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Original Article

IN SILICO EVALUATION OF BINDING INTERACTION AND ADME PROPERTIES OF NOVEL 5-(THIOPHEN-2-YL)-1,3,4-OXADIAZOLE-2-AMINE DERIVATIVES AS ANTI-PROLIFERATIVE AGENTS

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ABSTRACT

Objective: The objective of this research was the virtual design of nine novel 1,3,4-oxadiazole derivatives and evaluating their antiproliferative activity as potential cyclin-dependent kinase 2 (CDK-2) inhibitors, which is a major component in cell cycle and proliferation.

Methods: CDK-2 structure, PDB ID, 2R3J, co-crystallized with ligand SCJ from protein data bank was chosen to be docked with a series of nine 5-(thiophen-2-yl)-1,3,4-oxadiazol-2-amine derivatives to evaluate their abilities as potential anti-proliferative agents using Glide software (Maestro 11.4) one of Schrodinger software (Schrodinger, 2018). In addition, the pharmacokinetic properties of these derivatives were evaluated using the Swiss-ADME web tool.

Results: Molecular modeling proposed that these 1,3,4-oxadiazole derivatives have powerful binding interaction with the active binding site of CDK-2 protein. In this article, two molecules have been observed as the most effective as they have docking scores of (-10.654 and-10.169 kcal/mol) respectively, whereas the binding score of the reference ligand was (-9.919 Kcal/mol) and most of the derivatives have fulfilled the Swiss-ADME parameters as potential orally active compounds.

Conclusion: Novel 1,3,4-oxadiazole derivatives had shown promising results to be considered as lead compounds for developing new anti-proliferative agents as two compounds (P-1 and P-5) exhibit better docking score at 2R3J active site than the reference ligand with further biological and pharmacological evaluation required.

Keywords: Drug design, Molecular docking, Oxadiazole derivatives, Anti-proliferative

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INTRODUCTION

Cancer is ranked as the second leading cause of mortality [1]. According to estimates from GLOBOCAN 2020, there were over 19 million new cancer patients and nearly 10 million deaths from it in 2020. Colorectal Cancer (CRC) was found to have a high prevalence and an alarming growth rate recently. There are over 1.9 million cases of newly diagnosed and over 0.9 million death cases caused by CRC in 2020 globally [2].

Cyclin-dependent kinases (CDK) are in control of the initiation of the cell cycle and its progression. In tumor cells, many CDK genes activity is denormalized, where they are particularly important to phosphorylate essential components of the cell cycle [3]. CDK-2 is correlated with the regulation of the cell cycle through the phosphorylation of Cyclin A or E subunits. Through the G1 phase of cell proliferation, complexes are formed between CDK-4 and CDK-6 with D-type cyclin, activating CDK-2 by associating with cyclin E. Then at the S phase, cyclin A binds CDK-2. After that, at the G2/M phase, CDK-1 binds to cyclin B. CDK-2 activation by cyclin E is a key step for the cell cycle to progress through G1 to S phase, and this nominates CDK-2 as a major target for most anti-proliferative drugs [3, 4]. CDK-2 is found to be overexpressed in a variety of human cancer as breast, ovarian, endometrial, thyroid carcinomas, lung, and osteosarcoma [4, 5].

Cancer treatment recently directed to molecules having heterocyclic groups, from which structures that contain the active ring system 1,3,4-oxadiazole are constituting an attractive group of compounds with an interesting potency of cytotoxic activity [6]. Oxadiazole is a five-membered heterocyclic ring having one oxygen atom and two nitrogen atoms in its formula. Oxadiazole is present in multiple isomeric forms (fig. 1), 1,2,3-oxadiazole is particularly nonstable, and its form cannot occur freely but in rare mesoionic forms [7].

