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Insilico Admet Predictions of Dihydropyrimidinones using Swiss Adme, Pkcsm, Lazar and Protox.

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Abstract

Drug development and discovery failures are attributed to poor pharmacokinetics, bioavailability, efficacy and toxicity. By monitoring the physicochemical properties of lead compounds, it has become feasible to increase the quality of drug candidates. Toxicity determination of chemicals is crucial to identify their deleterious effects on humans, Animals, plants and the environment. Numerous Insilico models are thus developed for the prediction of Absorption, Distribution, Metabolism, Excretion (ADME) properties at the early stages of drug discovery to decrease the fraction of global pharmacokinetics related failures in the later phases of drug development. Dihyropyrimidinone derivatives possess a broad spectrum of biological activities like Antibacterial, Antifungal, Antiviral, Anticancer Antihypertensive activities. The objective of this study is to predict Pharmacokinetic, drug likeness properties and toxicity of Dihydropyrimidinone derivatives by using Swiss adme, PKCSM, Lazar and Pro toxsoftware's. All the compounds followed the Lipinski 'Rule of five' and showing good oral bioavailability. All the compounds were non-toxic except for Compound F6 which showed hepatotoxicity and reproductive toxicity.

Keywords: Dihydropyrimidinone derivatives; adme; Swiss ADME; PkCSM; Lazar; Protox

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Introduction

The drug discovery and development has seen a paradigm shift from traditional drug design to computer aided drug design (CADD) to efficiently predict the biological activity. As a consequence the insilico methods serve as an effective strategy in accelerating and encouraging drug discovery and development process. CADD is applied to nearly every stage of drug discovery from target identification, lead discovery to optimization tools.[1] Terminated projects when investigated revealed unsatisfactory Pharmacokinetic profiles and ADMET properties central to the drug failure. In Silico screening approaches help to reduce the risks of these failures. Computational algorithms can be used to assess the Pharmacokinetic activity and assist in organizing, analyzing, modeling, simulating, visualizing or predicting the chemical toxicity. Insilico toxicity prediction is undertaken prior to in-vitro and in-vivo testing to minimize time and cost. Such in silico tests include Swiss ADME, PKCSM, Lazar, Protox. Swiss ADME web tool gives free access to a pool of fast and predictive models for physicochemical properties, pharmacokinetics, drug-likeness and medicinal chemistry friendliness, among which in house proficient methods are the BOILED Egg, iLOGP and bioavailability radar.[2-4] The ADMET Predictor uses integrated sequences to analyze and examines the crucial role of the molecular structure of a compound

in its absorption, distribution, metabolism and excretion[5] Pkcsm is a freely accessible web server which provides an integrated platform to rapidly evaluate pharmacokinetic and toxicity properties. It uses graph-based signatures to develop predictive models of central ADMET properties for drug development.[6] Lazar is a web tool to predict the toxic of chemical structures; lazar creates local QSAR models for each compound to be predicted. The performance of the lazar software model in the external validation dataset has an accuracy of 86% and a sensitivity of 78% in the carcinogenicity test, with 95% accuracy for the mutagenic test.[7] Protox is a web server that incorporates molecular similarity, pharmacophores, fragment propensities and machine-learning models for the prediction of various toxicity end points, such as acute toxicity, hepatotoxicity, immunotoxicity, adverse outcomes pathways and toxicity targets.[8]

Dihydropyrimidinones are an important class of organic compounds. Owing to the presence of the pyrimidine ring, these compounds are involved in possessing biological activity against bacteria and fungi and viruses. Additionally they show Anticancer Antihypertensive activities.[9] We selected these dihydropyrimidinone derivatives as no previous works were reported on their pharmacokinetic and physicochemical parameters. Therefore, this study aims to minimize the time limitations, financial burden and ethical considerations of in vivo animal studies and thus predict the toxicity of Dihydropyrimidinone derivatives. The results will assist in the selection of dihydropyrimidinone derivatives with high activity, but low toxicity before the commencement of in vivo toxicity testing through preclinical testing.

