Discovery of BMS-986251: A Clinically Viable, Potent, and Selective RORγt Inverse Agonist

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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 Table 3 were performed in an analogous manner to the following literature procedures: selectivity (PXR, LXRα, and LXRβ),[1] recombinant cytochrome P450,[2] protein binding (human, mouse, and rat).[3] 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. ^{1}H NMR were obtained on a Bruker spectrometer (operating at 400 MHz or 500 MHz), and the signals are reported in ppm's relative to TMS (NMR abbreviations: s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, quin = quintuplet, sep = septet, m = multiplet). All mass spectra were recorded using electrospray ionization (ESMS) in the positive (pos) mode unless otherwise noted. All assayed compounds have a purity of >90% as assessed by analytical HPLC.

HPLC Conditions:

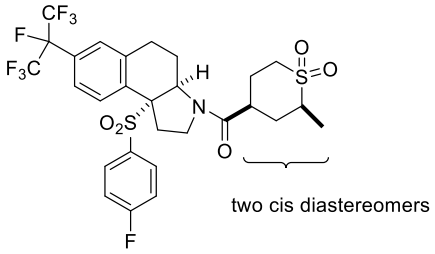
Method A: (analytical)

Column: Waters Acquity UPLC BEH C_{18} (2.1 x 50 mm, 1.7 μm); mobile phase A: water with 0.05% TFA; mobile phase B: MeCN with 0.05% TFA; temperature: 50 °C; flow rate 0.80 mL/min; gradient: 2-98% B over 1 min, then 0.5 min isocratic at 98% B.

Method B: (preparative)

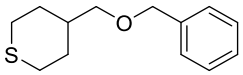
Column: XBridge C_{18} (19 x 200 mm, 5 μm); mobile phase A: 5:95 MeCN:water with 10 mM NH_4OAc; mobile phase B: 95:5 MeCN:water with 10 mM NH_4OAc; flow rate 20 mL/min; gradient: 20 min, then 5 min isocratic at 100% B.

((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[e]indol-3-yl)((2*R*/*S*,4*R*/*S*)-2-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methanone (Compound 3 and 4)



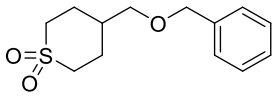
3 1st diastereomer
4 2nd diastereomer

Step 1: 4-((benzyloxy(methyl)tetrahydro-2*H*-thiopyran



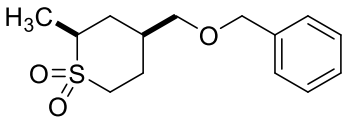
A suspension of NaH (60% in mineral oil; 1.23 g, 30.9 mmol) in DMF (50 mL) at 0 °C was treated portionwise with a solution of (tetrahydro-2*H*-thiopyran-4-yl)methanol (3.4 g, 25.7 mmol) in DMF (2 mL) and the mixture was stirred for 15 min. Benzyl bromide (3.36 mL, 28.3 mmol) was added dropwise over 2 min, and the mixture was left to warm to rt. After 1.5 h, the mixture was treated with saturated aqueous NH_4Cl (20 mL), diluted with water (50 mL) and extracted with EtOAc (75 mL). The organic phase was washed sequentially with 10% aqueous LiCl (3x30 mL) and brine (30 mL), dried over Na_2S0_4 and concentrated. The residue was purified by column chromatography on silica gel (120 g), eluting with EtOAc/hexanes (gradient from 0-10%), to give 4-((benzyloxy(methyl)tetrahydro-2*H*-thiopyran as a colorless oil (3.4 g, 60%): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43-7.27 (m, 5H), 4.50 (s, 2H), 3.31 (d, *J*=6.4 Hz, 2H), 2.75-2.66 (m, 2H), 2.66-2.57 (m, 2H), 2.16-2.07 (m, 2H), 1.79-1.62 (m, 1H), 1.51-1.34 (m, 2H).

Step 2: 4-((benzyloxy(methyl)tetrahydro-2*H*-thiopyran 1,1-dioxide



A solution of 4-((benzyloxy(methyl)tetrahydro-2*H*-thiopyran (4.7 g, 21.14 mmol) in DCM (125 mL) at 0 °C was treated portionwise with m-CPBA (77%; 9.95 g, 44.4 mmol) and the ice bath was removed to allow the mixture to warm to rt. After 2 h, the mixture was cooled to 0 °C, filtered and the filtrate was stirred at rt for 10 min with 10% aqueous $Na_2S_2O_3$ (120 mL). The organic phase was separated and washed with 10% aqueous K_2CO_3 (2x150 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (120 g), eluting with EtOAc/hexanes (gradient from 0-60%), to give 4-((benzyloxy)methyl)tetrahydro-2*H*-thiopyran 1,1-dioxide as a white solid (4.9 g, 91%): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42-7.28 (m, 5H), 4.51 (s, 2H), 3.43-3.30 (m, 2H), 3.14-2.87 (m, 4H), 2.20 (d, *J*=11.9 Hz, 2H), 2.00-1.76 (m, 3H).

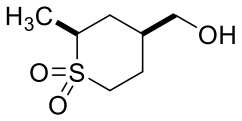
Step 3: (2*R*/*S*,4*R*/*S*)-4-((benzyloxy)methyl)-2-methyltetrahydro-2*H*-thiopyran 1,1-dioxide (*cis*-racemic)



cis-racemic

A solution of diisopropylamine (0.58 mL, 4.1 mmol) in THF (12 mL) under nitrogen was cooled to -78 °C and treated dropwise with *n*-butyllithium (2.4 M in hexanes; 1.6 mL, 3.7 mmol) and the mixture was stirred for 30 min, then at rt for 15 min. The mixture was cooled to -78 °C, treated over 3 min with a solution of 4-((benzyloxy)methyl)tetrahydro-2*H*-thiopyran 1,1-dioxide (1.0 g, 3.9 mmol) in THF (5 mL) and stirred for 1 h. The mixture was then treated with a solution of iodomethane (0.26 mL, 4.1 mmol) in THF (0.5 mL).[4] After 45 min, the cooling bath was removed and the mixture was allowed to warm to rt, and then was stirred for 1 h. The mixture was treated with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (2x50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (80 g), eluting with EtOAc/hexanes (gradient from 0-35%) to give *cis*-racemic (2*R*/*S*,4*R*/*S*)-4-((benzyloxy)methyl)-2-methyltetrahydro-2*H*-thiopyran 1,1-dioxide as a white solid (450 mg, 43%): LCMS m/z = 290.8 $(M+Na)^+$. HPLC t_R = 0.81 min (Method A). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41-7.28 (m, 5H), 4.51 (s, 2H), 3.33 (d, *J*=6.2 Hz, 2H), 3.12 (dt, *J*=14.3, 3.4 Hz, 1H), 3.04-2.87 (m, 2H), 2.23-2.12(m, 1H), 2.11-2.03 (m, 1H), 2.00-1.76 (m, 2H), 1.69-1.59 (m, 1H), 1.35 (d, *J*=6.8 Hz, 3H).

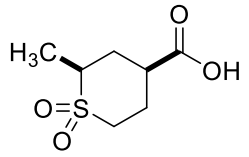
Step 4: (2*R*/*S*,4*R*/*S*)-4-(hydroxymethyl)-2-methyltetrahydro-2*H*-thiopyran 1,1-dioxide (*cis*-racemic)



cis-racemic

A solution of (2*R*/*S*,4*R*/*S*)-4-((benzyloxy(methyl)-2-methyltetrahydro-2*H*-thiopyran 1,1-dioxide (0.45 g, 1.68 mmol) in MeOH (2 mL) and ethanol (10 mL) was treated with palladium on carbon (160 mg, 0.075 mmol) and stirred under a hydrogen atmosphere (balloon pressure) for 1.5 h. The mixture was filtered to remove the catalyst and the filtrate was concentrated to give (2*R*/*S*,4*R*/*S*)-4-(hydroxymethyl)-2-methyltetrahydro-2*H*-thiopyran 1,1-dioxide as a white solid (280 mg, 94%): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.53 (d, *J*=5.7 Hz, 1H), 3.20-3.09 (m, 1H), 3.06-2.85 (m, 2H), 2.24-2.12 (m, 1H), 2.10-2.00 (m, 2H), 1.92-1.73 (m, 2H), 1.67-1.52 (m, 1H), 1.36 (d, *J*=6.8 Hz, 3H).

