RESEARCH PAPER

Insilco Drug Designing of Novel Pyridine Derivatives to Evaluate Significant Anti-Cancer Activity

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Abstract

Pyridine is a well-researched heterocyclic moiety that plays a significant role in a number of biological and medicinal processes. In modern research, pyridine derivative for Protein tyrosine kinases (PTKs) are the most explored of the numerous targets that have been found, confirmed, and inhibited at various cancer hallmarks. In the present study, using *in silico* approaches 14 pyridine derivatives were evaluated for ADME properties and Insulin receptor (IR) inhibition as potent anti-breast cancer agents. Results of ADME and Docking studies demonstrated that substituted pyridine derivatives bind effectively at the ATP-binding site of insulin receptor, particularly PC12, PC6, and PC7, may function as competitive inhibitors of the kinase domain, thereby blocking signal transduction pathways critical for cancer cell proliferation. Based on *in silico* studies, the derivatives likely function as competitive inhibitors of insulin receptor kinase as compared to existing market drugs. This inhibition blocks downstream PI3K/Akt and MAPK signaling pathways, thereby Reducing tumor proliferation, inducing apoptosis, preventing angiogenesis. These results lead to further research based on synthesis and *in-vitro* studies.

Keywords: Cancer, PTKs, Drug likeness, ADME and Docking studies.

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1. Introduction

Cancer is a serious and sometimes fatal ailment that happens when cells in the body grow and spread in an abnormal, uncontrolled way [1]. It can affect almost any part of the body. If not treated, it can spread to distant organs via the lymphatic or circulatory systems or infiltrate nearby tissues [2]. Cancer usually starts because of changes in the genes or changes in the cellular regulatory systems that control DNA repair, apoptosis, and cell division are the causes of cancer. These changes can be caused by unhealthy lifestyle habits, infections, inherited genetic risks, or exposure to harmful substances like tobacco, radiation, or certain chemicals [3].

In recent years, there have been major improvements in treatment of cancer. This advancement helped patients live longer and have a better quality of life. With the development of advanced imaging techniques like PET-CT, MRI, and mammography, along with new molecular diagnostic instruments such as liquid biopsy that can detect cancer-related genetic changes in blood, cancer screening has become more accurate and effective [4].

Next-generation sequencing (NGS) and biomarker-based diagnostics have made personalized medicine methods possible, enabling the customization of medicines to a patient's genetic profile [5]. In addition to traditional treatments like surgery, chemotherapy, and radiotherapy, newer, less invasive and more targeted treatment methods are now being used [6].

The development of anticancer therapeutics depends heavily on Heterocyclic compounds because they offer diverse structures which enable them to bind to multiple biological targets. The cyclic framework of

these compounds contains one or more heteroatoms which include nitrogen and oxygen and sulfur atoms. The cyclic framework of these compounds contains one or more heteroatoms which include nitrogen and oxygen and sulfur atoms [7].

The investigation of anticancer agents has shown that heterocyclic compounds including pyridine and quinoline and indole and imidazole and triazole exhibit strong potential by disrupting essential cellular processes which include DNA replication and cell cycle control and apoptosis and signal transduction pathways. The unique electronic properties and spatial arrangements of these compounds enable them to form strong bonds with enzymes and receptors and nucleic acids that contribute to cancer progression. The ability to make simple changes to their structure allows medicinal chemists to enhance their drugs' specificity and strength and drug-like properties [8]. The development of cancer medications depends on pyridine derivatives because these compounds possess unique chemical properties and strong biological effects.

The pyridine ring structure functions as a six-membered aromatic heterocycle which contains nitrogen to create diverse biological interactions thus making it suitable for pharmacological development [9]. The anticancer properties of pyridine-based compounds emerge from their ability to block tyrosine kinases and topoisomerases and tubulin polymerization and their capacity to insert into DNA. The FDA has approved multiple anticancer drugs which contain 16 pyridine structures in their molecular structure thus demonstrating the clinical value of pyridine moieties [10].

The position of modifications on the pyridine ring determines how the molecule will interact with biological targets and its pharmacokinetic properties and binding affinity and target specificity. The combination of pyridine derivatives with other active chemical components in hybrid molecules enhances their cancer-fighting potential while reducing drug resistance [11]. The pyridine ring serves as a useful bioisostere for benzene because it enhances drug molecule solubility and metabolic stability and binding properties [12]. The pharmacological properties of pyridine derivatives include antimicrobial and anti-inflammatory and antiviral effects as well as their well-documented anticancer activity [13].

The biological properties of pyridine derivatives depend heavily on their substitution patterns according to structure-activity relationship (SAR) [14]. The introduction of electron withdrawing groups such as nitro or halogen to the molecule leads to enhanced anticancer activity through improved molecular binding to active sites. The position of substitution on the pyridine ring determines how the molecule will interact with targets and how it will be metabolized. The combination of pyridine with other pharmacophores such as triazole and indole and quinoline results in hybrid compounds that show enhanced anticancer activity and synergistic effects [15]. The development of substituted pyridine derivatives for anticancer therapy has experienced significant growth during the last few years. The compounds demonstrate various biological actions which include kinase blockade and cell death promotion and CA IX carbonic anhydrase inhibition to create multiple treatment options for cancer patients [16]. The combination of SAR data with molecular docking results and metabolomic studies enables researchers to create optimized derivatives with enhanced efficacy [17].

