Supporting Information

Design, Synthesis and Pharmacological Characterization of a Neutral, Non-prodrug Thrombin Inhibitor with Good Oral Pharmacokinetics

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CONTENT

A. Experimental

General Procedures: All commercial reagents and catalysts were used as provided by the commercial supplier without purification. Solvents for synthesis, extraction and chromatography were reagent grade and used as received. Moisture-sensitive reactions were carried out under an atmosphere of argon and anhydrous solvents were used as provided by the commercial supplier. ^{1}H NMR spectra were recorded on Bruker Avance spectrometers. Chemical shifts (δ) are reported in ppm relative to TMS as an internal standard. The descriptions of the coupling patterns of ^{1}H NMR signals are based on the optical appearance of the signals and do not necessarily reflect the physically correct interpretation. In general, the chemical shift information refers to the center of the signal. LC-MS and GC-MS analysis was performed using the respective method 1a−10a, 1b-2b, and 1c, as noted. Unless otherwise indicated, all compounds have ≥95% purity.

Abbreviation: HATU, O-(7-Azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium-hexafluorphosphat; TBTU, 2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate.

LC-MS and GC-MS methods:

Method 1a: Instrument: Waters ACQUITY SQD UPLC System; column: Waters Acquity UPLC HSS T3 1.8 µ, 50 mm x 1 mm; mobile phase A: 1 L of water + 0.25 mL of 99% strength formic acid, mobile phase B: 1 L of acetonitrile + 0.25 mL of 99% strength formic acid; gradient: 0.0 min 90% A → 1.2 min 5% A → 2.0 min 5% A; oven: 50 °C; flow rate: 0.40 mL/min; UV detection: 208–400 nm.

Method 2a: Instrument: Micromass Quattro Premier with Waters UPLC Acquity; column: Thermo Hypersil GOLD 1.9 µ, 50 mm x 1 mm; mobile phase A: 1 L of water + 0.5 mL of 50% strength formic acid, mobile phase B: 1 L of acetonitrile + 0.5 mL of 50% strength formic acid; gradient: 0.0 min 97% A → 0.5 min 97% A → 3.2 min 5% A → 4.0 min 5% A; oven: 50 °C; flow rate: 0.3 mL/min; UV detection: 210 nm.

Method 3a: Instrument: Waters ACQUITY SQD UPLC System; column: Waters Acquity UPLC HSS T3 1.8 µ, 50 mm x 1 mm; mobile phase A: 1 L of water + 0.25 mL of 99% strength formic acid, mobile phase B: 1 L of acetonitrile + 0.25 mL of 99% strength formic acid; gradient: 0.0 min 95% A → 6.0 min 5% A → 7.5 min 5% A; oven: 50 °C; flow rate: 0.35 mL/min; UV detection: 210–400 nm.

Method 4a: MS instrument: Waters (Micromass) Quattro Micro; HPLC instrument: Agilent 1100 series; column: YMC-Triart C18 3 µ, 50 mm x 3 mm; mobile phase A: 1 L of water + 0.01 mol of ammonium carbonate, mobile phase B: 1 L of acetonitrile; gradient: 0.0 min 100% A → 2.75 min 5% A → 4.5 min 5% A; oven: 40 °C; flow rate: 1.25 mL/min; UV detection: 210 nm.

Method 5a: Instrument: Waters ACQUITY SQD UPLC System; column: Waters Acquity UPLC HSS T3 1.8 µ, 50 mm x 1 mm; mobile phase A: 1 L of water + 0.25 mL of 99% strength formic acid, mobile

phase B: 1 L of acetonitrile + 0.25 mL of 99% strength formic acid; gradient: 0.0 min 95% A → 6.0 min 5% A → 7.5 min 5% A; oven: 50 °C; flow rate: 0.35 mL/min; UV detection: 210–400 nm.

Method 6a: MS instrument: Micromass Quattro Premier; HPLC instrument: Waters UPLC Acquity; column: Thermo Hypersil GOLD 1.9 µ, 50 mm x 1 mm; mobile phase A: 1 L of water + 0.5 mL 50% strength formic acid, mobile phase B: 1 L of acetonitrile + 0.5 mL 50% strength formic acid; gradient: 0.0 min 90% A → 0.1 min 90% A → 1.5 min 10% A → 2.2 min 10% A; oven: 50 °C; flow rate: 0.33 mL/min; UV detection: 210 nm.

Method 7a: MS instrument: Waters ACQUITY SQD UPLC System; column: Waters Acquity UPLC HSS T3 1.8 µ, 50 mm x 1 mm; mobile phase A: 1 L of water + 0.25 mL of 99% strength formic acid, mobile phase B: 1 L of acetonitrile + 0.25 mL of 99% strength formic acid; gradient: 0.0 min 90% A → 1.2 min 5% A → 2.0 min 5% A; oven: 50 °C; flow rate: 0.40 mL/min; UV detection: 210–400 nm.

Method 8a: MS instrument: Waters SQD; HPLC instrument: Waters UPLC; column: Zorbax SB-Aq (Agilent) 1.8 µ, 50 mm x 2.1 mm; mobile phase A: water + 0.025% of 99% strength formic acid, mobile phase B: acetonitrile (ULC) + 0.025% of 99% strength formic acid; gradient: 0.0 min 98% A → 0.9 min 25% A → 1.0 min 5% A → 1.4 min 5% A → 1.41 min 98% A → 1.5 min 98% A; oven: 40 °C; flow rate: 0.60 mL/min; UV detection: DAD: 210 nm.

Method 9a: MS instrument: Waters ACQUITY SQD UPLC System; column: Waters Acquity UPLC HSS T3 1.8 µ, 30 mm x 2 mm; mobile phase A: 1 L of water + 0.25 mL of 99% strength formic acid, mobile phase B: 1 L of acetonitrile + 0.25 mL of 99% strength formic acid; gradient: 0.0 min 90% A → 1.2 min 5% A → 2.0 min 5% A; oven: 50 °C; flow rate: 0.60 mL/min; UV detection: 208–400 nm.

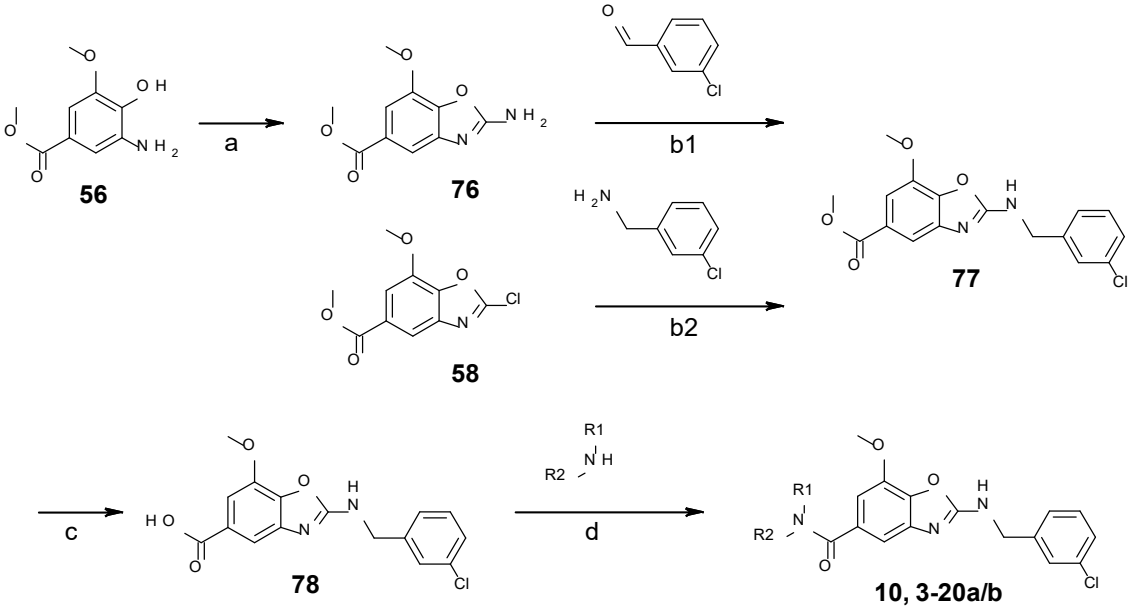
Method 10a: MS instrument: Micromass ZQ; HPLC instrument: Waters Alliance 2795; column: Phenomenex Synergi 2µ Hydro-RP Mercury, 20 mm x 4 mm; mobile phase A: 1 L of water + 0.5 mL of 50% strength formic acid, mobile phase B: 1 L of acetonitrile + 0.5 mL of 50% strength formic acid; gradient: 0.0 min 90% A → 2.5 min 30% A → 3.0 min 5% A → 4.5 min 5% A; flow rate: 0.0 min 1 mL/min, 2.5 min/3.0 min/4.5 min 2 mL/min; oven: 50 °C; UV detection: 210 nm.

Method 1b: Instrument: Micromass GCT, GC6890; column: Restek RTX-35, 15 m x 200 µm x 0.33 µm; constant helium flow rate: 0.88 mL/min; oven: 70 °C; inlet: 250 °C; gradient: 70 °C, 30 °C/min → 310 °C (maintain for 3 min).

Method 2b: Instrument: Thermo DFS, Trace GC Ultra; column: Restek RTX-35, 15 m x 200 µm x 0.33 µm; constant helium flow rate: 1.20 mL/min; oven: 60 °C; inlet: 220 °C; gradient: 60 °C, 30 °C/min → 300 °C (maintain for 3.33 min).

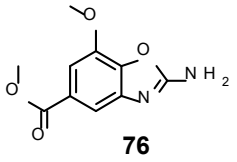
Method 1c: Instrument: Thermo Fisher-Scientific DSQ; chemical ionization; reactant gas: ammonia; source temperature: 200 °C; ionization energy 70 eV.

Synthesis of compounds 10, 13-20a/b



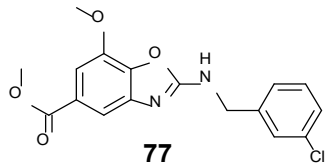
a) BrCN, DCM/MeOH, RT; b1) i) 3-chlorobenzaldehyde, DCM, RT, ii) Ti(O*i*-Pr)$_4$, RT, iii) $NaBH_4$, -10 °C to RT; b2) 3-chlorobenzylamine, DIEA, DMAP, DCM, 0 °C to RT; c) NaOH, 1,4-dioxane, RT; d) amine, TBTU, DIEA, DMSO, RT or amine, HATU, DIEA, DMF, RT or amine, (benzotriazol-1-yloxy)bisdimethyl-aminomethyliumfluoroborate, DIEA, DMSO, RT.

Methyl 2-amino-7-methoxy-1,3-benzoxazole-5-carboxylate (76).



Cyanic bromide solution in dichloromethane (3.0 M, 36.8 mL, 110.4 mmol, 1.01 equiv.) was added slowly within 10 min at room temperature to a solution of methyl 3-amino-4-hydroxy-5-methoxybenzoate (**56**) (21.5 g, 109.0 mmol) in a mixture of methanol (216 mL) and dichloromethane (37 mL). The reaction mixture was stirred at room temperature overnight. Additional cyanic bromide solution in dichloromethane (3.0 M, 3.7 mL, 11.0 mmol, 0.1 equiv.) was added. The reaction mixture was stirred at room temperature until full conversion was achieved. For workup, saturated aqueous sodium hydrogen carbonate solution (182 mL) was added dropwise at room temperature. The reaction mixture was stirred for about 30 min before all volatiles were removed under reduced pressure. The residue was mixed with water (300 mL) and the mixture stirred thoroughly. The forming precipitate was collected by filtration, washed with small volume of water and dried under vacuum to give **76** which was used without further purification. Yield: 22.3 g (92%). LC-MS (method 6a): t_R (min) = 0.76; MS (ESI+): m/z = 223 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ [ppm] = 7.61 (br s, 2H), 7.42 (d, *J* = 1.5 Hz, 1H), 7.28 (d, *J* = 1.5 Hz, 1H), 3.94 (s, 3H).

Methyl 2-[(3-chlorobenzyl)amino]-7-methoxy-1,3-benzoxazole-5-carboxylate (77).

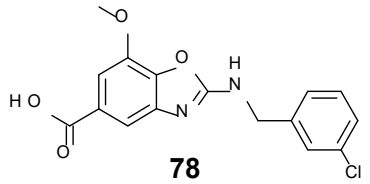


77

3-Chlorobenzaldehyde (19.7 mL, 168.8 mmol, 1.5 equiv.) was added under argon atmosphere at room temperature to a mixture of methyl 2-amino-7-methoxy-1,3-benzoxazole-5-carboxylate (**76**) (25.0 g, 112.5 mmol) in dichloromethane (878 mL) followed by addition of titanium(IV) tetraisopropanolate (66.4 mL, 225.0 mmol, 2.0 equiv.) within about 5 min. The reaction mixture was stirred at room temperature for 1 h and then cooled to -10 °C. Sodium borohydride (12.8 g, 337.5 mmol, 3.0 equiv.) was added in portions. The cooling bath was removed, and the reaction mixture stirred at room temperature overnight. For workup, water (25 mL) was added dropwise and cautiously (!), then additional water (200 mL) was added. The mixture was stirred at room temperature for 1 h before all volatiles were removed under reduced pressure. The residue was mixed with ethyl acetate (1 L) and water (200 mL). The remaining solids were filtered and washed with ethyl acetate (200 mL). All filtrates were combined, the aqueous phase was separated, and the organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was mixed with cyclohexane (400 mL) and stirred for 0.5 h. The solid was filtered, washed two times with cyclohexane and dried *in vacuo* to give **77** which was used without further purification. Yield: 35.2 g (75%, 83% purity). LC-MS (method 7a): t_R (min) = 1.08; MS (ESI+): m/z = 347 $[M+H]^+$.

Alternative synthesis of **77**: A solution of methyl 2-chloro-7-methoxy-1,3-benzoxazole-5-carboxylate (**58**) (10.1 g, 41.8 mmol) in dichloromethane (100 mL) was added under argon atmosphere at 0 °C within 15 min to a solution of 3-chlorobenzylamine (7.7 g, 54.3 mmol, 1.3 equiv.), *N,N*-diisopropylethylamine (21.8 mL, 125.4 mmol, 3.0 equiv.) and 4-dimethylaminopyridine (25.5 g, 0.21 mmol, 0.005 equiv.) in dichloromethane (100 mL). The reaction mixture was stirred at room temperature for 23 h and quenched with aqueous hydrochloric acid solution (0.5 M, 300 mL). After phase separation, the organic phase was washed two times with aqueous hydrochloric acid solution (0.5 M, 50 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: toluene / ethyl acetate 100:0 to 70:30) to give **77** which was used without further purification. Yield: 10.3 g (62%, 87% purity). LC-MS (method 1a): t_R (min) = 1.04; MS (ESI+): m/z = 347 $[M+H]^+$.

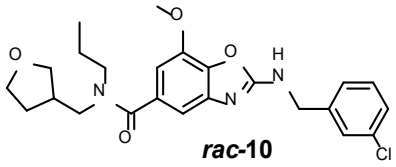
2-[(3-Chlorobenzyl)amino]-7-methoxy-1,3-benzoxazole-5-carboxylic acid (78).



78

A solution of sodium hydroxide (21.2 g, 529.8 mmol, 6.3 equiv.) in water (265 mL) was added at room temperature to a mixture of methyl 2-[(3-chlorobenzyl)amino]-7-methoxy-1,3-benzoxazole-5-carboxylate (**77**) (35.1 g, 83% purity, 84.0 mmol) in 1,4-dioxane (504 mL). The reaction mixture was stirred at room temperature for 20 h before all volatiles were removed under reduced pressure. The forming precipitate was filtered, suspended in water (500 mL), adjusted to pH 7 with concentrated hydrochloric acid solution (22 mL) and to pH 1.5 with 1 M hydrochloric acid solution. The precipitate was filtered, washed with some water and dried over sodium hydroxide *in vacuo* to give **78** which was used without further purification. Yield: 35.8 g (quantitative, 94% purity, might contain some sodium chloride). LC-MS (method 7a): t_R (min) = 0.92; MS (ESI+): m/z = 333 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 12.9 (br s, 1H), 8.73 (t, *J* = 6.1 Hz, 1H), 7.47-7.27 (m, 6H), 4.55 (d, *J* = 6.1 Hz, 2H), 3.94 (s, 3H).

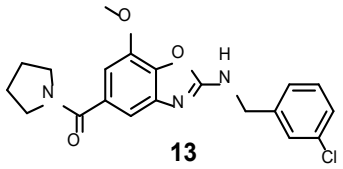
2-[(3-Chlorobenzyl)amino]-7-methoxy-*N*-propyl-*N*-(tetrahydrofuran-3-ylmethyl)-1,3-benzoxazole-5-carboxamide (10) as racemate.



***rac*-10**

TBTU (77.8 mg, 0.242 mmol, 1.3 equiv.) and *N,N*-diisopropylethylamine (65.0 µL, 0.373 mmol, 2.0 equiv.) were added to a solution of 2-[(3-chlorobenzyl)amino]-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**78**) (62.0 mg, 0.186 mmol) and *N*-(tetrahydrofuran-3-ylmethyl)propan-1-amine (26.7 mg, 0.186 mmol, 1.0 equiv.) in dimethyl sulfoxide (0.80 mL) and stirred at room temperature overnight. The reaction mixture was purified without further work-up by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient + 0.01% formic acid) to give **10**. Yield: 56 mg (65%). LC-MS (method 10a): t_R (min) = 2.17; MS (ESI+): m/z = 457 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.66 (t, *J* = 6.4 Hz, 1H), 7.44 (s, 1H), 7.41-7.30 (m, 3H), 6.80 (s, 1H), 6.63 (s, 1H), 4.53 (d, *J* = 6.4 Hz, 2H), 4.02-3.04 (m, 14H, partially concealed by water), 2.05-1.36 (m, 4H), 1.00-0.51 (m, 3H).

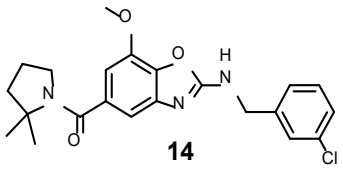
(2-{[(3-Chlorophenyl)methyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)(pyrrolidin-1-yl)methanone (13).



13

HATU (228 mg, 0.60 mmol, 1.2 equiv.) and *N,N*-diisopropylethylamine (192 µL, 1.10 mmol, 2.2 equiv.) were added to a solution of 2-[(3-chlorobenzyl)amino]-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**78**) (166 mg, 0.50 mmol) in *N,N*-dimethylformamide (5 mL) and stirred at room temperature for 30 min before pyrrolidine (39 mg, 0.55 mmol, 1.1 equiv.) was added. The reaction mixture was stirred for 1 h and, without further work-up, purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **13**. Yield: 143 mg (74%). LC-MS (method 6a): t_R (min) = 1.14; MS (ESI+): m/z = 386 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.62 (t, *J* = 6.1 Hz, 1H), 7.45-7.31 (m, 4H), 6.99 (d, *J* = 1.2 Hz, 1H), 6.83 (d, *J* = 1.2 Hz, 1H), 4.53 (d, *J* = 6.1 Hz, 2H), 3.91 (s, 3H), 3.49-3.37 (m, 4H), 1.91-1.73 (m, 4H).

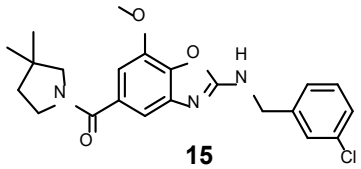
(2-{[(3-Chlorophenyl)methyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)(2,2-dimethylpyrrolidin-1-yl)methanone (14).



14

A solution of 2-{[(3-chlorophenyl)methyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**78**) (33 mg, 0.10 mmol) in dimethyl sulfoxide (400 µL), a solution of (benzotriazol-1-yloxy)bisdimethyl-aminomethyliumfluoroborate (42 mg, 0.13 mmol, 1.3 equiv.) in dimethyl sulfoxide (200 µL) and *N,N*-diisopropylethylamine (26 mg, 0.20 mmol, 2.0 equiv.) were subsequently added to 2,2-dimethylpyrrolidine hydrochloride (16 mg, 0.12 mmol, 1.2 equiv.). The reaction mixture was stirred at room temperature overnight and, without further work-up, purified by preparative LC-MS (reversed phase, eluent: acetonitrile / water gradient) to give **14**. Yield: 14 mg (33%). LC-MS (method 8a): t_R (min) = 1.19; MS (ESI+): m/z = 414 $[M+H]^+$.

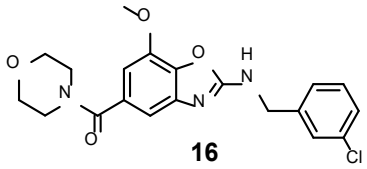
(2-{[(3-Chlorophenyl)methyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)(3,3-dimethylpyrrolidin-1-yl)methanone (15).



15

N,N-Diisopropylethylamine (105 µL, 0.60 mmol, 3.0 equiv.) was added at room temperature to a solution of 2-{[(3-chlorophenyl)methyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**78**) (67 mg, 0.20 mmol) and HATU (91 mg, 0.24 mmol, 1.2 equiv.) in *N,N*-dimethylformamide (5 mL) and stirred at room temperature for 15 min before 3,3-dimethylpyrrolidine (79 mg, 30% purity, 0.24 mmol, 1.2 equiv.) was added. The reaction mixture was stirred at room temperature overnight and evaporated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **15**. Yield: 25 mg (29%). LC-MS (method 1a): t_R (min) = 1.11; MS (ESI+): m/z = 414 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.63 (t, *J* = 6.1 Hz, 1H), 7.44-7.30 (m, 4H), 7.02 / 6.96 (2x s, 1H), 6.81 / 6.83 (2x s, 1H), 4.53 (d, *J* = 5.9 Hz, 2H), 3.57-3.44 (m, 2H), 3.22 / 3.16 (2x s, 2H), 1.71-1.58 (m, 2H), 1.10 (s, 3H), 0.96 (s, 3H).

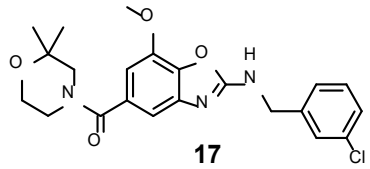
(2-{[(3-Chlorophenyl)methyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)(morpholin-4-yl)methanone (16).



16

HATU (91 mg, 0.24 mmol, 1.2 equiv.) and *N,N*-diisopropylethylamine (77 µL, 0.44 mmol, 2.2 equiv.) were added to a solution of 2-[(3-chlorobenzyl)amino]-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**78**) (67 mg, 0.20 mmol) in *N,N*-dimethylformamide (2 mL) and stirred at room temperature for 20 min before morpholine (21 µL, 0.24 mmol, 1.2 equiv.) was added. The reaction mixture was stirred at room temperature overnight and evaporated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **16**. Yield: 60 mg (75%). LC-MS (method 7a): t_R (min) = 0.93; MS (ESI+): m/z = 402 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.65 (br s, 1H), 7.45-7.30 (m, 4H), 6.38 (s, 1H), 6.73 (s, 1H), 4.53 (br s, 2H), 3.91 (s, 3H), 3.68-3.38 (m, 8H).

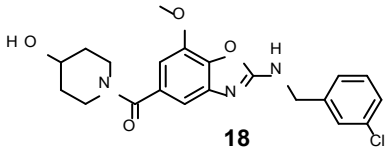
(2-{[(3-Chlorophenyl)methyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)(2,2-dimethylmorpholin-4-yl)methanone (17).



17

HATU (68 mg, 0.18 mmol, 1.2 equiv.) and *N,N*-diisopropylethylamine (84 µL, 0.48 mmol, 3.2 equiv.) were added to a solution of 2-[(3-chlorobenzyl)amino]-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**78**) (50 mg, 0.15 mmol) in *N,N*-dimethylformamide (1.5 mL) and stirred at room temperature for 30 min before 2,2-dimethylmorpholine hydrochloride (25 mg, 0.17 mmol, 1.1 equiv.) was added. The reaction mixture was stirred at room temperature for 1 h and, without further work-up, purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **17**. Yield: 48 mg (74%). LC-MS (method 1a): t_R (min) = 1.01; MS (ESI+): m/z = 430 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.66 (t, *J* = 6.1 Hz, 1H), 7.45-7.30 (m, 4H), 6.86 (br s, 1H), 6.71 (s, 1H), 4.53 (d, *J* = 6.1 Hz, 2H), 3.91 (s, 3H), 3.70-3.08 (m, 6H, partially concealed by DMSO), 1.12 (br s, 6H).

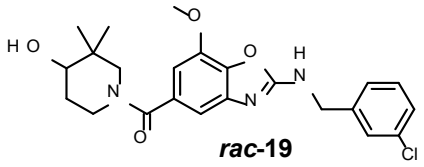
(2-{[(3-Chlorophenyl)methyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)(4-hydroxypiperidin-1-yl)methanone (18).



18

HATU (91 mg, 0.24 mmol, 1.2 equiv.) and *N,N*-diisopropylethylamine (77 µL, 0.44 mmol, 2.2 equiv.) were added to a solution of 2-[(3-chlorobenzyl)amino]-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**78**) (67 mg, 0.20 mmol) in *N,N*-dimethylformamide (4 mL) and stirred at room temperature for 30 min before piperidin-4-ol (24 mg, 0.24 mmol, 1.2 equiv.) was added. The reaction mixture was stirred at room temperature for 2 h and evaporated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **18**. Yield: 76 mg (91%). LC-MS (method 7a): t_R (min) = 0.84; MS (ESI+): m/z = 416 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.64 (t, *J* = 6.1 Hz, 1H), 7.45-7.30 (m, 4H), 6.83 (d, *J* = 1.0 Hz, 1H), 6.69 (s, 1H), 4.77 (d, *J* = 3.9 Hz, 1H), 4.53 (d, *J* = 6.1 Hz, 2H), 4.08-3.33 (m, 1H, partially concealed), 3.90 (s, 3H), 3.78-3.66 (m, 1H), 3.64-3.41 (m, 1H), 3.25-3.04 (m, 2H), 1.85-1.60 (m, 2H), 1.46-1.22 (m, 2H).

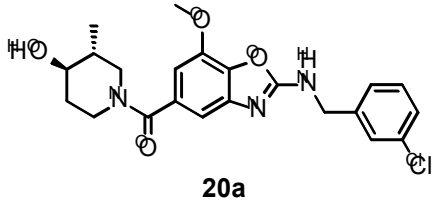
(2-{[(3-Chlorophenyl)methyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[(4*R*)-4-hydroxy-3,3-dimethylpiperidin-1-yl]methanone (19) as racemate.



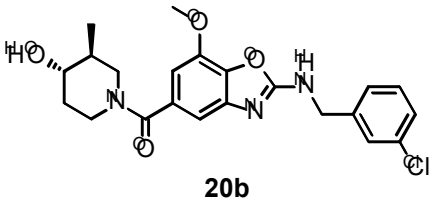
***rac*-19**

HATU (78 mg, 0.21 mmol, 1.2 equiv.) and *N,N*-diisopropylethylamine (96 µL, 0.55 mmol, 3.2 equiv.) were added to a solution of 2-[(3-chlorobenzyl)amino]-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**78**) (57 mg, 0.17 mmol) in *N,N*-dimethylformamide (3 mL) and stirred at room temperature for 30 min before 3,3-dimethylpiperidin-4-ol trifluoroacetate (46 mg, 0.19 mmol, 1.1 equiv.) was added. The reaction mixture was stirred at room temperature for 1.5 h and evaporated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **19**. Yield: 48 mg (74%). LC-MS (method 6a): t_R (min) = 1.07; MS (ESI+): m/z = 444 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.64 (t, *J* = 6.1 Hz, 1H), 7.46-7.30 (m, 4H), 6.81 (s, 1H), 6.66 (s, 1H), 4.71 (d, *J* = 4.7 Hz, 1H), 4.53 (d, *J* = 6.1 Hz, 2H), 4.11-3.96 / 3.83-3.68 / 3.62-3.42 / 3.23-3.06 / 2.98-2.82 (5x m, 5H), 3.90 (s, 3H), 1.73-1.54 (m, 1H), 1.51-1.36 (m, 1H), 1.05-0.59 (m, 6H).

{2-[(3-Chlorobenzyl)amino]-7-methoxy-1,3-benzoxazol-5-yl}[(*3R*,*4R*)-4-hydroxy-3-methylpiperidin-1-yl]methanone (20a) and {2-[(3-chlorobenzyl)amino]-7-methoxy-1,3-benzoxazol-5-yl}[(3*S*,4*S*)-4-hydroxy-3-methylpiperidin-1-yl]methanone (20b).



20a



20b

HATU (495 mg, 1.30 mmol, 1.2 equiv.) and *N,N*-diisopropylethylamine (416 µL, 2.39 mmol, 2.2 equiv.) were added to a solution of 2-[(3-chlorobenzyl)amino]-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**78**) (361 mg, 1.09 mmol) in *N,N*-dimethylformamide (10 mL) and stirred at room temperature for 30 min before 3-methylpiperidin-4-ol (150 mg, 1.30 mmol, 1.2 equiv.) was added. The reaction mixture was stirred at room temperature for 1.5 h and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: dichloromethane / methanol 100:2 to 100:4) to give **20a** and **20b** as a racemic mixture of diastereomers. Yield: 424 mg (84%).

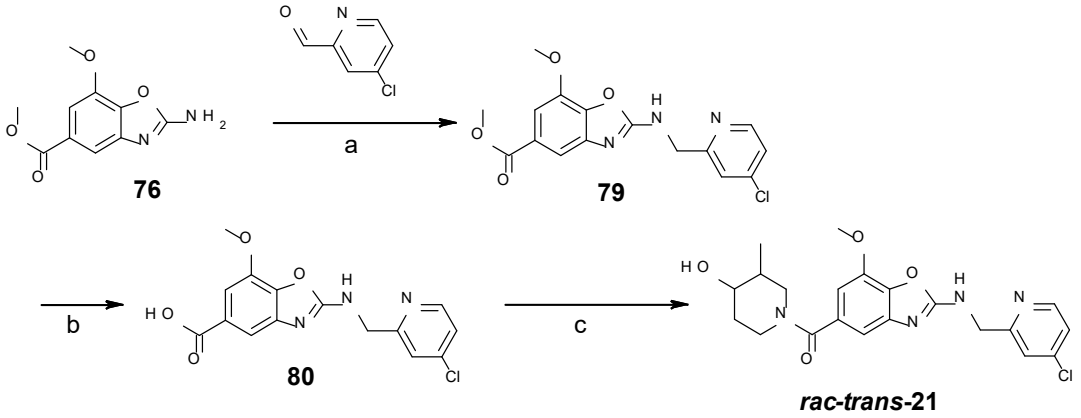
This mixture (424 mg) was submitted for stereoisomer separation (preparative method: HPLC: column: Daicel Chiralpak AD-H 5 µm, 250 mm x 20 mm; eluent: 50% *iso*-hexane / 50% ethanol; temperature: 40 °C; flow rate: 15 mL/min; UV detection: 220 nm) and gave four stereoisomers (analytical method: HPLC: column: Daicel Chiralpak AD-H 5 µm, 250 mm x 4.6 mm; eluent: 50% *iso*-hexane / 50%

ethanol; temperature: 40 °C; flow rate: 1 mL/min; UV detection: 220 nm) to give diastereomer 1: 109 mg (26%), HPLC: t_R (min) = 5.62, >99% ee; *ent*-diastereomer 1: 134 mg (32%), HPLC: t_R (min) = 7.58, >98% ee; diastereomer 2: 53 mg (13%), HPLC: t_R (min) = 6.16, >99% ee; *ent*-diastereomer 2: 54 mg (13%), HPLC: t_R (min) = 6.90, >99% ee.

ent-Diastereomer 1 (HPLC: t_R (min) = 7.58, >98% ee) corresponds to the desired stereoisomer **20a**. LC-MS (method 1a): t_R (min) = 0.84; MS (ESI+): m/z = 430 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.64 (br s, 1H), 7.46-7.30 (m, 4H), 6.82 (d, *J* = 1.2 Hz, 1H), 6.68 (s, 1H), 4.76 (d, *J* = 5.1 Hz, 1H), 4.53 (br s, 2H), 4.40-4.13 (m, 1H), 3.90 (s, 3H), 3.66-3.44 (m, 1H), 3.25-3.13 (m, 2H), 3.11-2.82 (m, 1H), 1.92-1.65 (m, 1H), 1.49-1.20 (m, 2H), 1.06-0.70 (m, 3H).

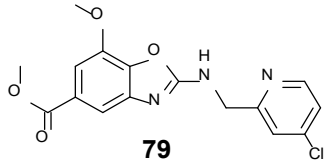
Diastereomer 1 (HPLC: t_R (min) = 5.62, >99% ee) corresponds to the stereoisomer **20b**. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.64 (t, *J* = 6.1 Hz, 1H), 7.46-7.30 (m, 4H), 6.82 (d, *J* = 1.2 Hz, 1H), 6.68 (s, 1H), 4.76 (d, *J* = 5.1 Hz, 1H), 4.53 (d, *J* = 6.1 Hz, 2H), 4.40-4.12 (m, 1H), 3.90 (s, 3H), 3.67-3.44 (m, 1H), 3.24-3.13 (m, 2H), 3.10-2.83 (m, 1H), 1.91-1.66 (m, 1H), 1.49-1.21 (m, 2H), 1.02-0.68 (m, 3H).

(2-{[(4-Chloropyridin-2-yl)methyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[4-hydroxy-3-methylpiperidin-1-yl]methanone (21) as mixture of *rac-trans* stereoisomers.



a) i) 4-chloropyridine-2-carbaldehyde, Ti(O*i*-Pr)$_4$, DCM, RT, ii) NaCNBH$_3$, RT; b) LiOH, THF/water, RT; c) *rac-trans*-3-methylpiperidin-4-ol hydrochloride, HATU, DIEA, DMF, RT.

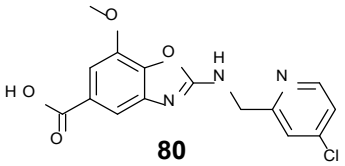
Methyl 2-{[(4-chloropyridin-2-yl)methyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylate (79).



Titanium(IV) tetrapropanolate (664 µL, 2.25 mmol, 2.0 equiv.) was added under argon atmosphere at room temperature to a mixture of methyl 2-amino-7-methoxy-1,3-benzoxazole-5-carboxylate (**76**) (250 mg, 1.13 mmol) and 4-chloropyridine-2-carbaldehyde (478 mg, 3.38 mmol, 3.0 equiv.) in

dichloromethane (8.5 mL). The reaction mixture was stirred at room temperature overnight, followed by addition of sodium cyanoborohydride (283 mg, 4.50 mmol, 4.0 equiv.) at room temperature. The reaction mixture was stirred for another 3 h, mixed with some water and evaporated under reduced pressure. The residue was suspended in a mixture of ethyl acetate and water. The solid was filtered, washed with ethyl acetate and dried *in vacuo*. Yield: 156 mg (13%, 32% purity). The combined filtrates were evaporated under reduced pressure and suspended in a mixture of methanol and water. The solid was filtered and dried *in vacuo* to give **79** which was used without further purification. Yield: 128 mg (21%, 64% purity).

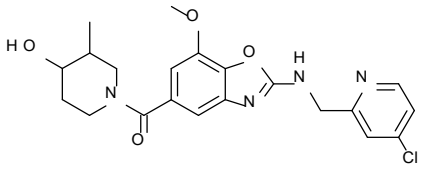
2-{[(4-Chloropyridin-2-yl)methyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (80).



80

Lithium hydroxide (17 mg, 0.71 mmol, 3.0 equiv.) was added at room temperature to methyl 2-{[(4-chloropyridin-2-yl)methyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylate (**79**) (128 mg, 64% purity, 0.24 mmol) in a mixture of tetrahydrofuran and water (3:1, 3.5 mL). The reaction mixture was stirred at room temperature overnight before additional lithium hydroxide (6 mg, 0.24 mmol, 1.0 equiv.) was added. After stirring for another 3 h, aqueous hydrochloric acid solution (1 N) was added. The forming precipitate was filtered and dried *in vacuo*. Yield: 39 mg (29%, 59% purity). The filtrate was evaporated under reduced pressure and the residue purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **80**. Yield: 52 mg (67%). LC-MS (method 1a): t_R (min) = 0.72; MS (ESI+): m/z = 334 $[M+H]^+$.

(2-{[(4-Chloropyridin-2-yl)methyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[4-hydroxy-3-methylpiperidin-1-yl]methanone (21) as mixture of *rac-trans* stereoisomers.

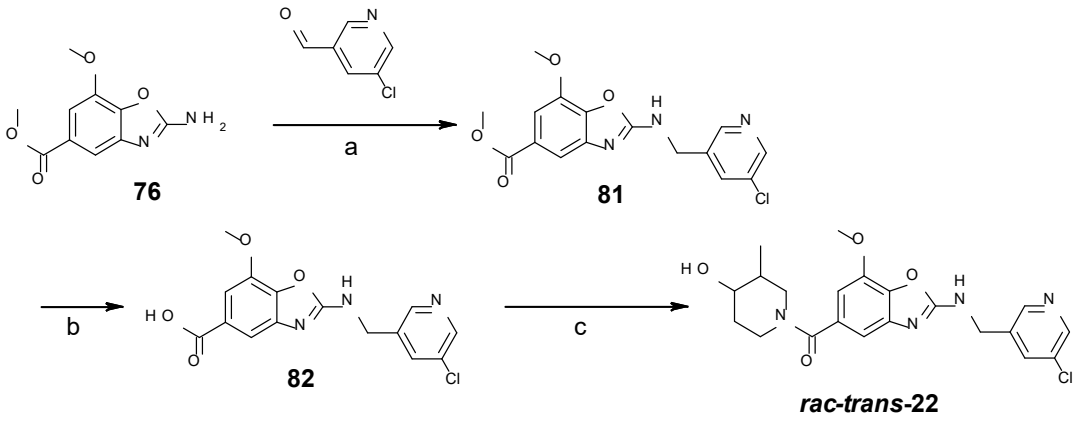


***rac-trans*-21**

HATU (72 mg, 0.19 mmol, 1.2 equiv.) and *N,N*-diisopropylethylamine (87 µL, 0.50 mmol, 3.2 equiv.) were added to a solution of 2-{[(4-chloropyridin-2-yl)methyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**80**) (52 mg, 0.16 mmol) in *N,N*-dimethylformamide (1.5 mL) and stirred at room temperature for 20 min before *rac-trans*-3-methylpiperidin-4-ol hydrochloride (29 mg, 0.19 mmol, 1.2 equiv.) was added. The reaction mixture was stirred at room temperature overnight and evaporated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent:

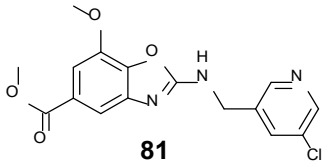
acetonitrile / water gradient) to give **21** as mixture of *rac-trans* stereoisomers. Yield: 16 mg (24%). LC-MS (method 7a): t_R (min) = 0.75; MS (ESI+): m/z = 431 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.69 (t, *J* = 5.9 Hz, 1H), 8.51 (d, *J* = 5.4 Hz, 1H), 7.52 (d, *J* = 1.7 Hz, 1H), 7.45 (dd, *J* = 5.4, 1.9 Hz, 1H), 6.81 (s, 1H), 6.69 (s, 1H), 4.76 (d, *J* = 5.1 Hz, 1H), 4.63 (d, *J* = 5.9 Hz, 2H), 4.41-4.06 (m, 1H), 3.91 (s, 3H), 3.69-3.38 (m, 1H), 3.23-3.12 (m, 2H), 3.10-2.82 (m, 1H), 1.90-1.67 (m, 1H), 1.47-1.21 (m, 2H), 1.04-0.70 (m, 3H).

(2-{[(5-Chloropyridin-3-yl)methyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[4-hydroxy-3-methylpiperidin-1-yl]methanone (22) as mixture of *rac-trans* stereoisomers.



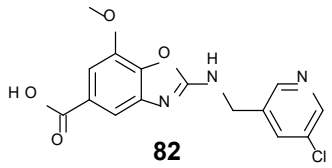
a) i) 5-chloropyridine-3-carbaldehyde, Ti(O*i*-Pr)$_4$, DCM, RT, ii) NaCNBH$_3$, RT; b) LiOH, THF/water, RT; c) *rac-trans*-3-methylpiperidin-4-ol hydrochloride, HATU, DIEA, DMF, RT.

Methyl 2-{[(5-chloropyridin-3-yl)methyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylate (81).



Titanium(IV) tetrapropanolate (411 µL, 1.39 mmol, 2.0 equiv.) was added under argon atmosphere at room temperature to a mixture of methyl 2-amino-7-methoxy-1,3-benzoxazole-5-carboxylate (**76**) (155 mg, 0.70 mmol) and 5-chloropyridine-3-carbaldehyde (148 mg, 1.05 mmol, 1.5 equiv.) in dichloromethane (5.5 mL). The reaction mixture was stirred at room temperature overnight, followed by addition of sodium cyanoborohydride (66 mg, 1.05 mmol, 1.5 equiv.) at room temperature. The reaction mixture was stirred for another 3 h and evaporated under reduced pressure. The residue was suspended in a mixture of ethyl acetate and water and the solid filtered off. After phase separation, the aqueous phase was extracted two times with ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered, evaporated under reduced pressure and dried *in vacuo* to give **81** which was used without further purification. Yield: 193 mg (35%, 44% purity). LC-MS (method 1a): t_R (min) = 0.86; MS (ESI+): m/z = 348 $[M+H]^+$.

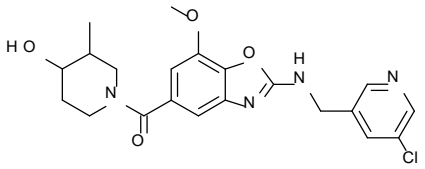
2-{[(5-Chloropyridin-3-yl)methyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (82).



82

Lithium hydroxide (18 mg, 0.73 mmol, 3.0 equiv.) was added at room temperature to methyl 2-{[(5-chloropyridin-3-yl)methyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylate (**81**) (193 mg, 44% purity, 0.25 mmol) in a mixture of tetrahydrofuran and water (3:1, 3.0 mL). The reaction mixture was stirred at room temperature overnight before additional lithium hydroxide (18 mg, 0.73 mmol, 3.0 equiv.) was added. After stirring at 35 °C (water bath) overnight, aqueous hydrochloric acid solution (1 N) was added. The mixture was evaporated under reduced pressure to give **82** which was used without further purification. Yield: 253 mg (>100%, 67% purity). LC-MS (method 1a): t_R (min) = 0.71; MS (ESI+): m/z = 334 $[M+H]^+$.

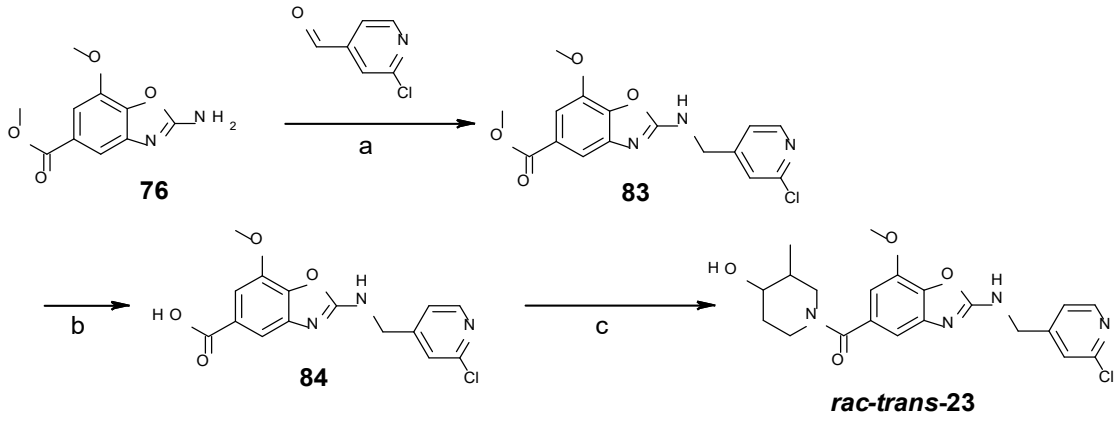
(2-{[(5-Chloropyridin-3-yl)methyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[4-hydroxy-3-methylpiperidin-1-yl]methanone (22) as mixture of *rac-trans* stereoisomers.



***rac-trans*-22**

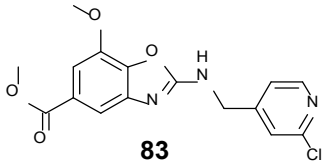
HATU (91 mg, 0.24 mmol, 1.2 equiv.) and *N,N*-diisopropylethylamine (111 µL, 0.64 mmol, 3.2 equiv.) were added to a solution of 2-{[(5-chloropyridin-3-yl)methyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**82**) (100 mg, 67% purity, 0.20 mmol) in *N,N*-dimethylformamide (2.0 mL) and stirred at room temperature for 20 min before *rac-trans*-3-methylpiperidin-4-ol hydrochloride (33 mg, 0.22 mmol, 1.1 equiv.) was added. The reaction mixture was stirred at room temperature overnight and evaporated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **22** as mixture of *rac-trans* stereoisomers. Yield: 17 mg (20%). LC-MS (method 1a): t_R (min) = 0.69; MS (ESI+): m/z = 431 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.65 (t, *J* = 6.1 Hz, 1H), 8.57 (d, *J* = 1.5 Hz, 1H), 8.55 (d, *J* = 2.5 Hz, 1H), 7.93 (s, 1H), 6.84 (d, *J* = 1.0 Hz, 1H), 6.70 (s, 1H), 4.76 (d, *J* = 5.4 Hz, 1H), 4.58 (d, *J* = 5.6 Hz, 2H), 4.38-4.11 (m, 1H), 3.90 (s, 3H), 3.68-3.42 (m, 1H), 3.23-3.14 (m, 1H), 3.11-2.82 (m, 1H), 2.80-2.55 (m, 1H, partially concealed), 1.89-1.67 (m, 1H), 1.46-1.21 (m, 1H), 1.04-0.70 (m, 3H).

(2-{[(2-Chloropyridin-4-yl)methyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)(4-hydroxy-3-methylpiperidin-1-yl)methanone (23) as mixture of *rac-trans* stereoisomers.



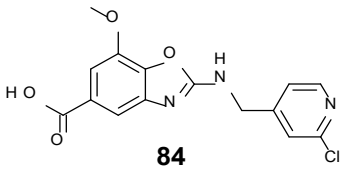
a) i) 2-chloropyridine-4-carbaldehyde, Ti(O*i*-Pr)$_4$, DCM, RT, ii) $NaBH_4$, RT; b) LiOH, THF/water, RT; c) *rac-trans*-3-methylpiperidin-4-ol, HATU, DIEA, DMF, RT.

Methyl 2-{[(2-chloropyridin-4-yl)methyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylate (83).



Titanium(IV) tetrapropanolate (19.6 mL, 68.1 mmol, 2.0 equiv.) was added under argon atmosphere at room temperature to a mixture of methyl 2-amino-7-methoxy-1,3-benzoxazole-5-carboxylate (**76**) (7.56 g, 34.0 mmol) and 2-chloropyridine-4-carbaldehyde (5.30 g, 37.4 mmol, 1.1 equiv.) in dichloromethane (500 mL). The reaction mixture was stirred at room temperature for 4 h, followed by addition of sodium borohydride (2.58 g, 68.1 mmol, 2.0 equiv.) at room temperature. The reaction mixture was stirred overnight and then water was added. The reaction mixture was filtered over Celite® and the filter cake was washed with dichloromethane. After phase separation, the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **83**. Yield: 660 mg (6%). LC-MS (method 9a): t_R (min) = 0.89; MS (ESI+): m/z = 348 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.84 (t, *J* = 6.0 Hz, 1H), 8.37 (d, *J* = 5.1 Hz, 1H), 7.51 (s, 1H), 7.45 (s, 1H), 7.41 (d, *J* = 5.1 Hz, 1H), 7.32 (s, 1H), 4.60 (d, *J* = 5.9 Hz, 2H), 3.96 (s, 3H), 3.84 (s, 3H).

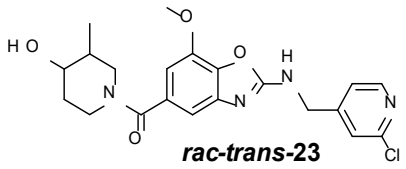
2-{[(2-Chloropyridin-4-yl)methyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (84).



84

Lithium hydroxide (114 mg, 4.7 mmol, 2.5 equiv.) was added at room temperature to methyl 2-{[(2-chloropyridin-4-yl)methyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylate (**83**) (660 mg, 1.90 mmol) in a mixture of tetrahydrofuran and water (2:1, 37.5 mL). The reaction mixture was stirred at room temperature overnight before the reaction mixture was neutralized with aqueous hydrochloric acid solution (1 N). After extraction with ethyl acetate, the organic phase was washed with brine and dried over sodium sulfate. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **84**. Yield: 420 mg (66%). LC-MS (method 7a): t_R (min) = 0.76; MS (ESI+): m/z = 334 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 12.87 (br s, 1H), 8.80 (br t, *J* = 5.9 Hz, 1H), 8.37 (d, *J* = 4.9 Hz, 1H), 7.50 (s, 1H), 7.37-7.46 (m, 2H), 7.32 (s, 1H), 4.60 (br d, *J* = 5.4 Hz, 2H), 3.95 (s, 3H), 3.34 (br s, 3H).

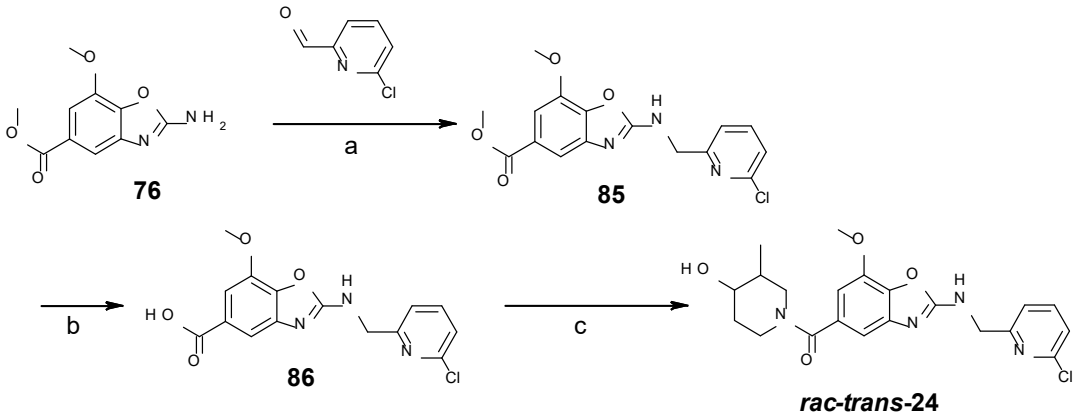
(2-{[(2-Chloropyridin-4-yl)methyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[4-hydroxy-3-methylpiperidin-1-yl]methanone (23) as mixture of *rac-trans* stereoisomers.



