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Computational Evaluation of Heterocyclic Steroids: Physicochemical and Pharmacokinetic Insights

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Abstract

Cancer remains a major global health challenge, necessitating the continuous development of new therapeutic agents with improved efficacy and reduced side effects. Steroidal compounds, particularly those incorporating heterocyclic rings, have shown significant potential in anticancer drug development due to their structural versatility and biological activity. This study evaluates the physicochemical and pharmacokinetic properties of two novel heterocyclic steroidal derivatives, Cpd 8 and Cpd 14, using SwissADME in silico analysis. The compounds were assessed for drug-likeness, bioavailability, lipophilicity, water solubility, and pharmacokinetics. Results indicate that both compounds adhere to Lipinski's rule of five and exhibit favorable bioavailability scores. However, their high lipophilicity and poor water solubility may limit their oral bioavailability. Additionally, pharmacokinetic predictions suggest differences in gastrointestinal absorption and interactions with cytochrome P450 enzymes, which could influence metabolic stability. These findings provide valuable insights into the potential of these steroidal derivatives as anticancer agents and highlight the need for further experimental validation.

Keywords: Heterocyclic Steroids; Pharmacokinetics; ADME Analysis; Cancer Drug Development; Lipinski's Rule; Bioavailability.

1. Introduction

Cancer is a worldwide health concern that is characterized by the abnormal growth of malignant cells that have the ability to invade or spread to other areas of the body (Hassanpour and Dehghani, 2017). After cardiovascular disease, it is thought to be the sec-ond most common cause of mortality worldwide. In high-income countries, it is now the top cause of mortality, surpassing cardiovascular disease (Mahase, 2019). WHO projects that approximately 13 million people would die from cancer globally by 2030, with low- and middle-income countries bearing the brunt of this rise. Nowadays, more than 10 mil-lion new cases of cancer are discovered every year (McCormack and Boffetta, 2011). Not-withstanding the recent decline in cancer-related mortality due to a better understanding of the tumor biological milieu, which has led to significant advancements in cancer detection, prevention, and re-mediation, the ultimate goal of cancer research remains to create new anticancer moieties with greater therapeutic efficiencies and fewer side effects.

Steroids have always attracted a lot of attention due to their amazing spectrum of bio-logical roles and extraordinary structural architecture. A precise alteration in the steroid molecule can result in significant therapeutic effect (Brown and Goldstein, 1986). Hetero-cyclic rings are the most important components that contribute to the therapeutic effects of medications due to their potent receptor binding capabilities (Watanabe et al., 2005). Het-erocyclic rings are a fantastic place to start when designing anticancer medications because of the large range of chemical space they can span due to their commensurate ease of mod-ification with new substituents (Nada et al., 2021). Together, steroids and heterocyclic rings enhanced a variety of physiological and biological processes. These derivatives of hetero-cyclic steroids may be used to treat a number of tumors, such as those of the liver, breast, and prostate (El-Far et al., 2009; Elmegeed et al., 2016; Nada et al., 2021).

This study aims to evaluate the physicochemical and pharmacokinetic properties of two novel heterocyclic steroidal derivatives, Cpd 8 and Cpd 14, using in silico analysis. By employing SwissADME, key parameters such as drug-likeness, bioavailability, lipophilici-ty, water solubility, and metabolic interactions were assessed to determine their potential as orally active anticancer agents. The findings provide insights into the compounds' pharma-cokinetic profiles, highlighting their suitability for further drug development. This analysis serves as a foundation for future experimental validation and structural optimization to en-hance therapeutic efficacy and minimize potential limitations.

2. Methodology

2.1. Physicochemical/Pharmacokinetic Properties Investigation

SwissADME online server (http://www.swissadme.ch/) was used to assess the physicochemical and pharmacokinetic parameters of the tested compounds using ADME (absorption, distribution, metabolism, and excretion) descriptors. Data regarding drug-likeness, bioavailability score, and P-glycoprotein interaction, as well as lipophilicity and water solubility were calculated and assessed for each test compound.

