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Research Article

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Synthesis, Characterisation and Docking Studies of Metal (II) Complexes of Anti-inflammatory Drug Celecoxib

E Vadivel* and Karuna Umakant Korgaonkar

Postgraduate Chemistry Department, Dnyanprassarak Mandal`s College and Research Center, Assagao-Bardez, Goa, India

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ABSTRACT

Co-ordination chemistry provides better opportunities to use metal complexes as therapeutic agents. These Co-ordination compounds show a wide variety of therapeutic action. Metal coordination can be used to improve the activity of biologically active molecules. Novel complexes of Cu(II), Co(II) and Ni(II) with Celecoxib (L) have been synthesized and characterized. The Celecoxib have a great attention because of its anti-inflammatory activity. The Celecoxib complexes were characterized by molar conductance, FTIR and UV-Vis. spectroscopy. Investigations of the infrared spectra of the celecoxib and their metal complexes indicated the vibrations due to–NH group are shifted with respect to the free molecule in line with their coordination to the metal. These complexes are formulated as [M(L)Cl$_2$]. The molecular docking study of metal complexes was performed by using Autodockvina against Cyclooxygenase-II enzyme. The docking study revealed that metal complexes are potential inhibitors of inflammation.

Keywords: Celecoxib; Metal complex; Molecular docking; Cyclooxygenase II; Antodockvina

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INTRODUCTION

The development of structurally novel coordination compounds with diverse biological activity, such as antimicrobial, anti-inflammatory, antifungal, antioxidant and anticancer, is a rapidly evolving field of Inorganic Chemistry with potential for direct impact on improving quality of life [1]. Metal-drug complexes are of increasing interest in Bioinorganic Chemistry, leveraging the synergistic effect of the metal to lead to compounds with improved pharmacological activity [2].

Cyclooxygenases (COX) is an important enzyme in the synthesis of prostaglandins, the main mediators of inflammation, pain and increased body temperature. Prostaglandins are formed from their precursor, arachidonic acid. Arachidonic acid is cleaved from cell membrane phospholipids by phospholipase A2. COX Convert arachidonic acid into unstable endoperoxides PGG2 and PGH2. After that PGG2 and PGH2 are metabolized by synthases to primary prostaglandins PGD2, PGE2, PGF2α, TXA2 (thromboxane A2) and PGI2 (prostacyclin). Prostaglandins (PGs) are the lipid mediators made by most cells in the body except by red blood cells and released upon almost any type of chemical or mechanical stimulus [3].

Celecoxib is a COX-2 selective nonsteroidal anti-inflammatory drug (NSAID). This drug is still among the most widely used drugs in the world. It is effective in the treatment of pain and inflammation [4]. Celecoxibis a 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide. It is used to treat the pain and inflammation ofosteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute painin adults, painful menstruation, and juvenile rheumatoid arthritis in people two years or older. In the present study, celecoxib metal complexes were synthesized and were docked with Cyclooxygenase II enzyme [5].

MATERIALS AND METHODS

Celecoxib was obtained from Centaur Pharmaceuticals as a gift sample. All the other solvents, reagents and chemicals used were of analytical grade (Figure 1).

Molar conductivities of freshly prepared 1 × 10^{-3} mol/dm^{-3} DMSO solutions of celecoxib and its complex were measured using Eaquiptronics conductometer. The IR spectra of the celecoxib and their metal complexes were recorded

on a Shimadzu FTIR (IR AFFINITY1) spectrophotometer in 4000-200 cm-^{1} range using KBr disc. The electronic absorption spectra of the Schiff bases and their Metal complexes in the range 200-1100 nm in a suitable solvent were recorded on a UV–Vis spectrophotometer (UV 3000+Make LAB INDIA). Absorbance values were plotted against the corresponding wavelengths. The spectra of the complexes were recorded using DMSO as a solvent.

The docking was carried out in Autodockvina software. The two-dimensional (2D) chemical structures of the ligand and its metal complex were sketched using Mervin sketch and converted to pdb using Chem3D Ultra. For docking study, the protein was downloaded from Protein Data Bank website and software's like Discovery studio 4.0 client and PyMol were used to find the intermolecular interaction.

