Journal of Saudi Chemical Society (2015) **19**, 392–398

King Saud University

Journal of Saudi Chemical Society

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ORIGINAL ARTICLE

Synthesis, characterization and comparative study the microbial activity of some heterocyclic compounds containing oxazole and benzothiazole moieties

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Received 10 March 2012; accepted 27 April 2012
Available online 9 May 2012

KEYWORDS

Oxazole;
Benzothiazole;
Microbial activity

Abstract New derivatives of five member heterocyclic compounds containing oxazole and benzothiazole rings are reported. These compounds have been characterized by elemental analysis, FT-IR and ^{1}H NMR spectroscopy. This study was designed to show the microbial activity difference for two types of five member heterocyclic rings. The compounds were screened for antibacterial activity against *Escherichia coli, Staphylococcus aureus and Pseudomonas aerugenosa* in nutrient agar medium, and for antifungal activity against *Aspergillus niger and Candida albicans* in Sabouraud's dextrose agar medium. The results show that the derivatives containing benzothiazole moiety are more active than the derivatives containing oxazole moiety.

1. Introduction

Chemistry of heterocyclic compounds is one of the leading lines of investigations in the organic chemistry. Heterocyclic compounds are widely distributed in nature and are essential for life. They play a vital role in the metabolism of all living cells. There are vast numbers of pharmacologically active heterocyclic compounds, many of which are a regular clinical use. Nitrogen, sulphur and oxygen containing five member heterocyclic compounds have occupied enormous significance in the field of drug discovery process. We report herein the synthesis and comparative the microbial activities for two types of five member heterocyclic derivatives (oxazole and benzothiazole).

Oxazoles play a vital role in the manufacture of various biologically active drugs as brain-derived neurotrophic factor inducers (Maekawa et al., 2003), analgesic (Serrano et al., 1995), trypanocidal activity (Pinto et al., 1997), antimitotic agents with pro-apoptotic activity (Uckun, 2001), antifungal activity (Kunes et al., 2001), anti-inflammatory (Kaspady et al., 2009), antidepressant (Elmegeed et al., 2010), anticancer (Liu et al., 2009), antimicrobial, antidiabetic and antiobesity. (Mesaik et al., 2004; Khan et al., 2006).

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jscs.2012.04.010

On the other hand, benzothiazoles are heterocyclic compounds with multiple applications and, although they have been known from long ago to be biologically active (Kaur et al., 2010; Prabhu et al., 2011; Yadav et al., 2011). It is bicyclic ring system with diverse chemical reactivity and broad spectrum of biological activities such as antimicrobial, antitumor, anti-inflammatory, antilieshmanial and antifungal (Latrofa et al., 2005; Shi et al., 2001; Paramashivappa et al., 2003; Delmas et al., 2004; Sonwane et al., 2008). They show, for example, very intensive antitumor activity, especially the phenyl-substituted benzothiazole (Bradshaw et al., 2002). 2-substituted-6-nitro- and 6-aminobenzothiazole (Delmas et al., 2002), fluorobenzothiazoles (Pattan et al., 2002), and Schiff bases derived from benzothiazoles (Mahmood-ul-Hasan et al., 2002) show microbiological activity.

In continuation of the work on the synthesis of biologically important heterocyclic compounds (Tomi et al., 2011; Tomi et al., in press), herein is reported the synthesis and biological activities of some oxazole and benzothiazole derivatives.

2. Experimental

All the chemicals used were procured from Sigma–Aldrich and Fluka, and used without further purification. Melting points were determined in open capillary tubes on Electrothermal capillary apparatus and are uncorrected, Elemental analysis (C, H, and N) were carried out using a Perkin–Elmer model 2400 instrument, IR spectra were recorded on Fourier Transform IR spectrophotometer (Shimadzu 8400S) using KBr disc method. ^{1}H NMR spectra were recorded in DMSO-d_6 on Bruker spectrometer model ultra shield at 300 MHz using TMS as an internal reference standard.

*2.1. 4-Methoxy-hippuric acid (**1A**)*

Glysine (1.5 g, 0.02 mol) in 1N sodium hydroxide solution (20 mL) was cooled at 0–5 °C and the cold solution was added dropwise to a solution of 4-methoxybenzoyl chloride (3.41 g, 0.02 mol) in chloroform (30 mL). The reaction mixture was continued under stirring for an additional 1 h. The aqueous layer was separated and acidified with 2N hydrochloric acid. The product **1A** was collected by filtration and recrystallized from ethanol as colorless needles. Yield (83%); mp: 178–180 °C; FT-IR (KBr disk, cm^{-1}) 3366 (N–H), 3190–2534 (O–H, carboxylic), 2933, 2847 (C–H aliph.) 1743 (C═O, acid), 1625 (C═O, amide); ^{1}H NMR (DMSO-d_6, 300 MHz, δ) 8.65–8.63 (t, 1H, NH), 7.86–7.79 (dd, 2H, Ar.H), 6.98–6.95 (dd, 2H, Ar.H), 3.86–3.84 (d, 2H, CH_2), 3.77 (s, 3H, OCH_3). Anal. Calcd. For $C_{10}H_{11}NO_4$ (209.07 g/mol): C, 57.41; H, 5.30; N, 6.70. Found: C, 57.44; H, 5.26; N, 6.72.

