SUPPORTING INFORMATION

Discovery of the Potent, Selective, Orally available CXCR7 Antagonist ACT-1004-1239

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Chemistry

This supporting information contains experimental details of the synthesis of target compounds and the corresponding building blocks not described in the main text. More details on the synthesis of some derivatives discussed in this account are described in a patent application[1]. LC-MS and NMR equipment and methods are described in the main text. In case NMR spectra were measured using 1mm Microprobe® tubes, the compounds were dissolved in non-deuterated DMSO. The spectra were then measured with double irradiation for suppression of the DMSO (2.5 ppm) and H_2O (3.5 ppm) peaks. The number of protons given in the description represent observed values. In some cases, signals close to either of the two solvent signals were not visible as they were suppressed by irradiation. In cases where compounds appear as a

mixture of conformational isomers, tautomers or rotamers particularly visible in their LC-MS spectra, the retention time of the most abundant conformer is given.

Characterization of hits 2 to 6

***Rac*-1-p-Tolyl-1H-[1,2,3]triazole-4-carboxylic acid (2-diethylamino-2-thiophen-3-yl-ethyl)-amide (2)** QC LC-MS: t_R = 0.65 min; $[M+H]^+$ =384.3. LC-HRMS: t_R = 0.57 min; m/z = 383.1780, found = 384.1860 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 9.25 (s, 1 H), 8.33 (t, J = 5.0 Hz, 1 H), 7.85 (d, J = 8.0 Hz, 2 H), 7.49 (d, J = 3.7 Hz, 1 H), 7.42 (m, 3 H), 7.13 (d, J = 4.9 Hz, 1 H), 4.20 (t, J = 7.5 Hz, 1 H), 3.64-3.73 (m, 2 H), 2.61-2.70 (m, 2 H), 2.39 (s, 3 H), 2.21 (m, 2 H), 1.01 (m, 6 H).

***Rac*-4-(2,4-Difluoro-phenyl)-N-(2-dimethylamino-2-thiophen-3-yl-ethyl)-4-oxo-butyramide (3)** QC LC-MS: t_R = 0.50 min; $[M+H]^+$ =367.1. LC-HRMS: t_R = 0.50 min; m/z = 366.1214, found = 367.1279 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.88 (s, 1 H), 7.84 (td, J_1 = 9.2 Hz, J_2 = 6.9 Hz, 1 H), 7.50 (dd, J_1 = 4.9 Hz, J_2 = 2.9 Hz, 1 H), 7.40 (dd, J_1 = 2.8 Hz, J_2 = 1.1 Hz, 1 H), 7.30 (ddd, J_1 = 11.7 Hz, J_2 = 9.2 Hz, J_3 = 2.5 Hz, 1 H), 7.16 (td, J_1 = 8.3 Hz, J_2 = 2.3 Hz, 1 H), 7.01 (dd, J_1 = 4.9 Hz, J_2 = 1.2 Hz, 1 H), 3.69 (dd, J_1 = 11.0 Hz, J_2 = 2.3 Hz, 1 H), 3.61 (dd, J_1 = 14.8 Hz, J_2 = 2.8 Hz, 1 H), 3.01 (dd, J_1 = 14.8 Hz, J_2 = 11.1 Hz, 1 H), 2.59-2.66 (m, 1 H), 2.37-2.43 (m, 1 H), 2.18-2.23 (m, 2 H), 1.91 (s, 6 H).

***Rac*-4-(2,4-Difluoro-phenyl)-N-(4-methyl-morpholin-2-ylmethyl)-4-oxo-butyramide (4)** QC LC-MS: t_R = 0.38 min; $[M+H]^+$ =237.2. LC-HRMS: t_R = 0.38 min; m/z = 326.1442, found = 327.1524 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 7.99 (t, J = 5.3 Hz, 1 H), 7.92 (q, J = 7.7 Hz, 1 H), 7.42 (m, 1 H), 7.24 (t, J = 8.5 Hz, 1 H), 3.76 (d, J = 11.2 Hz, 1 H), 3.47 (m, 1 H), 3.41 (m, 1 H), 3.15 (m, 2 H), 3.08 (t, J = 5.8 Hz, 2 H), 2.64 (d, J = 11.2 Hz, 1 H), 2.56 (d,

J = 11.4 Hz, 1 H), 2.47 (m, 2 H), 2.15 (s, 3 H), 1.93 (td, J_1 = 2.3 Hz, J_2 = 11.1 Hz, 1 H), 1.64 (t, J = 10.5 Hz, 1 H) .

1-(2,4-Difluoro-phenyl)-4-[4-(2-dimethylamino-ethyl)-piperazin-1-yl]-butane-1,4-dione (5) QC LC-MS: t_R = 0.68 min; $[M+H]^+$ =354.0. LC-HRMS: t_R = 0.39 min; m/z = 353.1915, found = 354.1999 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 7.92 (q, J = 8.1 Hz, 1 H), 7.42 (t, J = 11.0 Hz, 1 H), 7.24 (t, J = 8.5 Hz, 1 H), 3.47 (m, 2 H), 3.40 (m, 2 H), 3.13 (s, 2 H), 2.69 (t, J = 6.0 Hz, 2 H), 2.38-2.43 (m, 4 H), 2.31-2.36 (m, 4 H), 2.14 (s, 6 H).

5-(4-Bromo-phenyl)-isoxazol-3-yl]-(8-ethyl-1-oxa-4,8-diaza-spiro[4.5]dec-4-yl)-methanone (6) QC LC-MS: t_R = 0.72 min; $[M+H]^+$ =422.3. LC-HRMS: t_R = 0.64 min; m/z = 419.0845, found = 420.0924 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 7.90 (m, 2 H), 7.78 (m, 2 H), 7.45 (s, 1 H), 4.00 (m, 2 H), 3.89 (m, 2 H), 2.79-2.82 (m, 2 H), 2.72 (td, J_1 = 12.9 Hz, J_2 = 4.8 Hz, 2 H), 2.34 (q, J = 7.2 Hz, 2 H), 2.13 (t, J = 10.8 Hz, 2 H), 1.56 (d, J = 11.6 Hz, 2 H), 1.01 (t, J = 7.2 Hz, 3 H).

Preparation of amides 7a-7p

General procedure A:

To a solution of the respective carboxylic acid (commercially available) (0.1 mmol) in 1 mL DMF was added the respective amine (commercially available) (0.11 to 0.15 mmol). DIPEA (0.3 mmol; 0.6 mmol if the amine was a hydrochloride salt) was then added followed by HATU or TBTU (0.11 to 0.15 mmol). The reaction mixture was stirred overnight at rt. The crude mixture was directly purified by prep. LC-MS under basic conditions.

4-(2,4-Difluoro-phenyl)-N-(2-dimethylamino-ethyl)-4-oxo-butyramide (7a). General procedure A from 4-(2,4-difluorophenyl)-4-oxobutanoic acid and 2-(dimethylamino)ethylamine. QC LC-MS: t_R = 0.39 min; $[M+H]^+$ =285.2 . LC-HRMS: t_R = 0.36

min; m/z = 284.1336, found = 285.1415 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.39 (s, 1 H), 7.78 (td, J_1 = 6.9 Hz, J_2 = 9.1 Hz, 1 H), 7.27 (ddd, J_1 = 2.5 Hz, J_2 = 9.2 Hz, J_3 = 11.7 Hz, 1 H), 7.14 (td, J_1 = 2.1 Hz, J_2 = 8.3 Hz, 1 H), 2.53-2.62 (m, 1 H), 2.44-2.49 (m, 2 H), 2.32-2.41 (m, 2 H), 2.19-2.28 (m, 1 H), 2.14-2.17 (m, 1 H), 2.13 (s, 1 H), 2.03 (s, 6 H).

1-p-Tolyl-1H-[1,2,3]triazole-4-carboxylic acid (2-diethylamino-ethyl)-amide (7b). General procedure A from 1-(4-methylphenyl)-1H-1,2,3-triazole-4-carboxylic acid and 2-(diethylamino)ethylamine. QC LC-MS: t_R = 0.52 min; $[M+H]^+$ =302.3 . LC-HRMS: t_R = 0.46 min; m/z = 301.1903, found = 302.1983 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 9.21 (s, 1 H), 8.42 (t, J = 5.6 Hz, 1 H), 7.85 (td, J_1 = 4.2 Hz, J_2 = 2.4 Hz, 2 H), 7.40-7.44 (m, 2 H), 3.33-3.39 (m, 2 H), 2.58 (t, J = 7.0 Hz, 2 H), 2.50-2.55 (m, 4 H), 2.40-2.43 (m, 3 H), 0.98 (t, J = 7.1 Hz, 6 H).

1-(2,4-Difluoro-phenyl)-4-(8-ethyl-1-oxa-4,8-diaza-spiro[4.5]dec-4-yl)-butane-1,4-dione (7c). General procedure A from 4-(2,4-difluorophenyl)-4-oxobutanoic acid and 8-ethyl-1-oxa-4,8-diazaspiro[4.5]decane. QC LC-MS: t_R = 0.52 min; $[M+H]^+$ =367.3. LC-HRMS: t_R = 0.46 min; m/z = 366.1755, found = 367.184 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 7.93 (td, J_1 = 6.7 Hz, J_2 = 8.5 Hz, 1 H), 7.42 (ddd, J_1 = 2.4 Hz, J_2 = 9.4 Hz, J_3 = 11.6 Hz, 1 H), 7.24 (td, J_1 = 2.3 Hz, J_2 = 8.3 Hz, 1 H), 3.95 (t, J = 6.3 Hz, 2 H), 3.65 (t, J = 6.3 Hz, 2 H), 3.10-3.16 (m, 2 H), 2.69-2.74 (m, 2 H), 2.67 (t, J = 6.2 Hz, 2 H), 2.52-2.58 (m, 2 H), 2.28 (q, J = 7.2 Hz, 2 H), 2.01-2.09 (m, 2 H), 1.36 (d, J = 11.8 Hz, 2 H), 0.96 (t, J = 7.1 Hz, 3 H).

(8-Ethyl-1-oxa-4,8-diaza-spiro[4.5]dec-4-yl)-(1-p-tolyl-1H-[1,2,3]triazol-4-yl)-methanone (7d). General procedure A from 1-(4-methylphenyl)-1H-1,2,3-triazole-4-carboxylic acid and 8-ethyl-1-oxa-4,8-diazaspiro[4.5]decane. QC LC-MS: t_R = 0.57 min; $[M+H]^+$ =356.3. LC-HRMS: t_R = 0.53 min; m/z = 355.2008, found = 356.2088 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 9.25 (s, 1 H), 7.86 (d, J = 8.5 Hz, 2 H), 7.42 (d, J = 8.1 Hz, 2 H), 4.14 (t, J = 6.2 Hz,

2 H), 4.03 (t, *J* = 6.0 Hz, 2 H), 2.75-2.87 (m, 4 H), 2.40 (s, 3 H), 2.11-2.23 (m, 2 H), 2.08 (s, 2 H), 1.51-1.60 (m, 2 H), 1.02 (t, *J* = 7.1 Hz, 3 H).

***rac*-1-p-Tolyl-1H-[1,2,3]triazole-4-carboxylic acid (4-methyl-morpholin-2-ylmethyl)-amide (7e).** General procedure A from 1-(4-methylphenyl)-1H-1,2,3-triazole-4-carboxylic acid and (4-methylmorpholin-2-yl)methanamine. LC-MS method B: t_R = 0.73 min; $[M+H]^+$ =316.3. LC-HRMS: t_R = 0.45 min; m/z = 315.1695, found = 316.1771 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 9.23 (m, 1 H), 8.55 (t, *J* = 6.0 Hz, 1 H), 7.82-7.88 (m, 2 H), 7.39-7.45 (m, 2 H), 3.77-3.82 (m, 1 H), 3.60-3.66 (m, 1 H), 3.49 (td, J_1 = 2.4 Hz, J_2 = 11.2 Hz, 1 H), 3.29-3.40 (m, 1H), 2.68-2.72 (m, 1 H), 2.53-2.60 (m, 2 H), 2.40 (s, 3 H), 2.17 (s, 3 H), 1.97 (td, J_1 = 3.3 Hz, J_2 = 11.3 Hz, 1 H), 1.74 (t, *J* = 9.9 Hz, 1H).

1-p-Tolyl-1H-[1,2,3]triazole-4-carboxylic acid diethylcarbamoylmethyl-amide (7f). General procedure A from 1-(4-methylphenyl)-1H-1,2,3-triazole-4-carboxylic acid and 2-amino-N,N-diethyl acetamide hydrochloride. QC LC-MS: t_R = 0.92 min; $[M+H]^+$ =316.3. LC-HRMS: t_R = 0.86 min; m/z = 315.1695, found = 316.1772 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 9.28 (s, 1 H), 8.41 (t, *J* = 5.3 Hz, 1 H), 7.84-7.90 (m, 2 H), 7.42 (d, *J* = 8.1 Hz, 2 H), 4.11-4.17 (m, 2 H), 3.30-3.37 (m, 4 H), 2.40 (s, 3 H), 1.17 (t, *J* = 7.1 Hz, 3 H), 1.00-1.07 (m, 3 H).

***Rac*-1-p-Tolyl-1H-[1,2,3]triazole-4-carboxylic acid (1-ethyl-pyrrolidin-2-ylmethyl)-amide (7g).** General procedure A from 1-(4-methylphenyl)-1H-1,2,3-triazole-4-carboxylic acid and 2-(aminomethyl)-1-ethylpyrrolidine. QC LC-MS: t_R = 0.53min; $[M+H]^+$ =314.3. LC-HRMS: t_R = 0.48 min; m/z = 313.1903, found = 314.1989 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO, water suppression) δ: 9.13 (s, 1 H), 8.39 (t, *J* = 5.8 Hz, 1 H), 7.79 (d, *J* = 8.3 Hz, 2 H), 7.40 (d, *J* = 8.2 Hz, 2 H), 3.09-3.23 (m, 1 H), 2.99-3.07 (m, 1 H), 2.76-2.88 (m, 1 H), 2.57-2.65

(m, 1 H), 2.37 (s, 3 H), 2.19-2.33 (m, 1 H), 2.07-2.18 (m, 1 H), 1.71-1.84 (m, 1 H), 1.51-1.69 (m, 4 H), 1.04 (t, *J* = 7.1 Hz, 3 H).

1-p-Tolyl-1H-[1,2,3]triazole-4-carboxylic acid (3-diethylamino-propyl)-amide (7h). General procedure A from 1-(4-methylphenyl)-1H-1,2,3-triazole-4-carboxylic acid and N,N-diethyl-1,3-propanediamine. QC LC-MS: t_R = 0.54 min; $[M+H]^+$ = 316.3. LC-HRMS: t_R = 0.48 min; m/z = 315.2059, found = 316.2143 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 9.15-9.30 (m, 1 H), 8.78-8.98 (m, 1 H), 7.68-7.93 (m, 2 H), 7.36-7.56 (m, 2 H), 3.30-3.46 (m, 1 H), 2.91-3.18 (m, 6 H), 2.34-2.43 (m, 3 H), 1.79-1.98 (m, 2 H), 1.21-1.25 (m, 1 H), 1.16 (t, *J* = 7.2 Hz, 6 H).

1-(4-Diethylamino-piperidin-1-yl)-4-(2,4-difluoro-phenyl)-butane-1,4-dione (7i). General procedure A from 4-(2,4-difluorophenyl)-4-oxobutanoic acid and 4-diethylamino-piperidine. QC LC-MS: t_R =0.47 min; $[M+H]^+$ = 353.3. LC-HRMS: t_R = 0.43 min; m/z = 352.1962, found = 353.2035 $[M + H]^+$. ^{1}H NMR (500 MHz, DMSO) δ: 7.92 (td, J_1 = 7.0 Hz, J_2 = 8.9 Hz. 1H), 7.42 (ddd, J_1 = 2.6 Hz, J_2 = 9.3 Hz, J_3 = 11.7 Hz, 1H), 7.24 (td, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 4.32-4.39 (m, 1 H), 3.92-3.99 (m, 1 H), 3.07-3.19 (m, 2 H), 2.96-3.04 (m, 1 H), 2.66-2.74 (m, 3 H), 2.45-2.49 (m, 4 H), 1.69-1.75 (m, 1 H), 1.61-1.68 (m, 1 H), 1.31-1.42 (m, 1 H), 1.12-1.23 (m, 1 H), 0.96 (t, J = 7.0 Hz, 6 H).

***rac*-4-(2,4-Difluoro-phenyl)-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-4-oxo-butyramide (7j).** General procedure A from 4-(2,4-difluorophenyl)-4-oxobutanoic acid and 2-(2-aminoethyl)-1-methylpyrrolidine. QC LC-MS: t_R = 0.47 min; $[M+H]^+$ =325.3. LC-HRMS: t_R = 0.41 min; m/z = 325.1727, found = 325.1727 $[M + H]^+$.

***rac*-1-p-Tolyl-1H-[1,2,3]triazole-4-carboxylic acid [2-(1-methyl-pyrrolidin-2-yl)-ethyl]-amide (7k).** General procedure A from 1-(4-methylphenyl)-1H-1,2,3-triazole-4-carboxylic acid and 2-(2-aminoethyl)-1-methylpyrrolidine. QC LC-MS: t_R = 0.52 min; $[M+H]^+$ = 314.3.

LC-HRMS: t_R = 0.47 min; m/z = 313.1903, found = 314.1982 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 9.19 (s, 1 H), 8.71 (t, J = 5.6 Hz, 1 H), 7.85 (d, J = 8.4 Hz, 2 H), 7.42 (d, J = 8.2 Hz, 2 H), 2.92-3.02 (m, 1 H), 2.40 (s, 3 H), 2.23 (s, 3 H), 2.03-2.14 (m, 4 H), 1.83-2.00 (m, 2 H), 1.59-1.69 (m, 2 H), 1.40-1.53 (m, 2 H).

4-(2,4-Difluoro-phenyl)-N-(1-methyl-piperidin-4-yl)-4-oxo-butyramide (7l). General procedure A from 4-(2,4-difluorophenyl)-4-oxobutanoic acid and 4-amino-1-methylpiperidine. QC LC-MS: t_R = 0.40 min; $[M+H]^+$ = 311.2. LC-HRMS: t_R = 0.37 min; m/z = 311.1565, found = 311.1571 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 7.87-7.96 (m, 1 H), 7.80 (d, J = 7.6 Hz, 1 H), 7.42 (ddd, J_1 = 2.4 Hz, J_2 = 9.3 Hz, J_3 = 11.6 Hz, 1 H), 7.23 (td, J_1 = 2.3 Hz, J_2 = 8.3 Hz, 1 H), 3.40-3.52 (m, 1 H), 3.13 (td, J_1 = 2.7 Hz, J_2 = 6.6 Hz, 2 H), 2.65-2.71 (m, 2 H), 2.45 (t, J = 6.6 Hz, 2 H), 2.13 (s, 3 H), 1.85-1.93 (m, 2 H), 1.63-1.70 (m, 2 H), 1.32-1.43 (m, 2 H).

4-(2,4-Difluoro-phenyl)-N-(1-isopropyl-piperidin-4-yl)-4-oxo-butyramide (7m). General procedure A from 4-(2,4-difluorophenyl)-4-oxobutanoic acid and 1-isopropylpiperidin-4-amine dihydrochloride. QC LC-MS: t_R = 0.44 min; $[M+H]^+$ = 339.3. LC-HRMS: t_R = 0.41 min; m/z = 338.1806, found = 339.1886 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 7.92 (td, J_1 = 6.9 Hz, J_2 = 8.7 Hz, 1 H), 7.78 (d, J = 7.7 Hz, 1 H), 7.42 (ddd, J_1 = 2.4 Hz, J_2 = 9.3 Hz, J_3 = 11.6 Hz, 1 H), 7.23 (td, J_1 = 2.3 Hz, J_2 = 8.3 Hz, 1 H), 3.40-3.51 (m, 1 H), 3.13 (td, J_1 = 2.7 Hz, J_2 = 6.6 Hz, 2 H), 2.61-2.75 (m, 3 H), 2.45 (t, J = 6.6 Hz, 2 H), 2.07-2.15 (m, 2 H), 1.64-1.73 (m, 2 H), 1.26-1.38 (m, 2 H), 0.94 (d, J = 6.6 Hz, 6 H).

1-p-Tolyl-1H-[1,2,3]triazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide (7n). General procedure A from 1-(4-methylphenyl)-1H-1,2,3-triazole-4-carboxylic acid and 1-isopropylpiperidin-4-amine dihydrochloride. QC LC-MS: t_R = 0.52 min; $[M+H]^+$ =328.3. LC-HRMS: t_R = 0.48 min; m/z = 327.2059, found = 328.2135 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-

DMSO) δ: 9.21 (s, 1 H), 8.44 (d, J = 8.1 Hz, 1 H), 7.84 (d, J = 8.4 Hz, 2 H), 7.42 (d, J = 8.2 Hz, 2 H), 3.71-3.83 (m, 1 H), 2.76-2.86 (m, 2 H), 2.67-2.76 (m, 1 H), 2.40 (s, 3H), 2.13-2.24 (m, 2 H), 1.73-1.81 (m, 2 H), 1.55-1.68 (m, 2 H), 0.98 (d, J = 6.6 Hz, 6 H).

4-(2,4-Difluoro-phenyl)-N-(1-cyclohexyl-piperidin-4-yl)-4-oxo-butyramide (7o). General procedure A from 4-(2,4-difluorophenyl)-4-oxobutanoic acid and 1-cyclohexylpiperidin-4-ylamine. QC LC-MS: t_R = 0.55 min; $[M+H]^+$ =379.4. LC-HRMS: t_R = 0.50 min; m/z = 378.2119, found = 379.2190 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 7.92 (td, J_1 = 6.8 Hz, J_2 = 8.7 Hz, 1 H), 7.77 (d, J = 7.7 Hz, 1 H), 7.42 (ddd, J_1 = 2.5 Hz, J_2 = 9.4 Hz, J_3 = 11.6 Hz, 1 H), 7.23 (td, J_1 = 2.4 Hz, J_2 = 8.3 Hz, 1 H), 3.39-3.51 (m, 1 H), 3.13 (td, J_1 = 2.7 Hz, J_2 = 6.6 Hz, 2 H), 2.70-2.81 (m, 2 H), 2.45 (t, J = 6.6 Hz, 2 H), 2.13-2.29 (m, 3 H), 1.63-1.80 (m, 6 H), 1.52-1.62 (m, 1 H), 1.26-1.39 (m, 2 H), 1.12-1.26 (m, 4 H), 0.97-1.11 (m, 1 H).

1-*p*-Tolyl-1H-[1,2,3]triazole-4-carboxylic acid (1-cyclohexyl-piperidin-4-yl)-amide (7p). General procedure A from 1-(4-methylphenyl)-1H-1,2,3-triazole-4-carboxylic acid and 1-cyclohexylpiperidin-4-ylamine. QC LC-MS: t_R = 0.62 min; $[M+H]^+$ =368.4. LC-HRMS: t_R = 0.54 min; m/z = 367.2372, found = 368.2445 $[M + H]^+$. ^{1}H NMR (500 MHz, D6-DMSO) δ: 9.20 (d, J = 1.5 Hz, 1 H), 8.42 (d, J = 8.2 Hz, 1 H), 7.84 (d, J = 7.0 Hz, 2 H), 7.41 (d, J = 7.3 Hz, 2 H), 3.69-3.84 (m, 1 H), 2.80-2.87 (m, 2 H), 2.34-2.43 (m, 3 H), 2.17-2.33 (m, 3 H), 1.68-1.90 (m, 6 H), 1.49-1.69 (m, 3 H), 1.12-1.32 (m, 4 H), 1.00-1.13 (m, 1 H).

Preparation of amides 8a-8n

1-Phenyl-1H-[1,2,3]triazole-4-carboxylic acid (1-cyclohexyl-piperidin-4-yl)-amide (8a). General procedure A from 1-phenyl-1H-1,2,3-triazole-4-carboxylic acid and 1-cyclohexylpiperidin-4-ylamine. QC LC-MS: t_R = 0.55 min; $[M+H]^+$ =354.4. LC-HRMS: t_R = 0.49 min; m/z = 353.2216, found = 354.2286 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 9.27 (s, 1 H), 8.46 (d, J = 7.9 Hz, 1 H), 7.97 (d, J = 7.7 Hz, 2 H), 7.59-7.66 (m, 2 H), 7.49-7.57

(m, 1 H), 3.72-3.85 (m, 1 H), 2.79-2.92 (m, 2 H), 2.24-2.35 (m, 3 H), 1.70-1.83 (m, 6 H), 1.52-1.69 (m, 3 H), 1.15-1.28 (m, 4 H), 1.03-1.13 (m, 1 H).

5-(4-Bromo-phenyl)-isoxazole-3-carboxylic acid (1-cyclohexyl-piperidin-4-yl)-amide (8b). General procedure A from 5-(4-bromo-phenyl)isoxazole-3-carboxylic acid and 1-cyclohexylpiperidin-4-ylamine. QC LC-MS: t_R = 0.73 min; $[M+H]^+$ =432.3. LC-HRMS: t_R = 0.64 min; m/z = 431.1208, found = 432.1293 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.69 (d, J = 8.5 Hz, 1H), 7.87-7.91 (m, 2 H), 7.75-7.81 (m, 2 H), 7.41 (s, 1H), 3.66-3.79 (m, 1 H), 2.78-2.87 (m, 2 H), 2.18-2.31 (m, 3 H), 1.67-1.81 (m, 6 H), 1.50-1.63 (m, 3 H), 1.13-1.28 (m, 4 H), 1.00-1.12 (m, 1 H).

N-(1-Cyclohexyl-piperidin-4-yl)-4-oxo-4-phenyl-butyramide (8c). General procedure A from 3-benzoylpropionic acid and 1-cyclohexylpiperidin-4-ylamine. QC LC-MS: t_R = 0.49 min; $[M+H]^+$ =343.4. LC-HRMS: t_R = 0.46 min; m/z = 342.2307, found = 343.2383 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 7.94-8.00 (m, 2 H), 7.75-7.81 (m, 1 H), 7.61-7.67 (m, 1 H), 7.50-7.56 (m, 2 H), 3.40-3.51 (m, 1 H), 3.22 (t, J = 6.7 Hz, 2 H), 2.71-2.80 (m, 2 H), 2.45 (t, J = 6.6 Hz, 2 H), 2.14-2.28 (m, 3 H), 1.63-1.78 (m, 6 H), 1.53-1.61 (m, 1 H), 1.27-1.38 (m, 2 H), 1.12-1.24 (m, 4 H), 1.00-1.11 (m, 1 H).

N-(1-Cyclohexyl-piperidin-4-yl)-4-(4-fluoro-phenyl)-4-oxo-butyramide (8d). General procedure A from 3-(4-fluorobenzoyl)propionic acid and 1-cyclohexylpiperidin-4-ylamine. QC LC-MS: t_R = 0.52 min; $[M+H]^+$ =361.3. LC-HRMS: t_R = 0.48 min; m/z = 360.2213, found = 361.229 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.03-8.08 (m, 2 H), 7.77 (d, J = 7.7 Hz, 1 H), 7.32-7.39 (m, 2 H), 3.40-3.50 (m, 1 H), 3.20 (t, J = 6.6 Hz, 2 H), 2.72-2.79 (m, 2 H), 2.45 (t, J = 6.6 Hz, 2 H), 2.14-2.28 (m, 3 H), 1.65-1.77 (m, 6 H), 1.53-1.60 (m, 1 H), 1.26-1.37 (m, 2 H), 1.12-1.24 (m, 4 H), 0.99-1.11 (m, 1 H).

4-(4-Bromo-phenyl)-N-(1-cyclohexyl-piperidin-4-yl)-4-oxo-butyramide (8e). General procedure A from 4-(4-bromo-phenyl)-4-oxobutyric acid and 1-cyclohexylpiperidin-4-ylamine. QC LC-MS: t_R = 0.63 min; $[M+H]^+$=421.3. LC-HRMS: t_R = 0.56 min; m/z = 420.1412, found = 421.1495 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 7.90 (m, J_1 = 4.3 Hz, J_2 = 2.4 Hz, 2 H), 7.78 (d, J = 7.7 Hz, 1 H), 7.74 (m, J_1 = 4.3 Hz, J_2 = 2.4 Hz, 2 H), 3.39-3.50 (m, 1 H), 3.19 (t, J = 6.6 Hz, 2H), 2.71-2.80 (m, 2 H), 2.45 (t, J = 6.7 Hz, 2H), 2.14-2.28 (m, 3 H), 1.64-1.77 (m, 6 H), 1.52-1.60 (m, 1 H), 1.31 (qd, J_1 = 3.8 Hz, J_2 = 11.6 Hz, 2H), 1.13-1.22 (m, 4 H), 0.99-1.11 (m, 1 H).

4-(4-Chloro-2-fluoro-phenyl)-N-(1-cyclohexyl-piperidin-4-yl)-4-oxo-butyramide (8f). General procedure A from 4-(4-chloro-2-fluorophenyl)-4-oxobutyric acid and 1-cyclohexylpiperidin-4-ylamine. QC LC-MS: t_R = 0.58 min; $[M+H]^+$ =395.2. LC-HRMS: t_R = 0.56 min; m/z = 394.1823, found = 395.1906 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 7.84 (t, J = 8.3 Hz, 1 H), 7.78 (d, J = 7.7 Hz, 1 H), 7.62 (dd, J_1 = 2.0 Hz, J_2 = 11.0 Hz, 1 H), 7.44 (dd, J_1 = 2.0 Hz, J_2 = 8.5 Hz, 1 H), 3.39-3.49 (m, 1 H), 3.13 (td, J_1 = 2.6 Hz, J_2 = 6.6 Hz, 2 H), 2.72-2.78 (m, 2 H), 2.45 (t, J = 6.6 Hz, 2 H), 2.15-2.26 (m, 3 H), 1.64-1.75 (m, 6 H), 1.52-1.60 (m, 1 H), 1.26-1.36 (m, 2 H), 1.13-1.23 (m, 4 H), 1.01-1.10 (m, 1 H).

5-(2,4-Difluoro-phenyl)-isoxazole-3-carboxylic acid (1-cyclohexyl-piperidin-4-yl)-amide (8g). General procedure A from 5-(2,4-difluoro-phenyl)-isoxazole-3-carboxylic acid and 1-cyclohexylpiperidin-4-ylamine. LC-MS method B: t_R = 1.17 min; $[M+H]^+$ =390.4. LC-HRMS: t_R = 0.58 min; m/z = 389.1915, found = 390.1993 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.74 (d, J = 7.9 Hz, 1H), 8.06 (td, J_1 = 6.4 Hz, J_2 = 8.7 Hz, 1H), 7.59 (ddd, J_1 = 11.6 Hz, J_2 = 9.5 Hz, J_3 = 2.6 Hz, 1H), 7.34 (td, J_1 = 8.3 Hz, J_2 = 2.1 Hz, 1 H), 7.16 (d, J = 2.9 Hz, 1 H), 3.67-3.81 (m, 1 H), 2.78-2.88 (m, 2 H), 2.19-2.34 (m, 3 H), 1.65-1.84 (m, 6 H), 1.46-1.65 (m, 3 H), 1.13-1.28 (m, 4 H), 1.00-1.13 (m, 1 H).

5-(2-Fluoro-phenyl)-isoxazole-3-carboxylic acid (1-cyclohexyl-piperidin-4-yl)-amide (8h). General procedure A from 5-(2-fluoro-phenyl)-isoxazole-3-carboxylic acid and 1-cyclohexylpiperidin-4-ylamine. QC LC-MS: t_R = 0.66 min; $[M+H]^+$ =372.3. LC-HRMS: t_R = 0.57 min; m/z = 371.2009, found = 372.2082 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.73 (d, J = 8.0 Hz, 1 H), 7.99 (td, J_1 = 1.6 Hz, J_2 = 7.7 Hz, 1 H), 7.60-7.68 (m, 1 H), 7.40-7.53 (m, 2 H), 7.17 (d, J = 3.0 Hz, 1 H), 3.68-3.80 (m, 1 H), 2.79-2.87 (m, 2 H), 2.20-2.31 (m, 3 H), 1.68-1.82 (m, 6 H), 1.51-1.63 (m, 3 H), 1.13-1.28 (m, 4 H), 1.01-1.13 (m, 1 H).

5-(4-Fluoro-phenyl)-isoxazole-3-carboxylic acid (1-cyclohexyl-piperidin-4-yl)-amide (8i). General procedure A from 5-(4-fluoro-phenyl)-isoxazole-3-carboxylic acid and 1-cyclohexylpiperidin-4-ylamine. QC LC-MS: t_R = 0.66 min; $[M+H]^+$ =372.4. LC-HRMS: t_R = 0.58 min; m/z = 371.2009, found = 372.2092 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.68 (d, J = 8.1 Hz, 1 H), 7.97-8.03 (m, 2 H), 7.41 (m, 2 H), 7.35 (s, 1 H), 3.64-3.81 (m, 1 H), 2.76-2.89 (m, 2 H), 2.17-2.30 (m, 3 H), 1.67-1.84 (m, 6 H), 1.50-1.64 (m, 3 H), 1.13-1.32 (m, 4 H), 0.98-1.12 (m, 1 H).

5-Pyridin-3-yl-isoxazole-3-carboxylic acid (1-cyclohexyl-piperidin-4-yl)-amide (8j). General procedure A from 5-pyridin-3-yl-isoxazole-3-carboxylic acid and 1-cyclohexylpiperidin-4-ylamine. QC LC-MS: t_R = 0.48 min; $[M+H]^+$ =355.3. LC-HRMS: t_R = 0.42 min; m/z = 354.2056, found = 355.2125 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 9.14-9.16 (m, 1 H), 8.70-8.75 (m, 2 H), 8.30-8.35 (m, 1 H), 7.60 (dd, J_1 = 4.8 Hz, J_2 = 8.0 Hz, 1 H), 7.51 (s, 1 H), 3.67-3.80 (m, 1 H), 2.83 (d, J = 11.4 Hz, 2 H), 2.25 (t, J = 11.1 Hz, 3 H), 1.66-1.81 (m, 6 H), 1.49-1.64 (m, 3 H), 1.14-1.27 (m, 4 H), 1.00-1.12 (m, 1 H).

Preparation of amides 9a-9g

5-(2,4-Difluoro-phenyl)-isoxazole-3-carboxylic acid (1-acetyl-piperidin-4-yl)-amide (9a). General procedure A from 5-(2,4-difluoro-phenyl)-isoxazole-3-carboxylic acid and 1-acetyl 4-amino-piperidine. QC LC-MS: t_R = 0.88 min; $[M+H]^+$ =350.3. LC-HRMS: t_R = 0.83 min; m/z = 349.1238, found = 350.1317 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 8.81-8.87 (m, 1 H), 8.01-8.09 (m, 1 H), 7.54-7.61 (m, 1 H), 7.29-7.37 (m, 1 H), 7.15-7.18 (m, 1 H), 4.31-4.40 (m, 1 H), 3.98-4.10 (m, 1 H), 3.78-3.88 (m, 1 H), 3.08-3.18 (m, 1 H), 2.61-2.71 (m, 1 H), 2.01 (s, 3 H), 1.73-1.89 (m, 2 H), 1.35-1.58 (m, 2 H).

5-(2,4-Difluoro-phenyl)-isoxazole-3-carboxylic acid piperidin-4-yl-amide hydrochloride (9b). General procedure A from 5-(2,4-difluoro-phenyl)-isoxazole-3-carboxylic acid and 1-N-Boc-(4-amino)-piperidine, followed by N-Boc group deprotection with HCl 2M in dioxane/DCM 1/1. QC LC-MS: t_R = 0.54 min; $[M+H]^+$ =308.2. LC-HRMS: t_R = 0.48 min; m/z = 307.1132, found = 308.1213 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 9.06 (d, J = 7.6 Hz, 2 H), 8.94-8.94 (m, 1 H), 8.06 (td, J_1 = 8.7 Hz, J_2 = 6.5 Hz, 1 H), 7.59 (ddd, J_1 = 11.5 Hz, J_2 = 9.4 Hz, J_3 = 2.4 Hz, 1 H), 7.34 (td, J_1 = 8.3 Hz, J_2 = 2.1 Hz, 1 H), 7.22 (d, J = 2.9 Hz, 1 H), 4.05-4.16 (m, 1 H), 3.30 (d, J = 12.7 Hz, 2 H), 2.95-3.05 (m, 2 H), 1.96-2.03 (m, 2 H), 1.77-1.90 (m, 2 H).

5-(2,4-Difluoro-phenyl)-isoxazole-3-carboxylic acid (1-cyclopentyl-piperidin-4-yl)-amide (9c). General procedure A from 5-(2,4-difluoro-phenyl)-isoxazole-3-carboxylic acid and 1-cyclopentylpiperidin-4-ylamine. QC LC-MS: t_R = 0.62 min; $[M+H]^+$ =376.4. LC-HRMS: t_R = 0.56 min; m/z = 375.1758, found = 376.1837 $[M + H]^+$.^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.74 (d, J = 7.9 Hz, 1 H), 8.06 (td, J_1 = 6.5 Hz, J_2 = 8.6 Hz, 1 H), 7.58 (ddd, J_1 = 2.5 Hz, J_2 = 9.3 Hz, J_3 = 11.4 Hz, 1 H), 7.33 (td, J_1 = 2.6 Hz, J_2 = 8.7 Hz, 1 H), 7.15 (d, J = 2.9 Hz, 1 H), 3.70-3.84 (m, 1 H), 2.89-3.03 (m, 2 H), 1.90-2.05 (m, 2 H), 1.71-1.88 (m, 4 H), 1.45-1.71 (m, 6 H), 1.18-1.42 (m, 3 H).

5-(2,4-Difluoro-phenyl)-isoxazole-3-carboxylic acid (1-cyclobutyl-piperidin-4-yl)-amide (9d). General procedure A from 5-(2,4-difluoro-phenyl)-isoxazole-3-carboxylic acid and 1-cyclobutylpiperidin-4-ylamine. QC LC-MS: t_R = 0.59 min; $[M+H]^+$ =362.3. LC-HRMS: t_R = 0.53 min; m/z = 361.1602, found = 362.1687 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.76 (d, J = 8.0 Hz, 1 H), 8.06 (td, J_1 = 6.4 Hz, J_2 = 8.7 Hz, 1 H), 7.58 (ddd, J_1 = 2.5 Hz, J_2 = 9.3 Hz, J_3 = 11.5 Hz, 1 H), 7.29-7.37 (m, 1 H), 7.16 (d, J = 3.0 Hz, 1 H), 3.69-3.81 (m, 1 H), 2.77-2.83 (m, 2 H), 2.64-2.71 (m, 1 H), 1.92-2.00 (m, 2 H), 1.72-1.82 (m, 6 H), 1.53-1.65 (m, 4 H).

5-(2,4-Difluoro-phenyl)-isoxazole-3-carboxylic acid [1-(2,2-difluoro-ethyl)-piperidin-4-yl]-amide (9e). General procedure A from 5-(2,4-difluoro-phenyl)-isoxazole-3-carboxylic acid and 1-(2,2-difluoro-ethyl)-piperidin-4-ylamine. LC-MS method B: t_R = 0.95 min; $[M+H]^+$ =372.2. LC-HRMS: t_R = 0.57 min; m/z = 371.1257, found = 372.1337 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.77 (d, J = 8.0 Hz, 1 H), 8.06 (td, J_1 = 8.7 Hz, $J2$ = 6.4 Hz, 1H), 7.59 (ddd, J_1 = 11.6 Hz, J_2 = 9.2 Hz, J_3 = 2.6 Hz, 1H), 7.34 (td, J_1 = 8.5 Hz, J_2 = 2.4 Hz, 1H), 7.16 (d, J = 2.9 Hz, 1 H), 6.01-6.25 (m, 1 H), 3.73-3.83 (m, 1 H), 2.89-2.95 (m, 2 H), 2.72 (td, J_1 = 15.6 Hz, J_2 = 4.3 Hz, 2 H), 2.25 (td, J_1 = 11.7 Hz, J_2 = 2.0 Hz, 2 H), 1.72-1.79 (m, 2 H), 1.59-1.68 (m, 2 H).

5-(2,4-Difluoro-phenyl)-isoxazole-3-carboxylic acid [1-(2-methoxy-ethyl)-piperidin-4-yl]-amide (9f). General procedure A from 5-(2,4-difluoro-phenyl)-isoxazole-3-carboxylic acid and 1-(2-methoxy-ethyl)-piperidin-4-ylamine. QC LC-MS: t_R = 0.58 min; $[M+H]^+$ =366.2. LC-HRMS: t_R = 0.51 min; m/z = 365.1551, found = 366.1633 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.75 (d, J = 8.0 Hz, 1 H), 8.06 (td, J_1 = 6.4 Hz, J_2 = 8.7 Hz, 1 H), 7.58 (ddd, J_1 = 11.5 Hz, J_2 = 9.3 Hz, J_3 = 2.5 Hz, 1 H), 7.29-7.37 (m, 1 H), 7.16 (d, J = 2.9 Hz, 1 H), 3.70-3.81 (m, 1 H), 3.42 (t, J = 5.9 Hz, 2 H), 3.24 (s, 3 H), 2.84-2.92 (m, 2 H), 2.46 (t, J = 5.9 Hz, 2 H), 1.98-2.07 (m, 2 H), 1.70-1.79 (m, 2 H), 1.55-1.66 (m, 2 H).

5-(2,4-Difluoro-phenyl)-isoxazole-3-carboxylic acid (1-benzyl-piperidin-4-yl)-amide (9g). General procedure A from 5-(2,4-difluoro-phenyl)-isoxazole-3-carboxylic acid and benzylamine. QC LC-MS: t_R = 0.67 min; $[M+H]^+$ =398.3. LC-HRMS: t_R = 0.59 min; m/z = 397.1602, found = 398.1684 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.76 (d, J = 8.0 Hz, 1 H), 8.06 (td, J_1 = 6.4 Hz, J_2 = 8.7 Hz, 1 H), 7.58 (ddd, J_1 = 2.5 Hz, J_2 = 9.3 Hz, J_3 = 11.6 Hz, 1 H), 7.23-7.36 (m, 6 H), 7.16 (d, J = 2.9 Hz, 1 H), 3.73-3.85 (m, 1 H), 3.47 (s, 2 H), 2.77-2.88 (m, 2 H), 1.95-2.08 (m, 2 H), 1.72-1.82 (m, 2 H), 1.55-1.69 (m, 2 H).

Preparation of amides 10a-10f

1-(2,4-Difluoro-phenyl)-1H-pyrazole-4-carboxylic acid (1-cyclohexyl-piperidin-4-yl)-amide (10a). General procedure A from 1-(2,4-difluorophenyl)-1H-pyrazole-3-carboxylic acid and 1-cyclohexylpiperidin-4-ylamine. QC LC-MS: t_R = 0.58 min; $[M+H]^+$ =389.4. LC-HRMS: t_R = 0.50 min; m/z = 388.2075, found = 389.2147 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.63 (d, J = 2.0 Hz, 1 H), 8.16 (s, 1 H), 8.02 (d, J = 7.8 Hz, 1 H), 7.86 (td, J_1 = 6.0 Hz, J_2 = 9.0 Hz, 1 H), 7.61 (ddd, J_1 = 2.7 Hz, J_2 = 9.0 Hz, J_3 = 11.6 Hz, 1 H), 7.26-7.32 (m, 1 H), 3.64-3.74 (m, 1 H), 2.79-2.87 (m, 2 H), 2.19-2.32 (m, 3 H), 1.68-1.83 (m, 6 H), 1.54-1.62 (m, 1 H), 1.41-1.52 (m, 2 H), 1.14-1.27 (m, 4 H), 1.01-1.13 (m, 1 H)

1-(2,4-Difluoro-phenyl)-1H-[1,2,3]triazole-4-carboxylic acid (1-cyclohexyl-piperidin-4-yl)-amide (10b). a) To a solution of ethyl 2-diazo-3-oxopropanoate[2] (1.6 g, 8.85 mmol) in EtOH (3.15 mL) was added glacial acetic acid (1.27 mL, 22.1 mmol) followed by 2,4-difluoroaniline (1.22 g, 9.47 mmol). After stirring overnight, the reaction mixture was concentrated, and the residue was diluted with cold water (40 mL). The precipitate was filtered, washed with cold water (10 mL) and dried under HV to afford 1-(2,4-difluoro-phenyl)-1H-[1,2,3]triazole-4-carboxylic acid ethyl ester as a beige solid (2.03 g, 91%). LC-MS method A: t_R = 0.8 min; $[M+H]^+$ = 254.12.

b) To a solution of the above ester (1.93 g, 7.62 mmol) in THF (16 mL) was added LiOH hydrate (11.4 mmol) dissolved in water (16 mL). After stirring for 45 min, THF was evaporated and the aqueous residue was cooled to 0°C. A 1M HCl solution was added until pH=2. The precipitated product was filtered, washed with water (15 mL), and dried under HV. 1-(2,4-difluoro-phenyl)-1H-[1,2,3]triazole-4-carboxylic acid was obtained as a beige powder (1.71 g, 100%). LC-MS method A: t_R = 0.61 min; $[M+H]^+$ = 225.96, $[M+H+MeCN]^+$ = 267.10.

c) General procedure A from the above carboxylic acid and 1-cyclohexylpiperidin-4-ylamine to give **10b**. QC LC-MS: t_R = 0.56 min; $[M+H]^+$ =390.3; LC-HRMS: t_R = 0.50 min; m/z = 389.2027, found = 390.2113 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 9.00 (d, J = 1.5 Hz, 1 H), 8.49 (d, J = 8.1 Hz, 1 H), 7.93 (td, J_1 = 8.8 Hz, J_2 = 5.9 Hz, 1 H), 7.72 (m, J_1 = 11.1 Hz, J_2 = 8.9 Hz, J_3 = 2.7 Hz, 1 H), 7.35-7.42 (m, 1 H), 3.71-3.82 (m, 1 H), 2.79-2.89 (m, 2 H), 2.20-2.33 (m, 3 H), 1.69-1.81 (m, 6 H), 1.53-1.68 (m, 3 H), 1.14-1.28 (m, 4 H), 1.02-1.13 (m, 1 H).

