4-substituted 2-Hydroxyisoquinoline-1,3(2*H*,4*H*)-diones as a novel class of HIV-1 integrase inhibitors

Supporting information

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1. Docking studies

Previous work revealed that the 2-hydroxyisoquinoline-1,3(2*H*,4*H*)-dione scaffold complexes magnesium as the enol or enolate form.[1] Preliminary calculations using the SPARC online calculator[2] indicate that such enols are deprotonated in aqueous media at physiological pH in the presence of magnesium cations, hence we chose to model our ligands as the dianionic enolate form. Considering the difficulty to optimize the geometry of our scaffold with molecular mechanics or semi-empirical methods, ligand 33 and dolutegravir were created and minimized at the HF/3-21G level using the Gaussian 03 package.[3]

Our previous docking protocol was adapted to the 3S3M PDB of the PFV IN intasome in complex with dolutegravir. The co-crystallized ligand was extracted and the protein was prepared by adding hydrogens and removing water molecules and irrelevant heteroatoms in Accelrys DS Visualizer 3.0.[4] Magnesium cations were set to allow octahedral geometry. Docking calculations were carried out using the CCDC GOLD docking suite[5] with the active site defined as a sphere containing all atoms within 15 Å of the X-ray ligand centroid. The CHEMPLP fitness function[6] was used at default settings. After manual editing of atom and bond types in *mol2* files, dolutegravir and compound 33 were submitted to 1000 docking runs using a 0.75 Å RMSD clustering. The resulting docking poses were analyzed in DS Visualizer and selected poses were rendered using the UCSF Chimera software.[7] The docking procedure was first validated superimposing the X-ray ligand and the best obtained pose for dolutegravir (see figure 1).

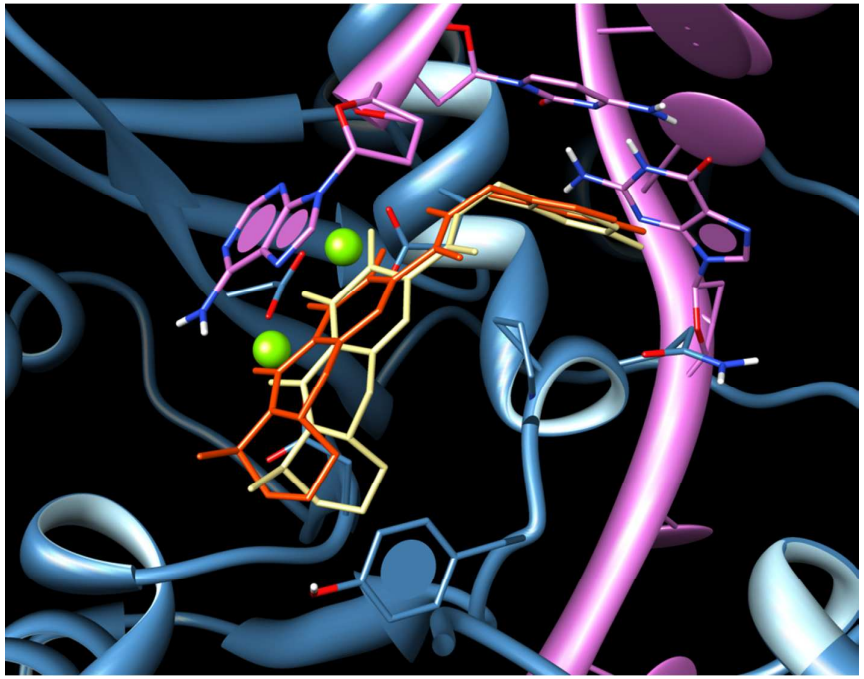

Figure 1. Superimposition of the X-ray position of dolutegravir (orange) and of the best obtained docking pose (cream). IN is depicted in blue, viral DNA in pink and magnesium cations in green.

2. Experimental

2.1. Chemistry - General

All reagents and solvents were purchased from Aldrich-Chimie (Saint-Quentin-Fallavier, France) of ACS reagent grade and were used as provided. Thin layer chromatography analyses were performed on plastic sheets precoated with silica gel 60F254 (Merck). SiO_2, 40-63 mesh (Merck) or 30 μm HP-Silprepacked SNAP columns (Biotage) were used for column chromatography. NMR spectra were obtained on an AC 300 Bruker spectrometer in the appropriate deuterated solvent with TMS as internal reference. Chemical shifts are reported in δ units (ppm) and are assigned as singlets (s), doublets (d), doublets of doublets (dd), triplets (t), quartets (q), quintets (quin), sextuplets (sext), multiplets (m), and broad signals (br). Melting points were obtained on a Reichert Thermopan melting point apparatus, equipped with a microscope and are uncorrected. Mass spectra (ElectroSpray Ionization, ESI) were recorded on a Micromass Quattro II spectrometer. HRMS measurements were made on an Apex Qe 9.4 T Bruker Daltonics spectrometer. Analytes dissolved in methanol (3 mM solutions) were diluted with a water/methanol/formic acid solution (50/50/0.1, % v/v) to afford 3 μM solutions and infused into the mass spectrometer nano ESI source in positive mode at a rate of 1 μL/min.

*2.2. Synthesis of the amide precursors, **2-4***

Methyl 2-{1-[(benzyloxy)amino]-3-methoxy-1,3-dioxopropan-2-yl}benzoate 2. BOP (1.69 g, 4.0 mmol) was added to an ice-cooled solution of 3-methoxy-2-[2-(methoxycarbonyl)phenyl]-3-oxopropanoic acid **1**[8](1.00 g, 4.0 mmol), *O*-benzylhydroxylamine (0.49 g, 4.0 mmol) and 4-methylmorpholine (2.2 mL, 20.0 mmol) in a minimum of CH_2Cl_2. After 30 min stirring at 0 °C and 3 h at room temperature, the mixture was washed with 1.0 M HCl, 1.0 M $NaHCO_3$ solutions and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. After column chromatography (eluent: petroleum ether /AcOEt, 70/30), the product was obtained as a pale yellow oil (69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.63 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 4.79 (s, 2 H, CH_2), 5.20 (s, 1 H, CH), 7.18-7.28 (m, 5 H, H_{Ar}), 7.33 (td, ^3J= 7.5 Hz, ^4J= 1.2 Hz, 1 H, H_{Ar}), 7.48 (td, ^3J= 7.5 Hz, ^4J= 1.2 Hz, 1 H, H_{Ar}), 7.57 (dd, ^3J= 7.5 Hz, ^4J= 1.2 Hz, 1 H, H_{Ar}), 7.87 (dd, ^3J= 7.5 Hz, ^4J= 1.2 Hz, 1 H, H_{Ar}), 9.64 (s, 1 H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.5 (OCH_3), 52.7 (OCH_3), 52.8 (CH), 78.0 (OCH_2), 116.7 (C), 128.1 (CH), 128.5 (2CH), 128.6 (CH), 128.8 (C), 129.3 (2CH), 130.8 (CH), 131.9 (CH), 132.8 (CH), 134.5 (C), 165.4 (CO), 168.3 (CO), 169.3 (CO); ESI-MS: m/z = 358 $(M+H)^+$.

Methyl 2-{1-Amino-3-methoxy-1,3-dioxopropan-2-yl}benzoate 3. Thionyl chloride (3.5 mL, 47.0 mmol) was added at 0 °C dropwise to a solution of 3-methoxy-2-[2-(methoxycarbonyl)phenyl]-3-oxopropanoic acid **1**(1.20 g, 4.7mmol) in ethyle acetate (15 mL). The solution was refluxed for 1 h 30 min and concentrated *in vacuo*. The residue was dissolved in dichloromethane (15 mL) and ammoniac was bubbled for 15 min until saturation of the solution and appearance of a precipitate. A large volume of dichloromethane (100 mL) was added. The organic phase was washed with water. After concentration *in vacuo*, the residue was taken up in ether and the white solid was filtrated.Yield: 75%; mp 130-133 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.65 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3),

5.25 (s, 1 H, CH),), 6.20 (bs, 1 H, NH), 7.27 (bs, 1 H, NH),7.38 (td, ^3J= 7.5 Hz, ^4J= 1.5 Hz, 1 H, H_{Ar}), 7.52 (td, ^3J= 7.5 Hz, ^4J= 1.5 Hz, 1 H, H_{Ar}), 7.62 (dd, ^3J= 7.5 Hz, ^4J= 1.5 Hz, 1 H, H_{Ar}), 7.93 (dd, ^3J= 7.5 Hz, ^4J= 1.5 Hz, 1 H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 52.4 (OCH_3), 52.7 (OCH_3), 55.2 (CH), 128.0 (CH), 129.0 (C_{IV}), 130.8 (CH), 131.8 (CH), 132.7 (CH), 135.4 (C_{IV}), 168.0 (CO), 169.9 (CO), 170.2 (CO); ESI-MS: m/z = 252 $(M+H)^+$.

Methyl 2-{1-Methylamino-3-methoxy-1,3-dioxopropan-2-yl}benzoate 4.

