ACCESSIBILITY OF TOPOLOGICAL DESCRIPTORS IN LIGAND BASED DRUG DESIGN OF CERTAIN NEVIRAPINE MOLECULAR ANALOGUES & GLYCOPROTEINS AGAINST HIV-REVERSE TRANSCRIPTASE

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Summary

The main objective is to acquire the best novel lead from the designed set of 17 analogues of nevirapine for complete antagonistic action against HIV reverse transcriptase enzyme & introducing some glycoproteins for antagonizing and agonizing dual effect against HIV infection with certain drug design topological descriptors. In this connection, Wiener index and Lipinski rules are applied for the designed substituted congeners, which includes Nevirapine, N-acetyl glucosamine, Adenosine 3,5 phosphate, Fucose, Glutamic acid, Benzothiophine inhibitor of factor Ixa (IZX), Tyrosine phosphatase shp2 (JZG), S54-10 antibody in complex with antigen kdo (KDA), N-acetyl β-glucosaminyl amine, Mannose 6-phosphate, Castanospermine-1,2, Ditiocarb-1,2,3, N-acetyl neuraminic acid (NANA), Malonic acid and Kbt as target leads. The higher wiener index values (W= 1266.688599; W= 565.22) for Kbt and KDA indicated the inhibition of HIV-1 RTase by both nucleosides & non-nucleosides, which profoundly inhibits the replication. In contrast, the lower wiener index (W= 0) for fucose, glutamic acid, JZG, NANA and malonic acid predicts the anti-HIV activity accuracy from 81-90%. The results showed that 11 set of congeners among 17 are found to be most effective. Further, the same 11 congeners are found to have drug-like characteristics viz., complete antagonistic action on virus surface site with the application of Lipinski rules. In addition, the designed glycoproteins have blocked the virus surface completely with pure agonistic effect.

Key Words: Wiener index, Lipinski rule, Nevirapine, Analogues, HIV-reverse transcriptase

Introduction

The development of new drugs with pharmacological efficacy and clinical utility is now a major activity in the chemical and biological sciences. Successes in mid-century have led to a level of confidence in our ability to make some predictions in the design of molecules with desirable characteristics. Today, we are on the threshold of rational drug design based on the occasional ability to recreate and model the molecular level scene of action of a ligand molecule and an effecter using computer graphic simulations. From such models, variations in structure may be made with the objective of improving the drug-receptor encounters leading to a better drug[1]. The opportunity to use this approach in drug design is limited to situations in which there is considerable information such as the specific sites of action on the structure of the enzymes involved and the ligands that interact. In the absence of a well defined molecular target, it is necessary to adopt other strategies to develop a drug. Beyond the attribute of biological activity, in the realm of pharmaceutical properties such as absorption, distribution, metabolism and excretion, it is not possible to build a model around a macromolecular system with an active site. These properties are in the domain of molecular systems where something resembling an effector is an evanescent group of water molecules in intimate contact with solutes or protein surface fragments forming a complex system[2].

This reflection leads us to the consideration of an alternate approach to drug design, one that we have called quantitative information analysis[3]. In this approach a series of molecules is presented to a biological system and the properties of interest are measured. We are concerned with the structure of the ligand, A, and the numerical readout from system B.

The process of quantitative information analysis has followed two paths over the years. One path has lead to the use of physical properties to describe a molecule in a model, relating it to a measured response[4]. This has come to be called quantitative structure-activity relationship (QSAR), where the word structure was loosely used to denote measured or estimated physical properties. At the same time, an alternative paradigm to physical property models arose in the form of theoretical models of structure derived from molecular orbital theory[5]. In particular, the introduction of a practical graph-based topological index by Randic[6], a quarter of a century ago and developed by Kier and Hall[7, 8], made possible a description of structure that is simple and demonstratively valuable in predictive power.

Hence our main objective is to acquire the best novel lead from the designed set of 17 analogues of nevirapine for complete antagonistic action against HIV reverse transcriptase enzyme and introducing some glycoproteins for antagonizing and agonizing dual effect against HIV infection, using certain drug design topological descriptors.

