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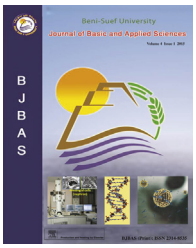

Full Length Article

Synthesis and antimicrobial evaluation of certain purine, benzothiazole and thiazole systems substituted with dialkylaminoalkyl-o-cresols

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ABSTRACT

Novel series of dialkylaminoalkyl-o-cresols incorporated with purine nucleus **2a–b**, benzothiazole nucleus **5a–b**, **8a–b** and thiazole nucleus **11a–d**, **13a–d** were synthesized through Mannich reaction. Structures of the newly synthesized compounds have been deduced on the basis of elemental analysis and spectral data. Antimicrobial activity evaluation was carried out for all synthesized compounds; most of them exerted comparable activity to ciprofloxacin and flucanazole. The thiazole derivatives **11a**, **13c**, **13d** are the most potent compounds.

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1. Introduction

The resistance to antimicrobial drugs is widespread; there is an increasing need for identification of novel structure leads that may be of use in designing new, potent and less toxic antimicrobial agents. The previous literature survey revealed that certain phenolic Mannich bases (Magarian and Sorenson, 1976; Pernak et al., 1999), purine (Bakkestuen et al., 2000; Gundersen et al., 2002), benzothiazole (Abdel-Rahman and Morsy, 2007; Hilal et al., 2006; Vicini et al., 2008; Yamazaki et al., 2005) and thiazole (Bozdag-Dundar et al., 2007; Karegoudar et al., 2008; Ozdemir et al., 2007; Vicini et al., 2006) derivatives exhibited significant antibacterial and antifungal activities. At the same time, presence of azo group (Bondock et al., 2007) or azomethine group (Chohan et al., 2003) enhances the antimicrobial activity of the above mentioned nuclei. Also, the introduction of an amidic linkage into the heteroaromatic ring systems increases its biological activity by increasing the lipophilicity of these compounds which facilitates their penetration into the bacterial and fungal cells (Turan-Zitouni et al., 2004, 2005; Zimenkovskii et al., 2006). In view of the aforementioned findings, it was

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interesting to make a link between phenolic Mannich bases and some heteroaromatic ring systems *via* one of the above pharmacophoric groups. Accordingly and in continuation of our previous work (Abdellatif et al., 2014), we now report combination between purine nucleus with dialkylamino-*o*-cresol moieties *via* an amidic linkage (**2a–b**), or an incorporation of a benzothiazole ring system with phenolic Mannich bases through the pharmacophoric azomethine group (**5a–b**) or *via* an amidic linkage (**8a–b**). Moreover, a number of substituted thiazoles incorporated with dialkylamino-*o*-cresol moieties *via* azo group (**11a–d**, **13a–d**) with the aim that the target compounds may show good antimicrobial activity.

2. Experimental

2.1. Chemistry

2.1.1. General

Melting points were determined on a Griffin apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu 435 Spectrometer, using KBr discs and values were represented in cm-1. ^{1}H NMR spectra were measured on a Varian Gemini 300 MHz spectrometer in $CDCl_3$ or DMSO-d_6 with TMS as the internal standard. Mass spectra were run on Hewlett Packard 5988 spectrometer. Microanalyses were performed for C, H, N (Micro Analytical Centre, Cairo University, Egypt) and were within± 0.4% of theoretical values. Progress of the reactions was monitored by TLC using TLC sheets precoated with UV fluorescent silica gel MERCK 60 F 254 that was visualized by UV lamp. 2-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-yl)-*N*-(4-hydroxyphenyl)acetamide (**1**), 4-benzothiazol-2-yl-phenylamine (**3**) (Shi et al., 1996), 4-[(4-benzothiazol-2-yl-phenylimino)-methyl]-phenol (**4**) (Nagarajan et al., 2010), *N*-(4-benzothiazol-2-yl-phenyl)-2-chloroacetamide (**6**) (Chua et al., 1999; Pan et al., 2013), 4-phenylthiazol-2-ylamine (**9a**) (Dodson and King, 1945), 4-(4-methylphenyl)thiazol-2-ylamine (**9b**) (King and Hlavacek, 1950), 2-amino-4-methylthiazole-5-carboxylic acid ethyl ester (**9c**) (Dodson and King, 1945), 4-(4-phenylthiazol-2-ylazo) phenol (**10a**), and 2-(4-hydroxy-phenylazo)-4-methylthiazole-5-carboxylic acid ethyl ester (**10b**) were prepared according to reported procedures.

