SUPPORTING INFORMATION

Novel $S1P_1$ receptor agonists – Part 1: From pyrazoles to thiophenes

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This supporting information contains experimental details on the synthesis of target compounds and the corresponding building blocks not described in the main text. More details on the synthesis of the pyrrole and thiophene derivatives discussed in this account have been published in four patent applications.[1-4] Furthermore, the structure and values of the crystallographic parameters of the 2-methyl isomer of compound **17** as determined by single crystal X-ray structure analysis are given.
NMR and **LC-MS spectra** of representative compounds are given. The LC-MS spectra represent data acquired on the Water Acquity UPLC system using the method described in the main text.

In addition, mean arterial blood pressure and heart rate recordings in male spontaneously hypertensive rats after oral administration of compounds **1**, **57** and **85** are given.

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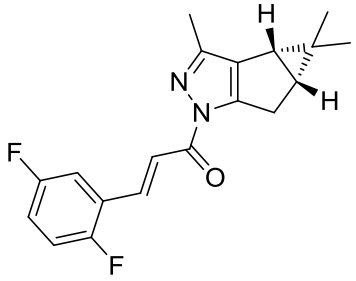
Preparation of Pyrazoles 2 to 5

(E)-3-Phenyl-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)prop-2-en-1-one (2). LC-MS: t_R = 1.04 min, $[M+1]^+$ = 293.23; ^{1}H NMR (H_6-DMSO, solvent suppression): δ 7.85 (d, *J* = 16.1 Hz, 1 H), 7.69-7.78 (m, 3 H), 7.44-7.51 (m, 3 H), 2.96-3.03 (m, 1 H), 2.80 (d, *J* = 18.3 Hz, 1 H), 2.21 (s, 3 H), 1.87-2.04 (m, 2 H), 1.08 (s, 3 H), 0.64 (s, 3); LC-HRMS: t_R = 1.63 min, [M+H]/z = 293.1654, found = 293.1659.

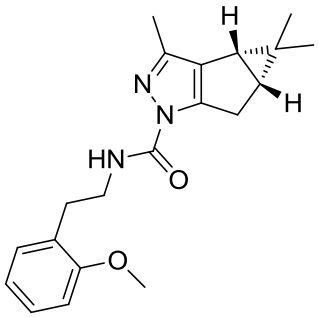
(E)-3-(2,5-Difluorophenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)prop-2-en-1-one (3)



To a solution of (3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4] cyclopenta[1,2-c]pyrazole **15**[5] (13 mg, 80 μmol) in DMF (0.5 mL) Hünig's base (28 mg, 240 μmol), TBTU (31 mg, 96 μmol) and 2,5-difluorocinnamic acid (9.5 mg, 80 μmol) are added. The mixture was stirred at rt for 2 h before it was separated by prep. HPLC to give **3** (15 mg, 57%) as a white lyophilisate; LC-MS: t_R = 1.07 min, $[M+1]^+$ = 329.18; LC-HRMS: t_R = 1.65 min, [M+H]/z = 329.1465, found = 329.1467.

3-(2-Methoxyphenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)propan-1-one (4). Prepared in analogy to **3**; LC-MS: t_R = 1.04 min, $[M+1]^+$ = 325.27; ^{1}H NMR (H_6-DMSO, solvent suppression): δ 7.18 (t, *J* = 7.8 Hz, 1 H), 7.12 (d, *J* = 6.4 Hz, 1 H), 6.93 (d, *J* = 7.1 Hz, 1 H), 6.84 (t, *J* = 7.1 Hz, 1 H), 3.76 (s, 3 H), 3.15-3.26 (m, 2 H), 2.83-2.94 (m, 1 H), 2.70-2.82 (m, 1 H), 1.91-2.04 (m, 2 H), 1.04 (s, 3 H), 0.84 (s, 3 H).

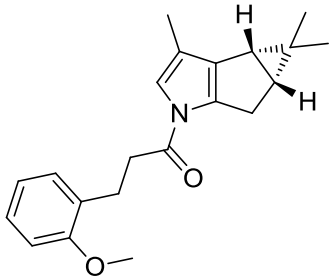
(3bS,4aR)-3,4,4-Trimethyl-3b,4,4a,5-tetrahydro-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-1-carboxylic acid [2-(2-methoxy-phenyl)-ethyl]-amide (5)



a) (3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4] cyclopenta[1,2-c]pyrazole **15** was prepared starting from (+)-3-carene following literature procedures;[6] LC-MS: t_R = 0.66 min, $[M+1]^+$ = 163.25.

b) A solution of 1,1'-carbonyldiimidazole (12.2 mg, 75 μmol) and 2-(2-methoxyphenyl)ethanamine (11.3 mg, 75 μmol) in THF (500 μL) was stirred at rt for 1 h before **15** (12.2 mg, 75 μmol) was added. The mixture was stirred at 50 °C for 1 h before it was separated by prep. HPLC (GromSil Saphir 30x30 mm, acetonitrile in water containing 0.5% of formic acid) to give **5** (8.1 mg, 32%) as a coloureless resin; LC-MS: t_R = 1.10 min, $[M+1]^+$ = 340.27; ^{1}H NMR (H_6-DMSO, solvent suppression): δ 7.18 (t, *J* = 7.3 Hz, 1 H), 7.12 (d, *J* = 6.6 Hz, 1 H), 6.93 (d, *J* = 7.6 Hz, 1 H), 6.85 (t, *J* = 7.1 Hz, 1 H), 3.75 (s, 3 H), 3.32-3.44 (m, 2 H), 2.90 (dd, *J* = 19.6, 6.8 Hz, 1 H), 2.74-2.83 (m, 1 H), 2.11 (s, 3 H), 1.71-1.82 (m, 2 H), 1.04 (s, 3 H), 0.59 (s, 3 H); LC-HRMS: t_R = 1.55 min, [M+H]/z = 340.2025, found = 340.2032.

3-(2-Methoxyphenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-b]pyrrol-1-yl)propan-1-one (6)



a) To a solution of diethyl aminomalonate hydrochloride (1.17 g, 5.5 mmol) in abs. ethanol (20 mL), was added a 1 M solution of sodium in abs. ethanol (11 mL, 11 mmol). The mixture was stirred at rt for 15 min before (1S, 5R)-2-(1-chloro-(E)-ethylidene)-6,6-dimethyl-bicyclo[3.1.0]hexan-3-one **14**[6, 7] (923 mg, 5.0 mmol) was added. Stirring was continued for 30 min, the mixture was diluted with water (75 mL) and extracted with DCM (100 mL). The organic extract was dried over $MgSO_4$ and evaporated to give crude (3bS,4aR)-ethyl 3,4,4-trimethyl-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-b]pyrrole-2-carboxylate (1.10 g) as a yellow oil. An analytical sample was purified by prep. HPLC to furnish (3bS,4aR)-ethyl 3,4,4-trimethyl-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-b]pyrrole-2-carboxylate as a pale yellow oil. LC-MS: t_R = 1.03 min, $[M+1]^+$ = 234.11 (calcd 234.15); ^{1}H NMR ($CDCl_3$): δ 8.41 (s br, 1 H), 4.27 (q, *J* = 7.6 Hz, 2 H), 2.81 (dd, *J* = 7.0, 17.0 Hz, 1 H), 2.49 (d, *J* = 17.0 Hz, 1 H), 2.29 (s, 3 H), 1.86 (dd, *J* = 1.2, 6.4 Hz, 1 H), 1.67-1.60 (m, 1 H), 1.34 (t, *J* = 7.6 Hz, 3 H), 1.10 (s, 3 H), 0.61 (s, 3 H).

b) To a solution of the above (3bS,4aR)-ethyl 3,4,4-trimethyl-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-b]pyrrole-2-carboxylate (1.17 g, 5.0 mmol) in ethanol (70 mL) was added a 2 N aq. LiOH solution. The reaction mixture was stirred at 75 °C for 16 h. The mixture was cooled to rt, diluted with water (250 mL), acidified by adding 10% aq. citric acid (75 mL) and extracted with DCM (125 mL). The organic extract was treated with TFA (1.5 mL) and allowed to stand at rt for 15 min before it was washed with sat. aq. $NaHCO_3$ (100 mL), dried over Na_2SO_4 and evaporated. The crude product was purified by HPLC (X-terra RP C18, as above, gradient of acetonitrile in water containing 0.5% sat. aq. ammonium hydroxide) to give **18** (250 mg) as a rose-coloured solid. LC-MS: t_R = 0.65 min, $[M+1]^+$ = 162.24 (calcd 162.13); ^{1}H NMR ($CDCl_3$): δ 7.38 (s br, 1 H), 6.32 (s, 1 H), 2.80 (dd, *J* = 7.0, 16.4 Hz, 1 H), 2.45 (d, *J* = 15.8 Hz, 1 H), 2.05 (s, 3 H), 1.88-1.82 (m, 1 H), 1.62-1.54 (m, 1 H), 1.08

(s, 3 H), 0.60 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ 136.7, 127.8, 117.0, 115.1, 32.8, 28.6, 26.9, 25.5, 22.8, 14.0, 11.3.

c) A mixture of 3-(2-methoxyphenyl)propionic acid (890 mg, 4.9 mmol) and phosphorus trichloride (247 mg, 1.8 mmol) was allowed to stand at rt for 20 h before it was added to a solution of **18** (360 mg, 2.23 mmol) and NaHMDS (3.35 mL of a 2 M solution in THF, 6.7 mmol) in dioxane (7.5 mL). The reaction mixture was allowed to stand at rt for 10 min. The mixture was directly subjected to prep. HPLC purification (X-terra RP C18, as above, gradient of acetonitrile in water containing 0.5% sat. aq. ammonium hydroxide) to yield **6** (100 mg) as a brownish oil. LC-MS: t_R = 1.16 min, $[M+1]^+$ = 324.11; ^{1}H NMR ($CDCl_3$): δ 7.23-7.14 (m, 2 H), 6.91-6.77 (m, 3 H), 3.83 (s, 3 H), 3.06-2.91 (m, 5 H), 2.74 (d, *J* = 17.6 Hz, 1 H), 1.99 (s, 3 H), 1.76 (dd, *J* = 1.8, 6.4 Hz, 1 H), 1.65-1.58 (m, 1 H), 1.08 (s, 3 H), 0.63 (s, 3 H).

Alternative route c): A mixture of pentafluorophenol (1.85 g, 10 mmol), 3-(2-methoxyphenyl)propionic acid (1.80 g, 10 mmol) and DCC (2.15 g, 10.5 mmol) in acetonitrile (40 mL) was stirred at rt for 45 min before it was diluted with diethyl ether (250 mL). The precipitate was removed by filtration and the filtrate was evaporated to yield 3-(2-methoxy-phenyl)-propionic acid pentafluorophenyl ester (3.40 g) as a white solid. A solution of **18** (1.20 g, 7.5 mmol) in abs. THF (40 mL) was treated with NaHMDS (8 mL of a 1 M solution in THF, 8 mmol). After stirring the mixture at rt for 2 min, a solution of the above 3-(2-methoxy-phenyl)-propionic acid pentafluorophenyl ester (3.40 g, 9.82 mmol) in THF (40 mL) was added. The mixture was allowed to stand at rt for 5 min, was diluted with water (500 mL) and extracted twice with DCM (120 mL). The organic extracts are dried over Na_2SO_4 and the solvent was evaporated. The crude product was purified by prep. HPLC (X-terra RP C18, 100x30 mm, 5 μm particle size, gradient of acetonitrile in water containing 0.5% sat. aq. ammonium hydroxide) to furnish **6** (830 mg, 34%) as a brownish oil with identical analytical data as the material prepared above.

(4aR,5aS)-1,5,5-Trimethyl-4,4a,5,5a-tetrahydro-1H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazole-3-carboxylic acid (17). To a solution of (4aR,5aS)-ethyl 5,5-dimethyl-4,4a,5,5a-tetrahydro-1H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazole-3-carboxylate[8, 9, 10, 11] (440 mg, 2.00 mmol) in dry DMF (10 mL), Cs_2CO_3 (3.20 g, 9.85 mmol) was added. The mixture was cooled to 0 °C before MeI (1.17 g, 6.00 mmol) was added. The mixture was stirred at rt for 2 h before it was filtered and diluted with methanol (3 mL) and water (2 mL). The solution containing the two crude alkylation products was separated by prep. HPLC (Waters Xterra, RP 18, 10 μm, 19x150 mm, gradient of MeCN in water containing 0.5% NH_3) and the product containing fractions are treated with 2 M aq. LiOH (10% of fraction volume) for 1 h. The organic solvent of the fractions was removed under reduced pressure (10 mbar) at 45 °C and the remaining solutions are extracted three times with EA (25 mL). The combined organic extracts of each fraction are concentrated and dried to give (4aR,5aS)-1,5,5-trimethyl-4,4a,5,5a-tetrahydro-1H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazole-3-carboxylic acid **17** (100 mg, 24%) as a white solid; LC-MS: t_R = 0.76 min, $[M+1]^+$ = 207.26 (calcd 207.11); ^{1}H NMR ($CDCl_3$): δ 3.87 (s, 3 H), 2.86 (dd, J_1 = 17.0, J_2 = 6.8 Hz, 1 H), 2.66 (d, *J* = 17.0 Hz, 1 H, 1.98-2.06 (m, 1 H), 1.92 (d, *J* = 6.4 Hz, 1 H), 1.12 (s, 3 H), 0.74 (s, 3 H); and (4aR,5aS)-2,5,5-trimethyl-4,4a,5,5a-tetrahydro-2H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazole-3-carboxylic acid (110 mg, 27%) as a white crystalline powder; LC-MS: t_R = 0.82 min, $[M+1]^+$ = 207.03 (calcd 207.11);^{1}H NMR

($CDCl_3$): δ 4.09 (s, 3 H), 2.93 (dd, J_1 = 17.8 Hz, J_2 = 6.9 Hz, 1 H), 2.68 (d, J = 17.6 Hz, 1 H), 2.07 (dd, J_1 = 6.3 Hz, J_2 = 0.6 Hz, 1 H), 1.91 (t, J = 6.4 Hz, 1 H), 1.13 (s, 3 H), 0.75 (s, 3 H); single crystal X-ray structure see below.

Single Crystal X-ray Structure Analysis of the 2-Methyl-isomer of Pyrazole-3-carboxylic acid 17. Crystals of 2-methyl isomer of compound **17** ($C_{11}H_{14}N_2O_2$, formula weight 206.24) formed in the monoclinic space group P1211. A total of 40336 reflections was measured at 173 K. Molecules/unit cell Z = 4, cell dimensions a = 5.8471(12) Å, b = 19.5623(8) Å, c = 9.0815(12) Å, α = 90°, β = 96.232(18)°, γ = 90°; calculated density = 1.33 g cm^{-3}. The final R-factor of 0.057 was obtained for 2752 observed reflections ($I > 3\sigma(I)$); largest difference peak and hole were 0.44 and -0.48 e$Å^{-3}$, respectively. CCDC code: 969024

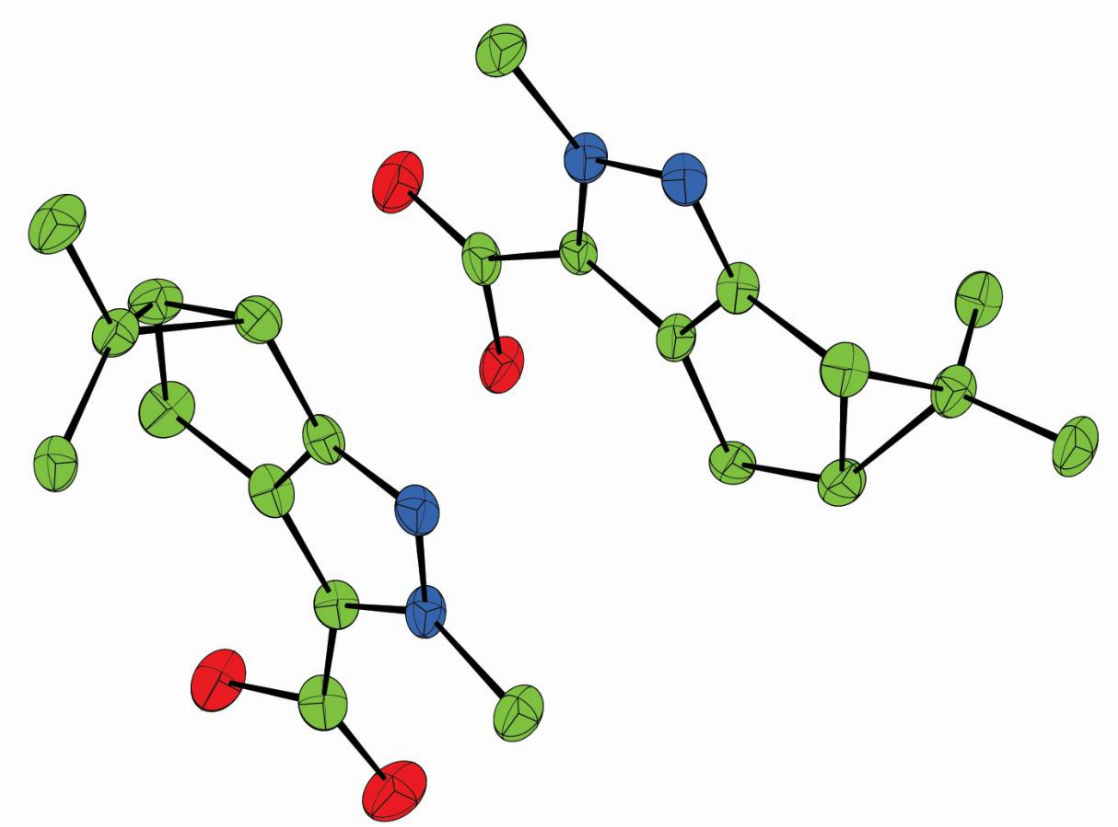
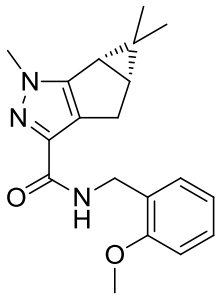


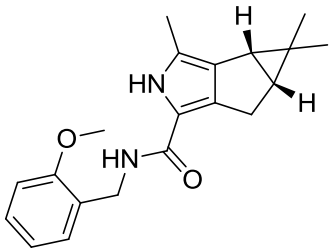
Figure A. Structure of the 2-methyl isomer of compound **17** as determined by single crystal X-ray structure analysis. Anisotropic thermal ellipsoids are drawn at a 50% level. Hydrogen atoms have been omitted for reasons of clarity.

(4aR,5aS)-N-(2-Methoxybenzyl)-1,5,5-trimethyl-4,4a,5,5a-tetrahydro-1H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazole-3-carboxamide (7).



The title compound was prepared from **17** in analogy to **9**; LC-MS: t_R = 0.89 min, $[M+1]^+$ = 326.27; ^{1}H NMR (H_6-DMSO, solvent suppression): δ 7.96 (t br, *J* = 7.0 Hz, 1 H), 7.16 (t, *J* = 7.0 Hz, 1 H), 7.06 (d, *J* = 7.0 Hz, 2 H), 6.91 (d, *J* = 8.4 Hz, 1 H), 6.82 (t, *J* = 7.5 Hz, 1 H), 4.31 (d, *J* = 5.6 Hz, 2 H), 3.79 (s, 3 H), 3.75 (s, 3 H), 2.72 (dd, *J* = 6.8, 16.6 Hz, 1 H), 1.96-2.04 (m, 2 H), 1.08 (s, 3 H), 0.66 (s, 3 H); LC-HRMS: t_R = 1.28 min, [M+H]/z =326.1868, found = 326.1866.

(3bS,4aR)-N-(2-Methoxybenzyl)-3,4,4-trimethyl-3b,4,4a,5-tetrahydro-2H-cyclopropa[3,4]cyclopenta[1,2-c]pyrrole-1-carboxamide (8)



a) To a solution of **14** (18.5 g, 100 mmol) in ethanol (350 mL) ethyl glycinate hydrochloride (21.1 g, 150 mmol), triethylamine (15.2 g, 150 mmol) and $NaHCO_3$ (42.0 g, 500 mmol) were added. The mixture was stirred at 70 °C for 15 h before it was diluted with 10% aq. citric acid solution (200 mL) and extracted twice with DCM (2x300 mL). The combined organic extracts are dried over Na_2SO_4, filtered and concentrated to give crude ethyl 2-(((Z)-1-((1S,5R)-6,6-dimethyl-3-oxobicyclo[3.1.0]hexan-2-ylidene)ethyl)amino)acetate (20.6 g) as a brown oil; LC-MS: t_R = 0.98 min, $[M+1]^+$ = 252.49 (calcd 252.16); ^{1}H NMR ($CDCl_3$): δ 10.12 (s br, 1 H), 4.24 (q, *J* = 7.1 Hz, 2 H), 4.01 (d, *J* = 6.3 Hz, 2 H), 2.61 (dd, J_1 = 19.1 Hz, J_2 = 7.6 Hz, 1 H), 2.22 (d, *J* = 19.1 Hz, 1 H), 2.00 (s, 3 H), 1.74 (d, *J* = 8.0 Hz, 1 H), 1.31 (t, *J* = 7.1 Hz, 3 H), 1.15 (td, J_1 = 7.9 Hz, J_2 = 0.9 Hz, 1 H), 1.10 (s, 3 H), 0.84 (s, 3 H).

b) Part of the above material (12.8 g, 51.1 mmol) was dissolved in ethanol (250 mL) and then added to a solution of Na (1.76 g, 76.6 mmol) in ethanol (80 mL). The resulting solution was stirred under microwave irradiation at 130 °C for 10 min. The mixture was diluted with water (500 mL), basified by adding 2 M aq. NaOH and extracted three times with DCM. The combined organic extracts are dried over $MgSO_4$, filtered and concentrated. The crude product was purified by CC on silica gel eluting with heptane:EA 9:1 to 1:1 to give (3bS,4aR)-ethyl 3,4,4-trimethyl-3b,4,4a,5-tetrahydro-2H-cyclopropa[3,4]cyclopenta[1,2-c]pyrrole-1-carboxylate (3.00 g, 25%) as a brownish solid; LC-MS: t_R = 1.07 min, $[M+1]^+$ = 234.20 (calcd 234.15); ^{1}H NMR ($CDCl_3$): δ 8.37 (s br, 1 H), 4.20-4.32 (m, 2 H), 2.91 (dd, J_1 = 17.9 Hz, J_2 = 6.8 Hz, 1

H), 2.67 (d, *J* = 17.9 Hz, 1 H), 2.24 (s, 3 H), 1.86 (d, *J* = 6.4 Hz, 1 H), 1.74 (t, *J* = 6.5 Hz, 1 H), 1.34 (t, *J* = 7.1 Hz, 3 H), 1.11 (s, 3 H), 0.70 (s, 3 H).

c) A solution of (3bS,4aR)-ethyl 3,4,4-trimethyl-3b,4,4a,5-tetrahydro-2H-cyclopropa[3,4]cyclopenta[1,2-c]pyrrole-1-carboxylate (850 mg, 3.64 mmol) in ethanol (55 mL) and 2 M aq. LiOH (60 mL) was stirred at 70 °C for 18 h. The mixture was concentrated, diluted with 10% aq. citric acid solution and extracted with DCM (100 mL). The organic extract was dried over $MgSO_4$, filtered concentrated and dried to give (3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydro-2H-cyclopropa[3,4]cyclopenta[1,2-c]pyrrole-1-carboxylic acid **19** (720 mg, 96%) as a red to brown solid; LC-MS: t_R = 0.92 min, $[M+1]^+$ = 206.46 (calcd 206.12); ^{1}H NMR ($CDCl_3$): δ 8.50 (s, 1 H), 2.95 (dd, J_1 = 18.1 Hz, J_2 = 6.8 Hz, 1 H), 2.71 (d, *J* = 18.1 Hz, 1 H), 2.26 (s, 3 H), 1.87 (d, *J* = 6.3 Hz, 1 H), 1.77 (t, *J* = 6.3 Hz, 1 H), 1.11 (s, 3 H), 0.70 (s, 3 H).

