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Research Article:

Computational Exploration and Optimization of 6-Aryl-5-Cyano Thiouracil Scaffolds as Type-II VEGFR-2 Tyrosine Kinase Inhibitors: Insights from Docking, Molecular Dynamics, DFT, and ADMET Studies

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Abstract

Background: This study presents the rationale for the in silico design and computational assessment of a novel set of six aryl 5-cyanothiouracil-based vascular endothelial growth factor receptor-2 (VEGFR-2) tyrosine kinase inhibitors as prospective anticancer agents. The compounds strategically integrate a hinge-binding pyrimidine core, a piperazine linker for alignment with the aspartate-phenylalanine-glycine (DFG) motif, and an oxadiazole-amide pharmacophore to mimic sorafenib's critical hydrogen bonding within the adenosine triphosphate (ATP) pocket. **Methods:** Computational evaluation was conducted via molecular docking against VEGFR-2. The structural stability of the leading complex was validated through a 100 ns molecular dynamics (MD) simulation and Molecular Mechanics-Generalized Born Surface Area (MM-GBSA) binding free energy calculations. Density functional theory (DFT) evaluated electronic properties, while absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles were predicted. **Results:** Docking revealed multiple candidates achieving canonical type II binding modes with scores superior to sorafenib, maintaining essential contacts with Cys919, Glu885, and Asp1046. The MD simulation of the VEGFR-2/compound 10d complex confirmed high structural stability, minimal Root-Mean-Square Deviation (RMSD) fluctuations, and favorable MM-GBSA energies driven by lipophilic interactions. DFT calculations confirmed electronic suitability, with compound 10d showing the narrowest frontier orbital gaps. Predicted ADMET profiles indicated adequate oral absorption, though showing class-wide liabilities for cytochrome P450 (CYP), human Ether-à-go-go-Related Gene (hERG), and hepatotoxicity. Compound 10a displayed the most favorable pharmacokinetic profile. **Conclusion:** Compounds 10a and 10d were successfully identified as promising lead scaffolds targeting VEGFR-2, providing a robust computational foundation for further experimental validation and optimization.

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1. Introduction

Cancer is a leading global health challenge, responsible for approximately 9.6 million deaths in 2020, with projections indicating a rise to 27.5 million new cases and 16.3 million deaths by 2040 (1-3), due largely to population growth and aging. In Egypt, major cancers contribute to over 50% of diagnoses, resulting in around 89,042 annual deaths, while the U.S. spent about \$208 billion on cancer treatment in 2020 (4). The core issue of cancer is the

failure of healthy cells to control division, leading to unchecked growth and metastasis, often driven by genetic mutations affecting tumor suppressor genes and oncogenes (5, 6).

Standard treatment options include surgery, radiation, immunotherapy, hormonal therapy, and chemotherapy, with the latter being a key approach for metastatic disease (7). However, typical chemotherapy faces challenges like lack of tumor specificity and multi-drug resistance, pushing research towards targeted molecular therapies (8). Protein kinases (PKs), which are essential for various cellular functions, have emerged as therapeutic targets due to their role in tumor formation when dysregulated (9,10). Receptor tyrosine kinases (RTKs) are significant players in cancer progression, with certain RTKs like VEGFR-2 facilitating tumor angiogenesis (11). Small-molecule tyrosine kinase inhibitors (TKIs), such as Sorafenib, target these pathways by blocking ATP binding in the kinase domain, thus inhibiting the signalling processes (12,13). Though several VEGFR-targeted drugs have received FDA

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approval, as shown in **Figure 1**, their association with severe side effects and drug resistance underscores the urgent need for developing more selective and well-tolerated treatment options.

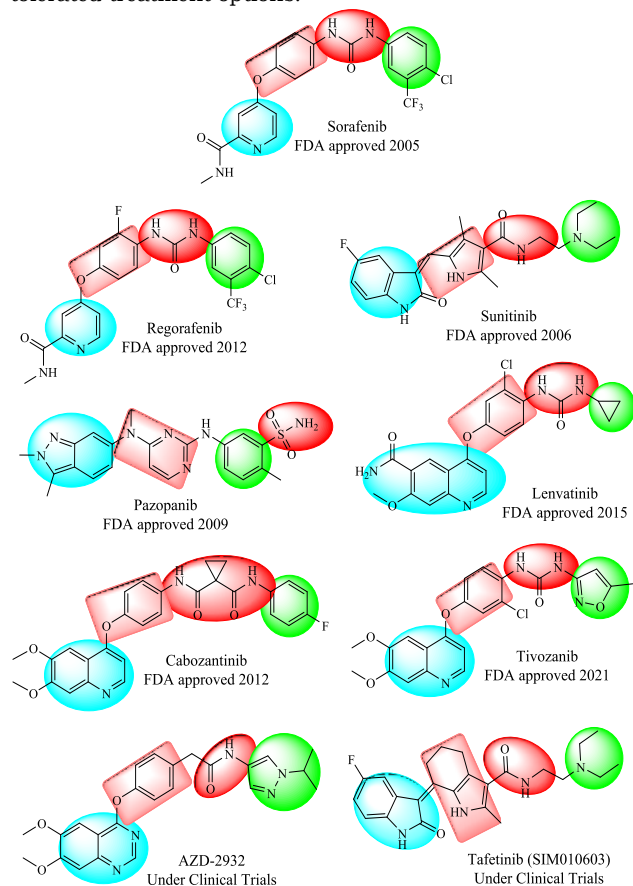


Figure 1. Basic pharmacophoric features of VEGFR-2 TK inhibitors

Structure-activity relationship (SAR) analyses of sorafenib and other clinically approved VEGFR-2 inhibitors have delineated four essential pharmacophoric features crucial for potency (**Figure 2**): a heteroaromatic core acting as an H-bond acceptor within the ATP-binding domain (Cys919) (14), a central aryl spacer occupying the linker region, a bifunctional urea or amide pharmacophore capable of forming critical H-bonds with DFG residues (Glu885 and Asp1046), and a terminal hydrophobic tail that stabilizes the inactive kinase conformation (15). Driven by these structural insights, the primary objective of the present study is the design and synthesis of novel small-molecule anticancer agents based on the 6-aryl-5-cyanothiouracil scaffold, effectively incorporating this established pharmacophoric framework to target VEGFR-2 (16,17).

Pyrimidines are one of the most pharmacologically privileged heterocyclic compounds and exhibit an exceptionally broad spectrum of biological activities. Pyrimidine ring as a structural motif embedded in naturally occurring nucleobases (cytosine, thymine, and uracil) is well tolerated in biological systems and shows excellent drug-like properties. The versatility of substitution patterns around the pyrimidine core has been utilized to generate molecules with diverse mechanisms of anticancer action, making pyrimidine-based scaffolds integral to modern targeted oncology drug discovery (18).

