

Novel Tricyclic Pyroglutamide Derivatives as Potent ROR γ t Inverse Agonists Identified using a Virtual Screening Approach

Qingjie Liu,* Douglas G. Batt, Carolyn A. Weigelt, Shihang Yip, Dauh-Rung Wu, Max Ruzanov, John S. Sack, Jinhong Wang, Melissa Yarde, Sha Li, David J. Shuster, Jenny H. Xie, Tara Sherry, Mary T. Obermeier, Aberra Fura, Kevin Stefanski, Georgia Cornelius, Purnima Khandelwal, Joseph A. Tino, John E. Macor, Luisa Salter-Cid, Rex Denton, Qihong Zhao, and T. G. Murali Dhar

Supporting Information

Experimental Procedures

All experiments involving animals were performed in accordance with institutional guidelines as defined by the Institutional Animal Care and Use Committee for U.S. institutions.

Assays in Tables 1 - 4 were performed as previously described.¹

Virtual Screening

A virtual library was enumerated using OEChem Toolkit (OpenEye Scientific Software, Inc.; <https://www.eyesopen.com>) and tools from Schrödinger, Inc. (<https://www.schrodinger.com>).

The virtual library of unique amides was prepared by combining the scaffold (*S*)-3-((4-fluorophenyl)sulfonyl)-3-(4-(perfluoropropan-2-yl)phenyl)pyrrolidine with carboxylic acids and acid chlorides, available in-house or commercially available, having mw <300. SMIRKS for the reaction transformations:

For carboxylic acids: [NX3;H1;!\$(N[C,S]=[!#6]):1][H:2].[C:3](=O)[OX2;H1:4]>>[N:1][C:3](=O)

For acid chlorides: [NX3;H1;!\$(N[C,S]=[!#6]):1][H:2].[Cl:4][C:3](=O)>>[N:1][C:3](=O)

Using this procedure, 57,986 unique amides were derived from carboxylic acids and carboxylic acid chlorides.

Each molecule of the virtual library was prepared for virtual screening as follows:

1. Tautomer expansion was performed using LigPrep (Schrödinger, Inc.): `ligprep -R t`
2. A single ionization state was identified for each tautomer using the `fixpka` utility of QuacPac (OpenEye).
3. A single conformation was generated using Omega (OpenEye), where undefined stereochemistry was expanded: `omega -flipper true -maxconfs 1`
4. The conformation was minimized using the MMFF94s forcefield with Sheffield solvation, as implemented in the Szybki Toolkit (OpenEye).

An in-house x-ray crystal structure of ROR γ t with a proprietary inverse agonist derived from (*S*)-3-((4-fluorophenyl)sulfonyl)-3-(4-(perfluoropropan-2-yl)phenyl)pyrrolidine was used for structure-based screening. The protein complex was prepared using the Schrödinger Protein Preparation wizard. During the protein preparation procedure crystallographic waters were retained, missing hydrogens were added and bond orders assigned. The hydrogen bond network was optimized and a restrained minimization, with RMSD heavy-atom displacement of 0.30 Å, was run to alleviate clashes within the protein complex. The prepared protein complex structure was submitted for Glide grid generation. The centroid of the bound ligand was used to define the center of the enclosing box and the Van der Waals radii for receptor atoms with a partial atomic charge of less than 0.25 were scaled by a factor of 0.80.

Structure-based screening of the virtual library was performed using Glide SP docking. Constraints were not required during docking. The 400 top scoring poses were requested as output. Docking poses were sorted by Glide docking score and inspected by eye. Fifteen novel, unique virtual molecules were selected as having reasonable poses and were recommended for potential synthesis.

Preparation of Compounds

Anhydrous solvents from commercial sources were used for all reactions. All other reagents and solvents were reagent grade and used as received from commercial sources. Column chromatography was performed on a Teledyne ISCO system with commercial silica gel columns. Final compounds were purified by reversed phase high-performance liquid chromatography (HPLC) as indicated. ¹H NMR were obtained on a Bruker spectrometer (operating at 400 MHz or 500 MHz), and the signals are reported in ppm relative to TMS. Mass spectra were recorded using electrospray ionization (ESMS) in the positive mode unless otherwise noted. All assayed compounds have a purity of >90% as assessed by two different analytical HPLC methods.

(3*aR*,9*bR*)-9*b*-((4-Fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[e]indole HCl (compound **35**) was prepared as previously described.¹

HPLC Conditions:

Method A: (analytical)

Column: Acquity UPLC[®] BEH C₁₈ 2.1 x 50 mm, 1.7 μm (Waters Corp.); mobile phase A: 5:95 MeCN-water with 0.1% TFA; mobile phase B: 95:5 MeCN-water with 0.1% TFA; temperature: 50 °C; flow rate 1.0 mL/min; gradient: 0-100% B over 3 min, then 0.75 min isocratic at 100% B.

Method B: (analytical)

Column: Acquity UPLC[®] BEH C₁₈ 2.1 x 50 mm, 1.7 μm (Waters Corp.); mobile phase A: 5:95 MeCN-water with 10 mM ammonium acetate; mobile phase B: 95:5 MeCN-water with 10 mM ammonium acetate; temperature: 50 °C; flow rate 1.0 mL/min; gradient: 0-100% B over 3 min, then 0.75 min isocratic at 100% B.

Method C: (analytical)

Column: ACE UCore Super C₁₈ 3 x 125 mm, 2.5 μm (Waters Corp.); mobile phase A: 5:95 MeCN-water with 0.05% TFA; mobile phase B: 95:5 MeCN-water with 0.05% TFA; flow rate 1.0 mL/min; gradient: 10-100% B over 12 min, then 3 min isocratic at 100% B; 220 nM detection.

Method D: (analytical)

Column: ACE UCore Super HexPh 3 x 125 mm, 2.5 μm (Waters Corp.); mobile phase A: 5:95 MeCN-water with 0.05% TFA; mobile phase B: 95:5 MeCN-water with 0.05% TFA; flow rate 1.0 mL/min; gradient: 10-100% B over 12 min, then 3 min isocratic at 100% B; 220 nM detection.

Method E: (preparative)

Column: XBridge[™] C18 19 x 200 mm, 5 μm (Waters Corp.); mobile phase A: 5:95 MeCN-water with 10 mM ammonium acetate; mobile phase B: 95:5 MeCN-water with 10 mM ammonium acetate; flow rate 20 mL/min; gradient: increasing B, then isocratic.

Method F: (preparative)

Column: XBridge™ C18 19 x 200 mm, 5 μm (Waters Corp.); mobile phase A: 5:95 MeCN-water with 0.1% TFA; mobile phase B: 95:5 MeCN-water with 0.1% TFA; flow rate 20 mL/min; gradient: increasing B, then isocratic.

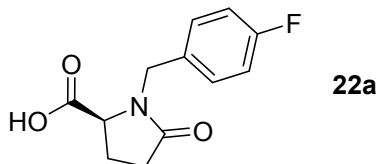
Method G: (preparative)

Column: Luna® C₁₈ 30 x 100 mm, 5 μm (Phenomenex Inc.); mobile phase A: water with 0.1% TFA; mobile phase B: MeCN with 0.1% TFA; flow rate 30 mL/min; gradient: increasing B, then isocratic.

Abbreviations:

BOP	benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
DIEA	diisopropylethylamine
EtOAc	ethyl acetate
HATU	hexafluorophosphate azabenzotriazole tetramethyl uronium
IPA	isopropanol
MeOH	methanol
TEA	triethylamine

(S)-1-(4-Fluorobenzyl)-5-oxopyrrolidine-2-carboxylic acid (compound 22a)



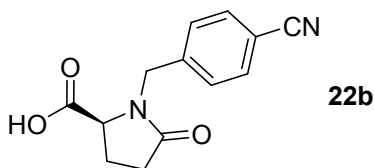
Step 1: (S)-Ethyl 1-(4-fluorobenzyl)-5-oxopyrrolidine-2-carboxylate

A suspension of NaH (60% in mineral oil; 0.336 g, 8.40 mmol) in THF (11 mL) was treated with (S)-ethyl 5-oxopyrrolidine-2-carboxylate (0.88 g, 5.60 mmol). The mixture was stirred at rt for 15 min, then 1-(bromomethyl)-4-fluorobenzene (0.837 mL, 6.72 mmol) was added and the mixture was stirred at rt for 4 days. The mixture was concentrated to give the crude product which was used for next step without further purification. LCMS (Method A) *m/z* 266.0 (M+H)⁺.

Step 2: (S)-1-(4-Fluorobenzyl)-5-oxopyrrolidine-2-carboxylic acid

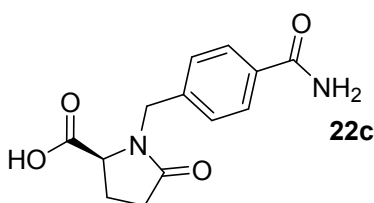
The crude product from step 1 was dissolved in THF-MeOH-water (3:1:1, 112 mL) and treated with LiOH monohydrate (0.267 g, 11.16 mmol). The mixture was stirred at rt for 20 h, then was concentrated to remove most of organic solvents. The aqueous residue was diluted with water and washed twice with EtOAc. The aqueous phase was acidified with 1 M aqueous HCl to about pH 2, and then was extracted with EtOAc. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated to provide the product as a yellow syrup (0.54 g) in 41% yield over two steps. ¹H NMR (400 MHz, DMSO-d₆) δ 12.90 (br s, 1H), 7.28 - 7.21 (m, 2H), 7.19 - 7.11 (m, 2H), 4.79 (d, J=15.0 Hz, 1H), 3.97 - 3.89 (m, 2H), 2.41 - 2.20 (m, 3H), 1.98 - 1.91 (m, 1H). LCMS (Method A) *m/z* 238.3 (M+H)⁺.

(S)-1-(4-Cyanobenzyl)-5-oxopyrrolidine-2-carboxylic acid (compound 22b)



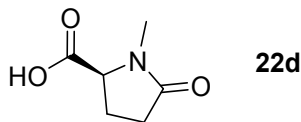
Compound **22b** was synthesized in 32% yield according to the two-step preparation procedures of **22a**, from (*S*)-ethyl 5-oxopyrrolidine-2-carboxylate (0.83 g, 5.28 mmol) and 4-(bromomethyl)benzonitrile (1.24 g, 6.34 mmol). LCMS (Method A) m/z 244.9 (M+H)⁺.

(S)-1-(4-Carbamoylbenzyl)-5-oxopyrrolidine-2-carboxylic acid (compound 22c)



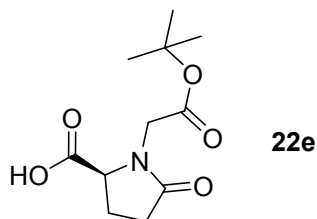
A suspension of compound **22b** (0.120 g, 0.491 mmol) in 80% H₂SO₄ (1.64 mL, 24.6 mmol) was heated at 60 °C for 100 min. The mixture was cooled to rt, poured into ice/water, and extracted with EtOAc. The organic phase was washed with brine, dried over Na₂SO₄, filtered, and concentrated to afford **22c** as a yellow solid (45.8 mg) in 36% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (br. s., 1H), 7.93 (br. s., 1H), 7.83 (d, J=8.4 Hz, 2H), 7.31 (br. s., 1H), 7.27 (d, J=8.1 Hz, 2H), 4.87 (d, J=15.6 Hz, 1H), 4.01 - 3.92 (m, 2H), 2.33 (d, J=2.9 Hz, 3H), 1.98 - 1.93 (m, 1H). LCMS (Method A) m/z 263.0 (M+H)⁺.

