A Simple Work-Up-free, Solvent-free Approach to Novel Amino Acid Linked 1,4-Disubstituted 1,2,3-Triazoles as Potent Antituberculosis Agents

Anirban Garg, Debajit Borah, Priyanka Trivedi, Dipshikha Gogoi, Amrita Kashyap Chaliha, Abdul Aziz Ali, Dipak Chetia, Vinita Chaturvedi,* and Diganta Sarma*

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ABSTRACT: An efficient, green strategy for synthesis of 1,4-disubstituted-1,2,3-triazole has been developed using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) acetate ionic liquid (200 μL) under a solvent- and external base-free condition. This protocol is further applied for the synthesis of novel amino acid containing 1,2,3-triazole molecules, which were then evaluated for potential antitubercular and antibacterial activities. Cytotoxicity assay of the compounds was also performed. In silico analysis of the promising compounds selected through experimental analysis was thereafter performed for visualizing molecular interactions and predicting binding affinities between our synthesized molecules, which exhibited good activity in experimental studies and the DprE1 target protein of Mycobacterium tuberculosis. Durg-likeness studies also show potential of the synthesized molecules as drug candidates.

INTRODUCTION

Over the last few decades, tuberculosis (TB) has been identified as one of the major reasons for human mortality.1 TB is caused by Mycobacterium tuberculosis (MTB) and generally spread via the inhalation of respiratory droplets. It grows best in the oxygen-rich tissues of the lung (pulmonary TB), while it may also affect other organs (extrapulmonary TB).2 The problem of tuberculosis is growing rapidly with the increasing number of individuals infected with HIV.3 It is estimated that globally over 10 million people fell ill with TB in the year 2018 itself. Out of which 1.2 million TB deaths accounted among HIV-negative people, whereas an additional 0.25 million deaths among HIV-positive people.4 Even though quadruple-drug therapy (a combination of isoniazid, rifampicin, pyrazinamide, and ethambutol) has been employed successfully for treatment of TB in the last few years, emergence of multi drug-resistant (MDR) and extensively drug resistant (XDR) Mycobacterium tuberculosis have emphasized the need to discover new antitubercular drugs. Similarly, development of new classes of antibacterial agent is standing out to be an important aspect with the appearance of drug resistant bacterial strains.5,6 Hence, there is an urgent need for the discovery of antibacterial agents universally with a new mode of action.

1,2,3-Triazoles have drawn attention of researchers owing to their easy preparation using a Cu-catalyzed azide-alkyne cycloaddition reaction7 and a wide spectrum of biological activity8 that includes antitubercular,9 antibacterial,10 antimalarial,11 anti-HIV,12 anticancer,13 antiallergic,14 antifungal,15 etc. 1,2,3-Triazoles recently caught special attention in designing new drug molecules due to the fact that several antibacterial drug molecules like tazobectum, cefatrizine, cephalosporin feature a 1,2,3-triazole moiety.16 Besides these drug molecules, many triazole-based entities with an amide bond in their side chain have been reported as an efficient pharmacophore (Figure 1).17 This encourages us to synthesize new 1,2,3-triazole molecules with an amino acid or dipeptide side chain.

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Recently, water as a reaction medium is becoming a preferred choice of synthetic chemists owing to its compatibility with nature. However, insolvency of the azide and acetylene reactants in an aqueous media can sometimes lead to the inferior yield of triazole products. Considering sustainable alternatives in synthetic chemistry, ionic liquids (ILs) are worthy green substitutes to existing solvents with their remarkable properties, such as tunable behavior with alteration of cations and anions, good solvating potentials, high thermal stability, etc. To date, a copious amount of functional ILs have been designed and applied in organic synthesis as solvents or catalysts. ILs have demonstrated its wide applicability both as a green solvent and as a catalyst particularly for the 1,3-dipolar cycloaddition reactions, such as the synthesis of amino-thiadiazoles and dihydroisoquinolines, proceed with higher condensation reactions, such as the synthesis of amino-phenyl acetylene under various reaction conditions (Table 1).

