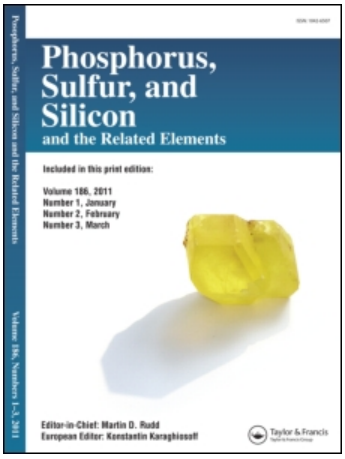


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

HETEROCYCLO-SUBSTITUTED SULFA DRUGS: PART X. NOVEL 5-IMINO-δ²-PYRAZOLIN-4-DITHIOCARBAMYL-AZO DYES AS ANTIMICROBIAL AGENTS

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

To cite this Article Awad, Ibrahim M. A.(1996) 'HETEROCYCLO-SUBSTITUTED SULFA DRUGS: PART X. NOVEL 5-IMINO-δ²-PYRAZOLIN-4-DITHIOCARBAMYL-AZO DYES AS ANTIMICROBIAL AGENTS', Phosphorus, Sulfur, and Silicon and the Related Elements, 114: 1, 17 — 28
To link to this Article: DOI: 10.1080/10426509608046407
URL: http://dx.doi.org/10.1080/10426509608046407

Phosphorus, Sulfur, and Silicon, 1996, Vol. 114, pp. 17–28
Reprints available directly from the publisher
Photocopying permitted by license only

HETEROCYCLO-SUBSTITUTED SULFA DRUGS: PART X. NOVEL 5-IMINO-Δ^2-PYRAZOLIN-4-DITHIOCARBAMYL-AZO DYES AS ANTIMICROBIAL AGENTS

IBRAHIM M. A. AWAD

Department of Chemistry, Faculty of Science, University of Assiut, Assiut 71516, Egypt

(Received November 22, 1995; in final form February 16, 1996)

Synthesis of a series of novel azo-sulfa drugs as 5-imino-3-methyl-1-phenyl-Δ^2-pyrazolin-4-dithiocarbamy-azo dyes (**I–XV**) are described via a reaction of 4-sulfamoyl and/or sulfonyl diazonium chloride with 5-imino-3-methyl 1-1-phenyl-Δ^2-pyrazolin-4-dithiocarbamic acid in acid medium. The corresponding iron, copper, mercury, cobalt, nickel, and lead chelates were obtained in 1:1 ligand-to-metal cation molar ratio at ice temperature as monochelate compounds (**Iaf–XVaf**). Furthermore, heating in 1:2 molar ratio gave di-chelate compounds (**I'a–f–XV'a–f**). All the synthesized azo-sulfa drugs (ligands) and their mono- and/or di-chelates were characterized by microanalysis, UV, IR and H-NMR spectroscopy and were screened *in vitro* for their antibacterial and antifungal activities.

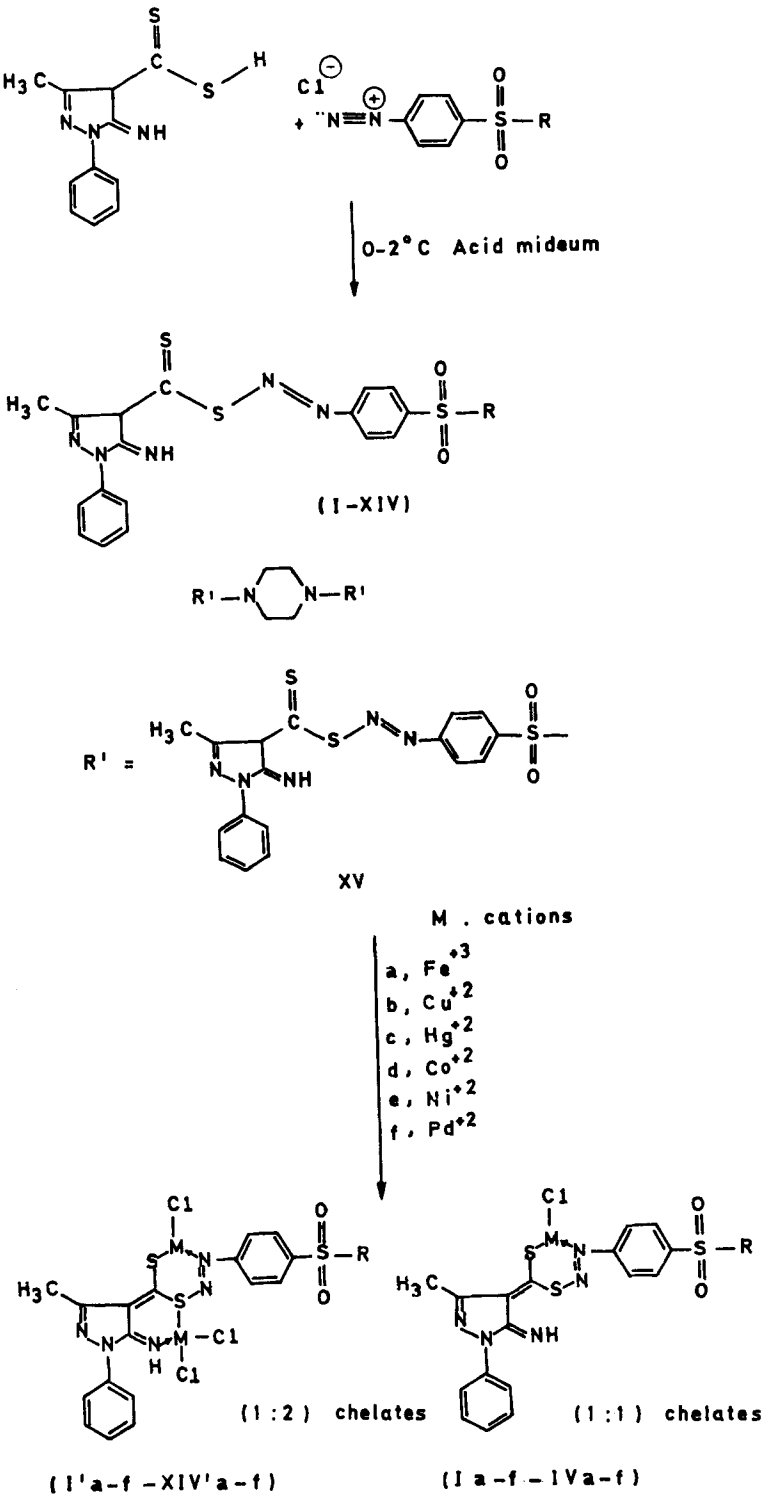
Key words: Imino-pyrazolin-, azo-sulfonamido-dithiocarbamate drugs, metal chelates, antimicrobial activity.

