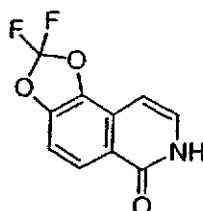


Compound 287 was prepared by following Scheme 2 of Example 269 except that 3-(2,2-difluoro-benzo[1,3]dioxol-4-yl)-acrylic acid was used in place of 2-trifluormethoxycinnamic acid in step 1.

5 Step 1:

Modifications: 4.56 g 3-(2,2-difluoro-benzo[1,3]dioxol-4-yl)-acrylic acid used, 2.2 g product obtained (55% yield).

Product:

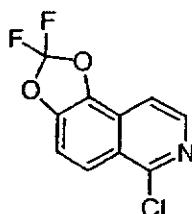


- 10 Data: ^1H NMR (400 MHz, CD_3DOD) δ ppm 6.63 (d, $J=7.09$ Hz, 1 H), 7.29 (d, $J=7.34$ Hz, 1 H), 7.40 (d, $J=8.80$ Hz, 1 H), 8.19 (d, $J=8.80$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 226.

Step 2:

- 15 Modifications: 2.2 g 2,2-difluoro-7H-1,3-dioxo-7-aza-cyclopenta[a]naphthalen-6-one used, 2.1 g product obtained (87% yield).

Product:



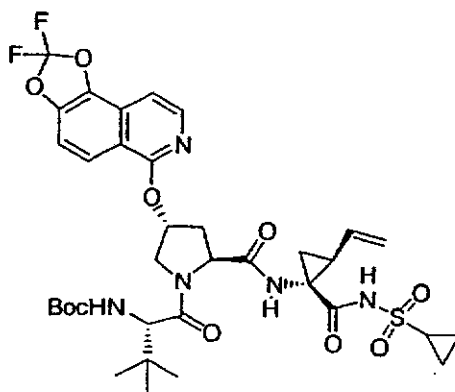
- 20 Data: ^1H NMR (500 Hz, CDCl_3) ppm 7.51 (d, $J=9.29$ Hz, 1 H), 7.65 (d, $J=5.87$ Hz, 1 H), 8.22 (d, $J=9.05$ Hz, 1 H), 8.32 (d, $J=5.87$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 244.

Step 3:

Modifications: 48 mg 6-chloro-2,2-difluoro-1,3-dioxo-7-aza-cyclopenta[a]naphthalene and 113 mg {1-[2-(1-cyclopropanesulfonylaminocarbonyl)-

2-vinyl-cyclopropylcarbamoyl)-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid *tert*-butyl ester used, 40 mg product obtained (27% yield).

Product:



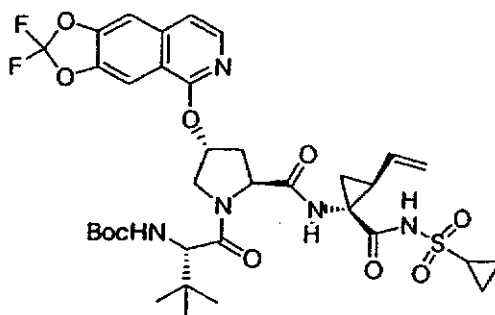
Compound 287

5

Data: ^1H NMR (400 Hz, CD_3OD) δ ppm 1.02 (s, 12 H), 1.24 (m, 10 H), 1.43 (m, 1 H), 1.88 (dd, $J=8.07, 5.38$ Hz, 1 H), 2.32 (d, $J=3.67$ Hz, 2 H), 2.64 (d, $J=13.45$ Hz, 1 H), 2.95 (m, 1 H), 4.05 (d, $J=11.49$ Hz, 1 H), 4.19 (d, $J=9.29$ Hz, 1 H), 4.53 (m, 2 H), 5.12 (d, $J=9.78$ Hz, 1 H), 5.32 (s, 1 H), 5.77 (m, 2 H), 7.34 (d, $J=5.87$ Hz, 1 H), 7.46 (d, $J=9.05$ Hz, 1 H), 8.11 (m, 2 H); MS: $(\text{M}+\text{H})^+$ 764.

10

Example 288: Preparation of Compound 288



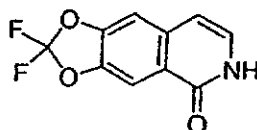
Compound 288

15 **Compound 288** was prepared by following Scheme 2 of Example 269 except that 3-(2,2-difluoro-benzo[1,3]dioxol-5-yl)-acrylic acid was used in place of 2-trifluoromethoxycinnamic acid in step 1.

Step 1:

Modifications: 1 g 3-(2,2-difluoro-benzo[1,3]dioxol-5-yl)-acrylic acid used, 0.55 g product obtained.

5 Product:

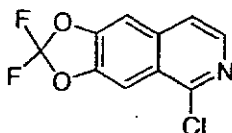


Data: ^1H NMR (400 MHz, CD_3DOD) δ ppm 6.69 (d, $J=7.09$ Hz, 1 H), 7.19 (d, $J=7.09$ Hz, 1 H), 7.47 (s, 1 H) 7.98 (s, 1 H); MS: $(\text{M}+\text{H})^+$ 226.

10 Step 2:

Modifications: 0.5 g 2,2-difluoro-6H-[1,3]dioxolo[4,5-g]isoquinolin-5-one used, 0.4 g product obtained.

Product:

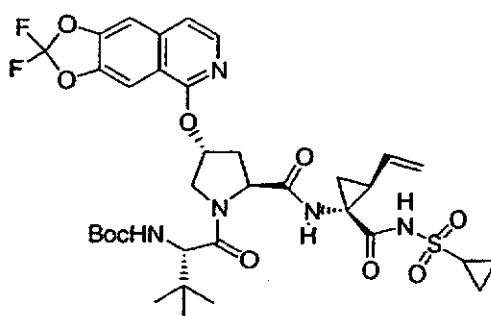


15 Data: ^1H NMR (400 Hz, CDCl_3) δ 7.41 (s, 1 H), 7.57 (d, $J=5.49$ Hz, 1 H), 7.94 (s, 1 H), 8.27 (d, $J=5.80$ Hz, 1 H); MS $(\text{M}+\text{H})^+$ 244.

Step 3:

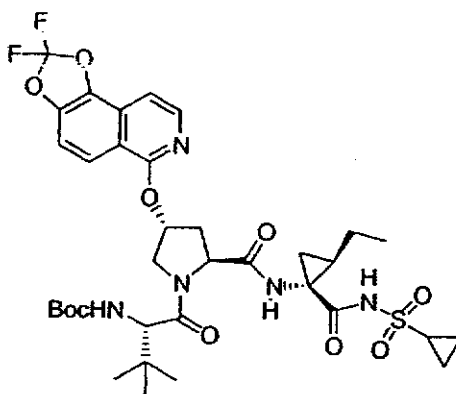
Modifications: 48 mg 5-chloro-2,2-difluoro-[1,3]dioxolo[4,5-g]isoquinoline and 112 mg {1-[2-(1-Cyclopropanesulfonylaminocarbonyl-2-vinyl-cyclopropylcarbamoyl)-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid *tert*-butyl ester used, 30 mg product obtained.

Product:

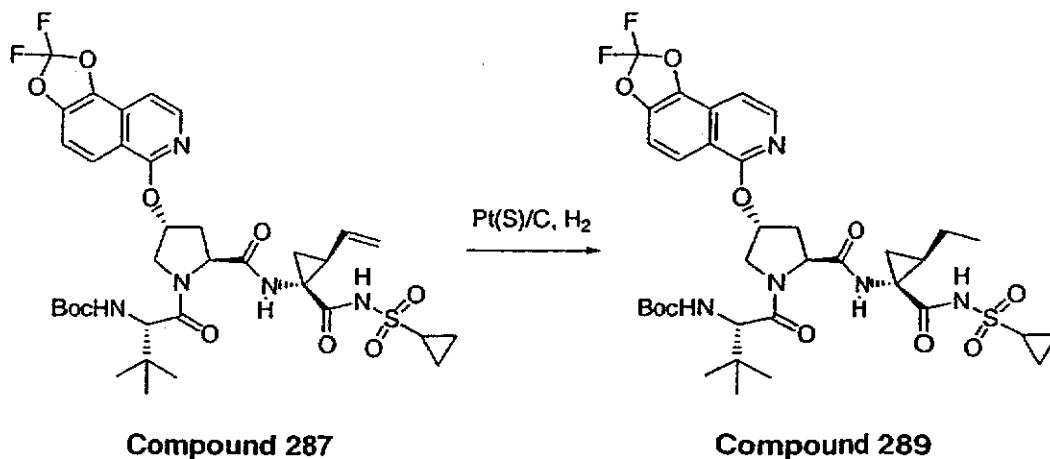
**Compound 288**

Data: ^1H NMR (400 Hz, CD_3OD) δ ppm 1.06 (m, 12 H), 1.25 (m, 10 H), 1.42 (m, 1 H), 1.87 (dd, $J=8.07, 5.62$ Hz, 1 H), 2.26 (m, 2 H), 2.61 (dd, $J=13.57, 6.97$ Hz, 1 H), 2.93 (m, 1 H), 4.07 (dd, $J=11.86, 2.81$ Hz, 1 H), 4.22 (m, 1 H), 4.40 (d, $J=11.98$ Hz, 1 H), 4.52 (m, 1 H), 5.11 (d, $J=10.52$ Hz, 1 H), 5.29 (d, $J=17.12$ Hz, 1 H), 5.37 (s, 1 H), 5.74 (m, 1 H), 7.39 (s, 1 H), 7.56 (s, 1 H), 7.63 (d, $J=5.62$ Hz, 1 H), 7.99 (d, $J=5.62$ Hz, 1 H).

10 Example 289: Preparation of Compound 289

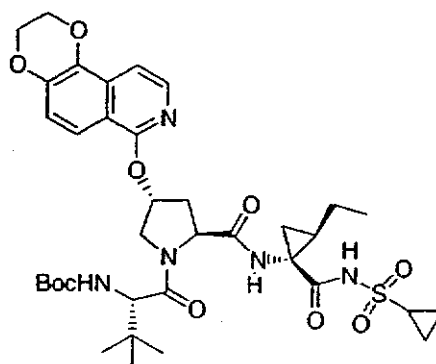
**Compound 289**

Scheme 3



A suspension of **compound 287** (15 mg) and Pt(S)/C (5%, 5 mg) in ethyl acetate (5 mL) was hydrogenated at 10 psi for 30 min. After filtration, concentration quantitatively gave 15 mg of **compound 289** as a solid. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.09 (m, 26 H), 1.57 (m, 4 H), 2.30 (m, 1 H), 2.61 (m, *J*=13.82, 7.21 Hz, 1 H), 2.96 (m, 1 H), 4.05 (m, *J*=13.94 Hz, 1 H), 4.19 (d, *J*=9.54 Hz, 1 H), 4.53 (m, 2 H), 5.89 (s, 1 H), 7.34 (d, *J*=5.87 Hz, 1 H), 7.46 (d, *J*=9.05 Hz, 1 H), 8.09 (d, *J*=5.87 Hz, 1 H), 8.12 (d, *J*=8.80 Hz, 1 H); MS: (M+H)⁺ 766.

Example 290: Preparation of Compound 290

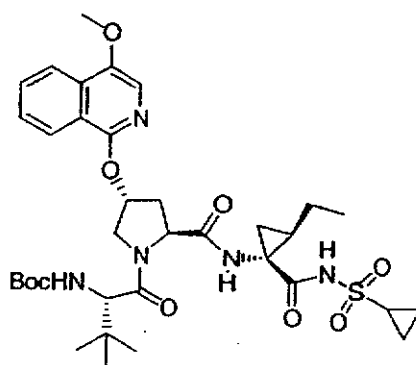


Compound 290

Compound 290 (15mg, 100%) was prepared by following Scheme 3 of Example 289 by using 15 mg of **compound 286**. Data: ¹H NMR (400 Hz, CD₃OD) δ ppm

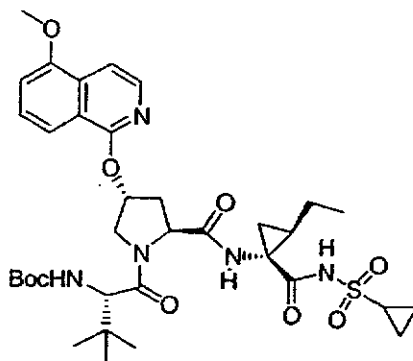
1.02 (m, 14 H), 1.23 (m, 12 H), 1.58 (m, 4 H), 2.25 (m, 1 H), 2.58 (dd, $J=13.82, 7.21$ Hz, 1 H), 2.96 (m, 1 H), 4.05 (m, $J=11.25, 2.93$ Hz, 1 H), 4.25 (d, $J=9.54$ Hz, 1 H), 4.39 (m, 5 H), 4.52 (m, $J=10.03, 7.34$ Hz, 1 H), 5.81 (s, 1 H), 7.03 (d, $J=9.05$ Hz, 1 H), 7.43 (d, $J=6.11$ Hz, 1 H), 7.69 (d, $J=9.05$ Hz, 1 H), 7.88 (d, $J=6.11$ Hz, 1 H); MS: (M+H)⁺ 744.

Example 291: Preparation of Compound 291



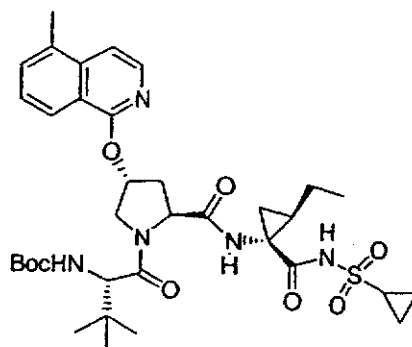
Compound 291

Compound 291 (28mg, 100%) was prepared by following Scheme 3 of Example 289 by using 28 mg of **compound 251**. Data: ¹H NMR (400 MHz, CD₃OD) δ ppm 1.01 (m, 15 H), 1.26 (m, 11 H), 1.37 (m, 1 H), 1.58 (m, 3 H), 2.25 (m, 1 H), 2.58 (dd, $J=13.6, 7.0$ Hz, 1 H), 2.96 (m, 1 H), 3.99 (s, 3 H), 4.06 (m, 1 H), 4.25 (m, 1 H), 4.44 (m, 1 H), 4.53 (dd, $J=10.3, 7.6$ Hz, 1 H), 5.78 (s, 1 H), 6.64 (d, $J=9.8$ Hz, 1 H), 7.55 (m, 2 H), 7.71 (t, $J=7.3$ Hz, 1 H), 8.09 (d, $J=8.6$ Hz, 1 H), 8.14 (d, $J=8.1$ Hz, 1 H); MS: (M+Na)⁺ 738.

Example 292: Preparation of Compound 292**Compound 292**

Compound 292 (16 mg, 84%) was prepared by following Scheme 3 of Example 289 by using 19 mg of **compound 253**. ^1H NMR (400 MHz, CD_3OD) δ ppm 0.90 (m, 15 H), 1.15 (m, 12 H), 1.48 (m, 3 H), 2.18 (m, 1 H), 2.51 (dd, $J=13.7, 6.9$ Hz, 1 H), 2.88 (m, 1 H), 3.90 (s, 3 H), 3.98 (dd, $J=11.6, 3.1$ Hz, 1 H), 4.18 (d, $J=9.5$ Hz, 1 H), 4.36 (d, $J=11.0$ Hz, 1 H), 4.45 (dd, $J=10.2, 7.2$ Hz, 1 H), 5.76 (s, 1 H), 6.56 (d, $J=9.3$ Hz, 1 H), 7.05 (d, $J=7.6$ Hz, 1 H), 7.34 (t, $J=8.1$ Hz, 1 H), 7.51 (d, $J=5.9$ Hz, 1 H), 7.65 (d, $J=8.3$ Hz, 1 H), 7.86 (d, $J=6.1$ Hz, 1 H); MS: $(\text{M}+\text{Na})^+$ 738.

10

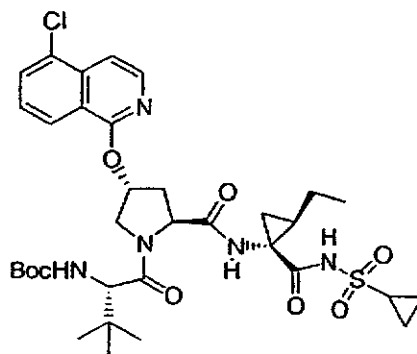
Example 293: Preparation of Compound 293**Compound 293**

Compound 293 (7 mg, 35%) was prepared by following Scheme 3 of Example 289 by using 20 mg of **compound 252**. ^1H NMR (400 MHz, CD_3OD) δ ppm 1.04 (m, 15 H), 1.27 (m, 12 H), 1.58 (m, 3 H), 2.27 (m, 1 H), 2.60 (m, 4 H), 2.96 (m, 1 H), 4.07 (dd, $J=11.7, 2.9$ Hz, 1 H), 4.25 (s, 1 H), 4.46 (d, $J=12.0$ Hz, 1 H), 4.54 (dd, $J=10.0,$

15

7.6 Hz, 1 H), 5.85 (s, 1 H), 7.39 (t, $J=7.7$ Hz, 1 H), 7.44 (d, $J=5.9$ Hz, 1 H), 7.53 (d, $J=6.9$ Hz, 1 H), 8.00 (d, $J=6.1$ Hz, 1 H), 8.06 (d, $J=8.6$ Hz, 1 H); MS: $(M+H)^+$ 700.

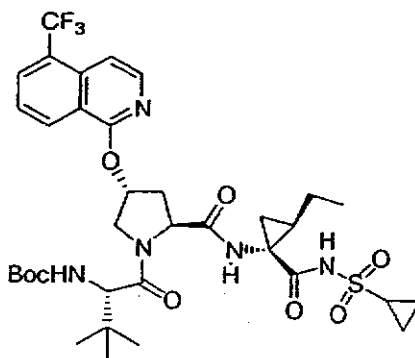
Example 294: Preparation of Compound 294



Compound 294

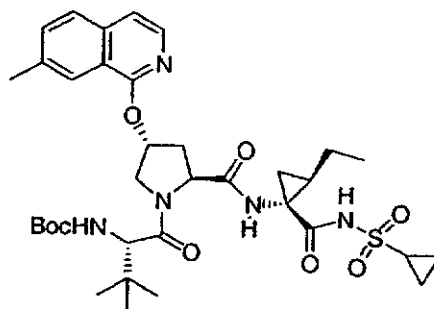
Compound 294 (14 mg, 78 %) was prepared by following Scheme 3 of Example 289 by using 18 mg of **compound 254**. ^1H NMR (400 MHz, CD_3OD) δ ppm 0.94 (m, 15 H), 1.13 (m, 10 H), 1.20 (m, 2 H), 1.50 (m, 3 H), 2.21 (m, 1 H), 2.53 (dd, $J=13.8, 7.0$ Hz, 1 H), 2.88 (m, 1 H), 3.99 (dd, $J=11.4, 2.6$ Hz, 1 H), 4.14 (d, $J=9.3$ Hz, 1 H), 4.45 (m, 2 H), 5.79 (s, 1 H), 6.53 (d, $J=9.1$ Hz, 1 H), 7.40 (t, $J=8.0$ Hz, 1 H), 7.54 (d, $J=5.9$ Hz, 1 H), 7.73 (d, $J=7.3$ Hz, 1 H), 8.02 (d, $J=6.1$ Hz, 1 H), 8.10 (d, $J=8.6$ Hz, 1 H); MS: $(M+\text{Na})^+$ 742.

Example 295: Preparation of Compound 295

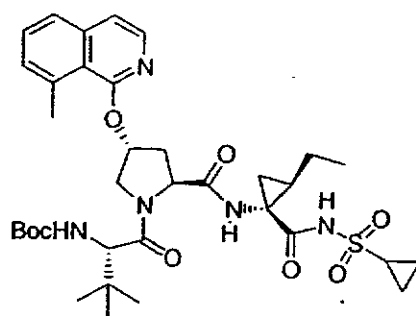


Compound 295

Compound 295 (30 mg, 100%) was prepared by following Scheme 3 of Example 289 by using 30 mg of **compound 270**. MS: $(M+\text{Na})^+$ 776.

Example 296: Preparation of Compound 296**Compound 296**

- 5 **Compound 296** (6.3 mg, 33%) was prepared by following Scheme 3 of Example 289 by using 20 mg of **compound 259**. ^1H NMR (400 MHz, CD_3OD) δ ppm 1.04 (m, 15 H), 1.24 (m, 12 H), 1.59 (m, 3 H), 2.29 (m, 1 H), 2.50 (s, 3 H), 2.60 (dd, $J=13.69, 6.85$ Hz, 1 H), 2.97 (m, 1 H), 4.09 (dd, $J=11.74, 2.93$ Hz, 1 H) 4.22 (s, 1 H) 4.43 (d, $J=11.74$ Hz, 1 H), 4.59 (dd, $J=10.27, 6.85$ Hz, 1 H), 5.87 (s, 1 H), 7.30 (d, $J=5.87$ Hz, 1 H), 7.57 (dd, $J=8.31, 1.47$ Hz, 1 H), 7.72 (d, $J=8.31$ Hz, 1 H), 7.89 (d, $J=5.87$ Hz, 1 H), 7.94 (s, 1 H); MS: $(\text{M}+\text{H})^+$ 700.
- 10

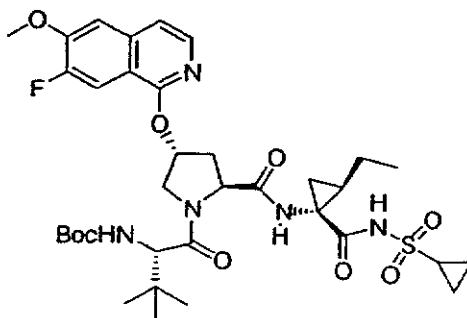
Example 297: Preparation of Compound 297**Compound 297**

15

Compound 297 (40 mg, 100%) was prepared by following Scheme 3 of Example 289 by using 40 mg of **compound 263**. ^1H NMR (400 MHz, CD_3OD) δ ppm 0.98 (m, 13 H) 1.07 (m, 2 H) 1.27 (m, 12 H) 1.57 (m, 3 H) 2.27 (m, 1 H) 2.58 (dd, $J=14.7, 7.1$ Hz, 1 H) 2.77 (s, 3 H) 2.96 (m, 1 H) 4.04 (m, 1 H) 4.27 (m, 1 H) 4.42 (d, $J=11.5$

Hz, 1 H) 4.55 (dd, $J=10.6, 7.0$ Hz, 1 H) 5.94 (s, 1 H) 6.65 (d, $J=9.5$ Hz, 1 H) 7.28 (m, 2 H) 7.50 (t, $J=7.6$ Hz, 1 H) 7.60 (d, $J=7.6$ Hz, 1 H) 7.89 (d, $J=5.6$ Hz, 1 H); MS: $(M+Na)^+$ 722.

5 Example 298: Preparation of Compound 298

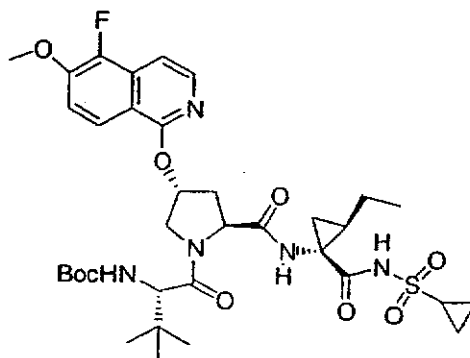


Compound 298

Compound 298 (29 mg, 100%) was prepared by following Scheme 3 of Example 289 by using 29 mg of **compound 261**. ^1H NMR (400 MHz, CD_3OD) δ ppm 0.99 (m, 15 H), 1.25 (m, 12 H), 1.60 (m, 3 H), 2.28 (m, 1 H), 2.58 (m, 1 H), 2.96 (m, 1 H), 4.02 (m, 4 H), 4.22 (dd, $J=8.8, 4.4$ Hz, 1 H), 4.43 (m, 2 H), 5.03 (s, 1 H), 7.27 (d, $J=5.6$ Hz, 1 H), 7.36 (d, $J=8.8$ Hz, 1 H), 7.75 (d, $J=11.3$ Hz, 1 H), 7.90 (d, $J=5.9$ Hz, 1 H); MS: $(M+Na)^+$ 756.

15

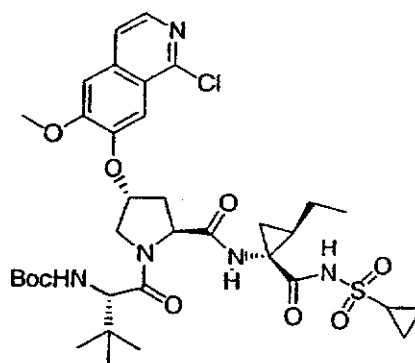
Example 299: Preparation of Compound 299



Compound 299

Compound 299 (34 mg, 97%) was prepared by following Scheme 3 of Example 289 by using 35 mg of **compound 274**. ^1H NMR (400 MHz, CD_3OD) δ ppm 1.01 (m, 16 H), 1.28 (m, 12 H), 1.58 (m, 2 H), 2.27 (s, 1 H), 2.59 (dd, $J=13.82$, 6.97 Hz, 1 H), 2.96 (m, 1 H), 4.02 (s, 3 H), 4.07 (m, 1 H), 4.21 (m, 1 H), 4.44 (m, $J=11.98$ Hz, 1 H), 4.55 (d, $J=10.27$ Hz, 1 H), 5.85 (s, 1 H), 7.39 (m, 2 H), 7.95 (d, $J=6.11$ Hz, 1 H), 8.00 (d, $J=9.29$ Hz, 1 H); MS: $(\text{M}+\text{Na})^+$ 756.

Example 300: Preparation of Compound 300



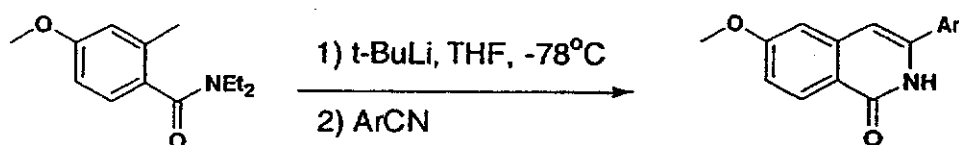
Compound 300

Compound 300 (30 mg, 100%) was prepared by following Scheme 3 of Example 289 by using 30 mg of **compound 262**. ^1H NMR (400 MHz, CD_3OD) δ ppm 1.27 (m, 30 H), 2.25 (s, 1 H), 2.54 (s, 1 H), 2.96 (m, 1 H), 3.97 (s, 3 H), 4.20 (m, 3 H), 4.51 (m, $J=10.52$, 6.85 Hz, 1 H), 5.37 (s, 1 H), 7.38 (s, 1 H), 7.62 (s, 1 H), 7.65 (d, $J=5.38$ Hz, 1 H) 8.06 (d, $J=5.62$ Hz, 1 H); MS: $(\text{M}+\text{Na})^+$ 773.

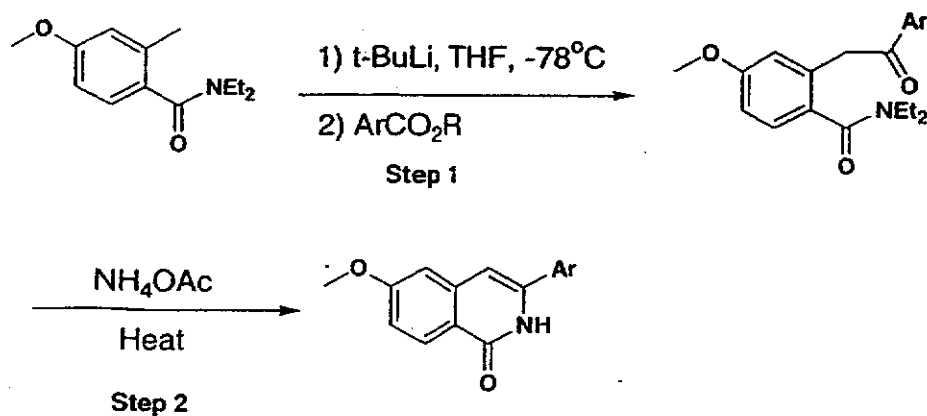
Section G:

The LC/MS method used in section G is the following:
4.6X50mm Xterra @3min gradient and 4 mL/min flow

Scheme 1: (General Scheme)

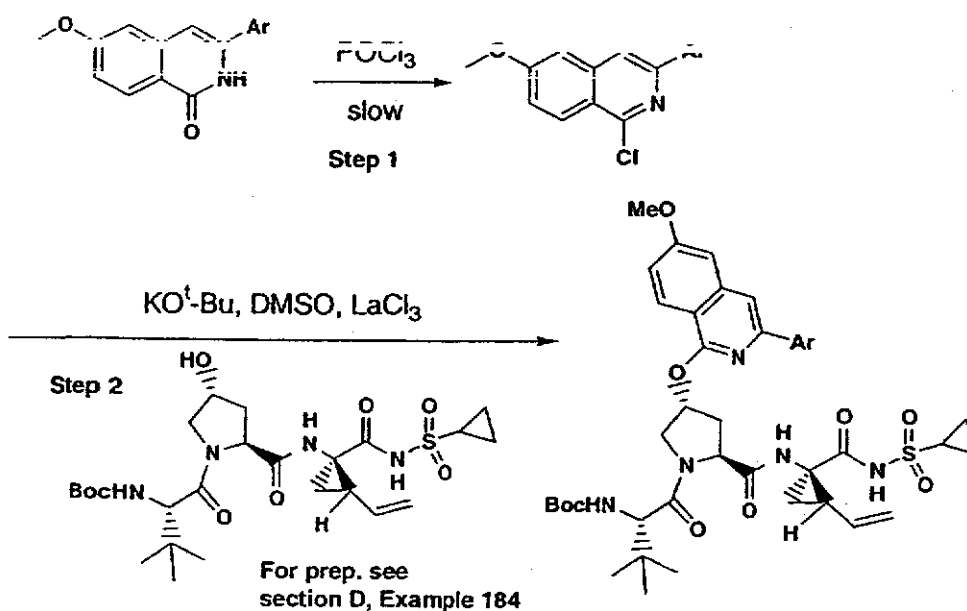


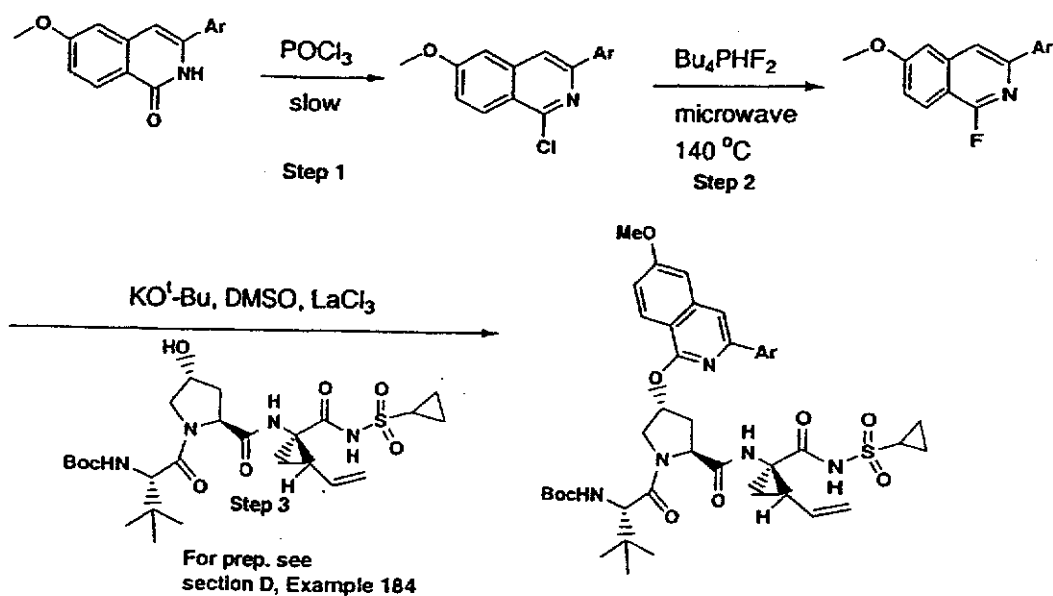
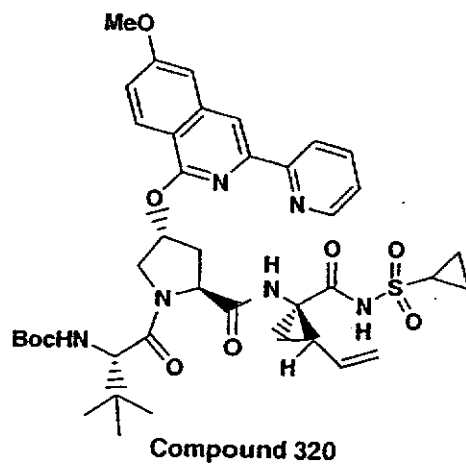
Scheme 2: (General Scheme)



5

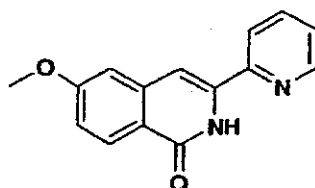
Scheme 3: (General Scheme)



Scheme 4: (General Scheme)**5 Example 320: Preparation of Compound 320**

Compound 320 was prepared by following Scheme 1 and Scheme 3 of above.

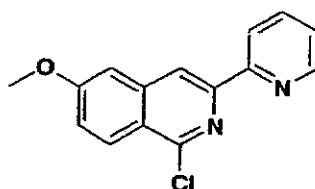
10 Step 1 (Scheme 1):



To a solution of N,N-Diethyl-4-methoxy-2-methyl-benzamide (332 mg, 1.5 mmol) in THF (15 mL) at -78°C , t-BuLi (1.7 M solution in pentane, 1.3 mL, 2.25 mmol) was added. The resulting red solution was stirred at -78°C for 10 min, then 2-cyanopyridine (156 mg, 1.5 mmol) was added. The reaction mixture was then warmed to rt and stirred for overnight. The reaction was quenched with saturated NH_4Cl solution and extracted with ethyl acetate twice. The combined organic layers were dried (MgSO_4) and concentrated. The crude product was purified by Prep. HPLC to give yellowish solid as TFA salt. (85 mg, 15% yield)

^1H NMR (400 MHz, CD_3OD) δ 3.91 (m, 3 H), 7.09 (dd, $J=9.05, 2.45$ Hz, 1 H), 7.17 (d, $J=2.45$ Hz, 1 H), 7.37 (s, 1 H), 7.42 (m, 1 H), 7.92 (m, 1 H), 8.08 (d, $J=8.07$ Hz, 1 H), 8.18 (d, $J=9.05$ Hz, 1 H), 8.65 (d, $J=4.89$ Hz, 1 H).
LC-MS (retention time: 2.14 min.), MS m/z 253 (MH^+).

Step 2 (Scheme 3, Step 1):

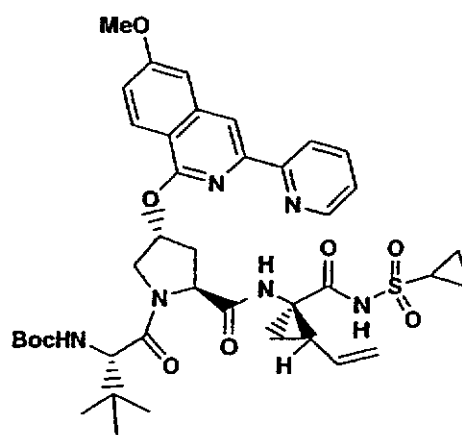


15

6-Methoxy-3-pyridin-2-yl-2H-isoquinolin-1-one TFA salt (85 mg, 0.232 mmol) was heated under reflux with POCl_3 (3.0 mL) for 2 days. Then POCl_3 was distilled off and the residue was quenched with ice. It was then neutralized with 10 N NaOH solution and the brown solid was collected as pure product. (62 mg, 99% yield)
LC-MS (retention time: 2.063 min.), MS m/z 271 (MH^+).

Step 3 (Scheme 3, Step 2):

20



Compound 320

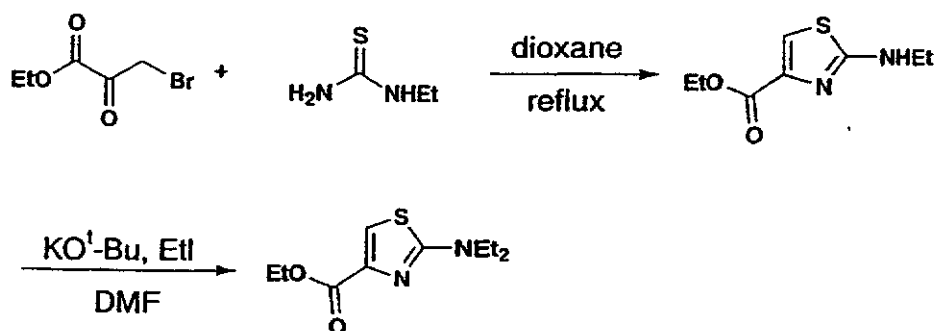
To a solution of {1-[2-(1-Cyclopropanesulfonylaminocarbonyl-2-vinyl-cyclopropyl-carbamoyl)-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid
 5 tert-butyl ester (82 mg, 0.148 mmol) and LaCl_3 (36 mg, 0.148 mmol) in DMF (1.5 mL), potassium t-butoxide (1.0 M solution in THF, 0.74 mL, 0.74 mmol) was added at -78°C . The reaction mixture was stirred for 1 hr, then 1-chloro-6-methoxy-3-pyridin-2-yl-isoquinoline (40 mg, 0.148 mmol) was added. It was warmed to rt and stirred for overnight. Then it was quenched with water and filtered. The filtrate
 10 was concentrated and the residue was purified by Prep. HPLC to give an off-white solid as product (**Compound 320**). (23 mg, 20 % yield)

^1H NMR (400 MHz, CD_3OD) δ 0.87-1.08 (m, 11 H), 1.20-1.30 (m, 11 H), 1.43 (m, 1 H), 1.87 (m, 1 H), 2.22 (m, 1 H), 2.35 (m, 1 H), 2.69 (m, 1 H), 2.93 (m, 1 H), 3.94 (s, 3 H), 4.16 (m, 1 H), 4.27 (m, 1 H), 4.45 (m, 1 H), 4.56 (m, 1 H), 5.10 (d, $J=11.3$ Hz, 1 H), 5.27 (d, $J=15.9$ Hz, 1 H), 5.74 (m, 1 H), 6.07 (s, 1 H), 7.12 (d, $J=7.33$ Hz, 1 H), 7.31 (d, $J=1.96$ Hz, 1 H), 7.40 (m, 1 H), 7.94 (dd, $J=7.8$ Hz, 1.5 Hz, 1 H), 8.11 (d, $J=9.29$ Hz, 1 H), 8.22 (s, 1 H), 8.45 (d, $J=8.07$ Hz, 1 H), 8.62 (m, 1 H).

LC-MS (retention time: 2.393min.), MS m/z 791 (MH^+).

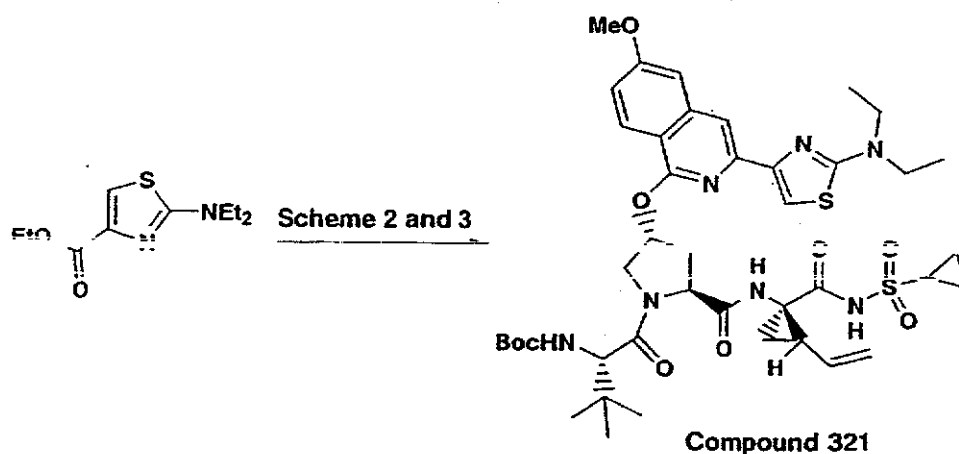
Example 321: Preparation of Compound 321

20 Scheme 5:



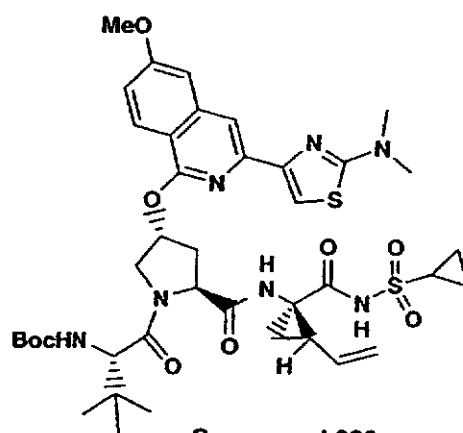
- Condensation of ethyl bromopyruvate with ethyl thiourea in refluxing dioxane afforded the monoalkylamino thiazole as HBr salt in quantitative yield. Alkylation of
- 5 2-ethylamino-thiazole-4-carboxylic acid ethyl ester with EtI in DMF provided 2-diethylamino-thiazole-4-carboxylic acid ethyl ester.

LC/MS m/z 229 (MH)⁺



- 10 **Compound 321** was prepared by following Scheme 2 and Scheme 3 above with that 2-diethylamino-thiazole-4-carboxylic acid ethyl ester was used in the step 1 of Scheme 2.

LC/MS (Retention time 2.76 min): m/z 868 (MH⁺).



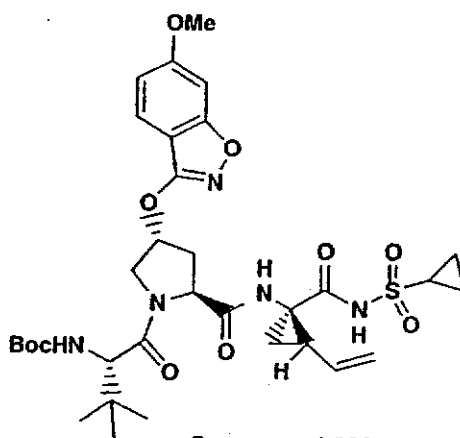
Compound 322

Compound 322 was prepared by following Example 321, except that 2-dimethylamino-thiazole-4-carboxylic acid ethyl ester (Prepared according to Scheme 5, except that methyl thiourea and methyl iodide were used in the place of ethyl thiourea and ethyl iodide) was used in the place of 2-dimethylamino-thiazole-4-carboxylic acid ethyl ester in step 1 of Scheme 2.

LC/MS (Retention time 2.56 min): m/z 840 (MH^+)

10

Example 323: Preparation of Compound 323



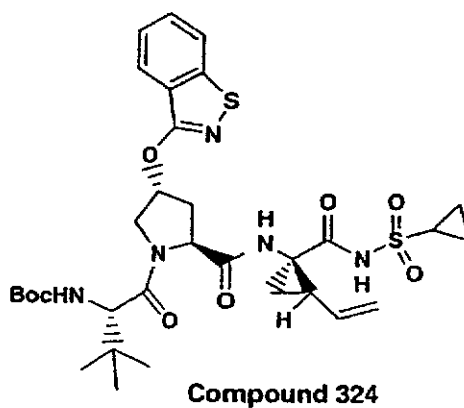
Compound 323

Compound 323 was prepared by following Step 3 of Example 324, except that 3-chloro-6-methoxy-benzo[d]isoxazole was used in the place of 1-chloro-6-methoxy-3-pyridin-2-yl-isoquinoline.

15

MS m/z 702 (M-H)⁻

Example 324: Preparation of Compound 324

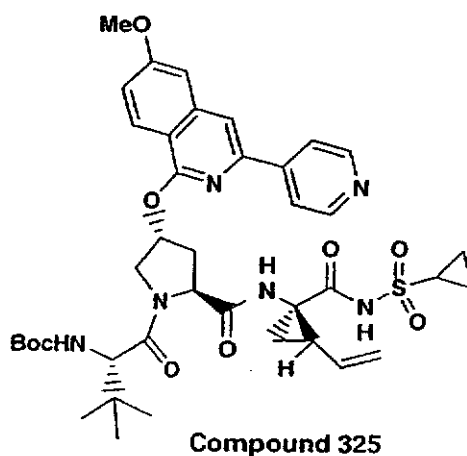


5

Compound 324 was prepared by following Step 3 of **Example 324**, except that 3-chloro-benzo[d]isothiazole was used in the place of 1-chloro-6-methoxy-3-pyridin-2-yl-isoquinoline.

10 LC/MS (Retention time 1.83 min): m/z 688 (M-H)⁻

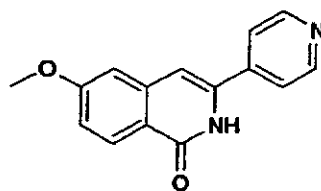
Example 325: Preparation of Compound 325



15

Compound 325 was prepared by following Scheme 1 and Scheme 3 of above.

Step 1 (Scheme 1):

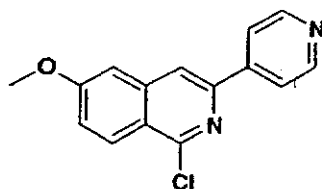


To a solution of *N,N*-Diethyl-4-methoxy-2-methyl-benzamide (332 mg, 1.5 mmol) in THF (15 mL) at -78°C , *t*-BuLi (1.7 M solution in pentane, 1.3 mL, 2.25 mmol) was added. The resulting red solution was stirred at -78°C for 10 min, then 4-cyanopyridine (164 mg, 1.575 mmol) was added. The reaction mixture was then warmed to rt and stirred for overnight. The reaction was quenched with saturated NH_4Cl solution and the yellow precipitate was collected as pure product. (145 mg, 38% yield)

^1H NMR(CD_3OD , 400 MHz) δ 3.91 (s, 3 H), 7.18 (dd, $J=8.8$ Hz, 2.8 Hz, 1 H), 7.26 (m, 2 H), 8.06 (d, $J=6.0$ Hz, 2H), 8.16 (d, $J=8.8$ Hz, 1H), 8.84 (d, $J=6.0$ Hz, 2H).

LC-MS (retention time: 1.300 min.), MS m/z 253 (MH^+).

Step 2 (Scheme 3, step 1):



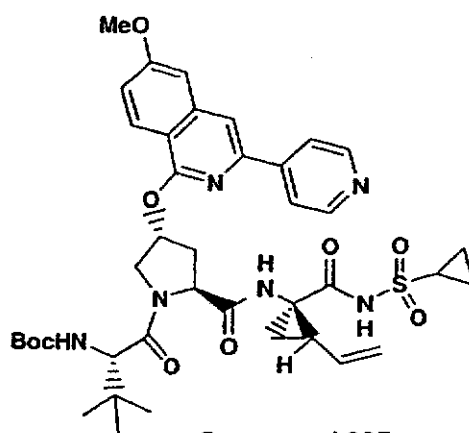
15

6-Methoxy-3-pyridin-4-yl-2H-isoquinolin-1-one (134 mg, 0.531 mmol) was heated under reflux with POCl_3 (6.0 mL) for 5 days. Then POCl_3 was distilled off and the residue was quenched with ice. It was then neutralized with saturated NaHCO_3 solution and the brown solid was collected as pure product. (125 mg, 87% yield)

^1H NMR($\text{DMSO}-d_6$, 400 MHz) δ 3.99 (s, 3 H), 7.53 (dd, $J=9.04$ Hz, 2.44 Hz, 1 H), 7.59 (d, $J=2.69$ Hz, 1 H), 8.26 (d, $J=9.05$ Hz, 1 H), 8.30 (d, $J=5.38$ Hz, 2 H), 8.73 (s, 1 H), 8.85 (d, $J=6.36$ Hz, 2 H).

LC-MS (retention time: 2.027 min.), MS m/z 271 (MH^+).

Step 3 (Scheme 3, Step 2):

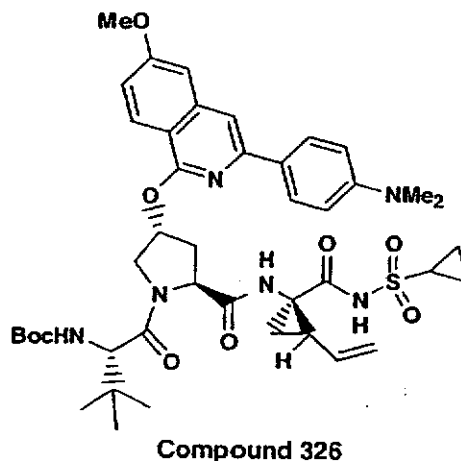


Compound 325

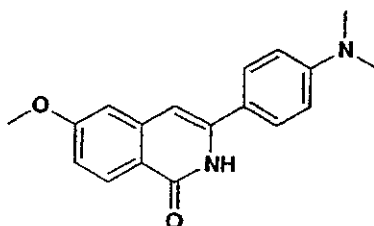
To a solution of {1-[2-(1-Cyclopropanesulfonylaminocarbonyl-2-vinyl-cyclopropyl-carbamoyl)-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid
 5 tert-butyl ester (83.5 mg, 0.15 mmol) and LaCl_3 (36.8 mg, 0.15 mmol) in DMF (1.5 mL), potassium t-butoxide (1.0 M solution in THF, 0.75 mL, 0.75 mmol) was added at -78°C . The reaction mixture was stirred for 1 hr, then 1-chloro-6-methoxy-3-pyridin-4-yl-isoquinoline (40.6 mg, 0.15 mmol) was added. It was warmed to rt and stirred for overnight. Then it was quenched with water and filtered. The filtrate was concentrated and the residue was purified by Prep. HPLC to give an off-white
 10 solid as product (Compound 325). (1.6 mg, 1.5 % yield)

^1H NMR (400 MHz, CD_3OD) δ 0.90(m, 2 H), 1.02 (s, 9 H), 1.17-1.31 (m, 11 H), 1.42 (m, 1 H), 1.87 (m, 1 H), 2.23 (m, 1 H), 2.35 (m, 1 H), 2.68 (m, 1 H), 2.93 (m, 1 H), 3.95 (s, 3 H), 4.15 (m, 1 H), 4.25 (m, 1 H), 4.45 (m, 1 H), 4.56 (m, 1 H), 5.10 (d, $J=10.76$ Hz, 1 H), 5.27 (d, $J=17.61$ Hz, 1 H), 5.74 (m, 1 H), 6.06 (s, 1 H), 7.14 (d, $J=8.07$ Hz, 1 H), 7.34 (s, 1 H), 8.01 (s, 1 H), 8.12 (d, $J=8.81$ Hz, 1 H), 8.19(d, $J=6.12$ Hz, 2 H), 8.61 (d, $J=5.63$ Hz, 2 H).

LC-MS (retention time: 2.523min.), MS m/z 791 (MH^+).

Example 326: Preparation of Compound 326

Compound 326 was prepared by following Scheme 1 and Scheme 4 of above.

Step 1 (Scheme 1):

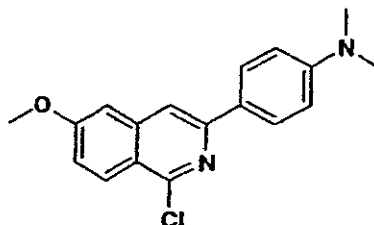
5

To a solution of N,N-Diethyl-4-methoxy-2-methyl-benzamide (332 mg, 1.5 mmol) in THF (15 mL) at -78°C , t-BuLi (1.7 M solution in pentane, 1.3 mL, 2.25 mmol) was added. The resulting red solution was stirred at -78°C for 10 min, then 4-dimethylamino benzonitrile (219 mg, 1.5 mmol) was added. The reaction mixture was then warmed to rt and stirred for overnight. The reaction was quenched with saturated NH_4Cl solution and the yellow precipitate was collected and triturated with ether to give an off-white solid as pure product. (247 mg, 56% yield)

^1H NMR(DMSO- d_6 , 400 MHz) δ 2.97 (s, 6 H), 3.87 (s, 3 H), 6.72 (s, 1 H), 6.78 (d, $J=8.80$ Hz, 2 H), 6.97 (dd, $J=8.80, 2.45$ Hz, 1 H), 7.10 (d, $J=2.45$ Hz, 1 H), 7.65 (d, $J=8.80$ Hz, 2 H), 8.05 (d, $J=8.80$ Hz, 1 H), 11.11 (s, 1 H).

LC-MS (retention time: 2.023 min.), MS m/z 295 (MH^+).

Step 2 (Scheme 4, Step 1):

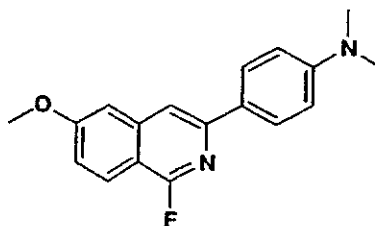


3-(4-Dimethylamino-phenyl)-6-methoxy-2H-isoquinolin-1-one (245 mg, 0.83 mmol) was heated under reflux with POCl_3 (10.0 mL) for 2 days. Then POCl_3 was distilled off and the residue was quenched with ice. It was then neutralized with 10 N NaOH solution and extracted with ethyl acetate twice. The organic layers were combined and dried (MgSO_4). Evaporation of solvent gave an orange solid as product (215 mg, 83% yield)

^1H NMR (400 MHz, CD_3OD) δ 3.01 (s, 6 H), 3.96 (s, 3 H), 6.88 (d, $J=9.05$ Hz, 2 H), 7.20 (dd, $J=9.17, 2.57$ Hz, 1 H), 7.28 (d, $J=2.45$ Hz, 1 H), 7.94 (s, 1 H), 7.96 (d, $J=9.05$ Hz, 2 H), 8.13 (d, $J=9.29$ Hz, 1 H).

LC-MS (retention time: 2.543 min.), MS m/z 313 (MH^+).

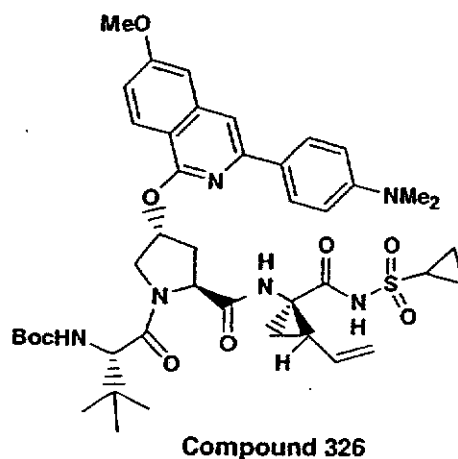
Step 3 (Scheme 4, Step 2):



A mixture of [4-(1-Chloro-6-methoxy-isoquinolin-3-yl)-phenyl]-dimethyl-amine (110 mg, 0.35 mmol) and tetrabutyl phosphonium hydrogen difluoride (0.5 g) was heated at 140°C in Smith microwave reactor for 20 min. Then it was added water and extracted with ethyl acetate. The organic layer was separated, washed with water and dried (MgSO_4). Evaporation of solvent gave a brownish solid as product. (85 mg, 82% yield)

LC-MS (retention time: 2.320 min.), MS m/z 297 (MH^+).

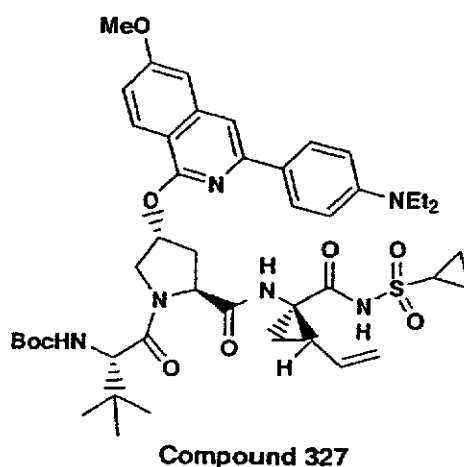
Step 4 (Scheme 4, Step 3):



- 5 To a solution of {1-[2-(1-Cyclopropanesulfonylaminocarbonyl-2-vinyl-cyclopropyl-carbamoyl)-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid tert-butyl ester (111 mg, 0.2 mmol) and LaCl_3 (49 mg, 0.2 mmol) in DMF (2.0 mL), potassium t-butoxide (1.0 M solution in THF, 1.0 mL, 1.0 mmol) was added at -78°C . The reaction mixture was stirred for 1 hr, then [4-(1-fluoro-6-methoxy-
- 10 isoquinolin-3-yl)-phenyl]-dimethylamine (59 mg, 0.2 mmol) was added. It was warmed to rt and stirred for overnight. Then it was quenched with water and filtered. The filtrate was concentrated and the residue was purified by Prep. HPLC to give yellowish solid as product (**Compound 326**). (17.5 mg, 11 % yield)
- ^1H NMR (400 MHz, CD_3OD) δ 0.97-1.08 (m, 11 H), 1.23 (m, 2 H), 1.31 (s, 9 H), 1.44 (m, 1 H), 1.87 (m, 1 H), 2.22 (m, 1 H), 2.34 (m, 1 H), 2.68 (m, 1 H), 2.93 (m, 1 H), 2.99 (m, 6 H), 3.91 (s, 3 H), 4.17 (m, 1 H), 4.29 (m, 1 H), 4.39 (m, 1 H), 4.52 (m, 1 H), 5.10 (d, $J=10.76$ Hz, 1 H), 5.27 (d, $J=17.11$ Hz, 1 H), 5.74 (m, 1 H), 6.03 (s, 1 H), 6.83 (m, 2 H), 6.95 (m, 1 H), 7.16 (s, 1 H), 7.59 (s, 1H), 8.01 (m, 3 H).
- LC-MS (retention time: 2.850 min.), MS m/z 834 (MH^+).

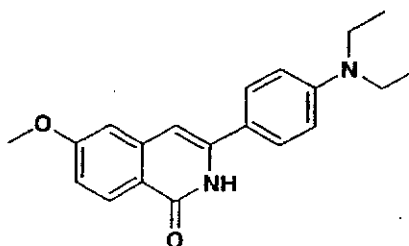
20

Example 327: Preparation of Compound 327



Compound 327 was prepared by following Scheme 1 and Scheme 4 of above.

Step 1 (Scheme 1):



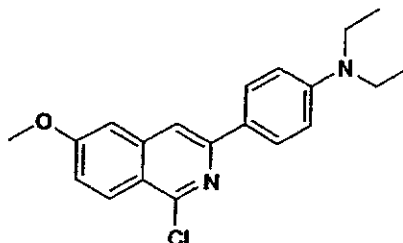
5

To a solution of N,N-Diethyl-4-methoxy-2-methyl-benzamide (332 mg, 1.5 mmol) in THF (15 mL) at -78°C , t-BuLi (1.7 M solution in pentane, 1.3 mL, 2.25 mmol) was added. The resulting red solution was stirred at -78°C for 10 min, then 4-diethylamino benzonitrile (261 mg, 1.5 mmol) was added. The reaction mixture was then warmed to rt and stirred for overnight. The reaction was quenched with saturated NH_4Cl solution and the yellow precipitate was collected as pure product. (215 mg, 44% yield)

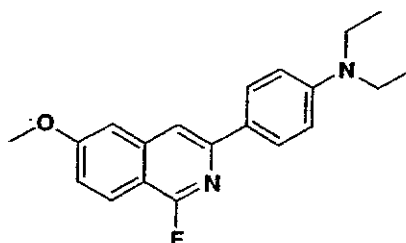
^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.12 (m, 6 H), 3.39 (m, 4H), 3.87 (s, 3 H), 6.69 (s, 1 H), 6.72 (d, $J=9.05$ Hz, 2 H), 6.96 (dd, $J=8.80, 2.45$ Hz, 1 H), 7.09 (d, $J=2.45$ Hz, 1 H), 7.61 (d, $J=9.05$ Hz, 2 H), 8.04 (d, $J=8.80$ Hz, 1 H), 11.06 (s, 1 H).

LC-MS (retention time: 1.883 min.), MS m/z 323 (MH^+).

15

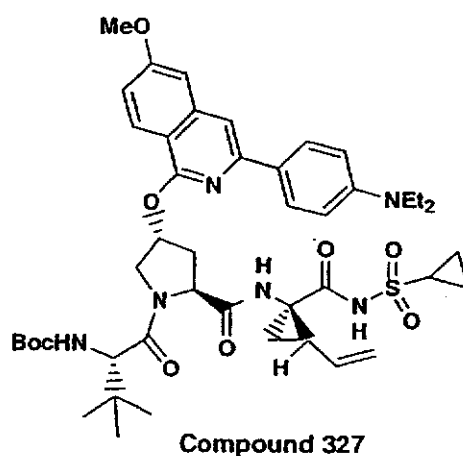
Step 2 (Scheme 4, Step 1):

- 3-(4-Diethylamino-phenyl)-6-methoxy-2H-isoquinolin-1-one (207 mg, 0.642 mmol) was heated under reflux with POCl_3 (8.0 mL) for one day. Then POCl_3 was distilled off and the residue was quenched with ice. It was then neutralized with saturated NaHCO_3 solution and extracted with ethyl acetate twice. The organic layers were combined and dried (MgSO_4). Evaporation of solvent gave a brownish solid as product. (180 mg, 82% yield)
- LC-MS (retention time: 2.397 min.), MS m/z 341 (MH^+).

Step 3 (Scheme 4, Step 2):

- A mixture of [4-(1-Chloro-6-methoxy-isoquinolin-3-yl)-phenyl]-diethylamine (90 mg, 0.264 mmol) and tetrabutyl phosphonium hydrogen difluoride (0.5 g) was heated at 140 °C in Smith microwave reactor for 20 min. Then it was added water and extracted with ethyl acetate. The organic layer was separated, washed with water and dried (MgSO_4). Evaporation of solvent gave a yellowish oil as product. (70 mg, 82% yield)
- LC-MS (retention time: 2.253 min.), MS m/z 325 (MH^+).

Step 4 (Scheme 4, Step 3):



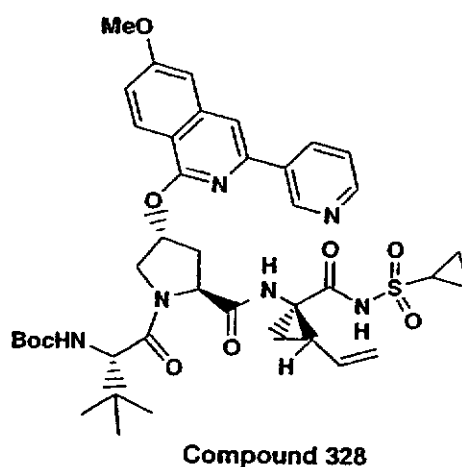
To a solution of {1-[2-(1-Cyclopropanesulfonylaminocarbonyl-2-vinyl-cyclopropyl-carbamoyl)-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid
 5 tert-butyl ester (100 mg, 0.18 mmol) and LaCl_3 (66 mg, 0.27 mmol) in DMF (2.0 mL), potassium t-butoxide (1.0 M solution in THF, 0.9 mL, 0.9 mmol) was added at -78°C. The reaction mixture was stirred for 1 hr, then [4-(1-Fluoro-6-methoxy-isoquinolin-3-yl)-phenyl]-diethylamine (70 mg, 0.216 mmol) was added. It was warmed to rt and stirred for overnight. Then it was quenched with water and filtered.

10 The filtrate was concentrated and the residue was purified by prep. HPLC to give white solid as product (Compound 327). (18 mg, 12 % yield)

^1H NMR (400 MHz, CD_3OD) δ 0.95-1.07 (m, 11H), 1.18 (m, 6 H), 1.25-1.38 (m, 11 H), 1.58 (m, 1 H), 1.85 (m, 1 H), 2.19 (m, 1 H), 2.34 (m, 1 H), 2.68 (m, 1 H), 2.92 (m, 1 H), 3.42 (m, 4 H), 3.90 (s, 3 H), 4.16 (m, 1 H), 4.28 (m, 1 H), 4.37 (m, 1 H),
 15 4.53 (m, 1 H), 5.07 (d, $J=11.0$ Hz, 1 H), 5.25 (d, $J=17.36$ Hz, 1 H), 5.74 (m, 1 H), 5.99 (s, 1 H), 6.77 (d, $J=8.8$ Hz, 2 H), 6.94 (d, $J=9.05$ Hz, 1 H), 7.14 (s, 1 H), 7.56 (s, 1H), 7.95-8.02 (m, 3 H).

LC-MS (retention time: 2.690 min.), MS m/z 862(MH^+).

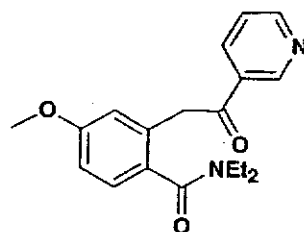
20 Example 328: Preparation of Compound 328



Compound 328 was prepared by following Scheme 2 and Scheme 3 of above.

Step 1 (Scheme 2, Step 1):

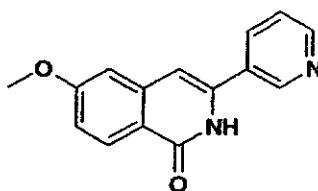
5



To a solution of N,N-Diethyl-4-methoxy-2-methyl-benzamide (332 mg, 1.5 mmol) in THF (15 mL) at -78°C , t-BuLi (1.7 M solution in pentane, 2.12 mL, 3.6 mmol) was added. The resulting red solution was stirred at -78°C for 10 min, then methyl nicotinate (206 mg, 1.5 mmol) was added. The reaction mixture was stirred at -78°C for 2h. Then the reaction was quenched with saturated NH_4Cl solution and extracted with ethyl acetate twice. The combined organic layers were dried (MgSO_4) and concentrated. The crude product was purified by Prep. HPLC to give yellowish thick oil as TFA salt. (124 mg, 19% yield)

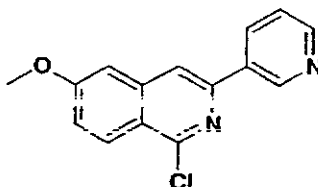
LC-MS (retention time: 1.740 min.), MS m/z 349 ($\text{M}+\text{Na}^+$).