3-(2,4-Difluoro-phenyl)-isoxazole-5-carboxylic acid (1-cyclohexyl-piperidin-4-yl)-amide (10c)

a) 2,4-Difluorobenzaldehyde oxime (4.25 g, 24.4 mmol) was dissolved in THF (50 mL). Then pyridine (2.46 mL, 30.5 mmol) was added. The mixture was heated up to 60°C and N-chlorosuccinimide (3.58 g, 26.8 mmol) was added. The reaction mixture was stirred at 60 ° C for 45 min and then TEA (4.11 mL, 29.2 mmol) and ethyl propiolate (2.72 mL, 26.8 mmol) are added. The reaction mixture was stirred overnight at 60°C and then concentrated under HV. The residue was taken up in DCM (100 mL) and diluted with aq. 1M HCl (100 mL). The separated organic phase was washed with water (100 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated under HV. The crude was purified by flash chromatography using n-heptane/EtOAc 9/1 as eluent to yield ethyl 3-(2,4-difluorophenyl)isoxazole-5-carboxylate (3.8 g, 62%) . LC-MS method A: t_R = 0.92 min.

b) 3-(2,4-Difluoro-phenyl)-isoxazole-5-carboxylic acid was obtained in quantitative yield by saponification of the above ester according to the procedure used for **10b**. LC-MS method A: t_R = 0.68 min. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 14.48 (bs, 1 H), 7.99-8.05 (m, 1 H), 7.50-7.56 (m, 2 H), 7.30 (m, 1 H).

c) General procedure A from the above carboxylic acid and 1-cyclohexylpiperidin-4-ylamine to give **10c**. QC LC-MS: t_R = 0.64 min; $[M+H]^+$ =390.3. LC-HRMS: t_R = 0.57 min; m/z = 389.1915, found = 390.1994 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.88 (d, J = 7.9 Hz, 1 H), 8.01 (td, J_1 = 6.6 Hz, J_2 = 8.7 Hz, 1H), 7.53 (ddd, J_1 = 2.4 Hz, J_2 = 9.0 Hz, J_3 = 11.4 Hz, 1 H), 7.49 (d, J = 2.6 Hz, 1 H), 7.30 (td, J_1 = 2.4 Hz, J_2 = 8.5 Hz, 1H), 3.66-3.77 (m, 1 H), 2.80-2.88 (m, 2 H), 2.20-2.32 (m, 3 H), 1.67-1.84 (m, 6 H), 1.48-1.62 (m, 3 H), 1.13-1.28 (m, 4 H), 0.98-1.13 (m, 1 H).

5-(2,4-Difluoro-phenyl)-[1,2,4]oxadiazole-3-carboxylic acid (1-cyclohexyl-piperidin-4-yl)-amide (10d)

a) Ethyl 2-amino(hydroxyimino)acetate (1.07 g, 8.1 mmol) dissolved in 2,6-dimethylpyridine (2.93 mL, 24 mmol) was treated dropwise with a solution of 2,4-difluorobenzoyl chloride (0.66 mL, 5.38 mmol) in DCM (15 mL). The reaction mixture was stirred overnight. The beige suspension was dissolved with DCM (150 mL) and washed with water (50 mL), then 1M HCl (50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent evaporated. The intermediate white powder ethyl 2-(2,4-difluorobenzamido)-2-(hydroxyimino)acetate was then heated 1h at 200 ° C in a DrySyn metal block (from Asynt Ltd.). After cooling down, the residue was purified by flash chromatography using a gradient of 2% to 20% EtOAc in n-heptane as eluent to yield ethyl 5-(2,4-difluorophenyl)-1,2,4-oxadiazole-3-carboxylate (1.20 g, 88%). LC-MS method A: t_R = 0.85 min; $[M+H]^+$ = 255.02.

b) 5-(2,4-Difluoro-phenyl)-[1,2,4]oxadiazole-3-carboxylic acid was obtained by saponification of the above ester according to the procedure used for **10b** (0.83 g, 78%). LC-MS method A: t_R = 0.57 min. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 8.27 (m, 1 H), 7.67 (m, 1 H), 7.41 (m, 1 H).

c) General procedure A from the above carboxylic acid and 1-cyclohexylpiperidin-4-ylamine to give **10d**. QC LC-MS: t_R =0.58 min; $[M+H]^+$ =391.4. LC-HRMS: t_R = 0.52 min; m/z = 390.1867, found = 391.1943 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.95 (d, J = 8.1 Hz, 1 H), 8.28 (td, J_1 = 6.4 Hz, J_2 = 8.6 Hz, 1 H), 7.67 (ddd, J_1 = 2.5 Hz, J_2 = 9.3 Hz, J_3 = 11.4 Hz, 1 H), 7.39-7.44 (m, 1 H), 3.70-3.81 (m, 1 H), 2.83 (d, J = 11.4 Hz, 2 H), 2.26 (t, J = 10.5 Hz, 3 H), 1.68-1.82 (m, 6 H), 1.54-1.65 (m, 3 H), 1.13-1.27 (m, 4 H), 0.99-1.12 (m, 1 H).

5-(2,4-Difluoro-phenyl)-[1,3,4]oxadiazole-2-carboxylic acid (1-cyclohexyl-piperidin-4-yl)-amide (10e)

a) To a solution of 2,4-difluorobenzoic acid hydrazide (2.65 g, 15.4 mmol) in 50 mL DCM was added TEA (9.67 mL, 69.4 mmol). The mixture was cooled to 0°C and ethyl chlorooxoacetate (2.44 mL, 21.2 mmol) was added. The mixture was stirred 2h at 0°C. Then, toluene-4-sulfonyl chloride (4.40 g, 23.1 mmol) was added and stirring was continued overnight at rt. A sat. aq. $NaHCO_3$ solution (50 mL) was added and the reaction mixture was extracted twice with DCM (2 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography using a gradient of eluent heptane/AcOEt (9:1 to 4:1) to give 5-(2,4-difluoro-phenyl)-[1,3,4]oxadiazole-2-carboxylic acid ethyl ester as a light yellow solid (2.43g, 60%). LC-MS method A: t_R = 0.80 min; $[M+H]^+$ = 255.13, $[M+H+MeCN]^+$ = 296.10.

b) To a solution of 1-cyclohexylpiperidin-4-amine (38 mg, 0.2 mmol) in 0.4 mL toluene cooled to 0°C was added trimethylaluminium 2.0 M in toluene (0.1 mL, 0.2 mmol) . After stirring for 30 min. a solution of the above ester (25.4 mg, 0.1 mmol) in toluene (0.4 mL) was added. The reaction was stirred for 3h and quenched with 1.25 M HCl in MeOH (0.240 mL, 0.3 mmol).

The solvents were evaporated and the residue purified by prep. HPLC under basic conditions to yield **10e** (21 mg, 54%). QC LC-MS: t_R = 0.57 min; [M+H]+ =391.3. LC-HRMS: t_R = 0.50 min; m/z = 390.1867, found = 391.1945 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 9.28 (d, J = 8.1 Hz, 1 H), 8.18 (td, J_1 = 6.5 Hz, J_2 = 8.5 Hz, 1 H), 7.63 (ddd, J_1 = 11.3 Hz, J_2 = 9.5 Hz, J_3 = 2.4 Hz, 1 H), 7.39 (td, J_1 = 2.1 Hz, J_2 = 8.3 Hz, 1 H), 3.69-3.81 (m, 1 H), 2.84 (d, J = 11.6 Hz, 2 H), 2.20-2.33 (m, 3 H), 1.67-1.83 (m, 6 H), 1.52-1.67 (m, 3 H), 1.13-1.29 (m, 4 H), 1.00-1.13 (m, 1 H).

6-(2,4-Difluoro-phenyl)-pyrimidine-4-carboxylic acid (1-cyclohexyl-piperidin-4-yl)-amide (10f).

a) To a degassed solution of 2,4-difluorophenylboronic acid pinacol ester (1.47 g, 6.13 mmol) and methyl-6-chloropyrimidine-4-carboxylate (0.96 g, 5.57 mmol) in DMF (15 mL) were added K_3PO_4 (1.67 g, 7.8 mmol) and Pd(dppf)Cl_2.DCM (0.91 g, 1.11 mmol). The reaction mixture was stirred at 60°C for 18 h. A sat. aq. $NaHCO_3$ solution (50 mL) was added and the reaction mixture was extracted twice with DCM (2 x 50 mL). The reaction mixture was diluted with H_2O (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography using a gradient of heptane/AcOEt (7:3 to 1:1) as eluent to give 6-(2,4-difluoro-phenyl)-pyrimidine-4-carboxylic acid methyl ester as a light yellow solid (0.96 g, 69%). LC-MS method A: t_R = 0.80 min; $[M+H]^+$ = 251.08; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.46 (s, 1 H), 8.53 (s, 1 H), 8.31 (q, J = 7.8 Hz, 1 H), 7.11 (t, J = 8.2 Hz, 1 H), 7.02 (m, 1 H), 4.10 (s, 3 H).

b) 6-(2,4-difluoro-phenyl)-pyrimidine-4-carboxylic acid (0.878 g, 97%) was obtained by saponification of the above ester according to the procedure used for **10b**. LC-MS method A: t_R = 0.66 min; $[M+H]^+$ = 237.07; ^{1}H NMR (400 MHz, D_6-DMSO) δ: 13.92-14.31 (broad s, 1

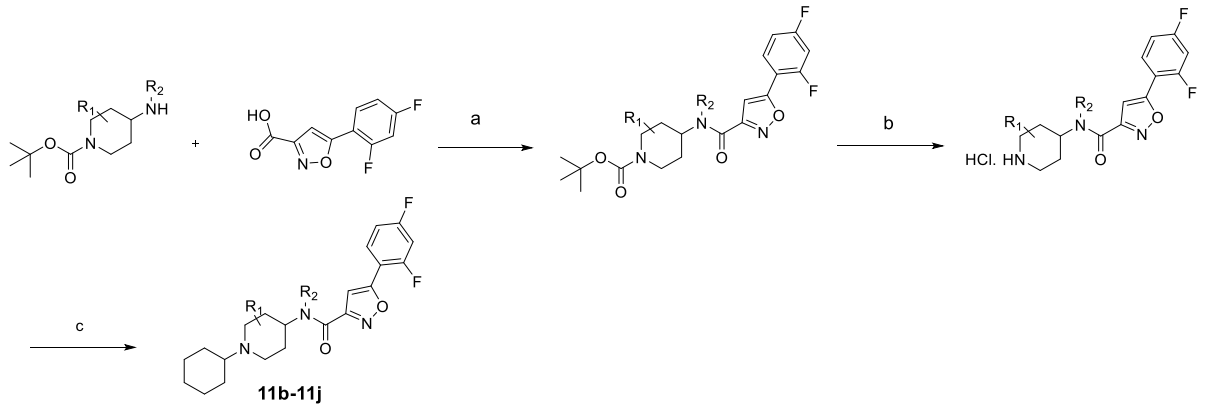
H), 9.48 (s, 1H), 8.34 (s, 1 H), 8.25 (q, *J* = 8.0 Hz, 1 H), 7.54 (t, *J* = 10.8 Hz, 1H), 7.35 (t, *J* = 8.3 Hz, 1H).

c) General procedure A from the above carboxylic acid and 1-cyclohexylpiperidin-4-ylamine to yield **10f**. QC LC-MS: t_R =0.64 min; $[M+H]^+$ = 401.4. LC-HRMS: t_R = 0.58 min; m/z = 400.2075, found = 401.215 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO) δ: 9.38-9.43 (m, 1 H), 8.83-8.91 (m, 1 H), 8.30-8.37 (m, 1 H), 8.18-8.29 (m, 1 H), 7.45-7.56 (m, 1 H), 7.27-7.39 (m, 1 H), 3.71-3.85 (m, 1 H), 2.77-2.89 (m, 2 H), 2.23-2.36 (m, 3 H), 1.52-1.81 (m, 9 H), 1.12-1.29 (m, 4 H), 0.96-1.12 (m, 1 H).

Preparation of compounds 11a-11j

5-(2,4-Difluoro-phenyl)-isoxazole-3-carboxylic acid benzyl-(1-cyclohexyl-piperidin-4-yl)-amide (11a).1-Cyclohexylpiperidin-4-amine (18.2 mg, 0.1 mmol, 1 eq), benzaldehyde (13 mg, 0.12 mmol) and AcOH (0.012 mL, 0.21 mmol) were dissolved in DCM (1 mL). Sodium triacetoxyborhydride (42.4 mg, 0.2 mmol) was added and the mixture was stirred overnight. Aq. 1M NaOH (1 mL) and DCM (2 mL) were added, the organic phase was separated, and the solvent evaporated under high vacuum. The obtained amine was then coupled according to general procedure A with 1-(2,4-difluorophenyl)-1H-pyrazole-3-carboxylic acid. LC-MS method B: t_R =1.39 min; $[M+H]^+$ = 480.1. LC-HRMS: t_R = 0.74 min; m/z = 479.2384, found = 480.2471 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ:7.93-8.14 (m, 1 H), 7.45-7.60 (m, 1 H), 6.99-7.37 (m, 7 H), 4.74 (s, 2 H), 3.78-4.25 (m, 1 H), 2.74-2.91 (m, 2 H), 2.13-2.28 (m, 2 H), 1.99-2.08 (m, 1 H), 1.60-1.76 (m, 8 H), 1.50-1.59 (m, 1 H), 1.07-1.23 (m, 4 H), 0.97-1.05 (m, 1 H).

General Scheme for the Preparation of Compounds **11b** to **11e** and **11j**



Reagents and conditions (a) HATU, DIPEA, DMF, rt, 18 h; (b) HCl 4 N in dioxane, DCM, rt, 30 min; (c) cyclohexanone, $NaBH(OAc)_3$, AcOH, DCM, rt, 24 h.

5-(2,4-Difluoro-phenyl)-isoxazole-3-carboxylic acid (1-cyclohexyl-3,3-difluoro-piperidin-4-yl)-amide (11b)

a) To a solution of 5-(2,4-difluorophenyl)isoxazole-3-carboxylic acid (67.5 mg, 0.3 mmol) in 2 mL DMF was added 4-amino-1-boc-3,3-difluoropiperidine (85 mg, 0.36 mmol). DIPEA (0.26 mL, 1.5 mmol) was then added followed by HATU (143 mg, 0.37 mmol). The reaction mixture was stirred overnight at rt. The crude mixture was directly purified by prep. LC-MS under basic conditions to yield *tert*-butyl 4-(5-(2,4-difluorophenyl)isoxazole-3-carboxamido)-3,3-difluoropiperidine-1-carboxylate (89 mg, 67%). LC-MS method B: t_R = 1.64 min; $[M+NH_3]^+$ = 361.1.

b) The above-mentioned amide (89 mg, 0.2 mmol) was dissolved in DCM (1 mL). HCl in dioxane 4M (1 mL, 4 mmol) was added dropwise. The mixture was stirred at rt for 1 hour. The solvents were evaporated, and the residue was dried on high vacuum to deliver 5-(2,4-difluorophenyl)-N-(3,3-difluoropiperidin-4-yl)isoxazole-3-carboxamide hydrochloride (77 mg, 100%). LC-MS method B: t_R = 0.86 min; $[M+H]^+$ = 344.0.

c) To a suspension of the above-mentioned amine hydrochloride (38 mg, 0.1 mmol) in DCM (0.5 mL) at rt was added cyclohexanone (15 mg, 0.15 mmol) followed by acetic acid (0.007 mL, 0.125 mmol) and sodium triacetoxyborohydride (32 g, 0.15 mmol). The reaction mixture

was stirred overnight at rt. The reaction mixture was evaporated. The crude compound was purified by prep. LC-MS under basic conditions to give **11b** (14 mg, 33%). LC-MS method B: t_R = 1.19 min; $[M+H]^+$ =426.1. LC-HRMS: t_R = 0.72 min; m/z = 425.1726, found = 426.1807 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO, solvent suppression) δ: 8.97 (d, *J* = 8.8 Hz, 1 H), 8.06 (td, J_1 = 8.6 Hz, J_2 = 6.4 Hz, 1 H), 7.57 (ddd, J_1 = 11.5 Hz, J_2 = 9.3 Hz, J_3 = 2.4 Hz, 1 H), 7.30-7.36 (m, 1 H), 7.23 (d, *J* = 2.8 Hz, 1 H), 4.25-4.44 (m, 1 H), 3.05-3.13 (m, 1 H), 2.78-2.91 (m, 1 H), 2.55-2.76 (m, 1 H), 2.34-2.45 (m, 2 H), 1.66-1.90 (m, 6 H), 1.52-1.63 (m, 1 H), 1.12-1.29 (m, 4 H), 1.01-1.12 (m, 1 H).

***Rac*-5-(2,4-Difluoro-phenyl)-isoxazole-3-carboxylic acid ((3S*,4S*)-1-cyclohexyl-3-methoxy-piperidin-4-yl)-amide (11c).** Prepared in analogy to compound **11b** from *tert*-butyl trans-4-amino-3-methoxy-piperidine-1-carboxylate. LC-MS method B: t_R = 1.09 min; $[M+H]^+$ =420.2 . LC-HRMS: t_R = 0.60 min; m/z = 419.2020, found = 420.21 $[M + H]^+$. ^{1}H NMR (500 MHz, D6-DMSO) *δ*: 8.81 (d, *J* = 8.6 Hz, 1 H), 8.06 (td, J_1 = 6.4 Hz, J_2 = 8.7 Hz, 1 H), 7.59 (ddd, J_1 = 2.5 Hz, J_2 = 9.3 Hz, J_3 = 11.5 Hz, 1 H), 7.34 (td, J_1 = 2.2 Hz, J_2 = 8.3 Hz, 1 H), 7.15 (d, *J* = 2.9 Hz, 1 H), 3.63-3.74 (m, 1 H), 3.30 (s, 3 H), 3.14-3.23 (m, 1 H), 2.71-2.79 (m, 1 H), 2.50-2.55 (m, 2 H), 2.30-2.36 (m, 1 H), 2.21 (m, 1 H), 1.96 (t, *J* = 10.4 Hz, 1 H), 1.69-1.81 (m, 4 H), 1.46-1.62 (m, 2 H), 1.14-1.27 (m, 4 H), 1.02-1.12 (m, 1 H).

***Rac*-5-(2,4-Difluoro-phenyl)-isoxazole-3-carboxylic acid ((3S*,4S*)-1-cyclohexyl-3-ethoxy-piperidin-4-yl)-amide (11d).** Prepared in analogy to compound **11b** from *tert*-butyl trans-4-amino-3-ethoxy-piperidine-1-carboxylate. LC-MS method B: t_R = 1.16 min; $[M+H]^+$ =434.1. LC-HRMS: t_R = 0.64 min; m/z = 433.2177, found = 434.2258 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO, solvent suppression) *δ*: 8.77 (d, *J* = 8.6 Hz, 1 H), 8.01-8.12 (m, 1 H), 7.53-7.62 (m, 1 H), 7.28-7.39 (m, 1 H), 7.13 (d, *J* = 2.7 Hz, 1 H), 3.52-3.73 (m, 1 H), 3.05-3.14 (m, 1 H), 2.66-2.80 (m, 1 H), 2.26-2.39 (m, 1 H), 2.14-2.26 (m, 1 H), 1.94-2.05 (m, 1 H), 1.62-1.82 (m, 5 H), 1.46-1.62 (m, 2 H), 1.12-1.25 (m, 4 H), 0.97-1.12 (m, 4 H).

***Rac*-5-(2,4-Difluoro-phenyl)-isoxazole-3-carboxylic acid ((3S*,4S*)-1-cyclohexyl-3-hydroxy-piperidin-4-yl)-amide (11e).** Prepared in analogy to compound **11b** from *tert*-butyl trans-4-amino-3-hydroxy-piperidine-1-carboxylate. QC LC-MS: t_R = 0.55 min; $[M+H]^+$ = 406.2 . LC-HRMS: t_R = 0.55 min; m/z = 405.1864, found = 406.1939 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (td, J_1 = 6.3 Hz, J_2 = 8.5 Hz, 1 H), 7.12 (d, J = 3.7 Hz, 1 H), 6.97-7.10 (m, 3H), 6.90 (d, J = 7.3 Hz, 1 H), 3.85-3.95 (m, 1 H), 3.68 (td, J_1 = 4.2 Hz, J_2 = 8.7 Hz, 1 H), 3.08-3.16 (m, 1 H), 2.81-2.90 (m, 1 H), 2.27-2.48 (m, 3 H), 2.07-2.16 (m, 1 H), 1.76-1.91 (m, 4 H), 1.60-1.72 (m, 2 H), 1.19-1.34 (m, 4 H), 1.05-1.19 (m, 1 H).

***Rac*-5-(2,4-Difluoro-phenyl)-isoxazole-3-carboxylic acid ((3S*,4S*)-1-cyclohexyl-3-hydroxymethyl-piperidin-4-yl)-amide (11f).** To a solution of ester **11g** (0.67 g, 1.5 mmol) in 17.1 mL dry THF was added LiCl (0.51 g, 12 mmol), followed by $NaBH_4$ (0.23 g, 6 mmol) and 8 mL dry EtOH. After stirring for 44 h, 20 mL water was added, THF and EtOH were evaporated under high vacuum and the mixture was diluted with 50 mL DCM. The organic phase was separated dried over Na_2SO_4 and the solvent evaporated under high vacuum to yield **11f** (0.50 g, 79%). LC-MS method B t_R = 1.03 min; $[M+H]^+$ = 420.23. LC-HRMS: t_R =0.56 min; m/z = 419.2020, found = 420.2098 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.73 (d, J = 8.7 Hz, 1 H), 8.06 (td, J_1 = 6.5 Hz, J_2 = 8.7 Hz, 1 H), 7.59 (ddd, J_1 = 2.5 Hz, J_2 = 9.3 Hz, J_3 = 11.5 Hz, 1 H), 7.34 (td, J_1 = 2.1 Hz, J_2 = 8.3 Hz, 1 H), 7.16 (d, J = 2.9 Hz, 1 H), 4.40 (t, J = 5.0 Hz, 1 H), 3.52-3.62 (m, 1 H), 3.43-3.50 (m, 1 H), 3.16-3.24 (m, 1 H), 3.03-3.09 (m, 1 H), 2.78-2.85 (m, 1 H), 2.17-2.32 (m, 2 H), 1.99 (t, J = 11.1 Hz, 1 H), 1.69-1.82 (m, 6 H), 1.54-1.66 (m, 2 H), 1.14-1.27 (m, 4 H), 1.02-1.13 (m, 1 H).

1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-4-carboxylic acid amide (11j). Prepared in analogy to compound **11b** from *tert*-butyl 4-amino-4-carbamoylpiperidine-1-carboxylate. QC LC-MS: t_R = 0.64 min; $[M+H]^+$ =433.4 . LC-HRMS: t_R = 0.57 min; m/z = 432.1973, found = 433.2047 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-

DMSO) δ: 8.14 (s, 1 H), 8.06 (td, J_1 = 6.6 Hz, J_2 = 8.6 Hz, 1 H), 7.58 (ddd, J_1 = 2.4 Hz, J_2 = 9.5 Hz, J_3 = 11.5 Hz, 1 H), 7.31-7.37 (m, 1 H), 7.19 (d, J = 2.8 Hz, 2 H), 6.93 (s, 1 H), 2.66 (d, J = 11.7 Hz, 2 H), 2.37 (t, J = 11.2 Hz, 2 H), 2.10-2.25 (m, 3 H), 1.86-1.98 (m, 2 H), 1.65-1.77 (m, 4 H), 1.51-1.59 (m, 1 H), 1.10-1.25 (m, 4 H), 1.00-1.10 (m, 1 H).

Preparation of racemic ester **11g**, and carboxylic acid **11h**

***rac*-(3*R**,4*R**)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid methyl ester (11g)**

a) To a solution of *rac*-(3*R**,4*R**)-4-*tert*-butoxycarbonylamino-piperidine-3-carboxylic acid methyl ester (3.0 g, 11.3 mmol) in DCM (56 mL) was added cyclohexanone (1.42 mL, 13.5 mmol) followed by acetic acid (0.966 mL, 16.9 mmol) and sodium triacetoxyborohydride (3.39 g, 15.2 mmol). After stirring for 5h, additional cyclohexanone (0.23 mL, 2.3 mmol), acetic acid (0.17 mL, 2.8 mmol) and sodium triacetoxyborohydride (0.59 g, 2.8 mmol) were added. The reaction mixture was stirred overnight. The reaction mixture was diluted with DCM (200 mL) and treated with aq. sat. $NaHCO_3$ (250 mL). The organic phase was dried over $MgSO_4$ and evaporated. Compound *rac*-methyl (3*R**,4*R**)-4-((*tert*-butoxycarbonyl)amino)-1-cyclohexylpiperidine-3-carboxylate was used in the next step without further purification (3.85 g, 100%); LC-MS method B t_R = 1.09 min; $[M+H]^+$ = 341.19.

b) The above-mentioned compound (3.85 g, 11.3 mmol) was dissolved in MeOH (56.5 mL). A 4 M solution of HCl in dioxane (56.5 mL, 226 mmol) was added and the reaction was stirred for 1 h. The reaction mixture was concentrated, dissolved in DCM (250 mL) and treated with aq. sat. $NaHCO_3$ (200 mL). The organic layer was separated, and the aqueous phase was extracted with DCM (150 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. The crude *rac*-methyl (3*R**,4*R**)-4-amino-1-cyclohexylpiperidine-3-carboxylate hydrochloride was obtained as a yellow oil (2.64g, 92%); LC-MS method B t_R = 0.79 min;

$[M+H]^+$ = 241.20. ^{1}H NMR (400 MHz, CDCl3) δ: 7.28 (s, 1 H), 3.61-3.79 (m, 4 H), 3.06-3.13 (m, 1 H), 2.83-2.92 (m, 2 H), 2.23-2.44 (m, 4 H), 1.04-1.93 (m, 18 H).

c) General procedure A from the above amine hydrochloride and 5-(2,4-difluorophenyl)isoxazole-3-carboxylic acid to yield **11g**. LC-MS method B: t_R =1.15 min; $[M+H]^+$ = 447.92. LC-HRMS: t_R = 0.60 min; m/z = 447.1970, found = 448.2046 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (td, J_1 = 6.3 Hz, J_2 = 8.5 Hz, 1 H), 7.11 (d, J = 3.8 Hz, 1 H), 7.04-7.10 (m, 1 H), 7.01 (ddd, J_1 = 2.4 Hz, J_2 = 8.6 Hz, J_3 = 10.8 Hz, 1 H), 6.82 (d, J = 8.5 Hz, 1 H), 4.20-4.31 (m, 1 H), 3.69 (m, 3 H), 3.05-3.15 (m, 1 H), 2.90-2.98 (m, 1 H), 2.65-2.74 (m, 1 H), 2.56-2.65 (m, 1 H), 2.44-2.53 (m, 1 H), 2.33-2.43 (m, 1 H), 2.15-2.23 (m, 1 H), 1.73-1.91 (m, 4 H), 1.57-1.72 (m, 2 H), 1.18-1.37 (m, 4 H), 1.06-1.19 (m, 1 H).

***Rac*-(3*R**,4*R**)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (11h).** Prepared in analogy to compound **19** from ester **11g.** LC-MS method B: t_R = 0.59 min; $[M+H]^+$ = 433.82. LC-HRMS: t_R = 0.62 min; m/z = 433.1813, found = 434.1896 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 11.76-12.73 (m, 1 H), 8.92 (d, J = 8.1 Hz, 1 H), 8.08 (td, J_1 = 8.8 Hz, J_2 = 6.5 Hz, 1H), 7.61 (ddd, J_1 = 2.5 Hz, J_2 = 9.3 Hz, J_3 = 11.5 Hz, 1 H), 7.32-7.38 (m, 1 H), 7.15 (d, J = 3.0 Hz, 1 H), 4.00-4.14 (m, 1 H), 3.03-3.16 (m, 1 H), 2.84-2.98 (m, 1 H), 2.68-2.80 (m, 1 H), 2.32-2.54 (m, 3 H), 1.70-1.90 (m, 5 H), 1.52-1.69 (m, 2 H), 1.18-1.24 (m, 4 H), 1.07-1.10 (m, 1 H).

***Rac*-(3*R**,4*R**)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid dimethylamide (11i)**. Prepared in analogy to compound (3*S*,4*S*)-**11i** from carboxylic acid **11h.** LC-MS method B: t_R = 1.0 min; $[M+H]^+$ = 460.95. LC-HRMS: t_R = 0.59 min; m/z = 460.2286, found = 461.2372 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.68 (d, J = 8.5 Hz, 1 H), 8.05 (td, J_1 = 8.7 Hz, J_2 = 6.5 Hz, 1 H), 7.58 (ddd, J_1 = 11.5 Hz, J_2 = 9.3 Hz, J_3 = 2.4 Hz, 1 H), 7.33 (td, J_1 = 8.3 Hz, J_2 = 2.1 Hz, 1 H), 7.09 (d, J = 2.9 Hz, 1 H), 4.03-4.13 (m, 1 H), 3.13 (td, J_1 = 10.7 Hz, J_2 = 3.5 Hz, 1 H), 3.06 (s, 3 H), 2.80-2.91

(m, 2 H), 2.77 (s, 3 H), 2.23-2.36 (m, 2 H), 2.19 (t, *J* = 11.2 Hz, 1 H), 1.79-1.87 (m, 1 H), 1.67-1.79 (m, 4 H), 1.53-1.64 (m, 2 H), 1.13-1.28 (m, 4 H), 0.99-1.13 (m, 1 H).

(3*R*,4*R*)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid dimethylamide (3*R*,4*R*)-11i. Prepared in analogy to compound (3*S*,4*S*)-**11i**, starting from (3*R*,4*R*)-4-((*R*)-1-phenyl-ethylamino)-piperidine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-ethyl ester **19**[39]. LC-MS method A: t_R = 0.71 min; $[M+H]^+$ = 461.23. Chiral HPLC: t_R = 9.1 min; 95.6 % ee; Column: Regis (R,R) Whelk-O1, 4.6x250 mm, 5 µm; Detector wavelength: 254 nm; Eluent: 30% Heptane 0.05% DEA; 70% Ethanol 0.05% DEA; Flow: 0.8 mL/min; BPR: 150 bar; Temperature: 25°C. Injection volume: 2.5 µl. LC-HRMS: t_R = 0.60 min; m/z = 460.2285, found = 461.2362 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 8.69 (d, *J* = 8.3 Hz, 1 H), 8.05 (q, *J* = 7.9 Hz, 1 H), 7.58 (m, 1 H), 7.33 (t, *J* = 8.4 Hz, 1 H), 7.09-7.11 (m, 1 H), 4.03-4.12 (m, 1 H), 3.13 (m, 2 H), 3.06 (s, 3 H), 2.85 (t, *J* = 13.5 Hz, 1 H), 2.77 (s, 3 H), 2.16-2.33 (m, 3 H), 1.83 (d, *J* = 11.0 Hz, 1 H), 1.73 (d, *J* = 7.2 Hz, 4 H), 1.57 (d, *J* = 12.0 Hz, 2 H), 1.12-1.26 (m, 4 H), 1.04-1.11 (m, 1 H).

Preparation of compounds 20a-20q and 21a-21g

The compounds were prepared in analogy to compound **(3*S*,4*S*)-11i** from carboxylic acid **11h** and the corresponding amine**.**

***Rac*-(3*R**,4*R**)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid amide (20a).** Prepared from ammonium chloride**.** LC-MS method B: t_R = 0.88 min; $[M+H]^+$ = 433.18. LC-HRMS: t_R = 0.53 min; m/z = 432.1973, found = 433.205 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.60 (d, *J* = 8.2 Hz, 1 H), 8.05 (td, J_1 = 6.5 Hz, J_2 = 8.7 Hz, 1 H), 7.58 (ddd, J_1 = 2.5 Hz, J_2 = 9.3 Hz, J_3 = 11.5 Hz, 1 H), 7.33 (td, J_1 = 2.1 Hz, J_2 = 8.3 Hz, 1 H), 7.16 (s, 1 H), 7.12 (d, *J* = 2.8 Hz, 1 H), 6.83 (s, 1 H), 3.90-4.03 (m,

1 H), 2.87-2.95 (m, 1 H), 2.77-2.86 (m, 1 H), 2.55-2.63 (m, 1 H), 2.21-2.35 (m, 3 H), 1.64-1.89 (m, 5 H), 1.42-1.63 (m, 2 H), 1.14-1.30 (m, 5 H), 0.98-1.13 (m, 1 H).

***Rac*-(3*R**,4*R**)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid methylamide (20b).** Prepared from methylamine hydrochloride. LC-MS method B: t_R = 0.95 min; $[M+H]^+$ = 446.95. LC-HRMS: t_R = 0.55 min; m/z = 446.2129, found = 447.2209 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.57 (d, J = 8.4 Hz, 1 H), 8.05 (td, J_1 = 6.4 Hz, J_2 = 8.7 Hz, 1 H), 7.56-7.64 (m, 2 H), 7.30-7.37 (m, 1 H), 7.11 (d, J = 2.9 Hz, 1 H), 3.91-4.05 (m, 1 H), 2.75-2.93 (m, 2 H), 2.54-2.62 (m, 1 H), 2.47-2.55 (m, 3 H), 2.21-2.35 (m, 3 H), 1.79-1.89 (m, 1 H), 1.65-1.79 (m, 4 H), 1.45-1.64 (m, 2 H), 1.13-1.28 (m, 4 H), 1.01-1.13 (m, 1 H).

***Rac*-(3*R**,4*R**)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid ethyl-methyl-amide (20c).** Prepared from N-ethylmethylamine. LC-MS method B: t_R = 1.04 min; $[M+H]^+$ = 474.91. LC-HRMS: t_R = 0.62 min; m/z = 474.2442, found = 475.2526 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.69 (d, J = 8.6 Hz, 0.5 H), 8.63 (d, J = 8.8 Hz, 0.5 H), 8.01-8.09 (m, 1 H), 7.58 (ddd, J_1 = 11.4 Hz, J_2 = 9.1 Hz, J_3 = 2.4 Hz, 1 H), 7.33 (td, J_1 = 8.5 Hz, J_2 = 2.1 Hz, 1 H), 7.08 (dd, J_1 = 6.1 Hz, J_2 = 2.9 Hz, 1 H), 4.01-4.16 (m, 1 H), 3.56-3.67 (m, 0.5 H), 3.34-3.41 (m, 0.5 H), 3.21-3.29 (m, 0.5 H), 3.05-3.16 (m, 1.5 H), 3.01-3.05 (m, 1.5 H), 2.79-2.91 (m, 2 H), 2.72-2.77 (m, 1.5 H), 2.19-2.36 (m, 3 H), 1.59-1.85 (m, 6 H), 1.51-1.59 (m, 1 H), 1.15-1.27 (m, 4 H), 1.11-1.15 (m, 1.5 H), 1.01-1.11 (m, 1 H), 0.88 (t, J = 7.0 Hz, 1.5 H).

***Rac*-5-(2,4-Difluoro-phenyl)-isoxazole-3-carboxylic acid [(3*R**,4*R**)-3-(azetidine-1-carbonyl)-1-cyclohexyl-piperidin-4-yl]-amide (20d).** Prepared from azetidine. LC-MS method B: t_R = 0.93 min; $[M+H]^+$ = 473.15. LC-HRMS: t_R = 0.58 min; m/z = 472.2286, found = 473.2365 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.71 (d, J = 8.1 Hz, 1H), 8.06 (td, J_1

= 6.4 Hz, J_2 = 8.5 Hz, 1H), 7.59 (ddd, J_1 = 2.6 Hz, J_2 = 9.3 Hz, J_3 = 11.4 Hz, 1H), 7.32-7.37 (m, 1 H), 7.12 (d, J = 2.9 Hz, 1 H), 4.29-4.38 (m, 1 H), 4.08-4.17 (m, 1 H), 3.94-4.06 (m, 1 H), 3.69-3.84 (m, 2 H), 2.79-2.93 (m, 2 H), 2.63-2.72 (m, 1 H), 2.05-2.37 (m, 5 H), 1.78-1.86 (m, 1 H), 1.68-1.78 (m, 4 H), 1.52-1.63 (m, 2 H), 1.14-1.28 (m, 4 H), 1.00-1.13 (m, 1 H).

***Rac*-5-(2,4-Difluoro-phenyl)-isoxazole-3-carboxylic acid [(3*R**,4*R**)-1-cyclohexyl-3-(pyrrolidine-1-carbonyl)-piperidin-4-yl]-amide (20e).** Prepared from pyrrolidine. LC-MS method B: t_R = 1.03 min; $[M+H]^+$ = 486.92. LC-HRMS: t_R = 0.62 min; m/z = 486.2442, found = 487.252 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.70 (d, J = 8.7 Hz, 1 H), 8.05 (td, J_1 = 6.5 Hz, J_2 = 8.7 Hz, 1 H), 7.58 (ddd, J_1 = 2.5 Hz, J_2 = 9.4 Hz, J_3 = 11.4 Hz, 1 H), 7.33 (td, J_1 = 2.1 Hz, J_2 = 8.4 Hz, 1 H), 7.09 (d, J = 2.9 Hz, 1 H), 4.02-4.13 (m, 1 H), 3.72-3.80 (m, 1 H), 3.33-3.40 (m, 1 H), 3.16-3.26 (m, 2 H), 2.88-2.96 (m, 2 H), 2.80-2.86 (m, 1 H), 2.19-2.36 (m, 3 H), 1.85-1.94 (m, 1 H), 1.78-1.85 (m, 2 H), 1.65-1.78 (m, 6 H), 1.53-1.64 (m, 2 H), 1.13-1.29 (m, 4 H), 1.01-1.13 (m, 1 H).

***Rac*-(3*R**,4*R**)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (2-methoxy-ethyl)-methyl-amide (20f).** Prepared from 2-methylamino-ethanol. LC-MS method B: t_R = 1.05 min; $[M+H]^+$ = 504.91. LC-HRMS: t_R = 0.62 min; m/z = 504.2548, found = 505.2622 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.70 (d, J = 8.7 Hz, 0.5 H), 8.45-8.52 (m, 0.5 H), 8.05 (td, J_1 = 6.5 Hz, J_2 = 8.6 Hz, 1 H), 7.58 (ddd, J_1 = 2.4 Hz, J_2 = 9.4 Hz, J_3 = 11.4 Hz, 1 H), 7.33 (td, J_1 = 2.2 Hz, J_2 = 8.4 Hz, 1 H), 7.09 (d, J = 2.9 Hz, 1 H), 4.01-4.13 (m, 1 H), 3.85-3.96 (m, 0.5 H), 3.43-3.56 (m, 1.5 H), 3.20-3.31 (m, 3.5 H), 3.10-3.19 (m, 1 H), 3.07-3.10 (m, 3 H), 2.88-2.94 (m, 0.5 H), 2.81-2.88 (m, 1.5 H), 2.77 (s, 1.5 H), 2.15-2.36 (m, 3 H), 1.78-1.84 (m, 1 H), 1.69-1.78 (m, 4 H), 1.60-1.68 (m, 1 H), 1.53-1.60 (m, 1 H), 1.12-1.28 (m, 4 H), 1.01-1.13 (m, 1 H).

***Rac*-(3*R**,4*R**)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (2-hydroxy-ethyl)-amide (20g).** Prepared from (2-hydroxy-ethyl)-amine. LC-MS method B: t_R = 0.89 min; $[M+H]^+$ = 476.89. LC-HRMS: t_R = 0.52 min; m/z = 476.2235, found = 477.2316 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.56 (d, J = 8.5 Hz, 1 H), 8.06 (td, J_1 = 8.7 Hz, J_2 = 6.5 Hz, 1 H), 7.66 (t, J = 5.6 Hz, 1 H), 7.58 (ddd, J_1 = 11.5 Hz, J_2 = 9.3 Hz, J_3 = 2.5 Hz, 1 H), 7.33 (td, J_1 = 8.3 Hz, J_2 = 2.1 Hz, 1 H), 7.11 (d, J = 2.9 Hz, 1 H), 4.57 (t, J = 5.5 Hz, 1 H), 3.90-4.01 (m, 1 H), 3.23-3.35 (m, 2 H), 3.00-3.12 (m, 2 H), 2.83-2.91 (m, 1 H), 2.77-2.83 (m, 1 H), 2.53-2.62 (m, 1 H), 2.22-2.40 (m, 3 H), 1.79-1.89 (m, 1 H), 1.67-1.79 (m, 4 H), 1.54-1.61 (m, 1 H), 1.49 (ddd, J_1 = 3.7 Hz, J_2 = 12.1 Hz, J_3 = 24.1 Hz, 1H), 1.12-1.27 (m, 4 H), 1.00-1.12 (m, 1 H).

***Rac*-(3*R**,4*R**)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid benzylamide (20h).** Prepared from benzylamine. LC-MS method B: t_R = 1.05 min; $[M+H]^+$ = 523.17. LC-HRMS: t_R = 0.67. min; m/z = 522.2442, found = 523.2515 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.64 (d, J = 8.6 Hz, 1H), 8.15-8.21 (m, 1 H), 8.07 (td, J_1 = 8.7 Hz, J_2 = 6.4 Hz, 1H), 7.60 (ddd, J_1 = 11.4 Hz, J_2 = 9.3 Hz, J_3 = 2.4 Hz, 1H), 7.32-7.38 (m, 1 H), 7.12-7.17 (m, 2 H), 7.04-7.12 (m, 4 H), 4.36-4.44 (m, 1 H), 3.98-4.12 (m, 2 H), 2.88-2.97 (m, 1 H), 2.80-2.88 (m, 1 H), 2.67-2.75 (m, 1 H), 2.25-2.43 (m, 3 H), 1.80-1.89 (m, 1 H), 1.69-1.80 (m, 4 H), 1.49-1.63 (m, 2 H), 1.15-1.28 (m, 4 H), 1.02-1.14 (m, 1 H).

***Rac*-(3*R**,4*R**)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid phenylamide (20i).** Prepared from aniline. LC-MS method B: t_R = 1.10 min; $[M+H]^+$ = 509.12. LC-HRMS: t_R = 0.69 min; m/z = 508.2286, found = 509.2355 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 9.83 (s, 1 H), 8.77 (d, J = 8.4 Hz, 1 H), 8.02 (td, J_1 = 6.4 Hz, J_2 = 8.7 Hz, 1 H), 7.54-7.60 (m, 3 H), 7.29-7.34 (m, 1 H), 7.23-7.28 (m, 2 H), 7.07 (d, J = 2.9 Hz, 1 H), 6.97-7.03 (m, 1 H), 4.06-4.16 (m, 1 H), 3.02-3.09 (m, 1 H), 2.81-2.91 (m,

2 H), 2.28-2.42 (m, 3 H), 1.84-1.93 (m, 1 H), 1.69-1.81 (m, 4 H), 1.51-1.62 (m, 2 H), 1.15-1.30 (m, 4 H), 1.02-1.14 (m, 1 H).

***Rac*-(3*R**,4*R**)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (pyridin-2-ylmethyl)-amide (20j).** Prepared from pyridin-2-ylmethanamine. LC-MS method B: t_R = 0.98 min; $[M+H]^+$ = 523.86. LC-HRMS: t_R = 0.54 min; m/z = 523.2395, found = 524.2479 $[M + H]^+$. 1H M-NMR (400 MHz, DMSO, water suppression) δ: 8.69-8.76 (m, 1 H), 8.35-8.41 (m, 1 H), 8.30-8.35 (m, 1 H), 8.03-8.11 (m, 1 H), 7.55-7.64 (m, 1 H), 7.38-7.45 (m, 1 H), 7.31-7.38 (m, 1 H), 7.15-7.22 (m, 1 H), 7.08-7.13 (m, 2 H), 4.40-4.49 (m, 1 H), 4.16-4.23 (m, 1 H), 3.96-4.08 (m, 1 H), 2.91-2.98 (m, 1 H), 2.79-2.86 (m, 1 H), 2.67-2.79 (m, 1 H), 2.25-2.43 (m, 3 H), 1.80-1.89 (m, 1 H), 1.69-1.80 (m, 4 H), 1.50-1.62 (m, 2 H), 1.14-1.28 (m, 4 H), 1.02-1.14 (m, 1 H).

***Rac*-(3*R**,4*R**)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid phenethyl-amide (20k).** Prepared from phenethylamine**.** LC-MS method B: t_R = 1.13 min; $[M+H]^+$ = 537.16. LC-HRMS: t_R = 0.71 min; m/z = 536.2599, found = 537.2678 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.55 (d, J = 8.4 Hz, 1 H), 8.05 (td, J_1 = 8.7 Hz, J_2 = 6.4 Hz, 1 H), 7.77 (t, J = 5.5 Hz, 1 H), 7.58 (ddd, J_1 = 2.6 Hz, J_2 = 9.3 Hz, J_3 = 11.6 Hz, 1H), 7.30-7.36 (m, 1 H), 7.18-7.24 (m, 2 H), 7.10-7.16 (m, 4 H), 3.92-4.03 (m, 1 H), 3.17-3.31 (m, 2 H), 2.74-2.84 (m, 2 H), 2.56-2.70 (m, 3 H), 2.20-2.33 (m, 3 H), 1.79-1.87 (m, 1 H), 1.66-1.79 (m, 4 H), 1.45-1.63 (m, 2 H), 1.13-1.28 (m, 4 H), 1.02-1.13 (m, 1 H).

***Rac*-(3*R**,4*R**)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid methyl-phenethyl-amide (20l).** Prepared from N-methyl-2-phenylethylamine. LC-MS method B: t_R = 1.18 min; $[M+H]^+$ = 551.17. LC-HRMS: t_R = 0.75 min; m/z = 550.2755, found = 551.2838 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.69 (d, J = 8.2 Hz, 1 H, 1H), 8.04 (td, J_1 = 8.5 Hz, J_2 = 6.6 Hz, 1H), 7.57 (m, J_1 = 2.1 Hz, J_2 = 9.8 Hz,

1 H), 7.30-7.36 (m, 2 H), 7.19-7.29 (m, 2 H), 7.12-7.18 (m, 2 H), 7.07-7.12 (m, 1 H), 4.01-4.14 (m, 1 H), 3.87-4.00 (m, 0.5 H), 3.51-3.63 (m, 0.5 H), 3.29-3.45 (m, 1 H), 3.00-3.13 (m, 1 H), 2.94-3.00 (m, 1.5 H), 2.86-2.94 (m, 0.5 H), 2.76-2.86 (m, 1.5 H), 2.72-2.76 (m, 1.5 H), 2.60-2.72 (m, 2 H), 2.15-2.35 (m, 2.5 H), 2.03-2.15 (m, 0.5 H), 1.50-1.87 (m, 7 H), 0.99-1.28 (m, 5 H).

