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Preliminary communication

Synthesis and investigation of tuberculosis inhibition activities of some 1,2,3-triazole derivatives

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Abstract

In this study, α-diazo-β-oxoaldehyde compounds were condensed with different amines to yield 4-acyl-1H-1,2,3-triazole derivatives. The 1,2,3-triazole compounds were investigated for their inhibition activities against tuberculosis.

Keywords: 1,2,3-Triazoles; Tuberculosis inhibition

1. Introduction

Triazoles, like many other five membered heterocyclic compounds are used very often in the pharmacological and medicinal applications. Condensation of amine derivatives with α-diazo-1,3-dicarbonyl compounds gives 1H-1,2,3-triazole derivatives [1,2]. This is a simple and regiospecific reaction and these make this method superior to the widely used acylacetylene+azide approach [3].

In this study, new 1,2,3-triazole derivatives were prepared. These triazoles and the triazoles from our previous work (**2**) were tested for their inhibition activities against tuberculosis.

2. Results

Eight different α-diazo-β-oxoaldehyde derivatives **1** were condensed with aniline, *p*-chloroaniline, 1-aminonaphthelene and 2-bromoethyl amine (Fig. 1) to yield 15 new and 5 known 1,2,3-triazole derivatives **2** in moderate-to-good yields. 37 different 1,2,3-triazole compounds were tested for their inhibition activities against tuberculosis (Table 1). α-diazo-β-oxoaldehyde derivatives **1** were synthesised by Vilsmeier-Haack formylation of 2-diazo-1-ethanone derivatives with chloromethylene dimethyliminium chloride [4,5].

Compounds demonstrating at least 90% inhibition in the primary screen are called 'active', and these compounds can be tested further. It was found that 4-(2-thiophenecarbonyl)-1-(bromoethyl)-1H-1,2,3-triazole has 94% inhibition activity and therefore it is an active compound against *Mycobacterium tuberculosis* $H_{37}Rv$ [6].

3. Experimental part

All diazo compounds were prepared as described in Refs. [4] and [5]. Minimum inhibitory concentration (MIC) is found by using Microplate Alamar Blue Assay (MABA) in BACTEC 12B medium against *Mycobacterium tuberculosis* $H_{37}Rv$ (**6**). M.p.: electrothermal glass-bath apparatus in capillary tubes. IR (KBr, cm^{-1}): Jasco FT-IR, model 5300. ^{1}H-NMR and ^{13}C-NMR were recorded with a 200-MHz *Bruker* apparatus, in D_6-DMSO, in δ (ppm) units, using TMS as internal standard. Elemental analysis: LECO-CHNS 932 apparatus.

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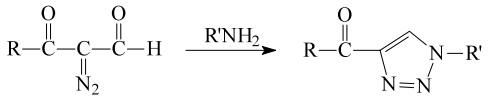

1 2

Fig. 1.

3.1. Synthesis of compounds **2.1**–**2.20**

To a solution of appropriate compound 1 (10 mmol) in 20 mL of EtOH, 10.1 mmol of the appropriate amine compound and 10.1 mmol of AcOH were added. The mixture was stirred at r.t. for 4 h. During this time, the triazoles precipitated. After recrystallization from EtOH, products were obtained in pure form.

3.1.1. 4-(2-Thiophenecarbonyl)-1-(bromoethyl)-1H-1,2,3-triazole (**2.1**)

Yield 65%. M.p.: 134–136 °C. IR (cm^{-1}): 3126, 1612, 1535, 1408, 1346, 1269, 1240, 1043, 1016, 943, 869, 825, 760, 698, 565, 461. ^{1}H-NMR: 9.04 (s, H–C(**5**)); 8.60 (d, 1 arom. H), 8.15 (d, 1 arom. H), 7.36 (t, 1 arom. H), 4.94 (t, 2H), 4.06 (t, 2H). ^{13}C-NMR: 176.52, 146.01, 141.69, 136.17, 135.65, 129.59, 128.77, 51.18, 30.98. $C_9H_8BrN_3OS$.