Step 2 (Scheme 2, Step 2):



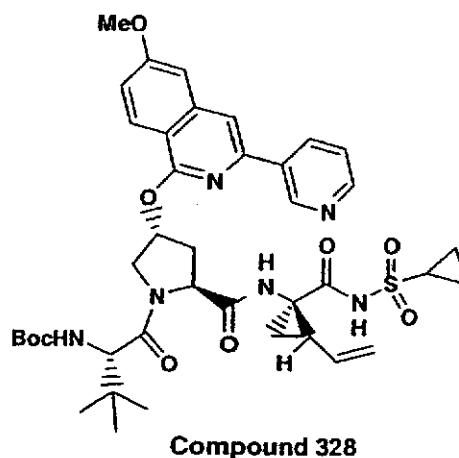
- N,N-Diethyl-4-methoxy-2-(2-oxo-2-pyridin-3-yl-ethyl)-benzamide (120 mg, 0.272 mmol) was heated with ammonium acetate (1 g) for 3 hr. Then it was cooled down and added water. Extracted with ethyl acetate and the organic layer was separated. It was then dried (MgSO_4) and concentrated to give a brownish solid as product. (65 mg, 95% yield)
- ^1H NMR (400 MHz, DMSO-d_6) δ 3.89 (s, 3 H), 6.93 (s, 1 H), 7.10 (dd, $J=8.80, 2.45$ Hz, 1 H), 7.19 (d, $J=2.45$ Hz, 1 H), 7.52 (dd, $J=7.46, 4.77$ Hz, 1 H), 8.15 (m, 2 H), 8.64 (dd, $J=4.89, 1.47$ Hz, 1 H), 8.96 (d, $J=1.71$ Hz, 1 H), 11.51 (s, 1 H).
- LC-MS (retention time: 1.377 min.), MS m/z 253 (MH^+).

Step 3 (Scheme 3, Step 1):



- 6-Methoxy-3-pyridin-3-yl-2H-isoquinolin-1-one (65 mg, 0.258 mmol) was heated under reflux with POCl_3 (2.5 mL) for 7 days. Then POCl_3 was distilled off and the residue was quenched with ice. It was then neutralized with 10 N NaOH solution and extracted with ethyl acetate twice. The combined organic layers were dried (MgSO_4) and concentrated to give yellow solid as product. (27 mg, 39% yield)
- LC-MS (retention time: 2.090 min.), MS m/z 271 (MH^+).

Step 4 (Scheme 3, Step 2):

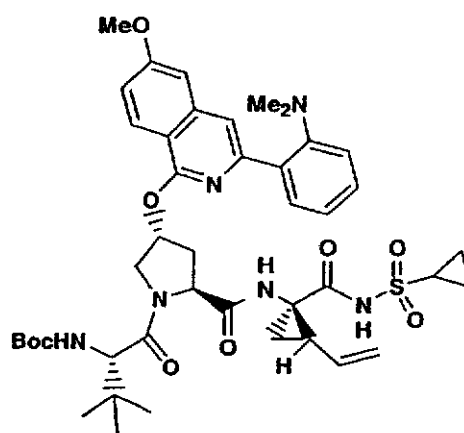


To a solution of {1-[2-(1-Cyclopanesulfonylaminocarbonyl-2-vinyl-cyclopropylcarbamoyl)-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl}-
 5 carbamic acid tert-butyl ester (56 mg, 0.10 mmol) and LaCl_3 (25 mg, 0.10 mmol) in DMF (1.5 mL), potassium t-butoxide (1.0 M solution in THF, 0.5 mL, 0.5 mmol) was added at -78°C . The reaction mixture was stirred for 1 hr, then 1-chloro-6-methoxy-3-pyridin-3-yl-isoquinoline (27 mg, 0.10 mmol) was added. It was warmed to rt and stirred for overnight. Then it was quenched with water and filtered. The
 10 filtrate was concentrated and the residue was purified by Prep. HPLC to give white solid as product (**Compound 328**). (17 mg, 21 % yield)

^1H NMR (400 MHz, CD_3OD) δ 0.95 (m, 2 H), 1.02 (s, 9 H), 1.20-1.30 (m, 11 H),
 1.41 (m, 1 H), 1.86 (m, 1 H), 2.21 (m, 1 H), 2.35 (m, 1 H), 2.67 (m, 1 H), 2.93 (m, 1
 H), 3.93 (s, 3 H), 4.14 (m, 1 H), 4.26 (m, 1 H), 4.47 (d, $J=11.99$ Hz, 1 H), 4.55 (m, 1
 15 H), 5.09 (d, $J=10.02$ Hz, 1 H), 5.26 (d, $J=17.85$ Hz, 1 H), 5.74 (m, 1 H), 6.07 (s, 1 H),
 7.09 (m, 1 H), 7.29 (d, $J=1.96$ Hz, 1 H), 7.53 (m, 1 H), 7.86 (s, 1 H), 8.09 (d, $J=9.05$
 Hz, 1 H), 8.50-8.58 (m, 2 H), 9.28 (s, 1 H).

LC-MS (retention time: 2.453 min.), MS m/z 791 (MH^+).

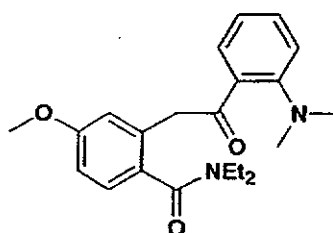
Example 329: Preparation of Compound 329



Compound 329

Compound 329 was prepared by following Scheme 2 and Scheme 4 of above.

Step 1 (Scheme 2, Step 1):



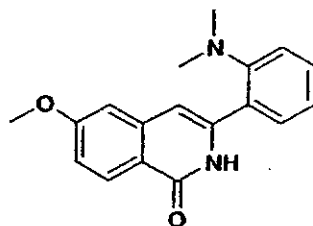
5

10 to a solution of N,N-dimethyl-4-methoxy-2-methylbenzamide (552 mg, 1.5 mmol) in THF (15 mL) at -78°C , t-BuLi (1.7 M solution in pentane, 2.2 mL, 3.75 mmol) was added. The resulting red solution was stirred at -78°C for 10 min, then N,N-dimethylantranilic acid methyl ester (269 mg, 1.5 mmol) was added. The reaction mixture was stirred at -78°C for 2h. Then the reaction was quenched with saturated NH_4Cl solution and extracted with ethyl acetate twice. The combined organic layers were dried (MgSO_4) and concentrated. The crude product was purified by Prep. HPLC to give yellowish thick oil as product. (256 mg, 46% yield)

15 ^1H NMR (400 MHz, CD_3OD) δ 0.99-1.13 (m, 6 H), 3.23-3.31 (m, 8 H), 3.39 (m, 2 H), 3.82 (s, 3 H), 4.35 (s, 2 H), 6.91 (dd, $J=8.44, 2.57$ Hz, 1 H), 6.99 (d, $J=2.45$ Hz, 1 H), 7.22 (d, $J=8.56$ Hz, 1 H), 7.69 (t, $J=7.70$ Hz, 1 H), 7.84 (m, 1 H), 7.96 (d, $J=8.31$ Hz, 1 H), 8.18 (d, $J=7.83$ Hz, 1 H).

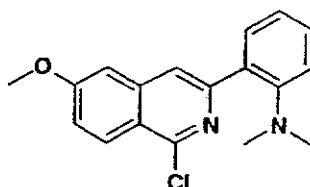
LC-MS (retention time: 1.557min.), MS m/z 369(MH^+).

20 **Step 2 (Scheme 2, Step 2):**



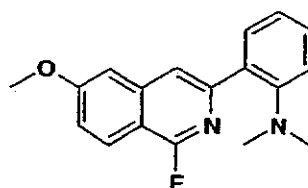
- 2-[2-(2-Dimethylamino-phenyl)-2-oxo-ethyl]-N,N-diethyl-4-methoxy-benzamide (250 mg, 0.678 mmol) was heated with ammonium acetate (1.5 g) for 2 hr. Then it was cooled down and added water. Extracted with ethyl acetate and the organic layer
- 5 was separated. It was then dried (MgSO_4) and concentrated to give a yellowish solid as product. (125 mg, 63% yield)
- ^1H NMR (400 MHz, CD_3OD) δ 2.95 (s, 6 H), 3.92 (s, 3 H), 6.92 (s, 1 H), 7.12 (dd, $J=8.80, 2.45$ Hz, 1 H), 7.16 (d, $J=2.45$ Hz, 1 H), 7.35 (m, 1 H), 7.55 (m, 2 H), 7.63 (d, $J=7.83$ Hz, 1 H), 8.20 (d, $J=9.05$ Hz, 1 H).
- 10 LC-MS (retention time: 2.097 min.), MS m/z 295 (MH^+).

Step 3 (Scheme 4, Step 1):



- 15 3-(2-Dimethylamino-phenyl)-6-methoxy-2H-isoquinolin-1-one (125 mg, 0.425 mmol) was heated under reflux with POCl_3 (4.0 mL) for one day. Then POCl_3 was distilled off and the residue was quenched with ice. It was then neutralized with 10 N NaOH solution and extracted with ethyl acetate twice. The organic layers were combined and dried (MgSO_4). Evaporation of solvent gave a brownish solid as
- 20 product (82 mg, 62% yield)
- LC-MS (retention time: 2.040 min.), MS m/z 313 (MH^+).

Step 4 (Scheme 4, Step 2):

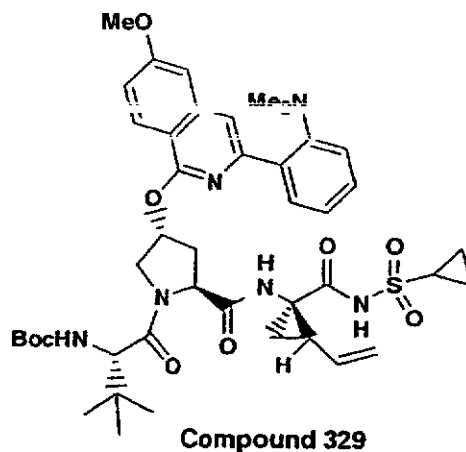


A mixture of [2-(1-Chloro-6-methoxy-isoquinolin-3-yl)-phenyl]-dimethyl-amine (82 mg, 0.262 mmol) and tetrabutyl phosphonium hydrogen difluoride (1.0 g) was heated at 140°C in Smith microwave reactor for 20 min. Then it was added water and extracted with ethyl acetate. The organic layer was separated, washed with water and dried (MgSO₄). Evaporation of solvent gave the crude product which was purified by Prep. HPLC to afford a yellowish oil as product. (85 mg)

¹H NMR (400 MHz, CD₃OD) δ 3.41 (s, 6 H), 4.00 (s, 3 H), 7.42 (dd, *J*=9.05, 2.45 Hz, 1 H), 7.53 (s, 1 H), 7.71 (m, 2 H), 7.99 (m, 1 H), 8.16 (m, 2 H), 8.31 (s, 1 H).

LC-MS (retention time: 1.873 min.), MS *m/z* 297 (MH⁺).

Step 5 (Scheme 4, Step 3):



To a solution of {1-[2-(1-Cyclopropanesulfonylamino-carbonyl-2-vinyl-cyclopropyl-carbamoyl)-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid tert-butyl ester (56 mg, 0.1 mmol) and LaCl₃ (25 mg, 0.1 mmol) in DMF (1.0 mL), potassium *t*-butoxide (1.0 M solution in THF, 0.5 mL, 0.5 mmol) was added at -78°C. The reaction mixture was stirred for 1 hr, then [2-(1-Fluoro-6-methoxy-isoquinolin-3-yl)-phenyl]-dimethyl-amine (30 mg, 0.1 mmol) was added. It was warmed to rt and stirred for overnight. Then it was quenched with water and filtered.

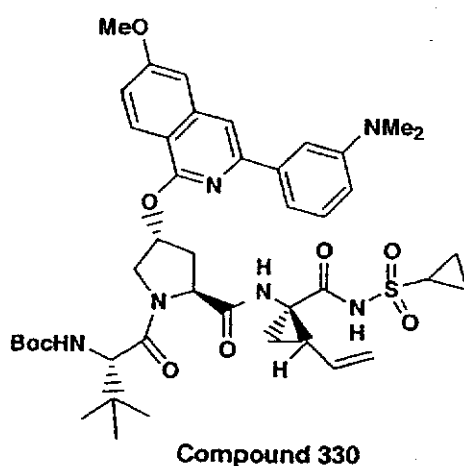
The filtrate was concentrated and the residue was purified by Prep. HPLC to give white solid as product (**Compound 329**). (4.0 mg, 5 % yield)

¹H NMR (400 MHz, CD₃OD) δ 0.98-1.08 (m, 11 H), 1.16-1.32 (m, 11 H), 1.40 (m, 1 H), 1.85 (m, 1 H), 2.16- 2.32 (m, 2 H), 2.60-2.71 (m, 7 H), 2.92 (m, 1 H), 3.91 (s, 3 H), 4.08 (m, 1 H), 4.26 (m, 1 H), 4.45 (m, 1 H), 4.55 (m, 1 H), 5.10 (d, *J*=10.27 Hz, 1 H), 5.28 (d, *J*=18.09 Hz, 1 H), 5.74 (m, 1 H), 5.89 (s, 1 H), 7.05 (d, *J*=6.85 Hz, 1 H), 7.10-7.20 (m, 2 H), 7.29 (m, 1 H), 7.63 (d, *J*=7.58 Hz, 1H), 7.78 (s, 1H), 8.07 (d, *J*=8.56 Hz, 1H).

LC-MS (retention time: 2.550 min.), MS *m/z* 834 (MH⁺).

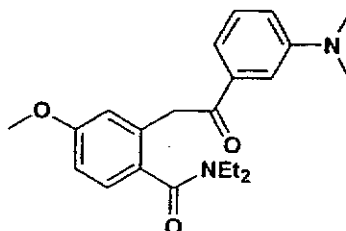
10

Example 330 : Preparation of Compound 330



15 **Compound 330** was prepared by following Scheme 2 and Scheme 4 of above.

Step 1 (Scheme 2, Step 1):

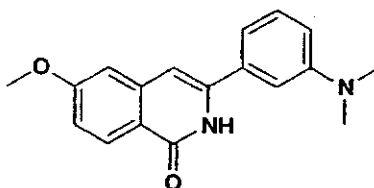


To a solution of N,N-Diethyl-4-methoxy-2-methyl-benzamide (332 mg, 1.5 mmol) in THF (15 mL) at -78°C, t-BuLi (1.7 M solution in pentane, 2.2 mL, 3.75 mmol) was

20

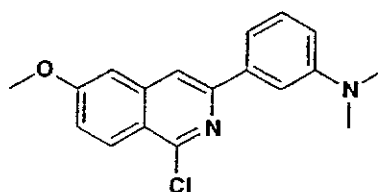
- added. The resulting red solution was stirred at -78°C for 10 min, then (3-dimethylamino)benzoic acid methyl ester (269 mg, 1.5 mmol) was added. The reaction mixture was stirred at -78°C for 2h. Then the reaction was quenched with saturated NH_4Cl solution and extracted with ethyl acetate twice. The combined
- 5 organic layers were dried (MgSO_4) and concentrated. The crude product was purified by Prep. HPLC to give yellowish thick oil as TFA salt. (245 mg, 33% yield)
- ^1H NMR (400 MHz, CD_3OD) δ 1.01 (t, $J=6.85$ Hz, 3 H), 1.09 (m, 3 H), 3.11 (s, 6H), 3.21 (m, 2 H), 3.40 (m, 2 H), 3.79 (s, 3 H), 4.39 (s, 2 H), 6.84-6.91 (m, 2 H), 7.19 (d, $J=8.32$ Hz, 1 H), 7.35 (m, 1 H), 7.49 (t, $J=8.07$ Hz, 1 H), 7.66-7.71 (m, 2 H).
- 10 LC-MS (retention time: 1.930 min.), MS m/z 369(MH^+).

Step 2 (Scheme 2, Step 2):



- 15 2-[(3-Dimethylamino-phenyl)-2-oxo-ethyl]-N,N-diethyl-4-methoxy-benzamide (240 mg, 0.497 mmol) was heated with ammonium acetate (2.0 g) for 2.5 hr. Then it was cooled down and added water. A brownish solid was collected as pure product. (95 mg, 65% yield)
- ^1H NMR (400 MHz, CD_3OD) δ 2.98 (s, 6 H), 3.88 (s, 3 H), 6.74-6.87 (m, 2 H), 7.01-7.07 (m, 3 H), 7.18 (d, $J=2.44$ Hz, 1 H), 7.28 (t, $J=7.82$ Hz, 1 H), 8.10 (d, $J=8.80$ Hz, 1 H).
- 20 LC-MS (retention time: 1.773 min.), MS m/z 295 (MH^+).

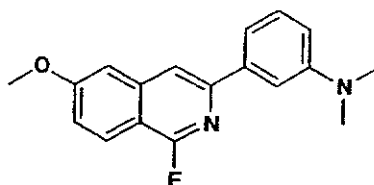
Step 3 (Scheme 4, Step 1):



3-(3-Dimethylamino-phenyl)-6-methoxy-2H-isoquinolin-1-one (92 mg, 0.312 mmol) was heated under reflux with POCl₃ (3.0 mL) for 2 days. Then POCl₃ was distilled off and the residue was quenched with ice. It was then neutralized with saturated NaHCO₃ solution and extracted with ethyl acetate twice. The organic layers were
5 combined and dried (MgSO₄). Evaporation of solvent gave a brownish thick oil as product. (72 mg, 74% yield)

LC-MS (retention time: 2.297 min.), MS m/z 313 (MH⁺).

Step 4 (Scheme 4, Step 2):

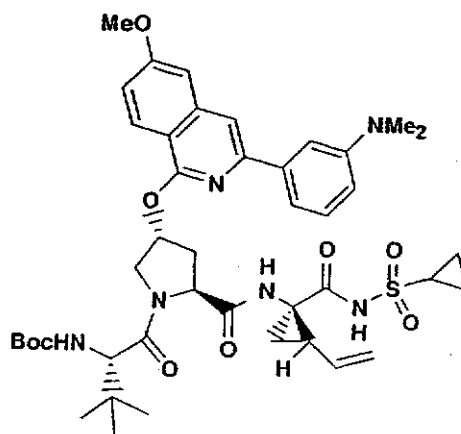


10

A mixture of [3-(1-Chloro-6-methoxy-isoquinolin-3-yl)-phenyl]-dimethylamine (72 mg, 0.23 mmol) and tetrabutyl phosphonium hydrogen difluoride (0.5 g) was heated at 140°C in Smith microwave reactor for 20 min. Then it was added water and extracted with ethyl acetate. The organic layer was separated, washed with water and
15 dried (MgSO₄). Evaporation of solvent gave a brownish oil as product. (58 mg, 85% yield)

LC-MS (retention time: 2.193 min.), MS m/z 297 (MH⁺).

Step 5 (Scheme 4, Step 3):



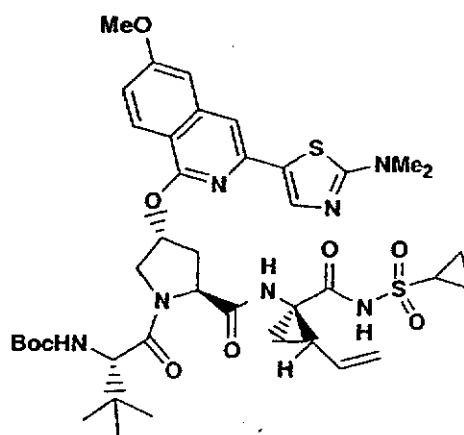
Compound 330

20

To a solution of {1-[2-(1-Cyclopropanesulfonylamino-carbonyl-2-vinyl-cyclopropyl-carbamoyl)-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid tert-butyl ester (86 mg, 0.155 mmol) and LaCl_3 (57 mg, 0.233 mmol) in DMF (1.5 mL), potassium t-butoxide (1.0 M solution in THF, 0.5 mL, 0.5 mmol) was added at
5 -78°C . The reaction mixture was stirred for 1 hr, then [3-(1-Fluoro-6-methoxy-isoquinolin-3-yl)-phenyl]-dimethylamine (55 mg, 0.185 mmol) was added. It was warmed to rt and stirred for overnight. Then it was quenched with water and filtered. The filtrate was concentrated and the residue was purified by Prep. HPLC to give an off-white solid as product (**Compound 330**). (8.0 mg, 6 % yield)

10 ^1H NMR (400 MHz, CD_3OD) δ 0.99-1.09 (m, 11 H), 1.23 (m, 2 H), 1.29 (s, 9 H), 1.42 (m, 1 H), 1.86 (m, 1 H), 2.21 (m, 1 H), 2.33 (m, 1 H), 2.70 (m, 1 H), 2.93 (m, 1 H), 3.00 (s, 6 H), 3.92 (s, 3 H), 4.14 (m, 1 H), 4.29 (m, 1 H), 4.44-4.57 (m, 2 H), 5.10 (d, $J=11.00$ Hz, 1 H), 5.27 (d, $J=16.87$ Hz, 1 H), 5.74 (m, 1 H), 6.01 (s, 1 H), 6.63 (d, $J=8.80$ Hz, 1 H), 7.03 (d, $J=6.85$ Hz, 1 H), 7.24 (s, 1 H), 7.28 (t, $J=8.07$ Hz, 1 H),
15 7.45 (d, $J=7.82$ Hz, 1 H), 7.59 (s, 1 H), 7.72 (s, 1 H), 8.05 (d, $J=8.80$ Hz, 1 H).
LC-MS (retention time: 2.707 min.), MS m/z 834 (MH^+).

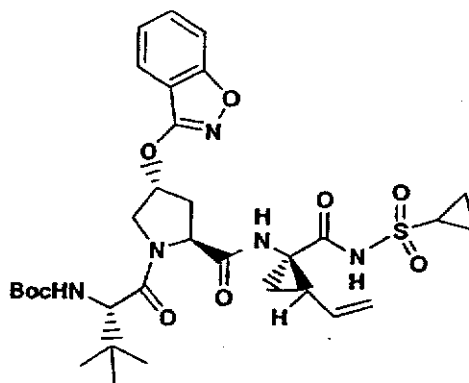
Example 331: Preparation of Compound 331



Compound 331

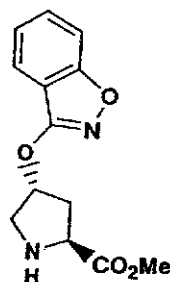
20

Compound 331 was prepared by the methods described herein.

Example 334: Preparation of Compound 334**Compound 334**

Compound 334 was prepared in the following manner:

5

Step 1:

To a solution of Boc-cis-HYP-OMe (122.6 mg, 0.5 mmol) in THF (15 mL) at 0°C, triphenylphosphine (196.7 mg, 0.75 mmol) and benzo[d]isoxazol-3-ol (81 mg, 0.6 mmol) were added. Then DEAD (0.118 mL, 0.75 mmol) was added. The reaction mixture was warmed to rt. and stirred for 3 hr. Then solvent was evaporated and the residue was purified by Prep. HPLC to give a colorless thick oil. (117 mg, 54% yield)

¹H NMR (400 MHz, CD₃OD) δ 1.41 (m, 9 H), 2.38 (m, 1 H), 2.75 (m, 1 H), 3.75 (m, 3 H), 3.81 (m, 1 H), 3.90 (m, 1 H), 4.47 (m, 1 H), 5.44 (m, 1 H), 7.31 (t, *J*=7.46 Hz, 1 H), 7.47 (d, *J*=8.56 Hz, 1 H), 7.59 (t, *J*=7.83 Hz, 1 H), 7.66 (d, *J*=8.07 Hz, 1 H).

15

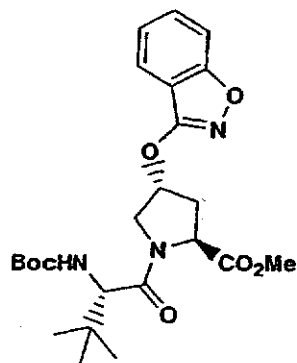
LC-MS (retention time: 2.65 min.), MS *m/z* 363(MH⁺).

Some of the coupling product (85 mg, 0.235 mmol) was then dissolved in 4N HCl in dioxane (1.5mL) and stirred for 3 hr. Evaporation of solvent gave a yellowing oil as

20 HCl salt. (85 mg, >100% yield)

LC-MS (retention time: 1.327 min.), MS m/z 263(MH^+).

Step 2:



5

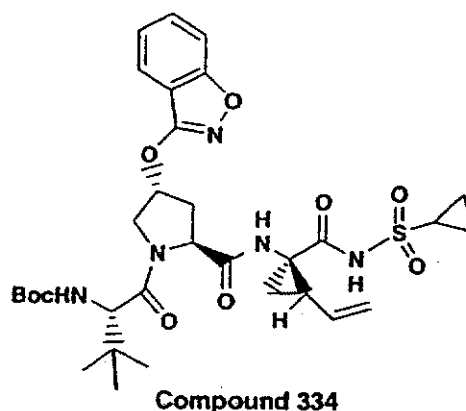
To a solution of 4-(Benzo[d]isoxazol-3-yloxy)-pyrrolidine-2-carboxylic acid methyl ester hydrochloride salt (85 mg, 0.285 mmol) in CH_3CN (10 mL) was added N-boc-L-t-leucine (99 mg, 0.427 mmol), DIEA (0.25 mL, 1.425 mmol) and the coupling reagent HOBt (65 mg, 0.427 mmol) and HBTU (162 mg, 0.427 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. It was then purified by Prep. HPLC column to give a colorless thick oil as product. (63 mg, 46% yield)

15 ^1H NMR (400 MHz, CD_3OD) δ 1.01 (s, 9 H), 1.17 (s, 9 H), 2.34 (m, 1 H), 2.78 (dd, $J=14.13, 7.83$ Hz, 1 H), 3.72 (s, 3 H), 4.00 (dd, $J=12.22, 3.42$ Hz, 1 H), 4.19 (s, 1 H), 4.57 (d, $J=12.23$ Hz, 1 H), 4.68 (m, 1 H), 5.51 (m, 1 H), 7.27 (m, 1 H), 7.47 (d, $J=8.56$ Hz, 1 H), 7.57 (m, 1H), 7.63 (d, $J=8.07$ Hz, 1 H).

LC-MS (retention time: 2.737 min.), MS m/z 498 ($M+Na^+$).

20

Step 3:

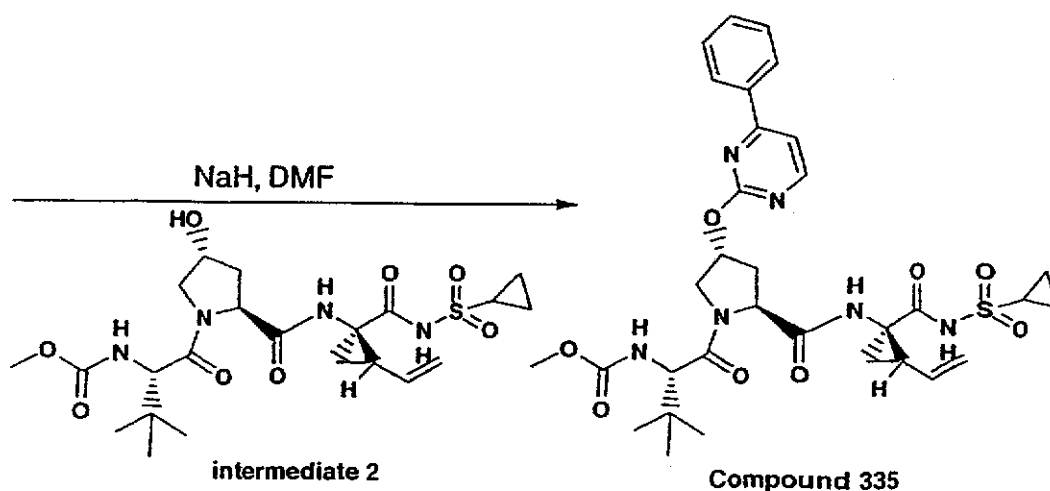


To a solution of 4-(Benzo[d]isoxazol-3-yloxy)-1-(2-tert-butoxycarbonylamino-3,3-dimethyl-butyl)-pyrrolidine-2-carboxylic acid methyl ester (63 mg, 0.132 mmol) in THF (3.5 mL), methanol (2.0 mL) and water (0.5 mL) mixture, lithium hydroxide monohydrate (83 mg, 1.89 mmol) was added. The reaction mixture was stirred at rt. for overnight. Then it was acidified with 1N HCl solution to pH=3 to 5 and concentrated. Extracted with ethyl acetate (2x30 mL) and the organic layers were combined and dried (MgSO₄). Evaporation of solvent gave a yellowish oil to carry on. (61 mg, 100 % yield)

To a solution of above compound (61 mg, 0.132 mmol) in CH₃CN (8 mL) was added (1R, 2S) (1-cyclopropanesulfonyl-aminocarbonyl-2-vinyl-cyclo-propyl)-carbamic acid hydrochloride (42 mg, 0.158 mmol), DIEA (0.115 mL, 0.66 mmol) and the coupling reagent HOBt (30 mg, 0.198 mmol) and HBTU (75 mg, 0.198 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated. It was then purified by Prep. HPLC column to give a yellow film as final product (Compound 334). (24 mg, 27% yield)

¹H NMR (400 MHz, CD₃OD) δ 1.01 (s, 9 H), 1.05 (m, 2 H), 1.12-1.26 (m, 11 H), 1.43 (m, 1 H), 1.86 (dd, *J*=8.07, 5.38 Hz, 1 H), 2.17-2.33 (m, 2 H), 2.67 (dd, *J*=12.96, 5.87 Hz, 1H), 2.93 (m, 1 H), 4.05 (m, 1 H), 4.22 (m, 1 H), 4.49 (m, 2 H), 5.11 (d, *J*=10.21Hz, 1 H), 5.29 (d, *J*=17.12 Hz, 1 H), 5.55 (s, 1H), 5.74 (m, 1 H), 7.29 (m, 1 H), 7.48 (d, *J*=8.32 Hz, 1H), 7.54-7.64 (m, 2 H).

LC-MS (retention time: 2.767 min.), MS *m/z* 696 (M+Na⁺).



Step 1: (Scheme 1, step 1)

- 5 To a solution of (2S, 4R) 4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (0.25 g, 1.08 mmol) in CH_3CN (10 mL) was added (1R, 2S) (1-cyclopropanesulfonyl-aminocarbonyl-2-vinyl-cyclo-propyl)-carbamic acid hydrochloride (0.346 g, 1.30 mmol), DIEA (0.94 mL, 5.41 mmol) and the coupling reagent HOBt (0.248 g, 1.62 mmol) and HBTU (0.615 mg, 1.62 mmol). The solution
- 10 was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO_4 and concentrated to give yellow oil. It was purified by Prep. HPLC column to give a colorless thick oil which was then dissolved in 4N HCl in dioxane (5 mL). The reaction mixture was stirred at rt. for overnight. Evaporation of
- 15 solvent gave white solid as product to carry on. (200 mg, 49% yield)
- LC-MS (retention time: 0.647 min.), MS m/z 344 (MH^+).

Step 2: (Scheme 1, step 2)

- To a solution of above compound (200 mg, 0.527 mmol) in CH_3CN (10 mL) was
- 20 added 2-methoxycarbonylamino-3,3-dimethyl-butyric acid (0.15 g, 0.79 mmol), DIEA (0.46 mL, 2.63 mmol) and the coupling reagent HOBt (0.121 g, 0.79 mmol) and HBTU (0.30 g, 0.79 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO_4 and

concentrated to give yellowish oil. It was purified by Prep. HPLC column to give white solid as final product (**intermediate 2**). (145 mg, 54% yield)

¹H NMR(CD₃OD, 500 MHz) δ 0.99-1.10 (m, 11 H), 1.24(m, 2 H), 1.41 (dd, $J=9.5$, 5.5 Hz, 1 H), 1.87 (dd, $J=7.9$, 5.5 Hz, 1 H), 1.97 (m, 1 H), 2.13 (m, 1 H), 2.24 (m, 1 H), 2.93 (m, 1 H), 3.65 (s, 3 H), 3.77-3.88 (m, 2 H), 4.33-4.39 (m, 2 H), 4.49 (m, br, 1 H), 5.13(d, $J=10.4$ Hz, 1 H), 5.31 (d, $J=17.1$ Hz, 1 H), 5.76 (m, 1 H).

LC-MS (retention time: 1.590 min.), MS m/z 515 (MH⁺).

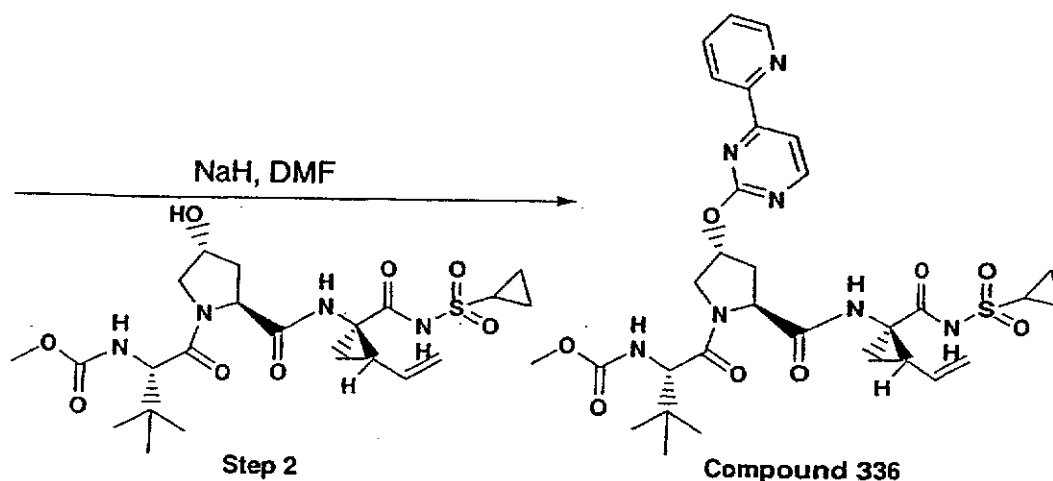
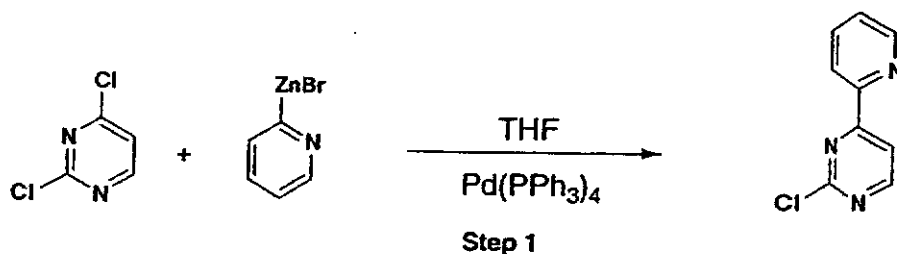
Step 3: (Scheme 2)

10 To a solution of 2,4-dichloropyrimidine (149 mg, 1 mmol) in THF (5 mL), tetrakis(triphenylphosphine) palladium (23 mg, 2 mol%) and 0.5M solution of phenylzinc bromide (2.1 mL, 1.05 mmol) in THF were added. The reaction mixture was stirred at 50°C for overnight. Then it was added saturated ammonium chloride solution and extracted with EtOAc twice. The organic layers were combined, washed
15 with water and dried (MgSO₄). Evaporation of solvent gave a yellow residue which was purified by Prep. HPLC to afford a yellowish oil as 2-chloro-4-phenylpyrimidine to carry on.

To a solution of **intermediate 2** (20 mg, 0.039 mmol) in DMF (3 mL), NaH (3.9 mg of 60% dispersion in mineral oil, 0.0975 mmol) was added at 0°C. The reaction
20 mixture was then warmed to rt. and stirred for 1 hr. Then 2-chloro-4-phenylpyrimidine prepared above (18 mg as crude) was added. The reaction mixture was stirred at rt. for overnight. It was then quenched with water and extracted with EtOAc. The organic layer was separated, washed with brine and dried (MgSO₄). Evaporation of solvent gave yellowish oil which was then purified by Prep. HPLC to
25 give a thick colorless oil as final product (**Compound 335**) as TFA salt.(5.5 mg, 18% yield)

¹H NMR(CD₃OD, 300 MHz) δ 0.92-1.12 (m, 11 H). 1.25 (m, 2 H), 1.44 (dd, $J=9.2$, 5.5 Hz, 1 H), 1.89 (dd, $J=8.1$, 5.5 Hz, 1H), 2.17-2.37 (m, 2 H), 2.57 (m, 1 H), 2.95 (m, 1 H), 3.52 (s, 3 H), 4.14 (m, 1 H), 4.24-4.38 (m, 2 H), 4.51 (m, 1 H), 5.13 (d, $J=10.2$ Hz, 1 H), 5.31 (d, $J=17.2$ Hz, 1 H), 5.77 (m, 1 H), 5.86 (s, 1 H), 7.48-7.60 (m, 3 H), 7.66 (d, $J=5.3$ Hz, 1 H), 8.18 (m, 2 H), 8.60 (d, $J=5.1$ Hz, 1 H).

LC-MS (retention time: 1.947 min.), MS m/z 669 (MH⁺).

Example 336: Preparation of Compound 336**Step 1:**

To a solution of 2,4-dichloropyrimidine (149 mg, 1 mmol) in THF (5 mL), tetrakis(triphenylphosphine) palladium (58 mg, 5 mol%) and 0.5M solution of 2-pyridinylzinc bromide (2.4 mL, 1.2 mmol) in THF were added. The reaction mixture was stirred at 50°C for overnight. Then it was added saturated ammonium chloride solution and extracted with EtOAc twice. The organic layers were combined, washed with water and dried (MgSO₄). Evaporation of solvent gave a yellow residue which was purified by Prep. HPLC to afford a yellowish oil as product. (11 mg, 3.6 % yield)

¹H NMR (500 MHz, CD₃OD) δ 7.61 (m, 1 H), 8.07 (m, 1 H), 8.36 (d, *J*=5.19 Hz, 1 H), 8.50 (d, *J*=7.94 Hz, 1 H), 8.75 (d, *J*=3.97 Hz, 1 H), 8.82 (d, *J*=5.19 Hz, 1 H).

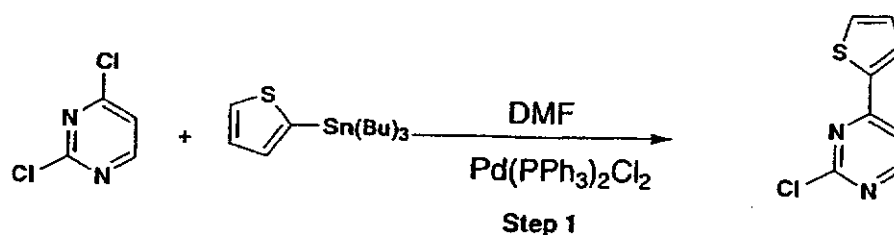
LC-MS (retention time: 1.440 min.), MS *m/z* 192 (MH⁺).

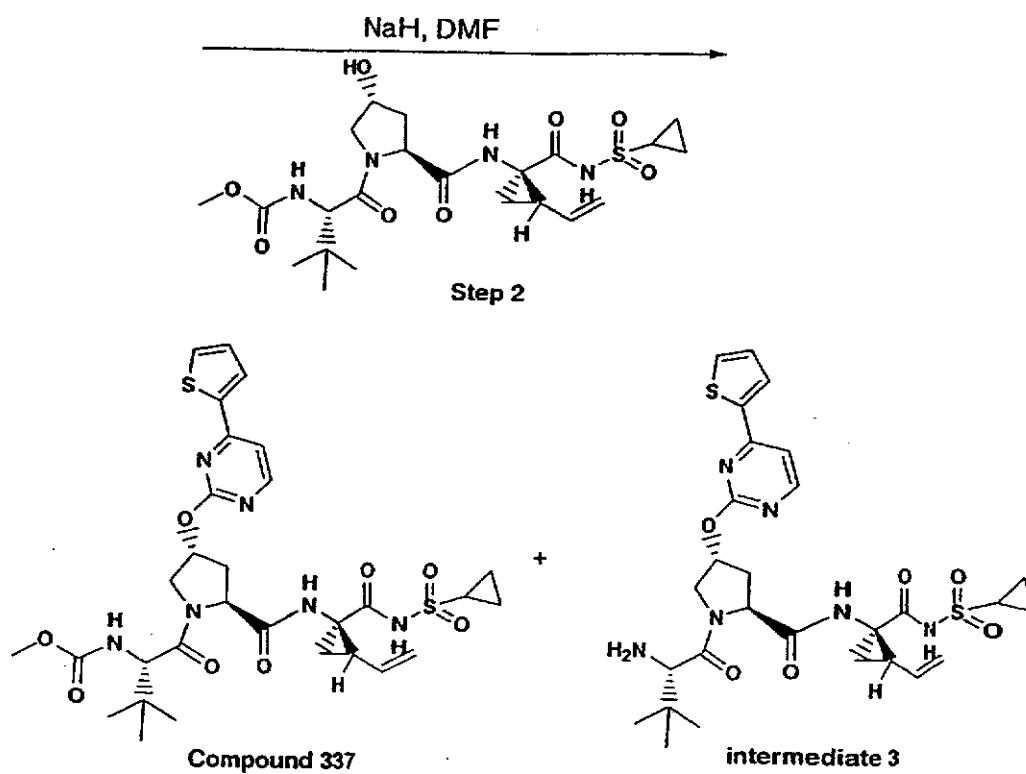
Step 2:

To a solution of **intermediate 2** from **Example 335** (15 mg, 0.029 mmol) in DMF (3 mL), NaH (1.75 mg of 60% dispersion in mineral oil, 0.0728 mmol) was added at 0°C. The reaction mixture was then warmed to rt. and stirred for 1 hr. Then 2-Chloro-4-pyridin-2-yl-pyrimidine (9.5 mg, 0.0311 mmol) was added. The reaction mixture was stirred at rt. for overnight. It was then quenched with water and extracted with EtOAc. The organic layer was separated, washed with brine and dried (MgSO₄). Evaporation of solvent gave yellowish oil which was then purified by Prep. HPLC to give a yellowish film as final product (**Compound 336**) as TFA salt. (3.5 mg, 15% yield)

¹H NMR(CD₃OD, 500 MHz) δ 1.03 (s, 9 H), 1.08 (m, 2 H), 1.24 (m, 2 H), 1.43 (dd, *J*=9.77, 5.50 Hz, 1 H), 1.89 (m, 1 H), 2.24 (m, 1 H), 2.31 (m, 1 H), 2.57 (m, 1 H), 2.95 (m, 1 H), 3.50 (s, 3 H), 4.13 (m, 1 H), 4.29 (s, 1 H), 4.36 (d, *J*=11.91 Hz, 1 H), 4.52 (m, 1 H), 5.13 (d, *J*=10.08 Hz, 1 H), 5.31 (d, *J*=16.79 Hz, 1 H), 5.76 (m, 1 H), 5.88 (m, 1 H), 7.64 (m, 1 H), 8.06-8.13 (m, 2 H), 8.54 (d, *J*=7.93 Hz, 1 H), 8.73-8.76 (m, 2 H).

LC-MS (retention time: 1.787 min.), MS *m/z* 670 (MH⁺).

Example 337: Preparation of Compound 337



Step 1:

- To a solution of 2,4-dichloropyrimidine (149 mg, 1 mmol) in DMF (5 mL), dichloro
 5 bis(triphenylphosphine) palladium (II) (35 mg, 5 mol%) and 2-(tributylstannyl)thiophene (0.38 mL, 1.2 mmol) were added. The reaction mixture was heated at 70°C for 3hr. Then it was added saturated KF solution in methanol (20 mL) and stirred at rt for 4 hr. The reaction mixture was concentrated with a small amount of silica gel and the residue was filtered through filter paper and washed with
 10 EtOAc. The filtrate was then concentrated and the residue was purified by Prep. HPLC to afford an off-white solid as product. (110 mg, 35 % yield)
- ¹H NMR (400 MHz, CD₃OD) δ 7.20 (dd, *J*=5.01, 3.79 Hz, 1 H), 7.74 (dd, *J*=5.01, 1.10 Hz, 1 H), 7.77 (d, *J*=5.38 Hz, 1 H), 7.98 (dd, *J*=3.79, 1.10 Hz, 1 H), 8.55 (d, *J*=5.38 Hz, 1 H).
- 15 LC-MS (retention time: 1.453 min.), MS *m/z* 197 (MH⁺).

Step 2:

To a solution of **intermediate 2** from **Example 335** (20 mg, 0.039 mmol) in DMF (3 mL), NaH (7.8 mg of 60% dispersion in mineral oil, 0.195 mmol) was added at 0°C. The reaction mixture was then warmed to rt. and stirred for 1 hr. Then 2-Chloro-4-thiophen-2-yl-pyrimidine (16.9 mg, 0.0544 mmol) was added. The reaction mixture was stirred at rt. for overnight. It was then quenched with water and extracted with EtOAc. The organic layer was separated, washed with brine and dried (MgSO₄). Evaporation of solvent gave yellowish oil which was then purified by Prep. HPLC to give two products (**Compound 337** and **intermediate 3**).

Compound 337: (yellowish film, 3.0 mg, 11% yield)

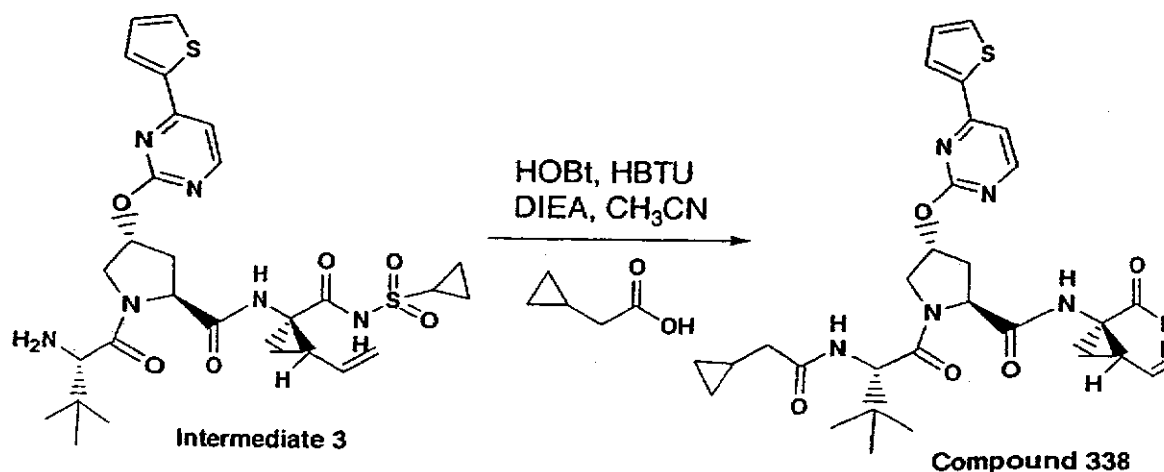
¹H NMR(CD₃OD, 500 MHz) δ 0.98-1.07 (m, 11 H), 1.22 (m, 2 H), 1.41 (dd, *J*=9.54, 5.62 Hz, 1H), 1.86 (dd, *J*=8.32, 5.63 Hz, 1 H), 2.19- 2.31 (m, 2 H), 2.52 (m, 1 H), 2.92 (m, 1 H), 3.50 (s, 3 H), 4.09 (m, 1 H), 4.25-4.32 (m, 2 H), 4.47 (dd, *J*=10.03, 7.34 Hz, 1 H), 5.11 (dd, *J*=10.27, 1.71 Hz, 1 H), 5.28 (dd, *J*=17.11, 1.46 Hz, 1 H), 5.69-5.79 (m, 2 H), 7.20 (dd, *J*=4.89, 3.66 Hz, 1 H), 7.51 (d, *J*=5.38 Hz, 1 H), 7.70 (d, *J*=4.89 Hz, 1 H), 7.95 (d, *J*=3.67 Hz, 1 H), 8.54 (d, *J*=5.14 Hz, 1 H).
LC-MS (retention time: 1.787 min.), MS *m/z* 696 (M+Na⁺).

Intermediate 3: (10 mg, 35% yield)

LC-MS (retention time: 1.477 min.), MS *m/z* 617(MH⁺).

20

Example 338: Preparation of Compound 338

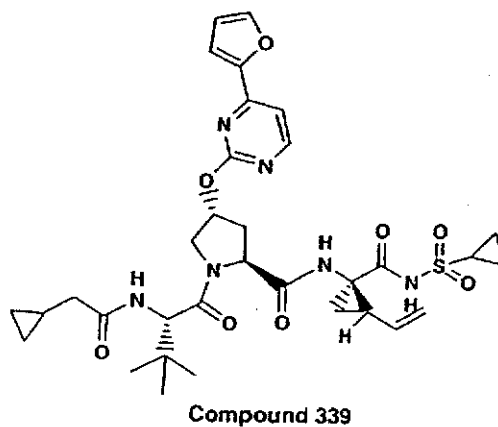


To a solution of 1-(2-Amino-3,3-dimethyl-butyl)-4-(4-thiophen-2-yl-pyrimidin-2-yloxy)-pyrrolidine-2-carboxylic acid (1-cyclopropanesulfonylaminocarbonyl-2-vinyl-cyclopropyl)-amide (10 mg, 0.0137 mmol) in CH₃CN (5 mL) was added cyclopropylacetic acid (2.1 mg, 0.0205 mmol), DIEA (0.012 mL, 0.742 mmol) and the coupling reagent HOBt (3.1 g, 0.0205 mmol) and HBTU (7.8 mg, 0.0205 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated to give yellow oil. It was purified by Prep. HPLC column to give a yellowish film as TFA salt (**Compound 338**). (4.6 mg, 41% yield)

¹H NMR(CD₃OD, 400 MHz) δ 0.12 (m, 2 H), 0.48 (m, 2 H), 0.90 (m, 1 H), 1.01-1.09 (m, 11 H), 1.23 (m, 2 H), 1.43 (dd, $J=9.29, 5.38$ Hz, 1 H), 1.87 (dd, $J=8.31, 5.62$ Hz, 1 H), 2.06 (m, 2 H), 2.19- 2.31 (m, 2 H), 2.52 (dd, $J=13.45, 6.85$ Hz, 1 H), 2.93 (m, 1 H), 4.12(dd, $J=11.98, 3.91$ Hz, 1 H), 4.27 (d, $J=11.74$ Hz, 1 H), 4.47 (dd, $J=10.27, 6.85$ Hz, 1 H), 4.63 (s, 1 H), 5.11 (dd, $J=10.27, 1.47$ Hz, 1 H), 5.28 (dd, $J=17.12, 1.47$ Hz, 1 H), 5.71-5.80 (m, 2 H), 7.20 (dd, $J=4.89, 3.67$ Hz, 1 H), 7.51 (d, $J=5.38$ Hz, 1 H), 7.70 (d, $J=5.20$ Hz, 1 H), 7.95 (d, $J=3.67$ Hz, 1 H), 8.48 (d, $J=5.13$ Hz, 1 H).

LC-MS (retention time: 1.833 min.), MS m/z 699 (MH⁺).

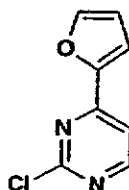
Example 339: Preparation of Compound 339



Compound 342 was prepared by following Schemes of Example 337 and Example 338, except that 2-(tributylstannyl)furan was used in the place of 2-(tributylstannyl)thiophene in the Step 1 of Example 337.

5

Step 1:

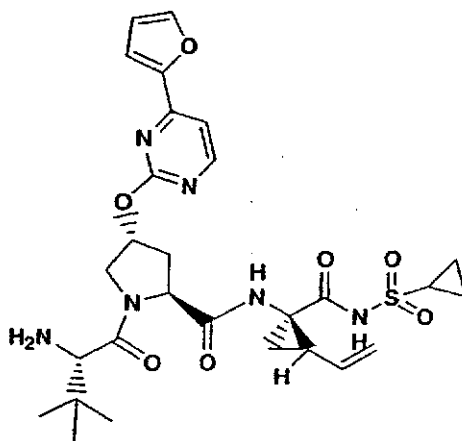


To a solution of 2,4-dichloropyrimidine (149 mg, 1 mmol) in DMF (5 mL), dichloro bis(triphenylphosphine) palladium (II) (35 mg, 5 mol%) and 2-(tributylstannyl)furan (0.35 mL, 1.1 mmol) were added. The reaction mixture was heated at 70°C for 3 hr. Then it was added saturated KF solution in methanol (20 mL) and stirred at rt for 4 hr. The reaction mixture was concentrated with a small amount of silica gel and the residue was filtered through filter paper and washed with EtOAc. The filtrate was then concentrated and the residue was purified by Prep. HPLC to afford a brownish solid as product. (80 mg, 27 % yield)

¹H NMR (400 MHz, CD₃OD) δ 6.68 (dd, *J*=3.67, 1.71 Hz, 1 H), 7.42 (d, *J*=3.67 Hz, 1 H), 7.67 (d, *J*=5.13 Hz, 1 H), 7.30 (d, *J*=1.71 Hz, 1 H), 8.62 (d, *J*=5.14 Hz, 1 H).

LC-MS (retention time: 1.233 min.), MS *m/z* 181 (MH⁺).

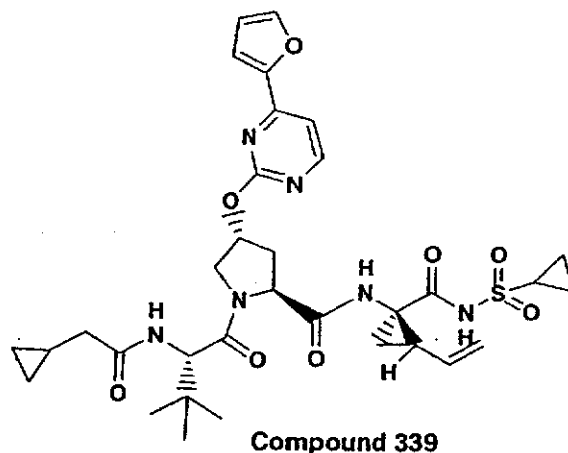
20 Step 2:



To a solution of {1-[2-(1-cyclopropanesulfonylaminocarbonyl-2-vinyl-cyclopropyl-carbamoyl)-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid methyl ester (20 mg, 0.039 mmol) in DMF (3 mL), NaH (7.8 mg of 60% dispersion in mineral oil, 0.195 mmol) was added at 0°C. The reaction mixture was then warmed to rt. and stirred for 1 hr. Then 2-Chloro-4-thiophen-2-yl-pyrimidine (16.0 mg, 0.0544 mmol) was added. The reaction mixture was stirred at rt. for overnight. It was then quenched with water and extracted with EtOAc. The organic layer was separated, washed with brine and dried (MgSO₄). Evaporation of solvent gave yellowish oil which was then purified by Prep. HPLC to give deboced coupling product. (3 mg, 11% yield)

LC-MS (retention time: 1.420 min.), MS m/z 601 (MH⁺).

Step 3:



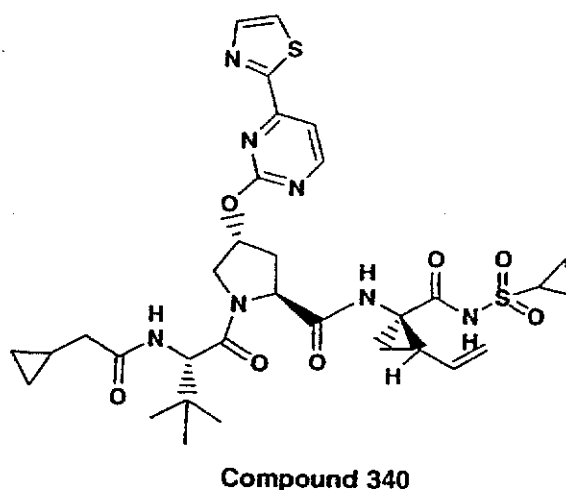
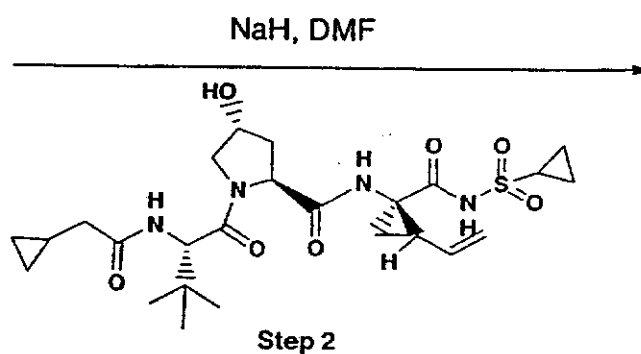
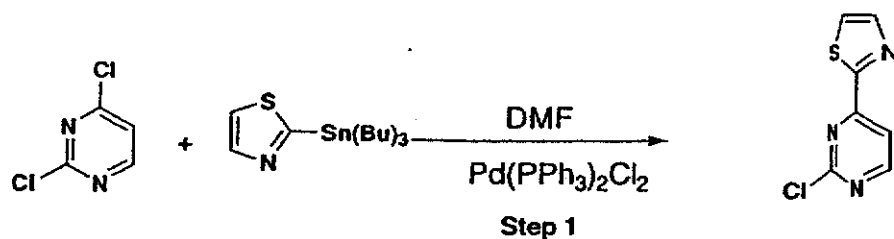
15

To a solution of 1-(2-Amino-3,3-dimethyl-butyl)-4-(4-furan-2-yl-pyrimidin-2-yloxy)-pyrrolidine-2-carboxylic acid (1-cyclopropanesulfonylaminocarbonyl-2-vinyl-cyclopropyl)-amide (3 mg, 0.0042 mmol) in CH₃CN (5 mL) was added cyclopropylacetic acid (0.6 mg, 0.0063 mmol), DIEA (0.004 mL, 0.021 mmol) and the coupling reagent HOBt (1.0 g, 0.0063 mmol) and HBTU (2.4 mg, 0.0063 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated to give yellow oil. It was purified by

Prep. HPLC column to give a yellowish film as TFA salt (Compound 339). (1.0 mg, 30% yield)

- ¹H NMR(CD₃OD, 400 MHz) δ 0.12 (m, 2 H), 0.48 (m, 2 H), 0.90 (m, 1 H), 0.99-1.09 (m, 11 H), 1.23 (m, 2 H), 1.43 (dd, $J=9.05, 5.31$ Hz, 1 H), 1.87 (m, 1 H), 2.05 (m, 2 H), 2.19- 2.29 (m, 2 H), 2.50 (m, 1 H), 2.93 (m, 1 H), 4.10 (dd, $J=12.23, 3.91$ Hz, 1 H), 4.25 (d, $J=11.99$ Hz, 1 H), 4.47 (dd, $J=10.52, 7.09$ Hz, 1 H), 4.63 (s, 1 H), 5.11 (dd, $J=10.52, 1.71$ Hz, 1 H), 5.29 (dd, $J=17.12, 1.47$ Hz, 1 H), 5.71-5.79 (m, 2 H), 6.65 (dd, $J=3.67, 1.96$ Hz, 1 H), 7.38 (d, $J=3.67$ Hz, 1 H), 7.40 (d, $J=5.38$ Hz, 1 H), 7.76 (m, 1 H), 8.54 (d, $J=5.38$ Hz, 1 H).
- 10 LC-MS (retention time: 1.790 min.), MS m/z 683 (MH⁺).

Example 340: Preparation of Compound 340

**Step 1:**

To a solution of 2,4-dichloropyrimidine (149 mg, 1 mmol) in DMF (5 mL), dichloro bis(triphenylphosphine) palladium (II) (35 mg, 5 mol%) and 2-(tributylstannyl)thiazole (412 mg, 1.1 mmol) were added. The reaction mixture was heated at 80°C for 3hr. Then it was added saturated KF solution in methanol (20 mL) and stirred at rt for 4hr. The reaction mixture was concentrated with a small amount of silica gel and the residue was filtered through filter paper and washed with EtOAc. The filtrate was then concentrated and the residue was purified by Prep. HPLC to afford a brownish solid as product. (9 mg, 3 % yield)

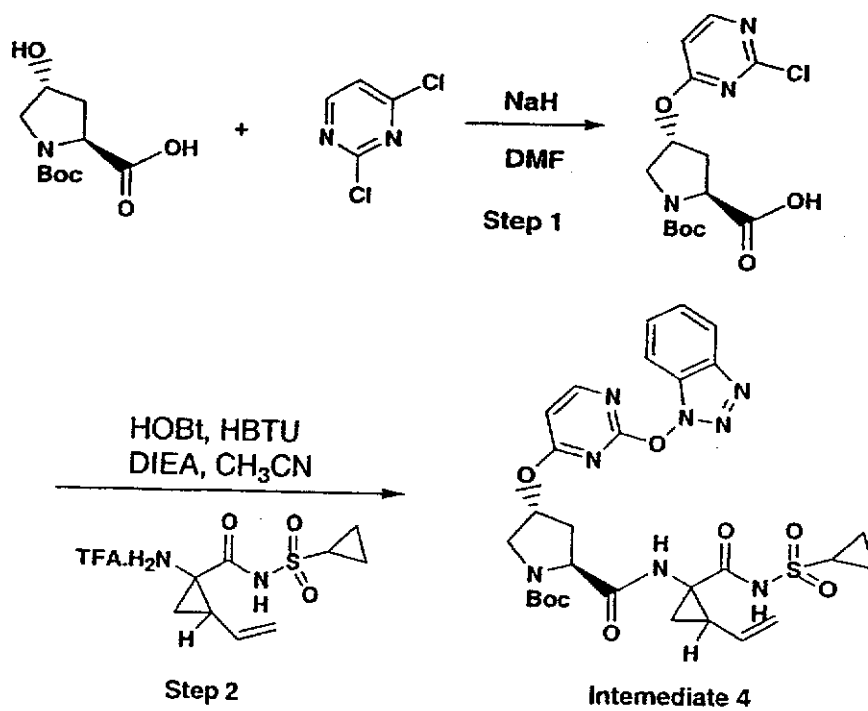
LC-MS (retention time: 1.320 min.), MS m/z 198 (MH^+).

Step 2:

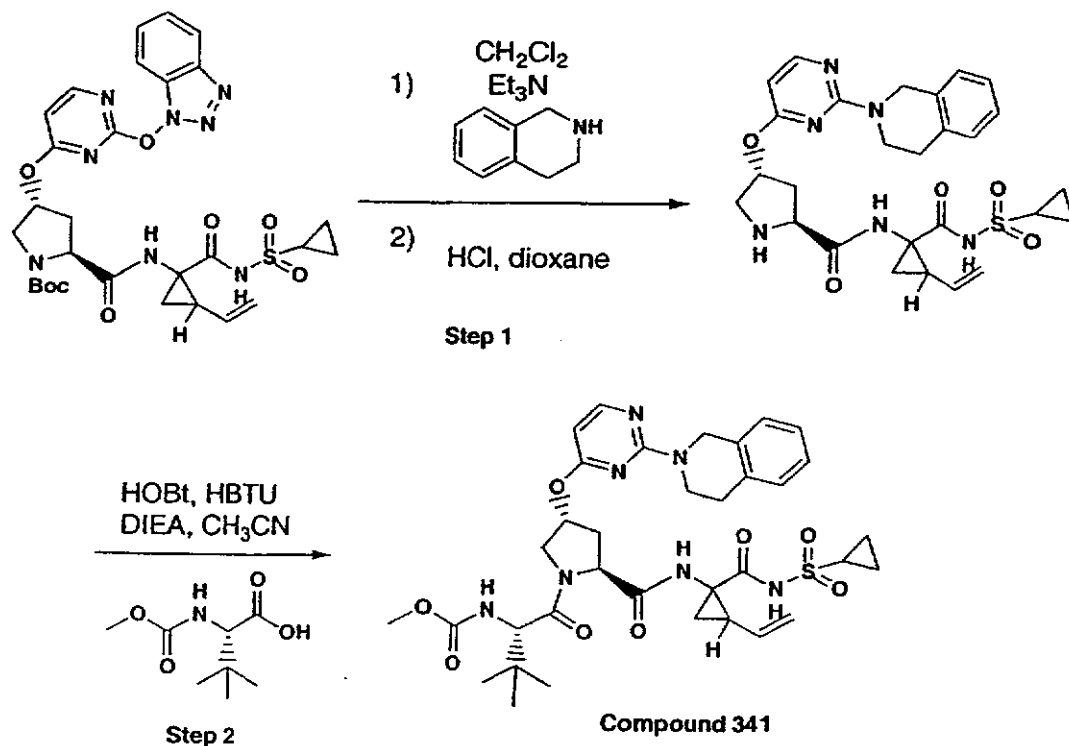
To a solution of 1-[2-(2-Cyclopropyl-acetylamino)-3,3-dimethyl-butyl]-4-hydroxy-pyrrolidine-2-carboxylic acid (1-cyclopropanesulfonylaminocarbonyl-2-vinyl-cyclopropyl)-amide (12.5 mg, 0.0232 mmol) in DMF (3 mL), NaH (3.7 mg of 60% dispersion in mineral oil, 0.0928 mmol) was added at 0°C. The reaction mixture was then warmed to rt. and stirred for 1 hr. Then 2-Chloro-4-thiazole-2-yl-pyrimidine (9.0 mg, 0.0289 mmol) was added. The reaction mixture was stirred at rt. for overnight. It was then quenched with water and extracted with EtOAc. The organic layer was separated, washed with brine and dried ($MgSO_4$). Evaporation of solvent gave crude product which was then purified by Prep. HPLC to give white solid as final product (**Compound 340**). (2.8 mg, 17% yield)

^1H NMR(CD_3OD , 400 MHz) δ 0.12 (m, 2 H), 0.47 (m, 2 H), 0.89 (m, 1 H), 1.00-1.09 (m, 11 H), 1.22 (m, 2 H), 1.44 (dd, $J=9.54$, 5.38 Hz, 1 H), 1.87 (dd, $J=8.07$, 5.38 Hz, 1 H), 2.06 (m, 2 H), 2.20- 2.32 (m, 2 H), 2.52 (dd, $J=13.70$, 6.85 Hz, 1 H), 2.93 (m, 1 H), 4.13 (dd, $J=11.98$, 3.91 Hz, 1 H), 4.30 (d, $J=11.98$ Hz, 1 H), 4.48 (dd, $J=10.51$, 7.09 Hz, 1 H), 4.63 (d, $J=9.54$ Hz, 1 H), 5.11 (d, $J=10.51$ Hz, 1 H), 5.29 (d, $J=17.12$ Hz, 1 H), 5.73-5.80 (m, 2 H), 7.81 (d, $J=5.14$ Hz, 1 H), 7.84 (d, $J=3.18$ Hz, 1 H), 8.03 (d, $J=2.93$ Hz, 1 H), 8.68 (d, $J=5.13$ Hz, 1 H).

LC-MS (retention time: 1.710 min.), MS m/z 700 (MH^+).

Example 341: Preparation of Compound 341**Scheme 1:**

Scheme 2:



5 **Step 1 (Scheme 1, step 1):**

To a solution of Boc-HYP-OH (1.0 g, 4.324 mmol) in DMF (20 mL), NaH (0.38 g of 60% dispersion in mineral oil, 9.513 mmol) was added at 0°C . The reaction mixture was stirred for 1 hr. Then 2,4-dichloropyrimidine (0.709 g, 0.0289 mmol) was added. The reaction mixture was warmed to rt and stirred for overnight. It was then quenched with 1N HCl solution and extracted with EtOAc. The organic layer was separated, washed with brine and dried (MgSO_4). Evaporation of solvent gave crude product which was then purified by Prep. HPLC to give colorless oil as product. (0.4 g, 27% yield)

^1H NMR(CD_3OD , 300 MHz) δ 1.13 (m, 9 H), 2.37 (m, 1 H), 2.62 (m, 1 H), 3.70-3.84 (m, 2 H), 4.38 (m, 1 H), 5.65 (m, 1 H), 6.88 (d, $J=5.86$ Hz, 1 H), 8.37 (d, $J=5.86$ Hz, 1 H).

