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Synthesis of Some Novel Imidazol-5-one Derivatives and their *In-vitro* screening for Non-Nucleoside Reverse Transcriptase Inhibitors.

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ABSTRACT

A novel series of 4-substituted ethylidene/benzylidene-2-methyl-1-(pyrimidine-2-yl)-1H-imidazol-5-one derivatives were efficiently synthesized. The synthesized compounds were evaluated for their *in-vitro* reverse transcriptase inhibition activity using reverse transcriptase colorimetric assay kit (Roche). Some of these compounds showed significant reverse transcriptase inhibitory activity. Docking study was performed to study the binding orientation and affinity of synthesized compounds for RT enzyme.

Keywords: Anti-HIV, Imidazol-5-one, Pyrimidine, reverse transcriptase inhibitors.

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INTRODUCTION

Acquired Immune Deficiency Syndrome (AIDS) is the leading cause of death and disability for both men and women in the world. AIDS caused by the human immunodeficiency virus (HIV). Current treatment strategies for HIV infection are mainly based on drugs that interfere with virus replication by inhibiting HIV protease, integrase or reverse transcriptase (RT) [1]. One such essential enzyme is reverse transcriptase (RT), which enables the integration of viral genetic information into the host genome [2]. The RT inhibitors are of two types: nucleoside reverse transcriptase inhibitors (NRTIs,) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Resistance has also been observed for old drug as well as newly approved drugs. So, there is need of new drugs that could combat the resistance [3]. Although the highly active antiretroviral therapy (HAART) combination regimens such as Nevirapine, Delaviridine, Efavirenz, Etravirine and Rilpivirine (Figure 1), which have been approved by US FDA as novel HIV-1 NNRTIs, are proving to be effective for AIDS therapy.

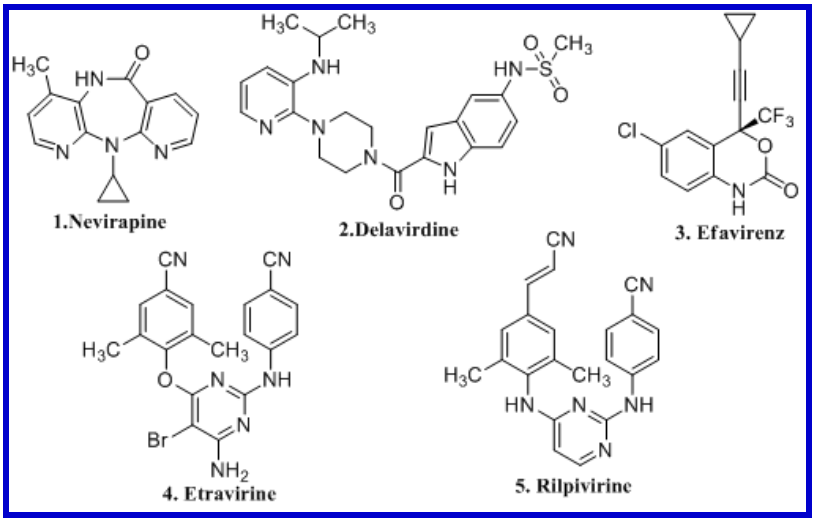

Figure 1: Currently drugs used to treat AIDS under NNRTIs.

It was observed that Aminopyrimidine (Lamivudine, 1,3-Oxathiolane) [4], five membered heterocyclic derivatives such as Thiazolidine [5], imidazole (Capravirine) [6], pyrazole [7], Tetrazole [8], Thiadiazole [9], Thiazole [10], Triazole [11], have major contribution in reverse transcriptase activity. Keto group adjacent to amine is also important for inhibition of reverse transcriptase (Figure 2) [12].

