SYNTHESIS AND ANTI-CANDIDA ACTIVITY OF COBALT(II) COMPLEXES OF BENZENE-1,2-DIOXYACETIC ACID (bdoaH₂).
X-RAY CRYSTAL STRUCTURES OF [Co(bdoa)(H₂O)₃]·3.5H₂O AND {[Co(phen)₃](bdoa)}₂·24H₂O (phen = 1,10-PHENANTHROLINE)

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Abstract

Co(CH₃CO₂)₂·4H₂O reacts with benzene-1,2-dioxyacetic acid (bdoaH₂) to give the Co²⁺ complexes [Co(bdoa)(H₂O)₃]·H₂O (1a) and [Co(bdoa)(H₂O)₃]·3.5H₂O (1b). Subsequent reaction of 1a with 1,10-phenanthroline produces [Co(phen)₃]bdoa·10H₂O (2a) and {[Co(phen)₃](bdoa)}₂·24H₂O (2b). Molecular structures of 1b and 2b were determined crystallographically. In 1b the bdoa²⁻ ligates the metal by two carboxylate oxygens and two ethereal oxygens, whereas in 2b the bdoa²⁻ is uncoordinated. The Mn²⁺ and Cu²⁺ complexes [Mn(bdoa)(phen)₂]·H₂O (3) and [Cu(bdoa)(imid)₂] (4) were also synthesised. 1a–4 and other metal complexes of bdoaH₂ (metal = Mn²⁺, Co²⁺, Cu²⁺, Cu⁺) were screened for their ability to inhibit the growth of the yeast Candida albicans. Complexes incorporating the 1,10-phenanthroline ligand were the most active.

Keywords: crystal structures; benzene-1,2-dioxyacetic acid, 1,10-phenanthroline; metal complexes; Candida albicans.

Introduction

Microbial infections in both humans and animals are diverse in their manifestations, ranging from superficial skin problems, chronic infection of the nails, mouth, throat or vagina to frequently fatal systemic diseases. The persistent use of cytotoxic drugs, corticosteroids, antibiotics and immunosuppressants has resulted in an increase in systemic opportunistic microbial infections. The yeast Candida albicans, a commensal of the human body, is considered to be the most important fungal pathogen. Over 75% of women suffer from vaginal candidosis (thrush) at some stage in their lifetime, and systemic candidosis is often fatal in immunocompromised patients.¹⁴ The search for novel antifungal drugs has intensified over the last decade and some literature has highlighted the use of metal complexes as useful antifungal agents.⁵

Benzene-1,2-dioxyacetic acid (bdoaH₂) contains six potential oxygen donor atoms (four carboxylate oxygens and two ethereal oxygens, Fig. 1) and is an extremely versatile ligand.

![Figure 1. Benzene-1,2-dioxyacetic acid (bdoaH₂).](image)

To date, K⁺,⁶ Mg²⁺,⁷ Ca²⁺,⁷ La³⁺,⁸ Mn²⁺,⁷,⁹ Ni²⁺,⁷ Cu²⁺,¹⁰,¹¹ Cu⁺¹² and Zn²⁺ complex of this aryloxydicarboxylic acid have been structurally characterised. In the present paper we report the full X-ray
crystal structures of two cobalt(II) complexes with bdoa$^{2-}$. In addition, the anti-
Candida activities of bdoaH$_2$ and its Mn$^{2+}$, Co$^{2+}$, Cu$^{2+}$ and Cu$^+$ complexes are presented and this, to our knowledge, is the first report of
the biological chemistry of both the diacid and its metal complexes.

