Referencias Bibliográficas

1 http://www1.inca.gov.br/conteudo_view.asp/ acessada em 27 de setembro de 2010.

2 OLIVEIRA, R.B.; ALVES, R.J. Agentes antineoplásicos biorredutíveis: uma nova alternativa para o tratamento de tumores sólidos. **Quim. Nova***,* v.25, n.6, p.976-984, 2002.

3 ALMEIDA, V.L.; LEITÃO, A.; REINA, L.C.B.; MONTANARI, C.A.; DONNICI, C.L. Câncer e agentes antineoplásicos ciclo-celular específicos e ciclo-celular não específicos que interagem com o DNA: Uma introdução.***Quim. Nova****,* v.28, n.1, p. 118-129, 2005.

4 http://www.medical-look.com/diseases_images/cancer.gif, acessada em 30 de agosto de 2010.

5 ALBERTS, B. **Fundamentos da Biologia Celular***.* Tradução*:* Ana L.C. Santiago-Santos. 2ª ed. Porto Alegre: Artmed, 2006, p.866.

6 http://www.planeta.terra.com.br/…/image004.jpg, acessada em 30 de agosto de 2010.

7 WORLD HEALTH ORGANIZATION. **World Cancer Report, 2008**. International Agency for Research on Cancer, Lyon. 2009.

8 http://www.prevencaoaocancer.com.br/risco.php, acessada em 9 de setembro de 2010.

9 http://www.oncoguia.com.br/site/interna.php, acessada em 9 de setembro de 2010.

10 http://www.radioterapiamg.med.br/info_gerais.html, acessada em 27 de setembro de 2010.

11 http://www.nacc.org.br/infantil/infantil_quimioterapia.shtml, acessada em 27 de setembro de 2010.

12 MACHADO, A. E. D. Terapia fotodinâmica: princípios, potencial de aplicação e perspectivas. **Quim. Nova,** v. 23, p. 237-243, 2000.

13 Rosenberg, B., Van Camp, L., Krigas, T. *Nature*, 1965, 205, pp. 698-699

14 http://www.chm.bris.ac.uk/motm/cisplatin/htmlonly/. Acessada em 29 de setembro de 2010.

15 http://chemcases.com/cisplat/cisplat08.htm. Acessada em 29 de setembro de 2010.

16 http://chemcases.com/cisplat/cisplat01.htm. Acessada em 29 de setembro de 2010.

17 HUANG, Z.; *et al*. Determination of cisplatin and its hydrolytic metabolite in human serum by capillary electrophoresis techniques. **Journal of chromatography A**. n.1106, p. 75-79, 2006.

18 http://www.ch.ic.ac.uk/local/projects/s_liu/Html/Frames.html. Acessada em 15 de outubro de 2010.

19 PULIDO, M. D.; PARRISH, A. R. **Mutat Res.,** v. 533, p. 227, 2003.

20 CARADONNA, J.P.; LIPPARD, S.J.; GAIT, M.J.; SINGH, M. The antitumor drug cis-dichlorodiammineplatinum forms an intrastrand d(GpG) crosslink upon reaction with $[d(ApGpGpCpCpT)]_2$. **J. Am. Chem. Soc**., v.104: p.5793–5795, 1982.

21 FONTES, A.P.S.; ELOI, T.C.; BERALDO, H. A Química Inorgânica na Terapia do Câncer. **Cadernos Temáticos de Química Nova na Escola**, n.6, p. 13-18, 2005.

22 PIZARRO, A.M.; SADLER, P.J. Unusual DNA binding modes for metal anticancer complexes. **Biochimie***,* v. 91, p.1198-1211, 2009.

23 KARTALOU, M.; ESSIGMANN, J. M. Mechanisms of resistance to cisplatin. **Mutat Res**., v.478, p. 23-43, 2001.

24 RABIK, C. A.; DOLAN, M. E. Molecular mechanisms of resistance and toxicity associated with platinating agents. **Cancer Treatment Reviews**, 2006.

25 PEREZ,R.S. Cellular and molecular determinants of cisplatin resistance. **Eur. J. Cancer**, v.**34**, p.1535-1542, 1998.

26 HECHT, S. M. **Bioinorganic Chemistry: Nucleic Acids.** New York: Oxford University Press, 1996.

27 REY, N.A.; *et al*. A synthetic dinuclear copper(II) hydrolase and its potential as antitumoral: Cytotoxicity, cellular uptake, and DNA cleavage. **Journal of Inorganic Biochemistry**, v. 103, p. 1323-1330, 2009.

