Supporting Information

Discovery of BAF312 (Siponimod), a Potent and Selective S1P Receptor Modulator

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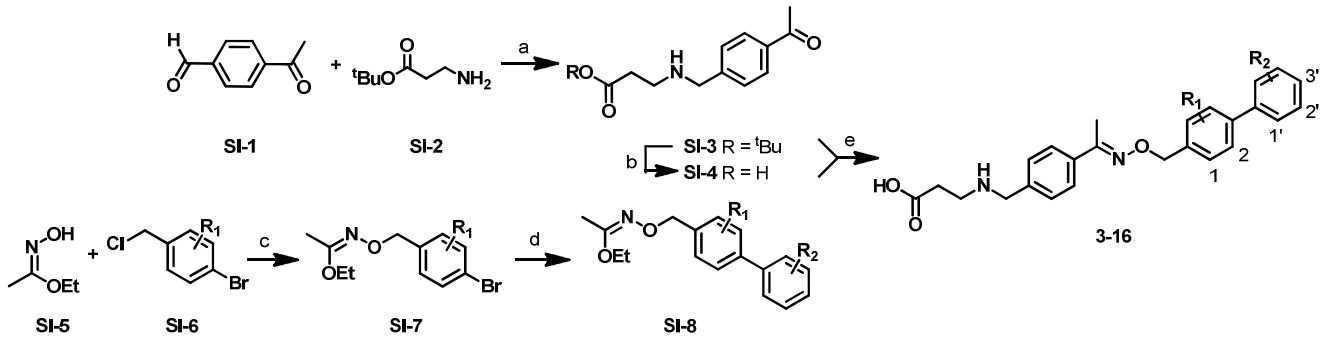
Contents include: general scheme and analytical data of compounds **3-31**; synthetic scheme, procedure and analytical data for compound **32**; and experimental procedure for PK/PD studies of **32**.

Scheme SI-1. General synthetic procedure[a]

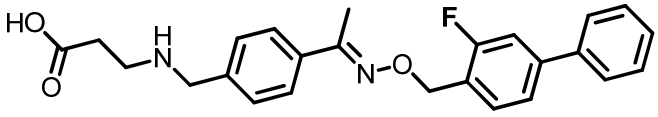


[a] Reagents and conditions: (a) $NaBH_4$, MeOH; (b) TFA, CH_2Cl_2; (c) Na_2CO_3, THF; (d) R_2-$PhB(OH)_2$, Pd(PPh3)4; (e) HCl, MeOH

The general synthetic scheme for compounds **3-16** (and compounds **17-31** can be prepared in a similar scheme) is outlined in Scheme SI-1. A common intermediate **SI-4** was synthesized in two easy steps from acetobenzaldehyde **SI-1** and β-alanine tert-butyl ester **SI-2**. Alkylation of

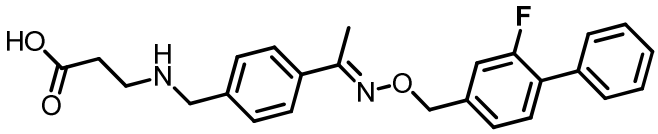
ethyl *N*-hydroxyacetimidate **SI-5** with substituted bromobenzylchloride **SI-6** produced compounds **SI-7**. Suzuki coupling of **SI-7** and substituted phenyl boronic acids gave the desired alkoxyamine precursors **SI-8**. They were then deprotected *in situ* using 1 equivalent of HCl in MeOH and subsequently reacted with intermediate **SI-4** to form the final compounds **3-16** as a mixture of E/Z isomers with a ratio approximately 9:1 that can be separated using HPLC.

(E)-3-((4-(1-(((3-fluoro-[1,1'-biphenyl]-4-yl)methoxy)imino)ethyl)benzyl)amino)propanoic acid (**3**)



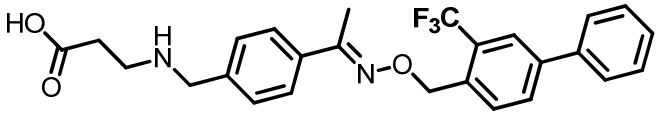
^{1}H NMR (400 MHz, CD_3OD): δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.63 (d, d = 8.4 Hz, 2H), 7.54-7.49 (m, 3H), 7.46-7.42 (m, 3H), 7.39-7.36 (m, 2H), 5.31 (s, 2H), 4.25 (s, 2H), 3.27 (t, *J* = 6.8 Hz, 2H), 2.74 (t, *J* = 6.8 Hz, 2H), 2.27 (s, 3H). MS *m/z* 421.2 (M+1).

(E)-3-((4-(1-(((2-fluoro-[1,1'-biphenyl]-4-yl)methoxy)imino)ethyl)benzyl)amino)propanoic acid (**4**)



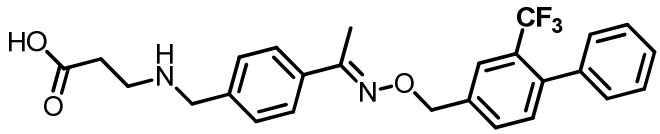
^{1}H NMR (400 MHz, CD_3OD): δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.54-7.48 (m, 4H), 7.46-7.41 (m, 3H), 7.38-7.34 (m, 1H), 7.30-7.28 (m, 1H), 7.24-7.21 (m, 1H), 5.27 (s, 2H), 4.25 (s, 2H), 3.29 (t, *J* = 6.8 Hz, 2H), 2.75 (t, *J* = 6.8 Hz, 2H), 2.31 (s, 3H). MS *m/z* 421.2 (M+1).

(E)-3-((4-(1-(((3-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methoxy)imino)ethyl)benzyl)amino) propanoic acid (**5**)



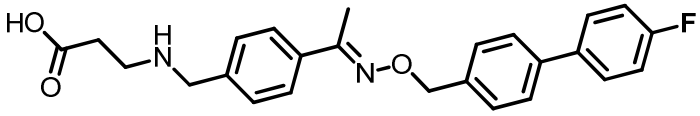
^{1}H NMR (400 MHz, CD_3OD): δ 7.89-7.84 (m, 2H), 7.77-7.74 (m, 3H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.50-7.38 (m, 5H), 7.39-7.36 (m, 2H), 5.44 (s, 2H), 4.24 (s, 2H), 3.29 (t, *J* = 6.7 Hz, 2H), 2.75 (t, *J* = 6.7 Hz, 2H), 2.31 (s, 3H). MS *m/z* 471.2 (M+1).

