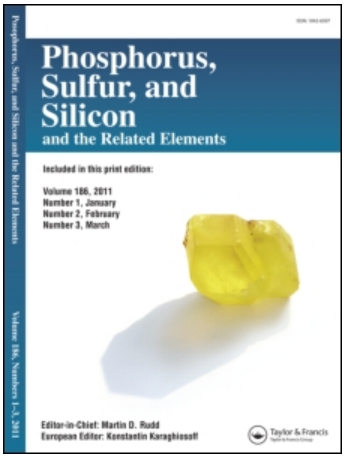

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SYNTHESIS AND APPLICATION OF SOME NEW 5-SULPHONYL-N-HETEROCYCLO-8-HYDROXYQUINOLINE DERIVATIVES AS POTENTIAL DRUGS

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Communication

SYNTHESIS AND APPLICATION OF SOME NEW 5-SULPHONYL-N-HETEROCYCLO-8-HYDROXYQUINOLINE DERIVATIVES AS POTENTIAL DRUGS

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Some new sulphonyl-N-heterocyclo-8-hydroxy quinolines have been synthesised by the reaction of 8-hydroxyquinoline-5-sulphonyl hydrazide with different active methylene compounds. The pyrazole, pyrazoline, pyrazolidine and pyridazine derivatives were reacted with some metal cations to give the corresponding chelates. All synthesized compounds have been screened in vitro for their biological activities.

Key words: Synthesis, 5-sulphonyl-8-Hydroxyquinoline derivatives; N-sulphonyl pyrazolines; their chelates and biological screening.

INTRODUCTION

A literature survey has revealed that the sulphonamide derivatives have been found to be biologically important compounds having anticancer, antimalaria, antitubercular, and other activities.[1–5] Some of the 8-hydroxyquinoline derivatives and their complexes with transition metals were reported to be active against bacteria.[6] In view of this biological significance, we wish to report an investigation concerning the synthesis of some new N-[5-sulphonyl-8-hydroxyquinoline]pyrazole derivatives and their complexes to test the change in antimicrobial activities of these ligands on chelation.

RESULTS AND DISCUSSIONS

Extensive efforts have been done to prepare new members of pyrazolines[7–14] for their wide application in different fields, but these containing 5-sulphonyl 8-hydroxyquinoline moiety were not mentioned before. In this work 5-sulphonylheterocyclo-8-hydroxyquinoline were prepared, to evaluate the effect of substitution on the microbial activity of the 8-hydroxyquinoline nucleus.

A series of 5-sulphonyl-N-heterocyclo-8-hydroxyquinoline ($\mathbf{1_a}$–$\mathbf{5_a}$) has been synthesized by condensation of 8-hydroxyquinoline-5-sulphonyl hydrazide[15] with active