Thionyl chloride (2.3 mL, 31.0 mmol) was added at 0 °C dropwise to a solution of 3-methoxy-2-[2-(methoxycarbonyl)phenyl]-3-oxopropanoic acid **1**(1.58 g, 6.2 mmol) in ethyle acetate (20 mL). The solution was refluxed for 1 h 30 min and concentrated *in vacuo*. The residue was dissolved in ethyle acetate (20 mL) and a solution of methylamine hydrochloride (2.12 g, 31.0 mmol), diisopropylethylamine (6.6 mL, 63.0 mmol) in ethyle acetate (10 mL) was added at 0 °C. After 2 h stirring at room temperature, the organic phase was washed with 1.0 M HCl, 1.0 M $NaHCO_3$ solutions and dried over sodium sulfate. After concentration *in vacuo*, the residue was taken up in ether and the beige solid was filtrated. Yield: 85%; mp145 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.22 (d, ^3J= 6.5 Hz, 3 H, CH_3),3.69 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 5.30 (s, 1 H, CH), 7.19 (d, ^3J = 6.5 Hz, 1 H, NH), 7.38 (td, ^3J= 7.5 Hz, ^4J= 1.5 Hz, 1 H, H_{Ar}), 7.52 (td, ^3J= 7.5 Hz, ^4J= 1.5 Hz, 1 H, H_{Ar}), 7.62 (dd, ^3J= 7.5 Hz, ^4J= 1.5 Hz, 1 H, H_{Ar}), 7.93 (dd, ^3J= 7.5 Hz, ^4J= 1.5 Hz, 1 H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 39.7 (CH_3), 52.4 (OCH_3), 52.5 (OCH_3), 54.9 (CH), 127.7 (CH), 128.5 (C_{IV}), 130.6 (CH), 131.6 (CH), 132.5 (CH), 135.6 (C_{IV}), 167.3 (CO), 168.2 (CO), 170.2 (CO);ESI-MS: m/z = 266 $(M+H)^+$.

2.3. Cyclization of the amide precursors, ***2-4*** *into the isoquinolines****5-7***

Amides **2-4**(1.0 mmol) were dissolved in a solution of methanol (10.0 mL) and 2.5 M KOH (10.0 mL). After 30 min stirring, the solution was acidified with 2.0 M HCl and extracted three times with ethyle acetate (20.0 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo.*The residue was taken up in ether and insoluble materials were filtrated.

Methyl 2-(benzyloxy)-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate 5

White crystals (99%); mp 126 °C; 82% enol, 18% keto form. **Keto form**; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.77 (s, 3 H, OCH_3), 5.03 (s, 1 H, CH), 5.18 (s, 2 H, CH_2), 7.29-7.65 (m, 8 H, H_{Ar}), 8.25 (1 H, H_{Ar}, dd, ^3J= 7.7 Hz, ^4J= 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 53.8 (CH_3), 54.8 (CH), 78.5 (CH_2), 119.3 (C), 123.5 (C), 127.3 (CH), 128.5 (2CH), 129.2 (CH), 129.3 (CH), 129.5 (CH), 130.0 (2CH), 131.4 (C), 133.5 (C), 134.4 (CH), 160.7 (CO), 162.9 (CO), 171.6 (CO); **Enol form**; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.11 (s, 3 H, OCH_3), 5.29 (s, 2 H, CH_2), 7.29-7.65 (m, 7 H, H_{Ar}),8.45 (m, 2 H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 53.1 (CH_3), 79.0 (CH_2), 84.3 (C_{IV}), 121.2 (C_{IV}), 124.3 (CH), 124.6 (CH), 128.3 (CH), 128.6 (2CH), 129.4 (CH), 130.1 (2CH), 132.9 (C_{IV}), 133.5 (C_{IV}), 133.8 (CH), 158.8 (CO), 163.0 (CO), 173.5 (CO); ESI-MS: *m/z* = 326 $(M+H)^+$.

Methyl 1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate6

White solid (65%); mp228-232 °C; 100% enol form.^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.97 (s, 3 H, OCH_3), 4.11 (s, 3 H, OCH_3), 7.33 (1 H, H_{Ar}, t, ^3J= 7.5 Hz), 7.67 (1 H, H_{Ar}, t, ^3J= 7.5 Hz), 8.13 (1 H, H_{Ar}, d, ^3J= 7.9 Hz),8.37 (1 H, H_{Ar}, d, ^3J= 8.5 Hz), 12.5 (s, 1 H,

NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 52.6 (CH_3), 83.3 (C_{IV}), 121.3 (C_{IV}), 124.0 (CH), 124.1 (CH), 127.2 (CH), 133.4 (CH), 134.7 (C_{IV}), 161.6 (CO), 163.1 (CO), 172.1 (CO); ESI-MS: *m/z* = 220 $(M+H)^+$.

Methyl 2-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate7

White solid (75%); mp201-204 °C; 100% enol form.^{1}H NMR (300 MHz,$CDCl_3$): δ = 3.50 (s, 3 H, NCH_3), 4.00 (s, 3 H, OCH_3), 7.22 (1 H, H_{Ar}, t, ^3J= 7.5 Hz), 7.52 (1 H, H_{Ar}, t, ^3J= 7.5 Hz), 8.28 (2 H, H_{Ar}, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 28.0 (CH_3),52.7 (CH_3), 83.4 (C_{IV}), 120.6 (C_{IV}), 123.9 (CH), 124.2 (CH), 128.3 (CH), 133.3 (CH), 133.5 (C_{IV}), 162.0 (CO), 164.2 (CO), 173.8 (CO); ESI-MS: *m/z* = 234 $(M+H)^+$.

2.4. General procedure for the synthesis of the isoquinoline-4-carboxamides ***8-21***

Intermediate **5-7** (1.0 mmol) and the appropriate amine (2.0 mmol) were dissolved in toluene (100 mL). The mixture was refluxed for 12 h using a Dean Stark apparatus. After cooling, the solution was concentrated *in vacuo*. The residue was dissolved in EtOAc. The organic layer was washed with 2.0 M HCl and dried over Na_2SO_4. After concentration *in vacuo*, the residue was triturated with ether and the precipitate was filtered and dried at room temperature.

***N*-(4-Fluorobenzyl)-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide 8**

White solid (81%); mp 210-215 °C; 100% keto form; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.27 (dd, 1 H, CH_2, ^2J = 11.9 Hz, ^3J = 5.1 Hz), 4.36 (dd, 1 H, CH_2, ^2J = 11.9 Hz, ^3J = 5.1 Hz), 4.92 (s, 1 H, CH), 7.22 (t, 2 H, H_{Ar}, ^3J= 8.6 Hz), 7.35 (dd, 2 H, H_{Ar}, ^3J= 8.2 Hz, ^3J= 5.7Hz), 7.44 (d, 1 H, H_{Ar},^3J = 7.8 Hz), 7.58 (t, 1 H, H_{Ar}, ^3J = 7.5 Hz), 7.75 (t, 1 H, H_{Ar}, ^3J = 7.5 Hz), 8.11 (d, 1 H, H_8, ^3J = 7.8 Hz), 9.29 (t, 1 H, NH, ^3J = 5.3 Hz), 11.6 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 41.9 (CH_2), 54.1 (CH), 115.8 (d, 2CH, $C_{3''}$, $C_{5''}$, $^2J_{C-F}$ = 21.4 Hz), 125.9 (C_{IV}), 127.6 (CH), 128.4 (CH), 128.9 (CH), 129.9 (d, 2 CH, $C_{2''}$, $C_{6''}$, $^3J_{C-F}$ = 8.2 Hz), 134.6 (CH),135.6 (C_{IV}), 137.1 (C_{IV}), 162.2 (d, C_{IV}, $C_{4''}$, $^1J_{C-F}$ = 242.6 Hz), 166.1 (CO), 167.6 (CO), 170.1 (CO); ESI-MS: *m/z*= 313 $(M+H)^+$; HRMS calc for $C_{17}H_{13}FN_2O_3$ 312.09102; found: 312.09227.

***N*-(4-Fluorobenzyl)-2-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide 9**

White solid (85%); mp 185-189 °C; 100% keto form; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.27 (dd, 1 H, CH_2, ^2J = 11.9 Hz, ^3J = 5.1 Hz), 4.36 (dd, 1 H, CH_2, ^2J = 11.9 Hz, ^3J = 5.1 Hz), 4.50 (s, 3 H, CH_3), 4.92 (s, 1 H, CH), 7.22 (t, 2 H, H_{Ar}, ^3J= 8.6 Hz), 7.35 (dd, 2 H, H_{Ar}, ^3J= 8.2 Hz, ^3J= 5.7 Hz), 7.44 (d, 1 H, H_{Ar},^3J = 7.8 Hz), 7.58 (t, 1 H, H_{Ar}, ^3J = 7.5 Hz), 7.75 (t, 1 H, H_{Ar}, ^3J = 7.5 Hz), 8.11 (d, 1 H, H_8, ^3J = 7.8 Hz), 11.6 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.2 (CH_3), 41.9 (CH_2), 54.1 (CH), 115.8 (d, 2CH, $C_{3''}$, $C_{5''}$, $^2J_{C-F}$ = 21.4 Hz), 125.9 (C_{IV}), 127.6 (CH), 128.4 (CH), 128.9 (CH), 129.9 (d, 2 CH, $C_{2''}$, $C_{6''}$, $^3J_{C-F}$ = 8.2 Hz), 134.6 (CH),135.6 (C_{IV}), 137.1 (C_{IV}), 162.2 (d, C_{IV}, $C_{4''}$, $^1J_{C-F}$ = 242.6 Hz), 166.1 (CO), 167.6 (CO), 170.1 (CO); ESI-MS: *m/z*= 327 $(M+H)^+$; HRMS calc for $C_{18}H_{15}FN_2O_3$ 326.10667; found: 326.10451.

