DOCKING STUDIES OF NOVEL TETRAHYDROQUINOLINE AND TETRAHYDROISOQUINOLINE ANALOGUES INTO THE NON-NUCLEOSIDE INHIBITOR BINDING SITE OF HIV-1 RT

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ABSTRACT

Molecular docking has been used as an important tool in Inhibitor Design. Fourteen novel 1, 2, 3, 4-tetrahydroquinoline and 1, 2, 3, 4-tetrahydroisoquinoline analogs were docked into the NNRTI binding pocket of HIV-1 RT with PDB ID 1FK-9 using Flexidock module of SYBYL 7.1 software. Among the twenty five docked analogs, 1d, 2c and 2d showed average docking energy of -20.05, -19.01and -18.06 k.cal/mol respectively indicates that these analogs are highly potent. Analog 4b showed average docking energy of -7.31 k.cal/mol indicating that it is less active than Efavirenz. The docking results indicate that quinoline and isoquinoline analogs share the same binding mode as the crystal inhibitors in the pocket geometries of Efavirenz and also gives an idea to design and synthesise novel quinoline and isoquinoline analogs with appropriate structural requirements active against HIV-1 RT mutant strains with minimum toxic effects.

Keywords : *Docking, 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline, Efavirenz, HIV-1 reverse transcriptase, Non-nucleoside inhibitor.*

INTRODUCTION

Human immuno deficiency virus (HIV) has been identified as the probable causative agent for AIDS. The reverse transcriptase (RT) of the human immunodeficiency virus type-1 is one of the major attractive targets in the treatment of the acquired immuno deficiency syndrome (AIDS)[1-3]. The main function of HIV-1 RT is to convert the single stranded RNA genome to double stranded DNA genome[4]. In general, the inhibitors of HIV-1 RT are classified into two main categories: nucleoside inhibitors (NRTIs) and non-nucleoside inhibitors (NNRTIs), depending upon their mechanism of action[5-9]. NRTIs are substrate analogs that act at the catalytic site of HIV-1 RT by terminating DNA synthesis, whereas NNRTIs are a chemically diverse group of compounds that noncompetitively bind to the unique allosteric hydrophobic binding pocket located about $10A^0$ away from the catalytic site and force the RT subunits into an inactive conformation[10-12]. When compared to NRTIs, NNRTIs have the advantage of high potency, low toxicity and high selectivity[2]. Nevertheless, the emergence of drug resistant viral strains has limited the therapeutic efficacy of these NNRTIs[13]. Compounds having quinoline and isoquinoline moiety have been used as broad-spectrum chemotherapeutic agents, which include anti-tubercular[15-18], anti-fungal[19-20], anti-malarial[21-24], anti-viral[25-27] and anticancer[28] since ancient days. Docking of small molecules to the active sites of receptor structures has become increasingly important in the context of drug discovery[29-31]. Generally speaking, docking is carried out using a computer program in order to dock computer-generated representations of small molecules to a receptor followed by evaluation of the molecules with respect to

complementarity in terms of shape and properties. Good complementarity of a molecule indicates that the molecule is potentially a good binder. Technically speaking, the placement of the molecules in the region of interest is referred to as docking, whereas the prediction of affinity is referred to as scoring[32]. The primary criteria for evaluating docking strategies are docking accuracy, scoring accuracy, screening utility and speed. Docking accuracy reflects an algorithm's ability to discover a conformation (pose) and alignment of a ligand relative to a cognate protein that is close to that experimentally observed and to recognize the pose as correct.

Scoring accuracy is the ability to correctly predict the rank order of binding affinities of ligands to a particular protein. Screening utility measures the ability of a docking algorithm to detect true ligands of a protein within a background of random ligands not thought to bind the protein. Speed denotes the time required for the completion of one successful docking process[33].

EXPERIMENTAL

Procedure for docking studies:

In order to perform flexible docking, the complex crystal structure of HIV-1 RT receptor and the standard drug, efavirenz was extracted from the Brookhaven Protein Databank (PDB code 1FK9) and was used for further docking studies. It was then optimized using restrain molecular dynamics using Tripos force field. Partial atom charges of HIV-1 RT were calculated with Kollman-all-atom and Gasteiger-Huckel for the ligands respectively by using Flexidock module in SYBYL 7.1[34] software installed in a Dell system (3.4 GHz processor, 512 MB RAM, 80 GB Hard Disk) with Red Hat Linux Enterprise version 3.0 as the Operating System.

