Supporting Information

Discovery of Oxadiazoyl Tertiary Carbinamine Inhibitors of β-Secretase (BACE-1).

Hemaka A. Rajapakse,* Philippe G. Nantermet, Harold G. Selnick, Sanjeev Munshi, Georgia B. McGaughey, Stacey R. Lindsley, Mary Beth Young, Ming-Tain Lai, Amy S. Espeseth, Xiao-Ping Shi, Dennis Colussi, Beth Pietrak, Ming-Chih Crouthamel, Katherine Tugusheva, Adam J. Simon, Lawrence Kuo, Daria J. Hazuda, Samuel Graham, and Joseph P. Vacca

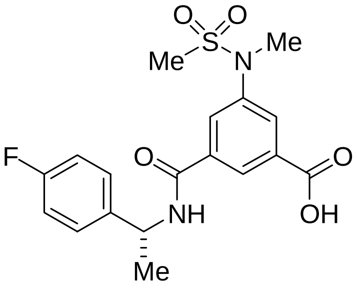
Experimental

General. All commercially available reagents and solvents were used without further purification unless stated otherwise. Automated flash chromatography was performed on a Gilson 215 liquid handler using Biotage Flash cartridges with peak detection at 254 nm. Reverse-phase purification was accomplished using a Gilson 215 liquid handler equipped with a YMC Pack Pro C18 column (150 x 20 mm I.D., S-5 μm). Peak collection was triggered by UV detection at 214 or 254 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 400 instrument operating at 400 and 125 MHz respectively with tetramethylsilane or residual protiated solvent used as a reference. Analytical HPLC was performed on an HP1100 equipped with an Agilent Zorbax SB C18 column (3.5 μm, 4.6 x 75 mm) with UV detection at 214 and 254 nm using an acetonitrile-water gradient with 0.9 % phosphoric acid. Low resolution mass spectra were recorded using a Waters 2690 LC-MS (YMC C18 column using 1% TFA containing acetonitrile-water gradient) coupled to a ZMD (MK II) using electrospray ionization. Accurate mass measurement was obtained by use of electrospray ionization (ESI) on a 7T Fourier transform ion cyclotron resonance (FTICR) mass spectrometer. Unless otherwise noted, all reactions were conducted in oven (80 °C) or flame dried glassware

For a complete description of assay conditions, see . *J. Alzheimer's Dis.* **2005**, 7, 139-148.

---

* To whom correspondence should be addressed. Phone (215) 652-5629. Fax (215) 652-3971. E-mail hemaka_rajapakse@merck.com.



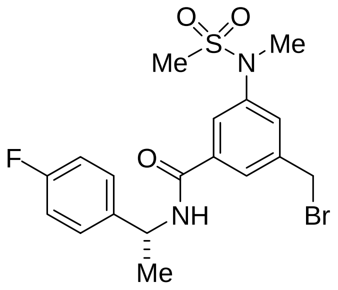
3-({[(1R)-1-(4-fluorophenyl)ethyl]amino}carbonyl)-5-[methyl(methylsulfonyl) amino] benzoic acid (**9**)

Amide bond formation:

A solution of 3-(methoxycarbonyl)-5-[methyl(methylsulfonyl)amino]benzoic acid (Stachel et al, *J. Med. Chem.* **2004**, *47*, 6447-6450) (8.00 g, 27.9 mmol), EDC (6.94 g, 36.2 mmol), (*R*)-(+)-α-methylbenzylamine (4.50 mL, 33.4 mmol), and HOAt (0.76 g, 5.57 mmol) in 50 mL $CHCl_3$ was stirred at ambient temperature for 50 h. Added H_2O and EtOAc, separated layers. Washed aqueous eith EtOAc (3x), washed combined organics with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified using column chromatography on silica gel (300 g silica gel, 50% EtOAc/Hexanes -> 90% EtOAc/Hexanes) afforded the desired benzyl amide (10.0 g, 24.5 mmol, 88%). ^{1}H NMR ($CDCl_3$) δ 8.26 (s, 1H), 8.17 (s, 1H), 8.06 (s, 1H), 7.31 (m, 5H), 6.50 (d, *J* = 7.1 Hz, 1H), 5.33 (q, *J* = 7.1 Hz, 1H), 3.96 (s, 3H), 3.37 (s, 3H), 2.88 (s, 3H), 1.64 (d, *J* = 7.0 Hz, 3H); LCMS $(M+H)^+ = 409$.

