INTRODUCTION: Retrieving the first case of acquired immunodeficiency syndrome (AIDS) of 1981 the Disease Expert Group (DEG) recently put forth the fact about nearly 40 million individuals were infected by HIV/AIDS.

The extent of antiretroviral therapy posing the success to change the infection of HIV from a deadly disease to controllable chronic disease significantly for the last three decades. Thus, the endurance in life expectancy has surged amongst folk infected with HIV.1,2.

Etiology and prevalence of the infection shown to have very rapid development of drug resistance to many existing drug classes and warrant for the discovery of new targets. Among the three major enzymes, i.e. HIV-1 protease, HIV-1 reverse transcriptase and HIV-1 integrase [IN]) of the viral
replication cycle, HIV-1 IN has been of particular interest due to the absence of human cellular homolog. HIV-1 IN process the integration of viral genetic material with the host genome, a key step in the viral duplication process. Several novel classes of HIV IN inhibitors have been explored by targeting different sites on the enzyme  

Persistent efforts were on to the development of the new HIV-1 duplication antiretroviral agents with significant efficacy equally should be devoid of inherent toxicity, development of drug resistance, and poor tolerability. The integrase enzyme is required to repeat HIV-1 catalyzes the integration of reverse-transcribed DNA into the genome of the host cell. Therefore, integration has emerged as an attractive site according to the review of the different targets. The structural study advocated that IN is the active site inhibited by the Raltegravir and Elvitegravir, needs a single binding site for Mg$^{2+}$ metal ions. Several integrase inhibitors having metal-binding potential have been illustrated as well as published by several researchers  

As a continuation of a series of many reviews on synthetic approaches and final forms of recently approved drugs on the design and development of routes to the integrase inhibitors such as Dolutegravir, Cabotegravir, and Bictegravir was found predominantly. Compounds like β-diketo acid (DKA) has emerged as the most powerful and promising blocker, Raltegravir is the first approved IN hindering to reach up to clinical development along with Elvitegravir and GSK364735 as shown in Fig. 1.

These DKA hindering share two common structural chemotypes essential for anti IN movement: a sequence of diketo acid which is capable to interact with Mg$^{2+}$ metal ions and a properly oriented moiety of hydrophobic benzyl. Manipulative of identical analogs targeting to integrase may give rise to the newer ideal drug to cure AIDS and decrease the unwanted results of the previous compounds and may be responsible for new generation integrase blockers.

The diketoquinolines were first designed and few active compounds were prepared using oxo quinoline-3-carboxylate compounds with substituted piperazine, benzoic acid, 2-phenoxy acetic acid and benzene-1-sulfonyl chloride. The study was performed with structure-based virtual screening approaches. In this context, we synthesized narrative quinolone derivatives 1-14.
and evaluated for their anti-HIV-1 integrase activity.

**MATERIALS AND METHODS:**

**Chemistry:**

**General:** The reagents and solvents were used as usual. Reactions were observed by TLC with silica gel plates. Silica gel (100-200 mesh) as a fixed phase was used for column chromatography. The melting points were firm were not corrected. MS spectra of the synthesized analogs were documented on the Shimadzu QP-5050 spectrophotometer. 1H NMR spectra were acquired on a Varian-300 (300 MHz NMR) spectrophotometer using CDCl₃ and DMSO-d₆ as a solvent.

The infrared (IR) spectra were retrieved using Perkin Elmer Spectrum ES Version 10.5.3 Fourier-transform infrared spectrometer. Elemental analysis was performed on FLASH EA 1112 CHN Elemental analyzer, Thermofinnigen, Italy.

**General Procedure for Synthesis of Compounds (1-6):**

Methyl-1-Cyclopropyl-6-Fluoro-1, 4-Hydro-4-Oxo-7-(Substituted Piperzin-1-Yl) Quinoline-3-Carboxylate (1a-6a): Added methyl 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (1 g, 3.53 mmole) in acetonitrile (10 ml), shook the reaction mixture at 35 °C, added DIPEA (N, Ndi isopropyl ethylamine) (0.5 ml) and substituted piperazine (3.53 m mole) to the reaction mixture, shacked at boiling temperature for 2 h. The reaction mixture was shaken with Ethyl acetate, dried over sodium sulphate, concentrated under vacuum. The basic product was cleansed by column chromatography using silica gel (100-200 mesh) to get methyl-1-cyclopropyl-6-fluoro-1, 4-hydro - 4 - oxo-7 - (substituted piperzin - 1-yl) quinoline-3-carboxylate as off-White solid.

**Comp. 1a:** Yield (0.9 g, 75%), MP-198-200 °C. 1H NMR (300 MHz, DMSO-d₆) δppm: 1.20 (s, 1H, cyclopropane H), 1.32-1.36 (d, 4H, cyclopropane CH₂), 3.32 (br-s, 4H, piperazine CH₂), 3.60 (br-s, 4H, piperazine CH₂), 3.73 (s, 3H, OCH₃), 3.80 (m, 1H, NH), 7.60-7.62 (d, 1H, ArH), 7.90-7.95 (d, 1H, Ar H), 8.68 (s, 1H, N-C=C-H). IR (KBr) cm⁻¹: 2925 (C=H Ar), 1710 (C=O quinoline), 1564, 1492 (C=O quinoline), 1564, 1492 (C=O quinoline), 1564, 1492 (C=O quinoline).

**Comp. 2a:** Yield (0.85 g, 70%), MP-162-164 °C. 1H NMR (300 MHz, DMSO-d₆) δppm: 1.21 (s, 1H, cyclo propane H), 1.26 (q, 1H, piperazine H), 1.33-1.36 (d, 4H, cyclopropane CH₂), 1.41 (d, 3H, CH₃), 3.10 (br-s, 2H, piperazine CH₂), 3.40 (br-s, 4H, piperazine CH₂), 3.72 (s, 3H, OCH₃), 3.85 (m, 1H, NH), 7.56-7.62 (d, 1H, Ar H), 7.88-7.95 (d, 1H, Ar H), 8.66 (s, 1H, N-C=C-H). IR (KBr) cm⁻¹: 2935 (C-H Ar), 1712 (C=OOCCH₃), 1680 (C=O quinoline), 1564, 1492 (C=O quinoline), 1564, 1492 (C=O quinoline).

