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Research Article

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Cd(II) Mixed Ligand Complex Containing 2-Aminothiazole and Triphenylphosphine; Synthesis, Spectral, DFT and Biological Activity Studies

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ABSTRACT
Mixed ligand Cd(II) complex containing phosphine and 2-aminothiazole ligand have been synthesized and their structures was elucidated using a various physico-chemical techniques. The mixed liagnd complex are screened for their pharmaceutical activity followed by antimicrobial and antioxidant. These studies showed interesting results and therefore their insilco molecular docking interaction of the complex with antimicrobial receptor 1STE studied. The result concludes that the complex having good docking interactions with amino acid residues of the receptor 1STE.

KEYWORDS: Antimicrobial activities; molecular docking studies; MIC level; Antioxidant activity.

INTRODUCTION

Cadmium is a highly toxic metal and a potent carcinogen. However, its mechanism of action still unclear. Complexes containing sulphur are of great importance from a bioinorganic point of view, mainly due to the presence of thiolate donors in the coordination sphere of many metal ions in very diverse metalloproteinase [1-4]. The coordinative behaviour of cadmium(II) is typical of a soft acid. This fact is its strong interactions with S^{2-} and HS^{-} groups leading to the formation of highly stable complexes. Cd^{II} is able to substitute Zn^{II} in the active site of several Zn-enzymes and to interfere with the metabolism of Ca^{II}. Therefore, interest has been devoted in the past decade to the coordination chemistry of cadmium. The coordinative behaviour of the cadmium(II) ion resembles that of mercury(II) and in a lesser extent of zinc(II). The main coordination numbers observed for Cd^{II} are 4, 5 and 6. Owing to the larger size, Cd^{II} assumes coordination number 6 more easily than Zn^{II} [5]. Metal complexes of biologically vital ligands are often more active than the free ligands [6]. Particularly phosphine based cadmium(II) complex has been reported to possess significant bioactivities [7, 8]. The presence of nitrogen and sulphur in these complexes can enhance antitumor, antibacterial and antifungal activities of transition metal complexes [9]. The interaction phases and the geometric position of

the transition metal ion in ligand chelation environment serve as models to enzyme containing metal ion [10].

In this context, an attempt has been made to synthesize a pharmacological active new mixed ligand Cd(II) metal complex. The antimicrobial activity, antioxidant activity, molecular docking and DFT studes of the Cd(II) complex have been evaluated.

MATERIALS AND METHODS

General Experiments

All the chemicals used in the present study were of AR grade. When they were not available, laboratory grade chemicals were purified and used. Dimethyl formamide and dimethylsulphoxide solvents were of spectroscopic grade and remaining solvents were of AR grade. The following were purchased from E. Merck (India), cadmium(II) chloride hexahydrate, triphenylphosphine (pph_3), aminothiazole(Ath) anhydrous calcium chloride and the mineral acids such as hydrochloric acid, sulphuric acid and nitric acid were employed as a drying agent at various stages for purification which were of Analytical Reagent grade obtained from S.D. Fine Chemicals Ltd. (India).

The other solvents used acetone, diethyl ether, and ethanol was purified according to the known procedures before use. Elemental analysis was done on a Perkin-Elmer Model 240-C CHN or on a Perkin-Elmer Model 2400 CHNS analyser. Acetanilide was used as a reference standard. The molar conductivities of the complexes in dimenthylformide (DMF) solution (10^{-3} M) at room temperature was measured using a direct reading conductivity meter. Infrared spectra of compounds were recorded using SHIMADZU FTIR –8400S. Bruker FT-NMR Spectrophotometer (400 MHz) was used for recording ^1H NMR spectra employing TMS as internal reference and DMSO-d_6 as solvent at ambient temperature.

PROCEDURE FOR SYNTHESIS OF MIXED LIGAND COMPLEX

Cadmium(II) chloride (1 mM) was dissolved in hot ethanol (10 mL) and mixed with ethanolic solution of triphenylphosphine (1 mM, 10 mL). The reaction mixture was refluxed on water bath for about 30 min, then the ethanolic solution of 2-aminothiazole (1 mM, 10 mL) was added and continued refluxing for 4-6 h [11]. The dark colored crystalline solid thus formed was collected by filtration, washed twice with hot ethanol (10 mL) followed by ether (10 mL) and dried under vacuum. Then recrystallized from ethanol (Fig.1). $C_{21}H_{19}CdCl_2N_2PS$ (545.94), elemental analysis cal (found), C - 46.32 (46.22), H- 3.58(3.51), N - 5.18 (5.13), M- 20.71 (20.60)

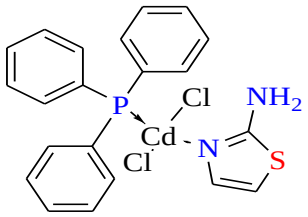

Fig. 1: Proposed structure of metal complex

ANTIMICROBIAL ACTIVITY

Antibacterial screening

The antibacterial activity of the metal complex was tested against five different bacteria namely *Staphylococcus aureus, Staphylococcus epidemidis, Bacillus cereus, Pseudomonas aeruginosa, Vibrio cholerae* and *Escherichia coli* by agar well diffusion method. Twenty four old Muller-Hinton broth cultures of test bacteria were swabbed on sterile Muller-Hinton agar plates using sterile cotton swab followed by punching wells of 9 mm with the help of sterile cork borer. The standard drug (chloramphenicol, 100 µg/mL of sterile distilled water), three different concentrations (100, 50 and 25 µg /mL in 10% DMSO) and control (10% DMSO) were added to respective labelled wells. The plates were allowed to stand for 30 min. and were incubated at 37 ºC for 24 h in upright position and the zone of inhibition was recorded [12]. During this period, the test solution diffused and zone of inhibition were recorded using vernier callipers.

Antifungal screening

Antifungal activity of the metal complex was evaluated against *Aspergillus aureus* and *Aspergillus fumigates* fungus, using the

sabouraud dextrose agar diffusion method [12]. Wells were made (9 mm diameter) with a sterile cork borer. The standard drug (Fluconazole, 100 µg/mL of sterile distilled water) and control (10% DMSO) were added to respectively labelled wells. To these wells 140 µl from each (100, 50 and 25 µg/mL in 10% DMSO) of the test stock solution compounds were added and the plates were allowed to cool for an hour to facilitate the diffusion. The plates were then incubated at 37 ºC for 48 h. At the end of the incubation period, the diameter of the zone of inhibition around the wells was measured using vernier callipers.

Molecular docking studies

Molecular docking has been done by following the literature method [13]**.** For macromolecular docking studies, the chemical structures of synthesized metal complex and standard S. aureus Gyrase complex with Ciprofloxacin were drawn using ChemDraw ultra. The 3D optimization was done in ChemDraw 3D ultra software and stored as .pdb file. Hex docking was carried out by setting suitable parameters this docking score can be interpreted as interaction energy. More negative E-Total value implies that there exists a strong interaction between drug and receptor and that leads to inhibition of receptor activity. The insilico molecular docking has been carried out on the antibacterial receptor on PDB code: 1STE, the crystal structure of the receptor has been obtained from the protein data bank and the all the water molecules and heteroatoms are removed before screened for docking studies.

Antioxidant activity

This activity for the synthesized Cd(II) complex was performed using DPPH method as per literature [14]. The compounds of different concentrations were dissolved in methanol and were introduced to each vials of 5mL. To this test vials 3 ml of 0.004% DPPH in methanol was added and the mixtures have been incubated in dark condition at ambient temperature for 30 min. Ascorbic acid is used as the standard. The absorbance reduced while the DPPH is scavenged by way of an antioxidant, through contribution of hydrogen to shape a strong DPPH molecule. DPPH scavenging activity calculated by the use of the following equation and absorbance measured at 517 nm.

Scavenging ratio (%) = [(Ai–Ao) / (Ac–Ao)] × 100%

Where,

Ai is the absorbance within the presence of the check compound.

Ao is absorbance of the clean inside the absence of the check compound.