**Materials and Methods**

Chemicals were purchased from commercial sources and used without further purification. Literature
methods were used to prepare $[\text{Mn(bdoa)}(\text{H}_2\text{O})_3]$ (5),$^9$ $[\text{Cu(bdoa)}(\text{H}_2\text{O})_2]$ (6),$^{11}$ $[\text{Cu}_2(\text{bdoa})(\text{phen})_4]\text{bdoa}\cdot 13\text{H}_2\text{O}$ (7) (phen = 1,10-phenanthroline),$^{11}$ $[\text{Cu}_2(\text{bdoa})(\text{bipy})_4]\text{bdoa}\cdot 8.66\text{H}_2\text{O}$ (8) (bipy = 2,2'-bipyridine),$^{10}$ $[\text{Cu}(\text{bdoa})(\text{an})_2]\text{bdoa} \cdot 9$ (an = aniline),$^{10}$ $[\text{Cu}(\text{bdoa})(\text{NH}_3)_2]\cdot \text{H}_2\text{O}$ (10),$^{11}$ $[\text{Cu}(\text{bdoa})(\text{py})_2]\cdot \text{H}_2\text{O}$ (11) (py = pyridine),$^{11}$ $[\text{Cu}(\text{bdoa})(\text{PPh}_3)_2] $bdoa (12),$^{12}$ $[\text{Cu}(\text{phen})(\text{PPh}_3)_2]\text{bdoaH}$ (13).$^{13}$

Infrared spectra were recorded as KBr discs in the region 4000-400 cm$^{-1}$ on a Nicolet Impact 400D FT-IR
Spectrometer. Magnetic susceptibility measurements were made at room temperature using a Johnson
Matthey Magnetic Susceptibility Balance and conductivity measurements were taken at 25 $^\circ$C using an AGB
Scientific Ltd. model 10 conductivity meter. Elemental analysis were carried out by the Microanalytical
Laboratory, University College Cork, Ireland. Biological susceptibility testing was conducted using a
Labsystems iEMS Reader MF.

**Table 1.** Crystal data.

|                         | [Co(bdoa)(H$_2$O)$_3$]·3.5H$_2$O (1b) | {[Co(phen)$_3$](bdoa)}$_2$·24H$_2$O (2b) |
|-------------------------|--------------------------------------|----------------------------------------|
| **Empirical formula**   | C$_{10}$H$_2$CoO$_{12.5}$            | C$_{92}$H$_{112}$Co$_2$N$_{12}$O$_{36}$ |
| **Formula weight**      | 400.20                               | 2079.80                                |
| **Crystal description**  | pink plate                           | orange block                           |
| **Temperature (K)**     | 153(2)                               | 153(2)                                 |
| **Wavelength (Å)**      | 0.71073                              | 0.71073                                |
| **Crystal system**       | monoclinic                           | monoclinic                             |
| **Space group**          | C2/c                                 | P2$_1$                                 |
| a (Å)                   | 29.151(4)                            | 13.123(4)                              |
| b (Å)                   | 6.700(1)                             | 21.166(6)                              |
| c (Å)                   | 17.215(2)                            | 18.809(9)                              |
| α (°)                   | 90                                   | 90                                     |
| β (°)                   | 108.74(2)                            | 110.15(4)                              |
| γ (°)                   | 90                                   | 90                                     |
| V (Å$^3$)               | 3184.0(7)                            | 4905(3)                                |
| Z                       | 8                                    | 2                                      |
| **Density (calculated, Mg/m$^3$)** | 1.670                               | 1.408                                  |
| µ (mm$^{-1}$)           | 1.142                                | 0.430                                  |
| F(000)                  | 1664                                 | 2180                                   |
| **Crystal size (mm)**   | 0.52x 0.27 x 0.15                    | 0.90 x 0.37 x 0.32                     |
| θ range for data collection (°) | 2.0 to 25.0                         | 2.0 to 25.0                            |
| **Index ranges**        | -1<h<34                              | 0<h<14                                 |
|                        | -1<k<7                               | -1<k<22                                |
|                        | -20<l<19                             | -20<l<19                               |
| **Reflections collected** | 3359                                | 7385                                   |
| **Independent reflections** | 2784 (R$_{int}$ = 0.087)            | 7033 (R$_{int}$ = 0.0526)              |
| **Data / restraints / parameters** | 2784 / 0 / 226                      | 7033 / 1 / 914                         |
| **T$_{max}$, T$_{min}$ (ψ-scans)** | 0.954, 0.807                      | none                                    |
| **Goodness-of-fit on F$^2$ (all data)** | 1.058                               | 1.089                                   |
| **Final R indices [I >2σ(I)]** | R$_1$ = 0.0584                 | R$_1$ = 0.0712                          |
|                        | wR$_2$ = 0.1419                      | wR$_2$ = 0.2001                         |
| **R indices (all data)** | R$_1$ = 0.0915                     | R$_1$ = 0.0949                          |
|                        | wR$_2$ = 0.1648                      | wR$_2$ = 0.2285                         |
| **Largest peak and hole (eÅ$^3$)** | 0.754 and -0.673                  | 0.958 and -0.611                        |
| **Absolute structure parameter** | -                                   | 0.04(4)                                |

