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Synthesis and antimicrobial activity of (Z)-3-(1H-imidazol-1-yl)-2-phenylpropenenitrile and its metal complexes: X-ray crystal structures of the Zn(II) and Ag(I) complexes

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Abstract

(Z)-3-(1H-imidazol-1-yl)-2-phenylpropenenitrile (imppn) reacts with $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$, $\text{Zn}(\text{CH}_3\text{CO}_2)_2 \cdot 2\text{H}_2\text{O}$ and AgClO_4 producing $[\text{Cu}(\text{imppn})_4](\text{ClO}_4)_2 \cdot \text{H}_2\text{O}$ (**1**), $[\text{Zn}(\text{imppn})_2(\text{CH}_3\text{CO}_2)_2] \cdot 2\text{H}_2\text{O}$ (**2**) and $[\text{Ag}_2(\text{imppn})_4(\text{ClO}_4)_2]$ (**3**), respectively. Complexes **2** and **3** were characterised by X-ray crystallography. In **2** the metal lies in a pseudo-tetrahedral environment and is ligated by the imine nitrogens of two imppn ligands and an oxygen atom from each of two monodentate acetate anions. In the dimeric Ag(I) complex **3** each metal is coordinated to the imine nitrogens of two imppn ligands in an almost linear fashion and the two $[\text{Ag}(\text{imppn})_2]^+$ units are linked by an Ag–Ag bond, supported by two *trans* bridging bidentate perchlorate groups and by π – π interactions between the ligands. In vitro tests on the ability of the compounds to inhibit the growth of the pathogenic yeast *Candida albicans* showed that imppn and its metal complexes were markedly less effective than the prescription drug, ketoconazole.

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Keywords: (Z)-3-(1H-imidazol-1-yl)-2-phenylpropenenitrile; Metal complexes; X-ray structures; Silver(I); Anti-fungal; *Candida albicans*

1. Introduction

Azole drugs, such as ketoconazole and fluconazole (Fig. 1), are currently prescribed to treat fungal infections such as those caused by the pathogenic yeast *Candida albicans*.

It is generally accepted [1–3] that the fungicidal activity of these *N*-substituted imidazole and triazole derivatives is derived, at least partly, from their ability to inhibit ergosterol biosynthesis in fungi and yeast cells. The inhibition leads to diminished levels of sterol in the fungal cell membrane as well as an accumulation of toxic ergosterol intermediates which may play a key role in the killing of the fungal cell [4]. Resistance to azole

drugs has been seen clinically [5] and is mediated by a combination of factors including alterations in the ergosterol biosynthetic pathway, increased expression of drug efflux pumps and, possibly, degradation of the drug before it exerts an effect [6].

Lanosterol is an obligatory precursor to ergosterol and the initial step of lanosterol metabolism is the removal of its 14 α -methyl group [7], a reaction catalyzed by a cytochrome P-450-containing monooxygenase system present in the microsomes. The interaction of the azoles with the cytochrome results in a depletion of ergosterol and coincides with an accumulation of lanosterol and some other 14 α -methylsterols in the cells. The decreased availability of ergosterol, together with the accumulation of 14 α -methylsterols, greatly disturbs the permeability of cell membranes, the activity of membrane-bound enzymes and ultimately curbs cell growth. The azoles interact with the cytochrome at

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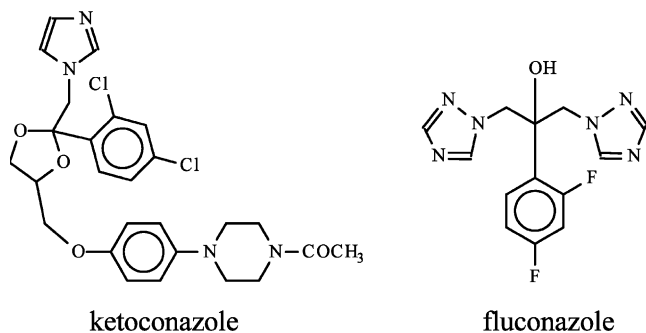


