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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

Table 1 – Physical and elemental analyses data for compounds IVa-l.

IV	R^1	R^2	mp.(°C)/Crystal color	Cryst. solvent	Yield (%)	Mol. form. (mol. wt.)	Analyses %	
							Calcd.	Found
a	CH_3	H	105–7/reddish brown	Methanol	61	$C_{22}H_{18}N_4O_4$ (402.41)	C 65.66	65.58
							H 4.51	4.84
							N 13.92	14.25
b	H	*o*-OH	204–6/orange	Ethanol	69	$C_{21}H_{16}N_4O_5$ (404.38)	C 62.37	62.09
							H 3.99	4.01
							N 13.85	13.72
c	H	*m*-OH	140–2/yellow	Ethanol	66	$C_{21}H_{16}N_4O_5$ (404.38)	C 62.37	62.61
							H 3.99	3.82
							N 13.85	13.75
d	H	*p*-OH	156–8/red	Methanol	63	$C_{21}H_{16}N_4O_5$ (404.38)	C 62.37	62.48
							H 3.99	4.00
							N 13.85	13.76
e	H	*o*-Cl	139–41/yellowish orange	Ethanol	70	$C_{21}H_{15}ClN_4O_4$ (422.83)	C 59.65	59.46
							H 3.58	3.44
							N 13.25	13.55
f	H	*m*-Cl	136–8/light yellow	Ethanol	68	$C_{21}H_{15}ClN_4O_4$ (422.83)	C 59.65	60.01
							H 3.58	3.76
							N 13.25	12.97
g	H	*p*-Cl	200–2/yellow	Ethanol	65	$C_{21}H_{15}ClN_4O_4$ (422.83)	C 59.65	59.89
							H 3.58	3.68
							N 13.25	13.56
h	H	*p*-$N(CH_3)_2$	285–7/red	Ethanol	73	$C_{23}H_{21}N_5O_4$ (431.45)	C 64.03	64.06
							H 4.91	5.00
							N 16.23	16.54
i	H	*o*-NO_2	275–7/orange	Ethanol	73	$C_{21}H_{15}N_5O_6$ (433.38)	C 58.20	57.86
							H 3.49	3.20
							N 16.16	16.16
j	H	*m*-NO_2	180–2/yellowish orange	Methanol	63	$C_{21}H_{15}N_5O_6$ (433.38)	C 58.20	57.88
							H 3.49	3.35
							N 16.16	15.86
k	H	*p*-NO_2	280–2/light yellow	Ethanol	75	$C_{21}H_{15}N_5O_6$ (433.38)	C 58.20	58.31
							H 3.49	3.86
							N 16.16	16.14
l	H	*o*-Br	160–2/yellow	Benzene	72	$C_{21}H_{15}BrN_4O_4$ (467.28)	C 53.98	53.63
							H 3.24	3.22
							N 11.99	11.69

(d, 2H, H_a of *p*-phenylene moiety), 8.36 (s, 1H, H_6 of salicyl group), 10.22 (s, 1H, COOH, D_2O exchangeable).

2.1.5. *General procedure for synthesis of (quinol-8-yloxy)-acetic acid (N^2-arylidene) hydrazides (Xa-i)*

To a solution of (quinol-8-yloxy)-acetic acid hydrazide (**IX**) (0.002 mole) in absolute ethanol (20 mL), the appropriate aromatic aldehyde (0.002 mol) was added and the mixture was heated under reflux for 2 hours. On cooling, the separated solid was filtered, dried and crystallized from the suitable solvent. Physical and elemental analyses data for compounds **Xa-i** are listed in Table 3. Spectral data are listed below:

IR(KBr, ν cm^{-1}) for Xa-I: 3500–3400 NH and (OH in **Xa**), 3100–3000 (CH str. aromatic), 3000–2900 (CH str. aliphatic), 1650–1630 (C═O), 1610–1590 (C═N), 1200 (C—O—C).

Table 2 – Physical and elemental analyses data for compounds Va-c.

V	mp.(°C)	Cryst. solvent	Yield (%)	Mol. form. (mol. wt.)	Analyses %	
					Calcd.	Found
a	185–7	Aq. ethanol	65	$C_{18}H_{12}N_4O_6$ (380.32)	C 56.85	56.90
					H 3.18	3.50
					N 14.73	14.52
b	198–200	ethanol	61	$C_{18}H_{14}N_4O_6$ (382.33)	C 56.55	56.60
					H 3.69	3.60
					N 14.65	14.56
c	270–2	methanol	74	$C_{22}H_{14}N_4O_6$ (430.38)	C 61.40	61.65
					H 3.28	3.52
					N 13.02	12.96

Table 3 – Physical and elemental analyses data for compounds Xa-i.

