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Computational Design of Aminopyrimidine Derivatives with FDA-Approved Anticancer Drugs and their ADMET Pharmacokinetics and Molecular Docking Evaluation against Cancer-Inducing AXL Kinase Activity

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Abstract: Cancer is a global health hazard that is linked to one in six deaths worldwide. Treatment for cancer has always been fraught with difficulties. Keeping that, in mind, the present study deals with the design of aminopyrimidine derivatives with FDA-approved molecules as templates to evaluate their potential as anticancer agents against AXL tyrosine kinase receptor as the target protein through molecular docking and ADMET studies. Functions of the protein with respect to cancer are proliferation, survival, invasion, and migration of cancer cells, and inhibiting this enzyme helps in the development of medication against cancer. Molecular docking results reveal that among the 11 tested compounds, 03 compounds (i.e., exemestane, sonidegib, and vemurafenib) displayed docking scores of -10 kcal/mol, -12.3 kcal/mol, and -10 kcal/mol, respectively. Further, these designed compounds were subjected to ADMET tests such as oral rat acute toxicity (LD50), and results indicated that among 11 compounds tested, 03 compounds (i.e., exemestane, sonidegib, and vemurafenib) indicated less toxic effect with LD50 values of 2.996 mol/kg, 3.462 mol/kg, 3.303 mol/ kg within the accepted range. Further, these compounds could serve as potential lead compounds for the development of novel anticancer drugs through *in-vitro* and *in-vivo* analysis.

Keywords: Amino-pyrimidines; Anticancer FDA approved drugs; AXL kinase; Cancer.

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1. Introduction

Cancer is a complex disease characterized by uncontrolled cell growth and division. AXL kinase, a receptor tyrosine kinase, is associated with cancer progression, metastasis, and drug resistance. Inhibition of AXL kinase activity has emerged as a potential therapeutic strategy in various types of cancer. AXL kinase plays an important role in cancer, including its occurrence, progression, drug resistance, and treatment tolerance. AXL belongs to the TAM receptor tyrosine kinase family, and its abnormal expression has been associated with poor prognosis in cancer patients [1,2]. In triple-negative breast cancer (TNBC), AXL is commonly expressed and is considered a promising therapeutic target [3]. AXL kinase inhibitors have

been investigated as potential therapeutic targets for cancer treatment. There are currently no FDA-approved AXL inhibitors, but several small molecule inhibitors and antibodies against AXL are being tested in clinical settings [4]. AXL inhibitors have shown promise in preclinical and clinical studies in neurological diseases such as Alzheimer's disease, intracerebral hemorrhage, ischemic stroke, and traumatic brain injury [5].

Aminopyrimidines are a class of compounds that have been studied for their potential in cancer treatment. Recent studies have shown that targeting amino acid metabolism, including pyrimidine nucleotide synthesis, is a promising approach for cancer therapy [6,7,8]. Amino acids significantly impact biosynthesis, energy control, redox balance and homeostasis and are therefore important components of cancer metabolism. For example, glutamine acts as an anaplerotic agent and adds amine groups to the TCA cycle. In addition, glutamate and other amino acids can also be used as fuel by cells. With the help of BCAAs, the leucine produced by lysosomal proteolysis can cleave lysosomes. Asparaginase and PEGylated arginine deiminase are two examples of amino acid degrading enzymes that are used in clinical settings to treat cancer and have shown encouraging antitumor benefits in patients [9,10,11].

Nitrogen heterocycles are considered bioactive chemicals and have piqued the curiosity of biologists and synthesizers alike over the past few decades. One of the essential structures of organic molecules, the heterocyclic framework, is essential for many medical scientific applications [12]. 2-Aminopyrimidines have a variety of effects, including as an antioxidant [13], antimalarial [14], anti-inflammatory [15], antitumor [16], antimicrobial, anti-trypanosome, and anti-leishmania [17]. Drugs containing 2-aminopyrimidine used today to treat cancer include, in particular, imatinib, palbociclib, ribociclib, and abemaciclib. Furthermore, these substances are essential precursors for synthesizing many fused heterocycles, including pyridopyrimidines, pyrimidopyrimidines, imidazolopyrimidines and triazolopyrimidines [18].