28 KRAMER. R. Bioinorganic models for the catalytic cooperation of metal ions and functional groups in nuclease and peptidase enzymes. **Coordination Chemistry Reviews**. v.182, p.243-261, 1999.

29 FRANKLIN, S. J. Lanthanide-mediated DNA hydrolysis. **Curr. Opin. Chem. Biol.,** v.5, p. 201-208, 2001.

30 LEWIS, E. A.; TOLMAN, W. B. Reactivity of Dioxygen-Copper Systems. **Chem. Rev.,** v. 104, p. 1047, 2004.

31 HEGG, E. L.; BURSTYN, J. N. Toward the development of metal-based synthetic nucleases and peptidases: a rationale and progress report in applying the principles of coordination chemistry. **Coord. Chem. Rev.,** v. 173, p. 133-165, 1998.

32 LIU, C.; WANG, M.; ZHANG, T.; SUN, H. DNA hydrolysis promoted by di- and multinuclear metal complexes. **Coord. Chem. Rev.,** v. 248, p. 147-168, 2004.

33 COWAN, J. A . Chemical nucleases. **Curr. Opin., Chem. Biol.** v. 5, p. 634-642, 2001.

34 TONDE, S. S.; KUMBHAR, A. S.; PADHYE, S. B.; BUTCHER, R. J. Self-activating nuclease activity of copper (II) complexes of hydroxyl-rich ligands. **Journal of Inorganic Biochemistry,** v. 100, p. 51-57, 2006.

35 DHAR, S.; REDDY , P. A. N.; CHAKRAVARTY, A. R. Intramolecular nucleophilic activation promoting efficient hydrolytic cleavage of DNA by (aqua)bis-(dipyridoquinoxaline)copper(II) complex. **Dalton Trans.,** p. 697-698, 2004.

36 JORGE, S.G.; et al. Fragmenteción de ADN por diferentes casiopeínas. **2º Congreso Nacional de Química Médica**

37 DE LA LUZ, Hernandez Esquivel Maria. **Efecto de la Casiopeina III sobre la función cardíaca em corazon aislado de rata.** Tesis de Licenciatura – Biologia Experimental. Universidad autónoma metropolitana unidad iztapalapa.

38 REY, Nicolás Adrian. **Novos Ligantes Binucleantes e seus Complexos Metálicos do tipo CuII–(mu-OH)–CuII**: 1) Modelos Estruturais para o Sítio Ativo das Catecol Oxidases e 2) Análogos Sintéticos com Atividade Redox e/ou Hidrolítica. Tese (Doutorado em Química) – Universidade Federal de Santa Catarina

39 JR. F. P. S.; *et al.* Experimental and theoretical structure characterization of two isoniazid derivatives: 2,4-Difluoro-N'-isonicotinoylbenzohydrazide and 2,4-dichloro N'isonicotinoylbenzohydrazide hydrochloride. **Journal of Molecular Structure**. v. 788, p 63–71, 2006.

40 BOTTARI, B. Isoniazid-Related Copper(II) and Nickel(II) Complexes with Antimycobacterial In Vitro Activity. Part 9. **Bioorganic & Medicinal Chemistry Letters**. v.10, p.657-660, 2000.

41 CARDOSO, S.H.; ASSIS, J.V.; ALMEIDA, M.V. Synthesis and antitubecular activity of isoniazid condensede with carbohydrate derivatives. **Quimica Nova**, v. 32, n. 6, p.1557-1560, 2009.

42 KANWAR, S.S.; *et al*. Synthesis and mycobactericidal properties of metal complexes of isonicotinoyldithiocarbazic acid. **Biotechnol Lett**, v.30, p.677–680, 2008.

43 LOGU, A.; *et al.* Activity of a new class of isonicotinoylhydrazones used alone combination with isoniazid, rifampicin,ethambutol, para-aminosalicylic acid and clofazimine against Mycobacterium tuberculosis*.* **Journal of antimicrobial Chemotherapy**, v.49, p.275-282, 2002*.*

44 HUNOOR, R.S.; *et al*. Spectroscopic, magnetic and thermal studies of Co(II), Ni(II), Cu(II) and Zn(II) complexes of 3-acetylcoumarin isonicotinoylhydrazone and their antimicrobial and anti-tubercular activity evaluation. **Spectrochimica Acta Part A**. p.1-29, 2010.

45 Chemical Journal of Chinese Universities, v. 13, n 1, p. 6-9, 1992.

46 Chemical Journal of Chinese Universities, v. 14, n 12, p. 1638-1641, 1993.

47 Xian-He Bu; *et al*. Novel homobinuclear lanthanide (III) complexes with isonicotinoyl hydrazone: synthesis and coordination chemistry. **Inorganica Chimica Acta**, v. 308, p. 143–149, 2000.

