

## DESIGN AND SYNTHESIS OF 3a, 4, 7, 7a-TETRAHYDRO-1H-ISOINDOLE-1, 3(2H)-DIONES AS INHIBITORS OF HIV-1 REVERSE TRANSCRIPTASE

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### ABSTRACT

**Objective:** In the present study, we have designed and synthesized 15 novel 3-(1,3-dioxo-3a,4-dihydro-1H-isoindol-2(3H,7H,7aH)-yl)-N-(substituted phenyl) propanamide **4(a-o)** analogs.

**Methods:** Docking studies for all the derivatives **4(a-o)** were performed using molecular modeling software autodock 4.2. Lipinski rule of five parameters and other molecular parameter were derived through online servers Molinspiration and Osiris property calculator. Designed analogs were synthesized using the synthetic protocols available in the literature. All the synthesized compounds were evaluated for their HIV-1 Reverse Transcriptase (RT) inhibitor activity by HIV-1 RT RNA dependent DNA polymerase activity assay at 2 and 20 $\mu$ M concentrations.

**Results:** Synthesized compounds were characterized by FTIR, <sup>1</sup>H NMR and Mass spectroscopy and Elemental analysis. Among the synthesized compounds, **4b**, **4i**, **4j** and **4n** showed weak Reverse Transcriptase inhibitor activity at 20 $\mu$ M concentration.

**Conclusion:** In these designed tetrahydrophthalimides derivatives, **4b**, **4i**, **4j** and **4n** showed weak Reverse Transcriptase inhibitor activity and no co-relation was observed between molecular modeling and *in-vitro* studies.

**Keywords:** AIDS, HAART, HIV-1 Reverse Transcriptase, Docking, Molecular Properties, Autodock.

### INTRODUCTION

Acquired Immune Deficiency Syndrome (AIDS) is one of the major infective diseases caused by the Human Immunodeficiency Virus (HIV). AIDS is one of the major leading causes to death. According to *UNAIDS-2012* report, 33 million people living with AIDS and 1.7 million people died in the year 2011[1]. Number of deaths due to HIV infection is decreasing, because of availability of HAART (Highly Active Anti Retroviral Therapy)[2]. HAART includes two NRTIs (Nucleotide or Nucleoside Reverse Transcriptase Inhibitor) and one PI (Protease Inhibitor) or one NNRTI (Non-Nucleoside Reverse Transcriptase Inhibitor). NNRTIs are the key components in HAART, because of their high potency, selectivity and less toxicity when compared to NRTIs and PIs[3]. Currently five NNRTIs are approved by United States Food and Drug Administration (USFDA). Among them, Nevirapine, Delavirdine, Efavirenz are first generation, which already got resistance. Etravirine and Rilpivirine are potent and currently using second generation NNRTIs. However occurrence of the high mutation rate of the virus and the resulting emergence of resistance makes the researchers to run a never ending marathon to keep developing new drugs active against both drug sensitive and resistance strain with better therapeutic profile[4,5]. To overcome these difficulties novel NNRTIs are searched by modifying the existing class of drugs with appropriate pharmacophoric requirements.

Many NNRTIs, including Tetrahydroimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one (TIBO) and  $\alpha$ -anilinophenyl acetamide ( $\alpha$ -APA) derivatives, adopt typical butterfly-like conformations in non-nucleoside inhibitor binding pocket, with one hydrophilic body and two hydrophobic wings (wing-1 and wing-2). Hydrophilic body contain mainly functional groups like -NH, -C=O and -OH which are able to form hydrogen bonding interactions with active site aminoacids like K101, K103 and P236. Hydrophobic wings are  $\pi$ -electron containing aromatic ring system, which can form hydrophobic interactions and pi-cationic interactions with amino acids Y181, Y188, W229, F227, V106, P236, L100, L234 and Y318[6,7].