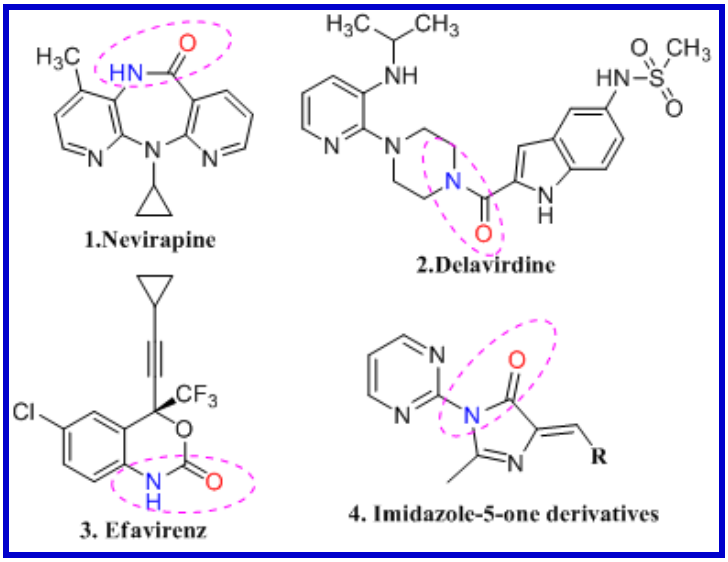

Figure 2: General structure of imidazol-5-one scaffold.

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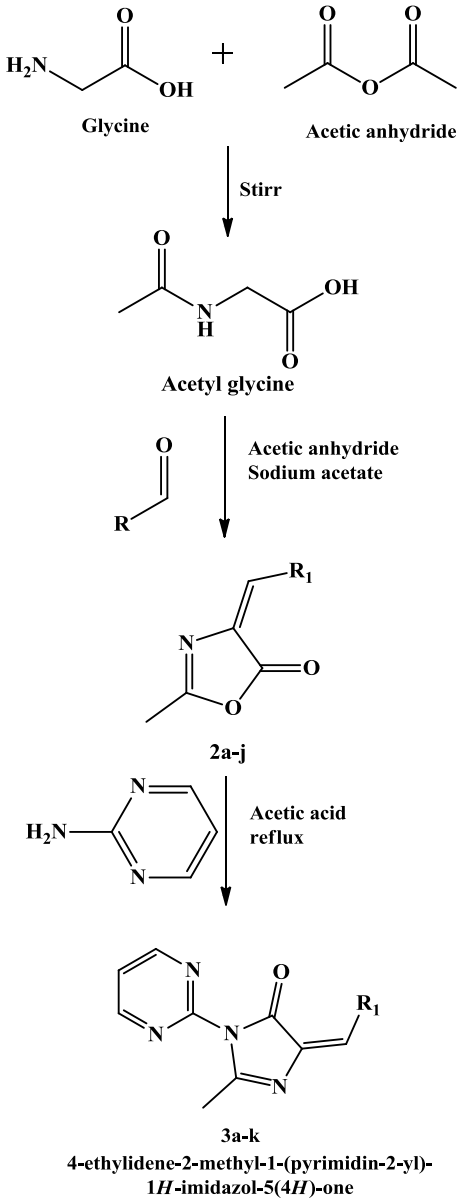
From the literature survey, it was observed that the butterfly like shape is important factor in the binding of the first generation NNRTIs. Despite their chemical diversity, they assume very similar butterfly-like shape. The butterfly structure has a hydrophilic centre as a 'body' and two hydrophobic moieties representing the 'wings' [13,14].

Based on above observation, we had decided to design a new molecular scaffold containing these three important cores i.e. Imidazole ring (a hydrophilic centre as a 'body'), pyrimidine ring and substituted ethylidene/ benzylidene group (two hydrophobic moieties representing the 'wings' of butterfly structure). In view of this we have attempted the synthesis of novel series of 4- substituted ethylidene/ benzylidene-2-methyl-1-(pyrimidine-2-yl)-1H-imidazol-5-one derivatives (Figure 2).

EXPERIMENTAL

Melting points were determined on scientific melting point apparatus in open capillaries and were uncorrected. FT-IR spectra were recorded on JASCO FT-IR 4000 using KBr powder. ^{1}H NMR spectra and ^{13}C NMR were recorded on a BRUKER AVANCE II 400 spectrometer (400MHz) with TMS as internal standard and DMSO as a solvent. Mass spectra were recorded on Time of flight mass spectrometer.