Ester Hydrolysis:

To a solution of ester (10.0 g, 24.48 mmol) from the above step in 200 mL THF was added 1N LiOH (1.76 g, 73.44 mmol) in 70 mL H_2O. After 5h at rt, the reaction was concentrated, and the residue was partitioned between H_2O and CH_2Cl_2. The layers were seperated, and 100 mL 1N HCl was added to the aqueous layer, resulting in the formation of a white suspension. The aqueous layer was extracted with ~4:1 CH_2Cl_2/THF (3x). The combined organics were dried over Na_2SO_4, filtered and concentrated to afford the title compound (8.27 g, 20.9 mmol, 86%) as a white solid, which was used without further purification. ^{1}H NMR (d_4-MeOH, 400 MHz) δ 9.02 (d, *J* = 7.3 Hz, 1H), 8.39 (s, 1H), 8.24 (t, *J* = 1.4 Hz, 1H), 8.06 (t, *J* = 2.0 Hz, 1H), 7.43-7.39 (m, 2H), 7.07-7.02 (m, 2H), 5.24 (q, *J* = 7.1 Hz, 1H), 3.37 (s, 3H), 2.94 (s, 3H), 1.56 (d, *J* = 7.1 Hz, 3H); LCMS $(M+H)^+$ = 395.



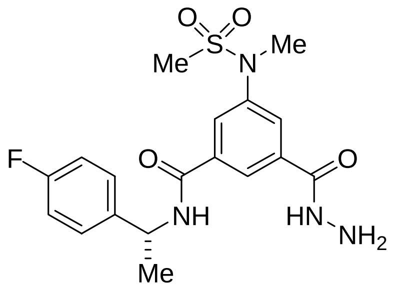
3-(bromomethyl)-*N*-[(1*R*)-1-(4-fluorophenyl)ethyl]-5-[methyl(methylsulfonyl)amino] benzamide (10)

Acid reduction:

To a solution of acid **9** (800 mg, 2.0 mmol) in 20 mL THF cooled to 0 °C was added borane (6.0 ml, 6.0 mmol, 1 M in THF) dropwise. The reaction mixture was stirred at 0 °C for 20 min and at room temperature for 2 h. The reaction mixture was quenched with MeOH, stirred at room temperature for 16 h, and concentrated in vacuo. The residue was taken in EtOAc, washed with water, brine, dried over sodium sulfate, filtered and concentrated in vacuo to provide the desired alcohol as a white solid (722 mg, 1.9 mmol, 95%), which was carried on without further purification. ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.74 (m, 2H), 7.58 (s, 1H), 7.39 (dd, J = 5.2, 2.1 Hz, 2H), 7.03 (dd, J = ddd, J = 6.4, 4.5, 1.0 Hz, 2 H), 5.21 (q, J = 7.1 Hz, 1H), 4.65 (s, 2H), 3.31 (s, 3H), 2.91 (s, 3H), 1.54 (d, J = 7.1 Hz, 3H); LCMS $(M+H_2O+H)^+$ = 409.

Bromination:

To a solution of alcohol from the above step (355 mg, 0.93 mmol) and carbon tetrabromide (400 mg, 1.2 mmol) in 4.6 mL 1:1 $CH_3CN:CH_2Cl_2$ was added triphenylphosphine (290 mg, 1.1 mmol) in 4.6 mL 1:1 $CH_3CN:CH_2Cl_2$ dropwise. After stirring at room temperature for 45 min, two additional batches of carbon tetrabromide and triphenyl phosphine (200 mg/150 mg and 20 mg/15 mg) were added at 30 min intervals, until the reaction appeared complete by LC/MS analysis. The reaction mixture was concentrated and purified by flash chromatography (40 g silica, 25 -> 60% EtOAc/hexanes) to afford the title compound (220 mg, 53%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.65 (s, 1H), 7.57 (s, 1H), 7.32-7.40 (m, 2H), 7.09-7.01 (m, 2 H), 6.32 (d, J = 7.6 Hz, 1H), 5.36-5.24 (m, 1H), 4.50 (s, 2H), 3.36 (s, 3H), 2.78 (s, 3H), 1.62 (d, J = 6.5 Hz, 3H). LCMS $(M+H)^+$ = 443 and 445 (Br pattern).