Table 1
Tuberculosis inhibition test results

Compound ***1*** *&* ***2***	R	R′	MIC [a] (μg mL^{-1})	Inhibition (%)	Activity [b]
2.1 [c] [7]	thiophene-2-yl	$BrCH_2CH_2$	< 12.5	94	+
2.2 [c]	2,5-Me_2-furan-3-yl	C_6H_5	> 12.5	82	–
2.3 [c]	furan-2-yl	C_6H_5	> 12.5	42	–
2.4 [c] [8]	C_6H_5	naphth-1-yl	> 12.5	22	–
2.5 [c]	4-Br–C_6H_4	C_6H_5	> 12.5	19	–
2.6 [c]	furan-2-yl	4-Cl–C_6H_4	> 12.5	17	–
2.7 [c] [9]	C_6H_5	4-Cl–C_6H_4	> 12.5	0	–
2.8 [c]	naphth-2-yl	naphth-1-yl	> 12.5	0	–
2.9 [c]	naphth-2-yl	4-Cl–C_6H_4	> 12.5	0	–
2.10 [c]	2,4-Cl_2–C_6H_3	naphth-1-yl	> 12.5	0	–
2.11 [c]	2,4-Cl_2–C_6H_3	4-Cl–C_6H_4	> 12.5	0	–
2.12 [c]	*i*-Pr	naphth-1-yl	> 12.5	0	–
2.13 [c]	*i*-Pr	4-Cl–C_6H_4	> 12.5	0	–
2.14 [c]	thiophene-2-yl	naphth-1-yl	> 12.5	0	–
2.15 [c]	thiophene-2-yl	4-Cl–C_6H_4	> 12.5	0	–
2.16 [c]	4-Br–C_6H_4	4-Cl–C_6H_4	> 12.5	0	–
2.17 [c]	2,5-Me_2-furan-3-yl	4-Cl–C_6H_4	> 12.5	0	–
2.18 [c] [1,10]	EtO	C_6H_5	> 12.5	0	–
2.19 [c] [11]	EtO	4-Cl–C_6H_4	> 12.5	0	–
2.20 [c]	4-MeO–C_6H_4	4-Cl–C_6H_4	> 12.5	0	–
2.21 [d]	naphth-1-yl	C_6H_5	> 12.5	83	–
2.22 [d]	*i*-Bu	C_6H_5	> 12.5	78	–
2.23 [d]	*i*-Pr	C_6H_5	> 12.5	50	–
2.24 [d]	2,4-Cl_2–C_6H_3	C_6H_5	> 12.5	49	–
2.25 [d]	2,4-Br_2–C_6H_3	C_6H_5	> 12.5	29	–
2.26 [d]	EtO	H	> 12.5	29	–
2.27 [d]	4-Cl–C_6H_4	C_6H_5	> 12.5	24	–
2.28 [d]	Me	H	> 12.5	14	–
2.29 [d,e]	Me	OH	> 12.5	12	–
2.30 [d]	2,4,6-Me_3–C_6H_3	C_6H_5	> 12.5	10	–
2.31 [d]	Me	C_6H_5	> 12.5	5	–
2.32 [d]	3,4-Cl_2–C_6H_3	C_6H_5	> 12.5	0	–
2.33 [d]	2,4-Cl_2–C_6H_3	H	> 12.5	0	–
2.34 [d]	2,4-Br_2–C_6H_3	H	> 12.5	0	–
2.35 [d]	EtO	OH	> 12.5	0	–
2.36 [d,e]	2,4-Br_2–C_6H_3	OH	> 12.5	0	–
2.37 [d]	EtO	–$NHCONH_2$	> 12.5	0	–

[a] MIC is found by using MABA in BACTEC 12B medium against *Mycobacterium tuberculosis* $H_{37}Rv$ (**6**).
[b] Compounds demonstrating at least 90% inhibition in the primary screen are called 'active', and these compounds can be tested further.
[c] These compounds were synthesised in this work.
[d] These compounds were synthesised in our previous work [2].
[e] In oxime form.

*3.1.2. 4-(2,5-Dimethyl-3-furancarbonyl)-1-phenyl-1H-1,2,3-triazole (**2.2**)*

Yield 82%. M.p.: 192–194 °C. IR (cm^{-1}): 1639, 1556, 1500, 1442, 1283, 1008, 879, 821, 507. ^{1}H-NMR: 9.46 (s, H–C(**5**)), 8.02–7.51 (m, 5 arom. H), 7.11 (s, 1 arom. H (furan)), 2.57 (s, CH_3), 2.30 (s, CH_3). ^{13}C-NMR: 197.87, 158.97, 149.70, 148.44, 136.04, 129.84, 129.26, 126.74, 120.61, 120.11, 107.27, 14.24, 12.81. $C_{15}H_{13}N_3O_2$.