Materials & Methods

Protocol 1

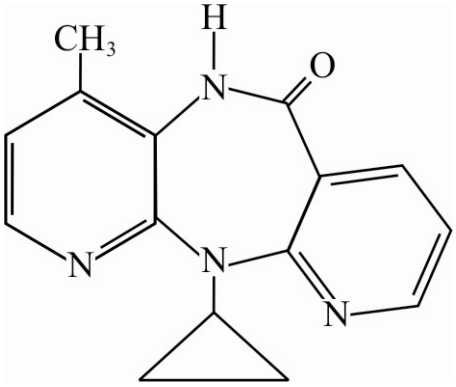
The HIV virus acts on the cell's respective receptor with the help of Glycoproteins (gp 120 and gp 40) and then after it weakening the cell and leave the material into the cell for multiplication, so that after incubation it results in the weakening of the immune system. Thus our target is to block that particular site on HIV virus envelop, that is responsible for the binding with the receptor with the help of analogues of nevirapine.

Protocol 2

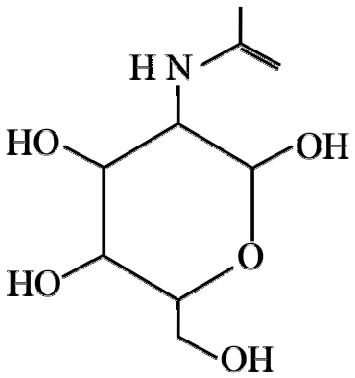
We can introduce the glycoproteins into the human body that may be making the virus busy by attaching on that site (responsible for binding with the human cell receptor and weakening the cell CD_4), thus results in the bloclcing of that site completely and causing no multiplication and thus no HIV infection.

Protocol 3

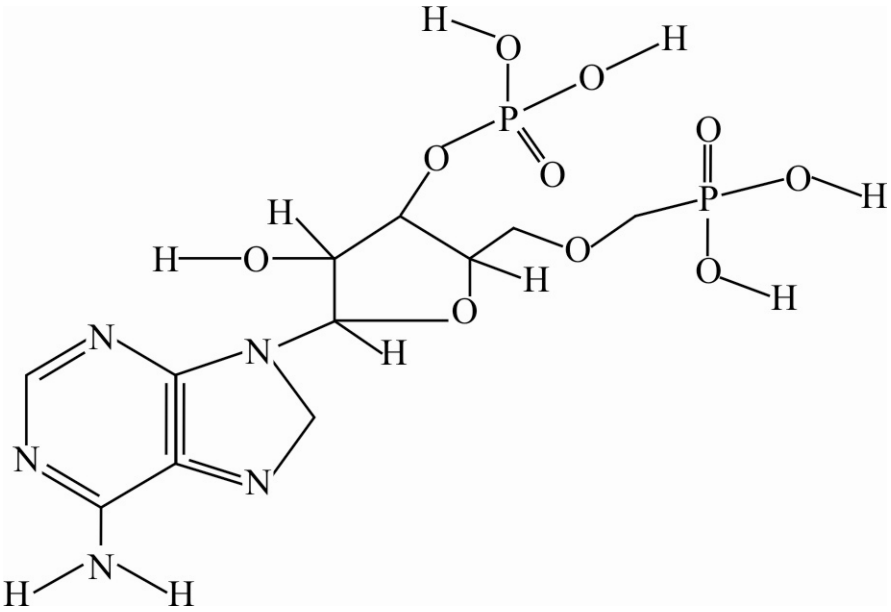
In order to antagonize HIV infection by using the prepared analogues of respective glyprotein, we added the same substituents as for the nevirapine, for the analogues of glycoproteins. The 17 substituted compounds used for the test study are nevirapine, N-acetyl glucosamine, Adenosine–3, 5–phosphate, Fucose, Glutamic acid, Benzothiophine inhibitor of factor Ix_a (IZX), Tyrosine phosphatase shp 2 (JZG), S 54–10 antibody in complex with antigen Kdo (KDA), N-Acetyl–β–glucosaminyl amine, Mannose–6–phosphate, Castanospermine–1, 2, Ditiocarb–1, 2, 3, N–Acetyl neuraminic acid (NANA), Malonic acid and Kbt as target leads. For this all analogues, we have calculated two accessible topological descriptors such as Wiener index and Lipinski rules in ligand based drug design for correlating their biopotency[9]. The study was carried out at Supercomputing facility for Bioinformatics and Computational Biology, IIT Delhi. Lipinski rules of five helps in distinguishing between drug like and non-drug like molecules.