INTRODUCTION

Many pyrazole derivatives are associated with antifungal,[1] antidiabetic,[2] anti-inflammatory properties[3] and antibacterial activities.[1–6] Furthermore, sulfonamide and azo-sulfonamide derivatives were later found to be biologically versatile drugs having anticancer, antimalarial, and antitubercular properties,[7–9] good chelating agents for occupational poisoning by metals,[10] and excellent azo dyes and occupy a good position as analytical reagents.[11] Hence, it was thought that a pyrazole ring, if coupled with different heterocyclo-substituted sulfamoyl moieties, another pharmacophore, the resulting sulfa drugs might have high biological potency. Futhermore, several chelating agents are regularly used as antidotes for occupational poisoning by metals and for chronic metal intoxication arising from therapy or household contamination.[12–15] Optimum dosages of these antidotes circulates in the bloodstream without much depletion of the body's essential heavy metals.[10]

D-Penicillamine has been used as an antidote for treatment of poisoning by copper in cystinurea and in rheumatoid arthritis.[13] Deferoxamine mesylate is selective for iron with little or no affinity for other metals. It[10] is nontoxic and has been used in the treatment of hemochromatosis and as an effective antidote for the treatment of acute iron poisoning in children.

The present paper deals with the synthesis of a number of novel azo-dye sulfa drugs containing mainly a pyrazole dithiocarbamate moiety[16] with different heterocyclosubstituted sulfonamid rings (pyridine, pyrimidine, methyl pyrimidine, dimethyl pyrimidine, thiazole, methoxazole, methoxy pyridazine, dimethoxy pyrimidine, mor-



SCHEME I

TABLE I

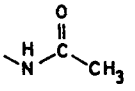
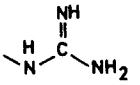
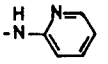
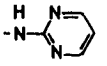
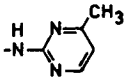
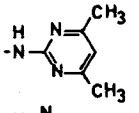
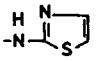
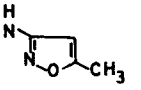
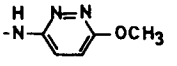
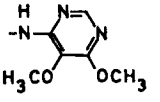
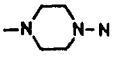
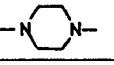
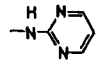
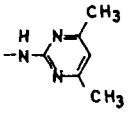
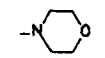
Compd. No. (Ligands)	Compd. No. (Chelates 1:1)	Compd. No. (Chelates 1:2)	R
I	Ia-f	I'a-f	
II	IIa-f	II'a-f	
III	IIIa-f	III'a-f	
IV	IVa-f	IV'a-f	
V	Va-f	V'a-f	
VI	VIa-f	VI'a-f	
VII	VIIa-f	VII'a-f	
VIII	VIIIa-f	VIII'a-f	
IX	IXa-f	IX'a-f	
X	Xa-f	X'a-f	
XI	XIa-f	XI'a-f	
XII	XIIa-f	XII'a-f	
XIII	XIIIa-f	XIII'a-f	
XIV	XIVa-f	XIV'a-f	
XV	XVa-f	XV'a-f	

TABLE IIa

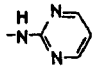
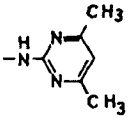
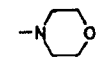
Microanalytical data of some representative mono-chelate compounds (Ia–f–Va–f)

