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Synthesis of quinoline coupled [1,2,3]-triazoles as a promising class of anti-tuberculosis agents

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ABSTRACT

A series of quinoline coupled 1,2,3-triazoles compounds have been synthesized by 'click chemistry' from azidomethyl quinoline with different alkynes. The efficiency and fidelity of the Cu(I)-catalyzed azide–alkyne reaction are substantiated by good yields and exclusive formation of the expected 1,4-disubstituted triazole product. All the synthesized compounds were screened for anti-tubercular activity against *Mycobacterium tuberculosis H37Rv* by luciferase reporter phage (LRP) assay. Quinoline coupled triazole sugar hybrid, **20** is the most potent compound in the series with 76.41% and 78.37% reduction calculated based on percentage reduction in Relative Light Units at 5 and 25 μg/mL, respectively.

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1. Introduction

One of the major challenging health problems around the world is tuberculosis. Although, tuberculosis is a treatable contagious disease, despite the availability of useful drugs, the disease causes about two million deaths annually due to infection by *Mycobacterium tuberculosis*.[1] Treatment of tuberculosis is a complex process due to several factors which include patients developing resistance to existing drugs, the emergence of multi drug-resistant TB (MDR-TB) and the association of human immunodeficiency virus (HIV) with TB. In particular, due to the mutation from *katG* and *inhA*, the resistance against the major anti-tuberculosis drugs such as isoniazide has caused intractable tuberculosis. Similarly, mutation of *rpoB*-gene and *pncA*-gene has also resulted in resistance against anti-tuberculosis drugs—rifampicin and pyrizinamide, respectively.[2–4] Therefore, over the past few years the design of new drugs as potent anti-tuberculosis agents have been carried out. As a result, new drugs with divergent, unique structure and also with mechanism of action possibly different from that of existing drugs are urgently required.

Quinolines and their analogs represent an important class of organic molecules that have attracted great deal of attention from synthetic as well as medicinal chemists due to their presence in various natural products, exhibiting a wide range of physiological activities.[5–8] In particular, derivatives of 8-hydroxy-2-methylquinoline (**1**) act as powerful prototypes for zinc sensors in biological systems.[9] Similarly, 4-amino-quinolines (**2**), with substitution at the second position qualified to be highly potent anti-HIV-1 agents.[10] In addition, imidazo[4,5-*c*]quinoline derivative (**3**),[11] and 1*H*-imidazo[4,5-*c*]quinoline-4-amine derivative (**4**),[12] acts as a potent tumor necrosis factor-α (TNF-α) suppressor and allosteric modulators of the human A_3 adenosine receptor, respectively. Furthermore, it is noteworthy to observe that 4-(adamant-1-yl)-2-quinolinecarbohydrazide (**5**)[13] (Fig. 1) displays promising activities against drug sensitive and resistant *M. tuberculosis H37Rv* strains. Owing to these remarkable biological activities of quinoline and its derivatives, there has been an increasing interest in the development of easy and simple methodologies for synthesizing such biologically active molecules.

Carbohydrates are the most abundant group of natural compounds, and their glycoconjugates, are involved in important functions, such as cell–cell recognition and communication, inflam mation, immunological response, bacterial and viral infection, tumorigenesis and metastasis.[14] The saccharide portions of various classes of natural products function as key molecular recognition elements, which are important for the biological properties of the natural compounds. Moreover, carbohydrates linked to a heterocyclic moiety are often a prerequisite for biological activity and can thus heavily influence the pharmacokinetics, drug targeting and mechanism of action. Similarly, N-heterocyclic compounds, such as [1,2,3]-triazoles are known to display wide range of biological activities.[15–17]

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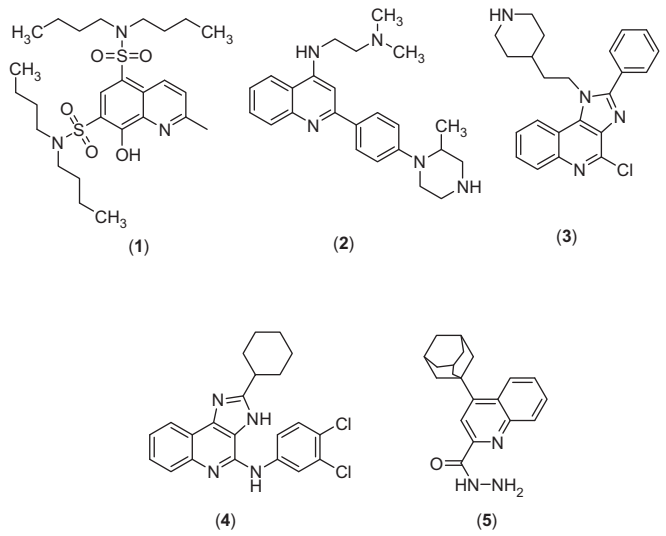


Figure 1. Representative examples of biologically active quinoline derivatives.[9–13]

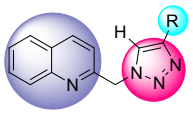


Figure 2. General structure of the synthesized quinoline triazole hybrid.