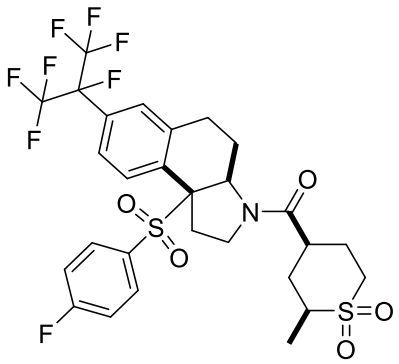
Step 5: (2*R*/*S*,4*R*/*S*)-2-methyltetrahydro-2*H*-thiopyran-4-carboxylic acid 1,1-dioxide (*cis*-racemic)



cis-racemic

A solution of (2*R*/*S*,4*R*/*S*)-4-(hydroxymethyl)-2-methyltetrahydro-2*H*-thiopyran 1,1-dioxide (0.275 g, 1.5 mmol) in MeCN (0.9 mL) and CCl_4 (0.9 mL) was treated with a solution of sodium periodate (1.353 g, 6.33 mmol) in water (1.3 mL), then with ruthenium(III) chloride hydrate (0.014 g, 0.062 mmol), and the mixture was stirred at rt. After 30 min, the mixture was a yellow emulsion, and stirring was continued at rt for 30 min with periodic sonication. An additional portion of ruthenium(III) chloride hydrate (0.014 g, 0.062 mmol) was added, and stirring was continued for 1 h with occasional sonication. The mixture was diluted with EtOAc (125 mL). The organic phase was separated and washed with water (25 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was treated with EtOAc (125 mL) and MeOH (10 mL), filtered (Acrodisc syringe filter) and concentrated to give (2*R*/*S*,4*R*/*S*)-2-methyltetrahydro-2*H*-thiopyran-4-carboxylic acid 1,1-dioxide as a gray solid (165 mg, 56%), used without further purification: ^{1}H NMR (400 MHz, Methanol-d_4) δ 3.28-3.04 (m, 3H), 2.69 (tt, *J*=12.4, 3.3 Hz, 1H), 2.37 (d quin, *J*=14.1, 3.5 Hz, 1H), 2.28 (dq, *J*=14.2, 3.2 Hz, 1H), 2.18-2.03 (m, 1H), 1.86 (dt, *J*=14.3, 12.5 Hz, 1H), 1.29 (d, *J*=6.8 Hz, 3H).

Step 6 (final step): <u>((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-4,5-dihydro-1*H*-benzo[e]indol-3(2*H*,3a*H*,9b*H*)-yl)((2*R*/*S*,4*R*/*S*)-2-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)</u> (3 and 4)



3 First Diastereomer
4 Second Diastereomer

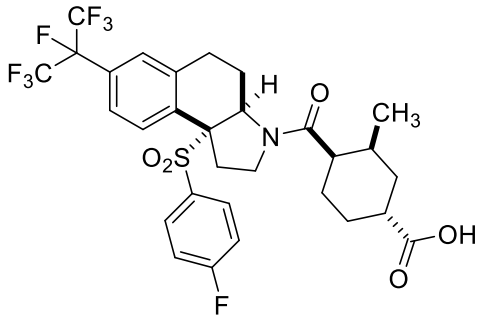
A solution of (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole **12** (125 mg, 0.23 mmol), (2*R*/*S*,4*R*/*S*)-2-methyltetrahydro-2*H*-thiopyran-4-carboxylic acid 1,1-dioxide (49.3 mg, 0.26 mmol, *cis*-racemic from above), DIPEA (0.12 mL, 0.7 mmol) and BOP (119 mg, 0.27 mmol) was stirred at rt overnight. The mixture was diluted with EtOAc (50 mL), washed with 1 M HCl (3x50 mL) and brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluted with 0-80% EtOAc/hexanes, $KMnO_4$ TLC staining) to give ((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-4,5-dihydro-1*H*-benzo[e]indol-3(2*H*,3a*H*,9b*H*)-yl)((2*R*/*S*,4*R*/*S*)-2-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-

yl) (110 mg, 0.16 mmol, 70.0%) as a pair of diastereomers as an off-white solid. The crude product was purified by preparative supercritical fluid chromatography (SFC) (column: Chiralpak IC, 3 x 25 cm, 5-µm particles; mobile phase CO_2/MeOH (72/28); Flow: 160 mL/min; monitored at 212 nm) to give **3** and **4**.

First diastereomer (Compound 3, preparative retention time = 3.7 min**)** (31 mg, 0.046 mmol, 20%): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (d, *J*=8.4 Hz, 1H), 7.59 (d, *J*=8.4 Hz, 1H), 7.23 (dd, *J*=8.8, 5.1 Hz, 2H), 7.18 (s, 1H), 6.94 (t, *J*=8.6 Hz, 2H), 4.73 (dd, *J*=12.1, 4.8 Hz, 1H), 4.12-3.95 (m, 1H), 3.88-3.77 (m, 1H), 3.67 (dd, *J*=14.7, 6.4 Hz, 1H), 3.24 (dt, *J*=14.3, 3.5 Hz, 1H), 3.17-2.94 (m, 2H), 2.77-2.59 (m, 2H), 2.59-2.44 (m, 3H), 2.29-2.20 (m, 2H), 2.17 (d, *J*=14.7 Hz, 1H), 1.84 (t, *J*=13.5 Hz, 1H), 1.45 (d, *J*=6.6 Hz, 3H), 1.21 (qd, *J*=12.5, 2.6 Hz, 1H). LCMS calculated for $C_{28}H_{28}F_8NO_5S_2$ $[M+H]^+$: m/z = 674.13; found: 674.10. Analytical HPLC t_R = 4.3 min (SFC; column: Chiralpak IC, 0.46 x 25 cm, 5-µm particles; mobile phase CO_2/MeOH (70/30); Flow: 3 mL/min; monitored at 200-400 nm).

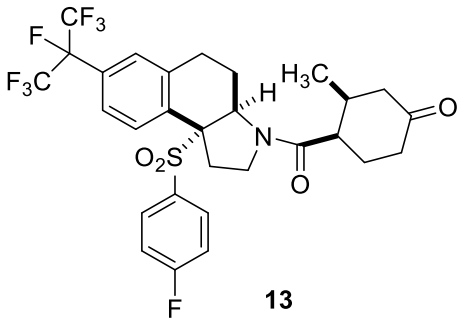
Second diastereomer (Compound 4, preparative retention time = 5.1 min**)** (28 mg, 0.042 mmol, 18%): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 (d, *J*=8.4 Hz, 1H), 7.58 (d, *J*=8.4 Hz, 1H), 7.21 (dd, *J*=8.8, 4.8 Hz, 2H), 7.16 (s, 1H), 6.92 (t, *J*=8.5 Hz, 2H), 4.71 (dd, *J*=12.0, 4.7 Hz, 1H), 4.09-3.98 (m, 1H), 3.88-3.76 (m, 1H), 3.71-3.57 (m, 1H), 3.26 (dt, *J*=14.3, 3.5 Hz, 1H), 3.13-2.95 (m, 2H), 2.74-2.60 (m, 2H), 2.59-2.43 (m, 3H), 2.42-2.22 (m, 2H), 2.07-1.95 (m, 1H), 1.81 (t, *J*=13.4 Hz, 1H), 1.40 (d, *J*=6.8 Hz, 3H), 1.25-1.10 (m, 1H); LCMS calculated for $C_{28}H_{28}F_8NO_5S_2$ $[M+H]^+$: m/z = 674.13, found: 674.10; Analytical HPLC t_R = 6.0 min (SFC; column: Chiralpak IC, 0.46 x 25 cm, 5-µm particles; mobile phase CO_2/MeOH (70/30); Flow: 3 mL/min; monitored at 200-400 nm).