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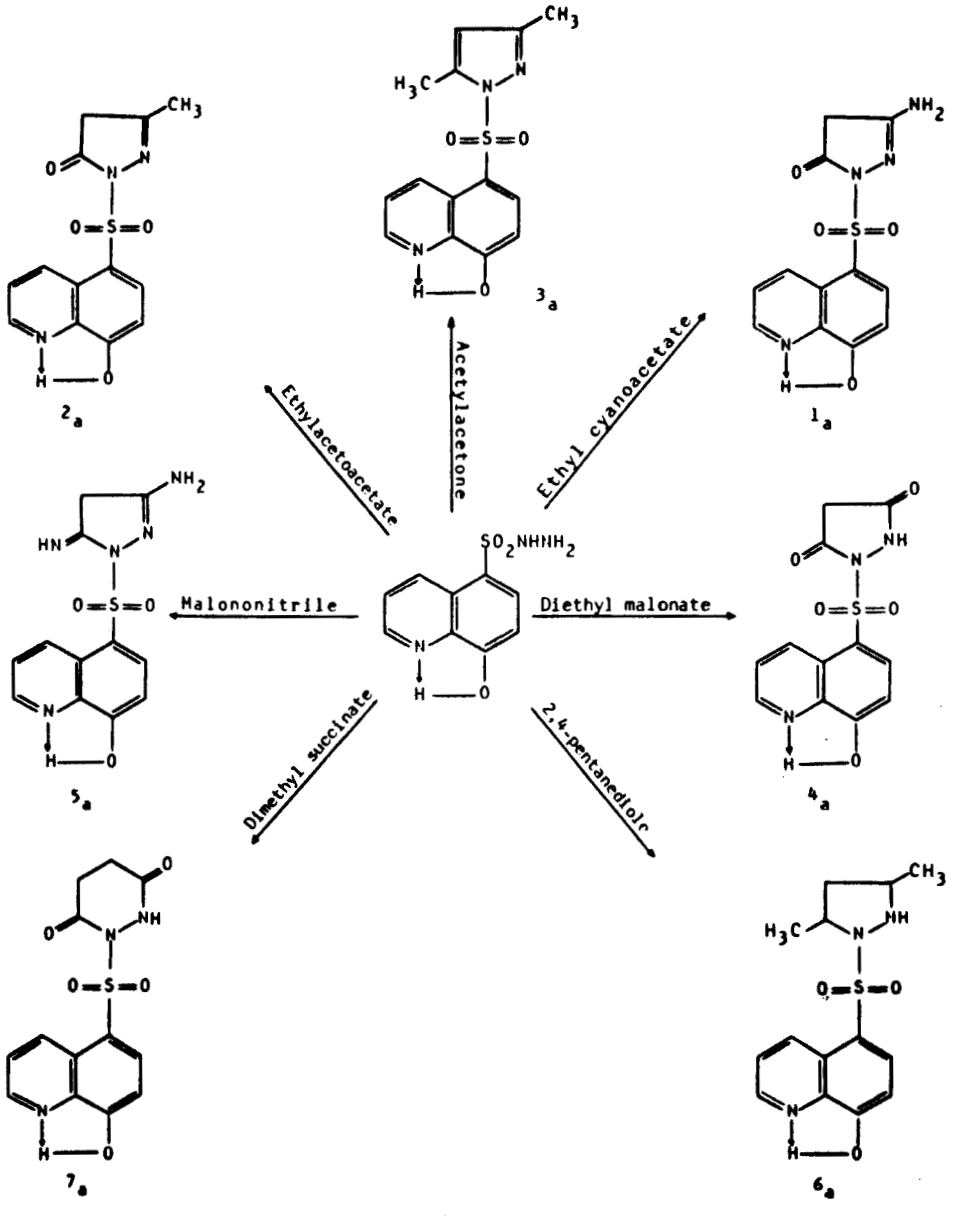
methylene compounds e.g. ethyl cyanoacetate, ethyl acetoacetate, acetyl acetone, diethyl malonate and malononitrile.

Also, on treatment of 8-hydroxyquinoline-5-sulphonyl hydrazide with 2,4-pentanediole and/or dimethyl succinate in presence of fused sodium acetate for 45–60 minutes gave (6_a) and (7_a) compounds, respectively (Scheme I).



Scheme I

TABLE I

Analysis and physical properties of the synthesized compounds $\mathbf{1}_{a-d}$–$\mathbf{7}_{a-d}$