The quinoline triazole hybrid general structure is illustrated in Figure 2. Quinoline was chosen because it is small in size, biocompatible and easy to manipulate synthetically. In particular, substitutions at the second position of quinoline are known to have strong impact on their biological activities.[13] Similarly, the 1,2,3-triazole moiety is a potential pharmacophore owing to its moderate dipole character and rigidity, thereby used as a passive linker between two respective fragments of structural space.[18]

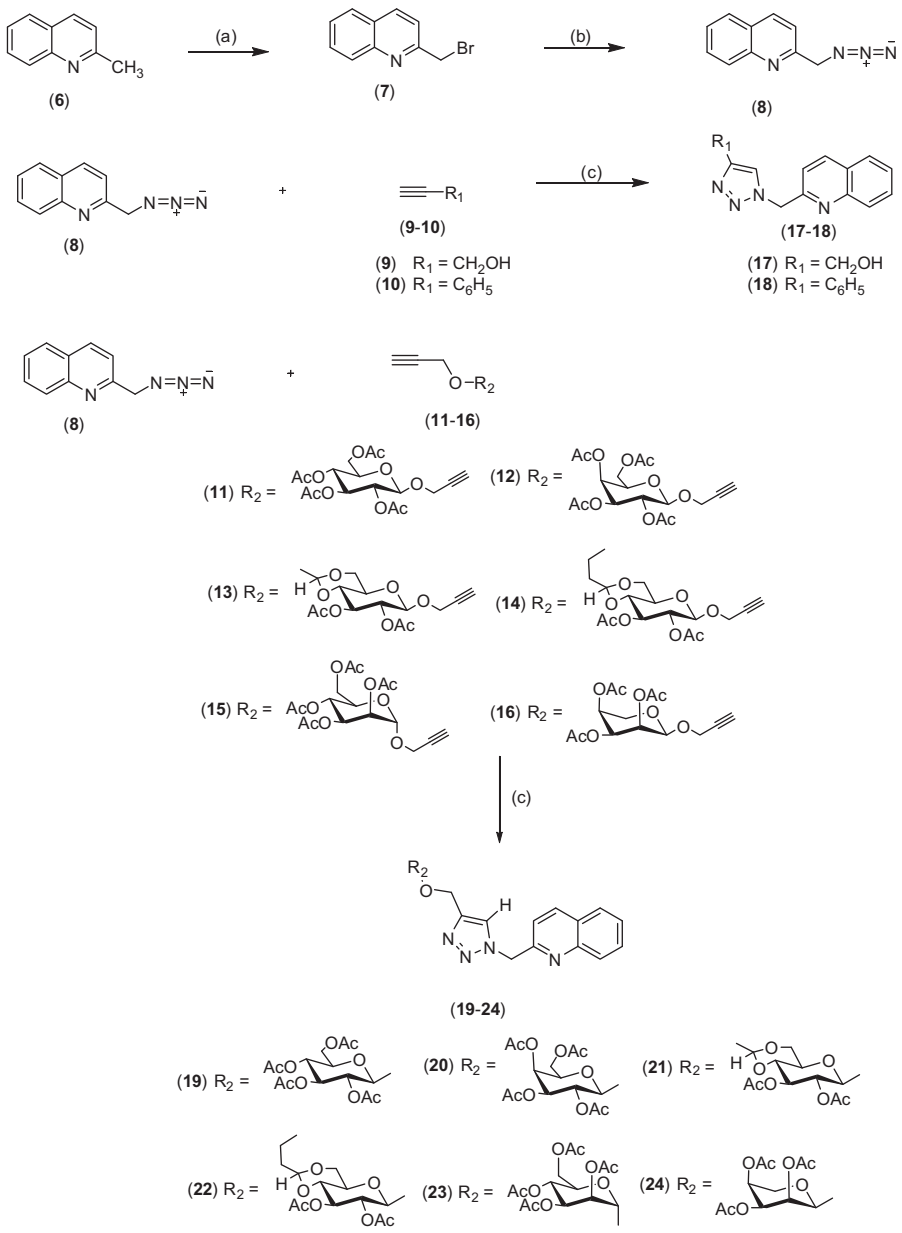
2. Chemistry

The short, facile and inexpensive synthesis of ring-substituted quinolines is considered another important factor that directed us to embark on further structural optimization of this class of compounds. The Cu(I)-catalyzed ligation of a terminal acetylene to an organic azide to form regiospecifically a 1,4-disubstituted triazole has emerged as the revered synthetic tool in drug/medicinal chemistry, as well as in biotechnology.[19,20] Following our ongoing interest in the use of click chemistry[21] and one-pot methodologies[22] in the synthesis of heterocyclic glycoconjugates we present herein the versatility of the click chemistry as an convenient methodology of generating 1,4-disubstituted-[1,2,3]-triazole quinoline glycoconjugates. These quinoline coupled triazole hybrids are synthesized containing quinoline moiety linked via methylene to the triazole moiety.

Terminal alkynes, such as propargyl alcohol and phenyl acetylene were purchased commercially and propargyl ethers of sugars, were synthesized from readily available sugars, for example, D-glucose, D-galactose, D-mannose, D-ribose, 4,6-*O*-ethylidene-D-glucopyranose and 4,6-*O*-butylidene-D-glucopyranose.[23] The mon osubstituted 2-(bromomethyl)-quinolines, **7**, has been synthesized in one step by reacting commercially available 2-methylquinoline, **6**, with N-bromosuccinimide (NBS) in the presence of benzoyl-peroxide (BPO) as catalyst at 70 °C for 12 h. 2-(Bromomethyl)-quinoline (**7**) was observed in a yield of 76%, and, not surprisingly, a negligible amount of 2-(dibromomethyl)-quinoline was also observed (>5%). Thus, 2-(bromomethyl)-quinoline (**7**) upon reaction with sodium azide in the presence of water and acetone (1:2) readily provided 2-(azidomethyl)-quinoline (**8**) in a yield of 95%. The synthesized 2-(azidomethyl)-quinoline (**8**) was treated with propargyl alcohol (**9**) in the presence of $CuSO_4$ and sodium ascorbate in THF/H_2O (1:1), which resulted in the quinolone-coupled triazole compound (**17**) in 86% yield, Scheme 1. Hence, analog **17** is considered as an excellent lead prototype and 'click chemistry' also seemed ideally suited for the synthesis of quinoline triazole non-sugar hybrid, **18** in 87% yield, from 2-azidomethylquinoline (**8**) upon reaction with phenylacetylene (**10**). We further reasoned that similar to that of non-sugar acetylenic derivatives such as propargyl alcohol and phenylacetylene, various sugar acetylenic derivatives such as, propargyl glycosides could serve as a suitable moiety for the synthesis of quinolone–triazole sugar hybrids. To explore the possibilities, the reaction was performed under the same reaction condition using propargyl glycosides of D-glucose, D-galactose, 4,6-*O*-ethylidene-D-glycopyranose, 4,6-*O*-butylidene-D-glycopyranose, D-mannose and D-ribose. According to Scheme 1, to synthesize 1,4-di-substituted-[1,2,3]-triazoles (**19**–**24**), a solution of 2-azidomethyl quinoline (**8**) in a solvent mixture of THF/H_2O in a 1:1 ratio was treated with propargyl glycosides (**11–16**) in presence of copper sulfate pentahydrate and sodium ascorbate. The efficiency of click chemistry methodology affords the expected quinoline coupled triazole hybrids (**19–24**) in yields ranging from 55% to 72% (Table 1).