(1*R*,3*S*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylic acid (5)



5

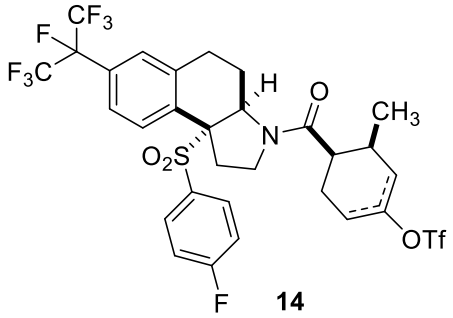
Step 1: (3*S*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-3-methylcyclohexan-1-one **13**



13

To a solution of (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole **12** (160 mg, 0.32 mmol) in DMF (1.5 mL) was added (1*R*,2*S*)-2-methyl-4-oxocyclohexanecarboxylic acid[5] (100 mg, 0.32 mmol), HATU (122 mg, 0.32 mmol), and 4-methylmorpholine (0.11 mL, 0.96 mmol). This was stirred overnight before EtOAc was added along with brine. The organic layer was washed with brine (x3), 1N HCl, and sat $NaHCO_3$ aq solution before it was dried ($MgSO_4$), filtered, and concentrated to give crude (3*S*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-3-methylcyclohexan-1-one **13** (170 mg, 0.27 mmol, 83%): LCMS calculated for $C_{29}H_{28}F_8NO_4S$ $[M+H]^+$: m/z = 638.15, found: 638.3.

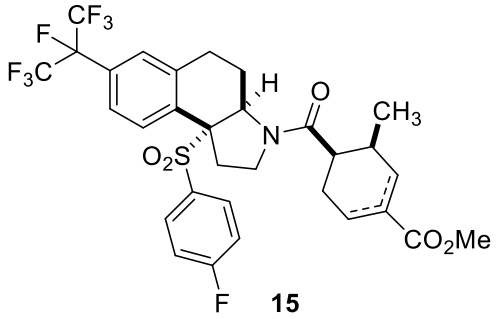
Step 2: Mixture of: (4*R*,5*S*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-5-methylcyclohex-1-en-1-yl trifluoromethanesulfonate and (3*S*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-3-methylcyclohex-1-en-1-yl trifluoromethanesulfonate **14**



14

To a solution of (3*S*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-3-methylcyclohexan-1-one **13** (120 mg, 0.19 mmol) in THF (2 mL) at -78 °C was added 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (101 mg, 0.28 mmol). Next, potassium bis(trimethylsilyl)amide (1 M solution in THF, 0.37 mL, 0.37 mmol) was added dropwise at -78 °C. After 30 min, the reaction was warmed to rt. This was quenched with water after 1.5 h at rt. This solution was extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. This provided a regioisomeric mixture of enol triflates (4*R*,5*S*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-5-methylcyclohex-1-en-1-yl trifluoromethanesulfonate and (3*S*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-3-methylcyclohex-1-en-1-yl trifluoromethanesulfonate **14** (111 mg, 0.14 mmol, 77%): LCMS calculated for $C_{30}H_{27}F_{11}NO_6S_2$ $[M+H]^+$: m/z = 770.10, found: 770.4.

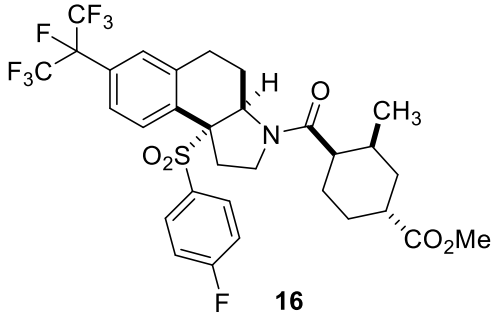
Step 3: Mixture of: methyl (4*R*,5*S*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-5-methylcyclohex-1-ene-1-carboxylate and methyl (3*S*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-3-methylcyclohex-1-ene-1-carboxylate **15**



15

To a solution of the mixture (4*R*,5*S*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-5-methylcyclohex-1-en-1-yl trifluoromethanesulfonate and (3*S*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-3-methylcyclohex-1-en-1-yl trifluoromethanesulfonate **14** (185 mg, 0.24 mmol) in DMF (1 mL) and MeOH (1 mL) was added palladium(II)acetate (5.4 mg, 0.02 mmol), 1,1'-bis(diphenylphosphino)ferrocene (13.3 mg, 0.02 mmol), and tributylamine (0.17 mL, 0.72 mmol). Carbon monoxide was bubbled through this solution for 10 min. The CO needle was taken out and a CO balloon was added via a needle through the vial septum. This solution was heated at 80 °C for 2 h. After cooling, EtOAc was added along with water. The organic layer was washed with brine (x3) before it was dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexane) to give a regioisomeric mixture of methyl (4*R*,5*S*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-5-methylcyclohex-1-ene-1-carboxylate and methyl (3*S*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-3-methylcyclohex-1-ene-1-carboxylate **15** (63 mg, 0.09 mmol, 38%): LCMS calculated for $C_{31}H_{30}F_8NO_5S$ $[M+H]^+$: m/z = 680.2, found: 680.5.

Step 4: methyl (1*R*,3*S*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylate **16**

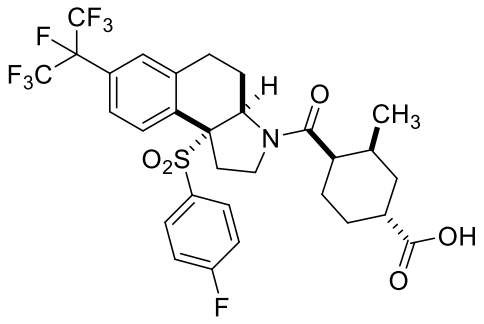


16

To a solution of the mixture methyl (4*R*,5*S*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-5-methylcyclohex-1-ene-1-carboxylate and methyl (3*S*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-

fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-3-methylcyclohex-1-ene-1-carboxylate **15** (36 mg, 0.05 mmol) in DCM (1.5 mL) was added Crabtree's catalyst (12.8 mg, 0.016 mmol) and a hydrogen balloon. This was then strirred overnight. The next day, the solution was filtered and concentrated to give crude methyl (1*R*,3*S*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylate **16** (36 mg, 0.053 mmol): LCMS calculated for $C_{31}H_{32}F_8NO_5S$ $[M+H]^+$: m/z = 682.2, found: 682.5.

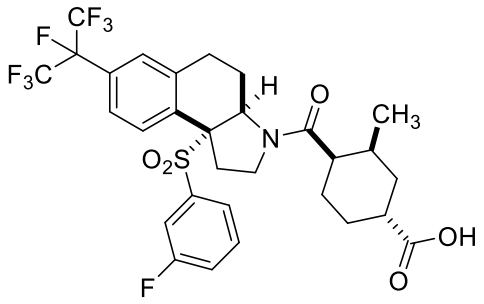
Step 5 (final step): **(1*R*,3*S*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylic acid 5**



5

To a solution of methyl (1*R*,3*S*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylate **16** (36 mg, 0.053 mmol) in THF (1.5 mL) and MeOH (0.5 mL) was added 1N LiOH (0.2 mL, 0.2 mmol). This was stirred overnight and then purified by preparative reverse-phase HPLC (Method B) to give (1*R*,3*S*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylic acid **5** (12.7 mg, 0.02 mmol, 36%): ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.98 (d, *J*=8.5 Hz, 1H), 7.62 (br d, *J*=8.4 Hz, 1H), 7.36-7.29 (m, 2H), 7.28-7.23 (m, 1H), 7.10-7.04 (m, 2H), 4.81-4.78 (m, 1H), 4.07-3.98 (m, 1H), 3.92-3.84 (m, 1H), 3.59-3.49 (m, 1H), 2.77-2.64 (m, 2H), 2.63-2.52 (m, 2H), 2.52-2.40 (m, 2H), 2.07-2.00 (m, 1H), 1.99-1.86 (m, 3H), 1.83-1.73 (m, 1H), 1.63-1.56 (m, 1H), 1.55-1.44 (m, 1H), 1.35-1.24 (m, 1H), 1.11-1.06 (d, 3H). LCMS calculated for $C_{30}H_{30}F_8NO_5S$ $[M+H]^+$: m/z = 668.17, found: 668.2. HPLC t_R = 1.05 min (Method A).

