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Medicinal Chemistry, Pharmacokinetics and Drug-Likeness Properties of Some Azetidinone Derivatives *via* Swiss-ADME Tool

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Abstract: Azetidinone derivatives, known for their potent biological activities, have garnered significant attention in medicinal chemistry. Swiss ADME, a web-based computational tool, is used in the present study to assess the pharmacokinetics and drug-likeness profiles of certain azetidinone derivatives. A comprehensive *in-silico* analysis was conducted to predict key parameters such as absorption, distribution, metabolism, and excretion (ADME), alongside physicochemical properties, lipophilicity, water solubility, and bioavailability scores. The drug-likeness was assessed using Lipinski's Rule of Five and other medicinal chemistry filters. Results revealed that most of the azetidinone derivatives exhibit favourable pharmacokinetic profiles with high gastrointestinal absorption, moderate to high lipophilicity, and good oral bioavailability. Several compounds also complied with multiple drug-likeness filters, indicating promising lead-like characteristics. These results highlight the potential of Swiss ADME as a predictive tool in early-stage drug development and offer insightful information for the logical design and optimisation of azetidinone-based therapies.

Keywords: Azetidinone, Lipinski's Rule, lipophilicity, bioavailability, Swiss ADME, *in-silico.*

I. Introduction

Azetidinone, sometimes referred to as β-lactams, is a well-known heterocyclic chemical among medicinal and organic chemists. It is found that a group of new substituted azetidinones are potent elastase inhibitors and therefore are useful as anti-inflammatory and antidegenerative agents. Granulocyte and macrophage proteases have been implicated in the chronic tissue degradation mechanisms linked to inflammation, such as emphysema and rheumatoid arthritis. Therefore, these proteases' specific and selective inhibitors are promising candidates for strong anti-inflammatory drugs that can be used to treat inflammatory diseases. (1)

In dentistry, eugenol is a common painkiller and anaesthetic. Several investigations have shown that it inhibits voltage-gated sodium channels (VGSC) in the teeth's main supply neurons. Eugenol is recognised as an antioxidant and an inhibitor of monoamine oxidase (MAO), and it is also believed to possess neuroprotective properties. (2)

There is a paucity of literature on substituted eugenol-targeted compounds of Azetidinone. In the present study, an effort is being undertaken to analyse the eugenol derivatives of azetidinone in the hopes of predicting the ADME properties of compounds using by Swiss ADME tool in order to synthesise them.

II. Materials And Methods

Swiss ADME:

The SwissADME web application, which is freely available at http://www.swissadme.ch, is designed to make submission and result analysis simple, even for those who are not experts in CADD. Aside from having exclusive access to sophisticated techniques (like iLOGP or the BOILED-Egg) and most advanced free web-based tools for ADME and pharmacokinetics (like pk-CSM and admetSAR) but we still use Swiss ADME, as its strengths include multiple input methods, computation for multiple molecules, and the ability to display, save, and share results per individual molecule through globally intuitive and interactive graphs. (3)

Physicochemical properties:

Molecular weight, number of heavy molecules, number of aromatic heavy atoms, TPSA, percentage csp3, number of rotatable bonds, range of H-bond donors and acceptors, and molar refractivity are all included in this section. To find such values, Open Babel (version 2.30) is utilised. (3)

Structure and bioavailability:

This segment contains the two-dimensional chemical structure with canonical SMILES to evaluate the molecules of interest. The six different physicochemical properties like lipophilicity. (LIPO), size (SIZE), polarity (POLAR), insolubility (INSOLU), in saturation (INSATU), and flexibility (FLEX) were taken into consideration by the bioavailability radar. The following criteria were considered: polarity should have a topological polar surface area (TPSA) between 20 and 130 $Å^2$, solubility, log S not greater than 6, saturation, fraction of carbons in the sp hybridization not less than 0.25, flexibility no more than 9 rotatable bonds, and lipophilicity should have an XLOGP3 value between -0.7 and +5.0. (4)

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Lipophilicity:

Lipophilicity is a crucial parameter in drug discovery and design, as it complements the most informative physicochemical property in medicinal chemistry. It is experimentally demonstrated as partition coefficients (log P) or distribution coefficients (log D). Swiss ADME provides five freely available models to evaluate the lipophilicity of compounds: XLOGP3, WLOGP, MLOGP, SILICOS-IT, and iLOGP. XLOGP3 is an atomistic approach, WLOGP is a fragmental system, MLOGP is a topological method, SILICOS-IT is a hybrid method, and iLOGP is a physics-based method. The consensus log P o/w that the five proposed methods predict is the arithmetic mean of the data. Higher log P values correspond to greater lipophilicity (4) (Table 3)

Solubility:

Solubility is crucial for drug development, particularly for oral administration and parenteral usage. SwissADME includes two topological methods to predict water solubility: the ESOL model adapted from Ali *et al*. By eschewing the melting point parameter, these techniques deviate from the usual solubility equation. They show a strong linear correlation between predicted and experimental values. A third predictor developed by SILICOS-IT has a linear correlation coefficient of 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 qualitative solubility classes. Overall, soluble molecules are essential for drug development and absorption. Logarithmic scale to categorise solubility: Insoluble<-10, Poorly soluble<-6, fairly soluble<-4, Soluble<-2, and very soluble<0. (5) (Table 4)

Pharmacokinetics:

Pharmacokinetic parameters such as GI absorption, BBB penetration, P-gp substrate, CYP1A2 inhibitor, CYP2C19 inhibitor, CYP2C9 inhibitor, CYP2D6 inhibitor, CYP3A4 inhibitor, and Log Kp (skin permeation) were predicted using the BOILED-Egg model (Figure 2) and a multiple linear regression model created by Potts *et al.* (5) (Table 5)

Drug-Likeness:

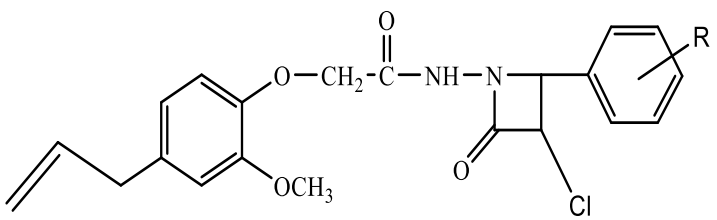
Drug-likeness is a concept that evaluates the likelihood of a molecule becoming an oral drug based on its bioavailability. It is established through structural or physicochemical inspections of advanced compounds. This concept is used to filter chemical libraries excluding molecules with properties that may not align with an acceptable pharmacokinetic profile. Swiss ADME provides access to five rule-based filters, including the Lipinski filter, Ghose, Veber, Egan, and Muegge methods, which are adapted from major pharmaceutical companies analyses to improve their chemical collections. These filters allow for consensus views or selection of methods that best fit end-users' specific needs. The Abbot Bioavailability Score forecasts the likelihood that a substance will have detectable Caco-2 permeability or at least 10% oral bioavailability in rats. This semi-quantitative rule-based score relying on total charge, TPSA and violation of the Lipinski filter defines four classes of compounds with probabilities of 11%, 17%, 56% or 85%. This semi-quantitative rule-based score focuses on fast screening of chemical libraries to select the best molecules for purchase, synthesis, or promotion at a later stage of a medicinal chemistry project. (6) (Table 6)

Medicinal Chemistry:

PAINS (Pan Assay Interference Compounds) are compounds that exhibit strong assay responses and are active in various assays, potentially serving as avenues for future research. If such properties are discovered in a molecule being evaluated, SwissADME issues warnings. Brenk expands lead optimisation possibilities by considering smaller, less hydrophobic molecules that are not covered by "Lipinski's rule of five." This model limits the number of heavy atoms to between 10 and 27, the cLogP/cLogD to between 0 and 4, and the number of hydrogen-bond donors and acceptors to less than 4 and 7. Only compounds of low complexity are considered medicinal. In high-throughput screening (HTS), the lead likeness idea is intended to provide leads with exceptional affinity that promise to take advantage of extra interactions during the lead optimisation stage. When leads undergo chemical changes, their size is likely to decrease and their lipophilicity increases. Using a rule-based approach, lead optimisation has been carried out using molecules with molecular weights between 100 and 350 Da and cLogP between 1 and 3.0.(7) (Table 7)

