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

By

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عقاقير السلفا الغير متجانسه الحلقه . الجزء العاشر

٥ - أمينو - ٢Δ - بيرازولين ثيوكربااميل - s - صبغة الأزو كمضادات حيويه

إبراهيم محمد علي عوض

أمكن تخليق سلسلة جديدة من عقاقير صبغات الآزو مثل : ٥ - أيمينو - ٣ - ميثيل -١- فـينيل - ٢Δ - بيـرازولين - ٤ - ثنائي ثيوكربامـيل - S - صـبـغـة الآزو (I-XV) بتفاعل ٤ - سلفاموبل (سلفونيل) ديازونيوم كلوريد مع ٥ - ايمينو - ٣ - ميثيل - ١ - فـينيل - ٢Δ - بيرازولين - ٤ - حمض ثنائي ثيو الكاربامبك في وسط حمض . كذلك امكن تخليق متراكبات هذه السلسلة مع عناصر الحديد والنحاس والزئبق والكوبلت والنيكل والرصاص ودراسة التأثير البيولوجي لهذه المركبات ومتراكباتها مع بعض من البكتريا والفطرات المختارة .

Key Words: Imino-pyrazolin-, Azo-sulphonamido-dithiocarbamate drugs, Metal chelates, Antimicrobial activity.

ABSTRACT

Synthesis of a series of novel azo-sulpha drugs as 5-imino-3-methyl-1-phenyl-Δ^2-pyrazolin-4-dithiocarbamyl-s-azo dyes (I-XV) are described by the reaction of 4-sulphamoyl and/or sulphonyl diazonium chloride with 5-imino-3-methyl-1-phenyl-Δ^2-pyrazolin-4-dithiocarbamic acid in acid medium. The corresponding iron, copper, mercury, cobalt, nickel and lead chelates are synthesized, in 1:1 ligand-to-metal cation molar ratio on cold giving monochelate compounds (Ia-f-XVa-f). Furthermore, in 1:2 molar ratio on hot gave dichelate compounds (I'a-f-XV's-f). All the synthesized azo-sulpha drugs (ligands) and their mono-and/or dichelates are characterized by microanalysis, UV, IR and ^{1}H-NMR spectroscopy and screened in vitro for their antibacterial and antifungal activities.

INTRODUCTION

Many pyrazole derivatives are associated with antifungal[1], antidiabetic[2], anti-inflammatory properties[3] and antibacterial activities[4-6]. Furthermore, sulphonamide and azo-sulphonamide derivatives were latter 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 pryazole ring, if coupled to a different heterocyclo-substituted sulphamoyl moieties, another pharmacophore, the resulting sulpha drugs might have highly considerable biological potency. Furthermore, 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[10]. It 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 large number of azo dye sulpha drugs containing mainly pryazole moiety with[16,23] different pyrazol-substituted sulphonamide rings (pyridine, pyrimidine, methyl pyrimidine, diethyl pyrimidine, thiazole, methoxazole,

methoxy pyridazine, dimethoxy pyrimidine, morpholine, 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 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. ^1H NMR spectra were done on a TEOL-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)sulphamoyl and/or sulphonyl]benzenediazonium chlorides

These compounds were prepared by diazotization of 4'-("H"-sulphonamido-) aniline, 4'-(acetylsulphonamido-) aniline, 4'-(quanidinyl sulphonamido-) aniline, 4'-(2"-Pyridyl sulphonamido-) aniline, 4'-(2"-pyrimidinyl sulphonamido-) aniline, 4'-(2"-(4-methyl) pyrimidinyl sulphonamido-) aniline, 4'-(2"-(4,6-dimethyl) pyrimidinyl sulphonamido-) aniline, 4'-(2"-thiazolyl sulphonamido-) aniline, 4'-(2"-methoxazolyl sulphonamido-) aniline, 4'-(6"-(3-methoxy)pyridazinyl sulphonamido-) aniline, 4'-(6"-(2,4-dimethoxy) pyrimidinyl sulphonamido-) aniline 4'-(morpholino-sulphonyl) aniline, 4'-(piperidino-sulphonyl) aniline, 4'-(piperazino-sulphonyl) aniline 4'-[bis-piperazino-disulphonyl) aniline (0.01 mol) dissolved in a mixture of either ethanol or acetone and 60 ml of 70% pure hydrochloric acid with sodium nitrite 0.7 g, (0.01 mol) at 0-2°C.

