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Design, synthesis and evaluation of 1,2,3-triazole-adamantylacetamide hybrids as potent inhibitors of *Mycobacterium tuberculosis*

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ABSTRACT

A series of novel 1,2,3-triazole-adamantylacetamide hybrids **5a**–**u**, designed by combining bioactive fragments from antitubercular I-A09 and substituted adamantyl urea, were synthesized using copper catalyzed click chemistry. *N*-(1-Adamantyl)-2-azido acetamide **3** prepared from 1-adamantylamine was reacted with a series of alkyl/aryl acetylenes in the presence of copper sulfate and sodium ascorbate to give new analogues **5a**–**u** in very good yields. Evaluation of all new compounds for *in vitro* antitubercular activity against *Mycobacterium tuberculosis* H37Rv (ATCC27294), resulted *N*-(1-adamantan-1-yl)-2-(4-(phenanthren-2-yl)-1*H*-1,2,3-triazol-1-yl)acetamide (**5t**) as most promising lead MIC: 3.12 μg/mL) with selectivity index >15.

Tuberculosis (TB) is a highly contagious airborne disease caused by pathogen *Mycobacterium tuberculosis* (*Mtb*) and is now ranked as second leading cause of death world-wide due to infections.[1] The 2012 WHO global tuberculosis report estimates nearly 1.5 million people die from TB each year and majority of them are from developing countries.[2] Further, TB is also a major cause of mortality among patients co-infected with HIV.[3] Additionally, the resurgence of its new virulent forms like multi drug resistant (MDR-TB) and extremely drug resistant (XDR-TB) has become a major threat to human kind.[4] All these facts necessitated re-engineering and repositioning of existing bioactives of natural and synthetic origin for the development of fast acting new antitubercular drugs with novel mechanism of action to achieve effective TB control.

In recent years, adamantane coupled pharmacophoric derivatives have gained importance in medicinal chemistry. It is often viewed as a readily available 'liphophilic bullet' for providing the critical liphophilicity to known pharmacophoric units.[5] Seven adamantane based drugs (Amantadine, Memantine, Rimantadine, Tromantadine, Vildagliptin, Saxagliptin and Arterolane)[6] are approved by US-FDA and among them Memantine has become a block buster drug[7] (Fig. 1). Several adamantane based new chemical entities exhibited diverse biological properties such as antiviral,[8] antibacterial,[9] antifungal,[10] anti-inflammatory, antidiabetic and 11b-HSD1 inhibitory activities.[6] Since mycobacteria have lipid-rich cell walls, its liphophilicity is considered as one of the important factor in designing novel antitubercular agents.[11] Two compounds SQ109[12] and SQ609[13] derived from adamantane are currently in human clinical trials for controlling TB. More recently McNeil *et al.* have identified adamantyl ureas as potent antitubercular agents.[14] On the other hand, 1,2,3-triazole based antitubercular agents **I**–**VI** (Fig. 2)[15] may be regarded as a new class providing truly effective lead candidates which are reported to inhibit bacteria and among them **IV** is presently in preclinical trials.[15f] Additionally, these 1,2,3-triazoles possess remarkable metabolic stability and prove to be amide surrogates in various bioactive compounds.[16] A series of 1,2,3-triazole based new molecules, designed and synthesized in our laboratory, exhibited promising antimycobacterial activity,[15a,b,17] and some of them are undergoing detailed investigations. Here we envisaged that 1,2,3-triazole based antitubercular agents with 'liphophilic bullet' adamantane could lead to new analogues for their evaluation as antimycobacterial agents.

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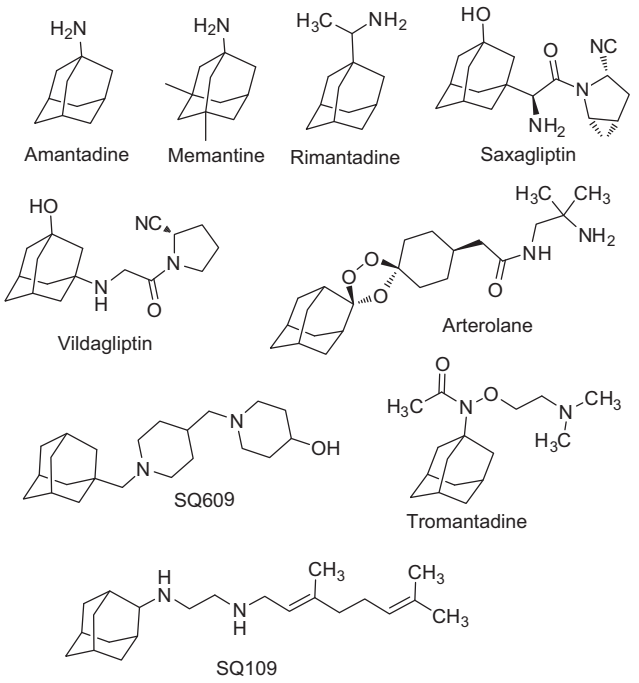


Figure 1. Representative adamantane based drug candidates.

