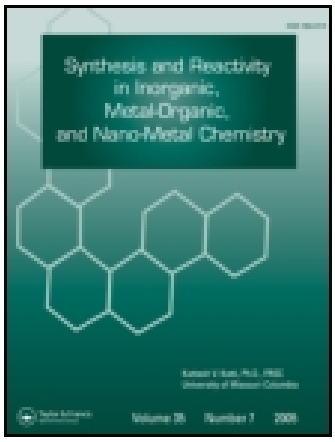

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Metal Complexes of Phenylpiperazine-Based Dithiocarbamate Ligands. Synthesis, Characterization, Spectroscopic, Thermal, and Antimicrobial Activity Studies

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Metal Complexes of Phenylpiperazine-Based Dithiocarbamate Ligands. Synthesis, Characterization, Spectroscopic, Thermal, and Antimicrobial Activity Studies

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ABSTRACT

Potassium salts of phenylpiperazine (Phpzdtc), fluorophenylpiperazine (F-Phpzdtc) and nitrophenylpiperazine (N-Phpzdtc) dithiocarbamates and their manganese(II), iron(II), cobalt(II), nickel(II), copper(II) and zinc(II) complexes have been synthesized and characterized by elemental analyses, IR, UV-VIS, magnetic moment measurements and thermal analysis techniques. On the basis of experimental data, the dithiocarbamates (dtcs) have been observed to coordinate to the metal ions via both sulphur atoms of the $-NCS_2$ group forming metal complexes with a metal

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to ligand ratio of 1:2. The thermal reactivity and antimicrobial activity of the ligands and their metal complexes were also studied. The decomposition of the metal complexes resulted in the formation of the corresponding metal thiocyanates or cyanates as stable intermediates. Phpzdtc was found to be microbiologically more active than its nitro and fluoro derivatives and biological activity of the dtc ligands either remained unaltered or decreased on complexation with metal ions.

Key Words: Phenylpiperazine dithiocarbamate; Fluorophenylpiperazine dithiocarbamate; Nitrophenylpiperazine dithiocarbamate; Antimicrobial activity; Thermal analysis.

INTRODUCTION

The coordination of dithiocarbamates (dtcs) to metals has been known for many years. Dtc ligands readily form chelates with all transition metal ions through its two donor sulfur atoms.[1] Furthermore, in some cases, the bidentate anion also acts as a bridge between two transition metal centers.[2] Their sodium salts were found to be good extracting agents for most transition metals.[3] Some salts of dtc derivatives exhibit interesting biological effects including anti-alkylation,[4,5] anti-HIV properties[6] and antitumor activity against leucemic cells.[7] They are also used for cadmium intoxication.[8] Large quantities of water-soluble dtc complexes are used in agriculture as fungicides[9] and also tested in various medical applications.[10]

In recent years, the study of transition metal complexes of substituted dtc complexes has been a subject of considerable interest because of their structural, magnetic, electrochemical and thermal properties. Studies on dtc compounds and their metal complexes were reviewed by Coucouvanis.[11,12] In this paper, we report the synthesis, characterization, spectral, thermal, and antimicrobial properties of new phenylpiperazine (Phpzdtc), fluorophenylpiperazine (F-Phpzdtc) and nitrophenylpiperazine (N-Phpzdtc) dithiocarbamates and their manganese(II), iron(II), cobalt(II), nickel(II), copper(II) and zinc(II) complexes. This work may also help to understand the inhibitory effect of the dtc compounds for medical and agricultural applications.

EXPERIMENTAL

Reagents and Instruments

All chemicals were purchased commercially and used without further purification. Electronic spectra were measured using a Unicam UV2

spectrophotometer in DMSO in the 200–800 nm range. IR spectra were recorded on a Mattson FTIR spectrophotometer as KBr pellets. Room temperature magnetic susceptibility measurements were carried out on a Sherwood Scientific MXI model Gouy magnetic balance. C, H and N analyses were carried out at the TUBITAK Marmara Research Centre (Gebze). The simultaneous TG, DTG and DTA curves were obtained using a Rigaku TG8110 thermal analyzer combined with a TAS100 thermogravimetric analyzer. The experiments were carried out in a dynamic nitrogen atmosphere with a flow rate of 80 mL min^{-1} in the temperature range 20–1000 °C, using platinum crucibles. Sample sizes of 5–10 mg and a heating rate of 10 °C min^{-1} were used. Sintered α-alumina was used as the reference material.