(E)-3-((4-(1-(((2-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methoxy)imino)ethyl)benzyl)amino) propanoic acid (**6**)



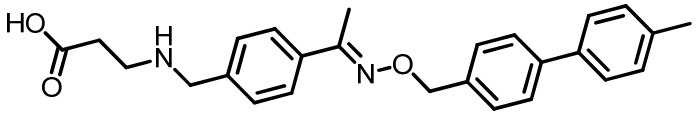
^{1}H NMR (400 MHz, CD_3OD): δ 7.77-7.73 (m, 3H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 2H), 7.37-7.26 (m, 6H), 5.30 (s, 2H), 4.22 (s, 2H), 3.26 (t, *J* = 6.8 Hz, 2H), 2.75 (t, *J* = 6.8 Hz, 2H), 2.28 (s, 3H). MS *m/z* 471.2 (M+1).

(E)-3-((4-(1-(((4'-fluoro-[1,1'-biphenyl]-4-yl)methoxy)imino)ethyl)benzyl)amino)propanoic acid (**7**)



^{1}H NMR (400 MHz, CD_3OD): δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.62-7.56 (m, 4H), 7.50-7.45 (m, 4H), 7.14 (t, *J* = 8.8 Hz, 2H), 5.25 (s, 2H), 4.24 (s, 2H), 3.28 (t, *J* = 6.7 Hz, 2H), 2.75 (t, *J* = 6.8 Hz, 2H), 2.27 (s, 3H). MS *m/z* 421.3 (M+1).

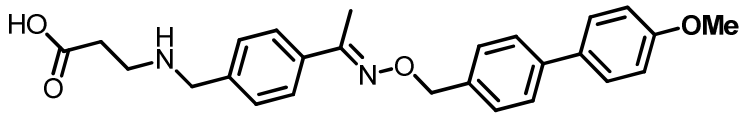
(E)-3-((4-(1-(((4'-methyl-[1,1'-biphenyl]-4-yl)methoxy)imino)ethyl)benzyl)amino)propanoic acid (**8**)



^{1}H NMR (400 MHz, DMSO-d_6): δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 7.6 Hz, 2H), 5.24 (s,

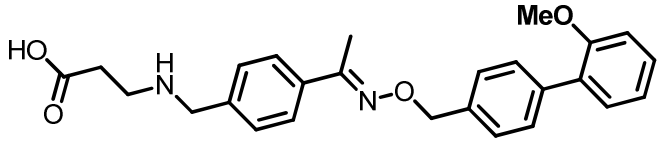
2H), 4.20 (s, 2H), 3.12 (t, *J* = 7.2 Hz, 2H), 2.66 (t, *J* = 7.2 Hz, 2H), 2.33 (s, 3H), 2.25 (s, 3H). MS *m/z* 417.2 (M+1).

(E)-3-((4-(1-(((4'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)imino)ethyl)benzyl)amino)propanoic acid (**9**)



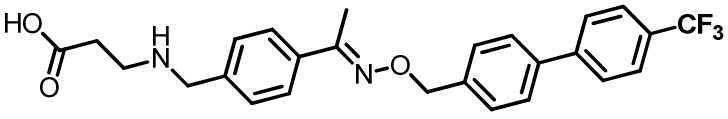
^{1}H NMR (400 MHz, DMSO-d_6): δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 5.23 (s, 2H), 4.18 (s, 2H), 3.79 (s, 3H), 3.10 (t, *J* = 7.0 Hz, 2H), 2.64 (t, *J* = 7.2 Hz, 2H), 2.25 (s, 3H). MS *m/z* 433.2 (M+1).

(E)-3-((4-(1-(((2'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)imino)ethyl)benzyl)amino)propanoic acid (**10**)



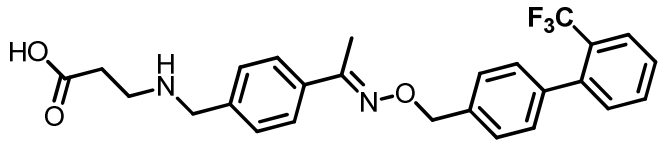
^{1}H NMR (400 MHz, CD_3OD): δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.50-7.39 (m, 5H), 7.29-7.25 (m, 3H), 7.04-6.96 (m, 2H), 5.24 (s, 2H), 4.24 (s, 2H), 3,76 (s, 3H) 3.27 (t, *J* = 6.7 Hz, 2H), 2.74 (t, *J* = 6.8 Hz, 2H), 2.27 (s, 3H). MS *m/z* 433.2 (M+1).

(E)-3-((4-(1-(((4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methoxy)imino)ethyl)benzyl)amino) propanoic acid (**11**)



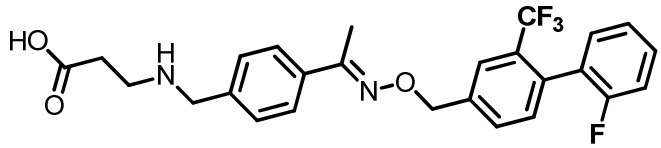
^{1}H NMR (400 MHz, CD_3OD+$CDCl_3$): δ 7.77-7.73 (m, 4H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 5.27 (s, 2H), 4.20 (s, 2H), 3.22 (t, *J* = 6.5 Hz, 2H), 2.67 (t, *J* = 6.5 Hz, 2H), 2.28 (s, 3H). MS *m/z* 471.2 (M+1).