Validation of the docking Protocol:

The docking protocol used was validated for the crystal structure predicting the binding mode of the corresponding inhibitor. To validate the docking method used, the standard NNRTI Efavirenz was removed from the active site of the receptor 1FK 9 and docked back into the binding pocket of HIV-1 RT. The conformation and orientation of the docked efavirenz was compared with the conformation and orientation of the original X-ray crystallographic structure downloaded from Brookhaven Protein Databank. The RMSD of the docked pose from the X-ray pose of efavirenz was also within the prescribed limit 1-2.5 A^0. This indicates that the docking method used has good ability to reproduce the X-ray bound conformation and it can be used for docking of novel quinoline and isoquinoline analogs to investigate their orientation and binding affinity in the binding pocket of HIV-1 RT.

Docking studies of novel quinoline and isoquinoline analogs

Structure of quinoline and isoquinoline analogs were drawn using sketch module option in the SYBYL 7.1 and was saved in the database. The same conformation as that of efavirenz was obtained for each analog by using Fit atom module in the SYBYL 7.1 by taking the pose of the extracted conformation of Efavirenz from the X-ray structure. Likewise the conformation of all analogs were predicted, saved in the same database and was used for further docking studies. The amino acid residues in NNRTI binding pocket used for the docking studies are Pro95, Leu100, Lys101, Lys103, Val106, Glu138, Val179, Tyr181, Tyr188, Gly190, Phe227, Trp229, Leu234, His235, Pro236 and Tyr318.All the analogs were docked in the active site of HIV-1 RT (PDB ID 1FK9) using Flexidock and the docking scores were obtained.

Based upon the docking scores, the HIV-1 reverse transcriptase inhibitory activity of the compounds has been predicted.

RESULTS AND DISCUSSION

Using the above said validated docking protocol and the results in terms of docking score have been shown in Table-1 carried out the flexible docking studies. The analogs **1d**, **2c** and **2d** showed the average docking energy of -20.05, -19.01 and -18.06 k.cal/mol respectively indicating that these analogs are highly potent when compared to the standard. This may be due to high structural and chemical complementary between the macromolecular target and the ligand. Their docked pose is shown in Fig-2. The analog **4b** showed average docking energy of -7.31 k.cal/mol, which indicates that this analog was less potent than the standard drug efavirenz. All the remaining analogs except **6a** and **6b,** showed comparable average docking score as that of efavirenz. The structures of all the analogs **1a-d**, **2a-d**, **3a, 4a-d, 5a-d, 6a-d, 7a-d** and efavirenz are presented in Figure 1.

It can be concluded that this docking study is an effective computational method in making qualitative predictions that discriminates the active analogs from inactive analogs. The docking results obtained also gives an idea to design and synthesize novel class of quinoline and isoquinoline analogs with appropriate structural requirements for better anti-HIV activity and with minimum toxic effects.

ACKNOWLEDGEMENTS

One of the authors, M.S. is grateful to QIP, AICTE for providing financial assistance in the form of a fellowship.

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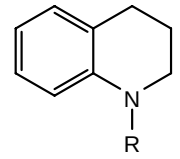
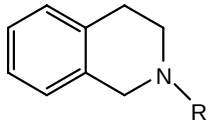
(Received: 9 May 2008 Accepted: 15 May 2008 RJC-189)

TABLE – 1: **DOCKING SCORES OF NOVEL 1,2,3,4-TETRAHYDROQUINOLINE AND 1,2,3,4- TETRAHYDROISOQUINOLINE ANALOGS**

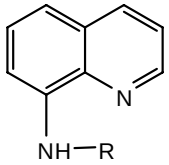
Entry	***Docking Score (K.cal/mol)***
Efavirenz	-12.91
1a	-14.65
1b	-12.18
1c	-9.14
1d	-20.05
2a	-15.75
2b	-12.03
2c	-19.01
2d	-18.06
3a	-12.01
4a	-8.85
4b	-7.31
4c	-11.05
4d	-12.44
5a	-12.50
5b	-12.06
5c	-12.60
5d	-16.58
6a	-9.40
6b	-7.96
6c	-11.70
6d	-12.48
7a	-11.87
7b	-11.65
7c	-12.69
7d	-16.93



