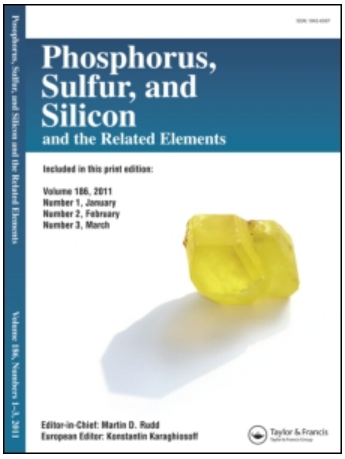


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS AND APPLICATION OF SOME NEW 5-SULFONYLHETEROCYCLO-8-QUINOLINOL DERIVATIVES

Ali A. Abdel Hafez[a]; Ibrahim M. A. Awad[a]
[a] Chemistry Department, Faculty of Science, Assiut University, Assiut, Egypt

To cite this Article Hafez, Ali A. Abdel and Awad, Ibrahim M. A.(1992) 'SYNTHESIS AND APPLICATION OF SOME NEW 5-SULFONYLHETEROCYCLO-8-QUINOLINOL DERIVATIVES', Phosphorus, Sulfur, and Silicon and the Related Elements, 71: 1, 253 — 259
To link to this Article: DOI: 10.1080/10426509208034519
URL: http://dx.doi.org/10.1080/10426509208034519

Phosphorus, Sulfur, and Silicon, 1992, Vol. 71, pp. 253–259
Reprints available directly from the publisher
Photocopying permitted by license only

Communication

SYNTHESIS AND APPLICATION OF SOME NEW 5-SULFONYLHETEROCYCLO-8-QUINOLINOL DERIVATIVES

ALI A. ABDEL HAFEZ† and IBRAHIM M. A. AWAD
Chemistry Department, Faculty of Science, Assiut University, Assiut-Egypt

(Received September 18, 1991; in final form May 12, 1992)

A new series of 5-(4′-arylidine-3′-methyl-5′-oxo-4′,5′-dihydropyrazol-1-yl-sulfonyl)-8-quinolinols (1_{a-c}) were prepared via the reaction of 5-(3′-methyl-5′-oxo-4′,5′-dihydropyrazol-1-yl-sulfonyl)-8-quinolinols with selected aldehydes. These compounds were condensed with hydrazine, hydroxylamine, urea and thiourea to give 5-(3′-methyl-5′-acetyl-4′-substituted pyrazolo-[3′,4′-c]pyrazol-1-yl-sulfonyl)-8-quinolinols (2_{a-c}), 5-[3′-methyl-4′-substituted pyrazol-1-yl-sulfonyl-[3′,4′-c]isoxazolo-]quinolinols (3_{a-c}) and 5-[3′-methyl-4′-substituted pyrazol-1-yl-sulfonyl[3′,4′-c]pyrimidine-6′ one (thione)]-8-quinolinols (4_{a-c}, 5_{a-c}) respectively. Metal chelate of $2_{a,b,d}$ and $3_{a,b,d}$ with Fe^{2+}, Cu^{2+}, Hg^{2+} have been synthesized and characterized by elemental and IR spectral analysis. The synthesized compounds were biologically screened in vitro to study the structure activity relationship and the effect of complexation and the type of metal cation on the more biologically active compounds.

Key words: Pyrazolino[3′,4′-c]pyrazolo-, isoxazolo-, and pyrimidino-(thiono-)-8-quinolinol.

INTRODUCTION

Sulfonamides are drugs of known therapeutic importance.[1–3] Extensive efforts have been made to prepare new members of pyrazolines,[4–14] isoxazolines[15–17] and pyrimidinethiones[15] for their wide application in different fields, but the title compounds were not mentioned before.

