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Research Article

ADME Study of Azole Derivatives with SwissADME Online Tool

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Abstract

Any drugs which reaches on the site of action in sufficient quantity will produces good pharmacological action. In the designing of new lead compound ADME study plays very important roll. ADME study covers pharmacokinetic aspects of any molecules. Now days in drug discovery and development the study of absorption, distribution, metabolism and excretion are very popular parameters. In current scenario ADME study became very easy because of In-silico method using online platforms. SwissADME is a very popular online platform for study of ADME of any compound. This web tool predicts various parameters like Physicochemical properties, Lipophilicity, Water solubility, Drug likeness, Medicinal chemistry friendliness of any lead compound in very easy way.

Keywords: *Lead Compound; ADME; Insilico; Human Gastrointestinal Absorption; Blood-Brain Barrier*

Introduction

Today, there is no doubt about the broad spectrum quality of the azole compound. So, nowadays intensive research work is going on azole class of compounds. *Insilico* ADME study of any lead compound may play major role in the development of effective drug moiety [1] with pharmacokinetic details [2,3].

Nowadays absorption, distribution, metabolism and excretion (ADME) studies are very important and popular among the drug developers during drug discovery and development process. These studies may provide answers related to:

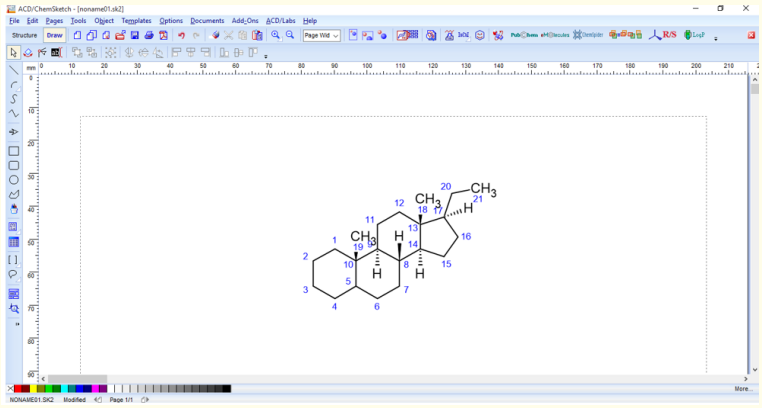
- Absorption: How much quantity of drugs absorbed in how much time. This is also related to bioavailability.
- Distribution: It explains the distribution of drugs in the body with rate and extent of distribution.
- Metabolism: It is related to metabolism of drugs and also identifies the metabolite that is formed.
- Excretion: This provides the answers related to time required for excretion of any drug from the body.

Materials and Methods

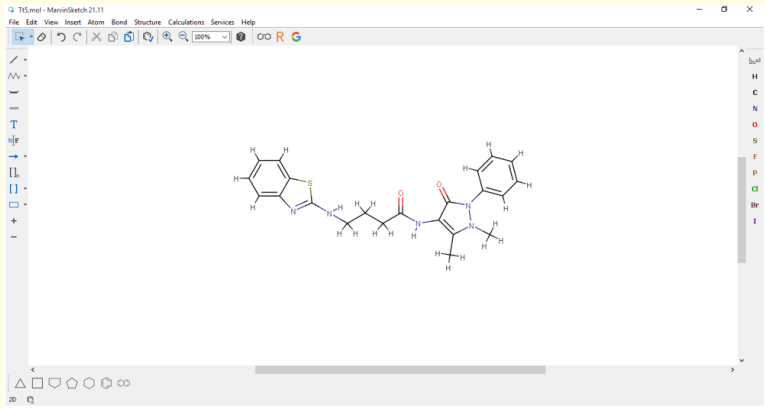
By using *insilico* computational method ADME study was performed [4,5] on online SwissADME tool. The configuration of system at which ADME study performed was running on 2.0 GHz AMD A8-6410 APU with Radeon R5 Graphics, 4 GB RAM, 256 GB SSD memory and 64 Bit Window operating system. The webpage address of SwissADME was http://www.swissadme.ch/. For offline chemical structure drawing Marvin Tools was used.