Compounds having phtalimide scaffold exhibit anti-inflammatory[8], anticancer[9], antibacterial[10], HIV-1 RT[11,12] and HIV-1 integrase inhibitory[13] activity. An extensive perusal of literatures revealed that, little work has been done on phtalimides and tetrahydrophthalimides as NNRTIs. In view of these facts and our

interest on development of novel NNRTIs, we have chosen Tetrahydrophthalimide scaffold as one of the hydrophobic wings in butterfly shape pharmacophore. All the newly synthesized compounds were designed based on the derived pharmacophoric model with acetamide moiety as hydrophilic body and Tetrahydrophthalimide and substituted aromatic amines as hydrophobic wings (general structure shown in Figure 1).

### MATERIALS AND METHODS

All solvents and reagents purchased from Sigma and Merck companies are used as received without further purification. Solvent system used throughout experimental work for running Thin Layer Chromatography was Ethyl acetate and Hexane Mixture (30:70) in order to monitor the reaction.

Melting points are uncorrected and were determined in open capillary tubes on a Precision Buchi B530 melting point apparatus containing silicon oil. IR spectra were recorded using a Jasco FTIR spectrophotometer. <sup>1</sup>H NMR spectra were recorded on a Bruker DPX-400 spectrometer, using TMS as an internal standard (chemical shifts in $\delta$ ). The ESMS were recorded on MICROMASS Quadro-II LCMS system.

### Docking study

#### Molecular docking

Docking is an approach to rational drug design that seeks to predict the structure and binding free energy of ligand-receptor complex. It not only gives an idea about how the ligand is going to bind with the receptor but also up to what extent conformational changes can be brought in the receptor structure[14]. The docking studies for all the derivatives **4(a-o)** were performed using molecular modeling software autodock 4.2[15,16], installed on a single machine running on a 3.4 GHz pentium processor with windows XP SP2 as the operating system. HIV-1 RT enzyme [pdb code: 1rt2 (shown in Figure 2)] was taken from the RCSB, used as target protein[7]. Target protein pdb was further refined by removal of water molecules and by adding polar hydrogens and kollmann charges. For the docking, a grid spacing of 0.375  $\text{\AA}$  and 63  $\times$  63  $\times$  63 number of points were used. The grid was centered on the active site. The auto grid program generated separate grid maps for all atom types of the ligand structures and one for electrostatic interactions. PRODRG online server was used to generate the energy minimized

conformations of the ligands in pdb format[17]. Energy minimized conformation of ligands were subjected to calculation of Gasteiger-Huckel charges and saved in default format of Autodock. Autodock generated 50 possible binding conformations i.e., 50 runs for each docking by using LGA search. Default protocol was applied, with initial population of 150 randomly placed individuals, a maximum number of  $2.5 \times 10^5$  energy evaluations and  $2.7 \times 10^4$  generations. A mutation rate of 0.02 and a crossover rate of 0.8 were used.

#### Validation of docking

Initially the receptor was docked with extracted ligand TNK 651 to validate the docking calculations, reliability and reproducibility of the docking parameters for the study. It was evident that the docked pose of the redocked ligand was almost superimposed with that of the co-crystallized ligand (Figure 3) with RMSD value of 0.5. Then docking was performed with the standard drug Efavirenz with 1tr2 for validation and the mode of interaction was shown in Figure 4.

The binding free energies (docking score) and predicted inhibitory constant ( $K_i$ ) values of the designed analogs were compared with

binding free energies and inhibitory constants of the co-crystallized ligand TNK-651 and standard drug Efavirenz. Binding free energies and predicted inhibitory constant values of TNK-651, Efavirenz and designed analogs were given in Table 1. Docking studies of designed compounds shown satisfactory results, hydrophilic body of designed analogs was showed Hydrogen bonding interactions with aminoacids of receptor protein 1rt2. Hydrogen bonding interactions of compound 4n with LYS 103 and PRO 236 was shown in Figure 5. All the designed analogs showed similar orientation in Non-Nucleoside Inhibitory Binding Pocket (NNIBP) of receptor protein. Orientation of some designed compounds in NNIBP of receptor was shown in Figure 6.