*3.1.3. 4-(2-Furancarbonyl)-1-phenyl-1H-1,2,3-triazole (**2.3**)*

Yield 80%. M.p.: 198–201 °C. IR (cm^{-1}): 3140, 1643, 1564, 1531, 1466, 1396, 1286, 1199, 1087, 1028, 945, 862, 763, 750. ^{1}H-NMR: 9.66 (s, H–C(**5**)), 8.18–7.56 (m, 7 arom. H), 7.86 (s, 1 arom. H (furan)). ^{13}C-NMR: 171.22, 150.40, 148.96, 146.09, 141.29, 135.99, 129.87, 129.34, 127.18, 122.35, 120.64, 112.89, 109.17. $C_{13}H_9N_3O_2$.

*3.1.4. 4-(Benzoyl)-1-(napht-1-yl)-1H-1,2,3-triazole (**2.4**)*

Yield 60%. M.p.: 141–142 °C. IR (cm^{-1}): 3121, 3047, 1641, 1597, 1575, 1521, 1273, 1253, 1168, 906, 767. ^{1}H-NMR: 9.46 (s, H–C(**5**)), 8.14–8.35 (m, 4 arom. H), 7.53–7.88 (m, 8 arom. H). ^{13}C-NMR: 146.43, 136.55, 133.52, 133.32, 132.53, 132.39, 130.72, 129.94, 128.54, 128.27, 128.13, 127.82, 127.18, 125.32, 124.33, 121.93. $C_{19}H_{13}N_3O$.

*3.1.5. 4-(4′-Bromobenzoyl)-1-phenyl-1H-1,2,3-triazole (**2.5**)*

Yield 90%. M.p.: 177–178 °C. IR (cm^{-1}): 3130, 3067, 1637, 1581, 1562, 1525, 1398, 1354, 1267, 1180, 1008, 904, 868, 754, 686, 584, 464, 414. ^{1}H-NMR: 9.61 (s, H–C(**5**)), 8.26–7.57 (m, 9 arom. H). ^{13}C-NMR: 183.92, 146.88, 135.34, 131.62, 129.84, 129.35, 128.05, 127.54, 120.64. $C_{15}H_{10}BrN_3O$.

*3.1.6. 4-(2-Furancarbonyl)-1-(p-chlorophenyl)-1H-1,2,3-triazole (**2.6**)*

Yield 76%. M.p.: 141–142 °C. IR (cm^{-1}): 3130, 1641, 1562, 1533, 1466, 1390, 1286, 1203, 1024, 1006, 985, 939, 841, 592, 513, 472. ^{1}H-NMR: 9.66 (s, H–C(**5**)), 8.63–7.36 (m, 7 arom. H). ^{13}C-NMR: 176.54, 147.07, 141.98, 136.78, 134.01, 130.12, 129.22, 122.69. $C_{13}H_8ClN_3O_2$.

*3.1.7. 4-(Benzoyl)-1-(p-chlorophenyl)-1H-1,2,3-triazole (**2.7**)*

Yield 85%. M.p.: 215–220 °C. IR (cm^{-1}): 3126, 30101, 3088, 3057, 1639, 1599, 1575, 1521, 1502, 1408, 1344, 1265, 1170, 1014, 841, 819, 735. ^{1}H-NMR: 9.62 (s, H–C(**5**)), 7.42–8.28 (m, 9 arom. H). ^{13}C-NMR: 147.07, 136.37, 134.80, 133.66, 133.37, 130.50, 129.89, 129.81, 128.54, 128.09, 122.38. $C_{15}H_{10}ClN_3O$.

*3.1.8. 4-(2-Naphthoyl)-1-(napht-1-yl)-1H-1,2,3-triazole (**2.8**)*

Yield 55%. M.p.: 161–163 °C. IR (cm^{-1}): 3126, 3057, 1635, 1597, 1523, 1471, 1361, 1280, 1238, 1124, 906, 777, 760. ^{1}H-NMR: 9.42 (s, H–C(**5**)), 8.72–7.64 (m, 14 arom. H). ^{13}C-NMR: 184.95, 146.56, 135.08, 133.85, 133.57, 132.59, 132.27, 131.97, 130.75, 129.82, 128.86, 128.31, 128.24, 128.16, 127.83, 127.66, 127.22, 126.98, 125.37, 125.09, 124.36, 122.01. $C_{23}H_{15}N_3O$.