Synthesis of the Ligands and Metal Complexes

The potassium salts of the phenylpiperazine based dtc ligands were prepared by direct reaction between phenylpiperazine, fluorophenylpiperazine and nitrophenylpiperazine and CS_2 in the presence of KOH in a water-ice bath at about 0 °C. The resulting precipitates were washed with diethyl ether for several times and dried in air. The metal complexes were obtained by direct reaction of the respective dtc potassium salt with the metal nitrates. The polycrystalline solids were filtered by suction, washed with H_2O, diethyl ether, and dried in air.

Antimicrobial Activity Screening

As a preliminary screening for antimicrobial activity, compounds were tested against standard strains of gram (−) *Escherichia coli W3110*, *Salmonella tyhimurium* LT2, *Pseudomonas aeruginosa* ATCC 27853, gram (+) *Bascillus pumilus*, *Staphylococcus aureus* ATCC 43300, a yeast *Candida albicans* ATCC 10231 and a mould *Aspergillus niger*. Antimicrobial studies were performed according to both broth dilution and agar diffusion methods. For broth dilution studies, starter cultures were grown overnight on nutrient broth (Merck) at 37 °C in an incubator (GLF, Germany) for 18 hours, and then transferred to the test tubes initially containing approximately 3×10^5 bacteria. Nutrient broth containing tubes then were supplemented with phenylpiperazine-, fluorophenylpiperazine- and nitrophenylpiperazine dithiocarbamates and their metal complexes for measuring the antimicrobial activity. MIC (Minimal Inhibitory Concentration) assays were performed in nutrient broth medium 1:10 dilutions and further dilutions in order to find suitable MIC values. The MIC was

expressed as the lowest compound concentration that inhibited bacterial growth in 24 hours. Viable bacterial counts were determined by the standard plate counting method. Agar diffusion experiments were based on the obtained MIC values by dilution methods. The following test conditions were applied. All the compounds (ligands and their complexes) were dissolved in dimethylsulfoxide (DMSO, Merck). Nutrient agar (Acumedia) plates were prepared and dried at 35–36 °C for about 30 min in an incubator. Test strains were spread on the solid nutrient agar surface by using a sterile glass rod. Spread inoculum was a 3.5×10^5 colony forming unit/mL^{-1} (0.5 McFarland standard). At the same time, absorbent paper discs were placed on an agar surface (10 mm for compounds and 6 mm for antibiotics) and impregnated with known concentrations, determined previously by MIC tests. Tetracyclin antibiotics (Bioanalyse) were also used for prokaryote microorganisms and *nystatin* (BDH) for eucaryotes (*Aspergillus niger* and *Candida albicans*) as positive control. Blank tests showed that DMSO in the preparation of the test solutions does not affect the test organisms. They were inverted and allowed to incubate at 37 °C. The inhibition zone around the disc was calculated as zone diameter in millimeters. All tests were repeated tree times and average data were taken as the final result.

RESULTS AND DISCUSSION

Synthesis

The structural formulae of the ligands are shown in Figure 1. Analytical data and some physico-chemical properties of the prepared compounds are listed in Table 1, and the proposed formulae are in agreement with the elemental analyses. The metal to ligand ratio is 1:2 for all metal complexes. All the compounds are air-stable and were obtained in high yield. The metal complexes are insoluble in water, but sparingly soluble in ethanol, benzene, dioxan, DMSO, acetone, chloroform and CCl_4. All attempts to prepare single crystals of the compounds in various solvents failed. The

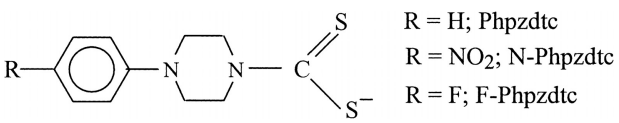

Figure 1. Structures of the dtc ligands.

Table 1. Analytical data for the compounds.