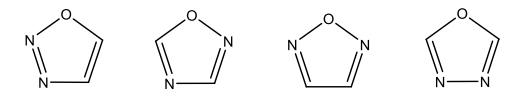


Fig. 1: Different isomers of oxadiazole ring

1,3,4-oxadiazole derivatives are particularly worthy due to the presence of 1,3,4-oxadiazole active moiety which has a significant effect on the physicochemical and pharmacokinetic properties of these derivatives. 1,3,4-oxadiazole has better metabolic stability, better hydrophilicity, and reduced lipophilicity. The 1,3,4-oxadiazole ring can function as bio-isostere for compounds that have carbonyl, ester, amide, and carbamate groups and it can be used as a major part of the leading pharmacophore which can interact with the ligand. Additionally, as a flat aromatic moiety, it provides the proper positioning of the molecule [8], and derivatives with the 1,3,4-oxadiazole nucleus exhibit ability of different biological actions such as anti-cancer [9,10], antioxidant [11], and antibacterial [12].

MATERIALS AND METHODS

Recently, drug discovery and design had raised a great challenge due to the cost and efforts made to advance the drug development process. Computational approaches are rapidly growing and playing a significant role in this process because they provide ways to avoid

loss of time, cost, and effort. Docking is one of these techniques, which anticipates the conformation and orientation of ligands within the active site of the target. Docking studies are aimed at proper structural modeling and exact knowledge of the activity of compounds [13]. The structures of nine 5-(thiophen-2-yl)-1,3,4-oxadiazol-2-amine derivatives were designed based on a literature review made by our team.

From the deposited crystallographic structures of CDK-2 in PDB (protein data bank), the selection was on 2R3J because it was crystalized with an inhibitor containing bicyclic cores and its structure 3-bromo-5-phenyl-N-(pyridin-3-ylmethyl) pyrazolo [1,5-a] pyrimidin-7-amine is well defined with its binding interactions with CDK-2 protein.

ChemDraw16.0 program, one of ChemOffice software (ChemOffice, 2016) was used to obtain the 3D analogous conformations of the nine derivatives, next, the lowest energy conformation of those molecules is saved in (SDF) format. Spartan 14.0 package (Spartan, 2014) was used for the optimization process beside the Monte-Carlo method supported with 200 optimizations of 1500 interactions. Molecular drug design and molecular docking evaluation were carried out using Glide software (Maestro 11.4) one of Schrodinger software (Schrodinger, 2018) running on a Windows 7 operating system on the workstation (Intel(R) Core (TM) i7 CPU 895 @ 3.4GHz, 32 GB RAM, 1TB HD). CDK-2 crystal structure was obtained from PDB under code 2R3J with a resolution of 1.65 Å. The preparation steps of this protein were performed by the ProPrep program for minimization and optimization and to prepare the structure of ligands, Lig Preprogram was used before applying the docking step to add hydrogen atoms and identify the proper orientation and ionization position to gain the lowest energy conformation of all derivatives using OPLS 2005 force field. The grid box is set to be calibrated at 1.20 Å with 0.27 partial atomic, this size allows the free rotation of each member of the tested compounds to locate the best conformation with binding free energy [14], all the 5-(thiophen-2-yl)-1,3,4-oxadiazol-2-amine derivatives have been saved for drug design evaluation.

The drug design and development process always demand the study of the pharmacokinetic parameters of each molecule including absorption, distribution, metabolism, and excretion (ADME) during the discovery process. The assessment of ADME was done earlier using an accessible tool which is the Swiss-ADME web tool that generates a pool of free reachable and solid anticipating models of PK parameters, medicinal chemistry, physicochemical properties, and drug-likeness such as lipophilicity, water solubility, bioavailability and BOILED-Egg [15].

