Original Article

Lack of human immunodeficiency virus-1 integrase inhibitory activity of novel 3a, 4, 7, 7a-tetrahydro-1*H*-isoindole-1,3 (2H)-dione derivatives

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Abstract

Background: Majority of reported integrase (IN) inhibitors had an important structural feature, i.e., 1,3-diketo functional group. It plays a vital role in IN inhibition by the formation of chelating triod with Mg^{+2} ions. **Materials and Methods:** A novel series of fifteen 3-(1,3-dioxo-3a, 4-dihydro-1*H*-isoindol-2 (3*H*,7*H*,7a*H*)-yl)-*N*-(substituted phenyl) propanamide 4(a-o) analogs were synthesized by reacting the corresponding 3-chloro-*N*-(substituted phenyl) propanamides 2(a-o) with 3a, 4,7,7a-tetrahydro-1*H*-isoindole-1,3 (2H)-dione (3) in acetonitrile medium in the presence of potassium carbonate. Various substituted 3-chloro-*N*-(substituted phenyl) propanamides 2(a-o) were synthesized by treating appropriate substituted anilines 1(a-o) with 3-chloro propionyl chloride in dichloromethane as solvent in the presence of triethylamine as base. The synthesized compounds have been characterized on the basis of fourier transform infrared spectrophotometerproton nuclear magnetic resonance spectrophotometer,^{1}H NMR, Mass spectral and Elemental Analysis. **Results:** All the synthesized compounds were evaluated for their human immunodeficiency virus (HIV)-1 INinhibitory activity. However, unlike other anti-IN agents, none of these molecules showed inhibition of either 3' processing, and strand transfer reactions of HIV-1 IN.

Key words: Acquired immune deficiency syndrome, highly active anti-retroviral therapy, human immunodeficiency virus-1 integrase, tetrahydrophthalimide

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 united nations programme on AIDS united nations programme on AIDS (UNAIDS)-2012 reports, 33 million people living with AIDS and 1.7 million people died in the year 2011.[1] Number of deaths due to the HIV infection is decreasing because of availability of highly active anti-retroviral therapy (HAART).[2] HAART includes two nucleotide or nucleoside reverse transcriptase inhibitors and one Protease Inhibitor or one non-nucleoside reverse transcriptase inhibitor. Even though, HAART decreases viral loads, but unable to eradicate the HIV-1 virus completely from infected patients. Hence, lifelong HAART therapy is required for infected individuals because of the chronic nature of HIV-1 infection.[3] Severe adverse effects from long-term HAART medication and the rapid development of resistance to available

Access this article online

Quick Response Code:

Website: www.pnrjournal.com

DOI: 10.4103/0976-9234.116759

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drugs creates emergency to develop the potent and safe drugs active against alternative targets in the HIV-1 replication process.[4]

HIV integrase (IN) is one of the essential enzymes, which play a key role in HIV lifecycle along with Reverse Transcriptase and Proteases.[5] IN mediates important reactions such as, assembly of a stable nucleoprotein complex with viral deoxyribonucleic acid (DNA) sequences, cleavage of two nucleotides from both 3′-ends of the proviral DNA, and covalent joining of 3′-processed proviral DNA with host DNA.[6,7] These unique catalytic properties make HIV IN as one of the attractive targets for development of new anti-HIV drugs. However, development of clinically effective IN inhibitors is challenging task. Majority of anti-IN agents possess 1,3-diketo functional group as common structural feature [Figure 1]. HIV-1 IN inhibitors form chelating tripod with Mg^{2} + ion present in IN enzyme with this 1, 3-diketo functionality and there by inhibit HIV-1 IN catalyzed 3′-processing and strand transfer (ST) reactions.[8-10]