Ac is the absorbance within the absence of the test compound.

RESULTS AND DISCUSSION

Chemistry

Synthesis of mononuclear mixed ligand Cd(II) complex was achieved by mixing stoichiometric amounts of 2-aminothiazole and triphenylphosphine (Fig. 1). The metal complex is amorphous in nature and soluble in DMSO and DMF. The composition of the complex was confirmed by spectroscopic analysis. The analytical data of the compound are consistent with their proposed molecular formula. The molar conductivities of 10^{-3} M of the complex (dissolved in DMF) at room temperature was measured and it was found that the value 3.29 $\Omega^{-1}mol^{-1}cm^2$. Melting point found was 193-198 ºC. Yield: 65 %. The elemental analyses of the Cd(II) complex was consistent with the calculated results from the empirical formula. Elemental analysis (%) found (Calculated) $C_{21}H_{19}Cl_2N_2CdPS$: C - 51.81 (51.22), H - 4.13 (3.89), N - 5.69 (5.01), Cd -12.92 (12.99). $C_{21}H_{19}Cl_2N_2CdPS$ = 494.987 g/mol.

The infrared spectral data of the $[CdCl_2(pph_3)(Ath)]$ metal complex displayed a characteristic (ν_{N-H}) band at 3378 cm^{-1}, a medium intensity band at 1674 assigned to ($\nu_{C=N}$) the thiazole moiety. A broad band at 1645 cm^{-1} is the aromatic $\nu_{C=C}$ stretching. The band due to the ν_{S-CH2} appeared at 720 cm^{-1}. the bands 620 and 480 cm^{-1} less intense absorption bands indicating ν_{M-O} and ν_{M-P} respectively (Fig. 2).

The ^1H NMR spectrum of the $[CdCl_2(pph_3)(Ath)]$ was obtained in DMSO-d_6 at room temperature. The spectrum of the Cd(II) complex showed a singlet due to the proton of thiazole -NH at 9.79 ppm. The multiplets appeared in the range 7.68 - 7.53 ppm for the aromatic ring protons of the triphenylphosphine and another two multiplets in the range 7.19 - 7.16 ppm represents the ring protons of the thiazole (Fig. 3).

BIOLOGICAL ACTIVITY STUDIES

***In vitro* antibacterial and antifungal activity**

The *in vitro* biological activity of the investigated of the Cd(II) complex was tested against the bacteria *Escherichia coli, Salmonella typhi, Staphylococcus aureus, Bacillus subtilis* by well diffusion method using nutrient agar as the medium and chloramphenicol as the standard. The antifungal activities of the compounds were also tested against the fungi, Aspergillus *niger* and *Candida albicans*, on potato dextrose agar as the medium and fluconazole as the standard. The obtained results are tabulated in Table 1 and Table 2. The complex showed good zone of inhibition for all tested pathogens.

Table 1: Antibacterial activity

Entry	Zone of Inhibition		
	25µL	**50 µL**	**100 µL**
AA	13mm	18mm	19mm
AF	18mm	22mm	23mm

Sa-Staphylococcus aureus, Se-Staphylococcus epidemidis , Bco-*Bacillus cereusa Pa-P.aeruginosa, and Vc-Vibrio cholerae*

Table 2: Antifungal activity

Entry	Zone of Inhibition		
	25µL	**50 µL**	**100 µL**
Pa	13mm	18mm	19mm
Sa	20mm	23mm	24mm
Vc	15mm	14mm	16mm
Se	19mm	22mm	24mm
Bco	20mm	23mm	26mm

AA-Aspergillus aureus and AF-*Aspergillus fumigates*

Molecular docking using HEX 8.2

The results of the anti-microbial docking studies which has been done by using *Protein receptor SEC2 (PDB code: 1STE) in Staphylococcus aureus* revealed that the complex showed good binding interactions with the antimicrobial receptor PDB, and has excellent docking score -287.45 kcalmol^{-1} compared to the standard cifrolaxin, which possess docking value of -231.03 kcalmol^{-1}. The lowest binding scores indicates the best docking infractions with the selected antimicrobial receptor and it supports for the wet analysis which is to be carried out on the different bacterial strains. The complex showed their best docking interactions with different amino acid residues as shown in Table 3 and indexed in the Fig. 4. Interaction of complex with amino acids residues of receptor and binding score value.

