Supporting Information

Discovery of BI 224436, a Non-Catalytic Site Integrase Inhibitor (NCINI) of HIV-1 Integrase LTR DNA 3′-Processing.

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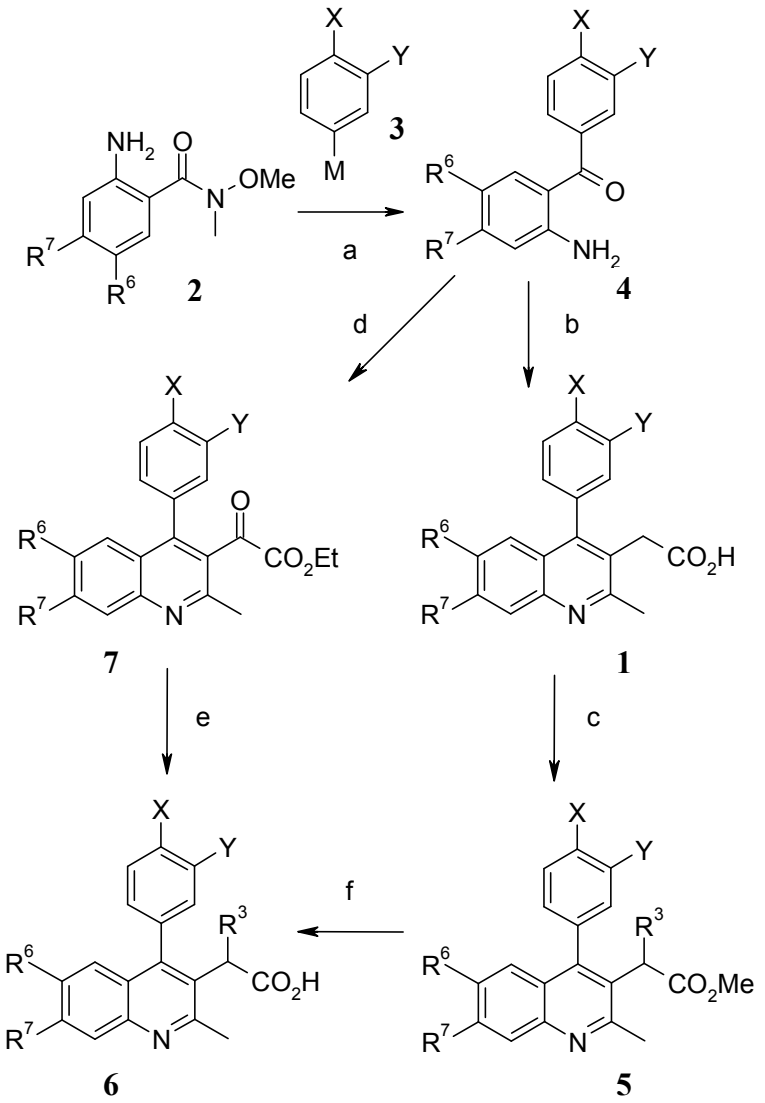
General.

All compounds were prepared as previously described.[1-3] NMR spectra were recorded on a Bruker AVANCEII (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) spectrometer and were referenced to DMSO-d^{6} (2.50 ppm). Data are reported as follows: chemical shift (ppm), multiplicity (s=singlet, d=doublet, t= triplet, br=broad, m=multiplet), integration, and coupling constant (J, reported to the nearest 0.1Hz). UPLC-MS were obtained on a Waters ACQUITY UPLC® System, using ESI+/- ion mode, a BEH column (2.1x50mm C18, 1.7um particle diameter) and the following gradient: 90%A to 100%B in 1.19 minutes hold at 100%B to 1.70 minutes and a flow rate of 0.8mL/min (A=95:5 Water/Acetonitrile with 0.05% Formic Acid; B= Acetonitrile with 0.05% Formic Acid). 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 positive ion mode (ESI source).