*2.1.1.1. N-(3-Diethylaminomethyl-4-hydroxyphenyl)-2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-yl)acetamide (**2a**).* To a solution of the purine derivative **1** (1.64 gm, 5 mmol) in dimethylformamide (15 mL), a mixture of diethylamine (6 mmol) and formaldehyde solution (37–40%) (0.62 mL, 7.5 mmol) in glacial acetic acid (5 mL) was added drop wise. After complete addition, the reaction mixture was stirred at room temperature for 12 h then poured onto ice-cooled water. The formed precipitate was filtered, dried and crystallized from dimethylformamide/water to afford 1.39 g of **2a** (67% yield); mp 249–250°; IR (cm^{-1}) 3306, 3257 (OH & NH), 3162, 3086 (CH aromatic), 2984, 2878 (CH aliphatic), 1703, 1651 (amidic C=O), 1555 (C=N), 1518 (C=C aromatic); ^{1}H NMR (DMSO-d_6) δ 0.95 (t, J = 7.5 *Hz*, 6H, $\underline{H}_3C-H_2C-N-CH_2-C\underline{H}_3$), 2.74 (q, J = 7.5 *Hz*, 4H, $H_3C-\underline{H}_2C-N-C\underline{H}_2-CH_3$), 3.17 (s, 3H, purinyl N3–$C\underline{H}_3$), 3.42 (s, 3H, purinyl N1–$C\underline{H}_3$), 3.55 (s, 2H, $C\underline{H}_2N$); 5.13 (s, 2H, $C\underline{H}_2CO$), 6.68–6.72 (m, 2H, phenyl H-2, H-6), 7.35 (d, J = 8.1 *Hz*, 1H, phenyl H-5), 8.04 (s, 1H, purinyl H-8), 9.33 (s, 1H, N$\underline{H}$, D_2O exchangeable), 10.17 (s, 1H, O$\underline{H}$, D_2O exchangeable); EIMS 414 (M$^+$). Anal. Calcd for $C_{20}H_{26}N_6O_4$: C, 57.96; H, 6.32; N, 20.28. Found: C, 58.22; H, 6.29; N, 20.40.

*2.1.1.2. 2-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-yl)-N-[4-hydroxy-3-(4-methylpiperidin-1-ylmethyl)-phenyl]-acetamide (**2b**).* The title compound **2b** was synthesized, using a similar procedure to that described for the preparation of **2a**, by using 4-methylpiperidine in place of diethylamine, in 80% yield as a pale brown powder; mp 188–190 °C; IR (cm^{-1}) 3300, 3200 (OH & NH), 3160, 3058 (CH aromatic), 2948, 2809 (CH aliphatic), 1705, 1659 (amidic C=O), 1548 (C=N), 1495 (C=C aromatic); ^{1}H NMR (DMSO-d_6) δ 0.92 (d, J = 7.2 *Hz*, 3H, piperidine $C\underline{H}_3$), 1.27–1.43 (m, 5H, piperidinyl H-3, H-4, H-5), 2.13 (t, J = 5.4 *Hz*, 4H, piperidinyl H-2, H-6), 3.41 (s, 3H, purinyl N3–$C\underline{H}_3$), 3.58 (s, 3H, purinyl N1–$C\underline{H}_3$), 3.66 (s, 2H, $C\underline{H}_2N$), 4.99 (s, 2H, $C\underline{H}_2CO$), 6.70–6.73 (m, 2H, phenyl H-2, H-6), 7.33 (d, J = 8.1 *Hz*, 1H, phenyl H-5), 7.77 (s, 1H, purinyl H-8), 9.31 (s, 1H, N$\underline{H}$, D_2O exchangeable), 10.41 (s, 1H, O$\underline{H}$, D_2O exchangeable); EIMS 441 (M + 1). Anal. Calcd for $C_{22}H_{28}N_6O_4$: C, 59.99; H, 6.41; N, 19.08. Found: C, 60.14; H, 6.19; N, 18.84.

