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Drug-Likeness and Pharmacokinetics of a bis-Phenolic Ligand: Evaluations by Computational Methods

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Abstract **Original Research Article**

Objectives: The aim of the present work was to predict physico-chemical, biological proprieties, bioactivity, oral bioavailability, Drug-Likeness and pharmacokinetics-toxicity (ADMET) of the ligand 2-[(1*E*)-*N*-{2-[(2-{(*Z*)-[1-(2-hydroxyphenyl) ethylidene] amino}ethyl) amino]ethyl}ethanimidoyl]phenol. ***Methods:*** *In silico*, physico-chemical, biological proprieties, bioactivity, oral bioavailability and pharmacokinetics-toxicity (ADMET), of the ligand were predicted by online computer software programs such as Molinspiration, Molsoft, ACD/I-Lab, pkCSM and admetSAR. ***Results:*** Our results indicate that the ligand acts as drug-like with an excellent maximum passive absorption (100%) and with drug likeness score of 0.21, and has a good oral bioavailability with a score of 0.55, which agrees with drug discovery rules: Lipinski (Pfizer), Ghose (Amgen), Veber (GSK), Egan (Pharmacia), and Muegge (Bayer). Results also showed that the enzymatic inhibitory effect of the ligand with predicted value of 0.01. In addition, non-carcinogenicity and non- mutagenicity were predicted. ***Conclusion:*** The ligand has an excellent bioavailability and enzymatic inhibitory effect, which was the possibility to be a safe oral drug-candidate in the future.
Keywords: molecular proprieties, bioactivity prediction, Drug-likeness, ADMET, oral bioavailability.

INTRODUCTION

Schiff bases are very important ligands in medicinal and pharmaceutical fields because of their wide spectrum of biological activities [1]. Several studies showed that the presence of alone pair of electrons in asp [2] hybridized orbital of a nitrogen atom of the azomethine group is of considerable chemical and biological importance [2]. These Schiff bases display activities such as antibacterial, anticonvulsant, anti-inflammatory, anticancer, anti-hypertensive, anti-fungal, antipyretic, antimicrobial, anti-HIV, cytotoxic activity, hypnotic, and herbicidal [3]. In addition, the interamolecular hydrogen bonding between the hydroxyl (OH) hydrogen and C=N nitrogen of Schiff bases determines the properties of various molecular systems and plays a significant role in many biochemical mechanisms[4].In recent years; there has been an increasing interest in the design and development of Schiff base derivatives. In this regard, a large number of heterocyclic Schiff bases have been reported with interesting biological activity including bactericidal, fungicidal, antipyretic, antitumor, antitubercular, anticancer, and sterease inhibitory activities[5].In addition, published reports indicated that Schiff bases of coumarin are well-known for their fluorescent properties and usefulness as laser dyes [6]. On the other hand, Schiff bases derived from aminopyridines are used as spectrofluorimetric analytical reagents [7]. They are also important intermediates in reactions involving interaction of an enzyme with an amino or a carbonyl group of the substrate [8].

Schiff's base derivatives from murrayanine were reported to possess remarkable anti-oxidant activity [9]. Yousif *et al*. [10] have described the synthesis of tetra Schiff bases; among the synthesized compounds 1, 2, 4, 5-tetra [5-(4-nitrobenzylidene amino)-1, 3, 4-thiadiazole-2-yl] benzenewas found to be the most potent antimicrobial activity. In addition, Salga *et al*. [11]; synthesized a series of Schiff bases from 1-(2-Ketoiminoethyl)piperazines, the highest inhibitory effect on human acetylcholinesterase is comparable with that of propidium, a known AChE inhibitor. On other hand, Shantharam and coworkers [12], synthesized and characterized a series of benzene-1,3,5-tricarboxylic acid-mediated Schiff base derivatives; these were considered as novel antiglycating agents. In a similar fashion, the synthesis and antibacterial activity of a Schiff base derived from indoline-2, 3-dione and 2-aminobenzoic acid has been

described by Salvat and colleagues13who observed a remarkable effect of this compound against Staphylococcus aureus, due to the presence of a hydroxyl and phenyl groups. On the basis of the above discussion and owing to the bioactivity of Schiff bases, we sought to undertake in silico studies such as physic-chemical and biological proprieties, bioactivity, oral bioavailability, pharmacokinetics, and toxicity (ADMET) of the Schiff base ligand 2-[(1E)-N-{2-[(2-{(Z)-[1-(2hydroxyphenyl)ethylidene] amino}ethyl)amino]ethyl} ethanimidoyl]phenol by means of an online computer software programs.