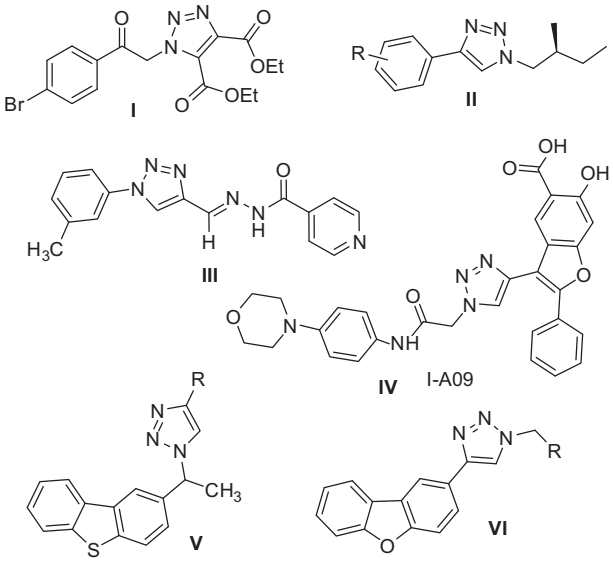


Figure 2. 1,2,3-Triazole based antitubercular agents **I**–**VI**.

In our continued efforts to develop newer antitubercular agents, we herein report an efficient synthesis and antitubercular evaluation of novel 1,2,3-triazole-adamantane acetamide hybrids **5a**–**u** via copper catalyzed click chemistry.[18] Screening all new compounds for *in vitro* activity against *M. tuberculosis* H37Rv (*Mtb*) resulted *N*-(1-adamantan-1-yl)-2-(4-(phenanthren-2-yl)-1*H*-(1,2,3-triazol-1-yl)acetamide (**5t**) as most promising lead antitubercular agent (MIC: 3.12 μg/mL). Compound **5t** has also exhibited lower cytotoxicity with good selectivity index (SI).

The designed scaffold (Fig. 3) is originated from the structures of two antitubercular agents' I-A09[15f] and adamantyl urea[14] is in three parts: N-substituted 1,2,3-triazole as a central backbone, 1-adamantylamine for enhancing desired liphophilicity behavior and aliphatic or aromatic groups appended to other side of 1,2,3-triazole moiety for tuning pharmacophoric nature. Variations in the proposed scaffold can be accomplished with the choice of aliphatic or aromatic alkynes **4a**–**u**. The method adopted for synthesis of 1,2,3-triazole-adamantane acetamide hybrids was based on Huisgen 1,3-dipolar cycloaddition reaction (click reaction) between azide **3** and alkynes **4a**–**u**.

Initiating the study, *N*-(1-adamantyl)-2-azidoacetamide **3** required for preparation of triazole hybrids was synthesized from 1-adamantylamine **1** (Scheme 1) by modifying the literature procedures.[19,20] Reaction of *N*-(1-adamantyl)-2-chloroacetamide **2**[21] (obtained by reacting **1** with chloroacetyl chloride and K_2CO_3), with sodium azide in the presence of tetra-*n*-butylammonium bromide produced, *N*-(1-adamantyl)-2-azidoacetamide **3**[22] in 98.1% yield. The azide **3** was characterized by IR, ^1H ^{13}C NMR and mass spectral data. Alkynes **4a**–**u** (Fig. 4) required was purchased from commercial sources and used as such in the click reaction with azide **3**.

Both azide building block **3** and alkynes **4a**–**u** in hand, we next employed copper catalyzed Huisgen's (3+2) cycloaddition reaction. For example, reaction of azide **3** with 1-hexyne **4a** in the presence of 20 mol % of $CuSO_4$ catalyst and sodium ascorbate in *t*-butanol and water (1:1, v/v) gave *N*-(1-adamantyl)-2-(4-butyl-1*H*-1,2,3-triazol-1-yl)acetamide (**5a**) in 79% yield. Similarly all other alkynes **4b**–**u** were reacted with *N*-(1-adamantyl)-2-azidoacetamide **3** to give a series of 1,2,3-triazole-adamantane acetamide hybrids **5b**–**u** in excellent yields (Scheme 1).[23] 1,2,3-Triazole-adamantane hybrids **5a**–**u** obtained was fully characterized by ^1H, ^{13}C NMR and mass (ESI and HR-MS) spectral data.[23] Purity of all the new compounds **5a**–**u** was determined by HPLC analysis.

The antitubercular activity of the synthesized 1,2,3-triazole-adamantaneacetamide hybrids **5a**–**u** has been screened against *M. tuberculosis* H37Rv (ATCC27294) by agar dilution method[24] for the determination of MIC in triplicates. The minimum inhibitory concentration (MIC) is defined as the minimum concentration of compound required to completely inhibit the bacterial growth. The MIC values (μg/mL) of **5a**–**u** along with the standard drugs for comparison are described in Table 1. Twenty one new compounds screened for in vitro activity against *Mtb* exhibited MICs

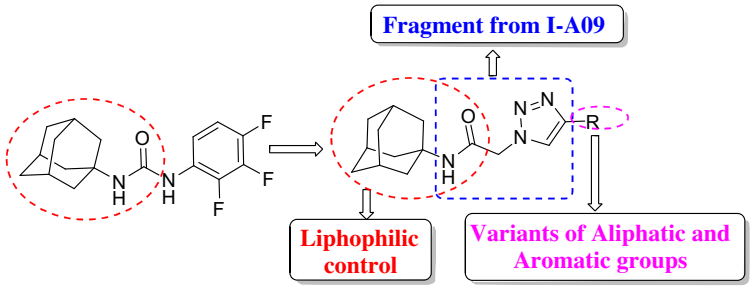
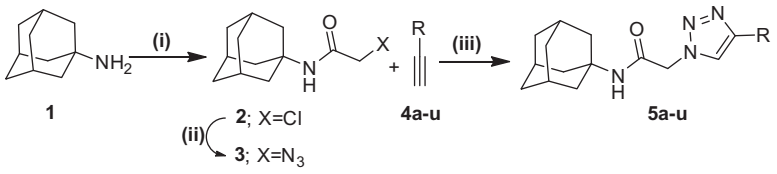


Figure 3. Design strategy for 1,2,3-triazole-adamantaneacetamide hybrids.