Synthetic Approaches.[1]

The NCINI class of inhibitor was divided into three strategic substructures for modification: the C3 acetic acid moiety, the C4 arene and the B-ring. We devised three routes to introduce these substructures late in the synthetic sequence. In the first approach designed to prepare analogs of the C3 substituent, anthranilic acid-derived Weinreb amides **S2** were reacted with a metallated arene **S3** (M = Li or Mg) to give polysubstituted benzophenones **S4**, establishing the B-ring and C4-aryl substitution patterns (Scheme S1). Condensation with levulinic acid then gave compound **S1** (R^{6} = Cl, X = Y = H). For further modification of the C3 position, the methyl ester of compound **S1** was prepared and then a range of chemical transformations at the α-position were performed to give ester **S5**, which was saponified to give acid **S6**. Alternatively, compound **S4** was condensed with ethyl acetopyruvate to provide ketone **S7**, which then underwent a range of transformations to give compound **S6**.

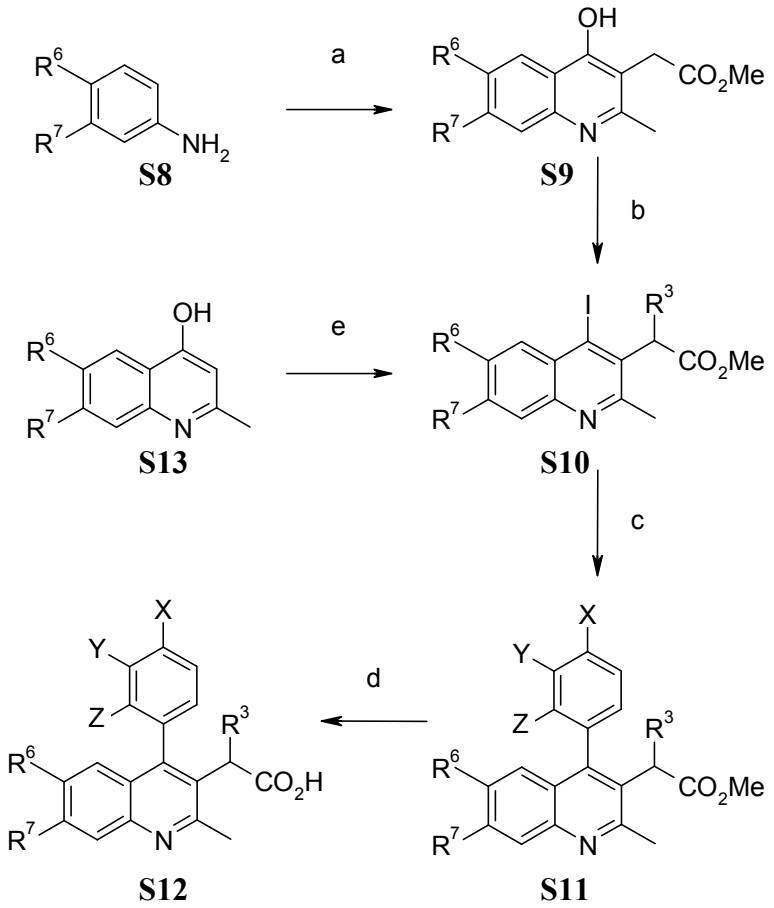
Scheme S1. Late stage modification at the C3 position.



Conditions: a) **S2** + **S3**, THF, 0 °C to rt, 20-85%; b) levulinic acid, H_2SO_4, AcOH, Δ, 17-87%; c) i. CH_2N_2/Et_2O; ii. see refs. 2-4; d) ethyl acetopyruvate, H_2SO_4, AcOH, Δ, 16-70%; e) see refs. 2-4; f) NaOH, THF, H_2O 50-95%.

When late stage introduction of the C4 arene is preferred, aniline **S8** was condensed with diethyl acetosuccinate to give quinoline **S9** (Scheme S2). The phenol was then converted to the corresponding iodide and then the R3 substituent was installed by one of a number of transformations to give compound **S10**. Suzuki coupling to give biaryl **S11** followed by saponification then yielded carboxylic acid **S12**. When convenient, iodide **S10** was also prepared from hydroxyquinoline **S13**.

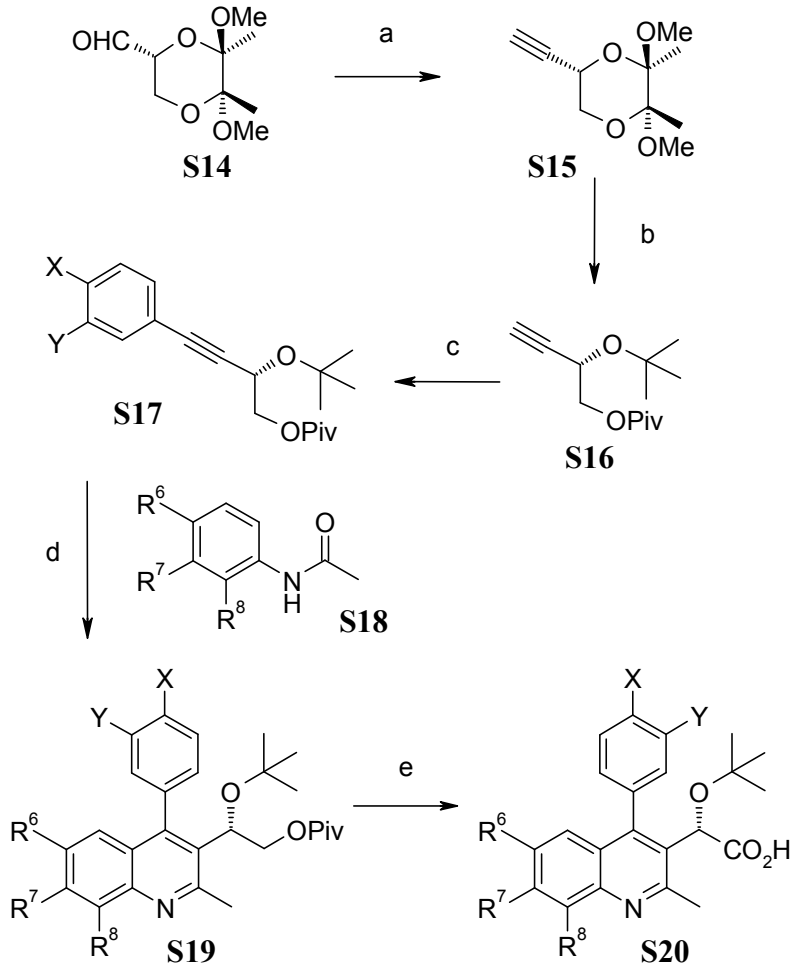
Scheme S2. Late stage introduction of the C4-arene.



Conditions: a) **S8** + diethyl acetosuccinate, Ph_2O, Δ, 19-79%; b) i. $POCl_3$, Δ, 27-97%; ii. HCl, NaI, Δ, 75-98%; iii. LiHMDS, Davis reagent, THF, 23-86%; iv) see ref. 3; c) Ar-$B(OR)_2$, $Pd[PPh_3]_4$, Na_2CO_3, DMF/H_2O, Δ or μW, 22-97%; d) NaOH, THF/ H_2O.; e) see ref. 2-4.

When exploring the substitution pattern on the B-ring, a third route beginning with the conversion of Ley's aldehyde **S14**[5] to alkyne **S15** also proved useful (Scheme S3). Deprotection of the diol, acylation of the primary alcohol and etherification of the remaining secondary alcohol then gave compound **S16**. The C4 arene was then introduced with a Sonogashira coupling to give internal alkyne **S17**. Late stage introduction of the B-ring using Movassaghi's quinoline synthesis involving activation of anilide **S18** and formal cyclocondensation with alkyne **S17** then gave compound **S19**.[6] The success of this approach was contingent on one of X or Y being an electron-donating group, as originally described.[6] Finally, removal of the Piv group and oxidation provided carboxylic acid **S20**.

Scheme 3. Late stage B-ring modification



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) **S18**, 2-ClPyr, Tf_2O, then **S17**, 47-93%; e) i. $LiBH_4$/THF,49-92%; ii. Dess-Martin periodinane, iii. $NaClO_2$, NaH_2PO_4, 1-methyl-1-cyclohexene, *i*BuOH/H_2O, 25-56% (2 steps).

