ORIGINAL ARTICLE

Molecular docking studies of 3,5-disubstituted hydantoin derivatives against cyclin-dependent kinase-5 receptor as potential anti alzheimer agents

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Abstract

Background: Alzheimer's disease (AD) is a devastating neurological condition for which there is an urgent need for novel treatment strategies. Here, we looked into the potential for 3,5-disubstituted hydantoins to inhibit Cyclin Dependent Kinase (CDK)-5, an enzyme crucial to the onset of AD. Using molecular docking research, promising compounds that interact with the CDK-5 receptor were identified. **Materials and Methods:** The ligands were sketched in MDL Mol file format using ChemSketch software, and then converted to Pdb format using Avogadro software. The iGEMDOCK software was used to conduct molecular docking studies, and the results were ultimately displayed using Discovery Studio Visualizer. **Results and Discussion:** Most ligands have demonstrated a greater affinity for binding to CDK-5. The majority of the ligands have demonstrated binding affinities that are fairly comparable to those of the conventional CDK-5, including Dinaciclib (−98.0225 kcal/mol) and Flavopiridol (−93.9411 kcal/mol). The top two compounds, Dv-07N (−101.748 kcal/mol) and Dv-01N (−98.0225 kcal/mol), were chosen for visualization. **Conclusion:** Hydantoin derivatives could be promising candidates for the development of new AD therapies.

Key words: Alzheimer's disease, cyclindependent kinase-5 receptor antagonists, discovery studio visualizer, hydantoin derivatives, iGEMDOCK software, molecular docking

INTRODUCTION

By reacting different α-amino methyl esters hydrochlorides with N-substituted carbamates, 3,5-disubstituted hydantoins[1] are produced. This introductory section will discuss the background of hydantoins as potential anti-Alzheimer agents,[2-7] emphasizing their pharmacological actions, structural characteristics, and encouraging findings from studies in this field. Phosphodiesterases, kinases,[8,9] histamine, insulin, muscarinic acetylcholine, and acetylcholinesterase are just a few of the many receptor targets that hydantoins can bind to. Protein kinases contain specific amino acid residues that must be phosphorylated by adding a phosphate group. This alters a protein's on/off state, which impacts its function and activity. More and more illnesses are being researched as possible targets for medications that alter phosphorylation status. Amyloid-beta plaques and neurofibrillary tangles build up in the brain to cause Alzheimer's disease (AD), a chronic neurodegenerative illness. One important protein, Cyclin Dependent Kinase (CDK)-5, is connected to the development of AD.[10] Neurodegenerative diseases like AD are brought on by aberrant hyperphosphorylation of CDK-5 substrates such as APP, tau, and neurofilament, which happens when pathogenic stimuli raise CDK-5 activity.[11] Senile plaques, neurofibrillary tangles, damaged synapses, mitochondrial

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dysfunction, and cell cycle reactivation are all consequences of CDK-5 dysregulation.

More significantly, by inhibiting β-amyloid-induced neurotoxicity and tauopathies, CDK-5 inhibitors may prevent memory loss and neuronal cell loss.[12] In AD, cyclin-dependent kinase inhibitors, including Dinaciclib,[13-16] Flavopiridol,[17-20] and Roscovitine,[21-23] are essential. Essential medicinal substances, hydantoins have a wide range of therapeutic uses, such as antibacterial, antiepileptic, and antiarrhythmic medications. They may selectively inhibit cyclooxygenase-2 and were created to treat baldness.

MATERIALS AND METHODS

Step - 1

The reaction between α-amino methyl ester hydrochlorides and carbamates results in the formation of the respective ureido derivatives. The hydantoin was synthesized successfully under all reaction conditions; however, the most favorable outcome was achieved when triethylamine was employed as a base in acetonitrile, resulting in the highest yield. The optimal yield was achieved by utilizing a mixture of acetonitrile and triethylamine in a ratio of 2:1.

