

## SYNTHESIS OF BINUCLEAR ZINC (II) COMPLEXES OF N2O2 DONORS CONTAINING 4-AMINOANTIPYRINE BASED SCHIFF BASE LIGAND AND THEORETICAL STUDIES

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### Abstract

Schiff-base polydentate ligands types of salen and salophen can form stable complexes with Zn and these metal complexes can act as a source of zinc. The ground state electronic structures of Zn(dptpp)<sub>2</sub>Cl<sub>2</sub> complexes were investigated by DFT/B3LYP theoretical analysis using 6-311G++(d,p) and LANL2DZ basis set level. The molecular docking studies showed that complex Zn(dptpp)<sub>2</sub>Cl<sub>2</sub> strongly binds with BCL-2 receptor. The results indicate that the metal complexes are more active as compared with the ligand. The docking score found to be -7.92kcal/mol against BCL-2 (PDB id: Bcl-xl: 2YXJ). From the present study, it can be conclude that the molecular docking studies showed that complex Ni (II) strongly binds with Bcl-2 receptor..

**Key words:** Metal (II) Complexes, Anticancer, Antimicrobial, Antifungal, Molecular docking, DFT Analysis.

### Introduction

A Schiff base (or azomethine), named after Hugo Schiff, is a functional group that contains a carbon-nitrogen double bond with the nitrogen atom connected to an aryl or alkyl group, but not hydrogen. Schiff bases can be synthesized from an aromatic amine and a carbonyl compound by nucleophilic addition forming a hemiaminal, followed by a dehydration to generate an imine. Complexes of Schiff base ligands with structural similarities to phthalocyanines (N<sub>4</sub>-macrocycles), and other related compounds [1-2], are currently used as modifiers of the active surface of electrodes to improve their catalytic activity in the selective detection of organic pollutants [3] and the entrainment of metals. Along the same line, Martínez et al. [4] are interest is to evaluate the capability of N,N'-bis(2-nitrobenzyl)ethylendiimine to bind diverse metallic ions such as Ni(II) and Co(II), and carried out selectivity studies. These complexes are later studied to test their potential in the development of chemically modified electrodes for use in pollutant detection. Silku et al (2016) synthesized novel Schiff bases of the type by reacting phydroxybenzaldehyde with aniline and substituted anilines, which on further reaction with Na and acryloyl chloride yielded acryloyl derivatives. As early as 1884 Knorr discovered the antipyretic (temperature reducing) action of a pyrazole derivative in humans, and due to its antipyretic property he named the compound "Antipyrene." Transition metal complexes of pyrazolone derivatives are of great interest due to their biological activities, especially pyrazolone Schiff-base derivatives. Among the pyrazolone derivatives, 4-aminoantipyrine forms a variety of Schiff bases with aldehydes/ketones, and they are reported to be superior reagents in biological, pharmacological, clinical and analytical applications [5]. 4-Aminoantipyrine has an N-phenyl group and a -CH group on either side of a polar carbonyl group, thus resembling N-substituted amides. Coordination chemists, medicinal chemists and analytical chemists have extensively studied 4-aminoantipyrine. The carbonyl group in 4-aminoantipyrine is a potential donor due to the large dipole moment (5.48 D) and strong basic character. Guru and Rao [6] prepared zinc complexes of 4-aminoantipyrine. Gopalakrishnan and Patel [6] carried out the physico-chemical studies on antipyrine complexes of CoCl<sub>2</sub>, CoBr<sub>2</sub>, CuCl<sub>2</sub>, and CuBr<sub>2</sub> of the type MX<sub>2</sub> 2AAP. Both electrical conductance and cryoscopic determination of molecular weight in nitrobenzene showed them to be monomeric non-electrolytes. Bose and Patel [8] prepared the Cu(II) nitrate and bromide complexes of 4-dimethylaminoantipyrine and characterized them by spectral studies. Prabhakaran and Patel [9] prepared antipyrine complexes of Fe(III) chloride and thiocyanate. The lowering value of the C=O stretch in IR spectra suggest coordination through the carbonyl oxygen to Fe(III). The largest group of Schiff-base metal complexes which have been synthesized and characterized represent complexes with 4-aminoantipyrine and its

derivatives with someb aldehyde, ketone etc. With respect to the applied methods and synthetic conditions of metal complexes bearing these ligands, practically all the complexes were obtained by the simple non-template method, i.e. by the reaction of ready-made ligands and metal salts, mainly in warm alcoholic solution under air.

