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Computer-Aided Drug Design of Novel Pyrimidine Derivatives Targeting S-Phase Kinase Associated Protein-2: Molecular Docking and ADMET Evaluation

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Abstract

S-Phase Kinase Associated Protein-2 (SKP2), an F-box protein component of the Skp1-Cul1-F-box (SCF) ubiquitin ligase complex, is an oncoprotein frequently overexpressed in various human cancers. It facilitates the targeted ubiquitination and proteasomal degradation of key tumour suppressors, most notably $p27^{Kip1}$, thereby promoting uncontrolled cellular proliferation and tumorigenesis. Consequently, SKP2 has emerged as a highly promising and validated molecular target for anticancer drug discovery.

This research aimed to design novel pyrimidine-based derivatives as potent and selective inhibitors of SKP2 (PDB ID: 2ASS) using an integrated computational drug design approach. A focused library of novel pyrimidine analogues was designed based on the structural insights of the native ligand and known SKP2 inhibitors. Molecular docking studies were performed to investigate the binding modes, affinity, and molecular interactions (hydrogen bonding, hydrophobic, and π-π stacking) between the designed ligands and the active site of the SKP2 protein.

The docking results revealed that several designed compounds exhibited superior binding affinity compared to the reference ligand, and formed critical interactions with key residues in the SKP2 binding pocket. The top-ranking ligands were subsequently subjected to comprehensive *in silico* ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) prediction to evaluate their drug-likeness and pharmacokinetic properties, including gastrointestinal absorption, blood-brain barrier penetration, cytochrome P450 inhibition, and potential hepatotoxicity.

The results demonstrate that the newly designed pyrimidine derivative, 6-((1H-pyrrole-2-carboxyl)oxy)2-(((2,3-dihydro-1H-benzo[d]imidazole-2-yl)methyl)thio)pyrimidin-4-carboxylic acid, possesses strong potential to inhibit SKP2 effectively and exhibits favourable ADMET properties with adherence to Lipinski's Rule of Five, indicating promising potential as an orally bioavailable therapeutic agent. This study provides a robust foundation for the development of novel SKP2 inhibitors, identifying specific lead compounds worthy of further synthesis and experimental validation through *in vitro* and *in vivo* anticancer assays.

Keywords: Computer-Aided Drug Design (CADD); SKP2; Pyrimidine Derivatives; Molecular Docking; ADMET; Anticancer Agents; 2ASS; Ubiquitin-Proteasome System.

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1. Introduction

Cancer encompasses a diverse set of diseases characterised by aberrant and uncontrolled cell proliferation resulting from genetic and epigenetic alterations. Globally, millions of new cancer cases are diagnosed annually, with India alone reporting approximately 1.2 million new cases each year.[1] At present, cancer is the leading cause of death worldwide, accounting for nearly 9.7 million deaths in 2024, representing 1 in 6 deaths. The most common cancers include breast, lung, colon, rectum, and prostate cancers.[2] Central to cancer

progression is the disruption of normal cell cycle control mechanisms.

Some of the earliest evidence of cancer was found among fossilised bone tumours in human mummies in ancient Egypt, with references documented in ancient manuscripts. The oldest description of the disease dates to approximately 3000 BC. The disease was first called cancer by the Greek physician Hippocrates (460–370 BC), considered the "Father of Medicine." Hippocrates used the terms *carcinos* and *carcinoma*—meaning crab in Greek—to describe non-ulcer-forming and ulcer-forming tumours.[1] Carcinogenesis is a gradual, multi-step process involving successive generations of cells. Multiple causative factors act cumulatively (multi-hit process) to drive tumour progression, ultimately producing genetically and phenotypically transformed cells exhibiting malignant features: excessive growth, invasiveness, and metastasis.[3]