Synthesis of 4-[4'-heterocyclo-substituted)-5-imino-3-methyl-1-phenyl-Δ^2-pyrazolin-] phenylazo-s-dithiocarbamate dyes (I-XV)

To an ice cold solution of 5-imino-3-methyl-1-phenyl-Δ^2-pyrazolin-4-dithiocarbamic acid 2.50g (0.01 mol) in 40 ml of 5% sodium hydroxide solution, a cold solution of the diazonium salt was added dropwise with stirring. The reaction mixture was further stirred and kept at 0-20°C for 5 hours while adding 5% aqueous sodium hydroxide to pH 8. The product was collected, washed well with water, and recrystallized from ethanol (Table 1).

Table 1

Physical and analytical data of the synthesized azo dyes (I-XV):

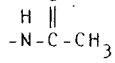
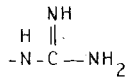
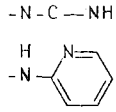
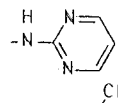
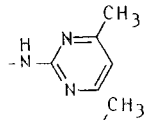
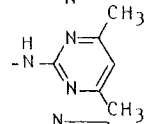
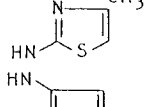
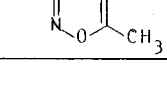
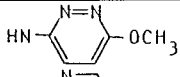
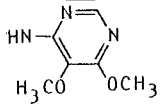
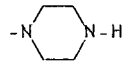
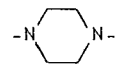
Compd. No.	R	M. P. (°C)	Yield (%)	Molecular formula (MW)	Microanalysis Calculated/(Found) %C	%H	%N	%S
I		225	85	$C_{17}H_{16}N_6O_2S_3$ (432.54)	47.20 (47.21)	3.72 (3.70)	19.42 (19.44)	22.23 (22.17)
II		173	88	$C_{19}H_{18}N_6O_3S_3$ (474.38)	48.08 (48.10)	3.82 (3.84)	17.70 (17.65)	20.26 (20.21)
III		225	92	$C_{18}H_{18}N_8O_2S_3$ (474.58)	45.55 (45.50)	3.82 (3.80)	23.61 (23.55)	20.26 (20.18)
IV		202	75	$C_{22}H_{19}N_7O_2S_3$ (510.67)	49.39 (49.31)	3.55 (3.60)	21.94 (21.91)	18.83 (18.80)
V		192	89	$C_{21}H_{18}N_8O_2S_3$ (510.67)	49.39 (49.31)	3.55 (3.60)	21.94 (21.91)	18.83 (18.80)
VI		210	77	$C_{22}H_{20}N_8O_2S_3$ (524.64)	50.36 (50.40)	3.84 (3.81)	21.35 (21.40)	18.33 (18.30)
VII		187	82	$C_{23}H_{24}N_8O_2S_3$ (540.69)	51.09 (51.00)	4.47 (4.40)	20.72 (20.76)	17.79 (17.82)
VIII		173	91	$C_{20}H_{17}N_7O_2S_4$ (515.66)	46.58 (46.50)	3.32 (3.38)	19.01 (19.00)	24.87 (24.78)
IX		181	80	$C_{21}H_{19}N_7O_3S_3$ (513.62)	58.99 (59.01)	3.72 (3.68)	19.08 (19.10)	18.73 (18.70)

Table 1, Contd.

