Supporting information

# Discovery of Clinical Candidate GSK1842799 as a Selective S1P$_1$ Receptor Agonist (Prodrug) for Multiple Sclerosis

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Supporting Information Contents:

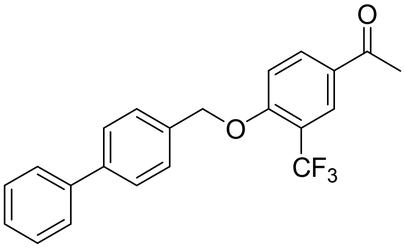
## Experimental procedures for synthesis and characterization of compounds

**General Chemistry:** $^1H$ NMR spectra were recorded on a Varian Mercury 400 plus. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants (*J*) are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), dt (double triplet), m (multiplet), br (broad). The purity of final compounds was checked using an Agilent 1100 HPLC system coupled with a Thermo Finnigan LCQ Mass Spectrometer. All mass spectra were performed by electrospray ionization (ESI). HPLC conditions: Phenomenex Luna 3μ C8(2) 30 × 3.00 mm 100A column running gradient of 30-98% MeCN/$H_2O$ (+0.1% TFA) over 3.5 minutes with flow rate 0.7 mL/min. High-resolution mass measurement was performed on Bruker MicroTOF electrospray mass spectrometer coupled with an Agilent 1100 HPLC system. Purification of final compounds for biological testing was performed on a Gilson GX-281 system with a Phenomenex Luna 5μ C8(2) 100 × 21.20 mm 100A column running gradient of 10-95% MeCN/$H_2O$ (+0.1% TFA) over 15-20 minutes with flow rate of 22 mL/min.

### General protocol for synthesis of substituted acetophenones (16, method A)

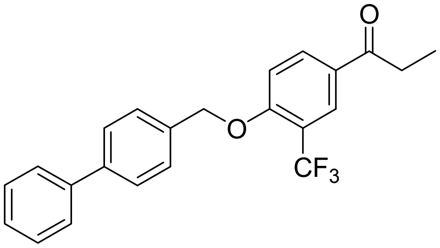
To a solution of the desired alcohol (1.0 equiv) in dry THF under nitrogen atmosphere was added $KO^tBu$ (either 1.0 M solution in THF or solid, 1.1 equiv). The reaction mixture was heated at 60-70 ºC for 15 minutes, followed by the addition of substituted 4-fluoroacetophenone (1.0 equiv). The reaction was then stirred for 30 minutes before cooling to room temperature and quenching with water. The mixture was then diluted with ethyl acetate (EtOAc) and washed with $H_2O$ (2 ×), saturated NaCl (1 ×), dried with $MgSO_4$. The organic layer was then concentrated under reduced pressure, and the residue purified by silica gel column chromatography using the Combi-Flash system eluted with hexanes : ethyl acetate (Hex:EtOAc) to afford desired compounds in good yield as stated for individual compounds.

**1-(4-(4-Phenylbenzyloxy)-3-(trifluoromethyl)phenyl)ethanone (16, $R_1$ = H, $R_2$ = 4-biphenyl)**



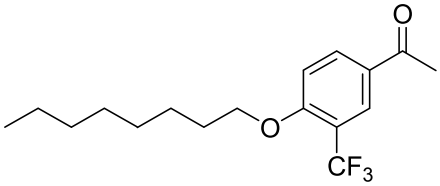
The product was purified by silica gel column chromatography using the Combi-Flash system (Hex:EtOAc) as white solid in 92% (5.88 g). $^1$H NMR and HPLC analyses confirmed the desired product with purity greater than 95%. TLC (EtOAc:Hex, 1:3), $R_f$ = 0.3; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, 1H, *J* = 2.3 Hz), 8.12 (dd, 1H, *J* = 8.6 Hz, *J* = 2.3 Hz), 7.57-7.65 (m, 4H), 7.42-7.53 (m, 4H), 7.33-7.39 (m, 1H), 7.12 (d, 1H, *J* = 8.6 Hz), 5.33 (s, 2H), 2.59 (s, 3H).

**1-(4-(Biphenyl-4-ylmethoxy)-3-(trifluoromethyl)phenyl)propan-1-one (16, $R_1$ = $CH_3$, $R_2$ = 4-biphenyl)**



The product was purified by silica gel column chromatography using the Combi-Flash system (Hex:EtOAc) as white solid in 83%. TLC (EtOAc:Hex, 1:3), $R_f$ = 0.4; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, 1H, *J* = 2.0 Hz), 8.12 (dd, 1H, *J* = 8.8 Hz, *J* = 2.4 Hz), 7.56-7.65 (m, 4H), 7.50 (d, 2H, *J* = 8.4 Hz), 7.45 (t, 2H, *J* = 8.2 Hz), 7.36 (t, 1H, *J* = 8.0 Hz), 7.11 (d, 1H, *J* = 8.8 Hz), 5.31 (s, 2H), 2.97 (q, 2H, *J* = 7.2 Hz), 1.23 (t, 3H, *J* = 7.2 Hz).

**1-(4-(Octyloxy)-3-(trifluoromethyl)phenyl)ethanone (16, $R_1$ = H, $R_2$ = *n*-heptyl)**



The product was purified by silica gel column chromatography using the Combi-Flash system (Hex:EtOAc) as white solid in 60% (1.20 g). TLC (EtOAc:Hex, 1:5), $R_f$ = 0.4; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, 1H, *J* = 2.0 Hz), 8.10 (dd, 1H, *J* = 8.8 Hz, *J* = 2.3 Hz), 7.02 (d, 1H, *J* = 8.8 Hz), 4.12 (t, 2H, *J* = 6.4 Hz), 2.58 (s, 3H), 1.80-1.89 (m, 2H), 1.42-1.54 (m, 2H), 1.22-1.40 (m, 8H), 0.89 (t, 3H, *J* = 6.7 Hz).

**General protocol for synthesis of substituted phenylimidazole/phenyloxazoles (method B)**

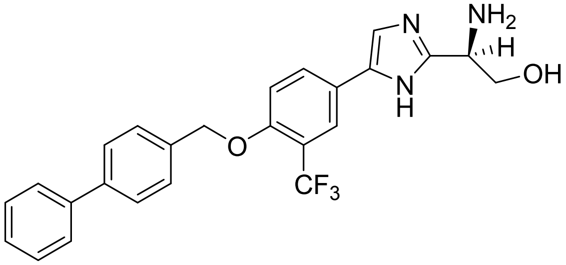
To a solution of the substituted acetophenone (1.0 equiv) in EtOAc/$CHCl_3$ (1:1) under nitrogen atmosphere was added $CuBr_2$ (3.0 equiv). The reaction mixture was heated at reflux for 2-5 hours. The reaction was then diluted with EtOAc and washed with $H_2O$ (2 ×) and saturated NaCl (1×). The organic layer was dried over anhydrous $MgSO_4$ then the solvent removed *in vacuo*. The crude product was either carried forward as is or was purified by silica gel column chromatography using the Combi-Flash system (Hex:EtOAc).

To a mixture of the desired bromo-acetophenone (from last step, 1.0 equiv), *N*-Boc-Ser (1.0 equiv) or its analogs (**19** and **20**), and $Cs_2CO_3$ (0.6 equiv) was stirred in DMF for 1-2 hours. The reaction mixture was diluted with EtOAc and washed with $H_2O$ (2×), and saturated NaCl

(1×) to remove access DMF and CsBr salt. The organic layer was dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo*. TLC generally showed a spot to spot conversion of the starting material to product.

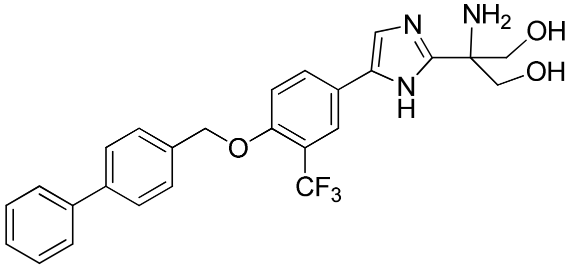
To the obtained ester was then added excess ammonium acetate (10 equiv), and the mixture was suspended in toluene and refluxed for 3-6 hours under Dean-Stark condition. The mixture was diluted with EtOAc and washed brine (2×). The organic layer was dried over $Na_2SO_4$ and condensed *in vacuo* to give the Boc protected imidazole product after silica gel column chromatography using the Combi-Flash system (Hex:EtOAc). The Boc protected imidazole product was treated with *p*-toluenesulfonic acid monohydrate (5.0 equiv) in methanol at 70 °C for 2 h to afford the title compound after preparative HPLC purification in good yield as stated for individual compounds. Preparative HPLC method: C8(2) column, Luna, 5μ, 100 × 21.10 mm, acetonitrile-$H_2O$ (0.1% TFA) as mobile phase and gradient 30-98% in 20 min, flow rate 22 mL/min, and UV detection at 254 nm.

**(*R*)-2-Amino-2-(5-(4-(biphenyl-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-1*H*-imidazol-2-yl)ethanol (1)**



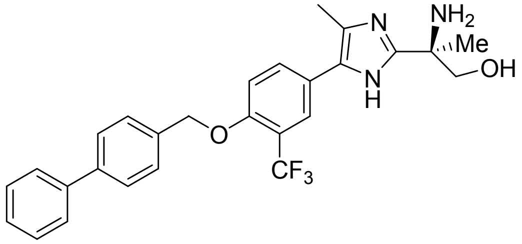
The final product was purified by reverse phase preparative HPLC, then lyophilized to dryness to obtain TFA salt of the product. The product was obtained as a white solid (35 mg) in 85% yield. MS (ESI, $M+H^+$) = 454.3; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 8.47 (br s, 3H), 8.07 (d, 1H, *J* = 1.6 Hz), 8.00 (dd, 1H, *J* = 8.8 Hz, *J* = 2.4 Hz), 7.66-7.76 (m, 5H), 7.55 (d, 2H, *J* = 8.4 Hz), 7.35-7.50 (m, 4H), 5.34 (s, 2H), 4.38 (br s, 1H), 3.76-3.90 (m, 2H).

**2-(5-(4-([1,1'-biphenyl]-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-1*H*-imidazol-2-yl)-2-aminopropane-1,3-diol (2)**



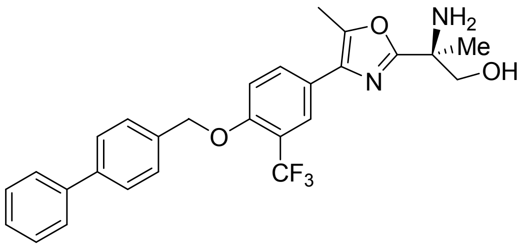
The final product was purified by reverse phase preparative HPLC, then lyophilized to dryness to obtain TFA salt of the product (38 mg, 12% yield) as a white solid. MS (ESI, M+H$^+$) = 483.2 (LC Rt = 2.59 min); $^1$H NMR (400 MHz, DMSO-d$_6$) δ 11.70 (s, 1H), 8.60 (s, 1H), 7.96 (s, 1H), 7.71(d, 2H, *J* = 8.4 Hz), 7.69 (d, 2H, *J* = 8.4Hz), 7.55 (d, 2H, *J* = 8.8 Hz), 7.47 (t, 2H, *J* = 7.4 Hz), 7.37 (d, 2H, *J* = 7.6 Hz), 5.32 (s, 2H), 4.79 (t, 2H, *J* = 5.2 Hz), 3.59 (d, 4H, *J* = 4.8 Hz), 3.30 (s, 2H).

