Supporting Information

Minimizing the contribution of enterohepatic recirculation to clearance in rat for the NCINI class of inhibitors of HIV.

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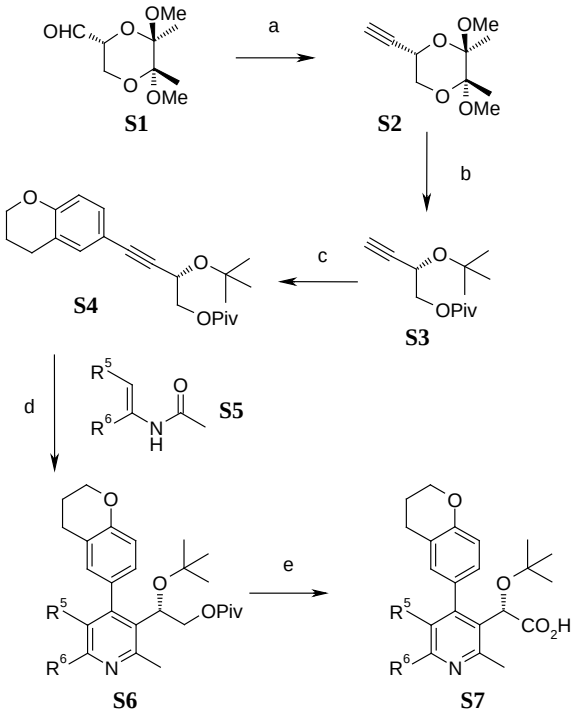
General.

All compounds were prepared as previously described.[1] NMR spectra were recorded on a Bruker AVANCEII (400 MHz for ^{1}H, 100 MHz for ^{13}C NMR) spectrometer and were referenced to DMSO-d^{6} (2.49 ppm for ^{1}H, 39.51 ppm for ^{13}C). Data are reported as follows: chemical shift (ppm), multiplicity (s=singlet, d=doublet, t= triplet, br=broad, m=multiplet), coupling constant (J, reported to the nearest 0.1Hz) and integration. HPLC purity was determined as previously described.[1] High resolution mass spectra were obtained on a Thermo Fisher Scientific LTQ OrbiTrap XL using a mobile phase of 85:15 water:CAN. The detector was set to negative ion mode (ESI source).

Synthetic Approaches.

Two distinct synthetic routes were used to prepare pyridine NCINIs analogs. In the Movassaghi approach, we relied on conversion of Ley's aldehyde **S1** to internal olefin **S4** as previously described. Using the protocol of Movassaghi, these alkynes were cyclocondensed with enamdes of general structure **S5** to introduce a range of substitutions at the R^{5} and R^{6} position. The route was then completed with removal of the Piv group and stepwise oxidation of the resulting primary alcohol to the corresponding acid **S7** (step e). In some cases **S7** was a final compound for biological evaluation, but in others **S7** served as an intermediate to further chemical modification at the R^{6} position. Generally this was accomplished by protection of the carboxylic acid followed by a range of chemical transformations, which were in turn followed by saponification to give final compounds. For full details, see reference 1.

Scheme S1. Movassaghi approach.