(S)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid (compound 22d)



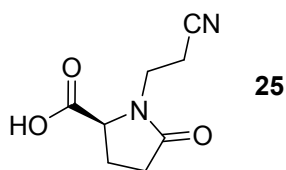
Compound **22d** was synthesized in 33% yield according to the two-step preparation procedures of **22a**, from (*S*)-ethyl 5-oxopyrrolidine-2-carboxylate (0.9 g, 5.73 mmol) and iodomethane (0.535 mL, 8.59 mmol). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.94 (br s, 1H), 4.14 - 4.09 (m, 1H), 2.69 (s, 3H), 2.32 - 2.16 (m, 3H), 1.96 - 1.87 (m, 1H). LCMS showed no ionization of desired mass.

(S)-1-(2-(tert-Butoxy)-2-oxoethyl)-5-oxopyrrolidine-2-carboxylic acid (compound 22e)



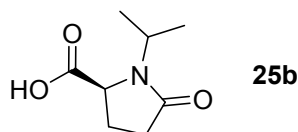
Compound **22e** was synthesized in 69% yield according to the two-step preparation procedures of **22a**, from (*S*)-methyl 5-oxopyrrolidine-2-carboxylate (2.50 g, 17.47 mmol) and tert-butyl 2-bromoacetate (2.8 mL, 19.21 mmol). ¹H NMR (400 MHz, CDCl₃) δ 4.53 (d, J=18.1 Hz, 1H), 4.52- 4.42 (m, 1H), 3.70 (d, J=17.8 Hz, 1H), 2.67 - 2.41 (m, 3H), 2.33 - 2.17 (m, 1H), 1.48 (s, 9H). LCMS (Method A) *m/z* 188 (M+H-C₄H₈)⁺ and 509 (2M+Na)⁺.

(S)-1-(2-Cyanoethyl)-5-oxopyrrolidine-2-carboxylic acid (25)

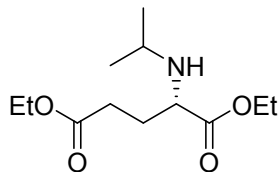


To a solution of NaOH (2.72 g, 68.0 mmol) in water (11.3 mL) at rt was added L-glutamic acid (5.00 g, 34.0 mmol), followed by acrylonitrile (2.68 mL, 40.8 mmol) and the reaction mixture was heated at 50 °C overnight. After 20 h, it was cooled in an ice bath and concentrated HCl (5.17 mL, 64.6 mmol) was added very slowly with stirring to pH about 4. The mixture was concentrated and the white residue was suspended in 40 mL acetone and heated at reflux for 20 h. The mixture was cooled to rt, the solid was removed by filtration and the filtrates were concentrated to afford a colorless oil (8.19 g). The oil was purified by supercritical fluid chromatography (column: Princeton Cyano 3 x 25 cm, 5 μM; mobile phase: CO₂/MeOH (80/20); flow rate: 160 mL/min; pressure: 100 bars; temperature: 40 °C; detection: 210 nm; sample preparation: 8.19 g in 75 mL MeOH; injection: 2.5 mL with cycle time 2.35 min) to provide the product as a white solid (3.72 g) in 60% yield. ¹H NMR (499 MHz, DMSO-d₆) δ 13.06 (br s, 1H), 4.35 - 4.29 (m, 1H), 3.75 (dt, J=14.0, 7.0 Hz, 1H), 3.21 - 3.13 (m, 1H), 2.73 (t, J=6.8 Hz, 2H), 2.35 - 2.22 (m, 3H), 2.02 - 1.96 (m, 1H). LCMS (Method A) *m/z* 183.1 (M+H)⁺.

(S)-1-Isopropyl-5-oxopyrrolidine-2-carboxylic acid (compound 25b)

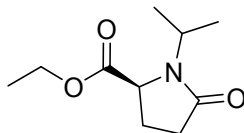


Step 1: (*S*)-Diethyl 2-(isopropylamino)pentanedioate



To a mixture of (*S*)-diethyl 2-aminopentanedioate hydrochloride (1.5 g, 6.26 mmol) in THF (19.3 mL) and MeOH (9.6 mL) was added crushed KOH (0.410 g, 6.57 mmol). The resulting reaction mixture was stirred at rt for 10 min, then a mixture of acetone (0.690 mL, 9.39 mmol) and acetic acid (0.376 mL, 6.57 mmol) in THF (2.4 mL) was added. After 10 min, the mixture was cooled in an ice bath and sodium borohydride (0.237 g, 6.26 mmol) was added in portions. The mixture was then stirred at rt. After 6 h, LCMS showed both starting material and product. More acetone (0.690 mL, 9.39 mmol) was added, followed by more sodium borohydride (0.237 g, 6.26 mmol) and the resulting mixture was stirred at rt overnight. After 25 h, the mixture was concentrated to remove solvents, then partitioned between EtOAc and 1.5 M K_2HPO_4 . The organic phase was washed with brine, dried over Na_2SO_4 , filtered and concentrated to afford the crude product as an almost colorless oil (1.34 g) in 87% yield. LCMS (Method A) m/z 246.2 (M+H)⁺.

Step 2: (*S*)-Ethyl 1-isopropyl-5-oxopyrrolidine-2-carboxylate

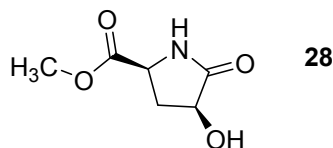


A solution of (*S*)-diethyl 2-(isopropylamino)pentanedioate (1.34 g, 5.46 mmol) in MeOH (10.9 mL) was heated on a heating block at 140 °C for 15 min, then was heated in microwave for 1.25 h at 150°C. The mixture was concentrated and the residue was partitioned between EtOAc and 0.3 M HCl. The organic phase was washed with water and saturated $NaHCO_3$, dried over Na_2SO_4 , filtered, and concentrated to afford the crude ester intermediate as a yellow oil in 28% yield (0.30 g). LCMS (Method A) m/z 200.1, 186.1 (M+H)⁺, indicating a mixture of ethyl and methyl esters.

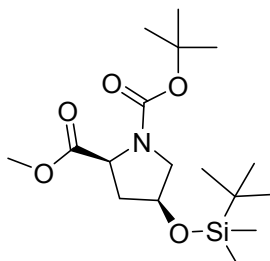
Step 3: (*S*)-1-Isopropyl-5-oxopyrrolidine-2-carboxylic acid

A mixture of (*S*)-ethyl 1-isopropyl-5-oxopyrrolidine-2-carboxylate (0.30 g, 1.506 mmol) and LiOH (0.112 g, 4.67 mmol) in THF (4.5 mL), MeOH (1.5 mL), and water (1.5 mL) was stirred at rt overnight. After 16 h, the mixture was concentrated, and the residue was partitioned between 1 M HCl and a mixture of $CHCl_3$ /IPA (3:1). The organic phase was washed with brine, dried over Na_2SO_4 , filtered and concentrated to afford the crude product as a solid in 89% yield (0.229 g). ¹H NMR (400 MHz, $CDCl_3$) δ 4.40 - 4.13 (m, 2H), 2.74 - 2.60 (m, 1H), 2.45 - 2.24 (m, 2H), 2.18 - 2.08 (m, 1H), 1.21 (d, J=6.8 Hz, 3H), 1.17 (d, J=6.8 Hz, 3H). LCMS (Method A) m/z 172.2 (M+H)⁺.

Methyl (2*S*,4*S*)-4-hydroxy-5-oxopyrrolidine-2-carboxylate (28)

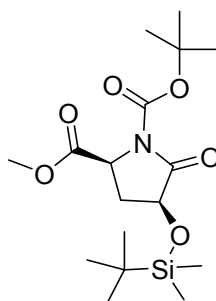


Step 1: 1-(*tert*-Butyl) 2-methyl (2*S*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)pyrrolidine-1,2-dicarboxylate



A solution of (2*S*,4*S*)-1-*tert*-butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate (3.10 g, 12.6 mmol) in THF (56 mL), cooled in an ice-water bath, was treated slowly with a solution of *tert*-butylchlorodimethylsilane (2.29 g, 15.2 mmol) in THF (7 mL), then with TEA (2.8 mL, 20.2 mmol). The mixture was stirred at rt overnight. After 18 h, imidazole (1.72 g, 25.3 mmol) was added and the resulting thick suspension was stirred at rt overnight. Additional imidazole (0.42 g), *tert*-butylchlorodimethylsilane (1.1 g) and DMF (6 mL) were added and the mixture was heated at 45 °C for 6 h, then stirred at rt overnight. The mixture was concentrated and the residue was partitioned between EtOAc and water. The organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel (80 g), eluting with EtOAc-hexanes (0-10%), to provide the product as a colorless oil (4.76 g, quantitative yield). ¹H NMR (400 MHz, CDCl₃) δ 4.47 - 4.27 (m, 2H), 3.71 (s, 3H), 3.68 - 3.54 (m, 1H), 3.39 - 3.24 (m, 1H), 2.38 - 2.22 (m, 1H), 2.15 - 2.06 (m, 1H), 1.48 (s, 3H), 1.43 (s, 6H), 0.89 - 0.83 (m, 9H), 0.08 - 0.03 (m, 6H). LCMS (Method A) *m/z* 382.2 (M+Na)⁺.

Step 2: 1-(*tert*-Butyl) 2-methyl (2*S*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)-5-oxopyrrolidine-1,2-dicarboxylate



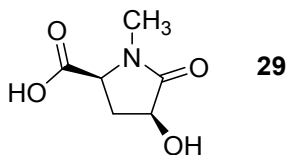
A solution of NaIO₄ (7.08 g, 33.1 mmol) in water (126 mL) was treated with RuO₂ hydrate (0.400 g, 2.65 mmol) and stirred at rt for 5 min. This mixture was then treated with a solution of (2*S*,4*S*)-1-*tert*-butyl 2-methyl 4-((*tert*-butyldimethylsilyl)oxy)pyrrolidine-1,2-dicarboxylate (4.76 g, 13.2 mmol) in EtOAc (63 mL) and stirred at rt. After 6 h, the mixture was diluted with EtOAc, filtered through Celite, and the solids were washed with water and EtOAc. The combined

filtrates were partitioned between water and EtOAc. The organic phase was washed sequentially with saturated NaHCO₃, 10% Na₂S₂O₃ and brine, dried over Na₂SO₄, filtered and concentrated to afford the product as a colorless syrup (4.85 g, 98% yield). ¹H NMR (400 MHz, CDCl₃) δ 4.47 (dd, *J*=7.8, 6.9 Hz, 1H), 4.29 (t, *J*=7.3 Hz, 1H), 3.77 (s, 3H), 2.57 (dt, *J*=13.0, 7.7 Hz, 1H), 2.00 (dt, *J*=13.0, 7.0 Hz, 1H), 1.51 (s, 9H), 0.89 (s, 9H), 0.17 (s, 3H), 0.13 (s, 3H). LCMS (Method A) *m/z* 396.2 (M+Na)⁺.