***rac-trans*-23**

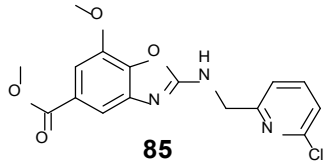
HATU (205 mg, 0.54 mmol, 1.2 equiv.) and *N,N*-diisopropylethylamine (172 µL, 0.99 mmol, 2.2 equiv.) were added to a solution of 2-{[(2-chloropyridin-4-yl)methyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**84**) (150 mg, 0.45 mmol) in *N,N*-dimethylformamide (3.7 mL) and stirred at room temperature for 30 min before *rac-trans*-3-methylpiperidin-4-ol (57 mg, 0.49 mmol, 1.1 equiv.) was added. The reaction mixture was stirred at room temperature for 1 h and then poured into water. After extraction with dichloromethane, the organic phase was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **23** as mixture of *rac-trans* stereoisomers. Yield: 100 mg (51%). LC-MS (method 7a): t_R (min) = 0.74; MS (ESI+): m/z = 431 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.73 (t, *J* = 6.2 Hz, 1H), 8.37 (d, *J* = 5.1 Hz, 1H), 7.49 (s, 1H), 7.40 (d, *J* = 5.1 Hz, 1H), 6.82 (s, 1H), 6.70 (s, 1H), 4.59 (d, *J* = 6.1 Hz, 2H), 4.12-4.40 (br m, 1H), 3.91 (s, 3H), 3.25-3.67 (br m, 3H, partially concealed), 3.18 (dt, *J* = 4.0, 9.4 Hz, 1H), 2.80-3.08 (br m, 1H), 1.63-1.92 (br m, 1H), 1.17-1.50 (m, 2H), 0.65-1.07 (m, 3H).

(2-{[(6-Chloropyridin-2-yl)methyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)(4-hydroxy-3-methylpiperidin-1-yl)methanone (24) as mixture of *rac-trans* stereoisomers.



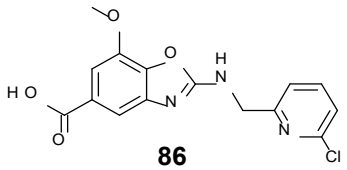
a) i) 6-chloropyridine-2-carbaldehyde, Ti(O*i*-Pr)$_4$, DCM, RT, ii) NaCNBH$_3$, RT; b) LiOH, THF/water, RT; c) *rac-trans*-3-methylpiperidin-4-ol, HATU, DIEA, DMF, RT.

Methyl 2-{[(6-chloropyridin-2-yl)methyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylate (85).



Titanium(IV) tetrapropanolate (3.36 mL, 11.7 mmol, 2.0 equiv.) was added under argon atmosphere at room temperature to a mixture of methyl 2-amino-7-methoxy-1,3-benzoxazole-5-carboxylate (**76**) (1.30 g, 5.84 mmol) and 6-chloropyridine-2-carbaldehyde (910 mg, 6.43 mmol, 1.1 equiv.) in dichloromethane (150 mL). The reaction mixture was stirred at room temperature for 4 h, followed by addition of sodium cyanoborohydride (735 mg, 11.7 mmol, 2.0 equiv.) at room temperature. The reaction mixture was stirred overnight and then water was added. The reaction mixture was filtered over Celite® and the filter cake was washed with dichloromethane. After phase separation, the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was triturated with acetonitrile, filtered under reduced pressure and the solid was dried under high vacuum to give **85**. Yield: 560 mg (25%, 89% purity). The mother liquor was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give another amount of **85**. Yield: 180 mg (9%, 94% purity). LC-MS (method 7a): t_R (min) = 0.95; MS (ESI+): m/z = 348 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.88 (t, *J* = 6.1 Hz, 1H), 7.85 (t, *J* = 7.8 Hz, 1H), 7.40-7.48 (m, 3H), 7.31 (s, 1H), 4.60 (d, *J* = 6.1 Hz, 2H), 3.95 (s, 3H), 3.84 (s, 3H).

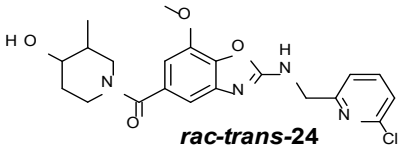
2-{[(6-Chloropyridin-4-yl)methyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (86).



86

Lithium hydroxide (120 mg, 5.0 mmol, 2.5 equiv.) was added at room temperature to methyl 2-{[(6-chloropyridin-2-yl)methyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylate (**85**) (695 mg, 2.00 mmol) in a mixture of tetrahydrofuran and water (2:1, 39.6 mL). The reaction mixture was stirred at room temperature overnight before the reaction mixture was neutralized with aqueous hydrochloric acid solution (1 N). After extraction with ethyl acetate, the organic phase was washed with brine and dried over sodium sulfate. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **86**. Yield: 375 mg (55%). LC-MS (method 6a): t_R (min) = 1.77; MS (ESI+): m/z = 334 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 12.9 (br s, 1H), 8.84 (t, *J* = 6.2 Hz, 1H), 7.85 (t, *J* = 7.8 Hz, 1H), 7.39-7.46 (m, 3H), 7.31 (d, *J* = 0.98 Hz, 1H), 4.60 (d, *J* = 5.9 Hz, 2H), 3.94 (s, 3H), 3.34 (s, 4H).

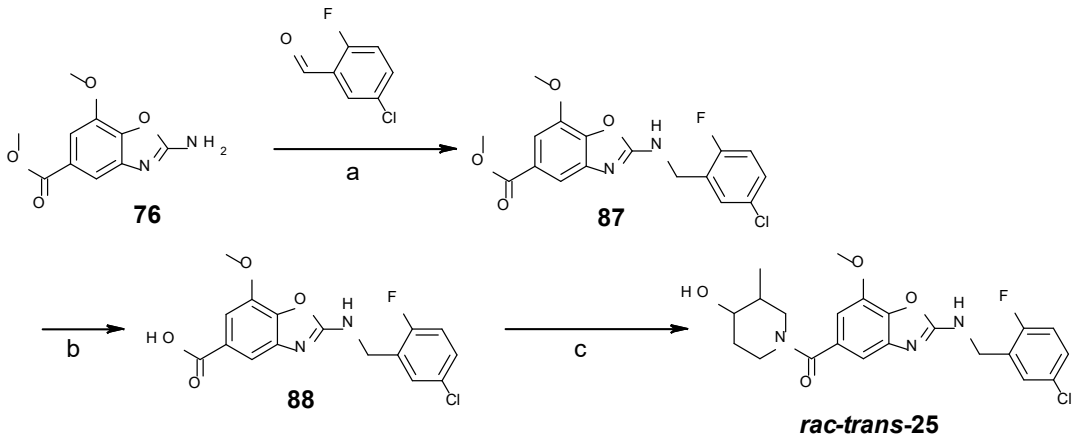
(2-{[(6-Chloropyridin-2-yl)methyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[4-hydroxy-3-methylpiperidin-1-yl]methanone (24) as mixture of *rac-trans* stereoisomers.



***rac-trans*-24**

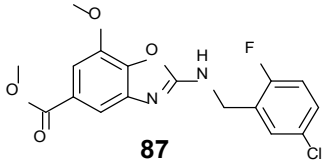
HATU (124 mg, 0.33 mmol, 1.2 equiv.) and *N,N*-diisopropylethylamine (190 µL, 1.1 mmol, 4.0 equiv.) were added to a solution of 2-{[(6-chloropyridin-2-yl)methyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**86**) (100 mg, 0.30 mmol, 1.1 equiv.) in *N,N*-dimethylformamide (1.5 mL) and stirred at room temperature for 30 min before *rac-trans*-3-methylpiperidin-4-ol (31 mg, 0.27 mmol) was added. The reaction mixture was stirred at room temperature overnight. The reaction mixture was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **24** as mixture of *rac-trans* stereoisomers. Yield: 68 mg (52%). LC-MS (method 6a): t_R (min) = 1.73; MS (ESI+): m/z = 431 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.77 (t, *J* = 6.2 Hz, 1H), 7.85 (t, *J* = 7.7 Hz, 1H), 7.43 (s, 1H), 7.41 (s, 1H), 6.81 (s, 1H), 6.69 (s, 1H), 4.59 (br d, *J* = 5.9 Hz, 2H), 4.12-4.37 (br m, 1H), 3.91 (s, 3H), 3.29-3.62 (br m, 3H), 3.18 (dt, *J* = 4.3, 9.4 Hz, 1H), 2.81-3.09 (br m, 1H), 1.67-1.92 (m, 1H), 1.23-1.48 (br m, 2H), 0.70-1.02 (br m, 3H).

{2-[(5-Chloro-2-fluorobenzyl)amino]-7-methoxy-1,3-benzoxazol-5-yl}[4-hydroxy-3-methylpiperidin-1-yl]methanone (25) as mixture of *rac-trans* stereoisomers.



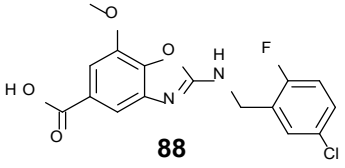
a) i) 5-chloro-2-fluorobenzaldehyde, Ti(O*i*-Pr)$_4$, DCM, RT, ii) NaCNBH$_3$, RT; b) LiOH, THF/water, RT; c) *rac-trans*-3-methylpiperidin-4-ol hydrochloride, HATU, DIEA, DMF, RT.

Methyl 2-[(5-chloro-2-fluorobenzyl)amino]-7-methoxy-1,3-benzoxazole-5-carboxylate (87).



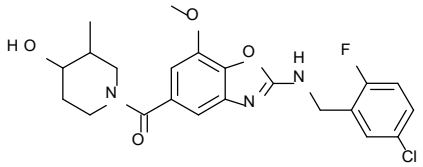
Titanium(IV) tetrapropanolate (717 µL, 2.43 mmol, 2.0 equiv.) was added under argon atmosphere at room temperature to a mixture of methyl 2-amino-7-methoxy-1,3-benzoxazole-5-carboxylate (**76**) (270 mg, 1.22 mmol) and 5-chloro-2-fluorobenzaldehyde (289 mg, 1.82 mmol, 1.5 equiv.) in dichloromethane (10 mL). The reaction mixture was stirred at room temperature overnight, followed by addition of sodium cyanoborohydride (115 mg, 1.82 mmol, 1.5 equiv.) at room temperature. The reaction mixture was stirred for another 3 h and evaporated under reduced pressure. The residue was suspended in a mixture of ethyl acetate and water and the solid filtered off. After phase separation, the aqueous phase was extracted two times with ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered, evaporated under reduced pressure and dried *in vacuo* to give **87** which was used without further purification. Yield: 463 mg (59%, 56% purity).

2-[(5-Chloro-2-fluorobenzyl)amino]-7-methoxy-1,3-benzoxazole-5-carboxylic acid (88).



Lithium hydroxide (68 mg, 2.84 mmol, 4.0 equiv.) was added at room temperature to methyl 2-[(5-chloro-2-fluorobenzyl)amino]-7-methoxy-1,3-benzoxazole-5-carboxylate (**87**) (463 mg, 56% purity, 0.71 mmol) in a mixture of tetrahydrofuran and water (3:1, 9 mL). The reaction mixture was stirred at room temperature overnight before additional lithium hydroxide (17 mg, 0.71 mmol, 1.0 equiv.) was added. After stirring at 40 °C (water bath) for 4 h, aqueous hydrochloric acid solution (1 N) was added. The mixture was evaporated under reduced pressure to give **88** which was used without further purification. Yield: 569 mg (>100%, 25% purity). LC-MS (method 1a): t_R (min) = 0.88; MS (ESI+): m/z = 351 $[M+H]^+$.

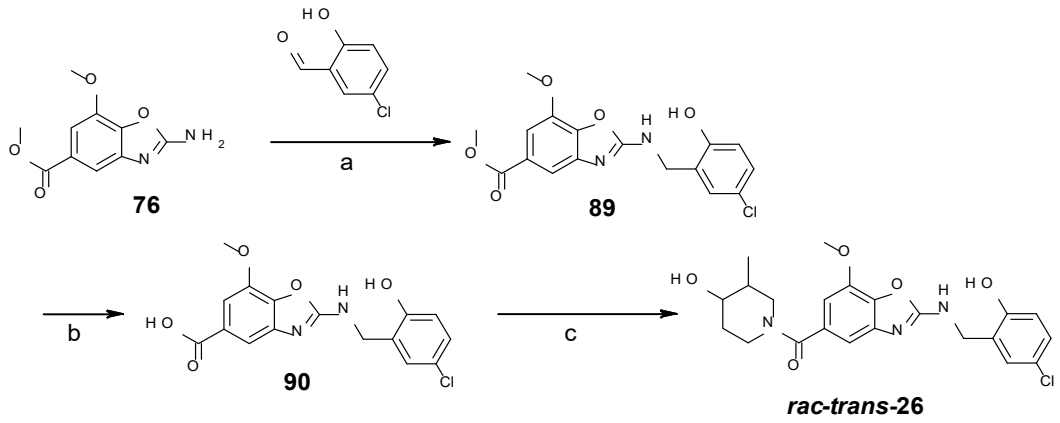
{2-[(5-Chloro-2-fluorobenzyl)amino]-7-methoxy-1,3-benzoxazol-5-yl}[4-hydroxy-3-methylpiperidin-1-yl]methanone (25) as mixture of *rac-trans* stereoisomers.



***rac-trans*-25**

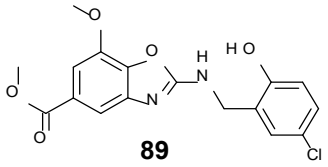
HATU (91 mg, 0.24 mmol, 1.2 equiv.) and *N,N*-diisopropylethylamine (111 µL, 0.64 mmol, 3.2 equiv.) were added to a solution of 2-[(5-chloro-2-fluorobenzyl)amino]-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**88**) (281 mg, 25% purity, 0.20 mmol) in *N,N*-dimethylformamide (2.0 mL) and stirred at room temperature for 20 min before *rac-trans*-3-methylpiperidin-4-ol hydrochloride (33 mg, 0.22 mmol, 1.1 equiv.) was added. The reaction mixture was stirred at room temperature overnight and evaporated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **25** as mixture of *rac-trans* stereoisomers. Yield: 25 mg (25%). LC-MS (method 7a): t_R (min) = 0.89; MS (ESI+): m/z = 448 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.63 (t, *J* = 6.1 Hz, 1H), 7.52-7.46 (m, 1H), 7.44-7.38 (m, 1H), 7.29 (t, *J* = 9.5 Hz, 1H), 6.84 (d, *J* = 1.0 Hz, 1H), 6.70 (s, 1H), 4.77 (d, *J* = 5.1 Hz, 1H), 4.58 (d, *J* = 5.4 Hz, 2H), 4.38-4.14 (m, 1H), 3.91 (s, 3H), 3.63-3.46 (m, 1H), 3.22-3.14 (m, 1H), 3.09-2.85 (m, 1H), 1.92-1.66 (m, 1H), 1.47-1.22 (m, 2H), 1.04-0.70 (m, 3H), 1 proton concealed (DMSO).

{2-[(5-Chloro-2-hydroxybenzyl)amino]-7-methoxy-1,3-benzoxazol-5-yl}[4-hydroxy-3-methylpiperidin-1-yl]methanone (26) as mixture of *rac-trans* stereoisomers.



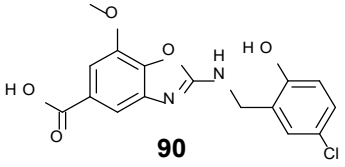
a) i) 5-chloro-2-hydroxybenzaldehyde, Ti(O*i*-Pr)$_4$, DCM, RT, ii) NaCNBH$_3$, RT; b) LiOH, THF/water, RT; c) *rac-trans*-3-methylpiperidin-4-ol, HATU, DIEA, DMF, RT.

Methyl 2-[(5-chloro-2-hydroxybenzyl)amino]-7-methoxy-1,3-benzoxazole-5-carboxylate (89).



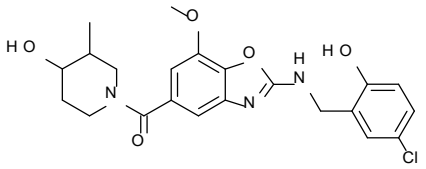
Titanium(IV) tetrapropanolate (7.54 mL, 25.55 mmol, 2.0 equiv.) was added under argon atmosphere at room temperature to a mixture of methyl 2-amino-7-methoxy-1,3-benzoxazole-5-carboxylate (**76**) (3.69 g, 12.77 mmol) and 5-chloro-2-hydroxybenzaldehyde (2.00 g, 12.77 mmol, 1.0 equiv.) in dichloromethane (100 mL). The reaction mixture was stirred at room temperature overnight, followed by addition of sodium cyanoborohydride (2.41 mg, 38.32 mmol, 3.0 equiv.) at room temperature. The reaction mixture was stirred at room temperature overnight, diluted with dichloromethane, filtered through diatomaceous earth and mixed with water. After phase separation, the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over magnesium sulfate, filtered, evaporated under reduced pressure and dried *in vacuo* to give **89** which was used without further purification. Yield: 8.18 g.

2-[(5-Chloro-2-hydroxybenzyl)amino]-7-methoxy-1,3-benzoxazole-5-carboxylic acid (90).



Lithium hydroxide (1.07 g) and water (50 mL) were added at room temperature to methyl 2-[(5-chloro-2-hydroxybenzyl)amino]-7-methoxy-1,3-benzoxazole-5-carboxylate (**89**) (8.10 g) in tetrahydrofuran and water (140 mL). The reaction mixture was stirred at room temperature overnight and then acidified with aqueous hydrochloric acid solution (1 M). The solid was filtered, washed with water and dried *in vacuo* at 45 °C overnight to give **90**. Yield: 4.21 g (43%, 80% purity). LC-MS (method 2a): t_R (min) = 1.92; MS (ESI+): m/z = 349 $[M+H]^+$.

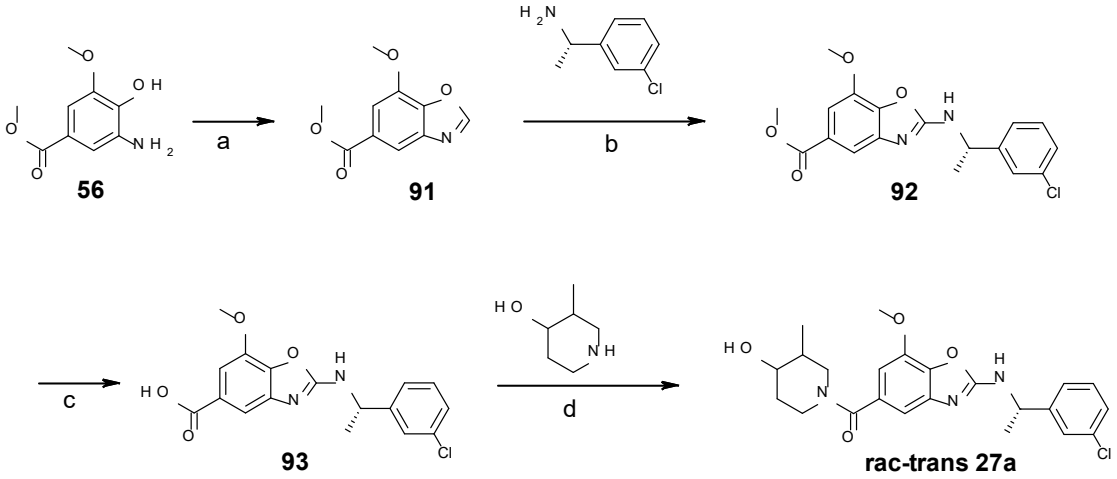
{2-[(5-Chloro-2-hydroxybenzyl)amino]-7-methoxy-1,3-benzoxazol-5-yl}[4-hydroxy-3-methylpiperidin-1-yl]methanone (26) as mixture of *rac-trans* stereoisomers.



***rac-trans*-26**

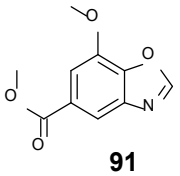
A mixture of 2-[(5-chloro-2-hydroxybenzyl)amino]-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**90**) (100 mg, 0.29 mmol), *rac-trans*-3-methylpiperidin-4-ol (36 mg, 0.32 mmol, 1.1 equiv.), HATU (131 mg, 0.34 mmol, 1.2 equiv.) and *N,N*-diisopropylethylamine (120 µL, 0.69 mmol, 2.4 equiv.) in *N,N*-dimethylformamide (2.0 mL) was stirred at room temperature overnight and evaporated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient + 0.01% formic acid) to give **26** as mixture of *rac-trans* stereoisomers. Yield: 3 mg (3%, 90% purity). LC-MS (method 1a): t_R (min) = 0.84; MS (ESI+): m/z = 446 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.21-7.15 (m, 2H), 7.01 (s, 1H), 6.91 (d, *J* = 8.6 Hz, 1H), 6.76 (d, *J* = 1 Hz, 1H), 5.87-5.79 (m, 1H), 4.62-4.45 (m, 1H), 4.51 (d, *J* = 6.1 Hz, 2H), 3.95 (s, 3H), 3.86-3.62 (m, 1H), 3.48-3.38 (m, 1H), 3.15-2.93 (m, 1H), 2.82-2.6 (m, 1H, partially concealed), 2.11-1.85 (m, 1H), 1.18-0.80 (m, 3H), 4 protons are concealed.

(2-{[(1*S*)-1-(3-Chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)(4-hydroxy-3-methylpiperidin-1-yl)methanone (27a) mixture of *rac-trans* stereoisomers.



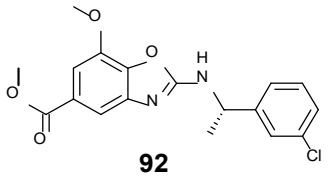
a) triethyl orthoformate, RF; b) (1*S*)-1-(3-chlorophenyl)ethanamine, benzoic acid, Ag_2CO_3, ACN, 60 °C; c) LiOH, THF/water, RT; d) *rac-trans*-3-methylpiperidin-4-ol, HATU, DIEA, RT.

Methyl 7-methoxy-1,3-benzoxazole-5-carboxylate (91).



Methyl 3-amino-4-hydroxy-5-methoxybenzoate **56** (30.0 g, 152 mmol) in triethyl orthoformate (350 mL, 2.10 mol) was stirred under reflux for 4 h. The hot reaction mixture was filtered and then concentrated under reduced pressure to yield **91** which was used without further purification within the next steps. Yield: 31.0 g (98%). LC-MS (method 9a): t_R (min) = 0.79; MS (ESI+): m/z = 208 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.87 (s, 1H), 7.96 (s, 1H), 7.58 (s, 1H), 4.04 (s, 3H), 3.90 (s, 3H).

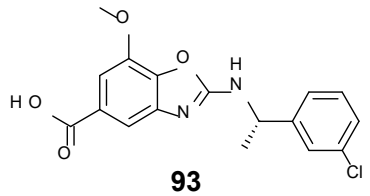
Methyl 2-{[(1*S*)-1-(3-chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylate (92).



A mixture of methyl 7-methoxy-1,3-benzoxazole-5-carboxylate (**91**) (2.50 g, 12.1 mmol, 1.2 equiv.), (1*S*)-1-(3-chlorophenyl)ethanamine (1.57 g, 10.1 mmol), benzoic acid (2.46 g, 20.1 mmol, 2.0 equiv.) and silver carbonate (3.33 g, 12.1 mmol, 1.2 equiv.) in acetonitrile (45 mL) was stirred at 60 °C overnight. A further amount of ((1*S*)-1-(3-chlorophenyl) ethanamine (785 mg, 5.50 mmol, 0.5 equiv.)

was added and stirring at 60 °C was continued overnight. The reaction mixture was filtered over Celite®, the residue was washed with acteonitrile and the filtrate was concetrated under reduced pressure. The crude material was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate 4:1) to give **92**. Yield: 2.75 g (47%, 74% purity). 200 mg of this material were purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient + 0.01% formic acid) to give **92** (160 mg) with 100% purity. LC-MS (method 6a): t_R (min) = 1.31; MS (ESI+): m/z = 361 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.80 (d, *J* = 8.3 Hz, 1H), 7.48 (s, 1H), 7.42 (d, *J* = 1.2 Hz, 1H), 7.35-7.41 (m, 2H), 7.27-7.34 (m, 2H), 4.95 (quin, *J* = 7.2 Hz, 1H), 3.94 (s, 3H), 3.83 (s, 3H), 1.49 (d, *J* = 7.1 Hz, 3H).

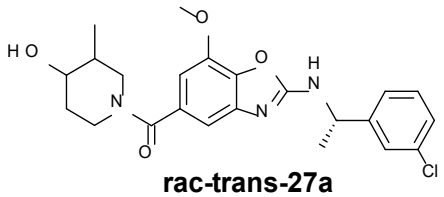
2-{[(1*S*)-1-(3-Chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (93).



93

Lithium hydroxide (415 mg, 17.3 mmol, 2.5 equiv.) was added at room temperature to methyl 2-{[(1*S*)-1-(3-chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylate (**92**) (2.50 g, 6.93 mmol) in a mixture of tetrahydrofuran and water (2:1, 138 mL). The reaction mixture was stirred at room temperature overnight before the reaction mixture was neutralized with aqueous hydrochloric acid solution (1 N). After extraction with ethyl acetate, the organic phase was washed with brine and dried over sodium sulfate. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient + 0.01% formic acid) to give **93**. Yield: 1.20 g (50%). LC-MS (method 1a): t_R (min) = 0.92; MS (ESI+): m/z = 347 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 12.83 (br s, 1H), 8.75 (d, *J* = 8.1 Hz, 1H), 7.49 (s, 1H), 7.44-7.36 (m, 3H), 7.34-7.26 (m, 2H), 4.95 (quin, *J* = 7.2 Hz, 1H), 3.93 (s, 3H), 1.49 (d, *J* = 6.8 Hz, 3H).

(2-{[(1*S*)-1-(3-Chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[4-hydroxy-3-methylpiperidin-1-yl]methanone as mixture of *rac-trans* stereoisomers (27a).

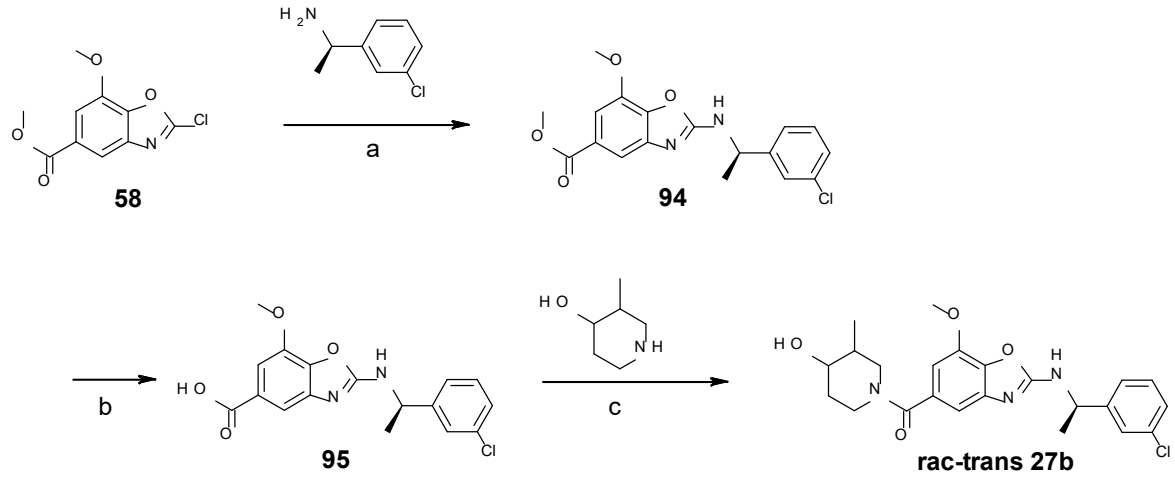


rac-trans-27a

HATU (197 mg, 0.52 mmol, 1.2 equiv.) and *N,N*-diisopropylethylamine (166 µL, 0.95 mmol, 2.2 equiv.) were added to a solution of 2-{[(1*S*)-1-(3-chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**93**) (150 mg, 0.43 mmol) in *N,N*-dimethylformamide (3.6 mL) and stirred at room temperature for 30 min before *rac-trans*-3-methylpiperidin-4-ol (55 mg, 0.48 mmol,

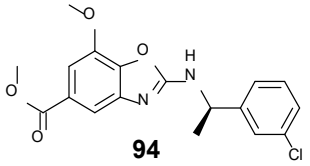
1.1 equiv.) was added. The reaction mixture was stirred at room temperature overnight and the reaction mixture was purified without any further work up by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient + 0.01% formic acid) to give **27a** as mixture of *rac-trans* stereoisomers. Yield: 127 mg (66%). LC-MS (method 7a): t_R (min) = 0.94; MS (ESI+): m/z = 444 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.68 (d, *J* = 8.1 Hz, 1H), 7.48 (s, 1H), 7.35-7.41 (m, 2H), 7.28-7.34 (m, 1H), 4.94 (quin, *J* = 7.2 Hz, 1H), 4.76 (d, *J* = 5.1 Hz, 1H), 4.14-4.35 (m, 1H), 3.90 (s, 3H), 3.42-3.62 (m, 1H), 3.17 (dt, *J* = 9.3, 4.6 Hz, 1H), 2.80-3.07 (m, 1H), 1.61-1.86 (m, 1H), 1.48 (d, *J* = 6.8 Hz, 3H), 1.19-1.42 (m, 2H), 0.69-1.00 (m, 3H), 2 protons are concealed.

(2-{[(1*R*)-1-(3-Chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)(4-hydroxy-3-methylpiperidin-1-yl)methanone (27b) mixture of *rac-trans* stereoisomers.



a) (1*R*)-1-(3-chlorophenyl)ethanamine, DIEA, THF, RT; b) LiOH, THF/water, RT; c) *rac-trans*-3-methylpiperidin-4-ol, HATU, DIEA, DMF, RT.

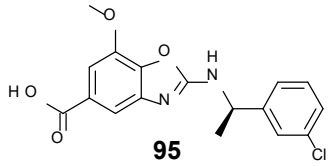
Methyl 2-{[(1*R*)-1-(3-chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylate (94).



N,N-Diisopropylethylamine (32.35 mL, 185.7 mmol, 3.0 equiv.) was added to a solution of methyl 2-chloro-7-methoxy-1,3-benzoxazole-5-carboxylate (**58**) (18.24 g, 82% purity, 61.90 mmol) and (1*R*)-1-(3-chlorophenyl)ethanamine (9.63 g, 61.90 mmol, 1.0 equiv.) in tetrahydrofuran (376 mL). The reaction mixture was stirred at room temperature for 18 h and evaporated under reduced pressure. The residue was dissolved in dichloromethane (500 mL) and washed with aqueous hydrochloric acid solution (0.5 M, 500 mL). The organic phase was dried over sodium sulfate, filtered and dried *in vacuo* to give **94**. Yield: 16.50 g (72%). LC-MS (method 1a): t_R (min) = 1.11; MS (ESI+): m/z = 361 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.80 (d, J = 8.1 Hz, 1H), 7.48 (s, 1H), 7.42 (d, J = 1.5 Hz, 1H), 7.26-7.40 (m, 4H), 4.96 (quin, J = 7.2 Hz, 1H), 3.94 (s, 3H) 3.83 (s, 3H), 1.49 (d, J = 6.8 Hz, 3H).

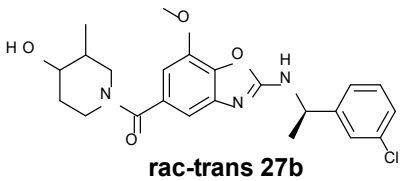
2-{[(1*R*)-1-(3-Chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (95).



95

Lithium hydroxide (15.43 g, 644.4 mmol, 5.0 equiv.) was added at room temperature to methyl 2-{[(1*R*)-1-(3-chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylate (**94**) (46.50 g, 360.8 mmol) in a mixture of tetrahydrofuran and water (3:1, 800 mL). The reaction mixture was stirred at room temperature for 72 h before all volatiles were removed under reduced pressure. The residue was diluted with water and acidified with aqueous hydrochloric acid solution (1 N) to pH = 2. The solid was extracted with ethyl acetate and the organic phase was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and dried *in vacuo* to give **95**. Yield: 44.1 g (93%). LC-MS (method 1a): t_R (min) = 0.95; MS (ESI+): m/z = 347 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 12.63-13.03 (m, 1H), 8.76 (d, J = 8.1 Hz, 1H), 7.49 (s, 1H), 7.27-7.42 (m, 5H), 4.91-5.01 (m, 1H), 3.93 (s, 3H), 1.49 (d, J = 7.1 Hz, 3H).

(2-{[(1*R*)-1-(3-Chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[4-hydroxy-3-methylpiperidin-1-yl]methanone (27b) as mixture of *rac-trans* stereoisomers

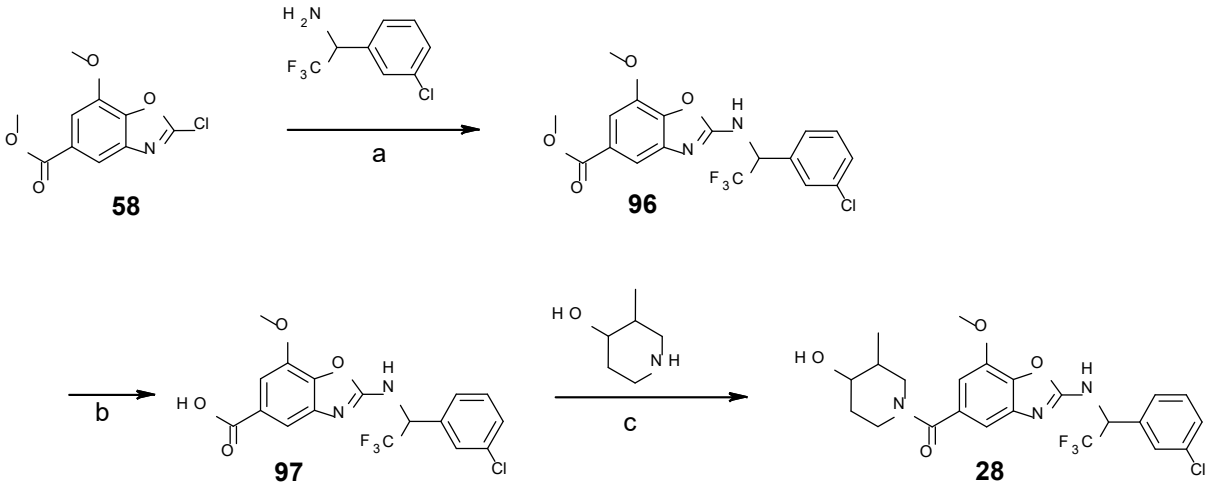


rac-trans 27b

HATU (197 mg, 0.52 mmol, 1.2 equiv.) and *N,N*-diisopropylethylamine (166 µL, 0.95 mmol, 2.2 equiv.) were added to a solution of 2-{[(1*R*)-1-(3-chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**95**) (150 mg, 0.43 mmol) in *N,N*-dimethylformamide (3.6 mL) and stirred at room temperature for 30 min before *rac-trans*-3-methylpiperidin-4-ol (55 mg, 0.48 mmol, 1.1 equiv.) was added. The reaction mixture was stirred at room temperature overnight and the reaction mixture was purified without any further work up by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient + 0.01% formic acid) to give **27b** as mixture of *rac-trans* stereoisomers. Yield: 71 mg (37%). LC-MS (method 7a): t_R (min) = 0.94; MS (ESI+): m/z = 444 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.68 (d, J = 8.3 Hz, 1H), 7.48 (s, 1H), 7.35-7.41 (m, 2H), 7.28-7.34 (m, 1H), 6.79 (s, 1H), 6.66 (d, J = 0.7 Hz, 1H), 4.94 (quin, J = 7.2 Hz, 1H), 4.76 (br d, J = 2.0 Hz, 1H),

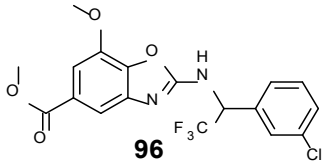
4.12-4.37 (m, 1H), 3.90 (s, 3H), 3.17 (m, 1H), 2.79-3.07 (m, 1H), 1.64-1.93 (m, 1H), 1.48 (d, *J* = 6.8 Hz, 3H), 1.18-1.42 (m, 2H), 0.64-1.01 (m, 3H), 2 protons are concealed.

(2-{[1-(3-Chlorophenyl)-2,2,2-trifluoroethyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)(4-hydroxy-3-methylpiperidin-1-yl)methanone (28) as mixture of *all rac-trans* stereoisomers.



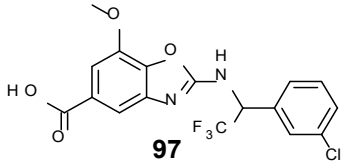
a) (*rac*)-1-(3-chlorophenyl)-2,2,2-trifluoroethanamine, DIEA, 1,4-dioxane, RF; b) LiOH, THF/water, RT; c) *rac-trans*-3-methylpiperidin-4-ol, HATU, DIEA, DMF, RT.

(*rac*)-Methyl 2-{[1-(3-chlorophenyl)-2,2,2-trifluoroethyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylate (96).



N,N-Diisopropylethylamine (14.8 mL, 84.4 mmol, 5.0 equiv.) was added to a solution of methyl 2-chloro-7-methoxy-1,3-benzoxazole-5-carboxylate (**58**) (4.10 g, 17.0 mmol) and (*rac*)-1-(3-chlorophenyl)-2,2,2-trifluoroethanamine (6.40 g, 30.5 mmol, 1.8 equiv.) in 1,4-dioxane (150 mL). The reaction mixture was stirred for 9 days under reflux and then evaporated under reduced pressure. The residue was dissolved in dichloromethane (100 mL), water (200 mL) was added and the mixture was vigorously stirred. The precipitate was filtered, washed with a small amount of acetonitrile and dried *in vacuo* to give **96**. Yield: 2.77 g (39%). LC-MS (method 9a): t_R (min) = 1.20; MS (ESI+): m/z = 415 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 9.74 (d, *J* = 10.0 Hz, 1H), 7.84 (s, 1H), 7.69 (br d, *J* = 6.4 Hz, 1H), 7.46-7.58 (m, 3H), 7.36 (d, *J* = 1.0 Hz, 1H), 5.98 (quin, *J* = 8.4 Hz, 1H), 3.98 (s, 3H), 3.85 (s, 3H).

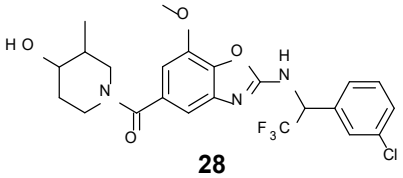
(*rac*)-2-{[1-(3-Chlorophenyl)-2,2,2-trifluoroethyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (97).



97

Lithium hydroxide (779 mg, 32.5 mmol, 5.0 equiv.) was added at room temperature to methyl (*rac*)-methyl 2-{[1-(3-chlorophenyl)-2,2,2-trifluoroethyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylate (**96**) (2.70 g, 6.51 mmol) in a mixture of tetrahydrofuran and water (3:1, 200 mL). The reaction mixture was stirred at room temperature overnight and then acidified with aqueous hydrochloric acid solution (1 N). The solid was extracted with dichloromethane and the organic phase was dried over magnesium sulfate, filtered and dried *in vacuo*. The residue was triturated with acetonitrile / water, filtered and dried *in vacuo* to give **97**. Yield: 920 mg (28%, 80% purity). 100 mg were again triturated with acetonitrile / water, filtered and dried *in vacuo* to give **97**. Yield: 53 mg (93% purity). LC-MS (method 7a): t_R (min) = 1.05; MS (ESI+): m/z = 401 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 12.96 (br s, 1H), 9.70 (br d, *J* = 10.3 Hz, 1H), 7.84 (s, 1H), 7.65-7.72 (m, 1H), 7.46-7.55 (m, 3H), 7.36 (d, *J* = 1.2 Hz, 1H), 5.92-6.07 (m, 1H), 3.96 (s, 3H).

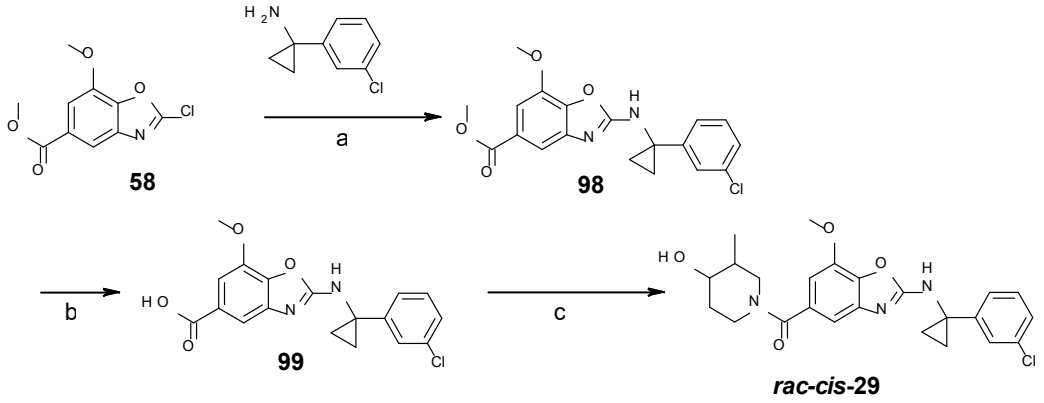
(2-{[1-(3-Chlorophenyl)-2,2,2-trifluoroethyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[4-hydroxy-3-methylpiperidin-1-yl]methanone (28) as mixture of *all rac-trans* stereoisomers.



28

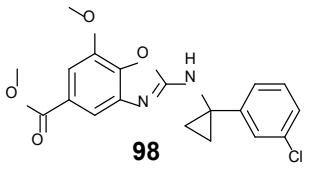
HATU (27.3 mg, 0.072 mmol, 1.2 equiv.) and *N,N*-diisopropylethylamine (23.0 µL, 0.132 mmol, 2.2 equiv.) were added to a solution of (*rac*)-2-{[1-(3-chlorophenyl)-2,2,2-trifluoroethyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**97**) (24.0 mg, 0.060 mmol) in *N,N*-dimethylformamide (2.0 mL) and stirred at room temperature for 30 min before *rac-trans*-3-methylpiperidin-4-ol (7.6 mg, 0.066 mmol, 1.1 equiv.) was added. The reaction mixture was stirred at room temperature for 1 h and the reaction mixture was purified without any further work up by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient + 0.01% formic acid) to give **28** as mixture of *all-rac-trans* stereoisomers. Yield: 8.4 mg (28%). LC-MS (method 7a): t_R (min) = 0.98; MS (ESI+): m/z = 498 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 9.63 (br d, *J* = 7.6 Hz, 1H), 7.83 (s, 1H), 7.67 (br d, *J* = 6.4 Hz, 1H), 7.43-7.58 (m, 2H), 6.88 (s, 1H), 6.75 (s, 1H), 5.87-6.05 (m, 1H), 4.60-4.86 (m, 1H), 4.1-4.50 (m, 1H), 3.93 (s, 3H), 3.44-3.87 (m, 1H), 3.19 (dt, *J* = 9.0, 4.7 Hz, 1H), 2.83-3.11 (m, 1H), 1.24-1.92 (m, 3H), 0.62-1.00 (m, 3H), 1 proton is concealed.

(2-{[1-(3-Chlorophenyl)cyclopropyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[4-hydroxy-3-methylpiperidin-1-yl]methanone (29) as mixture of *rac-cis* stereoisomers.



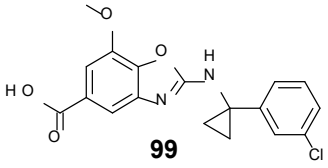
a) 1-(3-chloro-phenyl)cyclopropane amine hydrochloride, DIEA, THF, RF; b) LiOH, THF/water, 60 °C; c) *rac-cis*-3-methylpiperidin-4-ol hydrochloride, HATU, DIEA, DMF, RT.

Methyl 2-{[1-(3-chlorophenyl)cyclopropyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylate (98).



N,N-Diisopropylethylamine (22.76 mL, 130.65 mmol, 4.0 equiv.) was added to a solution of methyl 2-chloro-7-methoxy-1,3-benzoxazole-5-carboxylate (**58**) (7.89 g, 32.66 mmol) and 1-(3-chloro-phenyl)cyclopropane amine hydrochloride (8.67 g, 42.46 mmol, 1.3 equiv.) in tetrahydrofuran (395 mL). The reaction mixture was stirred at reflux for 96 h and evaporated under reduced pressure. The residue was mixed with dichloromethane (250 mL) and water (250 mL) and vigorously stirred for 30 min. The precipitate was filtered and dried *in vacuo* to give **98**. Yield: 11.27 g (91%). LC-MS (method 9a): t_R (min) = 1.11; MS (ESI+): m/z = 373 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 9.16 (s, 1H), 7.46 (s, 1H), 7.37-7.17 (m, 5H), 3.94 (s, 3H), 3.84 (s, 3H), 1.39 (s, 4H).

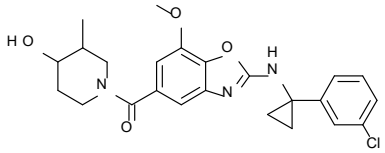
2-{[1-(3-Chlorophenyl)cyclopropyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (99).



Lithium hydroxide (2.06 g, 85.83 mmol, 4.0 equiv.) was added at room temperature to methyl 2-{[1-(3-chlorophenyl)cyclopropyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylate (**98**) (8.00 g,

21.46 mmol) in a mixture of tetrahydrofuran and water (3:1, 320 mL). The reaction mixture was stirred at room temperature overnight and at 60 °C for further 6 h before all volatiles were removed under reduced pressure. The residue was diluted with water and acidified with aqueous hydrochloric acid solution (1 N). The solid was filtered, washed with water and dried *in vacuo* to give **99**. Yield: 7.43 g (97%). LC-MS (method 9a): t_R (min) = 0.94; MS (ESI+): m/z = 359 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 9.21 (s, 1H), 7.44 (d, *J* = 1.5 Hz, 1H), 7.36-7.17 (m, 5H), 3.93 (s, 3H), 1.39 (s, 4H).

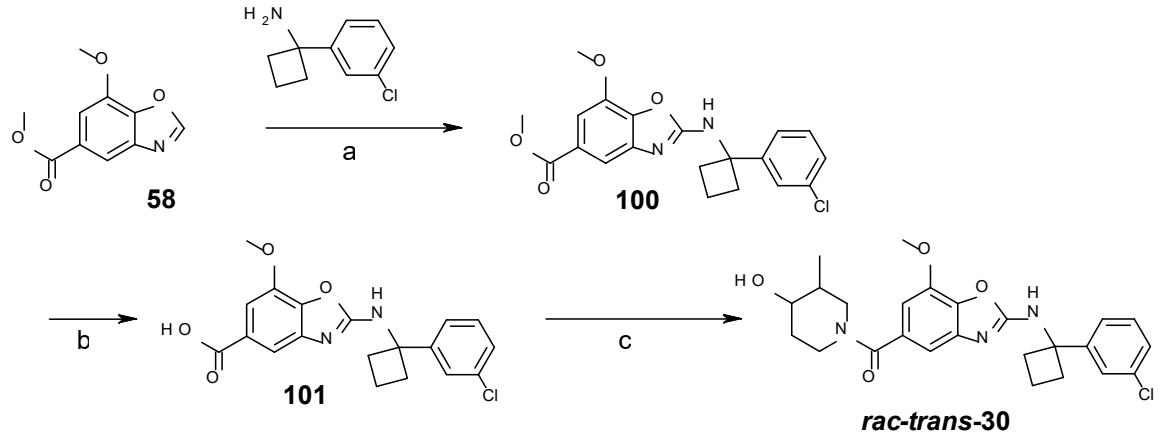
(2-{[1-(3-Chlorophenyl)cyclopropyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[4-hydroxy-3-methylpiperidin-1-yl]methanone (29) as mixture of *rac-cis* stereoisomers.



***rac-cis*-29**

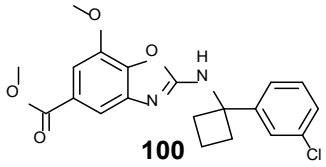
HATU (46 mg, 0.12 mmol, 1.2 equiv.) and *N,N*-diisopropylethylamine (56 µL, 0.32 mmol, 3.2 equiv.) were added to a solution of 2-{[1-(3-chlorophenyl)cyclopropyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**99**) (36 mg, 0.10 mmol) in *N,N*-dimethylformamide (1.0 mL) and stirred at room temperature for 20 min before *rac-cis*-3-methylpiperidin-4-ol hydrochloride (18 mg, 0.12 mmol, 1.2 equiv.) was added. The reaction mixture was stirred at room temperature overnight and evaporated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **29** as mixture of *rac-cis* stereoisomers. Yield: 31 mg (68%). LC-MS (method 1a): t_R (min) = 0.97; MS (ESI+): m/z = 456 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 9.03 (s, 1H), 7.36-7.17 (m, 4H), 6.83 (s, 1H), 6.68 (s, 1H), 4.76 (d, *J* = 5.1 Hz, 1H), 4.37-4.11 (m, 1H), 3.89 (s, 3H), 3.67-3.44 (m, 1H), 3.23-3.13 (m, 1H), 3.08-2.84 (m, 1H), 1.91-1.66 (m, 1H), 1.46-1.21 (m, 2H), 1.37 (s, 4H), 1.04-0.70 (m, 3H).

(2-{[1-(3-Chlorophenyl)cyclobutyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)(4-hydroxy-3-methylpiperidin-1-yl)methanone (30) as mixture of *rac-trans* stereoisomers.



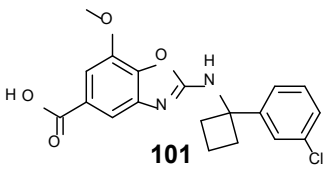
a) 1-(3-chlorophenyl)cyclobutanamine, benzoic acid, Ag_2CO_3, ACN, 80 °C; b) LiOH, THF/water, RT; c) *rac-trans*-3-methylpiperidin-4-ol, HATU, DIEA, DMF, RT.

Methyl 2-{[1-(3-chlorophenyl)cyclobutyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylate (100).



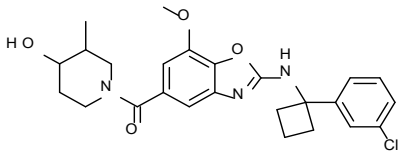
A mixture of methyl 7-methoxy-1,3-benzoxazole-5-carboxylate (**58**) (300 mg, 1.45 mmol, 1.2 equiv.), 1-(3-chlorophenyl)cyclobutanamine (219 mg, 1.21 mmol), benzoic acid (295 mg, 2.40 mmol, 2.0 equiv.) and silver carbonate (399 mg, 1.45 mmol, 1.2 equiv.) in acetonitrile (4.5 mL) was stirred at 80 °C under air atmosphere overnight. The reaction mixture was filtered over Celite®, the residue was washed with acteonitrile and the filtrate was concetrated under reduced pressure. The crude material was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient + 0.01% formic acid) to give **100**. Yield: 67.0 mg (12%). LC-MS (method 7a): t_R (min) = 1.20; MS (ESI+): m/z = 387 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 9.07 (s, 1H), 7.42-7.56 (m, 2H), 7.33-7.41 (m, 2H), 7.23-7.32 (m, 2H), 3.93 (s, 3H), 3.82 (s, 3H), 3.34 (s, 6H), 2.58 (m, 4H), 2.02-2.17 (m, 1H), 1.80-1.94 (m, 1H).

2-{[1-(3-Chlorophenyl)cyclobutyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (101).



Lithium hydroxide (5.2 mg, 0.22 mmol, 1.3 equiv.) was added at room temperature to methyl 2-{[1-(3-chlorophenyl)cyclobutyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylate (**100**) (65.0 mg, 0.17 mmol) in a mixture of tetrahydrofuran and water (3:1, 3.3 mL). The reaction mixture was stirred at room temperature overnight then acidified with aqueous hydrochloric acid solution (1 N). The solid was extracted with ethyl acetate, the organic phase was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and dried *in vacuo* to give **101**. Yield: 80.0 mg (127%). LC-MS (method 7a): t_R (min) = 1.03; MS (ESI+): m/z = 373 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 12.81 (br s, 1H), 9.03 (s, 1H), 7.50 (t, *J* = 1.8 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.34-7.41 (m, 2H), 7.25-7.32 (m, 2H), 3.92 (s, 3H), 2.55-2.63 (m, 4H), 2.09 (td, *J* = 9.0, 7.2 Hz, 1H), 1.84-1.94 (m, 1H).

