SPECTROCHEMICAL INVESTIGATION OF BIO-ACTIVE NOVEL HETEROCYCLICE ATOMEXETINE CARBAMODITHIOLATE METAL COMPLEXES-DOCKING STUDIES

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Abstract

Carbamodithiolates are a class of sulfur-based metal-chelating compounds with various applications in medicine. A new series of new transition metal [Cu(II),and Ru (II)] complexes of Carbamodithiolates were synthesized from Atomexetine and Carbon disulfide and further characterized. The investigation of these complexes confirmed that the stability of metal–ligands coordination through, S & S,N atoms as bidendate chelates. Docking studies showed that blocking the division of cancer cells and resulting in cell death. It is necessary to understand the binding properties in developing new potential Protein targeting against neurological disorders.

Keywords :Atomexetine,Metal complexes,Docking studies,Carbamodithiolates, neurological disorders.

Introduction:

The field of Carbamodithiolate metal complexes are vast and fast developing on account of their spectacular applications in various fields, also owing to the varieties of structural forms of the ligands. The ever-increasing applications of transition metal complexes in different fields of sciences are the driving force for the present research. The Carbamodithiolate are organo sulphur compounds considered to be versatile organic ligands which form complexes with many transition metals like Cu, Fe, Ni, Mn and Zn leading to the stabilization of a wide range of oxidation states.

The complexing ability of Carbamodithiolate is well established and this is due to two sulphur atoms, which are capable to donate a lone pair of electrons to the central metal atom to form the stable metal complexes. These are known to stabilize unusual oxidation states of metal complexes, because of the delocalization of positive charge from the metal to nitrogen. Besides, Carbamodithiolate ligand and its metal complexes exhibit their striking and diversified applications in many fields like Medicine, Agriculture Industry, Polymer technology, Inorganic and Environmental trace analysis.

Carbamodithiolate ligands are soft bases. They had been found to act almost as uni negative bi dentate ligands coordinating through sulphur atoms, and also both tetra and hexa co-ordinate complex of

many transitional metal ions have been isolated. They exhibit various applications in different fields especially in the production of petroleum derivatives, lubricants, as accelerators for vulcanization in Polymer Industry, as antioxidants and anti humidity agents. They are also having fungicidal, bactericidal, insecticidal, anticancer, and photochemical activities. Carbamodithiolate ligands itself acts as a good antibacterial and antifungal activity and are used as biocides (vapam, nabam).

Owing to wide applicability of sulphur bearing ligands in biological and industrial field, a bulk of literature is available on the Carbamodithiolate ligands and its complexes of transition and non-transition metals. A large number of transition metal complexes with various aliphatic and aromatic dithiocarbamate ligands have been reported. Though a number of Carbamodithiolates have been prepared in the literature, there is no attempt in preparation of Histamine.

Atomoxetine, a primary amine which in turn having many applications on its own. Atomoxetine might be a helpful adjunct in people with major depression, especially in cases where ADHD occurs comorbidly to major depression. Several randomized double-blind placebo-controlled trials found that atomoxetine was an efficacious treatment for various disorders like pediatric bedwetting, binge eating disorder, and is an efficacious weight loss medication.Valganciclovir It has been proposed that valganciclovir could be used in the treatment of chronic fatigue syndrome.

Insights gained from decades of research have begun to unlock the pathophysiology of these complex diseases and have provided targets for disease-modifying therapies. In the last decade, few therapeutic agents designed to modify the underlying disease process have progressed to clinical trials and none have been brought to market. With the focus on disease modification, biomarkers promise to play an increasingly important role in clinical trials. Among the histamine receptor subtypes, H3 receptors play an important regulatory role in the CNS. Activation of H3 auto receptors can inhibit histamine synthesis and release from histaminergic neurons (Arrang et al., 1983), while activation of H3 hetero receptors can inhibit release of other neurotransmitters such acetylcholine, noradrenaline, dopamine and 5-HT from non-histaminergic neurons (Schlicker et al., 1994; Blandina et al., 1996; Brown et al., 2001). Conversely, blockade of H3 receptors with selective antagonists can increase the release of neurotransmitters involved in cognitive processes (Fox et al., 2005; Medhurst et al., 2007). Selective H3 receptor antagonists have been shown to improve performance in a diverse range of rodent cognition paradigms (Hancock and Fox, 2004; Witkin and Nelson, 2004; Medhurst et al., 2007), and can also increase wakefulness (Brown et al., 2001; Barbier et al., 2004). This has led to the development of H3receptor antagonists for the potential treatment of several CNS disorders including cognitive dysfunction in Alzheimer's disease (AD) (Passani et al., 2004; Esbenshade et al., 2008).