III. Results

The structures of the Azetidinone derivatives (Figure 1) were drawn using ChemDraw software version 16.0.1.4, and their SMILES were extracted and pasted into Swiss ADME software to predict their Physicochemical Properties. The results obtained are tabulated



"Figure 1": Structures of eugenol derivatives of azetidinone

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Table 1- General physicochemical properties of compounds

SL.NO	R	CHEMICAL NAME AZETIDINONE DERIVATIVES	MOLECULAR FORMULA	SMILES	MOLECULAR WEIGHT(g/mol)
1.	4-Nitro	2-(4-allyl-2-methoxyphenoxy)-N-(3-chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl)acetamide	C21H20ClN3O6	C=CCc1ccc(c(c1)OC)OCC(=O)NN1C(=O)C(C1c1ccc(cc1)[N+](=O)[O-])Cl	445.85
2.	2,4-Dinitro	2-(4-allyl-2-methoxyphenoxy)-N-(3-chloro-2-(2,4-dinitrophenyl)-4-oxoazetidin-1-yl)acetamide	C21H19ClN4O8		490.85
3.	4-Fluro	2-(4-allyl-2-methoxyphenoxy)-N-(3-chloro-2-(4-fluorophenyl)-4-oxoazetidin-1-yl)acetamide	C21H20ClFN2O4	C=CCc1ccc(c(c1)OC)OCC(=O)NN1C(=O)C(C1c1ccc(cc1)F)Cl	418.85
4.	4-Chloro	2-(4-allyl-2-methoxyphenoxy)-N-(3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)acetamide	C21H20Cl2N2O4	C=CCc1ccc(c(c1)OC)OCC(=O)NN1C(=O)C(C1c1ccc(cc1)Cl)Cl	435.30
5.	2,4-Dicloro	2-(4-allyl-2-methoxyphenoxy)-N-(3-chloro-2-(2,4-dichlorophenyl)-4-oxoazetidin-1-yl)acetamide	C21H19Cl3N2O4	C=CCc1ccc(c(c1)OC)OCC(=O)NN1C(=O)C(C1c1ccc(cc1Cl)Cl)Cl	469.75
6.	2,4 Diethyl amine	2-(4-allyl-2-methoxyphenoxy)-N-(2-(2,4-bis(2-aminoethyl)phenyl)-3-chloro-4-oxoazetidin-1-yl)acetamide	C25H31ClN4O4	C=CCc1ccc(c(c1)OC)OCC(=O)NN1C(=O)C(C1c1ccc(cc1N(C)C)N(C)C)Cl	486.99
7.	2.4 Dimethoxy	2-(4-allyl-2-methoxyphenoxy)-N-(3-chloro-2-(2,4-dimethoxyphenyl)-4-oxoazetidin-1-yl)acetamide	C23H25ClN2O6	C=CCc1ccc(c(c1)OC)OCC(=O)NN1C(=O)C(C1c1ccc(cc1OC)OC)Cl	460.91
8.	4-OH	2-(4-allyl-2-methoxyphenoxy)-N-(3-chloro-2-(4-hydroxyphenyl)-4-oxoazetidin-1-yl)acetamide	C21H21ClN2O5	C=CCc1ccc(c(c1)OC)OCC(=O)NN1C(=O)C(C1c1ccc(cc1)O)Cl	416.85
9.	2-OH	2-(4-allyl-2-methoxyphenoxy)-N-(3-chloro-2-(2-hydroxyphenyl)-4-oxoazetidin-1-yl)acetamide	C21H21ClN2O5	C=CCc1ccc(c(c1)OC)OCC(=O)NN1C(=O)C(C1c1ccccc1O)Cl	416.85
10.	3,4,5 Trimethoxy	2-(4-allyl-2-methoxyphenoxy)-N-(3-chloro-2-oxo-4-(3,4,5-trimethoxyphenyl)azetidin-1-yl)acetamide	C24H27ClN2O7	C=CCc1ccc(c(c1)OC)OCC(=O)NN1C(=O)C(C1c1cc(OC)c(c(c1)OC)OC)Cl	490.93
11.	4-Methoxy	2-(4-allyl-2-methoxyphenoxy)-N-(3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl)acetamide	C22H23ClN2O5	C=CCc1ccc(c(c1)OC)OCC(=O)NN1C(=O)C(C1c1ccc(cc1)OC)Cl	430.88
12.	4-Br	2-(4-allyl-2-methoxyphenoxy)-N-(2-(4-bromophenyl)-3-chloro-4-oxoazetidin-1-yl)acetamide	C21H20BrClN2O4	C=CCc1ccc(c(c1)OC)OCC(=O)NN1C(=O)C(C1c1ccc(cc1)Br)Cl	479.75
13.	4-Methyl	2-(4-allyl-2-methoxyphenoxy)-N-(3-chloro-2-oxo-4-(p-tolyl)azetidin-1-yl)acetamide	C22H23ClN2O4	C=CCc1ccc(c(c1)OC)OCC(=O)NN1C(=O)C(C1c1ccc(cc1)C)Cl	414.88
14.	Pure Benzaldehyde	2-(4-allyl-2-methoxyphenoxy)-N-(3-chloro-2-oxo-4-phenylazetidin-1-yl)acetamide	C21H21ClN2O4	C=CCc1ccc(c(c1)OC)OCC(=O)NN1C(=O)C(C1c1ccccc1)Cl	400.86