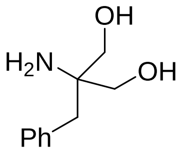
N-[(1R)-1-(4-fluorophenyl)ethyl]-3-(hydrazinocarbonyl)-5-[methyl(methylsulfonyl) amino]benzamide

Cooupling with Boc-hydrazine:

To a solution of acid **9** (300 mg, 0.761 mmol) in 6 mL DMF was added Boc-hydrazine (111 mg, 0.837 mmol), HOAt (10.4 mg, 0.076 mmol) and EDC (175 mg, 0.913 mmol). After 5h, the reaction was diluted with EtOAc and 10% $KHSO_4$. The layers were separated, the organics were washed with 3M LiCl (3x), brine, dried over Na_2SO_4, filtered and concentrated to obtain an off white foam (385 mg, 0.757 mmol, 99%) which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.81 (s, 1H), 7.76 (s, 1H), 7.38 (dd, J = 5.5, 2.0 Hz, 2H), 7.02 (dd, J = 11.4, 1.5 Hz, 2H), 6.63 (s, 1H), 5.21 (q, J = 7.1 Hz, 1H), 3.22 (s, 3H), 2.93 (s, 3H), 1.63 (d, J = 7.1 Hz, 3H), 1.53 (s, 9H); LCMS $(M+Na)^+$ = 531.

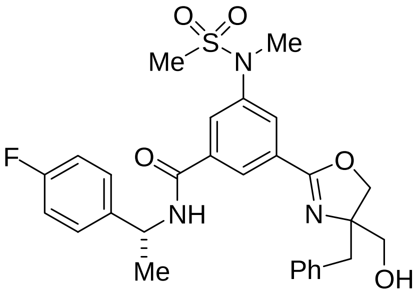
Boc deprotection:

A solution of product from the above step (385 mg, 0.757 mmol) in 4 mL CH_2Cl_2 was added 4M HCl in dioxane (1.9 mL, 7.57 mmol). After 1h, the reaction was concentrated and azeotroped with MeOH to obtain a yellow gum (332 mg, 0.749 mmol, 99%) as the title compound. ^{1}H NMR (400 MHz, d_4-MeOH) δ 8.21 (s, 1H), 8.13 (s, 1H), 8.08 (s, 1H), 7.22 (dd, J = 5.3, 2.0 Hz, 2H), 7.03 (dd, J = 10.7, 1.9 Hz, 2H), 5.21 (q, J =6.8 Hz, 1H), 3.20 (s, 3H), 2.87 (s, 3H), 1.59 (d, J = 6.8 Hz, 3H); LCMS $(M+H)^+$ = 409.



2-amino-2-benzylpropane-1,3-diol

To a solution of benzyl serine (4.00 g, 20.5 mmol) in 60 mL THF was added $NaBH_4$ in one portion. The reaction was cooled to 0 °C and a reflux condenser was fitted. Iodide (7.80 g, 30.7 mmol) was added dropwise, and the reaction was warmed to room temperature, then heated to reflux for 16h. Quenched by cooling to 0 °C and adding MeOH dropwise until the bubbling subsided, followed by 100 mL 20% KOH. Stirred at RT for 2h, then adjusted the pH of the solution to 1 using 6N HCl. Concentrated and azeotroped with CH_3CN to obtain a white gum. Divided into four batches and purified by SCX ion exchange chromatography (50 g, column was reused), loading reaction mixture in MeOH then eluting with 300 mL MeOH and 200 mL 2M NH_3 in MeOH for each batch. The desired product was isolated from the basic fractions as a white solid (2.85 g, 77%). ^{1}H NMR (400 MHz, d_3-MeOH) δ 7.30-7.20 (m, 5H), 3.38 (s, 4H), 2.72 (s, 2H); LCMS $(M+H)^+$ = 182.



