Discovery of BIIB042, a Potent, Selective and Orally Bioavailable γ-Secretase Modulator

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Contents:

General considerations:

Chemistry

All reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Flash chromatography was carried out with EM science Silica gel 60 (neutral, 230-400 mesh). Analytical thin-layer chromatography (TLC) was performed on silica gel 60F-254 plates by EMD Visualization was accomplished using ultraviolet light or Vaughn's stain reagent. Flash column chromatography was carried out with the use of standard 220-400 mesh silica gel or RediSep cartridges and CombiFlash apparatus. 1H NMR and 13C NMR spectra were recorded in cited solvent on a Bruker (300, 400 MHz) NMR Spectrometer with chemical shifts reported in ppm relative to the residual deuterated solvent. HRMS was recorded on a Thermo Fisher Scientific LTQ FT Ultra Hybrid mass spectrometer, which was equipped with a nanospray source. The instrument was operated at the positive mode. LCMS was recorded on Agilent Technology 6120 quadrupole LC/MS.

γ-Secretase Modulation in a Cell-based Assay

Chinese Hamster Ovary (CHO) cells expressing the APP V717F mutation were grown in α-MEM media containing 10% FBS, 2 mM L-Glutamine, and 1% pen/strep until nearly confluent. Cells were added to 96-well flat-bottom plates to a density of 25,000 cells per well in 80μL of media and the plates were then incubated at 37°C in a 5% CO_2 atmosphere for 4 hours prior to challenging with compound. Immediately prior to adding diluted compound solution to the cells, the media was replaced with 80 μL of serum-free media (α-MEM, 2mM L-Glutamine, 1% pen/strep supplemented with 2% B27). 10 mM DMSO stock solutions of test compounds were further diluted with DMSO to yield nine, 3-fold serial dilutions. 5 μl of these diluted solutions were further diluted into 828 μL of serum-free media. 80 μL of these resulting dilutions with serum-free media were added to the previously plated cells containing 80 μL of serum-free media. The final concentration of DMSO on the cells was 0.3%. The plates were incubated for 17 hours at 37°C in a 5% CO_2 atmosphere. Following incubation, conditioned media from the compound-challenged cells was transferred to new 96-well plates and centrifuged at 1,000 RPM at 4°C for 10 minutes. 20 μL of the collected media was measured for Aβ42, 40 and 38 levels using Human/Rodent Aβ Triplex Elisa plates according to the manufacturers protocol (Meso Scale Discovery). Nonlinear regression analysis (sigmoidal dose-response, variable slope) was used to fit curves for Aβ42, 40 and 38, and calculate EC_{50} values for Aβ42 inhibition (GraphPad by Prism). Typically, data are expressed as a percent of control.

To measure cell viability, a CellTiter-Blue Viability Assay (Promega) was used to determine the metabolic capacity of cells by their ability to reduce the indicator dye resazurin into resorufin. 50 μL of CellTiter-Blue Reagent diluted 5-fold in FBS-containing media was added to compound-challenged cells after the removal of media, as described above. Cells were incubated with the reagent for 1 hour at 37° in a 5% CO_2 atmosphere and the fluorescence was recorded ($560_{Ex}/590_{Em}$).

Measurement of Aβ from brain of wild-type mice and rats

To determine whether acute administration of an Aβ42 lowering agent would reduce Aβ42 levels *in vivo*, rat and mouse models were utilized. Male CF-1 mice or F344 rats from Charles River laboratories, over the age of 11 weeks, were used as subjects for testing compounds. Animals were dosed (10.0 ml/kg in mice and 5.0 ml/kg in rats) by oral gavage with experimental compounds in a vehicle consisting of ETOH (10%), propolenye glycol (10%) and a solution of water and solutol (20/80; v/v). A single oral dose (30 or 50 mg/kg) was given four hours before euthanasia. At the appointed time, animals were anesthetized with ketamine/xylazine (100/10 mg/kg, ip) at a volume of 10.0 ml/kg in mice and 1.0 ml/kg in rats. Blood was collected via cardiac puncture into a sterile syringe and transferred to EDTA treated collection tubes. The blood was mixed and then kept at 4 degrees Celsius until spun in a centrifuge (10 minutes at 10,000 rpm); serum was collected and kept on ice until frozen at -80 degrees. All experiments adhered to the Public Health Service Policy on Humane Use and Care of Laboratory Animals (NIH Publication 80-23, National Academy of Sciences Press, Washington, DC, 1996) and were reviewed and approved by the Biogen Idec Institutional Animal Care and Use Committee.

The brain was removed from the cranium and the hindbrain and forebrain were separated. The forebrain was divided evenly into left and right hemispheres by cutting along the sagital midline. Both sides were weighed and then quickly frozen on dry ice for analysis.

To measure brain Aβ levels, these previously weighed and excised frozen hemispheres in a 5 mL tubes were used. An ice-cold aqueous solution of 50 mM NaCl, 0.4% diethylamine, and EDTA-free protease inhibitors was added to the tube at 1 mL solution per 100 mg of wet brain weight. The brain tissue was homogenized using a tip sonicator and then 1.2 mL was centrifuged at 44,000 x g for 30 minutes at 4°C.

The resulting supernatant was further processed with a Waters 60 mg HLB Oasis column. The column was treated with methanol and water prior to loading 0.8 mL of the supernatant. The column was washed with 5% methanol and then 30% methanol prior to Aβ elution with 0.8 mL of an aqueous solution of 90% methanol and 2% ammonium hydroxide. The eluate was collected and evaporated in a vacuum dryer.

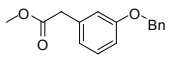
The Aβ levels were quantified using a MesoScale Discovery ELISA kit which was able to measure Aβ 38, 40, and 42 simultaneously. The residue of the dried elution buffer was resuspended in 0.4 mL of the blocking buffer provided in the MesoScale Discovery kit. 25 µL of this reconstituted mixture was added to the ELISA plate and the manufacturer's instructions were followed for analysis. Standard curves in the analysis were derived from Aβ 38, 40, and 42 peptides supplied in the kit.

***In Vitro* Notch Activity Assay:**

An *in vitro* biochemical assay for analysis of the direct effect of a GSM compound on endogenous Notch NICD-regulated transcription product, **HES1**. NICD stimulates transcription through interaction with DNA-binding proteins resulting in induction of the HES1 protein expression (Jarriault et al, 1998). In this assay, MC-IXC or H4 cells are seeded in a 6-well plate at 500,000 cells/well and allowed to grow overnight in an incubator. Cells are treated with GSM compounds at a single concentration of 10µM for 24 hours. Because MC-IXC/H4 cells have very low basal Notch cleavage activity, the cells are further exposed to 5µM EDTA for 10 minutes after the 24-hour GSM treatment to stimulate Notch processing due to calcium depletion (Rand et al, 2000). Cells are then harvested, subjected to Western blot analysis and probed for HES1 and β-Actin (loading control) using specific antibodies. The net intensities of HES1 immunoreactivity is determined and normalized to the control (untreated group).

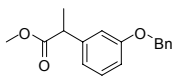
General procedure for Mannich route is illustrated by the preparation of compound 10a

Step 1



Methyl 2-(3-hydroxyphenyl)acetate (33 g, 0.2 mol, 1.0 equiv.), BnBr (24 ml, 0.2 mol, 1.0 equiv.) and K_2CO_3 (80 g, 0.58 mol, 2.9 equiv.) were dissolved in CH_3CN (200 ml). The mixture was stirred at rt for 6 h; then removed the solvent, partitioned between water and EtOAc. The organic layer was dried with Na_2SO_4 and concentrated in *v*acuum. Purified with a silica gel column chromatography (Petroleum ether/EtOAc = 10:1) to obtain methyl 2-(3-(benzyloxy)phenyl)acetate (44.2 g, 87%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.30-7.44 (m, 5H), 7.22 (d, 1H), 6.92 (s, 1H), 6.88 (d, 2H), 5.05 (s, 2H), 3.68 (s, 3H), 3.59 (s, 2H); LCMS m/z 257 $[M+1]^+$.

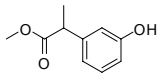
Step 2



Methyl 2-(3-(benzyloxy)phenyl)acetate (10 g, 39 mmol, 1.0 equiv.) was dissolved in dry THF (150 ml), and the solution was cooled to -78 °C, then LiHMDS (40 ml, 39 mmol, 1.0 equiv.) was added dropwise to the solution, allowed to stirred for about 1 h. Then CH_3I (2 ml, 39 mmol, 1.0 equiv.) was added in dropwise at -78 °C. The mixture was stirred at -78 °C for 1 h and then warmed to rt for 16 h. The mixture was quenched with $NaHCO_3$ solution, extracted with EtOAc and H_2O. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified with a silica gel column chromatography (Petrole-

um ether/EtOAc=100:1) to obtain methyl 2-(3-(benzyloxy)phenyl)propanoate (8 g, 76 %). ^{1}H NMR (400 MHz, $CDCl_3$): 7.34-7.47 (m, 5H), 7.25 (d, 1H), 6.96 (s, 1H), 6.91-6.93 (t, 2H), 5.07 (s, 2H) 3.69-3.75 (q, 1H), 3.67 (s, 3H), 1.50 (d, 3H); LCMS m/z 271 $[M+1]^+$.