Parkinson's disease (PD) is one of the most common diseases of the central nervous system (CNS). It is frequently heralded by speech disturbances, which are one of its first symptoms. Parkinson's disease (PD) is a progressive extra pyramidal motor disorder. Pathologically, this disease is characterized by the

selective dopaminergic (DAergic) neuronal degeneration in the substantia nigra. Correcting the DA deficiency in PD with levodopa (Ldopa) significantly attenuates the motor symptoms; however, its effectiveness often declines, and L-dopa-related adverse effects emerge after long-term treatment. Nowadays, DA receptor agonists are useful medication even regarded as first choice to delay the starting of L-dopa therapy. In advanced stage of PD, they are also used as adjunct therapy together with L-dopa. DA receptor agonists act by stimulation of presynaptic and postsynaptic DA receptors. Despite the usefulness, they could be causative drugs for valvulopathy and nonmotor complication such as DA dysregulation syndrome (DDS).

Over the past decade, the Protein-ligand binding metal complexes have been extensively studied as DNA structural probes, DNA-dependent electron transfer probes, DNA foot printing and sequence-specific cleaving agents and potential anticancer drugs. The numerous biological experiments performed so far suggest that DNA is the primary intracellular target of anticancer drugs because the interaction between small molecules and DNA can cause DNA damage in cancer cells, blocking the division of cancer cells and resulting in cell death. It is necessary to understand the binding properties in developing new potential Protein targeting against neurological disorders.

The present work has been extended to know antibacterial activity, anti inflammatory activity and antifungal activity and Docking studies of the Carbamodithiolate metal complexes.

The main thrust of the study is to prepare as such new Carbamodithiolate ligand from an amine having considerable amount of applications on its own with the hope that the resultant Carbamodithiolate may possess much more applications and find a place in major fields of interest.

MATERIALS AND METHODS

Experimental

Copper chloride anhydrous was obtained from Fluka, Atomoxetine and carbon disulfide were purchased from Aldrich. Other chemicals used were of analytical reagent or higher purity grade. Solvents used were of reagent grade and purified before use by the standard methods. Conductivity measurement was carried out by a Systronics Conductivity Bridge 305, using a conductivity cell of cell constant 1.0 double distilled water was used as solvent. Electronic absorption spectra were measured on JASCO UV/VIS-7850 recording spectrophotometer. Infrared spectra were recorded on a JASCO-460 plus FT-IR spectrophotometer in the range of 4000-400 cm^{-1} in KBr pellets. Micro chemical analysis of carbon, hydrogen and nitrogen for the complexes were carried out on a Herause CHNO-Rapid elemental analyzer. ^{1}H NMR spectra were recorded on a Brucker DRX-500 Advance Spectrometer at 500 MHz in DMSO-discussing tetra methyl silane as internal reference standard. Melting points were measured on a Unimelt Capillary Melting Point Apparatus and reported uncorrected.

Preparation of Sodium salt of Carbamodithiolate ligands

0.05 mol of amine was dissolved in 30 ml of absolute alcohol in a clean beaker which was placed in ice bath. To this cold solution add 5 ml of sodium hydroxide (10N) solution, and then add pure carbon disulphide (0.05 ml) drop-wise with constant stirring .The contents were stirred mechanically for about 30 min, sodium salt of Carbamodithiolate precipitated out. It was dried over and recrystallized from ethanol.

Preparation of Cu (II) and Ru(II)Complexes,

Synthesis of [Cu ((ACDT)$_2$)Cl$_2$]

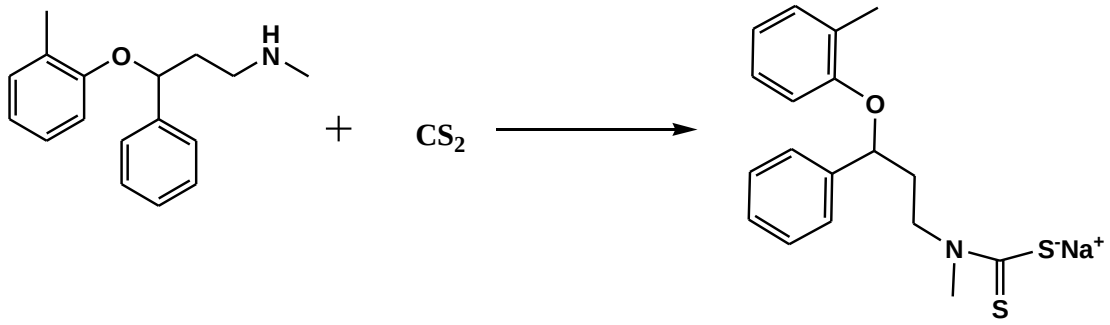
The aqueous solution of 0.05 mol of Ruthenium Chloride was added with constant stirring to an aqueous solution of 0.01 mol of Sodium salt of Atomexetine Carbamodithiolate ligand in the presence of small quantity of triethylamine. The reaction mixture was stirred at room temperature for 2 hours. The colored (light green) precipitates were obtained. The precipitates were filtered and washed with water and then with methanol and dried over calcium chloride in a desiccators. Yield: 80% and decomposes at 110^0 C.