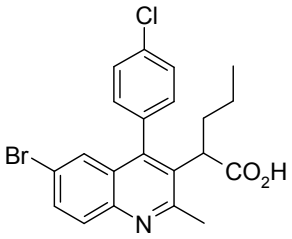
Table S1. *In vitro* ADME profile of compounds 16 and 19.

	16	**19**
EC_{50} range,[a] nM	23-110	13-130
HLM / RLM ($t_{1/2}$), min	82 / 130	230 / 160
Caco-2 (P_{app}), x 10^6, cm/s	23	14
CyP450 inh. (IC_{50}, 3A4 / 2D6), μM	>30 / >30	26 / >30
Solubility[b] (pH = 6.8), mg/mL	>1.0	0.70

[a] Determined with HxB2 virus (A124/T125 IN variant), NL4.3 virus (T124/T125 variant) or recombinant NL4.3 virus (T124A, T124A/T125A, T124N or T124N/T125A IN mutants). [b] For the amorphous powder.

Characterization of selected representative compounds.

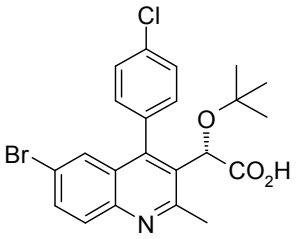
Compound **8**:



8

^{1}H NMR: 12.7 (br, 1H), 7.92 (d, 1H, 8.9 Hz), 7.86-7.83 (m, 1H), 7.70-7.66 (m, 2H), 7.37-7.35 (m, 1H), 7.31-7.28 (m, 1H), 7.23 (d, 1H, J = 2.2 Hz), 3.64 (br, 1H), 2.64 (s, 3H), 2.06-2.04 (m, 1H), 1.55 (s, 1H), 1.10-0.88 (m, 2H), 0.65 (t, 3H, J = 7.2). ^{13}C NMR: 174.0, 158.5, 145.6, 143.6, 134.4, 133.5, 132.4, 131.8, 131.5, 131.1, 130.1, 129.1, 128.8, 127.7, 127.3, 119.5, 46.0, 31.9, 24.0, 20.7, 13.7. HRMS: m/z calc. for $C_{21}H_{19}BrClNO_2 + H^+$: 432.0360, m/z found: 432.0347 (-3.1 ppm). UPLC-MS: rt = 1.25 min, m/z 432.1 $[M + H]^+$, purity: >99.9% @ 254 nm.

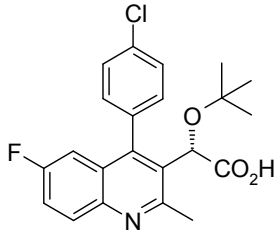
Compound **13**:



13

^{1}H NMR: 13.1 (br, 1H), 7.93 (d, 1H, J = 8.9 Hz), 7.88-7.85 (m, 1H), 7.75-7.68 (m, 2H), 7.47-7.44 (m, 2H), 7.33 (d, 1H, J = 2.0 Hz), 4.97 (s, 1H), 2.73 (s, 3H), 0.90 (s, 9H). HRMS: m/z calc. for $C_{22}H_{21}BrClNO_3 + H^+$: 462.0466, m/z found: 462.0451 (-3.3 ppm). UPLC-MS: rt = 1.27 min, m/z 462.1 $[M + H]^+$, purity: >99.9% @ 254 nm.

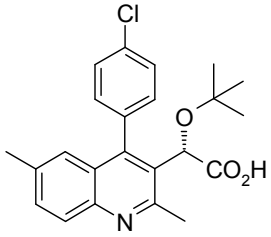
Compound **14**:



14

^{1}H NMR: 13.1 (br, 1H), 8.07-8.04 (m, 1H), 7.74-7.64 (m, 3H), 7.47-7.42 (m, 2H), 6.90-6.86 (m, 1H), 4.99 (s, 1H), 2.73 (s, 3H), 0.90 (s, 9H). HRMS: m/z calc. for $C_{22}H_{21}ClFNO_3 + H^+$: 402.1267, m/z found: 402.1257 (-2.4 ppm). UPLC-MS: rt = 1.13 min, m/z 402.2 $[M + H]^+$, purity: >99.9% @ 254 nm.

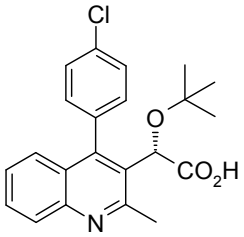
Compound **15**:



15

^{1}H NMR: 13.2 (br, 1H), 7.95 (d, 1H, J = 8.6 Hz), 7.75-7.66 (m, 3H), 7.47-7.40 (m, 2H), 7.09 (s, 1H), 4.98 (s, 1H), 2.78 (s, 3H), 2.36 (s, 3H), 0.91 (s, 9H). ^{13}C NMR: 172.8, 157.0, 137.2, 133.9, 133.5, 133.1 (br), 131.8, 131.4, 130.4, 128.9, 128.5, 125.7, 125.4 (br), 125.0, 75.7, 69.7, 27.7, 22.9, 21.3. HRMS: m/z calc. for $C_{23}H_{24}ClNO_3 + H^+$: 398.1517, m/z found: 398.1504 (-3.4 ppm). UPLC-MS: rt = 0.93 min, m/z 398.2 $[M + H]^+$, purity: >99.9% @ 254 nm.

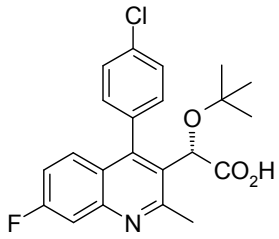
Compound **16**:



16

^{1}H NMR: 13.0 (br, 1H), 7.97 (d, 1H, J = 8.1 Hz), 7.75-7.71 (m, 2H), 7.69-7.66 (m, 1H), 7.49-7.45 (m, 2H), 7.42-7.39 (m, 1H), 7.25 (m, 1H), 5.00 (s, 1H), 2.74 (s, 3H), 0.90 (s, 9H). HRMS: m/z calc. for $C_{22}H_{22}ClNO_3 + H^+$: 384.1361, m/z found: 384.1351 (- 2.5 ppm). UPLC-MS: rt = 0.94 min, m/z 384.3 $[M + H]^+$, purity: >99.9% @ 254 nm.

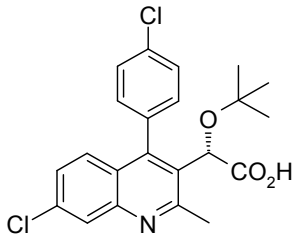
Compound **17**:



17

^{1}H NMR: 13.1 (br, 1H), 7.74-7.66 (m, 3H), 7.48-7.38 (m, 3H), 7.33-7.29 (m, 1H), 4.98 (s, 1H), 2.74 (s, 3H), 0.90 (s, 9H). HRMS: m/z calc. for $C_{22}H_{21}ClFNO_3 + H^+$: 402.1267, m/z found: 402.1258 (-2.1 ppm). UPLC-MS: rt = 1.13 min, m/z 402.2 $[M + H]^+$, purity: >99.9% @ 254 nm.

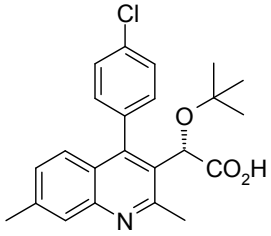
Compound **18**:



18

^{1}H NMR: 13.1, (br, 1H), 8.02 (d, 1H, J = 2.2 Hz), 7.74-7.67 (m, 2H), 7.52-7.41 (m, 3H), 7.27 (d, 1H, J = 9.0 Hz), 4.98 (s, 1H), 2.74 (s, 3H), 0.90 (s, 9H). HRMS: m/z calc. for $C_{22}H_{21}Cl_2NO_3 + H^+$: 418.0971, m/z found: 418.0959 (- 2.8 ppm). UPLC-MS: rt = 1.25 min, m/z 418.2 $[M + H]^+$, purity: >99.9% @ 254 nm.

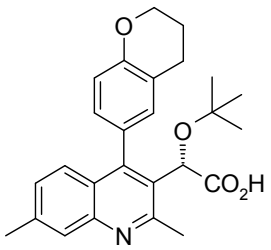
Compound **19**:



19

^{1}H NMR: 13.2 (br, 1H), 7.83 (s, 1H), 7.76-7.73 (m, 1H), 7.71-7.68 (m, 1H), 7.48-7.46 (m, 1H), 7.44-7.39 (m, 2H), 7.25 (d, 1H. J = 8.6 Hz), 5.03 (s, 1H), 2.81 (s, 3H), 2.52 (s, 3H), 0.92 (s, 9H). ^{13}C NMR: 172.8, 158.3, 157.9, 134.0, 133.4, 131.7, 131.4, 129.7 (br), 129.6, 128.9, 128.4, 126.3, 124.1 (br), 123.8, 75.7, 69.6, 27.6, 22.8, 21.3. HRMS: m/z calc. for $C_{23}H_{24}ClNO_3 + H^+$: 398.1517, m/z found: 398.1503 (- 3.6 ppm). UPLC-MS: rt = 0.90 min, m/z 398.2 $[M + H]^+$, purity: >99.9% @ 254 nm.

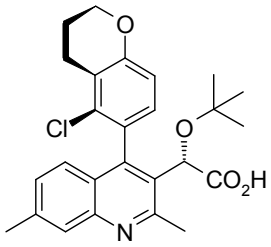
Compound **20**:



20

^{1}H NMR: (1:1 ratio of conformers) 13.2 (br, 1H), 7.84 (s, 1H), 7.48-7.39 (m, 2H), 7.18-6.96 (m, 3H), 5.17 and 5.14 (s, 1H), 4.26-4.23 (m, 2H), 2.88-2.72 (m, 5H), 2.54 (s, 3H), 1.99-1.93 (m, 2H), 0.90 (m, 9H). ^{13}C NMR: 172.9, 158.2, 157.9, 157.6, 155.3, 155.2, 131.3, 131.1, 130.2, 130.0, 128.6, 127.0, 125.4, 124.4, 122.7, 122.5, 116.6, 116.3, 75.8, 69.6, 69.5, 66.3, 66.2, 27.6, 27.5, 24.2, 22.0, 21.5, 21.4. HRMS: m/z calc. for $C_{26}H_{29}NO_4 + H^+$: 420.2169, m/z found: 420.2159 (- 2.4 ppm). UPLC-MS: rt = 0.78 min, m/z 420.3 $[M + H]^+$, purity: >99.9% @ 254 nm.

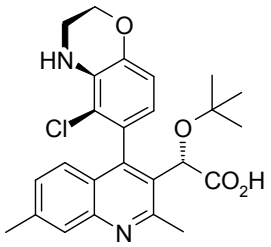
Compound **21**:



21

^{1}H NMR: 12.7 (br, 1H), 7.79 (s, 1H), 7.39-7.33 (m, 1H), 7.08-7.03 (m, 1H), 6.97-6.90 (m, 2H), 5.06 (s, 1H), 4.23-4.20 (m, 2H), 2.89 (s, 3H), 2.82-2.73 (m, 2H), 2.06-2.00 (m, 2H), 1.04 (s, 9H). HRMS: m/z calc. for $C_{26}H_{28}ClNO_4 + H^+$: 454.1780, m/z found: 454.1767 (-2.8 ppm). UPLC-MS: rt = 86 min, m/z 454.3 $[M + H]^+$, purity: 93.4% @ 254 nm.

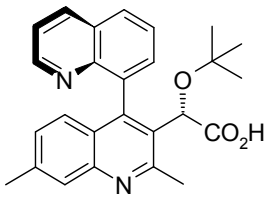
Compound **22**:



22

^{1}H NMR: 12.8 (br, 1H), 7.79 (s, 1H), 7.39 (d, 1H, J = 8.5 Hz), 7.11 (d, 1H, J = 8.7 Hz), 6.84 (d, 1H, J = 8.2 Hz), 6.37 (d, 1H, J = 8.2 Hz), 5.94 (br, 1H), 5.09 (s, 1H), 4.23-4.21 (m, 2H), 3.43 (br, 2H), 2.89 (s, 3H), 2.51 (s, 3H), 1.05 (s, 9H). HRMS: m/z calc. for $C_{25}H_{27}ClN_2O_4 + H^+$: 455.1732, m/z found: 455.1718 (-3.2 ppm). UPLC-MS: rt = 0.75 min, m/z 455.3 $[M + H]^+$, purity: 95.4% @ 254 nm.