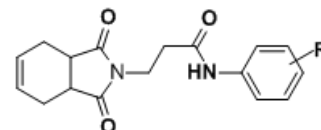


Fig. 1: General structure of synthesized compounds

Table 1: Binding free energies and predicted inhibitory constant values of the compounds

S. No.	Compound Code	R	Binding Free Energy (Kcal/mole)	Inhibitory Constant (nM)
1	Efavirenz	-	-12.02	1.56
2	TNK-651	-	-11.88	1.95
3	4a	H	-10.22	32.46
4	4b	4-OCH <sub>3</sub>	-10.05	42.81
5	4c	4-Cl	<b>-10.78</b>	<b>12.46</b>
6	4d	4-CH <sub>3</sub>	<b>-11.04</b>	<b>8.09</b>
7	4e	3-OCH <sub>3</sub>	-9.95	50.92
8	4f	3-Cl	-10.06	42.35
9	4g	3-CH <sub>3</sub>	<b>-10.58</b>	<b>17.69</b>
10	4h	2-Cl	-9.68	80.60
11	4i	2-CH <sub>3</sub>	-9.15	195.44
12	4j	4-NO <sub>2</sub>	-9.86	59.63
13	4k	3-NO <sub>2</sub>	-10.38	24.60
14	4l	2-NO <sub>2</sub>	-10.7	14.43
15	4m	2,4- diCH <sub>3</sub>	<b>-10.54</b>	<b>18.78</b>
16	4n	3,4- diCH <sub>3</sub>	<b>-11.31</b>	<b>5.09</b>
17	4o	2,6- diCH <sub>3</sub>	-8.94	279.16

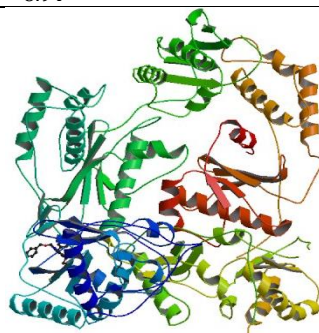


Fig. 2: Structure of HIV-1 Reverse Transcriptase co-crystallized with TNK-651 (Ref: 14)

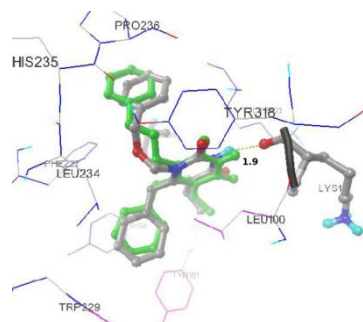


Fig. 3: Redocked mode of TNK 651 (3) (Green) superimposed with the co-crystallized ligand (Grey) in the NNIBP of HIV-1 RT (1rt2). Ligand is shown as stick model and the amino acid residues interacting with the ligands are shown as line model. Hydrogen Bond Interaction (1.9 Å) with LYS 103 amino acid residue of Reverse Transcriptase is shown as dotted spheres. Rest of the protein is suppressed for clarification purposes

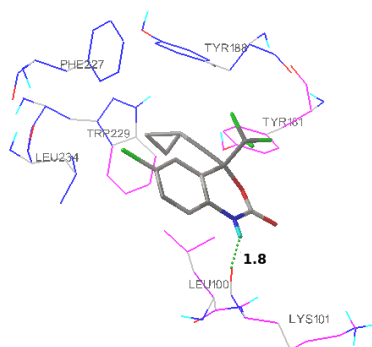


Fig. 4: Binding mode of standard drug Efavirenz in the NNIBP of HIV-1 RT (1rt2). Ligand is shown as stick model and the amino acid residues interacting with the ligands are shown as line model. Hydrogen Bond Interactions (1.8 Å) with LYS 101 amino acid residues of Reverse Transcriptase respectively are shown as dotted spheres. Rest of the protein is suppressed for clarification purposes

