Bioorganic & Medicinal Chemistry Letters 27 (2017) 3698–3703

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

# Synthesis and biological evaluation of novel 1,2,3-triazole derivatives as anti-tubercular agents

Abdul Aziz Ali [a], Dhrubajyoti Gogoi [b], Amrita K. Chaliha [b], Alak K. Buragohain [b], Priyanka Trivedi [c], Prakash J. Saikia [d], Praveen S. Gehlot [e], Arvind Kumar [e], Vinita Chaturvedi [c,*], Diganta Sarma [a,*]

[a] Department of Chemistry, Dibrugarh University, Dibrugarh 786004, Assam, India
[b] DBT-Bioinformatics Infrastructure Facility, Centre for Biotechnology and Bioinformatics, Dibrugarh University, Dibrugarh 786004, Assam, India
[c] Biochemistry Division, Central Drug Research Institute, CSIR, Lucknow 226001, India
[d] Analytical Chemistry Division, CSIR-North East Institute of Science & Technology, Jorhat 785006, Assam, India
[e] AcSIR, Salt and Marine Chemicals Division, CSIR-Central Salt and Marine Chemicals Research Institute, Bhavnagar 364002, India

ARTICLE INFO

*Article history:*
Received 28 March 2017
Revised 9 June 2017
Accepted 3 July 2017
Available online 5 July 2017

*Keywords:*
Tuberculosis
1,2,3-Triazoles
Antimycobacterial activity
Cytotoxicity
Molecular docking

ABSTRACT

A library of seventeen novel 1,2,3-triazole derivatives were efficiently synthesized in excellent yields by the popular 'click chemistry' approach and evaluated in vitro for their anti-tubercular activity against *Mycobacterium tuberculosis* H37Ra (ATCC 25177 strain). Among the series, six compounds exhibited significant activity with minimum inhibitory concentration (MIC) values ranging from 3.12 to 0.78 μg/mL and along with no significant cytotoxicity against MBMDMQs (mouse bone marrow derived macrophages). Molecular docking of the target compounds into the active site of DprE1 (Decaprenylphosphoryl-β-D-ribose-2′-epimerase) enzyme revealed noteworthy information on the plausible binding interactions.



Tuberculosis (TB), an infectious terrible disease caused by the acid fast bacillus *Mycobacterium tuberculosis* remains one of the most life threatening diseases to public health globally after human immunodeficiency virus (HIV).[1,2] Normally it attacks the lungs (pulmonary TB) but can attack other organs as well (extra-pulmonary TB) and spreads in the air when patients expel bacteria by coughing, sneezing, or spit. According to World Health Organization (WHO) report, 9.6 million new TB cases were estimated and claiming the lives of 1.5 million people in the year 2014 despite the great advances in chemotherapy and the Bacille-Calmette-Guérin (BCG) vaccine.[3] The current standard therapy attributed for TB is a six month regimen, termed DOTS (Directly Observed Therapy, Short-course) in which the initial 2 months include isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (E), followed by a 4 month continuation phase of RIF and INH.[4] Furthermore, TB attracts numerous interest of the scientific community due to high weakness of human immunodeficiency virus (HIV)-infected persons to this disease and the global emergence of multidrug resistant (MDR) defined as resistant to the two most efficient TB drugs, rifampin and isoniazid, and extensively drug-resistant (XDR) strains that are further resistant to the fluoroquinolones and one of the second-line injectable drugs (i.e. amikacin, kanamycin, or capreomycin).[5–7] The confines of long-term oral chemotherapy and scarce compliance to the current treatment regimen, the discovery of bedaquiline in the end of 2012, build a new hope for the treatment of TB and especially MDR-TB.[8] Nevertheless the side effects of bedaquiline such as nausea, joint pain and headache create a risk in clinical use.[9,10] Therefore, there is a still need for the development of new and effective antimycobacterials with reduced toxicity, synthetically feasible, stronger efficacy that function by novel mechanisms of action against emerging MDR and XDR TB bacteria and latent diseases in shorter treatment duration.