(E)-3-((4-(1-(((2'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methoxy)imino)ethyl)benzyl)amino) propanoic acid (**12**)



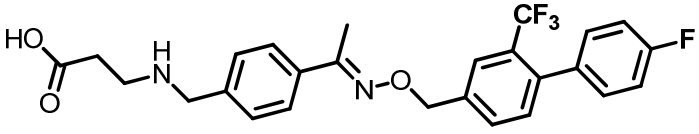
^{1}H NMR (400 MHz, CD_3OD): δ 7.78-7.75 (m, 3H), 7.64-7.60 (m, 2H), 7.55-7.44 (m, 5H), 7.36-7.29 (m, 2H), 5.28 (s, 2H), 4.25 (s, 2H), 3.28 (t, *J* = 6.7 Hz, 2H), 2.73 (t, *J* = 6.8 Hz, 2H), 2.29 (s, 3H). MS *m/z* 471.2 (M+1).

(E)-3-((4-(1-(((2'-fluoro-2-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methoxy)imino)ethyl)benzyl)amino)propanoic acid (**13**)



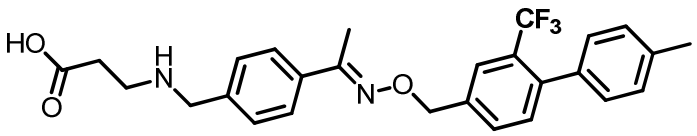
^{1}H NMR (400 MHz, CD3OD) δ 7.85 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.50-7.42 (m, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.20 (m, 3H), 5.37 (s, 2H), 4.28 (s, 2H), 3.33 (t, *J* = 6.8 Hz, 2H), 2.80 (t, *J* = 6.8 Hz, 2H), 2.33 (s, 3H). MS *m/z* 489.1 (M+1).

(E)-3-((4-(1-(((4'-fluoro-2-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methoxy)imino)ethyl)benzyl)amino)propanoic acid (**14**)



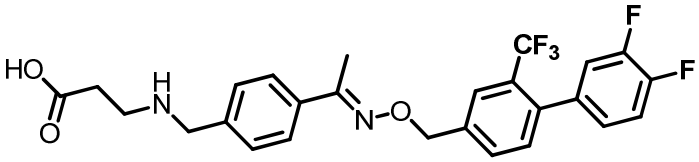
^{1}H NMR (600 MHz, DMSO) δ 7.85 (s, 1H), 7.76-7.71 (m, 3H), 7.52 (d, *J* = 9.0 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.38-7.33 (m, 2H), 7.30-7.25 (m, 2H), 5.35 (s, 2H), 4.19 (s, 2H), 4.26 (t, *J* = 7.2 Hz, 2H), 3.13 (t, *J* = 7.2 Hz, 2H), 2.99 (s, 3H). MS *m/z* 489.1 (M+1).

(E)-3-((4-(1-(((4'-methyl-2-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methoxy)imino)ethyl)benzyl)amino)propanoic acid (**15**)



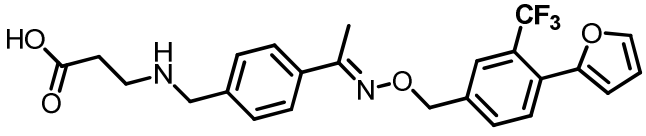
^{1}H NMR (400 MHz, CD3OD) δ 7.82-7.76 (m, 3H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.25-7.15 (m, 4H), 5.35 (s, 2H), 4.30 (s, 2H), 3.33 (t, *J* = 6.4 Hz, 2H), 2.80 (t, *J* = 6.4 Hz, 2H), 2.40 (s, 3H), 2.35 (s, 3H). MS *m/z* 485.1 (M+1).

(E)-3-((4-(1-(((3',4'-difluoro-2-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methoxy)imino)ethyl)benzyl)amino)propanoic acid (**16**)



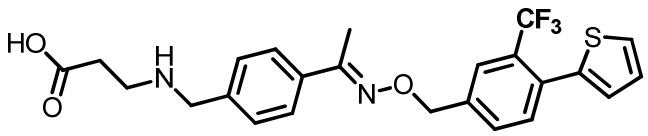
^{1}H NMR (400 MHz, CD3OD) δ 7.81 (s, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.33-7.17 (m, 2H), 7.13-7.06 (m, 1H), 5.32 (s, 2H), 4.25 (s, 2H), 3.29 (t, *J* = 6.8 Hz, 2H), 2.76 (t, *J* = 6.8 Hz, 2H), 2.29 (s, 3H). MS *m/z* 507.1 (M+1).

(E)-3-((4-(1-(((4-(furan-2-yl)-3-(trifluoromethyl)benzyl)oxy)imino)ethyl)benzyl)amino)propanoic acid (**17**)



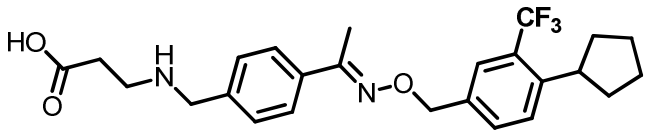
^{1}H NMR (400 MHz, CD3OD) δ 7.85 (s, 1H), 7.81-7.77 (m, 3H), 7.73-7.69 (m, 1H), 7.66-7.64 (m, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 6.75-6.72 (m, 1H), 6.58-6.56 (m, 1H), 5.34 (s, 2H), 4.28 (s, 2H), 3.33 (t, *J* = 6.4 Hz, 2H), 2.78 (t, *J* = 6.4 Hz, 2H), 2.30 (s, 3H). MS *m/z* 461.3 (M+1).

(E)-3-((4-(1-(((4-(thiophen-2-yl)-3-(trifluoromethyl)benzyl)oxy)imino)ethyl)benzyl)amino)propanoic acid (**18**)



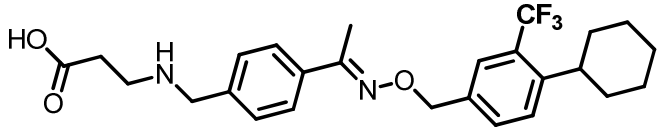
^{1}H NMR (400 MHz, CD_3OD+$CDCl_3$): δ 7.82 (s, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.52-7.49 (m, 4H), 7.09-7.06 (m, 2H), 5.32 (s, 2H), 4.24 (s, 2H), 3.27 (t, *J* = 6.7 Hz, 2H), 2.72 (t, *J* = 6.7 Hz, 2H), 2.30 (s, 3H). MS *m/z* 477.1 (M+1).

