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Synthesis, evaluation and molecular modeling studies of some novel tetrahydroisoquinoline derivatives targeted at the HIV-1 reverse transcriptase

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Abstract

*A novel series of sixteen 2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-(substituted phenyl)acetamides **3a-p** were synthesized by reacting 1,2,3,4-tetrahydroisoquinoline **2** with the corresponding 2-chloro-N-(substituted phenyl)acetamides **1a-p** in acetonitrile. The compounds have been characterized on the basis of elemental analysis and spectral data. All the synthesized compounds were evaluated for their HIV-1 RT inhibitory activity. Compounds **3k** and **3m** were identified as moderate inhibitors of HIV-1 reverse transcriptase with 25% RT inhibitory activity at the final concentration of 40 µM when compared with the standard drug efavirenz. Docking studies with HIV-1 RT (PDB ID 1rt2) were also performed for these compounds in order to investigate the binding pattern of these compounds in the active site of HIV-1 RT.*

Keywords: Tetrahydroisoquinoline, HIV, Reverse Transcriptase, NNRTI, Docking

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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

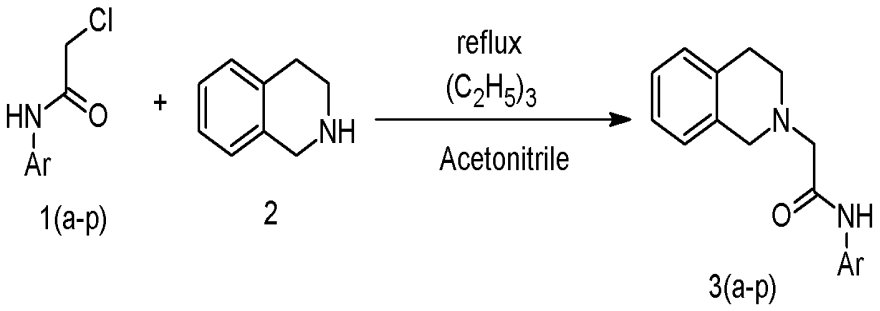
HIV-1 RT by terminating DNA synthesis, whereas NNRTIs are a chemically diverse group of compounds that non-competitively bind to the unique allosteric hydrophobic binding pocket located about 10 Å away from the RT DNA polymerase active catalytic site and 60 Å from the RT RNAse H active site and thereby 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. Nevertheless this real advantage is vanished due to cross resistance displayed by all approved NNRTIs. To overcome these difficulties novel NNRTIs are searched by modifying the existing drug classes with appropriate pharmacophoric requirements. Earlier studies reveals that, more than 30 different classes of NNRTIs have some features in common, that is, the overall structure may be considered reminiscent of a butterfly with hydrophilic centre ('body') and two hydrophobic outskirts ('wings') [13-16].

Compounds having quinoline and isoquinoline moiety exhibit potent antiviral [17-19], anti-tubercular [20-23], antibacterial [24-26], antifungal [27-30], antiprotozoal, antimalarial [31-48], and anticancer [49] activities since ancient days. In view of these various established biological activities of substituted isoquinoline analogues, the functions of reverse transcriptase enzyme and its pharmacophoric requirements, in the present work, an attempt has been made to synthesize some novel 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-(substituted-phenyl)acetamides **3** with "butterfly-like" congeners and these have been evaluated for their HIV-1 reverse transcriptase inhibitory activity. All the newly synthesized compounds were designed based on the derived pharmacophoric model [15-16] with acetamide moiety (-CH_2-CO-NH-) constituting the 'body' and the aryl rings of isoquinoline and substituted amines constituting the 'wings'.

RESULTS AND DISCUSSION

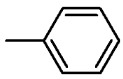
Chemistry

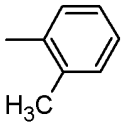
In the present investigation, 2-chloro-*N*-(substituted phenyl)acetamides **1a-p** were prepared by following the method reported by Ganguly *et al* [50]. Compounds **1a-p** were then refluxed with tetrahydroisoquinoline **2** in presence of triethylamine in acetonitrile to afford sixteen 2-(3,4-

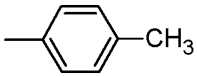


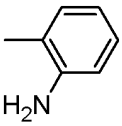
dihydroisoquinolin-2(*1H*)-yl)-*N*-(substituted phenyl)acetamides 3a-p (Scheme –1).

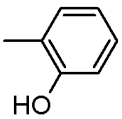
Where Ar =

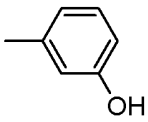
3a 

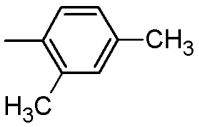
3b 

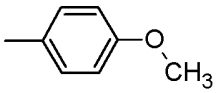
3c 

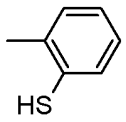
3d 

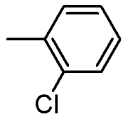
3e 

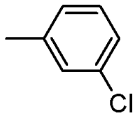
3f 

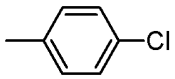
3g 

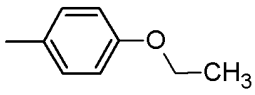
3h 

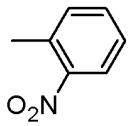
3i 

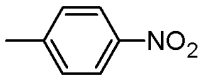
3j 

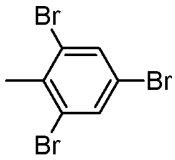
3k 

3l 

3m 

3n 

3o 

3p 

Scheme 1. Synthetic route of titled compounds

IR spectra of the compounds, a strong intense band appeared in the range of 3315-3251 cm^{-1} provides the strong evidence for the presence of NH stretching of aromatic secondary amide and a strong band in the range of 1683-1653 cm^{-1} confirms the presence of C=O stretching in all the synthesized compounds. Appearance of absorbance band around 3610 and 3590 cm^{-1} indicates the presence of phenolic hydroxyl group in the compounds **3e** and **3f** respectively. The compound **3i** showed strong absorption band at 2548 cm^{-1} confirms the presence of SH stretching. A sharp absorption band at 1577 and 1560 cm^{-1} confirms the presence of C-NO_2 stretching in the compounds **3n** and **3o** respectively. The compounds **3b**, **3c** and **3g** showed absorption band at 1452, 1409 and 1450 cm^{-1} respectively indicates the presence of C-CH_3 stretching. The C-O-C stretching appeared as strong absorption band at 1311 and 1394 cm^{-1} in