LC-MS (retention time: 1.370 min.), MS m/z 344(MH^+).

Step 2: (Scheme 1, step 2)

To a solution of (2S, 4R) 4-(2-Chloro-pyrimidin-4-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (0.34 g, 0.99 mmol) in CH₃CN (20 mL) was added (1R, 2S)/(1S, 2R) (1-cyclopropanesulfonyl-aminocarbonyl-2-vinyl-cyclopropyl)-carbamic acid (0.511 g, 1.48 mmol), DIEA (0.86 mL, 4.95 mmol) and the coupling reagent HOBt (0.226 g, 1.48 mmol) and HBTU (0.561 g, 1.48 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated. It was then purified by Prep. HPLC column to give a yellow solid (**intermediate 4**). (0.33 g, 41% yield)

¹H NMR(CD₃OD, 300 MHz) δ diastereomer mixture.

LC-MS (retention time: 2.907 min.), MS m/z 655 (MH⁺).

Step 3: (Scheme 2, step 1)

To a solution of **intermediate 4** (50 mg, 0.061 mmol) in CH₂Cl₂ (2.5 mL), 1,2,3,4-tetrahydroisoquinoline (0.011 mL, 0.0915 mmol) and Et₃N (0.021 mL, 0.153 mmol) were added. The reaction mixture was stirred at rt for overnight and at 40°C for 1 day. The solvent was stripped and the residue was purified by Prep. HPLC to give a colorless oil. It was then dissolved in 4N HCl in dioxane (1 mL) and stirred for overnight. Evaporation of solvent gave a colorless oil as hydrochloride salt. (20 mg, 52% yield)

LC-MS (retention time: 1.160 min.), MS m/z 553 (MH⁺).

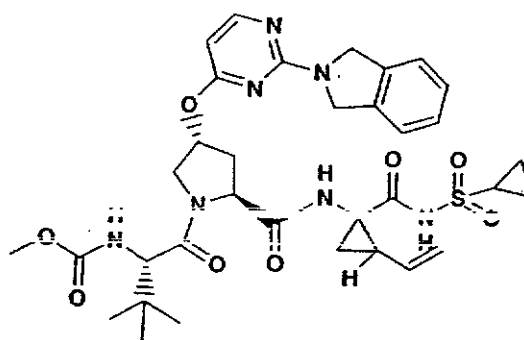
Step 4: (Scheme 2, step 2)

To a solution of 4-[2-(3,4-Dihydro-1H-isoquinolin-2-yl)-pyrimidin-4-yloxy]-pyrrolidine-2-carboxylic acid (1-cyclopropanesulfonylaminocarbonyl-2-vinyl-cyclopropyl)-amide hydrochloride (20 mg, 0.032 mmol) in CH₃CN (5 mL) was added 2-methoxycarbonylamino-3,3-dimethyl-butyric acid (9.1 mg, 0.048 mmol), DIEA (0.028 mL, 0.16 mmol) and the coupling reagent HOBt (7.3 mg, 0.048 mmol) and HBTU (18.2 mg, 0.048 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO₄ and

concentrated to give yellowish oil. It was purified by Prep. HPLC column to give a colorless oil as TFA salt (**Compound 341**). (16 mg, 60% yield)

- ¹H NMR(CD₃OD, 500 MHz) δ 0.98-1.06 (m, 13 H), 1.13 (m, 1 H), 1.22-1.32 (m, 1 H), 1.35-1.44 (m, 1 H), 1.82 (dd, $J=8.24, 5.19$ Hz, 0.5 H), 1.90 (dd, $J=8.24, 5.49$ Hz, 0.5 H), 2.26 (m, 1 H), 2.32-2.43 (m, 1 H), 2.56 (m, 1 H), 2.96 (m, 1 H), 3.11 (m, br, 2 H), 3.56 (s, 3 H), 4.14 (m, 1 H), 4.21 (m, 1 H), 4.38 (m, 1 H), 4.47 (m, 1 H), 5.15 (m, 1 H), 5.31 (m, 1 H), 5.75 (m, 1 H), 5.94 (s, 1 H), 6.47 (d, $J=7.02$ Hz, 1 H), 7.29 (s, 4 H), 7.49 (m, 1 H), 7.56 (m, 1 H), 7.74 (d, $J=8.24$ Hz, 1 H), 7.88 (d, $J=8.24$ Hz, 1 H), 8.11 (d, $J=7.02$ Hz, 1 H).
- 10 LC-MS (retention time: 1.517 min.), MS m/z 724 (MH⁺).

Example 342: Preparation of Compound 342

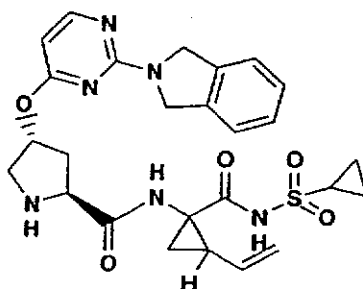


Compound 342

15

Compound 342 was prepared by following Scheme 2 of **Example 341**, except that isoindoline was used in the place of 1,2,3,4-tetrahydroisoquinoline in step 1 of scheme 2.

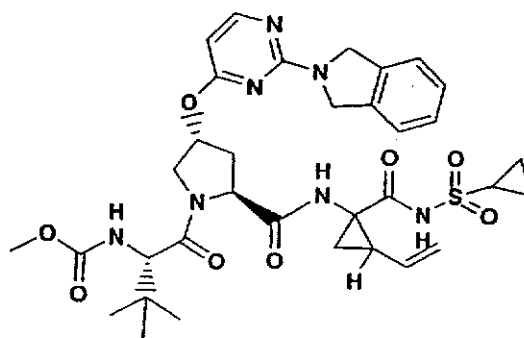
20 **Step 1:**



To a solution of intermediate 4 from Example 341 (50 mg, 0.061 mmol) in CH_2Cl_2 (2.5 mL), isoindoline (0.013 mL, 0.115 mmol) and Et_3N (0.026 mL, 0.19 mmol) were added. The reaction mixture was stirred at rt for 2 days. The solvent was stripped and the residue was purified by Prep. HPLC to give a colorless oil. It was then dissolved in 4N HCl in dioxane (1 mL) and stirred for overnight. Evaporation of solvent gave crude product which was purified by Prep.HPLC again to afford yellowish solid as TFA salt. (8.5 mg, 14% yield)

LC-MS (retention time: 1.860 min.), MS m/z 539 (MH^+).

Step 2:



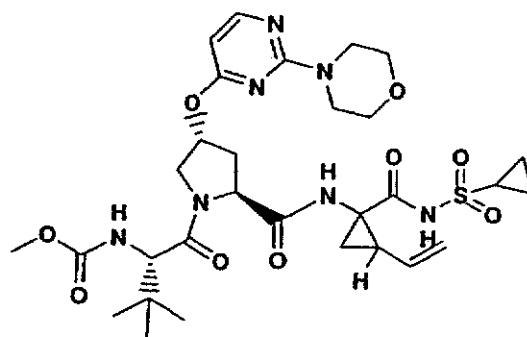
Compound 342

To a solution of 4-[2-(1,3-Dihydro-isoindol-2-yl)-pyrimidin-4-yloxy]-pyrrolidine-2-carboxylic acid (1-cyclopropanesulfonylaminocarbonyl-2-vinyl-cyclopropyl)-amide hydrochloride (8.5 mg, 0.0104 mmol) in CH_3CN (5 mL) was added 2-methoxycarbonylamino-3,3-dimethyl-butyrac acid (3.0 mg, 0.0156 mmol), DIEA (0.009 mL, 0.052 mmol) and the coupling reagent HOBt (2.4 mg, 0.0156 mmol) and HBTU (5.9 mg, 0.0156 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO_4 and concentrated to give yellowish oil. It was purified by Prep. HPLC column to give a colorless oil as TFA salt (Compound 342). (3 mg, 35% yield)

^1H NMR(CD_3OD , 300 MHz) δ diastereomer mixture.

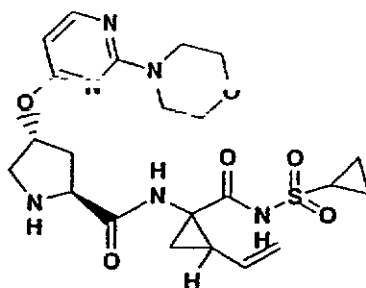
LC-MS (retention time: 2.547 min.), MS m/z 710 (MH^+).

Example 343: Preparation of Compound 343



Compound 343

Compound 342 was prepared by following Scheme 2 of Example 341, except that morpholine was used in the place of 1,2,3,4-tetrahydroisoquinoline in step 1 of scheme 2.

Step 1:

10

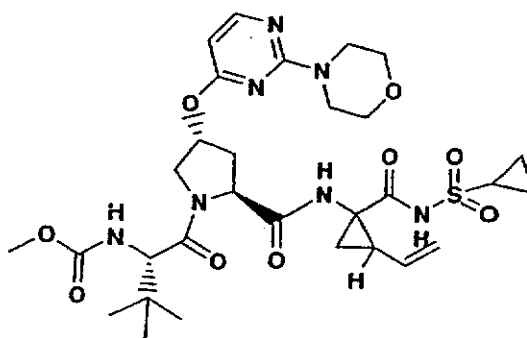
To a solution of intermediate 4 from Example 341 (50 mg, 0.061 mmol) in CH_2Cl_2 (2.5 mL), morpholine (0.008 mL, 0.0915 mmol) and Et_3N (0.021 mL, 0.153 mmol) were added. The reaction mixture was stirred at rt for overnight and at 40°C for 1 day. The solvent was stripped and the residue was purified by Prep. HPLC to give a colorless oil. It was then dissolved in 4N HCl in dioxane (1 mL) and stirred for overnight. Evaporation of solvent gave a colorless oil as hydrochloride salt. (12.6 mg, 36% yield)

LC-MS (retention time: 0.810 min.), MS m/z 507 (MH^+).

20

Step 2:

459

**Compound 343**

To a solution of 4-(2-Morpholin-4-yl-pyrimidin-4-yloxy)-pyrrolidine-2-carboxylic acid
 acid (1-cyclopropanesulfonylamino-2-vinyl-cyclopropyl)-amide
 5 hydrochloride (12.6 mg, 0.0217 mmol) in CH_3CN (5 mL) was added 2-
 methoxycarbonylamino-3,3-dimethyl-butyric acid (6.2 mg, 0.0326 mmol), DIEA
 (0.019 mL, 0.1085 mmol) and the coupling reagent HOBt (5.0 mg, 0.0326 mmol) and
 HBTU (12.4 mg, 0.0326 mmol). The solution was stirred at rt. overnight. Then it
 was concentrated, washed with water and extracted with ethyl acetate twice. The
 10 combined organic layers were washed with brine, dried over MgSO_4 and
 concentrated to give yellowish oil. It was purified by Prep. HPLC column to give a
 colorless oil as TFA salt (**Compound 343**). (7 mg, 41% yield)

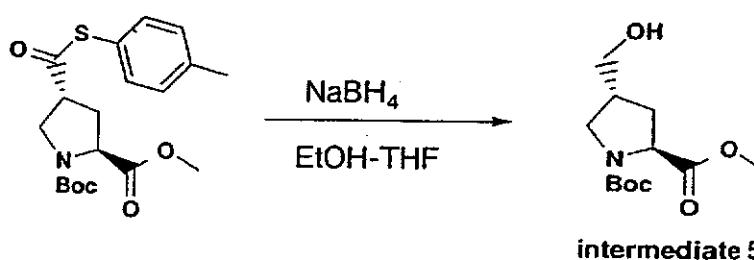
^1H NMR(CD_3OD , 500 MHz) δ diastereomer mixture.

LC-MS (retention time: 1.280 min.), MS m/z 678 (MH^+).

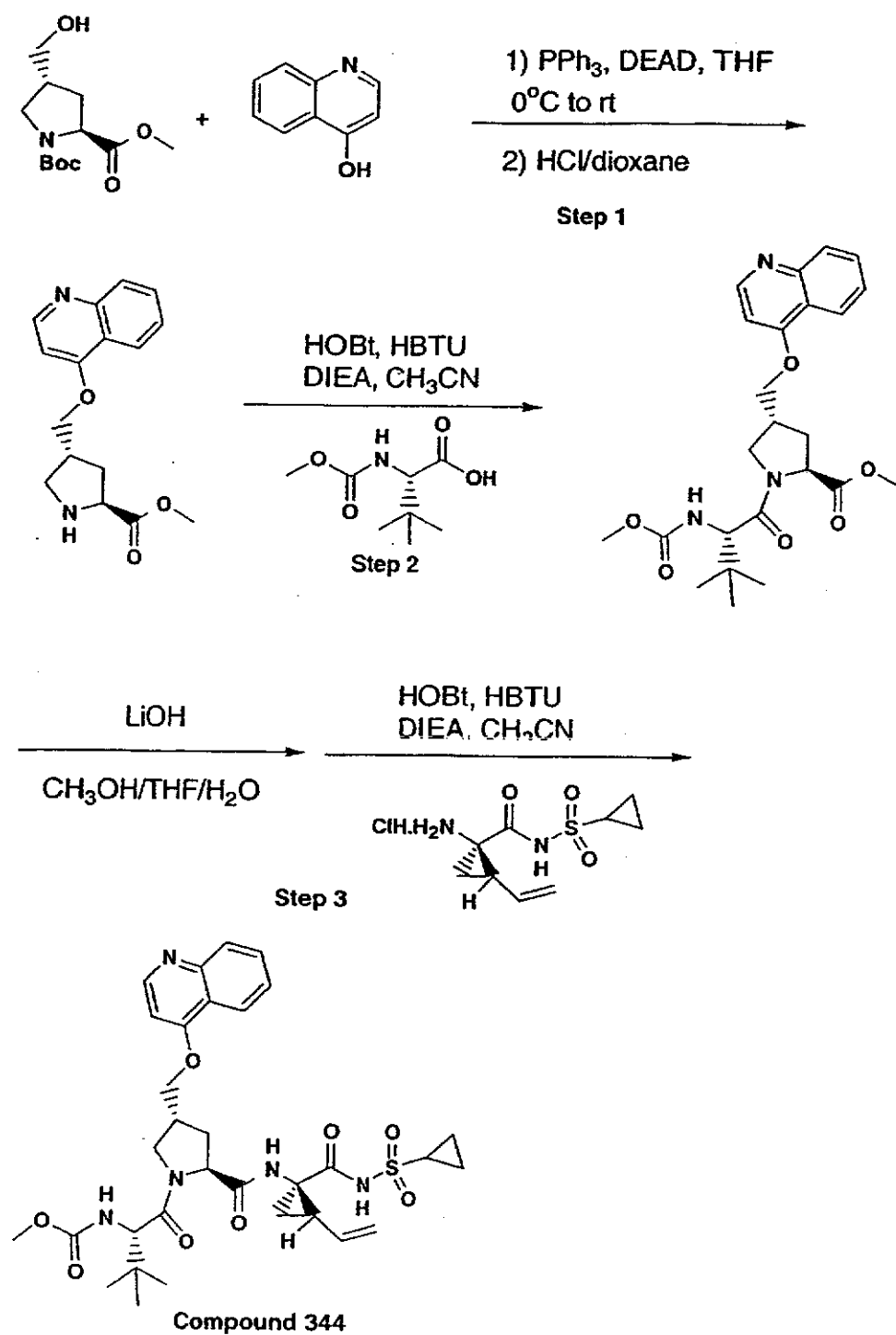
15

Example 344: Preparation of Compound 344

Scheme 1:



Scheme 2:



- To a solution of 4-p-tolylsulfanylcabonyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (3.0 g, 7.91 mmol) in ethanol (15 mL) and THF (30 mL) mixture, sodium borohydride (0.6 g, 15.8 mmol) was added. The reaction mixture was stirred at rt. for overnight. Then it was concentrated, washed with 1 N HCl solution and extracted with EtOAc three times. The organic layers were combined, washed with saturated NaHCO₃ solution and dried (MgSO₄). Evaporation of solvent gave yellowish oil which was purified by flash column chromatography (silica gel, 3:1 EtOAc: Hexanes) to afford colorless oil as product (**intermediate 5**). (1.77 g, 86% yield)
- ¹H NMR (CD₃OD, 500 MHz) δ 1.43 (m, 9 H), 2.00-2.13 (m, 2 H), 2.46 (m, 1 H), 3.19 (m, 1 H), 3.47-3.53 (m, 2 H), 3.61 (m, 1 H), 3.73 (m, 3 H), 4.31 (m, 1 H). LC-MS (retention time: 1.240 min.), MS m/z 282 (M+Na⁺).

Step 2: (Scheme 2, step 1)

- To a solution of **intermediate 5** (80 mg, 0.309 mmol) in THF (10 mL) at 0°C, triphenylphosphine (121.4 mg, 0.463 mmol) and 4-hydroxyquinoline (67.2 mg, 0.463 mmol) were added. Then DEAD (80.6 mg, 0.463 mmol) was added. The reaction mixture was warmed to rt. and stirred for 2 days. Then solvent was evaporated and the residue was purified by Prep. HPLC to give colorless oil. It was then dissolved in 4N HCl in dioxane (3 mL) and stirred for 2 hr. Evaporation of solvent gave thick colorless oil as bis HCl salt. (110 mg, 99% yield)
- ¹H NMR (500 MHz, CD₃OD) δ 2.52 (m, 1 H), 2.60 (m, 1 H), 3.19 (m, 1 H), 3.45 (m, 1 H), 3.66 (s, 3 H), 3.86 (m, 1 H), 4.61-4.75 (m, 3 H), 7.56 (d, $J=6.7$ Hz, 1 H), 7.94 (t, $J=7.3$ Hz, 1 H), 8.10-8.20 (m, 2 H), 8.55 (d, $J=8.2$ Hz, 1 H), 9.07 (d, $J=6.7$ Hz, 1 H).
- LC-MS (retention time: 0.570 min.), MS m/z 287 (MH⁺).

Step 3: (Scheme 2, step 2)

- To a solution of 4-(quinolin-4-yloxymethyl)-pyrrolidine-2-carboxylic acid methyl ester bis hydrochloride salt (110 mg, 0.306 mmol) in CH₃CN (10 mL) was added 2-methoxycarbonylamino-3,3-dimethyl-butyric acid (87 mg, 0.46 mmol), DIEA (0.27 mL, 1.53 mmol) and the coupling reagent HOBt (70 mg, 0.46 mmol) and HBTU (174

- mg, 0.46 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO_4 and concentrated to give yellowish oil. It was purified by Prep. HPLC column to give colorless oil as TFA salt. (105 mg, 60% yield)
- ^1H NMR (CD_3OD , 500 MHz) δ 1.07 (s, 9 H), 2.34 (m, 1 H), 2.45 (m, 1 H), 3.14 (m, 1 H), 3.27 (s, 3 H), 3.75 (s, 3 H), 4.05 (m, 1 H), 4.20 (m, 1 H), 4.31 (s, 1 H), 4.57-4.63 (m, 2 H), 4.73 (m, 1 H), 7.53 (d, $J=6.7$ Hz, 1 H), 7.91 (t, $J=7.6$ Hz, 1 H), 8.06-8.16 (m, 2 H), 8.43 (d, $J=8.6$ Hz, 1 H), 9.02 (d, $J=6.4$ Hz, 1 H).
- LC-MS (retention time: 1.250 min.), MS m/z 458 (MH^+).

Step 4:(Scheme 2, step 3)

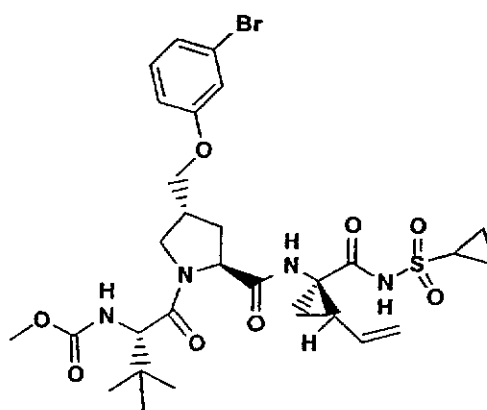
- To a solution of 1-(2-Methoxycarbonylamino-3,3-dimethyl-butyryl)-4-(quinolin-4-yloxymethyl)-pyrrolidine-2-carboxylic acid methyl ester (100 mg, 0.175 mmol) in THF (6 mL), methanol (3.25 mL) and water (1.0 mL) mixture, lithium hydroxide monohydrate (110 mg, 2.62 mmol) was added. The reaction mixture was stirred at rt. for overnight. Then it was acidified with 1N HCl solution to pH=3 to 5 and concentrated. Extracted with ethyl acetate (3x40 mL) and the organic layers were combined and dried (MgSO_4). Evaporation of solvent gave thick colorless oil to carry on (25 mg, 32% yield).
- To a solution of above compound (25 mg, 0.056 mmol) in CH_3CN (5 mL) was added (1R, 2S) (1-cyclopropanesulfonyl-aminocarbonyl-2-vinyl-cyclo-propyl)-carbamic acid hydrochloride (22.5 mg, 0.085 mmol), DIEA (0.05 mL, 0.28 mmol) and the coupling reagent HOBt (12.9 mg, 0.085 mmol) and HBTU (32 mg, 0.085 mmol).
- The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO_4 and concentrated to give yellow oil. It was purified by Prep. HPLC column to give colorless thick oil as TFA salt (Compound 344). (20 mg, 46% yield)
- ^1H NMR(CD_3OD , 500 MHz) δ 1.02-1.10 (m, 11 H), 1.24 (m, 2 H), 1.40 (dd, $J=9.2$, 5.5 Hz, 1 H), 1.90 (dd, $J=7.9$, 5.5 Hz, 1 H), 2.19-2.38 (m, 3 H), 2.95 (m, 1 H), 3.19 (m, 1 H), 3.28 (s, 3 H), 4.10 (m, 1 H), 4.15 (m, 1 H), 4.34 (s, 1 H), 4.55 (m, 1 H),

4.62 (d, $J=4.6$ Hz, 2 H), 5.15 (d, $J=10.7$ Hz, 1 H), 5.30 (d, $J=17.1$ Hz, 1 H), 5.72 (m, 1 H), 7.54 (d, $J=6.7$ Hz, 1 H), 7.93 (m, 1 H), 8.07-8.18 (m, 2 H), 8.41 (d, $J=8.6$ Hz, 1 H), 9.03 (d, $J=6.7$ Hz, 1 H), 9.09 (s, 1 H).

LC-MS (retention time: 1.617 min.), MS m/z 656 (MH^+).

5

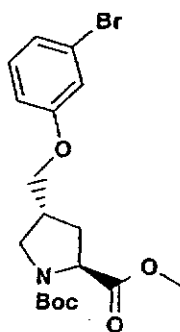
Example 345: Preparation of Compound 345



Compound 345

- 10 **Compound 345** was prepared by following Scheme 2 of **Example 344**, except that 3-bromophenol was used in the place of 4-hydroxyquinoline in step 1 of scheme 2.

Step 1:

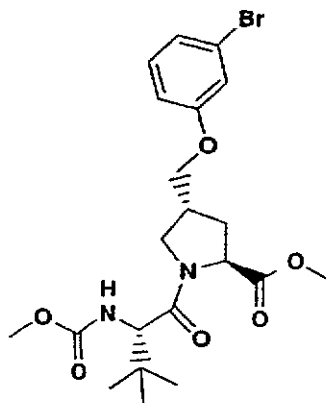


- 15 To a solution of **Intermediate 5** from **Example 344** (150 mg, 0.578 mmol) in THF (15 mL) at 0°C, triphenylphosphine (228 mg, 0.868 mmol) and 3-bromophenol (150 mg, 0.868 mmol) were added. Then DEAD (0.14 mL, 0.868 mmol) was added. The reaction mixture was warmed to rt. and stirred for 2 days. Then solvent was

evaporated and the residue was purified by Prep. HPLC to give colorless oil as product. (105 mg, 44% yield)

LC-MS (retention time: 2.023 min.), MS m/z 436 ($M+Na^+$).

5 Step 2:

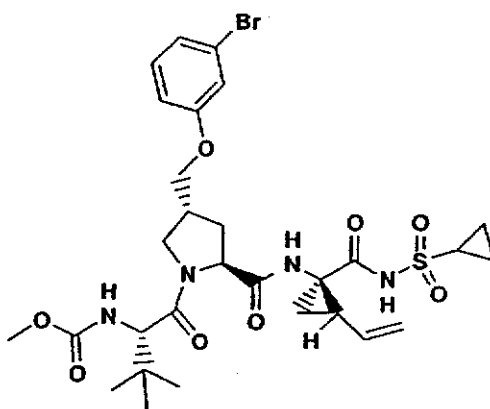


4-(3-Bromo-phenoxy-methyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (35 mg, 0.085 mmol) was dissolved in 4N HCl in dioxane (1.5 mL) and stirred for 2 hr. Evaporation of solvent gave thick colorless oil. To a solution of this oil in CH_3CN (10 mL) was added 2-methoxycarbonylamino-3,3-dimethyl-butyric acid (21.9 mg, 0.1155 mmol), DIEA (0.067 mL, 0.385 mmol) and the coupling reagent HOBt (17.7 mg, 0.1155 mmol) and HBTU (43.8 mg, 0.1155 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. It was then purified by Prep. HPLC column to give colorless oil as product. (20 mg, 49% yield)

^1H NMR (CD_3OD , 400 MHz) δ 1.03 (s, 9 H), 2.15 (m, 1 H), 2.24 (m, 1 H), 2.83 (m, 1 H), 3.54 (s, 3 H), 3.70 (s, 3 H), 3.87 (m, 1 H), 3.91-3.98 (m, 3 H), 4.31 (s, 1 H), 4.59 (dd, $J=8.80, 5.38$ Hz, 1 H), 6.89 (d, $J=8.32$ Hz, 1 H), 7.03-7.10 (m, 2 H), 7.15 (t, $J=8.07$ Hz, 1 H).

LC-MS (retention time: 1.943 min.), MS m/z 485 (MH^+).

Step 3:

**Compound 345**

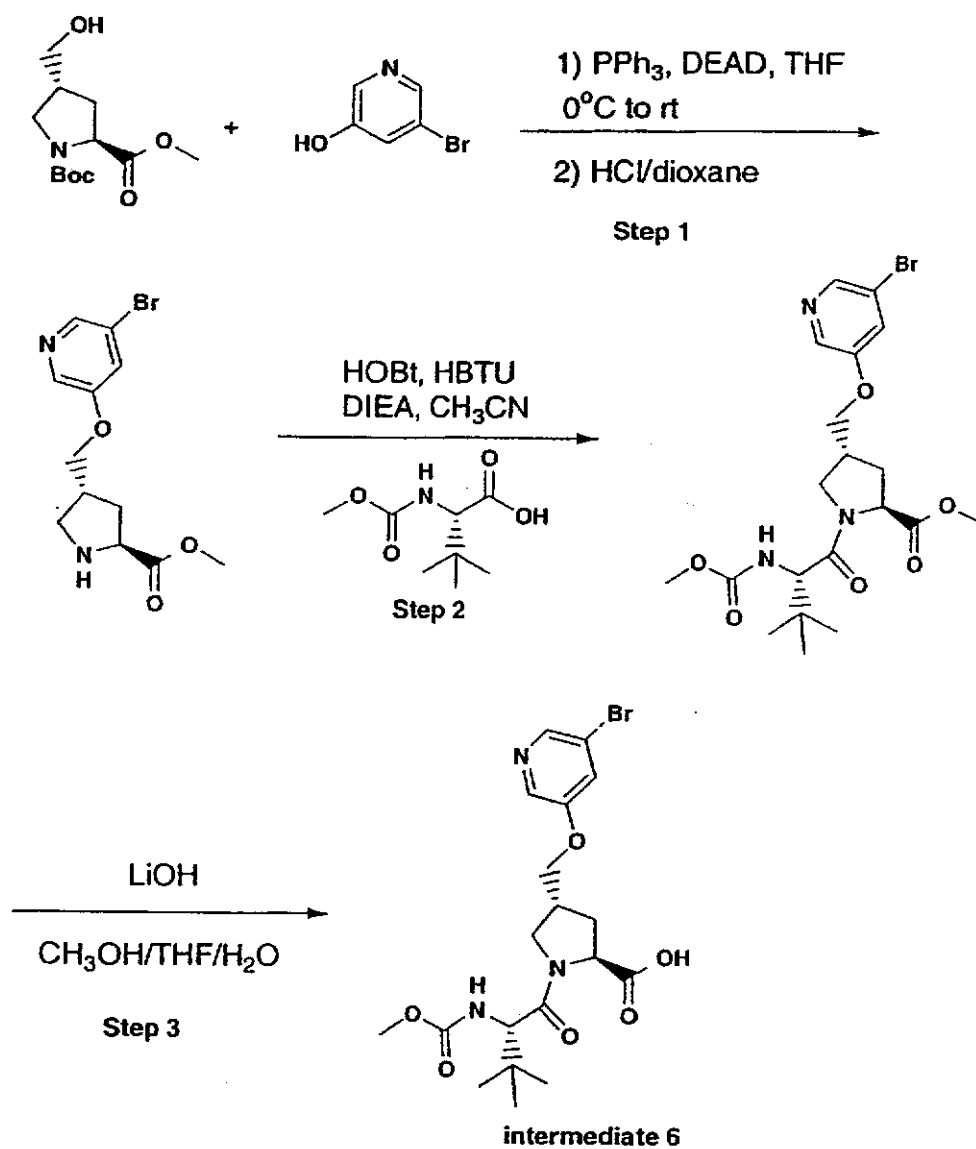
- To a solution of 4-(3-Bromo-phenoxy-methyl)-1-(2-methoxycarbonylamino-3,3-dimethyl-butyl)-pyrrolidine-2-carboxylic acid methyl ester (17 mg, 0.035 mmol) in THF (1.5 mL), methanol (0.8 mL) and water (0.25 mL) mixture, lithium hydroxide monohydrate (22 mg, 0.525 mmol) was added. The reaction mixture was stirred at rt. for 3 days. Then it was acidified with 1N HCl solution to pH=3 to 5 and concentrated. Extracted with ethyl acetate (2x20 mL) and the organic layers were combined and dried (MgSO₄). Evaporation of solvent gave thick colorless oil to carry on (15 mg, 91% yield).
- 10 To a solution of above acid (15 mg, 0.0318 mmol) in CH₃CN (5 mL) was added (1R, 2S) (1-cyclopropanesulfonyl-aminocarbonyl-2-vinyl-cyclo-propyl)-carbamic acid hydrochloride (12.7 mg, 0.0477 mmol), DIEA (0.028 mL, 0.159 mmol) and the coupling reagent HOBt (7.3 mg, 0.0477 mmol) and HBTU (18.1 mg, 0.0477 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated. It was then purified by Prep. HPLC column to give colorless thick oil as final product (**Compound 345**). (14 mg, 64% yield)

¹H NMR(CD₃OD, 400 MHz) δ 1.00-1.06 (m, 11 H), 1.21 (m, 2 H), 1.37 (dd, $J=9.53$ Hz, 5.62 Hz, 1 H), 1.86 (dd, $J=8.07$ Hz, 5.62 Hz, 1 H), 2.06 (m, 1 H), 2.14-2.24 (m, 2 H), 2.81-2.94 (m, 2 H), 3.53 (s, 3 H), 3.91-3.97 (m, 4 H), 4.33 (s, 1 H), 4.38 (m, 1 H), 5.11 (dd, $J=10.27$, 1.47 Hz, 1 H), 5.28 (dd, $J=17.12$, 1.22 Hz, 1 H), 5.70 (m, 1 H), 6.89 (m, 1 H), 7.05-7.11 (m, 2 H), 7.16 (t, $J=8.07$ Hz, 1 H).

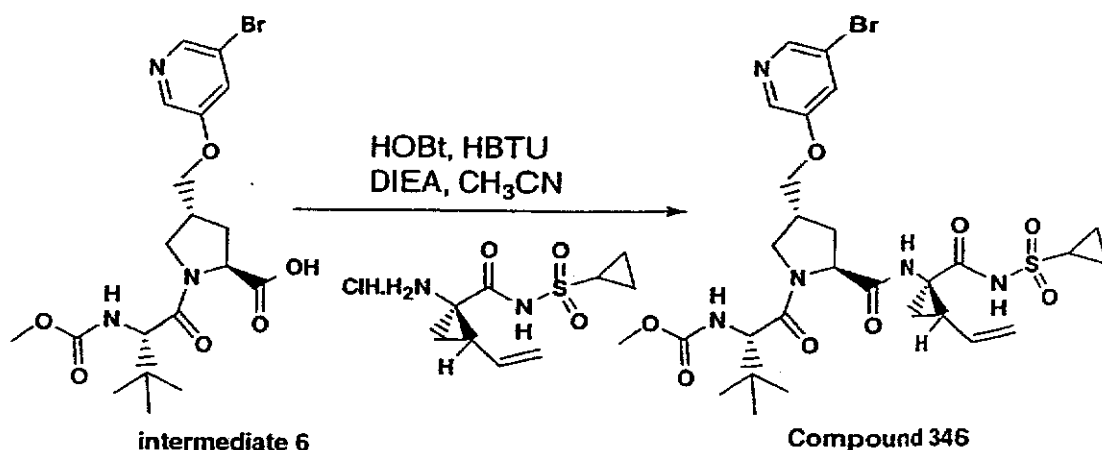
LC-MS (retention time: 3.500 min.), MS m/z 683 (MH⁺).

Example 346: Preparation of Compound 346

Scheme 1:



Scheme 2:



5 Step 1: (Scheme 1, step 1)

To a solution of 4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (300 mg, 1.157 mmol) in THF (15 mL) at 0°C, triphenylphosphine (455 mg, 1.735 mmol) and 5-bromo-pyridin-3-ol (prepared according to F.E.Ziegler et al., J.Am.Chem.Soc., (1973), 95, 7458) (302 mg, 1.735 mmol) were added. Then
 10 DEAD (0.273 mL, 1.735 mmol) was added. The reaction mixture was warmed to rt. and stirred for 2 days. Then solvent was evaporated and the residue was purified by Prep. HPLC to give a yellowish oil. Then it was dissolved in 4N HCl solution in dioxane (3.0 mL) and stirred for 4 hr. Evaporation of solvent gave crude product which was further purified by Prep. HPLC to afford a yellowish oil as TFA salt. (70
 15 mg, 11% yield)

LC-MS (retention time: 0.890 min.), MS m/z 315 (MH^+).

Step 2: (Scheme 1, step 2)

To a solution of 4-(5-Bromo-pyridin-3-yloxy)methyl)-pyrrolidine-2-carboxylic acid methyl ester (70 mg, 0.129 mmol) in CH₃CN (10 mL) was added 2-methoxycarbonylamino-3,3-dimethyl-butyric acid (36.5 mg, 0.193 mmol), DIEA (0.135 mL, 0.744 mmol) and the coupling reagent HOBt (30 mg, 0.193 mmol) and HBTU (73 mg, 0.193 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The
 20

combined organic layers were washed with brine, dried over MgSO_4 and concentrated. It was then purified by Prep. HPLC column to give colorless oil as product. (80 mg, 100% yield)

^1H NMR (CD_3OD , 400 MHz) δ 1.04 (s, 9 H), 2.17 (m, 1 H), 2.26 (m, 1 H), 2.87 (m, 1 H), 3.50 (s, 3 H), 3.70 (s, 3 H), 3.88-3.98 (m, 2 H), 4.04-4.12 (m, 2 H), 4.28 (s, 1 H), 4.60 (dd, $J=9.05, 5.87$ Hz, 1 H), 7.86 (m, 1 H) 8.31-8.35 (m, 2 H).

LC-MS (retention time: 1.697 min.), MS m/z 486 (MH^+).

Step 3: (Scheme 1, step 3)

To a solution of 4-(5-Bromo-pyridin-3-yloxymethyl)-1-(2-methoxycarbonylamino-3,3-dimethyl-butyryl)-pyrrolidine-2-carboxylic acid methyl ester (80 mg, 0.133 mmol) in THF (5.6 mL), methanol (3 mL) and water (1 mL) mixture, lithium hydroxide monohydrate (84 mg, 2.0 mmol) was added. The reaction mixture was stirred at rt. for 3 days. Then it was acidified with 1N HCl solution to pH=3 to 5. Extracted with ethyl acetate (2x20 mL) and the organic layers were combined and dried (MgSO_4). Evaporation of solvent gave thick colorless oil as product (intermediate 6) (50 mg, 80% yield).

^1H NMR (CD_3OD , 400 MHz) δ 1.04 (s, 9 H), 2.16-2.30 (m, 2 H), 2.88 (m, 1 H), 3.51 (s, 3 H), 3.92 (m, 2 H), 4.07 (m, 2 H), 4.29 (s, 1 H), 4.57 (dd, $J=8.56, 5.87$ Hz, 1 H), 7.79 (m, 1 H) 8.29 (m, 2 H).

LC-MS (retention time: 1.590 min.), MS m/z 472 (MH^+).

Step 4: (Scheme 2)

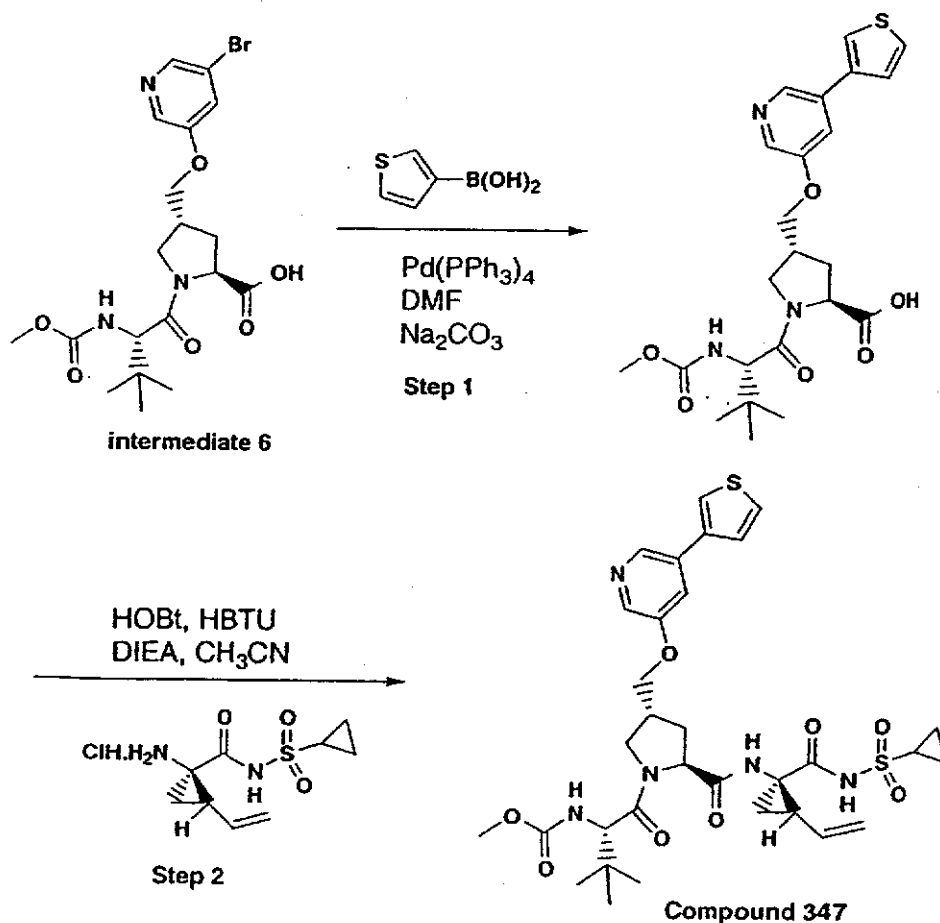
To a solution of 4-(5-Bromo-pyridin-3-yloxymethyl)-1-(2-methoxycarbonylamino-3,3-dimethyl-butyryl)-pyrrolidine-2-carboxylic acid (5 mg, 0.0106 mmol) in CH_3CN (5 mL) was added (1R, 2S) (1-cyclopropanesulfonyl-aminocarbonyl-2-vinyl-cyclo-propyl)-carbamic acid hydrochloride (4.2 mg, 0.0159 mmol), DIEA (0.009 mL, 0.053 mmol) and the coupling reagent HOBt (2.4 mg, 0.0159 mmol) and HBTU (6.0 mg, 0.0159 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO_4 and concentrated. It

was then purified by Prep. HPLC column to give colorless thick oil as final product (Compound 346). (2 mg, 24% yield)

^1H NMR(CD_3OD , 400 MHz) δ 1.00-1.07 (m, 11 H), 1.20 (m, 2 H), 1.37 (dd, $J=9.29$ Hz, 5.14 Hz, 1 H), 1.86 (dd, $J=8.07$ Hz, 5.38 Hz, 1 H), 2.08 (m, 1 H), 2.15-2.25 (m, 2 H), 2.87-2.94 (m, 2 H), 3.51 (s, 3 H), 3.92-3.97 (m, 2 H), 4.02-4.07 (m, 2 H), 4.31 (s, 1 H), 4.39 (m, 1 H), 5.10 (dd, $J=10.27$, 1.47 Hz, 1 H), 5.28 (dd, $J=17.12$, 1.46 Hz, 1 H), 5.70 (m, 1 H), 7.68 (m, 1 H), 8.24 (m, 2 H).

LC-MS (retention time: 1.727 min.), MS m/z 684 (MH^+).

10 Example 347: Preparation of Compound 347



Step 1:

To a solution of intermediate 6 from Example 346 (16 mg, 0.0339 mmol) in DMF (1 mL), 3-thiopheneboronic acid (5.6 mg, 0.044 mmol),

tetrakis(triphenylphosphine) palladium (2.0 mg, 0.0017 mmol) and 2M Na₂CO₃ solution (0.051 mL, 0.1017 mmol) were added. The reaction mixture was heated at 110°C for 4hr. Then it was filtered and washed with methanol. The filtrate was concentrated and purified by Prep.HPLC to give brownish oil as product.

5 (6mg, 37% yield)

¹H NMR (CD₃OD, 400 MHz) δ 1.05 (s, 9 H), 2.21-2.30 (m, 2 H), 2.95 (m, 1 H), 3.42 (s, 3 H), 3.93 (m, 1 H), 4.01 (m, 1 H), 4.20-4.30 (m, 3 H), 4.60 (dd, *J*=8.56, 5.87 Hz, 1 H), 7.64 (m, 2 H), 8.12 (m, 1 H) 8.37 (m, 1 H), 8.45 (m, 1 H), 8.75 (s, 1 H).

LC-MS (retention time: 1.353 min.), MS *m/z* 476 (MH⁺).

10

Step 2:

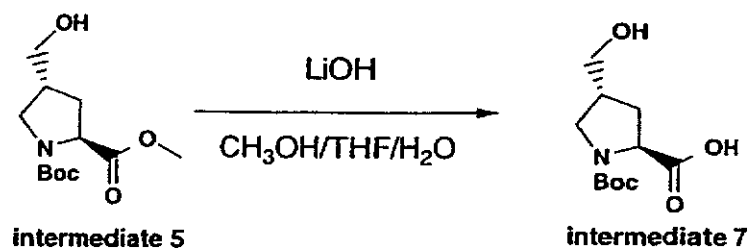
To a solution of 1-(2-Methoxycarbonylamino-3,3-dimethyl-butyl)-4-(5-thiophen-3-yl-pyridin-3-yloxymethyl)-pyrrolidine-2-carboxylic acid (6 mg, 0.0126 mmol) in CH₃CN (5 mL) was added (1R, 2S) (1-cyclopropanesulfonyl-aminocarbonyl-2-vinyl-
15 cyclo-propyl)-carbamic acid hydrochloride (5.0 mg, 0.0189 mmol), DIEA (0.011 mL, 0.063 mmol) and the coupling reagent HOBt (2.9 mg, 0.0189 mmol) and HBTU (7.2 mg, 0.0189 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO₄ and
20 concentrated. It was then purified by Prep. HPLC column to give yellowish film as TFA salt (Compound 347). (2.2 mg, 22% yield)

¹H NMR (CD₃OD, 400 MHz) δ 1.01-1.07 (m, 11 H), 1.19 (m, 2 H), 1.36 (m, 1 H), 1.88 (dd, *J*=8.07 Hz, 5.62 Hz, 1 H), 2.09-2.24 (m, 3 H), 2.91 (m, 1 H), 3.00 (m, 1 H), 3.45 (s, 3 H), 3.98 (d, *J*=5.86 Hz, 2 H), 4.20-4.31 (m, 3 H), 4.43 (m, 1 H), 5.12 (dd, *J*=10.27, 1.71 Hz, 1 H), 5.29 (dd, *J*=17.12, 1.22 Hz, 1 H), 5.69 (m, 1 H), 7.64 (m, 2
25 H), 8.11 (m, 1 H), 8.31 (m, 1 H), 8.43 (m, 1 H), 8.75 (s, 1 H).

LC-MS (retention time: 1.540 min.), MS *m/z* 688 (MH⁺).

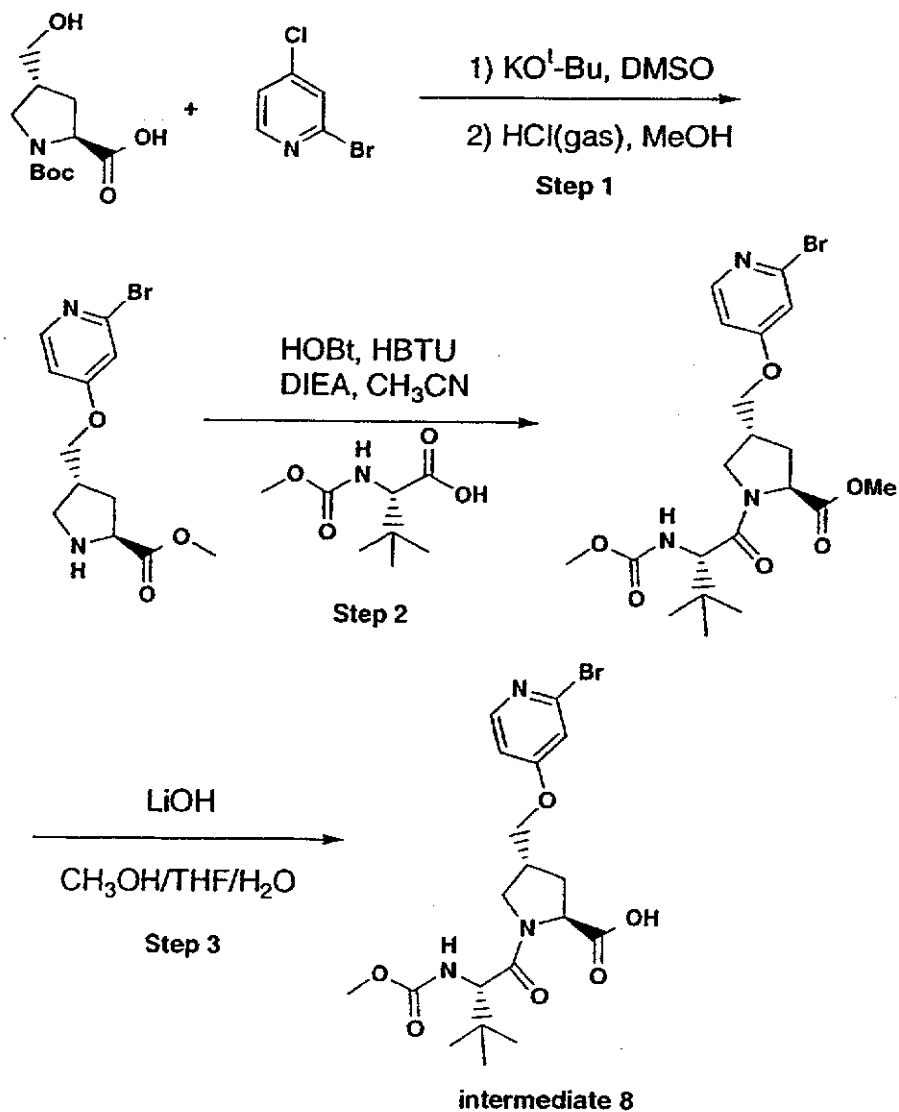
Example 348: Preparation of Compound 348

Scheme 1:

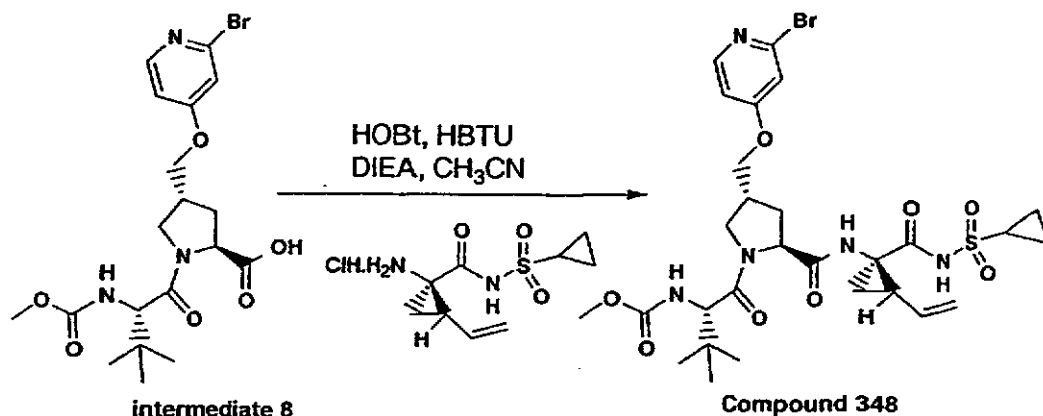


5

Scheme 2:



Scheme 3:

**Step 1: (Scheme 1)**

To a solution of **intermediate 5** from **Example 344** (700 mg, 2.7 mmol) in THF (90 mL), methanol (50 mL) and water (12 mL) mixture, lithium hydroxide monohydrate (1700 mg, 2.0 mmol) was added. The reaction mixture was stirred at rt. for overnight. Then it was acidified with 1N HCl solution to pH=3 to 5. Extracted with ethyl acetate (2x20 mL) and the organic layers were combined and dried (MgSO₄). Evaporation of solvent gave thick colorless oil as product (**intemediate 7**) (0.58, 88% yield).

¹H NMR (CD₃OD, 400 MHz) δ 1.42 (m, 9 H), 2.00 2.09 (m, 2 H), 2.45 (m, 1 H), 3.17 (m, 1 H), 3.49 (m, 2 H), 3.59 (m, 1 H), 4.24 (m, 1 H).

LC-MS (retention time: 1.08 min.), MS m/z 268 (M+Na⁺).

Step 2: (Scheme 2, step 1)

To a solution of **intermediate 7** (270 mg, 1.1 mmol) in DMSO (10 mL), potassium t-butoxide (309 mg, 2.75 mmol) was added. The reaction mixture was stirred at rt for 1hr. Then 2-Bromo-4-chloro-pyridine (254 mg, 1.32 mmol) was added. The reaction mixture was stirred at rt for overnight. Then it was quenched with water and washed with ethyl acetate. The aqueous layer was separated and acidified with 1N HCl solution to pH=3. Extracted with ethyl acetate twice and the organic layers were combined and dried (MgSO₄). Evaporation of solvent gave an orange oil. It was then dissolved in methanol and HCl (gas) was bubbled through for 2 min at -78°C. Then the reaction mixture was warmed to rt and stirred for overnight. Evaporation of solvent gave an orange oil as crude to carry on.

LC-MS (retention time: 0.65 min.), MS m/z 315 (MH^+).

Step 3: (Scheme 2, step 2)

To a solution of crude 4-(2-Bromo-pyridin-4-yloxymethyl)-pyrrolidine-2-carboxylic acid methyl ester in CH_3CN (20 mL) was added 2-methoxycarbonylamino-3,3-dimethyl-butyric acid (312 mg, 1.65 mmol), DIEA (1.15 mL, 6.6 mmol) and the coupling reagent HOBt (252 mg, 1.65 mmol) and HBTU (626 mg, 1.65 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. It was then purified by Prep. HPLC column to give colorless oil as product. (270 mg, 41% yield two steps)

^1H NMR (CD_3OD , 400 MHz) δ 1.03 (s, 9 H), 2.13-2.19 (m, 2 H), 2.87 (m, 1 H), 3.51 (s, 3 H), 3.70 (s, 3 H), 3.93 (d, $J=6.36$ Hz, 2 H), 4.11 (m, 2 H), 4.27 (s, 1 H), 4.60 (dd, $J=8.80, 5.87$ Hz, 1 H), 7.06 (d, $J=5.87, 2.20$ Hz, 1 H) 7.32 (d, $J=2.20$ Hz, 1 H), 8.18 (d, $J=6.11$ Hz, 1 H).

LC-MS (retention time: 1.657 min.), MS m/z 486 (MH^+).

Step 4: (Scheme 2, step 3)

To a solution of 4-(2-Bromo-pyridin-4-yloxymethyl)-1-(2-methoxycarbonylamino-3,3-dimethyl-butyryl)-pyrrolidine-2-carboxylic acid methyl ester (270 mg, 0.45 mmol) in THF (18 mL), methanol (10 mL) and water (3.3 mL) mixture, lithium hydroxide monohydrate (283 mg, 6.75 mmol) was added. The reaction mixture was stirred at rt. for overnight. Then it was concentrated and acidified with 1N HCl solution to pH=3 to 5. The off-white solid was collected as product (**intermediate 8**) (180 mg, 85% yield).

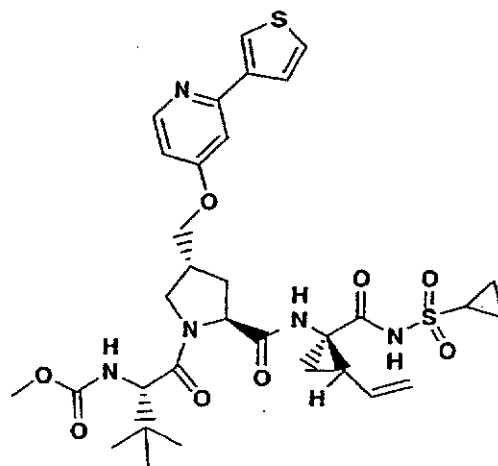
^1H NMR (CD_3OD , 500 MHz) δ 1.06 (s, 9 H), 2.20-2.29 (m, 2 H), 2.89 (m, 1 H), 3.54 (s, 3 H), 3.92 (d, $J=6.4$ Hz, 2 H), 4.06-4.13 (m, 2 H), 4.31 (d, $J=8.85$ Hz, 1 H), 4.59 (dd, $J=8.85, 5.50$ Hz, 1 H), 7.00 (dd, $J=6.10, 2.24$ Hz, 1 H), 7.22 (d, $J=1.83$ Hz, 1 H), 8.12 (d, $J=5.80$ Hz, 1 H).

LC-MS (retention time: 2.113 min.), MS m/z 472 (MH^+).

Step 5: (Scheme 3)

- To a solution of intermediate 8 (10 mg, 0.0212 mmol) in CH₃CN (5 mL) was added (1R, 2S) (1-cyclopropanesulfonyl-aminocarbonyl-2-vinyl-cyclo-propyl)-carbamic acid hydrochloride (8.5 mg, 0.00318 mmol), DIEA (0.018 mL, 0.106 mmol) and the coupling reagent HOBt (4.9 mg, 0.0318 mmol) and HBTU (12.1 mg, 0.0318 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated. It was then purified by Prep. HPLC column to give colorless thick oil as final product (Compound 348). (9 mg, 53% yield)
- ¹H NMR(CD₃OD, 400 MHz) δ 1.00-1.06 (m, 11 H), 1.20 (m, 2 H), 1.36 (dd, *J*=9.54 Hz, 5.38 Hz, 1 H), 1.87 (dd, *J*=8.07 Hz, 5.38 Hz, 1 H), 2.04-2.24 (m, 3 H), 2.88-2.94 (m, 2 H), 3.52 (s, 3 H), 3.93 (d, *J*=5.87 Hz, 2 H), 4.09 (m, 2 H), 4.30 (s, 1 H), 4.38 (t, *J*=7.58 Hz, 1 H), 5.11 (dd, *J*=10.27, 1.47 Hz, 1 H), 5.28 (dd, *J*=17.12, 1.47 Hz, 1 H), 5.70 (m, 1 H), 7.00 (dd, *J*=5.87, 2.20 Hz, 1 H), 7.24 (d, *J*=2.20 Hz, 1 H), 8.14 (d, *J*=5.87 Hz, 1 H).
- LC-MS (retention time: 1.670 min.), MS *m/z* 684 (MH⁺).

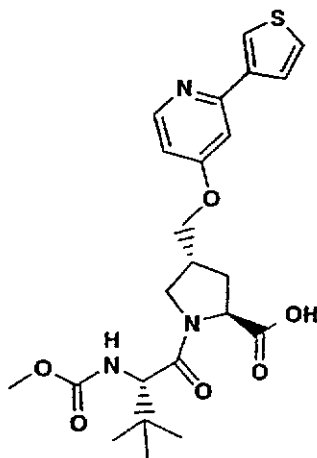
Example 349: Preparation of Compound 349



Compound 349

Compound 349 was prepared by following scheme of **Example 347**, except that intermediate **8** from **Example 348** was used in the place of intermediate **6** from **Example 346** in step 1.

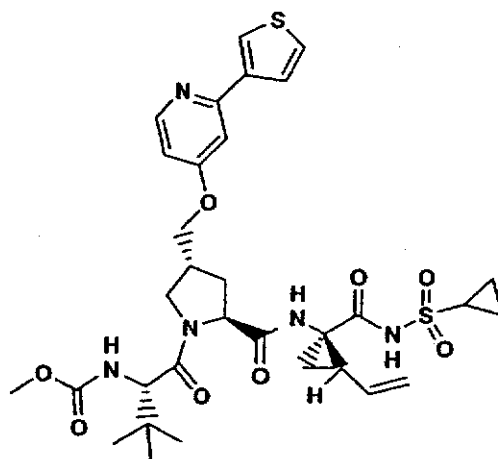
5 Step 1:



To a solution of intermediate 8 (20 mg, 0.0423 mmol) in DMF (1 mL), 3-thiopheneboronic acid (7.0 mg, 0.055 mmol), tetrakis (triphenylphosphine) palladium (2.4 mg, 0.00212 mmol) and 2M Na₂CO₃ solution (0.063 mL, 0.127 mmol) were added. The reaction mixture was heated at 110°C for 30 hr. Then it was filtered and washed with methanol. The filtrate was concentrated and purified by Prep.HPLC to give brownish oil as product. (10.5 mg, 42% yield) (50177-165)

15 LC-MS (retention time: 1.690 min.), MS m/z 476 (MH^+).

Step 2:



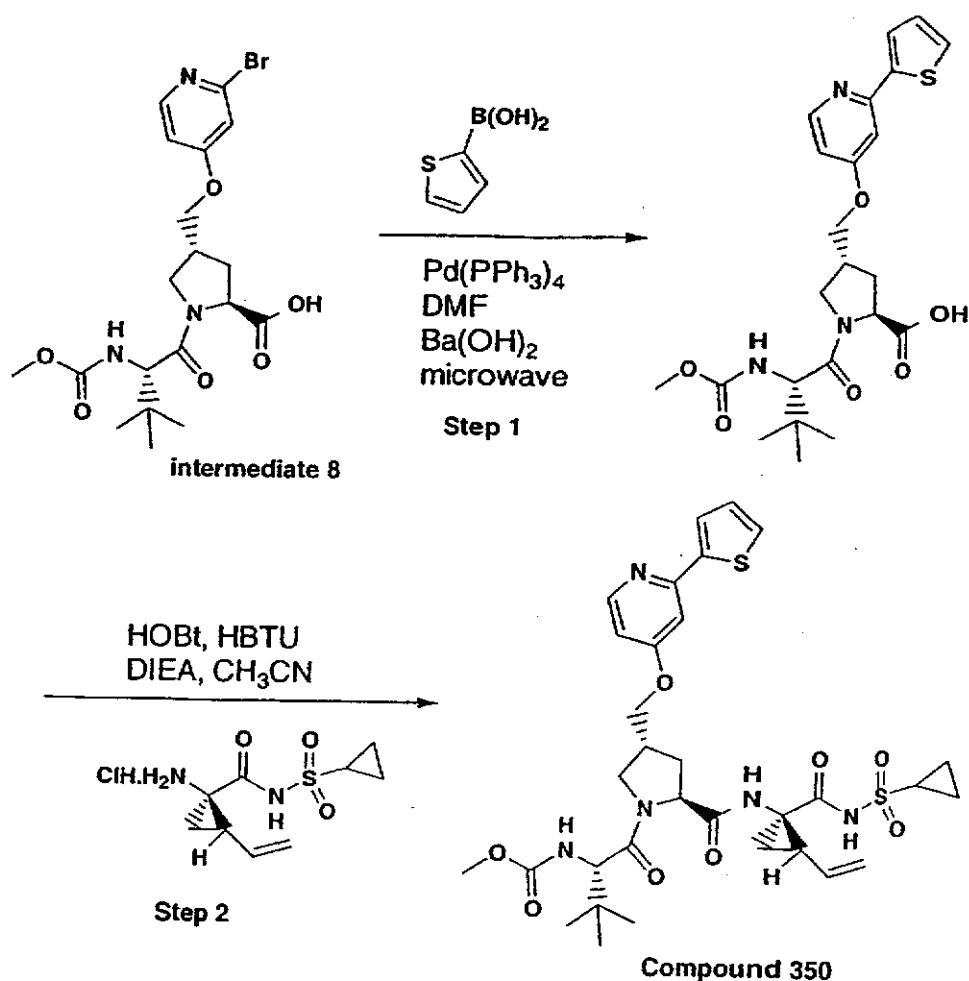
Compound 349

To a solution of 1-(2-Methoxycarbonylamino-3,3-dimethyl-butyl)-4-(2-thiophen-3-yl-pyridin-4-yloxymethyl)-pyrrolidine-2-carboxylic acid (10 mg, 0.017 mmol) in CH_3CN (5 mL) was added (1R, 2S) (1-cyclopropanesulfonyl-aminocarbonyl-2-vinyl-cyclo-propyl)-carbamic acid hydrochloride (6.8 mg, 0.0254 mmol), DIEA (0.015 mL, 0.085 mmol) and the coupling reagent HOBt (3.9 mg, 0.0254 mmol) and HBTU (9.6 mg, 0.0254 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO_4 and concentrated. It was then purified by Prep. HPLC column to give brownish film as TFA salt (Compound 349). (2.2 mg, 16% yield). (50177-172)

^1H NMR(CD_3OD , 400 MHz) δ 1.00-1.07 (m, 11 H), 1.20 (m, 2 H), 1.37 (dd, $J=9.04$, 5.38 Hz, 1 H), 1.88 (dd, $J=8.07$ Hz, 5.38 Hz, 1 H), 2.10-2.25 (m, 3 H), 2.90 (m, 1 H), 3.04 (m, 1 H), 3.47 (s, 3 H), 3.93-4.02 (m, 2 H), 4.29 (s, 1 H), 4.35-4.45 (m, 3 H), 5.12 (d, $J=10.51$ Hz, 1 H), 5.28 (d, $J=17.61$ Hz, 1 H), 5.69 (m, 1 H), 7.40 (dd, $J=6.84$, 2.44 Hz, 1 H), 7.71-7.80 (m, 3 H), 8.38 (m, 1 H), 8.51 (d, $J=7.09$ Hz, 1 H).

LC-MS (retention time: 1.443 min.), MS m/z 688 (MH^+).

Example 350: Preparation of Compound 350



Step 1:

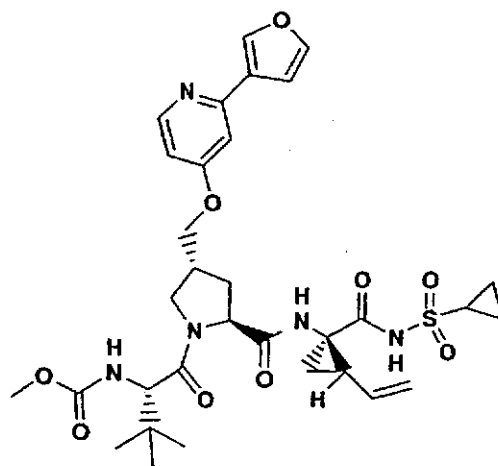
To a solution of intermediate 8 from Example 348 (20 mg, 0.0423 mmol) in DMF (2 mL), 2-thiopheneboronic acid (7.0 mg, 0.055 mmol), tetrakis(triphenylphosphine) palladium (2.4 mg, 0.00212 mmol) and barium hydroxide (40 mg, 0.127 mmol) were added. The reaction mixture was heated at 150°C in Smith microwave reactor for 110 min. Then it was filtered and washed with methanol. The filtrate was concentrated and purified by Prep.HPLC to give yellowish oil as product. (5.0 mg, 20% yield)

LC-MS (retention time: 2.137 min.), MS m/z 476 (MH^+).

Step 2:

- To a solution of above carboxylic acid (5.0 mg, 0.0085 mmol) in CH₃CN (5 mL) was added (1R, 2S) (1-cyclopropanesulfonyl-aminocarbonyl-2-vinyl-cyclo-propyl)-carbamic acid hydrochloride (3.4 mg, 0.0127 mmol), DIEA (0.007 mL, 0.0424 mmol) and the coupling reagent HOBt (1.9 mg, 0.0127 mmol) and HBTU (4.8 mg, 0.0127 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated. It was then purified by Prep. HPLC column to give yellowish oil as TFA salt (**Compound 350**). (2.6mg, 38% yield)
- ¹H NMR(CD₃OD, 400 MHz) δ 0.99-1.07 (m, 11 H), 1.19 (m, 2 H), 1.37 (dd, *J*=9.54, 5.63 Hz, 1 H), 1.87 (dd, *J*=8.07 Hz, 5.38 Hz, 1 H), 2.10-2.25 (m, 3 H), 2.91 (m, 1 H), 3.03 (m, 1 H), 3.48 (s, 3 H), 3.92-4.02 (m, 2 H), 4.30 (s, 1 H), 4.32-4.45 (m, 3 H), 5.11 (dd, *J*=10.27, 1.22 Hz, 1 H), 5.28 (d, *J*=17.11 Hz, 1 H), 5.69 (m, 1 H), 7.30-7.38 (m, 2 H), 7.66 (d, *J*=2.45 Hz, 1 H), 7.92 (m, 1 H), 7.95 (m, 1 H), 8.48 (d, *J*=6.85 Hz, 1 H).
- LC-MS (retention time: 2.067 min.), MS *m/z* 688 (MH⁺).

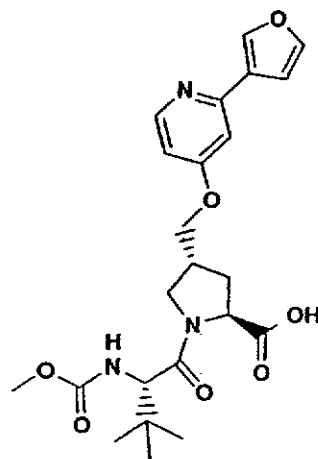
Example 351: Preparation of Compound 351



Compound 351

Compound 351 was prepared by following scheme of Example 350, except that 3-furanboronic acid was used in the place of 2-thiopheneboronic acid in step 1.