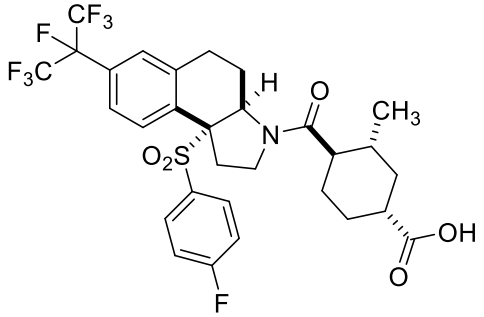
(1*R*,3*S*,4*R*)-4-((3a*R*,9b*R*)-9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylic acid 6



6

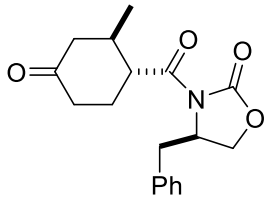
Starting with (3a*R*,9b*R*)-9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole (100 mg, 0.2 mmol) and (1*R*,2*S*)-2-methyl-4-oxocyclohexanecarboxylic acid[5] (40.7 mg, 0.26 mmol), compound **6** was synthesized in a manner analogous to compound **5**. Characterization of compound **6**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.00 (d, *J*=8.4 Hz, 1H), 7.63 (d, *J*=8.8 Hz, 1H), 7.50-7.34 (m, 2H), 7.30-7.18 (m, 2H), 6.81 (dd, *J*=8.1, 2.0 Hz, 1H), 4.87 (s, 1H), 4.12-3.98 (m, 1H), 3.89 (td, *J*=9.9, 3.1 Hz, 1H), 3.56 (ddd, *J*=14.7, 8.1, 2.5 Hz, 1H), 3.40-3.34 (m, 1H), 2.79-2.65 (m, 2H), 2.63-2.52 (m, 2H), 2.50-2.42 (m, 2H), 2.03 (d, *J*=9.0 Hz, 1H), 1.99-1.85 (m, 3H), 1.84-1.72 (m, 1H), 1.65-1.43 (m, 2H), 1.39-1.22 (m, 1H), 1.10 (d, *J*=7.0 Hz, 3H). LCMS calculated for $C_{30}H_{30}F_8NO_5S$ $[M+H]^+$: m/z = 668.17, found: 668.4. HPLC t_R = 1.06 min (Method A).

(1*R*,3*R*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylic acid 7



7

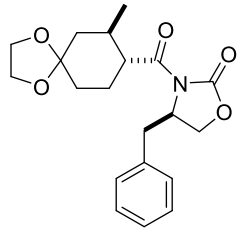
Step 1: (*R*)-4-benzyl-3-((1*R*,2*R*)-2-methyl-4-oxocyclohexane-1-carbonyl)oxazolidin-2-one



To a solution of (*R*,*E*)-4-benzyl-3-(but-2-enoyl)oxazolidin-2-one (8 g, 32.6 mmol) in DCM (40 mL) at -78 °C was added diethylaluminum chloride (1 M solution in hexane, 48.9 mL, 48.9 mmol). After 10 min, (buta-1,3-dien-2-yloxy)trimethylsilane (20.1 mL, 114 mmol) in DCM (5 mL) was added dropwise at -78 °C.[6,7] This solution was warmed to rt and stirred overnight. Then, 1:1 THF:6N HCl (8 mL total) was added. After 30 min, celite and EtOAc was added.

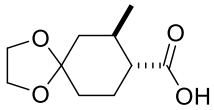
This mixture was filtered and the filtrate washed with brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexane) to give (*R*)-4-benzyl-3-((1*R*,2*R*)-2-methyl-4-oxocyclohexane-1-carbonyl)oxazolidin-2-one (1.2 g, 3.8 mmol, 12%): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38-7.28 (m, 3H), 7.24-7.19 (m, 2H), 4.74 (ddt, *J*=9.3, 7.4, 3.2 Hz, 1H), 4.32-4.20 (m, 2H), 3.79 (td, *J*=10.7, 3.4 Hz, 1H), 3.26 (dd, *J*=13.4, 3.3 Hz, 1H), 2.82 (dd, *J*=13.4, 9.5 Hz, 1H), 2.54-2.44 (m, 3H), 2.42-2.27 (m, 2H), 2.16 (dd, *J*=14.0, 12.7 Hz, 1H), 1.90-1.76 (m, 1H), 1.02 (d, *J*=6.4 Hz, 3H). LCMS m/z = 316.2 $(M+H)^+$; HPLC t_R = 0.87 min (Method A).

Step 2. (*R*)-4-benzyl-3-((7*R*,8*R*)-7-methyl-1,4-dioxaspiro[4.5]decane-8-carbonyl)oxazolidin-2-one



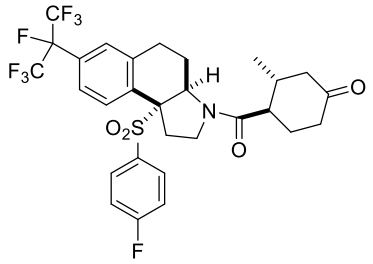
A solution of (*R*)-4-benzy1-3-((1*R*, 2*R*)-2-methyl-4-oxocyclohexanecarbonyl)oxazolidin-2-one (1.0 g, 3.2 mmol) was dissolved in DCM (10 mL) and cooled to 0 °C. The mixture was treated with 2,2,7,7-tetramethy1-3,6-dioxa-2,7-disilaoctane (0.97 mL, 3.9 mmol), stirred for 5 min, then treated with trimethylsilyl trifluoromethanesulfonate (0.06 mL, 0.32 mmol). The mixture was warmed to rt and stirred overnight. Et_3N (0.075 mL, 0.54 mmol) was added, followed by saturated aqueous $NaHCO_3$. The mixture was extracted with DCM, and the organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel (eluting with EtOAc/hexanes) to give (*R*)-4-benzyl-3-((7*R*,8*R*)-7-methyl-1,4-dioxaspiro[4.5]decane-8-carbonyl)oxazolidin-2-one (750 mg, 66%): LCMS m/z = 360.3 $(M+H)^+$. HPLC t_R = 0.94 min (Method A).

Step 3. (7*R*,8*R*)-7-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylic acid



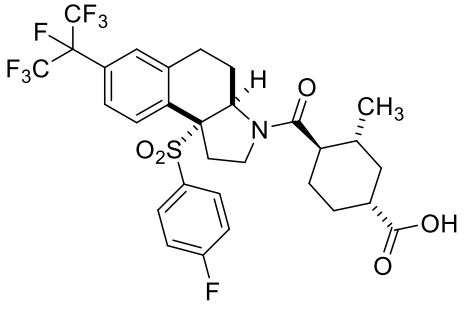
A solution of (*R*)-4-benzy1-3-((7*R*,8*R*)-7-methyl-1,4-dioxaspiro[4.5]decane-8-carbonyl)oxazolidin-2-one (750 mg, 2.1 mmol) in THF (15 mL) was cooled to 0 °C and treated with 35% aqueous hydrogen peroxide (0.85 mL, 8.3 mmol). After 5 min, 1 M aqueous LiOH (4.2 mL, 4.2 mmol) was added and the mixture was stirred for 2 h. Saturated aqueous Na_2SO_3 and saturated aqueous $NaHCO_3$ were added followed by water. The mixture was partially concentrated, and the aqueous residue was extracted with DCM (3x). The aqueous phase was acidified with 6 M aqueous HCl and extracted with EtOAc. This organic phase was dried over $MgSO_4$, filtered and concentrated to give crude (7*R*,8*R*)-7-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylic acid (290 mg, 69%), used without further purification: LCMS m/z = 201.1 $(M+H)^+$. HPLC t_R = 0.60 min (Method A).