**(*R*)-2-Amino-2-(5-(4-(biphenyl-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-4-methyl-1*H*-imidazol-2-yl)propan-1-ol (3)**



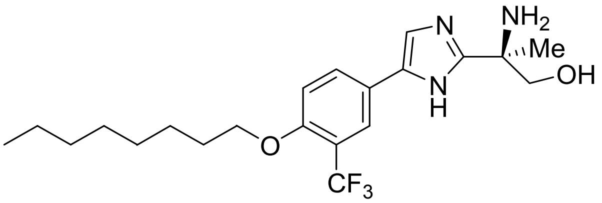
The reaction to synthesize the Boc protected precursor to imidazole product afforded a 1.6:1 ratio of the desired both Boc protected precursors imidazole and oxazole. The final product was purified by reverse phase preparative HPLC, then lyophilized to dryness to obtain TFA salt of the title product (34 mg, 16% yield) as a white solid. MS (ESI, M+H$^+$) = 482.4; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 8.37 (br s, 3H), 7.96 (br s, 1H), 7.82 (dd, 1H, *J* = 8.4 Hz, *J* = 2.0 Hz), 7.74 (d, 2H, *J* = 8.4 Hz), 7.70 (d, 2H, *J* = 7.2 Hz), 7.57 (d, 2H, *J* = 8.4 Hz), 7.47 (t, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 9.2 Hz, 1H), 7.37 (t, 1H, *J* = 7.6 Hz), 5.68 (br s, 1H), 5.34 (s, 2H), 3.76 (d, 1H, *J* = 11.6 Hz), 3.66 (d, 1H, *J* = 11.6 Hz), 2.39 (s, 3H), 1.54 (s, 3H).

**(*S*)-2-Amino-2-(4-(4-(biphenyl-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-5-methyloxazol-2-yl)propan-1-ol (4)**



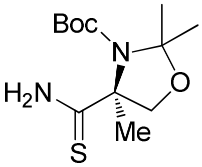
The reaction to synthesize the Boc protected precursor to imidazole analog afforded a 1.6:1 ratio of the Boc protected both imidazole and oxazole. The final product was purified by reverse phase preparative HPLC, then lyophilized to dryness to obtain TFA salt of the title product (8.1 mg, 10% yield) as a white solid. MS (ESI, M+H$^+$) = 483.4; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 8.70 (br s, 3H), 7.96 (d, 1H, *J* = 2.0 Hz, 1H), 7.92 (dd, 1H, *J* = 8.4 Hz, *J* = 2.0 Hz), 7.74 (d, 2H, *J* = 8.4 Hz), 7.70 (d, 2H, *J* = 7.2 Hz), 7.57 (d, 2H, *J* = 8.4 Hz), 7.50-7.45 (m, 3H), 7.37 (t, 1H, *J* = 7.6 Hz), 5.83 (br s, 1H), 5.38 (s, 2H), 3.86 (dd, 1H, *J* = 11.0 Hz, J = 4.4Hz), 3.71 (dd, 1H, *J* = 11.2 Hz, *J* = 4.4), 2.57 (s, 3H), 1.56 (s, 3H).

### (*R*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1*H*-imidazol-2-yl)propan-1-ol (15)



The final product was purified by reverse phase preparative HPLC, then lyophilized to dryness to obtain TFA salt of the product. The product was obtained as a white solid in 39% (40 mg) yield. MS (ESI, M+H$^+$) = 414.2; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 8.41 (br s, 3H), 8.03 (d, 1H, *J* = 1.5 Hz), 7.96 (dd, 1H, *J* = 8.8 Hz, *J* = 2.0 Hz), 7.72 (br s, 1H), 7.24 (d, 1H, *J* = 8.4), 5.70 (br s, 1H), 4.09 (t, 2H, *J* = 6.2 Hz), 3.75 (d, 1H, *J* = 11.2 Hz), 3.64 (d, 1H, *J* = 11.2 Hz), 1.65-1.76 (m, 2H), 1.54 (s, 3H), 1.36-1.48 (m, 2H), 1.18-1.36 (m, 8H), 0.84 (t, 3H, *J* = 6.8 Hz).

### (*S*)-*tert*-butyl 4-carbamothioyl-2,2,4-trimethyloxazolidine-3-carboxylate (22)

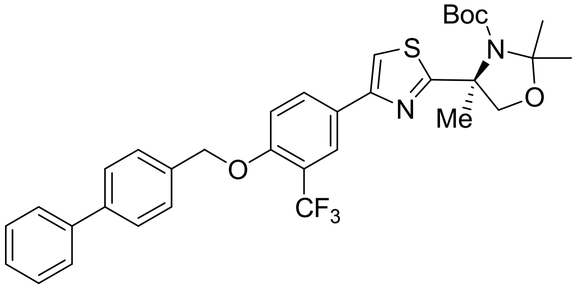


To a mixture of the (*S*)-3-(*tert*-butoxycarbonyl)-2,2,4-trimethyloxazolidine-4-carboxylic acid (0.50 g, 1.0 equiv), $NH_4Cl$ (1.03 g, 10.0 equiv), and HATU (1.10 g, 1.5 equiv) in DMF (10 mL) under nitrogen atmosphere was added DIPEA (2.50 mL, 10.0 equiv). The reaction mixture was stirred overnight. The reaction was then diluted with EtOAc (50 mL), washed with 10% $NH_4Cl$ (2 x 50 mL) and saturated NaCl (1 x 50 mL). The organic layer was dried over anhydrous

$MgSO_4$ then the solvent removed *in vacuo*. The crude product was carried forward as is. TLC (EtOAc), $R_f = 0.2$.

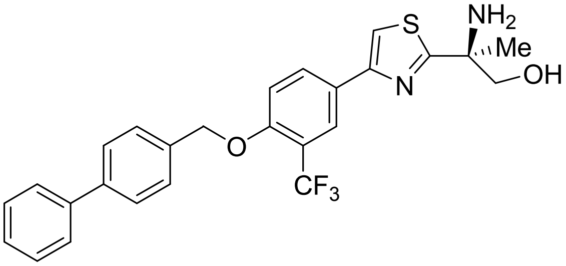
To a mixture of the desired amide (from last step, 1.0 equiv) and Lawesson's reagent (3.9 g, 5.0 equiv) was added dry THF (20 mL) then refluxed overnight. The solvent removed *in vacuo*. TLC showed a spot to spot conversion of the starting material to product. The product was purified by silica gel column chromatography using the Combi-Flash system (Hex:EtOAc). The product was obtained as a white solid in 76% (400 mg) yield. TLC (EtOAc), $R_f = 0.5$; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 4.15 (br s, 2H), 3.74-3.86 (m, 2H), 1.64 (s, 3H), 1.57 (s, 3H), 1.46 (s, 3H), 1.35 (s, 9H).

**(*S*)-*tert*-butyl 4-(4-(4-(biphenyl-4-ylmethoxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,2,4-trimethyloxazolidine-3-carboxylate (23)**



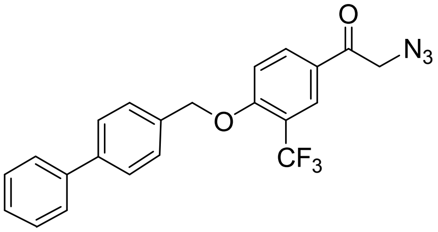
A mixture of the (*S*)-*tert*-butyl 4-carbamothioyl-2,2,4-trimethyloxazolidine-3-carboxylate (0.40 g, 1.0 equiv) and bromo-acetophenone (0.66 g, 1.0 equiv) were dissolved in dry THF (10 mL) under nitrogen atmosphere then refluxed overnight. The solvent was then evaporated to dryness *in vacuo*. The product was purified by silica gel column chromatography using the Combi-Flash system (Hex:EtOAc) to obtained a thick colorless oil in 60% (0.55 g) yield. TLC (3:1, Hex/EtOAc), $R_f = 0.6$.

**(*S*)-2-amino-2-(4-(4-(biphenyl-4-ylmethoxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propan-1-ol (5)**



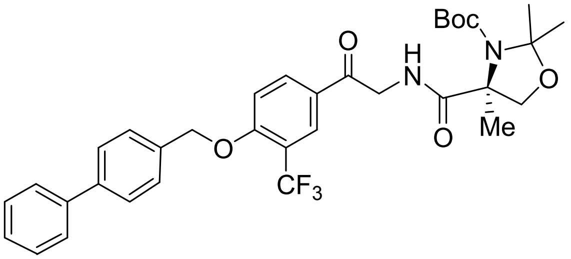
The product was purified by silica gel column chromatography using the Combi-Flash system ($CH_2Cl_2$:IPA) to afford as a white solid in 99% (430 mg) yield. MS (ESI, $M+H^+$) = 485.4; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 8.66 (br s, 3H), 8.34 (d, 1H, *J* = 2.0 Hz), 8.30 (s, 1H), 8.25 (dd, 1H, *J* = 8.8 Hz, *J* = 1.6 Hz), 7.66-7.75 (m, 4H), 7.44-7.58 (m, 5H), 7.34-7.40 (m, 1H), 5.39 (s, 2H), 3.82 (d, 1H, *J* = 11.6 Hz), 3.75 (d, 1H, *J* = 11.6 Hz), 1.66 (s, 3H).

**2-Azido-1-(4-(biphenyl-4-ylmethoxy)-3-(trifluoromethyl)phenyl)ethanone (24, R = 4-biphenyl)**



To a solution of the substituted acetophenone (1.65 g, 1.0 equiv) in EtOAc/$CHCl_3$ (1:1) under nitrogen atmosphere was added $CuBr_2$ (3.0 g, 3.0 equiv). The reaction mixture was heated at reflux for 3 hours. The reaction was then diluted with EtOAc and washed with $H_2O$ (2 x) and saturated NaCl (1 x). The organic layer was dried over anhydrous $MgSO_4$ then the solvent removed *in vacuo*. TLC (2:1, Hex/EtOAc), $R_f$ = 0.5. To a mixture of the desired bromo-acetophenone (from last step, 1.0 equiv), in DMF (20 mL) was added $NaN_3$ (0.87 g, 3.0 equiv), then stirred in DMF for 20 minutes. The reaction mixture was diluted with EtOAc (50 mL) and washed with $H_2O$ (2 x 50). The solvent removed *in vacuo* and the product was purified by silica gel column chromatography using the Combi-Flash system (Hex:EtOAc) as a white solid in 36% (0.65 g) yield. TLC (2:1, Hex/EtOAc), $R_f$ = 0.3; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, 1H, *J* = 2.4 Hz), 8.07 (dd, 1H, *J* = 8.8 Hz, *J* = 2.4 Hz), 7.56-7.65 (m, 4H), 7.42-7.52 (m, 4H), 7.38 (t, 1H, *J* = 8.2 Hz), 7.16 (d, 1H, *J* = 8.0 Hz), 5.34 (s, 2H), 4.52 (s, 2H).