Lanthanide perchlorate complexes with 4-N-(2-hydroxy-1-naphthalidene) aminoantipyrine,  $[\text{Ln}(\text{L})_2\text{ClO}_4]$  [where Ln = La(III), Pr(III), Nd(III) or Sm(III)] and  $[\text{Ln}(\text{HL})_4](\text{ClO}_4)_3$  [where Ln=Gd(III), Tb(III), Dy(III) or Ho(III)], have been synthesized and characterized [10]. Ni(II) complexes of 4-N-(2-hydroxy-1-naphthalidene) aminoantipyrine (1) and 4-N-(2-hydroxy-1-benzalidene)aminoantipyrine (2) were prepared by stoichiometric amounts of hot ethanolic solution of  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  and the ligand and sodium acetate in 1 : 1 ratio. The thermochromism in crystalline 1 and 2 has been attributed to dehydration of the complexes [11].

## **Experimental Methods**

### **Chemicals And Reagents**

Acetonitrile (HPLC) was purchased from SRL chemicals and used as received. Acetone (AR), chloroform (AR), N,N-dimethylformamide (AR), ethanol (commercial grade) and methanol (commercial grade) were purchased from Qualigens. Sulphuric acid (AR), p-cresol (AR), paraformaldehyde (AR) and perchloric acid (AR) were purchased from S.D Fine chemicals. Zinc (II) perchlorate hexahydrate and catechol (AR) were purchased from E-Merck and used as received. The commercial grade methanol and ethanol were refluxed for six hours with lime and distilled. The middle fraction was collected and used. Dimethylformamide was distilled azeotropically with benzene (10 % v/v, previously stirred over anhydrous  $\text{CuSO}_4$ ) at atmospheric pressure and distilled at 15-20 mm/Hg pressure.

### **Computational details**

All the computational calculations including representation of Highest occupied molecular orbital (HOMO) and Lowest unoccupied molecular orbital in the checkpoint files were performed with Gaussain 09 W program using density functional theory. The chemical structure of the compound was optimized with B3LYP/LANL2DZ basis set. The Gauss view software

### **Insilco Docking studies**

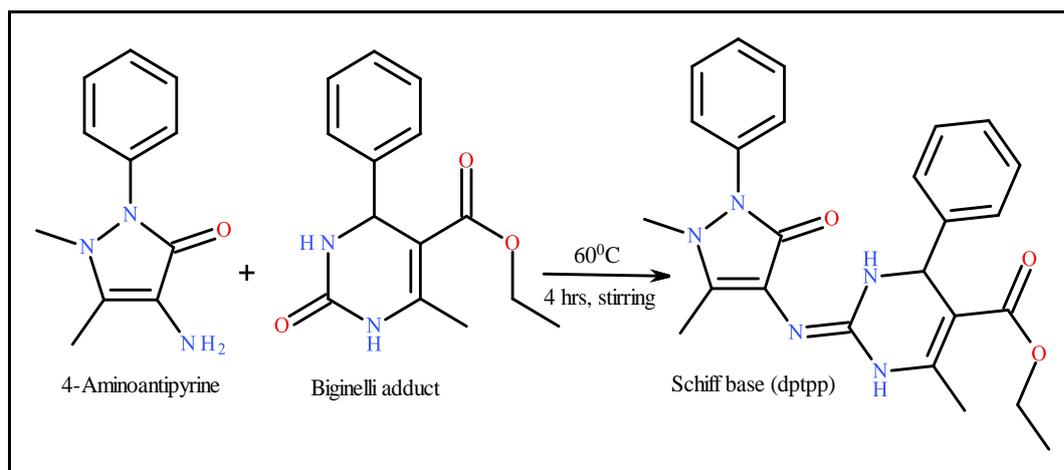
To investigate the potential binding mode of inhibitors, all the compounds were subjected to molecular docking using the AUTODOCK 1.5.6 docking program. Because of the critical roles of aberrant Signalling in cancer, BCL-2 (PDB id: Bcl-xl: 2YXJ) receptor is an attractive oncology target for therapeutic intervention. Ligand 2D structures were drawn using ChemDraw Ultra 8.0. Chem3D Ultra 8.0 was used to convert 2D structure into 3D and the energy minimized using semi-empirical MM2 method. Minimize energy to minimum RMS gradient of 0.100 was set in each iteration. All structures were saved as .pdb file format for input to Auto Dock-Tools (ADT) version 1.5.6. All the ligand structures were then saved in PDBQT file format, for input into AUTODOCK version 4.2.