**Comp. 3a:** Yield (0.80 g, 63%), MP-204-206 °C. 1H NMR (300 MHz, DMSO-d₆) δppm: 1.21 (s, 1H, cyclopropane H), 1.25 (q, 2H, piperazine H), 1.33-1.36 (d, 4H, cyclopropane CH₂), 1.41 (d, 6H, 2CH₃), 2.90 (br-s, 4H, piperazine CH₂), 3.70 (s, 3H, OCH₃), 3.82 (m, 1H, NH), 7.50-7.62 (d, 1H, Ar H), 7.88-7.90 (d, 1H, Ar H), 8.64 (s, 1H, N-C=C-H). IR (KBr) cm⁻¹: 2939 (C-H Ar), 1710 (C=OOCCH₃), 1678 (C=O quinoline), 1565, 1490 (C=O quinoline), 1453 (C-N st), 1380 (C-N=C=), 1260 (C-O-C).

**Comp. 4a:** Yield (0.95 g, 78%), MP-170-172 °C. 1H NMR (300 MHz, DMSO-d₆) δppm: 1.22 (s, 1H, cyclopropane H), 1.32-1.38 (d, 4H, cyclopropane CH₂), 3.22 (s, 3H, N-CH₃), 3.34 (br-s, 4H, piperazine CH₂), 3.61 (br-s, 4H, piperazine CH₂), 3.72 (s, 3H, OCH₃), 7.60-7.64 (d, 1H, Ar H), 7.92-7.98 (d, 1H, Ar H), 8.66 (s, 1H, N-C=C-H). IR (KBr) cm⁻¹: 2941 (C=H Ar), 1714 (C=OOCCH₃), 1678 (C=O quinoline), 1566, 1492 (C=O quinoline), 1460 (C-N st), 1382 (C-N=C=), 1260 (C-O-C).

**Comp. 5a:** Yield (0.90 g, 70%), MP-168-170 °C. 1H NMR (300 MHz, DMSO-d₆) δppm: 1.12 (q, 1H, piperazine H), 1.16-1.25 (t, 3H, CH₃), 1.21 (s, 1H, cyclopropane H), 1.33-1.36 (d, 4H, cyclopropane CH₂), 1.40 (d, 3H, NCH₂CH₃), 3.10 (br-s, 4H, piperazine CH₂), 3.40 (br-s, 4H, piperazine CH₂), 3.74 (s, 3H, OCH₃), 3.91 (q, 2H, NCH₂CH₃), 7.57-7.62 (d, 1H, Ar H), 7.88-7.97 (d, 1H, Ar H), 8.68 (s, 1H, N-C=C-H). IR (KBr) cm⁻¹: 2930 (C=H Ar), 1710 (C=OOCCH₃), 1680 (C=O quinoline), 1564, 1492 (C=O quinoline), 1459 (C=N st), 1382 (C-N=C=), 1260 (C-O-C).

**Comp. 6a:** Yield (0.95 g, 70%), MP-182-184 °C. 1H NMR (300 MHz, DMSO-d₆) δppm: 1.12-1.20 (t, 3H, NCH₂CH₃), 1.25 (q, 2H, piperazine H), 1.30
(s, 1H, cyclopropane H), 1.33-1.38 (d, 4H, cyclopropane CH₂), 3.92 (q, 2H, NCH₂CH₃), 1.45 (d, 6H, 2CH₃), 2.90 (br-s, 4H, piperazine CH₂), 3.78 (s, 3H, OCH₃), 7.50-7.62 (d, 1H, Ar H), 7.88-7.90 (d, 1H, Ar H), 8.62 (s, 1H, N=C-H). IR (KBr) cm⁻¹: 3035, 2932 (COOH), 1705 (C=O, COOH), 1680 (C=O quinoline), 1562, 1494 (C=C Ar), 1446 (C-N st), 1382 (C-N=C). MS: m/z (relint %) 345 (38) [M]+, 330 (45), 255 (66), 253 (37), 219 (100), 205 (68), 190 (73), 183 (53), 182 (51), 158 (48), 144 (65), 113 (68), 99 (70). CHN Analysis: C₁₈H₂₂F₃N₅O₇ Cal: C 62.60%, H 5.84%, N 12.17%, Found: C 62.62%, H 5.86%, N 12.18%.

Comp. 3: Yield (80%, 0.60 g). MP- 172-174 °C. 1H NMR (300 MHz, DMSO-d₆) δppm: 1.23 (s, 1H, cyclopropane H), 1.28 (q, 2H, piperazine C-H), 1.32-1.36 (d, 4H, cyclopropane CH₂), 1.42 (d, 6H, 2CH₃), 3.20 (br-s, 4H, piperazine CH₂), 3.84 (m, 1H, NH), 7.60-7.62 (d, 1H, Ar H), 7.90-7.95 (d, 1H, Ar H), 8.66 (s, 1H, N=C-H). IR (KBr) cm⁻¹: 3550 (COOH), 2928 (C-H Ar), 1700 (C=O, COOH), 1680 (C=O quinoline), 1562, 1494 (C=C Ar), 1446 (C-N st), 1382 (C-N=C). MS: m/z (relint %) 359 (22) [M]+, 340 (18), 315 (20), 290 (25), 274 (33), 255 (40), 253 (38), 219 (100), 199 (66), 205 (64), 183 (72), 182 (69), 156 (56), 144 (75), 113 (78). CHN Analysis: C₁₉H₂₂F₃N₅O₇ Cal: C 63.50%, H 6.17%, N 11.69%, Found: C 63.52%, H 6.74%, N 11.70%.

Comp. 4: Yield (72%, 0.60 g). MP- 152-154 °C. 1H NMR (300 MHz, DMSO-d₆) δppm: 1.24 (s, 1H, cyclopropane H), 1.32-1.38 (d, 4H, cyclopropane CH₂), 3.35 (br-s, 4H, piperazine CH₂), 3.50 (br-s, 4H, piperazine CH₂), 3.83 (s, 3H, CH₃), 7.60-7.66 (d, 1H, Ar H), 7.90-7.95 (d, 1H, Ar H), 8.66 (s, 1H, N-C-C-H), 9.60 (s, 1H, COOH). IR (KBr) cm⁻¹: 3550 (COOH), 2928 (C-H Ar), 1700 (C=O, COOH), 1682 (C=O quinoline), 1562, 1494 (C=C Ar), 1450 (C-N st), 1382 (C-N=C). MS: m/z (relint %) 345 (28) [M]+, 317 (22), 298 (26), 272 (31), 256 (48), 254 (47), 219 (100), 199 (57), 205 (60), 186 (72), 182 (69), 158 (72), 144 (34), 112 (75). CHN Analysis: C₁₈H₂₂F₃N₅O₇ Cal: C 62.60%, H 5.84%, N 12.17%, Found: C 62.59%, H 5.86%, N 12.18%.