*2.1.1.3. 4-[(4-benzothiazol-2-yl-phenylimino)methyl]-2-dimethylaminomethylphenol (**5a**).* A mixture of dimethylamine (0.005 mol) and formaldehyde solution (37–40%) (0.4 mL, 0.005 mol) in absolute ethanol (5 mL) was added to a solution of 4-[(4-benzothiazol-2-yl-phenylimino)-methyl]-phenol (**4**) (1.65 gm, 0.005 mol) in absolute ethanol (10 mL). The reaction mixture was heated under reflux for 5 h, allowed to cool to room temperature and poured onto ice cooled water. The formed precipitate was filtered off, dried and crystallized from aqueous ethanol to give 1.94 g of **5a** (65% yield); mp 161–163 °C; IR (cm^{-1}) 3420 (OH), 3104, 2955 (CH aromatic), 2924, 2851 (CH aliphatic), 1594 (C=N), 1500 (C=C aromatic); ^{1}H NMR (DMSO-d_6) δ 2.27 (s, 6H, $\underline{H}_3C-N-C\underline{H}_3$), 3.58 (s, 2H, $C\underline{H}_2N$), 7.34–8.12 (m, 12H, phenol H-3, H-5, H-6, phenyl H-2, H-3, H-5, H-6, benzothiazolyl H-4, H-5, H-6, H-7, N=C$\underline{H}$), 10.27 (s, 1H, O$\underline{H}$, D_2O exchangeable); EIMS 387 (M$^+$). Anal. Calcd for $C_{23}H_{21}N_3OS$: C, 71.29; H, 5.46; N, 10.84. Found: C, 70.98; H, 5.29; N, 10.58.

*2.1.1.4. 4-[(4-benzothiazol-2-yl-phenylimino)methyl]-2-(piperidin-1-ylmethyl)phenol (**5b**).* The title compound **5b** was synthesized, using a similar procedure to that described for the preparation of **5a**, by using piperidine in place of dimethylamine, in 62% yield as a pale brown powder; mp 110–112 °C; IR (cm^{-1}) 3420 (OH), 3096, 3027 (CH aromatic), 2932, 2801 (CH aliphatic), 1596 (C=N), 1516 (C=C aromatic); ^{1}H NMR (DMSO-d_6) δ 1.00–1.12 (m, 6H, piperidine H-3, H-4, H-5), 2.22 (t, 4H, J = 5.1 *Hz*, piperidine H-2, H-6), 3.96 (s, 2H, $C\underline{H}_2N$), 7.34–8.12 (m, 12H, phenol H-3, H-5, H-6, phenyl H-2, H-3, H-5, H-6, benzothiazolyl H-4, H-5, H-6, H-7, N=C$\underline{H}$), 10.27 (s, 1H, O$\underline{H}$, D_2O exchangeable); EIMS 427 (M$^+$). Anal. Calcd for $C_{26}H_{25}N_3OS$: C, 73.04; H, 5.89; N, 9.83. Found: C, 73.23; H, 5.73; N, 10.13.

*2.1.1.5. N-(4-Benzothiazol-2-ylphenyl)-2-(4-hydroxyphenylamino)acetamide (**7**).* A mixture of *N*-(4-benzothiazol-2-ylphenyl)-2-chloroacetamide (**6**) (1.5 g, 0.005 mol), 4-aminophenol (0.5 g, 0.005 mol) and few crystals

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