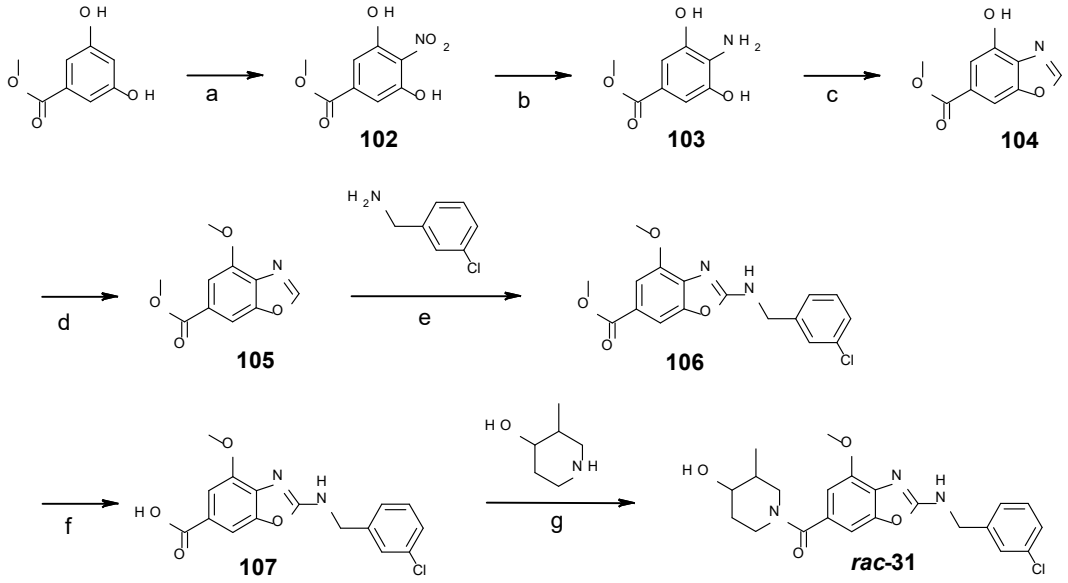
(2-{[1-(3-Chlorophenyl)cyclobutyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[4-hydroxy-3-methylpiperidin-1-yl]methanone (30) as mixture of *rac-trans* stereoisomers.



***rac-trans*-30**

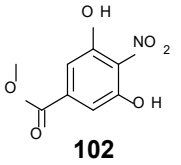
HATU (98.0 mg, 0.26 mmol, 1.2 equiv.) and *N,N*-diisopropylethylamine (82 µL, 0.47 mmol, 2.2 equiv.) were added to a solution of 2-{[1-(3-chlorophenyl)cyclobutyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**101**) (80 mg, 0.22 mmol) in *N,N*-dimethylformamide (1.8 mL) and stirred at room temperature for 30 min before *rac-trans*-3-methylpiperidin-4-ol (27.2 mg, 0.24 mmol, 1.1 equiv.) was added. The reaction mixture was stirred at room temperature overnight and then purified without any further work up by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient + 0.01% formic acid) to give **30** as mixture of *rac-trans* stereoisomers. Yield: 75 mg (75%). LC-MS (method 6a): t_R (min) = 1.23; MS (ESI+): m/z = 470 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.89-9.01 (m, 1H), 7.44-7.53 (m, 2H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.24-7.31 (m, 1H), 6.77 (d, *J* = 1.0 Hz, 1H), 6.65 (s, 1H), 4.63-4.81 (m, 1H), 4.08-4.38 (m, 1H), 3.89 (s, 3H), 3.43-3.83 (m, 2H), 3.17 (br t, *J* = 9.0 Hz, 1H), 2.80-3.11 (m, 1H), 2.56-2.68 (m, 4H), 2.00-2.17 (m, 1H), 1.84-1.95 (m, 1H), 1.13-1.81 (m, 3H), 0.59-1.03 (m, 3H).

{2-[(3-Chlorobenzyl)amino]-4-methoxy-1,3-benzoxazol-6-yl}(4-hydroxy-3-methylpiperidin-1-yl)methanone (31) as mixture of *rac-trans* stereoisomers.



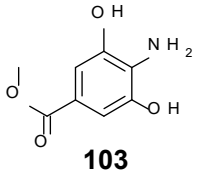
a) HNO_3, AcOH, -5 °C; b) H_2 (1 bar), 10% Pd/C, MeOH, RT; c) triethyl orthoformate, RF; d) MeI, K_2CO_3, DMF, RT; e) 1-(3-chlorophenyl)methanamine, benzoic acid, Ag_2CO_3, ACN, 60 °C; f) LiOH, THF/water, RT; g) *rac-trans*-3-methylpiperidin-4-ol, HATU, DIEA, DMF, RT.

Methyl 3,5-dihydroxy-4-nitrobenzoate (102).



Methyl 3,5-dihydroxybenzoate (13.9 g, 79.9 mmol) in acetic acid (250 mL) was treated very slowly and dropwise with nitric acid (65%, 5.10 mL, 79.9 mmol, 1.0 equiv.) at -5 °C. After stirring for 3 h at room temperature, another portion of nitric acid (65%, 2.55 mL, 39.9 mmol, 0.5 equiv.) was slowly added and the reaction mixture was stirred for 96 h. Afterwards, the reaction mixture was diluted with water and then extracted with ethyl acetate and the organic phase was dried over sodium sulfate, filtered in concentrated *in vacuo*. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient + 0.01% formic acid) to give **102**. Yield: 1.6 g (9%). LC-MS (method 6a): t_R (min) = 0.76; MS (ESI+): m/z = 214 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 11.21 (s, 2H), 7.05 (s, 2H), 3.84 (s, 3H).

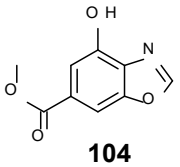
Methyl 4-amino-3,5-dihydroxybenzoate (103).



103

Methyl 3,5-dihydroxy-4-nitrobenzoate (**102**) (1.60 g, 7.51 mmol) in methanol (46.6 mL) was treated at room temperature with 10% Pd/C (200 mg) and then stirred for 2 h under an atmosphere of hydrogen (1 bar). The reaction mixture was filtered over Celite® and then concentrated *in vacuo* give to give **103**. Yield: 1.37 g (100%). LC-MS (method 1a): t_R (min) = 0.29; MS (ESI+): m/z = 184 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 9.36 (br s, 2H), 6.93 (s, 2H), 3.72 (s, 3H), 3.17 (s, 2H).

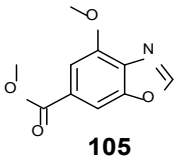
Methyl 4-hydroxy-1,3-benzoxazole-6-carboxylate (104).



104

Methyl 4-amino-3,5-dihydroxybenzoate (**103**) (1.37 g, 7.48 mmol) in triethyl orthoformate (50.0 mL, 301 mmol) was stirred under reflux for 4 h. Triethyl orthoformate (10.0 mL, 60.0 mmol) was added and stirring under reflux was continued for another 2 h. The hot reaction mixture was concentrated under reduced pressure to yield **104** which was used without further purification within the next steps. Yield: 1.28 g (89%). LC-MS (method 7a): t_R (min) = 0.66; MS (ESI+): m/z = 194 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 10.84 (br s, 1H), 8.78 (s, 1H), 7.74 (d, J = 1.0 Hz, 1H), 7.42 (d, J = 1.2 Hz, 1H), 3.87 (s, 3H).

Methyl 4-methoxy-1,3-benzoxazole-6-carboxylate (105).

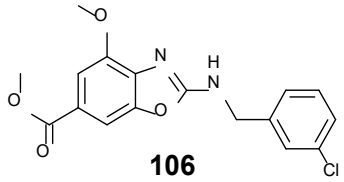


105

Methyl 4-hydroxy-1,3-benzoxazole-6-carboxylate (**104**) (1.08 g, 5.59 mmol) in *N,N*-dimethylformamide (50.0 mL) was treated with potassium carbonate (1.16 g, 8.39 mmol) and iodomethane (1.37 mL, 22.0 mmol, 3.9 equiv.). The reaction mixture was stirred for 1 h at room temperature and then iodomethane (0.20 mL, 3.21 mmol, 0.6 equiv.) was added. After stirring overnight, potassium carbonate (445 mg, 3.22 mmol, 0.6 equiv.) and iodomethane (0.20 mL, 3.21 mmol, 0.6 equiv.) were added and stirring was continued for 1 h at 50 °C. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in dichloromethane and washed

with saturated ammonium chloride solution. The organic phase was dried over sodium sulfate, filtered and then concentrated under reduced pressure. The crude material was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate 2:1) to give **105**. Yield: 605 mg (52%). LC-MS (method 7a): t_R (min) = 0.79; MS (ESI+): m/z = 208 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.85 (s, 1H), 7.94 (d, *J* = 1.2 Hz, 1H), 7.49 (d, *J* = 1.0 Hz, 1H), 4.04 (s, 3H), 3.90 (s, 3H).

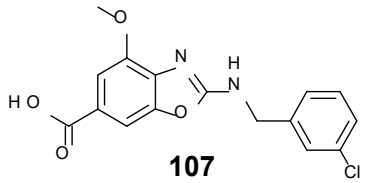
Methyl 2-{[1-(3-chlorophenyl)cyclobutyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylate (106).



106

A mixture of methyl 4-methoxy-1,3-benzoxazole-6-carboxylate (**105**) (300 mg, 1.43 mmol, 1.2 equiv.), 1-(3-chlorophenyl)methanamine (210 mg, 1.20 mmol), benzoic acid (292 mg, 2.39 mmol, 2.0 equiv.) and silver carbonate (395 mg, 1.43 mmol, 1.2 equiv.) in acetonitrile (5.3 mL) was stirred at 60 °C under air atmosphere overnight. The reaction mixture was filtered over Celite®, the residue was washed with acteonitrile and the filtrate was concetrated under reduced pressure. The crude material was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **106**. Yield: 69.0 mg (13%). LC-MS (method 1a): t_R (min) = 1.04; MS (ESI+): m/z = 347 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.86 (t, *J* = 6.1 Hz, 1H), 7.59 (d, *J* = 1.2 Hz, 1H), 7.28-7.46 (m, 5H), 4.56 (d, *J* = 6.1 Hz, 2H), 3.91 (s, 3H), 3.84 (s, 3H).

2-[(3-Chlorobenzyl)amino]-4-methoxy-1,3-benzoxazole-6-carboxylic acid (107).

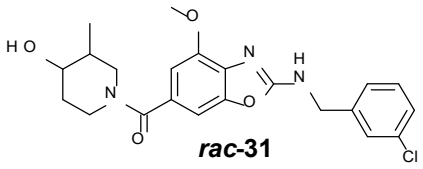


107

Lithium hydroxide (8.9 mg, 0.37 mmol, 2.0 equiv.) was added at room temperature to methyl 2-{[1-(3-chlorophenyl)cyclobutyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylate (**106**) (69.3 mg, 0.19 mmol) in a mixture of tetrahydrofuran and water (2:1, 1.5 mL). The reaction mixture was stirred at room temperature for 3 h and then lithium hydroxide (8.9 mg, 0.37 mmol, 2.0 equiv.) was added. After stirring overnight, lithium hydroxide (4.5 mg, 0.19 mmol, 1.0 equiv.) was added and stirring was continued for 3 h at 60 °C. The reaction mixture was acidified with aqueous hydrochloric acid solution (1 N), the solid was extracted with ethyl acetate, the organic phase was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and dried *in vacuo* to give **107**. Yield: 55.8 mg (88%). LC-MS (method 1a): t_R (min) = 0.87; MS (ESI+): m/z = 333 $[M+H]^+$. ^{1}H NMR (400 MHz,

DMSO-d_6): δ [ppm] = 12.78 (br s, 1H), 8.79 (t, J = 6.2 Hz, 1H), 7.55 (s, 1H), 7.25-7.46 (m, 5H), 4.56 (br d, J = 5.9 Hz, 2H), 3.90 (s, 3H).

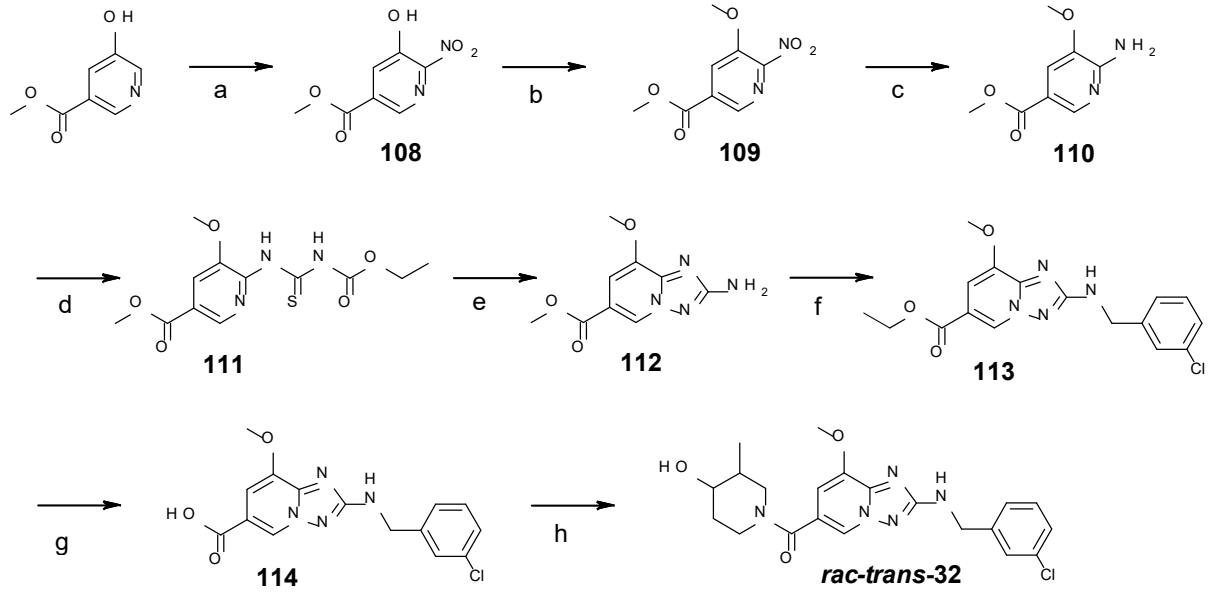
{2-[(3-Chlorobenzyl)amino]-4-methoxy-1,3-benzoxazol-6-yl}[4-hydroxy-3-methylpiperidin-1-yl]methanone (31) as mixture of *rac-trans* stereoisomers.



***rac*-31**

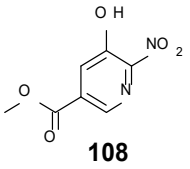
HATU (74.3 mg, 0.195 mmol, 1.2 equiv.) and *N,N*-diisopropylethylamine (62 µL, 0.36 mmol, 2.2 equiv.) were added to a solution of 2-[(3-chlorobenzyl)amino]-4-methoxy-1,3-benzoxazole-6-carboxylic acid (**107**) (55.8 mg, 0.163 mmol) in *N,N*-dimethylformamide (1.4 mL). The reaction mixture was stirred at room temperature for 30 min before *rac-trans*-3-methylpiperidin-4-ol (27.2 mg, 0.24 mmol, 1.1 equiv.) was added. The reaction mixture was stirred at room temperature overnight and then purified without any further work up by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **31** as mixture of *rac-trans* stereoisomers. Yield: 32.2 mg (46%). LC-MS (method 7a): t_R (min) = 0.89; MS (ESI+): m/z = 430 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.60 (t, J = 6.1 Hz, 1H), 7.29-7.48 (m, 4H), 7.04 (s, 1H), 6.76 (s, 1H), 4.78 (d, J = 4.9 Hz, 1H), 4.53 (br d, J = 5.9 Hz, 2H), 4.01-4.42 (m, 1H), 3.87 (s, 3H), 3.48-3.76 (m, 1H), 3.13-3.21 (m, 1H), 2.86-3.09 (m, 1H), 1.69-1.93 (m, 1H), 1.18-1.50 (m, 2H), 0.72-1.05 (m, 3H), 1 proton concealed.

{2-[(3-Chlorobenzyl)amino]-8-methoxy[1,2,4]triazolo[1,5-a]pyridin-6-yl}[4-hydroxy-3-methylpiperidin-1-yl]methanone (32) as mixture of *rac-trans* stereoisomers.



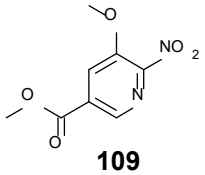
a) HNO_3, H_2SO_4, 0 °C; b) trimethylsilyl-diazomethane, toluene/MeOH, 0 °C to RT; c) H_2 (1 bar), 10% Pd/C, MeOH, RT; d) ethoxycarbonyl isothiocyanate, 1,4-dioxane, RT; e) hydroxylamine hydrochloride, DIEA, MeOH/EtOH, RT to 60 °C; f) i) 3-chlorbenzaldehyde, DMF, RT to RF, ii) $NaBH_4$, EtOH, RT to RF; g) LiOH, THF/water, RT; h) *rac-trans*-3-methylpiperidin-4-ol hydrochloride, HATU, DIEA, DMF, RT.

Methyl 5-hydroxy-6-nitronicotinate (108).



Nitric acid (1.28 mL) was added dropwise and slowly to concentrated sulfuric acid (8.00 mL) at 0 °C and the reaction mixture stirred for 10 min. The cooling bath was removed and methyl 5-hydroxynicotinate (1.00 g, 6.53 mmol) added in portions. The reaction mixture was stirred at room temperature overnight and poured onto iced water. The precipitate was filtered and dried *in vacuo* to give **108**. Yield: 529 mg (39%). LC-MS (method 1a): t_R (min) = 0.59; MS (ESI+): m/z = 199 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 12.16 (br s, 1H), 8.46 (d, *J* = 1.7 Hz, 1H), 8.05 (d, *J* = 1.7 Hz, 1H), 3.92 (s, 3H).

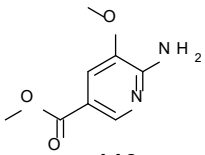
Methyl 5-methoxy-6-nitronicotinate (109).



109

A solution of trimethylsilyl-diazomethane (2 M in diethyl ether, 6.41 mL, 12.81 mmol, 5.0 equiv.) was added under argon atmosphere at 0 °C to a mixture of methyl 5-hydroxy-6-nitronicotinate (**108**) (529 mg, 2.56 mmol) in toluene (50 mL) and methanol (17 mL). The reaction mixture was allowed to warm to room temperature, stirred overnight, mixed with water and evaporated under reduced pressure. After addition of dichloromethane / water and phase separation, the aqueous phase was extracted two times with dichloromethane. The combined organic phases were washed with brine, dried over sodium sulfate, filtered, evaporated under reduced pressure and dried *in vacuo* to give **109**. Yield: 552 mg (92%, 91% purity). LC-MS (method 1a): t_R (min) = 0.75; MS (ESI+): m/z = 213 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.60 (d, *J* = 1.5 Hz, 1H), 8.28 (d, *J* = 1.5 Hz, 1H), 4.06 (s, 3H), 3.95 (s, 3H).

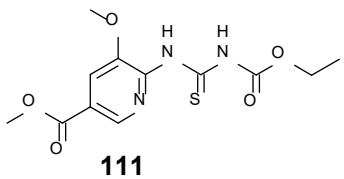
Methyl 6-amino-5-methoxynicotinate (110).



110

A solution of methyl 5-methoxy-6-nitronicotinate (**109**) (552 mg, 2.37 mmol) in ethanol (30 mL) was mixed at room temperature with palladium (10% on carbon, 62 mg), purged with hydrogen gas and stirred at room temperature overnight under hydrogen gas atmosphere (1 bar). The reaction mixture was filtered through a filter layer, which was successively washed with ethanol. The combined filtrates were concentrated under reduced pressure and dried *in vacuo* to give **110**. Yield: 336 g (80%). LC-MS (method 3a): t_R (min) = 0.56; MS (ESI+): m/z = 183 $[M+H]^+$.

Methyl 6-{[(ethoxycarbonyl)carbamothioyl]amino}-5-methoxynicotinate (111).

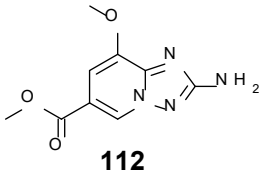


111

Ethoxycarbonyl isothiocyanate (296 µL, 2.62 mmol, 1.5 equiv.) was added under argon atmosphere at room temperature to a solution of methyl 6-amino-5-methoxynicotinate (**110**) (335 mg, 1.75 mmol) in 1,4-dioxane (6 mL). The reaction mixture was stirred at room temperature overnight. The formed precipitate was filtered and washed with little ethyl acetate. The combined filtrates were concentrated

under reduced pressure and dried *in vacuo* to give **111**. Yield: 381 mg (70%). LC-MS (method 1a): t_R (min) = 0.84; MS (ESI+): m/z = 314 $[M+H]^+$.

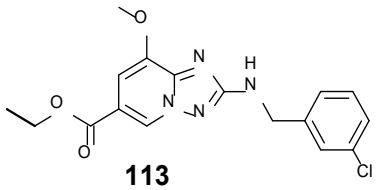
Methyl 2-amino-8-methoxy[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (**112**).



112

Hydroxylamine hydrochloride (456 mg, 6.56 mmol, 5.4 equiv.) was added at room temperature to a mixture of methyl 6-{[(ethoxycarbonyl)carbamothioyl]amino}-5-methoxynicotinate (**111**) (381 mg, 1.22 mmol) and *N,N*-diisopropylethylamine (686 µL, 3.94 mmol, 3.2 equiv.) in methanol / ethanol (1:1, 24 mL). The reaction mixture was stirred at room temperature for 2 h and at 60 °C for 1.5 h. The formed precipitate was filtered, washed with methanol and dried *in vacuo* to give **112**. Yield: 215 mg (80%). LC-MS (method 7a): t_R (min) = 0.53; MS (ESI+): m/z = 223 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.69 (s, 1H), 7.21 (s, 1H), 6.30 (br s, 2H), 3.97 (s, 3H), 3.87 (s, 3H).

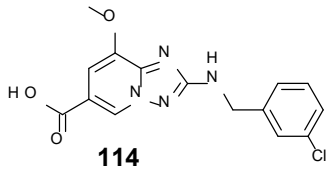
Ethyl 2-[(3-chlorobenzyl)amino]-8-methoxy[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (**113**).



113

3-Chlorbenzaldehyde (61 µL, 0.54 mmol, 1.2 equiv.) was added under argon atmosphere at room temperature to a solution of methyl 2-amino-8-methoxy[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (**112**) (100 mg, 0.45 mmol) in *N,N*-dimethylformamide (2 mL). The reaction mixture was stirred under reflux for 2 h. After cooling to room temperature, the reaction mixture was mixed with ethanol (20 mL), heated to 50 °C, mixed cautiously with sodium borohydride (31 mg, 0.81 mmol, 1.8 equiv.) and stirred under reflux for 30 min. After cooling to RT, water was added and the formed precipitate was filtered and dried *in vacuo* to give **113**. Yield: 56 mg (35%). LC-MS (method 9a): t_R (min) = 1.09; MS (ESI+): m/z = 361 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.73 (s, 1H), 7.53 (t, *J* = 6.4 Hz, 1H), 7.42-7.26 (m, 4H), 7.23 (s, 1H), 4.48 (d, *J* = 6.4 Hz, 2H), 4.32 (q, *J* = 7.1 Hz, 14.2 Hz, 2H), 3.97 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H).

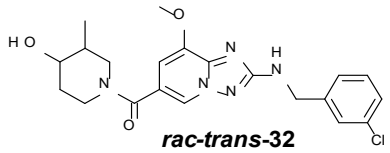
2-[(3-Chlorobenzyl)amino]-8-methoxy[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid (**114**).



114

Lithium hydroxide (11 mg, 0.47 mmol, 3.0 equiv.) was added at room temperature to a mixture of ethyl 2-[(3-chlorobenzyl)amino]-8-methoxy[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (**113**) (56 mg, 0.16 mmol) in a mixture of tetrahydrofuran / water (3:1, 2.0 mL). The reaction mixture was stirred at room temperature for 3 h, mixed with aqueous hydrochloric acid solution (1 N), concentrated under reduced pressure and dried *in vacuo* to give **114**. Yield: 64 mg (quantitative, 91% purity). LC-MS (method 1a): t_R (min) = 0.80; MS (ESI+): m/z = 333 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.67 (s, 1H), 7.48 (t, *J* = 6.4 Hz, 1H), 7.42-7.26 (m, 4H), 7.24 (s, 1H), 4.48 (d, *J* = 6.4 Hz, 2H), 3.96 (s, 3H).

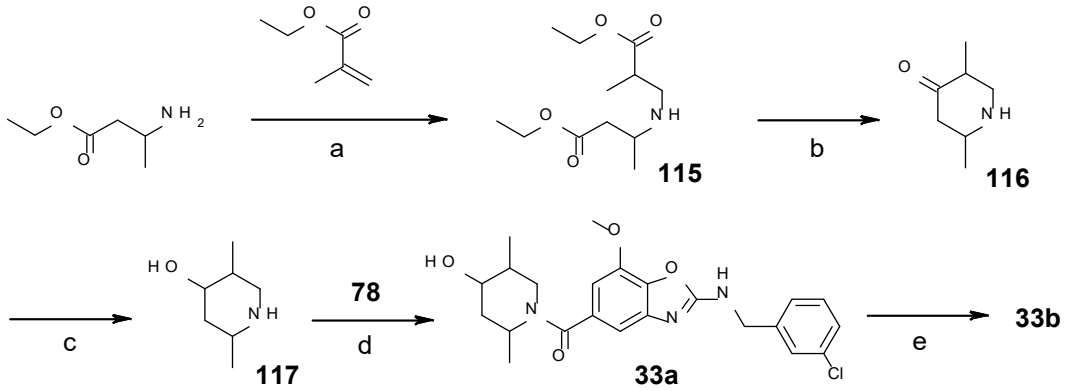
{2-[(3-Chlorobenzyl)amino]-8-methoxy[1,2,4]triazolo[1,5-a]pyridin-6-yl}[4-hydroxy-3-methylpiperidin-1-yl]methanone (32).



***rac-trans*-32**

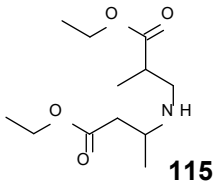
HATU (80 mg, 0.21 mmol, 1.2 equiv.) and *N,N*-diisopropylethylamine (67 µL, 0.38 mmol, 2.2 equiv.) were added to a solution of 2-[(3-chlorobenzyl)amino]-8-methoxy[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid (**114**) (64 mg, 91% purity, 0.17 mmol) in *N,N*-dimethylformamide (1.8 mL) and stirred at room temperature for 20 min before *rac-trans*-3-methylpiperidin-4-ol hydrochloride (32 mg, 0.21 mmol, 1.2 equiv.) was added. The reaction mixture was stirred at room temperature overnight and evaporated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **32** as mixture of *rac-trans* stereoisomers. Yield: 35 mg (47%). LC-MS (method 1a): t_R (min) = 0.77; MS (ESI+): m/z = 430 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.31 (s, 1H), 7.42-7.25 (m, 5H), 6.89 (s, 1H), 4.46 (d, *J* = 4.9 Hz, 2H), 3.92 (s, 3H), 3.24-3.16 (m, 1H), 3.11-2.94 (m, 1H), 3.11-2.92 (m, 1H), 1.87-1.73 (m, 1H), 1.49-1.28 (m, 2H), 1.01-0.75 (m, 3H), 3 protons are concealed.

{2-[(3-Chlorobenzyl)amino]-7-methoxy-1,3-benzoxazol-5-yl}[4-hydroxy-2,5-dimethylpiperidin-1-yl]methanone as mixture of 6 stereoisomers (33a) and as single stereoisomer of unknown absolute stereochemistry (33b).



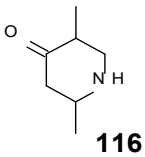
a) NH_4Cl, 2-propanol, RT to RF; b) NaOMe, toluene, RF; c) $NaBH_4$, EtOH, RT; d) **78**, HATU, DIEA, DMF, RT; e) diastereomer separation.

Ethyl 3-{[3-ethoxy-2-methyl-3-oxopropyl]amino}butanoate (115).



Ethyl 2-methylprop-2-enoate (2.66 mL, 21.30 mmol, 1.065 equiv.) and ammonium chloride (64 mg, 1.20 mmol, 0.06 equiv.) were added at room temperature to a solution of ethyl 3-aminobutanoate (2.94 mL, 20.00 mmol) in 2-propanol (1.1 mL). The reaction mixture was refluxed for 5 h and evaporated under reduced pressure and in high vacuum to remove unreacted ethyl 2-methylprop-2-enoate to give **115** (3.67 g) as raw material which was used without further purification.

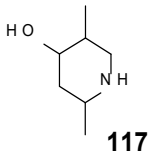
2,5-Dimethylpiperidin-4-one (116).



Sodium methanolate solution (25% in methanol, 3.5 mL, 0.14 mmol) was added dropwise under argon atmosphere to a refluxing mixture of ethyl 3-{[3-ethoxy-2-methyl-3-oxopropyl]amino}butanoate (**115**) (3.66 g, raw material) in toluene (10 mL). Methanol was removed *via* distillation (head temperature up to 90 °C), and the residual mixture was stirred for further 1 h under reflux. After cooling to room temperature, concentrated hydrochloric acid solution (5 mL) was added, and the reaction mixture stirred again for further 3 h under reflux. After cooling to room temperature, the mixture was neutralized by

addition of solid sodium hydrogen carbonate, set to pH 11 by addition of aqueous sodium hydroxide solution and stirred for 1 h at room temperature. After dilution with dichloromethane, filtration and phase separation, the organic phase was dried over sodium sulfate, filtered, evaporated under reduced pressure and dried *in vacuo* to give **116** as raw material which was used without further purification.

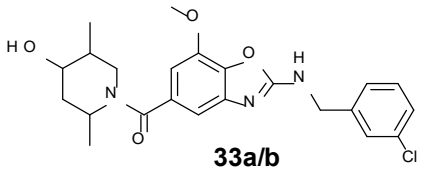
2,5-Dimethylpiperidin-4-ol (117).



117

Sodium borohydride (158 mg, 4.16 mmol) was added in portions to a mixture of 2,5-dimethylpiperidin-4-one (**116**) (662 mg, raw material) in ethanol (12 mL). The reaction mixture was stirred at room temperature for 1 h before acetone (5 mL) was added, then stirred for 10 min, evaporated under reduced pressure und dried in *vacuo* to give **117** as raw material which was used without further purification.

{2-[(3-Chlorobenzyl)amino]-7-methoxy-1,3-benzoxazol-5-yl}[4-hydroxy-2,5-dimethylpiperidin-1-yl]methanone as mixture of 6 stereoisomers (33a) and as single stereoisomer of unknown absolute stereochemistry (33b).



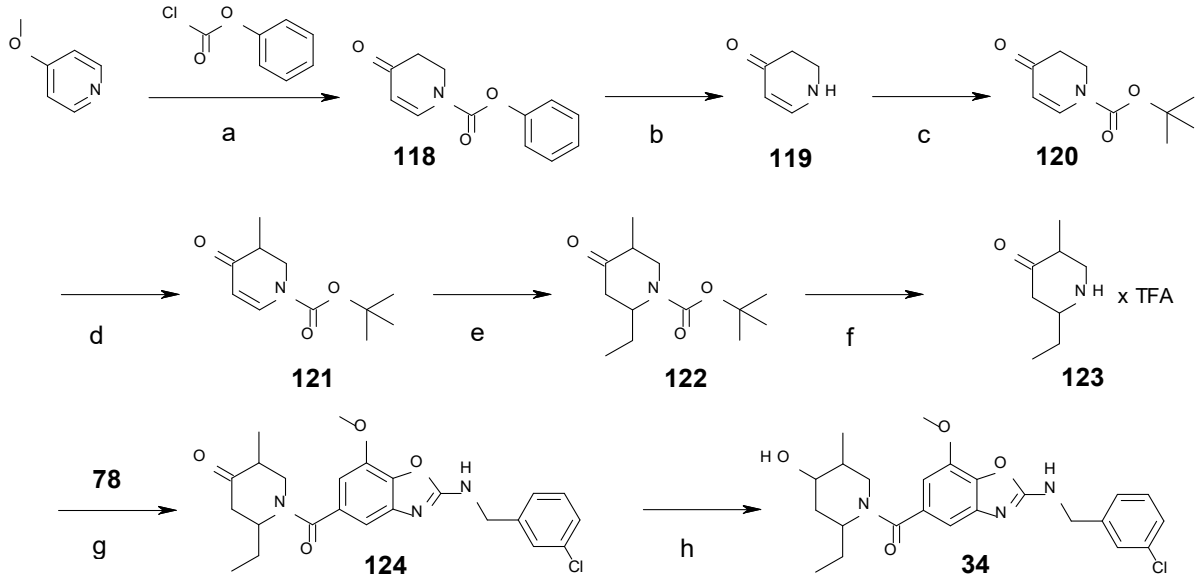
33a/b

HATU (336 mg, 0.88 mmol, 1.2 equiv.) and *N,N*-diisopropylethylamine (321 µL, 1.84 mmol, 2.5 equiv.) were added to a solution of 2-[(3-chlorobenzyl)amino]-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**78**) (245 mg, 0.74 mmol) in *N,N*-dimethylformamide (10 mL) and stirred at room temperature for 30 min before 2,5-dimethylpiperidin-4-ol (**117**) (571 mg, raw material with proposed 50% purity, 2.21 mmol, 3.0 equiv.) was added. The reaction mixture was stirred for 1 h, then additional 2,5-dimethylpiperidin-4-ol (285 mg, 50% purity, 1.10 mmol, 1.5 equiv.) was added in portions until the conversion was complete. The reaction mixture was evaporated under reduced pressure and purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **33a** in a mixture of three racemic diastereomers. Yield: 198 mg (58%). LC-MS (method 1a): t_R (min) = 0.85 / 0.87 / 0.90; MS (ESI+): m/z = 444 $[M+H]^+$.

This mixture was submitted for diastereomer separation (preparative method: HPLC: column: Sunfire C-18; eluent: 5% solution of 1% TFA / 50% water / 45% acetonitrile) and each racemic diastereomer 1-3 was then submitted to enantiomer separation (preparative method: HPLC: column: Daicel Chiralpak AD-H 5 µm, 250 mm x 20 mm; diastereomer 1 and 2: eluent: 65% *iso*-hexane / 35% ethanol; diastereomer 3: 60% *iso*-hexane / 40% ethanol; temperature: 35 °C; flow rate: 15 mL/min; UV

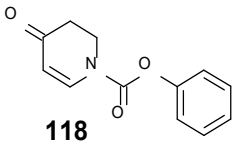
detection: 220 nm; analytical method: HPLC: column: Daicel Chiralpak AD-H 5 µm, 250 mm x 4.6 mm; eluent: 65% *iso*-hexane / 35% ethanol; temperature: 30 °C; flow rate: 1 mL/min; UV detection: 220 nm) to give six enantiomers: diastereomer 1: 12 mg (6%), HPLC: t_R (min) = 8.68, >99% ee; *ent*-diastereomer 1: 12 mg (6%), HPLC: t_R (min) = 13.21, >99% ee; diastereomer 2: 31 mg (16%), HPLC: t_R (min) = 7.52, >99% ee; *ent*-diastereomer 2: 47 mg (24%), HPLC: t_R (min) = 10.16, >99% ee; diastereomer 3: 10 mg (3%), HPLC: t_R (min) = 8.57, >99% ee; *ent*-diastereomer 3, which corresponds to the desired stereoisomer **33b**: 9 mg (5%), HPLC: t_R (min) = 9.73, >95% ee; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.63 (t, *J* = 6.2 Hz, 1H), 7.46-7.28 (m, 4H), 6.79 (s, 1H), 6.65 (s, 1H), 4.69 (d, *J* = 3.4 Hz, 1H), 4.52 (d, *J* = 5.4 Hz, 2H), 3.90 (s, 3H), 3.74 (br s, 1H), 2.99-2.86 (m, 1H), 1.77-1.62 (m, 3H), 1.48-1.22 (m, 1H), 1.30 (d, *J* = 6.9 Hz, 3H), 0.90-0.75 (m, 4H).

{2-[(3-Chlorobenzyl)amino]-7-methoxy-1,3-benzoxazol-5-yl}[2-ethyl-4-hydroxy-5-methylpiperidin-1-yl]methanone (34) as racemic diastereomer.



a) i) KBH(O*i*-Pr)$_3$, 2-propanol, -45 °C, ii) phenyl chloroformate, Et_2O, RT; b) NaOMe, MeOH, RT; c) Boc_2O, TEA, DMAP, DCM, RT; d) i) LDA, THF, -78 °C, ii) MeI, DMPU, -78 °C to RT; e) i) EtMgBr, CuI, THF, -78 °C to -20 °C, ii) **121**, THF, -78 °C to RT; f) TFA, DCM, RT; g) **78**, HATU, TEA, DMAP, DMF, RT; h) i) $NaBH_4$, EtOH, RT, ii) diastereomer separation.

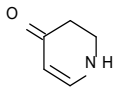
Phenyl 4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (118).



Potassium triisopropoxyborohydride solution (1 M in tetrahydrofuran, 784.4 mL, 784.4 mmol, 2.0 equiv.) was added dropwise at -45 °C to a solution of 4-methoxypyridine (42.8 g, 392.2 mmol) in

2-propanol (500 mL), followed by very slow addition of a solution of phenyl chloroformate (51.7 mL, 411.8 mmol, 1.05 equiv.) in diethyl ether (400 mL). The reaction mixture was stirred at room temperature for 2 h and added dropwise to aqueous hydrochloric acid solution (10% in water, 1 L). The resulting mixture was extracted with ethyl acetate. The organic phase was dried and concentrated under reduced pressure. The residue was suspended in diethyl ether and the solid filtered and dried *in vacuo* to give **118**. Yield: 60.0 g (70%). LC-MS (method 7a): t_R (min) = 0.79; MS (ESI+): m/z = 218 $[M+H]^+$.

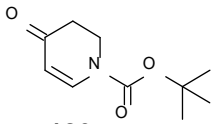
2,3-Dihydropyridin-4(1*H*)-one (119).



119

A solution of phenyl 4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (**118**) (30.0 g, 138.1 mmol) in methanol (270 mL) was added at room temperature dropwise to a solution of sodium methylate (7.85 g, 138.1 mmol, 1.0 equiv.) in methanol (30 mL). The reaction mixture was stirred at room temperature for 2 h, adjusted to pH 1 by addition of concentrated hydrochloric acid solution and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: dichloromethane / methanol 10:1 to 3:1 to 0:1) to give **119**. Yield: 10.7 g (79%). GC-MS (method 1b): t_R (min) = 4.09; MS (EI+): m/z = 97 $[M]^+$.

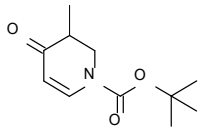
***tert*-Butyl 4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (120).**



120

Triethylamine (36.6 mL, 262.5 mmol, 1.3 equiv.), 4-dimethylaminopyridine (2.47 g, 20.19 mmol, 0.1 equiv.) and di-*tert*-butyldicarbonate (57.3 g, 262.5 mmol, 1.3 equiv.) were added at room temperature to a mixture of 2,3-dihydropyridin-4(1*H*)-one (**119**) (19.6 g, 201.9 mmol) in dichloromethane (200 mL). The reaction mixture was stirred at room temperature overnight, mixed with additional di-*tert*-butyldicarbonate (22.0 g, 101.0 mmol, 0.5 equiv.) and triethylamine (14.1 mL, 101.0 mmol, 0.5 equiv.) and stirred at room temperature overnight. The reaction mixture was poured onto aqueous hydrochloric acid solution (0.5 N). After phase separation, the organic phase was washed with aqueous hydrochloric acid solution (0.5 N) and brine, dried, filtered and evaporated *in vacuo*. The residue was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate 3:1 to 1:1) to give **120**. Yield: 3.54 g (7%, 80% purity). GC-MS (method 2b): t_R (min) = 5.63; MS (ESI+): m/z = 198 $[M+H]^+$.

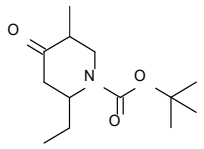
***tert*-Butyl 3-methyl-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (121).**



121

A solution of *tert*-butyl 4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (**120**) (500 mg, 2.54mmol) in tetrahydrofuran (5 mL) was added under argon atmosphere at -78 °C dropwise to a solution of lithium diisopropylamide solution (1 M in tetrahydrofuran, 3.80 mL, 3.80 mmol, 1.5 equiv.) in tetrahydrofuran (5 mL). The reaction mixture was stirred at -78 °C for 30 min before iodomethane (0.28 mL, 4.56 mmol, 1.8 equiv.) and *N,N'*-dimethylpropyleneurea (0.46 mL, 3.80 mmol, 1.5 equiv.) were added at -78 °C. The reaction mixture was allowed to warm to room temperature, stirred overnight, poured onto water and extracted several times dichloromethane. The combined organic phases were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **121**. Yield: 100 mg (19%). LC-MS (method 9a): t_R (min) = 0.92; MS (ESI+): m/z = 212 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 7.82 (d, *J* = 8.3 Hz, 1H), 5.17 (d, *J* = 8.3 Hz, 1H), 4.07 (dd, *J* = 5.9 Hz, 13.2 Hz, 1H), 3.40 (t, *J* = 12.6 Hz, 1H), 2.57-2.48 (m, 1H, partially concealed), 1.49 (s, 9H), 0.99 (d, *J* = 6.8 Hz, 3H).

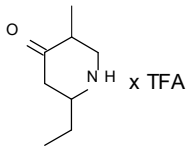
***tert*-Butyl 2-ethyl-5-methyl-4-oxopiperidine-1-carboxylate (122).**



122

Ethylmagnesium bromide solution (3 M in dichloromethane, 2.13 mL, 6.39 mmol, 3.0 equiv.) was added under argon atmosphere at -78 °C dropwise to a mixture of copper(I) iodide (580 mg, 3.04 mmol, 1.4 equiv.) in tetrahydrofuran (10 mL). The reaction mixture was allowed to warm to -20 °C, cooled again to -78 °C and mixed with a solution of *tert*-butyl 3-methyl-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (**121**) (600 mg, 75% purity, 2.13 mmol) in tetrahydrofuran (10 mL). The reaction mixture was stirred 1 h at -78 °C and 20 min after removal of the cooling bath, quenched with saturated aqueous ammonium chloride solution (10 mL) and extracted several times with diethyl ether. The combined organic phases were washed with brine, dried, filtered, evaporated under reduced pressure and dried *in vacuo* to give **122** which was used in the next step without further purification. Yield: 690 mg (quantitative, 88% purity). GC-MS (method 2b): t_R (min) = 5.05 / 5.18; MS (EI+): m/z = 142 $[M+H\text{-}Boc]^+$.

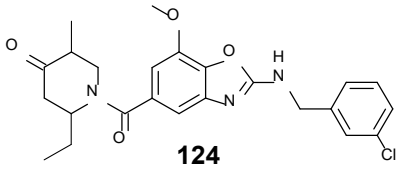
2-Ethyl-5-methylpiperidin-4-one trifluoroacetate (123).



123

Trifluoroacetic acid (1.15 mL, 14.88 mmol, 6.0 equiv.) was added to a solution of *tert*-butyl 2-ethyl-5-methyl-4-oxopiperidine-1-carboxylate (**122**) (680 mg, 88% purity, 2.48 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at room temperature overnight, evaporated *in vacuo*, mixed with some water and lyophilized to give **123** which was used in the next step without further purification. Yield: 768 mg (quantitative).

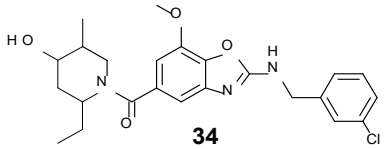
1-({2-[(3-Chlorobenzyl)amino]-7-methoxy-1,3-benzoxazol-5-yl}carbonyl)-2-ethyl-5-methylpiperidin-4-one (124).



124

A mixture of 2-[(3-chlorobenzyl)amino]-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**78**) (501 mg, 1.50 mmol), HATU (629 mg, 1.66 mmol, 1.1 equiv.), triethylamine (419 µL, 3.00 mmol, 2.0 equiv.) and 4-dimethylaminopyridine (202 mg, 1.66 mmol, 1.1 equiv.) in *N,N*-dimethylformamide (15 mL) was stirred at room temperature for 10 min before 2-ethyl-5-methylpiperidin-4-one (**123**) (768 mg, 3.00 mmol, 2.0 equiv.) was added. The reaction mixture was stirred at room temperature overnight and poured onto water (250 mL). The forming precipitate was filtered. After phase separation, the organic phase was evaporated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **124**. Yield: 122 mg (17%). LC-MS (method 3a): t_R (min) = 5.08 / 5.16; MS (ESI+): m/z = 456 $[M+H]^+$.

{2-[(3-Chlorobenzyl)amino]-7-methoxy-1,3-benzoxazol-5-yl}[2-ethyl-4-hydroxy-5-methylpiperidin-1-yl]methanone (34) as racemic diastereomer.



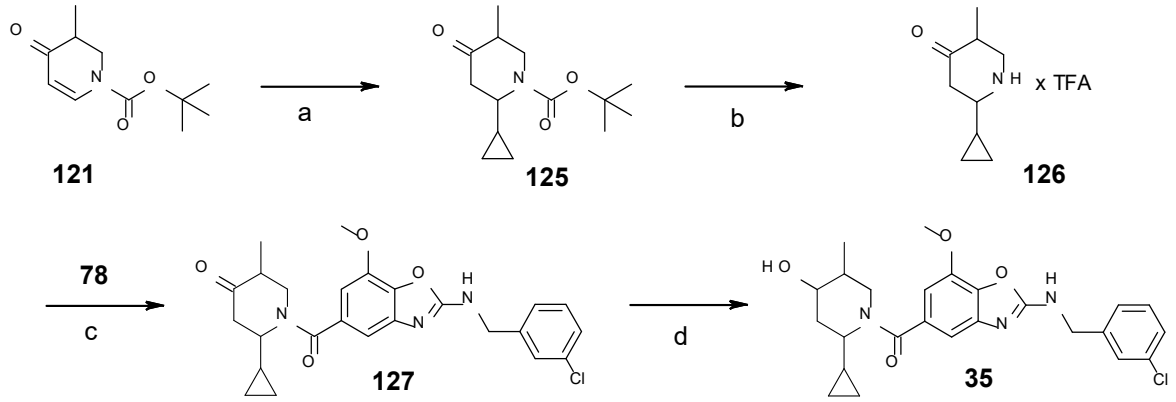
34

Sodium borohydride (27 mg, 0.73 mmol, 3.0 equiv.) was added in portions under argon atmosphere at room temperature to a mixture of 1-({2-[(3-chlorobenzyl)amino]-7-methoxy-1,3-benzoxazol-5-yl}carbonyl)-2-ethyl-5-methylpiperidin-4-one (**124**) (115 mg, 0.24 mmol) in ethanol (3.0 mL). The

reaction mixture was stirred at room temperature for 1.5 h, mixed with some water and filtered. The filtrate was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **34** in a mixture of racemic diastereomers. Yield: 91 mg (67%, 80% purity). LC-MS (method 3a): t_R (min) = 4.84 / 4.90 / 4.92 / 4.97; MS (ESI+): m/z = 458 $[M+H]^+$.

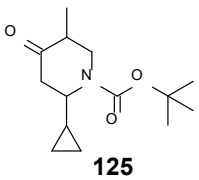
This mixture (89 mg) was submitted for diastereomer separation (preparative method: HPLC: column: Kromasil 100 C18 5 µm, 250 mm x 20 mm; eluent: A + B: 50% water / 50% acetonitrile, C: 2% trifluoroacetic acid, gradient of A + B while C was constantly dosed; temperature: 24 °C; flow A + B: 23.75 mL/min, flow C: 1.25 mL/min; UV detection: 210 nm) to give three racemic diastereomers: racemic diastereomer 1: 16 mg (14%, 98% purity), LC-MS (method 7a): t_R (min) = 0.95; MS (ESI+): m/z = 458 $[M+H]^+$; racemic diastereomer 2, which corresponds to the desired stereoisomer **34**: 12 mg (11%, >99% purity), LC-MS (method 7a): t_R (min) = 0.97; MS (ESI+): m/z = 458 $[M+H]^+$; racemic diastereomer 3: 18 mg (16%, 97% purity), LC-MS (method 7a): t_R (min) = 0.99; MS (ESI+): m/z = 458 $[M+H]^+$.

{2-[(3-Chlorobenzyl)amino]-7-methoxy-1,3-benzoxazol-5-yl}[(2-cyclopropyl-4-hydroxy-5-methylpiperidin-1-yl]methanone (35) as mixture of two racemic diastereomers.



a) i) cyclopropylmagnesium bromide, CuI, THF, -78 °C to -20 °C, ii) **121**, THF, -78 °C to RT; b) TFA, DCM, RT; c) **78**, HATU, TEA, DMF, RT; d) i) $NaBH_4$, EtOH, RT, ii) diastereomer separation.

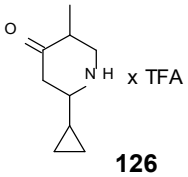
***tert*-Butyl 2-cyclopropyl-5-methyl-4-oxopiperidine-1-carboxylate (125).**



Cyclopropylmagnesium bromide solution (0.5 M in tetrahydrofuran, 12.78 mL, 6.39 mmol, 3.0 equiv.) was added under argon atmosphere at -78 °C dropwise to a mixture of copper(I) iodide (580 mg, 3.04 mmol, 1.4 equiv.) in tetrahydrofuran (5 mL). The reaction mixture was allowed to warm to -20 °C, cooled again to -78 °C and mixed with a solution of *tert*-butyl 3-methyl-4-oxo-3,4-dihydropyridine-

1(2*H*)-carboxylate (**121**) (600 mg, 75% purity, 2.13 mmol) in tetrahydrofuran (5 mL). The reaction mixture was stirred 1 h at -78 °C and 20 min after removal of the cooling bath, quenched with saturated aqueous ammonium chloride solution (10 mL) and extracted several times with diethyl ether. The combined organic phases were washed with brine, dried, filtered, evaporated under reduced pressure and dried *in vacuo* to give **125** which was used in the next step without further purification. Yield: 750 mg (82%, 59% purity). LC-MS (method 9a): t_R (min) = 1.07; MS (ESI+): m/z = 154 $[M+H\text{-}Boc]^+$.

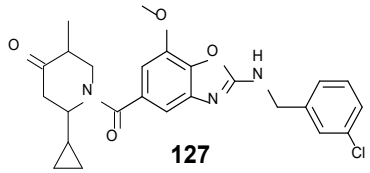
2-Cyclopropyl-5-methylpiperidin-4-one trifuoroacetate (126).



126

Trifluoroacetic acid (1.06 mL, 13.79 mmol, 8.0 equiv.) was added to a solution of *tert*-butyl 2-cyclopropyl-5-methyl-4-oxopiperidine-1-carboxylate (**125**) (740 mg, 59% purity, 1.72 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at room temperature overnight, evaporated *in vacuo*, mixed with some water and lyophilized to give **126** which was used in the next step without further purification. Yield: 874 mg (quantitative).