3. Results and Discussion

3.1. Analysing The Physicochemical/ pharmacokinetic characteristics of Cpd 8 and Cpd 14

In accordance with Lipinski's rule of five parameters, ADME was approximated to investigate the test substances' physicochemical and pharmacokinetic properties. Swiss ADME, the website used in our study, offers the capability to figure physicochemical properties and to expect pharmacokinetic properties (ADME parameters), to support drug discovery (El-mansy, 2021).

3.1.1. Bioavailability Radar and Physicochemical Properties

The bioavailability radar (**Fig. 1**) showed that compounds was within the coloured part which means that the compounds has an oral bioavailability. The following characteristics were taken into account when estimating the oral bioavailability of the compounds: size (molecular weight range of 150 g/mol to 500 g/mol), lipophilicity (X LOGP3 range of -0.7 to +5.0), insolubility (range of 0 to 6) range of log S (ESOL) studies, number of rotatable bonds between 0 and

9, topological polar surface area (TPSA) with a range from 20 to 130 Å^2, and unsaturation fraction (range of 0.25 to 1.0) indicating the fraction of carbon atoms in the sp^3 hybridization should not be below 0.25 (Gupta et al., 2021).
Open Babel 9, version 2.3.0 is used to compute the values of the physicochemical parameters. The fragmental technique (TPSA) is used to calculate the polar surface area (PSA), taking phosphorus and sulphur into account as polar atoms. The phrase "TPSA" is widely used to characterize a drug's capacity to enter cells (Daina et al., 2017). In many models and rules, this has shown to be a useful descriptor for quickly predicting different ADME aspects, especially biological barrier-crossing abilities such as absorption and brain access (Fedi et al., 2021)**.** The TPSA values for Cpd 8 and Cpd 14 were 85.49 Å^2 and 82.07 Å^2, respectively, suggesting that the gastrointestinal system may passively absorb these compounds but no penetration ability within the blood-brain barrier.
According to **Table 1**, the Cpd 8's physicochemical parameters show that its molecular formula is $C_{25}H_{25}NOS_2$, with a molecular weight of 419.6 g/mol, 29 heavy atoms total, and 17 aromatic heavy atoms. The sp^3 hybridization, revealed that 0.4 fraction of the atoms were carbon based. Additionally, the molar refractivity was 123.08, and there were one rotatable bond, one hydrogen bond acceptor, and one hydrogen bond donor.
Regarding Cpd 14, the physicochemical attributes (**Table 1**) revealed that the molecular formula was found to be $C_{28}H_{31}N_3O$, with a molecular weight of 425.57 g/mol, 32 heavy atoms overall, and 12 aromatic heavy atoms. In the sp^3 hybridization, it was found that 0.46 fraction ratio of the atoms were carbon. Furthermore, there were one rotatable bond, three hydrogen bond acceptors, and one hydrogen bond donor, with a molar refractivity of 130.17.

Table 1. Physicochemical Properties of compounds as calculated by Swiss ADME software

Properties	**Cpd 8**	**Cpd 14**
Formula	C25H25NOS2	C28H31N3O
Molecular weight	419.60 g/mol	425.57 g/mol
Number of heavy atoms	29	32
Number of aromatic heavy atoms	17	12
Fraction Carbon atoms in sp^3 hybridization	0.40	0.46
Number rotatable bonds	1	1
Number of H-bond acceptors	1	3
Number of H-bond donors	1	3
Molar Refractivity	123.08	130.17
TPSA	85.49 Å²	82.07 Å²

Five publicly available forecasting algorithms are available from Swiss ADME to forecast lipophilicity. Using the Generalized-Born and solvent accessible surface area (GB/SA) Approach, iLOGP provides a straightforward, reliable, and effective explanation of the n-Octanol/Water Partition Coefficient for drug design (Bakchi et al., 2022). Another model, which is an atomistic approach with knowledge-based libraries and correction factors, is called XLOGP3 (Sravika et al., 2021), while WLOGP is a wholly atomistic technique based on Wildman and Crippen's fragmental system (Pastewska et al., 2021). The MLOGP method is a topological technique archetype that utilizes a linear relationship with 13 chemical descriptors that were applied by Khan et al (Khan et al., 2021). Besides, SILICOS-IT is a hybrid approach that uses seven topological descriptors and twenty-seven pieces; http://silicos-it.be.s3-website-eu-west-1.amazonaws.com/software/filter-it/1.0.2/filter-it.html).