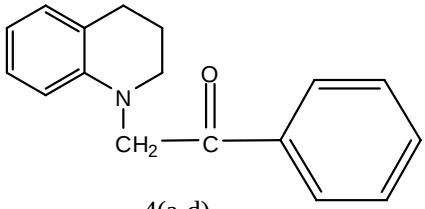
1(a-e)



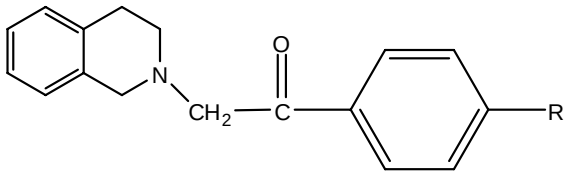
2(a-e)



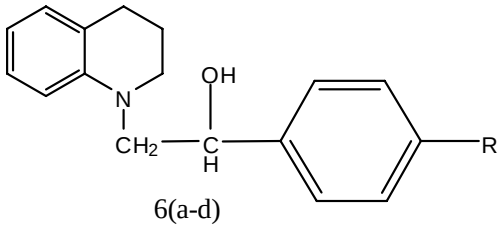
3a



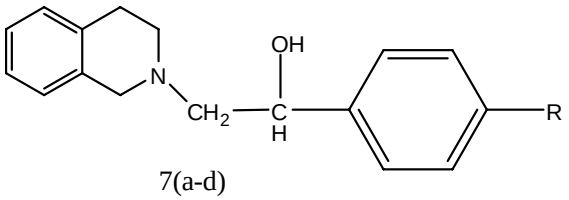
4(a-d)



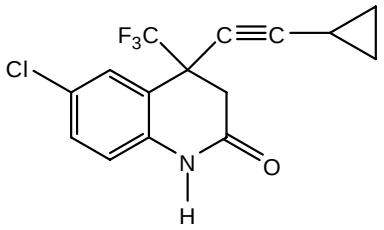
5(a-d)



6(a-d)

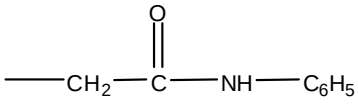


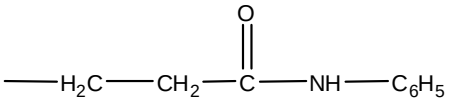
7(a-d)