Compd. No.	R	M.P. (°C)	Yield %	Molecular Formula (MW)	Calculated/(found) %S	%Cl
Va		300	75	$C_{21}H_{17}N_8O_2S_3 \cdot FeCl_2$ (636.33)	15.11 (15.18)	11.14 (11.21)
b		300	78	$C_{21}H_{17}N_8O_2S_3 \cdot CuCl$ (608.60)	15.80 (15.85)	5.82 (5.86)
c		250	81	$C_{21}H_{17}N_8O_2S_3 \cdot HgCl$ (745.65)	12.90 (12.83)	4.75 (4.81)
d		315	68	$C_{21}H_{17}N_8O_2S_3 \cdot CoCl$ (604.00)	15.92 (15.98)	5.86 (5.91)
e		215	63	$C_{21}H_{17}N_8O_2S_3 \cdot NiCl$ (603.77)	15.93 (16.01)	5.87 (5.94)
f		165	59	$C_{23}H_{20}N_8O_4S_3 \cdot Pb^*$ (775.84)	12.39 (12.43)	— —
VIIa		271	72	$C_{23}H_{21}N_8O_2S_3 \cdot FeCl_2$ (664.38)	14.47 (14.51)	10.67 (10.61)
b		253	76	$C_{23}H_{21}N_6O_2S_3 \cdot CuCl$ (636.66)	15.10 (15.16)	5.56 (5.61)
c		188	80	$C_{23}H_{21}N_8O_2S_3 \cdot HgCl$ (773.71)	12.43 (12.38)	4.58 (4.61)
d		220	62	$C_{23}H_{21}N_8O_2S_3 \cdot CoCl$ (632.05)	15.21 (15.28)	5.60 (5.65)
e		205	68	$C_{23}H_{21}N_8O_2S_3 \cdot NiCl$ (631.85)	15.22 (15.26)	5.61 (5.55)
f		192	66	$C_{25}H_{24}N_8O_4S_3 \cdot Pb^*$ (803.90)	11.16 (12.01)	— —
XIIa		153	86	$C_{21}H_{21}N_6O_3S_3 \cdot FeCl_2$ (628.38)	15.30 (15.38)	11.28 (11.32)
b		134	88	$C_{21}H_{21}N_6O_3S_3 \cdot CuCl$ (600.62)	16.01 (16.08)	5.90 (5.98)
c		145	82	$C_{21}H_{21}N_6O_3S_3 \cdot HgCl$ (737.69)	13.03 (13.00)	4.80 (4.72)
d		159	78	$C_{21}H_{21}N_6O_3S_3 \cdot CoCl$ (596.02)	16.13 (16.10)	5.96 (5.98)
e		165	75	$C_{21}H_{21}N_6O_3S_3\ NiCl$ (595.79)	16.14 (16.10)	5.95 (5.51)
f		136	76	$C_{23}H_{24}N_6O_5S_3\ Ph^*$ (767.88)	12.52 (12.58)	— —

* = Pb Cation as: $(CH_3COO)_2Pb$.

TABLE IIb

Microanalytical data of some representative di-chelate compounds (I'a–f–XV'a–f)

Compd. No.	R	N.P. (°C)	Yield %	Molecular Formula (MW)	Calculated/(found) %S	%Cl
V' a		225	81	$C_{21}H_{17}N_8O_2S_3.Fe_2Cl_5$ (798.50)	12.04q (12 10)	22.19 (22 23)
b		217	87	$C_{21}H_{17}N_8O_2S_3\cdot Cu_2Cl_3$ (743.05)	12.94 (13.10)	4.77 (4 71)
c		212	83	$C_{21}H_{17}N_8O_2S_3.Hg_2Cl_3$ (1017.15)	9.45 (9.39)	10.45 (10 50)
d		233	74	$C_{21}H_{17}N_8O_2S_3\cdot Co_2Cl_3$ (733.83)	13.10 (13.06)	14.49 (14.42)
e		210	68	$C_{21}H_{17}N_8O_2S_3\cdot Ni_2Cl_3$ (603 · 77)	15.93 (16.00)	5.87 (5·80)
f		198	62	$C_{27}H_{26}N_8O_8S_3\cdot Pb_2$* (1101.12)	8.73 (8.80)	— —
VIIa		228	78	$C_{23}H_{21}N_8O_2S_3\cdot Fe_2Cl_5$ (826.56)	11.63 (11 70)	21·44 (21·51)
b		215	80	$C_{23}H_{21}N_8O_2S_3\cdot Cu_2Cl_3$ (771.10)	12.47 (12 51)	13.79 (13.81)
c		168	84	$C_{23}H_{21}N_8O_2S_3\cdot Hg_2Cl_3$ (1045.20)	9.20 (9.25)	10·17 (10·20)
d		181	68	$C_{23}H_{21}N_8O_2S_3\cdot Co_2Cl_3$ (761.89)	12.62 (12.60)	13.95 (14.01)
e		193	73	$C_{23}H_{21}N_8O_2S_3.Ni_2Cl_3$ (761.44)	12.63 (12 70)	13.96 (14.02)
f		188	78	$C_{29}H_{30}N_8O_8S_3\cdot Pb_2$* (1129.18)	8.51 (8 57)	— —
XIIa		242	89	$C_{21}H_{21}N_6O_3S_3.Fe_2Cl_5$ (790.59)	12.16 (12.08)	14·46 (14·50)
b		218	91	$C_{21}H_{21}N_6O_3S_3\cdot Cu_2Cl_3$ (735.07)	13.08 (13·10)	14·46 (14·51)
c		202	88	$C_{21}H_{21}N_6O_3S_3\cdot Hg_2Cl_3$ (1009.21)	9.53 (9.60)	10·53 (10·50)
d		238	80	$C_{21}H_{21}N_6O_3S_3\cdot Co_2Cl_3$ (725.87)	13.25 (13.30)	14·65 (14·61)
e		208	78	$C_{21}H_{21}N_6O_3S_3\cdot Ni_2Cl_3$ (725.41)	13.26 (13.30)	14·66 (14·70)
f		198	81	$C_{27}H_{30}N_6O_9S_3\cdot Pb_2$* (1093.18)	13.26 (13.30)	— —