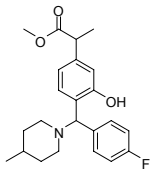
Step 3



To a solution of methyl 2-(3-(benzyloxy)phenyl) propanoate (15.6 g, 43 mmol, 1.0 equiv.) in methanol (150 ml) was added palladium charcoal (2.2 g, 10%wt), and the mixture was stirred under balloon pressure H_2 for 3 h. The solution was filtered through Celite and concentrated under reduced pressure. Then passed through a short silica gel column, eluted with PE/EtOAc=10:1 to afford methyl 2-(3-hydroxyphenyl)propanoate (9 g, 87 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.16-7.20 (t, 1H), 6.84 (d, 1H), 6.81 (s, 1H), 6.74 (d, 1H), 3.67 (s, 3H), 3.67-3.72 (q, 1H), 1.48 (d, 3H); LCMS m/z 181 $[M+1]^+$.

Step 4

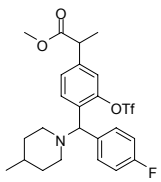
Methyl 2-(4-((4-fluorophenyl)(4-methylpiperidin-1-yl)methyl) hydroxyphenyl)propanoate.



To a mixture of methyl 2-(3-hydroxyphenyl)propanoate (5.0 g, 27.7 mmol), 4-methylpiperidine (4.1 mL, 34.7 mmol) in trifluoro-toluene (20 mL) was added 4-fluorobenzaldehyde (3.7 mL, 34.7 mmol). The mixture was heated using microwave irradiation at 120°C for 1 hour. The solution was partitioned between EtOAc and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on silica (10-30% EtOAc in hexane) to give the product (4.5 g, 42% yield) as a colorless oil: LCMS m/z = 386.1 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.46 (bs, 1H), 7.34 (bs, 2H), 7.01-6.96 (m, 2H), 6.79-6.77 (m, 2H), 6.62 (d, J = 8.0 Hz, 1H), 4.45 (s, 1H), 3.64 (s, 3H), 3.63-3.59 (m, 1H), 3.13 (bs, 1H), 2.68 (bs, 1H), 2.06-2.04 (m, 1H), 1.89 (bs, 1H), 1.69-1.60 (m, 2H), 1.44 (d, J = 7.6 Hz, 3H), 1.37-1.34 (m, 2H), 1.25-1.24 (m, 1H), 0.91 (d, J = 6.0 Hz, 3H).

Step 5

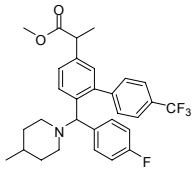
Methyl-2-(4-((4-fluorophenyl)(4-methylpiperidin-1-yl)methyl)-3-(trifluoromethylsulfonyloxy)phenyl) propanoate



To a solution of methyl 2-(4-((4-fluorophenyl)(4-methylpiperidin-1-yl)methyl) hydroxyphenyl)propanoate (10.0 g, 25.9 mmol) and Tf_2O (6.55 mL, 38.9 mmol) in 50 mL methylene chloride was slowly added pyridine (6.3 mL, 77.8 mmol). The mixture was stirred at room temperature for 2 hours. The organic solvent was removed and the residue was purified by flash chromatography on silica (10-20% EtOAc in hexane) to give the title product (10.0 g, 75%) as a colorless oil: LCMS m/z = 518.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (d, J = 8.0 Hz, 1H), 7.35-7.29 (m, 3H), 7.12 (s, 1H), 6.97-6.91 (m, 2H), 4.57 (s, 1H), 3.72-3.69 (m, 1H), 3.66 (s, 3H), 2.83 (bs, 1H), 2.68 (bs, 1H), 1.90-1.82 (m, 2H), 1.55-1.52 (m, 2H), 1.47 (d, J = 7.6 Hz, 3H), 1.40-1.34 (m, 1H), 1.27-1.17 (m, 2H), 0.91 (d, J = 6.8 Hz, 3H).

Step 6

Methyl 2-(6-((4-fluorophenyl)(4-methylpiperidin-1-yl)methyl)-4'-(trifluoromethyl)biphenyl-3-yl)propanoate

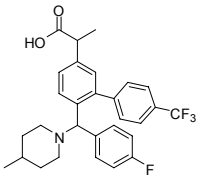


To a mixture of methyl methyl2-(4-((4-fluorophenyl)(4-methylpiperidin-1-yl)methyl)-3-(trifluoromethylsulfonyloxy)phenyl)propanoate (9.0 g, 17.4 mmol), 4-(trifluoromethyl)phenylboronic acid (5.3 g, 27.8 mmol), tetrakis(triphenylphosphine)palladium(0) (2.0 g, 1.74 mmol), in toluene, ethanol, water (5:2:1) was added sodium carbonate

(5.5 g, 53 mmol). The reaction mixture was heated at 80 °C, for 4 h. The reaction mixture was diluted with water, and extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (5-30% EtOAc in hexane) to get the title product as a yellow foam (6.0 g, 67%). LCMS m/z = 514.3 $[M+1]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.83-7.80 (m, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.33-7.12 (m, 5H), 6.97-6.94 (m, 3H), 6.86-6.82 (m, 1H), 4.23 (s, 1H), 3.72-3.68 (m, 1H), 3.64 (s, 3H), 2.85-2.81 (m, 1H), 2.52 (bs, 1H), 1.90-1.77 (m, 1H), 1.67-1.54 (m, 3H), 1.47 (d, J = 7.6 Hz, 3H), 1.32-1.14 (m, 3H), 0.91-0.88 (m, 3H).

Step 7

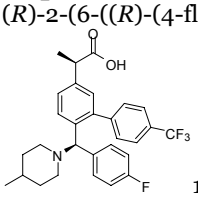
2-(6-((4-fluorophenyl)(4-methylpiperidin-1-yl)methyl)-4'-(trifluoromethyl)biphenyl-3-yl)propanoic acid



Methyl 2-(6-((4-fluorophenyl)(4-methylpiperidin-1-yl)methyl)-4'-(trifluoromethyl)biphenyl-3-yl)propanoate (1.44 g, 2.80 mmol) was dissolved in 1: 1 MeOH/THF (20 mL) and 4 M of sodium hydroxide in water (3.50 mL, 14.0 mmol). The solution was heated in microwave for 10 minutes at 100 °C. Hydrolysis was complete. The solution was quenched with equivalent amount of 1 N HCl. The resulting mixture was concentrated to remove MeOH. The residual solution was extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a residue which was purified using 0-10% MeOH in DCM to give the title compound as a white solid (1.2 g, 86%): LCMS m/z 500.2 $[M+1]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 12.50 (bs, 1H), 9.68 (bs, 1H), 8.16 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 7.6 Hz, 1H), 7.01-7.29 (m, 7H), 5.13 (d, J = 9.2 Hz, 1H), 3.74-3.79 (m, 1H), 3.38 (d, J = 7.2 Hz, 1H), 3.05 (d, J = 10.0 Hz, 1H), 2.76-2.88 (m, 2H), 1.69-1.80 (m, 2H), 1.24-1.39 (m, 6H).

Step 8

(*R*)-2-(6-((*R*)-(4-fluorophenyl)(4-methylpiperidin-1-yl)methyl)-4'-(trifluoromethyl)biphenyl-3-yl)propanoic acid



10a

The racemic material (1 g) from the previous step was separated using SFC condition (Chiralpak AD-H (2 x 15 cm) 08-9743, 10% isopropanol (0.1% DEA)/CO_2, 100 bar, 60 mL/min, 220 nm, inj vol.: 1 mL, 15 mg/mL methanol) to yield peak 1 (**10c** +**10d**, 440 mg), peak 2 (**10a**, 188 mg) and peak 3 (**10b**, 176 mg).

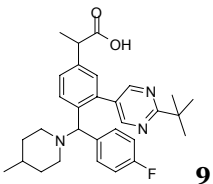
Compound **10a**: 1H NMR (400 MHz, DMSO-d6) δ 7.82 (d, J = 8.03 Hz, 2H), 7.75 (d, J = 8.03 Hz, 1H), 7.36 (dd, J = 1.88, 8.16 Hz, 3H), 6.97 - 7.02 (m, 5H), 4.27 (s, 1H), 3.64 (q, J = 7.03 Hz, 1H), 2.88 (d, J = 9.54 Hz, 1H), 2.42 - 2.45 (m, 1H), 1.78 - 1.86 (m, 1H), 1.52 - 1.66 (m, 2H), 1.47 (d, J = 12.05 Hz, 1H), 1.27 - 1.35 (m, 4H), 1.07 - 1.16 (m, 2H), 0.85 (d, J = 6.53 Hz, 3H); LCMS m/z 500.2 $[M+H]^+$**;**

Anal: Calc'd for $C_{29}H_{29}F_4NO_2$ C, 69.73; H, 5.85; N, 2.80;

Found: C, 69.45; H, 5.81; N, 2.84;