Table 3: Parameters used for docking study

Compound	Binding energy (kcal/mol)	Amino acid residues	Receptor PDB
Cd(II)	-287.45	Tyr238, Lue282, Arg70, Lys56, Leu56, Leu58, His283, Tyr136, Thr183,	PDB code: 1STE in Staphylococcus aureus

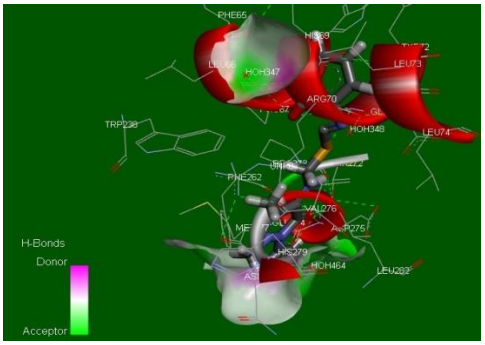

Fig. 4: 3D interactions of Cd complex with S. aureus Gyrase complex with Ciprofloxacin (PDB: 2XCT)

Antioxidant activity

The radical scavenging activity for the complex are examined for the various concentration 0-25 µL by adopting DDPH method and the results are index in the Table 4. The results showed the complex exhibit the increasing scavenging inhibition rate as the concentration increases and the complex showed their excellent rate of inhibition of 0.731 at 25 µL concentration.

Table 4: Antioxidant activity of the [CdCl2(pph3)]

Entry	Absorbance in 0µL	Absorbance in 05 µL	Absorbance in 10 µL	Absorbance in 15 µL	Absorbance in 20 µL	Absorbance in 25 µL
Complex	0.564	1.217	1.000	0.842	0.807	0.731

*Values are indicate in mean ± SEM and statistical significant values are expressed as *p < 0.05 and **p < 0.01*

DFT Studies of Cd(II) complex

The computational calculations of complex by Becke's three parameter hybrid exchange functional (B3LYP) with support of chemcraft 1.7 software has been used for visualisation of optimised structures [15]. The selected bond length, bond angle and dihedral angle is represented in Table 5. The optimised geometry determined by DFT studies (Fig.5) indicate the minimum energy for HOMO is -4.520 eV and that for LUMO is -10.847 eV. The HOMO-LUMO energy band gap of complex is found to be 6.327 eV(Fig.6) and is important for the electron transfer within the molecule.

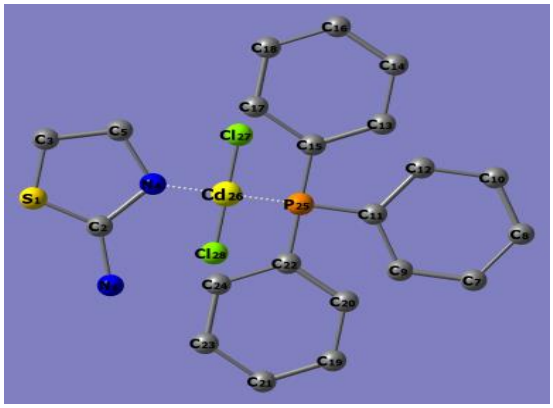

Fig. 5: Optimised geometry of [$CdCl_2(pph_3)$]

Table 5: Selected Bond length (Å), Bond angle (o) and Dihedral angles of [CdCl2(pph3)]