RESULTS AND DISCUSSION

The reaction of 5-[3′-methyl-5′-oxo-4′,5′-dihydropyrazol-1-yl-sulfonyl]-8-quinolinol with the selected aldehydes in the presence of triethylamine gave a new series of 5-[4′-arylidine-3′-methyl-5′-oxo-4′,5′-dihydropyrazol-1-yl-sulfonyl]-8-quinolinols (1_{a-e}). These compounds were identified by elemental analysis as well as by IR and ^{1}H-NMR spectral data. IR spectra showed absorption bands at 1680-1660 cm^{-1} (νCOCH=CH—), 1600 cm^{-1} (νC=C) and at 3345 cm^{-1} (νOH). ^{1}H-NMR spectra showed chemical shifts at δ2.85 (*s*, 3H, CH_3), δ7.10 (*s*, 1H, =CH-R), δ6.65–8.00 (*m*, 11H, aromatic) and δ5.40 (*s*, 1H, OH group).

Interaction of 1_{a-e} with hydrazines, hydroxylamine, urea and thiourea under the experimental conditions gave the corresponding 5-[3′-methyl-5′-acetyl-4′-substituted pyrazolo[3′,4′-c]pyrazol-1-yl-sulfonyl]-8-quinolinols (2_{a-e}); 5-[3′-methyl-4′-

†Author to whom correspondence should be addressed.

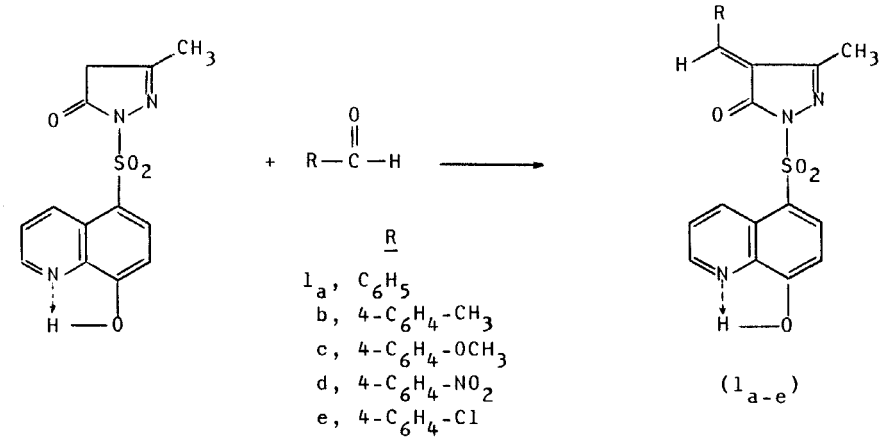
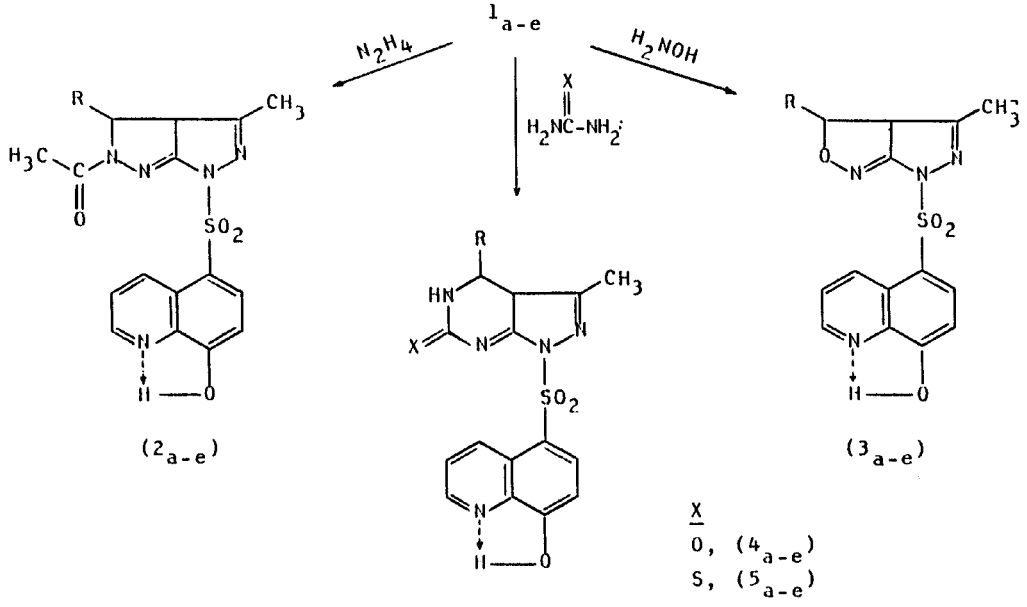