Compound No.	mp. °C	Yield %	Formula	% Calcd. C	% Calcd. H	% Calcd. S	% Found C	% Found H	% Found S
1a	312	70	$C_{12}H_{10}N_4O_4S$	47.06	3.27	10.46	47.10	3.26	10.44
b	>300	80	$Fe(C_{12}H_{10}N_4O_4S)_2NO_3$	39.46	2.74	8.77	39.44	2.76	8.78
c	>300	78	$Cu(C_{12}H_{10}N_4O_4S)_2$	42.63	2.96	9.47	42.60	2.97	9.48
d	289	82	$Hg(C_{12}H_{10}N_4O_4S)_2$	35.44	2.46	7.88	35.46	2.44	7.89
2a	287	78	$C_{13}H_{11}N_3O_4S$	51.15	3.61	10.49	51.17	3.60	10.48
b	258	84	$Fe(C_{13}H_{11}N_3O_4S)_2NO_3$	42.87	3.02	8.79	42.86	3.05	8.74
c	270	69	$Cu(C_{13}H_{11}N_3O_4S)_2$	46.32	3.27	9.50	46.34	3.25	9.52
d	250	77	$Hg(C_{13}H_{11}N_3O_4S)_2$	38.49	2.71	7.90	38.48	2.73	7.9?
3a	285	80	$C_{14}H_{13}N_3O_3S$	55.45	4.29	10.56	55.49	4.30	1? .4
b	305	87	$Fe(C_{14}H_{13}N_3O_3S)_2NO_3$	46.42	3.59	8.84	46.41	3.56	.86
c	330	78	$Cu(C_{14}H_{13}N_3O_3S)_2$	50.18	3.88	9.56	50.20	3.86	9.54
d	290	88	$Hg(C_{14}H_{13}N_3O_3S)_2$	41.66	3.22	7.94	41.68	3.24	7.90
4a	297	67	$C_{12}H_9N_3O_5S$	46.91	2.93	10.42	46.90	2.92	10.46
b	308	70	$Fe(C_{12}H_9N_3O_5S)_2NO_3$	39.35	2.46	8.46	39.38	2.47	8.79
c	>300	58	$Cu(C_{12}H_9N_3O_5S)_2$	42.51	2.66	9.46	42.52	2.67	9.48
d	282	70	$Hg(C_{12}H_9N_3O_5S)_2$	35.36	2.21	7.86	33.38	2.20	7.84
5a	273	71	$C_{12}H_{11}N_5O_3S$	47.21	3.61	10.49	47.22	3.60	10.48
b	>300	68	$Fe(C_{12}H_{11}N_5O_3S)_2NO_3$	39.57	3.02	8.79	39.59	3.00	8.77
c	>300	60	$Cu(C_{12}H_{11}N_5O_3S)_2$	42.76	3.27	9.50	42.79	3.26	9.49
d	305	74	$Hg(C_{12}H_{11}N_5O_3S)_2$	35.53	2.71	7.90	35.60	2.70	7.88
6a	175	62	$C_{14}H_{16}N_3O_3S$	54.89	5.26	10.47	54.90	5.23	10.66
b	>300	78	$Fe(C_{14}H_{16}N_3O_3S)_2NO_3$	45.98	4.40	8.64	46.00	4.42	8.60
c	>300	69	$Cu(C_{14}H_{16}N_3O_3S)_2$	49.68	4.76	9.40	49.70	4.77	9.69
d	278	80	$Hg(C_{14}H_{16}N_3O_3S)_2$	41.31	3.95	7.69	41.40	3.98	7.90
7a	302	65	$C_{13}H_{11}N_3O_5S$	47.13	3.32	9.67	47.15	3.30	9.66
b	310	71	$Fe(C_{13}H_{11}N_3O_5S)_2NO_3$	40.01	2.82	8.21	40.00	2.83	8.22
c	320	60	$Cu(C_{13}H_{11}N_3O_5S)_2$	43.00	3.03	8.82	42.88	3.05	8.84
d	290	78	$Hg(C_{13}H_{11}N_3O_5S)_2$	36.17	2.55	7.42	36.19	2.53	7.44

TABLE II

Important IR bands of synthesized compounds 1_a–7_a (ligands) cm^{-1}

Assignment	1_a	2_a	3_a	4_a	5_a	6_a	7_a
νOH	3180	3145	3175	3165	3160	3190	3180
$\nu_{asym.}$ S=O	1320	1325	1320	1330	1325	1330	1333
$\nu_{sym.}$ S=O	1160	1150	1145	1155	1160	1150	1160
νNH	-	-	-	3280	3210	3260	3280
νNH_2	3310	-	-	-	3320	-	-
νC=O	1760	1760	-	1775	-	-	1775
monocyclic							

TABLE III

Important IR bands of metal chelates (1_{b-d}–7_{b-d}) cm^{-1}

Assignment	1_{b-d}	2_{b-d}	3_{b-d}	4_{b-d}	5_{b-d}	6_{b-d}	7_{b-d}
νOH	-	-	-	-	-	-	-
$\nu_{asym.}$ S=O	1340	1330	1335	1340	1325	1340	1335
$\nu_{sym.}$ S=O	1150	1165	1170	1140	1145	1170	1165
νNH	-	-	-	3260	3220	3250	3260
νNH_2	3320	-	-	-	3330	-	-
νC=O	1750	1755	-	1745	-	-	1750
$\nu_{asym.}$ NO	1260	1265	1290	1265	1280	1285	1280
$\nu_{sym.}$ NO	1030	1025	1030	1035	1020	1025	1030
ν_{M-O}	350	345	340	390	355	360	370