RESULTS AND DISCUSSION

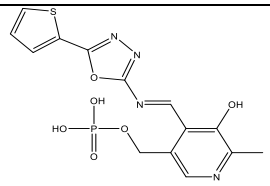
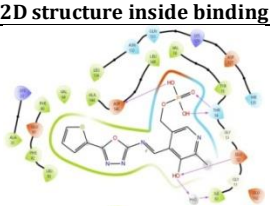
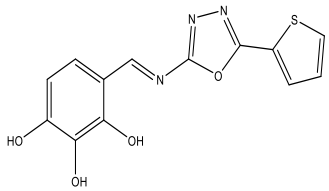
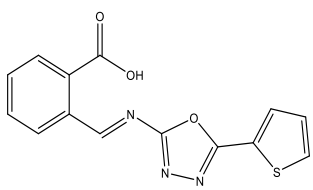
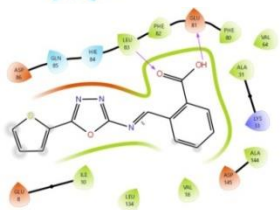
The design of novel compounds targeted against certain biological parts and the improvement of pharmacological characteristics of these molecules is the main objective of the drug design and discovery process [16]. Based on the facts that CDK-2 has an essential part to play in the cycle of cell proliferation and that its activation by cyclin E is important for the continuous phosphorylation of the retinoblastoma gene (pRB) which ensures the full expression of genes that guarantee cell cycle progression from G1 phase into the S phase [17]. The subsequent activation of CDK-2 by cyclin A drives the cell cycle through the S phase [18]. Any defect in the control of CDK activity is strongly linked to the pathogenesis of cancer [19] and therefore, studies have increasingly directed towards the inhibition of CDK-2 that could promote cancer cell apoptosis with no effects on normal cells.

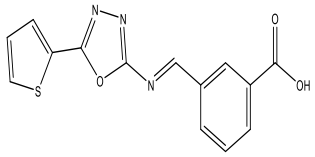
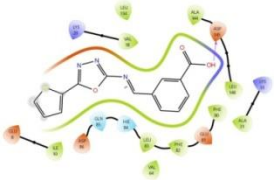
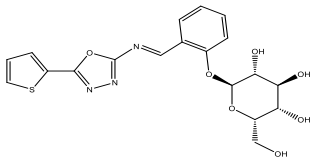
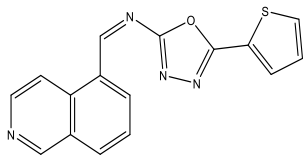
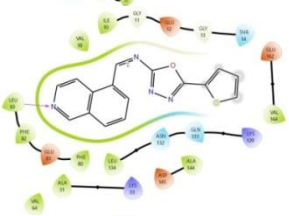
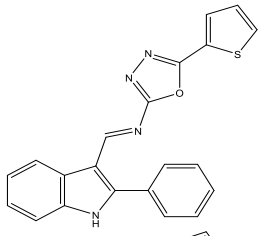
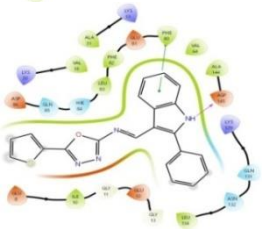
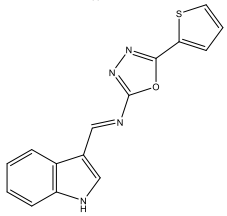
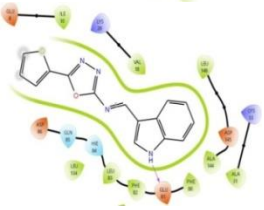
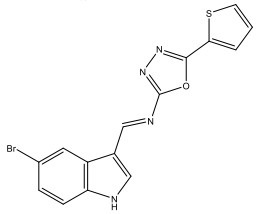
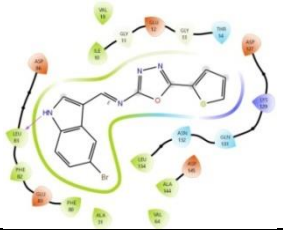
Bhatt *et al.*, 2020. targeted CDK-2 protein 2R3J for the docking of twelve (N-heterocycle) substituted 1,3,4-oxadiazole derivatives, one of the compounds exhibit a high docking score with strong interaction with the amino acids of 2R3J active site [20]. Santosh *et al.*, 2019. were able to synthesize a series of twelve 1,3,4-oxadiazole derivatives that showed good interaction when docked inside the active site of CDK-2 protein 5IEV alongside promising *in vitro* antiproliferative activity [21]. Therefore, CDK-2 is an incredibly attractive target for designing inhibitors of this protein as novel anti-proliferative agents [22].

