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In silico Prioritization of some Tetrazole Chalcones for Anticonvulsant Activity

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Abstract: *In silico* predictions of molecules have quenched the thirst of drug discovery as it provides insight for the prioritization of the molecules for *in vivo* or *in vitro* pharmacological evaluations. Molecules for series **PTC_{1-7}** and **$CPTC_{1-7}$** were subjected for *in silico* biological activity predictions, partition coefficient predictions (pLog P) and ADME predictions using PASS server, mol-inspiration software and PreADMET software respectively. This gave biological activity score (BAS), ADME predictions and LogP predictions (pLog P) for anticonvulsant activity. The standard Log P required for anticonvulsant activities being +2.00, molecules were also prioritized based on this pLogP criteria. In the protocol for BAS prediction, clinically used anticonvulsant agents were included and similarly followed for Log P predictions. The protocol was thus validated by comparing the correlation between pLog P and BAS. Molecules were also prioritized using the above protocol. The BAS score for selected the first five prioritized molecules was in the range of 0.30-0.61, Memantine showed a BAS of 0.93, which was used as standard in the prioritization protocol. The molecules $CPTC_3$ showed a BAS of 0.61 as compared with Memantine with BAS of 0.93. **PTC_3, PTC_2, PTC_1,$CPTC_2$, $CPTC_3$, & $CPTC_4$** can serve is an *in silico* lead and outcome of *in silico* virtual screening for BAS predictions with ADME property & pLog P prioritization. Thus molecules were prioritized for anticonvulsant activity.

Keywords: chalcones, In silico, BAS,PASS.

Introduction

An *in silico* study for the prioritization of 3-substituted phenyl-1-(5-phenyl-1*H*-tetrazol-1 yl)prop-2-en-1-one (**PTC_{1-7}**), 1-[5-(4-chlorophenyl)-1*H*-tetrazol-1-yl]-3-substitutd phenylprop-2-en-1-one (**$CPTC_{1-7}$**), derivatives was performed for Biological activity score (BAS) prediction for anticonvulsant activity , Predicted LogP Predictions (PLogP), and ADME Predictions Using Pass Server For Biological activity predictions (http//195.178.207.233/ PASS/BAS.html)[1], Mol inspiration Server (www.molinspiraion.com)[2]and PreADMET Server\ (www.bmdrc.com/04_product/01_preadme.asp)[3] respectively. In present work the N-heterocyclic chalcones were prioritized for anticonvulsant activity.

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1. PASS Server Biological Activity Predictions[1]

PASS Inlet predicts biological activity spectrum (783 pharmacological effects, mechanisms of action, specific toxicity) on the basis of structural formula of the compound. In the "Prediction Results" one obtains the total number of chemical descriptions of compound, and the number of descriptors which are new comparing to the descriptors in 30,900 compounds from the PASS training set. The compounds are considered equivalent in PASS if they have the same molecular formulae. The result of prediction is presented as the list of activities with appropriate Pa and Pi, sorted in descending order of the difference (Pa-Pi)>0 (Pa values are given in this research paper which are the Biological activity scores. Biological activity spectrum with Pa value is termed as biological activity score. Biological Activity Spectrum of a compound represents the complex of pharmacological effects, physiological & biochemical mechanisms of action, specific toxicity (mutagenicity, carcinogenicity, teratogenicity & embryo toxicity) which can be revealed in compound's interaction with biological system. Biological activity spectrum with Pa values is termed as biological activity score (BAS). Biological Activity Spectrum describes the intrinsic properties of the compound depended on it's the structural particularities. They may be revealed in experiment under any conditions (dosage, route of administration, biological object, age, sex, etc.). BAS for anticonvulsant activity were determined for some as chalcones of tetrazole molecules in this research paper.

2. pLogP predictions[5]

It is the ratio of the compound's organic (oil)-to-aqueous phase concentrations.

Partition Coefficient (P) = [Organic] / [Aqueous]

Log P of compound should be greater than 2.00 for compound to cross of blood brain barrier. Because central nervous system (CNS)-active compounds must pass across it and CNS-inactive compounds mustn't pass across it in order to avoid of CNS side effects. Hydrophobicity of a compound (as measured by its distribution coefficient) is a major determinant of how drug-like it is. More specifically, in order for a drug to be orally absorbed, it normally must first pass through lipid bilayers in the intestinal epithelium (a process known as transcellular transport). LogP is used in QSAR studies and rational drug design as a measure of molecular hydrophobicity.