(E)-3-((4-(1-(((4-cyclopentyl-3-(trifluoromethyl)benzyl)oxy)imino)ethyl)benzyl)amino)propanoic acid (**19**)



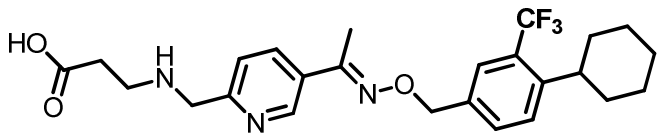
^{1}H NMR (400 MHz, CD3OD) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.68 (s, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 5.27 (s, 2H), 4.28 (s, 2H), 3.45-3.28 (m, 3H), 2.87-2.71 (m, 2H), 2.30 (s, 3H), 2.14-2.07 (m, 2H), 1.98-1.89(m, 2H), 1.82-1.63 (m, 4H). MS *m/z* 463.2 (M+1).

(E)-3-((4-(1-(((4-cyclohexyl-3-(trifluoromethyl)benzyl)oxy)imino)ethyl)benzyl)amino)propanoic acid (**20**)



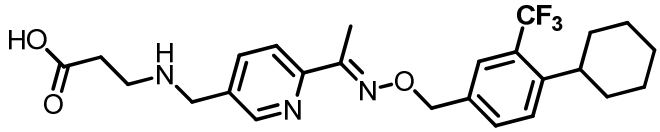
^{1}H NMR (400 MHz, CD3OD) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.69 (s, 1H), 7.64 (d, *J* = 8.4 Hz,1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 2H), 5.28 (s, 2H), 4.30 (s, 2H), 3.35 (t, *J* = 7.2 Hz, 2H), 2.94 (m, 1H), 2.79 (t, *J* = 7.2 Hz, 2H), 2.30 (s, 3H), 1.92-1.77 (m, 5H), 1.60-1.32 (m, 5H). MS *m/z* 477.2 (M+1).

(E)-3-(((5-(1-(((4-cyclohexyl-3-(trifluoromethyl)benzyl)oxy)imino)ethyl)pyridin-2-yl)methyl)amino)propanoic acid (**21**)



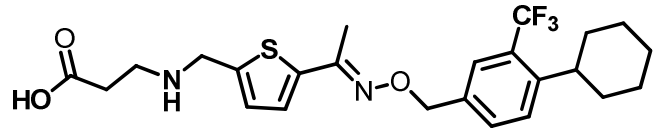
^{1}H NMR (400 MHz, CD3OD) δ 8.86 (s, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 7.61 (s, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 5.21 (s, 2H), 4.38 (s, 2H), 3.34 (t, *J* = 6.6 Hz, 2H), 2.91-2.85 (m, 1H), 2.79 (t, *J* = 6.6 Hz, 2H), 2.32 (s, 3H), 1.90-1.75 (m, 5H), 1.60-1.35 (m, 5H). MS *m/z* 478.1 (M+1).

(E)-3-(((6-(1-(((4-cyclohexyl-3-(trifluoromethyl)benzyl)oxy)imino)ethyl)pyridin-3-yl)methyl)amino)propanoic acid (**22**)



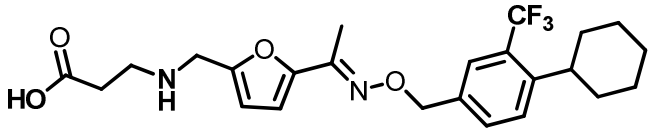
^{1}H NMR (400 MHz, CD3OD) δ 8.64 (s, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.62 (s, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 5.25 (s, 2H), 4.29 (s, 2H), 3.32 (t, *J* = 6.8 Hz, 2H), 2.90 (m, 1H), 2.74 (t, *J* = 6.8 Hz, 2H), 2.30 (s, 3H), 1.90-1.70 (m, 5H), 1.60-1.30 (m, 5H). MS *m/z* 478.4 (M+1).

(E)-3-(((5-(1-(((4-cyclohexyl-3-(trifluoromethyl)benzyl)oxy)imino)ethyl)thiophen-2-yl)methyl)amino)propanoic acid (**23**)



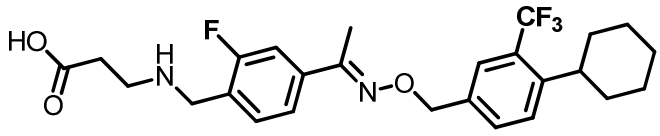
^{1}H NMR (400 MHz, CD3OD) δ 7.66-7.50 (m, 3H), 7.35-7.20 (m, 2H), 5.20 (s, 2H), 4.43 (s, 2H), 3.31 (t, *J* = 6.8 Hz, 2H), 3.00-2.90 (m, 1H), 2.77 (t, *J* = 6.8 Hz, 2H), 2.28 (s, 3H), 1.90-1.70 (m, 5H), 1.60-1.30 (m, 5H). MS *m/z* 483.1 (M+1).

(E)-3-(((5-(1-(((4-cyclohexyl-3-(trifluoromethyl)benzyl)oxy)imino)ethyl)furan-2-yl)methyl)amino)propanoic acid (**24**)



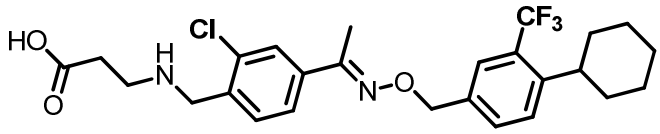
^{1}H NMR (400 MHz, CD3OD) δ 7.67-7.54 (m, 3H), 6.84-6.70 (m, 2H), 5.22 (s, 2H), 4.34 (s, 2H), 3.32 (t, *J* = 6.8 Hz, 2H), 2.94 (m, 1H), 2.77 (t, *J* = 6.8 Hz, 2H), 2.21 (s, 3H), 1.90-1.74 (m, 5H), 1.60-1.30 (m, 5H). MS *m/z* 467.1 (M+1).

