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Short Report

Synthesis and Evaluation of 1-Alkyl-4-phenyl-[1,2,3]-triazole Derivatives as Antimycobacterial Agent

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Este trabalho descreve a síntese e a caracterização de quatorze derivados do sistema 1-alquil-4-fenil-[1,2,3]-triazol, por uma metodologia regiosseletiva e eficiente. Esta metodologia consistiu em uma cicloadição 1,3-dipolar, catalisada por Cu(I), entre arilazidas e arilacetilenos terminais (click-reaction). Os compostos foram avaliados quanto a sua atividade antimicrobiana contra a bactéria resistente a múltiplos fármacos, *Mycobacterium tuberculosis H37Rv*, agente causador da tuberculose. Seis dos [1,2,3]-triazóis foram mais ativos contra o *M. tuberculosis* do que o etambutol, utilizado como controle positivo.

Fourteen small molar mass 1-alkyl-4-phenyl-[1,2,3]-triazole derivatives were prepared using a straightforward and efficient method for the regioselective synthesis of [1,2,3]-triazoles and the compounds were screened for antimycobacterial activity against multiple-drug-resistant strains of *Mycobacterium tuberculosis H37Rv*. The synthetic methodology consisted of a Cu(I)-catalyzed 1,3-dipolar cycloaddition of aryl azides to terminal arylacetylenes (click-reaction). Six [1,2,3]-triazoles were found to be more active against *M. tuberculosis* than the positive control ethambutol.

Keywords: tuberculosis, click reaction, 1,2,3-triazoles

Introduction

Infectious diseases continue to represent a major threat to the health of the human population. Tuberculosis (TB) is one of the oldest diseases known to man and is primarily an illness of the respiratory system spread by coughing and sneezing. Each year about 2 million people die from this curable disease. One-third of the world's population is infected with *Mycobacterium tuberculosis*, the causative agent of TB, with approximately eight million people developing the active form of the disease every year.[1] The HIV/AIDS pandemic has dramatically increased the incidence of this disease. It is estimated that between 2002 and 2020, approximately a billion people will be newly infected, more than 150 million people will get sick, and 36 million will die of TB if control is not further strengthened. Until recent years, global efforts to reduce the prevalence of multidrug-resistant tuberculosis (MDR-TB), defined as *in vitro* resistance to at least rifampicin and isoniazid, have focused on preventing new cases of acquired MDR-TB. However, countries that already have a high incidence of MDR-TB must implement additional strategies, such as reducing transmission by detecting cases earlier and improving infection control in settings with shared air spaces. Once a strain of MDR-TB develops, it can be spread to others just as "normal" TB. Each year, roughly 300,000 new cases of MDR-TB occur in more than 100 countries. The World Health Organization (WHO), estimates that the average MDR-TB patient infects up to 20 other people in his or her lifetime. MDR-TB is especially threatening because without proper treatment, super-resistant strains can emerge for which there currently is no cure.

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Due to this problem the development of faster-acting TB drugs is a critical strategy in the global response to the TB epidemic. Consequently, there is an urgent need to develop new, potent, fast-acting antimycobacterial drugs with low-toxicity profiles that can be used in conjunction with drugs used to treat HIV infections.[2]

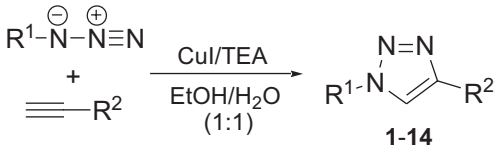
Several five-membered heterocyclic compounds, for instance pyrroles, imidazoles and oxazoles, have been shown to be promising as tuberculostatic agents.[3] Recently, Ghosh and Prakash establish a database of 847 compounds seeking new antitubercular agents and targets.[3] A search through diverse chemical classes, including marketed drugs and antimycobacterial compounds with known MICs, led to a cluster of 57 classes containing pyrrole derivatives and azole antifungals. The author points out that there is a common generic scaffold for these classes which involves the phenyl ring and the heterocyclic moiety. Furthermore, Ferreira and co-workers[4] reported that 1-phenyl-[1,2,3]-triazole derivatives are very active against *M. tuberculosis* H37Rv strain (ATCC 27294).

