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Exploring isoxazole and carboxamide derivatives as potential non-nucleoside reverse transcriptase inhibitors

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ABSTRACT

Nonnucleoside reverse transciptase inhibitors (NNRTI) are a class of drug molecules with a specific target of HIV-1 reverse transcriptase (RT). In the present work, we evaluated a set of selected oxazole and carboxamide derivatives to identify potential pharmacophoric features using molecular docking approach.

The docking approach employed has been validated by enrichment factor calculation at top 1% ($EF_{1\%}$). It shows a considerable improvement in $EF_{1\%}$value compared to earlier reported study carried out on specific dataset of ligands and decoys for RT, in the directory of useful decoys (DUD).

The carboxamide derivatives show better activity as NNRT inhibitors than oxazole derivatives. From this study, four pharmacophoric groups including a triazine ring, an aniline substituent, a benzyl amide moiety and a trimethylphenoxy substituent have been recognized and used for designing new NNRT inhibitors.

Newly designed molecules show significant enhancement in docking scores over the native ligand, parent and other training set molecules. In addition, some functional groups have also been identified to assist in improving the activity of these pharmacophores. Thus a nitrile group, an amide and fluoro substitution turn out to be an important requisite for NNRT potential inhibitors.

1. Introduction

Human immunodeficiency virus-1 (HIV-1) is a retrovirus responsible for acquired immunodeficiency syndrome (AIDS) [1–4]. The retroviral enzyme reverse transcriptase (RT) performs several critical roles in the replicative cycle of the HIV. Considerable efforts, therefore, have been directed towards this enzyme as a target for treating AIDS.

One of the major obstacles in the drug development against HIV is its nature to develop drug resistance [5–7]. Various methods have been employed to overcome this problem. HAART (highly active antiretroviral therapy) is one such treatment strategy, that involves use of combination of available drugs [8]. Owing to the drug resistance developed against the drugs used in combination, HAART therapy frequently fails to deliver the result [9]. This results in a need for continuous search for new drugs to block the replication of viruses that are resistant to the available drugs.

Different drugs that have been explored against RT can mainly be classified in two forms as Nucleosidic (NRTI) and Non-Nucleosidic Reverse Transcriptase Inhibitors. The NRTIs are competitive inhibitors which mimic normal nucleotides except for a hydroxyl group position. It binds at deoxynucleosidetriphosphate binding pocket and terminates chain elongation by preventing incorporation of additional nucleotides. NNRTI are chemically diverse set of compounds, which bind non-covalently and non-competitively at allosteric site thereby inhibiting HIV-1 replication specifically. NNRTIs when bound to RT, blocks the chemical steps of polymerization [10]. It restricts the conformational change required for polymerase catalysis. NNRTIs are therefore, presently preferred over NRTIs owing to their better side effect profile.

NNRT based inhibitors were first introduced when TIBO and nevirapine were recognized as NNRT inhibitors by Pauwels and Shih respectively. Many NNRTIs including 9-Cl-TIBO, loviride, delavirdine, efavirenz, phenylmethylthiazolylthiourea (PETT), HEPT,quinoxaline derivative HBY 097, diaryltriazine (DATA), and DAPY compounds were later considered for RT inhibition [11–14]. Among all, Nevirapine, Etravirine, Efavirenz and Delavirdine have been approved for treatment of HIV-1 infection.

Although many potential drug molecules are now available in market, due to the repeated drug resistance of HIV-1, there is always a need for continuous search for NNRTI's, which can be used in combination with NRTIs against natural as well as the mutated structures. Virtual screening is one of the most promis-

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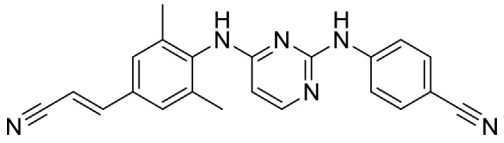
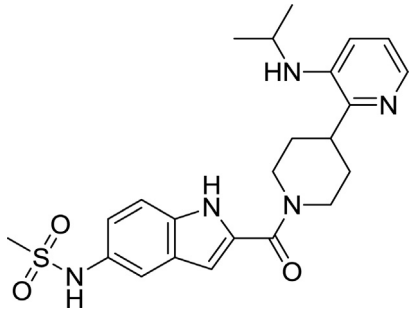
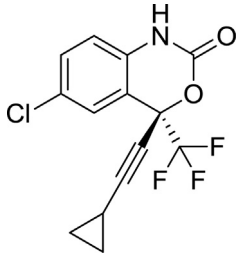
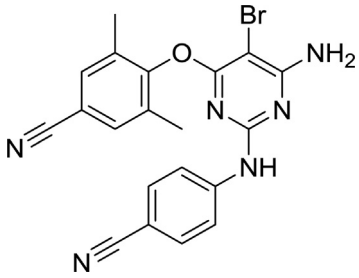
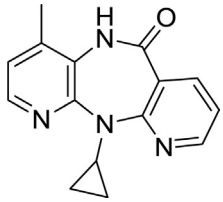
Table 1
The native ligand and parent drug moelculesused for benchmarking.

Sr. no.	Molecule	Structure	Docking score (kcal/mol)
1.	TMC278		−11.8
2.	Delavirdine		−9.0
3.	Efavirenz		−10.3
4.	Etravirine		−7.4
5	Nevirapine		−10.1

ing and time saving method for the search of inhibitors for any target [15,16]. Barreiro et al. [16] have reported a search for Non-Nucleoside Inhibitors of HIV-1 Reverse Transcriptase by screening huge databases. These screening results may further be refined using various methods like 3D virtual screening, pharmacophore based screening as well as incorporation of structure activity relationship analysis [17–19].

In this regard, carboxamide and oxazole derivatives have been frequently explored for their activities as non-nucleosidic reverse transcriptase inhibitors. Deng et. al have designed and synthesized different hydrolytically stable oxazolone and isooxazolone derivatives of alkenyldiarylmethanes as potential NNRT inhibitors [20]. Regina et al. have studied different nitrogen as well as cyclicindole-2-carboxamide substitution's inhibition for HIV-1 WT in MT-4 cells. Molecular Docking studies here, indicated the significance of Glu138 and nitrogen atoms of carboxamide [21].

Based on similar study, in the present work, we explore a set of carboxamide and oxazole derivatives to identify the pharmacophoric features associated with these molecules. The features thus identified have been further used in designing molecules with improved activity as NNRT inhibitors. The methodology employed is based on the molecular docking approach. Computational method has been explained in the next section.

1.1. Computational methods

Molecular docking has been performed using AutoDock Vina and AutoDock Tools software packages [22,23]. The functional form used to calculate the scoring function in AutoDockVina is given by

$$c = \sum_{i<j} f_{t_i t_j}\left(r_{ij}\right)$$