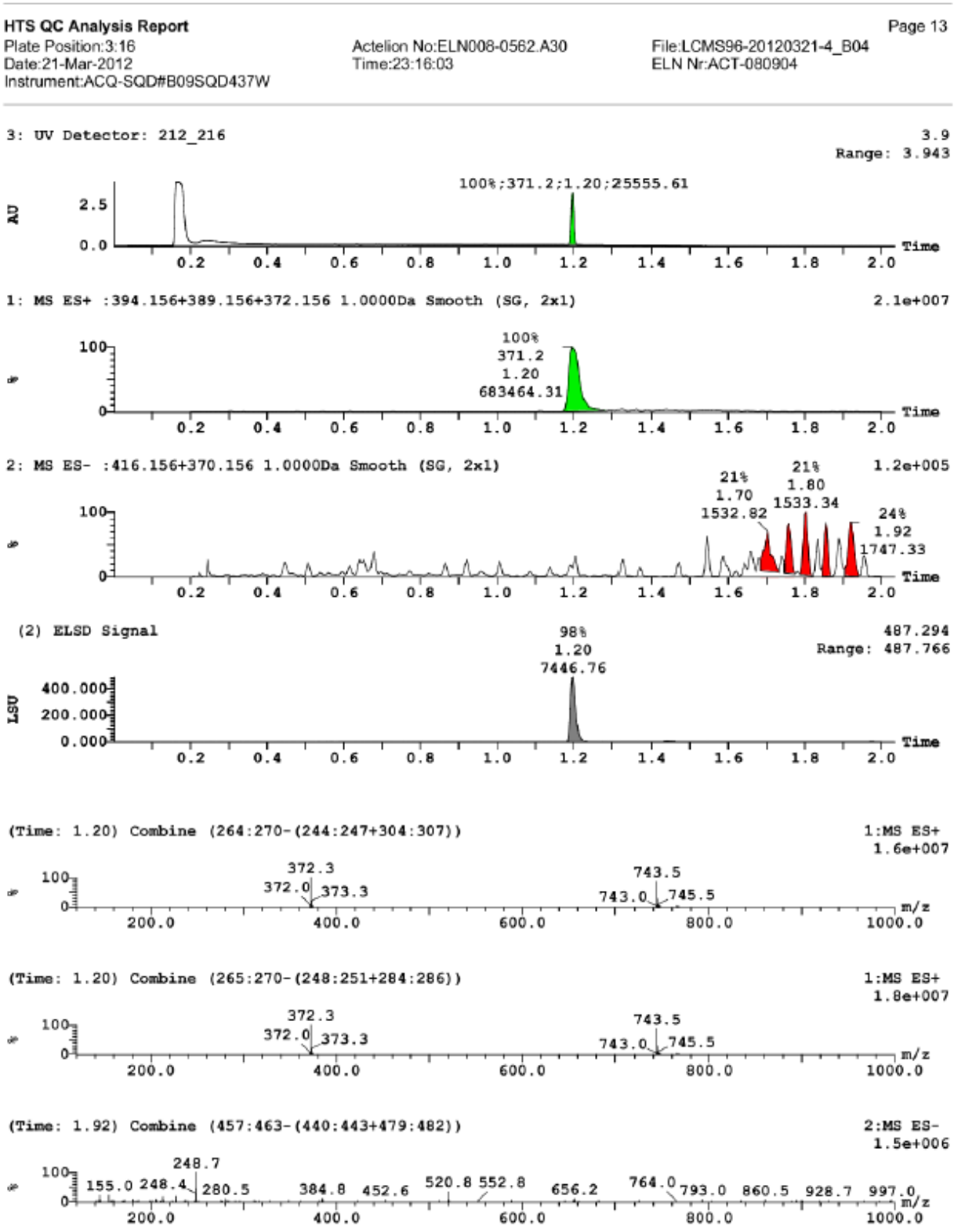
d) To a solution of **19** (10.2 mg, 50 μmol) in DMF (1 mL) Hünig's base (16.2 mg, 125 μmol) and TBTU (16 mg, 125 μmol) was added. The mixture was stirred at rt for 10 min before 2-methoxy-benzylamine (17 mg, 125 μmol) in DMF (100 μL) was added. Stirring was continued for 3.5 h. The reaction mixture was separated by prep. HPLC (Water XTerra Prep RP18, 19x50 mm, acetonitrile in water containing 0.5% ammonium hydroxide) to give the title compound (1.8 mg, 11%) as a colourless resin; LC-MS: t_R = 1.02 min, $[M+1]^+$ = 325.03; ^{1}H NMR (H_6-DMSO, solvent suppression): δ 10.46 (s, 1 H), 7.42 (d, *J* = 6.8 Hz, 1 H), 7.23-7.36 (m, 3 H), 4.44 (t, *J* = 6.8 Hz, 2 H), 2.84 (dd, J_1 = 17.4 Hz, J_2 = 6.8 Hz, 1 H), 2.11 (s, 3 H), 1.80 (d, *J* = 6.1 Hz, 1 H), 1.69 (t, *J* = 5.9 Hz, 1 H), 1.04 (s, 3 H), 0.63 (s, 3 H), LC-HRMS: t_R = 1.37 min, [M+H]/z = 325.1916, found = 325.1918.

Prepartion of thiophenes 21 to 84

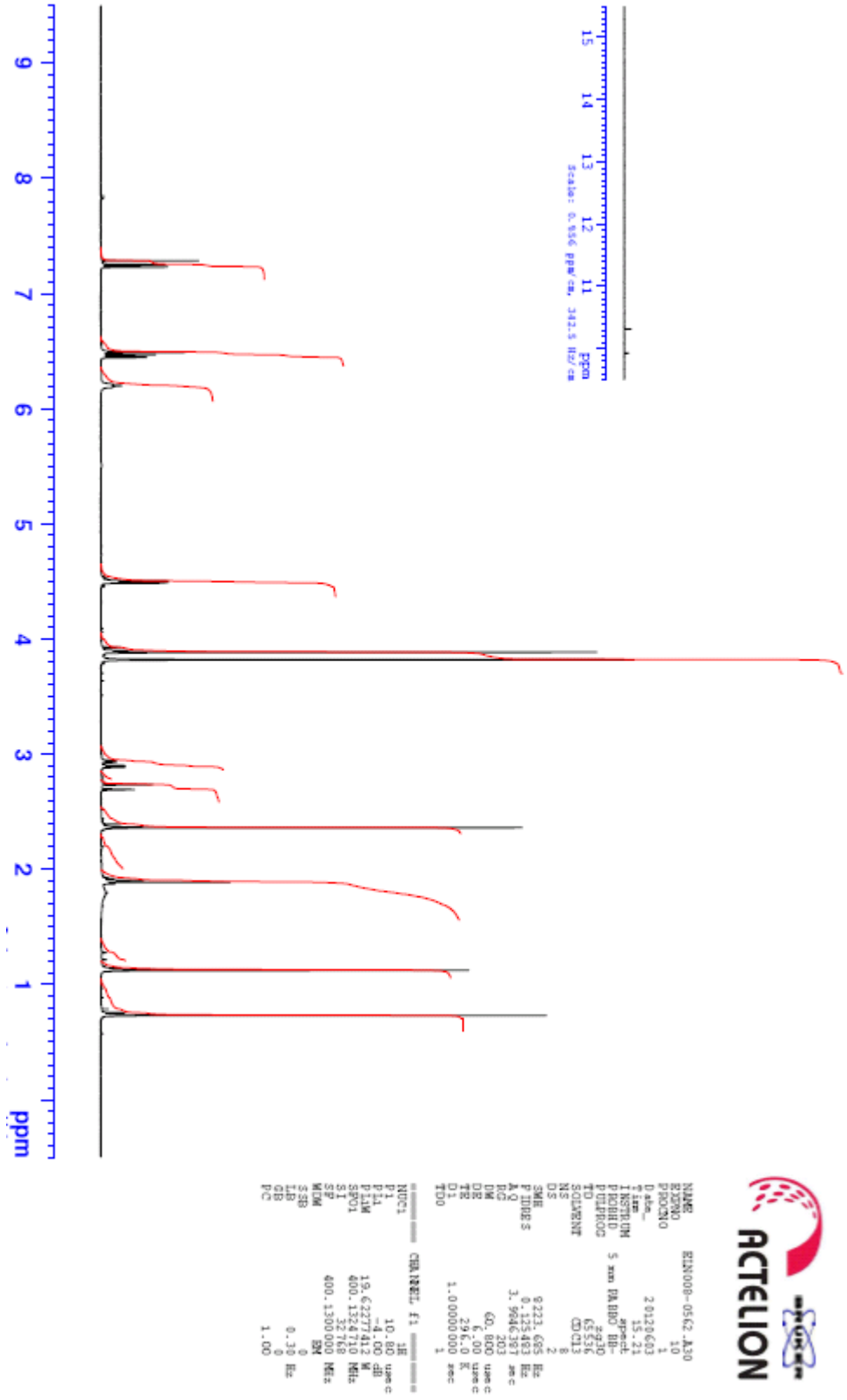
(3bS,4aR)-N-(2,3-Dimethoxybenzyl)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophene-1-carboxamide (21). Prepared in analogy to **9**; colourless resin; LC-MS: t_R = 1.06 min, $[M+1]^+$ = 372.18; ^{1}H NMR (H_6-DMSO, solvent suppression): δ 7.80 (s br, 1 H), 7.00 (t, *J* = 8.1 Hz, 1 H), 6.92 (d, *J* = 7.8 Hz, 1 H), 6.78 (d, *J* = 7.6 Hz, 1 H), 4.37 (d, *J* = 4.9 Hz, 2 H), 3.78 (s, 3 H), 3.74 (s, 3 H), 2.92 (dd, J_1 = 18.8 Hz, J_2 = 6.4 Hz, 1 H), 2.74 (d, *J* = 18.1 Hz, 1 H), 2.31 (s, 3 H), 1.85-1.95 (m, 2 H), 1.07 (s, 3 H), 0.67 (s, 3 H); LC-HRMS: t_R = 1.45 min, [M+H]/z = 372.1633, found = 372.1631.

(3bS,4aR)-N-(2,4-Dimethoxybenzyl)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophene-1-carboxamide (22). Prepared in analogy to **9**; colourless resin; LC-MS: t_R = 1.08 min, $[M+1]^+$ = 372.18; ^{1}H NMR ($CDCl_3$): δ 7.24 (d, *J* = 8.2 Hz, 1 H), 6.49 (d, *J* = 2.3 Hz, 1 H), 6.46 (dd, J_1 = 8.2 Hz, J_2 = 2.4 Hz, 1 H), 6.19 (t, *J* = 5.4 Hz, 1 H), 4.45-4.54 (m, 2 H), 3.89 (s, 3 H), 3.82 (s, 3 H), 2.92 (dd, J_1 = 17.7 Hz, J_2 = 5.7 Hz, 1 H), 2.71 (d, *J* = 17.7 Hz, 1 H), 2.36 (s, 3 H), 1.86-1.94 (m, 2 H), 1.12 (s, 3 H), 0.73 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ 162.0, 160.5, 158.6, 151.7, 146.2, 132.1, 130.6, 123.5, 119.0, 104.0, 98.7, 55.5,

55.4, 39.4, 36.3, 30.0, 28.2, 26.6, 22.8, 14.5, 13.7; LC-HRMS: t_R = 1.47 min, [M+H]/z = 372.1633, found = 372.1629.



LC-MS spectra of compound **22**.



^{1}H NMR spectrum of compound **22**.

(3bS,4aR)-N-(2,5-Dimethoxybenzyl)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophene-1-carboxamide (23). Prepared in analogy to **9**; colourless resin; LC-MS: t_R = 1.07 min, $[M+1]^+$ = 372.14; ^{1}H NMR ($CDCl_3$): δ 6.91 (d, J = 2.8 Hz, 1 H), 6.78-6.87 (m, 2 H), 6.30 (t, J = 5.6 Hz, 1

H), 4.52-4.59 (m, 2 H), 3.87 (s, 3 H), 3.78 (s, 3 H), 2.93 (dd, J_1 = 17.7 Hz, J_2 = 5.7 Hz, 1 H), 2.73 (d, J = 17.7 Hz, 1 H), 2.37 (s, 3 H), 1.87-1.93 (m, 2 H), 1.13 (s, 3 H), 0.74 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ 162.0, 153.7, 151.81, 151.78, 146.2, 132.3, 127.4, 123.4, 115.8, 113.3, 111.3, 55.9, 55.8, 40.0, 36.3, 30.0, 28.2, 26.6, 22.9, 14.5, 13.8; LC-HRMS: t_R = 1.46 min, [M+H]/z = 372.1633, found = 372.1633.

(3bS,4aR)-N-(2,6-Dimethoxybenzyl)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophene-1-carboxamide (24). Prepared in analogy to **9**; colourless resin; LC-MS: t_R = 1.09 min, $[M+1]^+$ = 372.06; ^{1}H NMR (H_6-DMSO, solvent suppression): δ 7.24 (t, J = 8.3 Hz, 1 H), 6.94 (s, 1 H), 6.67 (d, J = 8.3 Hz, 3 H), 4.43 (d, J = 3.2 Hz, 2 H), 3.80 (s, 6 H), 2.87 (dd, J_1 = 18.3 Hz, J_2 = 6.8 Hz, 1 H), 2.29 (s, 3 H), 1.86-1.92 (m, 2 H), 1.06 (s, 3 H), 0.64 (s, 3 H); LC-HRMS: t_R = 1.50 min, [M+H]/z = 372.1633, found = 372.1636.

2-(3-Methoxy-4-(((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydro-cyclopropa[3,4]cyclopenta[1,2-c]thiophene-1-carboxamido)methyl) phenoxy)acetic acid (25). Prepared in analogy to **9**; colourless resin; LC-MS: t_R = 0.98 min, $[M+1]^+$ = 416.12; ^{1}H NMR (H_6-DMSO, solvent suppression): δ 7.61 (t, J = 4.9 Hz, 1 H), 7.01 (d, J = 8.6 Hz, 1 H), 6.54 (s, 1 H), 6.41 (d, J = 8.3 Hz, 1 H), 4.62 (s, 2 H), 4.25 (d, J = 4.4 Hz, 2 H), 3.78 (s, 3 H), 2.86-2.95 (m, 1 H), 2.72 (d, J = 18.3 Hz, 1 H), 2.30 (s, 3 H), 1.85-2.05 (m, 2 H), 1.07 (s, 3 H), 0.67 (s, 3 H); LC-HRMS: t_R = 1.32 min, [M+H]/z = 416.1531, found = 416.1534.

(3bS,4aR)-N-(2-(2-Hydroxyethoxy)benzyl)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophene-1-carboxamide (26). Prepared in analogy to **9**; colourless resin; LC-MS: t_R = 1.00 min, $[M+1]^+$ = 372.15; ^{1}H NMR (H_6-DMSO, solvent suppression): δ 7.68 (s br, 1 H), 7.20 (t, J = 7.9 Hz, 1 H), 7.15 (d, J = 7.9 Hz), 6.97 (d, J = 7.1 Hz), 6.89 (t, J = 7.6 Hz, 1 H), 4.35-4.39 (s br, 2 H), 3.99-4.04 (m, 2 H), 3.71-3.77 (m, 2 H), 2.90-2.97 (m, 1 H), 2.76 (d, J = 18.6 Hz, 1 H), 2.31 (s, 3 H), 1.92-1.97 (m, 1 H), 1.86-1.92 (m, 1 H), 1.09 (s, 3 H), 0.69 (s, 3 H); LC-HRMS: t_R = 1.33 min, [M+H]/z = 372.1633, found = 372.1639.

(3bS,4aR)-N-(4-(2-Hydroxyethoxy)benzyl)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophene-1-carboxamide (28). Prepared in analogy to **27**, colourless resin; LC-MS: t_R = 0.96 min, $[M+1]^+$ = 372.20; ^{1}H NMR (H_6-DMSO, solvent suppression): δ 7.85 (t br, J = 5.2 Hz, 1 H), 7.18 (d, J = 8.1 Hz, 2 H), 6.81 (d, J = 8.1 Hz, 2 H), 4.79 (t, J = 5.2 Hz, 1 H), 4.26 (d, J = 5.5 Hz, 2 H), 3.89-3.95 (m, 2 H), 3.64-3.70 (m, 2 H), 2.91 (dd, J = 6.1, 18.2 Hz, 1 H), 2.72 (d, J = 18.4 Hz, 1 H), 2.30 (s, 3 H), 1.84-1.94 (m, 2 H), 1.08 (s, 3 H), 0.66 (s, 3 H); LC-HRMS: t_R = 1.26 min, [M+H]/z = 372.1633, found = 372.1630.

(3bS,4aR)-N-(4-(2-Hydroxyethoxy)-2-methoxybenzyl)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophene-1-carboxamide (29). Prepared in analogy to **9**; colourless resin; LC-MS: t_R = 0.98 min, $[M+1]^+$ = 402.16; ^{1}H NMR (H_6-DMSO, solvent suppression): δ 7.51 (t br, J = 5.1 Hz, 1 H), 6.98 (d, J = 8.3 Hz, 1 H), 6.50 (s, 1 H), 6.43 (d, J = 8.1 Hz, 1 H), 4.90 (t, J = 4.9 Hz, 1 H), 4.25 (d, J = 5.0 Hz, 2 H), 3.90-3.98 (m, 2 H), 3.78 (s, 3 H), 3.66-3.70 (m, 2 H), 2.92 (dd, J = 6.0, 18.3 Hz, 1 H), 2.72 (d, J = 18.4 Hz, 1 H), 2.31 (s, 3 H), 1.86-1.95 (m, 2 H), 1.08 (s, 3 H), 0.68 (s, 3 H); LC-HRMS: t_R = 1.30 min, [M+H]/z = 402.1739, found = 402.1747.

3-(2-Chloro-4-(2-hydroxyethoxy)phenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (34). Prepared in analogy to **32**; LC-MS: t_R = 1.10 min, $[M+1]^+$ = 405.21; ^{1}H NMR (H_6-DMSO, solvent suppression): δ 7.18 (d, *J* = 8.7 Hz, 1 H), 6.94 (s, 1 H), 6.80 (d, *J* = 8.2 Hz, 1 H), 4.90 (t, *J* = 5.2 Hz, 1 H), 3.95 (t, *J* = 4.3 Hz, 2 H), 3.66-3.72 (m, 2 H), 2.90-2.97 (m, 1 H), 2.74 (d, *J* = 18.8 Hz, 1 H), 2.34 (s, 3 H), 1.89-2.00 (m, 2 H), 1.08 (s, 3 H), 0.65 (s, 3 H); LC-HRMS: t_R = 1.52 min, [M+H]/z = 405.1291, found = 405.1290.

3-(4-(2-Hydroxyethoxy)-2,6-dimethoxyphenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (35). Prepared in analogy to **33**; LC-MS: t_R = 1.07 min, $[M+1]^+$ = 431.35; ^{1}H NMR (H_6-DMSO; solvent suppression): δ 6.20 (s, 2 H), 4.85 (s br, 1 H), 3.96-4.01 (m, 2 H), 3.72 (s, 6 H), 3.67-3.72 (m, 2 H), 2.90-2.97 (m, 1 H), 2.67-2.76 (m, 3 H), 2.35 (s, 3 H), 1.95-2.01 (m, 1 H), 1.88-1.94 (m, 1 H), 1.09 (s, 3 H), 0.67 (s, 3 H); LC-HRMS: t_R = 1.47 min, [M+H]/z = 431.1892, found = 431.1895.

3-(4-(2-Hydroxyethoxy)-2,6-dimethylphenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (36). Prepared in analogy to **32**; LC-MS: t_R = 1.09 min, $[M+1]^+$ = 399.37; ^{1}H NMR (H_6-DMSO; solvent suppression): δ 6.56 (s, 2 H), 4.86 (t, *J* = 4.4 Hz, 1 H), 3.86-3.93 (m, 2 H), 3.63-3.71 (m, 2 H), 2.93 (dd, *J* = 18.6, 6.6 Hz, 1 H), 2.91 (d, *J* = 6.6 Hz, 1 H), 2.68-2.82 (m, 2 H), 2.33 (s, 3 H), 2.21 (s, 6 H), 1.85-2.02 (m, 2 H), 1.06 (s, 3 H), 0.64 (s, 3 H); LC-HRMS: t_R = 1.51 min, [M+H]/z = 399.1994, found = 399.2001.

3-(4-(2-Hydroxyethoxy)-3-methoxyphenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (37). Prepared in analogy to **32**; LC-MS: t_R = 1.04 min, $[M+1]^+$ = 401.03; ^{1}H NMR (H_6-DMSO, solvent suppression): δ 6.83 (s, 1 H), 6.82 (d, *J* = 6.4 Hz, 1 H), 6.70 (d, *J* = 8.1 Hz, 1 H), 4.83-4.88 (t, *J* = 4.9 Hz, 1 H), 3.87-3.92 (m, 2 H), 3.71 (s, 3 H), 3.64-3.69 (m, 2 H), 2.90-2.97 (m, 1 H), 2.70-2.82 (m, 3 H), 2.33 (s, 3 H), 1.87-2.00 (m, 4 H), 1.07 (s, 3 H), 0.64 (s, 3 H); LC-HRMS: t_R = 1.40 min, [M+H]/z = 401.1786, found = 401.1788.

3-(4-(2-Hydroxyethoxy)-3-methylphenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (38). Prepared in analogy to **32**; LC-MS: t_R = 1.09 min, $[M+1]^+$ = 385.24; ^{1}H NMR (H_6-DMSO, solvent suppression): δ 6.98 (s, 1 H), 6.96 (d, *J* = 7.8 Hz, 1 H), 6.78 (d, *J* = 7.8 Hz, 1 H), 4.85 (t br, *J* = 4.6 Hz, 1 H), 3.89-3.95 (m, 2 H), 3.66-3.73 (m, 2 H), 2.91-2.96 (m, 1 H), 2.69-2.78 (m, 3 H), 2.33 (s, 3 H), 2.11 (s, 3 H), 1.87-2.02 (m, 2 H), 1.07 (s, 3 H), 0.64 (s, 3 H); LC-HRMS: t_R = 1.50 min, [M+H]/z = 385.1837, found = 385.1836.

3-(3-Chloro-4-(2-hydroxyethoxy)phenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (39). Prepared in analogy to **32**; LC-MS: t_R = 1.09 min, $[M+1]^+$ = 405.16; ^{1}H NMR (H_6-DMSO, solvent suppression): δ 7.28 (s, 1 H), 7.13 (d, *J* = 8.3 Hz, 1 H), 7.02 (d, *J* = 8.3 Hz, 1 H), 4.90 (t br, *J* = 5.4 Hz, 1 H), 3.97-4.05 (m, 2 H), 3.68-3.77 (m, 2 H), 2.70-

2.84 (m, 1 H), 2.33 (s, 3 H), 1.87-2.04 (m, 2 H), 1.07 (s, 3 H), 0.65 (s, 3 H); LC-HRMS: t_R = 1.49 min, [M+H]/z = 405.1291, found = 405.1297.

3-(4-(2-Hydroxyethoxy)-3,5-dimethoxyphenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (40). Prepared in analogy to **32**; LC-MS: t_R = 1.05 min, $[M+1]^+$ = 431.24; ^{1}H NMR (H_6-DMSO, solvent suppression): δ 6.53 (s, 2 H), 4.56 (t, *J* = 5.9 Hz, 1 H), 3.77-3.82 (m, 2 H), 3.72 (s, 6 H), 2.72-2.83 (m, 3 H), 2.33 (s, 3 H), 1.87-2.02 (m, 4 H), 1.07 (s, 3 H), 0.65 (s, 3 H); LC-HRMS: t_R = 1.43 min, [M+H]/z = 431.1892, found = 431.1900.

3-(4-(2-Hydroxyethoxy)-3,5-dimethylphenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (41). Prepared in analogy to **32**; LC-MS: t_R = 1.09 min, $[M+1]^+$ = 399.35; ^{1}H NMR (H_6-DMSO, solvent suppression): δ 6.85 (s, 2 H), 4.91 (t, *J* = 4.9 Hz, 1 H), 3.64-3.72 (m, 2 H), 2.93-2.99 (m, 1 H), 2.69-2.79 (m, 1 H), 2.32 (s, 3 H), 2.17 (s, 6 H), 1.88-1.99 (m, 2 H), 1.08 (s, 3 H), 0.65 (s, 3 H); LC-HRMS: t_R = 2.22 min, [M+H]/z = 399.1994, found = 399.1995.

3-(3,5-Dichloro-4-(2-hydroxyethoxy)phenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (42). Prepared in analogy to **32**; LC-MS: t_R = 1.12 min, $[M+1]^+$ = 439.30; ^{1}H NMR (H_6-DMSO, solvent suppression): δ 7.36 (s, 2 H), 4.91 (t br, *J* = 5.9 Hz, 1 H), 3.91-3.98 (m, 2 H), 3.68-3.77 (m, 2 H), 3.02-3.09 (m, 2 H), 2.72-2.86 (m, 2 H), 2.33 (s, 3 H), 1.88-2.05 (m, 2 H), 1.08 (s, 3 H), 0.66 (s, 3 H); LC-HRMS: t_R = 1.56 min, [M+H]/z = 439.0901, found = 439.0901.

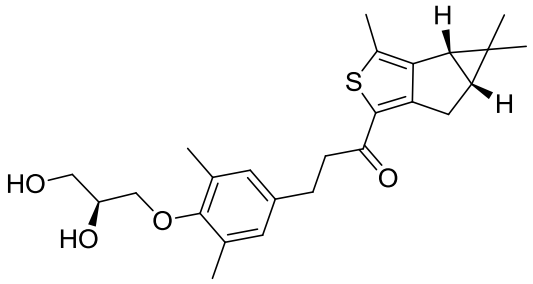
3-(3-Chloro-4-(2-hydroxyethoxy)-5-methylphenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (43). Prepared in analogy to **32**; LC-MS: t_R = 1.10 min, $[M+1]^+$ = 419.32; ^{1}H-NMR (H_6-DMSO, solvent suppression): δ 7.11 (s, 1 H), 6.99 (s, 1 H), 4.87 8t, *J* = 5.4 Hz, 1 H), 3.81-3.87 (m, 2 H), 3.65-3.72 (m, 2 H), 3.00-3.05 (m, 2 H), 2.74-2.80 (m, 2 H), 2.23 (s, 3 H), 1.88-2.00 (m, 2 H), 1.09 (s, 3 H), 0.67 (s, 3 H); LC-HRMS: t_R = 1.55 min, [M+H]/z = 419.1447, found = 419.1454.

3-(3-Ethyl-4-(2-hydroxyethoxy)-5-methylphenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (44). Prepared in analogy to **32**; LC-MS: t_R = 1.11 min, $[M+1]^+$ = 413.37; ^{1}H NMR (H_6-DMSO, solvent suppression): δ 6.86 (s, 2 H), 4.89 (t br, *J* = 5.9 Hz, 1 H), 3.64-3.73 (m, 4 H), 2.92-2.96 (m, 1 H), 2.69-2.80 (m, 3 H), 2.33 (s, 3 H), 2.17 (s, 3 H), 1.86-2.04 (m, 2 H), 1.11 (t, *J* = 7.6 Hz, 3 H), 1.07 (s, 3 H), 0.65 (s, 3 H); LC-HRMS: t_R = 1.57 min, [M+H]/z = 413.2150, found = 413.2155.

3-(4-(2-Hydroxyethoxy)-2,3,5-trimethylphenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (45). Prepared in analogy to **32**; LC-MS: t_R = 1.11 min, $[M+1]^+$ = 413.34; LC-HRMS: t_R = 1.56 min, [M+H]/z = 413.2150, found = 413.2153.