3-[4-benzyl-4-(hydroxymethyl)-4,5-dihydro-1,3-oxazol-2-yl]-*N*-[(1*R*)-1-(4-fluorophenyl)ethyl]-5-[methyl(methylsulfonyl)amino]benzamide (**2**)

Amide coupling:

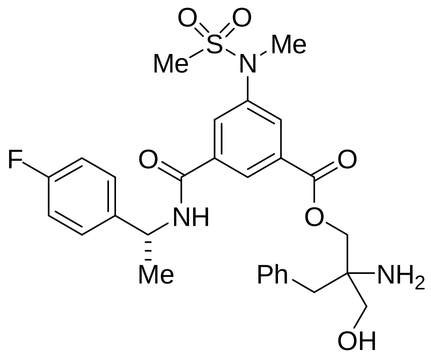
To a solution of benzoic acid **9** (200 mg, 0.531 mmol) and benzyl serine methyl ester hydrochloride (170 mg, 0.691 mmol) in 4 mL CH_2Cl_2 was added triethylamine (300 μL, 2.1 mmol) and BOP reagent (282 mg, 0.638 mmol). After 1h, the reaction was poured onto a normal phase silica gel column conditioned with 15% EtOAc/hex) and purified using a linear gradient (40g silica, 40 mL/min, 15%EtOAc/hex -> 100% EtOAc) to afford the desired product (115 mg, 0.201 mmol, 38%) as a viscous oil. ^{1}H NMR (Major amide rotamer) (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.17 (s, 1H), 8.11-7.98 (m, 3H), 7.38 (m, 2H), 7.38-7.01 (m, 3H), 7.06-6.97 (m, 2 H), 5.18 (m, 1H), 4.80 (s, 3H), 3.94 (q, J = 7.1 Hz, 1H), 3.71 (s, 2H), 3.51 (d, J = 11.1 Hz, 1H), 3.38 (d, J = 11.1 Hz, 1H), 3.33 (s, 3H), 2.92 (s, 3H), 1.53 (d, J = 7.1 Hz, 3H); LCMS $(M+H)^+$ = 587.

Dehydration

A solution of amide from the above step (115 mg, 0.203 mmol), tosyl chloride (154 mg, 810 mmol) and triethylamine (170 μL, 1.20 mmol) in 3 mL CH_2Cl_2 were heated at 45 oC for 16h. The reaction was loaded directly onto a normal phase silica gel column conditioned with 10% EtOAc/hex and purified using a linear gradient (40g silica, 40 mL/min, 10% EtOAc/hex -> 70 %EtOAc/hex) to afford the desired product (23 mg, 0.0442 mmol, 21%) as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 1.2 Hz, 1H), 8.00 (s, 2H), 7.38-7.33 (m, 2H), 7.38 (m, 2H), 7.21 (m, 3H), 7.16 (m, 2H), 7.03 (m, 2H), 6.48 (d, J = 7.4 Hz, 1H), 5.29 (q, J = 6.8 Hz, 1H), 4.74 (d, J = 9.1 Hz, 1H), 4.39 (d, J = 9.1 Hz, 1H), 3.80 (s, 3H), 3.33 (s, 3H), 2.85 (s, 3H), 1.59 (d, J = 6.8 Hz, 3H); LCMS $(M+H_2O+H)^+$ = 587.

Ester Reduction

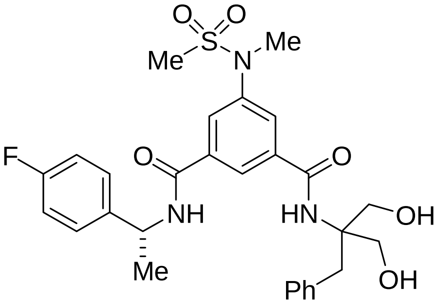
To a solution of oxazoline methyl ester from the above step (30 mg, 0.053 mmol) in 2 mL THF at 0 °C was added $LiBH_4$ (80 μL of 2M in THF, 0.159 mmol). After 3.5h at 0 °C, the reaction was quenched by adding 1 mL MeOH dropwise, concentrated, and the residue was redissolved in CH_2Cl_2. Purified using normal phase chromatography (20 g silica, 30 mL/min, 100% CH_2Cl_2 -> 10% MeOH/CH_2Cl_2) to afford the title compound (29 mg, 0.053 mmol, 100%) as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (m, 1H), 8.03 (s, 1H), 7.97 (t, J = 1.5 Hz, 1H), 7.42-7.40 (m, 2H), 7.21-7.11 (m, 5H), 7.04 (m, 2H), 5.20 (q, J = 6.6 Hz, 1H), 4.38 (d, J = 8.6 Hz, 1H), 4.31 (d, J = 8.6 Hz, 1H), 3.73 (d, J = 8.3 Hz, 1H), 3.65 (d, J = 8.3 Hz, 1H), 3.33 (s, 3H), 3.00 (d, J = 13.5 Hz, 1H), 2.93 (s, 3H), 2.88 (d, J = 13.5 Hz, 1H), 1.54 (d, J = 7.1 Hz, 1H); LCMS R_t = 2.01 min (>95% purity), $[M+H]^+$ = 540; HPLC R_t = 3.602 min (>95% purity); HRMS exact mass calc for $C_{28}H_{31}FN_3O_5S$ $[M+H]^+$: 540.1970; observed: 540.1972.