This study aids the discovery of new dihydropyrimidinone derivatives with minimal toxicity and enhanced biological activity.

Equipment and materials: The hardware used in this study was a PC with x 64-based with 4 gigabytes and Windows 10 pro-F3F9TVII operating system. The software used were, chemsketch (https://www.acdlabs.com/resources/freeware/chem sketch/download.php),

Swissadme (http://www.swissadme.ch/index.php), pkCSM (http://biosig.unimelb.edu.au/pkcsm/predict ion), lazar (https://lazar.in-silico.de/predict) and protox (http://tox.charite.de/protox_II/index.php?site=com pound_input).

Experimental procedure: The planned derivatives are generated in two-dimensional form by using chemsketch application (indicated in Table 1). ADMET properties of Dihydropyrimidinone derivatives were calculated using swissadme, pkcsm, protox and Lazar softwares. All smiles were generated and the brain or intestinal estimated permeation method (Boiled Egg) was carried out to get an accurate predictive model that works by computing the lipophilicity and polarity of small molecules.

Results and Discussions

ADMET properties of Dihydropyrimidinone derivatives were calculated using Swiss adme, pkcsm, protox and Lazar softwares to determine whether the compounds obey Lipinski's Rule of five and toxicity. The results of the predictions were presented in tables given below.

The predictions were in the form of quantitative and qualitative data. As shown in Fig. 1 and 2: Dihydropyrimidinone derivatives F1, F2, F5, F12, F15, F17, F18, F19, F20, F22, F23, F24 are in the yellow region, which is the physicochemical space of molecules with highest probability to penetrate the brain. The remaining dihydropyrimidinone derivatives are housed in the white region which showing highest probability of being absorbed by the gastrointestinal tract.[10]

As shown in Fig. 3: The bioavailability radar showed that the colored zone is the suitable physicochemical space for oral bioavailability where the following properties were taken into consideration: flexibility, lipophilicity, saturation, size, polarity and solubility. All compounds are within the pink area, representing optimal oral bioavailability.[11]

Lipinski's Rule of Five

The results of the Lipinski's Rule of five calculations using pkCSM are presented in table 2. All Dihydropyrimidinone compounds obey the Lipinski's, exhibiting good oral absorptivity. All the compounds showed Total Polar Surface Area (TSA) less than 140 Å. Lower TSA was found to better correlate with increased permeability compared to Lipophilicity.

ADMET Properties:

From Tables 3 and 4 it can be observed that ADMET properties of compounds specify threshold ADMET characteristics for the chemical structure of the molecules based on the available drug databases. All ADMET values were found within

an acceptable range.

a) Substrates for Metabolizing enzymes and P glycoprotein:

CYP2D6 ADMET properties showed that none of the compounds are substrates for it. As shown in Table 5, few of the compounds serve as substrates for CYP1A2, CYP2A9. CYP2A19 and CYP3A4.

Compounds F2, F5, F7-F12, F15-F19, F21 and F23 proved to be potential substrates for Pglycoprotein (P-gp) which effluxes drugs and various compounds to undergo further metabolism and clearance resulting in therapeutic failure because the drug concentration would be lower than expected.

Toxicity

Toxicity endpoints were predicted using protox and represented in Table 6. All the compounds showed absence of carcinogenicity, mutagenecity, immunotoxicity, cytoxicity, reproductive toxicity and hepatoxicity except the compound F6 which showed hepatotoxicity and reproductive toxicity

Table 1. Dihyropyrimidinone Derivatives

S. No	Comp. Code	Iupac name	Chemical Formula
1	F1	5-(ethoxyacetyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one	C15H18N2O2
2	F2	4-(4-bromophenyl)-5-(ethoxyacetyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one	C15H17BrN2O2
3	F3	4-(3-bromophenyl)-5-(ethoxyacetyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one	C15H17BrN2O2
4	F4	4-(2-bromophenyl)-5-(ethoxyacetyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one	C15H17BrN2O2
5	F5	4-(4-chlorophenyl)-5-(ethoxyacetyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one	C15H17ClN2O2
6	F6	4-(3-chlorophenyl)-5-(ethoxyacetyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one	C15H17ClN2O2
7	F7	5-(ethoxyacetyl)-4-(4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one	C15H18N2O3
8	F8	5-(ethoxyacetyl)-4-(3-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one	C15H18N2O3
9	F9	5-(ethoxyacetyl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one	C16H20N2O3
10	F10	5-(ethoxyacetyl)-4-(3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one	C16H20N2O3
11	F11	4-[5-(ethoxyacetyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl]benzaldehyde	C16H18N2O3
12	F12	4-[4-(dimethylamino)phenyl]-5-(ethoxyacetyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one	C17H23N3O2
13	F13	5-(ethoxyacetyl)-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one	C15H17N3O4
14	F14	5-(ethoxyacetyl)-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one	C15H17N3O4
15	F15	5-(ethoxyacetyl)-4-(4-fluorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one	C15H17FN2O2

Table 2: Predictions of Molecular weight, hydrogen bond donors, hydrogen bond acceptors, otal Polar Surface Area, log P values and bioavailability score

S. No	Compound Code	Mol Wt. [g/mol]	Hydrogen bond donors	Hydrogen bond acceptors	Log P	TPSA	Bioavailability Score
1	F1	258.32	2	2	2.21	50.36	0.55
2	F2	337.21	2	2	2.85	50.36	0.55
3	F3	337.21	2	2	2.84	50.36	0.55
4	F4	337.21	2	2	2.80	50.36	0.55
5	F5	292.76	2	2	2.77	50.36	0.55
6	F6	292.76	2	2	2.75	50.36	0.55
7	F7	274.32	3	3	1.80	70.59	0.55
8	F8	274.32	3	3	1.82	70.59	0.55
9	F9	288.34	2	3	2.18	59.59	0.55
10	F10	288.34	2	3	2.21	59.59	0.55
11	F11	286.33	2	3	1.94	67.43	0.55
12	F12	301.38	2	2	2.24	53.60	0.55
13	F13	303.31	2	4	1.65	96.18	0.55
14	F14	303.31	2	4	1.64	96.18	0.55
15	F15	276.31	2	3	2.54	50.36	0.55

Table 3: Predictions of Blood brain permeability and CNS permeability

S. No	VDss (human)	Fraction unbound (human)	BBB permeability	CNS permeability
1	0.229	0.382	0.283	-2.824
2	0.061	0.254	0.253	-2.835
3	0.221	0.345	0.27	-2.83
4	0.223	0.347	0.238	-2.823
5	0.05	0.262	0.254	-2.838
6	0.212	0.355	0.239	-2.825
7	0.711	0	0.056	-1.9
8	0.526	0	-0.202	-2.064
9	0.275	0	-0.088	-2.176
10	0.211	0.086	0.197	-1.698
11	0.126	0.236	0.224	-2.845
12	-0.034	0.287	-0.033	-2.906
13	0.083	0.301	0.294	-2.851
14	0.156	0.365	0.006	-2.868
15	-0.111	0.281	0.128	-2.877

Table 4: Predictions of solubility profile and human intestinal absorption

S. No	Log S	$CaCO_2$ permeability	Intestinal absorption (human)	Skin Permeability	P-glycoprotein substrate	P-glycoprotein IandII inhibitor
1	-3.135	1.27	92.748	-2.814	No	No
2	-3.735	1.32	92.042	-3.359	Yes	No
3	-4.178	1.301	91.975	-2.803	No	No
4	-3.997	1.302	91.441	-2.769	No	No
5	-3.621	1.315	92.109	-3.359	Yes	No
6	-3.887	1.297	91.508	-2.782	No	No
7	-5.254	1.621	90.637	-2.706	Yes	Yes
8	-5.568	0.789	94.524	-2.814	Yes	Yes
9	-5.384	0.642	93.733	-2.729	Yes	Yes
10	-5.687	1.611	93.863	-2.73	Yes	Yes
11	-4.503	1.349	91.818	-3.481	Yes	No
12	-3.184	1.276	94.489	-3.706	Yes	No
13	-4.512	1.362	89.475	-2.803	No	No
14	-3.518	1.271	92.865	-3.432	No	No
15	-3.152	1.279	93.177	-3.633	Yes	No

Table 5: Predictions of metabolism and excreation parameters

S. No	CYP1A2 inhibitor	CYP2 C19 inhibitor	CYP2 C9 inhibitor	CYP2 D6 inhibitor	CYP3 A4 inhibitor	Total Clearance	Renal OCT2 substrate
1	No	Yes	No	No	No	0.144	No
2	No	Yes	No	No	No	0.683	No
3	No	No	No	No	No	0.686	No
4	No	No	No	No	No	0.77	No
5	No	No	No	No	No	0.769	No
6	-	-	-	-	-	-	-
7	No	No	No	No	No	0.634	No
8	No	No	No	No	No	0.882	No
9	Yes	No	No	No	No	0.753	No
10	No	No	No	No	No	0.734	No
11	No	No	No	No	No	0.634	No
12	No	No	No	No	No	0.631	No
13	No	No	No	No	No	0.383	No
14	No	No	No	No	No	0.866	No
15	No	No	No	No	No	0.262	No

Table 6: 1- Carcinogenicity (Mouse), 2- Carcinogenicity (Rat), 3- Carcinogenicity (Rodents), 4- Mutagenecity, 5- LD50 value (mg/kg) , 6- Hepatotoxicity, 7- Immunotoxicity, 8 Cytotoxicity, 9- Androgen test, 10- Estrogen test, 11- Aromatase test, 12- Maximum tolerable dose (log/mg/kg/day), 13- Minnow Toxicity. 14- Predicted Toxicity class.

S. No	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	0.2	0.108	0.2	0.64	1644	0.60	0.99	0.70	0.95	0.84	0.87	0.289	1.336	4
2	0.2	0.2	0.2	0.65	1644	0.66	0.86	0.64	0.94	0.87	0.86	0.375	0.752	4
3	0.2	0.2	0.2	0.65	1644	0.66	0.86	0.64	0.94	0.87	0.86	0.375	0.752	4
4	0.2	0.2	0.2	0.64	785	0.62	0.96	0.66	0.94	0.87	0.84	0.423	0.658	4
5	0.2	0.2	0.2	0.63	1644	0.62	0.98	0.67	0.96	0.86	0.86	0.241	0.726	4
6	0.1	0.161	0.2	0.97	1190	0.69	0.96	0.93	0.99	0.99	1	0.386	0.898	4
7	0.2	0.2	0.2	0.65	3000	0.55	0.99	0.76	0.93	0.86	0.85	-	-	5
8	0	0	0	0.65	1644	0.55	0.96	0.76	0.93	0.86	0.85	-0.214	1623	4
9	0.1	0.2	0.2	0.61	3000	0.38	0.97	0.18	0.94	0.87	0.85	0.248	1.167	5
10	0.1	0.0693	0.1	0.61	3000	0.58	0.90	0.18	0.94	0.85	0.87	0.371	1.382	5
11	0.1	0.6693	0.1	0.64	1644	0.63	0.98	069	0.96	0.81	0.87	0.246	1.384	4
12	0.08	0.0146	0.129	0.63	1644	0.58	0.97	0.63	0.93	0.85	0.86	0	-	-
13	0.08	0.0743	0.129	0.062	785	0.53	0.98	0.61	0.97	0.84	0.37	-0.514	1.536	4
14	0.23	0.231	0.231	0.62	784	0.53	0.96	0.62	0.97	0.84	0.87	0.307	-	4
15	0.2	0.2	0.2	0.69	800	0.62	0.98	0.630	0.95	0.86	0.86	0.232	1.273	4

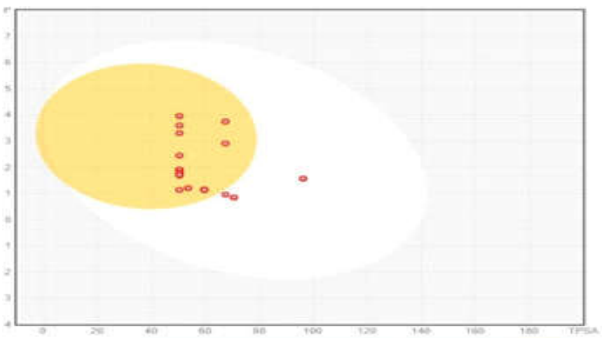

Fig. 1: Boiled egg (without molecule names)

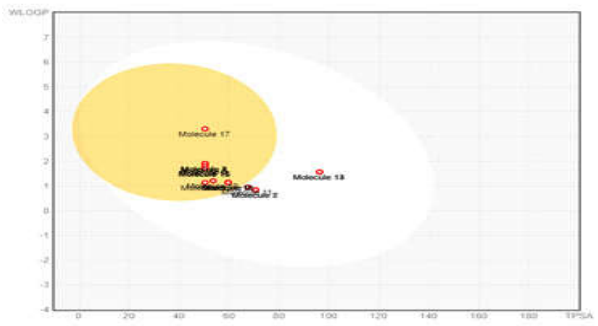

Fig. 2: Boiled egg (with molecule names)

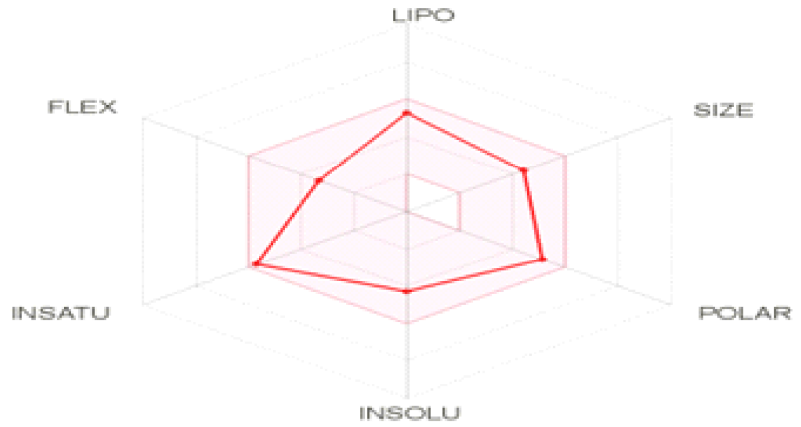

Fig. 3: The Bioavailability radar of F1 using Swiss ADME predictor.

Conclusion

In this study we have predicted ADMET properties, using Swiss adme, Pkcsm, Lazar and Protox for dihydropyrimidinone derivatives. Swiss adme data revealed that F1, F2, F5, F12, F15, F17, F18, F19, F20, F22, F23, F24 exhibited BBB permeability. The remaining dihydropyrimidinone derivates showed absorption by the gastrointestinal tract. All the compounds confirmed to the Lipinski's rule of five. All compounds showed optimal oral bioavailability. None of the compounds are substrates for CYP2D6. Compounds F2, F5, F7-F12, F15-F19, F21 and F23 proved to be potential substrates for Pglycoprotein (P-gp). Lazar and protox softwares predicted toxicity parameters, all the compounds were non toxic except F6, which exhibited hepatotoxicity and reproductive toxicity. In conclusion our in silico prediction are helpful for further synthesis, biological evaluation and formulations of Dihydropyrimidinone derivatives.

Conflict of Interest: None Declared.

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