Triazoles, like many other five-membered heterocyclic compounds, are frequently used in pharmacological and medicinal applications.[5] The [1,2,3]-triazoles are *N*-heterocyclic compounds, not present in natural products, which display high biological activity including anti-HIV,[6] b-lactamase inhibition[7,8] and antiepileptic activities.[9,10] The 4-aryl-[1,2,3]-triazoles were discovered to be a unique template for the inhibition of the metalloprotease MetAP2.[11] In the literature triazoles are described as antiplatelet agents,[12] dopamine D2 receptor ligands (related to Schizophrenia[13]) anti-inflammatory,[14,15] and antimicrobial agents.[16-18]

Based on the rationale above, the purpose of this study was to synthesize several 4-phenyl-[1,2,3]-triazole derivatives with small molar mass and test them for inhibition of the growth of *M. tuberculosis* H37Rv strain (ATCC 27294).

Results and Discussion

The most general methodology described in the literature for the synthesis of five-membered ring heterocycles is the Huisgen 1,3-dipolar cycloaddition. In particular, when the reaction occurs between alkyl or aryl azides and terminal acetylenes, [1,2,3]-triazoles are obtained.[9-21] If the cycloaddition is thermally conduced, a 1:1 mixture of the 1,4 and 1,5-regioisomers of triazole is usually obtained. Various attempts to control the regioselectivity without much success were reported until the discovery of the copper(I)-catalyzed reaction in 2002, which exclusively yields the 1,4-disubstituted-[1,2,3]-triazole.[23-26] Scheme 1 shows the general method used in this study for the synthesis of the *N*-heterocycle triazoles, where R^1 and R^2 are chiral and racemic alkyl or aryl substituents.

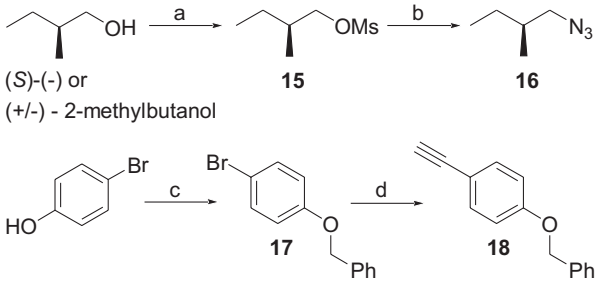


Scheme 1.

Table 1 summarizes the 1,4-disubstituted-[1,2,3]-triazole synthesized in this study, using the "click-reaction". The synthetic protocol applied was recently developed by us and uses an ethanol/water mixture and catalytic amounts of Cu(I) and triethylamine (TEA) as additives.[2] The goals were to obtain the target compounds in a high degree of purity and in good chemical yields using commercially available acetylenes, such as propargyl alcohol, 2-methyl-3-butyn-2-ol and phenyl acetylene or chiral and achiral azide derivatives specially prepared from 2-methylbutanol alcohol. Scheme 2 shows the preparation of the chiral and racemic azides and the terminal acetylene **18** as previously reported by Gallardo and co-workers[22] The latter aryl acetylene was synthesized from its respective aryl bromide **17** *via* palladium-copper-catalyzed cross-coupling (Sonogashira's coupling) using commercial 2-methyl-3-butyn-2-ol as source of the acetylene.[25]

Structural characterization of the chiral and racemic [1,2,3]-triazoles was carried out by NMR analysis based on the NOE effect observed between the proton of the triazole ring and the methyl group from the aliphatic chain, suggesting that the triazole proton and methyl group are in close proximity as in the 1,4-disubstituted compounds.[22]