EXPERIMENTAL SECTION

In silico physico-chemical and biological properties evaluation

Molinspiration (www.molinspiration.com), Molsoft (http://molsoft.com/mprop/) and ACD/I-Lab (http://www.acdlabs.com/) software were employed to calculate the physico-chemical properties of the ligand. In addition, Molinspiration and Molsoft software were used to compute the bioactivity and Drug-likeness model score of the ligand**.** The absorption percentage (% AB) was calculated using the formula [14, 15]:

$$AB\% = 109 - (0.345 \times TPSA).$$

SwissADME [16] web tool (http://www.swissadme.ch) was used to predict the physicochemical properties, lipophilicity, water solubility, bioavailability, and medicinal chemistry of the ligand. The pharmacokinetic parameters: Absorption, Distribution, Metabolism, Excretion and the Toxicity (ADMET) of the ligand can be predicted using pkCSM (http://structure.bioc.cam.ac.uk/pkcsm) [17], and admetSAR (http://www.admetexp.org) database.

RESULTS AND DISCUSSIONS

Molecular properties and bio-activity prediction

The computational method used to evaluate the physico-chemical properties, lipophilicity, water solubility, drug-likeness, bioavailability score, and medicinal chemistry of the synthesized ligand revealed that the compound is a hydrophobic and basic drug, with pKa =12.10 and pKb=10.50. Parameters obtained from computations are shown in Tables 1, 2, 3, and4. Lipophilicity of the ligand was investigated by the following denomination according to the tools used for prediction: miLogP, iLogP, Log P,and MolLogP. The miLogP, iLogP,and MolLogP values of the ligand were below 5, (miLogP = 3.44), (MolLogP =2.22), (iLogP= 3.44), (LogP=3.48), which imply that it has good permeability across cell membrane.

The solubility in water is an important parameter for drug absorption, which demonstrates that high log S values correspond to good absorption [18]. In our results, MolLogS = -3.21which is >-4.For polarity, results indicate that the ligand has a predicted polar surface area TPSA and MolPSA values of 77.21 and 60.96 $Å^2$, respectively; these results confirm one of the five important conditions for aprimary step of drug discovery process where the polar surface area(TPSA or MolPSA) is with optimal values ≤120 $Å^2$. In addition, the molecular mass of 339. 44g/mol, which is < 500g/mol. Number of violations is 0. The number of hydrogen bond donors (= 3), which is < 5, (The sum of OHs and NHs) and the number of hydrogen bond acceptors=5, which is <10 (The sum of Os and Ns). The absorption percentage AB% = 82.36%, which is an indication of an excellent bioavailability by oral route (>50%) [19].

Table-1: Physicochemical proprieties of the ligand usingSwiss ADMEsoftware.

Physicochemical proprieties								
MW(g/mol)	Number of heavy atoms	Number of arom. heavy atoms	Fraction Csp3	Number of rotatable bonds	Number of H-bond acceptors	Number of H-bond donors	Molar Refractivity	TPSA (Å²)
339.43	25	12	0.30	8	5	3	103.76	77.21

Lipophilicity					
Log $P_{o/w}$ (iLOGP)	Log $P_{o/w}$ (XLOGP3)	Log $P_{o/w}$ (WLOGP)	Log $P_{o/w}$ (MLOGP)	Log $P_{o/w}$ (SILICOS-IT)	Consensus Log $P_{o/w}$
3.44	2.07	3.01	1.68	4.47	2.93

Water solubility					
Log *S* (ESOL)	-3.08	Log *S* (Ali)	-3.32	Log *S* (SILICOS-IT)	-6.36
Solubility	2.85e-01 mg/ml ; 8.40e-04 mol/l	Solubility	1.62e-01 mg/ml ; 4.78e-04 mol/l	Solubility	1.47e-04 mg/ml ; 4.33e-07 mol/l
Class	Soluble	Class	Soluble	Class	Poorly soluble

Drug-likeness					
Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability Score
Yes; 0 violation	Yes	Yes	Yes	Yes	0.55

Medicinal Chemistry			
PAINS	Brenk	Lead-likeness	Synthetic accessibility
0 alert	1 alert: imine_1	No; 1 violation: Rotors>7	2.94

Table-2: Physicochemical proprieties of the ligand usingACD/I-Lab software

Physical proprieties						
Molar Refractivity (cm^3)	Molar Volume (cm^3)	Parachor (cm^3)	Index of Refraction	Surface Tension (dyne/cm)	Density (g/cm^3)	Polarizability (cm^3)
100.11 ± 0.5	304.4 ± 7.0	772.5 ± 8.0	1.571 ± 0.05	41.4 ± 7.0	1.11 ± 0.1	39.69 ± 0.5 10^{-24}

Main physico-chemical determinants										
LogP	pKa (Acid)	pKa (Base)	Maximum passive absorption (%)	Pe, Jejunum (pH=6.5), (cm/s)	Absorption rateKa)	Fraction unbound in plasma	LogBB	LogPS	LogPB	Log(PS*fu, brain)
3.48	12.10	10.50	100	4.88x10-4	0.03 $3min^{-1}$	0.24	0.05	-2.2	0.68	-3.5

Table-3: Physicochemical proprieties of the ligand using Molinspiration software

AB (%)	TPSA (Å²)	n-ROTB	MV (Å³)	MW (g/mol)	miLogP	n-ON (acceptors)	n-OHNH (donors)	Lipinski's violations
-	-	-	-	< 500	≤ 5	< 10	< 5	≤ 1
82.36	77.21	8	330.74	339.44	3.44	5	3	0

Table-4: Physicochemical proprieties of the ligand usingMolsoft software

MolPSA (Å²)	Number of stereo centers	MV (A^3)	MW (g/mol)	MolLogP	MolLogS		HBA	HBD	Drug-likeness model score
					Log(moles/L)	Log(moles/L)			
60.96	0	365.86	339.19	2.22	-3.21	210.90	5	3	0.21

In addition, our results show that the ligand has a drug-like with an excellent maximum passive absorption (100%) and adrug likeness score of 0.21(Figure 2), and has a good oral bioavailability with a bioavailability score of 0.55, from the five different methods: Lipinski [20] (Pfizer), Ghose[21] (Amgen), Veber [22] (GSK), Egan [23] (Pharmacia) and Muegge [24] (Bayer). These results are in good agreement with those obtained in the radar plot "pink area" of the plot which defines the oral drug-like limits for the six conditions (Figure 3):

- Lipophilicity : XLOGP between − 0.7 and + 5.0
- Size :MW between 150 and 500 g/mol
- Polarity : TPSA between 20 and 130 A^2

- Solubility : not higher than 6
- Saturation: of carbons in the sp^3 hybridization not less than 0.25
- Flexibility: no more than 9 rotatable bonds.

On the other hand, and for synthetic accessibility (SA) determination, results indicate "very easy" for the synthesis of the ligand L**,** with (SA=2.94). Remarkably, one structural alert was predicted from L which explains the possibility of an unstable or toxic agent, chemically reactive or to have poor pharmacokinetic proprieties [25].

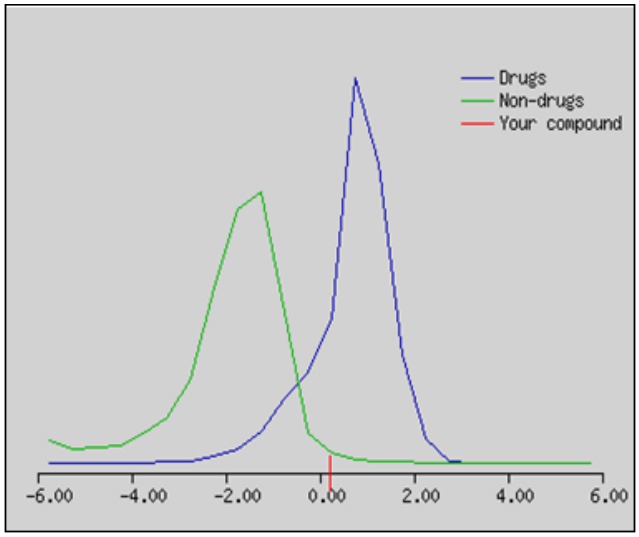

Fig-2: Drug-likeness model score of the ligand

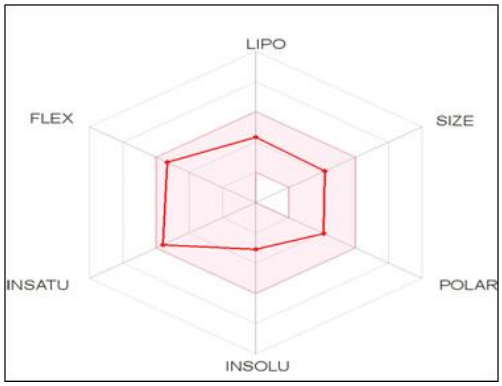

Fig-3: Bioavailability radar of the ligand Bio-activity prediction

The bioactivity scores can be interpreted as: active (bioactivity score > 0), moderately active (bioactivity score: -5.0–0.0) and inactive (bioactivity score < -5.0)[26].Bioactivity prediction of Land the value obtained is shown in Table5. The bioactivity score of the ligand towards GPCR ligand, ion channel modulator, nuclear receptor ligand and kinase, protease and enzymes inhibitions, indicated that the ligand exhibits active score on enzyme inhibition with bioactivity score of: 0.01, and moderately active towards GPCR ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, and protease inhibitor with bioactivity score of: -0.04, -0.04, -0.05, -0.25 and -0.010, respectively. These results reveal that the Schiff base can act asan enzyme inhibitor.

Table-5: Bioactivity prediction of the Schiff base ligand

GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
-0.04	-0.04	-0.25	-0.05	-0.10	0.01

Pharmacokinetic parameters and toxicity potential

Tow processes resulted from drug and human body interactions: the first is the effect of drug on human body as a result of activation or inhibition of receptors, blocking of pathways, and the second can be exerted by absorption, distribution, metabolism, and excretion [27]. This last process is the important factor in the drug discovery procedure; pharmacokinetics, which can be defined as the study of different processes

such as absorption, distribution, metabolism and excretion (ADME) of a drug.

Table-6: Prediction of ADME and toxicity proprieties of L using pkCSM and admetSAR

Pkc SM			admetSAR	
Model Name	Predicted Value	Unit	Result	Probability/ Unit
Absorption				
Water solubility	–2.784	Numeric(log mol/L)	-	-
Caco2 permeability	0.882	Numeric(log Papp in 10^{-6} cm/s)	Caco2+	0.5819
Intestinal absorption (human)	87.024	Numeric (% Absorbed)	HIA+	0.9698
Skin Permeability	–2.773	Numeric (log Kp)	-	-
P-glycoprotein substrate	Yes	Categorical (Yes/No)	Substrate	0.8263
P-glycoprotein II inhibitor	No	Categorical (Yes/No)	Non-inhibitor	0.6874
P-glycoprotein I inhibitor	Yes	Categorical (Yes/No)	-	-
Renal Organic Cation Transporter	-	-	Inhibitor	0.5966
Distribution				
Subcellular localization	-	-	Mitochondria	0.8310
VDss (human)	1.261	Numeric (log L/kg)	-	-
Fraction unbound (human)	0.253	Numeric (Fu)	-	-
BBB permeability	–0.596	Numeric (log BB)	BBB-	0.5966
CNS permeability	–2.509	Numeric (log PS)	-	-
Metabolism				
CYP2D6 substrate	Yes	Categorical (Yes/No)	Substrate	0.5930
CYP3A4 substrate	Yes	Categorical (Yes/No)	Non-substrate	0.6197
CYP1A2 inhibitior	Yes	Categorical (Yes/No)	Non-inhibitor	0.7311
CYP2C19 inhibitior	No	Categorical (Yes/No)	Non-inhibitor	0.8911
CYP2D6 inhibitior	Yes	Categorical (Yes/No)	Inhibitor	0.6691
CYP3A4 inhibitior	No	Categorical (Yes/No)	Non-inhibitor	0.7543
CYP Inhibitory Promiscuity	-	-	Low CYP Inhibitory Promiscuity	0.9299
Excretion				
Total Clearance	0.753	Numeric (log ml/min/kg)	-	-
Renal OCT2 substrate	Yes	Categorical (Yes/No)	-	-
Toxicity				
AMES toxicity	No	Categorical (Yes/No)	Non AMES toxic	0.7051
Honey Bee Toxicity	-	-	Low HBT	0.7402
Carcinogens	-	-	Noncarcinogens	0.7491
hERG II inhibitor	Yes	Categorical (Yes/No)	Inhibitor	0.7710
hERG I inhibitor	No	Categorical (Yes/No)	-	-
Hepatotoxicity	Yes	Categorical (Yes/No)	-	-
Max. tolerated dose (human)	0.119	Numeric (log mg/kg/day)	-	-
Oral Rat Acute Toxicity (LD50)	2.547	Numeric (mol/kg)	2.5122	LD50, mol/kg
Oral Rat Chronic Toxicity (LOAEL)	1.807	Numeric (log mg/kg_bw/day)	-	-
Skin Sensitisation	No	Categorical (Yes/No)	-	-
T. Pyriformis toxicity	0.879	Numeric (log ug/L)	0.6843	pIGC50, µg/L
Minnow toxicity	1.398	Numeric (log mM)	-	-
Fish Toxicity	-	-	1.2667	pLC50, mg/L

In the early stages of the drug discovery process, and before experimentation, the prediction of different pharmacokinetics parameters such as absorption, distribution, metabolism, excretion and toxicity are some of the most important aspects of drug development and discovery. The first parameter is the absorption, which can be influenced by a number factors such as solubility, membrane partitioning, metabolism, and transporters[28,29].In addition, blood-brain barrier(BBB) penetration, HIA (Human Intestinal

Absorption), human colon adenocarcinoma (Caco-2) cell permeability, P-glycoprotein substrate, P-glycoprotein inhibitor, and renal organic cation transporter arethe factors that influence the drug absorption. ADME and toxicity prediction of the ligand are given in Table6. Results show that the Schiff base exhibits an ability to cross the blood-brain barrier (BBB-), with a probability of 0.5966.In addition, an excellent human intestinal absorption of the ligand was predicted, and a moderate ability to penetrate human colon adenocarcinoma (Caco-2+) calculated, with Caco-2 permeability of 0.9401 cm/s; this result confirms the high drug absorption (AB %) predicted by Molinspiration.

CONCLUSIONS

The physico-chemical, biological proprieties, bioactivity, oral bioavailability and pharmacokinetics, toxicity (ADMET) of the ligand could be predicted by online computer software programs. Results revealed that the ligand has an excellent bioavailability and enzymatic inhibitory effect. Our theoretical results indicate the possibility of using the ligand as a safe drug in the future. However, more work involving animal models may be needed to establish the efficacy and safety of this compound.

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Abbreviations used

% AB: percentage absorption, TPSA: topological polar surface area, n-ROTB: number of rotatable bonds, MV: molecular volume, MW: molecular weight, miLog P, MolLogP: logarithm of partition coefficient of compound between n-octanol and water, n-ON acceptors: number of hydrogen bond acceptors, n-OHNH donors: number of hydrogen bonds donors, MolPSA: Polar Surface Area, HBA: Number of Hydrogen Bond Acceptors, HBD: number of Hydrogen Bond Donator, MolLogS :water solubility, Pe, Jejunum: Permeability in Human Jejunum scale (pH=6.5), LogPS: Rate of brain penetration, LogPB : Extent of brain penetration, Log(PS*fu, brain): Brain/plasma equilibration rate.

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