Comp. 5: Yield (78%, 0.67 g). MP- 156-158 °C. 1H NMR (300 MHz, DMSO-d₆) δppm: 1.20 (q, 1H, HCCH₃), 1.25-1.39 (t, 3H, CH₃), 1.28 (s, 1H, cyclopropane H), 1.31-1.35 (d, 4H, cyclopropane CH₂), 1.40 (d, 3H, CH₃), 3.30 (br-s, 2H, piperazine CH₂), 3.50 (br-s, 4H, piperazine CH₂), 3.95 (q, 2H, CH₂), 7.60-7.66 (d, 1H, Ar H), 7.90-7.95 (d, 1H, Ar H), 8.68 (s, 1H, N-C=C-H), 9.60 (s, 1H, COOH).
COOH). IR (KBr) cm⁻¹: 3550 (COOH), 2928 (C-H Ar), 1700 (C=O, COOH), 1678 (C=O quinoline), 1566, 1494 (C=C Ar), 1450 (C-N st), 1382 (C-N=C). MS: m/z (relint %) 373 (41) [M+], 352 (29), 320 (20), 292 (33), 277 (27), 244 (44), 240 (17), 222 (100), 199 (48), 190 (65), 183 (61), 182 (60), 158 (68), 144 (71), 131 (60), 112 (45). CHN Analysis: C₂₀H₂₄FN₅O₃ Cal: C 64.33%, H 6.48%, N 11.25%. Found: C 64.32%, H 6.50%, N 11.26%.

Comp. 6: Yield (72%, 0.61 g). MP- 174-176 °C. 1H NMR (300 MHz, DMSO-d₆) δ ppm: 1.18 (S, 1H, cyclopropane H), 1.21 (q, 2H, HCCCH₃), 1.27-1.30 (t, 3H, CH₃), 1.30-1.35 (d, 4H, cyclopropane CH₂), 1.41 (d, 6H, 2CH₃), 2.83 (br-s, 4H, piperazine 2CH₂), 3.96 (q, 2H, CH₂), 7.60-7.66 (d, 1H, Ar H), 7.90-7.95 (d, 1H, Ar H), 8.68 (s, 1H, N-C=H). 9.60 (s, 1H, COOH). IR (KBr) cm⁻¹: 3550 (COOH), 2930 (C-H Ar), 1700 (C=O), 1678 (C=O quinoline), 1566, 1494 (C=C Ar), 1450 (C-N st), 1382 (C-N=C). MS: m/z (relint %) 387 (21) [M+], 355 (18), 322 (18), 308 (16), 292 (21), 270 (34), 255 (33), 235 (219), 199 (44), 190 (23), 180 (34), 172 (14), 156 (18), 144 (66), 116 (72). CHN Analysis: C₂₁H₂₄FN₅O₃ Cal: C 65.10%, H 6.76%, N 10.85%. Found: C 65.13%, H 6.78%, N 10.84%.

General Procedure for Synthesis of Compounds (7-14) Methyl-1-Ethyl-6-Fluoro-1, 4-Dihydro-4-Oxo-7-(Substituted Piperazin-1-Yl) Quinoline-3-Carboxylate (7a-14a): A solution of methyl-7-chloro-1-ethyl-6-fluoro-1, 4-dihydro-4-oxo-quinoline-3-carboxylate (1 g, 3.53 m mol) added in acetonitrile (10 ml), DIPEA (0.5 ml) and substituted piperazine (3.53 m mol) was added and shaken at boiling temperature for 24 h and kept an eye by TLC. The reaction mixture was quenched with water, juiced with ethyl acetate, dried over sodium sulphate, intense under reduced pressure to obtain basic product and it was purified by column chromatography using silica gel (100-200 mesh) to get methyl-1-ethyl-6-fluoro-1, 4-dihydro - 4 - oxo - 7 - (substituted pipazin-1-yl) quinoline-3-carboxylate as off white solid.

Comp. 7a: Yield (72%, 0.84 g). MP- 190-192 °C. 1H NMR (300 MHz, DMSO-d₆) δ ppm: 1.39-1.45 (t, 3H, CH₃), 2.88-2.90 (s, 4H, piperazine 2CH₂), 3.21-3.24 (s, 4H, piperazine 2CH₂), 3.73 (s, 3H, OCH₃), 3.80 (m, 1H, NH), 4.55-4.62 (q, 2H, CH₂), 7.12-7.15 (d, 1H, Ar H), 7.86-7.90 (d, 1H, Ar H), 8.94 (s, 1H, NC=C-H). IR (KBr) cm⁻¹: 3450 (N-H st), 2910 (CH st, Alkyl), 1710 (C=O, COOCH₃), 1685 (C=O, quinoline), 1592, 1610 (C=C Ar), 1412 (C-N st), 1372 (C-N=C=), 1260 (C-O-C).

Comp. 8a: Yield: (76%, 0.92 g). MP- 158 -160 °C. 1H NMR (300 MHz, DMSO-d₆) δ ppm: 1.22 (q, 1H, near to CH₃), 1.39-1.45 (t, 3H, CH₃), 1.48 (d, 3H, CH₃), 2.88-2.90 (s, 4H, piperazine CH₂), 3.21-3.20 (s, 2H, piperazine CH₂), 3.73 (s, 3H, OCH₃), 3.80 (m, 1H, NH), 4.54-4.62 (q, 2H, CH₂), 7.12-7.15 (d, 1H, Ar H), 7.86-7.90 (d, 1H, Ar H), 8.94 (s, 1H, C=H). IR (KBr) cm⁻¹: 1592, 1610 (C=C Ar), 1412 (C-N st), 3450 (NH st), 1372 (C-N=C), 2910 (CH st, alkyl), 1710 (C=O, COOCH₃), 1680 (C=O, quinoline).

Comp. 9a: Yield: (78%, 0.99 g). MP- 196-198 °C. 1H NMR (300 MHz, DMSO-d₆) δ ppm: 1.22 (q, 2H, near to CH₃), 1.36-1.40 (t, 3H, CH₃), 1.44 (d, 6H, 2CH₂), 2.88-2.90(s, 4H, piperazine CH₂), 3.75 (s, 3H,OCH₃), 3.80 (m, 1H, NH), 4.55-4.65 (q, 2H, CH₂), 7.12-7.15(d, 1H, Ar H), 7.86-7.90 (d, 1H, Ar H), 8.94 (s, 1H, C=C-H). IR (KBr) cm⁻¹: 3450 (N-H st), 2910 (C-H st, alkyl), 1710 (C=O, COOCH₃), 1680 (C=O, quinoline), 1590, 1610 (C=C Ar), 1414 (C-N st), 1374 (C-N=C=), 1266 (C-O-C).