2. Material and Methods

2.1. Molecular Docking Studies:

Modern drug discovery heavily relies on molecular docking as a fundamental computational method. The method enables scientists to determine the optimal binding position of small molecules (ligands) when they interact with large protein targets (macromolecules) which helps scientists understand binding strength and molecular interactions. The research used docking analysis to predict anticancer properties of pyridine derivatives through their binding interactions with the insulin receptor (IR, PDB ID: 3ETA) which drives cancer development and signaling pathways. The docking studies used AutoDock Vina as the docking engine because it stands as a popular open-source tool which delivers precise results at high speed [18].

2.1.1. Rationale of Docking Studies: The research used molecular docking to link experimental pyridine derivative synthesis with computational models that predict their biological responses. The insulin receptor exists at 43 elevated levels in multiple cancer types including breast carcinoma which leads

to enhanced cell survival and proliferation and decreased apoptosis. The insulin receptor has become a key target for oncological treatment because small molecules can block its activity. The research focused on substituted pyridine derivatives because these compounds demonstrate wide-ranging pharmacological properties that include antimicrobial and anti-inflammatory and antiviral and anticancer effects.

The nitrogen atom in pyridine derivatives enables hydrogen bonding while the aromatic structure enables hydrophobic stacking which creates stable protein-ligand interactions. The research used molecular docking to determine which pyridine ring modifications produced better insulin receptor binding and to pick the best candidates for biological testing.

2.1.2. **Ligand Preparation**: The research started by preparing the ligand library which included the parent compound PC and its 13 derivative compounds (PC1–PC13). The research team used ChemDraw to create the ligand structures before converting them into three-dimensional (3D) models. The MM2 force field performed energy minimization to create stable conformations by optimizing bond lengths and angles and torsional angles and non-bonded interactions.

All derivatives were converted to their minimized structures into PDBQT format which AutoDock Vina requires for docking simulations [19]. The research included 13 derivatives which received different substitution patterns through electron-donating or electron-withdrawing groups at multiple positions on the pyridine core. The binding affinity of these compounds would change because of their different electronic properties and steric effects and hydrogen bonding abilities.

2.1.3. **Protein Preparation:** The research used the insulin receptor tyrosine kinase domain (PDB ID: 3ETA) from the Protein Data Bank (PDB) as the docking target. The docking process requires a protein structure that needs optimization through AutoDock Tools preprocessing to remove non-essential components including water molecules and ligands.

2.1.4. **Docking Procedure**: AutoDock Vina performs docking simulations through its scoring function which calculates empirical free energy of binding. The program produces various possible ligand conformations (poses) inside the specified grid area while it calculates docking scores in kcal/mol for each pose. The docking score value decreases when a compound shows better binding affinity to the target. The procedure followed was:

- Literature review was conducted to design a series of 100 novel pyridine derivatives that had undergone structural modifications.
- The AutoDock Vina molecular docking software was used to simulate the binding of the designed derivatives to Insulin receptor active site and finalized the synthesized compounds based on docking score.
- The finalized ligand (PC–PC13) was docked individually into the active site of the insulin receptor.
- For every ligand, ten different binding poses were generated.
- The best pose was selected based on the lowest binding energy and biological relevance (proper orientation and interactions with catalytic residues).
- Visualization of ligand–protein complexes was performed using Discovery Studio Visualizer, which allowed detailed analysis of hydrogen bonds, hydrophobic contacts, and π–π interactions.

2.2. *In-Silico* Studies

The development of computational methods has brought major changes to the process of drug discovery and development. The process of discovering new drugs through traditional methods requires extended periods of time while being expensive and producing unpredictable results for new chemical compounds. The *in-silico* approach enables fast and affordable compound screening and optimization before conducting extensive biological tests. The research used in silico methods to evaluate PC and its derivatives (PC1–PC13) for their drug potential and their pharmacokinetic characteristics and ADME properties which determine their suitability as anticancer medications.

The success of any drug molecule depends not only on its ability to bind to a biological target (as confirmed through molecular docking) but also on its pharmacokinetic and pharmacodynamic profile. Several promising compounds fail during preclinical or clinical development because they either exhibit poor absorption, rapid metabolism, toxicity, or lack of selectivity. Therefore, ADME and drug-likeness evaluation have become mandatory components of early-stage drug discovery pipelines.

For the pyridine derivatives under investigation, *in-silico* studies were essential to: Predict oral

bioavailability using Lipinski's Rule of Five, Evaluate ADME properties such as solubility, gastrointestinal absorption, blood brain barrier penetration, and metabolism, determine toxicity risks like hepatotoxicity or mutagenicity, support rational drug design, enabling refinement of substitution patterns on the pyridine nucleus for optimal pharmacological profiles.