X	R	mp.(°C)	Cryst. solvent	Yield (%)	Mol. form. (mol. wt.)	Analyses%	
						Calcd.	Found
a	*p*-OH	198–8	Methanol	62	$C_{18}H_{15}N_3O_3$ (321.34)	C 67.28	67.10
						H 4.71	4.39
						N 13.08	13.00
b	*o*-Cl	142–4	Ethanol	70	$C_{18}H_{14}ClN_3O_2$ (339.78)	C 63.63	63.30
						H 4.15	4.19
						N 12.37	12.51
c	*m*-Cl	110–1	Ethanol	54	$C_{18}H_{14}ClN_3O_2$ (339.78)	C 63.63	63.30
						H 4.15	4.23
						N 12.37	11.94
d	*o*-NO_2	170–1	Ethanol	64	$C_{18}H_{14}N_4O_4$ (350.33)	C 61.71	62.09
						H 4.03	4.01
						N 15.99	16.10
e	*m*-NO_2	207–9	Ethanol	60	$C_{18}H_{14}N_4O_4$ (350.33)	C 61.71	61.50
						H 4.03	4.22
						N 15.99	15.72
f	*p*-NO_2	306–8	Methanol	81	$C_{18}H_{14}N_4O_4$ (350.33)	C 61.71	61.69
						H 4.03	4.35
						N 15.99	16.31
g	*o*-Br	170–2	Benzene	74	$C_{18}H_{14}BrN_3O_2$ (384.23)	C 56.27	56.60
						H 3.67	3.51
						N 10.94	11.24
h	*m*-Br	158–60	Ethanol	76	$C_{18}H_{14}BrN_3O_2$ (384.23)	C 56.27	56.81
						H 3.67	3.60
						N 10.94	10.89
i	*p*-Br	207–8	Benzene	70	$C_{18}H_{14}BrN_3O_2$ (384.23)	C 56.27	56.30
						H 3.67	3.20
						N 10.94	10.91

^{1}H NMR (DMSO, δ ppm) for Xd: 3.31 (s, 2H, CH_2), 4.95 (s, 1H, CH=N), 5.30 (s, 1H, NH, D_2O exchangeable), 7.48–7.80 (m, 3H, H_5, H_6, H_7 of quinolyl group), 8.04–8.16 (m, 2H, H_4, H_6 of *o*-nitrobenzylidene moiety), 8.30–8.33 (d, 1H, H_3 of quinolyl group), 8.37–8.4 (d, 1H, H_5 of *o*-nitrobenzylidene moiety), 8.72–8.78 (d, 1H, H_4 of quinolyl group), 8.82–8.86 (d, 1H, H_3 of *o*-nitrobenzylidene moiety), 8.89–8.95 (d, 1H, H_2 of quinolyl group).

2.1.6. *General procedure for synthesis of N-Aryl-2-(quinol-8-yloxy) acetamides (XIIa-n)*

A mixture of the respective *N*-aryl-2-chloroacetamide **XIa-n** (0.01 mole), 8-quinoloxy sodium salt (**VII**) (1.67 g, 0.01 mole) and potassium carbonate (1.38 g, 0.01 mole) in dry dimethylformamide (15 mL) was heated at 100 °C for 3 hours. After cooling, the reaction mixture was poured onto crushed ice (20 g). The precipitated solid was filtered, washed with water, dried and crystallized from the suitable solvent. Physical and elemental analyses data for compounds **XIIa-n** are listed in Tables 4 and 5. Spectral data are listed below:

IR (KBr, ν cm^{-1}) for XIIa-n: 3490–3270 NH and (COOH of **XIIk**), 3016 (CH str. aromatic), 2920 (CH str. aliphatic), 1713 (C=O of COOH in **XIIk**), 1708 (C=O of $COOC_2H_5$ in **XIIn**), 1690–1665 (C=O amidic), 1620 (C=O of $COCH_3$ in **XIIj**).