Compd. No.·	R	M. P. (°C)	Yield (%)	Molecular formula (MW)	Microanalysis Calculated/(Found) %C	%H	%N	%S
X		250	77	$C_{22}H_{20}N_8O_3S_3$ (540.61)	48.87 (48.81)	3.72 (3.75)	20.72 (20.76)	17.79 (17.70)
XI		205	76	$C_{23}H_{22}N_8O_4S_3$ (570.54)	48.41 (48.38)	3.85 (3.80)	19.63 (19.69)	16.85 (16.88)
XII		187	95	$C_{21}H_{22}N_6O_3S_3$ (502.63)	50.18 (50.05)	4.41 (4.38)	16.72 (16.78)	19.13 (19.20)
XIII		222	70	$C_{22}H_{24}N_6O_2S_3$ (500.66)	52.77 (52.70)	4.83 (4.87)	16.78 (16.80)	19.21 (19.20)
XIV		201	92	$C_{21}H_{23}N_7O_2S_3$ (501.65)	50.28 (50.15)	4.62 (4.60)	19.54 (19.60)	19.17 (19.12)
XV		238	95	$C_{38}H_{36}N_{12}O_4S_6$ (917.17)	49.76 (49.70)	3.95 (3.90)	18.32 (18.39)	20.97 (20.92)

Synthesis of iron, copper, mercury, cobalt, nickel and lead azopyrazolin-4-yl dithiocarbamate monochelates (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 under stirring to a solution of the given metal salt (0.01 mol), ferric chloride, copper chloride, mercuric chloride, cobalt chloride, nickel chloride and lead acetate), in ethanol (30 ml). Stirring was continued for a further 30 min. at room temperature. The precipitated products were filtered, washed thoroughly with distilled water, dried and recrystallized from ethanol (Table 2).

Table 2a

Microanalytical data of some representative mono-chelate compounds (Ia-f-XVa-f).

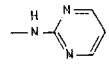
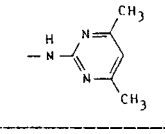
Compd. No.	R	M.P. (°c)	Yield (%)	Molecular Formula (MW)	Calculated/(found) %S	%Cl
a		300	75	$C_{21}H_{17}N_8O_2S_3.FeCl_2$ (636.33)	15.11 (15.18)	11.14 (11.21)
b		300	78	$C_{21}H_{17}N_8O_2S_3.CuCl$ (608.60)	15.80 (15.85)	5.82 (5.86)
c		250	81	$C_{21}H_{17}N_8O_2S_3.HgCl$ (745.65)	12.90 (12.83)	4.75 4.81)
d		315	68	$C_{21}H_{17}N_8O_2S_3.CoCl$ (604.00)	15.92 (15.98)	5.86 (5.91)
e		315	63	$C_{21}H_{17}N_8O_2S_3.NiCl$ (603.77)	15.93 (16.01)	5.87 (5.94)
f		165	59	$C_{23}H_{20}N_8O_4S_3.Pb$ (775.84)	12.39 (12.43)	- -
VIIa		-	72	$C_{23}H_{21}N_8O_2S_3.FeCl_2$ (664.38)	14.47 (14.51)	10.67 (10.61)
b		- -	76	$C_{23}H_{21}N_6O_2S_3.CuCl$ (636.66)	15.10 (15.16)	5.56 (5.61)
c		- -	80	$C_{23}H_{21}N_8O_2S_3.HgCl$ (773.71)	12.43 (12.38)	4.58 (4.61)
d		- -	62	$C_{23}H_{21}N_8O_2S_3.CoCl$ (632.05)	15.21 (15.28)	5.60 (5.65)

Table 2a: Contd.

Compd. No.	R	M.P. (°c)	Yield (%)	Molecular Formula (MW)	Calculated/(found) %S	%Cl
e		- -	68	$C_{23}H_{21}N_8O_2S_3$. NiCl (631.85)	15.22 (15.26)	5.61 (5.55)
f		-	66	$C_{25}H_{24}N_8O_4S_3$.Pb (803.90)	11.96 12.01	- -
XIIa		153	86	$C_{21}H_{21}N_6O_3S_3$. $FeCl_2$ (628.38)	15.30 (15.38)	11.28 (11.32)
b		134	88	$C_{21}H_{21}N_6O_3S_3$. CuCl (600.62)	16.01 (16.08)	5.90 (5.98)
c		145	82	$C_{21}H_{21}N_6O_3S_3$. HgCl (737.69)	13.03 (13.00)	4.80 (4.72)
d		159	78	$C_{21}H_{21}N_6O_3S_3$. 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	$C_{23}H_{24}N_6O_5O_5S_3$.Pb (767.88)	12.52 (12.58)	- -