3-(4-(3-Hydroxypropoxy)-3,5-dimethylphenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (46). A solution of 3-(4-hydroxy-3,5-dimethylphenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (3.00 g, 8.46 mmol, prepared in analogy to step a of **32**) in isopropanol (80 mL) and 2 N aq. NaOH (30 mL) was treated with 3-bromopropanol (2.35 g, 16.9 mmol). The dark red reaction mixture was stirred at 70 °C for 5 h. The solvent was removed under reduced pressure and the residue was dissolved in EA and washed twice with water. The organic layer was dried over $MgSO_4$ and evaporated. The crude product was purified by CC on silica gel eluting with heptane:EA 1:1 to give **46** (2.55 g, 73%) as a yellow oil; LC-MS: t_R = 1.10 min, $[M+1]^+$ = 413.33; ^{1}H NMR ($CDCl_3$): δ 6.87 (s, 2 H), 3.99-3.90 (m, 4 H), 3.04-2.85 (m, 5 H), 2.81 (d, *J* = 18.8 Hz, 1 H), 2.39 (s, 3 H), 2.27 (s, 6 H), 2.10-2.01 (m, 2 H), 1.93-1.88 (m, 2 H), 1.13 (s, 3 H), 0.72 (s, 3 H); LC-HRMS: t_R = 1.56 min, [M+H]/z = 413.2150, found = 413.2157.

3-(4-((S)-2,3-Dihydroxypropoxy)-3,5-dimethylphenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (47).



A solution of 3-(4-hydroxy-3,5-dimethylphenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one **31** (500 mg, 1.41 mmol) in isopropanol (20 mL) and 2 N aq. NaOH (7 mL) was treated with (S)-(+)-3-chloro-1,2-propanediol (780 mg, 7.05 mmol). The mixture was stirred at 65 °C for 18 h before another portion of (S)-(+)-3-chloro-1,2-propanediol (780 mg, 7.05 mmol) was added. Stirring was continued for 3 h. The mixture was diluted with diethyl ether (250 mL) and washed with sat. aq. $NaHCO_3$ solution (100 mL) and twice with water (2x50 mL). The organic extract was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by CC on silica gel eluting with heptane:EA 1:4 to give the title compound (441 mg, 73%) as a pale yellow foam; LC-MS: t_R = 0.95 min, $[M+1]^+$ = 428.9; HPLC with chiral stationary phase (Chiralpak AY-H 250x4.6 mm ID, 5 μm; 80% heptane containing 0.05% DEA, 20% ethanol containing 0.05% DEA): t_R = 15.3 min, 97 %; ^{1}H NMR ($CDCl_3$): δ 6.86 (s, 2 H), 4.04-4.14 (m, 1 H), 3.75-3.89 (m, 4 H), 2.74-3.06 (m, 6 H), 2.37 (s, 3 H), 2.25 (s, 6 H), 2.19-2.13 (m, 1 H), 1.84-1.93 (m, 2 H), 1.11 (s, 3 H), 0.70 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ 191.9, 156.0, 153.3, 147.2, 137.0, 136.5, 130.6, 129.2, 128.9, 73.4, 70.9, 64.0, 42.2, 36.1, 29.9, 29.8, 29.7, 26.6, 22.7, 16.3, 14.4, 14.1; LC-HRMS: t_R = 2.07 min, [M+H]/z = 429.2099, found = 429.2101.

Plate Position:3:54
Date:14-Sep-2012
Instrument:ACQ-SQD#B09SQD437W

Actelion No:ELN002-3356.1
Time:12:27:00

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ELN Nr:ACT-131171

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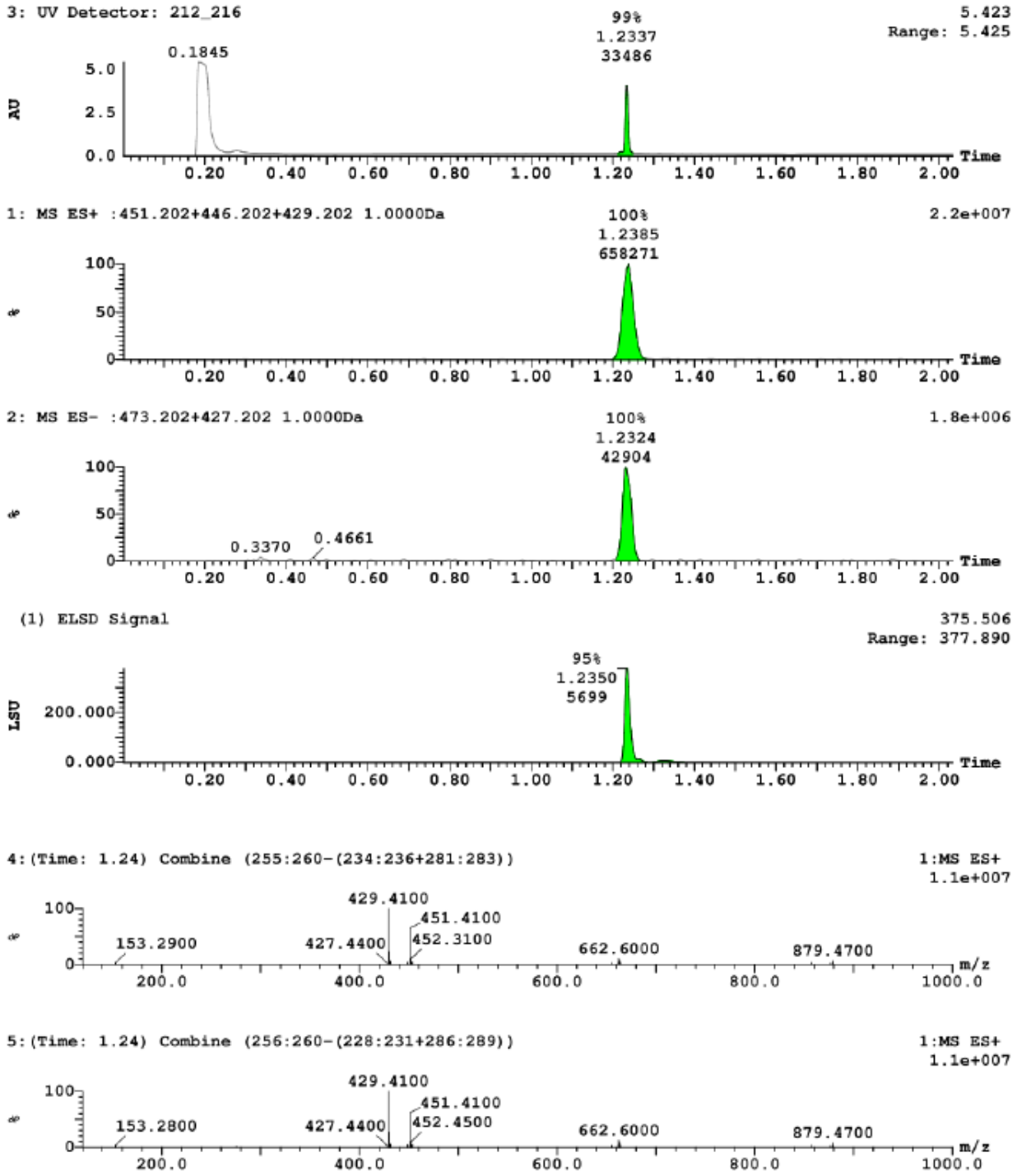
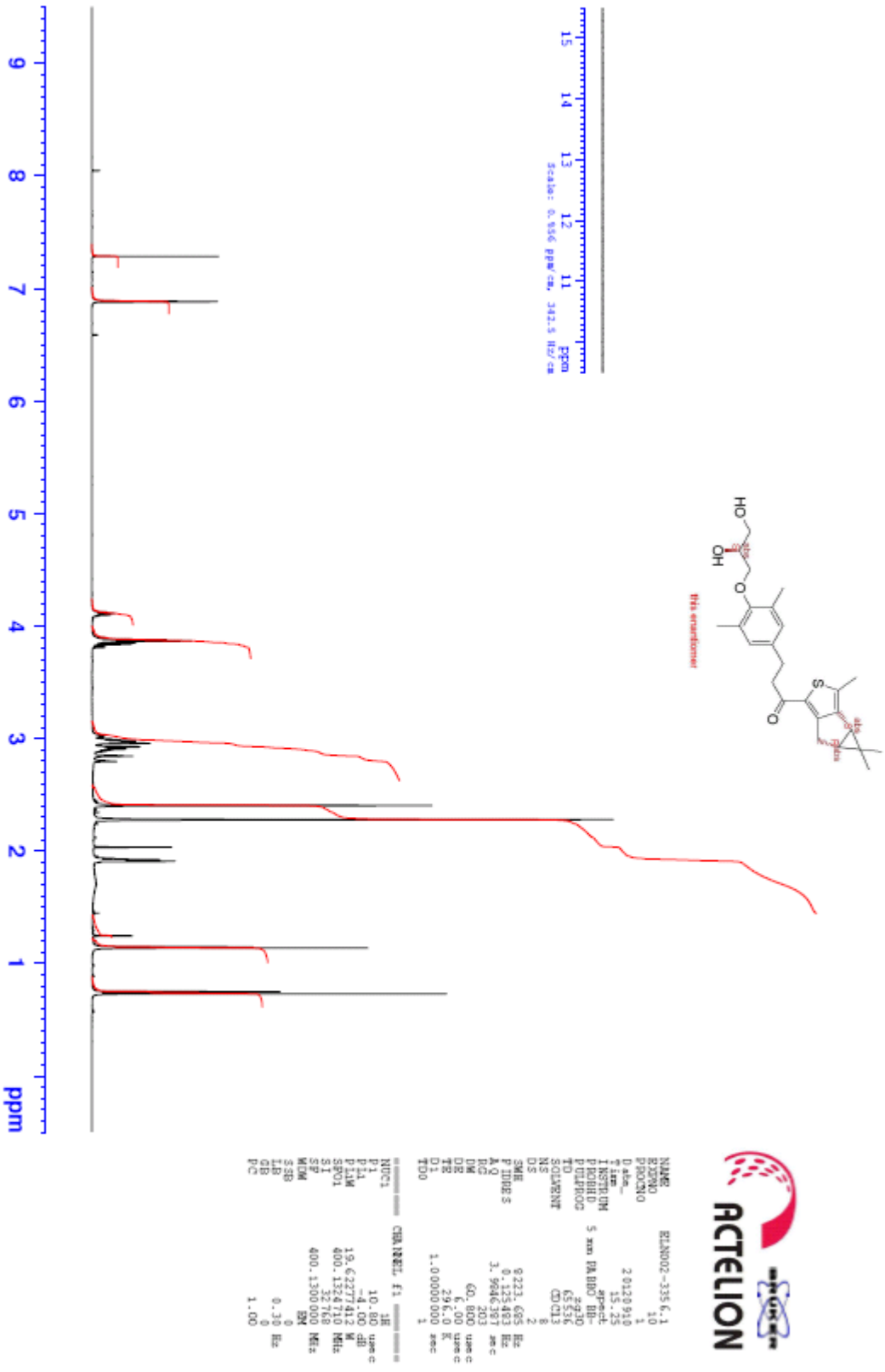


LC-MS spectra of compound **47**.

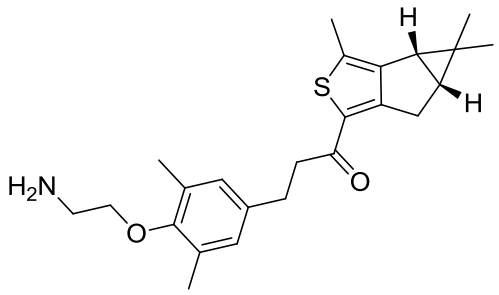


^{1}H NMR spectrum of compound **47**.

3-(4-((R)-2,3-Dihydroxypropoxy)-3,5-dimethylphenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (48). Prepared in analogy to **47**, LC-MS: t_R = 1.02 min, $[M+1]^+$ = 429.29; HPLC with chiral stationary phase (Chiralpak AY-H 250x4.6 mm ID, 5 μm; 80% heptane containing 0.05% DEA, 20% ethanol containing 0.05% DEA): t_R = 11.7 min, 99%; ^{1}H NMR (H_6-DMSO, solvent suppression): δ 6.84 (s, 2 H), 4.92 (d, *J* = 3.2 Hz, 1 H), 4.65 (t br, *J* = 5.9 Hz, 1 H), 3.73-3.81 (m, 1 H), 3.60-3.72 (m, 1 H), 2.92-2.96 (m, 1 H), 2.69-2.79 (m, 3 H), 2.33 (s, 3 H), 2.16 (s, 6 H), 1.87-2.03 (m, 2 H), 1.07 (s, 3 H), 0.65 (s, 3 H); LC-HRMS: t_R = 1.43 min, [M+H]/z = 429.2099, found = 429.2100.

3-(4-(3-Hydroxy-2-(hydroxymethyl)propoxy)-3,5-dimethylphenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (49). Prepared in analogy to **47** using methanesulfonic acid 2,2-dimethyl-[1,3]dioxan-5-ylmethyl ester;[12] LC-MS: t_R = 1.04 min, $[M+1]^+$ = 443.28; ^{1}H NMR ($CDCl_3$): δ 6.85 (s, 2 H), 4.03-3.96 (m, 4 H), 3.90 (d, *J* = 5.3 Hz, 2 H), 3.02-2.85 (m, 5 H), 2.78 (d, *J* = 18.8 Hz, 1 H), 2.37 (s, 3 H), 2.25 (s, 6 H), 2.25-2.15 (m, 1 H), 1.92-1.86 (m, 2 H), 1.11 (s, 3 H), 0.70 (s, 3 H); LC-HRMS: t_R = 1.45 min, [M+H]/z = 443.2256, found = 443.2258.

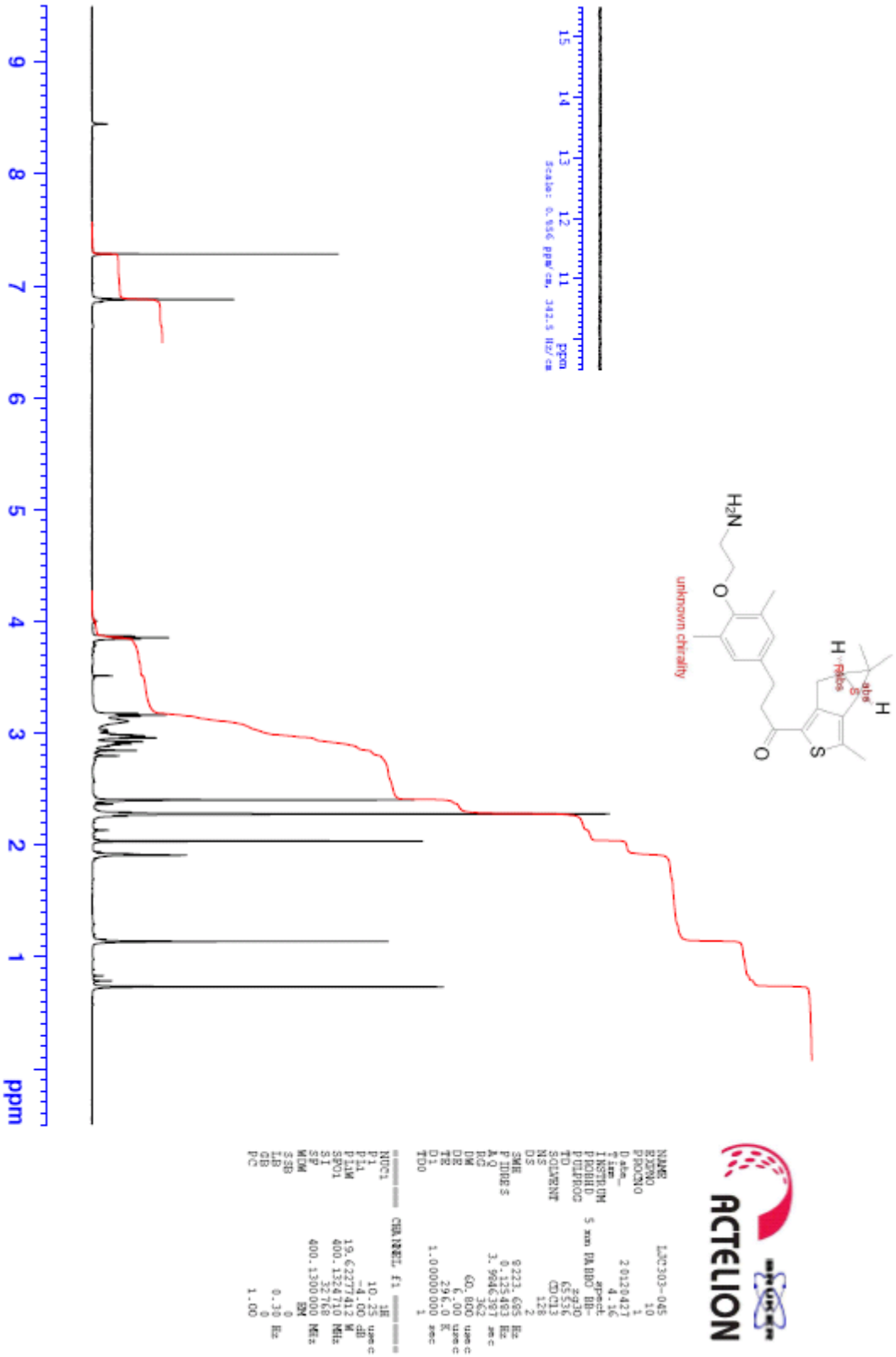
3-(4-(2-Aminoethoxy)-3,5-dimethylphenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (50).



a) To a solution of **41** (1.55 g, 3.89 mmol) in DCM (60 mL) and DIPEA (1.07 mL, 6.22 mmol) was added methane sulfonylchloride (0.362 mL, 4.67 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. Another portion of methane sulfonylchloride (0.362 mL, 4.67 mmol) was added and stirring was continued for 30 min. The reaction mixture was diluted with DCM, washed with 0.1 N aq. NaOH followed by 10% aq. citric acid solution, dried over $MgSO_4$ and evaporated to give 2-(2,6-dimethyl-4-(3-oxo-3-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4] cyclopenta[1,2-c]thiophen-1-yl)propyl)phenoxy)ethyl methanesulfonate (1.57 g) as an orange resin; LC-MS: t_R = 1.14 min, $[M+1]^+$ = 477.35 (calcd 477.18); ^{1}H NMR ($CDCl_3$): δ 6.86 (s, 2 H), 4.57-4.50 (m, 2 H), 4.05-4.00 (m, 2 H), 3.10 (s, 3 H), 3.03-2.85 (m, 5 H), 2.79 (d, *J* = 18.8 Hz, 1 H), 2.37 (s, 3 H), 2.25 (s, 6 H), 1.92-1.85 (m, 2 H), 1.11 (s, 3 H), 0.70 (s, 3 H).

b) A solution of the above methanesulfonate (550 mg, 1.15 mmol) in 7 N NH_3 in methanol (5 mL) was stirred at 70 °C for 22 h in a sealed vessel. The mixture was concentrated and the crude product was purified by CC on silica gel eluting with DCM:methnol 9:1 to give the title compound (205 mg, 45%) as a pale yellow oil; LC-MS: t_R = 0.89 min, $[M+1]^+$ = 389.14; ^{1}H NMR ($CDCl_3$): δ 6.85 (s, 2 H), 3.80-3.75 (m, 2 H), 3.07 (s br, 1 H), 3.03-2.84 (m, 7 H), 2.79 (d, *J* = 18.8 Hz, 1 H), 2.37 (s, 3 H), 2.25

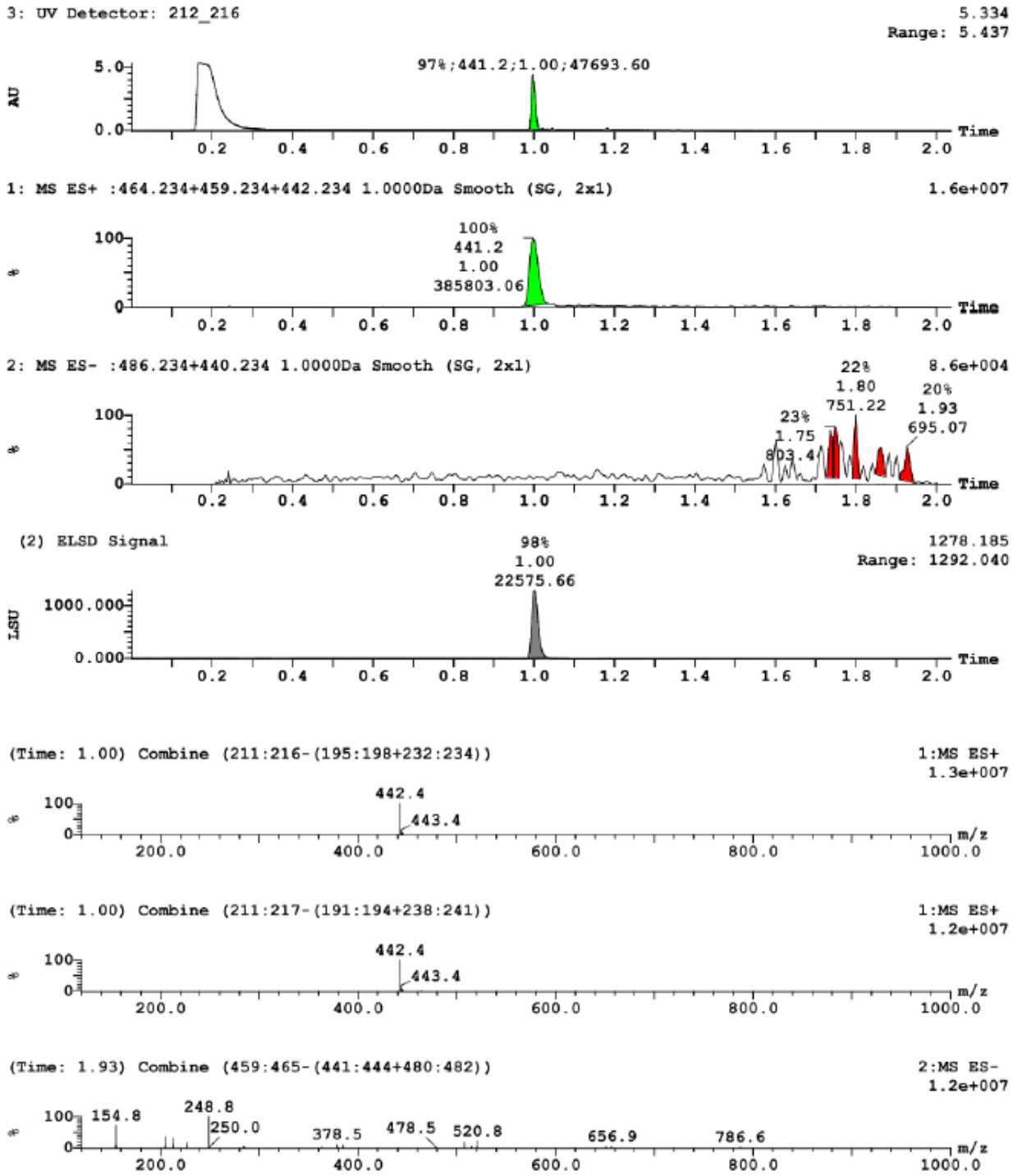
(s, 6 H), 1.92-1.85 (m, 2 H), 1.11 (s, 3 H), 0.70 (s, 3 H); LC-HRMS: t_R = 0.98 min, [M+H]/z = 398.2153, found = 398.2153.



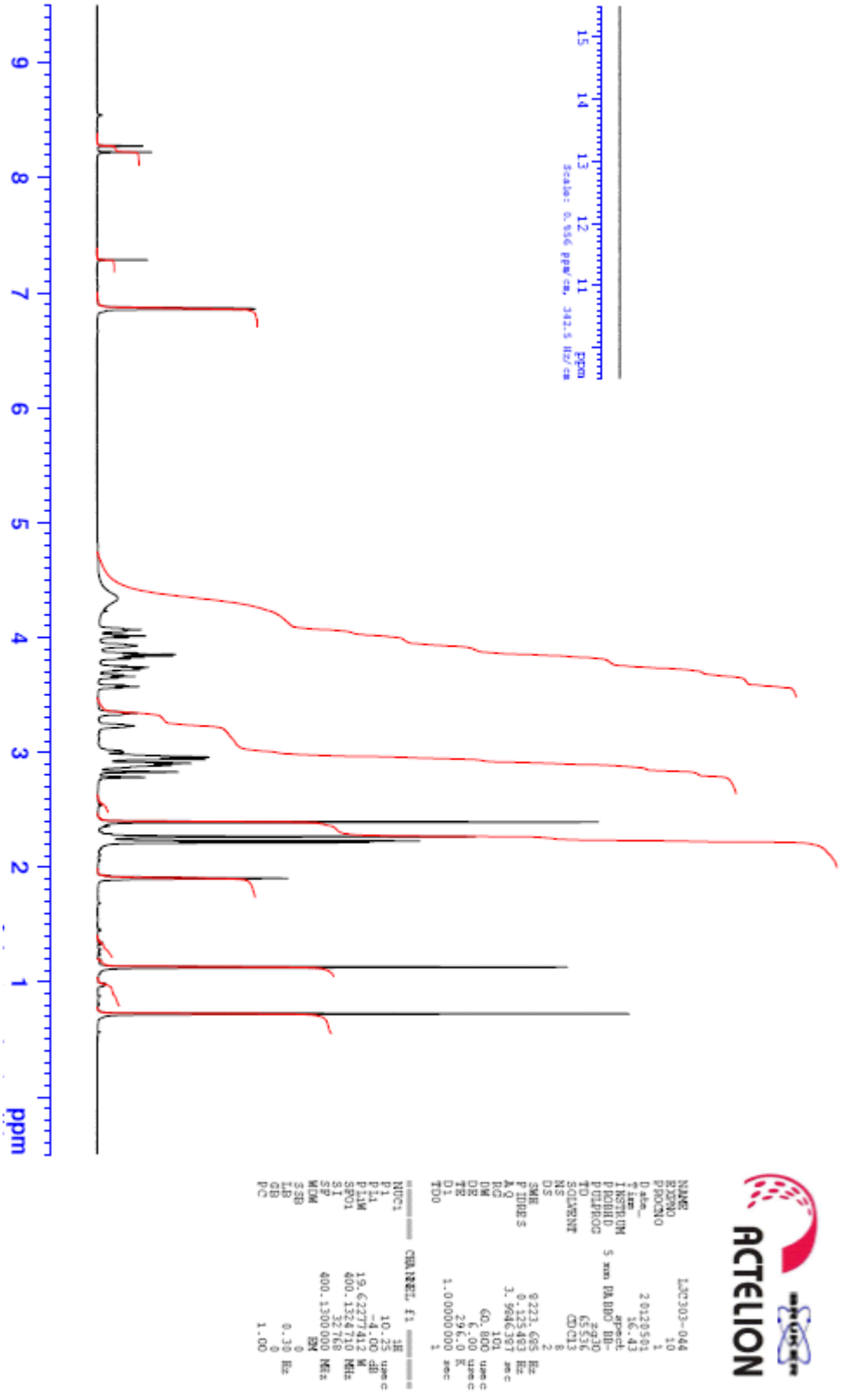
^{1}H NMR spectrum of compund **50**.

