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Synthesis, evaluation and molecular modelling studies of some novel 3-(3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-(substituted-phenyl)propanamides as HIV-1 non-nucleoside reverse transcriptase inhibitors

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Abstract. A novel series of fifteen 3-(3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-(substituted phenyl) propanamides **3(a–o)** were synthesized by reacting the corresponding 3-chloro-*N*-(aryl) propanamides **2(a–o)** with 1,2,3,4-tetrahydroisoquinoline **1** in acetonitrile. The compounds have been characterized on the basis of elemental analysis and spectral data. All the compounds were evaluated for their HIV-1 RT inhibitory activity. Among the synthesized compounds, 3-(3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-*o*-tolyl propanamide **3d** and 3-(3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-(2,4,6-tribromophenyl)propanamide **3f** were identified as significant inhibitors of HIV-1 reverse transcriptase with 56% and 43% residual RT activity respectively 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 in order to investigate the binding pattern of these compounds.

Keywords. HIV-1 reverse transcriptase (HIV-1 RT); non-nucleoside reverse transcriptase inhibitor (NNRTI); docking; autodock; 1,2,3,4-tetrahydroisoquinoline.

1. Introduction

Acquired immuno deficiency syndrome (AIDS) is one of the most serious pandemic public health challenges since 1981.[1] Human immuno deficiency virus (HIV) has been identified as the probable causative agent for AIDS.[2] HIV-1 is a retrovirus and the genome in the virion is encoded in single stranded RNA.[3] In an infected cell, the viral RNA is reverse transcribed to produce a double stranded DNA provirus by an enzyme known as DNA polymerase or reverse transcriptase (RT) which is able to insert itself into the host DNA.[4] Because of the vital role of RT to HIV replication, inhibitor of this enzyme is one of the major potential attractive targets in the treatment of AIDS.[5–8] In general, the inhibitors of HIV-1 RT are classified into two main categories: nucleoside/nucleotide inhibitors (NRTIs) and non-nucleoside inhibitors (NNRTIs).[9–13] NRTIs are substrate analogs of normal nucleotides that act competitively at the catalytic site of HIV-1 RT and there 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. NNRTI binding induces rotamer conformational changes in some residues and makes the thumb region more rigid and thereby force the RT subunits into an inactive conformation.[14–16] When compared to NRTIs, NNRTIs have the advantage of high potency, low toxicity, high selectivity and specificity as well as they will not interfere with the normal function of other host DNA polymerases.[6] The efficacy of NNRTIs is decreased due to emergence of drug resistance mutations. To overcome these difficulties novel NNRTIs are searched by modifying the existing drug classes with appropriate pharmacophoric requirements. Earlier studies reveals that, more than

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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').[17–20]

Compounds having isoquinoline moiety exhibit potent antiviral,[21–23] anti-tubercular,[24–27] antifungal,[28–29] antiprotozoal, antimalarial,[30–45] and anticancer[46] activities since ancient days. An extensive perusal of literatures showed that, little work has been done on synthetic tetrahydroisoquinolines as NNRTIs. In view of these facts and our continued interest in the chemistry of tetrahydroisoquinolines, we report the synthesis of some novel 3-(3,4-dihydroisoquinolin-2(*1H*)-yl)-*N*-(substituted-phenyl)propanamides **3** with 'butterfly-like' congeners, evaluation for their HIV-1 reverse transcriptase inhibitory activity and docking studies of the active compounds **3d** and **3f** on the HIV-1-reverse transcriptase enzyme (PDB entry 1RT2). All the newly synthesized compounds were designed based on the derived pharmacophoric model[19–20] with acetamide moiety (–CH2–CO–NH–) constituting the 'body' and the aryl rings of isoquinoline and substituted aromatic amines constituting the 'wings'.

