QSAR studies on iminobenzoxazole and its analogues

[a]Sadhna Puri, [b]Ginni Singh, [c]Abheek Chaudhuri
[a]Department of Chemistry, Dayanand Girls Post Graduation College, Kanpur, India

Abstract

Iminobenzoxazole has been known for its nematicidal activity and along with the advancement in computational chemistry; series of analogues have been designed by substituting alkyl group of iminobenzoxazole with either electron withdrawing group or electron donating group. The physicochemical and biological properties have been calculated and discussed on the basis of melting point, chemical structure, Lipinski's rule, and biological activities. The compounds fulfill Lipinski's rule and show good drug likeness score (Table 2.). milog P of these compounds have been found below 5 that mean they show good permeability across cell membrane. TPSA below 160 Å2, *n* violations =1 or <0 it means compound can easily bind to receptor, molecular mass <500, *n* rotb < 5, No. hydrogen bond donors ≤ 5 (The sum of OHs and NHs), No. hydrogen bond acceptor ≤ 10 (The sum of Os and Ns). Compounds 1-15 are taken for further calculation of bioactivity score. From Table 3 Compounds 1-15 have showed good bioactivity score whose results are <0 showing activeness of the compound. Compound ***S-1,3-benzoxazol-2-yl{[5-(2-cyanoethoxy)-1,3,4-thiadiazol-2-yl]amino}ethanethioate*** has showed good drug likeness score with mi logP value is 2.165, TPSA (hydrogen bonding potential) is 113.94, molecular wt. is 361 with no violations. Moreover bioactivity score of ***S-1,3-benzoxazol-2-yl {[5-(2-cyanoethoxy)-1,3,4-thiadiazol-2-yl]amino}ethanethioate*** has been calculated with GPCR ligand value -0.44. Comparing drug likeness score and bioactivity score of compounds (1-15) with respect to compound ***S-1,3-benzoxazol-2-yl {[5-(2-cyanoethoxy)-1,3,4-thiadiazol-2-yl]amino}ethanethioate*** has given good drug likeness score and bioactivity score, therefore it can be considered as a lead compound whose chemical structure can be further used for the improvisation of potency, selectivity and pharmacokinetic properties.

KEYWORDS: Nematicidal activity, mi LogP, Lipinski's rule, Drug likeness score

INTRODUCTION

Helminthiasis alternatively spelled **helminthosis**; plural **helminthiases**) is any macroparasitic disease of humans and animals in which a part of the body is infected with parasitic worms, called helminths. These parasites are broadly classified into tapeworms, flukes, and roundworms. They often live in the gastrointestinal tract of their hosts, but may also burrow into other organs, where they induce physiological damages. They remain as the major cause of wildlife diseases and economic crisis in livestock industry, and human socio-economic problems in developing countries.

Hookworms

Major helminthiases are among the neglected tropical diseases targeted under the joint action of the world's leading pharmaceutical companies and non-government organizations through an ambitious project called *London Declaration on Neglected Tropical Diseases* which was launched on 30 January 2012. It aims to control/eradicate the diseases by 2020, by ensuring necessary supply of drugs and other intervention, and promoting sanitation and health education

The most serious helminth infections are prevalent in poor tropical and subtropical areas, where helminthiases are classified as neglected tropical diseases. They remain the most common parasitic infection of human in developing countries. *Ascaris lumbricoides*, *Trichuris trichiura*, *Necator americanus*, *Ancylostoma duodenale*, schistosomes and filarial worms collectively infect more than a billion people, rivallingHIV/AIDS and malaria. Schistosomiasis alone is the second most prevalent parasitic disease of all times in humans, next only to malaria.

According to current estimate, over a billion people in Subsaharan Africa, Asia and the Americas are infected at any moment with at least one helminth species; most of them leading to severe morbidity, accompanied by persistent poverty, decreased productivity, and poor socioeconomic development. Helminthiasis can have immunomodulatory effects on the host with implications for any coinfectingpathogens. In fact, in endemic areas, malaria, HIV and tuberculosis are established to be exacerbated by helminthiases. In many cases, they can induce severe hypersensitivity reaction leading to chronic allergy called anaphylaxis.