^{1}H NMR (CDCl$_3$, δ ppm) for XIId: 2.14 (s, 6H, 2 CH_3), 5.02 (s, 2H, OCH_2), 7.04–7.14 (m, 3H, H_5, H_6, H_7 of quinolyl group), 7.27–7.33 (m, 2H, H_3, H_5 of dimethylphenyl group), 7.46–7.50 (m, 1H, H_4 of dimethylphenyl group), 7.52–7.56 (m, 1H, H_3 of quinolyl group), 8.20–8.23 (dd, 1H, H_4 of quinolyl group), 8.87–8.89 (dd, 1H, H_2 of quinolyl group), 9.45 (s, 1H, NH, D_2O exchangeable).

^{1}H NMR (CDCl$_3$, δ ppm) for XIIi: 4.9 (s, 2H, O—CH_2), 7.08–7.12 (d, 1H, H_5 of *m*-chlorophenyl moiety), 7.23–7.31 (m, 4H, H_3, H_5, H_6, H_7 of quinolyl group), 7.51–7.66 (m, 2H, H_4, H_6 of *m*-chlorophenyl moiety), 7.85 (s, 1H, H_2 of *m*-chlorophenyl moiety), 8.23–8.27 (d, 1H, H_4 of quinolyl group), 8.97–8.99 (d, 1H, H_2 of quinolyl group), 9.81 (s, 1H, NH, D_2O exchangeable).

2.1.7. *General procedure for synthesis of quinol-8-yl [4-(arylsulfamoyl)-phenyl]-aminoacetate (XIVa-e)*

To a mixture of 8-quinolyl α-chloroacetate (**XIII**) (1.1 g, 0.005 mole) and anhydrous potassium carbonate (0.69 g, 0.005 mole) in dry acetone (15 mL), the appropriate sulfonamide (0.005 mole) was added. The reaction mixture was then heated under reflux for 24 hours. After cooling to room temperature, the mixture was filtered and the filtrate was evaporated under reduced pressure and the crude product was crystallized from the suitable solvent to afford **XIVa-e**. Physical and elemental analyses data for compounds **XIVa-e** are listed in Table 6. Spectral data are listed below:

IR (KBr, ν cm^{-1}) for XIVa-e: 3500–3200 (2 NH) and (NH_2 of **XIVa**, **c** and NH of imine moiety in **XIVc**), 1660 (C=O of $COCH_3$ in **XIVb**), 1650–1600 (C=O of ester moiety), 1530 (C=N in **XIVc**), 1336, 1152 (S=O of SO_2).

^{1}H NMR (DMSO, δ ppm) for XIVa: 3.45 (s, 2H, CH_2), 5.86 (s, 1H, NH, D_2O exchangeable), 7.08–7.13 (d, 2H, H_b of *p*-phenylene moiety), 7.36–7.56 (m, 6H, H_3, H_5, H_6, H_7 of quinolyl group, $2H_a$ of *p*-phenylene moiety), 8.28–8.33 (d, 1H, H_4 of quinolyl

Table 4 – Physical and elemental analyses data for compounds XIIa-f.

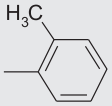
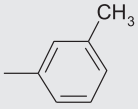
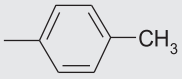
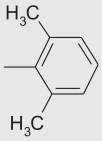
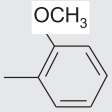
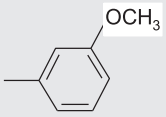
XII	Ar	mp.(°C)	Cryst. solvent	Yield (%)	Mol. form. (mol. wt.)	Analyses %	
						Calcd.	Found
a		95–6	Ethanol	66	$C_{18}H_{16}N_2O_2$ (292.34)	C 73.95 H 5.52 N 9.58	73.66 6.00 9.57
b		103–5	Ethanol	53	$C_{18}H_{16}N_2O_2$ (292.34)	C 73.95 H 5.52 N 9.58	73.86 5.70 9.52
c		99–100	Ethanol	64	$C_{18}H_{16}N_2O_2$ (292.34)	C 73.95 H 5.52 N 9.58	73.66 5.70 9.46
d		197–9	Aq. ethanol	55	$C_{19}H_{18}N_2O_2$ (306.37)	C 74.49 H 5.92 N 9.14	74.20 6.00 9.12
e		109–11	Aq. ethanol	52	$C_{18}H_{16}N_2O_3$ (308.34)	C 70.12 H 5.23 N 9.09	69.90 5.20 8.80
f		106–8	Aq. ethanol	59	$C_{18}H_{16}N_2O_3$ (308.34)	C 70.12 H 5.23 N 9.09	69.88 5.38 9.03

Table 5 – Physical and elemental analyses data for compounds XIIg-n.