2-Amino-2-benzyl-3-hydroxypropyl-3-({[(1*R*)-1-(4-fluorophenyl)ethyl]amino}-carbonyl)-5-[methyl(methylsulfonyl)amino]benzoate (3)

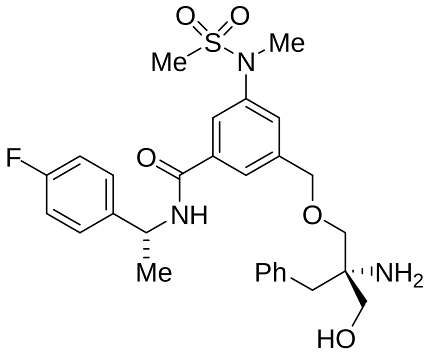
To a solution of amide **4** (19.2 mg, 0.0344 mmol) in 2 mL CH_3CN and 0.4 mL H_2O was added trifluroacetic acid (0.14 mL). The reaction was allowed to proceed at rt for 14h, then warmed to 45 °C for 7h. A further aliquot of trifluoroacetic acid (0.050 mL) was added, and the reaction was maintained at 45 °C for 14h. The reaction was concentrated, the residue was dissolved in 1 mL DMF, then purified by reverse-phase preparative HPLC to afford the desired ester **3** as a 1:1 mixture of diastereomers. Diastereomer A: ^1H NMR (400 MHz, *d*$_4$-MeOH,) δ 9.058 (br s, 1H), 8.425 (m, 1H), 8.260 (m, 1H), 8.136 (m, 1H), 7.438-7.403 (m, 2H), 7.355-7.247 (m, 5H), 7.068-7.020 (m, 2H), 5.246 (m, 1H), 4.469 (d, J = 12.1 Hz, 1H), 4.319 (d, J = 12.3 Hz, 1H), 3.700 (s, 2H), 3.386 (s, 3H), 3.140 (m, 2H), 2.964 (s, 3H), 1.576 (d, J = 7.1 Hz). Diastereomer B: ^1H NMR (400 MHz, *d*$_4$-MeOH,) δ 9.038 (br s, 1H), 8.400 (m, 1H), 8.260 (m, 1H), 8.136 (m, 1H), 7.438-7.403 (m, 2H), 7.355-7.247 (m, 5H), 7.068-7.020 (m, 2H), 5.246 (m, 1H), 4.469 (d, J = 12.1 Hz, 1H), 4.309 (d, J = 12.1 Hz, 1H), 3.700 (s, 2H), 3.386 (s, 3H), 3.140 (m, 2H), 2.964 (s, 3H), 1.576 (d, J = 7.1 Hz). LCMS R_t = 2.01 min (>98% purity), $[M+H]^+$ = 558; HPLC R_t

= 2.701 min (>98% purity). HRMS exact mass calc for $C_{28}H_{33}FN_3O_6S$ ($[M+H]^+$): 558.2069; observed: 558.2065.



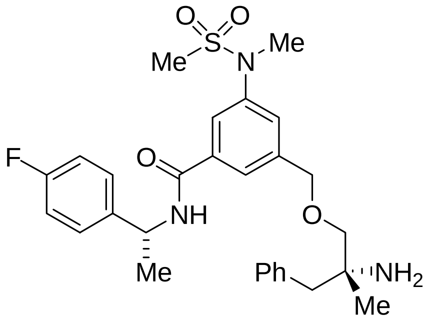
N-[1-benzyl-2-hydroxy-1-(hydroxymethyl)ethyl]-N'-{[(1R)-1-(4-fluorophenyl)ethyl]-5-[N-methyl-N-(methylsulfonyl)amino]}isophthalimide (4)