### RESULTS AND DISCUSSION

We initiated our study on the test reaction of benzyl azide and phenyl acetylene under various reaction conditions (Table 1).

| entry | catalyst (mol %) | solvent | time (h) | yield (%) |
|-------|-----------------|---------|----------|-----------|
| 1     | CuBr (1)        | [DBU]OAc | 5        | 98        |
| 2     | CuBr (1)        | [DBU]OAc | 0.5      | 98        |
| 3     | Cu (1)          | [DBU]OAc | 1        | 75        |
| 4     | CuCN (1)        | [DBU]OAc | 1        | 63        |
| 5     | CuO (1)         | [DBU]OAc | 1        | 47        |
| 6     | CuBr (1)        | [Omim]Br | 1        | 65        |
| 7     | CuBr (1)        | [Omim]OH | 1        | 84        |
| 8     | CuBr (1)        | [Omim]NTf₂ | 1 | 79 |
| 9     | CuBr (1)        | [Bmim]OH | 1        | 90⁹⁴      |
| 10    | CuBr (1)        | H₂O/1-butanol | 1 | 42 |
| 11    | CuBr (0.5)      | [DBU]OAc | 1        | 68        |

*Reaction condition: Benzyl azide (0.5 mmol), phenyl acetylene (1.2 equiv), Cu catalyst (0.5−1 mol %), IL (200 μL).<sup>4</sup>Isolated yield of product with respect to 1a after column chromatography: [DBU]-OAc, 1,8-diazabicyclo[5.4.0]undec-7-ene acetate; [Omim]Br: 1-Methyl-3-octyl imidazolium bromide; [Omim]OH: 1-Methyl-3-octyl imidazolium hydroxide; [Omim]NTf₂: 1-Methyl-3-octyl imidazolium bis(trifluoromethane)sulfonimide; [Bmim]OH: 1-Methyl-3-butyliimidazolium hydroxide *2 mL Water:t-Butanol (1:1) was used.

The use of only [DBU]OAc as a reaction medium in absence of other any catalytic species fails to promote 1,3-dipolar cycloaddition. To our contentment, introduction of just 1 mol % CuBr without incorporating any solvent other than 200 μL [DBU]OAc affects solidification of the reaction mixture in 30 min, resulting in the formation of requisite triazole, which was directly subjected to column chromatography to obtain 98% of the isolated yield (Table 1, entry 2). Change of counter anions in different copper-based catalysts showed that other Cu(I) species produce inferior results relative to CuBr (Table 1, entries 3−5). Similarly, different ionic liquids were screened out of which only [Bmim]OH delivers reasonably good results with 90% yields (Table 1, entries 6−9). Necessity of [DBU]OAc was confirmed by performing the reaction in presence a copper catalyst in water/t-Butanol (1:1), which produced a triazole product in a considerably reduced yield (Table 1, entry 10). Moreover, decreasing the catalyst loading resulted in the diminished yield of triazole products (Table 1, entry 11), which indicated 1 mol % of CuBr in [DBU]OAc furnishes the best result.

With the optimized condition in hand, the newly developed catalytic system was applied for the synthesis of various triazole products by variation of different azide and alkyne substrates.
Diverse azide substrates, featuring methoxy, halide, cyano, nitrile and trifluoromethyl, efficiently generate desired triazoles in excellent yields (Scheme 1, 3a–3k).

Scheme 1. Synthesis of Diverse Triazoles by Variation of Azides

\[
\text{R}^-\text{N}_3 + \text{Cu(i) 1 mol% (DBU)OAc} \rightarrow \text{R}^-\text{N}_3 \text{(3a-3k)}
\]

In the similar manner, various alkyne substrates whether be it aromatic, aliphatic or containing various functional groups underwent smooth transformation to corresponding triazoles within few minutes (Scheme 2, 3l–3t). Delighted by the robustness of the protocol, we planned for extending its scope for combinatorial synthesis of new triazole molecules with N-protected natural amino acids and dipeptide present as a side chain.

