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In-Silico ADME Analysis of 1, 3, 4-oxadiazole derivatives as CDK9 Inhibitors

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Abstract
Many drug targets have been identified in fighting against different types of cancer. Inhibition of cell cycle is strategy used in anti-cancer research. Cyclin dependent kinases were found to be promising drug targets. The goal is to find a molecule to inhibit CDK which are involved in cell cycle progression. Many drugs molecules fail during clinical trials as for streamlining study and ADME analysis is one of the crucial step. The ADME properties including blood brain barrier, GI absorption, aqueous solubility and skin permeabilitywere evaluated for these molecules. A various *in-silico* methods share the aim of ADME prediction from molecular structure. Swiss ADME is tool focus on specific property and it is most relevant computational methodsprovides pharmacokinetics properties of small molecules. ADME screening was carried out to know efficacy of molecules before proceeding to *in-vivo* or *in-vitro* assays.

Keywords: identified, CDK9, derivatives, cancer

1. Introduction
Cancer is terminology in which uncharacteristic cells grow and proliferate in an uncontrolled manner [1]. About millions of people worldwide are suffering from this deadlier disease which affecting health of patient. At end of year 2020, this disease touch approximately 10 million and considered to be one of the leading cause of mortality [2]. Chemotherapy is weapon against neoplastic disease and clinically used as anticancer agent are of synthetic molecule [3, 7]. Drug designing is considered to be important step in drug discovery. Inhibition of cell cycle progression by using cyclin dependent kinases is strategy to fight against cancer. Over a last 30 years CADD plays role in drug design. For any compounds which used in therapeutics depend not only on physiochemical properties but also pharmacokinetics and Pharmacodynamics properties of compounds. During resource-consuming processes of drug discovery and development, molecular structures were evaluated according to diverse parameters in order for selecting chemicals to synthetize, test, promote and final goal to know those with the best chance to become an effective medicine for the patients [8, 15]. The molecules must show good biological activity together with low toxicity. With help of microwave synthesis various derivatives were prepared before that it is needed to performed docking study and ADME analysis on software and also now a days in this pandemic COVID-19, we can perform such studies on software [16, 25]. Equally important is the to know concentration at the therapeutic target in the organism. In present study an *in-silico* screening has been utilized in determining the ADME of the compounds known to be CDK9 inhibitors. Thus it is prove to be useful tool in drug discovery [26, 27].

2. Materials and Methods
In-silico ADME analysis
The Compounds used in this work were found to be inhibiting CDK9 from molecular docking study. The compounds were evaluated for their ADME profile, including drug-likeness, partition coefficient, solubility, and several other parameters using SwissADME module provided Swiss Institute of Bioinformatics webserver.

Experimental
The test compounds to be used as potential CDK 9 inhibitors used in the study are listed in Table 1 and their structures are shown in Table 2.

Calculation of ADME properties
Structure were drawn in Chemsketchand SMILES of each compound was translated into molfile by online SMILES translator and structure file generator found in online tool SwissADME. In addition, pharmacokinetics such as gastrointestinal absorption, Skin permeability, Blood brain barrier and drug-likeness prediction such as bioavailability score.

Blood brain barrier (BBB)
BBB penetration is a parameter used to know whether the compound crosses blood brain barrier. Usually the most of the drugs must not pass the blood brain barriers if the target is not related to the nervous system.

Skin Permeability
Skin permeability of the compound is one of the importantfactor with reference to adverse drug response in case drugs taken orally to identify in case of accidental contact with skin and the skin permeability in case of the drugs to be taken transdermally where the skin penetration is an important aspect.
Skin permeability of a compound the result value is given as log Kp. Kp [cm/hour] is defined as:
Kp= Km*D/h
Where, Km is distribution coefficient between stratum

corneum and vehicle and D is average diffusion coefficient [cm^2/h], and h is thickness of skin [cm].

Permeability glycoprotein (P-gp)

The knowledge about compounds being substrate or non-substrate of the permeability glycoprotein. It suggests aboutthe most important member among ABC-transporters which is key to appraise active efflux through biological membranes, for instance from the gastrointestinal wall to the lumen or from the brain. One important role of P-gp is to protect the central nervous system from xenobiotics. P-gp is overexpressed in some tumour cells and leads to multidrug-resistant cancers.