the compounds **3h** and **3m**. Another band around 848, 873 and 823 cm^{-1} was appeared in the compounds **3j**, **3k** and **3l** respectively in mainly due to the presence of mono chloroalkanes.
^{1}H NMR spectrum of all the synthesized compounds **3a-p** showed a broad singlet of 1 proton assigned to NH proton between at δ 11.20 to 8.52 and broad singlet of 1 proton at δ 10.14 was assigned to NH_2 proton in the compound **3d**. A multiplet of 9 protons at δ 7.57-7.04 assigned to aromatic protons was observed for the compound **3a** while the remaining compounds **3b-o** showed a multiplet of 8 protons assigned to aromatic protons between at δ 8.37 to 6.86 and the compound **3p** showed a multiplet of 6 protons at δ 8.37-7.10. The OH and SH group in the compounds **3e**, **3f** and **3i** showed broad singlet of 1 proton at δ 5.20, 4.80 and 2.82 respectively. A broad singlet of 2 protons assigned to methylenic protons at H-1 position of tetrahydro isoquinoline nucleus at δ 3.84 and 3.83 was observed for the compounds **3o** and **3h** respectively and broad singlet of 2 protons at δ 3.82 was observed for the compounds **3a**, **3b**, **3c**, **3e**, **3f**, **3g**, **3i**, **3j**, **3l**, **3m**, **3n** and **3p** while a broad singlet of 2 protons was observed at δ 3.80 for the compounds **3d** and **3k**. A broad singlet of 2 protons for the compound **3o** was observed at δ 3.37 and for the compounds **3i**, **3m** and **3n** at δ 3.36 was assigned to methylenic proton of $C\underline{H}_2$-CO. The compounds **3b** and **3h** showed a broad singlet of 2 protons at δ 3.34 and 3.33 respectively was assigned to methylenic proton of $C\underline{H}_2$-CO. The compounds **3a, 3d, 3e, 3f, 3g, 3i, 3j**, **3k, 3l** and **3p** showed a broad singlet of 2 protons assigned to methylenic proton of $C\underline{H}_2$-CO at δ 3.32 while the compound **3c** showed broad singlet of 2 protons at δ 3.31. Double triplet of 4 protons between δ 3.01-2.87 was assigned to methylenic protons of H-3 and H-4 of tetrahydro isoquinoline nucleus was observed for all the compounds. Broad singlet of 3 protons assigned to methyl proton of C-$C\underline{H}_3$ and C-$OC\underline{H}_3$ at δ 2.29, 2.31 and 3.80 was observed for the compounds **3b**, **3c** and **3h** respectively. The compound **3g** showed singlet of 6 protons assigned to two methyl proton of C-$C\underline{H}_3$ at δ 2.31. The compound **3m** showed quartet of 2 protons and triplet of 3 protons at δ 2.90-2.72 and 1.90-1.70 assigned to methyl proton of $OC\underline{H}_2$-CH_3 and OCH_2-$C\underline{H}_3$ respectively.

The Mass spectra of the compounds **3a**, **3b**, **3c**, **3d**, **3e**, **3f**, **3g**, **3h**, **3i**, **3j**, **3k**, **3l**, **3m**, **3n**, **3o** and **3p** showed the molecular ion peaks at m/z (M^+) 266(50%), 280(40%), 280(30)%), 281(30%), 282(70%), 282 (70%), 294(70%), 296(30%), 298(60%), 301(100%), 301(100%), 301(100%), 310(70%), 311(40), 311(30%) and 503(97%) respectively. This data is in good agreement with the respective molecular formula.

The elemental analysis data of all the synthesized compounds were within ±0.4% of the theoretical values.

On the basis of all these IR, ^{1}H NMR, Mass and Elemental analysis data, the structures has been confirmed for the newly synthesized compounds.

HIV-1 RT inhibitory activity
All the synthesized compounds were evaluated for HIV-1 RT inhibitory activity using HIV-1 RT RNA Dependent DNA Polymerase Activity Assay [51]. Efavirenz was used as the standard. Compounds **3k** and **3m** showed moderate inhibitory activity (25% RT inhibitory activity) against HIV-1 reverse transcriptase at the final concentration of 40 µM (Table 1). All other compounds were found to be inactive and are presented in Figure 1.

Table 1. HIV-1 RT inhibitory activity of the synthesized compounds

S.No	Compound	% RT residual activity	% RT inhibitory activity
1.	3a	99	1
2.	3b	82	18
3.	3c	92	8
4.	3d	96	4
5.	3e	99	1
6.	3f	80	20
7.	3g	99	1
8.	3h	92	8
9.	3i	90	10
10.	3j	91	9
11.	3k	75	25
12.	3l	97	3
13.	3m	75	25
14.	3n	91	9
15.	3o	95	5
16.	3p	99	1
17.	Efavirenz	7	93

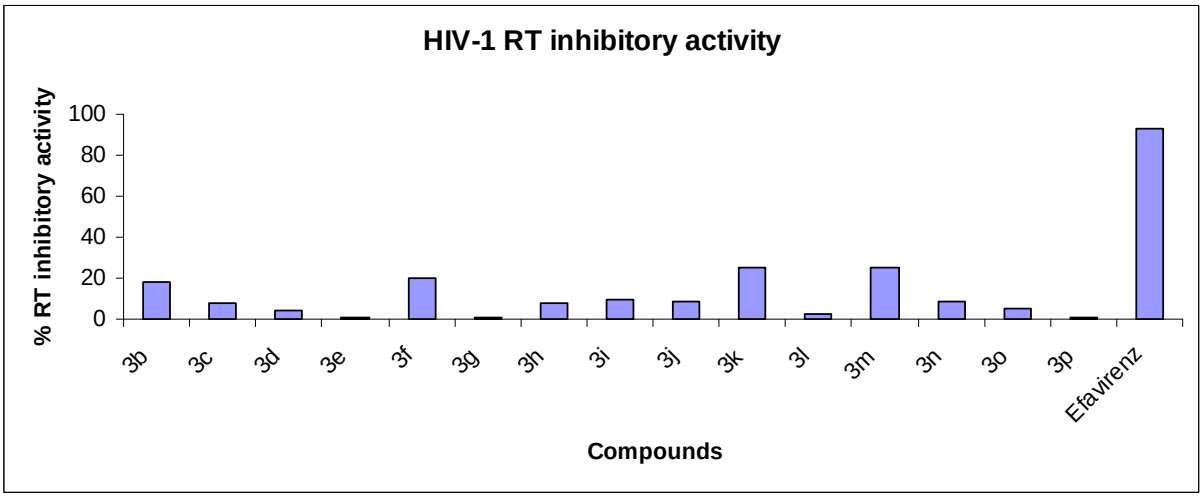
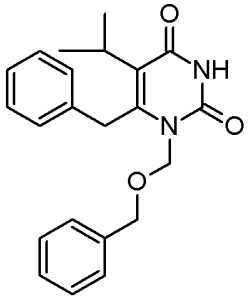