Synthesis of [Ru (ACDT)Cl$_2$]

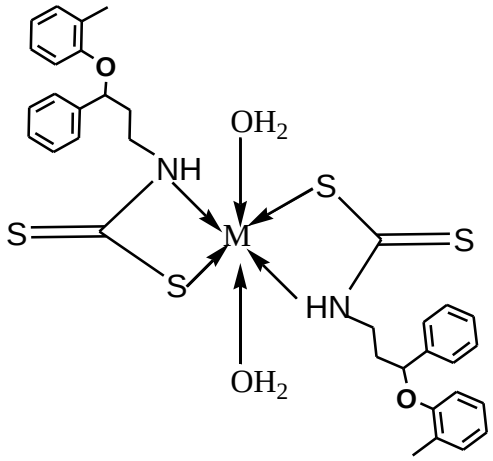
The aqueous solution of 0.05 mol of Ruthenium Chloride was added with constant stirring to an aqueous solution of 0.01 mol of Sodium salt of Atomexetine Carbamodithiolate ligand in the presence of small quantity of triethylamine. The reaction mixture was stirred at room temperature for 2 hours. The colored (light green) precipitates were obtained. The precipitates were filtered and washed with water and then with methanol and dried over calcium chloride in a desiccators. Yield: 80% and decomposes at 110^0 C.

RESULTS AND DISCUSSION

The solid reflectance spectra data for the Cu(II) and Ru(II), of Atomexetine metal complexes. The **[Cu ((ACDT)$_2$)Cl$_2$] and [Ru (ACDT)Cl$_2$],** complexes exhibit magnetic property and has an electronic spectrum which can be assigned to low spin Cu (II) and Ru (II) in an Octahedral Environment. Intra ligand electronic transition is then…C…S…S and S…C…S chronophers of the Carbamodithiolate moiety .Thus the peak at 646 nm and the shoulder at 499 nm arise from 1A1g_1T1g and 1A1g_ 1T2g transitions, respectively. The other lower peaks are probably charge-transfer in origin.



M= $CuCl_2$, $RuCl_2$



M= $CuCl_2$, $RuCl_2$

Infrared Spectrum

Infra Red Spectral Analysis of Atomexetine Carbamodithiolate (ACDT) Ligand

The typical I.R spectrum of ACDT Carbamodithiolate was presented in the Fig.2.6.1(a) as concern the Atomexetine Carbamodithiolate (ACDT),three main regions of the I.R. are of main interest the most significant bands recorded in the FT-IR spectra of the ligand and its metal complexes are reported in the Table .2.6.1.First, the (1400-1550 cm^{-1}) region, which was primarily associated with υ (N-CSS) stretching vibrations. Second, the 950-1000 cm^{-1} region, which is associated with υ (C-S) stretching vibrations[3].The characteristic band at 1440.27 cm^{-1}, was assigned to υ (N-CSS); this band defines a carbon Nitrogen bond order between a single bond (υ =1250-1350cm^{-1}) and a double bond (υ = 1640–1690cm^{-1}). The appearance of a band in that region 1640.55 cm^{-1} indicates that, of the three possible resonance structures reported by Chart et al., characterized by a strong delocalization of electrons in the Carbamodithiolate moiety.

A single sharp band at 1025.58 cm^{-1} was assigned to the stretching vibrations of the C-S bond. The band at 3447.66cm^{-1} associated with the υ(N-H)stretching vibrations. Sharp band absorbed in the region of 2925.25 cm^{-1} indicate aromatic =C-H Stretching vibration. The characteristic absorption band at 1640.55 cm^{-1} indicate aromatic C=C stretching vibration. The absorption band is appeared in between the region of 1025.58 –612.70 cm–1 (C–C, C–O, C–N).