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Table 1 - Physicochemical properties

Sl No	Number. heavy atoms	Num. arom heavy atoms	Fraction Csp3	Num. rotatable bonds	Num. H-bond acceptors	Num. H bond donors	Molar refractivity	TPSA ($^0A^2$)
1.	31	12	0.24	10	6	1	118.76	113.69
2.	34	12	0.24	11	8	1	127.59	159.51
3.	29	12	0.24	9	5	1	109.9	67.87
4.	29	12	0.24	9	4	1	114.95	67.87
5.	30	12	0.24	9	4	1	119.96	67.87
6.	34	12	0.36	11	4	1	138.36	74.35
7.	32	12	0.3	11	6	1	122.93	86.33
8.	29	12	0.24	9	5	2	111.96	88.1
9.	29	12	0.24	9	5	2	111.96	88.1
10.	34	12	0.33	12	7	1	129.42	95.56
11.	30	12	0.27	10	5	1	116.43	77.1
12.	29	12	0.24	9	4	1	117.64	67.87
13.	29	12	0.27	9	4	1	114.91	67.87
14.	28	12	0.24	9	4	1	109.94	67.87

Table 2 - Lipophilicity

Sl no	iLOGP	XLOGP3	WLOGP	MLOGP	Silicos-IT Log P	Consensus Log P
1.	2.4	3.76	2.23	2.35	1.33	2.41
2.	2.07	3.59	2.14	1.54	-0.78	1.71
3.	2.82	4.03	2.88	3.61	3.89	3.45
4.	3.06	4.56	2.97	3.72	4.11	3.69
5.	3.29	5.19	3.63	4.2	4.76	4.21
6.	3.37	4.18	2.45	3.02	2.92	3.19
7.	3.27	3.87	2.34	2.61	3.63	3.14
8.	2.32	3.58	2.02	2.7	2.99	2.72
9.	2.64	3.58	2.02	2.7	2.99	2.79
10.	3.71	3.84	2.35	2.31	3.72	3.19
11.	3.01	3.9	2.33	2.92	3.54	3.14
12.	2.91	4.62	3.08	3.82	4.15	3.72
13.	2.91	4.3	2.63	3.45	3.99	3.46
14.	3.21	3.93	2.32	3.24	3.46	3.23

Table 3 - Water solubility

Sl No	ESOL				Ali				SILICOS-IT			
	Log s	**solubility**		**class**	**Log s**	**solubility**		**class**	**Log s**	**solubility**		**class**
		mg/mL	**mol/L**			**mg/mL**	**mol/L**			**mg/mL**	**mol/L**	
1.	-4.6	1.12E-02	2.51E-05	MS	-5.84	6.44E-04	1.44E-	MS	-5.51	1.38E-	3.10E-	MS