We started with functionalization of N-protected L-alanine to form an alkyne derivative of the amino acid as shown in Scheme 3. L-Alanine (4a) is first protected at the N-terminal by benzylation, which was then alkylated with propargyl bromide in presence of K₂CO₃ in DMF to generate prop-2-yn-1-yl benzoyl-L-alaninate (6a) in an excellent yield. The formation of alkyne 6a is confirmed by appearance of an IR band at 3340 cm⁻¹ due to secondary amine stretching, whereas 3267 and 2129 cm⁻¹ due to C–H stretching of alkyne and C=C stretching. Additionally, appearance of the [M + H] ion peak in the mass spectrum at an m/z value of 232.0992 is in agreement with molecular formula C₁₃H₁₃NO₃. Similarly, two more alkynes, 6b and 6c, have been prepared by functionalizing benzoyl-protected L-phenyl alanine (5b) and glycylglycine (5c).

The synthesis of amino acid and dipeptide linked triazoles was performed using alkynes 6a–6c and various azides as shown in Figure 2, adopting the newly developed protocol.

All the desired 1,4-disubstituted triazole derivatives are formed within 4 h with good to excellent yields as shown in Scheme 4. The structures of the triazole products were characterized by FTIR, HRMS, ¹H NMR, and ¹³C NMR spectra. The FTIR spectrum of 7a shows distinct absorption peaks at 2939, 1644, and 1045 cm⁻¹, corresponding to −CH₂, phenyl, and CN group stretching. The ¹H NMR spectrum of compound 7a exhibits a particular signal at δ = 5.29 ppm, which ascertains the attachment of the −CH₂ group with the O atom. The signal at δ = 8.83 ppm confirms the presence of 1,2,3-triazole proton in the synthesized compound. In the ¹³C NMR spectrum of the same compound, the signal at δ = 57.89 ppm is of high significance, which corresponds to methylene carbon bonded to the carboxylic oxygen atom of N-protected L-alanine. Additionally, signals at δ = 117.04 and 143.38 ppm are characteristics for C₅ and C₄ atoms in the 1,2,3-triazole.
Scheme 4. Various Amino Acid and Glycylglycine-Containing 1,2,3-triazoles

The decoupled $^{13}$C NMR spectrum showed a doublet of doublet at 116.76 ppm ($J = 190.4, 4.4$ Hz) due to coupling of C$_5$ with a H atom, which indicates the formation of 1,4-disubstituted-1,2,3-triazole. This is further confirmed by the COSY NMR spectrum. Furthermore, the HRMS spectrum shows a signal at an m/z value of 369.1375 due to [M + H]$^+$ ion, which is in accordance with molecular formula C$_{19}$H$_{17}$FN$_4$O$_3$.

**Biological Part**

At first, synthesized compounds were evaluated for their potential to inhibit the growth of *M. tuberculosis* H$_{37}$Ra (ATCC 25177 strain) by the agar-based proportion assay at the single concentration of 25 (μg/mL). The compounds were dissolved in dimethyl sulfoxide (DMSO) to make stocks (5 mg/mL). Serial twofold dilutions from stocks were also made in DMSO. To 1.9 mL of MB7H10 agar medium (in tubes, temp 45−50 °C, with OADC supplement, final concentration 10%), 0.1 mL of the compound or DMSO (negative control) or anti-TB drugs (positive controls) was added. The contents were mixed and allowed to solidify as slants. A three week-old culture of *M. tuberculosis* H$_{37}$Ra was harvested from the L−J medium, and its suspension (1 mg/mL, equivalent to 10$^8$ bacilli approximately) was made in normal saline containing 0.05% Tween-80. Ten microliters of 1:10 dilution of this suspension (~10$^5$ bacilli) was inoculated into each tube and incubated at 37 °C for 4 weeks. Thus, the compounds were tested at twofold diluted concentrations starting from 25.0 to 1.56 μg/mL. The lowest concentration of a compound up to which there was no visible growth of bacilli was its minimal inhibitory concentration (MIC). Anti-TB drugs isoniazid and ethambutol were included as a positive reference.