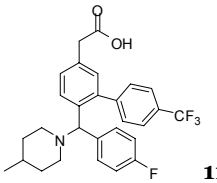
Compound **10b**: 1H NMR (300 MHz, DMSO-d6) δ 7.83 (d, J = 8.31 Hz, 2H), 7.76 (d, J = 7.93 Hz, 1H), 7.37 (d, J = 7.93 Hz, 3H), 6.99 - 7.04 (m, 5H), 4.28 (s, 1H), 3.66 (q, J = 6.92 Hz, 1H), 2.88 (d, J = 11.33 Hz, 1H), 2.44 (br. s., 1H), 1.78 - 1.87 (m, 1H), 1.55 - 1.69 (m, 2H), 1.48 (d, J = 12.09 Hz, 2H), 1.24 - 1.37 (m, 4H), 1.04 - 1.21 (m, 2H), 0.86 (d, J = 6.42 Hz, 3H); LCMS m/z 500.2 $[M+H]^+$

The following compounds were synthesized following the same synthetic procedures and similar condition as compound **10a**:



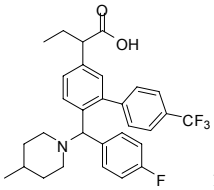
9

Compound **9.** 1H NMR (300MHz ,DMSO-d6) δ = 8.49 (s, 2 H), 7.74 (d, J = 7.9 Hz, 1 H), 7.40 (d, J = 8.3 Hz, 1 H), 7.06 (s, 1 H), 7.04 - 6.94 (m, 2 H), 6.94 - 6.82 (m, 2 H), 4.31 (s, 1 H), 3.72 - 3.56 (m, 1 H), 2.96 - 2.80 (m, 1 H), 2.45 - 2.38 (m, 1 H), 1.96 - 1.77 (m, 1 H), 1.74 - 1.60 (m, 1 H), 1.60 - 1.44 (m, 2 H), 1.42 (s, 9 H), 1.38 - 0.99 (m, 6 H), 0.86 (d, J = 6.0 Hz, 3 H); LCMS m/z 490.3 $[M+1]^+$.



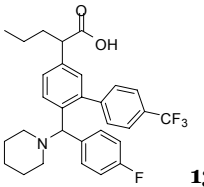
11

Compound **11**. 1H-NMR (400MHz, CD3OD) δ 8.06 (d, J = 7.6 Hz, 1H), 7.79 (d, J = 7.6 Hz, 2H), 7.61 (d, J = 8.4 Hz, 1H), 7.32-7.36 (m, 3H), 7.23 (d, J = 1.6 Hz, 2H), 7.15-7.19 (m, 2H), 5.08 (s, 1H), 3.71 (s, 2H), 3.55 (d, J = 10.8 Hz, 1H), 2.93-3.03 (m, 2H), 2.78-2.85 (m, 1H), 1.76-1.87 (m, 2H), 1.64 (bs, 1H), 1.39-1.52 (m, 2H), 0.96 (d, J = 6.4 Hz, 3H); LCMS m/z 486.0 $[M+1]^+$.



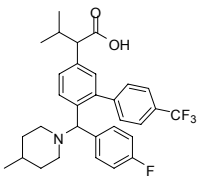
12

Compound **12**. 1H NMR (400 MHz, CD3OD) δ 8.05-8.08 (m, 1H), 7.83 (d, J = 7.2 Hz, 2H), 7.67-7.84 (m, 1H), 7.34 (bs, 3H), 7.28-7.29 (m, 1H), 7.18-7.23 (m, 3H), 5.12 (s, 1H), 3.56-3.61 (m, 1H), 3.23-3.33 (m, 3H), 3.03 (bs, 1H), 2.83-2.89 (t, J = 12.0 Hz, 1H), 2.08-2.16 (m, 1H), 1.76-1.91(m, 2H), 1.67 (bs, 1H), 1.43-1.53 (m, 2H), 0.93-1.00 (m, 6H); LCMS m/z 514.0 $[M+1]^+$.



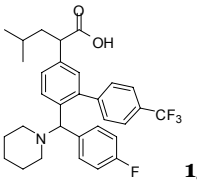
13

Compound **13**. 1H NMR (400 MHz, CHLOROFORM-d) δ 7.81 (d, J = 8.31 Hz, 1H), 7.56 (d, J = 7.55 Hz, 1H), 7.44 (t, J = 7.55 Hz, 1H), 7.31 - 7.38 (m, 1H), 7.23 (br. s., 2H), 6.94 (s, 1H), 6.80 - 6.88 (m, 1H), 6.62 - 6.79 (m, 3H), 4.11 (s, 1H), 3.41 - 3.53 (m, 1H), 2.25 (br. s., 2H), 2.04 - 2.15 (m, 2H), 1.98 (dd, J = 8.12, 13.79 Hz, 1H), 1.58 - 1.74 (m, 1H), 1.44 (br. s., 3H), 1.15 - 1.37 (m, 5H), 0.83 (t, J = 6.99 Hz, 3H); LCMS m/z 514.4 $[M+1]^+$.



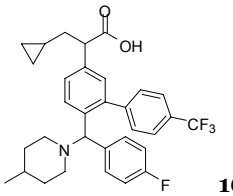
14

Compound **14**. 1H NMR (400 MHz, CHLOROFORM-d) δ 7.65 (d, J = 7.03 Hz, 1H), 7.16 - 7.44 (m, 4H), 6.88 - 7.05 (m, 5H), 6.79 (br. s., 1H), 4.27 (br. s., 1H), 3.04 - 3.18 (m, 1H), 2.16 - 2.40 (m, 2H), 1.82 (br. s., 1H), 1.68 (br. s., 1H), 1.56 (br. s., 1H), 1.47 (br. s., 1H), 1.25 (br. s., 3H), 1.06 (d, J = 6.27 Hz, 3H), 0.97 - 1.02 (m, 1H), 0.81 - 0.95 (m, 3H), 0.62 - 0.78 (m, 3H); LCMS m/z 528.4 $[M+1]^+$.



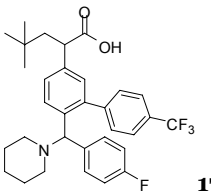
15

Compound **15**. 1H NMR (300MHz ,DMSO-d6) d = 12.32 (br. s., 1 H), 7.83 (d, J = 8.3 Hz, 2 H), 7.75 (dd, J = 2.3, 8.3 Hz, 1 H), 7.45 - 7.32 (m, 3 H), 7.05 - 6.96 (m, 5 H), 4..28, 4.28 (s, s, 1 H), 3.58 (t, J = 7.2 Hz, 1 H), 2.32 - 2.05 (m, 4 H), 1.96 - 1.76 (m, 1 H), 1.57 - 1.28 (m, 8 H), 0.86 (d, J = 6.0 Hz, 6 H); LCMS m/z 528.4 $[M+1]^+$.



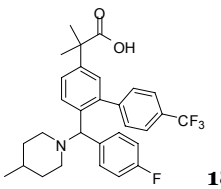
16

Compound **16**. 1H-NMR (400MHz, DMSO-d6) δ: 12.41 (bs, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.75-7.73 (m, 1H), 7.38-7.35 (m, 3H), 7.05-6.97 (m, 5H), 4.28-4.27 (m, 1H), 3.60-3.56 (m, 1H), 2.89-2.87 (m, 1H), 2.43 (bs, 1H), 2.00-1.42 (m, 7H), 1.10-1.04 (m, 2H), 0.86-0.85 (m, 3H), 0.60-0.57 (m, 1H), 0.35-0.27 (m, 2H), 0.08--0.01 (m, 2H); LCMS m/z 540.0 $[M+H]^+$.



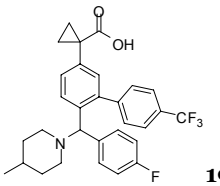
17

Compound **17**. 1H NMR (400 MHz, DMSO-d6) δ: 7.83 (d, J = 8.4 Hz, 2H), 7.73 (dd, J = 8.4, 4.0 Hz, 1H), 7.40-7.35 (m, 3H), 7.03-7.00 (m, 5H), 4.27 (s, 1H), 3.58-3.55 (m, 1H), 2.28-2.08 (m, 5H), 1.50-1.30 (m, 7H), 0.85 (bs, 9H); LCMS m/z 542.0 $[M+H]^+$.



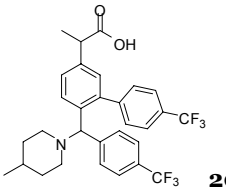
18

Compound **18**. 1H NMR (400 MHz, DMSO-d6) δ 12.34 (br. s., 1H), 7.74 - 7.86 (m, 3H), 7.34 - 7.47 (m, 3H), 6.97 - 7.05 (m, 5H), 4.28 (s, 1H), 2.89 (d, J = 10.04 Hz, 1H), 1.78 - 1.87 (m, 1H), 1.63 (br. s., 2H), 1.45 (s, 7H), 1.23 - 1.37 (m, 2H), 1.04 - 1.20 (m, 2H), 0.86 (d, J = 6.53 Hz, 3H); LCMS m/z 514.3 $[M+1]^+$.



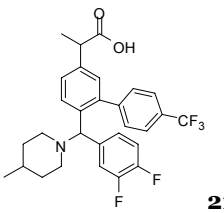
19

Compound **19**. 1H NMR (400 MHz, DMSO-d6) δ 12.23 (br. s., 1H), 7.76 (d, J = 8.28 Hz, 2H), 7.67 (d, J = 8.28 Hz, 1H), 7.30 - 7.35 (m, 3H), 6.91 - 6.97 (m, 5H), 4.22 (s, 1H), 2.84 (br. s., 1H), 1.73 - 1.81 (m, 1H), 1.59 (br. s., 1H), 1.49 (d, J = 11.55 Hz, 2H), 1.41 (d, J = 12.05 Hz, 1H), 1.32 - 1.36 (m, 2H), 0.96 - 1.13 (m, 5H), 0.79 (d, J = 6.27 Hz, 3H); LCMS m/z 512.2 $[M+H]^+$.