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							06			03	06	
2.	-4.68	1.03E-02	2.09E-05	MS	-6.63	1.16E-04	2.36E-07	PS	-4.84	7.09E-03	1.45E-05	MS
3.	-4.69	8.59E-03	2.05E-05	MS	-5.16	2.91E-03	6.94E-06	MS	-6.43	1.55E-04	3.69E-07	PS
4.	-5.12	3.27E-03	7.52E-06	MS	-5.71	8.52E-04	1.96E-06	MS	-6.75	7.65E-05	1.76E-07	PS
5.	-5.72	8.87E-04	1.89E-06	MS	-6.36	2.04E-04	4.34E-07	PS	-7.34	2.17E-05	4.61E-08	PS
6.	-5.03	4.57E-03	9.38E-06	MS	-5.45	1.73E-03	3.55E-06	MS	-6.31	2.40E-04	4.93E-07	PS
7.	-4.69	9.47E-03	2.05E-05	MS	-5.38	1.92E-03	4.17E-06	MS	-6.37	1.97E-04	4.28E-07	PS
8.	-4.39	1.69E-02	4.05E-05	MS	-5.12	3.19E-03	7.65E-06	MS	-5.58	1.09E-03	2.62E-06	MS
9.	-4.39	1.69E-02	4.05E-05	MS	-5.12	3.19E-03	7.65E-06	MS	-5.58	1.09E-03	2.62E-06	MS
10.	-4.77	8.30E-03	1.69E-05	MS	-5.54	1.41E-03	2.87E-06	MS	-6.46	1.69E-04	3.44E-07	PS
11.	-4.6	1.07E-02	2.49E-05	MS	-5.22	2.61E-03	6.06E-06	MS	-6.27	2.31E-04	5.36E-07	PS
12.	-5.44	1.75E-03	3.65E-06	MS	-5.77	8.14E-04	1.70E-06	MS	-6.95	5.45E-05	1.14E-07	PS
13.	-4.83	6.09E-03	1.47E-05	MS	-5.44	1.51E-03	3.64E-06	MS	-6.54	1.18E-04	2.85E-07	PS
14.	-4.52	1.20E-02	2.99E-05	MS	-5.05	3.53E-03	8.82E-06	MS	-6.17	2.71E-04	6.76E-07	PS

Table 4 - Pharmacokinetics

Sl no	GI absorption	BBB permeant	Pgp Substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	log Kp (cm/s)
1.	High	No	No	No	Yes	Yes	Yes	Yes	-6.35
2.	Low	No	No	No	Yes	Yes	Yes	Yes	-6.75
3.	High	Yes	No	Yes	Yes	Yes	Yes	Yes	-5.99
4.	High	Yes	No	Yes	Yes	Yes	Yes	Yes	-5.72
5.	High	Yes	No	Yes	Yes	Yes	Yes	Yes	-5.48
6.	High	Yes	No	No	Yes	Yes	Yes	Yes	-6.3
7.	High	No	No	No	Yes	Yes	Yes	Yes	-6.36
8.	High	No	No	No	Yes	Yes	Yes	Yes	-6.3
9.	High	No	No	No	Yes	Yes	Yes	Yes	-6.3
10.	High	No	No	No	Yes	Yes	Yes	Yes	-6.57
11.	High	Yes	No	No	Yes	Yes	Yes	Yes	-6.16
12.	High	Yes	No	Yes	Yes	Yes	Yes	Yes	-5.95
13.	High	Yes	No	Yes	Yes	Yes	Yes	Yes	-5.78
14.	High	Yes	No	Yes	Yes	Yes	Yes	Yes	-5.95

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Table 5 - Druglikeness rule and bioavailability score

Sl no	Lipinski violations	Ghose violations	Veber violations	Egan violations	Muegge violations	Bioavailability Score
1.	0	0	0	0	0	0.55
2.	1	1	2	1	1	0.55
3.	0	0	0	0	0	0.55
4.	0	0	0	0	0	0.55
5.	1	0	0	0	1	0.55
6.	0	2	1	0	0	0.55
7.	0	0	1	0	0	0.55
8.	0	0	0	0	0	0.55
9.	0	0	0	0	0	0.55
10.	0	1	1	0	0	0.55
11.	0	0	0	0	0	0.55
12.	0	0	0	0	0	0.55
13.	0	0	0	0	0	0.55
14.	0	0	0	0	0	0.55