In the case of adrenal insufficiency, AXL inhibitors (VEGFR) have been linked to the development of this condition, particularly when used in combination with immunotherapy. Currently, several AXL inhibitors are being tested in clinical settings, although there is no FDA-approved AXL inhibitor yet. Overall, AXL kinase is a potential target for cancer treatment, particularly in drug-resistant cancers like Triple-negative breast cancer (TNBC) and Osimertinib-resistant non-small cell lung cancer (NSCLC).

In continuation of our previous research towards the synthesis of potent, biologically important compounds [19,20,21], a few pyrimidine derivatives were designed using FDA-approved molecules and evaluated using docking studies as potential anticancer agents.

2. Materials and Methods

2.1 Ligand-based computational designing of aminopyrimidine derivatives with FDA-approved anticancer drug molecules.

The ligand-based computational design uses the structural information of known ligands (e.g., FDA-approved cancer drugs) to design new molecules with similar properties. In the case of aminopyrimidine derivatives known for their potential anticancer activity, this approach could include pharmacological screening and molecular docking to identify molecules with favorable interactions with the target protein involved in cancer pathways. First, we screened 11 cancer drugs accessible from PubChem (https://pubchem.ncbi.nlm.nih.gov)—table 1. FDA-approved anticancer drugs were used as

starting molecules for developing aminopyrimidine derivatives. Structural modifications were predicted using ChemDraw, which was introduced to optimize the compounds' binding affinity and pharmacokinetic properties.

Table 1. FDA-approved drug molecules used to design aminopyrimidines.

S. No	Compound Name	PubChem CID
1	Anastrozole	2187
2	exemestane (Aromasin)	60198
3	Letrozole	3902
4	Regorafenib	11167602
5	Abiraterone acetate	9821849
6	Apalutamide	24872560
7	Sonidegib	24775005
8	Trametinib	11707110
9	Vismodegib	24776445
10	Vemurafenib	42611257
11	Alitretinoin	449171

2.2 Accession of target protein.

The introduction of the target protein AXL receptor tyrosine kinase is a successful approach in the fight against cancer. Molecularly focused therapy has long been the focus of cancer research. AXL is a high-affinity ligand that interacts with growth inhibitory specific protein 6 (GAS6), a member of the receptor tyrosine kinase (TAM) family. The Gas6/AXL signaling pathway has a major impact on multiple aspects of carcinogenesis, including tumor cell proliferation, invasion, metastasis, epithelial-mesenchymal transition (EMT), angiogenesis, drug resistance, immunological modulation, and stem cell regulation. The three-dimensional structure of receptor AXL tyrosine kinase (PDB: 5U6B) was downloaded from the RCSB protein database [22].

2.3 Molecular docking.

Molecular docking simulations were performed to study the binding interactions between the designed aminopyrimidine derivatives and the active site of AXL kinase. All designed compounds were subjected to molecular docking analysis with cancer-inducing target proteins (AXL receptor tyrosine kinase) under control with standard inhibitors using cavity detection-guided blind docking (CB-Dock) [23,24]. The docked complex results were visualized using Molegro Molecular Viewer software and Accelyr's Discovery Studio Client (version 21.1). Docking provides information about binding affinity and possible interactions that contribute to the inhibition of AXL kinase activity.

2.4. ADMET pharmacokinetics evaluation.

To evaluate the pharmacokinetic properties of the designed compounds, we employed *in silico* models to predict their Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) through pkCSM (http://biosig.unimelb.edu.au/pkcsm/prediction) and SwissADME (http://www.swissadme.ch/) online tools [25,26]. These predictions provide valuable insights

into the drug-like properties of the compounds, aiding in the selection of candidates for further evaluation.

3. Results and Discussion

3.1. Design of aminopyrimidine derivatives.

The aminopyrimidine derivatives have been the research focus for their potential pharmaceutical applications, including antimicrobial, enzyme inhibitory, and antitumor effects. The studies mentioned in the search results used a combination of experimental and computational techniques to design and evaluate the biological activity of these derivatives [27,28]. The computational design of aminopyrimidine derivatives involves a multidisciplinary approach to drug discovery and development that integrates synthetic, computational, and biological aspects to identify potential drug candidates. By applying ligand-based design strategies, several aminopyrimidine derivatives based on FDA-approved anticancer drugs have been generated [29]. The modifications aimed to improve their potency, selectivity, and ADMET properties.

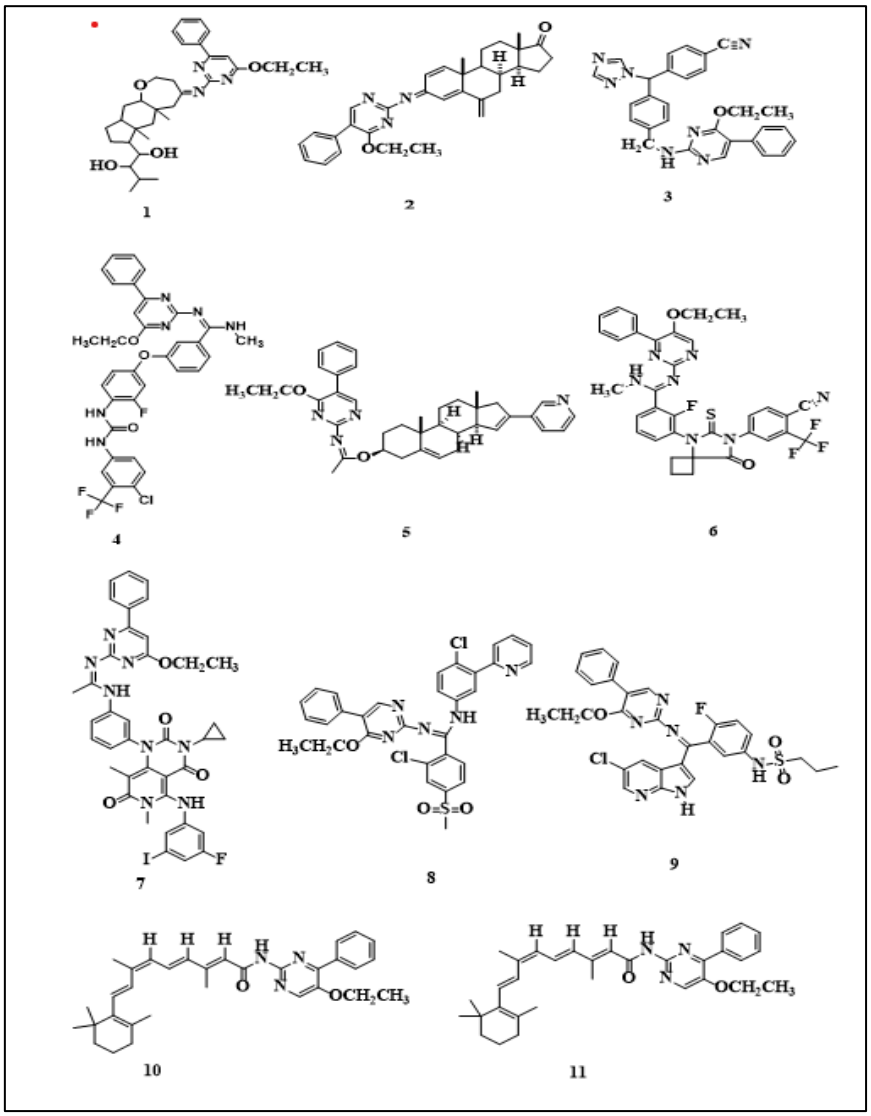

Figure 1. Computationally designed aminopyrimidine derivative structures were generated based on FDA-approved anticancer drugs.

3.2. Molecular docking.

Molecular docking simulations were performed to study the binding interactions between the designed compounds and the active site of AXL kinase [30]. AXL kinases are involved in almost all aspects of cellular activity, such as proliferation, growth, death, and signal transduction. It is believed that 50% of all proteins continuously undergo reversible phosphorylation and dephosphorylation. Many diseases, including cancer, dysregulated, overexpressed, or mutated protein kinases, have been the subject of extensive research in the last 20 years to develop novel anticancer drugs. The FDA has approved 53 kinase inhibitors (KIs), while more than 200 potential inhibitors are undergoing various clinical trials worldwide [31]. The results revealed potential binding modes and key interactions that contribute to inhibiting AXL kinase activity. Molecular interactions of aminopyrimidine compounds with FDA-approved molecules targeting AXL kinase are listed in Table 2. Sonidegib showed the highest binding affinity.