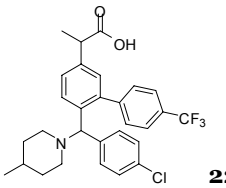
20

Compound **20**. 1H NMR (400 MHz, DMSO-d6) d 12.34 (br. s., 1H), 7.84 (d, J = 8.03 Hz, 2H), 7.71 - 7.78 (m, 1H), 7.57 (d, J = 7.78 Hz, 2H), 7.34 - 7.43 (m, 3H), 7.22 (dd, J = 3.76, 7.78 Hz, 2H), 7.03 (s, 1H), 4.41 (s, 1H), 3.67 (q, J = 6.94 Hz, 1H), 2.88 (br. s., 1H), 1.86 (br. s., 1H), 1.67 (br. s., 1H), 1.56 (br. s., 1H), 1.45 (br. s., 1H), 1.34 (dd, J = 1.88, 7.15 Hz, 4H), 1.07 - 1.20 (m, 3H), 0.87 (d, J = 6.27 Hz, 3H); LCMS m/z 550.3 $[M+1]^+$.



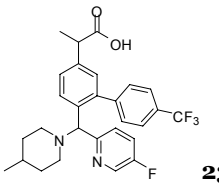
21

Compound **21**. 1H NMR (400 MHz, DMSO-d6) δ: 7.78 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.0 Hz, 1H), 7.34-7.31 (m, 3H), 7.23-7.16 (m, 1H), 6.97-6.90 (m, 2H), 6.68 (bs, 1H), 4.25 (s, 1H), 3.58-3.52 (m, 1H), 2.87 (bs, 1H), 2.40 (bs, 1H), 1.81-1.75 (m, 1H), 1.65-1.59 (m, 1H), 1.52-1.42 (m, 2H), 1.27-1.25 (m, 4H), 1.10-1.05 (m, 2H), 0.81 (d, J = 6.0 Hz, 3H); LC-MS m/z 518.0 $[M+H]^+$.



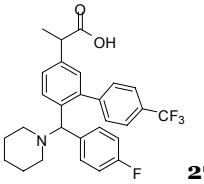
22

Compound **22**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68 - 7.72 (m, 3H), 7.22 - 7.27 (m, 4H), 7.12 (dd, *J* = 1.51, 8.53 Hz, 2H), 6.86 - 6.89 (m, 2H), 4.15 (s, 1H), 3.54 (q, *J* = 6.86 Hz, 1H), 2.75 (d, *J* = 8.78 Hz, 1H), 1.70 (t, *J* = 11.55 Hz, 1H), 1.40 - 1.55 (m, 2H), 1.28 - 1.38 (m, 2H), 1.19 - 1.24 (m, 2H), 1.08 - 1.18 (m, 2H), 0.93 - 1.06 (m, 2H), 0.70 - 0.77 (m, 3H)
LCMS m/z 516.2$[M+1]^+$.



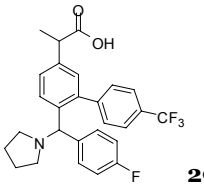
23

Compound **23**. 1H NMR (400MHz ,DMSO-d6) δ = 12.33 (br. s., 1 H), 8.39 (d, J = 2.3 Hz, 1 H), 7.81 (d, J = 8.0 Hz, 2 H), 7.72 - 7.59 (m, 2 H), 7.59 - 7.44 (m, 3 H), 7.33 (dd, J = 1.8, 8.3 Hz, 1 H), 7.07 - 7.02 (m, 1 H), 4.55 (s, 1 H), 3.68 (q, J = 7.2 Hz, 1 H), 2.75 - 2.62 (m, 1 H), 2.50 - 2.41 (m, 1 H), 1.81 - 1.61 (m, 2 H), 1.57 - 1.40 (m, 2 H), 1.35 (dd, J = 1.5, 7.0 Hz, 3 H), 1.30 - 1.17 (m, 1 H), 1.16 - 1.00 (m, 2 H), 0.83 (d, J = 6.3 Hz, 3 H); LCMS m/z 501.2 $[M+1]^+$.



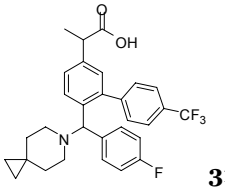
27

Compound **27**. 1H NMR (400 MHz, DMSO-d6) δ 12.49 (bs, 1H), 9.78 (bs, 1H), 8.20 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 8.0 Hz, 1H), 7.03-7.30 (m, 7H), 5.16 (d, J = 9.2 Hz, 1H), 3.72-3.78 (m, 1H), 3.37 (d, J = 7.2 Hz, 1H), 3.05 (d, J = 9.6 Hz, 1H), 2.79-2.81 (m, 2H), 1.69-1.79 (m, 5H), 1.27-1.39 (m, 4H); LCMS m/z 486.0 $[M+1]^+$.



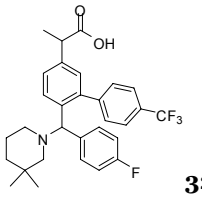
29

Compound **29**. 1H NMR (400 MHz, DMSO-d6) δ: 7.88-7.83 (m, 3H), 7.40-7.38 (m, 3H), 7.03-7.01 (m, 5H), 4.27-4.26 (m, 1H), 3.67 (q, J = 7.2 Hz, 1H), 2.16-2.21 (m, 4H), 1.66 (bs, 4H), 1.35-1.34 (m, 3H); LCMS m/z 472.0 $[M+1]^+$.



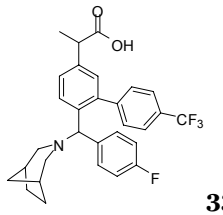
31

Compound **31**. 1H NMR (400 MHz, DMSO-d6) δ 12.32 (br. s., 1H), 7.75 - 7.91 (m, 3H), 7.22 - 7.50 (m, 3H), 6.88 - 7.16 (m, 5H), 4.35 (s, 1H), 3.67 (q, J = 7.03 Hz, 1H), 2.31 (br. s., 2H), 2.13 - 2.26 (m, 2H), 1.27 - 1.39 (m, 6H), 1.23 (s, 1H), 0.15 - 0.24 (m, 4H); LCMS m/z 512.3 $[M+H]^+$.



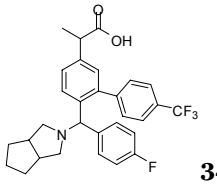
32

Compound **32**. 1H NMR (400MHz ,DMSO-d6) δ = 12.31 (br. s., 1 H), 7.83 (d, J = 8.3 Hz, 2 H), 7.77 (d, J = 8.0 Hz, 1 H), 7.47 - 7.27 (m, 3 H), 7.05 - 6.87 (m, 5 H), 4.25 (s, 1 H), 3.67 (q, J = 6.9 Hz, 1 H), 2.30 - 2.13 (m, 1 H), 2.12 - 1.99 (m, 1 H), 1.99 - 1.78 (m, 2 H), 1.60 - 1.42 (m, 2 H), 1.38 - 1.32 (d, 3 H), 1.26 - 1.11 (m, 2 H), 0.91 (s, 3 H) 0.86 (s, 3 H); LCMS m/z 514.3 $[M+1]^+$.



33

Compound **33.** 1H NMR (400 MHz, DMSO-d6) δ 12.31 (br. s., 1H), 7.75 - 7.94 (m, 3H), 7.28 - 7.45 (m, 3H), 6.92 - 7.06 (m, 5H), 4.20 - 4.35 (m, 1H), 3.66 (q, J = 7.19 Hz, 1H), 2.75 (d, J = 5.52 Hz, 1H), 2.25 - 2.32 (m, 1H), 1.98 (br. s., 1H), 1.90 (dd, J = 3.01, 10.29 Hz, 1H), 1.66 (d, J = 10.29 Hz, 3H), 1.52 (d, J = 5.52 Hz, 2H), 1.34 (dd, J = 1.38, 7.15 Hz, 4H), 1.21 - 1.30 (m, 2H); LCMS m/z 512.2 $[M+H]^+$.

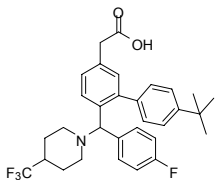


34

Compound **34**. 1H NMR (300 MHz, DMSO-d6) ppm 12.31 (s, 1 H) 7.70 - 8.00 (m, 3 H) 7.24 - 7.50 (m, 3 H) 6.87 - 7.13 (m, 5 H) 4.18 (d, J=1.51 Hz, 1 H) 3.67 (q, J=7.05 Hz, 1 H) 2.44 (br. s., 2 H) 2.25 - 2.39 (m, 2 H) 2.15 (d, J=8.31 Hz, 1 H) 1.98 (d, J=8.69 Hz, 1 H) 1.64 (br. s., 3 H) 1.19 - 1.49 (m, 6 H); LCMS m/z 512.2 $[M+H]^+$.