The S-phase kinase-associated protein 2 (SKP2), an F-box protein integral to the SCF (SKP1–Cullin–F-box) E3 ubiquitin ligase complex, mediates the ubiquitination and subsequent proteasomal degradation of key cell cycle regulators. SKP2 serves as the substrate recognition component of the SCF E3 ubiquitin ligase complex, mediating ubiquitination of various cell-cycle regulatory proteins, including $p27^{Kip1}$ and $p21^{Cip1}$. These tumour suppressor proteins regulate cyclin-dependent kinase activity and thereby maintain proper cell cycle progression. Overexpression or dysregulation of SKP2 has been implicated in facilitating unchecked cellular proliferation and tumorigenesis, positioning it as a strategic molecular target for therapeutic intervention.[4]

The pyrimidine nucleus is a six-membered heteroaromatic ring containing two nitrogen atoms at positions 1 and 3, forming the basis of many pharmacologically active compounds. Its inherent ability to engage in hydrogen bonding and π–π stacking interactions renders it a privileged structure in kinase inhibition and nucleic acid-targeting therapies.[5] Pyrimidine derivatives have long been fundamental scaffolds in medicinal chemistry owing to their structural versatility, biological activity, and capacity for extensive functional modification. These nitrogenous heterocycles form the core of essential biomolecules such as nucleic acids and serve as the foundation for various anticancer agents targeting enzymes involved in DNA synthesis and cell signalling pathways, including inhibitors of the epidermal growth factor receptor (EGFR) and cyclin-dependent kinases (CDKs).[6] The present study focuses on an *in silico* investigation of novel pyrimidine derivatives as SKP2 inhibitors for the treatment of cancer.

2. Methodology

The ZINC database (version 15) was used to download the structures of the reference ligands. The target protein SKP2 (PDB ID: 2ASS) was retrieved from the RCSB Protein Data Bank. AutoDock 4.2.1 was employed for molecular docking of small molecules. The docking protocol was validated by re-docking the co-crystallised ligand from the 2ASS structure back into the active site of SKP2. Analysis and visualisation of docking results were performed using Biovia Discovery Studio. *In silico* ADME properties of the molecules were evaluated using the online server SwissADME (https://www.swissadme.ch/).[7]

3. Results

3.1 Protein

The three-dimensional crystal structure of SKP2 (PDB ID: 2ASS) was retrieved from the Protein Data Bank. Analysis revealed a well-defined binding pocket crucial for its interaction with ubiquitination target molecules. The active site, located at the interface of the F-box and leucine-rich repeat domains, was identified and validated as the docking site. The structural profile of SKP2 confirms its role as a potential therapeutic target in oncology. The defined active site of the 2ASS structure provides an ideal template for the *in silico* molecular docking of novel pyrimidine derivatives. By targeting this specific site, the pyrimidine derivatives are expected to inhibit SKP2 function, exerting potential anticancer effects. This structural analysis provides the foundational data for subsequent molecular docking studies.[8]

3.2 Ligand Design

In the present work, the previously reported compound 2-{[1H-1,3-benzimidazol-2-yl)methyl]sulfanyl}-6-methylpyrimidine-4-ol was used as the core scaffold to design new SKP2 inhibitors. Molecular modifications were introduced to yield more promising active candidates. A total of 28 ligands were designed, drawn in 2D, converted to 3D, and energy-minimised using PyRx.[9]

