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Short Communication

In-Silico Evaluation Of Lamotrigine Schiff Base Of Cinnamonaldehyde And Its Metal Coordinates At Voltage Gated Sodium Channel

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Introduction

Lamotrigine belongs to a class of phenyltriazine compounds, chemically unrelated to other anticonvulsants [1]; used to control seizures and convulsions of various grades [2]. The antiepileptic effect of LTG entails from its binding with the voltage gated sodium channels (VNaC) and thus inhibiting the release of endogenous amino acids and acetylcholine [3,4]. Schiff bases of antiepileptic drugs protect against seizures through variety of cellular targets, like synaptic vesicle protein, neurotransmitter metabolic enzyme, neurotransmitter transporter and ion channels [5]. A homology model of VNaC was prepared for molecular docking studies of lamotrigine [6]. Docking of metal derived schiff base ligand is a new approach in computational chemistry; it predicts the binding affinity of small molecules with receptor that results in new complex with overall minimum energy [7,8].

Methodology /Molecular Modeling

Three dimensional (3D) crystal structure of the enzyme was retrieved from RCSB Protein Data Bank (PDB) with PDB-ID: 5kav (https://www.rcsb.org/structure/5KAV) for anticonvulsant activity. Two dimensional (2D) structures of lamotrigine schiff base metal complexes were drawn and optimized by ACD/Chem Sketch software and save as MDL file. The MDL files were 3D protonated and energy minimized to PDB by using Open Babel GUI [9]. Docking studies was carried out using Auto Dock 4.2 program [10]. The synthesis and structure of ligands were already reported by (Saima et al., 2021) in ACS Omega with 2KAV receptor. Now crystal structure of 5KAV was modelled using Auto Dock Tools 1.5.6; impurities were removed, whereas, partial charges and polar hydrogen were added. Macromolecule was saved in its respective PDBQT format for ligand interactions [11]. The best active region of enzyme was selected by targeting binding site with amino acid residues involved in binding to ligand [12]. The grid box was set at 100x100x100 Å along X, Y and Z axis with grid spacing of 0.375Å to recognize the binding site of ligand. The auto dock parameters used were: Genetic algorithm with population size = 150; Maximum number of energy evaluations = 250000; Genetic algorithm cross-over mode = 2 points. The rigidity parameters were set for receptor keeping ligand flexible. Ten docked orientations (poses) were obtained after protein-ligand docking at 5KAV receptor. The best conformation was screened in terms of lowest binding energy among several bioactive conformations generated by various interactions. Cluster analysis of protein binding sites with lowest binding energy was further explored using Pymol Molecular Graphics System [2,8]. The reliability of docking program was validated by using re-docking method; root mean square deviation (RMSD) was then calculated and in all cases RMSD value of <2.0 Å was considered accurate in predicting binding orientation of ligand [13].

Results and Discussion

Previous mechanistic investigations have provided evidence that the anti-epileptic effects of LTG originates from its binding at the voltage gated sodium channel [6]. LTG specifically block the sodium channel by binding to the pore in the inactivated open state. Therefore, we intended that the newly synthesized LTG-SB-M complexes must bind to the VNaC to elicit the anti-epileptic effect. To test this hypothesis, we docked the LTG-SB-M complex using co-crystal structure of human VNaC (PDB ID: 5KAV) for calculating binding interactions. The detailed results of LTG-SB-M complex docked with 5KAV were tabulated in Table 1; it is cleared from table 1 that compound 7c shows good interaction at VNaC. The interacting residues of LTG as standard and 7c were also demonstrated in (Figure 1) (a) and (b) respectively.

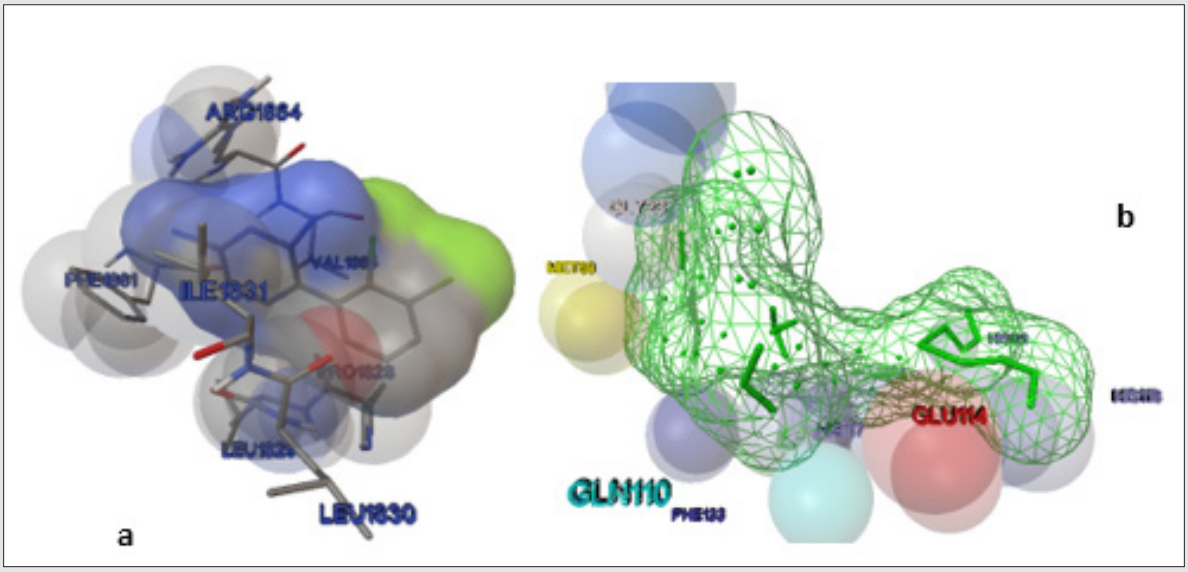

Figure 1: (a) Docked structure of LTG with modelled 5KAV receptor by Auto Dock; together with amino acid residues at the binding site of 5KAV. (b) Wire frame view of 7c on 5KAV receptor, generated by Auto Dock, along with interacting residues in the binding pocket of 5KAV.

Table 1: Binding properties of receptor protein (5KAV) to different ligands.

Active Compound	Molecular Formula	Molecular Weight (g/mol)	Binding Energy with Receptor (Kcal/mol)	No of Hydrogen Bonds	Interacting Residues
3a	$C_{27}H_{19}Cl_2N_5$	484	-6.75	1	LEU8, GLY52, ASP53, LEU54, ALA86, GLN136, LEU138, ILE148, GLU150, TRP152
4a	$C_{27}H_{19}Cl_2N_5Zn$	551	-6.83	2	GLU2, GLN4, GLN6, VAL96, PHE99, GLU100, GLU150
5a	$C_{27}H_{19}Cl_2CuN_5$	549	-6.19	1	GLU100, ALA101, GLN102, ALA108, GLN111, LYS112
6a	$C_{27}H_{19}AgCl_2N_5$	592	-6.41	1	GLU100, ALA101, GLN102, ALA108, GLN111, LYS112, GLU115
7a	**$C_{33}H_{37}Cl_2N_5Sn$**	**717**	**-8.62**	**2**	**GLY23, ARG24, MET69, GLN110, GLU114, HIS117, HIS118, HIS121, PHE133**
LTG (std.)	$C_9H_7Cl_2N_5$	256	-6.13	2	PRO1828, LEU1829, LEU1830, ILE1831, PHE1861, ARG1864, VAL1865

Conclusion

In this study it is confirmed that LTG-SB-M complexes synthesized from cinnamon aldehyde shows good binding energies at VNaC and hence can be used as antiepileptic drugs in future.

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