A clear inverse relationship was observed between lipophilicity and water solubility, where higher Log P values corresponded to lower Log S values. Although all compounds showed a bioavailability score of 0.55, those with moderate lipophilicity (Log P 2–3.5) exhibited better solubility and drug-likeness, suggesting favorable absorption potential. In contrast, highly lipophilic compounds (Log P > 4) showed poor solubility and more rule violations, indicating reduced bioavailability. (Figure 2)

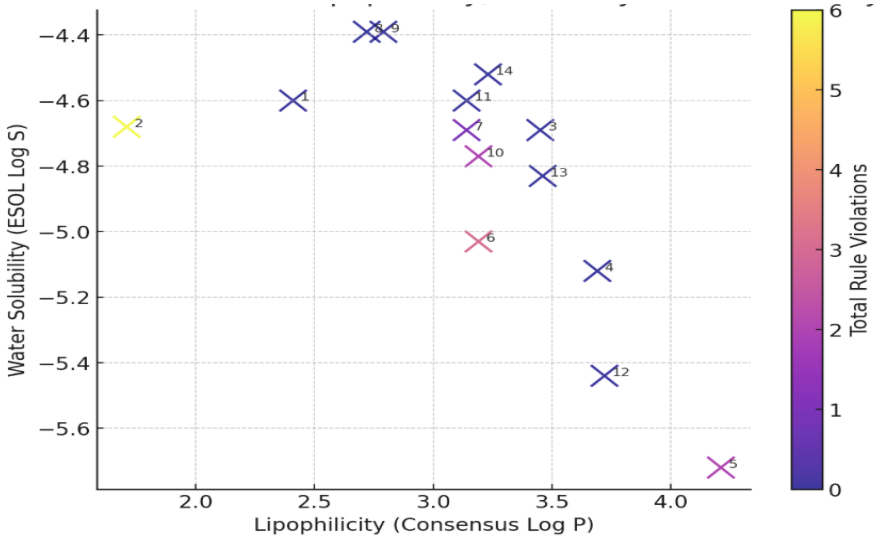

Figure 2: Correlation between Lipophilicity, Solubility and Bioavailability

Table 6 - Medicinal chemistry properties

Sl no	PAINS	Brenk	Leadlikeness	Synthetic Accessibility
1.	0.55	0	4	3
2.	0.55	0	4	3
3.	0.55	0	2	3
4.	0.55	0	2	3

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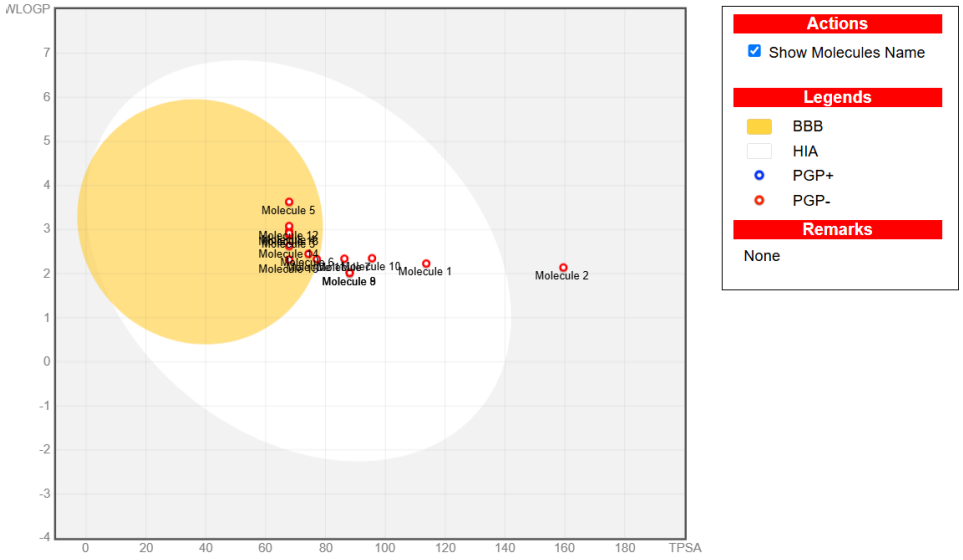
5.	0.55	0	2	3
6.	0.55	1	2	3
7.	0.55	0	2	3
8.	0.55	0	2	3
9.	0.55	1	2	3
10.	0.55	0	2	3
11.	0.55	0	2	3
12.	0.55	0	2	3
13.	0.55	0	2	3
14.	0.55	0	2	3