48 FRISCH, M.J.; *et al*. **Gaussian 03**, Revision E.01, Wallingford CT, 2004

49 YOUNG, David C. **Computational Chemistry: A Practical Guide for Applying Techniques to Real-World Problems.** John Wiley & Sons, New York, 2001.

50 C. N. VERANI. **Rational Synthesis and Characterization of Paramagnetic Heteropolynuclear Systems Containing [MA-MB-MC], [MA-MB]2 and [M1-2(R)1-2-3] Cores**. 169 p. Dissertation (Doktor der Naturwissenschaft) - Fakultat fur Chemie, Ruhr-Universitat Bochum, Mulheim an der Ruhr (2000).

51 CHRISTOU, George; *et al.* Preparation and Properties of the Triply Bridged, Ferromagnetically Coupled Dinuclear Copper(II) Complexes $[Cu_2(OAc)_3(bpy)_2](ClO_4)$ and $[Cu_2(OH)(H_2O)(OAc)(bpy)_2](ClO_4)_2$. **Inorg. Chem.,**v.29, p.3657-3666, 1990.

52 DEACON, G.B.;PHILLIPS, R.J. Ralationships between the carbon-oxygen stretching frequencies of carboxylato complexes and the type of carboxylate coordination. **Coordination Chemistry Reviews,** v.33, p.227-250, 1980.

53 NAKAMOTO, Kazuo. **Infrared and Raman Spectra of Inorganic and Coordination Compounds.** John Wiley & Sons, 4ª. Edição, 1986

54 K. D. KARLIN, J. C. HAYES, Y. GULTNEH, R. W. CRUSE, J. W. McKOWN, J. P.HUTCHINSON and J. ZUBIETA. Copper-Mediated Hydroxylation of an Arene: Model System for the Action of Copper Monooxygenases. Structures of a Binuclear Cu(I) Complex and Its Oxygenated Product. **J. Am. Chem. Soc**., v. 106, p. 2121-2128 (1984).

55 S. TORELLI, C. BELLE, I. GAUTIER-LUNEAU, J. L. PIERRE, E. SAINT-AMAN, J. M.LATOUR, L. Le PAPE and D. LUNEAU. pH-Controlled Change of the Metal Coordination in a Dicopper(II) Complex of the Ligand H-BPMP: Crystal Structures, Magnetic Properties, and Catecholase Activity. **Inorg. Chem**., v. 39, p. 3526-3536 (2000).

56 P. DAPPORTO, M. FORMICA, V. FUSI, M. MICHELONI, P. PAOLI, R. PONTELLINI and P. ROSSI. Synthesis of a Flexible Ligand for Assembling Two Metal Ions in Close Proximity. Crystal Structures of Binuclear Nickel and Copper Complexes. **Inorg. Chem**., v.39, p. 4663-4665 (2000).

57 ROMANOWSKI, S. M. M.; *et AL.* Síntese a caracterização de novos compostos de coordenação de cobre(II) com ligantes não-simétricos N,O-doadores: contribuições para o sítio ativo da galactose oxidase. **Química Nova**, v.24, n.5, p.592-598, 2001.

Anexos

A.1

A NEW UNSYMMETRIC BINUCLEATING LIGAND DERIVED FROM ISONIAZID AND ITS FIRST DICOPPER(II) COMPLEX

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DNA is an important target of antitumoral drugs. Recently, we reported the cytotoxic activity and DNA cleavage by a hydroxo-bridged $Cu^{II}Cu^{II}$ complex. [1] In this context, the present work describes the synthesis and structure of the new binucleating ligand H_3L, derived from the antituberculosis drug isoniazid (INH). A preliminary report on its first dicopper(II) complex is also included.

H_3L was obtained by reaction between 1.0 mmol of 2-{[(2-hydroxybenzyl)(2-pyridylmethyl)amino]methyl}-4-methyl-6-formylphenol [2] and INH (1.0 mmol), in a 1:1 MeOH:Et_2O mixture under reflux. After 24 hours, light-brown crystals suitable for X-ray diffraction were isolated by filtration and washed with cold MeOH. Yield 90%. Melting point: 200ºC. Elemental analysis: %Found(Calcd. for $C_{28}H_{27}O_3N_5$) - C, 69.6(69.8); H, 5.9(5.7); N, 14.5(14.5). Structure of H_3L is showed in Figure 1. The molecular conformation is influenced by intra- and intermolecular hydrogen bonds involving both phenol groups (dashed lines).

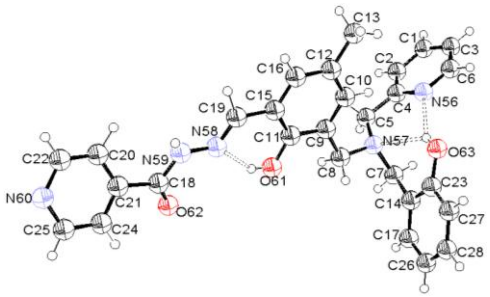

Figure 1. Molecular structure of the hexadentate binucleating ligand H_3L.

Microanalysis points to $[Cu_2(\mu\text{-}OH)(HL)]ClO_4 \cdot 3\ H_2O$ as a possible formula for the dicopper(II) complex of H_3L. %Found(Calcd.): C, 43.6(43.3); H, 3.7(4.2); N, 9.1(9.0). Some of the main vibrational IR bands of the ligand are shifted in the spectrum of the complex. Additional studies are in progress.

References

[1] N.A. Rey *et al. J. Inorg. Biochem.* **2009**, *103*, 1323.
[2] R. Jovito *et al. Inorg. Chem. Commun.* **2005**, *8*, 323.

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A. 2

NOVEL ISONICOTINOYL HYDRAZONE DICOPPER(II) COMPLEX: SYNTHESIS,CHARACTERIZATION AND DFT STUDY

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N,*N*'-diisonicotinoyl-2-hydroxy-5-methylisophthalaldehyde dihydrazone [1] is a compartmental ligand able to form dinuclear coordination compounds with several metal ions. The fact that the antituberculosis drug isoniazid is part of this ligand makes the study of its complexes specially interesting. This work presents the synthesis, characterization and structural/vibrational (B3LYP/6-31G) DFT investigation of a new dicopper(II) complex of this dihydrazone.

The ligand ($C_{21}H_{18}O_3N_6$) was synthesized according to the previous reported methodology. [2] A warm methanolic solution of $C_{21}H_{18}O_3N_6$ (0.5 mmol) readily reacts with copper(II) acetate monohydrate (1.0 mmol) to give a green solid. The precipitate was filtered off and washed with cold methanol. Yield 85%.

Elemental analysis points to $[Cu_2(\mu\text{-}CH_3COO)(H_2O)_2(C_{21}H_{15}O_3N_6)]\cdot 1½\ H_2O$ as a possible formula for the compound. %Found(Calcd.): C, 42.66(42.59); H, 3.57(3.89); N, 13.28(12.96). The TG curve reveals the lost of water of hydration below 100ºC, corresponding to 4.52% of the total mass (Calcd. for $1½\ H_2O$: 4.17%). Infrared data are in good agreement with the theoretical vibrational frequencies calculated for the proposed structure of the complex (Figure 1), which shows two doubly-bridged distorted square pyramidal five-coordinated copper(II) centers at a distance of 3.118 Å.

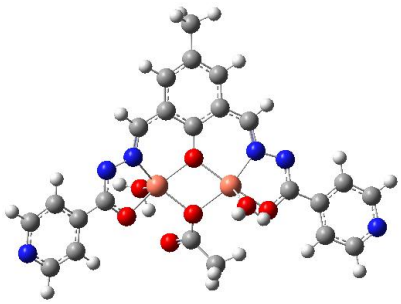

Figure 1. Optimized gas phase structure for $[Cu_2(\mu\text{-}CH_3COO)(H_2O)_2(C_{21}H_{15}O_3N_6)]$.

References

[1] X.-H. Bu *et al. Inorg. Chim. Acta* **2000**, *308*, 143.
[2] J.T. Chen *et al. Polyhedron* **1994**, *13*, 1701.

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A.3

XV BRAZILIAN MEETING ON INORGANIC CHEMISTRY

II LATIN AMERICAN MEETING ON BIOLOGICAL INORGANIC CHEMISTRY

August 16 - 20, 2010

Hotel do Frade, Angra dos Reis, RJ, Brazil

CERTIFICATE

The Organizing Committee certifies that the Poster entitled: **NOVEL ISONICOTINOYL HYDRAZONE DICOPPER(II) COMPLEX: SYNTHESIS,CHARACTERIZATION AND DFT STUDY**

of the authors: **R.S. Moraes, J. Felcman, N.A. Rey**

has been awarded with a Honorable Mention at the XV BRAZILIAN MEETING ON INORGANIC CHEMISTRY and II LATIN AMERICAN MEETING ON BIOLOGICAL INORGANIC CHEMISTRY.

Professor Maria Domingues Vargas

Conference Chair-XV BMIC/II LABIC