Compound	Color	Mp. (°C)	FW	Found (calcd.) (%)			Yield (%)
				C	H	N	
KPhpzdtc·H_2O	White	285	294.48	44.8 (44.9)	5.2 (5.1)	9.0 (9.5)	79
[Mn(Phpzdtc)$_2$]	Pale pink	179	529.67	49.5 (49.9)	4.8 (4.9)	10.5 (10.6)	86
[Fe(Phpzdtc)$_2$]	Dark-brown	233[a]	530.58	49.4 (49.8)	4.6 (4.9)	9.9 (10.2)	92
[Co(Phpzdtc)$_2$]	Dark-green	238[b]	533.66	49.1 (49.5)	5.1 (4.9)	10.1 (10.5)	83
[Ni(Phpzdtc)$_2$]	Green	333[b]	533.44	49.2 (49.5)	4.9 (4.9)	10.1 (10.5)	76
[Cu(Phpzdtc)$_2$]	Brown	238[b]	538.27	49.1 (49.1)	4.8 (4.9)	10.2 (10.4)	84
[Zn(Phpzdtc)$_2$]	White	298	540.10	48.6 (48.9)	4.9 (4.9)	10.1 (10.4)	72
KN-Phpzdtc	*Orange*	220[b]	321.46	40.2 (41.1)	3.9 (3.8)	12.8 (13.1)	73
[Mn(N-Phpzdtc)$_2$]·H_2O	Brown	218[b]	637.68	41.2 (41.4)	3.9 (4.1)	13.0 (13.2)	70
[Fe(N-Phpzdtc)$_2$]	Dark green	195[b]	620.57	42.2 (42.6)	4.0 (3.9)	13.2 (13.5)	81
[Co(N-Phpzdtc)$_2$]·2H_2O	Brown-green	275[b]	659.69	39.7 (40.1)	4.1 (4.3)	12.3 (12.7)	75
[Ni(N-Phpzdtc)$_2$]	Dark green	323[b]	623.44	42.4 (42.4)	4.1 (3.9)	13.1 (13.5)	84
[Cu(N-Phpzdtc)$_2$]	Brown	270[b]	628.27	42.2 (42.1)	4.1 (3.9)	13.0 (13.4)	91
[Zn(N-Phpzdtc)$_2$]	Yellow	330[b]	630.10	40.8 (41.9)	3.6 (3.8)	12.7 (13.3)	84
KF-Phpzdtc·1.5H_2O	White	295	321.48	40.9 (41.1)	4.5 (4.7)	8.4 (8.7)	82
[Mn(F-Phpzdtc)$_2$]	Pale pink	192[b]	565.65	46.6 (46.7)	4.2 (4.3)	9.6 (9.9)	84
[Fe(F-Phpzdtc)$_2$]	Dark-brown	295[b]	566.56	46.4 (46.6)	4.2 (4.3)	9.6 (9.9)	86
[Co(F-Phpzdtc)$_2$]·2H_2O	Dark-green	290[b]	605.68	43.3 (43.6)	4.5 (4.7)	9.0 (9.2)	88
[Ni(F-Phpzdtc)$_2$]	Green	360[b]	569.42	46.7 (46.4)	4.5 (4.3)	9.8 (9.8)	84
[Cu(F-Phpzdtc)$_2$]	Brown	257[a]	574.25	46.6 (46.0)	4.3 (4.2)	9.4 (9.8)	81
[Zn(F-Phpzdtc)$_2$]	White	307[a]	576.08	45.6 (45.9)	4.1 (4.2)	9.1 (9.7)	88

[a]melting with decomposition.
[b]decomposition point.

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Table 2. Electronic and IR spectral data and magnetic moments of the compounds.