***N*-Phenyl-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide 10**

Grey solid (60%); mp 143-146 °C; 100% keto form; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.04 (d, 1 H, C$\underline{H}_2$, ^2J = 9.6 Hz), 5.09 (d, 1 H, C$\underline{H}_2$, ^2J = 9.6 Hz), 5.39 (s, 1 H, CH), 7.13 (t, 1 H, H_{Ar}, ^3J = 7.3 Hz),

7.36 (t, 1 H, H_{Ar}, ^{3}J = 7.7 Hz), 7.42-7.44 (m, 4 H, H_{Ar}), 7.59-7.61 (m, 5H, H_{Ar}), 7.76 (t, 1 H, H_{Ar}, ^{3}J = 7.3 Hz), 8.15 (d, 1 H, H_{Ar}, ^{3}J = 7.3 Hz), 10.93 (s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 56.5 (CH), 77.4 (OCH_2), 119.4 (2 CH), 124.3 (CH), 125.3 (C_{IV}), 126.7 (CH), 128.2 (CH), 128.4 (2 CH), 128.5 (CH),128.9 (CH), 129.0 (2 CH),129.4 (2 CH),134.36 (CH), 134.39 (C_{IV}), 134.5 (C_{IV}),138.1 (C_{IV}), 161.0 (CO), 164.3 (CO), 164.7 (CO); ESI-MS: *m/z* = 387 $(M+H)^+$.

***N*-(3-Chloro-4-methoxyphenyl)-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide 11**

Purple oil (67%); 100% keto form; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 3 H, OCH_3), 4.17 (s, 1 H, CH), 5.15 (s, 2 H, OCH_2), 6.80 (d, 1 H, $H_{5''}$, ^{3}J = 7.2 Hz), 7.20-7.70 (m, 9 H, NH, 8 H_{Ar}), 8.23 (m, 2 H, H_{Ar}), 8.78 (d, 1 H, $H_{2''}$, ^{4}J = 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 56.0 (CH), 115.1 (CH), 116.1 (C_{IV}), 120.5 (CH), 120.8 (CH), 126.9 (C_{IV}), 127.1 (CH),127.6 (CH), 128.1 (CH),128.2 (C_{IV}), 128.8 (2CH),129.0 (CH),129.1 (CH),129.8 (2CH),131.3 (C_{IV}), 134.8 (C_{IV}), 148.6 (C_{IV}), 161.3 (CO), 163.3 (CO), 166.4 (CO); ESI-MS: *m/z* = 451 ($(M+H)^+$, 100%, ^{35}Cl); 453 ($(M+H)^+$, 32%, ^{37}Cl).

***N*-(3-Fluorophenyl)-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide 12**

Green oil (78%); 100% keto form; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.17 (s, 1 H, CH), 5.16 (s, 2 H, OCH_2), 6.82 (t, 1 H, H_{Ar}, ^{3}J = 7.6 Hz), 7.00-7.59 (m, 12 H, NH, 11 H_{Ar}), 8.23 (dd, 1 H, H_8, ^{3}J = 8.0 Hz, ^{4}J = 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.9 (CH), 78.5 (OCH_2), 109.1 (d, CH, $C_{2''}$, $^{2}J_{C\text{-}F}$ = 28.0 Hz), 110.7 (d, CH, $C_{4''}$, $^{2}J_{C\text{-}F}$ = 28.0 Hz), 118.4 (d, CH, $C_{6''}$, $^{4}J_{C\text{-}F}$ = 3.0 Hz), 126.9 (C_{IV}), 127.0 (CH), 127.6 (CH), 128.1 (CH), 128.6 (d, CH, $C_{5''}$, $^{3}J_{C\text{-}F}$ = 8.0 Hz), 128.7 (2CH),129.0 (CH), 129.1 (CH),130.0 (2CH), 131.6 (C_{IV}), 134.8 (C_{IV}), 136.1 (d, C_{IV}, $C_{1''}$, $^{3}J_{C\text{-}F}$ = 10.0 Hz), 161.1 (d, C_{IV}, $C_{3''}$, $^{1}J_{C\text{-}F}$ = 255.0 Hz), 161.6 (CO), 162.3 (CO), 165.4 (CO); ESI-MS: *m/z* = 405 $(M+H)^+$.

***N*-(4-Fluorophenyl)-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide 13**

Beige solid (78%); mp 177-180 °C;100% keto form; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.04 (d, 1 H, C<u>H</u>$_2$, ^{2}J = 9.6 Hz), 5.09 (d, 1 H, C<u>H</u>$_2$, ^{2}J = 9.6 Hz), 5.37 (s, 1 H, CH), 7.20 (t, 2 H, H_{Ar}, ^{3}J = 8.8 Hz), 7.41-7.43 (m, 3 H, H_{Ar}), 7.53-7.66 (m, 6 H, H_{Ar}), 7.76 (t, 1 H, H_{Ar}, ^{3}J = 7.7 Hz), 8.15 (d, 1 H, H_{Ar}, ^{3}J = 7.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.5 (CH), 77.4 (OCH_2), 115.6 (d, 2 CH, $C_{3''}$, $C_{5''}$, $^{2}J_{C\text{-}F}$ = 22.5 Hz), 121.3 (d, 2 CH, $C_{2''}$, $C_{6''}$, $^{3}J_{C\text{-}F}$ = 8.2 Hz), 125.3 (C_{IV}), 126.7 (CH), 128.2 (CH), 128.3 (2 CH), 128.5 (CH), 118.4 (d, CH, $C_{6''}$, $^{4}J_{C\text{-}F}$ = 3.0 Hz), 127.6 (CH), 128.1 (CH), 128.9 (CH), 129.4 (2 CH), 134.3 (CH), 134.4 (2 C_{IV}), 134.5 (d, C_{IV}, $C_{1''}$, $^{4}J_{C\text{-}F}$ = 2.2 Hz), 158.5 (d, C_{IV}, $C_{4''}$, $^{1}J_{C\text{-}F}$ = 240.0 Hz), 160.9 (CO), 164.3 (CO), 164.6 (CO); ESI-MS: *m/z* = 405 $(M+H)^+$.

***N*-Benzyl-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide 14**

White solid (52%); mp 153-155 °C;100% keto form; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.33 (s, 2 H, C<u>H</u>$_2$), 5.01-5.03 (m, 2 H, OC<u>H</u>$_2$), 5.21 (s, 1 H, CH), 7.18-7.52 (m, 12 H, H_{Ar}), 7.73 (t, 1 H, H_{Ar}, ^{3}J = 7.0 Hz), 8.10 (d, 1 H, H_{Ar}, ^{3}J = 7.7 Hz), 9.33 (s, 1 H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.6 (CH_2), 55.7 (CH), 77.4 (OCH_2), 125.3 (C_{IV}), 126.7 (CH), 127.08 (CH), 127.17 (2 CH), 128.1 (CH), 128.4 (5 CH), 128.9 (CH), 129.4 (2 CH), 134.1 (CH), 134.4 (C_{IV}), 134.6 (C_{IV}), 138.4 (C_{IV}), 161.0 (CO), 164.5 (CO), 166.1 (CO); ESI-MS: *m/z* = 401 $(M+H)^+$.

***N*-(4-Methylbenzyl)-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide 15**

White crystals (85%); mp 149-150 °C; 100% enol form; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.28 (s, 3 H, CH_3), 4.42 (d, 2 H, ^{3}J = 5.3 Hz), 5.01 (s, 2 H, OCH_2), 6.84 (td, 1 H, $H_{Ar,}$ ^{3}J = 7.0 Hz, ^{4}J = 1.5 Hz), 7.13 (d, 2 H, ^{3}J = 7.8 Hz), 7.20-7.38 (m, 6 H, H_{Ar}), 7.62 (d, 2 H, H_{Ar}, ^{3}J = 7.8 Hz), 7.94 (dd, 1 H, H_{Ar}, ^{3}J = 8.0 Hz, ^{4}J = 1.5 Hz), 8.38 (dd, 1 H, H_8, ^{3}J = 8.0 Hz, ^{4}J = 1.5 Hz), 10.65 (t, 1 H, NH, ^{3}J = 5.3 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.2 (CH_3), 42.1 (CH_2), 76.6 (OCH_2), 86.8 (C_{IV}, C_4), 118.5 (C_{IV}), 118.6 (CH), 124.0 (CH), 126.9 (CH), 127.8 (2CH), 128.6 (2 CH), 128.7 (CH), 129.2 (2 CH), 129.3 (2CH), 131.2 (C_{IV}), 131.3 (CH), 136.3 (C_{IV}), 138.3 (C_{IV}), 140.5 (C_{IV}), 159.8 (CO), 161.3 (CO), 169.6 (CO); ESI-MS: *m/z* = 415 $(M+H)^{+}$.

***N*-4-Methoxybenzyl-2-benzyloxy-1,3-dioxo-1,2,3,4 tetrahydroisoquinoline-4-carboxamide 16**

Grey solid (61%); mp 163-167 °C; 100% keto form; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.74 (s, 3 H, OCH_3), 4.24 (dd, 1 H, $CH_{2,}$ ^{2}J = 14.7 Hz, ^{3}J = 5.6 Hz), 4.29 (dd, 1 H, $CH_{2,}$ ^{2}J = 14.7 Hz, ^{3}J = 5.6 Hz), 5.00 (d, 1 H, OCH_2, ^{2}J = 9.6 Hz), 5.05 (d, 1 H, OCH_2, ^{2}J = 9.6 Hz), 5.19 (s, 1 H, CH), 6.91 (d, 2 H, H_{Ar}, ^{3}J= 8.5 Hz), 7.19 (d, 2 H, H_{Ar}, ^{3}J= 8.5 Hz), 7.40-7.44 (m, 4 H, H_{Ar}), 7.56-7.58 (m, 3 H, H_{Ar}), 7.74 (t, 1 H, H_{Ar}, ^{3}J = 7.4 Hz), 8.10 (d, 1 H, H_8, ^{3}J = 7.6 Hz), 9.25 (t, 1 H, NH, ^{3}J = 5.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.1 (CH_2), 55.3 (OCH_3), 56.1 (CH), 77.8 (OCH_2), 113.8 (2 CH), 125.2 (C_{IV}), 126.6 (CH), 128.0 (CH), 128.30 (CH), 128.37 (2CH), 128.6 (2 CH), 128.8 (CH), 129.3 (2CH), 130.2 (C_{IV}), 134.1 (CH), 134.4 (C_{IV}), 134.7 (C_{IV}), 158.4 (CO), 161.0 (CO), 164.4 (CO), 165.9 (CO); ESI-MS: *m/z* = 431 $(M+H)^{+}$.

***N*-(2,4-Dimethoxybenzyl)-2-benzyloxy-1,3-dioxo-1,2,3,4 tetrahydroisoquinoline-4-carboxamide 17**

Salmon solid (88%); mp 176-177 °C; 100% keto form; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.75 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.35 (dd, 1 H, $CH_{2,}$ ^{2}J = 11.9 Hz, ^{3}J = 5.1 Hz), 4.38 (dd, 1 H, $CH_{2,}$ ^{2}J = 11.9 Hz, ^{3}J = 5.1 Hz), 4.82 (s, 1 H, CH), 5.01 (d, 1 H, $OCH_{2,}$ ^{2}J = 9.2 Hz), 5.08 (d, 1 H, OCH_2, ^{2}J = 9.2 Hz), 6.40 (dd, 1 H, $H_{5''}$, $^{3}J_{5''\text{-}6'}$ = 7.5 Hz, $^{4}J_{5''\text{-}3''}$ = 1.2 Hz), 6.45 (d, 1 H, $H_{3''}$, $^{4}J_{3''\text{-}5''}$ = 1.2 Hz), 7.05 (t, 1 H, NH, ^{3}J = 5.1 Hz), 7.14 (d, 1 H, $H_{6''}$, $^{3}J_{6''\text{-}5''}$ = 7.6 Hz), 7.28-7.39 (m, 5 H, H_{Ar}), 7.51-7.70 (m, 3 H, H_{Ar}), 8.21 (dd, 1 H, H_8, ^{3}J = 7.6 Hz, ^{4}J = 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.3 (CH_2), 55.3 (CH_3), 55.4 (CH_3), 55.7 (CH), 78.4 (OCH_2), 98.6 (CH, $C_{3''}$), 103.9 (CH, $C_{5''}$), 118.5 (C_{IV}, $C_{1''}$), 125.6 (C_{IV}), 126.1 (CH), 128.5 (CH), 128.6 (2CH), 128.7 (CH), 129.0 (CH), 129.9 (2CH), 130.6 (CH), 133.8 (C_{IV}), 133.9 (CH), 135.0 (C_{IV}), 158.5 (CO), 160.8 (CO), 163.9 (CO), 165.0 (CO), 166.6 (CO); ESI-MS: *m/z* = 461 $(M+H)^{+}$.

***N*-(3,4-Dimethoxybenzyl)-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide 18**

White crystals (48%); mp 186-188 °C; 100% keto form; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.74 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 4.27 (dd, 1 H, $CH_{2,}$ ^{2}J = 11.9 Hz, ^{3}J = 5.1 Hz), 4.36 (dd, 1 H, $CH_{2,}$ ^{2}J = 11.9 Hz, ^{3}J = 5.1 Hz), 4.73 (s, 1 H, CH), 4.98 (d, 1 H, OCH_2, ^{2}J = 9.2 Hz), 5.02 (d, 1 H, OCH_2, ^{2}J = 9.2 Hz), 6.50-6.62 (m, 3 H, H_{Ar}), 6.96 (t, 1 H, H_{Ar}, ^{3}J= 7.6 Hz), 7.20-7.32 (m, 4 H, H_{Ar}), 7.40-7.54 (m, 3 H, H_{Ar}), 8.13 (dd, 1 H, H_8, ^{3}J = 7.6 Hz, ^{4}J = 1.5 Hz), 9.01 (t, 1 H, NH, ^{3}J = 5.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.2 (CH_2), 55.6 (CH), 55.8 (CH_3), 55.9 (CH_3), 78.6 (OCH_2), 110.8 (CH), 111.1 (CH), 118.5 (C_{IV}), 120.0 (CH), 125.6 (C_{IV}), 128.1 (CH), 128.5 (2CH), 128.8 (CH), 129.1 (CH), 129.2 (CH), 129.9 (2CH), 132.7 (C_{IV}), 134.0 (CH), 134.1 (C_{IV}), 158.8 (CO), 160.8 (CO), 163.9 (CO), 164.5 (CO), 166.6 (CO); ESI-MS: *m/z* = 461 $(M+H)^{+}$.

***N*-(4-Fluorobenzyl)-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide 19**

Beige solid (81%); mp 119-121 °C; 100% enol form; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.46 (d, 2 H, CH_2, ^{3}J = 5.8 Hz), 5.13 (s, 2 H, OCH_2), 6.84-7.20 (m, 4 H, H_{Ar}), 7.36-7.50 (m, 6 H, H_{Ar}), 7.68 (td, 1 H, H_{Ar}, ^{3}J = 8.0 Hz, ^{4}J = 1.5 Hz), 8.06 (dd, 1 H, H_{Ar}, ^{3}J = 8.0 Hz, ^{4}J = 1.5 Hz), 8.34 (dd, 1 H, H_{Ar}, ^{3}J = 8.0 Hz, ^{4}J = 1.5 Hz), 10.65 (t, 1 H, NH, ^{3}J = 5.8 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 42.5 (CH_2), 76.7 (OCH_2), 83.7 (C_{IV}, C_4), 115.0 (d, 2CH, $C_{3''}$, $C_{5''}$, $^{2}J_{C-F}$ = 21.4 Hz), 126.2 (C_{IV}), 127.0 (CH), 128.1 (CH), 128.3 (CH), 128.5 (2CH), 130.1 (d, 2 CH, $C_{2''}$, $C_{6''}$, $^{3}J_{C-F}$ = 8.6 Hz), 130.2 (2 CH), 131.1 (CH), 132.1 (CH), 133.8 (C_{IV}), 133.8 (d, C_{IV}, $C_{1''}$, $^{4}J_{C-F}$ = 3.1Hz), 135.1 (C_{IV}), 159.1 (CO), 161.2 (d, C_{IV}, $C_{4''}$, $^{1}J_{C-F}$ = 245.0 Hz), 161.3 (CO), 165.4 (CO); ESI-MS: *m/z* = 419 $(M+H)^{+}$.

***N*-(4-Fluorophenethyl)-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide 20**

White solid (61%); mp 155-165 °C; 100% keto form; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.73 (t, 2 H, CH_2, ^{3}J = 5.0 Hz), 3.36 (q, 2 H, CH_2, ^{3}J = 5.0 Hz), 4.97 (d, 1 H, OCH_2, ^{2}J = 9.5 Hz), 5.00 (d, 1 H, OCH_2, ^{2}J = 9.5 Hz), 5.09 (s, 1 H, CH), 7.12 (t, 2 H, H_{Ar}, ^{3}J = 8.8 Hz), 7.24-7.28 (m, 4 H, H_{Ar}), 7.41-7.43 (m, 3 H, H_{Ar}), 7.54-7.58 (m, 3 H, H_{Ar}), 7.68 (t, 1 H, H_{Ar}, ^{3}J = 7.6 Hz), 8.08 (d, 1 H, H_{Ar}, ^{3}J = 7.7 Hz), 8.85 (t, 1 H, NH, ^{3}J = 5.0 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 33.8 (CH_2), 40.6 (CH_2), 54.2 (CH), 77.6 (OCH_2), 115.7 (d, 2 CH, $C_{3''}$, $C_{5''}$, $^{2}J_{C-F}$ = 21.0 Hz), 125.2 (C_{IV}), 126.9 (CH), 127.6 (CH), 128.0 (CH), 129.2 (2CH), 129.6 (2 CH), 130.7 (d, 2 CH, $C_{2''}$, $C_{6''}$, $^{3}J_{C-F}$ = 8.3 Hz), 133.7 (2 CH), 134.7 (CH), 135.28 (C_{IV}), 135.30 (d, C_{IV}, $C_{1''}$, $^{4}J_{C-F}$ = 2.8Hz), 136.4 (C_{IV}), 162.0 (d, C_{IV}, $C_{4''}$, $^{1}J_{C-F}$ = 241.5 Hz), 165.2 (CO), 167.5 (CO), 169.2 (CO); ESI-MS: *m/z* = 433 $(M+H)^{+}$.

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide 21**

White solid (53%); mp 191-192 °C; 100% keto form; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.70 (m, 2 H, CH_2), 3.35 (m, 2 H, CH_2), 3.71 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 4.95 (d, 1 H, OCH_2, ^{2}J = 9.2 Hz), 5.04 (d, 1 H, OCH_2, ^{2}J = 9.2 Hz), 5.19 (s, 1 H, CH), 6.20 (d, 1 H, $H_{5''}$, ^{3}J = 7.8 Hz), 6.85-6.92 (m, 2 H, H_{Ar}), 7.31 (dd, 1 H, H_{Ar}, ^{3}J = 7.8 Hz, ^{4}J = 1.5 Hz), 7.40-7.51 (m, 3 H, H_{Ar}), 7.53-7.60 (m, 3 H, H_{Ar}), 7.65 (td, 1 H, H_{Ar}, ^{3}J = 7.8 Hz, ^{4}J = 1.5 Hz), 8.08 (dd, 1 H, H_8, ^{3}J = 7.8 Hz, ^{4}J = 1.5 Hz), 9.06 (t, 1 H, NH, ^{3}J = 5.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 34.6 (CH_2), 41.3 (CH_2), 55.8 (OCH_3), 55.9 (OCH_3), 55.9 (CH), 77.8 (OCH_2), 112.2 (CH), 113.0 (CH), 121.0 (CH), 125.6 (C_{IV}), 127.2 (CH), 128.4 (CH), 128.7 (CH), 128.8 (2CH), 129.3 (CH), 129.8 (2CH), 131.9 (C_{IV}), 134.4 (CH), 134.9 (C_{IV}), 135.2 (C_{IV}), 147.7 (C_{IV}), 149.0 (C_{IV}), 161.5 (CO), 165.0 (CO), 166.4 (CO); ESI-MS: *m/z* = 475 $(M+H)^{+}$.

*2.5. General procedure for the deprotection of compounds **10-21***

The protected intermediate **10-21** (1.0 mmol) was dissolved in a minimum of CH_2Cl_2 and boron trichloride or boron tribromide (1.0 M solution in CH_2Cl_2, 5.0 mL, 5.0 mmol) was added dropwise at room temperature. The solution was stirred for 1 h and water (20 mL) was slowly added. After 15 min stirring, the precipitate was filtered and the aqueous layer was extracted with ethyl acetate. Organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Organic residues and precipitate were gathered and triturated with ether. Insoluble materials were filtered and dried at room temperature giving the target compounds.

***N*-Phenyl-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide 22**

Intermediate 10 was treated with boron trichloride giving **compound 22**. Grey solid (73%); mp 170-175 °C; 100% keto form; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.33 (s, 1 H, CH), 7.11 (t, 1 H, H_{Ar}, ^{3}J = 7.0 Hz), 7.34 (t, 2 H, H_{Ar}, ^{3}J = 7.5 Hz), 7.52 (t, 1 H, H_{Ar}, ^{3}J = 7.2 Hz), 7.57-7.61 (m, 3 H, H_{Ar}), 7.69 (t, 1 H, H_{Ar}, ^{3}J = 7.0 Hz), 8.10 (d, 1 H, H_{Ar}, ^{3}J = 7.7 Hz), 10.94 (s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 56.1 (CH), 119.4 (2 CH), 124.2 (CH), 125.4 (C_{IV}), 126.7 (CH), 128.0 (CH), 128.4 (CH), 128.9 (2 CH),133.9 (CH), 134.3 (C_{IV}), 138.2 (C_{IV}), 161.5 (CO), 164.6 (CO), 164.8 (CO); ESI-MS: *m/z* = 297 $(M+H)^{+}$; HRMS calcd for $C_{16}H_{12}N_2O_4$296.07971; found: 296.07873.

***N*-(3-Chloro-4-methoxyphenyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide 23**

Intermediate 11 was treated with boron trichloride giving **compound 23**. Purple solid (79%); 33% keto form; 67% enol form; **Keto form**; ^{1}H NMR (300 MHz, Acetone-d_6): δ = 3.93 (s, 3 H, OCH_3), 5.27 (s, 1 H, CH), 7.04 (d, 1 H, $H_{5'}$, ^{3}J = 7.5 Hz), 7.35 (dd, 1 H, H_{Ar}, ^{3}J = 7.5 Hz, ^{4}J = 1.4 Hz), 7.51-7.62 (m, 2 H, H_{Ar}), 7.70 (td, 1 H, H_{Ar}, ^{3}J = 7.5 Hz, ^{4}J = 1.4 Hz), 7.78 (d, 1 H, $H_{2'}$, ^{4}J = 1.4 Hz), 8.11 (dd, 1 H, H_8, ^{3}J = 7.5 Hz, ^{4}J = 1.4 Hz), 9.82 (s, 1 H, NH); ^{13}C NMR (75 MHz, Acetone-d_6): δ = 55.5 (OCH_3), 56.2 (CH), 115.1 (CH), 116.2 (C_{IV}), 120.5 (CH), 120.7 (CH), 127.0 (C_{IV}), 127.1 (CH),127.8 (CH), 128.2 (CH),128.3 (C_{IV}), 129.1 (CH),131.5 (C_{IV}), 148.5 (CO), 161.3 (CO), 161.5 (CO), 164.4 (CO); **Enol form**; ^{1}H NMR (300 MHz, Acetone-d_6): δ = 3.95 (s, 3 H, OCH_3), 7.15 (d, 1 H, $H_{5'}$, ^{3}J = 7.5 Hz), 7.51-7.62 (m, 3 H, H_{Ar}), 7.71 (td, 1 H, H_{Ar}, ^{3}J = 7.6 Hz, ^{4}J = 1.5 Hz), 7.80 (d, 1 H, $H_{2'}$, ^{4}J = 1.5 Hz), 8.18 (dd, 1 H, H_8, ^{3}J = 7.6 Hz, ^{4}J = 1.5 Hz), 10.03 (s, 1 H, NH); ^{13}C NMR (75 MHz, Acetone-d_6): δ = 56.1 (OCH_3), 84.3 (C_{IV}, C_4), 117.8 (CH), 118.5 (C_{IV}), 119.2 (CH), 119.5 (CH), 127.6 (CH), 128.4 (CH),129.2 (C_{IV}), 130.1 (C_{IV}), 131.1 (CH),132.4 (CH),133.5 (C_{IV}), 148.6 (CO), 160.1 (CO), 160.5 (CO), 162.4 (CO); ESI-MS: *m/z* = 361 ($(M+H)^{+}$, 100%, ^{35}Cl); 363 ($(M+H)^{+}$, 32%, ^{37}Cl); HRMS calcd for $C_{17}H_{13}ClN_2O_5$ 360.05130; found: 360.04852.

***N*-(3-Fluorophenyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide 24**

Intermediate 12 was treated with boron trichloride giving **compound 24**. Black solid (68%); mp 170-172 °C; 100% keto form; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.27 (s, 1 H, CH), 6.82-6.95 (m, 2 H, H_{Ar}), 7.00-7.49 (m, 5 H, NH, 4 H_{Ar}), 7.75 (d, 1 H, H_{Ar}, ^{3}J = 7.5 Hz), 8.23 (dd, 1 H, H_8, ^{3}J = 8.0 Hz, ^{4}J= 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.9 (CH), 108.9 (d, CH, $C_{2'}$, $^{2}J_{C-F}$= 28.0 Hz), 111.2 (d, CH, $C_{4'}$, $^{2}J_{C-F}$ = 28.1 Hz), 118.4 (d, CH, $C_{6'}$, $^{4}J_{C-F}$ = 3.2 Hz), 126.8 (C_{IV}), 127.3 (CH), 128.4 (CH), 128.5 (d, CH, $C_{5'}$, $^{3}J_{C-F}$ = 8.4 Hz), 129.1 (CH),130.3 (CH), 131.4 (C_{IV}), 136.1 (d, C_{IV}, $C_{1'}$, $^{3}J_{C-F}$ = 10.0 Hz), 161.1 (d, C_{IV}, $C_{3'}$, $^{1}J_{C-F}$ = 255.6 Hz), 161.4 (CO), 161.8 (CO), 166.2 (CO); ESI-MS: *m/z* = 315 $(M+H)^{+}$; HRMS calcd for $C_{16}H_{11}FN_2O_4$ 314.07029; found: 314.07098.

***N*-(4-Fluorophenyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide 25**

Intermediate 13 was treated with boron trichloride giving **compound 25**. Beige solid (76%); mp 172-180 °C; 100% keto form; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.29 (s, 1 H, CH), 7.19 (t, 2 H, H_{Ar}, ^{3}J = 8.6 Hz), 7.48 (d, 1 H, H_{Ar}, ^{3}J = 7.5 Hz), 7.54-7.63 (m, 4 H, H_{Ar}), 7.71 (t, 1 H, H_{Ar}, ^{3}J = 7.0 Hz), 8.11 (d, 1 H, H_{Ar}, ^{3}J = 7.7 Hz), 10.94 (s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 56.3 (CH), 116.0 (d, 2 CH, $C_{3''}$, $C_{5''}$, $^{2}J_{C-F}$ = 22.5 Hz), 121.8 (d, 2 CH, $C_{2''}$, $C_{6''}$, $^{3}J_{C-F}$ = 9.0 Hz), 125.9 (C_{IV}), 127.1 (CH), 128.5 (CH), 128.9 (CH), 134.4 (CH), 134.7 (C_{IV}), 135.1 (C_{IV}), 158.9 (d, C_{IV}, $C_{4''}$, $^{1}J_{C-F}$ = 239.2 Hz), 161.9 (CO), 165.0 (CO), 165.3 (CO); ESI-MS: *m/z* = 315

$(M+H)^+$; HRMS calcd for $C_{16}H_{11}FN_2O_4$ 314.07029; found: 314.07167.

***N*-Benzyl-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide 26**

Intermediate 14 was treated with boron trichloridegiving **compound 26**. Beige solid (69%); mp 152-155 °C; 100% keto form; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.32 (s, 2 H, C$\underline{H}_2$), 5.17 (s, 1 H, CH), 7.28-7.33 (m, 5 H, H_{Ar}), 7.42 (m, 1 H, H_{Ar}), 7.55 (m, 1 H, H_{Ar}), 7.70 (m, 1 H, H_{Ar}), 8.07 (d, 1 H, H_{Ar}, ^3J = 7.7 Hz), 9.31 (s, 1 H, NH), 10.62 (s, 1 H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 42.6 (CH_2), 55.2 (CH), 125.3 (C_{IV}), 126.6 (CH), 127.0 (CH), 127.2 (2 CH), 128.0 (CH), 128.2 (CH), 128.4 (2 CH), 133.7 (CH), 134.4 (C_{IV}), 138.5 (C_{IV}), 161.5 (CO), 164.7 (CO), 166.2 (CO); ESI-MS: *m/z* = 311 $(M+H)^+$; HRMS calcd for $C_{17}H_{14}N_2O_4$ 310.09536; found: 310.09346.

***N*-(4-Methylbenzyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide 27**

Intermediate 15 was treated with boron trichloride giving **compound 27**. Beige solid (88%); mp 171 °C; 100% keto form; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.32 (s, 3 H, CH_3), 4.38 (d, 2 H, ^3J = 5.3 Hz), 5.27 (s, 1 H, CH), 7.27 (m, 4 H, H_{Ar}), 7.52 (dd, 1 H, H_5, ^3J = 7.9 Hz, ^4J = 1.2 Hz), 7.67 (td, 1 H, H_{Ar}, ^3J = 7.9 Hz, ^4J = 1.2 Hz), 7.82 (td, 1 H, H_{Ar}, ^3J = 7.9 Hz, ^4J = 1.2 Hz), 8.19 (dd, 1 H, H_8, ^3J = 7.9 Hz, ^4J = 1.2 Hz), 9.37 (t, 1 H, NH, ^3J = 5.3 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.2 (CH_3), 42.9 (CH_2), 55.8 (CH), 125.9 (C_{IV}), 127.1 (CH), 127.7 (2CH), 128.4 (CH), 128.7 (CH), 129.4 (2CH), 134.3 (CH), 135.0 (C_{IV}), 135.9 (C_{IV}), 136.6 (C_{IV}), 162.1 (CO), 165.2 (CO), 166.6 (CO); ESI-MS: *m/z* = 325 $(M+H)^+$; HRMS calcd for $C_{18}H_{16}N_2O_4$ 324.11101; found: 324.11169.

***N*-(4-Methoxybenzyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide 28**

Intermediate 16 was treated with boron trichloride giving **compound 28**. Brown solid (45%); mp> 170 °C (dec); 100% keto form; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.74 (s, 3 H, OCH_3), 4.24 (dd, 1 H, CH_2, ^2J = 14.7 Hz, ^3J = 5.6 Hz), 4.29 (dd, 1 H, CH_2, ^2J = 14.7 Hz, ^3J = 5.6 Hz), 5.14 (s, 1 H, CH), 6.90 (d, 2 H, H_{Ar}, ^3J= 8.2 Hz), 7.19 (d, 2 H, H_{Ar}, ^3J= 8.2 Hz), 7.39 (d, 1 H, H_{Ar}, ^3J= 7.5 Hz), 7.55 (t, 1 H, H_{Ar}, ^3J = 7.3 Hz), 7.70 (t, 1 H, H_{Ar}, ^3J = 6.9 Hz), 8.06 (d, 1 H, H_8, ^3J = 7.6 Hz), 9.21 (t, 1 H, NH, ^3J = 5.3 Hz), 10.59 (s, 1 H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 42.1 (CH_2), 55.0 (OCH_3), 55.2 (CH), 113.7 (2 CH), 125.3 (C_{IV}), 126.6 (CH), 127.9 (CH), 128.2 (CH), 128.6 (2 CH), 130.3 (C_{IV}), 133.7 (CH), 134.5 (C_{IV}), 158.4 (CO), 161.5 (CO), 164.7 (CO), 166.0 (CO); ESI-MS: *m/z* = 341 $(M+H)^+$; HRMS calcd for $C_{18}H_{16}N_2O_5$ 340.10592; found: 340.10486.

***N*-(2,4-Dimethoxybenzyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide 29**

Intermediate 17 was treated with boron trichloride giving **compound 29**. Salmon solid (93%); mp 125-127 °C; 100% keto form; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.75 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 4.15 (dd, 1 H, CH_2, ^2J = 11.9 Hz, ^3J = 5.1 Hz), 4.19 (dd, 1 H, CH_2, ^2J = 11.9 Hz, ^3J = 5.1 Hz), 5.17 (s, 1 H, CH), 6.48 (dd, 1 H, $H_{5'}$, ^3J= 7.6 Hz, ^4J= 1.2 Hz), 6.57 (d, 1 H, $H_{3'}$, ^4J= 1.2 Hz), 7.11 (d, 1 H, $H_{6'}$, ^3J= 7.6 Hz), 7.40 (dd, 1 H, H_{Ar}, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 7.54 (td, 1 H, H_{Ar}, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 7.69 (td, 1 H, H_{Ar}, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 8.05 (dd, 1 H, H_8, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 9.00 (t, 1 H, NH, ^3J = 5.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 38.2 (CH_2), 55.6 (OCH_3), 55.7 (OCH_3), 55.9 (CH), 98.8 (CH, $C_{3'}$), 104.7 (CH, $C_{5'}$), 118.3 (C_{IV}, $C_{1'}$), 125.8 (C_{IV}), 127.1 (CH), 128.3 (CH), 128.6 (CH), 129.7 (CH), 134.2 (CH), 135.0 (C_{IV}), 158.3

(CO), 160.5 (CO), 162.1 (CO), 165.3 (CO), 166.4 (CO); ESI-MS: *m/z* = 371 $(M+H)^+$; HRMS calcd for $C_{19}H_{18}N_2O_6$ 370.11649; found: 370.11456.

***N*-(2,4-Dihydroxybenzyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide 30**

Intermediate 17 was treated with boron tribromide giving **compound 30**. Pink solid (66%); mp> 111 °C (dec); 55% keto form; 45% enol form; **Keto form**; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.10 (dd, 1 H, CH_2, ^2J = 11.9 Hz, ^3J = 5.1 Hz), 4.12 (dd, 1 H, CH_2, ^2J = 11.9 Hz, ^3J = 5.1 Hz), 5.17 (s, 1 H, CH), 6.28 (dd, 1 H, $H_{5'}$, ^3J= 7.6 Hz, ^4J= 1.2 Hz), 6.31 (d, 1 H, $H_{3'}$, ^4J= 1.2 Hz), 6.88 (d, 1 H, $H_{6'}$, ^3J= 7.6 Hz), 7.43 (dd, 1 H, H_5, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 7.52 (td, 1 H, H_{Ar}, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 7.69 (td, 1 H, H_{Ar}, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 8.05 (dd, 1 H, H_8, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 8.90 (t, 1 H, NH, ^3J = 5.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 38.2 (CH_2), 56.0 (CH), 106.3 (CH), 108.3 (C_{IV}), 108.6 (CH), 125.9 (C_{IV}), 126.1 (CH), 128.3 (CH), 128.6 (CH), 129.7 (CH), 134.2 (CH), 135.0 (C_{IV}), 153.2 (CO), 159.3 (CO), 162.1 (CO), 163.3 (CO), 165.7 (CO); **Enol form**; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.29 (dd, 1 H, CH_2, ^2J = 11.9 Hz, ^3J = 5.1 Hz), 4.31 (dd, 1 H, CH_2, ^2J = 11.9 Hz, ^3J = 5.1 Hz), 6.15 (dd, 1 H, $H_{5'}$, ^3J= 7.6 Hz, ^4J= 1.2 Hz), 6.26 (d, 1 H, $H_{3'}$, ^4J= 1.2 Hz), 7.01 (d, 1 H, $H_{6'}$, ^3J= 7.6 Hz), 7.19 (td, 1 H, H_{Ar}, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 7.51 (td, 1 H, H_{Ar}, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 8.05 (dd, 1 H, H_5, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 8.27 (t, 1 H, NH, ^3J = 5.1 Hz), 8.89 (dd, 1 H, H_8, ^3J = 7.5 Hz, ^4J = 1.5 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 39.2 (CH_2), 84.3 (C_{IV}, C_4), 106.1 (C_{IV}), 106.3 (CH), 108.3 (CH), 126.8 (C_{IV}), 127.9 (CH), 128.3 (CH), 129.2 (CH), 129.7 (CH), 131.2 (CH), 134.5 (C_{IV}), 149.2 (CO), 156.5 (CO), 159.5 (CO), 161.3 (CO), 166.5 (CO); ESI-MS: *m/z* = 343 $(M+H)^+$; HRMS calcd for $C_{17}H_{14}N_2O_6$ 342.08519; found: 342.08471.