Scheme 1. Synthesis of 1-adamantane substituted-1,2,3-triazole hybrids **5a–u**. Reaction conditions: (i) Chloroacetyl chloride, K_2CO_3,CH_2Cl_2, reflux, 3 h, 98.1%; (ii) NaN_3, TBAB, CH_2Cl_2: H_2O (1:1), 12 h 95.7% ; (iii) 20 mol% $CuSO_4.5H_2O$, sodium ascorbate, t-BuOH, H_2O (1:1), 1–2 h, rt, 70–89%.

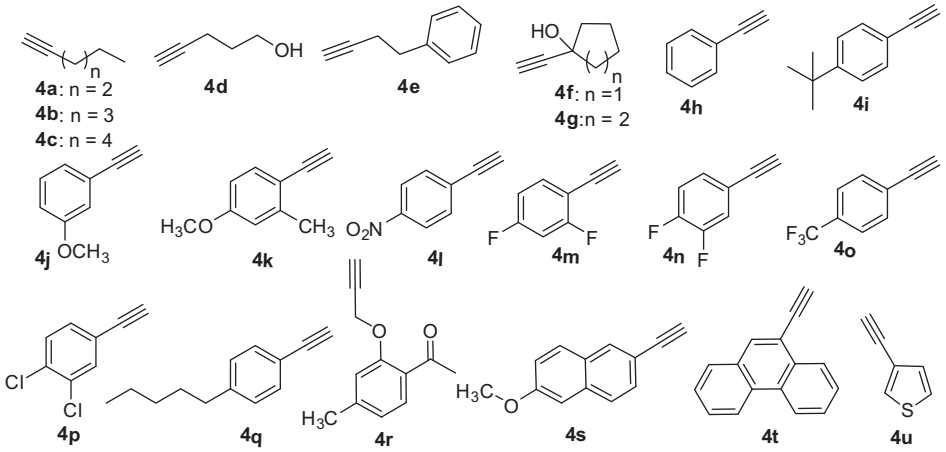


Figure 4. Alkynes **4a–u** used in the study.

Table 1
Physical data and antitubercular evaluation of **5a–u** against *M. tuberculosis* H37RV

Entry	Alkynes **4a–u**	Product **5a–u**	Yield[a] (%)	Mp (°C)	Log*P*/*C*Log*P*[b]	MIC (μg/mL)
1	**4a**	**5a**	79	Syrup	2.68/3.22	50.0
2	**4b**	**5b**	73	Syrup	3.1/3.75	50.0
3	**4c**	**5c**	70	Syrup	3.52/4.28	50.0
4	**4d**	**5d**	84	Syrup	0.61/0.33	6.25
5	**4e**	**5e**	81	72	3.03/3.21	50.0
6	**4f**	**5f**	75	Syrup	1.51/1.79	50.0
7	**4g**	**5g**	72	160	1.93/2.35	6.25
8	**4h**	**5h**	81	48	2.75/3.47	50.0
9	**4i**	**5i**	88	Syrup	4.46/5.29	50.0
10	**4j**	**5j**	83	98	2.63/3.45	25.0
11	**4k**	**5k**	82	Syrup	3.12/3.65	50.0
12	**4l**	**5l**	87	170	—/3.29	50.0
13	**4m**	**5m**	89	128	3.07/3.79	50.0
14	**4n**	**5n**	85	115	3.07/3.79	50.0
15	**4o**	**5o**	82	110	3.68/4.41	50.0
16	**4p**	**5p**	80	152	3.87/4.68	50.0
17	**4q**	**5q**	89	Syrup	4.91/6.08	6.25
18	**4r**	**5r**	83	Syrup	2.55/3.50	50.0
19	**4s**	**5s**	82	162	3.63/4.56	50.0
20	**4t**	**5t**	84	210	4.75/5.81	3.12
21	**4u**	**5u**	89	126	2.74/3.37	50.0
Isoniazid	—	—	—	—	—	0.1
Ethambutol	—	—	—	—	—	3.13
Pyrazinamide	—	—	—	—	—	50.0

[a] Isolated yields.
[b] Calculated using Chembiodraw 12.0.

ranging from 3.12 to 50.0 μg/mL. Among all the compounds, four hybrids **5d**, **5g**, **5q** and **5t** exhibited MIC ⩽6.25 μg/mL, a value postulated by the global program for the discovery of new antitubercular drugs as threshold for the evaluation of new *M. tuberculosis* therapies. Although all the new compounds are found to be less potent than first line antitubercular drug isoniazid (0.1 μg/mL), five compounds **5d**, **5g**, **5j**, **5q** and **5t** are more potent than other antitubercular drug pyrazinamide (MIC: 50 μg/mL) and one compound **5t** is equipotent to another antitubercular drug ethambutol (MIC 3.13 μg/mL). Among triazole hybrids **5h–p**, **5r**, **5s** and **5u** with substituted aryls appended to 1,2,3-triazole nucleus displayed reduced inhibitory activity. Compound **5t** bearing phenanthrene is the most active moiety inhibiting *Mtb*.