2. Experimental

2.1 *Materials, methods and instruments*

Melting points were taken in open capillaries on Thomas Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on KBr disks on a Shimadzu FTIR series1020 spectrometer. ^{1}H NMR spectra were recorded on a Jeol D-300 MHz Bruker FT-NMR spectrometer using $CDCl_3$ as solvent. Mass spectral data were obtained on a Jeol D-300 spectrometer using Fast Atom Bombardment (FAB positive). Elemental analysis was performed on a Vario Elementor C, H, N analyser. Compounds **2a–o** were prepared according to the literature method.[47] The reactions were monitored by thin layer chromatography (TLC) carried out on activated silica gel coated plates and the solvent system used was chloroform : benzene : methanol (3 : 0·3 : 0·1).

2.1a *Preparation of 3-(3,4-dihydroisoquinolin-2(1H)-yl)-N-phenyl propanamide* (**3a**): To a solution of 1,2,3,4-tetrahydroisoquinoline (0·012 mol) **1** in 16·7 ml of acetonitrile was added 3-chloro-*N*-phenyl propanamide (0·012 mol) **2a** and triethylamine (0·024 mol) drop-wise and refluxed for 8 h. 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 yield colourless crystals of **3a**.

IR (KBr) (cm^{-1}): 3298 (NH stretching of aromatic secondary amide), 1662 (C=O stretching), 1323 (CN stretching of aliphatic amine).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 6·9–7·6 (9H, *m*, Ar<u>H</u>), 3·5 (2H, *t*, –N–C<u>H</u>$_2$–CH$_2$–CONH), 2·9 (2H, *t*, N–CH$_2$–C<u>H</u>$_2$–CONH), 2·7 (2H, *t*, N–C<u>H</u>$_2$–CH$_2$–Ar); 2·3 (2H, *t*, N–CH$_2$–C<u>H</u>$_2$–Ar), 2·2 (2H, *s*, N–C<u>H</u>$_2$). MS: *m/z* 280 [M$^+$, $C_{18}H_{20}N_2O$, (18)], 281 (100), 279 (25), 203 (10), 188 (15), 160 (12), 148 (18), 146 (63), 134 (15), 132 (33) and 120 (18).

2.1b *3-(3,4-Dihydroisoquinolin-2(1H)-yl)-N-(2-chlorophenyl)propanamide* (**3b**): IR (KBr) (cm^{-1}): 3336 (NH stretching of aromatic secondary amide), 1680 (C=O stretching), 1350 (CN stretching of aliphatic amine), 756 (C–Cl stretching).

2.1c *3-(3,4-Dihydroisoquinolin-2(1H)-yl) N-(3-chlorophenyl)propanamide* (**3c**): IR(KBr) (cm^{-1}): 3335 (NH stretching of aromatic secondary amide), 1660 (C=O stretching), 1330 (CN stretching of aliphatic amine), 783 (C–Cl stretching).

2.1d *3-(3,4-Dihydroisoquinolin-2(1H)-yl)-N-o-tolyl propanamide* (**3d**): IR(KBr) (cm^{-1}): 3228 (NH stretching of aromatic secondary amide), 1653 (C=O stretching), 1303 (CN stretching of aliphatic amine), 2980 and 1498 (C–CH_3 stretching). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8·8 (*s*, 1H, N<u>H</u>), 6·8–7·7 (*m*, 9H, Ar<u>H</u>), 3·8 (*s*, 2H, N–C<u>H</u>$_2$–Ar), 2·9 (*t*, 4H, N–C<u>H</u>$_2$–C<u>H</u>$_2$–Ar), 3·0 (*t*, 2H, C<u>H</u>$_2$), 2·7 (*t*, 2H, C<u>H</u>$_2$), 1·9 (*s* 3H Ar-C<u>H</u>$_3$), MS: *m/z* 294 [M$^+$, $C_{19}H_{22}N_2O$, (30)], 295 (100), 293 (75), 146 (82), 132 (70) and 91 (30).