3. Pharmacology: anti-tuberculosis activity

Anti-mycobacterial activity of the synthesized compounds was evaluated by luciferase reporter phage (LRP) assay[24–27] against *Mycobacterium tuberculosis H37Rv* at two different concentrations (5 and 25 μg/mL). The Luciferase reporter phage assay methodology is rapid, inexpensive and less laborious method for high throughput screening of compounds for their antimycobacterial activity compared to BATEC methodology which is costly, cumbersome and uses radioactive reagents. Similarly in the Alamar blue assay the end point is measured visually, which can probably lead to ambiguity in the observed result. A compound is considered as an anti-tuberculosis agent if fifty percent reduction in relative lights units (RLU) is observed when compared to the control using luminometer. As a part of our studies on heterocyclic glycoconjugates, we are devoted to the biological applications of acetylated heterocyclic glycoconjugates,[28] which is less explored in comparison to deacetylated heterocyclic glycoconjugates. All the synthesized compounds, **17**–**24**, were evaluated for tuberculosis inhibition against *M. tuberculosis H37Rv* strain using rifampicine as a positive control. Among the tested compounds, **18**, **20**, **21** and **23** exhibited good anti-mycobacterial inhibitory activity at 25 μg/mL. Along the same line all other quinolone-coupled triazole compounds were found to be less effective (Table 2). In addition, the quinolone-coupled triazole compound, **20** exhibited potent activity, showing a reduction of 76.41% even at 5 μg/mL, whereas, rest of the quinoline coupled triazole compounds, **17**, **18**, **21** and **23** were found to be very less potent and no inhibitory activity for quinoline coupled triazoles **19**, **22**, and **24**. The quinoline glycoconjugate of D-galactose **20** was exceptional among the corresponding glycoconjugates of D-glucose (**19**), D-mannose (**23**) and D-ribose (**24**) whereby, exhibited potent inhibition against *M. tuberculosis H37Rv* strain at both 25 and 5 μg/mL concentrations (Table 2). The minimum inhibitory concentration, (**MIC**) of compound **20** against *M. tuberculosis H37Rv* strain was 5 μg/mL. Additionally, compound **20**, exhibited MIC of 5 μg/mL and 10 μg/mL against clinical isolate: S, H, R and E resistant and clinical isolate: S, H, R and E sensitive respectively. Thereby, this compound **20**, exhibits promising inhibitory activity among the

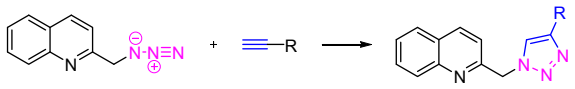


Scheme 1. Synthesis of quinoline coupled triazole compounds (**17**–**24**). Reagents and conditions: (a) CCl_4, NBS, BPO, reflux; (b) H_2O–acetone (1:2), NaN_3; (c) THF, H_2O, $CuSO_4{\cdot}5H_2O$, sodium ascorbate.

series when compared with rifampicine, the drug used as positive control.

These results prompted us to further preliminary investigation of the structure–activity relationship (SAR) within this promising chemical series. Our strategy to prepare such compounds was based on the extensive use of C-2 substituted quionoline compounds in the field of medicinal chemistry. We investigated the effect of substitution at the C-4 of triazole moiety, the methylene linker and the quinoline core were kept constant allowing brief derivation of structure–activity relationship. The anti-tuberculosis activity of the synthesized compounds is reported in Table 2. Introduction of the phenyl ring at the C-4 position of triazole induced reasonable inhibition against *M. tuberculosis H37Rv*. It was apparent that the introduction of bulky and lipophilic substituent such as benzene exhibits potent inhibition against *M. tuberculosis H37Rv*. However, introduction of small hydrophilic substituent such as OH linked to the C-4 of triazole via., methylene showed dramatic loss in potent inhibition against *M. tuberculosis H37Rv*. The good inhibition potency of compound, **18** on comparison to compound, **17** confirmed the need of bulky group at this C-2 position and similar kind of observation has been reported in literature.[29] Further investigations on structure–activity relationship among the synthesized quinoline glycoconjugates, **19**–**24** were carried out. Specifically, those pentoses or hexoses in the chair conformation with 3,4-trans diacetyl orientation such as quinoline glycoconjugate of D-galactose **20** (3*S*,4*R*), were generally more potent inhibitor than those with corresponding 3,4-cis-diacetyl orientation (3*S*,4*S*) among the saccharide coupled compounds. Additionally, comparison of 4,6-*O*-protected D-glucose coupled quinoline glycoconjugates (**21**, **22**) with D-glucose coupled glycoconjugate, **19** reveal that a correlation exists between them and activity. To illustrate using their anti-tuberculosis activity, 4,6-*O*-protected D-glucose coupled quinoline glycoconjugates (**21**, **22**) were found to be reasonably more potent than unprotected