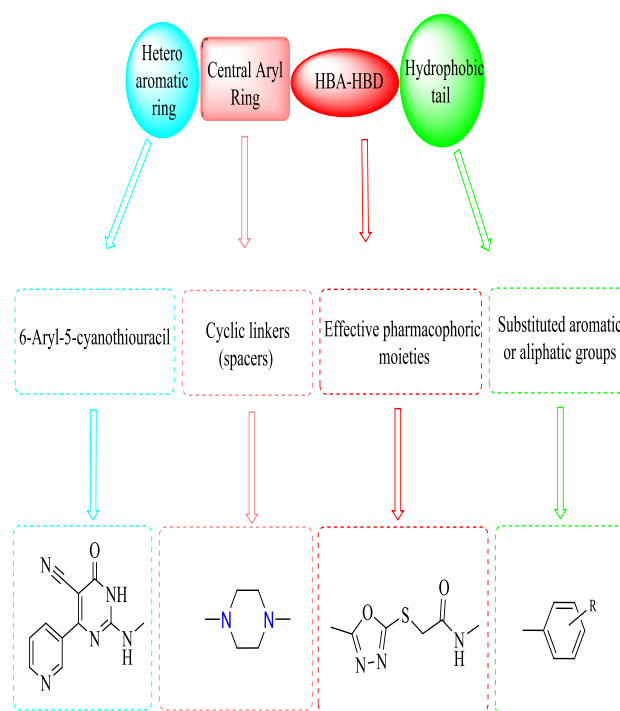


Figure 2. Summary for the possible modifications of VEGFR-2 inhibitors

Pyrimidine derivatives have demonstrated important anticancer activity through several mechanistic targets: (i) inhibition of VEGFR-2 TK, (ii) inhibition of EGFR TK, (iii) antagonism of DNA polymerases and ribonucleotide reductase (e.g., cytarabine, gemcitabine), (iv) inhibition of thymidylate synthase (e.g., 5-fluorouracil), (v) inhibition of dihydrofolate reductase (e.g., pemetrexed), (vi) inhibition of cyclin-dependent kinases CDK4/6 (e.g., ribociclib, abemaciclib), and (vii) inhibition of topoisomerase II. Several pyrimidine-based drugs have been approved by the FDA, such as Osimertinib (AZD9291), Brigatinib, and Olmutinib (19), which are the best examples of the clinical success of this scaffold in targeted cancer therapy. Pyrimidine derivatives, especially 5-cyanopyrimidine and 6-aryl-5-cyanothiouracil scaffolds, are of increasing interest as privileged anticancer frameworks. These compounds possess good physicochemical properties and potent biological activities and are well-tolerated in human biological systems. Cyano-pyrimidine analogues containing benzimidazole, trimethoxyphenyl, and benzothiazole groups were screened against the NCI-60 cancer cell panel and were observed to possess broad-spectrum antiproliferative activity with several confirmed mechanisms of action, including EGFR/HER2 inhibition, selective COX-2 inhibition, and induction of apoptosis (20). reported pyrimidine-5-carbonitrile derivatives with potent EGFR inhibitory activity (IC₅₀ = 8.29 nM) against HepG2, A549 and MCF-7 cell lines. The 6-aryl-5-cyanothiouracil derivatives also exhibited potent inhibition of growth against non-small cell lung cancer (HOP-92) and leukaemia (MOLT-4) cell lines, suggesting this subclass as a promising scaffold for further structural optimisation (21,22). The designed compounds are intended to exhibit potent and selective anti-proliferative activity with favorable predicted pharmacokinetic and drug-like properties.

2. Materials and methods

2.1. Design

The proposed schemes were designed based on the pharmacophoric features of VEGFR-2 ATP binding site, which is designed by using pyrimidine as a hinge binder that mimics the adenine ring in ATP molecule, and increasing the chance of binding with DFG motif by using an oxadiazole ring supported with an amid moiety to bind with Asp1046 and Glu885. Additionally, the terminal hydrophobic moieties were varied to achieve the optimal occupation with the allosteric site according to the reported methods (23).

The molecular design strategy employs bioisosteric modification derived from sorafenib and other clinically validated inhibitors. This approach enables systematic exploration of the structural requirements for optimal binding to the ATP-binding site and the DFG-out allosteric pocket of VEGFR-2 TK. The designed compounds occupy the ATP binding site by inserting the pyrimidine core inside the target pocket and increasing the number of hydrogen bond donors and acceptors to elevate the chance of binding with Cys919. Additionally, the linker group was replaced with piperazine to increase flexibility and ensure good direction of the pharmacophoric group to DFG motif. On the other hand, the sorafenib urea moiety was replaced by an oxadiazole ring supported by amid groups to increase interaction with Asp1046/Glu885 amino acids; this design may provide new promising VEGFR2 inhibitors (13,22).

2.2. Molecular docking

The Molecular docking was performed to assess the potential affinity of the tested compounds against VEGFR-2 TK obtained from the Protein Data Bank (PDB ID: 4asd) (24, 25). The protein structure was initially prepared by removing water molecules and other non-essential components from the complex. Subsequently, protonation was performed, and any incomplete valences were corrected. The optimized protein structure was then energy-minimized and saved in PDBQT format. The binding pocket was identified based on the position of the co-crystallized ligand. For ligand preparation, the 2D structures of the compounds were drawn and saved as SDF files. These structures were then protonated, energy-minimized, and converted into PDBQT format using AutoDockTools (MGLTools, version 1.5.7) (26).

Finally, molecular docking was performed against the VEGFR-2 tyrosine kinase active site using AutoDock Vina (27). The docking scores of the best-fit poses with the active sites were recorded, and 3D and 2D figures were generated using Discovery Studio 2024 visualizer (28). Validation of molecular docking was processed to check the validity of the target proteins to evaluate the docking results, the co-crystallized ligands, which complexed with VEGFR-2 TK (Sorafenib) redocked inside the target pockets.

2.3. Molecular dynamics (MD) simulation

To evaluate the dynamic stability of the most promising ligand-receptor interaction, MD simulations were applied exclusively to the docking complex of the single compound that exhibited the best docking score. The MD simulations were run in Desmond (Schrödinger) under NPT (300 K, 1 bar) for 100 ns using OPLS_2005, PME electrostatics (9.0 Å

cutoff), SPC water, Nosé-Hoover/Martyna-Tuckerman-Klein coupling (2.0 ps), and r-RESPA integrator (frames every 4.8 ps). The behavior and interactions between ligands and proteins were examined using the Simulation Interaction Diagram tool within the Desmond MD package. The stability of MD simulations was assessed by monitoring the root mean square deviation (RMSD) of ligand and protein atom positions over time (29, 30).

2.4. Density functional theory (DFT) calculations

DFT calculations were performed in BIOVIA Discovery Studio using the DMol³ quantum mechanical module integrated in the platform. Molecular structures were first energy minimized with the CHARMM force field, then exported to DMol³ for single point and geometry optimization calculations. Ground state DFT was carried out with standard local or GGA functionals (for example, BLYP or PBE) and numerical atom centered basis sets, with all electron or DSPP pseudopotential treatments as appropriate. Optimized geometries and electronic properties (total energy, HOMO-LUMO levels, electron density) were analyzed within the Discovery Studio environment using built in visualization and reporting tools (31).

2.5. Pharmacokinetics (ADMET) calculations

Deep PK was used as an online platform to predict pharmacokinetic and toxicity related properties of small molecules directly from chemical structure. The SMILES strings of the designed compounds were submitted to the Deep PK web server, selecting relevant ADMET/PK endpoints (e.g., absorption, distribution, metabolism, excretion, and toxicity). For each molecule, Deep PK applied pretrained graph neural network models using graph based molecular signatures as input features to generate probabilistic or continuous predictions for the chosen endpoints. Prediction outputs were obtained from the results and focus pages of the server, where individual properties, confidence scores, and literature based interpretation notes were collected and used to guide compound prioritization and pharmacokinetic optimization (32).

2.6. Prime MM-GBSA binding free energy calculations

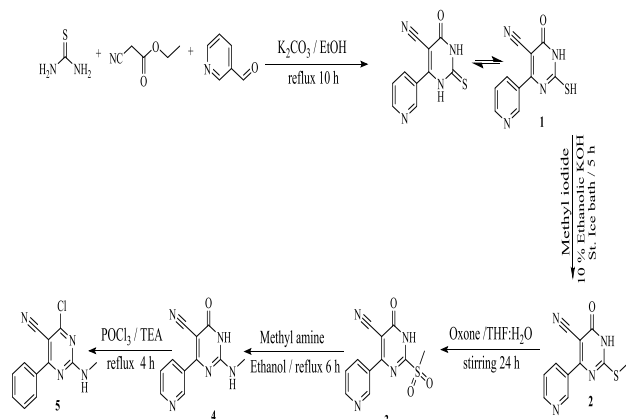
The binding free energy of the simulated complex (VEGFR-2 in complex with compound 10d) was calculated using the Molecular Mechanics-Generalized Born Surface Area (MM-GBSA) method implemented in the Prime module of the Schrödinger suite. The energy calculations were performed over the stable trajectory frames extracted from the final 20 ns of the molecular dynamics production run (33).

