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IN-SILICO ADMET AND DRUG LIKENESS PREDICTIONS OF SOME SCHIFF BASES BASED 1,2,4-TRIAZOLE MOIETY

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ABSTRACT

*The new concept of computer aided drug design (CADD) has revolutionized the entire drug discovery and development program. The potential uses of any drug candidate like a therapeutic agent mostly depend on their pharmacodynamics and pharmacokinetics features. The properties like absorption, distribution, metabolism, elimination and toxicity (ADMET) of any drug candidate is included in its pharmacokinetic phase. Thus, it is the need of the day in the drug development process to screen and optimize ADMET properties in the early stage. In this report, 1,2,4-Triazole Schiff bases **1-11** were screened with in-silico Bioactivity, Lipinski's rule of 5, Drug likeness and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) filters using various online simulation systems.*

Keywords: 1,2,4-Triazole Schiff base, in-silico, CADD, Drug likeness, ADMET, Bioactivity.

1. INTRODUCTION

In search of new drugs, the chemistry of 1,2,4-triazoles have drawn notable attention owing to their low toxicity, excellent stability, good pharmacokinetic and pharmacodynamics profiles [1]. Indeed, there are already accessible drugs having 1,2,4-triazole core in their structure such as alprazolam [2], voriconazole [3] and etizolam [4]. In particular, 1,2,4-triazoles encompassing mercapto and/or thione group, which been widely investigated for their therapeutic properties including antioxidant [5], anticonvulsant [6], antimicrobial [7,8],

antiflammatory [9], antileishmanial [10], antidepressant [11], antiviral [12], anticancer [13] and antimalarial[14].

On the other hand, Schiff bases bearing nitrogen containing heterocyclic scaffolds are considered privileged structures in drug discovery. They are known to exhibit significant pharmacological activities such as anthelmintic [15], antimicrobial [16–18], antiviral [19], analgesic [20], antiproliferative [21], antitubercular [22], antipyretic [23], anticonvulsant [24], anti-HIV [25], antitumor [26]activities. Moreover, the recent literature revealed that the incorporation of azomethine linkage within 1,2,4-triazole moiety enhanced biological and pharmacological properties [27–30].

In the present biomedical arena, computer-aided drug designing (CADD) or *in silico* concept is being utilized to aid and accelerate hit identification, selection of hit-to-lead, screen out large compound libraries into smaller clusters of predicted active compounds thus optimizing the ADMET (absorption, distribution, metabolism, excretion and toxicity) profile and avoid issues related to safety. CADD uses various methods like Bioactivity prediction [31], ADMET predictions[32-33] Lipinski's rule of 5 and Drug likeness predictions [34-36]. A large number of *in-silico* ADMET methods have been developed [37-38].

Our main objective is to *in-silico* investigate our previously reported compounds [39] for their pharmacokinetic, drug-likeness, toxicity and bioactivity profile on the basis of several physico-chemicalparameters by computational methods using Molinspiration, Molsoft and PreADMET tools.

2. EXPERIMENTAL

2.1 Ligand identification

The investigated Schiff bases tethered 1,2,4-triazole**1-11** have been synthesized and whole characterized previously [39], and are taken as drug candidates in this study.