Table 1
Synthesis of 1,4-disubstituted-[1,2,3]-triazole quinoline hybrids (**17**–**24**)



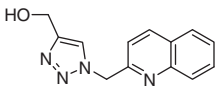
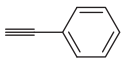
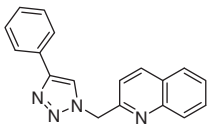
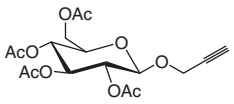
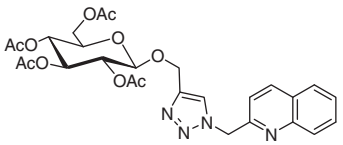
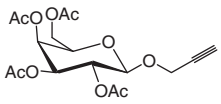
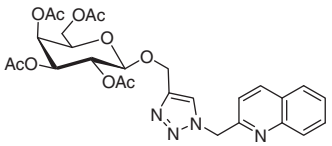
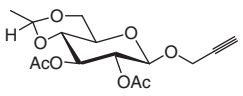
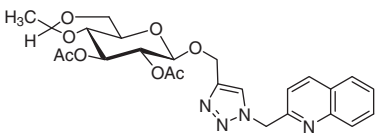
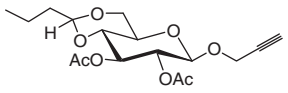
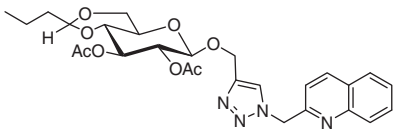
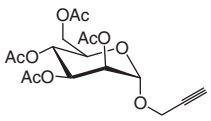
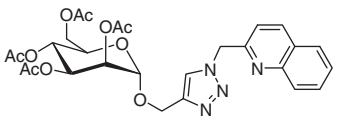
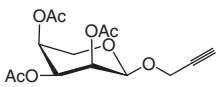
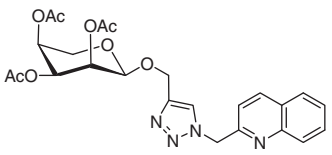
Entry	Compound	Acetylenic moiety	Product	Yield (%)
1	**17**			86
2	**18**			87
3	**19**			68
4	**20**			55
5	**21**			72
6	**22**			69
7	**23**			62
8	**24**			58

Table 2
% Reduction in relative light units (RLU) of quinoline coupled triazole compounds **17**–**24**, against drug sensitive strain of *M. tuberculosis H37Rv*

Entry	Compound	*M. tuberculosis H37Rv* % Reduction in relative light units (RLU)	
		5 μg/ml	25 μg/ml
1	**17**	33.35	42.93
2	**18**	58.20	80.79
3	**19**	1.70	17.93
4	**20**	76.41	78.37
5	**21**	44.07	71.46
6	**22**	0	31.79
7	**23**	23.52	63.21
8	**24**	0	19.24

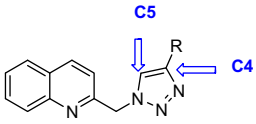
Rifampicine (2 μg/ml) 87% reduction in relative lights unit (RLU).

D-glucose coupled quinoline glycoconjugate **19**. Further insight into 4,6-*O*-protected D-glucose coupled quinoline glycoconjugates (**21**, **22**), reveals that the presence of small hydrophobic substituents such as methyl group, **21** exhibits good anti-tuberculosis activity than the quinoline glycoconjugate with long hydrophobic alkyl chain **22**. Therefore, it is evident that modification of the chain length in the saccharide moiety permits tunable potency which constitutes major avenue for future development of efficacious and selective anti-tuberculosis agents.

4. Results and discussion

Information of the expected triazole products (**17**–**24**) was obtained by NMR studies. The acetyl groups present in the saccharide moiety of the quinoline coupled triazole moiety is well resolved in both ^{1}H and ^{13}C NMR spectroscopy. The acetyl peaks resonate in the region around δ 2.01–2.13 ppm in ^{1}H NMR spectrum and around δ 20.47–21.02 ppm in the ^{13}C NMR spectrum. The anomeric proton of the saccharide moiety resonates around the region δ 4.63–4.95

Table 3
Δ ($\delta_{C4} - \delta_{C5}$) values of quinoline coupled triazole compounds **17–24**



Entry	Compound	C-4 of triazole ring (ppm)	C-5 of triazole ring (ppm)	Δ ($\delta_{C4} - \delta_{C5}$) ppm
1	**17**	148.5	122.3	26.2
2	**18**	148.3	125.7	22.6
3	**19**	147.7	123.4	24.3
4	**20**	147.6	123.4	24.2
5	**21**	145.1	125	20.1
6	**22**	147.6	123.3	24.3
7	**23**	144	123.7	20.3
8	**24**	147.6	123.5	24.1

and 96.9–102.5 ppm in the ^{1}H and ^{13}C NMR spectra, respectively. Moreover, the anomeric proton resonances exhibit that the saccharide moiety coupled to the quinoline ring is β in nature for compounds **19–22** and **24**, with exception for compound **23**, corresponding to the α-anomer as observed in the literature.[30–32] Moreover, the formation of the triazole ring is observed by the presence of triazole proton appearing as a singlet resonating at the region δ 7.59–7.93 ppm for the quinoline coupled triazole moiety. In the synthesized quinoline coupled triazole compounds (**17–24**), the corresponding methylene proton resonates at δ 5.83–5.89 and 56.3–62.7 ppm in ^{1}H NMR and ^{13}C NMR spectra, respectively.