Step - 2

Under basic conditions, ureido derivatives undergo cyclization, which produces substituted hydantoins. To cyclize the intermediate ureido derivative in a 2:1 mixture of acetonitrile and triethylamine, the base was added ten hours after the start of the reaction.

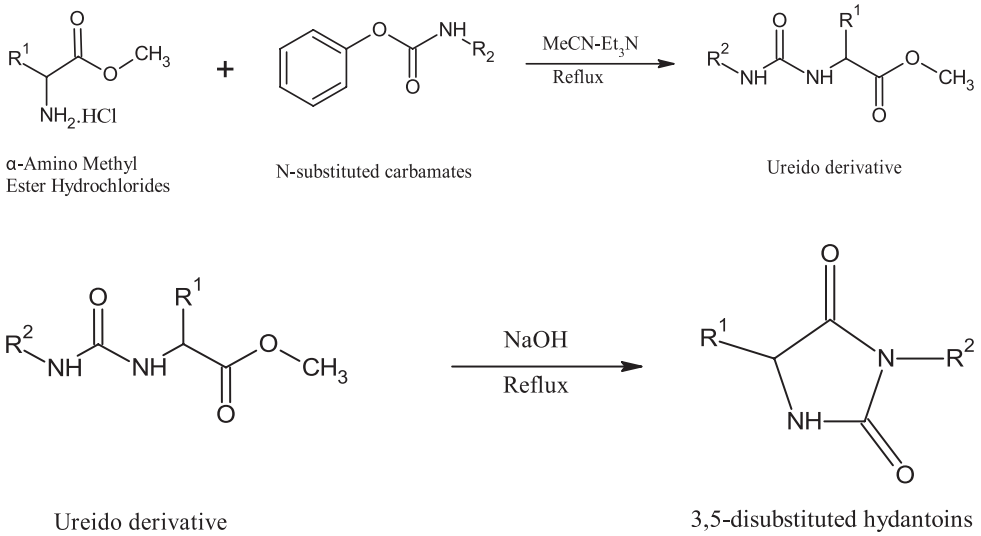
The reactions proceeded without any issues, except for the interaction between phenyl isopropyl carbamate and methyl phenylalaninate hydrochloride. This particular reaction only resulted in the formation of the ureido derivative, and no cyclization was detected. This is likely due to steric restriction surrounding the nitrogen atom, which reduces its nucleophilicity. Konnert and his colleagues have reported a comparable result.

MOLECULAR DOCKING PROCEDURE

The first step in the molecular docking process is the design and validation of a library of different test ligands using a predetermined synthesis scheme, making sure they satisfy drug-likeness requirements and using SwissADME software to predict target proteins.[24-26] ChemSketch software is then used to structure the test and standard ligands, and the files are saved in the MDL Mol format.[27-29] For docking software compatibility, ligand geometries are saved in PDB format after being optimized with the Avogadro application.[30-32] The RCSB PDB website provides the targeted protein in PDB format, such as CDK-5 (PDB code 1UNL, co-crystallized with roscovitine). The iGEMDOCK application is used for molecular docking,[33,34] which makes it easier for the test and standard compounds to interact inside CDK-5's binding pocket. To determine the tightness of fit (scoring) between the test ligands and the target protein, the docked poses of the compounds are examined, taking van der Waals interactions, hydrogen bonds, and electrostatic energy into account. The quality of interactions (total energy of interaction) seen during docking simulations is used to identify possible drug candidates. The protein-ligand interactions are then thoroughly investigated using BioVia Discovery Studio software, which visualizes these discovered possible drug candidates. Figure 1 depicts 1UNL (CDK-5).

