Journal Of Harmonized Research (JOHR)

Journal Of Harmonized Research in Applied Sciences
3(1), 2015, 33-39

ISSN 2321 – 7456

Original Research Article

CALCULATION OF MOLECULAR LIPOPHILICITY AND DRUG LIKENESS FOR FEW SCHIFF BASES DERIVED FROM 4- AMINO ANTIPYRINE

Dr. (Mrs) G. Valli & A. Jayalakshmi

The Standard Fireworks Rajaratnam College For Women, Sivakasi-626123.
Virudhunagar District, Tamilnadu State, India

Abstract: Schiff bases derived from 4-aminoantipyrine were selected for the calculation of molecular liphophilicity and drug likeness using molinspiration software. Seventeen Schiff bases structure were drawn using online molinspiration software for the bio-activity prediction as the literature resources reveals the importance of 4-amino antipyrine Schiff bases. All the seventeen compounds obeys lipinski's rule and showed drug likeness score. MiLog P values of these compounds were found to be below 5 that means these compounds showed good permeability across cell membrane. TPSA in the range of 39.228-85.127(well below 160 Å2) and *n* violations =0 ,molecular mass <500 ,*n* rotb < 5 .No of hydrogen bond donors ≤ 5 (The sum of OHs and NHs),No of hydrogen bond acceptor <8 (The sum of Os and Ns) were observed for these compounds. These indicated that these compounds can easily bind to receptor and were taken further for the calculation of bioactivity score by calculating the activity score of GPCR ligand, ion channel modulator, nuclear receptor legend, kinase inhibitor, protease inhibitor and enzyme inhibitor. All the compounds were found to exhibit moderately bio-active i.e.,< 0 as as GPCR ligands, Ion channel modulator, Kinase inhibitor, Nuclear receptor ligand, Protease inhibitor and Enzyme inhibitor .Compared to the Standard BHT[(butylated hydroxyl toluene) (5.435).], these compounds were found to have good drug likeness score.(1.683-4.544).