3-(3,5-Dimethyl-4-(2-(methylamino)ethoxy)phenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (51). Prepared in analogy to **50**; LC-MS: t_R = 0.91 min, $[M+1]^+$ = 412.29; ^{1}H NMR ($CDCl_3$, as formate salt): δ 8.46 (s 1 H), 6.85 (s, 2 H), 4.25 (s br, 3 H), 4.04-3.97 (m, 2 H), 3.24-3.16 (m, 2 H), 3.03-2.84 (m, 5 H), 2.78 (d, *J* = 18.8 Hz, 1 H), 2.73 (s, 3 H), 2.37 (s, 3 H), 2.25 (s, 6 H), 1.92-1.85 (m, 2 H), 1.11 (s, 3 H), 0.70 (s, 3 H); LC-HRMS: t_R = 1.00 min, [M+H]/z = 412.2310, found = 412.2310.

3-(4-(2-((2-Hydroxyethyl)amino)ethoxy)-3,5-dimethylphenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (52). Prepared in analogy to **50**; LC-MS: t_R = 0.90 min, $[M+1]^+$ = 442.19; ^{1}H NMR ($CDCl_3$, as formate salt): δ 8.49 (s, 1 H), 6.84 (s, 2 H), 5.58 (s br, 3 H), 4.05-3.98 (m, 2 H), 3.94-3.86 (m, 2 H), 3.34-3.25 (m, 2 H), 3.22-3.15 (m, 2 H), 3.03-2.84 (m, 5 H), 2.78 (d, *J* = 18.8 Hz, 1 H), 2.37 (s, 3 H), 2.24 (s, 6 H), 1.92-1.86 (m, 2 H), 1.11 (s, 3 H), 0.70 (s, 3 H); LC-HRMS: t_R = 0.98 min, [M+H]/z = 442.2416, found = 442.2416.



LC-MS spectra of compound **52**



^{1}H NMR spectrum of compound **52**.

3-(4-(2-(Dimethylamino)ethoxy)-3,5-dimethylphenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (53). Prepared in analogy to **50**; LC-MS: t_R = 0.93 min, $[M+1]^+$ = 426.18; ^{1}H NMR (H_6-DMSO, solvent suppression): δ 6.87 (s, 2 H), 3.74-3.80 (m, 2 H), 3.01-3.05 (m, 1 H), 2.66-2.80 (m, 2 H), 2.34 (s, 3 H), 2.27 (s, 6 H), 2.18 (s, 6 H), 1.95-2.01 (m, 1 H), 1.88-1.95 (m, 1 H), 1.09 (s, 3 H), 0.67 (s, 3 H); LC-HRMS: t_R = 1.01 min, [M+H]/z = 426.2466, found = 426.2472.

3-(4-(3-Aminopropoxy)-3,5-dimethylphenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (54). Prepared from **46** in analogy to **50**; LC-MS: t_R = 0.90 min, $[M+1]^+$ = 412.39; ^{1}H NMR ($CDCl_3$): δ 7.01 (s br, 2 H), 6.84 (s, 2 H), 3.86 (t, *J* = 5.2 Hz, 2 H), 3.28 (t, *J* = 6.7 Hz, 2 H), 3.02-2.84 (m, 5 H), 2.78 (d, *J* = 18.8 Hz, 1 H), 2.37 (s, 3 H), 2.20 (s, 6 H), 2.19-2.11 (m, 2 H), 1.92-1.85 (m, 2 H), 1.11 (s, 3 H), 0.70 (s, 3 H); LC-HRMS: t_R = 1.01 min, [M+H]/z = 412.2310, found = 412.2316.

3-(3,5-Dimethyl-4-(3-(methylamino)propoxy)phenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (55). Prepared from **46** in analogy to **50**; LC-MS: t_R = 0.93 min, $[M+1]^+$ = 426.25; ^{1}H NMR ($CDCl_3$): δ 6.84 (s, 2 H), 3.81 (t, *J* = 5.9 Hz, 2 H), 3.03-2.84 (m, 7 H), 2.79 (d, *J* = 18.8 Hz, 1 H), 2.55 (s, 3 H), 2.37 (s, 3 H), 2.22 (s, 6 H), 2.12-2.04 (m, 2 H), 1.92-1.85 (m, 2 H), 1.11 (s, 3 H), 0.70 (s, 3 H); LC-HRMS: t_R = 1.02 min, [M+H]/z = 426.2466, found = 426.2466.

3-(4-(3-((2-Hydroxyethyl)amino)propoxy)-3,5-dimethylphenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (56). Prepared from **46** in analogy to **50**; LC-MS: t_R = 0.90 min, $[M+1]^+$ = 456.31; ^{1}H NMR ($CDCl_3$): δ 6.85 (s, 2 H), 3.81 (t, *J* = 6.4 Hz, 2 H), 3.65 (t, *J* = 5.3 Hz, 2 H), 3.04-2.75 (m, 10 H), 2.37 (s, 3 H), 2.24 (s, 6 H), 1.98 (p, *J* = 6.4 Hz, 2 H), 1.92-1.87 (m, 2 H), 1.82 (s br, 2 H), 1.11 (s, 3 H), 0.70 (s, 3 H); LC-HRMS: t_R = 1.57 min, [M+H]/z = 456.2572, found = 456.2582.

2-((3-(2,6-Dimethyl-4-(3-oxo-3-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propyl)phenoxy)propyl)amino)-acetic acid (58). A solution of 2-(2,6-dimethyl-4-(3-oxo-3-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclo-propa[3,4] cyclopenta[1,2-c]thiophen-1-yl)propyl)phenoxy)-ethyl methanesulfonate (6 mg, 12.5 μmol), glycine (5 mg, 62.5 μmol) and Hünig's base (10 μL) in DMF (0.5 mL) was stirred at 75 °C for 7 h. The mixture was cooled to rt and separated by HPLC (Waters Xterra MS18, 19x50mm, 5μm, gradient of acetonitrile in waetr containing 0.5% of NH_3) to give the title compound (3 mg, 56%) as a colourless lyophilisate; LC-MS: t_R = 0.91 min, $[M+1]^+$ = 470.29; ^{1}H NMR (H_6-DMSO, solvent suppression): δ 6.86 (s, 2 H), 3.69-3.74 (m, 2 H), 3.23 (s, 2 H), 3.02-3.09 (m, 1 H), 2.92-2.96 (m, 1 H), 2.69-2.78 (m, 1 H), 2.33 (s, 3 H), 2.15 (s, 6 H), 1.99-2.07 (m, 2 H), 1.94-1.98 (m, 1 H), 1.88-1.93 (m, 1 H), 1.07 (s, 3 H), 0.65 (s, 3 H); LC-HRMS: t_R = 1.76 min, [M+H]/z = 470.2365, found = 470.2372.

1-(3-(2,6-Dimethyl-4-(3-oxo-3-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydro-cyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propyl)phenoxy)propyl) azetidine-3-carboxylic acid (59). Prepared in analogy to **58**; LC-MS: t_R = 0.93 min, $[M+1]^+$ = 496.30; ^{1}H NMR (H_6-DMSO, solvent suppression): δ 6.85 (s, 2 H), 3.67 (m, *J* = 6.6 Hz, 2 H), 3.34 (t, *J* = 6.6 Hz, 2 H), 3.09-3.20 (m, 1 H), 2.92-2.96 (m, 1 H), 2.67-2.78 (m, 3 H), 2.33 (s, 3 H), 2.14 (s, 6 H), 1.94-1.99 (m, 1 H), 1.87-1.94 (m, 1 H), 1.67-1.77 (m, 2 H), 1.07 (s, 3 H), 0.65 (s, 3 H); LC-HRMS: t_R = 1.09 min, [M+H]/z = 496.2521, found = 496.2522.

(2R/S)-2-((3-(2,6-Dimethyl-4-(3-oxo-3-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydro-cyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propyl)phenoxy) propyl)amino)-succinic acid (60). Prepared as mixture of epimers in analogy to **58**; LC-MS: t_R = 0.90 min, $[M+1]^+$ = 528.29; ^{1}H NMR (CD_3OD): δ 6.75 (s, 2 H), 4.26-4.39 (m, 2 H), 3.68-3.82 (m, 3 H), 2.61-3.03 (m, 8 H), 2.27 (s, 3 H), 2.11 (s, 6 H), 1.98-2.10 (m, 2 H), 1.78-1.88 (m, 2 H), 1.02 (s, 3 H), 0.59 (s, 3 H); LC-HRMS: t_R = 1.25 min, [M+H]/z = 528.2420, found = 528.2430.

(2R/S)-2-((3-(2,6-Dimethyl-4-(3-oxo-3-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydro-cyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propyl)phenoxy)-2-hydroxy-propyl)amino)acetic acid (61). A solution of 3-(3,5-dimethyl-4-(oxiran-2-ylmethoxy)phenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4] cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (246 mg, 0.60 mmol) and glycine (180 mg, 2.40 mmol) in ethanol (5 mL) and water (2.5 mL) was stirred at 65 °C for 5 h. The reaction mixture was separated by prep. HPLC to give the title compound (98 mg, 34%) as a white powder; LC-MS: t_R = 0.89 min, $[M+1]^+$ = 486.32; ^{1}H NMR ($CDCl_3$): δ 6.78 (s, 2 H), 4.48-4.42 (m, 1 H), 3.80-3.63 (m, 4 H), 3.36-3.25 (m, 2 H), 3.00-2.74 (m, 6 H), 2.35 (s, 3 H), 2.15 (s, 6 H), 1.90-1.85 (m, 2 H), 1.10 (s, 3 H), 0.69 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ 191.8, 171.3, 156.0, 153.1, 147.2, 136.9, 136.4, 130.5, 129.1, 128.8, 73.5, 66.1, 51.1, 50.3, 42.2, 36.2, 29.87, 29.83, 29.6, 26.6, 22.7, 16.3, 14.4, 14.1; LC-HRMS: t_R = 1.71 min, [M+H]/z = 486.2314, found = 486.2315.

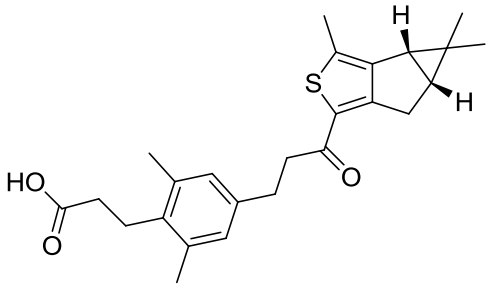
1-((2R/S)-3-(2,6-Dimethyl-4-(3-oxo-3-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydro-cyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propyl)phenoxy)-2-hydroxy-propyl)azetidine-3-carboxylic acid (62). Prepared in analogy to **61**; LC-MS: t_R = 0.90 min, $[M+1]^+$ = 512.25; HPLC with chiral stationary phase (ChiralCel OD-H 250x4.6 mm ID, 5 μm; 80% heptane, 20% ethanol containing 0.1% TFA): t_R = 8.1 min, 46%, t_R = 8.9 min, 54%; ^{1}H NMR ($CDCl_3$): δ 6.84 (s, 2 H), 4.64 (s br, 1 H), 4.50 (s br, 2 H), 4.15-3.95 (m, 2 H), 3.86-3.79 (m, 1 H), 3.77-3.70 (m, 1 H), 3.45-3.35 (m, 1 H), 3.30-3.15 (m, 2 H), 3.02-2.84 (m, 7 H), 2.79 (d, *J* = 18.8 Hz, 1 H), 2.37 (s, 3 H), 2.22 (s, 6 H), 1.92-1.85 (m, 2 H), 1.11 (s, 3 H), 0.70 (s, 3 H); LC-HRMS: t_R = 1.07 min, [M+H]/z = 512.2470, found = 512.2476.

N-(3-(2,6-Dimethyl-4-(3-oxo-3-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydro-cyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propyl)phenoxy)propyl)-2-hydroxyacetamide (63). A solution of **54** (18 mg, 0.043 mmol) in DCM (2 mL) was treated with DIPEA (22 mg, 0.171 mmol), TBTU (19 mg, 0.06 mmol) and glycolic acid (5 mg, 0.064 mmol). The mixture was stirred at rt for 1.5 h before it was separated by chromatography on prep. TLC plates with DCM:methanol 9:1 to give the title compound (7 mg, 35%) as a white solid; LC-MS: t_R = 1.01 min, $[M+1]^+$ = 470.07; ^{1}H NMR ($CDCl_3$): δ 6.86 (s, 2 H), 4.12(s, 2 H), 3.84 (t, *J* = 5.7 Hz, 2 H), 3.62

(q, *J* = 6.2 Hz, 2 H), 2.84-3.03 (m, 5 H), 2.80 (d, *J* = 19.1 Hz, 1 H), 2.38 (s, 3 H), 2.24 (s, 6 H), 1.99-2.08 (m, 2 H), 1.86-1.92 (m, 2 H), 1.11 (s, 3 H), 0.71 (s, 3 H); LC-HRMS: t_R = 1.45 min, [M+H]/z = 470.2365, found = 470.2367.

2-(2,6-Dimethyl-4-(3-oxo-3-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydro-cyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propyl)phenoxy)acetic acid (65). A solution of 3-(4-hydroxy-3,5-dimethylphenyl)-1-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propan-1-one (350 mg, 0.988 mmol) in isopropanol (5 mL) and 3 N aq. NaOH (1.5 mL) was treated with bromoacetic acid (274 mg, 1.98 mmol). The dark red reaction mixture was stirred at 70 °C. After 1, 2, 3 and 18 h an additional portion of bromoacetic acid (274 mg, 1.98 mmol) and 3N aq. NaOH (1.5 mL) was added and stirring was continued for 2 h after the last addition. The reaction mixture was diluted with EA, and washed with 1 N aq. HCl. The aq. phase was extracted with EA. The combined organic extracts are dried over $MgSO_4$ and evaporated. The crude product was purified by chromatography on prep. TLC plates with DCM containing 10% of methanol to give **65** (60 mg, 15%) as a pale yellow oil; LC-MS: t_R = 1.07 min, $[M+1]^+$ = 413.23; ^{1}H NMR (H_6-DMSO, solvent suppression): δ 6.86 (s, 2 H), 4.28 (s, 2 H), 2.93-2.96 (m, 1 H), 2.69-2.78 (m, 3 H), 2.33 (s, 3 H), 1.87-2.04 (m, 2 H), 1.07 (s, 3 H), 0.65 (s, 3 H); LC-HRMS: t_R = 2.17 min, [M+H]/z = 413.1786, found = 413.1790.

3-(2,6-Dimethyl-4-(3-oxo-3-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydro-cyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propyl)phenyl)propanoic acid (66).



a) To an ice-cooled solution of 4-hydroxy-3,5-dimethylbenzaldehyde (6.0 g, 40 mmol) in DCM (60 mL) and pyridine (10 mL), trifluoromethanesulfonic acid anhydride (12.4 g, 44 mmol) was added over a period of 20 min. Upon complete addition, the ice bath was removed and the reaction was stirred for further 2 h at rt. The mixture was diluted with EA (200 mL), washed three times with water, dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography on silica gel eluting with heptane:EA 4:1 to give trifluoro-methanesulfonic acid 4-formyl-2,6-dimethyl-phenyl ester (5.9 g, 52%) as a colourless oil; LC-MS: t_R = 1.04 min; ^{1}H NMR ($CDCl_3$): δ 9.97 (s, 1 H), 7.66 (s, 2 H), 2.48 (s, 6 H).

b) To a stirred solution of the above triflate (5.8 g, 20.6 mmol) in dry DMF (75 mL) was sequentially added triethylamine (4.16 g, 41.1 mmol), methyl acrylate (17.7 g, 206 mmol), DPPP (466 mg, 1.13 mmol) and $Pd(OAc)_2$ (231 mg, 1.03 mmol) under nitrogen. The mixture was stirred at 115 °C for 5 h cooled to rt, diluted with diethyl ether (350 mL) and washed twice with 1 N aq. HCl and once with a sat. aq. $NaHCO_3$ solution. The organic extract was dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography on silica gel eluting with heptane:EA 5:1 to give 3-(4-formyl-2,6-dimethyl-phenyl)-acrylic acid methyl ester (3.6 g, 80%) as

a colourless liquid; LC-MS: t_R = 0.96 min; ^{1}H NMR ($CDCl_3$): δ 9.95 (s, 1 H), 7.80 (d, *J* = 16.4 Hz, 1 H), 7.56 (s, 2 H), 6.11 (d, *J* = 16.4 Hz, 1 H), 3.84 (s, 3 H), 2.40 (s, 6 H).

c) A suspension of 3-(4-formyl-2,6-dimethyl-phenyl)-acrylic acid methyl ester (3.6 g, 16.5 mmol) in methanol (70 mL) and 1.25 N aq. NaOH (45 mL) was stirred at rt for 1 h. The methanol was evaporated and the aq. solution was extracted twice with DCM. The aq. layer was acidified with 2 N aq. HCl and extracted twice with EA. The combined organic extracts are dried over $MgSO_4$, filtered and evaporated. The obtained solid was recrystallized from EA (100 mL) to give 3-(4-formyl-2,6-dimethyl-phenyl)-acrylic acid (2.4 g, 71%) as a white solid; LC-MS: t_R = 0.84 min; ^{1}H NMR (D_6-DMSO): δ 12.65 (s br, 1 H), 9.92 (s, 1 H), 7.67 (d, *J* = 16.4 Hz, 1 H), 7.61 (s, 2 H), 6.12 (d, *J* = 16.4 Hz, 1 H), 2.34 (s, 6 H).

d) A solution of **30** (150 mg, 0.681 mmol) and 3-(4-formyl-2,6-dimethyl-phenyl)-acrylic acid (140 mg, 0.681 mmol) in methanolic NaOH (7 mL, 10 g NaOH/100 mL methanol) was stirred at rt for 3 days. The mixture was cooled to 0 °C and then neutralized with 2 N aq. HCl. The mixture was diluted with DCM and washed with water followed by brine. The organic extract was dried over $MgSO_4$, filtered and evaporated. The crude product was purified by prep. HPLC (Grom-Sil 120 ODS-4-HE, 30x75 mm, 10 μm, gradient of acetonitrile in water containing 0.5% HCOOH) to give (E)-3-(2,6-dimethyl-4-((E)-3-oxo-3-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)prop-1-en-1-yl)phenyl)acrylic acid (110 mg, 40%) as a yellow solid; LC-MS: t_R = 1.13 min, $[M+1]^+$ = 407.32 (calcd 407.17); ^{1}H NMR ($CDCl_3$): δ 7.96 (d, *J* = 16.3 Hz, 1 H), 7.67 (d, *J* = 15.5 Hz, 1 H), 7.30 (s, 2 H), 7.20 (d, *J* = 15.5 Hz, 1 H), 6.15 (d, *J* = 16.4 Hz, 1 H), 3.13 (dd, J_1 = 18.8 Hz, J_2 = 6.1 Hz, 1 H), 2.96 (d, *J* = 18.7 Hz, 1 H), 2.43 (s, 3 H), 2.42 (s, 6 H), 1.87-2.03 (m, 2 H), 1.14 (s, 3 H), 0.75 (s, 3 H).

e) To a solution of (E)-3-(2,6-dimethyl-4-((E)-3-oxo-3-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)prop-1-en-1-yl)phenyl)acrylic acid (106 mg, 0.261 mmol) in ethanol (10 mL) and DIPEA (90 μL), Pd/C (50 mg, 10% Pd, moistened with 50% water) was added and the mixture was stirred at rt under 10 bar of H_2 overnight. The catalyst was filtered off and the filtrate was evaporated. The crude product was purified by prep. HPLC (Grom-Sil 120 ODS-4-HE, 30x75 mm, 10 μm, gradient of acetonitrile in water containing 0.5% HCOOH) to give **66** (69 mg, 64%) as a colourless oil; LC-MS: t_R = 1.11 min, $[M+1]^+$ = 411.26; ^{1}H NMR ($CDCl_3$): δ 6.84 (s, 2 H), 3.02-2.83 (m, 7 H), 2.80 (d, *J* = 18.8 Hz, 1 H), 2.53-2.46 (m, 2 H), 2.38 (s, 3 H), 2.32 (s, 6 H), 1.91-1.88 (m, 2 H), 1.11 (s, 3 H), 0.71 (s, 3 H); LC-HRMS: t_R = 2.25 min, [M+H]/z = 411.1994, found = 411.2000.

2-(2,6-Dimethyl-4-(3-oxo-3-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydro-cyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propyl)phenoxy)acetamide (67). A solution of **65** (60 mg, 169 μmol) in DMF (2.5 mL) was treated with TBTU (54 mg, 169 μmol) and Hünig's base (88 mg, 677 μmol). The mixture was stirred at rt for 10 min before 7 N NH_3 in methanol (1 mL) was added. The reaction mixture was stirred at rt for 30 min before it diluted with water and diethyl ether. The organic phase was separated, washed with water, dried over $MgSO_4$, filtered and concentrated. The crude product was purified on prep. TLC plates using DCM:methanol 9:1 to give to give **67** (37 mg, 53%) as a brownish resin; LC-MS: t_R = 1.09 min, $[M+1]^+$ = 412.24;

^{1}H NMR ($CDCl_3$): δ 6.79-6.93 (m, 3 H), 5.77 (s br, 1 H), 4.26 (s, 2 H), 2.84-3.08 (m, 5 H), 2.79 (d, *J* = 18.8 Hz, 1 H), 2.37 (s, 3 H), 2.23 (s, 6 H), 1.84-1.94 (m, 2 H), 1.11 (s, 3 H), 0.70 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ 191.8, 171.5, 156.0, 152.6, 147.2, 137.7, 136.5, 130.3, 129.13, 129.09, 70.3, 42.1, 36.1, 29.9, 29.8, 29.6, 26.6, 22.7, 16.3, 14.4, 14.1; LC-HRMS: t_R = 1.45 min, [M+H]/z = 412.1946, found = 412.1946.

2-(2,6-Dimethyl-4-(3-oxo-3-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydro-cyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propyl)phenoxy)-N-methyl-acetamide (68). Prepared in analogy to **67** using methylamine, LC-MS: t_R = 1.15 min, $[M+1]^+$ = 426.30; ^{1}H NMR (H_6-DMSO; solvent suppression): δ 8.10 (s br, 1 H), 6.90 (s, 2 H), 4.12 (s, 2 H), 3.00-3.02 (m, 1 H), 2.99 (s, 3 H), 2.68-2.81 (m, 1 H), 2.34 (s, 3 H), 2.18 (s, 6 H), 1.89-2.02 (m, 2 H), 1.10 (s, 3 H), 0.68 (s, 3 H); LC-HRMS: t_R = 1.50 min, [M+H]/z = 426.2103, found = 426.2109.

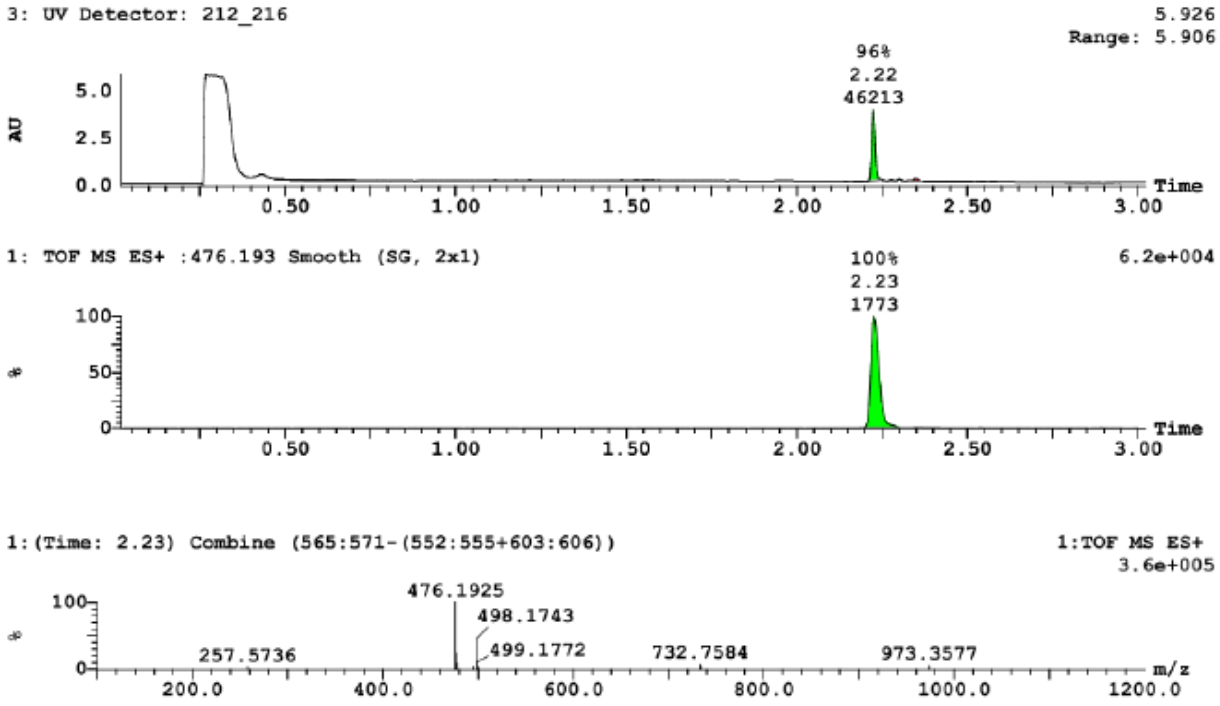
2-(2,6-Dimethyl-4-(3-oxo-3-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydro-cyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propyl)phenoxy)-N-(2-hydroxy-ethyl)acetamide (69). Prepared in analogy to **67** using ethanolamine; LC-MS: t_R = 1.06 min, $[M+1]^+$ = 456.32; ^{1}H NMR (H_6-DMSO, solvent suppression): δ 8.01 (s br, 1 H), 6.88 (s, 2 H), 4.79 (t br, *J* = 4.7 Hz, 1 H), 4.14 (s, 2 H), 3.22-3.30 (m, 2 H), 2.71-2.80 (m, 2 H), 2.33 (s, 3 H), 2.17 (s, 6 H), 1.88-2.04 (m, 2 H), 1.08 (s, 3 H), 0.66 (s, 3 H); LC-HRMS: t_R = 1.41 min, [M+H]/z = 456.2208, found = 456.2212.

