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Original Article

Molecular Properties Prediction of Phenothiazine Derivatives by Using Swiss ADME, PkCSM, Lazar and Protox

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ABSTRACT

Molecular absorption, distribution, metabolism and excretion (ADME) play primary role in drug discovery and development. Toxicity determination of chemicals is essential to identify their harmful effects on humans, animals, plants, or the environment. A large number of *insilico* models are hence developed for prediction of ADME properties, as a result enabling the reduction of time, costs and animal experiments. The objective of this study is to predict Pharmacokinetic, drug likeness properties and toxicity of phenothiazine derivatives by using swiss adme, PkCSM, Lazar and Pro tox softwares. As per the data all the compounds concur Lipinski's rule of five except F8, F11, F12 and F13 and the compounds F1, F14 and F15 were showed toxic properties.

Keywords: Phenothiazine derivatives, Swiss ADME, PkCSM, Lazar, Protox.

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INTRODUCTION

Drug discovery and development is a very complex and costly attempt, which includes disease selection, target identification and validation, lead discovery and optimization, preclinical and clinical trials[1,2]. Since, Investigation of terminated projects revealed that the primary cause for drug failure in the development phase was due to adverse pharmacokinetic profiles and ADMET properties, has necessitated the inclusion of the concept of drug-likeness at early stage of drug discovery [3].Computational strategies play vital roles in early stage of drug discovery and expected to minimize the risk of toxicity [4]. Phenothiazines have found widespread use in medicinal chemistry and its derivatives have been reported to possess various diverse biological activities including tranquilizers anti-inflammatory, antimalarial, antipsychotropic, antimicrobial, antitubercular, antitumor, antihistamine and analgesic properties [5,6].

The pharmacokinetic activity and toxicity can be assessed using computational algorithms to organize, analyse, model, simulate, visualize or predict chemical toxicity. Predicted toxicity insilico is performed prior to *in-vitro* and *in-vivo* testing to minimize time and cost. Such insilico 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 such as the BOILED-Egg, iLOGP and bioavailability rader [7].

Pkcsm 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 [9]. Lazar 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 [10]. 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 (Tox21) and toxicity targets.

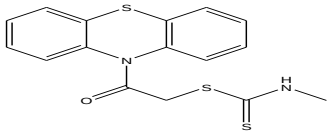
The molecular properties and their toxicity were not determined for Phenothiazine derivatives. Therefore, this study aimed to predict drug likeness and toxic properties of phenothiazine derivatives insilico using swiss adme, pkcsm, lazar, pro tox applications. The results will helpful to determine antioxidant activity, antimitotic activity and anticancer activity with high and low toxicity.

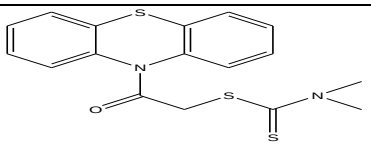
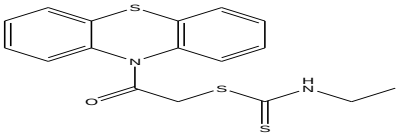
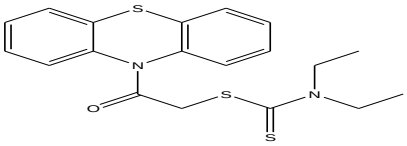
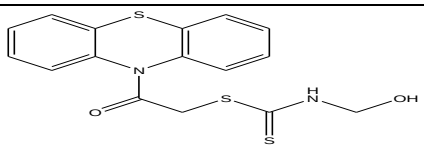
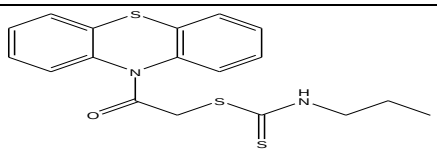
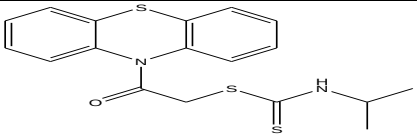
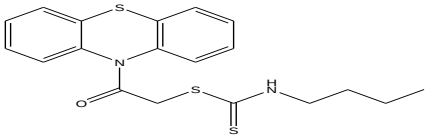
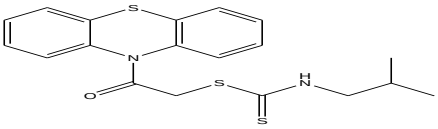
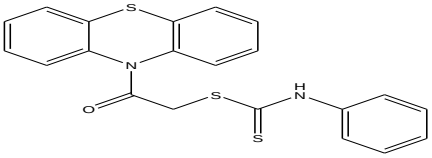
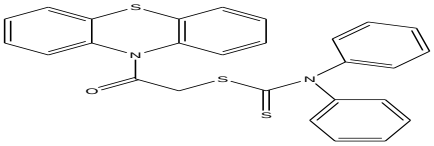
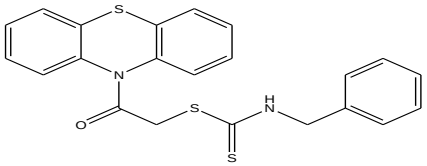
MATERIALS AND METHODS