The *in vitro* antimycobacterial activity of compounds **l** to **14** against *M. tuberculosis H37Rv* strain (ATCC 27294, susceptible to Rifampicin and Isoniazid) was assessed using the Microplate Alamar Blue Assay (MABA), which shows good correlation and proportionality with BACTEC radiometric methods.[28] This colorimetric method uses the Alamar Blue-resazurin-based oxidation-reduction indicator to obtain drug susceptibility measurements for

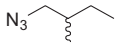
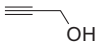
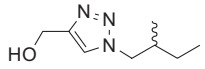
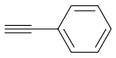
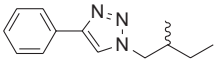
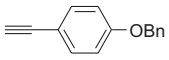
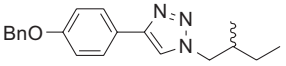
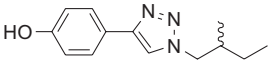
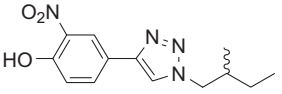
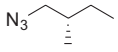
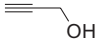
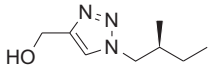
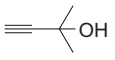
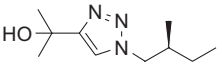
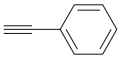
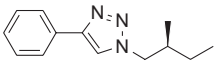
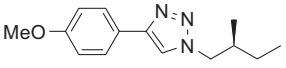
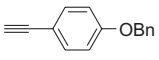
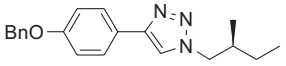
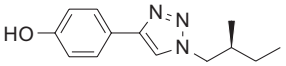
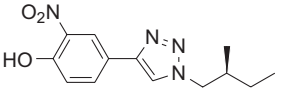
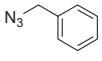
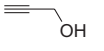
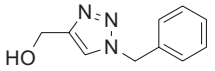
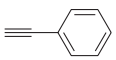
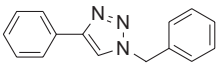


Scheme 2. a)MsCl, CH_2Cl_2 TEA 84%; (b) NaN_3, DMF 75%; (c) BnCl, K_2CO_3, 79%; (d) i. 2-methyl-3-butyn-2-ol, TEA TPP, $PdCl_2$ $(PPh_3)_2$, CuI 65%; ii. NaOH, toluene, 62%.

bacteria. The Minimum Inhibitory Concentration (MIC expressed in μg mL^{-1}) was defined as the lowest drug concentration that prevented a color change from blue (no growth) to pink (growth). Rifampicin and Ethambutol were used as positive controls (Table 1).

To summarize, the series of 4-phenyl-[1,2,3]-triazoles here synthesized demonstrated significant antimycobacterial activity (Table 1). The *in vitro* antimycobacterial screening of the series showed that 10 compounds were active. The 1-alkyl-4-phenyl-[1,2,3]-triazoles **2**, **4**, **8**, **9**, **10**, **11** and **12** showed the highest activity against *M. tuberculosis* (MIC = 3.1 μg mL^{-1}).[28] On the other hand, the mycobacteria was resistant to compounds **1**, **6**, **7** and **13**. Structural analysis of these two groups indicated that conjugation with the aromatic ring and, possibly, the planarity of the system are important molecular aspects for these kinds of compounds. In contrast with our previous results,[5] changing the phenyl from position 1 to 4 in the triazole ring did not change the activity of **2**, **4**, **8**,

Table 1. The 4-phenyl-[1,2,3]-triazoles (**1-14**) synthesized and inhibition of *M. tuberculosis* H37Rv

Entry	Azide	Alkyne	Product (**1-14**)	Yield / (%)[a]	MIC / (μg mL^{-1})
1				69	>100
2				83	3.1
3				65	25
4[b]				-	3.1
5[c]				-	12.5
6				65	>100
7				76	>100
8				70	3.1
9[d]				76	3.1
10				64	3.1
11[b]				-	3.1
12[c]				-	3.1
13				65	>100
14				71	6.2
Rifampicin[e]	-	-	-	-	1.0
Ethambutol[e]	-	-	-	-	3.25

[a]Isolated yields. [b]These triazole products were synthesized from **3** and **10**, respectively, by hydrogenolysis (20% m/m $Pd(OH)_2/C$, cyclohexene, ethanol, 93% and 97%). [c]Compounds **5** and **12** were prepared by nitration (HNO_3/HOAC, 82% and 88%) of **4** and **11**, respectively. [d]The triazole **9** was prepared by treating **11** with methyl iodide (76%). [e]Positive controls.