*2.2. 2-(4-Methoxyphenyl)-5-oxazolones (**2A**)*

The hippuric acid (**1A**) was treated with equimolar quantity of ethyl chloroformate in the presence of *N*-methylmorpholine in methylene chloride at room temperature to afford the corresponding azlactone (**2A**) as off white needles. Yield (80%); mp: 86–88 °C; FT-IR (KBr disk, cm^{-1}) 2944, 2843 (C–H aliph.), 1785 (C═O), 1633 (C═N); ^{1}H NMR (DMSO-d_6, 300 MHz, δ) 7.85–7.76 (dd, 2H, Ar.H), 7.07–7.01 (dd, 2H, Ar.H), 4.36 (s, 2H, CH_2), 3.87 (s, 3H, OCH_3). Anal. Calcd. For $C_{10}H_9NO_3$ (191.06 g/mol): C, 62.82; H, 4.74; N, 7.33. Found: C, 62.76; H, 4.69; N, 7.36.

*2.3. 2-Aza-1-(4-methoxyphenyl)-4-toluel-1,4-butanediones (**3A**)*

The azlactone (**2A**) (0.96 g, 0.005 mol) in (25 mL) of toluene in excess was treated portionwise with (2.00 g, 0.015 mol) of anhydrous aluminum chloride at room temperature. After the addition, the reaction mixture was continued under stirring for 24 h. The reaction mixture was then poured over crushed ice with hydrochloric acid and the organic component was extracted with methylene chloride, washed with water and dried. The solvent was removed to yield the crude azadiketones (**3A**), which was crystallized from ethanol as deep gray powder. Yield (71%); mp: >250 °C; FT-IR (KBr disk, cm^{-1}) 3282 (N–H), 2956, 2841 (C–H aliph.), 1691 (C═O ketone), 1634 (C═O amide); ^{1}H NMR (DMSO-d_6, 300 MHz, δ) 8.70–8.59 (t, 1H, NH), 7.93–7.91 (dd, 2H, Ar.H of phenyl attached CH_3), 7.74–7.72 (dd, 2H, Ar.H of phenyl attached OCH_3), 7.36–7.34 (dd, 2H, Ar.H of phenyl attached CH_3), 6.83–6.81 (dd, 2H, Ar.H of phenyl attached OCH_3), 4.10–4.08 (d, 2H, CH_2), 3.93 (s, 3H, OCH_3), 2.38 (s, 3H, CH_3). Anal. Calcd. For $C_{17}H_{17}NO_3$ (283.12 g/mol): C, 72.07; H, 6.05; N, 4.94. Found: C, 72.01; H, 6.10; N, 4.89.

*2.4. 2-(4-Methylphenyl)-5-(4-methoxyphenyl)-1,3-oxazole (**4A**)*

The compound (**3A**) (2.83 g, 0.01 mol) was refluxed with (10 mL) phosphorus oxychloride for 48 h. and the reaction mixture was then treated with ice water and the precipitate was washed with 10% sodium bicarbonate solution and water, dried and recrystalized in ethanol to afford the crude oxazole (**4A**) in 77% yield, mp: 145–147 °C; FT-IR (KBr disk, cm^{-1}) 2924, 2854 (C–H aliph.), 1641 (C═N), 1244, 1078 (C–O–C); ^{1}H NMR (DMSO-d_6, 300 MHz, δ) 8.07–8.05 (dd, 2H, Ar.H of phenyl attached CH_3), 7.73–7.71 (dd, 2H, Ar.H of phenyl attached OCH_3), 7.32–7.34 (dd, 2H, Ar.H of phenyl attached CH_3), 7.60 (s, 1H, –C═H of oxazole moiety), 6.92–6.90 (dd, 2H, Ar.H of phenyl attached OCH_3), 3.89 (s, 3H, OCH_3), 2.34 (s, 3H, CH_3). Anal. Calcd. For $C_{17}H_{15}NO_2$ (265.11 g/mol): C, 76.96; H, 5.70; N, 5.28. Found: C, 76.89; H, 5.65; N, 5.33.

*2.5. 2-(4-Methylphenyl)-5-(4-hydroxyphenyl)-1,3-oxazole (**5A**)*

To Compound (**4A**) (0.63 g, 0.00238 mol) suspended in dry benzene (25 mL), (1.00 g, 0.0075 mol) of anhydrous aluminum chloride was added. The reaction mixture was refluxed for 24 h. The solvent was evaporated and the residue was poured into ice-water. The solid was collected and purified by dissolving in (30 mL) of 10% sodium hydroxide solution. The reminder solid was filtered and the filtrate was neutralized with 10% hydrochloric acid. The crude product precipitate during the neutralization washed with water several times and dried to give the desired Compound (**5A**). Yield (71%); mp: >250 °C (decom.); FT-IR (KBr disk, cm^{-1}) 3479–3178 (broad O–H), 2922, 2852 (C–H aliph.), 1649 (C═N), 1240, 1057 (C–O–C); ^{1}H NMR (DMSO-d_6, 300 MHz, δ) 7.79–7.71 (dd, 2H, Ar.H