

Supplemental Materials

Synthesis Methods

General Methods. Commercially available reagents and solvents were used without further purification unless stated otherwise. LC-MS analyses were performed on an Agilent 1100 HPLC coupled to an Agilent G1946C electrospray mass spectrometer in positive ion mode with scan range was 100-1000d. Preparative normal phase chromatography was performed on a CombiFlash Rf+ (Teledyne Isco) with pre-packed RediSep Rf silica gel cartridges. Preparative reverse phase HPLC was performed on a CombiFlash Rf+ (Teledyne Isco) equipped with RediSep Rf Gold pre-packed C18 cartridges and an acetonitrile/water/0.05% TFA gradient. The purity of tested compounds was $\geq 95\%$ as determined by HPLC analysis conducted on an Agilent 1100 system using a reverse phase C18 column with diode array detector unless stated otherwise. NMR spectra were recorded on a Bruker 400 MHz spectrometer. The signal of the deuterated solvent was used as internal reference. Chemical shifts (δ) are given in ppm and are referenced to residual not fully deuterated solvent signal. Coupling constants (J) are given in Hz.

Compounds #125, 126, and 127 were synthesized as described by Summa and coworkers.¹ Compounds #148, 151, 152, 154, and 155 were synthesized as previously described by Williams and coworkers.² Synthesis of novel compounds #121, 149, 150 and 153 are described below.

N-[(4-fluorophenyl)methyl]-5-hydroxy-1-methyl-6-oxo-2-[2-(phenylformamido)propan-2-yl]-1,6-dihydropyrimidine-4-carboxamide (#121). A mixture of 2-(2-aminopropan-2-yl)-N-[(4-fluorophenyl)methyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide (50 mg, 0.150 mmol; ArkPharm), benzoic acid (37 mg, 0.299 mmol), EDC hydrochloride (57 mg, 0.299 mmol), and HOBT hydrate (57 mg, 0.299 mmol) in DCM (1 mL) was treated with DIEA (52 μ L, 0.299 mmol). The reaction was quenched after 7 h with two drops of water and concentrated under a stream of air overnight. The reaction was purified by reverse phase HPLC (10 to 80% acetonitrile/water/0.05% TFA). A precipitate formed upon concentration of the purified fractions. The precipitate was filtered and washed with water to give the title compound as a white solid (32.9 mg, 50%). HPLC purity 97%. LCMS ES+ m/z 439 (M+H)⁺, 461 (M+Na)⁺.

4-[(4-bromophenyl)methyl]-1-hydroxy-1,2-dihydro-1,8-naphthyridin-2-one hydrobromide (#149). Step 1. 1-Benzyloxy-2-oxo-1,8-naphthyridin-4-yl) trifluoromethanesulfonate (0.500 g, 1.25 mmol; Example 103 Step 1 in Williams et al.²) was added to a microwave vessel with THF (10 mL). The vessel was sparged with nitrogen for 5 min and then tetrakis(triphenylphosphine)palladium(0) (72 mg, 0.062 mmol) was added. The vessel was crimped shut and sparged again for 5 minutes using nitrogen. Bromo-[(4-bromophenyl)methyl]zinc (5 mL of a 0.5 M solution in THF) was added via syringe and the reaction was irradiated at 110 °C for 10 minutes using microwaves. TLC in 35% EtOAc/hexanes indicated the reaction to be complete. The reaction was taken up in EtOAc and washed using 1N HCl and then saturated brine. The EtOAc layer was dried over sodium sulfate, filtered and evaporated to give 1.18 g of crude product as a yellow oil. The material was chromatographed on 12 g of silica (linear gradient from 5% EtOAc/hexanes up to 60% EtOAc/hexanes over 12 minutes). Pure fractions were pooled and evaporated to furnish 1-benzyloxy-4-[(4-bromophenyl)methyl]-1,8-naphthyridin-2-one as an off-white solid (220 mg; 41% yield). LCMS ES+ m/z 421, 423 (M+H)⁺. Step 2. A round bottom flask was charged with 1-benzyloxy-4-[(4-bromophenyl)methyl]-1,8-naphthyridin-2-one (75 mg, 0.17 mmol), 33% HBr in HOAc (1 mL) and water (0.3 mL). The reaction was heated to 80 °C for 2 hours. After 2 h, the mixture was cooled to room temperature and water was added. The precipitate was filtered, rinsed using additional

