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Assessment of Molecular Property and Bio-Activity Scores of Imines Derived from Disubstituted Aromatic Aldehydes and 4-Amino Antipyrine using Molinspiration

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Abstract : The imines derived from 4-amino antipyrine were selected for the assessment of molecular property and bio-activity scores using molinspiration software as the literature reveals the importance of the 4-amino antipyrine. The structures of the fifteen imine compounds were drawn using molinspirstion software. All the fifteen compounds obeyed Lipinski's rule and showed good likeness scores. MiLog P values of these compounds were found below 5 that means these compounds showed good permeability across cell membrane. All compounds were found to have TPSA in the range of 39.228-85.554 and were well below 160. Low molecular weight drug molecules (<500) means they are easily transported, diffuse and absorbed as compared to heavy molecules. All the compounds were found to have number of hydrogen bond donors < 3 and number of hydrogen bond acceptors < 7 which were found to be within Lipinski's limit i.e. less than 5 and 10 respectively. These indicated that these compounds were easily bind to the receptor and further the calculation of bio-activity scores by calculating the activity scores on the basis of GPCR ligand, ion channel modulator, nuclear receptor ligand , kinase inhibitor, protease inhibitor and enzyme inhibitor indicated that all the compounds were moderately bio-active i.e.,< 0 towards GPCR ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor and enzyme inhibitor. Compared to standard BHT (Butylated hydroxyl toluene)[5.314)] these compounds were found to have good likeness scores(1.683-4.544)

Keywords : 4-aminoatipyrine, Lipinski's rule, MiLog P and BHT.

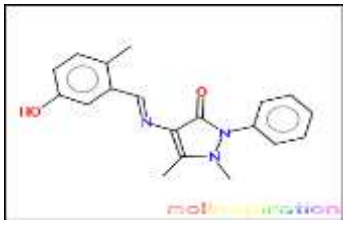
Introduction

Imines compounds and their metal complexes have varied applications in biological [1-3], clinical, analytical, corrosion science and pharmacological areas [4-6]. Imines are used as catalysts for certain chemical reactions. Aromatic Schiff bases and their complexes catalyze reactions like oxygenation [7-8] hydrolysis [9], electro-reduction [10], and decomposition [11]. Imines compounds were appeared to be an important intermediate in a number of enzymatic reactions involving interaction of an enzyme with an amino or a carbonyl group of the substrate [12]. Earlier works done by biochemists[13-14], reported that some drugs showed greater activity, as metal complexes when compared to the organic compounds[15]. The coordinating properties of 4-aminoantipyrine have been modified to give new ligands formed by the reaction with aldehydes, ketones, thiocarbazides and carbazides etc,[16]. Imines compounds of 4-amino antipyrine and its complexes have a variety of application in biological, clinical, analytical and pharmacological areas[17].Properties of 4-amino antipyrine imine compounds to coordinate with metal is varied by the presence of various substituents

present in the aldehydes, ketones, thiosemicarbazides and carbazides etc. Metal complexes of 4-amino antipyrine and biological behaviour involving the amino group of 4-aminoantipyrine has been studied exhaustively, when compared to the work carried out on the chemistry of transition metal complexes and biological behaviour involving the amino group of 4-amino antipyrine [18,19]. In order to predict the highly active compounds derived from disubstituted aromatic aldehyde and 4-amino antipyrine and in continuation of our work on mono substituted 4-amino antipyrine Schiff bases molinspiration molecular properties and bio-activity scores assessment were carried out [20].

Materials and Methods

The Structures of all the fifteen imines given as figure 1-15 were taken from the reported literature [21]. Online molinspiration software. (www.molinspiration.com) was used for the assessment of molecular properties (Log P, Total polar surface area, number of hydrogen bond donors and acceptors, molecular weight, number of atoms, number of rotatable bonds etc.) and prediction of bioactivity score for drug targets (GPCR ligands, kinase inhibitors, ion channel modulators, enzymes and nuclear receptors). The bioactivity score and drug likeness properties of the all the fifteen compounds were compared [22].



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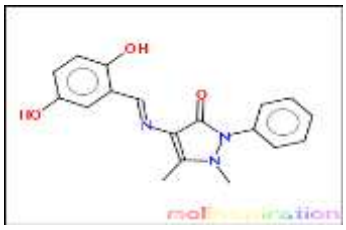

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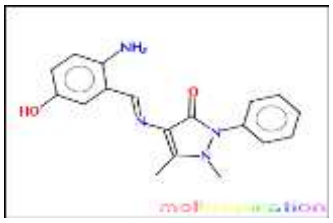

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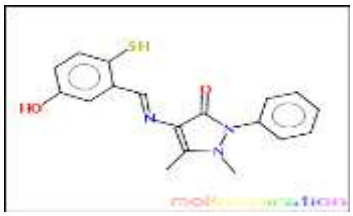