Comp. 10a: Yield: (70%, 0.85 g). MP- 164-166 °C. 1H NMR (300 MHz, DMSO-d₆) δ ppm: 1.35-1.45 (t, 3H, CH₃), 2.88-2.90 (s, 4H, piperazine 2CH₂), 3.10-3.40 (s, 4H, piperazine 2CH₂), 3.75 (s, 3H, OCH₃), 3.80 (s, 3H, N-CH₃), 4.55-4.65 (q, 2H, CH₂), 7.12-7.15 (d, 1H, Ar H), 7.86-7.90 (d, 1H, Ar H), 8.94 (s, 1H, C=C-H). IR (KBr) cm⁻¹: 1590, 1610 (C=C Ar), 1414 (C-N st), 1374 (C-N=C), 2910 (C-H st, alkyl), 1710 (C=O, COOCH₃), 1680 (C=O, quinoline), 1264 (C-O-C).

Comp. 11a: Yield (68%, 0.89 g). MP- 160-162 °C. 1H NMR (300 MHz, DMSO-d₆) δ ppm: 1.18 (q, 1H, piperazine H), 1.20-1.25 (t, 3H, quinoline CH₃), 1.35-1.38 (t, 3H, piperazine CH₃), 1.40 (d, 3H, CH₃), 3.98 (q, 2H, quinoline CH₂), 1.55-1.65 (q, 2H, piperazine CH₂), 3.10 (br-s, 4H, piperazine CH₂), 3.40 (br-s, 2H, piperazine CH₂), 3.74 (s, 3H, OCH₃), 7.60- 7.62 (d, 1H, Ar H), 7.88-7.98 (d, 1H, Ar H), 8.68 (s, 1H, N=C=C-H). IR (KBr) cm⁻¹: 2930 (C-H Ar), 1710 (C=O, COOCH₃), 1675 (C=O quinoline), 1564, 1492 (C=C Ar), 1459 (C-N st), 1382 (C-N=C=), 1264 (C-O-C).
Comp. 12a: Yield (66%, 0.90 g). MP- 178-180 °C. 1H NMR (300 MHz, DMSO-d6) δppm: 1.14-1.20 (t, 3H, quinoline CH3), 1.25 (q, 2H, piperazine H), 1.35-1.40 (t, 3H, piperazine CH3), 3.96 (q, 2H, CH2), 1.48 (d, 6H, 2CH3), 1.55-1.66 (q, 2H, piperazine CH2), 2.90 (br-s, 4H, piperazine CH2), 3.76 (s, 3H, OCH3), 7.50-7.62 (d, 1H, Ar H), 7.88-7.90 (d, 1H, Ar H), 8.64 (s, 1H, N-C=C-H). IR (KBr) cm⁻¹: 2930 (C-H Ar), 1710 (C=O, COOCH3), 1680 (C=O quinoline), 1565, 1490 (C=C Ar), 1456 (C=N st), 1380 (C-N=C-), 1268 (C=O-C).

Comp. 13a: Yield: (62%, 1.87 g). MP-252-254 °C. 1H NMR (300 MHz, DMSO-d6) δppm: 1.14-1.25 (t, 3H, CH3), 3.40 (br-s, 4H, piperazine 2CH2), 3.60 (br-s, 4H, piperazine 2CH2), 4.10 (q, 2H, CH2), 3.90 (s, 3H, OCH3), 7.42-7.62 (m, 5H), 7.90-7.97 (d, 1H), 8.68 (s, 1H, N-C=C-H). IR (KBr) cm⁻¹: 2922 (C-H Ar), 1710 (C=O, COOCH3), 1685 (C=O, quinoline), 1564, 1469 (C=C Ar), 1380 (C-N st), 1260 (C=O-C).

Comp. 14a: Yield: (68%, 1.90 g). MP-248-250 °C. 1H NMR (300 MHz, CDCl3) δppm: 1.14-1.25 (t, 3H, CH3), 3.40 (br-s, 4H, piperazine 2CH2), 3.60 (br-s, 4H, piperazine 2CH2), 3.80 (s, 3H, Ph OCH3), 3.90 (s, 3H, ester OCH3), 4.10 (q, 2H, CH2), 7.42-7.62 (m, 5H), 7.90-7.97 (d, 1H), 8.68 (s, 1H, N-C=C-H). IR (KBr) cm⁻¹: 2922 (C-H Ar), 1710 (C=O, COOCH3), 1682 (C=O, quinoline), 1564, 1470 (C=C Ar), 1380 (C-N st), 1265 (C=O-C).

1-Ethyl-6-fluoro-1, 4-dihydro-4-oxo-7-(substituted piperazin-1-yl) quinoline-3-carboxylic Acid (7-14): A solution of methyl-1-ethyl-6-fluoro-1, 4-dihydro-4-oxo - 7 - (substituted piperazin-1-yl) quinoline-3-carboxylate (2.1 m mol) in methanol (10 ml), water (4.2 ml), LiOH.H2O (0.34 ml, 8.10 m mol) was added, shaken at room temperature for 6 h. TLC showed completion of starting material. The reaction mixture was quenched with water, washed with ethyl acetate. The aqueous layer was nullifying with 1N HCl, juiced with ethyl acetate and dried over sodium sulphate, concentrated under reduced pressure.

The obtained basic product was refined by silica gel column chromatography using 30% ethyl acetate in hexane as an eluent to get 1-ethyl-6-fluoro-1, 4-dihydro-4-oxo-7-(substituted piperazin-1-yl) quinoline-3-carboxylic acid as white solid.

Comp. 7: Yield (65%, 0.43 g). MP- 168 -170 °C. 1H NMR (300 MHz, DMSO-d6) δppm: 1.39-1.43 (t, 3H, CH3), 2.87-2.90 (s, 4H, piperazine 2CH2), 3.21-3.24 (s, 4H, piperazine 2CH2), 4.55-4.62 (q, 2H, CH2), 7.12-7.15 (d, 1H, Ar H), 7.86-7.90 (d, 1H, Ar H), 8.94 (s, 1H, C=C-H), 15.20 (s, 1H, COOH). IR (KBr) cm⁻¹: 3640 (OH, COOH), 3450 (N-H st), 2910 (C-H st, alkyl), 1710 (C=O, COOH), 1685 (C=O, quinoline), 1590, 1610 (C=C Ar), 1410 (C-N st), 1370 (C-N=C=). MS: m/z (rel int%) 319 (24) [M+] 296 (18), 290 (24), 278 (45), 255 (48, 219 (56), 199 (100), 182 (65), 156 (68), 152 (73), 130 (70), 113 (78), 108(48). CHN Analysis: C16H18FN3O3 Cal: C 60.12%, H 5.63%, N 13.15%, Found: C 60.16%, H 5.62%, N 13.16%,

Comp. 8: Yield: (60%, 0.40 g). MP- 146 -148 °C. 1H NMR (300 MHz, DMSO-d6) δppm: 1.22 (q, 1H, near to CH3), 1.40 (d, 3H, CH3), 1.42-1.46 (t, 3H, CH3), 2.88-2.90 (s, 4H, piperazine CH2), 3.80 (m, 1H, NH), 3.21-3.20 (s, 2H, piperazine CH2), 4.55-4.65 (q, 2H, CH2), 7.12-7.15 (d, 1H, Ar H), 7.86-7.90 (d, 1H, Ar H), 8.94 (s, 1H, C=C-H), 15.20 (s, 1H, COOH), IR (KBr) cm⁻¹: 3550 (COOH), 3450 (N-H st), 2910 (C-H st, alkyl), 1710 (C=O, COOH), 1680 (C=O, quinoline), 1592, 1610 (C=C Ar), 1412 (C-N st), 1372(C-N=C=). MS: m/z (rel int%) 333 (18) [M+], 296 (25), 288 (16), 274 (41), 255 (55), 219 (58), 199 (100), 176 (65), 156 (66), 154 (70), 132 (75), 116 (88), 106 (58). CHN Analysis: C17H22FN3O3 Cal: C 61.25%, H 6.05%, N 12.61%, Found: C 60.30%, H 6.10%, N 12.68%.

Comp. 9: Yield: (58%, 0.38 g). MP- 180 -182 °C. 1H NMR (300 MHz, DMSO-d6) δppm: 1.20 (q, 2H, near to CH3), 1.28 (d, 6H, 2CH3), 1.42-1.45 (t, 3H, CH3), 2.88-2.90 (s, 4H, piperazine CH2), 3.80 (m, 1H, NH), 4.58-4.65 (q, 2H, CH2), 7.12-7.15 (d, 1H, Ar H), 7.86-7.90 (d, 1H, Ar H), 8.94 (s, 1H, C=C-H), 15.20 (s, 1H, COOH). IR (KBr) cm⁻¹: 3550 (COOH), 3450 (N-H st), 2910 (C-H st, alkyl), 1710 (C=O, COOH), 1680 (C=O, quinoline), 1592, 1610 (C=C Ar), 1412 (C-N st), 1372(C-N=C=). MS: m/z (rel int%) 347 (22) [M+], 312 (25), 292 (19), 272 (38), 258 (52), 214 (52), 198 (100), 178 (68), 151 (60), 142 (78), 132 (74), 114 (82), 104(38). CHN Analysis: C18H22FN3O3 Cal: C
Comp. 10: Yield: (62%, 0.41 g). MP-151-153 ºC. 1H NMR (300 MHz, DMSO-d6) δ: ppm 1.35-1.45 (t, 3H, CH3), 3.82 (s, 3H, N-CH3), 2.88-2.95 (s, 4H, piperazine CH2), 3.21-3.24 (s, 2H, piperazine CH2), 4.55-4.65 (q, 2H, CH2), 7.12-7.15 (d, 1H, Ar H), 7.86-7.90 (d, 1H, Ar H), 8.94 (s, 1H, C=H), 15.20 (s, 1H, COOH). IR (KBr) cm⁻¹: 3550 (OH st, COOH), 2910 (CH st, alkyl), 1710 (C=O, COOH), 1680 (C=O, quinoline), 1590, 1610 (C=C aromatic), 1420 (C=N st), 1374 (C-N=C=). MS: m/z (rel int %) 333 (18) [M+], 318 (20), 292 (18), 266 (32), 258 (50), 222 (100), 200 (60), 178 (68), 158 (45), 152 (74), 136 (80), 116 (87), 98 (56). CHN Analysis: C17H20FN3O3 Cal: C 61.25%, H 6.05%, N 12.61%. Found: C 61.30%, H 6.10%, N 12.70%.

Comp. 11: Yield: (64%, 0.42 g). MP-146-148 ºC. 1H NMR (300 MHz, DMSO-d6) δ: ppm 01.16 (d, 3H, CH3), 1.18-1.26 (t, 3H, CH3), 1.31 (q, 1H, piperazine H), 1.45-1.48 (t, 3H, CH3), 3.10 (br-s, 4H, piperazine CH2), 3.40 (br-s, 2H, piperazine CH2), 3.90 (q, 2H, CH2), 4.55-4.65 (q, 2H, CH2), 7.60-7.75 (d, 1H, Ar H), 8.74-7.98 (d, 1H, Ar H), 8.66 (s, 1H, N=C=H), 15.20 (s, 1H, COOH). IR (KBr) cm⁻¹: 3550 (OH st, COOH), 2930 (C=H Ar), 1710 (C=O, COOH), 1620 (C=O quinoline), 1564, 1494 (C=C Ar), 1460 (C-N st), 1384 (C-N=C=). MS: m/z (rel int %) 361 (28) [M+], 352 (18), 322 (20), 296 (31), 272 (38), 248 (100), 224 (51), 202 (58), 188 (40), 162 (70), 148 (76), 126 (78), 102 (45), 92(40). CHN Analysis: C19H22FN3O3 Cal: C 63.14%, H 6.69%, N 11.63%. Found: C 63.20%, H 6.75%, N 11.70%.

Comp. 12: Yield (68%, 0.45 g). MP-160-162 ºC. 1H NMR (300 MHz, DMSO-d6) δ: ppm 1.14-1.26 (t, 3H, CH3), 1.26 (q, 2H, piperazine H), 1.35-1.40 (t, 3H, CH3), 1.48 (d, 6H, 2CH3), 2.90 (br-s, 4H, piperazine CH2), 3.90 (q, 2H, CH2), 4.58-4.66 (q, 2H, CH2), 7.50-7.62 (d, 1H, Ar H), 7.88-7.90 (d, 1H, Ar H), 8.64 (s,1H,N=C=H), 15.22 (s, 1H, COOH). IR (KBr) cm⁻¹: 3550 (O-H st, COOH), 2930 (C=H Ar), 1710 (C=O, COOH), 1630 (C=O quinoline), 1565, 1490, (C=C Ar), 1456(C=N st), 1380 (C-N=C=). MS: m/z (rel int %) 375 (16) [M+], 366 (21), 346 (23), 320 (29), 292 (30), 282 (38), 272 (56), 254 (62), 199 (100), 158 (82), 136 (72), 118 (76), 102 (40), 90 (32). CHN Analysis: C20H26F3N3O3 Cal: C 63.98%, H 6.98%, N 11.19%. Found: C 64.04%, H 7.02%, N 11.25%.

Comp. 13: Yield (72%, 0.48 g). MP-225-227 ºC. 1H NMR (300 MHz, DMSO-d6) δ: ppm 1.14-1.22 (t, 3H, CH3), 3.40 (br-s, 4H, piperazine 2CH2), 3.60 (br-s, 4H, piperazine 2CH2), 3.90 (q, 2H, CH2), 7.42-7.62 (m, 4H, Ar H), 7.90-7.97 (d, 1H, ArH), 8.68 (s, s, 1H, N=C=H), 15.20 (s, 1H, COOH). IR (KBr) cm⁻¹: 3550 (O-H st, COOH), 2922 (C=H Ar), 1720 (C=O, COOH), 1710 (C=O, CCON), 1628 (C=O, quinoline), 1564, 1469(C=C Ar), 1380(C-N st). MS: m/z (rel int %) 492 (12) [M+], 480 (11), 462 (14), 446 (21), 412 (19), 395 (22), 378 (26), 332 (20), 284 (31), 272 (26), 240 (41), 214 (43), 196 (100), 165 (30), 146 (32), 120 (46), 98 (46). CHN Analysis: C23H22FN3O3 Cal: C 56.11%, H 4.09%, N 08.53%. Found: C 56.20%, H 4.16%, N 08.62%.

Comp. 14: Yield (76%, 0.50 g). MP-228-230 ºC. 1H NMR (300 MHz, DMSO-d6) δ: ppm 1.14-1.25 (t, 3H, CH3), 3.40 (br-s, 4H, piperazine 2CH2), 3.60 (br-s, 4H, piperazine 2CH2), 3.90 (q, 2H, CH2), 7.42-7.62 (m, 5H, Ar H), 7.90-7.97 (d, 1H, Ar H), 8.68 (s, s, 1H, N=C=H), 3.82 (s, 3H, OCH3). IR (KBr) cm⁻¹: 3550 (O-H st, COOH), 2922 (C=H Ar), 1720 (C=O, COOH), 1710 (C=O, CCON), 1628 (C=O, quinoline), 1564, 1470 (C=C Ar), 1380(C-N st). MS: m/z (rel int %) 453(11) [M+], 442 (12), 418 (16), 402 (16), 391 (18), 370 (24), 345 (21), 308 (24), 284 (33), 272 (21), 242 (44), 214 (32), 196 (100), 166 (30), 148 (36), 120 (48), 94 (66). CHN Analysis: C24H24F3N3 Cal: C 63.57%, H 5.33%, N 09.27%. Found: C 63.65%, H 5.40%, N 09.35%.

**Biological Assays:**

**Cells and Viruses:** Assay was executed at the Molecular Immuno pharmacology Laboratory, Kunming Zoology Institute, Chinese Academy of Science. Reagents made available in laboratory as HEPES (N-2 (hydroxyethyl) piperazine-N'-ethanesulfonic acid) and MTT (3, (4, 5 dimethyl thiazol-2-yl) -2, 5-diphenyl tetrazolium bromide) and DMF (N, N'- Dimethyl formamide).

Penicillin, Streptomycin sulfate, Glutamine were procured from Sigma; 2-ME (2-Mercapto ethanol) was obtained from Bio-Rad. RPMI-1640 and fetal bovine serum (FBS) were obtained from Gibco. C8166 cells and HIV-1IIIB were kindly contributed by the Medical Research Council, AIDS Regent
Project. The cells were sustained at 37 °C in 5% CO₂ in RPMI-1640 medium supplemented with 10% heat-inactivating FBS ( Gibco). HIV-1IIIB was ready from the floating of H9/HIV-1IIIB cells. The 50% HIV-1 tissue culture infectious dose (TCID50) in C8166 cells was firm and designed by Reed and Muench method 14-15. Virus stock was maintained in a small fraction at -76 °C. The virus titer stock was 1.0 × 108 TCID50 per ml.

**In-vitro Assays:**

**Inhibition of Syncytia Formation:** The syncytia formation assay was used to measure the inhibition effect of samples on acute HIV-1 infection. In the attendance or nonexistence of dissimilar sample concentrations, 4, 1104, 8166 cells were contaminated with HIV-1 at a multiplicity of 0.04 infections (MOI) and grown for 72 h in 96-well plates at 37 °C in 5% CO₂. As an affirmative control, NVP was used. Cytopathic effect (CPE) was measured at 72 h post-infection by together with the number of syncytia (multinucleated giant cell) under an inverted microscope (100) in each well of 96 well plates. The blockage percentage of syncytia formation was calculated by the percentage of syncytia number in the sample being treated compared to the percentage in the control being infected. An effective concentration of 50 percent (EC₅₀) was calculated 16.

**Cytotoxicity:** MTT colorimetric assay checked the cell toxicity of compounds on C8166 cells.15 Momentarily, 100 μl of 4 possibly 105 cells were plated in 96 well plates, 100 μl of diverse compound concentrations were added and constructed at 37 °C in a soaked atmosphere of 5% CO₂ for 72 h. Discard 100 μl airy liquid, added and nurtured MTT reagent for 4 h, added 50% DMF, 15% SDS of 100 μl. After the total ending of the formazan, a Bio Tek ELx 800 ELISA reader analyzed the plates at 570 nm/630 nm. The attentiveness of cytotoxicity (CC₅₀) was calculated at 50%.

**HIV-1 Integrase Inhibition Assay:** The enzymatic examinations were done with small changes as per the above method 17. We used an enzyme-linked immunosorbent assay (ELISA) adapted from Hwang et al.14 to decide the susceptibility of the HIV-1 IN enzyme to different compounds. The assay adopted was an oligonucleotide substrate for which one oligonucleotide (5’-ACTGCTAGAGA TTTTCACACTGAATAAAAGGGTC-3’) is designated with biotin at the 3’ end and the other oligonucleotide (5’-GACCTTTTATGTAGTGTG GAAAATCTCTAGCAGT-3’) is labeled with digoxigenin at the 5’ end. The strand transfer examination, a dissected oligonucleotide substrate (the second oligonucleotide lacks GT [underlined]) at the 3’ end) was accounted. The IN enzyme was thinned in 750 mM NaCl, 10 mM Tris (pH 7.6), 10% glycerol, and 1 mM β-mercaptoethanol. To carry out the reaction, 4 μl of thinned IN (corresponding to a concentration of 1.6 μM) and 4 μl of annealed oligonucleotides (7 nM) were mixed in a ending reaction volume of 40 μl containing 10 mM MgCl₂, 5 mM dithiothreitol, 20 mM HEPES (pH 7.5), 5% polyethylene glycol and 15% dimethyl sulfoxide. As such, the ending concentration of IN in this assay was 160 nM. The reaction was passed out for 1 h at 37 °C. Reaction products were altered with 30 mM NaOH and realized by ELISA on avidin-coated plates.