(E)-3-((4-(1-(((4-cyclohexyl-3-(trifluoromethyl)benzyl)oxy)imino)ethyl)-2-fluorobenzyl)amino)propanoic acid (**25**)



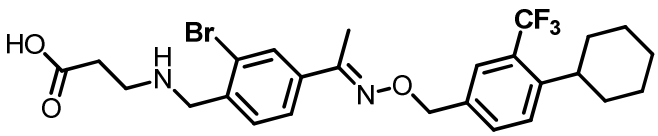
^{1}H NMR (400 MHz, CD3OD) δ 7.63 (s, 1H), 7.60 – 7.50 (m, 5H), 5.22 (s, 2H), 4.31 (s, 2H), 3.33 – 3.29 (m, 2H), 2.89 (t, *J* = 11.7 Hz, 1H), 2.75 (t, *J* = 6.7 Hz, 2H), 2.24 (s, 3H), 1.84 (d, *J* = 12.1 Hz, 2H), 1.75 (d, *J* = 13.1 Hz, 3H), 1.51 (m, 2H), 1.45 – 1.29 (m, 3H). MS *m/z* 495.2 $(M+1)^+$.

(E)-3-((2-chloro-4-(1-(((4-cyclohexyl-3-(trifluoromethyl)benzyl)oxy)imino)ethyl)benzyl)amino)propanoic acid (**26**)



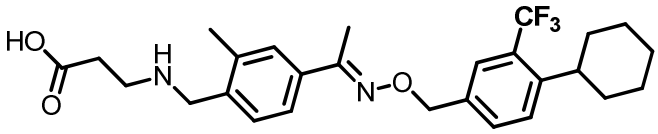
^{1}H NMR (400 MHz, CD3OD) δ 7.88 (d, *J* = 1.8 Hz, 1H), 7.74 (dd, *J1*= 7.8 Hz, *J2* = 1.8 Hz, 1H), 7.69 (s, 1H), 7.63 (d, *J* = 7.8 Hz, 2H), 7.58 (d, *J* = 7.8 Hz, 1H), 5.28 (s, 2H), 4.45 (s, 2H), 3.40 (t, *J* = 6.6 Hz, 2H), 2.98-2.92 (m, 1H), 2.83 (t, *J* = 6.6 Hz, 2H), 2.28 (s, 3H), 1.90-1.75 (m, 5H), 1.60-1.33 (m, 5H). MS *m/z* 511.1 $(M+1)^+$.

(E)-3-((2-bromo-4-(1-(((4-cyclohexyl-3-(trifluoromethyl)benzyl)oxy)imino)ethyl)benzyl)amino)propanoic acid (**27**)



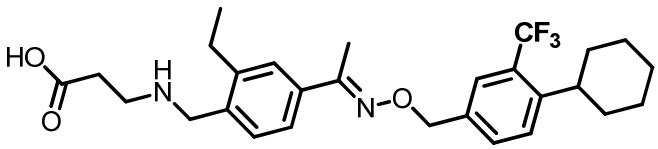
^{1}H NMR (400 MHz, CD3OD) δ 8.03 (d, *J* = 1.2 Hz, 1H), 7.76 (dd, *J1* = 8.0 Hz, *J2* = 1.2 Hz, 1H), 7.69-7.54 (m, 4H), 5.27 (s, 2H), 4.44 (s, 2H), 3.40 (t, *J* = 6.8 Hz, 2H), 2.96-2.89 (m, 1H), 2.85 (t, *J* = 6.8 Hz, 2H), 2.26 (s, 3H), 1.90-1.75 (m, 5H), 1.60-1.35 (m, 5H). MS *m/z* 555.1 $(M+1)^+$.

(E)-3-((4-(1-(((4-cyclohexyl-3-(trifluoromethyl)benzyl)oxy)imino)ethyl)-2-methylbenzyl)amino)propanoic acid (**28**)



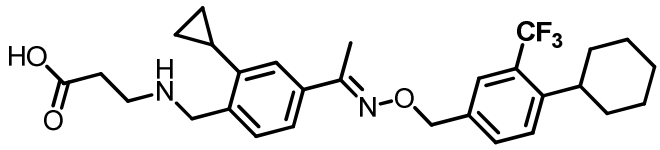
^{1}H NMR (400 MHz, MeOD) δ 7.63 (s, 1H), 7.60 – 7.50 (m, 4H), 7.40 (d, *J* = 8.0 Hz, 1H), 5.21 (s, 2H), 4.28 (s, 2H), 3.73–3.67 (m, 1H), 3.34 (t, *J* = 6.7 Hz, 2H), 2.95–2.84 (m, 1H), 2.76 (t, *J* = 6.7 Hz, 2H), 2.54–2.48 (m, 1H), 2.44 (s, 3H), 2.23 (s, 3H), 1.84 (d, *J* = 12.3 Hz, 2H), 1.76 (d, *J* = 12.9 Hz, 3H), 1.52 (m, 2H), 1.44–1.32 (m, 3H). MS *m/z* 491.5 $(M+1)^+$.

(E)-3-((4-(1-(((4-cyclohexyl-3-(trifluoromethyl)benzyl)oxy)imino)ethyl)-2-ethylbenzyl)amino)propanoic acid (**29**)



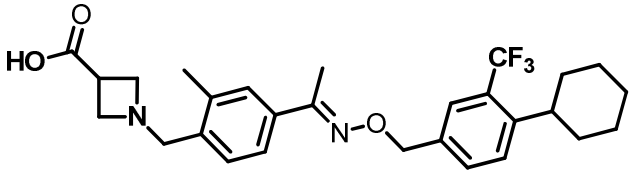
^{1}H NMR (400 MHz, CD3OD) δ 7.70-7.53 (m, 5H), 7.42 (d, *J* = 7.8 Hz, 1H), 5.26 (s, 2H), 4.31 (s, 2H), 3.36 (t, *J* = 6.6 Hz, 2H), 2.97-2.91 (m, 1H), 2.82-2.76 (m, 4H), 2.28 (s, 3H), 1.90-1.76 (m, 5H), 1.58-1.35 (m, 5H), 1.25 (t, *J* = 7.2 Hz, 3H). MS *m/z* 505.3 $(M+1)^+$.