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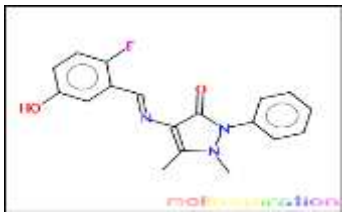

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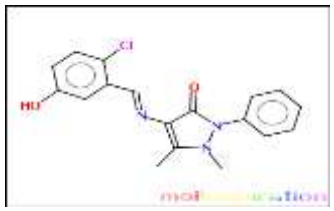

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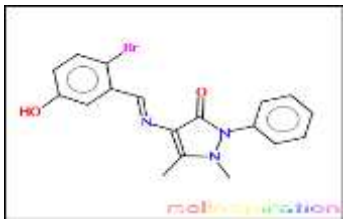

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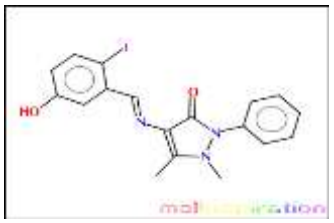

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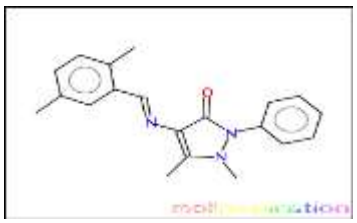

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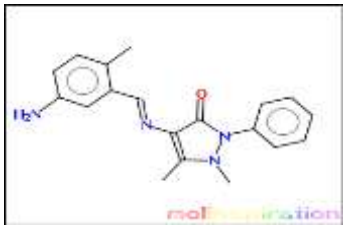

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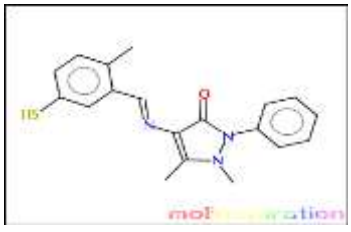

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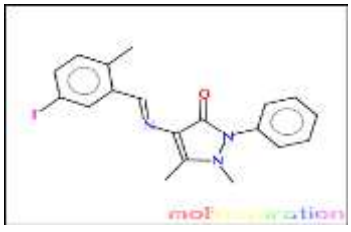

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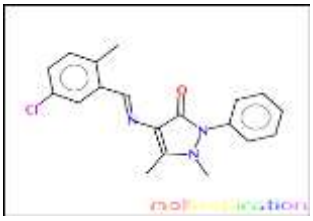

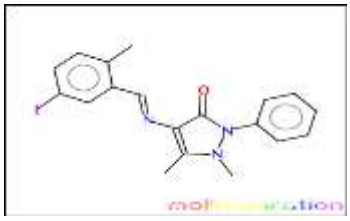

XIII **XIV** **XV**

For the assessment of the molecular properties and drug likeness scores the following steps were followed

- Open molinspiration online software
- Draw the structure of imines.
- In order to calculate the molecular properties such as MiLog P, TPSA, number of hydrogen bond donors, hydrogen bond acceptors, number of violations and molecular weight, ***click on the calculate properties icon*** and the values for the fifteen imines were tabulated in the **Table 1**
- The bio-activity scores such as GPCR ligand, ion channel modulator, nuclear receptor legend, kinase inhibitor, protease inhibitor and enzyme inhibitor of the imines were assessed by ***clicking the predict bio-activity*** icon and the values were tabulated in the **Table II**.

The drug likeness scores were assessed by considering MiLog P(partition coefficient), molecular weight, number of heavy atoms, number of hydrogen donor, number of hydrogen acceptor and number of violation, number of rotatable bonds and volume. The bioactivity scores of these imine compounds were assessed on the basis of GPCR ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor and enzyme inhibitor.

Table 1- Drug likeness score for imines.

S. No	Compound	miLogP	TPSA	nAtoms	n ON	nOHNH	n violation	n rotb.	volume	MW
1	**I**	2.756	59.531	24.0	5	1	0	3	297.54	321.38
2	**II**	2.296	79.759	24.0	6	2	0	3	288.996	323.352
3	**III**	1.79	85.554	24.0	6	3	0	3	292.267	322.368
4	**IV**	2.537	59.531	24.0	5	1	0	3	298.639	339.42
5	**V**	2.471	59.531	24.0	5	1	0	3	285.91	325.343
6	**VI**	2.985	59.531	24.0	5	1	0	3	294.514	341.798
7	**VII**	3.116	59.531	24.0	5	1	0	3	298.864	386.249
8	**VIII**	3.39	59.531	24.0	5	1	0	3	304.969	433.249
9	**IX**	3.684	39.303	24.0	4	0	0	3	306.083	319.408
10	**X**	2.311	65.326	24.0	5	2	0	3	300.81	320.396
11	**XI**	3.464	39.303	24.0	4	0	0	3	307.182	337.448
12	**XII**	3.399	39.303	24.0	4	0	0	3	294.453	323.371
13	**XIII**	3.913	39.303	24.0	4	0	0	3	303.058	339.826
14	**XIV**	4.044	39.303	24.0	4	0	0	3	307.407	384.277
15	**XV**	4.318	39.303	24.0	4	0	0	3	313.512	431.277
16	**Standard BHT**	5.435	20.228	16	1	1	0	2	240.996	220.356

Table II- Bio Activity scores of imines.

