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Full Length Article

Synthesis of certain 8-quinolyloxy and/or carbocyclic nitrogenous compounds for microbiological testing

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ABSTRACT

Two new series as azosalicylic acid derivatives **IVa-l** and **Va-c** in addition to three series containing 8-quinolyloxy moiety **Xa-i**, **XIIa-n** and **XIVa-e** were synthesized for evaluation as antimicrobial compounds. Structures of the newly synthesized compounds have been deduced on the basis of elemental analysis and spectral data. Antimicrobial activity evaluation was carried using agar dilution technique; there was variability in the susceptibilities of the different organisms to the tested compounds. *Staphylococcus aureus* was the most resistant organism while *Candida albicans* was the most sensitive. Some compounds showed both antibacterial and antifungal activity, while others showed antibacterial activity with no antifungal activity and vice versa. Compound **XIVe** was the most active against both bacteria and fungi, while compounds **Xe**, **XIIf**, **XIVa** and **XIVd** showed a moderate activity.

1. Introduction

There is still an increasing need for identification of novel structure leads that may be of use in designing new, potent and less toxic antimicrobial agents due to the increase in resistance to the available antimicrobial drugs. The previous literature survey revealed that compounds containing *p*-aminobenzoic acid ester (Prasad et al., 2012) or hydrazide moieties (Somashekhar et al., 2013) were documented to have antimicrobial activity. Also, several hydrazones (Kucukguzel et al., 1999) and azomethine derivatives (Pahontu et al., 2015) of benzocaine showed a significant antimicrobial activity. At the same time, many salicylic acid derivatives were reported to have strong antimicrobial activity (Yiase et al., 2014). In view of these observations and in continuation of our previous work (Abdellatif et al., 2014), certain

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azo compounds **IVa-l** and **Va-c** having some of the above pharmacophoric moieties were synthesized with the aim that the products may show better antimicrobial activity.

On the other hand, compounds having both quinoline and benzocaine moieties demonstrated a significant microbicidal activity (Khandarkar et al., 2013). The presence of halo-substituted aromatic residues in heterocyclic antifungal drugs was found to be very important for its activity (Baseer et al., 2011). Also, the presence of 5-nitro group in nitrofuran derivatives was indicated to be required for antibacterial activity (Emami et al., 2013). Moreover, the remarkable antibacterial activity of some nitrogenous heterocycles containing terminal acetamido groups was attributed to the increased lipophilicity of these compounds, which facilitate its penetration into the bacterial and fungal cells (Shams et al., 2011). This encouraged us to synthesize a number of derivatives **Xa-i** and **XIIa-n** having in common 8-quinolyloxy moiety.

Additionally, quinoline compounds having sulfonamide moiety showed a significant microbicidal activity (Srivatava and Kumar, 2013). Based on these facts, a number of target compounds **XIVa-e** were synthesized having a combination of sulfonamide group together with the pharmacophoric 8-quinolyl acetate moiety.

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}. ^1H 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. 5-(4-Ethoxycarbonylphenylazo)-2-hydroxybenzoic acid (**II**) (Raicharan and Guha, 1955), (quinol-8-yloxy)-acetic acid (**VI**) (Kidwai et al., 2000), quinol-8-yloxy sodium salt (**VII**) (Chandrasekhare and Bhat, 1995), ethyl (quinol-8-yloxy) acetate (**VIII**) (Rabhofer et al., 1979), (quinol-8-yloxy)-acetic acid hydrazide (**IX**) (Soliman and Hammouda, 1979), *N*-aryl-2-chloroacetamides **XIa-n** (El-Moghazy, 1992), and (quinol-8-yl) α-chloroacetate (**XIII**) (El-zohry et al., 1992) were prepared according to reported procedures.

2.1.2. 5-(4-Hydrazinocarbonylphenylazo)-2-hydroxybenzoic acid (III)