* = Pb Cation as: $(CH_3COO)_2Pb$.

TABLE III

IR spectra of some azo dye sulpha drug (ligands) and their metal chelates in cm^{-1}

Compd. No.	Imino ν C=NH-	νCH_3 pyrazole	S / νC \	νSO_2 (asym.)	νSO_2 (sym.)	νN=N-	νMe-S	νSO_2NH	νC-HAr	νCH_3 sulpha
IV	3345	2980	1325	1355	1160	1595	-	1375	755	-
IVa	3335	2970	1305	1345	1145	1575	355	1365	750	-
IV`c	3330	2975	1307	1345	1150	1572	345	1368	750	-
V	3340	2975	1320	1350	1155	1590	-	1375	750	-
Va	3345	2965	1305	1345	1150	1575	350	1365	750	-
V`c	3325	2970	1305	1340	1160	1570	340	1370	755	-
VI	3345	2973	1330	1355	1160	1587	-	1370	755	2995
VIa	3340	2965	1305	1340	1150	1560	350	1360	750	2990
VI`c	3340	2970	1300	1335	1155	1565	345	1360	750	2990
VII	3340	2970	1335	1360	1165	1596	-	1375	745	2990,3001
VIIa	3342	2965	1300	1335	1155	1565	355	1360	748	2995,3015
VII`c	3337	2968	1303	1330	1158	1568	348	1362	750	2990,3000

pholine, piperidine, piperazine) and the evaluation of their antimicrobial (antibacterial and antifungal) activities.

EXPERIMENTAL

All chemicals used were reagent grade and purified prior to use. All melting points were determined on a Kofler melting point apparatus and are uncorrected. Microanalysis were performed on a Perkin-Elmer 240 E microanalyser. IR spectra were run on a Pye Unicum SP 200 G spectrophotometer in KBr discs. UV spectra were recorded on a Shimadzu UV-200 S spectrophotometer in DMF. H NMR spectra were done on a JEOL-FT 270 MHz NMR instrument using TMS as an internal standard.

5-Imino-3-methyl-1-phenyl-Δ^2-pyrazolin-4-dithiocarbamic acid: This compound was prepared as reported previously.[16]

4-[(4'-Heterocyclo-substituted) sulfamoyl and/or surfonyl] benzenediazonium chlorides: These compounds were prepared by diazotization of 4'-(aminosulfonyl)-aniline, 4'-(acetylaminosulfonyl)aniline, 4'-(guanidinosulfonyl)-aniline, "-(2"-pyridylaminosulfonyl)anilin, 4'-(2"-pyrimidylaminosulfonyl)aniline, 4-(2"-(4-methyl)-pyrimidylaminosulfonyl)aniline, 4'-(2"-(4,6-dimethyl)pyrimidyl-aminosulfonyl)-aniline, 4'-(2"-thiazolylaminosulfonyl)aniline, 4'-(2"-methoxazolylamino-sulfonyl)-aniline, 4'-(6"-(3-methoxy)pyridazylamino-sulfonyl)aniline, 4'-(6"-(2,4-dimethoxy)-pyrimidylaminosulfonyl)aniline, 4'-(piperidinosulfonyl)aniline, 4'-(morpholino-sulfonyl)aniline, 4-((mono)-piperazinosulfonyl)aniline, and 4'-[(bis)-piperazino-disulfonyl]aniline, (0.01 mol) dissolved in a mixture of acetone (30 ml) and 60 ml of 70% pure hydrochloric acid with sodium nitrite (0.7 g, 0.01 mol) at 0–5°C.

Synthesis of 4-[(4'-heterocyclo-substituted)-5-imino-3-methyl-1-phenyl-Δ^2-pyrazolin-]phenylazo-dithiocarbate dyes (**I–XV**): To an ice cold solution of 5-imino-3-methyl-1-phenyl-Δ-pyrazolin-4-dithiocarbamic acid (2.50 g, 0.01 mol) in 40 ml of 50% sodium hydroxide solution, a cold hydrochloric acid solution of the diazonium salt was added dropwise with stirring. The reaction mixture was further stirred and kept at 0–2°C for a 5 h followed by addition of 5% aqueous sodium hydroxide to pH 8. The product was collected, washed well with water, and recrystallized from ethanol (Table I).