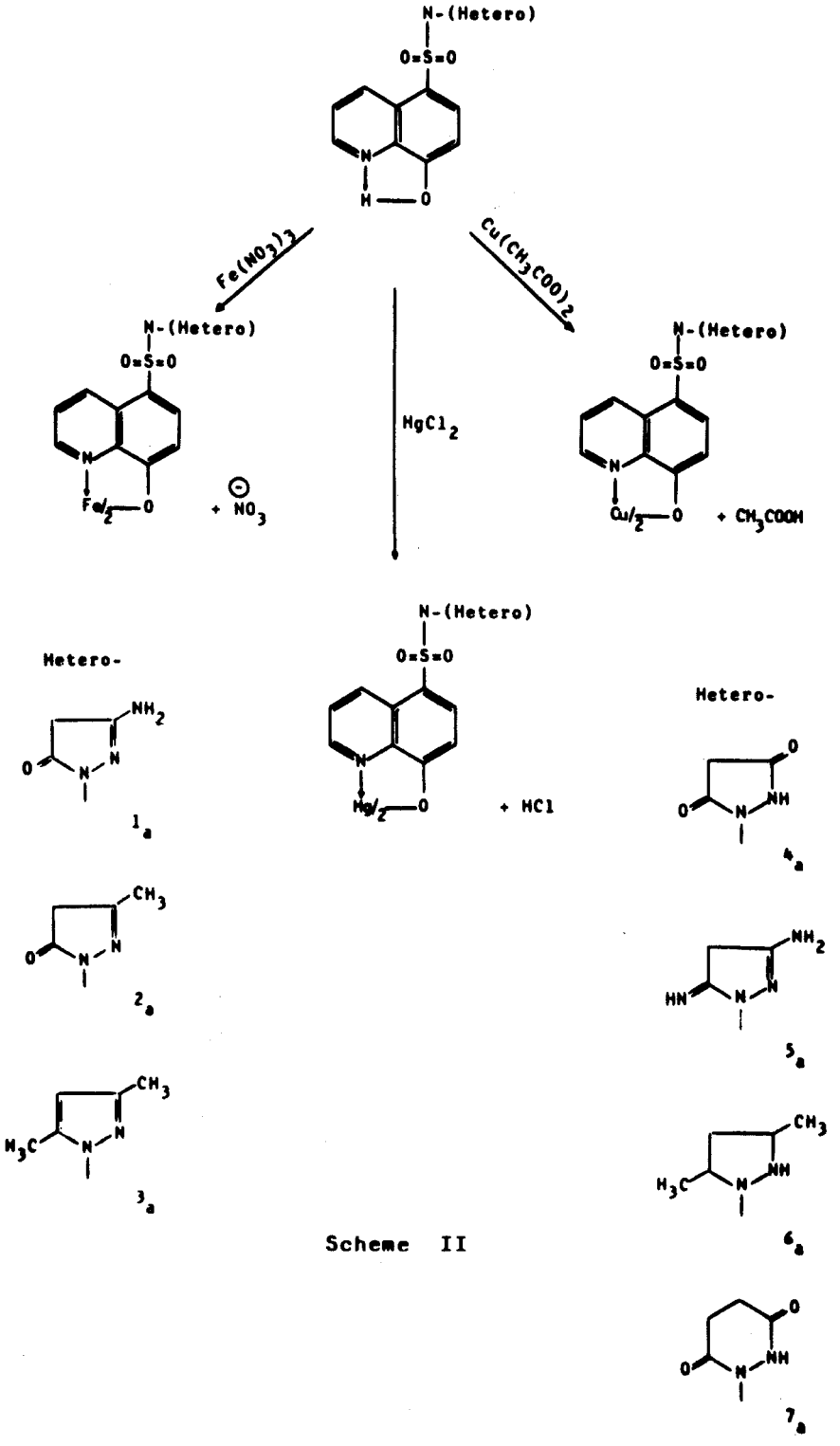
TABLE IV

^{1}H-NMR spectra of the synthesized compounds (Chemical shifts in δppm)