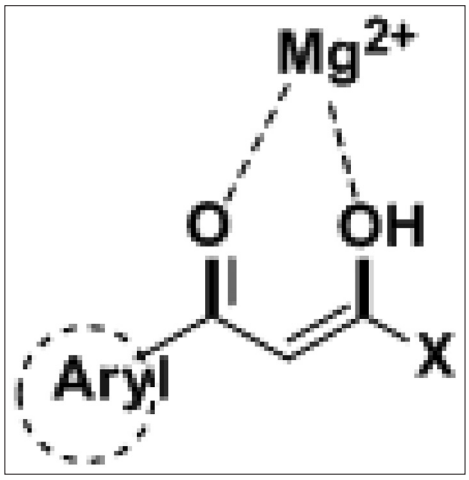


Figure 1: 1,3 diketo functional group chelating triod complex with Mg^{2+} ion

Many IN inhibitors are initially reported as potent inhibitors against HIV-1 IN-catalyzed 3′-processing (3′-P) and ST reactions *in vitro*. But these inhibitors failed to show good antiviral potencies in HIV-1 infected cells. Among the several IN inhibitors, the ′-diketo acidclass of compounds showed the most promising results. These class of compounds comprised of three important structural components (i.e.,) ′-diketo moiety, an aromatic or heteroaromatic portion and carboxylic acid group, which can be replaced with a variety of bioisosteric functions.[11,12] Among this class of compounds containing ′-diketo functional group, S-1360 [Figure 2 (1)] is the first IN inhibitor to enter into human clinical trials. S-1360 showed potent antiviral activity against a variety of HIV-1 clinical isolates; but unfortunately it failed to show efficacy in HIV-1 infected patients due to the metabolic instability.[13] Raltegravir [Figure 2 (2)] developed by Merck, is the first IN inhibitor approved by the U.S. Food and Drug Administration (FDA) in 2007. It showed potent antiviral activity against a wide range of clinical HIV-1 isolates, including strains resistant to almost all clinically

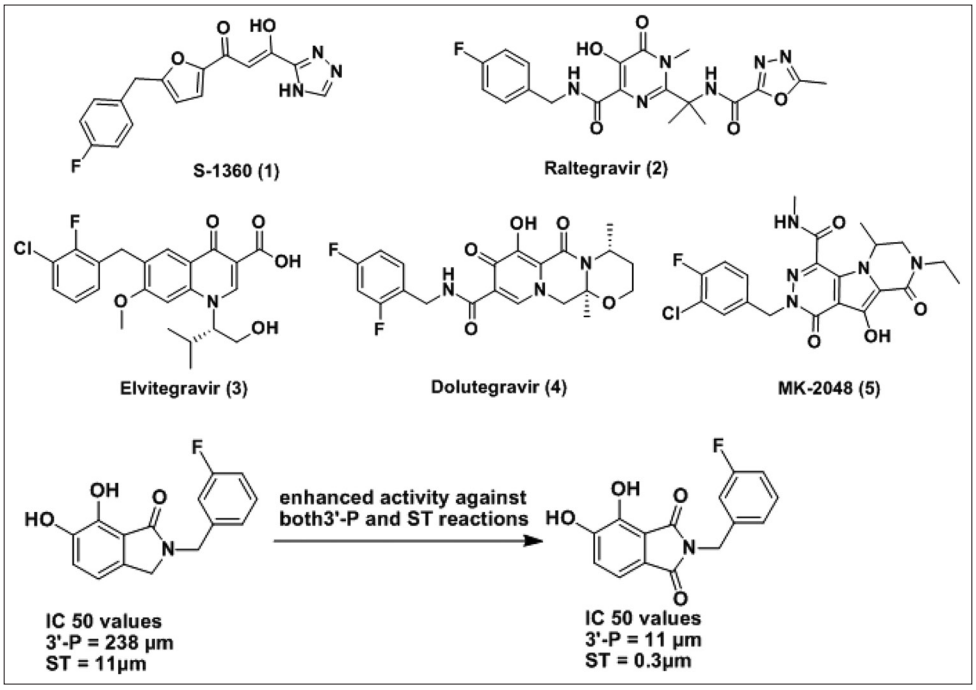


Figure 2: Structures of some integrase inhibitors

used antiretroviral drugs.[14] Elvitegravir [Figure 2 (3)] belongs to the quinolone-3-carboxylic acid class of IN inhibitors and approved by the U.S. FDA in 2012 to treat HIV patients.[15] Dolutegravir [Figure 2 (4)] is developed by GlaxoSmithKline, currently in late-stage clinical trials. Dolutegravir showing better results in the clinical trials.[16] MK-2048 [Figure 2 (5)] is the new second generation IN inhibitor developed by Merck in the year 2009, showing potent activity against Raltegravir and Elvitegravir resistance strains.[17]

Catechol based inhibitors are other important class of HIV-1 IN inhibitor. Increased potency was observed with maintained planar relationship between two hydroxyl groups on the aromatic ring. Zhao *et al.*, reported anti-IN activity of 2,3-Dihydro-6,7-dihydroxy-1*H*-isoindol-1-one analogs with potent IC_{50} values inhibiting both 3′-processing and ST reactions. Introduction of second carbonyl moiety on five membered lactam (isoindole-1-one to an isoindole-1,3-dione) showed enhanced activity against both 3′-processing (IC_{50} value increased from 238 μm to 11 μm) and ST (IC_{50} value increased from 11 μm to 0.3 μm) reactions.[16,18]

In light of these facts based upon an extensive perusal of literatures as well as our continued interest in the chemistry of *N*-substituted tetrahydrophthalimide, we have synthesized, characterized and evaluated HIV-1 IN inhibitory activity of novel 3-(1,3-dioxo-3a, 4-dihydro-1*H*-isoindol-2 (3*H*,7*H*,7a*H*)-yl)-*N*-(substituted phenyl) propanamides.