*3.1.9. 4-(2-Naphthoyl)-1-(p-chlorophenyl)-1H-1,2,3-triazole (**2.9**)*

Yield 50%. M.p.: 233–235 °C. IR (cm^{-1}): 3134, 3105, 3059, 1628, 1523, 1504, 1358, 1278, 1236, 1097, 1012, 987, 906, 833. ^{1}H-NMR: 9.69 (s, H–C(**5**)), 8.13–7.73 (m, 11 arom. H). ^{13}C-NMR: 183.91, 149.87, 141.03, 137.77, 137.00, 134.68, 131.53, 127.19, 127.50, 126.37. $C_{19}H_{12}ClN_3O$.

*3.1.10. 4-(2′,4′-Dichlorobenzoyl)-1-(napht-1-yl)-1H-1,2,3-triazole (**2.10**)*

Yield 65%. M.p.: 189–192 °C. IR (cm^{-1}): 3123, 1638, 1583, 1523, 1277, 1242, 999, 904, 800, 769. ^{1}H-NMR: 9.53 (s, H–C(**5**)), 8.27–7.48 (m, 10 arom. H). ^{13}C-NMR: 185.33, 146.10, 136.35, 136.09, 133.52, 132.32, 131.53, 131.46, 130.88, 129.64, 128.33, 128.22, 127.75, 127.41, 127.26, 125.34, 124.40, 121.80. $C_{19}H_{11}Cl_2N_3O$.

*3.1.11. 4-(2′,4′-Dichlorobenzoyl)-1-(p-chlorophenyl)-1H-1,2,3-triazole (**2.11**)*

Yield 80%. M.p.: 219–222 °C. IR (cm^{-1}): 3126, 3101, 3086, 1635, 1587, 1523, 1502, 1244, 1043, 910, 841, 688. ^{1}H-NMR: 9.66 (s, H–C(**5**)), 8.07-7.60 (m, 7 arom. H). ^{13}C-NMR: 185.20, 146.68, 136.12, 134.67, 133.86, 131.45, 131.25, 129.88, 129.61, 127.45, 122.42. $C_{15}H_8Cl_3N_3O$.

*3.1.12. 4-(2-Methylpropanoyl)-1-(napht-1-yl)-1H-1,2,3-triazole (**2.12**)*

Yield 75%. M.p.: 186–189 °C. IR (cm^{-1}): 3124, 3053, 3018, 1649, 1606, 1533, 1278, 995, 908, 790, 756. ^{1}H-NMR: 9.43 (s, H–C(**5**)), 8.29-7.43 (m, 7 arom. H), 3.66 (septet, CH); 1.20 (d, CH_3). ^{13}C-NMR: 184.57, 146.62, 143.89, 133.95, 133.53, 132.56, 132.24, 130.71, 130.13, 129.14, 128.28, 128.13, 127.82, 127.19, 125.33, 124.32, 121.93, 25.03, 21.19. $C_{16}H_{15}N_3O$.

*3.1.13. 4-(2-Methylpropanoyl)-1-(p-chlorophenyl)-1H-1,2,3-triazole (**2.13**)*

Yield 70%. M.p.: 221–223 °C. IR (cm^{-1}): 3124, 1637, 1606, 1568, 1267, 1170, 904, 841. ^{1}H-NMR: 9.59 (s, H–C(**5**)), 8.21–7.40 (m, 4 arom. H), 3.65 (septet, CH), 1.19 (d, CH_3). ^{13}C-NMR: 184.42, 147.28, 143.99, 134.86, 133.81, 133.67, 130.10, 129.84, 129.16, 122.41, 21.19. $C_{12}H_{12}ClN_3O$.

*3.1.14. 4-(2-Thiophenecarbonyl)-1-(napht-1-yl)-1H-1,2,3-triazole (**2.14**)*

Yield 65%. M.p.: 185–189 °C. IR (cm^{-1}): 3119, 1618, 1535, 1413, 1277, 1037, 997, 877, 833, 570, 424. ^{1}H-NMR: 9.48 (s, H–C(**5**)), 8.69–7.37 (m, 10 arom. H). ^{13}C-NMR: 176.45, 146.16, 141.85, 136.38, 135.89, 133.54, 132.51, 131.83, 130.78, 128.91, 128.30, 128.18, 127.79, 127.21, 125.34, 124.36, 121.88. $C_{17}H_{11}N_3OS$.