TABLE IV

^{1}H-NMR spectra of some azo dye ligands and their chelates in $CDCl_3$ (chemical shifts in δppm)

Compd No.	Aromatic protons (m)	Iminno >C=NH (S)	−C−H (pyrazole) (S)	$-CH_3$ pyrazole (S)	$-SO_2NH-$ (S)	CH_3-sulpha (S)
IV	6.95-8.35 (13 H)	5.50 (1 H)	6.80-7.00 (1 H)	2.45 (3 H)	8.50 (1 H)	-
IVa	7.10-8.30 (13 H)	5.80 (1 H)	-	2.35 (3 H)	8.45 (1 H)	-
IV'c	7.00-8.35 (13 H)	5.95 (1 H)	-	2.40 (3 H)	8.40 (1 H)	-
V	7.00-8.20 (12 H)	5.55 (1 H)	6.80-7.00 (1 H)	2.40 (3 H)	8.45 (1 H)	-
Va	7.05-8.10 (12 H)	5.75 (1 H)	-	2.35 (3 H)	8.50 (1 H)	-
V'c	6.95-8.00 (12 H)	6.05 (1 H)	-	2.45 (3 H)	8.40 (1 H)	-
VI	7.10-8.15 (11 H)	5.45 (1 H)	6.85-7.05 (1 H)	2.42 (3 H)	8.55 (1 H)	2.55 (3 H)
VIa	7.20-8.10 (11 H)	5.85 (1 H)	-	2.30 (2 H)	8.45 (1 H)	2.50 (3 H)
VI'c	7.15-8.15 (11 H)	5.90 (1 H)	-	2.40 (3 H)	8.40 (1 H)	2.52 (3 H)
VII	7.20-8.10 (10 H)	5.55 (1 H)	6.80-7.10 (3 H)	2.42 (3 H)	8.35 (1 H)	2.50(3 H),2.58(3 H)
VIIa	7.15-8.15 (10 H)	5.90 (1 H)	-	2.35 (3 H)	8.40 (1 H)	2.48(3 H),2.55(3 H)
VII'c	7.10-8.05 (10 H)	5.85 (1 H)	-	2.40 (3 H)	8.42 (1 H)	2.55(3 H),2.60(3 H)

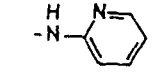
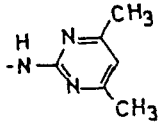
Synthesis of iron, copper, mercury, cobalt, nickel and lead azopyrazolin-4-yl dithiocarbamate mono-chelates (**Ia–f–XVa–f**): A solution of the appropriate azo-(heterocyclo-substituted) pyrazolin-4-yl dithiocarbamate dyes (ligands **I–XV**) (0.01 mol) in a mixture of ethanol and dilute acetic acid (5:1) was added dropwise with stirring to a solution of the given metal salt (0.01 mol) [ferric chloride, copper chloride, mercuric chloride, cobalt chloride, nickel chloride, lead acetate] in ethanol (30 ml). Stirring was continued for 30 min at room temperature. The precipitated products were filtered, washed throughly with distilled water, dried, and recrystallized from ethanol (Table II).

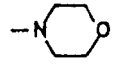
Synthesis of iron, copper, mercury, cobalt, nickel and lead azo-pyrazolin-4-yl dithiocarbamate di-chelates (**I'a–f–XV'a–f**): A boiling solution of the appropriate azo-(heterocyclo-substituted)pyrazolin-4-yl dithiocarbamate dye ligands (**I–XV**) (0.01 mol) in a mixture of ethanol and dilute acetic acid (8:1) was added dropwise with stirring to a solution of the given metal salt (0.02 mol) [ferric chloride, copper chloride, mercuric chloride, cobalt chloride, nickel chloride, lead acetate] in ethanol (50 ml). Stirring was continued for 1 h at 70°C. The reaction mixture was cooled and the precipitate was filtered, washed thoroughly with distilled water, dried and recrystallized from ethanol (Table III).

Antimicrobial activity: Antibacterial and antifungal activities: The disc-diffusion method was used to measure the antimicrobial activity.[34,35] The azo dye ligands and their metal chelates were dissolved in sterile dimethylformamide and added at a concentration of 0.5 mg/disc (Whatman No. 3 filter paper, 0.5 cm diameter). Antibacterial spectrum was tested with six strains of bacteria namely: *Staphylococcus aureus (DSM 346), Klebsiella pneumoniae (DSM 681), Micrococcus roseus (DSM 348), Bacillus cereus (DSM 345), Bacillus anthracis (DSM 344)*, and *Serratia marcmacecens (DSM 1608)*. Antifungal activity of the same compounds was tested with three species of fungi namely: *Alternaria alternata* (Fries) Keissler (AUCC-1110), *Penicillium chrysogenum* (Thom AUCC-530) and *Asperogillus terreus* (Wilhelm AUCC - 230). The culture medium for bacteria was nutrient agar (NA) (composed of beef extract, 3 g peptone, 5 g, agar, 15 g/L and adjusted to pH 7 before sterilization at 121°C for 30 min). Glucose-Czapek's agar medium ($NaNO_3$, 2 g; KH_2PO_4, 1 g; $MgSO_4$, $7H_2O$, 0.5 g; KCl. 0.5 g; glucose. 10 g; agar, 15 g/L of distilled water) was used for fungi. The inoculated plates were incubated at 37 + 1°C for 24–48 h in the case of bacteria and at 28°C for 7–8 days in the case of fungi. The inhibition zones of microbial growth produced by different compounds were measured.[36]