Step 4. (3*R*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-3-methylcyclohexan-1-one



A solution of (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-l*H*-benzo[e]indole **12** (100 mg, 0.2 mmol) in DMF (1.5 mL) was treated with (7R,8R)-7-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylic acid (40 mg, 0.2 mmol), HATU (76 mg, 0.2 mmol), and 4-methylmorpholine (0.07 mL, 0.6 mmol). The mixture was stirred overnight, then diluted with EtOAc and saturated brine. The organic layer was removed, and washed sequentially with brine (3x), 1 M aqueous HCl and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated to give a mixture of ((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[e]indo1-3-yl)((7*R*,8*R*)-7-methyl-1,4-dioxaspiro[4.5]decan-8-yl)methanone (LCMS m/z = 682.3 $(M+H)^+$, HPLC t_R = 1.11 min, Method A) and (3*R*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro- 1*H*-benzo[e]indole-3-carbonyl)-3-methylcyclohexan-1-one (LCMS m/z = 638.3 $(M+H)^+$, HPLC t_R = 1.07 min, Method A). The material was dissolved in THF (2 mL), treated with 6 M aqueous HCl (1 mL) and stirred at rt overnight. The mixture was extracted with EtOAc, and the organic phase was washed sequentially with brine (3x), 1 M aqueous HCl and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (eluting with EtOAc/hexanes) to give (3*R*,4*R*)-4-((3a*R*, 9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-3-methylcyclohexan-1-one (48 mg, 38%): LCMS m/z = 638.3 $(M+H)^+$. HPLC t_R = 1.06 min (Method A).

Step 5: (final step) (1*R*,3*R*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylic acid 7

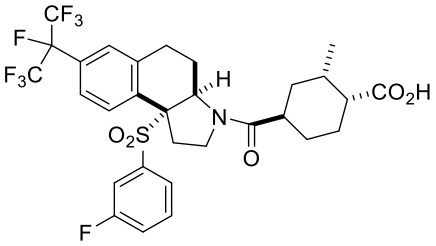


7

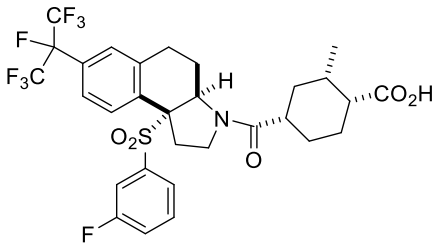
Starting with (3*R*,4*R*)-4-((3a*R*, 9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-3-methylcyclohexanone (ketone from above), compound **7** was synthesized in a manner analogous to compound **5**. Characterization of compound **7**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.98 (d, *J*=8.6 Hz, 1H), 7.62 (br d, *J*=8.4 Hz, 1H), 7.39-7.30 (m, 2H), 7.25 (s, 1H), 7.07 (t, *J*=8.7 Hz, 2H), 4.85 (br d, *J*=5.1 Hz, 1H), 4.11-4.00

(m, 1H), 3.87 (td, *J*=9.7, 2.3 Hz, 1H), 3.56 (ddd, *J*=14.9, 7.9, 2.1 Hz, 1H), 2.79-2.19 (m, 6H), 2.04 (br dd, *J*=13.0, 2.4 Hz, 2H), 1.95-1.79 (m, 3H), 1.59-1.39 (m, 1H), 1.35-1.16 (m, 2H), 1.04 (d, *J*=6.4 Hz, 3H). LCMS calculated for $C_{30}H_{30}F_8NO_5S$ $[M+H]^+$: m/z = 668.17, found: 668.3. HPLC t_R = 1.05 min (Method A).

(1*R*,2*S*,4*R*)-4-((3a*R*,9b*R*)-9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid (**8**) and (1*R*,2*S*,4*S*)-4-((3a*R*,9b*R*)-9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid (**9**)

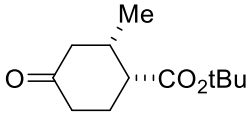


8



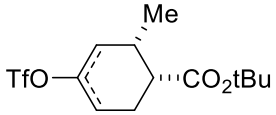
9

Step 1: *tert*-butyl (1*R*,2*S*)-2-methyl-4-oxocyclohexane-1-carboxylate



To a solution of (1*R*,2*S*)-2-methyl-4-oxocyclohexanecarboxylic acid[5] (150 mg, 0.96 mmol) in *tert*-butanol (2.5 mL) and THF (2.5 mL) was added (*E*)-*tert*-butyl N,N'-diisopropylcarbamimidate (385 mg, 1.9 mmol). This was stirred overnight, before it was filtered and concentrated. The resulting residue was dissolved in Et_2O and filtered again. The filtrate was concentrated. The resulting residue was purified by column chromatography on silica gel (eluting: 100% hexane to 10% EtOAc/hexanes) to give the desired product *tert*-butyl (1*R*,2*S*)-2-methyl-4-oxocyclohexane-1-carboxylate (62 mg, 0.3 mmol, 30%). LCMS m/z = 157.1 $(M+H-tBu)^+$. HPLC t_R = 0.9 min (Method A).

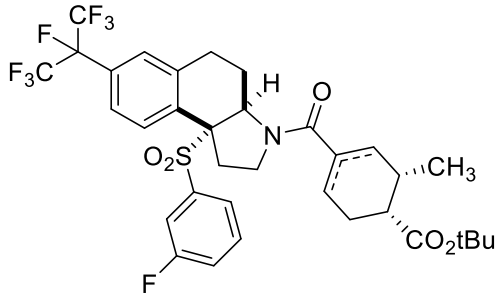
Step 2: Mixture of: *tert*-butyl (1*R*,6*S*)-6-methyl-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-ene-1-carboxylate and *tert*-butyl (1*R*,2*S*)-2-methyl-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-ene-1-carboxylate



To a solution of *tert*-butyl (1*R*,2*S*)-2-methyl-4-oxocyclohexane-1-carboxylate (50 mg, 0.2 mmol) in THF (2mL) at -78 °C was added 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (93 mg, 0.26 mmol). Next, potassium bis-(trimethylsilyl)amide (1 M in THF solution, 0.31 mL, 0.31 mmol) was added dropwise at -78 °C. After 30 min, the reaction was warmed to rt. This was quenched with water after 1.5 h at rt. This solution was extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated. An ^1H NMR of the resulting residue showed only a 50% conversion to the enol triflate (starting material was the other half). As a result, the 50:50 mixture was dissolved in THF (2 mL) and 1,1,1-trifluoro-N-phenyl-N-

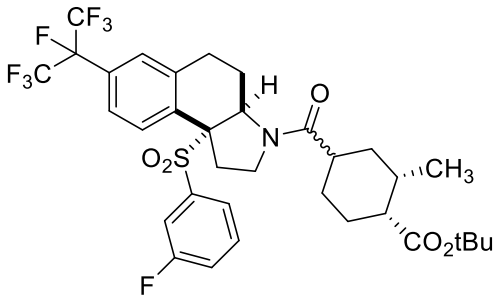
((trifluoromethyl)sulfonyl)methanesulfonamide (93 mg, 0.26 mmol) was added. After cooling to -78 °C, potassium bis-(trimethylsilyl)amide (1 M solution in THF solution, 0.31 mL, 0.31 mmol) was added. After 15 min at -78 °C, the solution was warmed to rt over 20 min. This was quenched with water, and this solution was extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated. This provided a regioisomeric mixture of crude enol triflates *tert*-butyl (1*R*,6*S*)-6-methyl-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-ene-1-carboxylate and *tert*-butyl (1*R*,2*S*)-2-methyl-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-ene-1-carboxylate (80 mg, 0.23 mmol, 99%): LCMS m/z = 367.1 $(M+Na)^+$. HPLC t_R = 1.15 min (Method A).