Scheme 1: Synthesis of designed compounds (3a-k)

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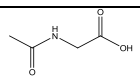
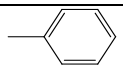
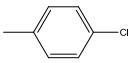
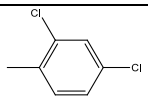
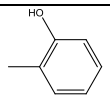
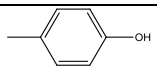
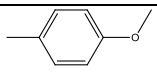
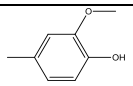
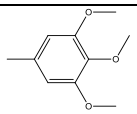
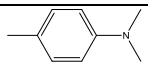
Synthesis of acetyl glycine (1)

In a 500-ml conical flask glycine (0.5mol, 37.5gm) was added in 150ml of water. Introduced a mechanical stirrer and stirred vigorously until the solid has a completely dissolved. Acetic anhydride (1 mol, 51ml) in one portion was added and stirred vigorously for 15-20 minutes; the solution becomes hot and some acetylglycine get crystallized. Cooled in a refrigerator, preferably overnight; collect the precipitate on a Buchner funnel, washed with ice-cold water and dry at 100°C. Recrystallise the residue from 40ml of boiling water, collect the solid which separates, wash and dry it as before.

Synthesis of 4- substituted ethylidene/ benzylidene -2-methyloxazol-5-one (2a-2k)

In a 500 ml conical flask equipped with a reflux condenser, add a mixture of aldehyde (1 mol, 10.6gm), acetyl glycine (1 mol, 11.7gm), acetic anhydride (3 mol, 30.6ml) and anhydrous sodium acetate (1 mol, 8.2gm) was placed and heated on an electric hot plate with constant shaking. As soon as the mixture liquefied completely, transferred the flask to a water bath and heated for 2 h. Then added 100 ml of ethanol slowly to the contents of the flask, allow the mixture to stood overnight, filtered the crystalline product with solution, washed with 25 ml of ice-cold alcohol and then finally washed with 25 ml of boiling water, dried at 100°C and recrystallized from suitable solvent to get desired product (**2a-2k**).

Table 1: Experimental data of synthesized compounds 1, 2a- 2k

Compound	R	Molecular Formula	Molecular Weight	% Yield	Melting Point(^{0}C)*
1		$C_4H_7N_1O_3$	117.04	65.21	206-208
2a	$-CH_3$	$C_6H_7NO_2$	125.13	59.11	96-98
2b		$C_{11}H_9NO_2$	187.19	74.25	88-90
2c		$C_{11}H_8ClNO_2$	221.64	78.14	142-144
2d		$C_{11}H_7Cl_2NO_2$	256.08	82.67	168-170
2e		$C_{11}H_9NO_3$	203.19	62.45	158-150
2f		$C_{11}H_9NO_3$	379.21	45.82	98-100
2g		$C_{12}H_{11}NO_3$	217.22	57.43	182-184
2h		$C_{12}H_{11}NO_4$	233.22	47.49	114-116
2i		$C_{14}H_{15}NO_5$	277.27	69.86	136-138
2j		$C_{13}H_{14}N_2O_2$	230.26	43.94	102-104
2k		$C_{13}H_{10}N_2O_2$	226.23	86.49	164-166

***melting points were uncorrected**

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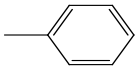
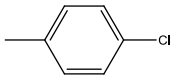
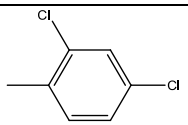
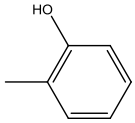
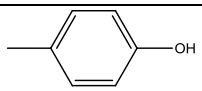
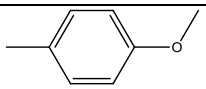
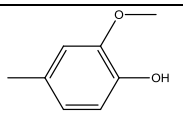
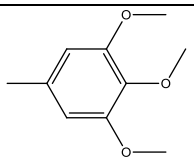
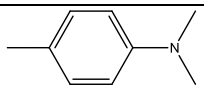
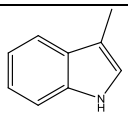
Synthesis of 4- substituted ethylidene/ benzylidene-2-methyl-1- (pyrimidine-2-yl) -1H imidazole -5 -one (3a-3k)

In a 250 ml conical flask equipped with a reflux condenser a mixture of 4- substituted ethylidene/ benzylidene-2-methyl-1,3-oxazol-5-one (1 mol, 1.9gm), 2-aminopyrimidine (1 mol, 0.95ml), 25 ml glacial acetic acid and about sodium acetate (1 mol, 0.82gm) was placed and was heated on heating mantle and monitored the completion of reaction on TLC plate. Then the reaction mixture was poured in ice. The precipitates were collected and re-crystallized from suitable solvent to get desired product (**3a-3k**).