Liphophilicity has long been recognized as an important factor for successful passage of drugs through clinical development.[25] Generally, calculated log*P* (*c*log*P*) is being used for assessment of

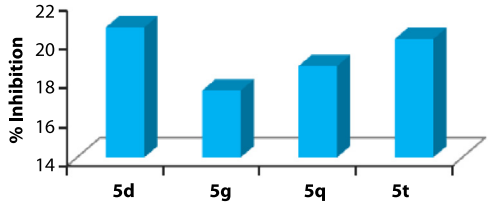


Figure 5. Percentage inhibition of HEK-293Tcells at a concentration of 50 μg/mL adamantane analogues.

liphophilicity and the key events of molecular desolvation, transfer from aqueous phases to cell membranes and protein binding sites.[26] With evidenced role as a predictor of eventual compound success, computation of log*P* (*c*log*P*) for liphophilicity is essential for the development of a successful therapeutic compound. To correlate antitubercular activity of present series compounds with respect to liphophilicity, log*p*/C log*p* were calculated using Chembiodraw ultra 12.0. Four potent hybrids **5d**, **5g**, **5q** and **5t** showed Log*p* (C log*p*) 0.61 (0.33), 1.93 (2.35), 4.91 (6.08) and 4.75 (5.81), respectively. To mention here that, among all new compounds examined **5t** bearing phenanthrene on triazole core is the most optimized analogue with best correlated to liphophilicity with Log*P* <5.0 (Table 1). The result clearly reveal that apart from adamantane unit the functional group 'R' appended to 1,2,3-triazole core (Scheme 1) also plays a significant role in controlling liphophilicity and *Mtb* inhibition activity.

The in vitro cytotoxicity of hybrid analogues evaluated for antitubercular activity with MIC ⩽6.25 μg/mL were assessed by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide assay (MTT) assay[27] against Human Embryonic Kidney (HEK-293T) cells at 50 μg/mL concentration. Percentage inhibition of cells was reported in Figure 5. The most promising antitubercular compounds **5d**, **5g**, **5q** and **5t** exhibited 20.72%, 17.46%, 18.72% and 20.12% inhibition, respectively, at 50 μg/mL with selectivity index of approximately >15. Compounds that exhibited selectivity index (SI) values greater than 10 in HEK-293Tcells were considered nontoxic. The results demonstrated that the compounds **5d**, **5g**, **5q** with MIC (6.25 μg/mL) and **5t** with (3.13 μg/mL) inhibitory activity against *M. tuberculosis* also exhibited lowest toxicity, that is, high SI (>15) against HEK-293Tcells.

In conclusion we have described a series of 1,2,3-triazole-adamantyl acetamide hybrids **5a**–**u** by using click chemistry. The required azide building block **3** was prepared from 1-adamantyl amine in two steps. New analogues **5a**–**u** were synthesized using Huisgen's (3+2) cycloaddition reaction between azide **3** and alkynes **4a**–**u** in presence of copper sulfate and sodium ascorbate. Evaluation of all the new hybrids **5a**–**u** against *M. tuberculosis* H37Rv (*Mtb*) and cytotoxicity revealed that four compounds **5d**, **5g**, **5q** with MIC 6.25 μg/mL and **5t** with MIC 3.13 μg/mL are best active antitubercular agents and with selectivity index >15. The results described here demonstrate the potential utility of new hybrid analogues of adamantane with appended 1,2,3-triazole fragment as potent antitubercular agents for further optimization.

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Supplementary data

Supplementary data (copies of ^{1}H, ^{13}C NMR and mass spectra of all the new compounds **2**, **3** and **5a**–**u**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.02.061.

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21. *N-(1-Adamantyl)-2-chloroacetamide* (***2***): To a solution of 1-adamantylamine hydrochloride **1** (5.0 g, 26.73 mmol), K_2CO_3 (7.37 g, 53.46 mmol) in DCM (50 mL) was added chloroacetyl chloride (2.53 mL, 32.08 mmol) at 0 °C and then heated at reflux for 3 h. The reaction mixture was cooled to RT, and was filtered at buckner funnel, concentrate the filterate under reduced pressure to give *N*-((3*s*,5*s*,7*s*)-adamantan-1-yl)-2-chloro acetamide (**2**) (5.95 g, 98.1%) as white solid. Mp: 114 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.23 (br s, 1H), 3.93 (s, 2H), 2.10 (br s, 3H), 2.02 (s, 6H), 1.69 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 52.3, 42.8, 41.2, 36.1, 29.3. IR (KBr) 3268, 3085, 2907, 2853, 1662, 1568, 1452, 1408, 1235, 1092, 998, 801, 705, 577 cm^{-1}. MS (ESI) *m*/*z* 228 $[M+H]^+$.
22. *N-(1-Adamantyl)-2-azidoacetamide* (***3***): Compound **2** (5.0 g, 22.02 mmol) in dichloromethane (40 mL) was added sodium azide (2.86 g, 44.05 mmol) in water (40 mL) and tetra-*n*-butyl ammonium bromide (0.07 g, 0.22 mmol) and stirred at RT for 12 h. The organic layer was separated, washed with water (3 × 50 mL), dried over sodium sulfate and concentrated under reduced pressure to give product **3** (4.93 g, 95.7%) as white solid.

*N-(1-Adamantyl)-2-azidoacetamide (**3**):* Mp: 75 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.27 (br s, 1H), 3.93 (s, 2H), 2.09 (br s, 3H), 2.01 (s, 6H), 1.68 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 52.3, 41.3, 41.1, 36.1, 29.2. IR (KBr) 2928, 2859, 1655, 1594, 1458, 1416, 1265, 1191, 1072, 966, 824, 731, 6163271, 3087, 2909, 2854, 2101, 1664, 1567, 1362, 1275, 1096, 998, 799, 701 cm^{-1}. MS (EI-HRMS) *m/z* 234.

