-one **8** (3.75 mM), 1.125 g of potassium carbonate (8 mM) and 0.25 g of tetra-*n*-butyl ammonium bromide (0.5 mM) in 30 mL of DMF was added

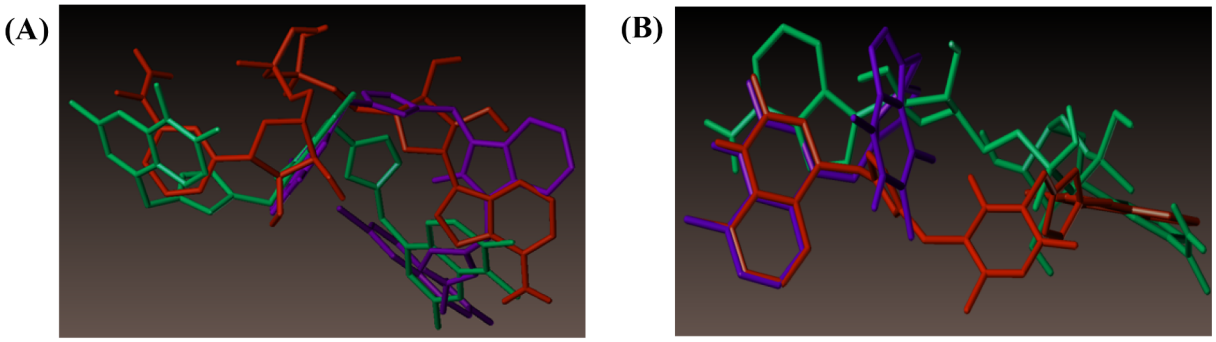


Fig. 8. Superimposition of compounds (A) **10h** (Green) and **10m** (Purple) and (B) **4d** (Purple) and **7e** (Green) with 4DQU ligand (Red orange). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

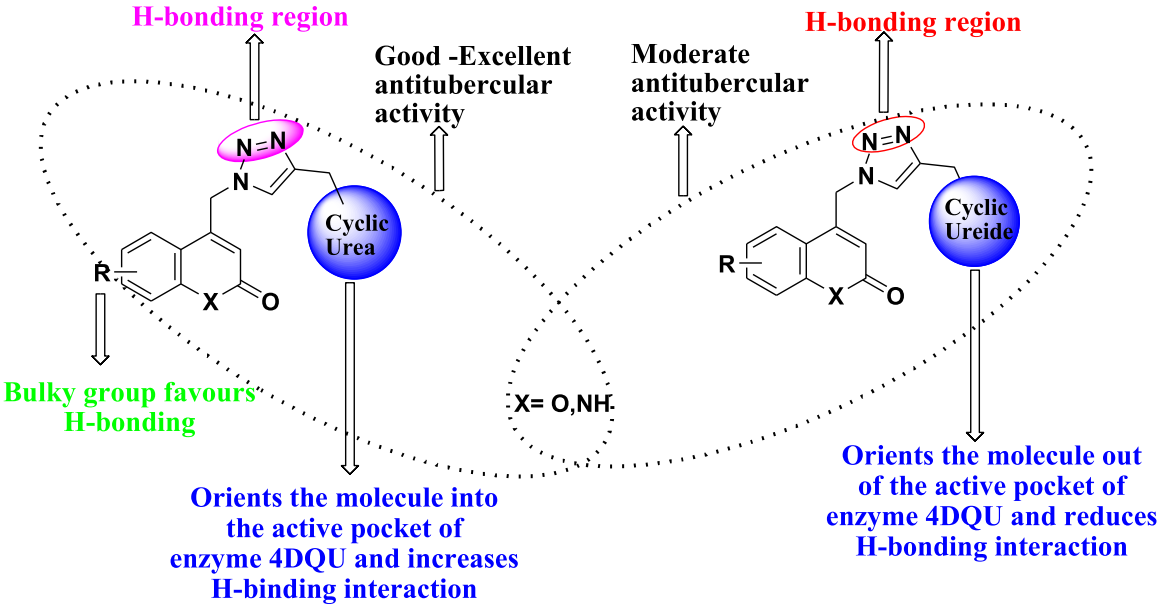


Fig. 9. Structure Activity Relationship of coumarinyl cyclic urea and ureide triazoles.

0.7 mL of propargyl bromide (8 mM). Stirring was continued at room temperature for 6 h. The salt was removed by filtration and the filtrate concentrated under reduced pressure. The product was purified by recrystallization from dichloromethane to give white crystals of **9** (M.P = 152 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.22–7.15 (m, 4H, Ar-H), 4.69 (d, 4H, J = 2.4 Hz, alkyne-CH_2), 2.29 (t, 2H, J = 2.0 Hz, alkyne-CH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 152.98, 128.46, 121.97, 108.60, 76.89, 72.84, 30.62.