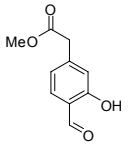
General procedure for Patesis route is illustrated by the preparation of compound 8

Synthesis of 2-(4'-tert-butyl-6-((4-fluorophenyl)(4-(trifluoromethyl)piperidin-1-yl)methyl)biphenyl-3-yl)acetic acid



Step 1

Methyl 2-(4-formyl-3-hydroxyphenyl)acetate

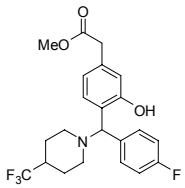


Triethylamine (757 mL, 5.43 mol) was added to a solution of methyl 2-(3-hydroxyphenyl) acetate in acetonitrile (10L) over 10 minutes. Magnesium chloride (516 g, 5.43 mol) was added over 15 minutes. The temperature of the reaction increased to ~40 ^{0}C during this addition. The reaction mixture was stirred for 1.5 h, during which time it went to a nearly homogeneous brown solution. The reaction was heated to reflux and paraformaldehyde (326g, 10.9 mol) was added quickly. The reaction was heated at reflux for an additional 4h, and was allowed to cool to room temperature and stir overnight. After cooling in an ice-salt bath, a 1.2N solution of HCl (8L) was added and the mixture stirred until all the solids dissolved. The reaction was poured into a 50 L separatory funnel and diluted with a 60% ethyl acetate/heptane solution (20L). The organic layer was washed with water (5L) and saturated brine (5L), dried over sodium sulfate and concentrated under reduced pressure. It was purified by

flash chromatography on silica gel (5-20% EtOAc in heptane). The fractions were collected and concentrated. The material was allowed to solidify overnight in a freezer and the resulting solid was triturated at -30 °C with a 1:1 hexane:MTBE mixture to give the desired product with a purity >95% (82.9g, 9%). ^{1}H NMR (300MHz ,$CDCl_3$) δ = 11.04 (s, 1 H), 9.87 (s, 1 H), 7.52 (d, *J* = 7.9 Hz, 1 H), 6.95 (d, *J* = 7.9 Hz, 1 H), 6.91 (s, 1 H), 3.71 (s, 3 H), 3.65 (s, 2 H); LCMS m/z 195.1 $[M+1]^+$.

Step 2

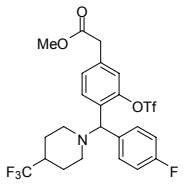
Methyl 2-(4-((4-fluorophenyl)(4-(trifluoromethyl) piperidin-1-yl)methyl)-3-hydroxyphenyl)acetate



The mixture methyl 2-(4-formyl-3-hydroxyphenyl)acetate (930 mg, 4.79 mmol), 4-fluorophenylboronic acid (737 mg, 5.26 mmol), 4-trifluoromethyl-piperidine (115 mg, 7.18 mmol) in 5 mL of trifluoro-toluene was heated using microwave irradiation at 120°C for 10 minutes. The organic solvent was then removed to give a crude product, which was purified by flash chromatography on silica (15-25% EtOAc in hexane) to give the desired methyl 2-(4-((4-fluorophenyl)(4-(trifluoromethyl)piperidin-1-yl)methyl)-3-hydroxyphenyl)acetate as a colorless oil (1.67 g, 82%). ^{1}H NMR (400MHz ,DMSO-d_6) δ = 10.36 (s, 1 H), 7.42 (dd, *J* = 5.6, 8.4 Hz, 2 H), 7.22 - 7.05 (m, 3 H), 6.72 - 6.59 (m, 2 H), 4.69 (s, 1 H), 3.58 (s, 3 H), 3.51 (s, 2 H), 3.05 - 2.94 (m, 1 H), 2.81 - 2.71 (m, 1 H), 2.40 - 2.31 (m, 1 H), 2.02 - 1.86 (m, 2 H), 1.85 - 1.72 (m, 2 H), 1.59 - 1.39 (m, 2 H); LCMS m/z 426.2 $[M+1]^+$.

Step 3

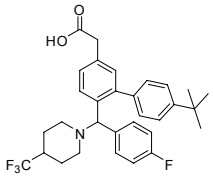
Methyl 2-(4-((4-fluorophenyl)(4-(trifluoromethyl)piperidin-1-yl)methyl)-3-(trifluoromethylsulfonyloxy)phenyl)acetate



To a solution of methyl 2-(4-((4-fluorophenyl)(4-(trifluoromethyl)piperidin-1-yl)methyl)-3-hydroxyphenyl)acetate (1.61 g, 3.78 mmol) and Tf_2O (1.28 g, 4.53 mmol) in 20 mL methylene chloride was slowly added Et_3N (763 mg, 7.56 mmol). The mixture was stirred at room temperature for 2 hours. The organic solvent was removed and the residue was purified by flash chromatography on silica (10-20% EtOAc in hexane) to give methyl 2-(4-((4-fluorophenyl)(4-(trifluoromethyl)piperidin-1-yl)methyl)-3-(trifluoromethylsulfonyloxy)phenyl)acetate as a colorless oil (1.75 g, 83%). ^{1}H NMR (400MHz ,DMSO-d_6) δ = 7.83 (d, *J* = 8.0 Hz, 1 H), 7.43 (d, *J* = 8.0 Hz, 1 H), 7.35 (dd, *J* = 5.5, 8.5 Hz, 2 H), 7.28 (s, 1 H), 7.17 (t, *J* = 8.8 Hz, 2 H), 4.58 (s, 1 H), 3.78 (s, 2 H), 3.61 (s, 3 H), 3.30 (d, *J* = 9.5 Hz, 3 H), 2.92 - 2.82 (m, 1 H), 2.77 - 2.68 (m, 1 H), 1.91 (q, *J* = 9.8 Hz, 2 H), 1.77 (d, *J* = 12.0 Hz, 2 H), 1.62 - 1.41 (m, 2 H); LCMS m/z 558.2 $[M+1]^+$.

Step 4

2-(4'-tert-butyl-6-((4-fluorophenyl)(4-(trifluoromethyl)piperidin-1-yl)methyl)biphenyl-3-yl)acetic acid

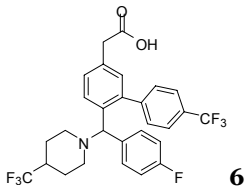


To a mixture of methyl 2-(4-((4-fluorophenyl)(4-(trifluoromethyl)piperidin-1-yl)methyl)-3-(trifluoromethylsulfonyloxy)phenyl)acetate (35 mg, 0.063 mmol), 4-tert-butylphenylboronic acid (17 mg, 0.094 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (3.1 mg, 0.0038 mmol) in 1,2-dimethoxyethane (0.6 mL) was added saturated aqueous sodium bicarbonate (80 µL, 2 mmol). The reaction mixture was heated using microwave irradiation at 110°C for 15 minutes. It was diluted with water, extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica (5-10% EtOAc in hexane) to get the ester as a colorless oil (23 mg).

The above ester in THF (0.5 mL)/MeOH (0.5 mL) was treated with 3M NaOH in water (70 µL) using microwave irradiation at 110°C for 15 minutes. Added 1M HCl (210 µL) and diluted with water, extracted with EtOAc. The organic phase was washed with water, dried over $MgSO_4$, filtered and concentrated to get 2-(4'-tert-butyl-6-((4-fluorophenyl)(4-(trifluoromethyl)piperidin-1-yl)methyl)biphenyl-3-yl)acetic acid as a white powder (17 mg, 51% for two steps). ^{1}H NMR (400MHz ,DMSO-d_6) δ = 12.29 (br. s., 1 H), 7.68 (d, *J* = 8.3 Hz, 1 H), 7.48 (d, *J* = 8.3 Hz, 2 H), 7.27 (dd, *J* = 1.5, 8.0 Hz, 1 H),

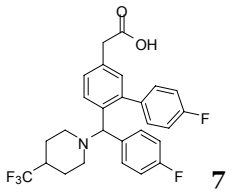
7.08 (d, *J* = 8.0 Hz, 2 H), 7.03 (d, *J* = 7.3 Hz, 4 H), 6.98 (d, *J* = 1.5 Hz, 1 H), 4.44 (s, 1 H), 3.54 (s, 2 H), 3.11 - 2.90 (m, 1 H), 2.63 - 2.57 (m, 1 H), 2.31 - 2.15 (m, 1 H), 2.01 - 1.81 (m, 1 H), 1.82 - 1.57 (m, 3 H), 1.56 - 1.39 (m, 2 H), 1.36 (s, 9 H); LCMS m/z 528.4 $[M+1]^+$.

The following compounds were synthesized following the same synthetic procedures and similar condition as compound **8**:



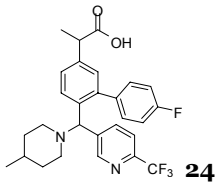
6

Compound **6**. 1H NMR (400MHz ,DMSO-d6) d = 12.34 (br. s., 1 H), 7.83 (d, J = 8.0 Hz, 2 H), 7.75 (d, J = 8.3 Hz, 1 H), 7.44 - 7.30 (m, 3 H), 7.08 - 6.96 (m, 5 H), 4.33 (s, 1 H), 3.57 (s, 2 H), 3.06 – 2.96 (m, 1 H), 2.62 - 2.55 (m, 1 H), 2.28 – 2.20 (m, 1 H), 1.92-1.88 (m, 1 H), 1.83 - 1.58 (m, 3 H), 1.55 - 1.35 (m, 2 H); LCMS m/z 540.3 $[M+1]^+$.