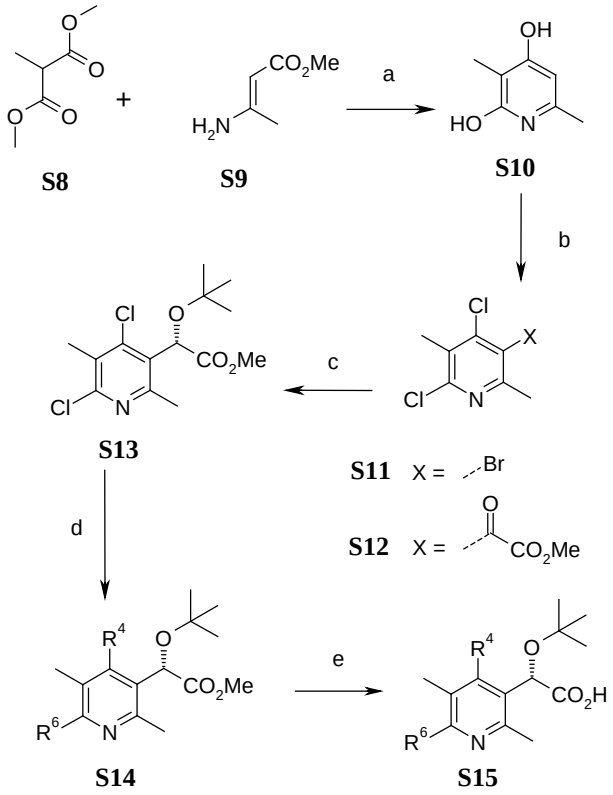


Conditions: a) Bestmann-Ohira reagent, MeOH, K_2CO_3, 53-97%; b) i. AcOH/H_2O, Δ, 35-68%; ii. PivCl, DIPEA, DCM, 40-58%; iii. isobutene, hexane, $HClO_4$, 74-95%; c) Ar-I, Pd[PPh_3]$_4$, Et_2NH, Δ, 54-95%; d) **S5**, 2-ClPyr, Tf_2O, then **S4**, 18-74%; e) i. $LiBH_4$/THF,41-99%; ii. Dess-Martin periodinane, iii. $NaClO_2$, NaH_2PO_4, 1-methyl-1-cyclohexene, *i*BuOH/H_2O, 25-56% following prep-HPLC purification (2 steps).

In the Knochel approach, condensation of **S8** and **S9** followed by saponification and decarboxylation provided tetrasubstituted pyridine **S10**. A two-step conversion of this compound to bromide **S11** allowed for metal-halogen exchange followed by quenching with methyl chlorooxoacetate to provide ketoester **S12**. CBS reduction followed by alkylation then provided ester **S13**. We found that oxidative addition of Pd(0) species

was selective at the C6 position over the C4 position and used this knowledge to introduce the R6 substituent under standard Suzuki coupling conditions. Introduction of the C4 arene to give compound **S14** was then accomplished with a more reactive catalyst bearing dicyclohexylphosphino-N,N-dimethylaminobiphenyl as the ligand in order to reduce the amount of dehalogenated side product formed under the reaction conditions. Finally, the ester was hydrolyzed to give the final prduct **S15**. For full details, see reference 1.

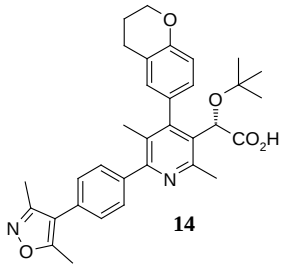
Scheme S1. Knochel approach.



Conditions: a) NaOEt/EtOH, PhH, Δ, 15-60%; b) i. Br_2/DCM 70-90%; ii. $PhPCl_2$, Cl_2, Δ, 80-90% ; iii. iPrMgBr.LiCl, THF, -20 °C, ClCOCOOMe, 60-70% ; c) i. (R)-CBS, catecholborane, PhH, 60-75%, 95% ee. ii. tBuOAc, $HClO_4$, 60-70% ; d) i. R^6-$B(OR)_2$, $PdCl_2[PPh_3]_2$, Na_2CO_3, DMF/H_2O, 50-97% ; ii. R^4-$B(OR)_2$, Pd_2dba_3, Na_2CO_3, DMA/H_2O, 50-97%; e) NaOH, THF/H_2O 34-80%, following prep-HPLC purification.

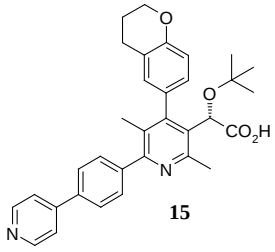
Characterization of selected representative compounds.