Ligand structure drawing

There are two methods available for ligand preparation. In one method, prepare on various offline tools like Chemdraw, Chemsketch, Marvin tools (Figure 1) and save the file in ".mol" format then open the file in online SwissADME platform in structure drawing section. In second method, we may directly draw the chemical structure on online SwissADME platform [6] (Figure 2). By literature survey azole derivatives was found very good antimicrobial activity so drawing of azole derivatives (Table 1) on Marvin tool was done by random method.

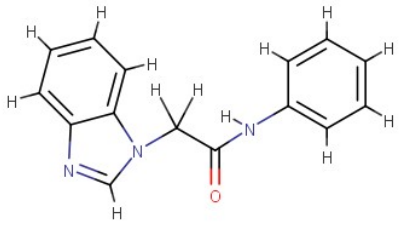
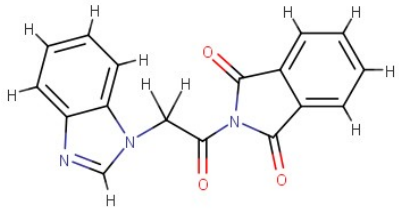
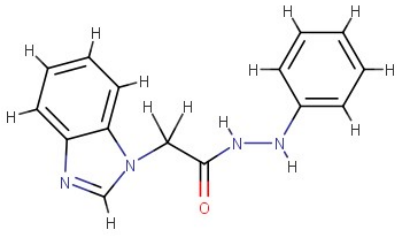
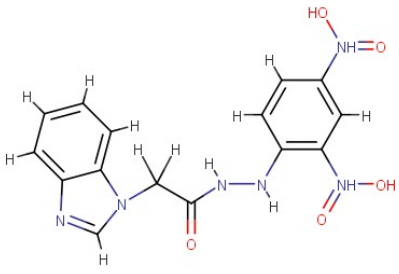
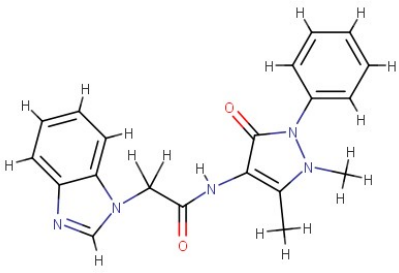
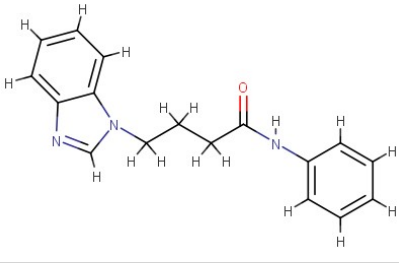


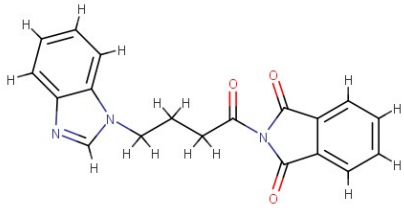
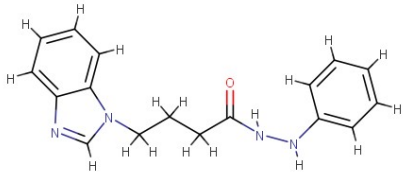
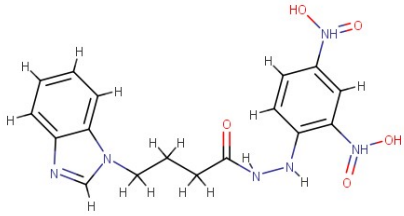
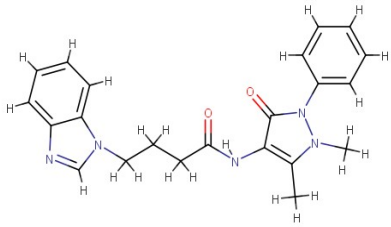
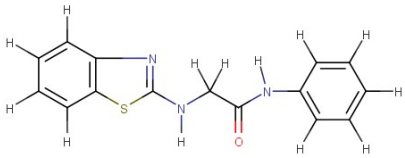
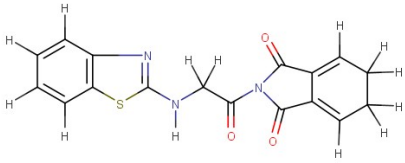
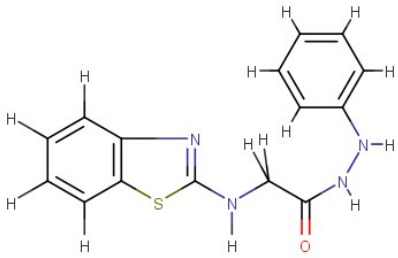
A