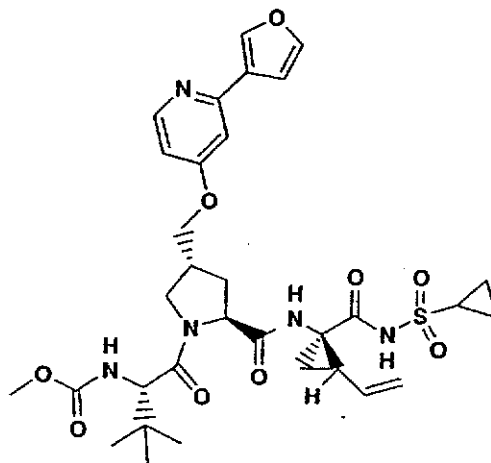
Step 1:



- 5 To a solution of intermediate 8 from Example 348 (20 mg, 0.0423 mmol) in DMF (2 mL), 3-furanboronic acid (6.2 mg, 0.055 mmol), tetrakis(triphenylphosphine) palladium (2.4 mg, 0.00212 mmol) and barium hydroxide (40 mg, 0.127 mmol) were added. The reaction mixture was heated at 150°C in Smith microwave reactor for 30 min. Then it was filtered and washed with methanol. The filtrate
10 was concentrated and purified by Prep.HPLC to give yellowish oil as product. (12 mg, 49% yield)

LC-MS (retention time: 1.937 min.), MS m/z 460 (MH^+).

Step 2:



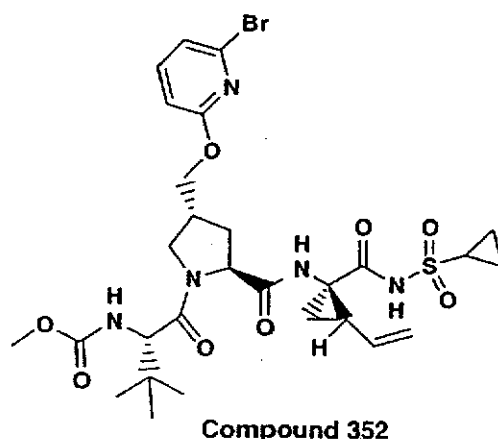
Compound 351

To a solution of above carboxylic acid (5.0 mg, 0.0209 mmol) in CH_3CN (5 mL) was added (1R, 2S) (1-cyclopropanesulfonyl-aminocarbonyl-2-vinyl-cyclo-propyl)-carbamic acid hydrochloride (8.4 mg, 0.0314 mmol), DIEA (0.018 mL, 0.1046 mmol) and the coupling reagent HOBt (4.8 mg, 0.0314 mmol) and HBTU (11.9 mg, 0.0314 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO_4 and concentrated. It was then purified by Prep. HPLC column to give yellowish oil as TFA salt (Compound 351). (4.0 mg, 24% yield).

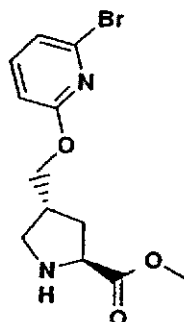
^1H NMR(CD_3OD , 400 MHz) δ 1.00-1.08 (m, 11 H), 1.21 (m, 2 H), 1.37 (dd, $J=8.80$, 5.62 Hz, 1 H), 1.87 (dd, $J=8.32$ Hz, 5.38 Hz, 1 H), 2.11-2.24 (m, 3 H), 2.91 (m, 1 H), 3.03 (m, 1 H), 3.49 (s, 3 H), 3.91-4.03 (m, 2 H), 4.29 (s, 1 H), 4.35-4.46 (m, 3 H), 5.12 (dd, $J=10.27$, 1.47 Hz, 1 H), 5.28 (d, $J=17.12$ Hz, 1 H), 5.69 (m, 1 H), 7.11 (m, 1 H), 7.38 (dd, $J=7.10$, 2.69 Hz, 1 H), 7.71 (d, $J=2.69$ Hz, 1 H), 7.81 (m, 1 H), 8.48 (s, 1 H), 8.50 (d, $J=7.09$ Hz, 1 H).

LC-MS (retention time: 1.410 min.), MS m/z 672 (MH^+).

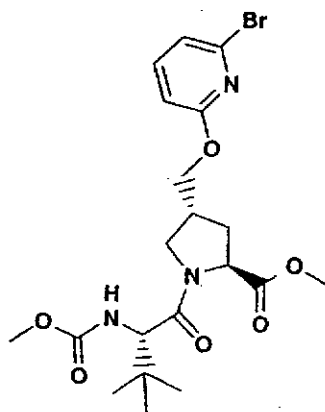
Example 352: Preparation of Compound 352



Compound 352 was prepared by following scheme 2 and scheme 3 of Example 348, except that 2,6-dibromopyridine was used in the place of 2-bromo-4-chloropyridine in step 1 of scheme 2.

Step 1: (Scheme 2, step 1)

- 5 To a solution of **intermediate 7** from **Example 348** (270 mg, 1.1 mmol) in DMSO (10 mL), potassium t-butoxide (309 mg, 2.75 mmol) was added. The reaction mixture was stirred at rt for 1hr. Then 2,6-dibromopyridine (313 mg, 1.32 mmol) was added. The reaction mixture was stirred at rt for overnight. Then it was quenched with water and washed with ethyl acetate. The aqueous layer was separated and acidified with
- 10 1N HCl solution to pH=3. Extracted with ethyl acetate twice and the organic layers were combined and dried (MgSO₄). Evaporation of solvent gave an orange oil. It was then dissolved in methanol and HCl (gas) was bubbled through for 2 min at -78°C. Then the reaction mixture was warmed to rt and stirred for overnight. Evaporation of solvent gave an orange oil as crude to carry on.
- 15 LC-MS (retention time: 1.480 min.), MS m/z 315 (MH⁺).

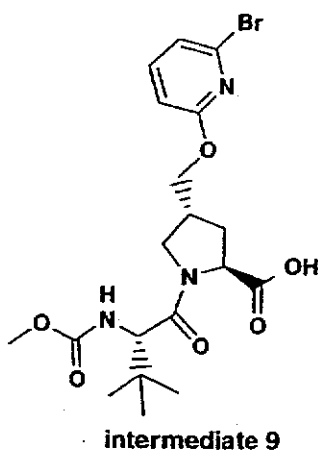
Step 2: (Scheme 2, step 2)

To a solution of crude 4-(6-Bromo-pyridin-2-yloxymethyl)-pyrrolidine-2-carboxylic acid methyl ester in CH_3CN (20 mL) was added 2-methoxycarbonylamino-3,3-dimethyl-butylric acid (312 mg, 1.65 mmol), DIEA (1.15 mL, 6.6 mmol) and the
 5 coupling reagent HOBt (252 mg, 1.65 mmol) and HBTU (626 mg, 1.65 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO_4 and concentrated. It was then purified by flash column chromatography (silica gel, 1:1 hexanes:ethyl acetate) to give a colorless oil as
 10 product. (340 mg, 63% yield two steps)

^1H NMR (CD_3OD , 400 MHz) δ 1.03 (s, 9 H), 2.10-2.24 (m, 2 H), 2.84 (m, 1 H), 3.55 (s, 3 H), 3.70 (s, 3 H), 3.83 (m, 1 H), 3.94 (m, 1 H), 4.20-4.29 (m, 2 H), 4.31 (s, 1 H), 4.59 (dd, $J=8.80$, 5.13 Hz, 1 H), 6.76 (d, $J=8.07$ Hz, 1 H) 7.11 (d, $J=7.58$ Hz, 1 H), 7.53 (t, $J=7.83$ Hz, 1 H).

15 LC-MS (retention time: 1.820 min.), MS m/z 486 (MH^+).

Step 3: (Scheme 2, step 3)



20

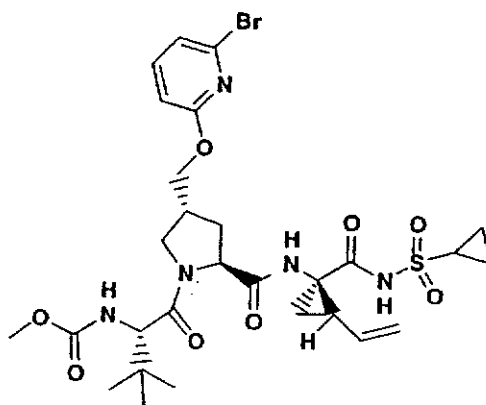
To a solution of 4-(6-Bromo-pyridin-2-yloxymethyl)-1-(2-methoxycarbonylamino-3,3-dimethyl-butyl)-pyrrolidine-2-carboxylic acid methyl ester (330 mg, 0.679 mmol) in THF (28 mL), methanol (15 mL) and water (5 mL) mixture, lithium hydroxide monohydrate (427 mg, 10.18 mmol) was added. The reaction mixture was

stirred at rt. for 2 days. Then it was concentrated and acidified with 1N HCl solution to pH=3 to 5. The white solid was collected as product (**intermediate 9**) (310 mg, 97% yield).

¹H NMR (CD₃OD, 500 MHz) δ 1.06 (s, 9 H), 2.18-2.25 (m, 2 H), 2.88 (m, 1 H), 3.57 (s, 3 H), 3.84 (m, 1 H), 3.96 (m, 1 H), 4.25 (m, 1 H), 4.28-4.35 (m, 2 H), 4.58 (m, 1 H), 6.79 (d, *J*=7.94 Hz, 1 H), 7.13 (d, *J*=7.32 Hz, 1 H), 7.55 (m, 1 H).

LC-MS (retention time: 3.030 min.), MS *m/z* 472 (MH⁺).

Step 4: (Scheme 3)



Compound 352

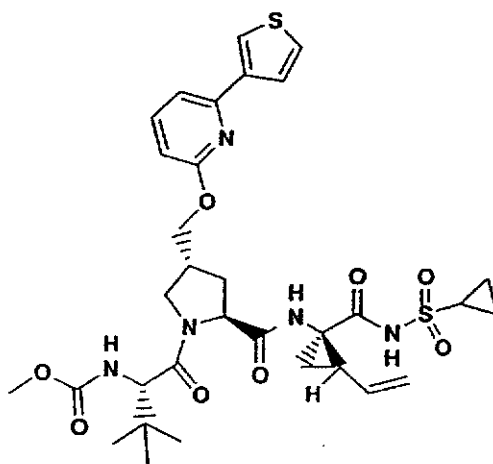
To a solution of intermediate 9 (10 mg, 0.0212 mmol) in CH₃CN (5 mL) was added (1R, 2S) (1-cyclopropanesulfonyl-aminocarbonyl-2-vinyl-cyclo-propyl)-carbamic acid hydrochloride (8.5 mg, 0.00318 mmol), DIEA (0.018 mL, 0.106 mmol) and the coupling reagent HOBt (4.9 mg, 0.0318 mmol) and HBTU (12.1 mg, 0.0318 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated. It was then purified by Prep. HPLC column to give yellowish film as TFA salt (**Compound 352**). (10.2 mg, 60% yield).

¹H NMR(CD₃OD, 400 MHz) δ 1.00-1.06 (m, 11 H), 1.20 (m, 2 H), 1.37 (dd, *J*=9.54 Hz, 5.63 Hz, 1 H), 1.86 (dd, *J*=8.07 Hz, 5.38 Hz, 1 H), 2.05 (m, 1 H), 2.12-2.25 (m, 2 H), 2.86-2.94 (m, 2 H), 3.54 (s, 3 H), 3.87 (m, 1 H), 3.94 (m, 1 H), 4.18-4.27 (m, 2 H), 4.33 (s, 1 H), 4.37 (m, 1 H), 5.11 (dd, *J*=10.27, 1.72 Hz, 1 H), 5.28 (dd, *J*=17.12,

1.47 Hz, 1 H), 5.70 (m, 1 H), 6.76 (d, $J=8.32$ Hz, 1 H), 7.11 (d, $J=7.33$ Hz, 1 H), 7.53 (t, $J=7.82$ Hz, 1 H).

LC-MS (retention time: 1.837 min.), MS m/z 684 (MH^+).

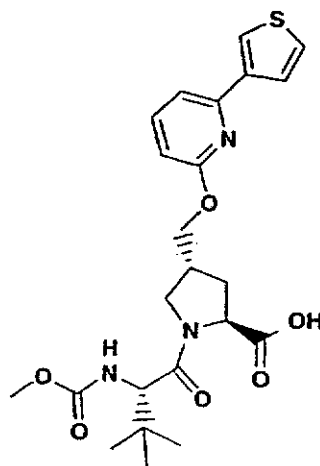
5 Example 353: Preparation of Compound 353



Compound 353

Compound 353 was prepared by following scheme of Example 347, except that intermediate 9 from Example 352 was used in the place of intermediate 6 from Example 346 in step 1.

Step 1:



To a solution of intermediate 9 (25 mg, 0.053 mmol) in DMF (1 mL), 3-thiopheneboronic acid (8.8 mg, 0.0688 mmol), tetrakis(triphenylphosphine) palladium (3.1 mg, 0.00265 mmol) and 2M Na₂CO₃ solution (0.080 mL, 0.159 mmol) were added. The reaction mixture was heated at 110°C for overnight.

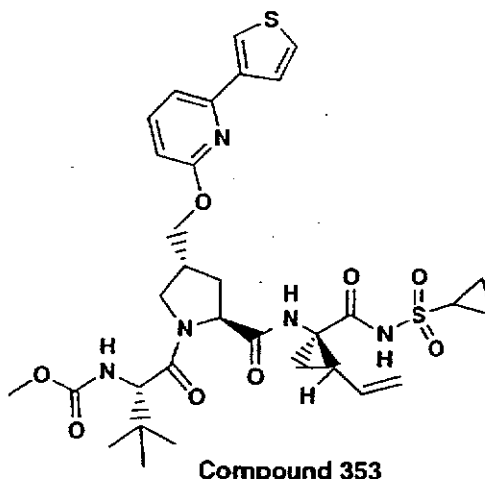
5 Then it was filtered and washed with methanol. The filtrate was concentrated and purified by Prep.HPLC to give brownish oil as product. (15 mg, 48% yield)

¹H NMR (CD₃OD, 500 MHz) δ 1.06 (s, 9 H), 2.20-2.31 (m, 2 H), 2.94 (m, 1 H), 3.55 (s, 3 H), 3.91 (m, 1 H), 3.98 (m, 1 H), 4.34 (s, 1 H), 4.37-4.46 (m, 2 H), 4.61 (dd, *J*=8.85, 5.19 Hz, 1 H), 6.77 (d, *J*=8.24 Hz, 1 H), 7.39 (d, *J*=7.32 Hz, 1 H), 7.48 (dd, *J*=5.19, 3.05 Hz, 1 H), 7.68 (dd, *J*=4.88, 1.22 Hz, 1 H), 7.77 (t, *J*=7.93 Hz, 1H), 8.04 (m, 1 H).

LC-MS (retention time: 1.857 min.), MS *m/z* 476 (MH⁺).

Step 2:

15



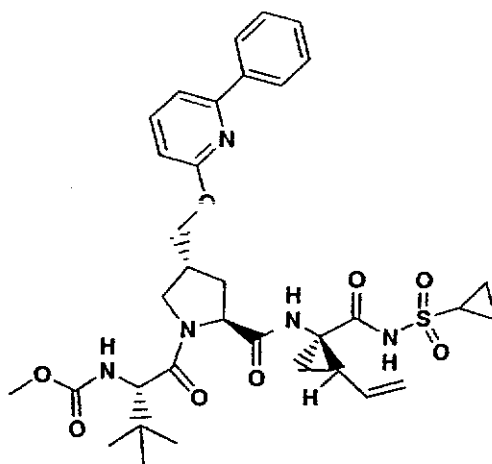
To a solution of 1-(2-Methoxycarbonylamino-3,3-dimethyl-butyl)-4-(6-thiophen-3-yl-pyridin-2-yloxymethyl)-pyrrolidine-2-carboxylic acid (15 mg, 0.0254 mmol) in CH₃CN (5 mL) was added (1R, 2S) (1-cyclopropanesulfonyl-aminocarbonyl-2-vinyl-cyclo-propyl)-carbamic acid hydrochloride (10.2 mg, 0.0382 mmol), DIEA (0.022 mL, 0.127 mmol) and the coupling reagent HOBt (5.8 mg, 0.0382 mmol) and HBTU (14.5 mg, 0.0382 mmol). The solution was stirred at rt. overnight. Then it was

concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO_4 and concentrated. It was then purified by Prep. HPLC column to give yellowish film as TFA salt (Compound 353). (6 mg, 29% yield)

- 5 ^1H NMR(CD_3OD , 400 MHz) δ 1.00-1.06 (m, 11 H), 1.20 (m, 2 H), 1.36 (dd, $J=9.29$, 5.38 Hz, 1 H), 1.86 (dd, $J=8.07$ Hz, 5.38 Hz, 1 H), 2.07 (m, 1 H), 2.16-2.25 (m, 2 H), 2.87-2.99 (m, 2 H), 3.54 (s, 3 H), 3.87-3.99 (m, 2 H), 4.31-4.44 (m, 4 H), 5.11 (dd, $J=10.27$, 1.46 Hz, 1 H), 5.28 (d, $J=17.12$ Hz, 1 H), 5.70 (m, 1 H), 6.67 (d, $J=8.31$ Hz, 1 H), 7.33 (d, $J=7.34$ Hz, 1 H), 7.44 (dd, $J=4.89$, 2.93 Hz, 1 H), 7.63-7.70 (m, 2 H),
10 7.99 (m, 1 H).

LC-MS (retention time: 2.770 min.), MS m/z 688 (MH^+).

Example 354: Preparation of Compound 354

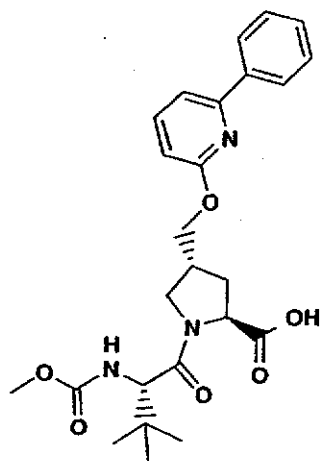


Compound 354

- 15 Compound 354 was prepared by following scheme of Example 347, except that intermediate 9 from Example 352 was used in the place of intermediate 6 from Example 346 and phenyl boronic acid was used in the place of 3-thiopheneboronic acid in step 1.

- 20 Step 1:

487

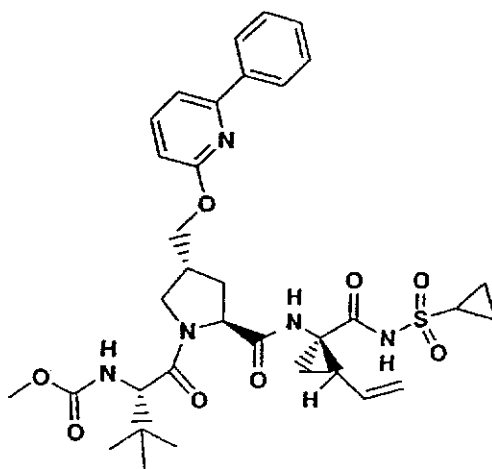


To a solution of intermediate 9 (20 mg, 0.0423 mmol) in DMF (1 mL), phenyl
boronic acid (6.7 mg, 0.0688 mmol), tetrakis(triphenylphosphine) palladium (2.4
5 mg, 0.00212 mmol) and Cs_2CO_3 (41 mg, 0.127 mmol) were added. The reaction
mixture was heated at 110°C for overnight. Then it was filtered and washed with
methanol. The filtrate was concentrated and purified by Prep.HPLC to give
yellowish oil as product. (12mg, 49% yield)

LC-MS (retention time: 2.733 min.), MS m/z 470 (MH^+).

10

Step 2:



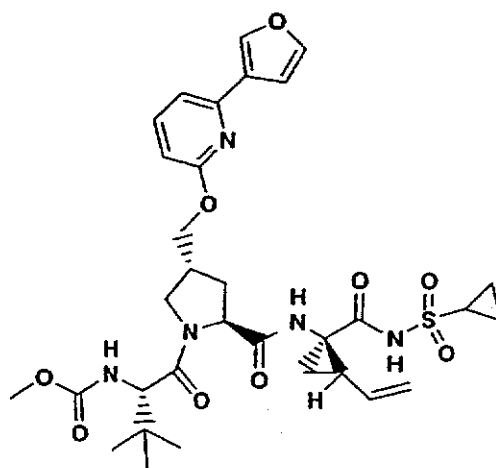
Compound 354

To a solution of 1-(2-Methoxycarbonylamino-3,3-dimethyl-butyl)-4-(6-phenyl-pyridin-2-yloxymethyl)-pyrrolidine-2-carboxylic acid (12 mg, 0.0206 mmol) in CH_3CN (5 mL) was added (1R, 2S) (1-cyclopropanesulfonyl-aminocarbonyl-2-vinyl-cyclo-propyl)-carbamic acid hydrochloride (8.2 mg, 0.0308 mmol), DIEA (0.018 mL, 0.1028 mmol) and the coupling reagent HOBt (4.7 mg, 0.0308 mmol) and HBTU (11.7 mg, 0.0308 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO_4 and concentrated. It was then purified by Prep. HPLC column to give a white solid as TFA salt (Compound 354). (1.5 mg, 9% yield)

^1H NMR(CD_3OD , 400 MHz) δ 1.00-1.07 (m, 11 H), 1.20 (m, 2 H), 1.36 (m, 1 H), 1.85 (m, 1 H), 2.09 (m, 1 H), 2.17-2.25 (m, 2 H), 2.87-3.00 (m, 2 H), 3.52 (s, 3 H), 3.84-4.00 (m, 2 H), 4.33-4.44 (m, 4 H), 5.11 (dd, $J=10.27$, 1.71 Hz, 1 H), 5.28 (d, $J=17.12$, 1.22 Hz, 1 H), 5.70 (m, 1 H), 6.71 (d, $J=8.31$ Hz, 1 H), 6.78 (m, 1 H), 7.34-7.44 (m, 3 H), 7.74 (m, 1 H), 7.95 (m, 1 H), 8.01 (d, $J=8.31$ Hz, 1H).

LC-MS (retention time: 3.553 min.), MS m/z 682 (MH^+).

Example 355: Preparation of Compound 355

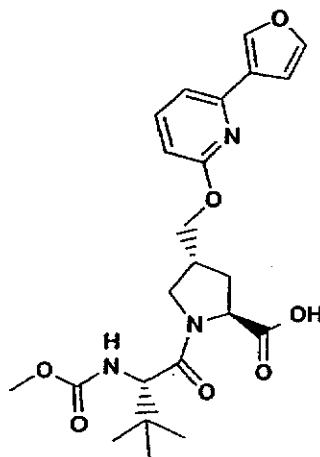


Compound 355

Compound 354 was prepared by following scheme of Example 347, except that intermediate 9 from Example 352 was used in the place of intermediate 6 from

Example 346 and 3-furan boronic acid was used in the place of 3-thiopheneboronic acid in step 1.

Step 1:

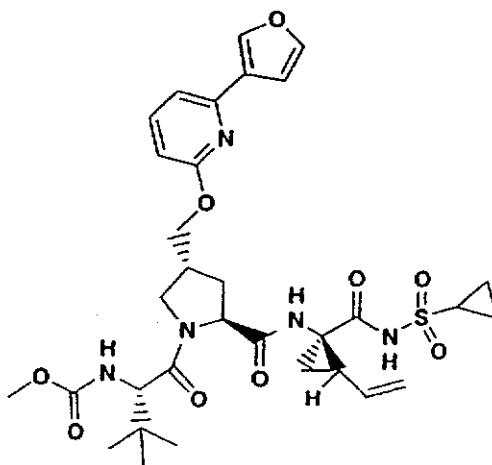


5

To a solution of intermediate 9 (20 mg, 0.0423 mmol) in DMF (1 mL), 3-furan boronic acid (6.2 mg, 0.055 mmol), tetrakis(triphenylphosphine) palladium (2.4 mg, 0.002115 mmol) and 2M Na₂CO₃ solution (0.064 mL, 0.127 mmol) were added. The reaction mixture was heated at 110°C for 2 days. Then it was filtered and washed with methanol. The filtrate was concentrated and purified by Prep.HPLC to give yellowish oil as product. (7.0 mg, 29% yield)

10

Step 2:



Compound 355

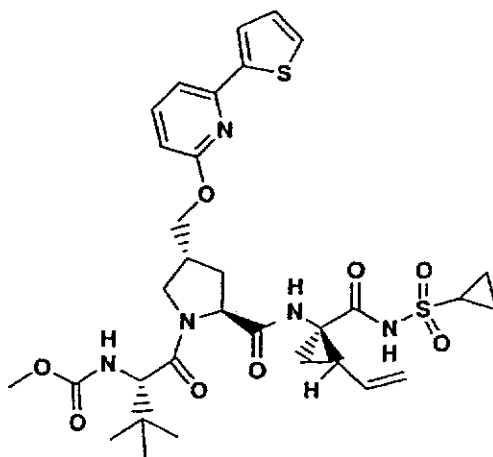
15

To a solution of above carboxylic acid (6.0 mg, 0.0109 mmol) in CH₃CN (5 mL) was added (1R, 2S) (1-cyclopropanesulfonyl-aminocarbonyl-2-vinyl-cyclo-propyl)-carbamic acid hydrochloride (4.4 mg, 0.0163 mmol), DIEA (0.0095 mL, 0.0544 mmol) and the coupling reagent HOBt (2.5 mg, 0.0163 mmol) and HBTU (6.2 mg, 0.0163 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated. It was then purified by Prep. HPLC column to give yellowish film as TFA salt (Compound 355). (1.5 mg, 18% yield)

¹H NMR(CD₃OD, 400 MHz) δ 0.98-1.07 (m, 11 H), 1.20 (m, 2 H), 1.35 (dd, *J*=9.54, 5.87 Hz, 1 H), 1.86 (dd, *J*=8.07 Hz, 5.62 Hz, 1 H), 2.06 (m, 1 H), 2.15-2.25 (m, 2 H), 2.85-2.98 (m, 2 H), 3.55 (s, 3 H), 3.89 (m, 1 H), 3.95 (m, 1 H), 4.28-4.42 (m, 4 H), 5.11 (dd, *J*=10.27, 1.71 Hz, 1 H), 5.28 (dd, *J*=17.12, 1.22 Hz, 1 H), 5.69 (m, 1 H), 6.63 (d, *J*=8.07 Hz, 1 H), 6.90 (m, 1 H), 7.16 (d, *J*=7.33 Hz, 1 H), 7.53 (m, 1 H), 7.63 (m, 1 H), 8.08 (s, 1 H).

LC-MS (retention time: 3.340 min.), MS *m/z* 672 (MH⁺).

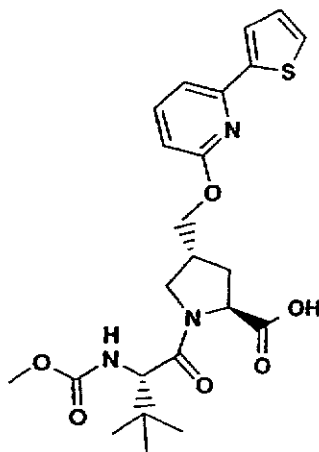
Example 356: Preparation of Compound 356



Compound 356

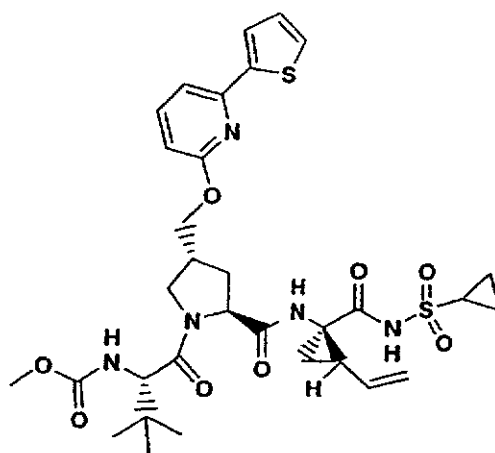
Compound 356 was prepared by following scheme of Example 350, except intermediate 9 from Example 352 was used in the place of intermediate 8 from Example 348 in step 1.

Step 1:



- To a solution of intermediate 9 (20 mg, 0.0423 mmol) in DMF (2 mL), 2-thiopheneboronic acid (7.0 mg, 0.055 mmol), tetrakis(triphenylphosphine) palladium (2.4 mg, 0.00212 mmol) and barium hydroxide (40 mg, 0.127 mmol) were added. The reaction mixture was heated at 150°C in Smith microwave reactor for 30 min. Then it was filtered and washed with methanol. The filtrate was concentrated and purified by Prep.HPLC to give brownish oil as product.
- (13.0 mg, 52% yield)
- ¹H NMR (CD₃OD, 400 MHz) δ 1.03 (s, 9 H), 2.18-2.25 (m, 2 H), 2.93 (m, 1 H), 3.55 (s, 3 H), 3.83 (m, 1 H), 3.98 (m, 1 H), 4.34 (s, 1 H), 4.38 (m, 2 H), 4.58 (dd, *J*=8.05, 5.14 Hz, 1 H), 6.63 (d, *J*=8.07 Hz, 1 H), 7.07 (dd, *J*=4.89, 3.67 Hz, 1 H), 7.33 (d, *J*=7.34 Hz, 1 H), 7.42 (d, *J*=5.14 Hz, 1 H), 7.60-7.66 (m, 2 H).
- LC-MS (retention time: 3.393 min.), MS *m/z* 476 (MH⁺).

Step 2:



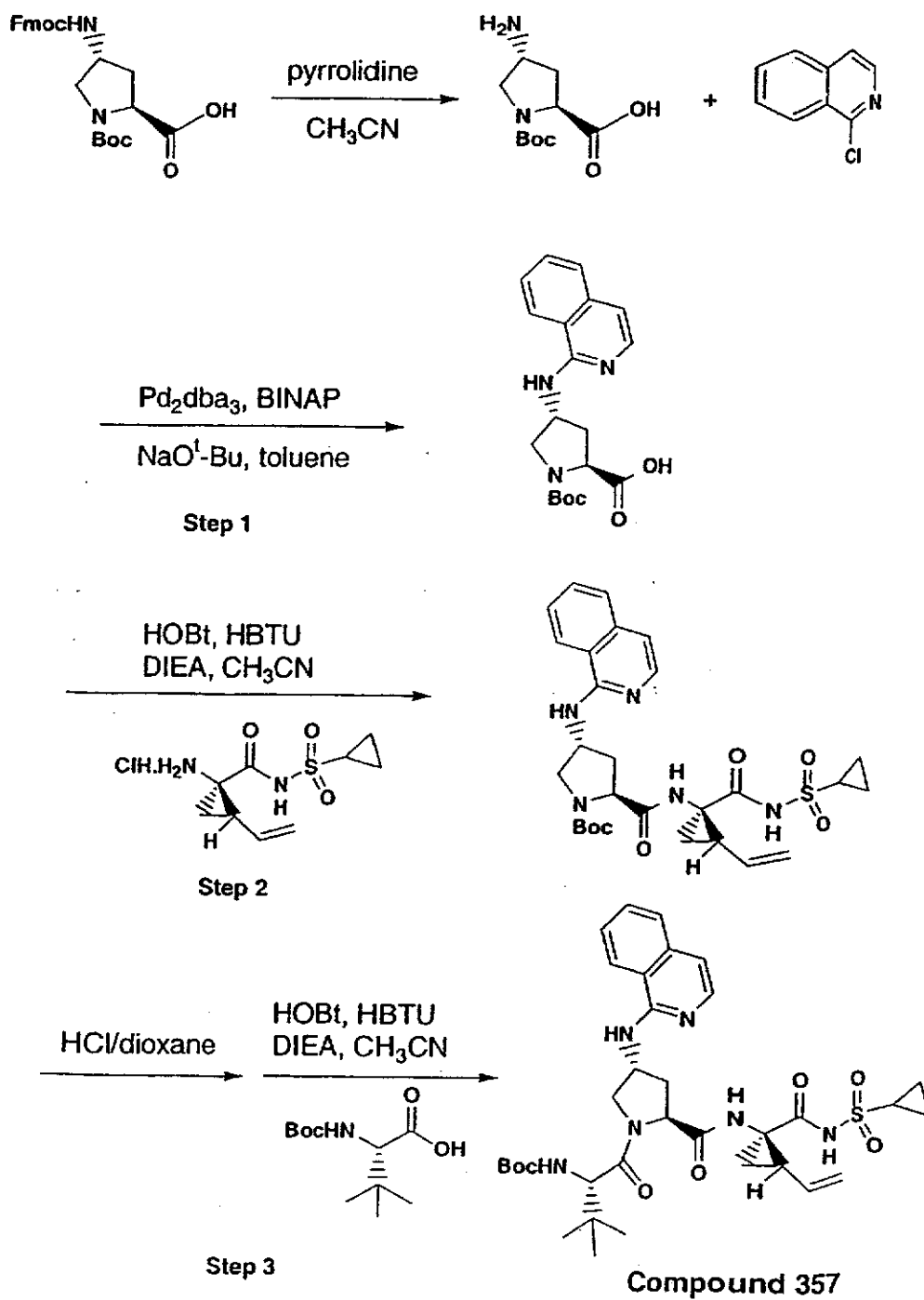
Compound 356

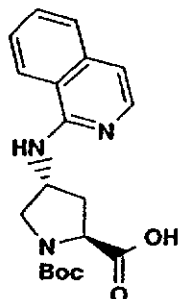
To a solution of 1-(2-Methoxycarbonylamino-3,3-dimethyl-buteryl)-4-(6-thiophen-2-yl-pyridin-2-yloxymethyl)-pyrrolidine-2-carboxylic acid (11.5 mg, 0.0195 mmol) in
 5 CH₃CN (5 mL) was added (1R, 2S) (1-cyclopropanesulfonyl-aminocarbonyl-2-vinyl-cyclo-propyl)-carbamic acid hydrochloride (7.8 mg, 0.0293 mmol), DIEA (0.017 mL, 0.0975 mmol) and the coupling reagent HOBt (4.5 mg, 0.0293 mmol) and HBTU (11.1 mg, 0.0293 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The
 10 combined organic layers were washed with brine, dried over MgSO₄ and concentrated. It was then purified by Prep. HPLC column to give an off-white solid as TFA salt (**Compound 356**). (8.5 mg, 54% yield)

¹H NMR(CD₃OD, 400 MHz) δ 0.99-1.06 (m, 11 H), 1.21 (m, 2 H), 1.36 (dd, *J*=9.54, 5.38 Hz, 1 H), 1.86 (dd, *J*=8.07 Hz, 5.62 Hz, 1 H), 2.06 (m, 1 H), 2.15-2.25 (m, 2 H),
 15 2.87-2.99 (m, 2 H), 3.54 (s, 3 H), 3.89 (m, 1 H), 3.96 (m, 1 H), 4.30-4.44 (m, 4 H), 5.11 (dd, *J*=10.51, 1.71 Hz, 1 H), 5.28 (dd, *J*=17.11, 1.22 Hz, 1 H), 5.70 (m, 1 H), 6.62 (d, *J*=8.07 Hz, 1 H), 7.07 (dd, *J*=4.89, 3.66 Hz, 1 H), 7.33 (d, *J*=7.59 Hz, 1 H), 7.42 (d, *J*=4.89 Hz, 1H), 7.60-7.66 (m, 2 H).

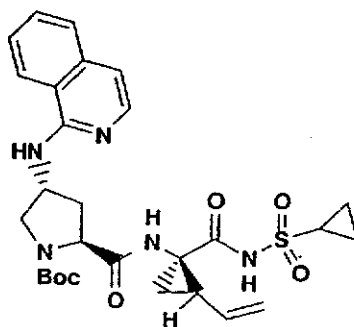
LC-MS (retention time: 1.967 min.), MS *m/z* 688 (MH⁺).

Example 357: Preparation of Compound 357



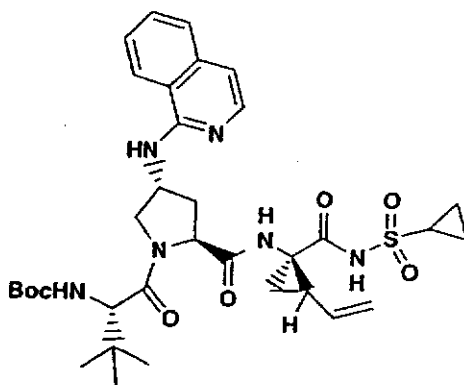
Step 1:

- To a solution of (2S, 4R) Fmoc-4-amino-1-boc-pyrrolidine-2-carboxylic acid (400 mg, 0.884 mmol) in acetonitrile (15 mL), five drops of pyrrolidine was added. The reaction mixture was stirred at rt for 3hr. Then it was concentrated and put on high vacuum to give crude 4-amino-1-boc-pyrrolidine-2-carboxylic acid. In another round-bottomed flask, a solution of Pd_2dba_3 (40 mg, 5% mol) and racemic-BINAP (56 mg, 10% mol) was stirred under nitrogen in degassed toluene (8 mL) at rt for 1h. Then 1-chloroisoquinoline (216 mg, 1.326 mmol) and sodium t-butoxide (340 mg, 3.536 mmol) were added and the reaction mixture was stirred for 30 min. Then 4-amino-1-boc-pyrrolidine-2-carboxylic acid was added and the reaction mixture was heated under reflux for 1h. Water was added to quench the reaction and the aqueous layer was separated and filtered through filter paper. It was then concentrated and purified by Prep. HPLC to give coupled product as TFA salt. (165 mg, 40% yield)
- ^1H NMR (CD_3OD , 400 MHz) δ 1.44 (m, 9H), 2.51-2.74 (m, 2H), 3.64 (m, 1H), 4.01 (m, 1H), 4.49 (m, 1H), 4.64 (m, 1H), 7.30 (d, $J=6.85$ Hz, 1H), 7.58 (d, $J=6.85$ Hz, 1H), 7.79(m, 1H), 7.91-7.99 (m, 2H), 8.56 (d, $J=8.56$ Hz, 1H).
- LC-MS (retention time: 1.707 min.), MS m/z 358 (MH^+).

Step 2:

- To a solution of 4-(Isoquinolin-1-ylamino)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (115 mg, 0.244 mmol) in CH₃CN (10 mL) was added (1R, 2S) (1-cyclopropanesulfonyl-aminocarbonyl-2-vinyl-cyclo-propyl)-carbamic acid hydrochloride (97 mg, 0.366 mmol), DIEA (0.255 mL, 1.464 mmol) and the coupling reagent HOBt (56 mg, 0.366 mmol) and HBTU (139 mg, 0.366 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated to give yellow oil. It was purified by Prep. HPLC column to a yellowish solid as TFA salt (112 mg, 67% yield).
- ¹H NMR (CD₃OD, 400 MHz) δ 1.05 (m, 2H), 1.20 (m, 2H), 1.40-1.48 (m, 10H), 1.87 (dd, J=8.19, 5.50 Hz, 1H), 2.23 (m, 1H), 2.39 (m, 1H), 2.50 (m, 1H), 2.93 (m, 1H), 3.65 (m, 1H), 4.08 (m, 1H), 4.33 (t, J=7.09 Hz, 1H), 4.69 (m, 1H), 5.12 (d, J=10.27 Hz, 1H), 5.29 (d, J=17.12 Hz, 1H), 5.74 (m, 1H), 7.31 (d, J=6.85 Hz, 1H), 7.60 (d, J=7.09 Hz, 1H), 7.80 (m, 1H), 7.93-8.00 (m, 2H), 8.56 (d, J=8.19 Hz, 1H).
- LC-MS (retention time: 2.023 min.), MS m/z 570 (MH⁺).

Step 3:



Compound 357

- 2-(1-Cyclopropanesulfonylaminocarbonyl-2-vinylcyclopropyl-carbamoyl)-4-(isoquinolin-1-ylamino)-pyrrolidine-1-carboxylic acid tert-butyl ester (31 mg, 0.0453 mmol) was dissolved in 4N HCl in dioxane (1.5 mL) and stirred at rt. for 2 hr. Evaporation of solvent gave yellowish oil as bis hydrochloride salt. To a solution of bis hydrochloride salt in CH₃CN (5 mL) was added N-boc-L-t-leucine (11.5 mg, 0.0498 mmol), DIEA (0.047 mL, 0.272 mmol) and the coupling reagent HOBt (10.4

mg, 0.068 mmol) and HBTU (25.8 mg, 0.068 mmol). The solution was stirred at rt. overnight. Then it was concentrated, washed with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO_4 and concentrated to give yellowish oil. It was purified by Prep. HPLC column to give an off-white solid as final product (**Compound 357**). (9 mg, 29% yield)

^1H NMR (CD_3OD , 400 MHz) δ 0.98 (m, 2H), 1.05 (s, 9H), 1.20 (m, 2H), 1.36-1.43 (m, 10H), 1.84 (m, 1H), 2.10-2.30 (m, 2H), 2.52 (m, 1H), 2.90 (m, 1H), 4.07 (m, 1H), 4.17-4.27 (m, 2H), 4.47 (m, 1H), 4.79 (m, 1H), 5.07 (d, $J=9.29$ Hz, 1H), 5.24 (d, $J=16.87$ Hz, 1H), 5.72 (m, 1H), 6.62 (m, 1H), 6.98 (d, $J=6.11$ Hz, 1H), 7.47 (m, 1H), 7.62 (m, 1H), 7.69 (d, $J=8.07$ Hz, 1H), 7.84 (d, $J=5.87$ Hz, 1H), 8.20 (d, $J=8.56$ Hz, 1H).

LC-MS (retention time: 2.043 min.), MS m/z 683 (MH^+).

Section H:

LC-MS condition for section H

Columns: (Method A) - YMC ODS S7 C18 3.0x50 mm
(Method B) - YMC ODS-A S7 C18 3.0x50 mm
(Method C) - YMC S7 C18 3.0x50 mm
(Method D) - YMC Xterra ODS S7 3.0x50 mm
(Method E) - YMC Xterra ODS S7 3.0x50 mm
(Method F) - YMC ODS-A S7 C18 3.0x50 mm
(Method H) - Xterra S7 3.0x50 mm
(Method I) - Xterra S7 C18 3.0x50 mm
(Method G) - YMC C18 S5 4.6x50 mm
(Method J) - Xterra ODS S7 3.0x50 mm
(Method K) - YMC ODS-A S7 C18 3.0x50 mm

Gradient: 100% Solvent A/0% Solvent B to
0% Solvent A/100% Solvent B

Gradient time: 2 min. (A, B, D, F, G, H, I); 8 min. (C, E); 4 min (J); 3 min (K)

Hold time: 1 min. (A, B, D, F, G, H, I, J, K); 2 min. (C, E)

Flow rate: 5 mL/min (A, B, C, D, E, F, G)

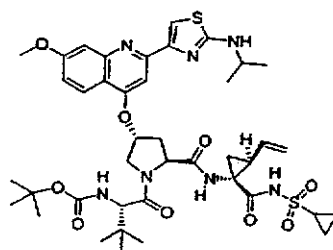
Flow rate: 4 mL/min (J, K)

Detector Wavelength: 220 nm

5 Solvent A: 10% MeOH / 90% H₂O / 0.1% TFA

Solvent B: 10% H₂O / 90% MeOH / 0.1% TFA.

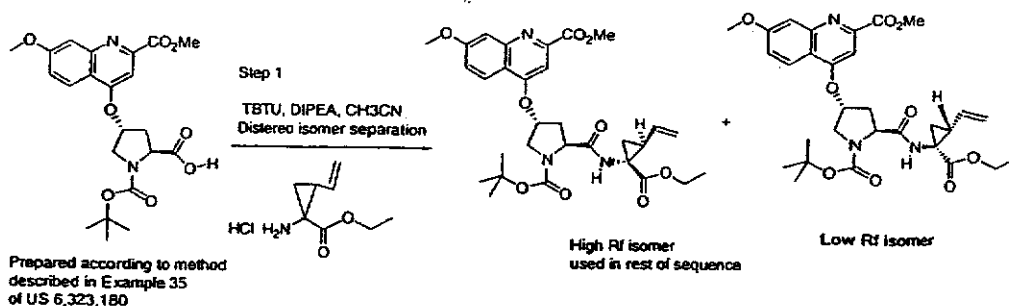
Example 370: Preparation of Compound 370



Compound 370

10

Scheme 1



Step 1:

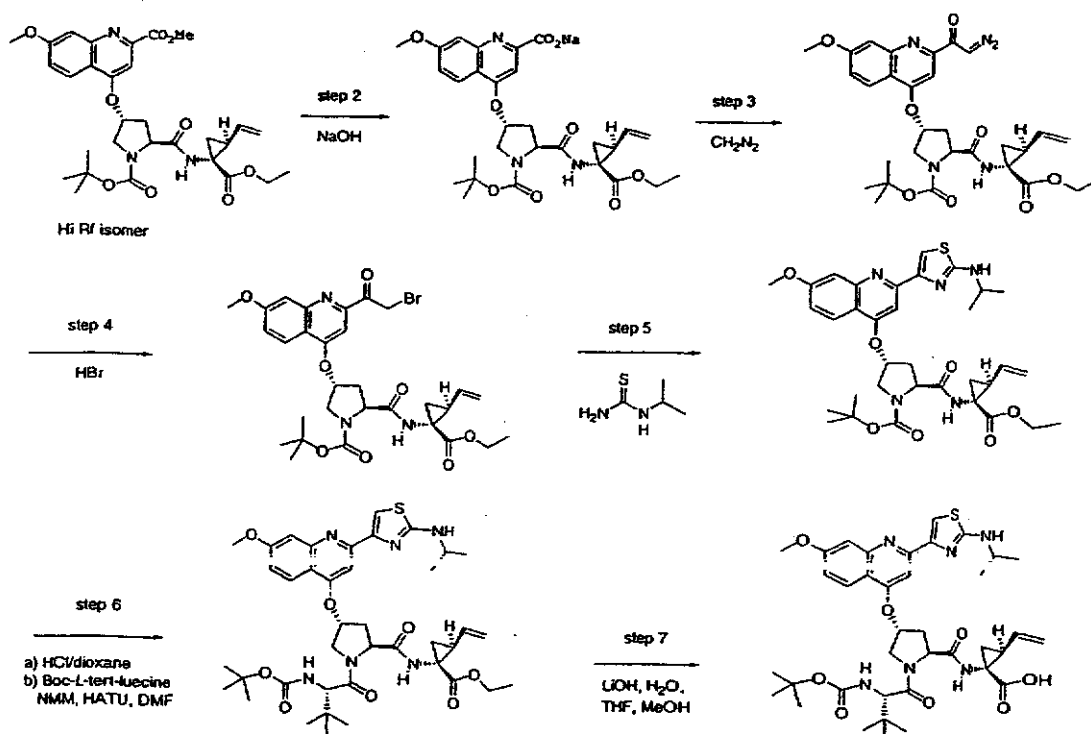
A solution of (1*R*,2*S*)/(1*S*,2*R*)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester hydrochloride (2.54 g, 12 mmol) in CH₃CN (70 mL) was treated with a solution of diisopropylethylamine (9.5 mL, 67 mmol), [(4*R*)-(2-methoxycarbonyl-7-methoxyquinoline-4-oxo)-*S*-proline] (5.9 g, 13.2 mmol), and TBTU (3.89 g, 12.21 mmol) in CH₃CN (50 mL). The reaction mixture was stirred for 14 h and concentrated. The residue dissolved in EtOAc was repeatedly washed with NaHCO₃ (aq.), brine, dried (MgSO₄), and concentrated. The residue was purified over Biotage 65M column (EtOAc/hexane: 45-100%) to provide the high Rf stereo isomer (Boc-P2[(4*R*)-(2-methoxycarbonyl-7-methoxyquinoline-4-oxo)-*S*-proline]-P1(1*R*,2*S*

15

20

Vinyl Acca) Acid ethyl ester 2.0 g (52%) as a white solid: ^1H NMR (methanol- d_4) δ ppm 1.24 (t, $J=7.02$ Hz, 3 H), 1.38 (m, 11 H), 1.76 (m, 1 H), 2.21 (m, 1 H), 2.45 (m, 1 H), 2.71 (m, 1 H), 3.92 (m, 2 H), 3.96 (s, 3 H), 4.03 (s, 3 H), 4.16 (q, $J=7.22$ Hz, 2 H), 4.42 (m, 1 H), 5.10 (m, 1 H), 5.30 (m, 1 H), 5.44 (s, 1 H), 5.77 (m, 1 H), 7.27 (d, $J=9.16$ Hz, 1 H), 7.48 (s, 1 H), 7.52 (s, 1 H), 8.05 (s, 1 H).

Scheme 2



Step 2:

A solution of the high Rf product (3.16g, 5.40 mmol) of Step 1 of Example 10 370 [Boc-P2[(4R)-(2-methoxycarbonyl-7-methoxylquinoline-4-oxo)-S-proline]-P1(1R,2S Vinyl Acca) COOEt] at 0 °C dissolved in MeOH/THF (1/1, 13.2 mL) was treated with aqueous 1.0 N NaOH (5.5 mL, 5.5 mmol), stirred for 1 h, neutralized by the addition of AcOH. The solvent was removed in vacuo. The residue was redissolved in THF/CH₂Cl₂ (1/1, 150 mL), dried (MgSO₄) and concentrated in vacuo to provide the product which was directly used in next step: LC-MS (retention time: 1.53 Method D), MS m/z 570 ($M^+ + 1$).

Step 3:

To a solution of the product (assumed at 5.4 mmol) of step 2 example 370 at 0°C dissolved in THF (35 mL) was added a solution of fresh made CH_2N_2 (30 mmol) in Et_2O (80 mL). The reaction mixture was stirred at the temperature for 0.5 h, and stirred at rt for 18.5 h. After bubbling nitrogen for 1 h to the reaction mixture, the solution was removed in vacuo. The residue redissolved in EtOAc (1 L) was washed with saturated NaHCO_3 (aq.), (2x200 mL), brine (100 mL), and dried (MgSO_4). The solvent was removed in vacuo to afford the product 3.10 g (97% two steps): LC-MS (retention time: 3.06, Method J), MS m/z 594 ($\text{M}^+ + 1$).

10 Step 4:

To a solution of the product (3.03g, 5.10 mmol) of step 3 of example 370 {Boc-P2[(4*R*)-(2-diazoacetyl-7-methoxyquinoline-4-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca) COOEt} at 0°C dissolved in THF (110 mL) was added 2 mL of 48% HBr. The mixture was stirred for 1 h, partitioned between EtOAc (500 mL) and saturated NaHCO_3 (aq.) (100 mL). The EtOAc layer was separated, dried (MgSO_4). The solvent was removed to afford the product (3.12g, 95%): LC-MS (retention time: 1.56 Method D). MS m/z 648 ($\text{M}^+ + 1$), MS m/z 646 ($\text{M}^- - 1$).

Step 5:

20 The product (1.0 g, 1.54 mmol) of step 4 of example 370 {Boc-P2[(4*R*)-(2-bromoacetyl-7-methoxyquinoline-4-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca) COOEt} was treated with isopropylthiourea (0.365 g, 3.09 mmol) in isopropyl alcohol (57 mL) for 2 h, and then the solvent was removed. The residue dissolved in aqueous 1.0 N HCl (30 mL) and EtOAc (200 mL) was adjusted pH to 7 by addition of 1.0 N NaOH (aq.). The aqueous layer was extracted with EtOAc (2x100 mL) and the combined extract was dried (MgSO_4), concentrated. The residue was purified by over Biotage 40+M column (EtOAc-hexanes: 30-100%) to afford the product 870 mg (84%) and ready for the next step.

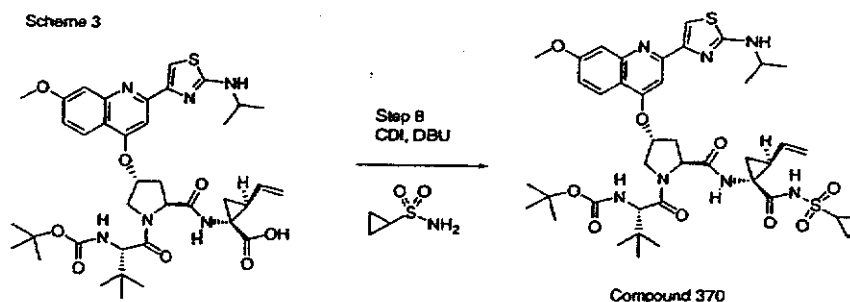
30 Step 6:

The product (0.250 g, 0.375 mmol) of step 5 of example 370 {Boc-P2[(4*R*)-[2-(2-isopropylaminothiazol-4-yl)-7-methoxyquinoline-4-oxo]-*S*-proline]-P1(1*R*,2*S*

Vinyl Acca) COOEt} was treated with 4N HCl/dioxane (2.5 mL, 10 mmol) for 2.5 h and concentrated in vacuo. To the residue was added N-methylmorpholine (0.206 mL, 1.875 mmol) in DMF (3 mL), N-Boc-*L*-tert-leucine (0.117 g, 0.506 mmol), and HATU (0.192 g, 0.506 mmol). The mixture was stirred overnight and partitioned
 5 between EtOAc and pH 4.0 buffer. The EtOAc layer was washed with water, NaHCO₃ (aq.), dried (MgSO₄), concentrated. The residue was purified over a Biotage 40M column (MeOH-CH₂Cl₂: 0-8%) to afford the product 0.289 g (99%): LC-MS (retention time: 2.53, Method K), MS *m/z* 779 (*M*⁺+1).

10 Step 7:

To a suspension of the product of Step 6 (274 mg, 0.352 mmol) of Example 370 {BOCNH-P3(*L*-*t*-BuGly)- {[2- (2-isopropylaminothiazol-4-yl)-7-methoxylquinoline-4-oxo]-*S*-proline} -P1(1*R*,2*S* Vinyl Acca)-COOEt} in THF(10.6 mL), CH₃OH (2.6 mL), and H₂O (5.3 mL) was added LiOH (0.068 g, 2.86 mmol).
 15 The reaction mixture was stirred for 24, adjusted to pH 6, removed the organic solvents in vacuo. The aqueous residue was acidified to pH 4, and extracted with CH₂Cl₂ repeatedly. Combined organic solvent was dried (MgSO₄), and concentrated in vacuo to afford the desired product 255 mg (95%): LC-MS (retention time: 2.58, Method K), MS *m/z* 751 (*M*⁺+1).



20

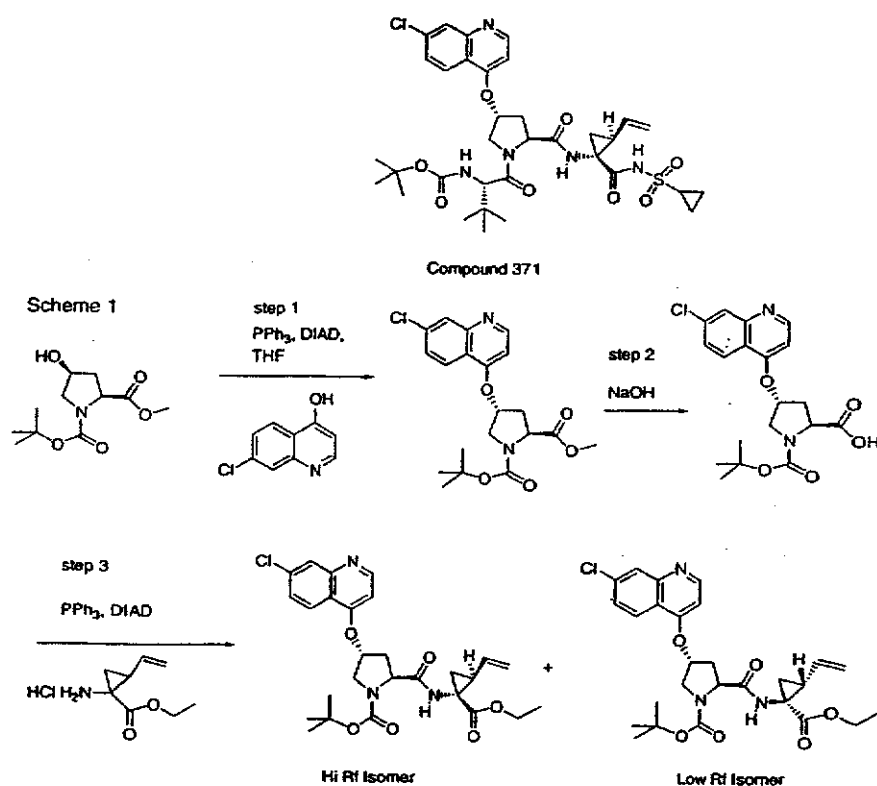
Step 8:

A solution of CDI (0.024 g, 0.15 mmol) and the product of Step 7 of Example 370 (0.0683 g, 0.09 mmol) {BOCNH-P3(*L*-*t*-BuGly)- {[2- (2-isopropylaminothiazol-4-yl)-7-methoxylquinoline-4-oxo]-*S*-proline} -P1(1*R*,2*S* Vinyl Acca)-COOH} in
 25 THF (2 mL) was refluxed for 60 min and allowed to cool down to rt. Cyclopropanesulfonamide (0.022 g, 0.18 mmol) was added followed by the addition of neat DBU (0.027 mL, 0.18 mmol). The reaction was stirred for overnight, worked

up by diluting with EtOAc and washed with pH 4.0 buffer, dried (MgSO_4), and concentrated. The residue was purified repeatedly by preparative HPLC (0-100% solvent B) and over 1000 μM preparative TLC plate from Analtech (20X40 cm) to afford 0.0032 g (4%) the desired product (**Compound 370**) as a pale yellow foam:

5 LC-MS (Retention time: 1.71, method I) MS m/z 854 ($\text{M}^+ + 1$).

Example 371: Preparation of Compound 371



10 Step 1:

To a suspension of *N*-Boc-*cis*-*L*-4-Hydroxyproline methyl ester (10 g, 40.7 mmol) and 7-chloroquinolin-4-ol (8.73 g, 49.0 mmol) in THF (200 mL) cooled to 0 °C was added PPh₃ (12.82 g, 48.9 mmol) and DIAD. (8.80 g, 42.13 mmol). The mixture was slowly allowed to warm to rt overnite, stirred at total of 30 h. The mixture was

15 dissolved in EtOAc (800 mL), washed with 1N aqueous HCl, 5% aqueous K₂CO₃ (3X100 mL), brine (2 X 100 mL) and dried (MgSO_4), and concentrated. The residue was purified several times over a Biotage 65M (MeOH-CH₂Cl₂: 0-10%) to afford cumulatively 10.57 g (68%) of the desired product as a glass: ¹H NMR (CDCl₃) δ 1.40 (s, 9H), 2.33-2.42 (m, 1H), 2.61-2.72 (m, 1H), 3.75 (s, 3H), 3.91 (m, 2H), 4.45-

4.59 (m, 1H), 5.13 (m, 1H), 6.61-6.64 (m, 1H), 7.41 (dd, $J=9$, 2 Hz, 1H), 7.98 (d, $J=2$ Hz, 1H), 8.03 (d, $J=9$ Hz, 1H), 8.67-8.71 (m, 1H). LC-MS (retention time: 1.39, method D), MS m/e 407 ($M^+ + 1$).

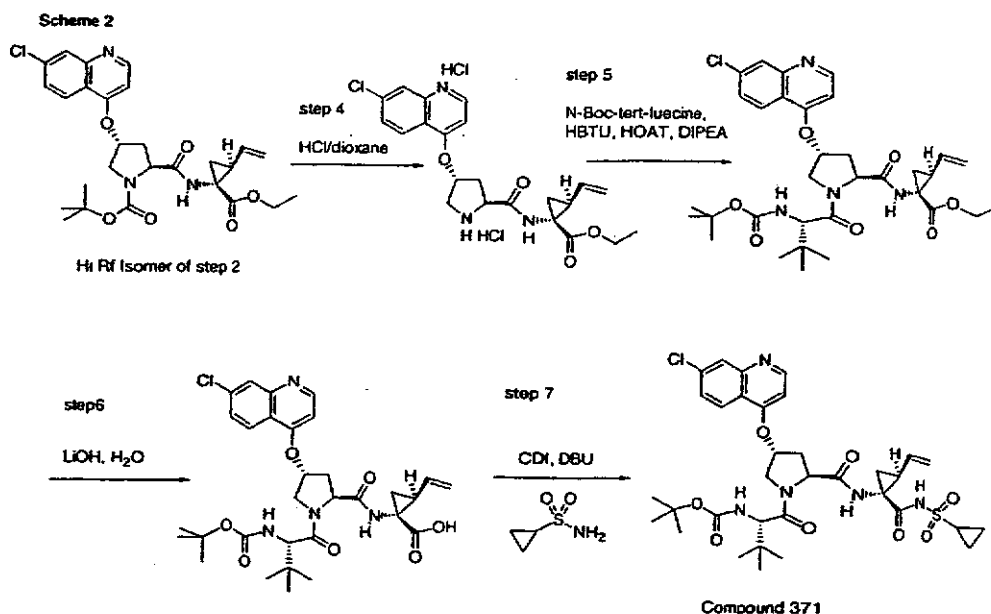
Step 2:

- 5 To a solution of the product (10.57 g, 26.0 mmol) of Step 1 of Example 371 (BOC-*N*-P2[(4*R*)-(7-chloroquinoline-4-oxo) proline methyl ester] dissolved in MeOH (800 mL) cooled to 0 °C was added an aqueous 1N NaOH solution (44.5 mL, 44.5 mmol). The mixture was warmed to rt after 6 h, stirred overnight, and the pH adjusted to pH 7 using 1.0 N aqueous HCl. The solution was concentrated until only the water layer
- 10 remained, the pH adjusted to 4 using 6N aqueous HCl and the mixture was partitioned repeatedly with EtOAc (3x500 mL). The combined organic layers were dried (MgSO₄) and concentrated to afford 10.16 g (100%) of the as a white solid. ¹H NMR (DMSO-*d*₆) δ 1.32, 1.34 (two s (rotamers) 9H), 2.31-2.40 (m, 1H), 2.58-2.69 (m, 1H), 3.65-3.81 (m, 2H), 4.33-4.40 (m, 1H), 5.34 (m, 1H) 7.10-7.11 (m, 1H), 7.57
- 15 (d, $J=9$ Hz, 1H), 7.98 (s, 1H), 8.09-8.14 (m, 1H), 8.75 (d, $J=5$ Hz, 1H), 12.88 (brs, 1H). ¹³C NMR (DMSO- *d*₆) δ 27.82, 35.84, 51.52, 57.75, 76.03, 79.33, 102.95, 119.54, 123.86, 126.34, 127.24, 134.49, 149.32, 152.88, 153.25, 159.08, 173.74. LC-MS (retention time: 1.48, method D), MS m/e 393 ($M^+ + 1$)

Step 3:

- 20 To a solution of the product (5.11 g, 13 mmol) of Step 2 of Example 371 {Boc-4(*R*)-(7-chloroquinoline-4-oxo) proline}, the HCl salt (3.48 g, 18.2 mmol) of vinyl Acca (existing as a 1:1 mixture of diastereoisomers (1*R*,2*S*/1*S*,2*R* where cyclopropyl carboxyethyl group is syn to vinyl moiety) and NMM (7.1 mL 65 mmol) in DMF (30 mL) was added HATU (6.92 g, 18.2 mmol). The mixture was stirred for 3 days. The
- 25 reaction mixture was diluted with EtOAc (180 mL) and was partitioned with pH 4.0 buffer (3x100 mL). The organic layer was washed with saturated aqueous NaHCO₃ (2x50mL), water (2x50mL), and brine (2x50mL). The organic solution was dried (MgSO₄) and concentrated. The residue was purified over a Biotage 40M column (EtOAc-Hexanes: 50% to 100%) to afford 2.88 g of the product existing as a
- 30 diastereomeric mixture. This mixture was partially separated using a Biotage 65M column (MeOH-EtOAc: 0% to 9%) to afford BOC-NH-P2[(4*R*)-(7-chloroquinoline-4-oxo)-*S*-proline]-P1(1*R*,2*S* vinyl acca P1 moiety)-COOEt as the initial eluted high

Rf isomer (1.20 g, 17.4%). ^1H NMR ($\text{CDCl}_3/\text{Methanol-}d_4$) δ 1.16 (t, $J=7$ Hz, 3H), 1.35 (s, 9H), 1.37-1.43 (m, 1H), 1.76-1.84 (m, 1H), 2.06-2.11 (m, 1H), 2.35-2.45 (m, 1H), 2.63 (m, 1H), 3.72-3.93 (m, 2H), 4.02-4.15 (m, 1H), 4.33-4.40 (m, 1H), 5.06 (d, $J=9$ Hz, 1H), 5.16 (m, 1H), 5.24 (d, $J=17$ Hz, 1H), 5.63-5.70 (m, 1H), 6.74 (m, 1H), 7.39 (dd, $J=9, 2$ Hz, 1H), 7.74-7.78 (m, 1H), 7.89 (d, $J=2$ Hz, 1H), 7.97 (d, $J=9$ Hz, 1H), 8.60 (d, $J=5$ Hz, 1H). ^1H NMR (methanol- d_4 , 60/40 Rotomers) δ 1.24 (t, $J=7$ Hz, 3H), 1.39, 1.43 (2s, 9H, ratio 4:6), 1.71-1.74 (m, 0.4H), 1.78-1.81 (m, 0.6H), 2.18-2.23 (m, 1H), 2.65-2.69 (m, 0.4H), 2.71-2.76 (m, 0.6H), 3.88-3.96 (m, 2H), 4.11-4.18 (m, 2H), 4.39-4.45 (m, 1H), 5.09-5.13 (m, 1H), 5.28-5.33 (m, 1H), 5.37 (m, 1H), 5.73-5.81 (m, 1H), 7.05 (d, $J=5$ Hz, 1H), 7.53 (d, $J=8.9$ Hz, 1H), 7.92 (s, 1H), 8.12 (d, $J=8.9$ Hz, 1H), 8.70 (d, $J=5$ Hz, 1H). LC-MS (retention time: 1.54, method A) MS m/z 530 (M^++1). The rest of the material (~1.66 g, 24%) was mixed fractions greatly enriched in the lower Rf isomer.



Step 4:

The product (0.65 g, 1.22 mmol) of step 3 of Example 371 {BOC-P2 [(4R)-(7-chloroquinoline-4-oxo)-S-proline]-P1(1R,2S Vinyl Acca-CO₂Et)} was dissolved in 4N HCl/dioxane (4.5ml, 18 mmol) and stirred for 1 h at rt. The reaction mixture was concentrated and the crude product was directly used in next step: LC-MS (retention time: 0.94, method A) LC-MS m/z 430 (M^++1).