TABLE V

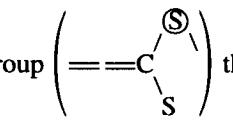
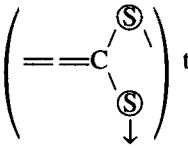
Antimicrobial results of some representative azo-sulpha drugs and their chelates (inhibition zones in mm)[a]

Cod. no.	R	Antibacterial screening						Antifungal screening		
		Staphylococcus aureus (DSM 346)[b]	*Klebsiella pneumoniae* (DSM 581)	*Micrococcus roseus* (DSM 346)	*Bacillus cereus* (DSM 345)	*Bacillus anthracis* (DSM 344)	*Serratia rhadnii* (DSM 1608)	*Alternaria alternata* (AUCC 1110)[c]	*Penicillium chrysogenum* (AUCC 530)	*Asperogillus terreus* (AUCC 230)
v		5.0 (−ve)	8.5 (−ve)	9.5 (−ve)	11.5 (−ve)	10.5 (−ve)	11.0 (6.0)	16.0 (−ve)	5.0 (−ve)	3.0 (−ve)
a		4.0	6.5	−ve	12.0	9.5	12.5	7.5	9.0	8.5
a′		6.0	7.0	3.5	13.0	10.5	13.5	8.0	10.5	9.5
b		5.0	−ve	−ve	11.0	8.5	11.5	−ve	−ve	−ve
b′		7.0	4.0	4.5	12.0	9.5	12.0	3.0	−ve	−ve
c		15.0	8.5	11.5	17.0	13.0	18.5	8.5	11.0	9.0
c′		11.5	12.0	13.0	19.0	16.5	19.5	9.0	12.5	10.5
d		8.0	−ve	−ve	9.5	−ve	7.5	−ve	−ve	−ve
d′		9.0	4.0	4.5	10.5	3.0	9.5	3.5	−ve	−ve
e		7.0	−ve	−ve	3.5	−ve	3.0	−ve	−ve	−ve
e′		8.5	1.5	5.0	5.5	4.5	7.5	−ve	2.5	−ve
f		3.0	−ve	−ve	10.5	8.0	9.5	−ve	−ve	−ve
f′		4.0	5.0	7.5	11.5	9.5	12.0	4.5	5.0	6.0
$\mathbf{v}_H$		8.5 (−ve)	11.0 (−ve)	9.0 (−ve)	10.5 (−ve)	11.5 (−ve)	12.0 (4.0)	3.0 (−ve)	3.0 (−ve)	5.0 (−ve)
a		4.5	−ve	11.0	11.5	−ve	11.5	6.5	11.5	6.5
a′		5.5	4.5	12.5	12.0	7.0	12.5	7.0	12.5	7.0
b		6.0	1.5	9.5	10.5	−ve	7.5	−ve	−ve	−ve
b′		7.0	3.3	10.5	11.0	6.0	8.5	2.0	3.5	−ve

c		11.0	13.0	14.5	17.5	13.0	14.5	11.0	12.5	9.5
d		5.5	−ve	6.0	−ve	−ve	6.0	−ve	−ve	−ve
d′		6.5	2.5	7.5	5.5	3.0	7.0	2.5	3.5	−ve
e		−ve	−ve	−ve	−ve	4.5	4.5	−ve	−ve	−ve
e′		3.5	4.0	−ve	6.0	7.5	6.5	−ve	4.5	3.5
f		10.5	7.0	−ve	7.0	8.5	13.0	3.0	6.5	−ve
f′		10.0	115	12.0	9.5	10.5	14.5	4.5	8.0	7.5
x_H		9.5 (−ve)	12.5 (−ve)	11.5 (−ve)	14.0 (−ve)	15.0 (−ve)	17.0 (30)	7.5 (−ve)	8.0 (−ve)	11.0 (−ve)
a		10.0	13.5	14.0	15.0	17.0	17.5	9.5	9.0	12.0
a′		11.0	14.0	15.0	16.0	16.5	18.0	11.5	11.0	13.5
b		3.5	13.5	9.5	12.0	10.5	16.5	11.0	12.0	16.0
b′		7.0	16.0	11.0	13.0	9.5	14.5	12.5	13.0	15.5
c		11.0	16.0	16.5	17.5	18.0	18.5	16.0	15.5	17.0
c′		13.0	17.5	18.5	19.0	19.5	19.0	14.5	17.5	18.5
d		6.5	−ve	−ve	−ve	4.5	−ve	−ve	−ve	−ve
d′		—	4.0	3.5	4.0	6.0	4.5	4.5	−ve	3.5
e		4.0	−ve	−ve	−ve	5.5	−ve	−ve	−ve	−ve
e′		−ve	3.5	−ve	5.0	6.5	3.5	3.5	−ve	2.5
f		5.0	8.0	6.0	7.0	9.5	10.5	7.5	7.0	8.0
f′		6.0	9.5	8.5	9.5	10.5	11.5	8.5	9.5	10.5

[a]Values = Inhibition Zones of the free P-aminobenzenesulphonamide derivatives (normal sulpha drugs).
[b]DSM = Deutsche Semmlungvon Microorgamifman (German collection of Microorganisms).
[c]AUCC = Assiut University Culture Collection.
(−ve) = Compound not active biologically.