For the molecular docking study, protein structure was obtained from the Protein Data Bank; For the protein structure, all hydrogen atoms were added, lower occupancy residue structures were deleted, and any incomplete side chains were replaced using the ADT version 1.5.6. Further ADT was used to remove crystal water, added Gasteiger charges to each atom, and merged the non-polar hydrogen atoms to the protein structure. The structures were then saved in PDBQT file format, for input into AUTODOCK version 1.5.4. A grid box with dimension of 60 X 60 X 60 Å<sup>3</sup> with 0.886 spacing and centred on 38.083, 46.914, 17.164 was created around the binding site of BCL-2 using Auto Dock Tools. For the AUTODOCK docking calculation, default parameters were used and 10 docked conformations were generated for each compound, the energy calculations were done using genetic algorithms. Docking of different ligands to protein was performed using AUTODOCK, same protocols used in as that of validation study. All docking were taken into 2.5 million energy evaluations were performed for each of the test molecules. Docked ligand conformations were analyzed in terms of energy,

hydrogen bonding, and hydrophobic interaction between ligand and receptor protein ALK. Detailed analyses of the ligand–receptor interactions were carried out, and final coordinates of the ligand and receptor were saved as pdb files. Docked structures were visualized using Discovery Studio Visualizer 2.5 (Accelrys Software Inc.). The free energy of binding (FEB) of all compounds were calculated.

## Result and Discussion

The Biginelli Adduct have been synthesized according to the reported procedure [28, 29] with 20 ml ethanolic solution of 4-aminoantipyrine (2.03g, 0.01mol) was added with constant stirring at 60°C for 4 hours. The precipitate was separated, filtered, re-crystallized with ethanol, and dried over anhydrous calcium chloride under vacuum to obtained E – ethyl 2- (2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazol-4-ylimino)-1,2,3,4-tetrahydro-6 methyl -4- phenylpyrimidine -5- carboxylate (dptpp) scheme 1. Yield 72%, Yellow solid, M.p. 232-234°C. The <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) spectra of dptpp shows multiplet at δ 6.10 to 7.52ppm (m,10H,Ar) due to phenyl group, -N-CH<sub>3</sub> at δ 2.3ppm(s,3H),=C-CH<sub>3</sub> at δ 1.72ppm(s,6H,2 =C-CH<sub>3</sub> ), CH<sub>3</sub> – CH<sub>2</sub> at δ 1.137-1.17ppm (t,3H), CH at δ 5.386-5.497ppm(d,1H,CH), CH<sub>3</sub>.CH<sub>2</sub> at δ 4.05 – 4.07ppm (q,2H), NH at δ 8.31ppm(s,br,1H). <sup>13</sup>CNMR 165.64(C-11,C-17), 153.36(C-10), 146.32 (C-9,C-16), 143.730(C-3), 133.013(C-18), 128.82(C-22,C-20), 128.709(C-19,C-23), 127.944(C-1,C-5), 127.57(C-2,C-4), 126.604(C-6), 119.760(C-21), 109.766 (C-15), 101.357(C-8), 60.24(C-12), 55.741(C-7), 35.09(C-24), 18.64(C-14,C-25), 14.135 (C-13). Anal.calcd. C<sub>25</sub>H<sub>27</sub> N<sub>5</sub>O<sub>3</sub>, C (66.89), H (6.08), N (15.87), found C (67.40), H (6.11), N(15.72). ESI-Mass: m/z (445).