**(*R*)-*tert*-Butyl 4-(2-(4-(biphenyl-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-2-oxoethylcarbamoyl)-2,2,4-trimetyloxazolidine-3-carboxylate (25, X = $CH_2$, R = 4-biphenyl)**

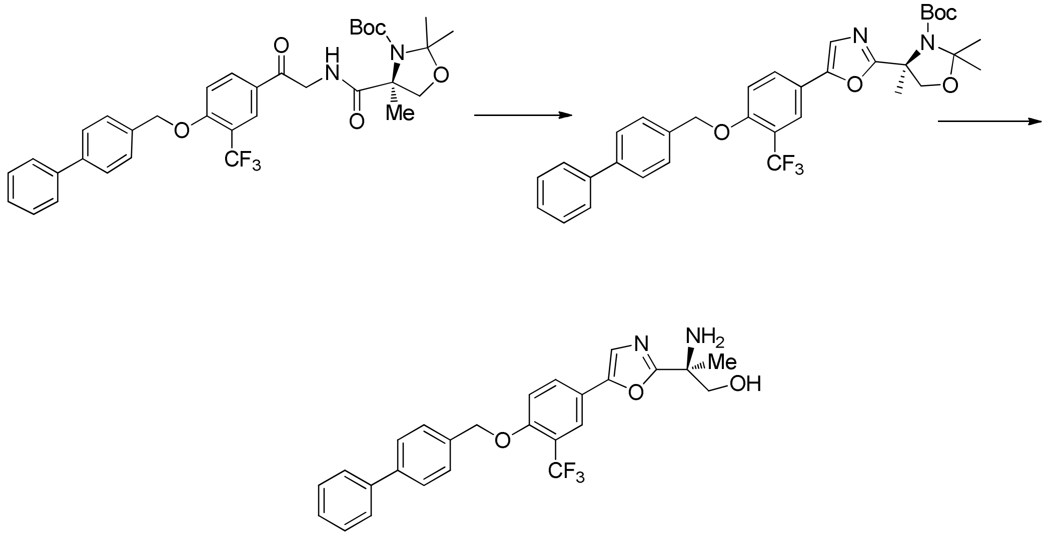


To a solution of the azido-acetophenone (0.99 g, 1.0 equiv) in MeOH (20 mL) was added concentrated HCl (3.0 mL), and 10% Pd/C (99 mg). The reaction mixture was stirred under an atmosphere of $H_2$ (g) for 2 hours. The reaction was then filtered through a thin layer of Celite then the solvent removed *in vacuo*. The obtained white solid amino-acetophenone was carried forward as is.

To a solution of protected oxazolidine-4-carboxylic acid (697 mg, 1 equiv), HATU (1.12 g, 1.2 equiv), and DIEA (2.13 mL, 4.5 equiv) in DCM:DMF (5:1, 20 mL) was added amino-acetophenone. The resultant mixture was stirred at RT for 1h. The reaction was then condensed *in vacuo* and the residue was purified by chromatography (silica gel, hexane:ethyl acetate, 70:30, v/v) to afford the title compound (860 mg, 57% yield) as a white solid. MS (ESI, M+Na) =

649.5; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.26 (s, 1H), 7.78 (d, 1H, *J* = 8.0 Hz), 7.64 (d, 2H, *J* = 8.0 Hz), 7.60 (d, 2H, *J* = 7.2 Hz), 7.51 (d, 2H, *J* = 8.0 Hz), 7.44 (t, 2H, *J* = 6.8 Hz), 7.35 (t, 1H, *J* = 7.2 Hz), 7.16 (d, 1H, *J* = 9.2 Hz), 5.33 (s, 2H), 4.73 (dd, 2H, *J* = 6.0 Hz, *J* = 4.8 Hz), 4.43 (d, 1H, *J* = 8.8 Hz), 4.18 (d, 1H, *J* = 8.4 Hz), 1.66-1.56 (m, 9H), 1.50 (s, 3H), 1.43 (s, 6H).

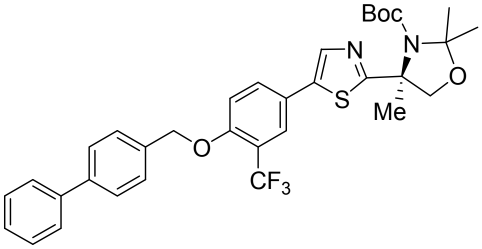
**(*S*)-*tert*-butyl 4-(5-(4-([1,1'-biphenyl]-4-ylmethoxy)-3-(trifluoromethyl)phenyl)oxazol-2-yl)-2,2,4-trimethyloxazolidine-3-carboxylate (28, Y=CH, Z = O) and (S)-2-(5-(4-([1,1'-biphenyl]-4-ylmethoxy)-3-(trifluoromethyl)phenyl)oxazol-2-yl)-2-aminopropan-1-ol (6)**



To a solution of triphenylphosphine (210 mg, 0.8 mmol), hexachloroethane (95 mg, 0.4 mmol), and triethylamine (224 uL, 1.6 mmol) in dichloromethane (1.0 mL) was added (*R*)-*tert*-Butyl 4-(2-(4-(biphenyl-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-2-oxoethyl-carbamoyl)-2,2,4-trimetyloxazolidine-3-carboxylate (100 mg, 0.16 mmol) in dichloromethane (2.0 mL). The reaction mixture was stirred at room temperature for 1 h followed by a direct preparative TLC purification (Silica Gel GF, preparative layer with UV254, 20x20cm, 1000 microns), eluted by 90 mL of hexanes:ethyl aceate, 2:1, v/v) to afford the cyclized oxazole intermediate **28** (77 mg, yield ~ 79%). MS (ESI, M+H$^+$) = 609.4; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.81 (d, 1H, *J* = 2.0

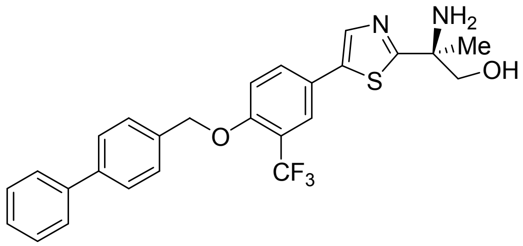
Hz), 7.68 (dd, 1H, *J* = 2.0 Hz, *J* = 8.8 Hz), 7.62 (d, 2H, *J* = 8.0 Hz), 7.60 (dd, 2H, *J* = 1.6 Hz, *J* = 8.0 Hz), 7.51 (d, 2H, *J* = 8.4 Hz), 7.44 (t, 2H, *J* = 8.0 Hz), 7.35 (t, 1H, *J* = 7.2 Hz), 7.25 (d, 1H, *J* = 8.0 Hz), 7.11 (t, 1H, *J* = 8.4 Hz), 5.27 (s, 2H), 4.21 (d, 1H, J = 8.4 Hz), 3.95 (d, 1H, J = 8.8 Hz), 1.87 (s, 3H), 1.78 (s, 3H), 1.72 (s, 3H), 1.45 (s, 3H), 1.12 (s, 6H). This intermediate was dissoved in THF (4 mL) and treated with HCl (2M) at 85 °C overnight. The reaction was diluted with ethyl acetate and basified by sodium bicarbonate (5%) to pH 9. The organic layer was separated, washed with brine, dried over $Na_2SO_4$ and condensed to provided crude product, of which, about 35% was used to prepare its corresponding phosphate and the rest was purified by preparative HPLC to afford the titel compound (23 mg, yield~58%) as a white solid. MS (ESI, $M+H^+$) = 469.2; $^1H$ NMR (400 MHz, $CD_3OD$) δ 7.98 (d, 1H, *J* = 2.0 Hz), 7.92 (dd, 1H, *J* = 2.0 Hz, *J* = 8.8 Hz), 7.65 (d, 2H, *J* = 8.0 Hz), 7.62 (dd, 2H, *J* = 0.8 Hz, *J* = 7.6 Hz), 7.45 (d, 1H, *J* = 8.2 Hz), 7.42 (d, 2H, *J* = 10.4 Hz), 7.43 (t, 2H, *J* = 7.6 Hz), 7.38 (d, 1H, *J* = 8.6 Hz), 7.33 (t, 1H, *J* = 7.6 Hz), 5.35 (s, 2H), 4.06 (d, 1H, J = 12.0 Hz), 3.85 (d, 1H, J = 11.6 Hz), 1.73 (s, 3H).

**(*R*)-*tert*-Butyl-4-(5-(4-(biphenyl-4-ylmethoxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,2,4-trimethyloxazolidine-3-carboxylate (28, Y = CH, Z = S)**



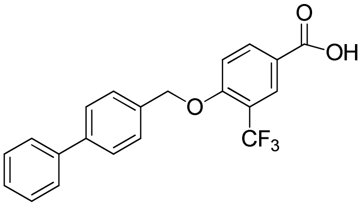
The suspension of protected oxazolidine-amide (120 mg, 1.0 equiv) and Lawesson's Reagent (387 mg, 5 equiv) in toluene (5 mL) was sealed and heated at 120 °C for 1.5 hours. After cooling to RT, the reaction was filterated and the filtrate was condensed and purified by chromatography (silica gel, hexane:ethyl acetate, 4:1, v/v) to afford the title compound (81 mg, yield 64%) as a white solid. MS (ESI, M+H$^+$) = 625.7; $^1$H NMR (400 MHz, CDCl3) δ 7.74 ( s, 2H), 7.63–7.58 (m, 5H), 7.52 (d, 2H, *J* = 8.4 Hz), 7.44 (t, 2H, *J* = 8.0 Hz), 7.35 (t, 1H, *J* = 7.2 Hz), 7.09 (d, 1H, *J* = 8.4 Hz), 5.27 (s, 2H), 4.18 (d, 1H, *J* = 8.8 Hz), 4.03 (d, 1H, *J* = 9.6 Hz), 1.90 (s, 3H), 1.80 (s, 3H), 1.67 (s, 3H), 1.50 (s, 3H), 1.27 (s, 6H).

### (*S*)-2-Amino-2-(5-(4-(biphenyl-4-ylmethoxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propan-1-ol (7)



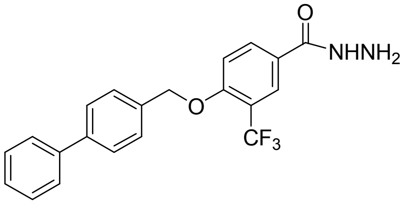
The protected compound **28** (28 mg, 1 equiv) was treated with TsOH (10 equiv in 5 mL of methanol 5 mL) at refluxing temperature for 4 hours. The reaction was condensed and the residue was purified by reverse phase preparative HPLC, then lyophilized to dryness to obtain TFA salt of the title compound (16 mg, 60% yield) as a white solid. MS (ESI, M+H$^+$) = 485.5; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 8.55 (br s, 2H), 8.33 (s, 1H), 7.95 (dd, 1H, *J* = 8.4 Hz, *J* = 2.0 Hz), 7.92 (s, 1H), 7.73 (d, 2H, *J* =8.4 Hz), 7.70 (d, 2H, *J* = 8.4 Hz), 7.56 (d, 2H, *J* = 8.4 Hz), 7.47 (t, 3H, *J* = 8.0 Hz), 7.37 (t, 1H, *J* = 7.2 Hz), 5.91 (br s, 1H), 5.40 (s, 2H), 3.81 (dd, 1H, *J* = 10.8, Hz, *J* = 4.8 Hz), 3.74 (dd, 1H, *J* = 10.8 Hz, *J* = 4.8 Hz), 1.646 (s, 3H).