23. *General procedure for synthesis of N-(1-adamantyl)-2-(1H-1,2,3-triazol-1-yl)acetamide hybrids hybrids **5a–u**:* Azide **3** (1.0 mmol), alkynes **4a–u** (1.0 mmol), copper sulfate·5H_2O (20 mol %) and sodium ascorbate (20 mol %) in *t*-butanol and water (1:1, v/v, 4 mL), was stirred at RT for 1–2 h. After completion (TLC), the reaction mixture was diluted with ethyl acetate (20 mL) and water (5 mL), the organic layer was separated, washed with brine solution (2 × 10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude residue thus obtained was purified over silica gel column chromatography eluted with ethyl acetate/hexane (1:2) to give pure 1,2,3-triazole hybrids **5a–u**.

*Spectral data for products **5a–u**: N*-(1-Adamantyl)-2-(4-butyl-1*H*-1,2,3-triazol-1-yl)acetamide (**5a**); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (s, 1H), 5.74 (br s, 1H), 4.91 (s, 2H), 2.74 (t, *J* = 7.62 Hz 2H), 2.05 (br s, 3H), 1.93 (br s, 6H), 1.65–1.70 (m, 8H), 1.35–1.45 (m, 2H), 0.93 (t, *J* = 7.47 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 146.9, 122.1, 53.5, 52.6, 41.2, 36.1, 29.2, 25.2, 22.2, 13.7. IR (KBr) 3305, 3073, 2910, 2853, 1672, 1551, 1457, 1361, 1222, 1050, 814, 772 cm^{-1}. MS (ESI) *m/z* 317 [M+H]$^+$; HR-MS (ESI) calcd for $C_{18}H_{29}N_4O$ [M+H]$^+$; 317.23359 found: 317.23349.

*N-(1-Adamantyl)-2-(4-pentyl-1H-1,2,3-triazol-1-yl)acetamide (**5b**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (s, 1H), 6.09 (br s, 1H), 4.94 (s, 2H), 2.72 (t, *J* = 7.55 Hz, 2H), 2.05 (br s, 3H), 1.94 (s, 6H), 1.65 (br s, 8H), 1.33 (br s, 3H), 0.89 (br s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 148.6, 122.2, 53.3, 52.5, 41.1, 36.0, 31.2, 29.2, 28.8, 25.4, 22.2, 13.8. IR (KBr) 3303, 3073, 2911, 2853, 1672, 1551, 1457, 1362, 1278, 1222, 1051, 814, 755 cm^{-1}. MS (ESI) *m/z* 331 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{19}H_{31}N_4O$ [M+H]$^+$; 331.24924, found: 331.24911.

*N-(1-Adamantyl)-2-(4-hexyl-1H-1,2,3-triazol-1-yl)acetamide (**5c**):* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (s, 1H), 5.87 (br s, 1H), 4.92 (s, 2H), 2.72 (t, *J* = 7.17 Hz 2H), 2.05 (br s, 3H), 1.93 (s, 6H), 1.64 (br s, 8H), 1.25–1.35 (m, 6H), 0.87 (br s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 122.2, 53.5, 52.5, 41.1, 36.06, 31.4, 29.2, 28.7, 25.5, 22.4, 13.9. IR (KBr) 3308, 3074, 2912, 2853, 1672, 1551, 1457, 1362, 1278, 1051, 814 cm^{-1}. MS (ESI) *m/z* 345 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{20}H_{33}N_4O$ [M+H]$^+$; 345.26489, found: 345.26495.

*N-(1-Adamantyl)-2-(4-(3-hydroxypropyl)-1H-1,2,3-triazol-1-yl)acetamide (**5d**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (s, 1H), 5.88 (br s, 1H), 4.92 (s, 2H) 3.71 (t, *J* = 6.04 Hz, 2H), 2.73–3.07 (m, 3H), 2.05 (br s, 3H), 1.93–1.99 (m, 8H), 1.65 (br s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 147.9, 122.6, 61.5, 53.5, 52.6, 41.1, 36.0, 31.7, 29.2, 21.9. IR (neat) 3299, 3075, 2909, 2853, 1673, 1552, 1453, 1362, 1223, 1057, 753, 663 cm^{-1}. MS (ESI) *m/z* 319 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{17}H_{27}N_4O_2$ [M+H]$^+$: 319.21285, found: 319.21286.

*N-(1-Adamantyl)-2-(4-phenethyl-1H-1,2,3-triazol-1-yl)acetamide (**5e**):* Mp: 72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.31 (m, 3H), 7.19 (t, *J* = 5.47 Hz, 3H), 5.61 (br s, 1H), 4.86 (s, 2H), 2.98–3.11 (m, 4H), 2.06 (br s, 3H), 1.92 (br s, 6H), 1.65 (br s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 140.8, 128.3, 126.1, 53.6, 52.6, 41.2, 36.1, 35.2, 29.2, 27.2. IR (KBr) 3227, 3112, 3060, 2912, 2854, 1678, 1565, 1450, 1290, 1146, 1053, 821, 741, 698 cm^{-1}. MS (ESI) *m/z* 365 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{22}H_{29}N_4O$ [M+H]$^+$: 365.23359, found: 365.23389.

