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MOLECULAR DOCKING STUDIES OF IMIDAZOLE DERIVATIVES AS HIV REVERSE TRANSCRIPTASE INHIBITORS

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ABSTRACT

Recent years have seen a focus on imidazole compounds containing two nitrogen atoms in a five-membered aromatic ring. The human immunodeficiency virus (HIV) targets the immune system. Many people are diagnosed with HIV each year, and up to one in seven HIV-positive individuals are unaware of their condition. A serious worldwide health concern continues to be the human immunodeficiency virus (HIV), particularly HIV-1 infection and the development of acquired immune deficiency syndrome (AIDS). Imidazole structure with two azole groups in the Meta position of a five-membered ring, and belongs to a significant class of heterocycles used in drug discovery. It has promising antiviral efficacy against both drug-sensitive and drug-resistant HIV strains and may exert anti-HIV action through a variety of pathways. With the use of SAR and docking study, this research has advanced regarding the anti-HIV potential of imidazole derivatives with receptor HIV-1RT. According to molecular docking, the compound's inhibitory effects were brought about by their ability to attach to the enzyme's active site. A novel imidazole derivative, (Substituted phenyl)-[2-(substituted phenyl)-imidazol-1-yl]-methanones was synthesized by diazotization reaction of substituted aniline forming intermediate 2-(Substitutes phenyl)-1-H imidazole and screened it for anti-HIV activity. New Chemical Entities anti-HIV-1 RT was investigated. It supports the possibility that these substances have HIV-1 RT inhibition activity

KEYWORDS: Imidazole, Docking, SAR, Diazotization, HIV-1RT.

BACKGROUND

In structural molecular chemistry and computer-assisted drug creation, molecular docking is a crucial tool. Predicting the prevailing binding mode(s) of a ligand with a protein having a known three-dimensional structure is the aim of ligand—protein docking. Effective docking methods use a scoring system that correctly ranks candidate dockings and efficiently explore high-dimensional spaces. Lead optimization benefits greatly from the use of docking to do virtual screening on huge libraries of compounds, rate the outcomes, and offer structural ideas for how the ligands inhibit the target. The setup of the input structures for the docking is just as crucial as the docking itself, and it can be difficult to interpret the findings of stochastic search methods.[1]

INTRODUCTION

The virus known as HIV (Human immunodeficiency virus) targets the immune system of the body. AIDS can develop from HIV if it is not treated (Acquired immunodeficiency syndrome).[2]

HIV weakens the immune system and impairs the body's capacity to fend against illness and infection. Contact with infected blood, semen, or vaginal secretions can transfer HIV. If a person contracts HIV, they are infected for life; however, drugs can control the infection and stop the spread of the disease. 2 to 4 weeks after contracting the infection, some HIV-positive individuals experience flu-like symptoms. For years, people on HIV drugs might not experience any other symptoms. Fever, exhaustion, and swollen lymph nodes are just a few signs that might emerge when the virus multiplies and kills immune cells. HIV usually progresses to AIDS if left untreated in 8 to 10 years.[3]

All antiretroviral medications that are currently on the market can develop resistance in HIV. Resistance has been noted for the recently approved medications as well. New medications are required that could combat resistance while having fewer or no negative effects. Because they target this enzyme specifically, non-nucleoside reverse transcriptase inhibitors (NNRTIs) of HIV play a significant role in the anti-HIV treatments that are currently available.[4]

Imidazole have a special place in heterocyclic chemistry, and in recent years, interest in their derivatives has grown significantly due to their many useful pharmacological and chemical properties. Imidazole is a heterocyclic ring made up of nitrogen that is significant in both

biology and medicine. As a result, researchers have found imidazole compounds to be interesting for more than a century. Purine, histamine, histidine, and nucleic acid are only a few significant natural compounds that contain the imidazole ring. It is utilised as a cure to optimise the solubility and bioavailability properties of proposed weakly soluble lead compounds since it is a polar and ionisable aromatic chemical that enhances the pharmacokinetic characteristics of lead molecules. The synthesis of compounds containing imidazoles can be done in a variety of ways, and the many structural reactions they can undergo have a huge impact on medicinal chemistry.[5]