(E)-3-((4-(1-(((4-cyclohexyl-3-(trifluoromethyl)benzyl)oxy)imino)ethyl)-2-cyclopropylbenzyl)amino)propanoic acid (**30**)



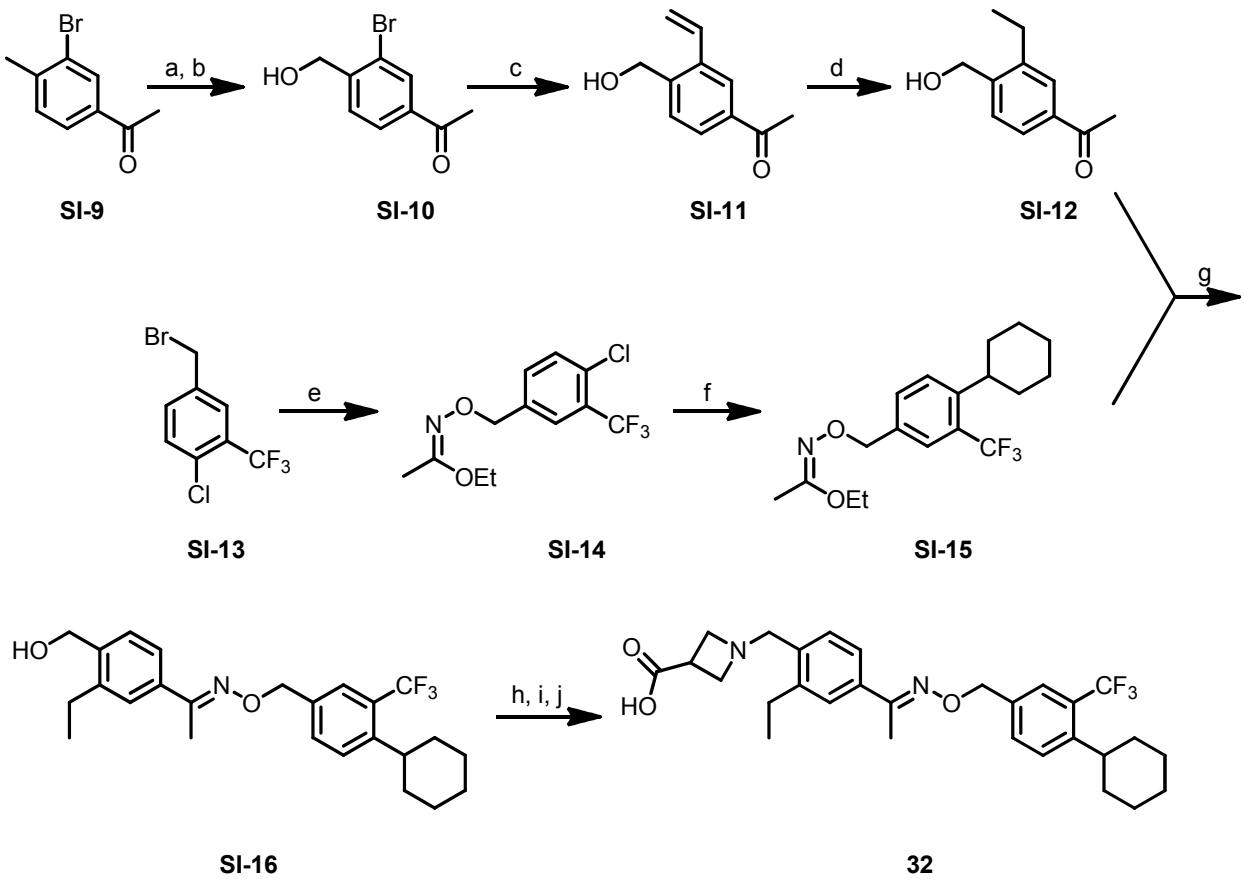
^{1}H NMR (600 MHz, DMSO) δ 7.70-7.61 (m, 3H), 7.53 (dd, *J1* = 8.4 Hz, *J2* = 1.8 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.30 (d, *J* = 1.8 Hz, 1H), 5.23 (s, 2H), 4.38 (s, 2H), 3.24 (t, *J* = 6.8 Hz, 2H), 2.99 (s, 3H), 2.81 (t, *J* = 6.4 Hz, 2H), 2.27-2.17 (m, 1H), 2.14-2.05 (m, 1H), 1.86-1.63 (m, 5H), 1.60-1.23 (m, 5H), 1.06-095 (m, 2H), 0.74-0.64 (m, 2H). MS *m/z* 517.3 $(M+1)^+$.

(E)-1-(4-(1-(((4-cyclohexyl-3-(trifluoromethyl)benzyl)oxy)imino)ethyl)-2-methylbenzyl)azetidine-3-carboxylic acid (**31**)



^{1}H NMR (400 MHz, CD_3OD) δ 7.63 (s, 1H), 7.61–7.50 (m, 4H), 7.35 (d, *J* = 7.9 Hz, 1H), 5.21 (s, 2H), 4.49 (s, 2H), 4.40–4.28 (m, 4H), 3.76–3.64 (m, 1H), 2.97–2.79 (m, 2H), 2.43 (s, 3H), 2.23 (s, 3H), 1.85 (d, *J* = 11.8 Hz, 2H), 1.76 (d, *J* = 13.2 Hz, 3H), 1.52 (m, 2H), 1.46–1.28 (m, 3H). MS *m/z* 503.5 $(M+1)^+$.

