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IN SILICO PHARMACOKINETIC PROFILING OF TRYPTAMINE DERIVATIVES BY SWISSADME AND ADMETSAR

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ABSTRACT

Profiling of different pharmacokinetic parameters like the absorption, distribution, metabolism and elimination known as ADME properties of drug molecules during initial phase of drug development might be beneficial in selection of molecules with less adverse ADME characteristics. ADME screening by *in vivo* testing is very time consuming, costly, and include theanimals. On the other hand, *in silico* ADME investigation is cheaper, better and offers correct results rapidly. In the current research study, *the in-silico* methods namely SwissADME and admetSAR were used for brief and complete ADME profiling of previously selected (SR7, SR9, SR11, SR29, SR41 and SR43) tryptamine derivatives. The webservers utilized in this research are available for free. *In-silico* analyses has revealed that all the derivatives under study have high gastrointestinal absorption which make them a good oral drug candidate. However, results showed that SR41 & SR43 were able to pass blood- brain barrier as compared to other synthetic compounds of this series.

Key Words: Tryptamine derivatives, SwissADME, admetSAR, pharmacokinetics

INTRODUCTION

Drug development encompasses the efficacy and toxicity profiling of novel drug molecules along with the generation of hypothesis including a biological target against a particular disease condition through the screening of the numerous *in vivo* and *in vitro* biological activities of the discovered new drug molecules. One of the very important steps in drug development is to conduct pharmacokinetic profile analysis which is referred as ADME (Absorption, distribution, metabolism and elimination) screening **[1-3]**. The instigation of preliminary ADME assessment has significantly reduced the ratio of the molecules failing in clinical investigations and offers input into the prediction of safety and toxicity profiles of novel drug candidates. The major objective of preclinical ADME testing is to eradicate poor

drug candidates in the initial stages of drug development and direct the focus of researcher on the compounds with potential therapeutic effect. The *in vivo* ADME study comprises of animal involvement which is very laborious, time consuming, expensive and sometimes leading to organism suffering **[4, 5]**.

Computer models deliver data regarding possible effects of the compounds on pharmacokinetic properties and whether they are appropriate to use as medicine without experimental studies. SwissADME and admetSAR are freely available user-friendly web tools which offer various physicochemical parameters as well as pharmacokinetic characteristics, medicinal chemistry friendliness and drug likeness of single or multiple compounds at a time **[6-8]**. Tryptamine derivatives are known for their potent and diverse biological activities such as antimicrobial, antiviral, antifungal, antioxidant, cardiovascular roles such as, vasoconstrictor, vasodilator, and particularly as neurotransmitters and neuromodulators **[9, 10].** The aim of the present study was toutilize SwissADME and admetSAR to predict the different physicochemical properties and ADME parameters of seven synthesized tryptamine derivatives.

MATERIAL AND METHOD

In the present study the pharmacokinetic analysis of already reported derivatives of tryptamine **[11]** was executed by *in silico* tools. The structures of the tryptamine derivatives were drawn by using Chem Draw 2D Ultra and saved in .mol file format. The .mol file of the compounds were converted into respective Simple Molecular Input Line Entry System (SMILES) format through online SMILES generator/checker [https://www.cheminfo.org/]. The SMILES format of the derivatives was uploaded to the free online web tools including SwissADME [http://www.swissadme.ch/index.php] and admetSAR [http://lmmd.ecust.edu.cn/admetsar1/predict] for physicochemical and pharmacokinetic analysis **[12]**.

RESULTS AND DISCUSSION

The usage of *in silico* tools has gained considerable popularity in modern day drug development which has contributed to availability of various free and paid algorithms. A chemometrics tool based on the QSAR molecular models has been developed by the Laboratory of molecular modelling and design (lmmd) using regression and classification analysis for the prediction of ADMET properties which are governed by the physicochemical characteristics **[13, 14]**. A similar tool is SwissADME for the in-silico predictions which are dependent on the structure and functional groups of the drug molecule. Molecular properties of the derivatives have been shownin Table- 1.

The SwissADME predicts a number of parameters such as physicochemical properties, lipophilicity, water solubility, pharmacokinetics, drug likeness shown in Table -2 and Table- 3 whichis based on a variety of studies, medicinal chemistry

parameters etc., while the admetSAR tool envisages toxicity profile in addition to ADME parameters.

According to the predictions by both software, the derivatives are moderately suitable for the drugcandidacy. The boiled-egg diagram (Figure 1) shows that SR7, 9, 11, 28 & 29 possess high probability of passive absorption in the GI tract while SR41 and SR43 are more likely to permeateblood-brain barrier to reach the central nervous system. The latter mentioned derivatives are also a possible substrate for P-glycoprotein and readily reach GI lumen.

The high absorption prediction in the GI tract renders the derivatives suitable for oral formulations as well. The metabolic possibilities of these derivatives are shown in table -2. The cellular distribution of these derivatives is likely to occur in lysosome and mitochondria. The results for genomic toxicity parameters show that all the derivatives are found to non-AMES toxic and non- carcinogens, however, the fathead minnow toxicity (FHMT) of SR9 & 28 is high requiring an environmental check on these two as all the derivatives are predicted to be non-biodegradable.

CONCLUSION AND FUTURE PERSPECTIVES

The in-silico prediction and profiling of ADMET properties help the medicinal chemist to shortlist the derivatives that are more suitable for the drug development. The online tools used in this study can be used as a routine for drug designing and also indicate the compounds that need to be chemically modified for improving the pharmacokinetics. The tryptamine derivatives that have been explored in this research are found to be a good candidate for oral formulation and twoof the derivatives can be investigated for CNS activity as those are capable of crossing blood-brain barrier. All of the derivatives are environment friendly with low to moderate toxicity which shows their potential for green chemistry.

Table -1: General molecular properties of tryptamine derivatives (SMILES).

SMILES (Simplified Molecular Input Line Entry System)	Formula	Molecular weight	TPSA (topological polar surface area)	ESOL Class
SR7 O=C(c1ccccc1)C[NH2+]CCc1c[nH]c2c1cccc2.[Br-]	C18H19BrN2O	359.26	49.47	Moderately soluble

SR9 Clc1ccc(cc1)C(=O)C[NH2+]CCc1c[nH]c2c1cccc2.[Br-]	C18H18BrClN2O	393.71	49.47	Moderately soluble
SR11 Brc1ccc(cc1)C(=O)C[NH2+]CCc1c[nH]c2c1cccc2.[Br-]	C18H18Br2N2O	438.16	49.47	Moderately soluble
SR28 Brc1ccc(cc1)C[NH2+]CCc1c[nH]c2c1cccc2.[Br-]	C17H18Br2N2	410.15	32.4	Moderately soluble
SR29 Cc1ccc(cc1)C[NH2+]CCc1c[nH]c2c1cccc2.[Br-]	C18H21BrN2	345.28	32.4	Moderately soluble
SR41 O=C(c1ccccc1)NCCc1c[nH]c2c1cccc2	C17H16N2O	264.32	44.89	Soluble
SR43 Cc1ccc(cc1)C(=O)NCCc1c[nH]c2c1cccc2.Cl	C18H19ClN2O	314.81	44.89	Moderately soluble

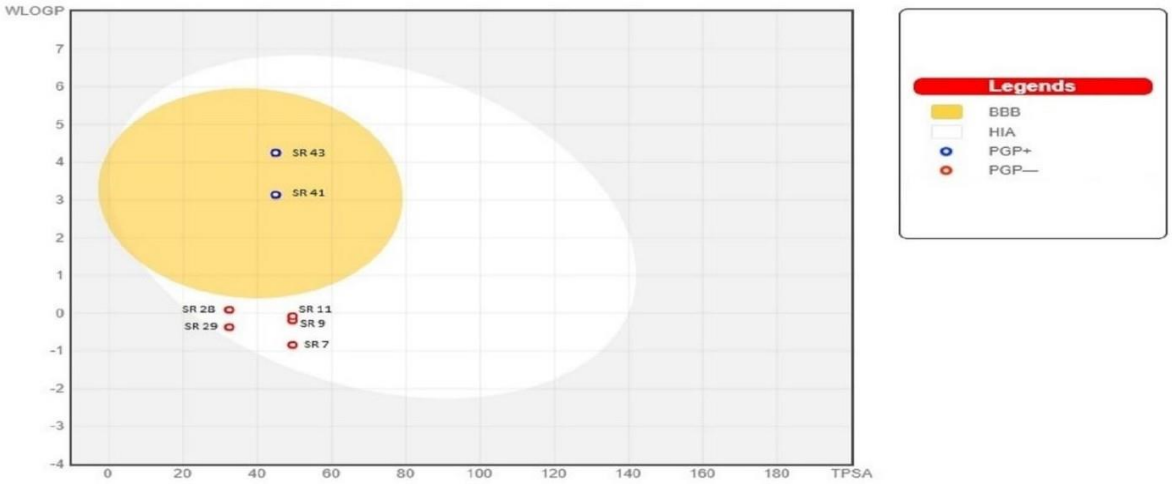

Figure -1: Boiled-egg for tryptamine derivatives

Table -2: ADMET profiles of Tryptamine derivatives using SwissADME and ADMETSAR.

Absorption				
Tryptamine Derivatives	**Human intestinal absorption**	**Blood-brain barrier penetration**	**P-glycoprotein substrate**	**Renal Organic Cation Transporter**
SR7	High	No	No	Inhibitor
SR9	High	No	No	Inhibitor
SR11	High	No	No	Inhibitor
SR28	High	No	No	Inhibitor
SR29	High	No	No	Inhibitor
SR41	High	Yes	Yes	Inhibitor
SR43	High	Yes	Yes	Inhibitor

Distribution	
Tryptamine Derivatives	**Subcellular localization**
SR7	Lysosome
SR9	Lysosome
SR11	Lysosome
SR28	Lysosome
SR29	Lysosome
SR41	Lysosome
SR43	Lysosome

Metabolism					
Tryptamine Derivatives	**CYP1A2 inhibitor**	**CYP2C19 inhibitor**	**CYP2C9 inhibitor**	**CYP2D6 inhibitor**	**CYP3A4 inhibitor**
SR7	No	No	No	No	No
SR9	Yes	No	No	Yes	No
SR11	Yes	No	No	Yes	No
SR28	No	No	No	Yes	No
SR29	No	No	No	Yes	No
SR41	Yes	Yes	No	Yes	Yes
SR43	Yes	Yes	No	Yes	Yes

Toxicity				
Tryptamine Derivatives	**AMES Toxicity**	**Carcinogens**	**Fish Toxicity**	**Biodegradation**
SR7	Non AMES toxic	Non-carcinogen	low FHMT	Not ready biodegradable
SR9	Non AMES toxic	Non-carcinogen	high FHMT	Not ready biodegradable
SR11	Non AMES toxic	Non-carcinogen	low FHMT	Not ready biodegradable
SR28	Non AMES toxic	Non-carcinogen	high FHMT	Not ready biodegradable
SR29	Non AMES toxic	Non-carcinogen	high FHMT	Not ready biodegradable
SR41	Non AMES toxic	Non-carcinogen	low FHMT	Not ready biodegradable
SR43	Non AMES toxic	Non-carcinogen	low FHMT	Not ready biodegradable

Table-3: Drug likeness of Tryptamine derivatives using SwissADME.

Drug-likeness							
Tryptamine Derivatives	SR7	SR9	SR11	SR28	SR29	SR41	SR43
log Kp (cm/s)	-5.94	-5.71	-5.93	-5.7	-5.54	-6.05	-5.54
Lipinski #violations	0	0	0	0	0	0	0
Ghose #violations	1	0	0	0	0	0	0
Veber #violations	0	0	0	0	0	0	0
Egan #violations	0	0	0	0	0	0	0
Muegge #violations	0	0	0	0	0	0	0
Bioavailability Score	0.55	0.55	0.55	0.55	0.55	0.55	0.55
PAINS #alerts	0	0	0	0	0	0	0
Brenk #alerts	0	0	0	0	0	0	0
Leadlikeness #violations	2	2	2	2	1	0	1
Synthetic Accessibility	2.03	2.12	2.15	2.04	2.04	1.76	1.96

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