Eur J Med Chem (1992) 27, 101–106

Synthesis and antimicrobial activity of Ni(II), Co(II), Zn(II) and Cd(II) complexes of 4-substituted-3-mercapto-5-phenyl-4H-1,2,4-triazoles

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(Received 15 January 1991; accepted 21 May 1991)

Summary — Ni(II), Co(II), Zn(II) and Cd(II) complexes of 3-mercapto-4-phenyl(cyclohexyl)-4H-1,2,4-triazoles were prepared and characterized by elemental analyses and standard spectroscopic techniques. *In vitro* antimicrobial activity of the complexes was determined against a variety of bacterial (Gram-positive and Gram-negative) and fungal species. While the Ni, Co and Zn complexes exhibited little or no activity against the organisms studied in this work, complexes of both the 4-phenyl **13** and 4-cyclohexyl **12** substituted triazoles were highly active as antifungal agents. Both **12** and **13**, while significantly superior to the prototypical antifungal nystatin in inhibiting the growth of *Candida albicans* and *Candida pseudotropicalis*, showed equal effectiveness against *Saccharomyces cerevisiae*. The antibacterial activity of the Cd complexes was better than that observed for any of the other metal complexes, but generally not comparable to that of the reference antibiotic, streptomycin with the exception of the 4-cyclohexyl triazole complex **12**, which was equivalent to streptomycin against *Staphylococcus aureus* and *Escherichia coli*.

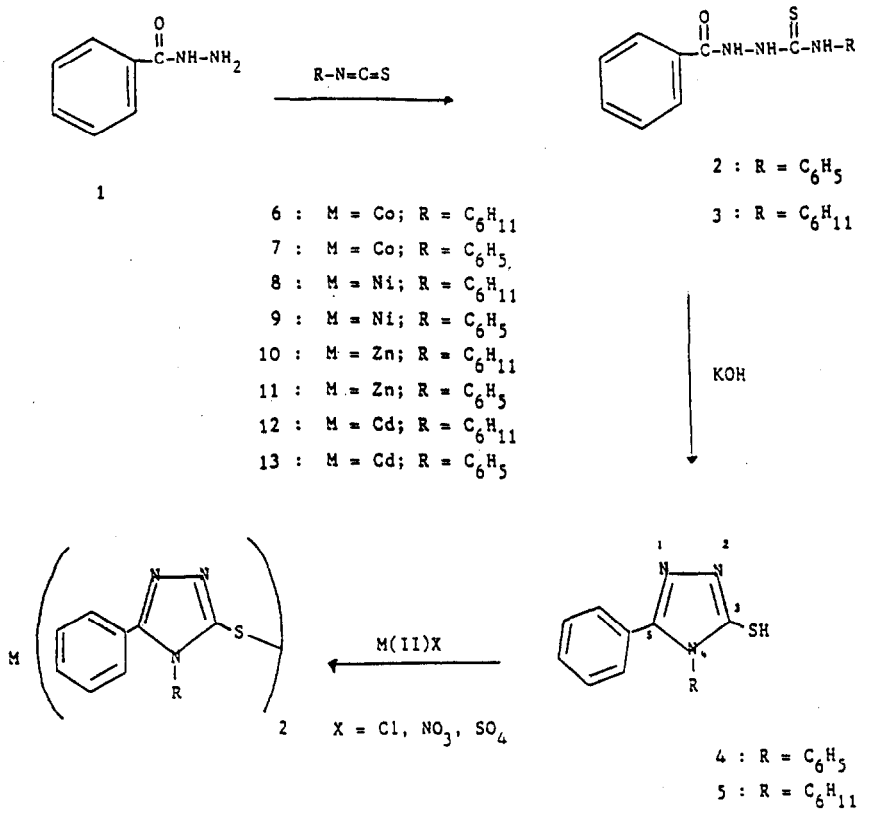
3-mercaptotriazoles / transition metal complexes / cadium complex / antimicrobial activity