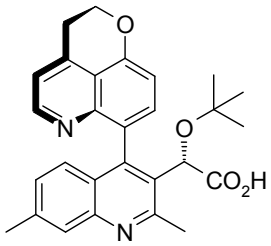
Compound **23**:



23

^{1}H NMR: 12.6 (br, 1H), 8.63-8.61 (m, 1H), 8.53 (d, 1H, J = 7.8 Hz), 8.23 (d, 1H, J = 8.1 Hz), 7.91 (s, 1H), 7.79 (t, 1H, J = 7.9 Hz), 7.63-7.55 (m, 2H), 7.34 (br, 1H), 6.98 (br, 1H), 4.95 (s, 1H), 3.04 (s, 3H), 2.53 (s, 3H), 0.78 (s, 9H). HRMS: m/z calc. for $C_{26}H_{26}N_2O_3 + H^+$: 415.2016, m/z found: 415.2001 (-3.7ppm). UPLC-MS: rt = 0.67 min, m/z 415.3 $[M + H]^+$, purity: 94.7% @ 254 nm.

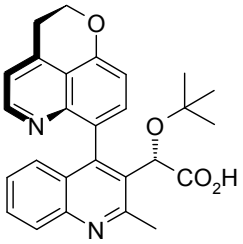
Compound **24**:



24

^{1}H NMR: 12.4 (br, 1H), 8.52 (d, 1H, J = 4.4 Hz), 7.73 (s, 1H), 7.43 (d, 1H, J = 7.8 Hz), 7.30 (d, 1H, J = 4.4 Hz), 7.12-7.09 (m, 2H), 6.82 (d, 1H, J = 8.5 Hz), 4.96 (s, 1H), 4.57-4.47 (m, 2H), 3.36-3.30 (m, 2H), 2.83 (s, 3H), 2.44 (s, 3H), 0.82 (s, 9H). HRMS: m/z calc. for $C_{28}H_{28}N_2O_4 + H^+$: 457.2122, m/z found: 457.2108 (-3.1 ppm). UPLC-MS: rt = 0.68 min, m/z 457.3 $[M + H]^+$, purity: >99.9% @ 254 nm.

Compound **26**:



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26

^{1}H NMR: 12.4 (br, 1H), 8.52 (d, 1H, J = 4.4Hz), 7.94 (d, 1H, J = 7.9 Hz),7.65-7.61 (m, 1H), 7.45 (d, 1H, J = 8.2 Hz), 7.31-7.24 (m, 2H), 7.12 (d, 1H, J = 7.9 Hz), 6.94-6.92 (m, 1H), 4.99 (s, 1H), 4.57-4.47 (m, 2H), 3.37-3.30 (m, 2H), 2.86 (s, 3H), 0.82 (s, 9H). ^{13}C NMR: 172.2, 158.4, 153.1, 150.1, 146.6, 146.1, 145.0, 141.0, 130.8 (br), 130.6 (br), 128.9, 128.0, 127.2, 127.1 (br) 126.4, 125.6, 118.0, 116.7, 109.1, 75.2, 70.8, 65.6, 27.7, 27.5, 24.9. HRMS: m/z calc. for $C_{27}H_{26}N_2O_4 + H^+$: 443.1965, m/z found: 443.1951 (-3.2 ppm). UPLC-MS: rt = 0.68 min, m/z 443.3 $[M + H]^+$, purity: >99.9% @ 254 nm.

References.

1. Detailed experimental procedures for Schemes S1-S3 have been described. See ref. 2-4.
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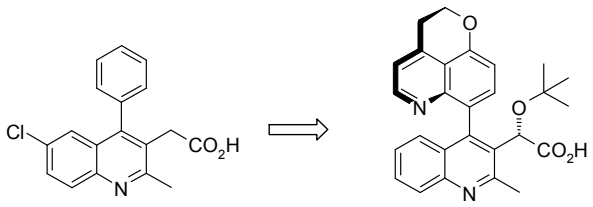

HTS hit
1a

EC_{50} = >40,000 nM

BI 224436
22

EC_{50} = 11-27 nM