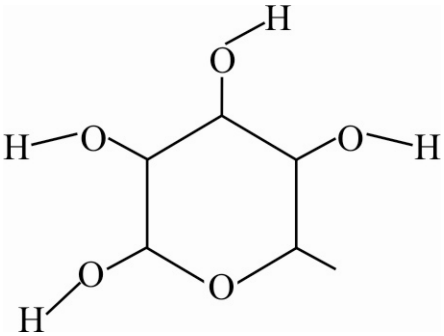
(1) Nevirapine



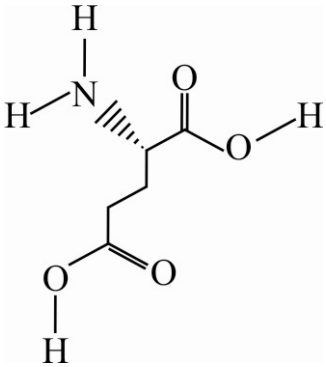
(2) Acetyl Glucosamine



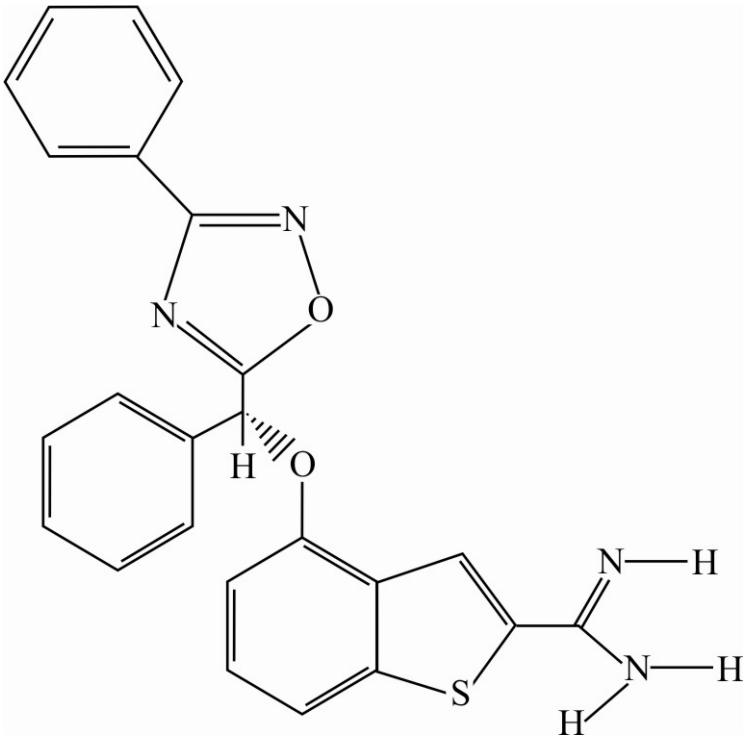
(3) Adenosine–3, 5–phosphate



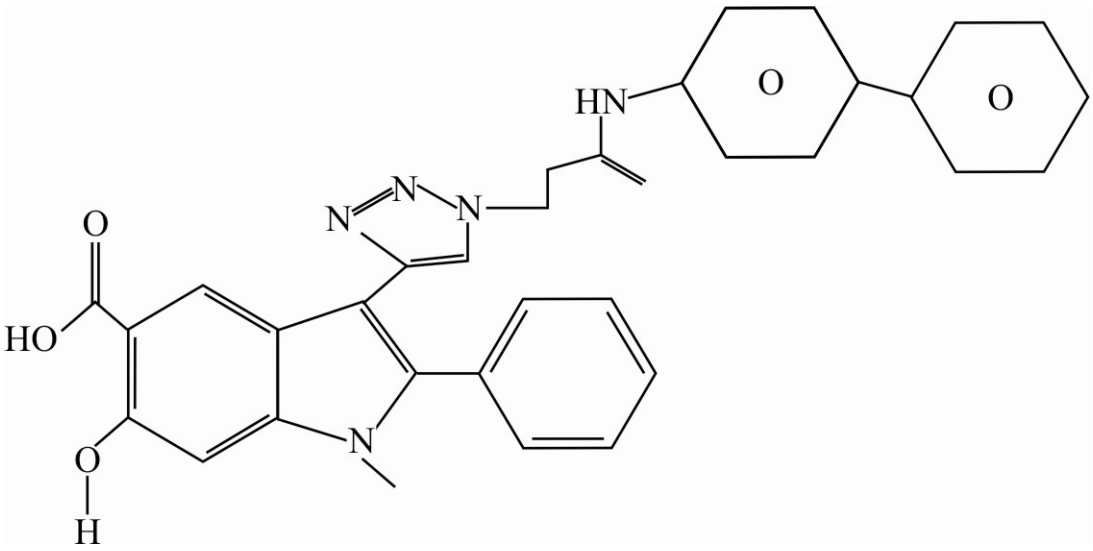
(4) Fucose



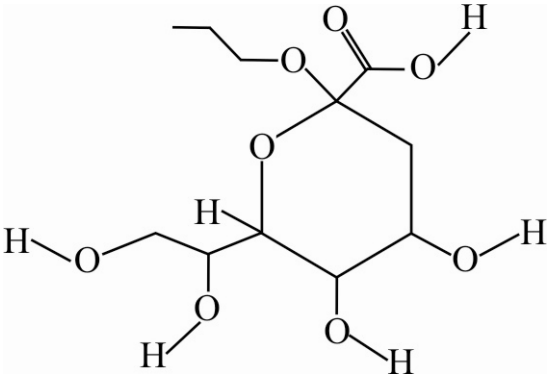