The lipophilicity characters of Cpd 8 has been found to have log Po/w (I log P) of 3.57, with log Po/w (X log P3) of 6.41, log Po/w (W log P) of 6.54, log Po/w (M log P) of 4.81, consensus log Po/w of 5.70, and log Po/w (SILICOS-IT) of 7.16. Regarding the lipophilicity characters of Cpd 14, it has been revealed that the log Po/w (I log P) is 3, the log Po/w (W log P) is 4.54, the log Po/w (X log P3) is 5.11, the log Po/w (SILICOS-IT) is 3.72, the log Po/w (M log P) is 3.93, and the consensus log Po/w is 4.06. Consequently, both Cpd 8 and Cpd 14 can be considered to have a highly lipophilic character.

Many drug development activities are considerably aided by the presence of a soluble molecule, primarily in terms of handling and formulation simplicity (Yadav and Mohite, 2020). Swiss ADME includes three topological techniques for predicting water solubility. The ESOL model is implemented in the first one (Sharma et al., 2022), while the second model is adapted from Ali et al (Ali et al., 2012) utilizing TPSA. Since the first and second model avoids the melting point parameter, the third predictor of Swiss ADME was developed by SILICOS-IT (http://silicos-it.be.s3-website-eu-west-1.amazonaws.com/software/filter-it/1.0.2/filter-it.html) where the linear coefficient is corrected by molecular weight.

The water solubility of both Cpd 8 and Cpd 14 was studied using log s (ESOL), ALI, and SILICOS-IT (**Table 2**). The SILICOS-IT value of Cpd 8 was -7.12, while the SILICOS-IT value of the Cpd 14 was -6.86, depicting that both compounds can be considered as poorly water-soluble moieties.

Table 2. The aqueous solubility of compounds as calculated by Swiss ADME software

		ESOL	Ali	SILICOS-IT
Cpd 8	Log S	-6.85	-8	-7.12
	Solubility	5.96 X 10^{-05} mg/ml; 1.42 X 10^{-07} mol/l	4.21 X 10^{-06} mg/ml; 1.00 X 10^{-08} mol/l	3.21 X 10^{-05} mg/ml; 7.64 X 10^{-08} mol/l
	Class	Poorly soluble	Poorly soluble	Poorly soluble
Cpd 14	Log S	-5.91	-6.58	-6.86
	Solubility	5.24 X 10^{-04} mg/ml; 1.23 X 10^{-06} mol/l	1.13 X 10^{-04} mg/ml; 2.65 X 10^{-07} mol/l	5.90 X 10^{-05} mg/ml; 1.39 X 10^{-07} mol/l
	Class	Moderately soluble	Poorly soluble	Poorly soluble

Solubility class: Log S Scale: Insoluble<-10, poorly<-6, moderately<-4, soluble<-2, very<0<highly.

3.1.2. Pharmacokinetics Prediction

Swiss ADME makes it possible to determine whether a substance inhibits the necessary CYP isoenzymes or is a substrate of P-glycoprotein. Utilizing the support vector machine approach, sizable datasets containing known substrates and non-substrates or inhibitors and non-inhibitors are carefully cleansed (Zadorozhnii et al., 2020).

To evaluate P-glycoprotein active-efflux mechanism through biological membranes from the GIT wall to the lumen, one must be aware of whether substances are substrates of the P-glycoprotein (Babu Singh et al., 2022; Halim et al., 2021). One important function of P-glycoprotein is that it can cause multidrug-resistant malignancies when it is overexpressed in certain tumour cells (Halder et al., 2022).

