Computer aided pharmacokinetic profiling and toxicity analysis of naphthalene

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Abstract:
Naphthalene is an aromatic hydrocarbon used as room freshner. Therefore, it is of interest to document the computer aided pharmacokinetic profiling and toxicity analysis data of naphthalene.

Keywords: Naphthalene; neurotoxicity; prediction data.

Background:
Naphthalene (PubChem Id-931) is a polynuclear arenes having a pungent smell with a density of ≈0.44 mg/m3 in air **[1]**. The sources in the environment are abundant of this aromatic hydrocarbon. Domestic exposure of this naphthalene is due to its use in form of mothballs **[2]**. Naphthalene exposure is also seen with cement-based materials, which can be a potential environmental exposure apart from mothballs **[3]**. There is an often misuse of naphthalene in contravention of the insect repellents mark. The National Pesticide Information Center found considerable incidents of mothball exposure during 2006, and majority incidents were due to misuse **[4]**. Frequent misuse includes air ducts or crawlspaces, where vapor can be reached all over the enclosed milieu. The unintentional pediatric contact to mothball is a concern **[5]**. Newborns were affected with hemolytic anemia due to naphthalene exposure **[6]**. Few studies demonstrated the toxicity of naphthalene exposure **[7, 8]**, but still there is a gap in profiling the compound. Therefore, it is

of interest to document the computer aided pharmacokinetic profiling and toxicity analysis data of naphthalene.

Materials and Methods:
QikProp tool is a fast, precise, easy-to-use in identification of drug like compounds through absorption, distribution, metabolism, and excretion (ADME) calculation software [9]. We used QikProp to calculate hydrogen bond donor and acceptor, molecular weight, octanol-water partition coefficient, skin permeability, MDCK cell permeability, humeral absorption and their position followed Lipinski's rule of five (ro5) [10]. The reference compounds with PubChem ID 15608 (Methyl Tridecanoate), 8181 (Methyl Palmitate), 5362717 (Methyl Petroselinate) and 931 is naphthalene is used.

Table 1: Physical descriptors of computed ADMET profile of naphthalene against standard ligands.

Physical Descriptors / PubChem ID	Standard range	15608	8181	5362717	931
ACxDN^.5/SA	0.0 – 0.05	0	0	0	0
dip^2/V	0.0 – 0.13	0	0	0	0
dipole	1.0 – 12.5	2.8	3	2.4	0
FISA	7.0 – 330.0	54.4	53.6	54.3	0
FOSA	0.0 – 750.0	566.3	657.5	691.5	0
glob	0.75 – 0.95	0.8	0.8	0.8	0.9
PISA	0.0 – 450.0	0	0	12.9	334.9
SAamideO	0.0 – 35.0	0	0	0	0
SAfluorine	0.0 – 100.0	0	0	0	0
SASA	300.0 – 1000.0	620.7	711	758.7	334.9
volume	500.0 – 2000.0	1025.2	1201.4	1292.1	517.6

ACxDN^.5/SA:Index of cohesive interaction in solids, dip^2/V†:Square of the dipole moment divided by the molecular volume, dipole†:Computed dipole moment of the molecule, FISA:Hydrophilic component of the SASA, FOSA:Hydrophobic component of the SASA, Glob:Globularity, PISA:ĉ component of the SASA, SAamideO:Solvent-accessible surface area of amide oxygen atoms, SAFluorine:Solvent-accessible surface area of fluorine atoms, SASA:Total solvent accessible surface area (SASA) in squareÅ, Volume:Total solvent-accessible volume in cubic angstroms.

Table 2: Descriptors for prediction of drug-likeliness of naphthalene against standard drugs.

Drug-Likeliness Descriptors / PubChem ID	Standard range	15608	8181	5362717	931
#stars	0-5	3	3	3	8
#acid	0-1	0	0	0	0
#amide	0-1	0	0	0	0
#amidine	0	0	0	0	0
#amine	0-1	0	0	0	0
#in34		0	0	0	0
#in56		0	0	0	10
#NandO	2 – 15	2	2	2	0
#noncon		0	0	0	0
#nonHatm		16	19	21	10
#ringatoms		0	0	0	10
#rotor	0-15	11	14	15	0
#rtvFG	0-2	1	1	1	0
accptHB	2.0 – 20.0	2	2	2	0
donorHB	0.0 – 6.0	0	0	0	0
mol MW	130.0 – 725.0	228.4	270.5	296.5	128.2
QPlogKp	–8.0 to –1.0	-1.5	-1.2	-1	-0.3
QPlogPC16	4.0 – 18.0	8	9.9	10.9	5.5
QPlogPo/w	–2.0 – 6.5	4.6	5.8	6.4	3.4
QPlogPoct	8.0 – 35.0	8.9	10.6	11.6	5.2
QPlogPw	4.0 – 45.0	1.1	0.7	0.7	2.2
RuleOfFive	maximum is 4	0	1	1	0
WPSA	0.0 – 175.0	0	0	0	0