Boiled Egg Model



"Figure 2": Boiled Egg Model of Some Azetidinone Derivatives

IV. Discussion

The majority of the compounds analysed had acceptable ranges for key descriptors like molecular weight (<500 g/mol), topological polar surface area (TPSA) between 67.87–159.51 Å², and hydrogen bond donors/acceptors, indicating their suitability for oral bioavailability. Notably, compounds with higher TPSA values, such as the 2,4-dinitro azetidinone (TPSA = 159.51), may exhibit lower membrane permeability, impacting absorption.

Lipophilicity, as measured by the consensus Log P, ranged from 1.71 to 4.21, falling within the acceptable range for passive diffusion and absorption. Compounds like 2,4-dichloro azetidinone showed relatively higher Log P values (~4.21), indicating strong lipophilic character, which may favour membrane permeability but risk poor aqueous solubility or bioaccumulation. Meanwhile, lower Log P compounds like 2,4-dinitro azetidinone (1.71) are more hydrophilic and have potentially limiting permeability.

Solubility is a critical factor for formulation and bioavailability. Most derivatives showed moderate to poor solubility (Log S < -4) across ESOL, Ali, and SILICOS-IT models.2,4-dichloroazetidinone and 2,4-diethylamineazetidinone were predicted to be poorly soluble by the SILICOS-IT model. This highlights a potential limitation and suggests the need for solubility-enhancing strategies such as salt formation or nanoformulations. All compounds, except 2,4-dinitroazetidinone, exhibited high gastrointestinal (GI) absorption, suggesting good oral bioavailability. However, none of the compounds were predicted to be P-gp substrates, minimising concerns for efflux-related bioavailability issues. Several compounds were predicted as CYP inhibitors (especially CYP3A4, CYP2D6), which could imply potential drug-drug interaction risks in polypharmacy settings. The Boiled Egg model supports this by visualising most compounds within the 'yolk' region, indicating optimal brain penetration and GI absorption for several derivatives. Compounds like 4-fluoro and 4-chloro azetidinone show BBB permeability, which might be advantageous for CNS-targeted drug design and compound 2 is seen to have the least absorption.

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Almost all compounds complied with Lipinski's Rule of Five, indicating a promising potential for oral bioavailability. A few violations were observed in Ghose and Veber filters (notably in compounds 2 and 5), suggesting deviations in molecular weight, polar surface area, or flexibility. Due to these violations, the synthesis of these compounds will not be carried out. The bioavailability score was consistently 0.55, indicating moderate predicted oral bioavailability, and it is correlated with three parameters.

From a medicinal chemistry standpoint, none of the derivatives triggered PAINS (Pan-Assay Interference Compounds) alerts, which enhances their reliability in bioassays. Synthetic accessibility scores ranged from 2 to 4, suggesting moderate ease of synthesis, making these derivatives viable for both lab-scale and industrial synthesis.

V. Conclusion

Computer-aided drug layout (CADD) has completely changed the research and development procedures for finding therapeutic candidates due to the exponential growth of organic and chemical statistics. When computational tools are employed, it is learnt that drug research and development techniques are cost-effective, less time-consuming and can implement green chemistry in drug synthesis. The freely available web-based application SwissADME is provided for this in order to evaluate the ADME residence of compounds. When it comes to biological and chemical data, computer-aided remedy creation is developing at an exponential rate. Hence, it can be concluded that, before the bioactive chemicals are evaluated in clinical trials, they must first be confirmed for their biological activity with minimal structural requirements.

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