Table 2: Experimental data of synthesized compounds 3a-3k

Compound	R	Molecular Formula	Molecular Weight	% Yield	Melting Point(^{0}C)*
3a	-CH_3	$C_{10}H_{10}N4O$	202.20	50.56	118-120
3b		$C_{15}H_{12}N4O$	264.26	62.45	150-152
3c		$C_{15}H_{11}ClN_4O$	298.71	75.16	124-126
3d		$C_{15}H_{10}Cl_2N_4O$	333.15	78.16	196-198
3e		$C_{15}H_{12}N_4O_2$	280.26	76.14	186-188
3f		$C_{15}H_{12}N_4O_2$	456.28	68.49	226-228
3g		$C_{16}H_{14}N_4O_2$	294.29	52.45	168-170
3h		$C_{12}H_{14}N_4O_3$	310.31	48.46	164-166
3i		$C_{18}H_{18}N_4O_4$	354.34	56.34	154-156
3j		$C_{17}H_{17}N_5O$	307.33	64.98	192-194
3k		$C_{17}H_{13}N_5O$	303.23	72.76	244-246

***melting points were uncorrected**

4-ethylidene-2-methyl-1-(pyrimidine-2-yl)-1H-imidazol-5(4H)-one **(3a)**

IR (KBr): 2984, 2877, 1735, 1632, 1585, 1441, 884 cm^{-1};
^{1}H NMR (400MHz, DMSO): δ= 8.52- 6.93 (m, 3H, 3,4,5 pyrimidine), 6.68 (q, 1H, =CH-CH_3), 2.05 (d, 3H, CH-CH_3), 2.01(s, 3H, CH_3);
^{13}C NMR (400MHz, DMSO): δ= 170, 169, 166, 157, 138, 129, 115, 109, 22, 10;
MS: *m/z* = 202 [M^+], 203 [M+1].

4-benzylidene-2-methyl-1-(pyrimidine-2-yl)-1H-imidazol-5(4H)-one **(3b)**

IR (KBr): 3057, 2877, 1730, 1638, 1575, 1454, 878 cm^{-1};
^{1}H NMR (400MHz, DMSO): δ =8.54-7.98 (m, 3H, 3,4,5 pyrimidine), 7.80-7.12 (m, 5H, phenyl), 6.62 (s, 1H, =CH-), 2.10 (s, 3H, CH_3);
^{13}C NMR (400MHz, DMSO): δ=171, 169, 168, 158, 157, 135, 130, 128, 127, 115, 114, 23;
MS: *m/z* = 265 [M+1].

4-(4-chlorobenzylidene)-2-methyl-1-(pyrimidine-2-yl)-1H-imidazol-5(4H)-one **(3c)**

IR (KBr): 305, 2878, 1730, 1638, 1575, 1454, 876, 658 cm^{-1};
^{1}H NMR (400MHz, DMSO): δ =8.60-7.92 (m, 3H, 3,4,5 pyrimidine), 7.94-7.22 (m, 4H, phenyl), 7.10 (s, 1H, =CH-), 2.08 (s, 3H, CH_3);
^{13}C NMR (400MHz, DMSO): δ=172, 168, 164, 133, 130, 129, 128, 115, 114, 23;
MS: *m/z* =299 [M]; 300 [M+2].

4-(2,4-dichlorobenzylidene)-2-methyl-1-(pyrimidine-2-yl)-1H-imidazol-5(4H)-one **(3d)**

IR (KBr): 3042, 2897, 1735, 1638, 1575, 1454, 864, 762, 658 cm^{-1};
^{1}H NMR (400MHz, DMSO): δ =8.70-7.88 (m, 3H, 3,4,5 pyrimidine), 7.78-7.34 (m, 3H, phenyl), 6.94 (s, 1H, =CH-), 2.20 (s, 3H, CH_3);
^{13}C NMR (400MHz, DMSO): δ=170, 169, 166, 156, 136, 131, 130, 128, 126, 125, 115, 108, 23;
MS: *m/z* = 333 [M]; 335 [M+2].