Infrared Characterization of [Cu(ACDT)$_2$] Metal Complex

The revelation of IR spectra of Carbamodithiolate complex of transition metals had arisen and considerable interest both diagnostically to determine the mode of co-ordination and as a mean of assessing the nature of bonding in these complexes. The Infrared spectrum of Cu (II) complex was compared the (ACDT) ligand. The typical IR Spectrum of [Cu(ACDT)$_2$] complex is presented in Fig. 2.6.1(b). A strong band appeared at 1440.27cm^{-1} in the I.R spectrum of the ligand, which was assigned to the thioureide bond was shifted to 1440.27-1443.60cm^{-1} region. On Passage from the free Carbamodithiolate ligand to their complex, the υ(N–CSS) mode is shifted to higher energies, showing an increase of Carbon-Nitrogen double

bond character and hence a greater contribution of the structure. The Infrared active υ (N–CSS) mode was sensitive to both chain length and the steric bulk of the substituents.As the double character was more pronounced in the complex it can be concluded that the ligand was co-ordinated through S, S atoms.

To discriminate the bonding type of the Carbamodithiolate ligand in their complexes, the Bonati-Ugo method is, by far, the most popular one. It consists of tracing the 904-1002 cm^{-1} spectral region, where the υ (C-S) modes were thought to appear. In fact, the bands due to CSS moiety were usually coupled to other vibrations and are very sensitive to the environment around this group, but they were also useful to distinguish Mono dentate and Bi dentate Co-ordination. The existence of only one band in the investigated region, commonly attributed to υ (SCS) mode, it indicates completely symmetrical bonding of the Carbamodithiolate ligand to metal in bi dentate mode where as a doublet was expected for the Mono dentate coordination. Basing on the above concept the emergence of single band at 1002.18 cm^{-1} region was assumed to υ (C-S) stretching vibrational mode and it indicates the symmetric bi dentate behaviour of the ligand that means the ACDT ligand was co-ordinated through both the sulphur atoms.

Along with bands new these bands were formed which are not observed in the spectrum of the ligand, the band in the region 542.17cm^{-1} was assigned to the υ (M-S) metal ligand bond of the complex. The appearance of the band at 1654.83 cm^{-1} indicate C=C Stretching of two aromatic rings the appearance of broad band at 3444.03cm^{-}can be assigned to the stretching vibrations of υ- NH and co-ordinated water molecules present in their complexes. In the spectra of both ligand and complex, significant change was observed, for molecular vibrational stretching mode. The one weaker band at 866-667 cm^{-1} were assigned respectively to –OH rocking and wagging vibrations of co-ordinated water in the complex.

Infrared Characterization of [Ru(ACDT)$_2$] Metal Complex

The elucidation of IR spectra of Carbamodithiolate complexes of transition metals had arisen and considerable interest both diagnostically to determine the mode of co-ordination and as a mean of assessing the nature of bonding in these complexes. The Infrared spectrum of Ru (III) complex was compared the (ACDT)ligand. The typical IR Spectrum of [Ru(ACDT)$_2$] complex is presented in Fig. 2.6.1(c). A strong band exhibited at 1440.27cm^{-1} in the I.R spectrum of the ligand, which was assigned to the thioureide bond, was shifted to 1440.27-1448.60 cm^{-1} region. On Passage from the free Carbamodithiolate ligand to their complex, the υ(N–CSS) mode is shifted to higher energies, showing an increase of Carbon-Nitrogen double bond character and hence a greater contribution of the structure. The Infrared active υ (N–CSS) mode was sensitive to both chain length and the steric bulk of the substituents. As the double character was more pronounced in the complex it can be concluded that the ligand was co-ordinated through S, S atoms.

To differentiate the bonding type of the Carbamodithiolate ligand in their complexes, the Bonati-Ugo method is, by far, the most popular one. It consists of tracing the 904-1002.18 cm^{-1} spectral region, where the υ (C-S) modes were thought to appear. In fact, the bands due to CSS moiety were usually coupled to other vibrations and are very sensitive to the environment around this group, but they were also useful to

discriminate Mono dentate and Bi dentate Co-ordination. The presence of only one band in the investigated region, commonly attributed to υ (SCS) mode, it indicates completely symmetrical bonding of the Carbamodithiolate ligand to metal in bi dentate mode where as a doublet was expected for the Mono dentate coordination. Basing on the above concept the presence of single band at 1002.18cm^{-1} region was assumed to υ (C-S) stretching vibrational mode and it indicates the symmetric bi dentate behaviour of the ligand that means the ACDT ligand was co-ordinated through both the sulphur atoms.