*5.1.4. General procedure for the synthesis of 4-(4azidomethyl)-2H-chromen-2-ones/quinolin-2(1H)-ones[15,17] (**3**)*

The required 4-(bromomethyl)-2*H*-chromen-2-ones[42a] were obtained by the Pechmann cyclization of substituted phenols with ethyl 4-bromoacetoacetate[48] whereas 4-(bromomethyl)quinolin-2(1*H*)-ones[42b] were obtained by a thermal condensation of substituted anilines with ethylacetoacate followed by bromination and cyclisation using H_2SO_4. Thus prepared 4-(bromomethyl)-2*H*-chromen-2-ones/quinolin-2(1*H*)-ones(0.01 M equiv) were taken in 20 mL of acetone/DMF in a round-bottom flask. To that, sodium azide (0.012 M equiv) in 3 mL of water was added drop wise with stirring, which was continued for 10 h (reaction was monitored by TLC). The reaction mixture was then poured into ice cold water. Separated solid was filtered, recrystallized using ethanol and melting points compared with the literature reports.[15,17]

*5.1.5. Synthesis of 1,3-dimethyl-7-((1-((6-methyl-2-oxo-2H-chromen-4-yl) methyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-purine-2,6(3H,7H)-dione (**4a**)*

To a solution of compound **2** (1.0 mM) in DMF/H_2O, 1:1 (v/v), $CuSO_4{\cdot}5H_2O$ (0.15 mM), sodium carbonate (0.30 mM) and ascorbic acid (0.30 mM) were added. The mixture was stirred at room temperature for 30 min, 6-methyl-4-azidomethyl coumarin **3a** (1.0 mM) were added, and the resulting reaction mixture was refluxed on oil bath until the starting material was consumed completely (monitored by TLC). Then the reaction mixture was cooled, separated solid was filtered and washed with water and recrystallized from ethanol/dioxane (1:1) mixture. White; yield 84%; m.p: 150–152 °C; IR (KBr): cm^{-1} 1652 and 1702 (cyclic ureide C=O), 1713 (lactone C=O); ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 8.26 (s, 1H, Tri-H), 8.24 (s, 1H, cyclic ureide -H), 7.61 (s, 1H, Cou-C_5-H), 7.47 (d, 1H, J = 8.4 Hz, Cou-C_7-H), 7.43 (d, 1H, J = 8.4 Hz, Cou-C_8-H), 5.93 (s, 2H, Cou-C_4-CH_2), 5.74 (s, 1H, Cou-C_3-H), 5.60 (s, 2H, cyclic ureide-N_9-CH_2), 3.41 (s, 3H, $-CH_3$), 3.20 (s, 3H, $-CH_3$), 2.44 (s, 3H, $-CH_3$); ^{13}C NMR (DMSO-d_6, 100 MHz): δ ppm 159.91, 154.96, 151.84, 151.64, 150.17, 149.08, 143.57, 143.05, 134.40, 124.86, 123.88, 117.39, 114.54, 114.50, 106.52, 103.98, 49.73, 41.83, 27.74, 25.03, 20.80; MS (EI) *m/z*: Calcd. for $C_{21}H_{19}N_7O_4$-433.1499; Found: 433 [$M^{+\cdot}$].

*5.1.5.1. 7-((1-((6-Methoxy-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione (**4b**).* Pale green; Yield 81%; m.p: 177–179 °C; IR (KBr): cm^{-1} 1645 and 1701 (cyclic ureide C=O),1715 (lactone C=O); ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 8.23 (s, 1H, Tri-H), 8.19 (s, 1H, cyclic ureide-H), 7.35–7.19 (m, 3H, Cou-$C_{8,7,5}$-H's), 5.91 (s, 2H, Cou-C_4-CH_2), 5.79 (s, 1H, Cou-C_3-H), 5.55 (s, 2H, cyclic ureide-N_9-CH_2), 3.72 (s, 3H, $-OCH_3$), 3.36 (s, 3H, $-CH_3$), 3.14 (s, 3H, $-CH_3$); ^{13}C NMR (DMSO-d_6, 100 MHz): δ ppm 160.01, 156.10, 154.79, 151.51, 150.28, 148.96, 147.86, 143.18, 125.52, 120.17, 123.88, 118.36, 117.97, 114.72, 108.07, 106.31, 56.29, 49.84, 41.82, 29.96, 28.04; MS (EI) *m/z*:Calcd. for $C_{21}H_{19}N_7O_5$-449.1448; Found: 449 [$M^{+\cdot}$].

*5.1.5.2. 7-((1-((5,7-Dimethyl-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione (**4c**).* Pale yellow; Yield 84%; m.p: 197–199 °C; IR (KBr): cm^{-1} 1650 and 1698 (cyclic ureide C=O), 1717 (lactone C=O); ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 8.22 (s, 1H, Tri-H), 8.14 (s, 1H, cyclic ureide-H), 7.08 (s, 1H, Cou-C_8-H), 7.01 (s, 1H, Cou-C_6-H), 6.01 (s, 2H, Cou-C_4-CH_2), 5.59 (s, 2H, cyclic ureide-N_9-CH_2), 4.49 (s, 1H, Cou-C_3-H), 3.37 (s, 3H, $-CH_3$), 3.15 (s, 3H, $-CH_3$), 2.64 (s, 3H, $-CH_3$), 2.31 (s, 3H, $-CH_3$); ^{13}C NMR (DMSO-d_6, 100 MHz): δ ppm 159.60, 155.01, 154.81, 153.83, 151.53, 148.99, 143.74, 143.21, 143.05, 137.07, 130.33, 125.69, 116.05, 114.96, 111.57, 106.33, 52.67, 41.85, 29.98, 28.07, 23.94, 21.16; MS (EI) *m/z*: Calcd. for $C_{22}H_{21}N_7O_4$-447.1655; Found: 447 [$M^{+\cdot}$].

*5.1.5.3. 1,3-Dimethyl-7-((1-((8-methyl-2-oxo-1,2-dihydroquinolin-4-yl) methyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-purine-2,6(3H,7H)-dione (**4d**).* Pale yellow; Yield 80%; m.p: 206–208 °C; IR (KBr): cm^{-1} 1652 (cyclic ureide C=O), 1698 (cyclic ureide and lactam C=O); ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 10.70 (s, 1H, −NH), 8.15 (s, 1H, Tri-H), 8.12 (s, 1H, cyclic ureide-H), 7.59 (d, 1H, Cou-C_5-H), 7.34 (d, 1H, Cou-C_7-H), 7.06 (d, 1H, Cou-C_6-H), 5.84 (d, 2H, Cou-C_4-CH_2), 5.92 (s, 1H, Cou-C_3-H), 5.55 (s, 2H, cyclic ureide-N_9-CH_2), 3.38 (s, 3H, $-CH_3$), 3.17 (s, 3H, $-CH_3$), 2.38 (s, 3H, $-CH_3$); MS (ESI) *m/z*: Calcd. for

$C_{21}H_{20}N_8O_3$-432.1652; Found: 433.0109 [M + H$^{+\cdot}$].

5.1.6. Synthesis of 6-methyl-1,3-bis((1-((6-methyl-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)pyrimidine-2,4(1H,3H)-dione ***(7a)***

To a stirred solution of cyclic ureide *bis*-alkyne **6** (0.5 mM) in DMF/H_2O, 1:1 (v/v), $CuSO_4{\cdot}5H_2O$ (0.15 mM), sodium carbonate (0.30 mM) and ascorbic acid (0.30 mM) were added. The mixture was stirred at room temperature for 20 min, 6-methyl-4-azidomethyl coumarin **3a** (1.0 mM) were added, and the resulting reaction mixture was refluxed on oil bath until the starting material was consumed completely (monitored by TLC). Then the reaction mixture was cooled, separated solid was filtered and washed with water and recrystallized from DMF. White; Yield 87%; m.p: 230–232 °C; IR (KBr) cm^{-1}1661 and 1707 (cyclic ureide C═O), 1727 (lactone C═O); ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 8.26 and 8.12 (2s, 2H, Tri-H's), 7.65 and 7.64 (2s, 2H, Cou-C_5-H's), 7.48 and 7.46 (2d, 2H, J = 8.4 Hz, Cou-C_7-H's), 7.33 and 7.31 (2d, 2H, J = 8.4 Hz, Cou-C_8-H's), 5.92 and 5.89 (2s, 4H, Cou-C_4-CH_2's), 5.80 (s, 1H, cyclic ureide-H), 5.73 (2s, 2H, Cou-C_3-H's), 5.11 and 5.06 (2s, 4H, cyclic ureide-N_1 & N_3-CH_2's), 2.41 (s, 3H, −CH_3), 2.37 and 2.36 (2s, 6H, −CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ ppm 161.47, 160.06, 153.66, 151.69, 150. 37, 150.49, 134.39, 133.90, 125.54, 124.98, 117.29, 117.08, 114.21, 113.98, 101.03, 49.64, 49.51, 20.96, 19.93; MS (EI) *m/z*: Calcd. for $C_{33}H_{28}N_8O_6$-632.2132; Found:632 [M$^{+\cdot}$].

5.1.6.1. 1,3-Bis((1-((7-methyl-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-6-methylpyrimidine-2,4(1H,3H)-dione ***(7b)***. White; Yield 84%; m.p: 277–279 °C; IR (KBr) cm^{-1} 1670 and 1709 (cyclic ureide C═O), 1731 (lactone C═O); ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 8.18 and 8.04 (2s, 2H, Tri-H's), 7.67 and 7.66 (2d, 2H, J = 8.0 Hz, Cou-C_5-H's), 7.20–7.16 (m, 4H, Cou-C_6 and C_8-H's), 5.85 and 5.82 (2s, 4H, Cou-C_4-CH_2's), 5.76 (s, 1H, cyclic ureide-H), 5.71 and 5.66 (2s, 2H, Cou-C_3-H's), 5.07 and 5.02 (2s, 4H, cyclic ureide-N_1 & N_3-CH_2's), 2.37 (s, 3H, −CH_3), 2.36 (s, 6H, −CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ ppm 161.42, 160.04, 153.74, 153.53, 151. 98, 150.58, 150.35, 144.01, 126.21, 124.95, 117.39, 117.18, 115.24, 109.29, 106.42, 49.72, 49.61, 21.65, 21.57; MS (EI) *m/z*: Calcd. for $C_{33}H_{28}N_8O_6$-632.2132; Found: 632 [M$^{+\cdot}$].

5.1.6.2. 1,3-Bis((1-((6-methoxy-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-6-methylpyrimidine-2,4(1H,3H)-dione ***(7c)***. Green; Yield 87%; m.p: 250–252 °C; IR (KBr) cm^{-1}1668 and 1714 (cyclic ureide C═O), 1734 (lactone C═O); ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 8.23 and 8.10 (2s, 2H, Tri-H's), 7.34 and 7.33 (2s, 2H, J = 8.8 Hz, Cou-C_8-H's), 7.248 and 7.241 (2s, 2H, Cou-C_5-H's), 7.22 and 7.21 (2d, 2H, J = 8.8 Hz, Cou-C_7-H's), 5.90 and 5.87 (2s, 4H, Cou-C_4-CH_2's), 5.85 and 5.80 (2s, 2H, Cou-C_3-H's), 5.69 (s, 1H, cyclic ureide-H), 5.06 and 5.01 (2s, 4H, cyclic ureide-N_1 & N_3-CH_2's), 3.75 (s, 6H, −OCH_3), 2.37 (s, 3H, −CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ ppm 161.46, 160.07, 156.11, 153.65, 150.36, 150.13, 147.89, 125.50, 125.14, 120.18, 118.39, 118.04, 114.92, 108.19, 101.03, 56.31, 49.82, 49.70, 19.37; MS (ES) *m/z*: Calcd. for $C_{33}H_{28}N_8O_8$-664.2030; Found: 664 [M$^{+\cdot}$].

5.1.6.3. 1,3-Bis((1-((5,7-dimethyl-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-6-methylpyrimidine-2,4(1H,3H)-dione ***(7d)***. White; yield 82%; m.p: 266–268 °C; IR (KBr) cm^{-1} 1659 and 1703 (cyclic ureide C═O), 1728 (lactone C═O); ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 8.12 and 7.98 (2s, 2H, Tri-H's), 7.02 and 7.01 (2s, 4H, Cou-C_6 and C_8H's), 6.08 and 6.05 (2s, 4H, Cou-C_4-CH_2's), 5.71 (s, 1H, cyclic ureide-H), 5.11 and 5.07 (2s, 4H, cyclic ureide-N_1 & N_3-CH_2's), 4.97 and 4.90 (2s, 2H, Cou-C_3-H's), 2.63 (s, 6H, −CH_3), 2.42 (s, 6H, −CH_3), 2.30 (s, 3H, −CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ ppm 161.46, 159.71, 154.96, 154.04, 153.77, 151.94, 143.01, 137.03, 130.37, 125.75, 125.25, 116.06, 114.95, 111.37, 101.37, 52.68, 52.56, 23.92, 21.17, 19.95; MS (ES) *m/z*: Calcd. for $C_{35}H_{32}N_8O_6$-660.2445; Found: 660 [M$^{+\cdot}$].

5.1.6.4. 1,3-Bis((1-((8-methyl-2-oxo-1,2-dihydroquinolin-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-6-methylpyrimidine-2,4(1H,3H)-dione ***(7e)***. Pale green; yield 80%; m.p: 286–288 °C; IR (KBr) cm^{-1} 1680 (br, cyclic ureide and lactam C═O), 1707 (cyclic ureide C═O); ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 10.71 (s, 2H, −NH), 8.17 and 7.99 (2s, 2H, Tri-H's), 7.62 and 7.61 (2d, 2H, J = 7.2 Hz, 1-Aza Cou-C_5H's), 7.32 (d, 2H, J = 7.2 Hz,1-Aza Cou-C_7H's), 7.07 (t, 2H, J = 7.2 Hz, 1-Aza Cou-C_6H's), 5.88 and 5.86 (2s, 2H, 1-Aza Cou-C_3-H's Cou-C_4-CH_2's), 5.85 and 5.81 (2s, 4H, 1-Aza Cou-C_4-CH_2's), 5.66 (s, 1H, cyclic ureide-H), 5.07 and 5.02 (2s, 4H, cyclic ureide-N_1 & N_3-CH_2's), 2.38 (s, 3H, −CH_3), 2.36 (s, 6H, −CH_3); MS (ESI +) *m/z*: Calcd. for $C_{33}H_{30}N_{10}O_4$-630.2451; Found: 631.3227[M + H$^{+\cdot}$].

5.1.7. Synthesis of 1,3-bis((1-((6-methyl-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one ***(10a)***

To a solution of compound **9** (0.5 mM) in DMF/H_2O, 1:1 (v/v), $CuSO_4{\cdot}5H_2O$ (0.15 mM), sodium carbonate (0.30 mM) and ascorbic acid (0.30 mM) were added. The mixture was stirred at room temperature for 30 min, 6-methyl-4-azidomethyl coumarin **3a** (1.0 mM) were added, and the resulting reaction mixture was refluxed on oil bath until the starting material was consumed completely (monitored by TLC). Then the reaction mixture was cooled, separated solid was filtered and washed with water and recrystallized from DMF. White; yield 81%; m.p: 240–242 °C; IR (KBr) cm^{-1} 1693 (cyclic urea C═O), 1724 (lactone C═O); ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 8.24 (s, 2H, Tri-H's), 7.57 (s, 2H, Cou-C_5-H), 7.43 (d, 2H, J = 8.4 Hz, Cou-C_7-H), 7.29 (d, 2H, J = 8.4 Hz, Cou-C_8-H), 7.15 (dd, 2H, J = 6 and 3.2 Hz, cyclic urea Ar-H), 6.98 (dd, 2H, J = 6 and 3.2 Hz, cyclic urea Ar-H), 5.87 (s, 4H, Cou-C_4-CH_2's), 5.72 (s, 2H, Cou-C_3-H's), 5.13 (s, 4H, cyclic urea-N_1 & N_3-CH_2's), 2.30 (s, 6H, −CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ ppm 160.03, 153.43, 151.71, 150.54, 143.50, 134.39, 133.91, 129.17, 125.26, 124.96, 121.68, 117.28, 117.09, 114.19, 108.95, 49.62, 36.39, 20.94; MS (ESI +) *m/z*: Calcd. for $C_{35}H_{28}N_8O_5$-640.2181; Found: 641.4010 [M + H$^{+\cdot}$].

5.1.7.1. 1,3-Bis((1-((7-methyl-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one ***(10b)***. White; yield 87%; m.p: 270–272 °C; IR (KBr) cm^{-1} 1698 (cyclic urea C═O), 1727 (lactone C═O); ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 8.23 (s, 2H, Tri-H's), 7.67 (d, 2H, J = 8.4 Hz, Cou-C_5-H), 7.24 (d, 2H, J = 8.4 Hz, Cou-C_6-H), 7.18 (s, 2H, Cou-C_8-H), 7.16–7.00 (m, 4H, cyclic urea Ar-H), 5.88 (s, 4H, Cou-C_4-CH_2's), 5.79 (s, 2H, Cou-C_3-H's), 5.15 (s, 4H, cyclic urea-N_1 & N_3-CH_2's), 2.41 (s, 6H, −CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ ppm 160.01, 153.76, 153.55, 150.37, 144.00, 143.50, 135.19, 132.47, 129.29, 126.19, 124.98, 115.23, 113.45, 108.84, 108.55, 49.77, 36.52, 21.71; MS (EI) *m/z*: Calcd. for $C_{35}H_{28}N_8O_5$-640.2181; [M$^{+\cdot}$]not found.

5.1.7.2. 1,3-Bis((1-((6-methoxy-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one ***(10c)***. Light green; yield 89%; m.p: 261–262 °C; IR (KBr) cm^{-1} 1691 (cyclic urea C═O), 1711 (lactone C═O); ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 8.24 (s, 2H, Tri-H's), 7.36–6.96 (m, 10*H*, Cou and cyclic urea Ar-H), 5.89 (s, 4H, Cou-C_4-CH_2's), 5.81 (s, 2H, Cou-C_3-H's), 5.12 (s, 4H, cyclic urea-N_1 & N_3-CH_2's), 3.74 (s, 6H, −OCH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ ppm 160.05, 156.10, 153.41, 150.21, 147.89, 143.55, 129.15, 125.21, 121.67, 120.19, 118.39, 118.01, 114.90, 108.94, 108.11, 56.28, 49.79, 36.37; MS (ESI +) *m/z*: Calcd. for $C_{35}H_{28}N_8O_7$-672.2081; Found: 673.2830 [M + H$^{+\cdot}$].

5.1.7.3. 1,3-Bis((1-((7-methoxy-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one ***(10d)***. Light pink; yield 83%; m.p: 278–280 °C; IR (KBr) cm^{-1} 1692 (cyclic urea

C═O), 1708 (lactone C═O); ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 8.22 (s, 2H, Tri-H's), 7.67 (d, 2H, J = 9.2 Hz, Cou-C_5-H), 7.15–6.92 (m, 8H, Cou and cyclic urea Ar-H), 5.84 (s, 4H, Cou-C_4-CH_2's), 5.57 (s, 2H, Cou-C_3-H's), 5.11 (2s, 4H, cyclic urea-N_1 & N_3-CH_2's), 3.81 (s, 6H, −OCH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ ppm 163.23, 160.32, 155.53, 153.42, 150.81, 143.49, 129.15, 126.35, 125.19, 121.67, 112.93, 110.96, 110.80, 108.95, 101.59, 56.53, 49.71, 36.37; MS (ESI+) *m/z*: Calcd. for $C_{35}H_{28}N_8O_7$-672.2081; Found: 673.2830 [M+H$^{+\cdot}$].