Bond	Bond length	Bond angle	(°)	Dihedral angles	(°)
P(25)-Cd(26)	2.574	S(1)-C(2)	1.790	C(23)-H(32)	1.122
Cd(26)-Cl(27)	2.470	S(1)-C(3)	1.742	C(24)-H(35)	1.122
Cd(26)-Cl(28)	2.470	C(2)-N(4)	1.446	P(25)-Cd(26)	2.574
C(2)-S(1)-C(3)	88.096	C(2)-N(6)	1.446	Cd(26)-Cl(27)	2.470
S(1)-C(2)-N(4)	111.000	C(3)-C(5)	1.324	Cd(26)-Cl(28)	2.470
S(1)-C(2)-N(6)	124.498	C(3)-H(31)	1.122	C(2)-S(1)-C(3)	88.096
N(4)-C(2)-N(6)	124.498	N(4)-C(5)	1.446	S(1)-C(2)-N(4)	111.000
S(1)-C(3)-C(5)	117.637	N(4)-Cd(26)	2.156	S(1)-C(2)-N(6)	124.498
S(1)-C(3)-H(31)	125.039	C(5)-H(47)	1.122	N(4)-C(2)-N(6)	124.498
C(11)-P(25)-Cd(26)	109.500	N(6)-H(29)	1.028	S(1)-C(3)-C(5)	117.637
C(15)-P(25)-C(22)	109.500	N(6)-H(30)	1.028	S(1)-C(3)-H(31)	125.039
C(15)-P(25)-Cd(26)	109.500	C(20)-C(22)	1.386	C(5)-C(3)-H(31)	117.322
C(22)-P(25)-Cd(26)	109.327	C(20)-H(36)	1.122	C(2)-N(4)-C(5)	110.999
N(4)-Cd(26)-P(25)	109.500	C(21)-C(23)	1.386	C(11)-P(25)-Cd(26)-N(4)	60.000
N(4)-Cd(26)-Cl(27)	109.499	C(21)-H(33)	1.122	C(11)-P(25)-Cd(26)-Cl(27)	150.001
N(4)-Cd(26)-Cl(28)	109.500	C(22)-C(24)	1.386	C(11)-P(25)-Cd(26)-Cl(28)	-179.894
P(25)-Cd(26)-Cl(27)	0.540	C(22)-P(25)	1.864	C(15)-P(25)-Cd(26)-N(4)	-179.929
P(25)-Cd(26)-Cl(28)	109.558	C(23)-C(24)	1.386	C(15)-P(25)-Cd(26)-Cl(27)	-89.928
Cl(27)-Cd(26)-Cl(28)	109.090	C(23)-H(32)	1.122	C(15)-P(25)-Cd(26)-Cl(28)	-59.823
		C(24)-H(35)	1.122	C(22)-P(25)-Cd(26)-N(4)	-59.965

	P(25)-Cd(26)	2.574	C(22)-P(25)-Cd(26)-Cl(27)	30.037
	Cd(26)-Cl(27)	2.470	C(22)-P(25)-Cd(26)-Cl(28)	60.141
	Cd(26)-Cl(28)	2.470		

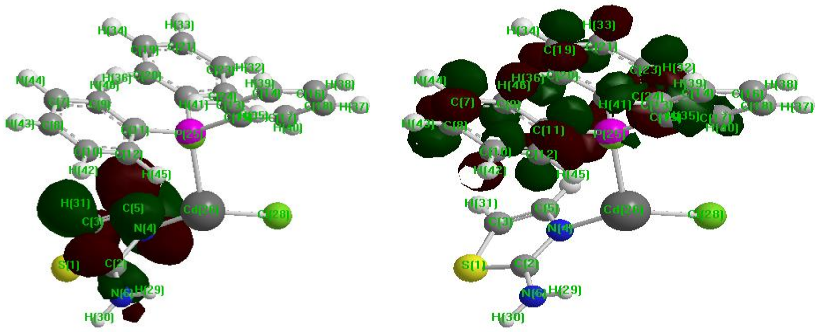

Fig. 6 HOMO- LUMO Frontier molecular orbital analysis

CONCLUSION

The mixed ligand complexes had been synthesized and characterized using various analytical techniques. The complex are biologically active and show enhanced antimicrobial and antioxidant activities, the antimicrobial activity is further supported by computational molecular docking studies, which conclude that the complex having lowest docking score compared to standard. The molecular modelling results obtained which are very close to experimental results.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this research article.

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