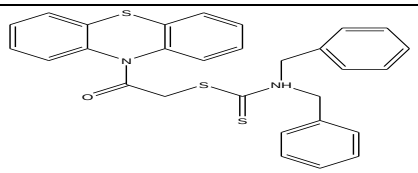
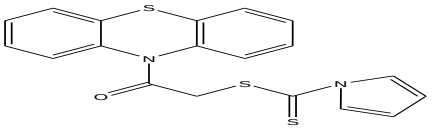
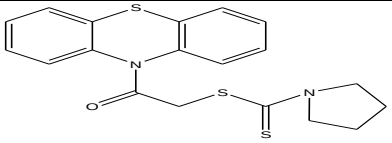
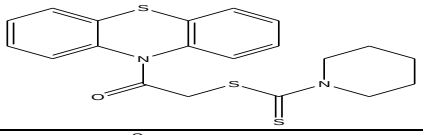
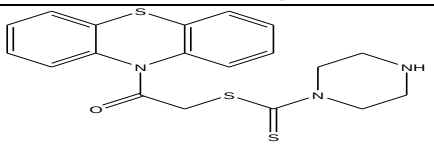
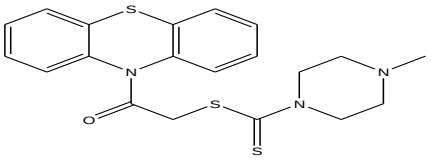
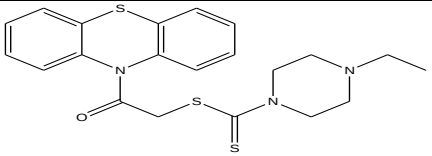
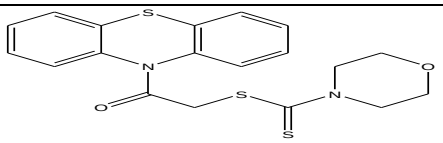
Equipment and materials: The hardware used in this study was a PC with x64-based with 4 gigabytes and Windows 10 pro-F3F9TVII operating system. The software used were,
chemsketch (https://www.acdlabs.com/resources/freeware/chemsketch/download.php),
swiss adme (http://www.swissadme.ch/index.php),
pkCSM(http://biosig.unimelb.edu.au/pkcsm/prediction),
lazar (https://lazar.in-silico.de/predict) and
protox (http://tox.charite.de/protox_II/index.php?site=compound_input).

Experimental procedure: The planned derivatives are generated in two-dimensional form by using chemsketch application. All phenothiazine derivatives were screened using the Swiss adme, pkCSM application to determine whether the compounds obey Lipinski's Rule of five. The toxicity of the screened phenothiazine derivatives was then predicted using Lazar for the carcinogenic end point, maximum daily dose, and mutagenicity. The protox application for toxicity classes, as well as the ADMET predictor application for hepatotoxicity end point, as well as reproductive system disorders and endocrine.

Table 1: Phenothiazine Derivatives.