9, **10**, **11** and **12**. On the other hand, the phenyl group at position 4 has a strong influence in defining the activity. In fact, all the compounds lacking this group (**1**, **6**, and **7**) are characterized by activity values higher than 100 μg mL^{-1}. The antimycobacterial profile of these compounds fits with the general subfragment phenyl-azole proposed by Prakash and Ghosh.[3] These chiral derivatives did not display better *in vitro* activity than their racemic counterparts. In fact, compounds **6**, **8**, and **11** are as active as their corresponding racemates **1**, **2**, and **4**. However, this observation was not true for the cases for compounds **3** /**10** and **5** /**12**. In these cases the differences might be related with higher activities of one of the enantiomer. The comparison of the MIC values for compounds **2**, **8** and **14** suggests that a chain at the N-1 position is also important in terms of the antimycobacterial activity.

Experimental

The melting points were determined using an Olympus BX50 microscope equipped with a Mettler Toledo FP-90 heating stage. The NMR spectra were obtained from homogeneous samples, as confirmed by TLC performed on silica gel (Kieselgel 60 F 254-Merck) plates, which were visualized with UV light. Flash chromatography was performed with Merck silica gel 60 (230-400 mesh). ^{1}H NMR spectra were obtained on a Varian Mercury Plus 400-MHz instrument, with tetramethylsilane (TMS) as the internal standard. ^{13}C NMR spectra were recorded on a Varian Mercury Plus 100-MHz spectrometer. The chemical shifts are given as delta (δ) values and the coupling constants (*J*) in Hertz (Hz). Infrared spectra were recorded with a Perkin Elmer FTIR 2000, in KBr pellets or in film. Elemental analyses were within +0.4% of theoretical values and were performed on a Perkin-Elmer 2400 instrument.

Antimycobacterial assay

Two hundred microliters of sterile deionized water was added to all outer-perimeter wells of sterile 96-well plates (Falcon, 3072: Becton-Dickinson, Lincoln Park, NJ) to minimize evaporation of the medium in the test wells during incubation. The 96 well-plates received 100 L of the Middlebrook 7H9 broth (Difco Laboratories, Detroit, MI, USA) and a serial dilution of the compounds **1**-**14** was made directly on the plate. The final drug concentrations tested were 1.0-100.0 mg mL^{-1}. The plates were sealed with Parafilm and incubated at 37 °C for five days. After this time, 25 L of a freshly prepared 1:1 mixture of 10X Alamar Blue (Accumed International, Westlake Ohio) reagent and 10% Tween 80 was added to the plate and reincubated at 37 °C for 24 h, and the colors of all wells were recorded.[28]

*General procedure for triazole synthesis from azides and terminal alkynes (**1-14**)*