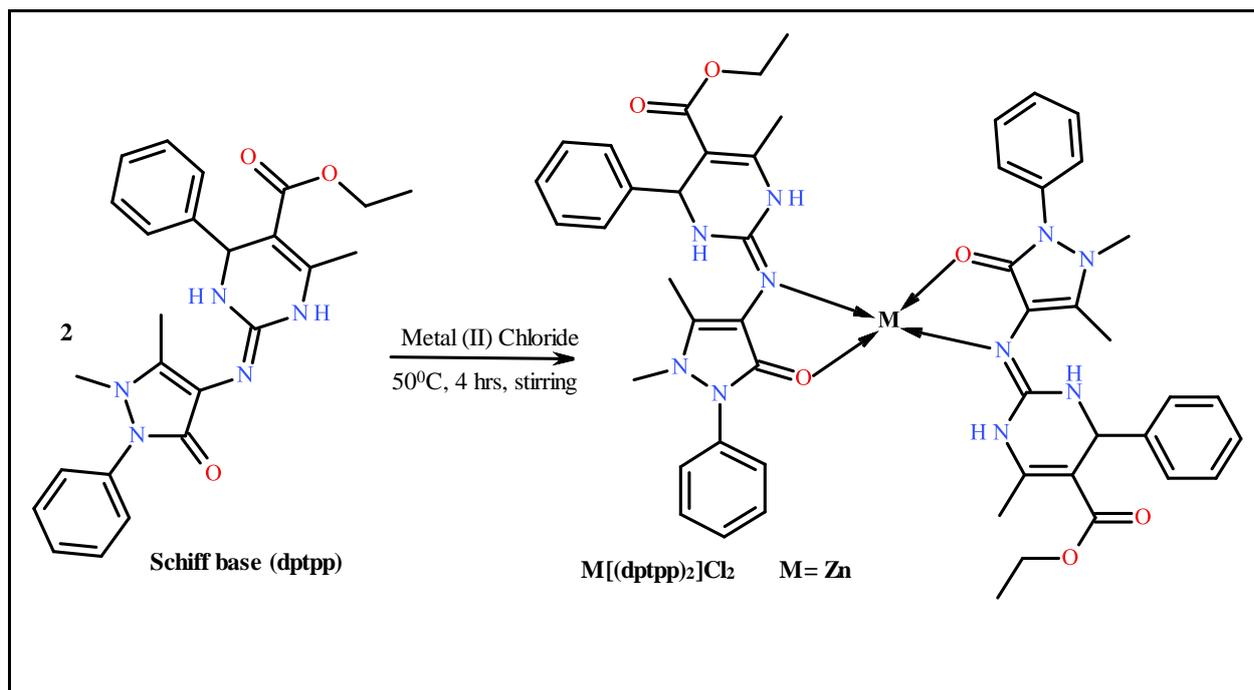


## Synthesis of Zinc (II) complexes

A solution of Zinc (II) chloride in ethanol (0.01mol) and hot ethanolic solution of Schiff base dptpp (0.02 mol) were mixed together in 1:2 ratio and refluxed for 4 hrs at 50 °C. The course of reaction was monitored by TLC. Colored solid metal complexes were precipitated after cooling, washed with ethanol and then with diethyl ether and dried. The pure product was then recrystallized with hot aqueous ethanol.

### [Zn (dptpp)<sub>2</sub>] Cl<sub>2</sub>

Yield: (78.6%). Colour: Light Yellow, Anal. Calc. for [Zn(C<sub>25</sub>H<sub>27</sub>N<sub>5</sub>O<sub>3</sub>)<sub>2</sub>]Cl<sub>2</sub> Zn(372.91): C, 58.33; H, 5.48; N, 13.60%; Found: C, 58.46; H, 5.30; N, 13.63%. Selected IR data (KBr, ν/cm<sup>1</sup>): 1615 ν (C=N), 1699 ν (C=O), 3425 ν (N-H), 602 ν (M-O), 528 ν (M-N), 1028 & 760 ν (Aromatic) UV-Vis (DMF) λ/nm (transition, ε/M<sup>1</sup> cm<sup>1</sup>): 401 (INCT,-----), 320 (INCT, -----), ESI-(m/z): 1027 [Zn (dptpp)<sub>2</sub>]<sup>+</sup>.