MATERIALS AND METHODS

Chemistry

All solvents and chemicals purchased from Sigma or Merck companies were used as received without further purification. Solvent system used throughout the experimental work for running thin layer chromatography (TLC) was Ethyl acetate and Hexane (30:70) mixture to the monitor reaction.

Melting points are uncorrected and were determined in capillary tubes on a Precision Buchi B530 melting point apparatus containing silicon oil. IR spectra were recorded using a Jasco fourier transform infrared spectrophotometer (FT-IR). Proton nuclear magnetic resonance spectrophotometer ^{1}H NMR spectra were recorded either on a Bruker DPX-400 spectrometer, using the TMS as an internal standard (chemical shifts in δ *ppm*). The electron spray ionization mass spectras ESMS (m/z) were recorded on MICROMASS Quadro-II LCMS system.

Synthesis route for designed analogs 3-(1,3-dioxo-3a, 4-dihydro-1*H*-isoindol-2 (3*H*,7*H*,7a*H*)-yl)-*N*-(substituted phenyl) propanamide (4a-o) and intermediates 3-chloro-*N*-(substituted phenyl) propanamide analogs (2a-o) was outlined in Scheme 1. Both the intermediates and final compounds were prepared by following below given method.[19] Substitutions on aryl ring of the synthesized compounds, some physical data, and isolated yields are presented in Table 1.

EXPERIMENTAL

General procedure for synthesis of 3-(1,3-dioxo-3a, 4-dihydro-1*H*-isoindol-2 (3*H*,7*H*,7a*H*)-yl)-*N*-(substituted phenyl) propanamides 4

To a solution of 3a, 4,7,7a-tetrahydro-1*H*-isoindole-1,3 (2*H*)-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 8 h. On completion of the reaction as monitored by TLC, the contents were 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)

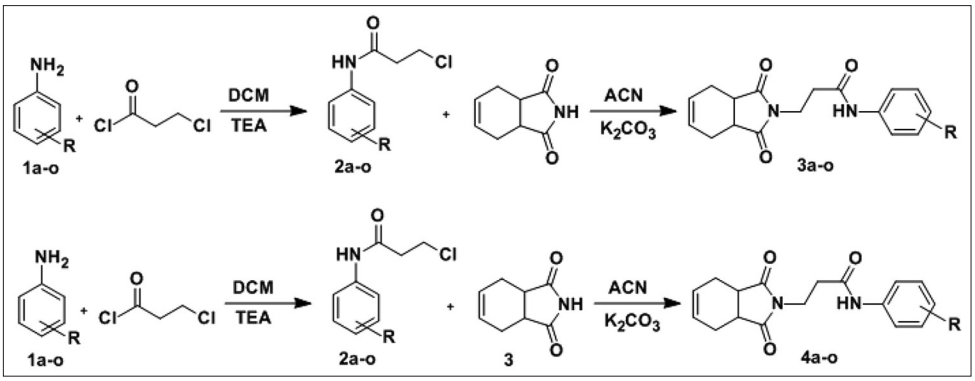
White solid, (80%, MP = 104-106°C). IR (KBr, cm^{-1}): 3271 (N-H), 1776 and 1712 (C = O, isoindole), 1693 (C = O, amide), ^{1}H NMR ($CDCl_3$): δ 2.17-2.64 (m, 2H, C*H*H, C*H*H), 2.57-2.64 (m, 2H, CH*H*, CH*H*), 2.68 (t, *J* = 8.0 Hz, 2H, NCH_2), 3.07-3.13 (m, 2H, CH-CH), 3.87 (t, *J* = 8.0 Hz, 2H, $COCH_2$), 5.78-5.85 (m, 2H, C*H* = C*H*), 7.10 (t, *J* = 8.0 Hz, 1*H*, ArH), 7.29 (dd, J = 16.0, 4.0 Hz, 2H, ArH), 7.50 (d, *J* = 8.0 Hz, 2H, ArH), 7.79 (brs, 1*H*, NH). MS (ES^+): *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, (88%, MP = 106-108°C). IR (KBr, cm^{-1}): 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-1 H-isoindol-2 (3H, 7H, 7aH)-yl)propanamide (4c)

White solid, (78%, MP = 114-116°C). IR (KBr, cm^{-1}): 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.