Table 2. Molecular interactions of aminopyrimidine designed compounds with AXL kinase.

S. No	Aminopyrimidine designed compounds	Hydrogen bond interaction	Amino acid residues interact with ligands	CB-Dock Vina score kcal/mol
1	Anastrozole	2	PHE A 547, ARG A 676	-8.4
2	Exemestane (Aromasin)	1	GLU A578, LEU A 693	-10
3	Letrozole	3	LYS A 567, GLY548, ASP 672	-8.3
4	Regorafenib	2	ARG A 676, ASP A 690	-9.6
5	Abiraterone acetate	2	ARG A 676,	-9.7
6	Apalutamide	4	GLU546, PHE 457, LEU542	-9.1
7	Sonidegib	2	ASP 690, LEU 620	-12.3
8	Trametinib	3	ASP690, LYS624, MET623	-9.8
9	Vismodegib	3	LYS540, ASP627GLY626	-8.8
10	Vemurafenib	1	ASP690, LEU542	-10
11	Alitretinoin	1	ASP672, ALA565	-8.7

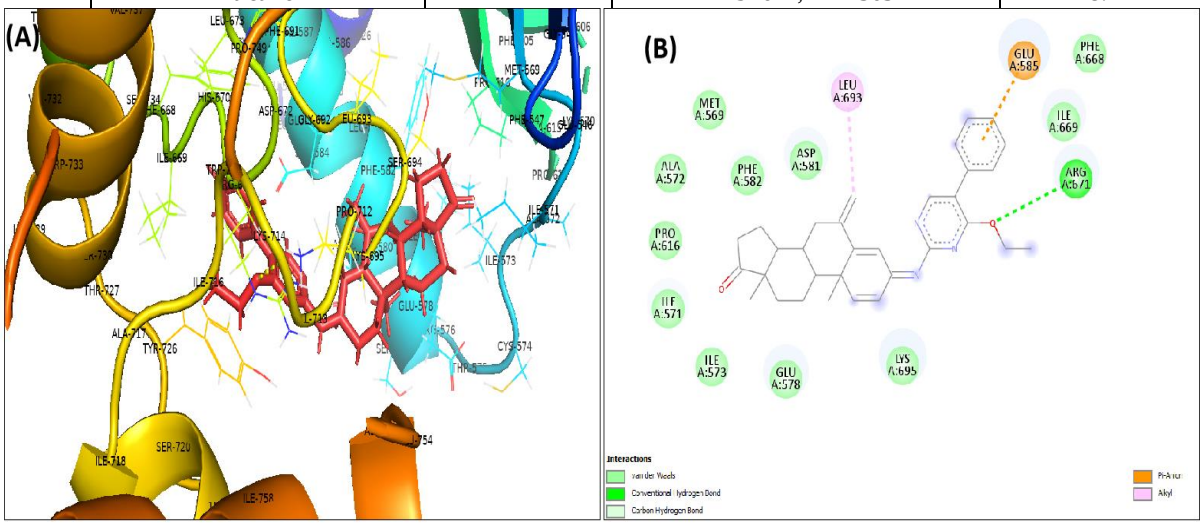

Figure 2. A. Three-dimensional and B. Two-dimensional Molecular interaction between ligand: exemestane (Aromasin) aminopyrimidine against the active site of AXL receptor tyrosine kinase subunit with the binding energy of -10 kcal/mol.