2.1e *3-(3,4-Dihydroisoquinolin-2(1H)-yl)-N-(4-chlorophenyl)propanamide* (**3e**): IR(KBr) (cm^{-1}): 3483 (NH stretching of aromatic secondary amide), 1640 (C=O stretching), 1338 (CN stretching of aliphatic amine), 742 (C–Cl stretching). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 11·10 (1H, s, N<u>H</u>), 7·70–7·32 (9H, *m*, Ar-<u>H</u>), 3·80 (2H, *s*, N–C<u>H</u>$_2$–Ar), 2·94–2·89 (4H, *m*, N–C<u>H</u>$_2$–C<u>H</u>$_2$–Ar), 3·03–3·00 (2H, *t*, N–CH$_2$–C<u>H</u>$_2$–

CO), 2·65–2·61 (2H, *t*, N–C$\underline{H}_2$–CH_2–CO). MS: *m/z* 315 [M^+, $C_{18}H_{19}N_2OCl$, (100)], 316 (30), 314 (20), 155 (20), 146 (90) and 132 (80).

2.1f *3-(3,4-Dihydroisoquinolin-2(1H)-yl)-N-(2,4,6-tribromophenyl)propanamide* (**3f**): IR(KBr) (cm^{-1}): 3282 (NH stretching of aromatic secondary amide), 1664 (C=O stretching), 1360 (CN stretching of aliphatic amine), 601 (C–Br stretching).

2.1g *3-(3,4-Dihydroisoquinolin-2(1H)-yl)-N-(2-hydroxyphenyl)propanamide* (**3g**): IR (KBr) (cm^{-1}): 3650 (Phenolic –OH stretching), 3360 (NH stretching of aromatic secondary amide), 1635 (C=O stretching), 1440 (OH stretching), 1360 (CN stretching of aliphatic amine).

2.1h *3-(3,4-Dihydroisoquinolin-2(1H)-yl)-N-(3-hydroxhphenyl)propanamide* (**3h**): IR (KBr) (cm^{-1}): 3566 (phenolic –OH stretching), 3481 (NH stretching of aromatic secondary amide), 1660 (C=O stretching), 1400 (OH stretching), 1320 (CN stretching of aliphatic amine).

2.1i *3-(3,4-Dihydroisoquinolin-2(1H)-yl)-N-(2-nitrophenyl)propanamide* (**3i**): IR(KBr) (cm^{-1}): 3320 (NH stretching of aromatic secondary amide), 1680 (C=O stretching), 1579 (C–NO_2 stretching), 1305 (CN stretching of aliphatic amine).

2.1j *3-(3,4-Dihydroisoquinolin-2(1H)-yl)-N-(4-nitrophenyl)propanamide* (**3j**): IR(KBr) (cm^{-1}): 3473 (NH stretching of aromatic secondary amide), 1680 (C=O stretching), 1560 (C–NO_2 stretching), 1336 (CN stretching of aliphatic amine).

2.1k *3-(3,4-Dihydroisoquinolin-2(1H)-yl)-N-m-tolyl propanamide* (**3k**): IR(KBr) (cm^{-1}): 3309 (NH stretching of aromatic secondary amide), 2891 (C–CH_3 stretching), 1670 (C=O stretching), 1332 (CN stretching of aliphatic amine).

2.1l *3-(3,4-Dihydroisoquinolin-2(1H)-yl)-N-p-tolyl propanamide* (**3l**): IR (KBr) (cm^{-1}): 3284 (NH stretching of aromatic secondary amide), 2821 (C-CH_3 stretching), 1653 (C=O stretching), 1320 (CN stretching of aliphatic amine).

2.1m *3-(3,4-Dihydroisoquinolin-2(1H)-yl)-N-(2,4-dimethyphenyl)propanamide* (**3m**): IR (KBr) (cm^{-1}): 3290 (NH stretching of aromatic secondary amide), 2887 (C–CH_3 stretching), 1647 (C=O stretching), 1379 (CN stretching of aliphatic amine).