3. Results and discussion

3.1. Chemistry

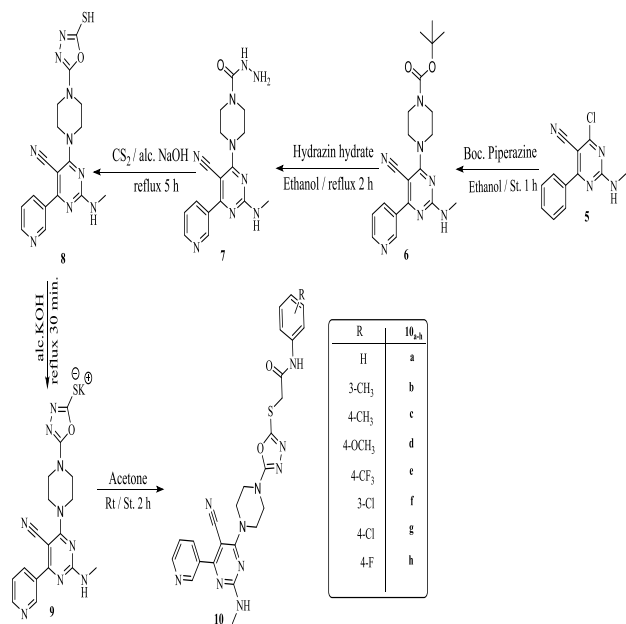
The proposed synthetic route of our designed compounds is based on a one-pot reaction to form the target pyrimidine using the reported conditions (34) After that, regioselective S-Alkylation will be done using methyl iodide as the alkylating agent in the alcohol. Potassium hydroxide solution according to the reported method (35). Oxidation

of S-alkyl may be established using a mild oxidative agent, such as Oxone ($2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$), which can convert the sulfur atom to sulfone (36), as shown in **Scheme 1**. A suitable amine can easily attack the sulfone to form compound 4. The key intermediate compound 5 may be prepared according to the following reported procedure (37) by heating compound 4 with an excess of phosphorus oxychloride in the presence of TEA as an acid binder.



Scheme 1. Expected synthesis route of the key intermediates 5

After chlorination, Boc protected piperazine may react with compound 5 to afford the ester derivative 6, as shown in **Scheme 2**. Subsequent treatment of compound 6 with hydrazine hydrate will convert the ester functionality into the corresponding hydrazide 7. Cyclization of hydrazide 7 with carbon disulfide will furnish the 1,3,4 oxadiazole derivative 8. Finally, the target compounds 10a-h will be obtained by reacting compound 9 with various substituted acetamides (38).



Scheme 2. The proposed synthesis route of the target final compounds 10a-h.

3.2. Molecular Modeling

3.2.1. Molecular docking of the tested compounds 10a-h against VEGFR-2 TK.

To validate the reliability and predictive accuracy of the docking protocol, the co-crystallized reference ligand, Sorafenib, was initially re-docked into the active site of VEGFR-2 TK. The docking protocol was demonstrated to be highly successful, as sorafenib accurately reproduced its experimental binding orientation, adopting the canonical type-II VEGFR-2 binding mode with a favorable docking score of -9.48 kcal/mol (**Table 1**). Mechanistically, its interaction profile was anchored by five crucial hydrogen bonds with key pharmacophoric residues, specifically Cys919 in the hinge region, and Asp1046 and Glu885 within the DFG motif along the ATP-binding cleft. Additionally, its terminal phenyl moieties deeply occupied the hydrophobic back pocket, engaging in alkyl and π -alkyl contacts with Leu840, Ala866, Val848, Val916, Leu1035, Leu889, and Phe1047, complemented by π - π contacts with Phe918 and a fluorine-mediated halogen bond. These established key interactions of Sorafenib served as the reference benchmark against which the binding modes and interactions of the newly designed compounds (10a-h) were subsequently evaluated and compared.

Compound 10a adopts a typical type II VEGFR 2 binding mode with a docking score of -9.07 kcal/mol, in which its pyrimidine scaffold extends from the hinge region and directed the pharmacophoric moiety toward the DFG motif; the core is anchored in the hinge pocket through hydrogen bonding with Leu840, while the terminal amide (Pharmacophoric moiety) bound with Asp1046 and Glu885 by two hydrogen bonds with distances of 1.96, and 1.84 Å, additionally the hydrophobic moieties showed many hydrophobic π -interactions with Leu840, Ala866, Val848, Val916, Leu1035, Leu889, and Phe1047 (**Figure S1**). Compound 10c follows the same overall topology with a docking score of -9.21 kcal/mol, being stabilized at the hinge by a typical hydrogen bond with Cys919 (2.58 Å), and at the DFG region by dual hydrogen bonding of its terminal amide to Asp1046 (2.46 Å) and Glu885 (2.32 Å), whereas its extended aryl system forms extensive hydrophobic and π - π/π -alkyl contacts with Leu840, Ala866, Val848, Val899, Val916, Leu1035, Phe918, and Phe1047 in the back pocket (**Figure S2**). On the other hand, Compound 10d also spans the hinge-DFG axis with a docking score of -9.61 kcal/mol, its pyrimidine core hydrogen bonded to Cys919 at the hinge and its terminal amide simultaneously hydrogen bonded to Glu885 and Asp1046; the central aryl linker is tightly packed against Leu840, Ala866, Val848, Val899, Val916, Leu1035, Leu889, and Phe1047, supporting stabilization of a DFG out like inactive conformation (**Figure S3**).

For compound 10f, the pyrimidine-based scaffold is anchored through strong hydrogen bonds with Gly922 and Leu840 at the hinge, while the distal amide moiety afforded two hydrogen bonds with Glu885 and Asp1046 in the DFG region; the central aromatic core and linker interact hydrophobically with Leu840, Ala866, Val848, Val899, Val916, Leu1035, Leu889, and Phe1047, complemented by π - π contacts with Phe921 with a docking score of -9.35 kcal/mol (**Figure S4**). Finally, compound 10h retains the same elongated type II typical orientation with a docking score of -9.63 kcal/mol, with hinge binding mediated predominantly through hydrogen bonds to Cys919 and Leu840, and activation loop anchoring through Glu885 and Asp1046; its aryl linker and terminal phenyl ring are

buried in the lipophilic back pocket, forming alkyl and π -alkyl contacts with Ala866, Val848, Val899, Val916, Leu1035, Leu889, and Phe1047 that collectively rationalize its favorable docking profile (Figure S5).

The observed binding patterns of the synthesized compounds, particularly the crucial hydrogen bonding with Cys919 in the hinge region and the dual interactions with Glu885 and Asp1046 within the DFG motif, are highly consistent with the well-established molecular requirements for Type-II VEGFR-2 kinase inhibition (39,40). Literature underscores that targeting the Cys919 backbone is fundamental for mimicking ATP-competitive binding, while anchoring to the DFG residues stabilizes the inactive conformation of the activation loop, effectively shutting down kinase autophosphorylation (41,42). Furthermore, the hydrophobic interactions within the allosteric back pocket (mediated by residues like Ala866, Leu1035, and Phe1047) have been thoroughly documented in the literature as major contributors to the high affinity and selectivity of small-molecule tyrosine kinase inhibitors (43).

Sorafenib, the co-crystallized reference ligand, adopts the canonical type II VEGFR 2 binding mode with a docking score of -9.48 kcal/mol (Figure S6). Its terminal phenyl moieties deeply occupy the hydrophobic back pocket and interact via alkyl contacts with Leu840, Ala866, Val848, Val916, Leu1035, Leu889, and Phe1047, complemented by contacts with Phe918, together with a fluorine mediated halogen bond. Additionally, the interaction was supported by five hydrogen bonds with essential pharmacophoric amino acid side chains such as Cys919, Asp1046, and Glu885, anchoring the hinge region and DFG motif along the ATP binding cleft (Figure S7). Crucially, the higher docking scores of compounds 10d (-9.61 kcal/mol) and 10h (-9.63 kcal/mol) compared to sorafenib (-9.48 kcal/mol) further validate our rational design strategy, confirming that the new 6-aryl-5-cyanothiouracil scaffold successfully establishes a comparable or slightly superior thermodynamic binding affinity within the VEGFR-2 active site by maintaining these benchmark key interactions (40, 44).

Table 1. Molecular Docking Analysis of the newly designed Compounds 10a-h against VEGFR-2 TK.