Step 5:

To suspension of the product 1 (0.22 mmol) of step 4 Example 371 { Bis HCl Salt of $\text{NH}_2\text{-P2}[(4R)\text{-(7-chloroquinoline-4-oxo)-S-proline}]\text{-P1(1R,2S-Vinyl Acca)-COOEt}$, N-BOC-*L-tert-leucine* (BOC *L-tBuGly*) (0.34g, 1.47 mmol), DIPEA (1.0 ml, 5.74 mmol), HOBT.H₂O (0.22g, 1.47 mmol) in CH₂Cl₂ (15mL) was added HBTU (0.56g, 1.47 mmol) at rt. The reaction mixture was stirred overnight, diluted with CH₂Cl₂ (50 mL), washed with pH 4.0 buffer (2x20 mL), saturated aqueous NaHCO₃ (50 mL), brine (50mL), dried (MgSO₄), and concentrated. The residue was purified over a Biotage 40 M column (EtOAc-Hexanes: 15% to 60%) to afford 607 mg (77%) of the product as a foam. ¹H NMR (CDCl₃-methanol-d₄) δ 1.00 (s, 9H), 1.19 (t, *J*=7 Hz, 1H), 1.30 (s, 9H), 1.38 (m, 1H), 1.78-1.83 (m, 1H), 2.01-2.46 (m, 2H), 2.73-2.82 (m, 1H), 3.96-4.03 (m, 1H), 4.04 (d, *J*=10 Hz, 1H), 4.11 (q, *J*=7 Hz, 2H), 4.42 (d, *J*=12 Hz, 1H), 4.68-4.73 (m, 1H), 5.09-5.13 (m, 1H), 5.23-5.31 (m, 2H), 5.67-5.79 (m, 1H), 6.78 (d, *J*=9 Hz, 1H), 7.38 (d, *J*=9 Hz, 1H), 7.70 (s, 1H), 7.96 (s, 1H), 8.08 (d, *J*=9 Hz, 1H), 8.68 (d, *J*=5 Hz, 1H). LC-MS (retention time: 1.64, method A), MS *m/z* 643 (*M*⁺+1).

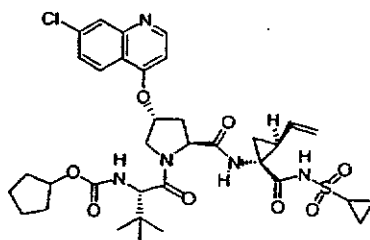
Step 6:

To a suspension of the product (207 mg, 0.32 mmol) of Step 5 of Example 371 {BOCNH P3(*L* : BuGly)-P2[(4*R*)-7-chloroquinoline-4-oxo)-S-proline]-P1(1*R*,2*S* Vinyl Acca)-CO₂Et} in THF(14 mL), CH₃OH (2 mL), and H₂O (8 mL) was added LiOH (62 mg, 2.60 mmol). The reaction mixture was stirred for one day, adjusted to neutral pH, and concentrated *in vacuo* until only the aqueous layer remained. The resulting aqueous residue was acidified to pH 4.0 by addition of 1.0 N aqueous HCl and then saturated with solid NaCl. This aqueous mixture was extracted repeatedly with EtOAc (3X60 mL), the combined organic solvent was dried (Mg₂SO₄) and concentrated *in vacuo* to afford 107 mg (54%) of the product {BOCNH-P3(*L-t*-BuGly)-P2[(4*R*)-(7-chloroquinoline-4-oxo)-S-proline]-P1(1*R*,2*S* Vinyl Acca)-CO₂H} as a white solid. ¹H NMR (CDCl₃) δ 1.06 (s, 9H), 1.23 (2s, 9H), 1.31-1.43 (m 1H), 1.63-1.70 (m, 1H), 1.85-1.89 (m, 1H), 2.19 (m, 1H), 2.65-2.78 (m, 1H), 4.03-4.10 (m, 1H), 4.18-4.21 (m, 1H), 4.55-4.62 (m, 1H), 5.03-5.12 (m, 1H), 5.23-5.31 (m, 1H), 5.51 (m, 1H), 5.88-5.95 (m, 1H), 7.12 (m, 1H), 7.47-7.50 (m, 1H), 7.96 (m, 1H), 8.26 (d, *J*=9 Hz, 1H), 8.75 (d, *J*=5 Hz, 1H). LC-MS (retention time: 1.46, method A), MS *m/z* 615 (*M*⁺+1).

Step 7:

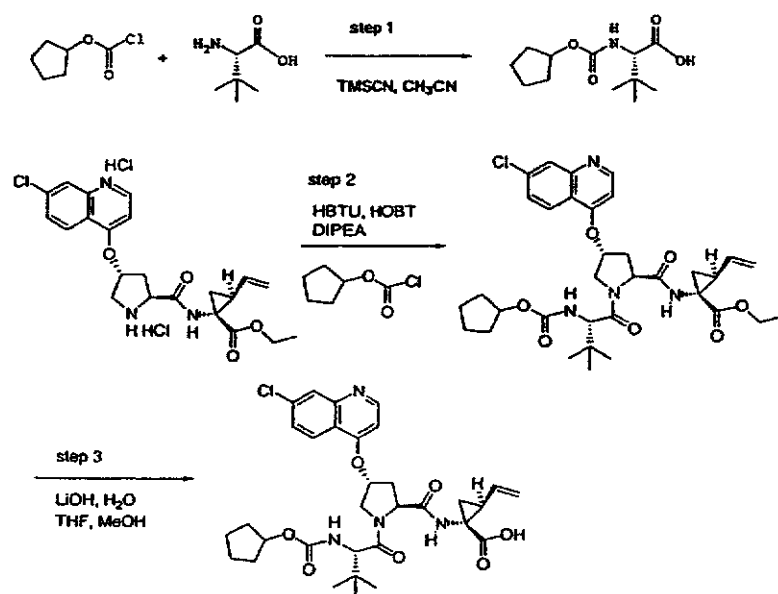
- To a solution of the tripeptide acid (0.0453 g, 0.074 mmol) of Step 6 Example 371 {BOC-NH-P3(*L*-*t*-BuGly)-P2[(4*R*)-(7-chloroquinoline-4-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-CO₂H} in THF (4 mL) was added CDI (17 mg, 0.10 mmol), and the
- 5 resulting solution refluxed for 45 min and allowed to cool down to rt.
- Cyclopropylsulfonamide (0.013g, 0.10 mmol) was added in one portion before the addition of neat DBU (0.015 mL, 0.10 mmol). The reaction was stirred for 18 h, diluted with EtOAc (200mL) and washed pH 4.0 buffer (3x30mL), water (2x30 mL), brine (30mL), dried (MgSO₄) and purified using one 20X40 cm 1000 μ Analtech
- 10 PTLC plate (MeOH - CH₂Cl₂: 0 to 2%) to afford the desired product (Compound 371) as a foam (0.040g, 76%): ¹H NMR δ 0.95-1.23 (m, 4H), 1.03 (s, 9H), 1.19 (s, 9H), 1.40-1.43 (m, 1H), 1.85 (dd, *J*=8, 5 Hz, 1H), 2.12-2.20 (m, 1H), 2.43 (m, 1H), 2.82 (m, 1H), 4.07-4.19 (m, 2H), 4.51-4.57 (m, 2H), 5.07 (d, *J*=10 Hz, 1H), 5.25 (d, *J*=17 Hz, 1H), 5.85 (m, 1H), 5.48 (s, 1H), 7.09 (d, *J*=5 Hz, 1H), 7.45 (d, *J*=9 Hz, 1H),
- 15 7.92 (m, 1H), 8.20 (d, *J*=9 Hz, 1H), 8.72 (d, *J*=5 Hz, 1H); LC-MS (retention time: 1.52, method B), MS *m/z* 718 (*M*⁺+1). HRMS *m/z* (*M*+H)⁺ calcd for C₄₁H₅₁N₅SO₉: 718.2677 found 718.2674.

Example 372: Preparation of Compound 372.



Compound 372

Scheme 1



Step 1:

To a solution of *L*-tert-leucine (2 g, 15.25 mmol) dissolved in CH_3CN (50 mL) was added TMSCN (7.06 mL, 56.41 mmol) and stirred for 15 min. The reaction mixture was heated to 75 °C for 30 min. Cyclopentyl chloroformate (2.83 g, 19.06 mmol) was added to the reaction mixture and the reaction mixture was heated at 80 °C overnight, concentrated in vacuo. The residue was treated with MeOH (40 mL), stirred for 10 min, and concentrated in vacuo. The residue was adjusted pH to 8.5, and extracted with Et_2O (2x200mL). The aqueous layer was acidified to pH 3 and extracted with CH_2Cl_2 (2x200mL). The combined extract was dried (MgSO_4), and concentrated in vacuo. The residue was recrystallized from minimal amount of Et_2O /hexanes to afford the product 3.48 g (94%): ^1H NMR (500 MHz, methanol- d_4) δ ppm 1.00 (s, 9 H), 1.59 (m, 2 H), 1.73 (m, 4 H), 1.84 (dd, $J=5.95, 3.20$ Hz, 2 H), 3.98 (s, 1 H), 5.02 (m, 1 H).

Step 2:

To a solution of the product (530.1 mg, 1.04 mmol) of Step 4 of Example 371 (HCl salt of P2[(4*R*)-7-chloroquinoline-4-oxo]-*S*-proline]-P1(1*R*,2*S* Vinyl Acca) COOEt, the product (328 mg, 1.35 mmol) of Step 1 of Example 372 {(*L*)-2-cyclopentylloxycarbonylamino-3,3-dimethyl-butyrlic acid}, HOBT (146 mg, 1.08 mmol), and diisopropylethylamine (0.755 mL, 4.32 mmol) in CH_2Cl_2 (7 mL) was

added HBTU (512 mg, 1.35 mmol). The reaction mixture was stirred for overnight and partitioned between CH_2Cl_2 and pH 4.0 buffer. The CH_2Cl_2 layer was washed with water, saturated NaHCO_3 (aq.), dried (MgSO_4), concentrated. The residue was purified over a Biotage 40M column (EtOAc-Hexanes: 35-100%) to afford the

5 product 640 mg (92%): ^1H NMR (methanol- d_4) δ ppm 1.02 (s, 9 H), 1.26 (m, 4 H), 1.56 (m, 10 H), 2.19 (q, $J=8.75$ Hz, 1 H), 2.41 (m, 1 H), 2.70 (dd, $J=14.19, 8.09$ Hz, 1 H), 4.01 (dd, $J=11.90, 3.05$ Hz, 1 H), 4.13 (m, 2 H), 4.20 (s, 1 H), 4.53 (m, 1 H), 4.62 (m, 1 H), 5.09 (d, $J=10.38$ Hz, 1 H), 5.26 (d, $J=17.09$ Hz, 1 H), 5.47 (m, 1 H), 5.77 (m, 1 H), 7.07 (d, $J=5.49$ Hz, 1 H), 7.47 (m, 1 H), 7.94 (m, 1 H), 8.20 (d, $J=8.85$

10 Hz, 1 H), 8.72 (d, $J=5.49$ Hz, 1 H). LC-MS (retention time: 1.71, Method B), MS m/z 655 (M^++1).

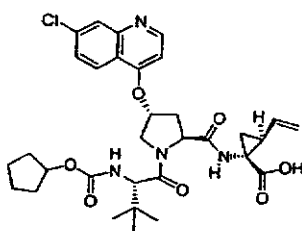
Step 3:

Tripeptide acid was prepared by following Step 7 of Scheme 2 of Example 370, except that cyclopentoxycarbonyl - NH-P3(*L*-*tert*-BuGly)-P2[(4*R*)-(7-

15 chloroquinoline-4-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-COOEt used in place of the product of Step 6 of Example 370.

Modification: 0.636 g (0.97 mmol) of the product of Step 2 of Example 372 used, 0.424 g obtained (69% yield).

Product:

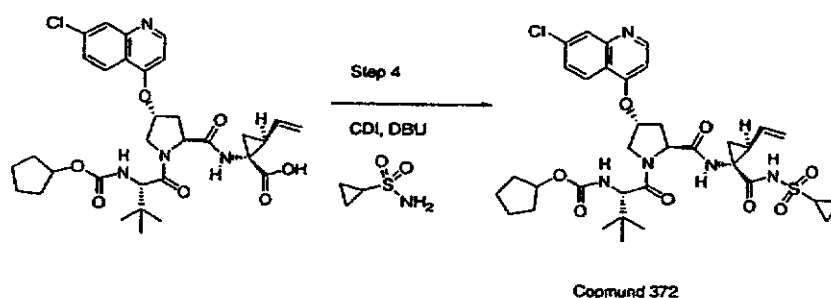


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Data: ^1H NMR (methanol- d_4) δ ppm 1.02 (s, 9 H), 1.57 (m, 11 H), 2.14 (q, $J=9.03$ Hz, 1 H), 2.46 (m, 1 H), 2.68 (m, 1 H), 4.02 (dd, $J=11.89, 3.11$ Hz, 1 H), 4.19 (m, 1 H), 4.50 (d, $J=26.35$ Hz, 1 H), 4.64 (t, $J=8.42$ Hz, 1 H), 5.04 (m, 1 H), 5.24 (d, $J=17.20$ Hz, 1 H), 5.44 (s, 1 H), 5.87 (m, 1 H), 7.05 (d, $J=5.12$ Hz, 1 H), 7.48 (m, 1

25 H), 7.92 (m, 1 H), 8.18 (d, $J=8.78$ Hz, 1 H), 8.71 (d, $J=5.49$ Hz, 1 H). LC-MS (retention time: 2.32, Method A), MS m/z 627 (M^++1).

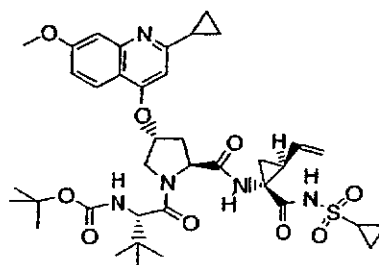
Scheme 2



Step 4:

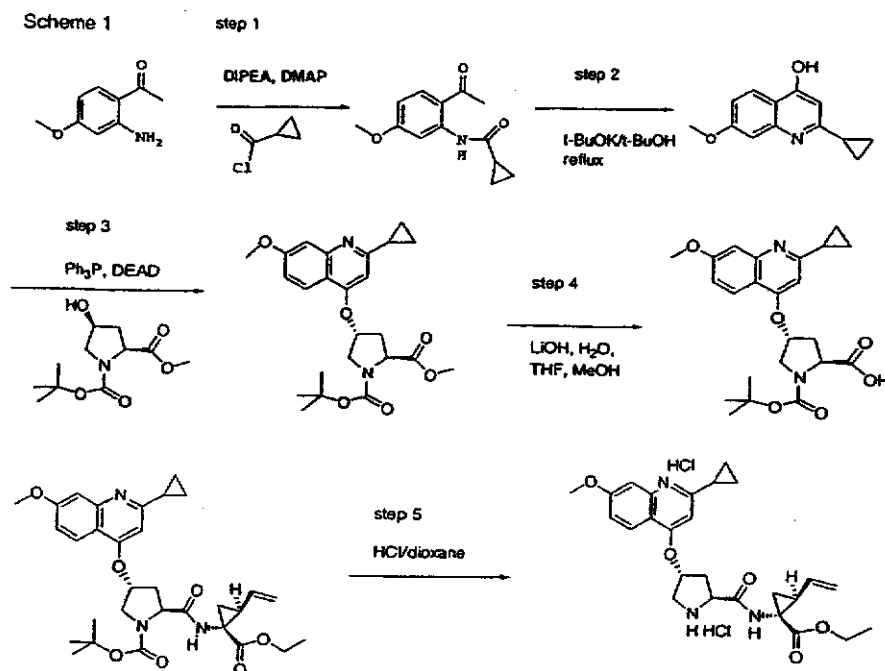
A solution of CDI (0.021 g, 0.13 mmol) and the product of Step 3 of Example 372 (0.058 g, 0.09 mmol) [BOC-NH-P3(*L*-*t*-BuGly)-P2[(4*R*)-7-chloroquinoline-4-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-CO₂H} in THF (2 mL) was refluxed for 40 min and allowed to cool down to rt. A total of 0.016 g (0.13 mmol) of cyclopropanesulfonamide, followed by the addition of a solution of neat DBU (0.019 mL, 0.13 mmol). The reaction was stirred for overnight, then diluted with EtOAc (100 mL) and washed pH 4.0 buffer (2x), dried (MgSO₄), concentrated and purified over three 1000 μ M preparative TLC plate from Analtech (20x40 cm, eluted sequentially with 50% to 0% to 2% MeOH in CH₂Cl₂) to provide product (Compound 372) 27.3 mg (40%). ¹H NMR (methanol-*d*₄) δ ppm: 0.04 (m, 2 H), 1.02 (s, 2 H), 1.14 (m, 1 H), 1.49 (m, 11 H), 1.86 (m, 1 H), 2.14 (m, 1 H), 2.49 (m, 1 H), 2.68 (dd, *J*=13.89, 7.48 Hz, 1 H), 2.78 (m, 1 H), 4.08 (m, 1 H), 4.22 (s, 1 H), 4.55 (m, 2 H), 5.05 (d, *J*=10.07 Hz, 1 H), 5.22 (d, *J*=17.09 Hz, 1 H), 5.46 (m, 1 H), 5.86 (m, 1 H), 7.07 (d, *J*=5.19 Hz, 1 H), 7.46 (d, *J*=8.55 Hz, 1 H), 7.91 (s, 1 H), 8.18 (d, *J*=8.85 Hz, 1 H), 8.72 (d, *J*=5.19 Hz, 1 H). LC-MS (retention time: 1.52 Method I), MS *m/z* 730 (*M*⁺+1).

Example 373: Preparation of Compound 373.



Compound 373

Scheme 1



Step 1:

A solution of 2-amino-4-methoxyacetophenone (4.45 g, 26.94 mmol) at 0 °C dissolved in CH_2Cl_2 (100 mL) was treated with cyclopropanecarbonyl chloride (3.1 mL, 33.68 mmol) diisopropylethylamine (19 mL, 107.8 mmol), DMAP (0.780 g, 6.4 mmol). The reaction mixture was stirred at rt overnight and concentrated in vacuo. The residue dissolved in CH_2Cl_2 (500 mL) was washed with aqueous 1 N HCl, water, NaHCO_3 (aq.), and dried (MgSO_4). The solvent was removed in vacuo and the solid residue was treated with EtOAc/hexanes (1/1) to provide the product (5.35 g, 85%):

^1H NMR (methanol- d_4) δ ppm 0.94 (m, 4 H), 1.69 (m, $J=3.97$ Hz, 1 H), 2.60 (s, 3 H), 3.84 (s, 3 H), 6.69 (d, $J=7.93$ Hz, 1 H), 7.98 (d, $J=8.85$ Hz, 1 H), 8.23 (s, 1 H).

Step 2:

A solution of product (5.35 g, 22.72 mmol) of Step 1 example 373 {cyclopropanecarboxylic acid (2-acetyl-5-methoxy-phenyl)-amide} and *tert*-BuOK (5.45 g, 48.6 mmol) in *tert*-butanol (130 g) was refluxed for 6 h. The reaction mixture was cooled, poured into ice cold buffer and adjusted to pH 7, filtered. The solid collection was recrystallized from MeOH/ Et_2O to provide the product (1 g, 20%): ^1H NMR (methanol- d_4) δ ppm 0.96 (m, 2 H), 1.15 (m, 2 H), 1.94 (m, 1 H), 3.87 (s, 3 H), 5.86 (m, 1 H), 6.93 (m, 2 H), 8.04 (d, $J=8.85$ Hz, 1 H).

Step 3:

To a solution of N-Boc-L-3-hydroxyproline (1.06 g, 4.32 mmol) and triphenylphosphine (2.27 g, 8.64 mmol) at 0 °C dissolved THF (25 mL) was added a solution of the product (0.93 g, 4.32 mmol) of Step 2 Example 373 {2-Cyclopropyl-7-methoxy-quinolin-4-ol} and DEAD (1.50 g, 8.64 mmol) in THF (25 mL) over 30 min. The reaction mixture was stirred overnight and concentrated. The residue was purified twice by a Biotage 40+M column (EtOAc-Hexanes: 20-65%) to afford the product 1.74 g (90%): LC-MS (retention time: 2.56, Method J), MS m/z 443 ($M^+ + 1$).

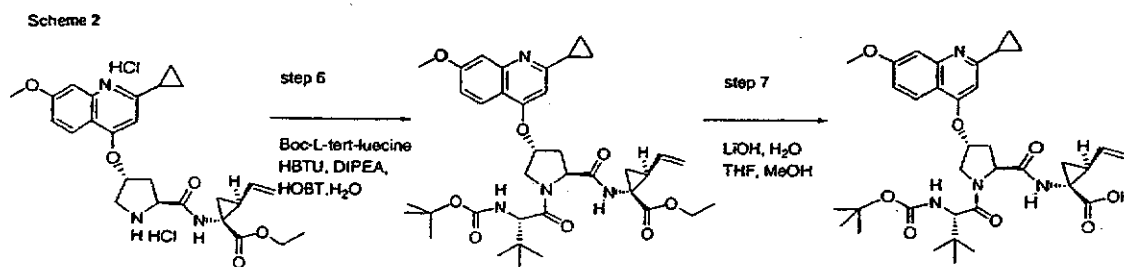
Step 4:

To a suspension of (1.70 g, 3.86 mmol) of the product of Step 3 of Example 373 (Boc-(4R)-(2-cyclopropyl-7-methoxy-quinoline-4-oxo)-S-proline methyl ester} in THF (91 mL), CH₃OH (18.2 mL), and H₂O (27 mL) was added LiOH (0.73 g, 30 mmol). The reaction mixture was stirred for 16 h, adjusted to pH 6, the organic solvent was removed in vacuo. The residue was acidified to pH 4, and extracted with EtOAc (4x100 mL). The combined organic extract was dried (MgSO₄), and concentrated in vacuo to supply the product 1.64 g (100%): ¹H NMR (methanol-d₄) δ ppm 1.32 (m, 13 H), 2.37 (m, 2 H), 2.71 (m, 1 H), 3.86 (m, 1 H), 3.95 (s, 3 H), 4.14 (m, 1 H), 4.43 (m, 1 H), 5.41 (s, 1 H), 6.65 (s, 1 H), 7.19 (m, 1 H), 7.30 (m, 1 H), 8.02 (dd, $J=12.63, 9.33$ Hz, 1 H).

Step 5:

The product (1.61 g, 2.79 mmol) of Step 4 of Example 373 {Boc-P2{(4R)-[2-cyclopropyl-7-methoxyquinoline-4-oxo]-S-proline}-P1(1R,2S Vinyl Acca) COOEt} was dissolved in HCl/dioxane (15 mL; 60 mmol) and stirred for 3 h at rt. The reaction mixture was concentrated and azeotroped with dry THF to afford the product (1.58 g, 100%): LC-MS (retention time: 2.12, Method K), MS m/z 566 ($M^+ + 1$).

25



Step 6:

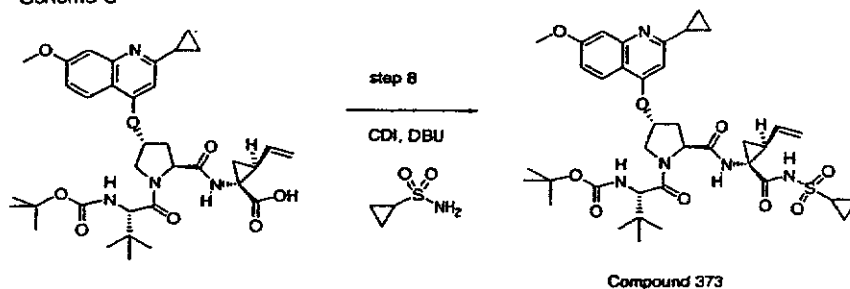
To a suspension of the product (1.58 g, 2.79 mmol) of Step 5 of Example 373 {Bis HCl salt of P2 [(4*R*)-[2- cyclopropyl-7-methoxy]quinoline-4-oxo]-*S*-proline]-P1(1*R*,2*S* Vinyl Acca) COOEt}, diisopropylethylamine (1.65 mL, 9.25 mmol), *N*-Boc-*L*-*tert*-leucine (0.775 g, 3.35 mmol), HOBT.H₂O (0.515 g, 3.36 mmol) in CH₂Cl₂ (13 mL) was added HBTU (1.28 g, 3.36 mmol). The mixture was stirred for 14 h and partitioned between EtOAc and pH 4.0 buffer. The EtOAc layer was dried (MgSO₄), concentrated. The residue was purified over a Biotage 40+M column (EtOAc-hexanes: 20-100%, followed MeOH) and further purified by 20X40 cm 1000 μ Analtech PTLC plate (MeOH-CH₂Cl₂ 2%) to afford the product 1.4 g (63%):

¹H NMR (methanol-d₄) δ ppm 1.04 (s, 9 H), 1.20 (m, 5 H), 1.28 (s, 9 H), 1.39 (m, 2 H), 1.69 (m, 1 H), 2.19 (m, 2 H), 2.36 (m, 1 H), 2.63 (dd, *J*=13.54, 7.68 Hz, 1 H), 3.90 (s, 3 H), 4.08 (m, 4 H), 4.19 (d, *J*=11.34 Hz, 1 H), 4.47 (d, *J*=11.71 Hz, 1 H), 4.56 (t, *J*=8.60 Hz, 1 H), 5.08 (m, 1 H), 5.24 (m, 1 H), 5.39 (s, 1 H), 5.78 (m, 1 H), 6.56 (s, 1 H), 6.96 (dd, *J*=9.15, 2.20 Hz, 1 H), 7.21 (d, *J*=2.56 Hz, 1 H), 7.97 (d, *J*=9.15 Hz, 1 H). LC-MS (retention time: 2.34, Method K), MS *m/z* 679 (*M*⁺+1).

Step 7:

To a suspension of the product of Step 6 of Example 373 (1.28 g, 1.89 mmol), Boc - NH-P3(*L*-*tert*-BuGly)-P2[(4*R*)-(2- cyclopropyl-7-methoxy]quinoline-4-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-COOEt, in THF(93 mL), CH₃OH (23 mL), and H₂O (45 mL) was added LiOH (0.491 g, 20.4 mmol). The reaction mixture was stirred for 18.5 h, adjusted to pH 4, removed the organic solvent in vacuo. The residue was extracted with EtOAc (5x 100mL). Combined organic solvent was dried (MgSO₄), and concentrated in vacuo to afford the desired product 1.17 g (97%): ¹H NMR (methanol-d₄) δ ppm 1.04 (s, 9 H), 1.24 (s, 9 H), 1.27 (m, 3 H), 1.42 (m, 2 H), 1.68 (dd, *J*=8.05, 5.12 Hz, 1 H), 2.17 (m, 1 H), 2.33 (m, 1 H), 2.47 (m, 1 H), 2.66 (m, 1 H), 3.95 (s, 3 H), 4.09 (m, 2 H), 4.51 (d, *J*=11.71 Hz, 1 H), 4.59 (t, *J*=8.60 Hz, 1 H), 5.07 (m, 1 H), 5.26 (m, 1 H), 5.52 (s, 1 H), 5.85 (m, 1 H), 6.69 (s, 1 H), 7.10 (dd, *J*=9.15, 2.20 Hz, 1 H), 7.27 (d, *J*=2.20 Hz, 1 H), 8.10 (d, *J*=9.15 Hz, 1 H). LC-MS (retention time: 2.21, Method K), MS *m/z* 651 (*M*⁺+1).

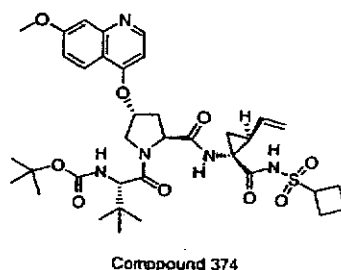
Scheme 3

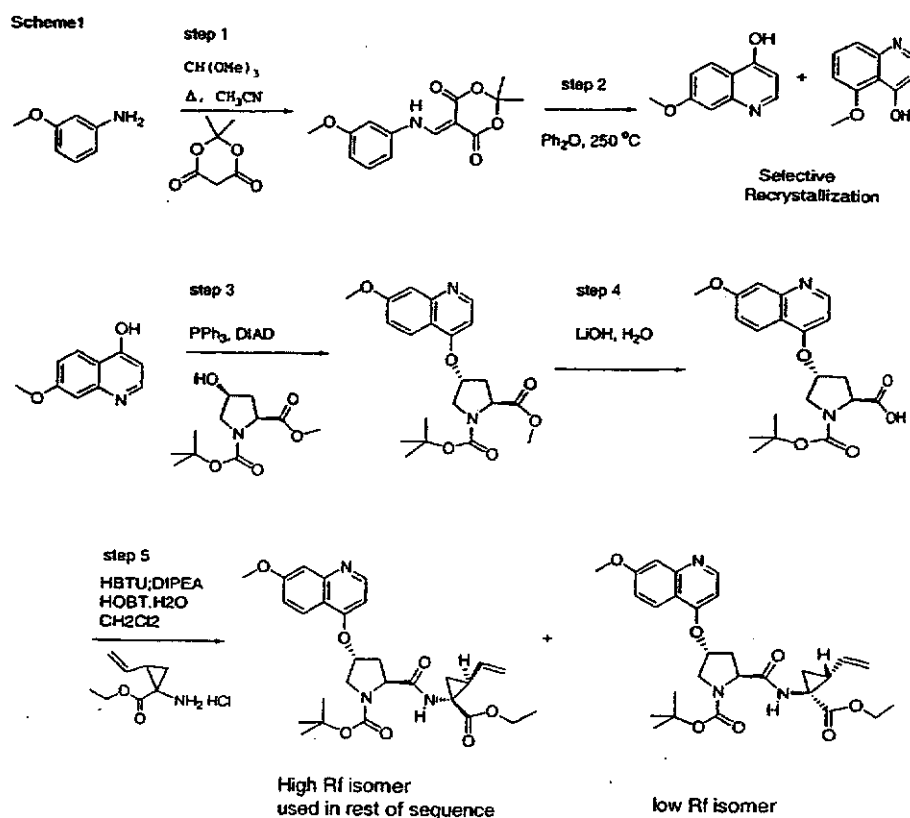


Step 8:

A solution of CDI (0.058 g, 0.344 mmol) and the product of Step 7 of Example 373 (0.160 g, 0.246 mmol) {Boc - NH-P3(*L*-*tert*-BuGly)-P2[(4*R*)-(2-cyclopropyl-7-methoxyquinoline-4-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-COOH} in THF (2 mL) was refluxed for 60 min and allowed to cool down to rt. Cyclopropanesulfonamide (0.041 g, 0.344 mmol) followed by the addition of neat DBU (0.051 mL, 0.344 mmol). The reaction was stirred for 24 h and worked up by partition the reaction mixture between pH 4.0 buffer and EtOAc. The organic layer was dried (MgSO₄), concentrated and purified by preparative HPLC (0-100% solvent B) to supply the product (Compound 373) 0.086 g (46%): ¹H NMR (TRIFLUOROACETIC ACID-D) δ ppm 1.04 (s, 9 H), 1.21 (m, 16 H), 1.41 (m, 1 H), 1.87 (dd, *J*=8.05, 5.49 Hz, 1 H), 2.26 (m, 3 H), 2.61 (dd, *J*=12.99, 6.77 Hz, 1 H), 2.93 (m, 1 H), 3.92 (s, 3 H), 4.09 (m, 1 H), 4.21 (m, 1 H), 4.49 (m, 2 H), 5.11 (d, *J*=11.71 Hz, 1 H), 5.27 (d, *J*=17.20 Hz, 1 H), 5.46 (s, 1 H), 5.76 (m, 1 H), 6.62 (m, 2 H), 7.01 (dd, *J*=8.97, 2.01 Hz, 1 H), 7.23 (d, *J*=2.56 Hz, 1 H), 8.00 (d, *J*=8.78 Hz, 1 H).

Example 374: Preparation of Compound 374.





Step 1:

To a solution of *m*-anisidine (58 g, 471 mmol) in 800 mL of CH_3CN was added Meldrum's acid (75g, 518 mmol), and trimethylformate (60g, 565 mmol). The heterogeneous mixture was refluxed for 2 h. The solvent was removed in vacuo, MeOH (30 mL) was added, and the resulting precipitate was filtered and washed with 10-15 mL of MeOH. The MeOH addition/filtration procedure was repeated on the concentrated mother liquor. The resulting combined solid was dried (~20 torr, 45°C overnite) to afford 117.6 g (90%) of the intermediate 5-[(3-Methoxyphenyl-amino)methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione.

Step 2:

To a solution of Ph_2O (500 g) heated to 250°C was added 108.7g (392 mmol) of 5-[(3-Methoxyphenyl-amino)methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione in portions over a 30 min period. The mixture was heated an additional 15 min, cooled to rt, diluted with hexanes (800 mL) and the resulting slurry stirred overnite. The hexanes was decanted off, the solid residue dissolved in 600 mL of MeOH at reflux, cooled to rt and the resulting solid filtered and washed with minimal CH_2Cl_2 . The

analogous recrystallization procedure was followed to afford a total of 20.73 g (30%) of 7-methoxyquinolin-4-ol as a light brown solid. ^1H NMR (methanol- d_4) δ 3.87 (s, 3H), 6.23 d, $J=7.3$ Hz, 1H), 6.68 (d, $J=2.4$ Hz, 1H), 6.96 (dd, $J=9.0$, 2.4 Hz, 1H), 8.11 (d, $J=9$ Hz, 1H); LC-MS (retention time: 0.77, method D), MS m/z 176 (M^++1).

5 Step 3:

To a solution of) of *N*-Boc-*cis*-*L*-4-Hydroxyproline methyl ester (12.24 g, 49.8 mmol) and PPh_3 (26.14 g, 99.7 mmol) in THF (200 mL) cooled to 0 °C was added a solution of DEAD (17.36 g, 99.7 mmol) and 7-methoxyquinolin-4-ol (8.73 g, 49.8 mmol) in (THF 700 mL) over a 45 min period. The mixture was slowly allowed to
10 warm to rt overnite, concentrated in vacuo. The residue was purified over a Biotage 65M column (MeOH-EtOAc: 0-10%) to afford 12.78g (64%) of the product as a colorless glass: ^1H NMR (CDCl_3) δ 1.36 (s, 9H), 2.26-2.35 (m, 1H), 2.57-2.68 (m, 1H), 3.71 (s, 3H), 3.75-3.92 (m, 2H), 3.86, 3.87 (two s (rotamers) 3H), 4.41-4.53 (m, 1H), 5.09 (m, 1H), 6.52 (d, $J=5.5$ Hz, 1H), 7.06-7.09 (m, 1H), 7.24-7.26 (m, 1H),
15 7.94 (d, $J=9.1$ Hz, 1H), 8.50-8.56 (m, 1H); LC-MS (retention time: 1.34, method D), MS m/e 403 (M^++1).

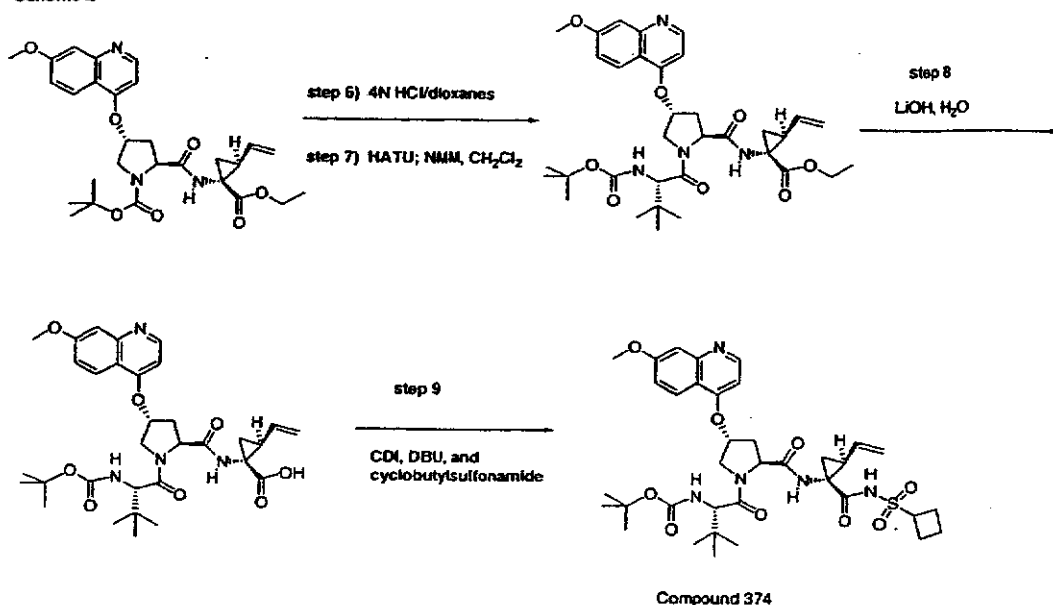
Step 4:

To a solution of the product (8.54 g, 21.2 mmol) of step 3 of Example 374 (BOC-*N*-P2[(4*R*)-(7-methoxyquinoline-4-oxo) proline methyl ester] in 600 mL of 5:1
20 THF/MeOH was added a solution of LiOH (4.0 g, 167 mmol) in 150 mL of water. The mixture was stirred overnite, the pH was adjusted to pH 7 using 6N aqueous HCl, and the solution concentrated until only the water layer remained. The residue was adjusted to pH 4 using 1N aqueous HCl, NaCl added to saturate the mixture and was partitioned repeatedly with first EtOAc and then THF as the product was
25 aqueous soluble. The combined organic layers were dried (MgSO_4) and concentrated to afford the product 8.18 g (99%) as a white solid. ^1H NMR (CDCl_3 -Methanol- d_4) δ 1.42 (s, 9H), 2.40-2.49 (m, 1H), 2.68-2.77 (m, 1H), 3.88 (m, 2H), 3.94 (s, 3H), 4.41-4.53 (m, 1H), 5.32 (m, 1H), 6.86-6.92 (m, 1H), 7.21 (dd, $J=9$, 2 Hz, 1H), 7.30 (d, $J=2$ Hz, 1H), 8.05-8.10 (m, 1H), 8.62 (d, $J=6$ Hz, 1H); LC-MS (retention time 1.20,
30 method A), MS m/z 389 (M^++1).

Step 5:

To a solution of the product (4.50 g, 11.60 mmol) of Step 4 of Example 374 {Boc-4(*R*)-(7-methoxyquinoline-4-oxo) proline}, 2.66 g (13.9 mmol) of the HCl salt of vinyl Acca (existing as a 1:1 mixture of diastereoisomers (1*R*,2*S*/1*S*,2*R* where cyclopropyl carboxyethyl group is syn to vinyl moiety), 10 mL (57.4 mmol) of
5 DIPEA, and 2.13 g (13.9 mmol) of HOBT.H₂O in 150 mL of CH₂Cl₂ was added 5.27 g (13.9 mmol) of HBTU, and the mixture stirred overnight. The solution was diluted with 200 mL of CH₂Cl₂ and was partitioned with pH 4.0 buffer (2x50 mL). The organic layer was washed with saturated aqueous NaHCO₃ (2x50mL), water (2x50mL), and brine (2x50mL). The organic solution was dried (MgSO₄),
10 concentrated and purified using a Biotage 65M column (eluted with 0- 9% MeOH/EtOAc) to provide of BOC-NH-P2[(4*R*)-(7-methoxyquinoline-4-oxo)-*S*-proline]-P1(1*R*,2*S* vinyl acca P1 moiety)-COOEt as the initial eluted isomer (2.21 g, 36% overall), followed by 1.13 g (19%) of pure lower R_f isomer BOC-NH-P2[(4*R*)-(7-methoxyquinoline-4-oxo)-*S*-proline]-P1(1*S*,2*R* Vinyl Acca P1 moiety)-CO₂Et.
15 Mixed fractions were also obtained. Data for BOCN-P2[(4*R*)-(7-methoxyquinoline-4-oxo)-*S*-proline]-P1(1*R*,2*S*)-(VinylAcca)-COOEt: ¹H NMR (CDCl₃) δ 1.16 (t, *J*=7 Hz, 3H), 1.35 (s, 9H), 1.37-1.47 (m, 1H), 1.74-1.88 (m, 1H), 2.04-2.13(m, 1H), 2.32-2.46(m, 1H), 2.58-2.69 (m, 1H), 3.76 (m, 1H), 3.87 (s, 3H), 4.02-4.13 (m, 2H), 4.30-4.44 (m, 1H), 5.05-5.19 (m, 2H), 5.24 (d, *J*=17 Hz, 1H), 5.63-5.71 (m, 1H), 6.61 (m,
20 1H), 7.07 (dd, *J*=9, 2Hz, 1H), 7.22 (d, *J*=2 Hz, 1H), 7.76-7.83 (m, 1H), 7.92 (d, *J*=9 Hz, 1H), 8.50 (d, *J*=5 Hz, 1H). LC-MS (retention time: 1.38, method A), MS *m/z* 526 (M⁺+1).

Scheme 2



Step 6:

A total of product (1.35 g, 2.90 mmol) of Step 5 of Example 374 {BOC-P2 [(4*R*)-(7-methoxyquinoline-4-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-COOEt} was dissolved in 4N HCl/dioxane (15ml, 60 mmol) and was stirred for 2.5 h at rt. The reaction mixture was concentrated in vacuo to supply 1.3 g (100%) of the product as a tan solid which was directly used in next step. ¹H NMR (methanol-*d*₄) δ 1.25 (t, *J*=7 Hz, 1H), 1.47-1.52 (m, 1H), 1.78 (dd, *J*=8, 5 Hz, 1H), 2.21-2.32 (m, 1H), 2.55-2.64 (m, 1H), 2.99 (dd, *J*=15, 7 Hz, 1H), 3.96 (s, 2H), 4.06 (s, 3H), 4.14 (q, *J*=7 Hz, 2H), 4.69-4.75 (m, 1H), 5.13 (d, *J*=10 Hz, 1H), 5.33 (d, *J*=17 Hz, 1H), 5.71-5.83 (m, 1H), 5.89 (m, 1H), 7.44 (m, 1H), 7.49-7.52 (m, 1H), 8.51-8.55 (m, 1H), 8.94-8.96 (m, 1H); ¹³C NMR (methanol-*d*₄) δ 14.62, 23.08, 30.89, 34.73, 36.97, 41.03, 52.42, 57.11, 60.17, 62.70, 81.13, 100.06, 103.07, 117.02, 118.53, 122.70, 126.86, 134.74, 143.15, 146.75, 166.62, 167.71, 169.37, 171.18. LC-MS (retention time: 0.94, method D), MS *m/z* 426 (*M*⁺+1)

Step 7:

To suspension of product (1.3 g, 2.61 mmol) of Step 6 of Example 374 {NH₂-P2[(4*R*)-(7-methoxyquinoline-4-oxo)-*S*-proline]-P1(1*R*,2*S*-Vinyl Acca)-COOEt, Bis HCl Salt}, *N*-BOC-*L*-*tert*-leucine (BOC *L*-*t*BuGly) (0.94 g, 4.25 mmol), NMM (1.7 ml, 15.5 mmol) in DMF (20mL) was added HATU (1.55g, 3.40 mmol) at rt. The reaction mixture was stirred overnight, diluted with 75% EtOAc-THF (300 mL),

washed with pH 4.0 buffer (2x50 mL), saturated aqueous NaHCO₃ (50 mL), brine (50mL), dried (MgSO₄), purified by a Biotage 40 M column (eluted with 15% to 100% EtOAc in Hexanes) to supply the product 0.702 g (42%) {BOCNH-P3(*L*-*t*-BuGly)-P2[(4*R*)-(7-methoxyquinoline-4-oxo)-*S*-proline]-P1-CO₂Et as a foam. ¹H NMR (Methanol-d₄) δ 1.06 (s, 9H), 1.22-1.32 (m, 3H), 1.28 (s, 9H), 1.42-1.46 (m, 1H), 1.73 (dd, *J*=8, 5 Hz, 1H), 2.19-2.25 (m, 1H), 2.67-2.72(m, 1H), 3.95 (s, 3H), 4.03-4.07(m, 1H), 4.10-4.18 (m, 2H), 4.20-4.24 (m, 1H), 4.54 (d, *J*=12 Hz, 1H), 4.60-4.63 (m, 1H), 5.11 (dd, *J*=10, 2 Hz, 1H), 5.28-5.30 (m, 1H), 5.43 (m, 1H), 5.76-5.83 (m, 1H), 6.50 (d, *J*=9 Hz, NH), 6.93 (d, *J*=5 Hz, 1H), 7.10 (dd, *J*=9, 2 Hz, 1H), 7.28 (m, 1H), 7.99 (m, 1H), 8.11 (d, *J*=9 Hz, 1H), 8.62 (d, *J*=5H); LC-MS *m/z* 639 (retention time: 1.53 method D).

Step 8:

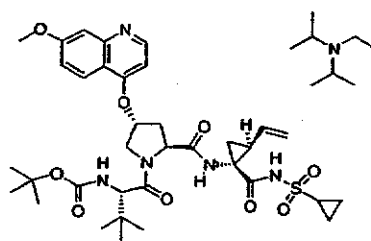
To a suspension of product (702 mg, 1.1 mmol) of Step 7 of Example 374 {BOCNH-P3(*L*-*t*-BuGly)-P2[(4*R*)-7-methoxyquinoline-4-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-COOEt} in THF (50 mL), CH₃OH (7 mL), and H₂O (22 mL) was added LiOH (211 mg, 8.80 mmol). The reaction mixture was stirred for one day, acidified to neutral pH, and concentrated *in vacuo* until only the aqueous layer remained. The resulting aqueous residue was acidified to pH 4.0 by addition of 1.0 N aqueous HCl and then saturated with solid NaCl. This aqueous mixture was extracted repeatedly with EtOAc and THF, the combined organic solvent washed with brine (50 mL), dried (MgSO₄), filtered, and concentrated *in vacuo* to supply the product 631 mg (92%), BOCNH-P3(*L*-*t*-BuGly)-P2[(4*R*)-(7-methoxyquinoline-4-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-CO₂H, as a solid. ¹H NMR (Methanol-d₄) δ 1.04 (s, 9H), 1.22 (s, 9H), 1.34-1.39 (m, 1H), 1.67 (dd, *J*=8, 5 Hz, 1H), 2.03-2.13 (m, 1H), 2.43-2.49 (m, 1H), 2.67-2.73 (m, 1H), 3.96 (s, 3H), 4.00-4.05 (m, 1H), 4.15-4.21 (m, 1H), 4.56-4.62 (m, 2H), 5.02 (d, *J*=10 Hz, 1H), 5.20 (d, *J*=17 Hz, 1H), 5.52 (m, 1H), 5.87-5.99 (m, 1H), 6.47 (d, *J*=8 Hz, 1H), 6.91 (s, 1H), 7.12 (d, *J*=5 Hz, 1H), 7.19 (dd, *J*=9, 2 Hz, 1H), 7.31 (d, *J*=2 Hz, 1H), 8.22 (d, *J*=9 Hz, 1H), 8.72 (d, *J*=5 Hz, 1H). LC-MS (retention time: 1.44, method D), MS *m/z* 611 (*M*⁺+1).

Step 9:

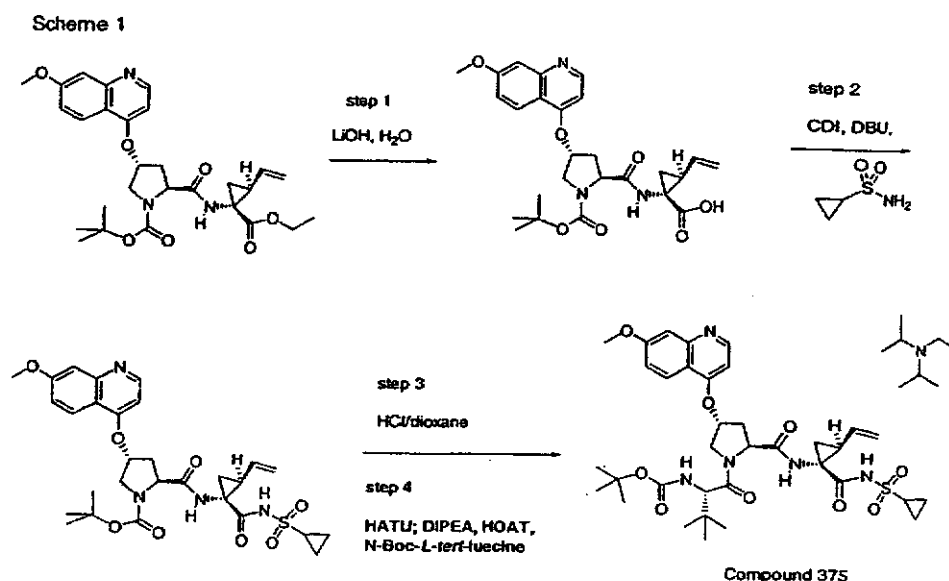
To a solution of the tripeptide acid (0.120 g, 0.195 mmol) of Step 8 of Example 374 in THF (2 mL) was added CDI (44.3 mg, 0.27 mmol) and the resulting solution was

refluxed for 60 min and allowed to cool down to rt. Cyclobutylsulfonamide (0.037 g, 0.273 mmol) was added in one portion before the addition of neat DBU (0.041 mL, 0.273 mmol). The reaction was stirred for 24 h, another one equivalent of CDI and cyclobutylsulfonamide added and the mixture stirred 48h more. The mixture was
 5 diluted with 50% THF/EtOAc (200mL) and washed brine saturated pH 4.0 buffer (30mL), dried (MgSO₄) and concentrated in vacuo. The residue was dissolved in 2 mL of 50% THF-CH₂Cl₂, 75 mg (0.39 mmol) of EDAC, 48 mg (0.39 mmol) of 4-DMAP, 58 μ L (0.39 mmol) of DBU and 53 mg (0.39 mmol) of cyclobutylsulfonamide added, and the mixture stirred 4 days. The mixture was
 10 purified by one 1000 μ Analtech PTLC plate (20 X 40 cm, eluted with 2% MeOH in CH₂Cl₂) to supply the desired product **Compound 374**, BOCNH-P3(L-t-BuGly)-P2[(4R)-(7-methoxyquinoline-4-oxo)-S-proline]-P1(1R,2S Vinyl Acca)-CONHSO₂-Cyclobutane, as a foam 2 mg (2%): ¹H NMR (methanol-d₄) δ 1.07, 1.08 (two s (rotamers) 9H), 1.20, 1.21 (two s (rotamers) 9H), 1.41-1.48 (m, 1H), 1.64-1.70 (m, 1H),
 15 1H), 1.72-1.91 (m, 2H), 1.95-2.11 (m, 2H), 2.23-2.37 (m, 2H), 2.40-2.58 (m, 2H), 2.72-2.75 (m, 1H), 4.06 (s, 3H), 4.12-4.17 (m, 2H), 4.35-4.38 (m, 1H), 4.58-4.62 (m, 1H), 4.65-4.70 (m, 1H), 5.16-5.18 (m, 1H), 5.24-5.37 (m, 1H), 5.69-5.76 (m, 2H), 7.40-7.46 (m, 3H), 8.35-8.40 (m, 1H), 8.92 (d, *J*=7 Hz, 1H). LC-MS (retention time: 1.58 method B), MS *m/z* 728 (M⁺+1).

20

Example 375: Preparation of Compound 375:

Compound 375



Step 1:

To a solution of product (794 mg, 1.51 mmol) of Step 5 of Example 374 {N-BOC-P2[(4R)-(7-methoxyquinoline-4-oxo)-S-proline]-P1(1R,2S VinylAcCa)-CO₂Et} in 68 mL of 12% MeOH/THF was added a solution of 218 mg (9.08 mmol) of lithium hydroxide in 30 mL of water and the mixture was stirred 16 h. The pH was adjusted to neutral by addition of 6N aqueous HCl, concentrated until only the water remained, the solution adjusted to pH 4 using aqueous 1N HCl and was then extracted with 50% THF-EtOAc (5x200-mL portions). The combined organic layers were dried (MgSO₄) and concentrated to provide the product 752 mg (100%) {N-BOC-P2[(4R)-(7-methoxyquinoline-4-oxo)-S-proline]-P1(1R,2S VinylAcCa)-CO₂H}:
¹H NMR (Methanol-d₄) δ 1.37-1.43 (m, 1H), 1.39 (s, 9H), 1.69-1.78 (m, 1H), 2.16-2.24 (m, 1H), 2.44-2.54 (m, 1H), 2.64-2.74 (m, 1H), 3.89-3.94 (m, 2H), 3.96 (s, 3H), 4.40-4.43 (m, 1H), 5.11 (d, J=10 Hz, 1H), 5.31 (d, J=17 Hz, 1H), 5.40 (m, 1H), 5.79-5.87 (m, 1H), 6.91 (s, 1H), 7.04 (d, J=6 Hz, 1H), 7.25 (dd, J=9.1, 2 Hz, 1H), 7.29 (m, 1H), 8.09 (d, J=9.1 Hz, 1H), 8.66 (d, J=6 Hz, 1H). LC-MS (retention time: 1.05, method H). MS *m/z* 498 (M⁺+1).

Step 2:

To a solution of product (399.5 mg, 0.668 mmol) of Step 1 of Example 375 {N-BOC-P2[(4R)-(7-methoxyquinoline-4-oxo)-S-proline]-P1(1R,2S VinylAcCa)-CO₂H} in THF (4 mL) and CDI (434 mg, 2.68 mmol) was refluxed for 60 min and allowed to cool down to rt. Cyclopropylsulfonamide (406 mg, 3.35 mmol) was added in one

portion before the addition of neat DBU (0.50 mL, 3.35 mmol). The reaction was stirred for 16 h, diluted with 50% THF-EtOAc (200mL) and washed with brine saturated pH 4.0 buffer (2x40mL). Organic layer was dried (MgSO₄), concentrated, and purified over a Biotage 25M column (MeOH in CH₂Cl₂, 0% to 15%) to supply 5 217 mg (54%) of the desired product [N-BOC-P2[(4R)-(7-methoxyquinoline-4-oxo)-S-proline]-P1(1R,2S Vinyl Acca)-CONHSO₂Cyclopropane}: ¹H NMR (Methanol-d₄) δ 1.01-1.10 (m, 2H), 1.11-1.18 (m, 1H), 1.20-1.27 (m, 1H), 1.39-1.48 (m, 1H), 1.44 (s, 9H), 1.87 (dd, *J*=8, 5 Hz, 1H), 2.01-2.38 (m, 2H), 2.57 (dd, *J*=14, 7 Hz, 1H), 2.91-2.96 (m, 1H), 3.83-3.92 (m, 2H), 3.94 (s, 3H), 4.36-4.39 (m, 1H), 5.11 (d, *J*=10 10 Hz, 1H), 5.29 (d, *J*=17 Hz, 1H), 5.38 (m, 1H), 5.74-5.81 (m, 1H), 6.91 (d, *J*=5.5 Hz, 1H), 7.20 (dd, *J*=9.2, 2.4 Hz, 1H), 7.29 (m, 1H), 8.07 (d, *J*=9.2 Hz, 1H), 8.60 (d, *J*=5.5 Hz, 1H). LC-MS (retention time: 1.28, method I). MS *m/z* 601 (M⁺+1)

Steps 3:

A total of product (198 mg, 0.33 mmol) of Step 2 of Example 375 {BOC-P2[(4R)- 15 (7-methoxyquinoline-4-oxo)-S-proline]-P1(1R,2S Vinyl Acca)-CONHSO₂Cyclopropane} was dissolved in 4N HCl/dioxane (4ml, 16 mmol) and stirred for 2h at rt. The reaction mixture was concentrated to supply the crude product as a tan solid which was used immediately in the next reaction.

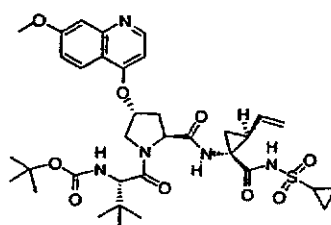
Step 4:

20 The crude product of Step 3 of Example 375 {HN-P2[(4R)-(7-methoxyquinoline-4-oxo)-S-proline]-P1(1R,2S Vinyl Acca)-CONHSO₂Cyclopropane, Bis HCl Salt} was suspended in 10 mL of dichloromethane. To this mixture was added *N*-BOC-*L*-tert-leucine (BOC *L*-tBuGly) [120 mg, 0.52 mmol], HOAT (30 mg, 0.20 mmol), DIPEA (0.29 ml, 1.65 mmol), and HATU (160 mg, 0.43 mmol) at rt. The reaction mixture 25 was stirred for 16 h, diluted with 50% EtOAc-THF (300 mL), washed with brine saturated pH 4.0 buffer (3x50 mL), dried (MgSO₄), concentrated. The residue was purified by a Isco 35g column (eluted with 0% to 15% MeOH in CH₂Cl₂) to supply the product (130.1 mg, 47%) as a Hunning's base salt (Compound 375): ¹H NMR (methanol-d₄) δ ppm 1.00-1.48 (m, 29 H), 1.47 (s, 9 H), 1.89 (m, 1 H), 2.26 (m, 1 H), 30 2.36 (m, 1 H), 2.69 (m, 1 H), 2.97 (m, 1 H), 3.25 (q, *J*=7.43 Hz, 2 H), 3.74 (m, 2 H), 3.97 (s, 3 H), 4.10 (m, 1 H), 4.23 (dd, *J*=19.68, 9.92 Hz, 1 H), 4.57 (m, 2 H), 5.15 (m, 1 H), 5.31 (m, 1 H), 5.50 (s, 1 H), 5.77 (m, 1 H), 7.01 (t, *J*=5.34 Hz, 1 H), 7.16 (d,

$J=9.16$ Hz, 1 H), 7.31 (d, $J=1.83$ Hz, 1 H), 8.14 (m, 1 H), 8.67 (d, $J=5.49$ Hz, 1 H).

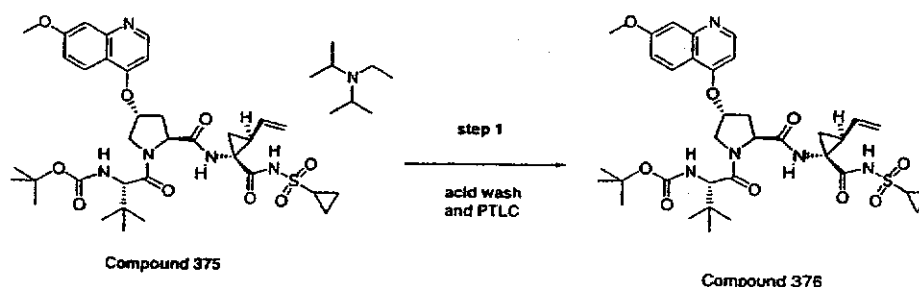
LC-MS (retention time: 1.49 Method d), MS m/z 714 (M^++1).

Example 376: Preparation of Compound 376.



Compound 376

Scheme 1

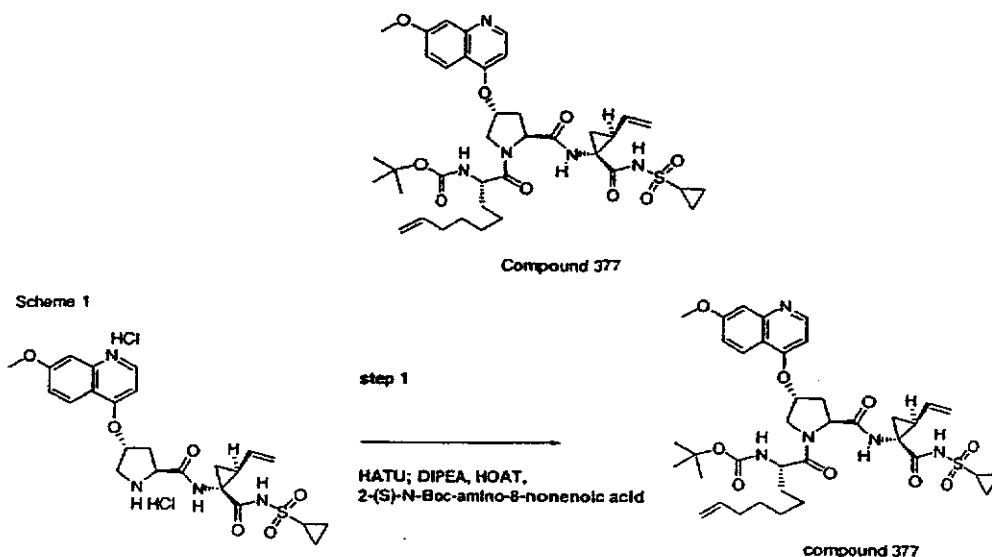


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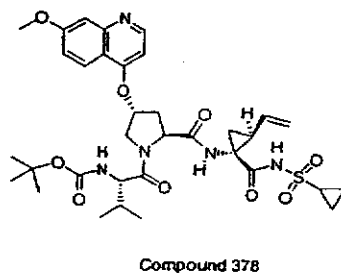
Step 1:

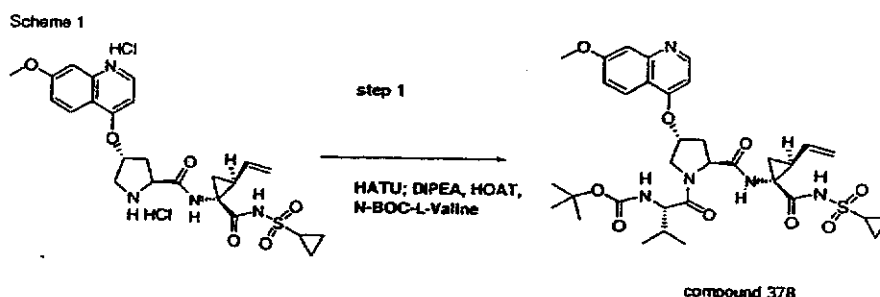
Of Compound 375 (130 mg) was dissolved in EtOAc, washed one more time with pH 4 buffer, brine and then dried ($MgSO_4$). The crude mixture was purified over two 1000 $\square$ PTLC plate from Analtech (20X40 cm, eluted with 3% MeOH in CH_2Cl_2) to afford the product (Compound 376) 54 mg (23% yield from the tripeptide acid): ^1H NMR (Methanol- d_4) δ 0.88-1.00(m, 2H), 1.01-1.14 (m, 2H), 1.03 (s, 9H), 1.25 (s, 9H), 1.34 (dd, $J=9, 5$ Hz, 1 H), 1.81-1.89 (m, 1H), 2.06-2.13 (m, 1H), 2.45-2.50 (m, 1H), 2.65-2.75 (m, 1H), 3.91 (s, 3H), 3.98-4.11 (m, 1H), 4.21-4.22 (m, 1H), 4.46-4.50 (m, 1H), 4.54-4.57 (m, 1H), 4.97-5.02 (m, 1H), 5.14-5.22 (m, 1H), 5.33-5.41 (m, 1H), 5.81-5.99 (m, 1H), 6.87-6.95 (m, 1H), 7.06-7.09 (m, 1H), 7.25 (m, 1H), 8.07-8.10 (m, 1H), 8.59 (d, $J=5.2$ Hz, 1H). HRMS m/z ($M-H$) $^-$ calcd. for $C_{35}H_{46}N_5O_9S$: 712.3016, found: 712.3024; LC-MS m/e 714 (retention time: 1.42, method I).

15

Example 377: Preparation of Compound 377.**Step 1:**

- 5 A total of 1.0 mmol the product of Step 2 of Example 375 {The Bis HCl Salt of HN-P2[(4*R*)-(7-methoxyquinoline-4-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acce)-CONHSO₂Cyclopropane} suspended in 20 mL of dichloromethane was added 352 mg (1.30 mmol) of 2-(*S*)-*tert*-butoxycarbonylamino-8-nonenic acid purchased from KSP AMINO ACIDS, HOAT (82 mg, 0.00 mmol), DIPEA (0.14 mL, 0.0 mmol), and
- 10 HATU (494 mg, 1.30 mmol) at rt. The reaction mixture was stirred 16 h, and the majority of the CH₂Cl₂ removed in vacuo. The mixture was diluted with saturated pH 4.0 buffer (150 mL), and extracted into EtOAc (4x200 mL). The combined organic layers were dried (MgSO₄), concentrated. The residue was purified over a Biotage 40M column (eluted with 0% to 15% MeOH in CH₂Cl₂) to afford the
- 15 product (**Compound 377**) 574 mg (76%); LC-MS *m/z* 754 (retention time: 1.64, method I).

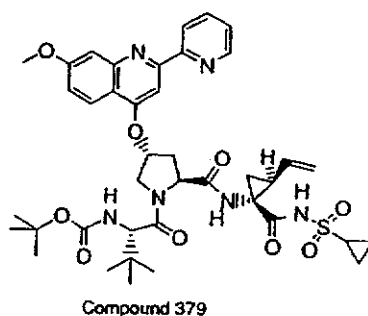
Example 378: Preparation of Compound 378.



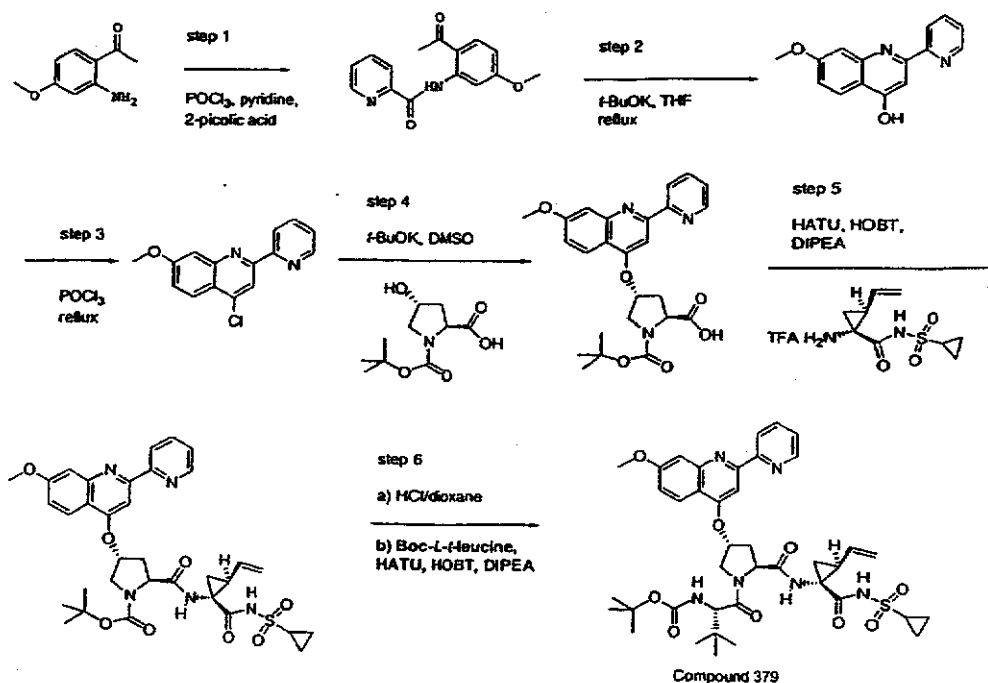
Step 1:

- A total of 0.34 mmol of the product of Step 2 of Example 375 {The Bis HCl Salt of HN-P2[(4R)-(7-methoxyquinoline-4-oxo)-S-proline]-P1(1R,2S Vinyl Acca)-CONHSO₂Cyclopropane} was suspended in 3 mL of dichloromethane. To this mixture was added N-BOC-L-Valine (*L*-Val) (120 mg, 0.55 mmol), HOAT (30 mg, 0.20 mmol), DIPEA (0.29 ml, 1.65 mmol), and HATU (160 mg, 0.43 mmol) at rt. The reaction mixture was stirred 16 h, diluted with saturated pH 4.0 buffer (150 mL), and extracted into EtOAc (3x200 mL). The combined organic layers were washed with brine, dried (MgSO₄), and concentrated. The residue was purified over an Isco 35g column (MeOH in CH₂Cl₂: 0% to 15%). This material was further purified over two δ PTLC plate from Analtech (20X40 cm, eluted with 3% MeOH in CH₂Cl₂) to afford the product 104.1 mg (44%), **Compound 378**: HRMS *m/z* (M-H)⁻ calcd. for C₃₄H₄₄N₅O₉S: 698.2860, found: 698.2865. LC-MS *m/e* 700 (retention time: 1.60, method D).