*(2S)-4-(4-benzyloxyphenyl)-1-(2-methylbutyl)-1H-[1,2,3]-triazole (**10**)*

1-ethynyl-4-benzyloxybenzene (0.586 g, 2.82 mmol), CuI (0.053 g, 0.282 mmol) and TEA (0.04 mL, 0.282 mmol) were suspended in 1:1 ethanol:water (20 mL). To the heterogeneous and vigorously stirred mixture the (*S*)-(+)-1-azido-2-methylbutane (0.318 g, 2.82 mmols) was added dropwise, and a gentle reflux (60 °C) maintained for 6 h. Water (30 mL) was added and the flask cooled in crushed ice; the precipitate was collected by filtration and washed with water. Recrystallization from heptane provided 0.508 g of compound. Yield (64%); mp 117.5-118.2 °C; IR (KBr) ν_{max}/cm^{-1}: 3095, 2957, 2870, 1612, 1496, 1455, 1382, 1236, 1174, 1073, 1018, 827; ^{1}H NMR ($CDCl_3$) δ: 0.91 (m, 6H), 1.26 (m, 1H), 1.39(m, 1H), 2.03 (m, 1H), 4.21 (m, 2H), 5.10 (s, 2H), 7.03 (d, *J* 8.6 Hz, 2H), 7.40 (m, 5H), 7.63 (s, 1H), 7.76 (d, *J* 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ: 11.0, 16.8, 26.6, 35.9, 56.0, 70.0, 115.1, 119.1, 123.7, 126.9, 127.4, 128.0, 128.5, 136.8, 147.4, 158.7; Anal. calc. for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07. Found: C, 74.71; H, 7.25; N, 13.12.

The following compounds were prepared according to this general procedure.

*{1-(2-Methylbutyl)-1H-[1,2,3]-triazol-4-yl} methanol (**1**)*

Compound **1** was purified by column chromatography (silica gel, hexane:ethyl acetate 8:2, v/v). Yield 69%; colorless oil; IR (film) ν_{max}/cm^{-1}: 3378, 2964, 2877, 1647, 1553, 1460, 1382, 1223, 1145, 1050, 1013, 783; ^{1}H NMR ($CDCl_3$) δ: 0.85 (m, 6H), 1.20 (m, 1H), 1.39 (m, 1H), 1.93 (m, 1H), 4.17(m, 1H), 4.23 (m, 1H), 4.75 (s, 2H), 7.60 (s 1H); MS (EI, 70 eV): *m/z*(%) 168 (1.38 [M-1]), 169 (3.69 [M^+]); 170 (0.71 [M+1]); 43 (100.0). Anal. calc. for $C_8H_{15}N_3O$: C, 56.78; H, 8.93; N, 24.83. Found: 56.83, H, 8.99; N, 25.07.

*1-(2-Methylbutyl)-4-phenyl-1H-[1,2,3]-triazole (**2**)*

Compound **2** was purified by column chromatography (silica gel, hexane:ethyl acetate 9:1, v/v). Yield 83%; mp 47.5-48.9 °C; IR (film) ν_{max}/cm^{-1}: 3092, 2963, 2931, 2876, 1461, 1358, 1224, 1176, 1076, 1046, 972, 813, 765, 696; ^{1}H NMR ($CDCl_3$) δ: 0.98 (m, 6H), 1.18 (m, 1H), 1.37 (m, 1H), 2.00 (m, 1H), 4.14 (dd, 1H), 4.22 (dd, 1H), 7.31 (t, *J*

6.8 Hz, 1H), 7.40 (dd, *J* 7.2 and 6.8 Hz, 2H), 7.77 (s, 1H), 7.83 (d, *J* 7.2 Hz, 2H); Anal. calc. for $C_{13}H_{17}N_3$: C, 72.52; H, 7.96; N, 19.52. Found: C, 72.55; H, 8.03; N, 19.72.

*4-(4-Benzyloxyphenyl)-1-(2-methylbutyl)-1H-[1,2,3]-triazole (**3**)*

Compound **3** was purified by recrystallization from heptane. Yield 65%; mp 118.2-119.1 °C; IR (KBr) ν_{max}/cm^{-1}: 3089, 2961, 2871, 1614, 1494, 1456, 1374, 1249, 1174, 1076, 1015, 827; ^{1}H NMR ($CDCl_3$) δ: 0.94 (m,6H), 1.22 (m, 1H), 1.41 (m,1H), 2.02 (m, 1H), 4.08 (m, 1H), 4.24 (m, 1H), 5.11 (s, 2H), 7.03 (d, *J* 8.8 Hz, 2H), 7.44 (m, 5H), 7.63 (s, 1H), 7.76 (d, *J* 8.8 Hz, 2H); Anal. calc. for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07. Found: C, 74.68; H, 7.26; N, 13.09.

