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ORIGINAL ARTICLE

Synthesis, characterization and antimicrobial activity of benzodioxane ring containing 1,3,4-oxadiazole derivatives

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Abstract A series of 1,3,4-oxadizole derivatives containing 1,4-benzodioxane ring system were synthesized starting from 2,3-dihydro-1,4-benzodioxane-2-carbohydrazide. The synthesized compounds were characterized and evaluated for antibacterial activity against *Staphylococcus aureus*, *Escherichia coli* and *Bacillus subtilis* and antifungal activity against *Aspergillus niger*, *Aspergillus flavus* and *Candida albicans* by twofold serial dilution technique. Some of the synthesized compounds displayed comparable or even better antibacterial and antifungal activities than reference drugs norfloxacin, chloramphenicol and fluconazole, against tested strains.

1. Introduction

In recent years, the incidence of fungal and bacterial infections has increased dramatically. The widespread use of antifungal and antibacterial drugs resulted in resistance to drug therapy against fungal and bacterial infections which led to serious health hazards. The resistance of wide spectrum antifungal and antibacterial agents has initiated discovery and modification of the new antifungal and antibacterial drugs.

It is well-known that azole moieties are important pharmacophore that appear extensively in various types of pharmaceutical agents, widely implicated in biochemical processes and display diversity of pharmacological activities (Mamolo et al., 2005). A large number of azole compounds are used as antimicrobial drugs in clinic, for example, miconazole, clotrimazole and econazole are administered topically, while ketoconazole, itraconazole and fluconazole are useful in the treatment of systemic infections. Furthermore, it has been found that some azoles such as miconazole gave remarkable antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) (Guven et al., 2007). The widespread use of azole antimicrobial drugs led numerous efforts to develop some azole derivatives as new antimicrobial agents.

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The compounds containing dioxane rings are of interest for the introduction of a variety of substituents into common skeleton, novel transformations, and can provide new and general routes to a variety of organic molecules. There are two important characteristics of these compounds, namely (i) readily opening to alkyletenes either under thermal or photochemical conditions and (ii) the C–C double bond, if present in the dioxane ring, acts as the enol form of masked acylacetic acids, which are important building blocks in organic syntheses. Benzodioxane represents a series of synthetic and natural compounds of considerable medicinal importance. Compounds containing dioxane ring systems exhibited different biological activities like antimicrobial (Mallesha and Mohana, 2011), antihepatotoxic (Ahmed et al., 2003; Khan et al., 2006), α-adrenergic blocking agent (Chapleo et al., 1983) and anti-inflammatory (Vazquez et al., 1997).

Oxadiazoles are an important type of oxygen and nitrogen containing aromatic heterocyclic compounds, possess desirable electronic and charge-transport properties and the various functional groups are easily introduced into the structurally rigid oxadiazole ring. These characteristics resulted in the extensive potential applications of oxadiazole based derivatives in the field of medicinal chemistry. Various methods have been reported recently for the synthesis of 1,3,4-oxadiazoles (Adib et al., 2009; Ramazani and Rezaei, 2010; Vechorkin et al., 2010). A large number of biological activities are associated with oxadiazole derivatives such as antitumor (Aboraia et al., 2006), anti-inflammatory (Palaska et al., 2002; Amir and Shikha, 2004), antimicrobial (Jha et al., 2010; Gilani et al., 2010; Manjunatha et al., 2010; El-Azab, 2007; Mamolo et al., 2005; Saleh et al., 2004), antifungal (Chen et al., 2008) and anticonvulsant (Zarghi et al., 2005).

In continuation to extend our research on antimicrobial compounds, we designed a series of new 1,3,4-oxadiazole derivatives containing 1,4-benzodioxane ring system. Herein, we wish to report the synthesis, antibacterial and antifungal activities of some novel 1,3,4-oxadiazole derivatives.

2. Experimental protocols

2.1. Chemistry

The IR spectra were recorded on Brucker. The mass spectra were recorded on a Bruker daltronics high resolution mass spectrometer, the ^{1}H NMR (300 MHz) was recorded on Bruker DPX 300 spectrometer in CD_3OD and DMSO-d_6 using TMS as internal standard reference and chemical shifts are in δ ppm. Elemental analyses were performed on Elementar Vario EL III, Carlo Erba 1108. The melting points were determined by capillary method.