Table 2b

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

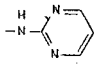
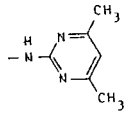
Compd. No.	R	M.P. (°c)	Yield (%)	Molecular Formula (MW)	Calculated/(found) %S	%Cl
V'a		225	81	$C_{21}H_{17}N_8O_2S_3.Fe_2Cl_5$ (798.50)	12.04q (12.10)	22.19 (22.23)
b		217	87	$C_{21}H_{17}N_8O_2S_3.Cu_2Cl_3$ (743.05)	12.94 (13.00)	4.77 (4.71)
c		212	83	$C_{21}H_{17}N_8O_2S_3$. Hg_2Cl_3 (1017.15)	9.45 (9.39)	10.45 (10.50)
d		233	74	$C_{21}H_{17}N_8O_2S_3$. Co_2Cl_3 (733.83)	13.10 (13.06)	14.49 (14.42)
e		210	68	$C_{21}H_{17}N_8O_2S_3.Ni_2Cl_3$ (603.77)	15.93 (16.00)	5.87 (5.80)
f		198	62	$C_{27}H_{26}N_8O_8S_3.Pb_2$ (1101.12)	8.73 (8.80)	- -
VII'a		228	78	$C_{23}H_{21}N_8O_2S_3.Fe_2Cl_5$ (826.56)	11.63 (11.70)	21.44 (21.51)
b		215	80	$C_{23}H_{21}N_8O_2S_3.Cu_2Cl_3$ (771.10)	12.47 (12.51)	13.79 (13.81)
c		168	84	$C_{23}H_{21}N_8O_2S_3.Hg_2Cl_3$ (1045.20)	9.20 (9.25)	10.17 (10.20)
d		181	68	$C_{23}H_{21}N_8O_2S_3.Co_2Cl_3$ (761.89)	12.62 (12.60)	13.95 (14.01)

Table 2b, Contd.

Compd. No.	R	M.P. (°c)	Yield (%)	Molecular Formula (MW)	Calculated/(found) %S	%Cl
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	$C_{29}H_{30}N_8O_8S_3.Pb_2$ (1129.18)	8.51 (8.57)	- -
XII'a		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	$C_{21}H_{21}N_6O_3S_3.Cu_2Cl_3$ (790.59)	13.08 (12.08)	14.46 (14.50)
c		202	88	$C_{21}H_{21}N_6O_3S_3.Hg_2Cl_3$ (1009.21)	9.53 (9.60)	10.53 (10.50)
d		238	80	$C_{21}H_{21}N_6O_3S_3.Co_2Cl_3$ (725.87)	13.25 (13.30)	14.65 (14.70)
e		208	78	$C_{21}H_{21}N_6O_3S_3.Ni_2Cl_3$ (725.41)	13.26 (13.30)	14.66 (14.70)
f		198	81	$C_{27}H_{30}N_6O_9S_3.Pb_2$ (1093.18)	13.26 (13.30)	- -

Synthesis of iron, copper, mercury, cobalt, nickel and lead azo-pyrazolin-4-yl dithiocarbamate dichelates (I'a-f-XV'a-f)

A hot 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 under 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 a further 1 hr at 70°C. The reaction was cooled and the precipitate was filtered, washed thoroughly with distilled water, dried and recrystallized from ethanol (Table 3).

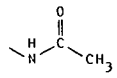
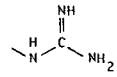
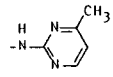
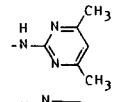
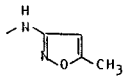
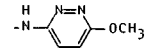
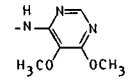
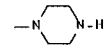
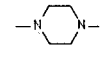
Table 3

