β-Secretase (BACE1) Inhibitors with High In Vivo Efficacy Suitable for Clinical Evaluation in Alzheimer’s Disease

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1. General and abbreviations

All solvents and reagents were obtained from commercial sources and were used as received. All reactions were followed by TLC (TLC plates F254, Merck) or LCMS (liquid chromatography-mass spectrometry) analysis. Silica gel chromatography was either performed using cartridges packed with silica gel (ISOLUTE® Columns, TELOS™ Flash Columns) or silica-NH₂ gel (TELOS™ Flash NH₂ Columns) on ISCO Combi Flash Companion or on glass columns on silica gel 60 (32-60 mesh, 60 Å). Proton NMR spectra were obtained on Bruker Avance 300, 400 or 600 MHz spectrometer with chemical shifts (δ in ppm) reported relative to tetramethylsilane or the residual solvent peak as the internal reference (i.e. CDCl₃ = 7.26 ppm, DMSOd₆ = 2.50 ppm) as the internal reference. ¹H resonances are reported to the nearest 0.01 ppm. NMR abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; quint, quintuplet; sext, sextuplet; m, multiplet; br, broadened. Coupling constants (J) are reported to the nearest 0.1 Hz. Purity was analyzed by reverse phase HPLC and for specific compounds by elemental analysis. HPLC was performed on Finnigan LTQ (Thermo Fisher Scientific) and Agilent RRLC 1200 equipment. Column: Agilent XDB C15, 30 mm x 4.6 mm, 3.5 µm. Analytical conditions: gradient used: 5% to 95% acetonitrile in water containing 0.1% trifluoroacetic acid in 3 min. Flow: 4.5 mL / min. UV-Detector: DAD 190-400 nm. Sample solvent: in water/acetonitrile (8/2). The UV detection was an averaged signal from wavelengths of 190-400 nm. Elemental analyses were performed by Sollvias AG (Mattenstrasse, Postfach, CH-4002 Basel, Switzerland). Mass spectra were recorded on a SSQ 7000 (Finnigan-MAT) spectrometer for electron impact ionization. The purities of final test compounds as measured by HPLC were found to be above 95%. Melting points were determined on a Büchi Melting Point B-540: heating rate 1 °C/min starting 15 °C below melting point. LC-HRMS spectra were recorded with an Agilent LC-system consisting of an Agilent 1290 high pressure system, a CTC PAL auto sampler and an Agilent 6520 QTOF. The separation was achieved on a Zorbax Eclipse Plus C18 1,7 µm 2.1*30mm column at 55°C; eluent A=0.01% formic acid in Water; B= 0.01% formic acid in acetonitrile : 2-propanol (8:2); flow: 1 mL/min. Gradient: 0 min 5% of B, 0.3 min 5% of B, 4.5 min 95 % of B, 5 min 99% of B. The injection volume was 2 µL. LC-MS (ESI, positive or negative ion) data were recorded on Waters UPLC-MS Systems equipped with Waters Acquity, a CTC PAL auto sampler and a Waters SQD single quadrupole mass spectrometer using ES ionization modes (positive and/or negative). The separation was achieved on a Zorbax Eclipse Plus C18 1,7 µm 2.1*30mm column at 50°C; A=0.01% formic acid in water, B= acetonitrile at flow 1; gradient: 0 min 3%B, 0.2 min 3%B, 2 min 97 %B, 1.7 min 97%B, 2.0 min 97%B. The injection volume was 2 µL. MS (ESI, positive or negative ion): FIA (flow injection analysis)-MS were recorded on an AppliedBiosystem API150 mass spectrometer. Sample introduction was made with a CTC PAL auto sampler and a Shimadzu LC-10ADVP Pump. The samples were directly flushed to the ESI source of the mass spectrometer with a flow 50µL/min of a mixture of acetonitrile and 10 mM ammonium acetate (1:1) without a column. The injection volume was 2 µL.

Abbreviations. DCM, dichloromethane; Deoxo-Fluor®, bis(2-methoxyethyl)aminosulfur trifluoride; DIBAH, disobutylaluminum hydride; DMF, N,N-dimethylformamide, DMSO, dimethyl sulfoxide; DMTMM, 4-(4,6-dimethoxy[1.3.5]triazin-2-yl)-4-methylmorpholinium chloride hydrate; EtOAc, ethyl acetate; EtOH, ethanol; MeOH, methanol; rt, room temperature; TBME, tert-butylmethyl ether; TEA, triethylamine; T₃P®, (2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinan-2,4,6-trioxide; TBAF, tetrabutylammonium fluoride; THF, tetrahydrofuran.

2. Preparation of oxazines 1a-b, 14b-c, 14e-v, 66–70, 88, 109–111

A solution of the carboxylic acid (0.23 mmol) in methanol (5 ml) was cooled to 0 °C. 4-(4,6-Dimethoxy[1.3.5]triazin-2-yl)-4-methylmorpholinium chloride hydrate* (DMTMM) (80 mg, 0.27 mmol) was added and the solution was stirred at 0 °C for 30 minutes. Thereafter, a solution of the intermediate aniline (0.21 mmol) in methanol (5 ml) was added dropwise at 0 °C via syringe. The reaction mixture was stirred at 23 °C for 18-60 hours. For the workup, the reaction mixture was
concentrated at reduced pressure, then poured into a solution of Na₂CO₃ (1M) followed by the extraction with DCM. The organic layer was separated, washed with brine and dried over Na₂SO₄. Removal of the solvent left the crude product which was purified by chromatography on silica gel using a mixture of DCM–MeOH or heptane–EtOAc or by preparative HPLC to give the pure amides.

* The chloride salt can be replaced by the corresponding tetrafluoroborate.

Alternatively, coupling agent T₃P® (2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide) can be used as follows:

Under an inert atmosphere a solution/suspension of the carboxylic acid (1.7 mmol) and the intermediate aniline (1.62 mmol) in EtOAc (6.7 ml) was treated dropwise with T₃P® (50% in EtOAc) (2.4 mmol, 1.43 ml) while keeping the temperature at 25 °C. After complete addition the reaction was stirred at 25 °C for 20 hours. For the workup, the reaction mixture was quenched with a saturated solution of NaHCO₃ (20 ml), the layers were separated and the aqueous phase was extracted with EtOAc (7 ml). The combined organic layers were washed with brine and dried over Na₂SO₄. Removal of the solvent left the crude product which was purified by chromatography on silica gel using a mixture of DCM–MeOH or heptane–EtOAc or by preparative HPLC to give the pure amides.

The following compounds were prepared following the general procedure and, depending on the reaction and purification conditions, they were isolated in either the free base form or as a salt.

(S)-N-(3-(2-Amino-4-methyl-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-5-chloropicolinamide (1a)¹,²

![Amide 1a](image)

Amide 1a (white solid, 61% yield) was obtained using DMTMM as the condensating agent and purified by flash chromatography on silica gel (eluent: DCM–MeOH–NH₄OH 9 : 0.9 : 0.1). ¹H NMR (400 MHz, CDCl₃) δ ppm 9.83 (br s, 1 H), 8.56 (dd, J=2.4, 0.8 Hz, 1 H), 8.24 (dd, J=8.3, 0.5 Hz, 1 H), 8.03 (dd, J=8.8, 4.1, 3.0 Hz, 1 H), 7.87 (dd, J=8.5, 2.3 Hz, 1 H), 7.54 (dd, J=7.0, 2.7 Hz, 1 H), 7.04 (dd, J=11.6, 8.9 Hz, 1 H), 4.16 (dd, J=10.8, 5.4, 3.9 Hz, 1 H), 3.92–4.25 (m, 2 H), 3.87 (ddd, J=10.7, 9.7, 3.2 Hz, 1 H), 2.35 (ddd, J=14.0, 5.6, 3.2 Hz, 1 H), 2.12 (ddd, J=14.0, 9.7, 3.9 Hz, 1 H), 1.59 (d, J=1.1 Hz, 3 H). LCdHRMS: m/z 363.1028 [(M+H)⁺ calcd for C₁₇H₁₇ClFN₄O₂⁺, 363.1019].

(S)-N-(3-(2-Amino-4-methyl-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-5-cyanopicolinamide (1b)¹,²

![Amide 1b](image)

Amide 1b (light brown amorphous material, 41% yield as formate) was obtained using DMTMM as the condensating agent and purified by preparative HPLC (Phenomenex, Gemini C18, 100 mm x 30 mm x 5 µm column; eluent: H₂O–MeOH–HCOOH (0.05%); gradient: 5–100% MeOH). ¹H NMR (400 MHz, CDCl₃) δ ppm 9.86 (br s, 1 H), 8.89 (dd, J=2.0, 0.9 Hz, 1 H), 8.43 (dd, J=8.1, 0.8 Hz, 1 H), 8.20
(dd, J=8.1, 2.1 Hz, 1 H), 8.03 (ddd, J=8.9, 4.3, 3.0 Hz, 1 H), 7.57 (dd, J=7.0, 2.7 Hz, 1 H), 7.06 (dd, J=11.6, 8.9 Hz, 1 H), 4.17 (ddd, J=10.8, 5.7, 3.9 Hz, 1 H), 3.85–4.20 (br s, 2H), 3.88 (ddd, J=10.8, 9.6, 3.2 Hz, 1 H), 2.34 (ddd, J=14.0, 5.6, 3.2 Hz, 1 H), 2.14 (ddd, J=13.8, 9.5, 3.9 Hz, 1 H), 1.59 (d, J=1.3 Hz, 3 H). LC-HRMS: m/z 354.1371 [(M+H)+ calcd for C₁₈H₁₇FN₅O₂+, 354.1361]. X-ray PDB accession code: 4J0P.

(R)-N-(3-(2-Amino-5,5-difluoro-4-methyl-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)picolinamide (14b)

Amide 14b (colorless solid, 73% yield) was obtained using DMTMM as the condensating agent and purified by preparative HPLC [gradient: H₂O (+0.5% TEA)–acetonitrile (10–95% acetonitrile)]. ¹H NMR (300 MHz, CDCl₃) δ ppm 10.01 (br s, 1 H), 8.62 (ddd, J=4.7, 1.6, 0.9 Hz, 1 H), 8.29 (dt, J=7.8, 0.9 Hz, 1 H), 7.97 (ddd, J=8.9, 3.8, 2.8 Hz, 1 H), 7.91 (td, J=7.7, 1.7 Hz, 1 H), 7.70 (dd, J=6.9, 2.8 Hz, 1 H), 7.49 (ddd, J=7.7, 4.8, 1.2 Hz, 1 H), 7.09 (dd, J=11.5, 8.9 Hz, 1 H), 4.23 (s, 2 H), 3.96–4.22 (m, 2 H), 1.80 (t, J=2.3 Hz, 3 H). LC-HRMS: m/z 365.1224 [(M+H)+ calcd for C₁₇H₁₆F₃N₄O₂+, 365.1220].

(R)-N-(3-(2-Amino-5,5-difluoro-4-methyl-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-5-fluoropicolinamide (14c)

Amide 14c (colorless solid, 89% yield) was obtained using DMTMM as the condensating agent and purified by flash chromatography on silica gel (eluent: heptane–EtOAc; gradient: 33d50% EtOAc). ¹H NMR (300 MHz, CDCl₃) δ ppm 9.81 (br s, 1 H), 8.44 (d, J=2.6 Hz, 1 H), 8.33 (dd, J=8.7, 4.6 Hz, 1 H), 7.94 (ddd, J=8.8, 3.8, 3.1 Hz, 1 H), 7.69 (dd, J=6.8, 2.7 Hz, 1 H), 7.59 (td, J=8.3, 2.8 Hz, 1 H), 7.09 (dd, J=11.5, 8.9 Hz, 1 H), 4.26 (s, 2 H), 3.98–4.24 (m, 2 H), 1.79 (t, J=2.3 Hz, 3 H). LC-HRMS: m/z 383.1139 [(M+H)+ calcd for C₁₇H₁₅F₄N₄O₂+, 383.1126].

(R)-N-(3-(2-Amino-5,5-difluoro-4-methyl-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-5-methylpicolinamide (14e)

Amide 14e (white powder, 27% yield) was obtained using DMTMM as the condensating agent and purified by preparative HPLC [gradient: H₂O (+0.05% TEA)–acetonitrile (2–98% acetonitrile)]. ¹H NMR (400 MHz, CDCl₃) δ ppm 9.96 (br s, 1 H), 8.42 (d, J=1.3 Hz, 1 H), 8.18 (d, J=8.1 Hz, 1 H), 7.95 (dt, J=8.7, 3.3 Hz, 1 H), 7.67–7.73 (m, 2 H), 7.08 (dd, J=11.6, 8.9 Hz, 1 H), 4.24 (s, 2 H), 4.16 (ddd,
$J$=15.8, 11.6, 6.4 Hz, 1 H), 4.03 (ddd, $J$=17.2, 11.6, 5.9 Hz, 1 H), 2.44 (s, 3 H), 1.79 (t, $J$=2.1 Hz, 2 H).

LC-HRMS: $m/z$ 379.1385 [(M+H)$^+$ calcd for C$_{18}$H$_{18}$F$_3$N$_4$O$_2$, 379.1376].

(R)-N-(3-(2-Amino-5,5-difluoro-4-methyl-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-5-ethynylpicolinamide (14f)

Amide 14f (white solid, 74% yield) was obtained using DMTMM as the condensating agent and purified by preparative HPLC [gradient: H$_2$O (+0.1% TEA)–acetonitrile (10–95% acetonitrile)]. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 9.83 (s, 1 H), 8.24 (s, 1 H), 8.22 (d, $J$=6.5 Hz, 1 H), 7.93 (dd, $J$=6.8, 2.7 Hz, 1 H), 7.32 (dd, $J$=8.6, 2.9 Hz, 1 H), 7.07 (dd, $J$=11.6, 8.8 Hz, 1 H), 4.38 (br s, 2 H), 3.95–4.22 (m, 2 H), 3.93 (s, 3 H), 1.80 (t, $J$=2.2 Hz, 3 H). LC-HRMS: $m/z$ 389.1338 [(M+H)$^+$ calcd for C$_{18}$H$_{18}$F$_3$N$_4$O$_3$, 389.1326].

(R)-N-(3-(2-Amino-5,5-difluoro-4-methyl-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-5-methoxypicolinamide (14g)

Amide 14g (colorless oil, 26% yield) was obtained using DMTMM as the condensating agent and purified by chromatography on silica-NH$_2$ gel (eluent: heptane–EtOAc; gradient: 0–75% EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 9.82 (br s, 1 H), 8.52 (dd, $J$=2.0, 0.6 Hz, 1 H), 8.36 (dd, $J$=8.7, 0.4 Hz, 1 H), 7.94 (dd, $J$=8.9, 3.8, 3.0 Hz, 1 H), 7.75 (dd, $J$=8.7, 2.6, 1.2 Hz, 1 H), 7.70 (dd, $J$=6.8, 2.7 Hz, 1 H), 7.10 (dd, $J$=11.5, 8.9 Hz, 1 H), 4.24 (br s, 2 H), 4.12–4.24 (m, 1 H), 4.04 (dd, $J$=16.3, 11.7, 6.5 Hz, 1 H), 1.80 (t, $J$=2.3 Hz, 3 H). LC-HRMS: $m/z$ 395.1338 [(M+H)$^+$ calcd for C$_{18}$H$_{18}$F$_3$N$_4$O$_3$, 395.1326].

(R)-N-(3-(2-Amino-5,5-difluoro-4-methyl-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-5-(trifluoromethoxy)picolinamide (14h)

Amide 14h (white solid, 83% yield) was obtained using DMTMM as the condensating agent and purified by chromatography on silica-NH$_2$ gel (eluent: heptane–EtOAc; gradient: 0–100% EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 9.89 (br s, 1 H), 8.68 (dd, $J$=2.0, 0.8 Hz, 1 H), 8.25 (dd, $J$=8.2, 0.9 Hz, 1 H), 7.97 (dd, $J$=8.0, 1.9 Hz, 1 H), 7.91–7.98 (m, 1 H), 7.72 (dd, $J$=6.9, 2.8 Hz, 1 H), 7.09 (dd, $J$=11.5, 8.9 Hz, 1 H), 4.28 (br s, 2 H), 4.18 (dd, $J$=16.3, 11.9, 6.5 Hz, 1 H), 4.04 (dd, $J$=16.1, 11.5, 6.3 Hz, 1 H), 3.38 (s, 1 H), 1.80 (t, $J$=2.3 Hz, 3 H). LC-HRMS: $m/z$ 449.1055 [(M+H)$^+$ calcd for C$_{18}$H$_{18}$F$_3$N$_4$O$_3$, 449.1043].
(R)-N-(3-(2-Amino-5,5-difluoro-4-methyl-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-5-ethoxypicolinamide (14i)

![Chemical Structure](image)

Amide 14i (colorless solid, 76% yield) was obtained using DMTMM as the condensating agent and purified by chromatography on silica-NH₂ gel (eluent: 1:1 mixture of heptane and EtOAc) followed by trituration in ether/pentane. ¹H NMR (300 MHz, CDCl₃) δ ppm 9.82 (br s, 1 H), 8.16–8.27 (m, 2 H), 7.88–7.98 (m, 1 H), 7.67 (dd, J=6.8, 2.7 Hz, 1 H), 7.31 (dd, J=8.6, 2.7 Hz, 1 H), 7.07 (dd, J=11.5, 8.7 Hz, 1 H), 3.96–4.25 (m, 6 H), 1.79 (t, J=2.2 Hz, 3 H). LC-HRMS: m/z 409.1483 [(M+H)+ calcd for C₁₉H₂₀F₃N₄O₃⁺, 409.1482]. X-ray PDB accession code: 4J0T (BACE1), 3ZLQ (BACE2).

(R)-N-(3-(2-Amino-5,5-difluoro-4-methyl-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-5-(2,2,2-trifluoroethoxy)picolinamide (14j)

Amide 14j (colorless solid, 38% yield) was obtained using DMTMM as the condensating agent and purified by chromatography on silica gel (eluent: DCM–MeOH; gradient: 100:1–100:2). ¹H NMR (600 MHz, CDCl₃) δ ppm 9.81 (s, 1 H), 8.33 (dd, J=2.5, 0.3 Hz, 1 H), 8.28 (dd, J=8.7, 0.4 Hz, 1 H), 7.93 (ddd, J=8.9, 3.8, 2.9 Hz, 1 H), 7.70 (dd, J=6.8, 2.8 Hz, 1 H), 7.40 (dd, J=8.7, 2.9 Hz, 1 H), 7.08 (ddd, J=11.5, 8.8 Hz, 1 H), 4.48 (q, J=7.9 Hz, 2 H), 4.31 (br s, 2 H), 4.17 (ddd, J=17.0, 11.4, 5.9 Hz, 1 H), 4.04 (dd, J=17.0, 11.5, 5.7 Hz, 1 H), 1.80 (t, J=2.2 Hz, 3 H). LC-HRMS: m/z 463.1195 [(M+H)+ calcd for C₁₉H₁₇F₆N₄O₃⁺, 463.1199].

(R)-N-(3-(2-Amino-5,5-difluoro-4-methyl-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-5-(2,2,3,3-tetrafluoropropoxy)picolinamide (14k)

Amide 14k (white solid, 44% yield) was obtained using DMTMM as the condensating agent and purified by chromatography on silica gel (eluent: DCM–MeOH; gradient: 0–10% MeOH). ¹H NMR (300 MHz, CDCl₃) δ ppm 9.80 (s, 1 H), 8.33 (d, J=2.8 Hz, 1 H), 8.29 (d, J=8.7 Hz, 1 H), 7.91–7.98 (m, 1 H), 7.69 (dd, J=6.7, 2.6 Hz, 1 H), 7.40 (dd, J=8.7, 2.8 Hz, 1 H), 7.09 (dd, J=11.3, 8.9 Hz, 1 H), 6.07 (tt, J=52.9, 4.2 Hz, 1 H), 4.49 (t, J=11.8 Hz, 2 H), 4.17–4.37 (br s, 2 H), 4.18 (ddd, J=15.9, 11.7, 6.5 Hz, 1 H), 4.04 (ddd, J=16.6, 11.3, 6.3 Hz, 1 H), 1.80 (s, 3 H). LC-HRMS: m/z 495.1270 [(M+H)+ calcd for C₂₀H₁₈F₇N₄O₃⁺, 495.1262].
(R)-N-(3-(2-Amino-5,5-difluoro-4-methyl-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-5-chloro-3-methylpicolinamide (14l)

![Chemical structure of 14l](image)

Amide 14l (colorless solid, 42% yield) was obtained using DMTMM as the condensing agent and purified by preparative HPLC [gradient: H$_2$O (+0.5% TEA)–acetonitrile (10%–95% acetonitrile)]. $^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 10.59 (s, 1 H), 8.58 (d, $J$=1.8 Hz, 1 H), 8.02 (d, $J$=1.4 Hz, 1 H), 7.84 (m, 2 H), 7.14 (dd, $J$=11.4, 8.8 Hz, 1 H), 4.22–4.38 (m, 1 H), 3.93–4.08 (m, 1 H), 3.30 (s, 2 H), 2.56 (s, 3 H), 1.64 (br s, 3 H). LC-MS: $m/z$ 413.0977 [(M+H)$^+$ calcd for C$_{18}$H$_{17}$ClF$_3$N$_4$O$_2$$^+$, 413.0987].

(R)-N-(3-(2-Amino-5,5-difluoro-4-methyl-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-3,5-dichloropicolinamide (14m)

![Chemical structure of 14m](image)

Amide 14m (white solid, 82% yield) was obtained using DMTMM as the condensing agent and purified by chromatography on silica gel (eluent: heptane–EtOAc; gradient: 3:2–1:1) followed by trituration in ether/pentane. $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 9.72 (s, 1 H), 8.46 (d, $J$=2.0 Hz, 1 H), 8.02 (dt, $J$=8.6, 3.4 Hz, 1 H), 7.90 (d, $J$=2.0 Hz, 1 H), 7.56 (dd, $J$=6.7, 2.8 Hz, 1 H), 7.09 (dd, $J$=11.4, 8.8 Hz, 1 H), 4.26 (s, 2 H), 4.19 (ddd, $J$=17.8, 11.7, 5.9 Hz, 1 H), 4.04 (ddd, $J$=15.1, 11.7, 6.5 Hz, 1 H), 1.79 (t, $J$=2.2 Hz, 3 H). LC-MS m/z 433.0447 [(M+H)$^+$ calcd for C$_{17}$H$_{14}$Cl$_2$F$_3$N$_4$O$_2$$^+$, 433.0440].

(R)-N-(3-(2-Amino-5,5-difluoro-4-methyl-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-5-chloropyrimidine-2-carboxamide (14n)

![Chemical structure of 14n](image)

Amide 14n (colorless solid, 27% yield) was obtained using T$_3$P$^*$ as the condensing agent and purified by chromatography on silica gel (eluent: heptane–EtOAc; gradient: 4:1). $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 9.75 (s, 1 H), 8.88 (s, 2 H), 7.89 (ddd, $J$=8.8, 3.8, 2.9 Hz, 1 H), 7.82 (dd, $J$=6.8, 2.7 Hz, 1 H), 7.10 (dd, $J$=11.4, 8.8 Hz, 1 H), 4.06–4.47 (br s, 2 H), 3.98–4.24 (m, 2 H), 1.80 (t, $J$=2.3 Hz, 3 H). LC-MS $m/z$ 400.0790 [(M+H)$^+$ calcd for C$_{16}$H$_{14}$ClF$_3$N$_5$O$_2$$^+$, 400.0783].

(R)-N-(3-(2-Amino-5,5-difluoro-4-methyl-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-5-methoxypyrazine-2-carboxamide (14o)
Amide 14o (white solid, 84% yield) was obtained using DMTMM as the condensating agent and purified by chromatography on silica-NH₂ gel [eluent: heptane–EtOAc (1:1)]. ¹H NMR (300 MHz, CDCl₃) δ ppm 9.51 (s, 1 H), 9.01 (d, J=1.2 Hz, 1 H), 8.13 (d, J=1.2 Hz, 1 H), 7.93 (dd, J=8.8, 3.9, 2.8 Hz, 1 H), 7.69 (dd, J=6.7, 2.8 Hz, 1 H), 7.08 (dd, J=11.5, 8.9 Hz, 1 H), 4.30 (s, 2 H), 4.17 (dd, J=16.6, 11.7, 6.3 Hz, 1 H), 4.06 (2, 3 H), 4.03 (dd, J=16.1, 11.5, 6.1 Hz, 1 H), 1.79 (t, J=2.4 Hz, 3 H). LC-HRMS m/z 396.1288 [(M+H)+ calcd for C₁₇H₁₇F₃N₅O₃⁺, 396.1278].

(R)-N-(3-(2-Amino-5,5-difluoro-4-methyl-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-5-(2,2,2-trifluoroethoxy)pyrazine-2-carboxamide (14p)

Amide 14p (white powder, 46% yield) was obtained using DMTMM as the condensating agent and purified by preparative HPLC [gradient: H₂O (+0.05% TEA)–acetonitrile (2%–98% acetonitrile)]. ¹H NMR (400 MHz, CDCl₃) δ ppm 9.49 (s, 1 H), 9.02 (d, J=1.3 Hz, 1 H), 8.30 (d, J=1.3 Hz, 1 H), 7.92 (ddd, J=8.9, 3.8, 3.0 Hz, 1 H), 7.70 (dd, J=6.9, 2.8 Hz, 1 H), 7.10 (dd, J=11.6, 8.9 Hz, 1 H), 4.86 (q, J=8.2 Hz, 2 H), 4.25 (s, 2 H), 4.19 (ddd, J=17.3, 11.6, 5.8 Hz, 1 H), 4.04 (dd, J=15.8, 11.6, 6.2 Hz, 1 H), 1.79 (t, J=2.3 Hz, 3 H). LC-HRMS m/z 464.1164 [(M+H)+ calcd for C₁₈H₁₆F₆N₅O₃⁺, 464.1152].

(R)-N-(3-(2-Amino-5,5-difluoro-4-methyl-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-5-(prop-2ynyloxy)pyrazine-2-carboxamide (14q)

Amide 14q (off-white solid, 52% yield) was obtained using DMTMM as the condensating agent and purified by chromatography on silica gel (elucent: heptane–EtOAc; gradient: 0–80% EtOAc). ¹H NMR (300 MHz, CDCl₃) δ ppm 9.50 (s, 1 H), 9.03 (d, J=1.4 Hz, 1 H), 8.21 (d, J=1.2 Hz, 1 H), 7.91 (ddd, J=8.9, 3.8, 3.0 Hz, 1 H), 7.69 (dd, J=6.9, 2.8 Hz, 1 H), 7.09 (dd, J=11.5, 8.9 Hz, 1 H), 5.09 (d, J=2.6 Hz, 2 H), 4.34 (br s, 2 H), 4.18 (ddd, J=16.5, 11.5, 6.3 Hz, 1 H), 4.04 (ddd, J=15.9, 11.5, 6.3 Hz, 1 H), 2.55 (t, J=2.4 Hz, 1 H), 1.80 (t, J=2.1 Hz, 3 H). LC-HRMS m/z 420.1289 [(M+H)+ calcd for C₁₉H₁₇F₃N₅O₃⁺, 420.1278].

(R)-N-(3-(2-Amino-5,5-difluoro-4-methyl-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-5-(but-2ynyloxy)pyrazine-2-carboxamide (14r)
Amide 14r (colorless foam, 36% yield) was obtained using DMTMM as the condensating agent and purified by chromatography on silica-NH₂ gel (eluent: heptane–EtOAc; gradient: 50–100% EtOAc). ¹H NMR (300 MHz, CDCl₃) δ ppm 9.50 (s, 1 H), 9.02 (d, J=1.4 Hz, 1 H), 8.19 (d, J=1.4 Hz, 1 H), 7.99 (dd, J=8.9, 3.8, 3.0 Hz, 1 H), 7.69 (dd, J=6.8, 2.7 Hz, 1 H), 7.08 (dd, J=11.5, 8.9 Hz, 1 H), 5.05 (q, J=2.2 Hz, 2 H), 4.29 (br s, 2 H), 3.97–4.24 (m, 2 H), 1.89 (t, J=2.3 Hz, 3 H), 1.79 (s, 3 H). LC-HRMS m/z 434.1441 [(M+H)⁺ calcd for C₂₀H₁₉F₃N₅O₃⁺, 434.1435].

(R)-N-(3-(2-Amino-5,5-difluoro-4-methyl-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-1-methyl-1H-pyrazole-3-carboxamide (14s)

Amide 14s (white solid, 71% yield) was obtained using DMTMM as the condensating agent and purified by chromatography on silica gel (eluent: DCM–MeOH; gradient: 0–10% MeOH). ¹H NMR (600 MHz, DMSO-d₆) δ ppm 10.06 (s, 1 H), 7.87 (dd, J=7.2, 2.8 Hz, 1 H), 7.84 (d, J=2.3 Hz, 1 H), 7.77 (dd, J=8.8, 3.9, 2.9 Hz, 1 H), 7.10 (dd, J=11.8, 8.8 Hz, 1 H), 6.74 (d, J=2.3 Hz, 1 H), 4.28 (ddd, J=17.7, 11.8, 5.7 Hz, 1 H), 3.96 (s, 3 H), 3.95–4.04 (m, 1 H), 1.63 (s, 3 H). LC-HRMS m/z 368.1332 [(M+H)⁺ calcd for C₁₆H₁₇F₃N₅O₂⁺, 368.1329].

(R)-N-(3-(2-Amino-5,5-difluoro-4-methyl-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-4-chloro-1-methyl-1H-pyrazole-3-carboxamide (14t)

Amide 14t (white solid, 98% yield) was obtained using DMTMM as the condensating agent and purified by chromatography on silica gel (eluent: DCM–MeOH; gradient: 0–10% MeOH). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.58 (s, 1 H), 7.93 (ddd, J=8.9, 3.8, 3.0 Hz, 1 H), 7.53 (dd, J=6.7, 3.0 Hz, 1 H), 7.44 (s, 1 H), 7.05 (dd, J=11.6, 8.9 Hz, 1 H), 4.32 (br s, 2 H), 4.16 (ddd, J=17.2, 12.1, 5.6 Hz, 1 H), 4.03 (ddd, J=16.9, 11.6, 6.2 Hz, 1 H), 3.91 (s, 3 H), 1.78 (s, 3 H). LC-HRMS m/z 402.0948 [(M+H)⁺ calcd for C₁₆H₁₆ClF₃N₅O₂⁺, 402.0939].

(R)-N-(3-(2-Amino-5,5-difluoro-4-methyl-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-1-(difluoromethyl)-1H-pyrazole-3-carboxamide (14u)
Amide 14u (white solid, 54% yield) was obtained using DMTMM as the condensating agent and purified by chromatography on silica gel (eluent: DCM–MeOH; gradient: 0–10% MeOH) and on preparative HPLC [column: Gemini 5µ C18 110Å AXIA (50x21.2mm), flow: 40 ml/min; gradient: H$_2$O (+0.1% TEA)–acetonitrile (10%–95% acetonitrile)]. $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 8.62 (s, 1 H), 7.87 (d, $J$=2.8 Hz, 1 H), 7.84 (ddd, $J$=8.8, 3.8, 2.9 Hz, 1 H), 7.64 (dd, $J$=6.9, 2.8 Hz, 1 H), 7.20 (t, $J$=60.3 Hz, 1 H), 7.07 (dd, $J$=11.5, 8.7 Hz, 1 H), 7.06 (d, $J$=2.8 Hz, 1 H), 4.23 (br s, 2 H), 3.97–4.22 (m, 2 H), 1.81 (t, $J$=2.3 Hz, 3 H). LC-HRMS m/z 404.1151 [(M+H)$^+$ calcd for C$_{16}$H$_{15}$F$_{5}$N$_5$O$_2^+$, 404.1140].

(R)-N-(3-(2-Amino-5,5-difluoro-4-methyl-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-4-chloro-1-(difluoromethyl)-1H-pyrazole-3-carboxamide (14v)

Amide 14v (colorless solid, 83% yield) was obtained using DMTMM as the condensating agent and purified by chromatography on silica gel [eluent: heptane–EtOAc (1:1)]. $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 8.55 (s, 1 H), 7.88–7.95 (m, 2 H), 7.57 (dd, $J$=6.7, 2.8 Hz, 1 H), 7.10 (t, $J$=60.3 Hz, 1 H), 7.08 (dd, $J$=11.4, 8.8 Hz, 1 H), 4.36 (br s, 2 H), 4.19 (ddd, $J$=17.8, 11.8, 5.8 Hz, 1 H), 4.03 (ddd, $J$=15.0, 11.6, 6.5 Hz, 1 H), 1.78 (t, $J$=2.3 Hz, 3 H). LC-HRMS m/z 438.0763 [(M+H)$^+$ calcd for C$_{16}$H$_{14}$ClF$_5$N$_5$O$_2^+$, 438.0751].

N-(3-((4R,5R)-2-Amino-5-fluoro-4-methyl-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-5-cyanopicolinamide (66)

Amide 66 (white crystalline solid, 77% yield) was obtained using DMTMM as the condensating agent and purified by chromatography on silica gel [eluent: DCM–MeOH (20:1)] (1:1)]. $^1$H NMR (300 MHz, DMSO-d$_6$) δ ppm 10.90 (s, 1 H), 9.20 (dd, $J$=2.0, 0.8 Hz, 1 H), 8.58 (dd, $J$=8.1, 2.0 Hz, 1 H), 8.28 (dd, $J$=8.2, 0.7 Hz, 1 H), 7.93 (dd, $J$=7.4, 2.5 Hz, 1 H), 7.79–7.86 (m, 1 H), 7.19 (dd, $J$=11.7, 8.9 Hz, 1 H), 5.10 (dd, $J$=47.6, 1.0 Hz, 1 H), 4.06–4.19 (m, 1 H), 3.67 (dd, $J$=40.8, 12.7 Hz, 1 H), 3.30 (s, 2 H), 1.48 (s, 3 H). LC-HRMS m/z 372.1276 [(M+H)$^+$ calcd for C$_{18}$H$_{16}$F$_2$N$_5$O$_2^+$, 372.1267]. X-ray PDB accession code: 4J0V.
N-(3-((4R,5S)-2-Amino-5-fluoro-4-methyl-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-5-cyanopicolinamide (67)

Amide 67 (white solid, 70% yield) was obtained using DMTMM as the condensating agent and purified by chromatography on silica-NH$_2$ gel (eluuent: heptane–EtOAc; gradient: 0–80% EtOAc). $^1$H NMR (600 MHz, CDCl$_3$) \( \delta \) ppm 9.88 (br s, 1 H), 8.83 (d, \( J=1.8 \) Hz, 1 H), 8.40 (d, \( J=8.2 \) Hz, 1 H), 8.18 (dd, \( J=8.1, 1.7 \) Hz, 1 H), 8.09 (ddd, \( J=8.8, 3.7, 2.9 \) Hz, 1 H), 7.87 (ddd, \( J=6.9, 2.8 \) Hz, 1 H), 7.08 (dd, \( J=11.5, 8.8 \) Hz, 1 H), 5.29 (d, \( J=46.7 \) Hz, 1 H), 4.41–4.51 (m, 2 H), 4.27 (br s, 2 H), 1.57 (s, 3 H). LC-HRMS m/z 372.1278 [(M+H)$^+$ calcd for C$_{18}$H$_{16}$F$_2$N$_5$O$_2$, 372.1267]. X-ray PDB accession code: 4J0Y.

N-(3-((4S,5R)-2-Amino-5-fluoro-4-(fluoromethyl)-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-5-cyanopicolinamide (68)

Amide 68 (light yellow solid, 74% yield) was obtained using DMTMM as the condensating agent and purified by chromatography on silica gel (eluuent: heptane–EtOAc; gradient: 0–85% EtOAc). $^1$H NMR (300 MHz, DMSO-$d_6$) \( \delta \) ppm 10.94 (s, 1 H), 9.20 (dd, \( J=1.9, 0.7 \) Hz, 1 H), 8.58 (dd, \( J=8.1, 2.0 \) Hz, 1 H), 8.28 (dd, \( J=8.2, 0.7 \) Hz, 1 H), 8.00 (dd, \( J=7.2, 2.5 \) Hz, 1 H), 7.87 (ddd, \( J=9.1, 4.2, 2.8 \) Hz, 1 H), 7.22 (dd, \( J=11.7, 8.9 \) Hz, 1 H), 5.89 (s, 2 H), 5.39 (d, \( J=46.6 \) Hz, 1 H), 4.88 (ddd, \( J=47.2, 8.5, 1.4 \) Hz, 1 H), 4.39 (dd, \( J=47.8, 9.3 \) Hz, 1 H), 4.21 (t, \( J=13.3 \) Hz, 1 H), 3.78 (dd, \( J=41.4, 12.9 \) Hz, 1 H). LC-HRMS m/z 388.1031 [(M-H)$^-$ calcd for C$_{18}$H$_{13}$F$_3$N$_5$O$_2^-$, 388.1027]. X-ray PDB accession code: 4J0Z.

(S)-N-(3-(2-Amino-4-(difluoromethyl)-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-5-cyanopicolinamide (69)

Amide 69 (white solid, 73% yield) was obtained using DMTMM as the condensating agent and purified by chromatography on silica gel (eluuent: DCM–MeOH; gradient: 0–10% MeOH). $^1$H NMR (300 MHz, CDCl$_3$) \( \delta \) ppm 9.88 (s, 1 H), 8.87 (dd, \( J=2.0, 0.8 \) Hz, 1 H), 8.41 (dd, \( J=8.1, 0.8 \) Hz, 1 H), 8.20 (dd, \( J=8.3, 2.0 \) Hz, 1 H), 8.12 (ddd, \( J=8.9, 4.2, 2.8 \) Hz, 1 H), 7.72 (dd, \( J=6.8, 2.7 \) Hz, 1 H), 7.11 (dd, \( J=11.5, 8.9 \) Hz, 1 H), 6.07 (td, \( J=56.5, 0.8 \) Hz, 1 H), 4.38 (br s, 2 H), 4.24 (dtt, \( J=10.9, 4.8, 4.8, 0.8, 0.8 \) Hz, 1 H), 3.86–3.97 (m, 1 H), 2.34–2.47 (m, 2 H). LC-HRMS m/z 390.1179 [(M+H)$^+$ calcd for C$_{18}$H$_{15}$F$_3$N$_5$O$_2^+$, 390.1172]. X-ray PDB accession code: 4J17.
(S)-N-(3-(2-Amino-5,5-difluoro-4-(fluoromethyl)-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-5-cyanopicolinamide (70)

Amide 7 (light yellow foam, 74% yield) was obtained using DMTMM as the condensing agent and purified by chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–67% EtOAc). $^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 10.90 (s, 1 H), 9.20 (dd, $J$=2.1, 0.9 Hz, 1 H), 8.59 (dd, $J$=8.1, 2.0 Hz, 1 H), 8.29 (dd, $J$=8.3, 0.8 Hz, 1 H), 8.10 (dd, $J$=6.9, 2.8 Hz, 1 H), 7.92 (ddd, $J$=8.9, 4.0, 2.8 Hz, 1 H), 7.22 (dd, $J$=11.6, 8.8 Hz, 1 H), 6.17 (s, 2 H), 5.01 (ddd, $J$=49.4, 9.1, 1.8 Hz, 1 H), 4.64 (dd, $J$=45.6, 8.7 Hz, 1 H), 4.14–4.27 (m, 2 H). LC-HRMS $m/z$ 408.1077 [(M+H)$^+$ calcd for C$_{18}$H$_{14}$F$_4$N$_5$O$_2$ $^+$, 408.1078]. X-ray PDB accession code: 4J1C.

N-(3-((4S,6S)-2-Amino-4-(fluoromethyl)-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-5-cyanopicolinamide (88)

Amide 88 (colorless solid, 66% yield) was obtained using DMTMM as the condensing agent and purified by chromatography on silica gel [eluent: heptane–EtOAc (3:2)]. $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 9.86 (s, 1 H), 8.88 (dd, $J$=2.0, 0.8 Hz, 1 H), 8.42 (dd, $J$=8.3, 0.8 Hz, 1 H), 8.20 (dd, $J$=8.3, 2.0 Hz, 1 H), 8.03 (ddd, $J$=8.8, 4.1, 2.8 Hz, 1 H), 7.62 (dd, $J$=6.9, 2.8 Hz, 1 H), 7.14 (dd, $J$=11.5, 8.9 Hz, 1 H), 4.69 (ddd, $J$=47.4, 8.7, 1.6 Hz, 1 H), 4.48 (ddd, $J$=46.8, 8.5, 0.8 Hz, 1 H), 4.44 (s, 2 H), 4.08–4.20 (m, 1 H), 2.70 (dd, $J$=13.6, 2.7 Hz, 1 H), 2.17 (t, $J$=13.1 Hz, 1 H). LC-HRMS $m/z$ 440.1147 [(M+H)$^+$ calcd for C$_{19}$H$_{15}$F$_5$N$_5$O$_2$ $^+$, 440.1140]. X-ray PDB accession code: 4J1E.

N-(3-((4S,6R)-2-Amino-4-methyl-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-5-cyanopicolinamide (109)

Amide 109 (light yellow foam, 73% yield) was obtained using DMTMM as the condensing agent and purified by chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–92% EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 9.87 (s, 1 H), 8.89 (dd, $J$=2.0, 0.8 Hz, 1 H), 8.20 (dd, $J$=8.3, 2.0 Hz, 1 H), 8.03 (ddd, $J$=8.8, 4.1, 2.8 Hz, 1 H), 7.62 (dd, $J$=6.9, 2.8 Hz, 1 H), 7.14 (dd, $J$=11.5, 8.9 Hz, 1 H), 4.69 (ddd, $J$=47.4, 8.7, 1.6 Hz, 1 H), 4.48 (ddd, $J$=46.8, 8.5, 0.8 Hz, 1 H), 4.44 (s, 2 H), 3.91–4.40 (br s, 2 H), 2.70 (dd, $J$=13.6, 2.7 Hz, 1 H), 1.80 (t, $J$=13.2 Hz, 1 H), 1.61 (s, 3 H). LC-HRMS $m/z$ 422.1244 [(M+H)$^+$ calcd for C$_{19}$H$_{16}$F$_4$N$_5$O$_2$ $^+$, 422.1235]. X-ray PDB accession code: 4J1H.
N-(3-((4R,5R,6R)-2-Amino-5-fluoro-4-methyl-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-5-cyanopicolinamide (110)

![Chemical structure of 110]

Amide 110 (white solid, 67% yield) was obtained using DMTMM as the condensating agent and purified by chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–80% EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 9.86 (br s, 1 H), 8.88 (d, $J$=1.0 Hz, 1 H), 8.43 (d, $J$=8.3 Hz, 1 H), 8.20 (dd, $J$=8.1, 2.0 Hz, 1 H), 7.88 (dt, $J$=8.6, 3.4 Hz, 1 H), 7.81 (dd, $J$=6.9, 2.6 Hz, 1 H), 7.11 (dd, $J$=11.5, 8.9 Hz, 1 H), 4.97 (dd, $J$=49.4, 7.7 Hz, 1 H), 4.56–4.72 (m, 1 H), 3.79–4.80 (br s, 2 H), 1.72 (br s, 3 H). LC-HRMS m/z 440.1141 [(M+H)$^+$ calcd for C$_{19}$H$_{15}$F$_5$N$_5$O$_2^+$, 440.1140]. X-ray PDB accession code: 4J1I.

N-(3-((4R,5R,6S)-2-Amino-5-fluoro-4-methyl-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-4-yl)-4-fluorophenyl)-5-cyanopicolinamide (111)

![Chemical structure of 111]

Amide 111 (light yellow foam, 83% yield) was obtained using DMTMM as the condensating agent and purified by chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–75% EtOAc). $^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 10.92 (s, 1 H), 9.20 (dd, $J$=1.9, 0.9 Hz, 1 H), 8.58 (dd, $J$=8.3, 2.0 Hz, 1 H), 8.28 (dd, $J$=8.3, 0.8 Hz, 1 H), 7.86–7.95 (m, 2 H), 7.23 (dd, $J$=11.8, 8.8 Hz, 1 H), 6.16 (s, 2 H), 5.28 (d, $J$=49.7 Hz, 1 H), 4.53 (ddd, $J$=29.9, 12.7, 6.7 Hz, 1 H), 1.53 (br s, 3 H). LC-HRMS m/z 440.1149 [(M+H)$^+$ calcd for C$_{19}$H$_{15}$F$_5$N$_5$O$_2^+$, 440.1140]. X-ray PDB accession code: 4J1K.

3. Characterization of thiazines 112 and 113

(S)-N-(3-(2-Amino-4-methyl-5,6-dihydro-4H-1,3-thiazin-4-yl)-4-fluorophenyl)-5-chloropicolinamide (112)$^7,8$

![Chemical structure of 112]

Preparation of amide 112 (off-white solid) see$^8$.

$^1$H NMR (300 MHz, CDCl$_3$) δ ppm 9.82 (br s, 1 H), 8.57 (dd, $J$=2.4, 0.6 Hz, 1 H), 8.23 (dd, $J$=8.5, 0.6 Hz, 1 H), 7.98 (ddd, $J$=8.8, 4.1, 2.8 Hz, 1 H), 7.87 (dd, $J$=8.4, 2.3 Hz, 1 H), 7.41 (dd, $J$=7.1, 2.6 Hz, 1 H), 7.08 (dd, $J$=11.7, 8.9 Hz, 1 H), 3.09–5.76 (br s, 2 H), 2.99 (ddd, $J$=12.3, 6.1, 3.6 Hz, 1 H), 2.76 (ddd, $J$=12.1, 11.2, 3.5 Hz, 1 H), 2.59 (ddd, $J$=14.1, 5.9, 3.4 Hz, 1 H), 1.97 (ddd, $J$=14.3, 10.9, 3.6 Hz, 1
H), 1.70 (d, J=1.0 Hz, 3 H). LC-HRMS m/z 379.0798 [(M+H)+ calcd for C_{17}H_{17}ClF_{4}N_{4}O_{3}, 379.0779]; m.p. 164–166 °C.

(R)-N-(3-(2-Amino-5,5-difluoro-4-methyl-5,6-dihydro-4H-1,3-thiazin-4-yl)-4-fluorophenyl)-5-chloropicolinamide Hydrochloride (113)\(^9\)

![Chemical structure of (R)-N-(3-(2-Amino-5,5-difluoro-4-methyl-5,6-dihydro-4H-1,3-thiazin-4-yl)-4-fluorophenyl)-5-chloropicolinamide Hydrochloride (113)](attachment)

Preparation of amide 113 (white solid) as the free base see\(^9\).

\(^1\)H NMR (600 MHz, DMSO-\(d_6\)) \(\delta\) ppm 11.19 (br s, 1 H), 10.98 (s, 1 H), 9.82 (br s, 1 H), 8.71–8.87 (br s, 1 H), 8.80 (dd, \(J=2.4, 0.7\) Hz, 2 H), 8.22 (dd, \(J=8.5, 2.4\) Hz, 1 H), 8.17 (dd, \(J=8.4, 0.6\) Hz, 1 H), 8.11–8.15 (m, 1 H), 8.09 (dd, \(J=7.3, 2.4\) Hz, 1 H), 7.33 (dd, \(J=12.3, 9.0\) Hz, 1 H), 3.96 (t, \(J=14.6\) Hz, 1 H), 3.56 (t, \(J=15.7\) Hz, 1 H), 1.92 (s, 3 H). LC-HRMS m/z 415.0608 [(M+H)+ calcd for C_{17}H_{15}ClF_{3}N_{4}O_{3}+, 415.0602]; m.p. 275 °C (decomp.).

4. Preparation of the intermediate sulfinyl imines 37 and 38

General procedure

A solution of the acetophenone (145 mmol) in THF (250 ml) was treated under an inert atmosphere at room temperature with (R)-(+)\text{-}tert-butylsulfinamide (21.1 g, 174 mmol) followed by the addition of titanium(IV)ethoxide (66.1 g, 290 mmol). The solution was stirred at 50–70 °C for 9–15 hours. For the workup, the solution was cooled to room temperature, then poured into a saturated solution of NH\(_4\)Cl. After addition of EtOAc, the mixture was stirred vigorously for 15 min. After separation of the layers, the aqueous phase was extracted twice with EtOAc. The combined organic layers were washed twice with water, dried over Na\(_2\)SO\(_4\) and evaporated at reduced pressure. The crude material was purified by flash chromatography on silica gel using mixtures of heptane and EtOAc as the eluent to give the sulfinyl imines.

(R,E)-N-(2-Fluoro-1-(2-fluorophenyl)ethylidene)-2-methylpropane-2-sulfinamide (37)\(^5\)

![Chemical structure of (R,E)-N-(2-Fluoro-1-(2-fluorophenyl)ethylidene)-2-methylpropane-2-sulfinamide (37)](attachment)

Sulfinyl imine 37 was obtained from 34 as an orange oil (52% yield) after chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–33% EtOAc). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) ppm 7.38–7.58 (m, 2 H), 7.21 (td, \(J=7.5, 1.0\) Hz, 1 H), 7.12 (ddd, \(J=10.3, 8.6, 0.9\) Hz, 1 H), 5.04–6.16 (m, 2 H), 1.30 (s, 9 H). MS (ESI, positive ion): m/z = 260.2 [M+H]\(^+\).

The 2-fluoro-1-(2-fluoro-phenyl)-ethanone (34)\(^10\) was obtained as follows:
A solution of 1-(2-fluorophenyl)-2-hydroxyethanone\textsuperscript{11} (2.77 g, 18.0 mmol) in DCM (42 ml) was treated consecutively at 0 °C with TEA (6.36 g, 62.8 mmol), triethylamine trihydrofluoride (3.05 g, 18.0 mmol) and nonafluoro-n-butansulfonyl fluoride (8.48 g, 26.9 mmol). The tube was sealed and the reaction mixture stirred overnight at rt. For the workup, the dark red solution was poured on a saturated solution of NaHCO$_3$ and ice, then extracted with DCM. The organic layer was separated, dried over Na$_2$SO$_4$ and evaporated. The crude material was purified by flash chromatography on silica gel (Telos Flash Silica) using DCM as the eluent to give the 2-fluoro-1-(2-fluoro-phenyl)-ethanone (1.23 g, 61% yield) as a yellow semisolid.

\begin{equation}
R,E)-\text{N-(1-(5-Bromo-2-fluorophenyl)-2,2-difluoroethylidene)-2-methylpropane-2-sulfinamide (38}\textsuperscript{5}
\end{equation}

Sulfinyl imine 38 was obtained from 35 (S. Badiger et al. WO2011009943, 2011) as a yellow oil (80% yield) after chromatography on silica gel (eluent: heptane–DCM; gradient: 0–100% DCM). $^1$H NMR (600 MHz, CDCl$_3$) δ ppm 8.04 (td, $J=7.5$, 1.9 Hz, 1 H), 7.61 (dd, $J=8.3$, 7.3, 5.3, 1.9 Hz, 1 H), 7.31 (td, $J=7.6$, 1.0 Hz, 1 H), 7.18 (m, $J=11.3$, 8.4, 0.9 Hz, 1 H), 5.48 (d, $J=3.6$ Hz, 1 H), 5.40 (d, $J=3.5$ Hz, 1 H).

5. Preparation of the intermediate sulfinamide esters 4, 39–43, 90

General procedure (via Reformatsky reaction)

A dry apparatus under an inert atmosphere was charged with activated zinc powder (1.38 g, 21.1 mmol) and CuCl (598 mg, 6.04 mmol), dry THF (12 ml) was added to produce a dark slurry which was heated to reflux and stirred vigorously for 30 min. The heating bath was removed and a solution of ethyl bromoacetate (15.1 mmol) in dry THF (6 ml) was added at such rate that reflux was re-initiated and a controllable reflux was maintained. Once addition was complete, the mixture was stirred at 50 °C for 30 min, then cooled to -20 °C. A solution of the sulfinyl imine (6.04 mmol) in THF (6 ml) was added dropwise, thereafter, the mixture left to warm up slowly to 0 °C. For the workup, the reaction mixture was quenched with a saturated solution of NH$_4$Cl, filtered through Dicalite® and which was washed with EtOAc. The filtrate was washed with a saturated solution of NaHCO$_3$ and brine, dried over Na$_2$SO$_4$ and evaporated. The crude material was purified by flash chromatography on silica gel using mixtures of heptane and EtOAc as the eluent to give the sulfinamide ester.

(S)-Ethyl 3-((R)-1,1-Dimethylethylsulfinamido)-3-(2-fluoro-5-nitrophenyl)butanoate (4)
Sulfinamide ester 4 was obtained from 3 and ethyl 2-bromoacetate as a yellow oil (96% yield) after chromatography on silica gel (eluent: heptane–EtOAc; gradient: 30–70% EtOAc). $^1$H NMR (600 MHz, CDCl$_3$) δ ppm 8.54 (dd, $J=7.0, 2.9$ Hz, 1 H), 8.18 (ddd, $J=9.0, 4.0, 2.9$ Hz, 1 H), 7.18 (dd, $J=11.2, 9.0$ Hz, 1 H), 5.59 (s, 1 H), 4.04 (qd, $J=7.1, 1.5$ Hz, 2 H), 3.37 (dd, $J=16.9, 1.6$ Hz, 1 H), 3.21 (dd, $J=16.9, 1.7$ Hz, 1 H), 1.86 (s, 3 H), 1.35 (s, 9 H), 1.16 (t, $J=7.2$ Hz, 3 H). LC-HRMS m/z 375.1392 [(M+H)$^+$ calcd for C$_{16}$H$_{24}$FN$_2$O$_5$S$^+$, 375.1384].

(2R,3R)-Ethyl 3-((R)-1,1-Dimethylethylsulfinamido)-2-fluoro-3-(2-fluorophenyl) butanoate (39)$^5$

Sulfinamide ester 39 was obtained from 36 (D. Banner et al. WO2011138293, 2011) and ethyl 2-bromo-2-fluoroacetate as the slower eluting major isomer (brown oil, 51% yield) after chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–66% EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.47 (td, $J=8.0, 1.7$ Hz, 1 H), 7.32–7.41 (m, 1 H), 7.17 (td, $J=7.7, 1.4$ Hz, 1 H), 7.06 (ddd, $J=12.9, 8.1, 1.2$ Hz, 1 H), 5.44 (dd, $J=46.2, 1.6$ Hz, 1 H), 4.81 (s, 1 H), 4.27 (qd, $J=7.1, 1.6$ Hz, 2 H), 1.91 (s, 3 H), 1.28 (t, $J=7.2$ Hz, 3 H), 1.22 (s, 9 H). MS (ESI, positive ion): m/z = 348.2 [M+H]$^+$. 

(2S,3R)-Ethyl 3-((R)-1,1-Dimethylethylsulfinamido)-2-fluoro-3-(2-fluorophenyl)-butanoate (40)$^5$

Sulfinamide ester 40 was obtained from 36 and ethyl 2-bromo-2-fluoroacetate as the faster eluting minor isomer (brown oil, 13% yield) after chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–66% EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.43 (td, $J=7.9, 1.4$ Hz, 1 H), 7.32–7.40 (m, 1 H), 7.15 (td, $J=7.9, 1.0$ Hz, 1 H), 7.06 (ddd, $J=12.5, 8.1, 1.0$ Hz, 1 H), 5.56 (d, $J=48.6$ Hz, 1 H), 4.29 (s, 1 H), 4.01 (dtt, $J=10.6, 7.1, 7.1, 3.5, 3.5$ Hz, 2 H), 1.93 (d, $J=1.8$ Hz, 3 H), 1.22 (s, 9 H), 0.96 (t, $J=7.1$ Hz, 3 H). MS (ESI, positive ion): m/z = 348.2 [M+H]$^+$. 

(2R,3S)-Ethyl 3-((R)-1,1-Dimethylethylsulfinamido)-2,4-difluoro-3-(2-fluorophenyl)-butanoate (41)$^5$
Sulfinamide ester 41 was obtained from 37 and ethyl 2-bromo-2-fluoroacetate as the faster eluting isomer (yellow oil, 32% yield) after chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–20% EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 7.42 (dddd, $J$=8.1, 7.4, 5.0, 1.8 Hz, 1 H), 7.34 (td, $J$=7.8, 1.7 Hz, 1 H), 7.21 (ddd, $J$=8.2, 7.2, 1.2 Hz, 1 H), 7.10 (ddd, $J$=12.6, 8.2, 1.2 Hz, 1 H), 5.34–5.41 (m, 1 H), 5.05–5.27 (m, 3 H), 4.31 (qd, $J$=7.2, 0.7 Hz, 2 H), 1.32 (t, $J$=7.1 Hz, 3 H), 1.27 (s, 9 H). MS (ESI, positive ion): $m/z = 366.2$ [M+H]$^+$.  

The isomer (2S,3S)-ethyl 3-((R)-1,1-dimethylethylsulfinamido)-2,4-difluoro-3-(2-fluorophenyl)-butanoate, isolated as a mixture together with 41 after chromatography as described above, was obtained as the second eluting minor isomer (yellow oil, 4% yield) after chromatography on preparative chiral HPLC (Chiralpak AD; eluent: 40% isopropanol/heptane). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 7.55 (tt, $J$=7.8, 1.8 Hz, 1 H), 7.43 (m, $J$=8.1, 7.4, 5.0, 1.6 Hz, 1 H), 7.21 (td, $J$=7.7, 1.2 Hz, 1 H), 7.09 (ddd, $J$=12.6, 8.2, 1.2 Hz, 1 H), 5.65 (dd, $J$=47.0, 2.0 Hz, 1 H), 5.30 (ddd, $J$=46.4, 10.1, 2.4 Hz, 1 H), 4.97 (ddd, $J$=46.2, 10.3, 1.4 Hz, 1 H), 4.20 (s, 1 H), 3.95–4.10 (m, 2 H), 1.21 (s, 9 H), 0.97 (t, $J$=7.2 Hz, 3 H). MS (ESI, positive ion): $m/z = 366.2$ [M+H]$^+$.  

(S)-Ethyl 3-((R)-1,1-dimethylethylsulfinamido)-3-(5-Bromo-2-fluorophenyl)-4,4-difluorobutanoate (42)$^{12}$

Sulfinamide ester 42 was obtained from 38 as a yellow oil (86% yield) after chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–50% EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 7.66 (ddd, $J$=6.9, 2.2, 1.2 Hz, 1 H), 7.47 (ddd, $J$=8.7, 4.2, 2.4 Hz, 1 H), 6.96 (dd, $J$=12.0, 8.8 Hz, 1 H), 6.43 (t, $J$=54.7 Hz, 1 H), 5.25 (s, 1 H), 4.13 (q, $J$=7.1 Hz, 2 H), 3.39 (d, $J$=16.6 Hz, 1 H), 3.26 (dd, $J$=16.6, 1.8 Hz, 1 H), 1.29 (s, 9 H), 1.23 (t, $J$=7.2 Hz, 3 H). LC-HRMS $m/z$ 444.0454 [(M+H)$^+$ calcd for C$_{16}$H$_{22}$BrF$_3$NO$_3$S$, 444.0450].  

(S)-Ethyl 3-((R)-1,1-Dimethylethylsulfinamido)-2,2,4-trifluoro-3-(2-fluorophenyl) butanoate (43)$^6$

Sulfinamide ester 43 was obtained from 37 and ethyl 2-bromo-2,2-difluoroacetate as a colorless oil (62% yield) after chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–33% EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 7.58 (t, $J$=7.6 Hz, 1 H), 7.43 (m, $J$=8.1, 7.4, 5.0, 1.8 Hz, 1 H), 7.20 (td,
$J$=7.7, 1.2 Hz, 1 H), 7.10 (ddd, $J$=12.9, 8.2, 1.3 Hz, 1 H), 5.45 (ddd, $J$=48.4, 10.3, 5.2 Hz, 1 H), 5.18 (s, 1 H), 5.16 (ddquin, $J$=44.9, 10.1, 1.8, 1.8, 1.8 Hz, 1 H), 4.34 (q, $J$=7.1 Hz, 2 H), 1.34 (t, $J$=7.1 Hz, 3 H), 1.34 (s, 9 H). MS (ESI, positive ion): $m/z$ = 384.3 $[\text{M+H}]^+$. 

(S)-Ethyl 3-((R)-1,1-Dimethylethylsulfinamido)-3-(2-fluorophenyl)butanoate (90)

Sulfinamide ester 90 was obtained from 36 and ethyl 2-bromo-acetate as a brown oil (84% yield) after chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–50% EtOAc). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ ppm 7.50 (td, $J$=8.1, 1.8 Hz, 1 H), 7.24–7.28 (m, 1 H), 7.12 (td, $J$=7.6, 1.3 Hz, 1 H), 7.01 (ddd, $J$=12.8, 8.1, 1.2 Hz, 1 H), 5.50 (s, 1 H), 4.02 (q, $J$=7.2 Hz, 2 H), 3.37 (d, $J$=16.4 Hz, 1 H), 3.10 (dd, $J$=16.3, 1.3 Hz, 1 H), 1.85 (s, 3 H), 1.30 (s, 9 H), 1.12 (t, $J$=7.1 Hz, 3 H). LC-MS (ESI, positive ion): $m/z$ = 330.5 $[\text{M+H}]^+$. 

6. Preparation of the intermediate amino alcohols 8, 44–48

General procedure

A solution of the sulfinamide ester (12.7 mmol) in dry THF (50 ml) was treated at 0 °C with lithium borohydride (25.3 mmol) and stirring was continued at 0 °C for 4 h. The reaction mixture was quenched by addition of acetic acid (2 ml) and water (50 ml), extracted with EtOAc, and the organic layer was dried and evaporated. The crude product was purified by chromatography on silica gel using mixtures of heptane and EtOAc as the eluent or was directly used in the next step without further purification.

A solution of the sulfinamide alcohol (3.4 mmol) in methanol (12 ml) was treated at 0 °C with a solution of HCl in dioxane (4M; 17.1 mmol). The reaction mixture was left to warm and kept at room temperature for 16 h. For the workup, the reaction mixture was evaporated at reduced pressure. The solid residue was partitioned between water (10 ml) and EtOAc (25 ml). The aqueous layer was separated, again extracted with EtOAc (25 ml). The combined organic layers were washed with water (5 ml), the aqueous layers combined and treated with an aqueous solution of Na$_2$CO$_3$ to adjust the pH to 9–10. Thereafter, the aqueous layer was extracted with ethyl ester (3 x 35 ml). The combined organic layers were dried over Na$_2$SO$_4$ and evaporated at reduced pressure. The crude product was purified by chromatography on silica gel using mixtures of heptane and EtOAc as the eluent or was directly used in the next step without further purification.

(S)-3-Amino-3-(2-fluoro-5-nitrophenyl)butan-1-ol (8)

(S)-3-Amino-3-(2-fluoro-5-nitrophenyl)butan-1-ol (8)
Reduction of sulfinamide ester 4 yielded the intermediate alcohol 6 (yellow solid, 76% yield) after chromatography on silica gel (eluent: heptane–EtOAc; gradient: 20–100% EtOAc). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 8.57 (dd, $J$=7.0, 3.0 Hz, 1 H), 8.17–8.22 (m, 1 H), 7.20 (dd, $J$=11.1, 9.0 Hz, 1 H), 5.26 (s, 1 H), 3.99 (dt, $J$=12.1, 4.3 Hz, 1 H), 3.53 (ddd, $J$=12.0, 7.4, 4.6 Hz, 1 H), 2.55–2.88 (br s, 1 H approx.), 2.39–2.43 (m, 2 H), 1.87 (s, 3 H), 1.34 (s, 9 H). MS (ESI, positive ion): $m/z$ = 333.2 [M+H]$^+$. 

Cleavage of the chiral auxiliary yielded the amino alcohol 8 (yellow oil, quant. yield) which was used without further purification. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 8.46 (dd, $J$=7.1, 2.8 Hz, 1 H), 8.18 (ddd, $J$=8.9, 4.0, 2.7 Hz, 1 H), 7.20 (dd, $J$=11.1, 9.0 Hz, 1 H), 3.84 (ddd, $J$=11.4, 7.4, 3.8 Hz, 1 H), 3.54 (ddd, $J$=11.4, 7.5, 3.8 Hz, 1 H), 2.54 (br s., 2 H), 2.24 (dddt, $J$=14.5, 7.2, 3.8, 1.6 Hz, 1 H), 1.97 (dddt, $J$=14.6, 7.3, 3.6 Hz, 1 H), 1.65 (d, $J$=1.1 Hz, 3 H). LC-MS (ESI, positive ion): $m/z$ = 229.5 [M+H]$^+$. 

(2R,3R)-3-Amino-2-fluoro-3-(2-fluorophenyl)butan-1-ol (44)

Reduction of sulfinamide ester 39 yielded the intermediate (R)-N-((2R,3R)-3-fluoro-2-(2-fluorophenyl)-4-hydroxybutan-2-yl)-2-methylpropane-2-sulfinamide (white foam, 95% yield) which was engaged in the next step without further purification. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 7.50 (td, $J$=8.1, 1.6 Hz, 1 H), 7.33 (dddd, $J$=8.1, 7.4, 5.0, 1.8 Hz, 1 H), 7.18 (td, $J$=7.9, 1.4 Hz, 1 H), 7.08 (dd, $J$=13.1, 8.1, 1.4 Hz, 1 H), 5.03 (dd, $J$=44.2, 4.6, 3.2 Hz, 1 H), 4.81 (br s, 1 H), 4.04 (tt, $J$=12.8, 4.4 Hz, 1 H), 3.56–3.75 (m, 1 H), 3.50 (dd, $J$=8.7, 4.4 Hz, 1 H), 1.87 (d, $J$=1.0 Hz, 3 H), 1.63 (s, 1 H), 1.26 (s, 9 H). MS (ESI, positive ion): $m/z$ = 306.5 [M+H]$^+$. 

Cleavage of the chiral auxiliary yielded the amino alcohol 44 (yellow oil, quant. yield) which was used without further purification. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 7.65 (td, $J$=8.2, 1.8 Hz, 1 H), 7.32 (dddd, $J$=8.1, 7.4, 5.0, 1.8 Hz, 1 H), 7.09–7.22 (m, 2 H), 4.76 (ddt, $J$=49.2, 7.5, 1.8, 1.8 Hz, 1 H), 4.75–4.85 (br s, 1 H), 3.40–3.56 (m, 1 H), 3.29 (dd, $J$=35.5, 13.1, 1.2 Hz, 1 H), 2.08 (br s, 2 H), 1.45 (t, $J$=1.3 Hz, 3 H). MS (ESI, positive ion): $m/z$ = 202.6 [M+H]$^+$. 

(2R,3S)-3-Amino-2-fluoro-3-(2-fluorophenyl)butan-1-ol (45)

Reduction of combined fractions of sulfinamide esters 39 and 40 yielded a 2.6:1-mixture of (R)-N-((2R,3R)-3-fluoro-2-(2-fluorophenyl)-4-hydroxybutan-2-yl)-2-methylpropane-2-sulfinamide which was separated by HPLC on Chiralpak AD (eluent: heptane:isopropanol = 90:10). The (R)-N-((2R,3R)-3-fluoro-2-(2-fluorophenyl)-4-hydroxybutan-2-yl)-2-methylpropane-2-sulfinamide (white solid) was obtained as the first eluting isomer, the (R)-N-((2R,3S)-3-fluoro-2-(2-fluorophenyl)-4-hydroxybutan-2-yl)-2-methylpropane-2-sulfinamide (colorless viscous oil) as the second eluting
isomer. $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.49 (td, J=8.0, 1.6 Hz, 1 H), 7.30–7.38 (m, 1 H), 7.17 (td, J=7.7, 1.0 Hz, 1 H), 7.06 (ddd, J=12.9, 8.2, 0.9 Hz, 1 H), 5.15 (ddd, J=47.0, 5.4, 3.4 Hz, 1 H), 4.46 (s, 1 H), 3.81–3.99 (m, 1 H), 3.52–3.70 (m, 1 H), 2.88 (dd, J=8.9, 4.8 Hz, 1 H), 1.91 (s, 3 H), 1.26 (s, 9 H). MS (ESI, positive ion): $m/z = 306.1$ [M+H]$^+$. 

Cleavage of the chiral auxiliary yielded the amino alcohol 45 (colorless oil, 98% yield) which was used without further purification. $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.39 (td, J=8.1, 1.7 Hz, 1 H), 7.25–7.34 (m, 1 H), 7.17 (td, J=7.7, 1.2 Hz, 1 H), 7.07 (ddd, J=12.8, 8.0, 1.2 Hz, 1 H), 4.95 (dt, J=45.2, 3.0 Hz, 1 H), 3.91–4.25 (m, 2 H), 2.30–3.57 (br s, 2 H), 1.61 (t, J=1.3 Hz, 3 H). MS (ESI, positive ion): $m/z = 202.3$ [M+H]$^+$. 

(2R,3S)-3-Amino-2,4-difluoro-3-(2-fluorophenyl)butan-1-ol (46)$^5$

Reduction of sulfinamide ester 41 yielded the intermediate (R)-N-((2S)-1,3-difluoro-2-(2-fluorophenyl)-4-hydroxybutan-2-yl)-2-methylpropane-2-sulfinamide (viscous colorless oil, quant. yield) which was engaged in the next step without further purification. $^1$H NMR (300 MHz, DMSO-d$_6$) δ ppm 7.61 (td, J=8.0, 1.4 Hz, 1 H), 7.44 (dddd, J=8.1, 7.4, 5.0, 1.8 Hz, 1 H), 7.27 (td, J=7.7, 1.2 Hz, 1 H), 7.24–7.31 (m, 1 H), 7.22 (ddd, J=13.1, 8.3, 1.2 Hz, 1 H), 5.52 (s, 1 H), 5.33 (t, J=5.4 Hz, 1 H), 5.05 (ddd, J=47.2, 30.1, 10.3 Hz, 3 H), 3.58–3.84 (m, 2 H), 1.16 (s, 9 H). MS (ESI, positive ion): $m/z = 324.3$ [M+H]$^+$. 

Cleavage of the chiral auxiliary yielded the amino alcohol 46 (viscous yellowish oil, 95% yield) which was used without further purification. $^1$H NMR (300 MHz, DMSO-d$_6$) δ ppm 7.71 (td, J=8.1, 1.8 Hz, 1 H), 7.38 (dd, J=8.1, 4.8, 1.8 Hz, 1 H), 7.24 (td, J=7.6, 1.2 Hz, 1 H), 7.17 (ddd, J=12.8, 8.2, 1.4 Hz, 1 H), 4.67–5.07 (m, 3 H), 4.52 (ddt, J=47.6, 8.9, 1.6, 1.6 Hz, 1 H), 3.50–3.70 (m, 1 H), 3.16–3.37 (m, 1 H), exchangeable H not fully assignable. MS (ESI, positive ion): $m/z = 220.2$ [M+H]$^+$. 

(S)-3-Amino-3-(5-bromo-2-fluorophenyl)-4,4-difluorobutan-1-ol (47)$^6$

Reduction of sulfonamide ester (42) yielded the intermediate (R)-N-((S)-2-(5-bromo-2-fluorophenyl)-1,1-difluoro-4-hydroxybutan-2-yl)-2-methylpropane-2-sulfonamide (colorless oil, 82% yield) after chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–50% EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.74 (dd, J=6.9, 2.4 Hz, 1 H), 7.48 (dd, J=8.7, 4.2, 2.4 Hz, 1 H), 6.98 (dd, J=11.9, 8.7 Hz, 1 H), 6.31 (t, J=55.3 Hz, 1 H), 4.70 (s, 1 H), 3.84–3.95 (m, 1 H), 3.65–3.78 (m, 1 H), 2.48–2.67 (m, 3 H), 1.31 (s, 9 H). LC-HRMS $m/z$ 402.0355 [(M+H)$^+$] calcd for C$_{14}$H$_{20}$BrF$_3$NO$_2$S$^+$, 402.0345. 

Cleavage of the chiral auxiliary yielded the amino alcohol 47 (white solid, 90% yield) which was used without further purification. $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.78 (dd, J=7.0, 2.5 Hz, 1 H), 7.48
(S)-3-Amino-2,2,4-trifluoro-3-(2-fluorophenyl)butan-1-ol (48)

Reduction of sulfonamide ester (43) yielded the intermediate (R)-2-methyl-N-((S)-1,3,3-trifluoro-2-(2-fluorophenyl)-4-hydroxybutan-2-yl)propane-2-sulfinamide (white foam, 97% yield) which was used without further purification. $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.53 (td, $J$ = 7.8, 0.7 Hz, 1 H), 7.40 (ddd, $J$ = 8.1, 7.4, 1.8 Hz, 1 H), 7.23 (ddd, $J$ = 8.1, 7.4, 1.4 Hz, 1 H), 7.11 (ddd, $J$ = 12.8, 8.2, 1.2 Hz, 1 H), 5.14 (ddd, $J$ = 47.8, 9.7, 3.8, 0.6 Hz, 1 H), 4.96 (ddd, $J$ = 47.0, 9.9, 1.2 Hz, 1 H), 3.67–3.87 (m, 2 H), 1.50–3.00 (br s, 3 H approx.). MS (ESI, positive ion): m/z = 342.2 [M+H]$^+$.

Cleavage of the chiral auxiliary yielded the amino alcohol 48 (colorless oil, 99% yield) which was used without further purification. $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.72 (td, $J$ = 8.0, 1.8 Hz, 1 H), 7.39 (ddd, $J$ = 8.1, 7.4, 1.8 Hz, 1 H), 7.23 (ddd, $J$ = 8.1, 7.4, 1.4 Hz, 1 H), 7.11 (ddd, $J$ = 12.8, 8.2, 1.2 Hz, 1 H), 5.14 (ddd, $J$ = 47.8, 9.7, 3.8, 0.6 Hz, 1 H), 4.96 (ddd, $J$ = 47.0, 9.9, 1.2 Hz, 1 H), 3.67–3.87 (m, 2 H), 1.50–3.00 (br s, 3 H approx.). MS (ESI, positive ion): m/z = 238.1 [M+H]$^+$.

7. Preparation of the intermediate amino oxazines 10, 49-54, 100-102

General procedure

A dried tube was charged with a mixture of the amino alcohol (18.8 mmol), cyanogen bromide (33.9 mmol) and ethanol (61 ml). The tube was sealed and heated at 80–95 °C for 15–20 h. For the workup, the reaction mixture was cooled and evaporated at reduced pressure. The residue was partitioned between EtOAc (150 ml) and a saturated aqueous solution of Na$_2$CO$_3$ (50 ml). The aqueous layer was separated and re-extracted with EtOAc (2 x 50 ml). The organic layers were washed with brine (50 ml), then combined, dried over Na$_2$SO$_4$ and evaporated at reduced pressure. The crude product was purified by chromatography on silica gel using mixtures of heptane and EtOAc as the eluent or was directly used in the next step without further purification.

(S)-4-(2-Fluoro-5-nitrophenyl)-4-methyl-5,6-dihydro-4H-1,3-oxazin-2-amine (10)

Amino oxazine 10 was obtained from 8 and cyanogen bromide as a colorless solid (21% yield) after chromatography on silica gel (eluent: heptane–EtOAc; gradient: 40–100% EtOAc). $^1$H NMR (400 MHz,
CDCl$_3$ δ ppm 8.56 (dd, $J$=7.0, 3.0 Hz, 1 H), 8.15 (ddd, $J$=8.9, 4.0, 3.0 Hz, 1 H), 7.16 (dd, $J$=10.7, 8.9 Hz, 1 H), 4.24 (ddd, $J$=10.9, 6.6, 4.0 Hz, 1 H), 3.91 (ddd, $J$=11.1, 8.2, 4.0 Hz, 1 H), 2.18–2.32 (m, 2 H), 1.63 (d, $J$=1.3 Hz, 3 H); NH$_2$-signal not detectable. MS (ESI, positive ion): $m/z$ = 254.2 [M+H]$^+$. (4R,5R)-5-Fluoro-4-(2-fluorophenyl)-4-methyl-5,6-dihydro-4H-1,3-oxazin-2-amine (49)$^5$

Amino oxazine 49 was obtained from 44 and cyanogen bromide as a light yellow liquid (63% yield) after chromatography on silica-NH$_2$ gel (eluent: heptane–EtOAc; gradient: 0–50% EtOAc). $^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 7.43 (td, $J$=8.0, 1.8 Hz, 1 H), 7.28–7.38 (m, 1 H), 7.13–7.25 (m, 2 H), 5.65 (s, 2 H), 5.11 (d, $J$=47.2 Hz, 1 H), 4.12 (td, $J$=12.7, 2.3 Hz, 1 H), 3.59 (ddd, $J$=11.1, 8.2, 4.0 Hz, 1 H), 1.46 (t, $J$=2.2 Hz, 3 H). MS (ESI, positive ion): $m/z$ = 227.5 [M+H]$^+$. (4R,5S)-5-Fluoro-4-(2-fluorophenyl)-4-methyl-5,6-dihydro-4H-1,3-oxazin-2-amine (50)$^5$

Amino oxazine 50 was obtained from 45 and cyanogen bromide as a colorless viscous oil (85% yield) after chromatography on silica-NH$_2$ gel (eluent: heptane–EtOAc; gradient: 0–34% EtOAc). $^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 7.90 (td, $J$=8.1, 1.6 Hz, 1 H), 7.27 (ddd, $J$=8.1, 7.4, 4.8, 2.0 Hz, 1 H), 7.06–7.18 (m, 2 H), 5.51 (br s, 2 H approx.), 5.23 (d, $J$=48.0 Hz, 1 H), 4.20–4.58 (m, 2 H), 1.40 (s, 3 H). MS (ESI, positive ion): $m/z$ = 227.2 [M+H]$^+$. (4S,5R)-5-Fluoro-4-(fluoromethyl)-4-(2-fluorophenyl)-5,6-dihydro-4H-1,3-oxazin-2-amine (51)$^5$

Amino oxazine 51 was obtained from 46 and cyanogen bromide as a white solid (72% yield) after chromatography on silica-NH$_2$ gel (eluent: heptane–EtOAc; gradient: 0–50% EtOAc). $^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 7.50 (td, $J$=8.0, 1.6 Hz, 1 H), 7.34–7.44 (m, 1 H), 7.13–7.30 (m, 2 H), 5.90 (s, 2 H), 5.40 (dd, $J$=47.4, 0.8 Hz, 1 H), 4.86 (ddd, $J$=47.2, 9.1, 1.6 Hz, 1 H), 4.38 (ddt, $J$=47.6, 8.7, 1.8, 1.8 Hz, 1 H), 4.20 (tt, $J$=13.4, 1.4 Hz, 1 H), 3.70 (ddd, $J$=41.8, 12.9, 0.6 Hz, 1 H). MS (ESI, positive ion): $m/z$ = 245.2 [M+H]$^+$. (S)-4-(5-Bromo-2-fluorophenyl)-4-(difluoromethyl)-5,6-dihydro-4H-1,3-oxazin-2-amine Hydrobromide (52)$^5$
The cyclization of the amino alcohol 47 with cyanogen bromide in 2-propanol during 20 h yielded intermediate 52 (white solid, 70% yield) which already started to precipitate during the reaction and which after filtration was used without further purification. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) ppm 10.26 (s, 1 H), 9.30 (br s, 1 H), 8.02 (br s, 1 H), 7.70–7.81 (m, 2 H), 7.38 (dd, \(J=12.1, 9.1\) Hz, 1 H), 6.70 (t, \(J=54.3\) Hz, 1 H), 4.50–4.60 (m, 1 H), 4.26 (ddd, \(J=11.9, 8.9, 3.4\) Hz, 1 H), 2.41–2.70 (m, 2 H approx.). LC-HRMS \(m/z\) 323.0009 \([\text{M+H}]^+\) calcd for C\(_{11}\)H\(_{11}\)BrF\(_3\)N\(_2\)O\(_2\), 323.0001.

The (S)-4-(Difluoromethyl)-4-(2-fluorophenyl)-5,6-dihydro-4H-1,3-oxazin-2-amine (53) was obtained as follows:

A solution of (S)d\(_4\)d(5dbromod2dfluorophenyl)d\(_4\)d(difluoromethyl)d5,6ddihydrod4Hd1,3doxazind2d amine hydrobromide (52) (4.49 g, 11.1 mmol) and sodium acetate (2.05 g, 25.0 mmol) in methanol (50 ml) was hydrogenated at room temperature under atmospheric pressure during 90 min using palladium (10% on carbon; 449 mg, 0.422 mmol) as the catalyst. The reaction mixture was filtered, the residue washed with EtOH (10 ml) and the combined solutions were evaporated at reduced pressure. The residue was partitioned between H\(_2\)O (100 ml) and TBME (100 ml), the organic layer was dried over Na\(_2\)SO\(_4\) and evaporated. The (S)-4-(difluoromethyl)-4-(2-fluorophenyl)-5,6-dihydro-4H-1,3-oxazin-2-amine (53) (white solid, 2.47 g, 91% yield) was engaged in the next step without further purification. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) ppm 7.67 (td, \(J=8.0, 1.8\) Hz, 1 H), 7.31 (m, \(J=8.1, 7.4, 4.8, 1.9\) Hz, 1 H), 7.20 (td, \(J=7.5, 1.2\) Hz, 1 H), 7.05 (dd, \(J=12.4, 8.2, 1.4\) Hz, 1 H), 6.09 (td, \(J=56.5, 1.0\) Hz, 1 H), 4.34 (br s, 2 H), 4.20 (dt, \(J=10.8, 4.4\) Hz, 1 H), 3.84 (td, \(J=10.5, 3.8\) Hz, 1 H), 2.26–2.46 (m, 2 H). LC-HRMS \(m/z\) 245.0903 \([\text{M+H}]^+\) calcd for C\(_{11}\)H\(_{12}\)F\(_3\)N\(_2\)O, 245.0896.

(S)-5,5-Difluoro-4-(fluoromethyl)-4-(2-fluorophenyl)-5,6-dihydro-4H-1,3-oxazin-2-amine (54) was obtained from 48 and cyanogen bromide as a white solid (41% yield) after purification on preparative HPLC [column: Gemini-NX, 100x30.00mm, 5µ, C18, 110A; eluent: H\(_2\)O (+0.05% TEA)–MeOH; gradient: 20–80% MeOH); flow rate: 40 ml/min]. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) ppm 7.69 (td, \(J=7.9, 1.8\) Hz, 1 H), 7.34 (m, \(J=8.1, 7.4, 4.8, 1.9\) Hz, 1 H), 7.20 (td, \(J=7.5, 1.2\) Hz, 1 H), 7.06 (dd, \(J=12.1, 8.1, 1.2\) Hz, 1 H), 5.29 (ddsxt, \(J=48.8, 9.3, 0.9, 0.9, 0.9, 0.9, 0.9\) Hz, 1 H), 4.55 (dddd, \(J=46.0, 9.3, 3.8, 1.2\) Hz, 1 H), 4.30–4.40 (br s, 2 H), 4.31 (dddd, \(J=26.2, 11.5, 3.2, 1.2\) Hz, 1 H), 4.13 (dddd, \(J=11.3, 10.5, 8.1, 2.4\) Hz, 1 H). MS (ESI, positive ion): \(m/z\) = 263.1 \([\text{M+H}]^+\).
(4S,6R)-4-(2-Fluorophenyl)-4-methyl-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-2-amine (100)

Amino oxazine 100 was obtained from 97 and cyanogen bromide as a light brown oil (61% yield) after chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–50% EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.78 (td, $J$=8.1, 1.9 Hz, 1 H), 7.19–7.33 (m, 1 H), 7.14 (dd, $J$=15.1, 7.5, 1.4 Hz, 1 H), 7.01 (dd, $J$=12.3, 8.1, 1.2 Hz, 1 H), 4.64 (dqd, $J$=12.6, 5.8, 5.8, 5.8, 3.0 Hz, 1 H), 3.86–4.33 (2 H), 2.68 (dt, $J$=13.7, 2.6 Hz, 1 H), 1.98–2.16 (m, 1 H), 1.59 (s, 3 H). LC-MS (ESI, positive ion): $m/z$ = 277.5 [M+H$^+$].

(4R,5R,6R)-5-Fluoro-4-(2-fluorophenyl)-4-methyl-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-2-amine (101)

Amino oxazine 101 was obtained from 98 and cyanogen bromide as a yellow oil (56% yield) after chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–100% EtOAc). $^1$H NMR (600 MHz, CDCl$_3$) δ ppm 7.50 (td, $J$=8.1, 1.8 Hz, 1 H), 7.29 (dd, $J$=8.1, 7.4, 4.9, 1.8 Hz, 1 H), 7.14 (td, $J$=7.6, 1.3 Hz, 1 H), 7.05 (dd, $J$=12.5, 8.2, 1.3 Hz, 1 H), 5.05 (dd, $J$=49.5, 7.5 Hz, 1 H), 4.63 (dd, $J$=13.5, 7.1, 6.2, 6.2 Hz, 1 H), 1.69 (dd, $J$=3.0, 1.5 Hz, 3 H), NH$_2$-signal not detectable. LC-HRMS (m/z): calcd for C$_{12}$H$_{11}$F$_5$N$_2$O, 294.0792; found, 294.0795.

(4R,5R,6S)-5-Fluoro-4-(2-fluorophenyl)-4-methyl-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-2-amine (102)

Amino oxazine 102 was obtained from 99 and cyanogen bromide as a light yellow oil (76% yield) after chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–50% EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.43 (td, $J$=8.0, 1.9 Hz, 1 H), 7.28–7.36 (m, 1 H), 7.18 (td, $J$=7.7, 1.4 Hz, 1 H), 7.07 (dd, $J$=12.3, 8.1, 1.2 Hz, 1 H), 5.41 (dd, $J$=48.4, 1.0 Hz, 1 H), 4.04 (dqd, $J$=28.1, 6.1, 6.1, 6.1, 0.8 Hz, 1 H), 1.68 (dd, $J$=2.6, 1.6 Hz, 3 H). NH$_2$-signal not detectable. LC-MS (ESI, positive ion): $m/z$ = 295.4 [M+H$^+$].

8. Preparation of the intermediate nitro oxazines 55–59, 103–105
General procedure

A dispersion of the amino oxazine (2.8 mmol) in sulfuric acid (22.1 g, 216 mmol) was cooled to 0 °C and stirring was continued until a complete solution was obtained. At 0 °C fuming nitric acid (300 mg, 214 µl, 4.29 mmol) was added dropwise in 4 portions. After complete addition, the ice bath was removed and stirring continued for 30 min at room temperature. For the workup, the solution was added dropwise to a mixture of crushed ice (50 g) and water (50 g). With an aqueous solution of NaOH the pH was adjusted to 7–8. The aqueous layer was extracted twice with EtOAc, thereafter the combined organic layers were washed with brine, then dried over Na₂SO₄ and evaporated at reduced pressure. The crude product was purified by chromatography on silica gel using mixtures of heptane and EtOAc as the eluent or was directly used in the next step without further purification.

\[
(4R,5R)-5\text{-Fluoro-4-(2-fluoro-5-nitrophenyl)-4-methyl-5,6-dihydro-4H-1,3-oxazin-2-amine (55)}
\]

\[
\text{Nitro-oxazine 55 was obtained from 49 as a white solid (76% yield) after chromatography on silica-NH₂ gel (eluent: heptane–EtOAc; gradient: 0–33% EtOAc).} \quad ^1\text{H NMR (300 MHz, DMSO-}d_6\text{)} \delta \text{ ppm 8.34 (dd,} J=6.8, 2.9 \text{ Hz, 1 H), 8.25 (ddd,} J=8.9, 4.0, 3.0 \text{ Hz, 1 H), 7.51 (dd,} J=11.0, 9.0 \text{ Hz, 1 H), 5.85 (s, 2 H), 5.15 (d,} J=46.8 \text{ Hz, 1 H), 4.14 (td,} J=12.7, 2.5 \text{ Hz, 1 H), 3.71 (ddd,} J=40.6, 13.1, 0.8 \text{ Hz, 1 H), 1.48 (t,} J=2.1 \text{ Hz, 3 H). MS (ESI, positive ion): m/z = 272.5 [M+H]^+.
\]

\[
(4R,5S)-5\text{-Fluoro-4-(2-fluoro-5-nitrophenyl)-4-methyl-5,6-dihydro-4H-1,3-oxazin-2-amine (56)}
\]

\[
\text{Nitro-oxazine 56 was obtained from 50 as a light yellow foam (86% yield) which was used without further purification.} \quad ^1\text{H NMR (300 MHz, DMSO-}d_6\text{)} \delta \text{ ppm 8.80 (dd,} J=6.8, 3.1 \text{ Hz, 1 H), 8.21 (dt,} J=8.9, 3.5 \text{ Hz, 1 H), 7.48 (dd,} J=11.2, 9.0 \text{ Hz, 1 H), 5.76 (br s, 2 H approx.), 5.32 (d,} J=47.4 \text{ Hz, 1 H), 4.24–4.63 (m, 2 H), 1.44 (s, 3 H). MS (ESI, positive ion): m/z = 272.1 [M+H]^+.
\]

\[
(4S,5R)-5\text{-Fluoro-4-(2-fluoro-5-nitrophenyl)-4-(fluoromethyl)-5,6-dihydro-4H-1,3-oxazin-2-amine (57)}
\]

\[
\text{Nitro-oxazine 57 was obtained from 51 as a light yellow solid (73% yield) after chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–50% EtOAc).} \quad ^1\text{H NMR (300 MHz, DMSO-}d_6\text{)} \delta \text{ ppm 8.41 (dd,} J=6.5, 3.0 \text{ Hz, 1 H), 8.26–8.33 (m, 1 H), 7.54 (dd,} J=11.1, 8.9 \text{ Hz, 1 H), 6.10 (s, 2 H), 5.46 (dd,}
\]

S25
\[ J = 47.2, 0.8 \text{ Hz, 1 H}, 4.88 (\text{ddd, } J = 47.4, 8.9, 1.6 \text{ Hz, 1 H}), 4.38 (\text{ddt, } J = 47.6, 8.9, 1.4, 1.4 \text{ Hz, 1 H}), 4.22 (\text{tt, } J = 13.0, 1.4 \text{ Hz, 1 H}), 3.83 (\text{ddd, } J = 41.2, 13.1, 0.6 \text{ Hz, 1 H}). \]  

MS (ESI, positive ion): \( m/z = 290.1 \) [M+H]+.

\( (S)-4-(\text{Difluoromethyl})-4-(2-\text{fluoro-5-nitrophenyl})-5,6\text{-dihydro-4H-1,3-oxazin-2-amine (58)} \)

![Chemical structure](attachment:image)

Nitro-oxazine 58 was obtained from 53 as a yellowish solid (86% yield) after chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–100% EtOAc). \( ^1 \text{H NMR (300 MHz, CDCl}_3) \delta \text{ ppm 8.77 (dd, } J = 6.7, 2.8 \text{ Hz, 1 H}), 8.21 (\text{ddd, } J = 8.9, 3.8, 2.8 \text{ Hz, 1 H}), 7.21 (\text{dd, } J = 10.8, 9.0 \text{ Hz, 1 H}), 5.96 (\text{td, } J = 56.3, 1.2 \text{ Hz, 1 H}), 4.57 (\text{br s, 2 H}), 4.28 (\text{dddt, } J = 11.0, 6.5, 4.3, 1.0, 1.0 \text{ Hz, 1 H}), 3.89–3.99 (\text{m, 1 H}), 2.33–2.55 (\text{m, 2 H}). \) LC-HRMS \( m/z = 290.0753 \) [(M+H)+] calcd for \( \text{C}_{11}\text{H}_{11}\text{F}_3\text{N}_3\text{O}_3^+ \), 290.0747.

\( (S)-5,5\text{-Difluoro-4-(2-\text{fluoro-5-nitrophenyl})-4-(fluoromethyl)-5,6\text{-dihydro-4H-1,3-oxazin-2-amine (59)}^6 \)

![Chemical structure](attachment:image)

Nitro-oxazine 59 was obtained from 54 as a light yellow solid (96% yield) which was used without further purification. \( ^1 \text{H NMR (300 MHz, DMSO-}d_6 \) \( \delta \text{ ppm 8.65 (dd, } J = 6.5, 3.0 \text{ Hz, 1 H}), 8.33 (\text{ddd, } J = 8.9, 3.5 \text{ Hz, 1 H}), 7.55 (\text{dd, } J = 10.9, 8.9 \text{ Hz, 1 H}), 6.41 (\text{s, 2 H}), 5.01 (\text{ddd, } J = 48.0, 9.3, 1.2 \text{ Hz, 1 H}), 4.62 (\text{ddd, } J = 45.8, 9.1, 1.0 \text{ Hz, 1 H}), 4.20–4.38 (\text{m, 2 H}). \) MS (ESI, positive ion): \( m/z = 308.3 \) [M+H]+.

\( (4S,6R)-4-(2-\text{Fluoro-5-nitrophenyl})-4\text{-methyl-6-(trifluoromethyl)-5,6\text{-dihydro-4H-1,3-oxazin-2-amine (103)} \)

![Chemical structure](attachment:image)

Nitro-oxazine 103 was obtained from 100 as a light yellow viscous oil (54% yield) after chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–50% EtOAc) and on silica-NH\(_2\) gel (eluent: heptane–EtOAc; gradient: 0–33% EtOAc). \( ^1 \text{H NMR (300 MHz, CDCl}_3) \delta \text{ ppm 8.80 (dd, } J = 6.9, 2.8 \text{ Hz, 1 H}), 8.15 (\text{ddd, } J = 8.9, 4.0, 3.0 \text{ Hz, 1 H}), 7.17 (\text{dd, } J = 10.8, 9.0 \text{ Hz, 1 H}), 4.66 (\text{ddq, } J = 12.6, 5.8, 5.8, 5.8, 3.2 \text{ Hz, 1 H}), 4.21 (\text{br s, 2 H}), 2.70 (\text{dt, } J = 13.5, 2.9 \text{ Hz, 1 H}), 1.77 (\text{t, } J = 13.0 \text{ Hz, 1 H}), 1.59 (\text{s, 3 H}). \) LC-MS (ESI, positive ion): \( m/z = 322.4 \) [M+H]+.

\( (4R,5R,6R)-5\text{-Fluoro-4-(2-\text{fluoro-5-nitrophenyl})-4\text{-methyl-6-(trifluoromethyl)-5,6\text{-dihydro-4H-1,3-oxazin-2-amine (104)} \)

![Chemical structure](attachment:image)

Nitro-oxazine 104 was obtained from 100 as a light yellow viscous oil (54% yield) after chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–50% EtOAc) and on silica-NH\(_2\) gel (eluent: heptane–EtOAc; gradient: 0–33% EtOAc). \( ^1 \text{H NMR (300 MHz, CDCl}_3) \delta \text{ ppm 8.80 (dd, } J = 6.9, 2.8 \text{ Hz, 1 H}), 8.15 (\text{ddd, } J = 8.9, 4.0, 3.0 \text{ Hz, 1 H}), 7.17 (\text{dd, } J = 10.8, 9.0 \text{ Hz, 1 H}), 4.66 (\text{ddq, } J = 12.6, 5.8, 5.8, 5.8, 3.2 \text{ Hz, 1 H}), 4.21 (\text{br s, 2 H}), 2.70 (\text{dt, } J = 13.5, 2.9 \text{ Hz, 1 H}), 1.77 (\text{t, } J = 13.0 \text{ Hz, 1 H}), 1.59 (\text{s, 3 H}). \) LC-MS (ESI, positive ion): \( m/z = 322.4 \) [M+H]+.
Nitro-oxazine 104 was obtained from 101 as a light yellow oil (68% yield) after chromatography on silica gel (elucent: heptane–EtOAc; gradient: 0–50% EtOAc). $^1$H NMR (600 MHz, CDCl$_3$) δ ppm 8.58 (dd, $J$=6.7, 2.8 Hz, 1 H), 8.21 (ddd, $J$=8.9, 3.9, 2.8 Hz, 1 H), 7.21 (dd, $J$=10.9, 8.9 Hz, 1 H), 4.83 (dd, $J$=49.9, 8.1 Hz, 1 H), 4.65 (ddq, $J$=12.4, 8.0, 6.0, 6.0 Hz, 1 H), 4.33 (br s, 2 H), 1.73 (t, $J$=2.2 Hz, 3 H). LC-MS (ESI, positive ion): $m/z$ = 340.4 [M+H]$^+$. 

(4R,5R,6S)-5-Fluoro-4-(2-fluoro-5-nitrophenyl)-4-methyl-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-2-amine (105)

Nitro-oxazine 105 was obtained from 102 as a white foam (53% yield) after chromatography on silica gel (elucent: heptane–EtOAc; gradient: 0–50% EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 8.43 (dd, $J$=6.8, 2.9 Hz, 1 H), 8.24 (ddd, $J$=8.9, 4.1, 2.9 Hz, 1 H), 7.22–7.30 (m, 1H), 5.40 (dd, $J$=47.8, 0.8 Hz, 1 H), 4.40 (br s, 2 H), 4.00 (ddq, $J$=27.7, 5.9, 5.9, 5.9, 0.8 Hz, 1 H), 1.68 (dd, $J$=2.9, 1.7 Hz, 3 H). LC-MS (ESI, positive ion): $m/z$ = 340.4 [M+H]$^+$. 

9. Preparation of the intermediate anilines 12, 60–64, 106–108

General procedure

A solution of the nitro oxazine (3 mmol) in ethanol (31 ml) was hydrogenated at atmospheric pressure using palladium (10% on carbon) (159 mg, 150 µmol) as the catalyst and, optionally, in presence of TEA (3 mmol). The progress of the reaction was followed by TLC. The reaction mixture was filtrated over a layer of Dicalite®, which was washed with ethanol (3 x 20 ml). The combined solutions of ethanol were evaporated at reduced pressure. The crude product was purified by chromatography on silica gel or silica-NH$_2$ phase using mixtures of heptane and EtOAc as the eluent or was directly used in the next step without further purification.

(S)-4-(5-Amino-2-fluorophenyl)-4-methyl-5,6-dihydro-4H-1,3-oxazin-2-amine (12)$^{13}$

Aniline 12 was obtained from 10 as a brown solid (94% yield) after trituration in hexane. $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 6.75–6.87 (m, 2 H), 6.50 (dt, $J$=8.4, 3.4 Hz, 1 H), 4.15 (dt, $J$=10.7, 4.2 Hz, 1 H), 3.86 (td, $J$=10.8, 2.8 Hz, 1 H), 3.04 (br s, 4 H approx.), 2.40 (dt, $J$=14.1, 3.7 Hz, 1 H), 2.04 (ddd,
$J=14.1, 10.4, 3.7 \text{ Hz, 1 H}, 1.58 \text{ (s, 3 H)}. \text{ LC-MS (ESI, positive ion): } m/z = 224.4 \text{ [M+H]}.\]

\[4R,5R\]-4-(5-Amino-2-fluorophenyl)-5-fluoro-4-methyl-5,6-dihydro-4H-1,3-oxazin-2-amine (60)$^5$

\[\begin{align*}
\text{Aniline 60 was obtained from 55 as a white solid (99\% yield) which was used without further purification.} \\
\text{\textsuperscript{1}H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 6.79 (dd, $J=12.1, 8.5$ Hz, 1 H), 6.60 (dd, $J=7.0, 2.9$ Hz, 1 H), 6.42 (ddd, $J=8.5, 4.1, 2.9$ Hz, 1 H), 5.56 (s, 2 H), 5.04 (approx.) (dd, $J= 44.0$ (approx.), 1.0 Hz, 1 H), 4.97 (s, 2 H), 4.11 (td, $J=12.5, 2.1$ Hz, 1 H), 3.64 (dd, $J=40.8, 12.7$ Hz, 1 H), 1.41 (t, $J=1.8$ Hz, 3 H). MS (ESI, positive ion): $m/z$ 242.5 (M+H)$^+$.}
\end{align*}\]

\[4R,5S\]-4-(5-Amino-2-fluorophenyl)-5-fluoro-4-methyl-5,6-dihydro-4H-1,3-oxazin-2-amine (61)$^5$

\[\begin{align*}
\text{Aniline 61 was obtained from 56 as a white foam (98\% yield) which was used without further purification.} \\
\text{\textsuperscript{1}H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 7.05 (dd, $J=7.1, 3.0$ Hz, 1 H), 6.74 (dd, $J=12.3, 8.5$ Hz, 1 H), 6.39 (dt, $J=8.3, 3.6$ Hz, 1 H), 5.37 (s, 2 H), 5.16 (dd, $J=46.8, 0.8$ Hz, 1 H), 4.75 (s, 2 H approx.), 4.43 (ddd, $J=42.0, 13.1, 1.2$ Hz, 1 H), 4.24 (ddd, $J=14.9, 13.1, 2.0$ Hz, 1 H), 1.35 (s, 3 H). MS (ESI, positive ion): $m/z$ 242.3 (M+H)$^+$.}
\end{align*}\]

\[4S,5R\]-4-(5-Amino-2-fluorophenyl)-5-fluoro-4-(fluoromethyl)-5,6-dihydro-4H-1,3-oxazin-2-amine (62)$^5$

\[\begin{align*}
\text{Aniline 62 was obtained from 57 as an off-white solid (89\% yield) which was used without further purification.} \\
\text{\textsuperscript{1}H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 6.82 (dd, $J=12.1, 8.7$ Hz, 1 H), 6.65 (dd, $J=6.7, 2.8$ Hz, 1 H), 6.45–6.51 (m, 1 H), 5.81 (br s, 2 H), 5.32 (dd, $J=48.6, 1.0$ Hz, 1 H), 5.03 (br s, 2 H), 4.78 (ddd, $J=47.2, 9.3, 1.0$ Hz, 1 H), 4.36 (dd, $J=48.0, 9.1$ Hz, 1 H), 4.19 (t, $J=13.4$ Hz, 1 H), 3.74 (dd, $J=41.6, 12.9$ Hz, 1 H). MS (ESI, positive ion): $m/z$ 260.2 (M+H)$^+$.}
\end{align*}\]

\[\text{(S)-4-(5-Amino-2-fluorophenyl)-4-(difluoromethyl)-5,6-dihydro-4H-1,3-oxazin-2-amine (63)}\]

$^5$ Aniline 60 was obtained from 55 as a white solid (99% yield) which was used without further purification. 

$^6$ Aniline 62 was obtained from 57 as an off-white solid (89% yield) which was used without further purification. 

$^7$ Aniline 63 was obtained from 58 as a white solid (89% yield) which was used without further purification.
Aniline 63 was obtained from 58 as a white solid (96% yield) which was used without further purification. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 6.96 (dd, $J$=6.7, 3.0 Hz, 1 H), 6.84 (dd, $J$=11.8, 8.6 Hz, 1 H), 6.57 (ddd, $J$=8.7, 3.8, 3.0 Hz, 1 H), 6.08 (td, $J$=56.3, 0.8 Hz, 1 H), 4.00–4.90 (br s, 2 H), 4.18 (dtt, $J$=10.7, 4.4, 4.4, 1.1, 1.1 Hz, 1 H), 3.88 (td, $J$=10.7, 3.4 Hz, 1 H), 2.90–3.70 (br s, 2 H), 2.38 (dt, $J$=13.9, 3.6 Hz, 1 H), 2.27 (ddd, $J$=14.5, 10.9, 4.4 Hz, 1 H). LC-MS m/z 260.1012 [(M+H)$^+$ calcd for C$_{11}$H$_{13}$F$_3$N$_3$O$^+$, 260.1012].

(S)-4-(5-Amino-2-fluorophenyl)-5,5-difluoro-4-(fluoromethyl)-5,6-dihydro-4H-1,3-oxazin-2-amine (64)

Aniline 64 was obtained from 59 as a light red solid (91% yield) which was used without further purification. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 6.76–6.86 (m, 2 H), 6.51 (ddd, $J$=8.7, 3.4 Hz, 1 H), 6.07 (br s, 2 H), 5.01 (m, $J$=49.5 (approx.), 8.9, 1.6 Hz, 2 H), 4.97 (br s, 2 H), 4.48 (ddd, $J$=45.4, 8.9, 1.6 Hz, 1 H), 4.10–4.22 (m, 2 H). MS (ESI, positive ion): m/z 278.2 (M+H)$^+$.

(4S,6R)-4-(5-Amino-2-fluorophenyl)-4-methyl-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-2-amine (106)

Aniline 106 was obtained from 103 in presence of TEA as a white solid (95% yield) which was used without further purification. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 7.12 (dd, $J$=6.8, 2.9 Hz, 1 H), 6.81 (dd, $J$=11.8, 8.6 Hz, 1 H), 6.50 (dt, $J$=8.5, 3.4 Hz, 1 H), 4.62 (ddq, $J$=12.6, 5.7, 5.7, 5.7, 3.0 Hz, 1 H), 3.80–4.43 (m, 2 H), 3.65 (br s, 2 H), 2.67 (dt, $J$=13.7, 2.5 Hz, 1 H), 1.77 (t, $J$=13.1 Hz, 1 H), 1.56 (s, 3 H). LC-MS (ESI, positive ion): m/z = 292.4 [M+H]$^+$. 

(4S,6R)-4-(5-Amino-2-fluorophenyl)-5-fluoro-4-methyl-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-2-amine (107)
Aniline 107 was obtained from 104 in presence of TEA as a light yellow oil (87% yield) which was used without further purification. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) ppm 6.84 (dd, \(J=12.0, 8.6\) Hz, 1 H), 6.81 (dd, \(J=6.6, 2.9\) Hz, 1 H), 6.56 (ddd, \(J=8.6, 3.7, 2.9\) Hz, 1 H), 5.01 (ddd, \(J=49.2, 7.3, 0.4\) Hz, 1 H), 4.61 (ddq, \(J=13.3, 7.1, 6.3, 6.3, 6.3\) Hz, 1 H), 1.65 (dd, \(J=3.0, 1.6\) Hz, 3 H); NH\(_2\)-signals not detectable. LC-MS (ESI, positive ion): \(m/z = 310.4\) [M+H].

\[(4R,5R,6S)-4-(5-Amino-2-fluorophenyl)-5-fluoro-4-methyl-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-2-amine (108)\]

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{O} \quad \text{CF}_3 \\
\text{H}_2\text{N} & \quad \text{N} \quad \text{F}
\end{align*}
\]

Aniline 108 was obtained from 105 in presence of TEA as a white solid (99% yield) which was used without further purification. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) ppm 6.84 (dd, \(J=12.1, 8.7\) Hz, 1 H), 6.57 (dd, \(J=7.0, 2.9\) Hz, 1 H), 6.47 (ddd, \(J=8.7, 4.0, 3.0\) Hz, 1 H), 6.08 (s, 2 H), 5.24 (d, \(J=49.9\) Hz, 1 H), 5.05 (s, 2 H), 4.41 (dq, \(J=29.7, 6.3\) Hz, 1 H), 1.46 (dd, \(J=2.3, 1.5\) Hz, 3 H). LC-MS (ESI, positive ion): \(m/z = 310.5\) [M+H].

10. Preparation of the intermediate aldehydes 91 and 92

\[(R)-N-((S)-2-(2-Fluorophenyl)-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide (91)\]

In a dry flask under an inert atmosphere a solution of (S)-ethyl 3-((R)-1,1-dimethylethylsulfinamido)-3-(2-fluorophenyl)butanoate (90) (3 g, 9.11 mmol) in toluene (15 ml) was cooled to –76 °C and DIBAH (1M in toluene; 10.0 ml, 10.0 mmol) was added dropwise during 9 min while keeping the temperature between –75 and –68 °C. After complete addition the reaction mixture was stirred at –76 °C for 3 h. The incomplete reaction was stopped by quenching the mixture at –76 °C with a saturated solution of NH\(_4\)Cl, then left to warm to r.t. Water (20 ml) and EtOAc (50 ml) were added under stirring. The emulsion was filtered through a layer of Dicalite\(^{®}\). Brine was added to the filtrate, the layers were separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na\(_2\)SO\(_4\), then evaporated. The crude product was purified by flash chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–66% EtOAc) to obtain the (R)-N-((S)-2-(2-fluorophenyl)-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide (91) (light yellow oil, 731 mg, 28% yield) and unreacted starting material (90) (orange oil, 2.05 g, 68% yield). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) ppm 9.70 (s, 1 H), 7.49 (td, \(J=8.1, 1.7\) Hz, 1 H), 7.23–7.31 (m, 1 H), 7.14 (td, \(J=7.9, 1.2\) Hz, 1 H), 7.02 (ddd, \(J=12.9, 8.1, 1.2\) Hz, 1 H), 4.84 (s, 1 H), 3.59 (d, \(J=18.4\) Hz, 1 H), 3.37 (ddd, \(J=18.4, 1.6, 0.6\) Hz, 1 H), 1.80 (s, 3 H), 1.27 (s, 9 H). LC-MS (ESI, positive ion): \(m/z = 308.4\) [M+Na].

\[(R)-N-((2R,3R)-3-Fluoro-2-(2-fluorophenyl)-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide (92)\]
A solution of (2R,3R)-ethyl 3-((R)-1,1-dimethylethylsulfinamido)-2-fluoro-3-(2-fluorophenyl)butanoate (39) (2.3 g, 6.62 mmol) in DCM (70 ml) was cooled to −78 °C and DIBAH (1 M in toluene; 9.93 ml, 9.93 mmol) was added dropwise during 15 min while keeping the temperature below −75 °C. After complete addition the reaction mixture was stirred at −78 °C for 1 h. Quenching of the reaction mixture with a saturated solution of NH₄Cl and diluting with DCM resulted in an emulsion which was filtered through a layer of Dicalite®. The layers were separated, and the aqueous layer was extracted three times with DCM. The combined organic layers were dried over Na₂SO₄, then evaporated. The crude product was purified by flash chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–50% EtOAc) to obtain the (R)-N-((2R,3R)-3-fluoro-2-(2-fluorophenyl)-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide (92) (light brown oil, 1.03 g, 51% yield). ¹H NMR (600 MHz, CDCl₃) δ ppm 9.79 (dt, J = 6.3, 0.8 Hz, 1 H), 7.43 (td, J = 8.0, 1.7 Hz, 1 H), 7.38 (dddd, J = 8.2, 7.4, 4.9, 1.6 Hz, 1 H), 7.20 (td, J = 7.7, 1.3 Hz, 1 H), 7.09 (ddd, J = 13.0, 8.2, 1.3 Hz, 1 H), 5.27 (dd, J = 46.6, 1.6 Hz, 1 H), 4.52 (s, 1 H), 1.92 (d, J = 1.7 Hz, 3 H), 1.23 (s, 9 H). HRMS (m/z): calcd for C₁₄H₁₉F₂NO₂S, 303.1105; found, 303.1101.

11. Preparation of the intermediate alcohols 93–96

(R)-2-Methyl-N-((2S,4R)-5,5,5-trifluoro-2-(2-fluorophenyl)-4-hydroxypentan-2-yl)propane-2-sulfinamide (93) and (R)-2-Methyl-N-((2S,4S)-5,5,5-trifluoro-2-(2-fluorophenyl)-4-hydroxypentan-2-yl)propane-2-sulfinamide (94)

In a dry flask under an inert atmosphere a solution of (R)-N-((S)-2-(2-fluorophenyl)-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide (1.236 g, 4.33 mmol) in THF (30 ml) was cooled to 0 °C and treated with trifluoromethyltrimethylsilane (Ruppert’s reagent) (1.24 g, 1.29 ml, 8.66 mmol). Thereafter TBAF (433 µl, 433 µmol, Eq: 0.1) was added dropwise within 6 min. The reaction mixture was stirred at 0 °C for 1 h before TBAF (3.9 ml, 3.9 mmol, Eq: 0.9) was added dropwise. After 1 h stirring at 0 °C the reaction mixture was quenched with a saturated solution of NH₄Cl. The mixture was extracted three times with EtOAc, the combined organic layers were washed with brine, dried over Na₂SO₄ and evaporated at reduced pressure. The crude product was purified by flash chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–33% EtOAc) to yield the first eluting isomer (R)-2-methyl-N-((2S,4R)-5,5,5-trifluoro-2-(2-fluorophenyl)-4-hydroxypentan-2-yl)propane-2-sulfinamide (94) (light yellow solid, 391 mg, 25.4% yield) and the (R)-2-methyl-N-((2S,4S)-5,5,5-trifluoro-2-(2-fluorophenyl)-4-hydroxypentan-2-yl)propane-2-sulfinamide (93) (light brown foam, 199 mg, 12.9% yield) as the second eluting isomer.

(93): ¹H NMR (300 MHz, CDCl₃) δ ppm 7.40 (td, J = 8.1, 1.8 Hz, 1 H), 7.25–7.34 (m, 1 H), 7.13 (td, J = 7.7, 1.2 Hz, 1 H), 7.07 (ddd, J = 12.9, 8.1, 1.4 Hz, 1 H), 5.66 (d, J = 6.1 Hz, 1 H), 4.86 (d, J = 1.8 Hz, 1
H), 4.28–4.42 (m, 1 H), 2.38 (dd, J=14.8, 10.6 Hz, 1 H), 2.15 (dd, J=14.6, 0.9 Hz, 1 H), 1.98 (s, 3 H), 1.24 (s, 9 H). LC-MS (ESI, negative ion): m/z = 354.5 [M-H].

(94): ¹H NMR (300 MHz, CDCl₃) δ ppm 7.46 (td, J=8.2, 1.6 Hz, 1 H), 7.33 (dddd, J=8.1, 7.4, 5.0, 1.6 Hz, 1 H), 7.19 (td, J=7.7, 1.2 Hz, 1 H), 7.10 (ddd, J=13.1, 8.1, 1.2 Hz, 1 H), 4.67 (s, 1 H), 4.59 (d, J=9.9 Hz, 1 H), 3.60 - 3.76 (m, 1 H), 2.82 (dd, J=15.3, 0.8 Hz, 1 H), 2.54 (ddd, J=15.5, 11.5, 1.0 Hz, 1 H), 1.77 (s, 3 H), 1.34 (s, 9 H). LC-MS (ESI, negative ion): m/z = 354.5 [M-H].

(R)-2-Methyl-N-((2R,3R,4R)-3,5,5,5-tetrafluoro-2-(2-fluorophenyl)-4-hydroxypentan-2-yl)propane-2-sulfinamide (95) and (R)-2-Methyl-N-((2R,3R,4S)-3,5,5,5-tetrafluoro-2-(2-fluorophenyl)-4-hydroxypentan-2-yl)propane-2-sulfinamide (96)

Alcohols 95 and 96 were obtained from 92 and Ruppert’s reagent in an analogous manner as described for 93 and 94. The crude product was purified by flash chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–100% EtOAc) to yield the first eluting isomer (R)-2-methyl-N-((2R,3R,4S)-3,5,5,5-tetrafluoro-2-(2-fluorophenyl)-4-hydroxypentan-2-yl)propane-2-sulfinamide (96) (light yellow solid, 21.8% yield) and the (R)-2-methyl-N-((2R,3R,4R)-3,5,5,5-tetrafluoro-2-(2-fluorophenyl)-4-hydroxypentan-2-yl)propane-2-sulfinamide (95) (light orange solid, 34.6% yield) as the second eluting isomer.

95: ¹H NMR (300 MHz, CDCl₃) δ ppm 7.42 (td, J=8.1, 1.6 Hz, 1 H), 7.31–7.39 (m, 1 H), 7.17 (td, J=7.7, 1.4 Hz, 1 H), 7.08 (ddd, J=13.0, 8.2, 1.4 Hz, 1 H), 7.00 (d, J=6.5 Hz, 1 H), 5.46 (d, J=1.6 Hz, 1 H), 5.11 (dd, J=45.0, 9.1 Hz, 1 H), 4.27–4.43 (m, 1 H), 2.02 (s, 3 H), 1.18 (s, 9 H). LC-MS (ESI, negative ion): m/z = 372.6 [M-H].

96: ¹H NMR (300 MHz, CDCl₃) δ ppm 7.53 (td, J=8.0, 1.7 Hz, 1 H), 7.39 (dddd, J=8.2, 7.5, 5.0, 1.8 Hz, 1 H), 7.25 (td, J=7.7, 1.4 Hz, 1 H), 7.14 (ddd, J=13.1, 8.2, 1.3 Hz, 1 H), 5.54 (d, J=45.2 Hz, 1 H), 5.01 (d, J=10.1 Hz, 1 H), 4.37 (s, 1 H), 3.63–3.84 (m, 1 H), 1.82 (s, 3 H), 1.33 (s, 9 H). LC-MS (ESI, positive ion): m/z = 374.6 [M+H].
12. Preparation of the intermediate amino alcohols 97–99

The amino alcohols 97–99 were obtained following the general procedure applied for the synthesis of the intermediate amino alcohols 8, 44–48 by cleavage of the chiral auxiliary with HCl in dioxane.

(2R,4S)-4-Amino-1,1,1-trifluoro-4-(2-fluorophenyl)pentan-2-ol (97)

\[
\text{H}_2\text{N}-\text{CF}_3
\]

Amino alcohol 97 was obtained from 93 as a light yellow solid (67% yield) after chromatography on silica-NH$_2$ gel (eluent: heptane–EtOAc; gradient: 0–50% EtOAc). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 7.55 (ddd, $J=8.8, 7.8, 1.8$ Hz, 1 H), 7.29 (dddd, $J=8.1, 7.4, 5.0, 1.8$ Hz, 1 H), 7.17 (td, $J=7.7, 1.7$ Hz, 1 H), 7.11 (ddd, $J=12.7, 7.9, 1.2$ Hz, 1 H), 4.10–4.23 (m, 1 H), 2.56 (br s, 2 H), 2.03 (dd, $J=14.1, 2.4$ Hz, 1 H), 1.87 (dd, $J=13.9, 10.1$ Hz, 1 H), 1.49 (d, $J=1.0$ Hz, 3 H). LC-MS (ESI, positive ion): $m/z = 252.5$ [M+H]$^+$. 

(2R,3R,4R)-4-Amino-1,1,1,3-tetrafluoro-4-(2-fluorophenyl)pentan-2-ol (98)

\[
\text{H}_2\text{N}-\text{CF}_3
\]

Amino alcohol 98 was obtained from 95 as a brown oil (95% yield); after chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–33% EtOAc) as a light brown oil (49% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 7.29–7.39 (m, 2 H), 7.08–7.20 (m, 2 H), 4.97 (dd, $J=46.0, 8.5$ Hz, 1 H), 4.29 (tqd, $J=8.6, 8.6, 6.3, 6.3, 1.1$ Hz, 1 H), 1.84–3.19 (m, 2 H), 1.78 (d, $J=0.8$ Hz, 3 H), 1.53 (s, 1 H). LC-MS (ESI, positive ion): $m/z = 270.4$ [M+H]$^+$. 

(2S,3R,4R)-4-Amino-1,1,1,3-tetrafluoro-4-(2-fluorophenyl)pentan-2-ol (99)

\[
\text{H}_2\text{N}-\text{CF}_3
\]

Amino alcohol 99 was obtained from 96 as a light brown solid (quant. yield) which was used in the following step without further purification. $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ ppm 7.75 (td, $J=8.2, 1.7$ Hz, 1 H), 7.39 (ddddd, $J=8.1, 7.4, 5.1, 1.8$ Hz, 1 H), 7.26 (td, $J=7.6, 1.3$ Hz, 1 H), 7.20 (ddd, $J=12.9, 8.2, 1.2$ Hz, 1 H), 5.00 (d, $J=46.4$ Hz, 1 H), 3.83 (dq, $J=26.6, 8.1$ Hz, 1 H), 1.52 (s, 3 H); NH$_2$- and OH-signals very broad. LC-MS (ESI, positive ion): $m/z = 270.4$ [M+H]$^+$. 

13. Preparation of the intermediate aniline 86
Ethyl 5-(Trifluoromethyl)-4,5-dihydroisoxazole-3-carboxylate (73)

Under an inert atmosphere at −78 °C, 3,3,3-trifluoroprop-1-ene (18.55 g, 193 mmol) was condensed by a gas inlet tube within 30 min into a suspension of NaHCO₃ (31.5 g, 375 mmol) in EtOAc (150 ml). EtOAc (150 ml) and a solution of (Z)-ethyl 2-chloro-2-(hydroxyimino)acetate (14.1 g, 90 mmol) in EtOAc (50.0 ml) were added dropwise within 20 min while keeping the internal temperature below −65 °C. After complete addition the cooling bath was removed and the white suspension was allowed to warm to r.t. The mixture was stirred at 25 °C for 3 d. For the workup, the solid was filtered off and washed twice with EtOAc. The filtrate was washed with water (100 ml) and the aqueous layer was re-extracted with EtOAc (100 ml). The combined organic layers were dried over MgSO₄ and evaporated to give 73 (16.85 g, quant. yield) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ ppm 5.06 (d, J=11.4, 6.6, 6.6, 6.6, 6.6 Hz, 1 H), 4.38 (q, J=7.3 Hz, 2 H), 3.50 (dd, J=18.6, 11.5 Hz, 1 H), 3.40 (dd, J=18.4, 6.9 Hz, 1 H), 1.39 (t, J=7.2 Hz, 3 H).

(5-(Trifluoromethyl)-4,5-dihydroisoxazol-3-yl)methanol (74)

Under an inert atmosphere a solution of ethyl 5-(trifluoromethyl)-4,5-dihydroisoxazole-3-carboxylate (73) (16.74 g, 79.3 mmol) in EtOH (168 ml) was treated portionwise at 0 °C within 1 h with sodium borohydride (3.3 g, 87.2 mmol). The yellow solution was stirred at 0 °C for 24 h. For the workup, the reaction mixture was concentrated at reduced pressure (70 mbar/40 °C), the residual volume quenched with a half-saturated solution of NH₄Cl and extracted three times with ether. The combined organic layers were washed with brine, dried over MgSO₄ and evaporated. The (5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)methanol (74) (11.31 g, 84% yield) was obtained as a white solid. ¹H NMR (300 MHz, CDCl₃) δ ppm 4.91 (d, J=11.2, 6.6, 6.6, 6.6, 6.6 Hz, 1 H), 4.47 (s, 2 H), 3.37 (dd, J=18.0, 11.1 Hz, 1 H), 3.24 (dd, J=18.0, 6.3 Hz, 1 H), 2.10 (br s, 1 H).

3-(Fluoromethyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (75)

Under an inert atmosphere a suspension of (5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)methanol (74) (9.53 g, 56.4 mmol) in DCM (190 ml) was treated dropwise at −78 °C with bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor®) (26.2 g, 21.9 ml, 113 mmol) within 20 min. The yellow reaction mixture was stirred at −78 °C for 20 min, then left to warm to r.t. and stirred during 15 h. For the workup, the reaction mixture was added dropwise at 0 °C to a saturated solution of NaHCO₃. After stirring for 1 h, the organic layer was separated, washed twice with a solution (5%) of citric acid and with a saturated solution of NaHCO₃. The aqueous solutions were re-extracted (3x) with DCM. The organic layers were combined and evaporated to yield 75 as a dark red oil (8.90 g, 92% yield) which was used in the next step without further purification. ¹H NMR (300 MHz, CDCl₃) δ ppm 5.18 (d, J=46.4
(3S,5S)-3-(Fluoromethyl)-3-(2-fluorophenyl)-5-(trifluoromethyl)isoxazolidine (78)

Under an inert atmosphere a solution of 1-bromo-2-fluorobenzene (6.44 g, 4.00 ml, 36.8 mmol) in THF (30 ml) and toluene (90.0 ml) was treated dropwise during 30 min at –78 °C with n-BuLi (1.6M in hexane; 21.9 ml, 35.1 mmol) while keeping the internal temperature below –70 °C. After complete addition the solution was stirred at –78°C for 1 h (solution A).

Under an inert atmosphere the light yellow solution of 3-(fluoromethyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (75) (3 g, 17.5 mmol) in toluene (210 ml) was treated at –78 °C with boron trifluoride etherate (4.98 g, 4.44 ml, 35.1 mmol) followed by the beforehand prepared solution A via a dry-ice cooled cannula while keeping the internal temperature below –71 °C. The now orange colored reaction mixture was stirred at –78 °C for 90 min. For the workup, the mixture was quenched with a saturated solution of NH₄Cl, then warmed to r.t. . The aqueous layer was extracted twice with EtOAc, the combined organic layers were washed with brine, dried over MgSO₄ and evaporated at reduced pressure. The crude product was purified by flash chromatography on silica gel (eluent: heptane–EtOAc 80:1) to give (3S,5S)- and (3R,5R)-3-(fluoromethyl)-3-(2-fluorophenyl)-5-(trifluoromethyl)isoxazolidine (1.7 g, 36% yield) as a light yellow liquid. Separation of the enantiomers by chromatography on Reprosil Chiral NR [eluent: heptane–isopropanol (2%)] yielded the (3R,5R)-3-(fluoromethyl)-3-(2-fluorophenyl)-5-(trifluoromethyl)isoxazolidine (colorless oil, 621 mg, 13% yield; e.e. >99%) as the first eluting enantiomer and (3S,5S)-3-(fluoromethyl)-3-(2-fluorophenyl)-5-(trifluoromethyl)isoxazolidine (78) (colorless oil, 624 mg, 13% yield; e.e. >98%) as the second eluting enantiomer. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.51 (td, J=8.0, 1.8 Hz, 1 H), 7.33–7.45 (m, 1 H), 7.25 (td, J=7.6, 1.5 Hz, 1 H), 7.12 (ddd, J=12.6, 10.1, 0.8 Hz, 1 H), 4.42 (ddd, J=48.6, 10.1, 1.2 Hz, 1 H), 4.28–4.42 (m, 1 H), 2.83–3.01 (m, 2 H). LC-MS (ESI, positive ion): m/z = 268.4 [M+H]+.

(2S,4S)-4-amino-1,1,1,5-tetrafluoro-4-(2-fluorophenyl)pentan-2-ol (80)

To a solution of (3S,5S)-3-(fluoromethyl)-3-(2-fluorophenyl)-5-(trifluoromethyl)isoxazolidine (78) (600 mg, 2.25 mmol) in EtOH (14.0 ml) was added under an inert atmosphere at r.t. ammonium formate (1.13 g, 18.0 mmol) followed by palladium (10% on carbon; 119 mg, 112 µmol). The suspension was stirred at 25 °C for 2 h, and the rate of conversion was checked by TLC. After 5 h the catalyst was filtered off, washed three times with ethanol, and the filtrate was evaporated. The colorless residue was treated with a saturated solution of NaHCO₃ and extracted three times with EtOAc. The organic layers were washed with brine, dried over MgSO₄ and evaporated to give (2S,4S)-4-amino-1,1,1,5-tetrafluoro-4-(2-fluorophenyl)pentan-2-ol (80) (colorless solid, 592 mg, 98% yield). ¹H NMR (300 MHz, CDCl₃) δ ppm 7.51 (td, J=8.0, 1.8 Hz, 1 H), 7.33–7.45 (m, 1 H), 7.25 (td, J=7.6, 1.5 Hz, 1 H), 7.12 (ddd, J=12.6,
8.1, 1.3 Hz, 1 H), 4.78 (ddd, $J=48.0, 8.9, 2.0$ Hz, 1 H), 4.32 (dd, $J=47.4, 9.3$ Hz, 1 H), 3.69 (ddq, $J=11.3, 6.6, 2.1$ Hz, 1 H), 2.39 (dt, $J=14.3, 1.8$ Hz, 1 H), 2.04 (dd, $J=14.2, 11.4$ Hz, 1 H); NH$_2$- and OH-signals not detectable. LC-MS (ESI, positive ion): $m/z = 270.4$ [M+H]$^+$. (4S,6S)-4-(Fluoromethyl)-4-(2-fluorophenyl)-6-(trifluoromethyl)-5,6-dihydro-4H,1,3-oxazin-2-amine (82)

In a reaction tube (25 ml) under an inert atmosphere a solution of (2S,4S)-4-amino-1,1,1,5-tetrafluoro-4-(2-fluorophenyl)pentan-2-ol (80) (386 mg, 1.43 mmol) in EtOH (7.8 ml) was treated at r.t. with cyanogen bromide (5M in acetonitrile; 430 µl, 2.15 mmol). The tube was sealed and the reaction mixture was stirred at 85 °C for 20 h. The mixture was cooled to r.t. and poured into a saturated solution of Na$_2$CO$_3$. The organic solvent was removed at reduced pressure, and the aqueous residue was partitioned between a saturated solution of Na$_2$CO$_3$ and EtOAc. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over MgSO$_4$ and evaporated. The crude product was purified by flash chromatography on silica gel (eluent: DCM–MeOH 50:1) to yield (4S,6S)-4-(fluoromethyl)-4-(2-fluorophenyl)-6-(trifluoromethyl)-5,6-dihydro-4H,1,3-oxazin-2-amine (82) (colorless oil, 251 mg, 60% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.18 (m, $J=7.7, 1.4$ Hz, 1 H), 7.33 (dddd, $J=8.1, 7.4, 5.0, 1.8$ Hz, 1 H), 7.19 (td, $J=7.6, 1.4$ Hz, 1 H), 7.07 (ddd, $J=12.5, 8.1, 1.2$ Hz, 1 H), 4.70 (ddd, $J=47.6, 8.7, 1.6$ Hz, 1 H), 4.46 (ddd, $J=47.2, 8.7, 1.2$ Hz, 1 H), 4.25–4.75 (br, 2 H), 4.02–4.13 (m, 1 H), 2.66 (dd, $J=13.5, 2.8$ Hz, 1 H), 2.15 (t, $J=12.9$ Hz, 1 H). LC-MS (ESI, positive ion): $m/z = 295.4$ [M+H]$^+$. (4S,6S)-4-(2-Fluoro-5-nitrophenyl)-4-(fluoromethyl)-6-(trifluoromethyl)-5,6-dihydro-4H,1,3-oxazin-2-amine (84)

A solution of (4S,6S)-4-(fluoromethyl)-4-(2-fluorophenyl)-6-(trifluoromethyl)-5,6-dihydro-4H,1,3-oxazin-2-amine (82) (321 mg, 1.09 mmol) in sulfuric acid (8.35 g, 4.54 ml, 85.1 mmol) was treated dropwise at 0 °C with fuming nitric acid (96.2 mg, 68.3 µl, 1.53 mmol). The solution was stirred at 0 °C for 30 min. For the workup, the light yellow viscous reaction mixture was added dropwise into an ice/water-mix 1:1 (70 ml) and the pH was adjusted to 6 with NaOH (4N, approx. 40 ml). Thereafter a saturated solution of Na$_2$CO$_3$ (20 ml) was added and the mixture extracted three times with EtOAc. The combined organic layers were washed with brine, dried over MgSO$_4$ and evaporated. The crude product was purified by flash chromatography on silica gel (eluent: heptane–EtOAc 3:1) to give the (4S,6S)-4-(2-fluoro-5-nitrophenyl)-4-(fluoromethyl)-6-(trifluoromethyl)-5,6-dihydro-4H,1,3-oxazin-2-amine (84) (colorless foam, 327 mg, 88% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 8.50 (dd, $J=6.9, 3.0$ Hz, 1 H), 8.25 (ddd, $J=8.9, 4.0, 3.0$ Hz, 1 H), 7.26 (ddd, $J=10.9, 8.9$ Hz, 1 H), 4.63 (ddd, $J=26.2, 8.7, 1.8$ Hz, 1 H), 4.48 (ddd, $J=25.8, 8.5, 1.2$ Hz, 1 H), 4.47–4.55 (br, 2 H), 4.024.13 (m, 1 H), 2.70 (dd, $J=13.7, 2.6$ Hz, 1 H), 2.16 (dd, $J=13.7, 12.9$ Hz, 1 H). LC-MS (ESI, positive ion): $m/z = 340.4$ [M+H]$^+$. 

\[ \text{H}_2\text{N} \quad \text{O} \quad \text{CF}_3 \]

\[ \text{F} \]

\[ \text{F} \]

\[ \text{O}_2\text{N} \]

\[ \text{F} \]

\[ \text{F} \]
(4S,6S)-4-(5-Amino-2-fluorophenyl)-4-(fluoromethyl)-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-2-amine (86)

A solution of (4S,6S)-4-(2-fluoro-5-nitrophenyl)-4-(fluoromethyl)-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-2-amine (84) (312 mg, 920 µmol) and TEA (93.1 mg, 128 µl, 920 µmol) in EtOH (18 ml) was hydrogenated at r.t. using palladium (10% on carbon; 48.9 mg, 46.0 µmol) as the catalyst. After 2 h the catalyst was filtered off, washed three times with EtOH, and the filtrate was evaporated to give (4S,6S)-4-(5-amino-2-fluorophenyl)-4-(fluoromethyl)-6-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazin-2-amine (86) (colorless solid, 302 mg, quant. yield) which was used in the following step without further purification.

1H NMR (300 MHz, CDCl₃) δ ppm 6.86 (dd, J=11.7, 8.7 Hz, 1 H), 6.76 (dd, J=6.6, 2.9 Hz, 1 H), 6.58 (ddd, J=8.7, 3.8, 3.0 Hz, 1 H), 4.68 (dd, J=47.6, 8.7, 1.6 Hz, 1 H), 4.43 (ddd, J=47.2, 8.7, 1.0 Hz, 1 H), 4.25–4.42 (br s, 2 H), 4.14 (dqd, J=11.9, 5.9, 5.9, 5.9, 3.3 Hz, 1 H), 3.62 (br s, 2 H), 2.63 (dd, J=13.4, 2.7 Hz, 1 H), 2.12 (t, J=13.0 Hz, 1 H). LC-MS (ESI, positive ion): m/z = 310.4 [M+H]+.

14. Preparation of non-commercial building blocks 23–27 and 30

5-(2,2,2-Trifluoro-ethoxy)-pyridine-2-carboxylic acid methyl ester (19)

Under an atmosphere of nitrogen a solution of 5-hydroxy-pyridine-2-carboxylic acid methyl ester (200 mg, 1.31 mmol) in DMF (2 ml) was treated at room temperature with sodium hydride (55% dispersion in oil, 64 mg). After the gas formation had ceased, the suspension was cooled to 0 °C and trifluoro-methanesulfonic acid 2,2,2-trifluoro-ethyl ester (364 mg, 1.57 mmol) was added. After stirring at room temperature for 2 hours about 50% of the starting material was left. Another 364 mg of trifluoro-methanesulphonic acid 2,2,2-trifluoro-ethyl ester were added and after 30 minutes the reaction was complete. For the workup, the reaction mixture was treated with a saturated solution of Na₂CO₃, then extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na₂SO₄, and evaporated at reduced pressure. The crude product was purified by chromatography on silica gel using a 3:1-mixture of heptane and EtOAc as the eluent. The 5-(2,2,2-trifluoro-ethoxy)-pyridine-2-carboxylic acid methyl ester (19) was obtained as a white solid (216 mg, 70% yield).

1H NMR (300 MHz, CDCl₃) δ ppm 8.47 (d, J=2.8 Hz, 1 H), 8.16 (d, J=8.7 Hz, 1 H), 7.34 (dd, J=8.7, 3.0 Hz, 1 H), 4.48 (q, J=7.9 Hz, 2 H), 4.00 (s, 3 H). MS (ESI, positive ion): m/z = 236.3 [M+H]+.

5-(2,2,3,3-Tetrafluoro-propoxy)-pyridine-2-carboxylic acid methyl ester (20)
A solution of 5-hydroxy-pyridine-2-carboxylic acid methyl ester (2.0 g, 13.1 mmol) in acetone (40 ml) was treated with K$_2$CO$_3$ (5.415 g, 39.2 mmol) and trifluoromethanesulphonic acid, 2,2,3,3-tetrafluoropropyl ester. After 4 h stirring at r.t. the suspension was diluted with diethylether. After filtration the solution was evaporated and the yellow solid purified by chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–70% EtOAc). The 5-(2,2,3,3-tetrafluoropropoxy)-pyridine-2-carboxylic acid methyl ester (20) was obtained as a light yellow solid (3.49 g, 76% yield).\(^1\) \(^1\)H NMR (300 MHz, DMSO-$d_6$) \(\delta\) ppm 8.49 (d, \(J=2.8\) Hz, 1 H), 8.08 (d, \(J=8.7\) Hz, 1 H), 7.67 (dd, \(J=8.7, 3.0\) Hz, 1 H), 6.72 (tt, \(J=51.9, 5.4\) Hz, 1 H), 4.83 (t, \(J=13.5\) Hz, 2 H), 3.86 (s, 3 H). LC-HRMS: \(m/z\) 267.05318 (calcd for C$_{10}$H$_9$F$_4$NO$_3$, 267.051856).

**Methyl 5-(prop-2ynyloxy)pyrazine-2-carboxylate (22)**

A suspension of methyl 5-chloropyrazine (250 mg, 1.45 mmol) and propargylalcohol (89.03 mg, 0.094 ml, 1.59 mmol) in dioxane (10 ml) was treated at r.t. with potassium tert-butoxide (179 mg, 1.59 mmol) and stirred for 3 h. The reaction mixture was concentrated at reduced pressure, the residue taken up in H$_2$O and extracted with EtOAc (3x). The combined organic layers were dried over Na$_2$SO$_4$. Removal of the solvent at reduced pressure left a brown solid (175 mg). The crude product was purified by flash chromatography on silica gel (eluent: heptane–EtOAc; gradient: 0–50% EtOAc) to give the methyl 5-(prop-2-ynyloxy)pyrazine-2-carboxylate (22) (90 mg, 32% yield) as an off-white solid. \(^1\)H NMR (300 MHz, CDCl$_3$) \(\delta\) ppm 8.90 (d, \(J=1.2\) Hz, 1 H), 8.35 (d, \(J=1.2\) Hz, 1 H), 5.07 (d, \(J=2.4\) Hz, 2 H), 4.01 (s, 3 H), 2.53 (t, \(J=2.5\) Hz, 1 H). LC-MS (ESI, positive ion): \(m/z = 193.5 [M+H]^+\).

**5-(2,2,2-Trifluoro-ethoxy)-pyridine-2-carboxylic acid (23)**\(^1\)

Under an atmosphere of nitrogen a solution of 5-(2,2,2-trifluoro-ethoxy)-pyridine-2-carboxylic acid methyl ester (216 mg, 0.92 mmol) in methanol (1 ml) was treated with a solution of lithium hydroxide monohydrate (78 mg, 1.84 mmol) in methanol (0.1 ml). After stirring for 2 hours the reaction mixture was evaporated at reduced pressure. The residue was treated with HCl (1N), the solid material was filtered then washed with water, finally dried at high vacuum. The 5-(2,2,2-trifluoro-ethoxy)-pyridine-2-carboxylic acid was obtained as a white solid (125 mg, 61% yield). \(^1\)H NMR (300 MHz, DMSO-$d_6$) \(\delta\) ppm 13.13 (br s, 1 H approx.), 8.49 (d, \(J=2.8\) Hz, 1 H), 8.07 (d, \(J=8.9\) Hz, 1 H), 7.66 (dd, \(J=8.8, 2.9\) Hz, 1 H), 4.99 (q, \(J=8.9\) Hz, 2 H).
5-(2,2,3,3-Tetrafluoro-propoxy)-pyridine-2-carboxylic acid (24)³

![Structure of 5-(2,2,3,3-Tetrafluoro-propoxy)-pyridine-2-carboxylic acid (24)](image)

In a manner analogous to that described for intermediate 23, the hydrolysis of the 5-(2,2,3,3-tetrafluoro-propoxy)-pyridine-2-carboxylic acid methyl ester (20) with lithium hydroxide yielded the title compound as a light yellow solid (94% yield). $^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 13.01 (br s, 1 H), 8.48 (d, $J$=2.8 Hz, 1 H), 8.07 (d, $J$=8.7 Hz, 1 H), 7.66 (dd, $J$=8.7, 2.8 Hz, 1 H), 6.72 (tt, $J$=51.9, 5.4 Hz, 1 H), 4.83 (t, $J$=13.4 Hz, 2 H). MS (ESI, positive ion): $m/z$ = 253 [M]$^+$.

5-(2,2,2-Trifluoro-ethoxy)-pyrazine-2-carboxylic acid (25)¹⁵

![Structure of 5-(2,2,2-Trifluoro-ethoxy)-pyrazine-2-carboxylic acid (25)](image)

Preparation via methylester 21.¹⁵ $^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 13.48 (br s, 1 H), 8.84 (d, $J$=1.2 Hz, 1 H), 8.59 (d, $J$=1.2 Hz, 1 H), 5.13 (q, $J$=8.9 Hz, 2 H).

5-(Prop-2-ynyloxy)pyrazine-2-carboxylic acid (26)

The methyl 5-(prop-2-ynyloxy)pyrazine-2-carboxylate (22) (45 mg, 0.23 mmol) was dissolved in THF (0.6 ml) and H₂O (4 ml) and treated with LiBH₄ (11.8 mg, 0.28 mmol). The reaction mixture was stirred at r.t. for 1 h. The solvent was evaporated at reduced pressure and the residue acidified with HCl (1N) to pH 1. The aqueous phase was extracted with EtOAc (3x), the organic layers combined, dried over Na₂SO₄ and evaporated. The 5-(prop-2-ynyloxy)pyrazine-2-carboxylic acid (26) (white solid, 34 mg, 81.5 % yield) was used in the next step without further purification. $^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 13.33 (br s, 1 H), 8.83 (d, $J$=1.4 Hz, 1 H), 8.45 (d, $J$=1.2 Hz, 1 H), 5.11 (d, $J$=2.4 Hz, 2 H), 3.62 (t, $J$=2.4 Hz, 1 H). LC-MS (ESI, positive ion): $m/z$ = 179.4 [M+H]$^+$.

5-(But-2-ynyloxy)pyrazine-2-carboxylic acid (27)¹⁶

![Structure of 5-(But-2-ynyloxy)pyrazine-2-carboxylic acid (27)](image)

A solution of 5-chloropyrazine-2-carboxylic acid (800 mg, 5.05 mmol) and but-2-yn-1-ol (4.99 g, 5.328 ml, 71.2 mmol) in DMF (10 ml) was treated with potassium tert-butoxide (2.266 g, 20.2 mmol). The light brown suspension was heated to 65 °C and stirred for 8 h. For the workup, the reaction
mixture was cooled to room temperature, neutralized with HCl (2N) and concentrated to half of its volume, and the product precipitated. After filtration the solid was washed with H2O, then dried. The 5-(but-2-ynloxy)pyrazine-2-carboxylic acid (27) (light brown solid, 260 mg, 27% yield) was used in the next step without further purification. 1H NMR (300 MHz, DMSO-d6) δ ppm 13.34 (br s, 1 H), 8.82 (d, J=1.2 Hz, 1 H), 8.42 (s, 1 H), 5.06 (q, J=2.2 Hz, 2 H), 1.85 (t, J=2.4 Hz, 3 H). MS (ESI, positive ion): m/z = 193.4 [M+H]+.

1-Difluoromethyl-1H-pyrazole-3-carboxylic acid methyl ester (28)

![1-Difluoromethyl-1H-pyrazole-3-carboxylic acid methyl ester](image1)

A solution of 1-difluoromethyl-1H-pyrazole-3-carboxylic acid (500 mg, 3.1 mmol) in MeOH (18 ml) was cooled to 0 °C and treated with H2SO4 (98%, 0.2 ml, 3.1mmol). The mixture was heated to reflux for 2 h. For the workup, the solution was cooled and concentrated at reduced pressure. The residue was partitioned between EtOAc (25 ml) and H2O (30 ml). The organic layer was separated, washed with water until the water phase showed a neutral pH. After drying over Na2SO4, the organic layer was evaporated at reduced pressure. The 1-difluoromethyl-1H-pyrazole-3-carboxylic acid methyl ester (28) was obtained as a colorless liquid (535 mg, 99% yield) pure enough to be engaged in the next step without further purification. 1H NMR (300 MHz, CDCl3) δ ppm 7.88 (d, J=2.6 Hz, 1 H), 7.27 (t, J=59.9 Hz, 1 H), 6.98 (d, J=2.6 Hz, 1 H), 3.97 (s, 3 H). MS (ESI, positive ion): m/z = 177.1 [M+H]+.

4-Chloro-1-difluoromethyl-1H-pyrazole-3-carboxylic acid methyl ester (29)

![4-Chloro-1-difluoromethyl-1H-pyrazole-3-carboxylic acid methyl ester](image2)

A mixture of 1-difluoromethyl-1H-pyrazole-3-carboxylic acid methyl ester (535 mg, 3 mmol) and N-chloro-succinimide (1.22 g, 9.1 mmol) in DMF (5 ml) was heated at 50 °C overnight. The reaction mixture was cooled, poured into H2O (20 ml), then extracted with EtOAc. The organic layer was separated, washed with water, dried over Na2SO4, finally evaporated at reduced pressure. The yellowish crude material was purified by chromatography on silica gel (eluent: cyclohexane–EtOAc 3:1). The 4-chloro-1-difluoromethyl-1H-pyrazole-3-carboxylic acid methyl ester (29) was obtained as a white solid (540 mg, 84% yield). 1H NMR (300 MHz, CDCl3) δ ppm 7.92 (s, 1 H), 7.19 (t, J=59.7 Hz, 1 H), 3.99 (s, 3 H). MS (ESI, positive ion): m/z = 209.9 [M]+.

4-Chloro-1-difluoromethyl-1H-pyrazole-3-carboxylic acid (30)

![4-Chloro-1-difluoromethyl-1H-pyrazole-3-carboxylic acid](image3)

A solution of 4-chloro-1-difluoromethyl-1H-pyrazole-3-carboxylic acid methyl ester (540 mg, 2.6 mmol) in THF (18 ml) was treated at room temperature with a solution of LiOH (135 mg, 5.6 mmol) in
a 1:1-mixture of H₂O and MeOH (12 ml). After 1 h the reaction was complete, and the solvents were evaporated at reduced pressure. The residue was dissolved in H₂O (10 ml) and acidified with HCl (2M). Extraction with EtOAc, drying of the organic layer over Na₂SO₄ and evaporation at reduced pressure yielded a white solid (555 mg) which was triturated with pentane (10 ml). The solid material was filtered, washed with pentane and dried. After drying at reduced pressure the 4-chloro-1-difluoromethyl-1H-pyrazole-3-carboxylic acid (30) was obtained as a white solid (477 mg, 95% yield).

1H NMR (300 MHz, CDCl₃) δ ppm 7.95 (s, 1 H), 7.23 (t, J=59.5 Hz, 1 H); acid-signal not detectable. MS (ESI, negative ion): m/z = 195.0 [M-H].

15. LogD determinations

Distribution coefficients are determined using the CAMDIS© (CArrier Mediated DIstribution System, EP2005102211A) method, which is derived from the conventional 'shake flask' method. CAMDIS© is carried out in 96-well microtiterplates in combination with DIFI©-tubes (Weidmann Plastics Technology AG, Rapperswil, Switzerland), which provide a hydrophobic layer for the 1-octanol phase. The hydrophobic layer (0.45 µm PVDF membranes) fixed on the bottom of each DIFI©-tube is coated (Microfluidic Dispenser BioRAPTR, Bechman Coulter) with 1.0 µl of 1-octanol. Next, the filter membranes are dipped into a 96-well plate which has been prefilled with 150 µl of aqueous buffer solution (25 mM Phosphate, pH 7.4) containing the compound of interest at a starting concentration of 100 µM. The plate is sealed and shaken for 24 h at room temperature (23 °C) to ensure that the partition equilibrium is reached. The next day, the DIFI©-tubes are removed from the 96-well plate and an aliquote of the aqueous solution is analyzed by LC/MS. The distribution coefficient is calculated from a control experiment without 1-octanol and the remaining compound concentration in the aqueous phase which was in equilibrium with 1-octanol. Sample preparation is carried out using a TECAN robotic system (RSP 100, 8 channels).

16. pKa determinations by capillary electrophoresis (CE)

The CE experiments were performed on a pKa Analyzer Pro system from Advanced Analytical Technologies capillary electrophoresis system (Ames IA, USA) with a diode array UV/VIS detector. 96 fused-silica capillaries of 55 cm total length, 75 µm ID, 214 nm OD and a sample volume of 50 µl was used in all experiments. The capillaries were thermostated at room temperature and a voltage of 3.5 kV was applied. The observed currents were about 30 µA. The initial sample concentration was 0.25 mM dissolved in a special CE buffer from Advanced Analytical Technology at an ionic strength of 0.05M. A plate with 24 pH values from pH 1.1-12.2 in replicates of 4 was prepared. 0.1 % v/v DMSO, as a neutral marker, was added to each sample. Prior to use, the sample solutions were filtered through a 0.22 µm hydrophilic Durapore membrane (Millipore, Billerica MA, USA) to avoid precipitation during the CE experiment. Finally, the pKa values were obtained with the proprietary software pKa Analyzer Pro from Advanced Analytical Technologies.

17. Stability in mouse microsomes

Incubations are performed in 96-well deep-well plates with a final incubation volume of 600 µL. Incubations contain (finally) 1 µM test compound, 0.5 mg/mL mouse liver microsomes and NADPH regenerating system consisting of glucose-6-phosphate dehydrogenase, NADPH and glucose-6-phosphate (equivalent to 1 mM NADPH). Reactions were initiated by addition of the NADPH regenerating system at 37 °C. 50 µL aliquots are removed after 1, 3, 6, 9, 15, 25, 35 and 45 minutes and
quenched in 3 volumes of 150 µL acetonitrile containing internal standard. Samples are then cooled and centrifuged before analysis by LC-MS/MS. Analysis is performed using an API4000 mass spectrometer and Shimadzu HPLC system. Intrinsic clearance is calculated from the rate constant of the exponential decay of test substance concentration with time. Log peak area ratio (test compound peak area / internal standard peak area) is plotted against incubation time and a linear fit made to the data with emphasis upon the initial rate of compound disappearance. The slope of the fit is then used to calculate the intrinsic clearance:

$$Cl_{int} (\mu L/min/mg) = \text{-slope (min}^{-1}) * 1000 / \text{[protein concentration (mg/mL)]}$$

18. Inhibition of CYP<sub>3A4</sub>, 2D6 and 2C9

Inhibition of cytochromes P450 (CYPs) 2C9, 2D6 and 3A4 was assessed using human liver microsomes and CYP-selective substrate metabolism reactions. 50 µl incubations were made up containing (finally) 0.2 mg/ml pooled human liver microsomes, 5 µM substrate (diclofenac for CYP2C9 [4’hydroxylase], dextromethorphan for CYP2D6 [O-demethylase] or midazolam for CYP3A4 [1’hydroxylase]), 0.25 µL DMSO containing test inhibitor and NADPH regenerating system. Test inhibitor concentrations of 50, 16.7, 5.6, 1.9, 0.6 and 0.2 µM were assessed in singlicate. Incubations were prewarmed to 37 °C for 10 minutes before initiation by addition of NADPH regenerating system. Incubations were quenched after 5 minutes (20 minutes for dextromethorphan) by addition of 50 µl cold acetonitrile containing 20 ng/ml 4dOHddiclofenacd13C6, 20 ng/mL dextrorphandD3 and 20 ng/mL 1dOHdmidazolamdD4. Quenched incubates were stored at -20 °C for at least 1 hour before centrifugation (20,000x g, 20 minutes). Supernatants were removed and diluted 1:1 with water prior to analysis using a RapidFire sample injector system and API4000 mass spectrometer. Peak areas for substrate, metabolite and stable-labelled metabolite standard were determined using MS/MS. The peak area ratios between the metabolite generated by the enzymatic reaction and the internal standard were used in subsequent calculations. The percentage of (DMSO) control activity was calculated for each incubate and IC50 values estimated by non-linear regression. Sulfaphenazole, quinidine or ketoconazole were tested in each CYP2C9, CYP2D6 or CYP3A4 inhibition experiment, respectively, to ensure assay sensitivity and reproducibility (Validated assays for human cytochrome P450 activities, R.L.Walsky and R.S.Obach, Drug Metabolism and Disposition 32: 647–660, 2004. and S.Fowler and H.Zhang, The AAPS Journal, Vol.10, No. 2, 410-424, 2008).

19. Time-dependent inhibition of CYP<sub>3A4</sub>

IC<sub>50</sub> Determination Experiments

Incubations were performed using an automated liquid handling system, with human liver microsomal protein content at 0.2 mg/mL. Incubation times, substrate concentrations and internal standards are shown below. In general the procedures, were followed as previously reported by Robert L. Walsky and R. Scott Obach: Validated Assays for Human Cytochrome P450 Activities; DMD 32:647–660, 2004.

Time-Dependent Inhibition Experiments

Test compounds were pre-incubated with 1 mg/mL HLM in 100 mM phosphate buffer, pH7.4. The pre-incubations were warmed prior to initiation of the reaction by addition of NADPH (1 mM final concentration). After pre-incubation times between 0.5 and 30 minutes, aliquots of the pre-incubate were removed and added to a substrate solution (0.05 mg/mL HLM). Samples were quenched by addition of 400 µL acetonitrile containing internal standards. Details of control inhibitors, preincubation times, substrate and incubation time are shown in the following table.
LC-MS/MS Analysis Method
An LC-MS/MS method with automated column switching was used for the quantification. An API 4000 (AB-Sciex) mass spectrometer and a CTC PAL autosampler were used, connected to an Agilent HPLC system. The trapping column was a Thermo Hypersil Gold C18 5 μm 2.0 x 10 mm, the analytical column a 2.1 x 50 mm Phenomenex Gemini C18 5 μm. Aliquots of the sample solutions (10 – 50 μL) were injected first onto the trapping column and then transferred to the analytical column. Total run time was 3.0 min. MS settings for all CYP metabolism analyses were as follows: collision gas (CAD) 10, curtain gas (CUR) 30, ion source gas 1 (GS1) 50, ion source gas 2 (GS2) 50, entrance potential (EP) 10, dwell time 50 msec, temperature 650 °C, ion spray voltage 5500 V. Nitrogen was used as ion source and curtain gas. Detection was achieved in positive ion MRM mode.

IC₅₀ Determinations
Metabolite peak areas were divided by the internal standard peak areas to give metabolite peak area ratios. After background subtraction, the metabolite peak area ratios were normalized with the mean of the zero inhibition controls set to 100%.

Where enzyme inhibition was observed, IC₅₀ values were estimated using the non-linear curve fitting procedure of xlfit v4 (IDBS, Guildford, UK). Within the fitting function (Eqn 1), the maximum activity asymptote was set at 100% and the minimum was set to 0%.

\[
\text{Percent Control Activity} = \frac{a}{1 + \left(\frac{\text{Inhibitor Conc}}{IC_{50}}\right)^b}
\]

Eqn 1

Time-Dependent Inhibition
Metabolite peak areas were divided by the internal standard peak areas to give metabolite peak area ratios. These data were then normalized, with 100% activity set to the reaction rate of the DMSO control / 0.5 minute pre-incubation time sample. Ln (normalized reaction rate) was plotted against preincubation time and rate constants (kₗₒ𝑏ₛ) for loss of enzyme activity calculated, with emphasis upon the lower preincubation time samples for which the most accurate data was generated.

20. References
5. Hilpert, H.; Wostl, W. Preparation of 1,3-oxazines as BACE1 and/or BACE2 inhibitors. US20120258962A1, 2012.
12. Hilpert, H.; Rogers-Evans, M.; Rombach, D. Preparation of 1,4-thiazepines/sulfones as therapeutic BACE1 and/or BACE2 inhibitors. US20120258962A1, 2012.