Drug-likeness

Drug-likeness means toassesses qualitatively the chance for a molecule to become an oral drug with respect to bioavailability. Drug-likeness generated from structural or physicochemical inspections of development compounds advanced enough to be considered oral drug-candidates. This notion is routinely employed to perform filtering of chemical libraries to exclude molecules with properties most probably incompatible with an acceptable pharmacokinetics profile. This SwissADME section gives access to 5 different rule-based filters, with diverse ranges of properties inside of which the molecule is defined as drug-like. These filters often generated from analyses by pharmaceutical companies aiming for improving the quality of their proprietary chemical collections. The Lipinski (Pfizer) filter is the pioneer rule-of-five implemented from the Ghose (Amgen), Veber (GSK), Egan (Pharmacia) and Muegge (Bayer) methods.

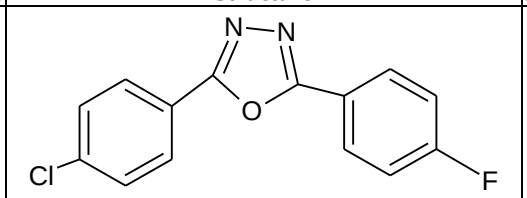
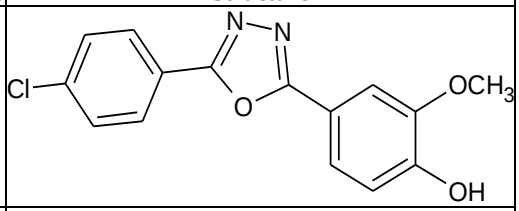
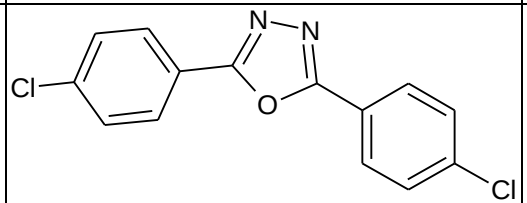
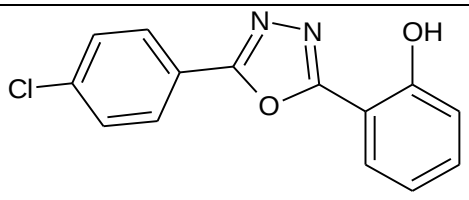
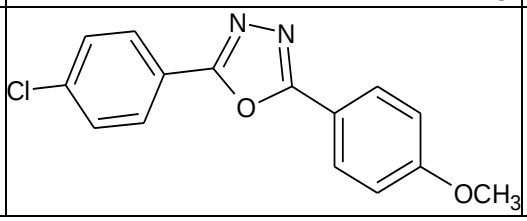
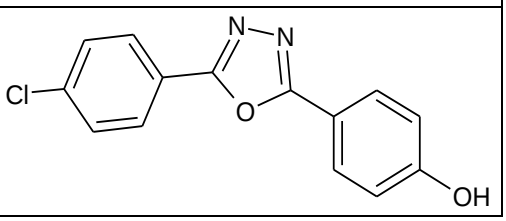
Water solubility

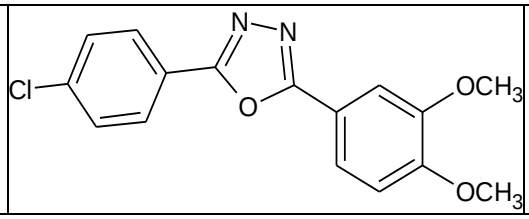
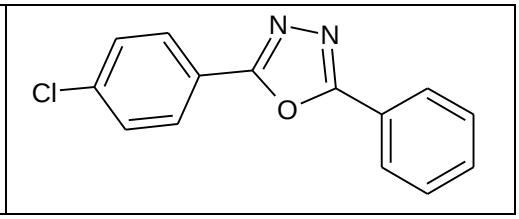
Having a soluble molecule is one of the greatly facilitates in many drug development activities, primarily the ease of handling and formulation. For discovery projects targeting oral administration, solubility is important property influences absorption and those drug meant for parenteral usage has to be highly soluble in water to deliver a sufficient quantity of active ingredient in the small volume of such pharmaceutical dosage. Two topological methods to predict Water Solubility are included in SwissADME. The first one is an implementation of the ESOL model and the second one is adapted from Ali *et al*. Both differ from the seminal general solubility equation since they avoid the melting point parameter then latter being challenging for prediction. They demonstrate strong linear correlation between predicted and experimental values (R2 = 0.69 and 0.81, respectively). SwissADME third predictor for solubility was developed by SILICOS-IT. The linear correlation coefficient of this fragmental method corrected by molecular weight is R2 = 0.75 All predicted values are the decimal logarithm of the molar solubility in water (log S). SwissADME also provides solubility in mol/l and mg/ml along with solubility classes [28].