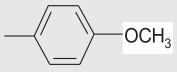
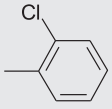
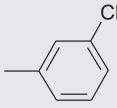
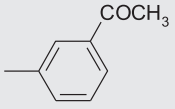
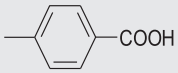
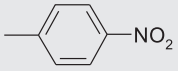
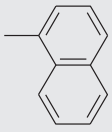
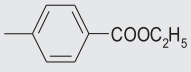
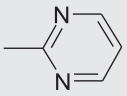
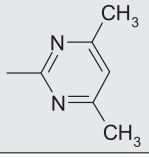
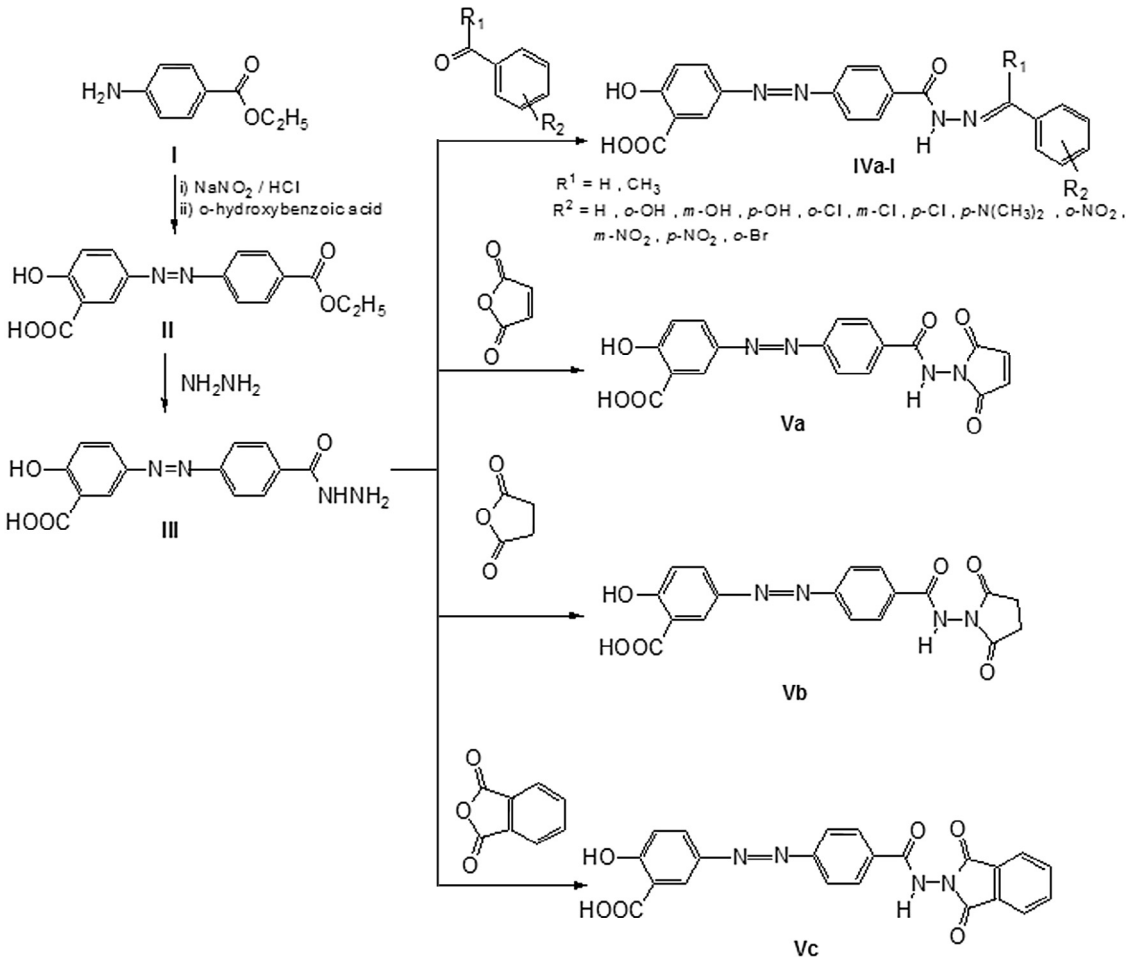
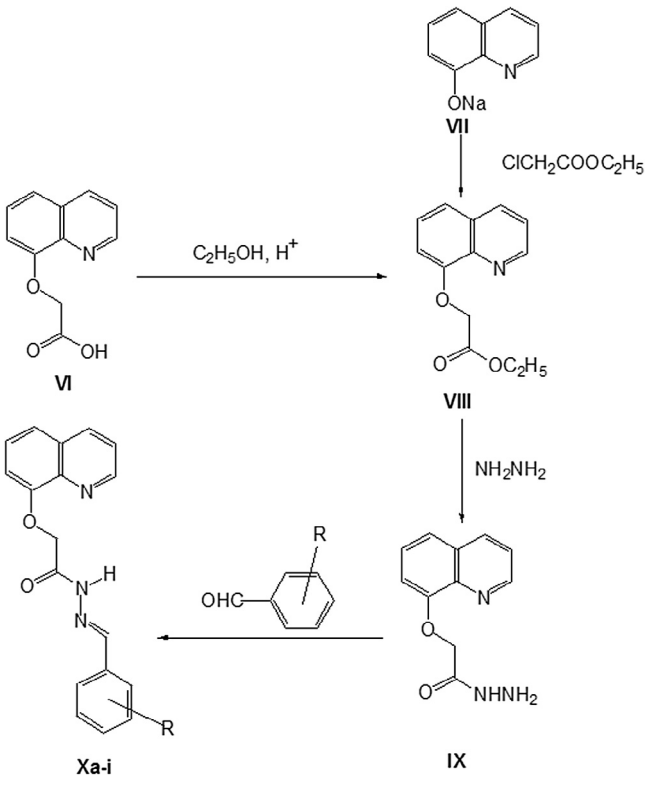
XII	Ar	mp.(°C)	Cryst. solvent	Yield (%)	Mol. form. (mol. wt.)	Analyses %	
						Calcd.	Found
g		114–6	Aq. ethanol	66	$C_{18}H_{16}N_2O_3$ (308.34)	C 70.12 H 5.23 N 9.09	69.94 5.05 8.93
h		178–9	Methanol	62	$C_{17}H_{13}ClN_2O_2$ (312.76)	C 65.29 H 4.19 N 8.96	65.08 4.37 8.89
i		197–9	Ethanol	57	$C_{17}H_{13}ClN_2O_2$ (312.76)	C 65.29 H 4.19 N 8.96	65.00 4.03 8.91
j		110–2	n-Hexane	70	$C_{19}H_{16}N_2O_3$ (320.35)	C 71.24 H 5.03 N 8.74	70.97 4.61 8.68
k		>300	Ethanol	45	$C_{18}H_{14}N_2O_4$ (322.32)	C 67.08 H 4.38 N 8.69	66.76 4.59 8.70
l		196–8	Ethanol	68	$C_{17}H_{13}N_3O_4$ (323.31)	C 63.16 H 4.05 N 12.99	63.30 4.23 12.86
m		274–5	n-Hexane	72	$C_{21}H_{16}N_2O_2$ (328.37)	C 76.81 H 4.91 N 8.53	76.60 5.00 8.58
n		117–9	Aq. ethanol	74	$C_{20}H_{18}N_2O_4$ (350.38)	C 68.56 H 5.18 N 7.99	68.37 4.87 8.05