*(S)-{1-(2-Methylbutyl)-1H-[1,2,3]-triazol-4-yl} methanol (**6**)*

Compound **6** was purified by column chromatography (silica gel, hexane:ethyl acetate 8:2, v/v). Yield 65%; colorless oil; $[\alpha]_D^{20}$ +2.9 (*c* 2.04, $CHCl_3$); IR (film) ν_{max}/cm^{-1}: 3377, 2963, 2876, 1648, 1553, 1460, 1382, 1223, 1145, 1050, 1013, 783; ^{1}H NMR ($CDCl_3$) δ: 0.91 (m, 6H), 1.21 (m, 1H), 1.38 (m, 1H), 2.10 (m, 1H), 4.18 (m, 1H), 4.24 (m, 1H), 4.79 (s, 2H), 7.60 (s 1H); Anal. Calc. for $C_8H_{15}N_3O$: C, 56.78; H, 8.93; N, 24.83. Found: C, 57.13; H, 8.99; N, 24.98.

*(S)-2-(1-(2-Methylbutyl)-1H-[1,2,3]-triazol-4-yl) propan-2-ol (**7**)*

Compound **7** was purified by column chromatography (silica gel, hexane:ethyl acetate 8:2, v/v). Yield 76%; colorless oil; $[\alpha]_D^{20}$ +4.9 (*c* 1.02, $CHCl_3$); IR (film) ν_{max}/cm^{-1}: 3383, 2969, 1647, 1551, 1459, 1373, 1218, 1167, 1054, 959, 853; ^{1}H NMR ($CDCl_3$) δ: 0.91 (m, 6H), 1.25 (m, 1H), 1.40 (m, 1H), 1.63 (s, 6H), 1.98 (m, 1H), 5.50 (s, 1H), 4.12 (m, 1H), 4.22 (m, 1H), 7.48 (s, 1H); MS (EI, 70 eV): *m/z*(%) 196 (0.20 [M-1]), 197 (3.51 [M$^+$]); 198 (0.56 [M+1]); 43 (100.0). Anal. calc. for $C_{10}H_{19}N_3O$: C, 60.88; H, 9.71; N, 21.30. Found: C, 60.95; H, 9.73; N; 21.24.

*(S)-1-(2-Methylbutyl)-4-phenyl-1H-[1,2,3]-triazole (**8**)*

Compound **8** was purified by column chromatography (silica gel, hexane:ethyl acetate 9:1, v/v). Yield 70%; mp 56.8-58.8 °C; $[\alpha]_D^{20}$ +6.3 (*c* 1.11, $CHCl_3$); IR (KBr) ν_{max}/cm^{-1}: 3076, 2960, 2919, 1455, 1359, 1218, 1178, 1079, 1059, 971, 855, 758, 688; ^{1}H NMR ($CDCl_3$) δ: 0.95 (m, 6H), 1.22 (m, 1H), 1.21 (m, 1H), 2.02 (m, 1H), 4.18 (m, 1H), 4.28 (m, 1H), 7.33 (t, *J* 6.8 Hz, 1H), 7.42 (dd, *J* 7.2 and 6.8 Hz, 2H), 7.73 (s, 1H), 7.83 (d, *J* 7.2 Hz, 2H); MS (EI, 70 eV): *m/z*(%) 215 (27.84 [M$^+$]); 216 (6.28 [M+1]); 43 (100.0). Anal. calc. for $C_{13}H_{17}N_3$: C, 72.52; H, 7.96; N, 19.52. Found: C, 72.58; H, 8.01; N, 19.41.

