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Advances in Bioresearch

ORIGINAL ARTICLE

In Silico Pharmacokinetics and Docking Study on novel Potential 5-Amino-Salicylic Acid derivatives against CDK- II

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ABSTRACT
Docking is a crucial tool in molecular design and development because it predicts the supported path of one particle to the next when they are bonded together to form a stable and flighty complex. As a result, information about the supported bearing can be used to estimate the strength of the connection and the binding attraction between a ligand and a target molecule. Aim: A number of possible compounds derived from the specified scheme were examined for their binding modes, interactions, and specific binding sites against Cyclin Dependent Kinase II as part of this study. Methods: In silico molecular docking of probable compounds acquired from designed scheme was executed utilizing Chemdraw, Swiss ADME, Molsoft, Molinspiration, Pymol and Autodock Vina software. Results: The current investigation was done to comprehend the drug-likeness character of novel derivatives and their binding affinity with 6GUH. Conclusion: The assessment offers confirmation to considered significant ligands auxiliaries potential Cyclin Dependent Kinase II inhibitor and further in vitro and in vivo assessments may demonstrate its remedial potential.
Key words: *Docking, Autodock Vina, 5-ASA, Anticancer activity, PDB, Pymol, Cyclin Dependent Kinase II*

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INTRODUCTION

Ulcerative colitis is one of two major types of inflammatory bowel illnesses. It is a flammable and progressive condition of the colon and rectal mucosa. The improvement of UC requires a continuous stimulation of mucosal immunity, which includes luminal antigens and intestinal epithelial cells, as well as cells of the inborn and adoptive immune systems that create mediators like cytokines and chemokines. Bacteria contaminate luminal segments on a regular basis, triggering a robust immunological response. Dendritic cells (DCs) in UC have higher TLR4 expression, which is linked to microbial identification, and these pro-inflammatory cytokines are produced as a result of these activated DCs. When UC is present, the tissue level of TNF α is measured and linked to gastrointestinal inflammation.

Sulfasalazine, the most normally utilized medication for ulcerative colitis, is powerful both to actuate reduction of midly to reasonably dynamic infection and for long haul upkeep treatment. In any case, dependent upon 33% of patients who take sulfasalazine experience some unfavorable response that restricts its utilization. Sulfasalazine comprises of the salicylate-5-aminosalicylic acid (5ASA) and a sulfa moiety, sulfpyridine, joined by a diazo bond. Oral sulfasalazine goes through negligible metabolism or absorption in the upper gastrointestinal tract, though colonic microbes corrupt the diazo attach to deliver free 5-ASA and sulfpyridine. Some sulfpyridine consumed and seems liable for most adverse reactions, though 5ASA is the remedially dynamic segment. For there to be remedial advantage, 5-ASA should contact the colonic mucosa straightforwardly, while 5-ASA goes about as topically effective. For more extensive disease, oral planning are ideal.

The mechanism of action of 5-ASA is currently unknown. The immunosuppressive, anti-inflammatory, and antioxidant properties of 5-ASA are attributed to a few components, including the suppression of the nuclear factor-kappa B pathway, protection of the epithelial barrier function of T84 cells against

peroxynitrite, free radical scavenging, and inhibition of leukotriene, prostaglandin, and pro-inflammatory cytokine synthesis.

Patients with UC have a higher risk of developing colon cancer. The duration, size, severity, and age at which the disease first appeared have all been linked to the etiology of CRC in UC patients. A positive family history of CRC, as well as the existence of a simultaneous essential sclerosing cholangitis, release ileitis, or a concomitant essential sclerosing cholangitis, increases the risk. The continuous and broad aggravation of the colon in Crohn's disease patients is thought to be a significant risk factor for colon cancer.