Throughout this research, approaches of binding affinity and theoretical design were considered for finding novel molecules as inhibitor ligands with increasing affinity at the active binding site of CDK-2 protein. These new inhibitors are Schiff's based moieties of a 1,3,4-oxadiazole core with high affinity to bind to CDK-2 active site. The connection of a series of different aldehydes to the intermediate 5-(thiophen-2-yl)-1,3,4-oxadiazol-2-amine as the core moiety result in the formation of various molecules with distinct docking scores on the CDK-2 protein 2R3J. PDB. Throughout virtual screening (VS), computer programs selected certain molecules to evaluate their binding affinity with a target receptor [23].

The results of this screening of these molecules bound to the target protein were between (-10.654) to (-8.026) Kcal/mol on 2R3J protein, whereas the binding ability of the reference ligand SCJ (3-bromo-5-phenyl-N-(pyridine-3-ylmethyl) pyrazolo[1,5-a] pyrimidin-7-amine) which is already crystallized with the receptor protein was (-9.916) Kcal/mol. As presented in table 1.

Table 1: Docking scores for different 5-(thiophen-2-yl)-1,3,4-oxadiazol-2-amine derivatives inside CDK-2 active site

No.	Structure	Docking score	Binding interactions	2D structure inside binding active site
P-1		-10.654	Five H-bonds with ASP145, THR14, GLU12 and ILE10. Hydrophobic interaction with LEU83, PHE82, GLU81, PHE80, VAL64, ALA144, ASP145, LEU148, VAL18, TYR15, THR14, GLY13, GLU12, GLY11 and ILE10.	
P-2		-8.694	Two H-bonds with LEU83. Hydrophobic interaction with ASP86, GLN85, HIE84, LEU83, PHE82, ALA31, LEU134, ASN132, GLN131, LYS129, GLU162, GLY13, GLU12, GLY11 and ILE10.	
P-3		-8.545	Two H-bonds with LEU83 and GLU81. Hydrophobic binding with ASP86, GLN85, HIE84, LEU83, PHE82, GLU81, PHE80, ALA31, LYS33, ALA144, ASP145, VAL18, LEU134, ILE10 and GLU8.	

No.	Structure	Docking score	Binding interactions	2D structure inside binding active site
P-4		-8.026	One H-bond with ASP145. Hydrophobic binding with LYS20, VAL18, ALA144, ASP145, LEU148, PHE80, GLU81, PHE82, LEU83, HIE84, GLN85, ASP86, ILE10 and GLU8.	
P-5		-10.169	Four H-bonds with ASP145, THR14, ILE10 and ASP86. Hydrophobic binding with LYS33, ALA31, PHE80, GLU81, PHE82, LEU83, HIE84, GLN85, ASP86, LYS20, VAL18, GLU8, ILE10, GLY11, GLU12, GLY13 and THR14.	
P-6		-9.286	One H-bond with LEU83. Hydrophobic binding with VAL18, ILE10, GLY11, GLU12, GLY13, THR14, GLU162, VAL164, LYS129, GLN131, ASN132, LEU134, PHE80, GLU81, PHE82 and LEU83.	
P-7		-9.272	One H-bond with ASP145. Pi-Pi stacking with PHE80. Hydrophobic interaction with ASP86, GLN85, HIE84, LEU83, PHE82, GLU81, PHE80, VAL64, ALA144, ASP145, LYS129, GLN131, ASN132, LEU134, GLY13, GLU12, GLY11, ILE10 and GLU8.	
P-8		-8.665	One H-bond with GLU81. Hydrophobic interaction with GLU8, ILE10, LYS20, VAL18, LEU148, ASP145, ALA144, PHE80, GLU81, PHE82, LEU83, HIE84, GLN85 and ASP86.	
P-9		-8.185	One H-bond with LEU83. Hydrophobic interaction with ILE10, GLY11, GLU12, GLY13, THR14, ASP127, LYS129, GLN131, ASN132, LEU134, ALA31, PHE80, GLU81, PHE82, LEU83 and ASP86.	