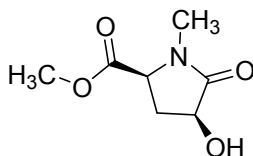
Step 3: Methyl (2*S*,4*S*)-4-hydroxy-5-oxopyrrolidine-2-carboxylate

A solution of (2*S*,4*S*)-1-*tert*-butyl 2-methyl 4-((*tert*-butyldimethylsilyl)oxy)-5-oxopyrrolidine-1,2-dicarboxylate (4.85 g, 13.0 mmol) in DCM (16 mL) was cooled in an ice-water bath and treated with TFA (3 mL). The mixture was warmed to rt, stirred for 2 h, and concentrated to provide the crude product as a yellow syrup in quantitative yield. LCMS (Method A) *m/z* 159.9 (M+H)⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.25 - 6.70 (m, 1H), 4.47 - 4.36 (m, 2H), 4.26 - 4.16 (m, 1H), 3.81 (d, *J*=10.1 Hz, 3H), 2.96 - 2.70 (m, 1H), 2.21 - 2.08 (m, 1H).

(2*S*,4*S*)-4-Hydroxy-1-methyl-5-oxopyrrolidine-2-carboxylic acid (29)



Step 1: (2*S*,4*S*)-Methyl 4-hydroxy-1-methyl-5-oxopyrrolidine-2-carboxylate

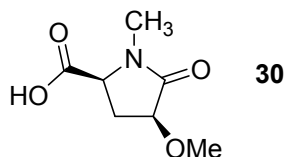


To a mixture of (2*S*,4*S*)-methyl 4-hydroxy-5-oxopyrrolidine-2-carboxylate (0.24 g, 1.54 mmol) and Cs₂CO₃ (2.01 g, 6.16 mmol) in acetonitrile (15.4 mL) was added iodomethane (0.863 mL, 13.9 mmol) and the resulting mixture was heated at 50 °C overnight in a sealed vial. After 18 h, the mixture was cooled to rt and partitioned between water and a mixture of CHCl₃ and IPA (3:1). The organic phase was washed with brine, dried over MgSO₄, filtered, and concentrated. The residue coated on silica gel and purified by column chromatography on silica gel (12 g) eluting with EtOAc-hexanes (50 - 100%). The product was obtained as a yellow solid (98 mg) in 37% yield. ¹H NMR (400 MHz, CDCl₃) δ 4.35 - 4.27 (m, 1H), 4.09 (dd, *J*=7.8, 6.7 Hz, 1H), 3.82 (s, 3H), 2.99 (d, *J*=3.5 Hz, 1H), 2.92 (s, 3H), 2.74 (dt, *J*=13.4, 8.0 Hz, 1H), 2.02 (dt, *J*=13.4, 6.6 Hz, 1H). LCMS (Method A) *m/z* 174.0 (M+H)⁺.

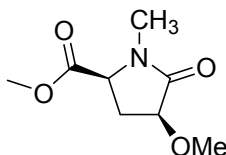
Step 2: (2*S*,4*S*)-4-Hydroxy-1-methyl-5-oxopyrrolidine-2-carboxylic acid

Compound **29** was synthesized, according to the 2nd step of the preparation of **22a**, from (2*S*,4*S*)-methyl 4-hydroxy-1-methyl-5-oxopyrrolidine-2-carboxylate (98 mg) in quantitative yield. LCMS (Method A) m/z 160.0 (M+H)⁺.

(2*S*,4*S*)-4-Methoxy-1-methyl-5-oxopyrrolidine-2-carboxylic acid (30)



Step 1: (2*S*,4*S*)-Methyl 4-methoxy-1-methyl-5-oxopyrrolidine-2-carboxylate

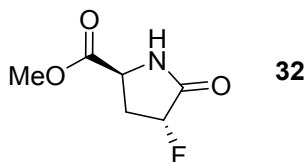


To a mixture of (2*S*,4*S*)-methyl 4-hydroxy-5-oxopyrrolidine-2-carboxylate **28** (0.27 g, 1.72 mmol) and NaH (0.254 g, 6.36 mmol) in DMF (6.9 mL) was added iodomethane (0.538 mL, 8.60 mmol) and the resulting mixture was stirred at 50 °C overnight. After 17 h, the mixture was cooled to rt and partitioned between water and EtOAc. The organic phase was washed with 10% LiCl and brine, dried over MgSO₄, filtered and concentrated. The residue was coated on silica gel and purified by column chromatography on silica gel (24 g), eluting with EtOAc-hexanes (50-100%). The product was obtained as a light brown oil (84 mg) in 26% yield. ¹H NMR (400 MHz, CDCl₃) δ 4.03 (dd, J=8.6, 5.3 Hz, 1H), 3.91 (dd, J=7.7, 5.1 Hz, 1H), 3.80 (s, 3H), 3.54 (s, 3H), 2.92 (s, 3H), 2.71 - 2.60 (m, 1H), 2.08 (dt, J=13.7, 5.1 Hz, 1H). LCMS (Method A) m/z 188.1 (M+H)⁺.

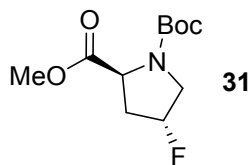
Step 2: (2*S*,4*S*)-4-Methoxy-1-methyl-5-oxopyrrolidine-2-carboxylic acid

Compound **30** was synthesized, according to the 2nd step of the preparation of **22a**, from (2*S*,4*S*)-methyl 4-methoxy-1-methyl-5-oxopyrrolidine-2-carboxylate (82 mg) in quantitative yield. LCMS (Method A) m/z 174.3 (M+H)⁺.

Methyl (2*S*,4*R*)-4-fluoro-5-oxopyrrolidine-2-carboxylate (32)

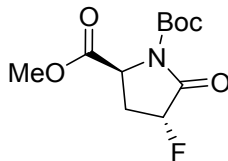


Step1: 1-(*tert*-Butyl) 2-methyl (2*S*,4*R*)-4-fluoropyrrolidine-1,2-dicarboxylate (**31**)



To a solution of 1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-hydroxypyrrolidine-1,2-dicarboxylate (15.5 g, 63.1 mmol) in DCM (300 mL), cooled in an ice bath, was added DAST (9.8 mL, 74.4 mmol) slowly and the resulting mixture was stirred at rt. After 4 h, it was partitioned between water and DCM. The organic phase was washed with saturated NaHCO₃ and brine, dried over Na₂SO₄, filtered, and concentrated to afford a light yellow syrup. The crude product was purified by column chromatography on silica gel (330 g), eluting with EtOAc-hexanes (20-40%). The product was obtained as a colorless liquid (5.37 g) in 34% yield. ¹H NMR (400 MHz, CDCl₃) δ 5.30 - 5.11 (m, 1H), 4.52 - 4.35 (m, 1H), 3.97 - 3.79 (m, 1H), 3.78 - 3.72 (m, 3H), 3.70 - 3.53 (m, 1H), 2.68 - 2.49 (m, 1H), 2.22 - 1.99 (m, 1H), 1.49 - 1.38 (m, 9H). LCMS (Method A) *m/z* 270.1 (M+Na)⁺.

Step 2: 1-(*tert*-Butyl) 2-methyl (2*S*,4*R*)-4-fluoro-5-oxopyrrolidine-1,2-dicarboxylate



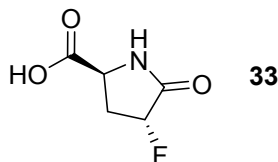
To a solution of NaIO₄ (25.7 g, 120 mmol) in water (267 mL) was added RuCl₃ hydrate (4.51 g, 20.0 mmol) forming a dark red solution which was stirred for 10 min. A solution of 1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-fluoropyrrolidine-1,2-dicarboxylate (4.95 g, 20.0 mmol) in EtOAc (133 mL) was added. The resulting mixture was stirred at rt overnight. After 16 h, IPA (30 mL) was added to the mixture, and stirring was continued at rt for 1 h. The mixture was filtered through a Celite pad and the solids were washed with EtOAc. The filtrates were partitioned between water and EtOAc. The organic phase was washed with saturated NaHCO₃, a solution of Na₂S₂O₄ (12.7 g, 80 mmol) in water (200 mL) and brine, dried over Na₂SO₄, filtered, and concentrated to afford a light yellow syrup. The crude product was purified by column chromatography on silica gel (80 g), eluting with 20% EtOAc in hexanes. The product was obtained as a colorless oil (4.64 g) in 89% yield. ¹H NMR (499 MHz, CDCl₃) δ 5.30 - 5.09 (m, 1H), 4.68 (dd, *J*=9.6, 2.1 Hz, 1H), 3.81 (s, 3H), 2.61 - 2.37 (m, 2H), 1.57 - 1.49 (m, 9H). LCMS (Method A) *m/z* 162.1 (M-Boc)⁺.

Step 3: Methyl (2*S*,4*R*)-4-fluoro-5-oxopyrrolidine-2-carboxylate

To a solution of 1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-fluoro-5-oxopyrrolidine-1,2-dicarboxylate (4.64 g, 17.8 mmol) in DCM (17.8 mL) cooled in an ice bath, was added 4 M HCl in dioxane (17.8 mL, 71.0 mmol) and the mixture was stirred at rt for 4 h. LCMS indicated some starting material remained, and more 4 M HCl in dioxane (4.5 mL) was added and stirring was continued. After 6 h total, the mixture was concentrated, then partitioned between EtOAc and water. The organic phase was washed with water, saturated NaHCO₃ and brine, dried over MgSO₄, filtered, and concentrated to afford a light yellow syrup (1.66 g). The aqueous phase was extracted with a mixture of IPA/CHCl₃ (1:3), and the organic phase was washed with saturated NaHCO₃ and brine, dried over MgSO₄, filtered, and concentrated to afford more product (0.16

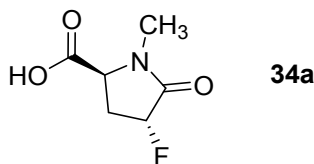
g). In total, 1.82 g of product was obtained in 63% yield. ^1H NMR (499 MHz, CDCl_3) δ 6.55 (br s, 1H), 5.22 - 5.04 (m, 1H), 4.42 - 4.37 (m, 1H), 3.82 (s, 3H), 2.70 - 2.60 (m, 2H). LCMS (Method A) m/z 162.1 (M+H) $^+$.