Example 379: Preparation of Compound 379



Scheme 1



Step 1:

To a suspension of 2-pyridinecarboxylic acid (3.73g, 30.3 mmol) and 2-amino-4-methoxybenzophenone (5.0 g, 30.3 mmol) at -30 °C dissolved in pyridine (150 mL) was added POCl₃ (3.7 mL, 45.4 mmol) in 5 min. the reaction mixture was stirred for 3 hr at the temperature, and stirred at rt overnight. The reaction mixture was poured into cold water and extracted with EtOAc (3x). The combined extract was dried to provide the product (7.67 g, 93%): ¹H NMR (methanol-d₄) δ ppm 2.65 (s, 3 H), 3.92 (s, 3 H), 6.78 (m, 1 H), 7.60 (m, 1 H), 8.00 (m, 1 H), 8.06 (m, 1 H), 8.21 (d, *J*=7.63 Hz, 1 H), 8.59 (t, *J*=2.29 Hz, 1 H), 8.76 (d, *J*=3.97 Hz, 1 H). LC-MS (retention time: 1.56, Method D), MS *m/z* 271 (*M*⁺+1).

Step 2:

To a suspension of 2-pyridinecarboxylic acid (2-acetyl-5-methoxyphenyl)-amide (2.90 g, 10.7 mmol) in THF (50 mL) was added t-BuOK/THF (1M, 24 mL, 24 mmol). The reaction mixture was heated at 70 °C for 3 h and stirred overnight. The solvent was removed in vacuo. Cold water was added to the residue and adjusted pH to 4.6 with aqueous 1.0 N HCl, filtered. The solid residue was purified

over a Biotage 65M column (MeOH/CH₂Cl₂: 0-15%) to provide the product (2.26 g, 84%): LC-MS (retention time: 1.19, Method D), MS *m/z* 253 (*M*⁺+1).

Step 3:

A mixture of 7-Methoxy-2-pyridin-2-yl-quinolin-4-ol (2.2 g, 8.71 mmol) in POCl₃ (92 mL) was refluxed for 3 h and then removed the solvent in vacuo. Ice water was added to the residue, adjusted the pH >10 with 1.0 N NaOH, and extracted with EtOAc (2x). The combined extract was washed with water, brine, dried (MgSO₄), removed solvent to supply the product as a yellow solid (89 %, 2.1 g): DMSO-D6) δ ppm 3.97 (s, 3 H), 7.40 (dd, *J*=9.16, 2.44 Hz, 1 H), 7.53 (m, 1 H), 8.01 (m, 1 H), 8.09 (d, *J*=9.16 Hz, 1 H), 8.46 (s, 1 H), 8.56 (d, *J*=7.93 Hz, 1 H), 8.74 (d, *J*=3.97 Hz, 1 H). LC-MS (retention time: 1.50, Method D), MS *m/z* 271 (*M*⁺+1).

Step 4:

To a solution of N-Boc-4-hydroxyproline (1.6 g, 6.7 mmol) in DMSO (20 mL) was added *t*-BuOK (1.9 g, 16.8 mmol). The generated mixture was stirred for 1.5 h and 4-Chloro-7-methoxy-2-pyridin-2-yl-quinoline (2.0 g, 7.4 mmol) and DMSO (10 mL) were added. The reaction mixture was stirred for 38 h, diluted with cold water and extracted with EtOAc/ether (1/4, 2x). the aqueous layer was acidified to pH 4 and extracted with EtOAc/THF (5x). the combined extract was dried (Na₂SO₄/MgSO₄), removed the solvent in vacuo and the residue was purified by preparative HPLC (0-80% solvent B) to provide the product (1.6 g, 50%): LC-MS (retention time: 1.23, Method I), MS *m/z* 466 (*M*⁺+1).

Step 5:

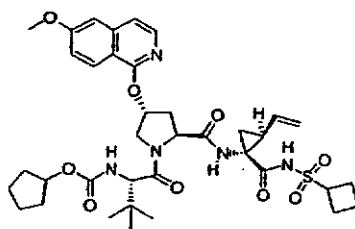
A solution of product (0.21 g, 0.65 mmol) of Step 4 of Example 379 {N-boc-(1*R*,2*S*)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester} in HCl/dioxane (4M, 5 mL, 20 mmol) was stirred for 3 h, and the solvent was removed in vacuo. To the residue was added CH₂Cl₂ (10 mL), diisopropylethylamine (0.4 mL, 3.23 mmol), HOBT (0.20 g, 1.35 mmol), Boc-(4*R*)-(2-cyclopropyl-7-methoxy-quinoline-4-oxo)-*S*-proline (0.20 g, 0.5 mmol) and HATU (0.415 g, 1.07 mmol). The reaction mixture was stirred overnight and diluted with pH 4.0 buffer, extracted with EtOAc. The extract was dried (MgSO₄) and purified by Biotage 40 M column using MeOH/CH₂Cl₂ (0 to 15%) as eluent to provide the product (204.7 mg, 70%): ¹H NMR (methanol-d₄) δ ppm 0.64 (m, 1 H), 0.96 (m, 2 H), 1.33 (m, 8 H), 1.39 (m, 9 H), 1.90

(m, 2 H), 2.18 (m, 1 H), 2.54 (m, 1 H), 2.81 (m, 1 H), 4.01 (m, 5 H), 4.44 (d, $J=28.99$ Hz, 1 H), 5.08 (m, 1 H), 5.31 (m, 1 H), 5.57 (s, 1 H), 6.03 (m, 1 H), 6.94 (s, 1 H), 7.27 (d, $J=8.24$ Hz, 1 H), 7.64 (m, 1 H), 7.92 (m, 1 H), 8.14 (m, 2 H), 8.66 (s, 1 H), 8.74 (s, 1 H).

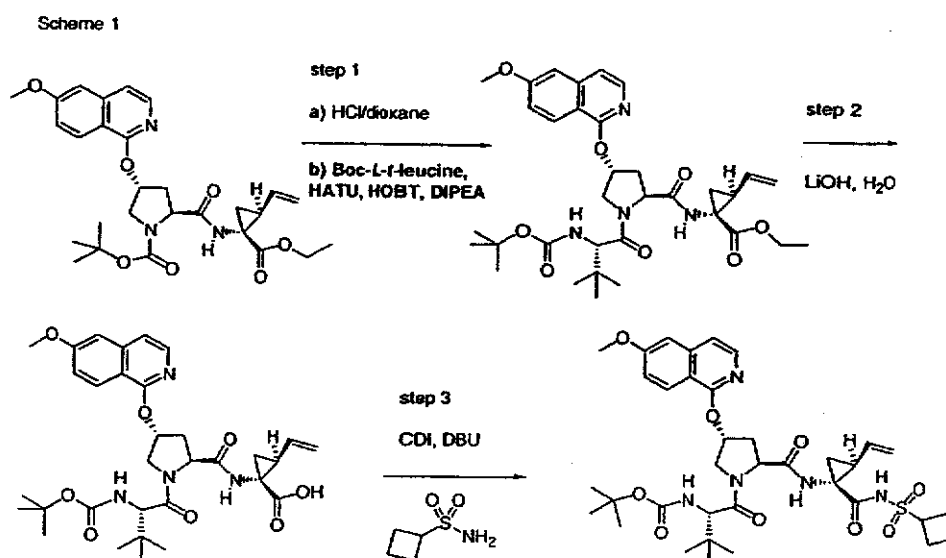
5 Step 6:

A slurry of P2 Boc-(4R)-(7-methoxy-2-Pyridin-2-yl-quinoline-4-oxo)-S-proline]-P1(1R,2S Vinyl Acca)-CONHSO₂(1-cyclopropylmethylcyclopropan-1-yl) (Step 5, Example 379) (203 mg, 0.3 mmol) in 4M HCl/dioxane (3.5 mL, 14 mmol) was stirred for 2 h, removed the solvent in vacuo. To the residue was added CH₂Cl₂ (2 mL), diisopropylethylamine (0.63 mL, 3.6 mmol), Boc-*L*-tert-leucine (83 mg, 0.36 mmol), HOAt (41 mg, 0.3 mmol), and HATU (148 mg, 0.39 mmol). The reaction mixture was stirred at rt for 7 h and removed the solvent in vacuo. The residue was purified by preparative HPLC (35-85% solvent B) to provide the desired product (Compound 379) 25.1 mg (11%): ¹H NMR (methanol-d₄) δ ppm -0.05 (m, 1 H), 0.30 (m, 1 H), 0.66 (m, 1 H), 0.91 (m, 2 H), 1.05 (s, 9 H), 1.28 (s, 9 H), 1.67 (m, 8 H), 2.15 (m, 1 H), 2.58 (m, 1 H), 2.77 (m, 1 H), 3.96 (s, 3 H), 4.19 (d, $J=40.25$ Hz, 2 H), 4.51 (d, $J=16.47$ Hz, 2 H), 4.95 (m, 1 H), 5.15 (m, 1 H), 5.53 (s, 1 H), 5.89 (dd, $J=16.65, 9.33$ Hz, 1 H), 7.09 (d, $J=8.42$ Hz, 1 H), 7.43 (d, $J=1.83$ Hz, 1 H), 7.50 (m, 1 H), 7.82 (s, 1 H), 7.99 (m, 1 H), 8.10 (d, $J=9.15$ Hz, 1 H), 8.48 (d, $J=7.68$ Hz, 1 H), 8.72 (s, 1 H). LC-MS (retention time: 1.59, Method I), MS m/z 791 (M^++1).

Example 380: Preparation of Compound 380.



Compound 380



Step 1:

The starting material in Scheme 1 of the present example was prepared by coupling of the product of step 3 in Example 11 of section B with the amino terminus of

5 P1(1*R*,2*S* Vinyl AcCa)-COOEt. A slurry of said coupling product, P2 Boc-(4*R*)-(6-methoxy-isoquinoline-1-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl AcCa)-COOEt (7.88 g, 14.99 mmol) in 4M HCl/dioxane (120 mL, 480 mmol) was stirred for 2 h, removed the solvent in vacuo and azeotroped with dry dioxane. To the residue was added DMF (75 mL), *N*-methylmorpholine (6.27 mL, 57.07 mmol), Boc-*L*-*tert*-leucine

10 (5.20 g, 22.49 mmol), and HATU (8.53 g, 22.49 mmol). The reaction mixture was stirred at rt overnight and worked up by pouring the reaction mixture into ice water and adjusted to pH 5 with aqueous 1.0 N HCl and extracted with EtOAc. The extract was washed with NaHCO₃ (aq.), brine, dried (MgSO₄) and concentrated. The residue was purified over Biotage 65M column (EtOAc-hexanes: 5-100%) to provide the

15 product (8.07 g, 84%); Retention time: 1.88 method I) MS *m/z* 639 (*M*⁺+1).

Step 2:

To a suspension of the product (4.0 g, 6.26 mmol) of Step 1 of Example 384 {Boc - NH-P3(*L*-*tert*-BuGly)-P2[(4*R*)-(6-methoxyl-isoquinoline-1-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl AcCa)-COOEt} in THF(250 mL), CH₃OH (31 mL), and H₂O (125 mL) was

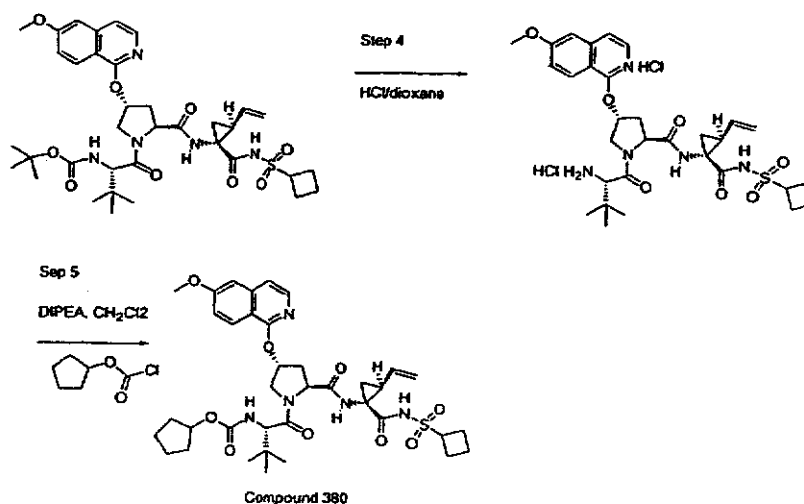
20 added LiOH (2.4 g, 100.2 mmol). The reaction mixture was stirred for overnight and then adjusted to pH 7 with aqueous 1.0 N HCl. The organic solvents were removed in vacuo. The aqueous residue was acidified to pH 4 and extracted with EtOAc (2x).

The combined organic solvent was dried ($\text{Na}_2\text{SO}_4/\text{MgSO}_4$), and concentrated in vacuo to supply the product (3.79 g, 99%): ^1H NMR (methanol- d_4) δ ppm 1.05 (s, 9 H), 1.25 (m, 1 H), 1.29 (s, 9 H), 1.46 (m, 1 H), 1.72 (dd, $J=8.24, 5.19$ Hz, 1 H), 2.23 (q, $J=8.55$ Hz, 1 H), 2.68 (dd, $J=13.89, 7.78$ Hz, 1 H), 3.94 (s, 3 H), 4.05 (dd, $J=11.60, 3.05$ Hz, 1 H), 4.23 (d, $J=8.85$ Hz, 1 H), 4.46 (d, $J=11.60$ Hz, 1 H), 4.63 (t, $J=8.39$ Hz, 1 H), 5.10 (d, $J=10.38$ Hz, 1 H), 5.29 (d, $J=17.40$ Hz, 1 H), 5.85 (m, 2 H), 7.10 (d, $J=9.16$ Hz, 1 H), 7.19 (s, 1 H), 7.26 (d, $J=5.49$ Hz, 1 H), 7.91 (d, $J=5.80$ Hz, 1 H), 8.12 (d, $J=9.16$ Hz, 1 H). Retention time: 1.81 method I) MS m/z 611 (M^++1).

Step 3:

- 10 A solution of CDI (0.052 g, 0.32 mmol) and the product (0.130 g, 0.21 mmol) of Step 2 of Example 384 {BOC-NH-P3(*L*-*t*-BuGly)-P2[(4*R*)-6-methoxy-sioquinoline-1-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-CO₂H} in THF (2 mL) was refluxed for 60 min and allowed to cool down to rt. Cyclobutanesulfonamide (0.043 g, 0.32 mmol) was added followed by the addition of a solution of neat DBU (0.048 mL, 0.32 mmol). The
- 15 reaction was stirred for overnite, then filtered through syringe filter and purified by preparative HPLC (30% to 100% solvent B) to provide the desired product 0.1422 mg (92%): ^1H NMR (methanol- d_4) δ ppm 1.04 (s, 9 H), 1.26 (d, $J=13.43$ Hz, 9 H), 1.39 (m, 1 H), 1.85 (dd, $J=7.63, 5.19$ Hz, 1 H), 1.98 (m, 2 H), 2.26 (m, 4 H), 2.50 (m, 2 H), 2.61 (m, 1 H), 3.92 (s, 3 H), 4.05 (m, 1 H), 4.24 (m, 1 H), 4.33 (m, 1 H), 4.43
- 20 (d, $J=11.60$ Hz, 1 H), 4.52 (m, 1 H), 5.13 (m, 1 H), 5.30 (m, 1 H), 5.71 (m, 1 H), 5.82 (s, 1 H), 7.08 (d, $J=8.85$ Hz, 1 H), 7.18 (s, 1 H), 7.24 (d, $J=5.80$ Hz, 1 H), 7.88 (m, 1 H), 8.08 (d, $J=9.16$ Hz, 1 H). Retention time: 1.89 method I) MS m/z 728 (M^++1).

Scheme 2



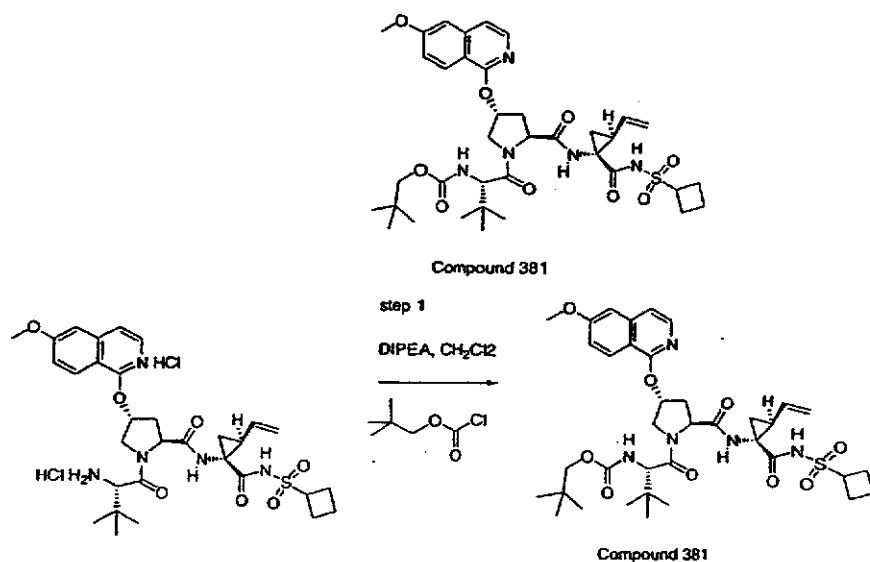
Step 4:

Example 380, Step 3 (0.196 mg, 0.27 mmol) {(BOCNH-P3(*L*-*t*-BuGly)-P2-(4*R*)-(6-methoxy-isoquinoline-1-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-CONHSO₂

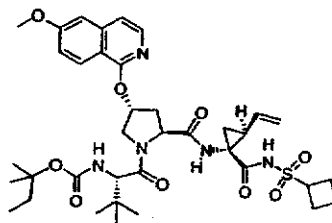
- 5 Cyclobutyl} was dissolved in HCl/dioxane (5 mL; 20 mmol) and was stirred for 2 h at rt. Removed the solvent in vacuo to supply the titled product 100% (0.1887 g) which was ready to next step.

Step 5:

- To a mixture of the product (0.037 g, 0.053 mmol) of Step 4 of Example 380(HCl salt of NH₂-P3(*L*-*t*-BuGly)-P2-(4*R*)-(6-methoxy-isoquinoline-1-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-CONHSO₂ Cyclobutyl} and diisopropylethylamine (0.046 mL), 0.26 mmol) in CH₂Cl₂ (2 mL) was added cyclopentyl chloroformate (0.7 M, 0.151 mL, 0.069 mmol). The reaction mixture was stirred overnite and purified by preparative HPLC (30% to 100% solvent B) to provide the desired product
- 15 (Comound 380) (0.0303 g, 77%): ¹H NMR (methanol-d₄) δ ppm 1.03 (s, 9 H), 1.48 (m, 9 H), 1.86 (dd, *J*=8.24, 5.49 Hz, 1 H), 1.99 (m, 2 H), 2.27 (m, 4 H), 2.51 (m, 2 H), 2.60 (dd, *J*=13.89, 6.87 Hz, 1 H), 3.92 (s, 3 H), 4.05 (dd, *J*=12.21, 3.97 Hz, 1 H), 4.32 (m, 2 H), 4.41 (d, *J*=11.90 Hz, 1 H), 4.53 (m, 1 H), 4.69 (m, 1 H), 5.12 (d, *J*=10.38 Hz, 1 H), 5.29 (d, *J*=17.09 Hz, 1 H), 5.71 (m, 1 H), 5.83 (s, 1 H), 7.11 (d, *J*=9.46 Hz, 1 H), 7.19 (s, 1 H), 7.25 (d, *J*=5.80 Hz, 1 H), 7.88 (d, *J*=5.80 Hz, 1 H), 8.08 (d, *J*=9.16 Hz, 1 H). retention time: 1.85 method H), MS *m/z* 740 (M⁺+1)
- 20

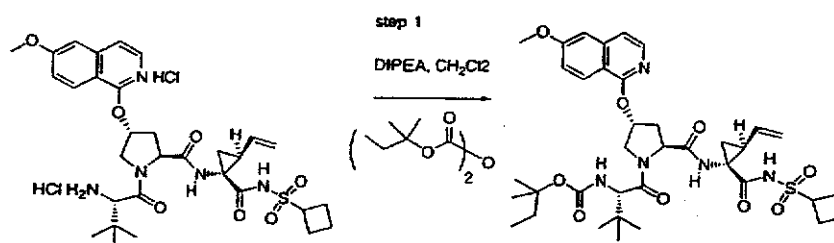
Example 381: Preparation of Compound 381.**Step 1:**

- 5 To a mixture of the product (0.037 g, 0.053 mmol) of Step 4 of Example 380 {HCl salt of NH₂-P3(*L*-*t*-BuGly)-P2-(4*R*)-(6-methoxy-isoquinoline-1-oxo)-*S*-proline]-PI(1*R*,2*S* Vinyl Acca)-CONHSO₂ Cyclobutyl} and isopropylethylamine (0.046 mL), 0.26 mmol) in CH₂Cl₂ (2 mL) was added new-pentyl chloroformate (0.012 mL, 0.069 mmol). The reaction mixture was stirred overnight and directly purified by preparative
- 10 HPLC (30% to 100% solvent B) to provide the desired product (**Compound 381**) (0.0252 g, 64%): ¹H NMR (methanol-*d*₄) δ ppm 0.84 (s, 9 H), 1.05 (s, 9 H), 1.40 (m, 1 H), 1.86 (m, 1 H), 2.00 (m, 2 H), 2.28 (m, 4 H), 2.51 (m, 2 H), 2.57 (m, 1 H), 3.39 (d, *J*=10.07 Hz, 1 H), 3.55 (d, *J*=10.38 Hz, 1 H), 3.92 (s, 3 H), 4.05 (m, 1 H), 4.33 (m, 2 H), 4.41 (d, *J*=11.29 Hz, 1 H), 4.53 (m, 1 H), 5.12 (d, *J*=10.07 Hz, 1 H), 5.29 (d, *J*=17.09 Hz, 1 H), 5.71 (m, 1 H), 5.82 (s, 1 H), 7.10 (d, *J*=9.16 Hz, 1 H), 7.19 (s, 1 H), 7.25 (d, *J*=5.80 Hz, 1 H), 7.88 (d, *J*=5.80 Hz, 1 H), 7.97 (s, 1 H), 8.07 (d, *J*=8.85 Hz, 1 H). retention time: 1.89 method H), MS *m/z* 742 (*M*⁺+1).

Example 382: Preparation of Compound 382.

Compound 382

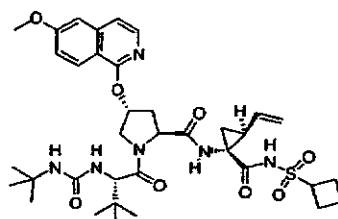
Scheme 1



Compound 382

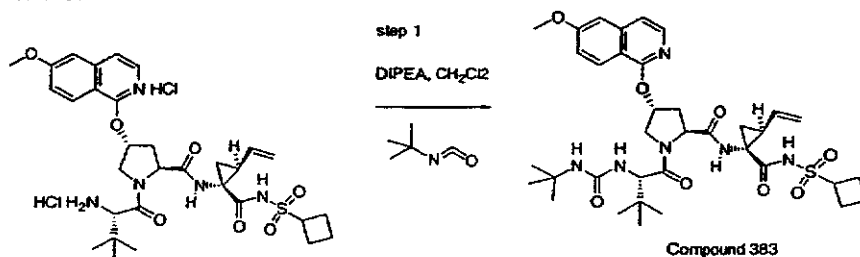
Step 1:

- 5 To a mixture of the product (0.037 g, 0.053 mmol) of Step 4 of Example 380 {HCl salt of $\text{NH}_2\text{-P3(L-}i\text{-BuGly)-P2-(4R)-(6-methoxy-isoquinoline-1-oxo)-S-proline-P1(1R,2S Vinyl Acca)-CONHSO}_2\text{ Cyclobutyl}$ } and diisopropylethylamine (0.046 mL, 0.26 mmol) in CH_2Cl_2 (2 mL) was added di-*t*-amyl dicarbonate (0.0169 g, 0.069 mmol). The reaction mixture was stirred overnight and directly purified by
- 10 HPLC (30% to 100% solvent B) to provide the desired product (**Compound 382**) (0.0175 g, 44%): $^1\text{H NMR}$ (methanol- d_4) δ ppm 0.79 (t, $J=6.87$ Hz, 3 H), 1.04 (s, 8 H), 1.21 (s, 3 H), 1.23 (s, 3 H), 1.41 (m, 2 H), 1.64 (m, 2 H), 1.83 (m, 1 H), 2.00 (m, 2 H), 2.26 (m, 4 H), 2.51 (m, 2 H), 2.60 (m, 1 H), 3.92 (s, 3 H), 4.07 (m, 1 H), 4.24 (m, 1 H), 4.33 (m, 1 H), 4.43 (d, $J=11.60$ Hz, 1 H), 4.52 (m, 1 H), 5.13 (m, 1 H), 5.29 (m, 1 H), 5.71 (m, 1 H), 5.82 (s, 1 H), 7.09 (d, $J=8.85$ Hz, 1 H), 7.18 (s, 1 H), 7.25 (d, $J=5.49$ Hz, 1 H), 7.88 (d, $J=5.80$ Hz, 1 H), 8.08 (d, $J=8.85$ Hz, 1 H). retention time: 1.90, method H), MS m/z 742 (M^++1).
- 15

Example 383: Preparation of Compound 383.

Compound 383

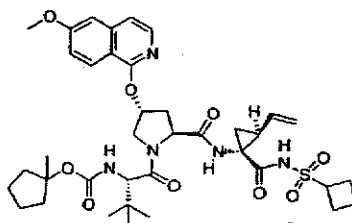
Scheme 1



Compound 383

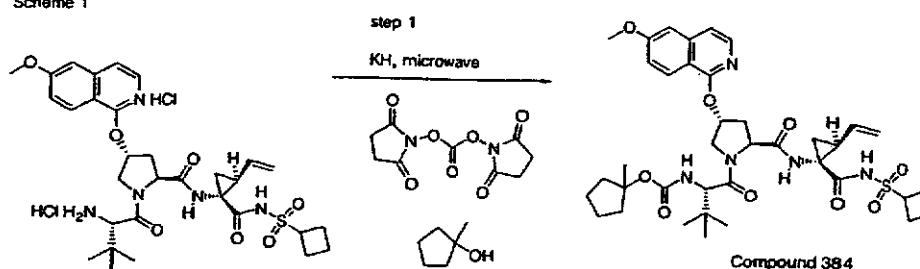
Step 1

- 5 To a mixture of the product (0.037 g, 0.053 mmol) of Step 4 of Example 380 {HCl salt of $\text{NH}_2\text{-P3(L-}t\text{-BuGly)-P2-(4R)-(6-methoxy-isoquinoline-1-oxo)-S-proline-P1(1R,2S Vinyl Acca)-CONHSO}_2\text{ Cyclobutyl}$ } and isopropylethylamine (0.046 mL, 0.26 mmol) in CH_2Cl_2 (2 mL) was added t-butyl-isocyanate (0.008 mL, 0.069 mmol). The reaction mixture was stirred overnight and directly purified by preparative HPLC
- 10 (30% to 100% solvent B) to provide the desired product (Compound 383) (0.024 g, 62%); $^1\text{H NMR}$ (methanol- d_4) δ ppm 1.05 (s, 9 H), 1.19 (s, 9 H), 1.37 (m, 1 H), 1.85 (dd, $J=8.09, 5.34$ Hz, 1 H), 2.00 (m, 2 H), 2.26 (m, 4 H), 2.50 (m, 2 H), 2.58 (m, 1 H), 3.92 (s, 3 H), 4.06 (m, 1 H), 4.32 (m, 2 H), 4.49 (m, 2 H), 5.11 (d, $J=10.38$ Hz, 1 H), 5.27 (d, $J=17.40$ Hz, 1 H), 5.69 (m, 1 H), 5.83 (s, 1 H), 7.08 (dd, $J=9.16, 2.44$ Hz,
- 15 1 H), 7.17 (d, $J=2.44$ Hz, 1 H), 7.24 (d, $J=5.80$ Hz, 1 H), 7.87 (d, $J=6.10$ Hz, 1 H), 8.12 (d, $J=8.85$ Hz, 1 H). retention time: 1.77, method H), MS m/z 727 (M^++1).

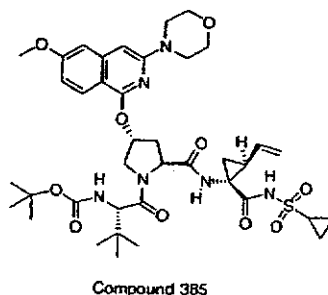
Example 384: Preparation of Compound 384.

Compound 384

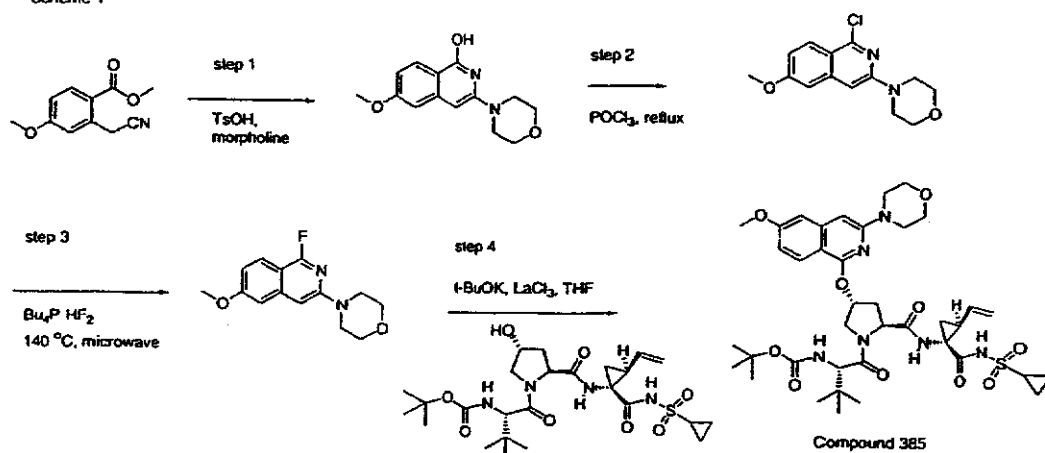
Scheme 1

**Step 1:**

A suspension of diisopropylethylamine (0.031 mL, 0.018 mmol), *N,N'*-disuccinimidyl carbonate (0.0274 g, 0.107 mmol) and the product (0.050 g, 0.0714 mmol) of Step 4 of Example 380 {HCl salt of $\text{NH}_2\text{-P3(L-}i\text{-BuGly)-P2-(4R)-(6-methoxy-isoquinoline-1-oxo)-S-proline-P1(1R,2S Vinyl Acca)-CONHSO}_2$ Cyclobutyl} in THF (2 mL) was sonicated at 80 °C for 15 min. KH (0.046 g, 1.14 mmol) and 1-methylcyclopentanol (0.079 mL, 0.714 mmol) was added. The reaction mixture was stirred for 20 min and worked up by diluting with cold water, adjusted pH to 4, extracted with EtOAc. The extract was dried (MgSO_4) and the residue was purified by preparative HPLC (30% to 100% solvent B) to provide the desired product (**Compound 384**) (0.018 g, 33%): (methanol- d_4) δ ppm 1.04 (s, 9 H), 1.29-1.79 (m, 10 H), 1.84 (m, 2 H), 1.99 (m, 3 H), 2.26 (m, 4 H), 2.49 (m, 2 H), 2.60 (dd, $J=13.73, 7.02$ Hz, 1 H), 3.92 (s, 3 H), 4.05 (dd, $J=11.29, 2.44$ Hz, 1 H), 4.26 (s, 1 H), 4.32 (m, 1 H), 4.44 (d, $J=11.90$ Hz, 1 H), 4.52 (m, 1 H), 5.12 (d, $J=10.07$ Hz, 1 H), 5.28 (d, $J=16.79$ Hz, 1 H), 5.71 (m, 1 H), 5.82 (s, 1 H), 7.10 (d, $J=8.85$ Hz, 1 H), 7.19 (s, 1 H), 7.26 (d, $J=5.80$ Hz, 1 H), 7.88 (d, $J=5.80$ Hz, 1 H), 8.08 (d, $J=9.16$ Hz, 1 H). LC-MS retention time: 1.91 method H), MS m/z 754 (M^++1).

Example 385: Preparation of Compound 385.

Scheme 1



Step 1:

A suspension of 2-cyanomethyl-4-methoxybenzoic acid methyl ester (1.9 g and TsOH, H₂O (0.15 g, mmol) in morpholine 5 mL) was refluxed for 4 h and removed the solvent in vacuo. The residue was recrystallized from EtOAc/hexanes with drops of MeOH to provide the product (0.43 g, 17%): LC-MS retention time: 1.07 method H, MS m/z 266 (M^+ +1).

Step 2:

A mixture of 6-methoxy-3-morpholin-4-yl-isoquinolin-1-ol (0.298 g, 1.15 mmol) in POC_l₃ (20 mL) was refluxed for 2 h, removed the solvent in vacuo and cold water was added. The pH was adjusted to >11 by addition of 1.0 N NaOH. The aqueous layer was extracted with EtOAc. The extract was dried (MgSO₄), removed the solvent in vacuo to provide the product (0.299 g, 94%): LC-MS retention time: 1.68 method H, MS m/z 279 (M^+ +1).

Step 3:

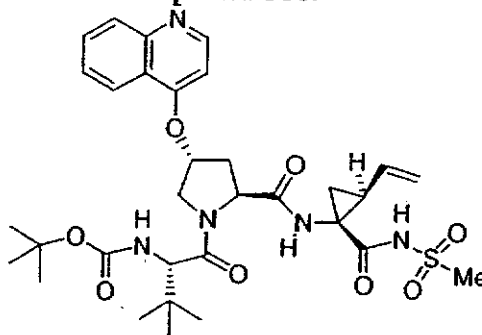
A mixture of 1-Chloro-6-methoxy-3-morpholin-4-yl-isoquinoline (0.050 g, 0.18 mmol) and tetrabutyl phosphonium hydrogen difluoride (0.8 g, 2.8 mmol) [Synlett 1992, (4), 345-6] was heated at 140 °C in microwave for 10 min. the reaction mixture was diluted with EtOAc and filtered through an ISCO 25g precolumn with a layer of silicon gel on the top, removed the solvent to provide the product (0.037 mg, 77%): ¹H NMR (CHLOROFORM-D) δ ppm 3.48 (m, 4 H), 3.84 (m, 4 H), 3.89 (s, 3 H), 6.46 (d, J =1.22 Hz, 1 H), 6.85 (s, 1 H), 6.90 (dd, J =9.16, 2.44 Hz, 1 H), 7.82 (d, J =8.85 Hz, 1 H). LC-MS retention time: 1.56 method H, MS m/z 263 (M^+ +1).

Step 4:

A mixture of 1-floro-6-methoxy-3-morpholin-4-yl-isoquinoline (0.037g, 0.14 mmol), LaCl_3 (0.020 g, 0.8 mmol), *t*-BuOK (1M/THF, 0.32 mL, 0.32 mmol), and Boc - NH-P3(*L*-*tert*-BuGly)-P2 [(4*R*)-4-hydroxyl-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-CONHSO₂Cyclopropane (0.045 g, 0.08 mmol) in THF (3 mL) was stirred for 3 days.

- 5 The reaction mixture was diluted with methanol filtered through syringe filter and purified by preparative HPLC to provide the product as a pale yellow foam (0.0158 g, 24%): ¹H NMR (methanol-*d*₄) δ ppm 1.03 (s, 9 H), 1.24 (m, 4 H), 1.31 (s, 9 H), 1.43 (m, 2 H), 1.88 (m, 1 H), 2.24 (m, 2 H), 2.59 (dd, *J*=13.43, 6.71 Hz, 1 H), 2.94 (m, 1 H), 3.47 (m, 4 H), 3.83 (m, 4 H), 3.86 (s, 3 H), 4.08 (m, 1 H), 4.28 (s, 1 H),
 10 4.48 (m, 1 H), 5.12 (d, *J*=10.38 Hz, 1 H), 5.29 (d, *J*=16.48 Hz, 1 H), 5.76 (m, 2 H), 6.74 (d, *J*=9.16 Hz, 1 H), 6.94 (s, 1 H), 7.85 (d, *J*=8.85 Hz, 1 H), 9.19 (s, 1 H).
 retention time: 1.86 method H), MS *m/z* 799 (*M*⁺+1).

Example 386: Preparation of Compound 386.



Compound 386

- 15 Compounds 386 was prepared using the methods described herein.

Section I:

All compounds in section I were analyzed by the LC/MS methodology, which has the following conditions.

- 20 Method A: Xterra C18 S7 3.0 x 50 mm

Gradient: 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B

Gradient time: 3 min.

Hold time: 1 min.

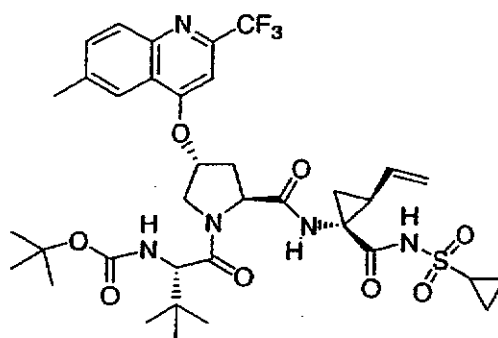
Flow rate: 4 mL/min.

- 25 Detector Wavelength: 220 nm

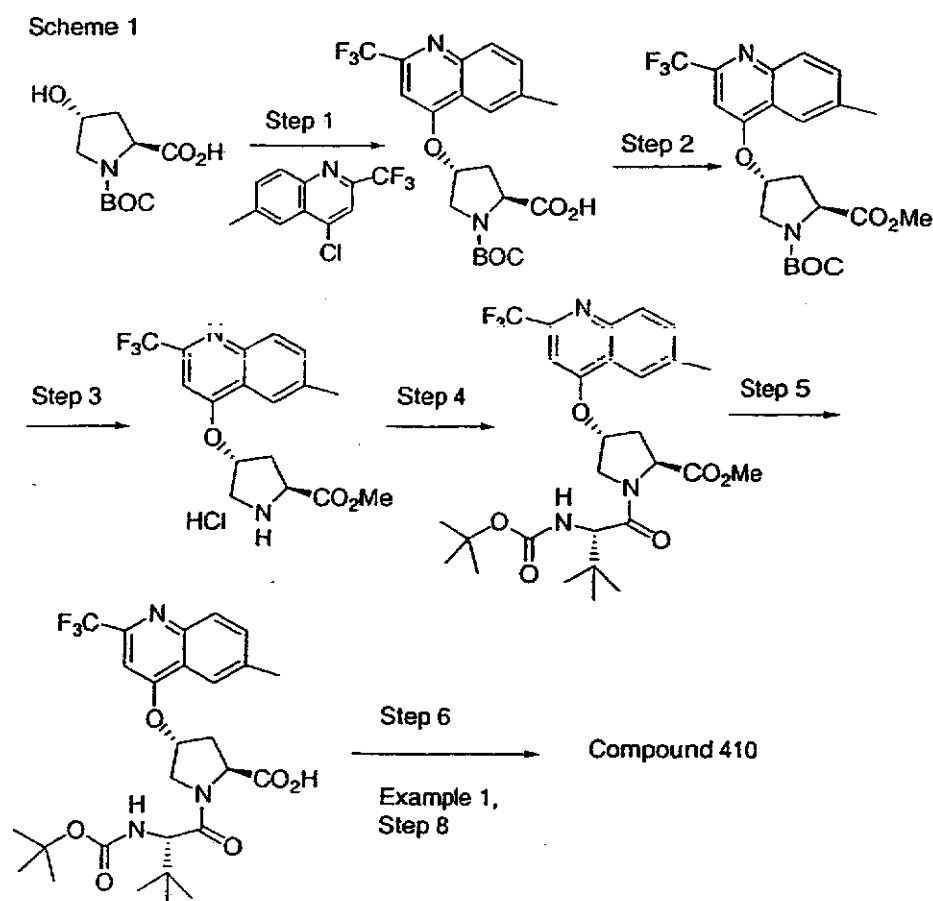
Solvent A: 10% MeOH / 90% H₂O / 0.1% TFA

Solvent B: 10% H₂O / 90% MeOH / 0.1% TFA

Example 410: Preparation of Compound 410



Compound 410



5

Step 1:

To a solution of Boc-L-hydroxyproline (0.723 g, 3.13 mmol) in DMSO, KO^tBu (0.808 g, 7.2 mmol) was added under a nitrogen atmosphere. The suspension

was stirred at room temperature for 1.5 hours, and 4-chloro-6-methyl-2-(trifluoromethyl)quinoline (0.916 g, 3.75 mmol) was added in two portions. The mixture was stirred at room temperature for three hours, and 1.3 equivalents of HCl (1N) was used to neutralize the reaction. Buffer solution of pH 4.0 was added and the pH was adjusted to pH 4-5. The aqueous layer was extracted with ethyl acetate, (3 x 25mL) and the combined organic layers were washed with brine (20 mL) and dried over MgSO₄ to yield the titled compound as a white solid (crude yield not calculated). The crude product was taken into the next step.

LC/MS rt-min (MH⁺): 2.48 (441.5) (method A).

10

Step 2:

A solution of the crude product from Step 1, 4-(6-methyl-2-trifluoromethyl-quinolin-4-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (assumed 3.13 mmol), in THF (10 mL) and methanol (10 mL) was cooled to 0° C. TMSCN₂ 2M in hexanes (~ 1.3 eq) was slowly added to the stirring solution under a nitrogen atmosphere until gas was no longer emitted from the solution. The fully reacted solution was then concentrated in vacuo, and purification by a Biotage 40M column (eluted 10% - 30% ethyl acetate in hexanes) afforded the pure titled compound as a white foam (976 mg, 69% over Step 1&2)

20 LC/MS rt-min (MH⁺): 2.60 (477) (method A).

Step 3:

A solution of the product from Step 2 (0.976 g, 2.15 mmol) in DCM (7 mL) and TFA (6.62 mL) was stirred at room temperature for one hour. The solvent was removed in vacuo and the residue was suspended in 1N HCl in diethyl ether (8 mL), gently stirred, and concentrated in vacuo. This procedure was repeated and the resulting product was placed on an oil pump overnight to yield a white solid in quantitative yield.

¹H NMR: (DMSO-d₆) δ 2.50 (s, 3H), 2.57- 2.6 (m, 1H), 2.66-2.71 (m, 1H), 3.62-3.65 (br d, J = 15 Hz, 1H), 3.80-3.81 (m, 4H), 4.8 (br s, 1H), 5.7 (s, 1H), 7.46 (s, 1H), 7.72-7.75 (d, J = 7.5 Hz, 1H), 7.98-7.8 (d, J = 8.5 Hz, 1H), 8.24 (s, 1H), 9.54 (br s, 1H); LC/MS rt-min (MH⁺): 1.61 (355) (method A).

30

Step 4:

The product from Step 3 (assumed quantitative yield, 2.746 mmol) was added to a solution of BOC-t-Butyl-L-glycine (0.635 g, 2.746 mmol) in DCM (20 mL) under a nitrogen atmosphere. This step was followed by the addition of HOBT (0.408 g, 3.02 mmol), DIPEA (3.35 mL, 19.2 mmol), and HBTU (1.56 g, 4.12 mmol). A peach colored solution immediately resulted and the reaction was left to stir at room temperature overnight. 10 mL DCM was added to the completed reaction in order to increase the volume, and the reaction was quenched with pH 4.00 buffer solution (25 mL). The mixture was acidified to a pH of 4.5 using 1N HCl, and the aqueous phase was extracted with DCM (3 x 20 mL). The organic phase was washed twice with pH 4.00 buffer solution (20 mL), saturated NaOH (25 mL), and brine (20 mL), and then dried with MgSO₄. The resulting solution was concentrated in vacuo and purified by a Biotage 40M column (eluted 10% - 40% ethyl acetate in hexanes). This purification afforded the pure titled compound as a white solid (1.11 g, 89%).

¹H NMR: (DMSO-d₆) δ 0.96-1.02 (rotamers, 3:2, s, 18H), 2.27-2.33 (m, 1H), 2.50 (s, 3H), 2.68-2.72 (m, 1H), 3.67 (s, 3H), 4.02-4.04 (m, 1H), 4.43-4.45 (br d, *J* = 15 Hz, 2H), 4.58-4.61 (t, 1H), 5.60 (br s, 1H), 6.72-6.74 (br d, *J* = 15 Hz, 1H), 7.38 (s, 1H), 7.68-7.73 (m, 1H), 7.95-7.97 (m, 2H);
LC/MS rt-min (MH⁺): 2.61 (590) (method A).

Step 5:

LiOH (0.138 g, 5.78 mmol) was dissolved in water (10 mL) by heating and sonication. The LiOH solution and MeOH (10 mL) were added to a solution of the pure material from Step 4 (1.09 g, 1.93 mmol) in THF (10mL). The mixture immediately turned a vivid blue color. The reaction was left to stir at room temperature for 3 hours and was then acidified with 1N HCl (5.78 mL, 5.78 mmol). The reaction was quenched with pH 4.00 buffer solution and the pH was adjusted to pH 4.5 using 1N aqueous NaOH. The aqueous layer was extracted with EtOAc (3 x 25 mL), washed with brine (20 mL), and dried over MgSO₄. The filtered solution

was concentrated in vacuo and left on a vacuum line overnight. The crude product (957 mg, 90% yield) was taken into the next step.

LC/MS rt-min (MH^+): 2.51 (577) (method A).

5 Step 6:

The crude product from Step 5 (60 mg, 0.11 mmol) was dissolved in DCM (5 mL) and cyclopropanesulfonic acid (1 (*R*)-amino-2 (*S*)-vinyl-cyclopropanecarbonyl)-amide hydrochloride salt (Example 1, Step 8) (0.029 g, 0.11 mmol) was added.

DIPEA (0.094 mL, 0.541 mmol), and then HATU (0.0575, 0.151 mmol) were added
10 under a nitrogen atmosphere. The reaction was left to stir at room temperature for about 8 hours. 10 mL DCM was added to the solution in order to increase the volume, and the reaction was quenched with pH 4.00 buffer solution (10 mL). The mixture was acidified using 1N HCl to a pH of 4-5, and the aqueous phase was extracted with DCM (3 x 20 mL). The organic phase was washed twice with pH 4.00
15 buffer solution (10 mL) and brine (10 mL), and then dried over $MgSO_4$. The resulting solution was concentrated in vacuo and purified by a Biotage 12M column (eluted 10% - 40% acetone in hexanes). This purification afforded Compound 410 as a white powder (29 mg, 35%).

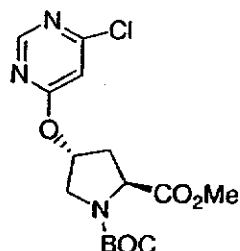
^1H NMR: ($DMSO-d_6$) δ 0.976-1.12 (m, 24 H), 1.36-1.39 (m, 1H), 1.70-1.72 (m, 1H), 2.15-2.25 (m, 2H), 2.50-2.52 (m, 4H), 2.91-2.96 (m, 1H), 3.97-4.01 (m, 2H), 4.40-4.47 (m, 2H), 5.09-5.11 (d, $J = 10Hz$, 1H), 5.21-5.24 (d, $J = 15Hz$, 1H), 5.59-5.66 (m, 2H), 6.65-6.67 (d, NH), 7.43 (s, 1H), 7.72-7.74 (d, $J = 10 Hz$, 1H), 7.90 (s, 1H), 7.98-8.0 (d, $J = 10 Hz$, 1H), 8.87 (s, NH), 10.35 (s, NH);
20

LC/MS rt-min (MH^+): 2.65 (789.61) (method A).

25

30

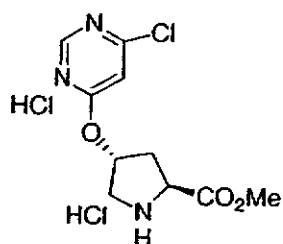
541



A solution of the crude product from Step 1, (assumed 8.65 mmol), in THF (40 mL) and methanol (40 mL) was cooled to 0°C. TMSCN₂ 2M in hexanes (~ 1.3 eq) was slowly added to the stirring solution under a nitrogen atmosphere until gas was no longer emitted from the solution. The fully reacted solution was then concentrated in vacuo, and purification by a Biotage 40M column (eluted 20% - 40% ethyl acetate in hexanes) to afford the pure titled compound as a white foam (497 mg, 16% over steps 2a - 2b).

¹H NMR: (DMSO-d₆) δ 1.34-1.38 (rotamers, 2:1, 9H), 2.25-2.29 (m, 1H), 2.53-2.56 (m, 1H), 3.58-3.75 (m, 2H), 3.69 (s, 3H), 4.28-4.33 (m, 1H), 5.59 (s, 1H), 7.24 (s, 1H), 8.69 (s, 1H);
LC/MS rt-min (MH⁺): 2.08 (380.14) (method A).

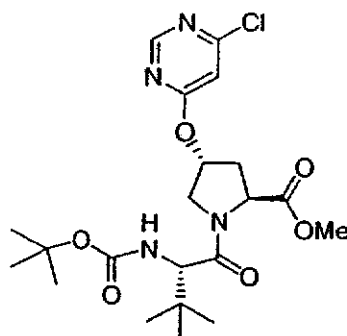
Step 3:



A solution of the pure product from Step 2 (472 mg, 1.83 mmol) in DCM (3 mL) and TFA (5.65 mL) was stirred at room temperature for one hour. The solvent was removed in vacuo, the residue was suspended in 1N HCl in diethyl ether (7.33 mL), gently stirred and concentrated in vacuo. This procedure was repeated, and the resulting product was placed on an oil pump overnight to yield a white solid in quantitative yield.

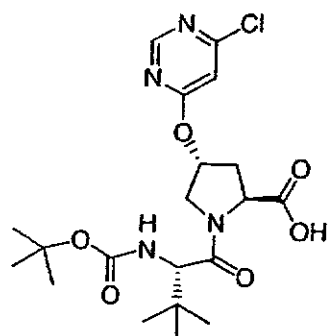
LC/MS rt-min (MH⁺): 0.55 (258.35) (method A).

Step 4:



- The product from Step 3 (assumed quantitative yield, 1.83 mmol) was added to a solution of BOC-t-Butyl-L-glycine (0.424 g, 1.83 mmol) in DCM (11 mL) under a nitrogen atmosphere. This step was followed by the addition of HOBt (0.272 g, 2.02 mmol), DIPEA (2.23 mL, 12.82 mmol), and HBTU (1.04 g, 2.75 mmol). The reaction was left to stir at room temperature for 15 hours. 15 mL DCM was added to the solution in order to increase the volume, and the reaction was quenched with pH 4.00 buffer solution (15 mL). The mixture was acidified to a pH of 4.5 using 1N HCl, and the aqueous phase was extracted with DCM (3 x 20 mL). The organic phase was washed twice with pH 4.00 buffer solution (20 mL), saturated NaOH (25 mL), brine (20 mL), and dried over MgSO₄. The resulting solution was concentrated in vacuo and purified by a Biotage 40S column (eluted 20% - 50% ethyl acetate in hexanes). This purification afforded the pure titled compound as a white solid (454 mg, 53%).
- ¹H NMR: (DMSO-d₆) δ 0.94 (s, 9H), 1.25 (s, 9H), 2.21-2.27 (m, 1H), 2.48-2.55 (m, 1H), 3.64 (s, 3H), 3.86-4.02 (m, 2H), 4.29-4.31 (d, *J* = 10 Hz, 1H), 4.46-4.49 (t, 1H), 5.75 (br s, 1H), 6.72-6.74 (d, NH), 7.12 (s, 1H), 8.71 (s, 1H);
- LC/MS rt-min (MH⁺): 2.27 (493.5) (method A).

20 Step 5:



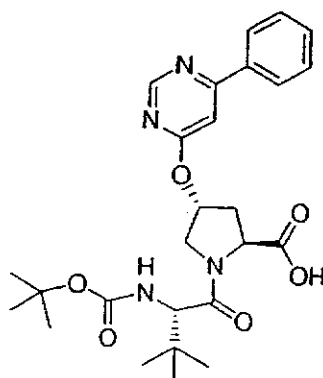
LiOH (0.0141 g, 0.589 mmol) was dissolved in water (7.5 mL) by heating and sonication. The LiOH solution was added to a solution of the pure material from Step 4 (252 mg, 0.535 mmol) in THF (7.5 mL), and left to stir at room temperature.

- 5 The reaction was complete after 3 hours. It was quenched with pH 4.0 buffer and acidified to a pH of approximately 4.5 with 1N HCl. The aqueous phase was extracted with EtOAc (3 x 25 mL), and the organic phase was washed with brine (20 mL) and dried over MgSO₄. The filtered solution was concentrated in vacuo and left on a vacuum line overnight. The crude product (231 mg, 95% yield) was taken into
- 10 the next step.

¹H NMR: (DMSO-d₆) δ 0.94 (s, 9H), 1.25 (s, 9H), 2.14-2.22 (m, 1H), 2.50-2.54 (m, 1H), 3.84-3.876 (d, *J* = 150 Hz, 1H), 3.97-3.99 (d, *J* = 10 Hz, 1H), 4.27-4.30 (d, *J* = 15 Hz, 1H), 4.37-4.40 (t, 1H), 5.63 (br s, 1H), 6.69-6.71 (d, NH), 7.12 (s, 1H), 8.71 (s, 1H), 12.56 (br s, OH);

- 15 LC/MS rt-min (MH⁺): 2.24 (479.5) (method A).

Step 6:



- The pure material from Step 5 (80 mg, 0.146 mmol), and phenylboronic acid (0.0178 g, 0.146 mmol) were solvated in DMF (2 mL). The solution was placed under a
- 20

nitrogen atmosphere and 2M aqueous Na_2CO_3 (0.146 mL, 0.292 mmol) was added. Five mole percent of Tetrakis(triphenyl)phosphine)-palladium (0) was added (8.44 mg, 0.0073 mmol) and the mixture was heated by microwave using the Personal Chemistry Emrys Optimizer for 50 minutes at 140°C . Palladium black precipitated out of the reaction upon completion. The mixture was acidified with one equivalent of 1N HCl, and filtered through a syringe, using MeOH to extract the product. The product was purified by prep HPLC (column - 4 Xterra S5 30 x 75 mm, solvent - 70% A / 30% B - 30% A / 70% B (where solvent A is 10% MeOH, 90% H_2O , 0.1% TFA and solvent B is 90% MeOH, 10% H_2O , 0.1% TFA), gradient time - 15 min., hold time - 1 min., flow rate - 40 mL/min, retention time of pure product - 10.45-11.37). Fractions containing the desired product were neutralized with 1N NaOH and placed in the speed vacuum for approximately 4 hours. The fractions were combined and pH 4.0 buffer (15mL) was added. The pH was adjusted to pH 4-5 using 1N HCl, and the aqueous layer was extracted with ethyl acetate (3 x 20mL). The organic layer was washed with brine (15 mL), dried over MgSO_4 , and concentrated in vacuo. The product was placed on an oil pump to dry overnight, and an viscous oil was obtained (37 mg, 50%).

LC/MS rt-min (MH^+): 2.37 (499.3) (method A).

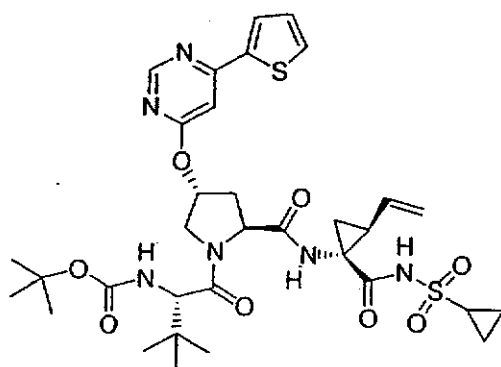
20 Step 7:

The product from Example 411, Step 6 (36.7 mg, 0.061 mmol) was dissolved in DCM (4 mL) and cyclopropanesulfonic acid (1 (*R*)-amino-2 (*S*)-vinyl-cyclopropanecarbonyl)-amide hydrochloride salt (Example 1, Step 8) (0.0164 g, 0.161 mmol) was added. DIPEA (0.0534 mL, 0.307 mmol), and then HATU (0.0326, 0.0858 mmol) were added under a nitrogen atmosphere. The reaction was left to stir at room temperature for 3 hours. 10 mL DCM was added to the solution in order to increase the volume, and the reaction was quenched with pH 4.00 buffer solution (10 mL). The mixture was acidified to a pH of 4-5 using 1N HCl, and the aqueous phase was extracted with DCM (3 x 15 mL). The organic phase was washed twice with pH 4.00 buffer solution (10 mL) and brine (10 mL), and then dried over MgSO_4 . The resulting solution was concentrated in vacuo and purified by a Biotage

12M column (eluted 20% - 40% acetone in hexanes). This purification afforded the pure Compound 411 as a white powder (7 mg, 15%).

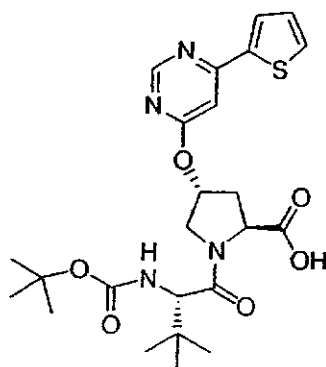
¹H NMR: δ 1.07-1.46 (m, 24 H), 1.87-1.90 (m, 1H), 2.22-2.32 (m, 2H), 2.51-2.55 (m, 1H), 2.92-2.97 (m, 1H), 4.04-4.07 (d, J = 15 Hz, 1H), 4.20-4.22 (d, J = 10 Hz, 1H), 4.36-4.38 (d, J = 10 Hz, 1H), 4.47-4.50 (t, 1H), 5.12-5.14 (d, J = 10 Hz, 1H), 5.29-5.33 (d, J = 20 Hz, 1H), 5.73-5.82 (m, 2H), 6.59-6.60 (d, NH), 7.29 (s, 1H), 7.50-7.51 (m, 3H), 8.03-8.05 (m, 2H), 8.81 (s, 1H);
LC/MS rt-min (MH⁺): 2.50 (711.4) (method A).

10 Example 412: Preparation of Compound 412.



Compound 412

Step 1:



The product from Example 411, Step 5 (80 mg, 0.146 mmol) was solvated in DMF (2 mL), and 2-thiopheneboronic acid (0.028 g, 0.219 mmol) was added to the solution. The reaction was placed under a nitrogen atmosphere and 2M aqueous Na₂CO₃ (0.146 mL, 0.292 mmol), and 5 mole percent of Tetrakis(triphenyl)phosphine)-palladium (0) were added (8.44 mg, 0.0073 mmol). The reaction was heated by

microwave using the Personal Chemistry Emrys Optimizer for 30 minutes at 150°C. Palladium black precipitated out of the reaction upon completion. The mixture was acidified with one equivalent of 1N HCl, and filtered through a syringe, using MeOH to extract the product. The product was purified by prep HPLC (column - 4 Xterra
5 S5 30 x 75 mm, solvent - 70% A / 30% B – 30% A / 70% B (where solvent A is 10% MeOH, 90% H₂O, 0.1% TFA and solvent B is 90% MeOH, 10% H₂O, 0.1% TFA), gradient time – 15 min., hold time – 1 min., flow rate - 40 mL/min, retention time of pure product - 10.45-11.37). The fractions containing the desired product were neutralized with 1N NaOH and placed in the speed vacuum for approximately 4
10 hours. The fractions were then combined, and pH 4.0 buffer (15mL) was added. The pH was adjusted to pH 4-5 using 1N HCl and the aqueous layer was extracted with ethyl acetate (3 x 20mL). The organic layer was washed with brine (15 mL), dried over MgSO₄, and concentrated in vacuo. The product was placed on an oil pump to dry overnight, and an oily liquid was obtained (37 mg, 50%).
15 LC/MS rt-min (MH⁺): 2.37 (499.3) (method A).

Step 2:

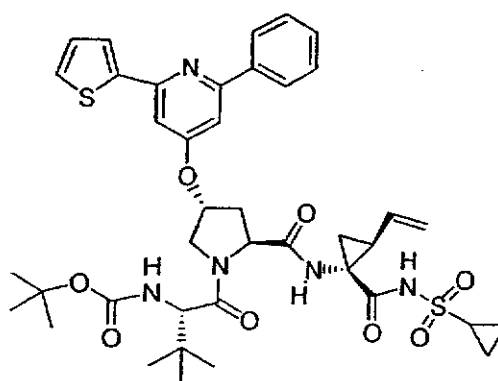
The product from Example 412, Step 1 (39 mg, 0.0773 mmol) was dissolved in DCM (4 mL) and cyclopropanesulfonic acid (1 (*R*)-amino-2 (*S*)-vinyl-
20 cyclopropanecarbonyl)-amide hydrochloride salt (Example 1, Step 8) (0.0206 g, 0.0773 mmol) was added. DIPEA (0.015 mL, 0.387 mmol), and then HATU (0.0411 g, 0.108 mmol) were added under a nitrogen atmosphere. The reaction was left to stir at room temperature for 15 hours. 10 mL DCM was added to the solution in order to increase the volume, and the reaction was quenched with pH 4.00 buffer
25 solution (10 mL). The mixture was acidified to a pH of 4-5 using 1N HCl and the aqueous phase was extracted with DCM (3 x 15 mL). The organic phase was washed twice with pH 4.00 buffer solution (10 mL) and brine (10 mL), and then dried over MgSO₄. The resulting solution was concentrated in vacuo and purified by a Biotage 12M column (eluted 20% - 50% acetone in hexanes). This purification afforded the
30 pure Compound 412 as a white powder (4 mg, 7%).

¹H NMR: δ 1.04-1.29 (m, 24H), 1.45-1.47 (m, 1H), 1.89-1.91 (m, 1H), 2.26-2.31 (m, 2H), 2.51-2.53 (m, 1H), 2.92-2.95 (m, 1H), 4.05-4.07 (d, *J* = 10 Hz, 1H), 4.22-

4.24 (d, $J = 10$ Hz, 1H), 4.38-4.40 (d, $J = 10$ Hz, 1H), 4.48-4.52 (m, 1H), 5.15-5.17 (d, $J = 10$ Hz, 1H), 5.32-5.36 (d, $J = 20$ Hz, 1H), 5.76-5.83 (m, 2H), 6.65-6.67 (d, NH), 7.19-7.21 (m, 2H), 7.66-7.67 (d, $J = 5$ Hz, 1H), 7.86-7.87 (d, $J = 5$ Hz, 1H), 8.69 (s, 1H);

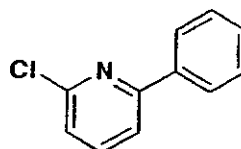
5 LC/MS rt-min (MH^+): 2.45 (739.4) (method A).

Example 413: Preparation of Compound 413



Compound 413

Step 1:



10

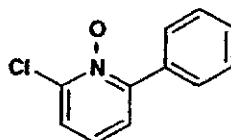
2-Bromo-6-chloropyridine (3.0 g, 15.55 mmol) and phenylboronic acid (1.896 g, 15.55 mmol) were solvated in a mixture of EtOH, toluene and water (2:1:1; 120 mL). Aqueous 1M Na_2CO_3 (15.55 mL, 31.10 mmol) and 5 mole percent of Tetrakis(triphenyl)phosphine)-palladium (0) (0.896 g, 0.775 mmol) were added under a nitrogen atmosphere. The reaction was refluxed at $90^{\circ}C$ for one hour. Water (20 mL) was added to quench the reaction, and the aqueous layer was extracted with diethyl ether (4 x 25 mL). The organic layer was then washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude mixture was purified by a Biotage 40S column (eluted 2% - 10% ethyl acetate in hexanes), to afford the pure titled compound (1.45 g, 74%).

20

^1H NMR: δ 7.24-7.26 (m, 1H), 7.42-7.48 (m, 3H), 7.63-7.70 (m, 2H), 7.98-8.00 (m, 2H);

LC/MS rt-min (MH^+): 2.04 (190.18) (method A)

Step 2:

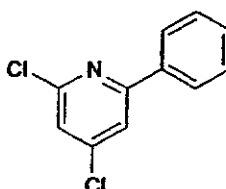


- 5 TFA (20 mL) was added to the pure solid obtained in Step 1 (3.27 g, 17.24 mmol). A 30% solution of H_2O_2 (5.55 mL, 48.9 mmol) was slowly added dropwise to the stirring solution under a nitrogen atmosphere. The reaction was heated to reflux at $100^\circ C$ for 3 hours, and 0.5 additional equivalents of H_2O_2 (2.27 mL, 25 mmol) were added to the solution. The reaction continued to stir at $100^\circ C$ for 2 hours. The flask
- 10 was allowed to cool to room temperature before the solution was concentrated in vacuo to approximately half of the original volume. Water (40 mL) was added to quench the reaction and the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The organic layer was washed once with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by Biotate 40M column
- 15 (eluted 10% - 75% ethyl acetate in hexanes) to yield a pale yellow liquid (0.81 g, 23%). Pure starting material was also recovered for future use (1.895 g, 58%).
- ^1H NMR: δ 7.40-7.42 (t, 1H), 7.49-7.50 (m, 3H), 7.59-7.61 (d, $J = 10$ Hz, 1H), 7.77-7.82 (m, 3H);

LC/MS rt-min (MH^+): 1.12 (206.37) (method A).

20

Step 3:



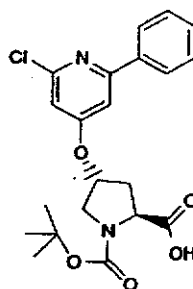
- The purified product from Step 2 (0.81 g, 3.94 mmol) was added to a solution of $SOCl_2$ (25 mL) and stirred at $60^\circ C$ for 2 hours. The temperature was then increased
- 25 to $80^\circ C$ in order to force the reaction to completion, and it was heated for an additional 30 min. The solution was concentrated in vacuo and quenched carefully with ice. The pH was adjusted to a pH of 4-5 using 10N NaOH, keeping the flask in

an ice bath. The aqueous phase was extracted with ether (4 x 25 mL), and the organic layer was washed with brine (20 mL), dried over MgSO_4 , and concentrated in vacuo. The crude, yellow liquid was purified by Biotage 40S column (eluted 2%-10% ethyl acetate in hexanes). A slightly yellow, viscous liquid was obtained (538 mg, 61%).