water and dried under high vacuum overnight to furnish the title compound as a tan solid (54 mg; 74% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.97 (br. s., 2 H), 8.63 - 8.68 (m, 1 H), 8.30 (dd, J=8.1, 1.7 Hz, 1 H), 7.49 - 7.55 (m, 2 H), 7.32 - 7.36 (m, 1 H), 7.27 - 7.31 (m, 2 H), 6.60 (s, 1 H), 4.24 (s, 2 H). HPLC purity 95%. LCMS ES+ m/z 331, 333 (M+H)⁺.

4-{{[4'-(aminomethyl)-[1,1'-biphenyl]-4-yl]methyl}-2,8-dihydro-1,8-naphthyridin-2-one hydrobromide (#150). Step 1. To a 5 mL microwave vial was added: 1-benzyloxy-4-[(4-bromophenyl)methyl]-1,8-naphthyridin-2-one (132 mg, 0.31 mmol; from Step 1 of the procedure for #149), DMF (5 mL) and water (1 mL). [4-[(tert-butoxycarbonylamino)methyl]phenyl]boronic acid (164 mg, 0.63 mmol), potassium carbonate (130 mg; 0.94 mmol) and Pd(dppf)Cl₂ (13 mg; 0.05 %) were added. The vessel was crimped shut and sparged using nitrogen for 10 minutes. The vessel was irradiated at 100 °C for 10 minutes. LC-MS analysis indicated a mixture of *tert*-butyl ((4'-((1-(benzyloxy)-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)methyl)-[1,1'-biphenyl]-4-yl)methyl)carbamate and des-*O*-benzylated product *tert*-butyl ((4'-((2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)methyl)-[1,1'-biphenyl]-4-yl)methyl)carbamate. The reaction was taken up in EtOAc and washed using 1N HCl, saturated sodium bicarbonate and then brine. The EtOAc layer was dried (sodium sulfate), filtered and evaporated to give 0.29 g of the crude mixture. Step 2. The crude mixture (0.29 g) was taken up in 2 mL HBr in HOAc (33%) with water (0.5 mL) and heated to 80 °C for 30 min to give primarily the des-*O*-benzylated product. Repeated trituration from MeOH and MeCN gave the title compound 4-{{[4'-(aminomethyl)-[1,1'-biphenyl]-4-yl]methyl}-2,8-dihydro-1,8-naphthyridin-2-one hydrobromide as a tan solid (50 mg, 28%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.07 (s, 1 H), 8.51 (d, J=3.4 Hz, 1 H), 8.26 (d, J=7.8 Hz, 1 H), 8.17 (br. s., 3H), 7.73 (d, J=8.3 Hz, 2 H), 7.66 (d, J=8.1 Hz, 2 H), 7.54 (d, J=8.1 Hz, 2 H), 7.43 (d, J=8.3 Hz, 2 H), 7.24 (dd, J=7.7, 4.8 Hz, 1 H), 6.40 (s, 1 H), 4.27 (s, 2 H), 4.08 (br. s., 2 H). HPLC purity 95%. LCMS ES+ m/z 342 (M+H)⁺.