Mol inspiration software

Mol inspiration is versatile cheminformatics software tool supporting molecule manipulation and processing, including SMILES and SDfile conversion, normalization of molecules, generation of tautomers, molecule fragmentation, calculation of various molecular properties needed in QSAR, molecular modelling and drug design, high quality molecule depiction, molecular database tools supporting substructure search or similarity and pharmacophore similarity search. Mol inspiration is independent platform and may be run on any PC, Mac, UNIX or LINUX machine. It offers contract research in all areas of cheminformatics, including: **1.** calculation of molecular properties for large molecular databases 2**.** QSAR and structure-activity analysis. **3.** Development of activity models for (nearly) any required target, efficient fragment-based virtual screening. **4**. Design of targeted combinatorial libraries. **5.** Diversity selection from large molecular collections.

3. ADME Predictions [6, 7, 10]

ADME means absorption, distribution, metabolism and excretion, which are major parts of pharmacokinetics. Statistics reports show that many of drug candidates are failed during clinical tests because of the problems related to ADME. Hence *In silico* ADME properties are used to prioritize molecules. The *in silico* ADME parameters and their ranges used for prioritization are mentioned under each ADME property.

a. Caco2 Cell Permeability [6,7]

Caco-2 cells tool for intestinal cell function and differentiation. Caco2 cells are derived from human **colon Adenocarcinoma** and possess multiple drug transport pathways through the intestinal epithelium. For prediction of Caco- 2 cell permeability in PreADMET, Molecules are solvated *in silico* at pH 7.4, because Caco-2 cell permeability measured at about pH 7.4. Caco2 cells are used to determine the apparent

permeability values of compounds. The ranges of Caco2 cell permeability used for *in silico* prioritization are shown in Table-1.

Table .1. Showing ranges of Caco2 cell permeability prediction

Classification	PCaco-2 (nm/sec)
Low permeability	less than 4
Middle permeability	4 ~ 70
High permeability	more than 70

2. MDCK cell permeability [6,10]

MDCK cell means Madin-Darby canine kidney cell. Experimental and computational screening models for the prediction of intestinal drug absorption. MDCK cells are used to determine out the apparent permeability values of compounds. The ranges of MDCK cell permeability used for *in silico* prioritization of molecule are shown in Table-2.

Table . 2. Showing ranges of MDCK cell permeability predictions

Classification	PMDCK (nm/ sec)
Low permeability	less than 25
Middle permeability	25 ~ 500
High permeability	more than 500

3. Human Intestinal Absorption (HIA)

Predicting human intestinal absorption of drugs is very important for identify potential drug candidate. PreADMET can predict percent human intestinal absorption (%HIA). Human intestinal absorption data are the sum of bioavailability and absorption evaluated from ratio of excretion or cumulative excretion in urine or bile. The ranges of HIA predictions are shown in Table-3.

Table .3. Showing ranges of HIA predictions

Classification	HIA (Human Intestinal Absorption)
Poorly absorbed compounds	0 ~ 20 %
Moderately absorbed compounds	20 ~ 70 %
Well absorbed compounds	70-100 %

4. Blood Brain Barrier Penetration

Blood-Brain Barrier (BBB) penetration is represented as BB = [Brain]/[Blood], where [Brain] and [Blood] are the steady-state concentration of radio labeled compounds in brain and peripheral blood. Predicting BBB penetration means predicting whether compounds pass across the blood-brain barrier. This is crucial in pharmaceutical sphere because CNS-active compounds must pass across it and CNS-inactive compounds mustn't pass across it in order to avoid of CNS side effects. PreADMET can predict *in vivo* data on rates for BBB penetration. The ranges of blood brain barrier predictions are shown in Table-4.

Table .4. Showing ranges of BBB predictions

Classification	BB (Cbrain/Cblood)
CNS - Active compounds	(+) more than 1.0
CNS- Inactive compounds	(-) less than 1.0

5. Plasma Protein Binding (PBB)

Generally, only the unbound drug is available for diffusion or transport across cell membranes, and also for interaction with a pharmacological target. As a result, a degree of plasma protein binding of a drug influences not only on the drug's action but also its disposition and efficacy. PreADMET can predict percent drug bound in plasma protein as *in vitro* data on human. The ranges of PBB used for *in siico* prioritization are shown in Table-5.

Table .5. Showing ranges of PBB predictions

Classification	Plasma Protein Binding (%PPB)
Chemicals strongly bound	more than 90%
Chemicals weakly bound	less than 90%

Our main objectives were to *in silico* prioritize molecules for actual synthesis and evaluation based upon BAS, pLogP and PreADMET predictions. Correlation coefficients were obtained for correlation between BAS and pLog P, to find a correlation between pLog P and BAS predicted by the Server.

Materials and Methods

***In silico* screening**[13-15]

Chemdraw 8.0 was used to convert 2-D chemskech files into 3-D Mol Files. Further these were uploaded into the server to obtain BAS activity Predictions, pLoP values and ADME predictions respectively.

a) BAS

Mol files of series of 3-substituted phenyl-1-(5-phenyl-1*H*-tetrazol-1 yl)prop-2-en-1-one (**PTC_{1-7}**), 1-[5-(4-chlorophenyl)-1*H*-tetrazol-1-yl]-3-substitutd phenylprop-2-en-1-one (**$CPTC_{1-7}$**), were subjected to predict BAS usin PASS server. The structures of the compounds are shown in figure no. 1. These values are shown in **Table No 6.**

b) Log P predictions pLogP

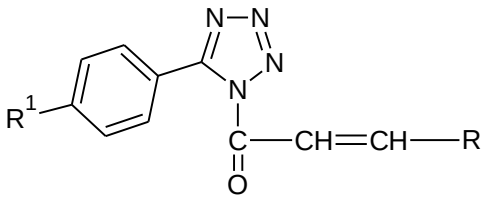
Mol files of series of molecules from **PTC_{1-7} and $CPTC_{1-7}$** series were subjected to predict Log P values (pLog P) using Molinspiration software available on line on www. Molinspiration.com an attempt was made to correlate the BAS with pLog P and its graph is shown in figure no 2.

c) ADME predictions

Mole files of series of molecules from series of molecule (**PTC1-7 and CPTC1-7**) were subjected to predict ADME properties mentioned earlier. These values are shown in **Table no-6.**

d) Prioritization of the molecules[12]

The molecules having acceptable BAS, LogP and ADME properties were prioritized for actual synthesis and biological evaluation as anticonvulsant agents.



R^1=H=PTC_{1-7} **R^1=Cl=$CPTC_{1-7}$**

R= C_6H_5, 4-ClC_6H_4, 4-BrC_6H_4, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-$NO_2C_6H_4$, 4-N $(CH_3)_2C_6H_4$.

Figure 2: Structures of different N-Heterocyclic Chalcones

Table 6: showing prioritization of molecules

Comp.	BAS	plogP	ADME prediction				
			Caco 2 cell	MDCK cell	HIA	PPB	BBB
PTC_1	0.45	3.66	21.00	-2.96	98.24	100	2.76
PTC_2	0.57	4.34	21.82	-2.96	97.64	99.54	2.27
PTC_3	0.50	4.47	21.66	-3.01	97.42	100	2.42
PTC_4	0.43	4.11	20.83	-2.88	98.11	100	3.13
PTC_5	0.32	3.76	22.08	-2.89	98.10	100	1.58
PTC_6	0.30	3.18	21.11	-3.21	96.80	94.67	0.50
PTC_7	0.30	3.72	21.79	-3.17	98.76	97.28	1.37
$CPTC_1$	0.57	4.34	21.64	-3.01	97.64	99.68	2.22
$CPTC_2$	0.56	5.01	22.35	-2.95	97.39	100	1.00
$CPTC_3$	0.61	5.15	22.18	-2.91	97.45	100	1.04
$CPTC_4$	0.52	4.79	21.99	-2.95	97.55	97.78	2.19
$CPTC_5$	0.41	4.43	20.79	-3.26	96.68	100	0.17
$CPTC_6$	0.39	3.86	24.00	-3.02	97.55	93.34	1.15
$CPTC_7$	0.39	4.39	22.23	-3.22	98.16	96.84	1.31

