Synthesis, Insilco studies and biological evaluation of Phenethylamine Dithiocarbamate metal complexes-Docking Studies

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Abstract

Dithiocarbamates are a class of sulfur-based metal-chelating compounds with various applications in medicine. A new series of new transition metal [Cu(II), and Fe (II)] complexes of Dithiocarbamates were synthesized from Phenethylamine 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.

Key Words: Phenethylamine,Metal Complexes, Docking Sudies, Dithiocarbamates,neurological disorders.

Introduction:

The field of Dithiocarbamates 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 Dithiocarbamates 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 Dithiocarbamates 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, Dithiocarbamates 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.

Dithiocarbamates ligands are soft bases. They had been found to act almost as uninegative 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. Dithiocarbamates 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 Dithiocarbamates 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 Dithiocarbamates have been prepared in the literature, there is no attempt in preparation of Phenethylamine.

Phenethylamine (PEA) is an organic compound, natural monoamine alkaloid, and trace primary amine, which acts as a central nervous system stimulant in humans. In the brain, phenethylamine regulates monoamine neurotransmission by binding to trace amine-associated receptor 1 (TAAR1) and inhibiting vesicular monoamine transporter 2 (VMAT2) in monoamine neurons to a lesser extent, it also acts as a neurotransmitter in the human central nervous system.In mammals, phenethylamine is produced from the amino acid L-phenylalanine by the enzyme aromatic L-amino acid decarboxylase via enzymatic decarboxylation. In addition to its presence in mammals, phenethylamine is found in many other organisms and foods, such as chocolate, especially after microbial fermentation.

Phenethylamines, or more properly, substituted phenethylamines, are the group of phenethylamine derivatives that contain phenethylamine as a "backbone"; in other words, this chemical class includes derivative compounds that are formed by replacing one or more hydrogen atoms in the phenethylamine core structure with substituents. The class of substituted phenethylamines includes all substituted amphetamines, and substituted methylenedioxyphenethylamines (MDxx),and contains many drugs which act as empathogens, stimulants, psychedelics, anorectics, bronchodilators, decongestants, and/or antidepressants, among others.

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

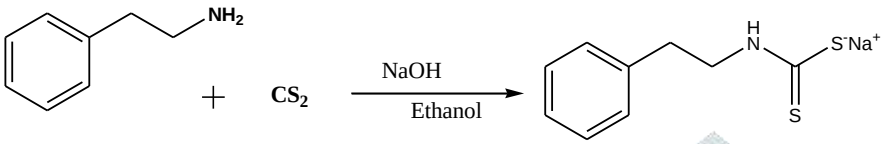
The main thrust of the study is to prepare as such new Dithiocarbamate ligand from an amine having considerable amount of applications on its own with the hope that the resultant Dithiocarbamate may possess much more applications and find a place in major fields of interest.

MATERIALS AND METHODS

Experimental Section

Copper chloride anhydrous was obtained from Fluka, Phenethylamine 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 on JAS.CO UV/VIS-7850 recording spectrophotometer. Infrared spectra was recorded on a JAS.Co-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 500MHz 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 Dithiocarbamate 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 (0.05ml) in 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 Fe (II) Complexes

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

The aqueous solution of 0.05 mol of Cupper Chloride was added with constant stirring to an aqueous solution of 0.01 mol of Sodium salt of Phenethylamine Dithiocarbamate ligand. The reaction mixture was stirred at room temperature for 2 hours. The colored (yellow) precipitates were obtained. The precipitates were filtered and washed with water and then with methanol and dried over calcium chloride in desiccator's Yield:78% and decomposes at 110 C.

