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ORIGINAL ARTICLE

Synthesis and *in vitro* study of some fused 1,2,4-triazole derivatives as antimycobacterial agents

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Abstract Because of the highly therapeutic nature of 1,2,4-triazoles, a new class of fused pyrazolo [3′,4′:4,5] thiazolo [3,2-b] [1,2,4]-triazole, isoxazolo [3′,4′:4,5] thiazolo [3,2-b] [1,2,4]-triazole moieties were prepared from the novel conventional methods via the reaction of 4-methyl benzoyl thiosemicarbazide with the appropriate chemical reagents. These compounds were screened for their antimicrobial activity against various bacterial and fungal strains. With the reference of antimicrobial activity data the synthesized compounds were further screened for their antimycobacterial activity against *Mycobacterium tuberculosis H37Rv* by the conventional methods. Among the synthesized compounds 4b, 4d, 4h, 5d and 5h have shown more activity compared to the standard drugs.

1. Introduction

The rapid development of mycobacterial resistance to conventional drugs is one of the major difficulties in the treatment of tuberculosis. The incidence of tuberculosis is increasing worldwide, partly due to poverty and inequity and partly to the HIV/AIDS pandemic, which greatly increase the risk of infection proceeding to overt disease. Moreover the development of drug resistant strains of mycobacterium species, has contributed to the inefficiency of the conventional antituberculosis therapy, thus it is still necessary to search for new antimicrobial agents. Since the discovery of hetero cyclic nucleus the chemistry of 1,2,4-triazoles and their fused heterocyclic derivatives represent an interesting class of compounds possessing a wide spectrum of biological activities. The huge number of 1,2,4-triazoles containing systems exhibits anti-inflammatory activity (Mullican et al., 1993; Tozkoparan et al., 2007), antibacterial (Foroumadi et al., 2003), antimycobacterial (Kucukguzel et al., 2001), anticonvulsant (Kelley et al., 1995), antifungal (Heubach et al., 1979), antidepressant (Chiu and Huskey, 1998), and plant growth regulator anti coagulants (Eliott et al., 1987). On the other hand thiazoles are also a familiar class of heterocyclic compounds possessing a wide variety of biological activities and their utility in medicine is very much established (Andrew et al., 2008). Several physiological activities of various thiazole derivatives have proved the efficacy and efficiency in combating various diseases and noticed to have good therapeutic agents such as anti tubercular agents (El-Shaaer et al., 1998), antimicrobial agents (Gouda et al., 2010; Liaras et al., 2011), anti-Candida spp. agents (Chimenti et al., 2011).

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Furthermore, diverse chemotherapeutic activities have been ascribed to fused 1,2,4-triazolo thiazole moieties as antimicrobial agents (Guzeldemirci and Kucukbasmac, 2010). Literature survey revealed that some pyrazoles have been implemented as antiviral (Genin et al., 2000), antimicrobial (Foks et al., 2005; Prakash et al., 2008), anti-neoplastic (Farag et al., 2008), anti-tumour (Xia et al., 2008) and analgesic agents (Khode et al., 2009).

In view of these above findings it was contemplated to design and synthesize a new class of heterocyclic derivatives in which 1,2,4-triazole, pyrazolo-thiazole or isoxazolo-thiazole derivatives in a single molecular frame work act as antimicrobial and anti tuberculosis agents.

2. Experimental

All melting points were measured on the open capillary method. IR spectra were recorded for KBr disc on Schimadzu-8400 FTIR spectrophotometer. ^{1}H NMR, ^{13}C NMR spectra were measured on a Bruker Avance II 400 spectrometer, operating at 400, 100.6 MHz respectively. Chemical shifts (δ) are reported in parts per million (ppm) and TMS as an internal standard. Molecular weights were determined with TOF MS ES Mass spectra. Reactions were monitored by thin layer chromatography (TLC) on silica gel, plates were visualized with ultraviolet light or iodine. Column chromatography was performed on silica gel 60(0.043–0.06 mm) Merck.

*2.1. 4-Methyl benzoyl thiosemicarbazide (**1**)*

A mixture of Ethyl-p-methyl-benzoate (0.01 mol) and thiosemicarbazide (0.01 mol) in methanol (25 ml) was refluxed for 10 h. The solvent was removed under reduced pressure and the viscous mass poured over ice water, filtered and recrystallized from methanol–water to afford compound **1**.

*2.2. 5-Mercapto-3-p-tolyl-s-triazole (**2**)*

P-methyl benzoyl thiosemicarbazide (2 g) in 8% NaOH Solution (30 ml) was heated under reflux temperature for 5 h. The reaction mixture was cooled to room temperature and acidified with dil. acetic acid. The product thus separated was filtered, washed with excess of water and recrystallized from ethanol to afford compound **2**.

*2.3. (Z)-5-(substituted-benzylidene)-2-(p-tolyl) thiazolo [3,2-b] [1,2,4] triazol-6(5H)-one (**3**)*

A mixture of compound **2** (0.01 mol), chloro acetic acid (0.01 mol), appropriate aromatic aldehyde (0.01 mol) fused sodium acetate (0.02 mol) in acetic anhydride (20 ml) and glacial acetic acid (30 ml) was refluxed on a heating mantle for 4 h, concentrated and cooled. The brown solid separated was filtered, washed well with water and recrystallized from glacial acetic acid as brown crystals. The compounds **3a**–**h** were prepared similarly by treating with corresponding aldehydes.