(2S,4R)-4-Fluoro-5-oxopyrrolidine-2-carboxylic acid (33)



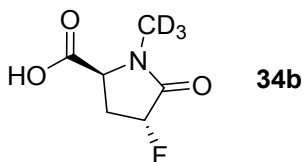
A mixture of methyl (2S,4R)-4-fluoro-5-oxopyrrolidine-2-carboxylate **32** (0.57 g, 3.54 mmol) and LiOH (0.232 g, 5.52 mmol) in 3:1:1 THF/MeOH/water (10 mL) was stirred at rt. After 1 h, 4 M HCl in dioxane (1.50 mL, 6.01 mmol) was added and the mixture was concentrated and lyophilized overnight. The product was obtained as a crude mixture with LiCl as a white waxy solid in quantitative yield. ^1H NMR (499 MHz, DMSO- d_6) δ 8.64 (br s, 1H), 5.36 - 4.99 (m, 1H), 4.20 (ddd, J=8.9, 3.0, 1.1 Hz, 0.5H), 3.86 (dd, J=8.1, 5.0 Hz, 0.5H), 2.48 - 2.26 (m, 2H). LCMS (Method A) m/z 146.2 (M-H) $^-$.

(2S,4R)-4-Fluoro-1-methyl-5-oxopyrrolidine-2-carboxylic acid (34a)



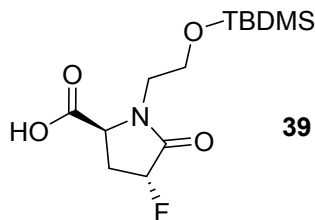
Compound **34a** was synthesized, according to the 2-step preparation of **29**, from methyl (2S,4R)-4-fluoro-5-oxopyrrolidine-2-carboxylate **31** (0.20 g, 1.241 mmol) and iodomethane (0.386 mL, 6.21 mmol). LCMS m/z 162.2 (M+H) $^+$.

(2S,4R)-4-Fluoro-1-(methyl-d3)-5-oxopyrrolidine-2-carboxylic acid (34b)



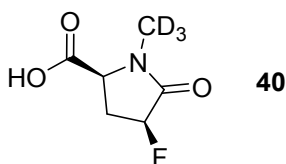
Compound **34b** was synthesized according to the 2-step preparation procedures of **29** from methyl (2S,4R)-4-fluoro-5-oxopyrrolidine-2-carboxylate **31** (0.48 g, 2.98 mmol) and iodomethane- d_3 (0.927 mL, 14.9 mmol). LCMS (Method A) m/z 165.0 (M+H) $^+$.

(2S,4R)-1-(2-((tert-Butyldimethylsilyl)oxy)ethyl)-4-fluoro-5-oxopyrrolidine-2-carboxylic acid (39)

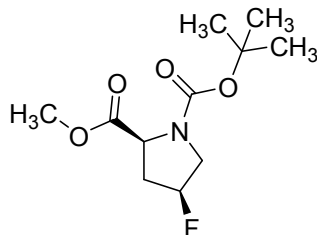


The product was synthesized according to the 2-step preparation of **29** from methyl (2*S*,4*R*)-4-fluoro-5-oxopyrrolidine-2-carboxylate **31** (0.20 g, 1.241 mmol) and (2-bromoethoxy)(*tert*-butyl)dimethylsilane (1.78 g, 7.45 mmol). LCMS (Method A) m/z 306.0 (M+H)⁺.

(2*S*,4*S*)-4-Fluoro-1-(methyl-*d*₃)-5-oxopyrrolidine-2-carboxylic acid (40)

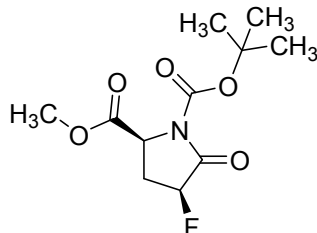


Step 1: 1-(*tert*-Butyl) 2-methyl (2*S*,4*S*)-4-fluoropyrrolidine-1,2-dicarboxylate



A solution of (2*S*,4*S*)-1-*tert*-butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate (10.0 g, 40.8 mmol) in DCM (204 mL) was cooled in an ice-water bath and treated slowly with DAST (6.5 mL, 48.9 mmol). The mixture was stirred at rt for 5.5 h, then was partitioned between water and additional DCM. The organic phase was washed with brine, dried over Na₂SO₄, filtered, and concentrated to afford the product as a light yellow syrup (10.58 g, 94% yield, 90% estimated purity). LCMS (Method A) m/z 270.2 (M+Na)⁺.

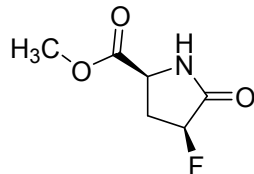
Step 2: 1-(*tert*-Butyl) 2-methyl (2*S*,4*S*)-4-fluoro-5-oxopyrrolidine-1,2-dicarboxylate



A solution of NaIO₄ (44.6 g, 209 mmol) in water (435 mL) was treated with RuCl₃ hydrate (7.84 g, 34.8 mmol), forming a dark red solution. This was treated slowly with a solution of crude (2*S*,4*S*)-1-*tert*-butyl 2-methyl 4-fluoropyrrolidine-1,2-dicarboxylate (9.55 g, 34.8 mmol) in EtOAc (145 mL). The mixture was stirred at rt for 17 h, then was treated with IPA (80 mL) and

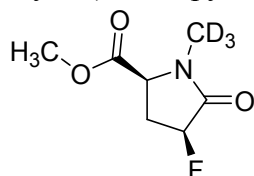
stirred at rt for 3 h. The mixture was filtered through Celite and the solids were washed with water and EtOAc. The combined filtrates were diluted with additional EtOAc and water. The organic phase was separated, washed with brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified by column chromatography on silica gel (120 g), eluting with EtOAc-hexanes (10-50%), to provide the product as a light yellow oil (67% yield). LCMS (Method A) *m/z* 284.0 (M+Na)⁺. ¹H NMR (400 MHz, CDCl₃): δ 5.30 - 5.11 (m, 1H), 4.68 (dd, *J*=9.5, 2.0 Hz, 1H), 3.81 (s, 3H), 2.61 - 2.40 (m, 2H), 1.53 (s, 9H).

Step 3: Methyl (2*S*,4*S*)-4-fluoro-5-oxopyrrolidine-2-carboxylate



A solution of (2*S*,4*S*)-1-*tert*-butyl 2-methyl 4-fluoro-5-oxopyrrolidine-1,2-dicarboxylate (7.75 g, 25.8 mmol) in DCM (32 mL) was cooled in an ice-water bath and treated with TFA (12 mL). The mixture was stirred at rt for 2 h, then was concentrated and the residue was partitioned between water and EtOAc. The organic phase was washed with 1.5 M K₂HPO₃ and brine, dried over Na₂SO₄, filtered, and concentrated. The aqueous phase was extracted with CHCl₃-IPA (3:1) to provide additional product. The two portions were combined to provide the product as a dark yellow syrup (3.38 g, 81% yield). LCMS (Method A) *m/z* 162.0 (M+H)⁺. ¹H NMR (400 MHz, CDCl₃) δ 6.86 (br s, 1H), 5.23 - 5.03 (m, 1H), 4.47 - 4.34 (m, 1H), 3.82 - 3.78 (m, 3H), 2.69 - 2.58 (m, 2H).

Step 4: Methyl (2*S*,4*S*)-4-fluoro-1-(methyl-*d*₃)-5-oxopyrrolidine-2-carboxylate



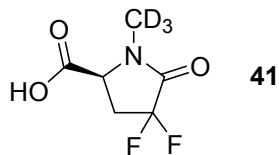
A mixture of (2*S*,4*S*)-methyl 4-fluoro-5-oxopyrrolidine-2-carboxylate (0.480 g, 2.98 mmol) and Cs₂CO₃ (2.43 g, 7.45 mmol) in acetonitrile (16.6 mL) was treated with iodomethane-*d*₃ (0.927 mL, 14.9 mmol) and heated at 45 °C overnight in a sealed vial. After 18 h, the mixture was cooled to rt, filtered and concentrated to afford the product as a light yellow solid (0.53 g, quantitative yield). LCMS (Method A) *m/z* 179.1 (M+H)⁺.

Step 5: (2*S*,4*S*)-4-Fluoro-1-(methyl-*d*₃)-5-oxopyrrolidine-2-carboxylic acid

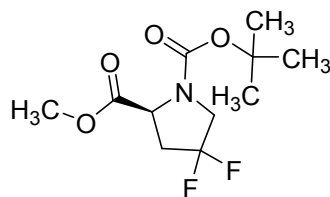
A mixture of methyl (2*S*,4*S*)-4-fluoro-1-(methyl-*d*₃)-5-oxopyrrolidine-2-carboxylate (0.53 g, 2.97 mmol) and LiOH monohydrate (0.221 g, 9.22 mmol) in THF-MeOH-water (3:1:1) (29.7 mL) was stirred at rt for 18 h. The mixture was concentrated, the residue was treated with HCl (4 M in 1,4-dioxane, 2.4 mL, 9.6 mmol), and the mixture was concentrated again to dryness. The

crude product containing LiCl was used without further purification. LCMS (Method A) m/z 165.0 (M+H)⁺.

(S)-4,4-Difluoro-1-(methyl-*d*₃)-5-oxopyrrolidine-2-carboxylic acid (41)

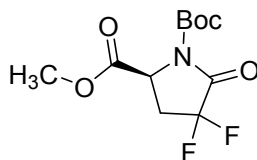


Step 1: 1-(*tert*-Butyl) 2-methyl (*S*)-4,4-difluoropyrrolidine-1,2-dicarboxylate



A solution of (*S*)-1-*tert*-butyl 2-methyl 4-oxopyrrolidine-1,2-dicarboxylate (5.02 g, 20.6 mmol) in DCM (83 mL) at -78 °C was treated dropwise with DAST (9.8 mL, 74.3 mmol). The mixture was stirred at this temperature for 15 min, then warmed to rt and stirred for 18 h. The mixture was cooled to 0 °C, diluted with additional DCM and treated with ice and saturated NaHCO₃. The organic phase was separated, washed with brine, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on silica gel (80 g), eluting with EtOAc-hexanes (10-20%), to provide the product as a light yellow oil (4.48 g) in 82% yield. ¹H NMR (400 MHz, CDCl₃) δ 4.64 - 4.40 (m, 1H), 3.93 - 3.73 (m, 5H), 2.83 - 2.60 (m, 1H), 2.47 (qd, $J=13.6, 5.3$ Hz, 1H), 1.46 (d, $J=18.5$ Hz, 9H). LCMS (Method A) m/z 288.1 (M+Na)⁺.

Step 2: (*S*)-1-*tert*-Butyl 2-methyl 4,4-difluoro-5-oxopyrrolidine-1,2-dicarboxylate



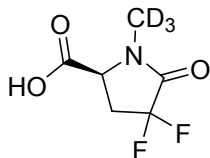
Following the procedure used in Step 2 of the preparation of **40**, (*S*)-1-*tert*-butyl 2-methyl 4,4-difluoropyrrolidine-1,2-dicarboxylate (4.48 g, 16.89 mmol) was converted to the product (0.57 g) in 12% yield, after column chromatography purification. ¹H NMR (400 MHz, CDCl₃) δ 4.69 (ddd, $J=9.2, 3.5, 1.8$ Hz, 1H), 3.83 (s, 3H), 3.00 - 2.80 (m, 1H), 2.66 - 2.49 (m, 1H), 1.55 (s, 9H). LCMS (Method A) m/z 302.1 (M+Na)⁺.