*(S)-4-(4-Methoxyphenyl)-1-(2-methylbutyl)-1H-[1,2,3]-triazole (**9**)*

Compound **9** was purified by column chromatography (silica gel, hexane:ethyl acetate 9:1, v/v). Yield 76%; $[\alpha]_D^{20}$ +1.06 (*c* 0.94, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 0.94 (m, 6H), 1.20 (m, 1H), 1.41 (m,1H), 2.19 (m, 1H), 3.84 (s, 3H), 4.19 (m,1H), 4.26 (m, 1H), 6.96 (d, *J* 8.8 Hz, 2H), 7.63 (s, 1H), 7.76 (d, *J* 8.8 Hz, 2H); Anal. calc. for $C_{14}H_{19}N_3O$: C, 68.54; H, 7.81; N, 17.13. Found: C, 68.57; H, 7.76; N, 17.05.

*(1-Benzyl-1H-[1,2,3]-triazol-4-yl)methanol (**13**)*

Compound **13** was purified by recrystallization from toluene. Yield 65%; mp 77.4-78.4 °C; IR (KBr) ν_{max}/cm^{-1}: 3261, 1613, 1493, 1449, 1327, 1216, 1130, 1011, 837, 718, 684; ^{1}H NMR ($CDCl_3$) δ: 2.83 (s, 1H), 4.75 (s, 2H), 5.51 (s, 2H), 7.28 (m, 5H), 7.44 (s, 1H); MS (EI, 70 eV): *m/z*(%) 189 (1.44 [M$^+$]); 190 (0.19 [M+1]); 91 (100.0). Anal. calc. for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.43; H, 5.88; N, 22.28.

*1-Benzyl-4-phenyl-1H-[1,2,3]-triazole (**14**)*

Compound **14** was purified by recrystallization from heptane. Yield 71%; mp 130-130.9 °C; IR (KBr) ν_{max}/cm^{-1}: 3032, 1607, 1489, 1459, 1356, 1218, 1072, 1044, 971, 765, 726, 694; ^{1}H NMR ($CDCl_3$) δ: 5.56 (s, 2H), 7.30 (dd, 2H, *J* 7.6, 5 and 6 Hz), 7.40 (m, 6H), 7.65 (s, 1H), 7.79 (d, 2H, *J* 7.6Hz); MS (EI, 70 eV): *m/z*(%) 235 (11.76 [M$^+$]); 236 (2.11 [M+1]); 116 (100.0). Anal. calc. for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; N, 17.86. Found: C, 76.54; H, 5.89; N, 17.97.

*General procedure for phenol deprotection. Synthesis of (2S)-(+)-4-{1-(2-methylbutyl)-1H-[1,2,3]-triazol-4-yl}phenol (**11**)*

To a solution of (2*S*)-4-(4-benzyloxyphenyl)-1-(2-methylbutyl)-1*H*-[1,2,3]-triazole (1.34 g, 4.17 mmol) in ethanol (20 mL) and cyclohexene (10 mL), 20% m/m $Pd(OH)_2$/C (0.134 g) was added in small portions. After complete addition the mixture was heated under reflux for 5 h then cooled to r.t. and filtered through a celite pad washing with ethanol. The filtrate was concentrated, furnishing 0.936 g of the analytically pure compound. Yield (97%); mp 131.2-133.5 °C; $[\alpha]_D^{20}$ +7.8 (*c* 1.02, $CHCl_3$); IR (KBr) ν_{max}/cm^{-1}: 2960, 2924, 2813, 1613, 1499, 1465, 1391, 1276, 1216, 1173, 844, 800; ^{1}H NMR ($CDCl_3$) δ: 0.94 (m, 6H), 1.25 (m, 1H), 1.40

(m, 1H), 2.03 (m, 1H), 4.21 (m, 2H), 6.93 (d, *J* 8.5 Hz, 2H), 7.63 (s, 1H), 7.65 (d, *J* 8.5 Hz, 2H); Anal. calc. for $C_{13}H_{17}N_3O$: C, 67.51; H, 7.41; N, 18.17. Found: C, 67.57; H, 7.44; 18.22.