RESULTS AND DISCUSSION

Most of the ligands that were created exhibit a higher affinity for binding to the CDK-5 receptor, particularly at the RRC site. The comparative analysis of molecular docking



α-Amino Methyl Ester Hydrochlorides

N-substituted carbamates

Ureido derivative

Ureido derivative

3,5-disubstituted hydantoins

Table 1: Interaction and binding energy summary of the ligands against cyclin-dependent kinase-5 receptor

Ligand code	Binding energy (K. Cal/mol)	Interacting active site amino acid residues
Dv-07N	−101.748	GLN:130, ASP:86, ASN:144, CYS:83, LEU:133, ILE:10, LYS:33, PHE:80, ALA:31, VAL:18, PHE:82
Dv-01N	−99.269	ASN:144, PHE:80, LEU:133, VAL:18, VAL:64, LYS:88, ALA:143, ALA:31, CYS:83, GLN:130, PHE:82, HOH:2019
Dinaciclib	−98.0225	CYS:83, GLU:81, ASN:144, VAL:18, ALA:31, PHE:80, LYS:33, LEU:133, ILE:10, LYS:128
Dv-03N	−95.2625	LYS:89, CYS:83, ASP:86, ILE:10, LYS:88, LEU:133
Flavopiridol	−93.9411	CYS:83, GLU:81, ASN:144, GLU:12, LEU:133, GLN:85, VAL:18, ALA:31, ALA:143, ILE:10, LYS:89
Roscovitine	−92.9641	ASP:84, GLU:8, ASP:86, PHE:80, VAL:18, ALA:31, ILE:10

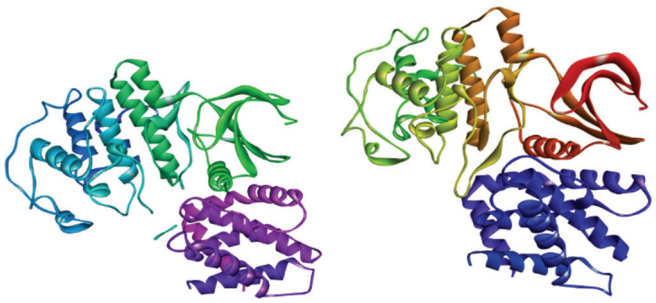


Figure 1: Cleaned structure of cyclin-dependent kinase-5 protein

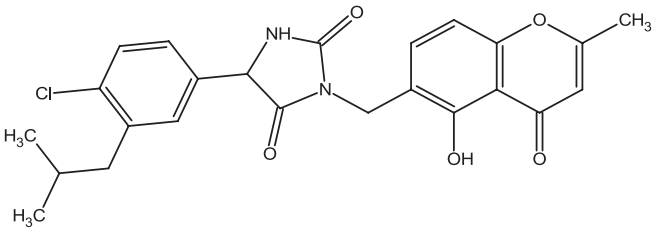


Figure 2: Dv-07N

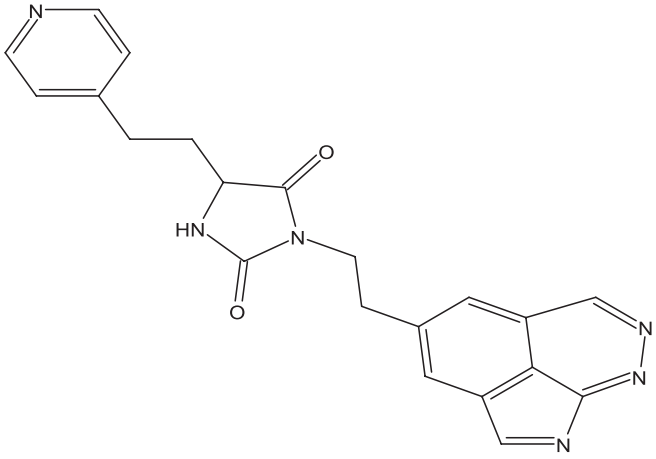


Figure 3: Dv-01N

results revealed that the 3,5-disubstituted hydantoins Dv-07N and Dv-01N exhibited superior performance compared to the standard inhibitor Dinaciclib. Dv-07N and Dv-01N had binding energies of −101.748 Kcal/mol