4-(2-hydroxybenzylidene)-2-methyl-1-(pyrimidine-2-yl)-1H-imidazol-5(4H)-one **(3e)**

IR (KBr): 3563, 3052, 2959, 1734, 1650, 1602, 1443, 888 cm^{-1};
^{1}H NMR (400MHz, DMSO): δ= 8.52-8.10 (m, 3H, 3,4,5 pyrimidine), 8.00-7.80 (m, 4H, phenyl), 7.70 (s, 1H, =CH-), 5.4 (s, 1H, OH), 2.1 (s, 3H, CH_3);
^{13}C NMR (400MHz, DMSO): δ= 173, 169, 168, 159, 157, 131, 129, 128, 117, 116, 115, 108, 23;
MS: *m/z* =280 [M]; 281 [M+1].

4-(4-hydroxybenzylidene)-2-methyl-1-(pyrimidine-2-yl)-1H-imidazol-5(4H)-one **(3f)**

IR (KBr): 3565, 3054, 2953, 1738, 1642, 1606, 1438, 882 cm^{-1};
^{1}H NMR (400MHz, DMSO): δ =8.60-8.10 (m, 3H, 3,4,5 pyrimidine), 8.00-7.80 (m, 4H, phenyl) 7.86 (s, 1H, =CH-), 5.6 (s, 1H, OH), 2.2 (s, 3H, CH_3);
^{13}C NMR (400MHz, DMSO): δ=171, 169, 166, 158, 157, 131, 130, 127, 118, 116, 115, 23;
MS: *m/z* =280 [M]; 281 [M+1].

4-(4-methoxybenzylidene)-2-methyl-1-(pyrimidine-2-yl)-1H-imidazol-5(4H)-one **(3g)**

IR (KBr): 3052, 2959, 1734, 1650, 1602, 1443, 1381, 888 cm^{-1};
^{1}H NMR (400MHz, DMSO): δ =8.50-8.00 (m, 3H, 3,4,5 pyrimidine), 7.90-7.76 (m, 4H, phenyl), 7.44 (s, 1H, =CH-), 3.82 (s, 3H, $-OCH_3$), 2.3 (s, 3H, $-CH_3$);
^{13}C NMR (400MHz, DMSO): δ=170, 169, 165, 160, 158, 131, 130, 127, 118, 115, 114, 56, 23;
MS: *m/z* =294 [M]; 295 [M+1].

4-(4-hydroxy-3-methoxybenzylidene)-2-methyl-1-(pyrimidine-2-yl)-1H-imidazol-5(4H)-one **(3h)**

IR (KBr): 3558, 3056, 2965, 1732, 1657, 1602, 1443, 1381, 892 cm^{-1};
^{1}H NMR (400MHz, DMSO): δ =8.60-8.30 (m, 3H, 3,4,5 pyrimidine), 8.00-7.70 (m, 3H, phenyl), 7.56 (s, 1H, =CH-), 5.32 (s, 1H, OH), 3.84 (s, 3H, OCH_3), 2.2 (s, 3H, CH_3);
^{13}C NMR (400MHz, DMSO): δ=171, 168, 166, 158, 150, 148, 132, 130, 122, 116, 115, 56, 22;
MS: *m/z* = 310 [M].

***2-Methyl-1-(pyrimidine-2-yl)-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one* (3i)**

IR (KBr): 3050, 2959, 1744, 1658, 1612, 1447, 1386, 875 cm^{-1};
^{1}H NMR (400MHz, DMSO): δ =8.70-8.34 (m, 3H, 3,4,5 pyrimidine), 8.10-7.86 (m, 2H, phenyl), 7.72 (s, 1H, =CH-), 3.9-3.80 (s, 9H, OCH_3), 2.1 (s, 3H, CH_3);
^{13}C NMR (400MHz, DMSO): δ=170, 169, 165, 158, 153, 139, 132, 115, 114, 103, 56, 60, 23;
MS: *m/z* = 354 [M]; 355 [M+1].