Figure 1. Comparison of HIV-1 RT inhibitory activity of the synthesized compounds and the standard drug efavirenz

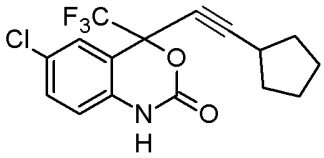
Molecular Docking and Binding Mode Analysis

The binding mode of the moderately active compounds **3k** and **3m** were investigated. Ligand structures were drawn and optimized using PRODRG online server [52] and saved in PDB format. Autodock 4.0.1 [53-56] program was used to dock **3k** and **3m** into the RT non-nucleoside inhibitory binding pocket (NNIBP). The NNIBP was obtained using the coordinates of HIV-1 RT/TNK 651 [57] taken from the Protein Brookehaven Database (PDB entry code 1rt2).

The docking experiments were carried out using the Lamarckian genetic algorithm with local search (GA-LS) hybrid formalism of the docking program Autodock 4.0.1 [53-56]. Initially, the docking of TNK 651 (**4)** which is extracted previously from 1rt2 receptor complex into the RT was performed to test the reliability and reproducibility of the docking protocol for our study (Figure 2). Second similar docking experiment was performed using standard molecule efavirenz (**5)** for comparison purpose (Figure 3).



TNK 651 (4)



Efavirenz (5)

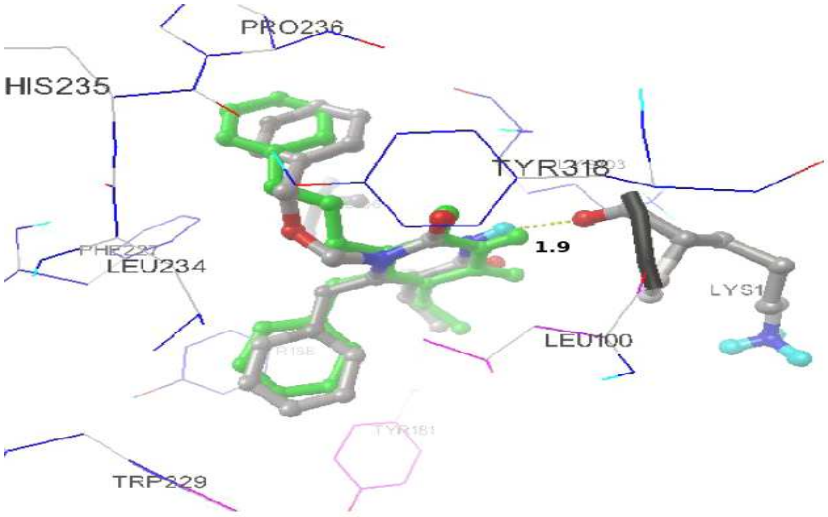


Figure 2. Redocked mode of TNK 651 (4)

(Green) superimposed with the co-crystallized ligand (Grey) in the NNIBP of HIV-1 RT (1rt2). Ligand is shown as stick model and the amino acid residues interacting with the ligands are shown as line model. Hydrogen Bond Interaction (1.9 Å) with LYS 103 amino acid residue of Reverse Transcriptase is shown as dotted spheres. Rest of the protein is suppressed for clarification purposes.

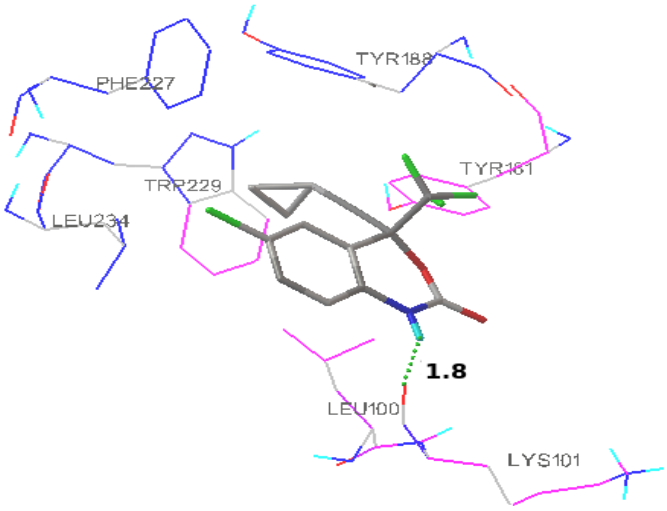


Figure 3. Binding mode of Efavirenz (5) in the NNIBP of HIV-1 RT (1rt2).
Ligand is shown as stick model and the amino acid residues interacting with the ligands are shown as line model. Hydrogen Bond Interactions (1.8 Å) with LYS 101 amino acid residues of Reverse Transcriptase respectively are shown as dotted spheres. Rest of the protein is suppressed for clarification purposes.

Autodock was able to reproduce the experimental binding conformation of **4** within a minimal root mean square deviation (RMSD = 0.56 Å). The estimated binding free energy and predicted inhibitory constant value for the compound **3k** was -9.83 and 126.58 nM respectively. The complex of 1rt2 with compound **3k** showed a hydrogen bond interaction between hydrogen atom of the amino (-NH) group of compound **3k** and oxygen atom of the LYS 101 residue (Figure 4).