The 2-D homonuclear ^{1}H–^{1}H NMR spectra of the triazole molecule **20**, shows that the interaction of the triazole proton with the –*CH*$_2$ of the quinolone, which thereby confirms the presence of 1,4-regioisomer and not the 1,5-regioisomer (see Supplementary data for more details). Moreover, ^{13}C NMR analysis of triazole derivatives, **17–24** confirms the 1,4-disubstituted triazole product formation. Large Δ ($\delta_{C4} - \delta_{C5}$) values for the different triazoles, ranging from 20.1 to 24.3 ppm, corroborated the 1,4-regioisomer, since much smaller values would be expected for 1,5-regioisomers (Table 3).[33] The DEPT-135 of quinoline coupled triazole sugar hybrid, **20** confirms the presence of the three methylene carbons (δ 56.3, 61.2, 62.7 ppm) corresponding to the proposed structure. All these evidences further confirm the formation of the expected products.

5. Conclusion

In conclusion, we have reported the synthesis and anti-tuberculous activities of quinoline coupled triazole conjugates. The most noteworthy aspect of this research is the exhibition of potent anti-tuberculosis activities in the reported compounds, which are synthesized from inexpensive and commercially available 2-methylquinoline via 'click chemistry'. The results clearly exhibit that the quinolone-coupled triazole compounds are a new class of anti-tuberculosis analog, making them very attractive for further chemical and biological optimization. Efforts are currently underway towards further optimization of the lead molecules through the replacement of methyl groups in the quinoline ring. Among the derivatives studied, compound **20** showed remarkably higher activity, and it can be concluded that this class of compounds certainly holds great prospects, and further exploration in this field may lead to potent anti-tuberculous analogs.

6. Experimental protocols

6.1. General methods

^{1}H and ^{13}C NMR spectra were measured on Bruker AVANCE 300 NMR spectrometer using tetramethylsilane (Me_4Si) as the internal standard. Thin-layer chromatography (TLC) was performed on manual coated plates (Acme's) with detection by UV-light or iodine chamber. Column chromatography was performed using SiO_2 (Acme's 100–200 mesh). Elemental analysis was carried out using Eager 300 C, H, N analyzer at IIT Bombay (Mumbai, India). While assigning the spectral data several short forms were used and these include, 'Trz' for triazole, 'Qui' for quinoline, 'Phe' for phenyl, 'Sacc' for saccharide, 'Ace' for acetyl, 'Ethy' for 4,6-*O*-ethylidene, 'Buty' for 4,6-*O*-butylidene and 'Ano' for anomeric.

6.2. Antimycobacterial activity: procedure

Antimycobacterial activities of the synthesized compounds were evaluated by Luciferase Reporter Phage assay method. The LRP assay method is as follows: fifty-microliter of bacterial suspension equivalent to MacFarlands No. 2 standard was added to 400 μL of G7H9 with and without the test compound. For each sample, two drug-free controls and two drug concentrations were prepared and this set up was incubated for 72 h at 37 °C. After incubation, 50 μL of the high titer Luciferase reporter phage (phAE129) and 40 μL of 0.1 M $CaCl_2$ were added to all the vials and this setup was incubated at 37 °C for 4 h. After incubation, 100 μL of the mixture was taken from each tube into a luminometer cuvette and equal amount of working D-luciferin (0.3 mM in 0.05 M sodium citrate buffer, pH 4.5) solution was added. The RLU was measured after 10 s of integration in the Luminometer (Monolight 2010). Duplicate readings were recorded for each sample and the mean was calculated. The percentage reduction in the RLU was calculated for each test sample and compared with control. The experiment was repeated when the mean RLU of the control was less than 1000.

6.3. Synthesis of 2-(azidomethyl)-quinoline (8)

To a solution mixture of H_2O–acetone in a ratio of 1:2, 2-bromomethyl quinoline (**7**) (1.35 mmol, 0.3 g) and sodium azide (2.7 mmol, 0.175 g) was added and stirred at room temperature. The reaction was followed through TLC. After completion of the reaction, the reaction mixture was suspended over chloroform, washed with water and after evaporation of the solvent afforded 2-azidomethyl quinoline (**8**). Dark pink solid (2.6 g, 95%); mp 72–75 °C; R_f = 0.46 (2:8 EtOAc–hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 8.06–8.16 (m, 2H, Qui-*H*), 7.71–7.83 (m, 2H, Qui-*H*), 7.26–7.27 (m, 2H, Qui-*H*), 4.74 (s, 2H, Qui-C*H*$_2$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 158.3 (1C, Qui-*C*), 145.6 (1C, Qui-*C*), 138.1 (1C, Qui-*C*), 130.3 (1C, Qui-*C*), 129.5 (1C, Qui-*C*), 127.5–127.8 (3C, Qui-*C*), 119.5 (1C, Qui-*C*), 42.3 (1C, Qui-*C*H$_2$). Anal. Calcd for $C_{10}H_8N_4$ (184.20): C, 65.21; H, 4.38; N, 30.42. Found: C, 65.76; H, 4.17; N, 30.82.