So there is a need to discover the novel malignancy drugs. The principle point of this investigation was to plan a systematic approach for the disclosure of novel inhibitors. In this study a series of probable compounds obtained from designed scheme were assessed against the target, CDK II, for binding orientations, dynamic interactions, and specific binding regions selected on the basis of Swiss Target Prediction and validated by analysis of amino residue through Ramchandran plot obtained from Procheck software. CDK II shows its significant aspect in the cellular performance procedure. They participate in the different processes such as transcription, cell division, metabolic control, cell motality, immune response, nervous system functioning. Kinase dysfunction is identified with numerous illnesses like cancer as well as inflammatory.Pharmacokinetics and Docking Study was finished by utilizing Chemdraw, Swiss ADME, Molsoft, Molinspiration, Pymol and Autodock Vina software [1-43].

MATERIAL AND METHODS

Ligand Preparation

2D and 3D potential structures of all derivatives were drawn by utilizing Chemdraw software. With the assistance of Pymol software, all drawn 2D/3D structures converted over into the PDB format and utilized for ADMET screening and Docking study.

Protein selection and Preparation

For Docking study, CDK II target was selected on the basis of Swiss Target Prediction Report. Three-dimensional crystallographic design of CDK II (6GUH) was bring back from PDB. Water molecules and heteroatoms were removed using Biovia. Procheck was used to examine a protein-pocket. To understand the φ and ψ dispersion of amino acid residues exhibited in Figure 1, the protein was plotted in a Ramachandran plot.

Predictions of pharmacokinetics (ADME) and toxicology

Molsoft, Molinspiration, and Swiss ADME tools were used to predict ADME and toxicological characteristics of bioactive molecules. This method computes pharmacokinetic and toxicological participants based on the compound's construction.

Bioactive Molecules' Drug Likeness Score

Each compound's drug similarity was predicted using an online server, Molsoft, Molinspiration, and Swiss ADME, which used atomic weight, the total number of H-donors and H-acceptors, and logP.

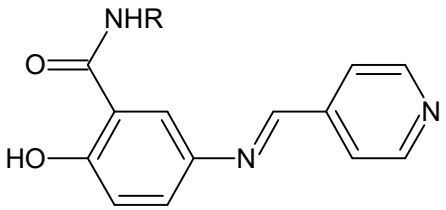
Ligand-Protein Docking

AutoDock 4.2 was used to accomplish the molecular docking. Hydrogen atoms, Kollman charges, and water molecules were added to the protein. The grid box was put in place, and docking was done. Following docking, the dlg file was used to determine the optimum ligand pose based on the binding energy. Finally, Biovia chose the pose with the least binding energy to illustrate the ligand-protein interaction [31-40].

RESULT AND DISCUSSION

The goal of this study was to learn more about the drug-like properties of new compounds as well as their affinity for 6GUH. If a compound's molecular weight is > 500 g/mol, it has >5 hydrogen bond donors, >5 log P, and >10 hydrogen bond acceptors, according to the Lipinski Rule of Five.

Novel derivatives obtained from designed scheme were assessed for their ADMET as well as anticancer action on Cyclin dependent kinase II target selected by Swiss Target prediction online tool. The ADMET parameters were anticipated by Swiss ADMET, Molsoft and Molinspiration. All the measured values are compared with reference compounds. Target selection is finished with the assistance of Swiss Target Prediction online tools and selected target (PDB: 6GUH) validate by generating Ramachandran Plot of selected protein through Procheck software. The protein was seen in Ramachandran plot to comprehend the φ and ψ dispersion of amino acid residues. It was found that among various novel derivatives got through designed scheme, compound obtained from 4-pyridinecarboxaldehyde shows drug likeness character as well as binding affinity towards target (**Cyclin Dependent Kinase II**).