It was observed that out of 21 compounds, two compounds with benzofuran and a 4-(methylsulfonyl)phenyl moiety attached to azide functionality that are being cyclized with 6a showed good activity with an MIC value of 3.12 (7g and 7i). Furthermore, phenylalanine containing triazoles, bearing a 4-(methylsulfonyl)phenyl group 7r and trifluoromethyl group 7s, showed an MIC value of 6.25 μg/mL. It can be speculated that the presence of the methylsulfonyl group may have some positive influence on anti-TB activity of these triazole molecules. Additionally, presence of a larger phenyl substituent in 7r may have caused reduced interaction with the active site of *M. tuberculosis* leading to slight reduction in anti-TB activity. These interactions are further studied by an *in silico* method by means of a molecular docking study. Moreover, three other compounds had an MIC value of 25.0 μg/mL (7f, 7h, and 7j). The rest of the compounds are associated with MICs > 25 μg/mL.

*In vitro* cytotoxicity of potent compounds 7g, 7i, 7r, and 7s (MIC ≤ 6.25 μg/mL) were examined toward mouse (bone marrow-derived) macrophages (MΦ). For preparation of macrophages, a Swiss mouse (bred in the Laboratory Animal Division of CDRI) was euthanized by exposure to CO$_2$, and femurs were dissected out. The bones were trimmed at each end and marrow was flushed out with a Dulbecco’s minimal essential medium (DMEM) containing 10% fetal bovine serum (DMEM-FBS) and antibiotics. The medium was also supplemented with a 15% (v/v) L929 fibroblast conditioned medium and nonessential amino acids. The cell suspension (macrophage) was plated in 96-well tissue culture plates (20,000 cells/200 μL/well) and incubated overnight (37 °C, 5% CO$_2$) to allow their adherence. Compounds at different concentrations were added to the wells. A known toxic compound was used as a positive control, and DMSO was used as a negative control. After 24 h of incubation, 20 μL of MTS solution (tetrazolium compound, Owen’s reagent) was added to each well and incubated further for 2 h (37 °C, 5% CO$_2$). O.D. was read at 490 nm using a plate reader. A compound
was considered as potentially toxic if its IC_{50} (concentration causing 50% loss in cell viability) was ≤10 times of its MIC for *M. tuberculosis* H37Rv. The study was approved by the Animal Ethics Committee of the Institute (CSIR-CDRI, Lucknow). All four were found nontoxic with CC_{50} > 100.0 μg/mL and selectivity index (SI = CC_{50}/MIC) of 32.0 and 16.0 (Table 2, last column). The inhibitory activity profile of compounds 7g and 7i was comparable to the first line anti-TB drug ethambutol (Table 2).

The graphical output of bioavailability radar in this web tool further gives a holistic diagrammatic representation for quick appraisal of the drug-likeness of a submitted compound by plotting six different physicochemical properties into different axes, viz., lipophilicity, size, polarity, solubility, flexibility, and saturation. The physicochemical ranges on each axis are depicted as a pink area (Figures S58–S61, Supporting Information). The radar plot of the submitted compound, outlined in red, has to fall entirely within this pink zone to be considered drug-like. All of the submitted compounds in this study encompassed the pink area of bioavailability but slightly exceeded it in different degrees. The least exceeding one, and hence the best score amongst them all, was compound 7g.

Furthermore, all compounds were computed and predicted to have high gastrointestinal absorption, no permeation to the blood–brain barrier (BBB), and also not to be inhibitors of key enzymes involved in liver metabolism like CYP2D6. This super family of isoenzymes features significantly in drug elimination through metabolic biotransformation. The compliance to these essential parameters favors the further optimization of the selected compounds for enhancing their druggability.

