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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design, synthesis and molecular docking studies of quinazolin-4-ones linked to 1,2,3-triazol hybrids as *Mycobacterium tuberculosis* $H_{37}Rv$ inhibitors besides antimicrobial activity

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Abstract

Quinazolin-4-ones linked to 1,2,3-triazol (**10**) were identified as inhibitors of the bisphosphonate BPH-700 transcriptional factor from a high throughput screen. A series of 1,4-disubstituted triazoles (**10a–j**) were synthesized by the Cu-catalyzed azide-alkyne cyclo addition of 5-methoxy-2-nitro-4-(prop-2-yn-1-yloxy) benzamide (**6**) with various substituted azido benzenes (**7**) in the presence of $CuSO_4$ under aerobic conditions followed by click reaction with substituted aldehydes. The target compounds were screened for antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ by Broth micro dilution method using Lowenstein Jensen medium (LJ) (MIC < 9 µg/mL). Majority of the compounds **10b**, **10d**, **10e**, **10i** and **10j** displayed good antitubercular activity with MIC 7–11 µg/mL. Further, **10e** exhibited a promising inhibition with MIC 7 µg/mL, compared to the reference drug Rifampicin. Docking studies have been performed to understand the interactions between the synthesized compounds and the active site of pantothenate synthetase *Mycobacterium tuberculosis* $H_{37}Rv$ organism. The study revealed that the target compounds showed good affinity toward the protein when compared to the standard drug Pefloxacin. Further, **10b** was found to interact with three amino acids, viz., Gln92, Arg200, Ser196, as evidenced by the large interaction energy ($\Delta G = -8.16$ kcal/mol). Besides the above, the synthesized quinazolinone triazoles **10a–j** were evaluated for their antibacterial activities against a panel of Gram +ve and Gram –ve bacteria. Among them **10a, 10e, 10 h** and **10j** showed promising broad spectrum antibacterial activity with inhibition in the range of 19–33-mm diameter of inhibition zone (DIZ).

Keywords 1,2,3-Triazoles · Quinazolinones · Antibacterial activity · Docking studies · *Mycobacterium tuberculosis* $H_{37}Rv$ · Pantothenate synthetase (3IVX)

Introduction

Heterocyclic structures are the basic elements of many pharmaceuticals, agrochemicals and veterinary products. Quinazolinones are a big family of heterocyclic compounds, which have been shown to display a broad range of biological activity profiles (Jhone 1982), for example, antispasm (Jatav et al. 2008), anticancer (Murugan et al. 2003), analgesic activity (Jones et al. 1997), antiviral (Desai et al. 1998), anti-inflammatory (Alagarsamy et al. 2003), anticytotoxin (Chandrika et al. 2009), antituberculosis (Viswanadh et al. 2018; Pattan et al. 2006), antibacterial (Nanda et al. 2007), antifungal (Nagarajan and Kavimani 2010), antioxidant (Saravanan et al. 2010), antihypertension (Hess et al. 1968), antiobesity (Sasmal et al. 2012), antipsychotic (Alvarado et al. 2006), antimalarial (Lakhan and Singh

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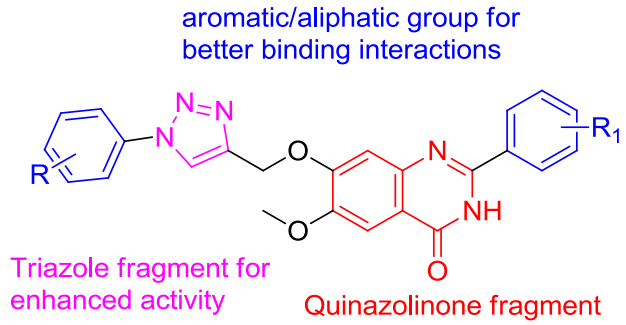


Fig. 1 Design of new hybrid molecules

1988), antidiabetes (Malamas and Millen 1991), etc. Furthermore, quinazolinones are most common heterocyclic core in medicinal chemistry research and act as the potent tyr Pattansine kinase and cellular phosphorylation inhibitors (Ouyang et al. 2006) various neurodegenerative disorders (Fry et al. 1994) bacterial carbonic anhydrases in pathogenesis (Elkamhawy et al. 2014) fluorescence for cysteine (Alafeefy et al. 2014) and chemodosimeter for NO (Anand et al. 2014) used as ligands for benzodiazepine and GABA receptors in the central nervous system (CNS) (Colotta et al. 2006) or as DNA binders (Doyle and Ross 2003). The quinazolinone skeleton is present in a variety of biologically active compounds, among these are several marketed drugs like Afloqualone, Cloroqualone and Diproqualone (Tiwary et al. 2015; Arora et al. 2011), and many compounds are in the development phase as potential new drugs acting against different targets.

1,2,3-Triazole ring system has found a broad spectrum of applications in the field of medicinal chemistry due to some unique features like hydrogen bond formation, dipole–dipole and π–π stacking interactions, stable to oxidation/reduction and stable to hydrolysis under acidic/basic conditions (Mohammed et al. 2015). An exploration of new and potential antibacterial agents is indispensable as the problem of multidrug-resistant microorganisms has reached a disturbing level. Incorporation of heterocycles and 1,2,3-triazole moiety as well in a single molecular entity is the current approach for making interesting novel bioactive molecules (Kumar et al. 2009; Majumdar et al. 2013; Suresh et al. 2017). This can produce a range of densely functionalized small molecules required by researchers working in the area of medicinal and pharmaceutical chemistry/drug discovery. In this context, we anticipated that integration of three basic groups can be selected for the design, synthesis and structure activity relationship (SAR) studies: quinazolinone core, substituted phenyl groups and substituted 1,2,3-triazole moiety (Fig. 1) for the generation of small molecules as potential antibacterial agents.

Molecular docking studies were performed at the active site of pantothenate synthetase protein to study the interaction modes of the synthesized compounds. The results of invitro and insilico studies clearly indicate that quinazolinones containing 1,2,3-triazoles may serve as a potential new drug candidate in the combat against PDB code, 3IVX *Mycobacterium tuberculosis* $H_{37}Rv$ organism. Based on the literature, we describe how the template was modified to improve its biological activity resulting in a series of novel 6-methoxyquinazolin-4(3H)-one-7-substituted-1,2,3-triazoles.