FIGURE 1

substituted pyrazol-1-yl-sulfonyl[3′,4′-c]-isoxazolo]-8-quinolinols (3_{a-e}) and 5-[3′-methyl-4-substituted pyrazol-1-yl-sulfonyl[3′,4′-c]-pyrimidine-5,6-dihydro-6′ one (thione)-8-quinolinols (4_{a-e}, 5_{a-e}) respectively, as shown in Scheme I.

The structure of these compounds was proved from the elemental analysis as well as by IR and ^{1}H-NMR spectral data. IR spectra showed absorption bands at 1600 cm^{-1} (υC=N), 1720-1700 cm^{-1} (υC=O) and 3350 cm^{-1} (υOH) for N-acetylpyrazoline derivatives 2_a; at 1190-1050 cm^{-1} (υ-isoxazoline ring), 1610 cm^{-1} (υC=N) and 3350 cm^{-1} (υOH) for 3_a and at 1170 cm^{-1} (υC=S), 1490 cm^{-1} (υC—N—S) and 3350 cm^{-1} (υOH) for the pyrimidine thione derivatives 5_a. The ^{1}H-NMR spectra showed chemical shifts at δ2.85 (*s*, 3H, CH_3), δ2.35 (*s*, 3H,



SCHEME I

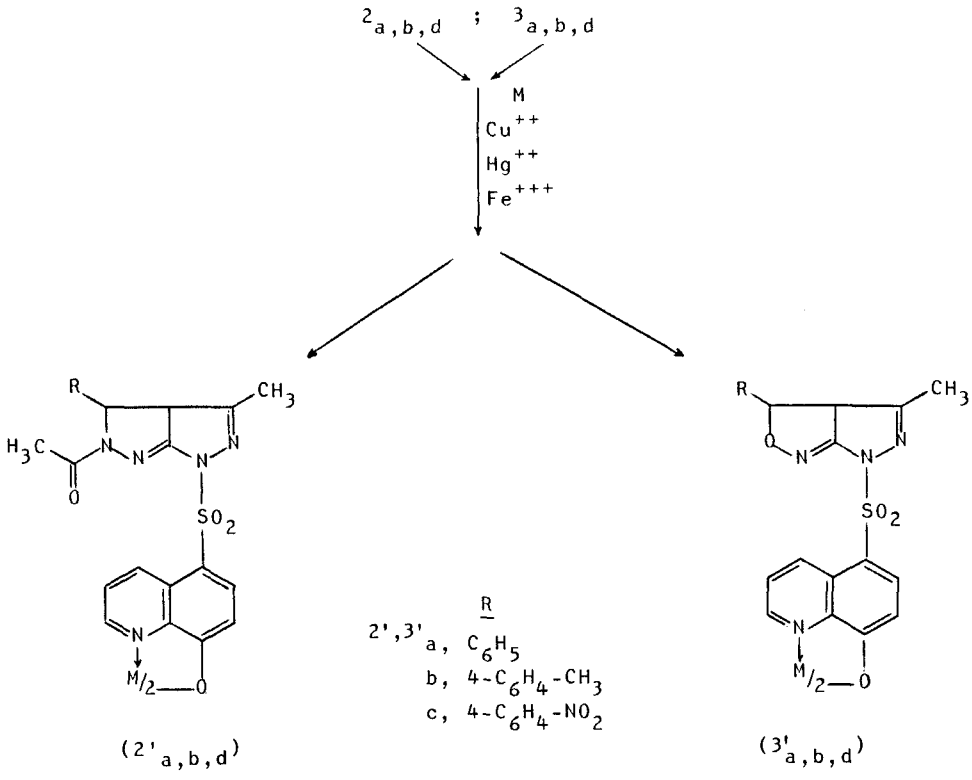


FIGURE 2

CH_3CO), δ6.70–8.00 (*m*, 13H, aromatic) for compound 2_a; δ2.80 (*s*, 3H, CH_3), δ6.60–7.90 (*m*, 13H, aromatic) for 3_a; δ2.50 (*s*, 3H, CH_3), δ2.10 (*s*, 3H, $COCH_3$) and δ6.95–7.95 (*m*, 12H, aromatic) for compound $2'_a$.