***N*-(3,4-Dimethoxybenzyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide 31**

Intermediate 18 was treated with boron trichloride giving **compound 31**. Salmon solid (67%); mp 126-127 °C; 66% keto form; 34% enol form; **Keto form**; ^{1}H NMR (300 MHz, Acetone-d_6): δ = 3.79 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.38 (m, 2 H, CH_2), 4.72 (s, 1 H, CH), 6.76-6.90 (m, 3 H, H_{Ar}), 7.36 (td, 1 H, H_{Ar}, ^3J= 7.5 Hz, ^4J= 1.5 Hz), 7.56 (td, 1 H, H_{Ar}, ^3J= 7.5 Hz, ^4J= 1.5 Hz), 7.69 (dd, 1 H, H_{Ar}, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 8.15 (dd, 1 H, H_8, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 9.82 (t, 1 H, NH, ^3J = 5.2 Hz); ^{13}C NMR (75 MHz, Acetone-d_6): δ = 46.1 (CH_2), 55.2 (OCH_3), 55.3 (OCH_3), 55.6 (CH), 111.0 (CH), 111.5 (CH), 114.4 (CH), 114.8 (CH), 118.6 (CH), 120.0 (CH), 128.6 (C_{IV}), 128.7 (CH), 131.9 (C_{IV}), 133.1 (C_{IV}), 149.9 (CO), 152.1 (CO), 160.5 (CO), 161.3 (CO), 164.2 (CO); **Enol form**; ^{1}H NMR (300 MHz, Acetone-d_6): δ = 3.82 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.34 (m, 2 H, CH_2), 6.76-6.90 (m, 3 H, H_{Ar}), 7.40 (td, 1 H, H_{Ar}, ^3J= 7.5 Hz, ^4J= 1.5 Hz), 7.59 (td, 1 H, H_{Ar}, ^3J= 7.5 Hz, ^4J= 1.5 Hz), 7.71 (dd, 1 H, H_{Ar}, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 8.17 (dd, 1 H, H_8, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 10.35 (t, 1 H, NH, ^3J = 5.2 Hz); ^{13}C NMR (75 MHz, Acetone-d_6): δ = 42.8 (CH_2), 55.1 (OCH_3), 55.2 (OCH_3), 84.2 (C_{IV}, C_4), 111.1 (CH), 111.7 (CH), 119.4 (CH), 125.8 (C_{IV}), 127.0 (CH), 128.1 (CH), 128.2 (CH), 128.9 (C_{IV}), 131.8 (C_{IV}), 133.6 (CH), 149.9 (CO), 151.0 (CO), 157.3 (CO), 161.3 (CO), 162.4 (CO); ESI-MS: *m/z* = 371 $(M+H)^+$; HRMS calcd for $C_{19}H_{18}N_2O_6$ 370.11649; found: 370.11512.

***N*-(3,4-Dihydroxybenzyl)-2-hydroxy-1,3-dioxoisoquinoline-4-carboxamide 32**

Intermediate 18 was treated with boron tribromide giving **compound 32**. Salmon solid (95%); mp> 150 °C (dec); 100% keto form; ^{1}H NMR (300 MHz, Acetone-d_6): δ = 4.15 (dd, 2 H, CH_2, ^2J= 11.9 Hz, ^3J= 5.0 Hz), 4.17 (dd, 2 H, CH_2, ^2J= 11.9 Hz, ^3J= 5.0 Hz),

5.12 (s, 1 H, CH), 6.52 (d, 1 H, $H_{5'}$, ^{3}J= 7.6 Hz), 6.64-6.73 (m, 2 H, H_{Ar}), 7.39 (dd, 1 H, H_5, ^{3}J= 7.6 Hz, ^{4}J= 1.5 Hz,), 7.54 (td, 1 H, H_{Ar}, ^{3}J= 7.6 Hz, ^{4}J= 1.5 Hz), 7.69 (td, 1 H, H_{Ar}, ^{3}J = 7.6 Hz, ^{4}J = 1.5 Hz), 8.06 (dd, 1 H, H_8, ^{3}J = 7.6 Hz, ^{4}J = 1.5 Hz), 9.12 (t, 1 H, NH, ^{3}J = 5.2 Hz); ^{13}C NMR (75 MHz, Acetone-d_6): δ = 42.6 (CH_2), 55.9 (CH), 114.8 (CH), 118.6 (CH), 122.8 (CH), 123.8 (C_{IV}), 127.2 (CH), 128.7 (CH), 129.3 (CH), 131.9 (C_{IV}), 132.4 (CH), 134.9 (C_{IV}), 146.2 (C_{IV}), 151.0 (C_{IV}), 161.5 (CO), 165.0 (CO), 166.4 (CO); ESI-MS: *m/z* = 343 $(M+H)^+$; HRMS calcd for $C_{17}H_{14}N_2O_6$ 342.08519; found: 342.08645.

_N_-(4-Fluorobenzyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide 33

Intermediate 19 was treated with boron trichloride giving **compound 33**. Compound 14: light yellow solid (81%); mp> 155 °C (dec); 100% keto form; ^{1}H NMR (300 MHz, Acetone-d_6): δ = 4.43 (m, 2 H, CH_2), 5.18 (s, 1 H, CH), 7.08 (t, 2 H, $H_{3'}$, $H_{5'}$, $^{3}J_{H-H}$ = $^{3}J_{H-F}$ = 7.7 Hz), 7.34 (m, 2 H, H_{Ar}), 7.46-7.60 (m, 2 H, H_{Ar}), 7.71 (td, 1 H, H_{Ar}, ^{3}J = 7.5 Hz, ^{4}J = 1.5 Hz), 8.15 (dd, 1 H, H_8, ^{3}J = 7.5 Hz, ^{4}J = 1.5 Hz), 8.51 (t, 1 H, NH, ^{3}J = 5.0 Hz); ^{13}C NMR (75 MHz, Acetone-d_6): δ = 42.5 (CH_2)**,** 55.8 (CH), 115.0 (d, 2 CH, $C_{3'}$, $C_{5'}$, $^{2}J_{C-F}$ = 21.4 Hz), 125.2 (C_{IV}), 127.0 (CH), 128.1 (CH), 128.3 (CH), 129.3 (d, 2CH, $C_{2'}$, $C_{6'}$, $^{3}J_{C-F}$ = 8.6 Hz), 133.7 (CH), 133.8 (C_{IV}), 134.2 (d, C_{IV}, $C_{1'}$, $^{4}J_{C-F}$ = 3.1Hz), 161.3 (d, C_{IV}, $C_{4'}$, $^{1}J_{C-F}$ = 241.2 Hz), 162.1 (CO), 163.0 (CO), 166.4 (CO); ESI-MS: *m/z* = 329 $(M+H)^+$; HRMS calcd for $C_{17}H_{13}FN_2O_4$ 328.08594; found: 328.08656.

_N_-(4-Fluorophenethyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide 34

Intermediate 20 was treated with boron trichloridegiving **compound 34**. Grey solid (60%); mp 100-110 °C; 100% keto form; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.73 (t, 2 H, CH_2, ^{3}J = 5.0 Hz), 3.37 (m, 2 H, CH_2), 5.03 (s, 1 H, CH), 7.12-7.24 (m, 5 H, H_{Ar}), 7.53 (t, 1 H, $H_{Ar,}$ ^{3}J = 7.3 Hz), 7.63 (t, 1 H, $H_{Ar,}$ ^{3}J = 6.8 Hz), 8.04 (d, 1 H, H_{Ar}, ^{3}J = 8.1 Hz), 8.83 (m, 1 H, NH), 10.58 (s, 1 H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 33.8 (CH_2), 40.7 (CH_2)**,** 55.2 (CH), 114.9 (d, 2 CH, $C_{3''}$, $C_{5''}$, $^{2}J_{C-F}$ = 20.9 Hz), 125.3 (C_{IV}), 126.6 (CH), 127.8 (CH), 128.1 (CH), 130.6 (d, 2 CH, $C_{2''}$, $C_{6''}$, $^{3}J_{C-F}$ = 8.2 Hz), 133.6 (CH), 134.4 (C_{IV}), 135.2 (C_{IV}), 160.9 (d, $C_{IV,}$ $C_{4''}$, $^{1}J_{C-F}$ = 241.5 Hz), 161.5 (CO), 164.7 (CO), 166.0 (CO); ESI-MS: *m/z* = 343 $(M+H)^+$; HRMS calcd for $C_{18}H_{15}FN_2O_4$ 342.10159; found: 342.09991.