Along with these, new bands were formed which are not observed in the spectrum of the ligand, the band in the region 866-667 cm^{-1} was assigned to the υ (M-S) metal ligand bond of the complex. The appearance of band at 1658.63 cm^{-1} indicate C=C Stretching of two aromatic rings the emergence of broad band at 3449 cm^{-1} can be assigned to the stretching vibrations of υ- NH and co-ordinated water molecules present in their complexes. In the spectra of both ligand and complex, significant change was observed, for molecular vibrational stretching mode. The two weaker bands at 866-667 cm^{-1} were assigned respectively to –OH rocking and wagging vibrations of co-ordinated water in the complex.

Table 2.6.1.

Infrared spectral analysis data of Atomexetine Carbamodithiolate (ACDT) ligand and its metal complexes

Compound name	Thioureidebond	-NH-	C=C-H	-C=C-	C-S	M-S	OH- (H_2O)
ACDT	1440.27	3447.66	2925.25	1640.55	1025.58	---	----
[Cu(ACDT)$_2$]	1443.60	3444.03	2895.4	1654.83	1002.18	542.17	3453.34
[Ru(ACDT)$_2$]	1448.60	3449.03	2965	1658.63	1002.18	542.17	3450

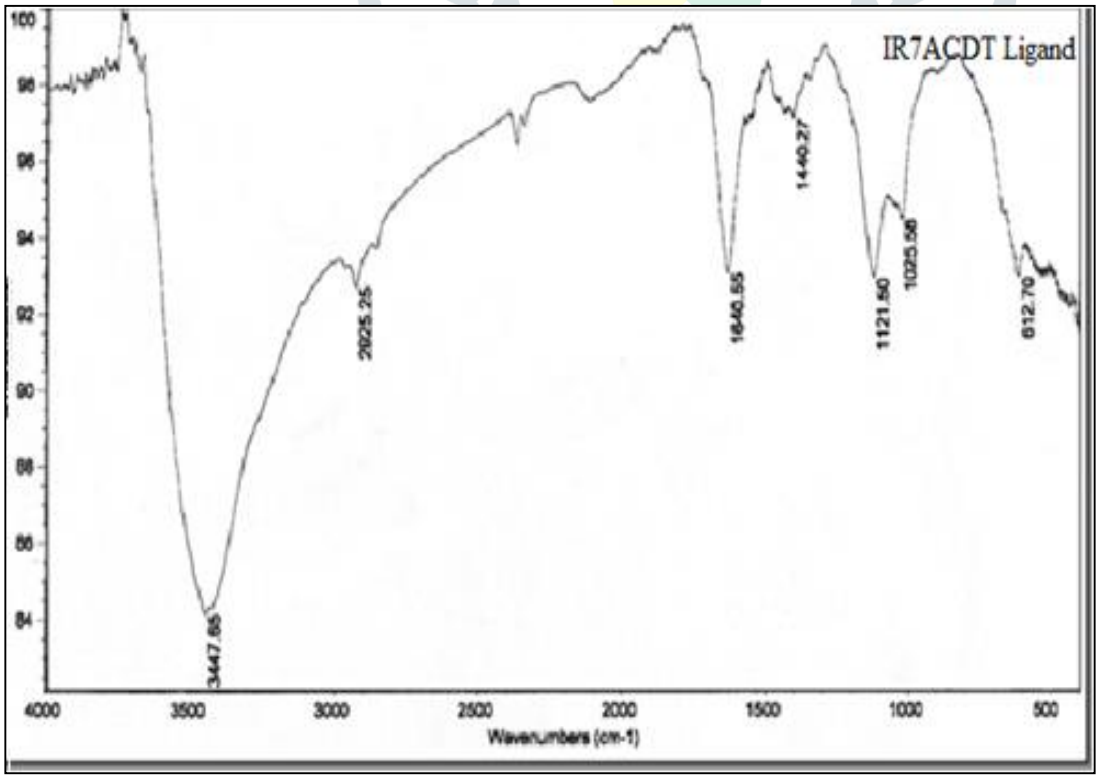


Fig. 2.6.1(a) : IR Spectrum of the ACDT ligand

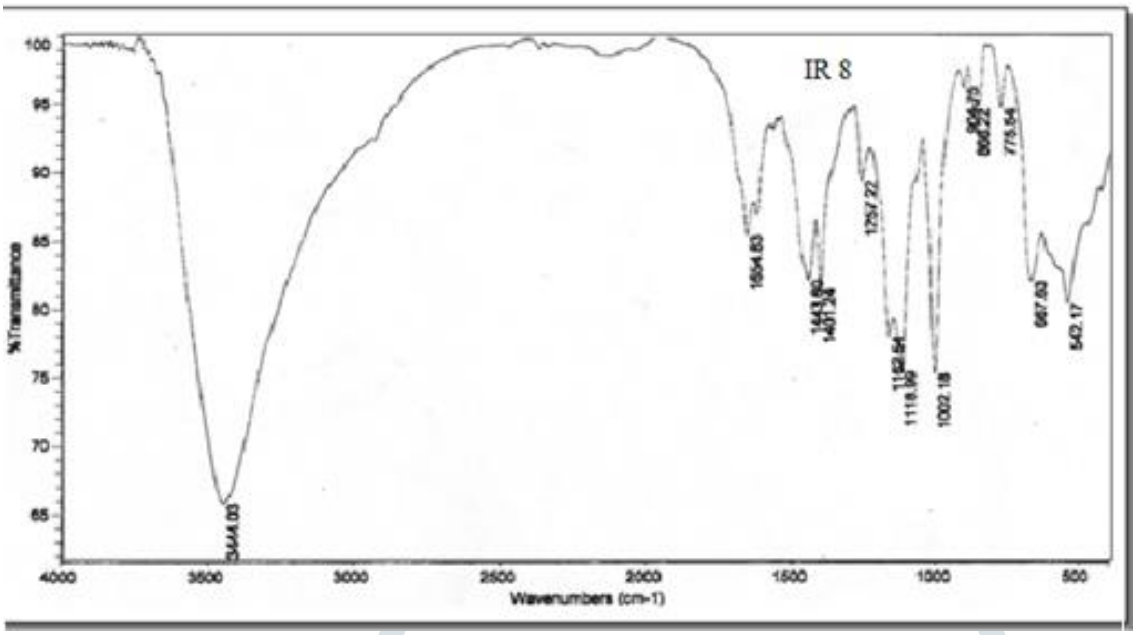


Fig. 2.6.1(b) : IR Spectrum of the [Cu(ACDT)$_2$] Metal Complex

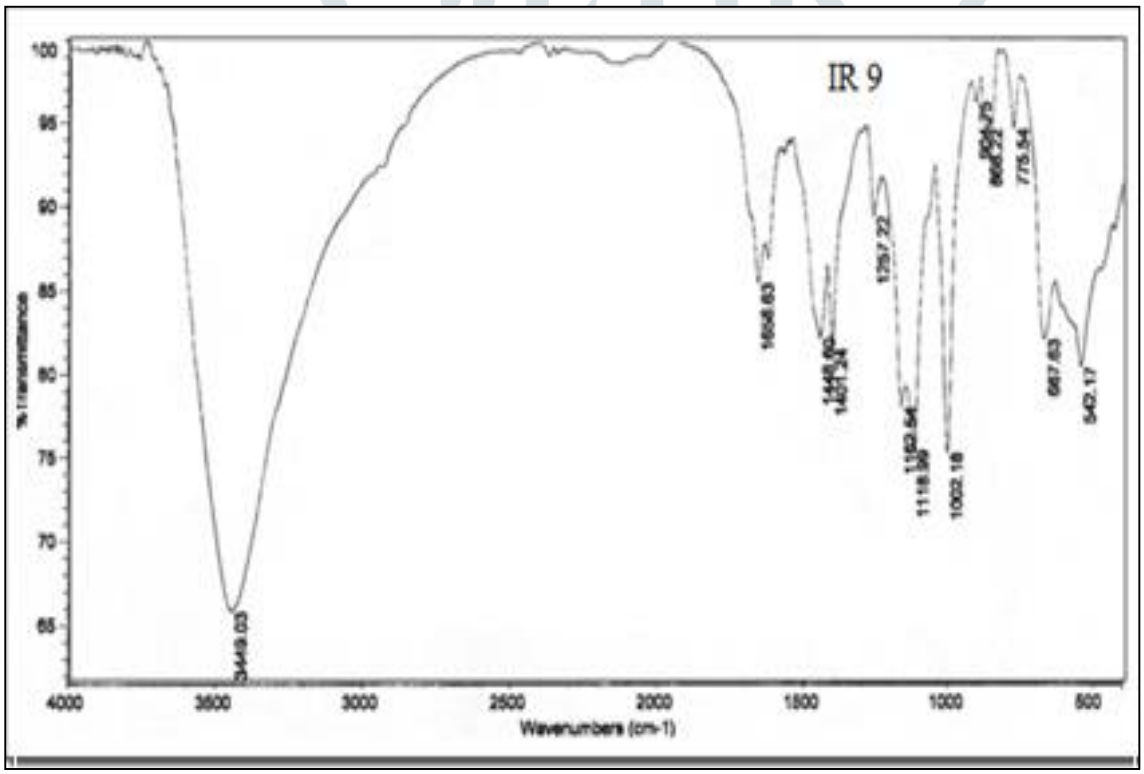


Fig. 2.6.1(c) : IR Spectrum of the [Ru(ACDT)$_2$] Metal Complex

^{1}HNMR Spectral Elucidation of Atomexetine Carbamodithiolate (ACDT) Ligand and its Metal Complexes