	IR (cm^{-1})			λ_{max} (nm) (ε (dm^3 mol^{-1} cm^{-1}))					
Compound	ν(CN)	$\nu(NCS_2)$	ν(CS)	L		CT	*d–d*		μ_{eff} (B.M.)[a]
KPhpzdtc·H_2O	1463	1149	1017	267 (19340)	302 (13740)	–	–	–	–
[Mn(Phpzdtc)$_2$]	1478	1152	1021	272 (27880)	299 (24280)	412 (750)	–	–	4.11(5.92)
[Fe(Phpzdtc)$_2$]	1438	1157	1017	265 (20460)	341 (4380)	386 (3390)	505 (1330)	580 (1140)	4.27(5.92)
[Co(Phpzdtc)$_2$]	1438	1154	1017	263 (18480)	323 (9410)	404 (3110)	479 (620)	638 (310)	2.63 (3.87)
[Ni(Phpzdtc)$_2$]	1438	1164	1017	261 (20190)	326 (30480)	392 (7270)	497 (440)		Dia.
[Cu(Phpzdtc)$_2$]	1438	1164	1018	268 (18040)	287 (13630)	439 (6180)	620 (650)		1.62(1.73)
[Zn(Phpzdtc)$_2$]	1442	1157	1024	264 (15160)	276 (9980)	–	–	–	–
KN-Phpzdtc	1478	1118	1008	265 (16490)	302 (15850)	407 (20920)	–	–	–
[Mn(N-Phpzdtc)$_2$]·-H_2O	1428	1114	1019	264 (149009	290 (10690)	401 (26420)			3.75 (5.92)
[Fe(N-Phpzdtc)$_2$]	1439	1124	1015	226 (15100)	264 (14710)	400 (2187)	509 (1160)	581 (900)	3.61 (5.92)
[Co(N-Phpzdtc)$_2$]·-$2H_2O$	1437	1119	1014	270 (22640)	323 (14990)	392 (27200)	641 (350)		2.80 (3.87)

$[Ni(N\text{-}Phpzdtc)_2]$	1442	1117	1023	260 (16250)	305 (16660)	398 (27916)	–	–	Dia.
$[Cu(N\text{-}Phpzdtc)_2]$	1438	1118	1014	250 (14340)	273 (10313)	398 (29068)	620 (470)		1.38 (1.73)
$[Zn(N\text{-}Phpzdtc)_2]$	1473	1116	1014	265 (18270)	278 (17006)	400 (25240)	–	–	–
KF-Phpzdtc·-$1.5H_2O$	1470	1107	1016	254 (11645)	292 (9065)	–	–	–	–
$[Mn(F\text{-}Phpzdtc)_2]$	1481	1152	1029	225 (17680)	247 (31780)	287 (20320)	353 (1320)	500 (420)	4.87 (5.92)
$[Fe(F\text{-}Phpzdtc)_2]$	1438	1113	1026	264 (18650)	352 (4260)	505 (1200)	580 (1020)		3.82 (5.92)
$[Co(F\text{-}Phpzdtc)_2]$·-$2H_2O$	1438	1160	1024	247 (23450)	277 (17790)	325 (12130)	634 (250)		2.10 (3.87)
$[Ni(F\text{-}Phpzdtc)_2]$	1445	1160	1030	247 (27600)	327 (22190)	394 (4360)	476 (170)	628 (70)	Dia.
$[Cu(F\text{-}Phpzdtc)_2]$	1490	1100	1024	246 (33380)	277 (42260)	436 (16860)	620 (1680)		1.47 (1.73)
$[Zn(F\text{-}Phpzdtc)_2]$	1466	1096	1021	255 (28740)	278 (24910)	–	–	–	Dia.

[a]Spin-only values in parentheses.

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relatively high melting or decomposition points suggest that the metal complexes may be dimeric or polymeric.

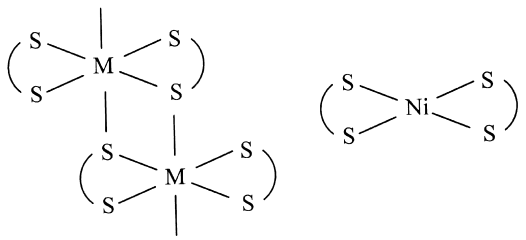
Spectral and Magnetic Characteristics

Table 2 summarizes the most significant IR bands of the prepared compounds. The bands in the range 1410–1525 cm^{-1} are attributed to the ν(CN) stretching vibration of the thioureide group of the ligands,[13] they shifted to higher frequency in the spectra of the metal complexes. The absorption of the NCS_2 groups in the ligands occurs between 1150–1110 cm^{-1} and shifts to higher frequency by about 10–45 cm^{-1} in the complexes. The ν(CS) stretching bands are located prominently in the range 1000–1040 cm^{-1} in the ligands and their metal complexes and are considered to be indicative of dtc acting as a bidentate ligand.[14] The same observations were reported for amino acid dtcs,[13] dipropyldtc[15] and dtc complexes with piperidine or pyrrolidine.[16]