Step 3: Mixture of: *tert*-butyl (1*R*,6*S*)-4-((3a*R*,9b*R*)-9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-6-methylcyclohex-3-ene-1-carboxylate and *tert*-butyl (1*R*,2*S*)-4-((3a*R*,9b*R*)-9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohex-3-ene-1-carboxylate



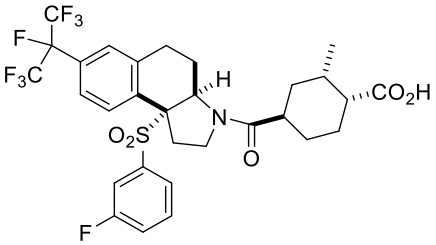
To a solution of the mixture *tert*-butyl (1*R*,6*S*)-6-methyl-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-ene-1-carboxylate and *tert*-butyl (1*R*,2*S*)-2-methyl-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-ene-1-carboxylate (80 mg, 0.23 mmol) in DMF (1.5 mL) was added (3a*R*,9b*R*)-9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole (116 mg, 0.23 mmol) and tributylamine (0.17 mL, 0.7 mmol). Carbon monoxide was bubbled through this solution for 5 min. Next, bis(triphenylphosphine)palladium(II)dichloride (8.15 mg, 0.012 mmol) was added and again CO was bubbled through the solution for 5 min. The CO needle was taken out and a CO balloon was added via a needle through the vial septum. This solution was heated at 98 °C for 2 h. After cooling, EtOAc was added along with water. The organic layer was washed with brine (x3) before it was dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexane) to give a regioisomeric mixture of t*ert*-butyl (1*R*,6*S*)-4-((3a*R*,9b*R*)-9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-6-methylcyclohex-3-ene-1-carboxylate and *tert*-butyl (1*R*,2*S*)-4-((3a*R*,9b*R*)-9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohex-3-ene-1-carboxylate (63 mg, 0.087 mmol, 38%): LCMS m/z = 722.5 $(M+H)^+$. HPLC t_R = 1.21 min (Method A).

Step 4: Mixture of: *tert*-butyl (1*R*,2*S*,4*R*)-4-((3a*R*,9b*R*)-9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylate and *tert*-butyl (1*R*,2*S*,4*S*)-4-((3a*R*,9b*R*)-9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylate



To a solution of the mixture *tert*-butyl (1*R*,6*S*)-4-((3a*R*,9b*R*)-9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-6-methylcyclohex-3-ene-1-carboxylate and *tert*-butyl (1*R*,2*S*)-4-((3a*R*,9b*R*)-9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohex-3-ene-1-carboxylate (30 mg, 0.042 mmol) in DCM (1.5 mL) was added Crabtree's catalyst (8 mg, 9.9 µmol) and a hydrogen balloon. This was then strirred overnight. The next day, the solution was filtered and concentrated to provide a crude mixture of two diastereomers *tert*-butyl (1*R*,2*S*,4*R*)-4-((3a*R*,9b*R*)-9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylate and *tert*-butyl (1*R*,2*S*,4*S*)-4-((3a*R*,9b*R*)-9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylate (25 mg, 0.035 mmol, 83%): LCMS m/z = 724.6 $(M+H)^+$. HPLC t_R = 1.23 min (Method A).

Step 5: (final step) (1*R*,2*S*,4*R*)-4-((3a*R*,9b*R*)-9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid (**8**) and (1*R*,2*S*,4*S*)-4-((3a*R*,9b*R*)-9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid (**9**)



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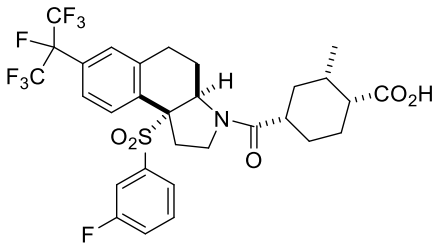

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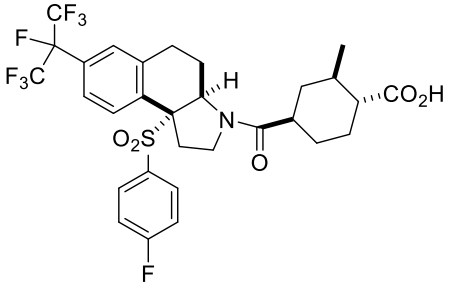
To a solution of the mixture of diastereomers *tert*-butyl (1*R*,2*S*,4*R*)-4-((3a*R*,9b*R*)-9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylate and *tert*-butyl (1*R*,2*S*,4*S*)-4-((3a*R*,9b*R*)-9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylate (25 mg, 0.035 mmol) in DCM (1 mL) was added TFA (3 mL). This was stirred for 30 min before it was concentrated. The resulting residue was purified on a preparative reverse-phase HPLC (column: Luna 30X100 mm, mobile phase A: 10:95 acetonitrile:water with 0.1% TFA; mobile phase B: 90:10 acetonitrile:water with 0.1% TFA, gradient: 20% B to 100%B over 10 min, then 100%B 10 min to 15 min, 30 mL/min, 220 wavelength, compound **8** t_R = 9.3 min and compound **9** t_R = 9.6 min): Compound **8** (1*R*,2*S*,4*R*)-4-((3a*R*,9b*R*)-9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid (9.5 mg, 0.014 mmol,

39%): ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.00 (d, *J*=8.4 Hz, 1H), 7.63 (d, *J*=8.6 Hz, 1H), 7.49-7.37 (m, 2H), 7.30-7.25 (m, 2H), 6.89 (dt, *J*=8.1, 1.9 Hz, 1H), 4.81-4.77 (m, 1H), 3.90 (dd, *J*=10.2, 5.4 Hz, 2H), 3.58 (dt, *J*=14.9, 5.2 Hz, 1H), 2.79-2.67 (m, 2H), 2.64-2.49 (m, 3H), 2.48-2.40 (m, 1H), 2.00-1.87 (m, 1H), 1.86-1.66 (m, 5H), 1.59-1.47 (m, 1H), 1.31 (qd, *J*=12.7, 3.2 Hz, 1H), 1.02 (d, *J*=7.0 Hz, 3H). LCMS calculated for $C_{30}H_{30}F_8NO_5S$ $[M+H]^+$: m/z = 668.17, found: 668.4. HPLC t_R = 1.06 min (Method A). Compound **9** (1*R*,2*S*,4*S*)-4-((3a*R*,9b*R*)-9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid (6.0 mg, 8.5 μmol, 25%): ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.00 (d, *J*=8.4 Hz, 1H), 7.63 (d, *J*=8.6 Hz, 1H), 7.48-7.36 (m, 2H), 7.31-7.25 (m, 2H), 6.87 (dt, *J*=8.2, 2.0 Hz, 1H), 4.80-4.78 (m, 1H), 4.01-3.82 (m, 2H), 3.57 (ddd, *J*=14.9, 8.0, 3.1 Hz, 1H), 2.72 (dt, *J*=14.8, 9.5 Hz, 1H), 2.65-2.51 (m, 4H), 2.49-2.39 (m, 1H), 2.17-2.08 (m, 1H), 2.02-1.64 (m, 5H), 1.52 (d, *J*=13.0 Hz, 1H), 1.37-1.23 (m, 1H), 1.07 (d, *J*=6.8 Hz, 3H). LCMS calculated for $C_{30}H_{30}F_8NO_5S$ $[M+H]^+$: m/z = 668.17, found: 668.3. HPLC t_R = 1.08 min (Method A).