B

Figure 1: *Offline chemical structure drawing tools. A) Chemsketch; B) Marvin Tools.*

S. No.	Abbreviation	Chemical Structure	IUPAC Name
1	B1		2-(1H-1,3-benzodiazol-1-yl)-N-phenyl-acetamide
2	B2		2-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-2,3-dihydro-1H-isoindole-1,3-dione
3	B3		2-(1H-1,3-benzodiazol-1-yl)-N'-phenyl-acetohydrazide
4	B4		{2-[2-(1H-1,3-benzodiazol-1-yl)acetohydrazido]-5-(hydroxynitroso)phenyl} azinic acid
5	B5		2-(1H-1,3-benzodiazol-1-yl)-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)acetamide
6	Bb1		4-(1H-1,3-benzodiazol-1-yl)-N-phenyl-butanamide

7	Bb2		2-[4-(1H-1,3-benzodiazol-1-yl)butanoyl]-2,3-dihydro-1H-isoindole-1,3-dione
8	Bb3		4-(1H-1,3-benzodiazol-1-yl)-N'-phenylbutanehydrazide
9	Bb4		{2-[4-(1H-1,3-benzodiazol-1-yl)butanehydrazido]-5-(hydroxynitroso)phenyl} azinic acid
10	Bb5		4-(1H-1,3-benzodiazol-1-yl)-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)butanamide
11	T1		2-[(1,3-benzothiazol-2yl)amino]-N-phenylacetamide
12	T2		2-{2-[(1,3-benzothiazol-2-yl)amino] acetyl}-2,3,5,6-tetrahydro-1H-isoindole-1,3-dione
13	T3		2-[(1,3-benzothiazol-2-yl)amino]-N'-phenylacetohydrazide

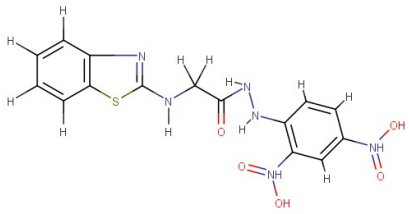
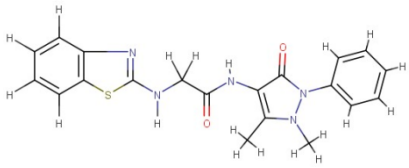
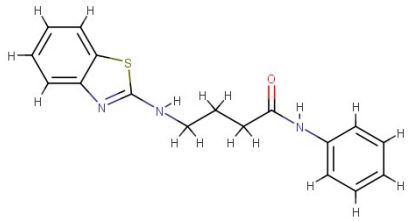
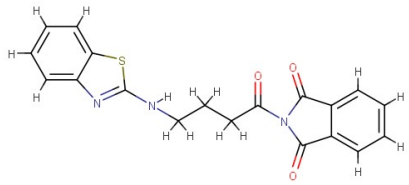
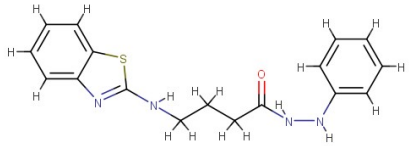
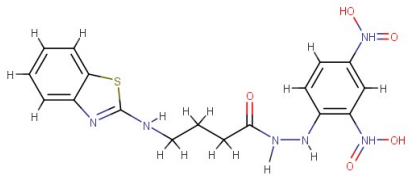
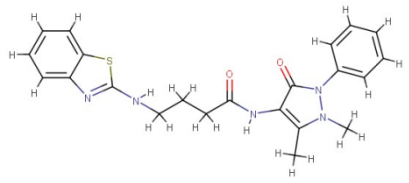
14	T4		(2-{2-[(1,3-benzothiazol-2-yl)amino]acetohydrazido}-5-(hydroxynitroso)phenyl) azinic acid
15	T5		2-[(1,3-benzothiazol-2-yl)amino]-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)acetamide
16	Tt1		4-[(1,3-benzothiazol-2-yl)amino]-N-phenylbutanamide
17	Tt2		2-{4-[(1,3-benzothiazol-2-yl)amino] butanoyl}-2,3-dihydro-1H-isoindole-1,3-dione
18	Tt3		4-[(1,3-benzothiazol-2-yl)amino]-N'-phenylbutanehydrazide
19	Tt4		(2-{4-[(1,3-benzothiazol-2-yl)amino] butanehydrazido}-5-(hydroxynitroso) phenyl)azinic acid
20	Tt5		4-[(1,3-benzothiazol-2-yl)amino]-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)butanamide

Table 1: *List of ligand compound sketched on Marvin tool (Marvin Sketch).*

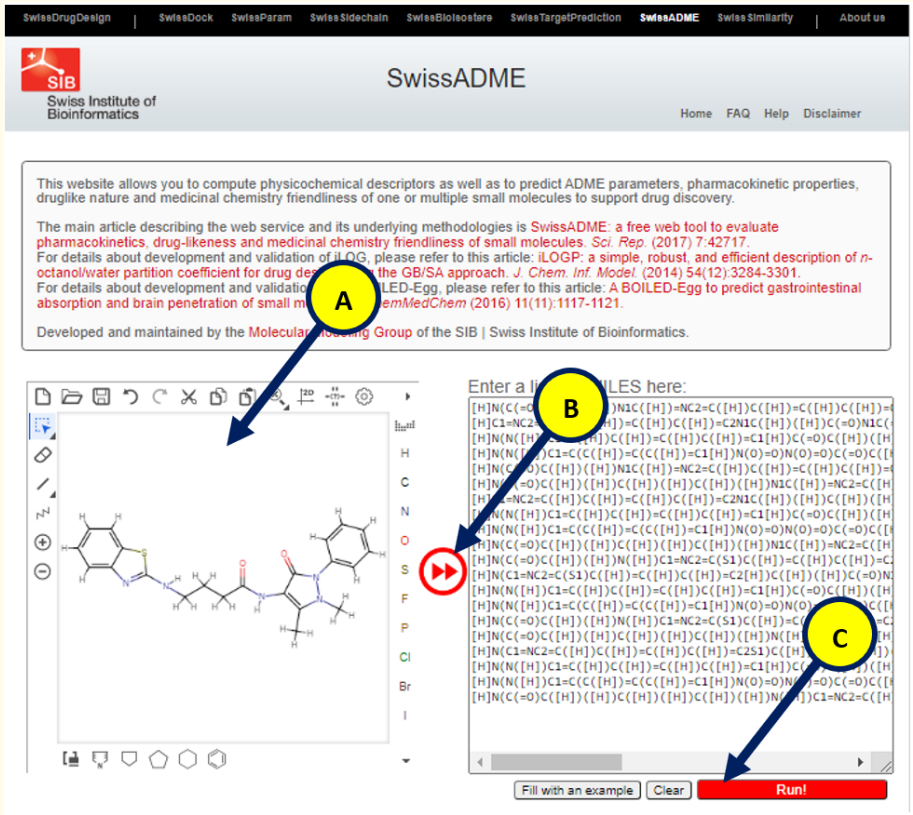


Figure 2: *Online chemical structure drawing tools "SwissADME". Here stepwise procedure is given i.e. A: Drawing tool; B: Transfer sketched structure to the input list of SMILES; C: Run the program.*

Transfer of sketched structure to the input list of SMILES

Because of I draw the all chemical structure on offline platform so imported all the saved structure in ".mol" format one by one and then converted into SMILES after clicking on where arrow "B" (Figure 2) pointed. If drawing was done on same platform where arrow "A" pointed, then there will be no need of save file in any format. After clicking on arrow "B" structure will automatically have converted into SMILES.

Run the SwissADME

After transfer of all the sketched structure to the input list of SMILES then started the running of program by clicking on the arrow marked with "C" pointed on "Run" tab (Figure 2).

After running the SwissADME all parameters like Physicochemical properties, Lipophilicity, Water solubility, Drug likeness, Medicinal chemistry friendliness related to lead compounds were generated (Figure 3).

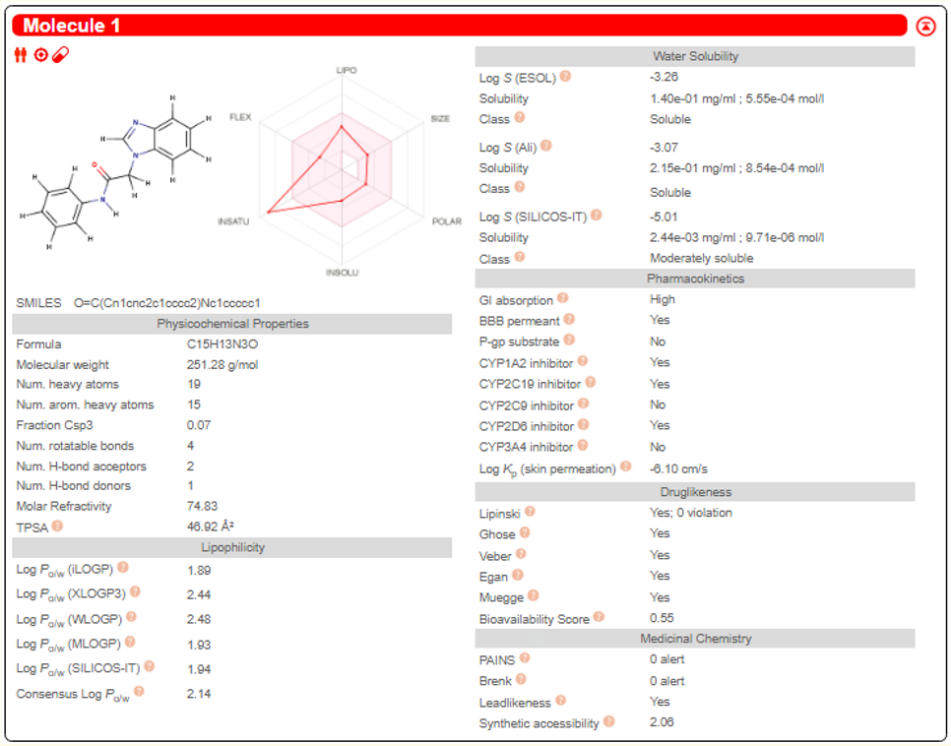
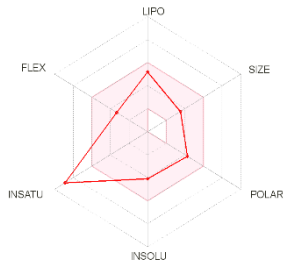
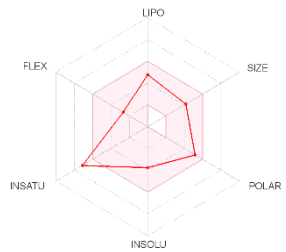
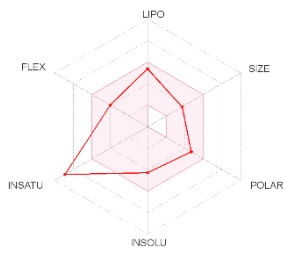
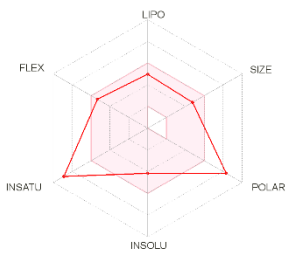
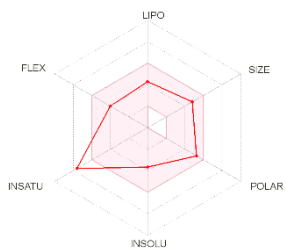
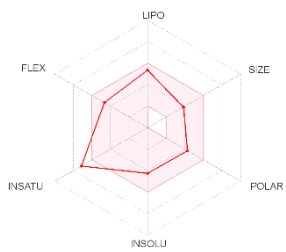


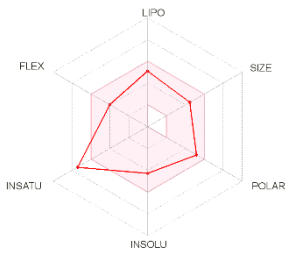
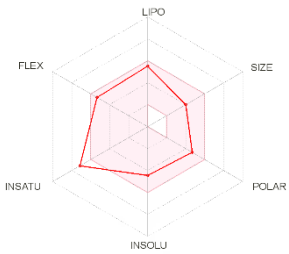
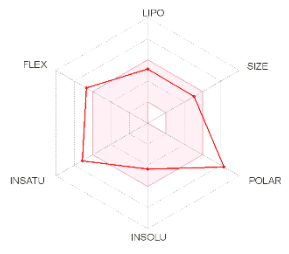
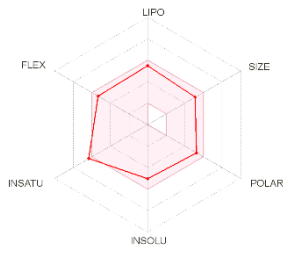
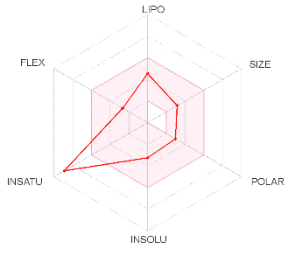
Figure 3: *Various parameters like physicochemical properties, lipophilicity, water solubility, drug likeness, medicinal chemistry friendliness generated after running the SwissADME.*

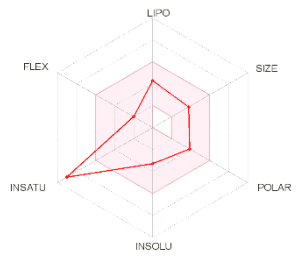
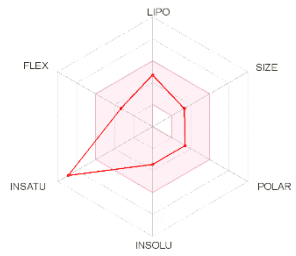
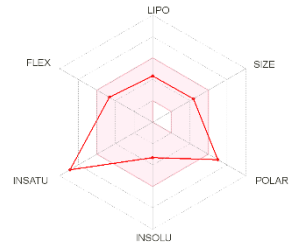
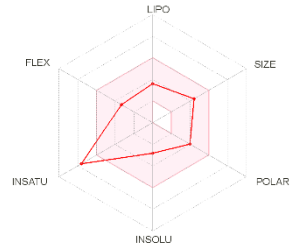
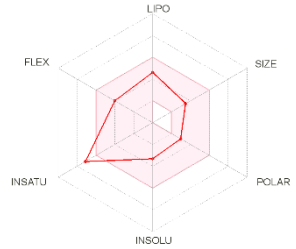
Result and Discussion

After running the SwissADME results were generated on different parameters. Results related with Bioavailability radar are shown below (Table 2).

S. No	Compounds (Ligand)	Bioavailability Radar	Result						Violation In
			Lipo	Size (g/mol)	Polar (Å^2)	Insolu	Insatu	Flex	
1	T1		3.60	283.35	82.26	-4.09	0.07	5	Insatu

2	T2		2.87	339.37	107.61	-3.77	0.18	4	Insatu
3	T3		3.92	298.36	94.29	-4.29	0.07	6	Insatu
4	T4		3.20	390.37	193.61	-4.16	0.07	8	Insatu Polar
5	T5		1.98	393.46	109.19	-3.66	0.15	6	Insatu
6	Tt1		3.86	311.40	82.26	-4.25	0.18	7	Insatu

7	Tt2		3.44	365.41	107.61	-4.30	0.16	6	Insatu
8	Tt3		4.18	326.42	94.29	-4.45	0.18	8	Insatu
9	Tt4		3.46	418.43	193.61	-4.34	0.18	10	Flex Insatu Polar
10	Tt5		4.13	421.52	109.19	-5.02	0.23	8	Insatu
11	B1		2.44	251.28	46.92	3.26	0.07	4	Insatu

12	B2		2.02	305.29	72.27	3.29	0.06	3	Insatu
13	B3		2.76	266.30	58.95	-3.45	0.07	5	Insatu
14	B4		2.04	358.31	158.27	-3.31	0.07	7	Insatu Polar
15	B5		0.82	361.40	73.85	-2.82	0.15	5	Insatu
16	Bb1		2.54	279.34	46.92	-3.30	0.18	6	Insatu

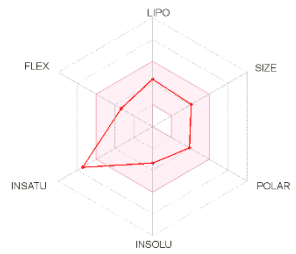
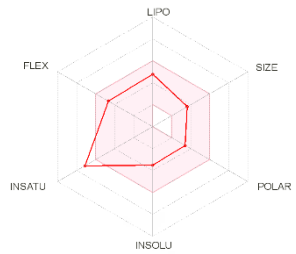
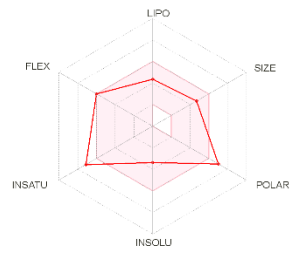
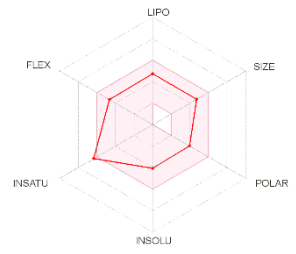
17	Bb2		2.12	333.34	72.27	-3.36	0.16	5	Insatu
18	Bb3		2.85	294.35	58.95	-3.50	0.18	7	Insatu
19	Bb4		2.13	386.36	158.27	-3.38	0.18	9	Insatu Polar
20	Bb5		2.81	389.45	73.85	-4.07	0.23	7	Insatu

Table 2: *The colored zone in Bioavailability Radar is the suitable physicochemical space for oral bioavailability. LIPO (Lipophilicity): -0.7 < XLOGP3 < +5.0; SIZE: 150 g/mol< MV < 500 g/mol; POLAR (Polarity): 20Å²<TPSA < 130 Å²; INSOLU (Insolubility}: 0 < Log S (ESOL) < 6 INSATU (Insaturation): 0.25 < Fraction Csp3 < 1; FLEX (Flexibility): 0 < Num. rotatable bonds < 9.*

After seeing the above table (Table 2) we may consider that out of the 20 lead compounds only Tt5 and Bb5 will be best possible lead compounds suitable for oral bioavailability. However, both lead compound was not qualifying the INSATU (Insaturation) parameter due to small value difference.

Results related to Hide BOILED-Egg are shown below (Figure 4).

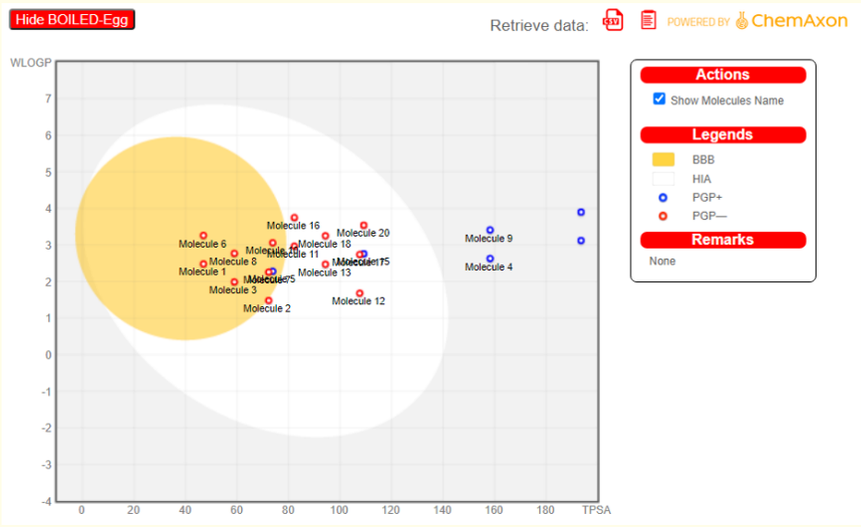


Figure 4: *Hide BOILED-Egg. Provides predictions for human gastrointestinal absorption (HIA) and blood-brain barrier (BBB) permeation of any lead compounds.*

In the above figure (Figure 4) that 7 molecules are present in yellow region (B1, B3, B5, Bb1, Bb2, Bb3, Bb5) predicted to passively permeate through the blood-brain barrier. 9 Molecules that are present in white region (B2, T1, T2, T3, T5, Tt1, Tt2, Tt3, Tt5) predicted to passively absorbed by the gastrointestinal tract. Rest 4 molecules (B4, Bb4, T4, Tt4) are not permeable enough when taken orally. In above figure (Figure 4) lead compound code are converted in molecule number. Here is a table (Table 3) mentioned below which may correlate the molecule number with lead compound code.

S. No.	Molecule Number	Lead Compound Code
1	1	B1
2	2	B2
3	3	B3
4	4	B4
5	5	B5
6	6	Bb1
7	7	Bb2
8	8	Bb3
9	9	Bb4
10	10	Bb5
11	11	T1
12	12	T2
13	13	T3
14	14	T4
15	15	T5
16	16	Tt1
17	17	Tt2
18	18	Tt3
19	19	Tt4
20	20	Tt5

Table 3: *Correlation of molecule number with lead compound.*

Conclusion

By the *insilico* computational ADME study we conclude that out of the 20 lead compounds only Tt5 and Bb5 may best possible lead compounds suitable for oral bioavailability [7-9].

Use of SwissADME enables the access the computation of one or more compound at a time. We can perform study of ADME of lead compound by generating various parameters like Physicochemical properties, Lipophilicity, Water solubility, Drug likeness, Medicinal chemistry friendliness [10,11] with understandable graphical representation in the form of Bioavailability Radar and Hide BOILED-Egg. Bioavailability Radar explains oral bioavailability very easy and quick manner on the other hand Hide BOILED-Egg provides predictions for Human gastrointestinal absorption (HIA) and Blood-brain barrier (BBB) permeation of any lead compounds. SwissADME don't needs heavy budget computer system with more RAM and graphics. Instead all of this online SwissADME tool is easy to use, and moreover this platform providing free of cost service.

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