Where,

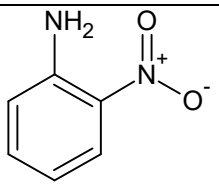
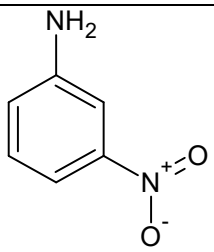
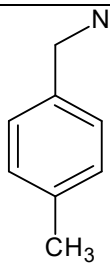
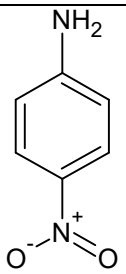
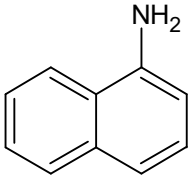
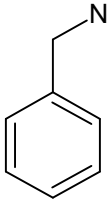
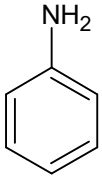
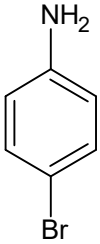
Compound	Amines	Compound	Amines
B1	 2-nitroaniline	**B2**	 3-nitroaniline
B3	 4-methylbenzylamine	**B4**	 4-nitroaniline
B5	 naphthalen-1-amine	**B6**	---
B7	 Benzylamine	**B8**	 aniline
B9	 4-bromoaniline		

Table 1: In silico ADMET screening for synthesized compound							
Compound	M.F.	M.W.	nHBA	nHBD	logP	TPSA (A^0)	Rule of Five
Accepted values	----------	<500 g/mol	<5	<10	<5	<110	Max 4
B1	$C_{19}H_{14}N_4O_4$	362.34	2	6	3.92	94.70	4
B2	$C_{19}H_{14}N_4O_4$	362.34	2	6	2.48	95.70	4
B3	$C_{21}H_{19}N_3O_2$	345.39	4	2	4.07	58.76	4
B4	$C_{19}H_{14}N_4O_4$	362.34	2	6	2.44	95.70	4
B5	$C_{23}H_{17}N_3O_2$	367.40	4	2	4.27	56,46	4
B6	$C_{13}H_{10}N_2O_3$	242.23	5	2	2.37	62.75	4
B7	$C_{20}H_{17}N_3O_2$	331.37	4	2	3.63	58.76	4
B8	$C_{19}H_{15}N_3O_2$	317.34	4	2	3,38	57.43	4
B9	$C_{19}H_{14}BrN_3O_2$	396.24	4	2	4.41	57.43	4