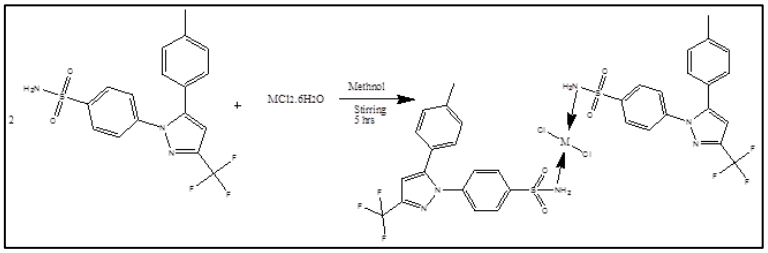

Figure 1: Synthesis of metal complexes from Celecoxib drug (L)

It was prepared by a general synthetic method in which methanolic solution (20 ml) of 1 mmol of metal salts was added to the methanolic solution of 2 mmol celecoxib in a 1:2 molar ratio which was stirred for 5 hrs. The completion of the reaction was monitored by TLC using solvent system Ethyl acetate: Pet ether (2:8). On completion, the reaction was poured into crushed ice. The solid obtained was filtered and washed with water. The product was further recrystallized using methanol.

Molecular Docking

Binding mode and interaction of cyclooxygenase with individual chemical celecoxib ligand and its metal complex was performed using AutoDockVina software. Docking was performed to obtain a population of possible conformations and orientations for the ligand at the binding site.

Cyclooxygenase II enzyme with protein code: 3nt1 was chosen for the docking studies because of its high resolution (1.73 Å) and also it consists of two chains A and B. The chain B was chosen for docking it contains natural ligand naproxen. The protein was loaded in Autodock 4.2 software, creating a PDBQT file that contains a protein structure with hydrogens in all polar residues. All bonds of ligands were set to be rotatable. The docking site on protein target was defined by establishing a grid box with the dimensions of X: 60 Y: 60 Z: 60 Å, with a grid spacing of 0.4 Å, centered on X: -49 Y:-37 Z: -65 Å. The best conformation was chosen with the lowest docked energy after the docking search was completed. Eight runs with AutoDockVina were performed in all cases per each ligand structure, and for each run the best pose was saved. The interactions of complex cyclooxygenase protein-ligand conformations, including hydrogen bonds and the bond lengths were analyzed using Discovery studio 4.0 client [6].

RESULTS AND DISCUSSION

All the metal complexes are colorless solids and are stable towards air and have high melting points (above 2500°C). The complexes are insoluble in water and common organic solvents but are partly soluble in DMSO.

Further, confirmation of the proposed structures of Celecoxib (L) with metal salts was done using different Analytical and Physico–chemical methods (Table 1).

Table 1: Analytical and physical-chemical data of Celecoxib and its metal complex

Compound	Formula	Molar conductivity (Ω-1cm^{2}mol-1)	N-H	M-N	M-Cl	Cl test
Celecoxib [L]	C17H14N3SO2F3	7.35	3334	-	-	
[Cu LCl_2]	$C_{34}H_{28}CuN_6F_6Cl_2S_2O_4$	7.7	3232	466	318	+
[Ni LCl_2]	$C_{34}H_{28}NiN_6F_6Cl_2S_2O_4$	8.85	3232	462	320	+
[Co LCl_2]	$C_{34}H_{28}CoN_6F_6Cl_2S_2O_4$	7.74	3336	460	318	+

Molar conductance (ΛM) measurements of the ligands and its metal complexes were carried out using DMSO as the solvent at the concentration of 10^{-3} M, Ligands and metal complexes indicate non-electrolyte behavior and conductivity values were found in the range 7-9 Ω^{-1} cm^{2} mol^{-1} (Table 1). The results were coinciding with the Chloride test, which means that chloride is present in the lattice NMR of ligand.

The IR spectrum of the ligand (Table 1) display sharp bands present in the region ~3334 cm^{-1} is due to N-H stretching frequencies. The N-H group of the free ligand was shifted to frequency 3232 cm^{-1} and 3336 cm^{-1} in the complexes confirms the coordination of the Nitro atom to the metal ion. The new bands appeared in the regions, 466 cm^{-1}, 462 cm^{-1}, 460 cm^{-1} and 448 cm^{-1} is due to the formation of M-N bands. And bands appeared at 318 cm^{-1}, 320 cm^{-1} and 328 cm^{-1} may be because of the M-Cl bands.

The electronic spectra of ligand and their complexes (Table 2) were displayed in DMSO. The spectra of complexes are dominated by intense intra-ligand charge transfer bands. The spectrum of L2 shows an intense absorption band at 33,783 cm^{-1} region assigned to n→π* transition of azomethine groups.