Tested targets	Tested Compounds	RMSD value (Å)	Affinity score (kcal/mol)
VEGFR-2 TK	Compound 10a	1.43	-9.07
	Compound 10b	1.53	-8.83
	Compound 10c	1.44	-9.21
	Compound 10d	1.48	-9.61
	Compound 10e	1.68	-9.08
	Compound 10f	1.04	-9.35
	Compound 10g	1.28	-8.97
	Compound 10h	1.20	-9.63
	Sorafenib	0.17	-9.48

3.3. Molecular Dynamics (MD) Simulation Study

Compound 10d was specifically selected for the 100 ns molecular dynamics (MD) simulation based on its exceptional performance in the preceding molecular docking studies. It not only exhibited one of the highest therapeutic binding affinities with an outstanding docking score of -9.61 kcal/mol—surpassing the co-crystallized reference ligand, Sorafenib (-9.48 kcal/mol)—but it also perfectly maintained the vital canonical hydrogen-bonding network with the key pharmacophoric residues Cys919,

Glu885, and Asp1046. To rigorously evaluate the dynamic stability, conformational flexibility, and structural persistence of this top-ranked docking pose within the VEGFR-2 active site under simulated physiological conditions, an MD trajectory was executed. The root-mean-square deviation (RMSD) profiles were subsequently calculated for both the protein backbone and the ligand relative to their initial coordinates, followed by a detailed, time-dependent analysis of the specific ligand-receptor interactions within the binding pocket (45).

3.3.1. Protein and ligand RMSD and RMSF analysis

Following molecular docking, the compound 10d complex with VEGFR-2 was subjected to a 100 ns molecular dynamics (MD) simulation to evaluate its stability within the binding pocket. The MD simulation of the VEGFR-2/10d complex revealed a generally stable system, as evidenced by the Ca-RMSD of VEGFR-2, which increased during the initial equilibration period and then stabilized, fluctuating around 2.2–3.2 Å over the 100 ns trajectory, indicating moderate structural relaxation without general destabilization. On the other hand, compound 10d, monitored as RMSD with respect to the protein, kept consistently lower values (around 1.2–2.4 Å) with no sustained drift, confirming preservation of a stable binding orientation within the ATP-binding cleft along the simulation.

Consistently, the RMSF analysis (Figure 3) showed that most residues displayed low to moderate flexibility (<2 Å), whereas higher fluctuations (up to ~5–6 Å) were restricted to terminal segments and a few solvent-exposed loops, as further supported by the corresponding B-factor profile that mirrored this distribution. Notably, residues delineating the ligand-binding pocket exhibited relatively modest fluctuations, suggesting that the local environment surrounding compound 10d remained conformationally well-ordered and capable of maintaining key intermolecular contacts.

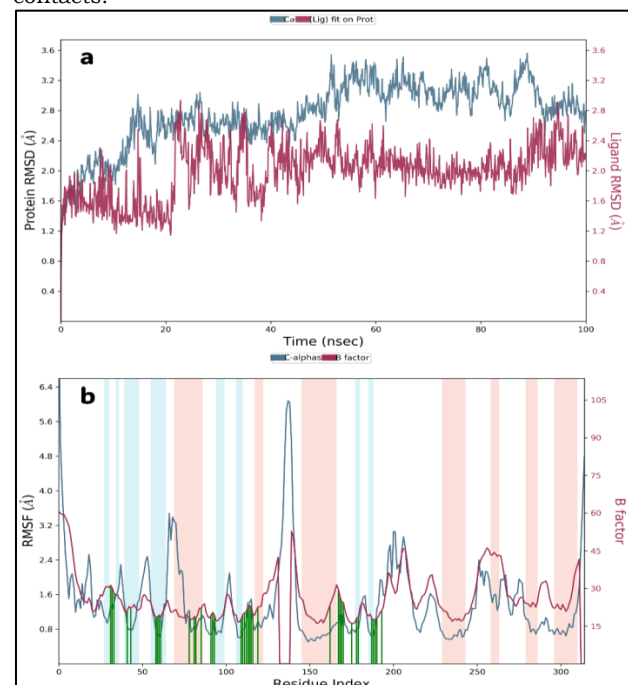


Figure 3. a) RMSD and b) RMSF of Compound 10d against VEGFR-2 over 100 ns

3.3.2. Protein-ligand interactions analysis

The trajectory of the target Compound 10d within the VEGFR-2 active site revealed a dense and highly stable network of intermolecular contacts. As illustrated in **Figure 4a**, the ligand engaged in numerous hydrophobic interactions with residues Leu840 (~10%), Ala866 (~30%), Lys868 (~25%), Val898 (~20%), Phe918 (~45%), Leu1035 (~35%), and Phe1047 (~30%). Concurrently, the complex was extensively stabilized by polar hydrogen bonds and water-mediated (water-bridged) hydrogen bonds with residues Leu840 (~15%), Glu850 (~65%), Val899 (~25%), Cys919 (~120%), Gly922 (~60%), Asn923 (~10%), and Asp1046 (~190%). Notably, the interaction occupancies for Cys919 and Asp1046 exceeded 100%, demonstrating that these residues participate in multi-valent interactions, forming simultaneous direct and water-bridged hydrogen bonds with the ligand throughout the simulation trajectory. Importantly, these dynamic simulation findings strongly correlate with the experimental evidence derived from the VEGFR-2 crystal structure (46). In the native crystal conformation, Cys919 (hinge region), Glu885, and Asp1046 (DFG motif) constitute the essential, non-negotiable anchor

points required for anchoring Type-II tyrosine kinase inhibitors. The high persistence and exceptional occupancy of hydrogen bonds at Cys919 (~120%) and Asp1046 (~190%) during our MD run confirm that compound 10d successfully maintains the target native binding architecture over time. Furthermore, the persistent hydrophobic contacts with Phe918, Leu840, and Phe1047 match the lipophilic stabilizing interactions observed in the crystallographic complex of sorafenib, verifying that the molecular simulation accurately mirrors the essential thermodynamic constraints of the receptor pocket.

Moreover, interaction timelines were further visualized by plotting contact frequencies over the simulation time. Heatmaps (**Figure 4b**) depict the number of specific interactions formed by compound 10d with VEGFR-2 residues per frame, where darker shades represent higher interaction occupancy. Analysis revealed that VEGFR-2 conformations sustained up to twelve simultaneous contacts with compound 10d. Additionally, the ligand maintained highly persistent interactions with these crystallographically crucial amino acids over the entire simulation course, particularly Asp1046, Cys919, Gly922, Phe918, Lys868, Glu850, and Leu840.