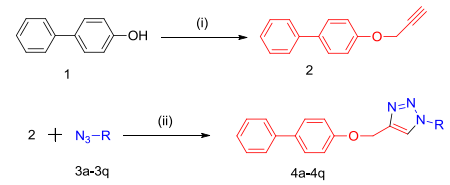
1,2,3-Triazoles are five member *N*-heterocyclic compounds and are stable to metabolic degradation. They are also capable of hydrogen bonding, which can be favorable in the binding of biomolecular targets and can improve the solubility.[11,12] Although absent in nature, the 1,2,3-triazoles have found a broad spectrum of biological applications such as anti-tubercular,[13] antibacterial,[14] anti-allergic,[15] anti-HIV,[16] anti-fungal,[17,18] anti-inflammatory,[19] anticancer,[20,21] and α-glycosidase inhibitor activities.[22] β-lactum antibiotic Tazobactum, anticancer compound carboxyamidotriazole (CAI), cefatrizine are some drugs available in the market that possess 1,2,3-triazole moiety.[23] Many approaches for the synthesis of 1,2,3-triazoles have been developed so far, in which a typical

* Corresponding authors.
*E-mail addresses:* vinita_chaturvedi@cdri.res.in (V. Chaturvedi), dsarma22@gmail.com, dsarma22@dibru.ac.in (D. Sarma).

http://dx.doi.org/10.1016/j.bmcl.2017.07.008
0960-894X/

click reaction, copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) is definitely the most effective strategies.[24] In recent years a wide range of 1,2,3-triazole derivatives were synthesized and reported to exhibit potent antitubercular activity (Fig. 1), especially benzofuran salicylic acid derivative (I-A09) is a lead antitubercular agent presently in clinical evaluations.[25–34] In continuation to our ongoing study aimed towards the development on 1,2,3-triazole synthesis[35–38] and previous research efforts toward the discovery of potent anti-TB agents[39] herein, we wish to disclose a facile click synthesis of a series of novel 1,4-disubstituted 1,2,3-triazole analogues and their antimycobacterial evaluation.

The synthetic strategy was initiated with the preparation of azides, one of the coupling partners of Cu-catalyzed azide alkyne cycloaddition reaction. As reported earlier, the benzyl azides were prepared from the corresponding organic bromides by stirring the bromide with $NaN_3$ in water/acetone (1:3) at room temperature to give the desired azide as yellow oil. Similarly octyl azide was prepared by refluxing1-bromooctane with $NaN_3$ in acetone/water mixture overnight affording the corresponding azide as colourless oil. Aromatic azides were synthesized by diazotization of the corresponding aromatic amines with $NaNO_2$ followed by addition of $NaN_3$. Aromatic azides were obtained as yellow oils with yields ranging from 70% to 95%. The azides were used directly in the next step without purification and the chemical structures of the azides were confirmed by analyzing the crude product using FT-IR spectroscopy. A strong absorption band at 2090–2100 $cm^{-1}$, attributed to the stretching vibrations of the $N_3$ bond of the azido group. The starting alkyne **2** was prepared by using commercially available 4-phenylphenol, **1** by simple alkylation with propargyl bromide in the presence of $K_2CO_3$ as a base in *N*,*N*-dimethylformamide (DMF) affording the corresponding alkyne in excellent yield as reported in Scheme 1. The synthesis of 1,2,3-triazole derivatives were accomplished through Cu(I) catalyzed Huisgen 1,3-dipolar cycloaddition reaction between **2** and appropriate azides in presence of CuI as catalyst and $DHQD_2$(PHAL) as ligand in $H_2O$/DCM for 0.5–2 h affording 1,4-disubstituted-1,2,3-triazoles in good to excellent yields as depicted in Scheme 1 (80–96%). The structures of the products were characterized by thin layer chromatography (TLC), $^1H$ NMR, $^{13}C$ NMR, FT-IR and mass spectrometry. IR spectrum of **4c** showed absorption bands at 2990, 1598 and 1049 $cm^{-1}$ indicating the presence of $-CH_2$, phenyl and C–N groups. The $^1H$ NMR spectrum of compound **4c** exhibited the presence of one distinctive singlet signal at around $\delta$ 5.32 ppm indicating the attachment of methylene group to oxygen respectively. In addition, the appearance of most informative singlet signal around at $\delta$ 8.05 ppm confirms the presence of triazole proton. In $^{13}C$ NMR, the most prominent carbon signals observed around $\delta$ 61.9 ppm accounted for the presence of methylene carbon attached to the oxygen to the biphenyl ring. In addition, the characteristic carbon signals appearing around $\delta$ 145.2 and 120.6 ppm were assigned to C-4 and C-5 of triazoles ring, while the various aromatic carbons resonated around $\delta$ 145.2–114.9 ppm. Further, LC mass spectrum showed [M+1] ion peak at *m*/*z* 407.9 which is in agreement with the molecular formula $C_{21}H_{16}BrN_3O$.