***4-(4-(dimethylamino)benzylidene)-2-methyl-1-(pyrimidine-2-yl)-1H-imidazol-5(4H)-one* (3j)**

IR (KBr): 3052, 2959, 1734, 1650, 1602, 1443, 888 cm^{-1};
^{1}H NMR (400MHz, DMSO): δ =8.70-8.20 (m, 3H, 3,4,5 pyrimidine), 8.00-7.68 (m, 4H, phenyl), 7.56 (s, 1H, =CH-), 3.24-3.18 (s, 6H, N-CH_3), 2.0 (s, 3H, CH_3);
^{13}C NMR (400MHz, DMSO): δ=172, 170, 168, 158, 157, 150, 131, 130, 124, 115, 111, 41, 22;
MS: *m/z* = 307 [M].

***4-((1H-indol-3-yl)methylene)-2-methyl-1-(pyrimidine-2-yl)-1H-imidazol-5(4H)-one* (3k)**

IR (KBr): 3353, 3053, 2972, 1750, 1662, 1618, 1444, 1380, 868 cm^{-1};
^{1}H NMR (400MHz, DMSO): δ =10.2 (s, 1H, NH), 8.60-8.22 (m, 3H, 3,4,5 pyrimidine), 8.10-7.72 (m, 5H, indol), 7.60 (s, 1H, =CH-), 2.1 (s, 3H, CH_3);
^{13}C NMR (400MHz, DMSO): δ=169, 168, 165, 158, 137, 136, 128, 122, 120, 118, 115, 112, 111, 108, 23;
MS: *m/z* = 303 [M]; 304 [M+1].

In vitro Anti-HIV activity

The standard drug and test compounds (**3a-3k**) were powdered finely and suspended in DMSO. Finally 20µg sample was use for I*n-vitro* assay. The HIV-RT inhibition assay was performed by using an RT assay kit (Roche), and the procedure for assaying RT inhibition was performed as described in the kit protocol. Briefly, the reaction mixture consists of template primer complex, dNTPs and reverse transcriptase (RT) enzyme in the lysis buffer with or without inhibitors. After 1-h incubation at 37^{0}C, the reaction mixture was transferred to streptavidine-coated microtitre plate (MTP). The biotin-labeled dNTPs that are incorporated in the template due to activity of RT were bound to streptavidine. The unbound dNTPs were washed using wash buffer and anti-DIG-POD was added to the MTP. The DIG-labeled dNTPs incorporated in the template were bound to anti-DIG-POD Antibody. The unbound anti-DIG-POD was washed and the peroxide substrate (ABST) was added to the MTP. A colored reaction product was produced during the cleavage of the substrate catalyzed by a peroxide enzyme. The absorbance of the sample was determined at O.D. 405 nm using microtiter plate ELISA reader [15,16].

$$\% \text{ inhibition} = 100 - \left(\frac{\text{OD at 405nm with inhibitor}}{\text{OD at 405nm without inhibitor}} \times 100 \right)$$

RESULTS AND DISCUSSION

Chemistry

The final derivatives 4-substituted ethylidene/benzylidene-2-methyl-1-(pyrimidine-2-yl)-1H-imidazol-5-ones were synthesized from the commercially available glycine (Scheme 1). Glycine was acetylated to form acetyl glycine (**1**). Acetyl glycine was subjected to Erlenmeyer synthesis to give 4-substituted methylidene-2-methyloxazol-5-one (**2a-2k,** Table 1). The 4-substituted ethylidene/benzylidene-2-methyloxazol-5-one was reacted with 2-aminopyrimidine to give mixture (*E* and *Z*) of 4- substituted ethylidene/ benzylidene -2-methyl-1-pyrimidine imidazol-5-one (**3a-3k,** Table 2).

Biological activity

The reverse transcriptase inhibitory activity of the synthesized compounds was studied by reverse transcriptase colorimetric assay kit (Roche). The absorbance of the sample was determined at O.D. 405 nm

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using microtiter plate ELISA reader. The % inhibition was determined by standard method (Table 3).