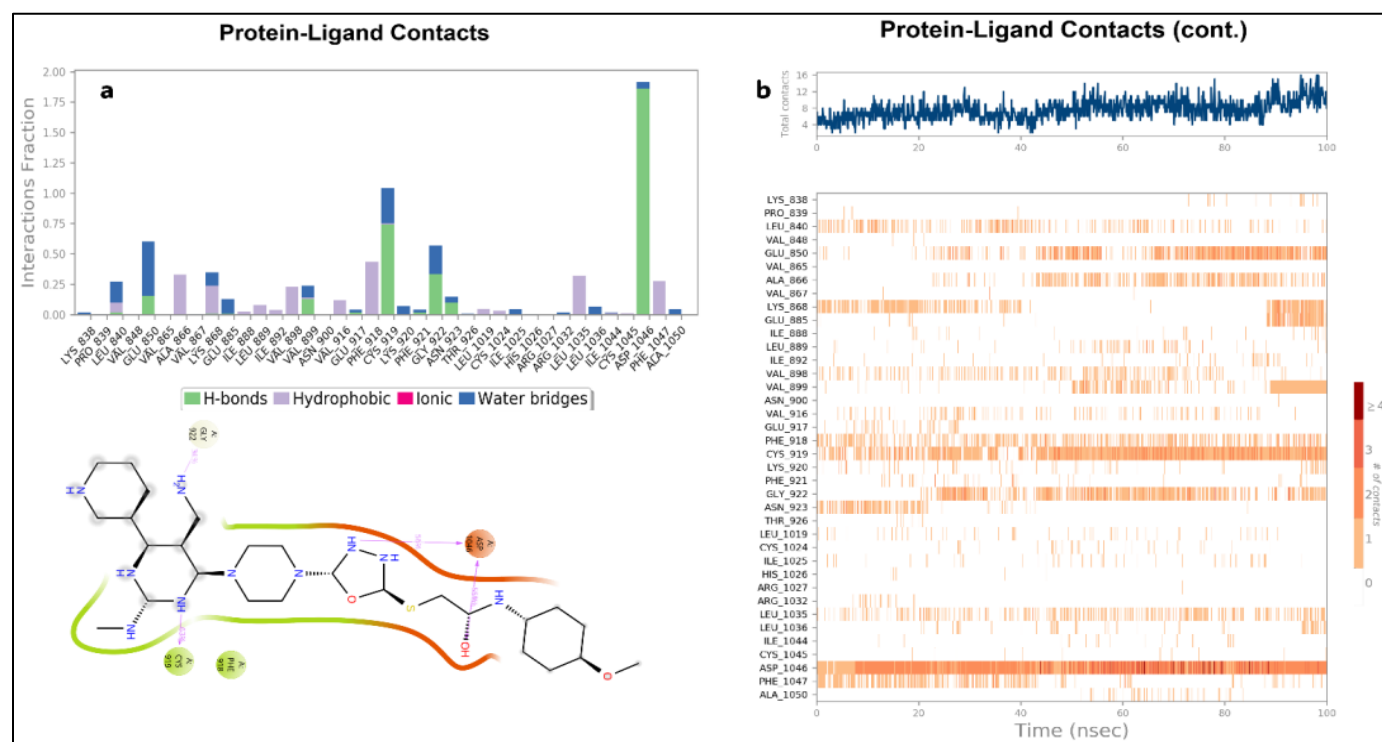


Figure 4. A) Histogram analysis describing the binding interactions of Compound 10d with VEGFR-2 and B) Heat map describing the total interactions during the simulation time (100 ns)

3.3.3. MMGPSA calculation

The MM-GBSA calculations indicate that compound 10d maintains a highly negative and significant binding free energy toward VEGFR-2 over the course of the simulation, with total values of -115.9, -122.15, and -111.73 kcal/mol at 0, 50, and 100 ns, respectively. These prominent thermodynamic values are in strong agreement with literature-reported MM-GBSA binding free energies for potent, structurally diverse Type-II VEGFR-2 kinase inhibitors, which characteristically fluctuate within the

range of -80 to -130 kcal/mol (47,48). The binding architecture is heavily dominated by lipophilic and van der Waals contributions, while Coulombic and hydrogen-bonding terms remain moderately favourable, and the covalent term is slightly positive. The steady magnitude across the 0, 50, and 100 ns intervals, coupled with the stable nonpolar contributions and persistent interactions with catalytic amino acids within the hinge pocket, strongly suggests that the VEGFR-2/10d complex preserves a structurally robust and highly stable binding mode throughout the 100 ns trajectory **Figure 5**.

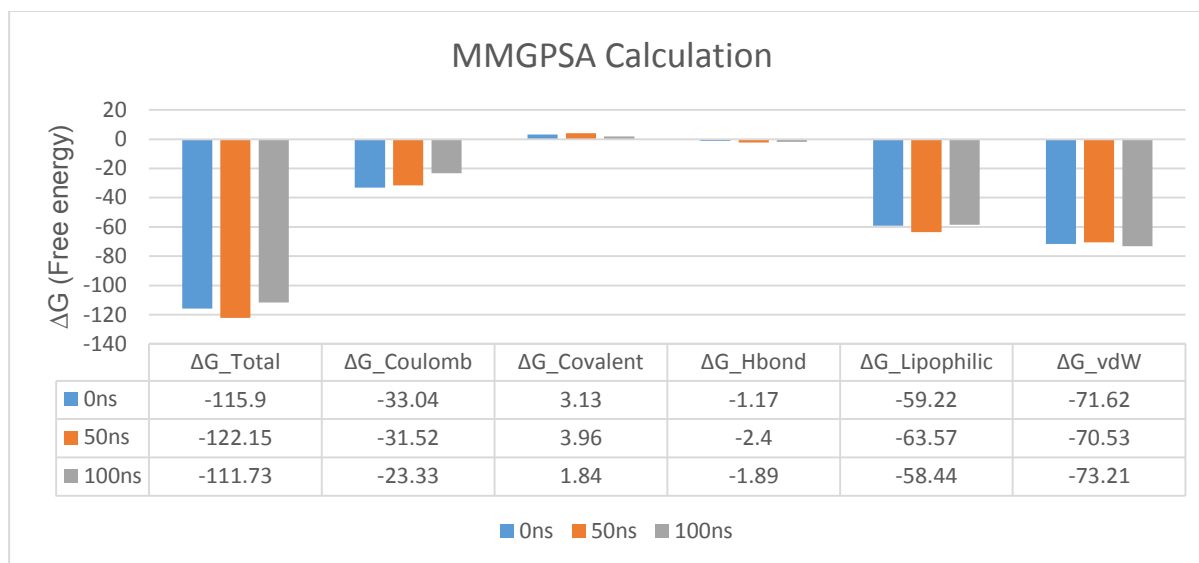


Figure 5. MMGPSA calculation describing the total energy of the tested compound 10d with VEGFR-2 during the simulation process.

3.4. Density functional theory (DFT) calculations

DFT calculations revealed the electronic properties and stability of the eight designed compounds (**Table 2**). Binding energies ranged from -12.11 to -12.82 Ha, with compound 10d exhibiting the most favorable binding energy (-12.82 Ha). Compounds 10f and 10g showed moderate scores (-12.12 and -12.11 Ha, respectively). HOMO energies ranged from -0.1817 to -0.1852 Ha; LUMO energies ranged from -0.1135 to -0.1207 Ha, resulting in band gap energies of 0.0645 to 0.0690 Ha. Compound 10e exhibited the smallest band gap (0.0645 Ha), indicating enhanced electronic excitability and charge-transfer

potential, whereas compound 10g exhibited the largest gap (0.0690 Ha), indicating greater kinetic stability and lower reactivity. Dipole moments ranged from 1.71 to 2.81 D; compound 10d was the most polar (2.81 D) and compound 10f the least polar (1.71 D). Visual inspection of frontier orbitals (**Table 3**) showed HOMO localization on electron-rich aromatic/heteroatom regions and LUMO distribution over the conjugated linker and acceptor moieties, consistent with intramolecular charge-transfer character facilitating pi-pi stacking and electronic interactions with the VEGFR-2 pocket.

Table 2. DFT Parameters for Compounds 10a-10h

Compound	Total Energy (Ha)	Binding Energy (Ha)	Dipole (D)	HOMO (Ha)	LUMO (Ha)	Band Gap (Ha)
10a	-2047.35	-12.15	2.19	-0.1823	-0.1138	0.0685
10b	-2086.30	-12.66	2.34	-0.1820	-0.1136	0.0684
10c	-2086.31	-12.67	2.21	-0.1817	-0.1135	0.0681
10d	-2160.97	-12.82	2.81	-0.1822	-0.1150	0.0672
10e	-2382.26	-12.74	2.68	-0.1852	-0.1207	0.0645
10f	-2505.49	-12.12	1.71	-0.1837	-0.1153	0.0683
10g	-2505.49	-12.11	2.34	-0.1836	-0.1146	0.0690
10h	-2146.00	-12.16	2.42	-0.1839	-0.1171	0.0668

All energy values (Total Energy, Binding Energy, HOMO, LUMO, Band Gap) are in Hartree (Ha). Dipole moment in Debye (D).

3.5. Pharmacokinetics (ADMET) calculations

The pharmacokinetics were investigated by ADMET descriptors of the designed compounds 10a-10h, which allowed for assessing the physicochemical properties, absorption, distribution, metabolism, excretion, and toxicity liabilities in an integrated way. Overall, the studied analogues occupied a limited chemical-property space, with molecular weights ranging from 528.18 to 596.17 Dalton and modest QED (Quantitative Estimate of Drug-likeness) values ranging from 0.284 to 0.324. Although these values suggest that the series is structurally related and broadly comparable, the compounds showed meaningful differences in exposure-related behavior and toxicity

burden, which are important for selecting candidates for deeper molecular simulation **Figure 6**.