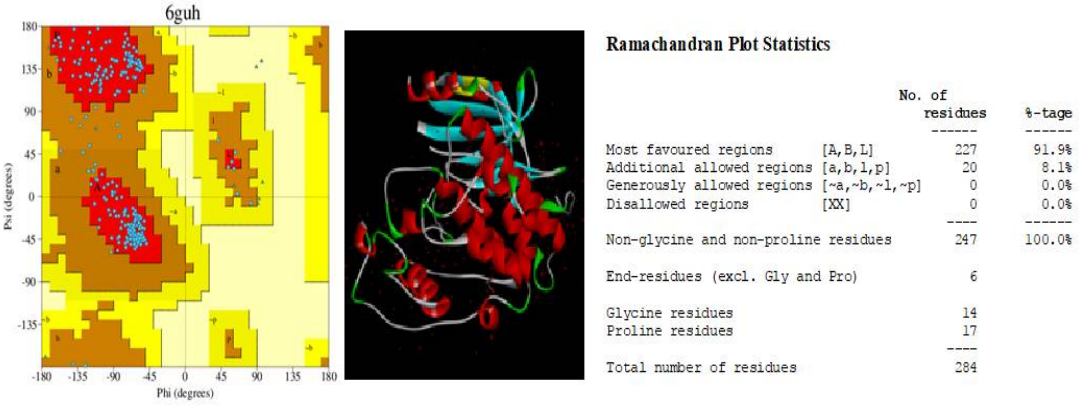
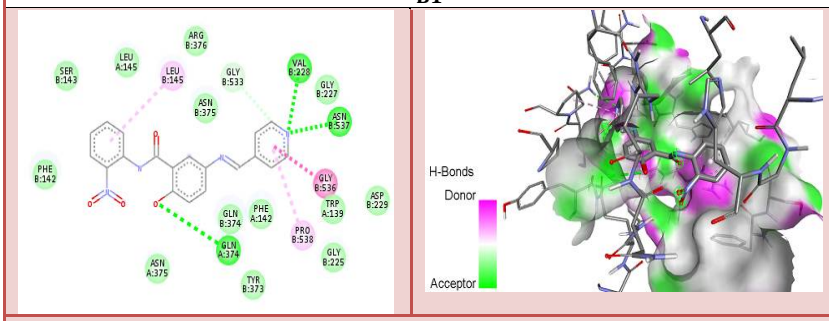
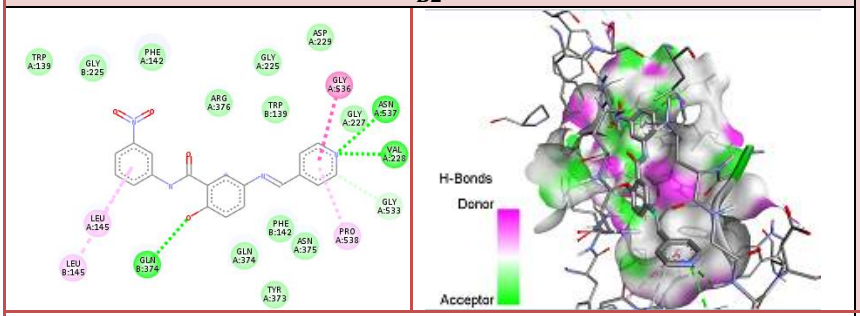
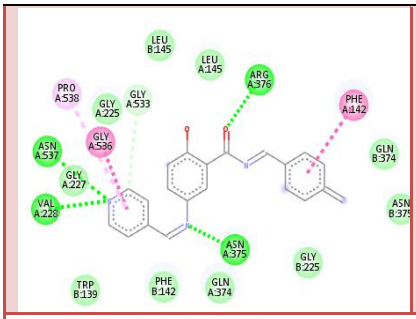
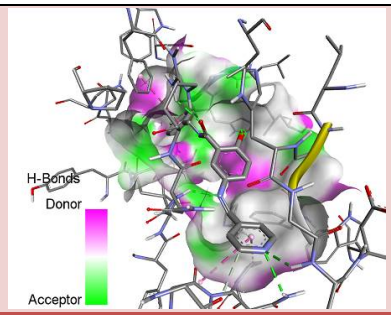
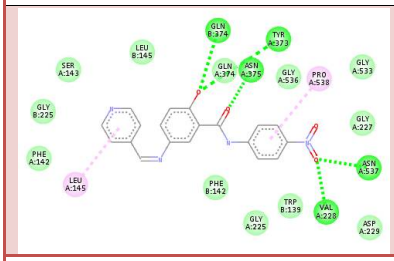
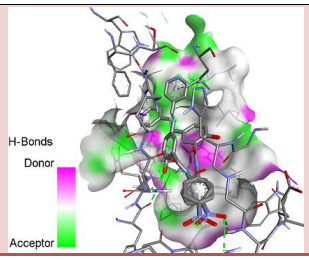
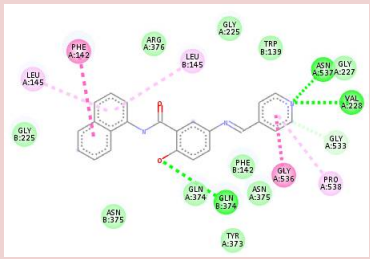
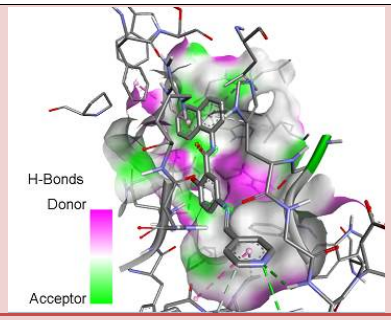
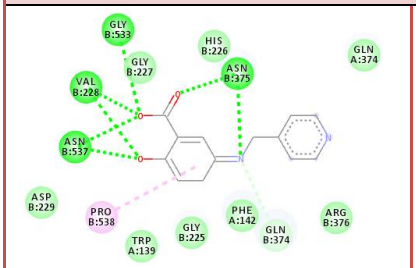
