Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2015, 7(10):650-654

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Molecular docking studies between two palladium complexes cis-[(1*S*, 2*S*)-(-)-N^1, N^2-bis(1-phenylethyl)-1,2-propanodiimine]$PdCl_2$ and cis-{(1*S*, 2*S*)-(-)-N^1, N^2-bis[1-(4-metilphenyl)ethyl]-1,2-propanodiimine}$PdCl_2$) and DNA for elucidated its possible action mechanism

***Oscar Zuñiga-Lemus[1], José Antonio Salgado-Zamora[2], José Jaime Vázquez-Bravo[3], Veronica Castro-Bear[4], Francisco L. Balderas-Gómez[4], Rogelio A. Delgado-Alfaro[5], Juan Saulo González-González[1], José Alfredo Sánchez-Meraz[1]**

[1]University of La Cañada, Carretera Teotitlán-San Antonio Nanahuatipan Paraje Titacuatitla, Km. 1.7 s/n; Teotitlán de Flores Magón, Oaxaca, C.P. 68540, México
[2]Faculty of High Studies - Cuautitlán, Av. 1ro de Mayo s/n, Cuautitlán Izcalli, Estado de México.
[3]Higher Technological Institute of Atlixco, Prolongación Heliotropo No. 1201, Col. Vista Hermosa C.P. 74218, Atlixco, Puebla, México
[4]AutonomousUniversity of Puebla. Carretera Libramiento Tecnológico San Marcos Necoxtla Km. 7.5, Lázaro Cárdenas Sur, C.P. 75859, Tehuacán, Puebla
[5]Faculty of Chemical Science of the University of Colima, Km 9 Carretera Colima-Coquimatlán, C.P. 28400, Coquimatlán, Col. México

---

ABSTRACT

Cis-diaminedichloroplatinum (II), [cis-$(NH_3)_2PtCl_2$], is one of the most successful anticancer compounds. In recent years the search for new drugs with antineoplastic activity has led to synthesis of palladium complexes, because of its analogy with Platinum (II). The aim in this study was to show the interaction between DNA and palladium complexes using docking studies, to elucidate the possible action mechanism of cis-[(1S, 2S)-(-)-N^1, N^2-bis(1-phenylethyl)-1,2-propanodiimine]$PdCl_2$ and cis-{(1S, 2S)-(-)-N1, N^2-bis[1-(4-metilphenyl)ethyl]-1,2- propano -diimine}$PdCl_2$). Our results suggest a possible interaction of palladium complex and the DNA, forming a covalent bond manner similar to cisplatin.

Keywords: Cancer, Chemotherapy Drugs, Palladium complex, Molecular Docking, DNA

INTRODUCTION

Cis-diaminedichloroplatinum (II), [cis-$(NH_3)_2PtCl_2$], clinically called cisplatin is one of the most successful anticancer compounds[1]. It is an antineoplastic drug most used on cervical, lymphoma, melanoma, testicle, head, and ovary cancer[2-8]. However, it has secondary and toxic effects that may develop a secondary tumor[3,5]. Many cellular components including RNA, proteins, DNA, membrane phospholipids, and microfilaments react with cisplatin[7], in membranes Cisplatin interacts with phospholipids and phosphatidylserine[9], disrupts the cytoskeleton[10], and affects the polymerization of actin microfilaments resulting from the formation of Pt-S bonds[11].

Research in the field of platinum-based cancer chemotherapy showed that cisplatin and its analogous compounds exhibit very similar patterns of antitumor sensitivity and susceptibility to resistance, which means that most of them produce identical adducts with DNA [12]. Several articles have appeared during recent years dealing with platinum-based anticancer agents[13-17], based on these studies, the proposed mechanism of action relies on the formation of

adducts with DNA, being the main of this interaction the purine bases to form bonds between the N7 and cisplatin[18-19].

On the other hand, due to the frequent resistance to this drug during cancer chemotherapy[20], as well as the limitation in dosing due to its toxic effects, there have been many attempts to find complexes with greater potency and less toxicity than the existing clinical drugs. As a consequence of this, previous studies focused naturally on the other platinum group metals, ruthenium, rhodium, palladium, osmium and iridium[21]. The significant similarity between the coordination chemistry of palladium (II) and platinum (II) compounds has advocated studies Palladium complex (II) as antitumor drugs[22]. A key factor that might explain why platinum is most useful when it comes from the ligand-exchange kinetics. The hydrolysis in palladium complexes is too rapid: 10^5 times faster than for their corresponding platinum analogues. They dissociative readily in solution leading to reactive species that are unable to reach their pharmacological target[1]. However, there is evidence that palladium complex has a biological activity such as, anti-viral, anti-fungal, anti-microbial and anti-tumor[23-31].