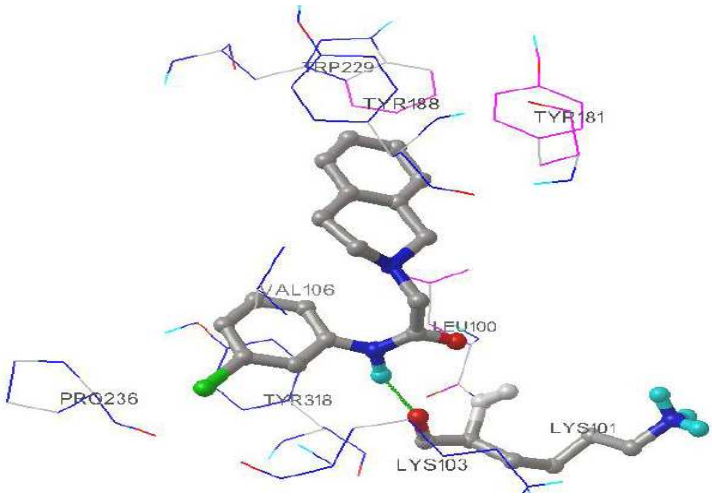


Figure 4. Binding mode of compound 3k in the NNIBP of HIV-1 RT (1rt2).
Ligand is shown as stick model and the amino acid residues interacting with the ligands are shown as line model. Hydrogen Bond Interactions with LYS 103 amino acid residues of Reverse Transcriptase respectively are shown as dotted spheres. Rest of the protein is suppressed for clarification purposes.

The tetrahydro isoquinoline moiety of **3k** was oriented towards the hydrophobic pocket formed by the side chains of TRP 229, TYR 181 and TYR 188 and the phenyl group substituted at the meta position with chlorine atom interacts with the side chain termini of VAL 106 and TYR 318. For the compound **3m**, the estimated binding free energy and predicted inhibitory constant value was -8.95 and 266.15 nM respectively. The complex of 1rt2 with compound **3m** exhibited a hydrogen bond interaction between oxygen atom of the carbonyl (C=O) group of compound **3m** and hydrogen atom of the amino (-NH) group of LYS 103 residue (Figure 5).

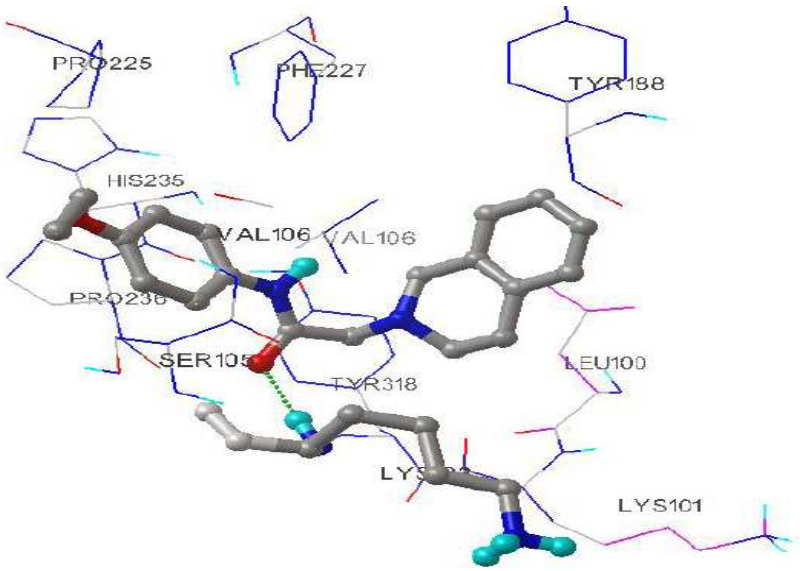


Figure 5. Binding mode of compound 3m in the NNIBP of HIV-1 RT (1rt2).
Ligand is shown as stick model and the amino acid residues interacting with the ligands are shown as line model. Hydrogen Bond Interactions with LYS 103 amino acid residues of Reverse Transcriptase respectively are shown as dotted spheres. Rest of the protein is suppressed for clarification purposes.

The tetrahydro isoquinoline moiety of **3m** interacts with the side chains of TYR 181 and PHE 227 to a certain extent while the ethoxy group substituted at the para position of the other phenyl group is oriented at the least hydrophobic section of NNIBP, exerting favorable contacts with backbone of HIS 235, PRO 236 and PRO 225. These interactions may explain the moderate inhibitory activity of the compounds **3k** and **3m** at the NNIBP of HIV-1 RT. The results of this research could encourage the synthesis of some more analogs of 1,2,3,4-tetrhydro isoquinoline with appropriate substitution in the phenyl portion of tetrahydro isoquinoline nucleus for better HIV-1 reverse transcriptase inhibitory properties with reduced side effects.

MATERIALS AND METHODS

Chemistry

Melting points (mp) were taken in open capillaries on Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on KBr disks on a Shimadzu FTIR series 1020 spectrometer. ^{1}H NMR spectra were recorded on a Jeol D-300 MHz Bruker FT-NMR

spectrometer using $CDCl_3$ as solvent. Mass spectra (m/z) of the compounds synthesized were taken on a Jeol D-300 spectrometer using fast atom bombardment (FAB positive) technique. Satisfactory elemental analysis was performed on a Vario Elementor C, H, N, S and O analyzer. The reactions were monitored on activated silica gel coated plates and the solvent system used was chloroform: benzene: methanol (3:0.3:0.1).

General Procedure for preparation of 2-chloro-(substituted phenyl)acetamides 1a-p.
The appropriate aromatic amine (0.033 mol.) was dissolved in 12.5 ml glacial acetic acid. 2-chloroacetyl chloride (0.037 mol.) was added drop wise to this solution while cooling in ice-bath. The reaction mixture was stirred in ice-bath for 30 min and then stirred for 1 h in room temperature. The mixture was poured into saturated sodium acetate solution. The precipitate was filtered and washed with cold water. Crystallization from ethanol/water mixture yielded crystalline mass.

Following the same procedure all the intermediates of this series were prepared.