Fig. 1. Ketoconazole and fluconazole.

two sites. One is the sixth coordination site of the heme Fe(III) in the protoporphyrin moiety of the cytochrome and the other is some region of the apoprotein near the heme. Azole structure/activity relationship studies suggest that the binding regions of the apoprotein for these fungicides must be located over the sixth coordination site of the heme. O_2 required for the demethylation process is activated at the sixth coordination position of the heme and the lanosterol-binding site must locate over the O_2 activating site. Thus, azole fungicides must occupy both the substrate-binding (major role) and the O_2 -activating sites (minor role) of the P-450 simultaneously, and therefore, strongly inhibit the catalytic activity of the cytochrome. Of great importance is the fact that the P-450 of fungal microsomes is much more sensitive to azole drugs than that of mammalian microsomes, thus, ensuring selective toxicity to fungal cells.

As part of our ongoing efforts into finding new and efficient metal-based anti-fungal drugs [8–15] we have prepared Cu(II), Zn(II) and Ag(I) complexes of the imidazole derivative, (Z)-3-(1H-imidazol-1-yl)-2-phenylpropenenitrile (imppn) (Fig. 2) [16], and structurally characterised the latter two. The *in vivo* anti-*Candida* activity of metal-free imppn and its metal complexes was also investigated.

2. Results and discussion

Treating imppn with simple Cu(II), Zn(II) and Ag(I) salts gave $[Cu(imppn)_4](ClO_4)_2 \cdot H_2O$ (1), $[Zn(imppn)_2](CH_3CO_2)_2 \cdot 2H_2O$ (2) and $[Ag_2(imppn)_4](ClO_4)_2$ (3) in good yield. The related complexes, $[Cu(imppn)_2Cl_2]$ and

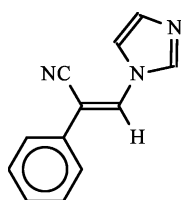


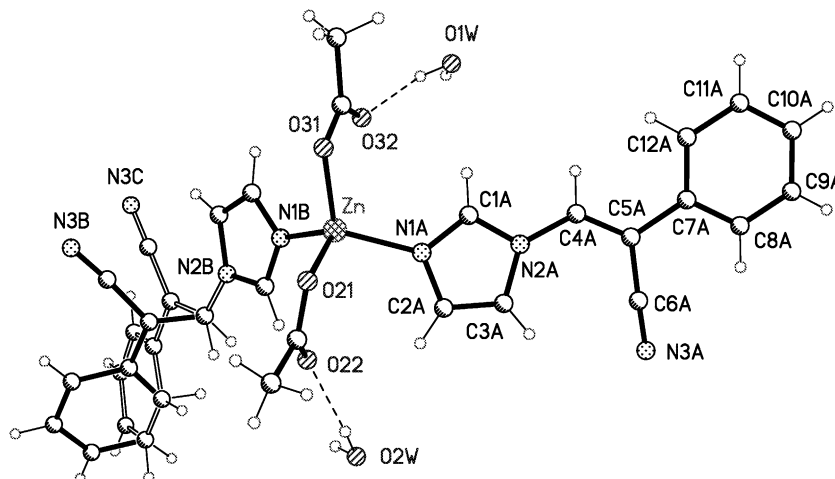
Fig. 2. (Z)-3-(1H-imidazol-1-yl)-2-phenylpropenenitrile (imppn).

$[Zn(imppnCl)_2Cl_2]$ {imppnCl = (Z)-3-(1H-imidazol-1-yl)-2-(2-chlorophenylpropenenitrile)} were previously prepared using $CuCl_2$ and $ZnCl_2$, respectively [16].

The X-ray crystal structure of the Zn(II) complex 2 is shown in Fig. 3 and important bond lengths and angles are given in Table 1. The metal lies in a pseudo-tetrahedral environment and is ligated by the imine nitrogens of two imppn ligands and an oxygen atom from each of two monodentate acetate anions. A water molecule is hydrogen-bonded to the uncoordinated oxygen of each acetate. The imppn ligand shown on the left of the metal in Fig. 3 is disordered 50:50 between two sites, sharing two carbon positions. The complex molecules are linked by hydrogen-bonding via the water molecules and the ligand labeled 'A' shows extensive π - π stacking in the unit cell (Fig. 4).