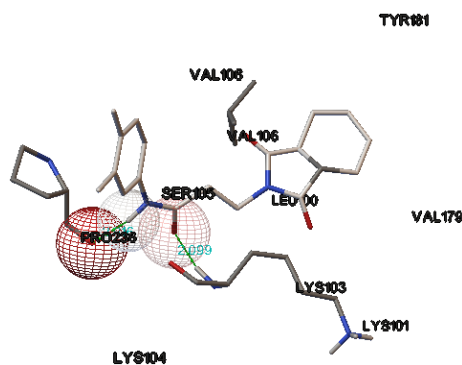


Fig. 5: Binding mode of compound 4n in the NNIBP of HIV-1 RT (1rt2). Ligand and the amino acid residues interacting with the ligands are shown as ball and sticks models. Hydrogen Bond Interactions (2.099 Å) with LYS 103 and (2.099 Å) with PRO 236 amino acid residues of Reverse Transcriptase are shown as dotted spheres. Rest of the protein is suppressed for clarification purposes

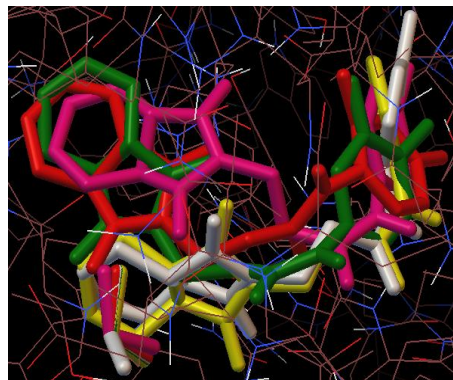


Fig. 6: Overlay stereoview of 4c (white), 4d (pink), 4g (yellow), 4m (red) and 4n (green) in the Non-Nucleoside inhibitory binding pocket of HIV-1 RT (1rt2).

Table 2: Molecular parameters of synthesized compounds

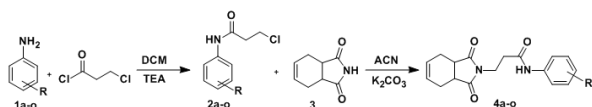
Compound Code	CLogP	M. Wt	No. of HBA	No. of HBD	Solubility	Drug likeness	Drug Score
4a	1.582	298.34	5	1	-2.72	2.44	0.69
4b	1.639	328.36	6	1	-2.74	2.82	0.33
4c	2.261	332.78	5	1	-3.46	4.85	0.66
4d	2.031	312.36	5	1	-3.06	2.68	0.41
4e	1.615	328.36	6	1	-2.74	3.4	0.42
4f	2.237	332.78	5	1	-3.46	4.07	0.66
4g	2.007	312.36	5	1	-3.06	3.71	0.69
4h	2.213	332.78	5	1	-3.46	4.32	0.53
4i	1.983	312.36	5	1	-3.06	4.21	0.69
4j	1.541	343.33	8	1	-3.18	-11.28	0.27
4k	1.517	343.33	8	1	-3.18	-1.19	0.27
4l	1.493	343.33	8	1	-3.18	-2.93	0.22
4m	2.408	326.39	5	1	-3.41	0.91	0.46
4n	2.408	326.39	5	1	-3.41	-0.07	0.32
4o	1.447	326.39	5	1	-3.41	5.99	0.67

## Molecular parameters

Lipinski rule of five parameters like ClogP, Molecular weight, number of hydrogen bond acceptors (HBA), number of hydrogen bond donors (HBD) and solubility, drug likeness, drug score were derived through online servers Molinspiration and Osiris property calculator. All the calculated values were given in Table 2[18,19].

## Chemistry

Designed analogs were synthesized by using synthetic protocol shown in Scheme 1. In the first step, substituted anilines were treated with chloropropionyl chloride in dichloromethane and triethylamine as base to get 3-chloropropionamide derivatives (**2a-o**) as intermediates. 3-chloropropionamide intermediates (**2a-o**) were treated with tetrahydrophthalimide in presence of base potassium carbonate and acetonitrile as solvent to yield desired compounds as final products **4(a-o)**[20, 21].



