Chapter – X

Docking Studies of Ligands and their metal complexes
Docking Studies of Ligands and Metal Complexes

The literature survey reveals that Protein-ligand binding Studies involved in neurological disorders of the metal complexes, of new dithiocarbamates is very scarce. Hence the present studies carried out a research program and analyzed the importance of Protein binding studies of the new dithiocarbamate with metal complexes like Cu, Ru, Ni, Mn, La, Pd, Y, Co, Zn and Fe.

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 as 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 H3 receptor 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 footprinting 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.

**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. Dopamine carbamodithiolate (DCDT), Pramepexole carbamodithiolate (PPCDT), Atomoxetine carbamodithiolate (ACDT), Valganciclovir carbamodithiolate (VCCDT),Histamine carbamodithiolate (HCDT) ligands and their metal complexes are docking with histamine H3 receptor the interactions studied

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.

<p>| Table1. Summary of docking results high ranked ligands and complex molecules with H3 receptor. |</p>
<table>
<thead>
<tr>
<th>S. No</th>
<th>Compound Name</th>
<th>Receptor Name</th>
<th>Cluster Rank</th>
<th>RMSD</th>
<th>Lowest binding Energy (Kcal/mole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dopamine (DCDT) Ligand</td>
<td>H3 Receptor</td>
<td>1</td>
<td>0.00</td>
<td>-4.41</td>
</tr>
<tr>
<td>2</td>
<td>[Cu(DCDT)]</td>
<td>H3 Receptor</td>
<td>1</td>
<td>1.05</td>
<td>-7.42</td>
</tr>
<tr>
<td>3</td>
<td>[Ru(DCDT)]</td>
<td>H3 Receptor</td>
<td>2</td>
<td>0.23</td>
<td>-6.53</td>
</tr>
<tr>
<td>4</td>
<td>Pramepexole (PPCDT) Ligand</td>
<td>H3 Receptor</td>
<td>1</td>
<td>0.00</td>
<td>-6.53</td>
</tr>
<tr>
<td>5</td>
<td>[Cu(PPCDT)]</td>
<td>H3 Receptor</td>
<td>1</td>
<td>0.78</td>
<td>-6.83</td>
</tr>
<tr>
<td>6</td>
<td>[Ru(PPCDT)]</td>
<td>H3 Receptor</td>
<td>1</td>
<td>0.00</td>
<td>-5.30</td>
</tr>
<tr>
<td>7</td>
<td>Atomoxetine (ACDT) Ligand</td>
<td>H3 Receptor</td>
<td>1</td>
<td>0.65</td>
<td>-4.80</td>
</tr>
<tr>
<td>8</td>
<td>[Cu(ACDT)]</td>
<td>H3 Receptor</td>
<td>3</td>
<td>0.10</td>
<td>-5.12</td>
</tr>
<tr>
<td>9</td>
<td>[Ru(ACDT)]</td>
<td>H3 Receptor</td>
<td>1</td>
<td>0.00</td>
<td>-6.35</td>
</tr>
<tr>
<td>10</td>
<td>Valganociclovir (VCCDT) Ligand</td>
<td>H3 Receptor</td>
<td>1</td>
<td>0.00</td>
<td>-5.07</td>
</tr>
<tr>
<td>11</td>
<td>[Cu(VCCDT)]</td>
<td>H3 Receptor</td>
<td>1</td>
<td>1.27</td>
<td>-6.50</td>
</tr>
<tr>
<td>12</td>
<td>[Ru(VCCDT)]</td>
<td>H3 Receptor</td>
<td>2</td>
<td>1.50</td>
<td>-7.03</td>
</tr>
<tr>
<td>13</td>
<td>Histamine (HCDT) Ligand</td>
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<td>14</td>
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<tr>
<td>15</td>
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<td>H3 Receptor</td>
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<td>2.0</td>
<td>-5.72</td>
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</tbody>
</table>

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), pramepexole ligand shown interaction with amino acids Glu 231, Glu 238 and Leu 247 (Figure 1b), Valganociclovir ligand shows interaction with amino acids Asp 234, Glu 243(Figure 1c), and Atomoxetine without showing any interaction it can binds the same pore of the h3 receptor. Synthesised ligand metal complexes are showing same interaction and binding.
pose with high energy values in detailed Tab.1, among all complex molecules Dopamine Copper complex, dopamine Ruthenium and Valganociclovir Ruthenium complexes gave best scores.

Fig. 1 The cartoon and electrostatic surface representation of the binding site of (a) H3 receptor model in olive, histamine ligand with sticks in pink, aminoacids Leu in cyan and Glu in green colour.
Fig. 2 The cartoon and electrostatic surface representation of the binding site of (b) H3 receptor model in light pink, Pramepexole ligand with sticks in green and amino acids Glu 231 in red, Glu 238 blue and Leu 247 in orange colour.

Fig. 3 The cartoon and electrostatic surface representation of the binding site of (c) H3 receptor model in limon, Valganociclovir ligand with sticks in hot pink and amino acids Asp 234 in orange Glu 243 in cyan colour.
Fig. 4 The cartoon and electrostatic surface representation of the binding site of (d) H3 receptor model in limon, Atomoxetine ligand with sticks in green colour.

Fig. 5, 6 The cartoon and electrostatic surface representation of the binding site of (e1.e2) H3 receptor model in sky blue, ligand complexes (Ru, Cu) with sticks in green and amino acids same.
in e1 and e2 that are represented Glu 238 in pink, Glu 241 in limon, Glu 243 in orange and Glu 247 in blue colour.

Fig. 7 The cartoon and electrostatic surface representation of the binding site of (c) H3 receptor model in limon, Valganociclovir Ru complex with sticks in blue and amino acids Glu 238 in pink, Ser 229 in cyan, Ser 230 in orange colour.

Conclusion:
In this Study, we have docking studies of H3 receptor model with carbamodithiolate ligands and metal complexes showed best of four ligands and three complexes having more favourable interaction among all with 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 as 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 ligands 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.

References:


