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IN-SILICO ESTIMATION ON ORAL BIOAVAILABILITY AND DRUG-LIKENESS OF MONO AND BIS-MANNICH BASES OF PIPERAZINE DERIVATIVES

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ABSTRACT

In-silico estimation on Oral bioavailability and Drug-likeness of Mono and Bis-mannich bases of piperazine derivatives (1a-1o) were performed using molinspiration and preADMET studies. Molecular properties like topological polar surface area, volume, number of rotatable bonds etc. Membrane permeability and bioavailability and associated basic molecular descriptors such as partition co-efficient (LogP), molecular weight (MW), hydrogen bonding acceptors (HBA) and donors (HBD) count in a molecule. Drug-likeness and oral bioavailability of compounds (1a-1o) were reported.

Keywords: Drug-likeness, topological polar surface area, Membrane permeability.

INTRODUCTION

Drug-likeness is described to encode the balance among the molecular properties of a compound that influences its pharmacodynamics, pharmacokinetics and ADME (absorption, distribution, metabolism and excretion) in human body like a drug (Vistoli *et al.,* 2008). These parameters allow to estimate oral absorption or membrane permeability, that occurs when evaluated molecules obey the Lipinski's rule-of-five [logP≤5, MW≤500, HBD≤5 and HBA≤10] (Menenzes *et al.,* 2011). Other parameters that included are number of rotatable bonds, molecular volume, molecular polar surface area, percentage absorption and the *in vitro* plasma protein binding.

Drug-likeness was calculated for the compounds based on the molecular descriptors as per Lipinski's "Rule-of-Five" and other parameters like TPSA, volume, number of rotatable bonds etc. Membrane permeability and bioavailability are associated with some basic molecular descriptors such as partition co-efficient (LogP), molecular weight (MW), hydrogen bonding acceptors (HBA) and donors (HBD) count in a molecule. Number of rotatable bonds is important to know the conformational changes, flexibility and for the binding with receptor or channels (Ahsan *et al.,* 2011).

Molecular polar surface area (TPSA) is a descriptor for the prediction of passive molecular transport through membranes. TPSA and molecular volume is inversely proportional to percentage absorption (%ABS). Therefore, it allows prediction of transport properties of drugs in the intestines and blood-brain barrier crossing. The polar surface area (PSA) of a molecule is a useful descriptor for the optimization of drugs ability to permeate cells. This has been calculated as Topological polar surface area (TPSA), which is recognized as a good indicator of drug absorption in the intestine (TPSA less than 140 Angstroms squared [$A^{\circ 2}$]) and blood-brain barrier penetration (TPSA less than 60 $A^{\circ 2}$) (Ertl *et al.,* 2000; Prasanna *et al.,* 2009).

The *in silico* estimation of human intestinal absorption of a drug candidate involves numerous *in vitro* methods like percent human intestinal absorption (HIA), Caco2 (P_{Caco2}) and MDCK (P_{MDCK}) cell models and BBB (C_{brain}/C_{blood}) for the prediction of oral drug absorption and blood-brain barrier penetrations respectively. Based on the literature obtained about the molecular properties, in the present paper it is reported that *in-silico* estimation of drug likeness and oral bioavailability of a series of mono and bis-mannich bases of piperazine derivatives.

Calculation of drug-likeness and ADME properties

The parameters for drug-likeness were evaluated according to the Lipinski's rule-of-five, using the Supercomputing Facility for Bioinformatics & Computational Biology-IIT Delhi [http://www.scfbio-iitd.res.in] and TPSA values from Molinspiration online property calculator tool kit [http://www.molinspiration.com/services/properties.html.]. Topological polar surface area was used to calculate the percentage of Absorption (%ABS) according to the equation: %ABS = 109 – [0.345× TPSA] [Ahsan et al., 2011]. In vitro %HIA, Caco2 and MDCK cell permeabilities, plasma protein binding and blood-brain barrier penetration values were obtained from ADME calculator [http://www.preadmet.bmdc.org/index.php].

RESULTS AND DISCUSSION

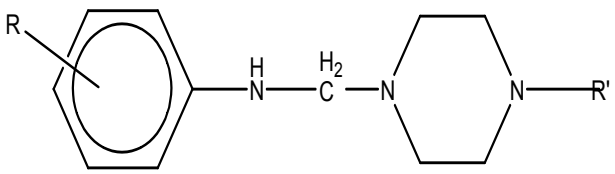
A series of mono and bis-mannich bases of piperazine derivatives were considered to calculate the molecular properties and presented in **Table 1-3**. The Lipinski's rule-of five is widely used as a filter for drug-likeness, which is estimated from the molecular properties such as partition coefficient (log P), molecular weight (MW), or hydrogen bond acceptors and donors of a molecule. All the compounds **1a-1o** obeyed the rule. These properties affect their absorption, distribution, metabolism and excretion (ADME) of the compounds and also indicate membrane permeability and bioavailability. It was reported that number of rotatable bonds should be ≤10 to pass the oral bioavailability and also explains the conformational changes and flexibility of molecules required for binding to the receptors (Ahsan *et al.,* 2011). Compounds **1a-1o** possess 3-8 rotatable bonds and therefore, exhibit optimum conformational flexibility (**Table 2**). The mono mannich bases possessing free-NH group (**1a-1d**) displayed low clogP values and less number of rotatable bonds when compared to other analogues.

Molecular polar surface area (TPSA) is a very useful parameter to predict the transport properties of drugs like intestinal absorption and blood-brain barrier penetration. It was observed that all the title compounds exhibited good %absorption ranging from 66.5 to 99.5%. Oral drug absorption can be predicted using *in vitro* models like human intestinal absorption (%HIA), Caco2 cell (P_{Caco2}) and MDCK cell (P_{MDCK}) permeabilities (**Table 3**). Compounds **1a-1o** showed % HIA ranging from 86 to 97%, optimum Caco2 cell permeability was displayed by the compounds **1a**, **1b** and **1d-1o** (4-70 nm/sec), while compounds **1a** and **1d** displayed optimum MDCK cell permeability (25-500 nm/sec). Compounds **1a-1d** and **1k-1m** showed optimum penetration into CNS via the blood-brain barrier. The significance of asymmetric bis mannich bases is supported by the molecular and preADME predictions and displayed optimum clogP, oral absorption, Caco-2 cell permeability and CNS penetrations than other substitutions, thus suggesting good oral bioavailability and drug-likeness.

CONCLUSION

From the data obtained it is revealed that, compounds 1a-1o obeyed the Lipinski's rule –of-five and displayed drug-likeness. Further the molecular prediction data supports that, the compounds showed good human intestinal absorptions, oral bioavailability and drug-likeness.

Table 1: Structural data of mono and bis-mannich bases of piperazines and their derivatives (1a-1o)



Compound	R	R'	M.F
1a	H	H	$C_{11}H_{17}N_3$
1b	2-NO_2	H	$C_{11}H_{16}N_4O_2$
1c	3-NO_2	H	$C_{11}H_{16}N_4O_2$
1d	4-NO_2	H	$C_{11}H_{16}N_4O_2$
1e	2-NO_2	C_6H_5	$C_{17}H_{20}N_4O_2$
1f	3-NO_2	C_6H_5	$C_{17}H_{20}N_4O_2$
1g	4-NO_2	C_6H_5	$C_{17}H_{20}N_4O_2$
1h	2-NO_2	-CH_2-NH-C_6H_4-2-NO_2	$C_{18}H_{22}N_6O_4$
1i	3-NO_2	-CH_2-NH-C_6H_4-3-NO_2	$C_{18}H_{22}N_6O_4$
1j	4-NO_2	-CH_2-NH-C_6H_4-4-NO_2	$C_{18}H_{22}N_6O_4$
1k	2-NO_2	-CH_2-NH-C_6H_5	$C_{18}H_{23}N_5O_2$
1l	3-NO_2	-CH_2-NH-C_6H_5	$C_{18}H_{23}N_5O_2$
1m	4-NO_2	-CH_2-NH-C_6H_5	$C_{18}H_{23}N_5O_2$
1n	2-NO_2	4-F-C_6H_4-	$C_{17}H_{19}FN_4O_2$
1o	2-NO_2	4-Cl-C_6H_4-	$C_{17}H_{19}ClN_4O_2$

Table 2: Prediction of the molecular properties for the N-((substitutedpiperazin-1-yl) methyl) benzenamine derivatives (1a-1o)

Compound	cLogP	M.Wt	HBA	HBD	Volume	nViola-tions	nrotb	TPSA	%ABS
1a	1.108	191	3	2	194.79	0	3	27.29	99.5
1b	1.019	236	6	2	218.13	0	4	73.11	83.7
1c	1.043	236	6	2	218.13	0	4	73.11	83.7
1d	1.067	236	6	2	218.33	0	4	73.11	83.7
1e	3.312	312	6	1	289.92	0	5	64.32	86.8
1f	3.336	312	6	1	289.92	0	5	64.32	86.8
1g	3.362	312	6	1	289.92	0	5	64.32	86.8
1h	2.995	386.	10	2	342.41	0	8	122.1	66.8
1i	3.043	386.	10	2	342.41	0	8	122.1	66.8
1j	3.091	386.	10	2	342.41	0	8	122.1	66.8
1k	3.084	341	7	2	319.12	0	7	76.35	82.6
1l	3.084	341	7	2	319.12	0	7	76.35	82.6
1m	3.132	341	7	2	319.12	0	7	76.35	82.6
1n	3.476	330	6	1	294.85	0	5	64.32	86.8
1o	3.99	346	6	1	303.45	0	5	64.32	86.8

%ABS, percentage of absorption; **MW**, molecular weight; **HBD**, number of H-bond donors; **HBA**, number of H-bond acceptors; **MR**, molar refractivity; **nrotb**, number of rotaTable bonds; **TPSA**, topological polar surface area.

Table 3: Calculation of ADME properties for the N-((substitutedpiperazin-1-yl) methyl) benzenamine derivatives **(1a-1o)**

Compound	HIA (%)	Invitro Caco-2 (nm/sec)	MDCK (nm/sec)	iPPB	C_{brain}/C_{blood}
1a	92.36	40.61	203.36	12.08	1.91
1b	87.43	1.218	14.59	31.36	0.46
1c	87.43	0.754	23.30	12.96	0.31
1d	87.43	20.63	31.07	20.13	0.04
1e	96.15	12.89	5.97	83.53	0.03
1f	96.15	7.57	5.49	69.24	0.09
1g	96.15	26.33	22.32	77.42	0.04
1h	86.65	9.06	9.29	58.30	0.013
1i	86.65	6.32	0.44	44.02	0.014
1j	86.65	20.62	1.51	60.25	0.013
1k	93.84	12.34	13.00	69.4	0.164
1l	93.84	23.43	1.66	80.96	0.25
1m	93.84	8.20	3.17	58.40	0.159
1n	96.15	24.61	0.43	83.73	0.054
1o	96.10	29.04	0.282	86.56	0.097

HIA(%), Percentage human intestinal absorption; P_{Caco2} (nm/sec), Caco2 cell permeability in nm/sec; P_{MDCK} (nm/sec), Madin-Darby canine kidney cell permeabity in nm/sec; PPB(%), in vitro plasma protein binding (percentage); BB(C_{brain}/C_{blood}), in vivo Blood-Brain Barrier penetration.

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