**Scheme 1.** Reagents and conditions: (i) Propargyl bromide, $K_2CO_3$, DMF, 90%; (ii) CuI (1 mol%), $DHQD_2$(PHAL) (1 mol%), $H_2O$/DCM (1:1), rt, 0.5–2 h, 80–96%.

The synthesized compounds were tested for their ability to inhibit the growth of *M. tuberculosis* H37Ra (ATCC 25177 strain) by Agar-based proportion Assay as shown in Table 1. The lowest concentration of a compound up to which there was no visible growth of bacilli was its minimal inhibitory concentration (MIC). Out of seventeen compounds screened for their in vitro anti-tubercular activity against *M. tuberculosis* H37Ra, six compounds were found active with MIC in the range of 3.12–0.78 μg/mL (Table 1) and the rest were with MIC > 12.5 μg/mL. The compounds with potent MIC of 3.12 and 1.56 μg/mL were also tested for their cytotoxicity against MBMDMQs (mouse bone marrow derived macrophages) and found to be nontoxic on their selectivity index (SI > 10, ratio of $CC_{50}$ against mammalian cells and the MIC). Among tested series, compound **4o** with fluoro group at second

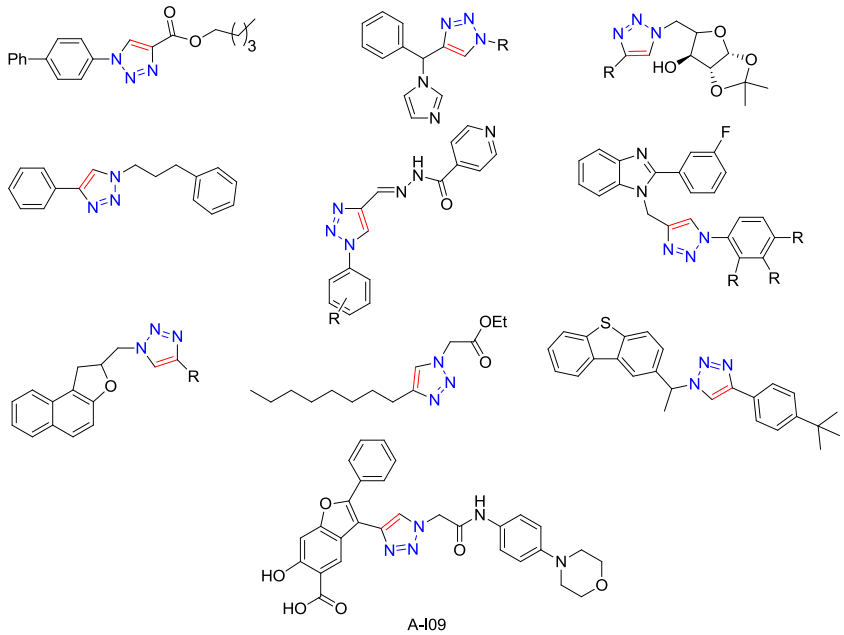



**Fig. 1.** Representative structure of 1,2,3-triazole derivatives that exhibit anti-tubercular activity.