Interaction of compounds $2_{a,b,d}$, $3_{a,b,d}$ with the appropriate amounts of metal salt solution gave the corresponding complexes, $2'_{a,b,d}$ and $3'_{a,b,d}$. The IR spectra showed a broad absorption at 3200–3300 cm^{-1} due to hydrogen bonding.[18,19] On this basis, the intramolecular hydrogen bonded chelate structures (—O—H—N) have been proposed for the ligands. A critical examination of the spectra of metal chelates indicates that the band at 3200 cm^{-1} present in the ligands is shifted to higher values (3500–3300 cm^{-1}) in the chelates and are not present in the original ligands. The disappearance of hydrogen bonded—OH in the ligands and its reappearance in the metal chelates are suggestive of O—M—N bond formation, where M is a metal atom. The bonds between 1600–1490 cm^{-1} are due to aromatic rings. The overall study and the analytical data show that the ligands form chelates of the type ML_2 (1:1 molar ratio) where L = ligand.

Biological Results

The antibacterial activities of the newly synthesized heterocyclic ligands and their metal Cu^{+2}, Hg^{+2}, Fe^{+3} chelates showed variable activities against the bacteria used. Compounds 1_{a-e} showed weak activities; whereby compounds 2_{a-e} and 3_{a-e}

TABLE I

Physical and analytical data of compounds 2_{a-e}–5_{a-e}.

Comp.	Yield %	m.p. (°C)	Molecular formula (M.W.)	Calculated*/Found % C	H	N	S	Cl
1_a	65	243-5	$C_{20}H_{15}O_4N_3S$	61.06	3.81	10.68	8.15	-
			(393.42)	61.00	3.72	10.55	8.04	-
b	55	328-30	$C_{21}H_{17}O_4N_3S$	61.91	4.21	10.31	7.87	-
			(407.45)	61.75	4.12.	10.29	7.71	-
c	74	210-12	$C_{21}H_{17}O_5N_3S$	59.57	4.05	9.92	7.57	-
			(423.45)	59.60	4.00	9.70	7.42	-
d	70	238-40	$C_{20}H_{14}O_6N_4S$	54.79	3.22	12.78	7.31	-
			(438.42)	54.61	3.12	12.68	7.27	-
e	59	256-8	$C_{20}H_{14}O_4N_3SCl$	56.14	3.30	9.82	7.49	8.29
			(427.87)	56.23	3.20	9.70	7.38	8.19
2_a	58	118	$C_{22}H_{19}O_4N_5S$	58.79	4.26	15.58	7.13	-
			(449.49)	58.63	4.14	15.40	7.00	-
b	47	178	$C_{23}H_{21}O_4N_5S$	59.60	4.57	15.11	6.92	-
			(463.52)	59.64	4.32	15.00	6.75	-
c	60	193-5	$C_{23}H_{21}O_5N_5S$	57.61	4.41	14.60	6.69	-
			(479.52)	57.58	4.27	14.48	6.52	-
d	50	202-4	$C_{22}H_{18}O_6N_6S$	53.44	3.67	17.00	6.48	-
			(494.49)	53.20	3.58	16.66	6.20	-
e	45	308-10	$C_{22}H_{18}O_4N_5SCl$	54.60	3.75	14.47	6.63	7.33
			(483.94)	54.68	3.63	14.40	6.40	7.46
3_a	64	270	$C_{20}H_{16}O_4N_4S$	58.81	3.95	13.73	7.84	-
			(408.44)	58.70	3.81	13.54	7.60	-
b	>58	320	$C_{21}H_{18}O_4N_4S$	59.70	4.29	13.26	7.59	-
			(422.47)	59.90	4.30	13.10	7.61	-
c	62	166-8	$C_{21}H_{18}O_5N_4S$	57.53	4.14	12.78	7.31	-
			(438.47)	57.60	4.21	12.58	7.28	-
d	68	>320	$C_{20}H_{15}O_6N_5S$	52.98	3.33	15.44	7.07	-
			(453.44)	53.01	3.30	15.28	7.10	-
e	56	>320	$C_{20}H_{15}O_4N_4SCl$	54.24	3.41	12.65	7.24	8.01
			(442.88)	54.17	3.40	12.60	7.30	7.89