(1*R*,2*R*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid (**10**) and **(1*R*,2*R*,4*S*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid** (**11**)



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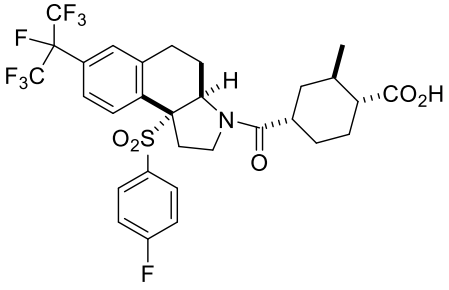

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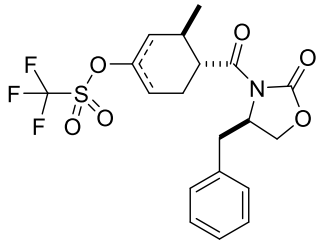
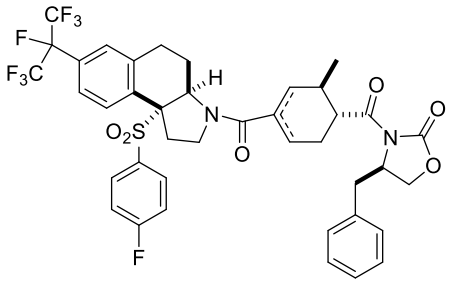
Step 1. Mixture of: (4*R*,5*R*)-4-((*R*)-4-benzyl-2-oxooxazolidine-3-carbonyl)-5-methylcyclohex-1-en-1-yl trifluoromethanesulfonate and (3*R*,4*R*)-4-((*R*)-4-benzyl-2-oxooxazolidine-3-carbonyl)-3-methylcyclohex-1-en-1-yl trifluoromethanesulfonate



To a solution of (*R*)-4-benzyl-3-((1*R*,2*R*)-2-methyl-4-oxocyclohexane-1-carbonyl)oxazolidin-2-one (120 mg, 0.38 mmol) in THF (2 mL) at -78 °C was added 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (204 mg, 0.57 mmol). Next, potassium bis-(trimethylsilyl)amide (1 M in THF solution, 0.68 mL, 0.68 mmol) was added dropwise at -78 °C. After 1 h, the reaction was quenched with water. This solution was extracted with Et_2O. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated. This provided a regioisomeric mixture of crude enol triflates (4R,5R)-4-((R)-4-benzyl-2-oxooxazolidine-3-carbonyl)-5-methylcyclohex-1-en-1-yl trifluoromethanesulfonate and (3R,4R)-4-((R)-4-benzyl-

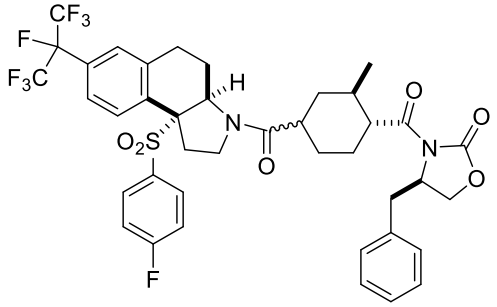
2-oxooxazolidine-3-carbonyl)-3-methylcyclohex-1-en-1-yl trifluoromethanesulfonate (165 mg, 0.37mmol): LCMS m/z = 448.0 $(M+Na)^+$.

Step 2. Mixture of: (*R*)-4-benzyl-3-((1*R*,6*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-6-methylcyclohex-3-ene-1-carbonyl)oxazolidin-2-one and (*R*)-4-benzyl-3-((1*R*,2*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohex-3-ene-1-carbonyl)oxazolidin-2-one



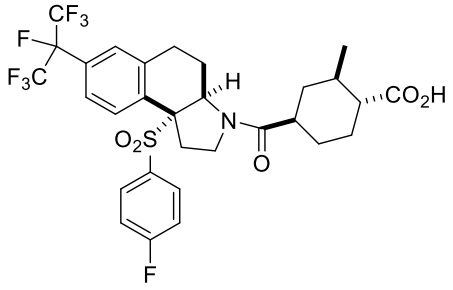
To a solution of regioisomeric mixture of enol triflates (4*R*,5*R*)-4-((*R*)-4-benzyl-2-oxooxazolidine-3-carbonyl)-5-methylcyclohex-1-en-1-yl trifluoromethanesulfonate and (3*R*,4*R*)-4-((*R*)-4-benzyl-2-oxooxazolidine-3-carbonyl)-3-methylcyclohex-1-en-1-yl trifluoromethanesulfonate (165 mg, 0.37 mmol) in DMF (1.5 mL) was added (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole **12** (226 mg, 0.37 mmol) and tributylamine (0.27 mL, 1.1 mmol). Carbon monoxide was bubbled through this solution for 5 min. Next, bis(triphenylphosphine)palladium(II)dichloride (12.9 mg, 0.018 mmol) was added and again CO was bubbled through the solution for 5 min. The CO needle was taken out and a CO balloon was added via a needle through the vial septum. This solution was heated at 98 °C for 2 h. After cooling, EtOAc was added along with water. The organic layer was washed with brine (x3) before it was dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexanes) to give a regioisomeric mixture of (*R*)-4-benzyl-3-((1*R*,6*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-6-methylcyclohex-3-ene-1-carbonyl)oxazolidin-2-one and (*R*)-4-benzyl-3-((1*R*,2*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohex-3-ene-1-carbonyl)oxazolidin-2-one (150 mg, 0.18 mmol, 49%): LCMS m/z = 825.7 $(M+H)^+$.

Step 3. Mixture of: (4*R*)-4-benzyl-3-((1*R*,2*R*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carbonyl)oxazolidin-2-one and (4*R*)-4-benzyl-3-((1*R*,2*R*,4*S*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carbonyl)oxazolidin-2-one



To a solution of regioisomeric mixture of (*R*)-4-benzyl-3-((1*R*,6*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-6-methylcyclohex-3-ene-1-carbonyl)oxazolidin-2-one and (*R*)-4-benzyl-3-((1*R*,2*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohex-3-ene-1-carbonyl)oxazolidin-2-one (50 mg, 0.06 mmol) in DCM (1.5 mL) was added Crabtree's catalyst (48 mg, 0.06 mmol) in a Parr bottle. This was then placed under 40 psi hydrogen and was shaken overnight. The next day, the solution was filtered and concentrated to provide a crude mixture of two diastereomers (4*R*)-4-benzyl-3-((1*R*,2*R*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carbonyl)oxazolidin-2-one and (4*R*)-4-benzyl-3-((1*R*,2*R*,4*S*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carbonyl)oxazolidin-2-one (26 mg, 0.031 mmol): LCMS m/z = 827.4 $(M+H)^+$.