In the dimeric Ag(I) complex 3 (Fig. 4 and Table 2) each metal is coordinated to the imine nitrogens of two imppn ligands in an almost linear fashion $\{N(1A)-Ag-N(1B) = 174.61(14)^\circ\}$. The two $[Ag(imppn)_2]^+$ units are linked by an Ag–Ag bond, supported by two *trans* bridging bidentate perchlorate groups (Ag–O 2.822(4) and 3.094(4) Å) and by π - π interactions (Fig. 5) between the ligands (interplanar separation approximately 3.6 Å). The Ag–O perchlorate distances in 3 (2.822(4) and 3.094(4) Å) are comparable to those found in the disilver(I) cryptate $[Ag_2(imBT)](ClO_4)_2$ [17], where the perchlorate anions link the disilver cations in zig-zag perchlorate-bridged chains (Ag–O interactions range from 2.681(6) to 3.335 Å). Although the formal closed-shell d^{10} character of Ag(I) would appear to rule out any intermetallic Ag–Ag bonding in silver(I) complexes there are many examples where small but definite attractive forces (argentophilic interactions) between the metal cations do occur [18]. The relatively large Ag–Ag distance in 3 (3.3357 Å) is comparable to those found in the related hexanuclear complex $[Ag(imidazole)_2]_6(ClO_4)_6$, where the unbridged structure had an Ag–Ag distance of 3.49 Å in the central Ag_3 triangle and 3.05 Å in the peripheral Ag_2 moieties [19]. Although there are no obvious inter-dimer interactions in 3 involving the silver atoms there are some π - π interactions running through the lattice (Figs. 6 and 7).

The results of the anti-*Candida* tests of metal-free imppn, simple metal salts and imppn metal complexes are given in Table 3. The tests were conducted in a water-based culture medium and data for the prescription anti-fungal drug ketoconazole and for a control experiment (no added drug) are also tabulated. On comparing the water-insoluble metal-free azoles, imppn and ketoconazole, the latter is seen to be a much more potent drug in its action on *Candida* cells, suggesting that there is little or no interaction between imppn and cytochrome P-450. Furthermore, coordination of imppn to produce water-insoluble Cu(II), Zn(II) and Ag(I) complexes did not enhance the antimicrobial activity.

Fig. 3. Structure of $[\text{Zn}(\text{imppn})_2(\text{CH}_3\text{CO}_2)_2] \cdot 2\text{H}_2\text{O}$ (2).Table 1
Selected bond lengths (Å) and angles (°) for complex 2

Bond lengths	
Zn–O(21)	1.9714(18)
Zn–O(31)	1.972(2)
Zn–N(1A)	2.012(2)
Zn–N(1B)	2.020(2)
Bond angles	
O(21)–Zn–O(31)	94.99(8)
O(21)–Zn–N(1A)	108.73(8)
O(31)–Zn–N(1A)	115.40(9)
O(21)–Zn–N(1B)	113.97(8)
O(31)–Zn–N(1B)	110.97(9)
N(1A)–Zn–N(1B)	111.80(9)