2-chloro-N-phenylacetamide **(1a).**
White crystalline solid (5.10 g, 91%); mp: 146-148 ˚C; IR: 3267, 1670, 1350 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 8.23 (s; 1H; NH), 7.56-7.18 (m; 5H; Ar-H), 4.20 (s; 2H; $C\underline{H_2}$-CO). MS: *m/z* (rel int %) 172 [M+2] (40), 171 [M+1] (30), 170 [M^+] [BP] (100), 169 [M-1] (40), 134 (20), 106 (30), 92 (20); Anal. found: C, 56.65; H, 4.75; N, 8.26; O, 9.43; Cl, 20.90%; Calc. for C_8H_8NOCl, C, 56.68; H, 4.73; N, 8.22; O, 9.45; Cl, 20.93%.

2-chloro-N-o-tolylacetamide **(1b).**
White crystalline mass (5.51 g, 91%); mp: 104-106 ˚C; IR: 3267, 1662, 1458, 1330 cm^{-1}

2-chloro-N-p-tolylacetamide **(1c).**
White crystalline solid (5.46 g, 90%); mp: 174-176 ˚C; IR: 3273, 1674, 1450, 1344 cm^{-1}

2-chloro-N-(2-aminophenyl)acetamide **(1d).**
White crystalline solid (5.67 g, 93%); mp: 190-192 ˚C; IR: 3255, 1676, 1338 cm^{-1}

2-chloro-N-(2-hydroxyphenyl)acetamide **(1e).**
White crystalline solid (4.16 g, 68%); mp: 130-132 ˚C; IR: 3365, 1653, 1458, 1369 cm^{-1}

2-chloro-N-(3-hydroxyphenyl)acetamide **(1f).**
White crystalline mass (2.08 g, 34%); mp: 140-142 ˚C; IR: 3273, 1672, 1490, 1400, 1300 cm^{-1}

2-chloro-N-(2,4-dimethylphenyl)acetamide **(1g).**
White crystalline solid (4.17 g, 64%); mp: 146-149 ˚C; IR: 3251, 1651, 1537, 1336 cm^{-1}

2-chloro-N-(4-methoxyphenyl)acetamide **(1h).**
Brown crystalline solid (5.74 g, 87%); mp: 118-120 ˚C; IR: 3294, 1666, 1346, 1112 cm^{-1}

2-chloro-N-(2-mercaptophenyl)acetamide **(1i).**
White crystals (3.81 g, 78%); mp: 80-83 ˚C; IR: 3357, 2580, 1676, 1348 cm^{-1}

2-chloro-N-(2-chlorophenyl)acetamide **(1j).**
White crystalline solid (5.40 g, 98%); mp: 70-72 ˚C; IR: 3277, 1674, 1328, 754 cm^{-1}

2-chloro-N-(3-chlorophenyl)acetamide **(1k).**
White crystalline solid (6. 08 g, 90%); mp: 106-108 ˚C; IR: 3271, 1680, 1336, 744 cm^{-1}

2-chloro-N-(4-chlorophenyl)acetamide **(1l).**
White crystalline solid (6. 14 g, 91%); mp: 192-193 ˚C; IR: 3263, 1670, 1340, 740 cm^{-1}

2-chloro-N-(4-ethoxyphenyl)acetamide **(1m).**
White crystalline mass (5.57 g, 79%); mp: 54-57 ˚C; IR: 3373, 1672, 1340, 1251 cm^{-1}

2-chloro-N-(2-nitrophenyl)acetamide **(1n).**
Yellow crystalline solid (5.46 g, 77%); mp: 72-74 ˚C; IR: 3307, 1695, 1506, 1338 cm^{-1}

2-chloro-N-(4-nitrophenyl)acetamide **(1o).**
Yellow crystalline solid (5.88 g, 83%); mp: 200-203 ˚C; IR: 3302, 1634, 1530, 1340 cm^{-1}

2-chloro-N-(2,4,6-tribromophenyl)acetamide **(1p).**
White crystalline mass (9.65 g, 72%); mp: 158-160 ˚C; IR: 3296, 1681, 1350, 545 cm^{-1}

General Procedure for preparation of 2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-(substituted-phenyl)acetamides 3a-p.

To a solution of 1,2,3,4-tetrahydroisoquinoline (0.012 mol.) in 16.7 ml of acetonitrile was added the corresponding 2-chloro-*N*-(substituted phenyl)acetamide (0.012 mol.) and triethylamine (0.024 mol.) drop wise. The reaction mixture was refluxed for 8 hr. The reaction mixture was then cooled, poured into crushed ice and basified with solid potassium carbonate. The resulting precipitate was filtered, washed with water, further washed with n-hexane, dried and recrystallized from ethanol to obtain **3**.
Following the same procedure all the compounds of this series were prepared.

2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-phenylacetamide **(3a).**
White crystals (2.6 g, 82%); mp: 42-44 ˚C; IR: 3315, 1660, 1340 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 9.12 (s; 1H; NH), 7.57-7.04 (m; 9H; Ar-H), 3.82 (s; 2H; N-C$\underline{H}_2$), 3.32 (s; 2H; C$\underline{H}_2$-CO), 3.01-2.90 (dt; 4H; N-C$\underline{H}_2$-C$\underline{H}_2$-); MS: *m/z* (rel int %) 268 [M+2] (60), 267 [M+1] [BP] (100), 266 [M^+] (50), 265 [M-1] (80), 264 [M-2] (20), 146 (75), 134 (10), 132 (30), 120 (10); Anal. found: C, 76.02; H, 6.80; N, 10.51%; Calc. for $C_{17}H_{18}N_2O$, C, 76.06; H, 6.81; N, 10.52%.

2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-o-tolylacetamide **(3b).**
White crystals (2.86 g, 85%); mp: 108-110 ˚C; IR: 3300, 1683, 1452, 1338 cm^{-1}; ^1H NMR($CDCl_3$, 300 MHz) δ 9.20 (s; 1H; NH), 7.85-7.03 (m; 8H; Ar-H), 3.82 (s; 2H; N-C$\underline{H}_2$), 3.34 (s; 2H; C$\underline{H}_2$-CO), 3.12-2.94 (dt; 4H; N-C$\underline{H}_2$-C$\underline{H}_2$), 2.29 (s; 3H; C-C$\underline{H}_3$); MS: *m/z* (rel int %) 281

[M+1] (70), 280 [M^+] (40), 279 [M-1] (88), 189 (30), 146 (84), 132 (20), 91 (15); Anal. found: C, 77. 21; H, 7.49; N, 9.96%; Calc. for $C_{18}H_{20}N_2O$, C, 77.11; H, 7.19; N, 9.99%.