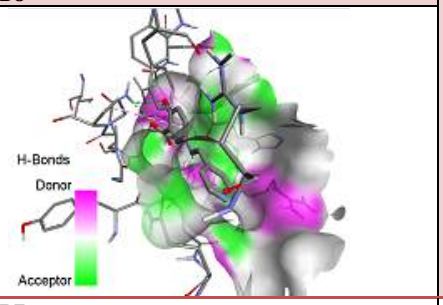
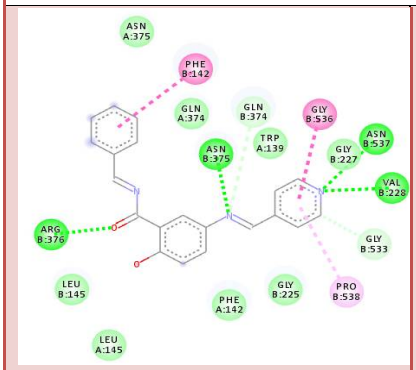
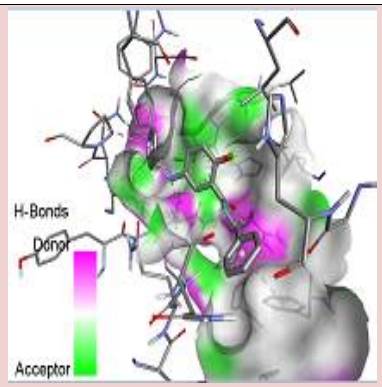
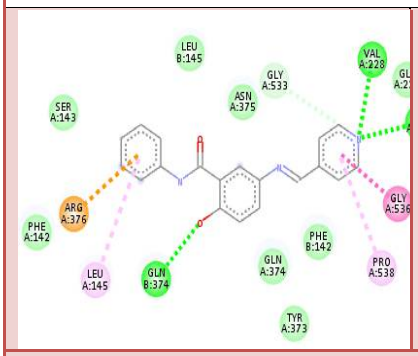
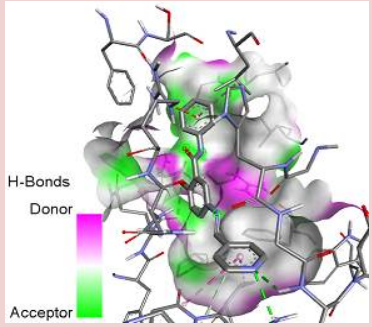
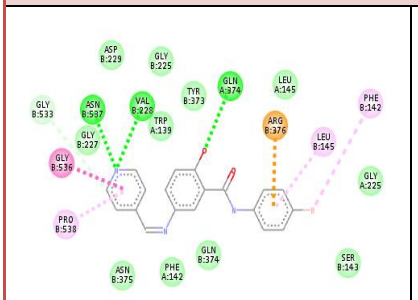
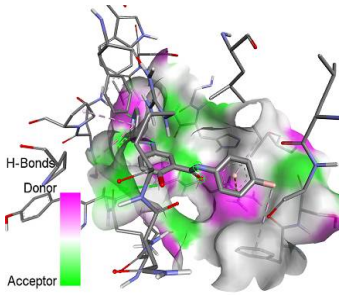
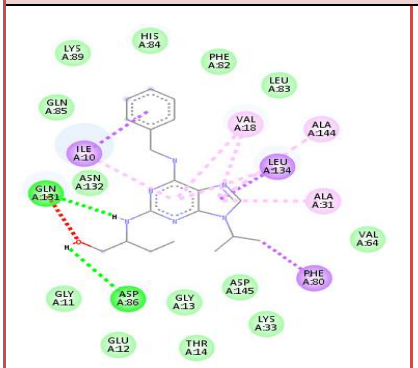
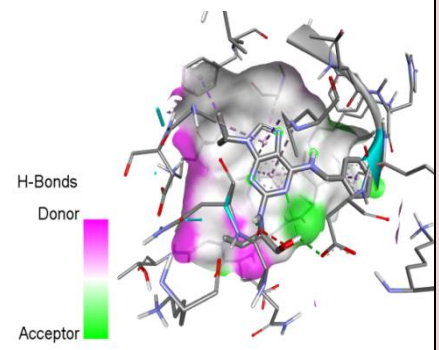