^1H NMR: δ 7.52-7.55 (m, 3H), 7.73 (s, 1H), 8.10-8.11 (m, 2H), 8.17 (s, 1H);

LC/MS $t_{\text{r-min}}$ (MH^+): 2.62 (225.33) (method A).

Step 4:



10

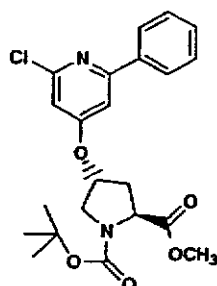
To a solution of Boc-L-hydroxyproline (555 mg, 2.40 mmol) in DMSO (4 mL), KO^tBu (0.619 g, 5.52 mmol) was added under a nitrogen atmosphere. The suspension was stirred at room temperature for 45 min., and 2,4-dichloro-6-phenylpyridine (purified in Step 3.) (538 mg, 2.40 mmol) was added in two portions. The mixture was stirred at room temperature for two hours and 1.3 equivalents of HCl (1N) were used to neutralize the reaction. Buffer solution of pH 4.0 was added, and the pH was adjusted to pH 4-5. Ethyl acetate was used to extract the aqueous phase, (3 x 25mL) and the organic phase was washed with brine (20 mL) and dried over MgSO_4 to yield the titled compound as a white solid (crude yield = 962 mg). The crude product was taken into the next step.

15

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LC/MS $t_{\text{r-min}}$ (MH^+): 2.55 (419.27) (method A).

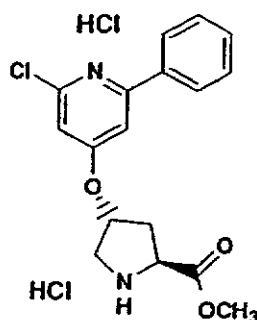
Step 5:



A solution of the crude product from Step 4 (assumed 2.4 mmol) in THF (10 mL) and methanol (10 mL) was cooled to 0° C. TMSN₂ 2M in hexanes (~ 1.3 eq) was slowly added to the stirring solution under a nitrogen atmosphere until gas was no longer emitted from the solution. The fully reacted solution was then concentrated in vacuo, and purification by a Biotage 25S column (eluted 10% - 50% ethyl acetate in hexanes) afforded the pure titled compound as a white foam (503 mg, 48% over steps 4d - 4e).

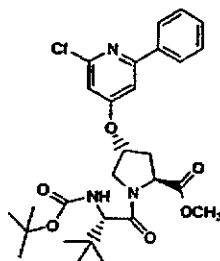
¹H NMR (DMSO-d₆) δ 1.35-1.38 (rotamers, 3H, s), 2.21-2.26 (m, 1H), 2.50-2.58 (m, 1H), 3.67-3.70 (m, 5H), 4.26-4.34 (m, 1H), 5.35 (br s, 1H), 7.14-7.15 (m, 1H), 7.47-7.55 (m, 4H), 8.05-8.09 (m, 2H);
LC/MS rt-min (MH⁺): 2.69 (455.52) (method A).

Step 6:



A solution of the pure product from Step 5 (503 mg, 1.16 mmol) in DCM (2.5 mL) and TFA (3.58 mL) was stirred at room temperature for one hour. The solvent was removed in vacuo, and the residue was suspended in 1N HCl in diethyl ether (6 mL), gently stirred, and concentrated in vacuo. This procedure was repeated and the resulting product was placed on an oil pump to yield a white solid in quantitative yield. The crude product was carried into the next step.

Step 7:

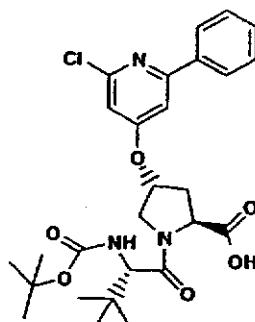


The product from Step 6 (assumed quantitative yield, 1.83 mmol) was added to a solution of BOC-t-Butyl-L-glycine (0.424 g, 1.83 mmol) in DCM (11 mL) under a nitrogen atmosphere. This step was followed by the addition of HOBt (0.272 g, 2.02 mmol), DIPEA (2.23 mL, 12.82 mmol), and HBTU (1.04 g, 2.75 mmol). The reaction was left to stir at room temperature for 15 hours. 15 mL DCM was added to the solution in order to increase the volume, and the reaction was quenched with pH 4.00 buffer solution (15 mL). The mixture was acidified to a pH of 4.5 using 1N HCl, and the aqueous phase was extracted with DCM (3 x 20 mL). The organic phase was washed twice with pH 4.00 buffer solution (20 mL), saturated NaOH (25 mL), brine (20 mL), and dried over MgSO₄. The resulting solution was concentrated in vacuo and purified by a Biotage 40S column (eluted 20% - 50% ethyl acetate in hexanes). This purification afforded the pure titled compound as a white solid (454 mg, 53%).

¹H NMR: (DMSO-d₆) δ 0.96 (s, 9H), 1.19 (s, 9H), 2.17-2.29 (m, 1H), 2.48-2.58 (m, 1H), 3.65 (s, 3H), 3.81-3.89 (m, 1H), 4.05-4.08 (m, 1H), 4.21-4.26 (m, 1H), 4.44-4.50 (t, 1H), 5.45 (br s, 1H), 6.72-6.75 (d, *J* = 15 Hz, 1H), 7.09 (s, 1H), 7.46-7.51 (m, 4H), 8.02-8.06 (m, 2H);

LC/MS rt-min (MH⁺): 2.27 (493.5) (method A).

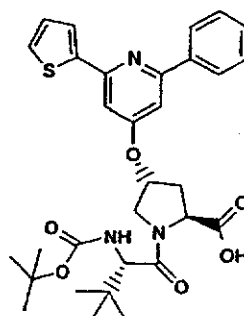
Step 8:



LiOH (0.0233 g, 0.973 mmol) was dissolved in water (10 mL) by heating and sonication. The LiOH solution was added to a solution of the pure material from Step 7 (483 mg, 0.885 mmol) in THF (10 mL), and the mixture immediately turned a pale peach color. The reaction was left to stir at room temperature for 1 hour and was acidified with 1N HCl (0.973 mL, 0.974 mmol). The reaction was quenched with pH 4.00 buffer solution and the pH was adjusted to a pH between 4 and 5. The aqueous layer was extracted with EtOAc (3 x 20 mL), washed with brine (15 mL) and dried over MgSO₄. The filtered solution was concentrated in vacuo and left on a vacuum line overnight. The crude product (480 mg, >95% yield) was taken into the next step.

¹H NMR: (DMSO-d₆) δ 0.94 (s, 9H), 1.20 (s, 9H), 1.32-1.34 (m, 1H), 2.12-2.4 (m, 1H), 2.51-2.55 (m, 1H), 3.81-3.83 (d, *J* = 10 Hz, 1H), 4.21-4.23 (d, *J* = 10 Hz, 1H), 4.32-4.35 (t, 1H), 5.4 (br s, 1H), 6.63-6.65 (d, NH), 7.09 (s, 1H), 7.47-7.49 (m, 4H), 8.03-8.06 (m, 2H), 12.56 (s, 1H).

Step 9:



The dipeptide from Step 8 (100 mg, 0.188 mmol) and 2-thiopheneboronic acid (0.0481 g, 0.376 mmol) were solvated in DMF (2 mL). The solution was placed under a nitrogen atmosphere and 2M aqueous KF (0.282 mL, 0.376 mmol) was added. Five mole percent of Tetrakis(triphenyl)phosphine)-palladium (0) was added

(0.011 mg, 0.0094 mmol) and the mixture was heated by microwave using the Personal Chemistry Emrys Optimizer for 30 minutes at 150°C. Palladium black precipitated out of the reaction upon completion. The mixture was acidified with one equivalent of 1N HCl and filtered through a syringe, using MeOH to extract the product. The product was purified by prep HPLC (column – 4 Xterra S5 Sum 30 x 75 mm, solvent – 85% A / 15% B – 10% A / 90% B (where solvent A is 10% MeOH, 90% H₂O, 0.1% TFA and solvent B is 90% MeOH, 10% H₂O, 0.1% TFA), gradient time – 15 min., hold time – 1 min., flow rate – 40 mL/min, retention time of pure product – 16.23). Fractions containing the desired product were neutralized with 1N NaOH and placed in the speed vac for approximately 2 hours. The fractions were combined, and pH 4.0 buffer (15mL) was added. The pH was adjusted to pH 4-5 using 1N HCl, and the aqueous layer was extracted with ethyl acetate (3 x 20mL). The organic layer was washed with brine (15 mL), dried over MgSO₄, and concentrated in vacuo. The product was placed on an oil pump to dry overnight, and a pale yellow oil was obtained (44 mg, 40%).
LC/MS rt-min (MH⁺): 2.7 (580.54) (method A).

Step 10:

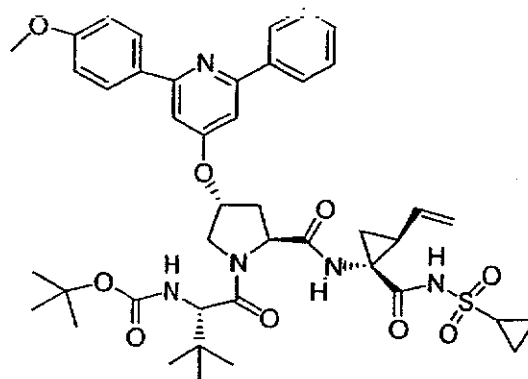
The product from Example 413, Step 9 (43 mg, 0.0742 mmol) was dissolved in DCM (2 mL) and cyclopropanesulfonic acid (1 (*R*)-amino-2 (*S*)-vinyl-cyclopropanecarbonyl)-amide hydrochloride salt (Example 1, Step 8) (0.0198 g, 0.0742 mmol) was added. DIPEA (0.0646 mL, 0.371 mmol), and then HATU (0.039 g, 0.0104 mmol) were added under a nitrogen atmosphere. The reaction was left to stir at room temperature for 4.5 hours. 10 mL of DCM was added to the solution in order to increase the volume, and the reaction was quenched with pH 4.00 buffer solution (10 mL). The mixture was acidified to a pH of 4-5 using 1N HCl, and the aqueous phase was extracted with DCM (3 x 15 mL). The organic phase was washed twice with pH 4.00 buffer solution (10 mL) and brine (10 mL), and then dried over MgSO₄. The resulting solution was concentrated in vacuo and purified by a Biotage 12S column (eluted 10% - 50% acetone in hexanes). The compound was isolated and re-purified by prep-HPLC (column – YMC ODS-A 20 x 50 mm s5, solvent – 60% A / 40% B – 10% A / 90% B (where solvent A is 10% MeOH, 90% H₂O, 0.1% TFA and

solvent B is 90% MeOH, 10% H₂O, 0.1% TFA), gradient time – 8 min., hold time – 2 min., flow rate - 25 mL/min, retention time of pure product – 8.702). This purification afforded the pure Compound 413 as a pale orange oil (22.3 mg, 38%).

- 5 ¹H NMR: δ 1.02-1.29 (m, 24H), 1.42-1.45 (m, 1H), 1.87-1.89 (m, 1H), 2.24-2.30 (m, 2H), 2.53-2.57 (m, 1H), 2.92-2.97 (m, 1H), 4.06-4.08 (d, J = 10 Hz, 1H), 4.25 (s, 1H), 4.31-4.33 (d, J = 10 Hz, 1H), 4.45-4.49 (t, 1H), 5.12-5.14 (d, J = 10 Hz, 1H), 5.29-5.32 (d, J = 15 Hz, 1H), 5.46 (br s, 1H), 5.73-5.80 (m, 1H), 7.13-7.15 (m, 1H), 7.29-7.30 (d, J = 5 Hz, 2H), 7.42-7.53 (m, 4H), 7.75-7.56 (d, J = 5 Hz, 1H), 8.07-8.09
- 10 (d, J = 10 Hz, 2H).

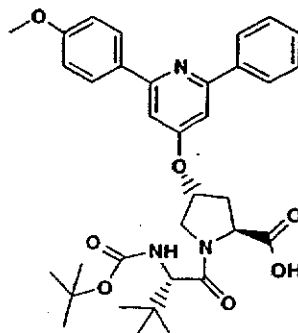
LC/MS rt-min (MH⁺): 2.79 (792.72) (method A).

Example 414: Preparation of Compound 414.



Compound 414

15 Step 1:



The pure material from Example 413, Step 8 (100 mg, 0.188 mmol), and 4-methoxyphenylboronic acid (0.0429 g, 0.282 mmol) were solvated in DMF (2.5 mL). The solution was placed under a nitrogen atmosphere and 2M aqueous Na₂CO₃

(0.188 mL, 0.376 mmol) was added. Five mole percent of Tetrakis(triphenyl)phosphine)-palladium (0) was added (0.011 mg, 0.0094 mmol), and the mixture was heated by microwave using the Personal Chemistry Emrys Optimizer for 30 minutes at 150°C. Palladium black precipitated out of the reaction upon completion. The mixture was acidified with one equivalent of 1N HCl and filtered through a syringe, using MeOH to extract product. The product was purified by prep HPLC (column - Xterra MS C18 5um 30 x 50 mm, solvent - 90% A / 10% B - 10% A / 90% B (where solvent A is 10% MeOH, 90% H₂O, 0.1% TFA and solvent B is 90% MeOH, 10% H₂O, 0.1% TFA), gradient time - 15 min., hold time - 1 min., flow rate - 45 mL/min, retention time of pure product - 13.72). Fractions containing the desired product were neutralized with 1N NaOH and placed in the speed vac for approximately 2 hours. The fractions were combined, and pH 4.0 buffer (15mL) was added. The pH was adjusted to pH 4-5 using 1N HCl, and the aqueous layer was extracted with ethyl acetate (3 x 20mL). The organic layer was washed with brine (15 mL), dried over MgSO₄, and concentrated in vacuo. The product was placed on an oil pump to dry overnight, and a viscous oil was obtained (44 mg, 50%). LC/MS rt-min (MH⁺): 2.23 (604.61) (method A).

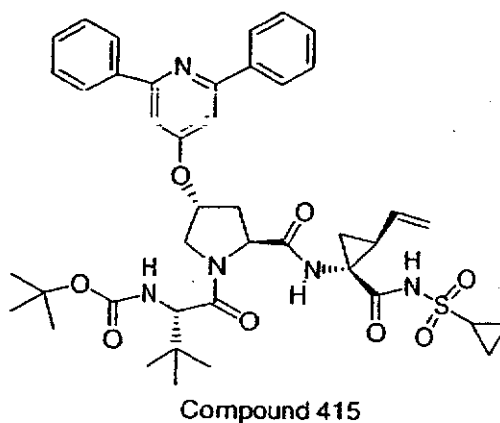
Step 2:

The product from Example 414, Step 1 (43 mg, 0.0712 mmol) was dissolved in DCM (2 mL) and cyclopropanesulfonic acid (1 (*R*)-amino-2 (*S*)-vinyl-cyclopropanecarbonyl)-amide hydrochloride salt (Example 1, Step 8) (0.01899 g, 0.0712 mmol) was added. DIPEA (0.062 mL, 0.356 mmol), and then HATU (0.038 g, 0.0997 mmol) were added under a nitrogen atmosphere. The reaction was left to stir at room temperature for 4.5 hours. 10 mL DCM was added to the solution in order to increase the volume, and the reaction was quenched with pH 4.00 buffer solution (10 mL). The mixture was acidified to a pH of 4-5 using 1N HCl, and the aqueous phase was extracted with DCM (3 x 15 mL). The organic phase was washed twice with pH 4.00 buffer solution (10 mL) and brine (10 mL), and then dried over MgSO₄. The resulting solution was concentrated in vacuo and purified by a Biotage 12S column (eluted 20% - 50% acetone in hexanes). The compound was isolated and re-purified by prep-HPLC (column - YMC ODS-A 20 x 50 mm s5, solvent - 60% A /

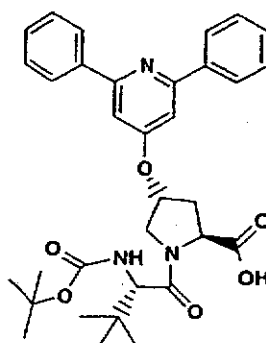
40% B – 10% A / 90% B (where solvent A is 10% MeOH, 90% H₂O, 0.1% TFA and solvent B is 90% MeOH, 10% H₂O, 0.1% TFA), gradient time – 10 min., hold time – 2 min., flow rate – 25 mL/min, retention time of pure product – 7.43-8.24). This purification afforded the pure Compound 414 as a pale orange oil (19.4 mg, 34%).

- 5 ¹H NMR: δ 1.02-1.23 (m, 24H), 1.29-1.44 (m, 1H), 1.89-1.95 (m, 1H), 2.24-2.30 (q, 1H), 2.32-2.40 (m, 1H), 2.59-2.62 (m, 1H), 3.90 (s, 3H), 4.10-4.12 (d, J = 10 Hz, 1H), 4.21 (s, 1H), 4.42-4.56 (m, 2H), 5.12-5.14 (d, J = 10 Hz, 1H), 5.28-5.31 (d, J = 15 Hz, 1H), 5.61 (br s, 1H), 5.72-5.80 (m, 1H), 7.14-7.16 (d, J = 10 Hz, 2H), 7.52-7.54 (d, J = 10 Hz, 2H), 7.61-7.62 (m, 2H), 7.95-7.98 (m, 4H);
- 10 LC/MS rt-min (MH⁺): 2.35 (816.76) (method A).

Example 415: Preparation of Compound 415.



Step 1:



15

The dipeptide from Example 413, Step 8 (174 mg, 0.327 mmol) and phenylboronic acid (0.06 g, 0.491 mmol) were solvated in DMF (4 mL). The solution was placed under a nitrogen atmosphere and 2M aqueous NaCO₃ (0.33 mL, 0.654 mmol) was added. Five mole percent of Tetrakis(triphenyl)phosphine)-palladium (0) was added

(0.019 mg, 0.0164 mmol) and the mixture was heated by microwave using the Personal Chemistry Emrys Optimizer for 30 minutes at 150°C. Palladium black precipitated out of the reaction upon completion. The mixture was acidified with one equivalent of 1N HCl and filtered through a syringe, using MeOH to extract the product. The product was purified by prep HPLC (column – 5 Xterra c-18 5µm 30 x 100 mm, solvent – 80% A / 20% B – 0% A / 100% B (where solvent A is 10% MeOH, 90% H₂O, 0.1% TFA and solvent B is 90% MeOH, 10% H₂O, 0.1% TFA), gradient time – 20 min., hold time – 1 min., flow rate – 40 mL/min, retention time of pure product – 11.28-11.72). Fractions containing the desired product were neutralized with 1N NaOH and placed in the speed vac for approximately 2 hours. The fractions were combined, and pH 4.0 buffer (15mL) was added. The pH was adjusted to pH 4-5 using 1N HCl, and the aqueous layer was extracted with ethyl acetate (4 x 15mL). The organic layer was washed with brine (15 mL), dried over MgSO₄, and concentrated in vacuo. The product was placed on an oil pump to dry overnight. (31.5 mg, 17%).

LC/MS rt-min (MH⁺): 2.54 (574.37) (method A).

Step 2:

The product from Example 415, Step 1 (31.5 mg, 0.055 mmol) was dissolved in DCM (3 mL) and cyclopropanesulfonic acid (1 (*R*)-amino-2 (*S*)-vinyl-cyclopropanecarbonyl)-amide hydrochloride salt (Example 1, Step 8) (0.0147 g, 0.055 mmol) was added. DIPEA (0.048 mL, 0.275 mmol), and then HATU (0.029 g, 0.077 mmol) were added under a nitrogen atmosphere. The reaction was left to stir at room temperature for 3.5 hours and an additional 0.3 equivalents of cyclopropanesulfonic acid (1 (*R*)-amino-2 (*S*)-vinyl-cyclopropanecarbonyl)-amide hydrochloride salt were added. The reaction was left to stir for 8 more hours. 10 mL of DCM was added to the solution in order to increase the volume, and the reaction was quenched with pH 4.00 buffer solution (10 mL). The mixture was acidified to a pH of 4-5 using 1N HCl, and the aqueous phase was extracted with DCM (4 x 10 mL). The organic phase was washed twice with pH 4.00 buffer solution (10 mL) and brine (10 mL), and then dried over MgSO₄. The resulting solution was concentrated in vacuo and purified by prep HPLC (column – YMC ODS-A 30 x 50 mm, solvent –

80% A / 20% B – 10% A / 90% B (where solvent A is 10% MeOH, 90% H₂O, 0.1% TFA and solvent B is 90% MeOH, 10% H₂O, 0.1% TFA), gradient time – 20 min., hold time – 3 min., flow rate - 30 mL/min, retention time of pure product – 19.6).

This purification did not afford a pure compound so it was re-purified by a Biotage 12

- 5 S column (eluted 10%-50% acetone in hexanes). This purification afforded the pure titled compound as a pale orange oil (22.3 mg, 38%).

¹H NMR: δ 1.02-1.45 (m, 24H), 1.85-1.86 (m, 1H), 2.03-2.11 (m, 2H), 2.42-2.46 (m, 1H), 2.77-2.85 (m, 1H), 4.10-4.12 (m, 1H), 4.25 (s, 1H), 4.31-4.33 (d, *J* = 10 Hz, 1H), 4.49-4.54 (m, 1H), 5.03-5.05 (d, *J* = 10 Hz, 1H), 5.20-5.24 (d, *J* = 20 Hz, 1H),
10 5.44 (br s, 1H), 5.82-5.94 (m, 1H), 7.33 (s, 2H), 7.43-7.50 (m, 6 H), 8.09-8.10 (d, *J* = 5 Hz, 4 H);

LC/MS rt-min (MH⁺): 2.37 (786.37) (method A).

Section J:

- 15 In section J the LC/MS method utilized was the following:

Columns: Method A: YMC ODS-A C18 S7 (4.6 x 33 mm)

Method B: YMC Xterra ODS S7 (3.0 x 50mm)

Method C: Xterra ms C18 (4.6 x 33mm)

- 20 Method D: YMC ODS-A C18 S3 (4.6 x 33 mm)

Gradient: 100% solvent A/ 0% solvent B to 0% solvent A/ 100% solvent B

Gradient time: 3 min.

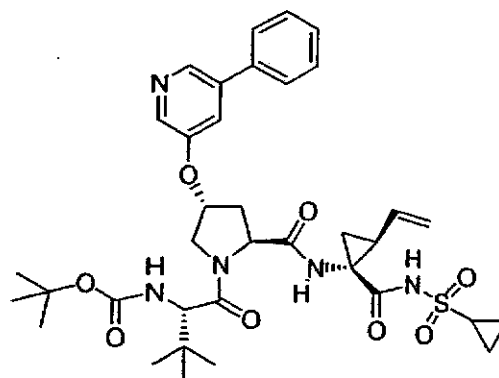
Hold Time: 1 min.

Flow Rate: 5 mL/min.

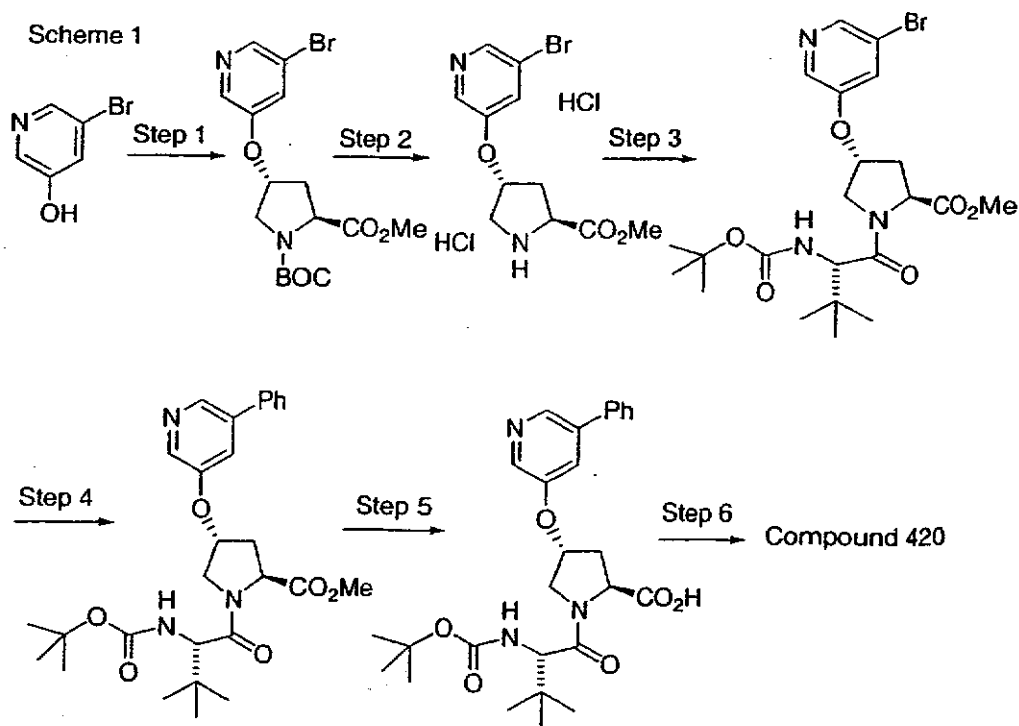
- 25 Detector Wavelength: 220 nm.

Solvents: Solvent A: 10% MeOH/ 90% water/ 0.1% TFA. Solvent B: 90% MeOH/ 10% water/ 0.1% TFA.

Example 420: Preparation of Compound 420



Compound 420



Step 1:

To a solution of PPh_3 (16.8 g, 63.9 mmol) in THF (150 mL) was added dropwise DEAD (10.1 mL, 63.9 mmol) and the solution was stirred for 30 min at room temperature. A solution of Boc-cis-(L)-Hyp-OMe (10.5 g, 42.6 mmol) in THF (50 mL) was added slowly, followed by 5-bromo-pyridin-3-ol (prepared according to F.E. Ziegler et al., J. Am. Chem. Soc., (1973), 95, 7458) (8.90 g, 51.1 mmol) portion wise. The resulting solution was stirred at 45°C for 18 hrs. The solution was concentrated in vacuo, and the residue partitioned between diethyl ether (200 mL) and 1N NaOH (50 mL). The organic phase was dried (MgSO_4) and the ethereal

solution was after filtration concentrated to half its volume. A precipitate formed that was removed by filtration. The filtrate was concentrated in vacuo and purified by a Biotage 65 M column (eluted with hexanes – EtOAc 2:1, 3:2, 1:1) to provide the title compound (11.9 g, 69%) as a red oil.

- 5 ¹H NMR: (CDCl₃) δ 1.42, 1.45 (s, 9H (rotamers)), 2.25-2.30 (m, 1H), 2.49-2.58 (m, 1H), 3.75, 3.81 (s, 3H (rotamers)), 3.66-3.81 (m, 2H (hidden)), 4.42, 4.50 (t, *J*=8 Hz, 1H (rotamers)), 4.92 (m, 1H), 7.36 (s, 1H), 8.20 (s, 1H), 8.32 (s, 1H).
LC/MS rt-min (MH⁺): 2.26 (401, 403)(method B).

10 Step 2:

The product of Step 1 (2.34 g, 5.83 mmol) was dissolved in DCM (20 mL) and TFA (18 mL, 0.23 mole) and stirred at room temperature for 2 hrs. The volatiles were removed in vacuo and the residue partitioned between EtOAc and water. The organic phase was extracted with 1N HCl (25 mL) and the combined aqueous
15 extracts were neutralized with satd. NaHCO₃ (40 mL). The aqueous phase was extracted with EtOAc (twice) and the combined organic extracts washed with brine and dried (MgSO₄) to give the title compound (1.02 g, 58%, free base) as a colorless oil.

- ¹H NMR: (DMSO-*d*₆) δ 2.12-2.20 (m, 2H), 2.94 (d, *J*=12 Hz, 1H), 3.19 (dd, *J*=4.5, 12 Hz, 1H), 3.64 (s, 3H), 3.90 (t, *J*=8 Hz, 1H), 5.07 (m, 1H), 7.69 (s, 1H), 8.26 (s, 20 1H), 8.29 (s, 1H).
LC/MS rt-min (MH⁺): 0.78 (301, 302)(method B).

Step 3:

- 25 To a suspension of the product of Step 2 (1.02 g, 3.39 mmol), *N*-BOC-*L*-tert-leucine (862 mg, 3.73 mmol), and HOBt (458 mg, 3.39 mmol) in DCM (15 mL) were added DIPEA (2.36 mL, 13.6 mmol) followed by HBTU (1.61 g, 4.24 mmol). The resulting solution was stirred at room temperature for 15 hrs and quenched with DCM and buffer pH 4 and some 1N HCl to adjust the pH to 4-5. The organic phase
30 was washed with buffer pH 4, satd. NaHCO₃ (twice), brine, and dried (MgSO₄). Purification using a Biotage 40 M column (eluted hexane – EtOAc 3:2, 1:1) afforded the title compound (1.48 g, 85%) as a white solid.

¹H NMR: (DMSO-d₆) δ 0.94 (s, 9H), 1.17 (s, 9H), 2.16-2.21 (m, 1H), 2.50 (m, (hidden), 1H), 3.64 (s, 3H), 3.82 (d, *J*=12 Hz, 1H), 4.06 (d, *J*=9.5 Hz, 1H), 4.16 (d, *J*=12 Hz, 1H), 4.45 (dd, *J*=8, 9.5 Hz, 1H), 5.26 (m, 1H), 6.71 (d, *J*=9 Hz, NH), 7.75 (s, 1H), 8.28 (s, 1H), 8.32 (s, 1H).

5 LC/MS rt-min (MH⁺): 2.35 (514, 516)(method B).

Step 4:

To a mixture of the product of Step 3 (98 mg, 0.19 mmol), Pd(PPh₃)₄ (6.6 mg, 0.00573 mmol), 2M aqueous Na₂CO₃ (0.191 mL, 0.381 mmol) in toluene (2 mL) was
10 added a solution of phenyl boronic acid (29 mg, 0.24 mmol) in methanol (0.1 mL).

The solution was heated at 85°C for 6 h under nitrogen. After cooling to room temperature the mixture was quenched with buffer pH 4 and extracted with EtOAc (2 x 10 mL), and dried (Na₂SO₄). Purification using a Biotage 12 M column (eluted hexane – EtOAc 2:3) afforded the title compound (72 mg, 74%) as a colorless oil.

15 ¹H NMR: (methanol-d₄) δ 1.05 (s, 9H), 1.31 (s, 9H), 2.29-2.35 (m, 1H), 2.68-2.72 (m, 1H), 3.77 (s, 3H), 4.00 (d, *J*=12 Hz, 1H), 4.24 (d, *J*=9.5 Hz, 1H), 4.41 (d, *J*=12 Hz, 1H), 4.67 (dd, *J*=7.5, 10 Hz, 1H), 5.36 (m, 1H), 6.51 (d, *J*=9.5 Hz, NH), 7.79-7.85 (m, 3H), 8.39 (s, 1H), 8.59 (s, 1H), 8.67-8.68 (m, 2H).

LC/MS rt-min (MH⁺): 2.16 (512)(method B).

20

Step 5:

To a solution of the product of Step 4 (150 mg, 0.293 mmol) in THF (2 mL) and methanol (2 mL) was added LiOH (14 mg, 0.59 mmol) in water (2 mL). The mixture was stirred for 2 h at room temperature and quenched with 1N HCl until
25 neutral pH. The organic volatiles were removed in vacuo and to the residue was added buffer pH 4. The product was extracted into EtOAc (3 x 10 mL), washed with brine/buffer pH 4 and dried (MgSO₄) to yield the title compound in quantitative yield as a white solid after trituration from pentane.

30 ¹H NMR: (methanol-d₄) δ 1.05 (s, 9H), 1.32 (s, 9H), 2.32-2.38 (m, 1H), 2.69-2.74 (m, 1H), 3.99 (dd, *J*=3, 12 Hz, 1H), 4.25 (s, 1H), 4.40 (d, *J*=12 Hz, 1H), 4.64 (dd, *J*=7.5, 9.5 Hz, 1H), 5.36 (m, 1H), 7.85-7.87 (m, 3H), 8.40 (s, 1H), 8.60 (s, 1H), 8.69-8.70 (m, 2H).

LC/MS rt-min (MH^+): 2.03 (499)(method B).

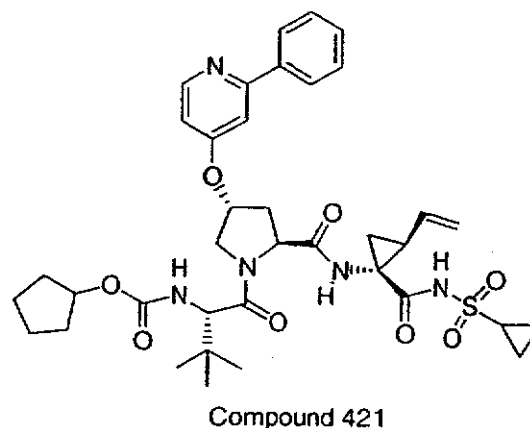
Step 6:

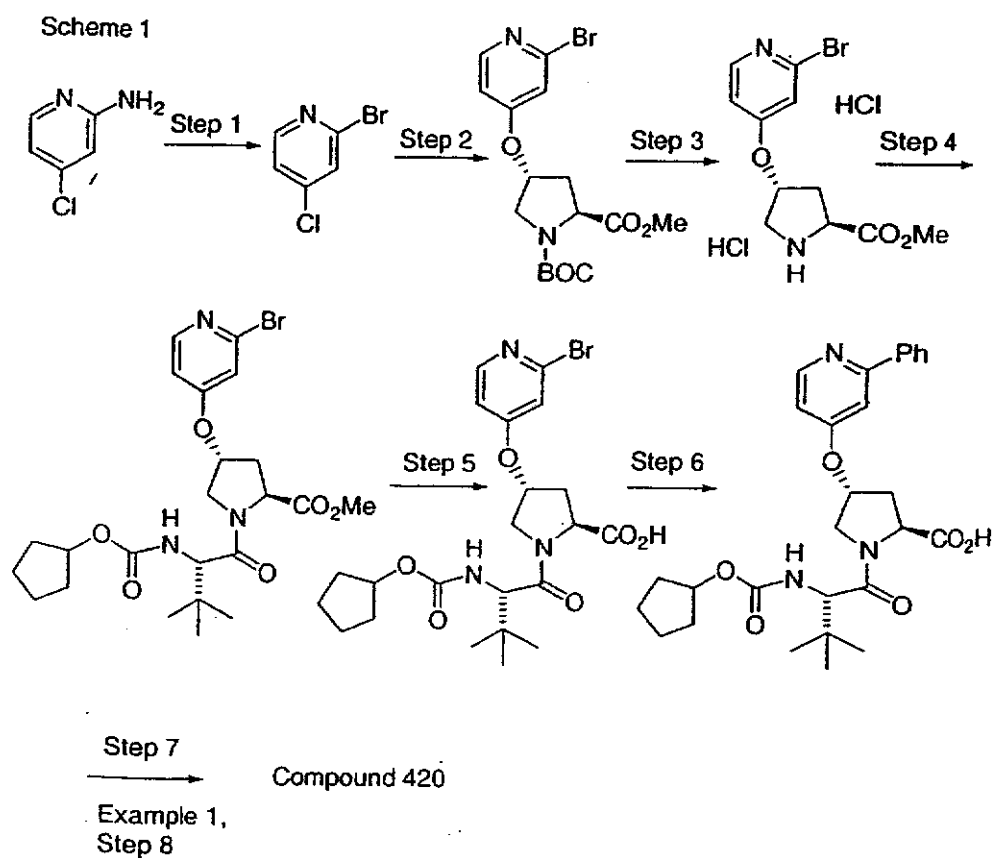
To a suspension of the product of Step 5 (93 mg, 0.19 mmol), and the product
5 from Example 1, Step 8 (50 mg, 0.19 mmol) in DCM (2 mL) was added DIPEA
(0.163 mL, 0.935 mmol), followed by HATU (92 mg, 0.243 mmol). The resulting
mixture was stirred at room temperature for 18 hrs and quenched with DCM and
buffer pH 4 and some 1N HCl to adjust the pH to 4-5. The layers were separated and
the aqueous phase extracted with DCM (10 mL) and dried (Na_2SO_4). Purification
10 using a Biotage 12 M column (eluted gradient hexane - acetone 20-60%) afforded
the title compound (65 mg, 49%) as a white powder.

^1H NMR: ($DMSO-d_6$) δ 0.95 (s, 9H), 1.03-1.05 (m, 2H), 1.08-1.10 (m, 2H), 1.26 (s,
9H), 1.36-1.39 (m, 1H), 1.69-1.72 (m, 1H), 2.09-2.21 (m, 2H), 2.41-2.45 (m, 1H),
2.92-2.94 (m, 1H), 3.91 (d, $J=11.5$ Hz, 1H), 4.06 (d, $J=11.5$ Hz, 1H), 4.16 (d, $J=11.5$
15 Hz, 1H), 4.36 (t, $J=8.5$ Hz, 1H), 5.10 (d, $J=10$ Hz, 1H), 5.23 (d, $J=17.5$ Hz, 1H),
5.38 (m, 1H), 5.59-5.67 (m, 1H), 6.54 (s, NH), 7.41-7.46 (m, 1H), 7.50-7.53 (m, 2H),
7.65 (s, 1H), 7.74-7.75 (m, 2H), 8.28 (s, 1H), 8.52 (s, 1H), 8.92 (s, NH).

LC/MS rt-min (MH^+): 2.08 (710)(method B).

20 Example 421: Preparation of Compound 421.





Step 1:

To a cold (-5°C) 48% aqueous HBr solution (35 mL) was added 4-chloro-pyridin-2-ylamine (4.18 g, 32.5 mmol; prepared according to K.S. Gudmundsson et al; Synth. Commun. (1997), 27, 861), followed by the slow addition of bromine (6.7 mL, 0.13 mole). After 20 min sodium nitrite (8.63 g, 0.125 mole) in water (40 mL) was added at the same temperature and stirring was continued for 30 min. The reaction was quenched under ice cooling with 10 N NaOH (ca 40 mL) to alkaline pH. The product was extracted into EtOAc (2 x 100 mL) and dried (Na_2SO_4). The crude material was purified using a Biotage 40 M column (eluted with 10% EtOAc in hexanes) to afford the title compound (2.50 g, 40%) as a colorless oil that solidified upon standing.

^1H NMR: ($\text{DMSO}-d_6$) δ 7.64 (dd, $J=1.5, 5.5$ Hz, 1H), 7.94 (d, $J=1.5$ Hz, 1H), 8.40 (d, $J=5.5$ Hz, 1H);

LC/MS rt-min (MH^+): 1.65 (192, 194, 196)(method B).

Step 2:

To a solution of *N*-BOC-*trans*-*L*-Hyp-OH (3.22 g, 13.9 mmol) in DMSO (30 mL) was added potassium *tert*-butoxide (3.90 g, 34.8 mmol) in portions at room temperature under a nitrogen atmosphere. After 1.5 h the product of Step 1 was added in DMSO (5 mL). The mixture was stirred overnight and quenched with water (150 mL). The solution was washed with EtOAc (100 mL). The aqueous phase was acidified to pH 4 with 1N HCl. The crude carboxylic acid was extracted into EtOAc (thrice) and dried (MgSO₄). The residue, as a brown solid, was suspended in THF (20 mL) and MeOH (20 mL) and cooled to 0°C. A solution of trimethylsilyl diazomethane (2 M in hexane, 12 mL) was dropwise added, and the solution concentrated in vacuo after 15 min. Purification using a Biotage 40 M column (eluted with hexanes – EtOAc 2:1, 1:1) gave the title compound (3.47 g, 62%) as an off-white powder.

¹H NMR: (DMSO-*d*₆) δ 1.34, 1.38 (s, 9H (rotamers)), 2.24–2.29 (m, 1H), 2.43–2.50 (m, 1H), 3.57 (d, *J*=12.5 Hz, 1H), 3.64–3.68 (m, 1H), 3.66, 3.69 (s, 3H (rotamers)), 4.27–4.34 (m, 1H), 5.21 (m, 1H), 7.06 (d, *J*=6 Hz, 1H), 7.28 (s, 1H), 8.20 (d, *J*=6 Hz, 1H);

LC/MS *rt*-min (MH⁺): 2.59 (401, 403)(method B).

Step 3:

The product of Step 2 (2.00 g, 4.98 mmol) was suspended in 4N HCl in dioxane (10 mL) and 1N HCl in diethyl ether (40 mL) and stirred overnight at room temperature. The resulting suspension was concentrated in vacuo and the residue triturated from pentane to give the title compound in quantitative yield as a white powder.

LC/MS *rt*-min (MH⁺): 0.24 (301, 303)(method B).

Step 4:

To a suspension of the product of Step 3 (assumed 4.98 mmol), *N*-cyclopentyloxycarbonyl-*L*-*tert*-leucine (1.24 g, 5.10 mmol), and HOBt (673 mg, 4.98 mmol) in DCM (25 mL) was added DIPEA (4.34 mL, 24.9 mmol) followed by HBTU (2.36 g, 6.23 mmol). The resulting solution was stirred at room temperature

for 15 hrs and quenched with DCM and buffer pH 4 and 10 mL 1N HCl to adjust the pH to 4. The aqueous phase was extracted with DCM (twice). The combined organic extracts were washed with satd. NaHCO₃ (twice), brine, and dried (MgSO₄).

Purification using a Biotage 40 M column (eluted hexane – EtOAc 3:2, 1:1) afforded
5 the title compound (2.09 g, 80%) as a white foam.

¹H NMR: (DMSO-d₆) δ 0.94 (s, 9H), 1.43–1.74 (m, 8H), 2.18–2.23 (m, 1H), 2.46–2.49 (m, 1H), 3.64 (s, 3H), 3.87 (d, *J*=12 Hz, 1H), 4.08–4.13 (m, 1H), 4.42 (dd, *J*=7.5, 9.5 Hz, 1H), 4.78 (m, 1H), 5.30 (m, 1H), 7.03–7.05 (m, 1H), 7.24 (s, 1H), 8.120 (d, *J*=6 Hz, 1H).

10 LC/MS rt-min (MH⁺): 2.34 (526, 528)(method C).

Step 5:

To a solution of the product of Step 4 (206 mg, 0.391 mmol) in THF (2 mL) and methanol (2 mL) was added LiOH (28 mg, 1.2 mmol) in water (2 mL). The
15 mixture was stirred for 2 h at room temperature and quenched with 1N HCl until neutral pH. The organic volatiles were removed in vacuo and to the residue was added buffer pH 4. The product was extracted into EtOAc (2 x 20 mL) and dried (MgSO₄) to yield the title compound (196 mg, 100%) as a white solid.

¹H NMR: (methanol-d₄) δ 1.05 (s, 9H), 1.60–1.85 (m, 8H), 2.30–2.36 (m, 1H), 2.62–2.67 (m, 1H), 3.97 (d, *J*=12 Hz, 1H), 4.26 (s, 1H), 4.32 (d, *J*=12 Hz, 1H), 4.58 (dd, *J*=7.5, 9.5 Hz, 1H), 4.89 (m (hidden), 1H), 5.29 (m, 1H), 7.03–7.05 (m, 1H), 7.26 (s, 1H), 8.19 (d, *J*=6 Hz, 1H);

LC/MS rt-min (MH⁺): 2.17 (512, 514)(method B).

25 Step 6:

This product was prepared according to Example 420, Step 4 (reaction time 20 h) in 20% yield starting from the product of Example 421, Step 5.

¹H NMR: (methanol-d₄) δ 1.03 (s, 9H), 1.45–1.74 (m, 8H), 2.31–2.37 (m, 1H), 2.65–2.69 (m, 1H), 3.99 (dd, *J*=12, 3.0 Hz, 1H), 4.26 (d, *J*=9.5 Hz, 1H), 4.33 (d, *J*=11.5
30 Hz, 1H), 4.60 (dd, *J*=8.0, 9.5 Hz, 1H), 4.80 (m, 1H), 5.35 (m, 1H), 6.72 (d, *J*=9.0 Hz, NH), 7.02 (dd, *J*=2.5, 6.0 Hz, 1H), 7.39 (s, 1H), 7.50 (m, 3H (hidden)), 7.91 (d, *J*=6.5 Hz, 1H), 8.46 (d, *J*=6.0 Hz, 1H).

LC/MS rt-min (MH^+): 2.03 (510)(method A).

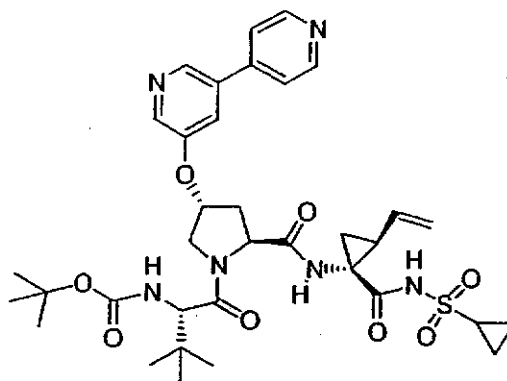
Step 7:

Compound 421 was prepared according to Example 420, Step 6 in 68% yield, starting from the product of Example 421, Step 6.

^1H NMR: (methanol- d_4) δ 1.03 (s, 9H), 1.06-1.09 (m, 2H), 1.23-1.26 (m, 2H), 1.43 (dd, $J=5.5, 9.5$ Hz, 1H), 1.47-1.77 (m, 8H), 1.88 (dd, $J=5.5, 8.5$ Hz, 1H), 2.21-2.29 (m, 2H), 2.50-2.54 (m, 1H), 2.91-2.96 (m, 1H), 4.06 (dd, $J=3.0, 11.5$ Hz, 1H), 4.28-4.30 (m, 2H), 4.44 (dd, $J=7.0, 10.5$ Hz, 1H), 4.82 (m, 1H (hidden)), 5.12 (d, $J=10$ Hz, 1H), 5.30 (d, $J=17$ Hz, 1H), 5.37 (m, 1H), 5.73-5.80 (m, 1H), 6.92 (d, $J=9.5$ Hz, NH), 6.98 (dd, $J=5.5, 2.0$ Hz, 1H), 7.37 (s, 1H), 7.43-7.50 (m, 3H), 7.90 (d, $J=7.0$ Hz, 1H), 8.45 (d, $J=5.5$ Hz, 1H).

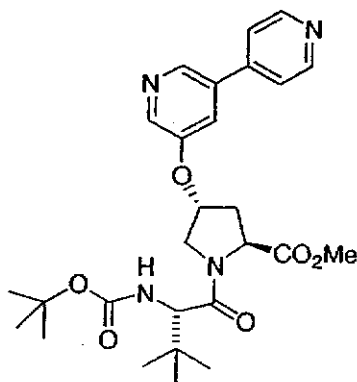
LC/MS rt-min (MH^+): 2.37 (723)(method A).

Example 422: Preparation of Compound 422.



Compound 422

Step 1:



To a mixture of the product of Example 420, Step 3 (102 mg, 0.198 mmol) and Pd(PPh₃)₄ (23 mg, 0.0198 mmol) in toluene (2 mL) was added 4-tributylstannanyl-pyridine (87 mg, 0.24 mmol). The solution was heated at 105°C for 20 h under nitrogen. After cooling to room temperature the mixture was quenched with satd.

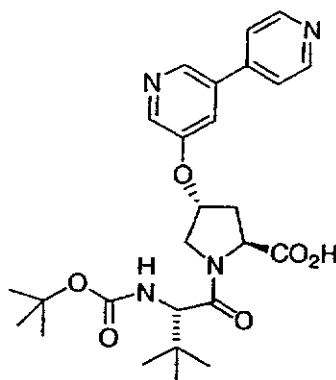
- 5 NaHCO₃ and extracted with EtOAc (2 x 10 mL), and dried (Na₂SO₄). Purification using a Biotage 12 M column (eluted gradient hexane-acetone 20-60%) afforded the title compound (49 mg, 49%) as a white solid.

¹H NMR: (methanol-d₄) δ 1.05 (s, 9H), 1.31 (s, 9H), 2.29-2.35 (m, 1H), 2.68-2.72 (m, 1H), 3.77 (s, 3H), 4.00 (d, *J*=12 Hz, 1H), 4.24 (d, *J*=9.5 Hz, 1H), 4.41 (d, *J*=12 Hz, 1H), 4.67 (dd, *J*=7.5, 10 Hz, 1H), 5.36 (m, 1H), 6.51 (d, *J*=9.5 Hz, NH), 7.79-7.85 (m, 3H), 8.39 (s, 1H), 8.59 (s, 1H), 8.67-8.68 (m, 2H).

10

LC/MS rt-min (MH⁺): 1.77 (514)(method C).

Step 2:



15

This product was prepared by the same procedure as described in Example 420, Step 5 in quantitative yield, except using the product from Example 422, Step 1 instead.

¹H NMR: (methanol-d₄) δ 1.05 (s, 9H), 1.32 (s, 9H), 2.32-2.38 (m, 1H), 2.69-2.74 (m, 1H), 3.99 (dd, *J*=3, 12 Hz, 1H), 4.25 (s, 1H), 4.40 (d, *J*=12 Hz, 1H), 4.64 (dd, *J*=7.5, 9.5 Hz, 1H), 5.36 (m, 1H), 7.85-7.87 (m, 3H), 8.40 (s, 1H), 8.60 (s, 1H), 8.69-8.70 (m, 2H).

20

LC/MS rt-min (MH⁺): 1.57 (500)(method B).

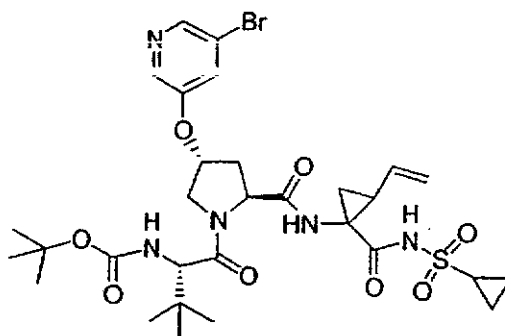
Step 3:

Compound 422 was prepared by the same procedure as described in Example 420, Step 6 in 51% yield as a white solid, except using the product from Example 422, Step 2 instead.

¹H NMR: (DMSO-d₆) δ 0.95 (s, 9H), 1.03 (m, 1H), 1.08 (m, 1H), 1.23 (s, 9H), 1.34-1.37 (m, 1H), 1.68-1.70 (m, 1H), 2.12-2.18 (m, 2H), 2.41-2.45 (m, 1H), 2.93 (m, 1H), 3.90 (d, *J*=11 Hz, 1H), 4.06 (d, *J*=9 Hz, 1H), 4.17 (d, *J*=11 Hz, 1H), 4.36 (dd, *J*=7, 10 Hz, 1H), 5.10 (d, *J*=12 Hz, 1H), 5.23 (d, *J*=16.5 Hz, 1H), 5.40 (m, 1H), 5.59-5.66 (m, 1H), 6.60 (d, *J*=9 Hz, NH), 7.81-7.82 (m, 3H), 8.38 (s, 1H), 8.65 (s, 1H), 8.68-8.70 (m, 2H), 8.93 (s, NH), 10.4 (s, NH).

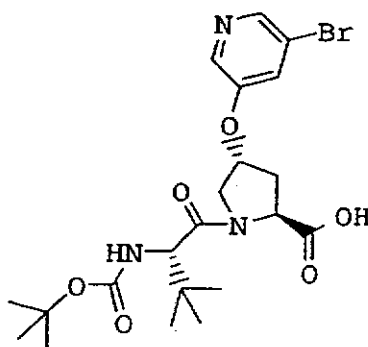
LC/MS rt-min (MH⁺): 2.14 (711)(method D).

Example 423: Preparation of Compound 423.



Compound 423

Step 1:



15

To a solution of the product of Example 420, Step 3 (1.00 g, 1.94 mmol) in THF (5 mL) and methanol (5 mL) was added LiOH (140 mg, 5.83 mmol) in water (5 mL). The mixture was stirred for 2 h at room temperature and quenched with 1N HCl until neutral pH. The organic volatiles were removed in vacuo, buffer pH 4 was added and

the product was extracted into EtOAc (3 x 25 mL) and dried (MgSO₄) to yield the title compound (1.0 g, 100%) as a white solid.

¹H NMR: (DMSO-d₆) δ 0.95 (s, 9H), 1.27 (s, 9H), 2.14-2.19 (m, 1H), 2.47-2.50 (m, 1H), 3.80 (d, *J*=11.5 Hz, 1H), 3.99-4.07 (m, 2H), 4.15 (d, *J*=11.5 Hz, 1H), 4.36 (dd, *J*=8, 10 Hz, 1H), 5.25 (m, 1H), 6.66 (d, *J*=9 Hz, NH), 7.75 (s, 1H), 8.28 (s, 1H), 8.31 (s, 1H), 12.5 (s, 1H).

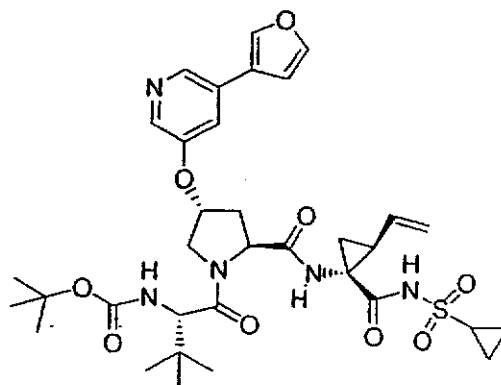
LC/MS rt-min (MH⁺): 2.47 (500, 502)(method A).

Step 2:

10 Compound 423 was accomplished according to Example 420, Step 6 in 52% yield, starting from the products of Example 423, Step 1 and Example 8, Step 3 (racemic P₁, (1*R*, 2*S*) and (1*S*, 2*R*)).

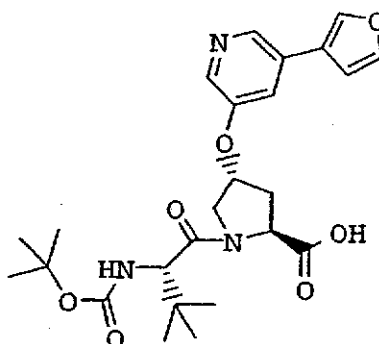
¹H NMR: (DMSO-d₆) δ 0.93, 0.95 (s, 9H), 1.00-1.09 (m, 4H), 1.28, 1.29 (s, 9H), 1.37-1.39 (m, 1H), 1.69-1.72 (m, 1H), 2.09-2.22 (m, 2H), 2.36-2.46 (m, 1H), 2.88-2.94 (m, 1H), 3.82-3.87 (m, 1H), 4.02-4.04 (m, 1H), 4.10-4.15 (m, 1H), 4.31-4.34 (m, 1H), 5.10 (d, *J*=10.5 Hz, 1H), 5.22-5.28 (m, 1H), 5.54-5.66 (m, 1H), 6.56, 6.60 (d, *J*=9.5 Hz, NH), 7.74, 7.76 (s, 1H), 8.28-8.29 (m, 1H), 8.32 (s, 1H), 8.79, 8.89 (s, 1H).
15 LC/MS rt-min (MH⁺): 2.42 (712, 714)(method B).

20 **Example 424: Preparation of Compound 424.**



Compound 424

Step 1:



To a solution of the product of Example 423, Step 1 (91 mg, 0.18 mmol), $\text{Pd}(\text{PPh}_3)_4$ (10.5 mg, 0.0091 mmol), and 3-furyl boronic acid (25.4 mg, 0.227 mmol) in DMF (2 mL) was added 2M aqueous Na_2CO_3 (0.273 mL, 0.546 mmol). The mixture was heated at 110°C for 2.5 h under nitrogen. After cooling to room temperature the solid was removed by filtration, and the filtrate concentrated in vacuo. The residue was purified by preparative HPLC (gradient 30-80% B) to afford the title compound (64 mg, 72%) as a white solid.

^1H NMR: ($\text{DMSO}-d_6$) δ 0.95 (s, 9H), 1.25 (s, 9H), 2.17-2.21 (m, 1H), 2.50 (m (hidden), 1H), 3.84-3.86 (m, 1H), 4.09-4.15 (m, 2H), 4.37 (t, $J=9$ Hz, 1H), 5.28 (m, 1H), 6.67 (d, $J=9$ Hz, NH), 7.08 (s, 1H), 7.62 (s, 1H), 7.79 (s, 1H), 8.17 (s, 1H), 8.33 (s, 1H), 8.51 (s, 1H), 12.6 (s, 1H).

LC/MS rt-min (MH^+): 1.60 (488)(method B).

Step 2:

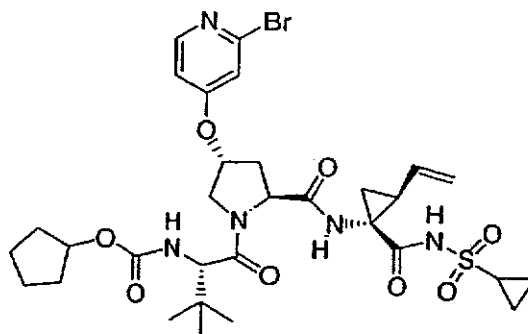
Compound 424 was prepared according to Example 420, Step 6 in 55% yield, starting from the product of Example 424, Step 1.

^1H NMR: (methanol- d_4) δ 1.02 (s, 9H), 1.05-1.09 (m, 2H), 1.22-1.25 (m, 2H), 1.34 (s, 9H), 1.42-1.45 (m, 1H), 1.86-1.89 (m, 1H), 2.21-2.26 (m, 1H), 2.48-2.52 (m, 1H), 2.91-2.96 (m, 1H), 4.02 (d, $J=12$ Hz, 1H), 4.24-4.29 (m, 2H), 4.43-4.47 (dd, $J=7.5$, 10.5 Hz, 1H), 5.12 (d, $J=10.5$ Hz, 1H), 5.28-5.32 (m, 1H), 5.73-5.81 (m, 1H), 6.63 (d, $J=9$ Hz, NH), 6.90 (s, 1H), 7.60-7.62 (m, 2H), 8.07 (s, 1H), 8.12 (s, 1H), 8.39 (s, NH).

LC/MS rt-min (MH^+): 2.30 (700)(method E).

Example 425: Preparation of Compound 425.

571

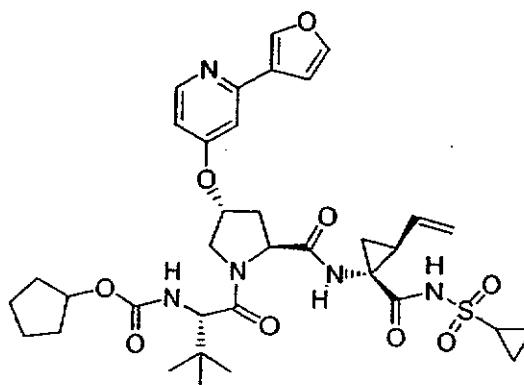


Compound 425

Compound 425 was accomplished according to Example 421, Step 7 in 45% yield, starting from the product of Example 421, Step 5.

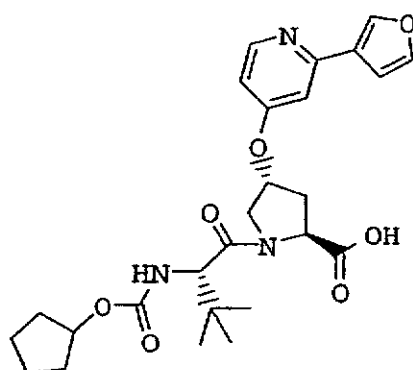
- ¹H NMR: (DMSO-d₆) δ 0.95 (s, 9H), 1.03-1.04 (m, 1H), 1.08-1.09 (m, 1H), 1.33-1.36 (m, 1H), 1.46-1.75 (m, 9H), 2.08-2.12 (m, 1H), 2.17 (q, *J*=9 Hz, 1H), 2.35-2.38 (m, 1H), 2.88-2.93 (m, 1H), 3.91 (d, *J*=9.5 Hz, 1H), 4.05-4.10 (m, 2H), 4.27 (dd, *J*=10, 7 Hz, 1H), 4.80 (m, 1H), 5.10 (d, *J*=12 Hz, 1H), 5.23 (d, *J*=16.5 Hz, 1H), 5.32 (m, 1H), 5.58-5.66 (m, 1H), 6.94 (d, *J*=9 Hz, NH), 7.03-7.05 (m, 1H), 7.26 (s, 1H), 8.21 (d, *J*=6 Hz, 1H), 8.86 (s, NH), 10.4 (s, NH).
- LC/MS rt-min (MH⁺): 2.56 (724, 726)(method D).

Example 426: Preparation of Compound 426.



Compound 426

Step 1:



This product was prepared according to Example 421, Step 6 in 65% yield, except using 3-furanoboronic acid.

¹H NMR: (methanol-d₄) δ 1.03 (s, 9H), 1.49-1.76 (m, 8H), 2.30-2.35 (m, 1H), 2.63-
 5 2.67 (m, 1H), 3.98 (d, *J*=12 Hz, 1H), 4.26 (t, *J*=9 Hz, 1H), 4.31 (d, *J*=12 Hz, 1H),
 4.58 (t, *J*=8.0 Hz, 1H), 5.32 (m, 1H), 6.71 (d, *J*=9.5 Hz, NH), 6.92 (dd, *J*=2.5, 6.0 Hz,
 1H), 6.98 (s, 1H), 7.25 (d, *J*=2.5 Hz, 1H), 7.60 (s, 1H), 8.15 (s, 1H), 8.35 (d, *J*=5.5
 Hz, 1H).

LC/MS rt-min (MH⁺): 1.94 (500)(method D).

10

Step 2:

Compound 426 was prepared according to Example 421, Step 7 in 57% yield, starting from the product of Example 426, Step 1.

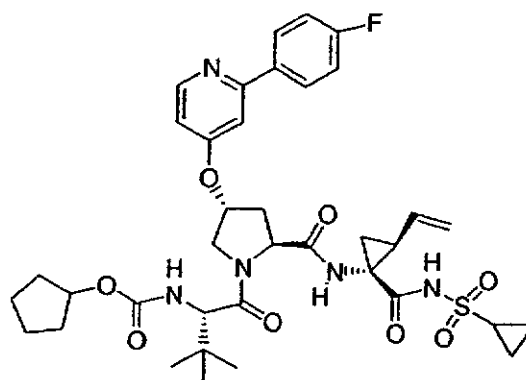
¹H NMR: (DMSO-d₆) δ 0.95 (s, 9H), 1.03-1.04 (m, 2H), 1.08-1.09 (m, 2H), 1.34-
 15 1.71 (m, 8H), 2.09-2.20 (m, 2H), 2.37-2.41 (m, 1H), 2.93 (m, 1H), 3.96 (d, *J*=9.5 Hz,
 1H), 4.07-4.11 (m, 2H), 4.29 (m, 1H), 4.78 (m, 1H), 5.10 (d, *J*=10.5 Hz, 1H), 5.23 (d,
J=17 Hz, 1H), 5.34 (m, 1H), 5.59-5.66 (m, 1H), 6.87-6.91 (m, 2H), 7.08 (s, 1H), 7.27
 (s, 1H), 7.75 (s, 1H), 8.33 (s, 1H), 8.39 (d, *J*=6 Hz, 1H), 8.90 (s, NH), 10.4 (s, 1H).

LC/MS rt-min (MH⁺): 2.38 (712)(method D).

20

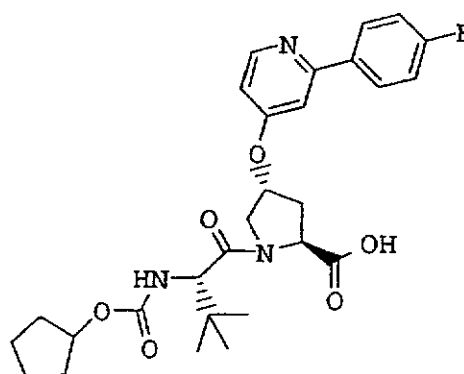
Example 427: Preparation of Compound 427.

573



Compound 427

Step 1:



This product was prepared according to Example 421, Step 6 in 86% yield, except
 5 using 4-fluorophenylboronic acid.

¹H NMR: (methanol-d₄) δ 1.03 (s, 9H), 1.44-1.75 (m, 8H), 2.30-2.36 (m, 1H), 2.64-
 2.69 (m, 1H), 3.99 (dd, *J*=12, 3.5 Hz, 1H), 4.26 (d, *J*=9.5 Hz, 1H), 4.32 (d, *J*=12
 Hz, 1H), 4.59 (dd, *J*=8.0, 9.5 Hz, 1H), 4.81 (m, 1H), 5.34 (m, 1H), 6.73 (d, *J*=9.5 Hz,
 NH), 6.99 (dd, *J*=2.5, 6.0 Hz, 1H), 7.20 (t, 2H (hidden)), 7.36 (s, 1H (hidden)), 7.94-
 10 7.97 (m, 2H), 8.44 (d, *J*=6.0 Hz, 1H).

LC/MS rt-min (MH⁺): 2.22 (528)(method A).

Step 2:

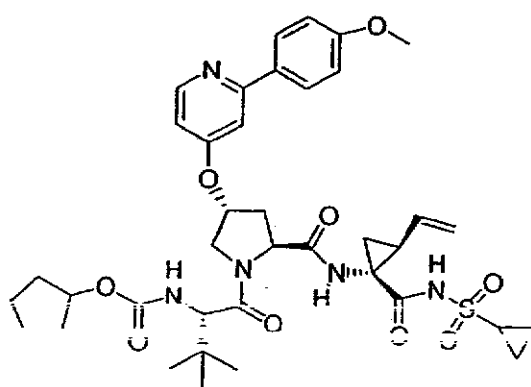
Compound 427 was prepared according to Example 421, Step 7 in 53% yield,
 15 starting from the product of Example 427, Step 1.

¹H NMR: (methanol-d₄) δ 1.03 (s, 9H), 1.06-1.09 (m, 2H), 1.23-1.26 (m, 2H), 1.43
 (dd, *J*=5.0, 9.5 Hz, 1H), 1.47-1.78 (m, 8H), 1.88 (dd, *J*=5.5, 8.0 Hz, 1H), 2.21-2.29
 (m, 2H), 2.49-2.53 (m, 1H), 2.91-2.96 (m, 1H), 4.05 (dd, *J*=3.0, 11.5 Hz, 1H), 4.27-

4.29 (m, 2H), 4.44 (dd, $J=7.0, 10.5$ Hz, 1H), 4.83 (m, 1H (hidden)), 5.12 (d, $J=10$ Hz, 1H), 5.29 (d, $J=17$ Hz, 1H), 5.37 (m, 1H), 5.73-5.80 (m, 1H), 6.93 (d, $J=9.5$ Hz, NH), 6.98 (m, 1H), 7.21 (t, $J=9.0$ Hz, 2H), 7.36 (s, 1H), 7.94-7.97 (m, 2H), 8.44 (d, $J=6.0$ Hz, 1H).