For shaping the effect of compounds on the 3’processing activity a usual cleavage assay with the finding of products by altering gel electrophoresis was done as mentioned earlier16-17. In a few words, 0.2 pmol of the radioactively labeled oligonucleotide substrate (INT1, 32P-5’ TGTGGAAA ATCTCTAGCAGT 3’; INT2, 5’ACTGCTAGAGA TTTTCACACA 3’) and 10 nmol IN in a final volume of 10 μl was constructed for 1 h at 37 o C. The last reaction mixture enclosed 20 mM HEPES pH 7.5), 5 mM dithiothreitol (DTT), 10 mM MgCl₂, 0.5% (v/v) polyethylene glycol 8000, 15% DMSO, IN was thinned earlier in 750 mM NaCl, 10 mM Tris (pH 7.6), 10% glycerol and 1 mM β mercaptoethanol. The reactions were blocked by the accumulation of formamide loading buffer (95% formamide, 0.1% xylene cyanol, 0.1% xylene cyanol, 0.1% bromophenol blue and 0.1% sodium dodecyl sulfate). The specimen was full on a 15% denaturating polyacrylamide/urea gel. The level of 3’ processing or DNA strand transfer depended on measuring the own amounts of -2 bands or strand transfer products comparative to the intensity of the sum radioactivity present in the lane. The statistics were resolute using the OptiQuant Acquisition and Analysis software (Perkin Elmer Corporate, Fremont, CA).
**Drug Susceptibility Assay:** The MTT examination was done to check the suppression effect of antiviral drugs on the HIV-1 induced CPE in MT-4 cell culture. This examination is placed on the drop of the yellow-colored 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) by mitochondrial dehydrogenase of metabolically lively cells to a blue formazan derivative, which can be considered spectro-photometrically. The 50% cell culture infective dose of the HIV strains was firm by titration of the virus stock using MT-4 cells.

The compound weakness assays, MT-4 cells were infected with 100 to 300 50% cell culture infective doses of the HIV strains in the presence of fivefold successive strength of the antiviral drugs. The attention of the compound achieving 50% protection against the CPE of HIV, which is defined as the 50% effective concentration (IC50), was firm. The amount of the compound killing 50% of the MT-4 cells, which is defined as the 50% cytotoxic concentration (CC50), was determined as well.

**Molecular Modelling:**

**Docking:** For ligand docking studies in the HIV-1 Integrase pouch, the molecular docking tool, GLIDE was used. The structure of HIV-1 Integrase crystal was received from the database of proteins, PDB ID: 1QS4. In two steps, preparation and refinement, the protein preparation was performed using the ' protein preparation wizard in Maestro 8.0. On co-crystallized ligand centering grids were generated. The ligands were prepared by the maestro build panel and ready by the Ligprep 2.2 module, which uses the OPLS 2005 force field to create the low energy ligands conformer. The low energy conformation of the ligands was selected and docked with standard precision (SP) docking mode into the grid generated from protein structure.

**RESULTS AND DISCUSSION:**

**Design of the Analogues:** The series of compounds to be considered for study was carried out using the virtual screening protocol. Considering the pharmacophoric requirements and the Elvitegravir standard compound, the database of Zinc was explored. The compounds screened in silico were then tested for the five fold Lipinsky rule to assess drug-likeness, which becomes a crucial means for drug innovation. SciFinder has been checked for the novelty of compounds in terms of HIV-1 Integrase inhibitory activity. These virtually screened hits have been synthesized and evaluated for their inhibitory potential along with their derivatives. It was found that for HIV-1 Integrase activity, diketoquinolines were not much explored. We, therefore, studied the motif of diketoquinoline for inhibition of Integrase. Two series of the compound were synthesized as diketoquinoline analogs.

**Chemistry:** The target diketoquinolines 1-14 were prepared from the commercially procured intermediates such as methyl-7-chloro-1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxoquinoline-3-carboxylate, methyl-7-chloro-1-ethyl-6-fluoro-1, 4-dihydro-4-oxo Quinoline-3-carboxylate and 1-ethyl-6-fluoro-1, 4-dihydro-4-oxo-7-(piperazin-1-yl) quinoline-3-carboxylate. The fabricated way is marked in Scheme 1.

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**Scheme 1:** REAGENTS AND CONDITIONS: (A) ACETONITRILE, DIPEA, SUBSTITUTED PIPERAZINE, REFLUXED 24 H, ETHYL ACETATE; (B) METHANOL, WATER, LIOH.H2O, STIRRED 6 H

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All the carboxylate compounds were reacted with substituted piperazine, benzoic acid, via substitution of chlorine by piperazine nitrogen in presence of DIPEA (N, N-di isopropyl ethyl amine) to produce the intermediate compound in excellent yield. In the same way, ring extension at the nitrogen of piperazine was carried out by substituted benzoic acid. The ester linkage in intermediate compound (COOCH₃) is hydrolyzed to a carboxylic acid (COOH) in an alkaline medium in the attendance of melted lithium hydroxide to yield the target compounds 1-14. The confirmation of removal of C-Cl and attachment of substituted compounds and conversion of carboxylate to carboxylic acid was verified by spectral analysis.

**Biological Activity:** Diketoquinoline derivatives 1-14 were tested in vitro for their cytotoxicity assay and inhibition of syncytia formation using MTT and CPE method. CC₅₀ and EC₅₀ reading was obtained from replica experiments in µM and selectivity index was also planned by dose-reaction loop Table 1.

**TABLE 1: CYTOTOXICITY (MTT) AND INHIBITION OF SYNCTIUM FORMATION (CPE) ACTIVITIES OF COMPOUNDS 1-14**

<table>
<thead>
<tr>
<th>Comp. no.</th>
<th>Method</th>
<th>CC₅₀ (µM)</th>
<th>EC₅₀ (µM)</th>
<th>Therapeutic index (TI)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>MTT</td>
<td>148</td>
<td>—</td>
<td>242</td>
</tr>
<tr>
<td></td>
<td>CPE</td>
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<td>—</td>
<td>260</td>
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<tr>
<td></td>
<td>CPE</td>
<td>—</td>
<td>0.50</td>
<td></td>
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<tr>
<td>3</td>
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<td>CPE</td>
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<td>—</td>
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<td>MTT</td>
<td>&gt;200</td>
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<td>714</td>
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</table>

As per the previous study for Diketoquinoline derivative series 27 acidic derivatives were more potent for a maximum sensation against integrase. The alternate of a hydrophobic ring from C6 of Elvitegravir by Flourine and C7 by substituted piperazine moiety did not direct to major upgrading in the HIV-1 integrase blocking effect. Substitution at quinoline N by ethyl and piperazine N by hydrophobic phenyl carbonyl group resulted in compounds 13 and 14 which showed IC₅₀ of 0.13 and 0.12 µM against integrase enzyme respectively. This suggests that substitution of quinoline N by alkyl and a hydrophobic moiety at C6 (Elvitegravir) or at C7 piperazine N affect the ability of the inhibitors to bind with integrase enzyme. Other substitution does not make any significant interaction with HIV-1 integrase enzyme Table 2.