The imidazole derivatives possess extensive spectrum of Anti HIV activity. In view of the structural diversity, unique mode of action, high efficacy and low toxicity, imidazole derivatives have the capacity to inhibit reverse transcriptase (RT) which are the potential targets for the development of novel anti-HIV agents.[6]

MATERIALS AND METHODS

Chemistry

In the present study, I have synthesized 2-(Substitutes phenyl)-1-H imidazole as an intermediate by the condensation of imidazoles with corresponding substituted aryldiazonium chlorides which in turn were prepared by the diazotization of substituted aniline, the intermediate were reacted with corresponding substituted benzoyl chloride to get final product named as (Substituted phenyl)-[2-(substituted phenyl)-imidazol-1-yl]-methanones.[7]

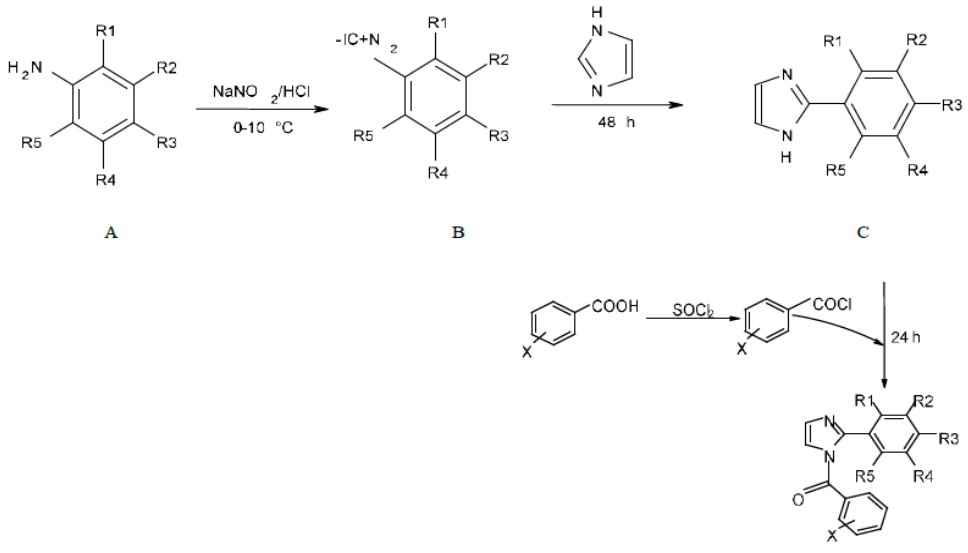


Fig. 1

Scheme 1: Synthetic scheme for the synthesis of (substituted phenyl)-[2-(substituted phenyl)-imidazol-1-yl]-methanones.

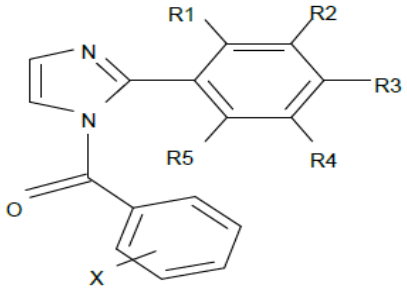


Fig. 2

Derivatives were prepared as

Table 1

Sr. No	R1	R2	R3	R4	R5
D1	Br	COOH	H	H	H
D2	Br	H	CH3	H	H
D3	Br	OCH3	H	H	H
D4	Br	H	H	Cl	H
D5	Br	H	H	NO2	H

Experimental

General procedure for the synthesis of 2-(substituted phenyl)-1H-imidazoles

Using a sodium nitrite solution at a temperature of 0^o to 10^o C, substituted anilines (0.13 mol) in a hydrochloric acid/water mixture (1:1) were diazotized. Imidazole (0.004 mol) was added to the diazotized mixture while being vigorously shaken. The above combination was added dropwise to a solution of sodium acetate (40 g in 100 ml) while keeping the temperature between 5^o and 10^o C. The above solution was first stirred for 3 hours while in a cold condition, and then for an additional 48 hours while at room temperature. The finished substance was extracted from the alcohol, dried, and recrystallised.