Introduction

The aromatic triazole nucleus is associated with a variety of pharmacologic actions. 1,2,4-triazole derivatives show pronounced antibacterial activity [1–3] and metal complexes of substituted triazoles have also demonstrated efficacy in inhibiting tumor growth [4]. The synthesis and pharmacological evaluation of the transition metal complexes of numerous substituted triazoles have been reported in the literature. Specifically, complexes of Mn(II), Co(II), Ni(II), Cu(II), Zn(II), Cd(II), and Hg(II) with 4-*n*-butyl-4H-1,2,4-triazole have been prepared and formulated as MR_nC1_2, where M = divalent metal ion, R = ligand species and n = 2–5 [5]. In addition, complexes of Zn(II), Cu(II), Ni(II), and Co(II) with 3-aryloxymethyl-4-aryl-5-mercapto-1,2,4-triazole have been prepared and screened for antifungal activity. It was proposed that the ligand in the latter series of complexes is coordinated with the metal ion through the sulfur atom [6]. In view of these and other observations [7], it was of interest to synthesize divalent metal complexes of 4-substituted 3-mercapto-5-phenyl-4H-1,2,4-triazoles as potential antimicrobial agents and to assess their activity against representative bacteria and fungi. Zn, Co, Ni and Cd were the metals selected for complexation with the mercaptotriazole nuclei.

Chemistry

The synthesis of the transition metal-mercaptotriazole complexes is outlined in scheme 1. Both 3-mercapto-5,5-diphenyl-4H-1,2,4-triazole **4** [8] and 3-mercapto-4-cyclohexyl-5-phenyl-4H-1,2,4-triazole **5** [9] were prepared *via* cyclization of 1-benzoyl-4-substituted thiosemicarbazides **2** and **3** under alkaline conditions [10]. These intermediates were characterized by elemental analyses IR spectrophotometry and ^1H NMR spectroscopy. The sodium salts of the cyclized mercaptotriazoles were generated by reacting the free ligands with an equimolar quantity of sodium hydroxide in ethanol. The desired metal complexes were obtained by combining freshly prepared ethanolic solutions of the ligands as their sodium salts and the metals as the chloride, sulfate or nitrate salts. The weight of the dried sodium salt reaction by-product indicated quantitative reactions which produced complexes containing a 1:2 ratio of metal ion to ligand. The structures of the complexes were verified



Scheme 1.

by elemental analyses (table I). IR spectrophotometry (table II) and, in the case of the Ni and Co complexes, UV-Vis spectrophotometry (table III).

The IR spectra of all complexes indicate the absence of SH stretching vibrations at 2550 and 2555 cm^{-1} which had been observed in the spectra of the free triazole ligands. The absorption bands observed at 480–498 cm^{-1} were attributed to M-N stretching vibrations [11]. These data indicate that the metal ions of the complexes are coordinated to both the sulfur atom and the pyridine-type N_2 nitrogen atoms of the triazole rings. The bidentate nature of the ligand is expected, as the 1:2 ratio of metal to ligand allows for saturation of the coordination number.

Stable complexes were isolated in all cases. Other characteristic frequencies of the complexed ligands were readily assigned based on comparison with literature references [11].

Theoretically, two isomeric forms are possible for some of the complexes. In the C_{2v} point group, the sulfur atom and N_2 nitrogen of one ligand assume a *cis* orientation with respect to their couterparts on the second coordinated ligand. The orientation of these heteroatomic groups is *trans* in the form designated as C_{2h} (fig 1). It is hypothesized that electron-electron repulsion involving lone pairs on the 2 sulfur atoms and the 2 uncomplexed N_1 atoms of each ligand might make the *cis* isomer less energetically favored and subsequently promote the formation of the more stable *trans* chelate. Extensive recrystallization utilizing a variety of solvent systems was undertaken in an attempt to separate any isomeric forms, and these efforts resulted in the isolation of a single product. Examination of the IR spectra of the complexes indicated this form to be the *trans* (2_{Ch}) isomer. Single stretching frequencies were observed for the M-N vibration in all complexes and for the M-S bonds in complexes **10–13**. Single frequencies would be expected for the symmetrical *trans* isomer while multiple vibrations would be anticipated for these molecular perturbations in the *cis* form.