Step 3: (*S*)-Methyl 4,4-difluoro-5-oxopyrrolidine-2-carboxylate

Following the procedure used in Step 3 of the preparation of **40**, (*S*)-1-*tert*-butyl 2-methyl 4,4-difluoro-5-oxopyrrolidine-1,2-dicarboxylate (0.57 g, 2.04 mmol) was converted to the product (0.34 g) in 93% yield. ¹H NMR (400 MHz, CDCl₃) δ 6.84 - 6.70 (m, 1H), 4.39 - 4.31 (m, 1H),

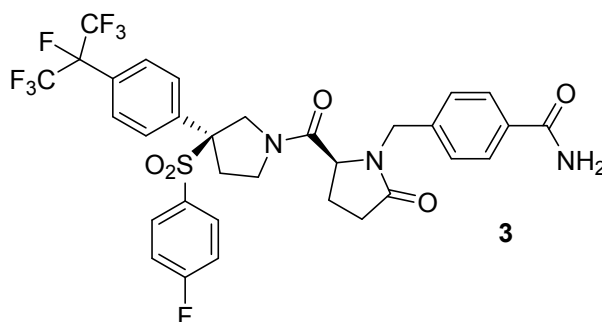
3.84 (s, 3H), 3.00 - 2.85 (m, 1H), 2.70 (qd, J=15.3, 5.5 Hz, 1H). LCMS (Method A) m/z 180.0 (M+H)⁺.

Step 4: (S)-4,4-Difluoro-1-(methyl-*d*₃)-5-oxopyrrolidine-2-carboxylic acid



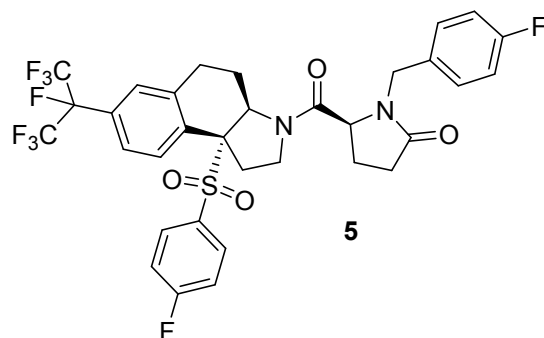
Following the procedures used in Steps 4 and 5 of the preparation of **34b**, (*S*)-methyl 4,4-difluoro-5-oxopyrrolidine-2-carboxylate (0.34 g, 1.898 mmol) was converted into the product in quantitative yield. LCMS (Method A) m/z 182.9 (M+H)⁺.

4-(((S)-2-((R)-3-((4-fluorophenyl)sulfonyl)-3-(4-(perfluoropropan-2-yl)phenyl)pyrrolidine-1-carbonyl)-5-oxopyrrolidin-1-yl)methyl)benzamide (3)



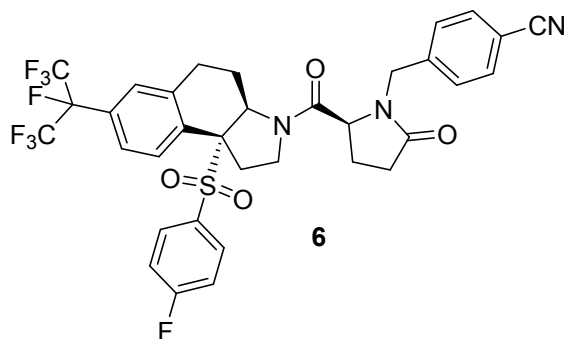
The mixture of (*R*)-3-((4-fluorophenyl)sulfonyl)-3-(4-(perfluoropropan-2-yl)phenyl)pyrrolidine hydrochloride² (18 mg, 0.035 mmol), **22c** (18.5 mg, 0.071 mmol) and DIEA (25 μ L, 0.141 mmol) in DMF (710 μ L) was stirred at rt for 18 h. The mixture was filtered and purified by preparative HPLC (method E) to provide the product (12.6 mg) in 50% yield. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.97 (d, J=17.8 Hz, 1H), 7.86 (d, J=8.0 Hz, 1H), 7.78 (d, J=8.0 Hz, 1H), 7.57 (dd, J=19.4, 8.2 Hz, 2H), 7.40 - 7.22 (m, 9H), 4.95 - 4.65 (m, 2H), 4.57 - 4.16 (m, 1H), 4.01 - 3.73 (m, 2H), 3.68 - 3.50 (m, 2H), 3.24 - 3.02 (m, 1H), 2.42 - 2.18 (m, 2H), 2.07 - 1.75 (m, 1H). LCMS calculated for C₃₂H₂₇F₈N₃O₅S [M+H]⁺: m/z 718.2; found: 718.1. HPLC (method A) t_R 1.821 min, purity 100%; (method B) t_R 1.799 min, purity 100%.

(S)-1-(4-Fluorobenzyl)-5-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)pyrrolidin-2-one (5)



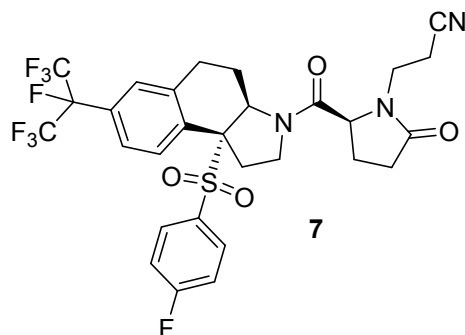
(3aR,9bR)-9b-((4-Fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole HCl **35** (30 mg, 0.056 mmol) was dissolved in DMF (1 mL) and treated with (*S*)-1-(4-fluorobenzyl)-5-oxopyrrolidine-2-carboxylic acid **22a** (26.6 mg, 0.112 mmol), BOP (58.3 mg, 0.112 mmol) and TEA (0.047 mL, 0.336 mmol). After 18 h, the mixture was filtered and purified by preparative HPLC (method E) to provide the product (16 mg) in 40% yield. ¹H NMR (500 MHz, DMSO-*d*₆) complex due to mixture of amide rotamers, ratio about 3:1. δ 7.88 - 7.76 (m, 1H), 7.66 - 7.53 (m, 1H), 7.34 - 7.06 (m, 9H), 4.91 - 4.18 (m, 3H), 3.77 - 3.12 (m, 4H), 2.74 - 2.56 (m, 2H), 2.43 - 2.19 (m, 4H), 1.97 - 1.41 (m, 2H), 1.37 - 1.18 (m, 1H). LCMS calculated for C₃₃H₂₇F₉N₂O₄S [M+H]⁺: *m/z* 719.2; found: 719.5. HPLC (method A) *t*_R 2.402 min, purity 100%; (method B) *t*_R 2.401 min, purity 100%.

4-(((*S*)-2-((3aR,9bR)-9b-((4-Fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-5-oxopyrrolidin-1-yl)methyl)benzonitrile (5)



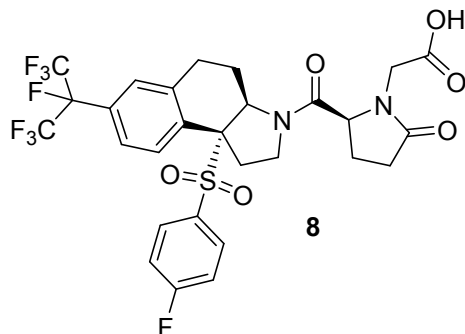
Compound **6** was prepared according to the preparation of **5**, from **35** (30 mg, 0.06 mmol) and **22b** (29.3 mg, 0.120 mmol), to provide the product (12.5 mg) in 29% yield after HPLC purification (method E). ¹H NMR (500 MHz, DMSO-*d*₆) mixture of amide rotamers, ratio about 3:1. δ 7.89 - 7.76 (m, 3H), 7.66 - 7.54 (m, 1H), 7.45 (d, *J*=7.7 Hz, 2H), 7.33 - 7.08 (m, 5H), 4.88 (d, *J*=15.9 Hz, 1H), 4.72 - 4.29 (m, 2H), 3.95 - 3.81 (m, 1H), 3.79 - 3.47 (m, 2H), 3.40 - 3.23 (m, 1H), 2.75 - 2.56 (m, 2H), 2.45 - 2.27 (m, 4H), 2.15 - 1.50 (m, 2H), 1.41 - 1.19 (m, 1H). LCMS calculated for C₃₄H₂₇F₈N₃O₄S [M+H]⁺: *m/z* 726.2; found: 726.5. HPLC (method A) *t*_R 2.309 min, purity 100%; (method B) *t*_R 2.269 min, purity 100%.

3-(((*S*)-2-((3aR,9bR)-9b-((4-Fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-5-oxopyrrolidin-1-yl)propanenitrile (7)



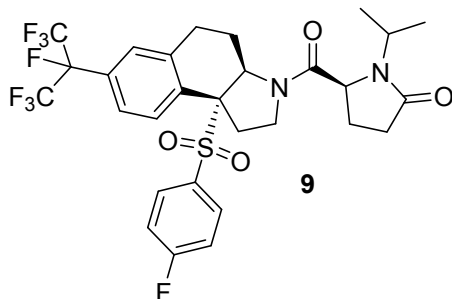
Compound **7** was synthesized according to the preparation of **compound 5**, from **35** (25 mg, 0.047 mmol) and **25** (20.7 mg, 0.093 mmol), providing the product (15.8 mg) in 51% yield after HPLC purification (method E). ^1H NMR (500 MHz, DMSO- d_6) mixture of amide rotamers, ratio about 4:1. Major isomer: δ 7.87 (br d, $J=8.2$ Hz, 1H), 7.62 (br d, $J=8.5$ Hz, 1H), 7.37 - 7.33 (m, 2H), 7.31 (br s, 1H), 7.23 (br t, $J=8.4$ Hz, 2H), 4.71 (br dd, $J=11.7, 4.7$ Hz, 1H), 4.61 (br d, $J=7.3$ Hz, 1H), 3.90 - 3.83 (m, 1H), 3.73 - 3.66 (m, 1H), 3.46 - 3.36 (m, 1H), 3.01 (dt, $J=13.5, 6.5$ Hz, 1H), 2.75 - 2.61 (m, 5H), 2.27 (br s, 4H), 1.92 - 1.79 (m, 2H), 1.35 - 1.24 (m, 1H). LCMS calculated for $\text{C}_{29}\text{H}_{25}\text{F}_8\text{N}_3\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$: m/z 664.2; found: 663.9. HPLC (method A) t_R 2.140 min, purity 100%; (method B) t_R 2.137 min, purity 100%.