General procedure for the synthesis of (substituted phenyl)-[2- (substituted phenyl)-imidazol-1-yl]-methanones

A solution of matching substituted benzoyl chloride (0.002 mol) in diethyl ether was combined with a solution of 2-(substituted phenyl)-1H-imidazoles (0.002 mol) in diethyl ether (50 ml) (50 ml). At room temperature, the preceding combination was stirred for 24

hours. Once ether was evaporated, the resulting product was separated and purified by recrystallization with methanol.

Molecular docking

Molecular docking provides useful information about drug receptor interactions and is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to predict the affinity and activity of the small molecule.

General procedure for molecular docking

- New chemical entities anti-HIV-1 RT were investigated by using docking software VLife MDS. Three dimensional structure of HIV-1 RT
- Receptors was downloaded in PDB format from protein data bank having a PDB Code 2ZD1 and 3LP1 respectively.
- The structure was loaded in VLife MDS then docking was performed using GA docking. Docking score and Ligand-receptor interactions were noted.

RESULT AND DISCUSSION

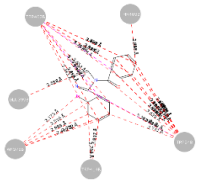
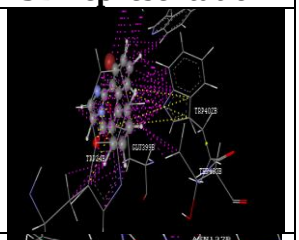
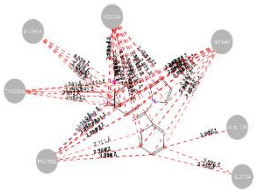
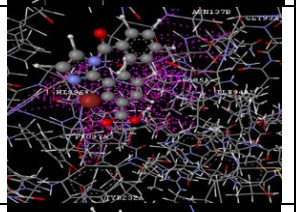
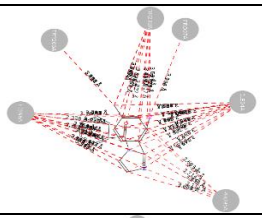
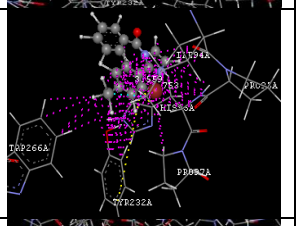
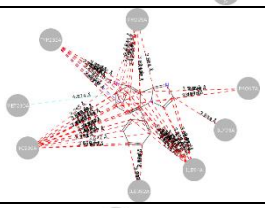
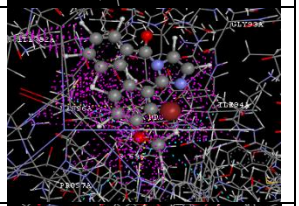
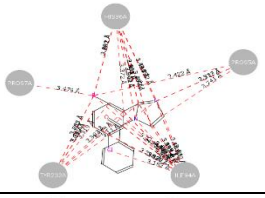
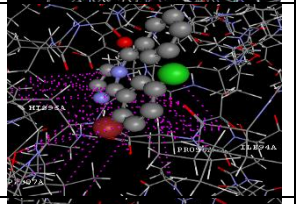
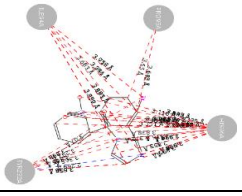
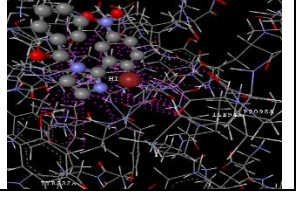
With the help of docking study using software VLife MDS I have studied drug-receptor interactions given in table 2. And the binding affinity of drug towards receptor so that we can know that if drug is effective as anti-HIV-1 RT. This research has advanced regarding the anti-HIV potential of imidazole derivatives with receptor HIV-1RT. Satisfactory docking results were obtained when ligand and its derivatives D1, D2, D3, D4 and D5 were docked against both the HIV-1 RT receptors with PDB code 2ZD1 and 3LP1 respectively.