The blue cobalt complexes exist in a divalent state with symmetrical tetrahedral geometry [12]. This hypothesis is supported by the number of maxima observed in the UV-Vis spectra of the complexes. The 3 maxima have been assigned to the transition of $^4A_2 \rightarrow {}^4T_2$, $^4A_2 \rightarrow {}^4T_1$ (F) and $^4A_2 \rightarrow {}^4T_1$ (F) (table III). The Ni complexes were both olive green

Table I. Structure and physical properties of 3-mercaptotriazole-transition metal complexes. All complexes decompose above 300°C. All complexes were analyzed for C, H and N. The results had a maximum deviation of ± 0.4% from theoretical value.

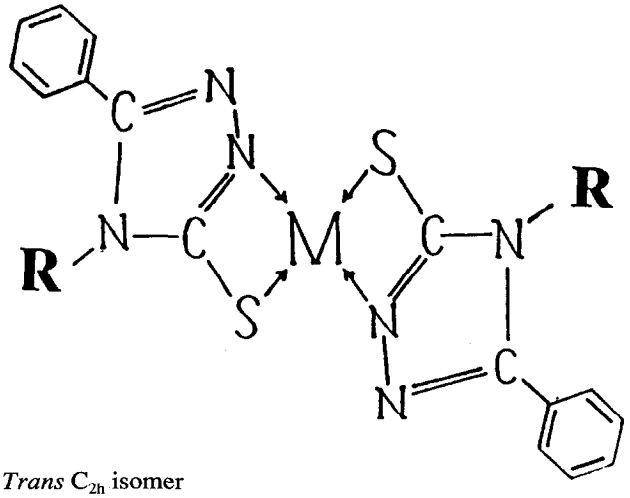
Complex	*M*	*R*	*Formula*	*Recrystallization solvent*	*% Yield*	*Color*
6	Co	C_6H_{11}	$Co(C_{14}H_{16}N_3S)_2 \cdot CHCl_3$	$C_2H_5OH/CHCl_3$	88	blue
7	Co	C_6H_5	$Co(C_{14}H_{10}N_3S)_2 \cdot CHCl_3$	$C_2H_5OH/CHCl_3$	85	blue
8	Ni	C_6H_{11}	$Ni(C_{14}H_{16}N_3S)_2 \cdot 2H_2O$	C_2H_5OH/H_2O	95	olive green
9	Ni	C_6H_5	$Ni(C_{14}H_{10}N_3S)_2 \cdot 2H_2O$	C_2H_5OH/H_2O	99	olive green
10	Zn	C_6H_{11}	$Zn(C_{14}H_{16}N_3S)_2 \cdot 2H_2O$	C_2H_5OH/H_2O	85	white
11	Zn	C_6H_5	$Zn(C_{14}H_{10}N_3S)_2 \cdot 2H_2O$	C_2H_5OH/H_2O	85	white
12	Cd	C_6H_{11}	$Cd(C_{14}H_{16}N_3S)_2 \cdot 2H_2O$	C_2H_5OH/H_2O	95	white
13	Cd	C_6H_5	$Cd(C_{14}H_{10}N_3S)_2 \cdot 2H_2O$	C_2H_5OH/H_2O	88	white

Table II. IR stretching frequencies of 3-mercapto-4,5-disubstituted-4H-1,2,4-triazole complexes (KBr, cm^{-1}).

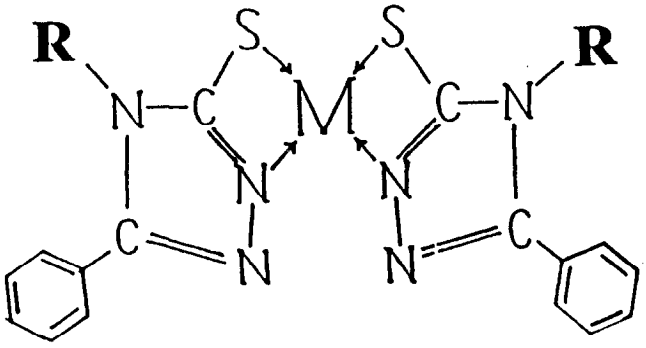
Complex	*Formula*	*C-H*	*C = C*	*C–N*	*N–N*	*C–C*	*C–S*	*M–S*	*M–N*	*N = C–S*
6	$Co(C_{14}H_{16}N_3S)_2 \cdot CHCl_3$	3056 2929	1590	1480 1495	1443 1412	720 590	769 818	303 368	498	980 893
7	$Co(C_{14}H_{10}N_3S)_2 \cdot CHCl_3$	3061 2923	1595	1495 1480	1443 1412	700 656	768	300 360	498	982 868
8	$Ni(C_{14}H_{16}N_3S)_2 \cdot 2H_2O$	3060 2985	1610 1550	1495 1480	1440	700 600	780 810	300 380	490	900 980
9	$Ni(C_{14}H_{10}N_3S)_2 \cdot 2H_2O$	2940 3053	1595 1534	1495 1479	1445 1414	691 623	768 808	300 440	480	918 987
10	$Zn(C_{14}H_{16}N_3S)_2 \cdot 2H_2O$	3040 2900	1600	1470	1430	700 600	770 810	350	440	915 980
11	$Zn(C_{14}H_{10}N_3S)_2 \cdot 2H_2O$	2940 2990	1590	1500	1450	700 600	790 840	330	450	950 985
12	$Cd(C_{14}H_{16}N_3S)_2 \cdot 2H_2O$	2900 2810	1580	1460	1430	700 600	770 810	350	440	890 980
13	$Cd(C_{14}H_{10}N_3S)_2 \cdot 2H_2O$	2810 2990	1590	1590	1450	720 630	790 880	320	440	930 990

Table III. UV-visible spectra of octahedral Ni(II) complexes and tetrahedral Co(II) complexes (frequency, cm^{-1}).

Complex	*Formula*	$^4A_2 \rightarrow {}^4T_2$	$^4A_2 \rightarrow {}^4T_1(F)$	$^4A_2 \rightarrow {}^4T_1(F)$
6	$Co(C_{14}H_{16}N_3S)_2 \cdot CHCl_3$	14300	16000	17700
7	$Co(C_{14}H_{10}N_3S)_2 \cdot CHCl_3$	14500	16100	17540
		$^3A_{2g} \rightarrow {}^3T_{2g}$	$^3A_{2g} \rightarrow {}^3T_{1g}(F)$	$^3A_{2g} \rightarrow {}^3T_{1g}$
8	$Ni(C_{14}H_{16}N_3S)_2 \cdot 2H_2O$	18100	24100	38000
9	$Ni(C_{14}H_{10}N_3S)_2 \cdot 2H_2O$	21500	23800	30400



Trans C_{2h} isomer



Cis C_{2v} isomer

Fig 1. Structure of the *trans* and *cis* isomeric forms of the mercaptotriazole-transition metal complexes. R = C_6H_5 or C_6H_{11}.

crystals, indicating that they were probably paramagnetic with a divalent metal ion, but with octahedral geometry, which may assume *cis* or *trans* orientation. The UV-Vis spectra of these complexes again showed 3 maxima which were assigned to the following transitions: $^3A_{2g} \rightarrow {}^3T_{2g}$, $\rightarrow {}^3A_2 \rightarrow {}^3T_{1g}$ (F), and $^3A_{2g} \rightarrow {}^3T_{1g}$ (table III).

Pharmacology

Complexes **6–13** were assayed *in vitro* for their ability to inhibit the growth of representative Gram-positive and Gram-negative bacteria and various fungal species. The prototypical antimicrobial agents streptomycin and nystatin were also assayed and served as reference antibacterial and antifungal standards, respectively. The results of the *in vitro* antimicrobial screening assay are presented in table IV.

Results and discussion

Most of the complexes proved inactive as antibacterial agents. Two of the 3 compounds that did exhibit appreciable activity against the representative bacteria were Cd containing complexes. Aromatic Cd complex **13**, while significantly more active against the bacteria studied than triazoles complexed with other metals, was always a less active antibacterial than either its saturated analog **12** or the reference compound streptomycin. In terms of MIC, both **12** and **13** demonstrated significantly greater activity against *S aureus* and *S typhimurium* than *E coli*. The molar concentrations (x 10^5) corresponding to the MIC values listed in table IV for complexes **12** and **13**, respectively are: *S aureus* 1.88, 3.94; *S typhimurium* 1.88, 9.57; and *E coli* 4.66, 31.90.

Complex **12** demonstrated significantly greater activity against *S typhimurium* than streptomycin (1.88 x 10^{-5} *versus* 4.59 x 10^{-5} M) but the two were statistically equivalent against *S aureus* and *E coli*. It should be noted that the metal complexes were utilized in the antimicrobial assays in suspension (Tween 80/sterile water). No attempt should be made to equate the minimum inhibitory concentrations (MIC) listed in table IV with physiological MIC values.

A potential explanation for the low antibacterial activity exhibited by most of these complexes could reside in their presumably low lipophilicity. In the penicillin family of antibiotics potency is directly related to lipophilic character, particularly when Gram-positive organisms are involved [11]. The mercaptotriazole aromatic nucleus is highly electron-rich and it is possible that the aromatic and alicylic rings found on positions **4** and **5** of the triazole systems do not sufficiently enhance the Log P of the complexes to allow for effective penetration of the bacterial cell membrane. Given this hypothesis, it is of interest to note that the most active antibacterial complex **12** has the more lipophilic 4-cyclohexyl substituent.

When antifungal activity was assessed, the Cd complexes again proved to be the most potent agents overall. Cadmium complexes **12** and **13** were equipotent with the reference antifungal nystatin against *S cerevisiae* (molar concentration x 10^5: **12**, 0.36; **13**, 0.11; nystatin, 1.81) and significantly more active than the reference compound against *C albicans* (molar concentration x 10^5: **12**, 0.36; **13**, 0.11; nystatin, 1.81). Saturated complex **12**, equally active against all fungi

Table IV. Minimum inhibitory concentration (MIC)[a] of 3-mercaptotriazole-transition metal complexes against selected bacteria and fungi.

Complex	*MIC (μg/ml)* *S aureus*	*E coli*	*S typhimurium*	*C albicans*	*C pseudotropicalis*	*S cerevisiae*
6	I[b]	I	I	125 ± 0	125 ± 0	62.5 ± 0
7	I	I	I	I	I	I
8	I	I	I	I	500 ± 0	500 ± 0
9	I	I	I	I	I	I
10	250 ± 0	500 ± 0	250 ± 0	I	500 ± 0	208.3 ± 72.2
11	I	I	I	I	I	I
12	12.5 ± 4.3	31 ± 0	12.5 ± 4.3	2.4 ± 1.1	3.1 ± 1.1	2.4 ± 1.1
13	25.7 ± 9.2	208.3 ± 72.2	62.5 ± 0	0.7 ± 0.2	31 ± 0	0.7 ± 0.2
Streptomycin	< 5	26.7 ± 2.9	26.7 ± 2.9	NA	NA	NA
Nystatin	NA	NA	NA	16.7 ± 2.9	13.3 ± 2.9	16.7 ± 2.9

[a]The MIC values represent the mean of 3 independent determinations; [b]inactive at inhibiting organism growth at concentrations ≥ 1 000 μg/ml.

assayed, was significantly more active than either nystatin or **13** against *C pseudotropicalis* (molar concentration x 10^5: **12**, 0.47; **13**, 4.75; nystatin, 1.44). Aromatic Cd complex **13** was significantly more active against *C albicans* and *S cerevisiae* than *C pseudotropicalis*. None of the remaining complexes containing a 4-phenyl ring were active as antifungal agents. The 4-cyclohexyl analogs of the Zn, Ni, and Co complexes (**6**, **8** and **10**, respectively) all demonstrated some — albeit weak — activity against most of the fungi in the assays. Complex **6**, the only non-Cd complex to demonstrate appreciable antifungal activity, was significantly more active against all fungi (particularly *S cerevisiae*) when compared to complexes **8** and **10** but less active than either Cd complex. Complex **6** was statistically equivalent to nystatin when tested against *S cerevisiae* (8.99 x 10^{-5} M).

The overall higher antifungal activity of the 4-cyclohexyl congeners could again point to the importance of lipophilic/hydrophilic balance in these polar complexes or it might be indicative of the need for a hydrophobic interaction (as opposed to a charge transfer or Van der Waals type of interaction) at the receptor surface for effective inhibition of fungal growth. Obviously the cadmium ion is contributing to the antimicrobial activity observed with complexes **12** and **13** but its potency-promoting role is at present unknown.

Experimental protocols

Chemical methods

Melting points were determined on a calibrated Thomas-Hoover melting point apparatus. IR spectra were recorded on a Perkin-Elmer 983 spectrophotometer. UV-visible spectra were recorded on a Beckman-Acta MVII spectrophotometer. Elemental analyses were performed in the laboratories of Prof Dipl-Ing. Dr H Malissa and G Reuter, Germany and Samara Laboratories, Samara, Iraq.

Benzoic acid hydrazide 1

The starting material was prepared from ethylbenzoate and hydrazine hydrate according to the method of Gatterman and Wieland [14].

1-Benzoyl-4-substituted thiosemicarbazides **2** and **3**, containing either a terminal phenyl or cyclohexyl ring at position 4 were prepared by reacting **1** with the appropriately substituted isothiocyanates following the method of Shah *et al* [15].

3-Mercapto-4,5-diphenyl-4H-1,2,4-triazole 4

1-Benzoyl-4-phenylthiosemicarbazide **2** (0.4 mol) was refluxed for 8 h with 100 ml of 8% sodium hydroxide. After neutralization with 10% acetic acid, the crude product was recrystallized in 85% yield from ethanol. mp = 278–280°C; anal ($C_{14}H_{11}N_3S$). Calcd: C 66.40, H 4.34, N 16.60, S 12.64. Found: C 66.62, H 4.28, N 16.25, S 12.45; IR (KBr): 3050 (CH, ArH), 2555 (SH), 1650 (C=N), 1540, 1450, 850 (C=C, Ar) cm^{-1}: ^{1}HNMR ($CDCl_3$): 5.75 (m, 5H, ArH), 7.3 (m, 5H, ArH), 2.90 (S, 1H, SH). The sodium salt was generated from the purified thiol by reacting equimolar quantities of the triazoles and sodium hydroxide in absolute ethanol. The sodium salt was isolated by filtration and dried.