Keywords: 4-amino antipyrine, Lipinski,s rule, MiLog P and BHT

Introduction

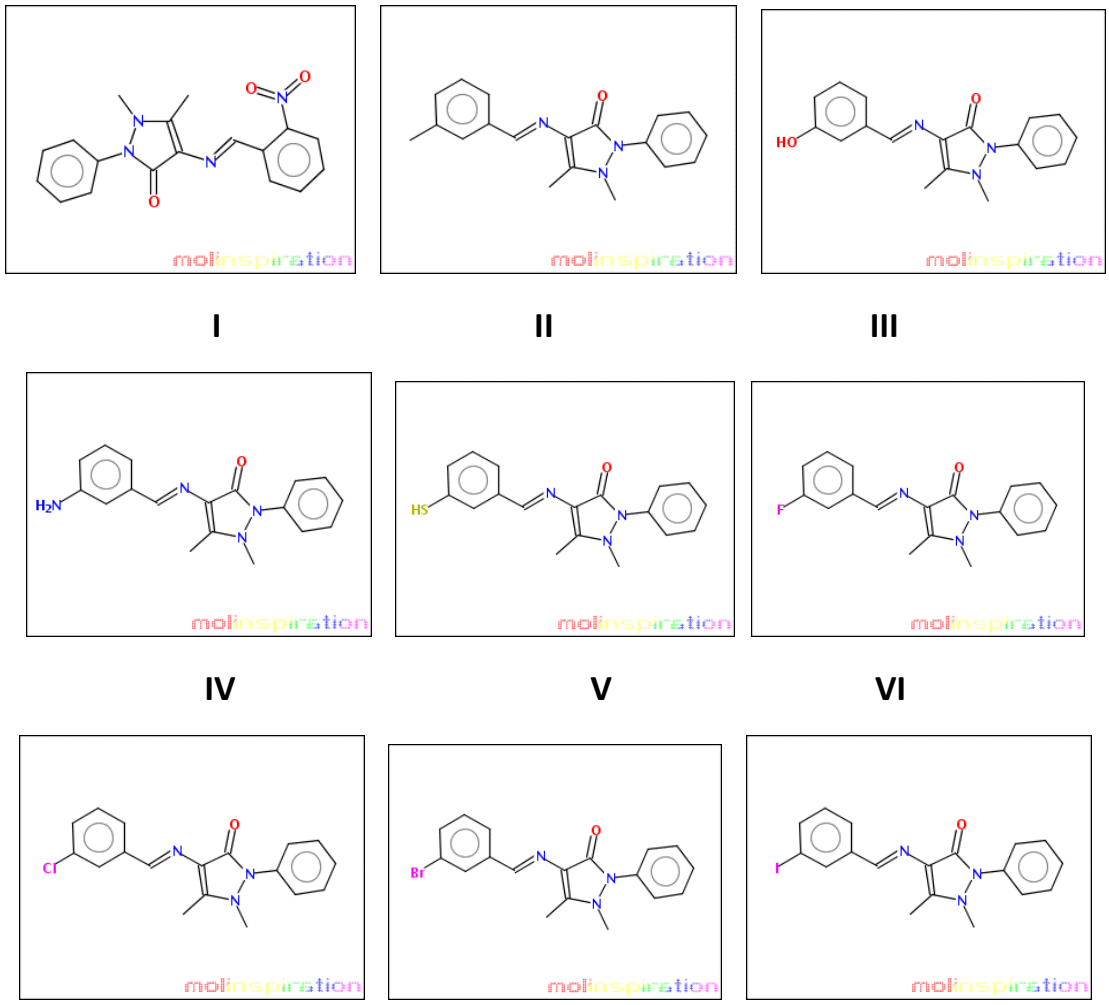
Schiff base and their metal complexes have varied applications in biological [1-3], clinical, analytical, corrosion science and pharmacological areas [4-6]. Schiff bases are used as catalysts for certain chemical reactions. Aromatic Schiff bases and their complexes catalyze reactions on oxygenation [7-8] hydrolysis [9], electro-reduction [10] and decomposition [11]. Schiff bases appear to be 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

For Correspondence:
mrs.valliravichandran@gmail.com
Received on: December 2014
Accepted after revision: January 2015
Downloaded from: www.johronline.com

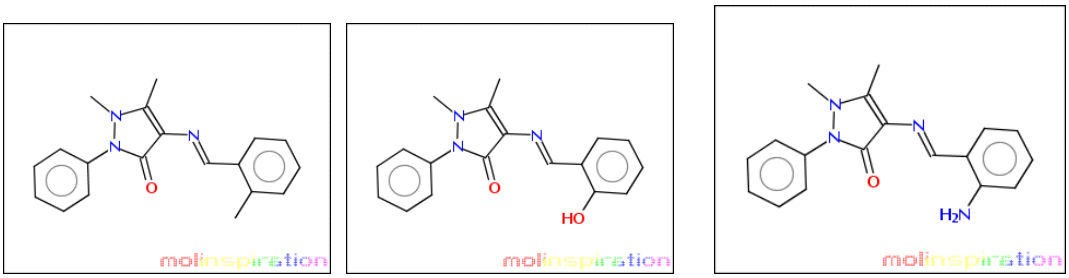
showed greater activity, as metal complexes when compared to the organic compounds [15]. The coordinating properties of 4-aminoantipyrine have been modified to give new ligands formed by the reaction with aldehydes, ketones, thiocarbazides and carbazides etc. [16]. Schiff bases of 4-amino antipyrine and its complexes have a variety of application in biological, clinical, analytical and pharmacological areas [17]. Metal complexes of 4-amino antipyrine and its biological behaviour involving the amino group of 4-aminoantipyrine has been studied extensively [18, 19]. In the present work, Molecular Lipophilicity and Drug Likeness Scores of Schiff bases derived from 4-amino antipyrine were calculated using molinspiration software

