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ORIGINAL ARTICLE

Synthesis and in vitro study of [1,3,4]thiadiazol-2yl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazoles as antimicrobial agents

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Abstract A variety of 3,5-diphenyl-6-(5-p-toly1-1,3,4 thiadiazol-2yl)-3,3a,5,6 tetrahydro-2H pyrazolo3,4-dthiazole **6ag** were synthesized by the reaction of chalcone derivatives of 1,3,4 thiadiazol-2-yl)-thiazolidin-4-one **5a–g** with hydrazine hydrate. The chemical structures of these compounds were confirmed by IR, NMR (^{1}H & ^{13}C) and mass spectral studies. Synthesized compounds **6a–g** were evaluated for their antimicrobial and anti-tubercular activities. Some of the compounds exhibited well antimicrobial and anti-tubercular activities compared to the standard drugs.

1. Introduction

Because the resistance of pathogenic bacteria towards available antibiotics is rapidly becoming a major worldwide problem; the design of new class of chemical moieties to deal with resistance bacteria has become one of the important areas of antibacterial research today. In addition, fungal infections continue to increase rapidly because of the increased number of immuno compromised patients. As known, not only biochemical similarity of the human cell and fungi forms a handicap for selective activity, but also the easily gained resistance is the main problem noticed in developing safe and efficient antifungals. On the other hand, *Mycobacterium tuberculosis* remains a leading infectious and most dangerous cause of death in the world today. So, it is necessary to design a new kind of antimicrobial and anti tubercular agents.

Thiazoles are familiar class of heterocyclic moieties possessing a wide variety of biological activities and their utility as medicine is very much-established (Liaras et al., 2011). Several physiological activities of thiazole derivatives have proved the efficiency in combating various diseases and noticed to have good antimicrobial activities (Vicini et al., 2006). Among the important heterocycles, thiadiazoles are one of the privileged structural fragments in medicinal chemistry due to various biological activities, such as anti cancer (Matysiak et al., 2007), anti tubercular (Solak et al., 2006; Foroumadi et al., 2002), antibacterial (Thomasco et al., 2003; Kadi et al., 2007; Faroumadi et al., 2005a,b), antidepressants (Varvaresou et al., 1998; Yusuf et al.,2008), leishmanicidal (Faroumadi et al., 2005a,b) and anti-inflammatory agents (Schenone et al., 2006). On the other hand pyrazoles are an important class of heterocycles and earlier workers have been synthesized and reported various pyrazole derivatives as antifungal (Prakash et al., 2008), antiviral (Genin et al., 2000), anti proliferative (Schenone et al., 2004),

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antimicrobial (Tanitame et al., 2005; Tandon et al., 2005; Kane et al., 2003; Kucukgezel et al., 2000), anti parasitic (Kuettel et al., 2007) and anti neoplastic agents (Farag et al. 2008; Diana et al., 2007).

In view of the above mentioned facts it was contemplated to design and synthesize some 3,5-diphenyl-6-(5-p-tolyl-1,3,4thiadiazol-2-yl)-3,3a,5,6-tetrahydro-2H pyrazolo3,4-dthiazole derivatives and evaluate their antimicrobial and anti-tubercular activities.

2. Experimental

2.1. Chemistry

All melting points were measured on open capillary method. IR spectra were recorded for KBr disc on a 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 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.

2.1.1. General procedure for the synthesis of p-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**. m.p. 128–30 °C, yield 75%, IR (KBr) ν in cm^{-1}: 2942.16 (CH_3), 3060 (C–H in aromatic), 3175 (N–H), 1661.53 (C═O), 1071.6 (C═S), ^{1}H NMR (400 MHz, $CDCl_3$) & in ppm: 7.60–7.45 (m, 4H, Ar–H), 8.15 (m, 4H, NHNHCSNH$_2$ exchangeable with D_2O), 2.91 (s, 3H, CH_3).

2.1.2. General procedure for the synthesis of 5-p-Tolyl-1,3,4thiadiazol-2-yl amine 2

A mixture of compound **1** (0.05 mol) and conc. H_2SO_4 (20 ml) was kept overnight at room temperature, then poured into cold water, neutralized with liquid ammonia and filtered. The product thus obtained was recrystallized from ethanol–water. m.p. 135 °C, yield 61%; IR (KBr) ν in cm^{-1} 3350 (NH_2); 3058 (C–H in aromatic), 2968.63 (CH_3); 1598 (C═N), 1221 (C–N), 1045 (N–N), 732.27 (C–S–C); ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm; 7.62–7.35 (m, 4H, Ar–H), 6.35 (bs, 2H, NH_2 exchangeable with D_2O), 3.01 (s, 3H, CH_3).

2.1.3. General procedure for the synthesis of Benzylidene-(5-p-tolyl-1,3,4thiadiazol-2-yl)-amine 3

A mixture of **2** (0.01 mol) and benzaldehyde (0.01 mol) was refluxed in ethanol for 5 h with a few drops of glacial acetic acid. The solid separated on cooling was filtered, dried and recrystallized from benzene as needle shaped crystals were obtained.

Yield 73.2%, m.p.162–64 °C; IR (KBr) ν in cm^{-1}: 3032.2 (Ar–H), 2946.76 (C–H in CH_3), 1040.6 (N–N), 1608.61 (C═N cyclic), 1221 (C–N), 683.7 (C–S); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.79–7.21 (m, 9H, Ar–H), 7.9 (s, 1H, N═CH), 2.96 (s, 3H,CH_3).