Stereoisomeric mixture (3*R,4*R**)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid ((R*)-1-pyridin-2-yl-ethyl)-amide (20m).** Prepared from 1-(2-pyridyl)ethylamine**.** QC LC-MS: t_R = 0.67 min; $[M+H]^+$ = 538.20 and t_R = 0.68 min; $[M+H]^+$ = 538.20. LC-HRMS: t_R = 0.58 min; m/z = 537.2551, found = 538.2631 $[M + H]^+$.

(3*R*,4*R*)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid ((*R*)-1-pyridin-2-yl-ethyl)-amide (20n) was synthesised by HATU amidation of (3*R*,4*R*)-1-cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid with (*R*)-1-(pyridin-2-yl)ethanamine. LC-MS method A: t_R = 0.63 min; $[M+H]^+$ = 538.33. Chiral HPLC: t_R = 11.3 min; > 99 % ee; column: ChiralPak IB 4.6x250 mm, 5 μM; detector wavelength: 254 nm; eluent: 90% heptane 0.05% DEA; 10% ethanol 0.05% DEA; flow: 0.8 mL/min; BPR: 150 bar; temperature: 25°C; injection volume: 4 μl. LC-HRMS: t_R = 0.58 min; m/z = 537.2551, found = 538.2631 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 8.69 (m, 1 H), 8.33 (d, J = 4.7 Hz, 1 H), 8.22 (d, J = 7.6 Hz, 1 H), 8.08 (m, 1 H), 7.60 (m, 1 H), 7.35 (td, J_1 = 8.5 Hz, J_2 = 2.3 Hz, 1 H), 7.24 (m, 2 H), 7.06 (d, J = 2.8 Hz, 1 H), 7.00 (m, 1 H), 4.87 (quint, J = 7.0 Hz, 1 H), 3.90-3.99 (m, 1 H), 2.93 (d, J = 9.3 Hz, 1 H), 2.81 (d, J = 11.3 Hz, 1 H), 2.75 (td, J_1 = 3.5 Hz, J_2 = 11.0 Hz, 1 H), 2.38 (m, 1 H), 2.26-2.34 (m, 2 H), 1.80-1.84 (m, 1 H), 1.74 (d, J = 8.0 Hz, 4 H), 1.49-1.60 (m, 2 H), 1.34 (d, J = 7.0 Hz, 3 H), 1.16-1.26 (m, 5 H).

(3*S*,4*S*)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid ((R)-1-pyridin-2-yl-ethyl)-amide (20o) was synthesised by HATU amidation of (3*S*,4*S*)-1-cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid **19** with (*R*)-1-(pyridin-2-yl)ethanamine. LC-MS method A: t_R = 0.64 min; $[M+H]^+$ = 538.21. Chiral HPLC: t_R = 15.8 min; >99% ee; column: ChiralPak IB 4.6x250 mm, 5 μM; detector wavelength: 254 nm; eluent: 90% heptane 0.05% DEA; 10% ethanol 0.05% DEA; flow: 0.8 mL/min; BPR: 150 bar; temperature: 25°C; injection volume: 5 μl. LC-HRMS: t_R = 0.59 min; m/z = 537.2551, found = 538.2633 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 8.71 (d, J = 8.6 Hz, 1 H), 8.50-8.51 (m, 1 H), 8.16 (d, J = 8.1 Hz, 1 H), 8.06 (td, J_1 = 8.7 Hz, J_2 = 6.4 Hz, 1 H), 7.72 (td, J_1 = 7.7 Hz, J_2 = 1.8 Hz, 1 H), 7.58 (ddd, J_1 = 11.5 Hz, J_2 = 9.3 Hz, J_3 = 2.5 Hz, 1 H), 7.31-7.35 (m, 2 H), 7.25 (ddd, J_1 = 7.5 Hz, J_2 = 4.8 Hz, J_3 = 1.0 Hz, 1 H), 7.15 (d, J = 2.9 Hz, 1 H), 4.92 (m, 1 H), 4.02 (m, 1 H), 2.90 (m, 2 H), 2.70-2.74 (m, 1 H), 2.37-2.47 (m, 3 H), 1.87-1.90 (m, 1 H), 1.73-1.74 (m, 4 H), 1.49-1.58 (m, 2 H), 1.17-1.22 (m, 7 H), 1.02-1.09 (m, 1 H).

(3*R*,4*R*)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid ((*S*)-1-pyridin-2-yl-ethyl)-amide (20p) was synthesised by HATU amidation of (3*R*,4*R*)-1-cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid with (*S*)-1-(pyridin-2-yl)ethanamine. LC-MS method A: t_R = 0.65 min; $[M+H]^+$ = 538.23. Chiral HPLC: t_R = 13.6 min; 96.5 % ee; column: ChiralPak IB 4.6x250 mm, 5 μM; detector wavelength: 260 nm; eluent: 90% heptane 0.05% DEA; 10% ethanol 0.05% DEA; flow: 0.8 mL/min; BPR: 150 bar; temperature: 25°C; injection volume: 2.5 μl. LC-HRMS: t_R = 0.59 min; m/z = 537.2551, found = 538.2628 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 8.68 (d, J = 8.7 Hz, 1 H), 8.52 (d, J = 4.2 Hz, 1 H), 8.13 (d, J = 8.1 Hz, 1 H), 8.07 (q, J = 8.6 Hz, 1 H), 7.73 (t, J = 7.3 Hz, 1 H), 7.58 (t, J = 9.3 Hz, 1 H), 7.33 (d, J = 8.0 Hz, 2 H), 7.26 (t, J = 5.6 Hz, 1 H), 7.14 (d, J = 2.4 Hz, 1 H), 4.93 (t, J = 7.8

Hz, 1 H), 3.96-4.03 (m, 1 H), 2.80-2.89 (m, 2 H), 2.65-2.72 (m, 1 H), 2.28-2.42 (m, 3 H), 1.86-1.91 (m, 1 H), 1.69-1.78 (m, 5 H), 1.55-1.60 (m, 1 H), 1.49-1.53 (m, 1 H), 1.19-1.23 (m, 6 H), 1.04-1.10 (m, 1 H).

(3*S*,4*S*)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid ((*S*)-1-pyridin-2-yl-ethyl)-amide (20q) was synthesised by HATU amidation of (3S,4S)-1-cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid **19** with (*S*)-1-(pyridin-2-yl)ethanamine. LC-MS method A: t_R = 0.67 min; $[M+H]^+$ = 538.28. Chiral HPLC: t_R = 17.3 min; 96 % ee; column: ChiralPak IB 4.6x250 mm, 5 μM; detector wavelength: 260 nm; eluent: 90% heptane 0.05% DEA; 10% ethanol 0.05% DEA; flow: 0.8 mL/min; BPR: 150 bar; temperature: 25°C; injection volume: 3 μl. LC-HRMS: t_R = 0.58 min; m/z = 537.2551, found = 538.2631 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 8.63 (d, J = 8.6 Hz, 1 H), 8.33 (d, J = 4.6 Hz, 1 H), 8.15 (d, J = 7.7 Hz, 1 H), 8.08 (td, J_1 = 8.7 Hz, J_2 = 6.6 Hz, 1 H), 7.60 (m, 1 H), 7.35 (td, J_1 = 8.5 Hz, J_2 = 2.2 Hz, 1 H), 7.22-7.29 (m, 2 H), 7.03 (d, J = 2.8 Hz, 1 H), 7.00 (m, 1 H), 4.88 (quint, J = 7.3 Hz, 1 H), 3.94 (m, 1 H), 2.93 (d, J = 9.2 Hz, 1 H), 2.81 (d, J = 11.1 Hz, 1 H), 2.74 (td, J_1 = 10.8 Hz, J_2 = 3.4 Hz, 1 H), 2.38 (m, 1 H), 2.26-2.34 (m, 2 H), 1.82 (dd, J_1 = 12.5 Hz, J_2 = 3.9 Hz, 1 H), 1.74 (d, J = 7.5 Hz, 4 H), 1.48-1.59 (m, 2 H), 1.35 (d, J = 7.0 Hz, 3 H), 1.21 (m, 4 H), 1.06-1.11 (m, 1 H).

(3*S*,4*S*)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid benzylamide (21a) was synthesised by HATU amidation of the chiral acid **19** with benzyl amine. LC-MS method A: t_R = 0.76 min; $[M+H]^+$ = 523.20. LC-HRMS: t_R = 0.68 min; m/z = 522.2442, found = 523.2525 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 8.66 (d, J = 8.5 Hz, 1 H), 8.19 (t, J = 5.8 Hz, 1 H), 8.07 (td, J_1 = 8.7 Hz, J_2 = 6.5 Hz, 1 H), 7.57-7.63 (m, 1 H), 7.35 (td, J_1 = 8.3 Hz, J_2 = 2.1 Hz, 1 H), 7.13-7.16 (m, 2 H), 7.11

(d, J = 2.9 Hz, 1 H), 7.07 (dd, J_1 = 5.1 Hz, J_2 = 2.0 Hz, 3 H), 4.40 (m, 1 H), 4.07 (dd, J_1 = 15.4 Hz, J_2 = 5.1 Hz, 2 H), 2.92 (d, J = 10.0 Hz, 1 H), 2.83 (d, J = 9.3 Hz, 1 H), 2.68-2.73 (m, 1 H), 2.27-2.43 (m, 3 H), 1.84 (d, J = 10.3 Hz, 1 H), 1.74 (d, J = 6.5 Hz, 4 H), 1.51-1.59 (m, 2 H), 1.15-1.23 (m, 5 H), 1.03-1.11 (m, 1 H).

(3*S*,4*S*)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid ((*R*)-1-phenyl-ethyl)-amide (21b) was synthesised by HATU amidation of the chiral acid **19** with (*R)*-(+)-α-methylbenzyl amine. QC LC-MS: t_R = 0.81 min; $[M+H]^+$ = 537.50. LC-HRMS: t_R = 0.73 min; m/z = 536.2598, found = 537.2678 $[M + H]^+$. ^{1}H NMR (400 MHz, CDCl3) δ: 7.96 (q, J = 8.3 Hz, 1 H), 7.28 (s, 3 H), 7.20-7.24 (m, 2 H), 6.99-7.09 (m, 4 H), 5.12 (m, 1 H), 4.23-4.31 (m, 1 H), 3.00-3.05 (m, 1 H), 2.83-2.87 (m, 1 H), 2.67-2.73 (m, 2 H), 2.56 (m, 1H), 2.35-2.45 (m, 1 H), 2.01-2.07 (m, 1 H), 1.79-1.88 (m, 7 H), 1.64-1.67 (m, 1 H), 1.43 (d, J = 7.0 Hz, 3 H), 1.26 (m, J = 10.1 Hz, 4 H).

(3*S*,4*S*)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid ((*S*)-2-hydroxy-1-phenyl-ethyl)-amide (21c) was synthesised by HATU amidation of the chiral acid **19** with (*S)*-2-amino-2-phenyl-ethanol. LC-MS method B: t_R = 0.98 min; $[M+H]^+$ = 553.21. LC-HRMS: t_R = 0.64 min; m/z = 552.2548, found = 553.2634 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 8.63 (d, J = 8.8 Hz,1 H), 8.06 (m, 2 H), 7.58 (t, J = 10.3 Hz, 1 H), 7.31-7.35 (m, 1 H), 7.27 (m, 5 H), 7.19-7.22 (m, 1 H), 7.14 (d, J = 2.2 Hz, 1 H), 4.70-4.77 (m, 2 H), 3.99-4.04 (m, 1 H), 2.79-2.90 (m, 1 H), 2.67-2.73 (m, 1 H), 2.26-2.38 (m, 2 H), 1.84-1.90 (m, 1 H), 1.67-1.77 (m, 5 H), 1.45-1.59 (m, 2 H), 1.13-1.26 (m, 6 H), 1.02-1.09 (m, 1 H).

(3*S*,4*S*)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (2-pyridin-2-yl-ethyl)-amide (21d) was synthesised by HATU amidation of the chiral acid **19** with 2-(pyridin-2-yl)ethan-1-amine. LC-MS method B: t_R = 0.99 min; $[M+H]^+$ = 538.22. LC-HRMS: t_R = 0.47 min; m/z = 537.2551, found = 538.2631 [M

+ H]. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 8.57 (d, J = 8.5 Hz, 1 H), 8.44 (d, J = 3.8 Hz, 1 H), 8.05 (m, 1 H), 7.78-7.81 (m, 1 H), 7.55-7.61 (m, 2 H), 7.31-7.35 (m, 1 H), 7.15 (m, 2 H), 7.11 (d, J = 2.8 Hz, 1 H), 3.92-4.02 (m, 1 H), 2.74-2.84 (m, 5 H), 2.23-2.29 (m, 3 H), 1.80-1.83 (m, 1 H), 1.70-1.73 (m, 5 H), 1.55-1.59 (m, 2 H), 1.47-1.52 (m, 1 H), 1.15-1.22 (m, 4 H), 1.06-1.12 (m, 1 H).

(3S,4S)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-methyl-1-pyridin-2-yl-ethyl)-amide (21e) was synthesised by HATU amidation of the chiral acid **19** with 2-(pyridin-2-yl)propan-2-amine. LC-MS method A: t_R = 0.68 min; $[M+H]^+$ = 552.23. LC-HRMS: t_R = 0.61 min; m/z = 551.2707, found = 552.2778 [M + H]. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 8.74 (d, J = 8.5 Hz, 1 H), 8.39 (d, J = 4.6 Hz, 1 H), 8.09 (m, 1 H), 8.00 (s, 1 H), 7.57-7.63 (m, 1 H), 7.31-7.39 (m, 3 H), 7.16 (d, J = 2.7 Hz, 1 H), 7.09 (m, 1 H), 3.87-3.96 (m, 1 H), 2.91 (d, J = 9.3 Hz, 1 H), 2.81 (d, J = 11.0 Hz, 1 H), 2.68-2.73 (m, 2 H), 2.24-2.37 (m, 4 H), 1.83-1.87 (m, 1 H), 1.69-1.75 (m, 4 H), 1.55-1.60 (m, 1 H), 1.52 (s, 3 H), 1.44 (s, 3 H), 1.21 (s, 4 H).

(3S,4S)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyridin-2-yl-cyclopropyl)-amide (21f) was synthesised by HATU amidation of the chiral acid **19** with 1-(pyridin-2-yl)cyclopropan-1-amine. LC-MS method B: t_R = 0.98 min; [M+H]+ = 550.22. LC-HRMS: t_R = 0.59 min; m/z = 549.2551, found = 550.2618 [M + H]. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 8.80 (d, J = 8.7 Hz, 1 H), 8.48 (m, 1 H), 8.35 (d, J = 4.6 Hz, 1 H), 8.10 (m, 1 H), 7.58-7.63 (m, 1 H), 7.33-7.37 (m, 1 H), 7.30 (s, 2 H), 7.18 (d, J = 2.7 Hz, 1 H), 7.00-7.06 (m, 1 H), 3.98-4.08 (m, 1 H), 2.95 (d, J = 9.8 Hz, 1 H), 2.84 (d, J = 10.8 Hz, 1 H), 2.68-2.75 (m, 1 H), 2.27-2.42 (m, 3 H), 1.85 (d, J = 11.0 Hz, 1 H), 1.75 (d, J = 7.5 Hz, 4 H), 1.52-1.60 (m, 2 H), 1.40-1.45 (m, 1 H), 1.30-1.35 (m, 1 H), , 1.20-1.26 (m, 4 H), 1.00-1.11 (m, 3 H).

(3*S*,4*S*)-1-Cyclohexyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide (21g) was synthesised in analogy to 7b by HATU amidation of the chiral acid **15** with 1-(pyrimidin-2-yl)cyclopropan-1-amine. LC-MS method B: t_R = 0.94 min; [M+H]+ = 551.21. LC-HRMS: t_R = 0.61 min; m/z = 550.2551, found = 551.2581. [M + H]. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 8.53 (s, 1 H), 8.50 (s, 2 H), 8.42 (s, 1 H), 8.08 (m, 1 H), 7.59 (m, 1 H), 7.34 (td, J_1 = 8.5 Hz, J_2 = 2.2 Hz, 1 H), 7.16-7.19 (m, 2 H), 3.94-3.97 (m, 1 H), 2.96 (d, J = 10.5 Hz, 1 H), 2.82 (d, J = 10.5 Hz, 1 H), 2.60-2.68 (m, 1 H), 2.26-2.40 (m, 4 H), 1.86 (d, J = 10.5 Hz, 1 H), 1.72-1.76 (m, 4 H), 1.52-1.60 (m, 2 H), 1.46-1.50 (m, 1 H), 1.36-1.40 (m, 1 H), 1.22 (m, 3 H), 1.07-1.11 (m, 3 H).

Preparation of compounds 28a-28e, 28g-31

(3*S*,4*S*)-4-{[5-(2,4-Difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-1-methyl-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide (28a) was synthesised in analogy to **28f** by reductive amination of (3*S*,4*S*)-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide hydrochloride **27** with formaldehyde 36.5 % aq. solution. LC-MS method A: t_R = 0.65 min; $[M+H]^+$ = 483.08. LC-HRMS: t_R = 0.55 min; m/z = 482.1878, found = 483.1951 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 8.54 (d, J = 8.5 Hz, 1 H), 8.50 (d, J = 4.9 Hz, 2 H), 8.44 (m, 1 H), 8.08 (m, 1 H), 7.56-7.62 (m, 1 H), 7.34 (td, J_1 = 8.5 Hz, J_2 = 2.2 Hz, 1 H), 7.18 (d, J = 4.8, Hz, 1 H), 7.16 (d, J= 3.0 Hz, 1 H), 3.92-4.01 (m, 1 H), 2.91 (d, J = 9.0 Hz. 1 H), 2.76-2.80 (m, 1 H), 2.73 (m, 1 H), 2.18-2.24 (m, 3 H), 2.07 (t, J = 11.5 Hz, 1 H), 1.96 (t, J = 11.3 Hz, 1 H), 1.83 (dd, J_1 = 12.8 Hz, J_2 = 4.3 Hz, 1 H), 1.63 (m, J = 3.8 Hz, 1 H), 1.46-1.50 (m, 1 H), 1.35-1.40 (m, 1 H), 1.04-1.12 (m, 2 H).

(3*S*,4*S*)-4-{[5-(2,4-Difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-1-ethyl-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide (28b) was synthesised by reductive

amination of the amine hydrochloride **27** with acetaldehyde. LC-MS method A: t_R = 0.65 min; $[M+H]^+$ = 497.03. LC-HRMS: t_R = 0.56 min; m/z = 496.2034, found = 497.2105 $[M + H]^+$. ^{1}H NMR (500 MHz, D_6-DMSO) δ: 8.57 (d, J = 8.4 Hz, 1 H), 8.50 (d, J = 4.8 Hz, 2 H), 8.46 (s, 1 H), 8.08 (m, 1 H), 7.60 (m, 1 H), 7.34 (td, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1 H), 7.18 (d, J = 4.8 Hz, 1 H), 7.17 (d, J = 3.0 Hz, 1 H), 3.97-4.03 (m, 1 H), 3.03 (d, J = 11.0 Hz, 1 H), 2.90-2.94 (m, 1 H), 2.69-2.75 (m, 1 H), 2.37-2.40 (m, 2 H), 2.06-2.12 (m, 1 H), 1.95-2.01 (m, 1 H), 1.86 (d, J = 11.0 Hz, 1 H), 1.56-1.64 (m, 1 H), 1.37-1.50 (m, 2 H), 1.22-1.29 (m, 1 H), 1.06-1.10 (m, 1 H), 1.03 (t, J = 7.1 Hz, 3 H).

(3*S*,4*S*)-4-{[5-(2,4-Difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-1-propyl-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide (28c). To a solution of (3*S*,4*S*)-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide hydrochloride **27** (70 mg, 0.14 mmol in EtOH (4 mL) was added 1-iodopropane (0.0137 mL, 0.14 mmol) followed by DIPEA (0.0712 mL, 0.416 mmol). The mixture was stirred overnight at 65°C. The mixture was concentrated, the residues dissolved in DMF and purified by prep. HPLC under basic conditions to yield **28c** (35 mg, 50%) as a white solid. LC-MS method A: t_R = 0.69 min; $[M+H]^+$ = 511.28. LC-HRMS: t_R = 0.57 min; m/z = 510.2191, found = 511.2266 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 8.55 (d, J = 8.5 Hz, 1 H), 8.50 (d, J = 4.9 Hz, 2 H), 8.45 (s, 1 H), 8.08 (td, J_1 = 8.7 Hz, J_2 = 6.4Hz, 1 H), 7.60 (m, 1 H), 7.34 (td, J_1 = 8.2 Hz, J_2 = 2.1 Hz, 1 H), 7.18 (m, 1 H), 7.16 (d, J = 2.7 Hz, 1 H), 3.99 (m, 1 H), 2.99 (d, J = 9.8 Hz, 1 H), 2.87 (d, J = 11.3 Hz, 1 H), 2.67-2.73 (m, 1 H), 2.28 (m, 2 H), 2.08 (t, J = 11.6 Hz, 1 H), 1.96 (m, J = 12.0 Hz, 1 H), 1.84 (dd, J_1 = 12.8 Hz, J_2 = 4.0 Hz, 1 H), 1.60 (m, 1 H), 1.43-1.50 (m, 3 H), 1.36-1.41 (m, 1 H), 1.08 (m, 2 H), 0.88 (t, J = 7.3 Hz, 3 H).

(3*S*,4*S*)-4-{[5-(2,4-Difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-1-isopropyl-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide (28d) was synthesised

by reductive amination of the amine hydrochloride **27** with acetone. LC-MS method A: t_R = 0.68 min; $[M+H]^+$ = 511.27. LC-HRMS: t_R = 0.56 min; m/z = 510.2191, found = 511.2275 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 8.54 (d, J = 8.5 Hz, 1 H), 8.50 (d, J = 4.9 Hz, 2 H), 8.44 (s, 1 H), 8.08 (td, J_1 = 8.7 Hz, J_2 = 6.4 Hz, 1 H), 7.60 (m, 1 H), 7.34 (td, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1 H), 7.18 (m, 1 H), 7.16 (m, 1 H), 3.96 (m, 1 H), 2.92 (d, J = 9.7 Hz, 1 H), 2.73-2.80 (m, 2 H), 2.62-2.68 (m, 1 H), 2.29 (t, J = 11.2 Hz, 1 H), 2.19 (m, 1 H), 1.85-1.89 (m, 1 H), 1.55 (dd, J_1 = 11.9 Hz, J_2 = 3.7 Hz, 1 H), 1.46-1.50 (m, 1 H), 1.36-1.40 (m, 1 H), 1.05-1.13 (m, 2 H), 0.99 (d, J = 6.5 Hz, 6 H)

(3*S*,4*S*)-1-Cyclopropyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide hydrochloride (28e) was synthesised by reductive amination of the amine hydrochloride **27** with (1-ethoxycyclopropoxy)trimethylsilane. LC-MS method B: t_R = 0.88 min; $[M+H]^+$ = 509.15. LC-HRMS: t_R = 0.63 min; m/z = 508.2034, found = 509.2120 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 8.88 (m, 1 H), 8.79 (s, 1 H), 8.53 (d, J = 4.8 Hz, 2 H), 8.06 (m, 1 H), 7.57 (m, 1 H), 7.31-7.35 (m, 2 H), 7.21 (t, J = 4.8 Hz, 1 H), 4.22-4.31 (m, 1 H), 3.26-3.51 (m, 3 H), 2.80-2.87 (m, 1 H), 1.99-2.10 (m, 3 H), 1.49-1.51 (m, 1 H), 1.36-1.39 (m, 1 H), 1.06-1.16 (m, 5 H), 0.81 (d, J = 6.4 Hz, 3 H).

(3*S*,4*S*)-1-Cyclobutyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide (28g) was synthesised by reductive amination of the amine hydrochloride **27** with cyclobutanone. LC-MS method A: t_R = 0.68 min; $[M+H]^+$ = 523.04. LC-HRMS: t_R = 0.57 min; m/z = 522.2191, found = 523.2266 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 8.57 (d, J = 8.5 Hz, 1 H), 8.50 (d, J = 4.8 Hz, 2 H), 8.45 (s, 1 H), 8.08 (m, 1 H), 7.60 (m, 1 H), 7.34 (td, J_1 = 8.4 Hz, J_2 = 2.1 Hz, 1 H), 7.18 (m, 1 H), 7.16 (d, J = 2.6 Hz, 1 H), 3.98 (m, 1 H), 2.92 (d, J = 9.1 Hz, 1 H), 2.80 (d, J = 10.8 Hz, 1 H), 2.63-2.74 (m, 2 H), 1.99 (d, J = 3.9 Hz, 2 H), 1.79-1.92 (m, 5 H), 1.60-1.65 (m, 2 H),

1.55 (dd, J_1 = 12.1 Hz, J_2 = 3.7 Hz, 1 H), 1.46-1.50 (m, 1 H), 1.35-1.39 (m, 1 H), 1.04-1.12 (m, 2 H).

(3*S*,4*S*)-1-Cyclobutylmethyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide hydrochloride (28h) was synthesised by reductive amination of the amine hydrochloride **27** with cyclobutanecarbaldehyde. LC-MS method B: t_R = 0.97 min; $[M+H]^+$ = 537.17. LC-HRMS: t_R = 0.60 min; m/z = 536.2347, found = 537.2430 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 10.62-10.67 (m, 1 H), 8.91 (d, J = 8.6 Hz, 1 H), 8.83 (s, 1 H), 8.52 (d, J = 4.9 Hz, 2 H), 8.06 (m, 1 H), 7.55-7.60 (m, 1 H), 7.31-7.35 (m, 2 H), 7.20 (t, J = 4.9 Hz, 1 H), 4.22-4.26 (m, 1 H), 3.10-3.29 (m, 5 H), 2.80-2.84 (m, 1 H), 1.98-2.13 (m, 5 H), 1.76-1.93 (m, 5 H), 1.50 (dd, J_1 = 9.8 Hz, J_2 = 4.1 Hz, 1 H), 1.34-1.37 (m, 1 H), 1.08-1.11 (m, 2 H).

(3*S*,4*S*)-1-Cyclopentyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide hydrochloride (28i) was synthesised by reductive amination of the amine hydrochloride **27** with cyclopentanone. LC-MS method A: t_R = 0.75 min; $[M+H]^+$ = 537.19. LC-HRMS: t_R = 0.59 min; m/z = 536.2347, found = 537.2423 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 10.66-10.77 (s, 1 H), 8.91 (d, J = 8.4 Hz, 1 H), 8.79 (s, 1 H), 8.51 (d, J = 4.9 Hz, 2 H), 8.07 (td, J_1 = 8.7 Hz, J_2 = 6.4 Hz, 1 H), 7.59 (m, 1 H), 7.35 (dd, J_1 = 8.4 Hz, J_2 = 2.2 Hz, 1 H), 7.31 (d, J = 2.8 Hz, 1 H), 7.20 (t, J = 4.9 Hz, 1 H), 4.24-4.33 (m, 1 H), 3.50-3.54 (m, 3 H), 3.15-3.30 (m, 3 H), 1.99-2.10 (m, 4 H), 1.83 (m, 2 H), 1.68-1.77 (m, 2 H), 1.49-1.60 (m, 3 H), 1.36-1.40 (m, 1 H), 1.08-1.11 (m, 2 H).

(3*S*,4*S*)-4-{[5-(2,4-Difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-1-(1-methyl-cyclopropylmethyl)-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide (28j) was synthesised by reductive amination of the amine hydrochloride **27** with 1-methylcyclopropane-1-carbaldehyde. LC-MS method A: t_R = 0.71 min; $[M+H]^+$ = 537.04. LC-HRMS: t_R = 0.59 min; m/z = 536.2347, found = 537.2416 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-

DMSO) δ: 8.56 (d, J = 8.5 Hz, 1 H), 8.51 (d, J = 4.8 Hz, 2 H), 8.48 (s, 1 H), 8.08 (td, J_1 = 8.7 Hz, J_2 =6.5Hz, 1 H), 7.60 (m, 1 H), 7.34 (td, J_1 = 8.4 Hz, J_2 = 2.3 Hz, 1 H), 7.19 (d, J = 4.8 Hz, 1 H), 7.17 (d, J = 3.0 Hz, 1 H), 3.99 (m, 1 H), 3.12 (dd, J_1 = 11.1 Hz, J_2 = 2.0 Hz, 1 H), 3.00 (d, J = 11.0 Hz, 1 H), 2.73 (td, J_1 = 10.9 Hz, J_2 = 3.6 Hz, 1 H), 2.23 (m, 1 H), 2.09 (d, J = 11.9 Hz, 1 H), 2.04 (m, 1 H), 1.84-1.94 (m, 2 H), 1.57-1.67 (m, 1 H), 1.48-1.52 (m, 1 H), 1.35-1.39 (m, 1 H), 1.07-1.11 (m, 5 H), 0.26-0.32 (m, 4 H).

(3*S*,4*S*)-4-{[5-(2,4-Difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-1-(1-fluoro-cyclopropylmethyl)-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide (28k) was synthesised by reductive amination of the amine hydrochloride **27** with 1-fluorocyclopropane-1-carbaldehyde. LC-MS method A: t_R = 0.71 min; $[M+H]^+$ = 541.24. LC-HRMS: t_R = 0.58 min; m/z = 540.2097, found = 541.2179 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 8.57 (d, J = 8.5 Hz, 1 H), 8.51 (d, J = 4.8 Hz, 2 H), 8.48 (s, 1 H), 8.08 (m, 1 H), 7.60 (m, 1 H), 7.34 (td, J_1 = 8.6 Hz, J_2 = 2.2 Hz, 1 H), 7.18 (t, J = 4.8 Hz, 1 H), 7.16 (d, J = 2.9 Hz, 1 H), 4.00 (m, 1 H), 3.16 (d, J = 9.3 Hz, 1 H), 3.01 (d, J = 11.3 Hz, 1 H), 2.71-2.78 (m, 3 H), 2.31 (t, J = 11.5 Hz, 1 H), 2.20 (t, J = 11.8 Hz, 1 H), 1.86 (d, J = 9.5 Hz, 1 H), 1.63 (m, 1 H), 1.48-1.52 (m, 1 H), 1.35-1.39 (m, 1 H), 1.02-1.10 (m, 3 H), 0.99 (m, J = 6.9 Hz, 1 H), 0.68 (m, 2 H).

(3*S*,4*S*)-4-{[5-(2,4-Difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-1-(3-fluoro-propyl)-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide (28l) was synthesised by N-alkylation of the amine hydrochloride **27** with 1-bromo-3-fluoro-propane. LC-MS method A: t_R = 0.67 min; $[M+H]^+$ = 529.06. LC-HRMS: t_R = 0.57 min; m/z = 528.2097, found = 529.2179 $[M + H]^+$. 1H NMR (400 MHz, D_6-DMSO) δ: 11.01-11.12 (s, 1 H), 8.91-8.93 (m, 1 H), 8.79-8.82 (m, 1 H), 8.51 (d, J = 4.8 Hz, 2 H), 8.07 (m, 1 H), 7.59 (t, J = 9.5 Hz, 1 H), 7.32-7.36 (m, 2 H), 7.20 (t, J = 4.8 Hz, 1 H), 4.61 (t, J = 5.5 Hz, 1 H), 4.49 (t, J = 5.3 Hz, 1 H),

4.22-4.32 (m, 1 H), 3.54-3.60 (m, 2 H), 3.19-3.26 (m, 4 H), 1.99-2.26 (m, 5 H), 1.45-1.51 (m, 1 H), 1.35-1.41 (m, 1 H), 1.05-1.13 (m, 2 H).

(3*S*,4*S*)-1-(3,3-Difluoro-cyclobutyl)-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide (28m) was synthesised by reductive amination of the amine hydrochloride **27** with 3,3-difluorocyclobutan-1-one. LC-MS method A: t_R = 0.69 min; $[M+H]^+$ = 558.96. LC-HRMS: t_R = 0.63 min; m/z = 558.2003, found = 559.2068 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 8.60 (d, J = 8.3 Hz, 1 H), 8.50 (d, J = 4.9 Hz, 2 H), 8.46 (s, 1 H), 8.08 (td, J_1 = 8.7 Hz, J_2 = 6.5 Hz, 1 H), 7.60 (m, 1 H), 7.34 (td, J_1 = 8.4 Hz, J_2 = 2.2 Hz, 1 H), 7.18 (d, J = 4.9 Hz, 1 H), 7.16 (m, 1 H), 4.01 (m, 1 H), 2.95 (d, J = 9.3 Hz, 1 H), 2.84 (d, J = 11.0 Hz, 1 H), 2.67-2.79 (m, 4 H), 2.33-2.47 (m, 2 H), 2.04 (t, J = 11.5 Hz, 1 H), 1.85-1.94 (m, 2 H), 1.53-1.63 (m, 1 H), 1.46-1.50 (m, 1 H), 1.36-1.40 (m, 1 H), 1.04-1.14 (m, 2 H).

(3*S*,4*S*)-4-{[5-(2,4-Difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-1-(2-methoxy-ethyl)-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide (28n) was synthesised by N-alkylation of the amine hydrochloride **27** with 1-bromo-2-methoxyethane. LC-MS method A: t_R = 0.63 min; $[M+H]^+$ = 527.20. LC-HRMS: t_R = 0.56 min; m/z = 526.2140, found = 527.2198 $[M + H]^+$. 1H NMR (400 MHz, D_6-DMSO) δ: 8.55 (d, J = 8.4 Hz, 1 H), 8.50 (d, J = 4.8 Hz, 2 H), 8.45 (s, 1 H), 8.08 (m, 1 H), 7.59 (m, 1 H), 7.34 (td, J_1 = 8.5 Hz, J_2 = 1.8 Hz, 1 H), 7.18 (m, 1 H), 7.16 (d, J = 3.1 Hz, 1 H), 3.98 (m, 1 H), 3.44 (t, J = 5.7 Hz, 2 H), 3.25 (s, 3 H), 3.01 (d, J = 9.5 Hz, 1 H), 2.90 (d, J = 11.1 Hz, 1 H), 2.70 (td, J_1 = 3.6 Hz, J_2 = 11.0 Hz, 1 H), 2.57 (m, 2 H), 2.20 (t, J = 11.3 Hz, 1 H), 2.08 (t, J = 11.0 Hz, 1 H), 1.83 (dd, J_1 = 2.8 Hz, J_2 = 12.3 Hz, 1 H), 1.54-1.65 (m, 1 H), 1.47-1.51 (m, 1 H), 1.36-1.40 (m, 1 H), 1.04-1.13 (m, 2 H).

(3*S*,4*S*)-1-Acetyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide (28o) was synthesised by N-acylation

of the amine hydrochloride **27** with acetic anhydride in DCM in the presence of triethylamine. LC-MS method A: t_R = 0.75 min; $[M+H]^+$ = 511.04. LC-HRMS: t_R = 0.79 min; m/z = 510.1827, found = 511.1913 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 8.61 (m, 1 H), 8.56 (s, 1 H), 8.53 (d, *J* = 4.7 Hz, 2 H), 8.05-8.11 (m, 1 H), 7.60 (t, *J* = 10.4 Hz, 1 H), 7.34 (t, *J* = 8.5 Hz, 1 H), 7.15-7.21 (m, 2 H), 4.57 (d, *J* = 11.3 Hz, 1 H), 4.21-4.29 (m, 1 H), 3.87 (d, *J* = 13.0 Hz, 1 H), 3.18 (m, 1 H), 2.62-2.72 (m, 2 H), 2.09 (s, 3 H), 1.89 (m, *J* = 13.5 Hz,1 H), 1.50-1.56 (m, 2 H), 1.35-1.43 (m, 1 H), 1.04-1.17 (m, 2 H).

(3*R*,4*R*)-1-Cyclopropylmethyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide (29) was synthesised by reductive amination of (3*R*,4*R*)-4-{[5-(2,4-Difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide hydrochloride with cyclopropanecarboxaldehyde. LC-MS method A: t_R = 0.69 min; $[M+H]^+$ = 523.03. Chiral HPLC: t_R = 4.6 min; 99 % ee; column: ChiralPak IC 4.6x250 mm, 5 µM; detector wavelength: 254 nm; eluent: 10% heptane 0.05% DEA; 90% ethanol 0.05% DEA; flow: 1.2 mL/min; BPR: 150 bar; temperature: 25 °C; injection volume: 6 µl. LC-HRMS: t_R = 0.57 min; m/z = 522.2191, found = 523.2270 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) *δ*: 8.57 (d, *J* = 8.5 Hz, 1 H), 8.51 (d, *J* = 4.9 Hz, 2 H), 8.47 (s, 1 H), 8.08 (td, J_1 = 8.7 Hz, J_2 = 6.4 Hz, 1 H), 7.59 (m, 1 H), 7.34 (td, J_1 = 8.3 Hz, J_2 = 2.1 Hz, 1 H), 7.18 (t, *J* = 4.9 Hz, 1 H), 7.16 (d, *J* = 3.0 Hz, 1 H), 3.99 (m, 1 H), 3.14 (d, *J* = 9.2 Hz, 1 H), 2.99 (d, *J* = 11.2 Hz, 1 H), 2.72 (td, J_1 = 11.0 Hz, J_2 = 3.6 Hz, 1 H), 2.22 (m, 2 H), 2.11 (t, *J* = 11.5 Hz, 1 H), 2.01 (t, *J* = 10.4 Hz, 1 H), 1.83-1.87 (m, 1 H), 1.61 (m, *J* = 3.8 Hz, 1 H), 1.48-1.52 (m, 1 H), 1.34-1.39 (m, 1 H), 1.08 (m, 2 H), 0.82-0.88 (m, 1 H), 0.46-0.51 (m, 2 H), 0.10 (m, 2 H).

(3*R*,4*S*)-1-Cyclopropylmethyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide (30) was synthesised by reductive amination of (3*R*,4*S*)-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-

piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide hydrochloride with cyclopropanecarboxaldehyde. LC-MS method A: tR = 0.81 min; [M+H]+ = 523.31. Chiral HPLC: tR = 12.0 min; > 99 % ee; column: ChiralPak IC 4.6x250 mm, 5 µm; detector wavelength: 254 nm; eluent: 10% heptane 0.05% DEA; 90% ethanol 0.05% DEA; flow: 1.2 mL/min; BPR: 150 bar; temperature: 25 °C; injection volume: 6 µl .LC-HRMS: t_R = 0.62 min; m/z = 522.2191, found = 523.2273 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 9.38-9.47 (s, 1 H), 8.65 (d, J = 4.7 Hz, 2 H), 8.10-8.11 (m, 1 H), 8.04 (td, J_1 = 8.7 Hz, J_2 = 6.5 Hz, 1 H), 7.58 (m, 1 H), 7.33 (td, J_1 = 8.6 Hz, J_2 = 2.2 Hz, 1 H), 7.27 (t, J = 4.7 Hz, 1 H), 7.13 (d, J = 2.8 Hz, 1 H), 4.17-4.23 (s, 1 H), 3.11-3.24 (m, 1 H), 2.81-2.96 (m, 1 H), 2.73 (m, 1 H), 2.38-2.44 (m, 1 H), 2.24-2.36 (m, 4 H), 1.81-1.91 (m, 1 H), 1.46-1.58 (m, 2 H), 1.22-1.30 (m, 2 H), 0.87-0.96 (m, 1 H), 0.45-0.55 (m, 2 H), 0.08-0.18 (m, 2 H).

(3*S*,4*R*)-1-Cyclopropylmethyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide (31) was synthesised by reductive amination of (3*S*,4*R*)-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide hydrochloride with cyclopropanecarboxaldehyde. LC-MS method A: t_R = 0.71 min; $[M+H]^+$ = 523.18. Chiral HPLC: t_R = 18.4 min; > 99 % ee; column: ChiralPak IC 4.6x250 mm, 5 µm; detector wavelength: 254 nm; eluent: 10% heptane 0.05% DEA; 90% ethanol 0.05% DEA; Flow: 1.2 mL/min; BPR: 150 bar; temperature: 25°C; injection volume: 6 µl .LC-HRMS: t_R = 0.62 min; m/z = 522.2191, found = 523.2275 $[M + H]^+$. ^{1}H NMR (400 MHz, D_6-DMSO) δ: 9.39-9.47 (s, 1 H), 8.65 (d, J = 4.9 Hz, 2 H), 8.10 (d, J = 7.8 Hz, 1 H), 8.04 (td, J_1 = 8.7 Hz, J_2 = 6.5 Hz, 1 H), 7.55-7.61 (m, 1 H), 7.33 (td, J_1 = 8.5 Hz, J_2 = 2.3 Hz, 1 H), 7.26 (t, J = 4.9 Hz, 1 H), 7.12 (d, J = 2.9 Hz, 1 H), 4.16-4.20 (broad s, 1 H), 3.12-3.24 (broad s, 1 H), 2.82-2.93 (m, 1 H), 2.72 (d, J = 4.0 Hz, 1 H), 2.37-2.42 (m, 1 H), 2.29-2.34 (m, 2 H), 2.24 (dd, J_1 = 6.5 Hz, J_2 =

4.7 Hz, 2 H), 1.82-1.91 (m, 1 H), 1.55-1.59 (m, 1 H), 1.48-1.52 (m, 1 H), 1.22-1.30 (m, 2 H), 0.88-0.94 (m, 1 H), 0.48 (m, 2 H), 0.12 (d, *J* = 4.3 Hz, 2 H).

hKV11.1 (“hERG”) assay

hKV11.1 ("hERG") assay. Compounds were evaluated for block of hKV11.1 channels using CHO cells stably expressing the hERG gene (bSys, Witterswil, Switzerland) and the QPatch platform (Sophion, Ballerup, Denmark). K+ tail currents were measured at –40 mV following a 500 ms depolarization to +20 mV from a holding voltage of –80 mV. The external solution contained 150 mM Na+ , 4 mM K+ , 1 mM Mg2+ , and 1.2 mM Ca2+. Compound effects were quantified 3 min after application to the cells.

In Vitro DMPK

Inhibition of Cytochrome P450 Enzymes. The potential of the compounds for inhibition of the main human P450 isoforms, i.e., 2C9, 2D6, and 3A4, was evaluated using human liver microsomes and specific marker reactions for each enzyme. Diclofenac 4’-hydroxylation was used for CYP2C9, dextromethorphan *O*-demethylation was used for CYP2D6 and midazolam-1’-hydroxylation and testosterone 6β-hydroxylation were used for CYP3A4. Experiments were performed around the respective *K*m val*u*es of the marker substrates, and metabolite formation was monitored by LC-MS/MS. Inhibitor concentrations up to 50 µM were added, and the performance of the assay was controlled by the use of specific inhibitors for each P450 isoform.

Metabolic Stability in Liver Microsomes. Incubation with human, rat and dog liver microsomes were performed to assess metabolic stability at a single substrate concentration of 1 µM. A 1 µL-aliquot of the compounds stock solutions in DMSO were added to 100 mM phosphate buffer (pH 7.4) containing the liver microsomes at a concentration of 0.5 mg/mL

and the mixture was incubated at 37 °C in an Eppendorf thermomixer at 450 rpm. The reaction was initiated by addition of 100 µL of NADPH-regenerating system containing the glucose-6-phosphate dehydrogenase and at the pre-defined time points, 0, 2.5, 5, 10, 15, 20, 30 and 45 min, 100 µL of the incubation was transferred in 100 µL of ice-cold methanol to stop the reaction. Samples were centrifuged at 3220 *g* for 20 min at 4 °C and the supernatants were submitted to LC/MS-MS analysis.

Plasma Protein Binding. The binding to plasma proteins was determined by equilibrium analysis using a Pierce rapid equilibrium dialysis (RED) device (Thermo Fisher Scientific, Reinach, Switzerland) and incubating on a shaker at 37 °C for 4 h. The device was comprised of two compartments (protein compartment and buffer compartment) separated by a dialysis membrane with a molecular weight cut-off of 8 kDa, which allowed unbound test compound but not proteins, to traverse the membrane and equilibrate between the two compartments. The donor compartment was either human, rat or dog plasma. Donor and receiver (containing phosphate buffer, pH 7.4) were analyzed by LC-MS/MS.

In Vivo DMPK

Pharmacokinetic Studies in Rat and Dog. The amorphous hydrochloric salt of ACT-1004-1239 was used. Male Wistar rats with a body weight of ca. 200–250 g were used for pharmacokinetic experiments. For intravenous sampling, a jugular vein catheter was implanted 2 days prior to drug dosing under aseptic conditions. After recovery from general isoflurane anesthesia, animals were housed individually with free access to water and food during the recovery period and the entire duration of the experiment. For intravenous use the compound was formulated as an aqueous solution in 5% mannitol and water and for oral gavage as a solution in purified water. For both formulations, pH was adjusted to a value of 5.2 and 3.6, respectively with an NaOH solution. Male Beagle dogs with body weights of 13.4–16.0 kg at

the start of treatment were used in a crossover design with a washout period of 7 days. All experiments were performed in fasted state, and gastric pH was controlled by giving intramuscular pentagastrin at a dose of 6 mg/kg 30 minutes after oral dosing For intravenous use the compound was formulated as an aqueous solution in 5% mannitol and water and for oral gavage as a solution in purified water and pH was adjusted to a value of 5.0 in both cases with an NaOH solution. Serial blood samples of 0.25 ml (rats) or 2 ml (dogs) were taken over a period of 24 hours and transferred into vials fortified with EDTA as anticoagulant. Blood samples after oral dosing to rats were taken under light isoflurane anesthesia. Plasma was generated by centrifugation and stored at –20°C pending analysis. Analysis was performed using liquid chromatography coupled to mass spectrometry (LC-MS-MS) after protein precipitation with methanol and centrifugation at 3220 g for 20 min at 4°C. Pharmacokinetic parameters were estimated with the WinNonlin software (Pharsight Corporation, Mountain View, CA, USA) using non-compartmental analysis.

Physico-Chemical Properties Measurement

Log D7.4 determination. The distribution coefficient $LogD_{7.4}$ of a compound was determined by a miniaturized shake-flask method in screening mode. After overnight equilibration at room temperature in the 1-octanol/phosphate buffer saline pH 7.4 system, the $LogD_{7.4}$ was calculated from the HPLC peak area ratio of both phases without pH control. LogD values higher than 4.1 were reported as >4.1 due to HPLC detection limit.

pKa determination. The ionization constant pKa of a compound was determined using SiriusT3 instrument and software from Pion, Inc. Measurement was done by potentiometric or spectroscopic titration, depending on chromophore, from pH 2 to 12 or from pH 12 to 2, at 25°C or 37°C in a 0.1 M KCl solution at concentrations respectively between 0.7 mM to 2 mM, introduced as powder, and 0.01 mM to 0.1 mM, introduced as 2 µL to 5 µL DMSO stock

solution of 10 mM to 30 mM. During titration, solution was stirred using a paddle under nitrogen flow at the liquid surface. In case of precipitation, the use of a co-solvent may have been needed.

Solubility determination. The solubility of a compound was determined by the screening solubility assay. Starting material was a 10 mM DMSO stock solution, from which the solvent was evaporated and then the medium of interest was added. The approximate solubility (in µg/mL) up to around 1000 µg/mL (depending on molar mass) of a compound was determined in the medium of interest after 24h of equilibration at 25°C and filtration of the possible solid remaining. Solubility was determined in the following medium: FaSSIF-V1, FeSSIF-V1, phosphate buffer saline pH 7.4 or phosphate buffer pH 7.

Differential scanning calorimetry (DSC). DSC data were collected on a Mettler Toledo STARe System (DSC822e module, measuring cell with ceramic censor and STAR software version 9.20) equipped with a 34-position auto-sampler. The instrument was calibrated for energy and temperature using certified indium. Typically, 1-5 mg of each sample, in an automatically pierced aluminium pan, was heated at 10 °C min^{-1}, unless stated otherwise, from -20°C to 280°C. A nitrogen purge at 20 mL min^{-1} was maintained over the sample. Peak temperatures were reported for melting points.

Single Crystal X-ray Structure Analysis of ACT-1004-1239 (28f)

Data collection and refinement statistics

Crystals of 40 ($C_{27}H_{28}F_2N_6O_3$•MeOH) formed in the orthorhombic chiral space group $P2_12_12_1$. A total of 3644 reflections were collected at 253 K. Molecules/unit cell Z = 2, cell dimensions a = 4.8267(1) Å, b = 21.2971(6) Å, c = 26.260(8) Å; V = 2699.4(1) $Å^3$; calculated density = 1.286 g cm^{-3}. The final R-factor of 4.83 % was obtained for 2177 observed reflections

($I > 4\sigma(I)$) for a resolution of 1.05 Å; largest difference peak and hole were 0.34 and -0.28 e^- $Å^{-3}$, respectively. Crystallographic file has been deposited under the number CCDC 1993933.

The terminal cyclo-propyl ring is disordered over two positions. With a free variable and fixed Uiso both partitions refine to a 52/48 ratio. In the final refinement they were fixed to 50/50 with EADP for each partition. They were left isotropic. If they are refined anisotropic, R1 goes down to app. 3.5 %, but the shifts of the atoms are big and they doesn´t remain stable. To avoid introduction of constrains for the thermal parameters, these disordered positions were refined isotropic to achieve displacement shifts to be zero.

There is a MeOH which is disordered over at least 3 positions. Due to the "not so good" data quality, the solvate positions can´t be fully refined, nor found completely. Therefore, to avoid such problems and instability of the refinement, the MeOH solvate was SQUEEZED out.

Biological Assays In Vitro

CXCR7-agonist 1 assay: CHO-K1 CXCR7 β-arrestin cells were detached from culture dishes with a cell dissociation buffer (Invitrogen, Catalogue #13151-014) and collected in their culture medium. Cells (5000 per well in 20 µL) were seeded in 384-well plates (Greiner, Catalogue #781098). The plates were incubated at 37°C / 5% CO_2 for 24 h. The medium of each well was replaced with 20 µL of OPTIMEM (Invitrogen, Catalogue #31985) for 3-4 h. Test compounds were dissolved at a concentration of 10 mM in DMSO and either tested at 10 uM or serially diluted in DMSO to 200X of the final concentration to be used for dose-response testing. Compounds were then further diluted 1:33.3 in 1X HBSS. The diluted compounds (5µL / well) were added to the assay plates and incubated for 15 minutes or 3 h at 37°C. Next, the agonist **1** was diluted in HBSS/20mM HEPES/0.2% BSA to 6X of the final concentration to be used (the final concentration used was 5 nM, equivalent to its EC_{80} value) and 5 µL / well was added to the assay plate. The effect of each compound was calculated as a percentage of the maximum

assay signal. The mean minimum and maximum values were obtained from control wells in the same plate and were set at 0% and 100%.

Insurmountability assay: For the insurmountability assay, serial dilution of CXCL12 or CXCL11 were used instead of 1. The plates were incubated for another 90 minutes at 37°C. The detection reagent (12 µL; Detection Kit, DiscoveRx, #93-0001) was then added to the wells and the plates were incubated for 1 h at room temperature. The resulting luminescent signal was read in a microplate reader (Envision, Perkin Elmer). Of note, the calculated IC_{50} values fluctuated depending on the daily performance of the cellular assay.

CXCR7-CXCL12 assay: CXCR7-bla U2OS cells were detached from culture dishes with 0.05% trypsin-EDTA and collected in growing medium (McCoy's 5A 90% (v/v), dialyzed fetal calf serum (FCS) 10% (v/v), 0.1mM non-essential amino acids (NEAA), 25mM HEPES (pH7.3), 1mM sodium pyruvate, P/S 1% (v/v) 50µg/ml Hygromycin, 100µg/ml Geneticin, 200µg/ml Zeocin), spinned down and resuspended in assay medium (McCoy's 5A 90% (v/v), dialyzed FCS 1% (v/v), 0.1mM NEAA, 25mM HEPES (pH7.3), P/S 1% (v/v)). 10'000 cells per well (in 30 µl) were seeded in a 384 well plate (black-walled, clear bottom). The plates were incubated at 37°C / 5% CO_2 for 24 hours. Test compounds were dissolved to 10mM in DMSO and serially diluted in DMSO to 500X of the final concentration for dose response curves. Compounds were then diluted 1:100 in assay medium to 5X of the final concentration. 10µl/well of diluted compounds were added to the assay plate and incubated for 15 minutes at 37°C. Thereafter CXCL12α was diluted in assay medium to 5X of the final concentration (Final concentration: 30 nM). This corresponds to its EC80 value for receptor activation) and 10µl/well were added to the assay plate. The plate was incubated for 22hrs at 37°C. 10µl/well of detection reagent (LiveBLAzerTM-FRET B/G (CCF4-AM) substrate) was transferred to the assay plate and the plate was incubated for 2 hours at room temperature protected from light. Fluorescent counts were determined (Scan1: Ex 409/20nm, Em 460/30nm, Scan 2: Ex

409/20nm, Em 530/30nm). The calculated emission ratio was used for IC50 determination. The effect of each compound was calculated as a percentage of the maximum assay signal. The mean minimum and maximum values were obtained from control wells in the same plate and were set at 0% and 100%. The calculated IC50 values may fluctuate depending on the daily cellular assay performance.

Determination of the Ki, Kon and Koff constants: HEK-SNAP.hCXCR7.NLuc cells were washed once with PBS and 100 nM SNAP Lumi4-Tb (Cisbio, Catalogue #SSNPTBC) prepared in 1x Tag-lite® buffer (TLB, Cisbio, Catalogue #LABMED) was added and further incubated for 1 h at 37°C, 5% CO_2. Excess SNAP-Lumi4-Tb was removed by washing cells 3 times with TLB 1x. Cells were detached from culture dishes with cell dissociation buffer (Gibco Catalogue #13151), resuspended in TLB and counted. Cells were then centrifuged at 200xg for 5 min, the supernatant was removed by aspiration and cell pellets were resuspended in 1x TLB at a density of 0.4 million cells/mL. Cells were gently mixed by pipetting up and down several times. Cells were frozen in FCS 90%/DMSO 10% as ready-to-use labeled cells. The day of the assay, cells were thawed, resuspended in 10 mL TLB 1x and centrifuged for 5 min at 200xg. The supernatant was removed by aspiration and cell pellets were resuspended in TLB 1x at 0.4 million cells/mL. Cells were gently mixed by pipetting up and down several times. ACT-1004-1239A was dissolved to 10 mM in DMSO and serially diluted in DMSO to 400x of the final concentration for dose-response curves. Compounds were further diluted 1/100 in TLB to 4x of the final concentration. 5 µL of this solution were transferred to a white low volume plate, where 5 µL of labeled ligand (3 nM CXCL12 AF647 diluted in TLB 1x to obtain a 4-fold concentrated solution) and 10 µL of cells (4000 cells per well) were added. The final percentage of DMSO in each well was 0.25%. The binding kinetics were measured immediately on a Pherastar FSX (measurement began 30 seconds after addition of the cells) every 30 seconds for 3 h at room temperature.

CXCR7 assay using CXCR7 from various species: we established stable *in vitro* systems where CXCR7 from different species and human β-arrestin were overexpressed either in Chinese hamster ovary (CHO), U2OS or human embryonic kidney cells 293 (HEK293) cell lines (thereafter the "β-Arrestin CXCR7 cell lines"). In these systems, cells are engineered to co-express a ProLink™ (PK) tagged CXCR7 and an Enzyme Acceptor (EA) tagged β-arrestin (Table S1).

Table S1: List of the CXCR7 β-arrestin stable cell lines

β-Arrestin CXCR7 cell lines	Medium	Idorsia cell Bank number
CHO-K1 humanCXCR7 β-arrestin	Ham's F12	CC548
HEK293 ratCXCR7 β-arrestin clone#2	DMEM	CC423
CHO-K1 guinea pigCXCR7 β-arrestin clone#41	Ham's F12	CC422
CHO-K1 macaqueCXCR7 β-arrestin clone#48	Ham's F12	CC420
CHO-K1 dogCXCR7 β-arrestin clone#12	Ham's F12	CC421
U2OS mouseCXCR7 β-arrestin	MEM	CC549

The β-arrestin CXCR7 cell lines were grown to near confluency in the indicated medium (Table S1) supplemented with 10% fetal calf serum containing penicillin and streptomycin (100 units/mL each) under standard mammalian cell culture conditions at 37 °C in a humidified atmosphere of 5% CO_2. Cells were detached from culture dishes with a cell dissociation buffer (Invitrogen, Catalogue #13151-014) and collected in their growing medium. Cells (5000 cells per well in 20 µL for all cell lines except HEK293 ratCXCR7, which were seeded at 20,000 cells per well in 20 uL) were seeded in a 384 well plate (Greiner, Catalogue #781098). HEK293 ratCXCR7 cells were seeded on poly-L-Lysine (Cultrex, Catalogue # 3438-100-01)-coated 384 well plates. The plates were incubated at 37°C/5% CO_2 for 24 h. The medium was replaced with 20 µL OPTIMEM (Invitrogen Catalogue #31985) for 3 to 5 h. ACT-1004-1239 was dissolved at a concentration of 10 mM in DMSO and serially diluted in DMSO to 200X of the final concentration to be used for the dose response experiments. ACT-1004-1239 was then diluted 1:33.3 in Hank's balanced salt solution (HBSS) 1X. Diluted compounds (5 µL/well) were added to the assay plates and incubated for 15 min at 37°C. Next, CXCL12 (Peprotech,

Catalogue # 300-28A) was diluted in HBSS/20 mM HEPES/0.2% BSA (Sigma, Catalogue# A7030) to 6X of the final concentration (its EC_{80} value) and 5 µL/well was added to the assay plates. The plates were incubated for 90 min at 37°C. The detection reagent (12 µL; Detection Kit, DiscoveRx, #93-0001) was transferred to the assay plate and the plate was incubated for 1 h at room temperature. The luminescent signal was read in a microplate reader (Envision, Perkin Elmer).

Human CXCR4 intracellular calcium liberation (FLIPR) Assay: Molt4 cells were grown to near confluency in Roswell Park Memorial Institute (RPMI) medium supplemented with 10% fetal calf serum containing penicillin and streptomycin (100 units/mL each) under standard mammalian cell culture conditions at 37 °C in a humidified atmosphere of 5% CO_2. Cells were centrifuged and resuspended in Dye Buffer (1X HBSS, 0.0375% $NaHCO_3$, 20 mM HEPES, 5.25 mM probenecid, 10 nM Fluoro-4). The cells were incubated for 45 min at 37°C. Cells were then washed 2 times with Wash Buffer (1X HBSS, 0.0375% $NaHCO_3$, 20 mM HEPES, 2.5 mM probenecid, 0.1% BSA), resuspended in Wash Buffer and 50 000 cells in 50 µL per well, were seeded onto a 384-well clear-bottom black assay plate (Greiner), and sedimented by centrifugation. Stock solutions of ACT-1004-1239 were made up at a concentration of 10 mM in DMSO and serially diluted in assay buffer to concentrations required for dose−response curves. CXCL12 (Peprotech, Catalogue # 300-28A) was used as an agonist. A FLIPRII instrument (Molecular Devices) was operated following the manufacturer's instructions. ACT-1004-1239 (10 µL) was added to each well and incubated for 20 min. Cells were activated by a final concentration of 17.5nM CXCL12 dissolved in the wash buffer. Fluorescence emission was recorded during test compound and CXCL12 addition, and emission peak values above base level after CXCL12 addition were exported. Values were normalized to high-level control (no antagonist added) after subt*rac*tion of baseline value control (no CXCL12 added).

Biological Assay In Vivo

Target engagement in vivo: Male DBA/1 mice (body weight at study start: 22-27 g) were purchased from Janvier Laboratories (Le Genest-Saint-Isle, France) and allowed to acclimatize for at least 7 days before use. All animals were housed in climate-controlled conditions within a 12h light/dark cycle and had free access to normal chow and drinking water, in accordance with the guidelines of the Swiss Animal Protection Law. All animal experiments were carried out in accordance with the Swiss animal protection law, under protocols approved by the Basel Cantonal Veterinary Office.

The compound was formulated in 20% volume of Solutol HS15 and in 80% volume of 0.25% (w/w) methylcellulose/water. Oral single doses of ACT-1004-1239 (1, 10, 30 or 100 mg/kg) or vehicle were given to healthy DBA/1 mice p.o. (n = 3–5 per time point) in a volume of 5 mL/kg. Blood samples were collected 0.5, 6 and 24 h post-administration of a single oral dose. Blood was centrifuged (20,000 *g*, 5 minutes at 4 °C) to prepare plasma samples and concentrations of CXCL12 were measured using a commercial mouse CXCL12/SDF1α Quantikine enzyme-linked immunosorbent assay kit (R&D Systems, catalog no. MCX120) according to manufacturer's instructions. All data are presented as mean + SEM. Statistical analysis were performed by One-way ANOVA followed by Dunnett's multiple comparisons test, using Graphpad Prism software (version 8).

References

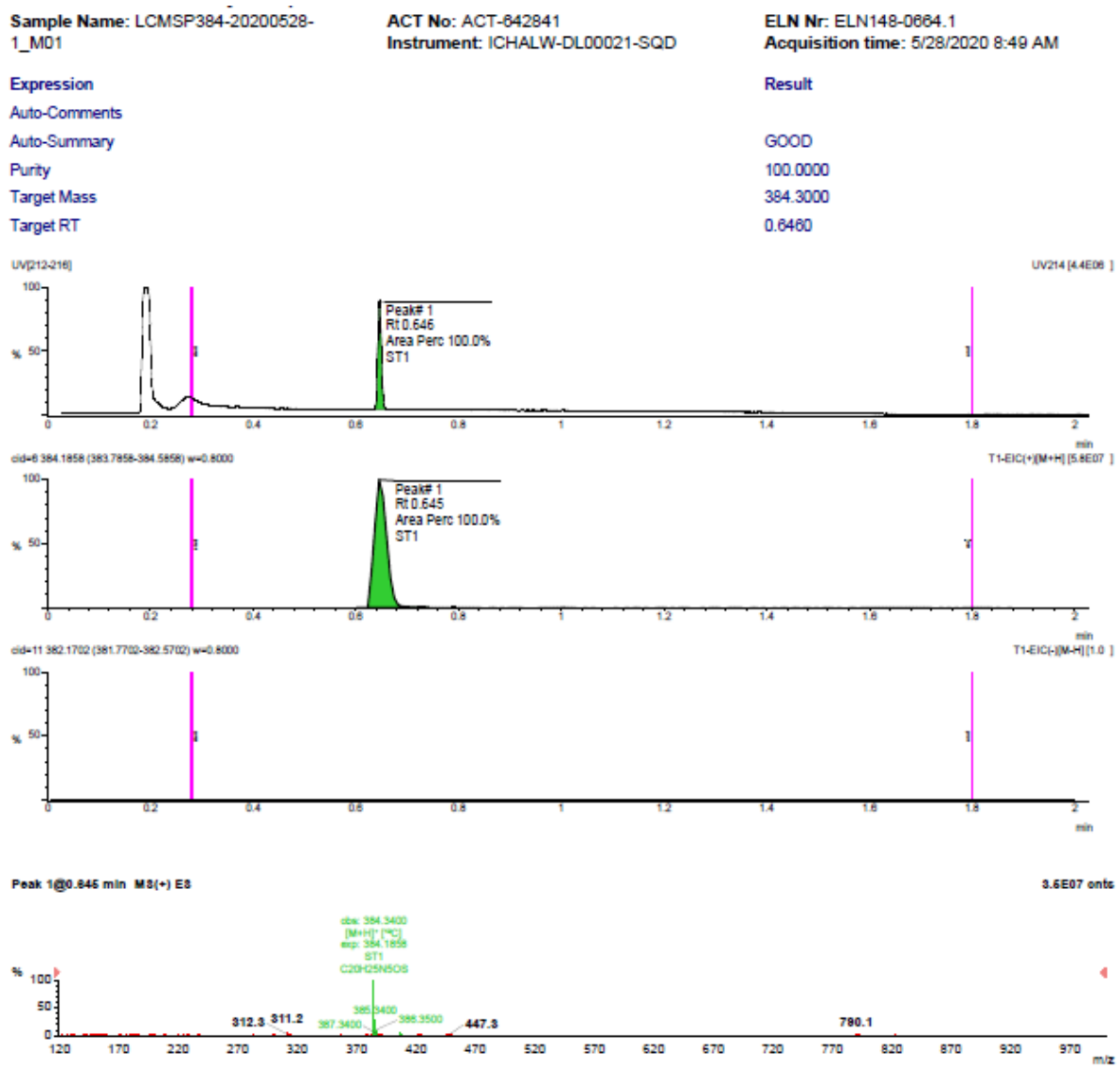
1. Aissaoui,A.; Guerry, P.; Lehembre, F.; Pothier, J.; Pouzol, L.; Richard-Bildstein, S.; Yuan, S.; Piperidine CXCR7 Receptor Modulators, World Patent WO 2018/019929, **2018**.

2. Linder, J; Garner, T. P.; Williams, H. E. L.; Searle, M. S.; Moody, C. J. Telomestatin: Formal Total Synthesis and Cation-Mediated Interaction of Its seco-Derivatives with G-Quadruplexes. *J. Am. Chem. Soc*. **2011**, *133*, 1044–1051.

LC-MS traces of compounds 2-31

The LC-MS methods used correspond to the descriptions in the chemistry part.

Compound **2**:



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Instrument: UPLC_SYNAPT1 **Acquisition time:** 6/2/2020 3:06 PM

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Auto-Summary	GOOD
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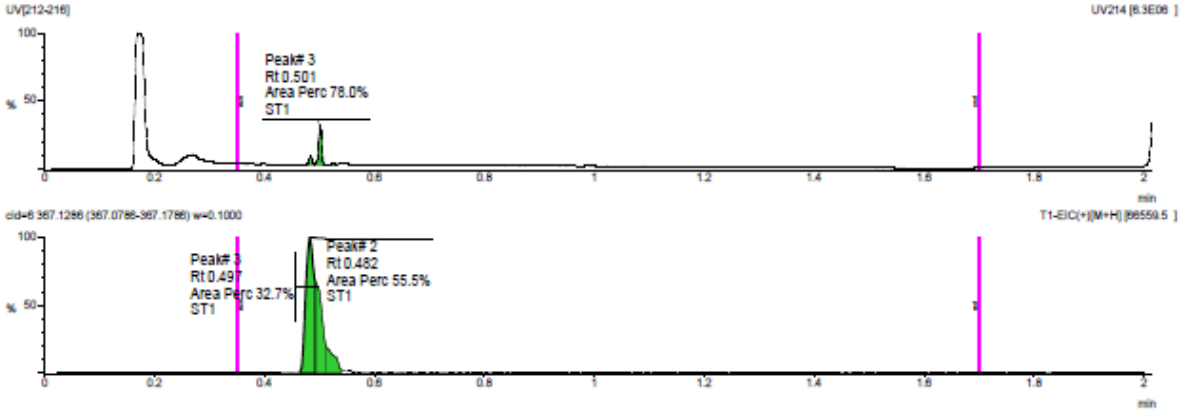
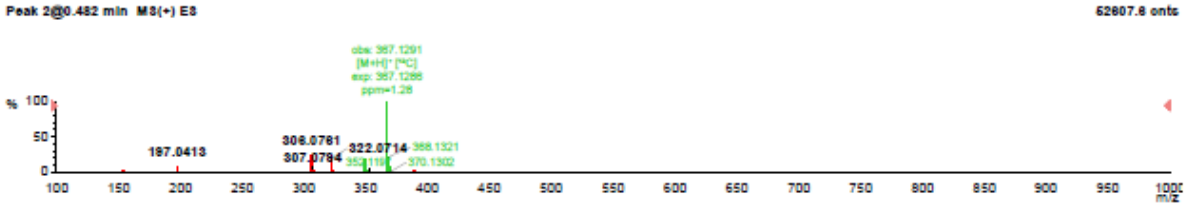
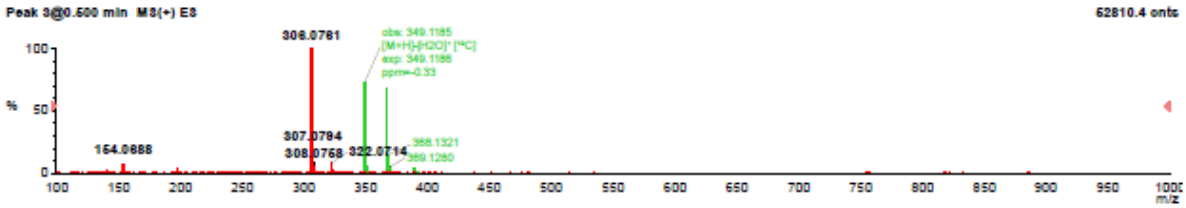
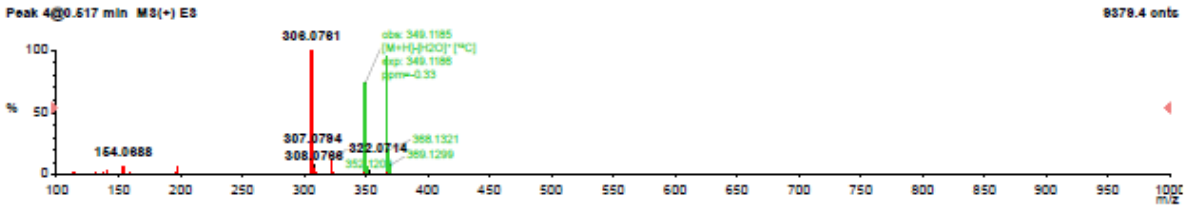
Target Mass	367.1291
Target RT	0.5010









Compound **4**:

Sample Name: LCMSH384-20200609-1_M05 **ACT No:** ACT-655552 **Instrument:** **ELN Nr:** ELN098-0668.A03 **Acquisition time:** 6/12/2020 11:26 AM

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Auto-Summary	GOOD
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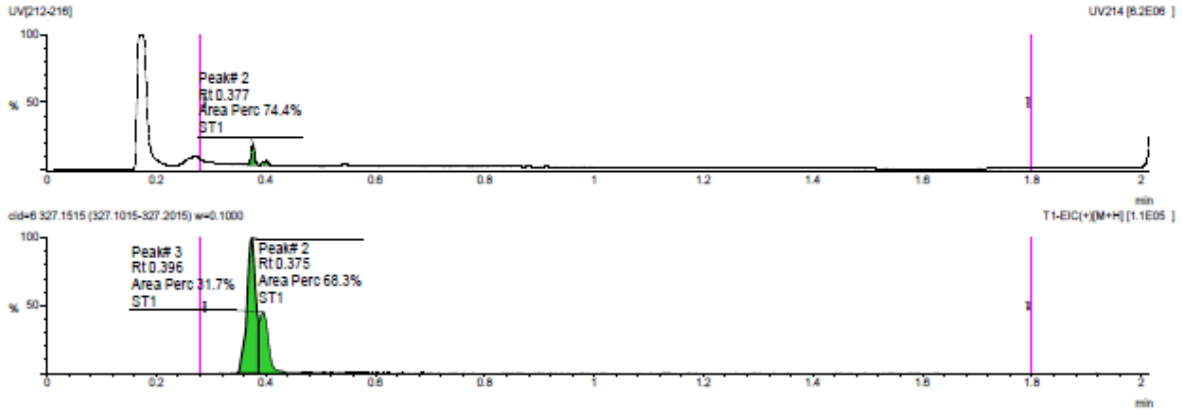
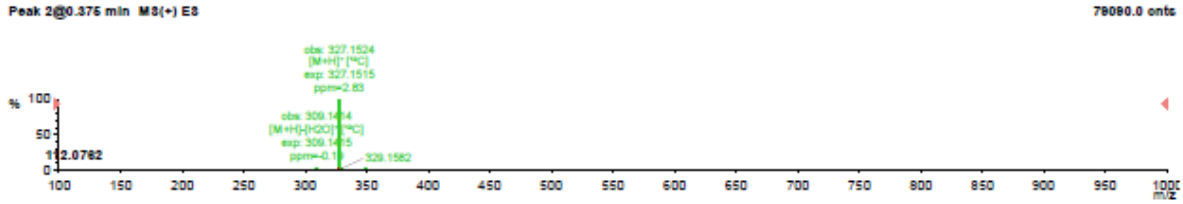
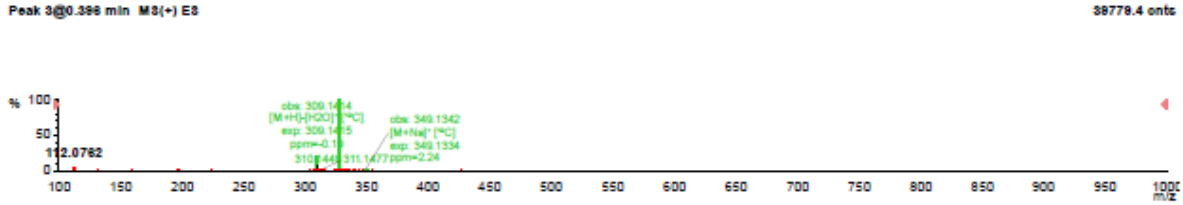
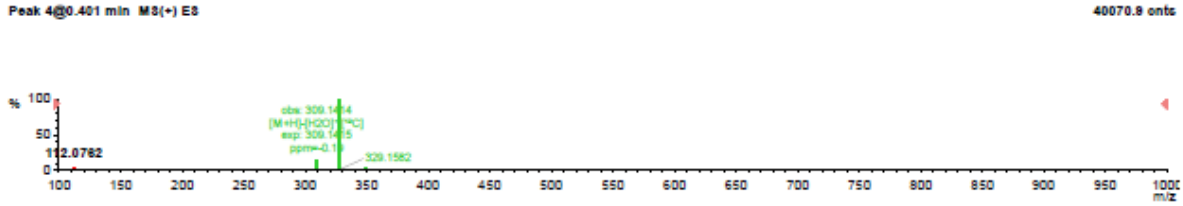
Target Mass	327.1524
Target RT	0.3770









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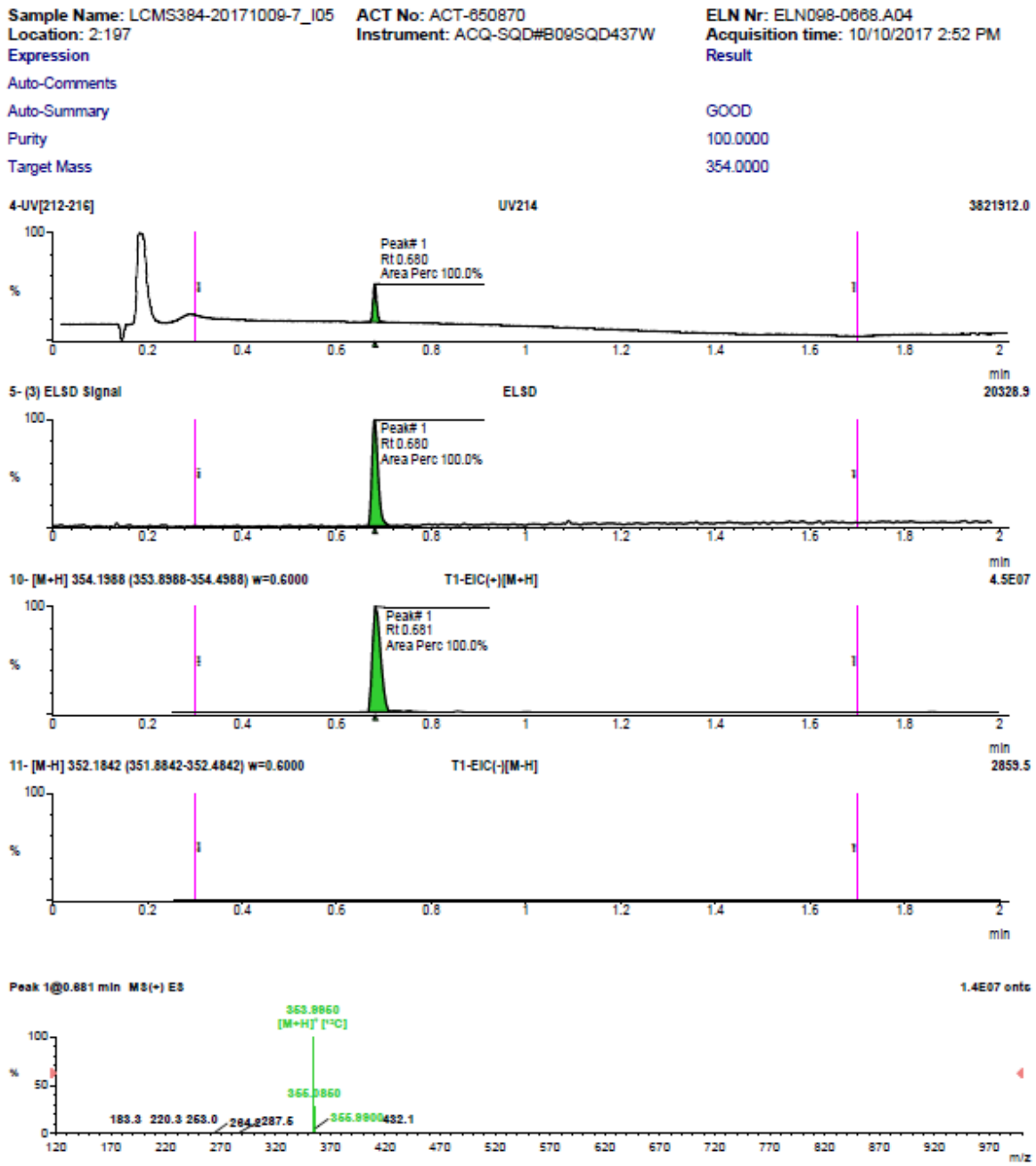
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Acquisition time: 10/10/2017 2:52 PM
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Result
Auto-Comments
Auto-Summary
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Target Mass
354.0000
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UV214
3821912.0
Peak# 1
Rt 0.680
Area Perc 100.0%
min
5- (3) ELSD Signal
ELSD
20328.9
Peak# 1
Rt 0.680
Area Perc 100.0%
min
10- [M+H] 354.1988 (353.8988-354.4988) w=0.6000
T1-EIC(+)[M+H]
4.5E07
Peak# 1
Rt 0.681
Area Perc 100.0%
min
11- [M-H] 352.1842 (351.8842-352.4842) w=0.6000
T1-EIC(-)[M-H]
2859.5
min
Peak 1@0.681 min MS(+) ES
1.4E07 onts
353.8860
[M+H]+ [13C]
355.0860
183.3 220.3 263.0 284.2 287.5 355.8900 432.1
m/z

Compound **6**:

Sample Name: LCMS384-20200624-1_M01 **ACT No:** ACT-582817 **ELN Nr:** ELN186-4537.1
Instrument: ICHALW-DL00021-SQD **Acquisition time:** 6/24/2020 2:44 PM

Expression	Result
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Auto-Summary	GOOD
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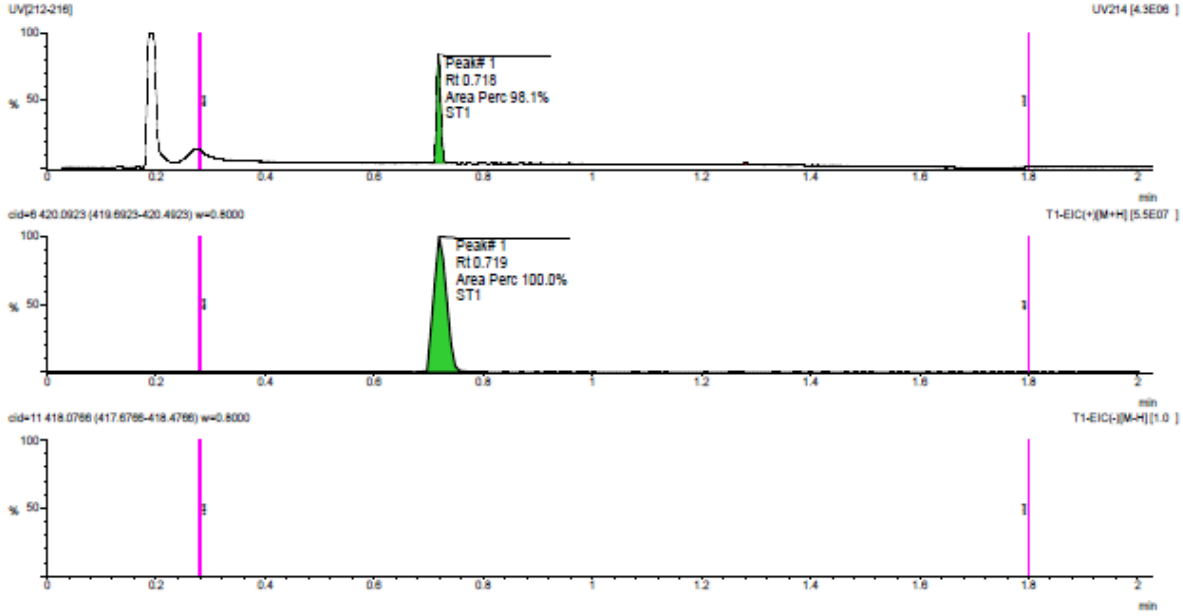
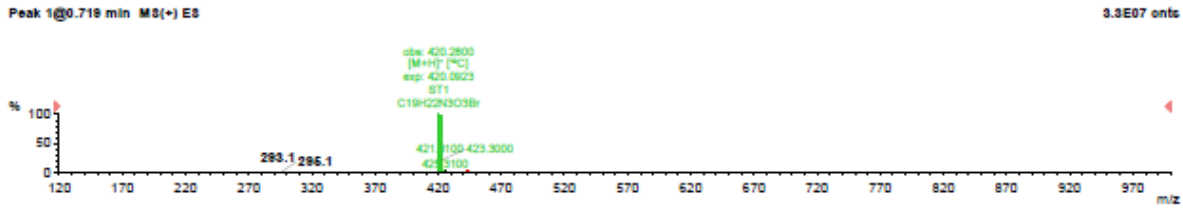
Target Mass	420.3000
Target RT	0.7180





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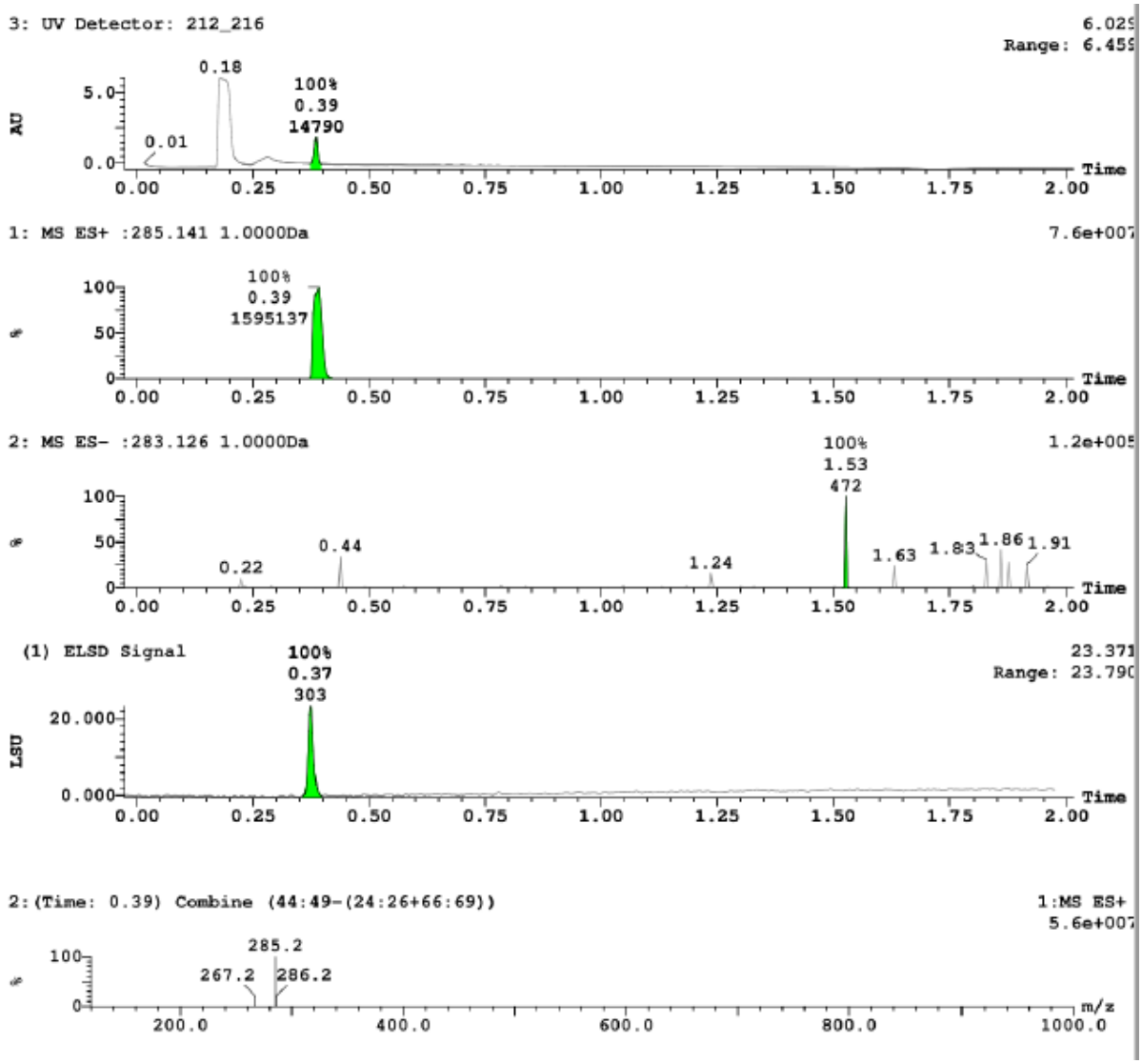
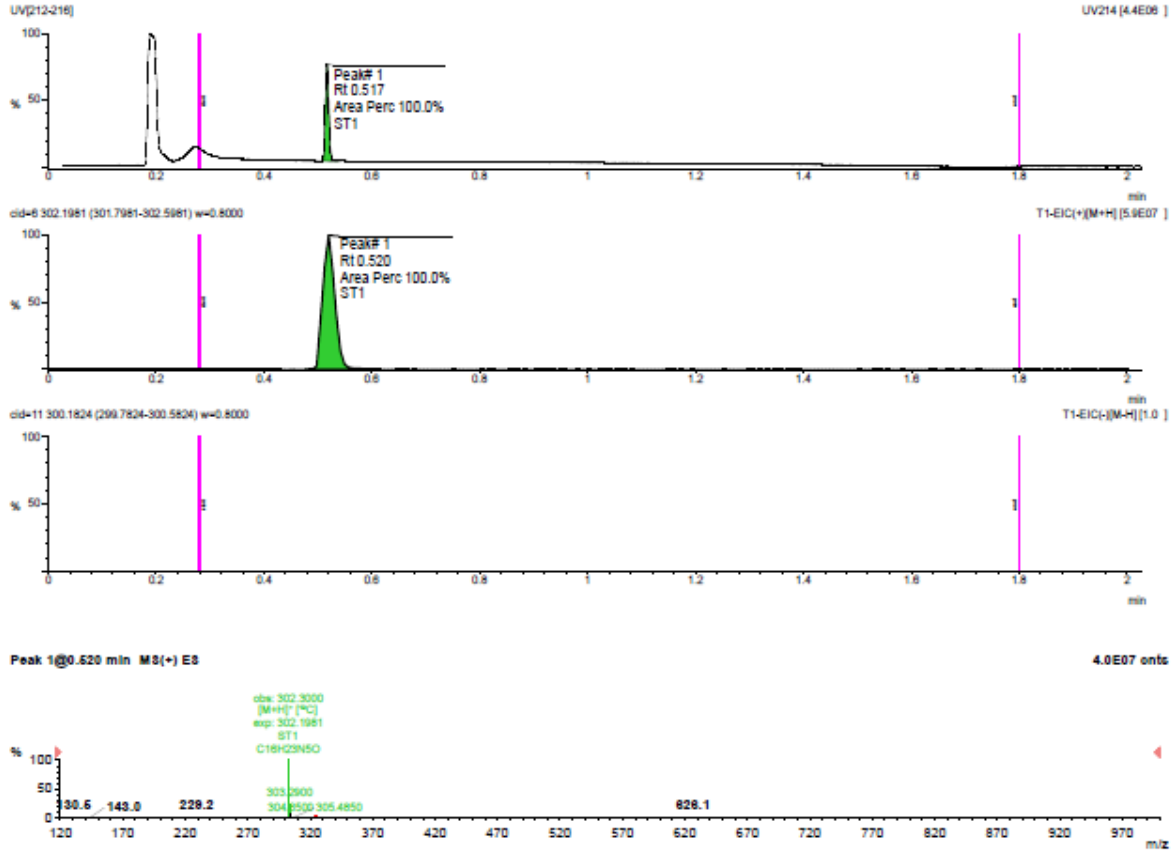

3: UV Detector: 212_216
Range: 6.45
0.18
100%
0.39
14790
0.01
AU
Time
1: MS ES+ :285.141 1.0000Da
7.6e+007
100%
0.39
1595137
2: MS ES- :283.126 1.0000Da
1.2e+00
100%
1.53
472
0.22
0.44
1.24
1.63
1.83
1.86
1.91
(1) ELSD Signal
100%
0.37
303
23.371
Range: 23.790
LSU
2:(Time: 0.39) Combine (44:49-(24:26+66:69))
1:MS ES+
5.6e+007
285.2
267.2
286.2
m/z

Compound **7b**:

Sample Name: LCMSP384-20200528-1_K07 **ACT No:** ACT-707103 **ELN Nr:** ELN098-0663.A01
Instrument: ICHALW-DL00021-SQD **Acquisition time:** 5/28/2020 9:55 AM

Expression	Result
Auto-Comments	
Auto-Summary	GOOD
Purity	100.0000
Target Mass	302.3000
Target RT	0.5170



Compound **7c**:

Sample Name: LCMS384-20200803-5_G23 **ACT No**: ACT-707785 **ELN Nr**: ELN227-1507.A06
Instrument: ICHALW-DL00012-TQD **Acquisition time**: 8/3/2020 10:08 PM