### 4-(Biphenyl-4-ylmethoxy)-3-(trifluoromethyl)benzoic acid (26, R = 4-biphenyl)



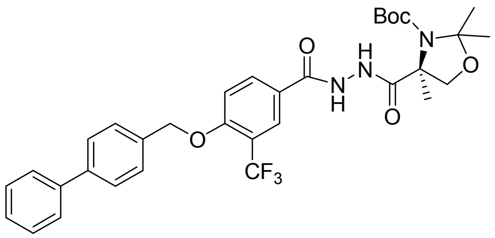
Using methyl 4-fluoro-3-(trifluoromethyl)benzoate as a starting material, the title compound was prepared analogously to 4-(octyloxy)-3-(trifluoromethyl)benzoic acid as a white solid (1.33 g, 83% yield). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, 1H, *J* = 2.0 Hz), 8.22 (dd, 1H, *J* = 9.2 Hz, *J* = 2.0 Hz), 7.64-7.58 (m, 4H), 7.51 (d, 2H, *J* = 8.4 Hz), 7.45 (t, 2H, *J* = 8.0 Hz), 7.36 (t, 1H, *J* = 7.2 Hz), 7.13 (d, 1H, *J* = 8.4 Hz), 5.33 (s, 2H).

**4-(Biphenyl-4-ylmethoxy)-3-(trifluoromethyl)benzohydrazide (27, R = 4-biphenyl)**



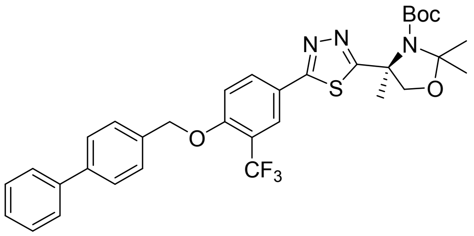
The title compound was prepared analogously to 4-(octyloxy)-3-(trifluoromethyl)-benzohydrazide in 74% yield (147 mg, white solid) except that preparative TLC (silica gel, dichloromethane:methanol:triethyl amine = 10:1:0.1, v/v/v, as mobile phase) purification was performed in order to obtain pure sample. MS (ESI): 386.9 ($MH^+$); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.90 (d, 1H, *J* = 7.6 Hz), 7.67-7.57 (m, 4H), 7.49 (d, 2H, *J* = 7.6 Hz), 7.44 (t, 2H, *J* = 7.2 Hz), 7.35 (t, 1H, *J* = 7.6 Hz), 7.11 (d, 1H, *J* = 8.8 Hz), 5.28 (s, 2H).

**4-{*N'*-[4-(Biphenyl-4-ylmethoxy)-3-trifluoromethyl-benzoyl]-hydrazinocarbonyl}-2,2,4-trimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (25, X = NH)**



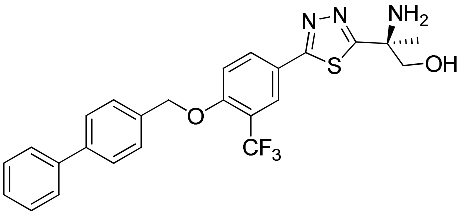
The title compound was prepared analogously to (*S*)-*tert*-butyl 2,2,4-trimethyl-4-(2-(4-(octyloxy)-3-(trifluoromethyl)benzoyl)-hydrazinecarbonyl)oxazolidine-3-carboxylate (**25**) in quantitative yield (32 mg, white solid). MS (ESI): 649.9 (M+Na), HPLC retention time on a C8(2) column (50 × 3.00 mm, 3 μ) is 3.69 min with gradient 50-95% acetonitrile-$H_2O$ (0.1% TFA) in 5 min as mobile phase.

**(*R*)-*tert*-Butyl 4-(5-(4-(biphenyl-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyloxazolidine-3-carboxylate (28, Y = H, Z = S)**



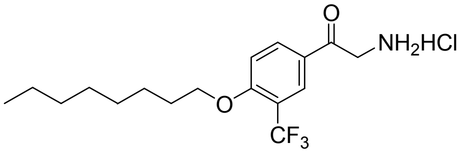
The title compound was prepared analogously to (*R*)-*tert*-butyl 2,2,4-trimethyl-4-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)oxazolidine-3-carboxylate (**28**) in 50% yield (45 mg, white solid). MS (ESI): 626.01 ($MH^+$), HPLC retention time on a C8(2) column (50 × 3.00 mm, 3 μ) is 4.12 min with gradient 40-98% acetonitrile-$H_2O$ (0.1% TFA) in 4.0 min as mobile phase.

**(*S*)-2-Amino-2-(5-(4-(biphenyl-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8)**



The title compound was prepared analogously to (*S*)-2-amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (**10**) in 43% yield (18 mg, white solid). MS (ESI): 485.91 ($MH^+$); NMR (400 MHz, DMSO-$d_6$) δ 8.26 (dd, 1H, *J* = 8.8 Hz, *J* = 2.0 Hz), 8.21 (d, 1H, *J* = 2.0 Hz), 7.73 (d, 2H, *J* = 8.0 Hz), 7.69 (d, 2H, *J* = 8.0 Hz), 7.58 (d, 1H, *J* = 8.8 Hz), 7.56 (t, 2H, *J* = 8.8 Hz), 7.45 (t, 2H, *J* = 7.2 Hz), 7.38 (t, 1H, *J* = 7.2 Hz), 6.01 (br, 1H), 5.46 (s, 2H), 3.82 (d, 1H, *J* = 11.2 Hz), 3.74 (d, 1H, *J* = 11.2Hz), 1.68 (s, 3H).

**2-Azido-1-(4-(octyloxy)-3-(trifluoromethyl)phenyl)ethanone (24, R = *n*-heptyl) and 2-Amino-1-(4-(octyloxy)-3-(trifluoromethyl)phenyl)ethanone hydrochloride**

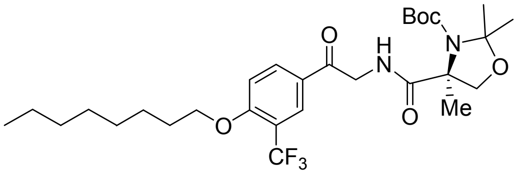


To a solution of the substituted acetophenone **16** ($R_1$ = H, $R_2$ = *n*-heptyl) (390 mg, 1.0 equiv) in dry $CH_2Cl_2$ (9 mL) under nitrogen atmosphere was added $Bu_4NBr_3$ (0.60 g, 1.0 equiv). To the solution was added anhydrous MeOH (1.0 mL). The reaction mixture was stirred at room temperature overnight. The solvent was removed *in vacuo*, and the bromo-acetophenone product (**17**, R = n-heptyl) was used as is in the next step. TLC (4:1, Hex/EtOAc), $R_f$ = 0.6.

To the desired bromo-acetophenone (from last step, 1.0 equiv), in DMF (10 mL) was added $NaN_3$ (0.24 g, 3.0 equiv). The resulting mixture was then stirred in DMF for 1 hour. The reaction mixture was diluted with EtOAc (50 mL) and washed with $H_2O$ (2 x 50). The solvent removed *in vacuo* and the product was purified by silica gel column chromatography using the Combi-Flash system (Hex:EtOAc) to give the azido-acetophenone product as a white solid in 99% (0.44 g) yield. TLC (4:1, Hex/EtOAc), $R_f = 0.4$.

To a solution of the azido-acetophenone (0.44 g, 1.0 equiv) in MeOH (10 mL) was added concentrated HCl (1.5 mL), and 10% Pd/C (44 mg). The reaction mixture was stirred under an atmosphere of $H_2$ (g) for 2 hours. The reaction mixture was then filtered through a thin layer of Celite and the solvent was removed *in vacuo*. The amino-acetophenone [2-amino-1-(4-(octyloxy)-3-(trifluoromethyl)phenyl)ethanone] was obtained a white solid in quantitative yield (0.46 mg) with 90% purity. TLC (1:5 EtOAc:Hex), $R_f = 0.4$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.18 (d, 1H, *J* = 2.0 Hz), 8.10 (dd, 1H, *J* = 8.8 Hz, *J* = 2.3 Hz), 7.02 (d, 1H, *J* = 8.8 Hz), 4.52 (s, 2H), 4.12 (t, 2H, *J* = 6.4 Hz), 1.80-1.89 (m, 2H), 1.42-1.54 (m, 2H), 1.22-1.40 (m, 8H), 0.89 (t, 3H, *J* = 6.7 Hz).

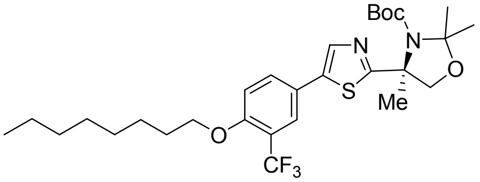
### **(*R*)-*tert*-Butyl 2,2,4-trimethyl-4-(2-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-2-oxoethylcarbamoyl)oxazolidine-3-carboxylate (25, X = $CH_2$)**



To a solution of protected oxazolidine-4-carboxylic acid **20** (176 mg, 1 equiv), HATU (310 mg, 1.2 equiv), and DIEA (1.2 mL, 10 equiv) in $CH_2CL_2$/DMF (1:1, 10 mL) was added amino-acetophenone [2-amino-1-(4-(octyloxy)-3-(trifluoromethyl)phenyl)ethanone](250 mg, 1.0 equiv). The resultant mixture was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc (50 mL) and washed with 10% $NH_4Cl$ (2 x 50 mL) and saturated NaCl

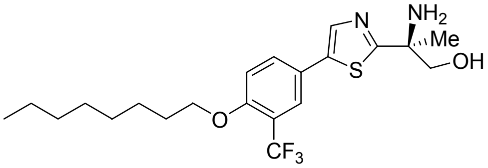
(1 x 50 mL). The solvent removed *in vacuo* and the product was obtained, silica gel column chromatography using the Combi-Flash system (Hex:EtOAc), as a white solid in 40% yield (185 mg). TLC (1:2 EtOAc:Hex), $R_f = 0.3$; MS (ESI, M+Na) = 572.99; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.11 (d, 1H, *J* = 8.4 Hz), 7.05 (d, 1H, *J* = 8.4 Hz), 4.62-4.79 (m, 2H), 4.13 (t, 2H, *J* = 6.4 Hz), 3.28 (br s, 1H), 1.22-1.90 (m, 30H), 0.89 (t, 3H, *J* = 6.4 Hz).

**(*R*)-*tert*-Butyl 2,2,4-trimethyl-4-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)oxazolidine-3-carboxylate (28, Y = CH, Z = S)**



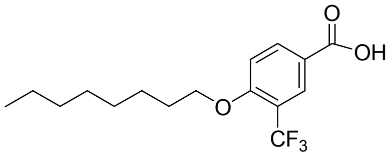
A suspension of protected oxazolidine-amide **25** (180 mg, 1.0 equiv) and Lawesson's Reagent (390 mg, 3.0 equiv) in toluene (5 mL) was sealed and heated at 100 °C for 1 hour. After cooling to room temperature, the reaction mixture was purified by silica gel column chromatography using the Combi-Flash system (Hex:EtOAc) as a thick colorless oil in 67% yield (120 mg). TLC (1:2 EtOAc:Hex), $R_f = 0.8$; MS (ESI, M+H$^+$) = 571.11; $^1$H NMR (400 MHz, CDCl3) δ 7.73 (br s, 1H), 7.70 (s, 1H), 7.61 (d, 1H, *J* = 6.8 Hz), 7.01 (d, 1H, *J* = 6.8 Hz), 3.96-4.28 (m, 4H), 1.21-1.99 (m, 30H), 0.89 (t, 3H, *J* = 7.6 Hz).