In a previous study we reported that the synthesis of two chiral palladium complexes *cis*-[(1*S*, 2*S*)-(-)-N^1, N^2-bis(1-phenylethyl)-1,2-propanediimine]$PdCl_2$ and *cis*-{(1*S*, 2*S*)-(-)-N^1, N^2-bis[1-(4-metilphenyl)ethyl]-1,2-propanedi imine}$PdCl_2$ have shown promising *in vitro* cytotoxic activity against different classes of cancer cells. In this paper we study the possible mechanisms of action of these compounds. The results have shown the docking studies indicated a favorable interaction between LQCP1 and LQCP2 (ligand) to DNA in the groove of the double helix. These results suggest that the interaction between the complexes of Palladium and the DNA is different from of adducts of DNA with cisplatin, but the formation of the adduct between DNA and the Palladium can be responsible for cell death previously demonstrated [32]. It should be noted that studies of molecular link provides a possible view more detailed drug-receptor interaction has created a new rational approach to the design of drugs where drug structure is designed based on its adjustment to three-dimensional structures in the recipient site, in this work the white therapeutic was DNA and ligands complexes of Palladium.

EXPERIMENTAL SECTION

Synthesis

Synthesis and Characterization of palladium complexes was reported previously [32].

Minimization of the Structures.

Palladium complex *cis*-[(1*S*, 2*S*)-(-)-N^1, N^2-bis(1-phenylethyl)-1,2-propanodiimine]$PdCl_2$ (LQCP1) and *cis*-{(1*S*, 2*S*)-(-)-N^1, N^2-bis[1-(4-metilphenyl)ethyl]-1,2- propanodiimine}$PdCl_2$) (LQCP2); was minimized with GAUSIAN 09 software using calculation DFT PW1PW/LANL2DZ (Fig. 1).

Molecular Docking

A structural model of the catalytic domain of DNA was constructed using a Molecular Operating Environment (MOE) ver 2010.10, with the structure published of X-Ray Diffraction of DNA – cisplatin complex, and the modeling template was downloaded from the Protein Data Bank (www.pdb.org) with code PDB-ID 3LPV and 1.77 Å resolution and the major grove was determined by MOE's Site-Finder. The most stable complex palladium was used as ligand; the structure was docked into the DNA structure. The docking process consisted of using the protocol for rigid-rigid docking, followed by rigid-flexible and flexible-flexible docking methods. Finally, the adduct DNA-ligand was visualized with MOE.

RESULTS AND DISCUSSION

Based on previous reports suggesting that Palladium complexes have different biological activities within them the antiproliferative[26, 32], our goal was to show that Palladium complexes can interact with DNA, and that this interaction could trigger death in cancer cells. To test this theory, molecular-using link studies were carried out GAUSSIAN 09 and MOE ver. 2010.10.

Initially we determined the physicochemical characteristics of the complex in order to know its solubility, topological area, and weight of the complexes, table 1illustrates the Molecular Weight (MW), Partition Coefficient Octanol: Water (LogP) and topological polar surface area (tPSA) to Palladium Complex *cis*-[(1*S*, 2*S*)-(-)-N^1, N^2-bis(1-phenylethyl)-1,2-propanodiimine]$PdCl_2$ (LQCP1) and *cis*-{(1*S*, 2*S*)-(-)-N^1, N^2-bis[1-(4-metilphenyl)ethyl]-1,2- propanodiimine}$PdCl_2$) (LQCP2) calculated using the MOE software, the tPSA in the two complexes studied are equivalent because both molecules have similar substituent, both complexes of Palladium comply with rules Lipinski important to know if these complexes may be considered as molecular candidates for new drugs, in both cases complexes fulfill these rules.

The HOMO/LUMO relationship (Table 1) shown stability complexes acquired to add groups phenyl (LQCP 1) and methyl (LQCP2) at the ends of the molecules (Fig 1). These results suggest that the LQCP2 complex was more likely to interact with DNA.

