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ScienceDirect
European Journal of Medicinal Chemistry 44 (2009) 365–372
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://www.elsevier.com/locate/ejmech

Original article

Synthesis, Raman, FT-IR, NMR spectroscopic data and antimicrobial activity of mixed aza-oxo-thia macrocyclic compounds

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Received 19 September 2007; received in revised form 22 February 2008; accepted 29 February 2008
Available online 18 March 2008

Abstract

Mixed aza-oxo-thia macrocyclic ligands 1,3,5,11,13,15-hexaaza-6,10,16,20-tetraoxo-8,18-dithia-2,3,4:12,13,14-dipyridine cyclocosane **(L_1)**; 1,3,5,12,14,16-hexeaza-6,11,17,22-tetraoxo-8,9,19,20-tetrathia-2,3,4:13,14,15-dipyridine cyclodocosane **(L_2)**; 1,3,5,13,15,17-hexaaza-6,12,18,24-tetraoxo-9,21-dithia-2,3,4:14,15,16-dipyridine cyclotetracosane **(L_3)** and 1,3,5,14,16,18-hexaaza-6,13,19,26-tetraoxo-9,10,22,23-tetrathia-2,3,4:15,16,17-dipyridine cyclohexacosane **(L_4)** were synthesised. The structural features of the ligands have been studied by elemental analyses, Raman, IR, ^{1}H and ^{13}C NMR spectroscopy. The antimicrobial activities of the ligands were evaluated using disk diffusion method in dimethyl sulfoxide (DMSO) as well as the minimal inhibitory concentration (MIC) dilution method, against nine bacteria. The obtained results from disk diffusion method were assessed in side-by-side comparison with those of penicillin G, ampicillin, cefotaxime, vancomycin, ofloxacin, and tetracycline well known antibacterial agents. The results from dilution procedure were compared with gentamycin as antibacterial and nystatin as antifungal. The antifungal activities are reported on five yeast cultures namely *Candida albicans*, *Kluyveromyces fragilis*, *Rhodotorula rubra*, *Debaryomyces hansenii*, and *Hanseniaspora guilliermondii*, and the results are referenced with nystatin, Ketoconazole, and clotrimazole, commercial antifungal agents. In most cases, the compounds show broad-spectrum (Gram$^+$ and Gram$^-$ bacteria) activities that were more active or equipotent to the antibiotic and antifungal agents in the comparison tests.

Keywords: Broad-spectrum; Clotrimazole; Disk diffusion; Nystatin; Raman

1. Introduction

For several decades, the design and synthesis of macro-hetero-multi-donor ligands have constituted one of the largest areas of research in organic and coordination chemistry [1–5]. In certain cases, nature prefers macrocyclic derivatives for many fundamental biological functions such as photosynthesis, storage and transport of oxygen in mammalian and other respiratory systems. Having various donor centres, macrocycles offer exciting possibilities to construct novel supramolecular assemblies that are capable of performing highly specific molecular functions. For instant, the precise molecular recognition between these compounds and their guests, mostly transition metal ions or biomolecules (nucleic acids, proteins…), provides a good opportunity for studying key aspects of supramolecular chemistry, which are also significant in a variety of disciplines including bioorganic chemistry, biocoordination chemistry, biology, medicine and related science and technology [6–8]. Chemically, multi-donor ligands and particularly mixed donor atoms of these ligands are important because of great availability as ligands due to the presence of several potential donor centres and their flexibility to bind with biomolecules or to coordinate with various metal ions. Among these, the N–S donor macrocycles also have theoretical interest, as they are capable of furnishing an environment of controlled geometry and ligand field strength [9–11].