Electronic spectra of the dtc ligands show two strong absorption bands in the UV region (Table 2). These bands may be due to $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions. In all the metal complexes, bands below 300 nm are attributed to the intra-ligand transitions. The intense bands in the range 325–436 nm in the spectra of complexes are ascribed to charge transfer processes,[13] probably from ligand to metal, mainly associated with the N–C=S and S–C=S and nitro groups, since the zinc(II) complexes of Phpzdtc and F-Phpzdtc do not show these transitions. The absorption bands at higher wave lengths are due to d–d transitions.

Magnetic moment measurements showed that the nickel(II) complexes are diamagnetic, while the manganese(II), iron(II), cobalt(II) and copper(II) complexes are paramagnetic (Table 2). The room temperature magnetic moment values are consistent with a square-planar coordination for the nickel(II) complex and an octahedral coordination for manganese(II), iron(II), cobalt(II) and copper(II) complexes. In most cases, the effective magnetic moments are found to be significantly lower than the spin-only values. This observation indicates the presence of a strong antiferromagnetic interaction in the complexes due to bridging of the metals by the dtc ligands through the sulphur atoms.

Single crystal X-ray analyses of the copper(II) and cadmium(II) complexes of the dialkyl substituted dtcs show that the neutral dtc complexes exhibit dimeric structures achieved by long secondary M-S interactions.[14,15] On the basis of the observed elemental analyses, spectral and magnetic data, the structures of the metal complexes may be suggested as illustrated in Figure 2.



(A) (B)

Figure 2. Proposed structures of the metal complexes. The manganese(II), iron(II), cobalt(II), copper(II) and zinc(II) complexes adopt structure (A).

Thermal Decomposition Behavior

The thermal behavior of the dtc ligands and their metal complexes has been followed up to 1000 °C. Thermoanalytical data including mass losses, temperature ranges and peak temperatures of the ligands and metal complexes are given in Table 3. KPhpzdtc·H_2O, decomposes in two steps. The first step, between 55 and 135 °C, corresponds to the dehydration of the compound. After dehydration, it melts at 285 °C and degradation of the organic part of the ligand takes place in the second decomposition stage in the range 287–775 °C, giving a final decomposition product of KSCN as identified by IR spectra and mass loss calculations. The manganese(II) complex melts at 179 °C. The endothermic decomposition of the Phpzdtc part of the complex takes place in the temperature range 182–352 °C with three DTG peaks. Mass loss calculations correspond to formation of $Mn(SCN)_2$, which decomposes at higher temperatures to give MnS at 800 °C. The iron(II), cobalt(II), nickel(II), copper(II) and zinc(II) complexes with the Phpzdtc ligand exhibit the similar decomposition behavior. These complexes show two main decomposition stages, and the first stage is due to degradation of the ligand to give the stable intermediates $Fe(SCN)_2$, $Co(SCN)_2$, $Ni(CN)_2$, $Cu(CN)_2$, and $Zn(CN)_2$ at around 330 °C. The decomposition of these intermediates occurs at the second stage between 300–800 °C. The experimental mass losses of the compounds are in very good agreement with the calculated values.

KN-Phpzdtc is anhydrous and is stable up to 250 °C, following a plateau in the TG curve, and begins to decompose exothermically above this temperature. It is violently explosive at 275 °C under nitrogen atmosphere, leaving an empty crucible at 282 °C. The explosive behavior of this compound is mainly due to the presence of the nitro group. In most

Table 3. Thermal decomposition data for the compounds.