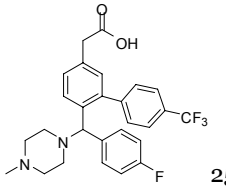
7

Compound **7**. 1H NMR (400MHz ,DMSO-d6) d = 7.72 (d, J = 8.0 Hz, 1 H), 7.34 - 7.24 (m, 3 H), 7.21 - 7.11 (m, 2 H), 7.03 (d, J = 7.3 Hz, 4 H), 6.99 (d, J = 1.5 Hz, 1 H), 4.35 (s, 1 H), 3.55 (s, 2 H), 3.06 - 2.96 (m, 1 H), 2.62 - 2.54 (m, 1 H), 2.23 (t, J = 7.4 Hz, 1 H), 1.91 - 1.85 (m, 1 H), 1.80 - 1.59 (m, 3 H), 1.53 - 1.36 (m, 2 H); LCMS m/z 490.3 $[M+1]^+$.



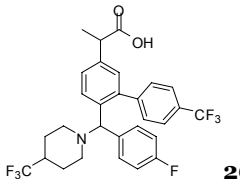
24

Compound **24**. 1H NMR (400 MHz, DMSO-d6) δ 12.34 (br. s., 1H), 8.26 (br. s., 1H), 7.84 (d, J = 8.03 Hz, 2H), 7.71 - 7.79 (m, 3H), 7.41 (d, J = 6.78 Hz, 3H), 7.06 (s, 1H), 4.53 (s, 1H), 3.69 (d, J = 7.03 Hz, 1H), 2.90 (br. s., 1H), 2.42 (d, J = 8.78 Hz, 1H), 1.82 - 1.95 (m, 1H), 1.68 - 1.78 (m, 1H), 1.55 - 1.62 (m, 1H), 1.44 - 1.53 (m, 1H), 1.35 (d, J = 6.78 Hz, 4H), 1.09 - 1.25 (m, 2H), 0.81 - 0.91 (m, 3H); LCMS m/z 551.2 $[M+1]^+$.



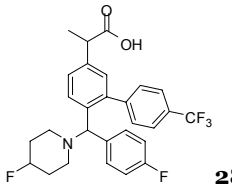
25

Compound **25**. 1H NMR (300MHz ,DMSO-d6) d = 7.84 (d, J = 7.9 Hz, 2 H), 7.74 (d, J = 8.3 Hz, 1 H), 7.45 - 7.33 (m, 3 H), 7.12 - 7.03 (m, 5 H), 4.40 (s, 1 H), 3.59 (s, 2 H), 3.41 - 3.24 (m, 2 H), 3.15 - 2.91 (m, 3 H), 2.78 (s, 3 H), 2.62 - 2.56 (m, 1 H), 2.24 - 2.11 (m, 1 H), 2.07 - 1.98 (m, 1 H); LCMS m/z 487.3 $[M+1]^+$.



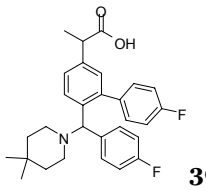
26

Compound **26**. 1H NMR (400 MHz, DMSO-d6) δ 12.33 (br. s., 1H), 7.83 (d, J = 8.03 Hz, 2H), 7.78 (d, J = 8.28 Hz, 1H), 7.39 (d, J = 8.03 Hz, 3H), 6.99 - 7.06 (m, 5H), 4.33 (s, 1H), 3.65 - 3.72 (m, 1H), 3.00 (br. s., 1H), 2.56 (d, J = 10.79 Hz, 1H), 2.19 - 2.30 (m, 1H), 1.90 (t, J = 11.80 Hz, 1H), 1.72 - 1.81 (m, 1H), 1.69 (d, J = 11.55 Hz, 2H), 1.39 - 1.52 (m, 2H), 1.35 (d, J = 7.03 Hz, 3H); LCMS m/z 554.3 $[M+1]^+$.



28

Compound **28**. 1H NMR (400 MHz, CDCl3) δ 7.82 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 1H), 7.23 (bs, 2H), 6.94-7.00 (m, 3H), 6.82-6.85 (m, 2H), 4.63 (bs, 1H), 4.28 (s, 1H), 3.62-3.66 (m, 1H),2.45-2.48 (m, 1H), 2.35-2.36 (m, 2H), 2.13-2.16 (m, 1H), 2.00 (d, J = 6.0 Hz, 1H), 1.79-1.86 (m, 3H), 1.44 (d, J = 6.8 Hz, 3H); LCMS m/z 503.9 $[M+1]^+$.

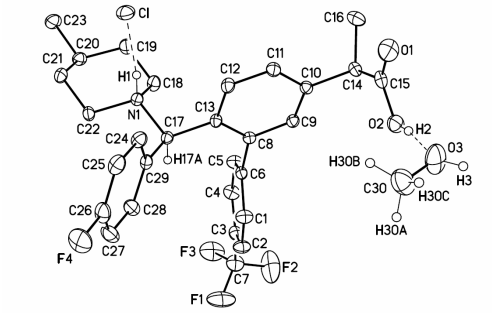


30

Compound **30**. 1H NMR (400MHz ,DMSO-d6) = 12.32 (br. s., 1 H), 7.83 (d, J = 8.3 Hz, 2 H), 7.79 (d, J = 8.0 Hz, 1 H), 7.45 - 7.29 (m, 3 H), 7.06 - 6.93 (m, 5 H), 4.32 (s, 1 H), 3.66 (q, J = 7.0 Hz, 1 H), 2.31 - 2.17 (m, 2 H), 2.17 - 2.06 (m, 2 H), 1.34 (d, J = 8.0 Hz, 3 H), 1.39 - 1.24 (m, 4 H), 0.85 (s, 6 H); LCMS m/z 514.3 $[M+1]^+$.

Crystal data for Compound 10[a]

Single crystal X-ray structure of BIIB042 (**10a**) HCl salt MeOH mono-solvate



A colorless block crystal with dimensions 0.37 x 0.22 x 0.12 mm was mounted on a MiTeGen MicroMesh mount using very small amount of Paratone oil.

Data were collected using a SMART APEX Bruker-AXS CCD (charge coupled device) based diffractometer equipped with an Kryoflex low-temperature apparatus operating at 200 K. Data were measured using omega and phi scans of 0.3° omega per frame for 30 s. Images were collected based on two overlapping Ewald spheres with completeness to 100% out to 0.75 Å. Cell parameters were retrieved using SMART software[1] and refined using SAINT on all observed reflections. Data reduction was performed using the SAINT software[2] which corrects for Lp. Scaling and absorption corrections were applied using SADABS[3] multi-scan technique, supplied by George Sheldrick. The structures are solved by the direct method using the SHELXS-97 program and refined by least squares method on F^2, SHELXL- 97, which are incorporated in SHELXTL-Linux V 6.10.[4]

The structure was solved in the space group $P2_1$(# 4). The Flack[5] parameter is used to determine chirality of the crystal studied, the value should be near zero, a value of one is the other enantiomer and a value of 0.5 is racemic. The Flack parameter refined to nil within experimental error indicating the correct enantiomer has been determined. The crystal used for the diffraction study showed no decomposition during data collection. A methanol molecule of solvation, H-bonded to the chloride ion and the acid moiety, was located in the asymmetric unit in addition to the ion pair. The chloride ion is H-bonded to the ammonium moiety. Hydrogen atoms involved in H-bonding interactions were located from the difference map and positionally refined with 1.2 Ueq of the attached nonhydrogen atom (N or C). All other hydrogen atoms were calculated by geo-

metrical methods and refined using a riding model. All non-hydrogen atoms are refined anisotropically. All drawings are done at 30% ellipsoids.

References

1. APEX2 V 1.2-0 Software *for the CCD Detector System*; Bruker Analytical X-ray Systems, Madison, WI (2006).
2. SAINT V 7.34 Software *for the Integration of CCD Detector System* Bruker Analytical X-ray Systems, Madison, WI (2001).
3. SADABS V2.10 Program *for absorption corrections using Bruker-AXS CCD based on the method of Robert Blessing*; Blessing, R.H.*Acta Cryst. A51,* 1995, 33-38.
4. Sheldrick, G.M. "A short history of SHELX". *Acta Cryst.* **A64**, 2008, 112-122.
5. Flack, H. D. *Acta Cryst.* **A39**, 1983, 876-881.

Table 1. Crystal data and structure refinement for compound 10a.