These triazole molecules were also tested against Gram-positive strains, viz., *Staphylococcus aureus* (MTCC 121) and *Bacillus subtilis* (MTCC 441), and negative bacterial models, viz., *Escherichia coli* (MTCC 40) and *Pseudomonas aeruginosa* (MTCC 4673). Preliminary antimicrobial investigation indicates that compound 7t shows an effective zone of inhibition against all the four bacterial models under consideration (Table 3). It was speculated that 7g exerted the maximum diameter of zone of inhibition against both Gram-positive (i.e., *S. aureus*) and negative (i.e., *P. aeruginosa*) followed by compound 7e (Table 3). The controlled study shows no zone of inhibition by DMSO against all these four bacterial samples.

Each of these three molecules with promising antibacterial activity were subjected to further antimicrobial studies against different bacterial strains.

### Table 2. Antitubercular Activity Studies of Compounds 7a–7u

| S. no. | entry | CLog P | MIC (μg/mL) | cytotoxicity in mouse | selectivity index (SI) |
|--------|-------|--------|-------------|----------------------|------------------------|
| 1      | 7a    | 2.7449 | >25         | ND                   | ND                     |
| 2      | 7b    | 2.8743 | >25         | ND                   | ND                     |
| 3      | 7c    | 2.7449 | >25         | ND                   | ND                     |
| 4      | 7d    | 3.5143 | >25         | ND                   | ND                     |
| 5      | 7e    | 3.1040 | >25         | ND                   | ND                     |
| 6      | 7f    | 3.0709 | 25          | ND                   | ND                     |
| 7      | 7g    | 1.4029 | 3.12        | Non Toxic,[>100]     | 32.05                  |
| 8      | 7h    | 2.5413 | 25          | ND                   | ND                     |
| 9      | 7i    | 2.9900 | 3.12        | Non Toxic,[>100]     | 32.05                  |
| 10     | 7j    | 2.8620 | 25          | ND                   | ND                     |
| 11     | 7k    | 4.9323 | >25         | ND                   | ND                     |
| 12     | 7l    | 4.1629 | >25         | ND                   | ND                     |
| 13     | 7m    | 4.1629 | >25         | ND                   | ND                     |
| 14     | 7n    | 4.3293 | >25         | ND                   | ND                     |
| 15     | 7o    | 4.5220 | >25         | ND                   | ND                     |
| 16     | 7p    | 3.6148 | >25         | ND                   | ND                     |
| 17     | 7q    | 4.6239 | >25         | ND                   | ND                     |
| 18     | 7r    | 2.8209 | 6.25        | Nontoxic,[>100]      | 16.00                  |
| 19     | 7s    | 4.2800 | 6.25        | Nontoxic,[>100]      | 16.00                  |
| 20     | 7t    | 1.8693 | >25         | ND                   | ND                     |
| 21     | 7u    | 1.3312 | >25         | ND                   | ND                     |
|        | anti-TB drugs | 0.025 | Nontoxic,[>100] | 4000.00              |                        |
|        | ethambutol | 2.00 | Nontoxic,100 | 50.00                |                        |

*CLog P* calculated using Chemdraw Ultra 12.0 software by Cambridge Soft; ND: not done.

### Table 3. Zone of Inhibition (mm) of Different Compounds against Test Bacterial Strains

| S. no. | entry | E. coli | S. aureus | P. aeruginosa | B. subtilis |
|--------|-------|---------|-----------|---------------|------------|
| 1      | 4a    | 13      | 13,12     |               |            |
| 2      | 4d    | 14      | 11,12     |               |            |
| 3      | 4e    | 17      | 12        |               |            |
| 4      | 4f    | 18      |           |               |            |
| 5      | 4g    | 18      | 16        |               |            |
| 6      | 4j    | 12      | 12        |               |            |
| 7      | 4k    | 10      |           |               |            |
| 8      | 4l    | 11      |           |               |            |
| 9      | 4o    | 17.5    |           |               |            |
| 10     | 4p    | 12      |           |               |            |
| 11     | 4q    | 14      |           |               |            |
| 12     | 4r    | 13      |           |               |            |
| 13     | 4s    | 12      | 14        |               |            |
| 14     | 4t    | 14      | 14        | 13            |            |
| 15     | 4u    | 12      | 13        |               |            |
the most sensitive Gram-positive and negative bacterial samples for the evaluation of MIC and MBC values exerted by the respective drug candidates (Table S1, Supporting Information).