2.1n *3-(3,4-Dihydroisoquinolin-2(1H)-yl)-N-(4-methoxyhenyl)propanamide* (**3n**): IR (KBr) (cm^{-1}): 3306 (NH stretching of aromatic secondary amide), 1660 (C=O stretching), 1354 (CN stretching of aliphatic amine), 1160 and 1031 (C–O–C stretching).

2.1o *3-(3,4-Dihydroisoquinolin-2(1H)-yl)-N-(4-ethoxyphenyl)propanamide* (**3o**): IR (KBr) (cm^{-1}): 3480 (NH stretching of aromatic secondary amide), 1680 (C=O stretching), 1360 (CN stretching of aliphatic amine), 1219 and 1040 (C–O–C stretching).

2.2 *HIV-1 RT RNA dependent DNA polymerase activity assay*

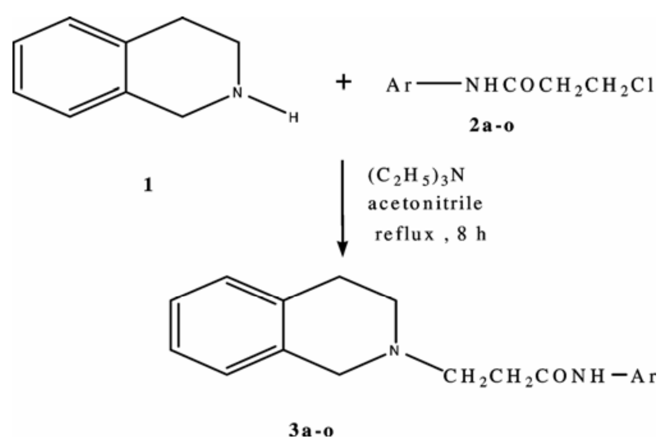
All the synthesized compounds were evaluated for HIV-1 RT inhibitory activity by using HIV-1 RT RNA dependent DNA polymerase activity assay.[48] Efavirenz was used as the standard. Poly(rA)/oligo(d*T*) was used as a template for the RNA-dependent DNA polymerase reaction by HIV-1 RT, either wt or carrying the mutations. For the activity assay, a 25 μl final reaction volume contained TDB buffer (50 mM Tris-HCl (pH 8·0), 1 mM 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 (1Ci/mmol) and finally, introduced into tubes containing aliquots of different enzyme concentrations (5 to 10 nM RT). After incubation at 37°C for indicated time, 20 μL from each reaction tube were spiked on glass fibre 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 min, 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.

2.3 *Computational studies*

All computational studies were carried out using Autodock 4.0.1[49–52] installed in a single machine running on a 3·4 GHz Pentium 4 processor with 512 MB RAM and 80 GB hard disk with Red Hat

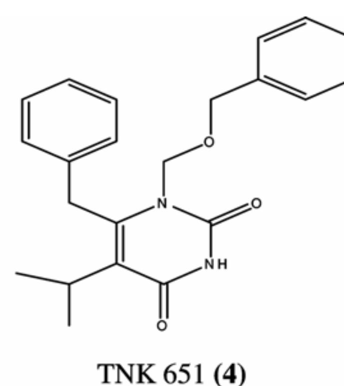
Table 1. Physical characterization data of compounds **3a–o**.