The synthesized pyrimidine-5-carbonitrile derivatives (10a-h) generally exhibited favourable gastrointestinal absorption profiles. All analogues were predicted to be orally bioavailable at both the 20% and 50% thresholds and exhibited high human intestinal absorption (HIA). This optimal absorption across the series is chemically rationalized by the balanced lipophilicity (log P) and moderate molecular weight inherent to the core pyrimidine-piperazine-oxadiazole scaffold. The peak absorption profile observed for compound 10e can be directly attributed to the presence of the highly lipophilic trifluoromethyl (4-CF₃) substituent, which significantly enhances membrane

permeability via passive transcellular diffusion. This was closely followed by the halogenated analogues 10f (3-Cl), 10g (4-Cl), and 10h (4-F), where the hydrophobic nature of the halogen atoms optimizes the hydrophilic-lipophilic balance required for permeation compared to the unsubstituted (10a) or more polar derivatives.

Conversely, metabolic and transporter liabilities represented a series-level concern. All compounds were predicted as P-glycoprotein (P-gp) inhibitors, which is structurally consistent with the extended, lipophilic, and flexible nature of the molecules; the combination of the basic nitrogen atoms (within the pyridine, pyrimidine, and piperazine rings) and multiple hydrogen bond acceptors facilitates strong binding within the large hydrophobic multi-drug binding cavity of P-gp. Similarly, CYP inhibition was predominantly concentrated around CYP2C9 and CYP3A4. This high probability of CYP inhibition across the series is chemically linked to the electron-dense heteroaromatic core (specifically the pyridine and pyrimidine rings), where the basic sp² hybridized nitrogen can coordinate with the prosthetic heme iron (Fe 3+) of these cytochrome enzymes, while the terminal substituted phenyl tails interact with the hydrophobic substrate-binding pockets. Consequently, future lead optimization must focus on modifying these peripheral aromatic rings to mitigate CYP2C9/CYP3A4 interactions while retaining the positive absorption profile (Figure 7).

The primary differentiation among the synthesized analogues was observed in their toxicity profiles. The series generally indicated potential risks for hERG channel inhibition and drug-induced liver injury (DILI). Rather than being interpreted as isolated, compound-specific defects, these findings represent well-documented class-effect liabilities inherently associated with the extended hydrophobic architectures of Type-II kinase inhibitors. This strongly mirrors the established clinical profile of approved reference drugs like sorafenib, which carries well-known regulatory warnings for QTc prolongation and hepatotoxicity. Therefore, cardiotoxicity and hepatotoxicity should be viewed as critical benchmark parameters for subsequent structural optimization phases rather than a disqualification of the scaffold. In contrast, the AMES mutagenicity assessment offered higher discrimination: only compounds 10d (4-OCH₃) and 10h (4-F) were flagged as mutagenic due to specific electronic configurations on their terminal phenyl rings, whereas the remaining derivatives were classified as safe for this endpoint. While the series was not strongly flagged for carcinogenicity, the collective presence of hERG, DILI, and isolated AMES liabilities underscores the necessity of structural prioritization, guiding future design to systematically minimize these off-target effects while preserving VEGFR-2 potency (Figure 8).

In the transparent ADMET-only ranking (favouring absorption and physicochemical balance, and penalising

hERG, DILI, CYP, P-gp, AMES, protein-binding, and respiratory-toxicity signals), compound 10a was the most balanced candidate. Although 10a did not have the highest absorption probability, it had the best overall drug-likeness profile, a relatively lower hERG burden, and no AMES toxicity, and would be the most suitable first choice for further simulation if the docking or interaction profile is acceptable. However, compounds 10b and 10c are reasonable, conservative follow-up candidates since they were AMES-safe and showed balanced ADMET behaviour, although persistent CYP and hERG concerns (Figure 9).

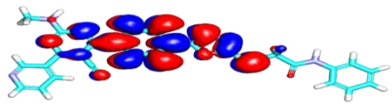
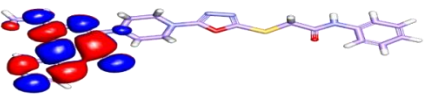
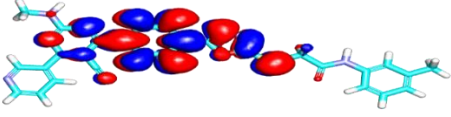
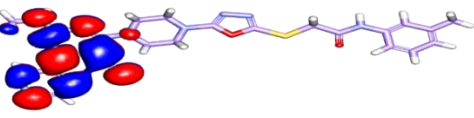
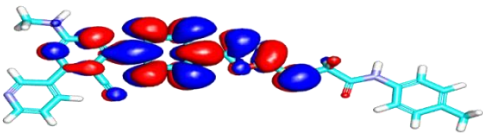
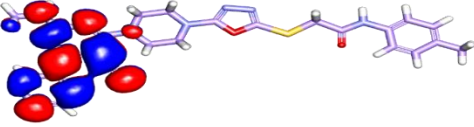
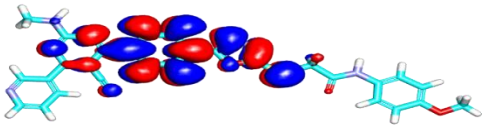
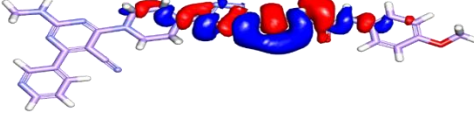
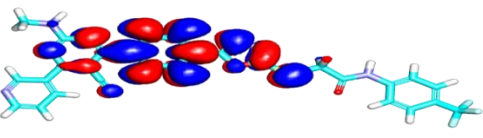
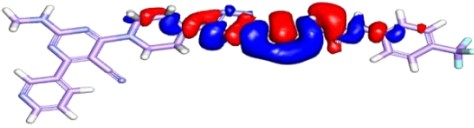
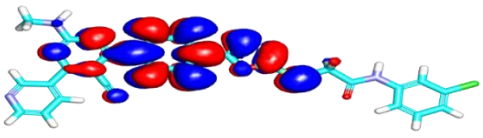
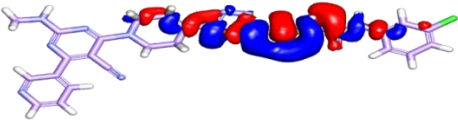
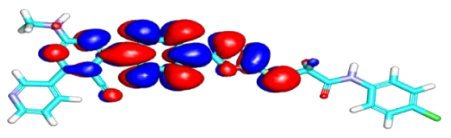
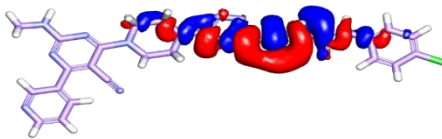
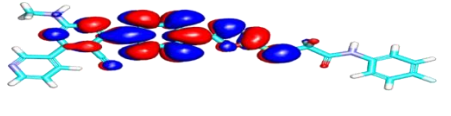
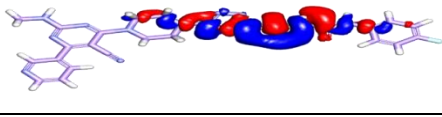
Compound 10e exhibited the best oral bioavailability and intestinal absorption probabilities, but it should be interpreted as exposure-favourable rather than liability-clean. Its higher molecular weight, higher lipophilicity, lower QED, and remaining hERG/liver-risk signals make it more suitable as a comparator/optimization reference than the cleanest lead candidate.

Compounds 10f and 10g may also be considered conditional alternatives because of their favorable absorption and P-gp non-substrate classification, but their CYP and hERG liabilities reduce their priority. In contrast, 10d and 10h should be deprioritized unless their potency or binding stability is exceptional, because both were associated with AMES mutagenicity alerts.