To understand the ligand–protein interaction, in silico studies were performed. In the present study, LibDock was used to compute the binding affinities between the selected compounds and the decaprenylphosphoryl-D-ribose oxidase protein (DprE1) of M. tuberculosis, which is an important emerging antimycobacterial target. It has been reported to be the target for new antituberculosis drugs, especially the potent mycobacterial inhibitor compounds: the benzothiazinones, which are now in the stage of late preclinical trials.

DprE1 is an important catalyst involved in a distinctive epimerization reaction to synthesize decaprenylphosphoryl arabinose. It is the sole donor of arabinosyl residues, which further lead to the synthesis of arabinans. Arabinans are fundamental components of the mycobacterial cell wall; hence, DprE1 is essential for mycobacterial cell wall biogenesis. Though the active site cavity of native DprE1 lies in proximity of the surface of the protein, it is shielded from the external surface by a loop formed by residues. This part of the DprE1 protein has been reported to exhibit a degree of plasticity. Inhibitors of DprE1 have been shown to displace this active site loop to interact with residues of the protein, and thus disrupt its catalytic activity. In the present study, all of the compounds tested against the DprE1 protein exhibited good docking scores (Table S3, Supporting Information). The potential drug ligands interacted with different residues of the active site of DprE1 with various chemical bonds, like carbon–hydrogen bonding, and pi-sulphur, pi-alkyl, pi-sigma, pi-anion, pi-donor, pi–pi stacked, pi–pi T shaped, etc., as depicted in the 2D pictures of the drug–target molecular interactions (Figure 3). Compound 7r is particularly promising in interacting with DprE1 as it was seen to form a pi-alkyl interaction with Leu363 and a pi–pi-shaped interaction with Phe320 (Figure S63A, Supporting Information). Both of these amino acid residues are involved in the formation of hydrophobic activity inside the active site of the DprE1 enzyme. Additionally, it presented the best LibDock score, along with 7s.

Finally, to study the efficiency of our protocol in terms of synthetic utility, we scaled up the reaction of 6c (4.8 mmol, 1.32 g) with 2-fluorophenyl azide (4 mmol, 0.55 g) under standard conditions. As per our expectation desired triazole product, 7t is formed with a 78.5% yield (1.29 g, 3.14 mmol). The pictorial representation of the reaction is shown in Scheme 5.

Scheme 5. Gram Scale Synthesis of 7t

In summary, we have developed a greener solvent and workup-free protocol for 1,2,3-triazole synthesis using copper bromide and [DBU]OAc ionic liquid under a solvent and workup-free approach at an ambient condition. This newly developed condition is successfully applied for the synthesis of a library of amino acid containing 1,4-disubstituted-1,2,3-triazoles. Among these compounds, seven compounds showed activity against M. tuberculosis; compounds 7g and 7i in particular displayed anti-TB activity comparable to first line anti-TB drug, ethambutol. Furthermore, few compounds showed good antibacterial activity, and among them 7g comes out with best activity against both Gram-positive and Gram-negative bacterial strains. Also, the molecular docking study revealed promising predictions of antimycobacterial activity of the compounds synthesized in the present study. Moreover, the drug-likeness study confirms 7g and 7i as potential drug candidates that can be forwarded further for lead optimization. Further studies, both computational and experimental, corroborating these findings, will undoubtedly help in the development of these compounds as potential antimycobacterial agents.

ASSOCIATED CONTENT

# Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c03862.

Copies of 1H and 13C NMR spectra of all the new triazoles molecules along with complete experimental procedures (PDF).

AUTHOR INFORMATION

Corresponding Authors
Vinita Chaturvedi — Biochemistry Division, Central Drug Research Institute, CSIR, Lucknow 226001, India; Email: vinita_chaturvedi@cdri.res.in
Diganta Sarma — Department of Chemistry, Dibrugarh University, Dibrugarh 786004, Assam, India; orcid.org/0000-0001-5174-418X; Email: dsarma22@gmail.com
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