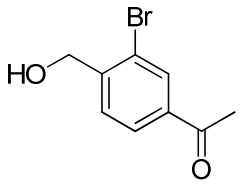
Scheme SI-2. Synthesis of **32**[a]



[a] Reagents and conditions: (a) NBS, AIBN, CCl_4; (b) $CaCO_3$, dioxane-H_2O; (c) dibutyl vinylboronate, $PdCl_2(PPh_3)_2$, Na_2CO_3,THF-H_2O; (d) Pd-C/H_2, EtOH; (e) intermediate **7**, $KOBu^t$, DMF; (f) cyclohexyl magnesium chloride, $ZnCl_2$, $Pd(PBu^t_3)_2$; (g) HCl, MeOH; (h) MnO_2, 1,4-dioxane; (i) 3-azetidine carboxylic acid, MeOH, AcOH; (j) $NaBH_3CN$, MeOH.

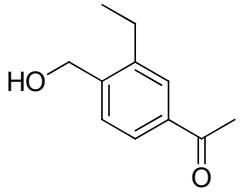
Synthesis of 32

1-(3-bromo-4-(hydroxymethyl)phenyl)ethanone (**SI-10**)



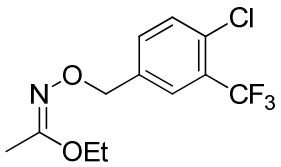
A solution of **SI-9** (11.5 g, 54.0 mmol), NBS (10.6 g, 59.4 mmol) and AIBN (1.8 g, 10.8 mmol) in CCl_4 (250 mL) was refluxed for 12 h. After cooling to room temperature, the mixture was filtered through a silica gel pad (depth of 1.5 cm) and washed with CH_2Cl_2. After concentration, to the residue was added $CaCO_3$ (16.2 g, 162 mmol) followed by the addition of a mixture of 1,4-dioxane/H_2O (180 mL, 1:1 v/v). The resulting suspension was refluxed for 16 h. After cooling to room temperature, the solid was removed by filtration. The filtrate was extracted with EtOAc and the organic layer was washed with brine and dried over Na_2SO_4. After concentration, the residue was passed through a silica gel pad (a depth of 5 cm) in a filtration funnel and eluted first with 5% EtOAc in hexane and then 30-40% EtOAc in hexane to give **SI-10** (8.33 g, 67%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1 H), 7.89 (d, J = 7.6 Hz, 1 H), 7.61 (d, J = 7.6 Hz, 1 H), 4.79 (s, 2 H), 2.58 (s, 3H), 2.01 (bs, 1H). LC-MS *m/z*: 229.0 (M+1).

1-(3-Ethyl-4-hydroxymethyl-phenyl)-ethanone (SI-12).



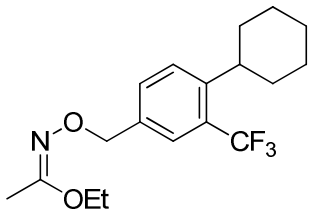
To a solution of **SI-10** (8.33 g, 36.4 mmol), vinyl dibutyl borate (10.0 g, 54.3 mmol), and $Pd(PPh_3)_2Cl_2$ (1.3 g, 1.8 mmol) in THF (440 mL) was added a solution of aqueous Na_2CO_3 (2M, 130 mL, 260 mmol). The resulting two-phase-solution was heated to reflux at 80 ^{o}C for 5 h. After cooling to room temperature, the mixture was partitioned between H_2O and EtOAc. The aqueous layer was further extracted with EtOAc. The combined organic layer was washed with brine and dried over Na_2SO_4. After concentration, the crude product **SI-11** (10.7 g) was directly subjected to hydrogenation in the presence of Pd/C (2.0 g, 20 w%, wet) and H_2 (1 atm, balloon) at room temperature for 3 h. After filtration through celite and concentration, the residue was purified by vacuum distillation to give compound **SI-12** (3.93 g, 61 %). b.p. 125-128 ^{o}C/0.13 mmHg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1 H), 7.70 (d, J = 7.2 Hz, 1 H), 7.46 (d, J = 8.4 Hz, 1 H), 4.71 (s, 2 H), 2.79 (bs, 1H), 2.63 (q, J = 7.6 Hz, 2H), 2.52 (s, 3H), 1.19 (t, J = 7.6 Hz, 3 H). LC-MS *m/z*: 179.1 (M+1).

***N*-(4-Chloro-3-trifluoromethyl-benzyloxy)-acetimidic acid ethyl ester (SI-14).**



To a solution of ethyl *N*-hydroxyacetimidate **7** (3.0 g, 29.3 mmol) in dry DMF (25 mL) was added $KOBu^t$ (3.3 g, 29.3 mmol) and the mixture was stirred at room temperature for 20 min. A solution of benzyl bromide **SI-13** (8.0 g, 29.3 mmol) in dry DMF (5 mL) was then added. The resulting mixture was stirred at room temperature for 5 h. The reaction mixture was partitioned in H_2O (200 mL) and 20% EtOAc/hexane (100 mL). After separation, the aqueous layer was further extracted with 20% EtOAc/hexane (2X50 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was passed through a silica gel pad (a depth of 3 cm) in a filtration funnel and washed with 10% EtOAc/hexane. The desired product **SI-14** was obtained after concentration as a colorless liquid (8.60 g, 100%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.44 (s, 2H), 4.90 (s, 2H), 3.94 (q, J = 7.2 Hz, 2H), 1.92 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H). LC-MS *m/z*: 296.1 (M+1).

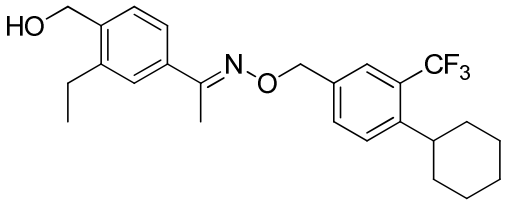
***N*-(4-Cyclohexyl-3-trifluoromethyl-benzyloxy)-acetimidic acid ethyl ester (SI-15).**