Step 4. (final step) (1*R*,2*R*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid (**10**) and **(1*R*,2*R*,4*S*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid** (**11**)



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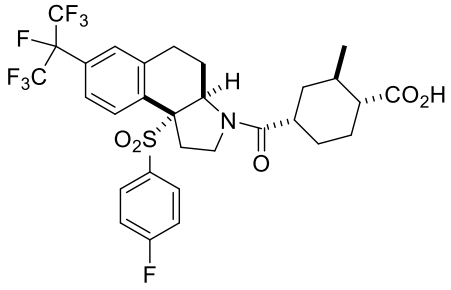

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To a mixture of the two diastereomers (4*R*)-4-benzyl-3-((1*R*,2*R*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carbonyl)oxazolidin-2-one and (4*R*)-4-benzyl-3-((1*R*,2*R*,4*S*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carbonyl)oxazolidin-2-one (30 mg, 0.036 mmol) in THF (1.5 mL) cooled to 0 °C was added H_2O_2 (0.015 mL, 0.145 mmol, 35% by wt. aq) and 1N LiOH aq (0.073 mL, 0.073 mmol). This was stirred for 2 h. Next, a small amount of 1N HCl aq (ca. 5 drops) was added and the solution was filtered before purification on preparative reverse-phase HPLC (column: Luna 30X100 mm, mobile phase A: 10:95 acetonitrile:water with 0.1% TFA; mobile phase B: 90:10 acetonitrile:water with 0.1% TFA, gradient: 20% B to 100%B over 10 min, then 100%B 10 min to 15 min, 30 mL/min, 220 wavelength, compound **10** t_R = 9.07 min and compound **11** t_R = 9.4 min). Compound **10**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.98 (d, *J*=8.4 Hz, 1H), 7.62 (br d, *J*=8.4 Hz, 1H), 7.41 (dd, *J*=8.9, 5.0 Hz, 2H), 7.28 (s, 1H), 7.10 (t, *J*=8.7 Hz, 2H), 4.79 (d, *J*=4.8 Hz, 1H), 3.99-3.81 (m, 2H), 3.56 (ddd, *J*=14.8, 7.9, 2.9 Hz, 1H), 2.71 (dt, *J*=14.8, 9.7 Hz, 1H), 2.64–2.54 (m, 2H), 2.50-2.41 (m, 1H), 2.05-1.91 (m, 3H), 1.88-1.68 (m, 3H), 1.65-1.45 (m, 2H), 1.36-1.13 (m, 2H), 0.99 (d, *J*=6.4 Hz, 3H). LCMS calculated for $C_{30}H_{30}F_8NO_5S$ $[M+H]^+$: m/z = 668.17, found: 668.5.

HPLC t_R = 1.05 min (Method A). Compound **11**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.99 (d, *J*=8.6 Hz, 1H), 7.62 (br d, *J*=8.4 Hz, 1H), 7.43-7.35 (m, 2H), 7.28 (s, 1H), 7.09 (t, *J*=8.7 Hz, 2H), 4.85 (m, 1H), 3.97-3.76 (m, 2H), 3.61-3.50 (m, 1H), 2.87-2.54 (m, 3H), 2.49-2.38 (m, 1H), 2.13-2.07 (m, 1H), 2.02-1.96 (m, 1H), 1.93-1.71 (m, 5H), 1.61 (ddd, *J*=17.4, 8.5, 3.6 Hz, 1H), 1.41-1.25 (m, 2H), 1.00 (d, *J*=6.8 Hz, 3H). LCMS calculated for $C_{30}H_{30}F_8NO_5S$ $[M+H]^+$: m/z = 668.17, found: 668.5. HPLC t_R = 1.08 min (Method A).

Imiquimod (IMQ)-Induced Model[8] of Skin Inflammation. Six to eight week old C57BL/6 female mice were housed 4 per cage. Individual body weights were obtained at the start of the study (17 to 20 grams) and daily during the study period.
Four (4) days before the start of treatments, the dorsal surface of each mouse, from the shoulders to the hips was shaved using an electric clipper. The shaved areas was depilated using Nair to remove remaining hair, and the area was wiped clean using sterile water.
5% IMQ cream was weighed (62 to 65 mg per mouse) and applied individually onto the shaved back skin of each animal for 8 consecutive days using a wooden applicator.
Animals were dosed orally with compound **5** as a spray dry dispersion (SDD) in 0.5% methocel E4M vehicle. The placebo/control group was dosed with a formulation of 6 mg/mL HPMCAS-MF in 0.5% methocel E4M. The addition of blank polymer to the control arm was done to confirm there was no effect of the polymer in the SDD formulation since the SDD is 25% compound **5**, and 75% polymer.
The amount of polymer added to the placebo was used to match the highest dose level of compound **5**. Compound **5** was administered as a dose response of 2, 7, 20 mg/kg, PO, BID from Day 0 to Day 7. On Day 3, the dosing solutions were diluted to adjust for new body weights (weight loss). The study ended on Day 8 and mice were euthanatized by CO_2 asphyxiation, or by cervical dislocation while under isoflurane anesthesia.
Mouse anti-muIL-23-His mAb E11272 was dosed SC at 10 mg/kg on Day -1 and Day 3 as a positive control.
Skin thickness, (in thousandths of an inch) was measured daily (Except for Day 5) at 2 locations on the back using a Mitutoyo (#2412F) dial caliper. The average of 2 measurements per mouse was calculated daily. The average daily measurement was used to calculate the % change from baseline for each mouse, and then group averages were calculated. The results are expressed as mean, standard deviation and/or standard error of the mean (SEM) for each group. Inhibition was based on the AUC of the Total Peak Area using Graphpad Prism. Individual body weights were recorded daily and the results are shown as % change from the starting weight on Day 0. Data calculations were performed in Excel (Microsoft, Redmond, WA), while statistical analysis (ANOVA with Dunnett's post test) and graphics were done using GraphPad Prism software (GraphPad, San Diego, CA).

Method for RORγt Co-Crystal Structure of Compound 5 (Figure 6A, pbd: 6VQF). The construct used for the co-crystal structure of compound 5, consisted of the RORγt ligand binding domain (UNP residues 265-508) fused to a SRC1 peptide (UNP residues 683-696) with six-residue (SGGSGG) linker between. The protein was grown in E. coli BL21(DE3) cells and purified by nickel capture and size exclusion chromatography. The final protein was at 8-10 mg/ml concentration in 25 mM Tris-HCl (pH 7.5), 200 mM NaCl, 5% Glycerol, 2mM DTT.

Crystals were obtained using the vapor diffusion method from RORγt / SRC1 chimera (8-10mg/ml protein concentration) with 0.2M $MgCl_2$, 22% PEG3350, 0.1M Bis-Tris pH 5.5. Crystals were obtained within one day after seeding with previously obtained RORγt crystals. Protein/ligand complexes were prepared by mixing the protein with ligand at 1:10 molar ratio at room temperature and were incubated at 20° C for 1 h prior to crystallization drop setup. Crystals were cryoprotected by adding glycerol and PEG400 to original crystallization buffer with final concentration 10% each and then flash-cooled in liquid nitrogen.
Data were collected on a Dectris Pilatus 6M detector at a temperature of 100 K on beamline 17ID at the Advanced Photon Source (APS), Argonne National Laboratoy. The data were processed autoPROC (Global Phasing LTD, Cambridge, UK). The reduced structure-factor data file was 96.4% complete to 2.0 Å resolution. The chimera crystallized in space group P41212 (unit-cell parameters a = b = 61.51 Å, c = 157.91 Å) with one molecule in the asymmetric unit (Matthews coefficient of 2.29 $Å^3$ /Da; solvent content 46.2%).
The previously determined structure of the chimera (PDB entry 6P9F)[9] was used as the starting point for autoBUSTER (Global Phasing LTD, Cambridge, UK) refinement. The model and electron-density maps were examined with Coot.[10] The final model has an Rwork of 20.4% (Rfree =24.1%) for the 2,096 atoms including 51 ligand atoms and 40 solvent molecules. The atomic coordinates and structure factors have been deposited in the RCSB Protein Data Bank (entry 6VQF).

Method for liver microsome $t_{1/2}$ assay (LM $t_{1/2}$, Table 1). Using compound **5** as an example, compound **5** (0.5 μM) was incubated with liver microsomes (1 mg/mL final conc,) fortified with NADPH (1 mM) at 37°C. Metabolic reactions were terminated after 0, 5, 10, 15, 30, and 45 minutes by transferring an aliquot of the reaction mixtures into an acetonitrile quench solution to denature microsomal enzymes. The relative amount of the compound **5** remaining in the reaction mixtures at each time point was quantified using LC-MS/MS analysis. The results for each time point were normalized to the relative amount of compound **5** in the 0-minute sample and expressed as percent remaining. Elimination rate constant (k_{el}) was determined using linear regression model (natural logarithm of % remaining versus time), and metabolic half-life was calculated (0.693 /k_{el}).

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