*N-(1-Adamantyl)-2-(4-(1-hydroxycyclopentyl)-1H-1,2,3-triazol-1-yl)acetamide (**5f**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63, (s, 1H), 5.70 (br s, 1H), 4.91 (s, 2H), 2.43 (br s, 1H), 1.82–2.13 (m, 17H), 1.65 (br s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 121.5, 78.8, 53.5, 52.7, 41.2, 36.0, 29.2, 23.5. IR (neat) 3459, 3267, 3095, 2912, 2851, 1682, 1582, 1454, 1364, 1223, 1096, 908, 811, cm^{-1}. MS (ESI) *m/z* 345 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{19}H_{29}N_4O_2$ [M+H]$^+$; 345.22850, found: 345.22849.

*N-(1-Adamantyl)-2-(4-(1-hydroxycyclohexyl)-1H-1,2,3-triazol-1-yl)acetamide (**5g**):* Mp: 160 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (s, 1H), 5.84 (s, 1H), 4.91 (s, 2H), 2.61 (br s, 1H), 2.17 (m, 1H), 2.05 (br s, 3H), 1.86–2.01 (m, 9H), 1.71–1.78 (m, 2H), 1.64 (br s, 6H), 1.53–1.59 (m, 2H), 1.24–1.38 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 121.3, 69.5, 53.6, 52.7, 41.2, 38.0, 36.0, 29.2, 25.2, 21.9.IR (KBr) 3455, 3285, 3097, 2910, 2853, 1684, 1578, 1454, 1369, 1221, 1059, 982, 895, 809 cm^{-1}. MS (ESI) *m/z* 359 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{28}H_{31}N_4O_2$ [M+H]$^+$; 359.24415, found: 359.24438.

*N-(1-Adamantyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)acetamide (**5h**):* Mp: 48 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.85 (d, *J* = 7.93 Hz, 2H), 7.44 (t, *J* = 7.47 Hz, 2H), 7.35 (t, *J* = 7.47 Hz, 1H), 5.97 (br s, 1H), 4.99 (s, 2H), 2.05 (br s, 3H), 1.95 (br s, 6H), 1.65 (br s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 148.2, 130.0, 128.8, 128.3, 125.7, 121.1, 53.7, 52.7, 41.2, 36.0, 29.2. IR (KBr) 3423, 2923, 1633, 1379, 1165, 1110, 1056, 590 cm^{-1}. MS (ESI) *m/z* 337 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{20}H_{25}N_4O$ [M+H]$^+$: 337.20229, found: 337.20233.

*N-(1-Adamantyl)-2-(4-(4-(tert-butyl)phenyl)-1H-1,2,3-triazol-1-yl)acetamide (**5i**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.76 (d, *J* = 8.30 Hz, 2H), 7.47 (d, *J* = 8.30 Hz, 2H), 6.04 (br s, 1H), 5.01 (s, 2H), 2.04 (br s, 3H), 1.95 (br s, 6H), 1.63 (br s, 6H), 1.34 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 151.5, 148.2, 127.3, 125.8, 125.5, 120.9, 53.7, 52.7, 41.2, 36.1, 31.2, 29.3. IR (neat) 3324, 3136, 3045, 2908, 2854, 1657, 1519, 1456, 1349, 1250, 1108, 1042, 856, 816, 745 cm^{-1}. MS (ESI) *m/z* 393 [M+H]$^+$: HR-MS (ESI) Calcd for $C_{24}H_{33}N_4O$ [M+H]$^+$: 393.26489, found: 393.26501.

*N-(1-Adamantyl)-2-(4-(3-methoxyphenyl)-1H-1,2,3-triazol-1-yl)acetamide (**5j**):* Mp: 98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.31–7.45 (m, 3H), 6.88–6.92 (m, 1H), 5.83 (br s, 1H), 4.99 (s, 2H), 3.87 (s, 3H), 2.06 (br s, 3H), 1.96 (br s, 6H), 1.65 (br s, 6H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 159.9, 148.0, 129.8, 121.3, 119.9, 118.1, 114.4, 110.7, 55.3, 53.7, 52.7, 41.1, 36.0, 29.2. IR (KBr) 3468, 3233, 3080, 2907, 2850, 1674, 1577, 1487, 1278, 1167, 1048, 991, 778, 688 cm^{-1}. MS (ESI) *m/z* 367 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{21}H_{27}N_4O_2$ [M+H]$^+$: 367.21285, found: 367.21313.

*N-(1-Adamantyl)-2-(4-(4-methoxy-2-methylphenyl)-1H-1,2,3-triazol-1-yl)acetamide (**5k**):* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.69 (d, 1H), 6.81–6.83 (m, 2H), 6.08 (br s, 1H), 5.02 (s, 2H), 3.82 (s, 3H), 2.44 (s, 3H), 2.04 (br s, 3H), 1.95 (s, 6H), 1.64 (s, 6H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 159.3, 147.2, 137.0, 130.0, 122.7, 122.1, 116.1, 111.3, 55.1, 53.5, 52.6, 41.1, 36.0, 29.2, 21.5. IR (neat) 3468, 3233, 3080, 2905, 2856, 1673, 1574, 1486, 1275, 1165, 1045, 990, 775, 685 cm^{-1}. MS (ESI) *m/z* 381 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{22}H_{29}N_4O_2$ [M+H]$^+$: 381.22850, found: 381.22894.