In conclusion, integrating the molecular docking scores, molecular dynamics (MD) simulations, MM-GBSA free energy calculations, and ADMET profiles allows for a holistic, multi-parametric prioritization of this chemical series. Based on thermodynamic binding affinity and structural stability within the VEGFR-2 active site, compound 10d emerges as the definitive leading candidate, demonstrating an outstanding docking score (-9.61 kcal/mol), a highly stable 100 ns MD trajectory, and a robust literature-compliant binding free energy up to -122.15 kcal/mol. However, from a comprehensive drug-likeness perspective, its predicted AMES mutagenicity structural alert poses a clear liability.

Consequently, compound 10c represents the most balanced conservative alternative, as it retains a strong docking profile (-9.21 kcal/mol), shares the same canonical Type-II binding framework, and is predicted to be safe from AMES mutagenicity. Meanwhile, compound 10e remains a valuable comparator due to its exposure-favourable pharmacokinetic profile driven by the 4-CF 3 group. Moving forward, the primary optimization goals for this 6-aryl-5-cyanothiouracil series do not require improving baseline intestinal absorption, but must strictly focus on structural modifications aimed at mitigating hERG/DILI risks, attenuating CYP2C9/CYP3A4 inhibition, and eradicating the specific mutagenic alert observed in 10d (Figure 10).

Table 3. HOMO and LUMO Frontier Orbital Images of Compounds 10a-10h.