Fig.1.Ramachandran Plot of Protein Molecules (6GUH) and 3D Structure of 6GUH

Table 2: Interaction with Free binding energy (kcal/mol)			
Interaction between Possible derivatives with 6GUH	**Free binding energy (kcal/mol)**	**Interaction group**	**Length (A^0)**
B1 	-8.8	B:VAL228	2.41735
		B:ASN537	2.61186
		A:GLN374	3.36831
		B:GLY533	3.59893
B2 	-8.7	A:VAL228	2.46603
		A:ASN537	2.83184
		B:GLN374	3.18615
		A:GLY533	3.72294
B3	-9.3	A:VAL228	2.42453

			A:ASN375	2.21994
			A:ARG376	2.16841
			A:ARG376	2.24864
			A:ASN537	2.62747
			A:GLY533	3.51599
B4		-8.8	A:VAL228	2.5257
			A:ASN375	2.10717
			A:ASN537	2.51828
			B:GLN374 A:TYR373	2.79865 3.31962
B5		-9.4	A:VAL228	2.44889
			A:ASN537	2.78594
			B:GLN374	3.19156
			A:GLY533	3.65313
B6		-8.4	A:VAL228	2.42896
			A:ASN537	2.73538
			B:GLN374	3.32341
			A:GLY533	3.63244
B7		-6.8	B:VAL228	2.82058
			B:VAL228	2.18264
			B:ASN375	2.404
			B:ASN375	2.63755
			B:ASN537	2.70172
			B:ASN537	2.23654
			B:GLY533	3.03186
			B:GLN374	3.61035
B8		-9.1	B:VAL228	2.3608

				9
			B:ASN375	2.34325
			B:ARG376	2.07027
			B:ARG376	2.30649
			B:ASN537	2.56922
			B:GLN374	3.48278
			B:GLY533	3.48525
B9		-8.4	A:VAL228	2.43938
			A:ASN537	2.75166
			B:GLN374	3.31261
			A:GLY533	3.60817
Std 1(Selecicliib)		-8.4	A:ASP86	2.57709
			A:GLN131	2.08923
				
Std 2 (Dinaciclib)		-8.0	A:THR14	2.48571
			A:LYS129	3.04456
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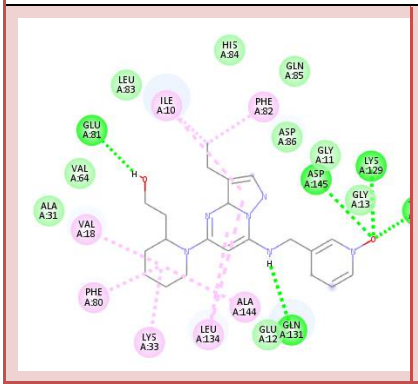
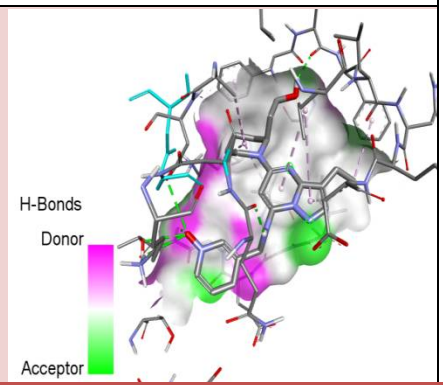
			A:GLN131	2.15047
			A:THR14	3.08582
			A:ASP145	3.25412
				

CONCLUSION

The outcome got from the examination confirms the hypothesis that novel derivatives obtained from 5-amino-salicylic acids interact with Cyclin dependent kinase II. The binding energy of the protein ligand interaction additionally confirms that ligand fit in the dynamic pocket. Henceforth, this examination gives proof to thought of important ligands obtained from 5-amino-salicylic derivatives as potential against

Cyclin dependent Kinase II inhibitor and further in vitro and in vivo assessments may demonstrate its remedial potential.

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