6.4. General procedure for the synthesis of quinoline coupled triazoles (17–24)

To a solution mixture of THF/H_2O in a ratio of 1:1, propargyl alcohol, **9** (2.47 mmol, 0.14 mL), was added, followed by addition of $CuSO_4{\cdot}5H_2O$ (0.2 mmol, 0.05 g) and sodium ascorbate (0.41 mmol, 0.08 g). The reaction mixture was stirred at room temperature for 15 min. A solution of 2-azidomethyl quinoline (**8**) (2.47 mmol, 0.453 g) in THF was added in drops to the reaction mixture. The reaction mixture was then heated at 30–45 °C for 6 h. After completion of the reaction the reaction mixture was suspended over chloroform and washed with water. Evaporation of the solvent resulted in the crude sample which was then purified through column chromatography using chloroform/MeOH (7:3) as eluant to afford the quinoline coupled triazole compound (**17**). White solid (0.51 g, 86%); mp 109–111 °C; R_f = 0.38 (1:9 MeOH–$CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 8.06–8.17 (m, 2H, Qui-*H*),

7.76–7.84 (m, 2H, Qui-*H*), 7.72 (s, 1H, Trz-*H*), 7.28–7.61 (m, 2H, Qui-*H*), 5.83 (s, 2H, Qui-CH_2), 4.79 (d, *J* = 1.2 Hz, 2H, Trz-CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 154.4 (1C, Qui-*C*), 148.5 (1C, Trz-*C*), 147.6 (1C, Qui-*C*), 137.7 (1C, Qui-*C*), 130.2 (1C, Qui-*C*), 127.2–129.1 (4C, Qui-*C*), 122.3 (1C, Trz-*C*), 119.6 (1C, Qui-*C*), 56.52 (1C, Qui-CH_2), 56.3 (1C, Trz-CH_2). HR-EIMS: calcd for $C_{13}H_{12}N_4O$ [M+1], 240.2606, found: 240.2605. Anal. Calcd for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.03; N, 23.32. Found: C, 64.45; H, 5.47; N, 23.66.

6.4.1. 2-((4-Phenyl-1*H*-1,2,3-triazol-1-yl)methyl)quinoline (18)

A mixture of 2-azidomethyl quinoline, **8** (2.47 mmol, 0.45 g) and phenyl acetylene, **10** (2.47 mmol, 0.27 g) in 1:1 ratio of THF/H_2O, afforded compound, **18**. White solid (0.61 g, 87%); mp 160–162 °C; R_f = 0.35 (1:9 MeOH–$CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 8.08–8.18 (m, 2H, Qui-*H*), 7.93 (s, 1H, Trz-*H*), 7.74–7.83 (m, 2H, Qui-*H*), 7.56–7.61 (m, 2H, Qui-*H*), 7.32–7.43 (m, 5H, Phe-*H*), 5.89 (s, 2H, Qui-CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 154.6 (1C, Qui-*C*), 148.3 (1C, Trz-*C*), 147.6 (1C, Qui-*C*), 137.7 (1C, Qui-*C*), 130.4 (1C, Qui-*C*), 130.19 (1C, Qui-*C*), 128.7–129.1 (3C, Qui-*C*), 127.1–128.1 (5C, Phe-*C*), 125.7 (1C, Trz-*C*), 120.2 (1C, Phe-*C*), 119.6 (1C, Qui-*C*), 56.4 (1C, Qui-CH_2). HR-EIMS: calcd for $C_{18}H_{14}N_4$ [M+1], 286.3306, found: 286.3354. Anal. Calcd for $C_{18}H_{14}N_4$: C, 75.50; H, 4.93; N, 19.57. Found: C, 75.94; H, 4.58; N, 19.13.

6.4.2. 2-((4-((2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyloxy) methyl)-1*H*-1,2,3-triazol-1-yl)methyl)-quinoline (19)

A mixture of 2-azidomethyl quinoline, **8** (2.47 mmol, 0.45 g) and 2-propyn-1-yl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside, **11** (2.47 mmol, 0.95 g) in 1:1 ratio of THF/H_2O, afforded compound, **19**. Oily liquid (0.96 g, 68%); R_f = 0.23 (1:9 MeOH–$CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) : δ_H 8.06–8.19 (m, 2H, Qui-*H*), 7.74–7.84 (m, 2H, Qui-*H*), 7.73 (s, 1H, Trz-*H*), 7.30–7.61 (m, 2H, Qui-*H*), 5.84 (s, 2H, Qui-CH_2), 4.81–5.20 (m, 4H, Sacc-*H*), 4.66 (d, *J* = 7.8 Hz, 1H ano-*H*), 4.08–4.27 (m, 4H, Sacc-*H*), 1.97–2.06 (m, 12H, Ace-*H*). ^{13}C NMR ($CDCl_3$) δ_C 169.2–170.6 (4C, Ace-*C*=*O*), 154.4 (1C, Qui-*C*), 147.7 (1C, Trz-*C*), 144.9 (1C, Qui-*C*), 137.7 (1C, Qui-*C*), 130.2 (1C, Qui-*C*), 127.2–129.2 (4C, Qui-*C*), 123.4 (1C, Trz-*C*), 119.6 (1C, Qui-*C*), 99.6 (1C, Ano-*C*), 68.2–72.0 (3C, Sacc-*C*), 62.8 (1C, Trz-*CH*$_2$), 60.4–61.8 (2C, Sacc-*C*), 56.3 (1C, Qui-CH_2), 20.4–21.0 (4C, Ace-*CH*$_3$). HR-EIMS: calcd for $C_{27}H_{30}N_4O_{10}$ [M+1], 570.5479, found: 570.5467. Anal. Calcd for $C_{27}H_{30}N_4O_{10}$: C, 56.84; H, 5.30; N, 9.82. Found: C, 56.43; H, 5.47; N, 9.66.