3.3 Validation of Molecular Docking

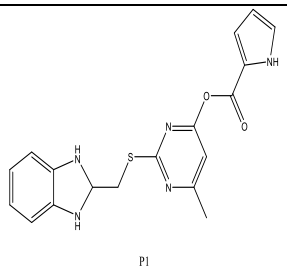
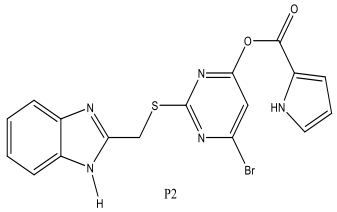
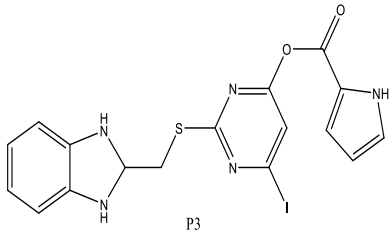
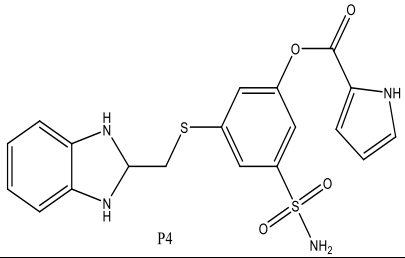
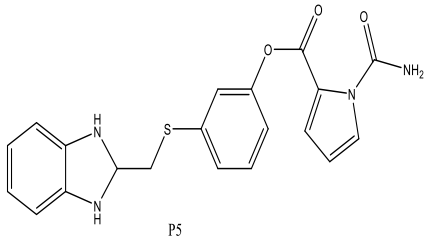
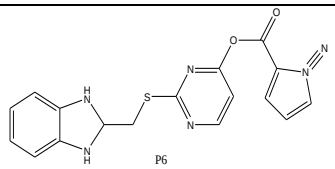
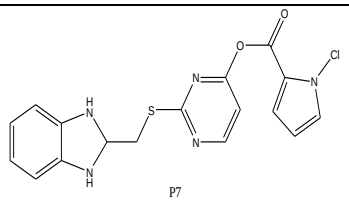
The molecular docking protocol was validated by re-docking the co-crystallised ligand from the 2ASS PDB structure back into the active site of SKP2. The re-docked pose was found to be in close proximity to the original crystal structure conformation, with a Root Mean Square Deviation (RMSD) value of less than 2.0 Å. This low RMSD confirms the accuracy and reliability of the docking protocol, demonstrating its ability to reproduce the experimentally determined binding pose. The validated protocol was therefore deemed suitable for predicting the binding modes of the novel pyrimidine derivatives.[10]

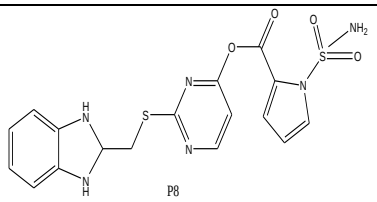
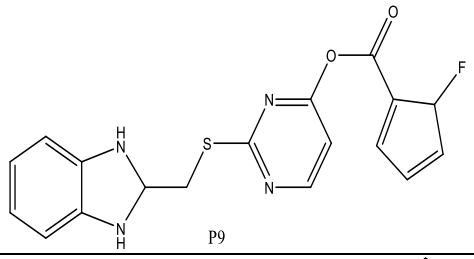
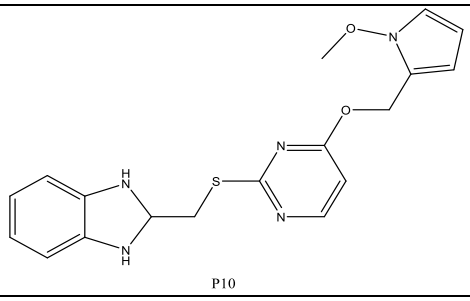
3.4 Molecular Docking Study