accptHB: Estimated number of hydrogen bonds accepted by the solute, acid: Number of carboxylic acid groups, amide: Number of non-conjugated amide groups, amidine: Number of amidine and guanidine groups, amine: Number of non-conjugated amine groups, donorHB: Estimated number of hydrogen bonds donated by the solute, in34:Number of atoms in 3- or 4-membered rings, in56:Number of atoms in 5- or 6-membered rings, mol_MW: Molecular weight of the molecule, NandO: Number of nitrogen and oxygen atoms, noncon: Number of ring atoms not able to form conjugated aromatic systems, noNHatm: Number of heavy atoms (no N Hydrogen atoms), ringatoms: Number of atoms in a ring, rotor: Number of rotatable bonds, rtvFG: Number of reactive functional groups, stars: Number of property or descriptor values that fall outside the 95 % range of similar values for known drugs, Rule of five:Numbers of violations of Lipinski's rule of five Compounds that satisfy these rules are considered drug like.

Table 3: Descriptors of bioavailability of naphthalene and standard ligands.

Descriptors / PubChem ID	Standard range	15608	8181	5362717	931
RuleOfThree	maximum is 3	0	1	1	0
#metab	1 – 8	1	1	3	0
#rotor	0-15	11	14	15	0
CIQPlogS	–6.5 – 0.5	-3	-3.9	-4.4	-3.7
Human Oral Absorption	1, 2, or 3 forlow, medium, or high	3	1	1	3
Percent Human Oral Absorption	>80% is high, <25% is poor	100	100	100	100
QPlogS	–6.5 – 0.5	-5.1	-6.4	-7.1	-3.6
QPPCaco	<25 poor,>500 great	3022.8	3076.6	3028.9	9906
QPpolrz	13.0 – 70.0	27.8	32.9	36	17.8

CIQPlogS: Conformation-independent predicted aqueous solubility, Humanoralabsorption: Predicted qualitative human oral absorption, #metab‡: Number of likely metabolic reactions, Percent human-oral absorption: Predicted human oral absorption on 0 to 100% scale, QPlogS: Predicted aqueous solubility, QPPCaco: Predicted apparent Caco-2 cell permeability in nm/sec, QPpolrz: Predicted polarizability in cubic angstroms, #rotor: Number of rotatable bonds, Rule of three: Number of violations of Jorgensen's rule of three.

Table 4: Descriptors of CNS activity of naphthalene and standard ligands.

Descriptors / PubChem ID	Standard range	15608	8181	5362717	931
QPlogBB	–3.0 – 1.2	-0.7	-0.9	-1.0	0.2
QPPMDCK	<25 poor,>500 great	1635.4	1666.9	1638.9	5899.3
CNS	-2 to +2	0	-1	-1	1

CNS: Predicted central nervous system activity, QPlogBB: Predicted brain/blood partition coefficient, QPPMDCK: Predicted apparent MDCK cell permeability in nm/sec.

Table 5: Descriptors of dermal penetration of naphthalene and standard drug like molecules.

Descriptors / PubChem ID	Standard range	15608	8181	5362717	931
Jm	> 100	0.1	0.0	0.0	11.5
QPlogS	–6.5 – 0.5	-5.1	-6.4	-7.1	-3.6
QPlogKp	–8.0 to –1.0	-1.5	-1.2	-1.0	-0.3
mol MW	130.0 – 725.0	228.4	270.5	296.5	128.2

Jm: Predicted maximum transdermal transport rate-Kp × MW × S. log S. S in mol dm–3, mol_MW: Molecular weight of the molecule, QPlogKp:Predicted skin permeability, log Kp, QPlogS: Predicted aqueous solubility.

Table 6: Descriptors of protein binding capacity of naphthalene and standard drug molecules.

Descriptors / PubChem ID	Standard range	15608	8181	5362717	931
QPlogKhsa	–1.5 – 1.5	0.6	1.0	1.2	0.1
donorHB	0.0 – 6.0	0	0	0	0
accptHB	2.0 – 20.0	2	2	2	0
PSA	7.0 – 200.0	36.2	35.7	36.5	0.0

accptHB: Estimated number of hydrogen bonds accepted by the solute, donorHB: Estimated number of hydrogen bonds donated by the solute, PSA: Van der Waals surface area of polar nitrogen and oxygen atoms and carbonyl carbon atoms, QPlogKhsa: Prediction of binding to human serum albumin.

Table 7: Descriptors of metabolism of naphthalene and standard drug like molecules.

Descriptors / PubChem ID	Standard range	15608	8181	5362717	931
#metab	1 – 8	1.0	1.0	3.0	0.0
QPlogHERG	Concernbelow–5	-4.9	-5.3	-5.5	-4.2

metab‡:Number of likely metabolic reactions, QPlogHERG:Predicted IC50 value for blockage of HERG K+ channels.

Results and Discussion:
The physical descriptors described in **Table 1**, shows favaourable physical properties for naphthalene as drug molecule. A drug molecule's physical and chemical properties decide its ability to traverse across tissue membranes. Main factors include molecular weight, molecular volume, and surface areas. The dipole moment of drug molecules decides the receptor interactions and its absorption. The present study evaluated these parameters of naphthalene using computational methods. Naphthalene showed satisfactory physical properties like globularity, surface area for accessibility of solvents, molecular volume, cohesive interaction index, and molecular dipole moment **[Table 1]**. The prediction of drug-likeliness of naphthalene was evaluated following ro5. Naphthalene showed very minimum number of violations against ro5 in terms of molecular weight, solubility, hydrogen bond donor, hydrogen bond acceptor, and rotatable bonds. The number of heavy atoms and rotatable bonds were minimum. Octanol/water coefficient decides the hydrophobicity, which is in satisfactory range for naphthalene. Hexadecane/gas partition coefficient also showed good polarizability by naphthalene **[11-13]**. There was no

weak surface polarity in naphthalene **(Table 2)**. The bioavailability descriptors of naphthalene satisfied Jorgensen's rule of three (ro3) **[14-18]**. This revealed the aqueous solubility, intestinal absorption and minimum metabolite formation of naphthalene, which implies its oral absorption and bioavailability **(Table 3)**. The CNS activity of naphthalene was revealed by blood/brain partition coefficient descriptor, which is in recommended range **[18]**. The computed MDCK tissue permeability was also maximum which implies traversal of naphthalene across cell membranes **(Table 4)**. Naphthalene showed dermal penetration rate of 11.5 Ĵg cm–2 hr–1, which is poor as per standard reference value **(Table 5)**. This is directly related to skin permeability (K$_p$), aqueous solubility (S), and molecular weight of the compound, and calculated as $J_m = K_p$ X **MW** X **S**

Plasma-protein binding decides the distribution of drug in the body **[10]**. The computed serum albumin protein binding of naphthalene was satisfactory, and in standard reference range **(Table 6)**. Naphthalene showed zero metabolite formation, which implies that it reaches the target site unchanged **(Table 7)**. In contrary, naphthalene-producing metabolites like 1,2-naphthquinone and 1,2-dihydroxynaphthalene were demonstrated in rabbit experiment. These metabolites were shown to have active interactions with many enzymes in the body causing toxic effects **[19]**. Few other studies revealed naphthalene metabolites from urine samples of four species fed with naphthalene. They found 1-naphthol, 2-naphthol, 1:2-dihydronaphthalene-1: 2-diol, 1:2-dihydro-2-hydroxy-1-naphthylglucosiduronic acid, 1-naphthylmercapturic acid in urine samples analyzed with chromatography techniques **[20-22]**. *In-vitro* study using bacterial cultures treated with naphthalene showed metabolites like 2-naphthoic acid, decahydro-2-naphthoic acid, 5,6,7,8-tetrahydro-2-naphthoic acid, octahydro-2-naphthoic acid through mass spectroscopy analysis **[23]**. The toxicity profile of this metabolite varied as revealed by an *in-vitro* study. The primary metabolites were less toxic to leucocytes compared to naphthalene-1, 2-epoxide, in causing glutathione depletion and genotoxicity **[24]**. Naphthalene has cardiac toxic potentiality revealed through the HERG K+ channel blockade descriptor **[25]**.

Conclusion:
We document the computer aided pharmacokinetic profiling and toxicity analysis data of naphthalene.

Conflicts of interest:
None

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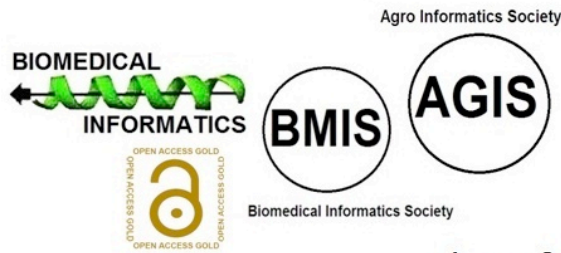[25] Alexandrou AJ et al. Br J Pharmacol. 2006 **147:** 905 [PMID: 16474415].

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