*4-{1-(2-Methylbutyl)-1H-[1,2,3]-triazol-4-yl} phenol (**4**)*

Yield 93%; mp 130.2-132.3 °C; IR (KBr) ν_{max}/cm^{-1}: 3117, 2962, 2816, 1606, 1467, 1389, 1273, 1221, 1174, 842; ^{1}H NMR ($CDCl_3$) δ: 0.94(m, 6H), 1.22 (m,1H), 1.41 (m,1H), 2.02 (m, 1H), 4.18 (m, 1H), 4.27 (m, 1H), 6.94 (d, *J* 8.4 Hz, 2H), 7.63 (s, 1H); 7.65 (d, *J* 8.4 Hz, 2H); MS (EI, 70 eV): *m/z*(%) 231 (16.48 [M$^+$]); 232 (2.41 [M+1]); 28 (100.0). Anal. calc. for $C_{13}H_{17}N_3O$: C, 67.51; H, 7.41; N, 18.17. Found: C, 67.58; H, 7.35; N, 18.16.

*General procedure for phenol nitration. Synthesis of (2S)-(+)-4-{1-(2-methylbutyl)-1H-[1,2,3]-triazol-4-yl}-2-nitrophenol (**12**)*

(2*S*)-(+)-4-{1-(2-methylbutyl)-1*H*-[1,2,3]-triazol-4-yl}phenol (0.200 g, 0.865 mmol) was suspended in concentrated acetic acid (7.0 mL) and concentrated HNO_3 (0.150 mL, 3.46 mmol) was then added dropwise. The solution was stirred for 15 min and poured into an ice/water mixture (20 mL). The yellow precipitate was collected by filtration, washing with water, and dried, furnishing 0.212 g of compound. Yield 88%; mp 109.6-111.4 °C; $[\alpha]_D^{20}$ +5.1 (*c* 0.77, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 0.93 (m, 6H), 1.27 (m, 1H), 1.41 (m, 1H), 2.05 (m, 1H), 4.27 (m, 2H), 7.24 (d, *J* 7.5 Hz, 1H), 7.76 (s, 1H), 8.15 (d, *J* 7.5 Hz, 1H), 8.49 (s, 1H), 10.52 (s, 1H); MS (EI, 70 eV): *m/z*(%) 276 (20.30 [M$^+$]); 277 (3.30 [M+1]); 43 (100.0). Anal. calc. for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.47; H, 5.81; N, 20.35.

*4-{1-(2-Methylbutyl)-1H-[1,2,3]-triazol-4-yl}-2-nitrophenol (**5**)*

Yield 82%; mp 111.9-112.4 °C; IR (KBr) ν_{max}/cm^{-1}: 3452, 2964, 1630, 1564, 1527, 1420, 1319, 1232, 1183, 669; ^{1}H NMR ($CDCl_3$) δ: 0.95 (m, 6H), 1.23 (m, 1H), 1.41 (m, 1H), 4.22 (m, 1H), 4.31(m, 1H), 7.25 (d, *J* 8.8 Hz, 1H), 7.76 (s, 1H), 8.15 (d, *J* 8.8 Hz, 1H), 8.49 (s, 1H), 10.61(s, 1H); Anal. calc. for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.54; H, 6.34; N, 20.36.

Conclusions

In conclusion, the present communication is the first report demonstrating the antimycobacterial potential of (*S*)-2-methylbutyl-1*H*-[1,2,3]-triazole derivatives against *M. tuberculosis H37Rv*. The high *in vitro* antimycobacterial activity of chiral compounds makes these compounds promising hits for the development of effective therapeutic agents. The significant activity of **2**, **4**, and **8-12** highlights them as promising hit molecules for further synthetic and biological exploration. These results confirm that the subfragment phenyl-[1,2,3]-triazole is important in terms of the antimycobacterial activity and this may lead to the discovery of a new and effective chemical anti-tuberculosis agent.

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