Scheme 1: Protocol of synthesis

Table 1: Physical data and isolated yields of synthesized compounds

Comp. code	R	Mol. formula	Mol. weight	MP (°C)	Isolated %yield
4a	H	$C_{17}H_{18}N_2O_3$	298.34	104-106	80
4b	4-methoxy	$C_{18}H_{20}N_2O_4$	328.36	106-108	88
4c	4-chloro	$C_{17}H_{17}ClN_2O_3$	332.78	114-116	78
4d	4-methyl	$C_{18}H_{20}N_2O_3$	312.36	104-106	82
4e	3-methoxy	$C_{18}H_{20}N_2O_4$	328.36	82-84	72
4f	3-chloro	$C_{17}H_{17}ClN_2O_3$	332.78	102-104	70
4g	3-methyl	$C_{18}H_{20}N_2O_3$	312.36	96-98	76
4h	2-chloro	$C_{17}H_{17}ClN_2O_3$	332.78	108-110	70
4i	2-methyl	$C_{18}H_{20}N_2O_3$	312.36	100-102	72
4j	4-nitro	$C_{17}H_{17}N_3O_5$	343.33	142-143	72
4k	3-nitro	$C_{17}H_{17}N_3O_5$	343.33	100-102	68
4l	2-nitro	$C_{17}H_{17}N_3O_5$	343.33	104-106	64
4m	2,4 di methyl	$C_{19}H_{22}N_2O_3$	326.39	98-100	76
4n	3,4 di methyl	$C_{19}H_{22}N_2O_3$	326.39	110-112	78
4o	2,6 di methyl	$C_{19}H_{22}N_2O_3$	326.39	90-92	72

3-(1,3-dioxo-3a, 4-dihydro-1H-isoindol-2 (3H,7H,7aH)-yl)-N-p-tolylpropanamide (4d)

White solid, (82%, MP = 104-106°C). IR (KBr, cm^{-1}): 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, (72%, MP = 82-84°C). IR (KBr, cm^{-1}): 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, (70%, MP = 102-104°C). IR (KBr, cm^{-1}): 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, (76%, MP = 96-98°C). IR (KBr, cm^{-1}): 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, (70%, MP = 108-110°C). IR (KBr, cm^{-1}): 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, (72%, MP = 100-102°C). IR (KBr, cm^{-1}): 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, (72%, MP = 142-143°C). IR (KBr, cm^{-1}): 3325 (N-H), 1779 and 1710 (C = O, isoindole), 1686 (C = O, amide), 1542, 1322 (C-NO_2). 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, (68%, MP = 100-102°C). IR (KBr, cm^{-1}): 3338 (N-H), 1774 and 1712 (C = O, isoindole), 1693 (C = O, amide), 1537, 1327 (C-NO_2). E lemental 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, (64%, MP = 104-106°C). IR (KBr, cm^{-1}): 3331 (N-H), 1774 and 1714 (C = O, isoindole), 1698 (C = O, amide), 1531, 1336 (C-NO_2). 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, (76%, MP = 99-100°C). IR (KBr, cm^{-1}): 3284 (N-H), 1782 and 1712 (C = , 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^{-1}): 3286 (N-H), 1778 and 1708 (C = O, isoindole), 1697 (C = O, amide), ^{1}H NMR ($CDCl_3$): δ 2.20 (s, 3H, CH_3), 2.23-2.24 (m, 2H, C*H*H, C*H*H), 2.28 (s, 3H, CH_3), 2.59-2.62 (m, 2H, CH*H*, CH*H*), 2.67 (t, *J* = 8.0 Hz, 2H, NCH_2), 3.09-3.10 (m, 2H, CH-CH), 3.88 (t, *J* = 8.0 Hz, 2H, $COCH_2$), 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^+): *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, (72%, MP = 90-92°C). IR (KBr, cm^{-1}): 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 IN assay