Compound	Temp. range (°C)	DTG peak temp. (°C)[a]	Mass loss (%) t.g.	(Calcd.)
KPhpzdtc·H_2O	55–135	102(+)	6.1	6.1
	287–775	298(+), 313(+)	60.4	60.9
[Mn(Phpzdtc)$_2$]	182–352	188(+), 215(−), 302(+)	66.9	67.7
	368–800	500(+)	20.8	21.9
[Fe(Phpzdtc)$_2$]	220–300	233(+), 267(+)	66.6	67.6
	310–630	400(−)	15.7	15.8
[Co(Phpzdtc)$_2$]	190–350	291(+)	67.1	67.2
	350–950	700(+)	15.7	15.8
[Ni(Phpzdtc)$_2$]	300–360	333(+)	75.5	79.2
	360–900	510(+)	10.5	9.8
[Cu(Phpzdtc)$_2$]	200–310	238(+), 277(+)	75.5	78.5
	320–900	570(+)	10.7	9.7
[Zn(Phpzdtc)$_2$]	300–382	326(+)	73.1	78.3
	392–805	510(+)	9.3	9.6
KN-Phpzdtc	250–282	275(−)	–	–
[Mn(N-Phpzdtc)$_2$]·H_2O	25–75	45(+)	3.0	2.8
	165–1000	218(−), 250(−)	83.5	83.5
[Fe(N-Phpzdtc)$_2$]	155–1000	195(−), 223(−), 281(−)	78.4	85.8
[Co(N-Phpzdtc)$_2$]·2H_2O	25–120	59(+)	5.8	6.3
	240–900	275(−)	79.1	79.9
[Ni(N-Phpzdtc)$_2$]	232–850	323(−)	84.6	90.6
[Cu(N-Phpzdtc)$_2$]	204–1000	270(−)	89.2	89.9
[Zn(N-Phpzdtc)$_2$]	263–1000	330(−)	86.6	89.6
KF-Phpzdtc·1.5H_2O	56–150	95(+)	5.7	5.6
	150–265	192(+)	2.9	2.8
	300–750	330(+)	60.5	61.4
[Mn(F-Phpzdtc)$_2$]	140–380	182(+), 324(+)	74.6	79.8
	380–600	460(+)	8.5	9.0
[Fe(F-Phpzdtc)$_2$]	160–330	209(+), 299(+)	70.4	69.6
	330–650	480(+)	15.4	14.8

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Table 3. Continued.

Compound	Temp. range (°C)	DTG peak temp. (°C)[a]	Mass loss (%) t.g.	(Calcd.)
$[Co(F\text{-}Phpzdtc)_2]\cdot 2H_2O$	25–110	50(+)	6.1	6.0
	190–350	290(+)	65.5	65.1
	350–900	560(+)	14.5	14.3
$[Ni(F\text{-}Phpzdtc)_2]$	310–385	360(+)	79.3	80.6
	385–1000	510(+)	9.2	9.1
$[Cu(F\text{-}Phpzdtc)_2]$	258–375	274(+), 284(+), 291(+)	79.4	79.9
	375–1000	600(+)	9.3	9.1
$[Zn(F\text{-}Phpzdtc)_2]$	310–390	323(+)	79.8	79.6
	390–100	530(+)	9.4	9.0

[a](+) = endothermic process; (−) = exothermic process.

cases, the metal complexes of Phpzdtc are also extremely explosive, which makes the mass loss calculations difficult by affecting the shape of the thermal curves. Therefore, there are significant differences between calculated and found mass loss values.

KF-Phpzdtc·$1.5H_2O$ dehydrates in the temperature range 56–150 °C and melts at 295 °C. The endothermic degradation of the F-Phpzdtc moiety takes place in a single stage between 300 and 700 °C to form KSCN. The metal complexes of the F-Phpzdtc ligand also show similar decomposition patterns. All the complexes, except the cobalt(II) complex, decompose endothermically in two stages. The first stage corresponds the degradation of the dtc ligand to give stable intermediates, which also decomposes at the second stage at higher temperatures.

The present thermoanalytical data showed that under nitrogen, the decomposition of the dtcs and their metal complexes gives the corresponding metal thiocyanates or cyanates as stable intermediates and metal sulfides or metals as the end products. IR spectroscopy was used for the identification of the metal thiocyanates or cyanates by the ν(CN) vibration frequency around 2053 and 2080 cm^{-1}, respectively.[17] The decompositions of the thiocyanates or cyanates proceed at a slow rate at higher temperatures. The literature suggests that metal thiocyanates are common products in the thermal decomposition of dtcs,[18] although this conclusion does not apply as a general rule at some cyclic dtcs.[13,16,19]

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Table 4. Antibacterial activity of the compounds.[a]