Expression	Result
Auto-Comments	
Auto-Summary	GOOD
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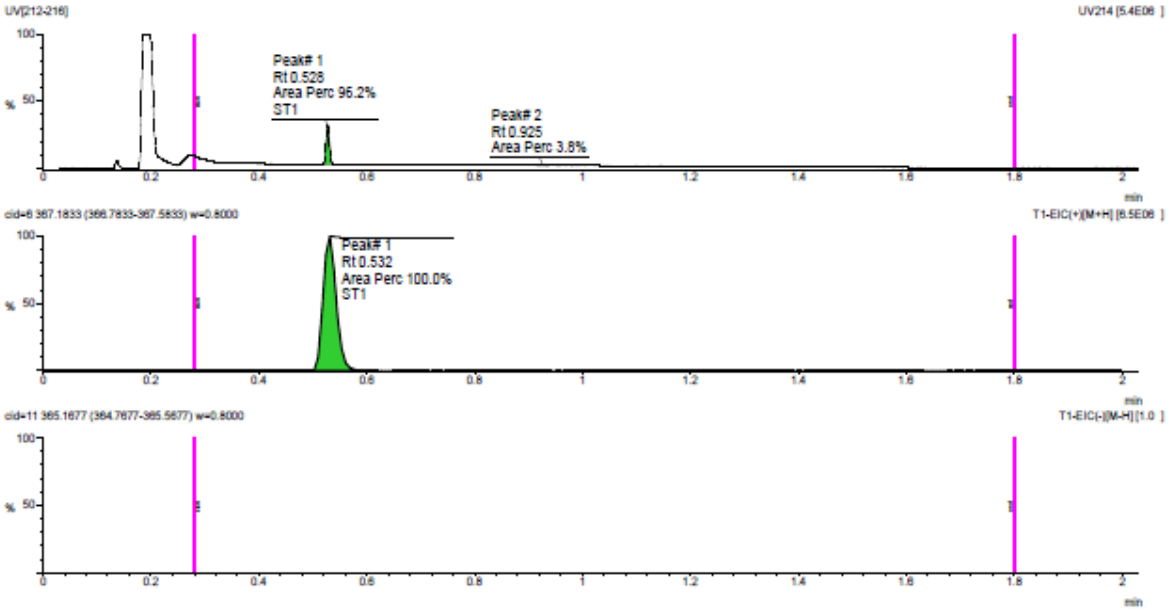
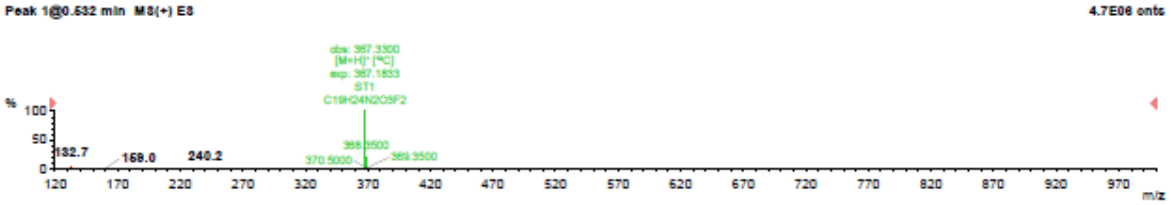
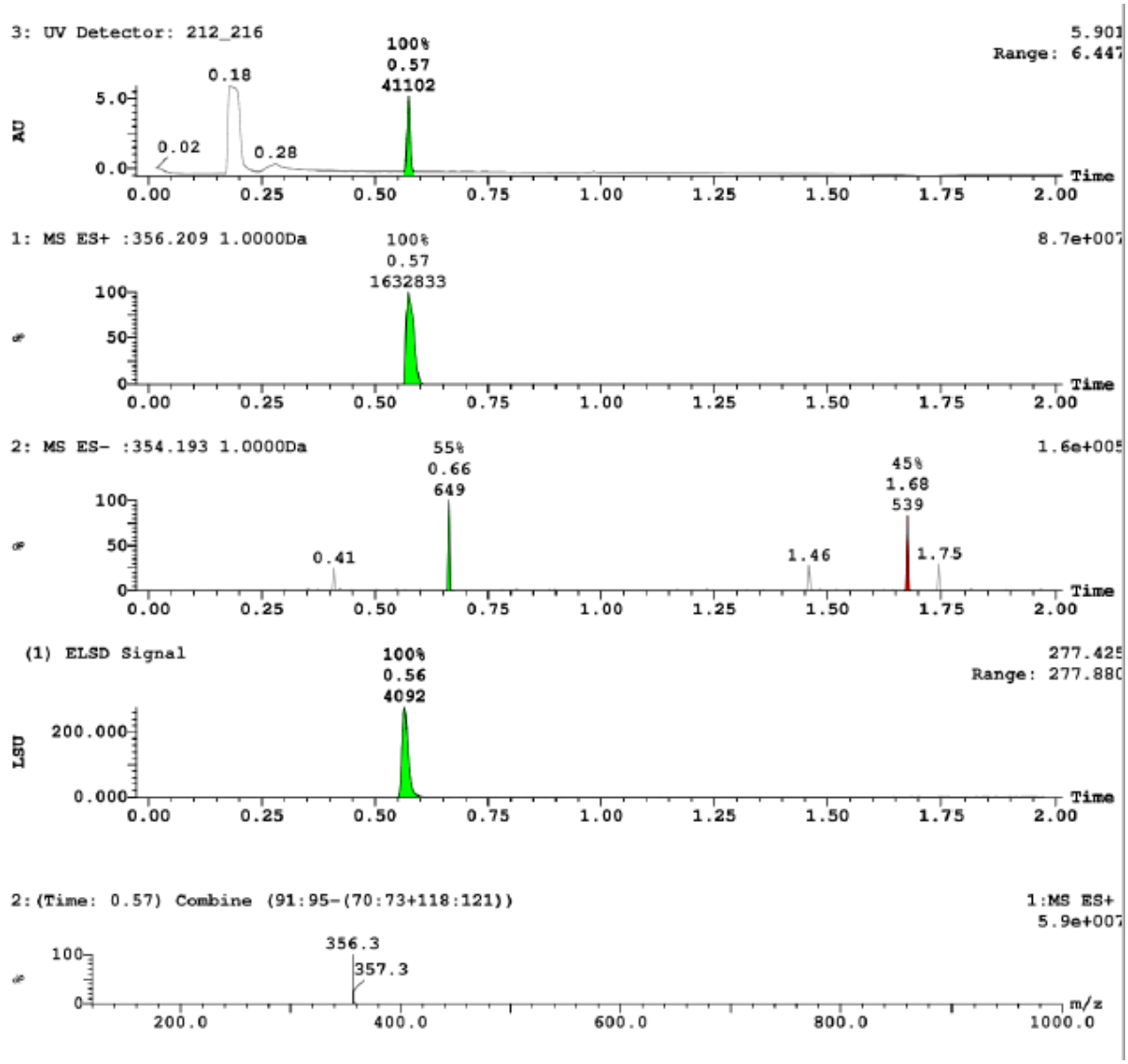
Target Mass	367.3000
Target RT	0.5280





Compound **7d**: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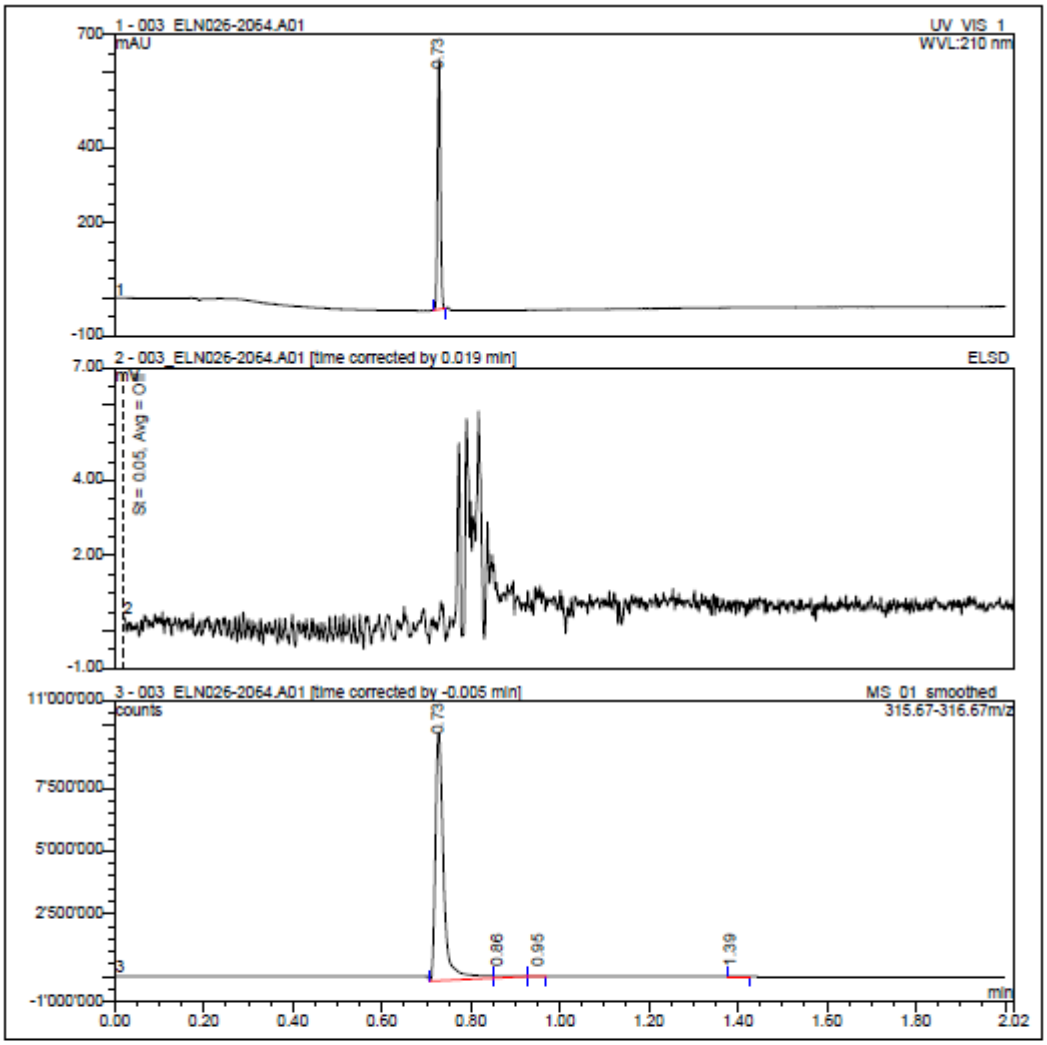
100%
0.57
41102
0.18
0.02
0.28
AU
Time
1: MS ES+ :356.209 1.0000Da
100%
0.57
1632833
%
Time
2: MS ES- :354.193 1.0000Da
55%
0.66
649
45%
1.68
539
0.41
1.46
1.75
%
Time
(1) ELSD Signal
100%
0.56
4092
LSU
Time
2:(Time: 0.57) Combine (91:95-(70:73+118:121))
1:MS ES+
356.3
357.3
%
m/z

Compound **7e**: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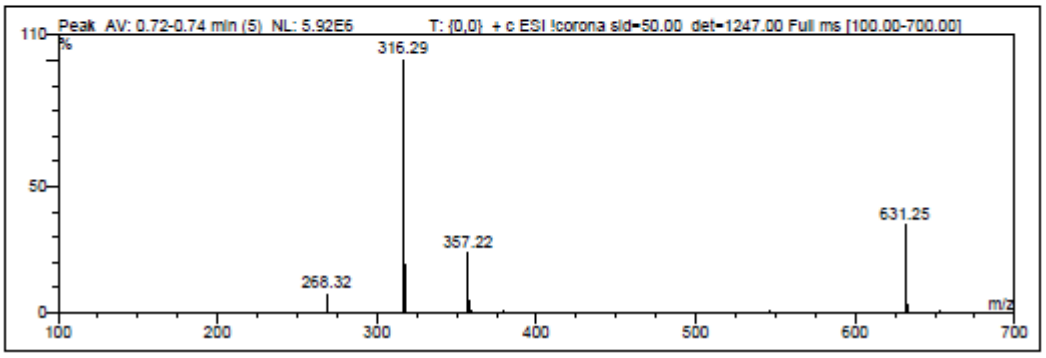
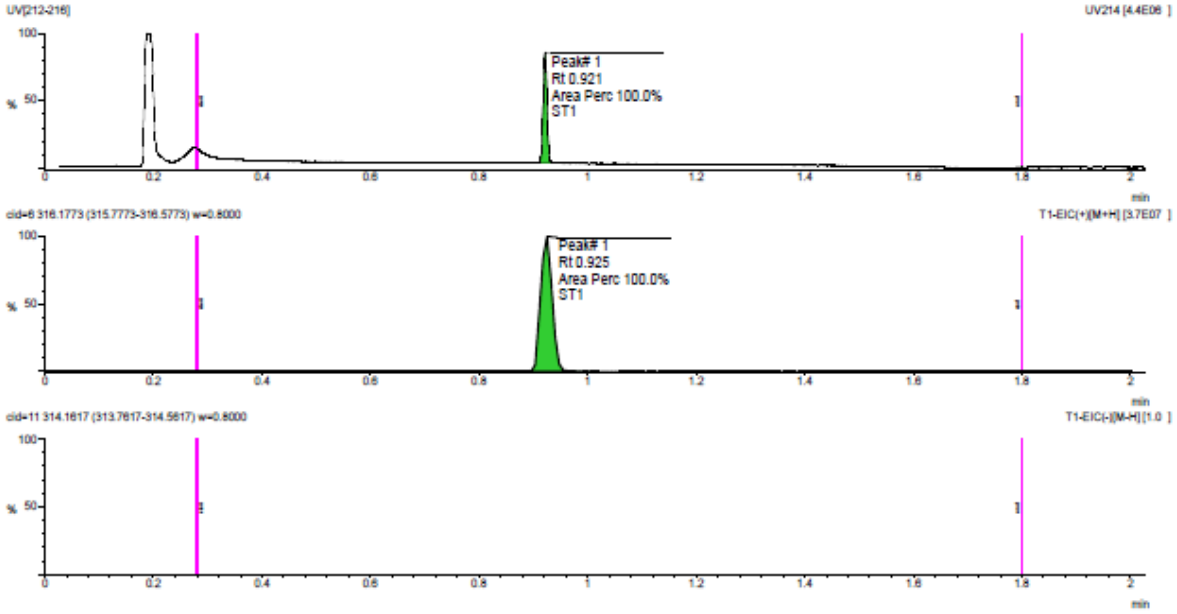
mAU
WVL:210 nm
0.73
2 - 003_ELN026-2064.A01 [time corrected by 0.019 min]
ELSD
3 - 003_ELN026-2064.A01 [time corrected by -0.005 min]
MS_01_smoothed
counts
315.67-316.67m/z
0.73
0.86
0.95
1.39
min

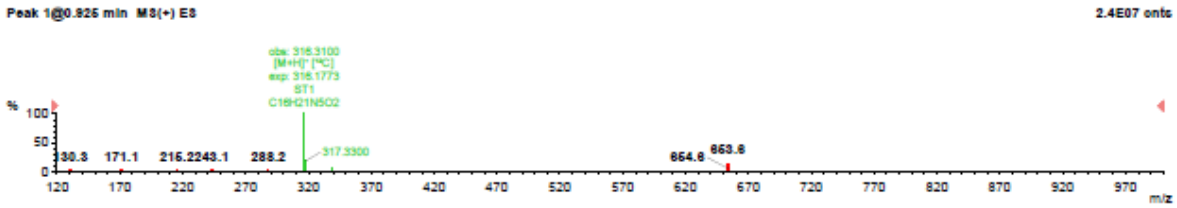

Peak_AV: 0.72-0.74 min (5) NL: 5.92E6
T: {0,0} + c ESI !corona sid=50.00 det=1247.00 Full ms [100.00-700.00]
316.29
631.25
357.22
268.32
m/z

Compound **7f**:

Sample Name: LCMSP384-20200528-1_O03 **ACT No:** ACT-707106 **ELN Nr:** ELN098-0663.A04
Instrument: ICHALW-DL00021-SQD **Acquisition time:** 5/28/2020 9:15 AM

Expression	Result
Auto-Comments	
Auto-Summary	GOOD
Purity	100.0000
Target Mass	316.3000
Target RT	0.9210

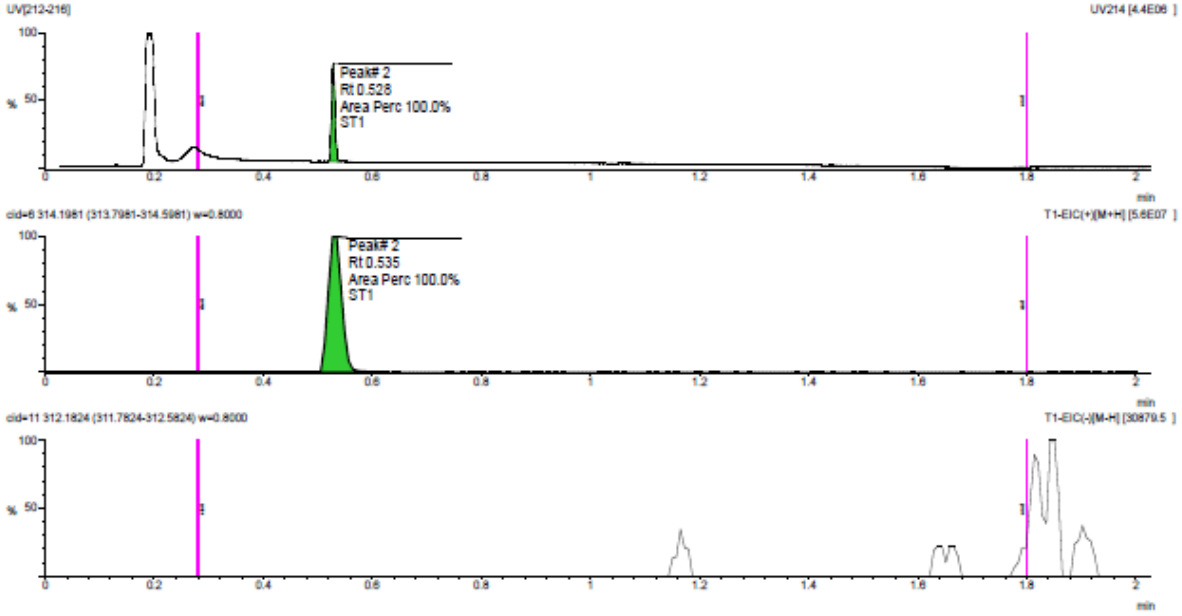


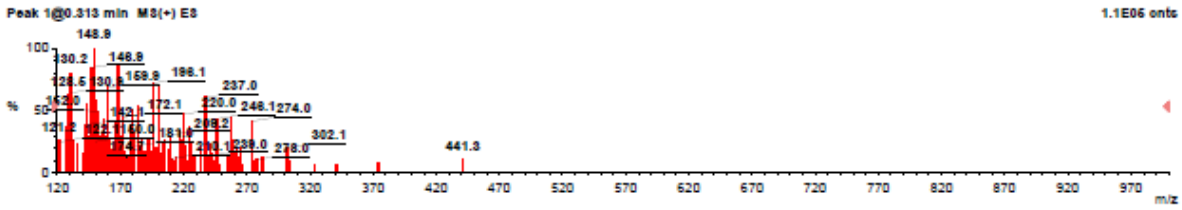


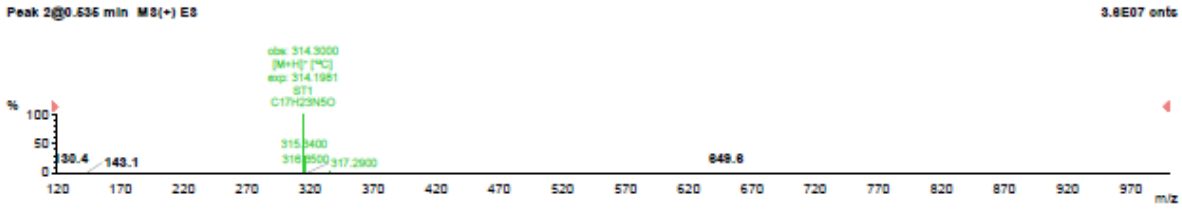
Compound **7g**:

Sample Name: LCMSP384-20200528-1_K05 **ACT No:** ACT-707109 **ELN Nr:** ELN098-0663.B02
Instrument: ICHALW-DL00021-SQD **Acquisition time:** 5/28/2020 9:32 AM

Expression	Result
Auto-Comments	
Auto-Summary	GOOD
Purity	100.0000
Target Mass	314.3000
Target RT	0.5280



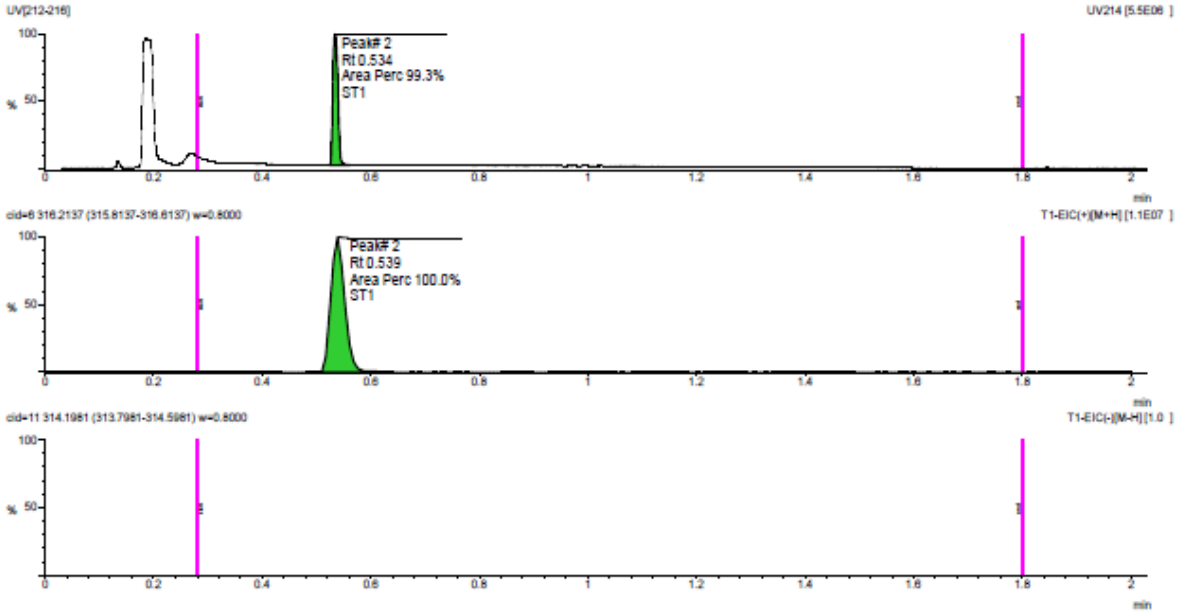


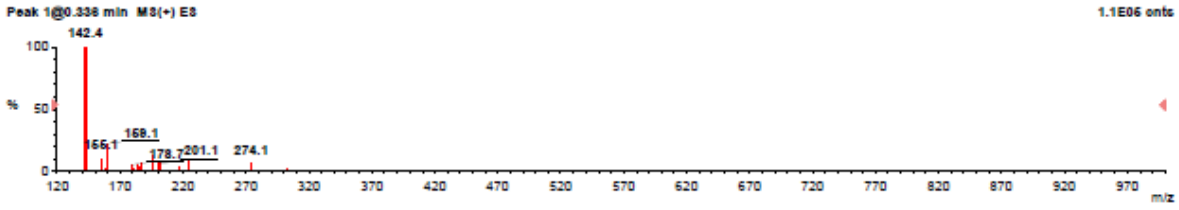


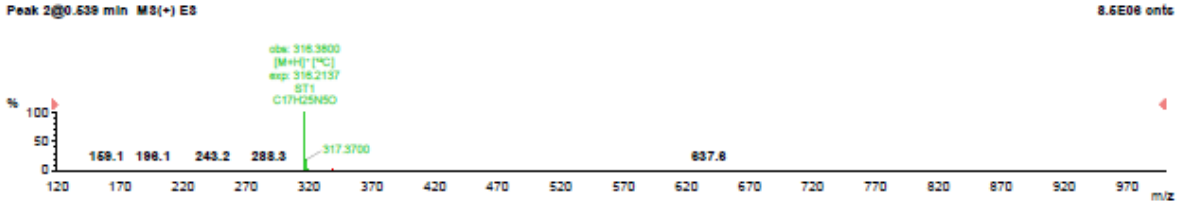
Compound **7h**:

Sample Name: LCMS384-20200715-2_C01 **ACT No:** ACT-709860 **ELN Nr:** ELN026-2083.A04
Instrument: ICHALW-DL00012-TQD **Acquisition time:** 7/15/2020 12:14 PM

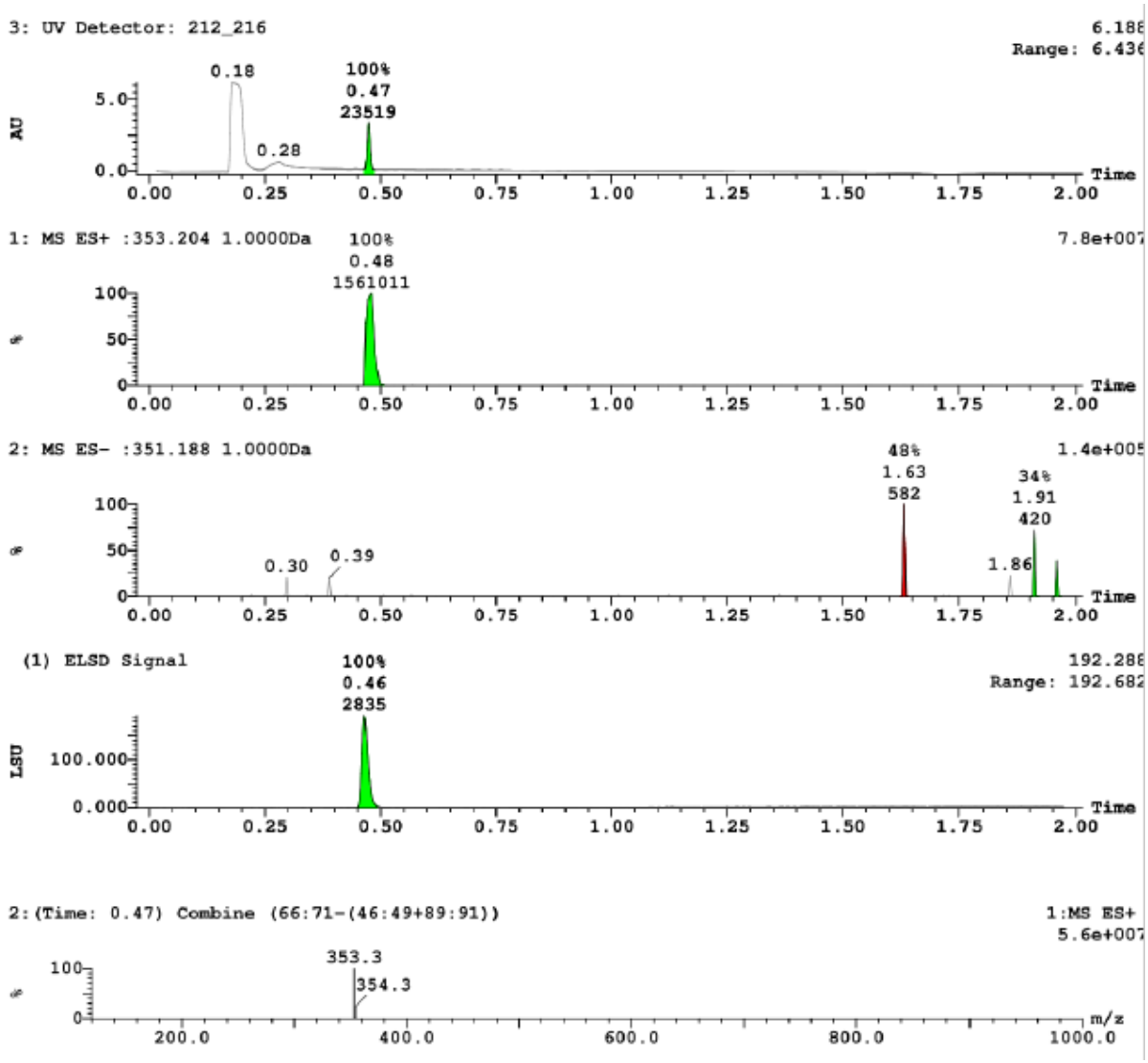
Expression	Result
Auto-Comments	
Auto-Summary	GOOD
Purity	99.3000
Target Mass	316.4000
Target RT	0.5340







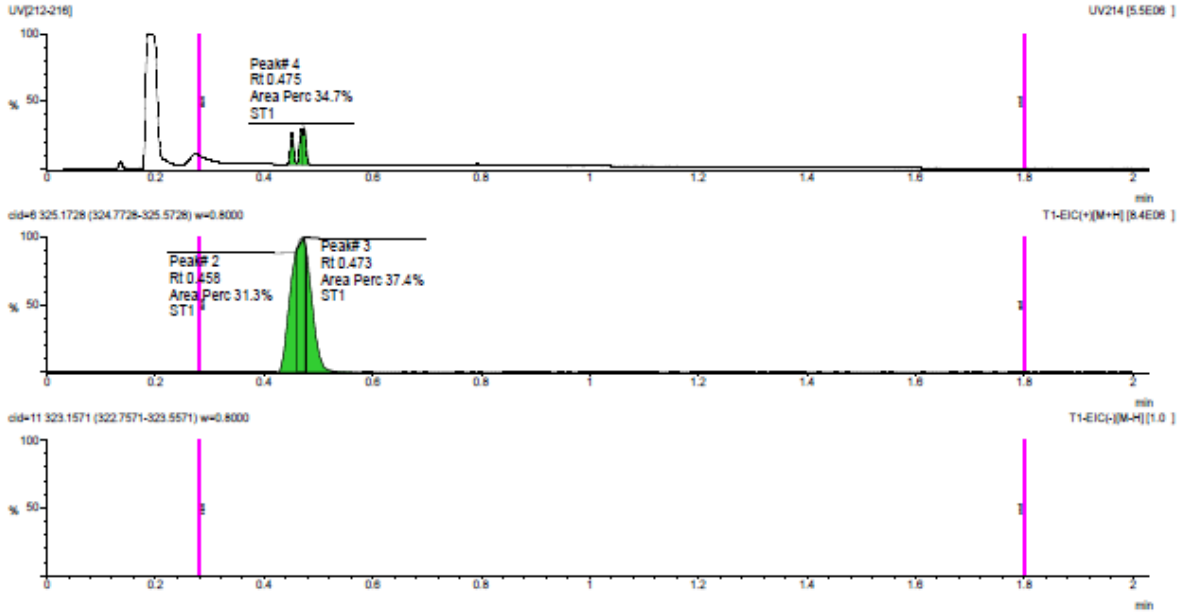
Compound **7i**:

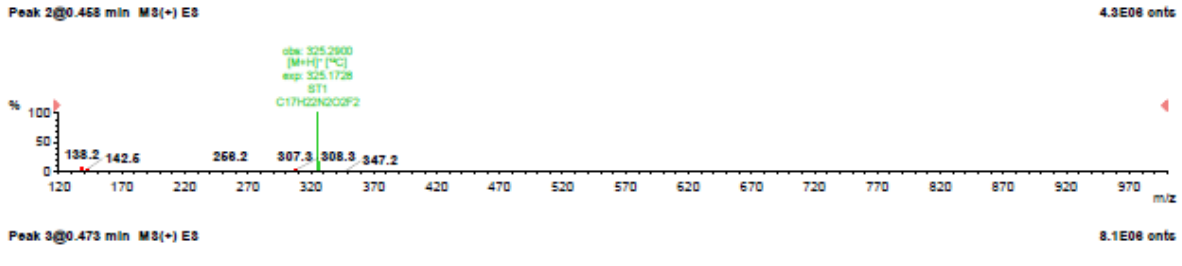

3: UV Detector: 212_216
Range: 6.436
0.18
100%
0.47
23519
0.28
AU
Time
1: MS ES+ :353.204 1.0000Da
100%
0.48
1561011
7.8e+007
2: MS ES- :351.188 1.0000Da
48%
1.63
582
34%
1.91
420
1.4e+005
0.30
0.39
1.86
(1) ELSD Signal
100%
0.46
2835
Range: 192.682
LSU
2:(Time: 0.47) Combine (66:71-(46:49+89:91))
1:MS ES+
5.6e+007
353.3
354.3
m/z

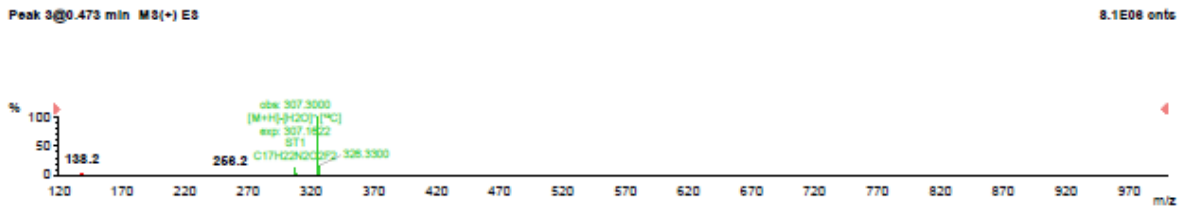
Compound **7j**:

Sample Name: LCMS384-20200803-5_A23 **ACT No:** ACT-709678 **ELN Nr:** ELN227-1507.A02
Instrument: ICHALW-DL00012-TQD **Acquisition time:** 8/3/2020 9:59 PM

Expression	Result
Auto-Comments	Possible Isomers
Auto-Summary	GOOD
Purity	98.2000
Target Mass	325.3000
Target RT	0.4750



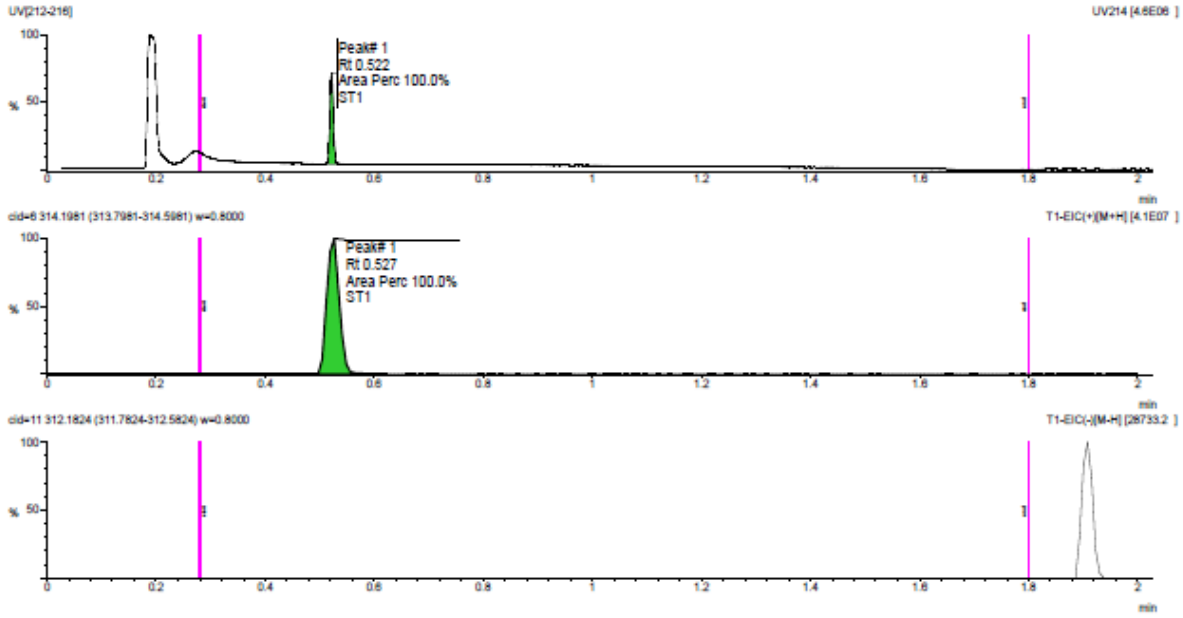


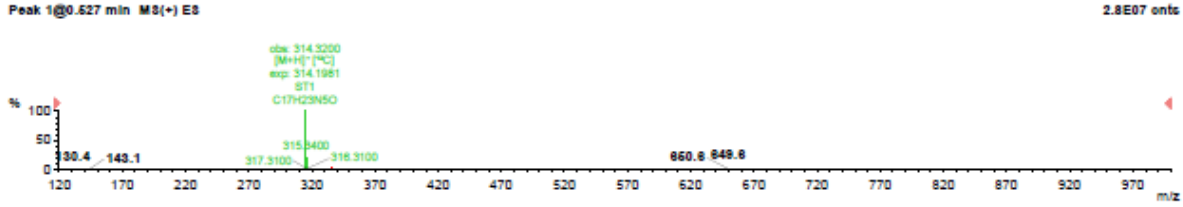


Compound **7k**:

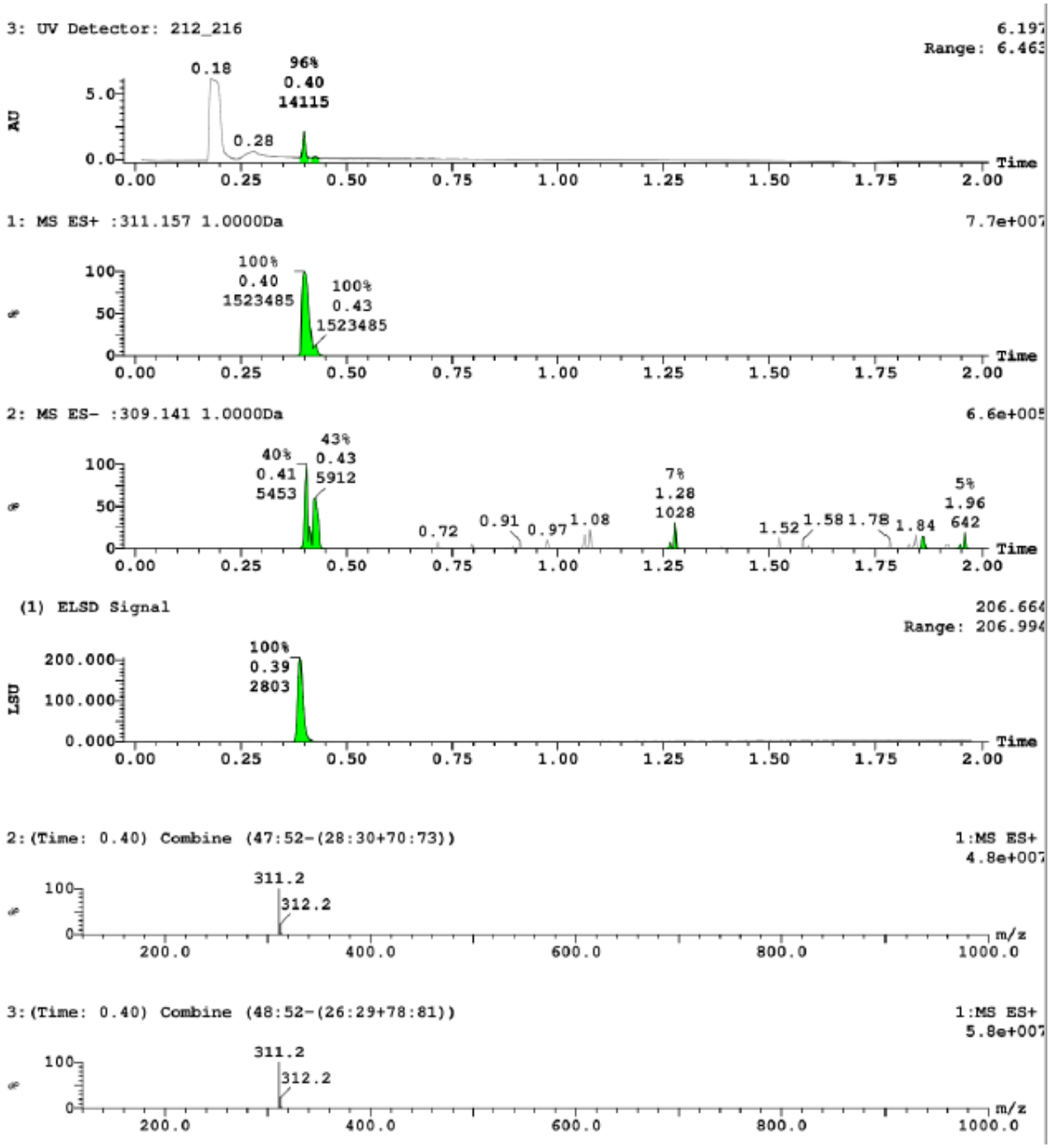
Sample Name: LCMS384-20200512-1_I05 **ACT No:** ACT-709631 **ELN Nr:** ELN026-2066.A01
Instrument: ICHALW-DL00021-SQD **Acquisition time:** 5/12/2020 4:51 PM

Expression	Result
Auto-Comments	
Auto-Summary	GOOD
Purity	100.0000
Target Mass	314.3000
Target RT	0.5220

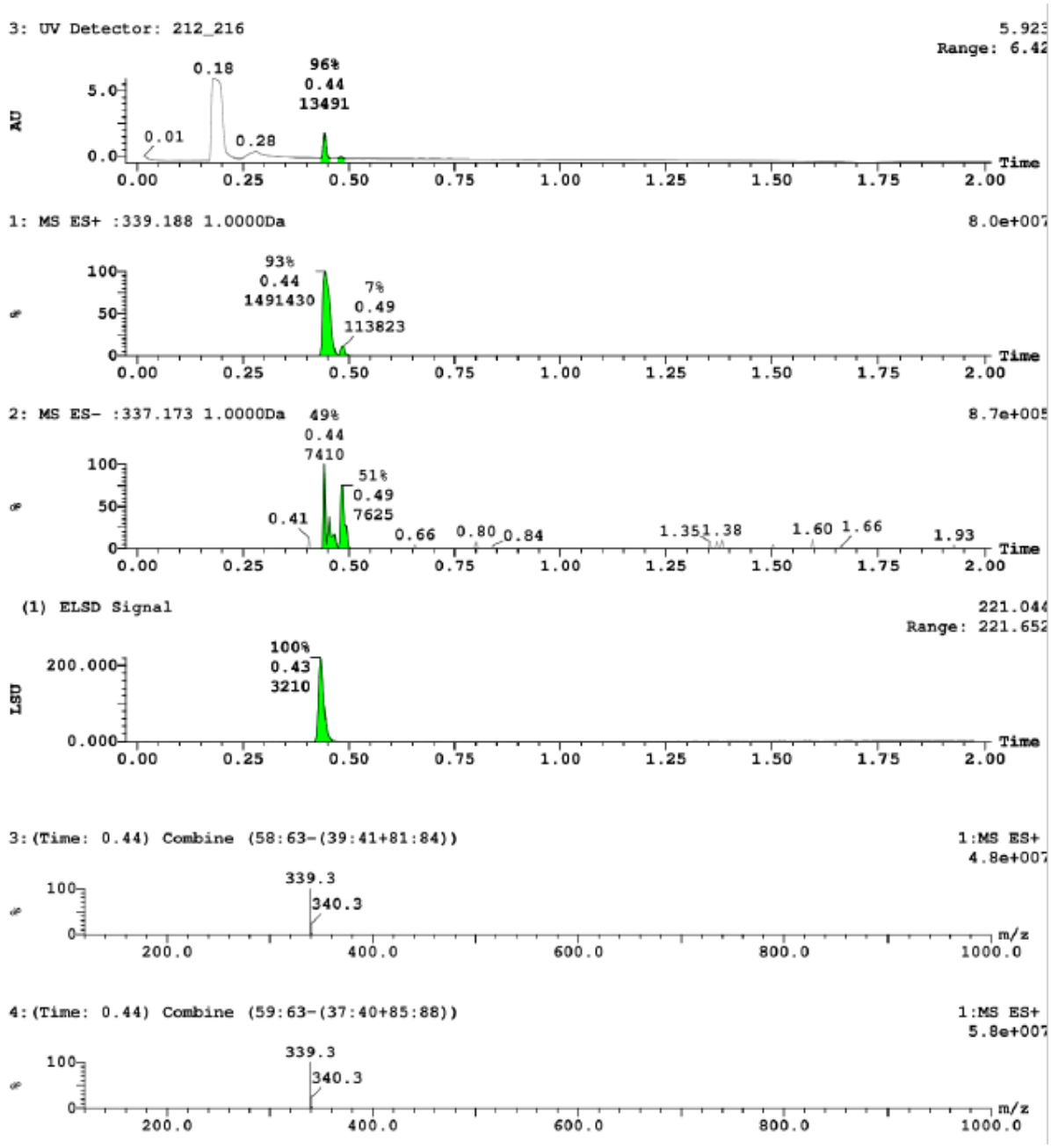




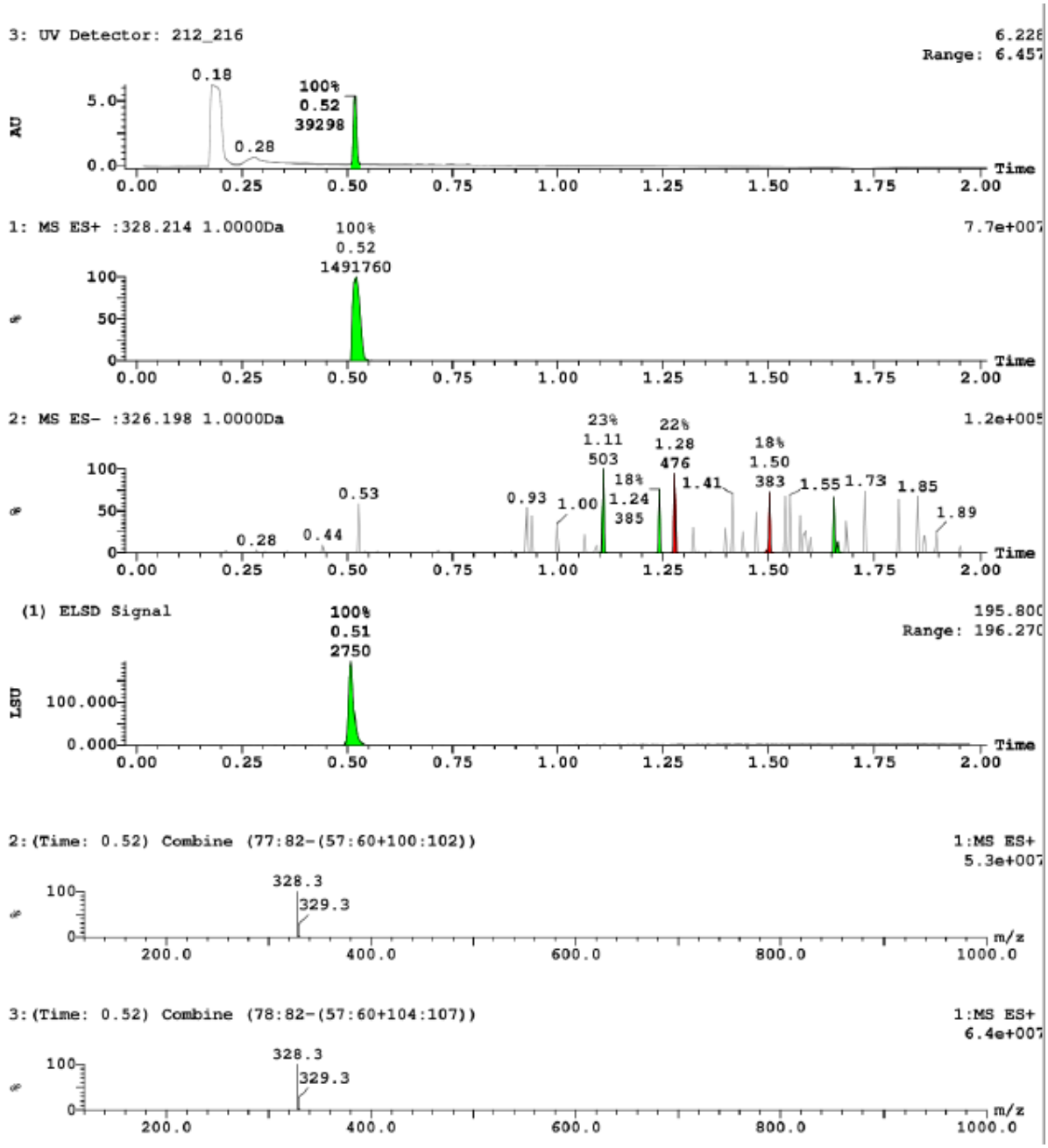
Compound **7l**:


3: UV Detector: 212_216
Range: 6.463
0.18
96%
0.40
14115
0.28
AU
Time
1: MS ES+ :311.157 1.0000Da
7.7e+007
100%
0.40
1523485
100%
0.43
1523485
%
Time
2: MS ES- :309.141 1.0000Da
6.6e+005
40%
0.41
5453
43%
0.43
5912
0.72
0.91
0.97
1.08
7%
1.28
1028
1.52
1.58
1.78
1.84
5%
1.96
642
%
Time
(1) ELSD Signal
Range: 206.996
100%
0.39
2803
LSU
Time
2:(Time: 0.40) Combine (47:52-(28:30+70:73))
1:MS ES+
4.8e+007
311.2
312.2
%
m/z
3:(Time: 0.40) Combine (48:52-(26:29+78:81))
1:MS ES+
5.8e+007
311.2
312.2
%
m/z

Compound **7m**:


3: UV Detector: 212_216
5.923
Range: 6.42
0.18
96%
0.44
13491
0.01
0.28
AU
Time
1: MS ES+ :339.188 1.0000Da
8.0e+007
93%
0.44
1491430
7%
0.49
113823
2: MS ES- :337.173 1.0000Da
49%
0.44
7410
51%
0.49
7625
0.41
0.66
0.80
0.84
1.35
1.38
1.60
1.66
1.93
(1) ELSD Signal
221.044
Range: 221.652
100%
0.43
3210
LSU
3:(Time: 0.44) Combine (58:63-(39:41+81:84))
1:MS ES+
4.8e+007
339.3
340.3
m/z
4:(Time: 0.44) Combine (59:63-(37:40+85:88))
1:MS ES+
5.8e+007
339.3
340.3
m/z

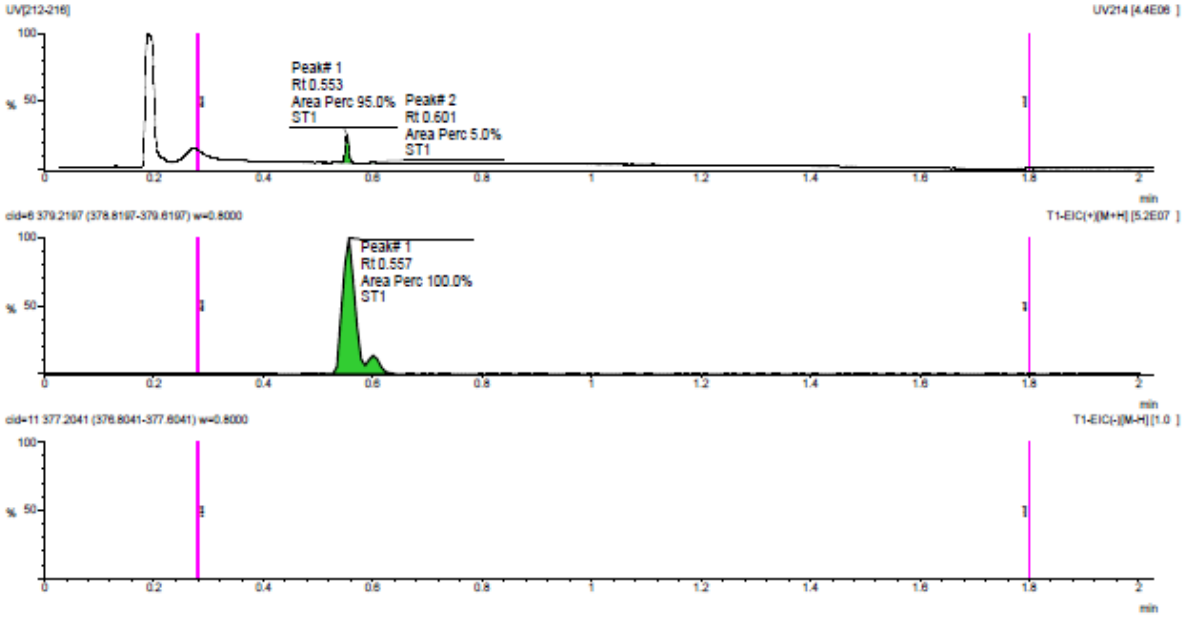
Compound **7n**:

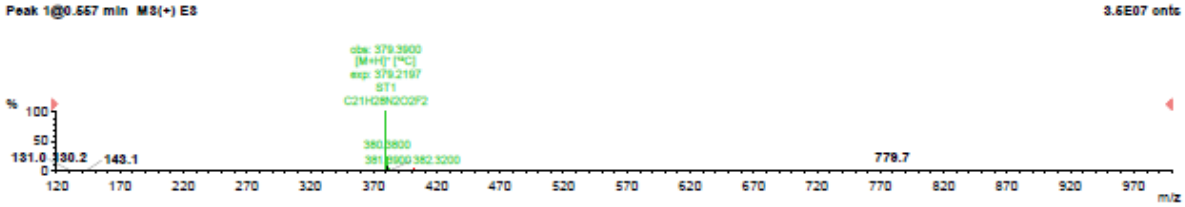

3: UV Detector: 212_216
Range: 6.457
0.18
100%
0.52
39298
0.28
AU
Time
1: MS ES+ :328.214 1.0000Da
100%
0.52
1491760
2: MS ES- :326.198 1.0000Da
23%
1.11
503
22%
1.28
476
18%
1.50
383
18%
1.24
385
0.53
0.93
1.00
1.41
1.55
1.73
1.85
1.89
0.28
0.44
(1) ELSD Signal
100%
0.51
2750
Range: 196.270
LSU
2:(Time: 0.52) Combine (77:82-(57:60+100:102))
1:MS ES+
328.3
329.3
m/z
3:(Time: 0.52) Combine (78:82-(57:60+104:107))
1:MS ES+
328.3
329.3
m/z

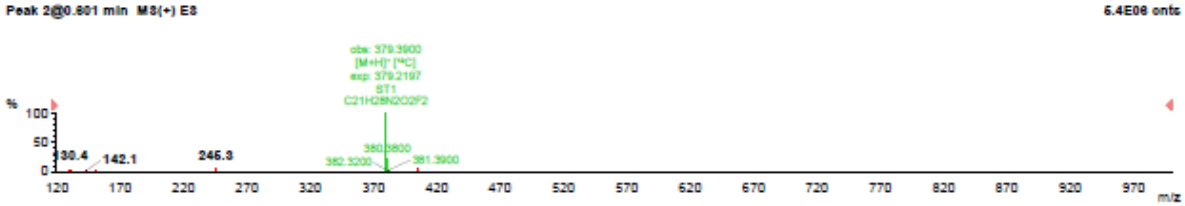
Compound **7o**:

Sample Name: LCMSP384-20200528-1_O09 **ACT No:** ACT-709653 **ELN Nr:** ELN026-1143.A01
Instrument: **Acquisition time:** 5/28/2020 10:24 AM

Expression	Result
Auto-Comments	
Auto-Summary	GOOD
Purity	100.0000
Target Mass	379.4000
Target RT	0.5530



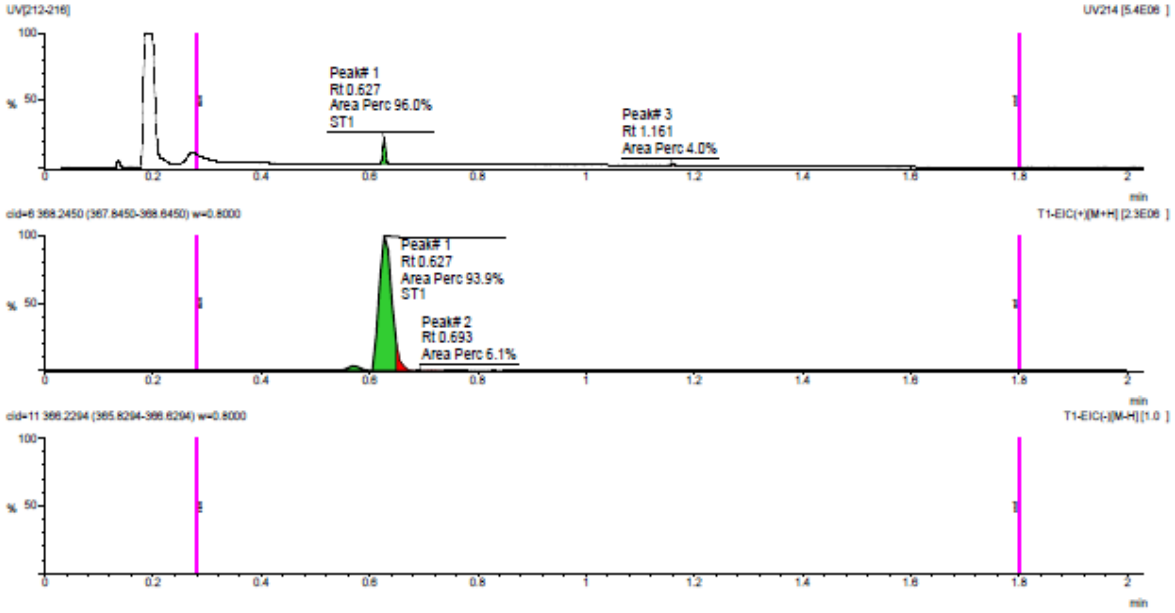


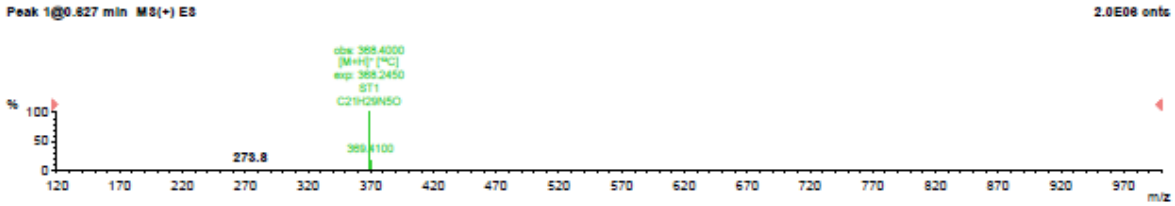


Compound **7p**:

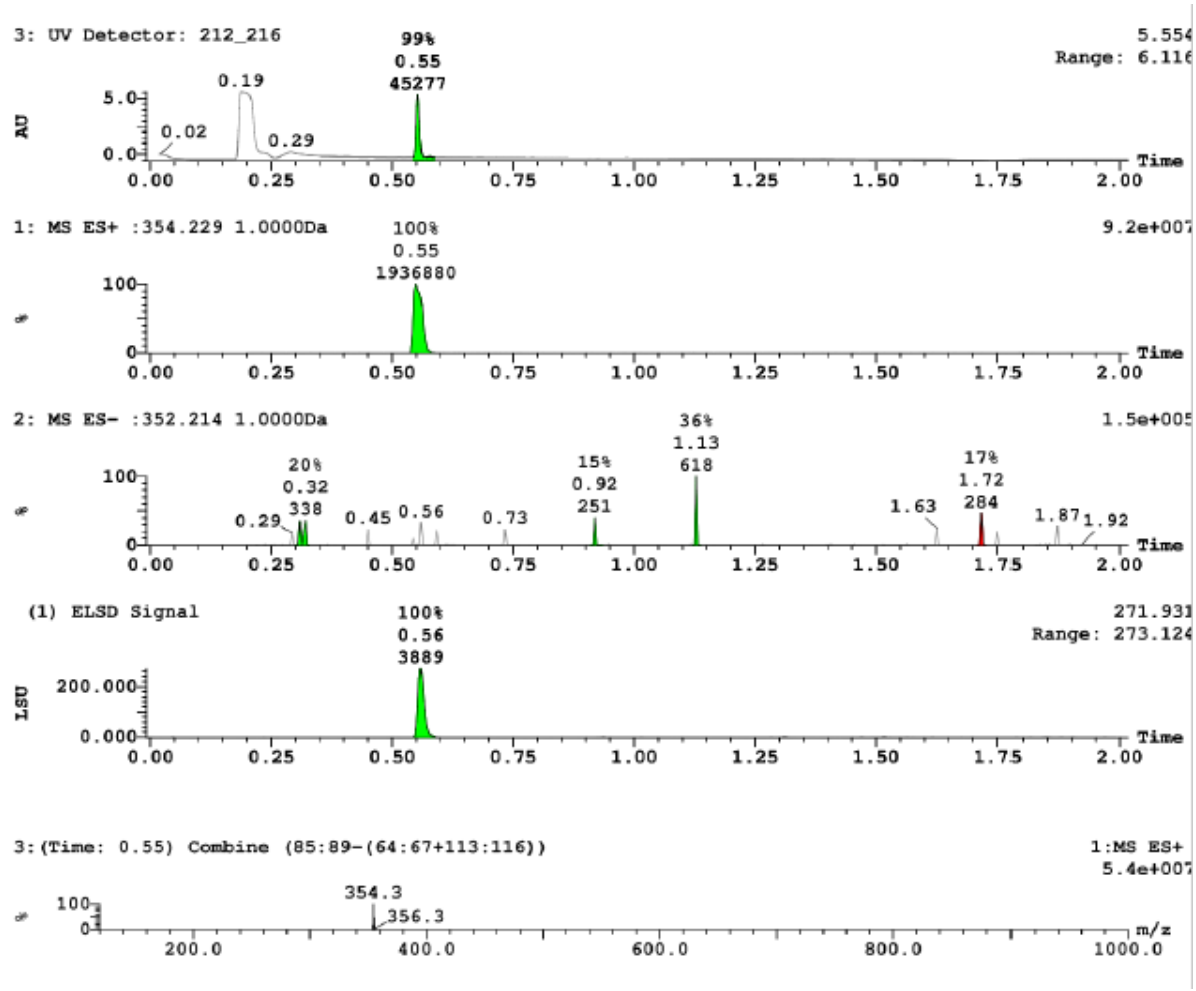
Sample Name: LCMS384-20200803-5_M23 **ACT No:** ACT-709865 **ELN Nr:** ELN227-1507.A04
Instrument: ICHALW-DL00012-TQD **Acquisition time:** 8/3/2020 10:17 PM

Expression	Result
Auto-Comments	
Auto-Summary	GOOD
Purity	96.0000
Target Mass	368.4000
Target RT	0.6270





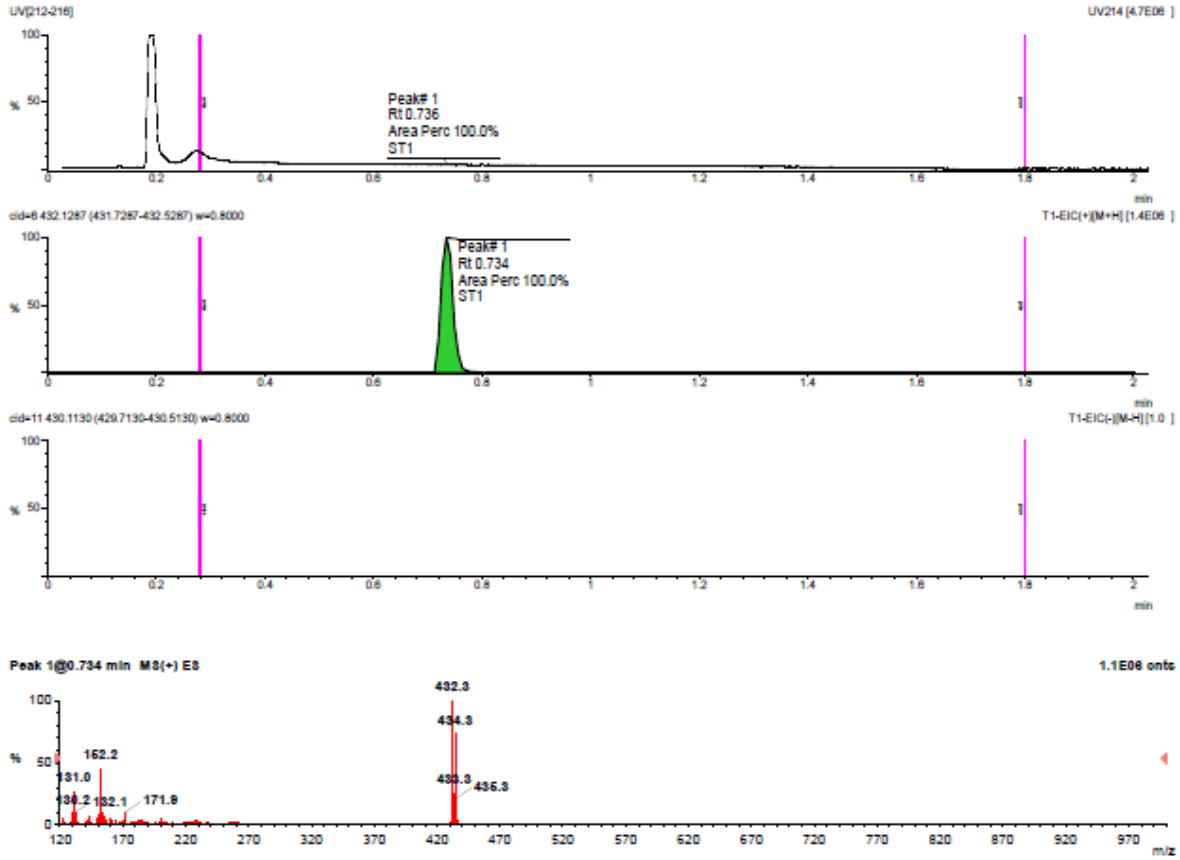
Compound **8a**:


3: UV Detector: 212_216
99%
0.55
45277
0.19
0.02
0.29
AU
Time
1: MS ES+ :354.229 1.0000Da
100%
0.55
1936880
2: MS ES- :352.214 1.0000Da
36%
1.13
618
20%
0.32
338
15%
0.92
251
17%
1.72
284
0.29
0.45
0.56
0.73
1.63
1.87
1.92
(1) ELSD Signal
100%
0.56
3889
LSU
3:(Time: 0.55) Combine (85:89-(64:67+113:116))
1:MS ES+
354.3
356.3
m/z

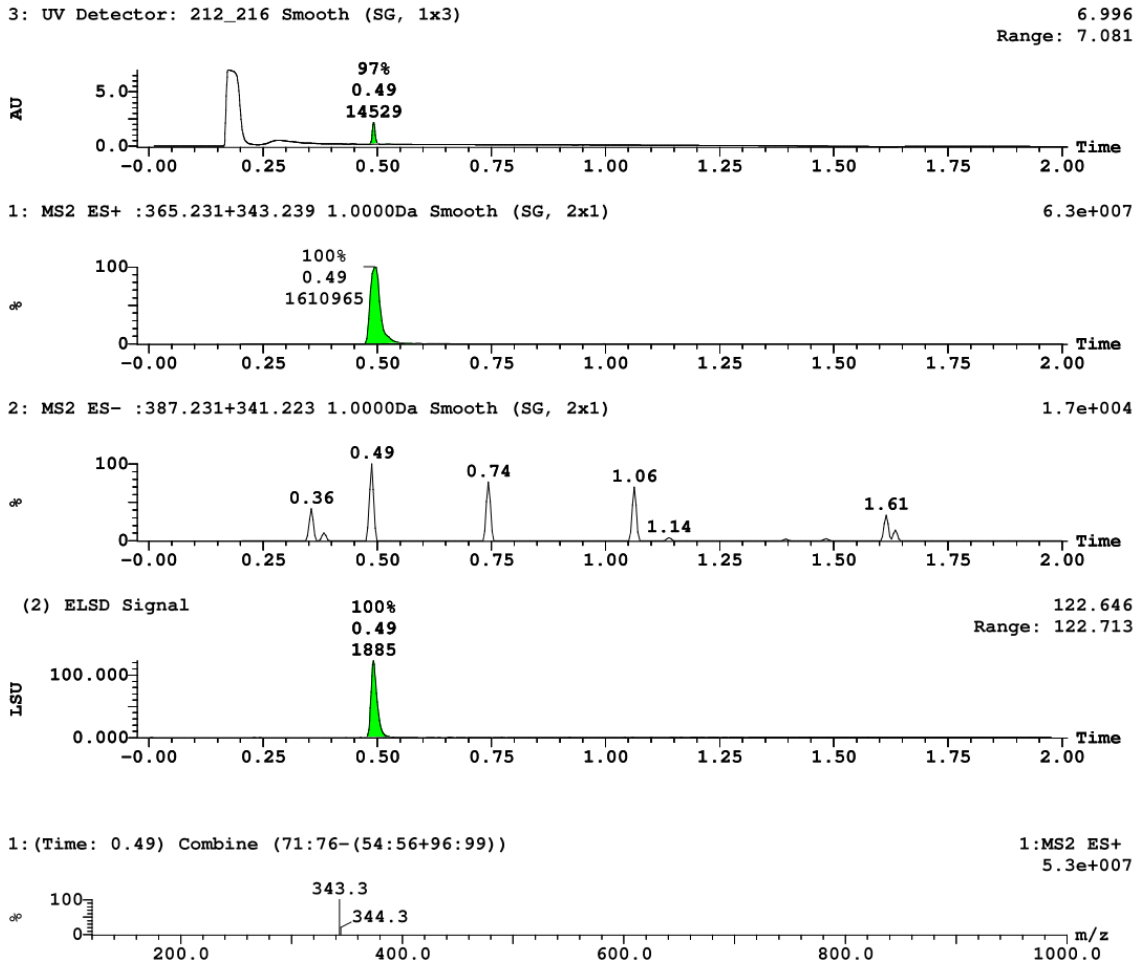
Compound **8b**:

Sample Name: LCMS384-20200713-3_K01 **ACT No:** ACT-710148 **ELN Nr:** ELN026-2083.B01
Instrument: ICHALW-DL00021-SQD **Acquisition time:** 7/13/2020 3:31 PM

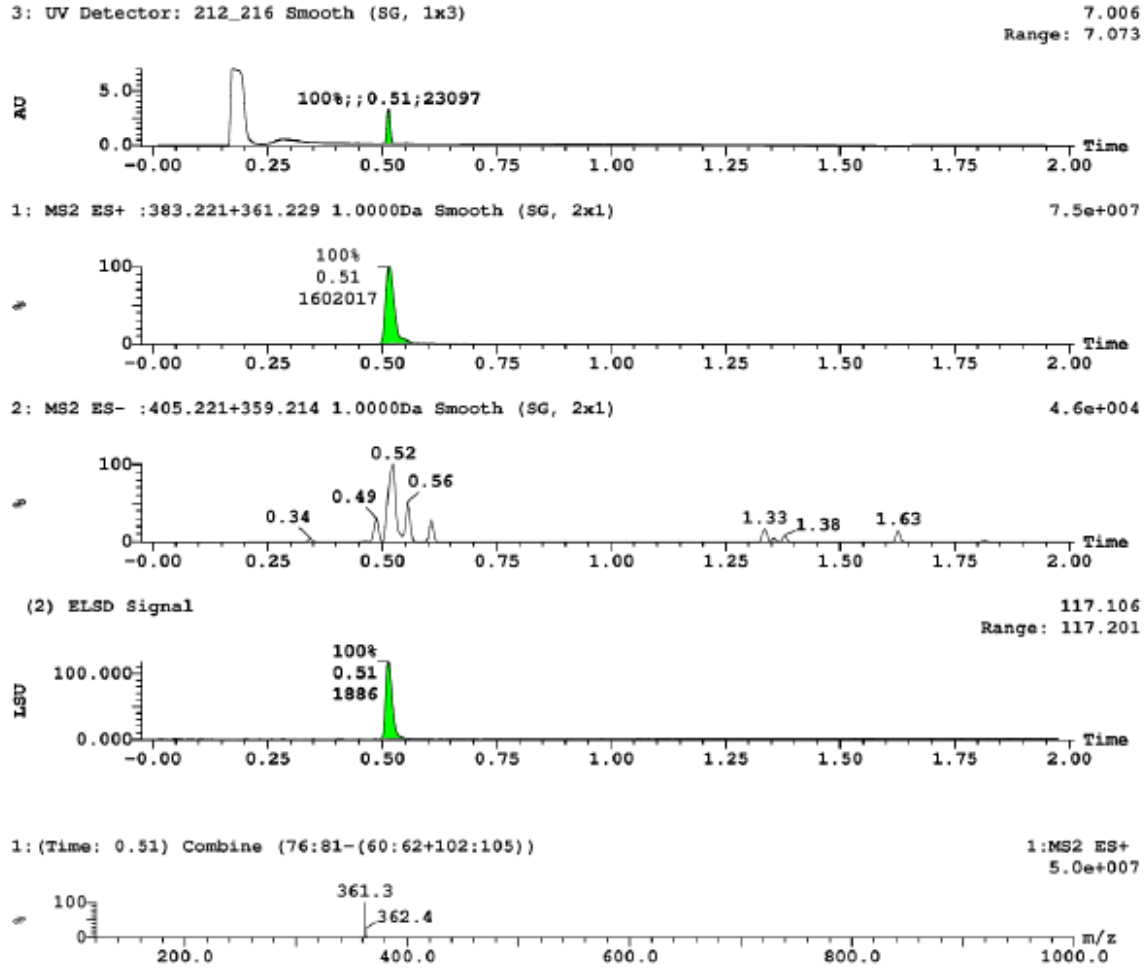
Expression	Result
Auto-Comments	
Auto-Summary	GOOD
Purity	100.0000
Target Mass	0.0000
Target RT	0.7360



Compound **8c**:


3: UV Detector: 212_216 Smooth (SG, 1x3)
6.996
Range: 7.081
97%
0.49
14529
AU
5.0
0.0
Time
1: MS2 ES+ :365.231+343.239 1.0000Da Smooth (SG, 2x1)
6.3e+007
100%
0.49
1610965
%
100
0
Time
2: MS2 ES- :387.231+341.223 1.0000Da Smooth (SG, 2x1)
1.7e+004
0.49
0.74
1.06
0.36
1.14
1.61
%
100
0
Time
(2) ELSD Signal
122.646
Range: 122.713
100%
0.49
1885
LSU
100.000
0.000
Time
1:(Time: 0.49) Combine (71:76-(54:56+96:99))
1:MS2 ES+
5.3e+007
343.3
344.3
%
100
0
m/z
200.0
400.0
600.0
800.0
1000.0

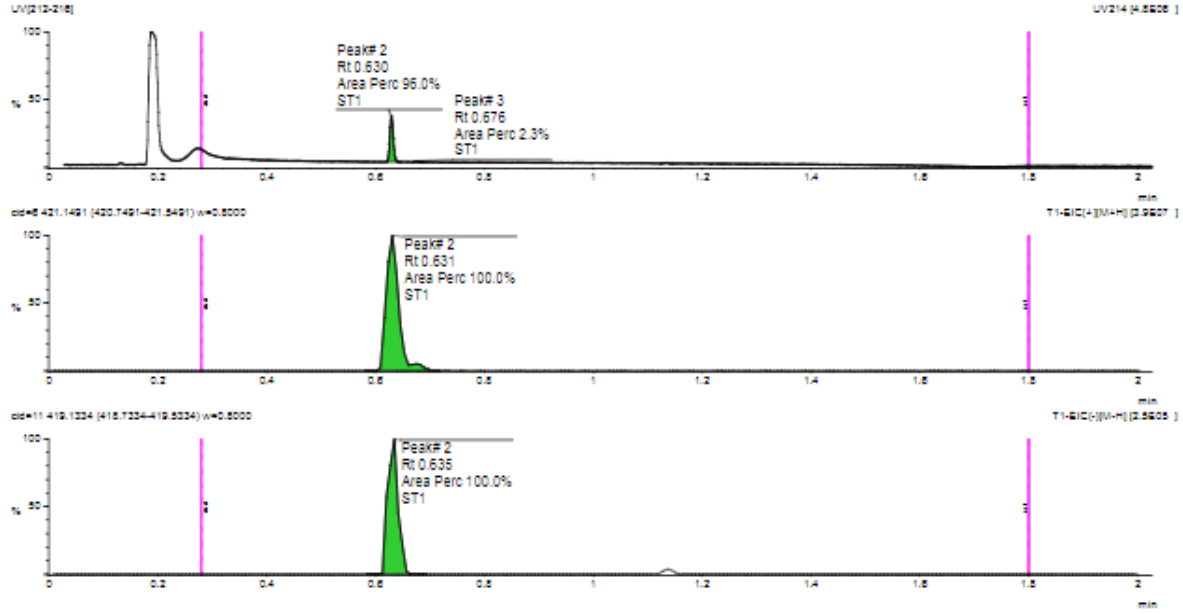
Compound **8d**:

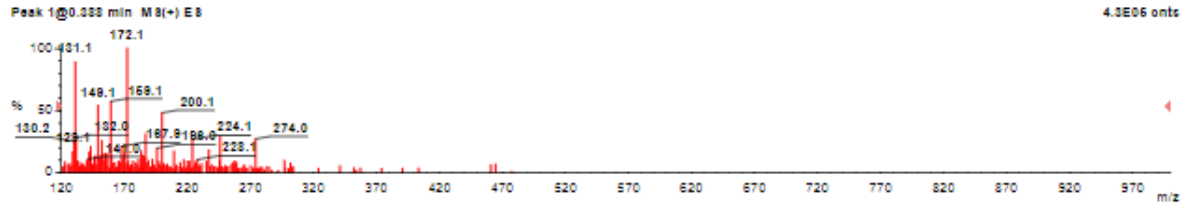

3: UV Detector: 212_216 Smooth (SG, 1x3)
7.006
Range: 7.073
AU
5.0
0.0
100%;;0.51;23097
Time
-0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00
1: MS2 ES+ :383.221+361.229 1.0000Da Smooth (SG, 2x1)
7.5e+007
%
100
0
100%
0.51
1602017
Time
2: MS2 ES- :405.221+359.214 1.0000Da Smooth (SG, 2x1)
4.6e+004
0.52
0.56
0.49
0.34
1.33
1.38
1.63
(2) ELSD Signal
117.106
Range: 117.201
LSU
100.000
0.000
100%
0.51
1886
1:(Time: 0.51) Combine (76:81-(60:62+102:105))
1:MS2 ES+
5.0e+007
361.3
362.4
m/z
200.0 400.0 600.0 800.0 1000.0

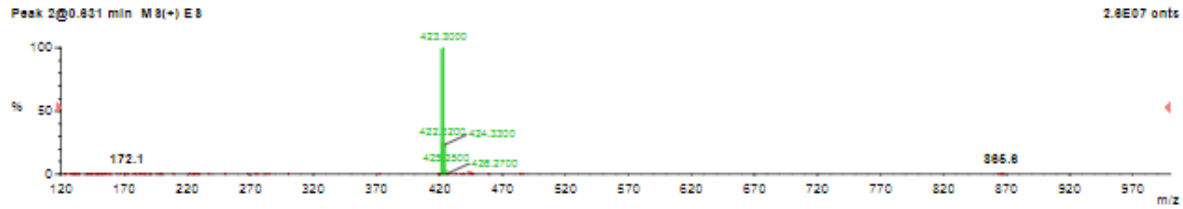
Compound **8e**:

Sample Name: LCMS384-20200713-3_M01 **ACT No:** ACT-730647 **ELN Nr:** ELN026-2064.A05
Instrument: ICHALW-DL00021-SQD **Acquisition time:** 7/13/2020 3:34 PM

Expression	Result
Auto-Comments	
Auto-Summary	GOOD
Purity	98.3000
Target Mass	423.3000
Target RT	0.6300



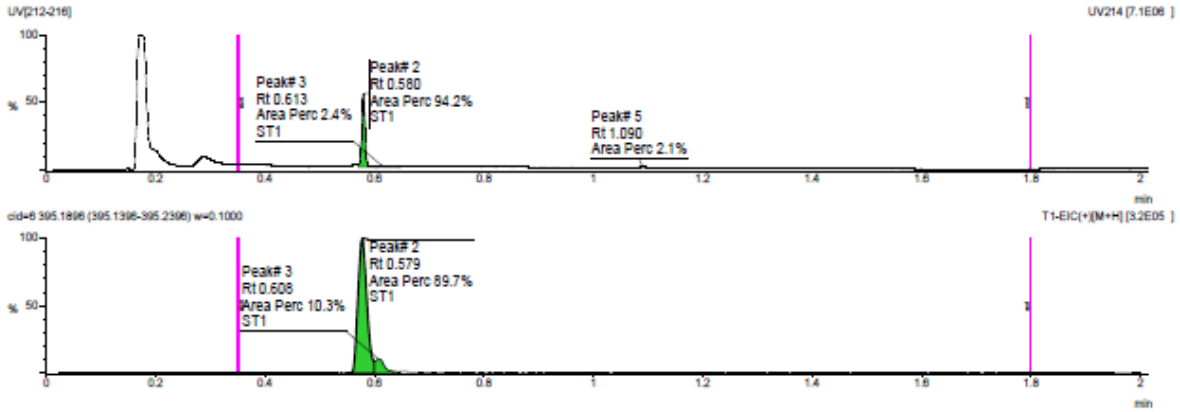


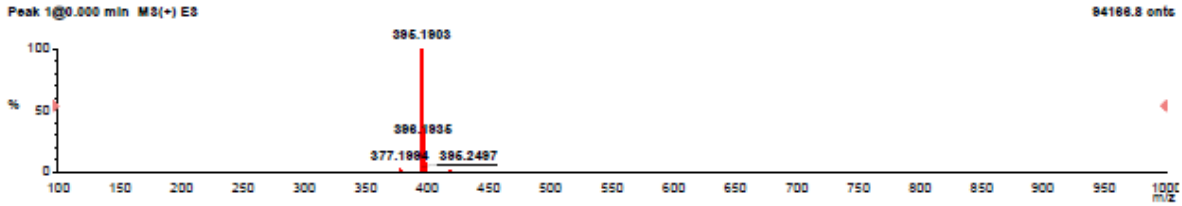


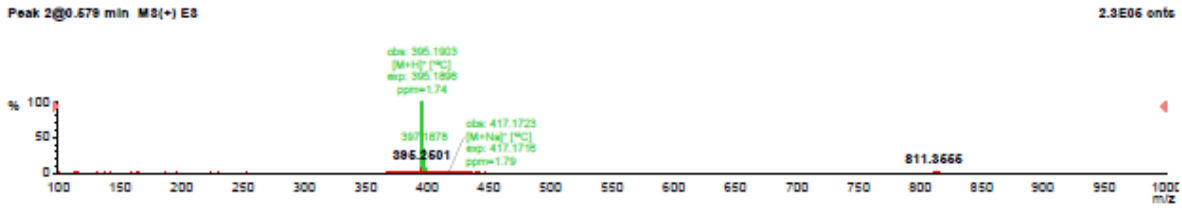
Compound **8f**:

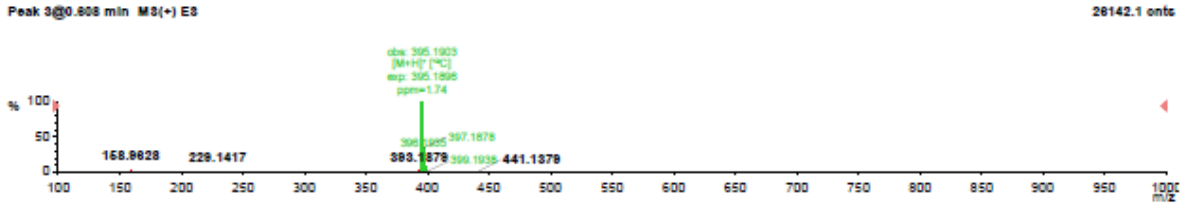
Sample Name: LCMSH384-20200720-1_A01 **ACT No:** ACT-730645 **ELN Nr:** ELN026-2083.A03
Instrument: **Acquisition time:** 7/24/2020 2:54 PM

Expression	Result
Auto-Comments	
Auto-Summary	GOOD
Purity	96.6000
Target Mass	395.1903
Target RT	0.5800

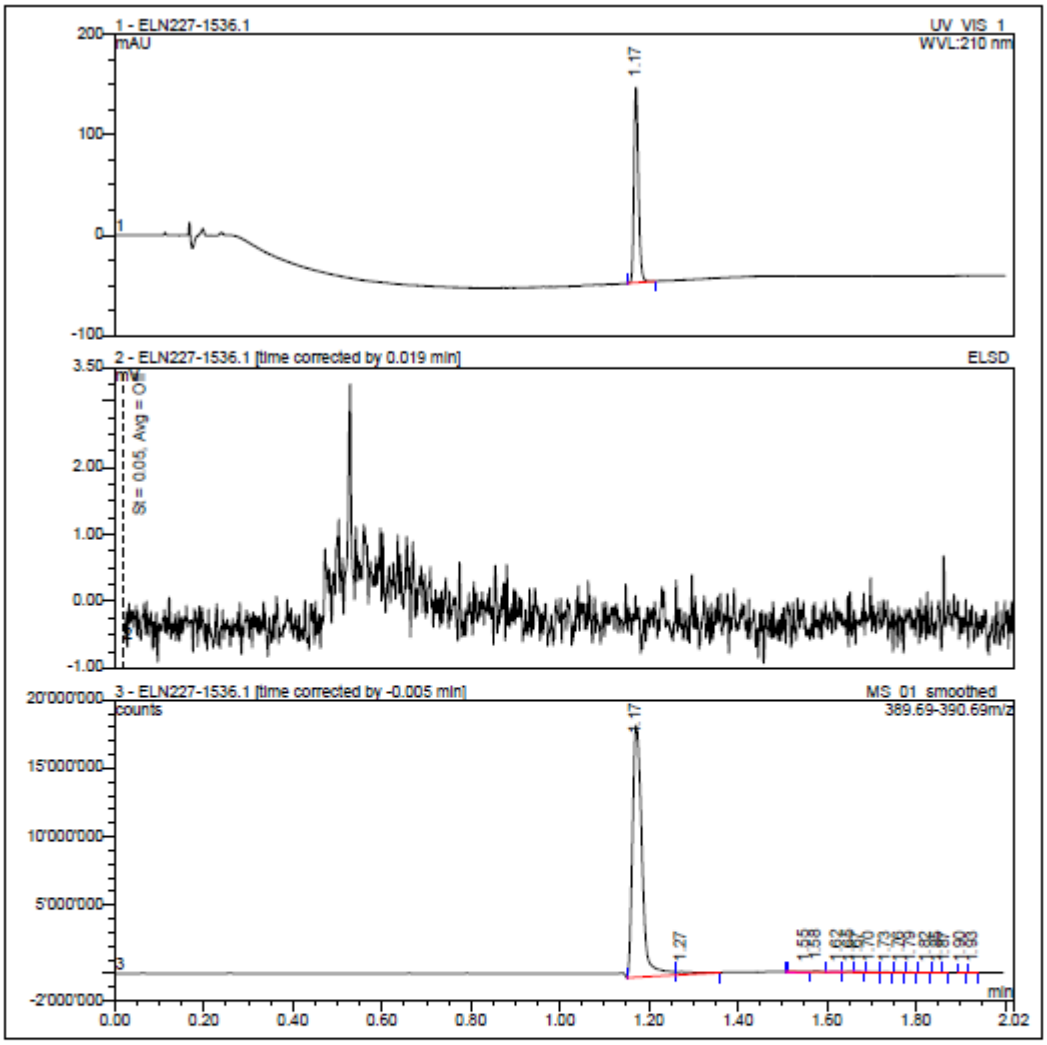


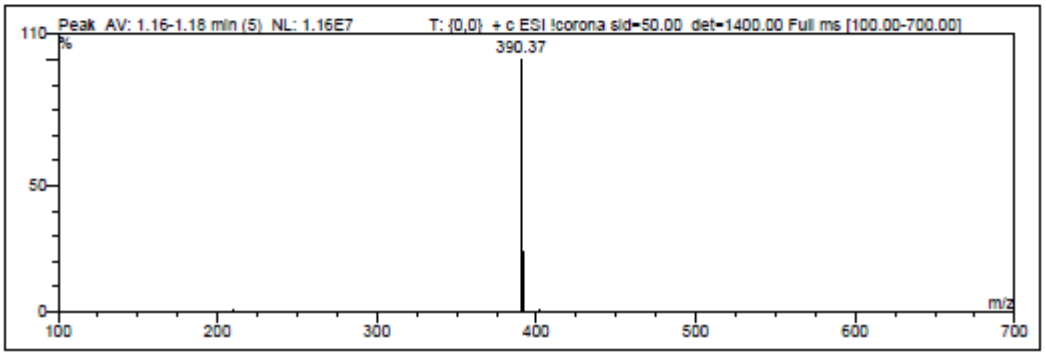




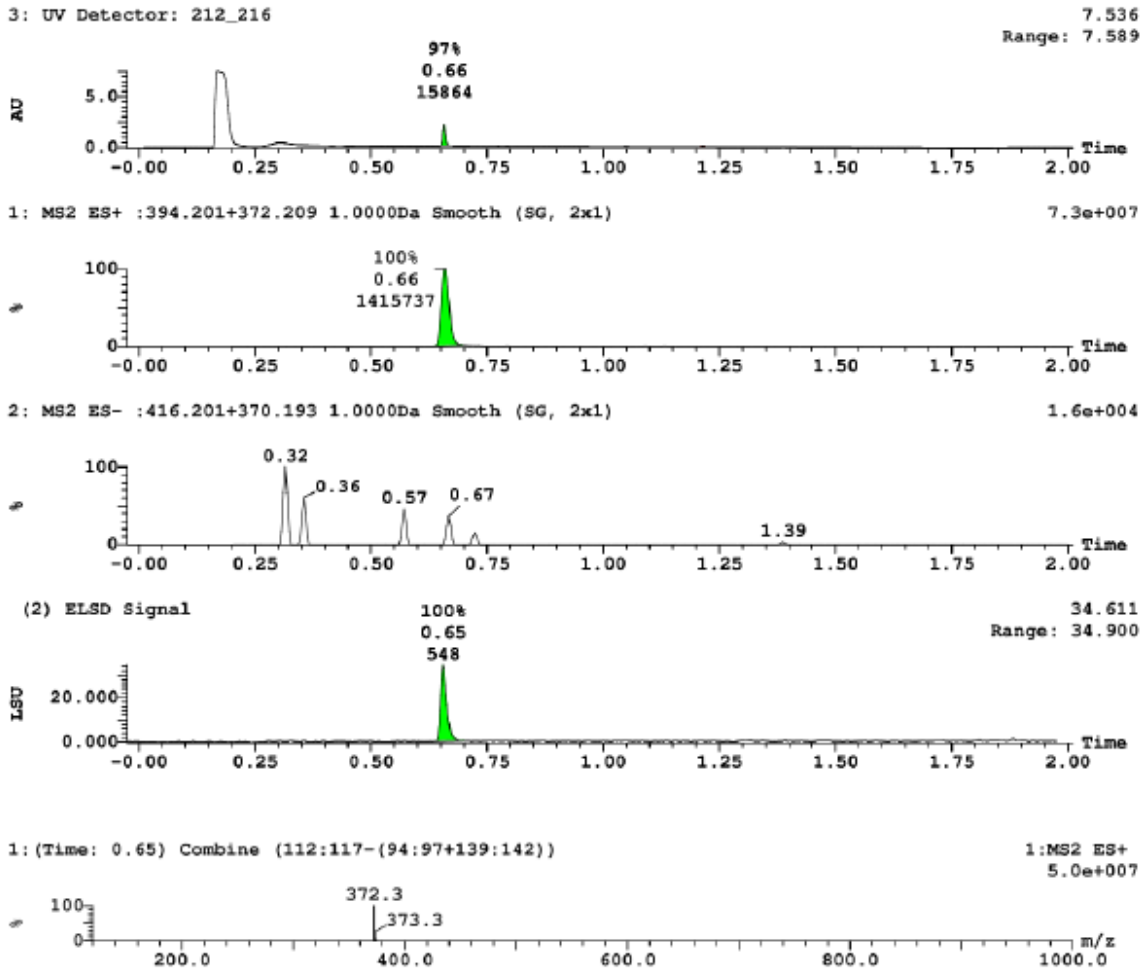


Compound **8g**:


1 - ELN227-1536.1
UV_VIS_1
mAU
WVL:210 nm
1.17
2 - ELN227-1536.1 [time corrected by 0.019 min]
ELSD
St = 0.05, Avg = 0.
3 - ELN227-1536.1 [time corrected by -0.005 min]
MS_01_smoothed
counts
389.69-390.69m/z
1.27
min


Peak AV: 1.16-1.18 min (5) NL: 1.16E7
T: {0,0} + c ESI !corona sid=50.00 det=1400.00 Full ms [100.00-700.00]
390.37
%
m/z