(5) Glutamic Acid



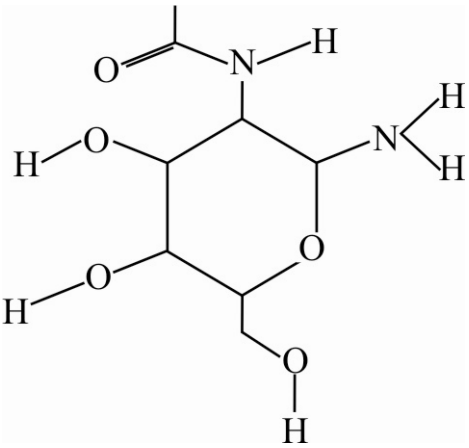
(6) Benzothiophine inhibitor of factor Ix a (IZX)



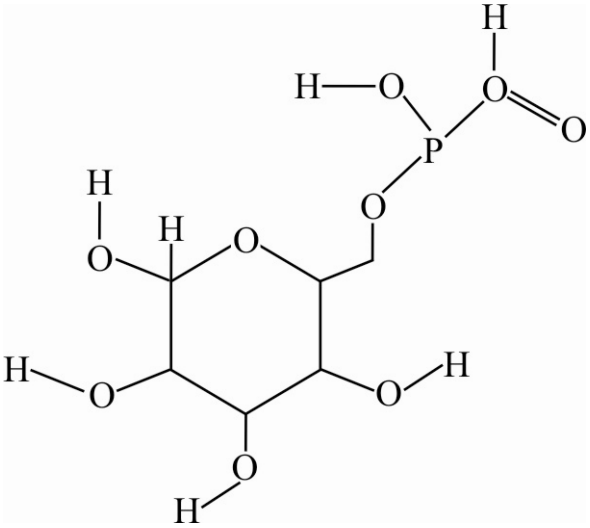
(7) Tyrosine phosphatase Shp 2 (JZG)



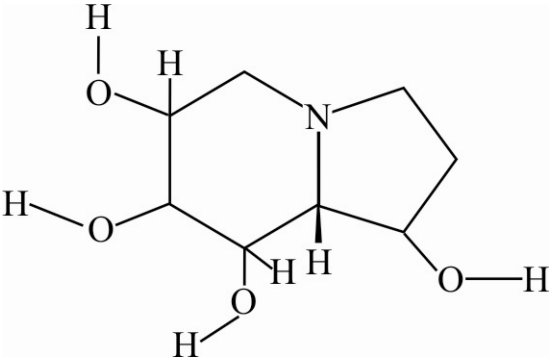
(8) S54-10 Antibody in Complex with Antigen Kdo (KDA)