2-((S)-2-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-5-oxopyrrolidin-1-yl)acetic acid (8)



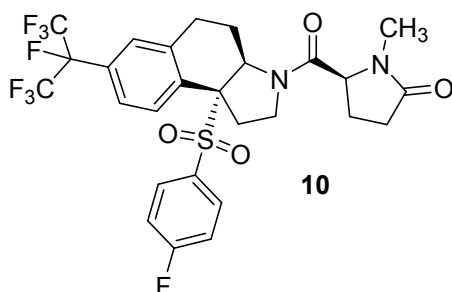
A solution of **35** (20 mg, 0.037 mmol) and **22d** (13.6 mg, 0.056 mmol) in DMF (0.5 mL) was treated with HATU (28.4 mg, 0.075 mmol) and DIEA (0.020 mL, 0.112 mmol), and stirred at rt. After 2.25 h, the solution was diluted with EtOAc, washed twice with 15% LiCl and once with saturated brine, dried over Na_2SO_4 and concentrated. The residue was dissolved in DCM (2 mL), treated with TFA (2 mL) and allowed to stand at rt. After 2.25 h, the mixture was concentrated, and the residue was dissolved in DMF, filtered and purified by preparative HPLC (method E) to provide the product (17 mg). ^1H NMR (500 MHz, DMSO- d_6) complex due to mixture of amide rotamers, ratio about 2:1. δ 7.93 - 7.82 (m, 1H), 7.69 - 7.57 (m, 1H), 7.42 - 7.11 (m, 5H), 5.05 - 4.51 (m, 2H), 4.45 - 4.23 (m, 1H), 3.86 - 3.37 (m, 2H), 2.84 - 2.52 (m, about 4H, DMSO peak interferes), 2.44 - 1.26 (m, 7H). LCMS calculated for $\text{C}_{28}\text{H}_{24}\text{F}_8\text{N}_2\text{O}_6\text{S}$ $[\text{M}+\text{H}]^+$: m/z 669.1; found: m/z 669.2. HPLC (method A) t_R 2.033 min, purity 100%; (method B) t_R 1.650 min, purity 100%.

(S)-5-((3aR,9bR)-9b-((4-Fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-1-isopropylpyrrolidin-2-one (9)



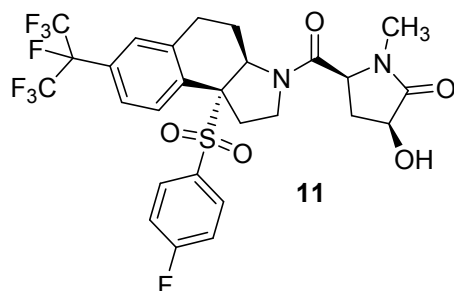
Compound 9 was synthesized according to the preparation of **5**, from **35** (25 mg, 0.047 mmol) and **22e** (12 mg, 0.070 mmol), providing the product (16.3 mg) in 49% yield after HPLC purification (method E). ¹H NMR (500 MHz, DMSO-d₆) mixture of amide rotamers, ratio about 4:1. Major isomer: δ 7.88 (d, J=8.4 Hz, 1H), 7.63 (d, J=8.5 Hz, 1H), 7.31 (br. s., 1H), 7.27 - 7.20 (m, 4H), 4.67 - 4.61 (m, 1H), 4.53 (d, J=8.2 Hz, 1H), 4.13 - 3.86 (m, 2H), 3.78 (br. s., 1H), 3.60 - 3.42 (m, 1H), 2.84 - 2.70 (m, 1H), 2.64 (d, J=14.4 Hz, 1H), 2.44 - 2.03 (m, 5H), 1.87 - 1.68 (m, 2H), 1.14 (d, J=6.7 Hz, 3H), 1.07 (d, J=6.7 Hz, 3H). LCMS calculated for C₂₉H₂₈F₈N₂O₄S [M+H]⁺: *m/z* 653.2; found: 653.2. HPLC (method A) t_R 2.110 min, purity 93.5%; (method B) t_R 2.157 min, purity 93.3%.

(S)-5-((3aR,9bR)-9b-((4-Fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-1-methylpyrrolidin-2-one (10)



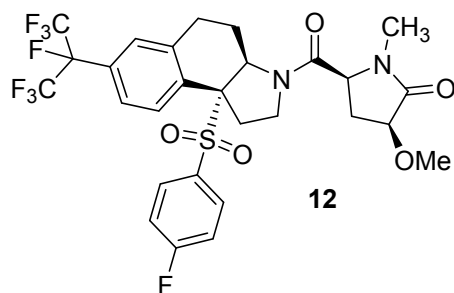
Compound 10 was synthesized according to the preparation of **compound 5**, from **35** (30 mg, 0.056 mmol) and **22c** (12 mg, 0.070 mmol), providing the product (19.3 mg) in 55% yield after HPLC purification (method E). ¹H NMR (500 MHz, DMSO-d₆) mixture of amide rotamers, ratio about 3:1. Major isomer: δ 7.88 (br d, J=8.4 Hz, 1H), 7.64 (br d, J=8.6 Hz, 1H), 7.41 - 7.37 (m, 2H), 7.35 (br s, 1H), 7.29 (br d, J=6.0 Hz, 1H), 7.26 (s, 1H), 4.71 (br dd, J=11.5, 4.5 Hz, 1H), 4.41 - 4.35 (m, 1H), 3.83 - 3.75 (m, 1H), 3.71 - 3.63 (m, 1H), 2.77 - 2.71 (m, 1H), 2.64 (s, 5H), 2.31 (br d, J=8.2 Hz, 2H), 2.24 - 2.20 (m, 2H), 1.93 (br t, J=14.7 Hz, 1H), 1.79 - 1.71 (m, 1H), 1.29 (q, J=12.1 Hz, 1H). LCMS calculated for C₂₇H₂₄F₈N₂O₄S [M+H]⁺: *m/z* 625.1; found: 625.3. HPLC (method A) t_R 2.038 min, purity 99.3%; (method B) t_R 2.041 min, purity 100%.

(3*S*,5*S*)-5-((3*aR*,9*bR*)-9*b*-((4-Fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-3-hydroxy-1-methylpyrrolidin-2-one (11)



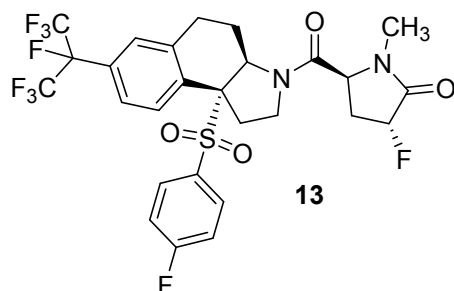
Compound **11** was synthesized according to the preparation of **5**, from **35** (30 mg, 0.056 mmol) and **29** (22 mg, 0.106 mmol), providing the product (13.9 mg) in 39% yield after HPLC purification (method E). ¹H NMR (500 MHz, DMSO-*d*₆) mixture of amide rotamers, ratio about 4:1. Major isomer: δ 7.88 (d, *J*=8.5 Hz, 1H), 7.64 (br d, *J*=8.0 Hz, 1H), 7.40 - 7.36 (m, 2H), 7.34 (br s, 1H), 7.26 (br t, *J*=8.6 Hz, 2H), 5.65 (br d, *J*=5.9 Hz, 1H), 4.73 (br dd, *J*=11.9, 4.9 Hz, 1H), 4.27 (br t, *J*=7.6 Hz, 1H), 4.13 - 4.08 (m, 1H), 3.85 - 3.76 (m, 1H), 3.74 - 3.68 (m, 1H), 2.76 - 2.70 (m, 1H), 2.70 - 2.62 (m, 6H), 2.33 - 2.26 (m, 1H), 1.93 (br t, *J*=14.1 Hz, 1H), 1.49 (dt, *J*=12.5, 7.8 Hz, 1H), 1.33 - 1.23 (m, 1H). LCMS calculated for C₂₇H₂₄F₈N₂O₅S [M+H]⁺: *m/z* 641.1; found: 641.2. HPLC (method A) *t*_R 2.010 min, purity 100%; (method B) *t*_R 2.017 min, purity 100%.

(3*S*,5*S*)-5-((3*aR*,9*bR*)-9*b*-((4-Fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-3-methoxy-1-methylpyrrolidin-2-one (12)



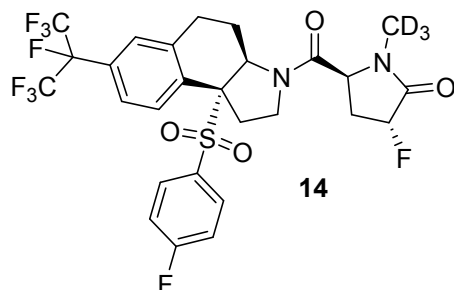
Compound **11** was synthesized according to the preparation of **5**, from **35** (30 mg, 0.056 mmol) and **30** (19 mg, 0.095 mmol), providing the product (16.2 mg) in 44% yield after HPLC purification (method F). ¹H NMR (500 MHz, DMSO-*d*₆) mixture of amide rotamers, ratio about 4:1. Major isomer: δ 7.88 (br d, *J*=8.5 Hz, 1H), 7.64 (br d, *J*=8.2 Hz, 1H), 7.40 - 7.36 (m, 2H), 7.34 (br s, 1H), 7.26 (br t, *J*=8.5 Hz, 2H), 4.73 (br dd, *J*=11.9, 4.9 Hz, 1H), 4.30 (br t, *J*=7.3 Hz, 1H), 3.95 (br t, *J*=7.6 Hz, 1H), 3.83 - 3.77 (m, 1H), 3.73 - 3.66 (m, 1H), 3.35 (s, 3H), 2.76 - 2.72 (m, 1H), 2.70 - 2.64 (m, 6H), 2.32 - 2.25 (m, 1H), 1.92 (br t, *J*=14.0 Hz, 1H), 1.57 (dt, *J*=13.2, 6.7 Hz, 1H), 1.34 - 1.24 (m, 1H). LCMS calculated for C₂₈H₂₆F₈N₂O₅S [M+H]⁺: *m/z* 655.2; found: 655.2. HPLC (method A) *t*_R 2.069 min, purity 100%; (method B) *t*_R 1.164 min, purity 100%.

(3*R*,5*S*)-3-Fluoro-5-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-1-methylpyrrolidin-2-one (13)



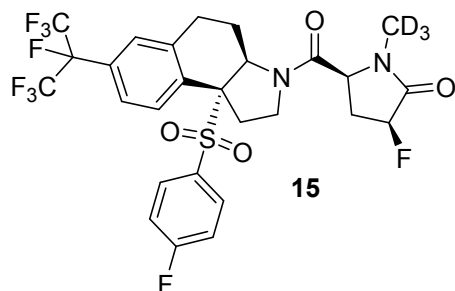
Compound **13** was synthesized according to the preparation of **5**, from **35** (25 mg, 0.050 mmol) and **34a** (16 mg, 0.100 mmol), providing the product (17.1 mg) in 53% yield after HPLC purification (method E). ¹H NMR (500 MHz, DMSO-*d*₆) mixture of amide rotamers, ratio about 3:1. Major isomer: δ 7.87 (d, *J*=8.4 Hz, 1H), 7.63 (br d, *J*=8.6 Hz, 1H), 7.35 - 7.31 (m, 3H), 7.23 (br t, *J*=8.6 Hz, 2H), 5.29 - 5.14 (m, 1H), 4.68 (br dd, *J*=11.9, 4.8 Hz, 1H), 4.60 (br d, *J*=8.3 Hz, 1H), 2.73 - 2.71 (m, 3H), 2.68 - 2.61 (m, 2H), 2.42 - 2.25 (m, 3H), 1.91 - 1.81 (m, 1H), 1.34 - 1.24 (m, 1H). LCMS calculated for C₂₇H₂₃F₉N₂O₄S [M+H]⁺: *m/z* 643.1; found: 643.2. HPLC (method A) *t*_R 2.159 min, purity 99.4%; (method B) *t*_R 2.175 min, purity 100%.