2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-p-tolylacetamide **(3c).**
Brown crystals (2.88 g, 86%); mp: 120-122 ˚C; IR: 3257, 1664, 1409, 1305 cm^{-1}; ^1H NMR($CDCl_3$, 300 MHz) δ 9.11 (s; 1H; NH), 7.45-7.05 (m; 8H; Ar-H), 3.82 (s; 2H; N-C$\underline{H_2}$), 3.31 (s; 2H; C$\underline{H_2}$-CO), 3.08-2.91 (dt; 4H; N-C$\underline{H_2}$-C$\underline{H_2}$), 2.31 (s; 3H; C-C$\underline{H_3}$); MS: *m/z* (rel int %) 282 [M+2] (28), 281 [M+1] [BP] (100), 280 [M^+] (30), 279 [M-1] (98), 278 [M-2] (10), 189 (30), 147 (10), 146 (80), 132 (15), 91 (5); Anal. found: C, 76. 99; H, 7.59; N, 9.81%; Calc. for $C_{18}H_{20}N_2O$, C, 77.11; H, 7.19; N, 9.99%.

2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-(2-aminophenyl)acetamide **(3d).**
Yellow crystals (1.74 g, 52%), mp: 105-108 ˚C; IR: 3348, 2999, 1691, 1452, 1361 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 11.20 (s; 1H; NH), 10.14 (s; 1H; NH_2), 7.87-7.12 (m; 8H; Ar-H), 3.80 (s; 2H; N-C$\underline{H_2}$), 3.32 (s; 2H; C$\underline{H_2}$-CO), 3.14-2.93 (dt; 4H; N-C$\underline{H_2}$-C$\underline{H_2}$-); MS: *m/z* (rel int %) 282 [M+1] (20), 281 [M^+] (30), 280 [M-1] (10), 189 (30), 174 (20), 149 (60), 147 (90), 146 [BP] (100), 135 (80), 134 (55), 132 (70), 107 (90), 92 (45); Anal. found: C, 72.49; H, 6.68; N, 14.89%; Calc. for $C_{17}H_{19}N_3O$, C, 72.57; H, 6.81; N, 14.94%.

2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-(2-hydroxyphenyl)acetamide **(3e).**
White crystals (2.51 g, 74%), mp: 170-172 ˚C; IR: 3610, 3282, 1654, 1458, 1334 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 8.52 (s; 1H; NH), 7.68-7.02 (m; 8H; Ar-H), 5.20 (s; 1H; OH), 3.82 (s; 2H; N-C$\underline{H_2}$), 3.32 (s; 2H; C$\underline{H_2}$-CO), 3.01-2.92 (dt; 4H; N-C$\underline{H_2}$-C$\underline{H_2}$-); MS: *m/z* (rel int %) 283 [M+1] (40), 282 [M^+] (70), 225 (40), 146 (60), 132 (30); Anal. found: C, 72.41; H, 6.51; N, 10.30%; Calc. for $C_{17}H_{18}N_2O_2$, C, 72.32; H, 6.43; N, 9.92%.

2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-(3-hydroxyphenyl)acetamide **(3f).**
White crystals (3.22 g, 95%), mp: 154-156 ˚C; IR: 3590, 3298, 1654, 1394, 1334 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 9.18 (s; 1H; NH), 7.72-7.14 (m; 8H; Ar-H), 4.80 (s; 1H; OH), 3.82 (s; 2H; N-C$\underline{H_2}$), 3.32 (s; 2H; C$\underline{H_2}$-CO), 3.01-2.90 (dt; 4H; N-C$\underline{H_2}$-C$\underline{H_2}$-); MS: *m/z* (rel int %) 283 [M+1] (40), 282 [M^+] (70), 281 [M-1] (50), 174 (20), 150 (30), 132 (40), 108 (60); Anal. found: C, 72.56; H, 6.65; N, 9.85%; Calc. for $C_{17}H_{18}N_2O_2$, C, 72.32; H, 6.43; N, 9.92%.

2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-(2,4-dimethylphenyl)acetamide **(3g).**
Brown crystals (3.28 g, 93%), mp: 70-72 ˚C; IR: 3279, 1695, 1450, 1321 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 9.22 (s; 1H; NH), 7.87-7.19 (m; 8H; Ar-H), 3.82 (s; 2H; N-C$\underline{H_2}$), 3.32 (s; 2H; C$\underline{H_2}$-CO), 3.12-2.94 (dt; 4H; N-C$\underline{H_2}$-C$\underline{H_2}$), 2.31 (s; 6H; C-C$\underline{H_3}$); MS: *m/z* (rel int %) 295 [M+1] (50), 294 [M^+] (70), 293 [M-1] (40), 189 (20), 162 (30), 146 (60), 105 (20); Anal. found: C, 77.32; H, 7.88; N, 9.54%; Calc. for $C_{19}H_{22}N_2O$, C, 77.52; H, 7.53; N, 9.52%.

2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-(4-methoxyphenyl)acetamide **(3h).**
Reddish brown crystals (2.99 g, 84%), mp: 102-104 ˚C; IR: 3302, 1664, 1311, 1151 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 9.08 (s; 1H; NH), 7.50-6.86 (m; 8H; Ar-H), 3.83 (s; 2H; N-C$\underline{H_2}$), 3.80 (s; 3H; C-OC$\underline{H_3}$) 3.33 (s; 2H; C$\underline{H_2}$-CO), 3.02-2.91 (dt; 4H; N-C$\underline{H_2}$-C$\underline{H_2}$); MS: *m/z* (rel int

%) 298 [M+2] (40), 297 [M+1] [BP] (100), 296 [M^+] (30), 295 [M-1] (70), 146 (70), 132 (30). Anal. found: C, 72.73; H, 6.82; N, 9.30%; Calc. for $C_{18}H_{20}N_2O_2$, C, 72.95; H, 6.80; N, 9.45%.