Table 1: Test compounds used in study

Sr. no	Compound code	Name of compound
1	1a	2-(4-chlorophenyl)-5-(4-fluorophenyl)-1,3,4-oxadiazole
2	1b	2-(4-chlorophenyl)-5-(4-chlorophenyl)-1,3,4-oxadiazole
3	1c	2-(4-chlorophenyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole
4	1d	2-(4-chlorophenyl)-5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazole
5	1e	2-(4-chlorophenyl)-5-(4-hydroxy-3-methoxyphenyl)-1,3,4-oxadiazole
6	1f	2-(4-chlorophenyl)-5-(2-hydroxyphenyl)-1,3,4-oxadiazole
7	1g	2-(4-chlorophenyl)-5-(4-hydroxyphenyl)-1,3,4-oxadiazole
8	1h	2-(4-chlorophenyl)-5-phenyl-1,3,4-oxadiazole

Table 2: Structure of test compounds

Sr. no	Structure	Sr. no	Structure
1		5	
2		6	
3		7	

4		8	

3. Results & Discussion

The pharmacokinetic properties and drug-likeness prediction of test compounds were performed by Swiss ADME online version and the data are shown in table 3 and water solubility prediction shown in table 4. According to the pharmacokinetic properties, all test compounds showed Moderately soluble and soluble gastrointestinal absorption also show no BBB permeability however drug likeness were predicted by bioavailability score.

Table 3: Pharmacokinetics and drug-likeness prediction for test compounds (1a-h)

Sr No.	Compound code	Pharmacokinetics			Drug-likeness
		GI absorption	BBB permeability	Log Kp (skin permeation) cm/s	Bioavailability Score
1	1a	ModeratelySoluble	No	-2.74	0.11
2	1b	Soluble	No	-2.54	0.22
3	1c	Soluble	No	-3.55	0.55
4	1d	Moderately soluble	No	-2.38	0.11
5	1e	Moderately soluble	No	-2.11	0.22
6	1f	Moderately soluble	No	-3.58	0.11
7	1g	Soluble	No	-2.32	0.55
8	1h	Soluble	No	-2.55	0.22

Table 4: Water solubility prediction for test compounds (1a-h)

Sr No.	Compound code	LogP	Water Solubility		
		(Consensus LogP)	LogS (ESOL)	LogS (Ali)	LogS (SILICOS-IT)
1	1a	2.73	Soluble	Moderately soluble	Moderately soluble
2	1b	2.24	Soluble	Moderately soluble	Moderately soluble
3	1c	2.77	Soluble	Moderately soluble	Moderately soluble
4	1d	2.84	Moderately soluble	Soluble	Poorly soluble
5	1e	2.58	Soluble	Soluble	Moderately soluble
6	1f	2.75	Soluble	Moderately soluble	Moderately soluble
7	1g	2.65	Soluble	Soluble	Poorly soluble
8	1h	2.58	Soluble	Soluble	Moderately soluble

4. Conclusions

The pharmacokinetic properties and drug-likeness prediction of the eighttest compounds were performed by Swiss ADME online version. The Lipinski's rule of five states that absorption or permeation of a molecule is more likely when the molecular weight is under 500 g/mol, the value of log P is lower than 5, and the molecule has utmost 5 H-donor and 10 H-acceptor atoms. All molecules demonstrated a significant drug-likeness based on Lipinski's rule-of-five (RO5).All molecules were predicted to be BBB non-permeant (blood–brain barrier), it means no expected neurological side effects. All the molecules demonstrated significant bioavailability, suggesting that the molecules could be absorbed and delivered throughout the body in case of use as drug. Thus, molecules were screened for their ADMET prediction and the molecules were confirmed to be suitable drug-like molecules.

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6. References

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