Identification code	harl002
Empirical formula	C30 H34 Cl F4 N O3
Formula weight	568.03
Temperature	200(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)
Unit cell dimensions	a = 8.984(2) A alpha = 90 deg. b = 16.115(4) A beta = 107.368(3) deg. c = 10.204(2) A gamma = 90 deg.
Volume	1409.8(6) A^3
Z, Calculated density	2, 1.338 Mg/m^3
Absorption coefficient	0.194 mm^-1
F(000)	596
Crystal size	0.37 x 0.22 x 0.12 mm
Theta range for data collection	2.09 to 28.28 deg.
Limiting indices	-11<=h<=11, -21<=k<=21, -13<=l<=13
Reflections collected / unique	17983 / 6981 [R(int) = 0.0203]
Completeness to theta = 25.00	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9775 and 0.9310
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6981 / 1 / 364
Goodness-of-fit on F^2	1.034
Final R indices [I>2sigma(I)]	R1 = 0.0402, wR2 = 0.1099
R indices (all data)	R1 = 0.0415, wR2 = 0.1119
Absolute structure parameter	-0.03(5)
Largest diff. peak and hole	0.299 and -0.251 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound 10a.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Cl	-3113(1)	891(1)	-1824(1)	41(1)
O(1)	1793(2)	2515(1)	-6014(2)	57(1)
O(2)	3450(2)	3362(1)	-4554(2)	43(1)
F(1)	6703(3)	4161(1)	5289(2)	86(1)
F(2)	8407(2)	3510(3)	4581(2)	134(1)
F(3)	7210(2)	2909(1)	5786(2)	78(1)
F(4)	-4192(2)	5025(1)	-304(2)	67(1)
N(1)	-528(2)	1600(1)	676(1)	24(1)
C(1)	3857(2)	3538(1)	1383(2)	35(1)
C(2)	4941(2)	3785(1)	2603(2)	37(1)
C(3)	5801(2)	3194(1)	3488(2)	33(1)
C(4)	5586(2)	2360(1)	3178(2)	37(1)
C(5)	4525(2)	2112(1)	1944(2)	34(1)
C(6)	3659(2)	2701(1)	1034(2)	24(1)
C(7)	7025(3)	3458(2)	4769(2)	49(1)
C(8)	2624(2)	2440(1)	-350(1)	23(1)
C(9)	3353(2)	2318(1)	-1375(2)	25(1)
C(10)	2511(2)	2109(1)	-2710(2)	25(1)
C(11)	903(2)	2007(1)	-3012(2)	29(1)
C(12)	171(2)	2099(1)	-2002(2)	29(1)
C(13)	1008(2)	2327(1)	-661(2)	24(1)
C(14)	3328(2)	1981(1)	-3810(2)	29(1)
C(15)	2756(2)	2637(1)	-4920(2)	32(1)
C(16)	3058(3)	1107(1)	-4417(2)	44(1)
C(17)	188(2)	2431(1)	447(2)	24(1)
C(18)	731(2)	952(1)	1142(2)	33(1)
C(19)	45(2)	116(1)	1341(2)	37(1)
C(20)	-870(2)	165(1)	2375(2)	32(1)
C(21)	-2102(2)	842(1)	1927(2)	33(1)
C(22)	-1413(2)	1676(1)	1717(2)	30(1)
C(23)	-1607(3)	-673(1)	2518(2)	44(1)
C(24)	-2347(2)	3138(1)	-931(2)	33(1)
C(25)	-3435(2)	3780(1)	-1107(2)	40(1)
C(26)	-3158(2)	4389(1)	-132(2)	44(1)
C(27)	-1872(3)	4392(1)	1009(2)	47(1)
C(28)	-792(2)	3751(1)	1171(2)	37(1)
C(29)	-1014(2)	3122(1)	201(2)	27(1)
O(3)	2339(3)	4658(1)	-6179(3)	80(1)
C(30)	1185(5)	5105(2)	-5909(3)	75(1)

Table 3. Bond lengths [A] and angles [deg] for compound 10a**.**

O(1)-C(15)	1.206(2)
O(2)-C(15)	1.324(2)
F(1)-C(7)	1.320(3)
F(2)-C(7)	1.314(3)
F(3)-C(7)	1.335(3)
F(4)-C(26)	1.359(2)
N(1)-C(18)	1.508(2)
N(1)-C(22)	1.510(2)
N(1)-C(17)	1.533(2)
C(1)-C(2)	1.391(2)
C(1)-C(6)	1.392(2)
C(2)-C(3)	1.380(3)
C(3)-C(4)	1.380(3)
C(3)-C(7)	1.498(2)
C(4)-C(5)	1.392(2)
C(5)-C(6)	1.391(2)
C(6)-C(8)	1.501(2)
C(8)-C(13)	1.403(2)
C(8)-C(9)	1.404(2)
C(9)-C(10)	1.388(2)
C(10)-C(11)	1.394(2)
C(10)-C(14)	1.527(2)
C(11)-C(12)	1.386(2)
C(12)-C(13)	1.399(2)
C(13)-C(17)	1.533(2)
C(14)-C(15)	1.523(2)
C(14)-C(16)	1.528(3)
C(17)-C(29)	1.518(2)
C(18)-C(19)	1.520(2)
C(19)-C(20)	1.520(2)
C(20)-C(21)	1.525(3)
C(20)-C(23)	1.529(2)
C(21)-C(22)	1.521(2)
C(24)-C(29)	1.395(2)
C(24)-C(25)	1.397(3)
C(25)-C(26)	1.367(3)
C(26)-C(27)	1.374(3)
C(27)-C(28)	1.392(3)
C(28)-C(29)	1.390(2)
O(3)-C(30)	1.357(4)
C(18)-N(1)-C(22)	109.72(12)
C(18)-N(1)-C(17)	110.08(12)
C(22)-N(1)-C(17)	111.61(12)
C(2)-C(1)-C(6)	120.56(16)
C(3)-C(2)-C(1)	119.55(17)
C(4)-C(3)-C(2)	120.67(16)
C(4)-C(3)-C(7)	119.49(18)
C(2)-C(3)-C(7)	119.79(18)
C(3)-C(4)-C(5)	119.84(17)
C(6)-C(5)-C(4)	120.23(16)
C(5)-C(6)-C(1)	119.11(14)
C(5)-C(6)-C(8)	120.22(14)
C(1)-C(6)-C(8)	120.50(14)
F(2)-C(7)-F(1)	109.5(3)
F(2)-C(7)-F(3)	104.7(2)
F(1)-C(7)-F(3)	104.34(19)

F(2)-C(7)-C(3)	111.74(18)
F(1)-C(7)-C(3)	113.75(19)
F(3)-C(7)-C(3)	112.3(2)
C(13)-C(8)-C(9)	119.65(13)
C(13)-C(8)-C(6)	123.91(13)
C(9)-C(8)-C(6)	116.43(13)
C(10)-C(9)-C(8)	121.76(13)
C(9)-C(10)-C(11)	118.10(13)
C(9)-C(10)-C(14)	120.87(14)
C(11)-C(10)-C(14)	121.02(13)
C(12)-C(11)-C(10)	120.89(14)
C(11)-C(12)-C(13)	121.31(14)
C(12)-C(13)-C(8)	118.24(13)
C(12)-C(13)-C(17)	120.94(13)
C(8)-C(13)-C(17)	120.81(13)
C(15)-C(14)-C(10)	108.86(13)
C(15)-C(14)-C(16)	111.10(15)
C(10)-C(14)-C(16)	111.75(14)
O(1)-C(15)-O(2)	123.44(19)
O(1)-C(15)-C(14)	124.44(19)
O(2)-C(15)-C(14)	112.12(15)
C(29)-C(17)-C(13)	115.66(12)
C(29)-C(17)-N(1)	110.86(11)
C(13)-C(17)-N(1)	109.41(12)
N(1)-C(18)-C(19)	111.06(13)
C(18)-C(19)-C(20)	111.86(15)
C(19)-C(20)-C(21)	108.84(14)
C(19)-C(20)-C(23)	111.10(15)
C(21)-C(20)-C(23)	111.38(16)
C(22)-C(21)-C(20)	112.69(14)
N(1)-C(22)-C(21)	110.40(13)
C(29)-C(24)-C(25)	121.05(18)
C(26)-C(25)-C(24)	118.01(19)
F(4)-C(26)-C(25)	118.6(2)
F(4)-C(26)-C(27)	118.4(2)
C(25)-C(26)-C(27)	122.93(18)
C(26)-C(27)-C(28)	118.55(19)
C(29)-C(28)-C(27)	120.68(19)
C(28)-C(29)-C(24)	118.77(16)
C(28)-C(29)-C(17)	118.28(15)
C(24)-C(29)-C(17)	122.92(15)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for compound 10a.