2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-(2-mercaptophenyl)acetamide **(3i).**
Brown crystals (1.72 g, 48%), mp: 132-134 ˚C; IR: 3270, 2548, 2899, 1676, 1394 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 9.12 (s; 1H; NH), 7.78-7.12 (m; 8H; Ar-H), 3.82 (s; 2H; N-C$\underline{H}_2$), 3.36 (s; 2H; C$\underline{H}_2$-CO), 3.01-2.90 (dt; 4H; N-C$\underline{H}_2$-C$\underline{H}_2$-), 2.82 (s; 1H; SH); MS: *m/z* (rel int %) 298 [M^+] (60), 297 [M-1] (30), 189 (20), 152 (30), 146 (40), 109 (20); Anal. found: C, 68.34; H, 6.18; N, 9.28; S, 10.70%; Calc. for $C_{17}H_{18}N_2OS$, C, 68.42; H, 6.08; N, 9.39; S, 10.75%.

2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-(2-chlorophenyl)acetamide **(3j).**
White crystals (2.88 g, 80%), mp: 124-126 ˚C; IR: 3267, 1691, 1338, 848 cm^{-1}; ^1H NMR(300 MHz $CDCl_3$) δ 9.22 (s; 1H; NH), 7.65-7.01 (m; 8H; Ar-H), 3.82 (s; 2H; N-C$\underline{H}_2$), 3.32 (s; 2H; N-C$\underline{H}_2$-CO), 3.05-2.87 (dt; 4H; N-C$\underline{H}_2$-C$\underline{H}_2$); MS: *m/z* (rel int %) 303 [M+2] (45), 302 [M+1] (40), 301 [M^+] [BP] (100), 146 (65); Anal. found: C, 67.78; H, 5.72; N, 9.38%; Calcd for $C_{17}H_{17}ClN_2O$, C, 67.88; H, 5.70; N, 9.31%.

2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-(3-chlorophenyl)acetamide **(3k).**
Brown crystals (2.99 g, 83%), mp: 50-52 ˚C; IR: 3338, 1676, 1334, 873 cm^{-1}; ^1H NMR(300 MHz $CDCl_3$) δ 9.34 (s; 1H; NH), 7.54-7.03 (m; 8H; Ar-H), 3.80 (s; 2H; N-C$\underline{H}_2$), 3.32 (s; 2H; N-C$\underline{H}_2$-CO), 3.12-2.94 (dt; 4H; N-C$\underline{H}_2$-C$\underline{H}_2$); MS: *m/z* (rel int %) 303 [M+2] (40), 302 [M+1] (30), 301 [M^+] [BP] (100), 146 (70); Anal. found: C, 67.92; H, 5.62; N, 9.36 %; Calcd for $C_{17}H_{17}ClN_2O$: C, 67.88; H, 5.70; N, 9.31%.

2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-(4-chlorophenyl)acetamide **(3l).**
White crystals (2.89 g, 80%), mp: 106-108 ˚C; IR: 3304, 1674, 1336, 823 cm^{-1}; ^1H NMR(300 MHz $CDCl_3$) δ 9.22 (s; 1H; NH), 7.54-7.03 (m; 8H; Ar-H), 3.82 (s; 2H; N-C$\underline{H}_2$), 3.32 (s; 2H; C$\underline{H}_2$-CO), 3.01-2.89 (dt; 4H; N-C$\underline{H}_2$-C$\underline{H}_2$); MS: *m/z* (rel int %) 303 [M+2] (35), 302 [M+1] (20), 301 [M^+] [BP] (100), 146 (85); Anal. found: C, 67.62; H, 5.72; N, 9.28%; Calcd for $C_{17}H_{17}ClN_2O$, C, 67.88; H, 5.70; N, 9.31%.

2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-(4-ethoxyphenyl)acetamide **(3m).**
White crystals (3.12 g, 84%), mp: 86-88 ˚C; IR: 3290, 1672, 1394, 1122 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 9.10 (s; 1H; NH), 7.77-7.14 (m; 8H; Ar-H), 3.82 (s; 2H; N-C$\underline{H}_2$), 3.36 (s; 2H; C$\underline{H}_2$-CO), 3.12-2.92 (dt; 4H; N-C$\underline{H}_2$-C$\underline{H}_2$-), 2.90-2.72 (q; 2H, OC$\underline{H}_2$-CH_3), 1.90- 1.70 (t; 3H; OCH_2-C$\underline{H}_3$); MS: *m/z* (rel int %) 310 [M^+] (70), 309 [M-1] (30), 268 (20), 146 (60), 132 (30); Anal. found: C, 73.28; H, 7.38; N, 9.19%; Calcd for $C_{19}H_{22}N_2O_2$, C, 73.52; H, 7.14; N, 9.03%.

2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-(2-nitrophenyl)acetamide **(3n).**
Yellow crystals (3.44 g, 92%), mp: 86-88 ˚C; IR: 3261, 1690, 1577, 1338 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$,) δ 9.45 (s; 1H; NH), 7.95-7.02 (m; 8H; Ar-H), 3.82 (s; 2H; N-C$\underline{H}_2$), 3.36 (s; 2H; C$\underline{H}_2$-CO), 3.08-2.92 (dt; 4H; N-C$\underline{H}_2$-C$\underline{H}_2$); MS: *m/z* (rel int %) 312 [M+1] [BP] (100), 311 [M^+] (40), 310 [M-1] (80), 266 (10), 255 (10), 189 (10), 179 (10), 178 (20), 165 (20), 146 (85), 137 (25), 134 (20), 132 (58), 122 (30); Anal. found: C, 65.36; H, 5.28; N, 13.25%; Calcd for $C_{17}H_{17}N_3O_3$, C, 65.58; H, 5.50; N, 13.50%.