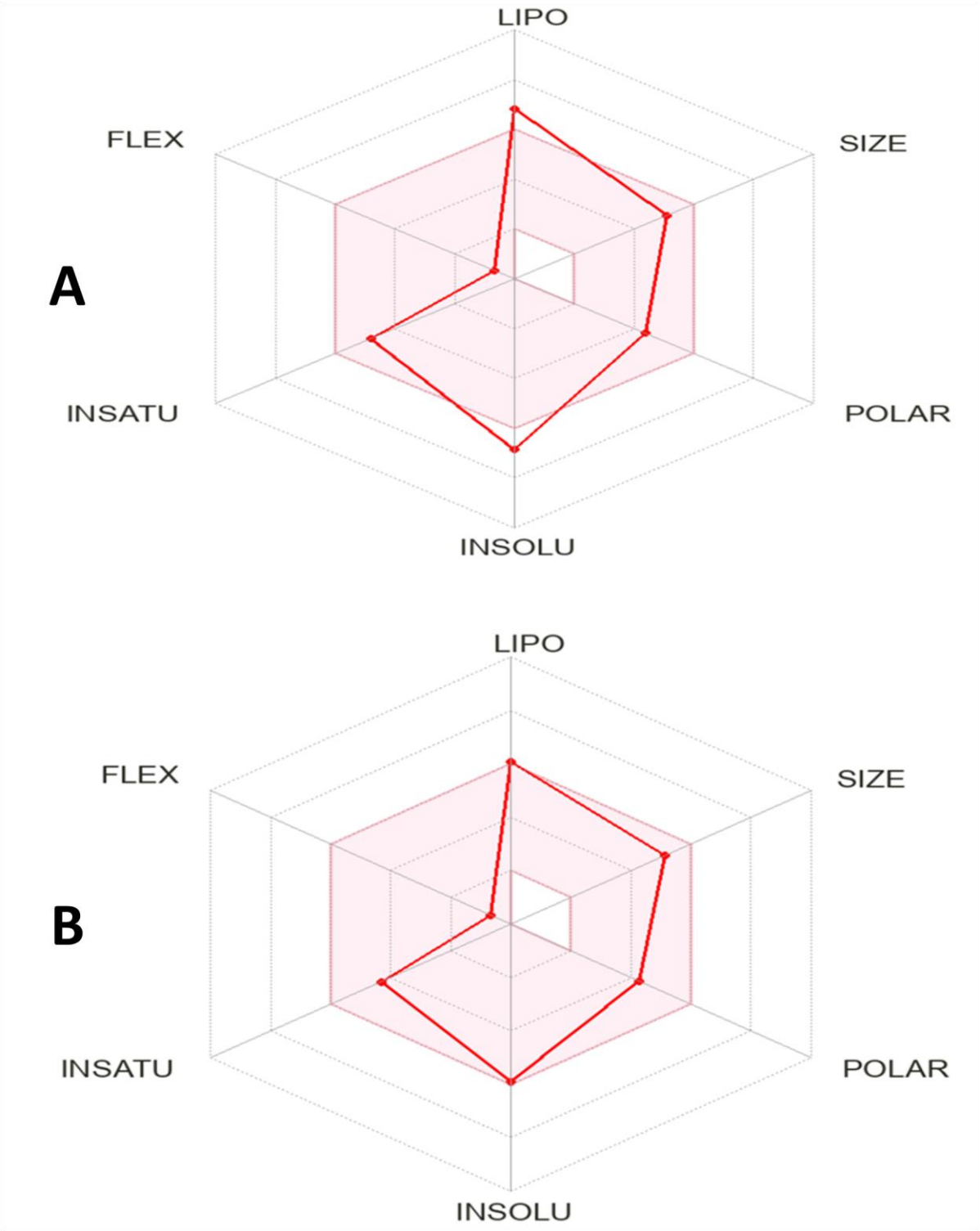

Fig.1. The bioavailability radar of Cpd 8 (A) and Cpd 14 (B) using Swiss ADME predictor.

Table 3 presents the findings on the predictive data for pharmacokinetics. The results showed that numerous ligands inhibit both compounds, and the skin permeability coefficient (Kp) for Cpd 8 and Cpd 14 was -4.31 cm/s and -5.27 cm/s, respectively. The Kp prediction was derived from Potts and Guy's research (El-Nashar et al., 2022), which indicated a linear correlation between Kp and molecular size and lipophilicity. The lower the skin penetration, the lower the log Kp value.