6.4.3. 2-((4-((2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyloxy) methyl)-1*H*-1,2,3-triazol-1-yl)methyl)-quinoline (20)

A mixture of 2-azidomethyl quinoline, **8** (2.47 mmol, 0.453 g) and 2-propyn-1-yl-2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside, **12** (2.47 mmol, 0.95 g) in 1:1 ratio of THF/H_2O, afforded compound, **20**. Oily liquid (0.78 g, 55%); R_f = 0.26 (1:9 MeOH–$CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.06–8.20 (m, 2H, Qui-*H*), 7.73–7.84 (m, 2H, Qui-*H*), 7.76 (s, 1H, Trz-*H*), 7.28–7.61 (m, 2H, Qui-*H*), 5.84 (s, 2H, Qui-CH_2), 5.16–5.38 (m, 2H, Sacc-*H*), 4.81–5.01 (m, 2H, Sacc-*H*), 4.63 (d, *J* = 7.8 Hz, 1H ano-*H*), 3.9–4.14 (m, 4H, Sacc-*H*), 1.84–2.13 (m, 12H, Ace-*H*). ^{13}C NMR ($CDCl_3$) δ_C 169.4–170.4 (4C, Ace-*C*=*O*), 154.3 (1C, Qui-*C*), 147.6 (1C, Trz-*C*), 144.7 (1C, Qui-*C*), 137.8 (1C, Qui-*C*), 130.2 (1C, Qui-*C*), 127.2–129.1 (4C, Qui-*C*), 123.4 (1C, Trz-*C*), 119.7 (1C, Qui-*C*), 100.2 (1C, Ano-*C*), 67–70.8 (3C, Sacc-*C*), 62.7 (1C, Trz-*CH*$_2$), 61.2 (1C, Sacc-*C*), 56.3 (1C, Qui-CH_2), 41 (1C, Sacc-*C*), 20.5–20.6 (4C, Ace-*CH*$_3$). HR-EIMS: calcd for $C_{27}H_{30}N_4O_{10}$ [M+1], 570.5479, found: 570.5493. Anal. Calcd for $C_{27}H_{30}N_4O_{10}$: C, 56.84; H, 5.30; N, 9.82. Found: C, 56.24; H, 5.52; N, 9.54.

6.4.4. 2-((4-((2,3-Di-*O*-acetyl-4,6-O-ethylidene-β-D-glucopyrano syloxy)methyl)-1*H*-1,2,3-triazol-1-yl)methyl)-quinoline (21)

A mixture of 2-azidomethyl quinoline, **8** (2.47 mmol, 0.453 g) and 2-propyn-1-yl-2,3-di-*O*-acetyl-4,6-*O*-ethylidene-β-D-glucopyranose, **13** (2.47 mmol, 0.81 g) in 1:1 ratio of THF/H_2O, afforded compound, **21**. Oily liquid (0.86 g, 72%); R_f = 0.20 (1:9 MeOH–$CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) : δ_H 7.72–7.79 (m, 2H, Qui-*H*), 7.59 (s, 1H, Trz-*H*), 7.57–7.49 (m, 2H, Qui-*H*), 7.36–7.26 (m, 2H, Qui-*H*), 5.46 (s, 2H, Qui-CH_2), 5.22–4.77 (m, 4H, Sacc-*H*), 4.67 (d, *J* = 7.8 Hz, 1H ano-*H*), 4.23–3.35 (m, 5H, Sacc-*H*), 2.04 (s, 3H, Ace-*H*), 1.989 (s, 3H, Ace-CH_3), 1.32 (d, *J* = 5.1 Hz, 3H, Ethy-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 170–169.5 (2C, Ace-*C*=*O*), 153.9 (1C, Qui-*C*), 145.1 (1C, Trz-*C*), 142.8–128.4 (3C, Qui-*C*), 125 (1C, Trz-*C*), 124.1–116.7 (5C, Qui-*C*), 99.8 (1C, Ano-*C*), 92.1 (1C, Ace-*C*), 71.8–66.9 (5C, Sacc-*C*), 49.3 (1C, Trz-*CH*$_2$), 29.9 (1C, Qui-*CH*$_2$), 20.7–20.6 (2C, Ace-*CH*$_3$), 20.1 (1C, Ethy-*CH*$_3$). Anal. Calcd for $C_{25}H_{28}N_4O_8$ (512.51): C, 58.59; H, 5.51; N, 10.93. Found: C, 58.91; H, 5.29; N, 10.56.

6.4.5. 2-((4-((2,3-Di-*O*-acetyl-4,6-O-butylidene-β-D-glucopyrano syloxy)methyl)-1*H*-1,2,3-triazol-1-yl)methyl)-quinoline (22)

A mixture of 2-azidomethyl quinoline, **8** (2.47 mmol, 0.453 g) and 2-propyn-1-yl-2,3-di-*O*-acetyl-4,6-*O*-butylidene-β-D-glucopyranose, **14** (2.47 mmol, 0.87 g) in 1:1 ratio of THF : H_2O, afforded compound, **22**. Oily liquid (0.96 g, 69%); R_f = 0.23 (1:9 MeOH–$CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) : δ_H 8.06–8.19 (m, 2H, Qui-*H*), 7.74–7.84 (m, 2H, Qui-*H*), 7.7 (s, 1H, Trz-*H*), 7.3–7.61 (m, 2H, Qui-*H*), 5.83 (s, 2H, Qui-CH_2), 4.77–5.16 (m, 4H, Sacc-*H*), 4.66 (d, *J* = 7.8 Hz, 1H ano-*H*), 3.37–4.49 (m, 5H, Sacc-*H*), 2.02 (s, 3H, Ace-*H*), 1.83 (s, 3H, Ace-*H*), 1.55–1.62 (m, 2H, Buty-CH_2), 1.32–1.4 (m, 2H, Buty-CH_2), 0.86–0.91 (m, 3H, Buty-CH_3). ^{13}C NMR ($CDCl_3$) δ_C 169.9–169.5 (2C, Ace-*C*=*O*), 154.3 (1C, Qui-*C*), 147.6 (1C, Trz-*C*), 144.6 (1C, Qui-*C*), 137.8 (1C, Qui-*C*), 130.2 (1C, Qui-*C*), 127.2–129.1 (4C, Qui-*C*), 123.3 (1C, Trz-*C*), 119.7 (1C, Qui-*C*), 102.5 (1C, Ano-*C*), 100.1 (1C, Ace-*C*), 72.1–66.5 (5C, Sacc-*C*), 62.8 (1C, Trz-*CH*$_2$), 56.3 (1C, Qui-*CH*$_2$), 35.9 (1C, Buty-*CH*$_2$), 20.5–20.7 (2C, Ace-*CH*$_3$), 17.3 (1C, Buty-*CH*$_3$), 13.8 (1C, Buty-*CH*$_2$). Anal. Calcd for $C_{27}H_{32}N_4O_8$ (540.56): C, 59.99; H, 5.97; N, 10.36. Found: C, 59.58; H, 5.54; N, 10.87.