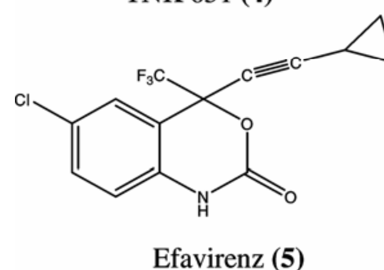
Compound	Molecular formula	Mol. wt.	m.p. (°C)	Yield (%)	Calculated (found)		
					C	H	N
3a	$C_{18}H_{20}N_2O$	280·37	165–170	82	77·11 (77·13)	7·19 (7·16)	9·79 (9·77)
3b	$C_{18}H_{19}N_2OCl$	314·82	80–88	97	68·67 (68·70)	6·08 (6·06)	8·90 (8·89)
3c	$C_{18}H_{19}N_2OCl$	314·82	65–70	95	68·67 (68·66)	6·08 (6·09)	8·90 (8·94)
3d	$C_{19}H_{22}N_2O$	294·40	98–104	75	77·52 (77·50)	7·53 (7·56)	9·52 (9·48)
3e	$C_{18}H_{19}N_2OCl$	314·82	78–82	89	68·67 (68·68)	6·08 (6·10)	8·90 (8·91)
3f	$C_{18}H_{17}N_2OBr_3$	517·06	90–94	84	41·81 (41·84)	3·31 (3·29)	5·42 (5·39)
3g	$C_{18}H_{20}N_2O_2$	296·37	82–90	98	72·95 (72·93)	6·80 (6·82)	9·45 (9·42)
3h	$C_{18}H_{20}N_2O_2$	296·37	108–112	98	72·95 (72·98)	6·80 (6·79)	9·45 (9·47)
3i	$C_{18}H_{19}N_3O_3$	325·37	84–90	82	66·45 (66·46)	5·89 (5·91)	12·91 (12·90)
3j	$C_{18}H_{19}N_3O_3$	325·37	78–82	82	66·45 (66·42)	5·89 (5·90)	12·91 (12·88)
3k	$C_{19}H_{22}N_2O$	294·40	58–64	90	77·52 (77·54)	7·53 (7·51)	9·52 (9·50)
3l	$C_{19}H_{22}N_2O$	294·40	90–96	91	77·52 (77·50)	7·53 (7·55)	9·52 (9·51)
3m	$C_{20}H_{24}N_2O$	308·42	108–112	97	77·89 (77·92)	7·84 (7·82)	9·08 (9·11)
3n	$C_{19}H_{22}N_2O_3$	310·52	90–96	96	73·52 (73·51)	7·14 (7·17)	9·03 (9·00)
3o	$C_{20}H_{24}N_2O_2$	324·42	70–74	78	74·04 (74·06)	7·46 (7·50)	8·64 (8·60)



a; Ar = C_6H_5, **b**; Ar = 2-ClC_6H_4, **c**; Ar = 3-ClC_6H_4, **d**; Ar = *o*-$CH_3C_6H_4$, **e**; Ar = 4-ClC_6H_4, **f**; Ar = 2,4,6-$Br_3C_6H_2$, **g**; Ar = 2-OHC_6H_4, **h**; Ar = 3-OHC_6H_4, **i**; Ar = 2-$NO_2C_6H_4$, **j**; Ar = 4-$NO_2C_6H_4$, **k**; Ar = *m*-$CH_3C_6H_4$, **l**; Ar = *p*-$CH_3C_6H_4$, **m**; Ar = 2,4-$(CH_3)_2C_6H_3$, **n**; Ar = *p*-$OCH_3C_6H_4$, **o**; Ar = *p*-$OC_2H_5C_6H_4$.

Scheme 1. Synthetic protocol of the compounds.





Linux Enterprise version 3.0 as the operating system.

The geometry of the NNBS of the wt RT strain was taken from the structure of HIV-1 RT/TNK 651 complex filed in the Brookhaven Protein Data Bank[53] (entry code 1rt2). All the residues within 20 Å core from TNK 651 **4** were used to define the NNBS. The starting conformations for docking studies were obtained using molecular dynamics with simulated annealing as implemented in SYBYL 7.1.

Autodock 4.0.1[49–52] was used to explore the binding conformation of TNK 651 **4** and active test molecules. The AutodockTools package version 1.4.6 was employed to generate the docking input files and to analyse the docking results. All the non-polar hydrogens were merged and the water molecules were removed. For the docking, a grid spacing of 0·375 Å and 60 × 60 × 60 number of points was used. The grid was centered on the mass center of the experimental bound TNK 651 coordinates. Autodock generated 50 possible binding conformations, i.e. 50 runs for each docking by using genetic algo-

rithm (GA-LS) searches. A default protocol was applied, with an initial population of 150 randomly placed individuals, a maximum number of $2{\cdot}5 \times 10^5$ energy evaluations, and a maximum number of $2{\cdot}7 \times 10^4$ generations. A mutation rate of 0·02 and a crossover rate of 0·8 were used.