Scheme 1: Synthetic Protocol of the titled compounds

## MATERIALS AND METHODS

**General procedure for synthesis of 3-(1,3-dioxo-3a,4-dihydro-1H-isoindol-2(3H,7H,7aH)-yl)-N-(substituted phenyl)propanamides 4:** To a solution of 3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (**3**) (2 mmol) in acetonitrile, potassium carbonate (6 mmol) and corresponding 3-chloro-N-(substituted phenyl) propanamides **2(a-o)** (2 mmol) were added and refluxed for 8h. On completion of the reaction as monitored by TLC, the contents was poured on crushed ice. Resulted precipitate was filtered, dried and recrystallized from ethanol to obtain pure product **4**.

**3-(1,3-dioxo-3a,4-dihydro-1H-isoindol-2(3H,7H,7aH)-yl)-N-phenylpropanamide (4a):** White solid, (Yield 80%, MP = 104-106°C). IR (KBr, cm<sup>-1</sup>): 3271 (N-H), 1776 and 1712 (C=O, isoindole), 1693 (C=O, amide), <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.17-2.64 (m, 2H, CHH, CHH), 2.57-2.64 (m, 2H, CHH, CHH), 2.68 (t, J = 8.0 Hz, 2H, NCH<sub>2</sub>), 3.07-3.13 (m, 2H, CH-CH), 3.87 (t, J = 8.0 Hz, 2H, COCH<sub>2</sub>), 5.78-5.85 (m, 2H, CH=CH), 7.10 (t, J = 8.0 Hz, 1H, ArH), 7.29 (dd, J = 16.0, 4.0 Hz, 2H, ArH), 7.50 (d, J = 8.0 Hz, 2H, ArH), 7.79 (brs, 1H, NH). MS (ES<sup>+</sup>): m/z = 299.6 [M+1]. Elemental Analysis: calcd; C, 68.50; H, 6.25; N, 9.60.

**3-(1,3-dioxo-3a,4-dihydro-1H-isoindol-2(3H,7H,7aH)-yl)-N-(4-methoxyphenyl) propanamide (4b):** White solid, (Yield 88%, MP = 106-108°C). IR (KBr, cm<sup>-1</sup>): 3305 (N-H), 1778 and 1710 (C=O, isoindole), 1697 (C=O, amide), 1249 (C-O-C). Elemental Analysis: calcd; C, 65.60; H, 6.30; N, 8.75.

**N-(4-chlorophenyl)-3-(1,3-dioxo-3a,4-dihydro-1H-isoindol-2(3H,7H,7aH)-yl) propanamide (4c):** White solid, (Yield 78%, MP = 114-116°C). IR (KBr, cm<sup>-1</sup>): 3408 (N-H), 1772 and 1712 (C=O, isoindole), 1698 (C=O, amide), 689 (C-Cl). Elemental Analysis: calcd; C, 61.60; H, 5.25; N, 8.70.

**3-(1,3-dioxo-3a,4-dihydro-1H-isoindol-2(3H,7H,7aH)-yl)-N-p-tolylpropanamide (4d):** White solid, (Yield 82%, MP = 104-106°C). IR (KBr, cm<sup>-1</sup>): 3363 (N-H), 1768 and 1706 (C=O, isoindole), 1698 (C=O, amide), Elemental Analysis: calcd; C, 69.35; H, 6.60; N, 8.80.

**3-(1,3-dioxo-3a,4-dihydro-1H-isoindol-2(3H,7H,7aH)-yl)-N-(3-methoxyphenyl) propanamide (4e):** White solid, (Yield 72%, MP = 82-84°C). IR (KBr, cm<sup>-1</sup>): 3259 (N-H), 1774 and 1712 (C=O, isoindole), 1703 (C=O, amide), 1234(C-O-C). Elemental Analysis: calcd; C, 65.40; H, 6.00; N, 8.65.

**N-(3-chlorophenyl)-3-(1,3-dioxo-3a,4-dihydro-1H-isoindol-2(3H,7H,7aH)-yl) propanamide (4f):** White solid, (Yield 70%, MP = 102-104°C). IR (KBr, cm<sup>-1</sup>): 3342 (N-H), 1776 and 1712 (C=O, isoindole), 1682 (C=O, amide), 678 (C-Cl). Elemental Analysis: calcd; C, 61.20; H, 5.35; N, 8.30.