Table 3. Pharmacokinetics prediction of compounds as calculated by Swiss ADME software

Ligands	**Cpd 8**	**Cpd 14**
Gastro-intestinal absorption	Low	**High**
Blood-brain permeant	No	No
P- glycoprotein substrate	No	**Yes**
CYP1A2 inhibitor	No	**Yes**
CYP2C19 inhibitor	No	No
CYP2C9 inhibitor	**Yes**	No
CYP2D6 inhibitor	No	No
CYP3A4 inhibitor	No	No
Skin permeation as log Kp (cm/s)	-4.31 cm/s	-5.27 cm/s

The boiled egg model, which enables an intuitive assessment of blood brain barrier penetration (BBB) and passive gastrointestinal absorption (HIA) as a function of the molecules' positions in the WLOGP-versus-TPSA referential, was also used to display the pharmacokinetic properties (**Fig. 2**). The Brain or Intestinal Estimated permeation predictive model (BOILED-Egg) is an updated and expanded version of the Edan–Egg model that uses graphics to illustrate HIA and BBB in relation to the absorption and distribution parameters, respectively (Anbu et al., 2022). The high likelihood of brain penetration is shown by the yellow region (yolk), while the high probability of passive absorption by the gastrointestinal system is represented by the white region.

3.1.3. Drug-likeness and Bioavailability Score

Drug-likeness evaluates a molecule's potential to be taken orally in terms of bioavailability. Five distinct rule-based filters, each with a different range of qualities within which the molecule is considered as drug-like, are accessible inside this section of the Swiss ADME. Major pharmaceutical companies' analyses, which strive to enhance the quality of their proprietary chemical collections, are frequently the source of these filters (Sirakanyan et al., 2021).

A general guideline for figuring out whether a chemical molecule with a specific pharmacological or biological activity has the chemical and physical properties necessary to make it a possible oral active medication for humans is Lipinski's rule, also referred to as Pfizer's rule (Coates and Hu, 2007; Lipinski et al., 2001). The following techniques were used: Ghose (Amgen) (Ghose et al., 1999), Veber (GSK) (Veber et al., 2002), Egan (Pharmacia) (Egan et al., 2000), and Muegge (Bayer) (Muegge et al., 2001).

Analogously, the Abbot Bioavailability Score (Martin, 2005) aims to forecast the likelihood that a chemical would exhibit significant Caco-2 permeability or at least 10% oral bioavailability in rats. Similar to the other techniques in this area, its main goal is to quickly screen chemical libraries in order to identify the best molecules to be synthesized, purchased, or advanced to a later stage of a medicinal chemistry project.