Table 3: In vitro reverse transcriptase assay data of synthesized derivatives

Compound	% Inhibition
Nevirapine	99.92
3a	86.32
3b	82.17
3c	90.38
3d	79.56
3e	84.51
3f	82.02
3g	85.75
3h	89.73
3i	93.05
3j	96.07
3k	71.70

It has been observed from in vitro screening that newly synthesized compounds possess RT inhibitory activity. Among the synthesized compounds **3c**, **3h**, **3i** and **3j** showed significant RT inhibitory activity. The compound with 2,4-dichlorobenzene, 2-hydroxy benzene, indole on the imidazole ring showed lesser RT inhibitory activity in comparison with N,N-dimethylanilline, trimethoxybenzene at C4 position. The hydrophobic groups are important for RT inhibitory activity at C4. However, less bulky methyl group showed lesser activity. This indicates the hydrophobic ring substituents are required for RT inhibiting activity at C4 position.

Docking Study

With the aim to investigate the binding mode of our newly synthesized compounds, molecular modeling study was performed by means of Glide XP for docking [17]. All compounds with standard Nevirapine was chosen to be docked into the NNRTIs binding pocket (NNIBP) of HIV-1 RT. Three-dimensional coordinates of the HIV-1 RT/11-cyclopropyl-5,11-dihydro-4-methyl-6h-dipyrido(1,4)diazepin-6-one (Nevirapine) complex (Brookhaven Protein Data Bank entry 1FKP) were used as the input structure for docking calculations. Default parameters were used as described in the Maestro Glide-5.8 (Schrödinger, LLC, New York, NY, 2010) manual unless otherwise specified. The theoretical binding mode of compounds to the NNIBP is shown in Figure 3.

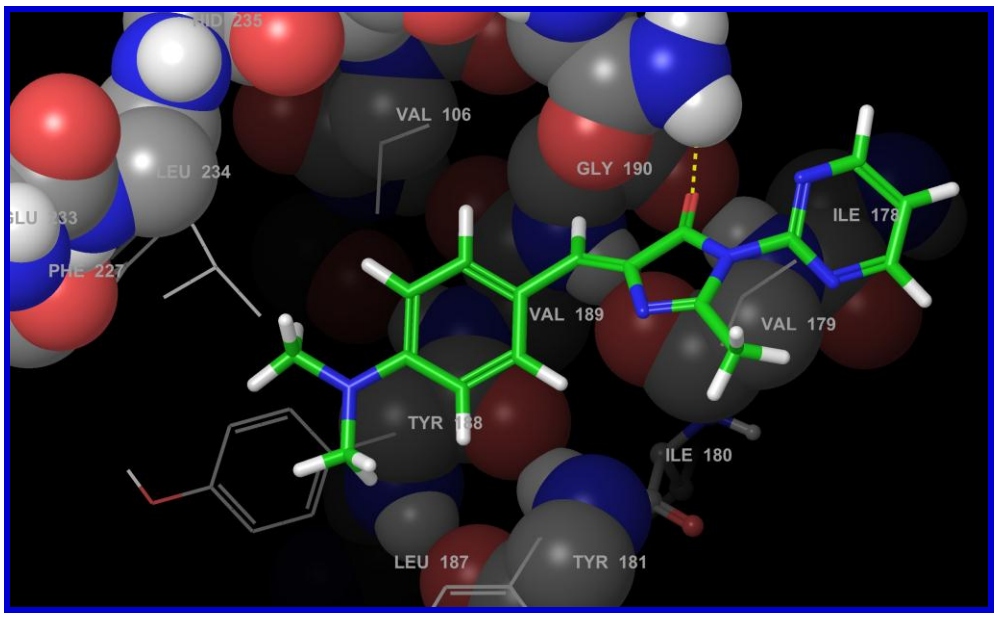

Figure 3: Docking poses of compound 3j

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The Glide XP descriptors include terms: lipophilic derived from hydrophobic grid potential and fraction of the total protein ligand vdw energy, hydrophobic enclosure reward, hydrophobic packed hydrogen bonds, ChemScore H-bond pair term, electrostatic rewards, π–π stacking, π-cation, SiteMap ligand-receptor non-H bonding polar-hydrophobic terms, reward for ligands with low molecular weight, polar atom burial and desolvation penalties, and penalty for intra-ligand contacts, rotatable bond penalty and other interactions.