*3.1.15. 4-(2-Thiophenecarbonyl)-1-(p-chlorophenyl)-1H-1,2,3-triazole (**2.15**)*

Yield 75%. M.p.: 246–252 °C. IR (cm^{-1}): 3130, 1618, 1533, 1502, 1269, 1170, 1041, 829, 715, 509. ^{1}H-NMR: 9.65 (s, H–C(**5**)), 8.62–7.35 (m, 7 arom. H). ^{13}C-NMR: 176.25, 146.79, 141.70, 136.47, 135.90, 134.79, 133.73, 129.83, 128.91, 127.55, 122.40. $C_{13}H_8ClN_3OS$.

*3.1.16. 4-(4′-Bromobenzoyl)-1-(p-chlorophenyl)-1H-1,2,3-triazole (**2.16**)*

Yield 88%. M.p.: 219–221 °C. IR (cm^{-1}): 3489, 1647, 1583, 1502, 1267, 1003, 900, 837, 760, 516. ^{1}H-NMR: 9.66 (s, H–C(**5**)), 8.24-7.71 (m, 8 arom. H). ^{13}C-NMR: 183.89, 146.92, 135.31, 134.76, 133.75, 131.88, 131.68, 129.85, 128.33, 127.62, 122.41. $C_{15}H_9BrClN_3O$.

*3.1.17. 4-(2,5-Dimethyl-3-furancarbonyl)-1-(p-chlorophenyl)-1H-1,2,3-triazole (**2.17**)*

Yield 78%. M.p.: 120–123 °C. IR (cm^{-1}): 3119, 2961, 1639, 1614, 1564, 1523, 1386, 1358, 1232, 1213, 1012, 999, 925, 877, 761, 688, 572. ^{1}H-NMR: 9.47 (s, H–C(**5**)), 7.60 (m, 4 arom. H), 7.12 (s, furan arom. H), 2.59 (s, CH_3), 2.32 (s, CH_3). ^{13}C-NMR: 179.84, 158.91, 149.65, 148.42, 136.03, 129.80, 129.22, 126.64, 120.58, 120.10, 107.25, 14.20, 12.77. $C_{15}H_{12}ClN_3O_2$.

*3.1.18. 4-(Ethylcarboxylate)-1-phenyl-1H-1,2,3-triazole (**2.18**)*

Yield 85%. M.p.: 84–86 °C. IR (cm^{-1}): 3140, 1712, 1597, 1548, 1508, 1469, 1375, 1269, 1170, 1039, 869, 839, 765, 688, 507. ^{1}H-NMR: 9.50 (s, H–C(**5**)), 7.99 (d, 2 arom. H), 7.66–7.54 (m, 3 arom. H), 4.37 (q, CH_2), 1.35 (t, CH_3). ^{13}C-NMR: 160.04, 139.71, 135.99, 129.81, 129.21, 127.12, 120.45, 60.68, 14.10. $C_{11}H_{11}N_3O_2$.

*3.1.19. 4-(Ethylcarboxylate)-1-(p-chlorophenyl)-1H-1,2,3-triazole (**2.19**)*

Yield 87%. M.p.: 170–172 °C. IR (cm^{-1}): 3151, 2980, 1720, 1552, 1500, 1369, 1342, 1267, 1163, 1091, 1039, 837, 769, 516, 459. ^{1}H-NMR: 9.51 (s, H–C(**5**)), 8.03 (d, 2 arom. H), 7.70 (d, 2 arom. H), 4.36 (q,CH_2), 1.34 (t, CH_3). ^{13}C-NMR: 159.93, 139.79, 134.79, 133.55, 129.76, 127.25, 122.17, 60.72, 14.08. $C_{11}H_{10}ClN_3O_2$.

*3.1.20. 4-(4′-Methoxybenzoyl)-1-(p-chlorophenyl)-1H-1,2,3-triazole (**2.20**)*

Yield 87%. M.p.: 217–219 °C. IR (cm^{-1}): 3124, 1639, 1523, 1504, 1267, 1170, 1014, 904, 841, 754, 625, 468. ^{1}H-NMR: 9.58 (s, H–C(**5**)), 8.09–7.40 (m, 8 arom. H). ^{13}C-NMR: 184.43, 147.30, 144.01, 134.86, 133.81, 133.68, 130.11, 129.86, 129.18, 127.94, 122.41. $C_{16}H_{12}ClN_3O_2$.

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