To validate the use of the Autodock program, re-docking was performed on the reference compound TNK 651 and for comparison purpose, cross docking was performed on the standard NNRTI Efavirenz **5**. Autodock successfully reproduced the experimental binding conformations of the reference drug TNK 651 with acceptable root-mean-square deviation (RMSD) of 0·56 Å. The structures of the newly synthesized 3-(3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-(substituted phenyl)propanamides were drawn and optimized using PRODRG online server[54] and saved in PDB format. These structures were used for the docking studies and the interactions of the active compounds **3d** and **3f** as shown in figures 1a and b.

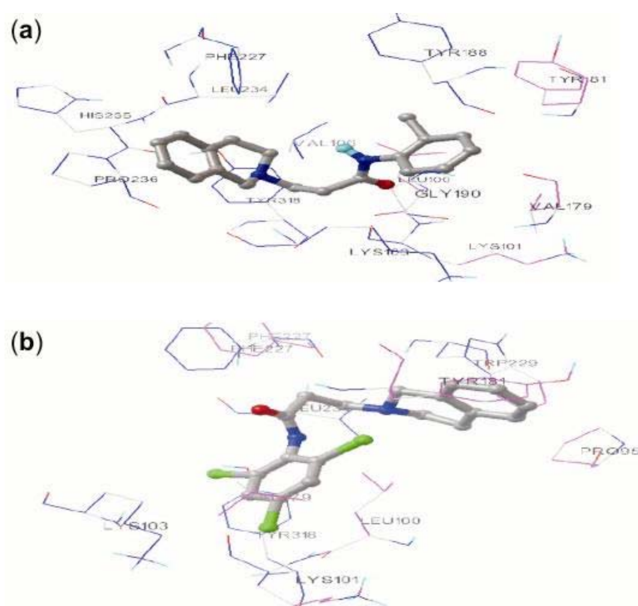


Figure 1. (**a**) interaction between the compound **3d** (ball and stick model) and residues (coloured line model with three letter codes) within the HIV-1 RT NNBP obtained by the docking procedure. The rest of the protein structure was suppressed for clarification purposes. (**b**) Interaction between the compound **3f** (ball and stick model) and residues (coloured line model with three letter codes) within the HIV-1 RT NNBP obtained by the docking procedure. The rest of the protein structure was suppressed for clarification purposes.

3. Results and discussion

3.1 *Synthesis of 3-(3,4-dihydroisoquinolin-2(1H)-yl)-N-(substituted-phenyl) propanamides*

Synthesis of title compound is effected by reacting the corresponding 3-chloro-*N*-(aryl) propanamide with 1,2,3,4-tetrahydroisoquinoline in presence of triethylamine by using acetonitrile as solvent. In this reaction, the liberated HCl is neutralized with solid anhydrous potassium carbonate, repeated washings with water and finally with *n*-hexane.

The FT–IR spectra of all the synthesized compounds and ^{1}H NMR spectra of the compounds **3a**, **3d** and **3e** were in complete agreement with the assigned structure. In case of IR spectral analysis, broad band in the region between 3228 and 3298 cm^{-1} confirms the presence of NH stretching of aromatic secondary amide in the title compounds. The carbonyl group appeared as sharp band in the region between 1653 and 1662 cm^{-1}. Another band around 744 cm^{-1} was appeared in the compound **3d** is mainly due to the presence of mono chloroalkanes. Appearance of absorbance band around 3650–3560 cm^{-1} indicates the presence of phenolic hydroxyl group in the compounds **3g** and **3h**. A sharp absorbance band around 1579–1560 cm^{-1} confirms the presence of C–NO_2 stretching in the compounds **3i** and **3j**. The compounds **3n** and **3o** showed absorbance band around 1219–1031 cm^{-1} indicates the presence of C–O–C stretching. ^{1}H NMR spectral analysis of the compounds **3d** and **3e** exhibited a broad singlet at δ 8·80 and 11·10 ppm respectively confirming the presence of NH group. Aromatic protons were appeared in the expected range of δ 6·80–7·30 ppm as multiplet which confirms the presence of aromatic functional group. A triplet in the range between δ 2·90 and 3·50 ppm is mainly due to the presence of N–CH_2–CH_2–CONH group. Compound **3d** exhibited singlet at δ 1·90 ppm assigned to methyl group at *ortho* position in the aromatic amino phenyl ring.

