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REVIEW ARTICLE

In silico study for the identification of potential compounds as PIM-1 kinase inhibitors

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ABSTRACT

PIM kinases are a group of serine/threonine kinases that are classified into three isoforms: PIM1, PIM2, and PIM3. Pim-1 kinase is a critical enzyme that is involved in cell growth, cell survival, differentiation, apoptosis, senescence and drug resistance. The PUBMED database has been taken for the screening of PIM-1 kinase inhibitor. This database, further, screened by Lipinski Rule of five, HTVS, standard precision (SP), and extra precision (XP) methodologies. 2OJF protein of PIM-1 kinase was taken for molecular docking. The compound 1a showed good docking scores, SP = −7.244 and XP = −8.6, whereas 1i showed minimal SP and XP scores. These studies may be used for the further development of potential compounds against PIM-1 kinase.

KEY WORDS: *In silico*, Lipinski Rule, PIM-1 kinase, PUBMED database

INTRODUCTION

In the 1980s, the oncogene PIM-1 was discovered in mice with leukemia caused by the Moloney murine leukemia virus.[1] The PIM-1 kinase, which is encoded by the PIM-1 gene, is the most studied and important of the three PIM kinases. PIM-2 and PIM-3, the other two members of the PIM kinase family found soon after, are highly similar to PIM-1.[2-4]

PIM kinase as crucial element for this specific pathway cause cell cycle regulation, cell proliferation, cell migration, and apoptosis occur [Figure 1].[5-7] By phosphorylating the proapoptotic Bcl-2–associated agonist of cell death, PIM kinases stop cells from dying. Phosphorylation of Bad on Serine (Ser) 112 and Ser136 by Pim-1 and Pim-2, respectively, induces 14-3-3 binding, resulting in a deprivation of binding with the anti-apoptotic protein Bcl-2, which cause cell survival.[8-10] PIM kinases regulate cell proliferation by phosphorylating the cyclin-dependent kinase inhibitors p21 at Thr145 and Ser146[11,12] and p27 at Thr157 and Thr198. Phosphorylation of p21 causes its migration from the nucleus to the cytoplasm, which promotes cell proliferation and survival.[13,14] PIM protein also controlled cell migration by a signaling pathway. Pim-1 regulates the expression of MET, a hepatocyte growth factor receptor involved in signaling normal and malignant cell motility and invasion. PIM regulates MET translation by phosphorylating eukaryotic initiation factor 4B (eIF4B) at Ser406, and PIM inhibitor use has been linked to a considerable reduction in MET expression.[15]

The main structure of the human PIM-1 kinase and the mouse PIM-1 protein is nearly identical.[16,17] Overexpression of PIM-1 kinase has been reported in a variety of human hematological malignancies[18-20] and solid cancers, including breast cancer,[21] prostate cancer,[21] gastric cancer,[22] and squamous cell carcinoma of the head and neck.[23] PIM-1-induced carcinogenesis' molecular pathways have been extensively researched. In the meanwhile, numerous small-molecule inhibitors of PIM-1 kinase have been produced [Table 1]. PIM-1 kinase importance in the therapy and diagnostics of cancers has received more attention in recent years.