N-(2-(2,6-Dimethyl-4-(3-oxo-3-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydro-cyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)propyl)phenoxy)ethyl)methane-sulfonamide (70). A solution of **50** (100 mg, 252 μmol) and Hünig's base (52 mg, 402 μmol) in DCM (2 mL) was treated with methane sulfonylchloride (35 mg, 302 μmol) and the reaction mixture was stirred at rt for 30 min. The mixture was diluted with EA, washed with 10% aq. citric acid and water, dried over $MgSO_4$, filtered and concentrated. The crude product was purified on prep. TLC plates using heptane:EA 1:1 to give **70** (41 mg, 34%) as a pale yellow oil; LC-MS: t_R = 1.07 min, $[M+1]^+$ = 476.04; ^{1}H NMR ($CDCl_3$): δ 6.87 (s, 2 H), 4.84 (t br, *J* = 5.9 Hz, 1 H), 3.88 (t, *J* = 4.8 Hz, 2 H), 3.51-3.56 (m, 2 H), 3.05 (s, 3 H), 2.84-3.03 (m, 5 H), 2.80 (d, *J* = 18.8 Hz, 1 H), 2.38 (s, 3 H), 2.25 (s, 6 H), 1.85-1.93 (m, 2 H), 1.12 (s, 3 H), 0.71 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ 191.8, 156.0, 153.2, 147.2, 137.2, 136.5, 130.5, 129.2, 129.0, 70.5, 43.7, 42.2, 40.7, 36.1, 29.9, 29.8, 29.6, 26.6, 22.7, 16.4, 14.4, 14.1; LC-HRMS: t_R = 2.22 min, [M+H]/z = 476.1929, found = 476.1925.

HR-MS Analysis Report Page 21

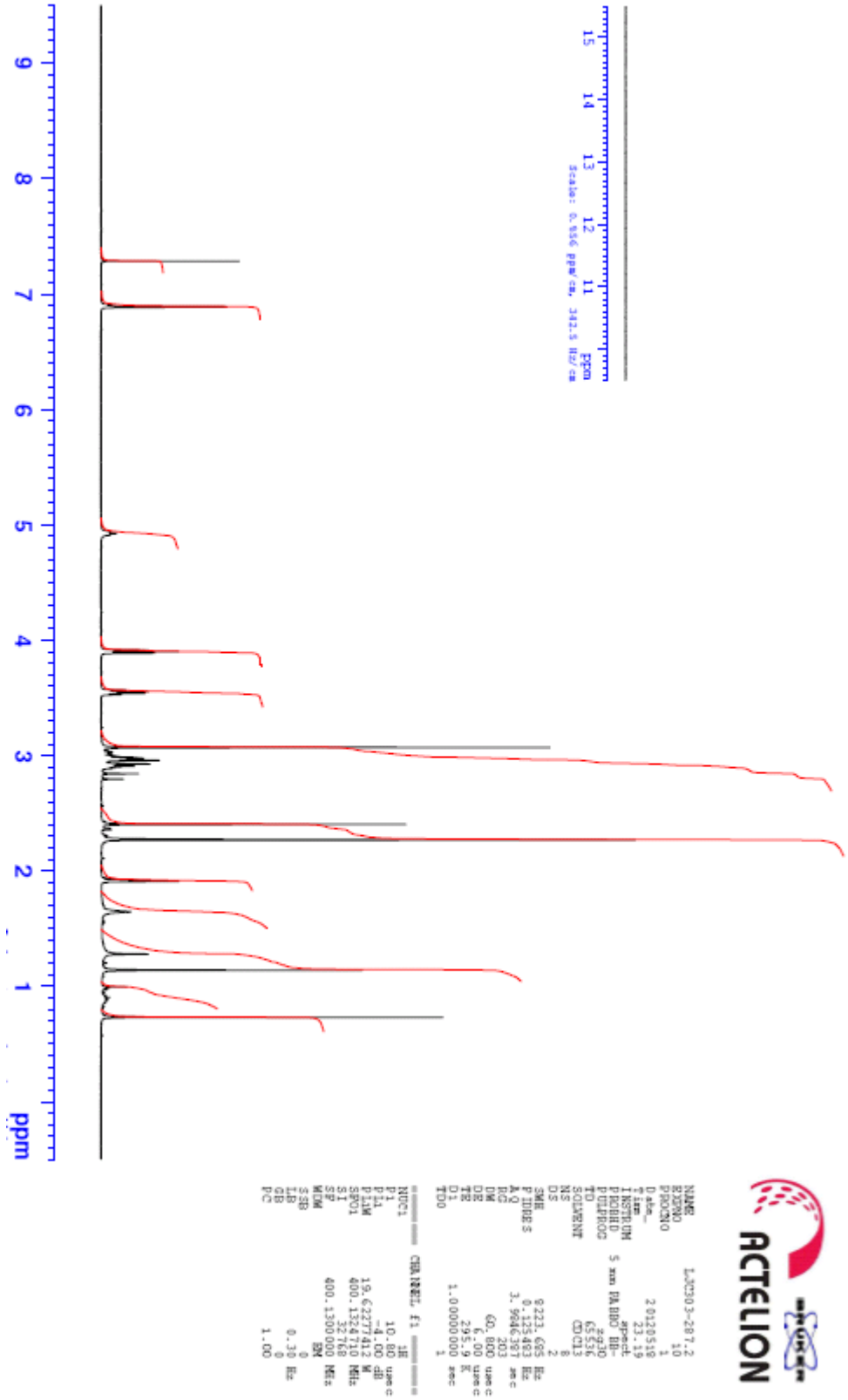
Plate Position:2:38 Actelion No:LJC303-287.2 File:LCMSH96-20120321-1_D02
Date:23-Mar-2012 Time:18:50:15 ELN Nr:ACT-152399
Instrument:SYNAPT-G2#UCA144

Printed: Tue Apr 03 10:30:34 2012



Formula	Calc. Mass	Mass	mDa	PPM	i-FIT (norm)
C19 H32 N4 O8 S	476.1941	476.1925	-1.6	-3.4	1.1
C17 H30 N7 O7 S	476.1927	476.1925	-0.2	-0.4	1.3
C19 H33 N O7 F3 S	476.1930	476.1925	-0.5	-1.0	1.6
C18 H27 N8 O2 F3 S	476.1930	476.1925	-0.5	-1.0	2.5
C20 H30 N4 O5 F2 S	476.1905	476.1925	2.0	4.2	3.1
C17 H31 N4 O6 F3 S	476.1916	476.1925	0.9	1.9	4.0
C20 H29 N5 O3 F3 S	476.1943	476.1925	-1.8	-3.8	4.8
C15 H28 N10 O6 S	476.1914	476.1925	1.1	2.3	4.8
C22 H32 N O6 F2 S	476.1918	476.1925	0.7	1.5	5.9
C20 H33 N4 O4 F S2	476.1927	476.1925	-0.2	-0.4	6.5
C21 H26 N8 O F2 S	476.1918	476.1925	0.7	1.5	6.6
C15 H29 N7 O5 F3 S	476.1903	476.1925	2.2	4.6	7.1
C15 H32 N7 O4 F2 S2	476.1925	476.1925	0.0	0.0	7.4
C14 H31 N7 O8 F S	476.1939	476.1925	-1.4	-2.9	7.5
C17 H34 N4 O5 F2 S2	476.1939	476.1925	-1.4	-2.9	7.5
C19 H37 O8 F S2	476.1914	476.1925	1.1	2.3	7.6
C12 H29 N10 O7 F S	476.1925	476.1925	0.0	0.0	7.8
C18 H31 N7 O3 F S2	476.1914	476.1925	1.1	2.3	7.9
C23 H32 N4 O3 S2	476.1916	476.1925	0.9	1.9	8.0
C21 H29 N8 F S2	476.1941	476.1925	-1.6	-3.4	8.2

LC-MS spectra of compound **70**.



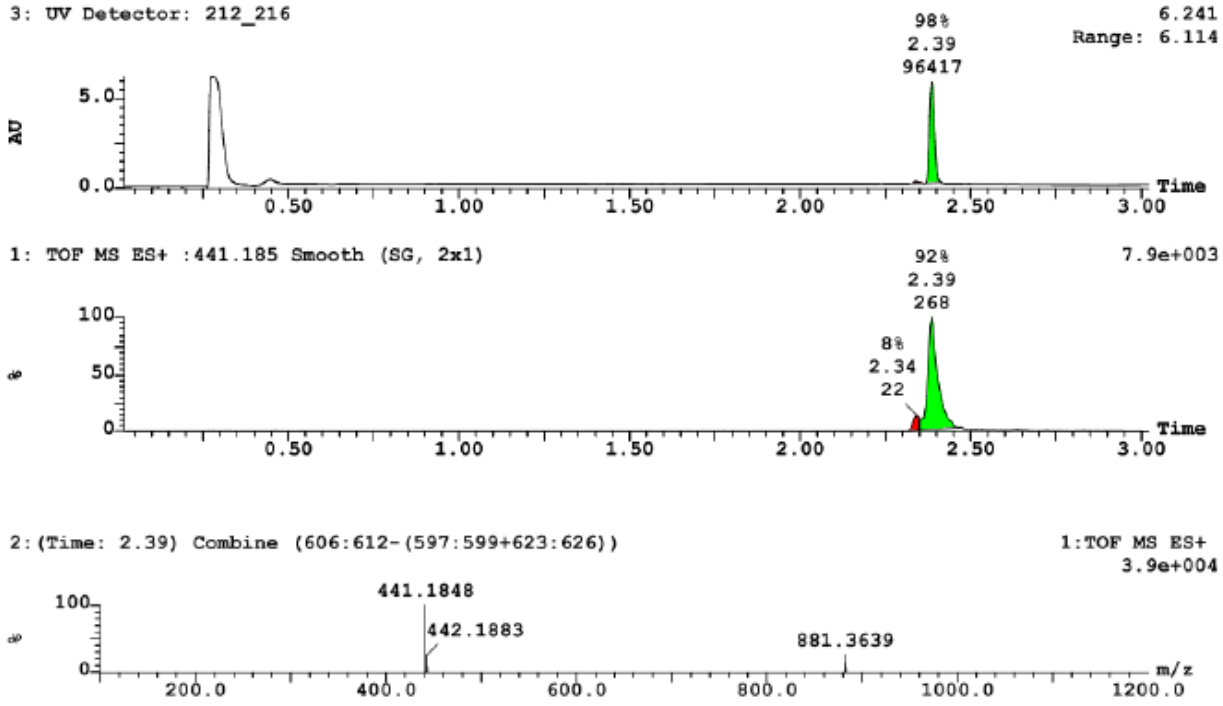
^{1}H NMR spectrum of compound **70**.

LC-MS Spectra of Compound 78

HR-MS Analysis Report Page 2

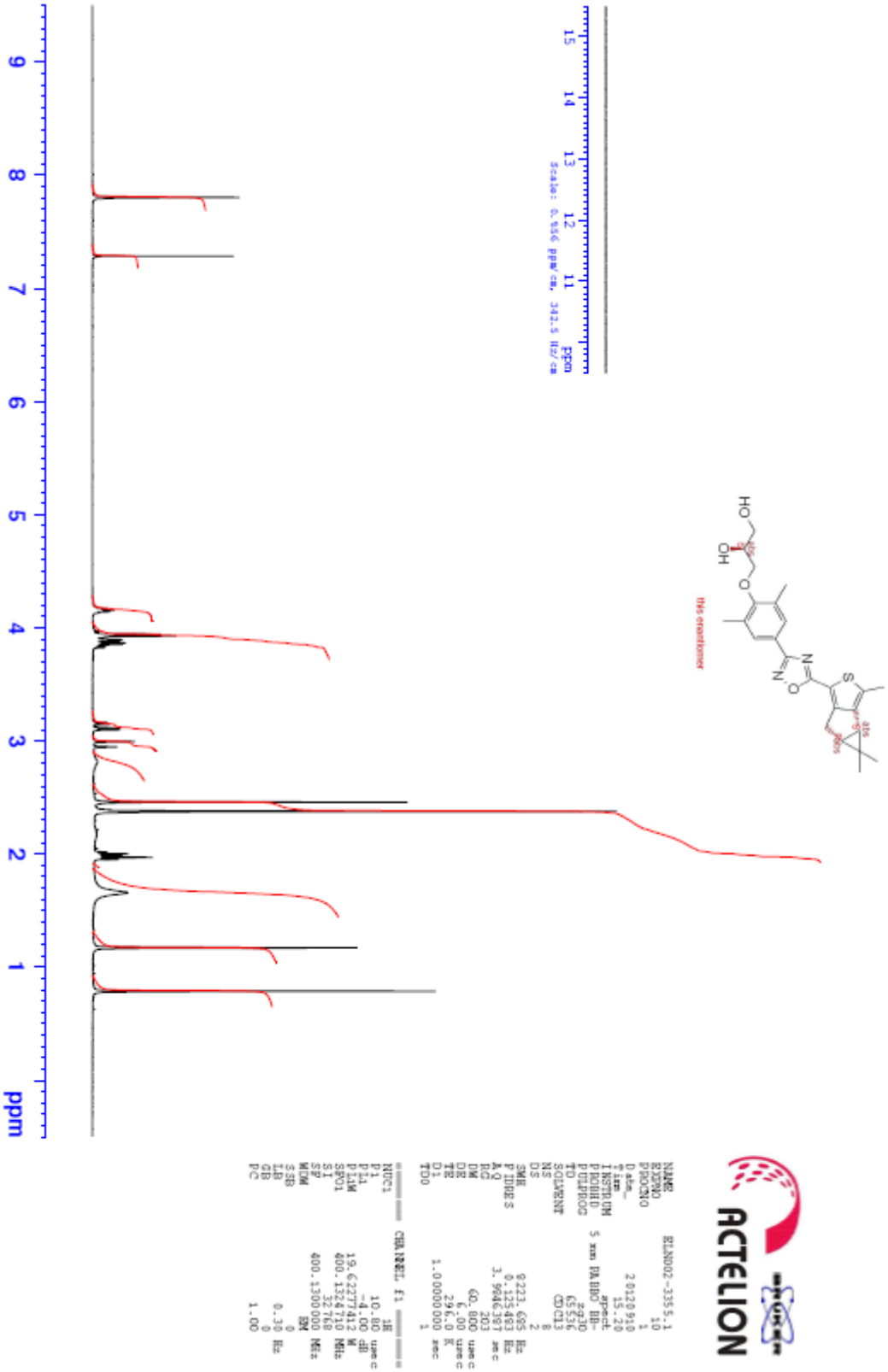
Plate Position:2:13 Actelion No:LJC039-536A01 File:LCMSH96-20120919-1_B01
Date:20-Sep-2012 Time:15:32:09 ELN Nr:ACT-131443
Instrument:SYNAPT-G2#UCA144

Printed: Thu Sep 20 15:59:47 2012

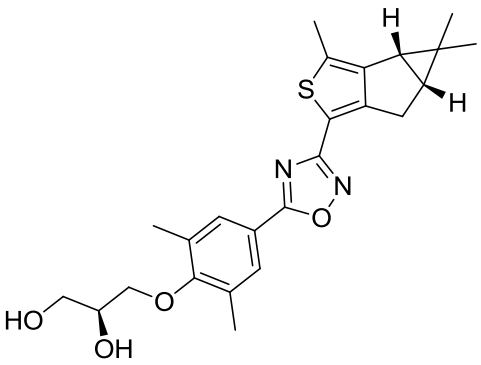


Formula	Calc. Mass	Mass	mDa	PPM	i-FIT (norm)
C14 H27 N8 O4 F2 S	441.1844	441.1848	0.4	0.9	1.0
C24 H29 N2 O4 S	441.1848	441.1848	0.0	0.0	1.0
C22 H31 N2 O F2 S2	441.1846	441.1848	0.2	0.5	2.4
C11 H28 N8 O5 F3 S	441.1855	441.1848	-0.7	-1.6	2.6
C17 H29 N8 O2 S2	441.1855	441.1848	-0.7	-1.6	3.0
C13 H34 N4 O7 F S2	441.1853	441.1848	-0.5	-1.1	4.1
C16 H33 N4 O6 S2	441.1842	441.1848	0.6	1.4	4.6
C8 H29 N10 O9 S	441.1840	441.1848	0.8	1.8	6.4
C16 H25 N8 O7	441.1846	441.1848	0.2	0.5	8.7
C9 H33 N10 O4 S3	441.1848	441.1848	0.0	0.0	9.0
C17 H37 N4 O S4	441.1850	441.1848	-0.2	-0.5	9.1
C18 H28 N2 O7 F3	441.1849	441.1848	-0.1	-0.2	9.1
C22 H23 N6 O2 F2	441.1851	441.1848	-0.3	-0.7	9.1
C27 H26 N4 Cl	441.1846	441.1848	0.2	0.5	9.4
C20 H32 O6 F2 Cl	441.1855	441.1848	-0.7	-1.6	9.7
C23 H31 O5 F Cl	441.1844	441.1848	0.4	0.9	10.0
C14 H25 N10 O F3 Cl	441.1853	441.1848	-0.5	-1.1	10.4
C24 H35 F S2 Cl	441.1853	441.1848	-0.5	-1.1	10.8
C16 H31 N6 O3 F S Cl	441.1851	441.1848	-0.3	-0.7	10.9
C19 H38 O6 Br	441.1852	441.1848	-0.4	-0.9	11.0

^{1}H NMR Spectrum of compound 78



(S)-3-(2,6-Dimethyl-4-(3-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydro-cyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)-1,2,4-oxadiazol-5-yl)phenoxy)-propane-1,2-diol (79).



a) A solution of **14** (997 mg, 5.40 mmol) and thioacetic acid S-cyanomethyl ester (746 mg, 6.48 mmol) in THF (37 mL) was treated with 2 N aq. NaOH (10.8 mL). The resulting mixture was stirred vigorously at rt for 2 h. Another portion of thioacetic acid S-cyanomethyl ester (100 mg, 0.87 mmol) and 2 N aq. NaOH (2 mL) was added and stirring was continued for 1 h. The reaction mixture was diluted with 2 N aq. NaOH and extracted twice with DCM. The organic extracts are dried over Na_2SO_4 and evaporated. The remaining brown oil was dissolved in THF (30 mL) and treated with 2 N aq. NaOH (3 mL). The mixture was heated to 90 °C for 4 h before it was diluted with 2 N aq. NaOH and extracted with DCM. The organic extracts are dried over Na_2SO_4 and evaporated. The crude product was purified by prep. HPLC (Phenomenex Aqua 30x75 mm, gradient 10 to 95% acetonitrile in water containing 0.5% formic acid) to give (3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophene-1-carbonitrile (650 mg, 59%) as a brown oil; LC-MS: t_R = 1.06 min, $[M+1+CH_3CN]^+$ = 245.11 (calcd 245.11); ^{1}H NMR ($CDCl_3$): δ 2.90 (dd, J = 5.9, 18.8 Hz, 1 H), 2.68 (d, J = 18.8 Hz, 1 H), 2.38 (s, 3 H), 1.96-1.88 (m, 2 H), 1.13 (s, 3 H), 0.72 (s, 3 H).
b) To a stirred suspension of K-tert.-butylate (281 mg, 2.5 mmol), hydroxylamine hydrochloride (208 mg, 3.0 mmol) in methanol (4 mL) was added (3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophene-1-carbonitrile (203 mg, 1.0 mmol). The reaction mixture was stirred at rt for 5 h before it was filtered. The filtrate was purified by prep. HPLC (Water XTerrra Prep MS C18 30x75 mm, gradient of acetonitrile in water containing 0.5% sat. aq. NH_3) to give **74** (200 mg, 85%) as a colourless solid; LC-MS: t_R = 0.72 min, $[M+1]^+$ = 237.09 (calcd 237.11); ^{1}H NMR (D_6-DMSO): δ 9.55 (s, 1 H), 5.38 (s br, 2 H), 2.91 (dd, J_1 = 17.9 Hz, J_2 = 6.7 Hz, 1 H), 2.66 (d, J = 17.9 Hz, 1 H), 2.27 (s, 3 H), 1.91-1.84 (m, 2 H), 1.08 (s, 3 H), 0.70 (s, 3 H).

c) To a solution of 3,5-dimethyl-4-hydroxy benzoic acid (508 mg, 3.06 mmol), TBTU (1039 mg, 3.24 mmol), DIPEA (1.57 mL, 9.17 mmol) in DMF (10 mL) was added **74** (759 mg, 3.21 mmol) in DMF (3.5 mL). The resulting suspension was stirred at rt for 2 h. The reaction mixture was diluted with water and extracted with EA. The organic extrac was dried over $MgSO_4$, filtered and concentrated to give the crude hydroxyamidine ester intermediate (309 mg) as a colourless solid; LC-MS: t_R = 1.04 min, $[M+1]^+$ = 385.20 (calcd 385.16).

d) A solution of the above hydroxyamidine ester (309 mg, 0.804 mmol) in dioxane was stirred at 60 °C for 24 h. The solvent was removed under reduced pressure and

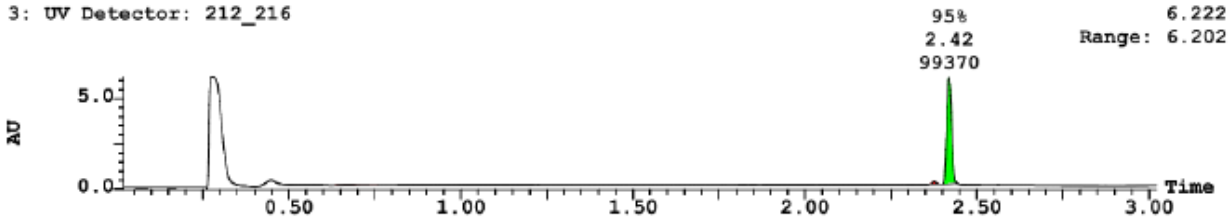
the residue was purified by column chromatography on silica gel eluting with heptane:EA 9:1 to give **75** (121 mg, 41%) as colourless oil; LC-MS: t_R = 1.19 min, $[M+1]^+$ = 367.18 (calcd 367.15); ^{1}H NMR ($CDCl_3$): δ 7.80 (s, 2 H), 5.07 (s, 1 H), 3.06 (dd, *J* = 5.9, 18.8 Hz, 1 H), 2.89 (d, *J* = 18.8 Hz, 1 H), 2.42 (s, 3 H), 2.33 (s, 6 H), 1.98-1.90 (m, 2 H), 1.15 (s, 3 H), 0.78 (s, 3 H).

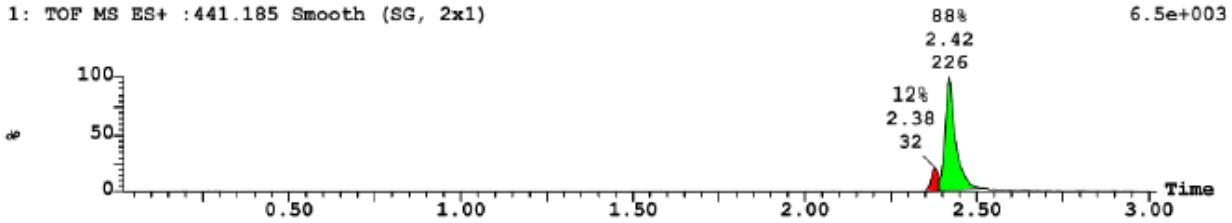
e) Compound **79** (75 mg, 52%) was obtained as a white solid starting from **75** (120 mg, 327 μmol) in analogy to **78**; LC-MS: t_R = 1.02 min, $[M+1]^+$ = 441.05; HPLC with chiral stationary phase (Chiralpak AS-H 250x4.6 mm ID, 5 μm; 95% heptane containing 0.05% DEA, 5 % ethanol containing 0.05% DEA): t_R = 15.6 min, 100%, ((R)-epimer: t_R = 13.2 min); ^{1}H NMR ($CDCl_3$): δ 7.86 (s, 2 H), 4.13-4.21 (m, 1 H), 3.81-3.98 (m, 4 H), 3.07 (dd, J_1 = 18.7 Hz, J_2 = 6.1 Hz, 1 H), 2.91 (d, *J* = 18.6 Hz, 1 H), 2.74 (d, *J* = 4.5 Hz), 2.44 (s, 3 H), 2.40 (s, 6 H), 2.08 (s br, 1 H), 1.93-1.99 (m, 2 H), 1.16 (s, 3 H), 0.79 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ 174.8, 164.9, 158.9, 153.5, 146.4, 131.9, 131.8, 129.1, 120.0, 113.3, 73.3, 70.9, 63.7, 36.5, 30.1, 28.7, 26.7, 22.8, 16.4, 14.6, 13.7; LC-HRMS: t_R = 2.42 min, [M+H]/z = 441.1848, found = 441.1848.

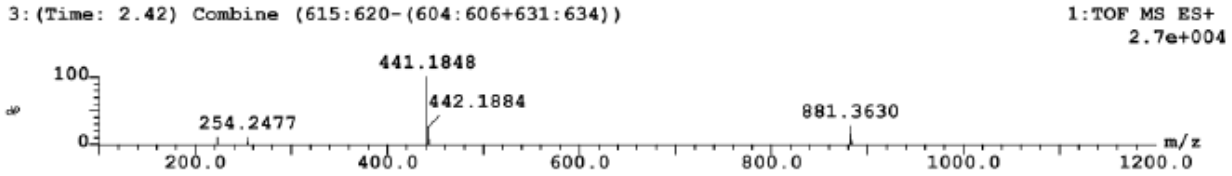
HR-MS Analysis Report Page 1

Plate Position:2:1 Actelion No:LJC039-536B01 File:LCMSH96-20120919-1_A01
Date:20-Sep-2012 Time:15:27:16 ELN Nr:ACT-131444
Instrument:SYNAPT-G2#UCA144

Printed: Thu Sep 20 15:59:47 2012

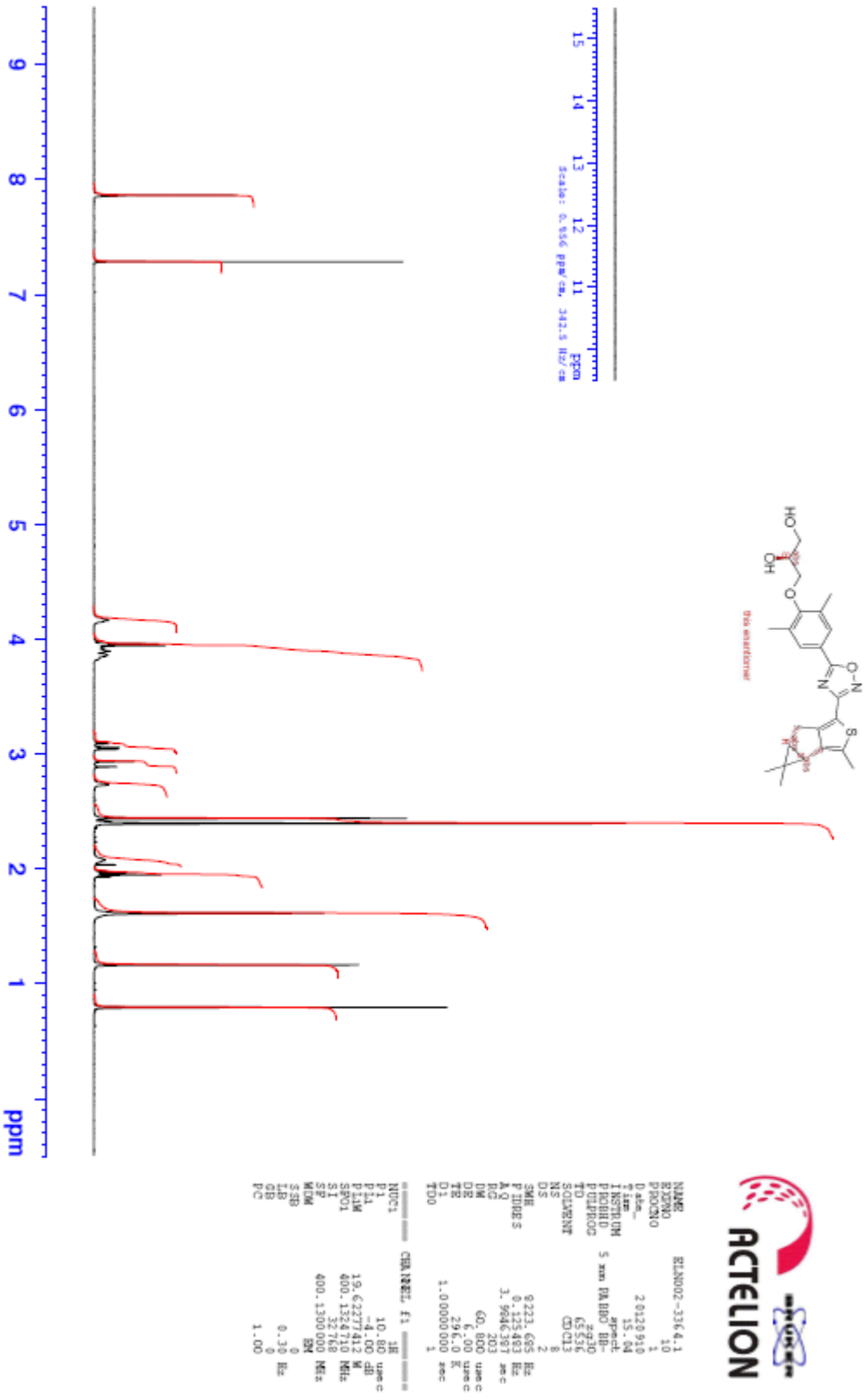






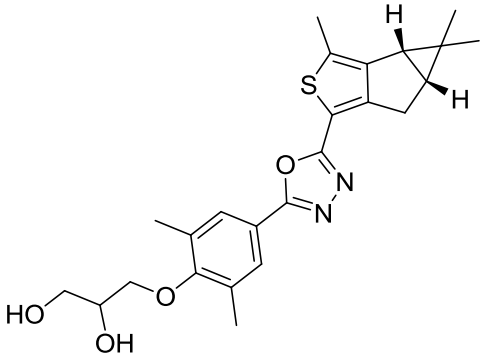
Formula	Calc. Mass	Mass	mDa	PPM	i-FIT (norm)
C24 H29 N2 O4 S	441.1848	441.1848	0.0	0.0	0.0
C14 H27 N8 O4 F2 S	441.1844	441.1848	0.4	0.9	6.3
C11 H28 N8 O5 F3 S	441.1855	441.1848	-0.7	-1.6	8.0
C22 H31 N2 O F2 S2	441.1846	441.1848	0.2	0.5	8.5
C17 H29 N8 O2 S2	441.1855	441.1848	-0.7	-1.6	8.6
C16 H33 N4 O6 S2	441.1842	441.1848	0.6	1.4	9.8
C16 H25 N8 O7	441.1846	441.1848	0.2	0.5	9.9
C13 H34 N4 O7 F S2	441.1853	441.1848	-0.5	-1.1	9.9
C22 H23 N6 O2 F2	441.1851	441.1848	-0.3	-0.7	10.1
C8 H29 N10 O9 S	441.1840	441.1848	0.8	1.8	10.3
C18 H28 N2 O7 F3	441.1849	441.1848	-0.1	-0.2	10.4
C9 H33 N10 O4 S3	441.1848	441.1848	0.0	0.0	13.2
C17 H37 N4 O S4	441.1850	441.1848	-0.2	-0.5	13.8
C27 H26 N4 Cl	441.1846	441.1848	0.2	0.5	14.8
C20 H32 O6 F2 Cl	441.1855	441.1848	-0.7	-1.6	15.0
C23 H31 O5 F Cl	441.1844	441.1848	0.4	0.9	15.2
C14 H25 N10 O F3 Cl	441.1853	441.1848	-0.5	-1.1	15.3
C17 H24 N10 F2 Cl	441.1842	441.1848	0.6	1.4	15.8
C16 H31 N6 O3 F S Cl	441.1851	441.1848	-0.3	-0.7	15.9
C24 H35 F S2 Cl	441.1853	441.1848	-0.5	-1.1	15.9

LC-MS spectra of compound **79**.



^{1}H NMR spectrum of compound **79**.

(2RS)-3-(2,6-Dimethyl-4-(5-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)-1,3,4-oxadiazol-2-yl)phenoxy)propane-1,2-diol (80).



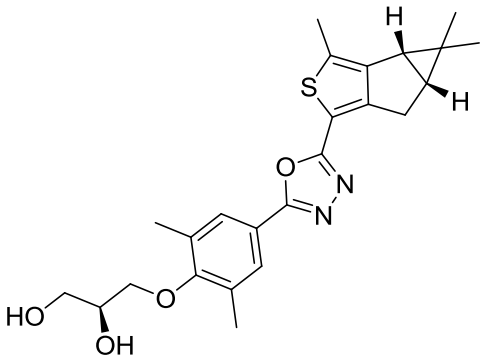
a) To a solution of 4-hydroxy-3,5-dimethyl-benzoic acid (2.49 g, 15.0 mmol) in isopropanol (25 mL) and 3 M aq. NaOH solution (15 mL) allylbromide (9.15 g, 75.7 mmol) was added. The mixture was stirred at rt for 16 h before it was acidified by adding 2 M aq. HCl and extracted with chloroform. The organic extract was dried over Na_2SO_4, filtered and concetrated. The residue was dissolved in THF (40 mL), water (10 mL) and 2 N aq. LiOH (5 mL) and the mixture was stirred at rt for 16 h. The mixture was diluted with 1 M aq. NaOH and extracted with diethyl ether. The aq. phase was acidified using 2 M aq. HCl and extracted with DCM. The second organic extract was dried over Na_2SO_4, filtered and dried to give crude 4-(allyloxy)-3,5-dimethylbenzoic acid (1.21 g, 39%) as a colourless oil. This material (1.21 g, 5.85 mmol) was dissolved in DCM (25 mL) and EDC HCl (2.30 g, 12.0 mmol), HOBt (1.94 g, 14.4 mmol), tert-butyl hydrazinecarboxylate (850 mg, 6.44 mmol) and triethylamine (1.24 g, 12.2 mmol) was added. The mixture was stirred at 0 °C for 18 h before it was diluted with EA and washed with 1 M KH_2SO_4 solution and sat. aq. $NaHCO_3$ solution. The organic extract was concentrated, the obtained residue (1.84 g) was dissolved in dioxane (15 mL) and 4 M HCl in dioxane (50 mL) and the mixture was stirred at rt for 16 h. The resulting suspension was diluted with diethyl ether (20 mL). The precipitate was collected, washed with diethyl ether and dried to give 4-(allyloxy)-3,5-dimethylbenzohydrazide hydrochloride (600 mg, 40%) as a beige solid; LC-MS: t_R = 0.70 min, $[M+1]^+$ = 221.20 (calcd 221.13); ^{1}H NMR (CD_3OD): δ 7.58 (s, 2 H), 6.05-6.20 (m, 1 H), 5.43 (dq, J_d = 17.0 Hz, J_q = 1.6 Hz, 1 H), 5.23-5.29 (m, 1 H), 4.38 (dt, J_d = 5.5 Hz, J_t = 1.4 Hz, 2 H), 2.32 (s, 6 H).

b) A solution of **20** (625 mg, 2.81 mmol), the above hydrazide (600 mg, 2.72 mmol), EDC HCl (632 mg, 3.30 mmol), HOBt (536 mg, 3.97 mmol) and triehylamine (582 mg, 5.75 mmol) in DCM (10 mL) was stirred at 0 °C for 16 h. The mixture was diluted with EA, washed with 1 M aq. $KHSO_4$ solution and sat. aq. $NaHCO_3$ solution. The organic extract was dried over Na_2SO_4, filtered and concentrated. The crude product was purified by CC on silica gel eluting with heptane:EA 1:1 to give (3bS,4aR)-N'-(4-(allyloxy)-3,5-dimethylbenzoyl)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophene-1-carbohydrazide (949 mg, 82%) as pale yellow foam; LC-MS: t_R = 1.05 min, $[M+1]^+$ = 425.30. A solution of part of this material (474 mg, 1.12 mg) and Burgess reagent (400 mg, 1.68 mmol) in THF (2 mL) was heated to 110 °C for 5 min under microwave irradiation. The mixture was diluted with EA, washed with sat. aq. $NaHCO_3$ solution. The organic extract was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by CC on silica gel eluting with heptane:EA 10:1 to give 2-(4-(allyloxy)-3,5-dimethylphenyl)-5-((3bS,4aR)-3,4,4-

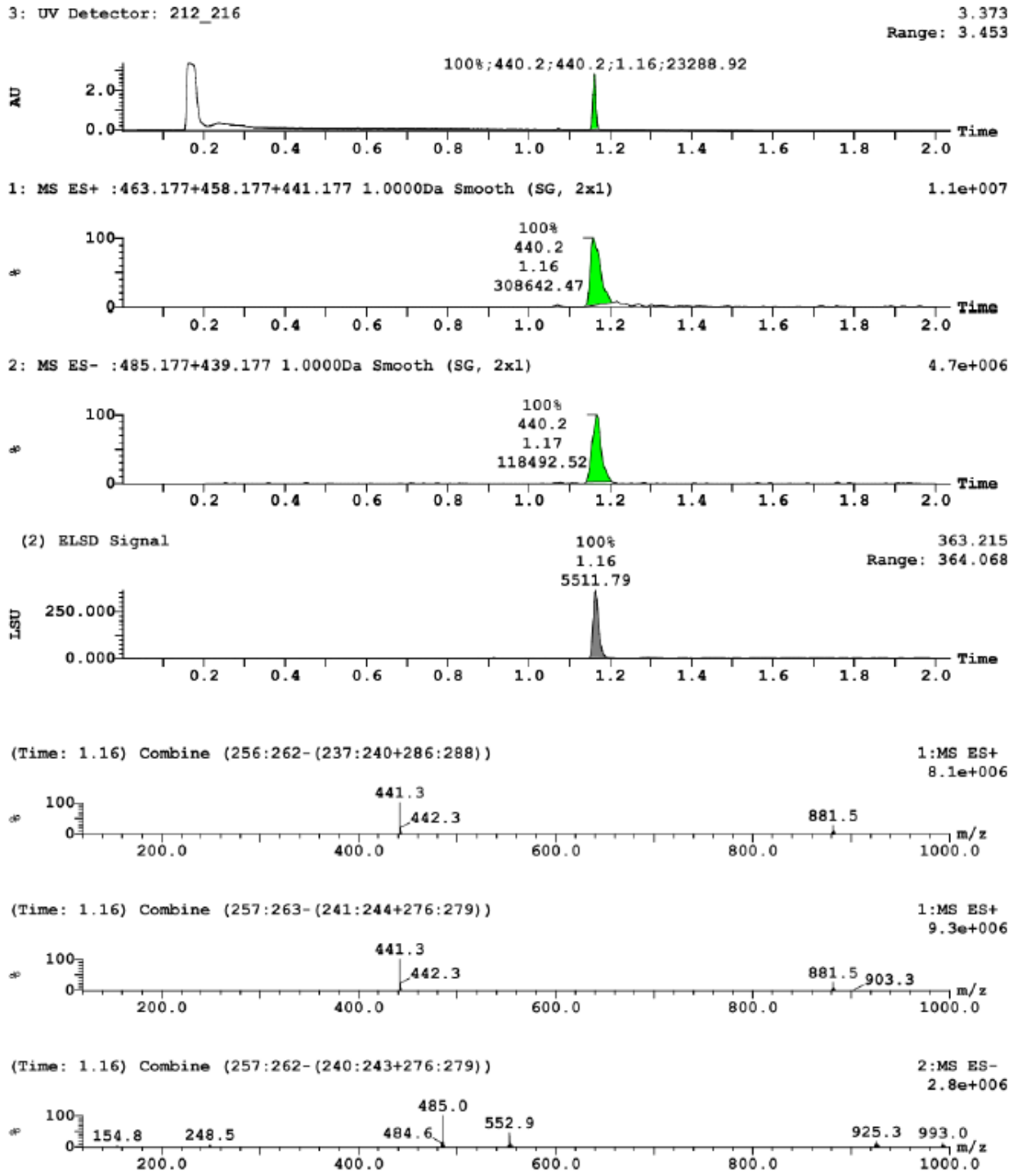
trimethyl-3b,4,4a,5-tetrahydro-cyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)-1,3,4-oxadiazole (316 mg, 70%) as a pale yellow oil; LC-MS: t_R = 1.24 min, $[M+1]^+$ = 407.30 (calcd 407.18); ^{1}H NMR ($CDCl_3$): δ 7.72 (s, 2 H), 6.03-6.20 (m, 1 H), 5.39-5.50 (m, 1 H), 5.25-5.33 (m, 1 H), 4.33-4.40 (m, 2 H), 3.10 (dd, J_1 = 18.7 Hz, J_2 = 6.2 Hz, 1 H), 2.92 (d, J = 18.6 Hz, 1 H), 2.42 (s, 3 H), 2.35 (s, 6 H), 1.91-2.02 (m, 2 H), 1.15 (s, 3 H), 0.77 (s, 3 H).

c) To a solution of the above allyl ether (101 mg, 249 μmol) in acetone (2.5 mL) a solution of N-methylmorpholine N-oxide hydrate (NMO, 38 mg 284 μmol) in water (0.2 mL) followed by OsO_4 (19 mg, 1.8 μmol) was added. The mixture was stirred at rt for 16 h before it was diluted with DCM and washed twice with 1 M aq. $KHSO_4$ solution. The organic extract was dried over Na_2SO_4, filtered and concentrated. The crude product was purified by prep. HPLC to give **80** (42 mg, 38%) as a mixture of epimers in form of a white lyophilisate; LC-MS: t_R = 0.95 min, $[M+1]^+$ = 440.98; HPLC with chiral stationary phase (Chiralpak IC-3 100x4.6 mm ID, 3 μm; 90% heptane containing 0.05% DEA, 10 % ethanol containing 0.05% DEA): t_R = 48.7 min, 52%, t_R = 52.9 min, 48%; ^{1}H NMR ($CDCl_3$): δ 7.74 (s, 2 H), 4.14-4.21 (m, 1 H), 3.89-3.98 (m, 3 H), 3.85 (dd, J_1 = 11.3 Hz, J_2 = 5.5 Hz, 1 H), 3.12 (dd, J_1 = 18.7 Hz, J_2 = 6.5 Hz, 1 H), 2.94 (d, J = 18.7 Hz, 1 H), 2.45 (s, 3 H), 2.39 (s, 6 H), 1.95-2.03 (m, 2 H), 1.17 (s, 3 H), 0.80 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ 163.1, 160.8, 157.9, 154.2, 146.5, 132.9, 131.9, 127.6, 119.8, 110.1, 73.3, 70.9, 63.8, 36.4, 30.1, 28.5, 26.7, 22.9, 16.4, 14.6, 13.8; LC-HRMS: t_R = 2.06 min, [M+H]/z = 441.1848, found = 441.1845.

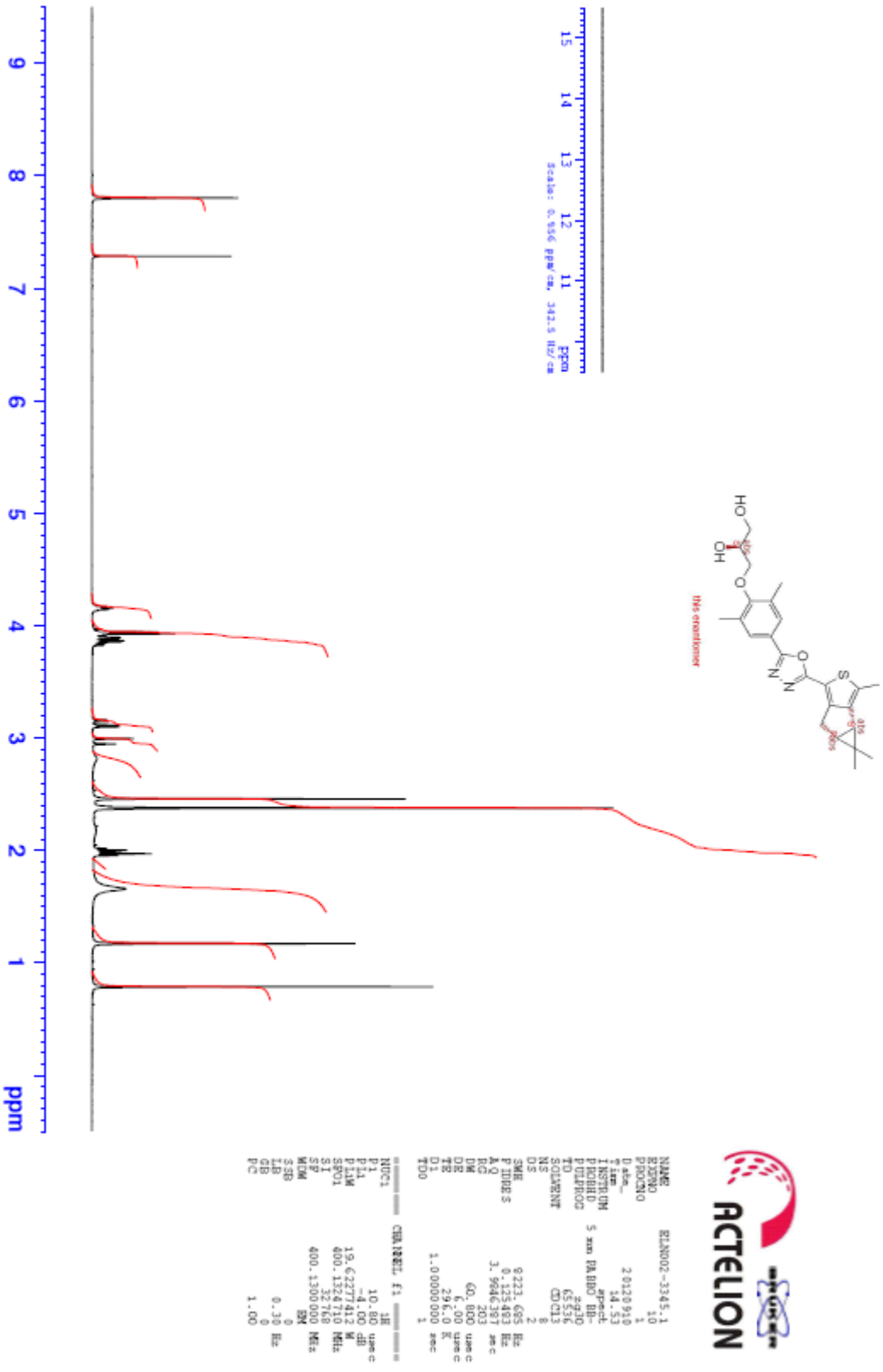
(S)-3-(2,6-Dimethyl-4-(5-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)-1,3,4-oxadiazol-2-yl)phenoxy)propane-1,2-diol ((S)-80).



The title compound was obtained as a white solid in analogy to compound **80**. LC-MS: t_R = 0.95 min, $[M+1]^+$ = 441.06; ^{1}H NMR ($CDCl_3$): δ 7.81 (s, 2 H), 4.12-4.19 (m, 1 H), 3.81-3.96 (m, 4 H), 3.13 (dd, J_1 = 19.0 Hz, J_2 = 6.4 Hz, 1 H), 2.97 (d, J = 19.0 Hz, 1 H), 2.81 (s), 2.46 (s, 3 H), 2.38 (s, 6 H), 1.95-2.03 (m, 2 H), 1.17 (s, 3 H), 0.79 (s, 3 H); LC-HRMS: t_R = 2.10 min, [M+H]/z = 441.1848, found = 441.1843.

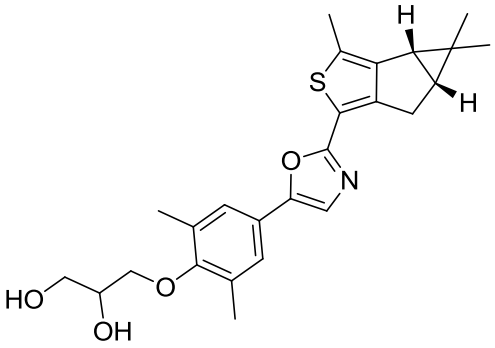


LC-MS spectra of compound (S)-**80**.



^{1}H NMR spectrum of compound (S)-**80**.

(2RS)-3-(2,6-Dimethyl-4-(2-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydro-cyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)oxazol-5-yl)phenoxy)propane-1,2-diol (81).



