Supporting Information

Discovery of Bicycloalkyl Urea Melanin Concentrating Hormone (MCH) Receptor Antagonists as Orally Efficacious Antiobesity Therapeutics.

Mark D. McBriar,* Henry Guzik, Ruo Xu, Jaroslava Paruchova, Shengjian Li,† Anandan Palani, John W. Clader, William J. Greenlee, Brian E. Hawes, Timothy J. Kowalski, Kim O'Neill, Brian Spar, and Blair Weig

Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, New Jersey 07033-0539

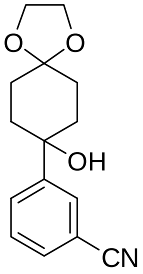
†*Current address: Johnson and Johnson Pharmaceutical Research Institute, Raritan, New Jersey.*

Synthetic procedures and characterization data for compounds **16**, **17**, **23**, **24**, **26, 28, 29-31**, and **38-40**.

Representative experimental:

Compounds **16** and **17:**

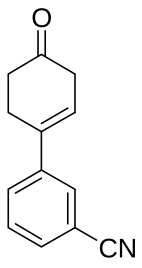
Step 1



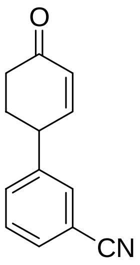
10

3-Bromobenzonitrile (20 g, 0.11 mole) was dissolved in THF (500 mL) and the solution was cooled to –100 °C. A solution of n-butyllithium (1.6 M in hexane, 68 mL, 0.11 mole) was added via an additional funnel over one hour. During this time, the temperature inside the reaction flask was kept below –95 °C. After addition was complete, the reaction was stirred at –95 °C for 10 minutes. A solution of 1, 4-dioxaspiro[4, 5]decan-8-one (17.1g, 0.11 mole) in THF (100 mL) was added over one hour. During this time the reaction temperature was kept below –75 °C. The reaction was then stirred for 30 minutes and the temperature slowly rose to –25 °C. The reaction was then quenched with H_2O and diluted with EtOAc. The organic layer was washed with water (3x), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was recrystallized from EtOAc/Hex to give rise to 15.5 g pure product as a white powder. The crude product from mother liquor was purified by flash chromatography (30% EtOAc/Hex) to provide an additional 8.0g (Total yield of **10**: 23.5 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 1 H), 7.76 (d, J = 7.7 Hz, 1 H), 7.54 (d, J = 7.7 Hz, 1 H), 7.45 (t, J = 7.7 Hz, 1 H), 3.99(t, J = 2.8 Hz, 4H), 2.0-2.2 (m, 4 H), 1.6-1.8 (m, 4 H).

Step 2



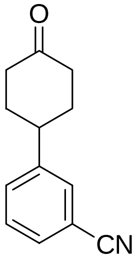
11



12

Alcohol **10** (10 g, 39 mmol) was dissolved in TFA (80 mL). The mixture was heated to 50 °C for 4 h. Trifluoroacetic acid was removed under vacuum and the residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was washed with water (2x) and dried over Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (15% EtOAc/Hex) provided 4-(3-cyanophenyl)-3-cyclohexene-1-one (**11,** 3.1 g, 41%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4-7.7 (m, 4H), 6.17 (t, J = 3.9 Hz, 1H). 3.11(s, 2H), 2.90 (t, J = 6.6 Hz, 2H), 2.67 (t, J = 6.6 Hz, 2 H) and 4-(3-cyanophenyl)-2-cyclohexene-1-one (**12,** 4.0 g, 53%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.63 (m, 4 H), 6.92 (d, J = 9.9 Hz, 1H), 6.92 (dd, J = 10.4, 2.7 Hz, 1H), 3.80 (m, 1H), 2.3-2.6 (m, 3H), 2.25 (m, 1H).

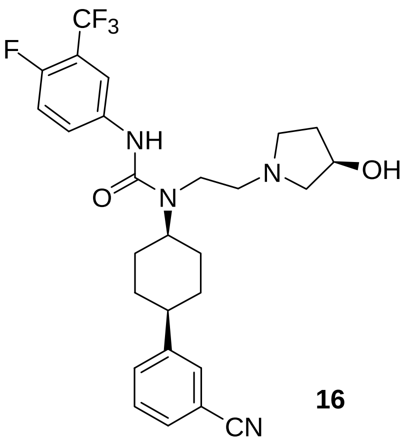
Step 3



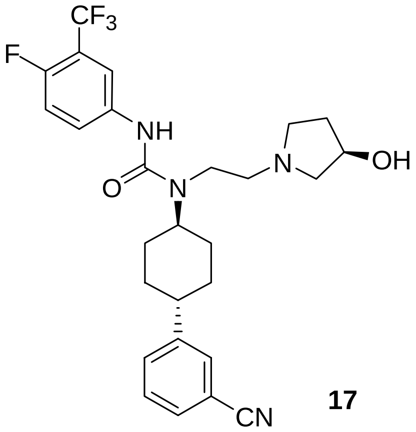
13

The mixture of **11** and **12** (1.8 g, 9.1 mmol) was dissolved in EtOAc (50 mL). The catalyst, 10 % Pt/C (0.5 g, 0.9 mmol) was then added and mixture was shaken at 45 psi hydrogen overnight. The catalyst was filtered and solvent was removed under vacuum. The residue was dissolved in CH_2Cl_2 (100 mL) and Dess-Martin periodinane (4.2 g, 10 mmol) was added. After 5 h, the solution was washed with water (3x), dried over Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (15% EtOAc/Hex) provided **13** (1.1g, 63%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4-7.6 (m, 4 H), 3.10 (t, J = 12.1, 3.3 Hz, 1H), 2.53 (m, 4H), 2.3 (m, 2H), 1.94 (m, 2H).

Step 4



16

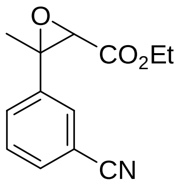


17

A solution of **13** (0.7 g, 3.5 mmol), N-(2-aminoethyl)-3-(S)-hydroxy-pyrrolidine[18] (1.36 g, 10.5 mmol) and sodium triacetoxyborohydride (2.2 g, 10.5 mmol) were refluxed in CH_2Cl_2 (50 mL). After 24 h, the organic layer was washed with water (3x), dried over sodium sulfate and concentrated in vacuo. The crude reaction mixture (60mg) and 3-chloro-4-(trifluoromethyl)phenyl isocyanate (50 mg, 0.29 mmol) were stirred in CH_2Cl_2 (5 mL). After 24 h, the reaction solution was loaded directly onto a preparative TLC plate and purified (15% EtOAc/Hex) to provide **16** (35.9 mg, 36%). ^{1}H NMR (300 MHz, CDCl3) δ 10.72 (s, 1H), 7.57-7.71 (m, 4H), 7.42-7.53 (m, 2H), 7.03 (t, J = 9.8 Hz, 1H), 4.48 (m, 1H), 4.29 (t, J = 12.0, 4.0 Hz, 1H), 3.00-3.17 (m, 4H), 2.66-2.85 (m, 4H), 1.76-2.52 (m, 8H), 1.60-1.70 (m, 2H), 1.30-1.45 (m, 2H). LCMS: 519.1, rt. = 5.46 min (M+H$^+$), 98% purity; HRMS (FAB) *m/z* 519.2392 [(M+H)$^+$; calcd for $C_{27}H_{30}F_4N_4O_2$: 519.2305], and **17** (38.6 mg, 39%). ^{1}H NMR (300 MHz, CDCl3) δ10.73 (s, 1H), 7.67-7.73 (m, 2H), 7.36-7.51 (m, 4H), 7.03 (t, J = 9.8 Hz, 1H), 4.51 (m, 1H), 4.24 (t, J = 12.0, 4.0 Hz, 1H), 3.35 (t, J = 4.0 Hz, 2H), 3.10 (m, 1H), 2.75-2.90 (m, 4H), 2.52 (m, 2H), 2.22 (m, 1H), 1.80-2.00 (m, 6H), 1.45-1.70 (m, 4H). LCMS: 519.1, rt. = 5.46 min (M+H$^+$), 98% purity; HRMS (FAB) *m/z* 519.2387 [(M+H)$^+$; calcd for $C_{27}H_{30}F_4N_4O_2$: 519.2305].

Compounds **23** and **24**:

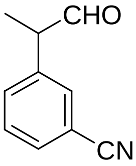
Step 1



19

A solution of 3-acetylbenzonitrile (10.2 g, 70 mmol) in t-butanol (100 mL) was treated with potassium t-butoxide (11.8 g, 105 mmol) potionwise and the reaction was stirred for 0.5 h. Ethyl chloroacetate (9.4 g, 77 mmol) was added dropwise and the reaction was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (30% EtOAc/Hex) provided **19** (4.9 g, 30%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.80 (m, 4H), 4.20-4.40 (m, 1H), 3.86-4.00 (m, 1H), 3.70 (s, 0.5H), 3.41 (s, 0.5H), 1.78 (s, 1.5H), 1.76 (s, 1.5H), 1.34 (t, J = 7.14 Hz, 1.5H), 0.96 (t, J = 7.14 Hz, 1.5H).

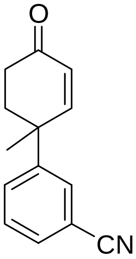
Step 2



20

Sodium hydroxide (0.73 g, 32 mmol) was dissolved in 20 mL EtOH and the reaction was cooled to 0 ^{o}C. A solution of **19** (4.9 g, 21.2 mmol) in 20 mL EtOH was added and the reaction was stirred for 0.5 h. Water (2 mL) was added and the reaction was stirred at room temperature overnight. The reaction mixture was concentrated to remove ethanol, diluted with water (45 mL) and 12 N HCl (8.4 mL) and heated to 100 ^{o}C for 1 h. The reaction was cooled to room temperature and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (30% EtOAc/Hex) gave **20** (0.46 g, 14%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.45-7.65 (m, 4H), 3.70 (q, J = 7.14 Hz, 1H), 1.49 (d, J = 7.14 Hz, 3H).

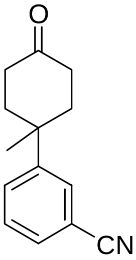
Step 3



21

A solution of **20** (0.46 g, 2.9 mmol) 1:1 Et_2O/EtOH (40 mL) was cooled to 0^{o}C. Potassium hydroxide (5 mg, 0.09 mmol) and methyl vinyl ketone (0.3 g, 4.35 mmol) were added. After 18 h, the reaction mixture was concentrated in vacuo and the residue was dissolved in CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to provide crude **21** (0.91 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ7.40-7.70 (m, 4H), 6.88 (d, J = 9.9 Hz, 1H), 6.17 (d, J = 9.9 Hz, 1H), 2.15-2.50 (m, 4H), 1.58 (s, 3H).

Step 4



22

A solution of crude **21** in EtOAc (50 mL) was treated with platinum on carbon (5%, 0.5 g) and the mixture was shaken at 45 psi hydrogen over the weekend. The reaction mixture was concentrated in vacuo and dissolved in CH_2Cl_2 (50 mL). Dess-Martin periodinane (1.7 g, 4.0 mmol) was added. After 12 h, the reaction mixture was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Preparative thin layer chromatography (30% EtOAc/Hex) afforded **22** (0.36 g, 77% for three steps) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.76 (m, 4H), 2.36-2.50 (m, 4H), 2.18-2.32 (m, 2H), 1.92-2.08 (m, 2H), 1.34 (s, 3H).

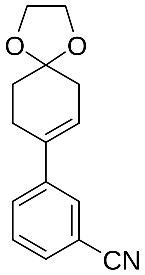
Following procedures similar to those described for compounds **16** and **17,** the following compounds were prepared**:**

Compound **23**: ^{1}H NMR (300 MHz, CDCl3) δ 10.7 (s, 1H), 7.40-7.80 (m, 6H), 7.06 (t, J = 9.9 Hz, 1H), 4.55 (m, 1H), 4.14 (m, 1H), 1.16-3.12 (m, 18H), 1.32 (s, 3H). LCMS: 533.3, rt. = 3.64 min (M+H$^+$), 99% purity; HRMS (FAB) *m/z* 533.2541 [(M+H)$^+$; calcd for $C_{28}H_{33}F_4N_4O_2$: 533.2540].

Compound **24:** ^{1}H NMR (300 MHz, CDCl3) δ 10.7 (s, 1H), 7.40-7.80 (m, 6H), 7.06 (t, J = 9.9 Hz, 1H), 4.49 (m, 1H), 4.30 (m, 1H), 1.16-3.12 (m, 18H), 1.14 (s, 3H). LCMS: 533.3, rt. = 3.61 min (M+H$^+$), 99% purity; HRMS (FAB) *m/z* 533.2552 (M+H)$^+$; calcd for $C_{28}H_{33}F_4N_4O_2$-533.2540.

Compounds **28** and **29**:

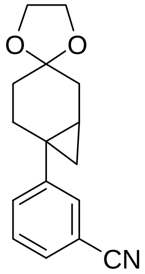
Step 1



25

A solution of alcohol **10** (20 g, 77 mmol) and triethylamine (15.6 g, 154 mmol) in CH_2Cl_2 (500 mL) was treated with a solution of methanesulfonyl chloride (9.7 g, 85 mmol) in CH_2Cl_2 (100 mL) over one hour. After 5h, additional triethylamine and mesyl chloride (same amount as the first time) were added. After 1 additional hour, the reaction was quenched with saturated aqueous $NaHCO_3$, washed with water (2x), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was recrystallized (EtOAc/Hex) to give rise to 9.1 g pure **25**. Flash chromatorgraphy of the filtrate (20% EtOAc/Hex) give rise to additional 7.8 g (Total yield:16.9 g, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.50 (d, J = 7.7 Hz, 1H), 7.40 (t, J = 7.7 Hz, 1H), 6.06 (m, 1H), 4.03 (s, 4H), 2.64 (m, 2H), 2.44 (m, 2H), 1.93 (t, J = 6.6 Hz, 2H).

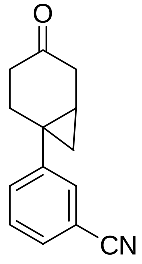
Step 2



27

A solution of diethylzinc (1 M in hexane, 19 ml, 19 mmol) in CH_2Cl_2 at 0 °C was treated with a solution of trifluoroacetic acid (2.1 g, 19 mmol) in CH_2Cl_2 (20 mL). After 20 minutes, a solution of diiodomethane (5 g, 19 mmol) in CH_2Cl_2 (10 mL) was then added, followed by a solution of **25** (1.5 g, 6.2 mmol) in CH_2Cl_2 (20 mL). After 18h, the reaction mixture was quenched with 1N HCl. The organic layer was separated, washed with water (2x), dried over Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (10% EtOAc/Hex) gave **27** (0.8 g, 50%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.45 (d, J = 7.7 Hz, 1H), 7.36 (t, J = 7.7 Hz, 1H), 3.9 (m, 4H), 2.10-2.35 (m, 2H), 1.4-1.9 (m, 4H), 1.25 (s, 1H), 1.05 (m, 1H), 0.82 (t, J = 5.5 Hz, 1H).

Step 3



41

A solution of **27** (0.8 g, 3.1 mmol) was stirred in 1:1 CH_2Cl_2/TFA (20 mL). After 30 min, the solvent was removed and the residue was diluted with EtOAc and saturated aqueous Na_2CO_3. The organic layer was separated, washed with water (2x), dried over Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (10% EtOAc/Hex) gave **41** (0.56 g, 85%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.49-7.51 (m, 2H), 7.42 (t, J = 7.7 Hz, 1H), 2.62-2.92 (m, 2H), 2.39-2.52 (m, 2H), 2.18-2.32 (m, 2H), 1.48-1.57 (m, 1H), 1.10 (d, J = 7.7 Hz, 2H).

Starting from compounds **11** and **41**, the following compounds were synthesized using the same method as that of compounds **16** and **17**:

Compound **26:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.05 (bs, 1H), 7.38-7.65 (m,5 H), 7.19 (m, 1H), 7.02 (t, J = 8.8 Hz, 1 H), 6.11 (s, 1H), 4.52 (m, 1H), 3.35 (m, 2H), 2.82-1.70 (m, 16 H). LCMS: 467.2, rt. = 5.26 min ($M+H^+$), 99% purity; HRMS (FAB) *m/z* 467.2021 [$(M+H)^+$; calcd for $C_{26}H_{29}ClFN_4O$: 467.2014].

Compound **28:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.75 (s, 1H), 7.67-7.73 (m, 2H), 7.33-7.53 (m, 4H), 7.05 (t, J = 9.3 Hz, 1H), 4.53 (m, 1H), 4.15 (dd, J = 11.5, 3.8 Hz, 1H), 3.35 (m, 2H), 3.11 (m, 1H), 2.75-2.92 (m, 4H), 2.55 (m, 1H), 1.36-2.30 (m, 9H), 1.08 (dd, J = 9.3, 4.9 Hz, 1H), 0.84 (t, J = 5.5 Hz, 1H). LCMS: 497.2, rt. = 5.06 min ($M+H^+$), 98% purity; HRMS (FAB) *m/z* 497.2126 [$(M+H)^+$; calcd for $C_{27}H_{31}ClFN_4O_2$ 497.2119].

Compound **29:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.71 (s, 1H), 7.67-7.78 (m, 2H), 7.34-7.53 (m, 4H), 7.05 (t, J = 9.3 Hz, 1H), 4.53 (m, 1H), 4.21 (m, 1H), 3.27 (m, 2H), 3.10 (m, 1H), 2.72-2.92 (m, 4H), 2.55 (m, 1H), 1.36-2.30 (m, 9H), 0.99 (dd, J = 9.3, 4.9 Hz, 1H), 0.76 (t, J = 5.5 Hz, 1H). LCMS: 497.2, rt. = 5.11 min ($M+H^+$), 100% purity; HRMS (FAB) *m/z* 497.2125 [$(M+H)^+$; calcd for $C_{27}H_{31}ClFN_4O_2$ 497.2119].

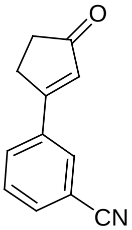
Diastereomers of **29** were separated via preparative HPLC using a chiral AD column (20% *i*-PrOH/Hex, isocratic), flow rate 40 mL/min to provide **(+)-30** and **(-)-31**:

Compound **(+)-30:** $[\alpha]^{25}_D$ +41.5° (*c* 1.0, MeOH); rt. = 160 min, 100% purity; HRMS (FAB) *m/z* 497.2125 [$(M+H)^+$; calcd for $C_{27}H_{31}ClFN_4O_2$ 497.2119].

Compound **(-)-31:** $[\alpha]^{25}_D$ -43.8° (*c* 1.0, MeOH); rt. = 137 min, 100% purity; HRMS (FAB) *m/z* 497.2125 [$(M+H)^+$; calcd for $C_{27}H_{31}ClFN_4O_2$ 497.2119].

Compound **38**:

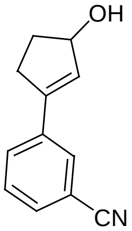
Step 1



34

A solution of 3-bromobenzonitrile (26.8 g, 147.1 mmol) in THF (1000 mL) at –78 °C was treated with a solution of n-butyllithium (2.5 M in hexanes; 61.0 mL, 155 mmol) such that the reaction temperature remained ≤ -78 °C. After 15 min, a solution of 3-methoxy-2-cyclopenten-1-one (15 g, 134 mmol) in THF (80 mL) was added such that the reaction temperature remained ≤ -78 °C. The reaction mixture was warmed to -20 °C over 1.5 h, quenched with a solution of 1N HCl and concentrated in vacuo to remove THF. A solution of 1N HCl (100 mL) was added, the solution was stirred for 45 min. and extracted with EtOAc (3x). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was crystallized at 0 °C from a solution of 1N HCl, filtered, rinsed with cold 1N HCl, H_2O and ether to provide **34** (14.4 g, 59%) as a pale yellow solid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 1.6 Hz, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.74 (d, *J* = 7.7 Hz, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 6.63 (d, *J* = 1.6 Hz, 1H), 3.07-3.03 (m, 2H), 2.65-2.62 (m, 2H).