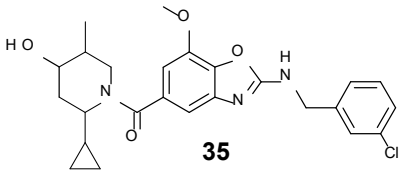
1-({2-[(3-Chlorobenzyl)amino]-7-methoxy-1,3-benzoxazol-5-yl}carbonyl)-2-cyclopropyl-5-methylpiperidin-4-one (127).



127

A mixture of 2-[(3-chlorobenzyl)amino]-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**78**) (544 mg, 1.64 mmol), HATU (684 mg, 1.80 mmol, 1.1 equiv.), triethylamine (456 µL, 3.27 mmol, 2.0 equiv.) and 4-dimethylaminopyridine (220 mg, 1.80 mmol, 1.1 equiv.) in *N,N*-dimethylformamide (15 mL) was stirred at room temperature for 10 min before 2-cyclopropyl-5-methylpiperidin-4-one (**126**) (874 mg, 3.27 mmol, 2.0 equiv.) was added. The reaction mixture was stirred at room temperature overnight and poured onto water (250 mL). The forming precipitate was filtered. After phase separation, the organic phase was evaporated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **127**. Yield: 110 mg (10%, 67% purity). LC-MS (method 7a): t_R (min) = 5.13 / 5.20; MS (ESI+): m/z = 468 $[M+H]^+$.

{2-[(3-Chlorobenzyl)amino]-7-methoxy-1,3-benzoxazol-5-yl}(2-cyclopropyl-4-hydroxy-5-methylpiperidin-1-yl)methanone (35) as mixture of two racemic diastereomers.

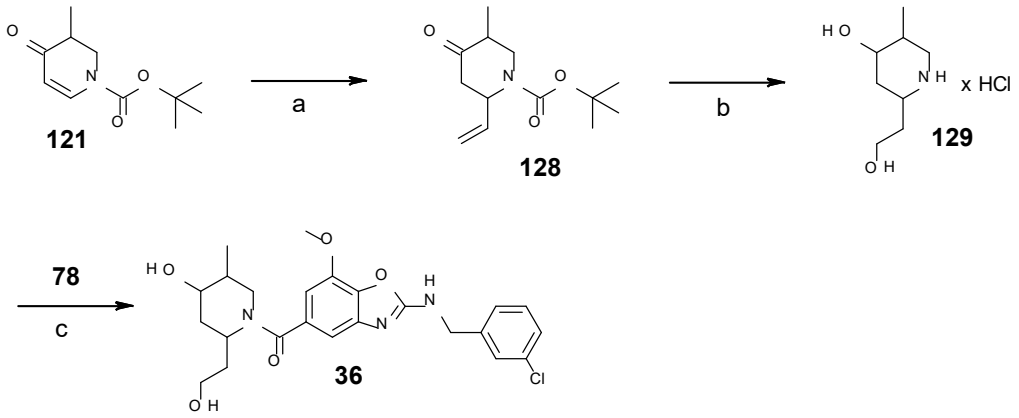


35

Sodium borohydride (18 mg, 0.47 mmol, 3.0 equiv.) was added in portions under argon atmosphere at room temperature to a mixture of 1-({2-[(3-chlorobenzyl)amino]-7-methoxy-1,3-benzoxazol-5-yl}carbonyl)-2-cyclopropyl-5-methylpiperidin-4-one (**127**) (110 mg, 0.16 mmol) in ethanol (2.0 mL). The reaction mixture was stirred at room temperature for 1.5 h, mixed with some water and filtered. The filtrate was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **35** in a mixture of racemic diastereomers. Yield: 70 mg (64%, 67% purity). LC-MS (method 3a): t_R (min) = 4.89 / 4.93 / 4.97 / 5.01; MS (ESI+): m/z = 470 $[M+H]^+$.

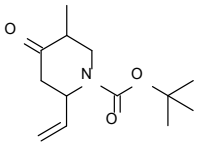
This mixture (70 mg) was submitted for diastereomer separation (preparative method: HPLC: column: Kromasil 100 C18 10 µm, 250 mm x 20 mm; eluent: A + B: 50% water / 50% acetonitrile, C: 2% trifluoroacetic acid, gradient of A + B while C was constantly dosed; temperature: 24 °C; flow A + B: 23.75 mL/min, flow C: 1.25 mL/min; UV detection: 210 nm) to give four racemic diastereomers: racemic diastereomer 1: 10 mg (13%, 92% purity), LC-MS (method 3a): t_R (min) = 4.88; MS (ESI+): m/z = 470 $[M+H]^+$; racemic diastereomer 2+3, which corresponds to the desired stereoisomer mixture **35**: 16 mg (21%, 98% purity), LC-MS (method 3a): t_R (min) = 4.93 / 4.96; MS (ESI+): m/z = 470 $[M+H]^+$; racemic diastereomer 3: 19 mg (25%, >99% purity), LC-MS (method 3a): t_R (min) = 5.00; MS (ESI+): m/z = 470 $[M+H]^+$.

{2-[(3-Chlorobenzyl)amino]-7-methoxy-1,3-benzoxazol-5-yl}[4-hydroxy-2-(2-hydroxyethyl)-5-methylpiperidin-1-yl]methanone (36) as racemic diastereomer.



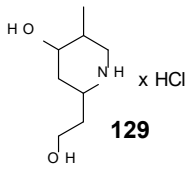
a) i) vinylmagnesium bromide, CuI, THF, -78 °C to -20 °C, ii) **121**, THF, -78 °C to RT; b) i) 9-BBN, THF, RT, ii) NaOH, H_2O_2, RT; c) i) **78**, HATU, TEA, DMF, RT, ii) diastereomer separation.

***tert*-Butyl 5-methyl-4-oxo-2-vinylpiperidine-1-carboxylate (128).**



Vinylmagnesium bromide solution (1.0 M in tetrahydrofuran, 16.62 mL, 16.62 mmol, 3.0 equiv.) was added under argon atmosphere at -78 °C dropwise to a mixture of copper(I) iodide (1.51 g, 7.91 mmol, 1.4 equiv.) in tetrahydrofuran (25 mL). The reaction mixture was allowed to warm to -20 °C, cooled again to -78 °C and mixed with a solution of *tert*-butyl 3-methyl-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (**121**) (1.33 g, 5.54 mmol) in tetrahydrofuran (25 mL). The reaction mixture was stirred for 1 h at -78 °C and for 20 min after removal of the cooling bath, quenched with saturated aqueous ammonium chloride solution (20 mL) and extracted several times with diethyl ether. The combined organic phases were washed with brine, dried, filtered, evaporated under reduced pressure and dried *in vacuo* to give **128** which was used in the next step without further purification. Yield: 1.45 g (93%, 85% purity). GC-MS (method 2b): t_R (min) = 4.90 / 5.04; MS (ESI+): m/z = 140 $[M+H\text{-Boc}]^+$.

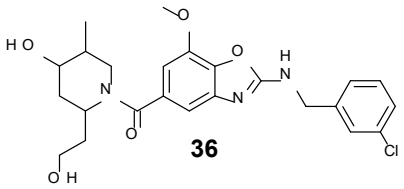
2-(2-Hydroxyethyl)-5-methylpiperidin-4-ol hydrochloride (129).



129

9-Borabicyclo(3.3.1)nonane solution (0.5 M in tetrahydrofuran, 22.66 mL, 11.33 mmol, 2.2 equiv.) was added under water cooling to a mixture of *tert*-butyl 5-methyl-4-oxo-2-vinylpiperidine-1-carboxylate (**128**) (1.45 g, 85% purity, 5.15 mmol) in tetrahydrofuran (21 mL). The reaction mixture was stirred at room temperature for 1.5 h, mixed with aqueous sodium hydroxide solution (2 N, 12.86 mL, 25.75 mmol, 5.0 equiv.) and stirred for 10 min, before hydrogen peroxide solution (35% in water, 4.51 mL, 51.50 mmol, 10.0 equiv.) was added dropwise (caution! strongly exothermic) under water cooling. The reaction mixture was stirred at room temperature for 30 min, mixed with ethyl acetate and saturated with sodium chloride. After phase separation, the aqueous phase was extracted several times with ethyl acetate. The combined organic phases were washed with aqueous sodium hydrogen sulfite solution (39% in water, 11.20 mL, 56.65 mmol, 11.0 equiv.) and brine, dried, filtered and evaporated under reduced pressure. The residue was dissolved in aqueous hydrogen chloride solution (100 mL) and evaporated *in vacuo* to give **129** which was used in the next step without further purification. Yield: 2.35 g.

{2-[(3-Chlorobenzyl)amino]-7-methoxy-1,3-benzoxazol-5-yl}[4-hydroxy-2-(2-hydroxyethyl)-5-methylpiperidin-1-yl]methanone (36) as racemic diastereomer.

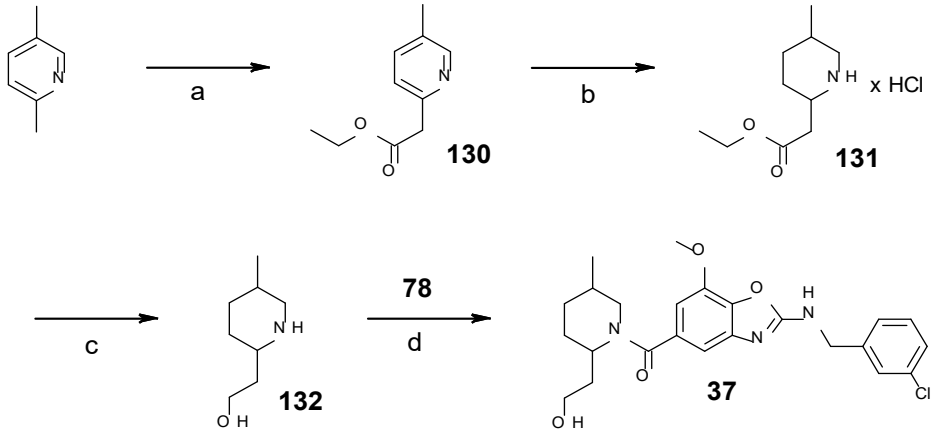


36

A mixture of 2-[(3-chlorobenzyl)amino]-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**78**) (2.66 g, 8.01 mmol), 2-(2-hydroxyethyl)-5-methylpiperidin-4-ol hydrochloride (**129**) (2.35 g, 12.01 mmol, 1.5 equiv.), HATU (4.57 g, 12.01 mmol, 1.5 equiv.), triethylamine (2.23 mL, 16.01 mmol, 2.0 equiv.) and 4-dimethylaminopyridine (978 mg, 8.01 mmol, 1.0 equiv.) in *N,N*-dimethylformamide (60 mL) was stirred at room temperature overnight and poured onto water. After phase separation, the aqueous phase was extracted several times with ethyl acetate. The combined organic phases were evaporated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **36** in a mixture of racemic diastereomers. Yield: 535 mg (13%, 89% purity). LC-MS (method 3a): t_R (min) = 4.47 / 4.58 / 4.69 / 4.74; MS (ESI+): m/z = 474 $[M+H]^+$.

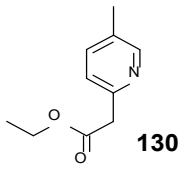
This mixture (535 mg) was submitted for diastereomer separation (preparative method: HPLC: column: Chiralcel OZ-H 5 µm, 250 mm x 20 mm; eluent: 50% *iso*-hexane / 50% ethanol; temperature: 30 °C; flow rate: 15 mL/min; UV detection: 220 nm) to give four racemic diastereomers of which after testing the most potent racemic diastereomer was repurified (preparative method: HPLC: column: Chiralpak AZ-H 5 µm, 250 mm x 20 mm; eluent: 50% *iso*-hexane / 50% ethanol; temperature: 40 °C; flow rate: 15 mL/min; UV detection: 220 nm; analytical method: HPLC: column: Chiralpak AZ-H 5 µm, 250 mm x 4.6 mm; eluent: 50% *iso*-hexane / 50% ethanol plus 0.2% trifluoroacetic acid and 1% water; temperature: 40 °C; flow rate: 1 mL/min; UV detection: 220 nm) to give **36** as racemic diastereomer. Yield: 10 mg (94% purity). HPLC: t_R (min) = 8.83; LC-MS (method 3a): t_R (min) = 4.57; MS (ESI+): m/z = 474 $[M+H]^+$; LC-MS (method 9a): t_R (min) = 0.81; MS (ESI+): m/z = 474 $[M+H]^+$.

{2-[(3-Chlorobenzyl)amino]-7-methoxy-1,3-benzoxazol-5-yl}[2-(2-hydroxyethyl)-5-methylpiperidin-1-yl]methanone (37) as single stereoisomer.



a) i) *n*-BuLi, $(i\text{-Pr})_2NH$, TMEDA, THF, -40 °C, ii) 2,5-dimethylpyridine, -40 °C to 0 °C, iii) ethyl chloroformate, -78 °C to RT; b) H_2 (1 bar), PtO_2 x H_2O, AcOH, RT; c) i) $LiBH_4$, THF, 0 °C to 50 °C, ii) $LiAlH_4$, 0 °C to RT; d) i) **78**, HATU, DMAP, DMF, RT, ii) diastereomer and enantiomer separation.

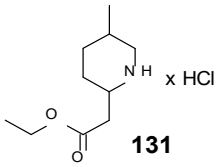
Ethyl (5-methylpyridin-2-yl)acetate (130).



n-Butyllithium solution (2.5 M in hexane, 82.12 mL, 205.31 mmol, 2.2 equiv.) was added dropwise under argon atmosphere at -40 °C to a solution of diisopropyl amine (28.78 mL, 205.31 mmol, 2.2 equiv.) and *N,N,N',N'*-tetramethylethylendiamine (10.00 mL, 66.26 mmol, 0.7 equiv.) in tetrahydrofuran (90 mL). The reaction mixture was stirred at -40 °C for 1 h, mixed with 2,5-dimethylpyridine (10.00 g, 93.32 mmol), stirred at 0 °C for 1 h, cooled to -78 °C, before slowly at -78 °C

ethyl chloroformate (8.92 mL, 93.32 mmol, 1.0 equiv.) was added. The reaction mixture was stirred overnight while allowing to warm to room temperature, poured onto iced water and saturated with sodium chloride. After phase separation, the aqueous phase was extracted several times with ethyl acetate. The combined organic phases were washed with brine, dried, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate 3:1 to 2:1) to give **130**. Yield: 5.40 g (29%, 91% purity). LC-MS (method 9a): t_R (min) = 0.49; MS (ESI+): m/z = 180 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.23 (d, *J* = 1.7 Hz, 1H), 7.57 (dd, *J* = 1.7 Hz, 7.8 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 4.07 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 2H), 2.27 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H).

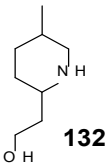
Ethyl (5-methylpiperidin-2-yl)acetate hydrochloride (131).



131

A solution of ethyl (5-methylpyridin-2-yl)acetate (**130**) (2.70 g, 14.76 mmol) in acetic acid (70 mL) was mixed under argon atmosphere at room temperature with platin(IV) oxide hydrate (54 mg), purged with hydrogen gas and stirred at room temperature for 5 days under hydrogen gas atmosphere (1 bar), mixed with palladium (10% on carbon, 236 mg) and stirred at room temperature for another 2 days under hydrogen gas atmosphere (1 bar). The reaction mixture was filtered through Celite® and concentrated under reduced pressure. The residue was dissolved in aqueous hydrogen chloride solution (100 mL), concentrated under reduced pressure and lyophilized to give **131** which was used in the next step without further purification. Yield: 3.06 g (73%, 78% purity). GC-MS (method 1b): t_R (min) = 3.59 / 3.68; MS (ESI+): m/z = 156 $[M-Et]^-$.

2-(5-Methylpiperidin-2-yl)ethanol (132).

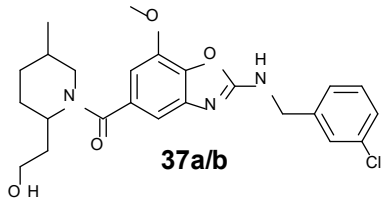


132

Lithium borohydride (557 mg, 25.58 mmol, 2.0 equiv.) was added at 0 °C to a solution of ethyl (5-methylpiperidin-2-yl)acetate (**131**) (3.00 g, 78% purity, 12.79 mmol) in tetrahydrofuran (60 mL). The reaction mixture was stirred at 50 °C for 2 h, before lithium aluminum hydride solution (1 M in tetrahydrofuran, 12.79 mL, 12.79 mmol, 1.0 equiv.) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 30 min and quenched with brine. The aqueous phase was extracted several times with ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered,

evaporated under reduced pressure and dried *in vacuo* to give **132**. Yield: 1.03 g (29% yield, 51% purity). GC-MS (method 1b): t_R (min) = 2.81 / 2.89; MS (method 1c): (ESI+): m/z = 144 $[M+H]^+$.

{2-[(3-Chlorobenzyl)amino]-7-methoxy-1,3-benzoxazol-5-yl}[2-(2-hydroxyethyl)-5-methylpiperidin-1-yl]methanone (37a) in a mixture of racemic diastereomers and (37b) as single stereoisomer.

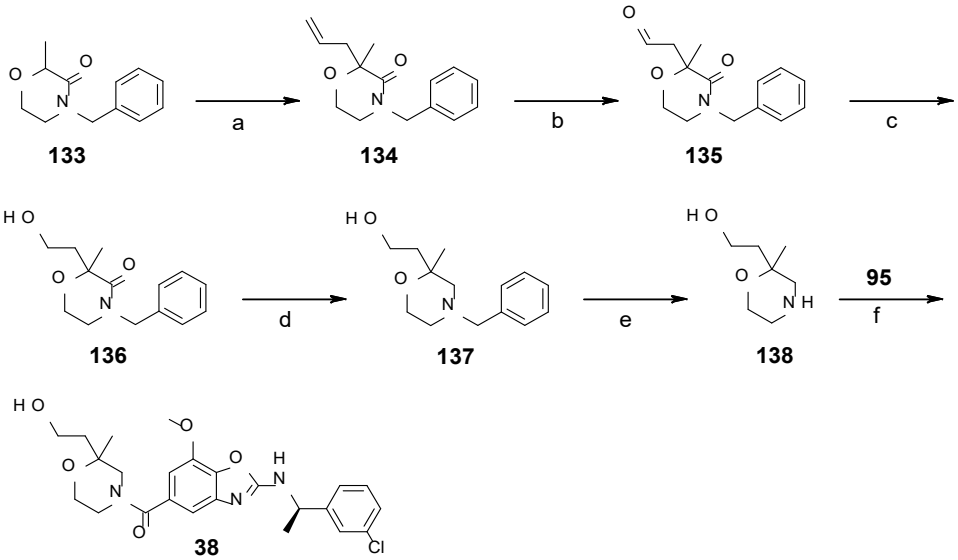


37a/b

A mixture of 2-[(3-chlorobenzyl)amino]-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**78**) (814 mg, 2.45 mmol), 2-(5-methylpiperidin-2-yl)ethanol (**132**) (1.03 g, 51% purity, 3.67 mmol, 1.5 equiv.), HATU (1.02 g, 2.69 mmol, 1.1 equiv.) and 4-dimethylaminopyridine (329 mg, 2.69 mmol, 1.1 equiv.) in *N,N*-dimethylformamide (20 mL) was stirred at room temperature for 2 days, filtered and evaporated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **37a** in a mixture of racemic diastereomers. Yield: 440 mg (37%, 93% purity). LC-MS (method 9a): t_R (min) = 5.05 / 5.10; MS (ESI+): m/z = 458 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.64 (br s, 1H), 7.47-7.29 (m, 4H), 6.80 (s, 1H), 6.65 (s, 1H), 4.83-4.68 / 4.45-4.20 / 3.9-3.77 (3x m, 2H), 4.53 (d, *J* = 6.1 Hz, 2H), 3.90 (s, 3H), 3.52-3.39 (m, 1H), 3.29-3.16 (m, 1H), 1.97-1.76 (m, 1H), 1.75-1.41 (m, 5H), 1.39-1.21 (m, 1H), 1.00-0.63 (m, 3H), 2 protons are concealed.

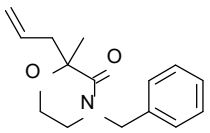
This mixture (440 mg) was submitted for diastereomer and enantiomer separation (preparative method: HPLC: column: Daicel Chiralpak AZ-H 5 µm, 250 mm x 30 mm; eluent: 30% *iso*-hexane / 70% ethanol; temperature: 25 °C; flow rate: 30 mL/min; UV detection: 230 nm; analytical method: HPLC: column: Daicel Chiralpak AZ-H 5 µm, 250 mm x 4.6 mm; eluent: 100% ethanol; temperature: 30 °C; flow rate: 1.0 mL/min; UV detection: 220 nm) to give four enantiomers: diastereomer 1: 15 mg (1%, 92% purity). HPLC: t_R (min) = 6.80, >99% ee; LC-MS (method 3a): t_R (min) = 5.08; MS (ESI+): m/z = 458 $[M+H]^+$; diastereomer 2: 95 mg (8%, 99% purity). HPLC: t_R (min) = 7.59, 98% ee; LC-MS (method 3a): t_R (min) = 5.12; MS (ESI+): m/z = 458 $[M+H]^+$; *ent*-diastereomer 2, which corresponds to the desired stereoisomer **37b**: 88 mg (8%, >99% purity). HPLC: t_R (min) = 8.97, 97% ee; LC-MS (method 3a): t_R (min) = 5.13; MS (ESI+): m/z = 458 $[M+H]^+$; *ent*-diastereomer 1: 21 mg (1%, 70% purity). HPLC: t_R (min) = 9.84, 40% de; LC-MS (method 3a): t_R (min) = 5.09; MS (ESI+): m/z = 458 $[M+H]^+$.

(2-{[(1*R*)-1-(3-Chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[2-(2-hydroxyethyl)-2-methylmorpholin-4-yl]methanone (38) as single stereoisomer.



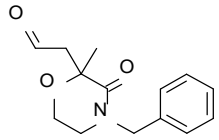
a) i) LHMDS, THF, -78 °C, ii) allyl iodide, 0 °C to RT; b) OsO_4, $NaIO_4$, THF/water, 0 °C; c) $NaBH_4$, MeOH, 0 °C; d) BH_3 x Me_2S, THF, RF; e) H_2 (1 bar), 10% Pd/C, 20% $Pd(OH)_2$/C, EtOH, RT; f) i) **95**, HATU, DIEA, DMF, RT, ii) diastereomer separation.

2-Allyl-4-benzyl-2-methylmorpholin-3-one (134) as racemate.



4-Benzyl-2-methylmorpholin-3-one (racemate **133**) (20.0 g, 97.4 mmol) [lit: Perrone, R. *et al.*, *Synthesis* **1976**, *9*, 598-600] was initially charged in tetrahydrofuran (500 mL), lithium hexamethyldisilazide solution in tetrahydrofuran (1 M, 136 mL, 136 mmol, 1.40 equiv.) was added under argon at -78 °C and the reaction mixture was then stirred for 15 min. Subsequently, at -78 °C, allyl iodide (19.6 g, 10.7 mL, 117 mmol, 1.20 equiv.) was added, and the reaction mixture was warmed to room temperature and stirred overnight. The mixture was then cooled to 0 °C, lithium hexamethyldisilazide solution in tetrahydrofuran (1 M, 68 mL, 68.0 mmol, 0.70 equiv.) and allyl iodide (9.80 g, 5.35 mL, 56.5 mmol, 0.60 equiv.) were added and the mixture was stirred at room temperature for 3 h. The reaction was terminated by addition of saturated aqueous ammonium chloride solution and then extracted with ethyl acetate. The organic phase was washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product **134** was used without further purification in the next step. Yield: 25.8 g (73%, 67% purity). LC-MS (method 1a): t_R (min) = 0.97; MS (ESI+): m/z = 246 $[M+H]^+$.

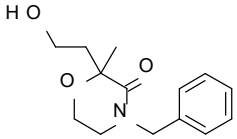
(4-Benzyl-2-methyl-3-oxomorpholin-2-yl)acetaldehyde (135) as racemate.



135

2-Allyl-4-benzyl-2-methylmorpholin-3-one (**134**) (racemate) (6.40 g, 26.1 mmol) in tetrahydrofuran (400 mL) and water (250 mL) was treated with 2.5% solution of osmium tetroxide in *tert*-butanol (6.55 mL, 2.41 mmol, 0.09 equiv.) and sodium periodate (16.7 g, 78.3 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 20 h. The reaction solution was filtered through Celite® and the filter residue was washed with tetrahydrofuran. The reaction solution was taken up in ethyl acetate, washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product **135** was used without further purification in the next step. Yield: 6.99 g of crude product. LC-MS (method 1a): $t_{R\ (min)}$ = 0.78; MS (ESI+): m/z = 248 $[M+H]^+$.

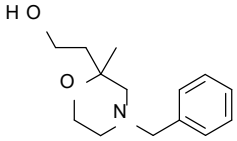
4-Benzyl-2-(2-hydroxyethyl)-2-methylmorpholin-3-one (136) as racemate.



136

(4-Benzyl-2-methyl-3-oxomorpholin-2-yl)acetaldehyde (**135**) (racemate) (6.99 g, about 28.3 mmol, crude product) in methanol (120 mL) was treated with sodium borohydride (3.04 g, 80.4 mmol, 2.84 equiv.) at 0 °C. The mixture was then warmed to room temperature and stirred for 30 min. Water was added to the reaction solution, most of the methanol was removed under reduced pressure and the residue was extracted with ethyl acetate. The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product **136** was used without further purification in the next step. Yield: 5.80 g (82%, crude product). LC-MS (method 2a): t_R (min) = 0.67; MS (ESI+): m/z = 250 $[M+H]^+$.

2-(4-Benzyl-2-methylmorpholin-2-yl)ethanol (137) as racemate.

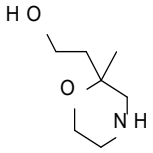


137

4-Benzyl-2-(2-hydroxyethyl)-2-methylmorpholin-3-one (racemate **136**) (5.80 g, about 23.3 mmol, crude product) in tetrahydrofuran (230 mL) was treated with borane-dimethyl sulfide complex solution

in tetrahydrofuran (2 M, 116 mL, 233 mmol, 10 equiv.) under argon and the reaction mixture was then stirred under reflux for 1 h. The mixture was subsequently cooled to room temperature, ethanol (90 mL) was added carefully and the mixture was then stirred under reflux for 1 h. The mixture was concentrated completely under reduced pressure, the residue was taken up in acetonitrile and purified directly by preparative HPLC (reversed phase, acetonitrile / water, isocratic) to give **137**. Yield: 4.58 g (83%). LC-MS (method 4a): t_R (min) = 2.42; MS (ESI+): m/z = 236 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 7.37-7.21 (m, 5H), 4.27 (t, *J* = 5.1 Hz, 1H), 3.59 (t, *J* = 4.9 Hz, 2H), 3.48-3.38 (m, 4H), 2.29 (br d, *J* = 2.9 Hz, 2H), 2.22-2.06 (m, 2H), 1.91 (dt, *J* = 13.8, 7.0 Hz, 1H), 1.56 (dt, *J* = 13.8, 7.5 Hz, 1H), 1.13 (s, 3H).

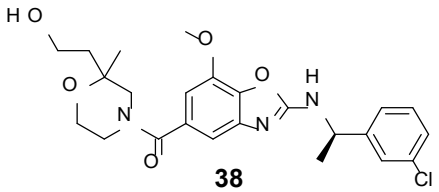
2-(2-Methylmorpholin-2-yl)ethanol (138) as racemate.



138

2-(4-Benzyl-2-methylmorpholin-2-yl)ethanol (racemate **137**) (4.65 g, 19.8 mmol) in ethanol (200 mL) was treated with 10% palladium on carbon (465 mg) and 20% palladium hydroxide on carbon (235 mg) under argon, and the mixture was then stirred under an atmosphere of hydrogen at standard pressure for 36 h. The reaction solution was filtered through Celite® and the filter residue was washed with methanol. The filtrate was concentrated under reduced pressure and the product **138** was dried under high vacuum. Yield: 2.66 g (90%). MS (method 2c): m/z = 146 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 3.52-3.42 (m, 4H), 2.58 (dd, *J* = 5.6, 4.2 Hz, 2H), 2.54-2.40 (m, 2H), 1.84 (dt, *J* = 13.9, 7.1 Hz, 1H), 1.55 (dt, *J* = 13.7, 7.6 Hz, 1H), 1.09 (s, 3H), 2 protons concealed.

(2-{[(1*R*)-1-(3-Chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[2-(2-hydroxyethyl)-2-methylmorpholin-4-yl]methanone (38) as single stereoisomer.



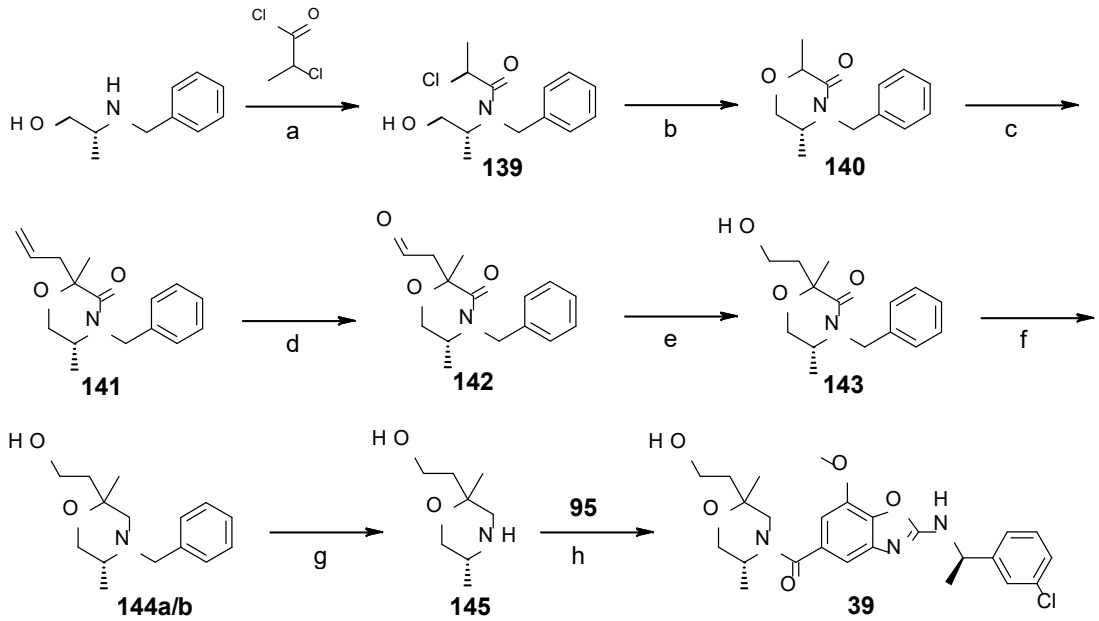
38

HATU (218 mg, 0.574 mmol, 1.2 equiv.) and *N,N*-diisopropylethylamine (292 µL, 1.68 mmol, 3.5 equiv.) were added to a solution of 2-{[(1*R*)-1-(3-chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**95**) (200 mg, 0.479 mmol) in *N,N*-dimethylformamide (2.2 mL) and stirred at room temperature for 30 min before 2-(2-methylmorpholin-2-yl)ethanol (**138**) (racemate) (83.4 mg, 0.574 mmol, 1.2 equiv.) was added. The reaction mixture was stirred at room temperature for 1 h and purified without any further work up by preparative HPLC (reversed phase, eluent: acetonitrile

/ water gradient) to give **38** in a mixture of racemic diastereomers. Yield: 173 mg (75%). LC-MS (method 1a): t_R (min) = 0.90; MS (ESI+): m/z = 474 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.70 (d, *J* = 8.1 Hz, 1H), 7.48 (s, 1H), 7.43-7.26 (m, 3H), 6.83 (br s, 1H), 6.69 (s, 1H), 4.93 (quin, *J* = 7.2 Hz, 1H), 4.42-4.23 (m, 1H), 3.90 (s, 3H), 3.68-3.35 (m, 7H), 1.85-1.53 (m, 2H), 1.48 (d, *J* = 7.1 Hz, 3H), 1.25-0.93 (m, 3H).

This mixture (168 mg) was submitted for diastereomer separation (preparative method: HPLC: column: Daicel Chiralpak AD-H 5 µm, 250 mm x 20 mm; eluent: 50% *iso*-hexane / 50% ethanol; temperature: 40 °C; flow rate: 20 mL/min; UV-detection: 210 nm; analytical method: HPLC: column: Daicel Chiralpak AD-H 5 µm, 250 mm x 4.6 mm; eluent: 50% *iso*-hexane / 50% ethanol; temperature: 40 °C; flow rate: 1.0 mL/min; UV-detection: 220 nm) to give two enantiopure diastereomers: single stereoisomer 1: Yield: 52 mg (23%). HPLC: t_R (min) = 7.68, >99% de; LC-MS (method 1a): t_R (min) = 0.87; MS (ESI+): m/z = 474 $[M+H]^+$; single stereoisomer 2, which corresponds to the desired stereoisomer **38**: Yield: 38 mg (17%). HPLC: t_R (min) = 8.39, >99% de; LC-MS (method 1a): t_R (min) = 0.87; MS (ESI+): m/z = 474 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.70 (d, *J* = 8.1 Hz, 1H), 7.48 (s, 1H), 7.43-7.26 (m, 3H), 6.83 (br s, 1H), 6.69 (s, 1H), 4.93 (quin, *J* = 7.2 Hz, 1H), 4.42-4.23 (m, 1H), 3.90 (s, 3H), 3.68-3.35 (m, 7H), 1.85-1.53 (m, 2H), 1.48 (d, *J* = 7.1 Hz, 3H), 1.25-0.93 (m, 3H).

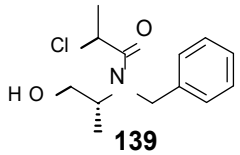
(2-{[(1*R*)-1-(3-Chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[(5*R*)-2-(2-hydroxyethyl)-2,5-dimethylmorpholin-4-yl]methanone (39) as single stereoisomer.



a) i) TEA, 2-propanol, 0 °C, ii) 2-chloropropionyl chloride, 0 °C to RT; b) KO*t*-Bu, 2-propanol, 0 °C to RT; c) i) LHMDS, THF, -78 °C, ii) allyl iodide, -78 °C to RT; d) OsO_4, $NaIO_4$, THF/water, 0 °C to

RT; e) $NaBH_4$, MeOH, 0 °C to RT; f) BH_3 x Me_2S, THF, RF; g) H_2 (1 bar), 10% Pd/C, 20% $Pd(OH)_2$/C, EtOH, RT; h) **95**, HATU, DIEA, DMF, RT.

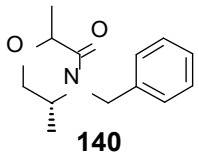
***N*-Benzyl-2-chloro-*N*-[(*2R*)-1-hydroxypropan-2-yl]propanamide (139) as diastereomer mixture (2 isomers).**



139

(*2R*)-2-(Benzylamino)propan-1-ol (16.4 g, 99.3 mmol) [lit: Tewson, T. J. *et al.*, *Synthesis* **2002**, *6*, 766-770] was initially charged in 2-propanol (500 mL), the mixture was cooled to 0 °C and triethylamine (20.1 g, 27.7 mL, 199 mmol) was added. 2-Chloropropionyl chloride (racemate) (13.9 g, 10.8 mL, 109 mmol) was then added dropwise, and the reaction solution was allowed to warm to room temperature, stirred overnight and then concentrated under reduced pressure. Aqueous hydrogen chloride solution (0.5 N) was added to the residue, and the mixture was extracted with ethyl acetate. The organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure to give **139** as a crude product which was used without further purification in the next step. Yield: 24.3 g (88%, 92% purity, diastereomer ratio about 1:1). LC-MS (method 1a): t_R (min) = 0.80 (diastereomer 1), t_R (min) = 0.84 (diastereomer 2); MS (ESI+): m/z = 256 $[M+H]^+$.

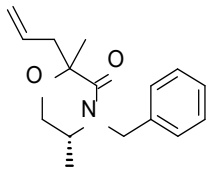
(*5R*)-4-Benzyl-2,5-dimethylmorpholin-3-one (140) as diastereomer mixture (2 isomers).



140

N-Benzyl-2-chloro-*N*-[(*2R*)-1-hydroxypropan-2-yl]propanamide (**139**, diastereomer mixture, 2 isomers) (30.0 g, 93% purity, 109 mmol) was initially charged in 2-propanol (588 mL), the mixture was cooled to 0 °C and potassium *tert*-butoxide (49.0 g, 436 mmol) was added. The reaction solution was allowed to warm to room temperature and stirred overnight. Most of the 2-propanol was removed under reduced pressure, and the residue was taken up in water. The mixture was extracted with ethyl acetate, and the organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure to give **140** as crude product which was used without further purification in the next step. Yield: 22.8 g (93%). LC-MS (method 1a): t_R (min) = 0.85; MS (ESI+): m/z = 220 $[M+H]^+$.

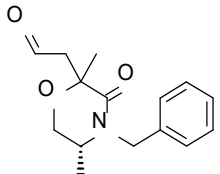
(*5R*)-2-Allyl-4-benzyl-2,5-dimethylmorpholin-3-one (141) as diastereomer mixture (2 isomers).



141

(*5R*)-4-Benzyl-2,5-dimethylmorpholin-3-one (**140**, diastereomer mixture, 2 isomers) (22.8 g, 104 mmol) was initially charged in tetrahydrofuran (1.34 L), lithium hexamethyldisilazide solution (1 M in tetrahydrofuran, 146 mL, 146 mmol) was added under argon atmosphere at -78 °C and the mixture was stirred for 15 min. At -78 °C, allyl iodide (21.0 g, 11.4 mL, 125 mmol) was then added, and the reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction was terminated by addition of saturated aqueous ammonium chloride solution, and the mixture was then extracted with ethyl acetate. The organic phase was washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and concentrated under reduced pressure to give **141** as crude product which was used without further purification in the next step. Yield: 27.5 g (77%, 75% purity). LC-MS (method 1a): t_R (min) = 0.99; MS (ESI+): m/z = 260 $[M+H]^+$.

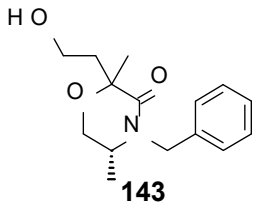
[(*5R*)-4-Benzyl-2,5-dimethyl-3-oxomorpholin-2-yl]acetaldehyde (142) as diastereomer mixture (2 isomers).



142

(*5R*)-2-Allyl-4-benzyl-2,5-dimethylmorpholin-3-one (**141**, diastereomer mixture, 2 isomers) (27.4 g, 75% purity, 79.9 mmol) was initially charged in tetrahydrofuran (620 mL) and water (370 mL), and a solution of osmium tetroxide (2.5% in *tert*-butanol, 4.35 mL, 1.60 mmol) and sodium periodate (51.2 g, 240 mmol) were added at 0 °C. The reaction solution was allowed to warm to room temperature and stirred overnight. The reaction solution was filtered through kieselguhr and the filter residue was washed with tetrahydrofuran. The reaction solution was taken up in ethyl acetate and diluted with water. After separation of the phases, the organic phase was washed with aqueous sodium sulfite solution (1 N, 2x 400 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give **142** as crude product which was used without further purification in the next step. Yield: 23.6 g. LC-MS (method 1a): t_R (min) = 0.81 (enantiomerically pure isomer 1) / 0.84 (enantiomerically pure isomer 2); MS (ESI+): m/z = 262 $[M+H]^+$.

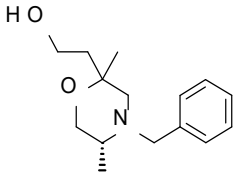
(*5R*)-4-Benzyl-2-(2-hydroxyethyl)-2,5-dimethylmorpholin-3-one (143) as diastereomer mixture (2 isomers).



143

[(*5R*)-4-Benzyl-2,5-dimethyl-3-oxomorpholin-2-yl]acetaldehyde (**142**, diastereomer mixture, 2 isomers) (7.00 g, about 26.8 mmol, crude product) was initially charged in methanol (200 mL), and sodium borohydride (3.04 g, 80.4 mmol) was added at 0 °C. The reaction solution was allowed to warm to room temperature and stirred for 30 min. Water was added to the reaction solution, most of the methanol was removed under reduced pressure and the residue was extracted with ethyl acetate. The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **143**. Yield: 6.82 g (70%, 73% purity). LC-MS (method 1a): t_R (min) = 0.71; MS (ESI+): m/z = 264 $[M+H]^+$.

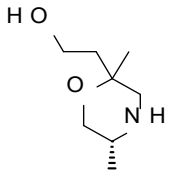
2-[(*5R*)-4-Benzyl-2,5-dimethylmorpholin-2-yl]ethanol as enantiomerically pure isomer (144a) and enantiomerically pure isomer (144b).



144a/b

(*5R*)-4-Benzyl-2-(2-hydroxyethyl)-2,5-dimethylmorpholin-3-one (**143**, diastereomer mixture, 2 isomers) (6.80 g, 18.9 mmol, 73% purity) was initially charged in tetrahydrofuran (191 mL), borane-dimethyl sulfide complex solution (2 M in tetrahydrofuran, 37.7 mL, 75.4 mmol) was added under argon and the mixture was stirred under reflux for 2 h. The mixture was subsequently cooled to 0 °C, methanol (37 mL) was added carefully and the mixture was stirred under reflux for 30 min. The mixture was concentrated completely under reduced pressure, and the residue was taken up in acetonitrile and subjected directly to purification and diastereomer separation by preparative HPLC (reversed phase, eluent: acetonitrile / water, isocratic) to give 1.34 g (28%) enantiomerically pure isomer **144a** (first compound eluted) and 2.28 g (47%) enantiomerically pure isomer **144b** (second compound eluted). LC-MS (method 4a): t_R (min) = 2.55 (enantiomerically pure isomer 1) / 2.64 (enantiomerically pure isomer 2); MS (ESI+): m/z = 250 $[M+H]^+$.

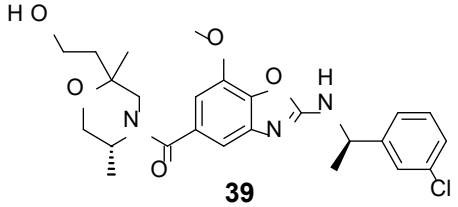
2-[(*5R*)-2,5-Dimethylmorpholin-2-yl]ethanol (145) as enantiomerically pure isomer.



145

2-[(*5R*)-4-Benzyl-2,5-dimethylmorpholin-2-yl]ethanol (enantiomerically pure isomer **144b**) (2.25 g, 9.02 mmol) was initially charged in ethanol (90.7 mL), palladium on carbon (10%, 227 mg) and palladium hydroxide on carbon (20%, 113 mg) were added under argon and the mixture was stirred under an atmosphere of hydrogen at standard pressure overnight. The reaction solution was filtered through kieselguhr and the filter residue was washed with ethanol. The filtrate was concentrated under reduced pressure and the product was dried under high vacuum to give **145**. Yield: 1.46 g (quantitative). MS (method 1c): m/z = 160 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 4.21 (t, 1H), 3.53-3.44 (d, 2H), 3.34 (dd, 1H), 3.14 (t, 1H), 2.65-2.52 (m, 3H), 2.07 (br s, 1H), 1.52 (td, 2H), 1.18 (s, 3H), 0.85 (d, 3H).

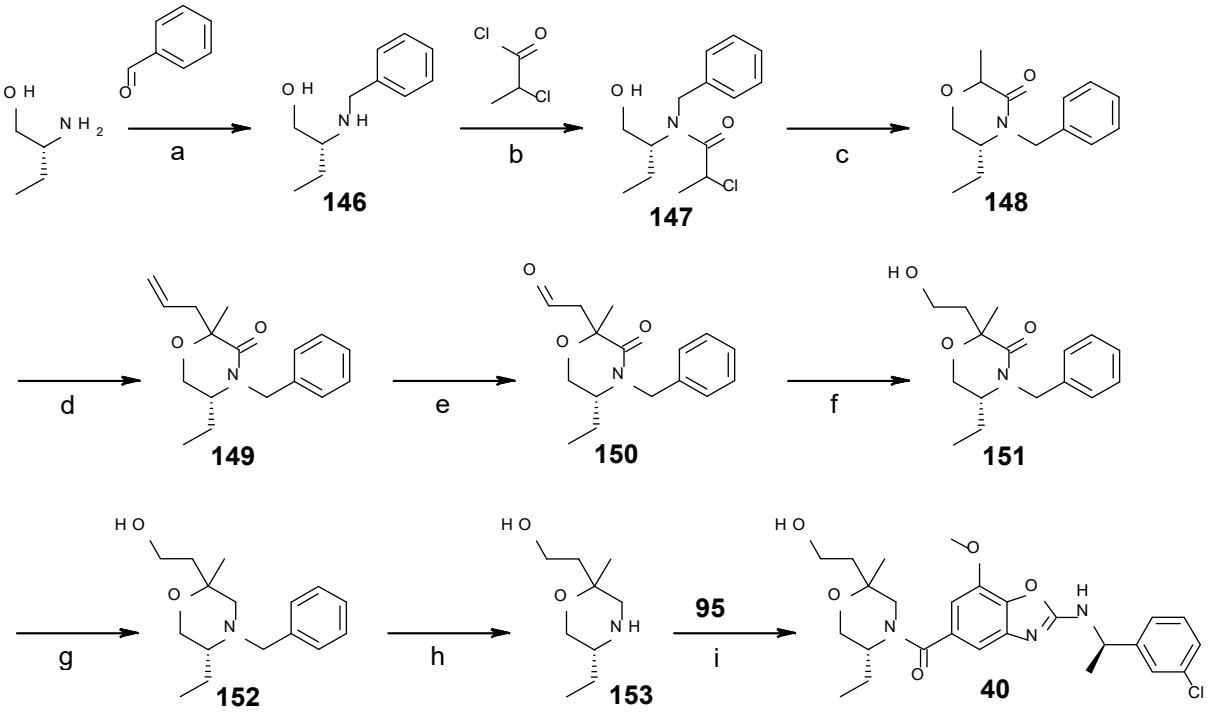
(2-{[(4-Chloropyridin-2-yl)methyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[(5*R*)-2-(2-hydroxyethyl)-2,5-dimethylmorpholin-4-yl]methanone (39) as enantiomerically pure isomer.



39

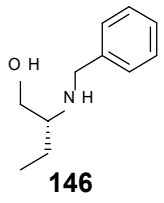
2-{[(1*R*)-1-(3-Chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**95**) (100 mg, 90% purity, 0.260 mmol) and 2-[(*5R*)-2,5-dimethylmorpholin-2-yl]ethanol (enantiomerically pure isomer **145**) were initially charged in *N,N*-dimethylformamide (1.19 mL), and *N,N*-diisopropylethylamine (117 mg, 158 µL, 0.908 mmol) was added. Subsequently, HATU (118 mg, 0.311 mmol) was added at room temperature and the mixture was stirred overnight. Without further work-up, the reaction solution was then purified directly by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **44** as enantiomerically pure isomer. Yield: 92.6 mg (73%). LC-MS (method 1a): t_R (min) = 0.95; MS (ESI+): m/z = 488 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.68 (d, *J* = 8.1 Hz, 1H), 7.47 (s, 1H), 7.42-7.35 (m, 2H), 7.33-7.23 (m, 1H), 6.79 (s, 1H), 6.64 (d, *J* = 1.0 Hz, 1H), 4.94 (quin, *J* = 7.2 Hz, 1H), 4.29 (t, *J* = 5.3 Hz, 1H), 3.91 (s, 3H), 3.73 (br dd, *J* = 11.9, 3.5 Hz, 1H), 3.44-3.33 (m, 2H), 3.28 (br d, *J* = 4.8 Hz, 1H), 3.03-2.88 (m, 1H), 2.06-1.93 (m, 1H), 1.58-1.38 (m, 4H), 1.20 (d, *J* = 6.8 Hz, 3H), 1.07 (br s, 3H), 2 protons are concealed.

(2-{[(1*R*)-1-(3-Chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[(5*R*)-5-ethyl-2-(2-hydroxyethyl)-2-methylmorpholin-4-yl]methanone (40) as single stereoisomer.



a) i) benzaldehyde, MeOH, RT, ii) $NaBH_4$, RT; b) 2-chloropropionyl chloride, TEA, 2-propanol, RT; c) KO*t*-Bu, 2-propanol, 0 °C to RT; d) i) LHMDS, THF, -78 °C, ii) allyl bromide, -78 °C to RT; e) O_3/O_2, Me_2S, MeOH, -78 °C to RT; f) $NaBH_4$, MeOH, 0 °C to RT; g) BH_3 x Me_2S, THF, RT; h) H_2 (1 bar), $Pd(OH)_2$, MeOH, RT; i) i) **95**, HATU, DIEA, DMF, RT, ii) diastereomer separation.

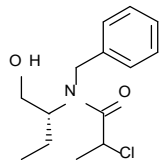
(2*R*)-2-(Benzylamino)butan-1-ol (146).



Benzaldehyde (23.8 g, 224.4 mmol, 1.0 equiv.) was added under argon atmosphere at room temperature to a mixture of (2*R*)-2-aminobutan-1-ol (20.0 g, 224.4 mmol) in methanol (230 mL). The reaction mixture was stirred at room temperature for 1 h, cooled to 0 °C, mixed with sodium borohydride (4.2 g, 122.2 mmol, 0.5 equiv.), stirred at room temperature for 1.5 h and quenched by addition of water. All volatiles were removed *in vacuo*. The mixture was extracted with dichloromethane. The organic phase was washed with water, dried over magnesium sulfate, filtered, evaporated under reduced pressure and dried *in vacuo* to give **146** which was used in the next step without further purification. Yield: 39.2 g (97%). LC-MS (method 1a): t_R (min) = 0.25; MS (ESI+): m/z = 180 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ [ppm] = 7.36-7.25 (m, 4H), 7.25-7.16 (m, 1H), 4.43 (t, *J* = 5.5 Hz, 1H), 3.77-3.65 (m,

2H), 3.43-3.35 (m, 1H), 3.32-3.24 (m, 1H), 2.40 (m, 1H), 1.84 (br s, 1H), 1.44-1.32 (m, 2H), 0.83 (t, *J* = 7.5 Hz, 3H).

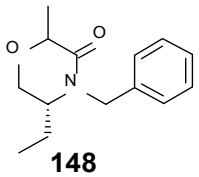
_N_-Benzyl-2-chloro-_N_-[(2_R_)-1-hydroxybutan-2-yl]propanamide (147).



147

Triethylamine (64.0 mL, 459.2 mmol, 2.1 equiv.) and 2-chloropropionyl chloride (23.4 mL, 240.5 mmol, 1.1 equiv.) were added under argon atmosphere at room temperature to a solution of (2*R*)-2-(benzylamino)butan-1-ol (**146**) (39.2 g, 218.7 mmol) in 2-propanol (500 mL). The reaction mixture was stirred at room temperature for 4 h and evaporated under reduced pressure. After addition of water, the aqueous phase was extracted with dichloromethane. The organic phase was dried over magnesium sulfate, filtered, evaporated under reduced pressure and dried *in vacuo* to give **147** which was used in the next step without further purification. Yield: 49.0 g (74%, 89% purity). LC-MS (method 1a): t_R (min) = 0.86 / 0.88; MS (ESI+): m/z = 270 $[M+H]^+$.

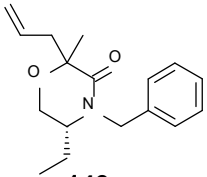
(5_R_)-4-Benzyl-5-ethyl-2-methylmorpholin-3-one (148).