A mixture of 5-(4-ethoxycarbonylphenylazo)-2-hydroxybenzoic acid (**II**) (3.14 g, 0.01 mole) and hydrazine hydrate (99%, 0.01 mole) in absolute ethanol (50 mL) was heated under reflux for 6 hours. After cooling to room temperature, the separated solid was filtered and then dried. Crystallization of the product from ethanol afforded the title compound **III** as dark orange-red crystals. m.p. 230–2 °C, Yield : 2.04 g, 68%; IR (cm^{-1}) 3316, 3166 (NH_2), 3448–2833 (OH of COOH, OH phenolic, NH amidic, CH str. aromatic), 1712 (C═O of COOH), 1686 (C═O amidic), 1606 (N═N), 1529 (C═C aromatic); ^1H NMR (DMSO-d_6) δ 4.24–4.37 (m, 3H, OH, NH_2, D_2O exchangeable), 7.70–7.75 (d, 2H, H_3, H_4 of salicyl group), 7.82 (s, 1H, NH, D_2O exchangeable), 7.88–7.91 (d, 2H, H_b of *p*-phenylene moiety), 8.09–8.13 (d, 2H, H_a of *p*-phenylene moiety), 8.30 (s, 1H, H_6 of salicyl group), 10.40 (s, 1H, COO<u>H</u>, D_2O exchangeable); EIMS 300 (M^+). Anal. calcd for $C_{14}H_{12}N_4O_4$: C, 56.00; H, 4.03; N, 18.66. Found: C, 56.34; H, 4.25; N, 18.37.

2.1.3. General procedure for synthesis of 5-[4-(N^2-arylidenehydrazinocarbonyl)phenylazo]-2-hydroxybenzoic acids (IVa-l)

To a solution of 5-(4-hydrazinocarbonylphenylazo)-2-hydroxybenzoic acid (**III**) (0.6 g, 0.002 mole) in absolute ethanol (20 mL), the appropriate aromatic carbonyl compound (0.002 mole) was added and the mixture was heated under reflux for 2 hours. After cooling to room temperature, the separated solid was filtered, washed with ethanol and crystallized from the suitable solvent. Physical and elemental analyses data for compounds **IVa-l** are listed in Table 1. Spectral data are listed below:

IR (KBr), ν cm^{-1} for IVa-l: 3500–2500 (OH phenolic, NH, COO<u>H</u>), 1680–1660 (C═O of COOH), 1660–1640 (C═O amidic), 1640–1620 (C═N), 1610–1590 (N═N).

^1H NMR (DMSO, δ ppm) for IVd: 6.83–6.93 (d, 2H, H_3, H_5 of *p*-hydroxybenzylidene moiety), 7.12–7.15 (d, 2H, H_b of *p*-phenylene moiety), 7.65 (s, 1H, C<u>H</u>═N), 7.71 (s, 1H, OH, D_2O exchangeable), 7.72–7.76 (d, 2H, H_3, H_4 of salicyl group), 7.90–7.94 (d, 2H, H_a of *p*-phenylene moiety), 8.05 (s, 1H, OH, D_2O exchangeable), 8.06–8.12 (d, 2H, H_2, H_6 of *p*-hydroxybenzylidene moiety), 8.34 (s, 1H, NH, D_2O exchangeable), 8.53 (s, 1H, H_6 of salicyl group), 9.76 (s, 1H, COO<u>H</u>, D_2O exchangeable).

^1H NMR (DMSO, δ ppm) for IVg: 7.28 (s, 1H, C<u>H</u>═N), 7.36–7.52 (m, 5H, 4H aromatic protons, NH, D_2O exchangeable), 7.72–7.92 (m, 7H, 6 aromatic protons, O<u>H</u>, D_2O exchangeable), 8.52–8.62 (m, 2H, 1 aromatic proton, COO<u>H</u>, D_2O exchangeable).

2.1.4. General procedure for synthesis of 2-hydroxy-5-(4-substituted-phenylazo)benzoic acid derivatives (Va-c)

To a solution of 5-(4-hydrazinocarbonylphenylazo)-2-hydroxybenzoic acid (**III**) (1.5 g, 0.005 mole) in glacial acetic acid (20 mL), the appropriate acid anhydride (0.005 mole) was added and the mixture was heated under reflux for 5 hours. After cooling, the reaction mixture was poured onto crushed ice (30 g). The precipitated solid was filtered, washed with water and crystallized from the appropriate solvent. Physical and elemental analyses data for compounds **Va-c** are listed in Table 2. Spectral data are listed below:

IR (KBr), ν cm^{-1} for Va-c: 3350–2740 (NH amidic, OH phenolic, COO<u>H</u>, CH str. aromatic), 1715 (C═O of <u>COO</u>H), 1680, 1663, 1603 (three amidic C═O), 1560 (N═N).

^1H NMR (DMSO, δ ppm) for Vc: 3.68 (s, 1H, NH, D_2O exchangeable), 4.33 (s, 1H, OH, D_2O exchangeable), 7.85–7.90 (m, 3H, aromatic protons), 7.92–7.95 (d, 2H, H_b of *p*-phenylene moiety), 8.05–8.09 (m, 3H, aromatic protons), 8.11–8.14