It gives the typical ^{1}HNMR spectrum of Atomexetine Carbamodithiolate (ACDT) ligand.Three C-H protons of the furan ring of Carbamodithiolate ligand forms a multiplet at different regions in between 7.37-7.89 and 7.90-8.31 ppm indicate two aromatic nucleus. The singlet appeared in the region 7.89 ppm was due to NH proton in thioureide region of Carbamodithiolate ligand shown in the table 2.11.

It describes the characteristic [1]HNMR spectrum of Cu metal complex. In the complexes signal due to proton bonded to Nitrogen in the thiouride bond was observed in the range of 7.89 to 8.12 ppm. The down field shift of the complex may attributed to an increase of the - bond character and the delocalization of electrons along the C-N bond contributed by the substituents and also by the bi dentate nature of the Carbamodithiolate ligand.On complexation, the electron density on – NH decreases, the processional frequency of proton bonded to nitrogen increases, hence the signal is shifted to down field regions.High NH stretching indicates as increased C-N double bond character which is due to a greater electron density on the – NCCS moiety [1].The broad signals in the range 7.2-8.97 ppm in the case of copper metal complex indicates the CH protons of two aromatic benzene rings and broad signals in the range 10.4 ppm in the case complexation of water molecule to metal ion, it was not observed in the case of free ligand. Fig. 2.6.2(c) describes the characteristic [1]HNMR spectrum of Ru metal complex. In the complexes signal due to proton bonded to Nitrogen in the thioureide bond was observed in the range of 7.89 to 8.19 ppm. The down field shift of the complex may attributed to an increase of the - bond character and the delocalization of electrons along the C-N bond contributed by the substituents and also by the bi dentate nature of the Carbamodithiolate ligand.On complexation, the electron density on – NH decreases, the processional frequency of proton bonded to nitrogen increases, hence the signal is shifted to down field regions.High NH stretching indicates as increased C-N double bond character which is due to a greater electron density on the – NCCS moiety [1].

The broad signals in the range 7.2-8.97 ppm in the case of Ru metal complex indicates the CH protons of fused two aromatic benzene rings and broad signals in the range 10.49 ppm in the case complexation of water molecule to metal ion, it was not observed in the case of free ligand.

Compound	**H–N–C (thioureide bond)**	**(H_2O) Coordinated water**
ACDT	7.89	------
$[Cu(ACDT)_2]$	8.12	10.4
$[Ru(ACDT)_2]$	8.19	10.49

Materials and Methods:

Keeping the aim of constructing novel ligand complexes for H3, a library of 10 molecules was synthesized. The Auto Dock 4.0/ADT (Laskowski RA et al., 2005) program was used to investigate ligand binding to structurally refined H3 model using a grid spacing of 0.375 Å and the grid points in X, Y and Z axis were set to 60×60×60. The search was based on the Lamarckian genetic algorithm (Oprea TI et al., 2001) and the results were analyzed using binding energy. For each ligand, a docking experiment consisting of 100 stimulations was performed and the analysis was based on binding free energies and root mean square deviation (RMSD) values. Substrate docking with synthesized substrates was also performed on to

H3 model with same parameters and PMV 1.4.5 viewer was then used to observe the interactions of the docked compounds to the H3 model.

Results and Discussion:

Binding energy for each docking was calculated using a semi-empirical free energy force field. Out of these 5 docked ligands and its Complexes molecules with receptor, top two molecules were filtered out on the basis of binding energy. The binding modes and geometrical orientation of all compounds were almost identical, suggesting that all the inhibitors occupied a common cavity in the receptor. The binding energy of top three inhibitor molecules with an active site of receptor protein is given in Table 1.

Table-I Summary of docking results high ranked ligands and complex molecules with H3 receptor.