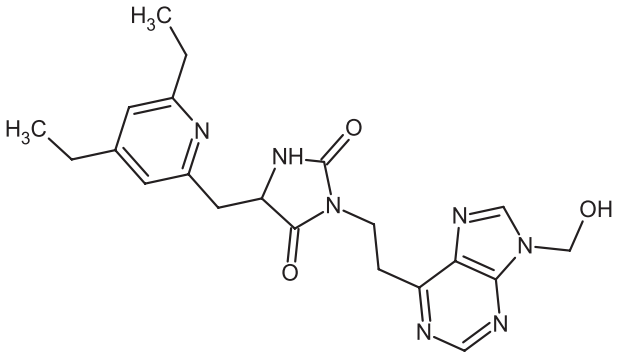


Figure 4: Dv-03N

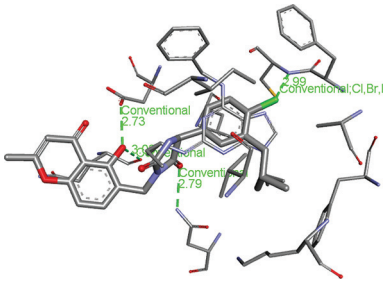
and −99.269 Kcal/mol, respectively, while Dinaciclib had a binding energy of −98.0225 Kcal/mol. The docking results of the designed hydantoin derivatives with the CDK-5 receptor are summarized in Table 1, showing the binding energies and key interacting amino acid residues. The ligand Dv-03N, with a binding energy of −95.2625 Kcal/mol, exhibited a moderate affinity by positioning itself between Dinaciclib and the conventional inhibitors Flavopiridol (−93.9411 Kcal/mol) and Roscovitine (−92.9641 Kcal/mol). The structures of Dv-07N, Dv-01N, and Dv-03N are illustrated in Figures 2-4, respectively.

The visualization of conventional hydrogen bonding was observed in 3D and 2D interactions that are shown in Table 2. 2D interaction provides an accurate picture of the amino acid residues involved in the interaction and their closeness to the ligand at the active site.

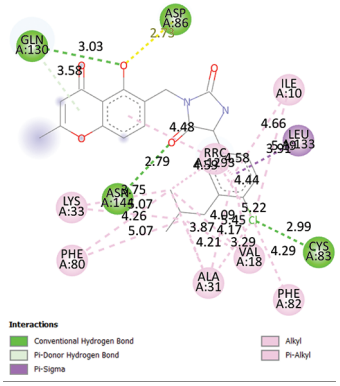
Compound Dv-07N Forms Four Conventional Hydrogen Bonds with the Amino Acid Residues

GLN:130 (3.03 Å), ASP:86 (2.73 Å), ASN:144 (2.79 Å), CYS:83 (2.99 Å), one Pi-Donar hydrogen bond with the amino acid residue GLN:130 (3.58 Å), one Pi-Sigma bond with the amino acid residue LEU:133 (3.91 Å) and six Alkyl and Pi-Alkyl bonds with the amino acid residues ILE:10 (4.66 Å), LYS:33 (3.75 Å), PHE:80 (4.26 Å), ALA:31 (3.87 Å), VAL:18 (3.29 Å), PHE:82(4.29 Å).

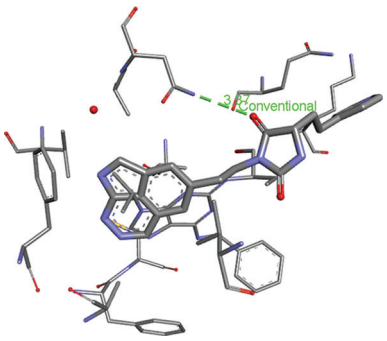
Table 2: Visualization data for best-docked poses against CDK-5