**3-(1,3-dioxo-3a,4-dihydro-1H-isoindol-2(3H,7H,7aH)-yl)-N-m-tolylpropanamide (4g):** White solid, (Yield 76%, MP = 96-98°C).

IR (KBr, cm<sup>-1</sup>): 3290 (N-H), 1768 and 1712 (C=O, isoindole), 1697 (C=O, amide). Elemental Analysis: calcd; C, 69.50; H, 6.20; N, 8.70.

**N-(2-chlorophenyl)-3-(1,3-dioxo-3a,4-dihydro-1H-isoindol-2(3H,7H,7aH)-yl)propanamide (4h):** White solid, (Yield 70%, MP = 108-110°C). IR (KBr, cm<sup>-1</sup>): 3265 (N-H), 1772 and 1705 (C=O, isoindole), 1694 (C=O, amide), 697 (C-Cl). Elemental Analysis: calcd; C, 61.50; H, 5.05; N, 8.35.

**3-(1,3-dioxo-3a,4-dihydro-1H-isoindol-2(3H,7H,7aH)-yl)-N-o-tolylpropanamide (4i):** White solid, (Yield 72%, MP = 100-102°C). IR (KBr, cm<sup>-1</sup>): 3302 (N-H), 1784 and 1702 (C=O, isoindole), 1676 (C=O, amide). Elemental Analysis: calcd; C, 69.15; H, 6.70; N, 8.95.

**3-(1,3-dioxo-3a,4-dihydro-1H-isoindol-2(3H,7H,7aH)-yl)-N-(4-nitrophenyl) propanamide (4j):**

Yellow solid, (Yield 72%, MP = 142-143°C). IR (KBr, cm<sup>-1</sup>): 3325 (N-H), 1779 and 1710 (C=O, isoindole), 1686 (C=O, amide), 1542, 1322 (C-NO<sub>2</sub>). Elemental Analysis: calcd; C, 59.80; H, 4.80; N, 12.20.

**3-(1,3-dioxo-3a,4-dihydro-1H-isoindol-2(3H,7H,7aH)-yl)-N-(3-nitrophenyl) propanamide (4k):** Yellow solid, (Yield 68%, MP = 100-102°C). IR (KBr, cm<sup>-1</sup>): 3338 (N-H), 1774 and 1712 (C=O, isoindole), 1693 (C=O, amide), 1537, 1327 (C-NO<sub>2</sub>). Elemental Analysis: calcd; C, 59.50; H, 5.05; N, 12.35.

**3-(1,3-dioxo-3a,4-dihydro-1H-isoindol-2(3H,7H,7aH)-yl)-N-(2-nitrophenyl) propanamide (4l):**

Yellow solid, (Yield 64%, MP = 104-106°C). IR (KBr, cm<sup>-1</sup>): 3331 (N-H), 1774 and 1714 (C=O, isoindole), 1698 (C=O, amide), 1531, 1336 (C-NO<sub>2</sub>). Elemental Analysis: calcd; C, 59.65; H, 4.80; N, 12.50.

**N-(2,4-dimethylphenyl)-3-(1,3-dioxo-3a,4-dihydro-1H-isoindol-2(3H,7H,7aH)-yl) propanamide (4m):** White solid, (Yield 76%, MP = 99-100°C). IR (KBr, cm<sup>-1</sup>): 3284 (N-H), 1782 and 1712 (C=O, isoindole), 1672 (C=O, amide). Elemental Analysis: calcd; C, 69.95; H, 6.90; N, 8.80.