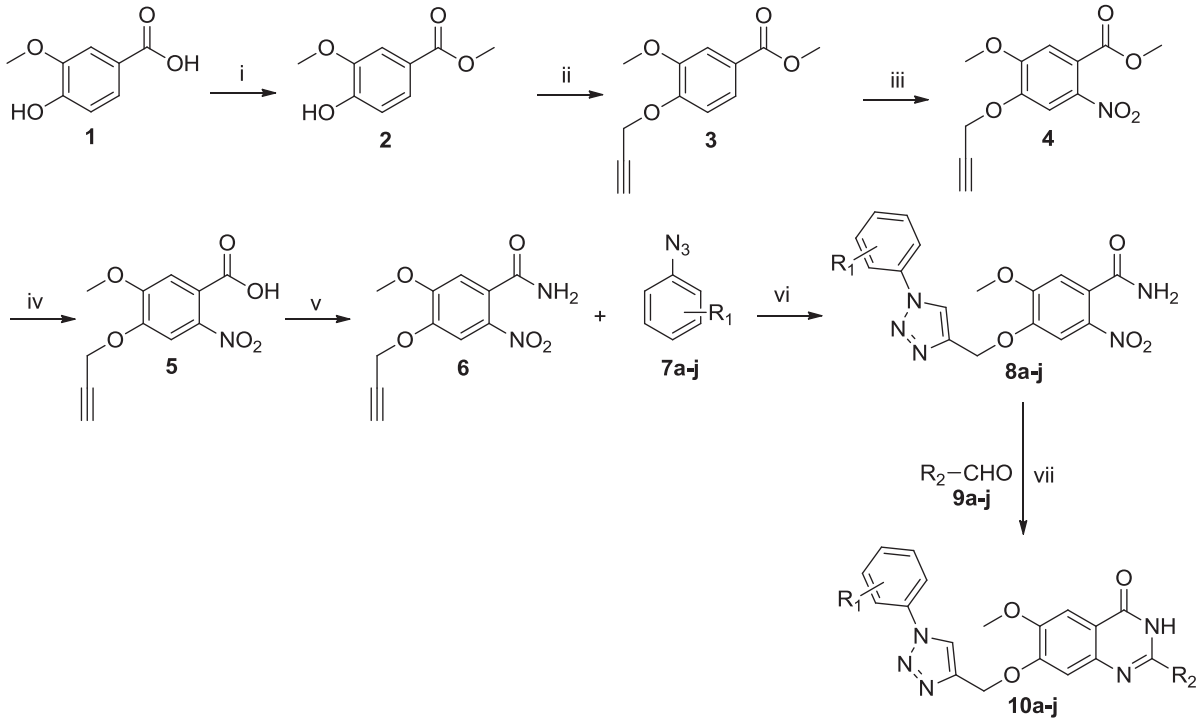
The present work is of three-fold: (a) to synthesize a series of novel antibacterial/antitubercular agents based on 7-((1H-1,2,3-triazol-4-yl) methoxy)-6-methoxyquinazolin-4(3H)-one framework, (b) biological screening of the synthesized compounds and (c) docking studies to understand the interactions of compounds with the active site of the protein.

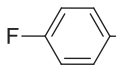
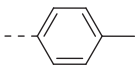
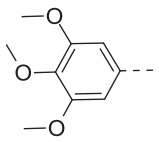
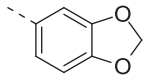
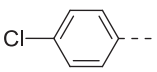
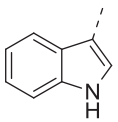
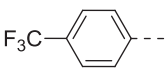
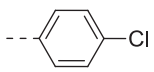
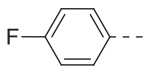
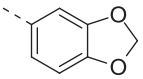
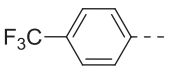
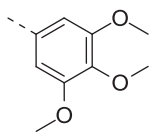
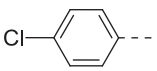
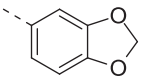
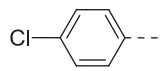
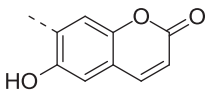
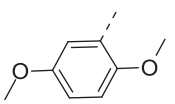
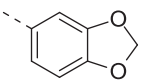
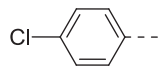
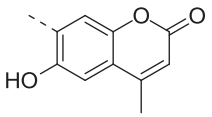
Results and discussions

Synthesis of the target compounds 10a–j

Esterification of vanillic acid (**1**) using MeOH resulted in the formation of 4-hydroxy-3-methoxy methylbenzoate (**2**), which was treated with propargyl bromide and K_2CO_3 to obtain the required methyl 3-methoxy-4-(prop-2-yn-1-yloxy) benzoate (**3**), and followed by nitration gave the corresponding nitro ester **4** in good yield. The compound **5** formed by base hydrolysis of **4** and further treatment of **5** in the presence of $SOCl_2$, THF and aq. NH_3 at room temperature (RT) to obtain 5-methoxy-2-nitro-4-(prop-2-yn-1-yloxy)benzamide (**6**). To synthesize the precursor molecule **8**, which contains 2,3-dihydro-1-benzoxepine and 1,2,3-triazole pharmacophores, we have decided to explore copper sulfate pentahydrate catalyzed reaction between azides **7 (a–j)** and **6** to obtain the desired product **8(a–j)** in good yields. A suitable precursor for the synthesis of target hybrid molecules **10(a–j)**, herein, we demonstrate a clean and convenient click reaction between the electronically divergent triazole compounds 5-methoxy-2-nitro-4-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)benzamide (**8a–j**), substituted aldehydes (**9a–j**)) in the presence of sodium dithionite in dimethyl sulfoxide (DMSO) solvent to give the corresponding target molecules (**10a–j**) in good yields (Scheme 1).

After thorough characterization of the synthesized molecules, the main aim of these investigations is to examine the anticancer activity to find a potent molecule. Herein, we present the (i) antituberculosis activity followed by (ii) antimicrobial activity in detail.



Compound	R_1	R_2	% Yield	Compound	R_1	R_2	% Yield
10a			70	**10f**			80
10b			78	**10g**			65
10c			72	**10h**			69
10d			75	**10i**			80
10e			78	**10j**			82

Scheme 1 Synthesis of novel quinazolinone-1,2,3-triazole analogs **10a–j**. (i) MeOH, conc. H_2SO_4, reflux, 8 h, 95%; (ii) propargyl bromide, K_2CO_3, acetone, reflux, 6 h, 85%; (iii) conc. HNO_3, −5 °C, 90%; (iv) THF:H_2O, 10% NaOH, 6 h, RT, 95%; (v) (a) $SOCl_2$, reflux, 2 h, (b) aq. NH_3, THF, 0 °C to RT, 85%; (vi) $CuSO_4{\cdot}5H_2O$ (10 mol), sodium ascorbate (10 mol), tert. butanol, water, RT; (vii) **8** (1 mmol), $Na_2S_2O_4$ (2 mmol), DMSO (5 mL), 100 °C

Table 1 Minimum inhibitory concentration (MIC) data for the anti-mycobacterial activity of target compounds (**10a–j**) obtained by micro dilution method toward MTB $H_{37}Rv$ clinical isolate of MTB

Compound	4 μg/mL		8 μg/mL	
	15th day	21st day	15th day	21st day
10a	NA	NA	NA	NA
10b	9	9	9	9
10c	NA	NA	NA	NA
10d	9	9	9	9
10e	7	7	7	7
10 f	NA	NA	NA	NA
10 g	16	16	16	16
10 h	10	10	17	17
10i	11	11	11	11
10j	9	9	18	18
Rifampicin	0.10	0.10	1.5	1.5

NA not active toward TB isolates

Antituberculosis activity

The anti-mycobacterium activity of the synthesized compounds was evaluated at different concentrations and at different time intervals and minimum inhibitory concentrations (MICs) were investigated and are presented in Table 1. The readings were obtained at different intervals to check the activity against mycobacteria that inhibit the growth. Thus, all the compounds have the capability to inhibit the mycobacteria at different concentrations and Rifampicin was taken as standard/control. $H_{37}Rv$ showed no growth in the tubes, whereas in the multidrug-resistant (MDR) strain inoculated tube, it showed visible growth pattern. The MIC values of selected compounds BTDHA-Ni, BTDHA-Cu, BTDHA-Pd, BDHA-Hg, were determined for *M. tuberculosis* $H_{37}Rv$ and drug-resistant clinical sample of *M. tuberculosis* using broth micro dilution method in Middlebrook 7H9 medium supplemented with Oleic Albumin Dextrose Catalase (OADC). The compounds were tested at the concentrations of 4 and 8 μg/mL. All the compounds exhibited >90% growth inhibition at the concentration of 4–8 μg/mL for 15 and 21 days, respectively.

The screening of the synthesized compounds **10a–j** against TB revealed that some of the compounds exhibited moderate to good inhibitory activity as it was evident from their MIC values, and the results are presented in Table 1. Compounds **10b, 10e** and **10j** show prominent activity, compared to other synthesized compounds. The most active inhibitor of tuberculosis, compound **10e**, showed an MIC value of 7 μg/mL. The data obtained may be useful for the design of novel anti-TB drugs with the skeleton of quinazolinone–triazoles hybrids.

SAR studies

Anti-mycobacterial study

The integration of three basic groups selected for the design, synthesis and SAR studies are: quinazolinone core, substitution on phenyl groups and substitution on 1,2,3-triazole moiety. Observation of Table 1 (anti-TB investigations): It is clear that compound **10e** having electron-donating groups on the phenyl rings exhibit potent activity followed by **10b**, **10d** and **10j**. Increase of concentrations does not enhance the activity.

Molecular docking studies

The three-dimensional crystal structure of pantothenate synthetase complexed with 2-(2-(benzofuran-2-ylsulfonylcarbamoyl)-5-methoxy-1H-indol-1-yl)acetic acid (3IVX) has been retrieved from protein data bank (Hung et al. 2009). All the synthesized compounds were docked against pantothenate synthetase protein by using Autodock 4.2 software (Morris et al. 2009). The docking score, H-bond interactions and Van der Waal forces were estimated for all the synthesized compounds used in this study (green color lines). Binding energies were measured; they consist of Van der Waals forces, hydrogen bonding, π–π interactions, cation–π interactions, etc. For each ligand, the docking score in terms of interaction energy was calculated and is presented in Table 2 along with the interacting amino acids. The generalized structure of 3IVX along with the docking ligand is shown in

Table 2 Docking scores ($\Delta G°$, kcal/mol) and the dissociation constant (KI, μM) of all the synthesized compounds **10a–10j** with pantothenate synthetase protein (3IVX)

Ligands	Interacting amino acids	Binding energy $\Delta G°$ (kcal/mol)	Dissociation constant KI (μM)
10a	–	−7.13	5.96
10b	Gln92, Ser196, Arg200	−8.16	1.01
10c	Arg200	−7.54	2.97
10d	Arg200	−7.59	2.72
10e	Arg200	−7.11	6.14
10 f	Arg200	−7.05	6.78
10 g	Arg200	−7.14	5.87
10 h	Gln92, Arg200, Arg207	−5.95	43.33
10i	Glu45, Glu189, Asn199, Arg200	−7.10	6.26
10j	Gln92, Arg200	−8.11	1.14
Pefloxacin	Ser196, Arg200	−7.12	6.15

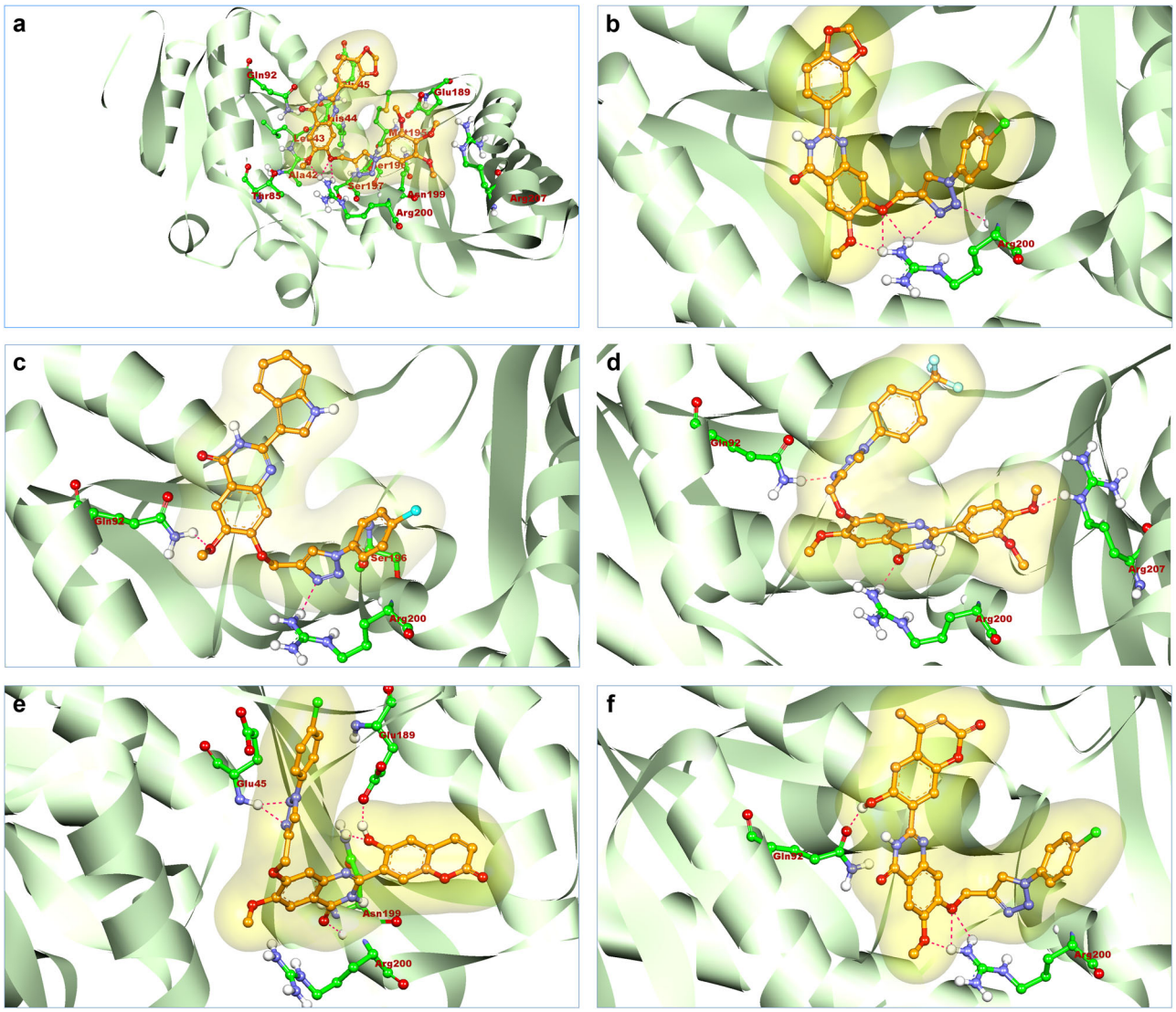


Fig. 2 Generalized structure of pantothenate synthetase protein (3IVX) along with the docked ligand **a** and zoomed protein structure with docked ligand 10b (Fig. 2c)

Fig. 2a. From the data, it is observed that except **10a** (the interaction energy of −7.13 kcal/mol present in Table 2 may be due to the Van der Waal forces and π–π stacking interactions), all other synthesized compounds showed strong interaction energies and Arg200 as a common interacting amino acid. Compounds **10c–10g** showed interaction energies with Arg200 in between −7.05 and −7.59 kcal/mol with an average hydrogen bond (HB) distance of ~1.61 Å (Fig. 2b). Compound **10b** showed an interaction energy of −8.16 kcal/mol with Gly92, Ser196 and Arg200 and the corresponding HB distances are 2.065, 1.942 and 1.939 Å (Fig. 2c). Compound **10h** showed a binding energy of −5.95 kcal/mol with Gln92, Arg200 and Arg207 and the corresponding HB distances are 2.12, 2.084 and 1.995 Å (Fig. 2d). Compound **10i** showed interactions with Glu45, Glu189, Asn199 and Arg200 and has the binding energy of −7.10 kcal/mol and the corresponding HB distances are 2.027, 1.854, 2.193 and 1.903 Å (Fig. 2e). Compound **10j** showed an interaction energy of −8.11 kcal/mol with Gln92 and Arg200, and HB distances are 1.985 Å and 2.098 Å (Fig. 2f). Finally, these interaction energies were compared with the standard drug molecule Pefloxacin where it showed a binding energy of −7.12 with Arg200 and Ser196. This indeed suggests that except **10a** and **10h**, rest of the synthesized compounds showed equivalent interaction energies compared with Pefloxacin. In addition, interaction with Gln92 contributes significantly toward the interaction energy. Overall, docking studies reveal that the interaction with Gln92, Ser196 and Arg200 is very crucial in the design of new chemical entities for potent inhibition of pantothenate synthetase protein and suggested that **10b**

Table 3 Antibacterial activity of the tested compounds (**10a–j**) at a concentration of 1.0 mg/50 µL and their activity in terms of diameter of inhibition zone (mm)

Compound	*P. aeruginosa* (−ve)	*E. coli* (−ve)	*K. pneumoniae* (−ve)	*B. subtilis* (+ve)	*S. aureus* (+ve)
10a	30 ± 0.4	NI	11 ± 0.1	15 ± 0.2	12 ± 0.4
10b	13 ± 0.4	14 ± 0.2	18 ± 0.2	21 ± 0.4	18 ± 0.3
10c	25 ± 0.3	12 ± 0.3	18 ± 0.2	11 ± 0.1	10 ± 0.3
10d	NI	18 ± 0.3	33 ± 0.2	16 ± 0.1	20 ± 0.5
10e	21 ± 0.5	24 ± 0.1	26 ± 0.1	NI	28 ± 0.5
10f	12 ± 0.3	16 ± 0.4	24 ± 0.1	19 ± 0.4	17 ± 0.3
10g	21 ± 0.2	28 ± 0.5	10 ± 0.2	28 ± 0.2	NI
10h	19 ± 0.4	17 ± 0.3	11 ± 0.1	29 ± 0.4	19 ± 0.1
10i	14 ± 0.2	25 ± 0.4	10 ± 0.2	22 ± 0.4	28 ± 0.1
10j	33 ± 0.2	16 ± 0.2	16 ± 0.1	26 ± 0.1	36 ± 0.3
Ciprofloxacin	36 ± 0.2	32 ± 0.1	35 ± 0.2	33 ± 0.1	37 ± 0.4

Data are means ($n = 3$) ± standard deviation of three replicates

NI no inhibition

(R_1 = chlorophenyl and R_2 = indole) and **10j** (R_1 = chlorophenyl and R_2 = methyl-2-chromenone) can be potent candidatures for the inhibition against the standard. Further, all these molecules are competent candidatures against the recently reported imidazo quinoline-5-carboxylic acid derivatives where they showed interaction energies between −5.8 and −6.92 kcal/mol (Mohana Rao et al. 2017).

Antibacterial activity

10a–j were evaluated for their in vitro antibacterial activity against Gram-(+) organisms, viz., *Bacillus subtilis* (MTCC121), *Staphylococcus aureus* (MTCC96), Gram-(–) organisms *Escherichia coli* (MTCC739), *Pseudomonas aeruginosa* (MTCC2453) and *Klebsiella species* strains by using standard techniques, and the zones of inhibition (millimeters) along with those of the reference drug Ciprofloxacin for comparison are shown in Table 3. All the prepared compounds showed potent antibacterial activity against the tested organisms at a concentration of 1.0 mg/50 µL except **10a, 10d, 10e and 10g**, which are inactive toward *E. coli, P. aeruginosa, B. subtilis* and *S. aureus*, respectively. In vitro assay results revealed that the antibacterial potency of target quinazolinone triazoles **10a, 10e, 10h** and **10j** showed magnificent broad spectrum activity against representative Gram-(+) and Gram-(–) strains. They generally exhibited good potency in inhibiting the growth of most tested Gram-(–) strains such as *P. aeruginosa* (33 mm zone of inhibition) and some of the tested Gram-(+) strains such as *S. aureus* (MTCC96) (36 mm zone of inhibition). Comparison of results for **10a, 10d** and **10j** against all the strains tested follows the trend: **10j > 10a > 10d** and suggests that introduction of the groups 6-hydroxy-4-methyl-2H-chromen-2-one > 4–methyl phenyl>benzo[d] [1,3] dioxole and 4-chloro, 4-fluoro substitutes on the quinazolinone and triazole ring is advisable. In addition, the compounds **10e** and **10j** (28 and 36 mm zone of inhibition) showed greater antibacterial activity against *S. aureus* than that of reference Ciprofloxacin (37 mm zone of inhibition). Further, the most active compounds **10a** and **10j** were found to have more potent antibacterial activity and the compound **10d** exhibited highest bacterial response against *Klebsiella pneumoniae*. As for Gram-(–) strains, the novel compounds **10 g** and **10i** provided satisfactory potency against *E. coli* (MTCC739). Further, the activity of the novel targets against Gram-(–) strains was in the order: benzo[d] [1,3] dioxole > 6-hydroxy-4-methyl-2H-chromen-2-one > 4-methyl phenyl > 4-chloro phenyl > 7-hydroxy-chromenes. From the screening results, it is found that some of them are potentially active with reference to Ciprofloxacin.

SAR studies

Antibacterial activity

From activity results, the final compounds **10h, 10j, 10e** and **10c** showed good antibacterial activity. Compound **10h**, which has electron-withdrawing trifluoromethylphenyl group on triazole ring and electron-donating *p*-chloro phenyl group on quinazolinone, showed good activity on all the tested strains. Compound **10j** having *p*-chloro phenyl group on triazole core and 7-hydroxy-4-methyl-chromenes group on quinazolinone showed good antibacterial activity. Overall, the SAR studies suggest that the electron-withdrawing groups on triazole core and electron-donating groups on quinazolinone ring enhance the antibacterial activity.

Experimental section

Materials and methods

All the substrates, reagents and solvents were obtained from commercial sources and were of analytical grade and used without any further purification. ^{1}H NMR ($CDCl_3$ or DMSO-d_6, 300 MHz) and ^{13}C NMR ($CDCl_3$ or DMSO-d_6, 75 MHz) were recorded on NMR spectrometer using TMS as an internal standard. Mass spectra (LCMS) were recorded on a VG micro mass 70-70H instrument. High-resolution mass spectra (HRMS) were recorded using electro spray ionization in Bruker Maxis machine. The purity of the compounds was checked by TLC on silica gel plates using a mixture of *n*-hexane and 30–70% of ethyl acetate.

General procedure for the synthesis of 4-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl) methoxy)-5-methoxy-2-nitrobenzamide (8b)

To a solution mixture of *t*-butanol/H_2O in a ratio of 1:1 (15 mL), compound 5-methoxy-2-nitro-4-(prop-2-yn-1-yloxy) benzamide **6** (1 g, 4 mmol) was added, followed by addition of $CuSO_4{\cdot}5H_2O$ (0.085 g, 0.4 mmol) and sodium ascorbate (0.16 g, 0.8 mmol). The reaction was stirred at ambient temperature for 10 min. A solution of substituted 1-azido-4-chlorobenzene **7b** (0.58 g, 4 mmol) in *t*-BuOH was added drop wise to the reaction mixture and stirred at RT for 6 h. After completion of the reaction, it is diluted with DCM (30 mL) and washed with water (2 × 15 mL), dried over anhydrous sodium sulfate and the solvent was evaporated under vacuo, which resulted in the crude material that was recrystallized using EtOH to get pure compound 4-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-5-methoxy-2-nitrobenzamide **8b** in 83% yield (1.52 g). ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ_{ppm} 8.80 (s, 2H, NH), 7.80 (s, 1H, ArH), 7.39 (d, 2H, J = 8.30 Hz, ArH), 7.24 (d, 2H, J = 8.30 Hz, ArH), 7.01 (s, 1H, ArH), 5.20 (s, 2H, OCH_2), 3.91 (s, 3H, OCH_3); ^{13}C-NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ_{ppm} 167.96, 152.65, 149.45, 146.91, 141.87, 138.19, 136.02, 127.85, 126.90, 122.91, 120.94, 113.72, 111.47, 53.17, 55.88; ESI-MS: *m/z* 403 $(M + H)^+$.

General procedure for the synthesis of title compounds 10a–j

To a stirred solution of compound **8b** (0.10 g, 0.22 mmol) and 1H-indole-3-carbaldehyde (**9b**) (0.036 g, 0.242 mmol) in DMSO (3 mL), sodium dithionite was added (0.087 g, 0.44 mmol) and the reaction mixture was heated at 100 °C for 3 h. After completion, the reaction mixture was poured in ice/water, resulted precipitate was filtered out and recrystallized from EtOH to get pure white crystalline solid in 81% yield (**10b**, 0.096 g). Remaining target quinazolinone–triazole compounds were prepared same as above and a series of novel hybrids **10a–j** was synthesized and characterized by ^{1}H NMR, ^{13}C NMR and mass spectral analysis.

7-((1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-6-methoxy-2-(p-tolyl)quinazolin-4(3 H)-one (10a)

^{1}H-NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ_{ppm} 10.22 (s, 1H, NH), 8.04 (s, 1H, ArH), 7.78 (d, 2H, J = 7.15 Hz, ArH), 7.69 (m, 2H, ArH), 7.45 (d, 2H, J = 7.15 Hz, ArH), 7.30 (s, 1H, ArH), 7.24 (m, 2H, ArH), 7.10 (s, 1H, ArH), 5.60 (s, 2H, OCH_2), 5.35 (s, 2H, OCH_3), 3.86 (s, 3H, CH_3); ^{13}C-NMR (125 MHz, DMSO-d_6): δ_{ppm} 161.57, 153.32, 152.81 (d, 1JCF = 245.4 Hz), 150.23, 148.52 (d, 3JCF = 9.0 Hz), 144.55, 142.38, 139.84, 138.25 (d, 4JCF = 3.0 Hz), 133.26, 130.69, 128.17, 127.91, 127.79, 126.77, 125.24, 114.09, 109.43, 61.76, 60.11, 36.05; ESI-MS: *m/z* 457.16 $(M + H)^+$; HRMS-ESI (*m/z*) [M] + calcd for $C_{25}H_{20}FN_5O_3$ 457.1550, found 457.1551.

7-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)-methoxy)-2-(1H-indol-3-yl)-6-methoxyquinazolin-4(3H)-one (10b)

^{1}H NMR (300 MHz, DMSO-d_6): δ_{ppm} 12.10 (s, 1H, NH), 8.24 (d, 1H, J = 8.30 Hz, ArH), 8.16 (s, 1H, NH), 7.98 (s, 1H, ArH), 7.83–7.76 (m, 4H, ArH), 7.68–7.61 (m, 1H, ArH), 7.50 (s, 1H, ArH), 7.42–7.32 (m, 2H, ArH), 7.26 (d, 1H, J = 7.93 Hz), 6.95 (d, 1H, J = 8.30 Hz), 5.50 (s, 2H, OCH_2), 3.90 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ_{ppm} 161.53, 153.28, 150.67, 150.17, 149.74, 148.45, 147.64, 144.62, 142.22, 132.97, 127.78, 126.63, 125.51, 125.14, 122.32, 113.96, 109.40, 108.26, 105.06, 61.74, 52.57. ESI-MS: *m/z* 498 $(M + H)^+$, 500 $(M + 2H)^+$. HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{26}H_{19}ClN_6O_3Na$ 521.1105, found 521.1106.

2-(benzo[d][1,3]dioxol-5-yl)-7-((1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-6-methoxyquinazolin-4(3H)-one (10c)

^{1}H NMR (300 MHz, DMSO-d_6): δ_{ppm} 11.27 (s, 1H, NH), 8.40 (s, 1H, ArH), 7.79 (d, 2H, J = 8.12 Hz, ArH), 7.73 (s, 1H, ArH), 7.37–7.51 (d, 1H, J = 7.51 Hz, ArH), 7.36–7.23 (m, 4H, ArH), 7.07 (s, 1H, ArH), 6.14 (s, 2H, OCH_2), 5.67 (s, 2H, OCH_2), 5.33 (s, 3H, OCH_3); ^{13}C-NMR (125 MHz, DMSO-d_6): δ_{ppm} 161.48, 153.25 (d, 1JCF = 248.5 Hz), 150.11, 149.67, 148.36, 147.60 (d, 3JCF = 9.1 Hz), 144.60, 142.31, 138.27 (d, 4JCF = 3.5 Hz), 133.24, 130.67, 128.14, 127.88, 126.72, 126.60, 125.26, 122.32, 113.91, 109.29, 108.19, 107.22, 61.67, 55.59; ESI-MS: *m/z* 487.13 $(M + H)^+$. HRMS-ESI (*m/z*) [M] + calcd for $C_{25}H_{18}FN_5O_5$ 487.1292, found 487.1294.

2-(benzo[d][1,3]dioxol-5-yl)-7-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-6-methoxyquinazolin-4(3H)-one (10d)

^{1}H NMR (300 MHz, DMSO-d_6): δ_{ppm} 11.38 (s, 1H, NH), 7.79 (s, 1H, ArH), 7.72–7.65 (m, 3H, ArH), 7.57 (m, 2H, ArH), 7.49–7.41 (m, 2H, ArH), 7.32–7.27 (d, 1H, $J = 7.5$ Hz, ArH), 7.00 (m, 1H, ArH), 6.10 (s, 2H, OCH_2), 5.37 (s, 2H, OCH_2), 3.99 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.43, 153.29, 150.10, 149.65, 148.38, 147.68, 147.57, 144.59, 142.13, 136.74, 128.28, 127.91, 127.85, 126.59, 124.67, 122.29, 121.15, 112.16, 109.28, 69.95, 61.72, 55.54; ESI-MS: *m/z* 503.10 $(M + H)^+$. HRMS-ESI (*m/z*) [M + Na] + calcd for $C_{25}H_{18}ClN_5O_5Na$ 526.0894, found 526.0896.

2-(benzo[d][1,3]dioxol-5-yl)-7-((1-(2,5-dimethoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)-6-methoxyquinazolin-4(3H)-one (10e)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 11.97 (s, 1H, NH), 7.70 (s, 1H, ArH), 7.62 (s, 1H, ArH), 7.51 (s, 2H, ArH), 7.36–7.29 (m, 2H, ArH), 7.20 (s, 1H, ArH), 7.15 (s, 2H, ArH), 5.93 (s, 2H, OCH_2), 5.43 (s, 2H, OCH_2), 3.86 (s, 6H, OCH_3), 3.73 (s, 3H, OCH_3); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 161.46, 159.29, 153.26, 150.61, 150.51, 148.64, 144.45, 142.19, 134.06, 132.92, 129.64, 127.73, 125.46, 119.75, 117.23, 114.25, 112.13, 109.56, 105.07, 61.75, 55.61, 52.25, 34.19, 30.95; ESI-MS: *m/z* 530.00 $(M + H)^+$. HRMS-ESI (*m/z*) [M + Na] + calcd for $C_{27}H_{23}N_5O_7Na$ 552.1495, found 552.1495.

2-(benzo[d][1,3]dioxol-5-yl)-6-methoxy-7-((1-(3,4,5-trimethoxyphenyl)-1H-1,2,3-triazol-4-yl) methoxy) quinazolin-4(3H)-one (10f)

^{1}H NMR (300 MHz, DMSO-d_6): δ_{ppm} 8.23 (s, 1H, NH), 7.98 (s, 1H, ArH), 7.70–7.51 (m, 4H, ArH), 7.43 (d, 2H, $J = 8.12$ Hz, ArH), 7.28 (s, 1H, ArH), 5.71 (s, 2H, OCH_2), 5.42 (s, 2H, OCH_2), 3.94 (s, 9H, OCH_3), 3.82 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ_{ppm} 161.48, 153.26, 152.96, 150.15, 149.69, 148.39, 147.60, 144.61, 142.22, 137.30, 131.18, 126.60, 125.02, 122.38, 113.91, 109.29, 108.21, 107.29, 105.74, 105.12, 101.76, 61.70, 59.92, 55.81, 55.60, 53.12; ESI-MS: *m/z* 559.00 $(M + H)^+$. HRMS-ESI (*m/z*) [M + Na] + calcd for $C_{28}H_{25}N_5O_8Na$ 582.1601, found 582.1602.

2-(4-chlorophenyl)-6-methoxy-7-((1-(4-(trifluoromethyl) phenyl)-1H-1,2,3-triazol-4-yl)methoxy)quinazolin-4(3H)-one (10g)

^{1}H-NMR (300 MHz, DMSO-d_6): δ_{ppm} 11.63 (s, 1H, NH), 8.40 (s, 1H, ArH), 8.29 (d, 2H, $J = 8.10$ Hz, ArH), 7.95 (d, 2H, $J = 8.10$ Hz, ArH), 7.55 (d, 2H, $J = 8.10$ Hz), 7.32–7.49 (m, 2H, ArH), 7.18 (s, 1H, ArH), 6.94 (s, 1H, ArH), 5.55 (s, 2H, OCH_2), 5.07 (s, 3H, OCH_3); ^{13}C-NMR (125 MHz, $CDCl_3$ + DMSO-d_6): δ_{ppm} 167.88, 152.85, 146.96, 142.15, 140.89 (q, $2JCF = 30.1$ Hz), 139.10, 138.61 (q, $3JCF = 4.2$ Hz), 128.11 (q, $1JCF = 251.6$ Hz), 127.65, 125.33, 125.31, 124.43, 122.41, 117.28, 110.57, 62.27, 56.07; ESI-MS: *m/z* 527.1 $(M + H)^+$, 528.1 $(M + 2\,H)^+$. HRMS-ESI (*m/z*) [M] + calcd for $C_{25}H_{17}ClF_3N_5O_3Na$ 550.0870, found 550.0873.

6-methoxy-7-((1-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(3,4,5-trimethoxyphenyl)quinazolin-4(3H)-one (10h)

^{1}H NMR (300 MHz, DMSO-d_6): δ_{ppm} 12.19 (s, 1H, NH), 7.85 (s, 1H, ArH), 7.64–7.47 (m, 5H, ArH), 7.43 (d, 2H, $J = 7.5$ Hz, ArH), 7.21 (d, 1H, $J = 7.8$ Hz, ArH), 5.38 (s, 2H, OCH_2), 3.98 (s, 9H, OCH_3), 3.85 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.3, 153.3, 145.3, 144.3, 142.7, 135.4, 134.5, 132.4, 128.6, 128.4, 127.2, 126.6, 124.8, 123.9, 122.5, 122.0, 121.3, 120.5, 118.0, 54.7, 52.1, 46.38; ESI-MS: *m/z* 583 $(M + H)^+$. HRMS-ESI (*m/z*) [M + Na] + calcd for $C_{28}H_{24}F_3N_5O_6Na$ 606.1576, found 606.1578.

7-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(6-hydroxy-2-oxo-2H-chromen-7-yl)-6-methoxyquinazolin-4 (3H)-one (10i)

^{1}H-NMR (300 MHz, DMSO-d_6): δ_{ppm} 11.88 (s, 1H, NH), 8.65 (d, 1H, $J = 6.75$ Hz, ArH), 8.49 (s, 1H, ArH), 8.40–8.36 (m, 2H, ArH), 8.02 (s, 1H, ArH), 7.56–7.42 (m, 3H, ArH), 7.36 (s, 1H, ArH), 7.21 (s, 1H, ArH), 7.09 (s, 1H, ArH), 5.67 (s, 1H, OH), 5.36 (s, 2H, OCH_2), 3.85 (s, 3H, OCH_3); ^{13}C-NMR (75 MHz, DMSO-d_6): δ_{ppm} 161.33, 153.43, 149.42, 147.93, 144.29, 142.50, 138.30, 136.83, 133.36, 130.79, 129.08, 128.27, 127.96, 126.84, 125.32, 122.77, 120.93, 113.33, 112.11, 108.41, 107.95, 61.85, 52.17; ESI-MS: *m/z* 543.09 $(M^+ + H)$, 545 $(M^+ + 2H)$. HRMS-ESI (*m/z*) [M] + calcd for $C_{27}H_{18}ClN_5O_6$ 543.0946, found 543.0947.

7-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(6-hydroxy-4-methyl-2-oxo-2H-chromen-7-yl)-6-methoxyquinazolin-4(3H)-one (10j)

^{1}H NMR (300 MHz, DMSO-d_6): δ_{ppm} 10.13 (s, 1H, NH), 8.89 (s, 1H, ArH), 8.37 (s, 1H, ArH), 7.78 (m, 2H, ArH), 7.44 (d, 2H, $J = 8.53$ Hz, ArH), 7.37 (s, 1H, ArH), 7.06 (d, 2H, $J = 8.08$ Hz), 6.73 (s, 1H, ArH), 5.66 (s, 1H, OH), 5.39 (s, 2H, OCH_2), 3.94 (s, 3H, OCH_3), 3.75 (s, 3H, CH_3); ^{13}C-NMR (75 MHz, DMSO-d_6): δ_{ppm} 161.51, 153.28, 152.78, 150.19, 148.49, 144.51, 142.36, 140.51, 139.82, 128.77,

128.67, 127.74, 125.62, 125.34, 125.08, 114.07, 109.47, 105.08, 61.74, 56.01, 55.58; ESI-MS: *m/z* 557 $(M + H)^+$, 558 $(M + 2H)^+$. HRMS-ESI (*m/z*) [M + Na] + calcd for $C_{28}H_{20}ClN_5O_6Na$ 580.1000, found 580.1002.

Antibacterial activity

A collection of three organisms were used for this study of clinical isolates, including Gram-(+) organisms such as *B. subtilis* (MTCC121) and *S. aureus* (MTCC96), and Gram-(−) strains *E. coli* (MTCC739), *P. aeruginosa* (MTCC2453) and *Klebsiella species* strains were obtained from Microbiology laboratory of Global Hospital, Hyderabad. All strains were tested for purity by standard microbiological methods. The bacterial stock cultures were maintained on Mueller Hinton Agar (MHA) slants and stored at 4 °C.

Determination of antibacterial activity

An agar-well diffusion method was employed for evaluation of antibacterial activity. (Clinical and Laboratory Standards Institute 2007; Kavanagh 1972; Banothu et al. 2017). The bacterial strains were reactivated from stock cultures by transferring into Mueller Hinton Broth (MHB) and incubating at 37 °C for 18 h. A final inoculum containing 10^6 colony forming units (1×10^6 CFU/mL) was added aseptically to MHA medium and poured into sterile Petri dishes. Different test compounds at a concentration of 1.0 mg/50 µL were added to wells (8 mm in diameter) punched on agar surface. Plates were incubated overnight at 37 °C and diameter of inhibition zone (DIZ) around each well was measured in millimeters. Experiments were performed in triplicates. Antibiotic such as Ciprofloxacin at a concentration of 1 mg/50 µL was used as a positive reference to determine the sensitivity of microorganisms tested. DMSO was used as a negative control.

Material and methods

Anti-mycobacterial agents

Test drug included Rifampicin, obtained by Sigma. The stock solution was prepared according to CDC (1985) recommendations. The following concentrations were used for the screening antimicrobial agents: Rifampicin: 0.25 to 16. All drugs were kept as a stock suspension of 1% in distilled water except for Rifampicin that was dissolved in methanol, and stored at −25 °C.

Lowenstein–Jensen medium preparation

Lowenstein–Jensen (LJ) medium is used with fresh egg and glycerol for the isolation and differentiation of *M. tuberculosis* spp. LJ medium is most widely used for tuberculosis culture. LJ medium containing glycerol favours the growth of inhibition.

Middlebrook medium preparation

Middlebrook 7H9 Broth is a liquid growth medium specially used for culture of Mycobacterium, notably *M. tuberculosis*. 7H9 supports the growth of mycobacterial species, which is supplemented with nutrients such as glycerol, oleic acid, albumin and dextrose. The medium is used for the preparation of inocula for anti-mycobacterial assays. 7H9 broth supports the growth of mycobacterial species when supplemented with nutrients such as glycerol, oleic acid, albumin and dextrose, except for *M. tuberculosis*, which is inhibited by glycerol. Cultures should be read within 5–7 days after inoculation and once a week thereafter for up to 8 weeks. Middlebrook broth is commonly used in the preparation of inocula for antimicrobial assays, biochemical tests (arylsulfatase and tellurite reduction) and for maintenance of stock strains.

Drug concentrations

Preparation of stock solution: 50 mg of Isoniazid was prepared by adding 5 mL of sterile distilled water. Working solution: 0.5 mL from the stock solution is taken and 24.5 mL of distilled water is added and 0.1 mL of the drug is added to the medium (con. 0.2 µg/mL).

Drug dilution

The compounds (1 mg) are dissolved in 1 mL of DMSO (con. 1 mg/mL), test samples were further diluted to attain final concentrations of 1000 µg/mL, 500 µg/mL, 250 µg/mL, 125 µg/mL, 62 µg/mL, 31 µg/mL, 15 µg/mL, 8 µg/mL and 4 µg/mL. Step-1: label the test tubes as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10. For MTB $H_{37}Rv$ (set A) and MDR strain (set B) separately. Step-2: take 2 mL of the stock solution in test tube no. 1 (in each set), concentration 1000 µg/mL. Step-3: transfer 1 mL of the solution into test tube no. 2 (in each set) and dilute it with 1 mL of Dimethylformamide (DMF) (in each set). Now the concentration becomes one half to the first test tube (no. 1), i.e., 500 µg/mL. Step-4: mix well the contents in the test tube, and transfer 1 mL of the solution from test tube no. 2 into test tube no. 3; add 1 ml of DMF to test tube no. 3 as mentioned in Step-3. We get the concentration 250 µg/mL (test tube no. 3). Step-5: repeat the dilution as mentioned in Steps 3 and 4 up to test tube no. 9 and discard the 1 mL of solution from test tube no. 9. Step-6: the test tube no. 10 remains as control (only DMSO).

