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Integrated Computational Approach to Rational Drug Design Targeting SIK2/3: From Theory to Practice

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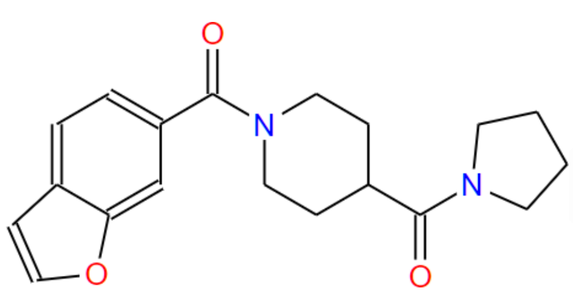
INTRODUCTION & AIM

Salt-Inducible Kinases 2 and 3 (SIK2 and SIK3) are key regulators of cellular metabolism and transcriptional regulation, implicated in various diseases such as cancer, inflammation, and metabolic disorders. Their pivotal roles make them attractive therapeutic targets, yet the development of selective and potent inhibitors for these kinases presents significant challenges due to their structural intricacies and biological functions.

In this study, we tackle these challenges by adopting a comprehensive computational approach, integrating multiple advanced methodologies, including de novo drug design, fragment-based drug design (FBDD), molecular docking, covalent docking, and molecular dynamics simulations. By leveraging these cutting-edge techniques, we aimed to streamline the identification and optimization of novel small molecule inhibitors with strong binding affinities, high specificity, and favorable pharmacokinetic properties. This approach not only accelerates the drug discovery process but also enhances the potential for developing effective therapeutics targeting SIK2 and SIK3, addressing diseases associated with dysregulated signaling pathways.

METHOD

We selected the reference(CHEMBL5090394) , curated a large dataset by retrieving SMILEs from the PubChem and Zinc databases. These compounds were filtered using Lipinski's Rule of Five, the Ghose filter , and Tanimoto similarity which narrowed the dataset to 250 SMILEs. We compiled several files based on the fingerprints used. This study employed two chemical language models: "Molecular Design with Beam Search" and "REINVENT 4. In the initial phase, we utilized the models to generate SMILES using SBDD. This process involved single-Step and two-Step Fine-Tuning. In Phase 2, FBDD. The process involved Transfer learning and Sampling steps. The model was further refined with fragment files.



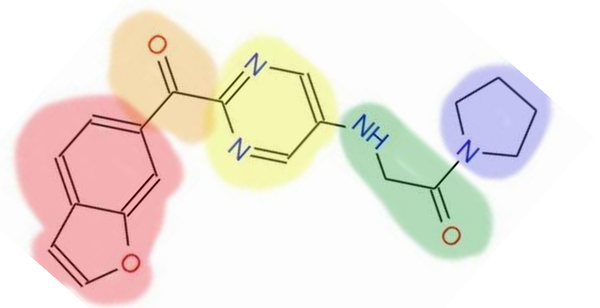


Figure 1: Chosen Lead Figure 2: Optimized Lead

the compound "`O=C(c1ccc2ccoc2c1)N1CCC(C(=O)N2CCCC2)CC1`“ (Figure 1) was chosen as a lead for molecular docking using MARK2-SIK2 chimera (PDB ID: 8TXY) as the receptor then the lead underwent human optimization like adding an amino bridge between a six-membered ring and a carbonyl group, forming an amino carbonyl group (Figure 2). The resulting initial SMILE led to the generation of 30 distinct optimized molecules. Docking simulations validated the optimized molecules using AutoDock Vina. For covalent docking we used Meeko and AutoDock GPU. As aminoacid of interest we selected Methionine 104. Fragmenstein was used to generate novel molecules. For molecular dynamics we used GROMACS 2024.1 with the AMBER force field for the receptor and OpenFF tools for ligand parameterization and SPC216 water model for 10 ns with a 2 fs time step.

RESULTS & DISCUSSION

Phase 1: Molecular Design with Beam Search was executed 42 times, generating 15 SMILES strings per run. This process yielded the best results with reasonable similarity and diversity. Model 2, REINVENT4, generated 628 SMILES strings without fine-tuning, followed by a two-step fine-tuning, which produced 154 SMILES strings. Phase 2: Fragment-Based Drug Design (FBDD) involved running the Molecular Design with Beam Search 16 times, producing 15 SMILES per run, but with lower similarity to the reference molecule. REINVENT4 generated 12 files, with a median output of 157 SMILES per run. These SMILES had high similarity but lacked diversity. Using AutoDock Vina, the reference molecule had a minimum binding energy of -9.2 kcal/mol, while the lead compound had -8.2 kcal/mol(Table 1). SMILE10 from the human optimization phase had the highest binding affinity, closely followed by other derivatives

SMILE	Mode	Affinity (kcal/mol)
Reference	1	-9.2
	2	-9.2
Lead	1	-8.2
	2	-7.9

Trial	Variant	Binding Energy (kcal/mol)
1	18	-10.42
1	5	-9.95
1	44	-10.39
1	48	-10.79

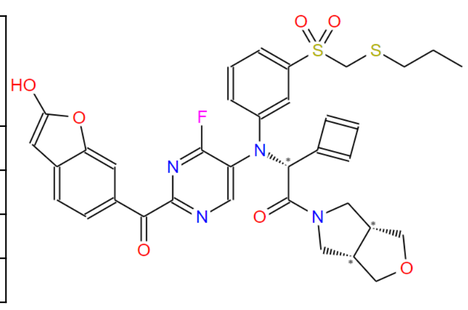


Table 1: Ref and Lead Docking scores Table 2: Ligand 10 v 1.3 variants Figure 3: variant 48 structure

Fragmenstein SMILE 13 from Step 1 exhibited a binding energy of -10.7 kcal/mol. Select molecules underwent MD simulations. Ligand 10 BSF Variant 1.3 showed consistent hydrogen bonding with MET 104 and GLU 120, stable binding (RMSD ~0.225 nm), and fluctuating interaction energy around 4850 kJ/mol. Fragmenstein Ligand 2 Step 1 had dynamic hydrogen bonding with ARG 102 and ILE 119, larger conformational changes (RMSD ~0.45 nm), and similar interaction energy stability. A total of 78 variants of Ligand 10 V1.3 were generated across two trials. Docking grid box adjustments significantly impacted the results, with seven variants selected for further MD simulations. Variants 5 and 48 showed the best performance. Variant 48 achieved a binding energy of -10.79 kcal/mol, an improvement over the reference, though it didn't surpass the parent ligand in stability(Table 2)(Figure 3). Variant 5 demonstrated better hydrogen bond stability but fluctuated more (RMSD ~0.6 nm). Optimization extended to other covalent inhibitors, altering the bonding of the BSF warhead in Ligand 1 variants. Ligand 1 variant 1.4 new 2 achieved a binding energy of -10.17 kcal/mol. After MD simulations, Ligand 1 Variant 1.1 New showed intermittent hydrogen bonding with RMSD values between 0.22 nm and 0.3 nm, Ligand 1 Variant 1.4 demonstrated stable hydrogen bonds with RMSD ~0.22 nm, and Ligand 1 Variant 1.4 New 2 exhibited stable hydrogen bonding with RMSD ~0.25 nm.

CONCLUSION

The optimized lead compounds showed strong interactions with the protein targets, evidenced by higher binding affinities, stable binding profiles, and reliable hydrogen bonding. These results lay a solid foundation for further testing. The study highlights the potential for, bridging computational predictions with experimental applications.

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