To a slurry of amine hydrochloride **2** (442 mg, 2.20 mmol) and acid **8** (100 mg, 0.254 mmol) in 3 mL CH_2Cl_2 was added diisopropylethylamine (0.180 mL, 1.014 mmol), followed by BOP-reagent (168 mg, 0.380 mmol). After 2.5 h, additional diisopropylethylamine (0.90 mL, 0.501 mmol) and BOP-reagent (85 mg, 0.190 mmol) was added. After 45 min, the reaction was concentrated, redissolved in 2 mL DMF and 0.25 mL H_2O, then purified by reverse-phase preparative HPLC (5% -> 95% CH_3CN in water containing 0.1 % TFA, C18 PRO YMC 20x150 mm, 15 mL/min). The mildly acidic fractions containing desired amide **4** were concentrated by lyophilization. ^1H NMR (400 MHz, *d_4*-MeOH) δ 8.83 (d, J = 7.1 Hz, 1H), 8.05 (m, 1H), 7.969 (m, 1H), 7.87 (m, 1H), 7.42-7.25 (m, 3H), 7.24-7.15 (m, 4H), 7.07-7.020 (m, 2H), 5.22 (m , 1H), 3.85 (d, J = 9.7 Hz, 2H), 3.73 (d, J = 9.7 Hz, 1H), 3.33 (s, 3H), 3.17 (s, 2H), 2.94 (s, 3H), 1.55 (d, J = 6.9 Hz, 3H).). LCMS R_t = 2.45 min (>96% purity), $[M+H]^+$ = 558; HPLC R_t = 3.408 min (>95% purity). HRMS exact mass calc for $C_{28}H_{33}FN_3O_6S$ ($[M+H]^+$): 558.2069; observed: 558.2066.



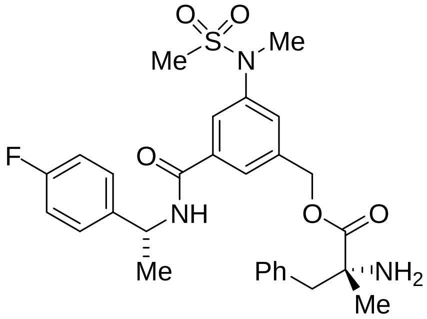
3-[(2-amino-2-benzyl-3-hydroxypropoxy)methyl]-*N*-[(1*R*)-1-(4-fluorophenyl)ethyl]-5-[methyl(methylsulfonyl)amino]benzamide (5)

To a solution of intermediate **10** benzylserine diol (2-amino-2-benzylpropane-1,3-diol) (90 mg, 0.50 mmol) in 2 mL DMF cooled to 0 °C was added sodium hexamethyldisylazide (0.50 mL, 0.50 mmol, 1 M in THF). The reaction mixture was stirred at 0 °C for 5 min and benzyl bromide **10** (100 mg, 0.23 mmol) in 1 mL DMF was added dropwise. The reaction mixture was stirred at 0 °C for 0.5 h, quenched with water, extracted with EtOAc, washed with aq LiCl (3x), dried over sodium sulfate, concentrated in vacuo, and purified by flash chromatography (40 g silica, 0 -> 8% (10% NH_4OH in MeOH)/CH_2Cl_2) to afford 3-[(2-amino-2-benzyl-3-hydroxypropoxy)methyl]-N-[(1R)-1-(4-fluorophenyl)ethyl]-5-[methyl(methylsulfonyl)amino]benzamide (90 mg, 0.17 mmol, 71%). ^{1}H NMR (400 MHz, *d_4*-MeOH) δ 7.80 (s, 2H), 7.64 (s, 1H), 7.44-7.40 (m, 2H), 7.26-7.20 (m, 5H), 7.07-7.02 (m, 2H), 5.24 (q, J = 7.0 Hz, 1H), 4.61 (s, 2H), 3.48 (d, J = 10.4 Hz, 1H), 3.43 (d, J = 10.4 Hz, 1H), 3.35 (s, 3H), 2.91 (s, 3H), 2.72 (d, J = 13.9 Hz, 1H), 2.66 (d, J = 13.9 Hz, 1H), 1.57 (d, J = 7.0 Hz, 3H). LCMS R_t = 1.78 min (>98% purity), $[M+H]^+$ = 544; HPLC R_t = 2.761 min (>98% purity); HRMS calculated for $C_{28}H_{35}FN_3O_5S$ ($[M+H]^+$): 544.2276, found: 544.2275. The diastereomers were separated using a ChiralPak AD column (5x50 cm, 20% *i*-PrOH/hexanes with 1% added diethylamine)



3-[(2-amino-2-methyl-3-phenylpropoxy)methyl]-*N*-[(1*R*)-1-(4-fluorophenyl)ethyl]-5-[methyl(methylsulfonyl)amino]benzamide (**6**).