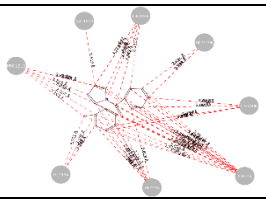
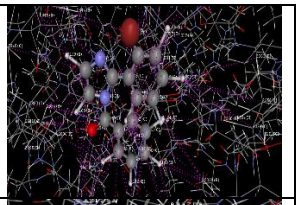
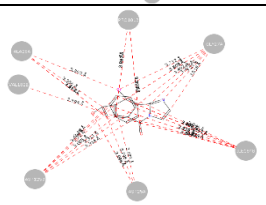
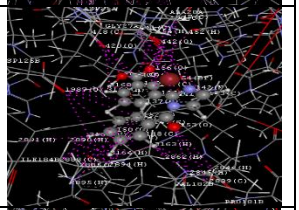
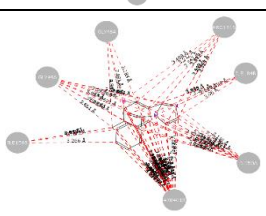
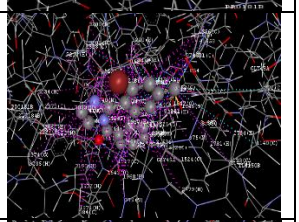
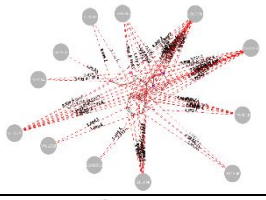
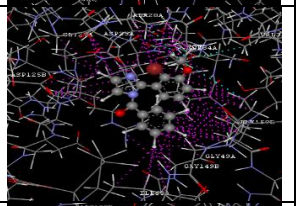
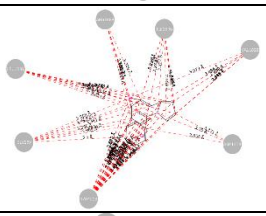
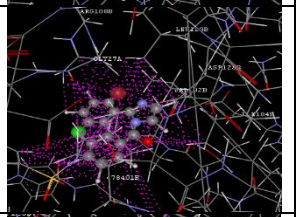
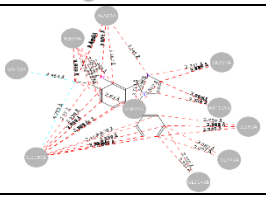
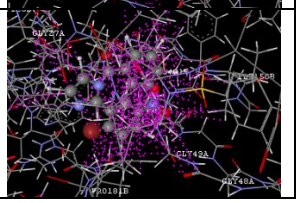
Table 2

Compound	PDB code	Docking Score	Interactions with amino acids
Ligand	2ZD1	-5.033	TRP24B, ARG78B, GLU399B, TRP402B THR403B, TRP414B
D1	2ZD1	-4.349	GLY93A, ILE94A, PRO95A, HIS96A PRO97A, TYR232A, ASN137B
D2	2ZD1	-5.049	ILE94A, PRO95A, HIS96A, PRO97A, TYR232A, TRP266A
D3	2ZD1	-4.070	GLY93A, ILE94A, PRP95A, HIS96A, PRO97A, MET230A, TYR232A, ILE382A
D4	2ZD1	-5.449	ILE94A, PRO95A, HIS96A, PRO97A, TYR232A
D5	2ZD1	-5.351	ILE94A, PRO95A, HIS96A, TYR232A
Ligand	3LP1	-5.291	GLY48A, GLY49A, ILE50A, GLY149B, ILE150B, PRO181B, VAL182B, ILE184B

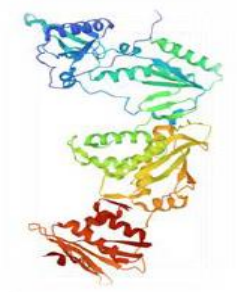
D1	3LP1	-5.297	ASP25A, GLY27A, ALA28A, ASP125B, PRO181B, VAL182B, ILE184B
D2	3LP1	-5.193	GLY48A, GLY49A, ILE50A, ILE150B, PRO181B, ILE184B
D3	3LP1	-5.019	ASP25A, THR26A, GLY27A, ALA28A, LEU123B, LEU124, ASP125B, VAL182B,ASN183B, ILE184B, ILE185B
D4	3LP1	-4.969	GLY27A, ARG108B, LEU123B, ASP125B, VAL182B, ILE184B
D5	3LP1	-4.947	ASP25A, GLY27A, ALA28A, VAL32A, GLY49A, ILE50A, ILE84A, ASP125B, GLY149B, ILE150B