## Result and Discussion

The synthesized  $[\text{Ni}(\text{dptpp})_2]\text{Cl}_2$  complex in the air were stable at room temperature and soluble in common organic solvents and insoluble in water. The low conductance of the complexes in DMSO supports the (1:2) non-electrolytic nature of the metal complexes [31]. Generally the IR spectra of the free ligand showed a broad band around  $3425\text{ cm}^{-1}$  which could be attributed to NH stretching Vibration of benzimidazole moiety. The position of this band remained at nearly the same frequency in the spectra of the metal complexes suggesting the non-Coordination of the NH group [32-33]. A comparative study of IR spectra of ligand and their metal chelates revealed that certain peaks are common and therefore, only the important peaks, which either shifted or newly appeared, are discussed. The frequency stretching of  $\text{V}(\text{C}=\text{O})$  in the region  $1702\text{ cm}^{-1}$  in the ligand is shifted to lower frequency ( $1699\text{-}1654\text{ cm}^{-1}$ ) in the complexes. The frequency corresponding to  $\text{V}(\text{C}=\text{N})$  at  $1647\text{ cm}^{-1}$  is shifted to lower frequency ( $1642\text{-}1599\text{ cm}^{-1}$ ) in the complexes [34]. The spectra of metal complexes also show some new bands in the  $615\text{-}580\text{ cm}^{-1}$  and  $535\text{-}417\text{ cm}^{-1}$  which are probably due to the formation of  $\text{V}(\text{M}-\text{O})$ ,  $\text{V}(\text{M}-\text{N})$  bond respectively [ 35, 36 ]. The (UV-Vis) spectra of the Ligand displayed absorption at the range of (286-301) nm which was assigned to the ligand field [37]. The absorption maxima of the metal chelates bare had resemblance with the free ligands which indicates that no structural alteration of the ligand has occurred during complexation. However the values shifted slightly to longer wavelength indicating the involvement of the nitrogen and oxygen molecules in metal complexation. The electronic structures of square planar complex indicate that the electronic energy levels vary according to the nature of the ligand [38- 40]. The observed diamagnetism and broad medium band at (426)nm in the spectrum of  $[\text{Zn}(\text{dptpp})_2]\text{Cl}_2$  complex gives only charge transfer in the range ( $25000\text{-} 3421\text{ cm}^{-1}$ ) due to the ( $d^{10}$ ) configuration the metal ions, suggesting tetrahedral structure to  $[\text{Zn}(\text{dptpp})_2]\text{Cl}_2$  complex. The magnetic susceptibility showed complexes were diamagnetic [43, 44]. In each fundamental  $\text{ML}_2$  unit, the metal ion is simultaneously bonded to nitrogen and oxygen of the 2 units of bidentate ligands. The proposed structure of the complexes, supported by the electronic spectral data is shown in Scheme-2.

## Geometry optimization

DFT calculation gives more information about structural perspectives, without crystal data, and also which provides the energy minimized conformation. Moreover, DFT calculation is a tool of expanding significance for

the structural investigation of coordination and organometallic complexes. Taking into account, the present complexes were optimized at B3LYP/LANL2DZ levels in gas phase, and the optimized ground state geometry structures are shown in Fig. 1 and Fig.2. The four coordinated  $[Zn(dptpp)_2]Cl_2$  complex coordinate through two carbonyl oxygen and two imine nitrogen atoms.

The observed M-O bond length values of  $N_2O_2$  donors containing complexes observed in the range from 1.81224 to 1.810971 Å as well as M-N bond length values are in between and 1.93831 to 1.93072 Å of Zn (II) complex.

The frontier molecular orbital's called Highest occupied molecular orbital (HOMO) and Lowest unoccupied molecular orbital (LUMO). The HOMO represents the ability to donate an electron, LUMO as an electron acceptor represents the ability to obtain an electron. These orbital's play an important role in the electric properties and determine the way of molecules interacts with other species. Both HOMO and LUMO are the main orbital taking part in chemical reactions/stability. While the energy of the HOMO is directly related to the ionization potential, LUMO energy is directly related to the electron affinity. Also, the frontier orbital gap between HOMO and LUMO, represents stability of structure. The HOMO and LUMO energy gap of ligand 2.0413 in Fig.3 and 4. Zinc complex are -0.753eV. A small HOMO-LUMO gap implies a low kinetic stability and high chemical reactivity as it is energetically favourable to add electrons to LUMO or to extract electrons from a HOMO.

#### **Global reactivity descriptors**

The energy difference between the HOMO and LUMO, energy gap for Zn complex is the maximum (0.753 eV). As a result, charge transfer and polarization can easily occur within the Zn complex than ligand with more reactivity. The chemical hardness,  $\eta$ , electronegativity,  $\chi$ , and global softness, S, were calculated using HOMO and LUMO energies and listed in Table 1. Zn complex has the lowest  $\eta$  and maximum S values which means that the charge transfer occurs easily in this complex and has a lower chemical hardness. It can be concluded that the large Eg gap indicates a hardness of the molecule, while smaller Eg gap is a characteristic for a soft and reactive molecule. Therefore, charge transfer and polarization can easily occur within the Zn complex than the other complexes due to its higher reactivity. The computed reactivity parameters shown in Table 1 reveals that Zn complex has the lowest  $\eta$  and maximum S values which means that the charge transfer occurs in this complex and has lower chemical hardness. A molecule of electrostatic potential map provides information about the electron acceptor and electron donor regions. The different values of the MEP at the surface are represented by different colors, red represents regions of most electro negative electrostatic potential, oxygen and nitrogen atoms have more negative charges. Most likely this region as recognized the docking results oxygen and nitrogen atoms have some interaction with the hydrogen bond receptor. The blue represents regions of most positive electrostatic potential were mainly distributed over the aromatic group which result hydrophobic interaction in Fig. 5.