Table 1. Values generated by molecular docking between LQCP1 and LQCP2 (ligands) to DNA (target)

	cis-[(1*S*, 2*S*)-(-)-N^1, N^2-bis(1-phenylethyl)-1,2-propanediimine]$PdCl_2$ (LQCP1).	*cis*-{(1*S*, 2*S*)-(-)-N^1, N^2-bis[1-(4-metilphenyl)ethyl]-1,2-propanediimine}$PdCl_2$ (LQCP2).
Molecular Weight (g/mol).	413.645	441.699
LogP	5.3	6.08
TPSA($Å^2$)	6.48	6.48
HOMO/LUMO (GAP) (eV)	3.2672	3.2754
Energyvalues kcal/mol	-93.09 ± 21.72	-106.95 ± 36.92
Affinity (pKi)	4.004 ± 0.076	3.55 ± 0.14
Efficiency	18.33 ± 2.94	15.2 ± 0.9574

DNA = Deoxyribonucleic acid

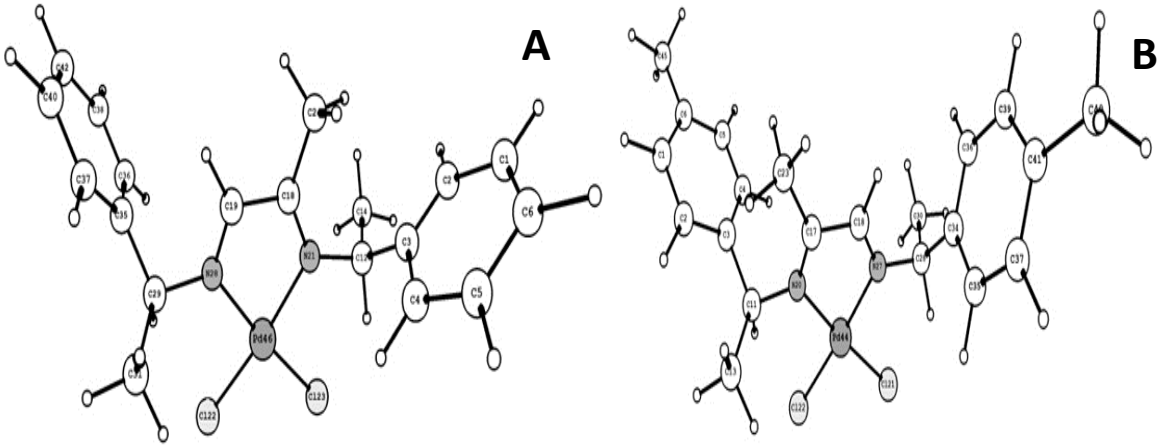

Figure 1. Palladium complexes minimized with GAUSSIAN 09. The Images, A corresponds *cis*-[(1*S*, 2*S*)-(-)-N^1, N^2-bis(1-phenylethyl)-1,2-propanediimine]$PdCl_2$ (LQCP1), the Image B corresponds *cis*-{(1*S*, 2*S*)-(-)-N^1, N^2-bis[1-(4-metilphenyl)ethyl]-1,2- propanediimine}$PdCl_2$ (LQCP2)

Results showed a favorable interaction between DNA and Palladium complex in major groove to DNA (Fig 2A and Fig 3A) similar to cisplatin[33-34], the data indicate a Free Gibbs energy of -93.09 ± 21.72 kcal/mol to LQCP1 and -106.95 ± 36.92 to LQCP2 (Table 1), similar to cisplatin -114kcal/mol[35], energy equivalent to the formation a covalent bond.

The interaction between the Palladium complexes and DNA occurred with the oxygen atom of the bases guanine and thymine to LQCP1 complex, and on the other hand cytosine and adenine to LQCP2 complex, but this interaction is not similar to cisplatin because the binding between DNA and Cis-platinum occurs on the Nitrogen atom (N7) of guanine [35]. Results showed contact between the metal (Pd^{2+}) of Palladium complexes with the structure of DNA (Fig 2B and 2D), in addition there is an interaction arene-cation between adenine and the Pd^{2+} LQCP2 which may explain the free energy more negative Gibbs thrown in the molecular docking (Fig 2D). Also, link distance between the atom of oxygen of the nitrogenous bases and Palladium was 1.19Å for LQCP1 (Fig 2A) and 1. 44Å to LQCP2 (Fig 2C), indicating a shorter distance with LQCP1.

Furthermore, the results show that the binding complexes of palladium occurs in DNA guanine and cytosine for LQCP2 (Fig 2C), and guanine and thymine to LQCP1 (Fig 2A), in the case of guanine is given interaction between the Oxo group in position 6 of the base with the Pd^{2+}, in the case of thymine is given in the Oxo group in position 4 of the nitrogenous base and the metal, but such interactions do not show contact with nitrogen and the Pd^{2+}, so that contact could be generated with the oxygen of the nitrogenous bases farthest from the deoxyribose ring.

The results of the molecular docking suggest a favorable interaction between LQCP1 and LQCP2 (ligand) to DNA in the major groove of the double helix. These results indicate that the palladium complex called LQCP1 has a higher affinity for this macromolecule that LQCP2 with values of 4.005 and 3.5 respectively (Table 1), this complex (LQCP1) has an efficiency of 18.33 compared with 15.2% for LQCP2, becoming better for LQCP1, which coincides with the distance of bond formation being shorter (1.19 Å), for this complex affinity that arises is higher with the target molecule (DNA).

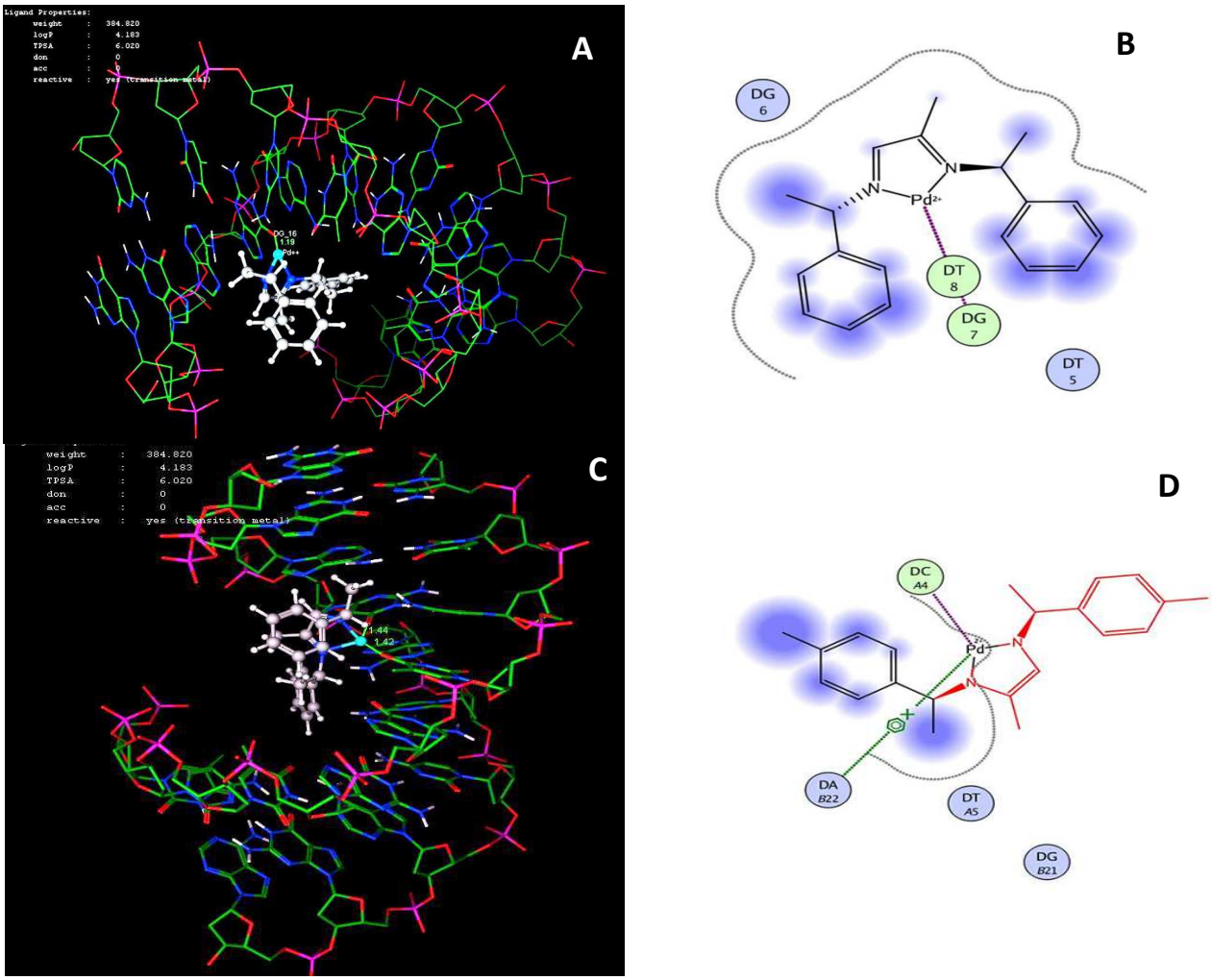

Figure 2.Molecular Docking between Paladium complexes versus DNA. Image A represents the Gaussian contact on the surface of DNA and cis-[(1S, 2S)-(-)-N1, N2-bis(1-phenylethyl)-1,2-propanediimine]PdCl2 (LQCP1), Image B represents the docking between DNA and LQCP1. Image C represent the Gaussian contact on the surface of DNA and *cis*-{(1*S*, 2*S*)-(-)-N^1, N^2-bis[1-(4-metilphenyl)ethyl]-1,2-propanediimine}PdCl2 (LQCP2); the Image D represents the docking between DNA and LQCP2

The results suggest that the interaction between the complexes of Palladium and the DNA is different to the DNA adducts in cisplatin, but the ADN-palladium adduct formation may be responsible for the death of cells previously demonstrated. Finally, the palladium complex Cis-{(1*S*, 2*S*)-(-)-N^1, N^2-bis[1-(4-metilphenyl)ethyl]-1,2-propanodiimine}$PdCl_2$) called LQCP2 has a better biological activity than LQCP1, according to the Physicochemical properties and molecular docking calculated which is consistent with the *in vitro* data[32].

In addition, the results suggest that the interaction between Palladium complexes and DNA would form an adduct between the two molecules due to the probable formation of a covalent bond, however without this then an adduct is formed between the metal and the oxygen atoms of the nitrogen bases being different from the adduct formed between DNA and cisplatin, which occurs with the metal contact with the atoms of nitrogen from the nitrogenous bases the result of this adduct formation could be responsible for the death of cells previously demonstrated.

Acknowledgement
Cuerpo Académico Farmacología Computacional by technical support and to PROMEP by financial support

REFERENCES

[1] AA Salim;HH Al-Sa'doni;MY Abdalla.*Cancer Ther.*,**2008**,6, 1-10.
[2] AS Abu-Surrah;M Kettunen.*Curr. Med. Chem.*,**2006**,13(11),1337-1357.
[3] EM Blanchard.*J. Solid Tumors*, **2012**, 2(1), 26-33.

