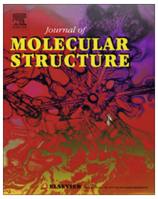
Journal of Molecular Structure 1093 (2015) 201–207

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstruc



Template engineered biopotent macrocyclic complexes involving furan moiety: Molecular modeling and molecular docking

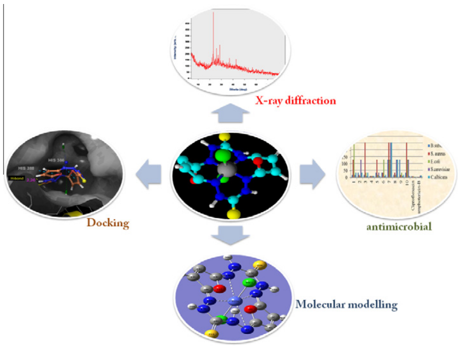
Parveen Rathi *, D.P. Singh

Department of Chemistry, National Institute of Technology, Kurukshetra 136 119, India

HIGHLIGHTS

- Macrocycles containing heterocycle-furan-2,5-dione.
- *In-vitro* antimicrobial and antioxidant screening.
- Molecular docking & modeling.
- Physico-chemical characterization including powder XRD.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 20 January 2015
Received in revised form 20 March 2015
Accepted 23 March 2015
Available online 31 March 2015

Keywords:
Octaazamacrocyclic ligand
Bioactivity
Furan-2,5-dione
Antioxidant activity
Template

ABSTRACT

Bioactive cobalt(II), nickel(II), copper(II) and zinc(II) complexes of octaazamacrocycle, 19, 20-dioxa-2,3,5,6,11,12,14,15-octaazatricyclo[14.2.1.1]icosa-1,6,8,10,15,17-hexaene-4,13-dithione, derived from furan-2,5-dione and thiocarbonohydrazide in the mole ratio 2:2:1 have been engineered via template methodology. The synthesized metal complexes have also been structurally characterized in the light of various physicochemical techniques and evaluated for antimicrobial and antioxidant activities. All these studies point toward the formation of divalent macrocyclic complexes possessing distorted octahedral geometry and having significant antimicrobial and antioxidant properties as compared to the starting precursors. Virtual screening of a representative complex was done through docking to the binding site of COX-2 to evaluate the anti-inflammatory activity of the series. Non-electrolytic nature of the complexes has been predicted on the basis of low value of molar conductivity in DMSO. All the complexes were having notable activities against pathogenic microbes as compared to precursors-thiocarbonohydrazide and furan-2,5-dione however, the complex **5**, [Ni ($C_{10}H_8N_8O_2S_2$) $(NO_3)_2$], shows the best antimicrobial activity.

Introduction

Transition metal complexes containing macrocyclic Schiff base derivatives of hydrazones are of interest to model the active sites of biologically important molecules. Metal complexes having hydrazone moiety have been given importance due to the high physiological activities and the presence of chelatophore group of donor atoms in the coordination sphere [1–4]. Metal–organic coordination architectures have achieved tremendous growth because of their intriguing potential and structural properties [5,6]. Many synthetic routes to macrocyclic ligand involve the use of the metal ion template to orient the reactant groups of linear substrate in the desired confirmation for the ring closure. The favorable

---

* Corresponding author. Mobile: +91 9729986865.
E-mail address: rathiparveen28@gmail.com (P. Rathi).

http://dx.doi.org/10.1016/j.molstruc.2015.03.045
0022-2860/

enthalpy for the formation of metal ligand bonds overcomes the unfavorable entropy of the ordering of the multidentate ligand around metal ion thus promotes the cyclization reaction [7,8]. Macrocyclic complexes of zinc play a diverse role in luminescence [9]. It seems reasonable to bear in mind the enhanced biological activity of macrocyclic complexes which contain heterocyclic moieties in the macrocyclic rings instead of carbocycles. This may afford a compound having not only the metal gripping potentiality but also possibly possess good biological efficiency. A number of acyclic furan derivatives have been reported as effective COX-2 inhibitor [10] but very little or no work has been reported on the evaluation of anti-inflammatory activity of macrocyclic complexes bearing heterocyclic ring. Thus, the attempts have been made in the present paper to synthesize and characterize a new series of macrocyclic metal complexes with Co(II), Ni(II), Cu(II) and Zn(II) metal ions containing heterocyclic ring, furan-2,5-dione, and thiocarbonohydrazide. *In vitro* antimicrobial, antioxidant and *in silico* molecular docking has been carried out to screen the complexes.