S.No.	Compound	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	I	-0.77	-1.08	-0.62	-0.81	-0.99	-0.45
2	II	-0.76	-1.08	-0.54	-0.81	-0.90	-0.44
3	III	-0.76	-0.96	-0.47	-0.86	-0.88	-0.41
4	IV	-0.72	-1.05	-0.60	-0.90	-0.75	-0.31
5	V	-0.74	-1.03	-0.48	-0.85	-0.95	-0.46
6	VI	-0.82	-1.04	-0.56	-0.90	-1.01	-0.48
7	VII	-0.90	-1.10	-0.64	-0.97	-1.07	-0.56
8	VIII	-0.75	-0.96	-0.55	-0.77	-0.98	-0.54
9	IX	-0.82	-1.14	-0.67	-0.97	-1.00	-0.52
10	X	-0.78	-1.06	-0.54	-1.02	-0.91	-0.43
11	XI	-0.88	-1.29	-0.81	-1.10	-0.93	-0.47
12	XII	-0.80	-1.12	-0.61	-0.92	-1.00	-0.51
13	XIII	-0.81	-1.11	-0.68	-0.99	-1.04	-0.53
14	XIV	-0.93	-1.20	-0.73	-1.10	-1.14	-0.59
15	XV	-0.80	-1.11	-0.66	-0.91	-1.09	-0.57
16	BHT	-0.34	0.00	-0.48	-0.08	-0.57	-0.07

Results and Discussion

I .Assessment of Drug likeness on the basis of Lipinski rule of five

The drug likeness scores were calculated by considering MiLog P(partition coefficient), molecular weight, number of heavy atoms, number of hydrogen donor, number of hydrogen acceptor and number of violation, number of rotatable bond and volume. These properties were calculated and discussed on the basis of Lipinski's rule and its component.

All the compounds obeyed the Lipinski's rule and showed good drug likeness score (**Table1**). MiLog P values of these compounds were found below 5 that means these compounds showed good permeability across cell membrane. All compounds were found to have TPSA in the range of 39.228-85.554 and were well below 160. Low molecular weight drug molecules (<500) means they are easily transported, diffuse and absorbed as compared to heavy molecules. All the compounds were found to have molecular weight less than 500.

The No. of hydrogen bond donors (The sum of OHs and NHs) and the No. of hydrogen bond acceptor (The sum of Os and Ns) should be less than 5 and 10. All the compounds were found to have hydrogen bond donors < 3 and hydrogen bond acceptors <7 which were found to be within Lipinski's limit i.e. less than 5 and 10 respectively. Number of rotatable bonds is a simple topological parameter that measures molecular flexibility and is considered to be a good descriptor of oral bioavailability of drugs. Among the screened compounds all the imines were flexible (3 rotatable bonds). N violations equal to 0 means that all the imines can easily bind to receptor. All the imines were found to have n violations equal to 0.

II. Bioactivity score of the compounds

The bioactivity scores of the fifteen imines selected for assessment on the basis of GPCR ligand, ion channel modulator, nuclear receptor ligand , kinase inhibitor, protease inhibitor, enzyme inhibitor as given in **Table -II** showed the following observations as per the rule. "For organic molecules the probability is if the bioactivity score is (>0), then it is active, if (-5.0-0.0) then moderately active, if (< -5.0) then inactive".

Calculation of drug likeness score towards GPCR ligands showed that all the imines were found to have moderate bioactivity (<0). All the imines were found to be moderately bioactive (<0) as ion channel modulator.

The imines II, III, V, VI, VIII and X were found to be biologically active and others were found to be moderately active as kinase inhibitor (> -0.5). Nuclear receptor properties of all imines were moderately active (< 0). All the imines were found to be moderate inhibitor activity (<0) towards Protease. The imines VII, VIII, IX, XII, XIII, XIV and XV were found to exhibit (-0.5-0.0) enzyme inhibitor moderately compared to others.

Conclusion

Among the fifteen imine compounds selected for the assessment of the drug likeness score, all the imines were found to obey the Lipinski's rule and showed good drug likeness score. (MiLogP below 5). Compared to the Standard BHT(butylated hydroxyl toluene), the above compounds were found to have drug likeness score in the range of 1.79 - 4.318 which were less than the Standard BHT(5.435) indicated that these imines were found to be better drugs than BHT. All the fifteen imines were found to be moderately active as GPCR ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor and enzyme inhibitor as their bioactivity scores lies in the range (-1.20 to - 0.31) .

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