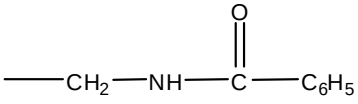


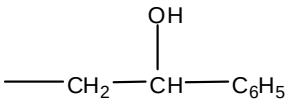
Efavirenz

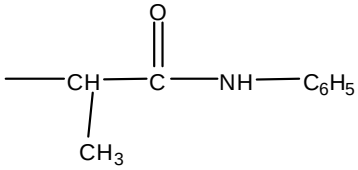
Where R,

1a, 2a, 3a = 

1b, 2b, = 

1c, 2c, = 

1d, 2d, = 

1e, 2e, = 

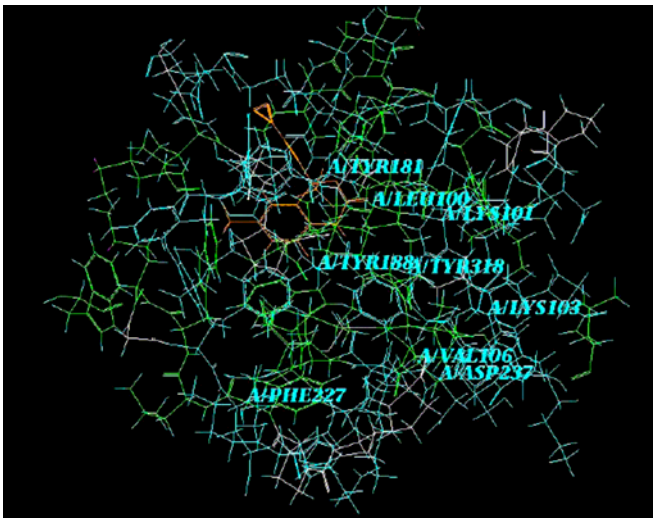
4a, 5a, 6a and 7a = Cl

4b, 5b, 6b and 7b = Br

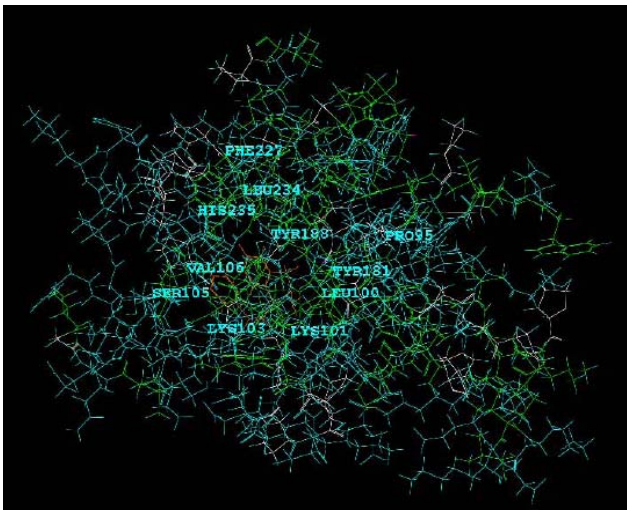
4c, 5c, 6c and 7c = NO_2

4d, 5d, 6d and 7d = C6H5

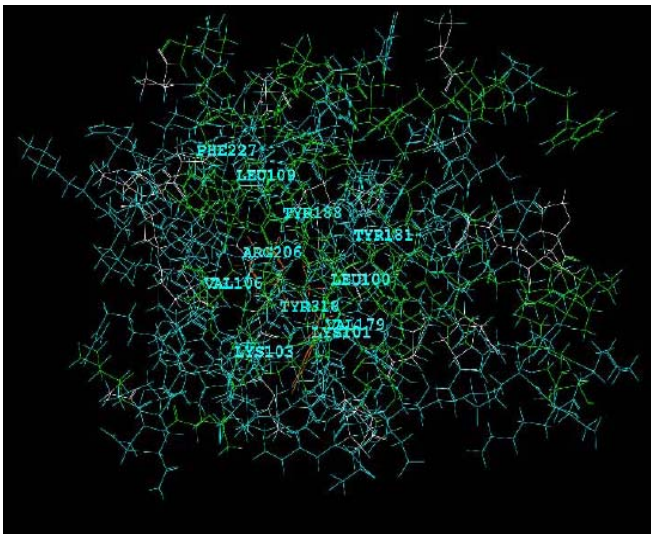
Fig. 1- Structures of compounds 1(a-e), 2(a-e), 3a, 4(a-d), 5(a-d), 6(a-d), 7(a-d) and Efavirenz



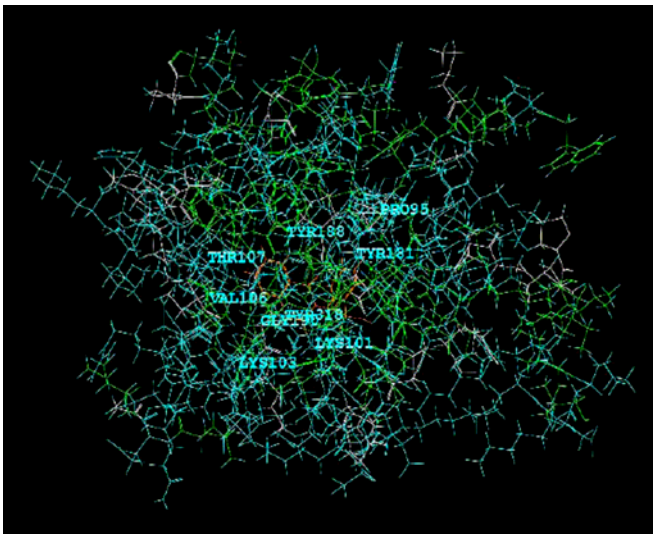
(a) Efaverinz



(b) Analog 1d



(c) Analog 2c



(d) Analog 2d

Fig. 2-Docked pose of (a)Efaverinz,(b) Analog 1d, (c)Analog 2c and(d) Analog 2d on HIV -1 RT(PDB ID 1FK9)