Table I (*Continued*)

Comp.	Yield %	m.p. (°C)	Molecular formula (M.W.)	Calculated*/Found % C	H	N	S	Cl
4_a	66	278	$C_{21}H_{17}O_4N_5S$	57.92	2.94	16.08	7.30	-
			(435.46)	58.01	4.00	16.16	7.27	-
b	56	210	$C_{22}H_{19}O_4N_5S$	58.79	4.26	15.58	7.13	-
			(449.49)	58.69	4.34	15.51	7.21	-
c	70	>320	$C_{22}H_{19}O_5N_5S$	56.77	4.11	15.05	6.89	-
			(465.49)	56.68	4.20	14.92	6.95	-
d	62	>320	$C_{21}H_{16}O_6N_6S$	52.50	3.36	17.49	6.67	-
			(480.46)	52.58	3.29	17.54	6.75	-
e	60	238	$C_{21}H_{16}O_4N_5SCl$	53.68	3.43	14.90	6.82	7.54
			(469.91)	53.77	3.37	14.96	6.76	7.46
5_a	62	>320	$C_{21}H_{17}O_3N_5S_2$	55.86	3.80	15.51	14.20	-
			(451.53)	55.97	3.91	15.40	15.00	-
b	54	178	$C_{22}H_{19}O_3N_5S_2$	56.76	4.11	15.04	13.77	-
			(465.56)	56.85	4.20	15.12	13.69	-
c	65	190	$C_{22}H_{19}O_4N_5S_2$	54.87	3.98	14.54	13.32	-
			(481.56)	54.76	3.91	14.61	13.25	-
d	60	>320	$C_{21}H_{16}O_5N_6S_2$	50.80	3.25	16.93	12.92	-
			(496.53)	50.91	3.18	16.85	13.01	-
e	58	110	$C_{21}H_{16}O_3N_5S_2Cl$	51.90	3.32	14.41	13.20	7.30
			(485.97)	51.81	3.25	14.50	13.12	7.23

* All compounds gave satisfactory C, ±0.16; H, ±0.11.

showed a scattered activities. Metal chelates $2'_{a,b,d}$ and $3'_{a,b,d}$ exerted predominant activities against the majority of the bacteria. Interestingly, the more potent complexes are that with mercury metal.

EXPERIMENTAL

All melting points are uncorrected and all chemical and solvents were reagent grade. Infrared spectra were determined with a PERKIN ELMER 599 B spectrophotometer using the KBr wafer technique. ^{1}H-NMR spectra were carried out in $CDCl_3$ using a Varian EM 390 (90 MHZ) spectrometer.

5-(4'-Arylidine-3'-methyl-5'-oxo-4',5'-dihydropyrazol-1-yl-sulfonyl)-8-quinolinol. These compounds were obtained by gentle fusion of 5-[3'-methyl-5'-oxo-4',5'-dihydropyrazol-1-yl-sulfonyl]-8-quinolinol (0.02 mole) with the selected aldehydes (0.02 mole) in the presence of a few drops of triethylamine, followed by reflux with ethanol (30 ml) for 1 hr. The reaction mixture was allowed to cool and acidified with dilute acetic acid. The precipitate formed were collected by filtration, washed with water then with 5 ml methanol and recrystallized from ethanol. These compounds gave green colour when their alcoholic solution were treated with $FeCl_3$ solution. Data are given in Table I.

5-(3'-Methyl-5'-acetyl-4'-substituted pyrazolo[3',4'-c]pyrazol-1-yl-sulfonyl)-8-quinolinols (1_{a-e}). A mixture of (0.002 mole) of compound 1_{a-c} and (0.002 mole) of 98% hydrazinehydrate in 20 ml of glacial acetic

TABLE II

Physical and analytical data of metal chelates $2_{a,b,d}$–$3'_{a,b,d}$.