Experimental

Materials

The metal salts were purchased from E. Merck, Ranbaxy, India or S. D. fine Mumbai, India. Furan-2,5-dione and DPPH were purchased from Sigma Aldrich. Organic solvents [(methanol, diethyl ether, acetone, dimethylsulfoxide (DMSO), dimethyformamide (DMF)] were reagent grade and were used as received.

Experimental protocol

Microanalyses of Carbon, Hydrogen and Nitrogen were carried out on EuroEA elemental analyzer. Electronic spectra (DMSO) were recorded on a cary 14 spectrophotometer. Melting points were determined using capillaries in electrical melting point apparatus. Molar Conductance of the complexes was measured in DMSO on a digital conductivity meter (HPG System, G-3001). Literature methods were used for the analysis of metal content in the complexes [11]. The magnetic susceptibility measurements were made at STIC, Cochin. TGA was recorded on Hitachi TG/DTA 7200. All the powder X-ray diffraction (PXRD), analysis was carried out on Bruker D8 X-ray diffractometer at Central University of Hyderabad. The IR spectra were recorded on FTIR spectrophotometer (Agilent Technologies), in the range 4000–400 cm^{-1} and Far IR spectra were recorded on FTIR spectrophotometer (Perkin Elmer RX-I), in the range 700–30 cm^{-1} at SAIF, Punjab University, Chandigarh. Mass spectra were recorded at SAIF, Punjab University, Chandigarh.

Procedure for the synthesis of macrocyclic complexes

Template methodology was used for the synthesis of complexes in 2:2:1 final composition. The synthesis of complexes may be shown by the following scheme: (see Scheme 1).

Synthesis of complexes **1–3** i.e., [Co $(C_{10}H_8N_8O_2S_2)$ X_2] (Where X = Cl^-, NO_3^-, OAc^-): The solution of thiocarbonohydrazide (5 mmol, 0.5308 g) and divalent metal salts (2.5 mmol, 0.5948 g, 0.7275 g, 0.6227 g of $CoCl_2{\cdot}6H_2O$, $Co(NO_3)_2{\cdot}6H_2O$, $Co(OAc)_2{\cdot}4H_2O$ resp.) in methanolic medium, was refluxed for 0.5 h. In the process of refluxing the color of the solution changes quickly. Subsequently, furan-2,5-dione (5 mmol, 0.4903 g), in methanol, was added to the refluxing mixture and refluxing was continued for 7.5 h. At completion of reaction as indicated by TLC (finally giving one spot) the mixture was cooled to room temperature and reduced to half volume, whereby pinkish to violet colored precipitates formed which were filtered, washed with cold methanol, then acetone and diethyl ether and finally air-dried. IR (neat, cm^{-1}): 3150–3160 (—NH), 2140 (C=S), 1610 (C=N), 1170 (C—O—C ring), 466 (Co—N), 335 (Co—Cl), 230 (Co—O).

Complex **1**

[Co $(C_{10}H_8N_8O_2S_2)$ Cl_2]: Yield-69%, pink, Calc. M = 12.64, C = 25.76, H = 1.73, N = 24.04, S = 13.76, M.Wt. = 466.19; Found M = 12.57, C = 25.66, H = 1.64, N = 24.01, S = 13.71, M.Wt. = 464.89; ^M = 02, $\mu_{eff.}$ = 3.98B.M. UV–VIS (DMSO, nm): 910, $^4T_{1g} \rightarrow {}^4T_{2g}$ (F), (υ_1); 536, $^4T_{1g} \rightarrow {}^4A_{2g}$ (F), (υ_2) and 404, $^4T_{1g}$ (F) $\rightarrow {}^4T_{1g}$ (P), (υ_3).

Complex **2**

[Co $(C_{10}H_8N_8O_2S_2)$ $(NO_3)_2$]: Yield-65%, Dark pink, Calc. M = 11.35, C = 23.13, H = 1.55, N = 26.97, S = 12.35, M.Wt. = 518.93; Found M = 11.27, C = 23.10, H = 1.51, N = 26.89, S = 12.30, M.Wt. = 517.3; ^M = 06, $\mu_{eff.}$ = 3.95B.M. UV–VIS (DMSO, nm): 899, $^4T_{1g} \rightarrow {}^4T_{2g}$ (F), (υ_1); 512, $^4T_{1g} \rightarrow {}^4A_{2g}$ (F), (υ_2) and 410, $^4T_{1g}$ (F) $\rightarrow {}^4T_{1g}$ (P), (υ_3).

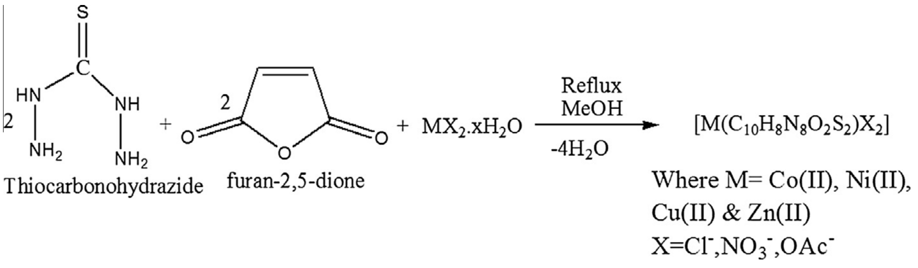
Complex **3**

[Co $(C_{10}H_8N_8O_2S_2)$ $(OAc)_2$]: Yield-62%, violet, Calc. M = 11.48, C = 32.75, H = 2.75, N = 21.83, S = 12.49, M.Wt. = 513.37; Found M = 11.48, C = 32.64, H = 2.60, N = 21.80, S = 12.45, M.Wt. = 512.0; ^M = 17, $\mu_{eff.}$ = 3.91B.M. UV–VIS (DMSO, nm): 890, $^4T_{1g} \rightarrow {}^4T_{2g}$ (F), (υ_1); 540, $^4T_{1g} \rightarrow {}^4A_{2g}$ (F), (υ_2) and 390, $^4T_{1g}$ (F) $\rightarrow {}^4T_{1g}$ (P), (υ_3).

Synthesis of complexes **4–6** i.e., [Ni $(C_{10}H_8N_8O_2S_2)$ X_2] (Where X = Cl^-, NO_3^-, OAc^-): The same procedure was adopted for the synthesis of nickel complexes except nickel salts (2.5 mmol, 0.5942 g, 0.7269 g, 0.6221 g of $NiCl_2{\cdot}6H_2O$, $Ni(NO_3)_2{\cdot}6H_2O$, $Ni(OAc)_2{\cdot}4H_2O$ resp.) were added in place of cobalt salts and refluxing was continued for 8 h. IR (neat, cm^{-1}): 3152–3155 (—NH), 2143 (C=S), 1622 (C=N), 1171 (C—O—C ring), 466 (Ni—N), 335 (Ni—Cl), 230 (Ni—O).

Complex **4**

[Ni $(C_{10}H_8N_8O_2S_2)$ Cl_2]: Yield-60%, Dirty brown, Calc. M = 12.60, C = 25.78, H = 1.73, N = 24.05, S = 13.76, M.Wt. = 465.95; Found M = 12.54, C = 25.79, H = 1.68, N = 24.01, S = 13.74, M.Wt. = 463.8; ^M = 13, $\mu_{eff.}$ = 3.71B.M. UV–VIS (DMSO, nm): 1050, $^3A_{2g} \rightarrow {}^3T_{2g}$ (F), (υ_1); 800, $^3A_{2g} \rightarrow {}^3T_{1g}$ (F), (υ_2) and 420, $^3A_{2g} \rightarrow {}^3T_{1g}$ (P), (υ_3); 242 nm ($\pi \rightarrow \pi^*$).



Scheme 1. Scheme for synthesis of complexes derived from Furan-2,5-dione and thiocarbonohydrazide with divalent metal salts.