_N_-[2-(3,4- Dimethoxyphenyl)ethyl]-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide 35

Intermediate 21 was treated with boron trichloride giving **compound 35**. Orange solid (95%); mp 112-114 °C; 100% keto form; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.70 (m, 2 H, CH_2), 3.35 (m, 2 H, CH_2), 3.74 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 4.72 (s, 1 H, CH), 6.80-6.90 (m, 3 H, H_{Ar}), 7.42 (dd, 1 H, H_5, ^{3}J= 7.9 Hz, ^{4}J= 1.5 Hz), 7.67 (td, 1 H, $H_{Ar,}$ ^{3}J= 7.9 Hz, ^{4}J= 1.5 Hz), 7.75 (td, 1 H, $H_{Ar,}$ ^{3}J = 7.9 Hz, ^{4}J = 1.5 Hz), 8.17 (dd, 1 H, H_8, ^{3}J = 7.9 Hz, ^{4}J = 1.5 Hz), 8.76 (t, 1 H, NH, ^{3}J = 5.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 34.5 (CH_2), 41.2 (CH_2), 55.1 (OCH_3), 55.2 (OCH_3), 55.8 (CH), 111.9 (CH), 112.7 (CH), 121.7 (CH), 125.6 (C_{IV}), 127.0 (CH), 128.0 (CH), 128.2 (CH), 131.9 (C_{IV}), 133.6 (CH), 134.5 (C_{IV}), 149.8 (CO), 152.1 (CO), 161.5 (CO), 162.1 (CO), 164.7 (CO); ESI-MS: *m/z* = 385 $(M+H)^+$; HRMS calcd for $C_{20}H_{20}N_2O_6$ 384.13214; found: 384.13317.

_N_-[2-(3,4-Dihydroxyphenyl)ethyl]-2-hydroxy-1,3-dioxoisoquinoline-4-carboxamide 36

Intermediate 21 was treated with boron tribromide giving **compound 36**. Orange solid (95%); mp 148-150 °C; 100% keto form; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.34 (m, 2 H, CH_2), 3.47

(m, 2 H, CH_2), 5.07 (s, 1 H, CH), 6.75-6.90 (m, 3 H, H_{Ar}), 7.40-7.55 (m, 2 H, H_{Ar}), 7.67 (dd, 1 H, H_{Ar}, ^3J= 7.9 Hz, ^4J= 1.5 Hz), 8.12 (dd, 1 H, H_8, ^3J = 7.9 Hz, ^4J = 1.5 Hz), 8.56 (t, 1 H, NH, ^3J = 5.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 35.0 (CH_2), 41.7 (CH_2), 55.9 (CH), 115.0 (CH), 116.1 (CH), 123.5 (CH), 127.7 (CH), 127.8 (C_{IV}), 128.0 (CH), 129.4 (CH), 129.7 (CH), 129.8 (C_{IV}), 131.3 (C_{IV}), 142.8 (CO), 144.0 (CO), 160.5 (CO), 161.4 (CO), 162.7 (CO); ESI-MS: *m/z* = 357 $(M+H)^+$; HRMS calcd for $C_{18}H_{16}N_2O_6$ 356.10084; found: 356.10290.

2.6. Biological procedures[1]

RNase H and integrase inhibition assays, in vitro anti-HIV and drug susceptibility assays were performed according previously reported methods.

Integrase inhibition

To determine the susceptibility of the HIV-1 integrase enzyme to different compounds, an enzyme-linked immunosorbent assay was used. This assay uses an oligonucleotide substrate in which one oligo (5′-ACTGCTAGAGATTTTCCACACTGACTAAAAGGGTC-3′) is labeled with biotin on the 3′ end and in which the other oligo is labeled with digoxigenin at the 5′ end. For the overall integration assay, the second 5′-digoxigenin-labeled oligo is 5′-GACCCTTTTAGTCAGTGTGGAAAATCTCTAGCA**GT**-3′. For the strand transfer assay, a pre-cleaved oligonucleotide substrate (the second oligonucleotide lacks GT [underlined] at the 3’ end) was used. The integrase was diluted in 750 mM NaCl, 10 mM Tris (pH 7.6), 10% glycerol, 1 mM β-mercaptoethanol, and 0.1 mg/mL bovine serum albumin. To perform the reaction, 4 μL of diluted integrase (corresponds to a concentration of WT integrase of 1.6 μM) and 4 μL of annealed oligos (7 nM) were added in a final reaction volume of 40 μL containing 10 mM $MgCl_2$, 5 mM dithiothreitol, 20 mM HEPES (pH 7.5), 0.5% polyethylene glycol, and 15% DMSO. As such, the final concentration of integrase in this assay was 160 nM. The reaction was carried out for 1 h at 37 °C. The reaction products were denatured with 30 mM NaOH and detected by ELISA on avidin-coated plates.

For determining the effect of compounds on the 3′-processing activity a classical cleavage assay with detection of products by denaturing gel electrophoresis was performed as described previously.[9] Briefly, 0.2 pmol of the radioactive oligonucleotide substrate (INT1, ^{32}P-5’-TGTGGAAAATCTCTAGCAGT 3’; INT2, 5’ ACTGCTAGAGATTTTCCACA 3’) and 10 mmol integrase in a final volume of 10 μL was incubated for 1 h at 37 °C. The final reaction mixture contained 20 mM HEPES (pH 7.5), 5 mM dithiothreitol, 10 mM $MgCl_2$, 0.5% (v/v) polyethylene glycol 8000, 15% DMSO. Integrase was diluted previously in 750 mM NaCl, 10 mM Tris (pH 7.6), 10% glycerol and 1 mM β-mercaptoethanol. The reactions were stopped by the addition of formamide loading buffer (95% formamide, 0.1% xylene cyanol, 0.1% bromophenol blue and 0.1% sodium dodecyl sulfate). Samples were loaded on a 15% denaturing polyacrylamide/ureum gel. The extent of 3-processing or DNA strand transfer was based on measuring the respective amounts of -2 bands or strand transfer products relative to the intensity of the total radioactivity present in the lane. These data were determined using the Opti Quant Acquisition and Analysis software (Perkin Elmer Corporate, Fremont, CA).

In vitro anti-HIV and drug susceptibility assays

The inhibitory effect of antiviral drugs on the HIV-1-induced cytopathic effect (CPE) in human lymphocyte MT-4 cell culture was determined by the MT-4/MTT assay. This assay is based on the reduction of the yellow colored 3-(4,5-dimethylthiazol-2-yl)-2,5-

diphenyltetrazolium bromide (MTT) by mitochondrial dehydrogenase of metabolically active cells to a blue formazan derivative, which can be measured spectrophotometrically. The 50% cell culture infective dose ($CCID_{50}$) of the HIV-1 (IIIB) strain was determined by titration of the virus stock using MT-4 cells. For the drug susceptibility assays, MT-4 cells were infected with 100−300 $CCID_{50}$ of the virus stock in the presence of 5-fold serial dilutions of the antiviral drugs. The concentration of various compounds achieving 50% protection against the CPE of the different HIV strains, which is defined as the EC_{50}, was determined. In parallel, the 50% cytotoxic concentration (CC_{50}) was determined.

Reverse transcriptase RNase H assay

The substrate for RNase H activity was prepared as previously described.[10] *E. coli* RNA polymerase used single-stranded calf thymus DNA as a template to synthesize complementary ^{3}H-labeled RNA. For RNase H activity, recombinant HIV-1 RT[11] (4.5 pmol) was incubated with the appropriate compound for 10 min at 37 °C in 20 μL. The components of the incubation mixture were added to reach a final concentration of 50 mM Tris-HCl (pH 8.0), 10 mM dithiothreitol, 6 mM $MgCl_2$, 80 mM KCl, and the labeled nucleic acid duplex (20000 cpm) in a final volume of 50 μL. After incubation for 10 min at 37 °C, the reaction was stopped by addition of 1 mL of cold 10% TCA containing 0.1 M sodium pyrophosphate, the acid-precipitable material was collected on nitrocellulose filters and washed, the radioactivity was determined and the radioactivity released from the hybrid was determined by subtraction from the undigested hybrid control.

ADMETox studies

Aqueous solubility[12] (PBS, pH 7.4; Cerep catalogue reference 0435), partition coefficient[13] (log D, n-octanol/PBS, pH 7.4; Cerep catalogue reference 0417), human plasma protein binding[14] (Cerep catalogue reference 2194) and A-B permeability coefficient[15] (P_{app}, Caco-2 cells, pH 6.5/7.4; Cerep catalogue reference 3318) were determined in standard assays by Cerep, France (www.cerep.fr).

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