S. No	Comp. Code	IUPAC Name	Structure
1	F1	2-oxo-2-(10*H*-phenothiazin-10-yl) ethyl methylcarbamodithioate	

2	F2	2-oxo-2-(10*H*-phenothiazin-10-yl) ethyl dimethylcarbamodithioate	
3	F3	2-oxo-2-(10*H*-phenothiazin-10-yl) ethyl ethylcarbamodithioate	
5	F4	2-oxo-2-(10*H*-phenothiazin-10-yl) ethyl diethylcarbamodithioate	
4	F5	2-oxo-2-(10*H*-phenothiazin-10-yl) ethyl (2-hydroxyethyl) carbamodithioate	
6	F6	2-oxo-2-(10*H*-phenothiazin-10-yl) ethyl propylcarbamodithioate	
7	F7	2-oxo-2-(10*H*-phenothiazin-10-yl) ethyl propan-2-ylcarbamodithioate	
8	F8	2-oxo-2-(10*H*-phenothiazin-10-yl) ethyl butylcarbamodithioate	
9	F9	2-oxo-2-(10*H*-phenothiazin-10-yl) ethyl (2-methylpropyl) carbamodithioate	
10	F10	2-oxo-2-(10*H*-phenothiazin-10-yl) ethyl phenylcarbamodithioate	
11	F11	2-oxo-2-(10H-phenothiazin-10-yl) ethyl diphenyl carbamodithioate	
12	F12	2-oxo-2-(10*H*-phenothiazin-10-yl) ethyl benzylcarbamodithioate	

13	F13	2-oxo-2-(10*H*-phenothiazin-10-yl) ethyl dibenzylcarbamodithioate	
14	F14	2-oxo-2-(10*H*-phenothiazin-10-yl) ethyl 1*H*-pyrrole-1-carbodithioate	
15	F15	2-oxo-2-(10*H*-phenothiazin-10-yl) ethyl pyrrolidine-1-carbodithioate	
M 16	F16	2-oxo-2-(10*H*-phenothiazin-10-yl) ethyl piperidine-1-carbodithioate	
17	F17	2-oxo-2-(10*H*-phenothiazin-10-yl) ethyl piperazine-1-carbodithioate	
18	F18	2-oxo-2-(10*H*-phenothiazin-10-yl) ethyl 4-methylpiperazine-1-carbodithioate	
19	F19	2-oxo-2-(10H-phenothiazin-10-yl) ethyl 4-ethylpiperazine-1-carbodithioate	
20	F20	2-oxo-2-(10*H*-phenothiazin-10-yl) ethyl morpholine-4-carbodithioate	

RESULTS AND DISCUSSION

The predictions were in the form of quantitative and qualitative data. Qualitative data were expressed in positive and negative statements, and then expressed in the form of scoring, where a positive toxic score is 1 and a negative toxic score is 2. All smiles were generated, the brain or intestinal estimated permeation method (BOILED-Egg) is carried to get an accurate predictive model that works by computing the lipophilicity and polarity of small molecules. From all F20 phenothiazine derivatives molecule F11 and molecule F13 are out of the region and remaining compounds are in the white region, is the physicochemical space of molecules with highest probability of being absorbed by the gastrointestinal track [8].The bioavailability radar(figure3) showed that the colored zone is the suitable physicochemical space for oral bioavailability where the following properties were taken into consideration as flexibility, lipophilicity, saturation, size, polarity and solubility. The data revealed by the pkCSM, lazar and protox gave information about the compounds with low toxicity. Highest LD_{50} value gave the highest average value with lowest toxicity and all the compounds are showing positive toxicity.

Figure 1

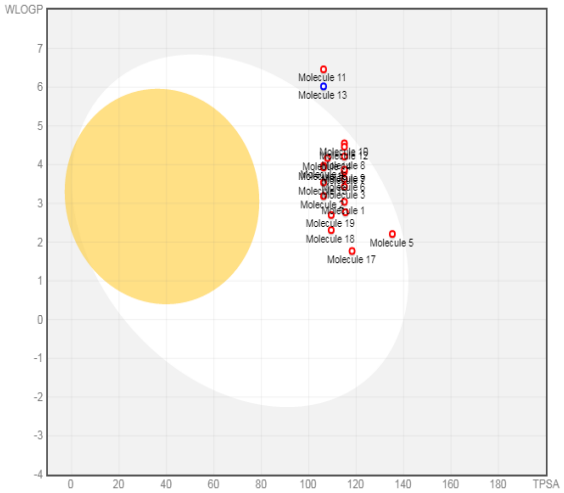


Figure 2

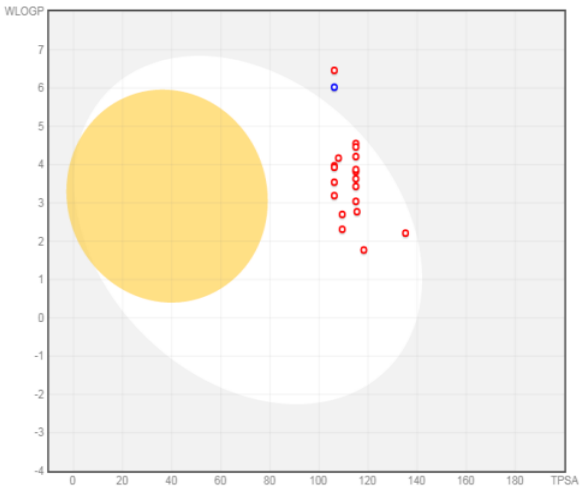
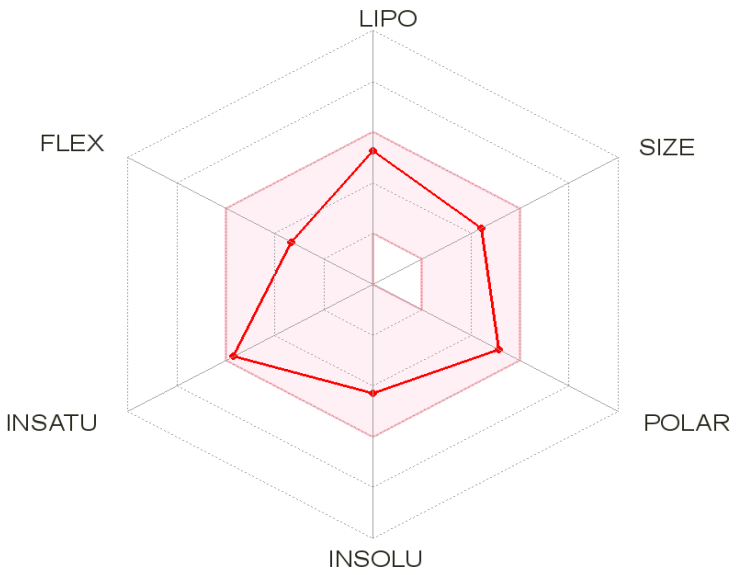


Figure 3: The Bioavailability radar of F1 using Swiss ADME predictor



Lipinski's Rule of Five: Lipinski's Rule if five helps to determine the level of absorption or permeability of lipid bilayers present in the human body, demonstrating the oral bioavailability of a compound. Good bioavailability will satisfy the Lipinski's rule, where the maximum molecular weight of a compound is 500, the log p is not more than 5, the hydrogen bond donor is not more than 5, and the number of hydrogen bond acceptor is less than 10.The results of the Lipinski's Rule of Five calculations using pkCSM are presented in table 2. According to Table 2, all phenothiazine compounds obey the Lipinski's, rule except compound F8,F11,F12 and F13(Eliminated), and remaining all the compounds have good absorptivity for oral medication.

Toxicity prediction: Based on the results of the scoring calculation of the all software applications in Table 3, the compound with the highest average scores are showing lowest toxicity , which is F1,F14 and F15. F5 is less effective than the best compound due to its high LD_{50} value and predicted to be toxic to the reproductive system. Therefore, further analysis is required by comparing the number of non-toxic endpoints for each compound. The admet [11] data revealed that all the compounds are having reproductive toxicity. By comparing all the values compound F1, F14 and F15 are shown to have low toxic effect.

Table 2: Lipinski's Rule of five Analysis Results

Comp. Code	BM (<500)	Log (<5)	Hydrogen Bond Acceptor	Hydrogen Bond Donor
F1	346.03	3.71	4	1
F2	362.06	3.03	4	0
F3	360.04	4.26	4	1
F4	390.09	3.97	4	0
F5	378.05	2.14	5	2
F6	376.07	3.78	4	1
F7	374.06	4.60	4	1
F8	388.07	5.22	4	1
F9	390.09	4.11	4	1
F10	410.06	4.50	4	1
F11	486.09	5.78	4	0
F12	422.06	5.43	4	1
F13	514.12	6.30	4	0
F14	382.03	4.59	4	0
F15	386.06	4.68	4	0
F16	400.07	5.04	4	0
F17	403.08	2.20	5	1
F18	415.08	3.78	5	0
F19	429.10	4.27	5	0
F20	402.05	3.73	5	0

Table 3: Toxicity results prediction from pkCSM, lazar and protox.

Comp. name	1	2	3	4	5	6	7	8	9	10	11	Total	Average
F1	0.146	0.0765	0.072	0.053	0.135	1792	0.66	0.65	0.90	0.71	0.78	1,796.26	163.29
F2	-	0.0626	0.0384	0.0235	0.112	560	0.55	0.68	0.97	0.66	0.67	563.76	51.25
F3	0.148	0.0826	0.069	0.0466	0.131	589	0.72	0.63	0.99	0.71	0.76	593.28	53.93
F4	0.174	0.1	0.0595	0.0789	0.127	560	0.62	0.71	0.98	0.69	0.64	564.19	51.28
F5	-	0.0818	0.0734	0.121	0.0872	1000	0.70	0.61	0.86	0.70	0.67	1003.90	91.26
F6	0.138	0.055	0.0555	0.0694	0.0958	560	0.63	0.61	0.94	0.68	0.68	563.95	51.26
F7	0.148	0.0767	0.0881	0.0614	0.138	589	0.67	0.70	0.98	0.71	0.78	593.3522	53.94
F8	0.208	0.103	0.114	0.101	0.0949	300	0.74	0.64	0.90	0.67	0.75	304.32	27.66
F9	-	0.0715	0.0345	0.0345	0.0913	560	0.63	0.62	0.97	0.68	0.64	563.73	51.24
F10	0.0873	0.0852	0.0633	0.048	0.0993	560	0.52	0.59	0.99	0.56	0.71	563.75	51.25
F11	0.129	0.0666	0.0645	0.0536	0.102	480	0.51	0.61	0.98	0.59	0.70	483.80	43.98
F12	0.143	0.0645	0.0945	0.0842	0.148	927	0.71	0.68	0.99	0.71	0.75	931.37	84.67
F13	0.118	0.0617	0.0877	0.0824	0.115	560	0.57	0.69	0.99	0.67	0.61	563.99	51.27
F14	0.148	0.0728	0.0936	0.0785	0.139	1792	0.67	0.68	0.99	0.75	0.79	1796.41	163.31
F15	0.139	0.0952	0.0868	0.0694	0.136	1792	0.67	0.68	0.99	0.75	0.79	1796.40	163.30
F16	0.149	0.0902	0.0943	0.0746	0.131	300	0.75	0.74	0.98	0.75	0.77	304.52	27.68
F17	-	0.11	0.1	0.1	0.0944	560	0.63	0.68	0.98	0.72	0.70	564.11	51.28
F18	0.2	0.098	0.102	0.0907	0.0845	589	0.74	0.71	0.98	0.68	0.74	593.42	53.94
F19	0.134	0.0848	0.0983	0.0812	0.121	589	0.74	0.70	0.96	0.71	0.75	593.37	53.94
F20	0.134	0.0848	0.0983	0.0812	0.121	589	0.74	0.70	0.96	0.71	0.75	593.37	53.94

1-B.B.B penetration (Human), 2-Carcinogenicity(Rat), 3-Carcinogenicity(Rodents), 4-Carcinogenicity(Mouse), 5-Mutagenicity, 6-LD_{50} mg/kg , 7-Hepatotoxicity, 8-Carcinogenicity, 9-Imminotoxicity, 10-Mutagenicity,11-Cytotoxicity.

CONCLUSION

In this study we have predicted ADMET properties, using Swiss adme, Pkcsm, Lazar and Protox for phenothiazine derivatives. Swiss adme data revealed that all the derivatives were observed in the white region indicating the probability of being absorbed by the gastrointestinal track, none of the compound crossed the BBB and most of the compounds obey Lipinski rule of five except F8, F11, F12 and F13 indicating, all the compounds have good oral absorption. Moreover Lazar and protox softwares predicted, all the compounds were non toxic except F1 (methyl), F14 (Pyrrolyl) and F15 (Pyrrolidinyl). Hence we conclude that our in silico prediction are helpful for further synthesis and biological evaluation of phenothiazine derivatives.

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