*N-(1-Adamantyl)-2-(4-(4-nitrophenyl)-1H-1,2,3-triazol-1-yl)acetamide (**5l**):* Mp: 170 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30(d, *J* = 9.06 Hz, 1H), 8.18 (s, 1H), 8.02 (d, *J* = 9.06 Hz, 2H), 5.79 (br s, 1H), 2.08 (br s, 3H), 1.98 (s, 6H), 1.66 (s, 6H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 147.3, 145.8, 136.5, 126.1, 124.2, 122.8, 53.6, 53.0, 41.2, 36.0, 29.2. IR (KBr) 3325, 3135, 3066, 2909, 2853, 1657, 1519, 1458, 1342, 1236, 1108, 1047, 854, 817, 755 cm^{-1}. MS (ESI) *m/z* 382 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{20}H_{24}N_5O_3$ [M+H]$^+$: 382.18737, found: 382.18802.

*N-(1-Adamantyl)-2-(4-(2,4-difluorophenyl)-1H-1,2,3-triazol-1-yl)acetamide (**5m**):* Mp: 115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23–8.31 (m, 1H), 8.07 (d, *J* = 3.58 Hz, 1H), 6.88–7.04 (m, 2H), 5.72 (br s, 1H), 5.01 (s, 2H), 2.06 (br s, 3H), 1.96 (br s, 6H), 1.65 (br s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 160.3, 141.0, 128.7, 123.6, 111.9, 112.1, 104.3, 104.1, 103.9, 53.7, 52.8, 41.2, 36.0, 29.2 IR (KBr) 3295, 3089, 2910, 2851, 1653, 1563, 1505, 1273, 1210, 885, 802, 773 cm^{-1}. MS (ESI) *m/z* 373 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{20}H_{23}N_4OF_2$ [M+H]$^+$: 373.18344, found: 373.18353.

*N-(1-Adamantyl)-2-(4-(3,4-difluorophenyl)-1H-1,2,3-triazol-1-yl)acetamide (**5n**):* Mp: 110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.65–7.77 (m, 1H), 7.52–7.56 (m, 1H), 7.17–7.26 (m, 1H), 5.87 (br s, 1H), 5.01 (s, 2H), 2.06 (br s, 3H), 1.97 (br s, 6H), 1.65 (br s, 6H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 160.3, 141.0, 128.7, 123.6, 111.9, 112.1, 104.3, 104.1, 103.9, 53.7, 52.8, 41.2, 36.0, 29.2. IR (KBr) 3277, 3088, 2911, 2853, 1662, 1566, 1453, 1361, 1132, 1030, 817, 752 cm^{-1}. MS (ESI) *m/z* 373 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{20}H_{23}N_4OF_2$ [M+H]: 373.18344, found: 373.18365.

*N-(1-Adamantyl)-2-(4-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-1-yl)acetamide (**5o**):* Mp: 152 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90–7.94 (m, 2H), 7.77 (d, *J* = 7.62 Hz, 1H), 7.65 (d, *J* = 7.47 Hz, 1H), 7.52 (t, *J* = 7.47 Hz 1H), 5.71 (br s, 1H), 5.04 (s, 2H), 2.05 (s, 3H), 1.94 (s, 6H), 1.65 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) 163.8, 132.0, 131.7, 128.5, 126.2, 126.1, 53.7, 52.7, 41.1, 36.1, 29.3. IR (KBr); 3224, 3070, 2912, 2852, 1686, 1572, 1452, 1314, 1170, 1106, 1033, 768 cm^{-1}. MS (ESI) *m/z* 405 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{21}H_{24}N_4OF_3$ [M+H]$^+$: 405.18967, found: 405.18982.

*N-(1-Adamantyl)-2-(4-(3,4-dichlorophenyl)-1H-1,2,3-triazol-1-yl)acetamide (**5p**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.96 (d, *J* = 1.51 Hz, 1H), 7.67 (dd, *J* = 1.51 Hz, *J* = 1.51 Hz, 1H), 7.50 (d, *J* = 8.30 Hz, 1H), 5.77 (br s, 1H), 5.00 (s, 2H), 2.07 (br s, 3H), 1.97 (s, 6H), 1.66 (s, 6H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 130.8, 127.5, 124.8, 121.5, 53.7, 52.9, 41.2, 36.0, 29.2 IR (neat) 3277, 3088, 2911, 2852, 1662, 1567, 1453, 1360, 1251, 1132, 819, 753 cm^{-1}. MS (ESI) *m/z* 405 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{20}H_{23}N_4OCl_2$ [M+H]$^+$: 405.12434, found: 405.12463.

*N-(1-Adamantyl)-2-(4-(4-pentylphenyl)-1H-1,2,3-triazol-1-yl)acetamide (**5q**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.73 (d, *J* = 7.55 Hz, 2H), 7.24 (d, *J* = 8.30 Hz, 2H), 6.08 (s, 1H), 5.00 (s, 2H), 2.62 (t, *J* = 7.55 Hz, 2H), 2.04 (br s, 3H), 1.95 (br s, 6H), 1.63 (br s, 8H), 1.25–1.35 (m, 4H), 0.89 (t, *J* = 6.04 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 148.3, 143.3, 128.8, 127.4, 125.6, 120.7, 53.8, 52.7, 41.2, 36.1, 35.6, 31.4, 31.0, 29.2, 22.4, 13.9. IR (neat) 3495, 3326, 3054, 2914, 2853, 1677, 1544, 1363, 1225, 1047, 802 cm^{-1}. MS (ESI) *m/z* 407 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{25}H_{35}N_4O$ [M+H]$^+$; 407.28054, found: 407.28058.