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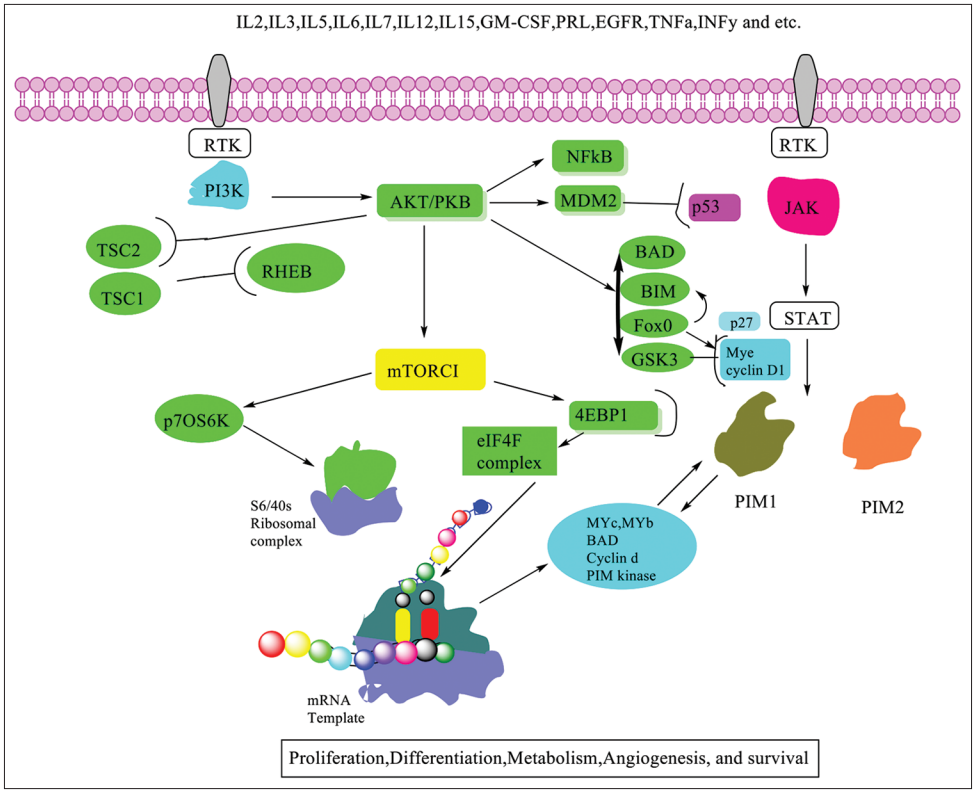


Figure 1: PIM Kinase pathway include cell proliferation, survival, differentiation, metabolism, and angiogenesis.

PIM-1 mRNA and protein both have a short half-life in most cases.[24,25] PIM-1 kinase activity is regulated in part by transcription and protein degradation, and it differs between cells. PIM-1 expression can be induced in hematological malignancies by a variety of cytokines, growth factors, and mitogens.[6,26,27] Hypoxia (HIF1),[28] DNA damage (KLF5),[29] and estrogen can all stimulate PIM-1 expression in solid tumors estrogen receptor.[30] Mostly, the element transfers their signal by various signaling pathways such as nuclear factor-kB,[31] Notch pathway,[21] and Janus kinase and signal transducer and activator of transcription (JAK/STAT) pathway.[27,32] PIM kinases overexpression in cancer, their roles in numerous areas of cancer biology, and their capacity to generate drug resistance suggest that they could be useful therapeutic targets.[33]

MATERIALS AND METHODS

Data collection

For our present study, we use PubChem, Drug bank, PDB(Protein Data Bank), and software such as Schrodinger, Chemdraw, and admetSAR. PDB contains structural data of almost all biological macromolecules. A set of eight compounds having PIM-1 inhibitory effect[34] in cancer taken for *in silico* (molecular modeling) studies.

Ligand preparation for docking

The preparation of ligand was done using Ligprep module through maestro suite. The 2D structures converted to 3D structures, added hydrogen atoms, removed counter ions and water molecules, generated stereoisomers, performed energy minimization, etc., were carried out by Cleanup wizard, these are essential steps of pharmacophore development and docking study.[35,36]

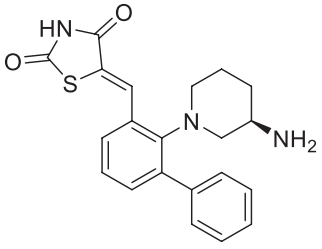
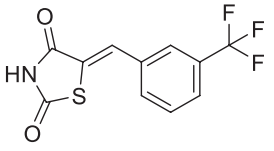
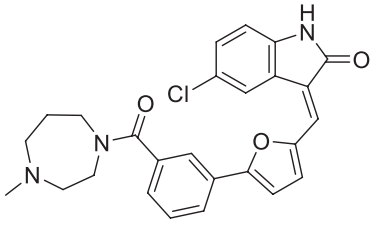
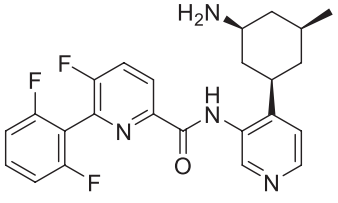
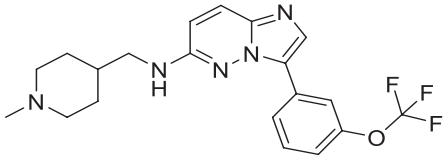
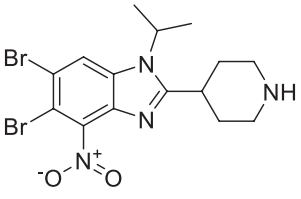
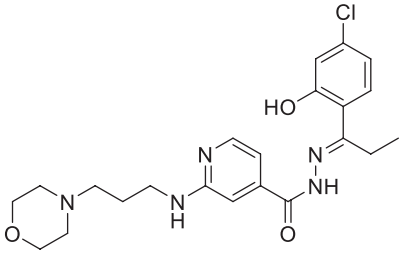
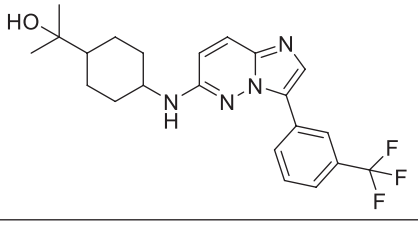
Protein preparation for docking

Using protein data bank (PDB code: 2OJF), the crystal structure of PIM 1 kinase activator was obtained and preprocessed using "protein preparation wizard" in Maestro wizard v10.3 (Schrodinger, LLC, New York). Addition of hydrogen atom and disulfide bonds at the missing site of protein molecules has been processed by steps such as generate states and refinements. The water molecules and other unwanted subunits were removed and protein structure was made single unit. The optimization of hydrogen-bonded groups, removal of water, and restrained minimization is the steps refinement using of OPLS_2005 force field.[37,38] The receptor grid generation had proceeded on the previously attached ligand site following optimization process.

Molecular docking

Molecular docking studies PIM 1 kinase inhibitor were performed by Glide v3.8 (Schrodinger, LLC, New York) module for the synthesized derivatives on binding site of PIM 1 kinase. Before docking, the GLIDE (grid-based ligand docking from energetics) module displayed the filtration of possible ligand sites in the binding pocket

Table 1: PIM kinase inhibitors

Compound name	Code	Structures	Compound CID (PUBCHEM)
AZD1208	1a		58423153
SMI-4a	1b		1361334
CX6258	1c		44545852
PIM447	1e		44814409
SGI-1776	1f		24795070
SEL24	1g		76286825
M-110	1h		136246423
TP-3654	1i		66598080

to minimize the number of pose candidates. Different sets of fields constitute a grid, which is specified by the geometry and features of the receptor. In this technique, ligand geometries are reduced in the binding pocket of the receptor using typical force fields to locate the required ligand poses.[39] The localization of these poses was additionally aided by a distance-dependent dielectric model. A model energy function integrating empirical and force-field variables are utilized to rank the best docked positions.[40,41] With addition to the standard precision (SP) scoring function, GLIDE, now, includes a new extra precision (XP) scoring function, which includes innovative terms and has been proved to improve the selection of actual binding positions.[42] The docked complexes were reranked using their comparative binding free energy using the molecular mechanics generalised born and surface area solvation (MM/GBSA)-based Rescoring technique.

MM/GBSA

MM/GBSA is a known method to calculate the free energy of the binding of ligands to protein.[43] It determines the energy of optimal free receptors, free ligands, and ligand-receptor complexes.

RESULTS AND DISCUSSION

Computational studies of selected derivatives

Molecular docking

Glide v5.8 was used to evaluate the potential interactions between the target molecule and the PIM 1 kinase activator (PDB code: 2OJF). To explore the necessary interactions of compounds with protein to induce anti-cancer activity, all of the identified compounds (1a-1i) were docked to active sites of PIM 1 kinase activator. Compound was docked in the allosteric site of PIM 1 kinase protein (PDB entry: 2OJF) and was validated by docking of the 2OJF ligand in the allosteric site. A crystal structure of PIM 1 kinase obtained from RCSB Protein Data Bank (PDB entry code: 2OJF) which was utilized to confirm the binding mechanism of PIM 1 structure with pyridine derivatives. All selected compound was co-crystallized with the binding site of PIM 1 kinase which showed good potency.

The selected PIM 1 kinase inhibitors were docked in the allosteric binding site comprising Val455,Tyr215,Tyr214, Arg63, Met210, Val452, and residues. Glide score by SP and XP and Glide energy of the selected derivatives is presented in Table 2. The docking studies of these compounds suggested admiring fit in the allosteric site of PIM 1 kinase protein. On the basis of their Glide score, lowest Glide energy (kcal/mol) and docking interactions, compounds 1i, 1h, 1g, and 1f were, further, analyzed in details using PyMOL to investigate the binding mode and docking interactions of the selected molecules with the amino acid residues in the allosteric site of PIM 1 kinase protein.

Crystal ligands showed that the selected compounds (1a-1i) have equivalent binding interactions with the receptor. The compound 1a (AZD1208) exhibits best PIM 1 kinase inhibitory effect having good docking score (-7.244) as anti-cancer agent [Figure 2]. The compound 1a showed hydrogen bond interaction between nitrogen atom of benzene substituted amine and amino acid residue Glu 127 and the hydroxyl gp with Asp 184 PIM 1 kinase. The other amino acids found that there are THR 183, LYS 72, GLU 170, LEU 49, ALA 70, MET 120, GLU 121, VAL 104, GLY 50, ASN 171, PHE 327. TYR 122, VAL 123, and TYR 330, Figure 3 showed docking interaction of compound 1b with active site residues LYS 72 of PIM 1 kinase. Figure 4 showed docking interaction of compound 1c compound with active site residues GLU 121 of PIM 1 kinase. Figure 5 showed docking interaction of compound 1d with active site residues LYS 72, of PIM 1 kinase. Figure 6 showed docking interaction of compound 1e

Table 2: HTVS, SP, and XP docking scores with MMGBSA binding energy of potent compounds

Compounds name	PDB: 2JOF		
	Docking score (sp) kcal/mol	Docking score (xp) kcal/mol	MMGBSA dG bind (xp complex) kcal/mol
1a	−7.244	−8.6	−61.2786
1b	−7.213	−7.727	−61.0468
1c	−6.817	−6.671	−93.5198
1d	−6.566	−6.053	
1e	−6.471	−5.985	
1f	−5.704	−5.894	
1g	−5.667	−5.598	
1h	−5.122	−5.334	
1i	−4.807	−5.331	

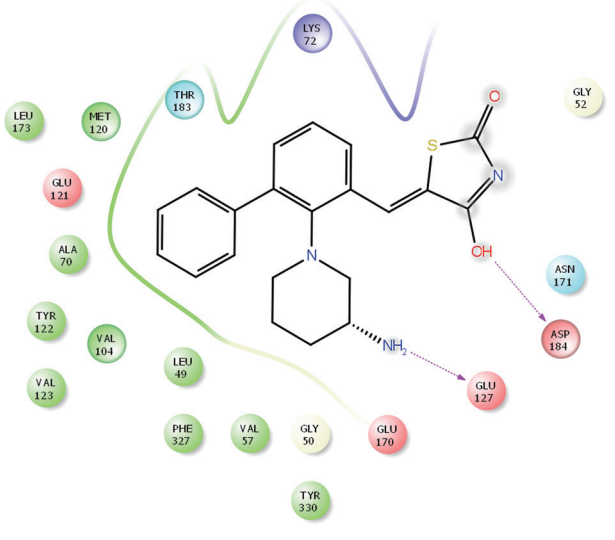


Figure 2: Docking interaction of compound 1a with active site residues of PIM 1 kinase.

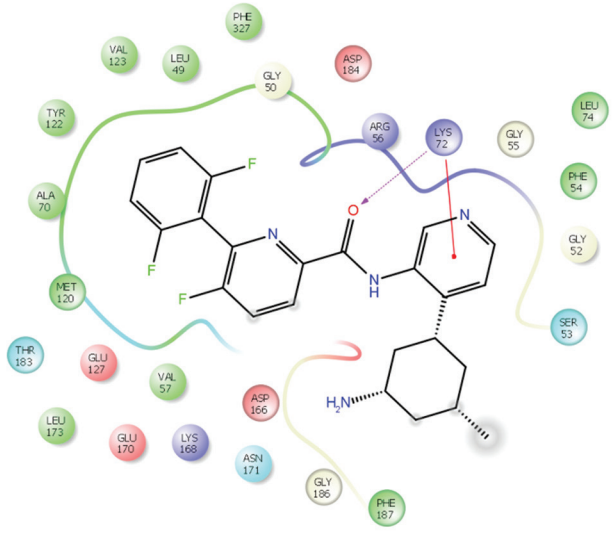


Figure 3: Docking interaction of compound 1b with active site residues of PIM 1 kinase.

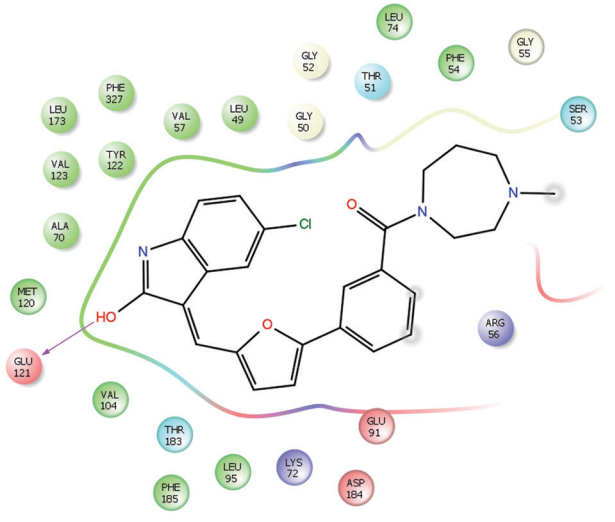


Figure 4: Docking interaction of compound 1c with active site residues of PIM 1 kinase.

with active site residues LYS 72 of PIM 1 kinase. Figure 7 showed docking interaction of compound 1f with active site residues TYR 214, of PIM 1 kinase inhibitors. Figure 8 showed docking interaction of compound 1g with active site residues LYS 72 and ASP 184 of PIM 1 kinase. Figure 9 showed docking interaction of compound 1h with the active site residue ASN 171 and Figure 10 showed docking interaction of active site residues LYS 72 and THR 51 of the PIM 1 kinase.

In silico prediction of ADME properties

ADME properties of all the synthesized derivatives are present in Table 3. There should be no more than two Lipinski rule violations for oral activities. All of the derivatives in the current series did not exceed the allowed

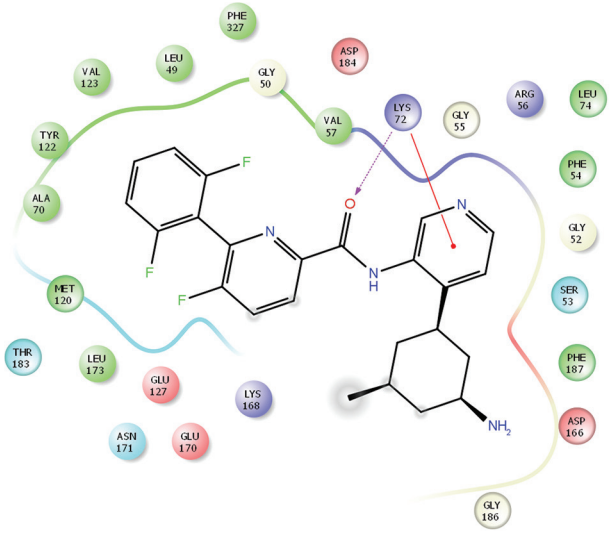


Figure 5: Docking interaction of compound 1d with active site residues of PIM 1 kinase.

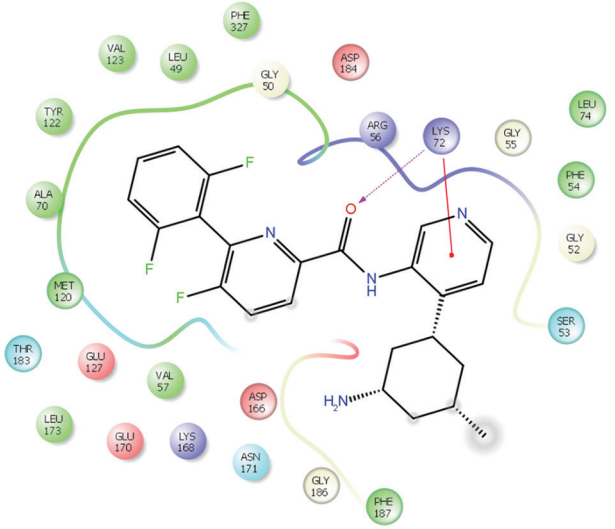


Figure 6: Docking interaction of compound 1e with active site residues of PIM 1 kinase.

limit of rule violation. The polar surface area (PSA) and rotatable bond of all of the compounds are within the permitted range of drug resemblance qualities.

The QikProp module of Schrodinger program was used to calculate the physicochemical parameters of the produced molecules (1a-1i). Different *in silico* pharmacokinetic properties of the selected compounds were predicted in this study, including PSA, QPlogPo/w, predicted apparent Caco-2 permeability (QPPCaco), predicted brain/blood partition coefficient (QPlogBB), predicted apparent MDCK cell permeability (QPPMDCK), solvent accessible surface area (SASA), and percent human oral absorption. These pharmacokinetic features were crucial in relating biological activity to physicochemical properties.

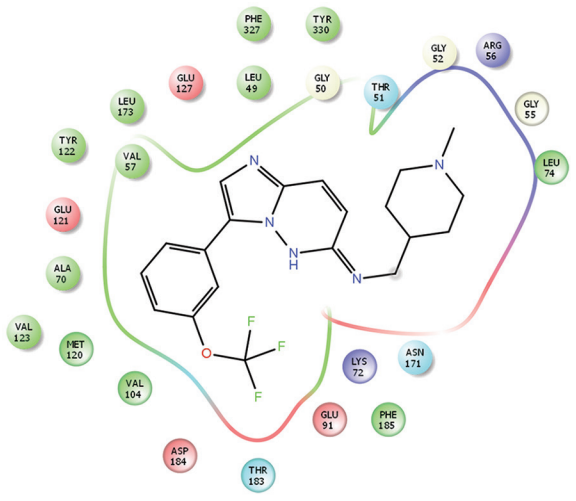


Figure 7: Docking interaction of compound 1f with active site residues of PIM 1 kinase.

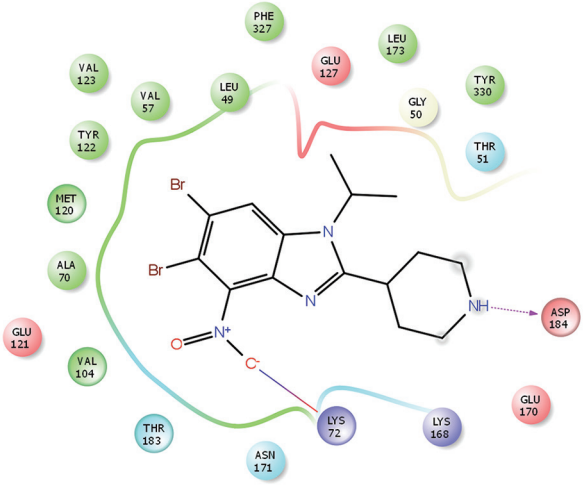


Figure 8: Docking interaction of compound 1g with active site residues of PIM 1 kinase.

Lipophilicity is a fundamental molecular property and an important criterion in drug development. Lipophilicity is a property of a molecule that allows it to mix with an oily phase rather than water. It is evaluated as the partition coefficient, P, between the two phases and is typically represented as logP. In this investigation, we used Schrodinger software to calculate the logP to determine the lipophilicity of the target compounds and the link between pyridine derivatives and anticancer activity. The compounds 1c, 1d, 1e, and 1i were found to be the most lipophilic in the series, whereas 1a, 1b, and 1g were shown to be the less lipophilic. *In vitro* anticancer activities demonstrated that these drugs inhibited PIM kinase well.

The Lipinski rule of five was applied to the molecular weight and PSA of molecules. These molecules had the perfect number of hydrogen bond donors and acceptors. Poor cell membrane permeability was caused by molecules having a PSA of more than 140Å^2. The majority of the series' compounds had a value of <140 Å^2. Compound 1i has a PSA value of 55 Å^2.

The apparent permeability across the Caco-2 cell membrane is represented by descriptors such as QPPCaco. A QPPCaco value of <25 indicated low permeability, whereas a value of >500 indicated high permeability. Caco-2 readings were good for all compounds in the series.

The brain/blood partition coefficient (−1.479–0.462) is represented by QPlogBB, and QPPMDCK seems to be the apparent permeability through MDCK cells, which can be used as an excellent non-active transport mimic for the blood brain barrier. QPlogBB and QPPMDCK values were highest in compound 1i.

Using a 1.4-radius probe, SASA represents the total SASA in square angstroms. The SASA values should fall

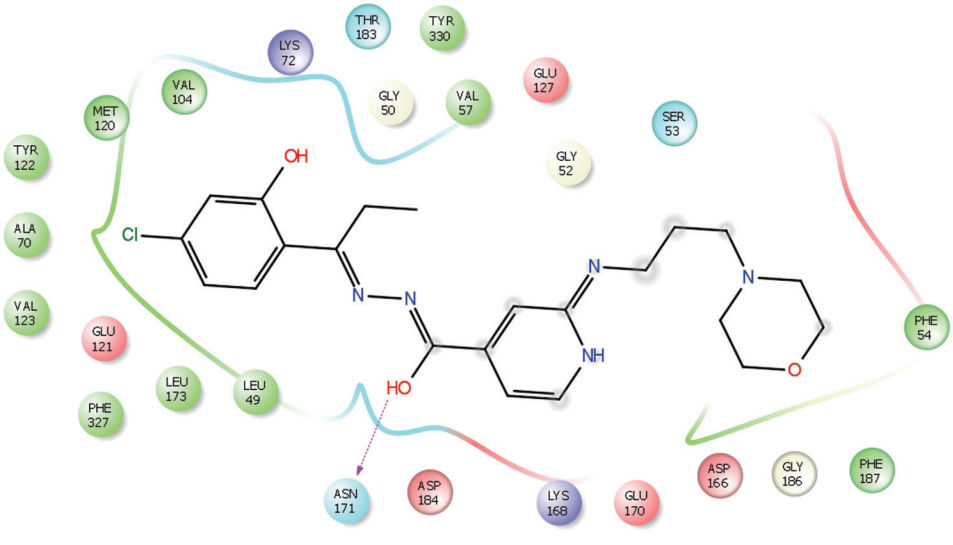


Figure 9: Docking interaction of compound 1h with active site residues of PIM 1 kinase.

Table 3: *In silico* predicted LogP and ADME properties of pyridine derivatives

Comp.	Mol.Wt.	PSA	QPlog Po/w[a]	QPP Caco[b]	QPlog BB[c]	QPP MDCK[d]	SASA[e]	Percent Human Oral Absorption[f]
1a	379.476	96.198	3.246	48.856	−1.479	31.268	762.293	76.178
1b	273.229	66.912	2.266	418.362	−0.522	1190.1	455.895	87.133
1c	461.947	72.316	4.871	184.598	−0.586	171.306	840.688	96.026
1d	440.467	83.565	4.175	147.709	−0.431	250.424	750.083	90.221
1e	440.467	83.751	4.19	149.139	−0.434	251.118	752.469	90.38
1f	405.422	53.062	3.456	828.429	0.462	1253.243	631.135	100
1g	446.141	71.322	3.31	198.848	0.092	470.743	580.413	87.467
1h	445.948	94.402	3.54	206.247	−0.816	244.651	764.078	89.096
1i	418.461	55.776	4.258	1730.296	−0.249	1996.007	636.702	100

[a]Predicted octanol/water partition coefficient (Range=−2.0–6.5), [b]Predicted apparent Caco-2 cell permeability in nm/s. Caco-2 cells are a model for the gut blood barrier (<25% is poor, >500 great. [c]predicted brain/blood partition coefficient, [d]Predicting apparent passive permeability of Caco-2 and MDCK cell, [e]Total solvent accessible surface area (SASA) in square angstroms using a probe with a 1.4 Å radius (range=300–1000), [f]Predicted human oral absorption on 0–100% scale. >80% is high, <25% is poor

Table 4: Predicted toxicity of pyridine derivatives

Comp. code	AMES Toxicity	Carcinogens	Tetrahymena Pyriformis Toxicity	Bio-Degradation	Acute Oral Toxicity	Carcinogenicity (Three-class)
1a	0.6816	0.8943	0.9454	0.9942	0.5632	0.5546
1b	0.5301	0.8719	0.9116	0.9799	0.5483	0.5312
1c	0.6375	0.8785	0.9527	1.0000	0.5819	0.6019
1d	0.6322	0.7867	0.8982	1.0000	0.4901	0.5979
1e	0.6322	0.7867	0.8982	1.0000	0.4901	0.5979
1f	0.6233	0.8697	0.9761	1.0000	0.6104	0.6169
1g	0.6743	0.7421	0.9807	0.9941	0.5676	0.4867
1h	0.5059	0.6690	0.9401	0.9951	0.6123	0.5167
1i	0.6239	0.7665	0.9763	1.0000	0.5726	0.5250

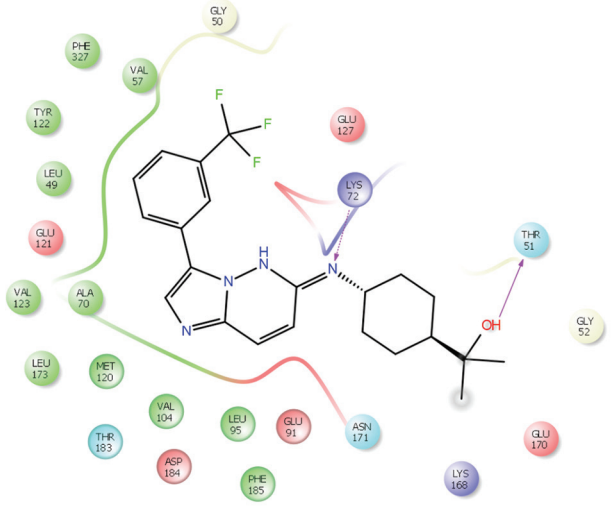


Figure 10: Docking interaction of compound 1i with active site residues of PIM 1 kinase.

between 300.0 and 1000.0. Compound 1c had the greatest SASA value, whereas compound 1b had the lowest. In conclusion, Qikprop predictions show that selected compounds have the best parameters for anti-cancer activity.

Prediction of toxicity

AdmetSAR software was used to assess the toxicity of all synthesized compounds. Table 4 shows the toxicity of all selected molecules.

CONCLUSION

In this study, the PIM-1 inhibitors potentiality has been determined. Aberrant elevation of Pim-1 kinase is associated with numerous types of cancer. Selected PIM-1 kinase inhibitors show good potency and have desired ADMET properties. Using Glide, docking has been done and 1a showed good docking scores, SP = −7.244 and XP = −8.6, whereas 1i showed minimal SP and XP score. With addition to SP, the XP and MM/GBSA have also been done. All compounds showed potency and low toxicity (acute oral toxicity −0.4901) score which was performed by admetSAR. Results of present study can be used for the further development of potential PIM-1 kinase inhibitors.

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