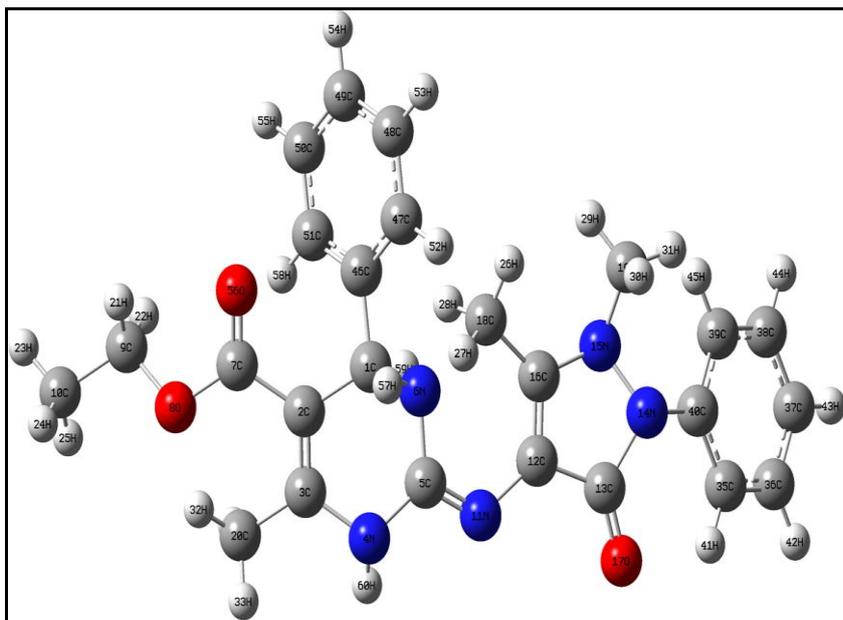


Fig. 1. Optimization structure of the ligand (dptpp)

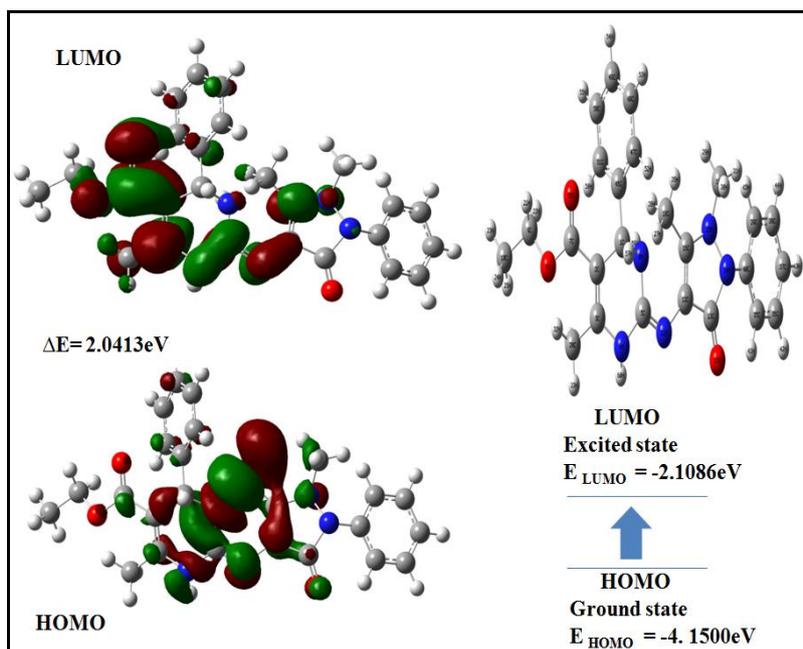


Fig. 2. Density functional of the ligand (dptpp)