*5.1.7.4. 1,3-Bis((1-((6-chloro-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one (**10e**)*. Light brown; yield 81%; m.p: 258–260 °C; IR (KBr) cm^{-1} 1699 (cyclic urea C═O), 1728 (lactone C═O); ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 8.19 (s, 2H, Tri-H's), 7.86 (d, 2H, J = 2.8, Cou-C_5-H), 7.65 (dd, 2H, J = 8.8 and 2.8 Hz, Cou-C_7-H), 7.42 (d, 2H, J = 8.8 Hz, Cou-C_8-H), 7.13 (dd, 2H, J = 6 and 3.2 Hz, cyclic urea Ar-H), 6.97 (dd, 2H, J = 6 and 3.2 Hz, cyclic urea Ar-H), 5.88 (s, 6H, Cou-C_4-CH_2's and Cou-C_3-H's), 5.12 (2s, 4H, cyclic urea-N_1 & N_3-CH_2's); ^{13}C NMR (DMSO-d_6, 100 MHz): δ ppm 159.34, 156.06, 152.34, 149.49, 143.58, 142.01, 139.08, 132.94, 129.29, 129.15, 124.83, 119.24, 119.10, 115.70, 49.81, 41.18, 35.34; MS (ESI+) *m/z*: Calcd. for $C_{33}H_{22}Cl_2N_8O_5$-680.1090; Found: 681.1902 [M+H$^{+\cdot}$].

*5.1.7.5. 1,3-Bis((1-((6-isopropyl-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one (**10f**)*. Off white; yield 89%; m.p: 252–254 °C; IR (KBr) cm^{-1} 1703 (cyclic urea C═O), 1726 (lactone C═O); ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 8.24 (s, 2H, Tri-H's), 7.56 (d, 2H, J = 2 Hz, Cou-C_5-H), 7.49 (dd, 2H, J = 8.4 and 2 Hz, Cou-C_7-H), 7.31 (d, 2H, J = 8.4 Hz, Cou-C_8-H), 7.14 (dd, 2H, J = 6 and 3.2 Hz, cyclic urea Ar-H), 6.96 (dd, 2H, J = 6 and 3.2 Hz, cyclic urea Ar-H), 5.91 (s, 4H, Cou-C_4-CH_2's), 5.81 (s, 2H, Cou-C_3-H's), 5.11 (2s, 4H, cyclic urea-N_1 & N_3-CH_2's), 2.87 (sept, 2H, J = 7 Hz, −CH), 1.12 (d, 12H, J = 7 Hz, −CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ ppm 160.07, 153.39, 151.90, 150.52, 145.28, 143.49, 131.40, 129.15, 125.20, 122.51, 121.65, 117.31, 117.15, 114.45, 108.91, 66.87, 49.77, 33.50, 24.23; MS (ESI+) *m/z*: Calcd. for $C_{39}H_{36}N_8O_5$-696.2809; Found: 697.3626 [M+H$^{+\cdot}$].

*5.1.7.6. 1,3-Bis((1-((5,7-dimethyl-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one (**10g**)*. Off white; yield 84%; m.p: 270–272 °C; IR (KBr) cm^{-1} 1692 (cyclic urea C═O), 1716 (lactone C═O); ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 8.10 (s, 2H, Tri-H's), 6.99 (s, 2H, Cou-C_6-H), 6.94 (s, 2H, Cou-C_8-H), 7.16 (dd, 2H, J = 6 and 3.2 Hz, cyclic urea Ar-H), 7.05 (m, 2H, cyclic urea Ar-H), 6.04 (s, 4H, Cou-C_4-CH_2's), 5.09 (s, 2H, Cou-C_3-H's), 5.16 (2s, 4H, cyclic urea-N_1 & N_3-CH_2's), 2.61 (s, 6H, −CH_3), 2.31 (s, 6H, −CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ ppm 159.57, 155.10, 153.38, 147.40, 145.54, 143.65, 142.96, 136.97, 130.40.26, 130.22, 129.29, 125.13, 116.12, 115.03, 108.85, 52.66, 39.66, 23.79, 21.25; MS (ESI−) *m/z*: Calcd. for $C_{37}H_{32}N_8O_5$-668.2496; Found: 667.0262 [M−1$^{+\cdot}$].

*5.1.7.7. 1,3-Bis((1-((7,8-dimethyl-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one (**10h**)*. Off white; yield 83%; m.p: 282–284 °C; IR (KBr) cm^{-1} 1698 (cyclic urea C═O), 1731 (lactone C═O); ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 8.20 (s, 2H, Tri-H's), 7.48 (d, 2H, J = 8.8, Cou-C_5-H), 6.97 (d, 2H, J = 9.2 Hz, Cou-C_6-H), 7.15–6.98 (m, 4H, cyclic urea Ar-H), 5.84 (s, 4H, Cou-C_4-CH_2's), 5.70 (s, 2H, Cou-C_3-H's), 5.11 (2s, 4H, cyclic urea-N_1 & N_3-CH_2's), 2.31 (s, 6H, −CH_3), 2.21 (s, 6H, −CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ ppm 160.11, 153.46, 151.69, 150.83, 143.49, 142.52, 129.20, 126.24, 125.14, 124.51, 121.91, 121.66, 115.28, 112.92, 108.94, 49.71, 36.43, 20.39, 11.72; MS (ESI−) *m/z*: Calcd. for $C_{37}H_{32}N_8O_5$-668.2496; Found: 667.0375 [M−1$^{+\cdot}$].