Table 3

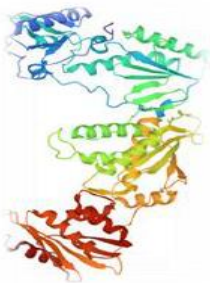
Compound	PDB Code	2D representation	3D representation
Ligand	2ZD1		
D1	2ZD1		
D2	2ZD1		
D3	2ZD1		
D4	2ZD1		
D5	2ZD1		

Ligand	3LP1		
D1	3LP1		
D2	3LP1		
D3	3LP1		
D4	3LP1		
D5	3LP1		

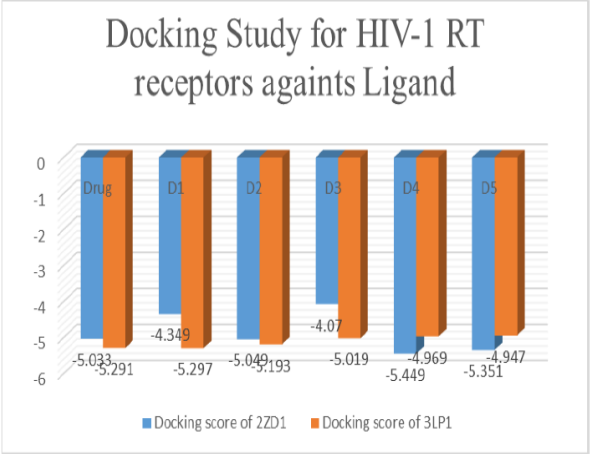
Receptors with PDB code 2ZD1 and 3LP1 have resoluions 1.80 Å and 2.23 Å, chain A, sequence length 557 and 563 respectively.



2ZD1



3LP1



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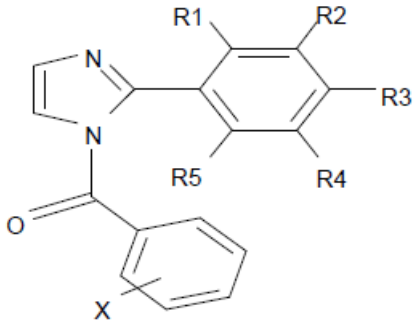

1. Nitro group at R3 position could enhance the activity.
2. Substituent on the phenyl ring had little influence on the activity
3. Electron-withdrawing group on the phenyl ring was beneficial for the activity
4. Halogen at R4 position (-Cl and -NO2) exhibited an enhancing anti-HIV-1 activity which could be due to the fact that incorporation of halogen atoms increased the lipophilicity.
5. The different substituents on the phenyl ring influenced the anti-HIV activity.
6. Electron withdrawing groups (-NO2, -COOH, -X) enhanced the activities.
7. The presence of electron-donating methoxy or electron-withdrawing chloro groups at ortho-position of phenyl ring significantly boosted up the anti-HIV activity.

CONCLUSION

In the present study, Anti-HIV activity of the Ligand and five novel azo derivatives D1, D2, D3, D4, and D5 were investigated. Molecular docking study of all the synthesized derivatives have been studied against the HIV-1 RT (2DZ1 & 3LP1). The docking results attributed various type of protein-ligand interactions. The result indicate that D4 and D5 have the best

affinity towards HIV-1 RT (2DZ1) than that of ligand and other derivatives. Whereas D1 and D2 have good affinity as close to ligand against the HIV-1 RT (3LP1) that can indicate that these molecules could have the most potential antiviral treatment of HIV. Structure activity relationship shows that NO2 group, electron-withdrawing group, substituent on phenyl ring and methoxy group enhance the anti-HIV activity of molecule against HIV-1 RT receptor.

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