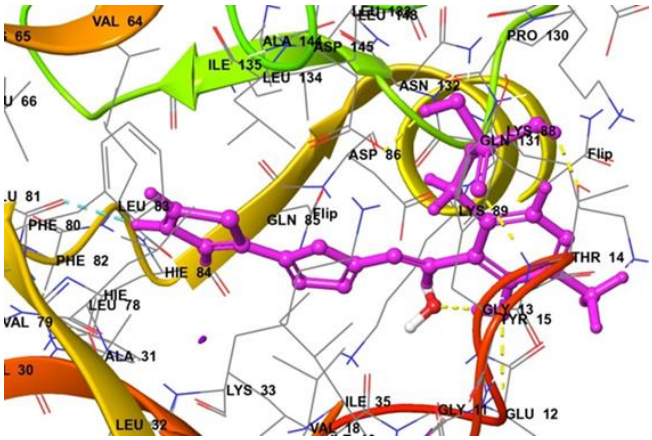


Fig. 2: 3D structure of the highest scoring molecule (compound P-1) presented at the active binding site of CDK-2 adjacent to its amino acids

From the results of table 1, compounds P-1 and P-5 showed the highest docking scores as evidence of their good binding affinity and proper orientation inside the active site of the target protein interacting with its essential amino acids which indicates a high potency of biological activity of these two molecules. The highest-scoring molecules from the listed compounds are oriented inside the active binding site of CDK-2 protein adjacent to the important amino acids as presented in fig. 2 and 3 respectively.

Inside the active site of the target protein, compound P-1 interacts with and binds to different amino acids. These interactions are mainly hydrogen bonds and hydrophobic Interactions, precisely there are five H-bonds between ASP145 with a hydroxyl group, THR14 with a hydroxyl group and an oxygen atom, GLU12 with a hydroxyl group, and ILE10 with a hydroxyl group through one water molecule in addition to the hydrophobic interactions that occur with surrounding amino acids (LEU83, PHE82, GLU81, PHE80, VAL64, ALA144, ASP145, LEU148, VAL18, TYR15, THR14, GLY13, GLU12, GLY11, and ILE10) as illustrated in fig. 2.

Compound P-5, which scores the second highest docking result, has the following interactions at CDK-2 active site: four H-bonds, ASP145 with a hydroxyl group, THR14 with the same hydroxyl group, ILE10 with a hydroxyl group and ASP86 with a hydroxyl group through one water molecule. Also, there are hydrophobic interactions with the nearby amino acids (LYS33, ALA31, PHE80, GLU81, PHE82, LEU83, HIE84, GLN85, ASP86, LYS20, VAL18, GLU8, ILE10, GLY11, GLU12, GLY13, and THR14) as illustrated in fig. 3.

All the mentioned interactions above have enhanced the abilities of the newly designed compounds and nominated them as potential anti-cancer agents with better activity and binding affinity.

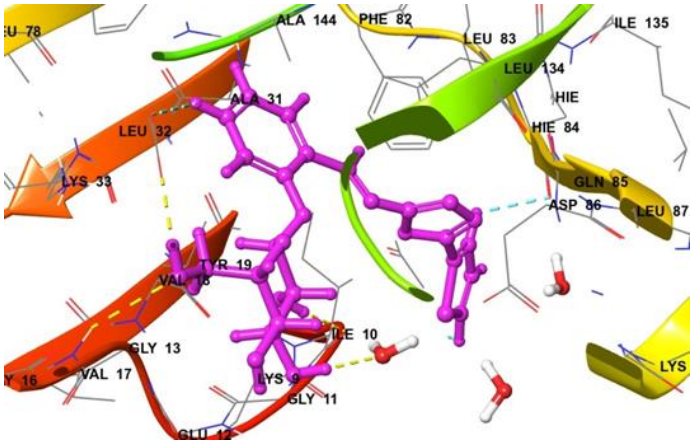


Fig. 3: 3D structure of the second highest scoring molecule (compound P-5) presented at the active binding site of CDK-2 adjacent to its amino acids