148

Potassium *tert*-butylate (34.3 g, 305.8 mmol, 3.3 equiv.) was added under argon atmosphere at 0 °C to a solution of *N*-benzyl-2-chloro-*N*-[(2*R*)-1-hydroxybutan-2-yl]propanamide (**147**) (25.0 g, 92.7 mmol) in 2-propanol (400 mL). The reaction mixture was stirred at room temperature overnight, evaporated to a quarter of volume and mixed with ethyl acetate. The organic phase was washed two times with water, once with aqueous hydrogen chloride solution (1 M) and with brine, dried over magnesium sulfate, filtered, evaporated under reduced pressure and dried *in vacuo* to give **148** which was used in the next step without further purification. Yield: 19.5 g (79%, 88% purity). LC-MS (method 9a): t_R (min) = 0.93; MS (ESI+): m/z = 234 $[M+H]^+$.

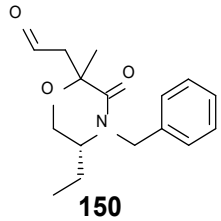
(5_R_)-2-Allyl-4-benzyl-5-ethyl-2-methylmorpholin-3-one (149).



149

Lithium bis(trimethylsilyl)amide solution (1 M in tetrahydrofuran, 82.5 mL, 82.5 mmol, 1.2 equiv.) was added slowly under argon atmosphere at -78 °C to a solution of (5*R*)-4-benzyl-5-ethyl-2-methylmorpholin-3-one (**148**) (17.5 g, 75.0 mmol) in tetrahydrofuran (300 mL). The reaction mixture was stirred at -78 °C for 30 min, before a solution of allyl bromide (7.8 mL, 90.0 mmol, 1.2 equiv.) in tetrahydrofuran (20 mL) was added dropwise. The reaction mixture was stirred at room temperature overnight and mixed with water. The aqueous phase was extracted with ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate gradient) to give **149**. Yield: 13.5 g (66%, 89% purity). LC-MS (method 7a): t_R (min) = 1.11; MS (ESI+): m/z = 274 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 7.38-7.30 (m, 2H), 7.30-7.19 (m, 3H), 5.88-5.72 (m, 1H), 5.18-5.04 (m, 2H), 5.02 / 4.94 (2x d, *J* = 15.2 Hz / 15.2 Hz, 1H), 4.14 / 4.11 (2x d, *J* = 15.2 Hz / 15.2 Hz, 1H), 3.86-3.75 (dt, *J* = 12.5 Hz, 2.9 Hz, 1H), 3.74-3.64 (m, 1H), 3.10-3.02 / 3.02-2.94 (2x m, 1H), 2.74 / 2.71 (2x d, *J* = 6.6 Hz / 6.6 Hz, 1H), 2.40-2.27 (m, 1H), 1.75-1.58 (m, 2H), 1.36 / 1.29 (2x s, 3H), 0.83 / 0.82 (2x t, *J* = 7.3 Hz / 7.3 Hz, 3H).

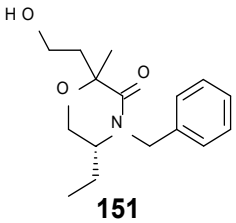
[(5*R*)-4-Benzyl-5-ethyl-2-methyl-3-oxomorpholin-2-yl]acetaldehyde (150).



150

A solution of (5*R*)-2-allyl-4-benzyl-5-ethyl-2-methylmorpholin-3-one (**149**) (10.5 g, 38.4 mmol) in methanol (300 mL) was purged at -78 °C for 30 min with ozone-containing oxygen, then with oxygen until the solution became colorless again. The reaction mixture was mixed with dimethyl sulfide (28.2 mL, 348 mmol, 10.0 equiv.), allowed to warm to room temperature overnight and evaporated under reduced pressure. After addition of ethyl acetate, the organic phase was washed with water, with aqueous hydrogen chloride solution (1 M) and with brine, dried over magnesium sulfate, filtered, evaporated under reduced pressure and dried *in vacuo* to give **150** which was used in the next step without further purification. Yield: 10.1 g (67%, 70% purity). LC-MS (method 1a): t_R (min) = 0.90; MS (ESI+): m/z = 276 $[M+H]^+$.

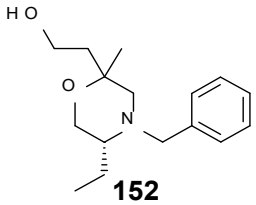
(5*R*)-4-Benzyl-5-ethyl-2-(2-hydroxyethyl)-2-methylmorpholin-3-one (151).



151

Sodium borohydride (1.41 g, 37.4 mmol, 1.05 equiv.) was added under argon atmosphere at 0 °C to a solution of [(5*R*)-4-benzyl-5-ethyl-2-methyl-3-oxomorpholin-2-yl]acetaldehyde (**150**) (9.80 g, 35.6 mmol) in methanol (100 mL). The reaction mixture was stirred for 30 min while allowing to warm to room temperature and quenched with water. The aqueous phase was extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate gradient) to give **151**. Yield: 9.79 g (84%, 85% purity). LC-MS (method 1a): t_R (min) = 0.79; MS (ESI+): m/z = 278 $[M+H]^+$.

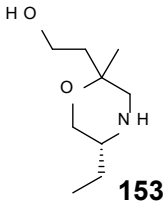
2-[(5*R*)-4-Benzyl-5-ethyl-2-methylmorpholin-2-yl]ethanol (152).



152

Borane-dimethyl sulfide complex (16.09 g, 211.78 mmol, 6.0 equiv.) was added under argon atmosphere at room temperature to a mixture of (5*R*)-4-benzyl-5-ethyl-2-(2-hydroxyethyl)-2-methylmorpholin-3-one (**151**) (9.79 g, 35.30 mmol) in tetrahydrofuran (180 mL). The reaction mixture was stirred at room temperature overnight, mixed with ethanol unless gas evolution stopped, stirred shortly under reflux and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate gradient) to give **152**. Yield: 8.60 g (80%, 86% purity). LC-MS (method 9a): t_R (min) = 0.46 / 0.49; MS (ESI+): m/z = 264 $[M+H]^+$.

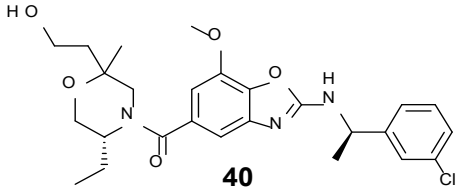
2-[(5*R*)-5-Ethyl-2-methylmorpholin-2-yl]ethanol (153).



153

A solution of 2-[(5*R*)-4-benzyl-5-ethyl-2-methylmorpholin-2-yl]ethanol (**152**) (1.00 g, 3.80 mmol) in methanol (53 mL) was mixed under argon atmosphere at room temperature with palladium(II) hydroxide (400 mg), purged with hydrogen gas and stirred at room temperature overnight under hydrogen gas atmosphere (1 bar). The reaction mixture was filtered, evaporated under reduced pressure and dried *in vacuo* to give **153** which was used in the next step without further purification. Yield: 587 mg. MS (method 1c): MS (ESI+): m/z = 174 $[M+H]^+$.

(2-{[(1*R*)-1-(3-Chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[(5*R*)-5-ethyl-2-(2-hydroxyethyl)-2-methylmorpholin-4-yl]methanone (40) as single stereoisomer.

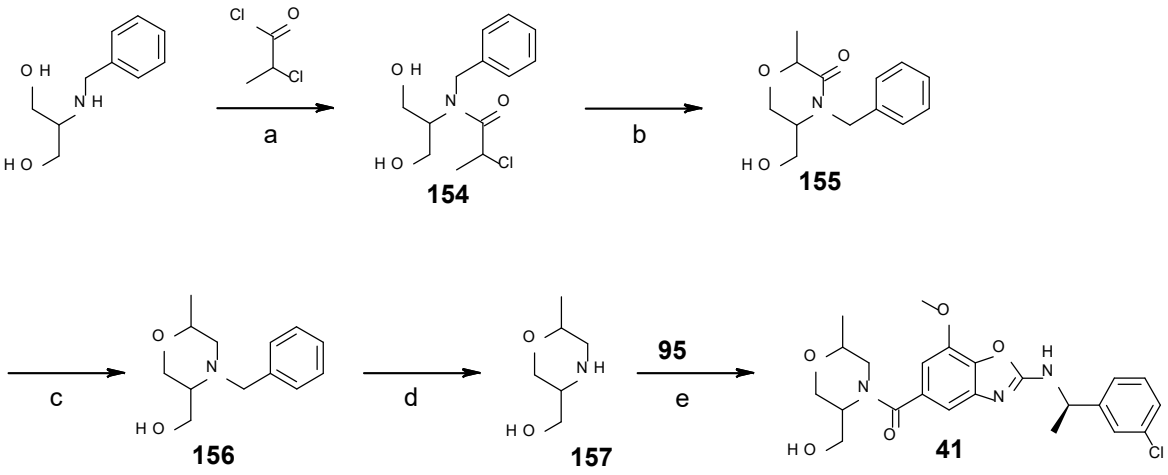


40

A mixture of 2-{[(1*R*)-1-(3-chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**95**) (364 mg, 1.05 mmol), 2-[(5*R*)-5-ethyl-2-methylmorpholin-2-yl]ethanol (**153**) (200 mg, 1.15 mmol, 1.1 equiv.), HATU (519 mg, 1.36 mmol, 1.3 equiv.) and *N,N*-diisopropylethylamine (457 µL, 2.62 mmol, 2.5 equiv.) in *N,N*-dimethylformamide (5 mL) was stirred at room temperature overnight and purified by preparative HPLC (reversed phase, eluent: acetonitrile / water + 0.1% acid gradient) to give **40** in a mixture of racemic diastereomers. Yield: 380 mg (72%). LC-MS (method 1a): t_R (min) = 0.94 / 0.96; MS (ESI+): m/z = 502 $[M+H]^+$.

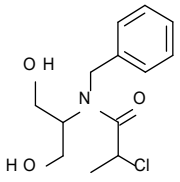
This mixture (350 mg) was submitted for diastereomer separation (preparative method: HPLC: column: Daicel Chiralcel OZ-H 5 µm, 250 mm x 20 mm; eluent: 50% *iso*-hexane / 50% ethanol + 0.2% diethylamine; temperature: 30 °C; flow rate: 15 mL/min; UV-detection: 220 nm; analytical method: HPLC: column: Daicel Chiralcel OZ-H 5 µm, 250 mm x 4.6 mm; eluent: 50% *iso*-hexane / 50% ethanol; temperature: 35 °C; flow rate: 1.0 mL/min; UV-detection: 220 nm) to give two enantiopure diastereomers: single stereoisomer 1: Yield: 70 mg (20%). HPLC: t_R (min) = 5.75, >99% de; LC-MS (method 9a): t_R (min) = 0.97; MS (ESI+): m/z = 502 $[M+H]^+$; single stereoisomer 2, which corresponds to the desired stereoisomer **40**: Yield: 148 mg (42%). HPLC: t_R (min) = 8.04, >99% de; LC-MS (method 9a): t_R (min) = 0.99; MS (ESI+): m/z = 502 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.72 (d, *J* = 8.1 Hz, 1H), 7.47 (s, 1H), 7.42-7.34 (m, 2H), 7.34-7.26 (m, 1H), 6.77 (br s, 1H), 6.62 (s, 1H), 4.98-4.87 (m, 1H), 4.32 (br s, 1H), 3.90 (s, 3H), 3.79-3.69 (m, 1H), 3.58-3.3 (m, 3H, partially concealed), 3.19-2.94 (m, 2H), 2.11-1.94 (m, 1H), 1.88-1.73 (m, 1H), 1.68-1.5 (m, 1H), 1.48 (d, *J* = 6.9 Hz, 3H), 1.22-0.55 (m, 6H), 2 protons are concealed.

(2-{[(1*R*)-1-(3-Chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[5-(hydroxymethyl)-2-methylmorpholin-4-yl]methanone (41) as single stereoisomer.



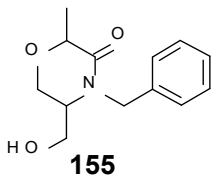
a) 2-chloropropanoyl chloride, TEA, 2-propanol, RT; b) KO*t*-Bu, 2-propanol, 0 °C to RT; c) BH_3 x Me_2S, THF, RT; d) H_2 (1 bar), 20% $Pd(OH)_2$/C, EtOH, RT and H_2 (1 bar), 10% Pd/C, MeOH, RT; e) i) **95**, HATU, DIEA, DMF, RT, ii) diastereomer separation.

***N*-Benzyl-2-chloro-*N*-(1,3-dihydroxypropan-2-yl)propanamide (154).**



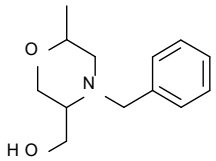
Triethylamine (48.5 mL, 347.6 mmol, 2.1 equiv.) and 2-chloropropanoyl chloride (17.7 mL, 182.1 mmol, 1.1 equiv.) were added under argon atmosphere at room temperature to a solution of 2-(benzylamino)propane-1,3-diol (30.0 g, 165.5 mmol) in 2-propanol (382 mL). The reaction mixture was stirred at room temperature overnight and evaporated under reduced pressure. The residue was mixed with water. The aqueous phase was extracted with dichloromethane. The organic phase was dried over magnesium sulfate, filtered, evaporated under reduced pressure and dried *in vacuo* to give **154** which was used in the next step without further purification. Yield: 33.0 g (66%, 90% purity). LC-MS (method 1a): t_R (min) = 0.65; MS (ESI+): m/z = 272 $[M+H]^+$.

4-Benzyl-5-(hydroxymethyl)-2-methylmorpholin-3-one (155).



Potassium *tert*-butylate (68.1 g, 607.2 mmol, 5.0 equiv.) was added under argon atmosphere at 0 °C to a solution of *N*-benzyl-2-chloro-*N*-(1,3-dihydroxypropan-2-yl)propanamide (**154**) (33.0 g, 121.4 mmol) in 2-propanol (500 mL). The reaction mixture was stirred at room temperature overnight and evaporated *in vacuo*. The residue was mixed with dichloromethane. The organic phase was washed with water, dried over magnesium sulfate, filtered, evaporated under reduced pressure and dried *in vacuo* to give **155** which was used in the next step without further purification. Yield: 23.0 g (81%). LC-MS (method 1a): t_R (min) = 0.59 / 0.61; MS (ESI+): m/z = 236 $[M+H]^+$.

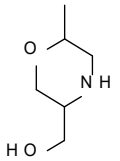
(4-Benzyl-6-methylmorpholin-3-yl)methanol (156).



156

Borane-dimethyl sulfide complex (44.6 g, 586.5 mmol, 6.0 equiv.) was added under argon atmosphere at room temperature to a mixture of 4-benzyl-5-(hydroxymethyl)-2-methylmorpholin-3-one (**155**) (23.0 g, 97.8 mmol) in tetrahydrofuran (460 mL). The reaction mixture was stirred at room temperature for 3 days, mixed with ethanol (200 mL) at 0 °C, stirred under reflux for 15 min, evaporated under reduced pressure and dried *in vacuo* to give **156**. Yield: 17.2 g (80%). LC-MS (method 9a): t_R (min) = 0.35; MS (ESI+): m/z = 222 $[M+H]^+$.

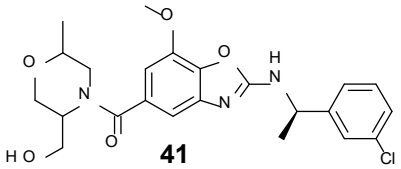
(6-Methylmorpholin-3-yl)methanol (157).



157

A solution of (4-benzyl-6-methylmorpholin-3-yl)methanol (**156**) (500 mg, 2.26 mmol) in ethanol (20 mL) was mixed under argon atmosphere at room temperature with palladium(II) hydroxide (20% on carbon, 159 mg), purged with hydrogen gas and stirred at room temperature for 1 h under hydrogen gas atmosphere (1 bar). In a second batch, a solution of (4-benzyl-6-methylmorpholin-3-yl)methanol (**157**) (500 mg, 2.26 mmol) in methanol (20 mL) was mixed under argon atmosphere at room temperature with palladium (10% on carbon, 240 mg), purged with hydrogen gas and stirred at room temperature for 1 h under hydrogen gas atmosphere (1 bar). Both reaction mixtures were combined, filtered over diatomaceous earth, evaporated under reduced pressure and dried *in vacuo* to give **157** which was used in the next step without further purification. Yield: 420 mg. MS (method 1c): MS (ESI+): m/z = 132 $[M+H]^+$.

(2-{[(1*R*)-1-(3-Chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[5-(hydroxymethyl)-2-methylmorpholin-4-yl]methanone (41) as single stereoisomer.

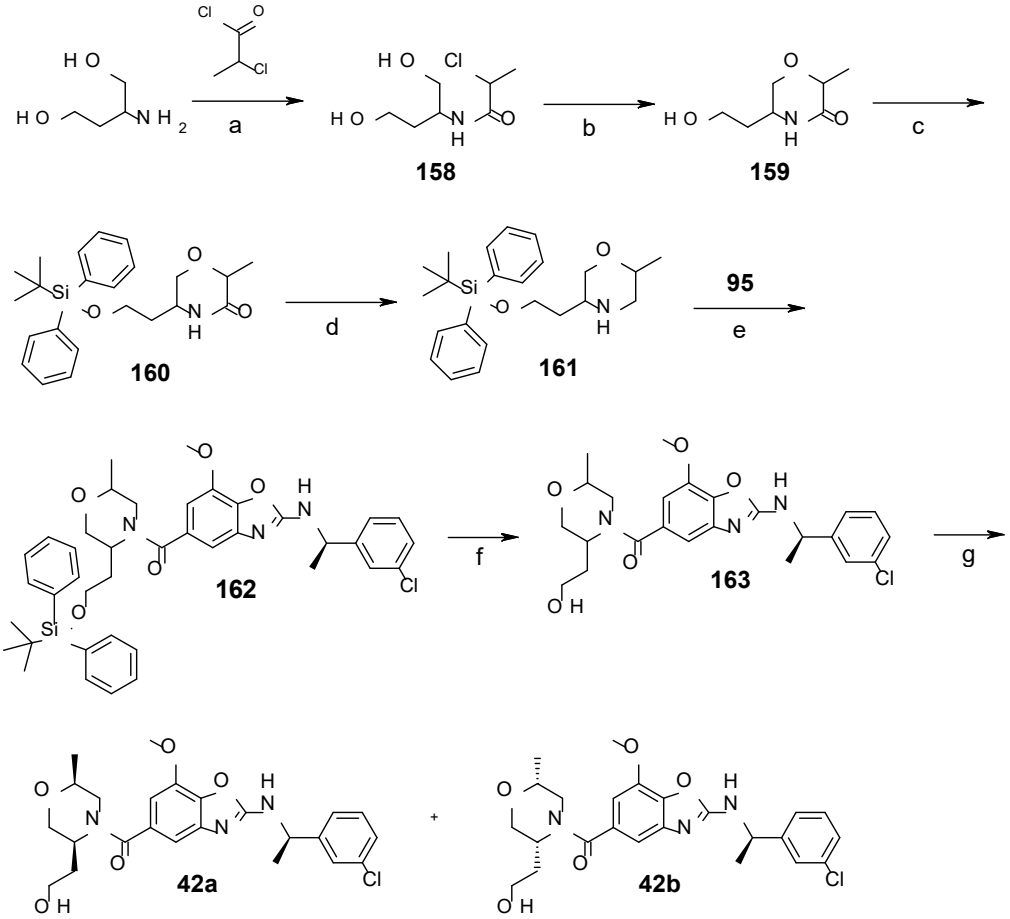


41

A mixture of 2-{[(1*R*)-1-(3-chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**95**) (312 mg, 0.90 mmol), (6-methylmorpholin-3-yl)methanol (**157**) (130 mg, 0.99 mmol, 1.1 equiv.), HATU (445 mg, 1.17 mmol, 1.3 equiv.) and *N,N*-diisopropylethylamine (392 µL, 2.25 mmol, 2.5 equiv.) in *N,N*-dimethylformamide (2 mL) was stirred at room temperature overnight and evaporated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water + 0.1% acid gradient) to give **41** in a mixture of racemic diastereomers. Yield: 197 mg (48%). LC-MS (method 1a): t_R (min) = 0.89; MS (ESI+): m/z = 460 $[M+H]^+$.

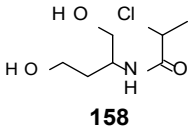
This mixture (162 mg) was submitted for diastereomer separation (preparative method: HPLC: column: Daicel Chiralpak AD-H 5 µm, 250 mm x 20 mm; eluent: 50% *iso*-hexane / 50% 2-propanol; temperature: 25 °C; flow rate: 20 mL/min; UV-detection: 230 nm; analytical method: HPLC: column: Daicel Chiralpak AD-H 5 µm, 250 mm x 4.6 mm; eluent: 50% *iso*-hexane / 50% 2-propanol; temperature: 35 °C; flow rate: 1.0 mL/min; UV-detection: 220 nm) to give four diastereomers: single stereoisomer 1: Yield: 9 mg (5%). HPLC: t_R (min) = 5.27, >99% de; LC-MS (method 9a): t_R (min) = 0.89; MS (ESI+): m/z = 460 $[M+H]^+$; single stereoisomer 2: Yield: 41 mg (21%). HPLC: t_R (min) = 5.51, >99% de; LC-MS (method 9a): t_R (min) = 0.91; MS (ESI+): m/z = 460 $[M+H]^+$; mixture of stereoisomer 3+4: Yield: 15 mg (8%). HPLC: t_R (min) = 7.55 / 8.20; LC-MS (method 9a): t_R (min) = 0.89 / 0.91; MS (ESI+): m/z = 460 / 460 $[M+H]^+$; single stereoisomer 4, which corresponds to the desired stereoisomer **41**: Yield: 36 mg (19%). HPLC: t_R (min) = 8.21, >99% de; LC-MS (method 9a): t_R (min) = 0.91; MS (ESI+): m/z = 460 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.72-8.63 (m, 1H), 7.47 (s, 1H), 7.41-7.34 (m, 2H), 7.34-7.27 (m, 1H), 6.90 / 6.85 (2x s, 1H), 6.75 / 6.69 (2x s, 1H), 4.99-4.80 / 4.39-4.29 (2x m, 2H), 4.21-4.11 / 4.01-3.94 (2x m, 1H), 3.90 (s, 3H), 3.75-3.64 (m, 1H), 3.61-3.45 (m, 4H), 2.99-2.87 / 2.69-2.58 (2x m, 1H), 1.48 (d, *J* = 7.1 Hz, 3H), 1.23 / 0.95 (2x d, *J* = 5.4 Hz, 3H), 0.90-0.76 (m, 1H).

(2-{[(1*R*)-1-(3-Chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[(2*S*,5*S*)-5-(2-hydroxyethyl)-2-methylmorpholin-4-yl]methanone (42a) as enantiomerically pure isomer and (2-{[(1*R*)-1-(3-chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[(2*R*,5*R*)-5-(2-hydroxyethyl)-2-methylmorpholin-4-yl]methanone (42b) as enantiomerically pure isomer.



a) 2-chloropropionyl chloride, TEA, 2-propanol, RT; b) KO*t*-Bu, 2-propanol, 0 °C to RT; c) *t*-BuPh_2SiCl, imidazole, DMF, 0 °C to RT; d) BH_3 x Me_2S, THF, RT; e) **95**, HATU, DIEA, DMF, RT; f) TBAF, THF, RT; g) diastereomer separation.

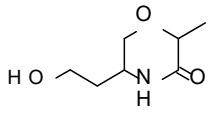
2-Chloro-*N*-(1,4-dihydroxybutan-2-yl)propanamide (158) as diastereomer mixture (4 isomers).



2-Aminobutane-1,4-diol (racemate) (5.50 g, 52.3 mmol) [lit: Jogalekar, A. S. *et al.*, WO 2008/151304, **2008**] was initially charged in 2-propanol (184 mL), and triethylamine (5.29 g, 7.29 mL, 52.3 mmol) was added. 2-Chloropropionyl chloride (racemate) (7.31 g, 5.59 mL, 57.5 mmol) was then added dropwise, and the mixture was stirred at room temperature overnight. The reaction solution was

concentrated under reduced pressure to give **158** as crude product which was used directly in the next step. MS (method 1b): m/z = 195 $[M+H]^+$.

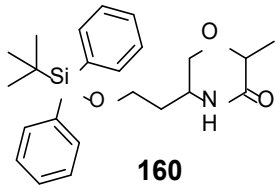
5-(2-Hydroxyethyl)-2-methylmorpholin-3-one (159) as diastereomer mixture (4 isomers).



159

2-Chloro-*N*-(1,4-dihydroxybutan-2-yl)propanamide (**158**, diastereomer mixture, 4 isomers) (10.2 g, about 52.3 mmol, crude product) was initially charged in 2-propanol (221 mL), the mixture was cooled to 0 °C and potassium *tert*-butoxide (29.3 g, 261 mmol) was then added in one portion. The mixture was warmed to room temperature and stirred for 60 h. The reaction solution was concentrated under reduced pressure to give **159** as crude product which was used directly in the next step. LC-MS (method 2a): t_R (min) = 0.34; MS (ESI+): m/z = 160 $[M+H]^+$.

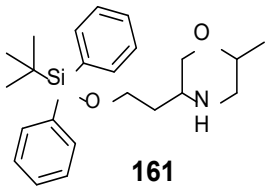
5-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-2-methylmorpholin-3-one (160) as main racemic diastereomer (2 isomers).



160

5-(2-Hydroxyethyl)-2-methylmorpholin-3-one (**159**, diastereomer mixture, 4 isomers) (3.93 g, about 24.7 mmol, crude product) was initially charged in *N*,*N*-dimethylformamide (50 mL), and then imidazole (5.05 g, 74.1 mmol) and *tert*-butyldiphenylsilyl chloride (10.2 g, 37.1 mmol) were added at 0 °C. The mixture was stirred for 24 h and warmed to room temperature during this time. Saturated aqueous ammonium chloride solution was then added, and the reaction solution was extracted with ethyl acetate. The combined organic phases were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give only the main diastereomer **160**. Yield: 2.05 g (20%). LC-MS (method 1a): t_R (min) = 1.31; MS (ESI+): m/z = 398 $[M+H]^+$.

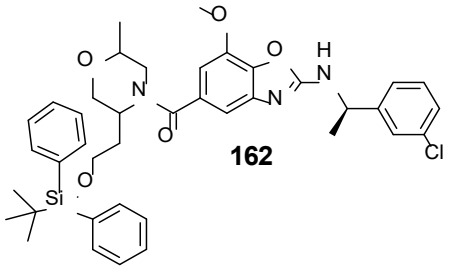
5-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-2-methylmorpholine (161) as racemic diastereomer (2 isomers).



161

5-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-2-methylmorpholin-3-one (**160**, racemic diastereomer, 2 isomers) (1.20 g, 3.02 mmol) was initially charged in tetrahydrofuran (70.6 mL), borane-dimethyl sulfide complex solution (2 M in tetrahydrofuran, 7.55 mL, 15.1 mmol) was added and the reaction mixture was then stirred at room temperature for 60 h. The reaction was then concentrated completely under reduced pressure and the residue was taken up in ethanol and stirred under reflux overnight. The reaction mixture was then concentrated completely under reduced pressure to give **161** as crude product which was used directly in the next step. Yield: 1.22 g (quantitative). LC-MS (method 1a): t_R (min) = 1.08; MS (ESI+): m/z = 383 $[M+H]^+$.

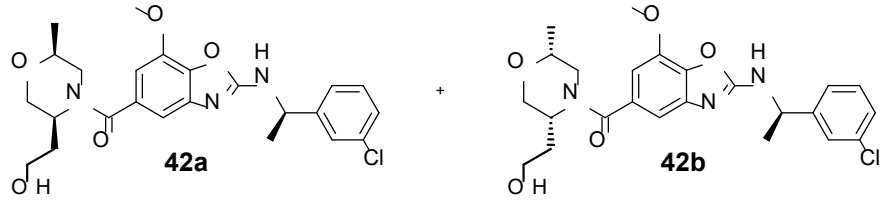
[5-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-2-methylmorpholin-4-yl](2-{[(1*R*)-1-(3-chlorophenyl) ethyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)methanone (162) as racemic diastereomer (2 isomers).



162

2-{[(1*R*)-1-(3-Chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**95**) (300 mg, 0.865 mmol) and 5-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-2-methylmorpholine (as racemic diastereomer, 2 isomers, **161**) (365 mg, 0.952 mmol, 1.1 equiv.) were initially charged in *N,N*-dimethylformamide (2.4 mL), and *N,N*-diisopropylethylamine (559 mg, 753 µL, 4.33 mmol) was added. Subsequently, HATU (395 mg, 1.04 mmol) was added at room temperature and the mixture was stirred overnight. Without further work-up, the reaction solution was then purified directly by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient + 0.1% formic acid) to give **162** as racemic diastereomer (2 isomers). Yield: 515 mg (84%). LC-MS (method 7a): t_R (min) = 1.55; MS (ESI+): m/z = 712 $[M+H]^+$.

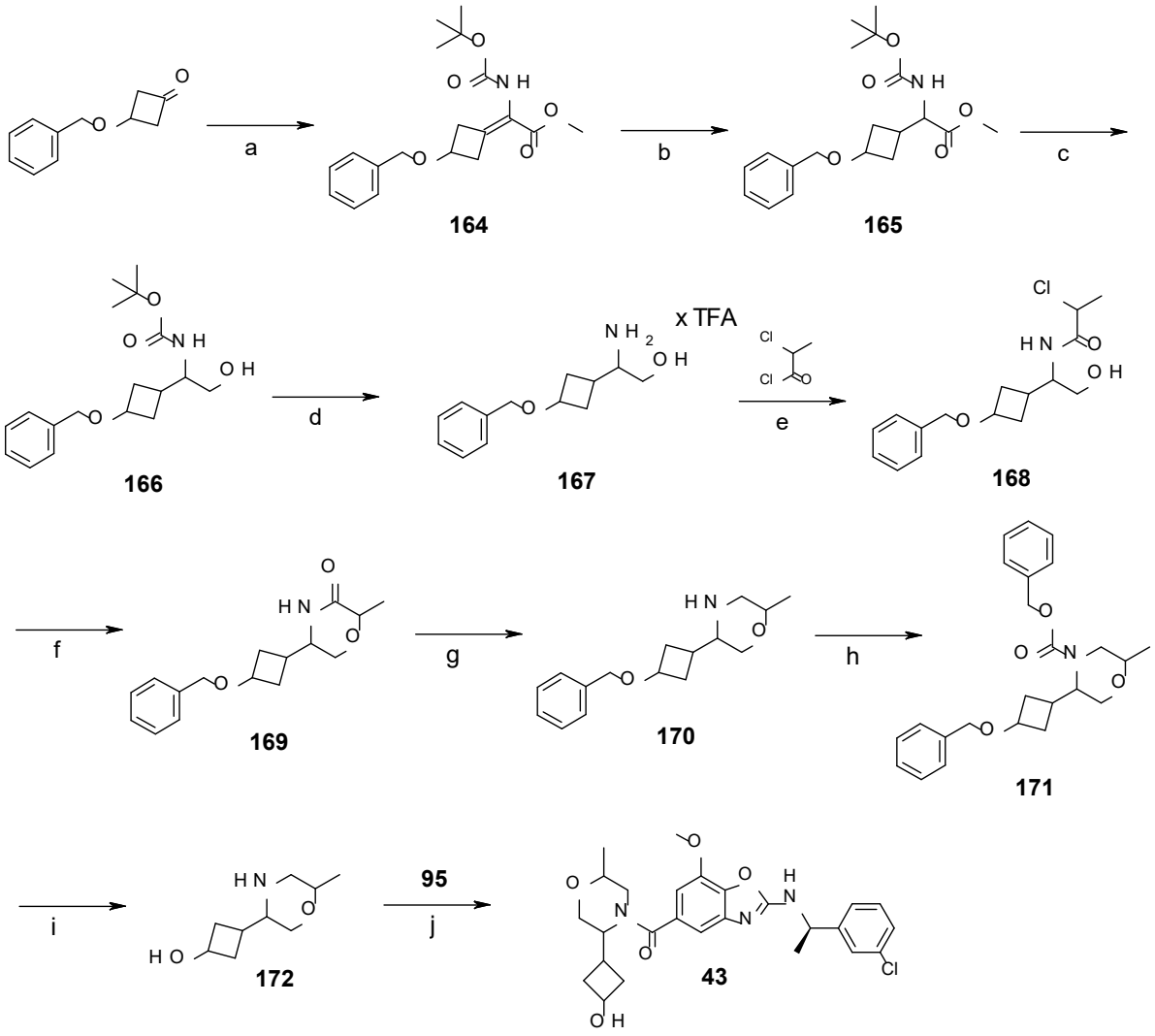
(2-{[(1*R*)-1-(3-Chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[(2*S*,5*S*)-5-(2-hydroxyethyl)-2-methylmorpholin-4-yl]methanone (42a) as enantiomerically pure isomer and (2-{[(1*R*)-1-(3-chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[(2*R*,5*R*)-5-(2-hydroxyethyl)-2-methylmorpholin-4-yl]methanone (42b) as enantiomerically pure isomer.



[5-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-2-methylmorpholin-4-yl](2-{[(1*R*)-1-(3-chlorophenyl) ethyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)methanone (as racemic diastereomer, 2 isomers, **162**) (515 mg, 0.723 mmol) in tetrahydrofuran (15 mL) was treated at room temperature with tetra-*n*-butylammonium fluoride (1 M in tetrahydrofuran, 378 µL, 1.45 mmol, 2.0 equiv.) and then stirred for 3 h. Water was added and the reaction mixture was concentrated under reduced pressure. The residue was then purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient + 0.1% formic acid) to give **163** in a mixture of racemic diastereomers. Yield: 224 mg (65%). LC-MS (method 7a): t_R (min) = 0.95, 1.27; MS (ESI+): m/z = 474 $[M+H]^+$.

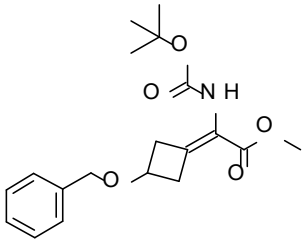
This mixture (220 mg) was submitted for diastereomer separation (preparative method: HPLC: column: Daicel Chiralcel OZ-H 5 µm, 250 mm x 20 mm; eluent: 50% *iso*-hexane / 50% ethanol; temperature: 40 °C; flow rate: 15 mL/min; UV-detection: 220 nm; analytical method: HPLC: column: Daicel Chiralcel OZ-H 5 µm, 250 mm x 4.6 mm; eluent: 50% *iso*-hexane / 50% ethanol; temperature: 40 °C; flow rate: 1.0 mL/min; UV-detection: 220 nm) to give two enantiopure diastereomers: single stereoisomer 1 (**42a**): Yield: 103 mg (30%). HPLC: t_R (min) = 6.34, >99% de; LC-MS (method 7a): t_R (min) = 0.95; MS (ESI+): m/z = 474 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.81-8.52 (m, 1H), 7.48 (s, 1H), 7.38 (d, *J* = 5.1 Hz, 2H), 7.33-7.26 (m, 1H), 6.87-6.78 (m, 1H), 6.67 (br s, 1H), 4.99-4.88 (m, 1H), 4.59-4.40 (m, 1H), 4.36-4.13 (m, 1H), 3.90 (s, 3H), 3.83-3.36 (m, 5H), 3.26 (br d, *J* = 7.3 Hz, 1H), 3.05-2.60 (m, 1H), 1.99-1.75 (m, 2H), 1.48 (d, *J* = 6.8 Hz, 3H), 1.18-0.92 (m, 3H); single stereoisomer 2 (**42b**): Yield: 103 mg (30%). HPLC: t_R (min) = 10.6, >99% de; LC-MS (method 7a): t_R (min) = 1.27; MS (ESI+): m/z = 474 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.69 (br d, *J* = 7.1 Hz, 1H), 7.47 (s, 1H), 7.38 (d, *J* = 5.1 Hz, 2H), 7.34-7.24 (m, 1H), 6.81 (br s, 1H), 6.68 (s, 1H), 4.93 (quin, *J* = 7.2 Hz, 1H), 4.57-4.40 (m, 1H), 4.37-4.14 (m, 1H), 3.90 (s, 3H), 3.83-3.36 (m, 5H), 3.27 (br s, 1H), 3.08-2.58 (m, 1H), 2.02-1.73 (m, 2H), 1.48 (d, *J* = 7.1 Hz, 3H), 1.21-0.92 (m, 3H).

(2-{[(1*R*)-1-(3-Chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[5-(3-hydroxycyclobutyl)-2-methylmorpholin-4-yl]methanone (43) as single stereoisomer.



a) methyl [(*tert*-butoxycarbonyl)amino](dimethoxyphosphoryl)acetate, DBU, DCM, RT; b) Mg, MeOH, ultrasonic bath, RT; c) $LiBH_4$, THF, 0 °C to RT; d) TFA, DCM, RT; e) 2-chloropropionyl chloride, TEA, 2-propanol, 0 °C; f) KO*t*-Bu, 2-propanol, 0 °C to RT to 50 °C; g) BH_3 x Me_2S, THF, RF; h) benzyl chloroformate, DIEA, DCM, 0 °C to RT; i) H_2 (1 bar), 10 % Pd/C, 20% $Pd(OH)_2$/C, EtOH, RT; j) i) **95**, HATU, DIEA, RT, ii) diastereomer separation.

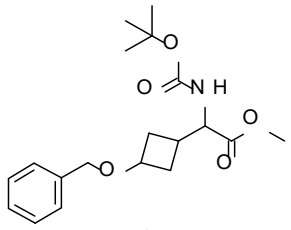
Methyl [3-(benzyloxy)cyclobutylidene][(*tert*-butoxycarbonyl)amino]acetate (164).



164

Methyl [(*tert*-butoxycarbonyl)amino](dimethoxyphosphoryl)acetate (racemate) (928 mg, 3.12 mmol) and 3-(benzyloxy)cyclobutanone (500 mg, 2.84 mmol) [lit: Ogura, K.; Tsuchihashi, G. *et al.*, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1637-1642] were initially charged in dichloromethane (50 mL), 1,8-diazabicyclo[5.4.0]undec-7-ene (605 mg, 0.590 mL, 3.97 mmol) was added at room temperature and the mixture was then stirred overnight. The reaction solution was concentrated under reduced pressure and the residue was taken up in ethyl acetate. The organic phase was washed with water, aqueous hydrogen chloride solution (0.5 N), saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **164**. Yield: 651 mg (60%). LC-MS (method 1a): t_R (min) = 1.15; MS (ESI+): m/z = 348 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.11 (br s, 1H), 7.41-7.25 (m, 5H), 4.42 (s, 2H), 4.13 (quin, 1H), 3.63 (s, 3H), 3.25 (br d, 1H), 2.99 (br d, 1H), 2.85 (br d, 1H), 2.65 (m, 1H), 1.37 (s, 9H).

Methyl [3-(benzyloxy)cyclobutyl][(*tert*-butoxycarbonyl)amino]acetate (165) as *cis* and *trans* isomer mixture (4 isomers).

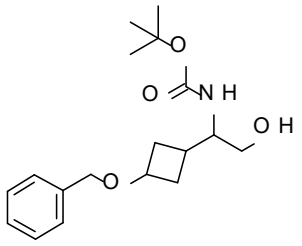


165

Methyl [3-(benzyloxy)cyclobutylidene][(*tert*-butoxycarbonyl)amino]acetate (**164**) (650 mg, 1.87 mmol) and magnesium turnings (455 mg, 18.7 mmol) were initially charged in methanol (50 mL) and reacted at room temperature in an ultrasonic bath [Elma, Transsonic T 780] for 3 h. Semisaturated aqueous ammonium chloride solution was added, and the reaction solution was extracted repeatedly with dichloromethane. The organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure to give **165** as crude product which was used without further purification in the next step. Yield: 630 mg (96%). LC-MS (method 1a): t_R (min) = 1.16; MS (ESI+): m/z = 350 $[M+H]^+$, 250 $[M+H\text{-}COOC(CH_3)_3]$; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 7.39-7.20 (m, 6H), 4.34 (s, 2H),

4.07 (quin, 0.3H), 3.99-3.73 (m, 1.7H), 3.60 (s, 3H), 2.34-1.94 (m, 3.5H), 1.74-1.59 (m, 1.5H), 1.45-1.27 (m, 9H).

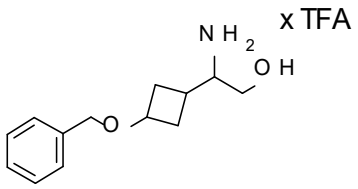
***tert*-Butyl {1-[3-(benzyloxy)cyclobutyl]-2-hydroxyethyl}carbamate (166) as *cis* and *trans* isomer mixture (4 isomers).**



166

Methyl [3-(benzyloxy)cyclobutyl][(*tert*-butoxycarbonyl)amino]acetate (**165**, *cis* and *trans* isomer mixture, 4 isomers) (620 mg, 1.77 mmol) was initially charged in tetrahydrofuran (6.0 mL), and lithium borohydride solution (2 M in tetrahydrofuran, 4.44 mL, 8.87 mmol) was added at 0 °C. The mixture was then stirred for 4 h and allowed to warm to room temperature during this time. The reaction was terminated by addition of ethyl acetate (50.0 mL) and the reaction solution was subsequently washed with aqueous hydrogen chloride solution (0.5 N). The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure to give **166** as crude product which was used without further purification in the next step. Yield: 560 mg (96%). LC-MS (method 1a): t_R (min) = 0.99; MS (ESI+): m/z = 322 $[M+H]^+$, 222 [M+H-Boc]; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 7.47-7.15 (m, 5H), 6.65-6.41 (m, 1H), 4.46 (br s, 0.5H), 4.33 (s, 2H), 3.88-3.70 (m, 0.7H), 3.67-3.09 (m, 3.8H), 2.36-1.78 (m, 3.5H), 1.74-1.48 (m, 1.5H), 1.38 (s, 9H).

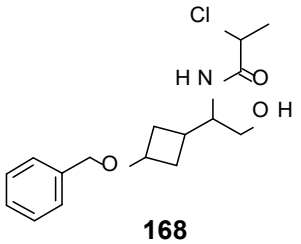
2-Amino-2-[3-(benzyloxy)cyclobutyl]ethanol trifluoroacetate (167) as *cis* and *trans* isomer mixture (4 isomers).



167

tert-Butyl {1-[3-(benzyloxy)cyclobutyl]-2-hydroxyethyl}carbamate (**166**, *cis* and *trans* isomer mixture, 4 isomers) (560 mg, 1.74 mmol) was initially charged in dichloromethane (8.0 mL), trifluoroacetic acid (1.0 mL, 12.9 mmol) was added at room temperature and the mixture was stirred for 2 h. The reaction solution was then concentrated completely under reduced pressure and excess trifluoroacetic acid was removed by repeated coevaporation with dichloromethane to give **167** as crude product which was used without further purification in the next step. Yield: 580 mg (95%). LC-MS (method 4a): t_R (min) = 2.10; MS (ESI+): m/z = 222 $[M+H-TFA]^+$.

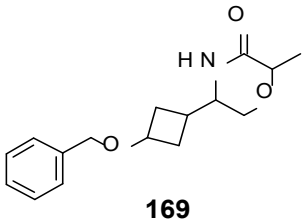
***N*-{1-[3-(Benzyloxy)cyclobutyl]-2-hydroxyethyl}-2-chloropropanamide (168) as diastereomer mixture (8 isomers).**



168

2-Amino-2-[3-(benzyloxy)cyclobutyl]ethanol trifluoroacetate (**167**, *cis* and *trans* isomer mixture, 4 isomers) (580 mg, 1.73 mmol) was initially charged in 2-propanol (15 mL), the mixture was cooled to 0 °C and triethylamine (700 mg, 960 µL, 6.92 mmol) was added. 2-Chloropropionyl chloride (racemate) (242 mg, 190 µL, 1.90 mmol) was then added dropwise, and the mixture was stirred at 0 °C for 1 h and then concentrated completely under reduced pressure. Aqueous hydrogen chloride solution (0.5 N, 50 mL) was added to the residue, and the mixture was extracted repeatedly with dichloromethane. The organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure to give **168** as crude product which was used without further purification in the next step. Yield: 638 mg (91%, 77% purity). LC-MS (method 4a): t_R (min) = 2.36; MS (ESI+): m/z = 312 $[M+H]^+$.

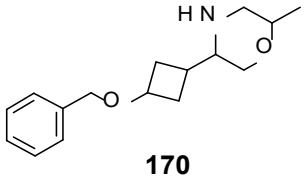
5-[3-(Benzyloxy)cyclobutyl]-2-methylmorpholin-3-one (169) as diastereomer mixture (8 isomers).



169

N-{1-[3-(Benzyloxy)cyclobutyl]-2-hydroxyethyl}-2-chloropropanamide (**168**, diastereomer mixture, 8 isomers) (1.15 g, 3.69 mmol) was initially charged in 2-propanol (30.0 mL), the mixture was cooled to 0 °C and potassium *tert*-butoxide (1.66 g, 14.8 mmol) was then added in one portion. The mixture was allowed to warm to room temperature and then stirred at 50 °C for 1 h. Most of the 2-propanol was removed under reduced pressure and the residue was taken up in ethyl acetate. The organic phase was washed with aqueous hydrogen chloride solution (1 N), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **169**. Yield: 953 mg (93%). LC-MS (method 1a): t_R (min) = 0.88; MS (ESI): m/z = 276 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.43-7.27 (m, 5H), 6.40 (br s, 0.16H), 6.24 (br s, 0.38H), 6.12-5.94 (m, 0.46H), 4.41 (s, 2H), 4.24-4.05 (m, 1.25H), 4.03-3.86 (m, 1.25H), 3.82-3.51 (m, 1.5H), 3.31-3.21 (m, 1H), 2.54-1.57 (m, 5H), 1.48-1.41 (m, 3H).

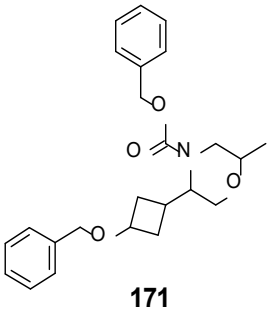
5-[3-(Benzyloxy)cyclobutyl]-2-methylmorpholine (170) as diastereomer mixture (8 isomers).



170

5-[3-(Benzyloxy)cyclobutyl]-2-methylmorpholin-3-one (**169**, diastereomer mixture, 8 isomers) (953 mg, 3.46 mmol) was initially charged in tetrahydrofuran (10 mL), borane-dimethyl sulfide complex solution (2M in tetrahydrofuran, 6.92 mL, 13.8 mmol) was added under argon and the mixture was stirred under reflux for 3 h. The reaction solution was then carefully added dropwise to ethanol (50.0 mL) and stirred under reflux for 8 h. The mixture was then concentrated under reduced pressure, and the residue was taken up in acetonitrile and purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **170**. Yield: 780 mg (84%). LC-MS (method 1a): t_R (min) = 0.57 / 0.60; MS (ESI+): m/z = 262 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 7.39-7.24 (m, 5H), 4.37-4.31 (m, 2H), 4.11-3.98 (m, 0.3H), 3.92-3.78 (m, 0.7H), 3.72-3.54 (m, 0.5H), 3.50-3.40 (m, 1.5H), 2.94-2.70 (m, 1H), 2.61 (td, 0.3H), 2.48-1.82 (m, 5.7H), 1.73-1.40 (m, 2H), 1.06-0.94 (m, 3H), 1 proton concealed.

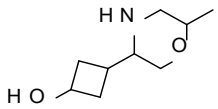
Benzyl 5-[3-(benzyloxy)cyclobutyl]-2-methylmorpholine-4-carboxylate (171) as diastereomer mixture (4 isomers).



171

5-[3-(Benzyloxy)cyclobutyl]-2-methylmorpholine (**170**, diastereomer mixture, 8 isomers) (900 mg, 3.44 mmol) and *N,N*-diisopropylethylamine (890 mg, 1.20 mL, 6.89 mmol) were initially charged in dichloromethane (45.0 mL), benzyl chloroformate (881 mg, 0.74 mL, 5.17 mmol) was added dropwise at 0 °C and the mixture was stirred overnight and allowed to warm to room temperature during this time. The reaction solution was concentrated under reduced pressure and the residue was taken up in acetonitrile. Purification and diastereomer separation by HPLC (achiral reversed phase, eluent: acetonitrile / water gradient) gave 537 mg (36%) of diastereomer mixture 1 (4 isomers) and 588 mg (43%) of diastereomer mixture 2 (4 isomers) which corresponds to the target compound **171**. LC-MS (method 1a): t_R (min) = 1.29; MS (ESI+): m/z = 396 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 7.44-7.22 (m, 10H), 5.20-4.98 (m, 2H), 4.36-4.20 (m, 2H), 4.14-3.34 (m, 6H), 2.88-2.57 (m, 1.5H), 2.44-1.53 (m, 4.5H), 1.10-1.03 (m, 3H).

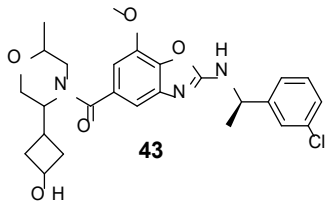
3-(6-Methylmorpholin-3-yl)cyclobutanol (172) as diastereomer mixture (4 isomers).



172

Benzyl 5-[3-(benzyloxy)cyclobutyl]-2-methylmorpholin-4-carboxylate (**171**, diastereomer mixture, 4 isomers) (580 mg, 1.47 mmol) was initially charged in ethanol (100 mL), palladium on carbon (10%, 58 mg) and palladium hydroxide on carbon (20%, 58 mg) were added under argon and the mixture was then stirred under an atmosphere of hydrogen at standard pressure overnight. The reaction solution was filtered through kieselguhr and the filter residue was washed with ethanol. The filtrate was concentrated under reduced pressure and the product was dried under high vacuum to give **172**. Yield: 245 mg (97%). GC-MS (method 1b): t_R (min) = 4.60 / 4.67; MS (EI+): m/z = 171 $[M]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 4.94-4.84 (m, 1H), 4.16-4.05 (d, 0.6H), 3.93-3.82 (m, 0.7H), 3.55-3.40 (m, 3.3H), 3.19-3.14 (m, 0.7H), 3.17 (d, 1H), 2.47-1.76 (m, 6H), 1.58-1.28 (m, 1.5H), 1.08-0.94 (m, 3.5H).

(2-{[(1*R*)-1-(3-Chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[5-(3-hydroxycyclobutyl)-2-methylmorpholin-4-yl]methanone (43) as single stereoisomer.



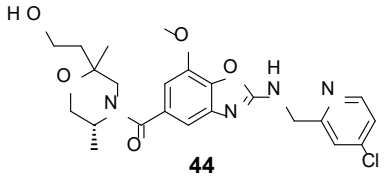
43

2-{[(1*R*)-1-(3-Chlorophenyl)ethyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**95**) (100 mg, 0.260 mmol, 90% purity) and 3-(6-methylmorpholin-3-yl)cyclobutanol as diastereomer mixture (4 isomers, **172**) (53.3 mg, 0.311, mmol, 1.2 equiv.) were initially charged in *N,N*-dimethylformamide (1.20 mL), and *N,N*-diisopropylethylamine (117 mg, 158 µL, 0.910 mmol, 3.5 equiv.) was added. Subsequently, HATU (118 mg, 0.311 mmol) was added at room temperature and the mixture was stirred overnight. Without further work-up, the reaction solution was then purified directly by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give a diastereomer mixture (4 isomers). Yield: 105 mg (80%). LC-MS (method 1a): t_R (min) = 0.97; MS (ESI+): m/z = 500 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.70 (br d, J = 7.2 Hz, 1H), 7.48 (br s, 1H), 7.43-7.24 (m, 3H), 6.95-6.53 (m, 2H), 5.09-7.78 (m, 2H), 4.49-4.02 (m, 1H), 3.90 (s, 3H), 3.82-3.41 (m, 3H), 3.32-3.17 (m, 1H), 3.06-2.72 (m, 1H), 2.70-2.56 (m, 1H), 2.38-2.22 (m, 1H), 2.13-1.55 (m, 3H), 1.48 (br d, J = 6.8 Hz, 3H), 1.30-0.85 (m, 4H).