2.1.4. General procedure for the synthesis of 2-Phenyl-3-(5-p-tolyl-1,3,4thiadiazol-2-yl)-thiazolidin-4-one.4

A mixture of compound **3** (0.01 mol) and mercapto acetic acid (0.01 mol) in 1,4-dioxane (30 ml) containing a pinch of $ZnCl_2$ was refluxed for 8 h. The hot solution was filtered and cooled in an ice bath. The solid obtained was filtered, washed with 10% $NaHCO_3$ solution and was recrystallized from alcohol. Yield 70.9%, m.p. 181–184 °C; IR (KBr) ν in cm^{-1}: 2946.73 (C–H in CH_3), 2918.69 (C–H in CH_2), 1665 (C═O), 1608.61 (C═N), 1045.1 (N–N), 691.6 (C–S), ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.91–7.8 (m, 9H, Ar–H), 5.13 (s, 1H, N–CH–Ar), 4.25 (s, 2H, SCH_2C═O), 2.91 (s, 3H, CH_3).

2.1.5. General procedure for the synthesis of 5-(4-Chloro-benzylidene)-2-phenyl-3-(5-p-tolyl-1,3,4thiadiazol-2-yl)-thiazolidin-4-one.5a

A mixture of compound 4 (0.01 mol), 4-chloro benzaldehyde (0.01 mol) and anhydrous sodium acetate (0.005 mol) in anhydrous glacial acetic acid (50 ml), was refluxed for 3 h. The reaction mixture was concentrated and then poured into ice cold water, the solid thus separated was filtered, washed with water and recrystallized from glacial acetic acid to afford pure brown color solid. Yield: 59.5%; m.p. 206–08 °C; IR (KBr) ν in cm^{-1}; 3032.2 (Ar–H), 2946.73 (CH in CH_3), 1608.61 (C═N), 1099.07 (C–Cl), 1042.61 (N–N), 1665 (C═O), ^{1}H NMR (400 MHz, DMSO-d6) δ: 7.22–7.9 (m, 11H, Ar–H), 7.13 (d, J = 9.1 MHz, 2H, Ar–H near Cl), 6.89(s, 1H, ═CH), 5.13 (s, 1H, N–CH–Ar), 2.93 (s, 3H, CH_3); ^{13}C NMR: δ: 157.1 (C═O in ring), 135.5, 131.9, 130.7, 129.5, 128.0, 127.7, 118.9 (Ar–H), 154.2, 152.1(C in thiadiazole ring), 50.7 (═CH), 69.9 (N–CH–Ar), 22.5 (CH_3). MS: *m*/*z* 477.90 ($M+2$, 32.5), 476.81 ($M+1$, 26.8), 475.95 (M^+, 28.9), 91 (100).

Similarly other compounds **5b–g** were also synthesized and their characteristic analytical data are given below.

2.1.5.1. 5-(4-Nitro-benzylidene)-2-phenyl-3-(5-p-tolyl-1,3,4thiadiazol-2-yl)-thiazolidin-4-one.5b. Yield: 58%; m.p. 197–99 °C; IR (KBr) ν in cm^{-1}; 3032.2 (Ar–H), 2948.72 (CH in CH_3), 1608.29 (C═N), 1665.49 (C═O), 1541.18 (N–O), 1042.61 (N–N), ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.86 (d, J = 8.3 MHz, 2H, Ar–H near NO_2), 7.1–7.7 (m, 9H, Ar–H), 6.99 (d, J = 9.1 MHz, 2H, Ar–H), 6.86(s, 1H, ═CH), 5.13 (s, 1H, N–CH–Ar), 2.76 (s, 3H, CH_3); ^{13}C NMR: δ: 162.3 (C═O in ring), 148.93, 138.7, 133.1, 128.7, 123.1, 119.6 (Aromatics), 155.7, 153.9 (C in thiadiazole ring), 69.9 (N–CH–Ar), 51.3 (═CH), 22.9 (CH_3). MS: *m*/*z* 487.34 ($M+1$, 30), 486.29 (M^+, 29.7), 91 (100).

2.1.5.2. 5-(4-Dimethylamino-benzylidene)-2-phenyl-3-(5-p-tolyl-1,3,4thiadiazol-2-yl)-thiazolidin-4-one.5c. Yield 61%, m.p. 208–10 °C, IR (KBr) ν in cm^{-1}; 3032.2 (CH in Ar), 2952(CH in CH_3), 1611.23 (C═N), 1683.09 (C═O), 1038.61 (N–N), 1225.6 (C–N); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.61 (d, J = 9.1 MHz, 2H, Ar–H near NMe_2), 6.49 (d, J = 9.1 MHz, 2H, Ar–H), 6.79(s, 1H, ═CH), 5.07 (s, 1H, N–CH–Ar), 2.93(s, 6H, CH_3), 2.68 (s, 3H, CH_3), 6.8–7.3 (m, 9H, Ar–H); ^{13}C NMR: δ: 159.7 (C═O), 151.1, 133.7, 135.6, 128.6, 117.01, 113.6 (Aromatics), 154.2, 153.01(C in thiadia-