2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-(4-nitrophenyl)acetamide **(3o).**
Yellowish brown amorphous powder (2.99 g, 80%), mp: 110-112 ˚C; IR: 3251, 1695, 1560, 1332 cm^{-1}, ^1H NMR(300 MHz, $CDCl_3$,) δ 9.59 (s; 1H; NH), 8.22-7.06 (m; 8H; Ar-H), 3.84 (s; 2H; N-C$\underline{H}_2$), 3.37 (s; 2H; C$\underline{H}_2$-CO), 3.02-2.94 (dt; 4H; N-C$\underline{H}_2$-C$\underline{H}_2$); MS: *m/z* (rel int %) 313 [M+2] (27), 312 [M+1] [BP] (100), 311 [M^+] (30), 310 [M-1] (90), 309 [M-2] (10), 266 (10), 255 (10), 189 (10), 179 (10), 178 (12), 174 (8), 165 (20), 146 (85), 137 (25), 134 (20), 132 (58), 123 (28), 122 (10); Anal. found: C, 65.62; H, 5.65; N, 13.66%; Calcd for $C_{17}H_{17}N_3O_3$, C, 65.58; H, 5.50; N, 13.50%.

2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-(2,4,6-tribromophenyl)acetamide **(3p).**
White crystals (3.93 g, 65%), mp: 70-72 ˚C; IR: 3115, 1653, 1369, 542 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 9.32 (s; 1H; NH), 8.37-7.10 (m; 6H; Ar-H), 3.82 (s; 2H; N-C$\underline{H}_2$), 3.32 (s; 2H; C$\underline{H}_2$-CO), 3.08-2.94 (dt; 4H; N-C$\underline{H}_2$-C$\underline{H}_2$-); MS: *m/z* (rel int %) 505 [M+2] (30), 504 [M+1] (20), 503 [M^+] (97), 501 [M-2] (90), 357 (40), 146 (60), 134 (30); Anal. found: C, 40.65; H, 3.23; N, 5.48; Calcd for $C_{17}H_{15}Br_3N_2O$, C, 40.59; H, 3.01; N, 5.57.

HIV-1 RT RNA Dependent DNA polymerase Activity Assay [51]
Poly(rA)/oligo(dT) was used as a template for the RNA-dependent DNA polymerase reaction by HIV-1 RT, either wt or carrying the mutations. For the activity assay, a 25 µl final reaction volume contained TDB buffer (50mM Tris-HCl (pH 8.0), 1mM dithiothreitol (DTT), 0.2 mg/ml bovine serum albumin (BSA), 2% glycerol), 10 mM $MgCl_2$, 0.5 mg of poly(rA):oligo$(dT)_{10:1}$ (0.3 mM 3'–OH ends), 10 mM ^{3}[H]dTTP 1 Ci/mmol was introduced into tubes containing aliquots of different enzyme concentrations (5 to 10 nM RT). After incubation at 37°C for indicated time, 20µL from each reaction tubes were spiked on glass fiber filters GF/C and immediately, immersed in 5% ice-cold trichloroacetic acid (TCA) (AppliChem GmbH, Darmstadt). Filters were washed three times with 5% TCA and once with ethanol for 5 minutes, then dried and, finally, added with EcoLume® Scintillation cocktail (ICN, Research Products Division, Costa Mesa, CA USA), to detect the acid-precipitable radioactivity by PerkinElmer® Trilux MicroBeta 1450 Counter.

Computational Studies
All computational studies were carried out using Autodock 4.0.1 [53-56] installed in a single machine running on a 3.4 GHz Pentium 4 processor with 512MB RAM and 80 GB Hard Disk with Red Hat Linux Enterprise version 3.0 as the Operating System.
The geometry of the NNIBP of the wt RT strain was taken from the structure of HIV-1 RT/TNK 651 complex filed in the Brookehaven Protein Data Bank [57] (entry code 1rt2). All the residues within 20 Å core from TNK 651 (**4)** were used to define the NNIBP. The starting conformations for docking studies were obtained using molecular dynamics with simulated annealing as implemented in Sybyl 7.1. [58]

Autodock 4.0.1 [53-56] was used to explore the binding conformation of TNK 651 (**4)** and active test molecules. The Autodock Tools package version 1.4.6 was employed to generate the docking input files and to analyze the docking results. The same procedures as described in the manual were followed. All the nonpolar hydrogens and the water molecules were removed. For the docking, a grid spacing of 0.375 Å and 60 x 60 x 60 number of points was used. The grid was

centered on the mass center of the experimental bound TNK 651 (**4**) coordinates. Autodock generated 50 possible binding conformations, i.e., 50 runs for each docking by using Genetic Algorithm (GA-LS) searches. A default protocol was applied, with an initial population of 150 randomly placed individuals, a maximum number of 2.5 x 10^5 energy evaluations, and a maximum number of 2.7 x 10^4 generations. A mutation rate of 0.02 and a crossover rate of 0.8 were used.

To validate the use of the Autodock program, the docking studies were performed on the reference compound TNK 651 (**4**) and for comparison purposes also on the standard NNRTI Efavirenz (**5**). Autodock successfully reproduced the experimental binding conformations of the reference drug TNK 651 (**4**) with acceptable root-mean-square deviation (RMSD) of 0.56 Å.

The structures of the moderately active compounds 2-(3,4-dihydroisoquinolin-2(*1H*)-yl)-*N*-(3-chlorophenyl)acetamide (**3k)** and 2-(3,4-dihydroisoquinolin-2(*1H*)-yl)-*N*-(4-ethoxyphenyl) acetamide (**3m)** were drawn and optimized using PRODRG online server [45] and saved in PDB format. These structures were used for the docking studies by using same procedure and their interactions were shown in Figure 4 and 5 respectively.

CONCLUSIONS

Sixteen compounds of 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-(substituted phenyl)acetamides **3a-p** were synthesized by reacting 1,2,3,4-tetrahydroisoquinoline **2** with the corresponding 2-chloro-*N*-(substituted phenyl)acetamides **1a-p**. All the final compounds have been characterized on the basis of Elemental analysis, FTIR, ^{1}H NMR and Mass spectral data. All the synthesized compounds were evaluated for their HIV-1 RT inhibitory activity. Compounds **3k** and **3m** showed moderate inhibitory activity against HIV-1 reverse transcriptase when compared with the standard drug efavirenz (**5**). Docking studies of these compounds with HIV-1 RT (PDB ID 1rt2) were also performed in order to better understanding of the binding pattern of these compounds in the hydrophobic binding pocket of HIV-1 RT.

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