*2.3.1. 3-Phenyl-6-(p-tolyl)-3, 3a-dihydro-2H-pyrazolo [3′,4′:4,5] thiazolo [3,2-b] [1,2,4] triazole (**4a**)*

A mixture of compound **3** (0.005 mol), hydrazine hydrate (0.005 mol) and anhydrous CH_3COONa (0.01 mol) in glacial acetic acid was heated under reflux conditions for 5 h, cooled to room temperature and poured into ice cold water. The dark brown solid thus separated was filtered, washed with excess of water and recrystallized from acetic acid to obtain the desired compound. Yield 61.8%, m.p. 218–220 °C; IR (KBr) in cm^{-1}: 3325.39, 3078.49, 3064.99, 2951.23, 1558.54, 1236.41, 1030.02, 698.25; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.01–7.45 (m, 9H, Ar–H), 7.87 (s, 1H, N–H), 4.99 (d, 1H, N–CH), 4.47 (d, 1H, S–CH), 2.81 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ ppm: 22.17, 41.3, 53.8, 121.8, 126.1, 128.5, 139.4, 147.2, 157.9; MS: m/z 334.38 [$M+1$].

The other compounds (**4b**–**h**) were also prepared similarly by treating with corresponding compounds **3b**–**h**. The physical and analytical data were given in Table 1.

*2.3.2. 3-(4-Chlorophenyl)-6-(p-tolyl)-3, 3a-dihydo-2H-pyrazolo [3′,4′:4,5] thiazolo[3,2-b] [1,2,4]-triazole (**4b**)*

Yield 64.7%, m.p. 254–257 °C; IR (KBr) cm^{-1}: 3296.18, 3078.49, 3064.99, 2953.11, 1600.97, 1558.54, 1236.41, 1107.18; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.91 (s, 1H, N–H), 7.09–7.41 (m, 6H, Ar–H), 7.01 (d, 2H, Ar–H near-Cl), 4.99 (d, 1H, N–CH), 4.32 (d, 1H, S–CH), 2.69 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ ppm: 22.7, 41.3, 53.6, 131.2, 118.3, 127.5, 130.1, 147.2, 156.5; MS: m/z 369.21 [$M+2$], 368.38 [$M+1$].

*2.3.3. 3-(3-Nitrophenyl)-6-(p-tolyl)-3, 3a-dihydo-2H-pyrazolo [3′,4′:4,5] thiazolo[3,2-b] [1,2,4]-triazole (**4c**)*

Yield-62.5%, m.p. 219–222 °C; IR (KBr) cm^{-1}: 3294.23, 3078.49, 3065.57, 2953.11, 1600.97, 1551.58, 1528.04, 1236.41; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.01 (s, 1H, N–H), 7.69 (d, 2H, Ar–H near NO_2), 7.03–7.41 (m, 6H, Ar–H), 5.09 (d, 1H, N–CH), 4.51 (d, 1H, N–CH), 2.78 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ ppm: 22.7, 41.3, 53.6, 119.6, 129.3, 133.7, 138.3, 147.2, 149.03, 156.9; MS: m/z 379.46 [$M+1$].

*2.3.4. 3-(4-Nitrophenyl)-6-(p-tolyl)-3, 3a-dihydo-2H-pyrazolo [3′,4′:4,5] thiazolo[3,2-b] [1,2,4]-triazole (**4d**)*

Yield-64.1%, m.p. 267–269 °C; IR (KBr) cm^{-1}: 3296.08, 3071.12, 3065.57, 2953.11, 1600.97, 1558.19, 1521.86; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.01 (s, 1H, N–H), 7.69 (d, 2H, Ar near NO_2), 7.12–7.53 (m, 6H, Ar–H), 5.06 (d, 1H, N–CH), 4.57 (d, 1H, S–CH), 2.42 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ ppm: 22.7, 41.3, 53.6, 119.6, 129.3, 134.2, 138.3, 146.9, 149.1, 157.41; MS: m/z 379.53 [$M+1$].

*2.3.5. 3-(2-Methoxyphenyl)-6-(p-tolyl)-3, 3a-dihydo-2H-pyrazolo [3′,4′:4,5] thiazolo[3,2-b] [1,2,4]-triazole (**4e**)*

Yield-59.7%, m.p. 237–239 °C; IR (KBr) cm^{-1}: 3287.11, 3071.12, 3065.68, 2959.45, 1600.97, 1558.16, 1249.98, 1236.41; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.91 (s, 1H, N–H), 7.1–7.46(m, 7H, Ar–H), 6.85 (d, 1H, Ar–H near OCH_3), 4.96 (d, 1H, N–CH), 4.67 (d, 1H, S–CH), 3.38 (s, 3H, OCH_3), 2.69 (s, 3H, CH_3); ^{13}C NMR (DMSO d_6) δ ppm; 22.3, 41.3, 53.1, 55.8, 115.7, 127.4, 136.9, 147.2, 158.1, 159.6; MS: m/z 364.33 [$M+1$].

*2.3.6. 3-(4-Methoxyphenyl)-6-(p-tolyl)-3, 3a-dihydo-2H-pyrazolo [3′,4′:4,5] thiazolo[3,2-b] [1,2,4]-triazole (**4f**)*

Yield. 61.3%, m.p. 258–260 °C; IR (KBr) cm^{-1}: 3287.11, 3071.49, 3065.68, 2954.81, 1600.97, 1543.27, 1249.98,