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doi:10.1016/j.ejmech.2008.02.038

Table 1
Prominent IR and Raman bands for the compound

Compounds	FT-IR (cm^{-1})	Raman (cm^{-1})
(L_1)	3439 ν(H–O–H), 3313 ν(N–H), 3117 ν(C–H)$_{py}$, 2963, 2927 ν(C–H), 1692, 1659 ν(C=O), 1640 δ(N–H), 1622 ν(C–C)$_{py}$, 1553 ν(C–N)$_{py}$, 1388–1310 [ν(C–N)$_{py}$, ν(C–C)$_{py}$], 976, 780 ω(C–H)$_{py}$, 712 ν(C–S), 565, 491, 448, 413	3084, 3051 ν(C–H)$_{py}$, 2972, 2921 ν(C–H), 1645 ν(C=O), 1624 ν(C–C)$_{py}$, 1557 ν(C–N)$_{py}$, 1314 [ν(C–N)$_{py}$, ν(C–C)$_{py}$], 1130, 1000, 975, 808 ω(C–H)$_{py}$, 711 ν(C–S), 603, 563, 545, 441, 356, 289, 222
(L_2)	3405 ν(H–O–H), 3346, 3211 ν(N–H), 3096, 3058 ν(C–H)$_{py}$, 2994, 2971 ν(C–H), 1671 ν(C=O), 1647 δ(N–H), ν(C–C)$_{py}$, 1571 ν(C–N)$_{py}$, 1404–1296 [ν(C–N)$_{py}$, ν(C–C)$_{py}$], 922, 773 ω(C–H)$_{py}$, 722 ν(C–S), 522 ν(S–S), 464, 444	3097, 3042 ν(C–H)$_{py}$, 2941, 2927 ν(C–H), 1686, 1650 ν(C=O), 1617 ν(C–C)$_{py}$, 1568 ν(C–N)$_{py}$, 1490–1306 [ν(C–N)$_{py}$, ν(C–C)$_{py}$], 987, 923, 763 ω(C–H)$_{py}$, 687 ν(C–S), 580, 566, 544, 522 ν(S–S), 356, 260
(L_3)	3444 ν(H–O–H), 3331, 3217 ν(N–H), 3077 ν(C–H)$_{py}$, 2965 ν(C–H), 1708, 1673 ν(C=O), 1644 δ(N–H), 1626 ν(C–C)$_{py}$, 1548 ν(C–N)$_{py}$, 1403–1301 [ν(C–N)$_{py}$, ν(C–C)$_{py}$], 1168, 974, 777 ω(C–H)$_{py}$, 727 ν(C–S), 683, 671, 560, 445	3078, 3041 ν(C–H)$_{py}$, 2919 ν(C–H), 1648 ν(C=O), 1622 ν(C–C)$_{py}$, 1561 ν(C–C)$_{py}$, 1408–1298 [ν(C–N)$_{py}$, ν(C–C)$_{py}$], 980, 928, 758, 668 ν(C–S), 558, 357, 208
(L_4)	3398 ν(H–O–H), 3370, 3216 ν(N–H), 3062 ν(C–H)$_{py}$, 2985 ν(C–H), 1657 ν(C=O), 1649 δ(N–H), 1622 ν(C–C)$_{py}$, 1567 ν(C–N)$_{py}$, 1416 [ν(C–N)$_{py}$, ν(C–C)$_{py}$], 1164, 1137, 819, 795 ω(C–H)$_{py}$, 715 ν(C–S), 690, 589, 564, 515 ν(S–S), 483	3095, 3041 ν(C–H)$_{py}$, 2955, 2922 ν(C–H), 1644 ν(C=O), 1622 ν(C–C)$_{py}$, 1562 ν(C–C)$_{py}$, 1410–1304 [ν(C–N)$_{py}$, ν(C–C)$_{py}$], 763, 691, 659, 638 ν(C–S), 565, 546, 510 ν(S–S), 362, 210

ν, stretching; δ, bending; ω, out-of-plane wagging; and py, pyridine-ring.

2. Experimental protocols

2.1. Chemistry

All chemicals and solvents were reagent grade and were used as purchased without further purification. Melting points were determined using an Electro-thermal 9100 melting-point apparatus. Analytical data were obtained with a Thermo Finnigan Flash EA 1112 analyser. FT-IR spectra were recorded as KBr pellets on a Jasco FT/IR-600 Plus spectrometer. FT-Raman spectra were obtained from powdered samples placed in a Pyrex tube using the Bruker RFS 100/S spectrometer in the range 4000–20 cm^{-1}. The 1064 nm line, provided by a near infrared Nd:YAG air-cooled laser was used as excitation line. The output laser power was set to 180–200 mW. Routine ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded at ambient temperature in DMSO-d_6. Chemical shifts (δ) are expressed in units of parts per million relative to TMS. The analytical data and physical properties are summarized for each experiment and the spectral data are presented in Tables 1–3. The synthetic pathway for the compounds is shown in Scheme 1.

2.1.1. Synthesis

*2.1.1.1. 1,3,5,11,13,15-hexaaza-6,10,16,20-tetraoxo-8,18-dithia-2,3,4:12,13,14-dipyridine cyclocosane **(L_1)***. Centrifuged hot ethanolic solution (10 mL, absolute) of 2,6-pyridinediamine (2.25 g, 20.64 mmol) was mixed with hot ethanolic solution of (10 mL) of thiodiglycolic acid (3.0 g, 20.64 mmol) in the presence of few drops of concentrated HCl. The solution mixture was refluxed for 6–8 h at 85 °C. The resulting reaction mixture was refrigerated overnight. The light yellow crystalline solid was formed, which was filtered, washed with cold EtOH and dried under vacuum (3.80 g, 82%). M.p. 197 °C. Found (calculated) **(L_1)(H_2O)**, $C_{18}H_{20}N_6O_5S_2$: C, 46.15 (46.55); H, 4.27 (4.31); N, 18.33 (18.10); S, 13.88 (13.79).

The other ligands were prepared in a similar manner to the ligand **(L_1)** and the results are presented as following.

*2.1.1.2. 1,3,5,12,14,16-hexeaza-6,11,17,22-tetraoxo-8,9,19,20-tetrathia-2,3,4:13,14,15-dipyridine cyclodocosane **(L_2)***. Hot ethanolic solution (10 mL) of 2,6-pyridinediamine (2.25 g, 20.64 mmol) was reacted with ethanolic solution of (10 mL) of dithiodiacetic acid (3.64 g, 20.64 mmol) in the presence of few drops of HCl. The off white crystalline solid was obtained (4.31 g, 82%). M.p. 131–136 °C. Found (calculated) **(L_2)(H_2O)$_3$**, $C_{18}H_{24}N_6O_7S_4$: C, 37.78 (38.30); H, 4.67 (4.26); N, 14.56 (14.89); S, 22.13 (22.69).

*2.1.1.3. 1,3,5,13,15,17-hexaaza-6,12,18,24-tetraoxo-9,21-dithia-2,3,4:14,15,16-dipyridine cyclotetracosane **(L_3)***. Hot ethanolic solution (10 mL) of 2,6-pyridinediamine (2,25 g,

Table 2
^{1}H chemical shift values (ppm) for the **(L_1–L_4)** compounds

Compound	a(8H)	b(8H)	d(4H)	e(2H)	NH(4H)
(L_1)	3.30 (s)	–	5.7 (d, J = 8.0 Hz)	7.34 (t, J = 8.0 Hz)	9.80–7.50
(L_2)	3.60 (s)	–	5.79 (d, J = 8. 06 Hz)	7.31 (t, J = 8.06 Hz)	10.60–6.50
(L_3)	2.70 (t, J = 7.17 Hz)	2.48 (t, J = 7.17 Hz)	5.67 (d, J = 7.80 Hz)	7.08 (t, J = 7.80 Hz)	7.00–5.80
(L_4)	2.89 (t, J = 6.92 Hz)	2.58 (t, J = 6.92 Hz)	5.71(d, J = 7.90 Hz)	7.16 (t, J = 7.90 Hz)	9.10–6.20

For the (a–e) definition, please refer to Figs. 4, 5 and Scheme 1.