Crystal data are summarised in Table 1. Data sets for [Co(bdoa)(H$_2$O)$_3$]·3.5H$_2$O (1b) and
{[Co(phen)$_3$](bdoa)}$_2$·24H$_2$O (2b) were collected on a Siemens P4 four-circle diffractometer and were
corrected for Lorentz and polarisation effects. \(1b\) was also corrected for absorption. Both structures were solved by direct methods (TREF) and refined by full matrix least-squares on \(F^2\), using all of the data. All the non-hydrogen atoms were refined with anisotropic atomic displacement parameters; hydrogen atoms bonded to carbon were inserted at calculated positions. In \(1b\) hydrogen atoms on the full-occupancy water molecules and on \(O7W\) were located from difference Fourier maps and not further refined. Hydrogen atoms on the water molecules of \(2b\) were not included. All programs used in the structure solution and refinement are contained in the SHELXL97 package.14

\[\text{[Co(bdoa)(H}_2\text{O})_3\text{]}\cdot\text{H}_2\text{O (1a) and [Co(bdoa)(H}_2\text{O})_3\text{]}\cdot3.5\text{H}_2\text{O (1b). Complex (1a) was prepared using a modification of the literature method.}\]

To a solution of \(\text{bdoaH}_2\) (1.13 g, 5.0 mmol) in water/ethanol (1:4, 150 cm\(^3\)) was added cobalt(II) acetate tetrahydrate (1.87 g, 7.5 mmol). An immediate color change to deep red was observed and upon stirring the product precipitated as a deep red solid. The solid was filtered off, washed with two portions of ethanol, one portion of diethylether and then dried in air. Yield: 1.46 g (82%). Microanalysis for 1a: Calc.: C 33.83; H 4.54. Found: C 34.22; H 5.05%. The complex was soluble in water and in ethanol. \(\mu_{\text{eff}} = 5.02\) B.M.. \(\Lambda_M(\text{H}_2\text{O}) = 154\) S cm\(^2\) mol\(^{-1}\). IR: 3387, 2929, 2854, 1567, 1474, 1345, 1314, 1105, 1030, 723, 673, 615, 532 cm\(^{-1}\).

Dark pink crystals of \([\text{Co(bdoa)(H}_2\text{O})_3\text{]}\cdot3.5\text{H}_2\text{O (1b)}\) deposited overnight from the reaction filtrate and were used for X-ray structure determination.

\[\text{[Co(phen)]_2\text{bdoa}·10\text{H}_2\text{O (2a) and \{[Co(phen)]_3\text{bdoa}\}·24\text{H}_2\text{O (2b). Complex (1a) was prepared using a modification of the literature method.}\]