6.4.6. 2-((4-((2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl oxy)methyl)-1*H*-1,2,3-triazol-1-yl)methyl)-quinoline (23)

A mixture of 2-azidomethyl quinoline, **8** (2.47 mmol, 0.453 g) and 2-propyn-1-yl-2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside, **15** (2.47 mmol, 0.95 g) in 1:1 ratio of THF/H_2O, afforded compound, **23**. Oily liquid (0.87 g, 62%); R_f = 0.27 (1:9 MeOH–$CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) : δ_H 8.08–8.21 (m, 2H, Qui-*H*), 7.77–7.85 (m, 1H, Qui-*H*), 7.76 (s, 1H, Trz-*H*), 7.73–7.74 (s, 1H, Qui-*H*), 7.55–7.61 (m, 1H, Qui-*H*), 7.32–7.35 (m, 1H, Qui-*H*), 5.86 (s, 2H, Qui-CH_2), 5.21–5.30 (m, 2H, Sacc-*H*), 4.95 (d, *J* = 1.6 Hz, 1H ano-*H*), 4.66–4.86 (m, 2H, Sacc-*H*), 4.25–4.31 (m, 2H, Sacc-*H*), 4.05–4.15 (m, 2H, Sacc-*H*), 1.97–2.13 (m, 12H, Ace-*H*). ^{13}C NMR ($CDCl_3$) δ_C 169.7–170.7 (4C, Ace-*C*=*O*), 154.2 (1C, Qui-*C*), 144 (1C, Trz-*C*), 137.9 (1C, Qui-*C*), 130.2 (1C, Qui-*C*), 127.2–129.2 (5C, Qui-*C*), 123.7 (1C, Trz-*C*), 119.7 (1C, Qui-*C*), 96.9 (1C, Ano-*C*), 66.2–69.4 (4C, Sacc-*C*), 62.3 (1C, Trz-*CH*$_2$), 61.0 (1C, Sacc-*C*), 56.3 (1C, Qui-*CH*$_2$), 20.6–20.8 (4C, Ace-*CH*$_3$). Anal. Calcd for $C_{27}H_{30}N_4O_{10}$ (570.55): C, 56.84; H, 5.30; N, 9.82. Found: C, 56.43; H, 5.71; N, 9.56.

6.4.7. 2-((4-((2,3,4-Tri-*O*-acetyl-β-D-ribopyranosyloxy)methyl)-1*H*-1,2,3-triazol-1-yl)methyl)-quinoline (24)

A mixture of 2-azidomethyl quinoline, **8** (2.47 mmol, 0.453 g) and 2-propyn-1-yl-2,3,4,-tri-*O*-acetyl-β-D-ribopyranoside, **16** (2.47 mmol, 0.77 g) in 1:1 ratio of THF/H_2O, afforded compound, **24**. Oily liquid (0.72 g, 58%); R_f = 0.21 (1:9 MeOH–$CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 8.06–8.18 (m, 2H, Qui-*H*), 7.8–7.83 (m, 1H, Qui-*H*), 7.78 (s, 1H, Trz-*H*), 7.29–7.75 (m, 3H, Qui-*H*), 5.84 (s, 2H, Qui-CH_2), 5.23–5.46 (m, 2H, Sacc-*H*), 4.84–5.14 (m, 2H, Sacc-*H*), 4.66 (d, *J* = 13.8 Hz, 1H ano-*H*), 4.35–4.31 (m, 2H, Sacc-*H*), 3.81–4.29 (m, 1H, Sacc-*H*), 2.01–2.11 (m, 9H, Ace-*H*). ^{13}C

NMR ($CDCl_3$) δ_C 169.6–170.1 (3C, Ace-*C*=*O*), 154.3 (1C, Qui-*C*), 147.6 (1C, Trz-*C*), 144.7 (1C, Qui-*C*), 137.8 (1C, Qui-*C*), 130.2 (1C, Qui-*C*), 127.2–129.2 (4C, Qui-*C*), 123.5 (1C, Trz-*C*), 119.7 (1C, Qui-*C*), 97.7 (1C, Ano-*C*), 64.2–68.1 (3C, Sacc-*C*), 61.4 (1C, Trz-*C*H_2), 61.3 (1C, Sacc-*C*), 56.3 (1C, Qui-*C*H_2), 20.6–20.9 (3C, Ace-*C*H_3). Anal. Calcd for $C_{24}H_{26}N_4O_8$ (498.49): C, 57.83; H, 5.26; N, 11.24. Found: C, 57.52; H, 5.59; N, 11.64.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2011.06.028.

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