Compd. No.	m.p. °C	Yield %	Molecular formula (M.W.)	Calculated*/Found % N	S	Cl
2'a	281-3	83	$(C_{22}H_{19}O_4N_5S)_2Cu$ (962.52)	14.55 14.71	6.66 6.73	-
	>320	86	$(C_{22}H_{19}O_4N_5S)_2Hg$ (1099.57)	12.74 12.82	5.83 5.91	-
	>320	73	$(C_{22}H_{19}O_4N_5S)_2FeCl$ (990.28)	14.14 14.25	6.48 6.42	3.58 3.61
b	275-7	78	$(C_{23}H_{21}O_4N_5S)_2Cu$ (990.58)	14.14 14.22	6.47 6.55	-
	311-13	81	$(C_{23}H_{21}O_4N_5S)_2Hg$ (1127.63)	12.42 12.39	5.69 5.59	-
	>320	75	$(C_{23}H_{21}O_4N_5S)_2FeCl$ (1018.34)	13.75 13.84	6.30 6.39	3.48 3.52
d	>320	88	$(C_{22}H_{18}O_6N_6S)_2Cu$ (1052.52)	15.97 15.92	6.09 6.12	-
	268-70	82	$(C_{22}H_{18}O_6N_6S)_2Hg$ (1189.57)	14.13 14.17	5.39 5.42	-
	>320	74	$(C_{22}H_{18}O_6N_6S)_2FeCl$ (1080.28)	15.56 15.62	5.94 5.87	3.28 3.31
3'a	>320	81	$(C_{20}H_{16}O_4N_4S)_2Cu$ (880.42)	12.73 12.76	7.28 7.32	-
	312-14	78	$(C_{20}H_{16}O_4N_4S)_2Hg$ (1017.47)	11.01 11.10	6.30 6.25	-
	287-9	71	$(C_{20}H_{16}O_4N_4S)_2FeCl$ (908.18)	12.34 12.26	7.06 7.11	3.90 3.88
3'b	>320	81	$(C_{21}H_{18}O_4N_4S)_2Cu$ (908.48)	12.33 12.26	7.06 7.15	-
	278-80	83	$(C_{21}H_{13}O_4N_4S)_2Hg$ (1045.53)	10.72 10.69	6.13 6.22	-
	306-8	68	$(C_{21}H_{18}O_4N_4S)_2FeCl$ (936.24)	11.97 12.01	6.85 6.91	3.79 3.93
d	296-8	78	$(C_{20}H_{15}O_6N_5S)_2Cu$ (970.42)	14.43 14.54	6.60 6.72	-
	310-12	81	$(C_{20}H_{15}O_6N_5S)_2Hg$ (1107.47)	12.65 12.55	5.79 5.81	-
	>320	72	$(C_{20}H_{15}O_6N_5S)_2FeCl$ (998.18)	14.03 14.00	6.42 6.61	3.55 3.65

* All compounds gave satisfactory C, ±0.15; H, ±0.12.

acid was heated under reflux for 8 hr. The reaction mixtures were cooled, whereby the corresponding products were precipitated. The products were filtered off, washed with alcohol and recrystallized from dioxane. Data are given in Table I.

5-[3'-Methyl-4'-substituted pyrazol-1'-yl-sulfonyl[3',4'-c]isoxazolo-]-8-quinolinols (3_{a-e}). A mixture of (0.002 mole) of compound 1_{a-c}, (0.004 mole) or hydroxylamine hydrochloride and (0.001 mole) of KOH in 30 ml absolute ethanol was heated under reflux for 10 hr. The reaction mixture was concentrated, neutralized with dilute HCl, whereby the corresponding products were precipitated. The products were filtered off, washed with ethanol and recrystallised from ethanol. Data are given in Table I.