Table 6 – Physical and elemental analyses data for compounds XIVa-e.

XIV	R	mp.(°C)	Cryst. solvent	Yield (%)	Mol. form. (mol. wt.)	Analyses %	
						Calcd.	Found
a	H	137–9	Ethanol	61	$C_{17}H_{15}N_3O_4S$ (357.38)	C 57.13 H 4.23 N 11.76	57.60 4.20 11.50
b	$COCH_3$	207–9	Ethanol	55	$C_{19}H_{17}N_3O_5S$ (399.43)	C 57.13 H 4.29 N 10.52	57.60 4.20 10.32
c		146–8	Methanol	59	$C_{18}H_{17}N_5O_4S$ (399.43)	C 54.13 H 4.29 N 17.53	54.60 4.40 17.55
d		240–2	Ethanol	64	$C_{21}H_{17}N_5O_4S$ (435.47)	C 57.92 H 3.94 N 16.08	58.00 4.00 16.58
e		245–7	Methanol	57	$C_{23}H_{21}N_5O_4S$ (463.52)	C 59.60 H 4.57 N 15.11	59.79 4.27 14.99



Scheme 1 – Synthetic protocol for compounds IVa-l **and** Va-c.



R = *p*-OH, *o*-Cl, *m*-Cl, *o*-NO_2, *m*-NO_2, *p*-NO_2, *o*-Br, *m*-Br, *p*-Br.

Scheme 2 – Synthetic protocol for compounds Xa-i.

group), 8.82–8.85 (d, 1H, H_2 of quinolyl group), 9.87 (s, 2H, NH_2, D_2O exchangeable).

2.2. *Antimicrobial evaluation*

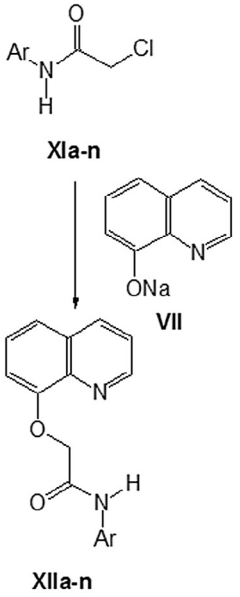
The antimicrobial activity was determined using the agar dilution technique using ofloxacin and clotrimazole as positive controls and the solvent, dimethylformamide (DMF), as a negative control according to a previously reported procedure (Hewitt and Vincet, 1989).

3. Results and discussion

3.1. *Chemistry*

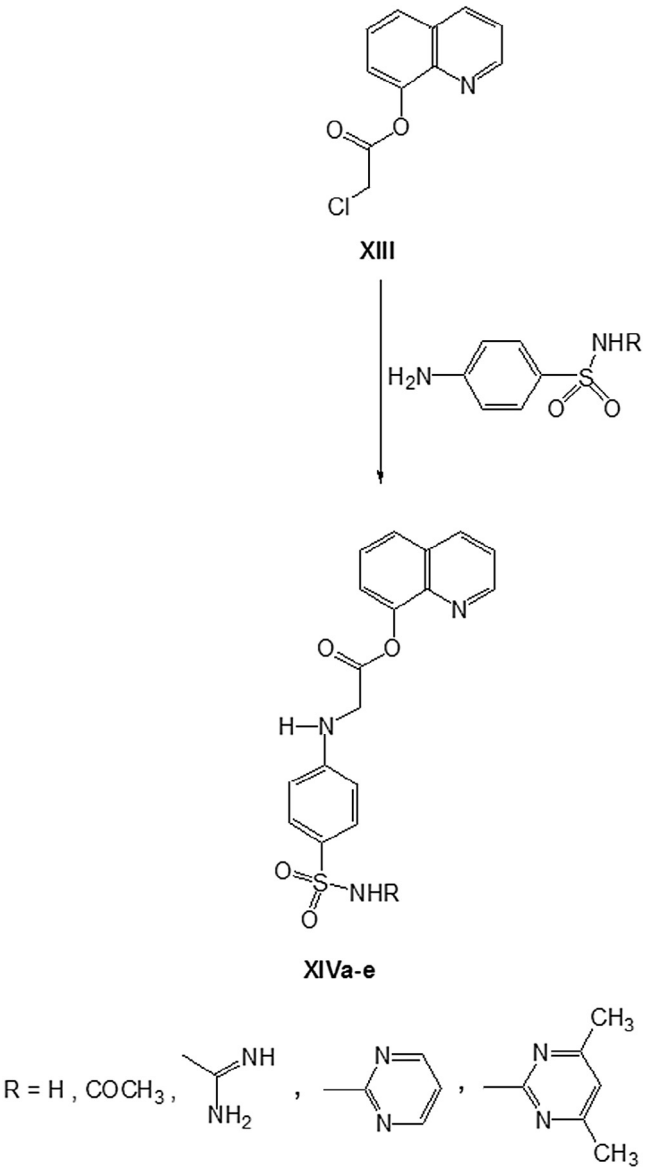
5-(4-Ethoxycarbonylphenylazo)-2-hydroxybenzoic acid (**II**) was prepared from benzocaine (**I**) in two steps according to a reported procedure (Raicharan and Guha, 1955). Reacting **II** with hydrazine hydrate yielded the corresponding hydrazide **III** in 68% yield, which upon reaction with the appropriate aromatic carbonyl compound under reflux condition gave 5-[4-(N^2-arylidenehydrazino-carbonyl)phenylazo]-2-hydroxybenzoic acids (**IVa-l**) in good yields (61–75%). Also, reacting 5-(4-hydrazinocarbonylphenylazo)-2-hydroxybenzoic acid (**III**) with maleic, succinic or phthalic anhydride in glacial acetic acid yielded the corresponding substituted amides (**Va-c**) (Scheme 1).