To a solution of (*R*)-α-Me-phnylalaninol ((*R*)-2-amino-2-methyl-3-phenylpropan-1-ol) (28 mg, 0.17 mmol) in 0.5 mL DMF cooled to 0 °C was added sodium hexamethyldisylazide (0.17 mL, 0.17 mmol, 1 M in THF). The reaction mixture was stirred at 0 °C for 5 min benzyl bromide **10** (25 mg, 0.061 mmol) in 0.5 mL DMF was added dropwise. The reaction mixture was stirred at 0 °C for 0.5 h and purified by preparative HPLC (5% -> 95% CH_3CN in water containing 0.1 % TFA, C18 PRO YMC 20x150 mm, 15 mL/min) and the fractions containing the desired product were combined and lyophilized to afford the title compound as a white solid (28.4 mg, 0.048 mmol, 74%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 8.87 (d, J = 8.2 Hz, 1H), 7.86-7.80 (m, 2H), 7.66 (s, 1H), 7.45-7.40 (m, 2H), 7.36-7.24 (m, 3H), 7.22-7.16 (m, 2H), 7.10-7.02 (m, 2H), 5.30-5.20 (m, 1H), 4.73-4.64 (m, 2H), 3.44 (d, J = 10.0 Hz, 1H), 3.39 (d, J = 10.0 Hz, 1H), 3.35 (s, 3H), 3.09 (d, J = 13.2 Hz, 1H), 2.94 (s, 3H), 2.87 (d, J = 13.2 Hz, 1H), 1.59 (d, J = 7.2 Hz, 3H), 1.25 (s, 3H); LCMS R_t = 1.78 min (>98% purity), $[M+H]^+$ = 528; HPLC R_t = 2.845 min (>98% purity); HRMS calculated for $C_{28}H_{36}FN_3O_4S$ ($[M+H]^+$): 528.2327, found: 528.2319.



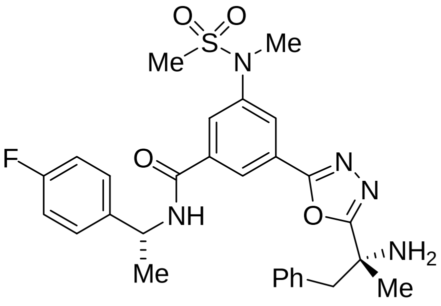
3-[4-benzyl-4-(hydroxymethyl)-4,5-dihydro-1,3-oxazol-2-yl]-*N*-[(1*R*)-1-(4-fluorophenyl)ethyl]-5-[methyl(methylsulfonyl)amino]benzamide (**7**).

Esterification:

To a solution of benzyl bromide **10** (41 mg, 0.090 mmol) and (*R*)-*N*-Boc-α-Me-Phe-OH (30 mg, 0.108 mmol) in 0.70 mL DMF was added Cs_2CO_3 (35 mg, 0.108 mmol). After 2h, 10 μL of water was added, the reaction was filtered through a pad of cotton wool and purified by preparative HPLC (5% -> 95% CH_3CN in water containing 0.1 % TFA, C18 PRO YMC 20x150 mm, 15 mL/min). The fractions containing the desired ester were lyophilized to obtain protected **7** as a white solid (50 mg, 0.077 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.67 (s, 1H), 7.51 (s, 1H), 7.37 (m, 2H), 7.25-7.22 (m, 3H), 7.06-6.97 (m, 4H), 5.31 (q, J = 6.8 Hz, 1H), 3.38 (d, J = 13.1 Hz, 1H), 3.31 (s, 3H), 3.11 (d, J = 13.1 Hz, 1H), 2.81 (s, 3H), 1.60 (d, J = 6.8 Hz, 3H), 1.45 (s, 3H), 1.28 (s, 9H); LCMS $(M+H)^+$ = 642.