2-(substituted phenoxy methyl)-5-(2-mercaptoacetyl iminobenzol-2-ly)-1,3,4-thiadiazole is a lead compound which is used against **Helminthiasis.**Now in the place of alkyl group we put Electron Withdrawing and Electron Donating Groups and make derivatives of such compound and do (**Quantitative Structure-Activity Relationships (QSAR) f**or finding Bioactivity score of the compounds.

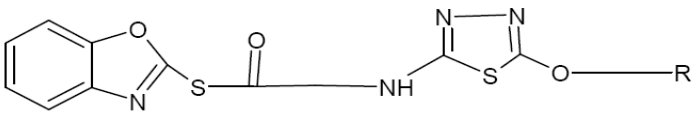

Figure 1: chemical structure 2-(substituted phenoxy methyl)-5-(2-mercaptoacetyl iminobenzol-2-ly)-1,3,4-thiadiazole

MATERIALS AND METHODS

Lipinski's Rule

Lipinski's rule of five also known as the Pfizer's rule of five or simply the Rule of five (RO5) is a rule of thumb to evaluate drug likeness or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans. The rule was formulated by Christopher A. Lipinski in 1997.

The rule describes molecular properties important for a drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism, and excretion ("ADME")

Components of the Lipinski's rule:

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 octanal-water partition coefficient log *P* not greater than 5
- No more than one number of violation.

Molinspiration

Molinspiration, web based software was used to obtain parameter such as MiLogP, TPSA, drug likeness. MiLogP, is calculated by the methodology developed by Molinspiration as a sum of fragment based contributions and correction factors [6,7]. MiLog P parameter is used to check good permeability across the cell membrane. TPSA is related to hydrogen bonding potential of compound .Calculation of volume developed at Molinspiration is based on group contributors. Number of rotatable bonds measures molecular flexibility. It is a very good descriptor of absorption and bioavailability of drugs. Through drug likeness datas of molecule, it can be checked molecular properties and structure feature in respect to known drugs.

Bioactivity score

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. All the parameters were checked with the help of software Molinspiration drug-likeness score online (www.molinspiration.com). Calculated drug likeness score of each compounds and compared with the specific activity of each compound, and the results were compared with standard drug. 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.

OSIRIS Property Explorer

The OSIRIS Property Explorer shown in this page is an integral part of Actelion's (1) inhouse substance registration system. It lets you draw chemical structures and calculates on-the-fly various drug-relevant properties whenever a structure is valid. Prediction

results are valued and colour coded. Properties with high risks of undesired effects like mutagenicity or a poor intestinal absorption are shown in red. Whereas a green colour indicates drug-confirm behaviour.

RESULTS

Physiochemical properties

The physicochemical properties as melting point, smiles (Simplified molecular-input line-entry system) of the compounds (1-15) are summarized in Table 1.

Drug likeness calculation on the basis of Lipinski rule of five

The drug likeness score was 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 bonds, volume. The drug likeness score and the calculated value of various parameters of the isolated compounds (1-15)are in Table 2.

Table 1. Physio-chemical properties of compounds

Compound code	Compound name	Molecular formula	M.P	Smile notation
1	2-[(5-{[2-(1,3-benzoxazol-2-ylsulfanyl)-2-oxoethyl]amino}-1,3,4-thiadiazol-2-yl)oxy]ethanaminium	C13H14N5O3S2	90	O=C(Sc1nc2ccccc2o1)CNc3nnc(OCC[NH3+])s3
2	methyl 3-[(5-{[2-(1,3-benzoxazol-2-ylsulfanyl)-2-oxoethyl]amino}-1,3,4-thiadiazol-2-yl)oxy]propanoate	C15H14N4O5S2	210	O=C(Sc1nc2ccccc2o1)CNc3nnc(OCCC(=O)OC)s3