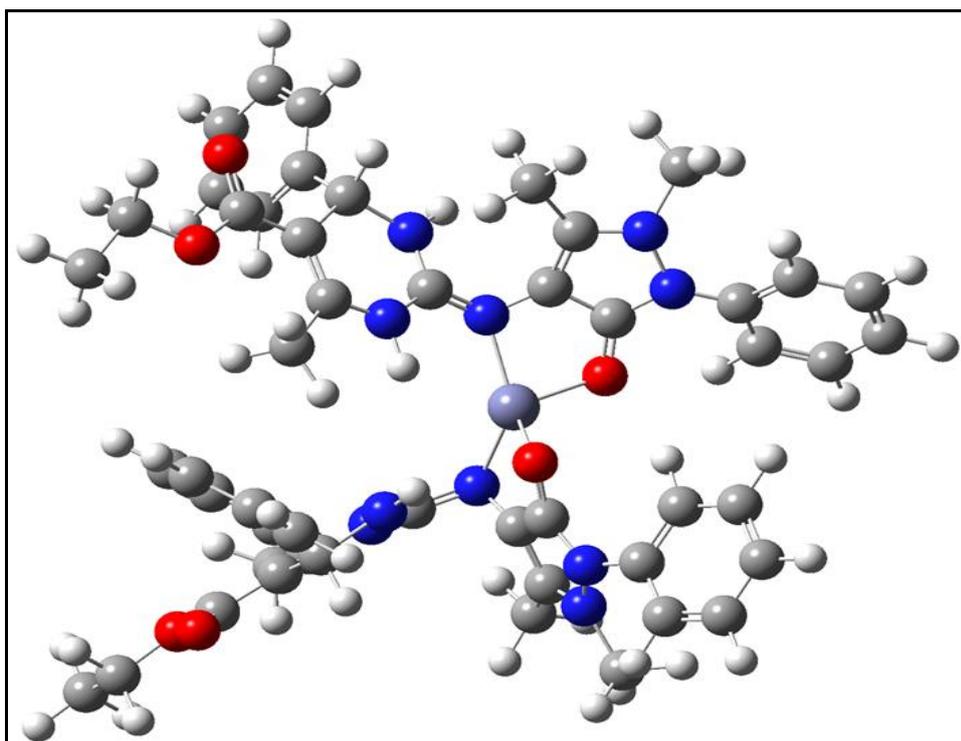
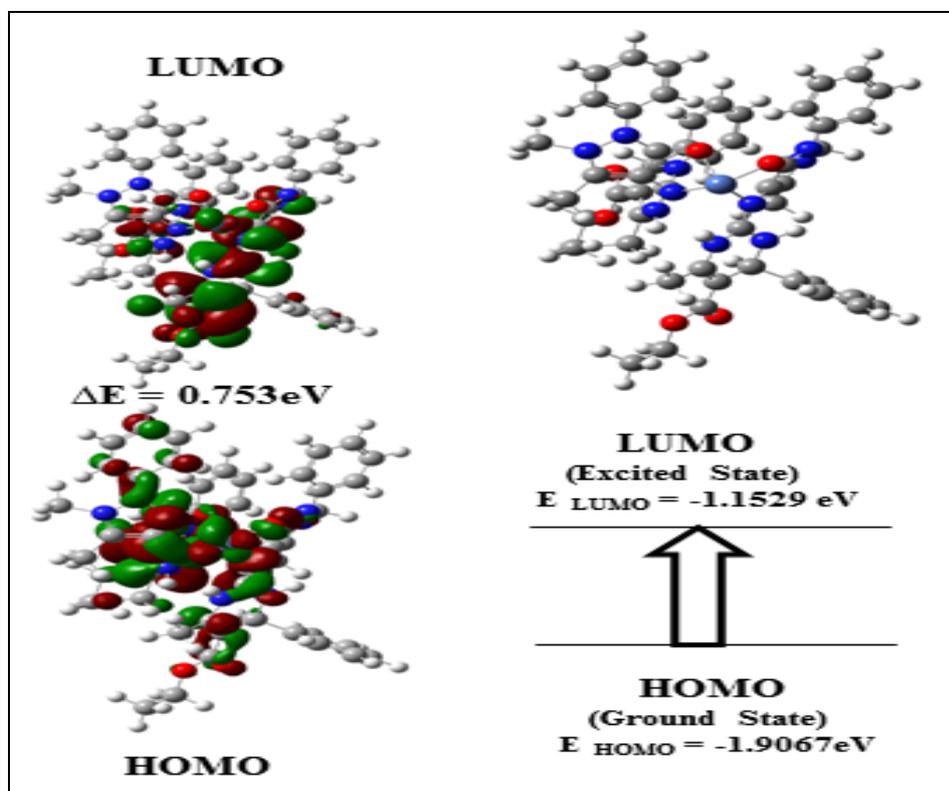


Fig. 3. Optimization structure of the Zn (II) complexes



Density functional of the Zn (II) complexes

Table 1 Global reactivity descriptors of the studied 1:2 complexes using B3LYP level.