Boc deprotection:

Gaseous HCl was bubbled through a solution of coupled adduct from the above step (50 mg, 0.077 mmol) in 2 mL CH_2Cl_2 at 0 °C. After 2 h at room temperature, the reaction was cooled back to 0 °C and HCl was bubled for a further 5 min. After 1 h at room temperature, the reaction was concentrated, redissolved in H_2O/CH_3CN and lyophilized to obtain the title compound as a white solid (45 mg, 0.076 mmol, 99%). ^{1}H NMR (400 MHz, *d_4*-MeOH) δ 8.89 (d, J = 7.9 Hz, 1H), 7.87 (d, J = 1.5 Hz, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.63 (s, 1H), 7.40 (m, 2H), 7.25-7.22 (m, 3H), 7.06-7.01 (m, 4H), 5.23 (q, J = 6.9 Hz, 1H), 3.34 (s, 3H), 3.26 (d, J = 14.1 Hz, 1H), 3.08 (d, J = 14.1 Hz, 1H), 2.91 (s, 3H), 1.62 (s, 3H), 1.56 (d, J = 6.9 Hz, 3H); LCMS R_t = 1.77 min (>98% purity), $[M+H]^+$ = 542; HPLC R_t = 2.731 min (>98% purity); HRMS exact mass calc for $C_{28}H_{33}FN_3O_5S$ $[M+H]^+$: 542.2120; observed: 542.2013.



3-{5-[(1*R*)-1-amino-1-methyl-2-phenylethyl]-1,3,4-oxadiazol-2-yl}-*N*-[(1*R*)-1-(4-fluorophenyl)ethyl]-5-[methyl(methylsulfonyl)amino]benzamide (**8**).

Coupling/dehydration:

To a solution of (*R*)-*N*-Boc-a-Me-Phe-OH (158 mg, 0.566 mmol) in 4 mL CH_2Cl_2 was added CDI (94 mg, 0.58 mmol) After 30 min, *N*-[(1*R*)-1-(4-fluorophenyl)ethyl]-3-(hydrazinocarbonyl)-5-[methyl(methylsulfonyl) amino]benzamide (252 mg, 0.57 mmol) was added, and the reaction was allowed to proceed at room temperature for 48h. LCMS showed completion of coupling, then CBr_4 (376 mg, 1.133 mmol) and Ph_3P (297 mg, 1.13 mmol) were added in one portion. After 5h, the reaction was loaded directly onto a normal phase silica gel column conditioned with 20% EtOAc/hex and purified using a linear gradient (90g silica, 80 mL/min, 20%EtOAc/hex ->100%EtOAc/hex) to afford the desired product (369 mg, 0.42 mmol, 75%) as a white foam. ^{1}H NMR ($CDCl_3$) δ 8.29 (s, 1H), 8.12 (s, 1H), 7.98 (s, 1H), 7.38-7.7.35 (m, 2H), 7.29-7.24 (m, 3H), 7.08-7.02 (m, 4H), 6.52 (d, *J* = 7.5 Hz, 1H), 5.30 (m, 1H), 3.60 (d, *J* = 13.4 Hz, 1H), 3.40 (d, *J* = 13.4 Hz, 1H), 3.40 (s, 3H), 2.88 (s, 3H), 1.69 (s, 3H), 1.62 (d, *J* = 7.0 Hz, 3H) 1.40 (s, 9H); LCMS $[M+H]^+$ = 652.

Boc deprotection:

Gaseous HCl was bubbled through a solution of adduct (68 mg, 0.11 mmol) from the above step in 6 mL CH_2Cl_2 at 0 °C for 10 min. The reaction was warmed to rt for 20 min, cooled back to 0 °C and HCl was bubbled through the solution for a further 5 min. After 30 minutes at rt, the reaction was concentrated, and the residue was freeze dried to obtain the title compound (59 mg, 0.10 mmol, 97%) as a flocculent white solid. ^{1}H NMR (d_4-MeOH) δ 9.07 (d, *J* = 7.5 Hz, 1H), 8.38 (d, *J* = 1.5 Hz, 1H), 8.20 (d, *J* = 1.8 Hz, 1H), 8.12 (d, *J* = 1.6 Hz, 1H), 7.45-7.42 (m, 2H), 7.30-7.28 (m, 3H), 7.09-7.03 (m, 4H), 5.25 (m, 1H), 3.44 (s, 2H), 3.40 (s, 3H), 3.00 (s, 3H), 1.87 (s, 3H), 1.59 (d, *J* = 7.1 Hz, 3H). LCMS R_t = 1.74 min (>95% purity), $[M+H]^+$ = 552; HPLC R_t = 2.781 min (>98% purity); HRMS exact mass calc for $C_{28}H_{31}FN_5O_4S$ ($[M+H]^+$): 552.2076; observed: 552.2088.