3	*S*-1,3-benzoxazol-2-yl [(5-butoxy-1,3,4-thiadiazol-2-yl)amino]ethanethioate	C15H16N4O3S2	133	O=C(Sc1nc2ccccc2o1)CNc3nnc(OCCCC)s3
4	*S*-1,3-benzoxazol-2-yl [(5-propoxy-1,3,4-thiadiazol-2-yl)amino]ethanethioate	C14H14N4O3S2	135	CCCOc3nnc(NCC(=O)Sc1nc2ccccc2o1)s3
5	*S*-1,3-benzoxazol-2-yl {[5-(2-aminoethoxy)-1,3,4-thiadiazol-2-yl]amino}ethanethioate	C13H13N5O3S2	240	NCCOc3nnc(NCC(=O)Sc1nc2ccccc2o1)s3
6	*S*-1,3-benzoxazol-2-yl {[5-(2-cyanoethoxy)-1,3,4-thiadiazol-2-yl]amino}ethanethioate	C14H11N5O3S2	110	O=C(Sc1nc2ccccc2o1)CNc3nnc(OCCC#N)s3
7	*S*-1,3-benzoxazol-2-yl {[5-(2-fluoroethoxy)-1,3,4-thiadiazol-2-yl]amino}ethanethioate	C13H11FN4O3S2	125	FCCOc3nnc(NCC(=O)Sc1nc2ccccc2o1)s3

8	*S*-1,3-benzoxazol-2-yl {[5-(2-hydroxyethoxy)-1,3,4-thiadiazol-2-yl]amino}ethane thioate	C13H12N4O4S2	110	OCCOc3nnc(NCC(=O)Sc1nc2ccccc2o1)s3
9	*S*-1,3-benzoxazol-2-yl {[5-(2-nitroethoxy)-1,3,4-thiadiazol-2-yl]amino}ethane thioate	C13H11N5O5S2	210	O=C(Sc1nc2ccccc2o1)CNc3nnc(OCC[N+]([O-])=O)s3
10	*S*-1,3-benzoxazol-2-yl {[5-(2-phenylethoxy)-1,3,4-thiadiazol-2-yl]amino}ethane thioate	C19H16N4O3S2	170	O=C(Sc1nc2ccccc2o1)CNc4nnc(OCCc3ccccc3)s4
11	*S*-1,3-benzoxazol-2-yl {[5-(but-3-en-1-yloxy)-1,3,4-thiadiazol-2-yl]amino}ethane thioate	C15H14N4O3S2	132	O=C(Sc1nc2ccccc2o1)CNc3nnc(OCCC=C)s3
12	*S*-1,3-benzoxazol-2-yl {[5-(3-methylbutoxy)-1,3,4-thiadiazol-2-yl]amino}ethane thioate	C16H18N4O3S2	244	O=C(Sc1nc2ccccc2o1)CNc3nnc(OCCC(C)C)s3

13	*S*-1,3-benzoxazol-2-yl {[5-(3-oxobutoxy)-1,3,4-thiadiazol-2-yl]amino}ethane thioate	C15H14N4O4S2	130	O=C(Sc1nc2ccccc2o1)CNc3nnc(OCCC(C)=O)s3
14	*S*-1,3-benzoxazol-2-yl {[5-(3-oxopropoxy)-1,3,4-thiadiazol-2-yl]amino}ethane thioate	C14H12N4O4S2	155	O=C(Sc1nc2ccccc2o1)CNc3nnc(OCCC=O)s3
15	*S*-1,3-benzoxazol-2-yl {[5-(3,3,3-trifluoropropoxy)-1,3,4-thiadiazol-2-yl]amino}ethane thioate	C14H11F3N4O3S2	244	O=C(Sc1nc2ccccc2o1)CNc3nnc(OCCC(F)(F)F)s3

Table 2. Drug likeness score for compounds

Compd.No.	**miLogP**	**TPSA**	**nAtoms**	**n ON**	**nOHNH**	***n violation***	**n rotb.**	**volume**	**MW**
1	-0.622	117.79	23.0	8	4	0	8	280.246	352.421
2	2.532	116.453	26.0	9	1	0	10	312.688	394.434
3	4.145	90.148	24.0	7	1	0	9	301.522	364.452
4	3.586	90.148	23.0	7	1	0	8	284.72	350.425
5	1.512	116.171	23.0	8	3	0	8	279.447	351.413
6	2.165	113.94	24.0	8	1	0	8	285.018	361.408

7	3.006	90.148	23.0	7	1	0	8	273.09	354.388
8	2.076	110.376	23.0	8	2	0	8	276.177	352.397
9	2.491	135.972	25.0	10	1	0	9	291.49	381.395
10	4.512	90.148	28.0	7	1	0	9	339.567	412.496
11	3.623	90.148	24.0	7	1	0	9	295.89	362.436
12	4.361	90.148	25.0	7	1	0	9	318.109	378.479
13	2.524	107.219	25.0	8	1	0	9	303.703	378.435
14	2.798	107.219	24.0	8	1	0	9	287.142	364.408
15	3.904	90.148	26.0	7	1	0	9	299.456	404.395