Compound No.	Aromatic protons (m, 5H)	-OH (s, 1H)	
1_a	7.80-7.20	9.01	δ5.50(s, 2H, NH_2), δ4.30(s, 2H, CH_2-
$1_{b,c,d}$	7.90-7.00	-	pyrazolyl ring).
2_a	7.80-7.10	9.02	δ2.20 (s, 3H, CH_3 of pyrazole ring),
$2_{b,c,d}$	8.00-7.20	-	δ4.20 (s, 2H, CH_2 pyrazolyl ring).
3_a	8.00-7.10	9.00	δ2.40-2.10 (t, 6H, 2 CH_3 of pyrazol
$3_{b,c,d}$	7.80-7.00	-	ring), δ7.76 (s, CH pyrazolyl ring).
4_a	7.90-7.10	8.90	δ3.70 (s, 1H, NH), δ4.20 (s, 2H,
$4_{b,c,d}$	8.00-7.00	-	CH_2 pyrazolyl ring).
5_a	7.70-7.20	9.00	δ4.20 (s, 2H, CH_2 pyrazolyl ring),
$5_{b,c,d}$	7.90-7.30	-	δ3.40 (s, 1H, NH), δ5.50 (s, 2H, NH_2).
6_a	7.60-7.20	8.92	δ3.50 (s, 1H, NH), δ4.50-4.00 (s, 2H,
$6_{b,c,d}$	7.80-7.10	-	CH_2 of pyrazolyl ring), δ2.50-2.15 (t, 6H, $2CH_3$ of pyrazole ring).
7_a	7.60-7.10	8.94	δ4.40-4.10 (d, 4H, 2 CH_2 of diazine
$7_{b,c,d}$	7.90-7.20	-	ring, δ3.50 (s, 1H, NH).

The structures of the synthesised compounds were confirmed on the basis of microanalytical data, ^{1}H-NMR and IR spectroscopic evidence (Tables I, II, III and IV). Complexation of the ligand ($\mathbf{1_a}$–$\mathbf{7_a}$) was carried out by refluxing an ethanolic solution of 5-sulphonyl-N-heterocyclo-8-hydroxyquinoline $\mathbf{1_a}$–$\mathbf{7_a}$ with metal salts at 50–60°C, to give $\mathbf{1_{b-d}}$–$\mathbf{7_{b-d}}$ compounds, respectively (Scheme II).

The overall study and the analytical data (Table I) shows that all compounds form chelates of the type ML_2 where L = ligand. The IR spectra of ligands shows bands at 3 100 cm^{-1} and 3 150–3 050 cm^{-1}. Instead, these bands are located at 370–340 cm^{-1} in the corresponding chelates due to the involvement of —OH group of quinoline in chelate formation.[16,17] The bands around 1 600 cm^{-1} in the spectra of ligands due to $\nu\left(\diagdown\!\!\diagup C{=}N{-}\right)$ shift to lower values with weak intensity



Scheme II

TABLE V

Antibacterial screening of compounds $\mathbf{1}_{a-d}$–$\mathbf{7}_{a-d}$ (inhibition zones mm)

Compound No.	Formula	Bacillus cereus	Serratia sp.	Bacillus subtilis	Pesudomonas aeruginosa	Escherichio coli	Micrococcus roseus	Staphylococcus aureus
1a	$C_{12}H_{10}N_4O_4S$	20	15	20	10	15	10	25
b	$Fe(C_{12}H_{10}N_4O_4S)_2NO_3$	-ve	-ve	10	10	30	10	15
c	$Cu(C_{12}H_{10}N_4O_4S)_2$	30	20	-ve	10	30	30	40
d	$Hg(C_{12}H_{10}N_4O_4S)_2$	60	50	80	60	60	60	90
2a	$C_{13}H_{11}N_3O_4S$	35	20	25	30	10	20	25
b	$Fe(C_{13}H_{11}N_3O_4S)_2NO_3$	25	-ve	-ve	40	10	15	20
c	$Cu(C_{13}H_{11}N_3O_4S)_2$	20	10	-ve	40	15	15	30
d	$Hg(C_{13}H_{11}N_3O_4S)_2$	60	50	50	50	60	50	80
3a	$C_{14}H_{13}N_3O_3S$	50	30	20	50	50	60	40
b	$Fe(C_{14}H_{13}N_3O_3S)_2NO_3$	40	50	-ve	10	80	-ve	15
c	$Cu(C_{14}H_{13}N_3O_3S)_2$	45	10	15	40	10	20	30
d	$Hg(C_{14}H_{13}N_3O_3S)_2$	80	90	75	80	80	60	85
4a	$C_{12}H_9N_3O_5S$	40	50	40	40	40	45	50
b	$Fe(C_{12}H_9N_3O_5S)_2NO_3$	20	10	-ve	15	15	-ve	50
c	$Cu(C_{12}H_9N_3O_5S)_2$	15	-ve	20	40	20	-ve	15
d	$Hg(C_{12}H_9N_3O_5S)_2$	80	60	70	50	60	45	75

in the spectra of chelates due to M ← N bond formation (Table III).

