Journal of Saudi Chemical Society (2017) **21**, 291–299

King Saud University

Journal of Saudi Chemical Society

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ORIGINAL ARTICLE

Synthesis, characterization and DNA cleavage studies of isomeric pyridyl-tetrazole ligands and their Ni(II) and Zn(II) complexes

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Received 16 March 2015; revised 3 July 2015; accepted 4 July 2015
Available online 23 July 2015

KEYWORDS

Isomeric pyridyl-tetrazole derivative ligands;
Nickel and Zinc complexes;
DNA cleavage studies

Abstract A new series of Ni(II) and Zn(II) complexes were synthesized from bidentate isomeric pyridyl tetrazole ligands such as 2-(1-vinyl-1H-tetrazol-5-yl)pyridine (**L**^{1}), N,N-dimethyl-3-(5-(pyridin-2-yl)-1H-tetrazol-1-yl)propan-1-amine(**L**^{2}), 2-(2-vinyl-2H-tetrazol-5-yl)pyridine(**L**^{3}), N,N-dimethyl-3-(5-(pyridin-2-yl)-2H-tetrazol-2-yl)propan-1-amine (**L**^{4}). All the complexes were characterized by the elemental analysis, molar conductance, FTIR, UV–vis and magnetic studies. The conductance and spectroscopic data suggested that, the ligands act as monobasic bidentate ligands and form octahedral complexes with general formula $[M(\mathbf{L}^{1-4})_2Cl_2]$, (M = Ni(II) and Zn(II)). In addition metal complexes displayed good antioxidant and moderate nematicidal activities. The cytotoxicity of ligands and their metal complexes have been evaluated by MTT assay. The DNA cleavage activity of the metal complexes was performed using agarose gel electrophoresis in the presence and absence of oxidant H_2O_2. All metal complexes showed significant nuclease activity in the presence of H_2O_2.

1. Introduction

Biologically active isomeric pyridyl tetrazole derivatives have been under great investigations as part of inorganic chemistry. Polyazole rings are versatile ligands [1] for coordinating transition metals, therefore synthesis of transition metal complexes containing polyazole rings, particularly tetrazoles and their derivatives has been given enormous significance, due to their practical applications [2–4]. There is an increasing interest of tetrazole derivatives for the development of "click" chemistry

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jscs.2015.07.003

which was reported by Sharpless and co-workers [5]. Conversely, tetrazole-based compounds have made known special functionalities with interesting structures [6]. Tetrazole derivatives have found applications in therapeutics as antihypertensive agents [7], antibiotics [8] and drugs for AIDS treatment [9].

Even though many tetrazole containing derivatives are available in the literature, there is always an increasing demand for the development of novel and effective tetrazole containing therapeutic agents. In continuation of our ongoing research on DNA binding and cleavage activities of transition metal complexes [10], in this paper we presented the synthesis, characterization and DNA cleavage activities of Ni(II) and Zn(II) complexes which are obtained by the reaction of pyridyl-tetrazole derivatives which contain pendant arms like vinyl or propyl-N$(CH_3)_2$ group.

2. Experimental materials and measurement

Chemicals were purchased from Sigma–Aldrich and metal salts used in the preparation of the complexes are of reagent grade. The solvents used in the synthesis of the ligands and metal complexes were distilled before use. All other chemicals were of AR grade and were used without further purification. The elemental analysis of carbon, hydrogen, and nitrogen contents was performed using Perkin Elmer CHNS analyzer. Molar conductance of the complexes was measured using a Digisun conductivity metre in DMF. The electronic absorption spectra of the complexes were recorded on a JASCO V-670 Spectrophotometer in the wavelength region of 250–1400 nm in the solid state. The FTIR spectra of the complexes were recorded on a Tensor 2 FTIR spectrophotometer in the region of 4000–400 cm^{-1} using KBr disc. The magnetic susceptibilities of Ni(II) complexes were measured with a Sherwood scientific balance. Diamagnetic corrections were calculated from Pascal's constants. The magnetic moment values were calculated using the relation $\mu_{eff} = 2.83\ (\chi mT)1/2$ B.M.

2.1. Synthesis of ligands

2.1.1. Ligands

The preparation of **L** is carried as per literature [11] M.p. 221–223 °C. C, 48.98; H, 3.43; N, 47.60, ^{1}H NMR (CD_3OD): 8.56 (d, 1H, J = 7.9 Hz, pyr-H), 8.0 (d, 1H, J = 7.8 Hz, pyr-H), 7.79 (t, 1H, J = 7.8 Hz, pyr-H), 7.26 (t, 1H, J = 7.9 Hz, pyr-H), 7.1 (s, 1H, tetrazole-H) ppm.

2.1.1.1. N,N-dimethyl-3-(5-(pyridin-2-yl)-1H-tetrazol-1-yl)-propan-1-amine(L^2) and N,N-dimethyl-3-(5-(pyridin-2-yl)-2H-tetrazol-2-yl)propan-1-amine (L^4). To a solution of compound **L** (1.0 g, 6.8 mmol) in DMF (30 mL) was added potassium carbonate (4.6 g, 33 mmol) followed by 3-chloro-*N,N*-dimethyl propan-1-amine. HCl (2.1 g, 13.6 mmol). The reaction mixture was stirred at 70 °C for 50 h. After cooling, the insoluble material was filtered, the solvent was removed under reduced pressure, the crude mass was diluted with EtOAc (50 mL) and washed successively with water (3 x 40 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford a crude oil, which was purified by column chromatography on silica gel (Ethyl acetate: Hexane, 20:80 v/v) to elute first $\mathbf{L^2}$ followed by $\mathbf{L^4}$.