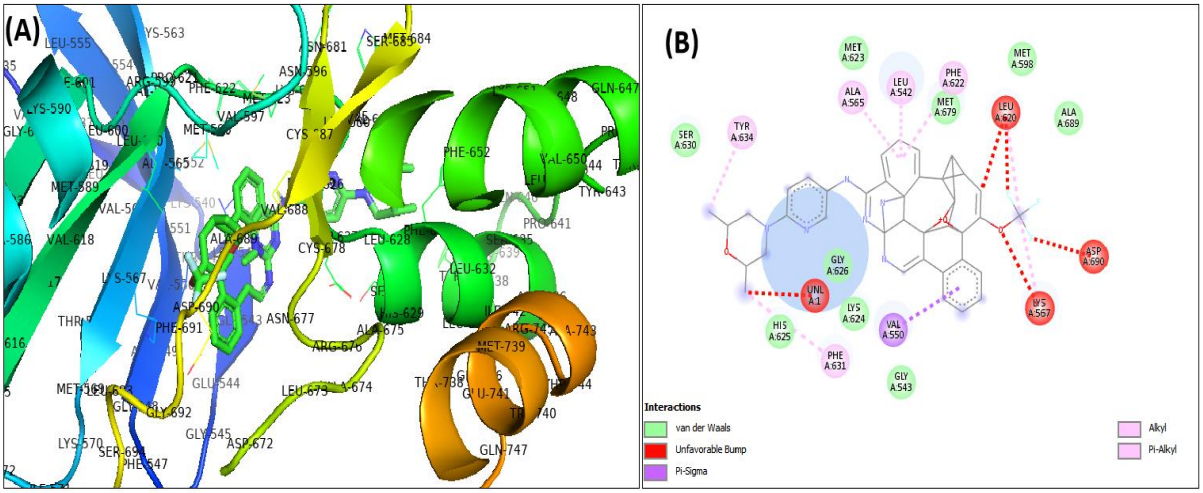

Figure 3. A. Three-dimensional and B. Two-dimensional Molecular interaction between ligand: Sonidegib aminopyrimidine against the active site of AXL receptor tyrosine kinase subunit with a binding energy of -12.3 kcal/mol.

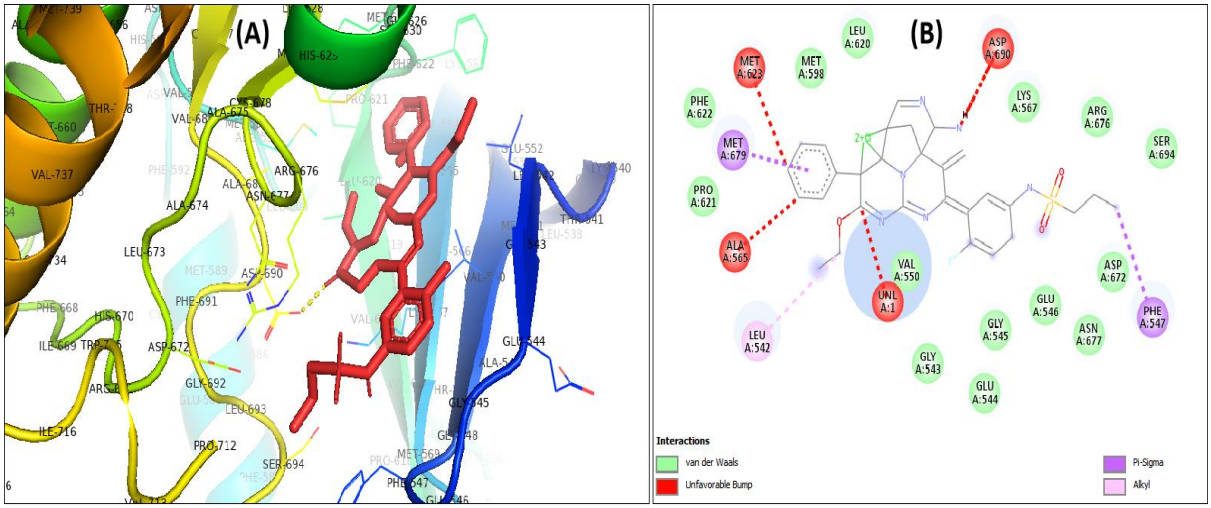

Figure 4. A. Three-dimensional and B. Two-dimensional molecular interaction between ligand: vemurafenib aminopyrimidine against the active site of AXL receptor tyrosine kinase subunit with the binding energy of -10 kcal/mol.

3.3. ADMET Pharmacokinetics and bioactive - to have protein as target identification.

Drug development requires an understanding of toxicity and the processes of absorption, distribution, metabolism, and excretion (ADME). The range of tests it offers allows for investigating several factors, including toxicity, metabolic stability, and membrane permeability. Applying ADMET prediction can significantly reduce the labor and cost of the subsequent experiments. Reducing drug development costs, minimizing drug toxicity and side effects, addressing the problem of species differences, and greatly boosting the success rate of drug development are all achievable with the particular, personalized scientific study known as ADMET prediction [32].