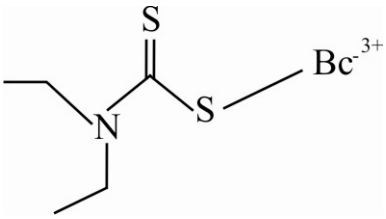
(9) N–acetyl β–glucosaminylamine



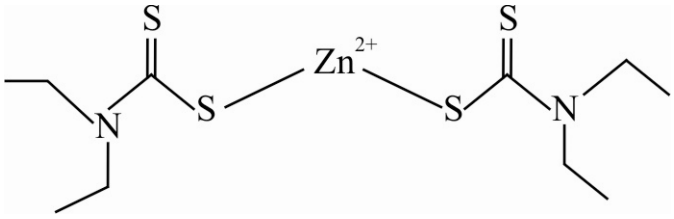
(10) Mannose–6–phosphate



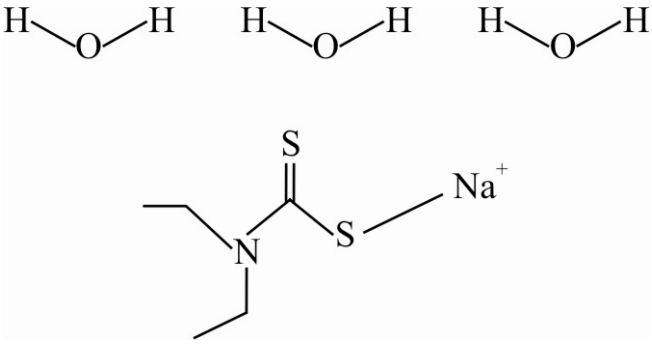
(11) Castanospermine 1, 2



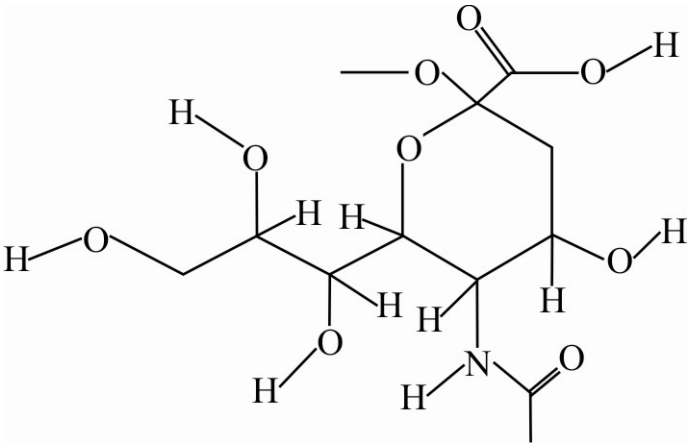
(12) Ditiocarb–1



(13) Ditiocarb–2



(14) Ditiocarb–3



(15) N–Acetyl neuraminic acid (NANA)

Chemical Structure of Test Sets

It predicts the high probability of success or failure due to drug likeness for molecules complying with 2 or more of the following rules.

1) Molecular mass less than 500 Dalton.
2) High lipophilicity (Log P less than 5).
3) Less than 5 hydrogen bond donors.
4) Less than 10 hydrogen bond acceptors.
5) Molar refractivity should be between 40–130.

Results & Discussion

The results of correlation for wiener index are expressed in Table 1.

Table 1. Wiener index values of test sets

S.No.	Test Set	Wiener index (W) (Manual)	Wiener index (W) (Software)
1.	Nevirapine	11	NT
2.	N–Acetyl Glucosamine	1.5	NT

3.	Adenosine 3, 5 phosphate	21	NT
4.	Fucose	0.5	0.0
5.	Glutamic acid	2	0.0
6.	IZX	7	NT
7.	JZG	7.5	0.0
8.	KDA	3	565.22
9.	N–Acetyl β–glucosaminyl amine	1.5	NT
10.	Mannose 6–phosphate	3	NT
11.	Castanospermine 1, 2	0.5	196.453454
12.	Ditiocarb-1	5	52.822968
13.	Ditiocarb-2	13.5	52.822968
14.	Ditiocarb-3	5	52.822968
15.	NANA	NT	0.0
16.	Malonic acid	NT	0.0
17.	Kbt	NT	1266.688599

NT- Not Tested

The results of Lipinski rules are indicated in Table 2.