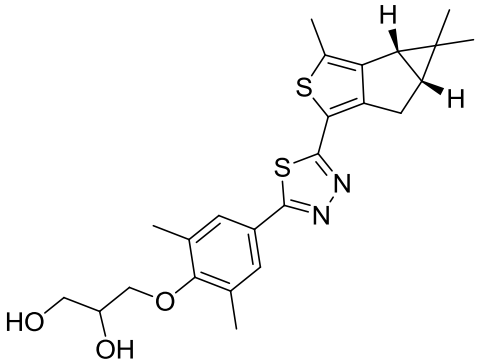
a) To a mixture of 4-bromo-2,6-dimethylphenol (2.01 g, 10.0 mmol) in isopropanol (60 mL) and 3 M aq. NaOH (20 mL) allylbromide (2.99 g, 39.1 mmol) was added slowly. The mixture was stirred at 60 °C for 15 h before it was cooled to rt, diluted with diethyl ether and washed with 1 M aq. NaOH (2x50 mL), 1 M aq. HCl (50 mL) and brine (50 mL). The organic extract was dried over Na_2SO_4, filtered and concentrated to give 2-(allyloxy)-5-bromo-1,3-dimethylbenzene (2.49 g, quant.) as a pale yellow oil sufficiently pure for the next step; LC-MS: t_R = 1.07 min, $[M+1]^+$ = not detectable. To a solution of this material (2.40 g, 9.95 mmol) in THF (60 ml) a solution of n-BuLi (7 mL of a 1.6 M in diethyl ether) was added at -78 °C. The mixture was stirred at -78 °C for 30 min before chloroacetic anhydride (1.70 g, 9.95 mmol) in THF (20 mL) was added slowly. Stirring was continued at -78 °C for 1 h before the reaction was quenched by adding 1 M aq. NaH_2PO_4 solution (50 mL). The mixture was extracted three times with diethyl ether (3x75 mL). The organic extracts are washed with sat. aq. Na_2CO_3 (2x50 mL), combined, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by CC on silica gel eluting with gradient of EA in heptane to give 1-(4-(allyloxy)-3,5-dimethylphenyl)-2-chloroethanone (1.01 g, 43%) as a pale yellow oil; LC-MS: t_R = 1.01 min, $[M+1]^+$ = not detectable; ^{1}H NMR ($CDCl_3$): δ 7.66 (s, 1 H), 7.64 (s, 1 H), 6.01-6.17 (m, 1 H), 5.43 (d, J = 17.1 Hz, 1 H), 5.29 (dd, J_1 = 10.3 Hz, J_2 = 0.7 Hz, 1 H), 4.66 (s, 1 H), 4.40 (s, 1 H), 4.36 (d, J = 5.4 Hz, 2 H), 2.33 (s, 6 H).

b) To a solution of the above 1-(4-(allyloxy)-3,5-dimethylphenyl)-2-chloroethanone (1.01 g, 4.24 mmol) in DMSO NaN_3 (1.50 g, 23.1 mmol) was added. The mixture was stirred at rt for 24 h. The mixture was poured onto sat. aq. NH_4Cl solution (150 mL) and extracted four times with diethyl ether (4x50 mL). The combined organic extracts are washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in THF:water 3:1 (20 mL) and PPh_3 (1.10 g, 4.19 mmol) was added. The mixture was stirred at rt and gas evolution was observed. After 10 min the gas evolution ceased, 1 M aq. HCl (2 mL) was added. and the mixture was extracted with EA (100 mL). The organic phase was extracte with 1 M aq. HCl (5 mL) and water (2x5 mL). The aq. extracts are combined, washed with EA (50 mL), concentrated and dried to give 1-(4-(allyloxy)-3,5-dimethylphenyl)-2-aminoethanone hydrochloride (79 mg, 7%) as a beige solid, LC-MS: t_R = 0.69 min, $[M+1]^+$ = 220.0 (calcd 220.13); ^{1}H NMR (CD_3OD): δ 7.58 (s, 2 H), 5.96-6.11 (m, 1 H), 5.26-5.36 (m, 1 H), 5.16-5.25 (m, 1 H), 4.49 (s, 2 H), 4.29 (d, J = 6.1 Hz, 2 H), 2.16 (s, 6 H).

c) To a solution of the above amino ketone (79 mg, 309 μmol) and **20** (80 mg, 260 μmol) in DCM (10 mL), HOBt (60 mg, 444 μmol), EDC HCl (100 mg, 522 μmol) followed by triethylamine (200 μL) was added. The mixture was stirred at rt for 5 h before it was poured into diethyl ether (100 mL), washed with 1M aq. HCl (2x50 mL) and 1M aq. NaOH (2x50 mL). The organic extract was dried over Na_2SO_4, filtered and concentrated to give crude (3bS,4aR)-N-(2-(4-(allyloxy)-3,5-dimethylphenyl)-2-oxoethyl)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c] thiophene-1-carboxamide (67 mg, 51%), LC-MS: t_R = 1.16 min, $[M+1]^+$ = 424.26. A solution of a part of this material (34 mg, 79 μmol) and Burgess reagent (36 mg, 151 μmol) in THF (0.5 mL) was heated to 110 °C for 5 min under microwave irradiation. The mixture was cooled to rt and separated on prep. TLC plates using heptane:EA 3:1 to give 5-(4-(allyloxy)-3,5-dimethylphenyl)-2-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)oxazole **76** (19 mg, 58%) as pale yellow oil; LC-MS: t_R = 1.25 min, $[M+1]^+$ = 406.26 (calcd 406.18).

d) Starting from the above allyl ether **76** (19 mg, 46 μmol), **81** (3.4 mg, 17%) was obtained as a mixture of epimers in analogy to **80** step c; LC-MS: t_R = 1.06 min, $[M+1]^+$ = 440.29; HPLC with chiral stationary phase (Chiralpak AS-H 250x4.6 mm ID, 5 μm; 90% heptane containing 0.05% DEA, 10 % ethanol containing 0.05% DEA): t_R = 8.0 min, 48%, t_R = 10.1 min, 52%; ^{1}H NMR ($CDCl_3$): δ 7.29 (s, 2 H), 7.25 (s, 1 H), 4.08-4.18 (m, 1 H), 3.76-3.94 (m, 4 H), 3.09 (dd, J_1 = 18.5 Hz, J_2 = 6.2 Hz, 1 H), 2.91 (d, J = 18.5 Hz, 1 H), 2.40 (s, 3 H), 2.34 (s, 6 H), 1.88-2.00 (m, 2 H), 1.14 (s, 3 H), 0.78 (s, 3 H); LC-HRMS: t_R = 2.19 min, [M+H]/z = 440.1895, found = 440.1892.

(2RS)-3-(2,6-Dimethyl-4-(5-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)-1,3,4-thiadiazol-2-yl)phenoxy)propane-1,2-diol (82).



a) A solution of (3bS,4aR)-N'-(4-(allyloxy)-3,5-dimethylbenzoyl)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophene-1-carbohydrazide (474 mg, 1.12 mmol, see **80**) and Lawesson reagent (447 mg 1.10 mmol) in THF (2 mL) was heated to 110 °C for 5 min under microwave irradiation. The mixture was cooled to rt, diluted with EA and washed with sat. aq. Na_2CO_3 solution. The organic extract was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by CC on silica gel eluting with heptane:EA 10:1 to 1:1 to give 2-(4-(allyloxy)-3,5-dimethylphenyl)-5-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydro-cyclopropa[3,4] cyclopenta[1,2-c]thiophen-1-yl)-1,3,4-thiadiazole **73** (468 mg, 99%) as a pale orange oil; LC-MS: t_R = 1.26 min, $[M+1]^+$ = 423.20 (calcd 423.16); ^{1}H NMR ($CDCl_3$): δ 7.62 (s, 2 H), 6.03-6.23 (m, 1 H), 5.44 (dq, J_1 = 17.1 Hz, J_2 = 1.4 Hz, 1 H), 5.24-5.33 (m, 1 H), 4.35 (dt, J_1 = 5.5 Hz, J_2 = 1.4 Hz, 2 H), 2.94 (dd, J_1 = 17.9 Hz, J_2

= 5.5 Hz, 1 H), 2.73 (d, *J* = 18.0 Hz, 1 H), 2.40 (s, 3 H), 2.34 (s, 6 H), 1.91-1.99 (m, 2 H), 1.14 (s, 3 H), 0.77 (s, 3 H).

b) Starting from the above allyl ether **73** (97 mg, 230 μmol), **82** (16 mg, 15%) was obtained as a mixture of epimers in analogy to **80** step c; LC-MS: t_R = 1.06 min, $[M+1]^+$ = 457.40; HPLC with chiral stationary phase (Chiralpak AS-H 250x4.6 mm ID, 5 μm; 90% heptane containing 0.05% DEA, 10 % ethanol containing 0.05% DEA): t_R = 13.3 min, 50%, t_R = 16.9 min, 50%; ^{1}H NMR ($CDCl_3$): δ 7.66 (s, 2 H), 4.13-4.19 (m, 1 H), 3.88-3.97 (m, 3 H), 3.85 (dd, J_1 = 11.3 Hz, J_2 = 5.3 Hz, 1 H), 2.96 (dd, J_1 = 17.8 Hz, J_2 = 5.9 Hz, 1 H), 2.76 (d, *J* = 18.0 Hz, 1 H), 2.43 (s, 3 H), 2.38 (s, 6 H), 1.94-2.02 (m, 2 H), 1.17 (s, 3 H), 0.79 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ 166.3, 161.1, 157.4, 152.5, 146.1, 132.4, 131.8, 128.5, 126.1, 117.9, 73.4, 70.9, 63.8, 36.2, 30.1, 28.5, 26.6, 22.8, 16.4, 14.5, 13.8; LC-HRMS: t_R = 2.20 min, [M+H]/z = 457.1619, found = 457.1617.

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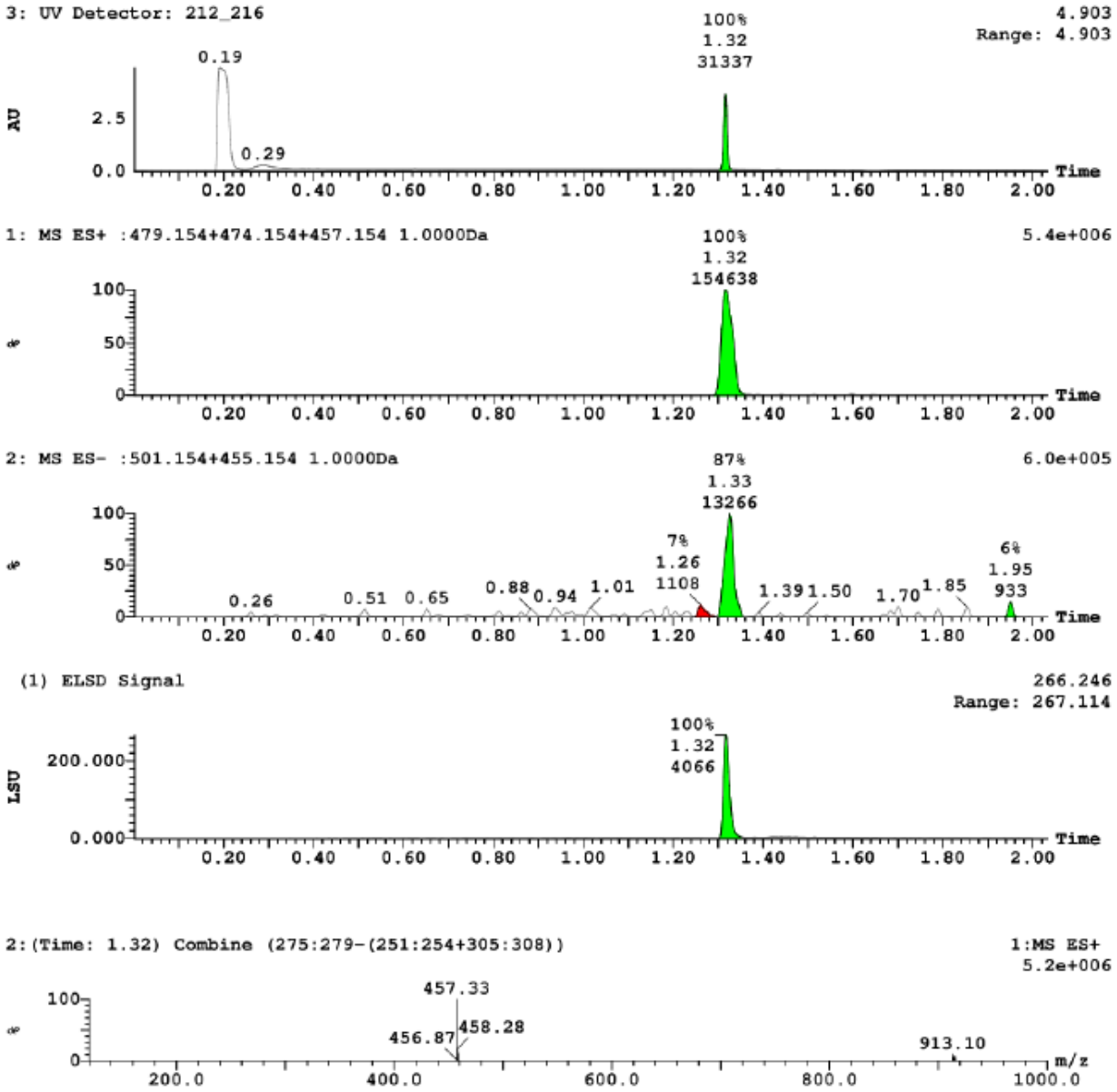
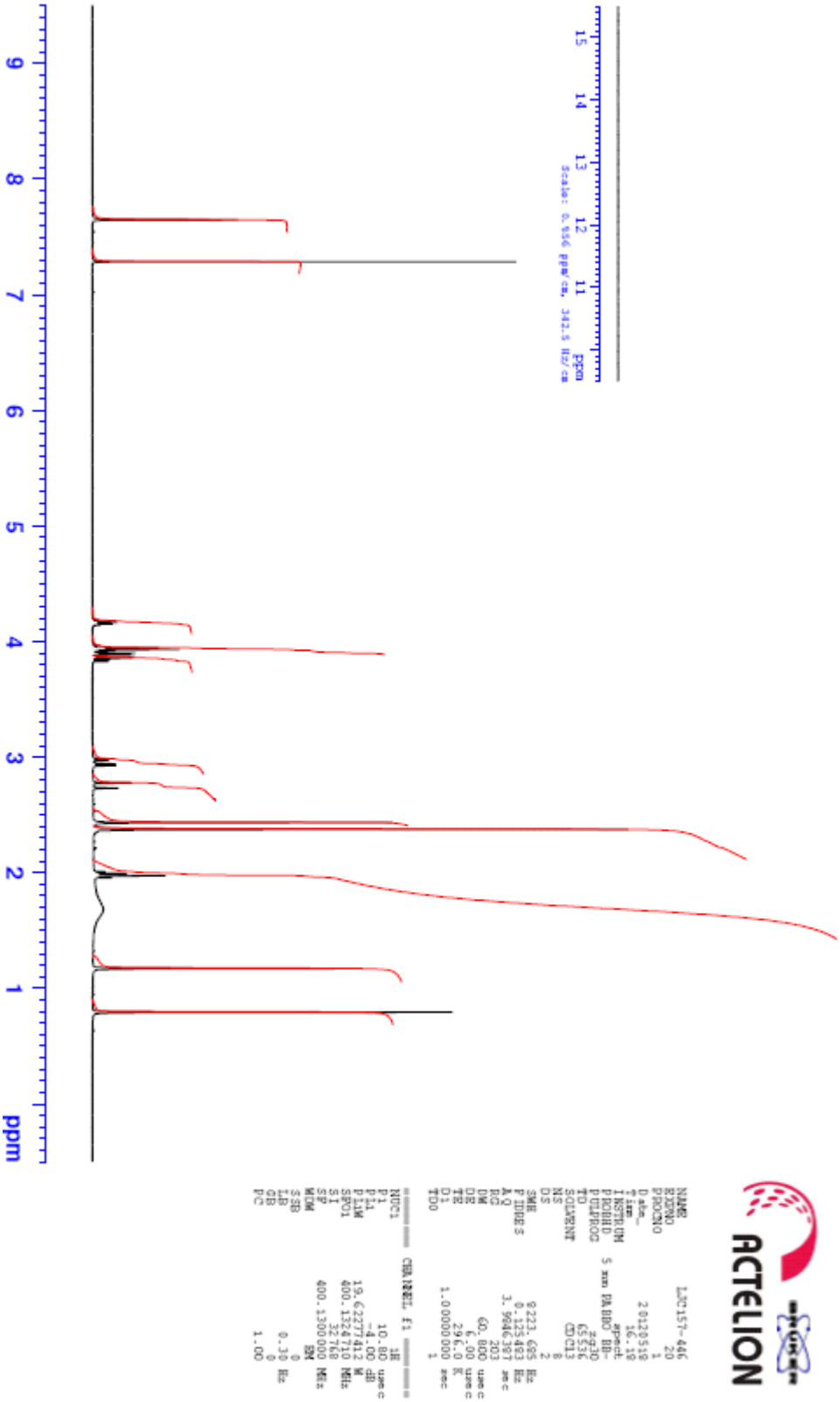
Date:25-Jun-2012 Time:10:16:26 ELN Nr:ACT-152911
Instrument:ACQ-SQD#B09SQD437W

Printed: Mon Jun 25 12:46:21 2012

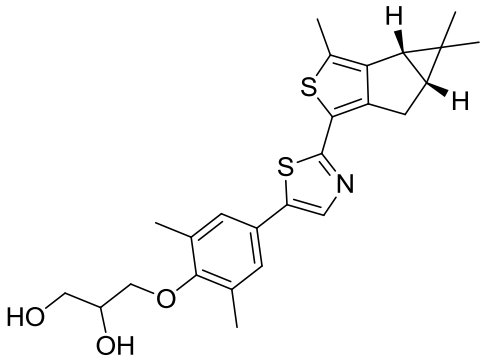


LC-MS spectra of compound **82**.



^{1}H NMR spectrum of compound **82**.

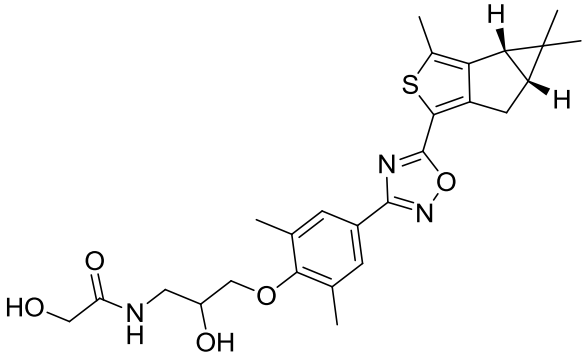
(2RS)-3-(2,6-Dimethyl-4-(2-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)thiazol-5-yl)phenoxy)propane-1,2-diol (83).



a) A solution of (3bS,4aR)-N-(2-(4-(allyloxy)-3,5-dimethylphenyl)-2-oxoethyl)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophene-1-carboxamide (30 mg, 71 μmol, see **81** step b) and Lawesson reagent (50 mg, 124 μmol) in THF (0.5 mL) was heated to 110 °C for 5 min under microwave irradiation. The mixture was cooled to rt and separated on prep. TLC plates using heptane:EA 3:1 to give 5-(4-(allyloxy)-3,5-dimethylphenyl)-2-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)thiazole **77** (12 mg 41%) as a pale yellow oil; LC-MS: t_R = 1.28 min, $[M+1]^+$ = 422.22 (calcd 422.16).

b) Starting from the above allyl ether **77** (12 mg, 29 μmol), **83** (6 mg, 48%) was obtained as a mixture of epimers in analogy to **80** step c; LC-MS: t_R = 1.09 min, $[M+1]^+$ = 456.26; HPLC with chiral stationary phase (Chiralpak AS-H 250x4.6 mm ID, 5 μm; 90% heptane containing 0.05% DEA, 10 % ethanol containing 0.05% DEA): t_R = 8.1 min, 47%, t_R = 10.0 min, 53%; ^{1}H NMR ($CDCl_3$): δ 7.27 (s, 2 H), 7.21 (s, 1 H), 4.07-4.17 (m, 1 H), 3.76-3.96 (m, 4 H), 2.92 (dd, J_1 = 17.6 Hz, J_2 = 6.2 Hz, 1 H), 2.73 (d, J = 17.9 Hz, 1 H), 2.39 (s, 3 H), 2.33 (s, 6 H), 1.89-2.01 (m, 2 H), 1.14 (s, 3 H), 0.77 (s, 3 H); LC-HRMS: t_R = 2.34 min, [M+H]/z = 456.1667, found = 456.1674.

N-(3-(2,6-Dimethyl-4-(5-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)-1,2,4-oxadiazol-3-yl)phenoxy)-(2RS)-2-hydroxypropyl)-2-hydroxyacetamide (84)



To a solution of **71** (486 mg, 1.33 mmol) in isopropanol (50 mL) and 3 N aq. NaOH (15 mL) rac-epichlorohydrin (2.45 g, 26.5 mmol) was added and the resulting mixture was stirred at rt for 16 h. Water and sat. aq. $NaHCO_3$ solution was added and the mixture was extracted with EA. The organic extract was dried over $MgSO_4$, filtered and concentrated to give crude 3-(3,5-dimethyl-4-(oxiran-2-ylmethoxy)phenyl)-5-

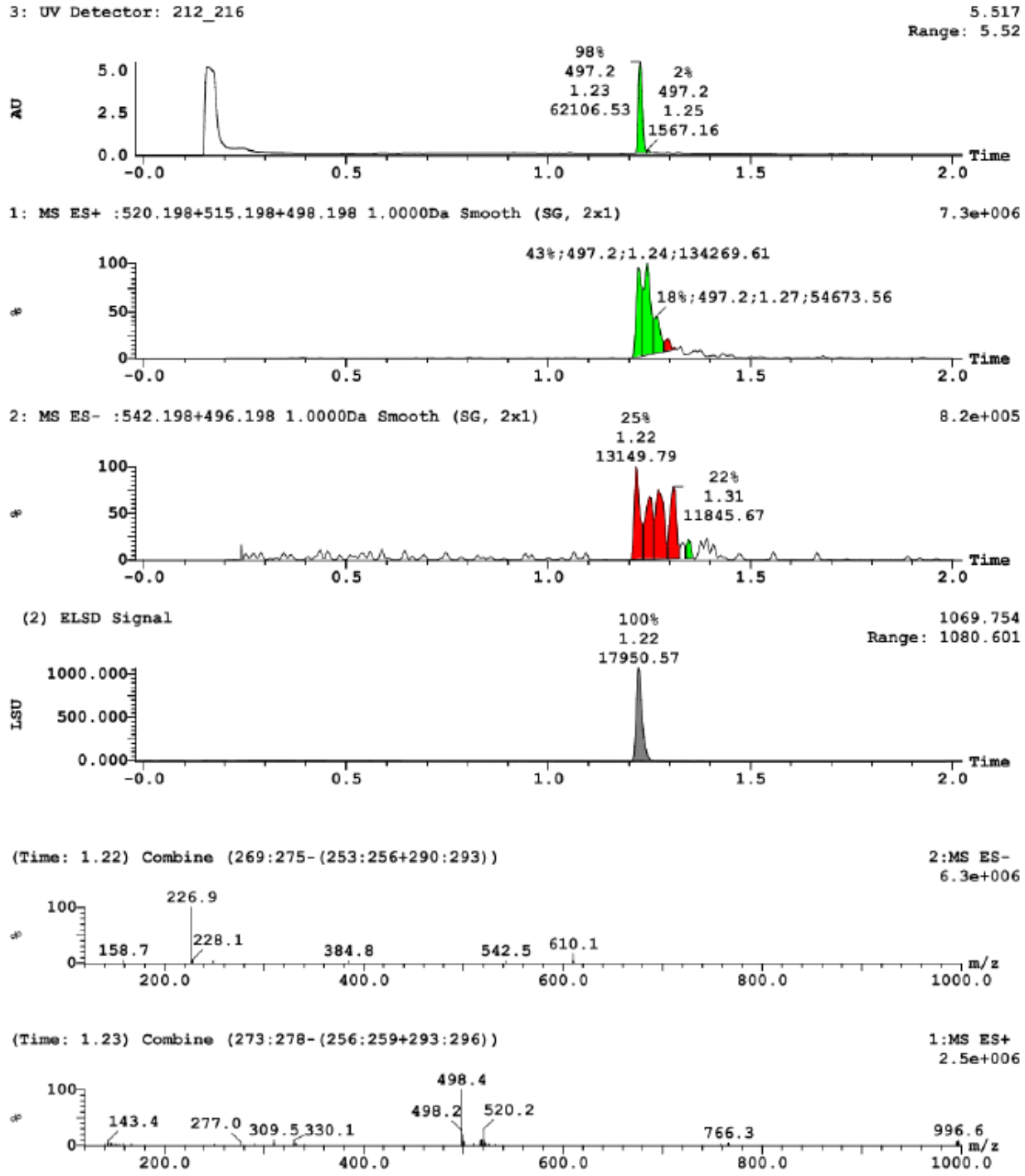
((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)-1,2,4-oxadiazole (905 mg) as an orange oil; LC-MS: t_R = 1.15 min, $[M+1]^+$ = 423.20. This material was dissolved in 7 M NH_3 in methanol (30 mL) and the resulting solution was stirred in a sealed vessel at 45 °C for 16 h. The solvent was removed in vacuo to give crude 1-amino-3-(2,6-dimethyl-4-(5-((3bS,4aR)-3,4,4-trimethyl-3b,4,4a,5-tetrahydro-cyclopropa[3,4]cyclopenta[1,2-c]thiophen-1-yl)-1,2,4-oxadiazol-3-yl)phenoxy)propan-2-ol (893 mg) as a yellow oil; LC-MS: t_R = 0.84 min, $[M+1]^+$ = 440.19. To a solution of this crude material (888 mg) and glycolic acid (128 mg, 1.68 mmol) in DMF (20 mL) and DIPEA (0.35 mL, 2.02 mmol), EDC (387 mg, 2.02 mmol) followed by HOBt (273 mg, 2.02 mmol) were added. The mixture was stirred at rt for 20 min before water and sat. aq. $NaHCO_3$ solution was added. The mixture was extracted twice with EA and the combined organic extracts are dried over $MgSO_4$, filtered and concentrated. The crude product was purified by prep. HPLC. The material obtained was dissolved in methanol (10 mL) and 2 N aq. LiOH (10 mL) and the mixture was stirred at rt for 1 h before it was extracted with EA. The organic extract was dried over $MgSO_4$, filtered and dried to give **84** (48 mg, 7%) as a white solid; LC-MS: t_R = 0.97 min, $[M+1]^+$ = 497.83; ^{1}H NMR ($CDCl_3$): δ 7.80 (s, 2 H), 7.02 (t, J = 6.0 Hz, 1 H), 4.17-4.24 (m, 3 H), 3.89 (dd, J_1 = 9.6 Hz, J_2 = 4.6 Hz, 1 H), 3.75-3.86 (m, 2 H), 3.48-3.57 (m, 1 H), 3.13 (dd, J_1 = 19.1 Hz, J_2 = 6.5 Hz, 1 H), 2.97 (d, J = 19.0 Hz, 1 H), 2.46 (s, 3 H), 2.36 (s, 6 H), 1.94-2.02 (m, 2 H), 1.17 (s, 3 H), 0.79 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ 172.6, 171.4, 168.2, 157.4, 156.7, 147.0, 135.2, 131.3, 128.4, 122.8, 111.0, 73.4, 70.3, 62.2, 42.2, 36.4, 30.1, 28.8, 26.6, 22.9, 16.4, 14.5, 13.9; LC-HRMS: t_R = 1.50 min, [M+H]/z = 498.2062, found = 498.2060.