Parameter (eV)	Ligand (dptpp)	Zn (II) complex
$E_{\text{HOMO}}$	-4.1500	-1.9067
$E_{\text{LUMO}}$	-2.1086	-1.1529
$E_g$ ,	2.0413	0.7530
I	4.1500	1.9067
A	2.1086	1.1529
$\chi_s$	3.1293	1.5298
S	0.5103	0.1884
$\eta$	1.0207	0.3769

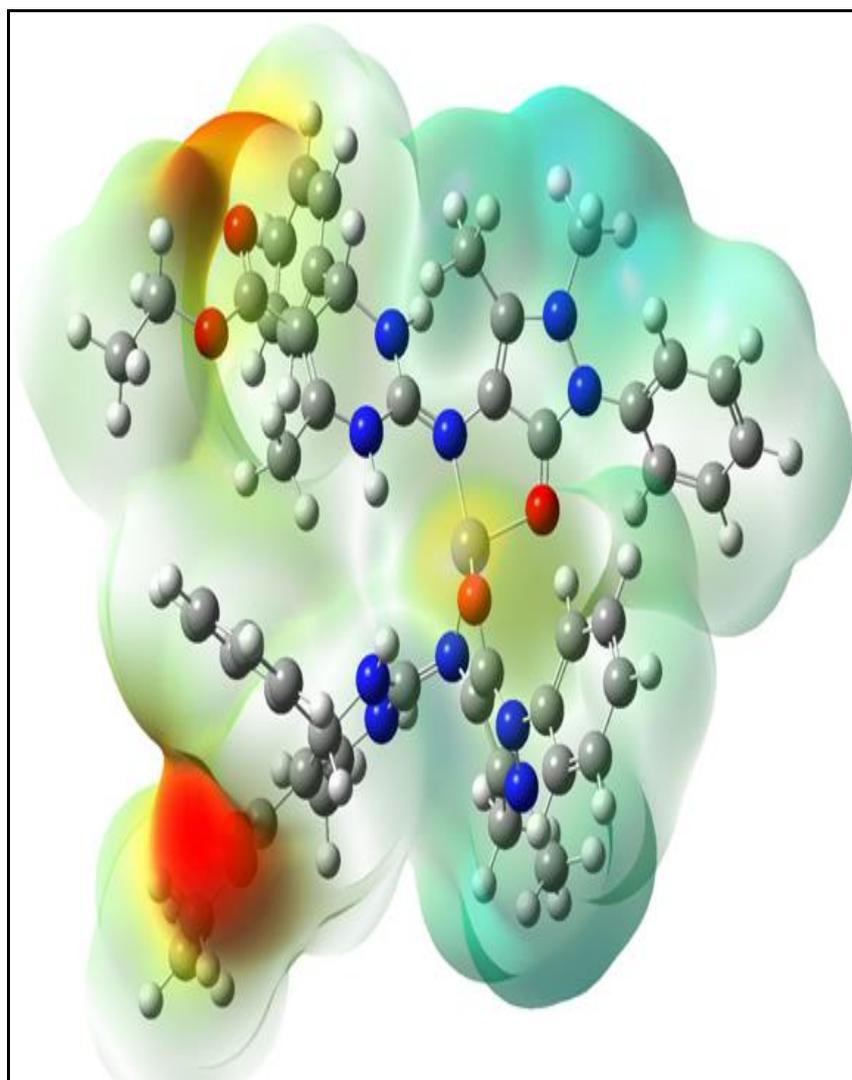


Figure 5. Electrostatic potential mapping on the electron density of Zn (II) complexes

### Conclusion

The synthesis, characterization and biological activities of novel  $\text{Zn}(\text{dptpp})_2\text{Cl}_2$  complexes, obtained using the ligand dptpp [dptpp is 2E-ethyl 2- (2,3-dihydro-1,5-dimethyl -3-oxo-2- phenyl- 1H- pyrazol-4-ylimino)-1,2,3,4-tetrahydro-6 methyl-4-phenyl pyrimidine-5-carboxylate. The  $\text{Zn}(\text{dptpp})_2\text{Cl}_2$  complexes were synthesized via condensation of 4-aminoantipyrine with Biginelli Adduct and characterized on the basis of spectral (FTIR,

NMR, ESI-mass and UV–visible), elemental analysis, thermal and molar conductivity measurements. The ground state electronic structures of  $Zn(dptpp)_2Cl_2$  complexes were investigated by DFT/B3LYP theoretical analysis using 6-311G++(d,p) and LANL2DZ basis set level. The molecular docking studies showed that complex  $Zn(dptpp)_2Cl_2$  strongly binds with BCL-2 receptor. The results indicate that the metal complexes are more active as compared with the ligand.

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