Compound	Inhibition zone (average diameter/mm)						
	Escherichia coli	*Pseudomonas auroginosa*	*Salmonella typhimurium*	*Bacillus pumilus*	*Staphylococcus aureus*	*Candida albicans*	*Aspergillus niger*
KPhpzdtc·H_2O	–	16	24	45	14	40	36
[Mn(Phpzdtc)$_2$]	–	16	23	25	–	24	23
[Fe(Phpzdtc)$_2$]	–	–	–	25	17	24	24
[Co(Phpzdtc)$_2$]	22	–	25	21	22	25	22
[Ni(Phpzdtc)$_2$]	–	–	22	25	20	30	22
[Cu(Phpzdtc)$_2$]	16	29	22	27	20	28	24
[Zn(Phpzdtc)$_2$]	–	–	–	24	–	28	24
KN-Phpzdtc	–	–	–	42	30	25	36
[Mn(N-Phpzdtc)$_2$]·H_2O	–	20	19	25	–	–	–
[Fe(N-Phpzdtc)$_2$]	–	–	18	17	–	–	16
[Co(N-Phpzdtc)$_2$]·2H_2O	24	–	27	–	–	–	–

[Ni(N-Phpzdtc)$_2$]	24	30	30	22	24	32	26
[Cu(N-Phpzdtc)$_2$]	22	31	27	20	20	25	25
[Zn(N-Phpzdtc)$_2$]	–	–	18	25	18	–	38
KF-Phpzdtc·1.5H$_2$O	37	23	29	36	34	40	42
[Mn(F-Phpzdtc)$_2$]	16	19	22	28	–	24	22
[Fe(F-Phpzdtc)$_2$]	16	25	19	28	–	29	25
[Co(F-Phpzdtc)$_2$]·2H$_2$O	31	33	27	26	25	33	26
[Ni(F-Phpzdtc)$_2$]	29	30	24	30	28	31	26
[Cu(F-Phpzdtc)$_2$]	–	38	25	24	–	32	18
[Zn(F-Phpzdtc)$_2$]	–	–	–	22	–	–	–
DMSO	–	–	–	–	–	–	–
Tetracycline (30 μg)	21	13	16	22	22	–	–
Nystatin (10 μg)						26	25

KN-Phpzdtc and its metal complexes at 1000 μgmL^{-1}.
KF-Phpzdtc·1.5H$_2$O and its metal complexes at 2500 μgmL^{-1}.
[a]KPhpzdtc·H$_2$O and its metal complexes at 1750 μgmL^{-1}.

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Antimicrobial Activity

Phenylpiperazine-, fluorophenylpiperazine- and nitrophenylpiperazine dithiocarbamates and their metal complexes have been screened for antimicrobial activities against three gram-negatives namely *E. coli*, *S. typhimurium*, *P. aeruginosa* and two gram-positives namely *S. aureus*, *B. pumilus* and a yeast *C. albicans*, a mold *A. niger* using the agar disc diffusion method. Table 4 lists the zone of inhibitions and effective concentrations used (MICs).

The dtc ligands and their metal complexes showed different antimicrobial activities against test strains. For example, KPhpzdtc·H_2O was active against 6 test organisms with the exception of *E. coli*, while it showed a remarkable inhibition on *B. pumilus*, *C. albicans* and *A. niger*. The modest inactivation was detected for *P. aeruginosa*, *S. typhimurium* and *S. aureus*. [Mn(Phpzdtc)$_2$] exhibited modest activity on test bacteria and also fungies. In contrast, this complex was not able to inhibit the growth of *E. coli* cells. [Fe(Phpzdtc)$_2$] showed modest activity against *B. pumilus*, *S. aureus*, *C. albicans* and *A. niger*. However, a similar effect was not observed against gram (−) test bacteria. [Ni(Phpzdtc)$_2$] was detected as effective against *S. typhimurium*, *B. pumilus*, *S. aureus*, *C. albicans* and *A. niger*. The highest antimicrobial activity among the group of these organisms was observed against *C. albicans*. [Zn(Phpzdtc)$_2$] only inhibited the growth of *B. pumilus*, *C. albicans* and *A. niger*, and it was ineffective against gram (−) bacterial strains, whereas [Cu(Phpzdtc)$_2$] was capable of inhibiting all test organisms.