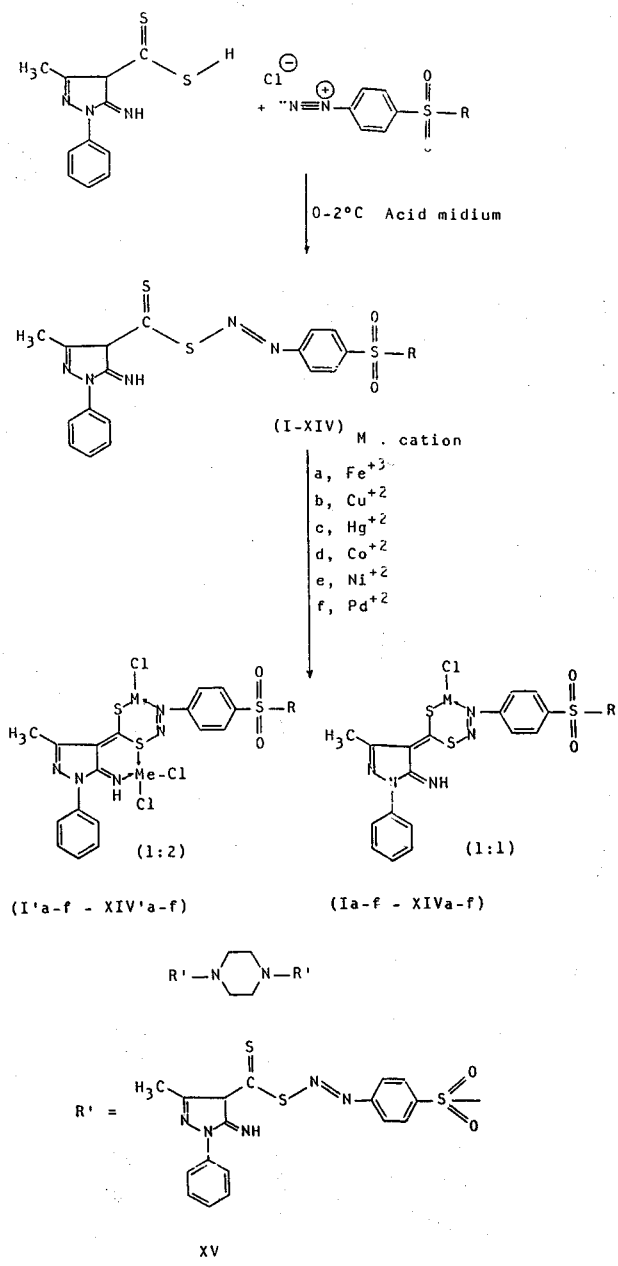
IR Spectra of some (azo dye) sulpha drugs and their metal chelates in cm^{-1}

Compd. No.	Imino ν>C=NH-	νCH3	ν 	νSO_2 (asym.)	νSO_2 (sym.)	νN=N-	νMe-O*	νSO_2NH	νC-HAr
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

Antimicrobial activity: Antibacterial and antifungal activities

Disc-diffusion method was used to measure the antimicrobial activity[32-34]. The tested azo dye ligands and their metal chelates were dissolved in sterile dimethylformamide and added at a concentration of 0.5 mg/disc (Whatman No. 4 filter paper, 0.5 cm diameter). Antibacterial spectrum was tested with seven strains of bacteria, ie. *Staphylococcus aureus* (DSM 346), *Klebsiella pneumonia* (DSM 581), *Micrococcus roseus* (DSM 348), *Bacillus cereus* (DSM 345), *Bacillus anthracis* (DSM 344) and *Serratia marcmacecens* (DSM 1608). Antifungal activity for the same compounds was tested with four species of fungi namely *Asperyllus fflavus* (Lank AUCC 1640, *Alternaria alternata* (Fries) Keissler (AUCC 1110), *Penicillium chrysogenum* (Thom AUCC 530) and *Aspeogillus tereus* (Wilhelm AUCC 230). The culture medium for bacteria was nutrient agar (NA) composed of beef extract, 3 g. peptone, 5 g agar, 15 g litre and was adjusted to pH 7 before sterilization at 121°C for 30 min). Glucose-Czapek's agar medium ($NaNO_3$, 2g; KH_2PO4, 1 g; MgSO4. $7H_2O$, 0.5 g; KCl, 0.5 g; glucose, 10g; agar, 15 g litre of distilled water) was used for fungi. The inoculated plates were incubated at 37± 1°C for 24-48 hrs in the case of bacteria and at 282°C for 7.8 days in the case of fungi. The inhibition zones of microbial growth produced by different compounds were measured[34].