(3*R*,5*S*)-3-Fluoro-5-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-1-(methyl-*d*₃)pyrrolidin-2-one (14)



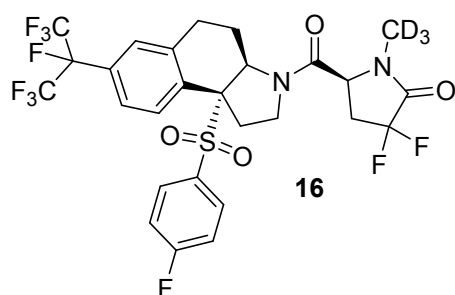
Compound **14** was synthesized according to the preparation of **5**, from **35** (25 mg, 0.050 mmol) and **34b** (16 mg, 0.100 mmol), providing the product (14.2 mg) in 44% yield after HPLC purification (method E). ¹H NMR (500 MHz, DMSO-*d*₆) mixture of amide rotamers, ratio about 3:1. Major isomer: δ 7.87 (d, *J*=8.5 Hz, 1H), 7.62 (br d, *J*=8.7 Hz, 1H), 7.34 - 7.30 (m, 3H), 7.22 (br t, *J*=8.5 Hz, 2H), 5.29 - 5.13 (m, 1H), 4.67 (br dd, *J*=11.9, 4.8 Hz, 1H), 4.58 (br d, *J*=8.6 Hz, 1H), 3.85 (q, *J*=8.8 Hz, 1H), 3.43 (br dd, *J*=11.6, 8.0 Hz, 1H), 2.73 (dt, *J*=14.8, 9.2 Hz, 1H), 2.68 - 2.59 (m, 2H), 2.42 - 2.25 (m, 3H), 1.86 (br t, *J*=14.4 Hz, 1H), 1.34 - 1.22 (m, 1H). LCMS calculated for C₂₇H₂₀D₃F₉N₂O₄S [M+H]⁺: *m/z* 646.1; found: 646.1. HPLC (method A) *t*_R 2.174 min, purity 98.0%; (method B) *t*_R 2.134 min, purity 96.9%.

(3*S*,5*S*)-3-Fluoro-5-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-1-(methyl-*d*₃)pyrrolidin-2-one (15)



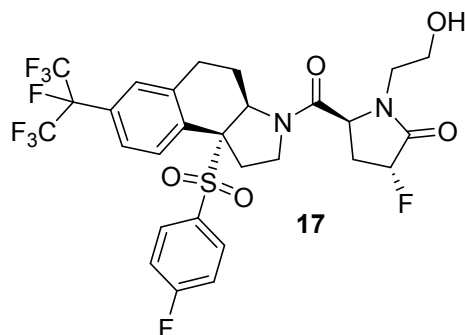
Compound **15** was synthesized according to the preparation of **5**, from **35** (36 mg, 0.072 mmol) and **40** (14 mg, 0.087 mmol), providing the product (13.3 mg) in 31% yield after HPLC purification (method F). ¹H NMR (500 MHz, DMSO-d₆) mixture of amide rotamers, ratio about 4:1. Major isomer: δ 7.89 (br d, J=8.4 Hz, 1H), 7.64 (br d, J=8.1 Hz, 1H), 7.39 - 7.33 (m, 3H), 7.27 (br t, J=8.5 Hz, 2H), 5.19 - 5.03 (m, 1H), 4.73 (br dd, J=11.5, 4.8 Hz, 1H), 4.43 - 4.37 (m, 1H), 3.85 - 3.78 (m, 1H), 3.71 (br t, J=7.7 Hz, 1H), 2.87 - 2.61 (m, 4H), 2.30 (br d, J=7.5 Hz, 1H), 1.95 - 1.79 (m, 2H), 1.35 - 1.24 (m, 1H). LCMS calculated for C₂₇H₂₀D₃F₉N₂O₄S [M+H]⁺: *m/z* 646.1; found: 646.1. HPLC (method A) *t*_R 2.087 min, purity 95.9%; (method B) *t*_R 2.089 min, purity 95.6%.

(S)-3,3-Difluoro-5-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-1-(methyl-d3)pyrrolidin-2-one (16)



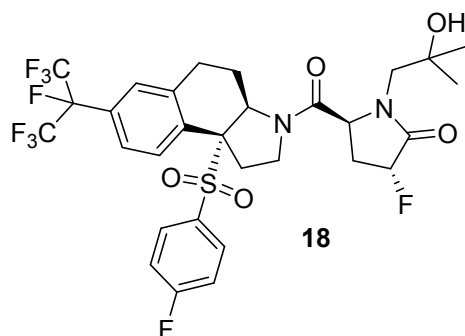
Compound **16** was synthesized according to the preparation of **5**, from **35** (25 mg, 0.050 mmol) and **41** (19 mg, 0.100 mmol), providing the product (13.3 mg) in 46% yield after HPLC purification (method F). ¹H NMR (500 MHz, DMSO-d₆) mixture of amide rotamers, ratio about 3:1. δ 7.92 - 7.80 (m, 1H), 7.65 (br d, J=8.2 Hz, 1H), 7.42 - 7.13 (m, 5H), 5.01 - 4.51 (m, 2H), 3.93 - 3.79 (m, 1H), 3.78 - 3.64 (m, 1H), 3.62 - 3.39 (m, 1H), 3.10 - 2.85 (m, 1H), 2.81 - 2.63 (m, 2H), 2.46 - 2.01 (m, 2H), 1.95 - 1.57 (m, 1H), 1.46 - 1.13 (m, 1H). LCMS calculated for C₂₇H₁₉D₃F₁₀N₂O₄S [M+H]⁺: *m/z* 664.1; found: 664.4. HPLC (method A) *t*_R 2.335 min, purity 100%; (method B) *t*_R 2.302 min, purity 100%.

(3R,5S)-3-Fluoro-5-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-1-(2-hydroxyethyl)pyrrolidin-2-one (17)

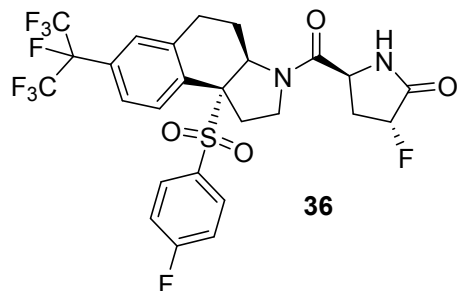


A mixture of **35** (50 mg, 0.100 mmol), **39** (55 mg, 0.180 mmol), BOP (94 mg, 0.180 mmol) and TEA (70 μ L, 0.501 mmol) in DMF (1.25 mL) was stirred at rt over the weekend. After 3 days, the mixture was filtered and purified by HPLC (method G). The appropriate fractions were concentrated to afford the TBDMS intermediate as a light brown solid (29 mg). LCMS m/z 787.2 (M+H)⁺. This material was dissolved in DCM (5 mL), 4 M HCl in dioxane (125 μ L, 0.501 mmol) was added, the mixture was stirred at rt. After 3.5 h, it was concentrated, and the residue was dissolved in DMF and purified by preparative HPLC (method E) to provide the product (9.6 mg) in 14% yield. ¹H NMR (500 MHz, DMSO-*d*₆) mixture of amide rotamers, ratio about 2:1 δ 7.90 - 7.82 (m, 1H), 7.68 - 7.57 (m, 1H), 7.35 - 7.26 (m, 3H), 7.25 - 7.13 (m, 2H), 5.36 - 5.14 (m, 1H), 5.10 - 4.52 (m, 3H), 3.98 - 3.52 (m, 2H), 3.45 (br s, 3H), 2.89 - 2.58 (m, 4H), 2.43 - 2.26 (m, 3H), 2.12 - 1.75 (m, 1H), 1.61 - 1.25 (m, 1H). LCMS calculated for C₂₈H₂₅F₉N₂O₅S [M+H]⁺: m/z 673.1; found: 672.9. HPLC (method A) t_R 2.098 min, purity 100%; (method B) t_R 2.110 min, purity 100%.

(3*R*,5*S*)-3-Fluoro-5-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-1-(2-hydroxy-2-methylpropyl)pyrrolidin-2-one (18)



Step 1: (3*R*,5*S*)-3-Fluoro-5-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)pyrrolidin-2-one (**36**)



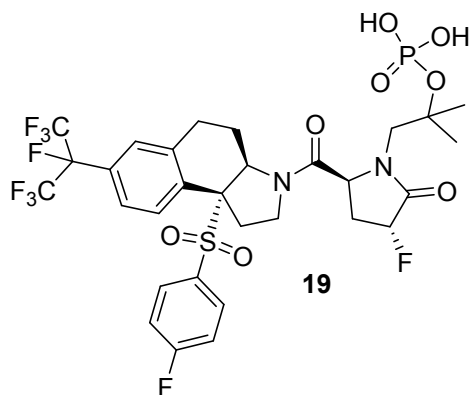
A mixture of **35** (0.385 g, 0.771 mmol), **33** (0.227 g, 1.54 mmol), HATU (0.528 g, 1.39 mmol) and TEA (0.537 mL, 3.85 mmol) in THF (12.9 mL) and DMF (4.3 mL) was stirred at rt overnight. After 17 h, LCMS revealed some unreacted starting material. More DMF (5 mL) and **33** (0.13 g) were added and stirring was continued for 4 days. The mixture was concentrated, and partitioned between water and EtOAc. The organic phase was washed with 1.5 M K_2HPO_4 and brine, dried over $MgSO_4$, filtered, and concentrated to afford a yellow syrup. The residue was coated on silica gel and purified by column chromatography on silica gel (24 g), eluting with EtOAc-hexanes (50 - 100%) to provide a syrup which was further purified by preparative HPLC (method G) to afford the product as a white solid (169 mg) in 35% yield. LCMS m/z 629.2 ($M+H$)⁺.