IN was pre-incubated at a final concentration of 100 μM with the inhibitor in reaction buffer (50 mM NaCl, 1 mM 4-(2-hydroxyethyl)-1-piperazineethane sulfonicacid 4-(2-hydroxyethyl)-1-piperazineethane sulfonicacid (HEPES), pH 7.5, 50 μM ethylene diamine tetraacetic acid ethylene diamine tetraacetic acid (EDTA), 50 μM dithiothreitol, 10% glycerol (w/v), 7.5 mM MnCl2, 0.1 mg/mL bovine serum albumin, 10 mM 2-mercaptoethanol, 10% dimethyl sulfoxide, and 25 mM 3(N-morpholino) propane sulfonicacid 3(N-morpholino) propane sulfonicacid (MOPS), pH 7.2) at 30°C for 30 min. Then, 20 nM of the 5′-end ^{32}P-labeled linear oligonucleotide substrate was added, and the incubation was continued for an additional 1 h. Reactions were quenched by the addition of an equal volume (16 mL) of loading dye (98% deionized formamide, 10 mM EDTA, 0.025% xylene cyanol, 0.025% bromophenol blue). An aliquot (5 μL) was electrophoresed on a denaturing 20% polyacrylamide gel (0.09 M tris-borate pH 8.3, 2 mM EDTA, 20% acrylamide, 8 M urea).

Gels were dried, exposed in a Molecular Dynamics Phosphorimager cassette, and analyzed using a Molecular Dynamics Phosphorimager (Sunnyvale, CA). Percent inhibition was calculated using the following equation:

$$\%\, I = 100 \times (1(D - C)/(N - C))$$

where C, N, and D are the fractions of 21-mer substrate converted to 19-mer (3′-processing product) or ST products for DNA alone, DNA plus IN, and IN plus drug, respectively. IC_{50} values were determined by plotting the drug concentration versus percent inhibition and determining the concentration, which produced 50% inhibition.[7]

RESULTS

All the designed analogs (4a-o) were synthesized by using the conditions mentioned in the Scheme 1. Synthesized compounds were characterized by FT-IR, ^{1}H NMR, Mass spectral and Elemental Analysis data. They were tested for inhibitory activity against HIV-1 IN using ^{32}P-labeled assay and results were shown in Figure 3.

[in Mn^{+2} containing reactions. Lane 1 and 18. DNA plus IN; lane 2 and 19. DNA alone; lanes 3 to17 DNA and

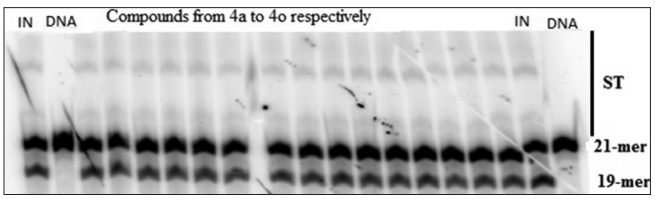


Figure 3: Concentration-dependent inhibition of HIV-1 IN by synthesized compounds 4a to 4o

IN in the presence of compounds 4a to 4o respectively (concentration of compounds is 100 μg/mL).

DISCUSSION

All the synthesized tetrahydrophthalimide analogs 4(a-o) were tested for HIV-1 IN inhibitory activity using ^{32}P-labeled assays. Even though, all the above synthesized analogs contains 1,3-diketo functional groups in their structure, which is essential for anti-IN activity. In the study, none of the compounds showed any significant IN inhibitory activity (both 3′ processing and ST) at tested concentration 100 μg/mL. This may be due to a) substitution on 2nd position, i.e., in between two keto (1,3-diketo) functional groups. Hence because of some steric effects and electronic effects of the alkyl side chain, both keto groups may be unable to form chelating tripod with Mg^{2+} ion present in IN enzyme. b) The distance between carbonyl carbon (phthalimide) and amide carbonyl carbon present in the side chain is also more; hence they may be unable to form chelation with Mg^{2+} ion, which is essential for inhibition of HIV-1 IN functions.

CONCLUSION

In the present study, all the analogs were designed based on the essential pharmacophoric requirements for HIV-1 IN inhibitory activity. However, none of the synthesized compounds showed any significant anti HIV-1 IN activity. Hence, further detailed study will be required to find out the exact reason for lack of activity of the synthesized analogs as well as to generate analogs with significant HIV-1 IN inhibitory activity.

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How to cite this article: Penta A, Babu KK, Ganguly S, Murugesan S. Lack of human immunodeficiency virus-1 integrase inhibitory activity of novel 3a, 4, 7, 7a-tetrahydro-1*H*-isoindole-1,3 (2H)-dione derivatives. J Pharm Negative Results 2013;4:13-8.

Source of Support: BITS-PILANI, UGC-BSR, New Delhi, Nouri Neamati, University of Southern California, USA for anti-HIV-1 IN screening. **Conflict of Interest:** None declared.