Anhydrous $ZnCl_2$ (7.96 g, 58.4 mmol) was dissolved in dry degassed NMP (25 mL) in a 2-neck flask while heated at 100 ^{o}C under argon and the resulting solution was allowed to cool to room temperature. One neck of the flask was connected with a distillation set-up while the other was sealed with septa. To the above $ZnCl_2$ solution was added cyclohexyl magnesium chloride (2 M in Et_2O, 26.5 mL, 53 mmol) via syringe. The reaction was exothermic and Et_2O was evaporated. After the completion of addition, the viscous mixture was stirred at room temperature for 5 min before elevating the temperature to 80 ^{o}C to allow for the complete evaporation of Et_2O (ca. 30 min) to give an unstirrable solid. After cooled to room temperature, chloride **SI-14** (7.85 g, 26.5 mmol) and $Pd(PBu^t_3)_2$ (0.678 g, 1.33 mmol) were added. The flask was flushed with argon and sealed with septa. The mixture was then heated to 140 ^{o}C and stirred for 1 h. After cooled to room temperature, the mixture was partitioned between 2% aqueous HCl and 20% EtOAc/hexane. The aqueous layer was further extracted with 20% EtOAc/hexane. The combined organic layer was washed with brine and dried over Na_2SO_4. After concentration, the residue was

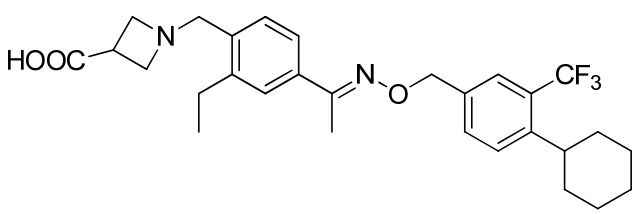
allowed to pass through a silica gel pad (ca. a depth of 3 cm) and washed with 5% EtOAc/hexane. After concentration, the residue was further purified by vacuum distillation to give the desired product **SI-15** (5.23 g, 58%): b.p. 115-120°C/0.15 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.48 (d, *J* = 7.2 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 4.91 (s, 2H), 3.99 (q, *J* = 7.2 Hz, 2H), 2.92 (m, 1H), 1.94 (s, 3H), 1.82 (m, 5H), 1.43 (m, 5H), 1.25 (t, *J* = 7.2 Hz, 3H). LC-MS *m/z*: 344.2 (M+1).

1-(3-Ethyl-4-hydroxymethyl-phenyl)-ethanone *O*-(4-cyclohexyl-3-trifluoromethyl-benzyl)-oxime (SI-16).



To a solution of **SI-15** (9.88 g, 28.8 mmol) in MeOH (120 mL) was added HCl (60 mL of a 1 M solution in Et_2O, 60 mmol). After stirring at room temperature for 30 min, Et_3N (ca 42 mmol) was added to adjust the pH of the solution to 4-6, followed by the addition of compound **SI-12** (5.64 g, 31.6 mmol). The resulting mixture was stirred at room temperature for 16 h. After concentration, the residue was partitioned between EtOAc and H_2O. The aqueous layer was further extracted with EtOAc. The combined organic solution was washed with brine and dried over Na_2SO_4. After concentration, the crude product was purified by flash column chromatography (450 g silica gel) eluted with 10-20% EtOAc/hexane to give **SI-16** as a colorless oil (10.55 g, 85%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.48 (s, 1H), 7.43 (m, 2H), 7.36 (d, *J* = 8.4 Hz, 1H), 5.20 (s, 2H), 4.71 (d, *J* = 5.4 Hz, 2H), 2.92 (m, 1 H), 2.70 (q, *J* = 8.4 Hz, 2 H), 2.25 (s, 3 H), 1.83 (m, 5 H), 1.47 (m, 5 H), 1.23 (t, *J* = 8.4 Hz, 3 H). LC-MS *m/z*: 434.2 (M+1).

1-{4-[1-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid (32).



To a solution of **SI-16** (10.55 g, 24.5 mmol) in 1,4-dioxane (100 mL) was added MnO_2 (21.3 g, 245 mmol). The mixture was heated at reflux for 30 min. After cooling to room temperature, it was filtered through Celite and washed with EtOAc. After concentration, the residue was dissolved in MeOH (300 mL) and 3-azetidine carboxylic acid (4.95 g, 49.0 mmol, and AcOH (13 mL) were added. The resulting mixture was stirred at room temperature for 20 min and a solution of $NaBH_3CN$ (0.77 g, 12.3 mmol) in MeOH (30 mL) was then added. The resulting mixture was stirred at room temperature for 1 h. After concentration, the residue was dissolved in EtOAc and washed with minimum amount of H_2O. The aqueous layer was extracted with EtOAc 3 times. The organic layers were combined and concentrated. The residue was purified by column chromatography first eluted with 2% MeOH/CH_2Cl_2 and then 15% MeOH/CH_2Cl_2 to give compound **32** as a white foam (8.86 g, 70%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.67 (s, 1 H), 7.60 (m, 2 H), 7.55 (m, 2H), 7.35 (d, *J* = 8.4 Hz, 1 H), 5.23 (s, 2 H), 4.32 (bs, 2 H), 4.08 (bs, 4 H), 3.38 (m, 1 H), 2.93 (m, 1 H), 2.78 (q, *J* = 7.6 Hz, 2 H), 2.26 (s, 3 H), 1.83 (m, 5 H), 1.47 (m, 5 H), 1.24 (t, *J* = 8.4 Hz, 3 H). LC-MS *m/z*: 517.2 (M+1).

Experimental procedures for PK/PD studies

Compound **32** was administered at 1 mg/kg in 3% PEG200 und 97% Glucose 2.85% to male Lewis rats via the oral route (n=3). The pH was adjusted to pH 3-4 by adding HCl 0.1 M. Animals were fasted from approximately 8 h prior to and 2 h post drug administration. Blood samples were taken at 0.5, 1, 2, 4, 8, 24, 48, 72 h post administration from the sublingual vein and collected in EDTA tubes. Following determination of lymphocyte counts (PD), the remaining blood was stored at -80 °C for analysis of compound exposure (PK). Absolute lymphocyte counts were analyzed with the Technicon H1-E analyzer (Bayer Diagnostics, Zuerich, CH). An analytical method for direct quantification of compound **32** in whole blood after liquid/liquid extraction was developed. Compound determination was based on microLC-MS-MS technology using a Zorbax SB-C8 0.5x75 mm separation column and ESI-MS-MS detection in MRM mode.