Bacterial strains and cultures

All the clinical samples were collected from District Tuberculosis Center, MGM hospital, Warangal, and inoculated onto the LJ solid medium and incubated for 8 weeks at Department of Microbiology, Sri Shivani College of Pharmacy; cultures were identified as *M. tuberculosis* based on morphological and biochemical methods. Fifty clinical isolates were preserved. Mono resistant strain of *M. tuberculosis* was identified by testing drug susceptibility for isoniazid (H) and it was taken as test strain and *M. tuberculosis* $H_{37}Rv$ taken as a control strain for testing anti-mycobacterial activity of compounds. The bacterial strains were stored in trypticase soy broth containing glycerol at −70 °C. All the strains were recovered on LJ medium for 21–28 days at 37 °C.

Preparation of inoculums

The isolates grown on LJ medium were sub-cultured in Middlebrook 7H9 broth (Gupta et al. 2011; Camacho et al. 2011; Issar 2003) supplemented with OADC at 37 °C for 15–21 days. The bacterial suspension was homogenized by vortex shakeup and the turbidity was adjusted in agreement with tube which is the scales of McFarland no. 1 (3.2×10^6 cfu/mL). The inoculum was prepared diluting the bacterial suspension in the proportion of 1:20 in Middlebrook 7H9 broth medium. This diluted suspension (100 µL) was used to inoculate. The mycobacteria were grown in Middlebrook 7H9 medium (HiMedia, India) supplemented with 10% ADC (HiMedia, India). Log phase cultures were centrifuged, washed twice with sterile saline and adjusted to McFarland standard corresponding to 1×10^7 cfu/mL. The size of inoculum was confirmed by plating serial dilutions on Middlebrook 7H11 media (HiMedia, India) plates supplemented with 10% OADC (HiMedia, India). The plates were incubated for 4 weeks prior to CFU enumeration.

Broth dilution method

The MIC for *M. tuberculosis* $H_{37}Rv$ and drug-resistant clinical sample of *M. tuberculosis* was determined using a broth micro dilution method (Delogu et al. 2013; Zhang et al. 2011; Vanderberg 2007) in Middlebrook 7H9 medium supplemented with OADC, with a final inoculum of 5×10^2 cells/mL. The compounds were dissolved in DMF (1.25 mg/mL) and used as a stock solution. Concentrations ranging from 1 to 1000 µg/mL were used to assess the effectiveness of the compounds. Microtiter tubes were incubated at 37 °C for 72 h. The MIC value represents the lowest dilution of the compound at which no bacterial growth was detected.

Culture inoculation

Each tube was inoculated with 0.01 mL of bacterial suspension (0.5 McFarland standard). The medium without antimicrobial agents was inoculated with the same suspension and with a 100-fold diluted suspension, as a growing control. The tubes were sealed and incubated at 37 °C for 28 days in a moisturized incubator. The tubes were rechecked for growth of non-tuberculosis matter (NTM) on the third and fifth day, respectively. The presence of turbidity/growth of mycobacterium was checked at seventh, 14th and 21st days, respectively (the mean time for detecting the growth of mycobacterium is 7–21 days) (Ahmet et al. 2004). The MIC values were recorded on days 14 and 21. Slides were prepared from each well for acid-fast staining. No organisms other than acid-fast bacilli were observed.

Determination of MIC

The evaluation of in vitro anti-mycobacterial activity of the compounds was performed against *M. tuberculosis* $H_{37}Rv$ and MDR strain. The dilutions were carried out in the broth medium, i.e., Middlebrook 7H9 medium (Himedia, Mumbai) supplemented with OADC (Himedia, Mumbai) was used to determine the MIC method. The compounds were dissolved as tabulated in Table 3. The inoculum was prepared by transferring colonies from the culture to sterile water. The cell density was adjusted to 1 McFarland standard (10^8 cells/mL). The final inoculum was made by 1:1000 dilution of the suspension with sterile water. Isoniazid was used as the drug control for the compounds. The controls used are drug-free media for sterility check and the media inoculated with *M. tuberculosis* $H_{37}Rv$ and MDR strain for the growth patterns in drug-inoculated tubes. The tubes were incubated at 37 °C. The determination of results was performed visually after 3 days of static incubation at 37 °C, after 6 days static incubation at 37 °C and 21 days of static incubation at 37 °C. The MICs were defined as the lowest concentration of the compound at which no visible bacterial growth was observed.

Docking studies

The ligands were sketched in Sybyl6.7 and saved it in. mol2 format (Gunda et al. 2015). All the sketched molecules were converted to energy minimized 3D structures by using Gasteiger-Huckel charges for in silico protein–ligand docking using autodock Tools (Banu et al. 2018). Each molecule was docked separately. Initially the molecule was loaded, torsions were set and saved it in PDBQT format. All the hetero atoms were removed from the 3IVX.PDB (crystal structure of pantothenate

synthetase in complex with 2-(2-(benzofuran-2-ylsulfonyl carbamoyl)-5-methoxy-1H-indol-1-yl) acetic acid) (Hung et al. 2009), to make complex receptor free of any ligand before docking (Morris et al. 2009, Narender et al. 2015; Gunda et al. 2015). The PDB was also saved in PDBQT format. All calculations for protein-ligand flexible docking were performed using the Lamarckian Genetic Algorithm (LGA) method. A grid box with the dimensions of X: 15.137, Y: 17.850 and Z: –3.573 Å, with a default grid spacing of 0.375 Å was used. The best conformation was chosen with the lowest docked energy (Goodsell et al. 1990; Banu et al. 2018), after the docking search was completed. The interactions of pantothenate synthetase protein and ligand conformations, including hydrogen bonds and the bond lengths were analyzed.

Conclusions

A series of novel 1,2,3-triazole hybrids linked to quinazolinones were synthesized and evaluated for their antibacterial and antitubercular activities. Synthesized derivatives (**10a**–**10j**) were evaluated for antibacterial activity against five bacterial strains. Target compounds **10a**, **10d**, **10e**, **10h** and **10j** exhibited promising broad-spectrum activity against Gram +ve organisms (*Pseudomonas* species and *S. aureus*) and Gram –ve organisms (*P. aeruginosa* (−ve), *K. pneumoniae*) with good zone of inhibition, whereas remaining compounds showed moderate activity. In general, majority of these compounds displayed moderate to promising activity against the tested *M. tuberculosis* $H_{37}Rv$ organism. Compounds **10d**, **10e** and **10j** showed significant activity with MIC in the range of 7–9 μg/mL. Furthermore, molecular modeling study indicated that the interactions of the synthesized compounds **10b**, **10i** and **10j** with Gln92, Glu189, Ser196, Asn199 and Arg200 amino acids of pantothenate synthetase *M. tuberculosis* $H_{37}Rv$ are essential for biological activities of the investigated quinazolinones with triazole hybrids.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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