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	Va-f	V'a-f	
VII	VIa-f	VI'a-f	
VIII	VIIa-f	VII'a-f	
IX	VIIIa-f	VIII'a-f	
X	IXa-f	IX'a-f	
XI	Xa-f	X'a-f	
XII	XIa-f	XI'a-f	
XIII	XIIa-f	XII'a-f	
XIV	IVa-f	IV'a-f	
XV	Va-f	V'a-f	



RESULTS AND DISCUSSION

Observation on the antimicrobial importance of azo sulpha 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)-phenylazo-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 sulphamoyl and/or sulphonyl moiety were chosen as to ensure a wide variation in their size, electronegativity, chemical activity, solubility, antitubercular properties and their biological activities. Analytical data and melting point of the novel azo-dye sulpha drugs (ligands) and their metal chelates were recorded in Tables 1,2a, 2b. The IR spectra of the synthesized sulpha drugs confirmed the presence in the azo precursor compounds of the imino group C=NH-band at 3325 cm^{-1} and at 1365 cm^{-1}, for sulphonamide group -SO_2NH-and at 1582 cm^{-1}, for azo group -N=N-, these absorptions shifted to the lower frequency on chelation. In case of 1:1 molar ratio, chelation formed on cold concerning azo group -N=N- and dithiocarbamyl group =C through thionyl group forming six membered ring. In case of 1:2 molar ratio ligand to metal cation, chelation formed on hot concerning the imino C=NH group and dithiocarbamyl group through sulphor atom -C forming another six membered ring (Table 3).

The ^{1}H NMR spectrum of compound (V) in $CDCl_3$ showed signals at δ = 8.80 (s, 1H, -SO_2NH-) at δ = 2.15 (s, 3H, -CH_3) at δ = 7.00-8.15 (m, 13H, aromatic protons) (Table 4).

Table 4

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

Compd. No.	Aromatic protons (m)	C=NH	-CH_3 (S)	-SO_2NH- (S)
V	7.00-8.20(13 H_1)	5.55	2.40	8.45 (1H)
Va	7.05-8.10(12 H)	5.75	2.35	8.50 (1H)
V'C	6.95-8.00(12 H)	6.05	2.45	8.40 (1H)

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 a clear activities against all bacteria isolates used (inhibition zones ranged from 20 to 195 mm). Azo dye derivatives I, II, IV, V, VIII, X, XI have remarkable effects (inhibition zones 40-95 mm), and also complexes Va-f, Va-f, VIIa-f, VIII'a-f, XIIa-f, XII'a-f (inhibition zones ranged from 70 to 160 mm) against *Serratia rhadenii* and *Bacillus cereus* (Table 5). Interestingly, iron, copper and lead complexes VII'a, VII'b and VII'f are particularly strongly effects (inhibition zones 160-195 mm).

Table 5

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

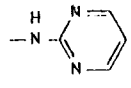
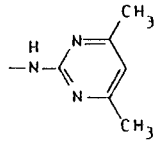
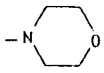
		Antibacterial Screening						Antifungal Screening		
Compd. No.	R	Staphyl-ococcus aureus (DSM 346)	Klebsiella pneumoniae (DSM 581)	Micro-coccus ruseus (DSM 346)	Bacillus cereus (DSM 345)	Bacillus anthracis (DSM 344)	Serratia rhadnii (DSM 1608)	Alternaria alternata (AUCC 1110)	Penicillium chrysogenum (AUCC 530)	Asperogillus tereus (AUCC 230)
V		50(-ve)	85(-ve)	95(-ve)	110(-ve)	105(-ve)	110(60)	60(-ve)	50(-ve)	30(-ve)
a		40	65	-ve	120	95	125	75	90	85
a'		60	70	35	130	105	135	80	105	95
b		50	-ve	-ve	115	85	115	-ve	-ve	-ve
b'		70	40	45	120	95	120	30	-ve	-ve
c		105	85	110	170	135	185	85	110	90
c'		115	120	135	190	165	195	90	125	105
d		80	-ve	-vc	95	-ve	75	-ve	-ve	-ve
d'		90	40	45	105	30	95	35	-ve	-ve
e		70	-ve	-ve	35	-ve	30	-ve	-ve	-ve
e'		85	15	50	55	45	75	-ve	25	-ve
f		30	-ve	-ve	105	80	95	-ve	-ve	-ve
f'		40	50	75	115	95	120	45	50	60
VII		85(-ve)	110(-ve)	90(-ve)	105(-ve)	115(-ve)	120(40)	30(-ve)	30(-ve)	50(-ve)
a		45	-ve	110	115	-ve	115	65	115	65
a'		55	45	125	120	75	125	70	125	70

Table 5, Contd.