**(*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propan-1-ol (9)**



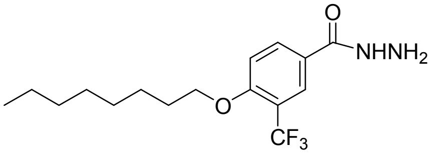
A solution of thiazole **28** (120 mg) and *para*-toluenesulfonic acid (PTSA, 400 mg, 10 equiv) in MeOH (6 mL) was refluxed for 6 hours. The solvent was removed *in vacuo* and the product was purified by reverse phase preparative HPLC, then lyophilized to dryness to obtain the trifluoroacetate salt of the product as a white solid in 79% yield (90.5 mg). MS (ESI, M+H$^+$) = 431.01; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 8.27 (s, 1H), 7.88 (dd, 1H, *J* = 8.8 Hz, *J* = 2.4 Hz), 7.85 (d, 1H, *J* = 2.4 Hz), 7.34 (d, 1H, *J* = 8.4 Hz), 5.77 (br s, 1H), 4.14 (t, 2H, *J* = 6.4 Hz), 3.76 (dd, 1H, *J* = 11.2, Hz, *J* = 1.2 Hz), 3.66 (dd, 1H, *J* = 11.2 Hz, *J* = 1.2 Hz), 1.73 (q, 2H, *J* = 6.8 Hz), 1.58 (s, 3H), 1.36-1.48 (m, 2H), 1.20-1.36 (m, 8H), 0.85 (t, 3H, *J* = 6.4 Hz).

### 4-(Octyloxy)-3-(trifluoromethyl)benzoic acid (26, R = *n*-heptyl)



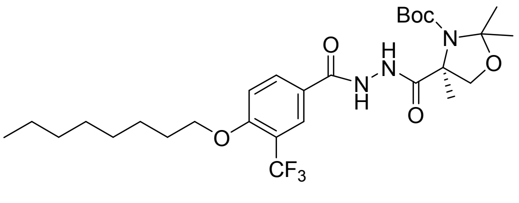
To a solution of 1-octanol (315 μL, 2.0 mmol) in anhydrous THF (5 mL) was added potassium *t*-butoxide (5 mL, 1M solution in THF). The mixture was heated at 70 ºC for 15 min then cooled down to room temperature. 4-Fluoro-3-trifluoromethylbenzoid acid (417 mg, 2.0 mmol) in THF (5 mL) was added and the resultant was heated at 75 ºC overnight. After cooling down to room temperature, the reaction mixture was diluted with ethyl acetate and washed with water. The water layer was acidified to a pH of approximately 3 with HCl (2M) and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $Na_2SO_4$ and concentrated *in vacuo* to afford the title compound (632 mg, HPLC purity > 95%), which was used for next reaction without further purification. HPLC retention time on a C8(2) column (30 × 3.00 mm, 3 μ) was 3.28 min with gradient 50-98% acetonitrile-$H_2O$ (0.1% TFA) in 3.5 min as mobile phase.

**4-(Octyloxy)-3-(trifluoromethyl)benzohydrazide (27, R = *n*-heptyl)**



4-(Octyloxy)-3-(trifluoromethyl)benzoic acid (**26**, R = *n*-heptyl) (632 mg, 1.0 equiv) was stirred with HATU (905 mg) and DIEA (1.7 mL) in $CH_2Cl_2$-DMF (10 mL, 4:1) for 10 min followed by addition of hydrazine (297 μL) dropwise. The reaction mixture was continuously stirred for another hour, then was diluted with ethyl acetate (30 mL) and washed with water (10 mL) and brine (3 × 15 mL). The organic layer was dried over $Na_2SO_4$ and concentrated *in vacuo* to afford the title compound in 94% yield (661 mg, white solid, HPLC purity > 90%), which was used for next reaction without further purification. MS (ESI): 333.08 ($MH^+$); HPLC retention time on a C8(2) column (30 × 3.00 mm, 3 μ) is 1.61 min with gradient 50-98% acetonitrile-$H_2O$ (0.1% TFA) in 3.5 min as mobile phase.

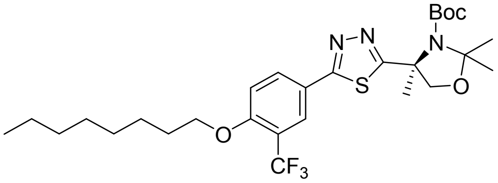
**(*S*)-*tert*-Butyl 2,2,4-trimethyl-4-(2-(4-(octyloxy)-3-(trifluoromethyl)benzoyl)-hydrazinecarbonyl)oxazolidine-3-carboxylate (25, X = NH)**



(*R*)-3-(*tert*-Butoxycarbonyl)-2,2,4-trimethyloxazolidine-4-carboxylic acid (**20**) (210 mg, 0.81 mmol) was stirred with HATU (372 mg, 0.98 mmol) and diisopropylethyl amine (DIEA) (0.705 mL, 4.1 mmol) in $CH_2Cl_2$:DMF (2:1, 6 mL) for 10 min followed by addition of 4-(octyloxy)-3-(trifluoromethyl)benzohydrazide (**27,** R = *n*-heptyl) (270 mg, 0.81 mmol) in

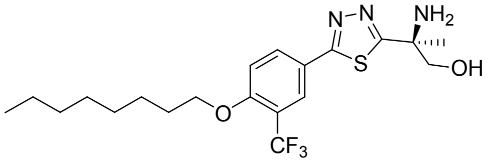
$CH_2Cl_2$ (2 mL). The reaction was stirred at room temperature for 1 hour and then was concentrated under vacuum. The residue was diluted with ethyl acetate (20 mL) and washed with water (5 mL), brine (2 × 10 mL) and dried over $Na_2SO_4$. The organic layer was concentrated *in vacuo* and chromatographed on a silica gel column (ethyl acetate-hexane, 0-33%, as eluent) to afford the title compound (428 mg, white solid, 82% yield). MS (ESI): 573.84 ($MH^+$); $^1$H NMR (400 MHz, $CDCl_3$) δ 9.43 (br, 2H), 8.06 (d, 1H, *J* = 2.0 Hz), 7.94 (dd, 1H, *J* = 8.8 Hz, *J* = 2.0 Hz), 6.96 (d, 1H, *J* = 8.8 Hz), 4.52 (br, 1H), 4.07 (t, 2H, *J* = 6.4 Hz), 3.76 (br, 1H), 1.82 (m, 2H), 1.67 (s, 6H), 1.57 (s, 3H), 1.51 (s, 9H), 1.51-1.43 (m, 4H), 1.38-1.24 (m, 6H), 0.88 (t, 3H, *J* = 7.2 Hz).

**(*R*)-*tert*-Butyl 2,2,4-trimethyl-4-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)oxazolidine-3-carboxylate (28, Y = N, Z = S)**



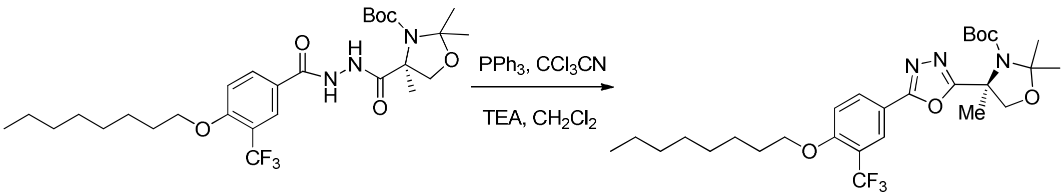
A solution of (*S*)-*tert*-butyl 2, 2, 4-trimethyl-4-(2-(4-(octyloxy)-3-(trifluoromethyl)-benzoyl)hydrazinecarbonyl)oxazolidine-3-carboxylate (**25**, X = NH) (228 mg, 0.39 mmol) in toluene (5 mL) was treated with Lawesson's reagent (473 mg, 1.17 mmol) at 85 °C for 2 hours. The reaction was cooled down to room temperature and the supernatant was chromatographed on a silica gel column eluted with ethyl acetate-hexane (0-30%, v/v) to afford the title compound (156 mg, white solid, 70% yield). MS (ESI): 572.17 ($MH^+$), $^1$H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, 1H, *J* = 8.8 Hz), 8.08 (d, 1H, *J* = 6.8 Hz), 7.06 (d, 1H, *J* = 8.0 Hz), 4.41 (d, 1H, *J* = 8.0 Hz), 4.18 (d, 1H, *J* = 9.6 Hz), 4.13-4.07 (m, 3H), 2.00 (s, 3H), 1.88-1.81 (m, 2H), 1.78 (s, 3H), 1.71-160 (m, 4H), 1.51 (s, 3H), 1.52-1.45 (m, 2H), 1.39-1.28 (m, 13H), 0.89 (t, 3H, *J* = 7.2 Hz).

## **(*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (10)**



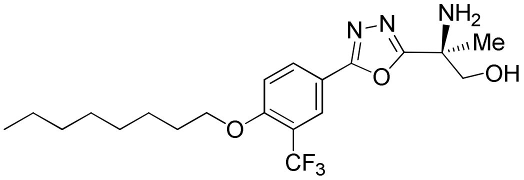
A solution of (*S*)-*tert*-butyl 2,2,4-trimethyl-4-(2-(4-(octyloxy)-3-(trifluoromethyl)-benzoyl)hydrazinecarbonyl)oxazolidine-3-carboxylate (**28**, Y = N, Z = S) (156 mg, 0.27 mmol) in methanol (5 mL) was treated with *p*-toluenesulfonic acid monohydrate (259 mg, 1.36 mmol) at 70 °C for 2 hours. The reaction mixture was then cooled to room temperature and purified by prep HPLC on a C8(2) column ((Luna, 5μ, 100 × 21.10 mm) with acetonitrile-$H_2O$ (0.1% TFA) as mobile phase and gradient 30-98% in 20 min. The title compound was obtained as the bis-TFA salt (36 mg, white solid, 20%). MS (ESI): 432.00 ($MH^+$); $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 8.21 (dd, 1H, *J* = 2.0 Hz, *J* = 8.8 Hz), 8.15 (d, 1H, *J* = 2.0 Hz), 8.09 (br s, 2H), 7.45 (d, 1H, *J* = 8.8 Hz), 5.96 (t, 1H, *J* = 4.8 Hz), 4.21 (t, 2H, *J* = 6.4 Hz), 3.81 (dd, 1H, *J* = 11.2 Hz, *J* = 5.2 Hz), 3.73 (dd, 1H, *J* = 11.2 Hz, *J* = 5.2 Hz), 1.79-1.72 (m, 2H), 1.66 (s, 3H), 1.47-1.40 (m, 2H), 1.37-1.23 (m, 8H), 0.86 (t, 3H, *J* = 6.8 Hz).