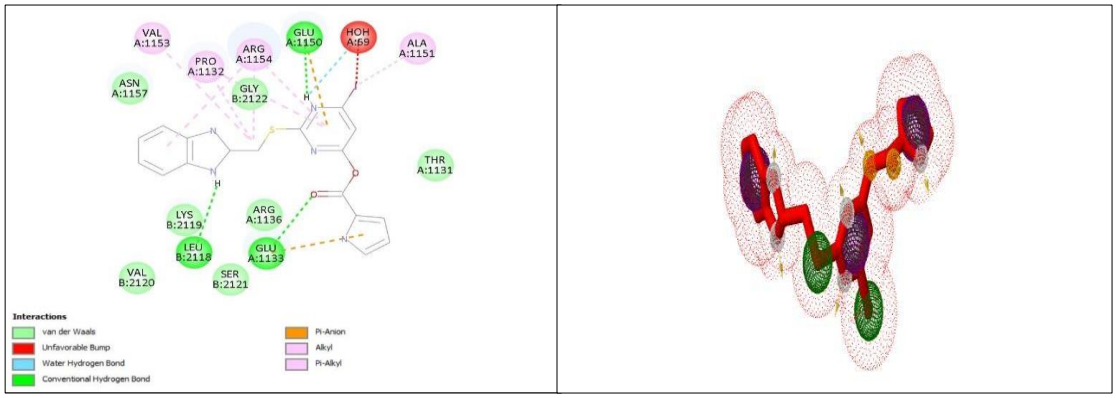
The molecular docking analysis of molecules P1–P10 revealed a range of binding affinities, with values spanning from −7.3 to −8.8 kcal/mol (Table 1). A more negative binding energy indicates stronger affinity and greater ligand-protein complex stability. Molecule P5 exhibited the strongest binding affinity (−8.8 kcal/mol), followed closely by P7 (−8.6 kcal/mol), suggesting they are the most promising candidates for further study. Molecules P1 (−8.3 kcal/mol) and P3 (−8.1 kcal/mol) also showed significant binding potential. Molecule P10 demonstrated the weakest binding affinity (−7.3 kcal/mol).

The protein–ligand interaction of P1 was stabilised by several key amino acid residues: GLU B:2260, THR B:2395, ILE B:2396, HIS B:2314, and HIS B:2339. The participation of water molecules (HOH B:30 and HOH B:49) indicates that solvent-mediated hydrogen bonding plays a crucial role in anchoring P1 (Fig. 1) within the active site. Overall, the docking scores indicate a relatively high level of affinity across the series, with P5 serving as the lead compound based on its superior binding energy.[11]It has also shown interactions with amino acid residues covering hydrogen bond, pi-alkyl, pi-lone pair,pi-sulphur interactions with various amino acids (Fig. 2).

Table 1: Molecular Docking Results of Designed Pyrimidine Derivatives against SKP2 (PDB ID: 2ASS)

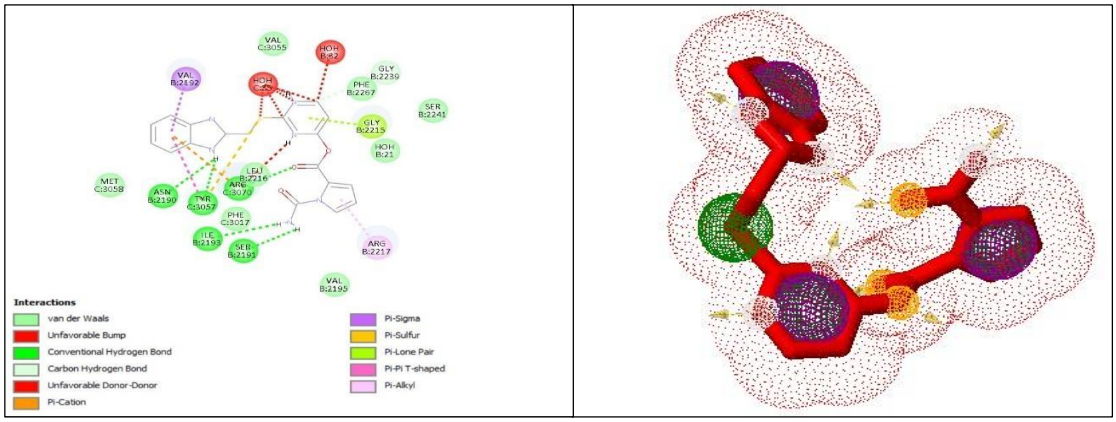
S. No	Molecule Code	Structure	Binding energy (Kcal/ mol)	Amino Acid Residues
1	P1		-8.3	GLU B:2260, THR B:2395, ILE B:2396, HIS B:2314, HIS B:2339,
2	P2		-7.9	PRO C:3072, HOH B:32, ARG C:3070, LEU B:2216, GLY B:2215, ASN B:2190, MET C:3058
3	P3		-8.1	LEU B:2118, GLU A:1133, VAL A:1153, PRO A:1132, ARG A:1154, ALA A:1151, HOH A:69,
4	P4		-7.6	ASN B:2190, HOH C:35, GLY B:2215, PHE B:2267, VAL C:3055, ARG C:3070, ARG B:2217
5	P5		-8.8	**ARG B:2217, SER B:2191, ILE B:2193, ARG C:3070, TYR C:3057, ASN B:2190, VAL B:2192, HOH C:35, PHE B:2267, GLY B:2215**
6	P6		-7.8	ARG B:2164, THR B:2143, ARG B:2167, ILE C:3059, MET C:3058, GLU C:3061
7	P7		-8.6	ARG C:3070, HOH C:35, VAL C:3055, HOH B:32, HOH C:12, HOH C:20, MET C:3038, VAL B:2192