The FAB mass spectra of the compounds **3a**, **3d** and **3e** showed a molecular ion peak at *m/z* 280, 294 and 315 respectively confirming the molecular weight of the appropriate title compounds.

The elemental analysis data of the all synthesized compounds were within ± 0·4% of the theoretical values.

3.2 *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.[48] Efavirenz was used as the standard. The screening results indicate that compounds **3d** and **3f** were significantly active against HIV-1 reverse transcriptase at the final concentration of 40 μM with 56% and 43% residual RT activity respectively.

3.3 *Molecular docking and binding mode analysis*

The binding mode of the active compounds **3d** and **3f** were investigated. Ligand structures were drawn and optimized using PRODRG online server and saved in PDB format. Autodock 4.0.1 program was used to dock **3d** and **3f** into the RT non-nucleoside inhibitor binding pocket (NNIBP). The NNIBP was obtained using the coordinates of HIV-1-RT/TNK 651 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. 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. Secondly similar docking experiment was performed using standard molecule Efavirenz **5** for comparison purpose.

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 **3d** was –10·48 and 20·86 nM respectively. From the figure 1a, it was observed that, the tetrahydroisoquinoline moiety of **3d** was oriented towards the hydrophobic pocket formed by the side chains of TYR 318, PRO 236, HIS 235 and PHE 227 and the phenyl group substituted at the *ortho* position with methyl group is surrounded by the residues VAL 106, LEU 100 and GLY 190 of HIV-1 RT NNIBP. For the compound **3f**, the estimated binding free energy and predicted inhibitory constant value was –10·36 and 25·62 nM respectively. From the figure 1b, it was observed that, the tetrahydroisoquinoline moiety of **3f** was oriented towards the side chains of TRP 229, TYR 181 and PRO 96 and the phenyl group substituted with three bromine atoms at 2nd, 4th and 6th position is embedded into the residues of LYS 103, LYS 101, LEU 100, TYR 318 and VAL 179. These interactions may explain the significant inhibitory activities of the compounds **3d** and **3f** at the NNIBP of HIV-1-RT. From these docking studies, it was predicted that both the active analogs **3d** and **3f** adopt a common type of 'butterfly-like' confirmation within the active site of NNIBP of HIV-1 RT which resembles the same binding confirmation as that of first generation NNRTIs (i.e. nevirapine, delavirdine and efavirenz).

4. Conclusion

In this study, some novel analogs of 3-(3,4-dihydroisoquinolin-2(*1H*)-yl)-*N*-(substituted phenyl) propanamide were synthesized based on common pharmacophoric requirements for NNRTIs and has been confirmed by spectral and elemental analysis. All the analogs were screened for HIV-1 RT inhibitory assay. Docking studies of the most active analogs **3d** and **3f** were carried out to understand their exact binding mode in the active site of HIV-1 RT as well as to study their interaction with amino acid residues of HIV-1 RT. This led us to conclude that, the active analogs **3d** and **3f** adopt a similar 'butterfly-like' orientation like some classical NNRTIs (nevirapine, delavirdine and efavirenz) within the active site of NNIBP of HIV-1 RT. Further modifications in the phenyl portion of the tetrahydroisoquinoline nucleus in the two active analogs **3d** and **3f** could be carried out, which may lead to significantly active compounds with improved *in vitro* potency and *in vivo* efficacy against both wild and resistant strains of HIV-1.

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