Compd. No.	R	Antibacterial Screening: Staphylococcus aureus (DSM 346)	Klebsiella pneumoniae (DSM 581)	Micrococcus ruseus (DSM 346)	Bacillus cereus (DSM 345)	Bacillus anthracis (DSM 344)	Serratia rhadnii (DSM 1608)	Antifungal Screening: Alternaria alternata (AUCC 1110)	Penicillium chrysogenum (AUCC 530)	Asperogillus tereus (AUCC 230)
b		60	15	95	105	-ve	75	-ve	-ve	-ve
b'		70	35	105	110	60	85	20	35	-ve
c		110	130	145	175	130	145	110	125	95
c'		125	145	165	190	145	165	120	145	105
d		55	-ve	60	-ve	-ve	60	-ve	-ve	-ve
d'		65	25	75	55	30	70	25	35	-ve
e		-ve	-ve	-ve	-ve	45	45	-ve	-ve	-ve
e'		35	40	-ve	60	75	65	-ve	45	35
f		105	70	-ve	70	85	130	30	65	-ve
f'		100	115	120	95	105	145	45	80	75
XII		95(-ve)	125(-ve)	115(-ve)	140(-ve)	150(-ve)	170(30)	75(-ve)	80(-ve)	110(-ve)
a		100	135	140	150	170	175	95	90	120
a'		110	140	150	160	165	180	115	110	135
b		35	135	95	120	105	165	110	120	160
b'		70	160	110	130	95	145	125	130	155
c		110	160	165	175	180	185	160	155	170
c'		130	175	185	190	195	190	145	175	185
d		65	-ve	-ve	-ve	45	-ve	-ve	-ve	-ve
d'		-	40	35	40	60	45	45	-ve	35
e		40	-ve	-ve	-ve	55	-ve	-ve	-ve	-ve
e'		-ve	35	-ve	50	65	35	35	-ve	25
f		50	80	60	70	95	105	75	70	80
f'		60	95	85	95	105	115	85	95	105

Antifungal activity

The synthesized compounds also possessed variable and attractive antifungal activities (inhibition zones ranged from 16 to 165 mm). Ligand azo dye dithiocarbamate V, VIII, X, derivatives are strongly effects against *Penicillium chrysogenum* and *Aspergillus terreus* (inhibition zones 15-45-90 mm), but IV, XII compounds exhibited a pronounced activities and are more potent effects (inhibition zones 75-120 mm). Further more, chelated compounds VII'a-b, XII'e are highly active (inhibition zones ranged from 30 to 160 mm) against *Aspergillus terreus* and *Penicillium*. On the other hand, V'a, XII'a, f have potent effects (inhibition zones 30-90 mm) only against *Penicillium chrysogenum* (Table 5).

REFERENCES

[1] **Pathk, R. B.** and **S. C. Bahel, 1980**. J. Indian Chem. Soc., 57: 1108.

[2] **Trikura, T., 1975.** Jap. Pat., 7570367, Chem. Abstr., 1976, 84: 59445.

[3] **Eid, A. I., M. A. Kira** and **H. N. Fahmy, 1978**. J. Pharm. Belg., 33: 303-311.Chem. Abstr., 90 **(1979)** 152073.

[4] **Nanda, R., S. Padmanabhan, B. Triparthy** and **A. S. Mittra, 1975.** J. Indian Chem. Soc., 52: 533.

[5] **Nayak, A.,' S. Das, C. R. Misra** and **A. S. Mittra, 1977**. J. Indian Chem. Soc., 54: 485.