S. No.	Compound Name	Receptor Name	Cluster Rank	RMSD	Lowest binding Energy (Kcal/mole)
1	Atomexetine(ACDT)Ligand	H3 Receptor	1	0.65	-4.80
2	[Cu(ACDT)]	H3 Receptor	3	0.10	-5.12
3	[Ru(ACDT)]	H3 Receptor	1	0.00	-6.35

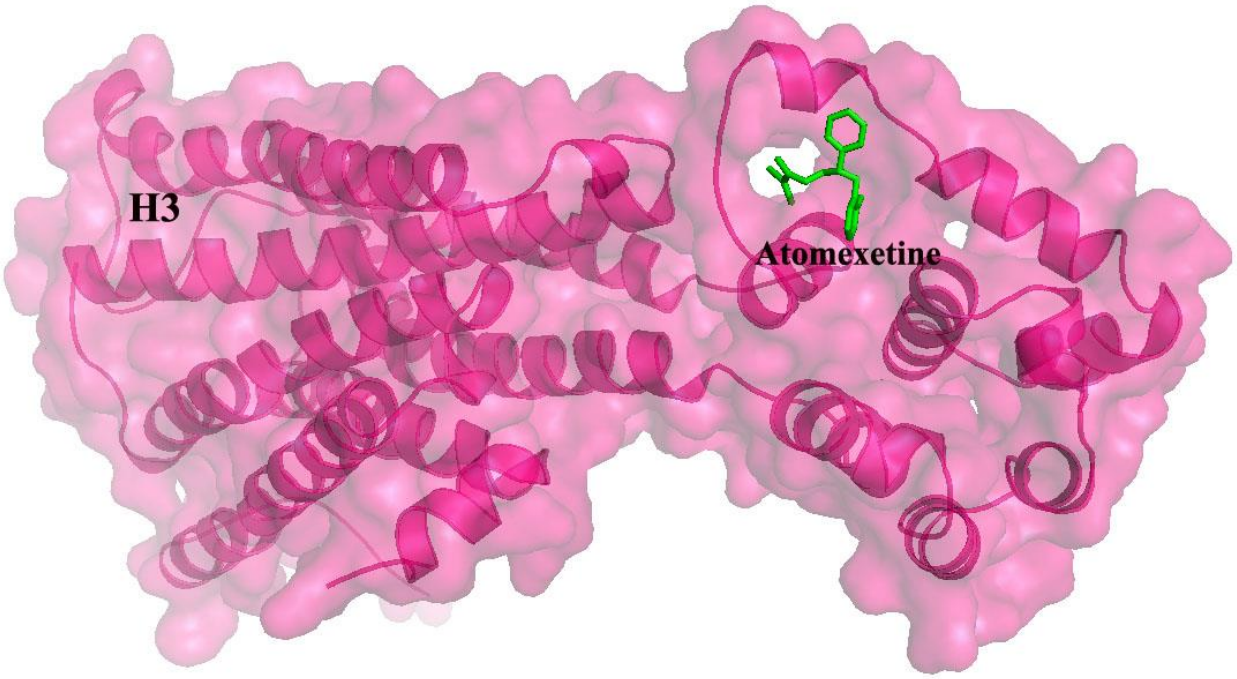


Fig. 1 The cortoon and electrostatic surface representation of the binding site of (d) H3 receptor model in limon , Atomexetine ligand with sticks in green colour

Most docked inhibitors interacted by the same mode of the inhibitors, histamine H3 receptor binding site. The different surface pocket for residue seems to be an important factor in determining the binding mode of histamine ligand of Glu 241 and Leu 231 amino acid residues (Figure 1a), Sythesised ligand metal complexes are showing same interaction and binding pose with high energy values in among all complex molecules Histamine Copper complex and Ruthenium complexes gave best scores.

Conclusion:

Cu (II) and Ru(II) complexes of Atomexetine Carbamodithiolate Ligand with have been synthesized and characterized. The ligand moiety exhibit a bidentate coordination mode in the Cu (II) and Ru (II) complexes. Solid reflectance spectra and magnetic data indicate that the complexes are Paramagnetic and Octahedral. The complexes show selective activity towards some of the test microorganisms. In this Study, we have docking studies of H3 receptor model with carbamodithiolate ligand and metal complexes having more favourable rank score, docking score and hydrogen bonding energy and the binding pocket of the H3 receptor. Activation of H3 hetero receptors can inhibit release of other neurotransmitters such acetylcholine, noradrenaline, dopamine, conversely blockade of H3 receptors with our synthesized selective antagonists can increase the release of neurotransmitters involved in cognitive processes. Docking studies of carbamodithiolate ligand and metal complexes with H3 receptor and detailed analyses of metal inhibitors, H3 receptor interactions were done and the residues in binding responsible for binding to the inhibitors of metal substrates with high binding affinity were identified. Hence we conclude that these carbamodithiolate ligands and metal complexes could be a potential anti

Neurological disorders lead molecules for modulating the expression of H3 receptor in Parkinson's disease (PD) and Alzheimer's disease (AD) supports for experimental testing.

Acknowledgement

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