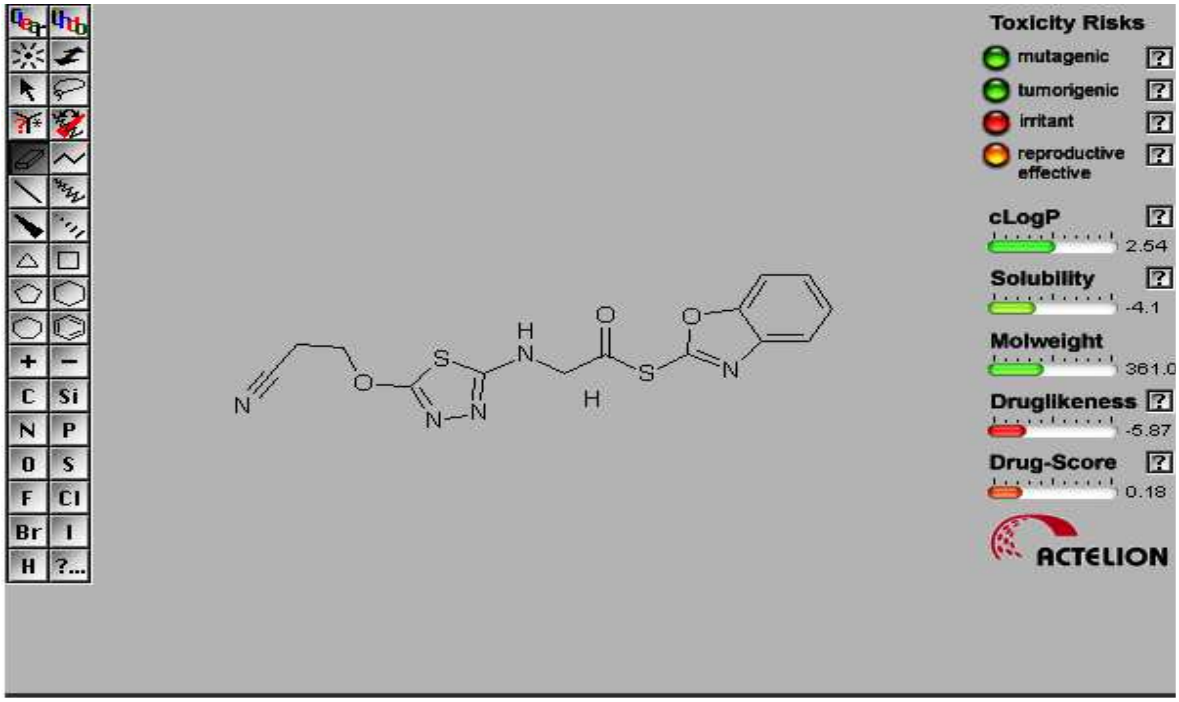

Figure 2: showing *S*-1,3-benzoxazol-2-yl {[5-(2-cyanoethoxy)-1,3,4-thiadiazol-2-yl]amino}ethanethioate which indicates no mutagenicity and tumorigenic risks through OSIRIS Property Explorer.

Bioactivity score of the compounds

The bioactivity scores of the isolated compounds (1-15) are compared with standard drug on the basis of GPCR ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor, enzyme inhibitor in Table 3.

Table 3. Bioactivity score of the compounds.

Compound	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1.	-0.22	-0.69	-0.25	-0.68	0.12	0.09
2.	-0.36	-0.77	-0.50	-0.55	-0.04	-0.05
3.	-0.28	-0.81	-0.45	-0.56	-0.02	-0.00
4.	-0.36	-0.87	-0.50	-0.62	-0.08	-0.04
5.	-0.22	-0.69	-0.25	-0.68	0.12	0.09
6.	-0.44	-0.97	-0.50	-0.73	-0.09	-0.07
7.	-0.04	-0.61	-0.22	-0.43	0.22	0.11
8.	-0.33	-0.84	-0.39	-0.59	-0.04	0.01
9.	-0.45	-0.83	-0.49	-0.65	-0.11	-0.06
10.	-0.18	-0.61	-0.31	-0.40	0.08	0.05
11	-0.28	-0.74	-0.40	-0.45	0.04	0.02
12	-0.28	0.76	-0.46	-0.55	0.06	-0.03
13	-0.38	-0.81	-0.63	-0.58	-0.01	-0.00
14	-0.28	-0.69	-0.42	-0.53	0.18	0.08
15	-0.25	-0.71	-0.40	-0.46	0.12	0.09