Anal. Calcd. For
C,38.59;H,4.97;N,6.16;Cu,12.70;O,:18.67,S,24.61;Found:C,37..59;H,4.27;N,5.16;Cu,11.70;O,:17.67,S,23.61

Synthesis of [Fe (PEADCT)Cl$_2$]

The aqueous solution of 0.05 mol of Manganese Chloride was added with constant stirring to an aqueous solution of 0.01 mol of Sodium salt of Phenethylamine Dithiocarbamate ligand in the presence of small quantity of triethylamine. The reaction mixture was stirred at room temperature for 2 hours. The colored (gray) precipitates were obtained. The precipitates were filtered and washed with water and then with methanol and dried over calcium chloride in a desiccator Yield: 80% and decomposes at 110^{0}C. Anal. Calcd. For C, 26.43; H, 4.44; N, 6.17; Cl,15.60; Fe,12.09 Found: C:35.16; H:3.9; N:4.82; O:16.53; Fe,17.40; S:22.09

RESULTS AND DISCUSSION

Solid reflectance spectra data for the Cu and Fe of Phenethylamine metal complexes. The complexes $[Cu(PEADCT)_2)Cl_2]$ and $[Fe(PEADCT)_2Cl_2]$ complexes exhibit magnetic property and has an electronic spectrum which can be assigned to low spin Cu (II) and Fe (II) in an Octahedral Environment. Intra ligand electronic transition in then…C…S…S and S…C…S chronophers of the Dithiocarbamate 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.

Infrared Spectrum

Two regions of the IR spectrum of the $[Cu(PEADCT)_2)Cl_2]$ and $[Fe(PEADCT)_2Cl_2]$ complex have proven valuable in arguments concerning the electronic and structural characteristics of this compound. The presence of the thiouride band between 1545-1430 cm^{-1} suggest a considerable double bond character in the C…N bond vibration of the $S_2C\text{-}NR_2$ group. The band present in the 967 cm^{-1} range is attributed to the prevailing contribution of (C…S) Vibrations in these ranges have been used defectively in differentiating between monodentate, bidentate carbamodithiolate ligands. The presence of only one strong band supports bidentate coordination of the dithioligands, where as a doublet is expected in the case of monodentate coordination. (C…S) and (C..N) Stretching frequencies fall in the 1035 cm^{-1} (1001 cm^{-1} for the free ligand) and 1478 cm^{-1} respectively. The methyl group in the complex, as medium strong bands in the 2960 cm^{-1} range can be related to the asymmetric CH_3 stretching vibration.

H^1-NMR Spectra

The NMR spectrum of the $[Cu(PEADCT)_2)Cl_2]$ and $[Fe(PEADCT)_2Cl_2]$ complexes showed at 2.3-2.4 ppm. Which may be assigned to the hydroxyl protons. The peak at 7.9-7.98 attributed to NH protons of thiouraide nitrogens in both complexes. In other signals is also appeared in the region 0.98, 1.5, 3.8 ppm.

Docking Studies:

Docking techniques, designed to find the correct conformation of a ligand and its receptor, have now been used for decades. The process of binding a small molecule to its protein target is not simple; several entropic and enthalpic factors influence the interactions between them. The mobility of both ligand and receptor, the effect of the protein environment on the charge distribution over the ligand and their interactions with the surrounding water molecules, further complicate the quantitative description of the process. The idea behind this technique is to generate a comprehensive set of conformations of the receptor complex, and then to rank them according to their stability. The most popular docking programs include DOCK, AutoDock, FlexX, GOLD, and GLIDE among others.

In the field of molecular modeling, docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex Lengauer T, Rarey M (Jun 1996). Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules using, for example, scoring functions. Molecular docking is one of the most frequently used methods in structure-based drug design, due to its ability to predict the binding-conformation of small molecule ligands to the appropriate target binding site. Characterisation of the binding behaviour plays an important role in rational design of drugs as well as to elucidate fundamental biochemical processes (Kitchen DB et al., 2004). During the course of the docking process, the ligand and the protein adjust their conformation to achieve an overall "best-fit" and this kind of conformational adjustment resulting in the overall binding is referred to as "induced-fit" (Wei BQ et al 2004). Molecular docking research focusses on computationally simulating the molecular recognition process. It aims to achieve an optimized conformation for both the protein and ligand and relative orientation between protein and ligand such that the free energy of the overall system is minimized.

A binding interaction between a small molecule ligand and an enzyme protein may result in activation or inhibition of the enzyme. If the protein is a receptor, ligand binding may result in agonism or antagonism. Docking is most commonly used in the field of drug design - most drugs are small organic molecules, and docking may be applied to: hit identification – docking combined with a scoring function can be used to quickly screen large databases of potential drugs in silico to identify molecules that are likely to bind to protein target of interest (see virtual screening). Lead optimization – docking can be used to predict in where and in which relative orientation a ligand binds to a protein (also referred to as the binding mode or pose). This information may in turn be used to design more potent and selective analogs. Bioremediation – Protein ligand docking can also be used to predict pollutants that can be degraded by enzymes (Bursulaya BD et al.,2003).

The present work all the calculations were performed on a workplace by AMD 64 bits dual processing hi end server machines. Molecular docking calculations were performed with AutoDock 4.0. If not otherwise stated, default settings were used during all calculations. Phenethylamine (PEADCT).

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

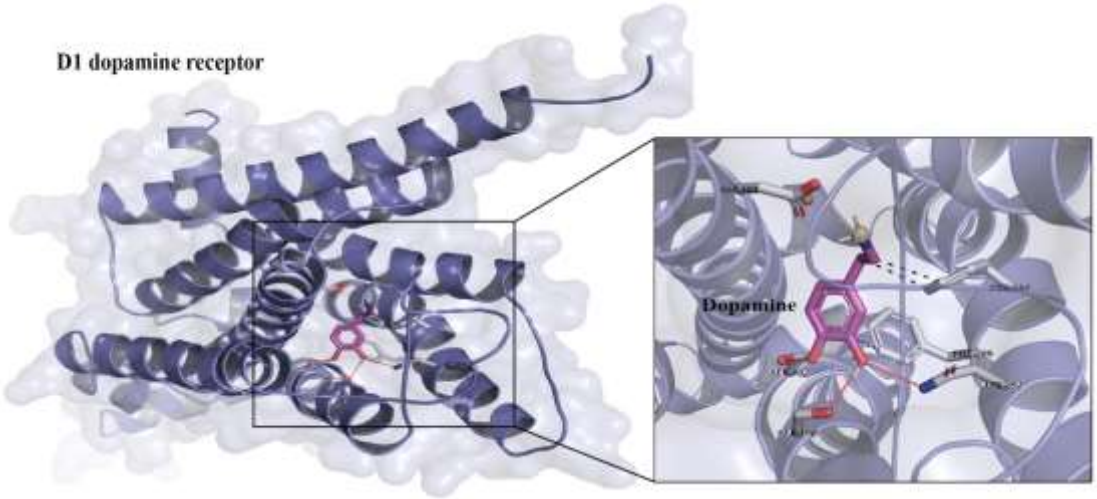
parameters and PMV 1.4.5 viewer was then used to observe the interactions of the docked compounds to the D1 model.

Results and Discussion:

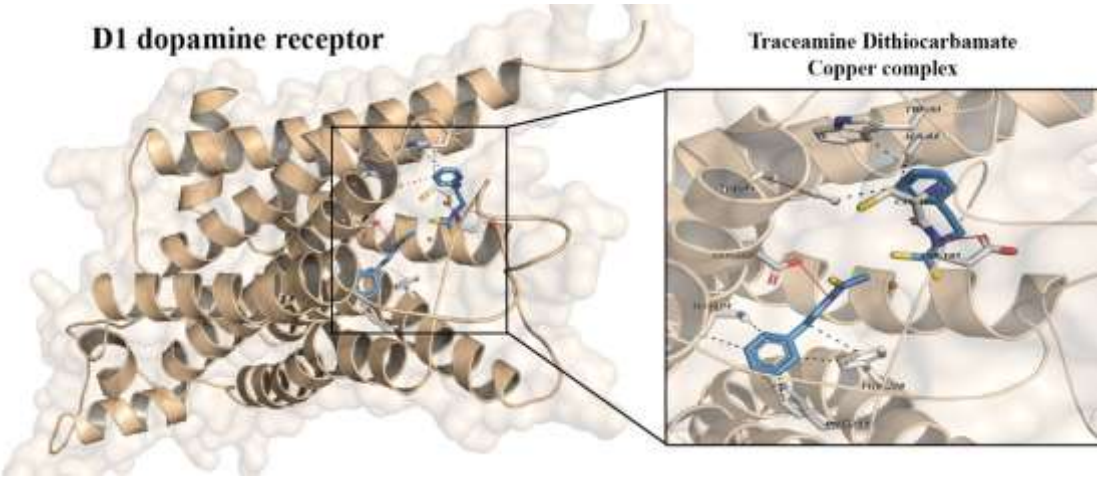
Binding energy for each docking was calculated using a semi-empirical free energy force field. Out of these 5 docked ligands and its Complexes molecules with receptor, top two molecules were filtered out on the basis of binding energy. The binding modes and geometrical orientation of all compounds were 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 D1 receptor.

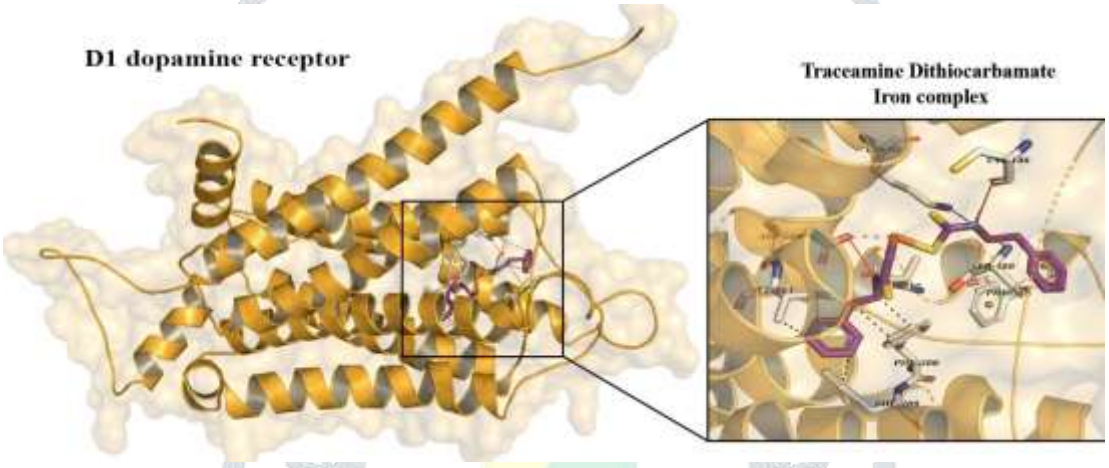
S. No	Compound Name	Receptor Name	Cluster Rank	RMSD	Lowest binding Energy (Kcal/mole)
1	Phenethylamine (PEADCT) Ligand	H3 Receptor	1	0.00	-4.41
2	[Cu(PEADCT)]	H3 Receptor	1	1.05	-7.42
3	[Ru(PEADCT)]	H3 Receptor	2	0.23	-6.53



1.1(a) D1 Dopamine Receptor



1.1(b)Phenethylamine dithiocarbamate(Traceamine) Copper Complex docking with D1 dopamine receptor



1.1(c)Phenethylamine dithiocarbamate(Traceamine) Iron Complex docking with D1 dopamine receptor

Most docked inhibitors interacted by the same mode of the inhibitors, Dopamine D1 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 detailed Tab.1, among all complex molecules Phenethylamine Copper complex , Phenethylamine Iron complexes gave best scores.

Conclusion:

Cu (II) and Fe(II) complexes of Phenethylamine Dithiocarbamate Ligand with have been synthesized and characterized. The ligand moiety exhibit a bidentate coordination mode in the Cu (II) and Fe (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 D1 receptor model with Dithiocarbamate ligand and metal complexes having more favourable rank

score, docking score and hydrogen bonding energy and the binding pocket of the D1 receptor. Activation of D1 hetero receptors can inhibit release of other neurotransmitters such acetylcholine, noradrenaline, dopamine, conversely blockade of D1 receptors with our synthesized selective antagonists can increase the release of neurotransmitters involved in cognitive processes. Docking studies of Dithiocarbamate ligand and metal complexes with D1 receptor and detailed analyses of metal inhibitors, D1 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 Dithiocarbamate ligands and metal complexes could be a potential anti Neurological disorders lead molecules for modulating the expression of D1 receptor for experimental testing.

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