Prioritization of molecules

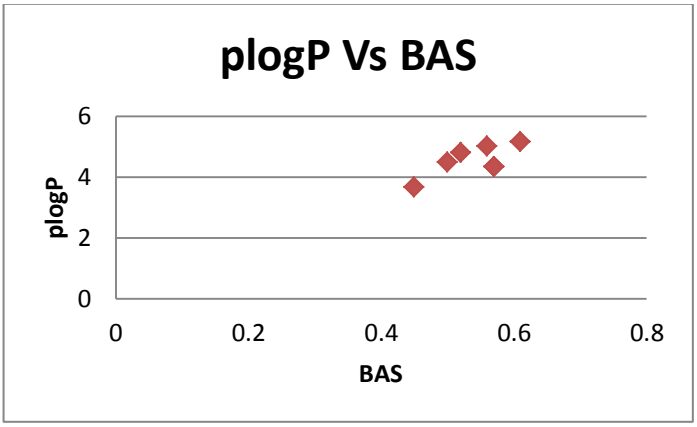


Figure 2: showing the correlation between plogP and BAS

Result and Discussion

1. BAS

Pa and Pi are the estimates of probability for the compound to be active and inactive respectively for each type of activity from the biological activity spectrum. Their values vary from 0.000 to 1.000. It is reasonably that only those types of activities may be revealed by the compound, where Pa > Pi (only Pa is reported here) and so they are put into the biological activity spectrum. The Pa and Pi values obtained from the Pass server shall be utilized as follows: **1)** If Pa > 0.7 the compound is very likely to reveal this activity in experiments, but in this case the chance of being the analogue of the known pharmaceutical agents for this compound is also high. **2)** If 0.5 < Pa < 0.7 the compound is likely to reveal this activity in experiments, but this probability is less, and the compound is not so similar to the known pharmaceutical agents. **3)** If Pa < 0.5 the compound is unlikely to reveal this activity in experiments, but if the presence of but this probability is less, and the compound is not so similar to the known pharmaceutical agents. **4)** If Pa < 0.5 the compound is unlikely to reveal this activity in experiments, but if the presence of this activity is confirmed in the experiment the compound might be a New Chemical Entity. The BAS of selected molecules was found to be **PTC_2-** 0.57, **PTC_3**-0.50 ,**PTC_1**-0.45 , **$CPTC_3$**-0.61, **$CPTC_2$**-0.55 ,**$CPTC_4$-** 0.52, respectively. Hence these compounds have high Pa value for being prioritized for actual synthesis and evaluation for anticonvulsant activity.

2. pLog P

For anticonvulsant activity the pLog P should be greater than 2.00, hence compounds above 2.00 pLog P were prioritized based on pLog P criteria. CNS active compounds must pass across it, in order to avoid of CNS side effects. The pLogP value of selected molecule was found to be **PTC_2-** 4.34, **PTC_3**-4.47 ,**PTC_1**-3.66 , **$CPTC_3$**-5.15, **$CPTC_2$**-5.01 ,**$CPTC_4$-** 4.79 ,respectively. And comply for being prioritized as CNS active agents for anticonvulsant activity.

3. Correlation between the Biological activity score and Log P

In order to determine correlation between the BAS and pLogP, correlation coefficient was obtained for the BAS and pLogP, However it was found that the BAS and predicted Log P are not in any relation and the BAS is independent of pLog P predictions since the Coefficient of correlation between the pLog P and biological activity score was found to be 0.73.

4. ADME predictions

ADME predictions based on *in silico* predictions of Caco2, MDCK, PBB, HIA, BBB etc. they are mentioned in Table no-6. The compound such as **PTC_2**, **PTC_3** ,**PTC_1** , **$CPTC_3$**, **$CPTC_2$**,**$CPTC_4$**, lie in the range of *in silico* Caco2 cell, MDCK cell, HIA, PBB and BBB predictions and hence prioritized *in silico* for ADME properties.

Conclusion

BAS and pLogP were devoid of any correlations. Following the above protocol molecules from series **PTC_2**, **PTC_3** ,**PTC_1** ,series viz. **$CPTC_2$**,**$CPTC_3$**,**$CPTC_4$**, were prioritized with *in silico* technique, for synthesis and pharmacological screening as anticonvulsant agents. The molecules showed comparable score of 0.61-0.45 as anticonvulsant agents as compared with Memantine used as standard in the BAS prediction. These molecules can serves as leads for anticonvulsant activity and are outcome of *in-silico* screening for pLogP, ADME and BAS score prioritization.

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