Table 2. Hydrogen bond donors and acceptors of Test set analogues by Lipinski rules.

S. No.	Test Set	Observed H–bonds		Expected H–bonds		Drug like fulfillment with respect to		Final Remark
		Number of H–bond donor	Number of H–bond acceptor	Number of H–bond donor	Number of H–bond acceptor	H–bond donor	H–bond acceptor	
1.	Fucose	4	5	4	9	S	S	DL
2.	Castanos-permine–1,2	4	5	4	9	S	S	DL
3.	Ditiocarb–1	0	0	4	9	S	S	DL
4.	N–Acetyl Glucosamine	5	6	4	9	NS	S	PDL

5.	Glutamic acid	3	5	4	9	S	S	DL
6.	IZX	2	6	4	9	S	S	DL
7.	JZG	3	6	4	9	S	S	DL
8.	NANA	6	9	4	9	NS	S	PDL
9.	KDA	5	8	4	9	NS	S	PDL
10.	Adenosine 3, 5–phosphate	6	14	4	9	NS	NS	NDL
11.	Mannose-6-phosphate	6	14	4	9	NS	NS	NDL
12.	KDE	5	8	4	9	S	S	DL
13.	Ditiocarb-3	3	5	4	9	S	S	DL

S–Satisfied; NS–Not Satisfied; DL–Drug like characteristics; PDL–Partial drug like Characteristics; NDL–Non-drug like characteristics.

The higher wiener index was obtained for the test set Kbt (w=1266.688599) along with next higher w value for KDA (w=565.22). Inhibition of HIV virus type–1 reverse transcriptase by both nucleosides and non-nucleosides RT profoundly inhibit the replication. Nucleoside RT inhibitors are known to be toxic but there is a little information regarding to the toxicities of non-nucleoside RT inhibitors.

The lower wiener index (w=0) for fucose, glutamic acid, JZG, NANA and malonic acid predicts the anti-HIV accuracy from 81 to 90%. This lower value offers a vast potential for virtual screening of combinatorial libraries, structure activity studies and drug design. As evidenced above, nucleoside's toxicity is high and non-nucleoside's toxicity is not clear. Hence, we can definitely say that our drug sets are having less toxicity and are very much effective in both the classes of above mentioned category of drugs. Thus our 11 drug sets among 17 are found to be the most effective than the conventional older drugs with the application of wiener index.

As per Lipinski rules, we observed that 11 out of 17 test sets are found to be drug like molecule, which clearly indicated that the drug design what we have performed is a rational drug design. Among the test set of 17 analogues analyzed, the following 9 test sets namely fucose, castanospermine 1, 2, Ditiocarb–1, Ditiocarb–2, Ditiocarb–3, Glutamic acid, IZX, JZG and KDE were found to have complete antagonistic activity on the surface of virus site and 3 were found to have partial antagonistic activity namely, N–acetyl neuraminic acid (NANA), KDA and N–acetyl glucosamine. In addition, only 2 sets sets were found to have very less antagonistic activity such as Adenosine 3, 5–phosphate and Mannose–6–phosphate as they doesn't satisfy the lipinski rules with their respective H-bond donors and H-bond acceptors. Moreover, the glycoproteins were found to be completely blocking the virus surface (by making them busy on attaching at that site) and thus having a successful & complete agonist replacement messenger's action.

Conclusion

As with the above results and discussion, we come to conclusion that there are many drugs used for the treatment of AIDS against HIV-reverse transcriptase enzyme. Among them, nevirapine is the most effective one to protect the infant from infection from mother to infant. Thus we are making the drug more effective and it may be completely inhibiting the action of HIV RTase. The more potent drugs are Castanospermine–1, 2, N–Acetylneuraminic acid, Ditiocarb, JZG, KDA, Malonic acid, Glutamic acid and will be used as target lead for the other drugs which are going to be synthesized in near future. It was also found that glycoproteins will have complete inhibition of HIV infection. Hence the results of this study lead to a detailed structural interpretation of topological descriptors. This realization should finally, correctly categorize these indices in their rightful place in the pantheon of quantitative descriptors of molecular structure.

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