In addition, there was a high-intensity band in the region 26178-26881 cm^{-1}. This band is due to symmetry forbidden ligand → metal charge transfer transition. The band above 33783 cm^{-1} was assigned as ligand band.

Table 2: Electronic spectra of Celecoxib (L) and its complex

Compound	Absorption	Geometry	Band assignment
Celecoxib (L)	33783 cm^{-1}(296 nm)	-	n JI*
[Ni LCl_2]	33783 cm^{-1}(296 nm)	-	n JI*
	26178 cm^{-1}(382 nm)	LMCT	n JI*
	20283 cm^{-1}(493 nm)	Square planar	^{3}A1g ^{3}B1g
[Cu LCl_2]	33783 cm^{-1}(296 nm)	-	n JI*
	26881 cm^{-1}(372 nm)	LMCT	n JI*
	21052 cm^{-1}(475 nm)	Distorted square planar	^{2}B1g ^{2}A1g
[Co LCl_2]	33783 cm^{-1}(296 nm)	-	n JI*
	26666 cm^{-1}(375 nm)	LMCT	n JI*
	21276 cm^{-1}(470 nm)	Distorted square planar	4A2(F) 4T1(F)

From the above data, thus the complexes may be formulated as follows:

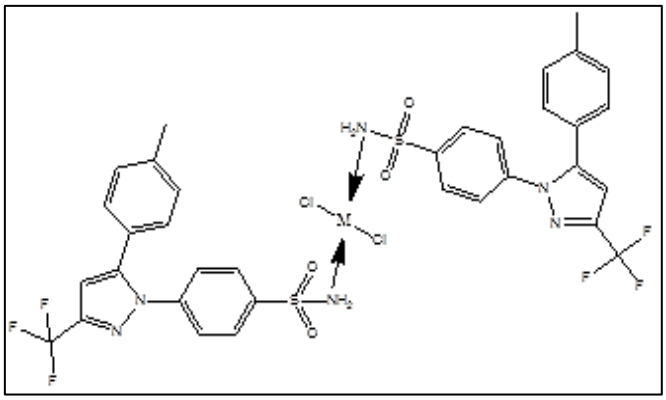

Figure 2: Structure of formulated complex (M=Cu, Co, Ni)

Docking Studies

Table 3: Binding affinity of Celecoxib and its metal complex with Cyclooxygenase-II

Compound	Binding affinity (kcal/mol)
Celecoxib [L]	-7.9
[Cu LCl_2]	-8.1
[Ni LCl_2]	-8.8
[Co LCl_2]	-7.1

The ten different orientations of the celecoxib and its metal complex to the receptor Cyclooxygenase II were carried out. The binding energy of the best orientation of the celecoxib and its metal complex are presented in Table 3. The binding affinity [7-9] of copper and nickel complexes is higher than that of the celecoxib whereas cobalt metal complex showed less binding affinity than celecoxib (Figure 2).

Table 4: Hydrogen bonding interactions of Celecoxiband its metal complexes with Cyclooxygenase-II (D.I – Direct interaction; W.M – water-mediated interaction)

Compound	Atom of Compound Involving Interaction	Amino Acid Residue Involving Interaction	Atom Amino Acid Residue Involving Interaction	Type of Interaction	Distance (A°)
Celecoxib [L]	Hydrogen	TRY115	Oxygene	W.M (2.28)	2.05
	Hydrogen	SER119	Oxygene	D.I	2.38
[Cu LCl_2]	No interaction	-	-	-	-
[Ni LCl_2]	No interaction	-	-	-	-
[Co LCl_2]	Fluorine	LEU111	Oxygene	W.M (2.92)	3.03

The hydrogen bonding and hydrophobic interactions [10,11] of the best orientations are presented in Table 4 and Table 5 respectively and in Figure 1. Celecoxib with cyclooxygenase-II showed two hydrogen bonding with amino acid TRY 115 and SER 119 water-mediated hydrogen bonding and direct interaction respectively. There is no hydrogen bonding in Copper and Nickel complexes. Cobalt complex showed only one weak water-mediated hydrogen bond with LEU111.