To a solution of \(\text{bdoaH}_2\) (1.13 g, 5.0 mmol) and 1,10-phenanthroline monohydrate (1.6 g, 8.1 mmol) were dissolved in water/ethanol (1:4, 200 cm\(^3\)) and the deep yellow solution was refluxed for 0.5 h and then concentrated in vacuo to ca 100 cm\(^3\). Orange crystals deposited slowly (21 days) from the solution. Some of the crystals were collected in a small portion of the mother liquor and used for X-ray crystal structure determination where the formulation was shown to be \({\{[\text{Co(phen)}_2]\text{bdoa}}\}_2\cdot24\text{H}_2\text{O (2b)}\). The remaining crystals 2a were filtered off, washed twice with a small portion of ethanol and then dried in air. Yield: 0.82 g (51%). Microanalysis for 2a: Calc.: C 55.04; H 5.22; N 8.37. Found: C 54.50; H 3.38; N 7.91%. Complex 2a was soluble in water and in ethanol. \(\mu_{\text{eff}} = 4.83\) B.M.. \(\Lambda_M(\text{H}_2\text{O}) = 162\) S cm\(^2\) mol\(^{-1}\). IR: 3387, 2930, 2854, 1567, 1474, 1345, 1313, 1160, 1098, 867, 849, 772, 726, 643 cm\(^{-1}\).

\[\text{[Mn(bdoa)(phen)]}_2\cdot\text{H}_2\text{O (3). To a solution of [Mn(bdoa)(H}_2\text{O})_3\text{]} (5) (0.60 g, 1.80 mmol) in ethanol (80 cm\(^3\)) was added 1,10-phenanthroline (1.05 g, 5.83 mmol) and the resulting solution was refluxed for 2 h. The precipitated yellow product was filtered off, washed with two small portions of ice-cold ethanol and then dried in air. Yield: 1.10 g (93%). Microanalysis for 3: Calc.: C 62.10; H 4.30; N 8.52. Found: C 62.00, H 4.30; N 8.13%. The complex was soluble in water and in methanol. \(\mu_{\text{eff}} = 5.76\) B.M.. \(\Lambda_M(\text{H}_2\text{O}) = 54\) S cm\(^2\) mol\(^{-1}\). IR: 1608, 1510, 1462, 1393, 1344, 1295, 1264, 1240, 1203, 1135, 1043, 913, 870, 849, 818, 778, 760, 700, 636, 587 cm\(^{-1}\).

\[\text{[Cu(bdoa)(imid)]}_2\cdot2\text{H}_2\text{O (4). To a solution of imidazole (imid) (0.92 g, 1.35 mmol) in ethanol (30 cm\(^3\)) was added [Cu(bdoa)(H}_2\text{O})_2\text{]} (6) (0.20 g, 0.62 mmol). The resulting solution was refluxed for 2 h and then filtered whilst hot. The blue product deposited from the filtrate upon standing for 24 h. The solid product was filtered off and the filtrate allowed to stand. The product was washed with cold ethanol and ether, and then dried in air. On standing for a prolonged period the filtrate yielded ca. 0.2 g of a blue tar. Yield: 0.18 g (68%). Microanalysis for 4: Calc.: C 45.3; H 3.8; N 13.2. Found: C 43.6; H 3.6; N 13.8%. The complex was soluble in water and in ethanol. \(\mu_{\text{eff}} = 1.82\) B.M.. \(\Lambda_M(\text{H}_2\text{O}) = 105\) S cm\(^2\) mol\(^{-1}\). \(\Lambda_M(\text{EtOH}) = 2\) S cm\(^2\) mol\(^{-1}\). IR: 3130, 1600, 1500, 1410, 1390, 1325, 1255, 1210, 1120, 1070, 1045, 935, 820, 780, 740, 695, 650, 615 cm\(^{-1}\).