Compound No	HOMO	LUMO
10a		
10b		
10c		
10d		
10e		
10f		
10g		
10h		

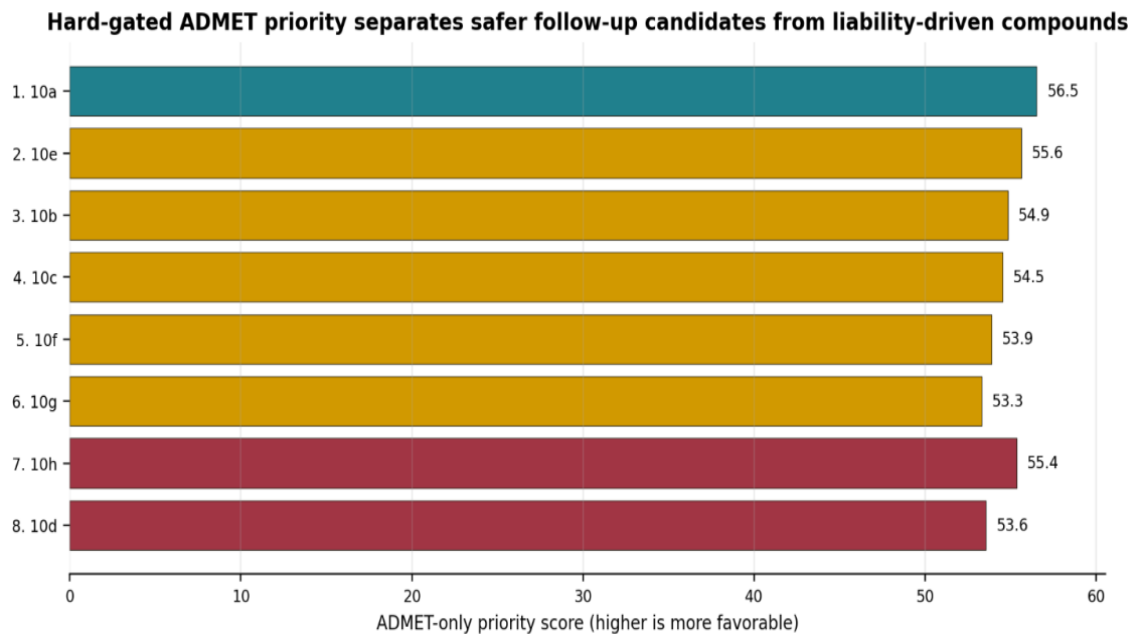


Figure 6. ADMET-only priority ranking

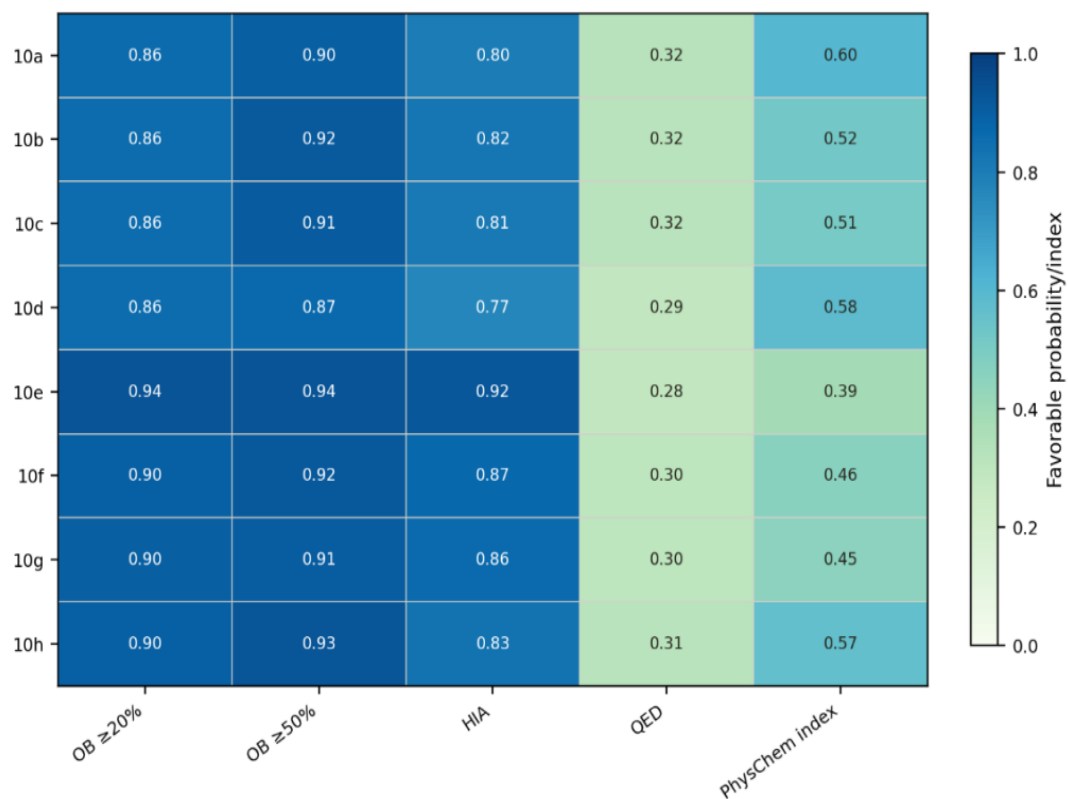


Figure 7. Absorption and physicochemical heatmap

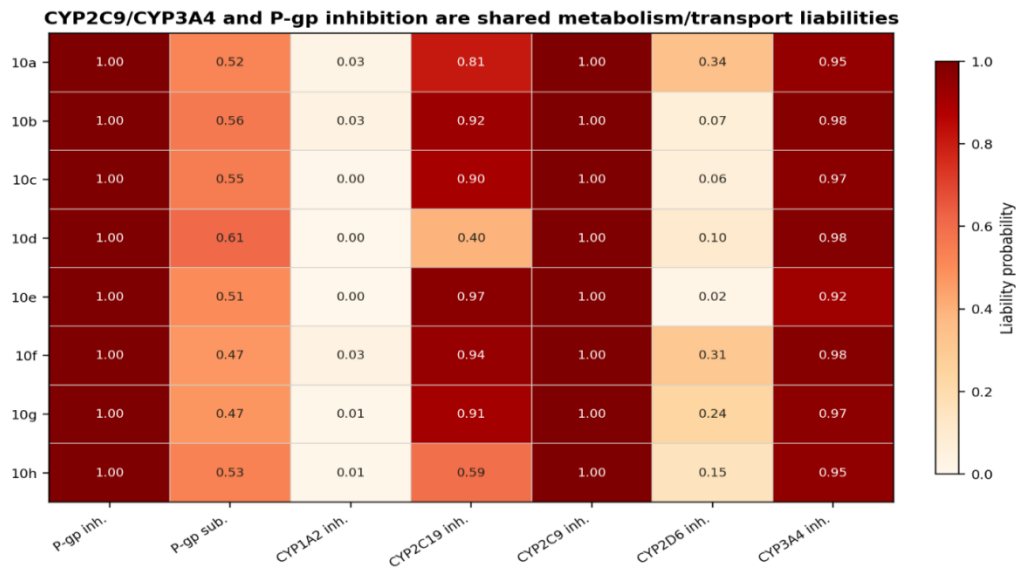


Figure 8. CYP and transporter liability heatmap

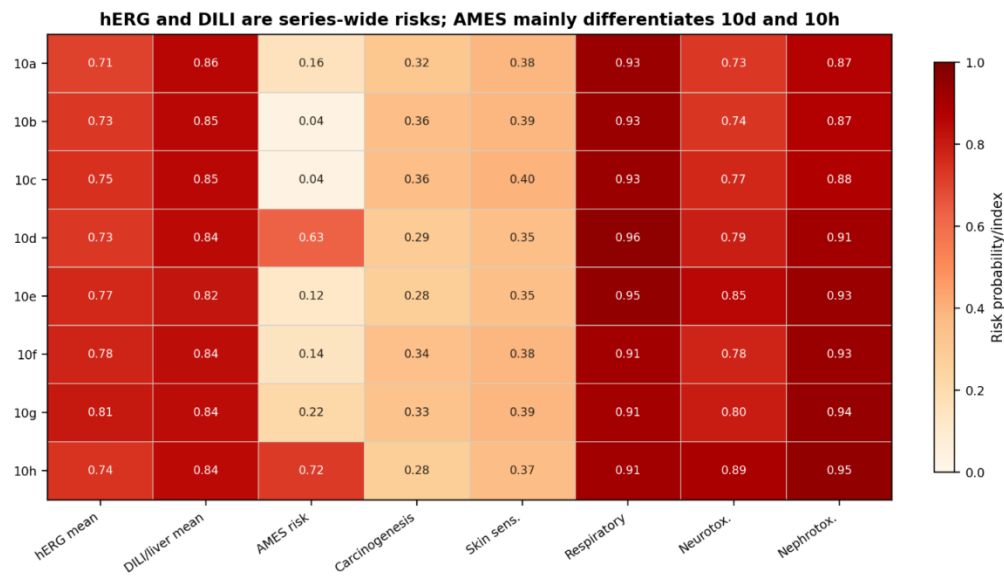


Figure 9. Toxicity liability heatmap

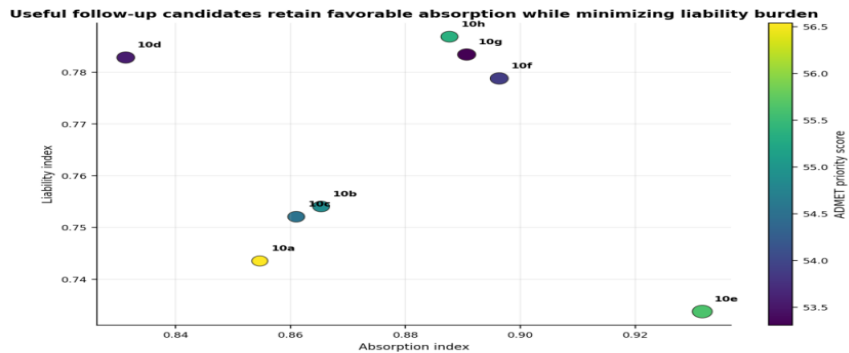


Figure 10. Absorption-liability tradeoff plot

4. Conclusions

In this work, new 6-aryl-5-cyanothioracil derivatives were rationally designed as VEGFR-2 inhibitors based on type- II kinase pharmacophore features. The series was prepared by an efficient multistep process and evaluated by docking, MD, MM-GBSA, DFT, and ADMET analyses. Most of the compounds showed strong VEGFR 2 binding in docking studies with several analogues comparable to or better than sorafenib. Compound 10d showed the best binding profile with interaction with critical hinge and DFG residues. MD simulation for 100 ns confirmed the stability of the VEGFR 2/10d complex. MM-GBSA calculations revealed very favorable binding free energies that were mainly driven by hydrophobic and van der Waals interactions. The DFT studies showed that 10d has a good balance of stability and reactivity and the most favorable electronic properties. On the other hand, ADMET profiling indicated that compound 10a was the most promising candidate overall in terms of pharmacokinetics and safety. Thus, 6-aryl-5-cyanothioracil is identified as a promising scaffold for the development of VEGFR 2 inhibitors. Compound 10a is proposed as the main lead for further optimization with 10d as a high-affinity binder.

CRedit Authorship Contribution Statement: Sarah Sedqi Ismael : Investigation, Methodology, Formal analysis, Data curation, Visualization, Writing – original draft, and Writing–review and editing.

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Data Availability: All relevant data are included within the Supplementary Materials file.

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VEGFR-2: الاستكشاف الحسابي وتحسين هياكل 6-أريل-5-سيانو ثيويوراسيل كمثبطات لكيناز التيروسين من النوع الثاني ADMET رؤى من دراسات الإرساء، والديناميكا الجزيئية، ونظرية الكثافة الوظيفية، و

الخلاصة:

المقدمة: تقدم هذه الدراسة الأساس المنطقي للتصميم الحاسوبي والتقييم الحسابي لمجموعة جديدة من ستة مثبطات لكيناز التيروسين لمستقبل عامل نمو بطانة الأوعية الدموية-2 (VEGFR-2) تعتمد على أريل 5-سيانو ثيويوراسيل، كعوامل محتملة مضادة للسرطان. تدمج هذه المركبات استراتيجياً نواة بيريميدين رابطة بالمفصل، ورابطة بيبيرازين للتوافق مع وحدة أسبارتات-فينيل ألانين-جليسين (DFG)، ومجموعة دوائية من أوكساديازول-أميد لمحاكاة الترابط الهيدروجيني الحاسم للسورافينيب داخل جيب الأدينوسين ثلاثي الفوسفات (ATP). **طرق العمل:** أجري التقييم الحسابي عبر الإرساء الجزيئي مع VEGFR-2. تم التحقق من الاستقرار البنوي للمركب الرئيسي من خلال محاكاة ديناميكا جزيئية (MD) لمدة 100 نانوثانية وحسابات طاقة الارتباط الحرة باستخدام طريقة ميكانيكا الجزيئات - مساحة سطح بورن المعممة (MM-GBSA). استُخدمت نظرية الكثافة الوظيفية (DFT) لتقييم الخصائص الإلكترونية، مع التنبؤ بملامح الامتصاص والتوزيع والتمثيل الغذائي والإخراج والسمية (ADMET). **النتائج:** كشفت عملية الإرساء عن عدة مرشحين يحققون أنماط ارتباط من النوع الثاني المتعارف عليها، بنتائج أفضل من السورافينيب، مع الحفاظ على روابط أساسية مع Asp1046 و Glu885 و Cys919. أكدت محاكاة الديناميكا الجزيئية لمركب VEGFR-2/المركب d10 استقراراً بنيوياً عالياً، وتقلبات طفيفة في متوسط الجذر التربيعي (RMSD)، وطاقات MM-GBSA مواتية مدفوعة بالتفاعلات المحبة للدهون. أكدت حسابات DFT الملاءمة الإلكترونية، حيث أظهر المركب d10 أضيق فجوات مدارية حدودية. أشارت ملامح ADMET المتوقعة إلى امتصاص فموي كافٍ، على الرغم من إظهارها مخاطر عامة على مستوى الفئة فيما يتعلق بالسيتوكروم (P450 (CYP و جين herg البشري، وسمية الكبد. أظهر المركب a10 أفضل خصائص حركية دوائية. **الخلاصة:** تم بنجاح تحديد المركبين d10 و a10 كمركبات رائدة واعدة تستهدف مستقبل عامل نمو بطانة الأوعية الدموية 2 (VEGFR-2)، مما يوفر أساساً حسابياً متيناً لمزيد من التحقق التجريبي والتحسين.

الكلمات المفتاحية: تكوين الأوعية الدموية، عوامل مضادة للسرطان، النمذجة الجزيئية، بيريميدين، سورافينيب