**Molecular Docking:** The putative binding mechanism of the synthesized compounds was investigated using molecular docking studies. The
docking studies of the designed and synthesized molecules were performed using Schrodinger Suite. The molecular docking device, GLIDE was utilized for ligand docking observation into the HIV-1 integrase pouch. The crystal formation of HIV-1 integrase was taken from the protein data bank, PDB ID: IJPS4.

The preparation of protein was done by device ‘protein preparation wizard’ in Maestro 8.0 in two ladders such as groundwork and improvement. Grids were generated centering on the co-crystallized ligand. The ligands were established by using the maestro build panel and arranged by the Ligprep 2.2 module that generates the small power conformer of ligands using the OPLS 2005 force field. The small power arrangement of the ligands was chosen and docked into the lattice prepared from protein arrangement using standard precision (SP) docking manner.

As per the literature, the active site comprises of Thr 66, Lys 156, Lys 159 and DDE motif (Asp 64, Asp 116 and Glu 152). The docked poses revealed the interaction of a few ligands with desired amino acids. The standard drug Elvitegravir showed a docking score of -8.93 and displayed interactions with lys 156, Asn 155, Lys 159 and Thr 66 Fig. A. When Elvitegravir and Nevirapine were docked in the same active site, they displayed comparable docking scores and interaction patterns. Raltegravir revealed hydrogen bonding with Asp 116 while Nevirapine showed hydrogen bonding with Asp 64. The synthesized compounds which displayed fair integrase inhibition were also docked in order to ascertain the interactions and were compared with a standard pose. Compound 14 exhibited maximum potency with EC_{50} of 0.12 mM and 0.25 mM in enzyme inhibition and cell line assay respectively. Its methoxy group was involved in hydrogen bonding with Gln 146. It also showed interactions with Lys 156, Lys 159 and Asp 116 Fig. B. Other compounds were also evaluated for ligand-protein interaction and compared with the standard drug.

The unsubstituted piperazine in compound 1 favored the hydrogen bonding interaction with Asp 116 through the –NH of piperazine ring system while the carbonyl group on the quinoline system displayed hydrogen bond with Thr 66. Positioning two methyl substituents on the piperazine system (compound 3) helped a molecule align in such a manner that the carboxyl group extended its interactions with Lys 156 and Lys 159.

Its EC_{50} value was 0.22 mM and 0.48 mM in enzyme inhibition and cell line assay respectively. The series with compounds 7-14 having N-ethyl substituted quinoline also displayed a similar type of interaction pattern with improved activity than the previous series. The docking analysis also shows that though the compounds favored interactions with desired amino acids but none of the compounds could show interactions with the important Mg^{2+} ions i.e. Mg1001 and Mg1002.

Compound 8 displayed strong hydrogen bonding interactions through its carboxyl group with Lys 156, Lys 159 and piperazine NH showed interaction with Glu 92. Its EC_{50} value was 0.16 mM. A similar type of interaction pattern was revealed by other compounds of this series. Some additional interactions were observed with Asp 64 and Asp 116 in the compounds 9, 10, 11, 12, 13 and 14. The activity profile was concomitant with the docking analysis. The docking analysis also revealed that the interaction pattern of the designed compounds was similar to the standard drug Elvitegravir. The docking scores are given in Table 2 and Fig. 2 represents the docked view.

<table>
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<tr>
<th>Comp no.</th>
<th>Docking score</th>
<th>(µM) EC_{50}</th>
<th>(µM) CC_{50}</th>
<th>SI</th>
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</table>

Not Determined (ND); Selective Index (SI)

Note: When data indicate >200 for EC_{50} and CC_{50} it means that the compounds were neither active not toxic at 200 µM which is the highest concentration we can test to stay in the DMSO tolerance levels. When data indicates a number lower than 200 for EC_{50} and then the same number with the equality sign in the CC_{50} it means that we observed toxicity at this concentration.
A. DOCKED POSE VIEW OF ELVITEGRAVIR IN THE ACTIVE SITE OF HIV-1 IN (PDB ID: 1QS4). ACTIVE SITE NUCLEIC ACID RESIDUES WERE REPRESENTED AS STICKS. REST OF THE NUCLEIC ACID RESIDUES ARE SUPPRESSED FOR CLARIFICATION PURPOSE. HYDROGEN BOND INTERACTIONS ARE REPRESENTED BY DOTTED LINES

B. DOCKED POSE VIEW OF COMPOUND 14 IN THE ACTIVE SITE OF HIV-1 IN (PDB ID: 1QS4). ACTIVE SITE NUCLEIC ACID RESIDUES WERE REPRESENTED AS STICKS. REST OF THE NUCLEIC ACID RESIDUES ARE SUPPRESSED FOR CLARIFICATION PURPOSE. HYDROGEN BOND INTERACTIONS ARE REPRESENTED BY DOTTED LINES

C. DOCKED POSE VIEW OF COMPOUND 3 IN THE ACTIVE SITE OF HIV-1 IN (PDB ID: 1QS4). ACTIVE SITE NUCLEIC ACID RESIDUES WERE REPRESENTED AS STICKS. REST OF THE NUCLEIC ACID RESIDUES ARE SUPPRESSED FOR CLARIFICATION PURPOSE. HYDROGEN BOND INTERACTIONS ARE REPRESENTED BY DOTTED LINES
CONCLUSION: To make clear the precise binding mode of the upper-class diketoacid quinolonyl chain of compounds, fresh derivatives were prepared by altering the 6-position with Fluorine atom instead of Elvitegravir’s replaced hydrophobic benzyl moiety and replacing piperazine, benzoic acid, 2-phenoxycetic acid and benzene-1-sulfonyl chloride at 7-position substitution. For their enzymatic action, these compounds have been examined.

Replacing Elvitegravir C6 hydrophobic ring with F and C7 by piperazine group does not result in a major development in integrase blocking of HIV-1. Substitution at quinoline N by ethyl and piperazine N by hydrophobic phenyl carbonyl group 13, 14 showed IC50 value 0.13 and 0.12 µM against integrase enzyme. This result suggests that substitution of quinoline N by alkyl and a hydrophobic moiety at C6 (Elvitegravir) or at C7 piperazine N by phenyl carbonyl affect the ability of the inhibitors to bind with integrase enzyme. Other substitution does not make any significant interaction with HIV-1 integrase enzyme. Hence further lead optimization studies will be required to find more potent HIV-1 Inhibitors.

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CONFLICTS OF INTEREST: Authors articulate that they neither have any disagreement of interest.

REFERENCES: