In-silico drug likeness predictions of novel 9-benzyl-6-(furan-2-yl)-2-(N,N dimethylamino)-9H-purine compound

Mr. Arvinder Pal Singh[*1], Mr. Ankush Goyal[1], Dr. Navjot Singh Sethi[2]

1. Department of Pharmaceutical Chemistry, Maharaja Agrasen University School of Pharmacy, Baddi, H.P.

2. Department of Pharmaceutical Chemistry, CGC, Landran, SAS Nagar, Punjab.

[*]*Address of correspondence: Department of Pharmaceutical Chemistry, Maharaja Agrasen University School of Pharmacy, Baddi, H.P. Tel: +919417667810, email: arvsodhi19@gmail.com*

ABSTRACT:

In silico studies, are increasing now-a-days, as through computer mechanics, screening of novel compounds based upon their physicochemical properties is important to reduce the cost of synthesizing novel medicinal compounds. In silico studies by network analysis and throughout screening helps to know and calculate biological activity of medicinal compounds. Novel 9-benzylpurine derivatives synthesized previously are used to study its structure and bioavailability radar, physicochemical properties, lipophilicity, solubility, pharmacokinetics, drug likeness and medicinal chemistry properties. These properties are calculated by use of Chem draw, open babel[16] and SwissADME software available freely. The novel 9-benzyl-6-(furan-2-yl) -2-(N,N dimethylamino)-9H-purine compound[17] shows good druglikeness properties to make it orally active.

1. INTRODUCTION:

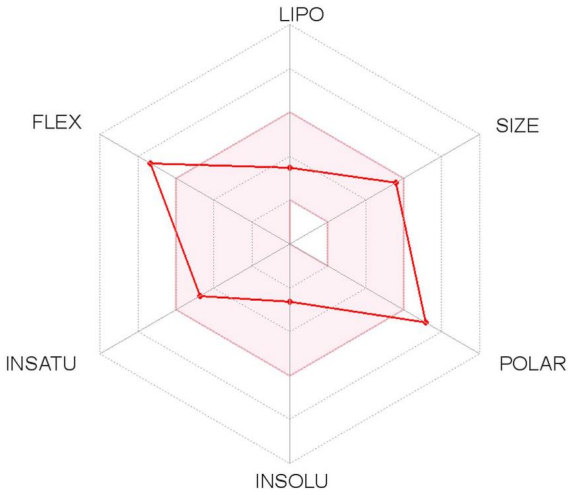
Drug discovery is very time and money consuming process with low success rate. Despite advancements in new technology, drug discovery is very lengthy, difficult, expensive and inefficient process. A single entity takes 12-15 years with costs about US$1.8 billion as per US FDA to bring it as drug in market. only 20% drug candidates reach clinical trials but only 1% in drug discovery, many new molecules don't reach target due to poor ADME and high toxicity. Poor bioavailability doesnot give threshold potential therapeutic effect while high toxicity makes compound unsuitable. This poor pharmacokinetics of drugs can be minimized by computational methods. So, drug development is a method of optimizing drug likeness to maximize safety, efficacy and pharmacokinetics. Pharmacokinetics of drugs helps to calculate drug's absorption, distribution, metabolism, excretion properties. [5]Lipinski rule of 5 helps in constituting a successful drug candidate. It states that orally active drug has one or more of the following properties i.e hydrogen bond acceptors less than 10, hydrogen bond donors less than 5, molecular mass less than 500 daltons and log P less than 5. More than 5 hydrogen bond donors and more than 10 hydrogen bond acceptors hinders permeability of drug across membrane bilayer.

2. MATERIALS AND METHODS:

2.1 Swiss ADME [1]

2.2 Structure and bioavailability radar: biovailability radar give the first glimpse of the drug-likeliness of the molecule in graphical view. By viewing it, a drug can be judge whether it is orally available bioactive or bioinactive. This bioavailability radar consists of 6 physicochemical properties like LIPO(Lipophlicity), SIZE, POLAR(Polarity),

INSOLU(Insolubility), INSATU(Insaturation), and FLEX(Flexibility). The exquisite range for each property are: LIPO, (XLOGP3 between -0.7 and + 5.0), SIZE (150-500 g/mol molecular weight), POLAR(TPSA between 20 and 130 ^{0}A, INSOLU(logS < 6), INSATU(Sp^3 hybridisation carbon fraction not less than 0.25, and FLEX (not more than 9 rotatable bonds)



The shaded portion represents exquisite range for each properties.

2.3 Physicochemical properties [4]: Physicochemical properties are the intrinsic physical and chemical characteristics of drugs that include molecular formula, molecular weight, no. of heavy and aromatic heavy atoms, Sp3 carbon fraction, number of hydrogen bond acceptor and donor, molar refractivity, total polar surface area.

2.4 Lipophilicity[18][19]: the overall quality of new drug candidate can by improved by lipophilicity. Lipophilicity is attributed with ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicology) porperties of drugs. Improving ADMET properties will improve lipophicity that increases druglikeness and bioavailability.

Lipophilicity parameters calculated through swiss ADME are iLOGP,XLOGP3, WLOGP,MLOGP, SILICOS-IT, and consenus Log P.

Solubility: Solubility is important parameter to considered while administering drug as it greatly influenced absorption of drug in-vivo. Drugs intended for parenteral administration should be highly water solution to release maximum concentration of API. Two topological methods are available in SwissADME online plateform for predicting water solubility.

Pharmacokinetics[20]:

Drug likeness: Drug-likeness aims to predict whether drug is orally active or not with respect to its bioavailability. The SwissADME gives admittance to five different rule based approaches with variable ranges of properties which helps to identify drug likeness properties of drugs. These rule of five approaches helps in improving the quality of their proposed drug.

3. RESULT:

Physicochemical Properties (Table 1)	
Formula	C18H17N5O
Molecular weight	319.36 g/mol
Num. heavy atoms	24
Num. aromatic heavy atoms	20
Fraction Csp3	0.17
Num. rotatable bonds	4

Num. H-bond acceptors	4

Lipophilicity (Table 2)	
Log $P_{o/w}$ (iLOGP) [3]	3.03
Log $P_{o/w}$ (XLOGP3) [4]	2.87
Log $P_{o/w}$ (WLOGP)	3.20
Log $P_{o/w}$ (MLOGP)[5]	1.72
Log $P_{o/w}$ (SILICOS-IT)	2.30
Consensus Log $P_{o/w}$	2.62

Water Solubility (Table 3)	
Log *S* (ESOL)[6]	-3.98
Solubility	3.34e-02 mg/ml ; 1.05e-04 mol/l
Class	Soluble
Log *S* (Ali)[7]	-3.79
Solubility	5.19e-02 mg/ml ; 1.63e-04 mol/l
Class	Soluble
Log *S* (SILICOS-IT)	-6.08
Solubility	2.63e-04 mg/ml ; 8.24e-07 mol/l
Class	Poorly soluble

Pharmacokinetics (Table 4)	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.21 cm/s

Druglikeness (Table 5)	
Lipinski	Yes; 0 violation
Ghose[8]	Yes
Veber[9]	Yes
Egan[10]	Yes
Muegge[11]	Yes
Bioavailability[12]	0.55

Medicinal Chemistry (Table 6)	
PAINS[13]	0 alert
Brenk [14]	0 alert

Leadlikeness[15]	Yes
Synthetic accessibility	3.11

Swiss Target Prediction :

Target	**Common name**	**Uniprot ID**	**ChEMBL ID**	**Target Class**	**Probability***	**Known actives (3D/2D)**
Adenosine A1 receptor	ADORA1	P30542	CHEMBL226	Family A G protein-coupled receptor	0.5004279094	564 /298
Adenosine A2a receptor	ADORA2A	P29274	CHEMBL251	Family A G protein-coupled receptor	0.5004279094	625 /337
Adenosine A2b receptor	ADORA2B	P29275	CHEMBL255	Family A G protein-coupled receptor	0.1046719412	238 / 135
Adenosi	ADOR	P0DM	CHEMB	Family A G	0.1046719412	298 /

ne A3 receptor	A3	S8	L256	protein-coupled receptor	128	167
GABA-A receptor; alpha-3/beta-3/ gamma-2	GABRB3 GABRA3 GABRG2	P28472 P34903 P18507	CHEMBL2094120	Ligand-gated ionchannel	0.10467194128	53 / 0
GABA-A receptor; alpha-1/beta-3/ gamma-2	GABRB3 GABRG2 GABRA1	P28472 P18507 P14867	CHEMBL2094121	Ligand-gated ionchannel	0.10467194128	49 / 0
GABA-A receptor; alpha-5/beta-3/ gamma-2	GABRB3 GABRG2 GABRA5	P28472 P18507 P31644	CHEMBL2094122	Ligand-gated ionchannel	0.10467194128	57 / 0
GABA-A receptor;	GABRA2	P47869	CHEMBL209413	Ligand-gated ionchannel	0.10467194128	55 / 0

alpha-2/beta-3/gamma-2	GABRB3 GABRG2	P28472 P18507	0			
Phosphodiesterase 5A	PDE5A	O76074	CHEMBL1827	Phosphodiesterase	0.10467194128	173 / 0
GABA receptor alpha-5 subunit	GABRA5	P31644	CHEMBL5112	Ligand-gated ionchannel	0.10467194128	133 / 0
Metabotropic glutamate receptor 5 (by homology)	GRM5	P41594	CHEMBL3227	Family C G protein-coupled receptor	0.10467194128	213 / 0
Serine/threonine- protein kinase PLK1	PLK1	P53350	CHEMBL3024	Kinase	0.10467194128	44 / 0
Butyrylcholinesterase	BCHE	P06276	CHEMBL1914	Hydrolase	0.10467194128	64 / 0
Estrogen receptorbeta	ESR2	Q92731	CHEMBL242	Nuclear receptor	0.10467194128	52 / 0
Acetylcholineste	ACHE	P22303	CHEMB	Hydrolase	0.104671941	102 / 0

rase			L220		128	
Serine/threonine-protein kinase Aurora-B	AURKB	Q96GD4	CHEMBL2185	Kinase	0.10467194128	178 / 0
Glycogen synthase kinase-3 beta	GSK3B	P49841	CHEMBL262	Kinase	0.10467194128	273 / 0
Serine/threonine-protein kinase Aurora-A	AURKA	O14965	CHEMBL4722	Kinase	0.10467194128	321 / 0
Arachidonate 5-lipoxygenase	ALOX5	P09917	CHEMBL215	Oxidoreductase	0.10467194128	93 / 0
Cathepsin K	CTSK	P43235	CHEMBL268	Protease	0.10467194128	214 / 0
Cathepsin S	CTSS	P25774	CHEMBL2954	Protease	0.10467194128	235 / 0
Cathepsin (V and K) (by homology)	CTSV	O60911	CHEMBL3272	Protease	0.10467194128	35 / 0
Prostanoid	PTGER	P43115	CHEMB	Family A G	0.10467194	162 / 0

EP3 receptor	3		L3710	protein-coupled receptor	128	

4. DISCUSSION:

The most important step in drug designing is find out whether the synthesized novel moiety is orally active or not. So, for carrying out ADMET studies, SwissADME web tool is used describes disposition of drug compound in the body. SwissADME online plateform helps for computation of physicochemical, pharmacokinetic, drug-like and related parameters.

9-benzyl-6-(furan-2-yl) -2-(N,N dimethylamino)-9H-purine follows lipinski's rule of five with 0 violation (Table 5) that makes this moiety clinically effective. In Swiss target prediction, this novel 9-benzylpurine makes good binding with adenosine receptors that belongs to target class Family A G protein- coupled receptor. Both A_1 receptors and A_{2A} play roles in the heart, regulating myocardial oxygen consumption and coronary blood flow while A_{2A} receptor also has broader anti-inflammatory effects throughout the body. Also, these receptors are responsible for the regulating the release of various neurotransmitters like dopamine and glutamate. Adenosine A_{2B} and A_3 receptors are located mainly peripherally and are involved in processes such as inflammation and immune responses.

A_1 receptors binding probability 0.50042790394, A_{2A} has 0.50042790394, A_{2B} has 0.104671941128 and A_3 has 0.104671941128.

5. **CONCLUSION:**

ADMET in-silico studies provides an invaluable method in lead identification and optimization. In this study, novel 9-benzyl-6-(furan-2-yl) -2-(N,N dimethylamino)-9H-purine, shows anti-

malarial agents were designed. ADMET in-silico studies of this 9-benzylpurine derivatives showed good pharmacokinetic profile that makes it orally active and less toxic. This novel 9-benzylpurine derivative has good pharmacological adenosine receptors binding and also can be used as leadlikeness (Table 6)

6. REFERENCES:

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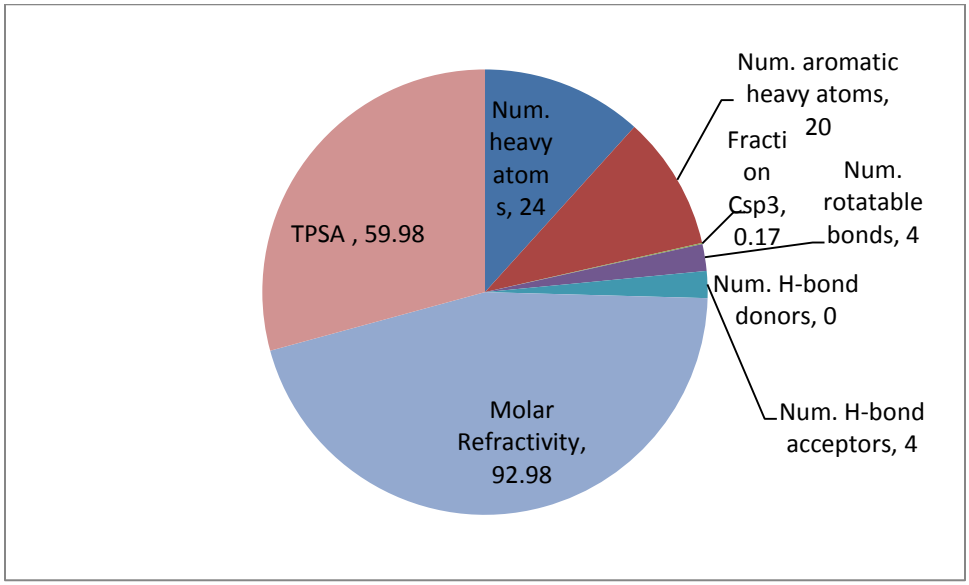
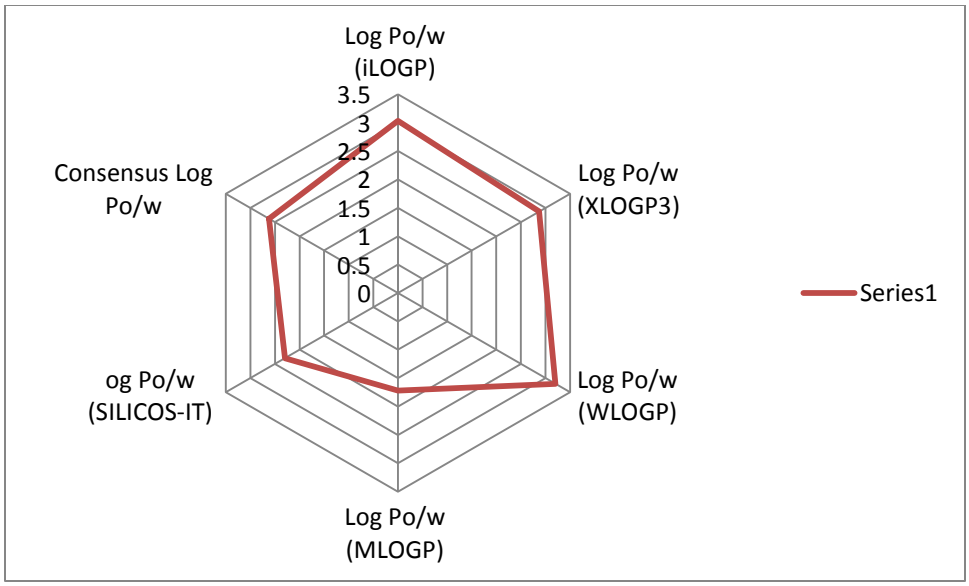
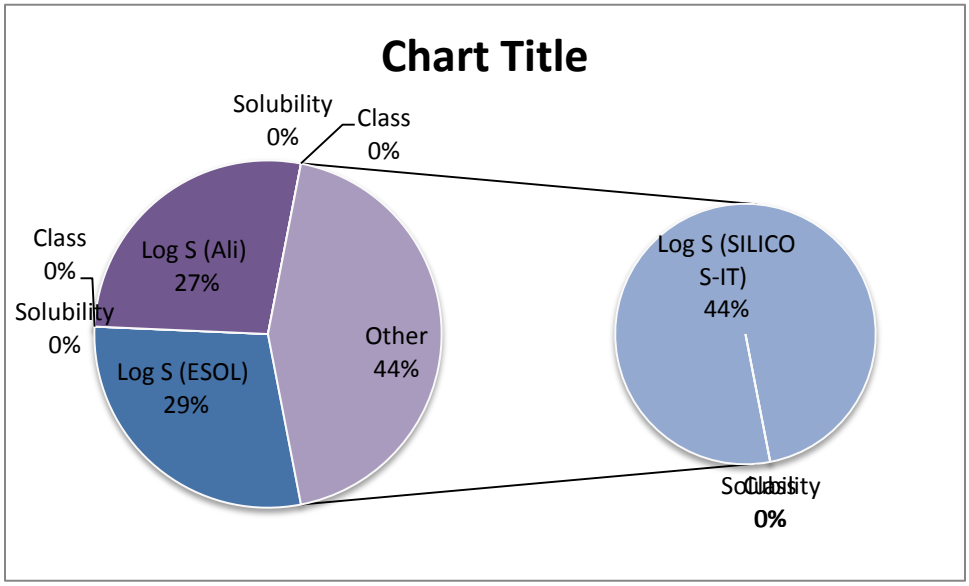
GRAPHS:



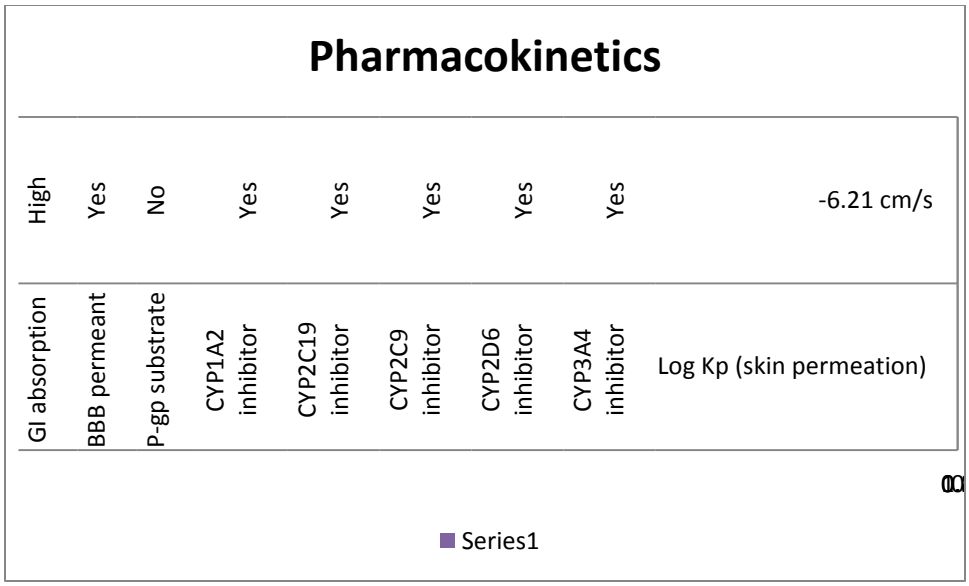
Graph 1: Physicochemical Properties of 9-benzylpurine derivatives



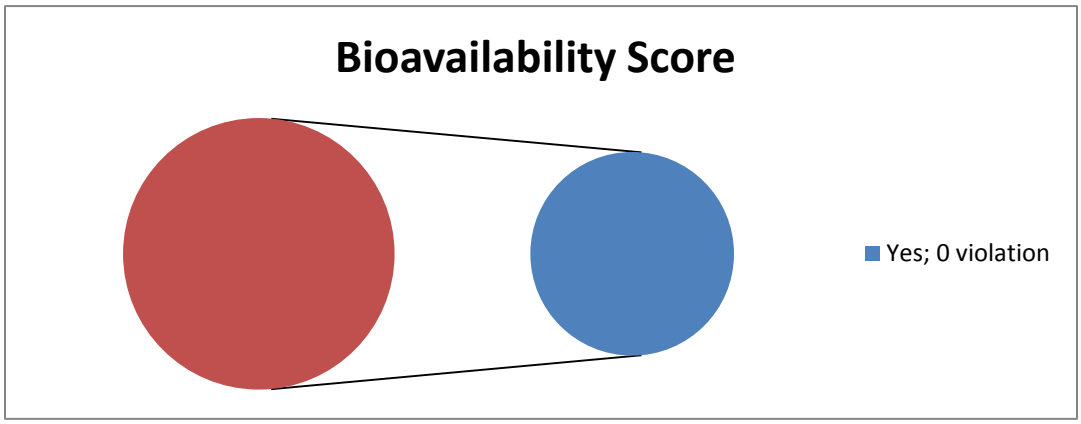
Graph 2: Lipophilicity of 9-benzylpurine derivatives



Graph 3: water solubility



Graph 4: Pharmacokinetics



Graph 5: Drug likeness