5-[3'-Methyl-4'-substituted pyrazol-l'-yl-sulfonyl[3',4'-c]-pyrimidine-5',6'-dihydro-6'-one (thion)]-8-quinolinols (4_{a-e}, 5_{a-e}). A mixture of (0.002 mole) of compound 1_{a-c}, (0.002 mole) of urea (thiourea), (0.002 mole) of potassium hydroxide in 30 ml of absolute ethanol was heated under reflux for 12 hr. The reaction mixture was concentrated, neutralised with dilute HCl, whereby the corresponding products 4_{a-c}, 5_{a-c} were precipitated. The products were filtered off, washed with water and recrystallized from alcohol. Data are given in Table I.

Complexation. The ligands (0.1 M) in ethyl alcohol were treated with (0.1 M) aqueous solution of the metal salt at 50–60°C. The resulting precipitates of the chelate were digested on a water bath for 30 min., filtered and washed with hot distilled water and dried. The physical data are depicted in Table II.

Biological Screening. The tested compounds were dissolved in sterile dimethylformamide 0.5 mg/disk (Whatman No. 3 filter paper, 0.5 cm diameter). The antibacterial spectrum of the synthesized compounds and their chelates was screened and tested with six strains of Gram-positive bacteria namely *Bacillus cereus*, *Staphylococcus aureus*, *Micrococcus luteus*; and Gram-negative bacteria namely: *Serratia sp.*, *Escheriea coli*, *Pseudomonas actuginosa*.

The culture medium for bacteria was nutrient agar (NA) (composed of beef extract, 3 gm, peptone, 5 gm, agar, 15 gm/L. and adjusted to pH 7 before sterilization at 121°C for 20 min).

REFERENCES

1. D. B. Clayson, J. A. S. Sringle and G. M. Ranses, *Biochem. Pharmacol.*, **16,** 614 (1967).
2. W. N. Beerlev, W. Peters and K. Mager, *Ann. Trop. Med. Parasitol*, **62,** 288 (1960).
3. G. Tarbini, *Inst. Congr. Chemother. Proc.*, 5th, **2(2),** 909 (1967).
4. L. Raiford and H. Davis, *J. Am. Chem. Soc.*, **50,** 156 (1928).
5. R. Lacouir and R. Heilman, *Bull. Soc. Chem. Fr.*, **45,** 541 (1929).
6. L. Raiford and G. Gundy, *J. Org. Chem.*, **3,** 265 (1933).
7. S. G. Beech, J. H. Turnbull and W. Wilson, *J. Chem. Soc.*, 4686 (1962).
8. A. Samour, M. I. B. Selim and G. H. El-Sayed, *U.A.R. J. Chem.*, **14,** 235 (1971).
9. A. Samour, A. Marei and M. H. G. Hussein, *U.A.R.J. Chem.*, **12,** 461 (1969).
10. A. Samour and M. El Kasaby, *U.A.R.J. Chem.*, **13,** 248 (1970).
11. A. Schönberg and M. M. Sidky, *J. Amer. Chem. Soc.*, **75,** 5128 (1953).
12. A. Schönberg, A. E. K. Fateen and A. E. M. A. Samour, *J. Amer. Chem. Soc.*, **78,** 4689 (1956).
13. A. E. M. A. Samour and A. Marei, *U.A.R.J. Chem.*, **11,** 1 (1968).
14. A. M. Osman, Kh. M. Hassan and M. A. El Maghraby, *Ind. J. Chem.*, **14b,** 282 (1976).
15. R. P. Barnes and L. B. Dodson, *J. Amer. Chem. Soc.*, **67,** 132 (1945).
16. K. V. Auwers and H. Müller, *J. Prakt. Chem.*, **137,** 102 (1933); C. Harries and L. Jaelonski, *Ber.*, **31,** 1380 (1898).
17. A. H. Blatt, *J. Amer. Chem. Soc.*, **53,** 1133 (1931).
18. J. B. Vendickson, D. J. Cram and G. S. Hammond, "Organic Chemistry" Megrow Hill Kogakuana Ltd. Tokyo 3rd ed. (1970) p. 260.
19. C. N. R. Ras, "Chemical application of infrared spectroscopy," Academic Press, Inc., New York (1968) p. 184.
20. British Pharmacopoeia, Pharmaceutical Press, London, (1953) p. 796.