Furthermore, ethyl (quinol-8-yloxy)-acetate (**VIII**) was prepared as a precursor to the hydrazide **IX**. Condensation of the latter with a number of aromatic aldehydes led to the azomethine derivatives **Xa-i** in moderate yield (54%) to high yield (81%). The precursor ester **VIII** was obtained *via* two methods starting either from the corresponding acid **VI** or from quinolyloxy sodium salt **VII** (Scheme 2).



Ar = *o*-$CH_3C_6H_4$, *m*-$CH_3C_6H_4$, *p*-$CH_3C_6H_4$, 2,6-$(CH_3)_2C_6H_3$, *o*-$CH_3OC_6H_4$, *m*-$CH_3OC_6H_4$, *p*-$CH_3OC_6H_4$, *o*-ClC_6H_4, *m*-ClC_6H_4, *m*-$CH_3OCC_6H_4$, *p*-$HOOCC_6H_4$, *p*-$NO_2C_6H_4$, 1-naphthyl, *p*-$H_5C_2OOCC_6H_4$.

Scheme 3 – Synthetic protocol for compounds XIIa-n.



Scheme 4 – Synthetic protocol for compounds XIVa-e**.**

Also, the target amides **XIIa-n** were successfully synthesized *via* reacting α-chloroacetamides **XIa-n** with quinol-8-yloxy sodium salt (**VII**) in dimethylformamide with catalytic amount of anhydrous K_2CO_3 (Scheme 3).

Moreover, reaction of (quinol-8-yl) α-chloroacetate (**XIII**) with different sulfonamides in dry acetone using catalytic amounts of anhydrous K_2CO_3 gave the target compounds quinol-8-yl [4-(arylsulfamoyl)-phenyl]-aminoacetates (**XIVa-e**) (Scheme 4).

3.2. *Pharmacological screening*

The antimicrobial activity of twenty representative compounds was studied using the agar dilution technique using ofloxacin and clotrimazole as positive controls and the solvent, dimethylformamide (DMF), as a negative control. The synthesized compounds were screened for their *in vitro* antimicrobial testing using five selected standard isolates as a representative examples of different types of microorganisms as follows:

Table 7 – MIC (μg/mL) of twenty representative compounds.

Comp no.	MIC (μg/mL)				
	S. aureus	*B. subtilis*	*E. coli*	*Ps. aeruginosa*	*C. albicans*
IVe	≥800	≥800	≥800	400	400
IVh	≥800	400	≥800	200	400
IVj	≥800	200	≥800	200	200
IVk	≥800	≥800	400	200	200
IVl	≥800	≥800	≥800	400	400
Xc	≥800	400	≥800	400	400
Xe	200	100	≥800	400	200
Xg	≥800	≥800	≥800	400	100
XIIc	≥800	400	≥800	400	200
XIIf	≥800	400	400	400	100
XIIg	≥800	400	≥800	≥800	100
XIIi	≥800	≥800	≥800	200	50
XII l	≥800	≥800	≥800	200	400
XIIm	≥800	≥800	≥800	400	100
XIIn	≥800	≥800	≥800	≥800	400
XIVa	200	100	≥800	400	400
XIV b	≥800	≥800	≥800	≥800	400
XIVc	≥800	400	≥800	400	400
XIVd	200	200	≥800	200	400
XIVe	12.5	12.5	50	200	25
DMF	>800	>800	>800	>800	>800
Ofloxacin	<12.5	<12.5	<12.5	<12.5	>800
Clotrimazole	>800	>800	>800	>800	<12.5

gram-positive both non-sporulated bacteria as *Staphylococcus aureus*, sporulated as *Bacillus subtilis*, gram-negative bacteria both sensitive as *Escherichia coli*, resistant as *Pseudomonas aeruginosa* and a fungus as *Candida albicans*. The results are recorded in Table 7 and it was clear that there is variability in the susceptibilities of the different organisms to the different 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.

4. Conclusion

It can be concluded that the combination of 8-quinolyl acetate moiety with compounds having sulfonamide moiety gives a significant antimicrobial activity as shown for compounds **XIVa**, **XIVd** and **XIVe**.

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