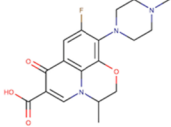
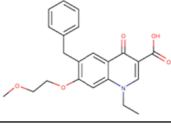
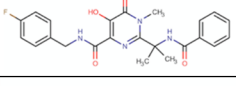
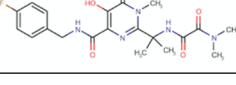
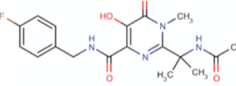
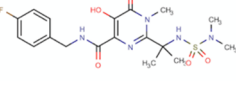
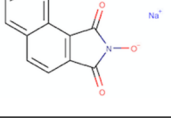
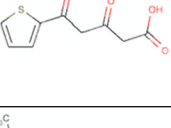
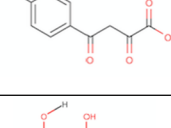
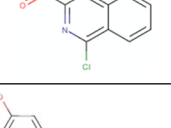
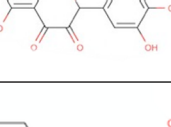
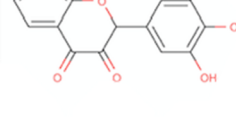
4-{{[3'-(aminomethyl)-[1,1'-biphenyl]-4-yl]methyl}-1-hydroxy-1,2-dihydro-1,8-naphthyridin-2-one trifluoroacetate (#153). Step 1. To a microwave vial was added 1-benzyloxy-4-[(4-bromophenyl)methyl]-1,8-naphthyridin-2-one (256 mg; from Step 1 of the procedure for #149) and anhydrous THF (7 mL). [3-[(tert-butoxycarbonylamino)methyl]phenyl]boronic acid (317 mg), cesium acetate (350 mg) and tetrakis(triphenylphosphine)palladium(0) (35 mg) were added. The vessel was crimped shut and sparged using nitrogen for 10 minutes. The vessel was irradiated at 90 °C for 20 minutes. The reaction was taken up in EtOAc and washed using water, then brine. The EtOAc layer was dried (sodium sulfate), filtered and evaporated to give 0.265 g of crude material as a yellow solid. The material was chromatographed on 40 g of silica (10-80% EtOAc/hexanes) to yield *tert*-butyl N-[[3-[4-[(1-benzyloxy-2-oxo-1,8-naphthyridin-4-yl)methyl]phenyl]phenyl]methyl]carbamate as a clear oil (75 mg, 38% yield). LCMS ES+ m/z 570 (M+Na)⁺. Step 2. A round bottom flask was charged with *tert*-butyl N-[[4-[4-[(1-benzyloxy-2-oxo-1,8-naphthyridin-4-yl)methyl]phenyl]phenyl]methyl]carbamate (75 mg), HBr in HOAc (2 mL of 33% w/w) and water (1 mL) and heated to 80 °C for 3 h. The reaction was evaporated to give 0.139 g of crude material which was chromatographed on a 120 g C-18 column (5%-40% MeCN/water/0.05% TFA) to yield a deep yellow oil which was lyophilized from 1mL MeCN and 3 mL water to obtain the title compound 4-[[4-[4-(aminomethyl)phenyl]phenyl]methyl]-1-hydroxy-1,8-naphthyridin-2-one trifluoroacetate as a yellow foam (32 mg, 67% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.94 (br. s., 1 H), 8.61 - 8.73 (m, 1 H), 8.34 (dd, J=7.9, 1.6 Hz, 1 H), 8.17 (br. s., 2 H), 7.78 (s, 1 H), 7.61 - 7.72 (m, 3 H), 7.51 (dd, J=7.6 Hz, 1 H), 7.40 - 7.49 (m, 3 H), 7.34 (dd, J=8.1, 4.6 Hz, 1 H), 6.60 (s, 1 H), 4.31 (s, 2 H), 4.11 (d, J=5.6 Hz, 2 H). HPLC purity 98%. LCMS ES+ m/z 358 (M+H)⁺.

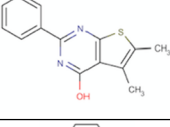
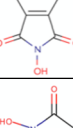
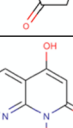
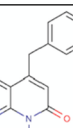
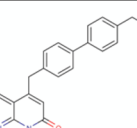
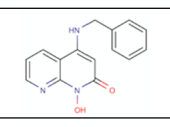
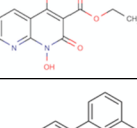
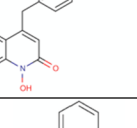
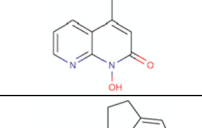
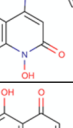
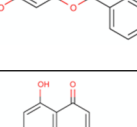
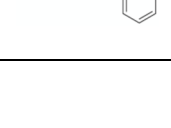