This mixture (100 mg) was submitted for diastereomer separation (preparative method: HPLC: column: Daicel Chiralpak AZ-H 5 µm, 250 mm x 30 mm; eluent: 50% *iso*-hexane / 50% ethanol; temperature:

25 °C; flow rate: 40 mL/min; UV-detection: 230 nm; analytical method: HPLC: column: Daicel Chiralpak AD-H 5 µm, 250 mm x 4.6 mm; eluent: 50% *iso*-hexane / 50% ethanol; temperature: 30 °C; flow rate: 1.0 mL/min; UV-detection: 220 nm) to give four diastereomers: single stereoisomer 1, which corresponds to the desired stereoisomer **43**: Yield: 29.6 mg (21%). HPLC: t_R (min) = 9.97, >99% de; LC-MS (method 1a): t_R (min) = 1.00; MS (ESI+): m/z = 500 $[M+H]^+$; 1H NMR (400 MHz, DMSO-d6): δ [ppm] = 8.70 (br d, *J* = 7.2 Hz, 1H), 7.48 (br s, 1H), 7.43-7.24 (m, 3H), 6.95-6.53 (m, 2H), 5.09-7.78 (m, 2H), 4.49-4.02 (m, 1H), 3.90 (s, 3H), 3.82-3.41 (m, 3H), 3.32-3.17 (m, 1H), 3.06-2.72 (m, 1H), 2.70-2.56 (m, 1H), 2.38-2.22 (m, 1H), 2.13-1.55 (m, 3H), 1.48 (br d, *J* = 6.8 Hz, 3H), 1.30-0.85 (m, 4H); single stereoisomer 2: Yield: 14.2 mg (10%). HPLC: t_R (min) = 11.2, >93% de; LC-MS (method 1a): t_R (min) = 0.99; MS (ESI+): m/z = 500 $[M+H]^+$; single stereoisomer 3: Yield: 26.8 mg (19%). HPLC: t_R (min) = 13.9, >99% de; LC-MS (method 1a): t_R (min) = 1.00; MS (ESI+): m/z = 500 $[M+H]^+$; single stereoisomer 4: Yield: 14.9 mg (11%). HPLC: t_R (min) = 16.9, >90% de; LC-MS (method 1a): t_R (min) = 0.99; MS (ESI+): m/z = 500 $[M+H]^+$.

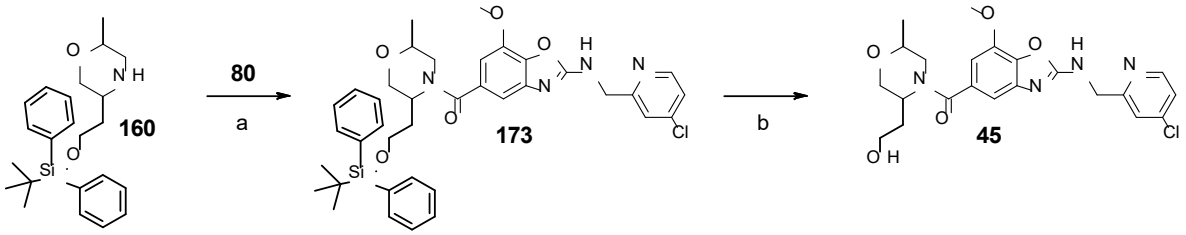
(2-{[(4-Chloropyridin-2-yl)methyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[(5*R*)-2-(2-hydroxyethyl)-2,5-dimethylmorpholin-4-yl]methanone (44) as enantiomerically pure isomer.



44

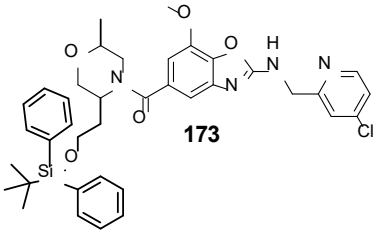
2-{[(4-Chloropyridin-2-yl)methyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**80**) (100 mg, 0.282 mmol) and 2-[(*5R*)-2,5-dimethylmorpholin-2-yl]ethanol (enantiomerically pure isomer **145**) (53.8 mg, 0.338 mmol) were initially charged in *N,N*-dimethylformamide (1.30 mL), and *N,N*-diisopropylethylamine (127 mg, 172 µL, 0.986 mmol) was added. Subsequently, HATU (129 mg, 0.338 mmol) was added at room temperature and the mixture was stirred overnight. Without further work-up, the reaction solution was then purified directly by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **44** as enantiomerically pure isomer. Yield: 96.6 mg (72%). LC-MS (method 1a): t_R (min) = 0.77; MS (ESI+): m/z = 475 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.69 (t, 1H), 8.52 (d, 1H), 7.53 (d, 1H), 7.45 (dd, 1H), 6.82 (s, 1H), 6.67 (s, 1H), 4.63 (d, 2H), 4.30 (t, 1H), 3.92 (s, 3H), 3.74 (dd, 1H), 3.38 (br s, 2H), 2.96 (br s, 1H), 2.02 (m_c, 1H), 1.45 (br s, 1H), 1.22 (d, 3H), 1.08 (br s, 3H), 3 protons concealed.

(2-{[(4-Chloropyridin-2-yl)methyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[5-(2-hydroxyethyl)-2-methylmorpholin-4-yl]methanone (45) as enantiomerically pure isomer.



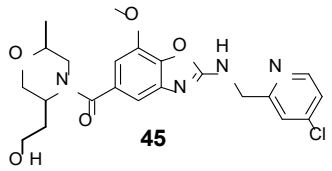
a) **80**, HATU, DIEA, DMF, RT; b) i) TBAF, THF, RT, ii) enantiomer separation.

[5-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-2-methylmorpholin-4-yl](2-{[(4-chloropyridin-2-yl)methyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)methanone (173) as racemate.



2-{[(4-Chloropyridin-2-yl)methyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**80**) (600 mg, 1.80 mmol) and 5-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-2-methylmorpholine (racemate **160**) (759 mg, 1.98 mmol) were initially charged in *N,N*-dimethylformamide (4.90 mL), and *N,N*-diisopropylethylamine (744 mg, 1.00 mL, 5.75 mmol) was added. HATU (820 mg, 2.16 mmol) was then added at room temperature, and the mixture was stirred for 1 h. Without further work-up, the reaction solution was then purified directly by preparative HPLC (reversed phase, eluent: acetonitrile / water + 0.1% formic acid) to give **173**. Yield: 845 mg (67%). LC-MS (method 2a): t_R (min) = 2.94; MS (ESI+): m/z = 699 $[M+H]^+$.

(2-{[(4-Chloropyridin-2-yl)methyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[5-(2-hydroxyethyl)-2-methylmorpholin-4-yl]methanone (45) as enantiomerically pure isomer.

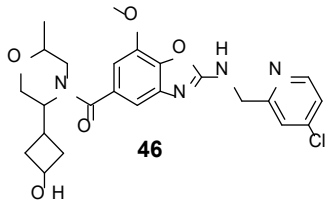


[5-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-2-methylmorpholin-4-yl](2-{[(4-chloropyridin-2-yl) methyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)methanone (racemate **173**) (840 mg, 1.20 mmol) was initially charged in tetrahydrofuran (25.2 mL), tetra-*n*-butylammonium fluoride (628 mg, 2.40 mmol) was added at room temperature and the mixture was stirred for 30 min. The reaction solution was then

concentrated under reduced pressure and the residue was purified directly by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give a racemic mixture. Yield: 525 mg (91%). LC-MS (method 9a): t_R (min) = 0.73; MS (ESI+): m/z = 461 $[M+H]^+$.

This racemic mixture (512 mg) was submitted for enantiomer separation (preparative method: HPLC: phase: Daicel Chiralpak OD-H 5 µm, 250 mm x 4 mm, mobile phase: 50% *iso*-hexane, 50% ethanol + 0.2% diethylamine; flow rate: 1 mL/min; temperature: 40 °C; detection: 220 nm; analytical method: HPLC: phase: Daicel IA 5 µm, 250 mm x 4.6 mm; mobile phase: *tert*-butyl methyl ether / methanol 50:50; flow rate: 1 mL/min; temperature: 30 °C; UV detection: 220 nm) to give, after re-purification by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient), two enantiopure diastereomers: single stereoisomer 1: Yield: 179 mg (32%). HPLC: t_R (min) = 4.65, >99.0% ee; LC-MS (method 2a): t_R (min) = 0.74; MS (ESI+): m/z = 461 $[M+H]^+$; single stereoisomer 2, which corresponds to the desired stereoisomer **45**: Yield: 169 mg (29%). HPLC: t_R (min) = 6.21, >99.0% ee; LC-MS (method 2a): t_R (min) = 0.74; MS (ESI+): m/z = 461 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.70 (d, 1H), 8.52 (d, 1H), 7.52 (d, 1H), 7.45 (dd, 1H), 6.84 (br s, 1H), 6.70 (br s, 1H), 4.62 (d, 2H), 4.56-4.14 (m, 2H), 3.91 (s, 3H), 3.84-3.37 (m, 5H), 3.07-2.60 (m, 1H), 2.01-1.75 (m, 2H), 1.21-0.87 (m, 3H), 1 proton concealed.

(2-{[(4-Chloropyridin-2-yl)methyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[5-(3-hydroxycyclobutyl)-2-methylmorpholin-4-yl]methanone (46) as enantiomerically pure isomer.



46

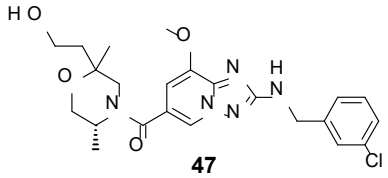
2-{[(4-Chloropyridin-2-yl)methyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (**80**) (100 mg, 0.282 mmol) and 3-(6-methylmorpholin-3-yl)cyclobutanol (**172**, diastereomer mixture, 4 isomers) (57.9 mg, 0.338 mmol) were initially charged in *N*,*N*-dimethylformamide (1.30 mL), and *N*,*N*-diisopropylethylamine (127 mg, 172 µL, 0,986 mmol) was added. Subsequently, HATU (129 mg, 0.338 mmol) was added at room temperature and the mixture was stirred overnight. Without further work-up, the reaction solution was then purified directly by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give a diastereomer mixture (4 isomers). Yield: 91.8 mg (67%). LC-MS (method 1a): t_R (min) = 0.78 (diastereomer 1, 2 isomers), t_R (min) = 0.79 (diastereomer 2, 2 isomers); MS (ESI+): m/z = 487 $[M+H]^+$.

Diastereomer separation of this mixture (86.0 mg) on achiral phase (preparative method: HPLC: phase: Sunfire C-18 5 µm, 250 mm x 20 mm, mobile phase: water / acetonitrile gradient 80:20 → 5:95, flow rate: 23.75 mL/min + constant addition of 2% strength formic acid; flow rate: 1.25 mL/min; UV

detection: 210 nm) gave 18.1 mg of diastereomer 1 (2 isomers) and 49.3 mg of diastereomer 2 (2 isomers). LC-MS (method 1a): t_R (min) = 0.81 (diastereomer 1) / 0.82 (diastereomer 2); MS (ESI+): m/z = 487 $[M+H]^+$.

Enantiomer separation of 45.0 mg of diastereomer 2 (2 isomers) on chiral phase (preparative method: HPLC: phase: Daicel Chiralpak OZ-H 5 µm, 250 mm x 20 mm, mobile phase: *iso*-hexane / ethanol 30:70 + 0.2% diethylamine; flow rate: 15 mL/min, temperature: 40 °C; UV detection: 220 nm; analytical method: HPLC: phase: Daicel Chiralpak AD-H 5 µm, 250 mm x 4.6 mm, mobile phase: *iso*-hexane / ethanol 50:50; flow rate: 1 mL/min, temperature: 40 °C; UV detection: 220 nm) gave 14.2 mg of enantiomerically pure isomer 1 which corresponds to **46** (HPLC: t_R (min) = 5.23, >99.9% ee) and 19.8 mg of enantiomerically pure isomer 2 (HPLC: t_R (min) = 10.4, >99.9% ee). LC-MS (method 1a): t_R (min) = 0.78 (enantiomerically pure isomer 1, **46**) / 0.78 (enantiomerically pure isomer 2); MS (ESI+): m/z = 487 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.71 (t, 1H), 8.51 (d, 1H), 7.53 (d, 1H), 7.45 (d, 1H), 6.82 (d, 1H), 6.67 (d, 1H), 5.03-4.81 (2x m, 1H), 4.70-4.56 (m, 2H), 4.41-4.04 (2x m, 1H), 3.85-3.42 (m, 5H), 3.28-2.91 (2x m, 1H), 2.69-2.5 (2x m, 1H, partially concealed), 2.43-2.05 (2x m, 3H), 1.74-1.54 (m, 1H), 1.34-0.82 (m, 5H), 1 proton concealed.

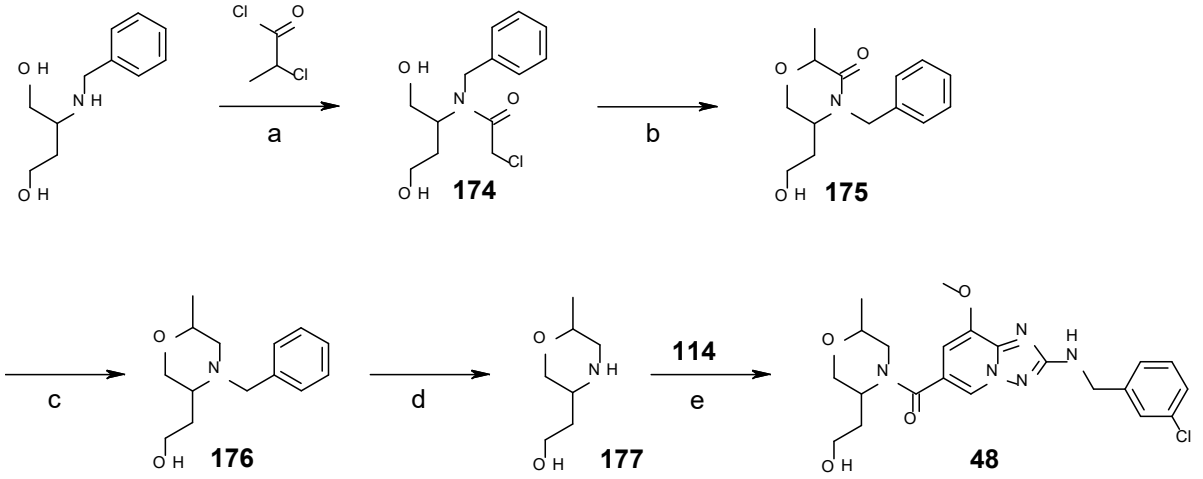
{2-[(3-Chlorobenzyl)amino]-8-methoxy[1,2,4]triazolo[1,5-a]pyridin-6-yl}[(5*R*)-2-(2-hydroxyethyl)-2,5-dimethylmorpholin-4-yl]methanone (47) as enantiomerically pure isomer.



47

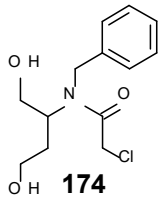
2-[(3-Chlorobenzyl)amino]-8-methoxy[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid (**114**) (100 mg, 0.301 mmol) and 2-[(*5R*)-2,5-dimethylmorpholin-2-yl]ethanol (enantiomerically pure isomer **145**) (57.4 mg, 0.361 mmol) were initially charged in *N,N*-dimethylformamide (1.38 mL), and *N,N*-diisopropylethylamine (136 mg, 183 µL, 1.05 mmol) was added. Subsequently, HATU (137 mg, 0.361 mmol) was added at room temperature and the mixture was stirred overnight. Without further work-up, the reaction solution was then purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give **47**. Yield: 97.6 mg (67%). LC-MS (method 1a): t_R (min) = 0.88; MS (ESI+): m/z = 474 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.30 (s, 1H), 7.40 (s, 1H), 7.37-7.20 (m, 4H), 6.86 (d, 1H), 4.46 (d, 2H), 4.28 (t, 1H), 4.19 (br s, 1H), 3.93 (s, 3H), 3.78 (dd, 1H), 3.68 (br s, 1H), 3.48-3.32 (m, 3H), 3.10-2.98 (m, 1H), 2.00 (m_c, 1H), 1.49 (m_c, 1H), 1.25 (d, 3H), 1.09 (s, 3H).

{2-[(3-Chlorobenzyl)amino]-8-methoxy[1,2,4]triazolo[1,5-a]pyridin-6-yl}[5-(2-hydroxyethyl)-2-methylmorpholin-4-yl]methanone (48) as enantiomerically pure isomer.



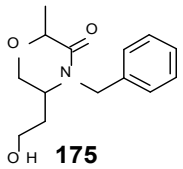
a) 2-chloropropionyl chloride, TEA, 2-propanol, 0 °C to RT; b) KO*t*-Bu, 2-propanol, 0 °C; c) BH_3 x Me_2S, THF, RF; d) H_2 (1 bar), 10% Pd/C, 20% $Pd(OH)_2$/C, EtOH, RT; e) i) **114**, HATU, DIEA, DMF, RT, ii) enantiomer separation.

***N*-Benzyl-2-chloro-*N*-(1,4-dihydroxybutan-2-yl)propanamide (174) as diastereomer mixture (4 isomers).**



2-(Benzylamino)butane-1,4-diol (racemate) (20.6 g, 106 mmol) [lit: Feringa, B. L.; de Lange, B. *Heterocycles* **1988**, *27*, 1197-1205] was initially charged in 2-propanol (500 mL), the mixture was cooled to 0 °C and triethylamine (21.4 g, 29.4 mL, 211 mmol) was added. 2-Chloropropionyl chloride (racemate) (16.1 g, 12.6 mL, 127 mmol) was then added dropwise. After 30 min of stirring, a further 2-chloropropionyl chloride (racemate) (10.4 g, 8.37 mL, 84.4 mmol) was added dropwise, and the reaction solution was allowed to warm to room temperature. The solution was then concentrated under reduced pressure and the residue was taken up in ethyl acetate (500 mL) and washed with aqueous hydrogen chloride solution (0.5 N, 400 mL). The aqueous phase was extracted repeatedly with ethyl acetate. The organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure to give **174** as crude product which was used without further purification in the next step. Yield: 37.5 g (78%, 63% purity, diastereomer ratio about 2:1). LC-MS (method 1a): t_R (min) = 0.71 (diastereomer 1, 2 isomers), t_R (min) = 0.72 (diastereomer 2, 2 isomers); MS (ESI+): m/z = 286 $[M+H]^+$.

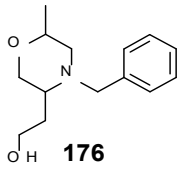
4-Benzyl-5-(2-hydroxyethyl)-2-methylmorpholin-3-one (175) as diastereomer mixture (4 isomers).



175

A mixture of *N*-benzyl-2-chloro-*N*-(-1,4-dihydroxybutan-2-yl)propanamide (**174**, diastereomer mixture, 4 isomers) (37.5 g, 82.5 mmol, 63% purity) in 2-propanol (500 mL) was cooled to 0 °C, and potassium *tert*-butoxide (73.5 g, 655 mmol) was then added in one portion. The mixture was stirred at 0 °C for 1 h and most of the 2-propanol was then removed under reduced pressure. The residue was taken up in ethyl acetate and washed with an aqueous hydrogen chloride solution (1 N, 400 mL). The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure to give **175** as crude product which was used without further purification in the next step. Yield: 28.8 g (quantitative, 82% purity, diastereomer ratio about 2.5:1). LC-MS (method 3a): t_R (min) = 1.42 (diastereomer 1, 2 isomers), t_R (min) = 1.46 (diastereomer 2, 2 isomers); MS (ESI+): m/z = 250 $[M+H]^+$.

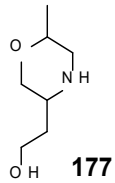
2-(4-Benzyl-6-methylmorpholin-3-yl)ethanol (176) as racemate.



176

4-Benzyl-5-(2-hydroxyethyl)-2-methylmorpholin-3-one (**175**, diastereomer mixture, 4 isomers) (28.8 g, 94.7 mmol, 82% purity) was initially charged in tetrahydrofuran (800 mL), borane-dimethyl sulfide complex solution (2 M in tetrahydrofuran, 231 mL, 462 mmol) was added under argon and the mixture was stirred under reflux for 2 h. The mixture was subsequently cooled to 0 °C, methanol (220 mL) was added carefully and the mixture was stirred under reflux for 30 min. The mixture was subsequently concentrated completely under reduced pressure, and 6.0 g of the residue were taken up in acetonitrile and subjected to purification and diastereomer separation by preparative HPLC (reversed phase, eluent: acetonitrile / water, isocratic) to give the minor diastereomer 1 (698 mg, racemate) and **176** as second eluating component and main diastereomer 2 (1.95 g, racemate); LC-MS (method 4a): t_R (min) = 2.23 (diastereomer 1) / 2.33 (diastereomer 2, **176**); MS (ESI+): m/z = 236 $[M+H]^+$.

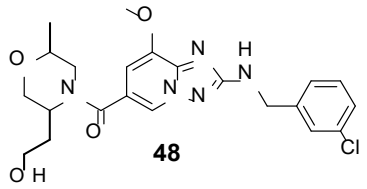
2-(6-Methylmorpholin-3-yl)ethanol (177) as racemate.



177

2-(4-Benzyl-6-methylmorpholin-3-yl)ethanol (racemate **176**) (1.95 g, 8.29 mmol) was initially charged in ethanol (83 mL), palladium on carbon (10%, 208 mg) and palladium hydroxide on carbon (20%, 104 mg) were added under argon, and the mixture was then stirred under an atmosphere of hydrogen at standard pressure overnight. The reaction solution was filtered through kieselguhr and the filter residue was washed with ethanol. The filtrate was concentrated under reduced pressure and the product was dried under high vacuum to give **177**. Yield: 1.37 g (quantitative). MS (method 1c): m/z = 146 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 3.53-3.41 (m, 5H), 2.69 (m_c, 1H), 2.60-2.43 (m, 2H), 1.82-1.69 (m, 1H), 1.58-1.44 (m, 1H), 1.03 (d, 3H), 2 protons concealed.

{2-[(3-Chlorobenzyl)amino]-8-methoxy[1,2,4]triazolo[1,5-a]pyridin-6-yl}[5-(2-hydroxyethyl)-2-methylmorpholin-4-yl]methanone (48) as enantiomerically pure isomer.



48

2-[(3-Chlorobenzyl)amino]-8-methoxy[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid (**114**) (120 mg, 0.361 mmol) and 2-(6-methylmorpholin-3-yl)ethanol (racemate **177**) (62.8 mg, 0.433 mmol) were initially charged in *N,N*-dimethylformamide (1.66 mL), and *N,N*-diisopropylethylamine (163 mg, 220 µL, 1.26 mmol) was added. Subsequently, HATU (165 mg, 0.433 mmol) was added at room temperature and the mixture was stirred overnight. Without further work-up, the reaction solution was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to a racemate. Yield: 143 mg (86%). LC-MS (method 1a): t_R (min) = 0.88; MS (ESI+): m/z = 460 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.33 (br s, 1H), 7.39 (s, 1H), 7.37-7.24 (m, 4H), 6.89 (br s, 1H), 4.59-4.06 (m, 4H), 3.93 (s, 3H), 3.86-3.39 (m, 5H), 2.01-1.76 (m, 2H), 1.24-0.94 (m, 3H), 2 protons concealed.

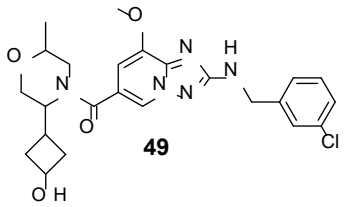
Enantiomer separation of this racemate (138 mg) on chiral phase (preparative method: HPLC: phase: Daicel Chiralpak IC 5 µm, 250 mm x 20 mm; mobile phase: *tert*-butyl methyl ether / methanol 50:50; flow rate: 20 mL/min; temperature: 25 °C; UV detection: 220 nm; analytical method: HPLC: phase: Daicel Chiralpak IC 5 µm, 250 mm x 4.6 mm; mobile phase: *tert*-butyl methyl ether / methanol 50:50; flow rate: 1 mL/min; temperature: 30 °C; UV detection: 220 nm) gave 35.2 mg of enantiomerically

pure isomer 1 which corresponds to **48** (HPLC: t_R (min) = 5.43, >99.0% ee) and 35.9 mg of enantiomerically pure isomer 2 (HPLC: t_R (min) = 9.08, >99.0% ee).

Enantiomerically pure isomer 1, **48**: LC-MS (method 1a): t_R (min) = 0.87; MS (ESI+): m/z = 460 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.32 (br s, 1H), 7.39 (s, 1H), 7.37-7.23 (m, 4H), 6.89 (br s, 1H), 4.61-4.08 (m, 4H), 3.93 (s, 3H), 3.86-3.37 (m, 5H), 2.01-1.76 (m, 2H), 1.22-0.91 (m, 3H), two protons obscured.

Enantiomerically pure isomer 2: LC-MS (method 1a): t_R (min) = 0.87; MS (ESI+): m/z = 460 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.32 (br s, 1H), 7.39 (s, 1H), 7.37-7.22 (m, 4H), 6.89 (br s, 1H), 4.62-4.09 (m, 4H), 3.93 (s, 3H), 3.84-3.38 (m, 5H), 2.00-1.72 (m, 2H), 1.19-0.93 (m, 3H), two protons obscured.

{2-[(3-Chlorobenzyl)amino]-8-methoxy[1,2,4]triazolo[1,5-a]pyridin-6-yl}[5-(3-hydroxycyclobutyl)-2-methylmorpholin-4-yl]methanone (49) as two diastereoisomers.

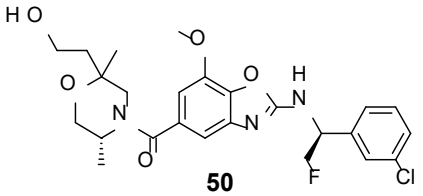


49

2-[(3-Chlorobenzyl)amino]-8-methoxy[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid (**114**) (100 mg, 0.301 mmol) and 3-(6-methylmorpholin-3-yl)cyclobutanol (**172**, 4 isomers) (61.8 mg, 0.361 mmol) were initially charged in *N,N*-dimethylformamide (1.38 mL), and *N,N*-diisopropylethylamine (136 mg, 183 µL, 1.05 mmol) was added. Subsequently, HATU (137 mg, 0.361 mmol) was added at room temperature and the mixture was stirred overnight. Without further work-up, the reaction solution was then purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give a diastereomer mixture (4 isomers). Yield: 97.6 mg (67%). LC-MS (method 1a): t_R (min) = 0.87; MS (ESI+): m/z = 486 $[M+H]^+$.

Diastereomer separation of this mixture (93.0 mg) on chiral phase (preparative method: HPLC: phase: Daicel Chiralcel AD-H 5 µm, 250 mm x 20 mm; mobile phase: *iso*-hexane / ethanol 50:50 + 0.2% diethylamine; flow rate: 20 mL/min; temperature: 20 °C; UV detection: 220 nm; analytical method: HPLC: phase: Daicel Chiralcel AD-H 5 µm, 250 mm x 4.6 mm; mobile phase: *iso*-hexane / ethanol 50:50 + 0.2% diethylamine; flow rate: 1 mL/min; temperature: 40 °C; UV detection: 220 nm) gave 30.2 mg of diastereomer 1 + diastereomer 2: HPLC: t_R (min) = 11.5; LC-MS (method 1a): t_R (min) = 0.87 (diastereomer 1), t_R (min) = 0.88 (diastereomer 2); MS (ESI+): m/z = 486 $[M+H]^+$ and 34.8 mg of diastereomer 3 + diastereomer 4 which corresponds to **49**: HPLC: t_R (min) = 25.0; LC-MS (method 1a): t_R (min) = 0.87 (diastereomer 3), t_R (min) = 0.88 (diastereomer 4); MS (ESI+): m/z = 486 $[M+H]^+$.

(2-{[(1*S*)-1-(3-Chlorophenyl)-2-fluoroethyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[(*5R*)-2-(2-hydroxyethyl)-2,5-dimethylmorpholin-4-yl]methanone (50) as enantiomerically pure isomer.



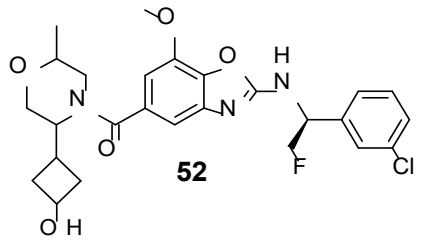
50

2-{[1-(3-Chlorophenyl)-2-fluoroethyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (racemate of **75**) (120 mg, 77% purity, 0.250 mmol) and 2-[(*5R*)-2,5-dimethylmorpholin-2-yl]ethanol (**145**, enantiomerically pure isomer) (48.4 mg, 0.300 mmol) were initially charged in *N,N*-dimethylformamide (1.17 mL), and *N*,*N*-diisopropylethylamine (115 mg, 154 µL, 0.890 mmol) was added. HATU (116 mg, 0.300 mmol) was then added at room temperature, and the mixture was stirred for 2 h. Without further work-up, the reaction solution was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give a 1:1 diastereomer mixture (2 isomers). Yield: 112 mg (84%). LC-MS (method 1a): t_R (min) = 0.93; MS (ESI+): m/z = 506 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 9.00 (dd, 1H), 7.58 (br s, 1H), 7.50-7.32 (m, 3H), 6.82 (br s, 1H), 6.67 (s, 1H), 5.24 (m_c, 1H), 4.80-4.52 (m, 2H), 4.31 (t, 1H), 3.92 (s, 3H), 3.73 (d, 1H), 2.96 (br s, 0.5H), 2.02 (m_c, 1H), 1.43 (br s, 0.5H), 1.29-1.02 (m, 6H), 6 protons concealed.

Diastereomer separation of this mixture (102 mg) on chiral phase (preparative method: HPLC: phase: Daicel Chiralpak AZ-H 5 µm, 250 mm x 30 mm, mobile phase: *iso*-hexane / ethanol 50:50; flow rate: 40 mL/min, temperature: 25 °C; UV detection: 220 nm; analytical method: HPLC: phase: Daicel Chiralcel AZ-H 5 µm, 250 mm x 4.6 mm, mobile phase: *iso*-hexane / ethanol 50:50; flow rate: 1 mL/min; temperature: 30 °C; UV detection: 220 nm) gave, after re-purification by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient), 24.7 mg of enantiomerically pure isomer 1 (HPLC: t_R (min) = 13.6, >99.0% *de*) and 24.0 mg of the enantiomerically pure isomer 2 (HPLC: t_R (min) = 15.6, 98.5% *de*) which corresponds to **50**.

Enantiomerically pure isomer 1: LC-MS (method 1a): t_R (min) = 0.93; MS (ESI+): m/z = 506 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 9.00 (d, 1H), 7.59 (s, 1H), 7.51-7.36 (m, 3H), 6.83 (s, 1H), 6.67 (s, 1H), 5.24 (m_c, 1H), 4.80-4.52 (m, 2H), 4.32 (t, 1H), 3.92 (s, 3H), 3.73 (dd, 1H), 2.96 (br s, 0.5H), 2.00 (m_c, 1H), 1.43 (br s, 0.5H), 1.26-1.02 (m, 6H), six protons obscured; enantiomerically pure isomer 2, **50**: LC-MS (method 1a): t_R (min) = 0.93; MS (ESI+): m/z = 506 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 9.01 (br s, 1H), 7.58 (s, 1H), 7.51-7.29 (m, 3H), 6.81 (s, 1H), 6.67 (s, 1H), 5.24 (br d, 1H), 4.86-4.48 (m, 2H), 4.32 (t, 1H), 3.92 (s, 3H), 3.73 (dd, 1H), 2.96 (br s, 0.5H), 2.00 (m_c, 1H), 1.43 (br s, 0.5H), 1.21 (d, 3H), 1.07 (br s, 3H), 6 protons concealed.

(2-{[(1*S*)-1-(3-Chlorophenyl)-2-fluoroethyl]amino}-7-methoxy-1,3-benzoxazol-5-yl)[5-(3-hydroxycyclobutyl)-2-methylmorpholin-4-yl]methanone (52) as enantiomerically pure isomer.



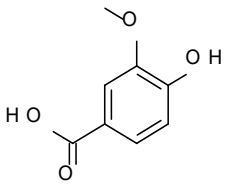
52

2-{[1-(3-Chlorophenyl)-2-fluoroethyl]amino}-7-methoxy-1,3-benzoxazole-5-carboxylic acid (enantiomerically pure isomer ***S*-75**) (200 mg, 60% purity, 0.33 mmol) and 3-(6-methylmorpholin-3-yl)cyclobutanol (**172**, diastereomer mixture, 4 isomers) (67.6 mg, 0.40 mmol) were initially charged in *N,N*-dimethylformamide (2.50 mL), and *N*,*N*-diisopropylethylamine (170 mg, 229 µL, 1.32 mmol) was added. HATU (150 mg, 0.40 mmol) was then added at room temperature, and the mixture was stirred for 2 h. Without further work-up, the reaction solution was then purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient) to give a diastereomer mixture. Yield: 83.9 mg (48%). LC-MS (method 1a): t_R (min) = 0.94, 0.95; MS (ESI+): m/z = 518 $[M+H]^+$.

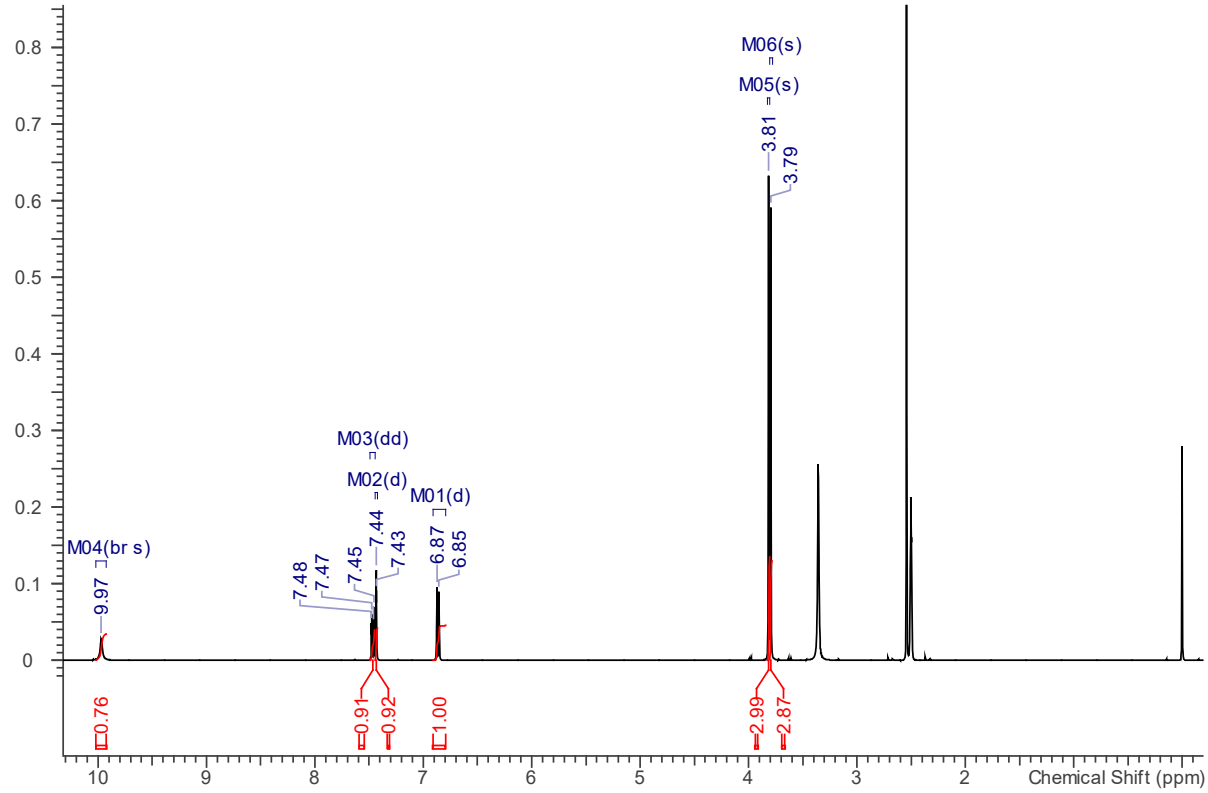
Diastereomer separation of this mixture (75.0 mg) on chiral phase (preparative method: HPLC: phase: Daicel Chiralpak AZ-H 5 µm, 250 mm x 30 mm, mobile phase: *iso*-hexane / ethanol 50:50; flow rate: 40 mL/min; temperature: 20 °C; UV detection: 220 nm; analytical method: HPLC: phase: Daicel Chiralcel OZ-H 5 µm, 250 mm x 4.6 mm, mobile phase: *iso*-hexane / ethanol 50:50; flow rate: 1 mL/min; temperature: 30 °C; UV detection: 220 nm) gave 17.4 mg of enantiomerically pure isomer 1 (HPLC: t_R (min) = 11.1, >99% *de*), 8.6 mg of enantiomerically pure isomer 2 which corresponds to **52** (HPLC: t_R (min) = 12.6, 94.3:5.7 *dr*), 17.7 mg of enantiomerically pure isomer 3 (HPLC: t_R (min) = 14.5, >99% *de*) and 9.5 mg of enantiomerically pure isomer 4 (HPLC: t_R (min) = 17.2, 96.1:3.9 *dr*. LC-MS (method 1a): t_R (min) = 0.95 (enantiomerically pure isomer 1) / 0.95 (enantiomerically pure isomer 2, **52**) / 0.95 (enantiomerically pure isomer 3) / 0.94 (enantiomerically pure isomer 4); MS (ESI+): m/z = 518 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 9.05-8.96 (m, 1H), 7.58 (s, 1H), 7.50-7.35 (m, 3H), 6.83 (d, 1H), 6.71 (d, 1H), 5.31-5.16 (m, 1H), 5.04-4.84 (2x m, 1H), 4.81-4.53 (3x m, 2H), 4.44-4.08 (3x m, 2H), 3.77-3.44 (2x m, 4H), 3.3-3.19 (m, 1H, partially concealed), 2.95-2.72 (2x m, 1H), 2.08-1.84 (m, 2H), 1.84-1.64 (m, 2H), 1.35-0.77 (m, 6H).

B. ^{1}H NMR data of intermediates 53-58, 60-62, 64-65, 67-69, 72-75, and BAY 1217224 (51):

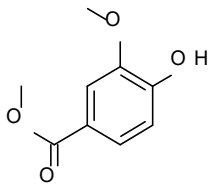
^{1}H NMR compound **53**



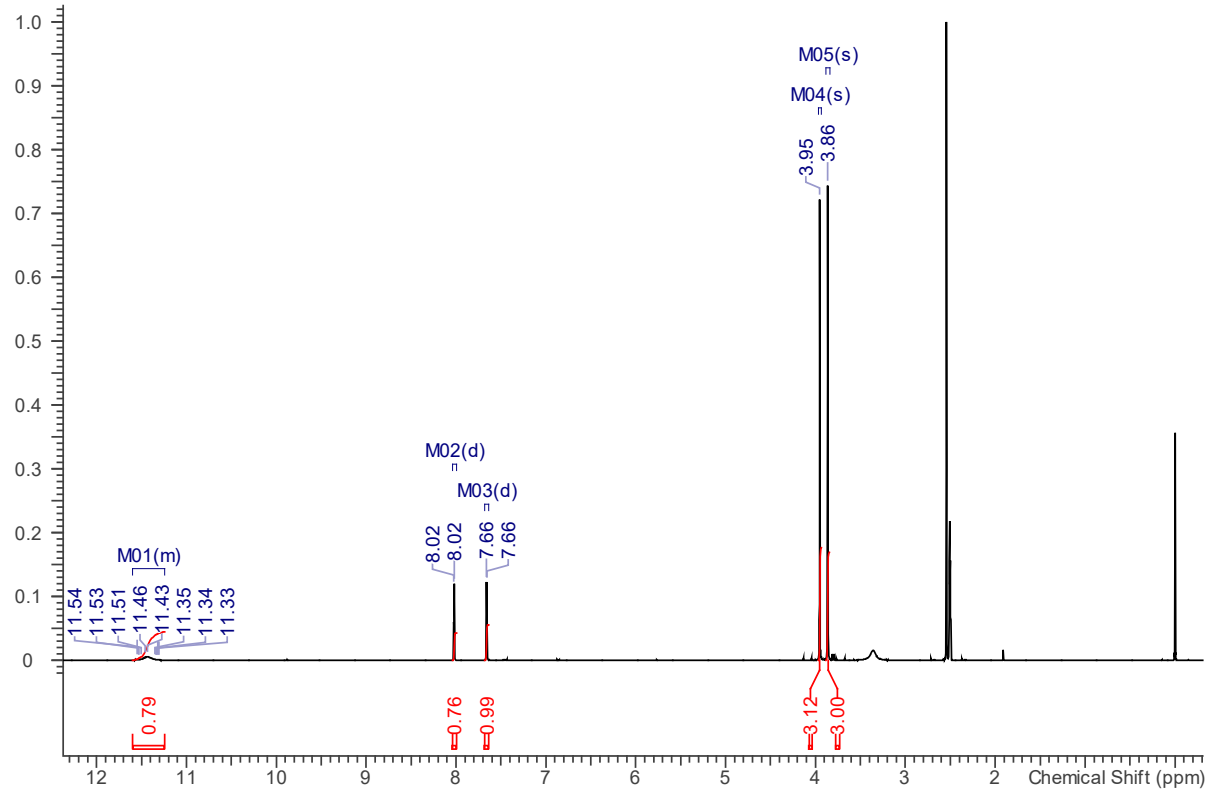
53



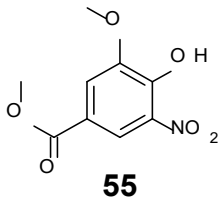
^{1}H NMR of compound **54**



54



^{1}H NMR of compound **55**



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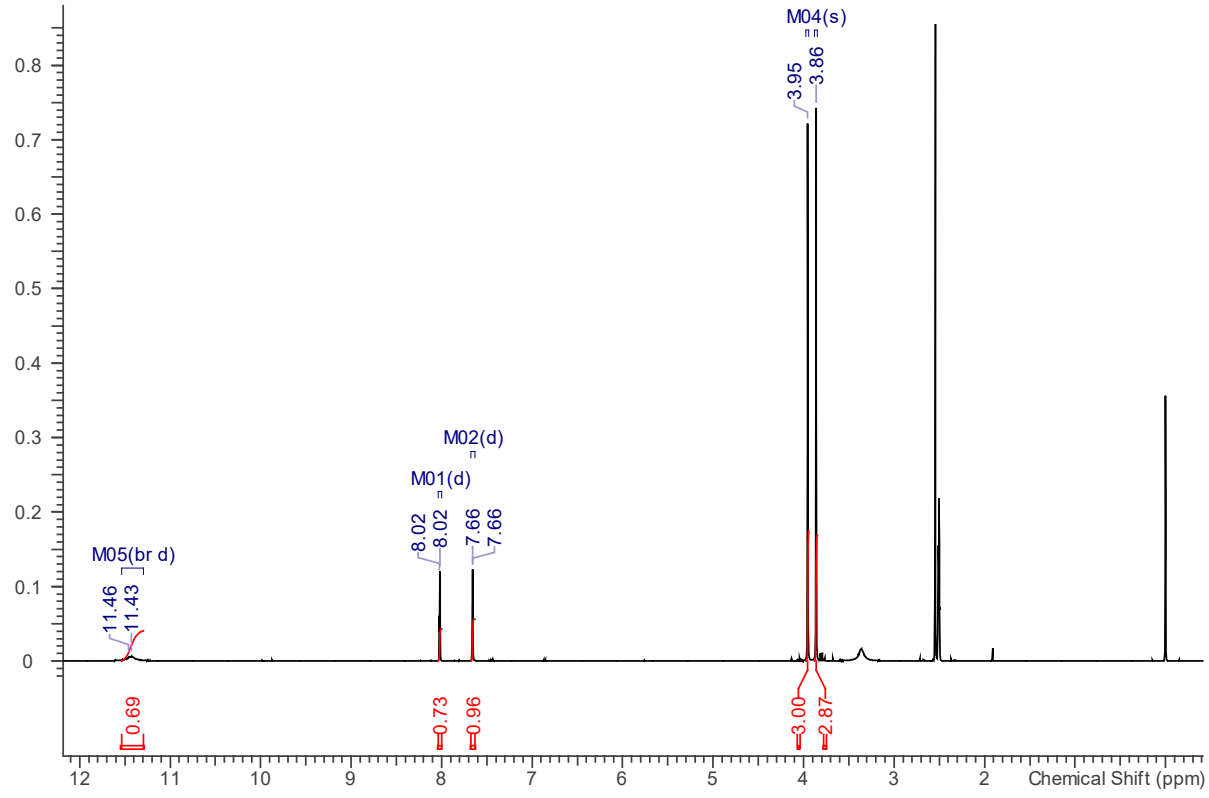
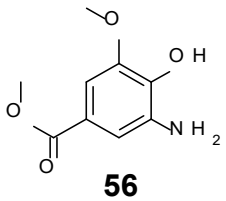
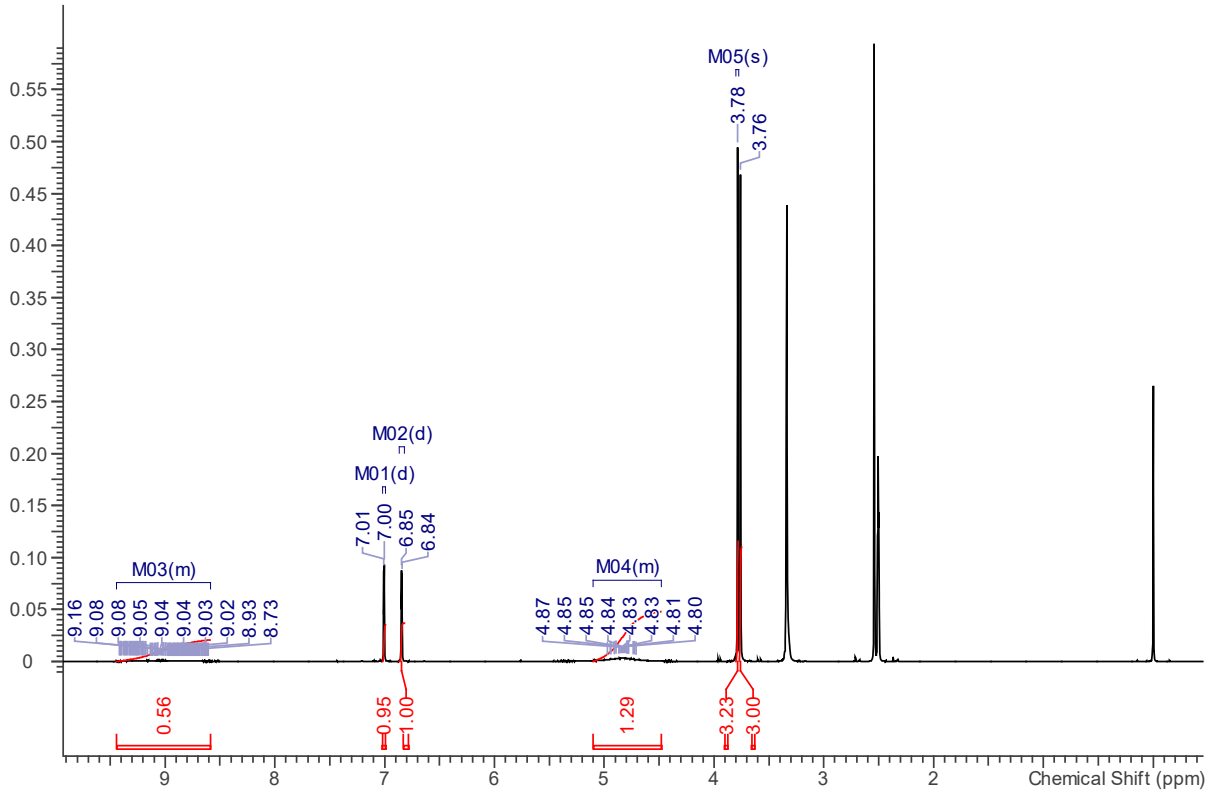


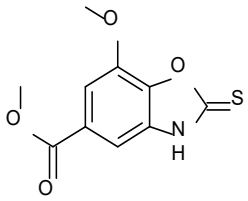
^{1}H NMR of compound **56**



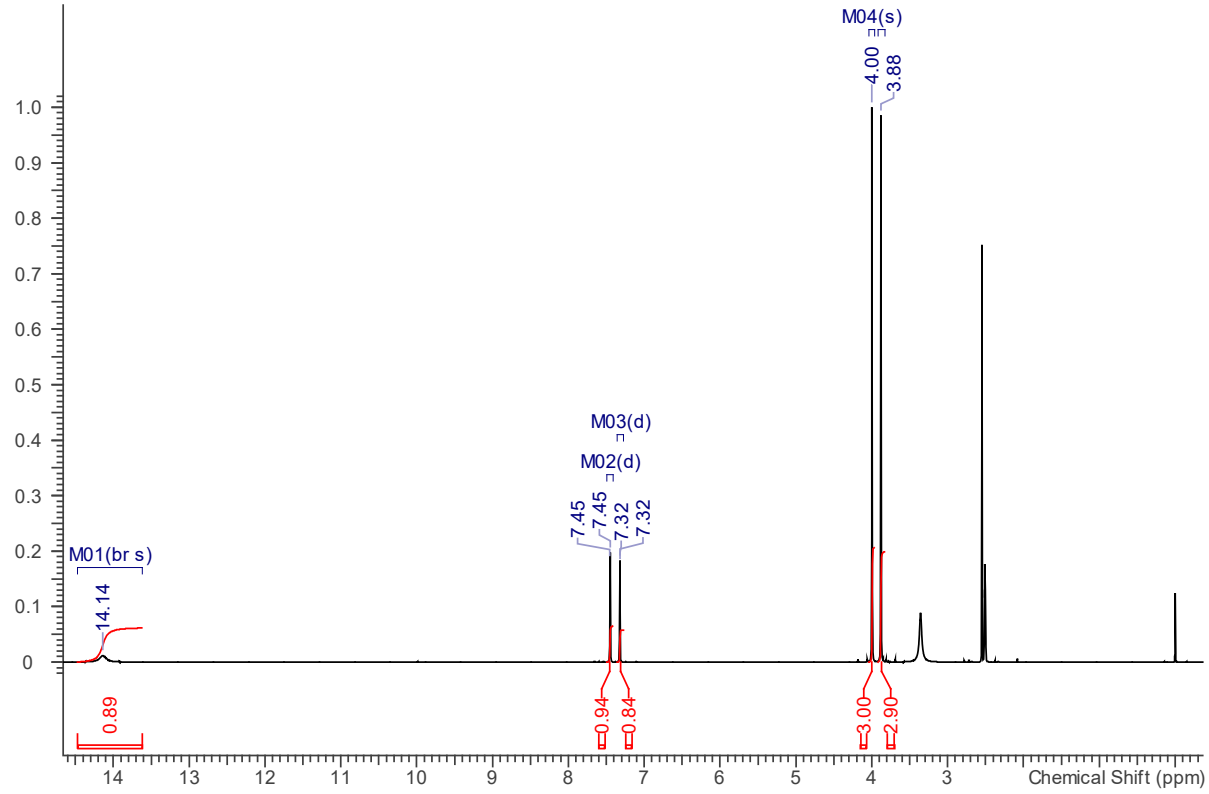
56



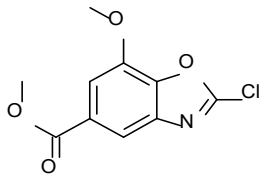
^{1}H NMR of compound **57**



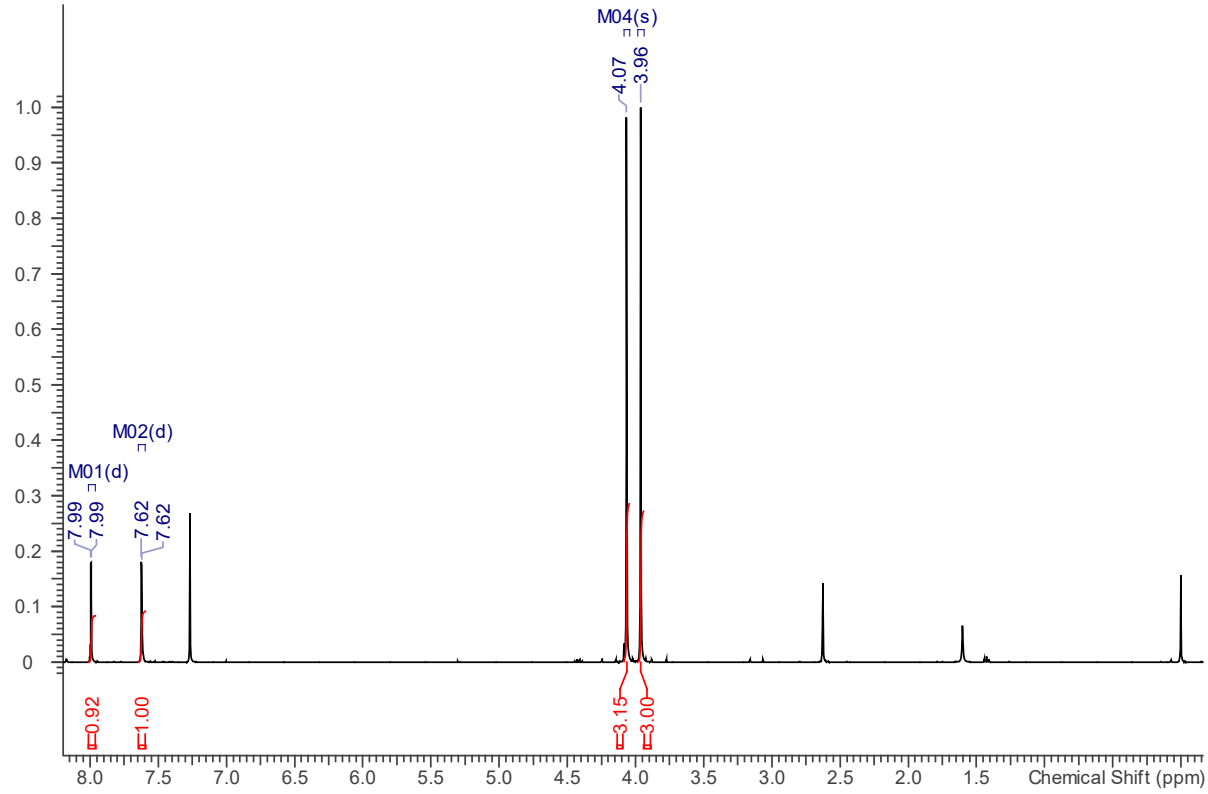
57



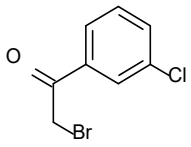
^{1}H NMR of compound **58**



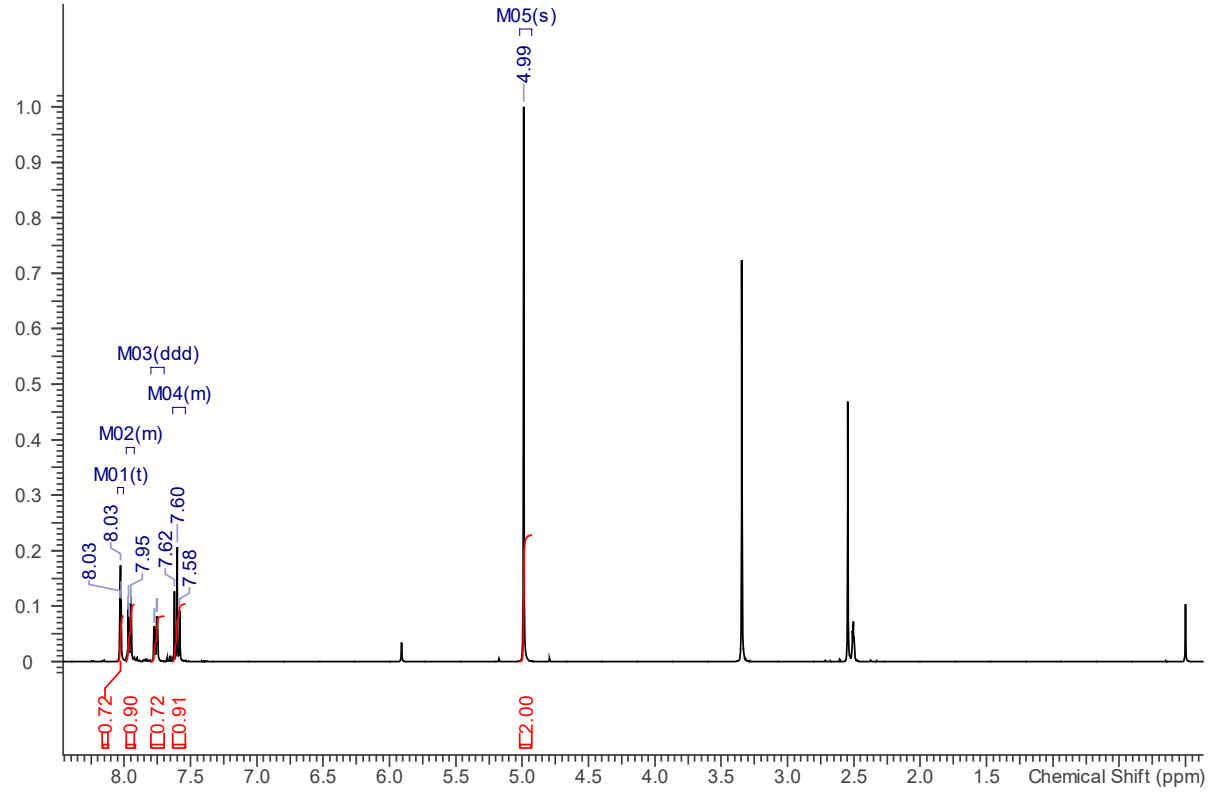
58



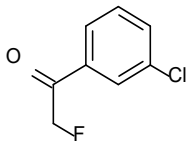
^{1}H NMR of compound **60**



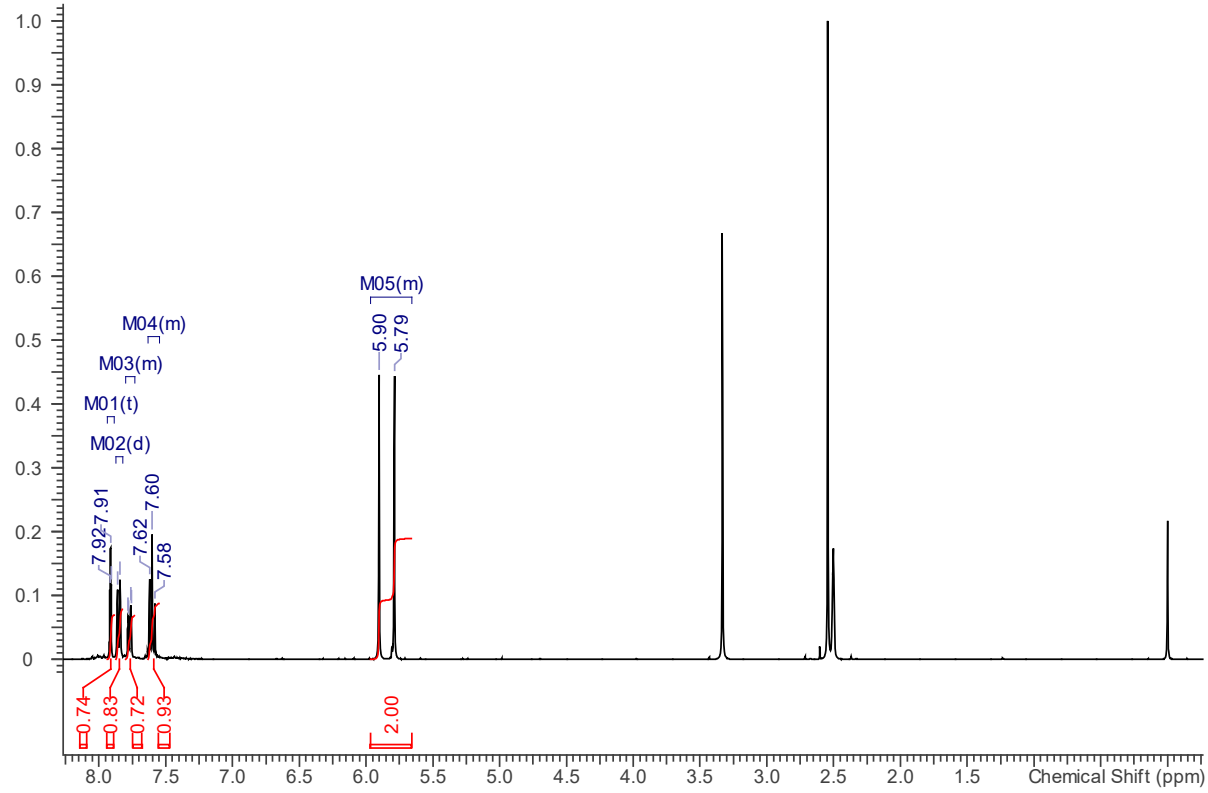
60



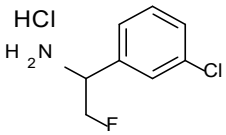
^{1}H NMR of compound **61**



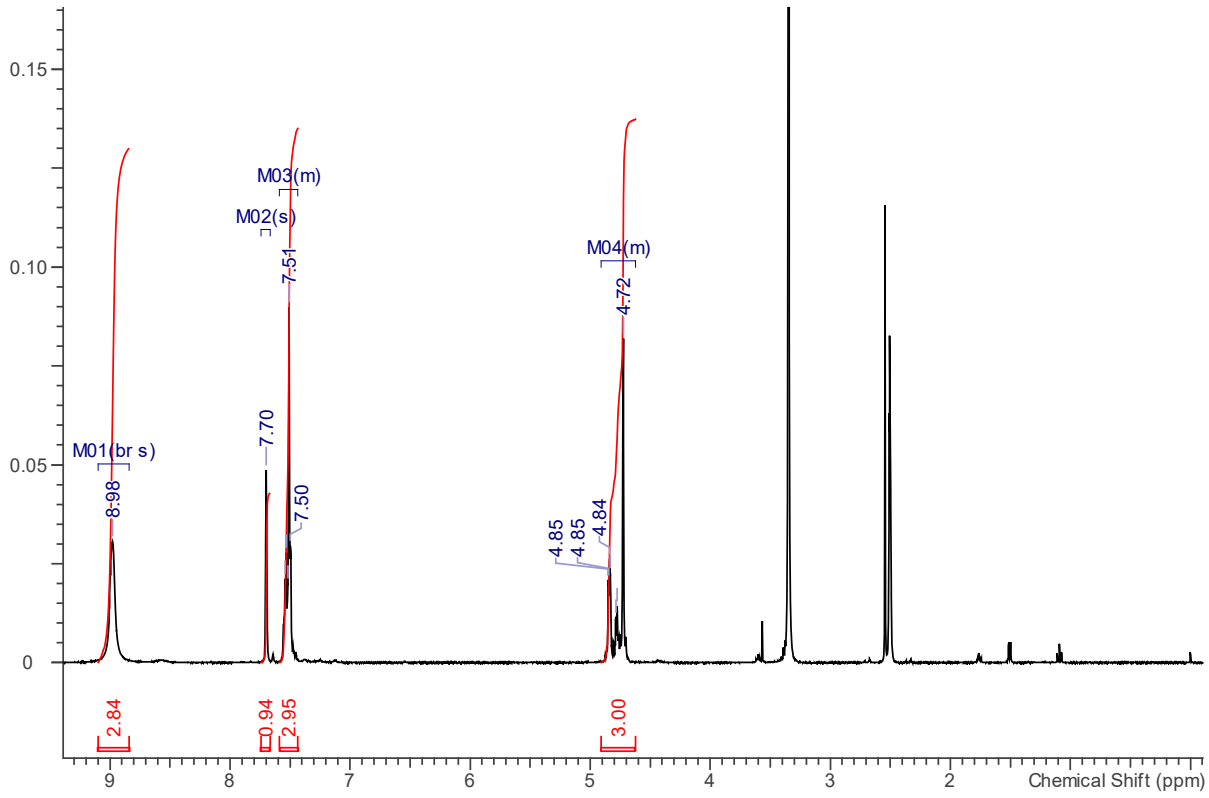
61



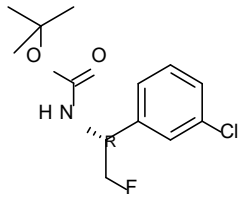
^{1}H NMR of compound **62**



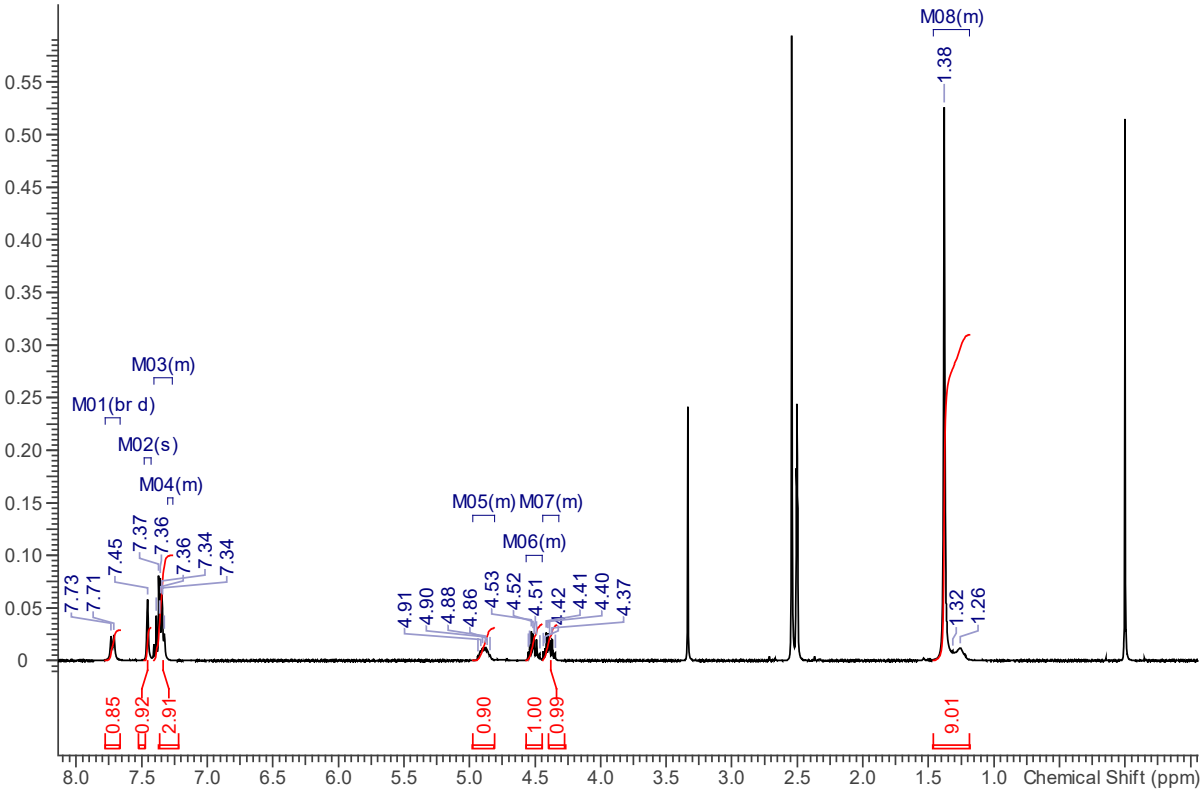
***rac*-62**



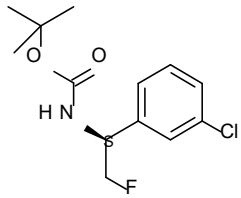
^{1}H NMR of compound (*R*)-**64**



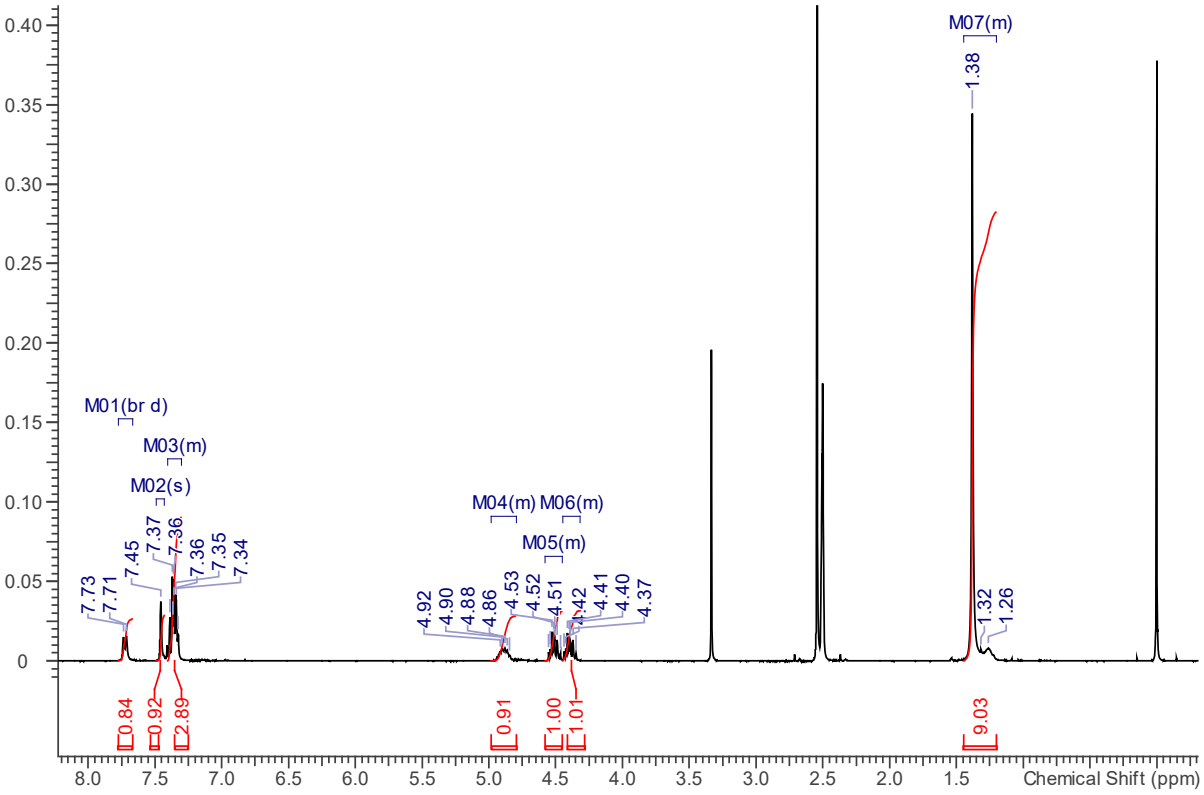
(*R*)-**64**



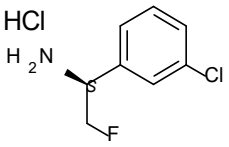
^{1}H NMR of compound (*S*)-**64**



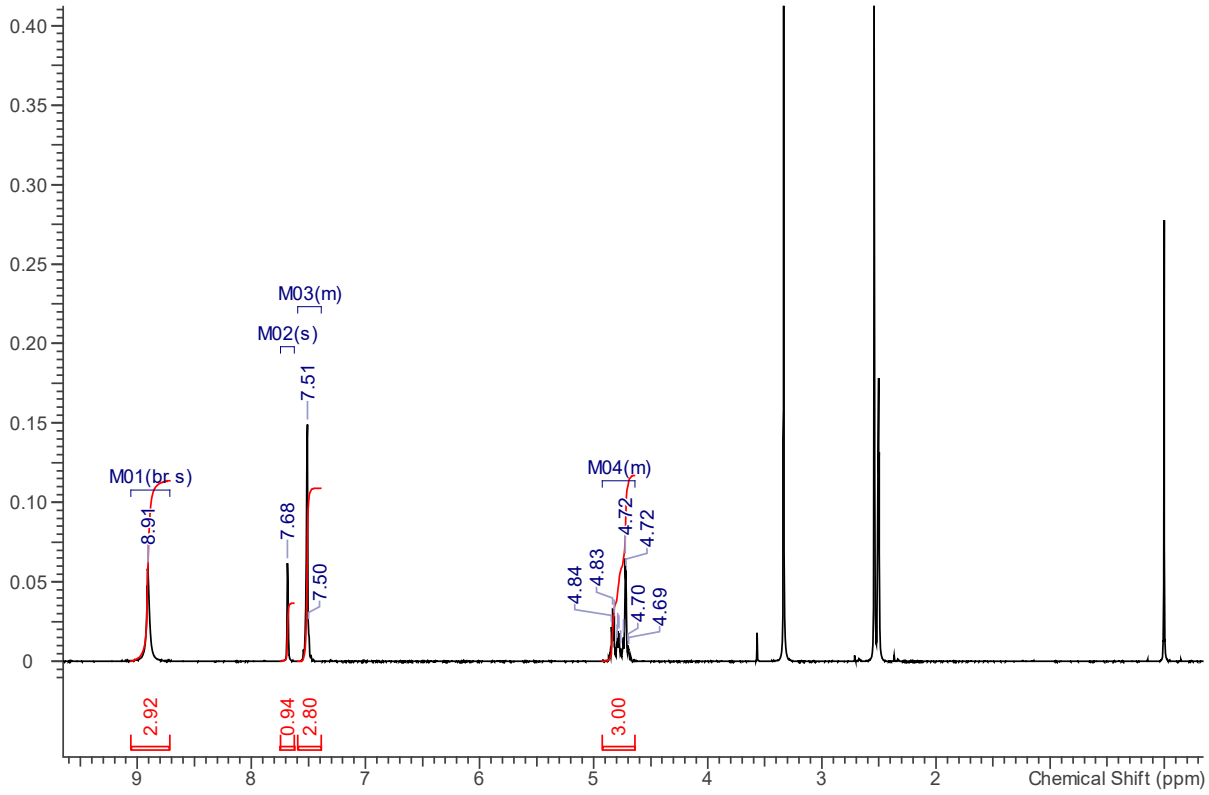
(*S*)-**64**



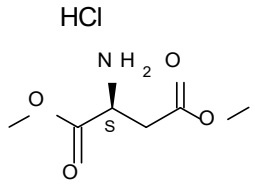
^{1}H NMR of compound (*S*)-**65**



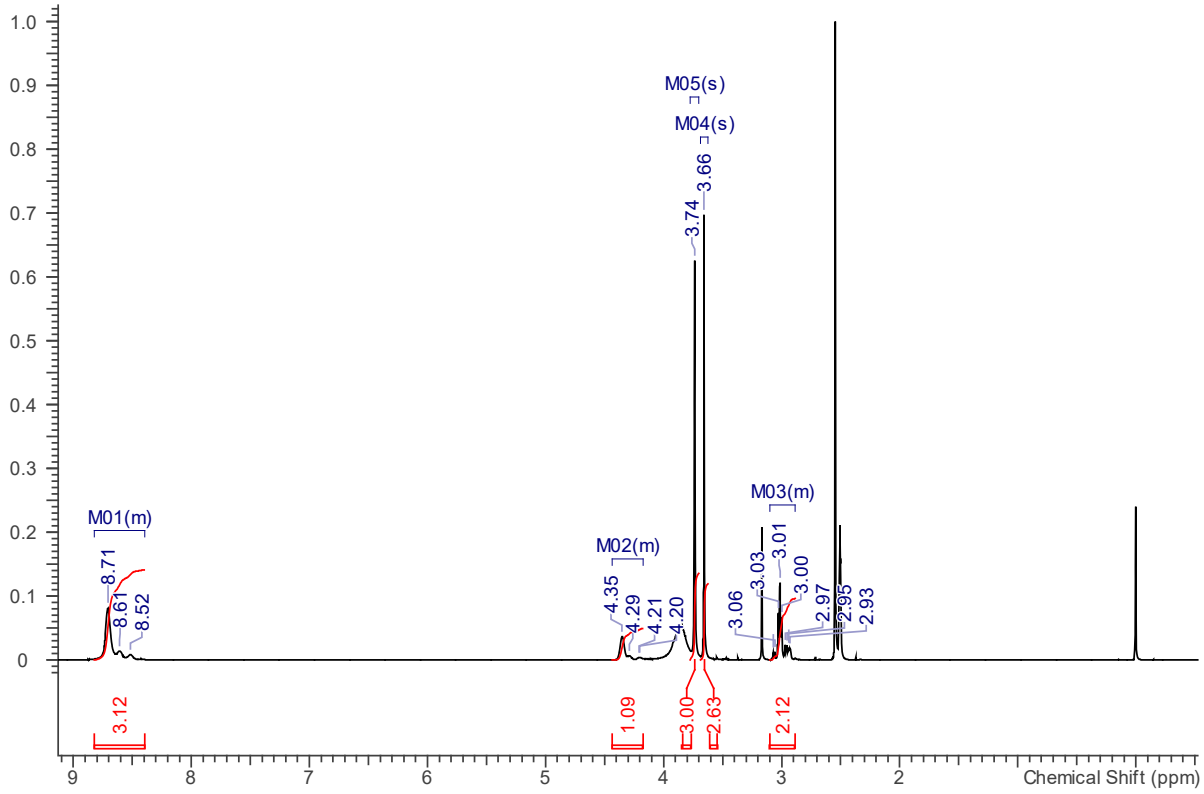
(*S*)-**65**



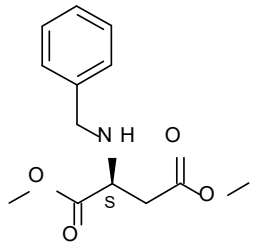
^{1}H NMR of compound **67**



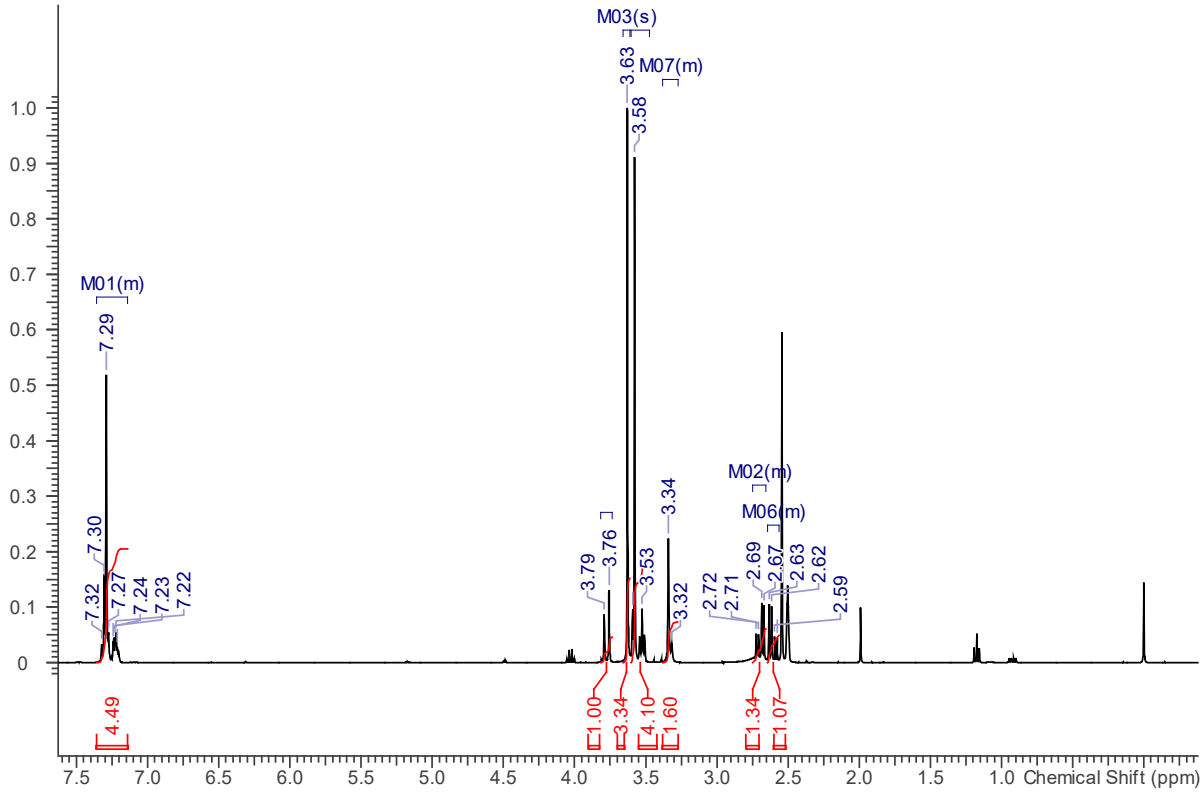
(*S*)-**67**



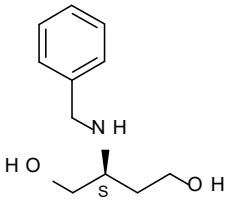
^{1}H NMR of compound **68**



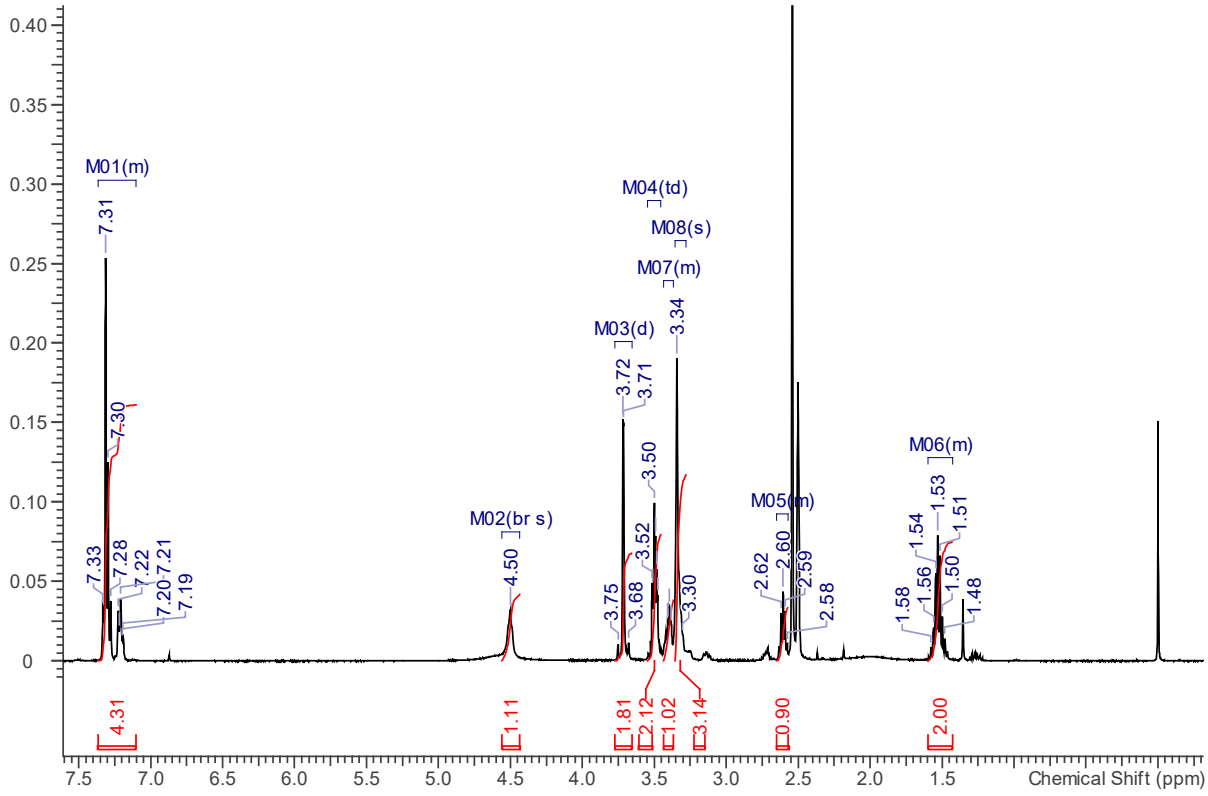
(*S*)-**68**



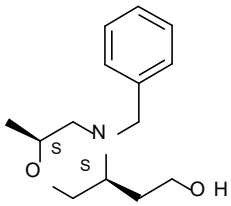
^{1}H NMR of compound **69**



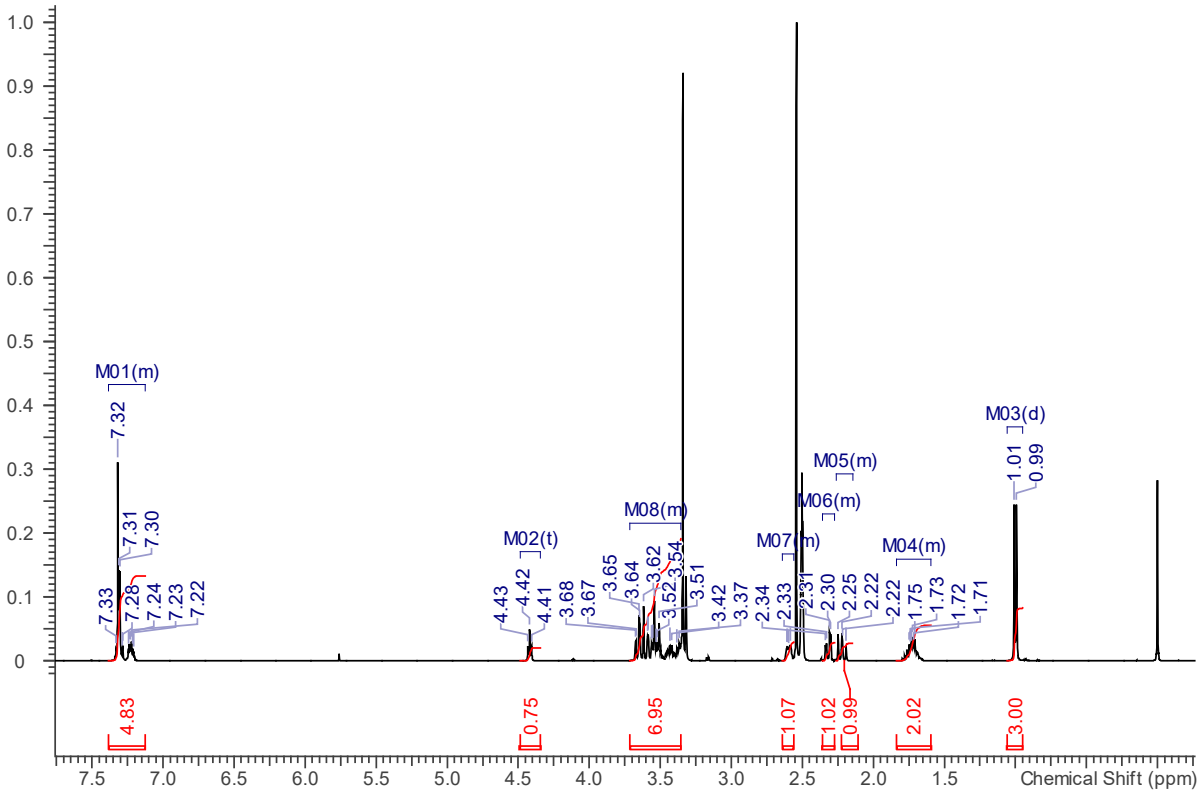
(*S*)-**69**



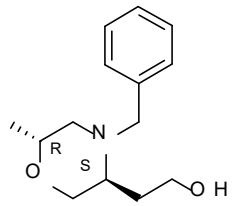
^{1}H NMR of compound (*S*,*S*)-**72**



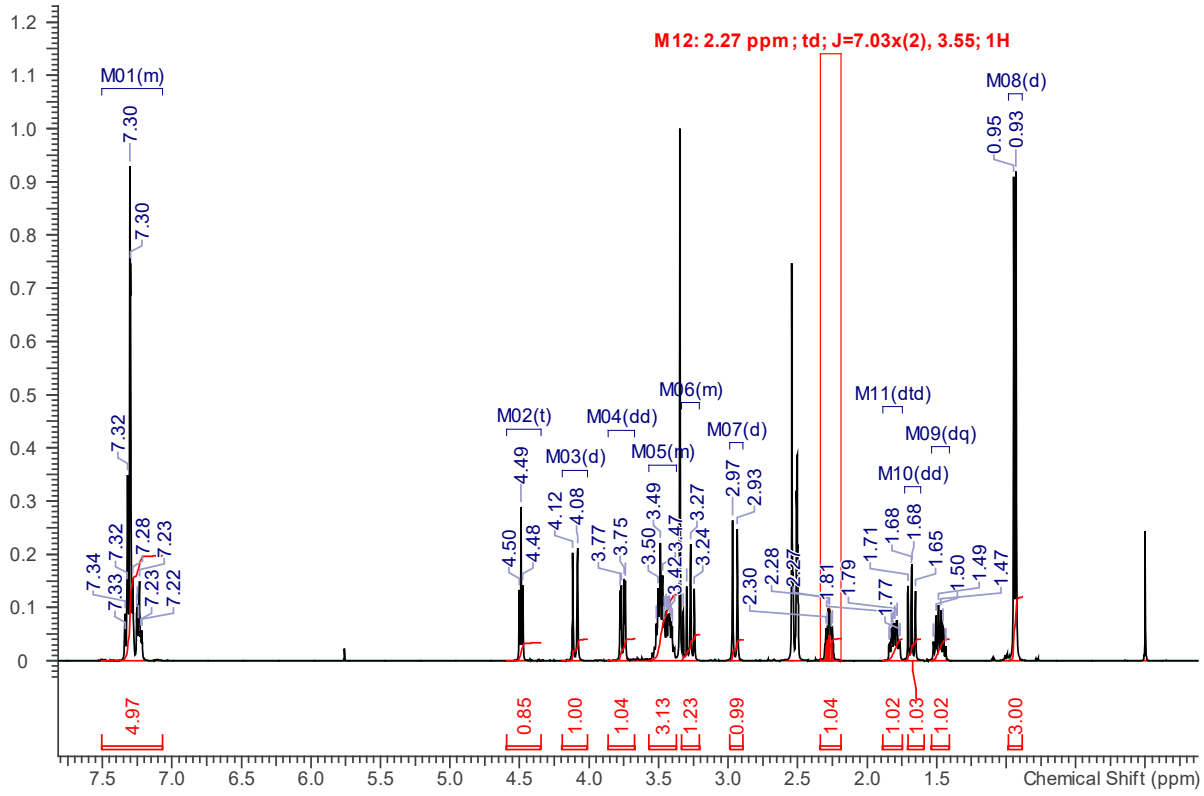
(*S*,*S*)-**72**



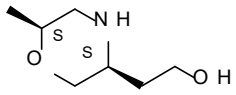
^{1}H NMR of compound (*S*,*R*)-**72**



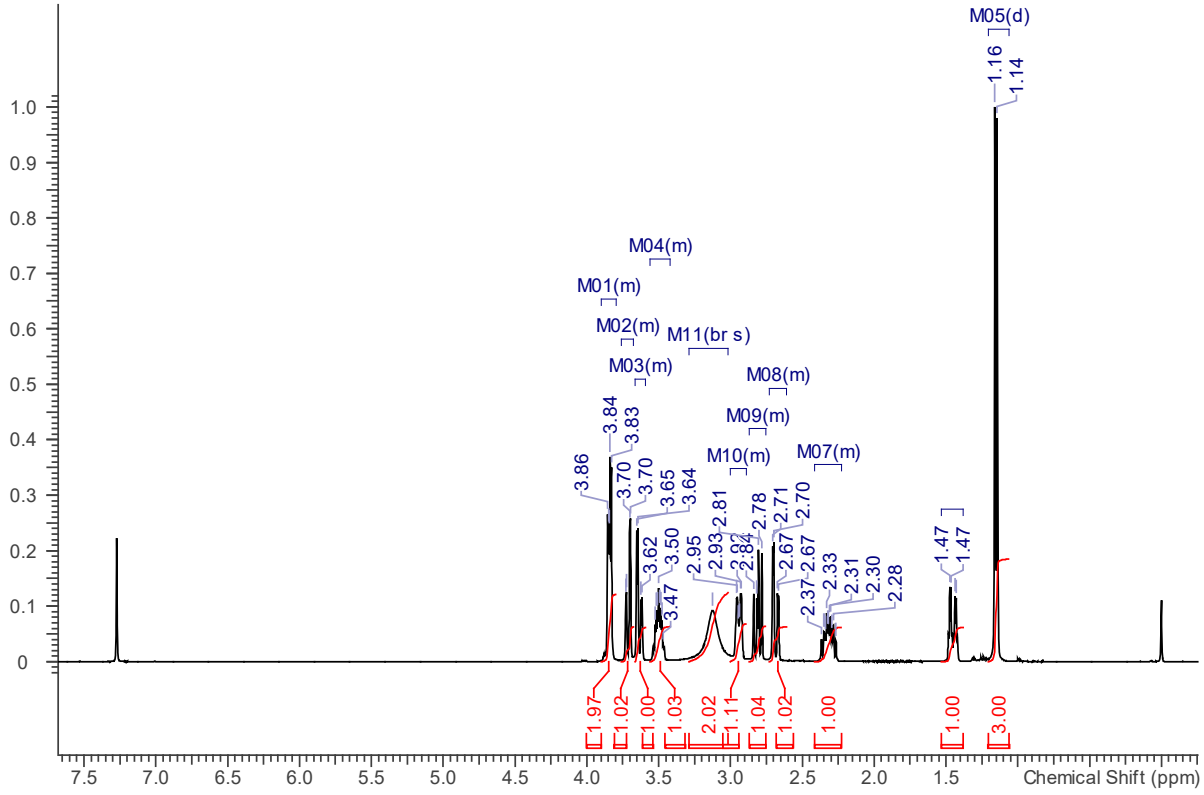
(*S*,*R*)-**72**



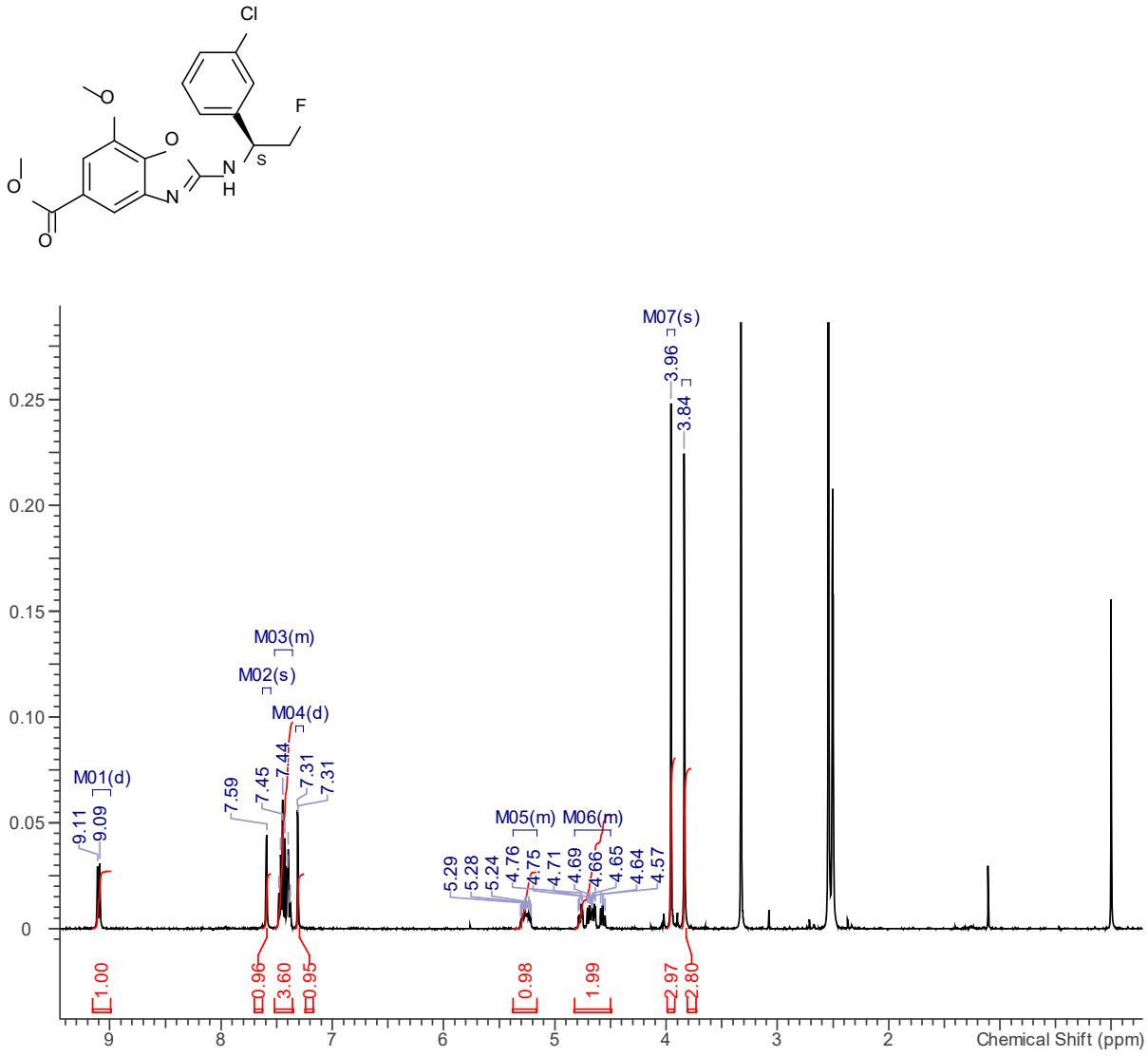
^{1}H NMR of compound (*S*,*S*)-**73**



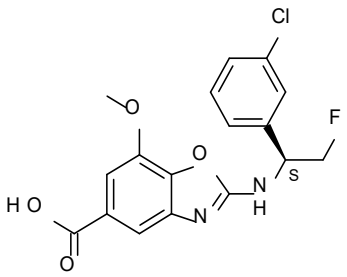
(*S*,*S*)-**73**



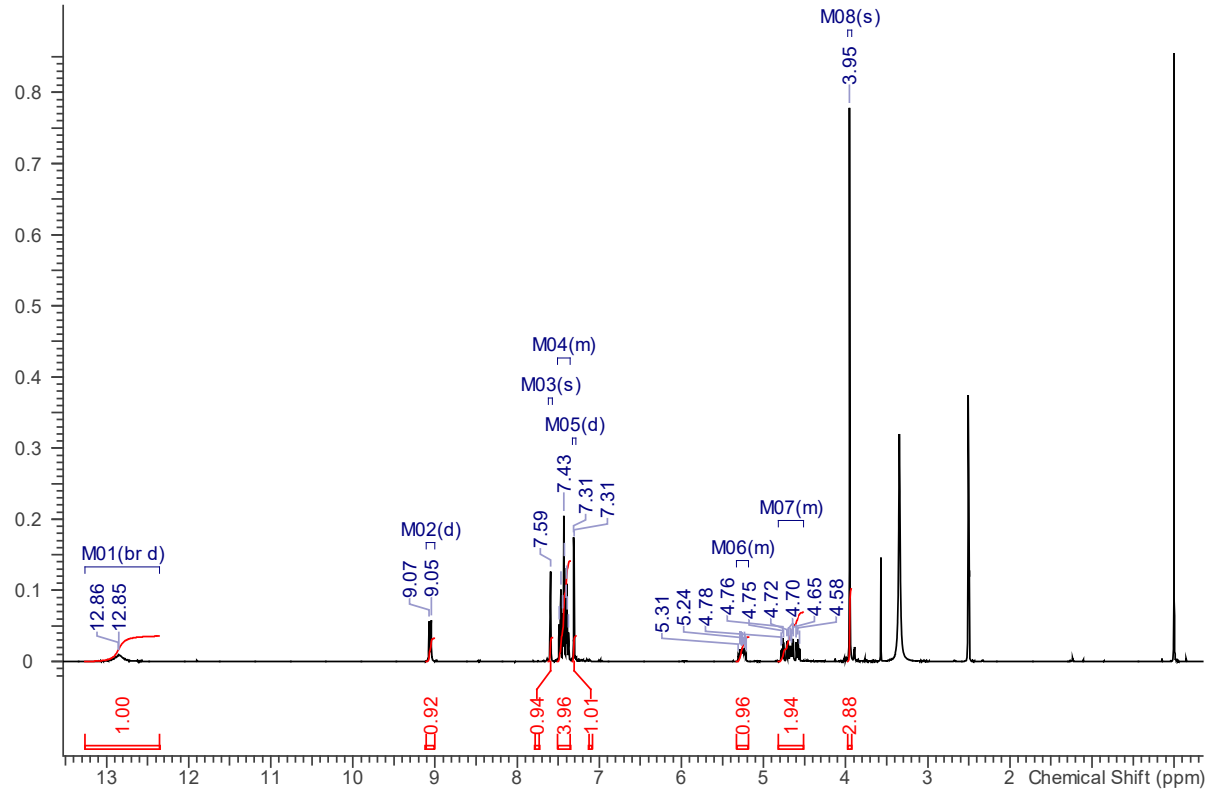
^{1}H NMR of compound **74**



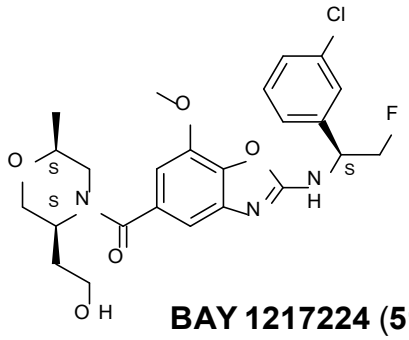
^{1}H NMR of compound **75**



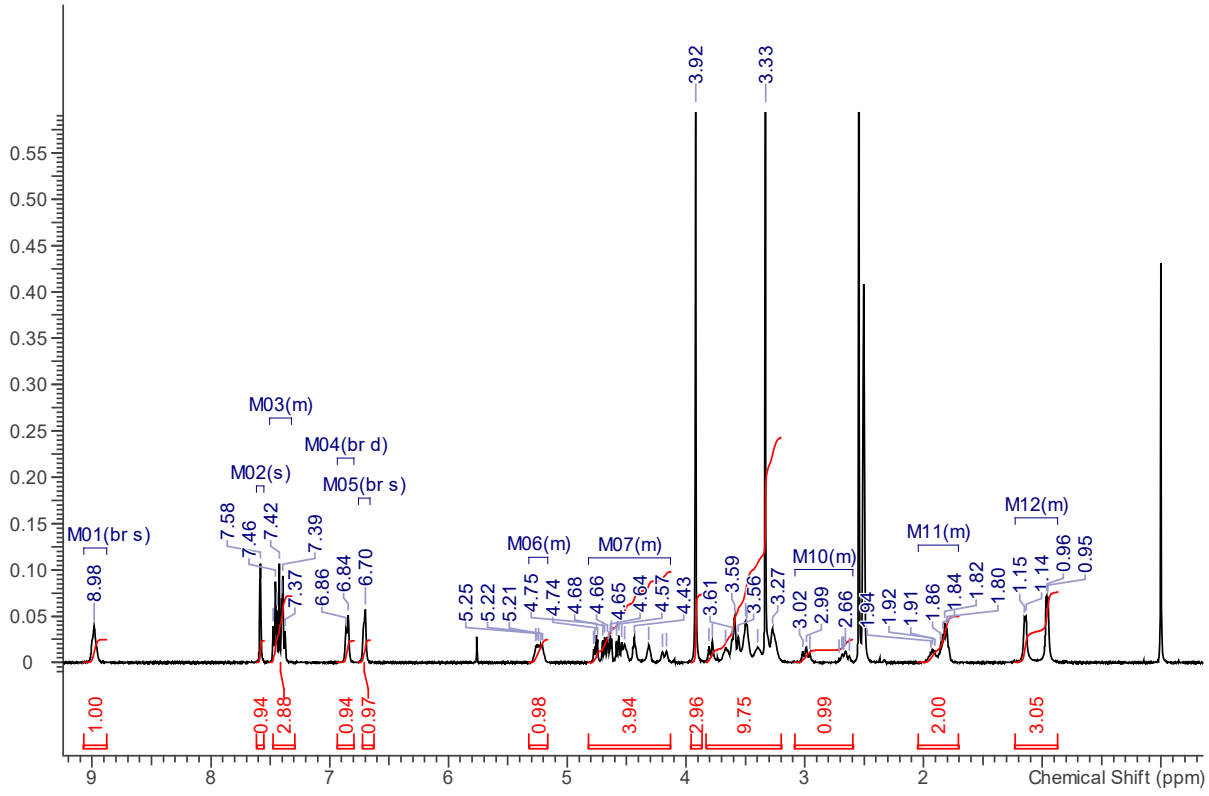
(*S*)-**75**



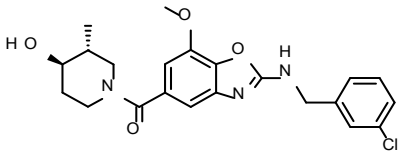
^{1}H NMR of BAY 1217224 (**51**)