2.1.1. Synthesis of ethyl-l,4-benzodioxane-2-carboxylate (**1**)

Anhydrous potassium carbonate (50 g) was added in portions to a stirred solution of 55 g of catechol in 200 mL of dry acetone followed by the dropwise addition of 34.5 g of ethyl-2,3-dibromopropionate. Another 50 g of potassium carbonate and 34.5 g of the dibromoester were added similarly and this was repeated two times more using a total of 200 g of potassium carbonate and 137.5 g of ester. Stirring and refluxing was continued for another 15 h. The reaction mixture was then filtered and the solid was washed several times with acetone. The filtrate was concentrated to about 75 mL and the residue was diluted with 50 mL of cold water. The oily layer was separated from the aqueous layer; the latter was extracted repeatedly with ether. The combined oily layer and ether extracts were washed with water, dried over magnesium sulfate, and evaporated. The dark residue was distilled at 96–97 °C (0.1 mm/Hg) to yield 38 g of ester **1** as a colorless semisolid. ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 1.23 (3H, t, J = 7.1 Hz, CH_3-12), 4.20 (2H, q, J = 7.1, 5.7 Hz, CH_2-12), 4.30 (2H, d, J = 2.7, CH_2-3), 4.77 (1H, t, J = 2.7, CH-2), 6.84 (4H, m, Ar-H); FTIR cm^{-1}: 3052 (=C–H, aromatic), 1772 (C=O), 1653 (C=C), 1292 (C–O, ester).

2.1.2. Synthesis of 2,3-dihydro-1,4-benzodioxane-2-carbohydrazide (**2**)

To a solution of ethyl-1,4-benzodioxane-2-carboxylate (0.01 mol) in ethanol (20 mL), hydrazine hydrate (0.01 mol) was added and the reaction mixture was refluxed. The progress of the reaction was monitored by TLC. After the completion of the reaction (usually 16 h), the excess solvent was removed under reduced pressure. The reaction mixture was poured over crushed ice. The solid thus separated was filtered, dried and crystallized with methanol to give a white powder; m.p.: 110–112 °C; Yield: 80%; ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 3.91 (2H, brs, NH_2-13), 4.24 (1H, dd, J = 6.0, 11.4 Hz, H_a-3), 4.46 (1H, dd, J = 6.0, 11.4 Hz, H_b-3), 4.78 (1H, d, J = 6.0, CH_2), 6.91 (4H, m, Ar-H), 7.78 (1H, s, NH-12); FTIR (KBr) cm^{-1}: 3052 (=C–H, aromatic), 1772 (C=O), 1673 (C=C), 1259 (–NH_2), 1195 (–NH), 758 (C=C); Anal Calcd. for $C_9H_{10}N_2O_3$ (%): C, 55.67; H, 5.19; N, 14.43; O, 24.72. Found: C, 55.37; H, 5.02; N, 14.67; O, 24.73.

2.1.3. Synthesis of 2-(phenyl)-5-(2,3-dihydro-1,4-benzodioxane-2-yl)-1,3,4-oxadiazole (**3a**)

A solution of 0.01 mol of 2,3-dihydro-1,4-benzodioxane-2-carbohydrazide, 0.01 mol benzoic acid and 5 mL of $POCl_3$ was refluxed with stirring for 6–7 h. The reaction mixture was cooled and poured over crushed ice. The precipitate thus obtained was filtered washed with sodium bicarbonate, dried and recrystallised with benzene: methanol. ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 4.33 (2H, m, unresolved doublet, CH_2-3), 5.02 (1H, brs, unresolved doublet, CH-2), 6.88–7.67 (4H, m, Ar-H, ring A), 7.87 (5H, m, Ar-H, ring B); FTIR (KBr) cm^{-1}: 3162 (=C–H, aromatic), 1678 (C=C), 1492 (C=N), 1078 (C–O–C). HR-MS (m/z): 281.1970 $[MH]^+$ (Calcd. for $C_{16}H_{12}N_2O_3$, 280.2782); Anal Calcd. for $C_{16}H_{12}N_2O_3$ (%): C, 68.56; H, 4.32; N, 9.99; O, 17.13; Found: C, 68.46; H, 4.42; N, 10.05; O, 17.12.

2.1.4. 2-(2-Bromo-phenyl)-5-(2,3-dihydro-1,4-benzodioxane-2-yl)-1,3,4-oxadiazole (**3b**)

^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 4.24 (2H, m, unresolved doublet, CH_2-3), 5.15 (1H, brs, unresolved doublet, CH_2-2), 6.67–7.91 (4H, m, Ar-H, ring A), 7.65 (5H, m, Ar-H, ring B); FTIR (KBr) cm^{-1}: 3069 (=C–H, aromatic), 1670 (C=C), 1485 (C=N), 1067 (C–O–C), 756 (C-Br); Anal Calcd. for $C_{16}H_{11}BrN_2O_3$ (%): C, 53.50; H, 3.09; N, 7.80; O, 13.36; Found: C, 53.43; H, 3.19; N, 7.67; O, 13.43.

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