**N-(3,4-dimethylphenyl)-3-(1,3-dioxo-3a,4-dihydro-1H-isoindol-2(3H,7H,7aH)-yl) propanamide (4n):** White solid, (Yield 78%, MP = 110-112°C). IR (KBr, cm<sup>-1</sup>): 3286 (N-H), 1778 and 1708 (C=O, isoindole), 1697 (C=O, amide), <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.20 (s, 3H, CH<sub>3</sub>), 2.23-2.24 (m, 2H, CHH, CHH), 2.28 (s, 3H, CH<sub>3</sub>), 2.59-2.62 (m, 2H, CHH, CHH), 2.67 (t, J = 8.0 Hz, 2H, NCH<sub>2</sub>), 3.09-3.10 (m, 2H, CH-CH), 3.88 (t, J = 8.0 Hz, 2H, COCH<sub>2</sub>), 5.84-5.86 (m, 2H, CH=CH), 6.98-7.00 (m, 2H, ArH), 7.11 (brs, 1H, NH), 7.51 (d, J = 8.0 Hz, 1H, ArH). MS (ES<sup>+</sup>): m/z = 327.4 [M+ 1]. Elemental Analysis: calcd; C, 69.75; H, 6.60; N, 8.60.

**N-(2,6-dimethylphenyl)-3-(1,3-dioxo-3a,4-dihydro-1H-isoindol-2(3H,7H,7aH)-yl) propanamide (4o):** White solid, (Yield 72%, MP = 90-92°C). IR (KBr, cm<sup>-1</sup>): 3253 (N-H), 1786 and 1714 (C=O, isoindole), 1695 (C=O, amide). Elemental Analysis: calcd; C, 69.80; H, 6.90; N, 8.75.

## HIV-1 Reverse Transcriptase Screening

All the synthesized compounds were evaluated for HIV-1 RT inhibitory activity at concentrations 2μM and 20μM by using HIV-1 RT RNA Dependent DNA Polymerase Activity Assay[22]. Rilpivirine was used as the standard drug in the assay.

## HIV-1 RNA Dependent DNA polymerase Activity Assay

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<sub>2</sub>, 0.5 mg of poly(rA):oligo(dT)10:1 (0.3 mM 3'-OH ends), 10 mM <sup>3</sup>[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, 20μL from each

reaction tube 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.

## RESULTS AND DISCUSSION

Fifteen novel designed 3-(1,3-dioxo-3a,4-dihydro-1*H*-isoindol-2(3*H*,7*H*,7*aH*)-yl)-*N*-(substituted phenyl) propanamide **4(a-o)** analogs were synthesized using the conditions reported in the literature (Scheme 1). Synthesized compounds were isolated as pure and characterized by IR, <sup>1</sup>H NMR, Mass and Elemental Analysis data. The compounds were tested for HIV-1 RT inhibitory activity and results were shown in Table 3.

Table 3: HIV-1 RT inhibitory activity of synthesized compounds

S. No.	Comp. Code	%RT inhibition	
		2μM	20μM
1.	4a	NA	NA
2.	4b	5	15
3.	4c	NA	NA
4.	4d	NA	NA
5.	4e	NA	NA
6.	4f	NA	NA
7.	4g	NA	NA
8.	4h	NA	NA
9.	4i	NA	10
10.	4j	5	15
11.	4k	NA	NA
12.	4l	NA	NA
13.	4m	NA	NA
14.	4n	NA	10
15.	4o	NA	NA

\* NA indicates Not Active

Among the designed analogs **4b**, **4i**, **4j** and **4n** showed weak HIV-1 RT inhibitory activity at 20μM concentration. Especially the compound **4n** showed two hydrogen bond interactions with LYS 103 and PRO 236 amino acid residues of HIV-1 RT. None of the compounds showed HIV-1 RT inhibition at 2μM concentration.

## CONCLUSION

All synthesized 3-(1,3-dioxo-3a,4-dihydro-1*H*-isoindol-2(3*H*,7*H*,7*aH*)-yl)-*N*-(phenyl) propanamide **4(a-o)** analogs were evaluated for HIV-1 Reverse Transcriptase inhibitor activity. Among these synthesized compounds **4b**, **4i**, **4j** and **4n** showed weak HIV-1 RT inhibitor activity at 20μM concentration. For these synthesized compounds no correlation was observed between molecular modeling and *in-vitro* studies.

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