*2-(4-((2-Acetyl-5-methylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(1-adamantyl)acetamide (**5r**):* Mp: 128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.65 (d, *J* = 7.93 Hz, 1H), 6.92 (s, 1H), 6.84 (d, *J* = 7.93 Hz, 1H), 6.06 (br s, 1H), 5.30 (s, 2H), 5.00 (s, 2H), 2.54 (s, 3H), 2.38 (s, 3H), 2.04 (br s, 3H), 1.94 (s, 6H), 1.64 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 163.5, 157.5, 144.8, 143.6, 130.5, 125.7, 124.4, 122.0, 113.5, 62.1, 53.4, 52.6, 41.1, 36.0, 31.8, 29.2, 21.7 cm^{-1}. MS (ESI) *m/z* 423 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{24}H_{31}N_4O_3$ [M+H]$^+$: 423.23907, found: 423.23957.

*N-(1-Adamantyl)-2-(4-(6-methoxynaphthalen-2-yl)-1H-1,2,3-triazol-1-yl)acetamide (**5s**):* Mp: 162 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.02 (d, *J* = 1.37 Hz, 1H), 7.89 (d, *J* = 8.54 Hz, 1H), 7.78 (t, *J* = 8.24 Hz, 2H), 7.14–7.18 (m, 2H), 5.86 (br s, 1H), 5.01 (s, 2H), 3.93 (s, 3H), 2.05 (br s, 3H), 1.97 (br s, 6H), 1.64 (br s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 158.0, 148.4,, 134.4, 129.7, 128.9, 127.4, 125.2, 124.5, 124.2, 120.9, 119.3, 105.7, 55.3, 53.9, 52.8, 41.2, 36.1, 29.3. IR (KBr) 3140, 3077, 2906, 2850, 1678, 1612, 1550, 1356, 1263, 1213, 1122, 1023, 904, 853, 812 cm^{-1}. MS (ESI) *m/z* 417 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{25}H_{29}N_4O_2$ [M+H]$^+$: 417.22850, found: 417.22806.

*N-(1-Adamantyl)-2-(4-(phenanthren-2-yl)-1H-1,2,3-triazol-1-yl)acetamide (**5t**):* Mp: 210 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (d, *J* = 8.24 Hz 1H), 8.72 (d, *J* = 8.24 Hz, 1H), 8.38 (d, *J* = 8.08 Hz, 1H), 8.05 (s, 1H), 8.03 (s, 1H), 7.92 (d, *J* = 7.93 Hz, 1H), 7.69 (q, *J* = 7.09 Hz, *J* = 6.04 Hz, 2H), 7.63 (q, *J* = 6.71 Hz, *J* = 7.01 Hz, 2H), 5.78 (br s, 1H), 5.09 (s, 2H), 2.08 (br s, 3H), 2.00 (br s, 6H), 1.67 (br s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 147.2, 131.2, 130.6, 130.4, 129.9, 128.9, 128.6, 127.2, 126.9, 126.92, 126.7, 125.9, 124.3, 123.0, 122.5, 53.8, 52.9, 41.3, 36.1, 29.3 IR (KBr) 3290, 3070, 2907, 2851, 1681, 1551, 1452, 1365, 1220, 1061, 752, 726 cm^{-1}. MS (ESI) *m/z* 437 [M+H]$^+$; HR-MS (ESI) Calcd for $C_{28}H_{29}N_4O$ [M+H]$^+$: 437.23359, found: 437.23291.

N-(1-Adamantyl)-2-(4-(thiophen-3-yl)-1H-1,2,3-triazol-1-yl)acetamide (***5u***): Mp: 126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.71 (d, J = 1.88 Hz, 1H), 7.45 (d, J = 4.91 Hz, 1H), 7.38–7.40 (m 1H), 5.89 (br s, 1H), 4.99 (s, 2H), 2.05 (br s, 3H), 1.94 (br s, 6H), 1.64 (br s, 6H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 144.3, 131.3, 126.4, 125.7, 121.4, 120.9, 53.6, 52.7, 41.2, 36.0, 29.2. IR (KBr) 3277, 3108, 3083, 2910, 2851, 1662, 1561, 1458, 1359, 1092, 1047, 855, 778 cm^{-1}. MS (ESI) m/z 333 $[M+H]^+$; HR-MS (ESI) Calcd for $C_{18}H_{23}N_4OS$ $[M+H]^+$: 343.15871, found: 343.15897.

24. *Antitubercular evaluation assay:* Twofold serial dilutions (50.0, 25.0, 12.5, 6.25, 3.13, 1.56, 0.78 and 0.4 μg/mL) of each test compounds **5a–u** and drugs were prepared and incorporated into Middlebrook 7H11 agar medium with OADC Growth Supplement. Inoculum of *M. tuberculosis* H37Rv ATCC 27294 was prepared from fresh Middlebrook 7H11 agar slants with OADC (oleic acid, albumin, dextrose and catalase; Difco) Growth Supplement adjusted to 1 mg/mL (wet weight) in Tween 80 (0.05%) saline diluted to 10^{-2} to give a concentration of $\sim 10^7$ cfu/mL. A 5 μL amount of bacterial suspension was spotted into 7H11 agar tubes containing 10-fold serial dilutions of drugs per mL. The tubes were incubated at 37 °C, and final readings were recorded after 28 days. This method is similar to that recommended by the National Committee for Clinical Laboratory Standards for the determination of MIC in triplicate.
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27. *Evaluation of cytotoxicity:* Antitubercular active compounds with MIC $\leqslant$6.25 μg/mL were further examined for toxicity in a HEK-293T cell line at the concentration of 50 μg/mL. After 72 h of exposure, viability was assessed on the basis of cellular conversion of MTT into a formazan product using the Promega Cell Titer 96 non-radioactive cell proliferation assay.