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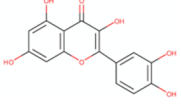

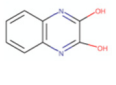
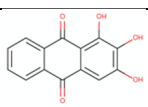
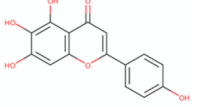
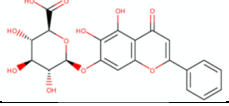
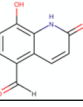
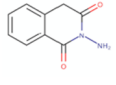

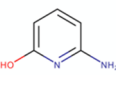
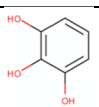
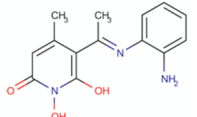
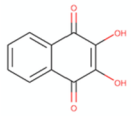
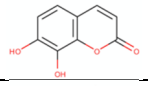
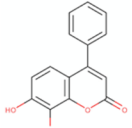
1. Summa, V.; Petrocchi, A.; Bonelli, F.; Crescenzi, B.; Donghi, M.; Ferrara, M.; Fiore, F.; Gardelli, C.; Gonzalez Paz, O.; Hazuda, D. J.; Jones, P.; Kinzel, O.; Laufer, R.; Monteagudo, E.; Muraglia, E.; Nizi, E.; Orvieto, F.; Pace, P.; Pescatore, G.; Scarpelli, R.; Stillmock, K.; Witmer, M. V.; Rowley, M., Discovery of raltegravir, a potent, selective orally bioavailable HIV-integrase inhibitor for the treatment of HIV-AIDS infection. *J Med Chem* **2008**, *51* (18), 5843-55.
2. Williams, P. D.; Venkatraman, S.; Langford, H. M.; Kim, B.; Booth, T. M.; Grobler, J. A.; Staas, D.; Ruzek, R. D.; Embrey, M. W.; Wiscount, C. M.; Lyle, T. A. 1-Hydroxynaphthyridine Compounds as Anti-HIV Agents. 24 January 2008, WO2008/010964 A1.

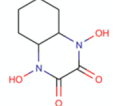
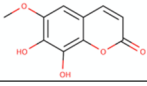
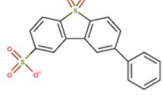
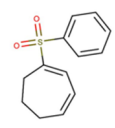
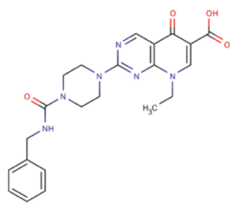
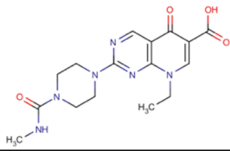
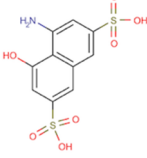
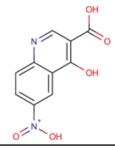
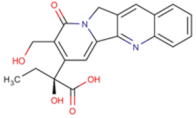
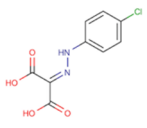

Table S1. Compounds used in the study.

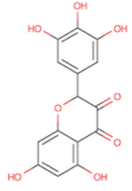
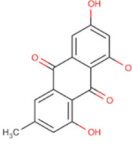