S. No	Molecule Code	Structure	Binding energy (Kcal/ mol)	Amino Acid Residues
8	P8		-7.8	CYS A:1160, PRO A:1132, ARG A:1154, VAL A:1153, LEU B:2118, LYS B:2119, ASN A:1157, HOH A:52
9	P9		-7.7	PHE B:2393, THR B:2395, HOH B:9, HOH B:58, SER B:2391, HIS B:2314
10	P10		-7.3	ARG A:1154, PRO A:1132, HOH A:52, CYS A:1160, LYS B:2119, ASN A:1157



(a) (b)

Figure 1: a) 2D interaction diagram of ligand P1 with protein 2ASS; b) 3D pharmacophore view of P1.



(a) (b)

Figure 2: a) 2D interaction diagram of ligand P5 with protein 2ASS; b) 3D pharmacophore view of P2.

3.5 ADME Study

The absorption of the series was evaluated using four primary parameters: Water Solubility (WS), Skin Permeation (SP), Gastrointestinal Absorption (GIA), and P-glycoprotein (P-gp) interaction. All compounds (P1–P10) exhibited High GIA, suggesting they are likely to be well-absorbed following oral administration. Most compounds showed log WS values between 2.0 and 2.7, with P10 being the most soluble (2.70), while P1 was a notable outlier with significantly lower solubility (−3.5). Skin permeability values ranged from 0.45 (P1) to 3.5 (P4). All compounds except P9 acted as P-gp substrates; however, only P4, P6, and P7 were identified as P-gp inhibitors (Table 2).

Distribution was assessed through Volume of Distribution (VDss) and Blood-Brain Barrier (BBB) penetration. The series generally exhibited low VDss values, with P4 (0.091) and P7 (0.035) having the highest distribution volumes. The majority of compounds did not cross the BBB; which is a critical consideration for drugs targeting or avoiding the central nervous system. Metabolism assessment focused on CYP1A2 and CYP3A4 enzyme interactions. All compounds except P10 were classified as CYP3A4 substrates. Most compounds inhibited both CYP1A2 and CYP3A4, with notable exceptions: P2 did not inhibit either enzyme, and P10 did not inhibit CYP3A4. Excretion, measured by Total Clearance (CL), ranged from −0.42 (P6) to 0.42 (P5), with P2, P4, P5, and P9 showing positive clearance values, while negative values suggest slower elimination or altered kinetic behaviour.[12] The core scaffold conferred a favorable hERG safety profile, with most compounds displaying negligible cardiotoxicity risk and less risk of carcinogenicity overall. Drug-induced liver injury (DILI) is a leading cause of drug withdrawal from the market, and early-stage hepatotoxicity prediction is therefore of high practical importance. The series has shown least to maximum hepatotoxicity. Bust most of them are in the range of low to moderate indicating the probable safety towards hepatotoxicity. Most of the molecules predicted to show the skin sensitivity indicating that the topical or dermal routes of administration should be avoided, or that structural modifications aimed at reducing electrophilicity should be explored.

Table 2: In Silico ADME Properties of Designed Pyrimidine Derivatives (SwissADME)

Code	Absorption				Distribution		Metabolism			Excretion	Toxicity studies			
	WS	SP	P-gp Sub.	GIA	VDss	BBB	CYP1A2 Inh.	CYP3A4 Inh.	CYP3A4 Sub.	Total CL	h-ERG	H-HT	SkinSen	Carcinogenicity
P1	-3.5	0.45	Yes	High	-0.068	0.15	Yes	Yes	Yes	-0.01	0.014	0.413	0.931	0.25
P2	2.31	0.55	Yes	High	-0.076	0.413	No	No	Yes	0.081	0.012	0.225	0.939	0.362
P3	2.40	2.1	Yes	High	-0.046	0.413	Yes	Yes	Yes	-0.050	0.012	0.261	0.934	0.303
P4	2.01	3.5	Yes	High	0.091	0.008	Yes	No	Yes	0.40	0.011	0.706	0.154	0.213
P5	2.12	1.7	Yes	High	-0.215	0.5-0.7	Yes	Yes	Yes	0.42	0-0.1	0-0.1	0.7-0.9	0.1-0.3
P6	2.35	2.5	Yes	High	-0.19	0.5-0.7	Yes	Yes	Yes	-0.42	0-0.1	0.7-0.9	0.7-0.9	0.3-0.5
P7	2.01	2.8	Yes	High	0.035	0.3-0.5	Yes	Yes	Yes	-0.12	0-0.1	0.7-0.9	0.9-1.0	0.59
P8	2.31	3.09	Yes	High	-0.118	0-0.1	Yes	Yes	Yes	-0.1	0-0.1	0.9-1.0	0.3-0.5	0.4
P9	2.0	2.1	No	High	-0.106	0.3-0.5	Yes	Yes	Yes	0.090	0-0.1	0.7-0.9	0.9-1.0	0.65
P10	2.70	1.4	Yes	High	-0.1	0.5-0.7	Yes	No	No	-0.051	0-0.1	0.5-0.7	0.5-0.7	0.3-0.5

WS = Water Solubility (log mol/L); SP = Skin Permeation (log Kp, cm/s); P-gp Sub. = P-glycoprotein Substrate; GIA = Gastrointestinal Absorption; VDss = Volume of Distribution at Steady State (log L/kg); BBB = Blood-Brain Barrier penetration; Inh. = Inhibitor; Sub. = Substrate; Total CL = Total Clearance (log mL/min/kg).

4. Discussion

This study explored the development of novel pyrimidine derivatives as targeted treatments for cancer by focusing on SKP2, a critical regulator of the cell cycle that promotes tumour progression when overexpressed.

The compound P5; 2-(((2,3-dihydro-1H-benzo[d]imidazol-2-yl)methyl)thio)pyrimidin-4-yl 1-carbamoyl-1H-pyrrole-2-carboxylate, can be considered as one of the most promising candiate among the designed pyrimidine analogues owing to its superior binding affinity (−8.8 kcal/mol) and interaction stability. The compound demonstrated binding affinity superior to the parent scaffold and showed stable interactions within the active site of the SKP2 protein. It may be attributed to the presence of the carbamoyl group, which increased the hydrogen bonding capacity and improved ligand accommodation within the receptor cavity. The compound exhibited favorable interactions with many amino acid residues present in the active binding pocket, contributing to

the stabilization of the ligand–protein complex. The results also implying that the benzimidazole and pyrimidine nuclei played an important role in maintaining hydrophobic and π–π interactions with amino acid residues of the receptor. The sulfur linker between the heterocyclic systems observed to contribute to conformational flexibility, allowing optimal fitting of the ligand inside the binding pocket. The docking score confirmed that structural modification with a carbamoyl moiety significantly improved receptor binding when compared to several other derivatives in the series.

In silico ADMET analysis revealed that P5 possessed acceptable physicochemical and pharmacokinetic properties. The molecular weight of the compound was found to be 396.425 Da, which falls within the acceptable range recommended by Lipinski's rule of five, indicating good oral drug-likeness. The LogP value of 3.380 suggested a little higher lipophilicity, but considered to be favorable for membrane permeability and absorption. The blood–brain barrier (BBB) permeability value predicted to be in the range of 0.5–0.7, indicating moderate CNS penetration. Though for an anti-cancer drug minimal BBB permeability is expected, moderate results of P5 can be accepted due to other favourable parameters as well as better binding affinity. Plasma protein binding (PPB) was predicted to be 96.909%, indicating longer duration, prolonged systemic circulation and adequate distribution characteristics. Furthermore, it also exhibited moderate CYP2C19 inhibition probability and very low CYP substrate probability, indicating a comparatively stable metabolic profile with lower chances of rapid biotransformation.

Toxicity prediction demonstrated encouraging safety characteristics for P5. The hERG inhibition value indicated very low cardiotoxic potential and minimal risk of cardiac arrhythmia. Similarly, the carcinogenicity score was also comparatively lower than many other derivatives in the series, suggesting reduced carcinogenic risk. But it was predicted to have the moderate hepatotoxic potential. The skin sensitization value was maximum indicating skin sensitivity potential. However, the absence of other significant toxicities in the prediction model supports its suitability as a lead candidate for further optimization.

There are various inhibitors reported for SKP2 like SKPin C1[13] and SZL-P1-41[14], the important structure-based inhibitors, SZL-P1-41 (a 1,3-Diphenylpyrazine Derivative which is also called as compound #25) inhibits interaction between SKP1 and SKP2, SMIP004[15] a small molecule inhibitor. In spite of discovery of various inhibitors and their promising preclinical results, none of the molecule reached the stage of clinical trials. It may be because of limitations like insufficient selectivity, poor pharmacokinetics, metabolic instability, and toxicity concerns. Apart from that, the discovery of small-molecule inhibitors for SKP2 that involve protein-protein interactions is a challenging task due to flexible nature of these interfaces. Continuous research in this area is crucial for potentially offering new avenues for treating various cancers.

Our designed molecules shown comparable docking scores and acceptable ADMET properties. Especially the compound P5 shown better binding affinity, low hERG liability and reduced carcinogenicity indicating that it may be considered as a promising lead molecule for further optimization and biological evaluation as a novel SKP2 inhibitor. The current results are demonstrating the anticancer potential of pyrimidine scaffolds as kinase inhibitors. But as *in silico* studies are only the initial steps towards the development of novel SKP2 inhibitors, it needs justification by means of experimental validation.

These findings suggest that pyrimidine-based SKP2 inhibitors offer a promising therapeutic strategy for disrupting cancer cell proliferation at the molecular level. The current results are consistent with published literature demonstrating the anticancer potential of pyrimidine scaffolds as kinase inhibitors and provide strong justification for advancing these compounds to experimental validation.

5. Conclusion

This study successfully identified and evaluated a series of novel pyrimidine derivatives as potential SKP2 inhibitors for cancer therapy using *in silico* techniques. A validated docking protocol with an RMSD of less than 2.0 Å provided a reliable framework for assessing binding interactions with the SKP2 protein. These findings suggest that pyrimidine-based SKP2 inhibitors offer a promising therapeutic strategy for disrupting cancer cell proliferation at the molecular level. Compound P5 can be considered for further wet lab research and evaluation of biological activity. Our results provided a computational basis for the future development of SKP2-targeted anticancer agents.

Conflict of Interest

The authors declare no conflict of interest.

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