*5.1.7.8. 1,3-Bis((1-((3-oxo-3H-benzo[f]chromen-1-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one (**10i**)*. Green; yield 79%; m.p: 286–288 °C; IR (KBr) cm^{-1} 1708 (cyclic urea C═O), 1731 (lactone C═O); ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 8.35 (d, 2H, J = 8.8 Hz, Cou-C_7-H), 8.240 (m, 4H, Tri-H's and Cou-C_8-H), 8.05–8.03 (m, 2H, Ar-H), 7.58–7.52 (m, 6H, Ar-H), 7.12–6.99 (m, 4H, cyclic urea Ar-H), 6.36 (s, 4H, Cou-C_4-CH_2's), 5.45 (s, 2H, Cou-C_3-H's), 5.14 (2s, 4H, cyclic urea-N_1 & N_3-CH_2's); ^{13}C NMR (DMSO-d_6, 100 MHz): δ ppm 159.49, 154.77, 153.47, 153.13, 143.58, 135.04, 131.46, 130.19, 129.18, 129.11, 128.96, 126.30, 125.95, 125.39, 121.68, 117.94, 113.43, 112.96, 108.94, 53.66, 36.44; MS (EI) *m/z*: Calcd. for $C_{41}H_{28}N_8O_5$-712.2183; [M$^{+\cdot}$]not found.

*5.1.7.9. 1,3-Bis((1-((2-oxo-2H-benzo[h]chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one (**10j**)*. Pink; yield 82%; m.p: 290–292 °C; IR (KBr) cm^{-1} 1713 (Cyclic urea C═O), 1736 (lactone C═O); ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 8.29–8.24 (m, 4H, Tri-H's and Ar-H), 8.02–7.96 (m, 6H, Ar-H), 7.45 (d, 2H, J = 8.8 Hz, Cou-C_6-H), 7.29 (d, 2H, J = 8.8 Hz, Cou-C_5-H), 7.14–6.96 (m, 4H, cyclic urea Ar-H), 5.94 (s, 4H, Cou-C_4-CH_2's), 5.56 (s, 2H, Cou-C_3-H's), 5.15 (2s, 4H, cyclic urea-N_1 & N_3-CH_2's); MS (ESI+) *m/z*: Calcd. for $C_{41}H_{28}N_8O_5$-712.2183; Found: 713.3038 [M+H$^{+\cdot}$].

*5.1.7.10. 4-((4-((2-Oxo-3-((1-((2-oxo-1,2-dihydroquinolin-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-2,3-dihydrobenzo[d]imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)quinolin-2(1H)-one (**10k**)*. White; yield 85%; m.p: 274–276 °C; IR (KBr) cm^{-1} 1670 (lactam C═O), 1695 (cyclic urea C═O), 3411 (−N−H); ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 11.76 (s, 2H, −NH), 8.19 (s, 2H, Tri-H's), 7.74–6.96 (m, 12H, Ar-H), 5.84 (s, 4H, 1Aza cou-C_4-CH_2's), 5.92 (s, 2H, 1-Aza cou-C_3-H's), 5.10 (2s, 4H, cyclic urea-N_1 & N_3-CH_2's); ^{13}C NMR (DMSO-d_6, 100 MHz): δ ppm 161.69, 153.44, 145.83, 143.36, 139.45, 131.33, 129.21, 124.96, 124.53, 122.45, 121.66, 120.94, 117.59, 116.27, 108.94, 50.19, 36.43; MS (ESI−) *m/z*: Calcd. for $C_{33}H_{26}N_{10}O_3$-610.2189; Found: 609.1113 [M−1$^{+\cdot}$].

*5.1.7.11. 8-Methyl-4-((4-((3-(((1-((8-methyl-2-oxo-1,2-dihydroquinolin-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-2-oxo-2,3-dihydrobenzo[d]imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)quinolin-2(1H)-one (**10l**)*. White; yield 82%; m.p: 268–270 °C; IR (KBr) cm^{-1} 1668 (lactam C═O), 1706 (cyclic urea C═O), 3428 (−N−H); ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 11.45 (s, 2H, −NH), 8.21 (s, 2H, Tri-H's), 7.24–6.83 (m, 10*H*, Ar-H), 5.87 (s, 4H, 1Aza cou-C_4-CH_2's), 5.95 (s, 2H, 1-Aza cou-C_3-H's), 5.14 (2s, 4H, cyclic urea-N_1 & N_3-CH_2's); MS (ESI−) *m/z*: Calcd. for $C_{35}H_{30}N_{10}O_3$-638.2502; Found: 639.3233 [M+H$^{+\cdot}$].