Materials and Methods

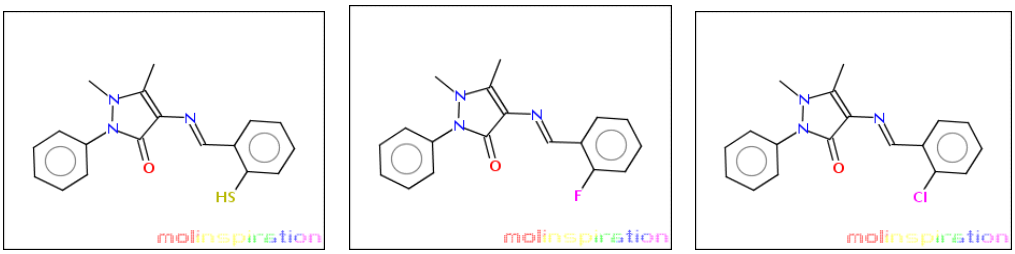
Structures of Schiff bases derived from 4-amino antipyrine were selected from the reported literature[20] for the present work given as **fig.I-XVII** and their structures were drawn using online molinspiration software (www.molinspiration.com) for calculation of molecular properties (Log P, Total polar 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 seventeen compounds were compared.



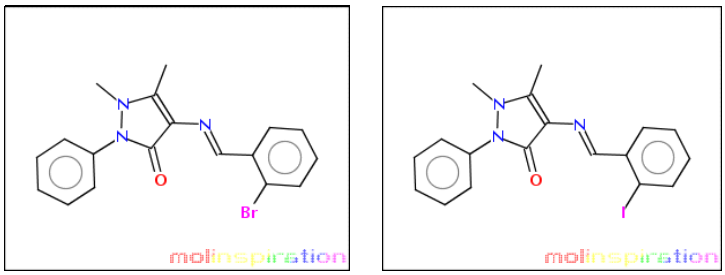
VII VIII IX



X XI XII



XIII XIV XV



XVI XVII

Lipinski,s Rule [21,22]

Lipinski's rule is used to evaluate drug likeness properties that describes molecular properties in the human body, including their absorption, distribution, metabolism, and excretion ("ADME")

Lipinski's rule states:

- Not more than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms)
- Not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms)
- A molecular mass less than 500 daltons
- An octanol-water partition coefficient log P not greater than 5
- No more than one number of violation.

Molinspiration software

Molinspiration, software was used to obtain parameter such as MiLogP, TPSA, drug likeness. Log P is an important parameter used in rational drug design to measure molecular hydrophobicity,that affects drug absorption, bioavailability, drug-receptor interactions, metabolism of molecules, as well as their toxicity[23,24] .

Molecular Polar Surface Area (TPSA) are calculated based as a sum of fragment contributions of O- and N- centered polar fragments and related to the hydrogen bonding potential of a molecule [25]. TPSA is a very good predictor of drug transport properties

such as intestinal absorption, bioavailability, blood brain barrier penetration etc.

The molecular properties and structure features of a drug can be checked by drug likeness datas of molecule. The calculated value for the drug likeness score and the various parameters of the all the Schiff base compounds were given in **Table 1.**

Table 1-Drug likeness score for compounds

S.N0	Compound	miLogP	TPSA	nAtoms	n ON	nOHNH	n violation	n rotb.	volume	MW
1	I	2.769	85.127	25.0	7	0	0	4	296.295	336.351
2	II	3.283	39.303	23.0	4	0	0	3	289.522	305.381
3	III	2.355	59.531	23.0	5	1	0	3	280.979	307.353
4	IV	1.911	65.326	23.0	5	2	0	3	284.249	306.369
5	V	3.064	39.303	23.0	4	0	0	3	290.621	323.421
6	VI	2.998	39.303	23.0	4	0	0	3	277.892	309.344
7	VII	3.513	39.303	23.0	4	0	0	3	286.497	325.799
8	VIII	3.644	39.303	23.0	4	0	0	3	290.846	370.250
9	IX	3.917	39.303	23.0	4	0	0	3	296.951	417.250
10	X	3.259	39.303	23.0	4	0	0	3	289.522	305.381

