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Medicinal Properties Of Usnic Acid And Its Analogues – A Swissadme Study

[1]Olimathi A, [1]Akilandeswari Lakshminarayanan* and [2]Kalpana Padmanaban

[1]Department of Chemistry, Sri Sarada College for Women, Salem-636 016, India.

[2]Department of Chemistry, K.L.E. Society's Science and Commerce College, Kalamboli, Navi Mumbai-410 218, India.

ABSTRACT

Usnic acid (UA) and its analogues (UA1 - UA10) have been selected to study and the physicochemical and medicinal properties were analysed using SwissADME web tool. It is inferred that all the studied molecules have no blood brain barrier (BBB) permeation and (except UA9) possess high Gastrointestinal (GI) absorption. The positive nuclear receptor interaction value for each molecule indicates that it plays a part in gene creation, which may have an impact on reproduction and anti-carcinogenic activity.

KEYWORDS: Phytochemical, secondary metabolite, Usnic acid, Medicinal properties and SwissADME

I. INTRODUCTION

More than 4,000 phytochemicals have been cataloged and are classified by protective function, physical characteristics and chemical characteristics. They have biological properties such as antioxidant activity, antimicrobial effect, modulation of detoxification enzymes, stimulation of the immune system, decrease of platelet aggregation and modulation of hormone metabolism and anticancer properties [1-10]. Lichens are symbiotic organisms consisting of a fungus partner and a photosynthetic organism, either an alga or Cyanobacteria. These organisms have historically been used as a cure for human diseases, food, dyes, in the production of alcohol and in the perfume industry [11]. Usnic acid (UA) is a phytochemical and a secondary metabolite isolated predominately from lichen species and has been shown to exhibit antiproliferative properties. However, its application is limited by poor drug-like properties and low specificity. Numerous studies have investigated the various biological activity exhibited by Usnic Acid including antibacterial, antiviral and antiprotozoal activity [12].

Usnic acid is not a carboxylic acid, instead it gets acidity from the phenolic hydroxyl groups. Its pKa is 4.4. In the 1840s, German and Austrian scientists isolated yellow-colored usnic acid from several lichen genera, such as Usnea, from which it derives its name. The bitter-tasting acid exists naturally as its (R) - and (S) -enantiomers as well as the racemate. More than 90 years after it was isolated, usnic acid's structure was elucidated by Frank H. Curd and Alexander Robertson at the University of Liverpool (UK). In a long series of articles, these authors reported the structure and laboratory synthesis of usnic acid and many of its derivatives. Usnic acid is hazardous to health and the environment. Nevertheless, it is an ingredient in some over-the-counter dietary supplements. The Memorial Sloan Kettering Cancer Center, among other reputable organizations, warns against using it. Even with its hazards, usnic acid is being studied for medical applications, especially in cancer research [13]. Several in vitro studies described the anti-inflammatory activity of usnic acid in an attempt to discover the potential mechanism at the cellular level. The published studies involved experiments on leukocytes or platelets isolated from blood, referring to the production of an eicosanoid inflammatory mediator, but also on RAW 264. Macrophages stimulated by LPS, where no or a different cytokine release was measured [14].

In this work, usnic Acid is the lead compound. Its structure is tuned to get its derivatives and their drug properties are studied. The usnic acid and its derivatives are studied computationally using SwissADME software [15,16].

II. METHODOLOGY

SwissADME

SwissADME [15] is a drug development software involving assessment of absorption, distribution, metabolism and excretion (ADME) increasingly earlier in the discovery process. The ADMET properties are extracted by the method shown in Figure 1-3. Drug development involves assessment of ADME increasingly earlier in the discovery process, at a 5 stage when considered compounds are numerous but access to the physical samples is limited. To be effective as a drug, a potent molecule must reach its target in the body in sufficient concentration, and stay there in a bioactive form long enough for the expected biologic events to occur. Drug development involves assessment of absorption, distribution, metabolism and excretion (ADME) increasingly earlier in the discovery process, at a stage when considered compounds are numerous but access to the physical samples is limited. In that context, computer models constitute valid alternatives to experiments. SwissADME web tool gives free access to a pool of fast yet robust predictive models for physicochemical properties, pharmacokinetics, druglikeness and medicinal chemistry friendliness, among which in-house proficient methods such as the BOILED-Egg, iLOGP and Bioavailability Radar. Specialists, but also non-expert in cheminformatics or computational chemistry can predict rapidly key parameters for a collection of molecules to support their drug discovery endeavours [15].

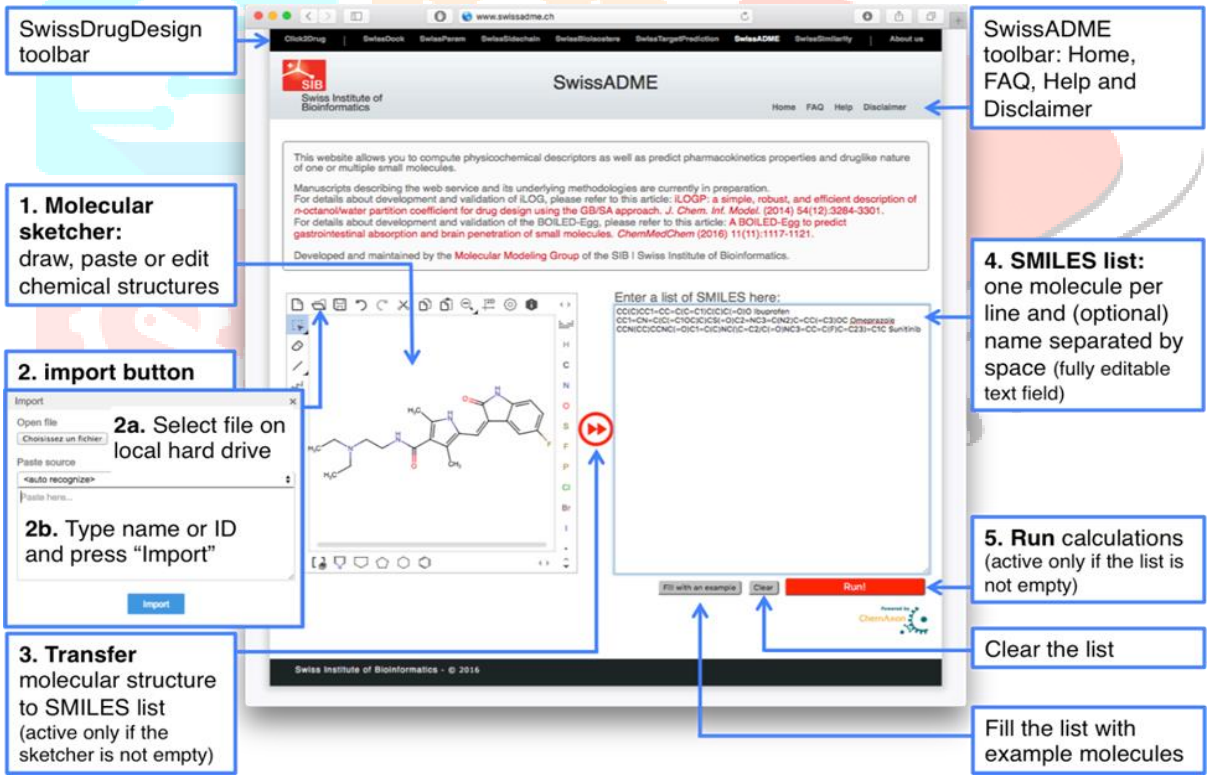


Figure 1. Outline of SwissADME slide to get SMILES of a molecule

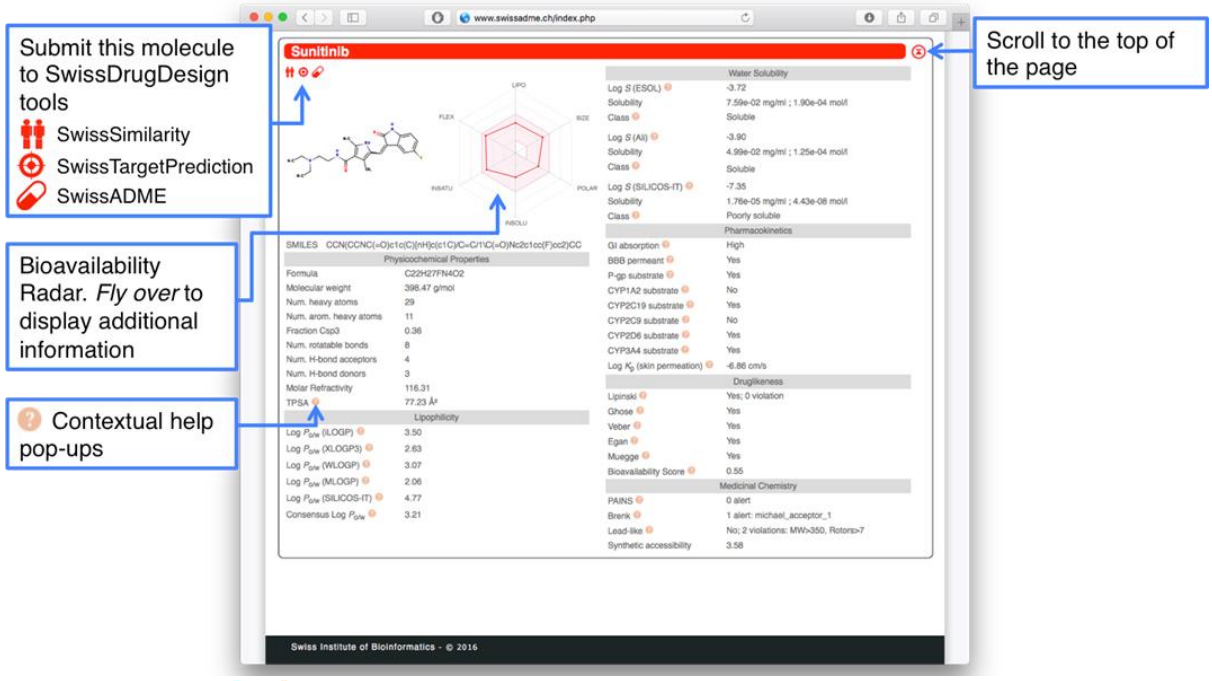


Figure 2. Outline of SwissADME slide to get ADME properties of a molecule

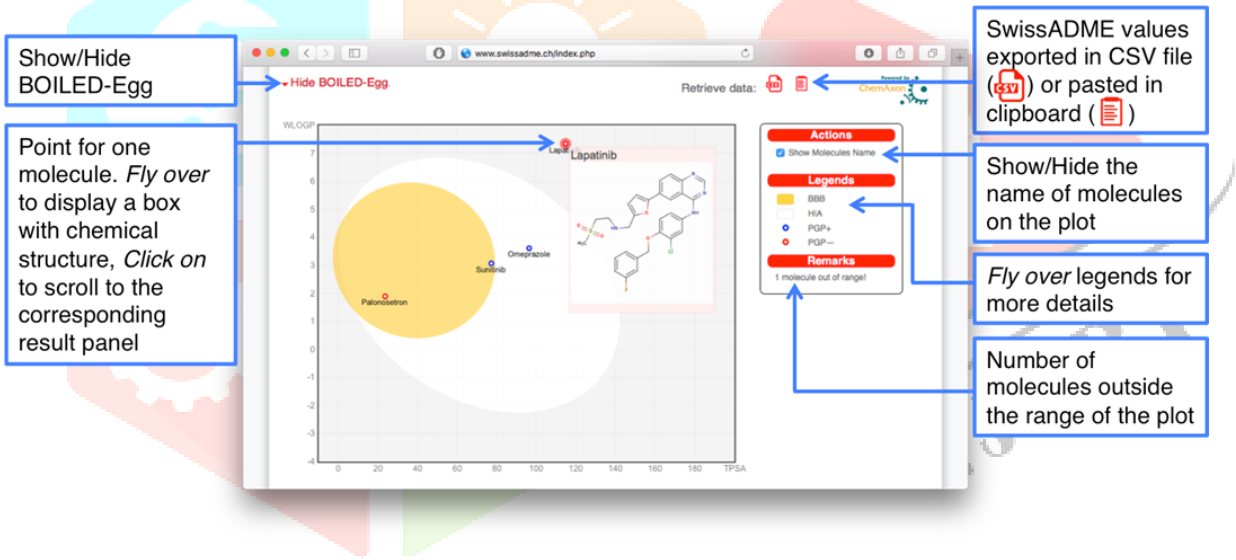


Figure 3. Outline showing the BOILED Egg of a molecule using SwissADME web tool

Some features of swissADME are listed below.

Chemical Structure and Bioavailability Radar

The first section, including two-dimensional chemical structure and canonical SMILES, is located below the title. It shows chemical form for which the predictions were calculated. Moreover, Bioavailability Radar is displayed for a rapid appraisal of drug-likeness. Six physicochemical properties are taken into account: lipophilicity, size, polarity, solubility, flexibility and saturation. A physicochemical range on each axis was defined by descriptors adapted from [15] and depicted as a pink area in which the radar plot of the molecule has to fall entirely to be considered druglike. Leaving the mouse over the radar gives further information about the descriptors [15].

Physicochemical Properties

Simple molecular and physicochemical descriptors like molecular weight (MW), molecular refractivity (MR), count of specific atom types and polar surface area (PSA) are compiled in this section. The values are computed with OpenBabel. The PSA is calculated using the fragmental technique called

topological polar surface area (TPSA), considering sulfur and phosphorus as polar atoms. This has proven a useful descriptor in many models and rules to quickly estimate some ADME 6 properties, especially with regards to biological barrier crossing such as absorption and brain access [15].

Lipophilicity

The partition coefficient between n-octanol and water (log Po/w) is the classical descriptor for Lipophilicity. It has a dedicated section in SwissADME due to the critical importance of this physicochemical property for pharmacokinetics drug discovery. Many computational methods for log Po/w estimation were developed with diverse performance on various chemical sets. Common practice is to use multiple predictors either to select the most accurate methods for a given chemical series or to generate consensus estimation [15].

Water Solubility

Having a soluble molecule greatly facilitates many drug development activities, primarily the ease of handling and formulation. Moreover, for drug discovery projects targeting oral administration, solubility is one major property influencing absorption. As well, a 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 Swiss ADME [15].

Pharmacokinetics

Specialized models, whose predictions are compiled in the Pharmacokinetics section, evaluate individual ADME behaviours of the molecule under investigation. One model is a multiple linear regression, which aims at predicting the skin permeability coefficient (Kp). It is adapted from Potts and Guy, who found Kp linearly correlated with molecular size and lipophilicity (R2 = 0.67). The more negative the log Kp (with Kp in cm/s), the less skin permeate is the molecule. The predictions for passive human gastrointestinal absorption (HIA) and blood-brain barrier (BBB) permeation both consist in the readout of the BOILED-Egg model, an intuitive graphical classification model, which can be displayed in the Swiss ADME result page by clicking the red button appearing below the sketcher when all input molecules have been processed (refer to Graphical Output). Other binary 7 classification models are included, which focus on the propensity for a given small molecule to be substrate or inhibitor of proteins governing important pharmacokinetic behaviours [15].

Drug-likeness

Drug-likeness assesses qualitatively the chance for a molecule to become an oral drug with respect to bioavailability. Drug-likeness was established 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. Swiss ADME gives access to five different rule-based filters, with diverse ranges of properties inside of which the molecule is defined as drug-like [15].

Boiled egg model

Apart from effectiveness and toxicity, poor pharmacokinetics and bioavailability are blamed for multiple drug discovery failures. Two pharmacokinetic activities important for estimating at different stages of the drug development process are gastrointestinal absorption and brain access. To this end, as an effective predictive model that operates by measuring the lipophilicity and polarity of small molecules, the Brain or IntestinaL EstimateD permeation system (BOILED egg) is proposed. Due to the speed, accuracy, conceptual simplicity and consistent graphical performance of the model, concomitant predictions for both brain and intestinal permeation are derived from the same two physicochemical descriptors and directly converted through molecular architecture. From the filtering of chemical libraries at the early stages of drug research to the assessment of drug candidates for growth, BOILED Egg can be used in a number of settings [15].

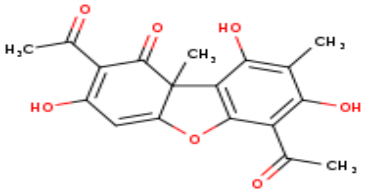
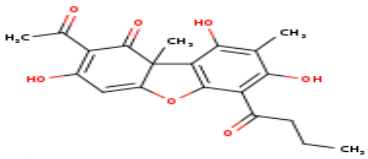
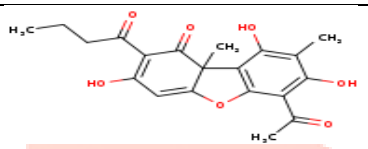
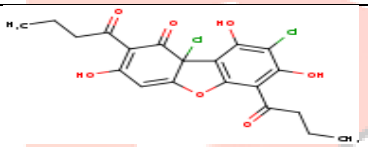
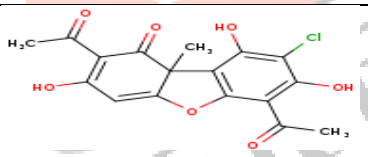
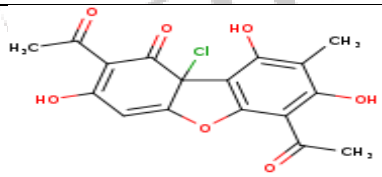
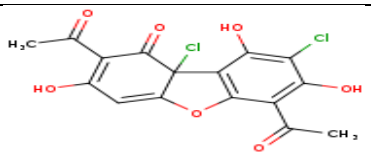
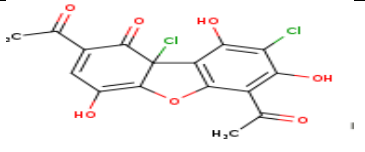
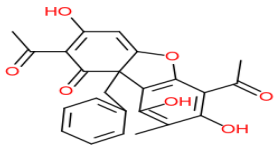
Lipinski's rule:

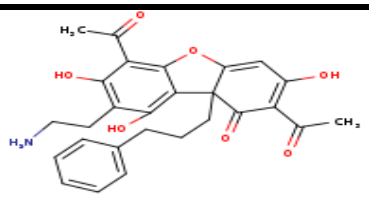
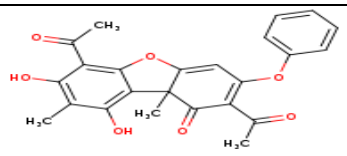
- A molecular weight less than 500.
- No more than 5 hydrogen bond donor (HBD) groups.
- No more than 10 hydrogen bond acceptor (HBA) groups.
- Log P value less than +5.
- TPSA less than 140.

III. RESULTS AND DISCUSSION

The molecule chosen (Table 1.) for virtual screening and drug action studies are lichen class of phytochemical viz. UA-UA10 which have been analyzed for various QSAR descriptors using SwissADME software.

Table 1. The selected molecules for virtual sceerning by SwissADME web tool

S. No.	IUPAC name	Structure	Label
1.	4,10-diacetyl-5,11,13-trihydroxy-2,12-dimethyl-8-oxatricyclo[7.4.0.0^{2,7}]trideca-1(9),4,6,10,12-pentaen-3-one (**Usnic acid**)		UA
2.	4-acetyl-10-butanoyl-5,11,13-trihydroxy-2,12-dimethyl-8-oxatricyclo[7.4.0.0^{2,7}]trideca-1(9),4,6,10,12-pentaen-3-one		UA1
3.	10-acetyl-4-butanoyl-5,11,13-trihydroxy-2,12-dimethyl-8-oxatricyclo[7.4.0.0^{2,7}]trideca-1(9),4,6,10,12-pentaen-3-one		UA2
4.	4,10-dibutanoyl-2,12-dichloro-5,11,13-trihydroxy-8-oxatricyclo[7.4.0.0^{2,7}]trideca-1(9),4,6,10,12-pentaen-3-one		UA3
5.	4,10-diacetyl-12-chloro-5,11,13-trihydroxy-2-methyl-8-oxatricyclo[7.4.0.0^{2,7}]trideca-1(9),4,6,10,12-pentaen-3-one		UA4
6.	4,10-diacetyl-2-chloro-5,11,13-trihydroxy-12-methyl-8-oxatricyclo[7.4.0.0^{2,7}]trideca-1(9),4,6,10,12-pentaen-3-one		UA5
7.	4,10-diacetyl-2,12-dichloro-5,11,13-trihydroxy-8-oxatricyclo[7.4.0.0^{2,7}]trideca-1(9),4,6,10,12-pentaen-3-one		UA6
8.	4,10-diacetyl-2,12-dichloro-6,11,13-trihydroxy-8-oxatricyclo[7.4.0.0^{2,7}]trideca-1(9),4,6,10,12-pentaen-3-one		UA7
9.	4,10-diacetyl-2-benzyl-5,11,13-trihydroxy-12-methyl-8-oxatricyclo[7.4.0.0^{2,7}]trideca-1(9),4,6,10,12-pentaen-3-one		UA8

10.	4,10-diacetyl-12-(2-aminoethyl)-5,11,13-trihydroxy-2-(3-phenylpropyl)-8-oxatricyclo[7.4.0.0^{2,7}]trideca-1(9),4,6,10,12-pentaen-3-one		UA9
11.	4,10-diacetyl-11,13-dihydroxy-2,12-dimethyl-5-phenoxy-8-oxatricyclo[7.4.0.0^{2,7}]trideca-1(13),4,6,9,11-pentaen-3-one		UA10

The following parameters have been calculated by submitting the structure of the query compounds in the free web based SwissADME software portal - Bioavailability radar, list of physiochemical properties. (Molecular refractive, total polar surface area Number of hydrogen bond acceptor, Number of hydrogen bond donor, etc.) Liphophlicity indices, Solubility indices, Pharmacokinetics properties, Drug likeness indices, and boiled egg analysis. The data generated for the query molecule, Usnic acid and its derivatives are presented in the Tables 2 - 6 and Figures 1 - 4.

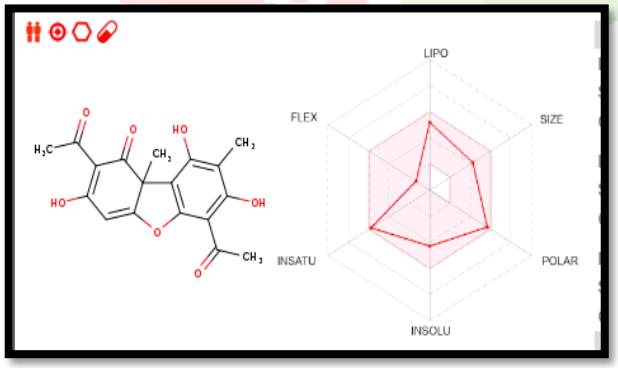
Bioavailability radar of usnic acid and its derivatives

Bioavailability Radar is a tool that predicts the druglikeness of the molecules easily. In the figures below, the Bioavailability Radar of Usnic acid and its derivatives are presented. This pictures the parameters namely lipophilicity, size, molarity, solubility, saturation and flexibility.

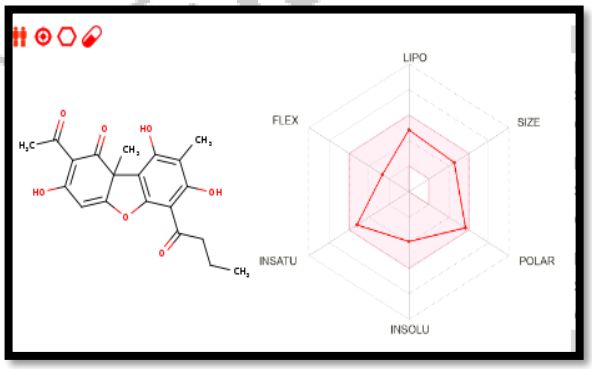
The pink area represents the optimal range for each property (lipophilicity: XLOGP3 between − 0.7 and + 5.0, size: MW between 150 and 500 g/mol, polarity: TPSA between 20 and 130 Å 2, solubility: log S not higher than 6, saturation: fraction of carbons in the sp3 hybridization not less than 0.25, and flexibility: no more than 9 rotatable bonds. In this example, the compound is predicted not orally bioavailable, because too flexible and too polar.

All the drug molecules have the parameters in the pink area showing that they may be bioavailable to act as drugs. UA6, UA7, UA8 and UA7 have less saturation and UA9 has poor polarizability.

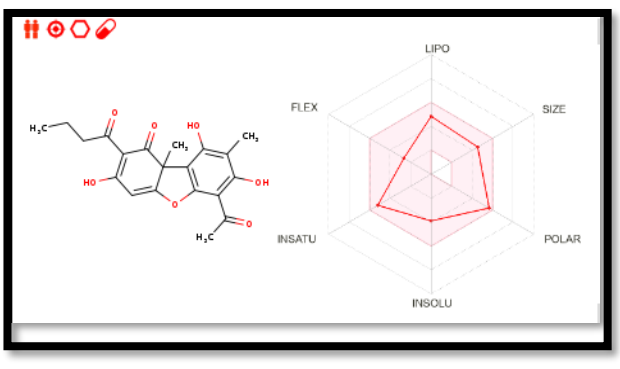
Table 2. Bioavailability radar of UA and UA1-UA10 from SwissADME

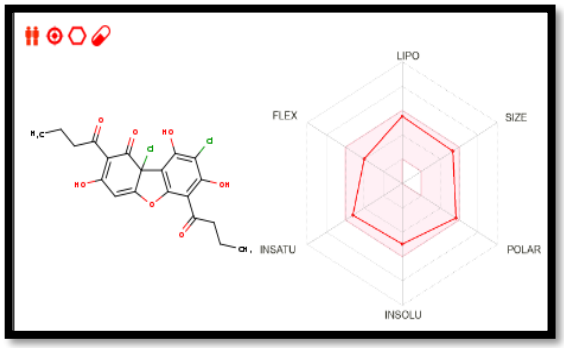


Bioavailability radar of UA



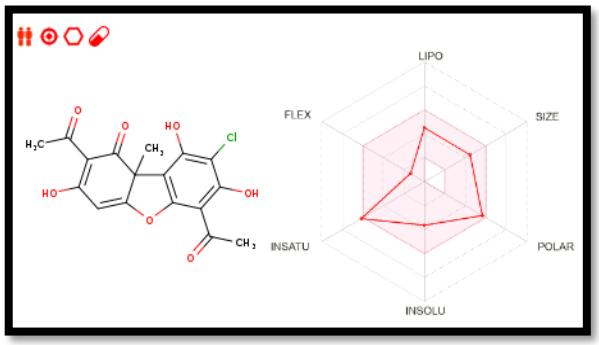
Bioavailability radar of UA1



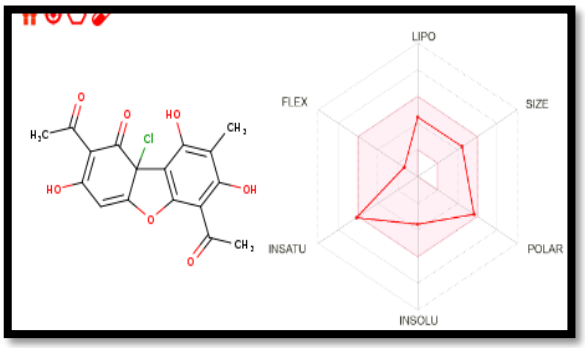


Bioavailability radar of UA3

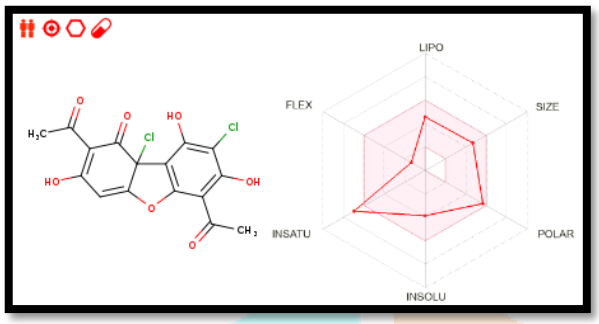
Bioavailability radar of UA2



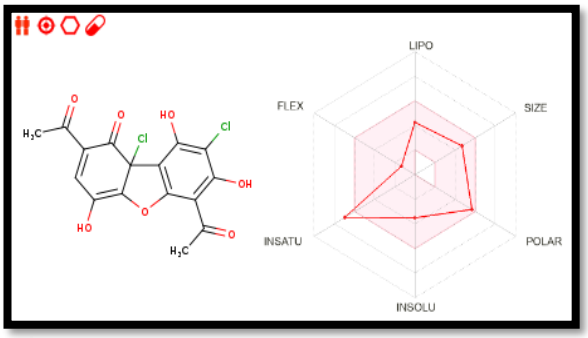
Bioavailability radar of UA4



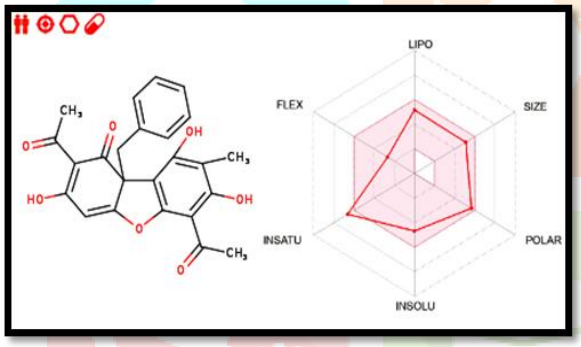
Bioavailability radar of UA5



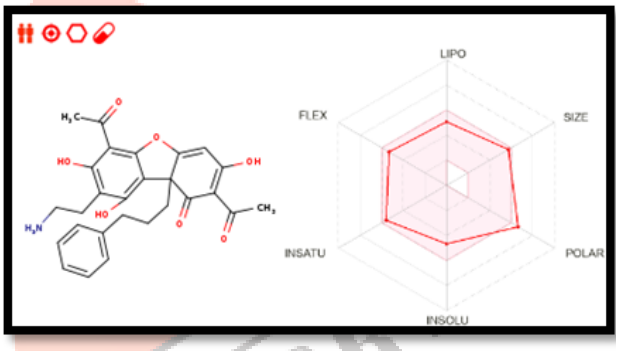
Bioavailability radar of UA6



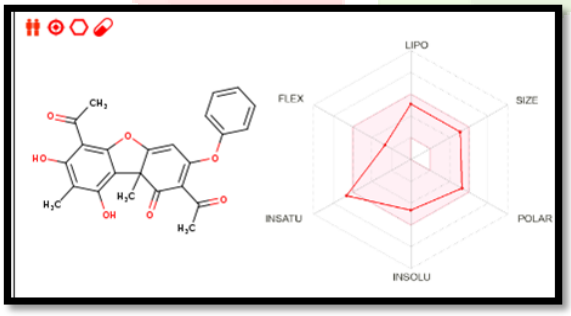
Bioavailability radar of UA7



Bioavailability radar of UA8

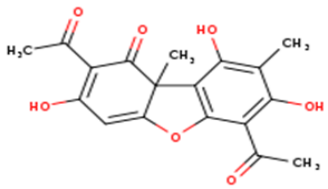
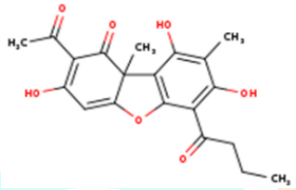
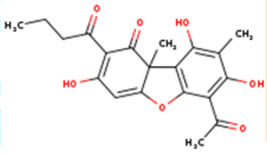
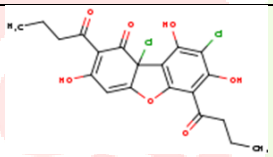
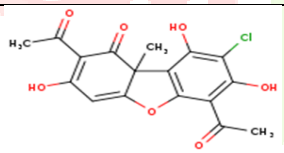
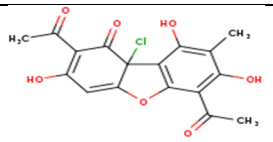
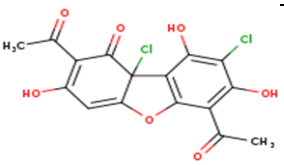


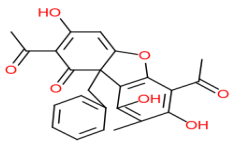
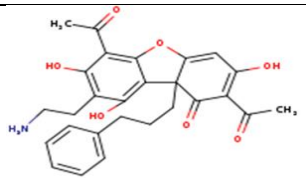
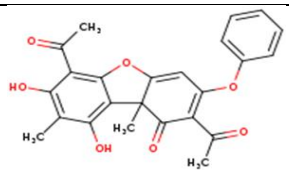
Bioavailability radar of UA9



Bioavailability radar of UA10

Table 3. Physicochemical properties from SwissADME

Name	Structure	MW	Heavy atoms	Aromatic heavy atoms	Fraction Csp3	Rotatable bonds	H- bond acceptors	H- bond donor	MR	TPSA
UA	 $C_{18}H_{16}O_7$	344.32	25	6	0.28	2	7	3	87.43	121.13
UA1	 $C_{20}H_{20}O_7$	372.37	27	6	0.35	4	7	3	97.05	121.13
UA2	 $C_{21}H_{22}O_7$	386.4	28	6	0.38	5	7	3	101.86	121.13
UA3	 $C_{20}H_{18}Cl_2O_7$	441.26	29	6	0.35	6	7	3	106.7	121.13
UA4	 $C_{17}H_{13}ClO_7$	364.73	25	6	0.24	2	7	3	87.48	121.13
UA5	 $C_{17}H_{13}ClO_7$	364.73	25	6	0.24	2	7	3	87.42	121.13
UA6	 $C_{16}H_{10}Cl_2O_7$	385.15	25	6	0.19	2	7	3	87.47	121.13
UA7	 $C_{16}H_{10}Cl_2O_7$	385.15	25	6	0.19	2	7	3	87.47	121.13

UA8	 $C_{24}H_{20}O_7$	420.41	31	12	0.21	4	7	3	111.92	121.13
UA9	 $C_{27}H_{27}NO_7$	477.51	35	12	0.3	8	8	4	129.05	147.15
UA10	 $C_{24}H_{20}O_7$	420.41	31	12	0.21	4	7	2	111.88	110.13

From the table 4a, one can see the constituent descriptors which includes Molecular Formula, Molecular weight, number of rotatable bonds, aromatic heavy atoms, Fraction Csp3, number of hydrogen bond acceptor, Number of hydrogen bond donor, molar refractivity and Total Surface Polar Area (TPSA). Among these, Fraction of Csp3 is a key factor for drug-likeness.

In order for molecule to act as drug, it is studied that increased saturation measured by Fraction Csp3 increases the clinical success rate. Generally, it is accepted that Fraction Csp3 should be greater than or equal to 0.5 for any drug molecule. This Fraction Csp3 descriptor act as drug screening indicator.

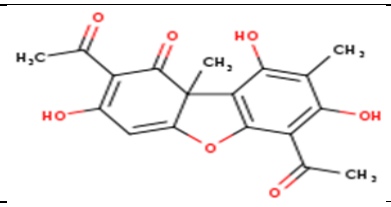
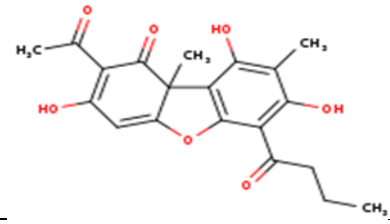
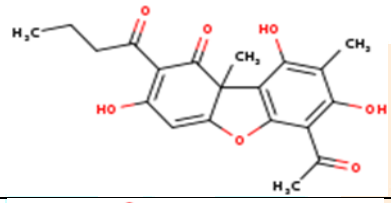
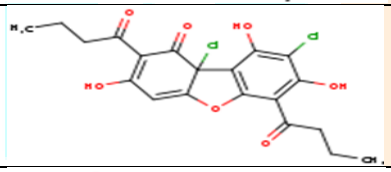
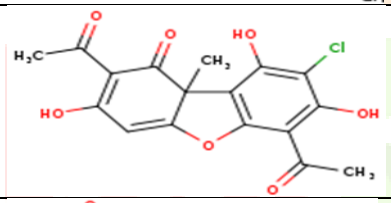
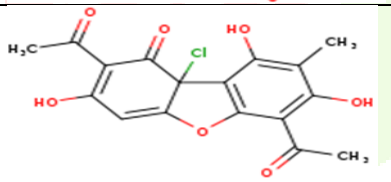
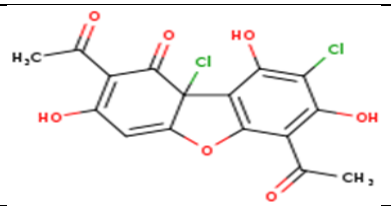
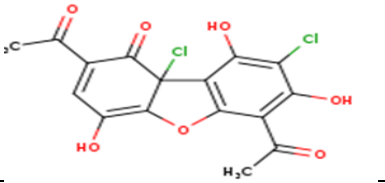
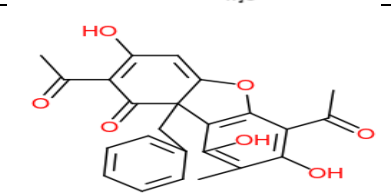
When the number of rotatable bonds is a measure of molecular flexibility and important in determining the oral Bioavailability. Generally, number of rotatable bonds are in the range 1 to 10. Here, all the molecules have the number of rotatable bonds ranging between 2 and 8.

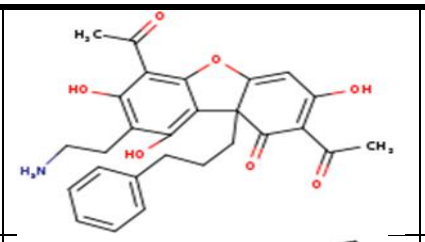
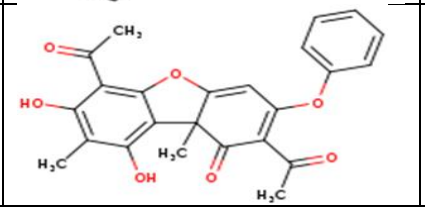
Hydrogen bond donor and hydrogen bond acceptor are important criteria for drug interactions. Generally, the molecules should have the number of hydrogen bond acceptor less than 10 and number of hydrogen bond donor less than 5 to act as drugs.

Here all the molecules have the number of HBA less than 10 and number of HBD less than 5.

Molar refractivity (MR) is a molecular descriptor that contains information on the compound's volume corrected by the refractive index (the ratio of the velocity of light in a vacuum to the velocity of light in the substance of interest). Generally, according to Lipinski rule of five, for a molecule to act as drug, it should have the value of molar refractivity in the range 40 to 130. Here, all the molecules under study satisfy the Lipinski rule. Therefore, they can act as drugs.

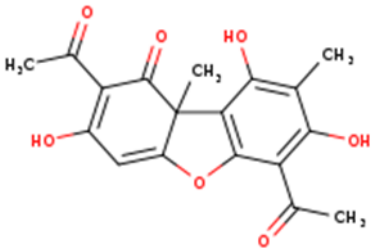
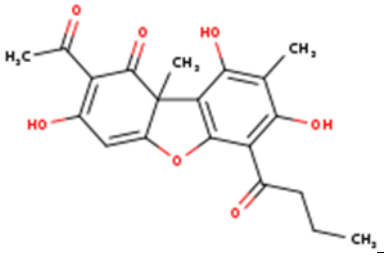
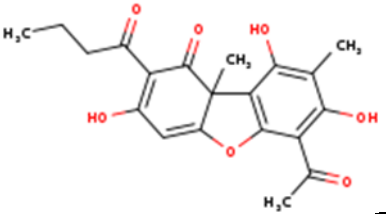
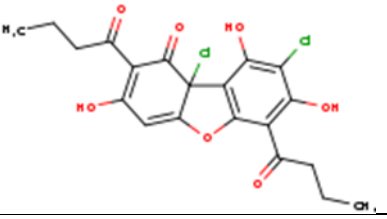
Table 4. Lipophilicity indices from SwissADME

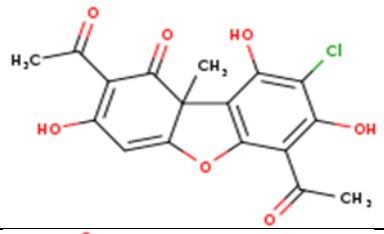
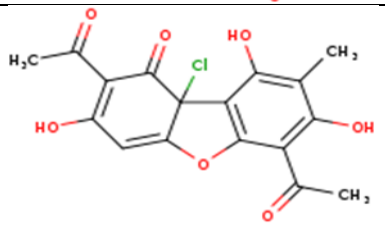
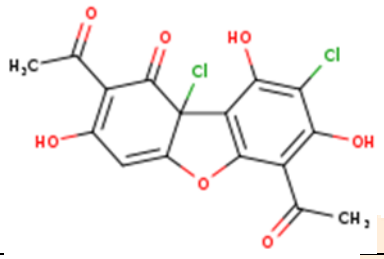
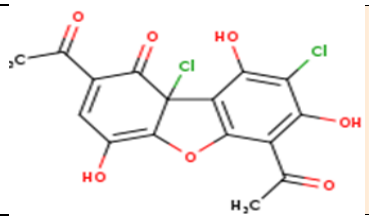
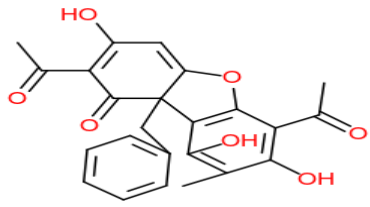
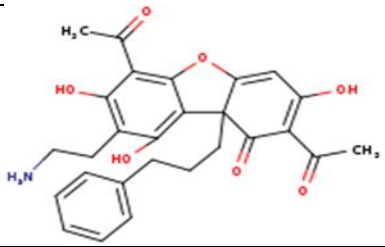
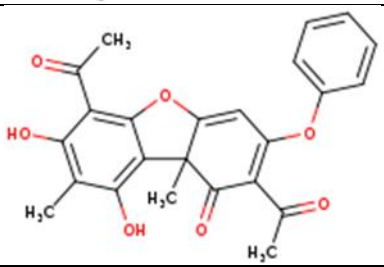
Name	STRUCTURE	iLOGP	XLOGP3	WLOGP	MLOGP	Silicos-IT Log P	Consensus Log P
UA		1.66	3.58	2.13	-0.52	2.59	1.89
UA1		2.75	2.94	2.91	-0.06	3.39	2.39
UA2		2.96	3.41	3.3	0.16	3.8	2.73
UA3		2.35	4.18	4.1	0.65	4.45	3.15
UA4		1.33	2.37	2.47	-0.25	2.72	1.73
UA5		1.74	2.26	2.19	-0.52	2.72	1.68
UA6		0.82	2.53	2.54	-0.25	2.86	1.7
UA7		1.32	1.97	2.54	-0.25	2.86	1.69
UA8		2.39	3.53	3.35	0.59	4.09	2.79

UA9		3.2	3.38	3.32	0.41	4.47	2.96
UA10		3.31	3.44	3.65	0.85	4.24	3.1

From the Table 4, it is seen that the molecules UA1, UA2, UA3, UA8, UA9 and UA10 are having Log P value greater than 2 which indicates that these molecules can't enter CNS.

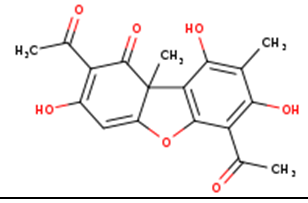
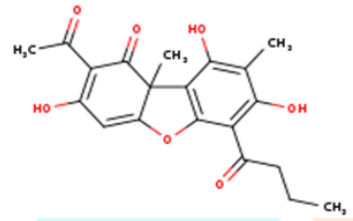
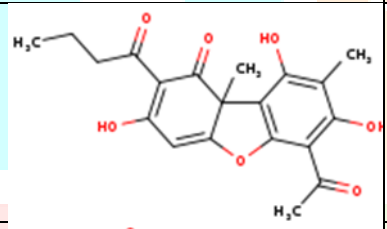
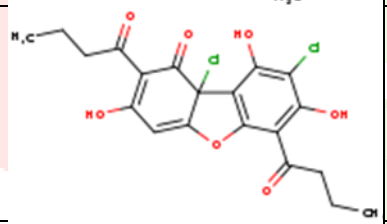
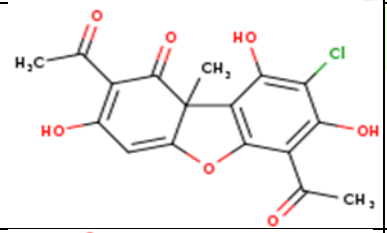
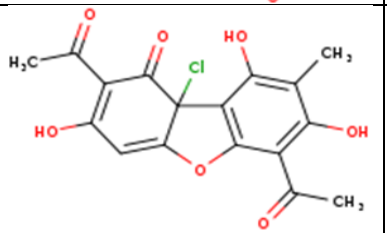
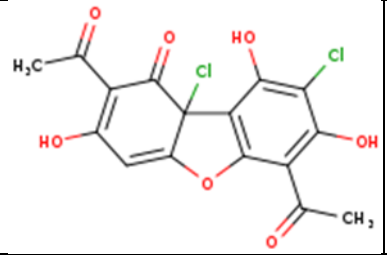
Table 5. Pharmacokinetics from SwissADME

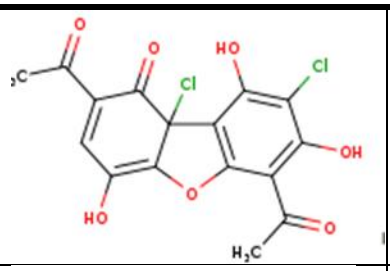
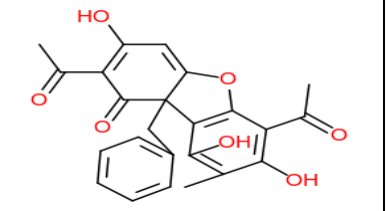
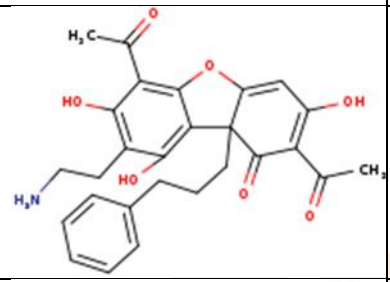
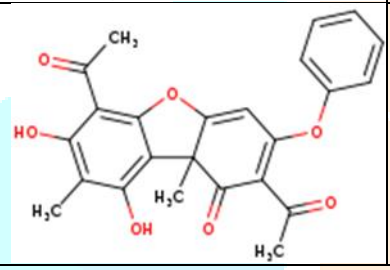
Name	Structure	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	log Kp (cm/s)
UA		High	No	No	Yes	No	Yes	No	Yes	-5.86
UA1		High	No	Yes	Yes	No	Yes	No	Yes	-6.48
UA2		High	No	Yes	Yes	No	Yes	No	Yes	-6.24
UA3		High	No	Yes	Yes	No	Yes	No	Yes	-6.02

UA 4		High	No	No	Yes	No	Yes	No	Yes	-6.84
UA5		High	No	No	Yes	No	Yes	No	Yes	-6.92
UA6		High	No	No	Yes	No	Yes	No	Yes	-6.85
UA7		High	No	No	Yes	No	Yes	No	Yes	-7.25
UA8		High	No	No	No	No	Yes	No	Yes	-6.36
UA9		Low	No	Yes	No	No	Yes	No	Yes	-6.81
UA10		High	No	No	Yes	No	Yes	No	Yes	-6.42

All the molecules except UA9 have high GI absorption which shows that they can be used as oral drug. All the molecules don't have BBB permeation. Therefore, they can't be used for brain related diseases. The drug interactions for some Cytochrome P450 enzymes are also presented in the table. UA can be act as an inhibitor for CYP2C9, CYP2C9 and CYP1A2. All the molecules can act as inhibitors for CYP2C9 and CYP3A4. UA1, UA2, UA3, UA4, UA5, UA6, UA7 and UA10 can act as inhibitors for CYP1A2 enzyme.

Table 6. Drug likeness from SwissADME

Name	Structure	Lipinski #violations	Ghose #violations	Veber #violations	Egan #violations	Muegge #violations	Bioavailability Score	PAINS #alerts	Brenk #alerts	Leadlikeness #violations
UA		0	0	0	0	0	0.56	0	1	1
UA1		0	0	0	0	0	0.56	0	1	1
UA2		0	0	0	0	0	0.56	0	1	1
UA3		0	0	0	0	0	0.56	0	2	2
UA4		0	0	0	0	0	0.56	0	1	1
UA5		0	0	0	0	0	0.56	0	2	1
UA6		0	0	0	0	0	0.56	0	2	1

UA7		0	0	0	0	0	0.55	0	2	1
UA8		0	0	0	0	0	0.56	0	1	2
UA9		0	0	1	1	0	0.56	0	1	2
UA10		0	0	0	0	0	0.56	0	1	1

All the molecules obey all the rules given in the table indicates that they can act as drugs.

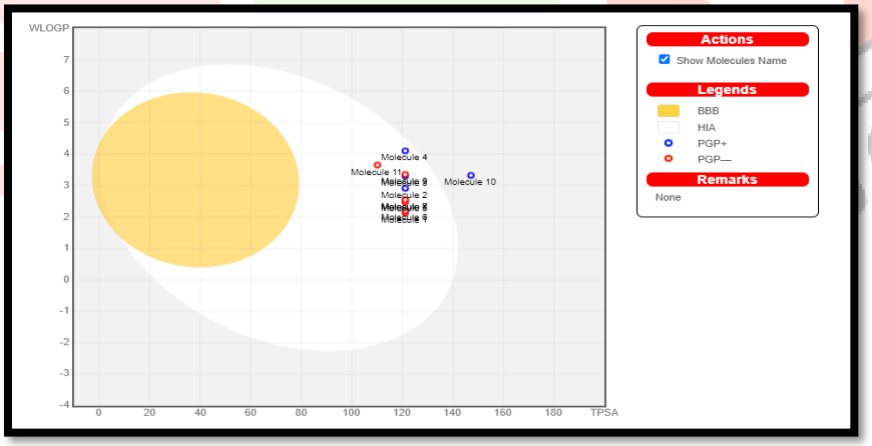


Figure 4. Boiled egg model for molecule under study

Boiled egg predicts the penetration of the drug through gastro intestinal (HIA) wall and blood brain barrier (BBB). It is very useful for statistical method in drug designing. The white region (Figure 4.) shows the probability of passive absorption in the GI tract and yellow is the brain penetration. All the molecules are in the white portion indicates that they have high intestinal absorption. Only one molecule is out of the boiled egg which indicates its poor drug nature.

IV. CONCLUSION

The software predicts that all the molecules except UA9 have high GI absorption which shows that they can be used as oral drug. All the molecules don't have BBB permeation. For the molecules UA1, UA2, UA3, UA8, UA9 and UA10 are having Log P value greater than 2 which indicates that these molecules can't enter CNS. Except UA6 and UA7, remaining molecules show effective binding for the enzyme kinase that catalyzes the transfer of phosphate groups from high-energy, phosphate-donating molecules to specific substrates. UA6 has high binding percentage for the enzyme nuclear receptor which directly regulate

transcription of genes that control a wide variety of biological processes, including cell proliferation, development, metabolism, and reproduction. UA7 has high binding percentage for the enzymes secreted protein and nuclear receptor. For the molecules under study, the values of solubility are in the range -4.85 to – 2.88 which is greater than -6 shows that all the molecules have good drug dissolution. All the molecules have the positive value for nuclear receptor interaction which suggests that the molecule place a role in gene formation which may have its effect in reproduction and anti-carcinogenic activity.

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