RESULTS AND DISCUSSION

Observations on the antimicrobial importance of azo sulfa drugs and their metal chelates[17–31] prompted us to synthesize a novel series of drugs related to 5-imino-Δ^2-pyrazolin-4-dithiocarbamic acid moiety[16] as 4-[(4′-heterocyclo-substituted)-phenyl-azo-3-methyl-1-phenyl-Δ^2-pyrazolin-]dithiocarbamate azo dyes (**I–XV**). Their iron (Fe^{+3}), copper (Cu^{+2}), mercury (Hg^{+2}) cobalt (Co^{+2}), nickel (Ni^{+2}), and lead (Pb^{+2}) chelates (**Ia–f–XVa–f**) and or (**I′a–f–XV′a–f**) were synthesized to examine and study their antimicrobial activities. Heterocyclo-substituents of the sulfamoyl and/or sulfonyl moiety were chosen so as to ensure a wide variation in their size, electronegativity, chemical activity, solubility, antitubercular properties and their biological activities. Analytical data and melting points of the novel azo-dye sulfa drugs (ligands) and their metal chelates are recorded in Tables I, IIa, and IIb. The IR spectra of the synthesized sulfa drugs confirmed the presence in the azo precursor compounds of the imino group (C═NH) band at 3325 cm^{-1} and for sulfonamide group (SO_2NH.) band at 1365 cm^{-1} and for the azo group (—N═N—) band at 1582 cm^{-1}. These absorptions shifted to the lower frequency on chelation. In case of 1:1 molar ratio of reactants, chelation formed in the cold involving an azo group (—N═N—) and a dithiocarbamyl group  through thiole group forming six membered ring. In the case of the 1:2 molar ratio of ligand to metal cation, chelation formed in a hot solution with the imino (C═NH) group and dithiocarbamyl group through the sulfur atom  to form another six membered ring (Table III). The H NMR spectrum of compound (V) in $CDCl_3$ showed signals at δ = 8.80 (S, 1 H, —SO_2 NH—) at δ = 2.15 (s, 3H, —CH_3) at δ = 7.00–8.15 (m, 12 H, aromatic protons) and at δ = 6.85–7.05 (s, 1H) of the pyrazole ring which disappeared during the formation of the first chelated six membered ring with metal cation 1:1 molar ratio (Table IV).

BIOLOGICAL EVALUATION

Antibacterial Activity

The results for the inhibition zones of various isolates of bacteria indicated that, the ligand compounds 5-imino-pyrazolindithiocarbamate azo dyes **I–XV** and most of their metal chelates in 1:1 (**Ia–f–XVa–f**) and/or 1:2 (**I′a–f–XV′a–f**) molar ratio of Fe^{+3}, Cu^{+2}, Hg^{+2}, Co^{+2}, Ni^{+2}, Pb^{+2} cations exhibited clear activities against all bacteria isolates (inhibition zones ranged from 2.0 to 19.5 mm). Azo dye derivatives **I, II, IV, V, VIII, X,** and **XI**, have remarkable effects (inhibition zones 4.0–9.5 mm), and also complexes **Va–f, Va–f, VIIa–f, VIII′a–f,** and **XII′a–f** (inhibition zones ranged from 7.0 to 16.0 mm) against *Serratia rhadenii* and *Bacillus cereus*

(Table V). Interestingly, iron, copper and lead complexes **VII'a**, **VII'b**, and **VII'f** exhibit particularly strongly effects (inhibition zones 16.0–19.5 mm).

Antifungal Activity

The synthesized compounds also possessed variable and attractive antifungal activities (inhibition zones ranged from 1.5 to 16.5 mm). Ligand azo dye dithiocarbamate **V**, **VIII**, and **X**, derivatives showed strong effects against *Penicillium chrysogenum* and *Aspergillus terreus* (inhibition zones 1.5–9.0 mm), but **IV**, and **XII**, compounds exhibited pronounced activities and are more potent effect (inhibition zones 7.5–12.0 mm). Furthermore, chelated compounds **VII'a–b**, **XII'e** are highly active (inhibition zones ranged from 3.0 to 16.0 mm), against *Aspergillus terreus* and *Penicillium chrysogenum*. On the other hand, **V'a** and **XII'a–f** have potent effects (inhibition zones 3.9–9.0 mm) only against *Penicillium chrysogenum* (Table V).