KN-Phpzdtc was found to be active against gram (+) test organisms but not against gram (−) *E. coli, S. typhimurium* and *P. aeruginosa* and fungi. This is probably due to the outer membrane layer of these bacteria, which did not allow this compound to enter the cell. [Fe(F-Phpzdtc)$_2$] showed weak antimicrobial activity that only inhibited the growth of *S. typhimurium* and *B. pumilus*, while [Co(N-Phpzdtc)$_2$]·2H_2O had inhibition only against *S. typhimurium*. Among the compounds with Phpzdtc, [Cu(N-Phpzdtc)$_2$] showed an effective antimicrobial activity to all test strains, which was similar to [Cu(Phpzdtc)$_2$]. [Ni(N-Phpzdtc)$_2$] was capable of inhibiting growth of gram (+), gram (−) and fungi. It can be seen from Table 4 that the widest inhibition zones were observed for [Ni(N-Phpzdtc)$_2$] against *P. aeruginosa, S. typhimurium* and *C. albicans*. Among the metal complexes of the N-Phpzdtc ligand, [Zn(F-Phpzdtc)$_2$] showed the highest antifungal activity against *A. niger*, but it had no effect on *P. aureginosa*, *S. typhimurium* and *B. pumilus*.

KF-Phpzdtc·1.5H_2O, [Co(F-Phpzdtc)$_2$]·2H_2O and [Ni(F-Phpzdtc)$_2$] exhibited antibacterial activity against all bacterial test organisms. KF-Phpzdtc·1.5H_2O especially had the strongest effect on *C. albicans* and *A. niger*. [Mn(F-Phpzdtc)$_2$] and [Fe(F-Phpzdtc)$_2$] did not inhibit growth of *S. aureus*. On the other hand, [Cu(F-Phpzdtc)$_2$] was found to be important in

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selective and effective inhibition against *P. aeruginosa* and *C. albicans* and the rest of the test strains was affected moderately by [Cu(F-Phpzdtc)$_2$], whereas [Zn(F-Phpzdtc)$_2$] seemed to be less effective among these metal complexes and showed the slightest inhibition on *B. pumilus*.

When the antimicrobiological effect of ligands and their metal complexes on test strains was categorized on the basis of cell wall structure, there seemed some differences. For instance, as given in Table 4, KF-Phpzdtc·1.5·H_2O [Co(F-Phpzdtc)$_2$]·2H_2O, [Ni(N-Phpzdtc)$_2$], [Cu(Phpzdtc)$_2$] and [Cu(N-Phpzdtc)$_2$] inhibited all test microorganisms including gram (+), gram (−) and fungi. [Co(N-Phpzdtc)$_2$]·2H_2O affected only gram (−) *E. coli* and *S. typhimurium* cells. However, while [Zn(F-Phpzdtc)$_2$], [Fe(Phpzdtc)$_2$] and KN-Phpzdtc were active against gram (+) and fungi, they did not cause any inhibition on growth of gram (−) bacteria. On the other hand, among used ligands and metal complexes, [Mn(N-Phpzdtc)$_2$]·H_2O and [Co(N-Phpzdtc)$_2$]·2H_2O were not found to be effective on fungi. [Ni(Phpzdtc)$_2$] and [Zn(Phpzdtc)$_2$] showed a selective inhibition on gram(+) bacteria with the exception of *S. aureus*. In general, the growth of fungi was inhibited by KPhpzdtc·H_2O and its manganese(II), iron(II), cobalt(II), nickel(II) and copper(II) complexes, KF-Phpzdtc·1.5H_2O and their metal complexes, KN-Phpzdtc, [Cu(N-Phpzdtc)$_2$] and [Ni(N-Phpzdtc)$_2$].

In conclusion, the rate of antimicrobial activities of ligands and metal complexes on microorganisms partly depends on the dtc chemical complex used. Here, we found that the phenylpiperazine-based dtc ligands have the strongest effect on fungi and also remarkable effects on bacteria and KPhpzdtc·H_2O was found to be more active than its nitro and fluoro derivatives. In contrast to a review on dtc pesticides by Malik and Faubel,[20] it was observed that some of the metal complexes reduce the inhibitory effect of dithiocarbamates. Therefore, it may be concluded that this field needs further work to clarify the effect of dtcs and their metal complexes on microorganisms.

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