## **(*S*)-*tert*-butyl 2,2,4-trimethyl-4-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)oxazolidine-3-carboxylate (28, Y = N, Z = O)**



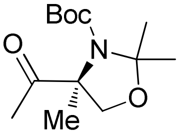
The title compound was prepared from (*S*)-*t*-butyl- 2,2,4-trimethyl-4-(2-(4-(octyloxy)benzoyl)hydrazinecarbonyl)oxazolidine-3-carboxylate (**25**, X = NH) using published procedure[1] in 85% yield (38 mg, white solid). MS (ESI, M+H+) = 556.1; $^1$HNMR (400 MHz, CDCl3) δ 8.22 (d, 1H, *J* = 1.6 Hz), 8.14 (d, 1H, *J* = 8.8 Hz), 8.10 (dd, 1H, *J* = 8.8 Hz, *J* = 1.6 Hz), 4.22 (d, 1H, *J* = 8.8 Hz), 4.12 (t, 2H, *J* = 6.0 Hz), 4.02-3.99 (m, 1H), 1.94 (s, 3H), 1.87-1.82 (m, 2H), 1.76 (s, 3H), 1.72 (s, 3H), 1.51-1.46 (m, 4H), 1.24-1.20 (m, 7H), 1.25 (s, 6H), 0.89 (t, 3H, *J* = 7.2 Hz).

**(*S*)-2-amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)propan-1-ol (11)**



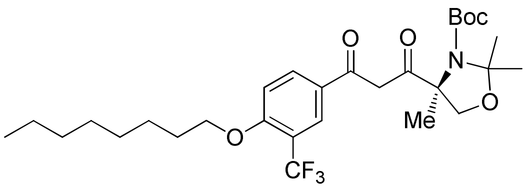
Standard 20% TFA deprotection of (*R*)-t-butyl 2,2,4-trimethyl-4-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-oxadi-azol-2-yl)oxazolidine-3-carboxylate (**28,** Y=N, Z=O) afforded the title compound in 55% yield (20 mg, white solid). (ESI, M+H+) = 416.0; $^1$H NMR (400 MHz, CD3OD) δ 8.18 (d, 1H, *J* = 8.8 Hz), 8.18 (s, 1H), 7.30 (d, 1H, *J* = 8.8 Hz), 4.12 (t, 2H, *J* = 6.0 Hz), 4.01, 3.79 (AB, 2H, *J* = 11.6 Hz), 1.74 (m, 2H), 1.68 (s, 3H), 1.43 (m, 2H), 1.31-1.19 (m, 8H), 0.81 (t, 3H, *J* = 2.8 Hz).

**(*R*)-*tert*-Butyl 4-acetyl-2,2,4-trimethyloxazolidine-3-carboxylate (29)**



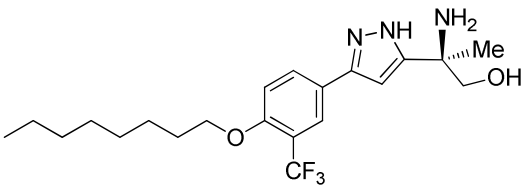
To a solution of (*R*)-3-(*tert*-butoxycarbonyl)-2,2,4-trimethyloxazolidine-4-carboxylic acid **20** (2.6 g, 10 mmol, 1.0 equiv) in DMF (25 mL) was added HATU (4.6 g, 12 mmol, 1.2 equiv) and DIPEA (8.7 mL, 50 mmol, 5.0 equiv). The reaction mixture was stirred at room temperature for 10 min and then treated with *N*,*O*-dimethylhydroxylamine hydrochloride (2.9 g, 30 mmol, 3.0 equiv) for 2 days at room temperature. The reaction was quenched with saturated $NaHCO_3$, extracted with EtOAc. The organic layer was dried over $Na_2SO_4$, concentrated to afford the corresponding Weinreb amide in 92% (2.78 g) yield. HPLC retention time on a C18 column (30 x 4.6 mm, 3.5 m) was 2.20 min with gradient 10-95% acetonitrile-H2O (0.1% TFA) in 3.5 min as mobile phase. MS (ESI, $MH^+$) = 303.3. The crude Weinreb amide (2.78 g, 9.2 mmol) was dissolved in THF (50 mL), cooled to -78 °C and treated with a solution MeLi (1.6 M in ether, 14.7 mL, 2.5 equiv) drop-wise. After being stirred at -78 °C for 3 h, the reaction mixture was allowed to warm up to room temperature and quenched with saturated aqueous $NH_4Cl$, extracted with EtOAc. The organic layer was dried over $Na_2SO_4$, concentrated *in vacuo* to afford an oil which was purified by silica gel column chromatography (hexanes/EtOAc =85:15) to give the title compound (*R*)-*tert*-butyl 4-acetyl-2,2,4-trimethyloxazolidine-3-carboxylate as a white solid in 82% (1.94 g) yield. HPLC retention time on a C18 column (30 x 4.6 mm, 3.5 m) was 2.39 min with gradient 10-95% acetonitrile-$H_2O$ (0.1% TFA) in 3.5 min as mobile phase. MS (ESI, $MH^+$) = 258.4; $^1$H NMR (400 MHz, $CDCl_3$) δ 3.95 (d, 1H, *J* = 9.6 Hz), 3.74 (d, 1H, *J* = 9.6 Hz), 2.21 (s, 3H), 1.69 (s, 2H), 1.65-1.64 (m, 1H), 1.61 (s, 2H), 1.57-1.55 (m, 2H), 1.49 (s, 5H), 1.42 (s, 6H).

## (*S*)-*tert*-Butyl 2,2,4-trimethyl-4-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-3-oxopropanoyl)oxazolidine-3-carboxylate (30)



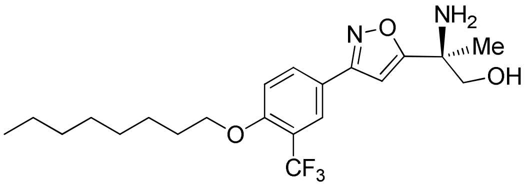
4-(Octyloxy)-3-(trifluoromethyl)benzoic acid (460 mg, 1.0 equiv) was treated with oxalyl chloride (244 mL, 2.0 equiv) for 30 min. The reaction was condensed and part of the residue (81 mg, 1.2 equiv) was dissolved in THF and transferred to a solution of (*S*)-tert-butyl 4-acetyl-2,2,4-trimethyloxazolidine-3-carboxylate (**29**, 51 mg, 1.0 equiv) and LiHMDS (1 M in THF, 0.72 mL, 3.0 equiv) at -78 ºC. The resultant was stirred at 0 ºC for 1 hour. The reaction was quenched with aqueous $NH_4Cl$ and extracted with ethyl acetate. The organic layer was washed with brine and dried over $Na_2SO_4$ and condensed *in vacuo*. The residue was purified on a silica gel column with ethyl acetate-hexane (0-30%) as eluent system to afford the title compound in 39% yield (55 mg, white solid). MS (ESI, M+H+) = 557.9

## (*R*)-2-Amino-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1*H*-pyrazol-5-yl)propan-1-ol (12)



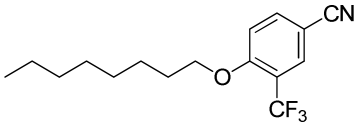
The solution of (*S*)-*tert*-butyl 2,2,4-trimethyl-4-(3-(4-(octyloxy)-3-(trifluoromethyl)-phenyl)-3-oxo-propanoyl)oxazolidine-3-carboxylate (**30**, 27 mg, 0.05 mmol, 1.0 equiv) and hydrazine monohydrate (2.7 mL, 0.055 mmol, 1.1 equiv) in methanol (0.2 mL) was stirred at room temperature for 2 hours. The reaction was condensed and the residue was treated with 20 % TFA-DCM for 30 min. After removal of excess amount of TFA and DCM, the crude product was purified by prep. HPLC and afford the title compound as mono-TFA salt (5.0 mg, white solid, 20% yield). MS (ESI, M+H+) = 414.0; 1HNMR (400 MHz, CD3OD) d 7.81 (s, 1H), 7.76 (d, 1H, *J* = 9.2 Hz), 7.14 (d, 1H, *J* = 9.2 Hz), 6.56 (s, 1H), 4.03 (t, 2H, *J* = 6.0 Hz), 3.79, 3.67 (AB, 2H, *J* = 12.0 Hz), 1.76-1.69 (m, 2H), 1.59 (s, 3H), 1.46-1.38 (m, 2H), 1.32-1.16 (m, 8H), 0.81 (t, 3H, *J* = 7.2 Hz).

### (*S*)-2-Amino-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)isoxazol-5-yl)propan-1-ol (13)



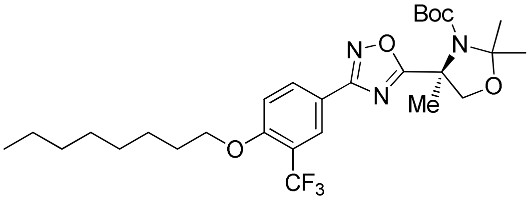
The solution of (*S*)-tert-butyl 2,2,4-trimethyl-4-(3-(4-(octyloxy)-3- (trifluoromethyl)-phenyl)-3-oxo-propanoyl)oxazolidine-3-carboxylate (**30**, 27 mg, 0.05 mmol, 1.0 equiv) and hydroxylamine hydrochloride (6.6 mg, 0.10 mmol, 2.0 equiv) in pyridine (0.5 mL) was stirred at 60 °C for 2 days. The reaction was condensed and the residue was treated with 20 % TFA-DCM for 30 min. After removal of excess amount of TFA and DCM, the crude product was purified by prep. HPLC and afforded the title compound as mono-TFA salt (6.0 mg, white solid, 24% yield). MS (ESI, M+H+) = 415.0; 1H NMR (400 MHz, CD3OD) d 8.06 (s, 1H), 8.04 (d, 1H, *J* = 9.6 Hz), 7.31 (d, 1H, *J* = 9.6 Hz), 7.03 (s, 1H), 4.16 (t, 2H, *J* = 6.0 Hz), 4.01, 3.83 (AB, 2H, *J* = 12.0 Hz), 1.87-1.80 (m, 2H), 1.75 (s, 3H), 1.56-1.47 (m, 2H), 1.40-1.32 (m, 8H), 0.91 (t, 3H, *J* = 7.2 Hz).

**4-(Octyloxy)-3-(trifluoromethyl)benzonitrile (32)**



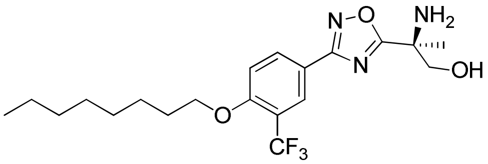
Using 4-fluoro-3-(trifluoromethyl)benzonitrile as starting material, the title compound was prepared analogously to **16** in >95% yield as a gel-like material. $^1$H NMR (400 MHz, CDCl3) δ 7.85 (d, 1H, *J* = 0.2 Hz), 7.77 (dd, 1H, *J* = 8.8 Hz, *J* = 2.0 Hz), 7.04 (d, 1H, *J* = 8.8 Hz), 4.11 (t, 2H, *J* = 5.6 Hz), 1.84 (m, 2H), 1.47(m, 2H), 1.32 (m, 8H), 0.89 (t, 3H, *J* = 7.2 Hz).

**(*R*)-*tert*-Butyl 2,2,4-trimethyl-4-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)oxazolidine-3-carboxylate (35)**



A suspension of 4-(octyloxy)-3-(trifluoromethyl)benzonitrile (600 mg, 1.0 equiv), $NH_2OH{\cdot}HCl$ (280 mg, 2.0 equiv), $Na_2CO_3$ (636 mg, 3.0 equiv) in ethanol-water (12 mL, 5:1) was refluxed for 3 h. The reaction was condensed under vacuum and the residue was treated with water followed by extraction with ethyl acetate. The ethyl acetate layer was washed with saturated NaCl (1×), dried over $Na_2SO_4$, and condensed to afford hydroxyamindine intermediate (750 mg). Part of the intermediate (166 mg, 1.0 equiv) was treated with HATU (190 mg, 1.0 equiv), DIEA (260 mL, 3.0 equiv) and (*R*)-3-(tert-butoxycarbonyl)-2,2,4-trimethyloxazolidine-4-carboxylic acid (**20**, 130 mg, 1.0equiv) in DMF (1 mL) for 1 h. The reaction was diluted with ethyl acetate and washed with water followed by saturated NaCl (1×), dried over $Na_2SO_4$, and condensed under vacuum. The residue was dissolved in DMF and heated at 120 $^{0}$C for 2 hours. Aqueous workup followed by silica gel column purification provided the title compound in 28% (70 mg, white solid) yield over three steps. MS (ESI, MH$^{+}$) = 558.1; $^{1}$H NMR (400 MHz, CDCl3) δ 8.28 (d, 1H, *J* = 1.6 Hz), 8.18 (dd, 1H, *J* = 8.4 Hz, *J* = 1.6 Hz), 7.07 (d, 1H, *J* = 8.4 Hz), 4.23, 4.00 (d, 2H, *J* = 9.2 Hz), 4.11 (t, 2H, *J* = 7.2 Hz), 1.92 (s, 3H), 1.84 (m, 2H), 1.76 (s, 3H), 1.70 (s, 3H), 1.51-1.46 (m, 4H), 1.25 (m, 9H), 1.25 (s, 6H), 0.89 (t, 3H, *J* = 7.2 Hz).

### (*S*)-2-Amino-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)propan-1-ol (14)

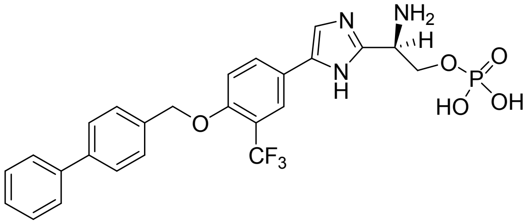


The title compound was prepared analogously to compound **10** from compound **35** in 52% yield (34 mg, white solid). MS (ESI, MH$^{+}$) = 416.0; $^{1}$H NMR (400 MHz, CD$_3$OD) δ 8.28 (m 2H), 7.34 (d, 1H, *J* = 9.6 Hz), 4.19 (t, 2H, *J* = 5.6 Hz), 4.11, 3.89 (AB, 2H, *J* = 11.6 Hz), 1.84 (m, 2H), 1.77 (s, 3H), 1.53 (m, 2H), 1.40-1.32 (m, 8H), 0.91 (t, 3H, *J* = 7.2 Hz).

### General protocol for synthesis of phosphates (method C)

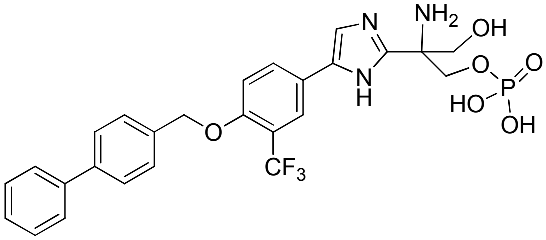
To a solution of unprotected amino alcohol (1.0 equiv) in dry $CH_2Cl_2$ at room temperature was added excess diethyl chlorophosphate (10.0 equiv) and triethylamine (20.0 equiv) and the reaction stirred for 12-18 hours. The reaction was monitored by LC-MS. The reaction mixture was then evaporated to dryness *in vacuo*. The obtained crude phospho-diester intermediate was reacted with excess bromotrimethylsilane (10.0-20.0 equiv) in dry $CH_2Cl_2$ at room temperature over a period of 6-10 hours. The reaction mixture was condensed in vacuo and the residue purified by reverse-phase preparative HPLC to afford the desired phosphates in 20-50% yields. All the phosphates generated via this one-pot synthesis were obtained as white solids with a purity of >95%.

**(*R*)-2-amino-2-(5-(4-(biphenyl-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-1*H*-imidazol-2-yl)ethyl dihydrogen phosphate (1-P)**



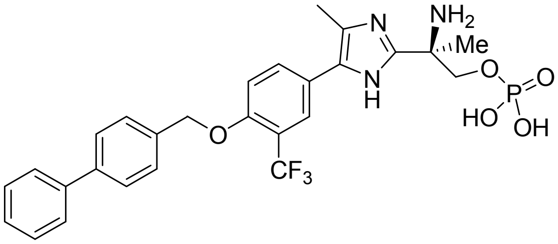
The title product was obtained according to general procedure (Method C) from the corresponding amino-alcohol as a white solid in 30% (33 mg) yield. MS (ESI, M+H$^+$) = 534.1; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 8.07 (d, 1H, *J* = 1.2 Hz), 8.00 (dd, 1H, *J* = 8.6 Hz, *J* = 1.6 Hz), 7.65-7.75 (m, 5H), 7.54 (d, 2H, *J* = 8.6 Hz), 7.34-7.50 (m, 4H), 5.34 (s, 2H), 4.62 (d, 1H, *J* = 5.2), 4.18-4.30 (m, 2H).

**2-(5-(4-([1,1'-biphenyl]-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-1*H*-imidazol-2-yl)-2-amino-3-hydroxypropyl dihydrogen phosphate (2-P)**



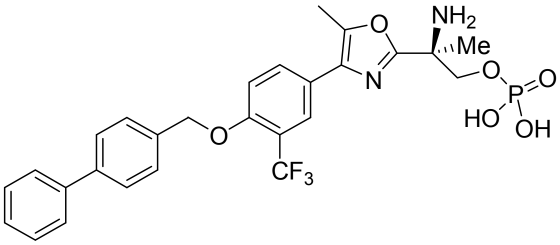
The title product was obtained according to general procedure (Method C) from the corresponding amino-alcohol as a white solid. MS (ESI, M+H$^+$) = 564.6.

**(*R*)-2-Amino-2-(5-(4-(biphenyl-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-4-methyl-1*H*-imidazol-2-yl)propyl dihydrogen phosphate (3-P)**



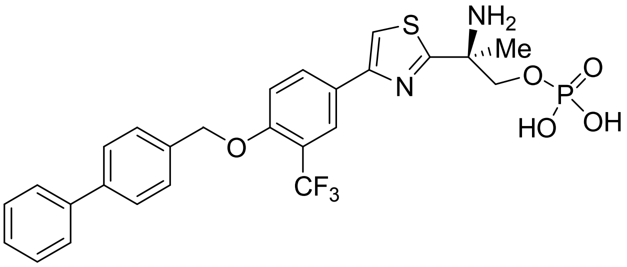
The title product was obtained according to general procedure (Method C) from the corresponding amino-alcohol as a white solid. MS (ESI, $M+H^+$) = 562.6

**(*S*)-2-Amino-2-(4-(4-(biphenyl-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-5-methyloxazol-2-yl)propyl-dihydrogen phosphate (4-P)**



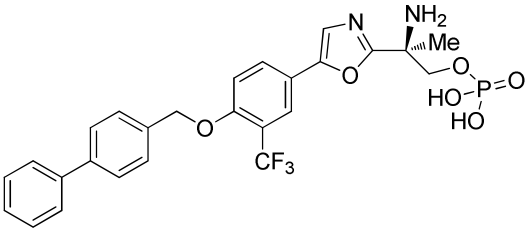
The title product was obtained according to general procedure (Method C) from the corresponding amino-alcohol as a white solid. MS (ESI, $M+H^+$) = 563.3

**(*S*)-2-amino-2-(4-(4-(biphenyl-4-ylmethoxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propyl dihydrogen phosphate (5-P)**



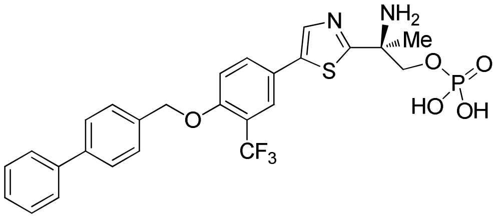
The title product was obtained according to general procedure (Method C) from the corresponding amino-alcohol as a white solid in 22% (20 mg) yield. MS (ESI, M+H$^+$) = 565.6; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.24 (d, 1H, *J* = 1.6 Hz), 8.22 (s, 1H), 8.18 (dd, 1H, *J* = 8.8 Hz, *J* = 2.0 Hz), 7.57-7.67 (m, 4H), 7.47 (d, 2H, *J* = 8.4 Hz), 7.34-7.44 (m, 3H), 7.29 (t, 1H, *J* = 7.6 Hz), 5.30 (s, 2H), 4.01-4.18 (m, 2H), 1.63 (s, 3H).

**(*S*)-2-(5-(4-([1,1'-biphenyl]-4-ylmethoxy)-3-(trifluoromethyl)phenyl)oxazol-2-yl)-2-aminopropyl dihydrogen phosphate (6-P)**



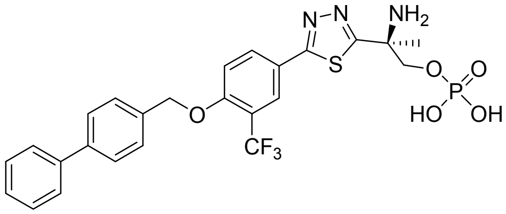
The title product was obtained according to general procedure (Method C) from the corresponding amino-alcohol in 12.3% yield as a white solid. MS (ESI, M+H$^+$): 549.6

**(*S*)-2-Amino-2-(5-(4-(biphenyl-4-ylmethoxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl) propyl-dihydrogen phosphate (7-P)**



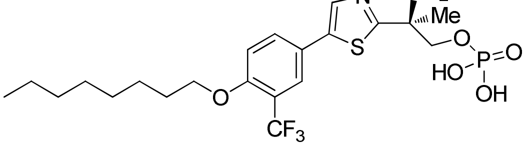
The title product was obtained according to general procedure (Method C) from the corresponding amino-alcohol as a white solid. MS (ESI, M+H$^+$) = 565.3

### (*S*)-2-Amino-2-(5-(4-(biphenyl-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate (8-P)



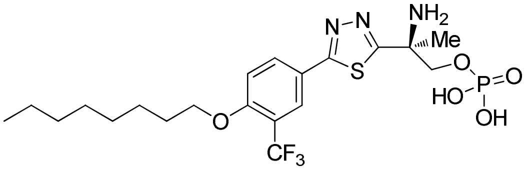
The title product was obtained according to general procedure (Method C) from the corresponding amino-alcohol as a white solid. MS (ESI, M+H$^+$): 565.8

### (*S*)-2-amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propyl dihydrogen phosphate (9-P)



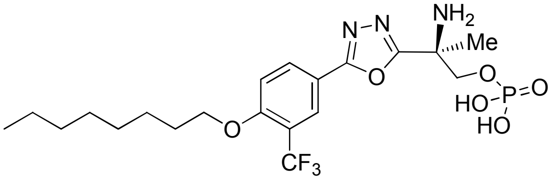
The title product was obtained according to general procedure (Method C) from the corresponding amino-alcohol as a white solid. MS (ESI, M+H$^+$): 511.1. $^1$H NMR (400 MHz, MeOD) δ 8.05 (s, 1H), 7.84 (d, 1H, *J* = 8.2 Hz), 7.82 (s, 1H), 7.25 (d,1H, *J* = 8.4 Hz), 4.28 (dd, 1H, *J* = 9.6 Hz, *J* = 5.2 Hz), 4.18 (dd, 1H, *J* = 9.6 Hz, *J* = 5.2 Hz), 4.13 (t, 2H, J = 6.0 Hz), 1.92-1.75 (m, 4H), 1.56-1.48 (m, 2H), 1.42-1.26 (m, 6H), 0.92 (t, 3H, *J* = 6.0 Hz).