[6] **Sundar, R.** and **A. S. Mittra, 1977**. Indian J. Chem. 15B: 1062.

[7] **Hoffman-La Roche** and **A. G. Co, 1967.** Aromatic ethers. Swiss Patent, Neth. Appl. 66-610, 566 (Cl. CO7d), 31, Chem. Abstr., 67: 73523r.

[8] **Veichulis, J. A.,** US patent 3271251, **1966**; Chem. Abstr. 40: 1993 e.

[9] **Dietrich, M., 1969.** Swiss patent 424767, , Chem. Abstr. 68: 682708q.

[10] **Moeschlin, S.** and **U. Schnider, 1963**. New Eng. J. Med., 57: 269

[11] **Sirki, M.** and **D. Jerdjevice, 1971,** Anal Chem. 43: 1375.

[12] **Weiss, A. S., J. A. Markenson, M. S. Weiss** and **W. H. Kammerer, 1978.** Am. J. Med., 64: 114.

[13] **Australian National Drug Information Service, 1982.** Aust. J. Pharm. October 647 .

[14] **Abdel Hafez, A. A., I. M. A. Awad** and **Kh. M. Hassan, 1987**. Collect. Czech. Chem. Commun., 52: 2753-7.

[15] **Awad, I. M. A., A. M. A. Aly, A. A. Abdel Ala** and **S. H. Ahmed, 1988.** J. Inorg. Biochem., 33: 77-89.

[16] **Matolesy, G., P. Sohar** and **B. Bordas, 1971.** Chem. Ber., 104: 1155.

[17] **Awad, I. M. A., A. M. A. Aly, A. A. Abdel Hafez** and **Kh. M. Hassan, 1989.** J. Chin. Chem. Soc., 36: 107-14.

[18] **Awad, I. M. A.** and **Kh. M. Hassan, 1989.** Phosphorus, Sulphur. Silicon, 44: 135.

[19] **Awad, I. M. A.** and **A. A. Aly, 1991.** Synth. React. Inorg. Met. Org. Chem., 21(3): 375-83.

[20] **Aly, A. M. A.** and **I. M. A. Awad, 1991.** Phosphorus, Sulphur and Silicon, 60: 135-8.

[21] **Awad, I. M. A.** "33rd IUPAC Congress", Budapest, 17-22, August 1991, Abstr., No. 4048, 152.

[22] **Awad, I. M. A., 1991.** "33rd IUPAC Congress", Budapest, 17-22, August , Abstr., No. 4230-174.

[23] **Hassan, M. K.** and **I. M. A. Awad, 1991.** Bull. Fac., Assiut Univ., 29(1-B): 145-5.

[24] **Aref, A. M. A.** and **I. M. A. Awad, 1991.** Phosphorus, Sulphur and Silicon, 60: 135-8.

[25] **Awad, I. M. A., 1991**. J. Dyes and Pigments, 17: 123-39.

[26] **Abdel Hafez, A. A.** and **I. M. A. Awad, 1992.** Dyes and Pigments, 20: 197-209.

[27] **Awad, I. M. A., A. A. Abdel Hafez** and **M. F. El-Zohry, 1992.** J. Chem. Tech. Biotechnol., 55: 217-25.

[28] **Awad, I. M. A., 1992.** J. Chem. Tech. Biotechnol., 53: 227-236.

[29] **Awad, I. M. A., 1993.** Bull. Chem. Soc. Jpn., 66: 167-173.

[30] **Awad, I. M. A., 1992.** J. Chem. Tech. Biotechnol., 56: 345.

[31] **Awad, I. M. A., 1993.** Organic Preparations and Procedures International, 25(3): 347.

[32] **Moss, E. S.** and **A. L. Mequos, 1969**. Atlas of Medical Myeolgoyt, 3rd Ed., The Willams and Wiking Co., Baltimore, U. S. A., p. 366.

[33] **Chaturredi, K. K., Jain, Nok., P. Jain.** and **Kwashal, 1978.** Indian Drugs, 15: 57.

[34] **Sleight, J. D.** and **M. C. Timbury, 1981**. Notesan Medical Bacteriology, Chur Chill, Livingstone, C. S. A. p. 43.