The computationally designed and potentially docked compounds against anticancer-inducing protein AXL receptor tyrosine kinase subunit were subjected to ADMET predictions to evaluate their pharmacokinetic properties. These predictions aid in identifying compounds with optimal Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) profiles. The highly interacted and energy compounds predicted the pharmacokinetic properties such as ADME - toxicity by using pkCSM server [33]; the results are shown in Table 3. The

potential aminopyrimidine small molecule exemestane (Aromasin) (-10 kcal/mol), Sonidegib (-12.3 kcal/mol) and Vemurafenib (-10 kcal/mol) and Oral Rat Acute Toxicity (LD50 values are exemestane (Aromasin) (2.996 mol/kg, Sonidegib (3.462 mol/kg, Vemurafenib (3.303 mol/kg). The probability for the query molecule may act as a bioactive and have protein as a target by Swiss Target Prediction Figure 5. The pink zone in the bioavailability radar is the ideal physicochemical space for oral bioavailability. The moleule should have a molecular weight of less than 500 g/mol, lipophilicity between -0.7 and 5, polarity with a Topological polar surface area (TPSA) of less than 140 Å2, insolubility with Log S (Esol − Estimated SOLubility) less than 6, in saturation with a fraction of C sp3 less than 1, and flexibility with less than 9 rotatable bonds [34,35].