REFERENCES

1. R. B. Pathk and S. C. Bahel, *J. Indian Chem. Soc.*, **57,** 1108 (1980).
2. T. Trikura, Jap. Pat., 7570367, *Chem. Abstr.*, **84,** 5944 (1976).
3. I. A. Eid, M. A. Kira and H. H. Fahmy, *J. Pharm. Beig.*, **33,** 303–11 (1978).
4. R. Nanda, S. Padmanabhan, B. Triparthy and A. S. Mittra, *J. Indian Chem. Soc.*, **52,** 533 (1975).
5. A. Nayak, S. Das, C. R. Misra and A. S. Mittra, *J. Indian Chem. Soc.*, **54,** 485 (1977).
6. R. Sundar and A. S. Mittra, *Indian J. Chem.*, **15B,** 1062 (1977).
7. Hoffmann-La Roche and A.G. Co., Swiss Patent, Neth. Appl. 66610, 566 (Cl. CO7d), 31: *Chem. Abstr.*, **67,** 73523r (1967).
8. A. Veichulis John., US Patent, 3, 271, 251 (Cl. 167-65): *Chem. Abstr.*, **40,** 19938e (1996).
9. M. Dietrich, Swiss Patent, 424767: *Chem. Abstr.*, **68,** 682 7089g (1969).
10. S. Moeschlin and U. Schnider, *New Eng. J. Med.*, **57,** 269 (1963).
11. M. Sirki and D. Jerdjevice, *Anal. Chem.*, **43,** 1375 (1971).
12. A. S. Weiss, J. A. Markenson, M. S. Weiss and W. H. Kammerer, *Am. J. Med.*, **64,** 114 (1978).
13. Australian National Drugs Information Service, Aust. J. Pharm. October, p. 647, 1982.
14. A. A. Abdel Hafez, I. M. A. Awad and Kh. M. Hassan, *Coll. Czech. Chem. Commun.*, **52,** 2753 (1987).
15. I. M. A. Awad, A. M. A. Aly, A. M. Abdel-Alim, R. A. Abdel-Aal and S. H. Ahmed, *J. Inorganic Biochemistry*, **33,** 77–89 (1988).
16. G. Matolesy, P. Sohar and B. Bordas, *Chem. Ber.*, **104,** 1155 (1971).
17. I. M. A. Awad, A. M. A. Aly, A. A. Abdel-Hafez and Kh. M. Hassan, *J. Chinese Chem. Soc.*, **36,** 107–114 (1989).
18. I. M. A. Awad and Kh. M. Hassan, *Phosphorus, Sulfur, and Silicon*, **44,** 135–141 (1989).
19. I. M. A. Awad and A. M. A. Aly, *J. Synth. React. Inorg. Met.-Org. Chem.*, **21,** 375–383 (1991).
20. A. M. A. Aly and I. M. A. Awad, *Phosphorus, Sulfur, and Silicon*, **60,** 135–8 (1991).
21. M. K. Hassan and I. M. A. Awad, *Bull. Fac. Sci., Assiut Univ.*, **20,** 148 (1991).
22. A. A. Abdel Hafez, I. M. A. Awad and M. F. El-Zohry, *J. Chem. Techn. and Biotechnol.*, **54,** 369–374 (1992).
23. I. M. A. Awad, *Dyes and Pigments*, **17,** 123–39 (1991).
24. A. A. Abdel Hafez and I. M. A. Awad, *Dyes and Pigments*, **20,** 197–209 (1992).
25. I. M. A. Awad, A. A. Abdel-Hafez and M. F. El-Zohry, *J. Chem. Techn. and Biotechnol.*, **55,** 217–225 (1992).
26. I. M. A. Awad, *J. Chem. Techn. and Biotechnol.*, **53,** 227–36 (1992).
27. A. A. Abdel Hafez, I. M. A. Awad and M. E. Abdel Monem, *J. Chem. Techn. and Biotechnol.*, **55,** 333–338 (1992).
28. I. M. A. Awad, A. A. Abdel-Hafez and M. F. El-Zohry, *Collect. Czech. Chem. Conmun.*, **59,** 482–488 (1992).
29. I. M. A. Awad., *Bull. Chem. Soc. Jpn.*, **66,** 167–73 (1993).
30. I. M. A. Awad, *Org. Prep. Proc. Int.*, **25,** 347 (1993).
31. A. A. Abdel Hafez, I. M. A. Awad and R. A. Ahmed, *J. Chinese Chem. Soc.*, **40,** 289–296 (1993).
32. C. Preti, G. Tosi, *J. Inorg. Nucl. Chem.*, **38,** 1746 (1976).

33. G. Carlo Franchini, A. Giusti, C. Perti, L. Tassi and P. Zannini, *Polyhedron*, **4**, 1553 (1985).
34. E. S. Moss and A. L. Mequon, "Atlass of Medical Myeolgot," 3rd Ed., The Williams and Wilkins Co., Baltimore, U. S. A., p. 366, 1969.
35. K. K. Chaturred, Jain Nok, P. Jain and R. Kaushal, *Indian Drugs*, **15**, 57 (1978).
36. J. D. Sleight and M. C. Timburg, "Notes on Medical Bacterology," Churchill Livingston, C. S. A., p. 43, 1981.