*5.1.7.12. 6-Chloro-4-((4-((3-(((1-((6-chloro-2-oxo-1,2-dihydroquinolin-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-2-oxo-2,3-dihydrobenzo[d]imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)quinolin-2(1H)-one (**10m**)*. White; yield 78%; m.p: 286–288 °C; IR (KBr) cm^{-1} 1670 (lactam C═O), 1701 (cyclic urea C═O), 3431 (−N−H); ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 11.81 (s, 2H, −NH), 8.16 (s, 2H, Tri-H's), 7.81 (s, 2H, Cou-C_5-H), 7.51 (d, 2H, J = 8.8 Hz, Cou-C_7-H), 7.30 (d, 2H, J = 9.2 Hz, Cou-C_8-H), 7.14–6.96 (m, 4H, cyclic urea Ar-H), 5.83 (s, 4H, 1Aza cou-C_4-CH_2's), 6.02 (s, 2H, Cou-C_3-H's), 5.11 (2s, 4H, cyclic urea-N_1 & N_3-CH_2's), 2.30 (s, 6H, −CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ ppm 161.41, 153.52, 145.01, 142.39, 141.50, 138.28, 134.33, 131.18, 129.28, 126.59, 124.03, 123.34, 122.27, 121.10, 118.84, 49.99, 38.91; MS (EI) *m/z*: Calcd. for $C_{33}H_{24}Cl_2N_{10}O_3$-678.1410; [M+H$^{+\cdot}$] not found.

*5.1.7.13. 7-Chloro-4-((4-((3-(((1-((7-chloro-2-oxo-1,2-dihydroquinolin-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-2-oxo-2,3-dihydrobenzo[d]imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)quinolin-2(1H)-one (**10n**)*. White; yield 75%; m.p: 294–296 °C; IR (KBr) cm^{-1} 1667 (lactam C═O), 1698 (cyclic urea C═O), 3443 (−N−H); ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 11.75 (s, 2H, −NH), 8.15 (s, 2H, Tri-H's), 7.73 (d, 2H, J = 8.4 Hz, Cou-C_5-H), 7.31 (s, 2H, Cou-C_8-H), 7.17

(d, 2H, $J = 8.4$ Hz, Cou-C_6-H), 7.13–6.95 (m, 4H, cyclic urea Ar-H), 5.81 (s, 4H, Cou-C_4-CH_2's), 5.96 (s, 2H, Cou-C_3-H's), 5.10 (2s, 4H, cyclic urea-N_1 & N_3-CH_2's); MS (ESI−) *m/z*: Calcd. for $C_{33}H_{24}Cl_2N_{10}O_3$-678.1410; Found: 677.1089 [$M-1^{+\cdot}$].

5.2. In vitro antitubercular activity

Antitubercular activity of compounds has been assessed against *M. tuberculosis* strain H37Rv using microplate Alamar Blue assay (MABA). This methodology is non-toxic, uses a thermally stable reagent and shows good correlation with proportional and BACTEC radiometric method. Briefly, 200 µL of sterile deionized water was added to all outer perimeter wells of sterile 96 wells plate to minimize evaporation of medium in the test wells during incubation. The 96 wells plate received 100 µL of the Middlebrook 7H9 broth and serial dilution of compounds were made directly on plate. The final drug concentrations tested were 100–0.2 µg/mL. Plates were covered and sealed with parafilm and incubated at 37 °C for five days. After this time, 25 µL of freshly prepared 1:1 mixture of Almar Blue reagent and 10% tween 80 was added to the plate and incubated for 24 hrs. A blue color in the well was interpreted as no bacterial growth, and pink color was scored as growth. MIC was defined as lowest drug concentration which prevented the color change from blue to pink.

5.3. Cytotoxicity

Cytotoxicity of compounds has been estimated using Human Embryonic kidney Cells (HEK293) by MTT assay. MTT is a colorimetric assay that measures the reduction of yellow 3-(4,5-dimethythiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) by mitochondrial succinate dehydrogenase. The cells were seeded at a density of approximately 5×10^3 cells/well in a 96-well flat-bottom micro plate and maintained at 37 °C in 95% humidity and 5% CO_2 for overnight. Different concentration (500, 250, 125, 62.5, 31.25, and 15.625) of samples was treated. Cells were incubated for another 48 h. The cells in well were washed twice with phosphate buffer solution, and 20 µL of the MTT staining solution (5 mg/mL in phosphate buffer solution) was added to each well and plate was incubated at 37 °C. After 4 h, 100 µL of di-methyl sulfoxide (DMSO) was added to each well to dissolve the formazan crystals, and absorbance was recorded at a 570 nm using micro plate reader.

5.4. UV–Visible and fluorescence studies

Stock solutions were prepared by dissolving 0.001 mM of coumarinyl triazoles in DMF and further diluted with DMF and buffers of pH 6–8 to 5×10^{-5} M concentration using appropriate volumes of solvent/buffer. Standard solutions were stable for more than 15 days in refrigerator and even at the boiling point of DMF. UV–Visible and fluorescence spectra were recorded at room temperature on U-3310 Spectrophotometer and Hitachi F-7000, Japan instrument respectively, in all the cases.

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Appendix A. Supplementary data

Supplementary data (various spectra of synthesized compounds, single crystal X-ray data of compounds **6** and **4c** and *in silico* studies) to this article can be found online at https://doi.org/10.1016/j.bmc.2019.115054.

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