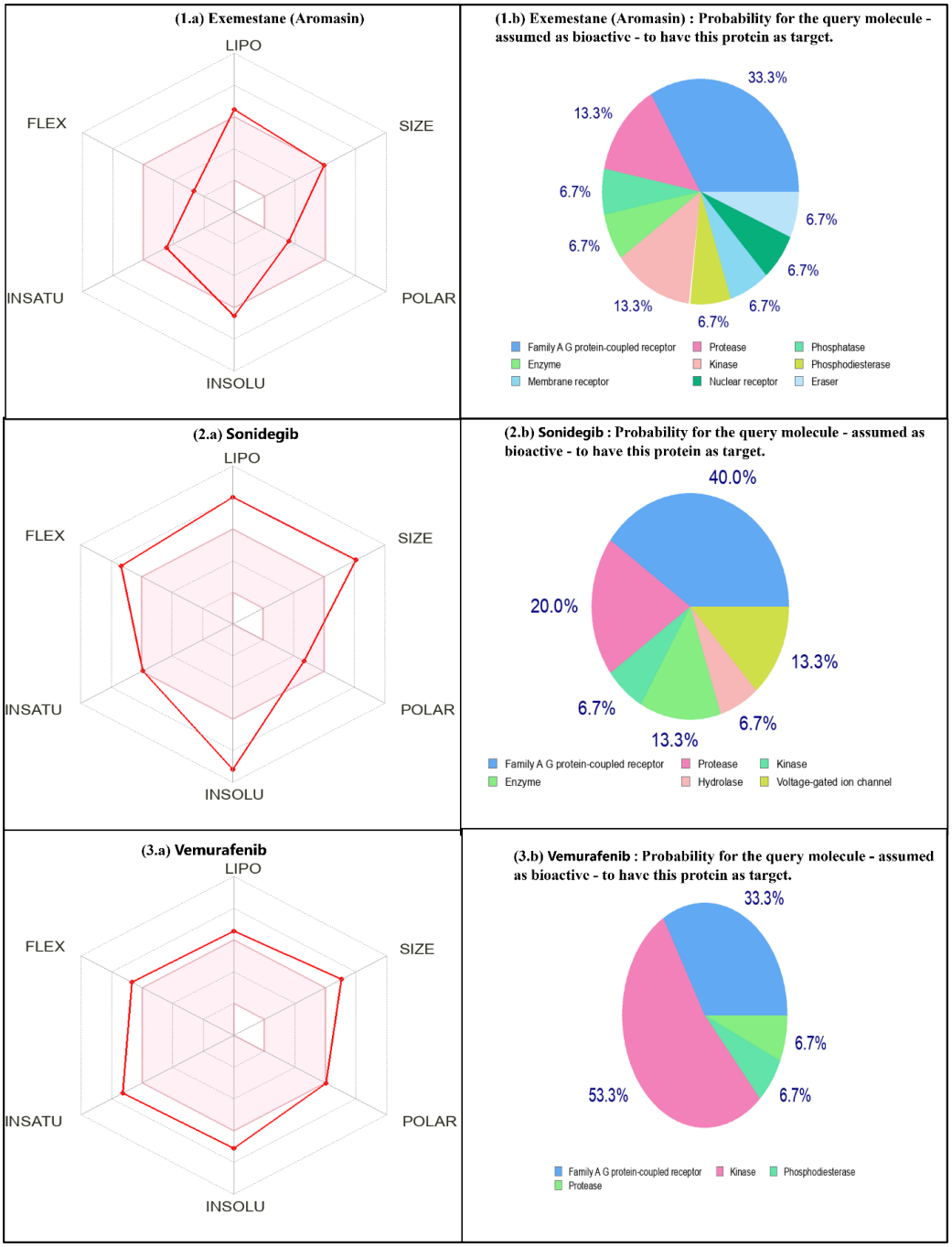

Figure 5. Bioavailability radar and protein targets of aminopyrimidine small molecule with FDA-approved drug molecules (1. Exemestane (Aromasin), 2. Sonidegib, 3. Vemurafenib).

Table 3. ADMET Pharmacokinetics evaluation of aminopyrimidine – derivatives.

Model Name	Exemestane	Sonidegib	Vemurafenib	Units
Absorption				
Water solubility	-6.567	-4.425	-3.944	log mol/L
Caco-2 permeability	0.566	0.334	0.186	log Papp in 10-6 cm/s
Intestinal absorption (human)	97.396	100	97.736	% Absorbed
Skin Permeability	-2.725	-2.735	-2.735	log Kp
P-glycoprotein substrate	Yes	Yes	Yes	Yes/No
P-glycoprotein I inhibitor	Yes	Yes	Yes	Yes/No
P-glycoprotein II inhibitor	Yes	Yes	Yes	Yes/No
Distribution				
VDss (human)	0.87	0.32	-0.196	log L/kg
Fraction unbound (human)	0	0.217	0.163	Fu
BBB permeability	0.264	-1.588	-2.215	log BB
CNS permeability	-1.336	-2.539	-3.373	log PS
Metabolism				
CYP2D6 substrate	No	No	No	Yes/No
CYP3A4 substrate	Yes	Yes	Yes	Yes/No
CYP1A2 inhibitor	No	No	No	Yes/No
CYP2C19 inhibitor	Yes	Yes	Yes	Yes/No
CYP2C9 inhibitor	Yes	Yes	Yes	Yes/No
CYP2D6 inhibitor	No	No	No	Yes/No
CYP3A4 inhibitor	Yes	Yes	Yes	Yes/No
Excretion				
Total Clearance	0.022	-0.511	0.399	log ml/min/kg
Renal OCT2 substrate	No	No	No	Yes/No
Toxicity				
AMES toxicity	No	No	No	Yes/No
Max. tolerated dose (human)	-0.206	0.507	0.491	log mg/kg/day
hERG I inhibitor	No	No	No	Yes/No
hERG II inhibitor	No	Yes	Yes	Yes/No
Oral Rat Acute Toxicity (LD50)	2.996	3.462	3.303	mol/kg
Oral Rat Chronic Toxicity (LOAEL)	1.101	-0.293	1.021	log mg/kg_bw/day
Hepatotoxicity	No	No	Yes	Yes/No
Skin Sensitisation	No	No	No	Yes/No
T.Pyriformis toxicity	0.374	0.285	0.285	log ug/L
Minnow toxicity	-0.836	-0.317	2.881	log mM

4. Conclusions

Computationally designed and used to develop aminopyrimidine derivatives with FDA-approved drug molecules as a potential anticancer property by targeting the tumour-inducing protein AXL kinase. The designed compounds were evaluated for their molecular docking simulations and subjected to ADMET pharmacokinetic properties against the AXL kinase inhibitors. The results of the designed aminopyrimidine with FDA small molecules (1. Exemestane (Aromasin), 2. Sonidegib, 3. Vemurafenib) showed that the successful compounds displayed less toxicity. Therefore, these designed novel aminopyramidine compounds can be used as potential drugs for inhibiting AXL kinase inhibitor anticancer therapeutics.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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