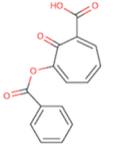
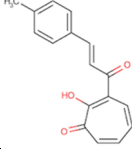
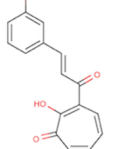
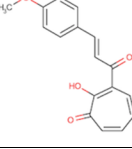
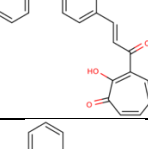
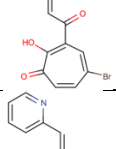
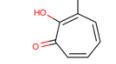
Compound	Structure	Formal Name
1		TRC 939800 ("D")
2		Sigma 74540
3		Sigma n8164
4		TimTec ST029023
5		Enamine T0506-3483
7		Idofine 02030
9		Sigma 70050
10		Selleck S2001 (Elvitegravir)
11		Selleck S2005 (Raltegravir)
12		Napthyridin-one
19		Sigma 586862
20		Sigma - L133671
23		Sigma - 28605
34		Indofine-D-009
49		Nootkatin
50		5-nitrosotropolone
51		tropolone p-nitrobenzoate
52		NSC 79556
54		3-bromotropolone
60		Chembridge 5942159
62		Chembridge 5946384
64		Sigma CDS015295
65		Sigma O0877
67		Sigma 17850

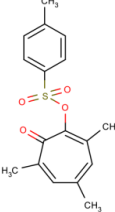
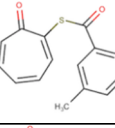
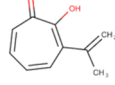
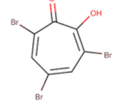
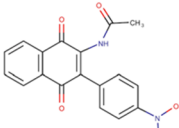
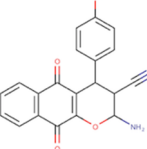
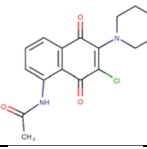
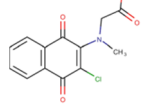
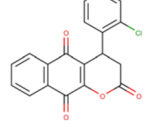
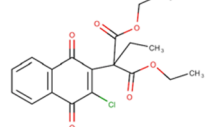
68		Sigma O8757
69		Sigma R747092
121		CWHM- 000527
125		CWHM- 000555
126		CWHM- 000556
127		CWHM- 000557
128		Aldrichsele ct CNC_ID 100615760
129		Aldrichsele ct CNC_ID 249465147
130		Aldrichsele ct CNC_ID 343616947
132		Aldrichsele ct CNC_ID 389306767
<u>134</u> (#134 and # 158 are tautomer)		Aldrichsele ct CNC_ID 110964023
135		Aldrichsele ct CNC_ID 361173301

136		Aldrichsele ct CNC_ID 187741800
138		Sigma H53704
139		Sigma 130672
148		CWHM- 000613
149		CWHM- 000614
150		CWHM- 000615
151		CWHM- 000616
152		CWHM- 000617
153		CWHM- 000631
154		CWHM- 000632
155		CWHM- 000633
156		Sigma 465119, Baicalein
157		Sigma C80105, Chrysin

158 (#134 and #158 are tautomer)		Sigma Q4951, Quercetin
197		Benzoylene-urea
198		2,3-dihydroxy-quinoxaline
200		Anthragallo I
201		Scutellarein
202		Baicalin
203		TRC 700465
204		AK-830/13217 043
205		AH-034/32461 056
206		AJ-333/25006 202
207		AB-131/40221 933
208		Sun B8155
209		2,3-Dihydroxynaphthoquinone
214		Sigma D5564
215		Sigma 576441

217		Visas M Lab 444035142
218		Aldrichselect
304		2-SO3H-8-PhDBTOO
307		2-(Phenylsulfonyl)-1,3-cycloheptadiene
321		AMS 149974043
322		AMS 239435306
323		AMS 388708402
324		AMS 295104760
325		AMS 295182442
326		CPHM
327		AMS 444085867

328		Myricetin
329		Emodin
338		Specs AN-584/43416 481
339		Specs AA-504/34235 011
340		Specs AP-355/40633 884
341		Specs AP-355/40802 214
342		Specs AP-355/40633 885
343		Specs AP-355/42609 671
344		Specs AP-355/42609 657
345		Specs AP-355/40810 250

346		Specs AG-690/13416 737
348		MolPort-007-556-276
349		MolPort-002-899-110
350		MolPort-002-514-431
352		Labotest LT0011262 2
353		Visas-M Labs STK35858 5
354		ChemDiv 5271-0027
355		Visas-M Labs STK60515 1
356		Visas-M Labs STK65869 1
357		Visas-M Labs STK66385 0