Targeting Flap Backbone of BACE1 Active Site Led to A Potent 6-Dimethylisoxazole Substituted Aminothiazine Carboxamide BACE1 Inhibitor That Elicits Robust Brain Aβ Reduction in Rodents

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Cellular assay conditions

see: Gillman, K. W.; Starrett, J. E.; Parker, M. F.; Xie, K.; Bronson, J. J.; Marcin, L. R.; McElhone, K. E.; Bergstrom, C. P.; Mate, R. A.; Williams, R.; Meredith, J. E.; Burton, C. R.; Barten, D. M.; Toyn, J. H.; Roberts, S. B.; Lentz, K. A.; Houston, J. G.; Zaczek, R.; Albright, C. F.; Decicco, C. P.; Macor, J. E.; Olson, R. E., Discovery and Evaluation of BMS-708163, a Potent, Selective and Orally Bioavailable g-Secretase Inhibitor. *ACS Medicinal Chemistry Letters* **2010,** *1* (3), 120-124.

In vivo studies

see: Toyn, J.H.; Lin, X; Thompson, M.W.; Guss, V.; Meredith Jr., J.E.; Sankaranarayanan, S.; Barrezueta, N.; Corradi, J.; Majumdar, A.; Small, D.L.; Hansard, M.; Lanthorn, T.; Westphal, R.; Albright, C.F. *BMC Neuroscience* **2010**, *11:143*, 1471-2202.

Human cytochrome P450 inhibition assay conditions

see: Wu, Y.-J; He, H.; Hu, S.; Huang, Y.; Scola, P.M.; Grant-Young, K.; Bertekap, R.L.; Wu, D.; Gao, Q.; Li, Y. Klakouski, C.l; Westphal, R.S. Identification of a potent and selective 5-HT_6 antagonist: one-step synthesis of (*E*)-3-(benzenesulfonyl)-2-(methylsulfanyl)pyrido[1,2-

a]pyrimidin-4-ylidenamine from 2-(benzenesulfonyl)-3,3- bis(methylsulfanyl)acrylonitrile. *J. Med. Chem*. **2003**, *46*, 4834-4837.

Table 1. X-ray data summary

	Compound 10 structure	**Compound 17 structure**
Data Collection		
Space group	$P6_122$	$P6_122$
Cell Dimensions		
a,b,c (Å)[a]	102.2, 102.2, 170.6	101.9, 101.9, 171.0
a, b, g (°)	90.0, 90.0, 120.0	90.0, 90.0, 120.0
Resolution (Å)	1.98	1.91
Rmerge[b]	0.099	0.094
Average I/s(I)	21.5	28.6
Completeness (%)	99.98	99.81
Redundancy	19.2	19.1
No. Reflections	719820	586610
No. Unique Reflections	37581	30771
Refinement		
Resolution (Å)	1.98	1.91
Rwork/Rfree	25.5%/28.4%	23.2%/24.4%
No. Reflections	35629	39555
R.m.s deviations		
Bond lengths (Å)	0.005	0.006
Bond angles (°)	0.864	0.873

[a] Data for the highest resolution shell are given in parentheses.

[b] Rmerge = $\Sigma|Ij - \langle Ij \rangle|/\Sigma\langle Ij \rangle$.

[c] Apo BACE1 crystals were grown by crystallizing 6.8 mg/ml protein (in 3.1% DMSO, 50 mM Tris buffer) against pH 8.5, & 150 mM NaCl precipitant made from 10% PEG MME 5K, 9% PEG 8K, 0.2 M NH4I, 0.2 M Na-citrate pH 6.4 via hanging drop vapor diffusion at room temperature. These crystals were then soaked with 3.5 mM compound at room temperature for 7 to 11 days. They were then briefly transferred to a cryo solution made of 12% PEG MME 5K, 17% PEG8K, 0.16 M NH4I, 1 mM compound,

and 80 mM NaCitrate pH 6.4 then flash-frozen in liquid nitrogen. Diffraction data was collected on the frozen crystals at the APS synchrotron beamline 17ID at a wavelength of 1.00 Å.

General Chemistry Experimental Details

All non-aqueous reactions were carried out under an argon or nitrogen atmosphere at room temperature, unless otherwise noted. All commercial reagents and anhydrous solvents were purchased from Aldrich and were used without further purification or distillation, unless otherwise stated. Analytical thin layer chromatography (tlc) was performed on EM Science silica gel 60 F254 (0.25 mm). Compounds were visualized by UV light and/or stained with either p-anisaldehyde, potassium permanganate, or cerium molybdate solutions followed by heating. Flash column chromatography was performed on TeledyneISCO CombiFlash Rf instruments, using TeledyneISCO SiO2 columns of the appropriate S2 sizes, with gradients of solvents as indicated. Analytical high pressure liquid chromatography (HPLC) and LC-MS analyses were conducted using Shimadzu LC-10AS pumps and a SPD-10AV UV-vis detector set at 220 nm or 254 nm with MS detection performed with a Micromass Platform LC spectrometer. Analytical HPLC analyses were performed using the following conditions:

HPLC Method A: Sunfire C18 3.5 μ 4.6 x 150 mm column, solvent A: 5% acetonitrile – 95% water – 0.05% TFA, solvent B: 5% water – 95% acetonitrile – 0.05% TFA, flow rate 2 mL/min; linear gradient time = 12 min; start %B = 10, end %B = 100%, stop time 3 min.

HPLC Method B: Xbridge Phenyl 3.5 □ 4.6 x 150 mm column, solvent A: 5% acetonitrile – 95% water – 0.05% TFA, solvent B: 5% water – 95% acetonitrile – 0.05% TFA, flow rate 2 mL/min; linear gradient time = 12 min; start %B = 10, end %B = 100%, stop time 3 min.

HPLC Method C: YMC S5 ODS 4.6x50 mm column, solvent A: 10% methanol – 90% water – 0.2% H_3PO4, solvent B: 10% water – 90% methanol – 0.2% H3PO4, flow rate 4 mL/min; linear gradient time = 3 min; start %B = 10, end %B = 100%, stop time 4 min.

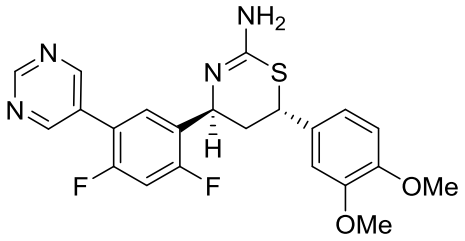
HPLC Method D: Sunfire C18 3.5um, 3.0x150mm column, solvent A: 5% acetonitrile – 95% water – 0.05% TFA, solvent B: 95% acetonitrile – 5% water – 0.05% TFA, flow=0.5 mL/min, gradient from 10%B to 100%B over 15min, 254 nm detector.

HPLC Method E: Xbridge Phenyl 3.5um, 3.0x150mm column, solvent A: 5% acetonitrile – 95% water – 0.05% TFA, solvent B: 95% acetonitrile – 5% water – 0.05% TFA, flow=0.5 mL/min, gradient from 10%B to 100%B over 15min, 254 nm detector. Chiral LC/Analytical SFC conditions: Column: Lux-Cellulose-2 (0.46 x 25cm), Mobile phase: 10% methanol in CO_2, Flow rate: 3 mL/min, wavelength: 220 nm; Temp.: 35□C. Preparative SFC chromatography (Lux-Cellulose-2 (3 x 25cm), 8% methanol in CO2, 140 mL/min at 220 nm and 35°C; Sample in methanol, conc. = 70 mg/mL, Stack injection: 0.5 mL/9.2min. Fractions S3 containing product were concentrated, and dried overnight under vacuum to provide desired compounds.

NMR (^{1}H and ^{13}C) spectra were recorded on one of the following instruments: JEOL GSX-500 MHz or Bruker ARX-400 MHz spectrometers and calibrated using an internal reference. Elemental analyses were performed by Robertson Microlit laboratories and the results obtained are within 0.4% of the theoretical values. All compounds exhibited purity of >95% using analytical HPLC conditions given above. High resolution mass spectra (HRMS) were recorded on a ThermoFinnigan LTQ Orbitrap XL mass spectrometer using positive ion electrospray with an ESI Voltage of 5 kV.

Detailed Chemistry Experimental Procedures

(±)-4-(2,4-difluoro-5-(pyrimidin-5-yl)phenyl)-6-(3,4-dimethoxyphenyl)-5,6-dihydro-4*H*-1,3-thiazin-2-amine (**8**)



To a solution of 2,4-difluoro-5-(pyrimidin-5-yl)benzaldehyde (100 mg, 0.454 mmol) in DMF (454 µL) was added thiourea (41.5 mg, 0.545 mmol), 3,4-dimethoxystyrene (67.2 µL, 0.454 mmol), and chlorotrimethylsilane (58.1 µL, 0.454 mmol). The resulting mixture was brought to 120 °C and stirred for 1 h. The mixture was then diluted with chloroform (10 mL, a precipitate formed) and filtered. The filtrate was concentrated and purified by flash

chromatography (MeOH/$CHCl_3$) to give a yellow oil consisting primarily of 2 peaks with the desired MW by LC/MS. This oil was further purified (diastereomer separation) by prep HPLC (C18, MeOH/Water/NH_4OAc) to give (±)-4-(2,4-difluoro-5-(pyrimidin-5-yl)phenyl)-6-(3,4-dimethoxyphenyl)-5,6-dihydro-4*H*-1,3-thiazin-2-amine (16.4 mg, 8.2% yield), the first major peak to elute, as an oil.

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.26 (s, 1H), 9.01 (d, *J*=1.2 Hz, 2H), 7.97 (s, 1H), 7.54 - 7.42 (m, 2H), 7.00 (s, 1H), 6.95 (d, *J*=0.9 Hz, 2H), 6.12 (br. s., 2H), 4.96 (dd, *J*=6.3, 4.1 Hz, 1H), 4.35 (dd, *J*=8.2, 4.0 Hz, 1H), 3.76 (d, *J*=1.2 Hz, 6H), 2.91 (s, 2H), 2.75 (d, *J*=0.6 Hz, 1H), 2.29 - 2.21 (m, 1H), 2.03 (ddd, *J*=13.6, 6.6, 4.0 Hz, 1H), 1.87 (s, 2H).

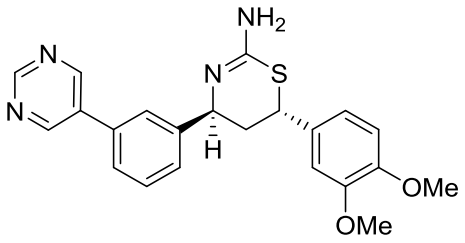
MS (M+H)+ = 443.2.

The racemate was separated by chiral prep SFC (Chiralpak AS-H, 20% MeOH (0.1% DEA) in CO_2, 150bar, 35°C) to give (4*S*,6*S*)-4-(2,4-difluoro-5-(pyrimidin-5-yl)phenyl)-6-(3,4-dimethoxyphenyl)-5,6-dihydro-4*H*-1,3-thiazin-2-amine (first to eluted enantiomer) as an opaque glass.

^{1}H NMR (400 MHz, MeOH-d_4) δ 9.18 (s, 1H), 9.00 (d, *J*=1.5 Hz, 2H), 7.48 (t, *J*=8.4 Hz, 1H), 7.20 (t, *J*=10.3 Hz, 1H), 6.98 (s, 1H), 6.93 (d, *J*=1.0 Hz, 2H), 5.14 (t, *J*=4.8 Hz, 1H), 4.25 (dd, *J*=9.3, 3.8 Hz, 1H), 3.82 (d, *J*=1.8 Hz, 6H), 2.75 (q, *J*=7.3 Hz, 1H), 2.39 - 2.17 (m, 2H).

MS $(M+H)^+$ = 443.1

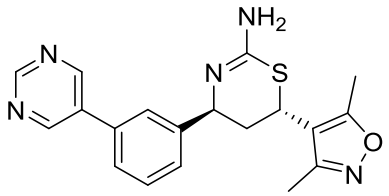
(4*S*,6*S*)-6-(3,4-dimethoxyphenyl)-4-(3-(pyrimidin-5-yl)phenyl)-5,6-dihydro-4*H*-1,3-thiazin-2-amine (**7**)



2.9% yield.

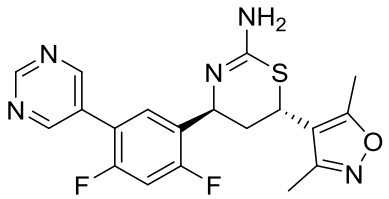
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.96 (s, 2H), 7.55 - 7.42 (m, 3H), 7.34 (d, *J*=7.3 Hz, 1H), 6.92 - 6.76 (m, 3H), 5.02 (t, *J*=4.6 Hz, 1H), 4.20 (dd, *J*=9.2, 4.0 Hz, 1H), 3.86 (d, *J*=1.8 Hz, 4H), 2.34 - 2.18 (m, 2H).
MS: 407.1 $(M+H)^+$.

(4SR,6SR)-6-(3,5-dimethylisoxazol-4-yl)-4-(3-(pyrimidin-5-yl)phenyl)-5,6-dihydro-4H-1,3-thiazin-2-amine (**9**)



2.1% yield.
^{1}H NMR (599MHz, DMSO-d_6) δ 9.28 - 9.20 (m, 2H), 8.29 (br. s., 1H), 7.87 (br. s., 2H), 7.70 (br. s., 1H), 7.51 (d, *J*=7.0 Hz, 1H), 5.21 (br. s., 1H), 4.42 (d, *J*=8.2 Hz, 1H), 2.76 (br. s., 2H), 2.40 (br. s., 3H), 2.25 (br. s., 3H).
MS: 366.0 $(M+H)^+$.

(4*S*,6*S*)-4-(2,4-difluoro-5-(pyrimidin-5-yl)phenyl)-6-(3,5-dimethylisoxazol-4-yl)-5,6-dihydro-4*H*-1,3-thiazin-2-amine (**10**)



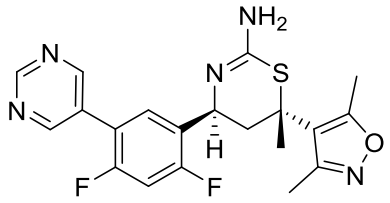
To a solution of 2,4-difluoro-5-(pyrimidin-5-yl)benzaldehyde (250 mg, 1.135 mmol) in DMF (1135 µL) was added thiourea (104 mg, 1.363 mmol), 3,5-dimethyl-4-vinylisoxazole (280 mg, 2.271 mmol), and chlorotrimethylsilane (218 µL, 1.703 mmol). The resulting mixture was

brought to 120 °C and stirred for 1 h. The mixture was then diluted with EtOAc (12 mL), washed with 1 N aqueous NaOH (2 x 4 mL), water (4 mL), brine (4 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (Silica, MeOH/$CHCl_3$) gave a slightly yellow oil consisting primarily of 2 peaks with the desired MW by LC/MS. This oil was further purified (diastereomer separation) by prep HPLC (C18, MeOH/Water/TFA) to give (±)-4-(2,4-difluoro-5-(pyrimidin-5-yl)phenyl)-6-(3,5-dimethylisoxazol-4-yl)-5,6-dihydro-4*H*-1,3-thiazin-2-amine (20.0 mg, 0.035 mmol, 3.1% yield), the first major peak to elute, as an opaque white glass. This racemic material was separated by Chiral SFC (Chiralpak AD-H, MeOH/CO_2/Diethyl amine) to give (4*S*,6*S*)-4-(2,4-difluoro-5-(pyrimidin-5-yl)phenyl)-6-(3,5-dimethylisoxazol-4-yl)-5,6-dihydro-4*H*-1,3-thiazin-2-amine (5.1 mg, 0.011 mmol, 1.0% yield, first peak to elute) as a clear, colorless glass.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.99 (d, *J*=1.4 Hz, 2H), 7.51 (t, *J*=8.4 Hz, 1H), 7.23 (t, *J*=10.3 Hz, 1H), 5.15 (t, *J*=4.7 Hz, 1H), 4.23 (dd, *J*=9.7, 3.9 Hz, 1H), 2.36 (s, 3H), 2.35 - 2.29 (m, 1H), 2.25 (s, 3H), 2.20 (dt, *J*=13.8, 4.8 Hz, 1H).

MS $(M+H)^+$ = 402.3;

(4SR,6SR)-4-(2,4-difluoro-5-(pyrimidin-5-yl)phenyl)-6-(3,5-dimethylisoxazol-4-yl)-6-methyl-5,6-dihydro-4H-1,3-thiazin-2-amine (**11**)

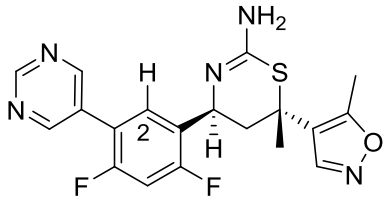


6.1% yield.

^{1}H NMR (400MHz, DMSO-d_6) δ 9.28 (s, 1H), 9.08 (d, *J*=1.5 Hz, 2H), 8.06 (t, *J*=8.4 Hz, 1H), 7.65 (t, *J*=10.7 Hz, 1H), 5.36 - 5.23 (m, 1H), 2.66 (d, *J*=6.5 Hz, 2H), 2.57 (s, 3H), 2.41 (s, 3H), 2.10 (s, 3H).

MS: 416.1 $(M+H)^+$.

(4SR,6SR)-4-(2,4-difluoro-5-(pyrimidin-5-yl)phenyl)-6-methyl-6-(5-methylisoxazol-4-yl)-5,6-dihydro-4H-1,3-thiazin-2-amine (**12**)

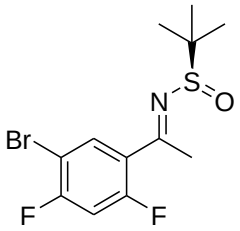


13% yield.

^{1}H NMR (500 MHz, CD_3OD) δ 9.70 (br. s., 2H), 8.58 - 8.45 (m, 1H), 7.85 (t, *J*=7.9 Hz, 1H), 7.36 (t, *J*=10.4 Hz, 1H), 5.40 (dd, *J*=11.6, 4.3 Hz, 1H), 2.86 - 2.65 (m, 2H), 2.63 (s, 3H), 2.19 - 2.06 (m, 3H).

MS: 402.4 $(M+H)^+$.

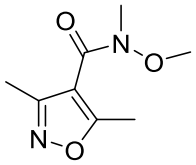
(*R*,*E*)-*N*-(1-(5-Bromo-2,4-difluorophenyl)ethylidene)-2-methylpropane-2-sulfinamide



To a solution of 1-(5-bromo-2,4-difluorophenyl)ethanone (7.4 g, 31.5 mmol) and (*R*)-2-methylpropane-2-sulfinamide (4.86 g, 40.9 mmol) in THF (79 mL) was added ethyl orthotitanate (15.8 g, 69.3 mmol), and the reaction mixture was heated at 65 °C for 48 h. Water was added, and the resulting suspension was filtered through a pad of Celite. The filtrate was worked up with EtOAc, and the crude product was purified by silica gel chromatography eluting with 10-40% EtOAc/Hexanes to give the title compound as a yellow oil (7.3 g, 68% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (t, *J*=7.7 Hz, 1H), 6.97 (dd, *J*=10.5, 8.1 Hz, 1H), 2.76 (d, *J*=3.7 Hz, 3H), 1.33 (s, 9H).

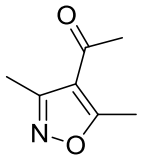
N-Methoxy-*N*,3,5-trimethylisoxazole-4-carboxamide



A solution of 3,5-dimethylisoxazole-4-carboxylic acid (15 g, 106 mmol), N,O-dimethylhydroxylamine hydrochloride (11.40 g, 117 mmol), HATU (44.5 g, 117 mmol) and Hunig's Base (46.4 ml, 266 mmol) in DCM (304 ml) was stirred at rt for 2 days. Water was added and the aqueous layer was extracted with DCM (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and filtered, and the filltrate was evaporated in vacuo to give the crude product. The crude product was purified by silica gel chromatography eluting with 0-40% EtOAc/Hexane to give *N*-methoxy-*N*,3,5-trimethylisoxazole-4-carboxamide (19 g) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.53 (s, 3H), 3.36 (s, 3H), 2.48 (s, 3H), 2.34 (s, 3H).

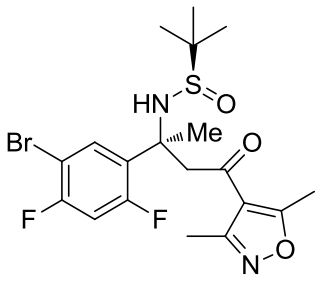
1-(3,5-Dimethylisoxazol-4-yl)ethanone



To a solution of *N*-methoxy-*N*,3,5-trimethylisoxazole-4-carboxamide (20 g, 109 mmol) in THF (362 ml) at 0 °C was added MeMgBr (155 ml, 217 mmol) dropwise via a dropping funnel, and the reaction mixture was stirred at 0 °C for 3 h and then at rt for 10 h. A lot of white precipitae appeared by the end of the addition of MeMgBr. 1 N aqueous HCl (109 ml, 109 mmol) was added dropwise, ethyl acetate was added, and the organic layer was separated. The aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and filtered, and the filltrate was evaporated *in vacu*o to give the crude product. The crude product was purified by silica gel chromatography eluting with 0-40% EtOAc/Hexane to give 1-(3,5-dimethylisoxazol-4-yl)ethanone (13 g, 93 mmol, 86 % yield) as a colorless oil, which solidified upon standuing at rt.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.697 (s, 3H), 2.481 (s, 3H), and 2.478 (s, 3H).

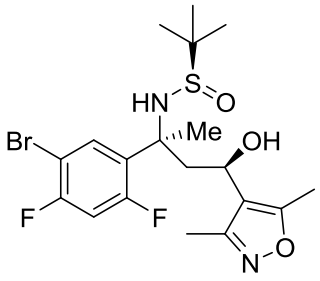
(*R*)-*N*-((*S*)-2-(5-Bromo-2,4-difluorophenyl)-4-(3,5-dimethylisoxazol-4-yl)-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide



To a solution of 1-(3,5-dimethylisoxazol-4-yl)ethanone (3.70 g, 26.6 mmol) in THF (36 mL) at -78 °C was added n-BuLi (10.64 ml, 26.6 mmol), and the reaction mixture was stirred at -78 °C for 20 min. Then a solution of (*R*,E)-*N*-(1-(5-bromo-2,4-difluorophenyl)ethylidene)-2-methylpropane-2-sulfinamide (5 g, 14.78 mmol) in THF (15 mL) was added adropwise, and the reaction mixture was stirred at -78 °C for 30 min, warmed up to -40 °C over a 30 min period, and then stirred at -40 °C for 30 min. Water was added and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and filtered, and the filltrate was evaporated *in vacuo* to give the crude product. The crude product was purified by silica gel chromatography eluting with 1-40% EtOAc/Hexanes followed by 40% EtOAc/Hexanes to give (*R*)-*N*-((*S*)-2-(5-bromo-2,4-difluorophenyl)-4-(3,5-dimethylisoxazol-4-yl)-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide (3.9 g, 8.17 mmol, 55.3 % yield) as a foam.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (t, *J*=8.2 Hz, 1H), 6.82 (dd, *J*=12.2, 7.9 Hz, 1H), 5.48 (s, 1H), 3.95 - 3.84 (m, 1H), 3.64 (dd, *J*=18.3, 2.9 Hz, 1H), 2.65 (s, 3H), 2.41 (s, 3H), 1.80 (s, 3H), 1.34 (s, 9H).

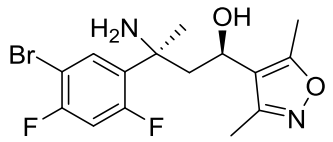
(R)-N-((2S,4R)-2-(5-Bromo-2,4-difluorophenyl)-4-(3,5-dimethylisoxazol-4-yl)-4-hydroxybutan-2-yl)-2-methylpropane-2-sulfinamide



To a solution of (*R*)-*N*-((*S*)-2-(5-bromo-2,4-difluorophenyl)-4-(3,5-dimethylisoxazol-4-yl)-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide (3.3 g, 6.91 mmol) in ether (46.1 ml) at -78 °C was added lithium tri-*tert*-butoxyaluminum hydride (1 M solution in toluene, 27.7 ml, 27.7 mmol) dropwise, and the reaction mixture was stirred at -78 °C for 10 min and then warmed up to -20 °C over a period of 1 h. The reaction mixture was diluted with 100 mL of ether, crystals of sodium sulfate decahydrate were added, and the reaction mixture was stirred at rt for 12 h and then filtered. The filtrate was evaporated in vacuo to give (*R*)-*N*-((2*S*,4*R*)-2-(5-bromo-2,4-difluorophenyl)-4-(3,5-dimethylisoxazol-4-yl)-4-hydroxybutan-2-yl)-2-methylpropane-2-sulfinamide (2.9 g, 6.05 mmol, 88 % yield) as a white foam.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (t, *J*=8.0 Hz, 1H), 6.88 (dd, *J*=11.8, 8.0 Hz, 1H), 5.41 (s, 1H), 5.11 - 5.01 (m, 1H), 4.28 (d, *J*=3.2 Hz, 1H), 2.59 (dd, *J*=14.8, 10.4 Hz, 1H), 2.39 (s, 3H), 2.30 (s, 3H), 2.04 (s, 3H), 1.94 - 1.88 (m, 1H), 1.28 - 1.24 (m, 9H).

(1*R*,3*S*)-3-amino-3-(5-bromo-2,4-difluorophenyl)-1-(3,5-dimethylisoxazol-4-yl)butan-1-ol (**13**)



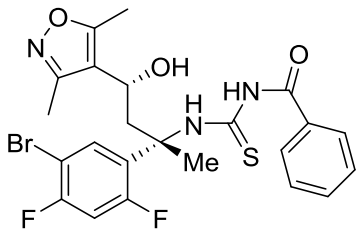
To a solution of (R)-N-((2S,4R)-2-(5-bromo-2,4-difluorophenyl)-4-(3,5-dimethylisoxazol-4-yl)-4-hydroxybutan-2-yl)-2-methylpropane-2-sulfinamide (400 mg, 0.834 mmol) in methanol (4 mL) was added HCl in dioxane (2.086 mL, 8.34 mmol), and the reaction mixture was stirred at rt for 30 min. The solvent was evaporated in vacuo, and saturated sodium bicarbonate solution was added. The aqueous layer was extracted with DCM (x3), and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and

filtered, and the filltrate was evaporated in vacuo to give the crude product. The crude product was purified by silica gel chromatography eluting with 0-8% chloroform/ methanol product to give (1*R*,3*S*)-3-amino-3-(5-bromo-2,4-difluorophenyl)-1-(3,5-dimethylisoxazol-4-yl)butan-1-ol (270 mg, 86 % yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (1H, dd, J = 7.6, 8.4 Hz), 6.92 (1H, dd, J = 8.0 Hz, 12.0 Hz), 5.05 (1H, dd, J = 2.4, 11.2 Hz), 2.41 (3H, s), 2.28 (3H, s), 2.16 (1H, m), 1.82(1H, m), and 1.79 (3H, s),

MS $(M+H)^+$: 377.20.

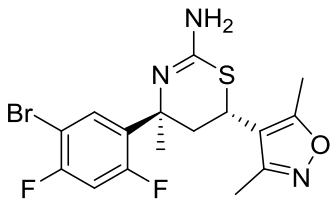
N-(((2S,4R)-2-(5-bromo-2,4-difluorophenyl)-4-(3,5-dimethylisoxazol-4-yl)-4-hydroxybutan-2-yl)carbamothioyl)benzamide (**14**)



To a solution of (1*R*,3*S*)-3-amino-3-(5-bromo-2,4-difluorophenyl)-1-(3,5-dimethylisoxazol-4-yl)butan-1-ol (90 mg, 0.240 mmol) in CH_2Cl_2 (1.2 mL) at rt was added benzoyl isothiocyanate (51.6 µl, 0.384 mmol), and the reaction mixture was stirred at rt for 30 min. The solvent was removed, and the crude product was purified by preparative TLC eluting with 30% EtOAc/Hexanes to give the title compound as a white solid (122 mg, 94% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 11.65 (s, 1H), 8.82 (s, 1H), 7.85 (dd, *J*=8.5, 1.1 Hz, 2H), 7.70 - 7.48 (m, 4H), 6.86 (dd, *J*=11.6, 8.1 Hz, 1H), 4.92 (dd, *J*=9.6, 2.7 Hz, 1H), 4.20 - 4.20 (m, 1H), 2.95 (s, 1H), 2.38 (s, 3H), 2.33 (3H, s), 2.21 (s, 3H).

(4*S*,6*S*)-4-(5-bromo-2,4-difluorophenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4*H*-1,3-thiazin-2-amine (**15**)

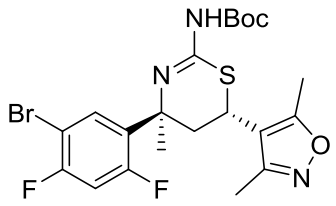


To a solution of N-(((2S,4R)-2-(5-bromo-2,4-difluorophenyl)-4-(3,5-dimethylisoxazol-4-yl)-4-hydroxybutan-2-yl)carbamothioyl)benzamide (0.3 g, 0.557 mmol) in dioxane (1.857 ml) was added HCl (8.92 ml, 44.6 mmol), and the reaction mixture was heated at 100 °C for 5 h. Dioxane was removed in vacuo, and 50% aqueous NaOH was added dropwise until pH reached 12. The aqueous layer was extracted with EtOAc (x4), and tthe combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and filtered, and the filltrate was evaporated in vacuo to give the crude product (230 mg) as a yellow foam. The crude product was purified by preparative TLC eluting with 95% DCM/5% MeOH/1% ammonium hydroxide to give50% EtOAc/Hexane to give (4S,6S)-4-(5-bromo-2,4-difluorophenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-2-amine (113 mg, 48.7 % yield) as a yellow foam.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 - 7.47 (m, 1H), 6.96 (dd, *J*=11.5, 7.9 Hz, 1H), 3.83 (d, *J*=11.3 Hz, 1H), 2.86 (d, *J*=14.0 Hz, 1H), 2.33 (s, 3H), 2.24 (s, 4H), 2.12 - 2.00 (m, 1H), 1.74 (s, 3H).

MS $(M+H)^+$: 418.2

tert-butyl (4*S*,6*S*)-4-(5-bromo-2,4-difluorophenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4*H*-1,3-thiazin-2-ylcarbamate (**16**)



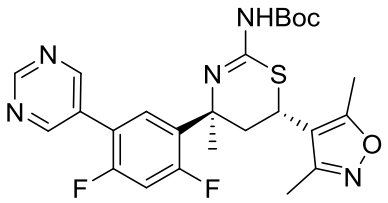
A suspension of (4S,6S)-4-(5-bromo-2,4-difluorophenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-2-amine (47 mg, 0.113 mmol) in dioxane (525 µl), sat. NaHCO3 (525 µl) and water (79 µl) was stirred at rt for 12 h. Water was added and the aqueous layer was extracted with EtOAc (x3). Tthe combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and filtered, and the filltrate was evaporated in vacuo to

give the crude product. The crude product was purified by preparative TLC on silica gel eluting with 30% EtOAc/Hexane to give tert-butyl ((4S,6S)-4-(5-bromo-2,4-difluorophenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-2-yl)carbamate (43 mg, 73.8 % yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 - 7.43 (m, 1H), 6.98 (dd, *J*=11.4, 7.8 Hz, 1H), 3.73 (d, *J*=11.6 Hz, 1H), 2.87 (d, *J*=13.6 Hz, 1H), 2.31 (s, 3H), 2.22 (s, 3H), 2.21 (1H, m), 1.73 (s., 3H), 1.55 (s, 9H). MS $(M+H)^+$: 518.2.

The structure of this compound was confirmed by X-ray analysis.

tert-butyl ((4*S*,6*S*)-4-(2,4-difluoro-5-(pyrimidin-5-yl)phenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4*H*-1,3-thiazin-2-yl)carbamate (**17**)

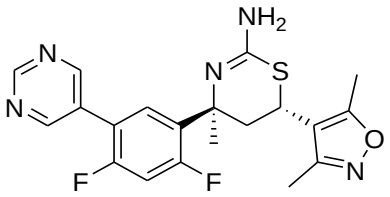


A suspension of tert-butyl ((4S,6S)-4-(5-bromo-2,4-difluorophenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-2-yl)carbamate (120 mg, 0.232 mmol), pyrimidin-5-ylboronic acid (115 mg, 0.930 mmol),$PdCl_2(P(Ph_3)_2$ (32.6 mg, 0.046 mmol) and cesium carbonate (303 mg, 0.930 mmol) in DME (1162 µL), EtOH (581 µL) and water (581 µL) was heated at 100 °C for 6 min. The crude product was purified by reverse phase preparative HPLC on a Luna C18 column (10 µM, 30x100 mm) eluting with 0-100% B (A: 95% eater/5% MeCN/10 nM NH4OAc, B: 5% water/95% MeCN/10 mM NH4OAc) over 12 min to give tert-butyl ((4S,6S)-4-(2,4-difluoro-5-(pyrimidin-5-yl)phenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-2-yl)carbamate (72 mg, 0.140 mmol, 60% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) d 9.27 (s, 1H), 8.93 (d, J=1.2 Hz, 2H), 7.39 (t, J=8.6 Hz, 1H), 7.09 (dd, J=11.4, 9.7 Hz, 1H), 3.75 (br. s., 1H), 2.93 (dd, J=14.2, 2.6 Hz, 1H), 2.32 (s, 3H), 2.28 - 2.19 (m, 4H), 1.77 (s, 3H), 1.52 (s, 9H).

MS $(M+H)^+$ 516.5.

(4*S*,6*S*)-4-(2,4-difluoro-5-(pyrimidin-5-yl)phenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4*H*-1,3-thiazin-2-amine (**18**)

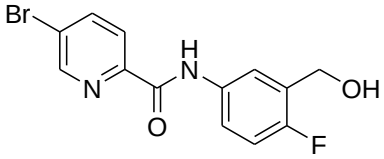


A solution of tert-butyl ((4S,6S)-4-(2,4-difluoro-5-(pyrimidin-5-yl)phenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-2-yl)carbamate (72 mg, 0.140 mmol) and TFA (194 µl, 2.51 mmol) in DCM (1.4 mL) was stirred at rt for 2 h. The solvents were removed to give (4S,6S)-4-(2,4-difluoro-5-(pyrimidin-5-yl)phenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-2-amine as TFA salt (90 mg, 100 % yield).

^{1}H NMR (500 MHz, methanol-d_4) δ 9.33 (br. s., 1H), 9.14 (br. s., 2H), 7.61 - 7.36 (m, 2H), 4.27 (dd, *J*=13.1, 3.4 Hz, 1H), 3.14 (dd, *J*=14.9, 3.3 Hz, 1H), 2.61 (dd, *J*=14.6, 13.4 Hz, 1H), 2.38 (s, 3H), 2.28 (s, 3H), 1.90 (s, 3H).

MS: 416.4 $(M+H)^+$.

5-bromo-*N*-(4-fluoro-3-(hydroxymethyl)phenyl)picolinamide



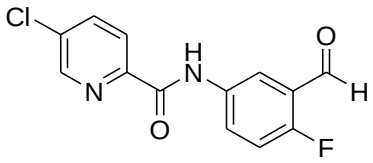
To a solution of (5-amino-2-fluorophenyl)methanol (1.043 g, 7.39 mmol) in DMF (37.0 ml) was added 5-bromopyridine-2-carboxylic acid (1.493 g, 7.39 mmol) and HATU (2.81 g, 7.39 mmol). DIEA (1.291 ml, 7.39 mmol) was then added to the mixture which was stirred at rt for 1 h. The mixture was then diluted with EtOAc (50 mL), washed with water (3 x 25 mL), brine (25

mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chloroform was added to the resulting oil at which time a precipitate formed. The precipitate was isolated by filtration to give 5-bromo-*N*-(4-fluoro-3-(hydroxymethyl)phenyl)picolinamide (1.69 g, 5.20 mmol, 70.3 % yield) as an off-white crystalline solid .

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.70 (s, 1H), 8.86 (dd, *J*=2.3, 0.6 Hz, 1H), 8.33 (dd, *J*=8.4, 2.3 Hz, 1H), 8.08 (dd, *J*=8.3, 0.5 Hz, 1H), 8.06 (dd, *J*=6.8, 2.7 Hz, 1H), 7.75 (ddd, *J*=8.7, 4.7, 2.7 Hz, 1H), 7.18 - 7.10 (m, 1H), 5.30 (t, *J*=5.6 Hz, 1H), 4.55 (d, *J*=5.6 Hz, 2H).

MS $(M+H)^+$ = 325.1.

5-chloro-*N*-(4-fluoro-3-formylphenyl)picolinamide

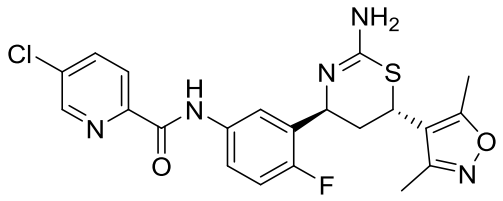


To a suspension of 5-chloro-*N*-(4-fluoro-3-(hydroxymethyl)phenyl) picolinamide (1.6 g, 5.70 mmol) in DCM (28.500 mL) was added a mixture of PCC (4.92 g, 22.80 mmol) and finely ground 4 A molecular sieves (4.92 g, 5.70 mmol). The resulting mixture was stirred at rt for 1 h. The mixture was then applied directly to a silica gel column. Purification by flash chromatography (MeOH/$CHCl_3$) gave 5-chloro-*N*-(4-fluoro-3-formylphenyl)picolinamide (1.4 g, 88 % yield) as a white solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.01 (s, 1H), 10.24 (s, 1H), 8.79 (dd, *J*=2.3, 0.6 Hz, 1H), 8.48 (dd, *J*=6.3, 2.9 Hz, 1H), 8.24 - 8.13 (m, 3H), 7.44 (dd, *J*=10.1, 9.2 Hz, 1H).

MS $(M+H)^+$ = 323.1.

N-(3-((4*S*,6*S*)-2-amino-6-(3,5-dimethylisoxazol-4-yl)-5,6-dihydro-4*H*-1,3-thiazin-4-yl)-4-fluorophenyl)-5-chloropicolinamide (**20**)

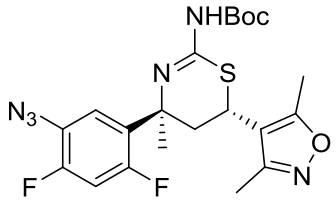


The racemic material was separated by Chiral prep HPLC (Chiralpak AD-H, EtOH/Heptane/Diethyl amine) to give *N*-(3-((4*S*,6*S*)-2-amino-6-(3,5-dimethylisoxazol-4-yl)-5,6-dihydro-4*H*-1,3-thiazin-4-yl)-4-fluorophenyl)-5-chloropicolinamide (28.5 mg, 0.059 mmol, 3.2% yield, first peak to elute) as a tacky, opaque oil.

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.77 (s, 1H), 8.79 (d, *J*=1.8 Hz, 1H), 8.24 - 8.13 (m, 2H), 7.82 - 7.73 (m, 2H), 7.16 (t, *J*=9.5 Hz, 1H), 6.14 (s, 2H), 5.02 (t, *J*=4.8 Hz, 1H), 4.27 (dd, *J*=9.4, 3.6 Hz, 1H), 2.31 (s, 3H), 2.17 (s, 4H), 1.95 - 1.85 (m, 1H).

MS $(M+H)^+$ = 460.0.

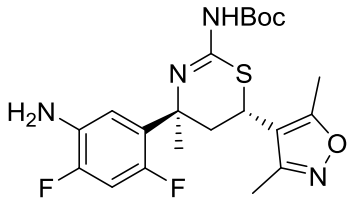
tert-butyl ((4S,6S)-4-(5-azido-2,4-difluorophenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-2-yl)carbamate



A solution of tert-butyl ((4S,6S)-4-(5-bromo-2,4-difluorophenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-2-yl)carbamate (200 mg, 0.387 mmol) in ethanol (6 mL) and water (1.2 mL) added sodium azide (76 mg, 1.162 mmol), trans-1,2-bis(methylamino)cyclohexane (0.020 ml, 0.125 mmol), 0.66 M solution of sodium ascorbate (0.258 ml, 0.170 mmol) and 0.33 M solution of copper (II) sulfate pentahydrate (0.258 ml, 0.085 mmol) was purged with nitrogen for 10 min and then heated at 80 °C for 1.5 h. Water was added and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were

washed with brine, dried over anhydrous sodium sulfate, and filtered, and the filltrate was evaporated *in vacuo* to give the crude product (170 mg). This material was used directly in the next step.

tert-butyl ((4S,6S)-4-(5-amino-2,4-difluorophenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-2-yl)carbamate (**21**)

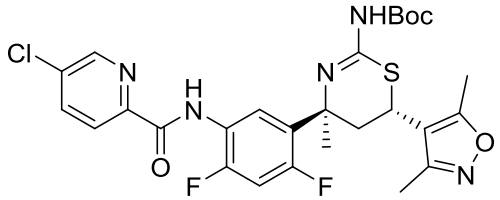


To a tert-butyl ((4S,6S)-4-(5-azido-2,4-difluorophenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-2-yl)carbamate (170 mg, 0.355 mmol) in ethanol (6 mL) was added 10% Pd/C (25 mg) and then hydrogenated at 30 psi for 12 h. The reaction mixture was filtered through Celite, and the filtrate was evaporated in vacuo. The crude product was purified by silica gel chromatography eluting with 30% of ethyl acetate fractions on evaporation to give tert-butyl ((4S,6S)-4-(5-amino-2,4-difluorophenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-2-yl)carbamate (60 mg, 37%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (1H, dd, J = 10.4, 11.2 Hz), 6.68 (1H, dd, J = 8.0, 9.6 Hz), 3.8 (1H, dd, J = 2.8, 12.8 Hz), 2.9 (1H, dd, J = 2.8, 12.8 Hz), 2.28 (3H, s), 2.16 (1H, m), 2.18 (3H, s), and 1.54 (9H,s).

MS $(M+H)^+$ 453.2.

((4S,6S)-4-(5-(5-chloropicolinamido)-2,4-difluorophenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-2-yl)carbamate

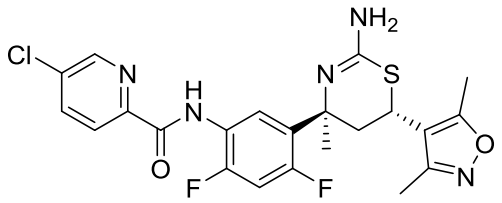


A solution of 5-chloropicolinic acid (28.2 mg, 0.179 mmol), tert-butyl ((4S,6S)-4-(5-amino-2,4-difluorophenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-2-yl)carbamate (54 mg, 0.119 mmol), HATU (68.1 mg, 0.179 mmol), Hunig'sBase (41.7 µl, 0.239 mmol) in DMF (1193 µl) was stirred at rt for 2 h. The crude reaction mixture was purified by reverse phase preparative HPLC on a Luna C18 column (10 µM, 30x100 mm) eluting with 0-100% B (A: 95% eater/5% MeCN/10 nM NH_4OAc, B: 5% water/95% MeCN/10 mM NH_4OAc) over 12 min to give tert-butyl ((4S,6S)-4-(5-(5-chloropicolinamido)-2,4-difluorophenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-2-yl)carbamate (57 mg, 0.096 mmol, 81 % yield) as a white solid.

^{1}H NMR (500MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.61 (d, *J*=1.8 Hz, 1H), 8.53 (br. s., 1H), 8.21 (d, *J*=8.4 Hz, 1H), 7.91 (dd, *J*=8.4, 2.3 Hz, 1H), 7.02 (t, *J*=10.7 Hz, 1H), 3.92 (d, *J*=12.7 Hz, 1H), 2.92 (dd, *J*=14.3, 2.7 Hz, 1H), 2.33 (s, 3H), 2.31 - 2.27 (m, 1H), 2.25 (s, 3H), 1.78 (s, 3H), 1.58 (s, 9H).

MS $(M+H)^+$ 592.2.

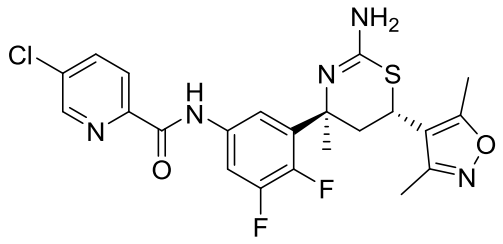
N-(5-((4S,6S)-2-amino-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-4-yl)-2,4-difluorophenyl)-5-chloropicolinamide (**22**)



A solution of N-(5-((4S,6S)-2-amino-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-4-yl)-2,4-difluorophenyl)-5-chloropicolinamide (57 mg, 0.116 mmol) and TFA TFA (134 µl, 1.738 mmol) in DCM (1159 µl) was tirred at rt for 3 h. The crude material was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 19 x 200 mm, 5-µmparticles; Guard Column: Waters XBridge C18, 19 x 10 mm, 5-µm particles; Mobile Phase A: water with 20-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 20-mM ammonium acetate; Gradient: 20-100% B over 20 minutes, then a

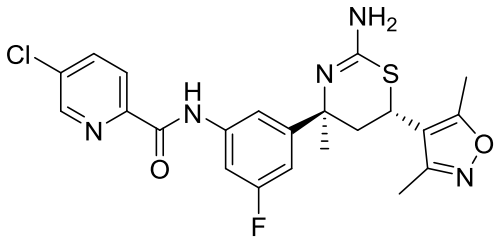
4-minute hold at100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation. The yield of the product was 34.5 mg (61%).
^{1}H NMR (500MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.80 (d, *J*=1.8 Hz, 1H), 8.24 - 8.18 (m, 1H), 8.17 - 8.12 (m, 1H), 7.95 (s, 1H), 7.73 (t, *J*=8.9 Hz, 1H), 7.38 (t, *J*=11.0 Hz, 1H), 3.69 (dd, *J*=13.1, 2.7 Hz, 1H), 2.58 (d, *J*=11.6 Hz, 1H), 2.25 (s, 3H), 2.14 (s, 3H), 1.85 (t, *J*=13.4 Hz, 1H), 1.56 (s, 3H). MS $(M+H)^+$ 492.2.

N-(3-((4S,6S)-2-amino-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-4-yl)-4,5-difluorophenyl)-5-chloropicolinamide (**23**)



The title compound was prepared in 48% yield from tert-butyl ((4S,6S)-4-(5-amino-2,3-difluorophenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-2-yl)carbamate using the same procedure as above.
^{1}H NMR (500MHz, DMSO-d_6) δ 10.89 (s, 1H), 8.80 (s, 1H), 8.26 - 8.11 (m, 2H), 7.95 (br. s., 1H), 7.61 (br. s., 1H), 3.73 (d, *J*=11.6 Hz, 1H), 2.61 (d, *J*=12.8 Hz, 1H), 2.26 (s, 3H), 2.14 (s, 3H), 1.94 - 1.82 (m, 1H), 1.58 (s, 3H).
MS $(M+H)^+$ 492.4.

N-(3-((4S,6S)-2-amino-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-4-yl)-5-fluorophenyl)-5-chloropicolinamide (**24**)

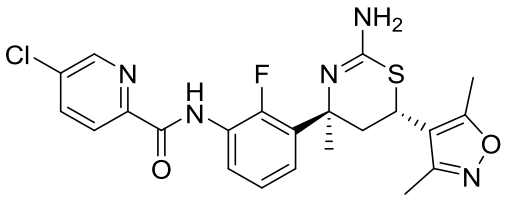


The title compound was prepared in 59% yield from tert-butyl ((4S,6S)-4-(3-amino-5-fluorophenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-2-yl)carbamate.

^{1}H NMR (400MHz, $CDCl_3$) δ 10.04 (s, 1H), 8.63 - 8.56 (m, 1H), 8.22 (dd, *J*=8.4, 0.6 Hz, 1H), 7.90 (dd, *J*=8.4, 2.4 Hz, 1H), 7.67 (dt, *J*=10.0, 1.9 Hz, 1H), 7.44 (s, 1H), 7.37 - 7.11 (m, 2H), 6.80 (dt, *J*=9.5, 1.8 Hz, 1H), 4.01 (dd, *J*=12.8, 3.0 Hz, 1H), 2.62 (dd, *J*=14.2, 2.9 Hz, 1H), 2.41 - 2.30 (m, 1H), 2.28 (s, 3H), 2.22 (s, 3H), 1.78 (s, 3H).

MS $(M+H)^+$474.3.

N-(3-((4S,6S)-2-amino-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-4-yl)-2-fluorophenyl)-5-chloropicolinamide (**25**)

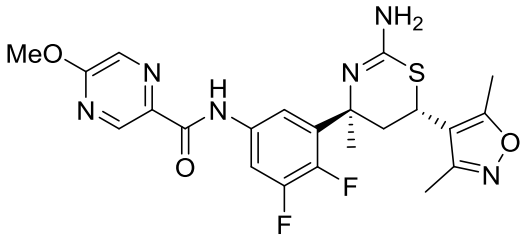


The title compound was prepared in 75% yield from tert-butyl ((4S,6S)-4-(3-amino-2-fluorophenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-2-yl)carbamate

^{1}H NMR (500 MHz, methanol-d_4) δ 8.75 - 8.70 (m, 1H), 8.23 (dd, *J*=8.4, 0.5 Hz, 1H), 8.21 - 8.17 (m, 1H), 8.10 (dd, *J*=8.4, 2.3 Hz, 1H), 7.29 (t, *J*=8.0 Hz, 1H), 7.17 (td, *J*=7.8, 1.6 Hz, 1H), 3.93 (dd, *J*=13.0, 3.2 Hz, 1H), 2.94 - 2.84 (m, 1H), 2.30 (s, 3H), 2.22 (s, 3H), 2.16 (t, *J*=13.6 Hz, 1H), 1.78 (s, 3H).

MS $(M+H)^+$ 474.2.

N-(3-((4S,6S)-2-amino-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-4-yl)-4,5-difluorophenyl)-3,5-dimethoxypyrazine-2-carboxamide (**26**)



The title compound was prepared in 63% yield from tert-butyl ((4S,6S)-4-(5-amino-2,3-difluorophenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-2-yl)carbamate.

^{1}H NMR (500MHz, DMSO-d_6) δ 10.72 (br. s., 1H), 8.88 (s, 1H), 8.41 (s, 1H), 7.94 (br. s., 1H), 7.61 (br. s., 1H), 4.02 (s, 3H), 3.73 (d, *J*=12.8 Hz, 1H), 2.60 (d, *J*=14.3 Hz, 1H), 2.25 (s, 3H), 2.13 (s, 3H), 1.89 - 1.83 (m, 1H), 1.57 (s, 3H).
MS $(M+H)^+$ 489.4.

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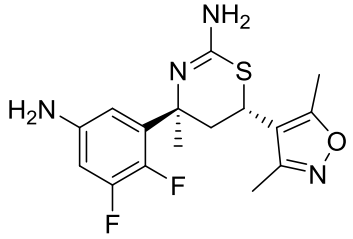
(4S,6S)-4-(5-amino-2,3-difluorophenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-2-amine (**28**)



To a solution of tert-butyl ((4S,6S)-4-(5-amino-2,3-difluorophenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-2-yl)carbamate (1.1 g, 2.431 mmol) in DCM (24.31 mL) was added TFA (4.8 mL, 62.3 mmol). The resulting mixture was stirred at rt for 30 min. The mixture was then concentrated *in vacuo*. The resulting residue was taken up in EtOAc (100 mL), washed with saturated aqueous sodium bicarbonate (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (Silica, 40g, 20 - 100% EtOAc/Hexanes) gave a white solid. This was re-crystallized from EtOH

(~ 5 mL) and hexanes (~ 100 mL) to give a white crystalline solid which was dried at 50 °C under high vac. for 3 days to give (4S,6S)-4-(5-amino-2,3-difluorophenyl)-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-5,6-dihydro-4H-1,3-thiazin-2-amine (530 mg, 1.500 mmol, 61.7 % yield).

^{1}H NMR (500MHz, methanol-d_4) δ 6.54 - 6.47 (m, 1H), 6.41 - 6.36 (m, 1H), 3.88 (dd, *J*=13.0, 3.1 Hz, 1H), 2.75 - 2.67 (m, 1H), 2.30 (s, 3H), 2.20 (s, 3H), 1.93 (s, 1H), 1.65 (s, 3H).

MS $(M+H)^{+}$353.1.

MP = 184°C.

The structure of this compound was confirmed by X-ray analysis.