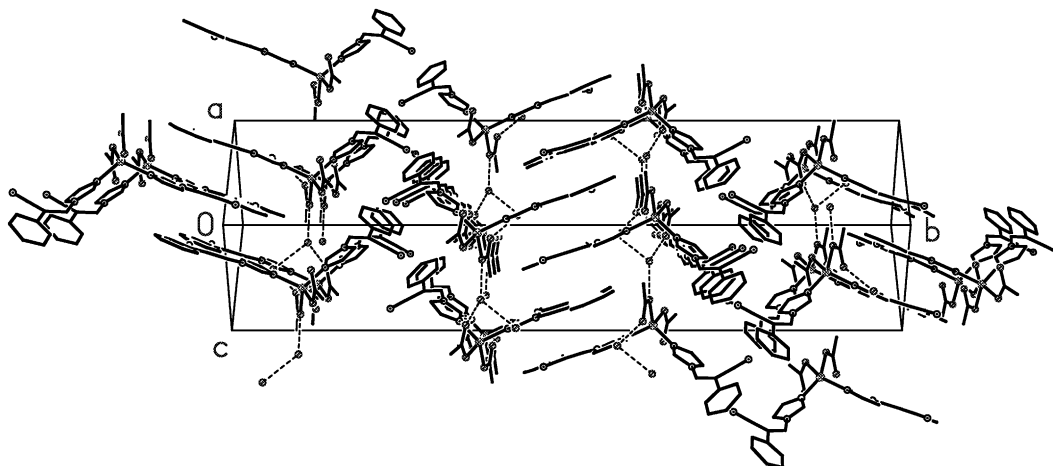
Table 2
Selected bond lengths (Å) and angles (°) for complex 3

Bond lengths	
Ag–N(1A)	2.115(4)
Ag–N(1B)	2.117(4)
Ag–Ag#1	3.3357(9)
Ag–O(14)#1	2.822(4)
Ag–O(12)	3.094(4)
Bond angles	
N(1A)–Ag–N(1B)	174.61(14)
N(1A)–Ag–O(14)#1	97.27(12)
N(1B)–Ag–O(14)#1	83.78(13)
N(1A)–Ag–O(12)	77.06(12)
N(1B)–Ag–O(12)	103.92(12)
O(14)#1–Ag–O(12)	157.57(10)

Symmetry transformations used to generate equivalent atoms: #1 $-x+1, -y+1, -z+1$.

These complexes were also insoluble in the test media. In contrast, the simple water-soluble metal salts, AgClO_4 , $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ and, to a lesser extent $\text{Zn}(\text{CH}_3\text{CO}_2)_2 \cdot 2\text{H}_2\text{O}$, were much superior in their ability to inhibit fungal cell growth than their respective imppn com-

plexes, with AgClO_4 being the most effective of all of the test drugs down to a concentration of $10 \mu\text{g cm}^{-3}$. At lower drug concentrations ketoconazole exerts the greatest inhibitory effect.

Fig. 4. π – π stacking in the unit cell of (2).

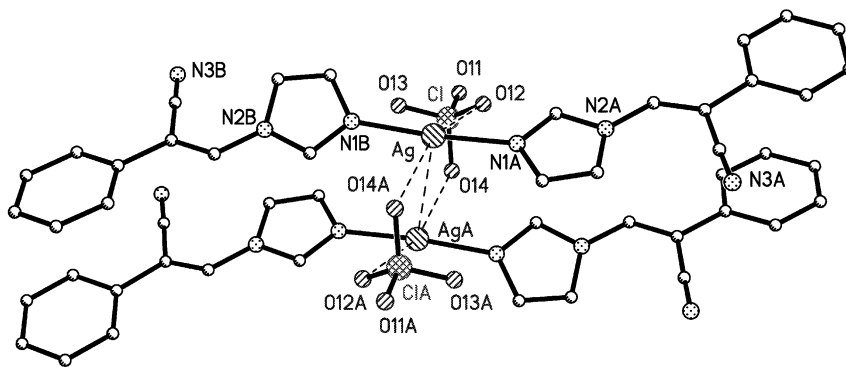


Fig. 5. Structure of $[\text{Ag}_2(\text{imppn})_4(\text{ClO}_4)_2]$ (**3**).

It is unlikely that the stark difference in the anti-fungal activity of AgClO_4 and $[\text{Ag}_2(\text{imppn})_4(\text{ClO}_4)_2]$ (**3**) can be explained solely in terms of inequalities in water-solubility. The antimicrobial effects of silver metal and silver complexes is well established [20–22] and there are contrasting effects regarding drug solubility. For example, the water-insoluble, polymeric complex sulphadiazinesilver(I) (commercially known as silvadene and flumazine) [23] is administered topically as an antibacterial and antifungal agent to treat burn wounds. The antimicrobial activity of sulphadiazinesilver(I) has been ascribed to the slow release of Ag^+ ions at the site of the wound. Aqueous solutions of silver nitrate and water/DMSO solutions of sulphadiazinesilver(I) and other silver(I) complexes irreversibly deactivate isolated phosphomannose isomerase (PMI), a zinc metalloenzyme importance in cell wall biosynthesis in *C. albicans*. [24]. The thiol functional group of an accessible surface cysteine Cys-150 residue of *C. albicans* PMI was confirmed as the site of action of the silver complex, and the drug also inactivates human PMI. In addition, electron microscopy studies on *C. utilis* revealed that sorption of Ag^+ ions from solution was accompanied by the formation of silver-containing granules, either bound to cells or located among them [25]. It is also known that the toxicity of Ag^+ in an aqueous environ-

ment depends on the concentration of active, free Ag^+ ion and that decreasing the availability of the free metal ion by complexing ligands (thiosulphate or chloride) curtails the inhibitory effects on microorganisms [26].

Cyclic voltammetry data for acetonitrile solutions of the simple $\text{Ag}(\text{I})$ salts, AgClO_4 , AgNO_3 and AgCH_3CO_2 , and also the imppn complex **3** are given in Table 4. Potentials are quoted with respect to the saturated calomel electrode (SCE). An acetonitrile solution of metal-free imppn was electroinactive in the potential range -1000 to $+1000$ mV. All of the samples containing Ag^+ ion showed a single, irreversible cathodic wave (E_c) for the reduction process $\text{Ag}^+ \rightarrow \text{Ag}^0$. In addition to the cathodic wave each voltammogram also contained a large anodic stripping peak (E_a) for the reoxidation of the plated silver metal ($\text{Ag}^0 \rightarrow \text{Ag}^+$). Not surprisingly, more negative potentials were required to reduce the metal ion ($\text{Ag}^+ \rightarrow \text{Ag}^0$) in complexes containing the better complexing ligands CH_3CO_2^- and imppn, compared to those with just ClO_4^- and NO_3^- . It is expected that AgClO_4 and AgNO_3 would completely ionize in acetonitrile and exist as the solvated cation $[\text{Ag}(\text{CH}_3\text{CN})_n]^+$.

In conclusion, the derivatised imidazole imppn readily coordinates to transition metal ions through its imine N-atom, and in the case of $\text{Ag}(\text{I})$ a dimeric complex forms

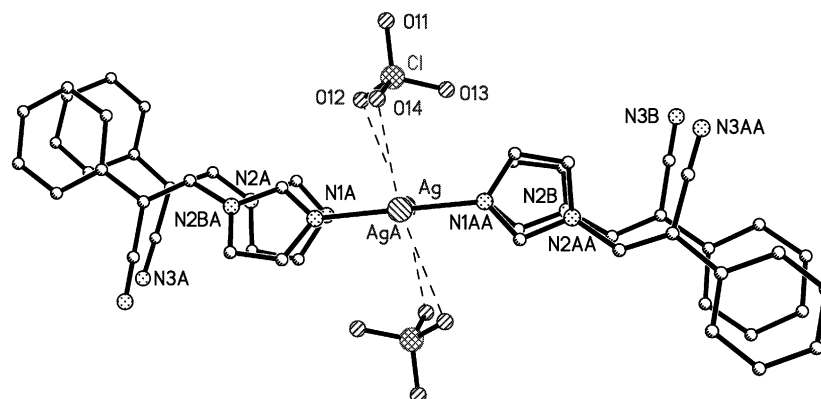
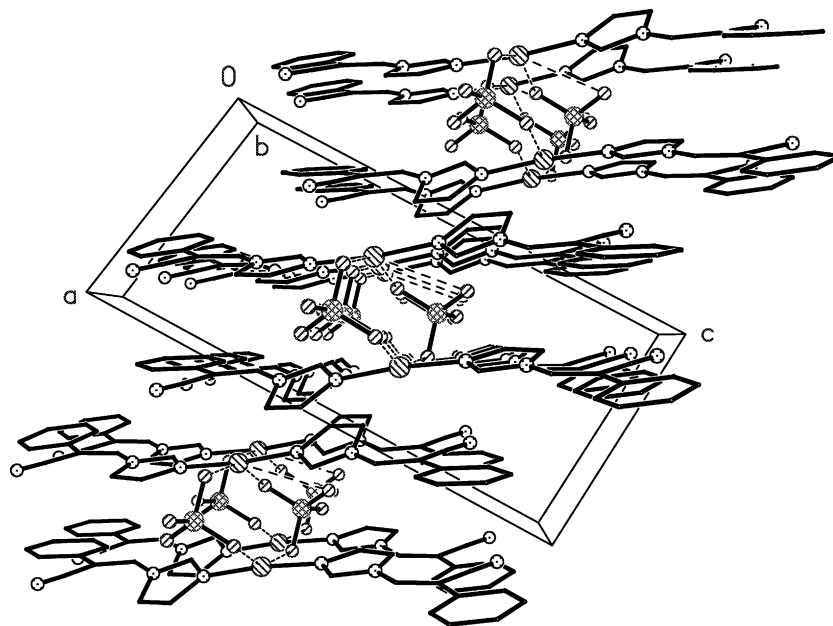


Fig. 6. π - π interactions within the dimer molecule **3**.

Fig. 7. π - π stacking in the unit cell of **3**.

containing an Ag–Ag bond. Impppn and its metal complexes are markedly less effective than the prescription drug ketoconazole at preventing the growth of *C. albicans*, in vitro. AgClO_4 , $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ and, to a lesser extent $\text{Zn}(\text{CH}_3\text{CO}_2)_2 \cdot 2\text{H}_2\text{O}$, were much better at inhibiting fungal cell growth than their respective impppn complexes.

3. Experimental

Chemicals were purchased from commercial sources and, unless specified, were used without further purification. The preparation of impppn and related compounds will be published elsewhere. Cyclic voltammetry experiments were performed using a low noise potentiostat (Biostat II, Electrochemical and Medical systems, Newbury, UK) and data acquisition was carried out

Table 4
Cyclic voltammetry data^a

	E_c (mV)	E_a (mV)
AgClO_4	+152	+288
AgNO_3	+134	+310
AgCH_3CO_2	+25	+282
$[\text{Ag}_2(\text{imppn})_4(\text{ClO}_4)_2]$ (3)	+92	+322

^a Potentials are quoted with respect to the SCE.

using a Gateway GP6-350 computer, a Powerlab/400 interface system (AD Instruments Ltd, East Sussex, UK) and Echem for Windows software (AD Instruments Ltd). The Pt disk working electrode (5-cm length) was made from Teflon-insulated platinum/iridium (90%/10%) wire (125- μm bare diameter, 160- μm coated diameter (5 T) obtained from Advent Research Materials, Suffolk, UK). A silver wire and a SCE were used as

Table 3
Anti-*Candida* activity (expressed as % growth of fungal cells)

	Drug concentration ($\mu\text{g cm}^{-3}$)						
	100 (%)	50 (%)	20 (%)	10 (%)	5 (%)	2.5 (%)	1.25 (%)
Control	100	100	100	100	100	100	100
Ketoconazole	5	7	14	20	23	25	54
AgClO_4	1	2	2	3	79	100	100
$\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	6	6	71	93	94	100	100
$\text{Zn}(\text{CH}_3\text{CO}_2)_2 \cdot 2\text{H}_2\text{O}$	48	74	94	100	100	100	100
imppn	73	88	90	95	95	96	100
$[\text{Cu}(\text{imppn})_4](\text{ClO}_4)_2 \cdot \text{H}_2\text{O}$ (1)	85	90	97	100	100	100	100
$[\text{Zn}(\text{imppn})_2(\text{CH}_3\text{CO}_2)_2] \cdot 2\text{H}_2\text{O}$ (2)	74	83	100	100	100	100	100
$[\text{Ag}_2(\text{imppn})_4(\text{ClO}_4)_2]$ (3)	75	95	100	100	100	100	100

the auxiliary and reference electrodes, respectively. Fresh solutions (1 mmol) of the complexes were made up in the supporting electrolyte solution (0.1 mol dm⁻³ solution of tetraethylammonium perchlorate in dry, purified acetonitrile). The complex solutions were deaerated with O₂-free N₂ for 20 min prior to each experiment and cycles were run at a scan rate of 100 mV s⁻¹. Infrared spectra of solids (in a KBr matrix) were recorded in the region 4000–400 cm⁻¹ on a Nicolet FT-IR Impact 400D infrared spectrometer. ¹H NMR spectra were run on a Bruker Avance 300 MHz instrument. Solid state magnetic susceptibility measurements were made at room temperature using a Johnson Matthey Magnetic Susceptibility Balance and [HgCo(SCN)₄] was used as a reference standard. Micro-analytical data were provided by the Microanalytical Laboratory, National University of Ireland, Cork, Ireland.

3.1. [Cu(imppn)₄](ClO₄)₂·H₂O (1)

Into a solution of Cu(ClO₄)₂·6H₂O (0.37 g, 1 mmol) in ethanol (10 cm³) was added imppn (0.78 g, 4 mmol). The light purple suspension was stirred for 1 h at room temperature. The purple precipitate was filtered and washed with small volumes of water, ethanol and ether and then allowed to air dry. Yield 0.88 g (83%). The complex was insoluble in water and all common organic solvents. *Anal.* Found: C, 54.46; H, 3.42; N, 15.63. *Calc.*: C, 54.37; H, 3.42; N, 15.84%. IR: 3149, 2236, 1646, 1553, 1516, 1123, 627 cm⁻¹. μ_{eff}: 2.15 BM.

3.2. [Zn(imppn)₂(CH₃CO₂)₂]·2H₂O (2)

A mixture of Zn(CH₃CO₂)₂·2H₂O (0.27 g, 1.2 mmol) and imppn (1 g, 5.1 mmol) in acetonitrile (10 cm³) was refluxed for 3 h. On cooling the complex crystallised and was then recrystallised from acetonitrile. Yield: 0.59 g (80%). The complex was soluble when warmed in acetonitrile, ethanol and methanol and was insoluble in water. *Anal.* Found: C, 55.11; H, 4.57; N, 13.65. *Calc.*: C, 55.14; H, 4.63; N, 13.78%. IR: 3432, 3124, 2224, 1670, 1603, 1510, 1406, 1233, 1116, 941, 689, 492 cm⁻¹. ¹H NMR (ppm DMSO): 8.61 (s, 1H), 8.53 (s, 1H), 8.06 (s, 1H), 7.7 (m, 2H), 7.5 (m, 3H), 7.33 (s, 1H), 1.87 (s, 3H).

3.3. [Ag₂(imppn)₄(ClO₄)₂] (3)

Into a solution of AgClO₄ (0.2 g, 1 mmol) in ethanol (10 cm³) was added imppn (0.39 g, 2 mmol). The cream coloured suspension was stirred for 1 h at room temperature. The white solid product was filtered off, washed with small volumes of water, ethanol and ether and then allowed air dry. Yield: 0.51 g (85%). The complex was soluble only in acetonitrile and was

recrystallised using this solvent. *Anal.* Found: C, 48.45; H, 3.06; N, 14.34. *Calc.*: C, 48.27; H, 3.04; N, 14.06%. IR: 3112, 2236, 1646, 1535, 1492, 1092, 633 cm⁻¹. ¹H NMR (ppm DMSO): 8.45 (s, 1H), 8.33 (s, 1H), 7.9 (s, 1H), 7.6 (m, 2H), 7.4 (m, 3H), 7.2 (s, 1H).

3.4. X-ray crystallography

Crystal data for [Zn(imppn)₂(CH₃CO₂)₂]·2H₂O (2) and [Ag₂(imppn)₄(ClO₄)₂] (3) are summarized in Table 5. Data sets for both complexes were collected using a Bruker SMART1000 diffractometer. Structure 2 data was solved by Patterson methods and refined by full-

Table 5
Summary of crystal data, data collection, structure solution and refinement details for complexes 2 and 3

	2	3
Complex	[Zn(imppn) ₂ (CH ₃ CO ₂) ₂]·2H ₂ O	[Ag ₂ (imppn) ₄ (ClO ₄) ₂]
Empirical formula	C ₂₈ H ₂₈ N ₆ O ₆ Zn	C ₂₄ H ₁₈ AgClN ₆ O ₄
Formula weight	609.93	1195.52
Temperature (K)	150(2)	150(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	monoclinic	triclinic
Space group	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> $\bar{1}$
Unit cell dimensions		
<i>a</i> (Å)	8.7381(6)	8.5902(19)
<i>b</i> (Å)	44.059(3)	9.300(2)
<i>c</i> (Å)	7.9784(5)	16.240(4)
α (°)	90	96.715(3)
β (°)	112.7320(10)	92.875(3)
γ (°)	90	116.427(3)
Volume(Å ³)	2833.0(3)	1146.2(4)
<i>Z</i>	4	2
<i>D</i> _{calc} (g cm ⁻³)	1.430	1.732
Absorption coefficient (mm ⁻¹)	0.919	1.042
<i>F</i> (0 0 0)	1264	600
Crystal size (mm)	0.37 × 0.25 × 0.03	0.35 × 0.22 × 0.02
θ Range (°)	2.53–28.62	2.48–25.00
Index ranges	–11 ≤ <i>h</i> ≤ 11, –59 ≤ <i>k</i> ≤ 58, –10 ≤ <i>l</i> ≤ 10	–10 ≤ <i>h</i> ≤ 10, –11 ≤ <i>k</i> ≤ 11, –19 ≤ <i>l</i> ≤ 19
Reflections collected	21 784	8012
Independent reflections	6596 [<i>R</i> _{int} = 0.0427]	3984 [<i>R</i> _{int} = 0.0383]
Completeness to theta	(= 28.62°) 90.7%	(= 25.00°) 98.7%
Absorption correction	multiscan	Multiscan
Max and min transmission	1.00000 and 0.451998	1.000000 and 0.817122
Refinement method	full-matrix least-squares on <i>F</i> ²	full-matrix least-squares on <i>F</i> ²
Data/restraints/parameters	6596/0/435	3984/0/325
Goodness-of-fit on <i>F</i> ²	1.137	1.031
Final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> ₁ = 0.0504, <i>wR</i> ₂ = 0.0972	<i>R</i> ₁ = 0.0407, <i>wR</i> ₂ = 0.0891
<i>R</i> indices (all data)	<i>R</i> ₁ = 0.0706, <i>wR</i> ₂ = 0.1035	<i>R</i> ₁ = 0.0620, <i>wR</i> ₂ = 0.0960
Largest diff. peak and hole (e Å ⁻³)	0.403 and –0.743	0.696 and –0.671

matrix least-squares on F^2 using all the data [27]. All the non-hydrogen atoms were refined with anisotropic atomic displacement factors and hydrogen atoms attached to carbon were inserted at calculated positions. The hydrogen atoms bonded to oxygen were located from difference maps and not further refined. Structure **3** was solved by direct methods and refined by full-matrix least-squares on F^2 [27]. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters and hydrogen atoms were inserted at calculated positions.

3.5. Anti-Candida testing

C. albicans ATCC 10231 was obtained from the American Type Culture Collection (Manassas, VA). Culture conditions and measurement of drug minimum inhibitory concentrations (MICs) were as previously described [14,15]. Only AgClO_4 , $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ and $\text{Zn}(\text{CH}_3\text{CO}_2)_2 \cdot 2\text{H}_2\text{O}$ were soluble in the aqueous test media.

4. Supplementary material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos. 173759 and 173760 for the compounds Ag(I) and Zn(II), respectively. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, England (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: <http://www.ccdc.cam.ac.uk>).

Acknowledgements

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