DISCUSSION

These properties are calculated and discussed on the basis of Lipinski's rule and its component. The compounds 5 fulfill Lipinski's rule and show good drug likeness score (Table 2.) . Milog P of these compounds was found below 5 that means these shows good

permeability across cell membrane. TPSA below 160 Å2, *n* violations =1 or <0 it means compound easily bind to receptor, molecular mass <500, *n* rotb < 5 [10], No. hydrogen bond donors ≤ 5 (The sum of OHs and NHs), No. hydrogen bond acceptor ≤ 10 (The sum of Os and Ns). Compound 1-15 were taken further calculation of bioactivity score. From Table 3 Compounds 2-15 showed good bioactivity score. Compound ***S*-1,3-benzoxazol-2-yl {[5-(2-cyanoethoxy)-1,3,4-thiadiazol-2-yl]amino}ethanethioate** showed good drug likeness score and bioactivity score, on comparison with other compounds with no toxicity risks.

CONCLUSION

Comparing drug likeness score and bioactivity score of compounds (1-15) compounds in respect of standard compound. Above from the listed derivatives ***S*-1,3-benzoxazol-2-yl {[5-(2-cyanoethoxy)-1,3,4-thiadiazol-2-yl]amino}ethanethioate** showed good drug likeness score with mi logP value 2.165, TPSA (hydrogen bonding potential) 113.94, molecular wt. 361, and bioactivity score with GPCR ligand values as -0.44. The present work has been attempted to identify the structural requirement of iminobenzoxazole analogs for nematicidal activity. The models derived from this investigation having good predictive ability, which could aid new nematicidal prior to their synthesis.

ACKNOWLEDGEMENT

We are thankful to Department of Chemistry, Dayanand girls post-graduation college,Kanpur for providing necessary facilities.

REFERENCES

1. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Adv Drug Deliv Rev 2001; 46 (1-3): 3-26.
2.Lipinski CA. Drug Discovery Today: Technologies 2004; 1 (4): 337-341.
3. Molinspiration cheminformatics [homepage on the internet], Novaulica, SK-900 26 Slovensky Grob, Slovak Republic; [cited 2012 July 3], Available from http://www.molinspiration.com.
4. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Adv Drug Delivery Rev 1997; 23(1-3): 3-25.
Bhatia, M; Choudhari, P; Ingale, K and Sawnat, R (2009), "Two- and Three-Dimensional Quantitative Structure-Activity Relationships Studies on a Series, of diuretics", LAJP, 28(6), 927-931.
5. Bhatia, M; Choudhari, P; Ingale, K; Bhatia, N et al. (2009), "3D QSAR Analysis of 2, 4-Disubstituted 1, 5-Benzodiazepine Derivatives As CNS Depressants", DJNB, 4, 579-585.
6. Choudhari, P and Bhatia, M, "3D QSAR, Docking Studies and Pharmacophore Modeling of Selected Factor Xa Inhibitors", Med Chem Res.
7. Drissa, S and Mahama, O, "Synthesis and in vitro nematicidal activity of new chalcone Vectorised by imidazopyridine", African Journal of Pharmacy and Pharmacology, 5(18), 2086-2093.
8. Noureen, N; Kalsoom, S and Rashid, H (2010), "Ligand based pharmacophore modelling of anticancer histone deacetylase inhibitors", Afri J Biotech, 9(25), 3923-3931.
9. Chafiq, H; Jesds, E; Juan, AV; Juan, JV; Julio, AB and Beverly, AH (1999), "Short Synthesis and Anti-Rhinoviral Activity ofImidazo [1, 2-a] Pyridines: The Effect of Acyl Groups at 3-1.Position", Bioorg. Med. Chem. Lett., 9, 1391-1394.
10. Ertepinarl, H; Gok, Y; Geban, O and Ozden, S (1995), "A QSAR study of the biological activities of some benzimidazoles and imidazopyridines against Bacillus subtilis", Eur. J. Med. Chem., 30, 171-175.