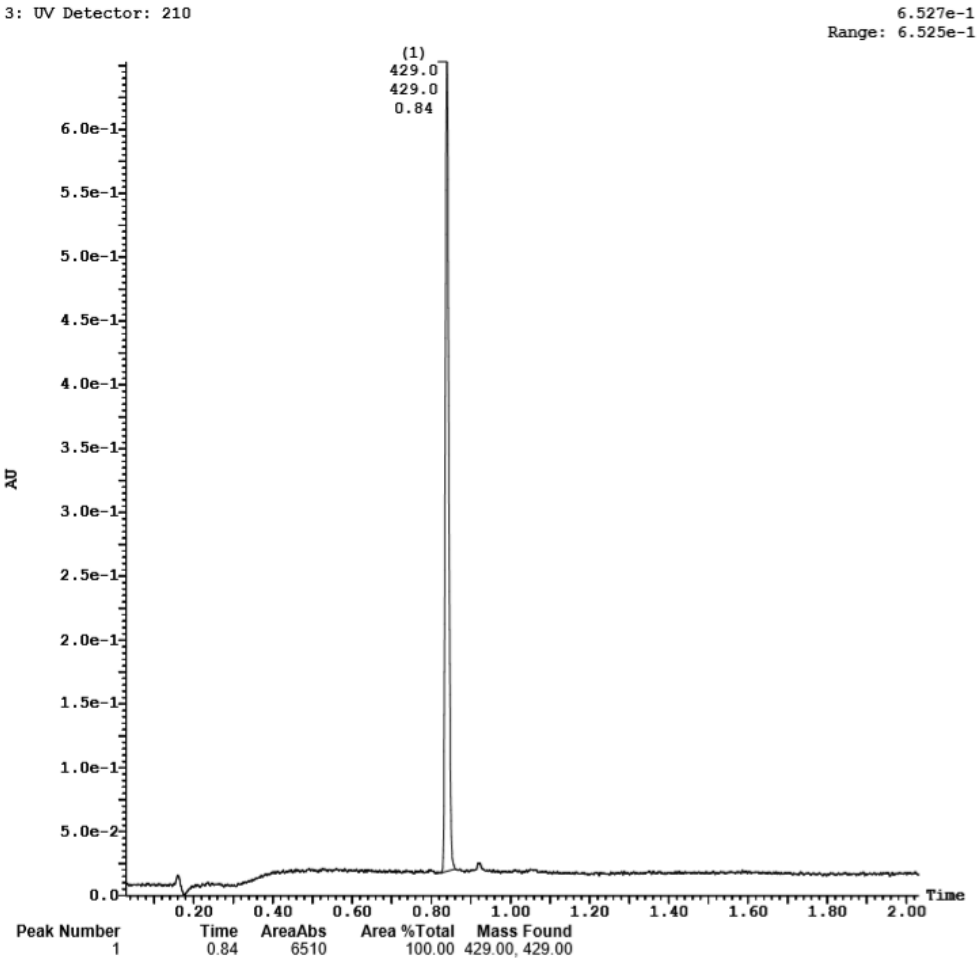
BAY 1217224 (51)

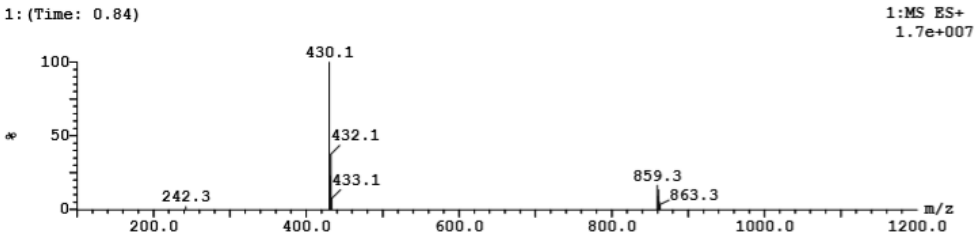


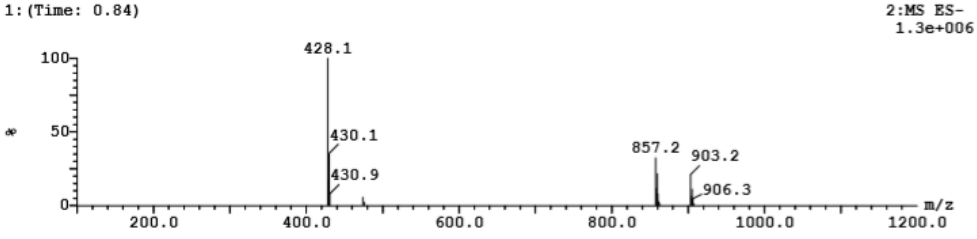
LC-MS (method 1a) of **20a**



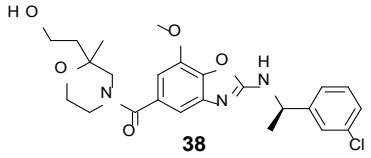
20a







LC-MS (method 1a) of **38**



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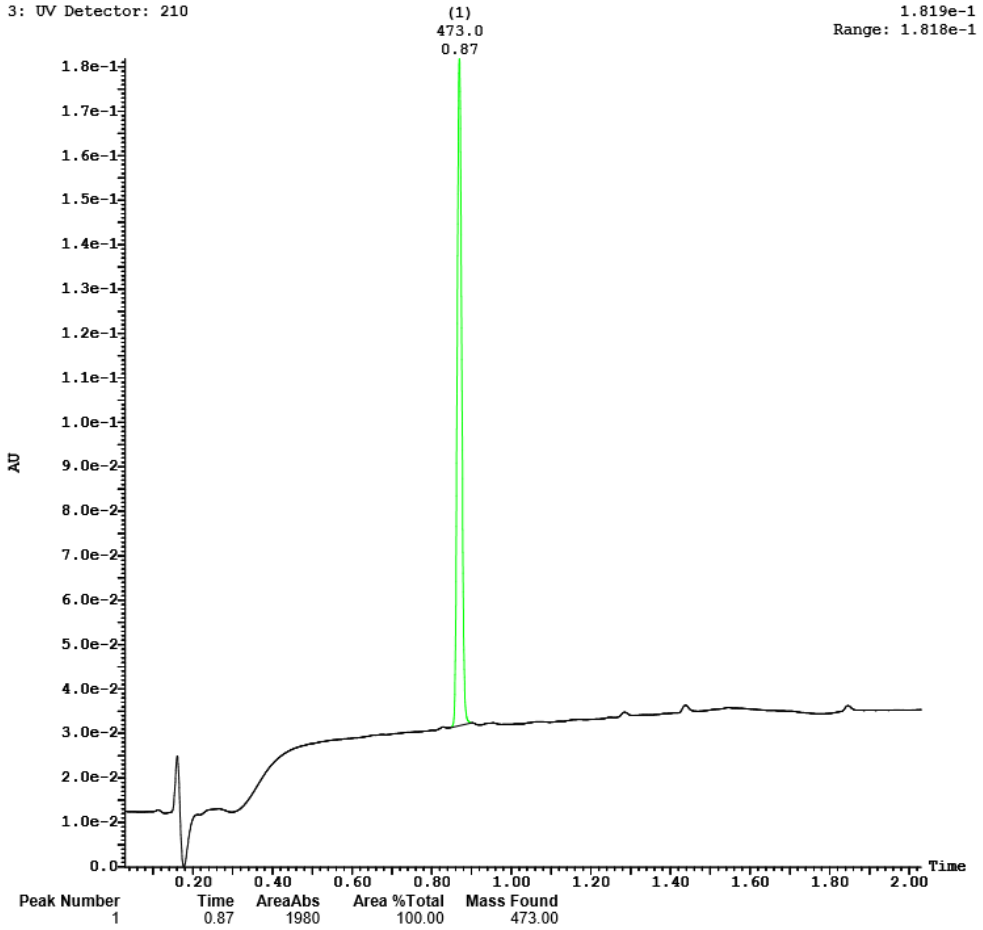
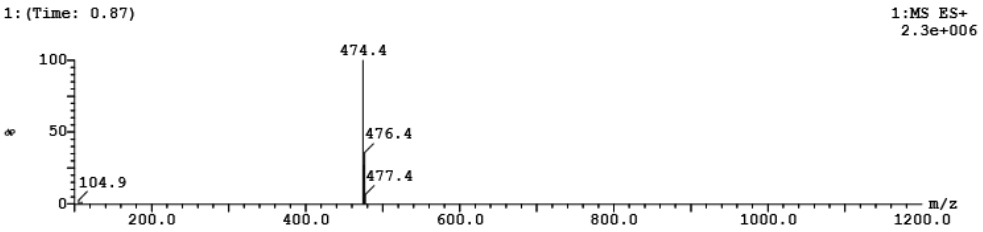
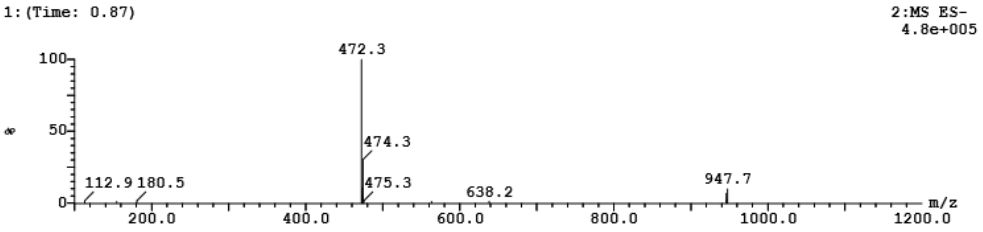
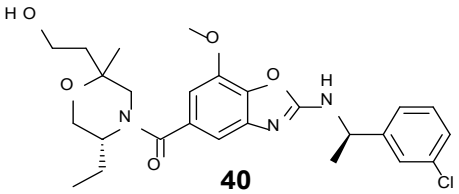






LC-MS (method 9a) of **40**



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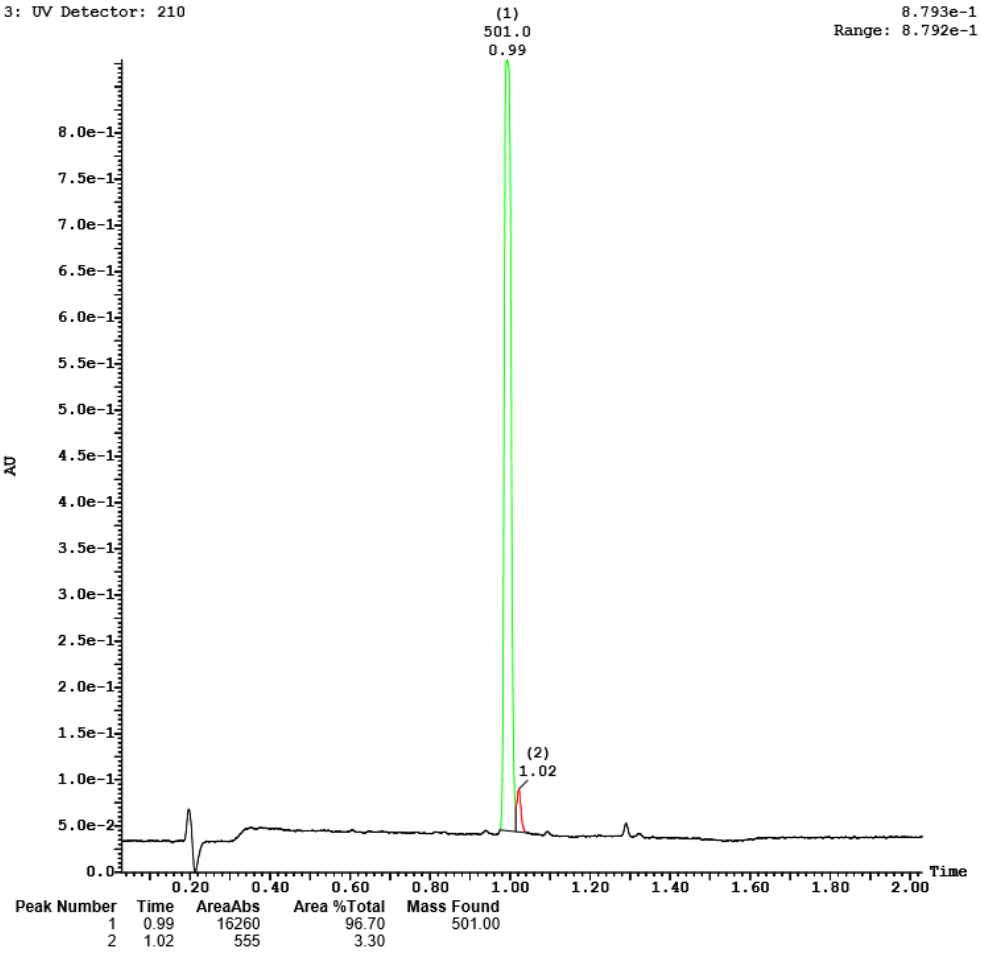

Peak Number	Time	AreaAbs	Area %Total	Mass Found
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2	1.02	555	3.30	

Peak ID Time
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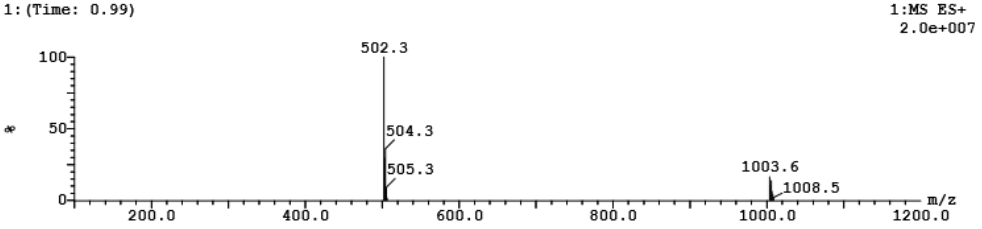
1:(Time: 0.99)



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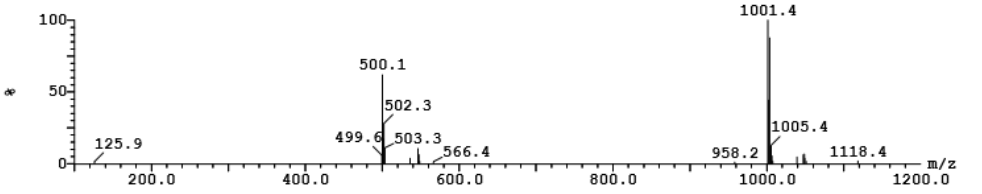
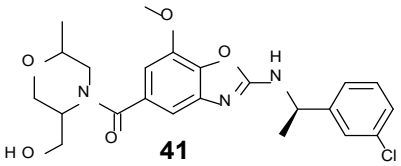


LC-MS (method 9a) of **41**



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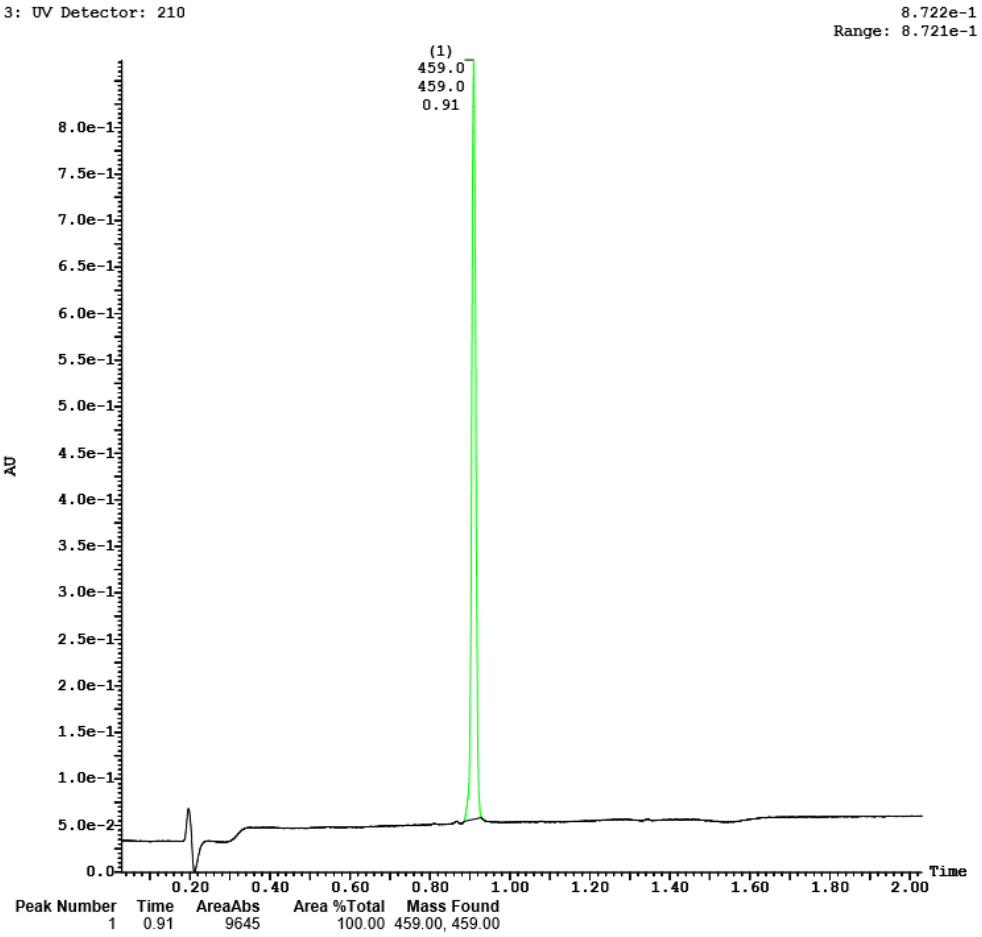
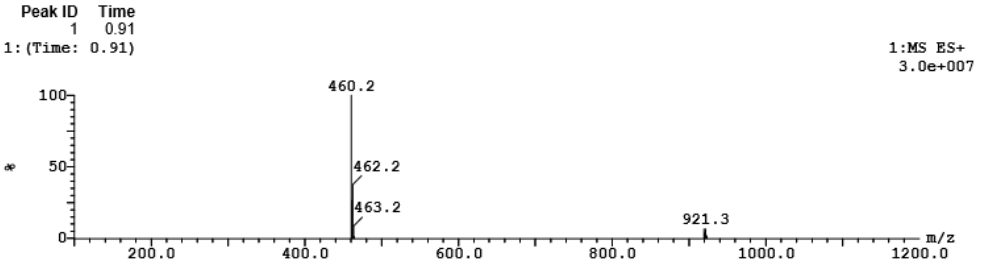
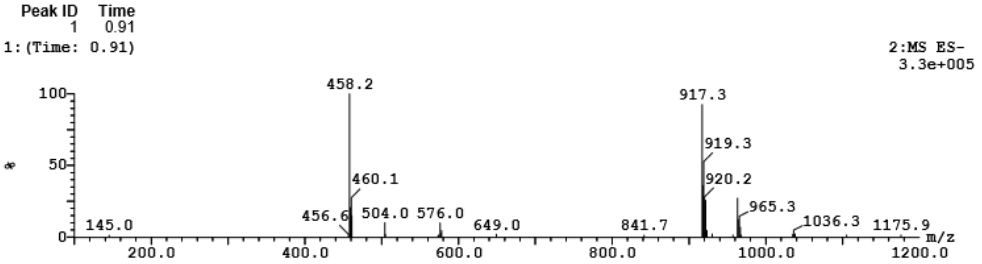
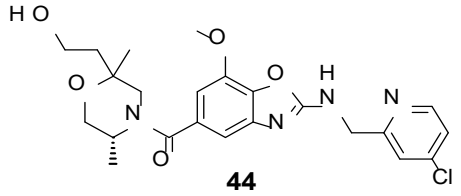






LC-MS (method 1a) of **44**



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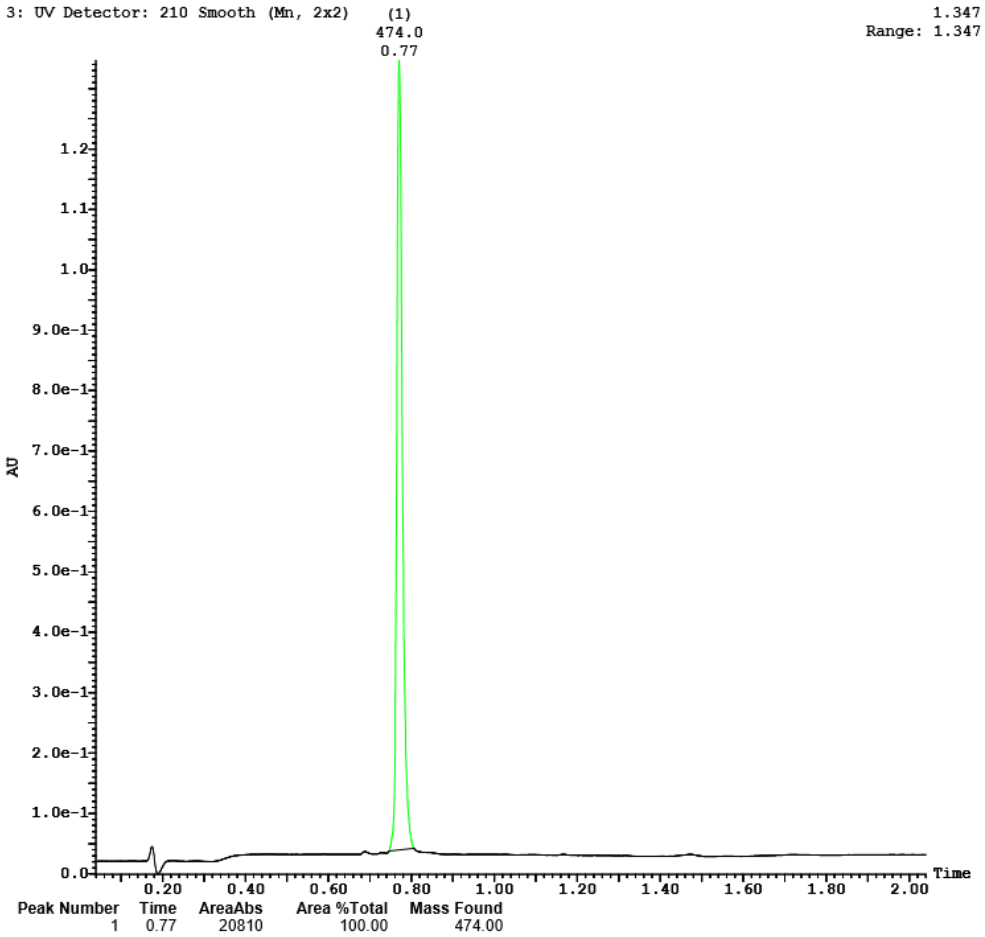
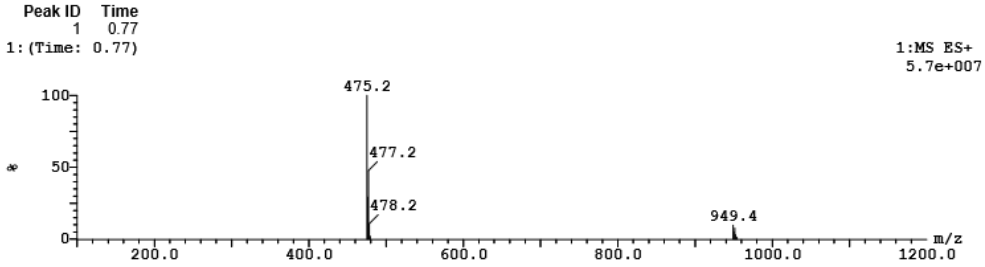
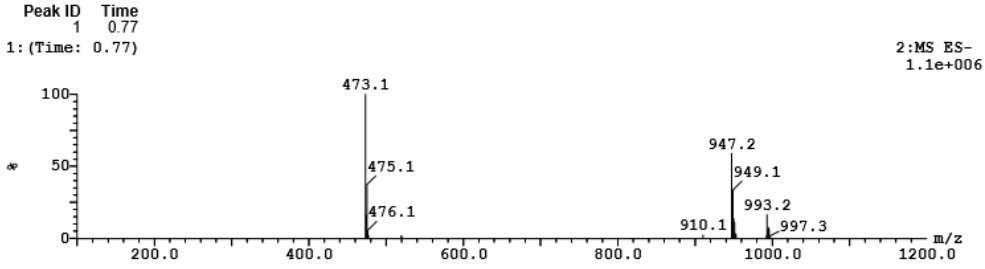
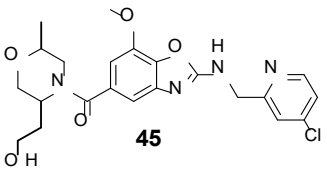






LC-MS (method 2a) of **45**



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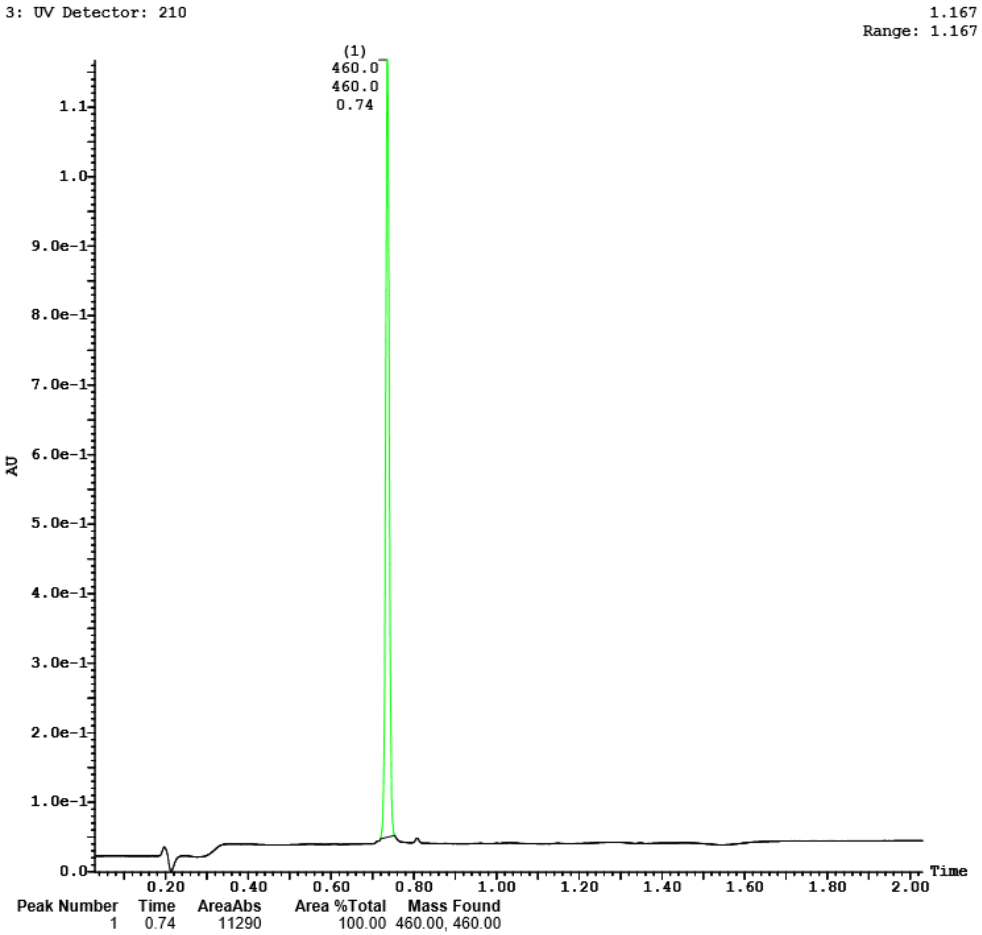
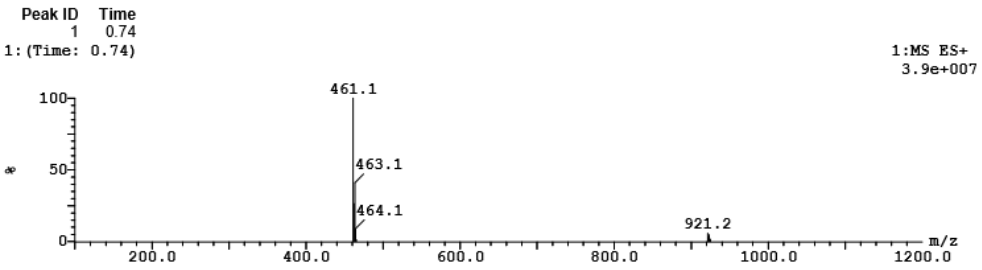
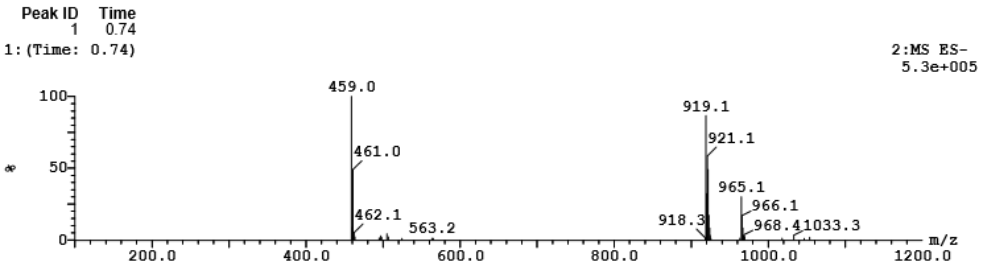
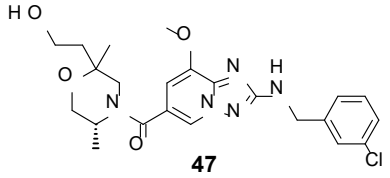






LC-MS (method 1a) of **47**



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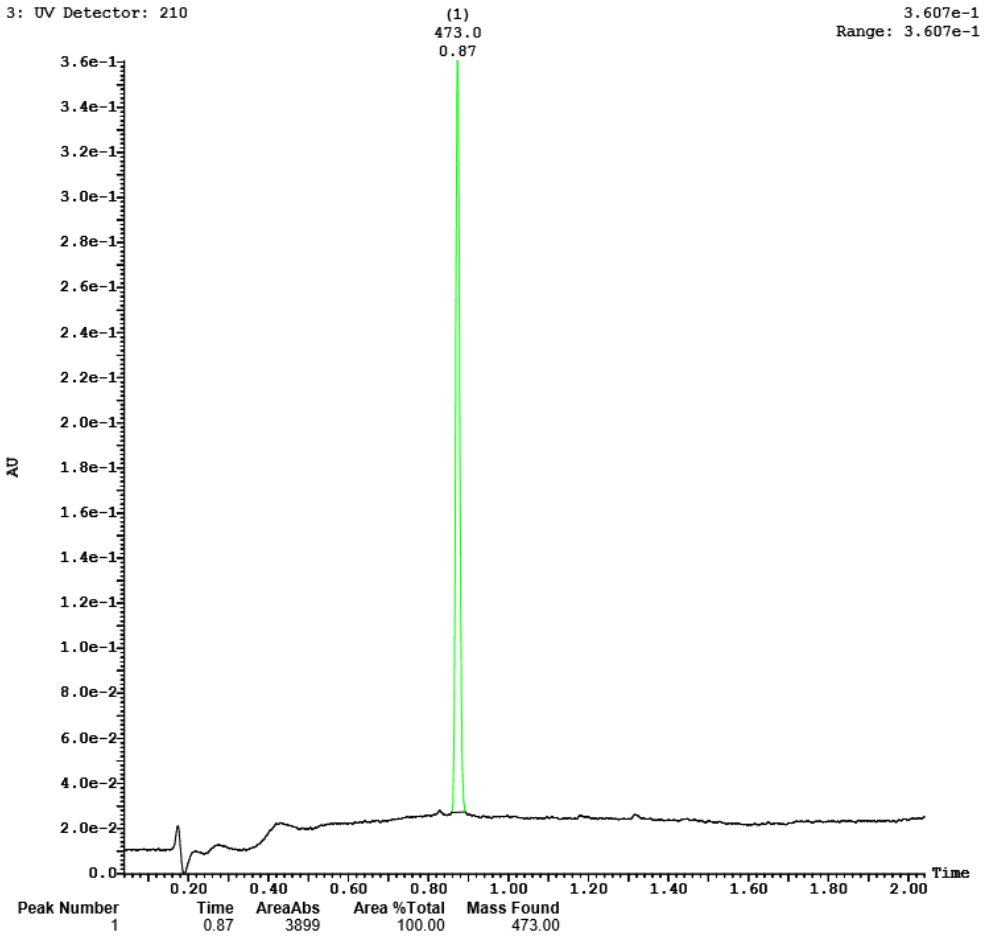
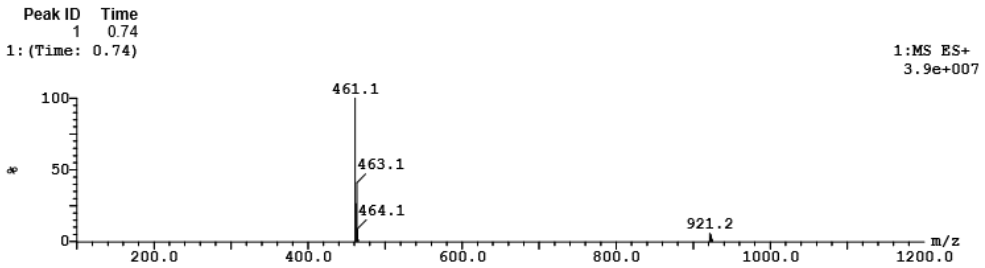
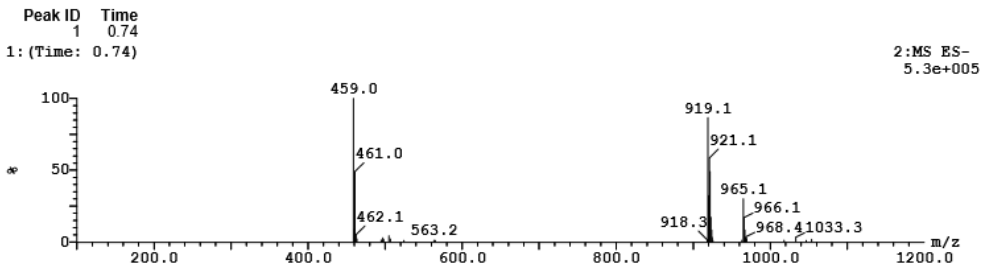
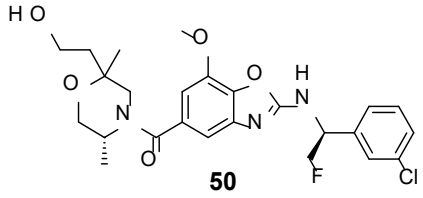






LC-MS (method 1a) of **50**



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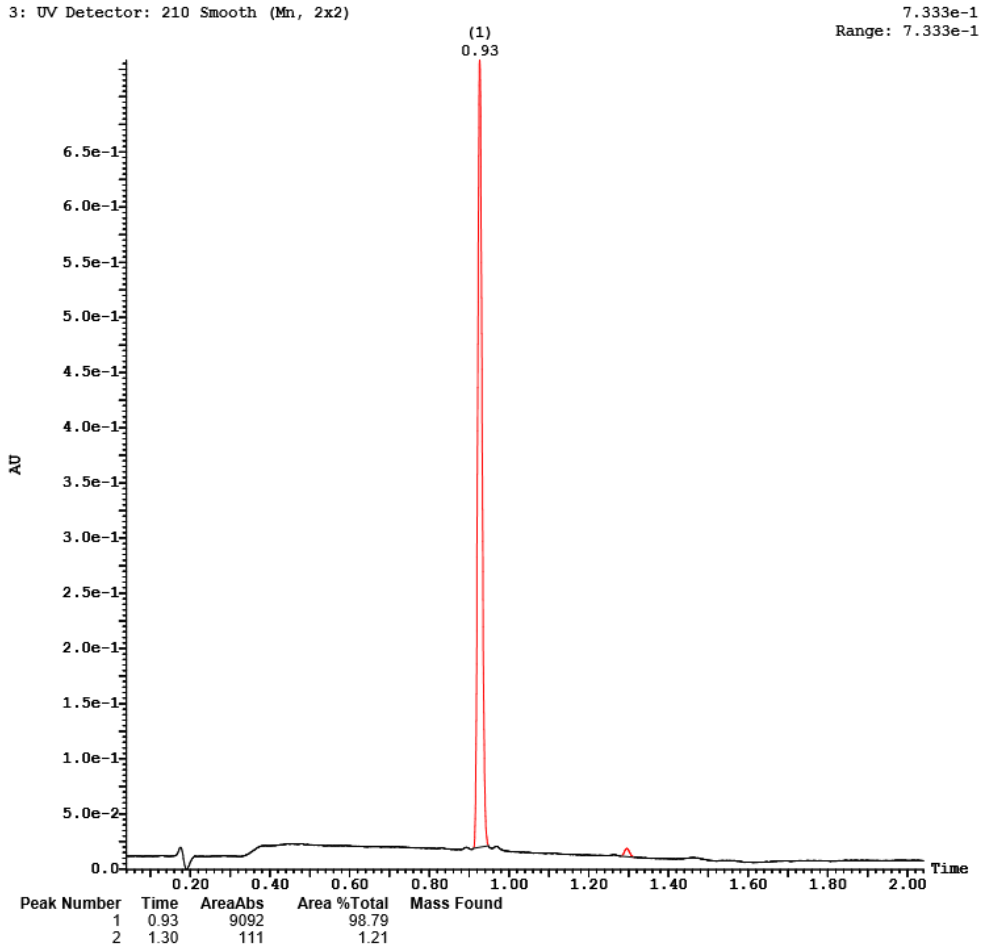
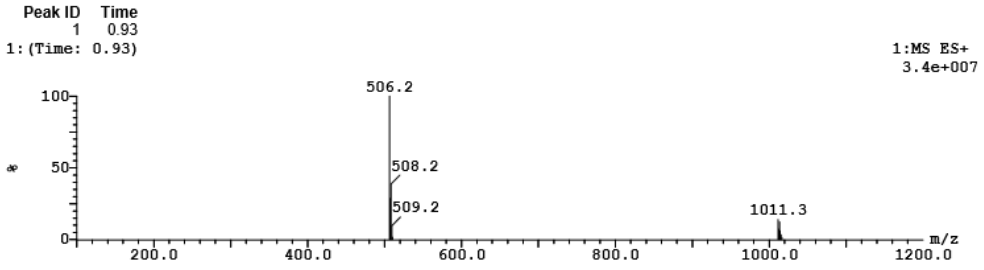
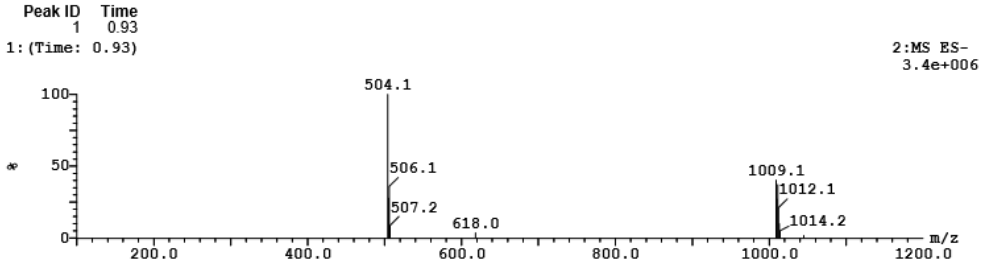
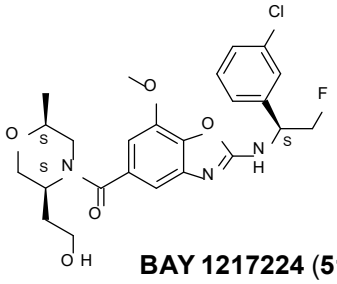


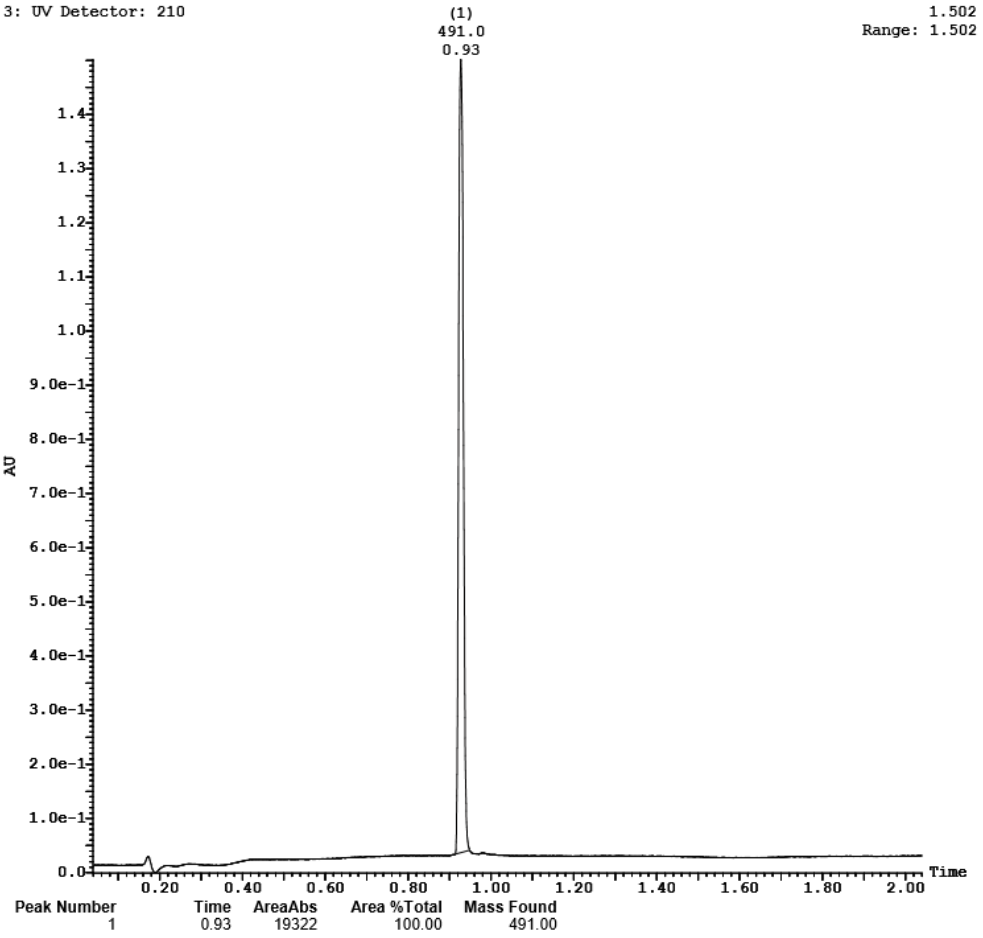


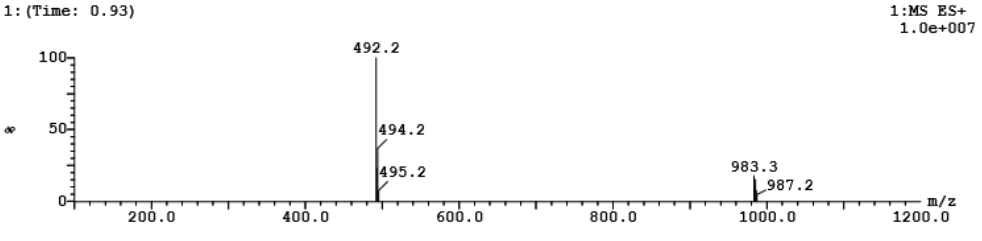


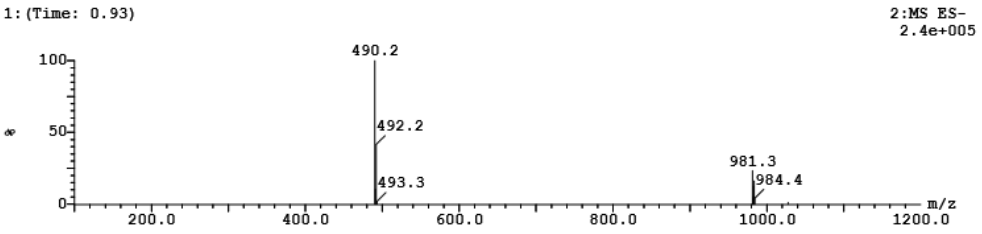
LC-MS (method 1a) of BAY 1217224 (**51**)



BAY 1217224 (**51**)







C. Table S1-S4

Table S1. Structure-based druggability assessment using SiteMap. PDB IDs used for the analysis and details on the output of SiteMap[1]

Target	PDB ID	Dscore	SScore	Volume [Å^3]	Size	Enclosure	'Philic'	'Phobic'
FIIa	1KTS[2]	1.055	1.016	412	172	0.683	0.905	0.938
FVIIa	2EC9[3]	0.771	0.813	119	46	0.750	0.970	0.698
FIXa	1RFN[4]	0.997	1.002	287	104	0.701	1.116	0.388
FXa	2W26[5]	1.081	1.013	280	120	0.624	0.716	1.098
FXIa	3SOS[6]	1.055	1.019	312	113	0.694	0.926	0.806

Table S2. WaterMap Analysis on Thrombin.

Analyzed x-ray structure PDB ID 1KTS[2]. Hydration site number as provided by WaterMap[7, 8] and details on the energetics of respective water sites. ΔG and ΔH given in kcal/mol, occupancy: 1 equals 100 %.

Site No.	ΔG	ΔH	-TΔS	Occupancy
3	6.9	3.8	3.1	0.87
36	6.6	5.7	0.9	0.28
1	5.6	2.4	3.2	0.95
8	5.5	2.9	2.6	0.74
31	3.5	2.6	0.9	0.31
34	3.4	2.6	0.7	0.29
11	2.6	0.6	2.1	0.66
5	2.6	-0.5	3.1	0.86

Table S3. Average Physicochemical Properties of the Four Compound Series

MWcorr[9] stands for corrected molecular weight, LE ligand efficiency[10], LLE lipophilic ligand efficiency[11].

Series	No. of compounds	Av. clogP	Av. tPSA [Å^2]	Av. MW_{corr}	Av. LE	Av. LLE	Av. IC_{50} [nM]
Indazoles	48	4.6	68	421	0.28	1.8	530
Oxazolidinones	51	3.2	96	480	0.29	4.0	95
Imidazoles	263	5.6	91	521	0.26	1.7	384
Benzoxazoles	159	5.1	75	457	0.28	1.7	538

Table S4. Data Collection and Refinement Statistics (Values in Brackets Refer to the Highest Resolution Shell)

Protein	**Thrombin**								**PXR**
Compd No.	**10**	**17**	**20a**	**31**	**40**	**51**	**42a**	**42b**	**17**
PDB ID	6ZUG	6ZUH	6ZUN	6ZUU	6ZUW	6ZV8	6ZUX	6ZV7	6TFI
Data Collection and Processing									
Wavelength [Å]	1.541870	1.541870	1.541870	1.541870	1.541870	1.541870	1.541870	1.541870	0.91841
Space group (no.)	*C*2	*C*2	*C*2	*C*2	*C*2	*C*2	*C*2	*C*2	$P2_12_12_1$
Unit cell parameters, *a*, *b*, *c* [Å], beta [°]	70.151 71.058 72.316 100.270	70.091 71.054 72.620 100.512	69.73 71.04 71.79 99.52	69.97 71.30 71.86 99.92	70.16 71.31 72.08 100.25	69.166 70.342 71.372 100.28	70.26 71.30 72.45 100.43	69.66 71.40 71.47 99.61	85.36 88.96 105.66 90
Resolution limit [Å]	1.8–31.78 (1.8–1.9)	1.7–20.43 (1.7–1.79)	1.79–42.99 (1.79–1.89)	1.93–43.19 (1.93–2.03)	2.00–43.33 (2.00–2.11)	1.59–70.23 (1.55–1.64)	1.93–43.45 (1.55–1.64)	1.93–43.01 (1.93–2.03)	1.85–44.48 (1.85–1.96)
No. of reflections	93178 (12782)	109295 (3367)	69947 (8688)	803764 (9533)	23699	130734	68635	185521	344156
No. of unique reflections	30046 (4154)	31839 (1760)	28450 (3929)	23907 (2905)	23699	40347	25381	25162	67925
Multiplicity	3.1	3.4	2.46	3.36	7.1	2.8	2.7	7.4	5.1
$I/\sigma(I)$	10.64 (3.65)	12.89 (2.92)	8.57 (2.38)	5.77 (1.26)	12.7 (5.0)	12.95 (2.85)	13.0 (4.8)	9.17 (2.55)	17.15 (1.82)
R_{meas} [%]	4.9 (24.4)	4.7 (36.0)	8.0 (42.0)	13.0 (69.0)	9.90 (38.1)	6.42 (26.78)	5.5 (19.9)	6.2 (30.0)	5.9 (97.7)
Completeness [%]	92.91 (88.43)	82.64 (31.50)	87.67 (83.37)	90.99 (90.99)	100 (100)	89.2 (90.2)	95.4 (85.4)	96.41 (82.53)	97.9 (98.7)
Refinement									
R_{work}/R_{free} [%]	16.88/21.17	17.82/21.78	22.65/26.22	16.37/21.20	16.58/21.35	20.90/24.05	16.21/20.60	15.18/19.02	17.47/20.21
RMSD bond length [Å]	0.016	0.012	0.030	0.022	0.020	0.018	0.020	0.019	0.017
RMSD bond angles [°]	2.566	2.342	3.009	2.303	2.199	1.952	2.011	2.639	1.73
B factors [Å^2]	41.386	26.847	57.292	35.132	35.252	35.081	28.009	29.767	44.75

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