### (*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate (10-P)



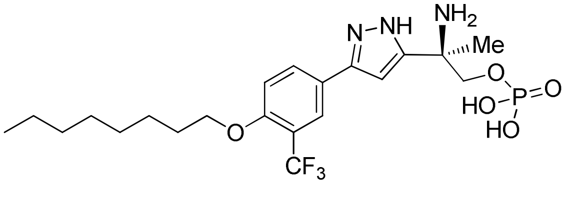
The title product was obtained according to general procedure (Method C) from the corresponding amino-alcohol as a white solid. MS (ESI, M+H$^+$): 511.98. $^1$H NMR (400 MHz, MeOD) δ 8.22 (s, 1H), 8.18 (d, 1H, *J* = 8.4 Hz), 7.35 (d,1H, *J* = 8.4 Hz), 4.29 (dd, 1H, *J* = 9.6 Hz, *J* = 5.2 Hz), 4.25 (dd, 1H, *J* = 9.6 Hz, *J* = 5.2 Hz), 4.20 (t, 2H, *J* = 6.0 Hz), 1.90-1.80 (m, 4H), 1.52-1.49 (m, 2H), 1.40-1.30 (m, 6H), 0.91 (t, 3H, *J* = 6.0 Hz).

### (*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)propyl dihydrogen phosphate (11-P)



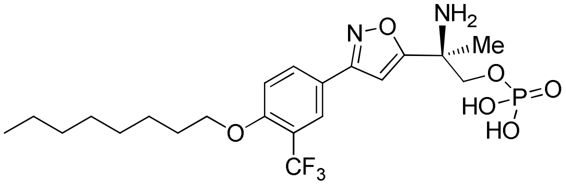
The title product was obtained according to general procedure (Method C) from the corresponding amino-alcohol as a white solid. MS (ESI, M+H$^+$) = 496.0

### (*R*)-2-Amino-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1*H*-pyrazol-5-yl)propyl dihydrogen phosphate(12-P)



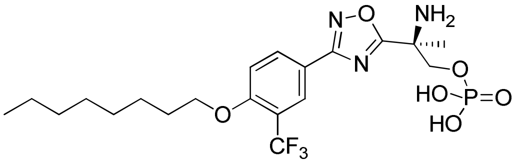
The title product was obtained according to general procedure (Method C) from the corresponding amino-alcohol as a white solid. MS (ESI, M+H+) = 494.1

**(*S*)-2-Amino-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)isoxazol-5-yl)propyl dihydrogen phosphate(13-P)**



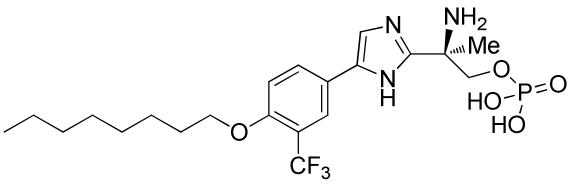
The title product was obtained according to general procedure (Method C) from the corresponding amino-alcohol as a white solid. MS (ESI, M+H+) = 495.0

**(*S*)-2-Amino-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)propyl dihydrogen phosphate (14-P)**



The title product was obtained according to general procedure (Method C) from the corresponding amino-alcohol as a white solid. MS (ESI, M+H+) = 496.0

**(*R*)-2-amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1*H*-imidazol-2-yl)propyl dihydrogen phosphate (15-P)**



The title product was obtained according to general procedure (Method C) from the corresponding amino-alcohol as a white solid in 21% (25 mg) yield. MS (ESI, $M+H^+$) = 494.8; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.02 (d, 1H, *J* = 2.4 Hz), 7.96 (dd, 1H, *J* = 8.6 Hz, *J* = 1.6 Hz), 7.70 (br, s, 1H), 7.24 (d, 1H, *J* = 8.8 Hz), 5.70 (br, s, 1H), 4.12-4.20 (m, 1H), 4.01-4.11 (m, 3H), 1.66-1.76 (m, 2H), 1.59 (s, 3H), 1.36-1.46 (m, 2H), 1.20-1.35 (m, 8H), 0.84 (t, 3H, *J* = 7.2 Hz).

**GTPγS assay experimental protocol:**

***Membrane preparation:*** Membranes were prepared from HEK293T cells expressing transiently human $S1P_1$ or $S1P_3$ receptors for use in $^{35}$S-GTPγS binding studies.

***[$^{35}$S]GTPγS binding:*** For the binding assay, 5 µg of membranes were incubated in 200 µL of GTP-binding buffer (50 mM HEPES, pH 7.5, 10 mM MgCl2, 100 mM NaCl) containing 0.005% saponin, 0.1 µM ($S1P_1$ receptor) or 1 µM GDP ($S1P_3$ receptor), 0.1 nM [$^{35}$S]GTPγS and the test compound. After incubating for 30 min at 30°C, bound radionuclide was separated from free by filtration through GF/B filter plates and the final samples were analyzed for bound radionuclide using a TopCount scintillation counter.

**EAE IACUC (Institutional Animal Care and Use Committee) Protocol:**

**Disease induction:** C57BL/6 mice (8 week old, female) were immunized subcutaneously in the flank with 50 µL containing 50 µg of MOG (35-55) peptide in PBS plus 50 µL of complete Freund's adjuvant containing 2 mg/ml of heat-killed Mycobacterium tuberculosis H37Ra (Becton-Dickinson). The sequence of the mouse MOG (35-55) peptide is MEVGWYRSPFSRVVHLYRNGK. In some studies, a group received a control peptide with the same amino acids in a scrambled sequence instead of the MOG peptide. Following the immunization, mice received an IV injection of 100 µL of PBS containing 150 ng of Bordetella pertussis toxin (List Biologicals Laboratories). Forty-eight hours later, they received a second IV administration of pertussis toxin. Freund's adjuvant is a skin irritant that has general stimulatory effects on the immune system and pertussis toxin has toxic effects with overexposure. Standard precautions (gloves, etc.) were followed when working with these reagents.

**Lymphopenia Study:** Animals were dosed by oral gavage with the desired compounds at 10 mg/kg dissolved in 1% methylcellulose and a dose response for the compounds was evaluated at 3, 1, 0.3 mg/kg. Peripheral blood was collected 6 hours after dosing and total circulating cell counts were analyzed on a Hemavet 950 veterinary blood analyzer to determined the total lymphocyte counts.

**Table 1.** In vitro ADME data summary of prodrugs **9** and **10** and their phosphates **9-P** and **10-P**.

| | | **9** | **10** | **9-P** | **10-P** |
|---|---|---|---|---|---|
| Aqueous Solubility (uM) @ pH3 – 9 | | PH3: 232<br>pH7: 99<br>pH9: 26 | PH3: 988<br>pH7: 58<br>pH9: 91 | --- | --- |
| Protein Binding - %Free (Human plasma) | | <1.0% | 2.3% | 1.5% | <1.0% |
| CaCO-2 Permeability | | Permeability high, no efflux | Permeability high, no efflux | --- | --- |
| CYP450 Inhibition ($IC_{50}$) – 1A, 2C9, 2C19, 2D6, 3A4 | | > 25 mM | > 25 mM | > 25 mM | > 25 mM |
| Metabolic stability in Liver Microsomes: CL-int | Rat | 5.0 | 9.6 | Stable | Stable |
| | Dog | 4.6 | 7.3 | Stable | Stable |
| | Monkey | 6.0 | 5.4 | Stable | Stable |

| | | | | | |
|---|---|---|---|---|---|
| (μL/min/mg) | Human | 0.5 | 0.9 | Stable | Stable |

**Table 2.** Pharmacokinetic parameters and bioavailability of lead prodrugs **9** and **10** in dogs.

| | | | **9** | **9-P** | **10** | **10-P** |
|---|---|---|---|---|---|---|
| *In vivo* PK (Dog, Single dose) | IV (1mg/kg) | Cmax (ng/mL) | 1530 | 24.8 | 889 | 13.2 |
| | | AUC0-t (hr.ng/mL) | 3470 | 368 | 3640 | 85.0 |
| | | CL (mL/hr/kg) | 285 | --- | 274 | --- |
| | | Vss (mL/kg) | 4600 | --- | 2630 | --- |
| | | T1/2 (hr) | 15.3 | 18.5 | 10.3 | 6.4 |
| | PO (5mg/kg) | Cmax (ng/mL) | 276 | 23.2 | 434 | 27.9 |
| | | Tmax (hr) | 4.0 | 4.0 | 4.0 | 4.0 |
| | | AUC0-t (hr.ng/mL) | 4990 | 376 | 5790 | 328 |
| | | Oral bioavailability (F) | 28.5% | --- | 31.8% | --- |

**Table 3.** Plasma PO4 - PK/PD Correlation Following a Single PO Dose of Prodrug **10**.

| Species | Dog | Monkey | Rat |
|---|---|---|---|
| Dose (mg/kg) | 5.0 | 3.8 | 3.0 |
| Cmax (ng/mL)[a] | 27.9 | 50.9 | 229.0 |
| Tmax (hr) | 4.0 | 2.0 | 8.0 |
| T1/2 (hr) | 7.3 | 35.4 | 16.0 |
| AUC0-t (hr.ng/mL) | 328.3 | 423.0 | 4029.5 |
| EC90 (ng/mL) | 11.3 | 16.2 | 50.1 |
| TimeLow (hr) | 84.4 | 66.5 | 50.7 |
| TimeHgh (hr) | 11.6 | 5.5 | 21.3 |
| AUCLow (hr.ng/mL) | 262.4 | 288.2 | 1770.1 |
| AUCHigh (hr.ng/mL) | 71.1 | 134.8 | 2259.4 |

TimeLow = Total time when $C < EC90$, TimeHigh = Total time when $C > EC90$,

AUCLow = AUC for time $< EC90$, AUCHigh = AUC for time $> EC90$

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1) Wang, Y.; Sauer, D. R.; Djuric, S. W. A simple and efficient one step synthesis of 1,3,4-oxadiazoles utilizing polymer-supported reagents and microwave heating. *Tetrahedron Lett.* **2006**, *47*, 105-108.