BOILED-Egg illustration of the two highest scoring molecules is presented in fig. 4, it shows that both compounds cannot penetrate the BBB and it is predicted to have low GIT absorption. Compound P-1 (blue dot) can be removed from the central nervous system (CNS) by P-glycoprotein while compound P-5 (red dot) is not a substrate for P-glycoprotein. TPSA which stands for Topological Polar Surface Area is an essential descriptor of the drug transport process such as the intestinal absorption and bioavailability of orally administered drugs, it represents the total contributions of polar atoms such as nitrogen, oxygen, and their attached hydrogen to the molecular surface area [24], molecules with a TPSA>140 A° are thought to have poor oral bioavailability [25]. Another important measure is the Lipinski rule of five which is developed to describe drug-ability and set oral bioavailability guidelines, it states that a drug should have lower than five hydrogen bond donors, an octanol-water partition coefficient log P lower than 5, ≤ 10 hydrogen bond acceptors and molecular weight (M. Wt.) ≤ 500 to be given orally [26].

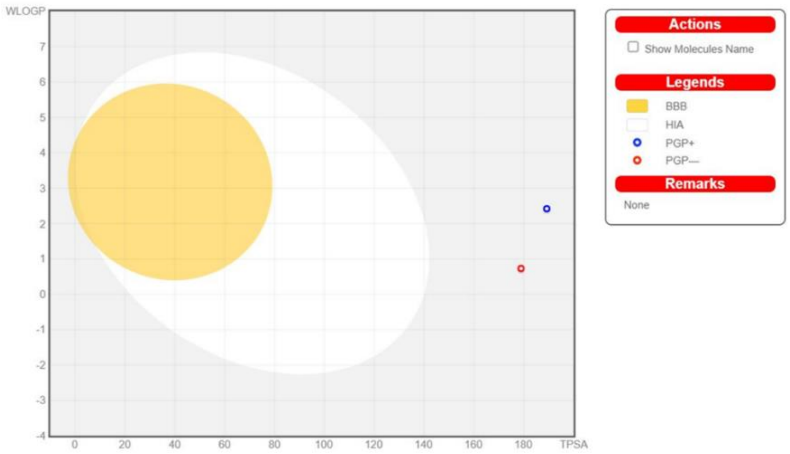


Fig. 4: BOILED-Egg of compounds P-1 (blue dot) and P-5 (red dot). Molecules inside the yellow ovule passively permeate BBB. Molecules inside the white ovule are predicted to be absorbed by the GIT. Blue dots are the derivatives that can be exported out of the CNS by the P-glycoprotein (PGP+). Red dots are the derivatives that cannot be removed from the CNS by the P-glycoprotein (PGP-)

Fig. 5 and 6 illustrate the results of the Swiss-ADME tool of both compounds P-1 and P-5 respectively showing TPSA scores of 189.21 A° and 178.90 A°, the bioavailability of compound P-5 was 0.55 indicating its ability to reach blood circulation, they have fulfilled Lipinski rule as an essential descriptor of drug-likeness beside physicochemical and pharmacokinetic properties. The other designed compounds show promising potential activity as they have fulfilled most of the mentioned parameters and most of them demonstrate high intestinal absorption with docking score between (-9.286 and-8.026) Kcal/mol which is approximate to reference ligand score (-9.919).

