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Imidazole Schiff base ligands: Synthesis, coordination complexes and biological activities

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ABSTRACT

1-(3-Aminopropyl)imidazole (Apim) reacts with salicylaldehyde and a selection of imidazole aldehydes and the resulting Schiff base ligands readily coordinate to Zn(II), Cu(II) and Ag(I) centres. X-ray crystal structures were obtained for two of the free ligands and also the Ag(I) complex of the Apim-salicylaldehyde ligand. Encouragingly, all of free ligands and most of their metal complexes are relatively non-toxic, *in vivo*, towards *Galleria mellonella*. Although the free ligands and the Cu(II) and Zn(II) complexes are inactive, *in vitro*, against a selection of microbial pathogens, most of the Ag(I) complexes exhibit moderate anti-bacterial activity and good anti-fungal activity.

1. Introduction

In recent years, metal complexes comprising Schiff base ligands have been shown to exhibit significant anticancer, antiviral and antimicrobial activity [1–4]. Commercially available 1-(3-aminopropyl)imidazole (Apim) (Fig. 1) has recently been complexed to the Ag(I) ion and the structurally characterised complexes, [Ag(Apim)]ClO_4 [5] and [Ag(Apim)](9-aca)·H_2O (9-acaH = 9-anthracenecarboxylic acid) [6], exhibit high antimicrobial activities, *in vitro*. In addition, metal complexes comprising Schiff base ligands derived from Apim have also attracted attention. For example, polymeric Ag(I) complexes of **3** (Fig. 1) show interesting structural and luminescent properties [7], whilst Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) complexes of **2** have been screened for their ability to inhibit the growth of bacterial and fungal pathogens [8].

In the present paper we detail the synthesis, coordination chemistry, *in vivo* toxicity and antimicrobial activities of the uncoordinated Apim-derived Schiff base ligands **2**–**6** (Fig. 1) and their Ag(I), Cu(II) and Zn(II) complexes.

2. Experimental

2.1. Reagents and instrumentation

^1H and ^{13}C NMR (δ ppm; J Hz) spectra were recorded on a BrukerAvance 300 MHz NMR spectrometer using saturated d_6-DMSO solutions with Me_4Si reference, unless indicated otherwise, with resolutions of 0.18 Hz and 0.01 ppm, respectively. Infrared spectra (cm^{-1}) were recorded as KBr discs using a Perkin Elmer System2000 FT-IR spectrometer. UV–vis spectra were run on a Unicam UV 540 spectrometer. Melting point analyses were carried out using a Stewart Scientific SMP 1 melting point apparatus and are uncorrected. Electrospray (ESI) mass spectra were collected on an Agilent Technologies 6410 Time of Flight LC/MS. Compounds were dissolved in acetonitrile–water (1:1) solutions containing 0.1% formic acid, unless stated otherwise. The interpretation of mass spectra was made with the help of the program, "Agilent Masshunter Workstation Software". Magnetic susceptibility measurements were carried out at room temperature using a Johnson Matthey Magnetic Susceptibility Balance with [$HgCo(SCN)_4$] as reference. Microanalytical data were carried out using an Electron Corporation Thermo FlashEA 1112 Series analyser. Starting materials were commercially obtained and used without further purification.

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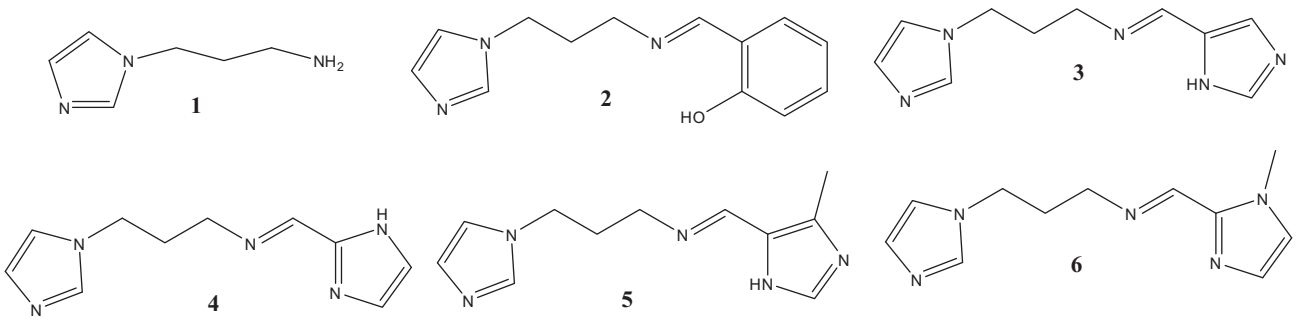

Fig. 1. Structures of Apim (**1**) and its Schiff base derivatives, **2**–**6**.

Caution! Although not encountered in our experiments, perchlorate salts of metal ions are potentially explosive and should be manipulated with care and used only in small quantities.

2.2. Synthesis of ligands

2.2.1. 2-([3-(1H-imidazol-1-yl)propyl]aminopropyliminomethyl)phenol (*2*)

This compound was prepared using a method similar to those previously reported [8,9]. To a solution of Apim (5.43 g, 43.4 mmol) in dry methanol (30 mL) was added salicylaldehyde (5.30 g, 43.4 mmol) with constant stirring. The resulting yellow solution was refluxed for 3 h and then stirred overnight at room temperature. The solvent was then removed under reduced pressure to give a yellow oil, which, on standing for 4 h, yielded yellow crystals of **2**. The crystals were recrystallised from toluene, filtered, washed with cold, dry methanol and air-dried (9.5 g, yield 95%). M.p. 83–84 °C (lit. 78–80 °C). $C_{13}H_{15}N_3O$ (229.28): Calc. C, 68.10; H, 6.59; N, 18.33. Found: C, 68.23; H, 6.40; N, 18.24%. ^{1}H NMR (d_6-DMSO): δ = 13.36 (br s, 1H), 8.54 (s, 1H), 7.64 (s, 1H), 7.43 (d, 1H, J = 6.3 Hz), 7.34 (t, 1H, J = 6.6 Hz), 7.21 (s, 1H), 6.91 (m, 3H), 4.05 (t, 2H, J = 6.9 Hz), 3.54 (t, 2H, J = 6.9 Hz), 2.10 (p, 2H, J = 6.9, 7.2 Hz) ppm. ^{13}C NMR (d_6-DMSO): δ = 166.3, 160.5, 137.2, 132.3, 131.6, 128.5, 119.2, 118.6, 118.5, 116.4, 55.4, 43.8, 31.6 ppm. IR (KBr): ν = 3434, 3101, 1632, 1576, 1491, 1401, 1276, 1225, 1151, 1079, 887, 808, 760 cm^{-1}. LC/TCOF-MS: Calc. for $C_{13}H_{16}N_3O$ $[M+1]^+$ 230.3. Found: 230.1%.

2.2.2. N-[(E)-1H-Imidazol-5-ylmethylidene]-N-[3-(1H-imidazol-1-yl)propyl]amine (*3*)

This compound was prepared using a method similar to those previously reported [7]. To a solution of Apim (2.83 g, 22.6 mmol) in dry methanol (17 mL) was added 4(5)-imidazolecarboxaldehyde (2.17 g, 22.6 mmol). The resulting light-yellow suspension was heated to reflux for 3 h and the yellow solution was then stirred overnight at room temperature. The solvent was removed under reduced pressure to give an orange-yellow oil, which, on standing for 2 h, yielded the orange-yellow solid (**3**). The solid was recrystallised from hot ethanol, filtered, washed with cold, dry ethanol and air-dried (4.3 g, yield 94%). M.p. 178–180 °C (lit. 180–182 °C). $C_{10}H_{13}N_5$(203.24): Calc. C, 59.09; H, 6.45; N, 34.46. Found: C, 59.14; H, 6.28; N, 34.46%. ^{1}H NMR (d_6-DMSO): δ = 12.59 (br s, 1H), 8.19 (s, 1H), 7.74 (s, 1H), 7.63 (s, 1H), 7.19 (s, 1H), 6.90 (s, 1H), 4.03 (t, 2H, J = 6.9 Hz), 3.42 (t, 2H, J = 6.6 Hz), 2.01 (p, 2H, J = 6.9, 6.6 Hz) ppm. ^{13}C NMR (d_6-DMSO): δ = 137.2, 128.4, 119.2, 57.2, 43.9, 31.9 ppm. IR (KBr): ν = 3436, 3137, 3103, 2844, 1647, 1509, 1429, 1355, 1307, 1236, 1220, 1111, 1081, 1026, 827, 749 cm^{-1}. LC/TCOF-MS: Calc. for $C_{10}H_{14}N_5$ $[M+1]^+$ 204.2. Found: 204.1%.

2.2.3. N-[(E)-1H-Imidazol-2-ylmethylidene]-N-[3-(1H-imidazol-1-yl)propyl]amine (*4*)

To a solution of Apim (2.81 g, 22.5 mmol) in dry methanol (17 mL) was added imidazole-2-carboxaldehyde (2.17 g, 22.5 mmol). The resulting solution was heated to reflux for 3 h and then stirred overnight at room temperature. The solvent was removed under reduced pressure to give a brown oil, which, on standing for 2 months, yielded the orange-brown solid (**4**) (3.69 g, yield 86%). M.p. 44–46 °C. $C_{10}H_{13}N_5{\cdot}0.5H_2O$ (212.15): Calc. C, 56.56; H, 6.59; N, 33.01. Found: C, 56.08; H, 6.32; N, 32.87%. ^{1}H NMR (d_6-DMSO): δ = 8.17 (s, 1H), 7.65 (s, 1H), 7.19 (s, 1H), 7.13 (s, 1H), 7.11 (s, 1H), 6.91 (s, 1H), 4.06 (t, 2H, J = 6.9 Hz), 3.43 (t, 2H, J = 6.0 Hz), 2.01 (t, 2H, J = 6.9 Hz) ppm. ^{13}C NMR (d_6-DMSO): δ = 152.3, 144.4, 137.2, 128.2, 119.4, 56.7, 43.9, 31.7 ppm. IR (KBr): ν = 3114, 1650, 1513, 1446, 1397, 1232, 1109, 1083, 771 cm^{-1}. LC/TCOF-MS: Calc. for $C_{10}H_{14}N_5$ $[M+1]^+$ 204.2. Found: 204.1%.

2.2.4. 3-(1H-Imidazol-1-yl)-N-[(E)-(5-methyl-1H-imidazol-4-yl)methylidene]-1-propanamine (*5*)

To a solution of Apim (2.81 g, 22.5 mmol) in dry methanol (17 mL) was added 4-methyl-5-imidazolecarboxaldehyde (2.17 g, 22.5 mmol). The resulting light-yellow suspension was heated to reflux for 3 h. The suspension was dissolved completely after 5 min. The solution was then stirred overnight at room temperature. After 0.5 h the solution turned orange in colour. The solvent was removed under reduced pressure to give an orange oil, which, on standing for 3 weeks, yielded the orange solid (**5**) (3.10 g, yield 76%). M.p. 113–115 °C. $C_{11}H_{15}N_5$ (217.27): Calc. C, 60.81; H, 6.96; N, 32.23. Found: C, 60.60; H, 6.72; N, 31.35%. ^{1}H NMR (d_6-DMSO): δ = 8.23 (s, 1H), 7.64 (s, 1H), 7.61 (s, 1H), 7.18 (s, 1H), 6.91 (s, 1H), 4.04 (t, 2H, J = 7.2 Hz), 3.42 (t, 2H, J = 6.6 Hz), 2.32 (s, 3H), 2.03 (p, 2H, J = 6.9, 6.6 Hz) ppm. ^{13}C NMR (d_6-DMSO): δ = 137.2, 128.3, 119.3, 57.3, 48.5, 43.9, 32.1 ppm. IR (KBr): ν = 3113, 1643, 1529, 1452, 1395, 1354, 1233, 1110, 1082, 826, 747 cm^{-1}. LC/TCOF-MS: Calc. for $C_{10}H_{14}N_5$ $[M+1]^+$ 218.3. Found 218.1%.

2.2.5. 3-(1H-Imidazol-1-yl)-N-[(E)-(1-methyl-1H-imidazol-2-yl)methylidene]-1-propanamine (*6*)

To a solution of Apim (2.81 g, 22.5 mmol) in dry methanol (17 mL) was added 1-methyl-2-imidazolecarboxaldehyde (2.47 g, 22.5 mmol). The resulting light-yellow solution was refluxed for 3 h and then stirred overnight at room temperature. After 0.5 h the solution turned orange in colour. The solvent was removed under reduced pressure to give the yellow oil (**6**) (3.11 g, yield 73%). $C_{11}H_{15}N_5$ (217.27): Calc. C, 60.81; H, 6.96; N, 32.23. Found: C, 60.20; H, 6.35; N, 31.83%. ^{1}H NMR (d_6-DMSO): δ = 8.25 (s, 1H), 7.64 (s, 1H), 7.30 (s, 1H), 7.20 (s, 1H), 7.04 (s, 1H), 6.90 (s, 1H), 4.07 (t, 2H, J = 7.5 Hz), 3.92 (s, 3H), 3.51 (t, 2H, J = 6.9 Hz), 2.05 (p, 2H, J = 6.9, 6.9 Hz) ppm. ^{13}C NMR (d_6-DMSO): δ = 153.6, 142.3,