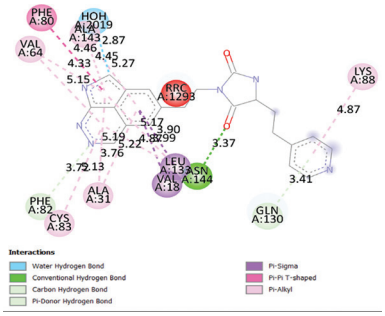
Dv-07N 3D interaction with CDK-5



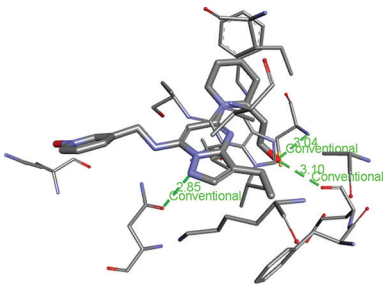
Dv-07N 2D interaction with CDK-5



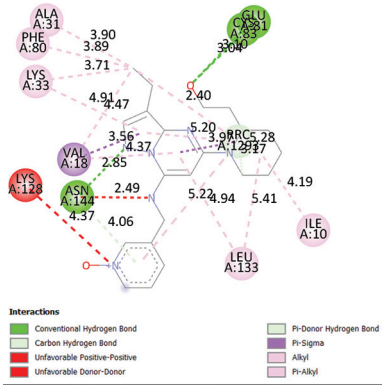
Dv-01N 3D interaction with CDK-5



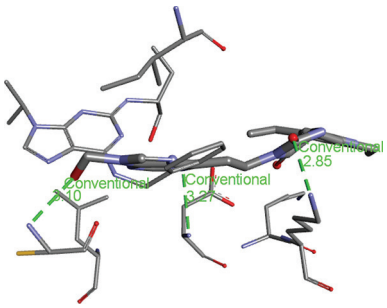
Dv-01N 2D interaction with CDK-5



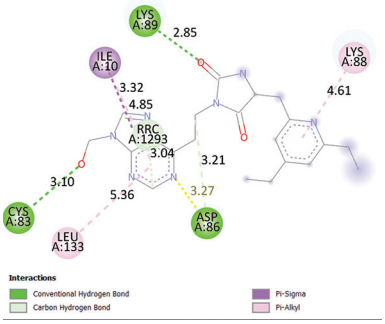
Dinaciclib 3D interaction with CDK-5



Dinaciclib 3D interaction with CDK-5



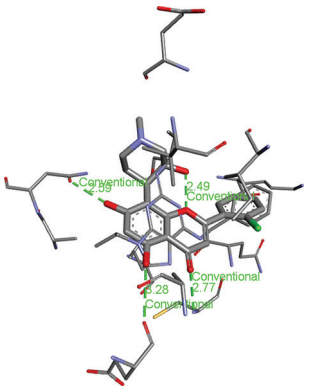
Dv-03N 3D interaction with CDK-5



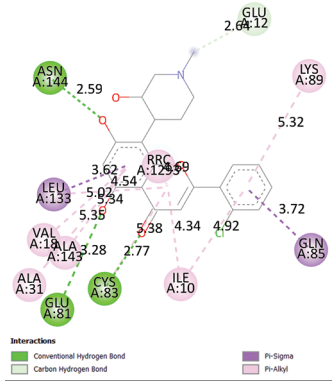
Dv-03N 2D interaction with CDK-5

(Contd...)

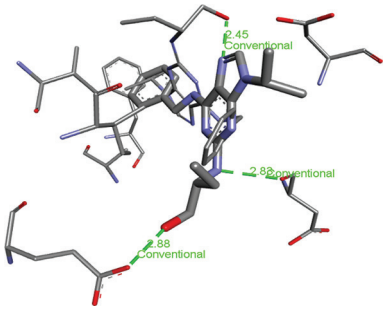
Table 2: *(Continued)*



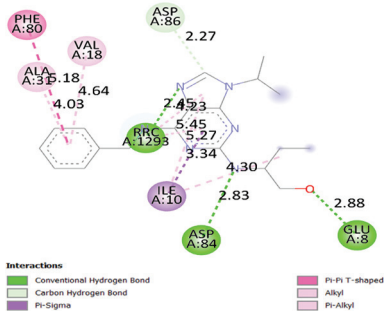
Flavopiridol 3D interaction with CDK-5



Flavopiridol 2D interaction with CDK-5



Roscovitine 3D interaction with CDK-5



Roscovitine 2D interaction with CDK-5

CDK5: Cyclin dependent kinase 5

Compound Dv-01N forms one conventional hydrogen bond with the amino acid residue ASN:144 (3.37 Å), two carbon hydrogen and Pi-Donar bonds with the amino acid residues GLN:130 (3.41 Å), PHE:82 (3.72 Å), two Pi-Sigma bonds with the amino acid residues LEU:133 (3.90 Å), VAL:18 (4.87 Å), one Pi-Pi T-Shaped bond with the amino acid residue PHE:80 (4.46 Å), five Pi-Alkyl bonds with the amino acid residuesVAL:64 (4.33 Å), LYS:88 (4.87 Å), ALA:143 (4.45 Å), ALA:31 (3.76 Å), CYS:83(5.13 Å) and one water hydrogen bond amino acid residueHOH:2019 (2.87 Å).

Compound Dinaciclib forms three conventional hydrogen bonds with the amino acid residuesCYS:83 (3.04 Å), GLU:81 (3.10 Å), ASN:144 (2.85 Å), one carbon hydrogen and Pi-Donar hydrogen bond with the amino acid residues ASN:144 (4.06 Å), two Unfavorable positive- positive and Donar-Donar bonds ASN:144 (2.49 Å), LYS:128 (4.37 Å),one Pi-Sigma bonds VAL:18 (3.56 Å) and five Alkyl and Pi-Alkyl bonds with the amino acid residues ALA:31 (3.90 Å), PHE:80 (3.89 Å), LYS:33 (3.71 Å), LEU:133 (4.94 Å), ILE:10 (4.19 Å).

Compound Dv-03N forms three conventional hydrogen bonds with the amino acid residues LYS:89 (2.85 Å), CYS:83 (3.10 Å), ASP:86 (3.27 Å), one carbon hydrogen bond with the amino acid residueASP:86 (3.21 Å), one Pi-Sigma bond with the amino acid residue ILE:10 (3.32 Å) and three Pi-Alkyl bonds with the amino acid residues LYS:88 (4.61 Å), LEU:133 (5.36 Å), ILE:10 (4.85 Å).

Compound Flavopiridol forms three conventional hydrogen bonds with the amino acid residues CYS:83 (2.77 Å), GLU:81 (3.28 Å), ASN:144 (2.59 Å), one carbon hydrogen bond with the amino acid residue GLU:12 (2.64 Å), two Pi-Sigma bonds with the amino acid residues LEU:133 (3.62 Å), GLN:85 (3.72 Å) and six Pi-Alkyl bonds with the amino acid residues LEU:133(5.02 Å), VAL:18 (4.54 Å), ALA:31 (5.35 Å), ALA:143 (5.34 Å), ILE:10 (4.34 Å), LYS:89 (5.32 Å).

Compound Roscovitine forms two conventional hydrogen bonds with the amino acid residues ASP:84 (2.83 Å), GLU:8 (2.88 Å), one carbon hydrogen bond with the amino acid residueASP:86 (2.27 Å), one Pi-Sigma bond with the amino acid residue ILE:10 (3.34 Å), one Pi-Pi T-Shaped bond with the amino acid residue PHE:80 (5.18 Å) and three Alkyl and Pi-Alkyl bonds with the amino acid residues ILE:10 (4.30 Å), VAL:18 (4.64 Å), ALA:31 (4.30) Å.

BINDING POCKET ANALYSIS

The antagonist's Dinaciclib, Flavopiridol, Roscovitine, and the most effective ligands were positioned in the central region of the RRC binding pocket using docking techniques.

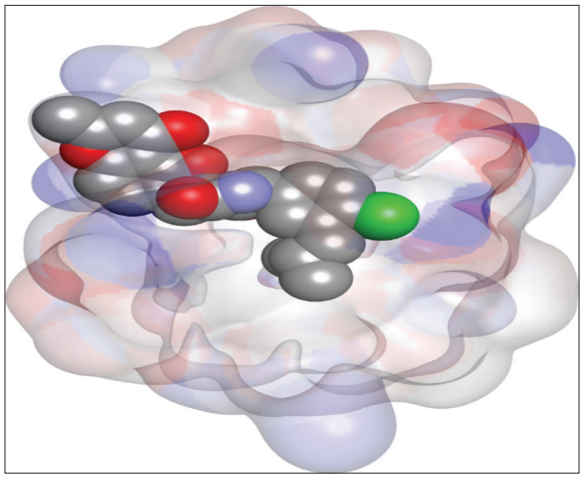


Figure 5: Active site pocket surface and binding mode of Dv-07N

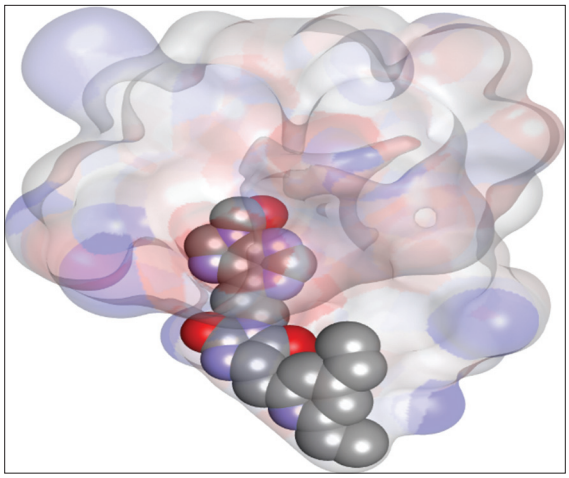


Figure 8: Active site pocket surface and binding mode of Dinaciclib

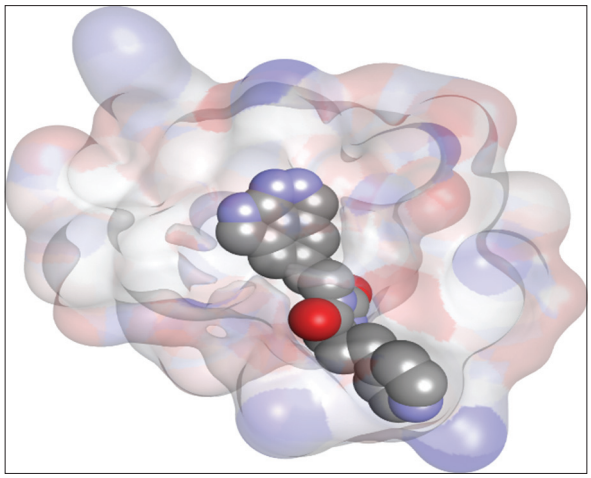


Figure 6: Active site pocket surface and binding mode of Dv-01N

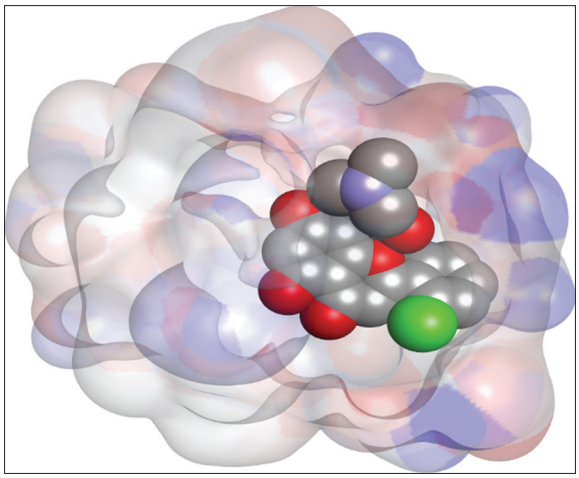


Figure 9: Active site pocket surface and binding mode of Flavopiridol

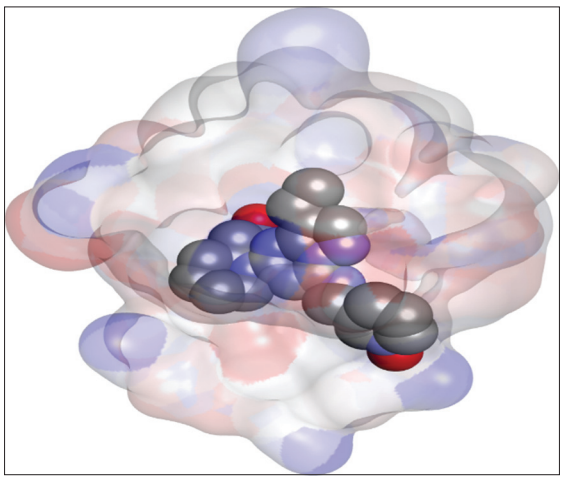


Figure 7: Active site pocket surface and binding mode of Dv-03N

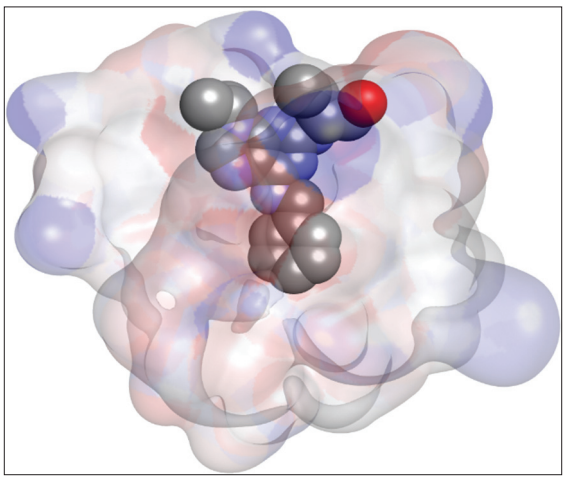


Figure 10: Active site pocket surface and binding mode of Roscovitin

This has contributed to the improvement of binding energy. Dv-07N consists of a chromone group, which withdraws electrons, whereas Dv-01N has a pyridine group, which donates electrons. This could have contributed to the enhanced binding energies of Dv-07N and Dv-01N. Due to their similar binding affinities and energies to well-known

inhibitors such as Dinaciclib, Flavopiridol, and Roscovitine, compounds Dv-07N and Dv-01N can be produced and employed for additional research purposes.

Active site pocket surface and binding modes of Dv-07N, Dv-01N, and Dv-03N, along with Standard Protein Kinase inhibitors Dinaciclib, Flavopiridol, and Roscovitine, were shown in Figures 5-10, respectively.

CONCLUSION

The common amino acids involved in interactions with both the Compound Dv-07N and the Compound Dinaciclib are ASN:144, CYS:83, LEU:133, ILE:10, LYS:33, PHE:80, ALA:31, and VAL:18.

The common amino acids involved in interactions with both Compound Dv-01N and the Compound Dinaciclib are ASN:144, CYS:83, LEU:133, VAL:18, PHE:80, and ALA:31.

The common amino acids involved in interactions with both the Compound Dv-03N and the Compound Flavopiridol are LYS:89, CYS:83, LEU:133, and ILE:10.

The common amino acids involved in interactions with both the Compound Dv-03N and the Compound Roscovitine are ASP:86 and ILE:10.

Finally, our docking study concluded that the designed hydantoin derivatives, especially Dv-07N, have binding energies higher than those of conventional inhibitors and show great promise as CDK-5 inhibitors. These results imply that these substances may be good options for creating novel treatments for AD. Their safety profile and efficacy need to be confirmed through additional experimental validation, which could greatly advance the field of treating neurodegenerative diseases.

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