2.3. SwissADME Analysis

SwissADME, a freely accessible web tool, was employed to calculate pharmacokinetic properties and drug-likeness of all compounds [20]. The following descriptors were evaluated:

- Molecular Weight (MW) – Should be ≤ 500 g/mol for good permeability.
- LogP (Lipophilicity) – A measure of lipophilicity; ideal range: –0.5 to +5.0.
- Hydrogen Bond Donors (HBD) – ≤ 5.
- Hydrogen Bond Acceptors (HBA) – ≤ 10.
- Topological Polar Surface Area (TPSA) – < 140 Å² favors oral bioavailability.
- Number of Rotatable Bonds – ≤ 10 for conformational stability.

3. Results and Discussion

3.1. Molecular Docking Studies

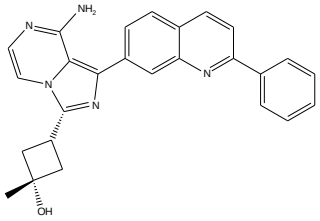
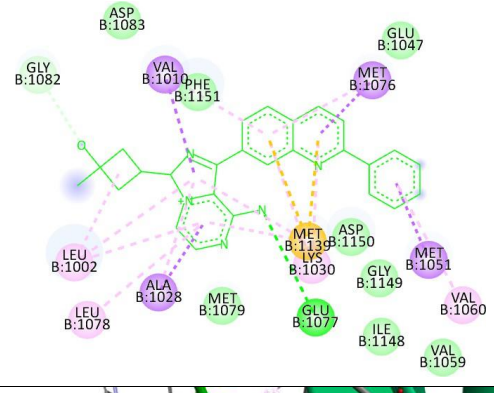
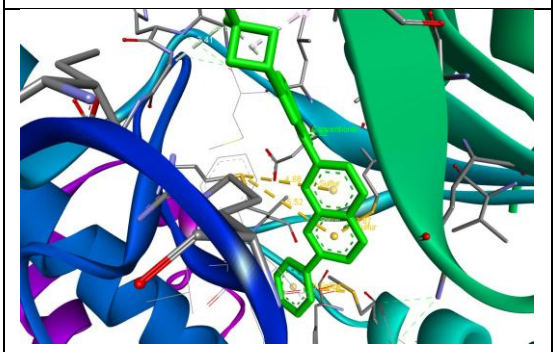
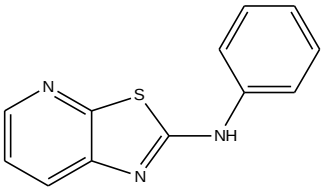
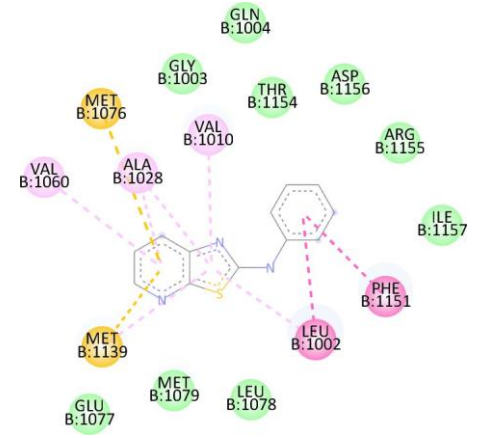
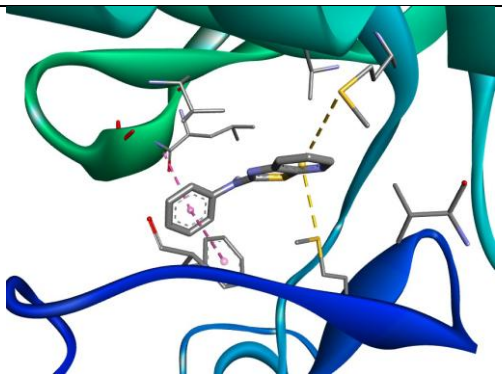
Molecular docking was undertaken to explore the interactions between the designed pyridine derivatives and the Insulin receptor kinase domain (PDB ID: 3ETA). This receptor is known to be involved in tumor progression, as its activation promotes cell survival, proliferation, and resistance to apoptosis. Inhibition of this receptor's kinase activity is therefore a rational therapeutic strategy against cancers, particularly Breast Carcinoma.