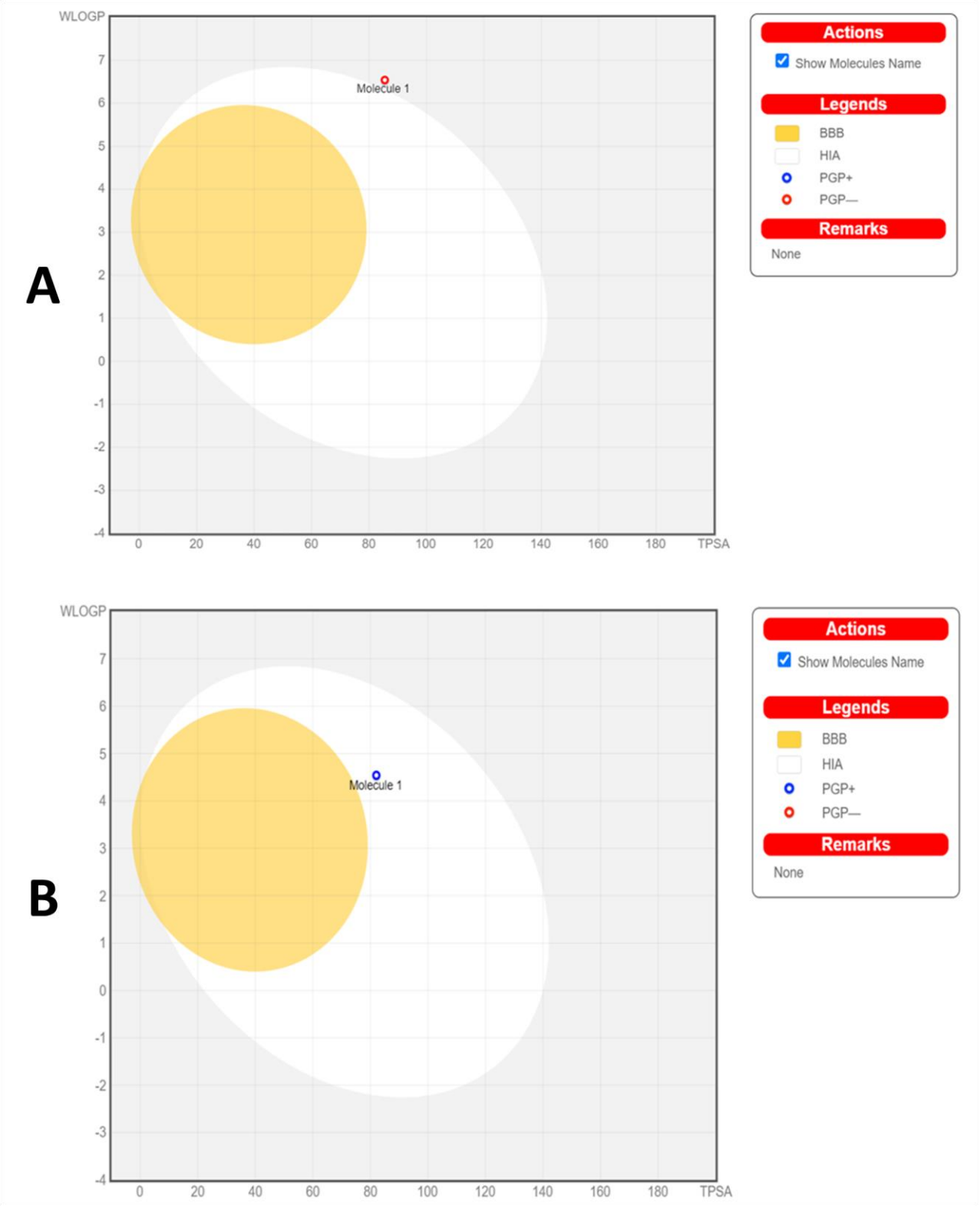

Fig. 2. Boiled Egg model of Cpd 8 (A) and Cpd 14 (B) using Swiss ADME predictor.

In terms of bioavailability, the drug-likeness data (**Table 4**) qualitatively evaluate a molecule's likelihood of becoming an oral medication. According to the results, the compounds' estimated bioavailability score was 0.55 and they complied with Lipinski's criteria deprived of any issues. These findings demonstrate that both compounds are safe to be taken orally, however, and because of their low water solubility and restricted permeability, they have a low oral bioavailability.

Table 4. Drug-likeness data of compounds as obtained from Swiss ADME software

Drug likeness	Cpd 8	Cpd 14
Lipinski	Yes; 1 violation: MLOGP>4.15	Yes; 0 violation
Ghose	No; 1 violation: WLOGP>5.6	No; 1 violation: MR>130
Veber	Yes	Yes
Egan	No; 1 violation: WLOGP>5.88	Yes
Muegge	No; 1 violation: XLOGP3>5	No; 1 violation: XLOGP3>5
Bioavailability Score	0.55	0.55

4. Conclusions

This study evaluated the physicochemical and pharmacokinetic properties of two novel heterocyclic steroidal derivatives, Cpd 8 and Cpd 14, using in silico analysis. The findings demonstrated that both compounds exhibit favorable drug-likeness properties, adhering to Lipinski's rule of five, with acceptable bioavailability scores. The analysis of lipophilicity, water solubility, and absorption characteristics revealed that both compounds possess high lipophilicity but limited aqueous solubility, which may affect their oral bioavailability. Pharmacokinetic predictions highlighted variations in gastrointestinal absorption, metabolic stability, and interactions with cytochrome P450 enzymes, with Cpd 14 showing higher gastrointestinal absorption than Cpd 8. Additionally, both compounds exhibited no blood-brain barrier permeability, reducing the likelihood of central nervous system-related side effects.

Despite their promising drug-likeness profiles, the low solubility and potential metabolic interactions indicate the need for structural modifications or formulation strategies to enhance their bioavailability and therapeutic efficacy. Further experimental studies, including in vitro and in vivo assessments, are required to validate these computational findings and determine their anticancer potential. These results provide a foundation for future optimization efforts, contributing to the development of more effective steroid-based anticancer therapies.

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