Step 2: (3*R*,5*S*)-3-Fluoro-5-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-1-(2-hydroxy-2-methylpropyl)pyrrolidin-2-one

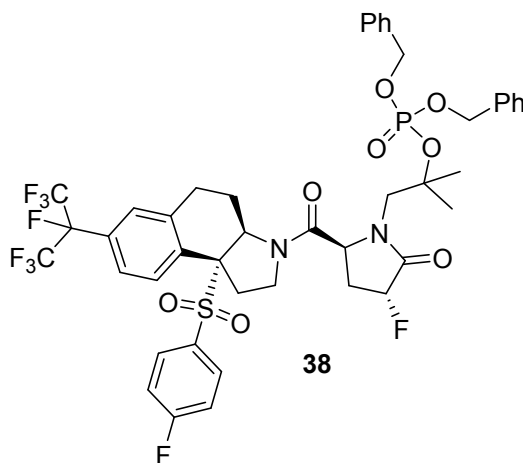
To a mixture of (3*R*,5*S*)-3-fluoro-5-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)pyrrolidin-2-one (169 mg, 0.269 mmol) and K_2CO_3 (74.3 mg, 0.538 mmol) in IPA (3.4 mL) was added 2,2-dimethyloxirane (467 μ L, 5.38 mmol) and the mixture was heated at 100 °C in a sealed vial. After 15 h, the mixture was cooled to rt, filtered, and purified by preparative HPLC (method G). The fractions containing the major, less polar, peak were concentrated, and the aqueous residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated to afford **18** as a white solid (99 mg) in 51% yield. ¹H NMR (499 MHz, DMSO-*d*₆) mixture of amide rotamers, ratio about 2:1. δ 7.92 - 7.82 (m, 1H), 7.68 - 7.56 (m, 1H), 7.39 - 7.13 (m, 5H), 5.41 - 4.99 (m, 2H), 4.77 - 4.50 (m, 2H), 4.15 - 3.32 (m, 5H), 2.78 - 2.59 (m, 3H), 2.45 - 2.25 (m, 2H), 2.13 - 1.75 (m, 1H), 1.58 - 1.27 (m, 1H), 1.19 - 1.07 (m, 6H). ¹³C NMR (126 MHz, DMSO-*d*₆, major rotamer) δ 170.95 - 170.66 (m, 1C), 170.50 - 170.33 (m, 1C), 165.77 (d, $J = 254.3$ Hz, 1C), 141.33 (s, 1C), 136.18 (s, 1C), 133.45 - 132.77 (m, 2C), 131.91 - 131.29 (m, 2C), 125.68 (d, $J = 20.9$ Hz, 1C), 125.55 - 125.12 (m, 1C), 124.18 - 123.66 (m, 1C), 122.29 - 118.80 (m, 2C), 116.84 - 116.61 (m, 2C), 92.62 - 91.55 (m, 1C), 88.63 (d, $J = 180.7$ Hz, 1C), 74.42 (s, 1C), 71.10 (s, 1C), 59.83 (s, 1C), 57.00 - 56.80 (m, 1C), 52.57 - 52.27 (m, 1C), 45.49 - 45.14 (m, 1C), 33.42 (s, 1C), 31.31 - 30.93 (m, 1C), 28.79 (s, 1C), 27.33 (s, 1C), 27.18 (s, 1C), 25.64 (s, 1C). LCMS calculated for $C_{30}H_{30}F_9N_2O_5S$ [$M+H$]⁺: m/z 701.2; found: 701.2. High resolution MS calculated for $C_{30}H_{30}F_9N_2O_5S$ [$M+H$]⁺ m/z 701.1726; found: 701.1708 (-2.59 ppm). HPLC (method A) t_R 2.232 min, purity 100%; (method B) t_R 2.187 min, purity 99.3%.

A minor side product, (3*R*,5*S*)-3-fluoro-5-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-1-(1-hydroxy-2-methylpropan-2-yl)pyrrolidin-2-one, was isolated similarly from the HPLC fractions from the minor, more polar, peak as a white solid (24 mg) in 12% yield. ¹H NMR (500 MHz, DMSO-*d*₆) mixture of amide rotamers, ratio about 5:1. δ 7.88 (d, *J*=8.2 Hz, 1H), 7.65 (d, *J*=8.8 Hz, 1H), 7.37 - 7.11 (m, 5H), 5.33 - 4.60 (m, 3H), 3.83 - 3.50 (m, 3H), 2.94 - 2.57 (m, 4H), 2.43 - 1.12 (m, 6H), 1.11 - 0.93 (m, 6H). LCMS *m/z* 701.3 (M+H)⁺.

1-((3*R*,5*S*)-3-Fluoro-5-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-2-oxopyrrolidin-1-yl)-2-methylpropan-2-yl dihydrogen phosphate (19)



Step 1: Dibenzyl (1-((3*R*,5*S*)-3-fluoro-5-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-2-oxopyrrolidin-1-yl)-2-methylpropan-2-yl) phosphate (**38**)



To a mixture of **18** (0.270 g, 0.385 mmol) and 5-methyl-1*H*-tetrazole (0.194 g, 2.31 mmol) in DCM (7.71 mL), which was purged with N₂ and cooled in an ice bath, was added dibenzyl diisopropylphosphoramidite (0.423 mL, 1.16 mmol) and the resulting mixture was stirred at 0 °C for 5 min, then at rt overnight. After 22 h, LCMS showed one major peak

corresponding to the intermediate dibenzyl (1-((3*R*,5*S*)-3-fluoro-5-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-2-oxopyrrolidin-1-yl)-2-methylpropan-2-yl) phosphite, *m/z* 945.3 (M+H)⁺. The mixture was cooled again in an ice bath and 35% H₂O₂ (0.101 mL, 1.16 mmol) was added. After 1.5 h, the mixture was partitioned between EtOAc and saturated NaHCO₃. The organic phase was washed with 10% Na₂S₂O₃ and brine, dried over MgSO₄, filtered, and concentrated to afford a colorless syrup. This was purified by column chromatography on silica gel (40 g), eluting with EtOAc-hexanes (30-80%) to provide the product as a white glassy solid (0.33 g) in 89% yield. ¹H NMR (499 MHz, DMSO-*d*₆) showed a mixture of amide rotamers, ratio about 4:1. δ 7.95 (s, 1H), 7.85 - 7.75 (m, 1H), 7.67 - 7.58 (m, 1H), 7.43 - 7.30 (m, 11H), 7.23 - 7.18 (m, 3H), 5.39 - 5.22 (m, 1H), 5.11 - 4.98 (m, 4H), 4.88 - 4.75 (m, 1H), 4.68 (dd, *J*=11.7, 5.0 Hz, 1H), 3.89 - 3.81 (m, 1H), 3.71 - 3.60 (m, 2H), 3.19 (ddd, *J*=14.6, 7.9, 3.0 Hz, 1H), 2.69 - 2.55 (m, 3H), 2.45 - 2.38 (m, 1H), 2.33 - 2.18 (m, 2H), 1.83 - 1.72 (m, 1H), 1.52 - 1.44 (m, 6H), 1.36 - 1.25 (m, 1H). LCMS *m/z* 961.3 (M+H)⁺.

Step 2: 1-((3*R*,5*S*)-3-fluoro-5-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-2-oxopyrrolidin-1-yl)-2-methylpropan-2-yl dihydrogen phosphate

To a solution of the material from Step 1 (0.33 g, 0.343 mmol) in 1:1 MeOH-EtOAc (17.2 ml) under N₂ was added 10% Pd-C (0.091 g, 0.086 mmol). The mixture was stirred under a balloon of H₂ overnight. After 17 h, the mixture was filtered and the filtrates were concentrated. The residue was purified by preparative HPLC (method G). The appropriate fractions were partially concentrated and the aqueous residue was lyophilized overnight. The product was obtained as a white solid (212 mg) in 78% yield. ¹H NMR (499 MHz, MeOH-*d*₄) showed a mixture of amide rotamers, ratio about 5:1. δ 8.04 - 7.90 (m, 1H), 7.69 - 7.59 (m, 1H), 7.41 - 7.33 (m, 2H), 7.32 - 7.23 (m, 1H), 7.14 - 7.05 (m, 2H), 5.56 - 5.30 (m, 1H), 5.23 - 5.14 (m, 1H), 4.89 (dd, *J*=12.2, 5.0 Hz, 1H), 4.42 - 3.48 (m, 4H), 3.15 - 2.36 (m, 6H), 2.18 - 1.89 (m, 1H), 1.58 (m, 7H). ¹³C NMR (126 MHz, DMSO-*d*₆, major rotamer) δ 170.95 (d, *J* = 20.0 Hz, 1C), 170.05 (s, 1C), 165.61 (d, *J* = 255.2 Hz, 1C), 141.19 (s, 1C), 136.00 (s, 1C), 132.94 (d, *J* = 10.9 Hz, 2C), 131.45 (s, 1C), 131.25 (s, 1C), 125.52 (br d, *J* = 20.9 Hz, 1C), 125.14 (d, *J* = 11.8 Hz, 1C), 123.76 (d, *J* = 10.0 Hz, 1C), 122.14 - 118.92 (m, 2C), 116.58 (d, *J* = 22.7 Hz, 2C), 92.24 - 90.23 (m, 1C), 88.25 (d, *J* = 180.7 Hz, 1C), 81.38 (s, 1C), 74.21 (s, 1C), 59.61 (s, 1C), 56.44 (d, *J* = 4.5 Hz, 1C), 52.08 (d, *J* = 9.1 Hz, 1C), 45.25 (s, 1C), 33.31 (s, 1C), 31.01 (d, *J* = 20.0 Hz, 1C), 27.17 (s, 1C), 26.09 (s, 1C), 25.41 (s, 1C), 24.37 (s, 1C). LCMS calculated for C₃₀H₃₁F₉N₂O₈PS [M+H]⁺: *m/z* 781.1, [M+H-H₃PO₄]⁺: *m/z* 683.2; found: 781.1, 683.1. High resolution MS calculated for C₃₀H₃₁F₉N₂O₈PS [M+H]⁺ *m/z* 781.1390; found: 781.1379 (-1.31 ppm). HPLC (method C) *t*_R 8.413 min, purity 99.3%; (method D) *t*_R 7.916 min, purity 99.2%.

References

1. Marcoux, D.; Duan, J. J. W.; Shi, Q.; Cherney, R. J.; Srivastava, A. S.; Cornelius, L.; Batt, D. G.; Liu, Q.; Beaudoin-Bertrand, M.; Weigelt, C. A.; Khandelwal, P.; Vishwakrishnan, S.; Selvakumar, K.; Karmakar, A.; Gupta, A. K.; Basha, M.; Ramlingam, S.; Manjunath, N.; Vanteru, S.; Karmakar, S.; Maddala, N.; Vetrichelvan, M.; Gupta, A.; Rampulla, R. A.; Mathur, A.; Yip, S.; Li, P.; Wu, D.-R.; Khan, J.; Ruzanov, M.; Sack, J. S.; Wang, J.; Yarde, M.; Cvijic, M. E.; Li, S.; Shuster, D. J.; Borowski, V.; Xie, J. H.; McIntyre, K. W.; Obermeier, M. T.; Fura, A.; Stefanski, K.; Cornelius, G.; Hynes, J.; Tino, J. A.; Macor, J. E.; Salter-Cid, L.; Denton, R.; Zhao, Q.; Carter, P. H.; Dhar, T. G. M. Rationally designed, conformationally constrained inverse agonists of ROR γ t — identification of a potent, selective series with biologic-like in vivo efficacy. *J. Med. Chem.* **2019**, *62*, 9931.
2. Duan, J. J. W.; Lu, Z.; Jiang, B.; Stachura, S.; Weigelt, C. A.; Sack, J. S.; Khan, J.; Ruzanov, M.; Galella, M. A.; Wu, D.-R.; Yarde, M.; Shen, D. R.; Shuster, D. J.; Borowski, V.; Xie, J. H.; Zhang, L.; Vanteru, S.; Gupta, A. K.; Mathur, A.; Zhao, Q.; Foster, W.; Salter-Cid, L. M.; Carter, P. H.; Dhar, T. G. M. Structure-based discovery of phenyl (3-phenylpyrrolidin-3-yl)sulfones as selective, orally active ROR γ t inverse agonists. *ACS Med. Chem. Lett.* **2019**, *10*, 367.