11	XI	2.799	59.531	23.0	5	1	0	3	280.979	307.353
12	XII	2.294	65.326	23.0	5	2	0	3	284.249	306.369
13	XIII	3.04	39.303	23.0	4	0	0	3	290.621	323.421
14	XIV	2.974	39.303	23.0	4	0	0	3	277.892	309.344
15	XV	3.489	39.303	23.0	4	0	0	3	286.497	325.799
16	XVI	3.62	39.303	23.0	4	0	0	3	290.846	370.25
17	XVII	3.893	39.303	23.0	4	0	0	3	296.951	417.25

Bioactivity score [23, 24, 26]

Bioactivity of the drug can be checked by calculating the activity score of GPCR ligand, ion channel modulator, nuclear receptor legend, kinase inhibitor, protease inhibitor, enzyme inhibitor. 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. The bioactivity scores of these compounds were given in **Table 2.**

Table 2- Bioactivity score of the compounds

S.No.	Compound	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	I	-0.97	-1.06	-0.76	-0.97	-1.05	-0.65
2	II	-0.86	-1.13	-0.62	-1.03	-1.03	-0.55
3	III	-0.80	-1.04	-0.56	-0.86	-1.00	-0.46
4	IV	-0.80	-1.02	-0.48	-1.08	-0.92	-0.43

5	V	-0.91	-1.26	-0.76	-1.17	-0.93	-0.48
6	VI	-0.83	-1.08	-0.55	-0.98	-1.00	-0.52
7	VII	-0.84	-1.07	-0.62	-1.05	-1.05	-0.54
8	VIII	-0.96	-1.16	-0.67	-1.16	-1.15	-0.60
9	IX	-0.83	-1.07	-0.60	-0.97	-1.10	-0.58
10	X	-0.85	-1.16	-0.68	-1.01	-1.05	-0.52
11	XI	-0.82	-1.14	-0.58	-0.92	-0.95	-0.48
12	XII	-0.84	-1.04	-0.53	-1.06	-0.94	-0.48
13	XIII	-0.80	-1.13	-0.66	-1.10	-0.80	-0.38
14	XIV	-0.82	-1.11	-0.54	-1.05	-1.01	-0.53
15	XV	-0.90	-1.12	-0.62	-1.09	-1.08	-0.55
16	XVI	-0.99	-1.18	-0.71	-1.17	-1.14	-0.64
17	XVII	-0.83	-1.04	-0.61	-0.96	-1.04	-0.62

>0- active, -5.0-0.0- moderately active , < -5.0- inactive.

Results and Discussion

I. Drug likeness calculation on the basis of Lipinski rule.

The compounds from I to XVII compounds obeyed the Lipinski's rule and showed good drug likeness score. These compounds showed good permeability across cell membrane as MiLog P values were found below 5. All these compounds were found to have TPSA in the range of 39.228-85.127. Molecular weights of all compounds were found to be less than 500. Number of hydrogen bond donors (< 5) and hydrogen bond acceptors (<8) for all these compounds. n violations =1 or <0 it means compound easily bind to receptor. All the compounds were found to have n violations =0

II. Bioactivity score of the compounds.

Calculation of druglikeness score as given in **Table 2** showed that all these compounds were found to be moderately bioactive (<0) as GPCR ligands, Ion channel modulator, Kinase inhibitor, Nuclear receptor ligand, Protease inhibitor and Enzyme inhibitor

Conclusion

Among the 17 compounds selected as Schiff base derived from 4-amino antipyrine for the prediction of the drug likeness score (MiLogP), showed the following observations:

- All the compounds were found to obey the Lipinski's rule and showed good drug likeness score. (MiLog P below 5).
- Compared to the Standard BHT[(butylated hydroxyl toluene) (5.435).], these Compounds were found to have good drug likeness score.(1.683-4.544).
- Moderately bioactive(<0). as GPCR ligands, Ion channel modulator, Kinase inhibitor, Nuclear receptor ligand, Protease inhibitor and Enzyme inhibitor

References

[1] Thaker,B.T. Bhattacharya ,P.K. Ind. J. Chem., Sec. A1979, 17A (4), 371-379.