The bacteriostatic activities of the synthesized compounds $\mathbf{1}_{a-d}$ to $\mathbf{7}_{a-d}$ showed variable effects (inhibition zones ranged from 10 to 90 mm) against bacteria used (Table V). Whears compounds from $\mathbf{I}_d$ to $\mathbf{7}_d$ showed high potential activities (inhibition zones ranged from 50 to 90 mm) against all bacteria used. Furthermore, all of tehse compounds showed mild and strong activities (inhibition zones ranged from 10 to 90 mm) against *Bacillus cereus*, *Pesudomonas aeruginosa*, *Escherichia coli* and *Staphylococcus aureus*. Interestingly, compounds from $\mathbf{I}_a$ to $\mathbf{7}_a$ as ligands showed mild and strong activities (inhibition zones from 10 to 75 mm) against all of the bacteria used.

EXPERIMENTAL

All melting points are uncorrected. Microanalysis were done at the Department of Chemistry, Faculty of Science, Assiut University. IR spectra were rune on a Pye Unicam sp 200 G spectrophotometer in KBr discs. ^{1}H-NMR spectra were done on a EOL-FT 270 MHz NMR Instrument using TMS as an internal standard.

Synthesis of 5-sulphonyl-N-heterocyclo-8-hydroxyquinolines ($\mathbf{1}_a$–$\mathbf{7}_a$).

General procedure: A mixture of 8-hydroxyquinoline-5-sulphonyl hydrazide (**A**) (2.08 g, 0.01 mole), was reacted with active methylene compounds (equal molar ratio) e.g. ethyl cyanoacetate, ethyl acetoacetate, acetyl acetone, diethyl malonate, malononitrile, 2,4-pentanediol and dimethyl succinate in presence of fused sodium acetate (0.7 g) by fusion on an oil bath at 200–220°C for 20–30 minutes, then refluxed with 10 ml absolute ethanol for 2–4 hours. The reaction mixture was poured into ice water and stirred for 1 hour. The solid thus obtained was collected and crystallized from the proper solvent (Table I) gave the following synthesized compounds listed as follows:

N-(5-Sulphonyl-8-hydroxyquinoline)-3-amino-2-pyrazoline-5-one ($\mathbf{1}_a$); N-(5-Sulphonyl-8-hydroxyquinoline)-3-methyl-2-pyrazoline-5-one ($\mathbf{2}_a$); N-(5-Sulphonyl-8-hydroxyquinoline)-3,5-dimethylpyrazole ($\mathbf{3}_a$); N-(5-Sulphonyl-8-hydroxyquinoline)-N-2-(**H**)-pyrazolidine-3,5-dione ($\mathbf{4}_a$); N-(5-Sulphonyl-8-hydroxyquinoline)-3-amino-5-amino-5-imino-2-pyrazoline ($\mathbf{5}_a$); N-(5-Sulphonyl-8-hydroxyquinoline)-3,5-dimethyl-N-2-(**H**)-pyrazolidine ($\mathbf{6}_a$); and N-(5-sulphonyl-8-hydroxyquinoline)-N-2-(**H**)-4,5-dihydro pyridazine-3,6-dione ($\mathbf{7}_a$), respectively.

Preparation of the complexes: A hot ethanolic solution of an appropriate amount of the ligand was mixed at continuous stirring with a calculated amount of the respective metal salt (ferric nitrate, copper acetate and mercuric chloride) suspended in ethyl alcohol in the molar ratio 2:1; precipitation of the complex occurs immediately. The product was filtered, washed with little alcohol and dried.

Screening for biological activity: The antibacterial activities of all synthesized compounds $\mathbf{1}_{a-d}$ to $\mathbf{7}_{a-d}$ have been studied and screened in vitro against Gram-positive and Gram-negative bacteria used namely: *Bacillus cereus*, *Serratia sp.*, *Bacillus subtilis*, *Pesudomonas aeruginosa*, *Escherichia coli*, *Micrococcus roseus* and *Staphylococcus aureus*.

The bacteriostatic activities were tested by the usual cup plate agar diffusion technique,[18,19] 1% dimethyl formamide solution of the chelates were prepared. The dishes were allowed to stand in a refrigerator at 4–8°C for 0.5 hr. to allow diffusion of the solutions and were incubated at 37 ± 1°C for 48 hr. The inhibition zones were measured with the callipers.

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