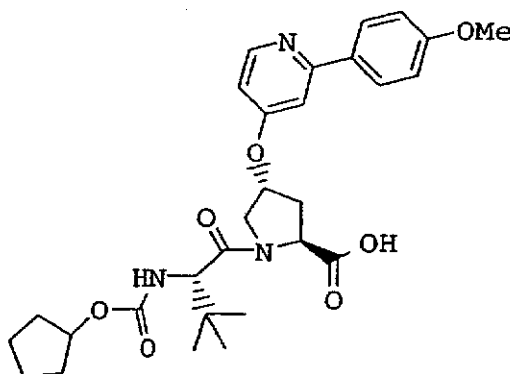
5 LC/MS rt-min (MH^+): 2.42 (741)(method A).

Example 428: Preparation of Compound 428.



Compound 428

Step 1:



10

This product was prepared according to Example 421, Step 6 in 37% yield, except using 4-methoxyphenylboronic acid.

^1H NMR: (methanol- d_4) δ 1.03 (s, 9H), 1.45-1.74 (m, 8H), 2.31-2.36 (m, 1H), 2.64-2.68 (m, 1H), 3.85 (s, 3H), 3.98 (dd, $J=12, 3.5$ Hz, 1H), 4.25 (d, $J=9.0$ Hz, 1H), 4.33 (d, $J=11.5$ Hz, 1H), 4.59 (dd, $J=8.0, 10$ Hz, 1H), 4.77 (m, 1H), 5.36 (m, 1H), 6.72 (d, $J=9.0$ Hz, NH), 7.01 (m, 1H), 7.04 (d, $J=9.0$ Hz, 2H), 7.37 (d, $J=2.0$ Hz), 7.86 (d, $J=9.0$ Hz, 2H), 8.42 (d, $J=6.0$ Hz, 1H).

15

LC/MS rt-min (MH^+): 2.09 (540)(method A).

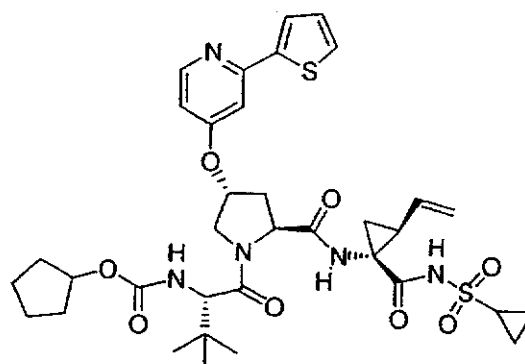
Step 2:

Compound 428 was prepared according to Example 420, Step 6 in 72% yield, starting from the product of Example 428, Step 1.

- 5 ^1H NMR: (methanol- d_4) δ 1.03 (s, 9H), 1.06-1.09 (m, 2H), 1.23-1.25 (m, 2H), 1.43 (dd, $J=5.5, 9.5$ Hz, 1H), 1.48-1.77 (m, 8H), 1.88 (dd, $J=5.0, 8.0$ Hz, 1H), 2.21-2.28 (m, 2H), 2.50-2.54 (m, 1H), 2.91-2.96 (m, 1H), 3.85 (s, 3H), 4.05 (d, $J=12$ Hz, 1H), 4.27-4.29 (m, 2H), 4.44 (dd, $J=7.0, 10.5$ Hz, 1H), 4.84 (m, 1H (hidden)), 5.12 (d, $J=10$ Hz, 1H), 5.30 (d, $J=17$ Hz, 1H), 5.37 (m, 1H), 5.72-5.80 (m, 1H), 6.89 (d, $J=9.5$ Hz, NH), 6.95 (dd, $J=2.5, 6.0$ Hz, 1H), 7.03 (d, $J=9.0$ Hz, 1H), 7.33 (d, $J=2.5$ Hz, 1H), 7.86 (d, $J=9.0$ Hz, 2H), 8.41 (d, $J=6.0$ Hz, 1H).

LC/MS rt-min (MH^+): 2.40 (753)(method A).

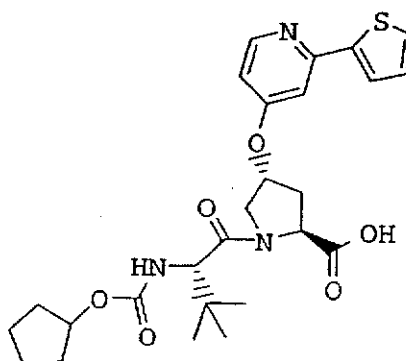
Example 429: Preparation of Compound 429.



Compound 429

15

Step 1:



This product was prepared according to Example 421, Step 6 in 22% yield, except using 2-thiopheneboronic acid.

¹H NMR: (methanol-d₄) δ 1.03 (s, 9H), 1.46-1.74 (m, 8H), 2.29-2.35 (m, 1H), 2.63-2.67 (m, 1H), 3.97 (d, J=12 Hz, 1H), 4.26 (d, J=8.5 Hz, 1H), 4.31 (d, J=12 Hz, 1H),
 5 4.60 (t, J=8.5 Hz, 1H), 4.81 (m, 1H (hidden)), 5.31 (m, 1H), 6.87-6.89 (m, 2H), 7.13 (d, J=5.0 Hz, 1H), 7.52 (s, 1H (hidden)), 7.70 (d, J=2.5 Hz, 1H), 8.32 (d, J=6.0 Hz, 1H).

LC/MS rt-min (MH⁺): 1.96 (516)(method A).

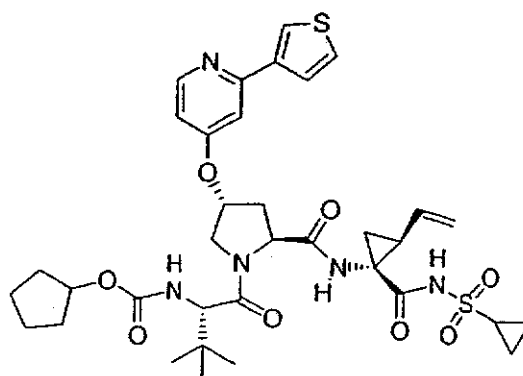
10 Step 2:

Compound 429 was prepared according to Example 420, Step 6 in 57% yield, starting from the product of Example 429, Step 1.

¹H NMR: (methanol-d₄) δ 1.02 (s, 9H), 1.07 (m, 2H), 1.24 (m, 2H), 1.43 (dd, J=5.5, 9.5 Hz, 1H), 1.55-1.78 (m, 8H), 1.88 (dd, J=5.5, 8.0 Hz, 1H), 2.21-2.28 (m, 2H),
 15 2.49-2.53 (m, 1H), 2.92-2.96 (m, 1H), 4.04 (d, J= 10 Hz, 1H), 4.26-4.29 (m, 2H), 4.43 (t, J=9.0 Hz, 1H), 4.82 (m, 1H (hidden)), 5.12 (d, J=10.5 Hz, 1H), 5.29 (d, J=17.5 Hz, 1H), 5.35 (m, 1H), 5.73-5.80 (m, 1H), 6.89 (d, J=4.5 Hz, 1H), 6.92 (d, J=4.5 Hz, 1H), 7.13 (s, 1H), 7.35 (s, 1H), 7.51 (d, J=4.5 Hz, 1H), 7.70 (s, 1H), 8.32 (d, J=5.5 Hz, 1H).

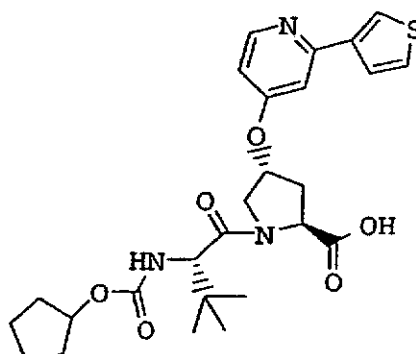
20 LC/MS rt-min (MH⁺): 2.37 (728)(method A).

Example 430: Preparation of Compound 430.



Compound 430

Step 1:



This product was prepared according to Example 421, Step 6 in 17% yield, except using 3-thiopheneboronic acid.

¹H NMR: (methanol-d₄) δ 1.03 (s, 9H), 1.43-1.74 (m, 8H), 2.30-2.36 (m, 1H), 2.64-2.68 (m, 1H), 3.98 (dd, *J*=11.5, 3.0 Hz, 1H), 4.25 (d, *J*=9.0 Hz, 1H), 4.32 (d, *J*=11.5 Hz, 1H), 4.60 (dd, *J*=8.0, 9.5 Hz, 1H), 4.80 (m, 1H (hidden)), 5.33 (m, 1H), 6.96 (dd, *J*=2.5, 6.0 Hz, 1H), 7.36 (s, 1H (hidden)), 7.51 (s, 1H (hidden)), 7.67 (d, *J*=5.0 Hz, 1H), 8.03 (s, 1H), 8.39 (d, *J*=6.0 Hz, 1H).

LC/MS rt-min (MH⁺): 1.94 (516)(method A).

10

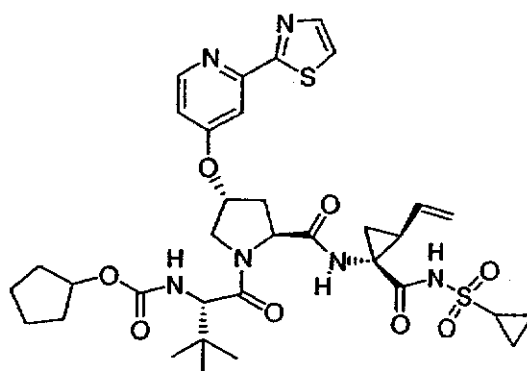
Step 2:

Compound 430 was prepared according to Example 420, Step 6 in 45% yield, starting from the product of Example 430, Step 1.

¹H NMR: (methanol-d₄) δ 1.02 (s, 9H), 1.06 (m, 2H), 1.29 (m, 2H), 1.43 (dd, *J*=5.5, 9.5 Hz, 1H), 1.43-1.75 (m, 8H), 1.87 (dd, *J*=6.0, 7.5 Hz, 1H), 2.20-2.27 (m, 2H), 2.49-2.53 (m, 1H), 2.93-2.95 (m, 1H), 4.05 (d, *J*=9.0 Hz, 1H), 4.27-4.29 (m, 2H), 4.42-4.45 (m, 1H), 4.85 (m, 1H (hidden)), 5.12 (d, *J*=10.0 Hz, 1H), 5.29 (d, *J*=17.5 Hz, 1H), 5.36 (m, 1H), 5.73-5.80 (m, 1H), 6.92-6.94 (m, 2H), 7.35 (s, 1H), 7.51 (s, 1H), 7.66 (d, *J*=4.5 Hz, 1H), 8.00 (s, 1H), 8.38 (d, *J*=5.5 Hz, 1H).

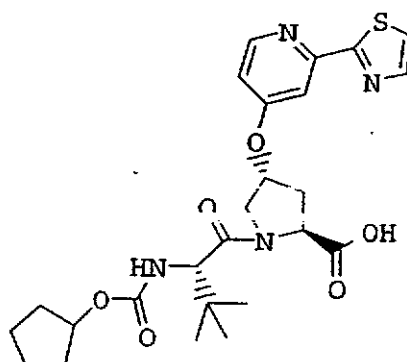
20 LC/MS rt-min (MH⁺): 2.36 (728)(method A).

Example 431: Preparation of Compound 431.



Compound 431

Step 1:



To a mixture of the product of Example 421, Step 5 (100 mg, 0.195 mmol) and
 5 Pd(PPh₃)₄ (23 mg, 0.0195 mmol) in dioxane (3 mL) was added 2-
 tributylstannylthiazole (95 mg, 0.254 mmol) and triethylamine (82 μL, 0.585
 mmol). The solution was heated at 95°C for 5 h under nitrogen, then at 105°C for 15
 h. After cooling to room temperature the mixture was filtered and concentrated. The
 residue was purified by preparative HPLC (gradient 30-80% B). The combined
 10 fractions were partitioned between buffer pH 4 and dichloromethane. The aqueous
 phase was extracted with dichloromethane and the combined organic extracts washed
 with brine and dried (MgSO₄). The title compound (31 mg) was obtained as a
 colorless oil, significantly contaminated with tributylstannyl residue.

¹H NMR: (methanol-d₄) δ 1.03 (s, 9H), 1.4 (m, 8H (hidden)), 2.32-2.36 (m, 1H),
 15 2.64-2.68 (m, 1H), 4.00 (d, *J*=11.5 Hz, 1H), 4.25 (s, 1H), 4.33 (d, *J*=11.5 Hz, 1H),
 4.60 (t, *J*=8.5 Hz, 1H), 4.80 (m, 1H (hidden)), 5.33 (m, 1H), 7.03 (br s, 1H), 7.70 (s,
 1H), 7.73 (s, 1H), 7.93 (s, 1H), 8.41 (d, *J*=5.5 Hz, 1H).

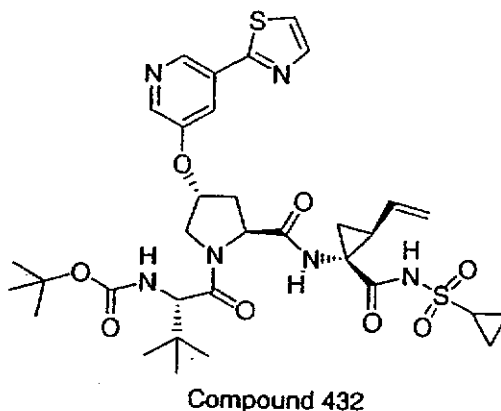
LC/MS rt-min (MH⁺): 2.25 (517)(method A).

Step 2:

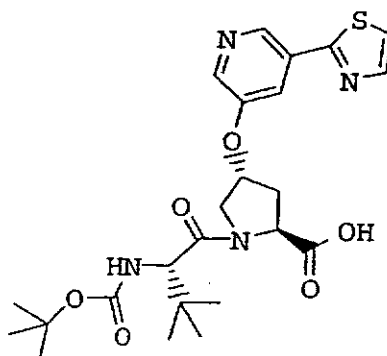
Compound 431 was prepared according to Example 420, Step 6 in 41% yield, starting from the product of Example 431, Step 1.

- 5 ¹H NMR: (methanol-d₄) δ 1.02 (s, 9H), 1.06-1.70 (m, 13H), 1.86-1.89 (m, 1H), 2.22-2.31 (m, 2H), 2.51-2.55 (m, 1H), 2.92-2.94 (m, 1H), 4.06 (d, *J*= 11.5 Hz, 1H), 4.23-4.32 (m, 2H), 4.44-4.47 (m, 1H), 4.82 (m, 1H (hidden)), 5.12 (d, *J*=11 Hz, 1H), 5.30 (d, *J*=17 Hz, 1H), 5.36 (m, 1H), 5.73-5.81 (m, 1H), 6.90 (d, *J*=9.0 Hz, NH), 7.04 (m, 1H), 7.71 (m, 2H), 7.93 (s, 1H), 8.42 (d, *J*=5.5 Hz, 1H).
- 10 LC/MS rt-min (MH⁺): 2.46 (729)(method A).

Example 432: Preparation of Compound 432.



Step 1:



15

To a mixture of the product of Example 423, Step 1 (102 mg, 0.204 mmol) and Pd(PPh₃)₄ (24 mg, 0.0204 mmol) in dioxane (3 mL) was added 2-tributylstannylthiazole (99 mg, 0.265 mmol) and triethylamine (85 μL, 0.612

mmol). The solution was heated at 95°C for 5 h under nitrogen, then at 105°C for 15 h. After cooling to room temperature the mixture was filtered and concentrated. The residue was purified by preparative HPLC (gradient 30-80% B). The combined fractions were neutralized with conc. ammonia and concentrated. The residue was
5 partitioned between buffer pH 4 and dichloromethane. The aqueous phase was extracted with dichloromethane and the combined organic extracts washed with brine and dried (MgSO₄). The title compound (33 mg) was obtained as a colorless oil, significantly contaminated with tributylstannyl containing residue.

¹H NMR: (methanol-d₄) δ 1.03 (s, 9H), 1.30 (s, 9H), 2.28-2.32 (m, 1H), 2.62-2.67
10 (m, 1H), 3.98 (d, J=11.5 Hz, 1H), 4.21 (s, 1H), 4.34 (d, J=11.5 Hz, 1H), 4.58 (t, J=9.0 Hz, 1H), 5.31 (m, 1H), 7.71 (d, J=2.5 Hz, 1H), 7.94-7.96 (m, 2H), 8.33 (s, 1H), 8.73 (s, 1H).

LC/MS rt-min (MH⁺-Boc): 2.21 (405)(method A).

15 Step 2:

Compound 432 was prepared according to Example 420, Step 6 in 42% yield, starting from the product of Example 432, Step 1.

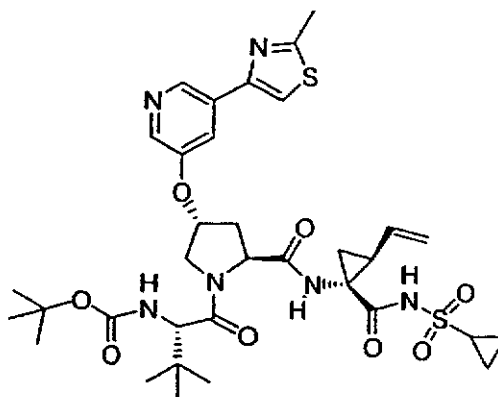
¹H NMR: (methanol-d₄) δ 1.02 (s, 9H), 1.07-1.08 (m, 2H), 1.24 (m, 2H), 1.32 (s, 9H), 1.44 (m, 1H (hidden)), 1.86-1.89 (m, 1H), 2.21-2.29 (m, 2H), 2.51-2.55 (m, 1H),
20 2.93-2.95 (m, 1H), 4.04 (d, J= 12 Hz, 1H), 4.23 (d, J= 9.5 Hz, 1H), 4.33 (d, J= 12 Hz, 1H), 4.47 (t, J= 9.5 Hz, 1H), 5.12 (d, J=10.0 Hz, 1H), 5.30 (d, J=18 Hz, 1H), 5.36 (m, 1H), 5.72-5.81 (m, 1H), 6.62 (d, J= 8.5 Hz, NH), 7.73 (s, 1H), 7.96 (m, 1H), 8.34 (s, 1H), 8.74 (s, 1H).

LC/MS rt-min (MH⁺): 2.42 (717)(method A).

25

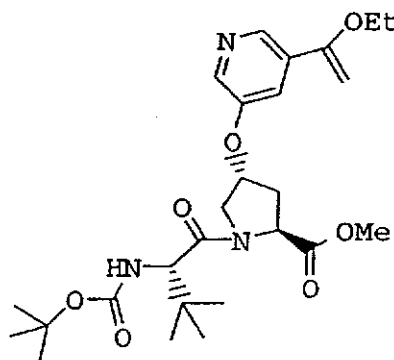
Example 433: Preparation of Compound 433.

581



Compound 433

Step 1:

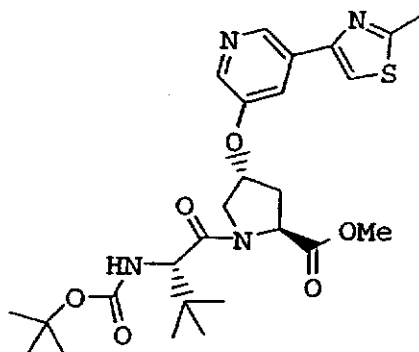


To a mixture of the product of Example 420, Step 3 (1.00 g, 1.94 mmol) and
 5 Pd(PPh₃)₄ (112 mg, 0.097 mmol) in dioxane (15 mL) was added tributyl(1-ethoxyvinyl)tin (876 mg, 2.43 mmol). The solution was heated at 105°C for 6 h under nitrogen. After cooling to room temperature the mixture was filtered and concentrated. The residue was partitioned between satd NaHCO₃ and ethyl acetate. The aqueous phase was extracted with ethyl acetate and the combined organic
 10 extracts washed with 5% aq. KF and brine and dried (MgSO₄). Purification using a Biotage 40 M column (eluted gradient hexane – EtOAc 40-70%) afforded the title compound (624 mg, 64%) as a yellow oil.

¹H NMR: (DMSO-d₆) δ 0.95 (s, 9H), 1.27 (s, 9H), 1.35 (t, *J*=7.0 Hz, 3H), 2.16-2.21 (m, 1H), 2.50 (m, 1H (hidden)), 3.64 (s, 3H), 3.85 (d, *J*= 11 Hz, 1H), 3.90 (q, *J*=7.0
 15 Hz, 2H), 4.09 (d, *J*= 9.0 Hz, 1H), 4.13 (d, *J*= 11 Hz, 1H), 4.40 (d, *J*=2.5 Hz, 1H), 4.45 (t, *J*=8.0 Hz, 1H), 4.91 (d, *J*=2.5 Hz, 1H), 5.27 (m, 1H), 6.69 (d, *J*= 9.0 Hz, NH), 7.48 (s, 1H), 8.25 (s, 1H), 8.46 (s, 1H).

LC/MS rt-min (MH⁺): 2.14 (507)(method B).

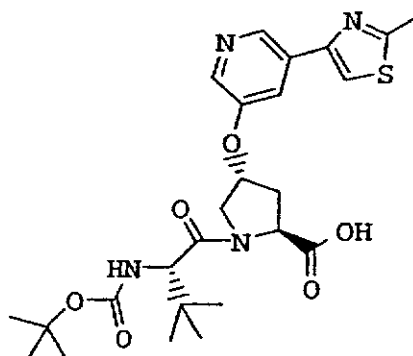
Step 2:



- To a solution of the product of Example 433, Step 1 (125 mg, 0.247) in THF (3 mL) and water (111 μ L, 6.18 mmol) was added NBS (44 mg, 0.247 mmol). After stirring
- 5 at room temperature for 20 min. the mixture was concentrated and partitioned between ethyl acetate and brine. The organic phase was dried (MgSO_4) to give the intermediate bromomethyl ketone. This intermediate was dissolved in DMF and treated with *N*-acetylacetamide (24 mg, 0.521 mmol) and NaHCO_3 (51 mg, 0.571 mmol). The mixture was stirred for 2 h at room temperature, concentrated and suspended in
- 10 satd. NaHCO_3 . The product was extracted with ethyl acetate (2x), washed with brine, and dried (MgSO_4). Purification using a Biotage 12 M column (eluted gradient hexane – EtOAc 50-70%) afforded the title compound (50 mg, 38%) as a pale oil.
- ^1H NMR: (methanol- d_4) δ 1.02 (s, 9H), 1.31 (s, 9H), 2.27-2.31 (m, 1H), 2.63-2.67 (m, 1H), 2.77 (s, 3H), 3.74 (s, 3H), 3.98 (d, J = 10.0 Hz, 1H), 4.22 (d, J = 9.5 Hz, 1H),
- 15 4.34 (d, J = 10.5 Hz, 1H), 4.64 (t, J =9.0 Hz, 1H), 5.29 (m, 1H), 6.38 (s, NH), 7.87 (s, 1H), 7.91 (s, 1H), 8.20 (s, 1H), 8.71 (s, 1H).
- LC/MS *rt*-min (MH^+): 1.96 (533)(method B).

Step 3:

583



This product was prepared according to Example 420, Step 5, except using the product of Example 433, Step 2 instead.

¹H NMR: (DMSO-d₆) δ 0.96 (s, 9H), 1.25 (s, 9H), 2.18-2.23 (m, 1H), 2.50 (m, 1H (hidden)), 2.73 (s, 3H), 3.86 (d, J= 11.5 Hz, 1H), 4.10 (d, J= 9.0 Hz, 1H), 4.14 (d, J= 11.5Hz, 1H), 4.39 (t, J=8.5 Hz, 1H), 5.30 (m, 1H), 6.60 (br s, NH), 7.84 (s, 1H), 8.14 (s, 1H), 8.24 (s, 1H), 8.78 (s, 1H).

LC/MS rt-min (MH⁺): 1.84 (519)(method B).

10 Step 4:

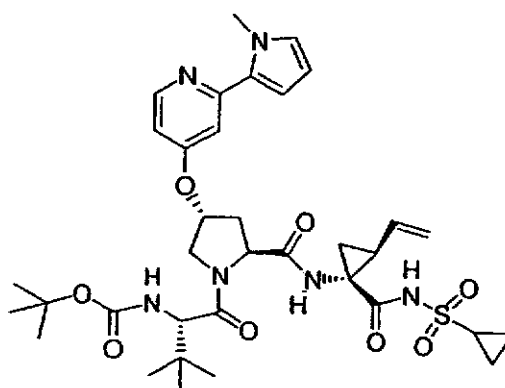
Compound 433 was prepared according to Example 420, Step 6 in 46% yield, starting from the product of Example 433, Step 3.

¹H NMR: (methanol-d₄) δ 1.05 (s, 9H), 1.09-1.11 (m, 2H), 1.26-1.29 (m, 2H), 1.36 (s, 9H), 1.45-1.48 (m, 1H), 1.89-1.92 (m, 1H), 2.25-2.30 (m, 2H), 2.53-2.57 (m, 1H), 2.80 (s, 3H), 2.94-3.00 (m, 1H), 4.06 (d, J= 10.5 Hz, 1H), 4.27 (s, 1H), 4.32 (d, J= 12 Hz, 1H), 4.48 (dd, J= 10.5, 7.0 Hz, 1H), 5.15 (d, J=10.5 Hz, 1H), 5.33 (d, J=17 Hz, 1H), 5.35 (m, 1H), 5.76-5.83 (m, 1H), 7.93 (s, 1H), 7.95 (m, 1H), 8.22 (s, 1H), 8.74 (s, 1H).

20 LC/MS rt-min (MH⁺): 2.21 (732)(method B).

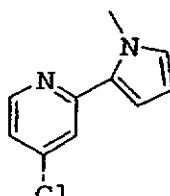
Example 434: Preparation of Compound 434.

584



Compound 434

Step 1:

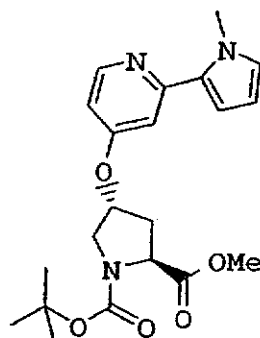


To a solution of the product of Example 421, Step 1 (300 mg, 1.56 mmol) and
 5 Pd(PPh₃)₄ (90 mg, 0.078 mmol) in DMF (6 mL) was added 1-methyl-2-(tributylstannyl)-1H-pyrrole (750 mg, 2.03 mmol) and triethylamine (0.435 mL, 3.12 mmol). The solution was heated at 150°C for 30 min under nitrogen in a microwave oven (Emrys, Personal Chemistry). After cooling to room temperature the mixture was diluted with diethyl ether and 5% aq. KF and filtered. The aqueous phase was
 10 extracted with diethyl ether (2x). The combined organic extracts were washed with 5% aq. KF, water and brine and dried (MgSO₄). Purification using a Biotage 25 S column (eluted gradient hexane – diethyl ether 0-5%) afforded the title compound (169 mg, 56%) as a colorless oil.

¹H NMR: (DMSO-d₆) δ 3.94 (s, 3H), 6.10 (s, 1H), 6.77 (d, J=2.0 Hz, 1H), 6.93 (s, 1H), 7.27 (d, J=4.0 Hz, 1H), 7.77 (s, 1H), 8.49 (d, J=5.0 Hz, 1H),
 15 LC/MS rt-min (MH⁺): 1.15 (193, 195)(method B).

Step 2:

585

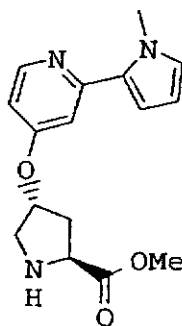


This product was prepared according to Example 421, Step 2 in 39% yield, starting from the product of Example 434, Step 1.

¹H NMR: (methanol-d₄) δ 1.42, 1.43 (s, 9H (rotamers)), 2.27-2.34 (m, 1H), 2.55-
 5 2.62 (m, 1H), 3.75 (m, 2H), 3.76, 3.74 (s, 3H (rotamers)), 3.84 (s, 3H), 4.39-4.45 (m, 1H), 5.19 (m, 1H), 6.10 (m, 1H), 6.49 (m, 1H), 6.78 (s, 1H), 6.80-6.82 (m, 1H), 7.07 (s, 1H), 8.35 (d, J=6.0 Hz, 1H).

LC/MS rt-min (MH⁺, carboxylic acid): 1.49 (389)(method B).

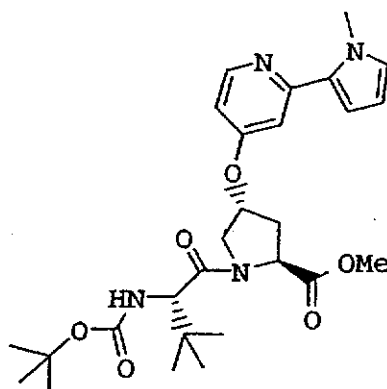
10 Step 3:



The product of Example 434, Step 2 (90 mg, 0.22 mmol) was dissolved in dichloromethane (1.5 mL) and TFA (1.0 mL, 9.0 mmol). The solution was stirred at room temperature for 45 min., and concentrated. The residue was treated with 1N
 15 HCl in diethyl ether (5 mL) and concentrated. The title compound was obtained in quantitative yield as a pale oil.

LC/MS rt-min (MH⁺): 0.32 (302)(method B).

Step 4:



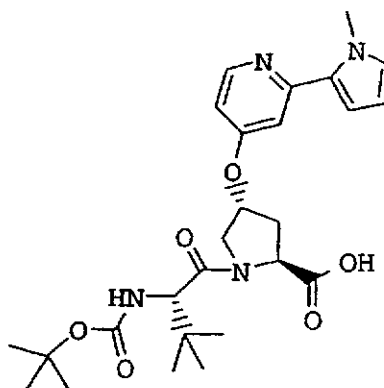
This product was prepared according to Example 420, Step 3 in 80% yield, starting from the product of Example 434, Step 3.

¹H NMR: (methanol-d₄) δ 1.02 (s, 9H), 1.31 (s, 9H), 2.25-2.31 (m, 1H), 2.61-2.64 (m, 1H), 3.73 (s, 3H), 3.84 (s, 3H), 3.97-3.99 (m, 1H), 4.22 (d, *J*= 9.5 Hz, 1H), 4.32 (d, *J*= 11.5 Hz, 1H), 4.61 (t, *J*=7.5 Hz, 1H), 5.27 (m, 1H), 6.10 (m, 1H), 6.42 (br d, *J*= 9.0 Hz, 1H), 6.49 (m, 1H), 6.78 (m, 1H), 6.81 (m, 1H), 7.07 (s, 1H), 8.24 (d, *J*=5.5 Hz, 1H).

LC/MS rt-min (MH⁺): 1.81 (516)(method B).

10

Step 5:



To a solution of the product of Example 434, Step 4 (92 mg, 0.179 mmol) in THF (1 mL) and methanol (1 mL) was added LiOH (13 mg, 0.536 mmol) in water (1 mL). The mixture was stirred for 1.5 h at room temperature and quenched with 1N HCl until neutral pH. The organic volatiles were removed in vacuo, and the residue purified by preparative HPLC (gradient 10-80% B). The combined fractions were neutralized with conc. ammonia and concentrated. The residue was partitioned

15

between buffer pH 4 and ethyl acetate. The aqueous phase was extracted with ethyl acetate and the combined organic extracts washed with brine and dried (MgSO_4). The title compound (56 mg, 62%) was obtained as a white solid.

^1H NMR: (methanol- d_4) δ 1.03 (s, 9H), 1.32 (s, 9H), 2.31-2.35 (m, 1H), 2.62-2.67 (m, 1H), 3.85 (s, 3H), 3.98 (d, $J=11.5$ Hz, 1H), 4.21-4.23 (m, 1H), 4.33 (d, $J=11.5$ Hz, 1H), 4.58 (t, $J=8.0$ Hz, 1H), 5.31 (m, 1H), 6.12 (m, 1H), 6.40 (br d, $J=8.0$ Hz, NH), 6.52 (m, 1H), 6.82 (m, 1H), 6.87 (m, 1H), 7.12 (s, 1H), 8.36 (d, $J=5.5$ Hz, 1H).
LC/MS rt-min (MH^+): 1.73 (502)(method B).

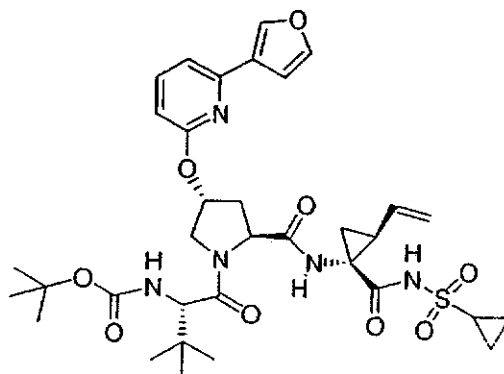
10 Step 6:

Compound 434 was prepared according to Example 420, Step 6 in 68% yield, starting from the products of Example 434, Step 5.

^1H NMR: (methanol- d_4) δ 1.02 (s, 9H), 1.06-1.09 (m, 2H), 1.23-1.26 (m, 2H), 1.33 (s, 9H), 1.42-1.45 (m, 1H), 1.86-1.89 (m, 1H), 2.21-2.27 (m, 2H), 2.47-2.51 (m, 1H), 2.91-2.96 (m, 1H), 3.85 (s, 3H), 4.04 (d, $J=12$ Hz, 1H), 4.24 (d, $J=10.0$ Hz, 1H), 4.28 (d, $J=12$ Hz, 1H), 4.43 (dd, $J=10.0, 7.0$ Hz, 1H), 5.12 (d, $J=10.0$ Hz, 1H), 5.30 (d, $J=17$ Hz, 1H), 5.32 (m, 1H), 5.73-5.80 (m, 1H), 6.10 (m, 1H), 6.49 (m, 1H), 6.64 (br d, $J=9.0$ Hz, NH), 6.79 (m, 1H), 6.82 (m, 1H), 7.08 (s, 1H), 8.35 (d, $J=5.5$ Hz, 1H).

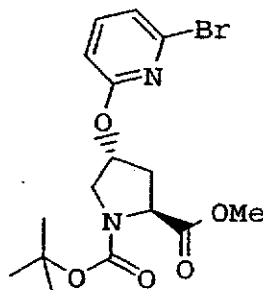
20 LC/MS rt-min (MH^+): 2.08 (714)(method B).

Example 435: Preparation of Compound 435.



Compound 435

Step 1:



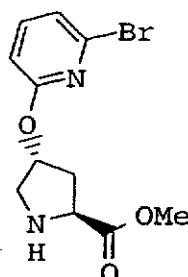
This product was prepared according to Example 421, Step 2 in 74% yield, starting from 2,6-dibromopyridine

- 5 ¹H NMR: (DMSO-d₆) δ 1.34, 1.38 (s, 9H (rotamers)), 2.23-2.31 (m, 1H), 2.43-2.47 (m, 1H (hidden)), 3.53 (d, J=12 Hz, 1H), 3.66, 3.69 (s, 3H (rotamers)), 3.72-3.75 (m, 1H), 4.29-4.34 (m, 1H), 5.42 (m, 1H), 6.89 (d, J=7.5 Hz, 1H), 7.26 (d, J=7.5 Hz, 1H), 7.68 (t, J=7.5 Hz, 1H).

LC/MS rt-min (MH⁺): 2.02 (323, 425)(method A).

10

Step 2:

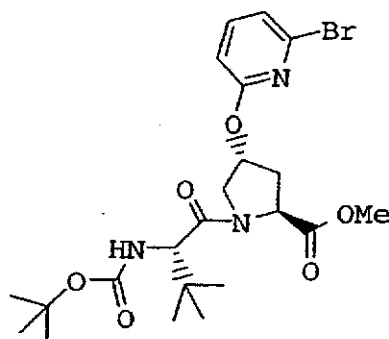


This product was prepared according to Example 420, Step 2 in quantitative yield, starting from the product of Example 435, Step 1.

- 15 LC/MS rt-min (MH⁺): 1.42 (301, 303)(method B).

Step 3:

589

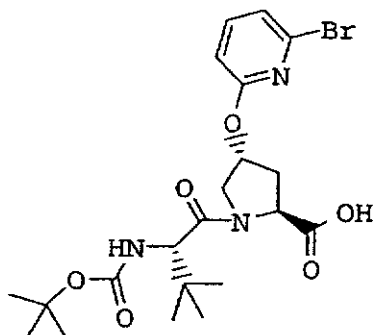


This product was prepared according to Example 420, Step 3 in 96% yield, starting from the product of Example 435, Step 2.

¹H NMR: (DMSO-d₆) δ 0.95 (s, 9H), 1.28 (s, 9H), 2.20-2.26 (m, 1H), 2.45-2.48 (m, 1H), 3.64 (s, 3H), 3.94 (d, *J*=9.5 Hz, 1H), 4.01-4.08 (m, 2H), 4.45 (t, *J*=8.5 Hz, 1H), 5.53 (m, 1H), 6.66 (d, *J*=7.0 Hz, 1H), 6.82 (d, *J*=7.0 Hz, 1H), 7.25 (d, *J*=7.0 Hz, 1H), 7.64-7.69 (m, 1H).

LC/MS rt-min (MH⁺): 2.73 (514, 516)(method A).

10 Step 3:

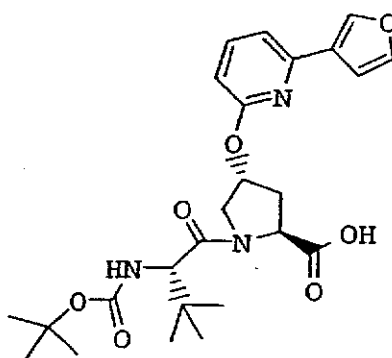


This product was prepared according to Example 420, Step 5 in quantitative yield, starting from the product of Example 435, Step 2.

¹H NMR: (DMSO-d₆) δ 0.95 (s, 9H), 1.28 (s, 9H), 2.19-2.25 (m, 1H), 2.43-2.47 (m, 1H), 3.94 (m, 1H), 4.01-4.08 (m, 2H), 4.36 (t, *J*=8.5 Hz, 1H), 5.52 (m, 1H), 6.65 (d, *J*=8.0 Hz, 1H), 6.82 (d, *J*=7.5 Hz, 1H), 7.25 (d, *J*=7.5 Hz, 1H), 7.67 (t, *J*=7.5 Hz, 1H), 12.6 (s, 1H).

LC/MS rt-min (MNa⁺): 2.51 (522, 524)(method B)..

20 Step 4:



To a solution of the product of Example 435, Step 3 (125 mg, 0.250 mmol),
 Pd(PPh₃)₄ (14.4 mg, 0.0125 mmol), and 3-furyl boronic acid (35 mg, 0.313 mmol) in
 DMF (2 mL) and water (0.025 mL) was added Cs₂CO₃ (244 mg, 0.750 mmol). The
 5 mixture was heated at 105°C for 3 h under nitrogen. After cooling to room
 temperature the solid was removed by filtration, and the filtrate concentrated in
 vacuo. The residue was purified by preparative HPLC (gradient 30-100% B). The
 combined fractions were neutralized with conc. ammonia and concentrated. The
 residue was partitioned between buffer pH 4 and dichloromethane. The aqueous
 10 phase was extracted with dichloromethane and the combined organic extracts washed
 with brine and dried (MgSO₄). The title compound (90 mg, 76%) was obtained as a
 white foam.

¹H NMR: (methanol-d₄) δ 1.06 (s, 9H), 1.39 (s, 9H), 2.36-2.42 (m, 1H), 2.61-2.65
 (m, 1H), 4.12 (dd, *J*=4.0, 11 Hz, 1H), 4.19 (d, *J*=11 Hz, 1H), 4.28 (s, 1H), 4.62 (t,
 15 *J*=8.5 Hz, 1H), 5.79 (m, 1H), 6.64 (d, *J*=8.0 Hz, 1H), 6.96 (s, 1H), 7.22 (d, *J*=8.0 Hz,
 1H), 7.58 (m, 1H), 7.66 (t, *J*=8.0 Hz, 1H), 8.13 (s, 1H).

LC/MS rt-min (MNa⁺): 2.53 (511)(method B).

Step 5:

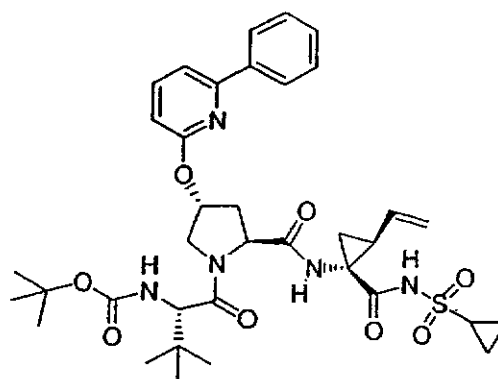
20 Compound 435 was prepared according to Example 420, Step 6 in 57% yield,
 starting from the product of Example 435, Step 4.

¹H NMR: (DMSO-d₆) δ 0.96 (s, 9H), 1.02-1.05 (m, 2H), 1.09-1.11 (m, 2H), 1.19 (s,
 9H), 1.35-1.38 (m, 1H), 1.71 (dd, *J*=5.5, 8.0 Hz, 1H), 2.15-2.22 (m, 2H), 2.37-2.41
 (m, 1H), 2.93 (br m, 1H), 4.03-4.08 (m, 3H), 4.35 (br t, 1H), 5.10 (d, *J*=10.5 Hz, 1H),
 25 5.24 (d, *J*=17 Hz, 1H), 5.60-5.67 (m, 1H), 5.73 (m, 1H), 6.47 (br s, 1H), 6.64 (d,

$J=7.5$ Hz, 1H), 7.04 (s, 1H), 7.31 (d, $J=7.5$ Hz, 1H), 7.72 (t, $J=7.5$ Hz, 1H), 7.77 (s, 1H), 8.32 (s, 1H), 8.92 (s, NH), 10.4 (s, NH).

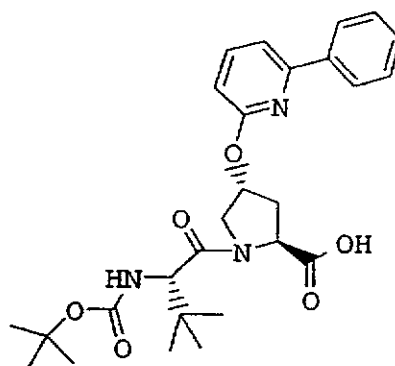
LC/MS rt-min (MNa^+): 2.64 (723)(method B).

5 **Example 436: Preparation of Compound 436.**



Compound 436

Step 1:



10 This product was prepared according to Example 435, Step 4 in 73% yield, except using phenylboronic acid instead.

^1H NMR: (methanol- d_4) δ 1.06 (s, 9H), 1.39 (s, 9H), 2.39-2.45 (m, 1H), 2.65-2.77 (m, 1H), 4.18-4.30 (m, 3H), 4.64 (t, $J=8.0$ Hz, 1H), 5.72 (m, 1H), 6.74 (d, $J=8.0$ Hz, 1H), 7.44-7.55 (m, 4H), 7.75 (t, $J=8.0$ Hz, 1H), 8.07 (d, $J=7.5$ Hz, 2H).

LC/MS rt-min (MNa^+): 2.72 (521)(method B).

15

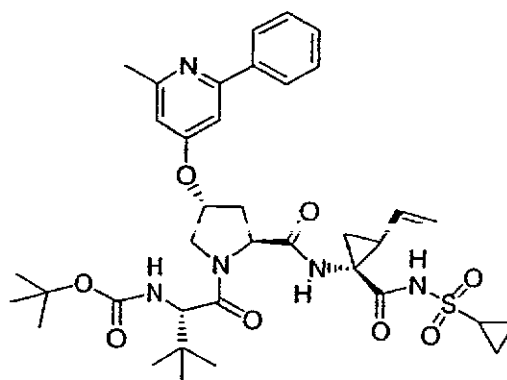
Step 2:

Compound 436 was prepared according to Example 420, Step 6 in 66% yield, starting from the product of Example 436, Step 1.

¹H NMR: (DMSO-d₆) δ 0.96 (s, 9H), 1.04-1.05 (m, 2H), 1.09 (m, 2H), 1.30 (s, 9H), 1.36-1.39 (m, 1H), 1.71 (t, *J*=7.5 Hz, 1H), 2.16-2.24 (m, 2H), 2.41-2.45 (m, 1H), 2.93 (m, 1H), 4.06-4.09 (m, 3H), 4.38 (br t, 1H), 5.10 (d, *J*=10.5 Hz, 1H), 5.30 (d, *J*=17 Hz, 1H), 5.60-5.67 (m, 1H), 5.80 (m, 1H), 6.49 (br s, 1H), 6.75 (d, *J*=7.5 Hz, 1H), 7.43-7.51 (m, 3H), 7.59 (d, *J*=7.5 Hz, 1H), 7.81 (t, *J*=7.5 Hz, 1H), 8.09 (d, *J*=7.0 Hz, 2H), 8.91 (s, NH), 10.4 (s, NH).

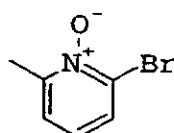
LC/MS rt-min (MH⁺): 2.77 (711)(method B).

Example 437: Preparation of Compound 437.



Compound 437

Step 1:

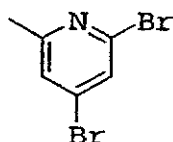


To a solution of 2-bromo-6-methyl-pyridine (7.65 g, 44.4 mmol) in dichloromethane (50 mL) was added a solution of *m*CPBA (77%, 12.9 g, 57.7 mmol) in dichloromethane (100 mL). The solution was stirred for 18 h at ambient temperature. The mixture was neutralized with solid Na₂CO₃ and water was added. The aqueous phase was extracted with dichloromethane (2x). The combined organic fractions were washed with 5% Na₂S₂O₃, 5% Na₂CO₃, brine and dried (MgSO₄). Purification using a Biotage 40 M column (eluted gradient hexane – ethyl acetate 40-70%) afforded the title compound (5.0 g, 60%) as a colorless oil that solidified upon standing.

¹H NMR: (DMSO-d₆) δ 2.43 (s, 3H), 7.15 (t, *J*=8.0 Hz, 1H), 7.50 (s, 1H), 7.78 (s, 1H).

LC/MS rt-min (MH^+): 0.32 (188, 190)(method B).

Step 2:



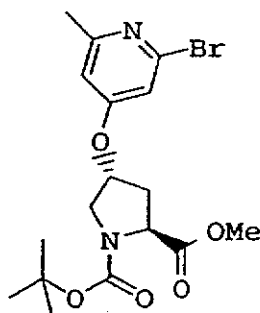
- 5 To a solution of the product of Example 437, Step 1 (4.5 g, 24 mmol) in DMF (20 mL) was added $POBr_3$ (8.2 g, 29 mmol) in portions. A strong exothermic reaction occurred and a precipitate formed. The mixture was left for 2 h at ambient temperature. The mixture was quenched with water and satd. $NaHCO_3$ until neutral pH. The aqueous phase was extracted with diethyl ether (2x). The combined organic
- 10 fractions were washed with brine and dried ($MgSO_4$). Purification using a Biotage 40 M column (eluted gradient hexane – diethyl ether 0-10%) afforded the title compound (1.78 g, 30%) as a colorless oil.

^1H NMR: (DMSO- d_6) δ 2.45 (s, 3H), 7.64 (s, 1H), 7.80 (s, 1H).

LC/MS rt-min (MH^+): 1.85 (250, 252, 254)(method B).

15

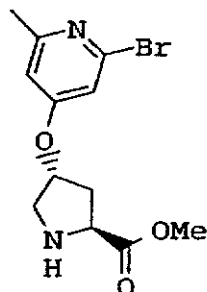
Step 3:



This product was prepared according to Example 421, Step 2 in 46% yield, starting from the product of Example 437, Step 1.

- 20 ^1H NMR: (DMSO- d_6) δ 1.34, 1.38(s, 9H (rotamers)), 2.20-2.27 (m, 1H), 2.38 (s, 3H), 2.43-2.50 (m, 1H), 3.55 (d, $J=12.5$ Hz, 1H), 3.64-3.67 (m, 1H), 3.66, 3.69 (s, 3H (rotamers)), 4.26-4.32 (m, 1H), 5.17 (m, 1H), 6.93 (s, 1H), 7.08 (s, 1H).
- LC/MS rt-min (MH^+): 2.17 (415, 417)(method B).

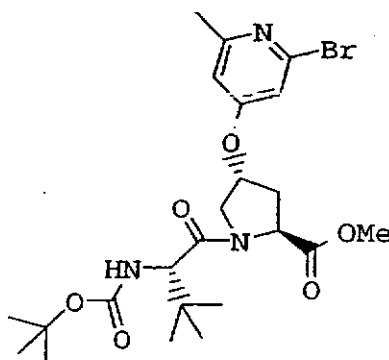
Step 4:



This product was prepared according to Example 420, Step 3 in quantitative yield, starting from the product of Example 437, Step 3.

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Step 4:



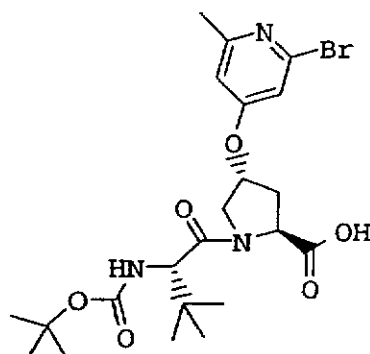
This product was prepared according to Example 420, Step 3 in 75% yield, starting from the product of Example 437, Step 3.

10 ^1H NMR: (DMSO- d_6) δ 0.94 (s, 9H), 1.27 (s, 9H), 2.16-2.21 (m, 1H), 2.36 (s, 3H), 2.48 (m, 1H (hidden)), 3.64 (s, 3H), 3.83 (d, $J=10.5$ Hz, 1H), 4.06 (d, $J=8.5$ Hz, 1H), 4.14 (d, $J=10.5$ Hz, 1H), 4.42 (t, $J=9.0$ Hz, 1H), 5.27 (m, 1H), 6.68 (br s, NH), 6.88 (s, 1H), 7.03 (s, 1H).

LC/MS rt-min (MH^+): 2.19 (528, 530)(method B).

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Step 5:

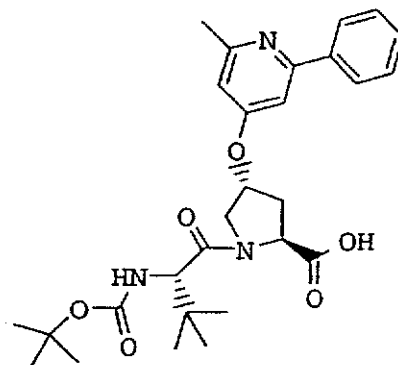


This product was prepared according to Example 420, Step 5 in quantitative yield, starting from the product of Example 437, Step 4.

¹H NMR: (DMSO-d₆) δ 0.95 (s, 9H), 1.27 (s, 9H), 2.15-2.19 (m, 1H), 2.36 (s, 3H),
 5 2.44-2.48 (m, 1H), 3.81 (d, *J*=10.5 Hz, 1H), 4.04-4.06 (m, 1H), 4.13 (d, *J*=10.5 Hz, 1H), 4.33 (t, *J*=8.5 Hz, 1H), 5.26 (m, 1H), 6.66 (br d, *J*=9.0 Hz, NH), 6.88 (s, 1H), 7.03 (s, 1H).

LC/MS rt-min (MNa⁺): 2.14 (536, 538)(method B).

10 Step 6:



To a solution of the product of Example 437, Step 5 (101 mg, 0.196 mmol),
 Pd(PPh₃)₄ (11.3 mg, 0.0098 mmol), and phenyl boronic acid (34 mg, 0.275 mmol) in
 DMF (2 mL) was added 2M aqueous Na₂CO₃ (0.294 mL, 0.588 mmol). The tube was
 15 sealed and heated in a microwave oven (Emrys, Personal Chemistry) at 150°C for 15
 min. under nitrogen. After cooling to room temperature the mixture was acidified
 with 1N HCl (0.5 mL). The solid was removed by filtration, and the filtrate
 concentrated in vacuo. The residue was purified by preparative HPLC (gradient 20-
 80% B). The combined fractions were neutralized with conc. ammonia and

concentrated. The residue was partitioned between buffer pH 4 and ethyl acetate. The aqueous phase was extracted with ethyl acetate (2x) and the combined organic extracts washed with brine and dried (MgSO₄). The title compound (115 mg, >100%) was obtained as a white solid.

- 5 ¹H NMR: (methanol-d₄) δ 1.06 (s, 9H), 1.30 (s, 9H), 2.36-2.41 (m, 1H), 2.69 (s, 3H), 2.65-2.76 (m, 1H), 4.01 (dd, *J*=3.0, 12 Hz, 1H), 4.21 (s, 1H), 4.44 (d, *J*=12 Hz, 1H), 4.64 (dd, *J*=8.0, 10 Hz, 1H), 5.46 (m, 1H), 6.91 (s, 1H), 7.29 (s, 1H), 7.39 (m, 3H), 7.57 (d, *J*=7.5 Hz, 2H).

LC/MS rt-min (MH⁺): 1.84 (513)(method B).

10

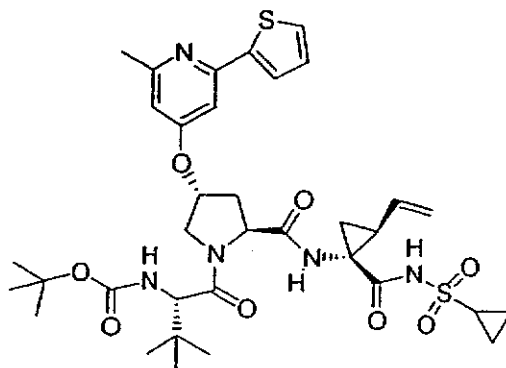
Step 7:

Compound 437 was prepared according to Example 420, Step 6 in 31% yield, starting from the product of Example 437, Step 6.

- 15 ¹H NMR: (DMSO-d₆) δ 0.95 (s, 9H), 0.99-1.04 (m, 4H), 1.25 (s, 9H), 1.54-1.57 (m, 1H), 1.69-1.71 (m, 1H), 2.11-2.20 (m, 2H), 2.39-2.43 (m, 1H), 2.48 (s, 3H), 2.93 (m, 1H), 3.92 (d, *J*=8.5 Hz, 1H), 4.07 (d, *J*=9.0 Hz, 1H), 4.11 (d, *J*=12 Hz, 1H), 4.32 (t, *J*=7.0 Hz, 1H), 5.10 (d, *J*=10.5 Hz, 1H), 5.23 (d, *J*=17.5 Hz, 1H), 5.39 (m, 1H), 5.60-5.67 (m, 1H), 6.58 (d, *J*=8.5 Hz, 1H), 6.83 (s, 1H), 7.27 (s, 1H), 7.40-7.48 (m, 3H), 8.04-8.06 (m, 2H), 8.92 (s, NH), 10.4 (s, NH).

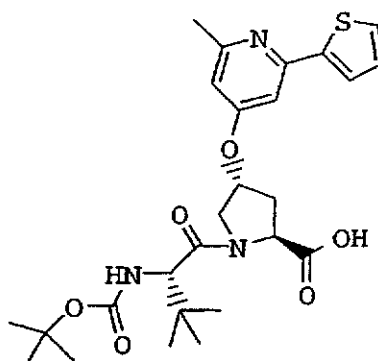
- 20 LC/MS rt-min (MH⁺): 2.10 (725)(method B).

Example 438: Preparation of Compound 438.



Compound 438

Step 1:



This product was prepared according to Example 437, Step 6 in quantitative yield, starting from 2-thiopheneboronic acid.

¹H NMR: (methanol-d₄) δ 1.05 (s, 9H), 1.32 (s, 9H), 2.32-2.38 (m, 1H), 2.56 (s, 3H), 2.66-2.70 (m, 1H), 3.99 (dd, *J*=3.0, 12 Hz, 1H), 4.23 (s, 1H), 4.36 (d, *J*=12 Hz, 1H), 4.61 (t, *J*=8.5 Hz, 1H), 5.35 (m, 1H), 5.86 (s, 1H), 7.16-7.18 (m, 1H), 7.21 (s, 1H), 7.56 (m, 1H), 7.72 (d, *J*=3.0 Hz, 1H).

LC/MS rt-min (MH⁺): 1.80 (519)(method B).

10 Step 2:

Compound 438 was prepared according to Example 420, Step 6 in 41% yield, starting from the product of Example 438, Step 1.

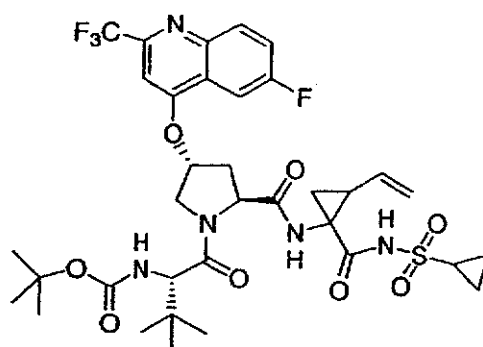
¹H NMR: (DMSO-d₆) δ 0.91 (s, 9H), 0.99-1.04 (m, 4H), 1.20 (s, 9H), 1.35-1.37 (m, 1H), 1.69-1.71 (m, 1H), 2.09-2.20 (m, 2H), 2.33 (m, 1H), 2.42 (s, 3H), 2.93 (m, 1H), 3.92 (d, *J*=8.5 Hz, 1H), 4.07-4.11 (m, 2H), 4.29-4.32 (m, 1H), 5.10 (d, *J*=10.5 Hz, 1H), 5.23 (d, *J*=17.0 Hz, 1H), 5.36 (m, 1H), 5.60-5.67 (m, 1H), 6.58 (d, *J*=8.5 Hz, 1H), 6.75 (s, 1H), 7.14 (t, *J*=4.5 Hz, 1H), 7.28 (s, 1H), 7.59 (d, *J*=5.5 Hz, 1H), 7.80 (d, *J*=3.5 Hz, 1H), 8.92 (s, NH), 10.4 (s, NH).

LC/MS rt-min (MH⁺): 2.06 (731)(method B).

20

Section K:

Example 450: Preparation of Compound 450.

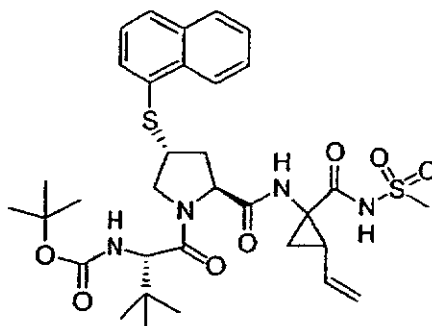


Compound 450

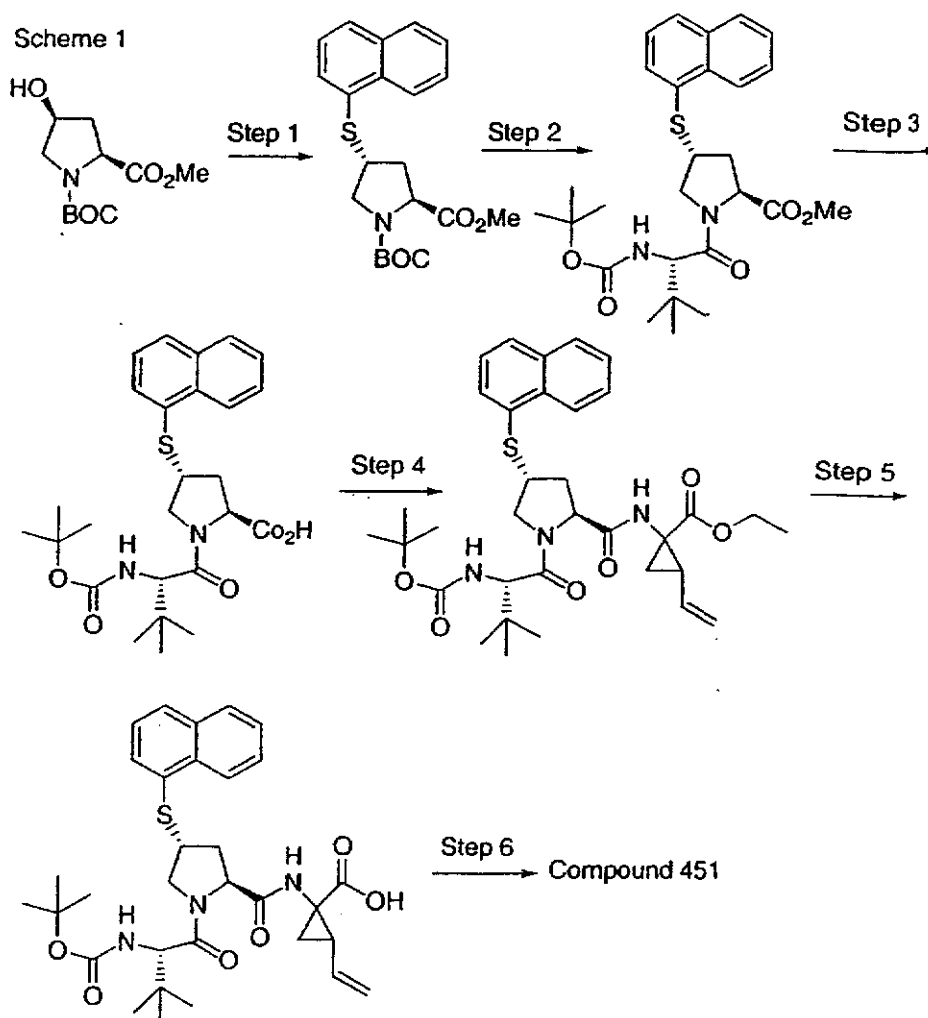
Compound 450 was prepared according to Example 8, Step 5, except using 4-chloro-6-fluoro-2-trifluoromethylquinoline instead.

- ¹H NMR (CD₃OD) δ 0.97-1.04 (m, 12H), 1.17-1.24 (m, 10H), 1.39-1.46 (m, 1H),
 5 1.82-1.87 (m, 1H), 2.20-2.23 (m, 1H), 2.35-2.39 (m, 1H), 2.55-2.65 (m, 1H), 2.91-
 2.96 (m, 1H), 4.09-4.11 (m, 1H), 4.18-4.21 (m, 1H), 4.56 (b, 2H), 5.10-5.14 (m, 1H),
 5.28-5.31 (m, 1H), 5.60 (b, 1H), 5.70-5.80 (m, 1H), 7.41 (s, 1H), 7.65-7.68 (m, 1H),
 7.86 (s, 1H), 8.13-8.15 (m, 1H).

10 Example 451: Preparation of Compound 451.



Compound 451



Step 1:

The tosylate was prepared as described in the literature (Patchett, A. A.; Witkof, B. *J. Am. Chem. Soc.* 1957, 185-192) and was used without further purification.

- 5 To a slurry of NaH (76 mg, 1.90 mmol) in DMF (20 ml) was added 1-thionaphthol (0.29 mg, 1.80 mmol) and the mixture stirred for 30 minutes. A solution of the tosylate (0.61 g, 1.80 mmol) was added and the mixture stirred for 12 h at 23°C. The mixture was concentrated and the residue partitioned between EtOAc/H₂O. The
- 10 organic extracts are dried (MgSO₄) and concentrated. The residue was purified by column chromatography (elution with 5% EtOAc/hexanes to 30% EtOAc/hexanes to give 261 mg (38%) of the product as a yellow oil.

¹H NMR (CDCl₃, 3:2 mixture of rotamers) δ 1.41 (s, 9H), 1.44 (s, 9H), 2.25-2.29 (m, 2H), 3.69 (s, 3H), 3.35-3.42 (m, 1H), 3.51-3.53 (m, 1H), 3.80-3.86 (m, 2H), 4.38-4.39 (m, 1H), 4.46-4.48 (m, 1H), 7.41-7.46 (m, 1H), 7.42-7.54 (m, 1H), 7.57-7.59 (m, 1H), 7.58 (d, J = 4 Hz, 1H), 7.82-7.88 (m, 2H), 8.46 (d, J = 5 Hz, 1H);

5 LC-MS (retention time: 1.93), MS m/z 388 (M⁺+1).

Step 2:

A mixture of 4-(naphthalen-1-ylsulfanyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (0.38 g, 0.98 mmol) and 4N HCl (1.0 ml) was stirred at
10 23°C for 2 h. The solvent was removed and the residue dissolved in CH₃CN (20 ml) and treated with acid (0.37 g, 2.16 mmol), TBTU (0.23 g, 0.98 mmol) and DIPEA (0.37 g, 2.16 mmol) and stirred for 12 h. The mixture is concentrated and the residue dissolved in EtOAc and washed with 1 N HCl, saturated NaHCO₃ then dried over
MgSO₄ and concentrated. The residue was used without further purification.

15 ¹H NMR (CDCl₃, 1:1 mixture of rotamers) δ 0.99 (s, 9H), 1.02 (s, 9H), 1.44 (s, 9H), 1.46 (s, 9H), 2.2-2.25 (m, 2H), 3.70 (s, 3H), 3.82-3.86 (m, 1H), 3.89-3.92 (m, 2H), 4.26 (s, 1H), 4.28 (s, 1H), 4.70-4.75 (m, 1H), 7.40-7.48 (m, 1H), 7.54-7.55 (m, 1H), 7.59-7.62 (m, 1H), 7.72-7.74 (m, 1H), 7.86-7.89 (m, 2H), 8.48-8.50 (m, 1H);

LC-MS (retention time: 1.59), MS m/z 523 (M+Na).

20

Step 3:

To a mixture of 1-(2-tert-butoxycarbonylamino-3,3-dimethyl-buteryl)-4-(naphthalen-1-ylsulfanyl)-pyrrolidine-2-carboxylic acid methyl ester (Example 451, Step 2) (0.49 g, 0.98 mmol), in THF/H₂O (2:1) was added LiOH hydrate (0.20 g, 4.9
25 mmol) and the mixture stirred for 12 h. The solution was concentrated and washed with EtOAc. The aqueous layer is acidified with 1N HCl and extracted with EtOAc. The product was observed in the first EtOAc extract. The first organic extract was dried over MgSO₄ and concentrated to 328 mg (71%) of a tan solid.

¹H NMR (DMSO-d₆, 2:1 mixture of rotamers) δ 0.88 (s, 9H), 0.92 (s, 9H), 1.34 (s, 9H), 1.38 (s, 9H), 2.18-2.25 (m, 2H), 3.66-3.75 (m, 1H), 3.89-4.00 (m, 2H), 4.10-4.13
30 (m, 1H), 4.25-4.32 (m, 1H), 7.45-7.751 (m, 1H), 7.56-7.61 (m, 2H), 7.65-7.769 (m, 1H), 7.88-7.91 (m, 1H), 7.97 (d, J = 4.8 Hz, 1H), 8.27-8.35 (m, 1H);