**Biological studies**

*Candida albicans* (three isolates) were obtained from the In St. James’s Hospital, Dublin. The isolates were stored on Sabouraud dextrose agar (SDA) plates at 4°C. Solutions of the test complexes were prepared by dissolving the complex (0.02 g) in distilled water (100 cm\(^3\)) to yield a stock solution at a concentration of 200 µg cm\(^{-3}\). The solution was filtered sterilised using a Millipore membrane filter (0.45 µm). Complexes which were insoluble in water were ground to a fine powder and then suspended in sterile distilled water (100 cm\(^3\)).

**Susceptibility testing method**

RPMI-1640 broth medium (Sigma R 7755) was used for the anti-*Candida* susceptibility testing. The medium (1 dm\(^3\)) was supplemented with L-glutamine (0.3 g) and morpholinepropanesulfonic acid (MOPS) (34.6 g) and was adjusted to pH 7.0 using sterile NaOH (0.2 M).

The broth microdilution reference method was used.15 Prior to testing yeast cells were grown on Sabouraud dextrose agar (SDA) at 37 °C for 24 h. Cell suspensions were prepared in sterile phosphate buffer.
buffered saline (5 cm$^3$) to a density of 0.5 McFarland standard. A 1:100 dilution of the 0.5 McFarland standard yeast suspension was made in RPMI-1640 medium. The cell concentration of the final inoculum was $3.5 \times 10^4$ - $5.0 \times 10^5$ cells cm$^{-3}$. The prepared cell suspension (90 µl) was dispensed into microtitre plates and to this was added the test stock complex solution (10 µl) to yield working solutions of the test complexes of concentration 20 µg cm$^{-3}$. Plates were then incubated for 24 h at 37 °C with continuous shaking. Each complex was assessed in triplicate and three independent experiments were performed. The resulting nine data points were statistically analysed using ANOVA one-way analysis of variance followed by Tukey’s family error rate.

Results and Discussion

The pink complex $[\text{Co(bdoa)}(\text{H}_2\text{O})_3]\cdot\text{H}_2\text{O}$ (1a) was prepared in high yield by reacting cobalt(II) acetate tetrahydrate with bdoaH$_2$, and crystals of composition $[\text{Co(bdoa)}(\text{H}_2\text{O})_2] \cdot 3.5\text{H}_2\text{O}$ (1b) were isolated from the reaction filtrate. The X-ray crystal structure of 1b was determined (Fig. 2, Table 2) and the cobalt(II) ion is seven-coordinate, being bonded to three water molecules, a carboxylate oxygen from each end of the bdoa$^2-$ and, much more weakly, to the two ether oxygens. The $[\text{Co(bdoa)}(\text{H}_2\text{O})_3]$ unit of 1b is isostructural with the manganese(II) species $[\text{Mn(bdoa)}(\text{H}_2\text{O})_3]$ (5).9

![Figure 2. X-ray crystal structure of $[\text{Co(bdoa)}(\text{H}_2\text{O})_3] \cdot 3.5\text{H}_2\text{O}$ 1b](image-url)

Reaction of 1a with 1,10-phenanthroline (1:5 mol ratio) gave the tris(phenanthroline) adduct $[\text{Co(phen)}_3] \cdot \text{bdoa} \cdot 10\text{H}_2\text{O}$ (2a), and crystals of composition $[[\text{Co(phen)}_3](\text{bdoa})]_2 \cdot 24\text{H}_2\text{O}$ (2b) were isolated from the mother liquor. The X-ray crystal structure of 2b (Fig. 3 and 4, Table 3) shows that the bdoa$^2-$ and the three water ligands have been displaced from the coordination sphere of the metal in 1b and replaced by three chelating phenanthrolines. The bdoa$^2-$ simply functions as a counter di-anion. The asymmetric unit of 2b contains two independent (but similar) $[\text{Co(phen)}_3]^{2+}$ cations, two independent (and different) bdoa$^2-$ anions and twenty four water molecules. There is nothing remarkable in the geometry of the $[\text{Co(phen)}_3]^{2+}$ cations, although they interact with each other by π−π stacking, forming chains along the $a$ direction (interplanar distance between the Ni-C12C ring, coordinated to Co1, and the N1D-C12D ring, coordinated to Co2, is ~3.5 Å). The two bdoa$^2-$ anions differ in that the first is approximately coplanar while, in the second, one of the carboxylate groups is almost perpendicular to the phenyl ring. This is likely to be a
consequence of the very extensive hydrogen-bonding network which links the anions and all twenty four water molecules into a three-dimensional grid with spaces for the cation chains.

Table 2. Selected bond lengths [Å] and angles [°] for [Co(bdoa)(H₂O)₃]·3.5H₂O (1b).

| Bond/Angle                  | Value     |
|-----------------------------|-----------|
| Co-O(1)                     | 2.125(4)  |
| Co-O(3)                     | 2.440(4)  |
| Co-O(1W)                    | 2.084(4)  |
| Co-O(3W)                    | 2.051(4)  |
| O(1)-Co-O(3)                | 68.71(15) |
| O(1W)-Co-O(1)               | 83.06(18) |
| O(2W)-Co-O(1)               | 90.12(2)  |
| O(3W)-Co-O(1)               | 87.20(18) |
| O(1W)-Co-O(3)               | 151.66(17)|
| O(2W)-Co-O(3)               | 86.82(18) |
| O(3W)-Co-O(3)               | 81.88(17) |
| O(1)-Co-O(4)                | 129.59(15)|
| O(5)-Co-O(1)                | 162.95(17)|
| O(1W)-Co-O(5)               | 80.94(18) |
| O(2W)-Co-O(5)               | 95.92(2)  |
| O(3W)-Co-O(5)               | 89.77(19) |
| O(1W)-Co-O(4)               | 146.89(17)|
| O(2W)-Co-O(4)               | 84.52(2)  |
| O(3W)-Co-O(4)               | 88.65(18) |
| O(5)-Co-O(3)                | 127.40(16)|
| O(3)-Co-O(4)                | 60.96(14) |
| O(1W)-Co-O(1W)              | 99.80(19) |

Figure 3. Structure of the [Co(phen)₃]²⁺ moieties in {[Co(phen)₃][bdoa]}₂·24H₂O (2b) (hydrogen atoms omitted).

The bdoa complexes, the metal-free ligands and the simple acetate complexes of Co²⁺, Mn²⁺ and Cu²⁺ were each tested for their ability to inhibit the growth of three clinical isolates of C. albicans (Table 4). Although uncomplexed bdoaH₂ is essentially inactive against all three isolates coordination to Co²⁺ and Mn²⁺ (complexes 1a and 5) leads to slightly increased activity, with the Co²⁺ complex being marginally the better. The equivalent Cu²⁺ complex 6 was inactive. The simple monocarboxylate salt Co(O₂CCH₃)₂·4H₂O showed moderate anti-Candida activity against isolate 1 and isolate 3 but was
relatively inactive against isolate 2. Mn(O₂CCH₃)₂·4H₂O and [Cu₂(O₂CCH₃)₄(H₂O)₂] were essentially inactive against the three Candida isolates.

Figure 4. Structure of the bdoa²⁻ counterions in {{Co(phen)₃}(bdoa)}₂·24H₂O (2b).

The Co²⁺, Mn²⁺ and Cu²⁺ 1,10-phenanthroline adducts 2a, 3 and 7 dramatically inhibit the growth of all isolates, with the Mn²⁺ and Cu²⁺ species being the more superior. Furthermore, the Mn²⁺ complex 3 is significantly more active than its Cu²⁺ analogue 7 against isolate 2. Thus, it is evident that complexation of 1,10-phenanthroline to the metal centres in the conversion of the Mn²⁺ and Cu²⁺ species 5 and 6 to 3 and 7, respectively, greatly enhances their anti-Candida activities. In contrast to this improved activity with the Mn²⁺ and Cu²⁺ complexes the Co²⁺ non-phenanthroline and 1,10-phenanthroline chelated complexes (1a and 2a), have very similar activities. “Metal-free” 1,10-phenanthroline showed very high anti-Candida activity and, indeed, this was only surpassed by the activity of the Mn²⁺ 1,10-phenanthroline complex 3 (on isolates 2 and 3).
Table 3. Selected bond lengths [Å] and angles [°] for \(\{\text{Co(phen)}_3\}(\text{bdoa})_2\cdot2\text{H}_2\text{O}\) (2b).

| Bond/Angle | Distance/Angle |
|------------|----------------|
| Co(1)-N(2C) | 2.113(11)      |
| Co(1)-N(1B) | 2.131(11)      |
| Co(1)-N(2B) | 2.145(10)      |
| Co(2)-N(1D) | 2.125(11)      |
| Co(2)-N(1F) | 2.126(10)      |
| Co(2)-N(1E) | 2.144(10)      |
| N(2C)-Co(1)-N(1B) | 167.1(4) |
| N(1C)-Co(1)-N(1B) | 94.6(4)   |
| N(1E)-Co(1)-N(1B) | 93.4(4)   |
| N(1A)-Co(1)-N(1B) | 93.4(4)   |
| N(1F)-Co(2)-N(1F) | 94.3(4)   |
| N(1E)-Co(2)-N(1F) | 94.3(4)   |
| N(1D)-Co(2)-N(1D) | 95.3(4)   |
| N(2E)-Co(2)-N(1E) | 95.0(4)   |
| N(2F)-Co(2)-N(1E) | 95.0(4)   |
| N(1D)-Co(2)-N(1D) | 95.1(4)   |
| N(IF)-Co(2)-N(1E) | 95.0(4)   |
| N(IF)-Co(2)-N(1E) | 95.1(4)   |
| N(1F)-Co(2)-N(1F) | 94.3(4)   |
| N(2E)-Co(2)-N(1D) | 94.6(4)   |
| N(2E)-Co(2)-N(1D) | 94.3(4)   |
| N(2A)-Co(2)-N(1A) | 93.7(4)   |
| N(2A)-Co(2)-N(1A) | 93.3(4)   |
| N(2A)-Co(2)-N(1A) | 93.2(4)   |

Table 4. Anti-Candida activity.\(^a\)

| Test compound | Isolate 1 | Isolate 2 | Isolate 3 |
|---------------|-----------|-----------|-----------|
| Control       | 100       | 100       | 100       |
| bdoaH2        | 91 ± 8    | 105 ± 12  | 103 ± 9   |
| aniline       | 86 ± 7    | 84 ± 10   | 68 ± 8    |
| imidazole     | 78 ± 5    | 92 ± 8    | 98 ± 9    |
| ammonia       | 102 ± 10  | 89 ± 8    | 86 ± 7    |
| pyridine      | 104 ± 11  | 95 ± 4    | 83 ± 7    |
| triphenylphosphine | 98 ± 12  | 91 ± 4    | 83 ± 7    |
| 1,10-phenanthroline | 12 ± 0.3 | 14 ± 0.5  | 15 ± 2    |
| 2,2'-bipyridine | 75 ± 6   | 80 ± 4    | 104 ± 8   |
| Co(Cl\(_2\)CO\(_2\)_2\cdot4H\(_2\)O | 78 ± 5   | 85 ± 8    | 68 ± 5    |
| Mn(Cl\(_2\)CO\(_2\)_2\cdot4H\(_2\)O | 85 ± 8   | 94 ± 5    | 102 ± 8   |
| [Cu\(_2\)(CH\(_3\)CO\(_2\))\(_4\)H\(_2\)O\(_2\)] | 108 ± 9  | 89 ± 5    | 92 ± 7    |
| [Co(bdoa)(H\(_2\)O\(_3\))\cdot2H\(_2\)O \(_{\text{1a}}\)] | 63 ± 6   | 70 ± 3    | 78 ± 6    |
| [Mn(bdoa)(H\(_2\)O\(_3\)) \(_{\text{5}}\)] | 80 ± 1   | 84 ± 4    | 85 ± 1    |
| [Cu(bdoa)]\(_2\)H\(_2\)O \(_{\text{6}}\) | 101 ± 6  | 93 ± 6    | 91 ± 10   |
| [Co(phen)]\(_3\)bdoa\cdot10H\(_2\)O \(_{\text{2a}}\) | 55 ± 3   | 65 ± 9    | 77 ± 10   |
| [Mn(bdoa)(phen)]\(_2\)H\(_2\)O \(_{\text{3}}\) | 15 ± 2   | 6 ± 2     | 7 ± 1     |
| [Cu\(_2\)(bdoa)(phen)]\(_4\)bdoa\cdot13H\(_2\)O \(_{\text{7}}\) | 15 ± 2   | 22 ± 5    | 11 ± 3    |
| [Cu\(_2\)(bdoa)(bipy)]\(_4\)bdoa\cdot8.6H\(_2\)O \(_{\text{8}}\) | 96 ± 15  | 87 ± 9    | 97 ± 8    |
| [Cu\(_2\)(bdoa)(an)]\(_2\)an \(_{\text{9}}\) | 91 ± 3   | 88 ± 4    | 98 ± 11   |
| [Cu(bdoa)(imid)]\(_2\) \(_{\text{4}}\) | 95 ± 9   | 99 ± 9    | 98 ± 6    |
| [Cu(bdoa)(NH\(_3\)]\(_2\)\cdot2H\(_2\)O \(_{\text{10}}\) | 96 ± 6   | 96 ± 11   | 82 ± 7    |
| [Cu(bdoa)(py)]\(_2\)H\(_2\)O \(_{\text{11}}\) | 91 ± 5   | 97 ± 5    | 77 ± 7    |
| [Cu(bdoa)(PPH\(_3\)]\(_3\)H\(_2\)O \(_{\text{12}}\) | 99 ± 1   | 89 ± 5    | 72 ± 6    |
| [Cu(phen)(PPH\(_3\)]\(_3\)bdoaH \(_{\text{13}}\) | 63 ± 10  | 88 ± 11   | 65 ± 7    |

\(^a\)Compounds were tested at a concentration of 20 µg cm\(^{-3}\) of aqueous RPMI medium. Complexes 5-7, 9-13 were insoluble in water and were used as suspensions. Yeast cells were grown for 24 h at 37°C. Results are presented as % cell growth and the effectiveness of the compounds are compared to the growth of the control (no added compound).
In contrast to the performance of 1,10-phenanthroline the other NN chelating agent used in this study, 2,2'-bipyridine, is inefficient at preventing the growth of Candida cells. Also, the Cu²⁺ bipyridine complex 8 is ineffective.

Complexation of the monodentate N donor ligands aniline, imidazole, ammonia and pyridine to Cu²⁺ (complexes 9, 4, 10 and 11, respectively) does not improve the poor anti-Candida activity of the respective free ligands. Whereas the tris(triphenylphosphine) Cu⁺ complex 12 is only moderately active against isolate 3 the bis(triphenylphosphine)/phenanthroline Cu⁺ species 13 is relatively active against isolates 1 and 3.

In conclusion, the 1,10-phenanthroline molecule, whether it be uncomplexed or chelated to a metal centre, exhibits potent anti-Candida activity. It is also apparent that the nature of the metal centre to which the 1,10-phenanthroline is coordinated is also of significance given that the Mn²⁺ and Cu²⁺ complexes are superior to Co²⁺ complex. The fact that the related NN chelating ligand 2,2'-bipyridine and its copper complex both show negligible activity against the yeast serves to highlight the fundamental structural and reactivity differences between 2,2'-bipyridine and 1,10-phenanthroline.

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