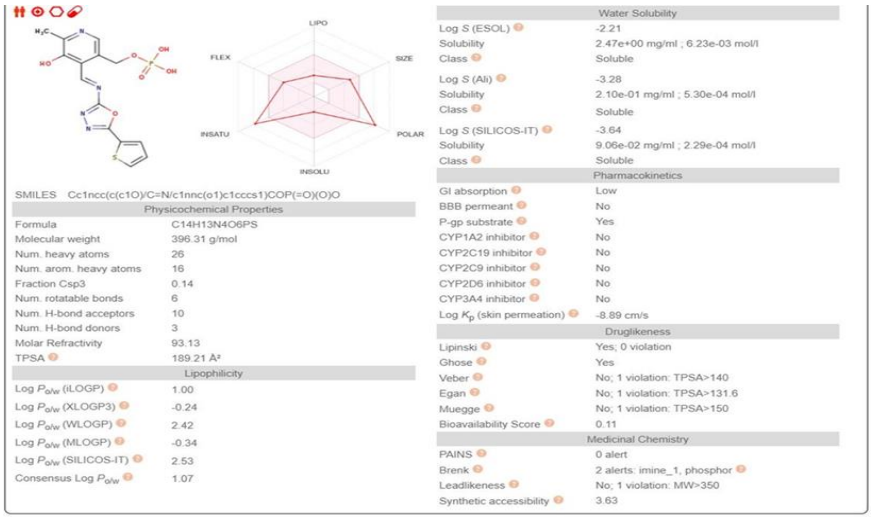


Fig. 5: Swiss-ADME web tool anticipated virtual properties of compound P-1

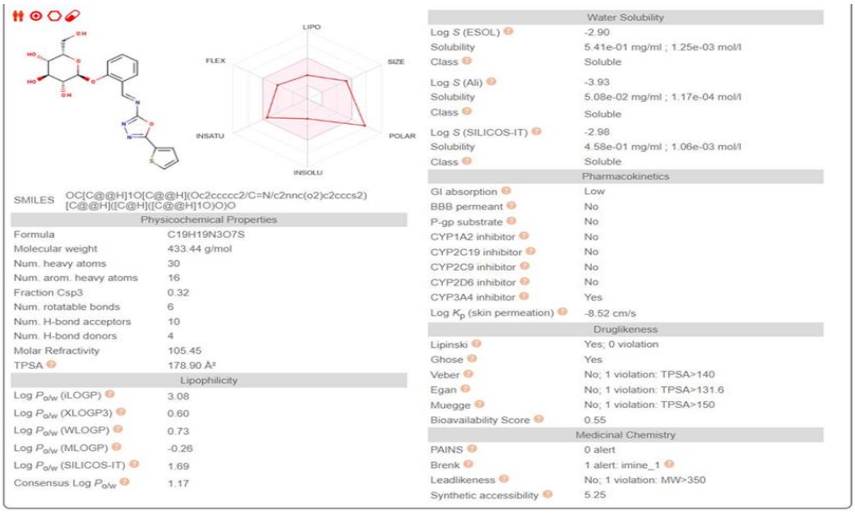


Fig. 6: Swiss-ADME web tool anticipated virtual properties of compound P-5

CONCLUSION

Molecular modeling has been one of the most attractive approaches used in the drug design process as it enables researchers to virtually enhance binding affinity and develop more potent pharmacological agents before laboratory work. By applying this method, a variety of novel derivatives with 5-(thiophen-2-yl)-1,3,4-oxadiazol-2-amine cores were designed and evaluated as potential agents for the treatment of CRC. These molecules have shown high affinity of binding inside CDK-2 protein active site with various chemical interactions in addition to higher docking scores for compound P-1 and P-5 (-10.654 and-10.169 Kcal/mol) respectively, aside from other designed derivatives which show high docking scores, similar pharmacokinetic and physicochemical characteristics, bioavailability and drug-likeness. Furthermore, the two best-scoring derivatives meet the rules of Lipinski as an essential descriptor in the evaluation of the oral activity of newly designed molecules. In the end, these novel derivatives had shown promising results to be considered as lead compounds for developing new anti-proliferative agents and further biological and pharmacological evaluation studies are required to fully understand the pharmacodynamics of these molecules.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

Declared none

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