Compound **14**:



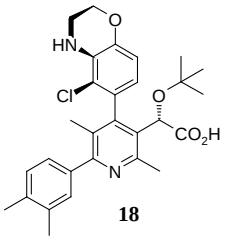
^{1}H NMR: 7.69 (br, 2H), 7.55 (br 2H), 7.05-7.02 (m, 2H), 6.93-6.89 (m, 2H), 4.97 and 4.94 (s, two rotamers, 1H), 4.20 (br, 2H), 2.61 (br, 2H), 2.45 (s, 3H), 2.28 (s, 3H), 2.01-1.91 (br m, 5H), 0.93 and 0.92 (s, 9H). HRMS: m/z calc. for $C_{33}H_{36}N_2O_5$ – H^+: 539.2552, m/z found: 539.2550 (+0.2 ppm). HPLC purity: >99% @ 254 nm.

Compound **15**:



^{1}H NMR: 8.83 (br, 2H), 8.11 (br, 2H), 8.04 (br d, J = 8.2Hz, 2H), 7.78 (br d, J = 8.0 Hz, 2H), 7.04-7.02 (m, 2H), 6.92-6.87 (m, 1H), 4.97 and 4.94 (s, two totamers, 1H), 4.20 (m, 2H), 2.85-2.5 (m, 5H), 2.05-1.89 (m, 5H), 0.93 (s, 9H). HRMS: m/z calc. for $C_{33}H_{34}N_2O_4$ – H^+: 521.2446, m/z found: 521.2445 (-0.1 ppm). HPLC purity: >99% @ 254 nm.

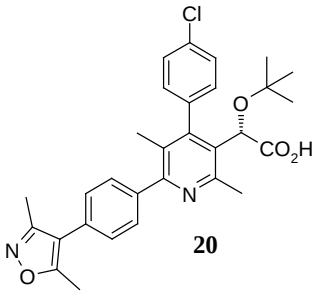
Compound **18**:



^{1}H NMR: 7.38 (br, 1H), 7.31 (br, 2H), 6.80 (d, J = 8.5 Hz, 1H), 6.30 (d, J = 8.1 Hz), 5.94 (br, 1H), 4.96 (s, 1H), 4.18 (br, 2H), 3.40 (br, 2H), 2.76 (br, 3H), 2.30 (br, 6H) 1.85 (s, 3H), 1.06 (s, 9H). HRMS: m/z calc. for $C_{29}H_{33}ClN_2O_4$ – H^+:

507.2056, m/z found: 507.2058 (+0.4 ppm). HPLC purity: 96% @ 254 nm.

Compound **20**:



20

^{1}H NMR: 7.64-7.57 (m, 4H), 7.48-7.45 (m, 2H), 7.43-7.34 (m, 2H), 4.76 (s, 1H), 2.55 (br s, 3H), 2.44 (br s, 3H), 2.27 (s, 3H), 1.92 (s, 3H), 0.91 (s, 9H). ^{13}C NMR: 173.29, 165.26, 158.15, 155.66, 154.56, 148.49, 139.62, 136.46, 132.86, 131.33, 130.97, 130.31, 129.71, 129.32, 128.57, 128.34, 125.67, 115.61, 75.04, 67.79, 27.77, 23.27, 18.14, 11.44, 10.57. HRMS: m/z calc. for $C_{30}H_{31}ClN_2O_4$ – H^+: 517.1900, m/z found: 517.1901 (+0.4 ppm). Two lots of compound **20** were used for biological testing: Lot 1 (HPLC purity: 93% @ 254 nm) was used to acquire the antiviral potency, $K_{d\text{-}app}$, caco-2 permeability, CYP inhibition and metabolic stability presented in this Letter. Lot 2 (HPLC purity: >99.5% @ 254 nm) was used to confirm the antiviral potency (although fewer variants of IN were tested), $K_{d\text{-}app}$, metabolic stability and caco-2 data, as well as acquire the solubility, logD, rat PK and bile duct cannulated rat PK data presented in this Letter.

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[1] Yoakim, C.; Bailey, M. D.; Bilodeau, F.; Carson, R. J.; Fader, L.; Kawai, S.; Laplante, S.; Simoneau, B.; Surprenant, S.; Thibeault, C.; Tsantrizos, Y. S. Inhibitors of human immunodeficiency virus replication. WO 2010/130034