[2] Saxena,C.G.;Shrivastava,S.V.;J Ind Chem. Soc1987, 64,685-686.
[3] Bhardwaj,C.N.;Singh,V.R.;Ind J Chem1994, 33A,423-425.
[4] Raman,N.; Syed, A.F.S.;Dhaveethu Raju J.Ser.Chem.Soc2005, 73 (11), 1063-1071.
[5]Raman,N.; Thalamuthu,S. Dhaveethuraja,J. Neelakandan,M.A. Sharmila Banerjee. J. Chil. Chem.Soc2008, 53 (1) doi: 10.4067/S0717-97072008000100025.
[6] Toliwal,S.D.;KalpeshJadav.;TejasParagadhi.; J.Scie.Ind.Res2010, 69(1), 43-47.
[7] Nishinga,A.;Yamada,T.; Fujisawa,H.; Ishizaki,K.; J. Mol. Cat,1988,48, 249-264.
[8] Xi Z.; Liu,W.;Cao,G.; Du,W.; Huang,J.; Cai,K.; Guo, H.;Cuihau Xuebao1986, 7, 357-363.
[9] Chakraborty,H.;Paul.N.; Rahman,M. L.;Trans Met Chem (Lond)1994,19, 524-526.
[10] Zhao,Y.D.;Pang.D.W.;Zong,Z.;CHemg.J.K.;Luo .Z.F.;Feng,C.J.;Shen,H.Y. Zhung,X.C. , Huaxe Xuebao1988, 56, 178-183.
[11] A.L.Lehlinger, "Biochemistry", 2ndedn. Worth Publisher.P. 84, 85, 220, 563 and 564, 1975.
[12] ZelihaHayvali.; BAV Fen Bil. Enst. Dergisi2005, 7.2.1321-1329.
[13] Hitoshi.T. Tamao.N. Hideyyki, A. Manabu,F.Takayuki, M. Polyhedron1997,16, 3787-3794.
[14] Raman,N. Raja.J.J. Joseph.J. Raja.J.D.;J. Chil.Chem.Soc2007, 52, 1138-1147.
[15] Vogel,A.I.; A text book of quantitative analysis, (Longman, London).162-171,1969.
[16] Argarago,W.L.F.;D.D.Perin.; Text book on the Purification of laboratory chemicals, 4th edition, Butter Worth, Hennemann, Oxford,1997.203-205
[17] Y.Y.Liu, H. Wang and F.Li, *J.Molecules*, 2013, 18, 877-893.
[18] Y. Yamaguchi and C. Hayashl, Clin. Chem. 23/11, 2151-2154 (1977).
[19] K.Ismail, *Transition Metal Chemistry*, 2000, 25, 522-528.
[20]. Dalwadi et al. Tephrosia purpurea Linn (Sharpunkha, Wild Indigo):A Review on Phytochemistry and Pharmacological Studies. Indian J.Pharm.Biol.Res. 2014, 2(1),108-121
[21]. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Adv Drug Deliv Rev 2001, 46 (1-3), 3-26.
[22]. Lipinski CA. Drug Discovery Today: Technologies 2004, 1 (4), 337-341.
[23]. Verma A. Asian Pacific Journal of Tropical Biomedicne 2012, 3, S1735-S1737 .
[24]. Molinspiration cheminformatics [homepage on the internet], Novaulica, SK-900 26 Slovensky Grob, Slovak Republic; [cited 2012 July 3], Available from http://www.molinspiration.com.
[25]. Ertl P, Rohde B, Selzer P. J Med Chem 2000, 43 (20), 3714-3717.
[26]. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Adv Drug Delivery Rev 1997, 23(1-3), 3-25.