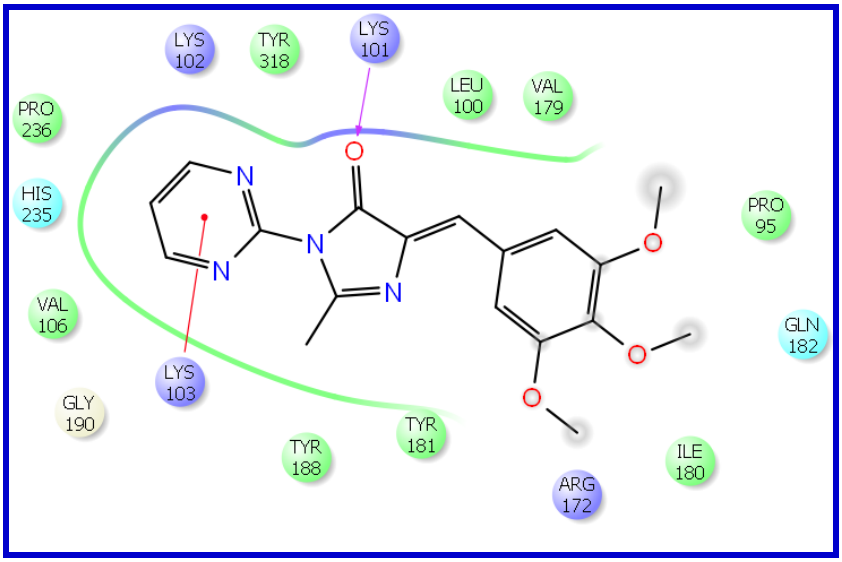

Figure 4: Ligand interaction diagram of compound 3i (red line show π-stacking interaction).

The docking simulation showed the binding mode of the compound into the NNIBP. The docking study results showed that the imidazole C=O moiety at position 5 was engaged in a hydrogen bond with the NH moiety of Lys101 (Figure 3 and Figure 4). The substituent was well accommodated in the large pocket mainly defined by Val106, Pro225, Leu234, Pro236, and Phe227. Compound **3i** of trimethoxy benzyl substituent and compound **3j** N,N-dimethylanilline at position 4 of the imidazole-5-one ring accommodated in a hydrophobic pocket mainly defined by the aromatic side chains of Pro95, Tyr181, Tyr188, Phe227, and Trp229 as well as by Leu234. In particular, the pyrimidine ring interacts favorably with the Gly99, Leu100, Asn103, Ile178; giving rise to a positive π-stacking interaction (Figure 4). Moreover, the pyrimidine ring at C-1 position and substituted benzene at C-4 positioned of imidazole-5-one ring acquired the 'V' or 'butterfly' like binding pose showing body attached to two wings (aromatic rings). In summary, the results of the docking analysis supported our newly designed and synthesized 4- substituted ethylidene/benzylidene-2-methyl-1-(pyrimidine-2-yl)-1H-imidazol-5-one derivative.

CONCLUSION

We have designed, synthesized and evaluated of 4- substituted ethylidene/ benzylidene-2-methyl-1-(pyrimidine-2-yl)-1H-imidazol-5-ones for reverse transcriptase inhibition activity. All the title compounds possess RT inhibitory activity. Among the synthesized compounds **3h**, **3i** and **3j** was found to be the most active agents as compared with standard. The docking studies were performed for newly synthesized molecules which indicate that imidazole ring is important for RT inhibition activity. The –C=O group of imidazole ring help to form the hydrogen bonding with in hydrophobic pocket of enzyme and thus increases the affinity of compounds toward RT enzyme. It is further concluded that compounds with imidazole ring having methyl group substitution on C2 position and combine hydrophobic group like substituted benzene ring on C4 position with pyrimidine on C1 position showed higher activity. This may form the possible butterfly-like conformation of 1,4 substitutions on imidazole ring required for RT inhibition.

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