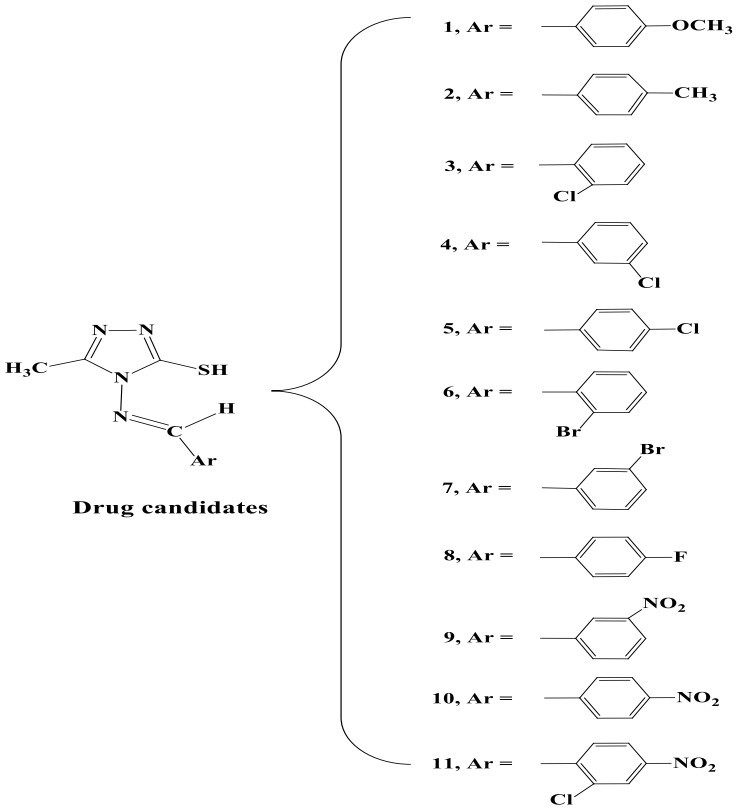

Figure 1: Structures of the selected compounds **1-11** for *in-silico* studies.

2.2 Bioactivity prediction using Molinspiration

The selected compounds were evaluated for *in-silico* bioactivity prediction using the online software from Mol inspiration Chemin for matics server (http://www.molinspiration.com). A broad range of cheminformatics software tools has been offered by Molinspiration including SMILES and SD file conversion, molecule manipulation and processing, calculation of various molecular properties needed for QSAR studies, drug design and molecular modelling, etc. This server also supports virtual screening which is fragment-based, prediction of bioactivity and visualization of data. It can be practically used on any computer platform because Molinspiration tools are written in Java. The miscreen engine in the Molinspiration tool analyze a training set of active structures first (even single active molecule is sufficient in extreme cases to build a usable model) and then by using sophisticated Bayesian statistics, compares it with inactive molecules.

As it is fragment based, it calculates the bioactivity contribution for each substructure fragment. The chemical structures were drawn directly into the designated window and then the bioactivity was predicted by the calculated sum of activity contributions of fragments in these molecules. Resulting into molecule activity score (a numerical value, typically between

-3 and 3).Molecules with possess highest activity score tend to have the highest probability to be active.

On the basis of above described protocols, screening models are developed for 4 important classes of drugs, i.e. G protein-coupled receptors ligand (GPCR ligands), kinase inhibitors, ion channel blockers/modulators, and nuclear receptor ligands. Along with this protease inhibition and enzyme inhibition was also done. Thus, by using the miscreen built-in functionality, a virtual screening model for any target candidate/ligand may be easily developed. Along with this another advantage based on Bayesian statistics is, that it is able to learn general structure requirements i.e. to generalize, that are necessary for bioactivity.

2.3 Lipinski's Rule of 5 and Drug likeness prediction using Molsoft

The selected compounds **1-11**were evaluated for Lipinski's rule of 5 and drug likeness score predictions using the online software from Molsoft server (http://www.molsoft.com). MolSoft offers various services and software tools for structure prediction which helps in understanding the spatial organization of drug candidates and their interactions with each other, their biological substrates and drug-like molecules at the atomic level by the application of some rules and algorithms to specific biomedical problems. A qualitative concept used for drug like property is Drug-likeness. It is described as a complex balance of various structural and molecular properties which play a key role in determining whether the particular drug candidate is similar to the known drugs or not. Various molecular properties like hydrophobicity, molecule size and flexibility, hydrogen bonding characteristics, electronic distribution, presence of various pharmacophoric features which have control on the behaviour of the molecule in the living organism, including bioavailability, affinity to proteins, transport properties, toxicity, metabolic stability, reactivity, and many others. According to Lipinski's rule of 5 (RO5), the drug candidate will have a poor absorption or permeation when the molecular weight (MWT) is greater than 500, the calculated Log P (CLogP) is greater than 5 (or MlogP > 4.15), there are more than 5 H-bond donors and10 H-bond acceptors. So, in order to be a drug, the candidate should not violate any of the above RO5.

2.4 ADMET prediction using PreADMET

The selected compounds (**1-11**were subjected to ADMET predictions using the online software from Pre ADMET server (http://www.preadmet.com).Molecular structure is the key factor in determining the ADMET properties of the investigated molecules. It can be used as

a predictor of their pharmacokinetic properties. Blood Brain Barrier (BBB) penetration prediction means predicting whether the selected compounds will be able to pass across the blood-brain barrier or not, which is crucial in pharmaceutical sphere. Central Nervous System (CNS) active compounds are able to pass across it while CNS-inactive compounds are not able to pass across it in order to avoid CNS side effects [40].On the general basis, only the drug which is unbound is available for diffusion or transportation across cell membranes, as well as for interaction with pharmacological targets. Therefore, a degree of plasma protein binding of a drug not only influences the drug's action but also its efficacy and disposition. As a result, the PPB% is an important pharmacokinetic factor [41]. For the development of potential drug candidates, predicting human intestinal absorption (HIA%) of drugs is very important. The sum of bioavailability and absorption as HIA% data is evaluated from ratio of excretion or cumulative excretion in urine, bile and feces[42]. In order to identify bioactive molecules as therapeutic agents, oral bioavailability is considered to be a salient feature. Madin-Darby canine kidney (MDCK) cell model and Caco-2 cell model has been identified as a reliable *in-vitro* model for the predicting oral drug absorption. Caco-2 cells is a well-differentiated intestinal cell line which is derived from human colorectal carcinoma. It is known to display many of the functional and morphological properties of the *in-vivo* intestinal epithelial cell barrier [43]. MDCK cells have advantage over Caco-2 as its growth period is shorter than Caco-2 cell. Thus, MDCK cells model may be used as key tool for screening rapid permeability [44]. Consideration of toxicity is a very important feature in the conception of drugs, as it can predict whether the new compounds is toxic or not on basis of carcinogenicity and mutagenicity. Ames test is a simple method which can predict mutagenicity of a compound [45]. Carcinogenicity is a type of toxicity which can lead to the growth of cancer in body. The test usually uses mice or rats, exposing them to a molecule/drug candidate. Pre ADMET server was used to predict the results of mutagenicity and carcinogenicity which has been constructed from the data obtained from National Toxicology Program (NTP) and FDA (USA Food and Drug Administration), obtained in *in-vivo* testing of mice and rats for carcinogenicity for at least about 2 years.

3. RESULTS AND DISCUSSION

The work reported here was carried out with the intention to predict the bioactivity, drug likeness and ADMET properties of our previously reported 1,2,4-Triazole Schiff bases **1-11** using *in-silico* tools.

Prediction of bioactivity scores for six different protein structures namely GPCR ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand, protease inhibitor, and enzyme inhibitor was done using Molinspiration software. The bioactivity score profile of the all selected compounds **1-11** is given in Table 1. All these values so obtained indicate binding affinity of the selected compounds/drug candidates to the mentioned receptors and enzymes (positive values indicate greater affinity, while negative values mean low affinity). All the tested compounds have shown negative bioactivity that means they have low affinity towards the selected protein structures.

Molsoft was used to predict Lipinski "Rule of Five", calculate some important physicochemical properties such as molecular weight, logP, polar surface area, number of hydrogen bond acceptors, number of hydrogen bond donors, and drug likeness scores (Table 2). The drug likeness of the selected compounds is shown in Figure 2. None of the selected compounds **1-11** has violated the RO5 along with moderate drug likeness scores ranging from -1.83 to -0.25.

Pre ADMET was used to predict *in-vivo* ADMET i.e. data on rates for BBB penetration, percent drug bound in plasma protein, HIA%, Caco-2 and MDCK cell permeability (Table 3). Most of the tested compounds **2-8** showed BBB absorption values to the CNS more than 1, thus, can be classified as active CNS candidates. Rest of the compounds were not able to cross BBB as their value is less than 1, so they can be classified as CNS inactive candidates. Same compounds **2-8**emerged as potent plasma protein binding agents with PPB > 90%. All the tested compounds exhibited good human intestinal absorption with HIA% values more than 70%. Compounds**2** and **8** showed the highest value of HIA% equal to 97.2%, whereas compound **9** and **10** showed the lowest absorption equal to 89.7%, as shown in Table 3. All the tested compounds **1-11** showed moderate Caco-2 cell permeability ranging from 10.2% to 28.6%. Compounds **6**, **7**, **10** and **11** came up to be low permeable compounds for MDCK cells (7.6%-21.6%). Rest of the compounds have shown moderate MDCK cell permeability (37.9%-277%). Toxicological properties of mutagenicity (Ames Test) and carcinogenicity (mouse and rat) for selected compounds **1-11** is reported in Table 4. All the selected compounds are predicted as mutagenic by Ames test. In the prediction of carcinogenicity in mouse, compounds **8** showed positive prediction, which means there is no evidence of carcinogenic activity. Rest of all others compounds were predicted to be negative, i.e. there is evidence of carcinogenic activities in mouse, for such compounds **1-7**, **9-11**. In the prediction of carcinogenicity in rat, only compound**7**had shown positive prediction, i.e. it is not carcinogenic in nature. While all the other compounds **1-6**, **8-**

11 showed negative prediction, demonstrating that these compounds might exhibit carcinogenic activity as given in Table 4.

4. CONCLUSION

The present research work reports the prediction of the *in-silico* bioactivity, drug likeness and ADMET studies of some previously reported 1,2,4-Triazole Schiff bases using various online available servers. The predictive study reveals that all the selected compounds **1-11** has shown low bioactivity scores, moderate drug likeness scores and all these compounds do not violate the Lipinski's rule of 5. The predictive *in-vivo* ADMET studies shows that compound **2-8** have good BBB, PPB and HIA scores. None of the compounds have shown high Caco-2 and MDCK cell permeability and non-mutagenicity. Compound **8** emerged as a non-carcinogen in mouse and compound **7** as non-carcinogenic in rat. In conclusion, these predictive studies give the information about the physico-chemical properties as well as pharmacokinetics of the selected compounds thus facilitating the lead for the drug development program with more effectiveness and lesser toxicity.

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Table 1: Bioactivity of the selected compounds **1-11**.

Compound No.	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	-1.72	-1.64	-1.73	-1.93	-1.87	-1.33
2	-1.86	-1.72	-1.89	-2.15	-2.02	-1.45
3	-1.90	-1.72	-1.89	-2.22	-2.07	-1.44
4	-1.81	-1.64	-1.89	-2.15	-2.02	-1.44
5	-1.82	-1.65	-1.87	-2.14	-2.03	-1.44
6	-2.02	-1.80	-2.01	-2.33	-2.16	-1.58
7	-1.99	-1.78	-1.96	-2.32	-2.17	-1.52
8	-1.80	-1.67	-1.80	-2.07	-2.00	-1.41
9	-1.74	-1.53	-1.72	-1.90	-1.84	-1.35
10	-1.73	1.52	-1.72	-1.89	-1.83	-1.33
11	-1.67	-1.50	-1.60	-1.82	-1.81	-1.30

Table 2: Lipinski's rule of 5 with drug likeness scores of the selected compounds **1-11**.

Compound No.	Mol. wt	Log P[a]	HBA[b]	HBD[c]	Drug likeness score
1	248.07	2.18	4	1	-0.95
2	231.08	2.49	3	1	-0.73
3	252.02	2.69	3	1	-0.79
4	252.02	2.81	3	1	-0.58
5	252.02	2.81	3	1	-0.25
6	295.97	2.82	3	1	-1.21
7	295.97	2.94	3	1	-0.83
8	236.05	2.36	3	1	-0.49
9	263.05	1.76	5	1	-0.93
10	263.05	1.76	5	1	-1.83
11	297.01	2.36	5	1	-1.07

[a]solubility parameter, [b]number of hydrogen bond acceptors, [c]number of hydrogen bond donors

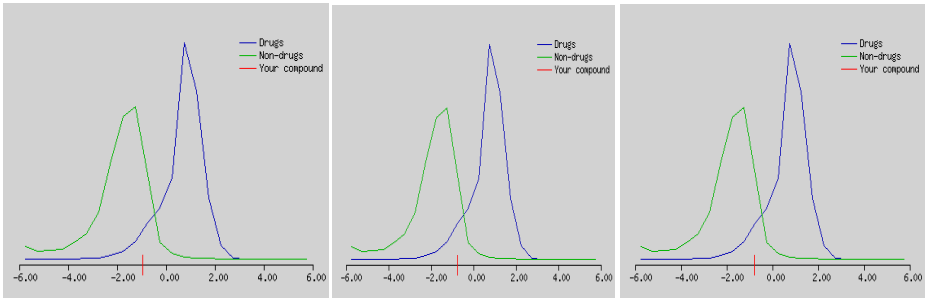
Table 3: ADME properties of the selected compounds **1-11**.

Compound No.	BBB[a]	PPB[b]	HIA[c]	Caco-2[d]	MDCK[e]
1	0.03	84.5	94.5	21.2	119
2	1.58	95.8	97.2	22.6	277
3	1.65	92.5	96.9	24.7	228
4	1.65	92.6	96.9	27.5	229
5	1.65	94	97	10.2	229.1
6	1.67	92.3	96.7	28.6	7.6
7	1.67	93.7	96.7	28.6	8.1
8	1.44	90.8	97.2	19.6	124
9	0.40	78.8	89.7	16.2	37.9
10	0.16	77.7	89.7	16.4	21.6
11	0.21	85	94.7	14.2	10.4

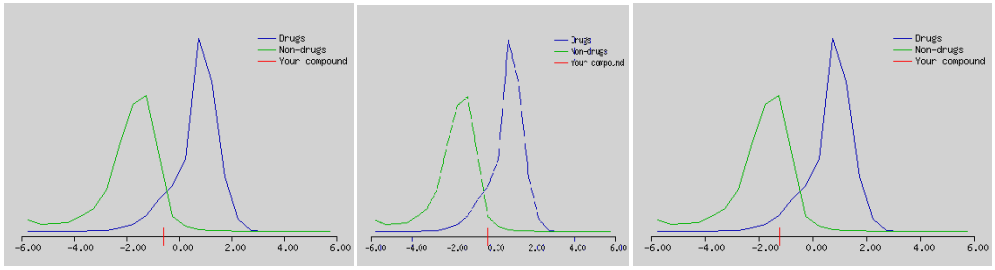
[a]blood brain barrier penetration, [b]plasma protein binding, [c]human intestinal absorption, [d]Caco-2 cell permeability, [e]MDCK cell permeability

Table 4: Toxicity prediction of the selected compounds **1-11**.

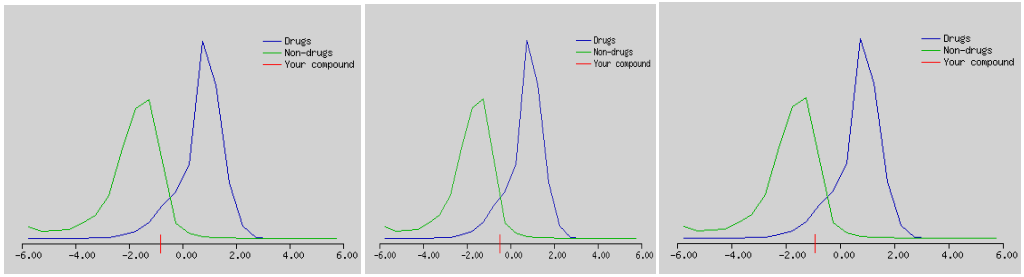
Compound No.	Ames Test Mutagenicity	Mouse Carcinogenicity	Rat Carcinogenicity
1	Mutagenic	Negative	Negative
2	Mutagenic	Negative	Negative
3	Mutagenic	Negative	Negative
4	Mutagenic	Negative	Negative
5	Mutagenic	Negative	Negative
6	Mutagenic	Negative	Negative
7	Mutagenic	Negative	Positive
8	Mutagenic	Positive	Negative
9	Mutagenic	Negative	Negative
10	Mutagenic	Negative	Negative
11	Mutagenic	Negative	Negative



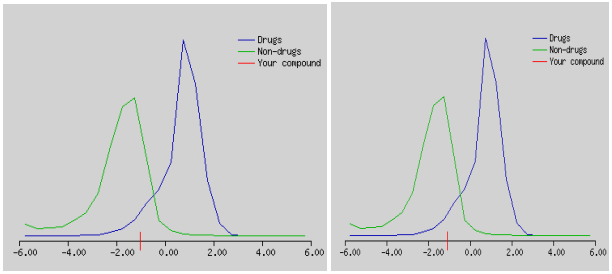
Compound **1** Compound **2** Compound **3**



Compound **4** Compound **5** Compound **6**



Compound **7** Compound **8** Compound **9**



Compound **10** Compound **11**

Figure 2: Drug likeness score of the selected compounds **1-11**.