Plate Position:3:49
Date:05-Oct-2011
Instrument:ACQ-SQD#B09SQD437W

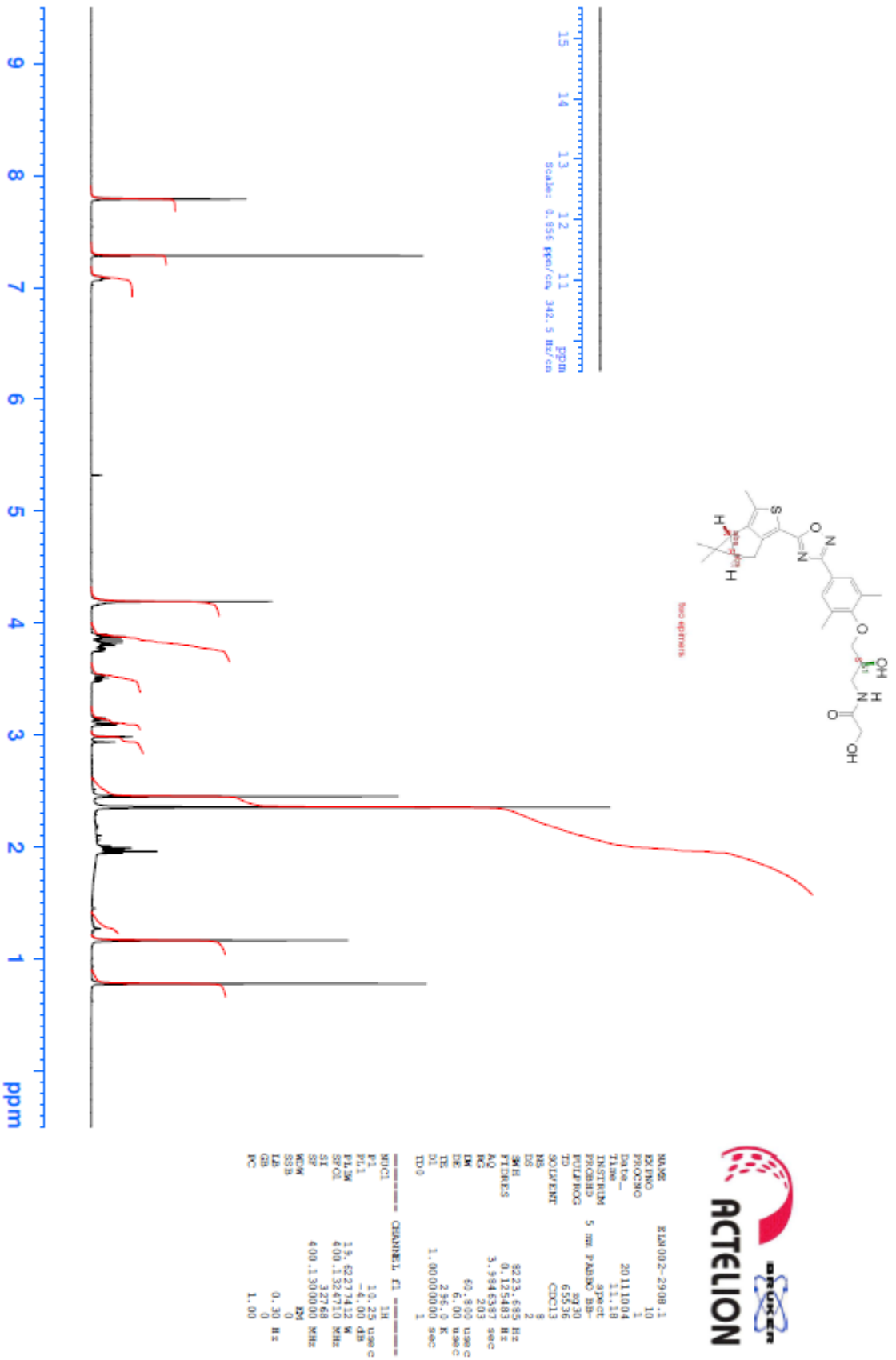
Actelion No:ELN002-2908.1
Time:14:04:52

File:LCMS96-20111005-3_E01
ELN Nr:ACT-542663

Printed: Wed Oct 05 15:45:05 2011



LC-MS spectra of compound **84**.



^{1}H NMR spectrum of compound **84**.

LC-MS Spectra of Compound 85

HR-MS Analysis Report Page 8

Plate Position:2:13 Actelion No:ELN036-0100.2 File:LCMSH96-20120321-1_B01
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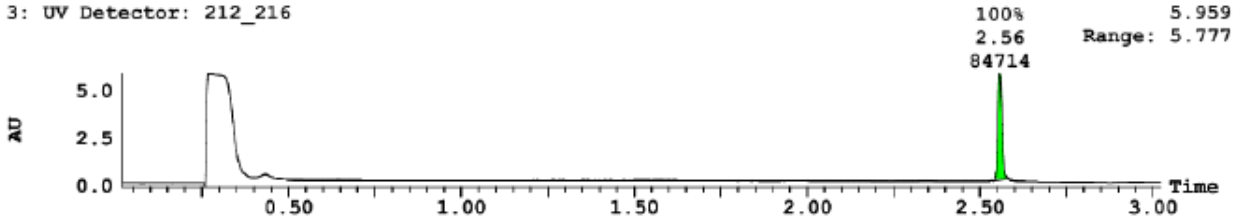
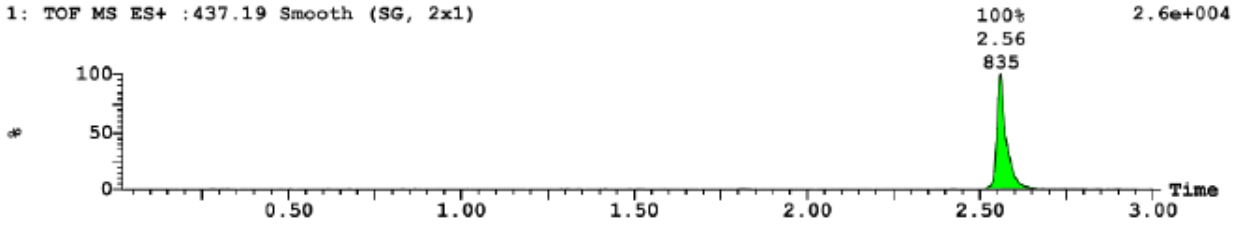
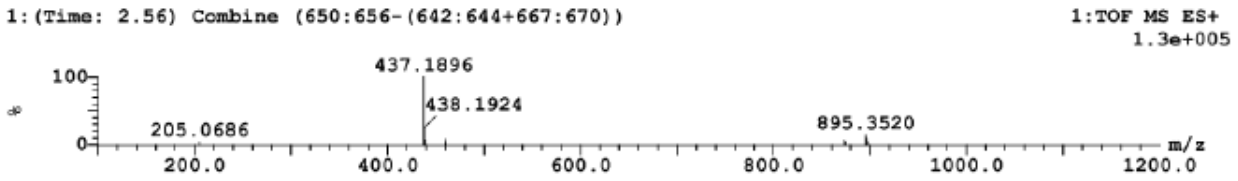
Printed: Tue Apr 03 10:30:34 2012

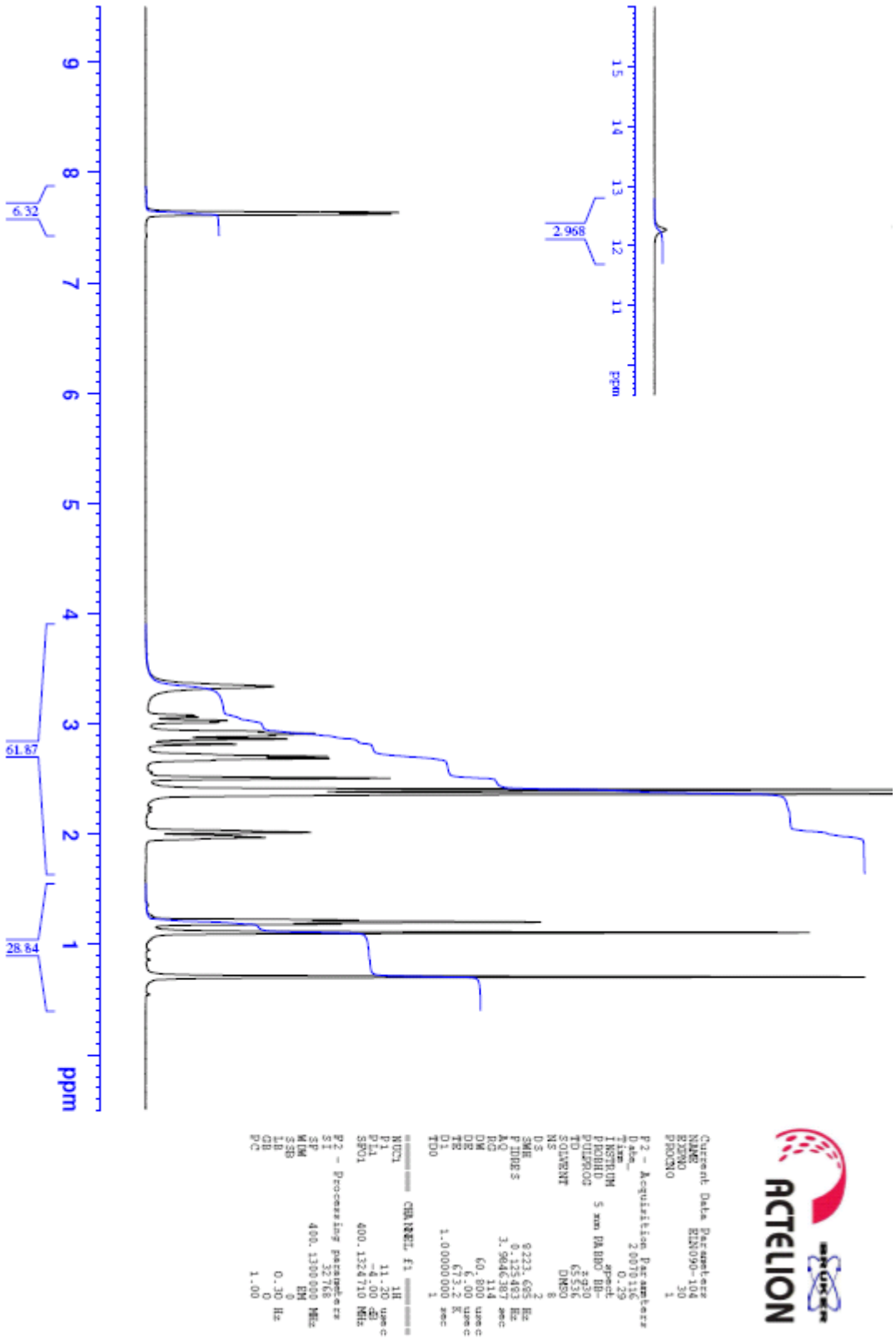




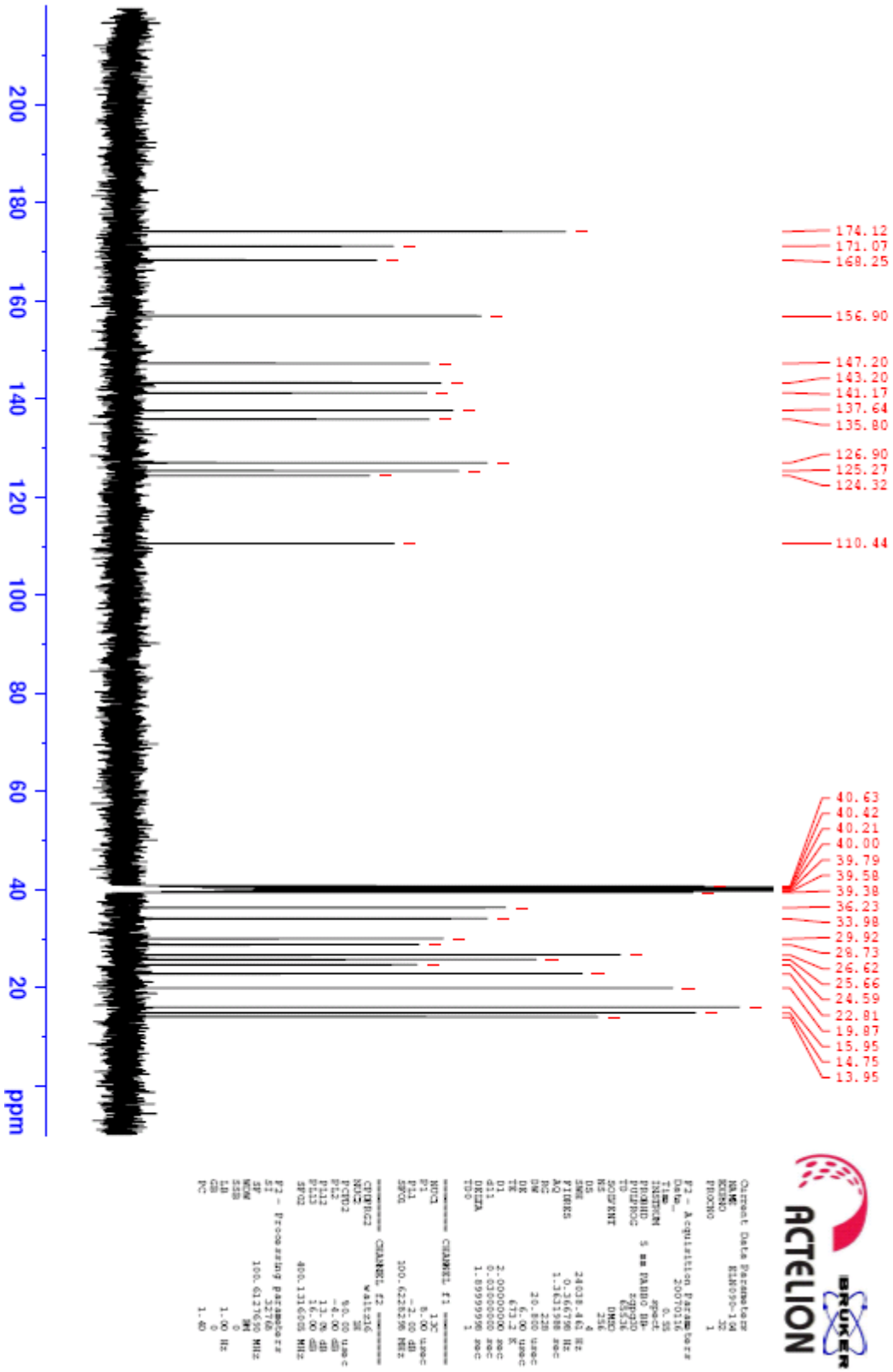


Formula	Calc. Mass	Mass	mDa	PPM	i-FIT (norm)
C20 H28 N5 O3 F S	437.1897	437.1896	-0.1	-0.2	1.2
C18 H26 N8 O2 F S	437.1883	437.1896	1.3	3.0	1.5
C25 H29 N2 O3 S	437.1899	437.1896	-0.3	-0.7	2.0
C22 H30 N2 O4 F S	437.1910	437.1896	-1.4	-3.2	2.1
C17 H29 N5 O4 F2 S	437.1908	437.1896	-1.2	-2.7	2.9
C23 H27 N5 O2 S	437.1885	437.1896	1.1	2.5	3.0
C19 H32 N O7 F S	437.1884	437.1896	1.2	2.7	3.1
C23 H28 N2 O F3 S	437.1874	437.1896	2.2	5.0	3.3
C15 H27 N8 O3 F2 S	437.1895	437.1896	0.1	0.2	4.5
C16 H33 N O8 F2 S	437.1895	437.1896	0.1	0.2	5.0
C13 H33 N4 O10 S	437.1917	437.1896	-2.1	-4.8	6.6
C14 H31 N4 O7 F2 S	437.1882	437.1896	1.4	3.2	6.6
C11 H31 N7 O9 S	437.1904	437.1896	-0.8	-1.8	7.1
C12 H28 N8 O4 F3 S	437.1906	437.1896	-1.0	-2.3	7.3
C19 H27 N5 O7	437.1910	437.1896	-1.4	-3.2	8.0
C22 H27 N2 O5 F2	437.1888	437.1896	0.8	1.8	8.2
C17 H25 N8 O6	437.1897	437.1896	-0.1	-0.2	8.2
C16 H29 N4 O10	437.1884	437.1896	1.2	2.7	8.4
C20 H25 N5 O4 F2	437.1875	437.1896	2.1	4.8	8.5
C9 H29 N10 O8 S	437.1891	437.1896	0.5	1.1	8.5

^{1}H NMR spectrum of compound 85.



^{13}C NMR spectrum of compound 85.



Mean arterial blood pressure and heart rate recordings in male spontaneously hypertensive rats.

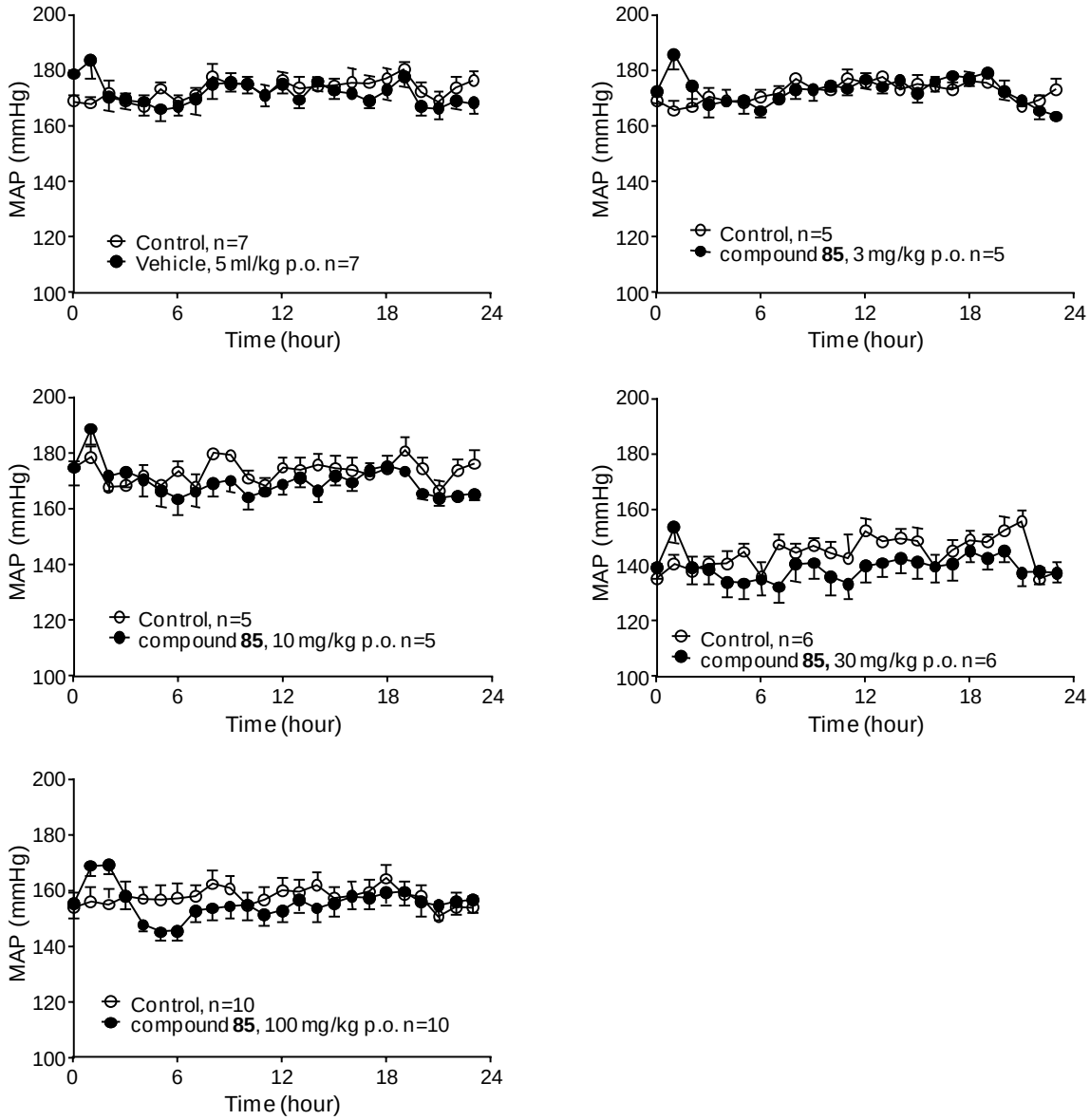


Figure B. Mean arterial pressure (MAP) recordings in telemetrized spontaneously hypertensive rats (SHR) after administration of vehicle, 3, 10, 30 and 100 mg/kg of compound **85**.

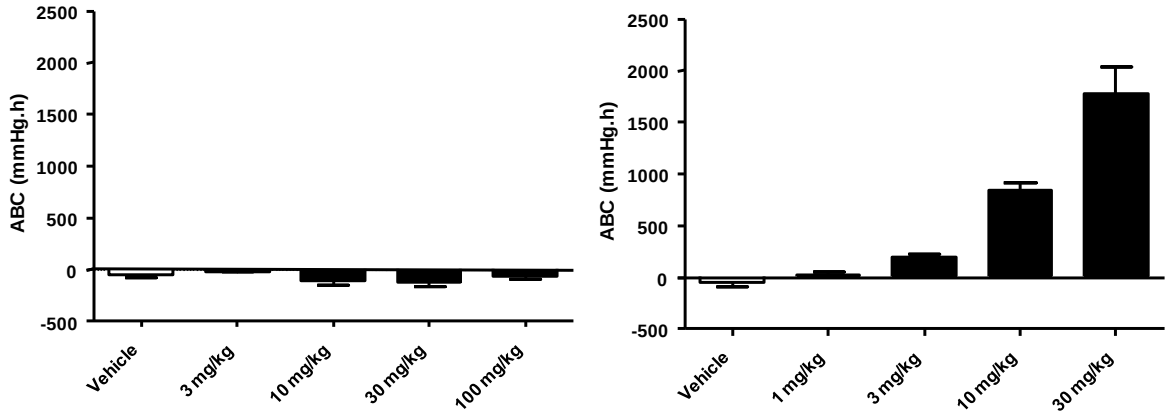


Figure C. Area between curve (ABC) values as calculated from mean arterial pressure (MAP) recordings in telemetrized spontaneously hypertensive rats (SHR) after administration of vehicle and 3, 10, 30 and 100 mg/kg of compound **85** (left) and 1, 3, 10, and 30 mg/kg of **1** (right).

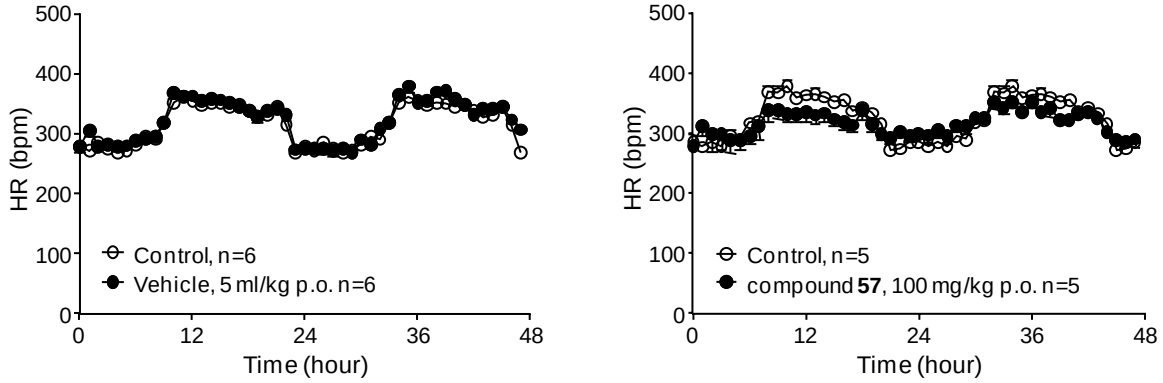


Figure D. Heart rate (HR) recordings in telemetrized male spontaneously hypertensive rats (SHR) after administration of vehicle (left) and 100 mg/kg of compound **57** (IC_{50} (GTPγS) $hS1P_3$ = 7470 nM; $ratS1P_3$ = >10'000 nM).

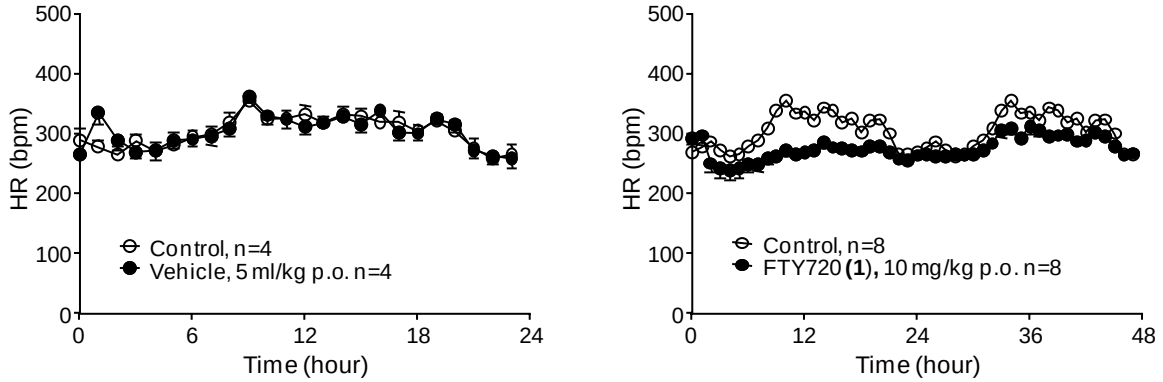


Figure E. Heart rate (HR) recordings in telemetrized spontaneously hypertensive rats (SHR) after administration of vehicle (left) and 10 mg/kg of **1**.

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