The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
Cl	37(1)	40(1)	41(1)	-9(1)	4(1)	-7(1)
O(1)	53(1)	76(1)	32(1)	11(1)	-1(1)	-5(1)
O(2)	58(1)	37(1)	38(1)	5(1)	19(1)	4(1)
F(1)	114(1)	61(1)	50(1)	-17(1)	-25(1)	-6(1)
F(2)	44(1)	288(4)	62(1)	-37(2)	3(1)	-55(2)
F(3)	98(1)	80(1)	32(1)	4(1)	-19(1)	6(1)
F(4)	59(1)	52(1)	93(1)	7(1)	29(1)	29(1)
N(1)	24(1)	24(1)	26(1)	2(1)	9(1)	0(1)
C(1)	38(1)	31(1)	28(1)	1(1)	-1(1)	1(1)
C(2)	43(1)	33(1)	30(1)	-4(1)	0(1)	-3(1)
C(3)	29(1)	45(1)	23(1)	-3(1)	5(1)	-1(1)
C(4)	37(1)	40(1)	29(1)	2(1)	0(1)	7(1)
C(5)	36(1)	31(1)	30(1)	0(1)	2(1)	3(1)
C(6)	21(1)	31(1)	21(1)	-2(1)	6(1)	-1(1)
C(7)	44(1)	63(1)	30(1)	-5(1)	-4(1)	-5(1)
C(8)	22(1)	23(1)	22(1)	1(1)	4(1)	1(1)
C(9)	21(1)	29(1)	26(1)	-1(1)	6(1)	-1(1)
C(10)	27(1)	26(1)	23(1)	1(1)	8(1)	0(1)
C(11)	27(1)	36(1)	23(1)	-2(1)	5(1)	-3(1)
C(12)	21(1)	40(1)	26(1)	0(1)	5(1)	-4(1)
C(13)	23(1)	28(1)	22(1)	2(1)	7(1)	-1(1)
C(14)	28(1)	34(1)	25(1)	-2(1)	10(1)	2(1)
C(15)	31(1)	43(1)	27(1)	2(1)	15(1)	5(1)
C(16)	50(1)	41(1)	42(1)	-13(1)	14(1)	3(1)
C(17)	24(1)	26(1)	22(1)	1(1)	7(1)	-2(1)
C(18)	30(1)	30(1)	42(1)	7(1)	15(1)	6(1)
C(19)	43(1)	27(1)	45(1)	5(1)	21(1)	5(1)
C(20)	40(1)	27(1)	30(1)	2(1)	11(1)	-4(1)
C(21)	35(1)	32(1)	37(1)	3(1)	17(1)	-4(1)
C(22)	34(1)	29(1)	34(1)	1(1)	20(1)	1(1)
C(23)	62(1)	30(1)	44(1)	2(1)	22(1)	-10(1)
C(24)	29(1)	30(1)	39(1)	3(1)	9(1)	0(1)
C(25)	28(1)	38(1)	54(1)	11(1)	11(1)	4(1)
C(26)	38(1)	40(1)	60(1)	11(1)	26(1)	12(1)
C(27)	60(1)	39(1)	48(1)	-6(1)	26(1)	10(1)
C(28)	43(1)	37(1)	34(1)	-2(1)	15(1)	3(1)
C(29)	26(1)	27(1)	30(1)	4(1)	13(1)	1(1)
O(3)	101(2)	65(1)	93(2)	41(1)	56(1)	29(1)
C(30)	98(2)	71(2)	61(2)	8(1)	32(2)	14(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for compound 10a

	x	y	z	U(eq)
H(2)	3080(30)	3721(19)	-5130(30)	52
H(1)	-1230(30)	1406(14)	-110(20)	29
H(1A)	3245	3943	783	41
H(2A)	5090	4358	2825	45
H(4A)	6162	1957	3806	45
H(5A)	4391	1539	1723	41
H(9A)	4453	2379	-1149	30
H(11A)	300	1873	-3923	35
H(12A)	-920	2006	-2225	35
H(14A)	4473	2060	-3376	34
H(16A)	3446	698	-3685	66
H(16B)	3615	1044	-5104	66
H(16C)	1939	1020	-4854	66
H(17A)	1015	2567	1322	28
H(18A)	1488	1130	2018	40
H(18B)	1297	898	450	40
H(19A)	898	-293	1663	44
H(19B)	-653	-79	449	44
H(20A)	-136	321	3288	39
H(21A)	-2881	673	1058	40
H(21B)	-2649	903	2632	40
H(22A)	-2260	2089	1394	36
H(22B)	-701	1874	2601	36
H(23A)	-787	-1094	2813	66
H(23B)	-2333	-834	1631	66
H(23C)	-2172	-628	3201	66
H(24A)	-2518	2706	-1593	39
H(25A)	-4341	3792	-1881	48
H(27A)	-1722	4822	1674	56
H(28A)	106	3744	1953	45
H(3)	2580(50)	4930(30)	-6720(50)	97
H(30A)	1641	5505	-5174	112
H(30B)	484	4730	-5619	112
H(30C)	596	5404	-6739	112

Table 9. Torsion angles [deg] for WPT1796-14B-23

C(6)-C(1)-C(2)-C(3)	-1.6(3)
C(1)-C(2)-C(3)-C(4)	-0.4(3)
C(1)-C(2)-C(3)-C(7)	177.01(19)
C(2)-C(3)-C(4)-C(5)	1.8(3)
C(7)-C(3)-C(4)-C(5)	-175.65(18)
C(3)-C(4)-C(5)-C(6)	-1.2(3)
C(4)-C(5)-C(6)-C(1)	-0.8(3)
C(4)-C(5)-C(6)-C(8)	174.38(16)
C(2)-C(1)-C(6)-C(5)	2.1(3)
C(2)-C(1)-C(6)-C(8)	-172.99(16)
C(4)-C(3)-C(7)-F(2)	84.3(3)
C(2)-C(3)-C(7)-F(2)	-93.1(3)
C(4)-C(3)-C(7)-F(1)	-151.1(2)
C(2)-C(3)-C(7)-F(1)	31.5(3)
C(4)-C(3)-C(7)-F(3)	-32.9(3)
C(2)-C(3)-C(7)-F(3)	149.6(2)
C(5)-C(6)-C(8)-C(13)	99.28(19)
C(1)-C(6)-C(8)-C(13)	-85.6(2)
C(5)-C(6)-C(8)-C(9)	-81.45(19)
C(1)-C(6)-C(8)-C(9)	93.63(19)
C(13)-C(8)-C(9)-C(10)	2.0(2)
C(6)-C(8)-C(9)-C(10)	-177.32(14)
C(8)-C(9)-C(10)-C(11)	-1.2(2)
C(8)-C(9)-C(10)-C(14)	179.86(14)
C(9)-C(10)-C(11)-C(12)	-1.0(2)
C(14)-C(10)-C(11)-C(12)	177.97(15)
C(10)-C(11)-C(12)-C(13)	2.4(3)
C(11)-C(12)-C(13)-C(8)	-1.6(2)
C(11)-C(12)-C(13)-C(17)	179.69(15)
C(9)-C(8)-C(13)-C(12)	-0.6(2)
C(6)-C(8)-C(13)-C(12)	178.69(15)
C(9)-C(8)-C(13)-C(17)	178.16(13)
C(6)-C(8)-C(13)-C(17)	-2.6(2)
C(9)-C(10)-C(14)-C(15)	-116.37(17)
C(11)-C(10)-C(14)-C(15)	64.7(2)
C(9)-C(10)-C(14)-C(16)	120.55(17)
C(11)-C(10)-C(14)-C(16)	-58.4(2)
C(10)-C(14)-C(15)-O(1)	-101.1(2)
C(16)-C(14)-C(15)-O(1)	22.4(2)
C(10)-C(14)-C(15)-O(2)	79.47(17)
C(16)-C(14)-C(15)-O(2)	-157.06(15)
C(12)-C(13)-C(17)-C(29)	-63.9(2)
C(8)-C(13)-C(17)-C(29)	117.41(16)
C(12)-C(13)-C(17)-N(1)	62.12(18)
C(8)-C(13)-C(17)-N(1)	-116.57(15)
C(18)-N(1)-C(17)-C(29)	-170.90(12)
C(22)-N(1)-C(17)-C(29)	-48.81(16)
C(18)-N(1)-C(17)-C(13)	60.38(15)
C(22)-N(1)-C(17)-C(13)	-177.53(12)
C(22)-N(1)-C(18)-C(19)	58.22(18)
C(17)-N(1)-C(18)-C(19)	-178.58(13)
N(1)-C(18)-C(19)-C(20)	-57.9(2)
C(18)-C(19)-C(20)-C(21)	54.7(2)
C(18)-C(19)-C(20)-C(23)	177.67(16)
C(19)-C(20)-C(21)-C(22)	-54.76(19)
C(23)-C(20)-C(21)-C(22)	-177.58(15)
C(18)-N(1)-C(22)-C(21)	-57.41(18)

C(17)-N(1)-C(22)-C(21)	-179.72(13)
C(20)-C(21)-C(22)-N(1)	57.11(19)
C(29)-C(24)-C(25)-C(26)	-0.3(3)
C(24)-C(25)-C(26)-F(4)	178.78(18)
C(24)-C(25)-C(26)-C(27)	-0.7(3)
F(4)-C(26)-C(27)-C(28)	-178.54(19)
C(25)-C(26)-C(27)-C(28)	0.9(3)
C(26)-C(27)-C(28)-C(29)	-0.2(3)
C(27)-C(28)-C(29)-C(24)	-0.7(3)
C(27)-C(28)-C(29)-C(17)	-178.85(17)
C(25)-C(24)-C(29)-C(28)	0.9(3)
C(25)-C(24)-C(29)-C(17)	179.01(15)
C(13)-C(17)-C(29)-C(28)	-120.46(16)
N(1)-C(17)-C(29)-C(28)	114.27(16)
C(13)-C(17)-C(29)-C(24)	61.47(19)
N(1)-C(17)-C(29)-C(24)	-63.80(18)

Symmetry transformations used to generate equivalent atoms:

Table 10. Hydrogen bonds for WPT1796-14B-23 [A and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2)...O(3)	0.82(3)	1.86(3)	2.669(3)	170(3)
N(1)-H(1)...Cl	0.91(2)	2.20(2)	3.1092(15)	173(2)
O(3)-H(3)...Cl#1	0.78(5)	2.29(5)	3.070(2)	171(4)

Symmetry transformations used to generate equivalent atoms:
#1 -x,y+1/2,-z-1