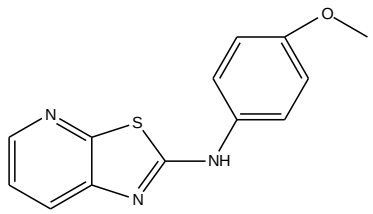
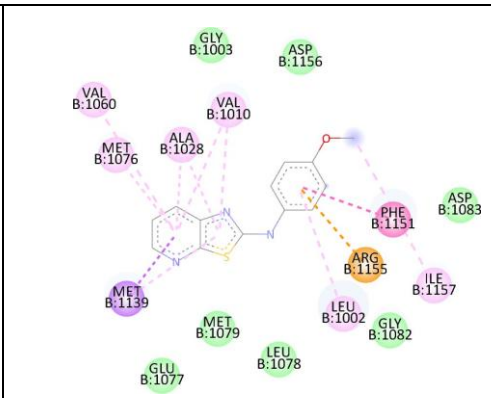
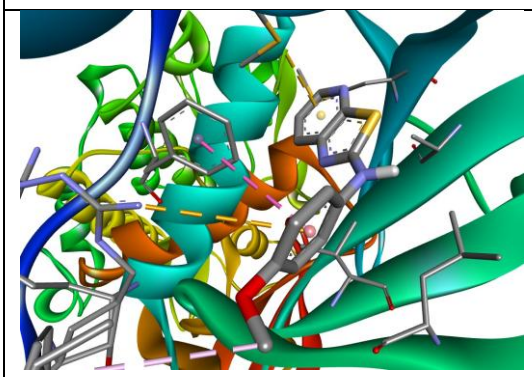
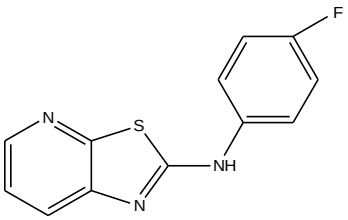
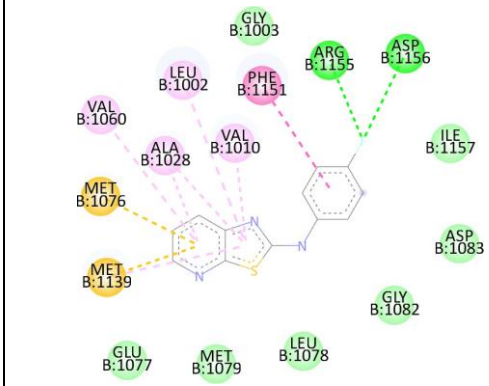
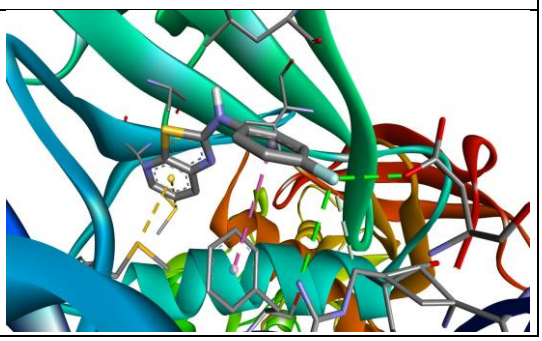
Table 1: List of thiazolo[5,4-b]pyridine derivatives based on highest minimum docking score with Docking details:

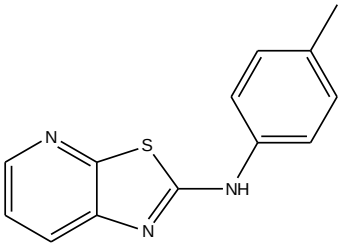
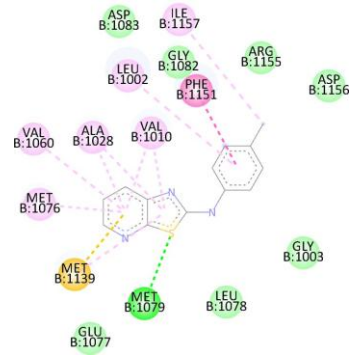
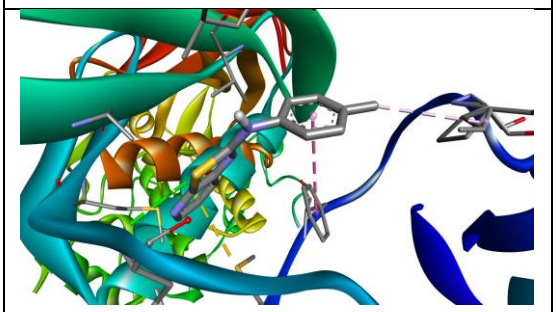
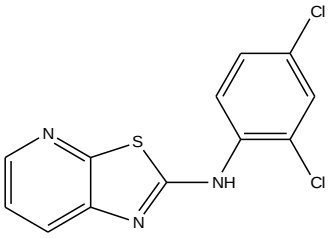
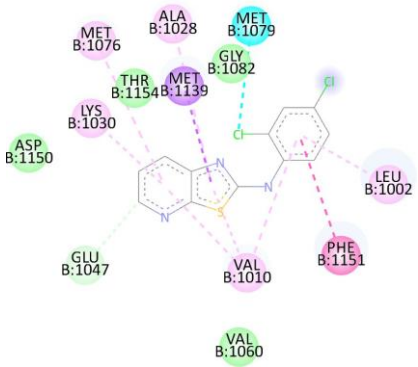
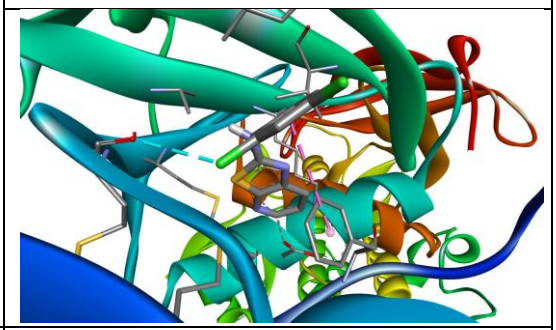
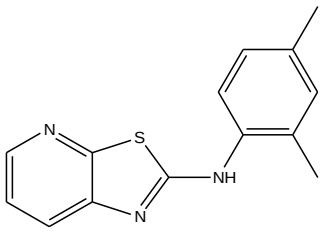
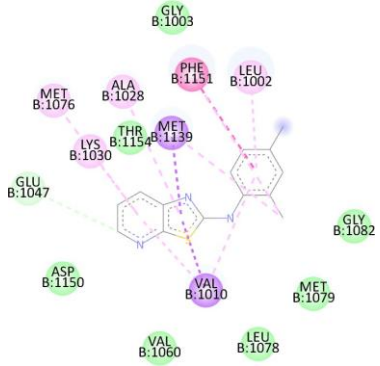
Ligand	Docking Score (kcal/mol)	Active residues	H-bonding residues	H-bonding distance
Reference drug	-6.2	MET1079, ASP1150, MET1076, ALA1028, GLY1149	GLU1077	3.32
PC	-8.1	MET1079, MET1076, ALA1028, PHE1151	ARG1155	3.24
PC1	-7.9	VAL1060, MET1076, ALA1028, PHE1151, MET1139	GLU1077	3.18
PC2	-8.2	VAL1060, MET1076, ALA1028, PHE1151, MET1139	ASP1156 ARG1155	3.05 3.29
PC3	-7.9	VAL1060, MET1076, ALA1028, PHE1151, MET1139	MET1079	3.26
PC4	-7.9	VAL1060, MET1076, ALA1028, PHE1151, GLY1082	GLU1047	2.98
PC5	-8.3	VAL1060, MET1076, ALA1028, PHE1151, GLY1082	GLU1047	3.25
PC6	-8.7	GLU1077, MET1076, ALA1028, PHE1151, ASP1083	GLY1082	3.36
PC7	-8.5	LEU1002, MET1076, ALA1028, PHE1151, MET1139	GLU1077	3.02
PC8	-8.3	LEU1002, MET1076, ALA1028, PHE1151, GLU1077	MET1079	3.3
PC9	-8.3	GLU1077, MET1076, ALA1028, PHE1151, ASP1083	MET1079	3.2
PC10	-7.8	GLU1077, MET1076, ALA1028, PHE1151, ASP1083	GLY1003	3.52
PC11	-7.8	MET1139, ALA1028, PHE1151, MET1076, VAL1060	GLU1047	3.32
PC12	-9.9	ALA1028, MET1139, LYS1030, ASP1150, VAL1060	ASP1156 GLY1082	3.2 3.42

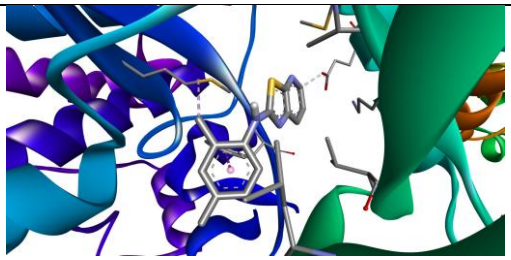
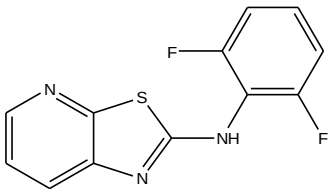
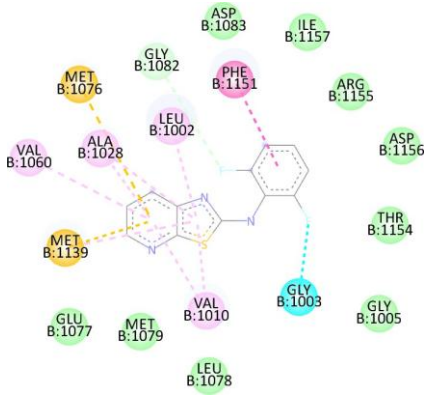
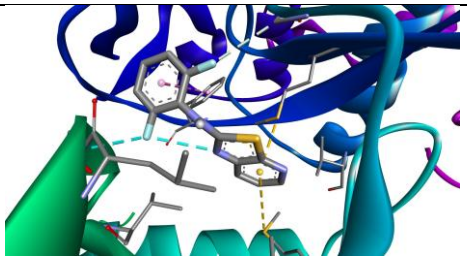
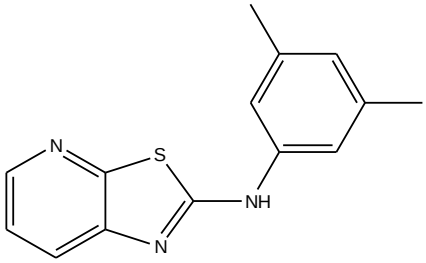
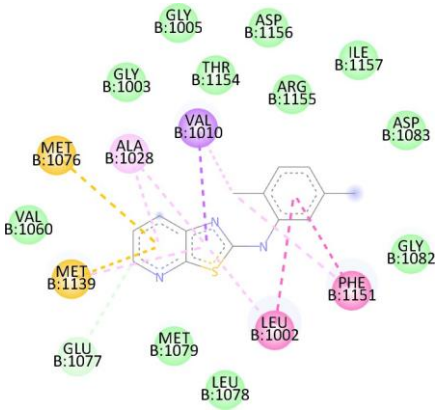
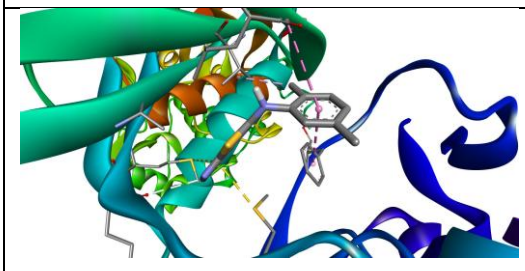
PC13	-8.6	ALA1028, MET1139, LYS1030, ASP1150, VAL1060	ASP1156 ASP1156	3.10 3.11

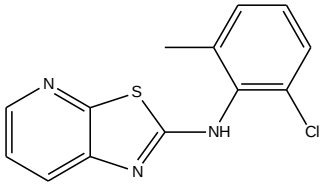
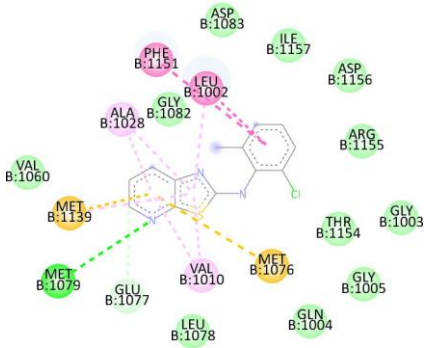
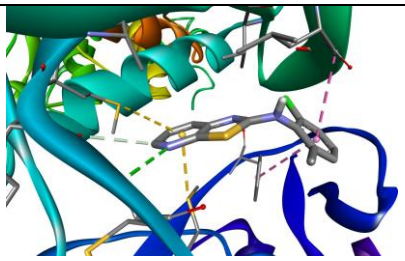
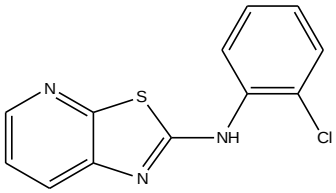
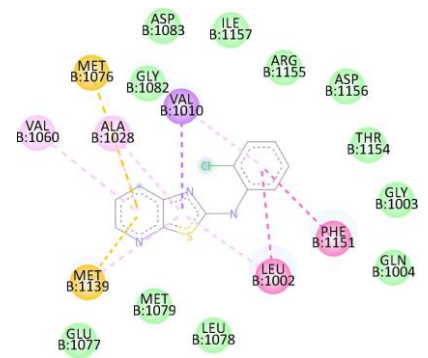
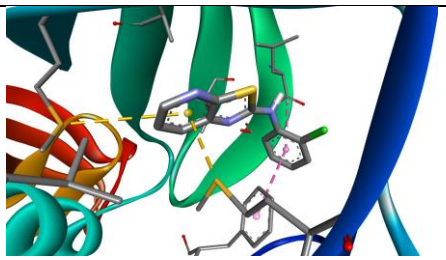
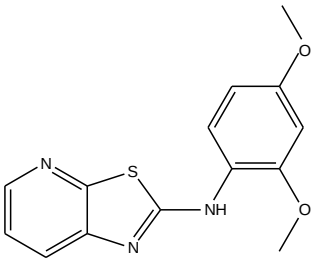
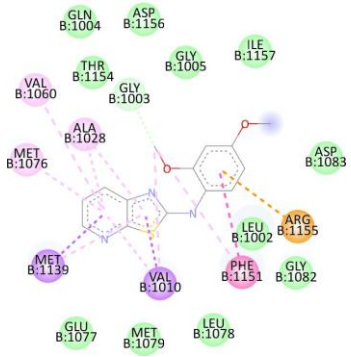
Table 2: List of derivatives based on highest minimum docking score with their 2D and 3D docking poses:

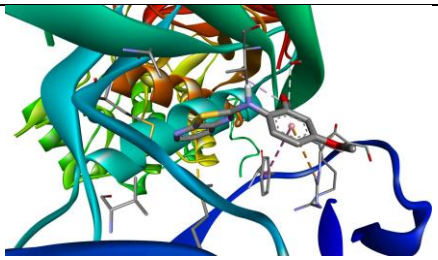
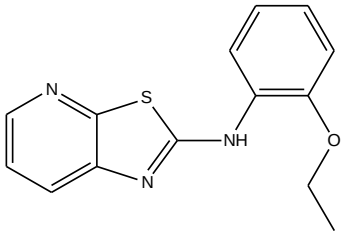
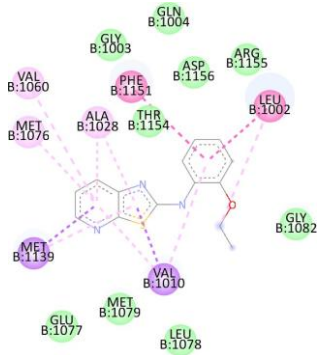
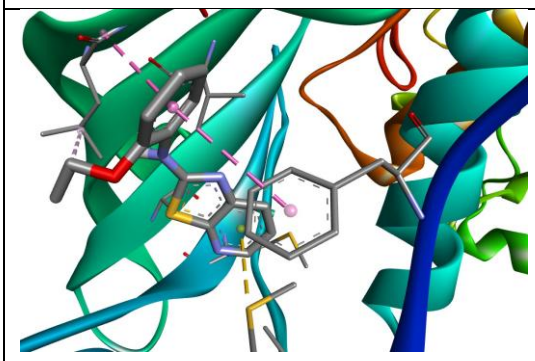
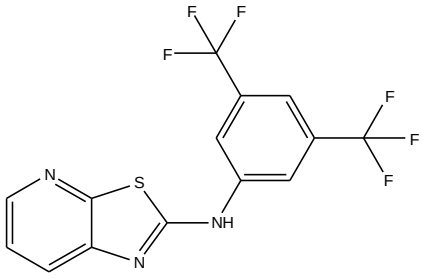
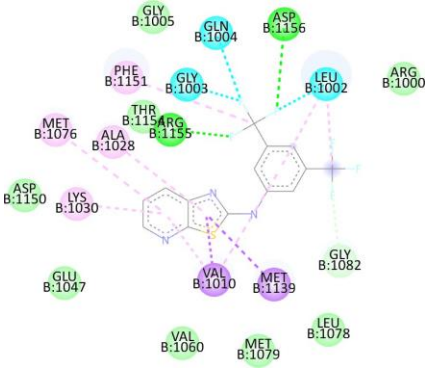
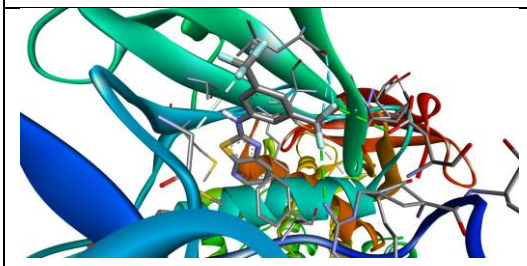
Ligand	Name & Structure of derivative	2D Pose & 3D Pose
Reference drug	Linsitinib (OSI-906) 	 
PC	 ***N*-phenylthiazolo[5,4-*b*]pyridin-2-amine**	 

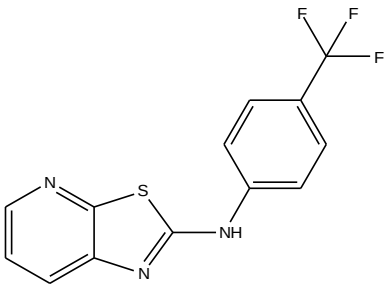
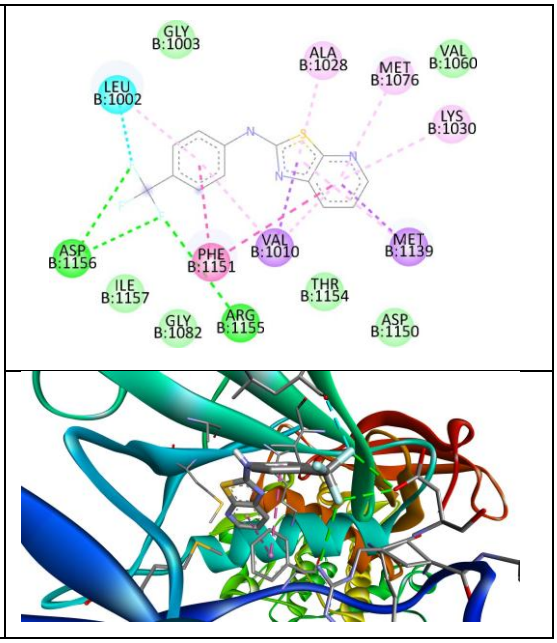
PC1	 ***N*-(4-methoxyphenyl)thiazolo[5,4-*b*]pyridin-2-amine**	 
PC2	 ***N*-(4-fluorophenyl)thiazolo[5,4-*b*]pyridin-2-amine**	 

PC3	 ***N*-*p*-tolylthiazolo[5,4-*b*]pyridin-2-amine**	 
PC4	 ***N*-(2,4-dichlorophenyl)thiazolo[5,4-*b*]pyridin-2-amine**	 
PC5	 ***N*-(2,4-dimethylphenyl)thiazolo[5,4-*b*]pyridin-2-amine**	

		
PC6	 ***N*-(2,6-difluorophenyl)thiazolo[5,4-*b*]pyridin-2-amine**	 
PC7	 ***N*-(3,5-dimethylphenyl)thiazolo[5,4-*b*]pyridin-2-amine**	 

PC8	 ***N*-(2-chloro-6-methylphenyl)thiazolo[5,4-*b*]pyridin-2-amine**	 
PC9	 ***N*-(2-chlorophenyl)thiazolo[5,4-*b*]pyridin-2-amine**	 
PC10	 ***N*-(2,4-dimethoxyphenyl)thiazolo[5,4-*b*]pyridin-2-amine**	

		
PC11	 ***N*-(2-ethoxyphenyl)thiazolo[5,4-*b*]pyridin-2-amine**	 
PC12	 ***N*-(3,5-bis(trifluoromethyl)phenyl)thiazolo[5,4-*b*]pyridin-2-amine**	 

PC13	 ***N*-(4-(trifluoromethyl)phenyl)thiazolo[5,4-*b*]pyridin-2-amine**	

The docking studies revealed that most synthesized pyridine derivatives exhibited strong affinity towards the insulin receptor. The parent compound (PC) showed moderate binding energy, but several substituted derivatives outperformed it significantly. The parent compound PC (unsubstituted pyridine derivative) showed a docking score of –7.1 kcal/mol. This score reflected moderate affinity, primarily through hydrogen bonding with Lys1030 and Asp1150. However, once substituents were introduced, docking scores improved significantly, demonstrating that structural modification enhanced receptor affinity.

Docking results clearly demonstrated that substituted pyridine derivatives bind effectively at the ATP-binding site of insulin receptor. The binding affinities are comparable to or better than reported values for known pyridine-based anticancer drugs.

3.2. *In-silico* Studies

The *in-silico* ADME profiling was conducted using **SwissADME**. All synthesized derivatives adhered to **Lipinski's Rule of Five**, confirming drug-likeness.

Table 3: Molecular properties of the thiazolo[5,4-b]pyridine derivatives by SwissADME

Comp	MW <500	TPSA <140	LogP <5	HBA <10	HBD <5	nRotB <10	Lipinski violations	Molar Refractivity (40-130)
Ref. drug	421.49	89.33	3.60	4	2	3	0	126.84
PC	227.28	66.05	2.25	2	1	2	0	66.96
PC1	257.31	75.28	2.26	3	1	3	0	73.45
PC2	245.28	66.05	2.37	3	1	2	0	66.92
PC3	241.31	66.05	2.51	2	1	2	0	71.92

PC4	296.18	66.05	2.91	2	1	2	0	76.98
PC5	255.34	66.05	2.82	2	1	2	0	76.89
PC6	263.27	66.05	2.36	4	1	2	0	66.87
PC7	255.34	66.05	2.81	2	1	2	0	76.89
PC8	275.76	66.05	2.62	2	1	2	0	76.93
PC9	261.73	66.05	2.68	2	1	2	0	71.97
PC10	287.34	84.51	3.00	4	1	4	0	79.94
PC11	271.34	75.28	2.93	3	1	4	0	78.26
PC12	363.28	66.05	2.77	8	1	4	0	76.96
PC13	295.28	66.05	2.53	5	1	3	0	71.96

All compounds satisfied MW < 500, LogP < 5, and TPSA < 140 Å², ensuring oral bioavailability. ADME results predicted metabolism via CYP450 enzymes (CYP3A4, CYP2D6). Halogenated derivatives were expected to resist rapid metabolism due to electron-withdrawing groups, improving half-life and stability. No compound violated PAINS filters, suggesting low likelihood of assay interference. Predicted mutagenic and hepatotoxic risks were minimal, though trifluoromethyl derivatives warrant further *in vitro* safety studies.

4. Conclusion

The present work involved the *in-silico* studies of substituted thiazolo[5,4-b]pyridine derivatives (PC–PC13) as potential anticancer agents. The study was conceptualized based on the recognition that pyridine scaffolds play a crucial role in medicinal chemistry and are integral to several clinically approved anticancer drugs. The AutoDock Vina molecular docking software was used to simulate the binding of the designed derivatives to Insulin receptor active site. ADME and Pharmacokinetic studies were also performed for ligand (PC-PC13) SwissADME tool and results revealed that PC12, PC6 and PC7 showed remarkable binding energy of -9.9, -8.7 and -8.5 respectively. This suggests that the designed derivatives, particularly PC12, PC6, and PC7, may function as **competitive inhibitors of the kinase domain**, thereby blocking signal transduction pathways critical for cancer cell proliferation. All the designed ligands satisfactorily accepted and developing a new agent.

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