Table 5: Hydrophobic interactions of celecoxib and its metal complexes with Cyclooxygenase-II

Compound	Hydrophobic Interaction of Compounds with Cyclooxygenase-II (Distance A°)										
	TRY 115	**TRP 110**	**PRO 84**	**ILE 92**	**ILE 112**	**LEU 108**	**LEU 111**	**VAL 89**	**PHE 96**	**VAL 99**	**VAL 116**
Celcoxib [L]	4.45	5.35		4.89	4.91	-	4.89	5	-	-	3.66
[Cu LCl_2]	4.07	-	5.42	3.87	5.42	-	4.37	-	-	-	-
[Ni LCl_2]	-	-	4.72	5.08	4.86	-	-	4.74	3.8	3.66	-
[Co LCl_2]	5.07	5.19	5.01	5.18	5.48	5.33	-	5.18	-	-	-

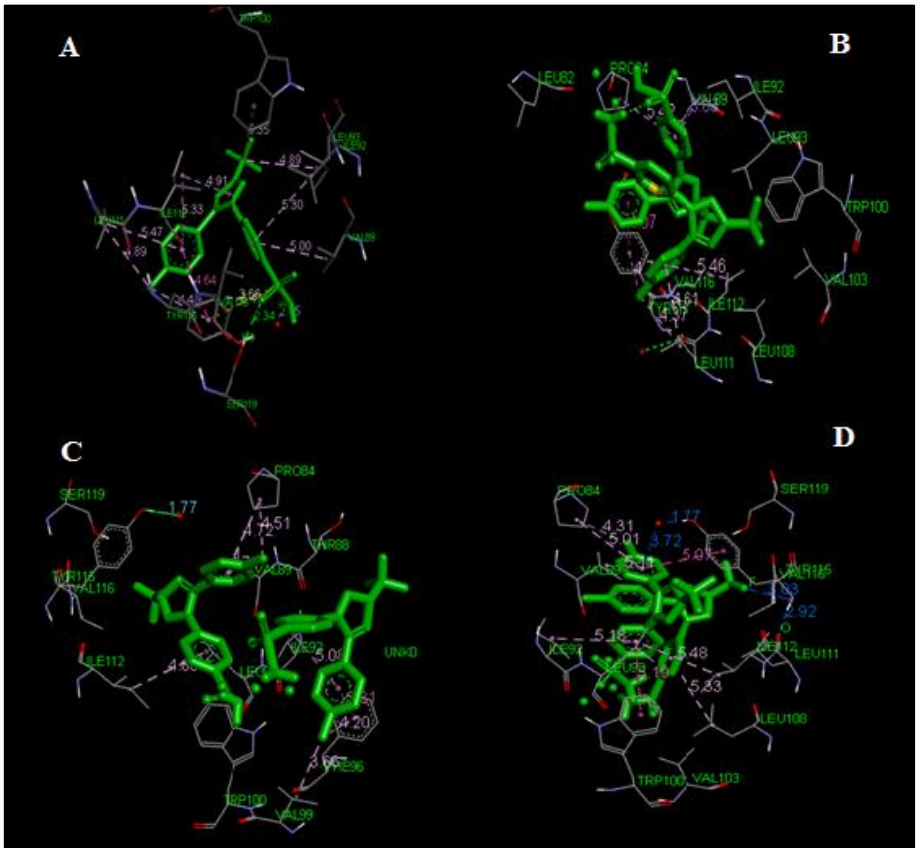

Figure 3: Hydrogen bonding and hydrophobic interaction of Celecoxib and its metal complex with Cyclooxygenase II(A) Celecoxib (L);(B) [Cu LCl_2];(C) [Ni LCl_2];(D) [Co LCl_2]

The hydrophobic phenyl ring and pyrazole ring of the celecoxib and its metal complex was surrounded by active site amino acid residues TRY 115, TRP 110, PRO 84, ILE 92, ILE112, LEU108, LEU111, VAL89, PHE96, VAL 99 and VAL 116. The hydrophobic interactions of celecoxib and its metal complex with cyclooxygenase II is very higher than the hydrogen bonding interaction (Figure 3).

CONCLUSION

Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. The goal of ligand-protein docking is to predict the predominant binding model(s) of a ligand with a protein of known three-dimensional structure. The present study concludes that Nickel metal complex of the celecoxib is found to be most active against Cyclooxygenase II enzyme. The results indicate that the molecular modelling is a valuable tool for predicting the biological activity of metal complex. The analysis of the docking result allowed us to know the efficiency of the metal complex to control inflammation.

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