3-Mercapto-4-cyclohexyl-5-phenyl-4H-1,2,4-triazole 5

Utilizing **3** and 8% sodium hydroxide, a cyclization reaction identical to that described for the preparation of **4** was conducted. Recrystallization from ethanol provided the pure triazole in 81.0% yield, mp = 178–218°C; anal ($C_{14}H_{17}N_3S$). Calcd: C 64.86, H 6.56, N 16.21, S 12.37. Found: C 64.99, H 6.59, N 16.23, S 12.21: IR (KBr): 3040 (CH, ArH), 2950 (CH_2, aliphatic), 2550 (SH), 2545, 1460, 775 (C = C, Ar): ^{1}H-NMR ($CDCl_3$): 7.3 (m, 5H, ArH), 3.0 (1H, SH), 2.18 (m, 1H, N-CH), 1.75 (m, 4H, $(CH_2)_2$), 1.25 (m, 6H, $(CH_2)_3$). The sodium salt was prepared in the manner previously described. Compounds **4** and **5** were already described in [8, 9].

Transition metal complexes of 3-mercapto-4,5-diphenyl-4H-1,2,4-triazole and 3-mercapto-4-cyclohexyl-5-phenyl-4H-1,2,4-triazole ***6–13***

Ethanolic solutions containing 0.008 mol of the sodium salt of **4** or **5** were added dropwise to 0.004 mol of the appropriate chloride, sulfate and nitrate transition metal salts. The solutions were stirred for 0.5 h and left to stand at room temperature for 12 h at which time a colored or white precipitate was obtained. The precipitate was filtered and the filtrate was tested with small quantities of both reactants to ensure completion of reaction which was indicated by the absence of additional precipitation. Precipitates were thoroughly washed with absolute ethanol and taken up in chloroform. The chloroform-insoluble sodium chloride, sulfate, or nitrate by-product was filtered, dried and weighed to ensure a stoichiometric recovery. The theoretical amount of sodium salt was consistently recovered, indicating a complete reaction in each case. Evaporation of the chloroform *in vacuo* afforded the crude metal complexes. Recrystallization from ethanol–chloroform or ethanol–water afforded the clean complexes (see table I for complex structures and physical properties).

Microbiological methods

The antimicrobial activity of the transition metal complexes **6** and **13** were assayed utilizing the agar-dilution technique [16].

Test organisms and culture media

Organisms utilized in the assay included *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATTC 25922, *Salmonella typhimurium* ATCC 14628, *Candida albicans* (local isolate), *Candida pseudotropicalis* ATCC 612, and *Saccharomyces cerevisiae* (local isolate). All bacteria were cultivated in trypton soya broth and agar (Oxoid). Fungi were grown in yeast glucose medium (prepared by dissolving 5 g yeast extract and 30 g glucose in 1 l distilled water) and yeast glucose agar (prepared by the addition of 2% agar (Oxoid) to the above solution).

Antimicrobial assays

A stock milky suspension of each transition metal complex was prepared by suspending 100 mg of complex in 1 ml of Tween 80 and diluting to 20 ml with sterile water (5 mg/ml in 5% v/v Tween 80). This stock milky suspension was used to prepare dilutions in sterile molten agar with complex concentrations ranging from 1 000 to 0.1 μg/ml [17]. The maximum concentration of Tween 80 in agar was 1%. After agar solidification, 10 μl of bacterial and fungal suspensions were added in drop form to the surface of the drug-treated agar plates. The drops were allowed to dry without spreading. The plates were incubated at 37°C and examined after 18 h for organism growth. Control plates spotted with Tween 80 were assayed concurrently, as were plates treated with the reference standards streptomycin sulfate (antibacterial) and nystatin (antifungal). All assays were run in triplicate. The minimum inhibitory concentration (MIC), defined as the lowest concentration of each complex that totally inhibited visible microorganism growth, was recorded for each compound assayed. Tween 80 did not show any antimicrobial activity at the concentration employed. The MIC values reported in table IV represent the mean obtained from 3 independent determinations. Significant differences between the means of active compounds were assessed utilizing Fisher's protected *t*-test (LSD test) with $P < 0.05$.

Acknowledgments

The authors acknowledge Drs JV Lupo and MC Makoid of Creighton University for valuable discussion on statistical analysis. Barbara Samson is acknowledged for clerical assistance in the preparation of the manuscript.

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