[4] RN Bose;L Maurmann;RJ Mishur;L Yasui;S Gupta; WS Grayburn; H Hofstetter;T Salley. *Proc. Natl. Acad. Sci. U. S. A.*,**2008**,105(47), 18314-18319.
[5] AM Florea;D Büsselberg.*Cancers*.,**2011**, 3, 1351-1371.
[6] VM González; MA Fuertes;C Alonso;JM Pérez.*Mol.Pharmacol*.,**2001**,59(4), 657–663.
[7] ER Jamieson;SJ Lippard.*Chem. Rev.*,**1999**,99(9), 2467-2498.
[8] RP Miller; RK Tadagavadi; G Ramesh;WB Reeve.*Toxins.*,**2010**,2(11), 2490-2518.
[9] G Speelmans; WH Sips;RJH Grisel;RWHM Staffhorst;AMJ Fichtinger-Schepman; J Reedijk; B de Kruijff. *Biochim.Biophys.Acta*.,**1996,** 1283(1), 60-66.
[10] P Köpf-Maier; SK Mühlhausen.*Chem. Biol. Interact*.,**1992**,82(3), 295-316.
[11] H Zeng, B Wang, Y Zhang, K Wang.*Thermochim.Acta*.,**1995**, 265, 31-38.
[12] J Reedijk. *Proc. Natl. Acad. Sci*.,**2003**, 100(7), 3611-3616.
[13] SE Dahlberg; RJ Gray;BE Johnson.*J.Clin.Oncol*.,**2008**, 26(26), 4233-4235.
[14] MA Fuertes;C Alonso;JM Pérez. *Chem. Rev.*,**2003**, 103(3), 645-660.
[15] I Kostova. *Recent. Pat. Anti-Canc.*,**2006**, 1(1), 1-22.
[16] AI Matesanz;J Perles;P Souza.*Dalton Trans.*,**2012**, 41, 12538-12547.
[17] D Wang; SJ Lippard. *Nat. Rev. Drug.Discov.*,**2005,4**(4), 307-320.
[18] V Foltinová; SL Švihálková; V Horváth; P Sova; M Hofmanová; RJanisch; AKozubík.*ScriptaMedica (BRNO)*.,**2008**, 81(2), 105-116.
[19] T Torigoe; H Izumi; H Ishiguchi; Y Yoshida; M Tanabe; T Yoshida; T Igarashi; INiina; TWakasugi; TImaizumi; Y Momii; M Kuwano; K Kohno.*Curr. Med. Chem*.,**2005**, 5, 15-27.
[20] R Zendehdel; AMasoudi-Nejad; J Mohammadzadeh; FH Shirazi. *Iranian J. Pharm. Res*., **2012**, 11, 235-240.
[21] PCA Bruijnincx, PJSadler. *Adv.Inorg. Chem*.,**2009,** 61, 1-62.
[22] T Rau; R van Eldik. In Metal Ions In Biological Systems. Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy Sigel H, Sigel A, Eds, Marcel Dekker: New York, **1996**; pp 339-378.
[23] N Aryanpour; HMansouri-Torshizi; M Nakhjavan; F Shirazi. *Iranian J. Pharm. Res.*,**2012**, 11, 689-695.
[24] SSH Elgazwy; NSM Ismail; SR Atta-Allah; MT Sarg; DHS Soliman; MY Zaki; MA Elgamas. *Agents.Curr. Med. Chem*.,**2012**, 19, 3967-3981.
[25] I Kizilcikli;YD Kurt; B Akkurt; AY Genel; S Birteksöz; G Otük G; B. Ülküseven. *Fol.Microbiol*.,**2007**, 52(1), 15-25.
[26] DD Kovala-Demertzi;MA Demertzis;JR Miller;C Papadopoulou;C Dodorou; G Filousis; *J. Inorg. Biochem.*, **2001**, 86, 555-563.
[27] AK Mishra; SB Mishra;N Manav; NK Kaushik. *J. Coord.Chem*., **2007**, 60, 1691-1700.
[28] J Quirante; D Ruiz; A Gonzalez; C López; M Cascante; R Cortés; R Messeguer; C Calvis; L Baldomà; A Pascual; Y Guérardel; B Pradines; M Font-Bardía; T Calvet; C Biot.*J.Inorg.Biochem*.,**2011**, 105, 1720-1728.
[29] F Shaheen; A Badshah; M Gielen; M Dusek; K Fejfarova; DB de VosMirza.*J.Organomet. Chem*.,**2007**, 692(14), 3019-3026.
[30] NS Shailendra; N Bharti; MT Gonzalez-Garza; DE Cruz-Vega; J Castro-Garza; K Saleem; F Naqvi; A Azam. *Bioorg.Med.Chem.Lett*. **2007,** 11(20), 2675-2678.
[31] DRIlić; JMVujić; IDRadojević; ODStefanović; LR Čomić; DD Banković; SR Trifunović. *Hem. Ind.*,**2012**,66 (3), 349–355.
[32] J Vázquez; S Bernès; PSharma; J Pérez; G Hernández;A Tovar; UPeña; R Gutiérrez. *Polyhedron*. **2011**, 30, 2514-2522.
[33] DF Bancroft; CA Lepre; SJ Lippard.*J. Am. Chem. Soc.*,**1990**, 112, 6860-6871.
[34] KJ Barnham; SJ Berners-Price; TA Frenkiel; U Frey; PJ Sadler.*Angew. Chem. Int. Ed. Engl*.,**1995**,34, 1874-1877.
[35] T Zimmerman;M Zeizinger; J Burda. *J.Inorg. Biochem*.,**2005**, 99, 2184-2196.