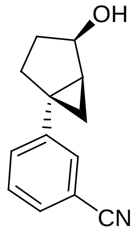
Step 2



42

A solution of **34** (7.88 g, 43.0 mmol) in methanol (100 mL) at 0 °C was treated with $CeCl_3$•$7H_2O$ (20.5 g, 55.0 mmol) followed portionwise by $NaBH_4$ (2.10 g, 55.0 mmol). The reaction was warmed to ambient temperature over 12 h, quenched with saturated aqueous NH_4Cl and concentrated to remove MeOH. The concentrate was diluted with H_2O and extracted with EtOAc (3x). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, brine, dried and concentrated in vacuo. Trituration (10% EtOAc/Hex) at 0 °C and filtration afforded the alcohol **42** (6.39 g, 80%) as a white powder: ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 1.6 Hz, 1H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.55 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 6.30 (dd, *J* = 3.8, 1.6 Hz, 1H), 5.05 (m, 1H), 2.90 (m, 1H), 2.65 (m, 1H), 2.56 (m, 1H), 1.92 (m, 1H), 1.62 (br s, 1H).

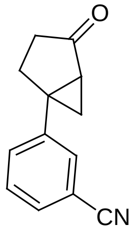
Step 3



35

A solution of allylic alcohol **42** (0.50 g, 2.7 mmol) in CH_2Cl_2 (75 mL) was treated with Et_2Zn (1.0 M in hexanes; 14 mL, 14 mmol). After 10 min, the reaction mixture was cooled to 0 °C, treated with a solution of CH_2I_2 (1.13 mL, 14 mmol) in CH_2Cl_2 (10 mL) dropwise over 10 min and allowed to warm to ambient temperature. After 48h, the reaction mixture was quenched slowly with saturated aqueous NH_4Cl and stirred 10 min. The reaction mixture was extracted with CH_2Cl_2 (2x), and the combined organic phases were washed with saturated aqueous $NaHCO_3$, dried and concentrated in vacuo. Flash chromatography (40% EtOAc/Hex) gave **35** (500 mg, 93%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.32 (m, 4 H), 4.69 (ddd, *J* = 12.1, 7.7, 4.4 Hz, 1H), 2.20-1.85 (m, 4H), 1.80 (br s, 1H), 1.38-1.25 (m, 2H), 0.85 (dd, *J* = 8.2, 5.5 Hz, 1H).

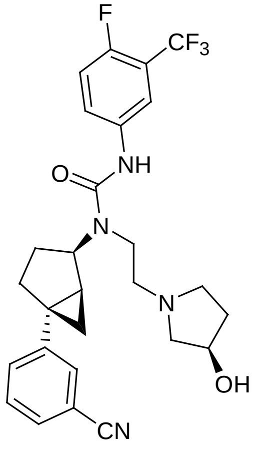
Step 4



36

A solution of alcohol **35** (0.50 g, 2.51 mmol) in CH_2Cl_2 (25 mL) at 0 °C was treated with pyridine (445 μL, 5.50 mmol) followed by Dess-Martin periodinane (2.12 g, 5.0 mmol) and warmed to ambient temperature. After 2h, 3 drops of H_2O were added. After 30 min further, the reaction was quenched with saturated aqueous $NaHCO_3$, saturated aqueous Na_2SO_3, and extracted with CH_2Cl_2 (3x). The combined organic phases were dried and concentrated in vacuo. Flash chromatography (25% EtOAc/Hex) gave **36** (440 mg, 89%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.52 (m, 2 H), 7.47-7.43 (m, 2H), 2.45 (m, 1H), 2.40-2.25 (m, 3H), 2.17 (dd, *J* = 9.3, 5.5 Hz, 1H), 1.61-1.52 (m, 2H).

Step 5



38

A solution of ketone **36** (80 mg, 0.41 mmol) in CH_2Cl_2 (1 mL) was treated with amine **(+)-14** (79 mg, 0.61 mmol) followed by titanium tetraisopropoxide (145 μL, 0.49 mmol). After 18 h, the reaction mixture was diluted with MeOH (1 mL) and sodium borohydride (31 mg, 0.81 mmol) was added. After 2.5 h further, the reaction mixture was diluted with a solution of saturated aqueous sodium/potassium tartrate and extracted with CH_2Cl_2 (4x). The combined organic phases were dried and concentrated in vacuo. The crude product was dissolved in CH_2Cl_2 (4 mL) and treated with diisopropylethyl amine (78 μL, 0.45 mmol) followed by 4-fluoro-(3-trifluoromethyl)phenyl isocyanate (61 μL, 0.43 mmol). After 18h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organic phases were dried and concentrated in vacuo. Preparative thin layer chromatography (5% MeOH/ CH_2Cl_2), followed by filtration, an EtOH rinse and concentration in vacuo furnished **38** (100 mg, 48% over 2 steps) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ : ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.68 (d, *J* = 14.3 Hz, 1H), 7.71-7.68 (m, 2H), 7.46-7.36 (m, 4H), 7.04 (dd, *J* = 9.9, 9.9 Hz, 1H), 5.06 (ddd, *J* = 9.9, 7.1, 3.3 Hz, 1H), 4.50 (m, 1H), 3.50 (dd, *J* = 15.4, 7.1 Hz, 1H), 3.41(dd, *J* = 15.4, 7.1 Hz, 1H), 3.13 (ddd, *J* = 15.9, 15.4, 8.2 Hz, 1H), 2.98-2.71 (m, 4H), 2.55 (ddd, *J* = 15.9, 15.9, 8.8 Hz, 1H), 2.42 (br s, 1H), 2.28-1.80 (m, 5H), 1.72 (ddd, *J* = 7.7, 7.1, 3.3 Hz, 1H), 1.34-1.19 (m, 2H), 0.94 (dd, *J* = 7.1, 6.0 Hz, 1H); LCMS: 517.1, rt. = 4.50 min ($M+H^+$), 98.3% purity; HRMS (FAB) *m/z* 517.2250 [$(M+H)^+$; calcd for $C_{27}H_{29}N_4O_2F_4$: 517.2227].

Anal. calcd for $C_{27}H_{28}N_4O_2F_4 \cdot HCl \cdot 0.5H_2O$: C, 57.70; H, 5.38, N, 9.97. Found: C, 57.78; H, 5.19; N, 9.80.

Following procedures similar to those described for compound **38**, the following compounds were prepared:

Compound **39**: ^{1}H NMR (300 MHz, $CDCl_3$) δ : ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.24 (br s, 1H), 7.57-7.54 (m, 2H), 7.30-7.22 (m, 4H), 6.92 (s, 1H), 5.05 (s, 1H), 3.72-3.34 (m, 2H), 2.95-2.66 (m, 6H), 2.19-1.95 (m, 7H), 1.77 (ddd, *J* = 12.1, 8.2, 4.4 Hz, 1H), 1.35-1.19 (m, 2H), 0.99 (dd, *J* = 6.6, 6.0 Hz, 1H). LCMS: 483.1, rt. = 5.27 min ($M+H^+$), >99% purity; HRMS (FAB) *m/z* 483.1725 [$(M+H)^+$; calcd for $C_{26}H_{29}N_4OCl_2$: 483.1718].

Compound **40**: ^{1}H NMR (300 MHz, $CDCl_3$) δ : ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.93 (br s, 1H), 8.80 (s, 1H), 7.99 (d, *J* = 4.4 Hz, 1H), 7.87 (dd, *J* = 8.2, 4.4 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 4.85 (m, 1H), 3.78-3.17 (m, 8H), 2.81 (m, 4 H), 2.48 (dd, *J* = 2.2, 1.6 Hz, 1H), 2.15-1.98 (m, 6H), 1.82 (ddd, *J* = 13.2, 11.5, 7.7 Hz, 1H), 1.64 (dd, *J* = 4.9, 4.4 Hz, 1H), 1.43 (m, 1H), 1.08 (m, 1H). LCMS: 544.1, rt. = 4.45 min ($M+H^+$), >99% purity; HRMS (FAB) *m/z* 544.2699 [$(M+H)^+$; calcd for $C_{29}H_{34}N_5OF_4$: 544.2699].

Anal. calcd for $C_{29}H_{33}N_5OF_4 \cdot 2HCl \cdot H_2O$: C, 54.89; H, 5.88, N, 11.04. Found: C, 55.12; H, 5.85; N, 11.12.