2.1.1.2. 2-(1-vinyl-1H-tetrazol-5-yl)pyridine (L^1) and 2-(2-vinyl-2H-tetrazol-5-yl)pyridine(L^3). The same procedure which was used to synthesize $\mathbf{L^2}$ and $\mathbf{L^4}$ was followed with 2-chloro-*N,N*-dimethylehylamine. HCl (1.9 g, 13.6 mmol) to afford $\mathbf{L^1}$ and $\mathbf{L^3}$.

$\mathbf{L^1}$: Off white solid, (0.35 g, yield 30%). M.p. 57–59 °C. Anal. Calc. for $C_8H_7N_5$ (173.17): C, 55.48; H, 4.07; N, 40.44; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.70 (d, 1H, J = 4.8 Hz, pyr-H), 8.46–8.35 (m, 2H, pyr-H + vinyl-H), 7.93 (dt, 1H, J = 8.4, 1.5 Hz, pyr-H), 7.47 (dd, 1H, J = 7.5, 5.7 Hz, pyr-H), 6.26 (d, 1H, J = 15.6, vinyl-H), 5.2 (d, 1H, J = 8.7, Vinyl-H); ^{13}C NMR ($CDCl_3$, 60 MHz): δ 152.9, 149.3, 144.3, 138.1, 127.3, 125.9, 124.3, 102.9 ppm.

$\mathbf{L^3}$: Off white solid, (0.30 g, yield 26%). M.p. 57–58 °C. Anal. Calc. for $C_8H_7N_5$ (173.17): C, 55.48; H, 4.07; N, 40.44; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.82 (d, 1H, J = 4.8 Hz, pyr-H), 8.30 (d, 1H, J = 8.1 Hz, pyr-H), 7.89 (dt, 1H, J = 7.8, 1.8 Hz, pyr-H), 7.70–7.56 (m, 2H, pyr-H + vinyl-H), 7.46–7.40 (m, 1H, pyr-H), 6.42 (dd, 1H, J = 15.9, 1.8 Hz, Vinyl-H), 5.46 (dd, 1H, J = 8.7, 1.5 Hz, Vinyl-H); ^{13}C NMR ($CDCl_3$, 60 MHz): δ 164.5, 150.5, 146.7, 138.3, 127.3, 125.7, 122.35, 102.1.

$\mathbf{L^2}$: white brown solid (0.55 g, yield 34%). M.p. 72–76 °C. Anal. Calc. for $C_{11}H_{16}N_6$ (232.28): C, 56.88; H, 6.94; N, 36.18; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.79 (d, 1H, J = 3.2 Hz, pyr-H), 8.26 (d, 1H, J = 7.8 Hz, pyr-H), 7.87 (dt, 1H, J = 7.8, 1.5 Hz, pyr-H), 7.41 (dd, 1H, J = 7.8, 5.4 Hz, pyr-H), 4.80 (t, 2H, J = 6.9 Hz, CH_2N), 2.53 (t, 2H, J = 6.9 Hz, CH_2), 2.4–2.2 (m, 8H, $N(CH_3)_2 + CH_2$) ppm; ^{13}C NMR ($CDCl_3$, 60 MHz): δ 152.5, 149.5, 144.6, 137.6, 125.4, 122.4, 54.4, 48.2, 43.7, 26.8 ppm.

$\mathbf{L^4}$: white brown solid (0.51 g, yield 32%). M.p. 66–68 °C. Anal. Calc. for $C_{11}H_{16}N_6$ (232.28): C, 56.88; H, 6.94; N, 36.18; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.8 (d, 1H, J = 4.5 Hz, pyr-H), 8.26 (d, 1H, J = 7.8 Hz, pyr-H), 7.88 (t, 1H, J = 6.3 Hz, pyr-H), 7.42 (t, 1H, J = 6.0 Hz, pyr-H), 5.02–4.80 (m, 2H, CH_2N), 2.68 (m, 2H, CH_2), 2.4–2.2 (m, 8H, $N(CH_3)_2 + CH_2$) ppm. ^{13}C-NMR ($CDCl_3$, 60 MHz): δ 164.4, 150.1, 146.6, 138.8, 124.6, 122.1, 56.4, 47.4, 43.5, 26.8 ppm.

2.2. Synthesis of complexes

The appropriate ligand ($\mathbf{L^1}$–$\mathbf{L^4}$) (1.36 mmol) was dissolved in methanol (30 mol) and added to a $MCl_2.H_2O$ (0.68 mmol) methanol solution (10 mol). The resulting pale green to green colored solutions were then heated to reflux for 2–3 h; the solution was left overnight at room temperature and filtered to collect respective precipitate.

$[Ni(L^1)_2]Cl_2$: Dark Green solid (0.12 g, yield 28%) Anal. Calc. for $C_{16}H_{14}Cl_2N_{10}Ni$ (475.95): C, 40.38; H, 2.96; N, 29.43; Found: C, 40.76; H, 2.98; N, 29.96% IR (KBr): v = 3245, 2945, 1648, 1594, 1496, 1196, 1147, 1023, 835, 785 cm^{-1}. λ_{max} (MeOH) 376 nm, ε = 40 M^{-1} cm^{-1}. Magnetic moment: 3.2 B.M.

$[Ni(L^3)_2]Cl_2$: Pale Green crystals (0.14 g, yield 32%) Anal. Calc. for $C_{16}H_{14}Cl_2N_{10}Ni$ (475.95): C, 40.38; H, 2.96; N, 29.43; Found: C, 40.76; H, 2.98; N, 29.96% IR (KBr): v = 3245, 2945, 1648, 1594, 1496, 1196, 1147, 1023, 835, 785 cm^{-1}. λ_{max} (MeOH) 388 nm, ε = 38 M^{-1} cm^{-1}. Magnetic moment: 3.2 B.M.