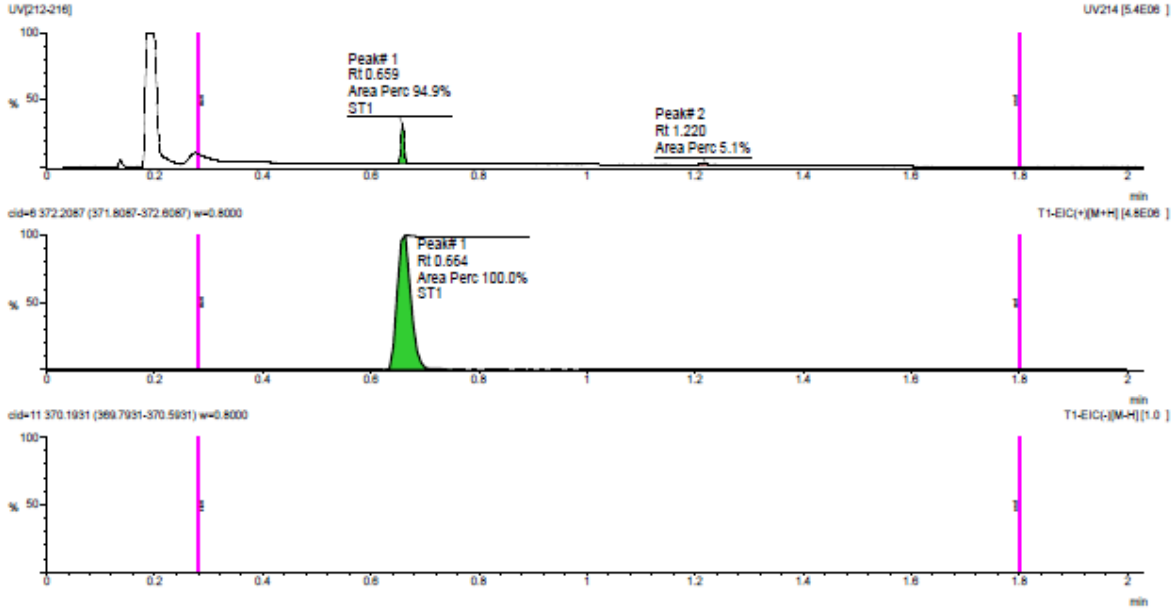
Compound **8h**:

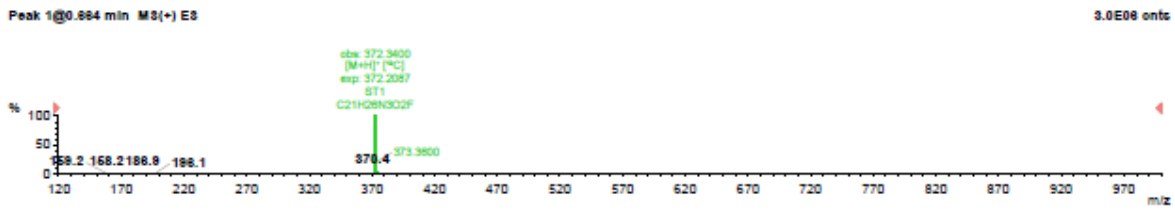

3: UV Detector: 212_216
7.536
Range: 7.589
97%
0.66
15864
AU
5.0
0.0
Time
-0.00
0.25
0.50
0.75
1.00
1.25
1.50
1.75
2.00
1: MS2 ES+ :394.201+372.209 1.0000Da Smooth (SG, 2x1)
7.3e+007
100%
0.66
1415737
%
100
0
Time
2: MS2 ES- :416.201+370.193 1.0000Da Smooth (SG, 2x1)
1.6e+004
0.32
0.36
0.57
0.67
1.39
(2) ELSD Signal
34.611
Range: 34.900
100%
0.65
548
LSU
20.000
0.000
1:(Time: 0.65) Combine (112:117-(94:97+139:142))
1:MS2 ES+
5.0e+007
372.3
373.3
m/z
200.0
400.0
600.0
800.0
1000.0

Compound **8i**:

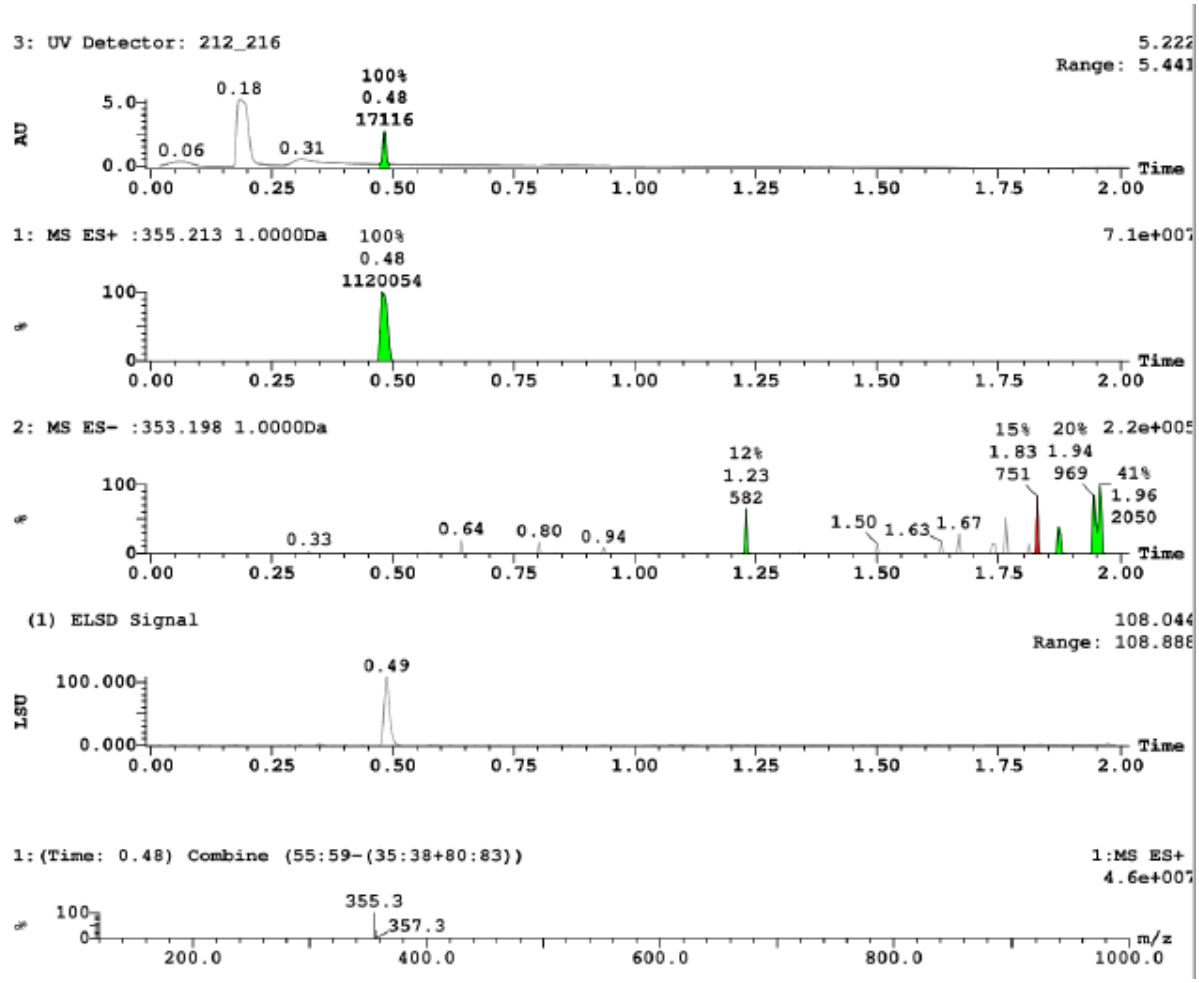
Sample Name: LCMS384-20200803-5_K23 **ACT No:** ACT-773703 **ELN Nr:** ELN227-1507.A01
Instrument: ICHALW-DL00012-TQD **Acquisition time:** 8/3/2020 10:14 PM

Expression	Result
Auto-Comments	
Auto-Summary	GOOD
Purity	94.9000
Target Mass	372.3000
Target RT	0.6590





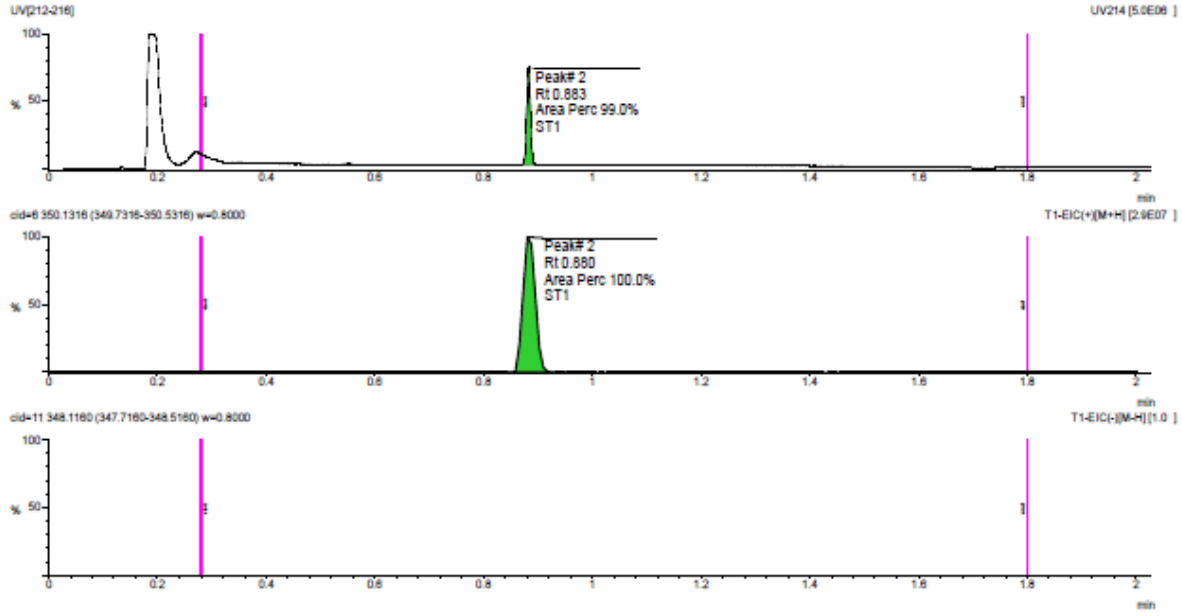
Compound **8j**:

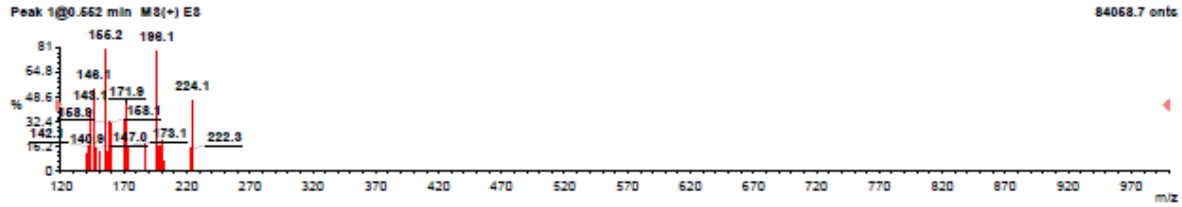

3: UV Detector: 212_216
Range: 5.441
AU
0.18
100%
0.48
17116
0.06
0.31
Time
1: MS ES+ :355.213 1.0000Da
100%
0.48
1120054
%
2: MS ES- :353.198 1.0000Da
12%
1.23
582
15%
1.83
751
20%
1.94
969
41%
1.96
2050
0.33
0.64
0.80
0.94
1.50
1.63
1.67
(1) ELSD Signal
Range: 108.888
LSU
100.000
0.000
0.49
1:(Time: 0.48) Combine (55:59-(35:38+80:83))
1:MS ES+
355.3
357.3
m/z
200.0
400.0
600.0
800.0
1000.0

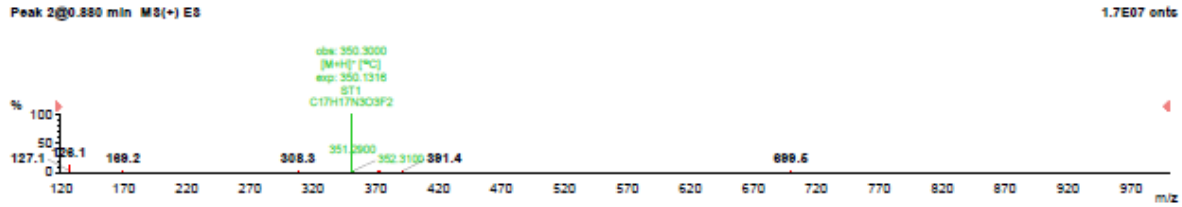
Compound **9a**:

Sample Name: LCMS384-20191018-2_E05 **ACT No:** IDOR-1119-5082 **ELN Nr:** ELN057-1675.1
Instrument: ICHALW-DL00021-SQD **Acquisition time:** 10/18/2019 3:42 PM

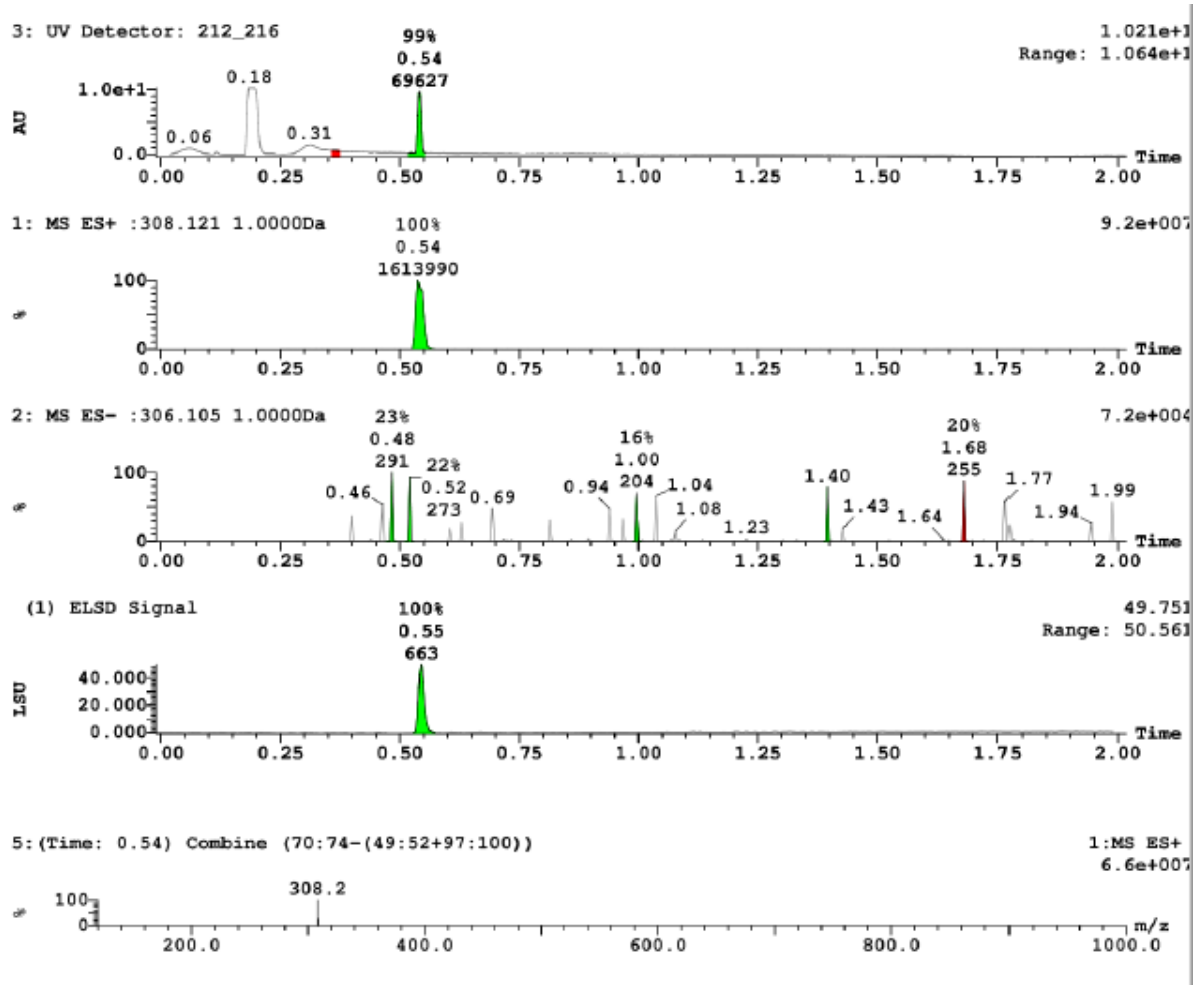
Expression	Result
Auto-Comments	
Auto-Summary	GOOD
Purity	99.0000
Target Mass	350.3000
Target RT	0.8830







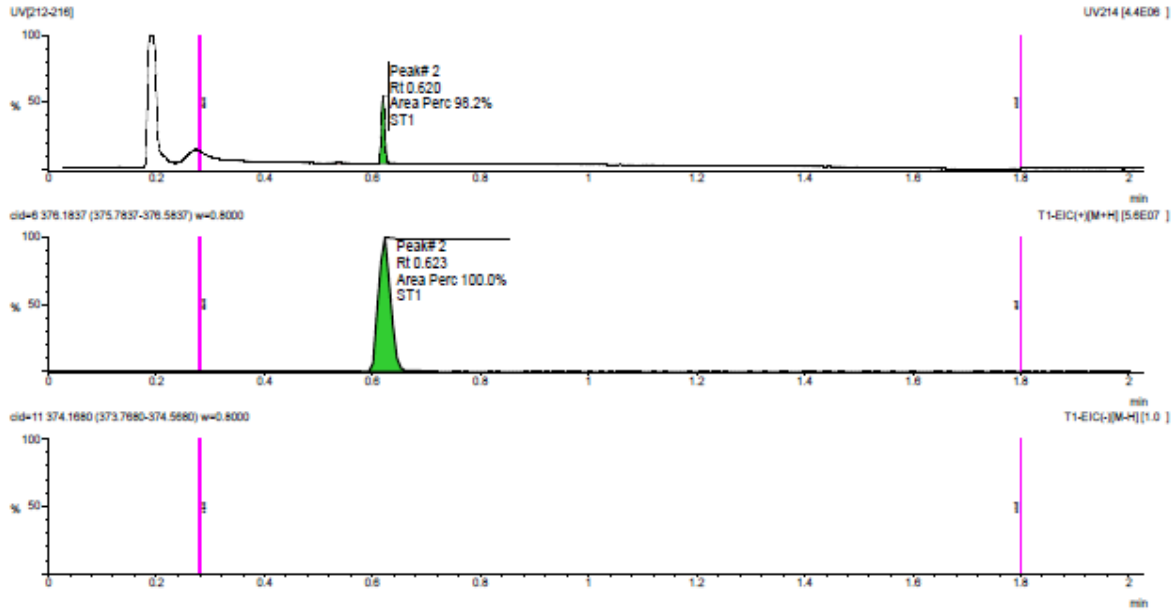
Compound **9b**:

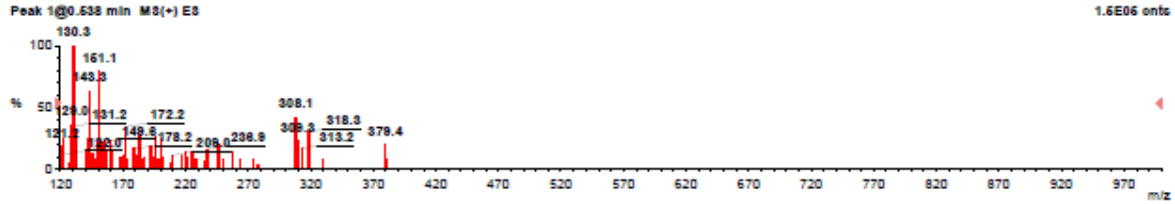

3: UV Detector: 212_216
99%
0.54
69627
0.18
0.06
0.31
1.021e+1
Range: 1.064e+1
AU
Time
1: MS ES+ :308.121 1.0000Da
100%
0.54
1613990
9.2e+007
2: MS ES- :306.105 1.0000Da
23%
0.48
291
22%
0.52
273
0.46
0.69
16%
1.00
204
0.94
1.04
1.08
1.23
1.40
1.43
1.64
20%
1.68
255
1.77
1.94
1.99
7.2e+004
(1) ELSD Signal
100%
0.55
663
49.751
Range: 50.561
LSU
5:(Time: 0.54) Combine (70:74-(49:52+97:100))
308.2
1:MS ES+
6.6e+007
m/z

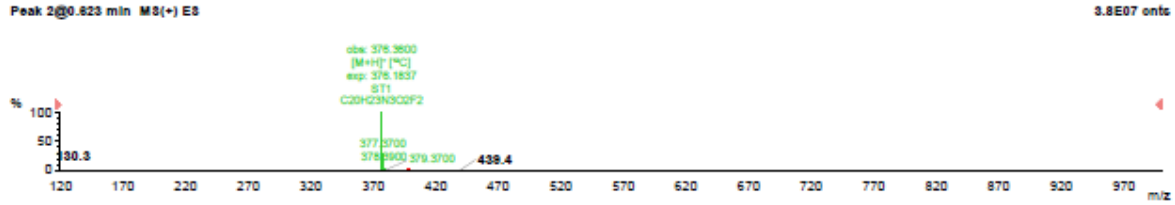
Compound **9c**:

Sample Name: LCMSP384-20200528-1_C11 **ACT No:** ACT-735356 **ELN Nr:** ELN026-1200.B01
Instrument: ICHALW-DL00021-SQD **Acquisition time:** 5/28/2020 10:29 AM

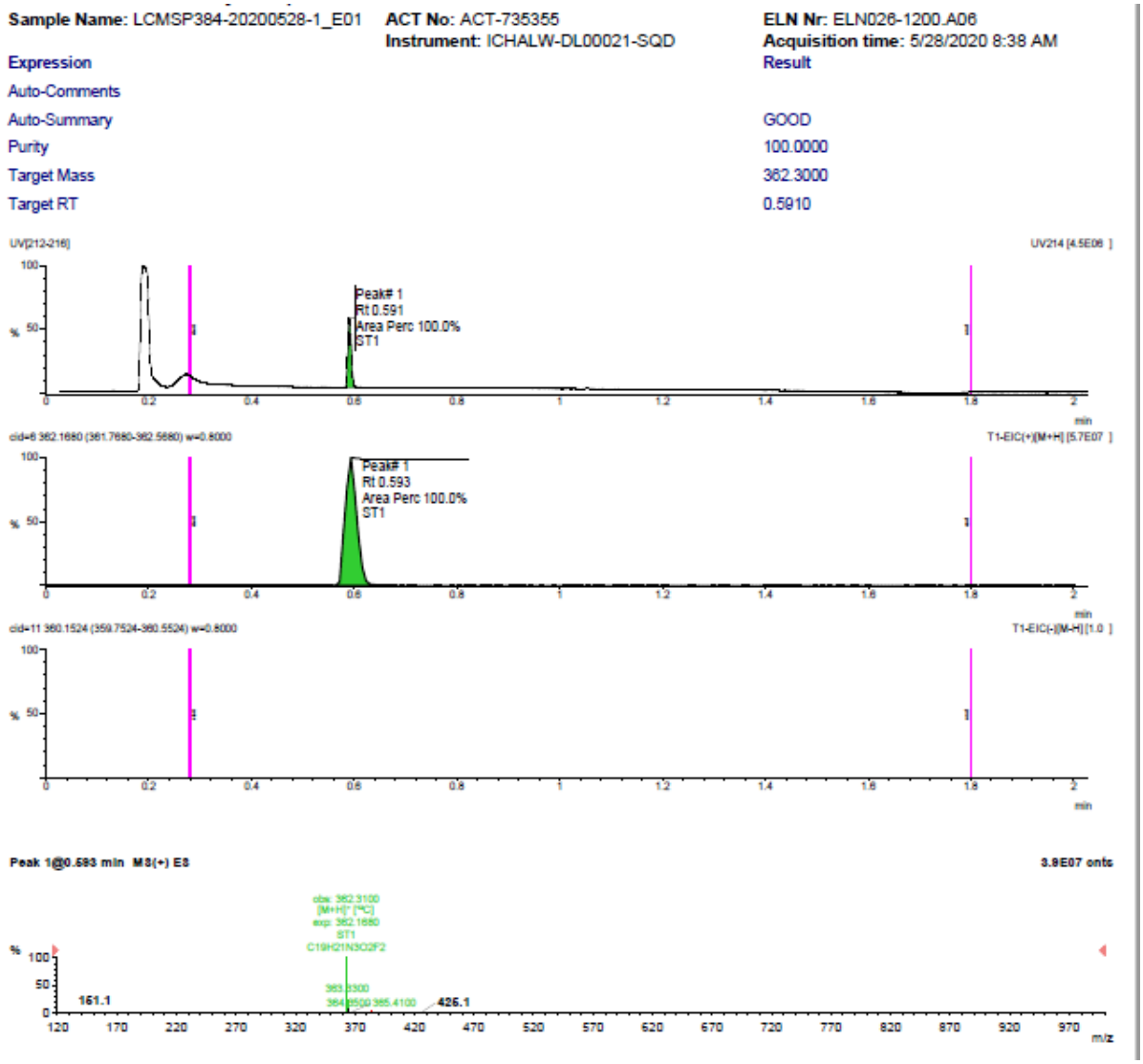
Expression	Result
Auto-Comments	
Auto-Summary	GOOD
Purity	98.2000
Target Mass	376.4000
Target RT	0.6200



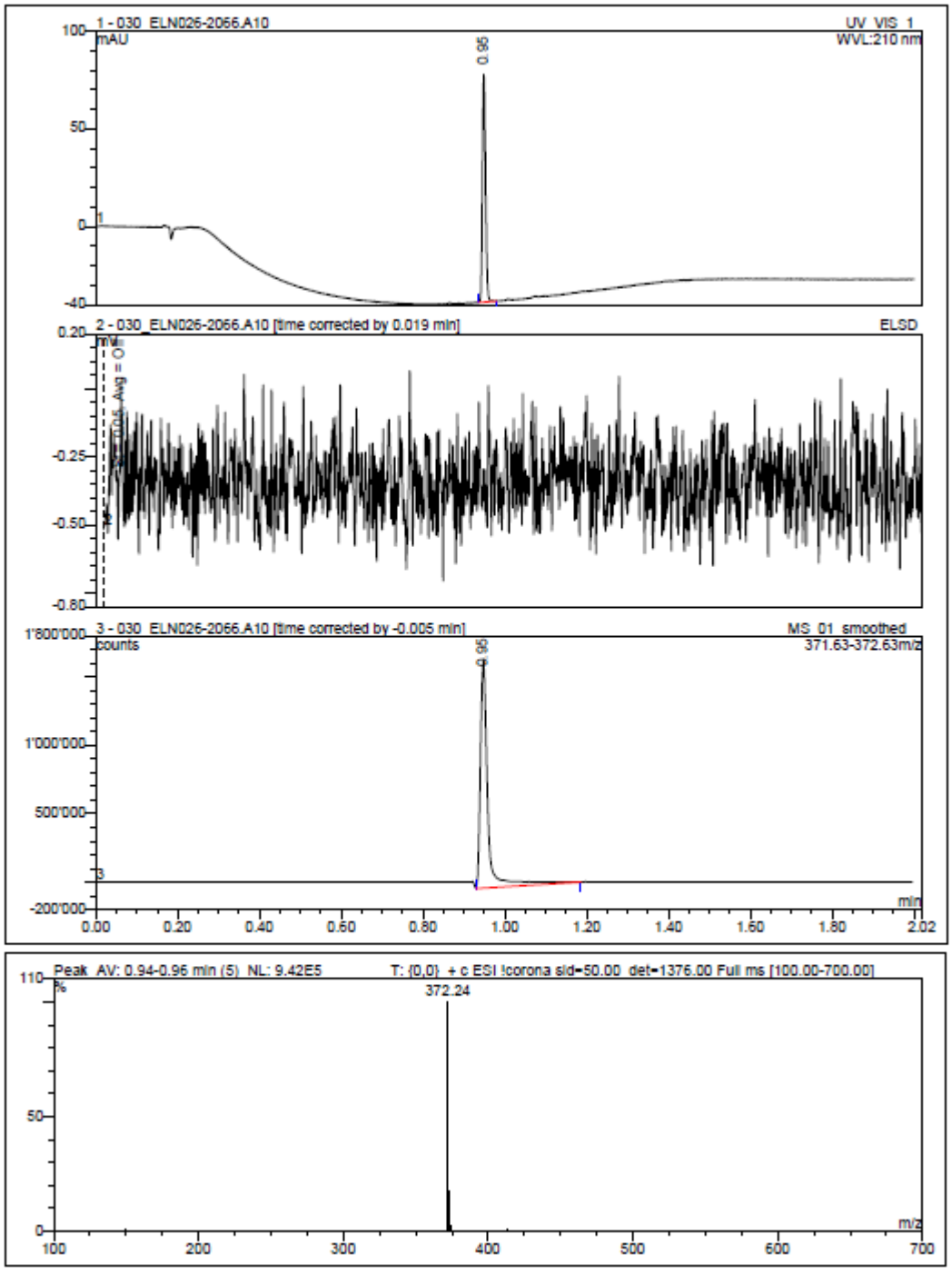




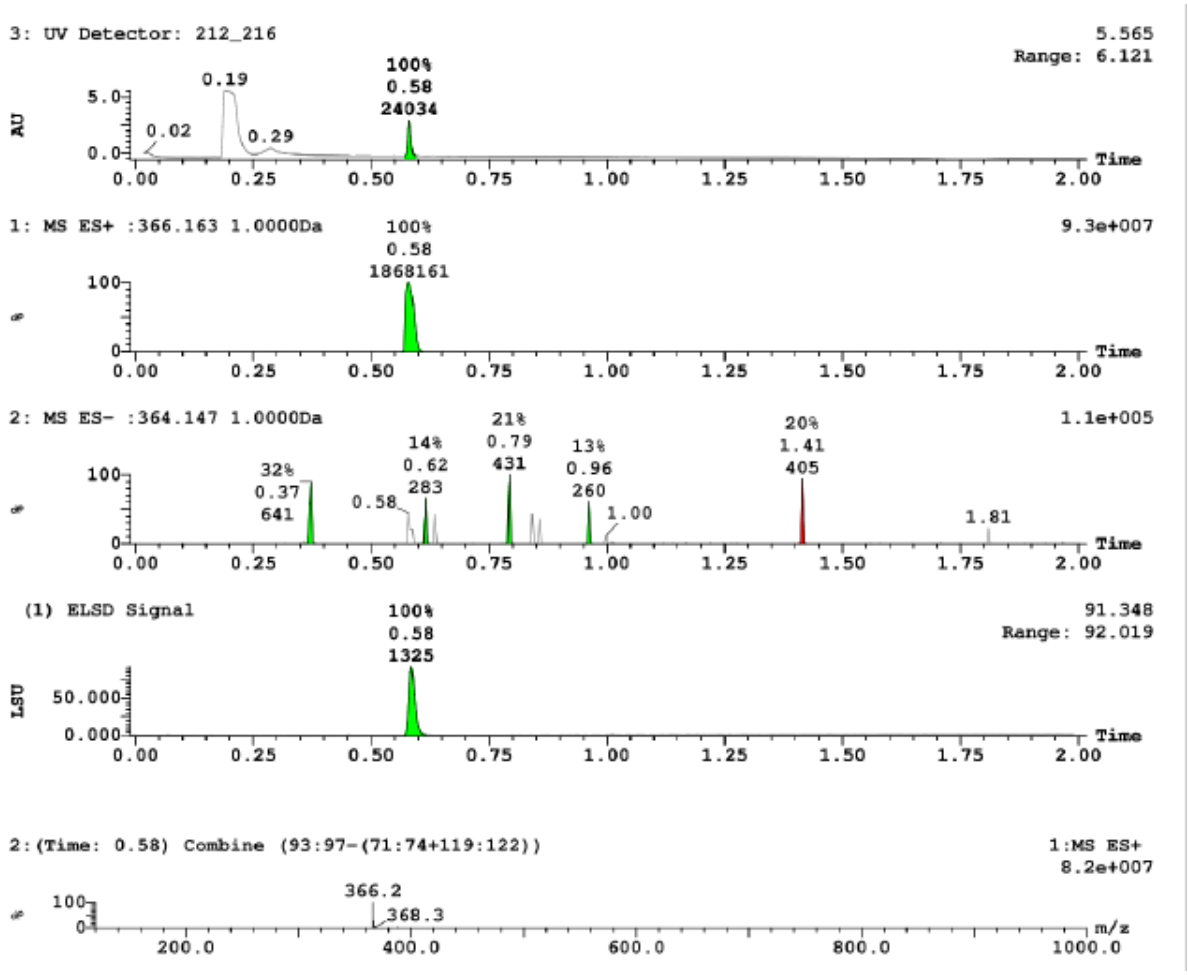
Compound **9d**:


Sample Name: LCMSP384-20200528-1_E01
ACT No: ACT-735355
Instrument: ICHALW-DL00021-SQD
ELN Nr: ELN026-1200.A06
Acquisition time: 5/28/2020 8:38 AM
Expression
Result
Auto-Comments
Auto-Summary
GOOD
Purity
100.0000
Target Mass
362.3000
Target RT
0.5910
UV[212-216]
UV214 [4.5E06]
Peak# 1
Rt 0.591
Area Perc 100.0%
ST1
cid=6 362.1680 (361.7680-362.5680) w=0.8000
T1-EIC(+)[M+H] [5.7E07]
Peak# 1
Rt 0.593
Area Perc 100.0%
ST1
cid=11 360.1524 (359.7524-360.5524) w=0.8000
T1-EIC(-)[M-H] [1.0]
min
Peak 1@0.583 min MS(+) ES
3.9E07 onts
obs: 362.3100
[M+H]+ [%C]
exp: 362.1680
ST1
C19H21N3O2F2
383.2300
384.2500 385.4100
161.1
426.1
m/z

Compound **9e**:


1 - 030_ELN026-2066.A10
UV_VIS_1
mAU
WVL:210 nm
0.95
2 - 030_ELN026-2066.A10 [time corrected by 0.019 min]
ELSD
3 - 030_ELN026-2066.A10 [time corrected by -0.005 min]
MS_01_smoothed
counts
371.63-372.63m/z
min
Peak AV: 0.94-0.96 min (5) NL: 9.42E5
T: {0,0} + c ESI !corona sid=50.00 det=1376.00 Full ms [100.00-700.00]
372.24
m/z

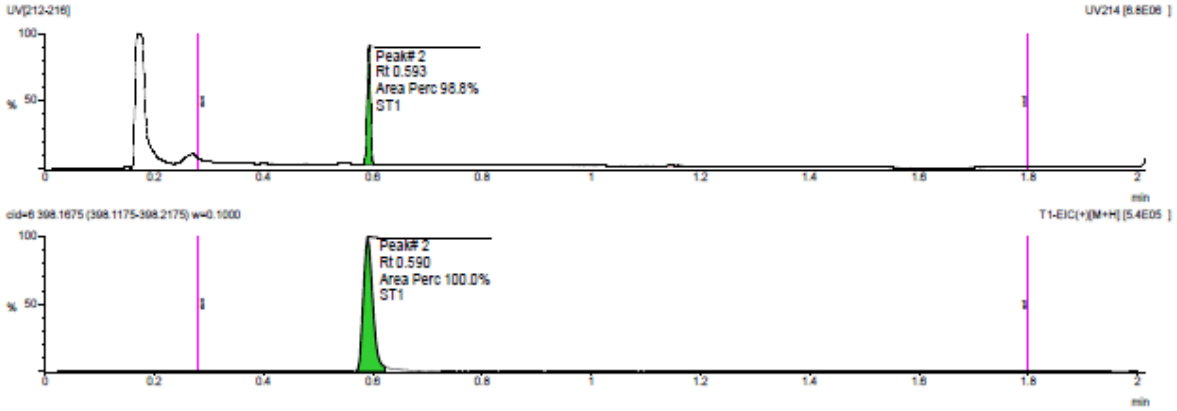
Compound **9f**:

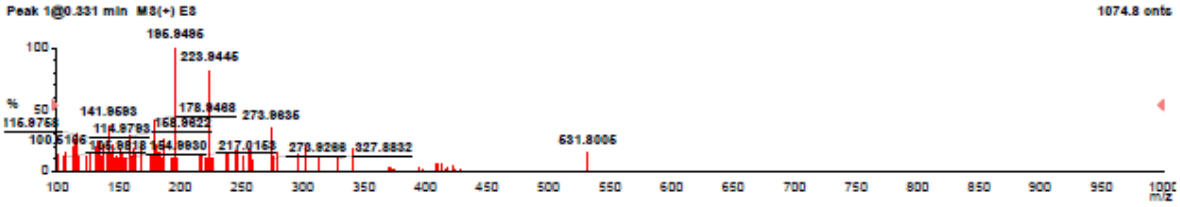

3: UV Detector: 212_216
5.565
Range: 6.121
100%
0.58
24034
0.19
0.02
0.29
AU
Time
1: MS ES+ :366.163 1.0000Da
9.3e+007
100%
0.58
1868161
2: MS ES- :364.147 1.0000Da
1.1e+005
32%
0.37
641
14%
0.62
283
0.58
21%
0.79
431
13%
0.96
260
1.00
20%
1.41
405
1.81
(1) ELSD Signal
91.348
Range: 92.019
100%
0.58
1325
LSU
2:(Time: 0.58) Combine (93:97-(71:74+119:122))
1:MS ES+
8.2e+007
366.2
368.3
m/z

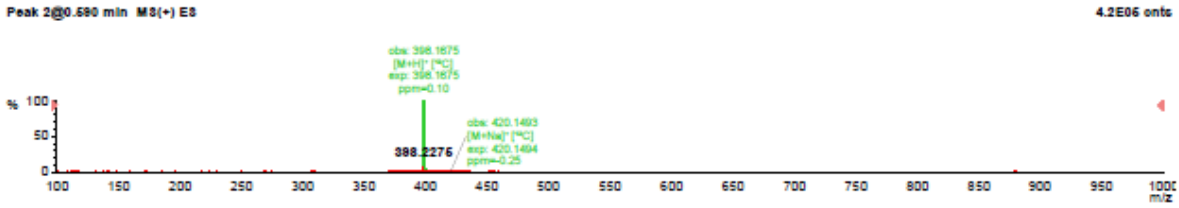
Compound **9g**:

Sample Name: LCMSH384-20200714-1_K01 **ACT No:** ACT-735364 **ELN Nr:** ELN026-2066.A07
Instrument: UPLC_SYNAPT1 **Acquisition time:** 7/15/2020 2:42 PM

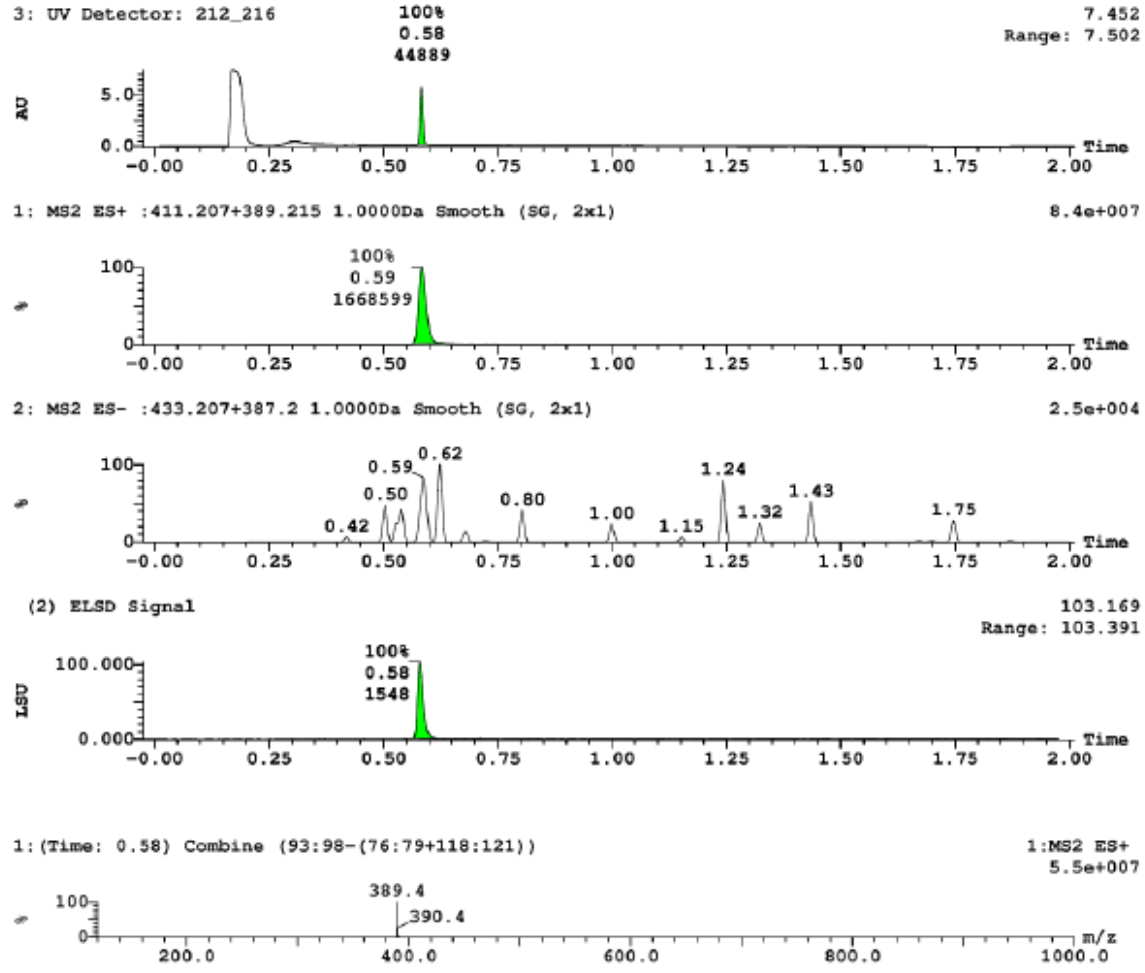
Expression	Result
Auto-Comments	
Auto-Summary	GOOD
Purity	98.8000
Target Mass	398.1675
Target RT	0.5930



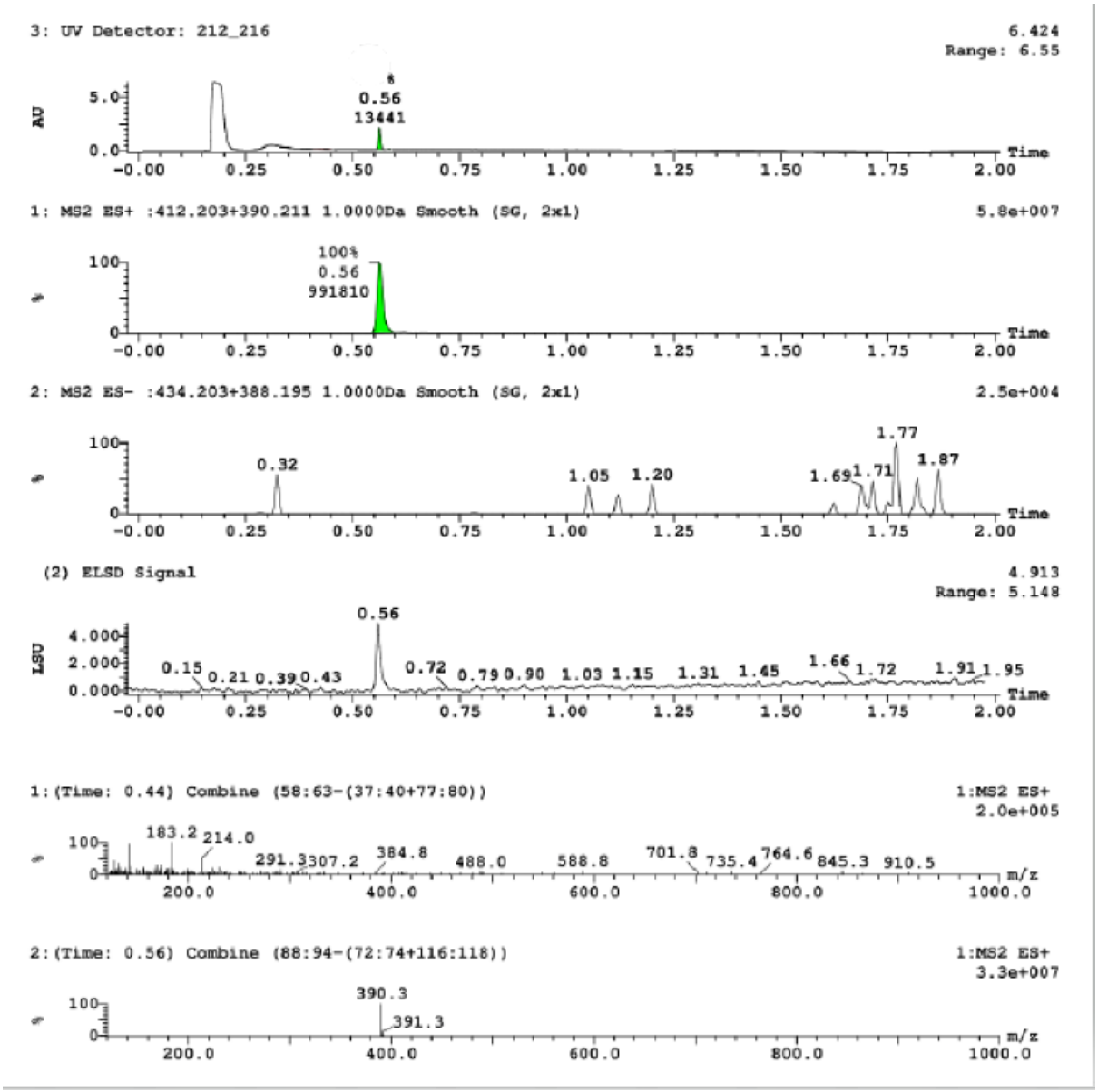




Compound **10a**:



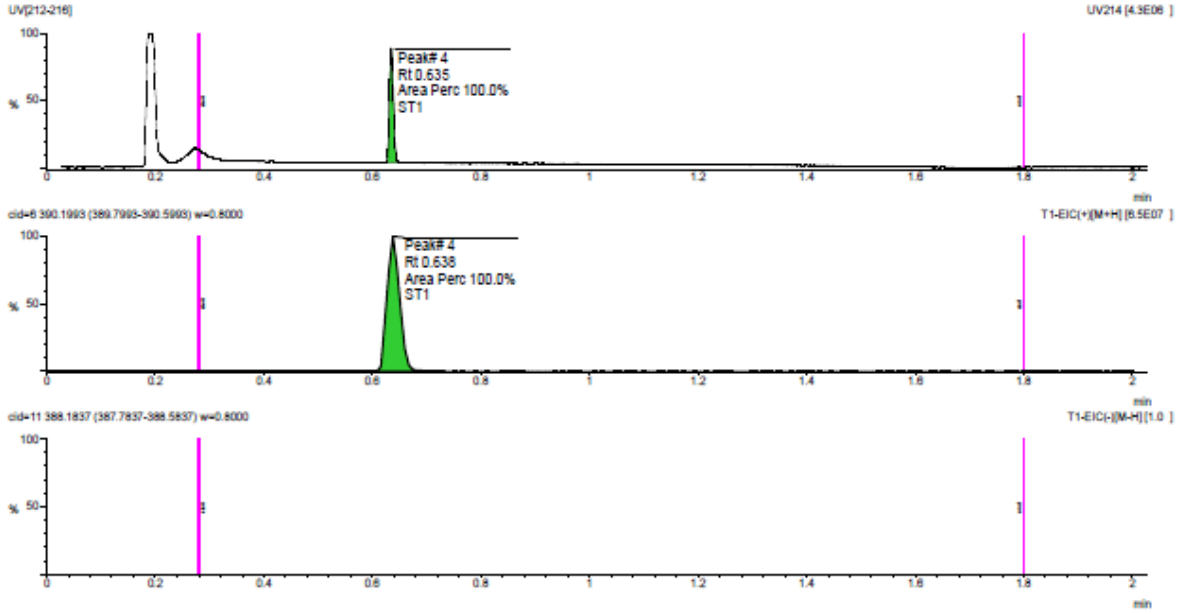
Compound **10b**:

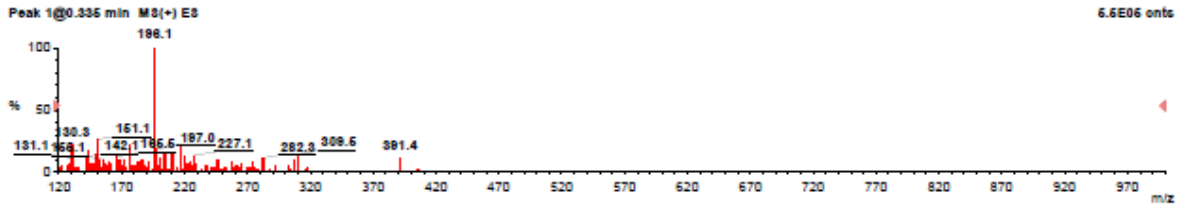


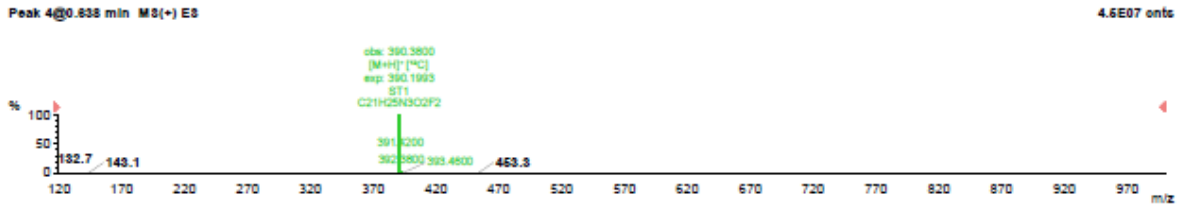
Compound **10c**:

Sample Name: LCMS384-20200615-4_G05 **ACT No:** ACT-736695 **ELN Nr:** ELN227-1496.1
Instrument: ICHALW-DL00021-SQD **Acquisition time:** 6/15/2020 5:52 PM

Expression	Result
Auto-Comments	
Auto-Summary	GOOD
Purity	100.0000
Target Mass	390.4000
Target RT	0.6350



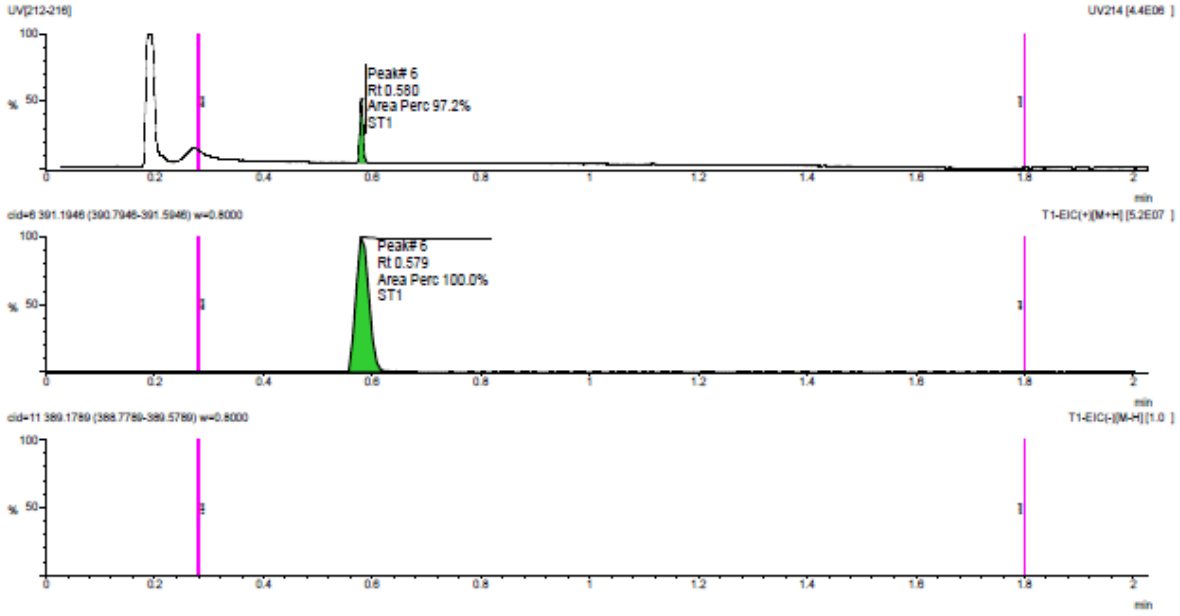


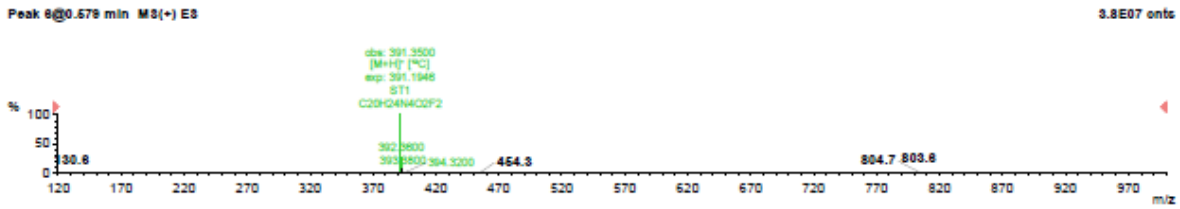


Compound **10d**:

Sample Name: LCMSP384-20200528-1_G01 **ACT No:** ACT-736699 **ELN Nr:** ELN008-1108.G02
Instrument: ICHALW-DL00021-SQD **Acquisition time:** 5/28/2020 8:41 AM

Expression	Result
Auto-Comments	
Auto-Summary	GOOD
Purity	97.2000
Target Mass	391.4000
Target RT	0.5800

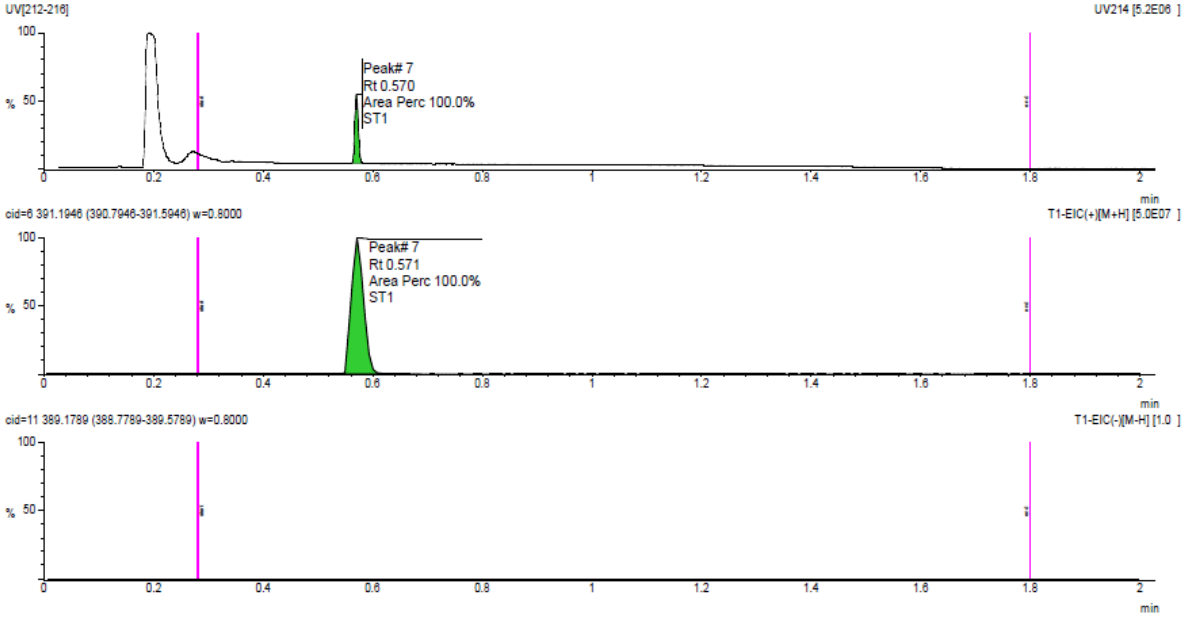


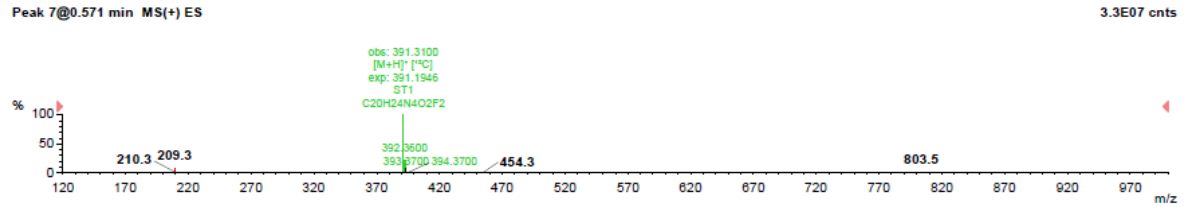


Compound **10e**:

Sample Name: LCMS384-20191128-1_E01 **ACT No:** ACT-761438 **ELN Nr:** ELN057-0939.1
Instrument: ICHALW-DL00021-SQD **Acquisition time:** 11/28/2019 2:10 PM

Expression	Result
Auto-Comments	
Auto-Summary	GOOD
Purity	100.0000
Target Mass	391.3000
Target RT	0.5700

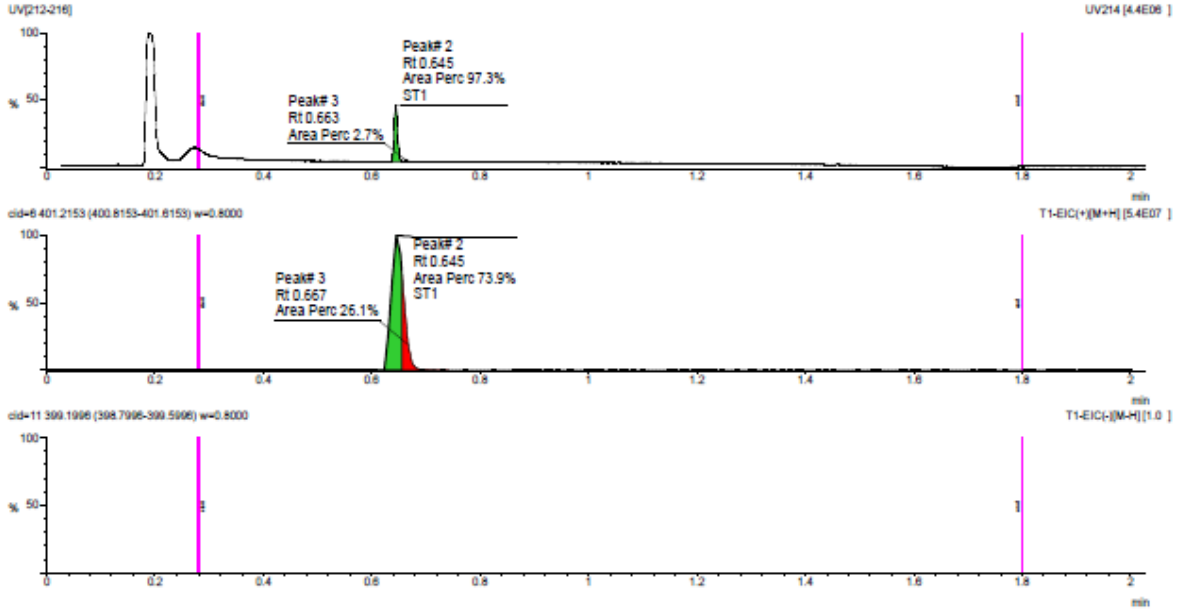


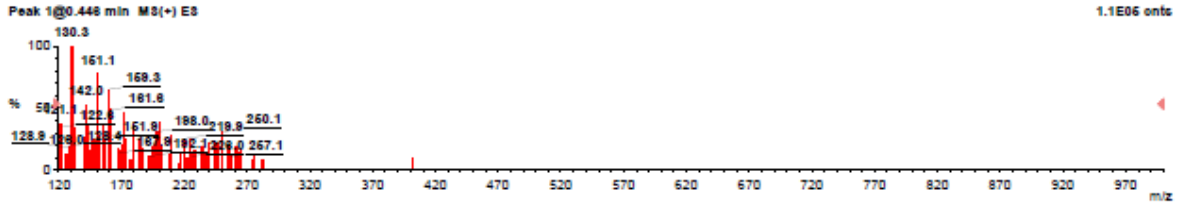


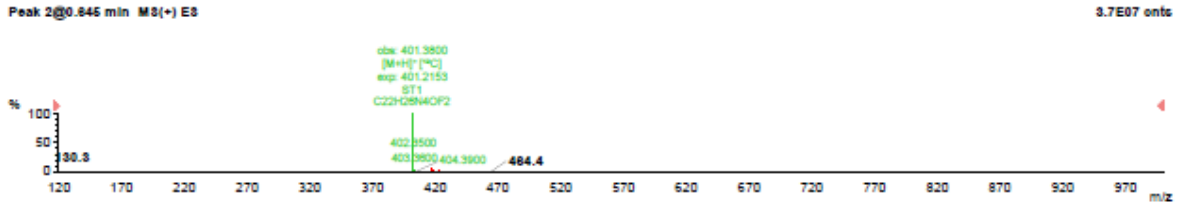
Compound **10f**:

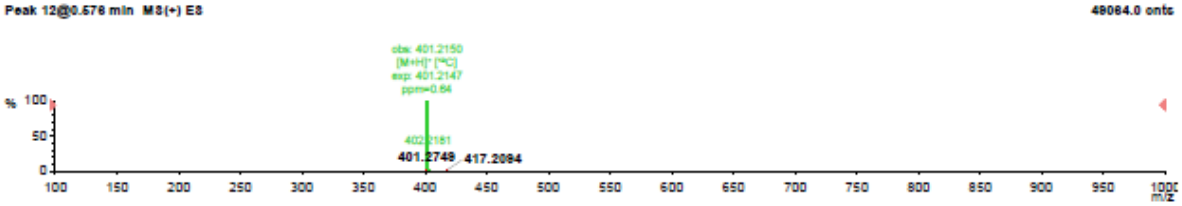
Sample Name: LCMSP384-20200528-1_C01 **ACT No:** ACT-737915 **ELN Nr:** ELN057-0929.B03
Instrument: **Acquisition time:** 5/28/2020 8:35 AM

Expression	Result
Auto-Comments	
Auto-Summary	GOOD
Purity	97.3000
Target Mass	401.4000
Target RT	0.6450

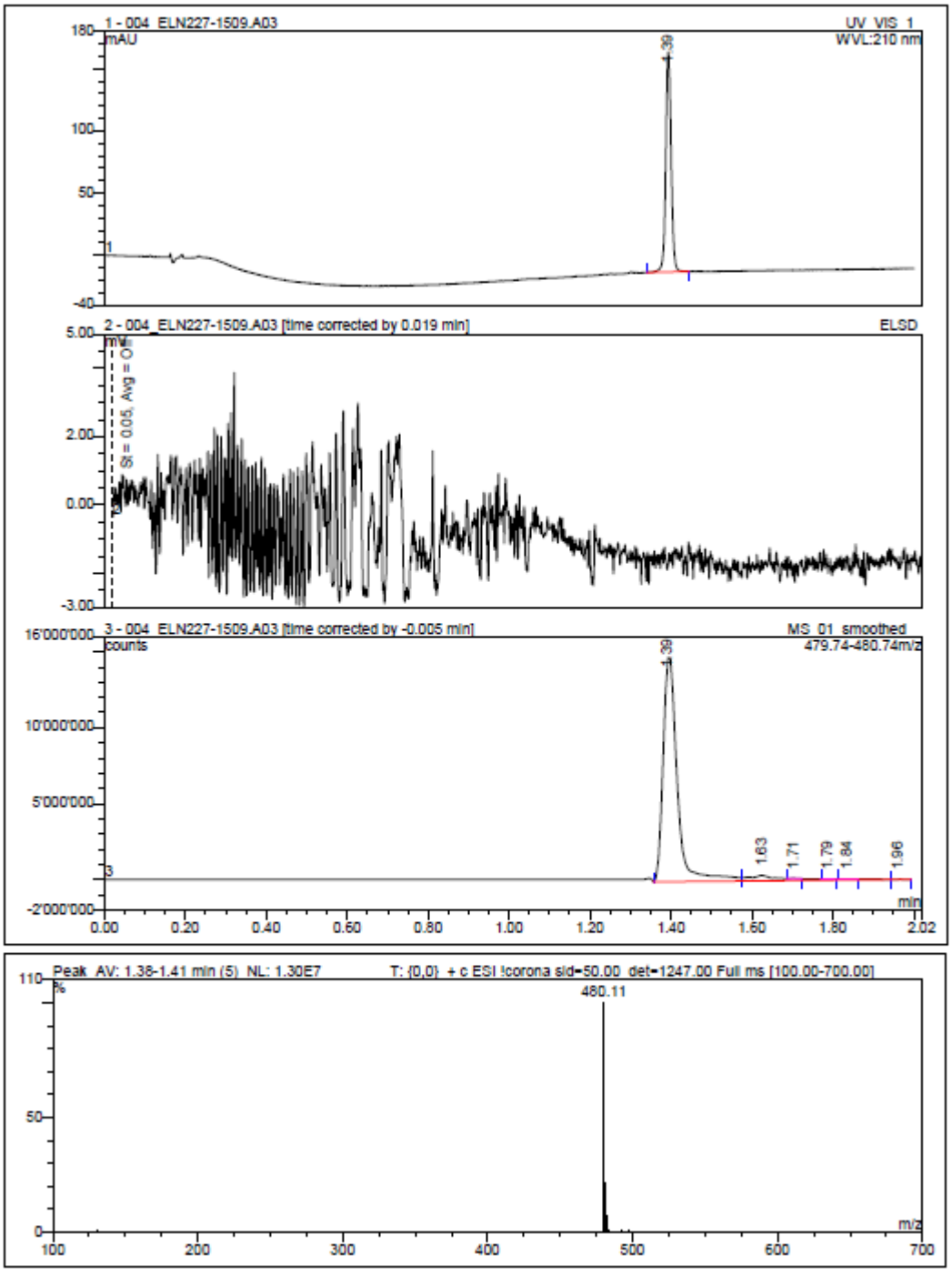




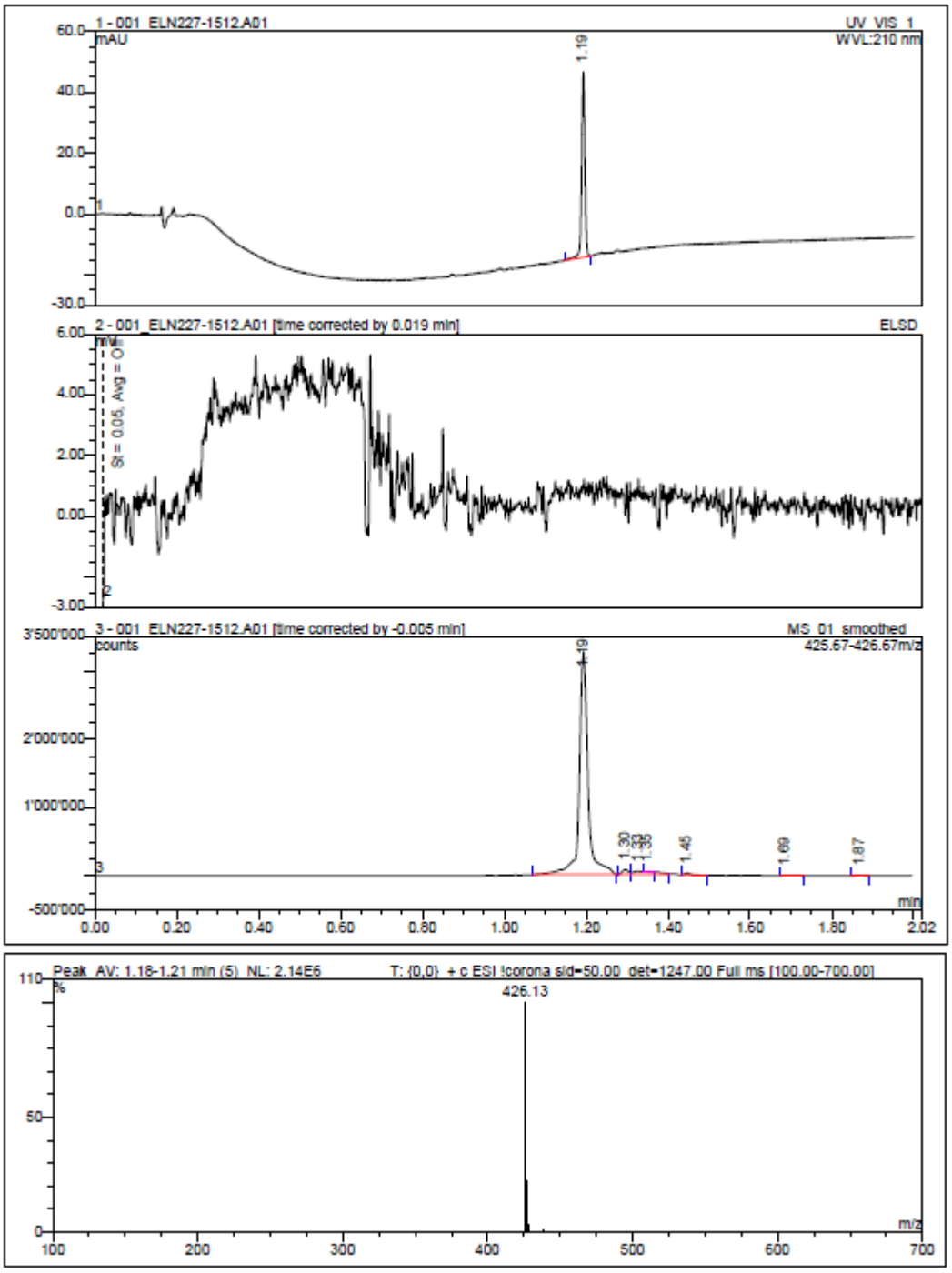




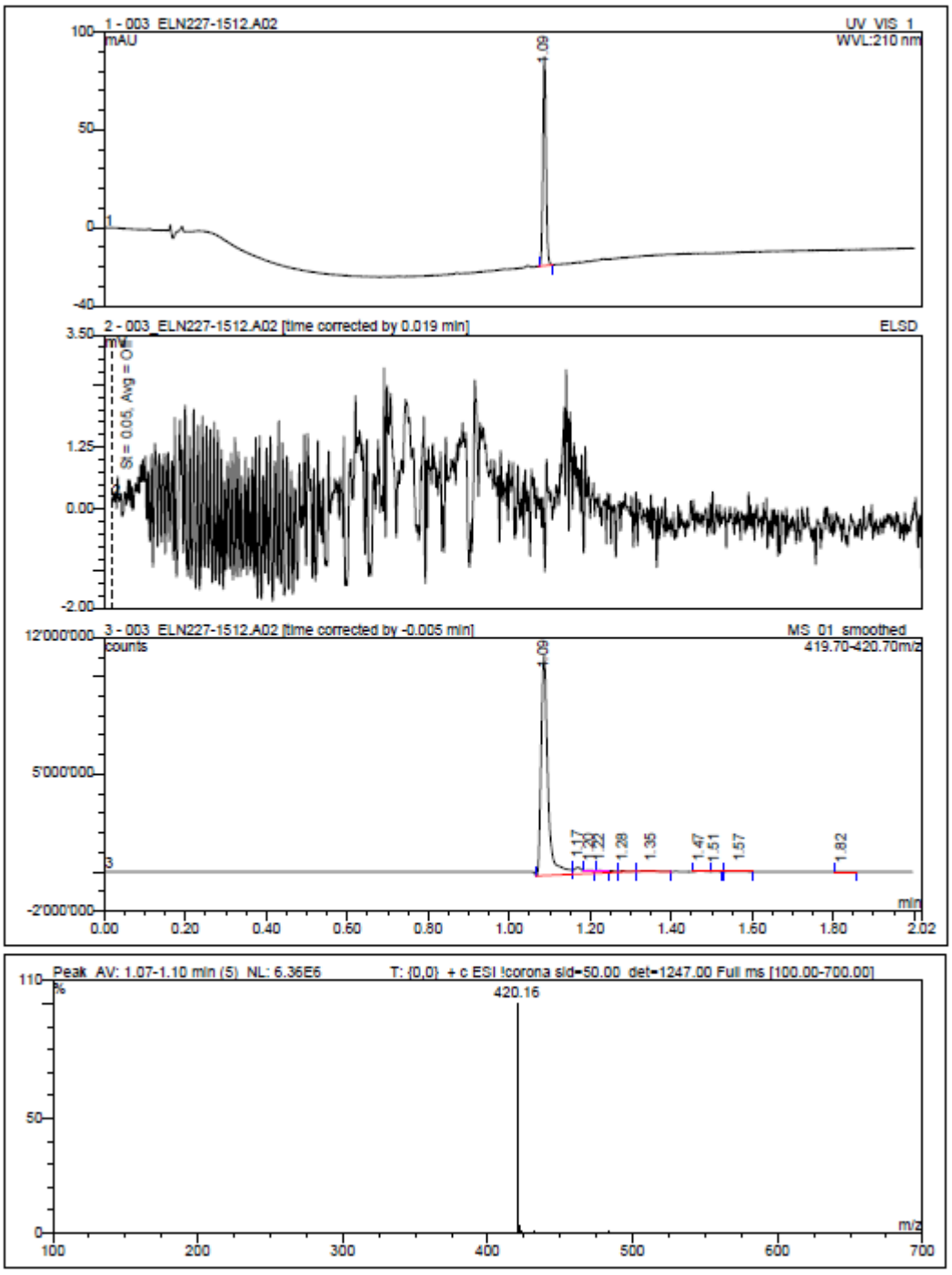
Compound **11a**:



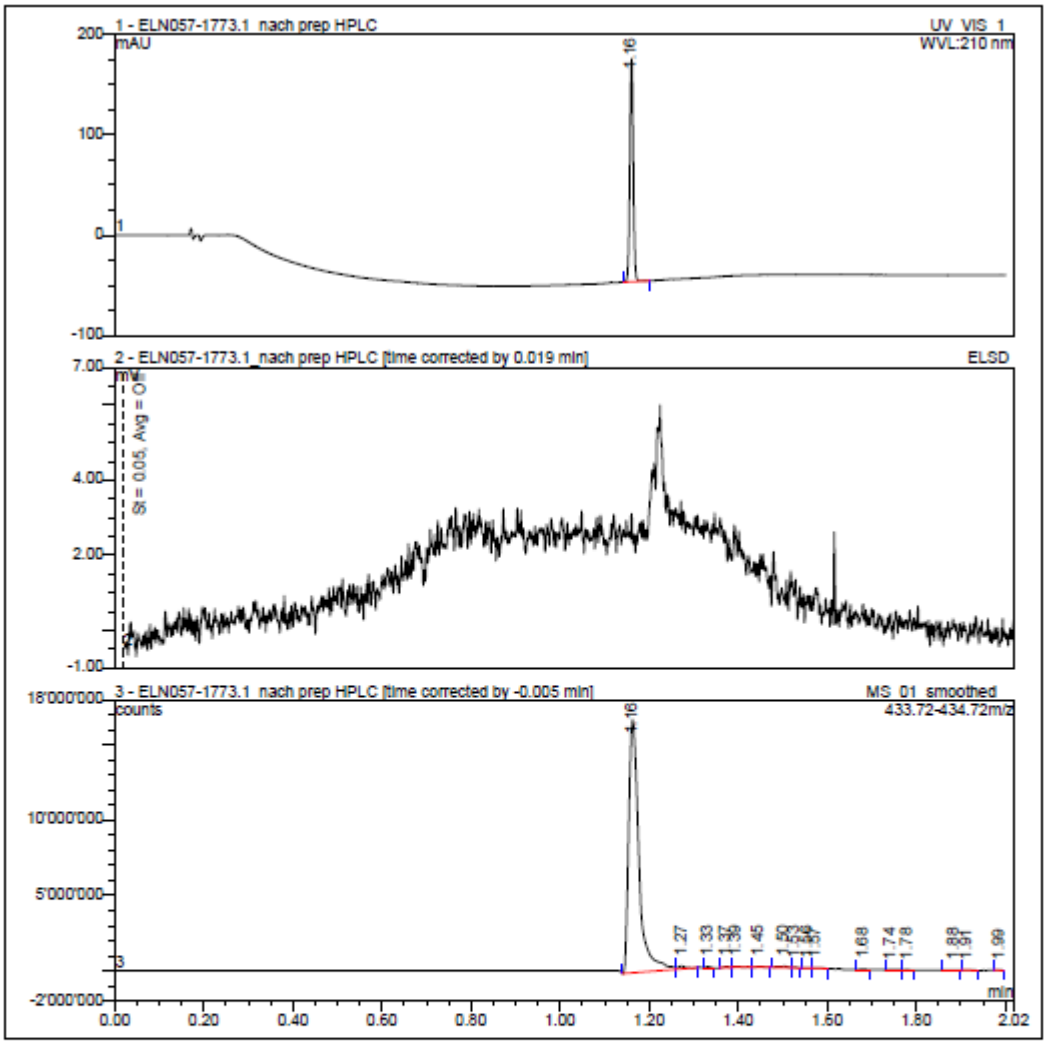
Compound **11b**:

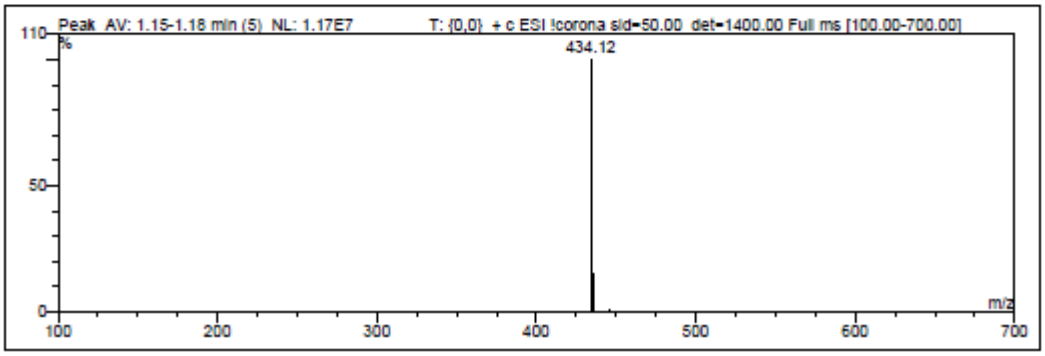


Compound **11c**:



Compound **11d**:

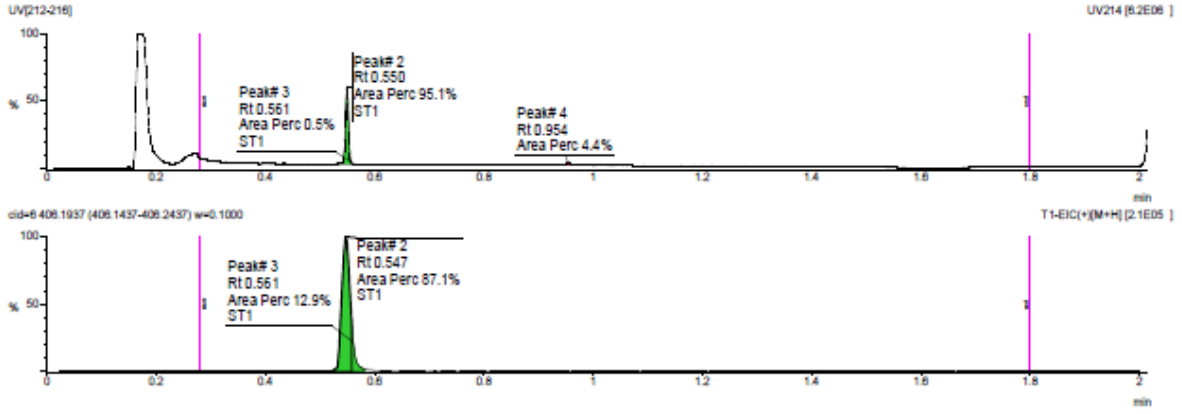


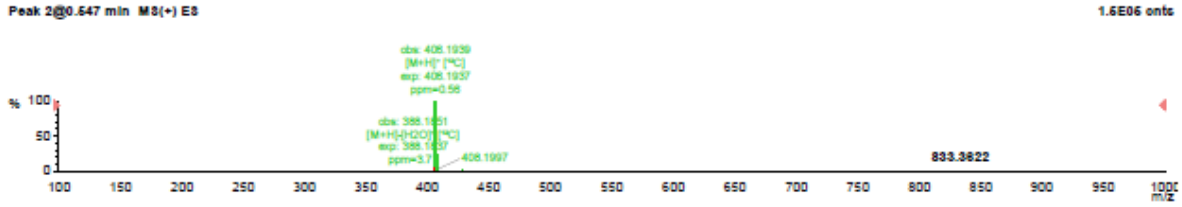


Compound **11e**:

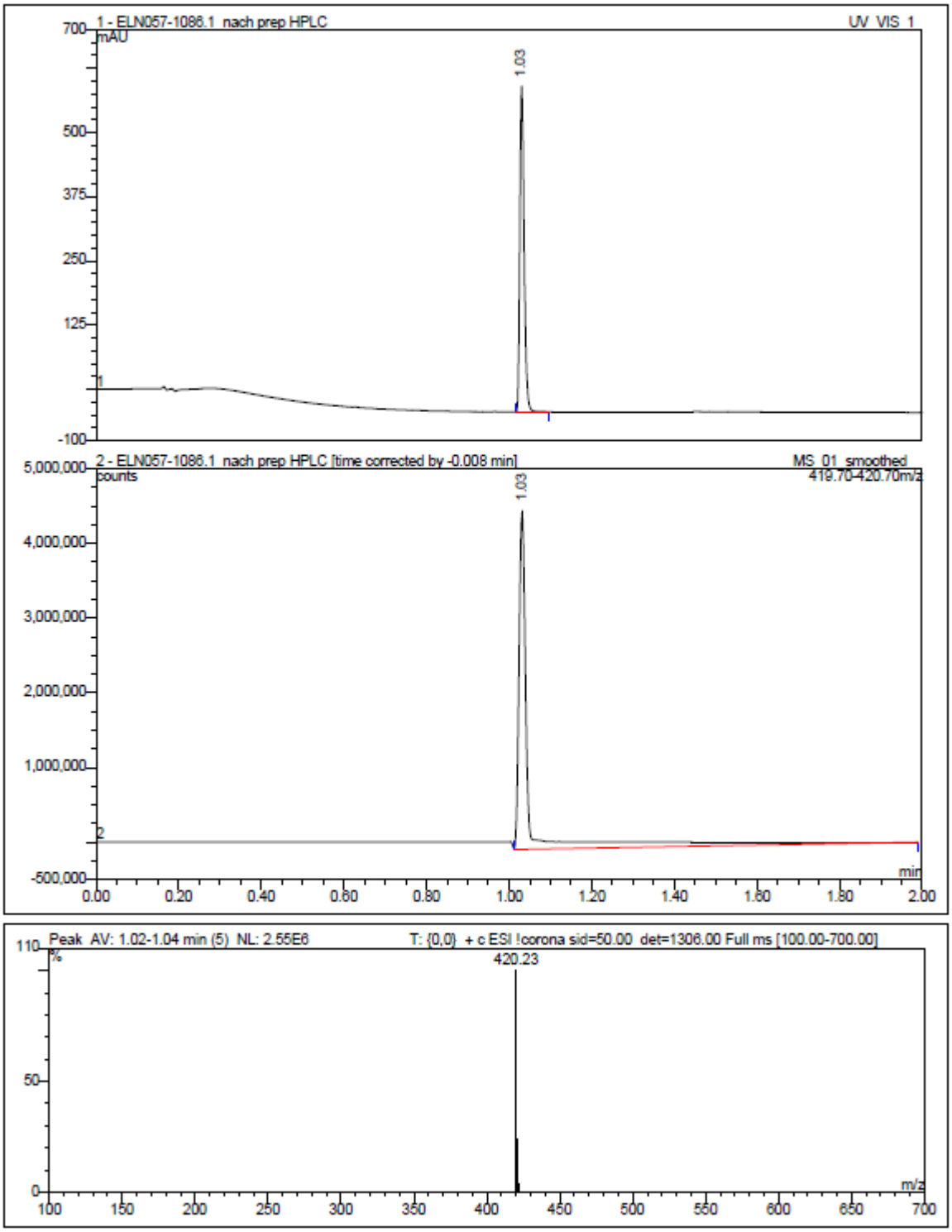
Sample Name: LCMSH384-20200609-1_C03 **ACT No:** ACT-747595 **ELN Nr:** ELN026-1219.A01
Instrument: **Acquisition time:** 6/12/2020 9:32 AM

Expression	Result
Auto-Comments	
Auto-Summary	GOOD
Purity	95.6000
Target Mass	406.1939
Target RT	0.5500

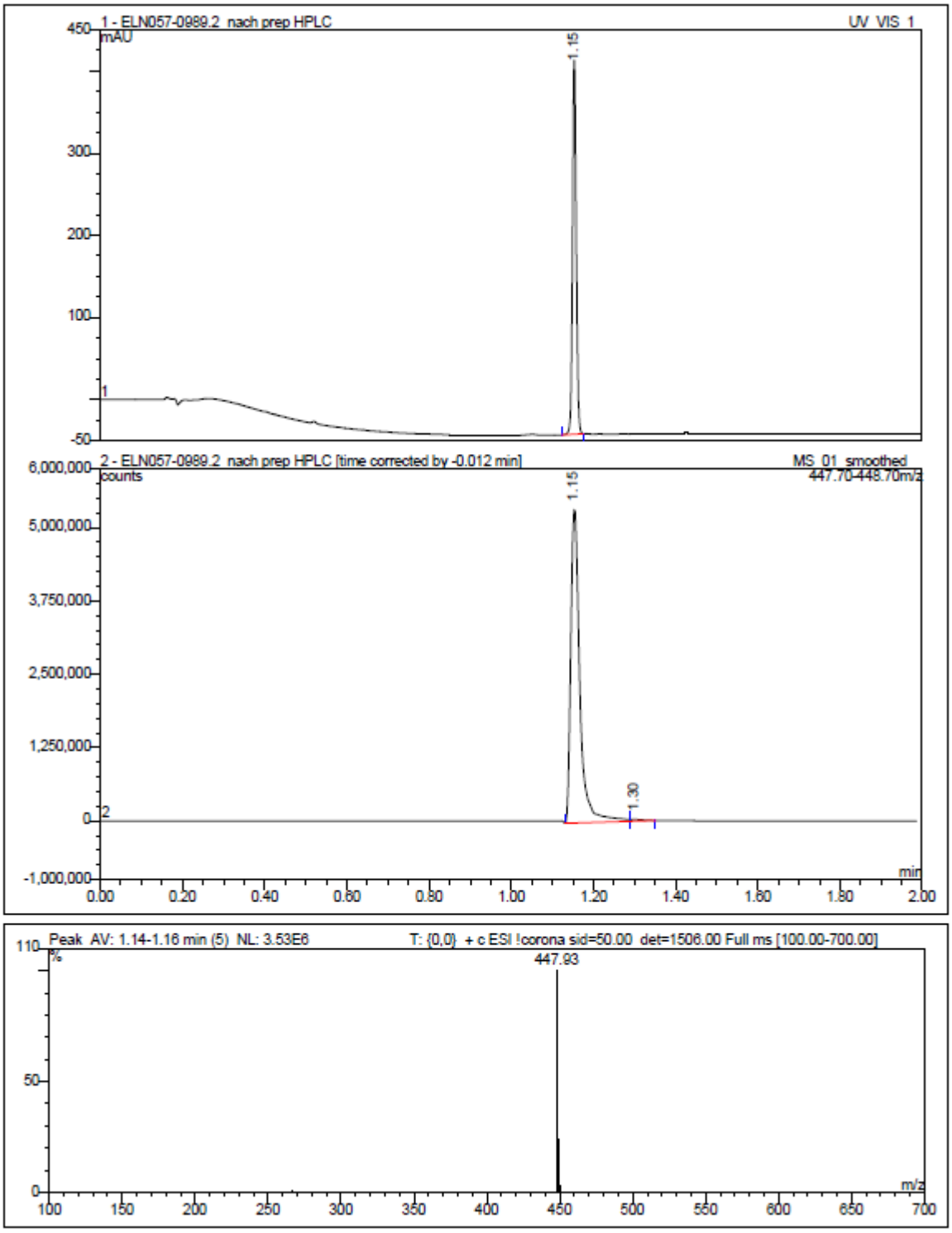




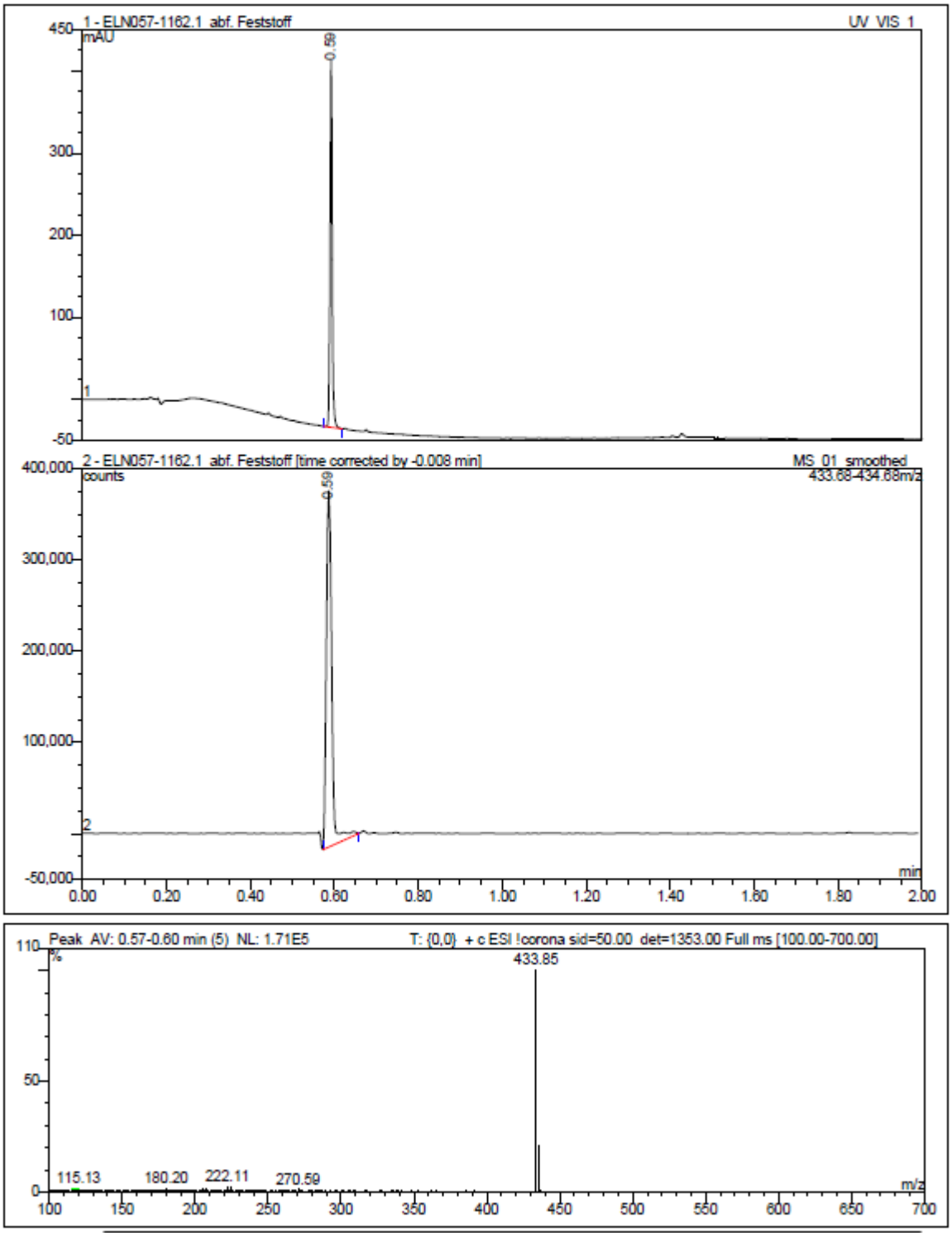
Compound **11f**:



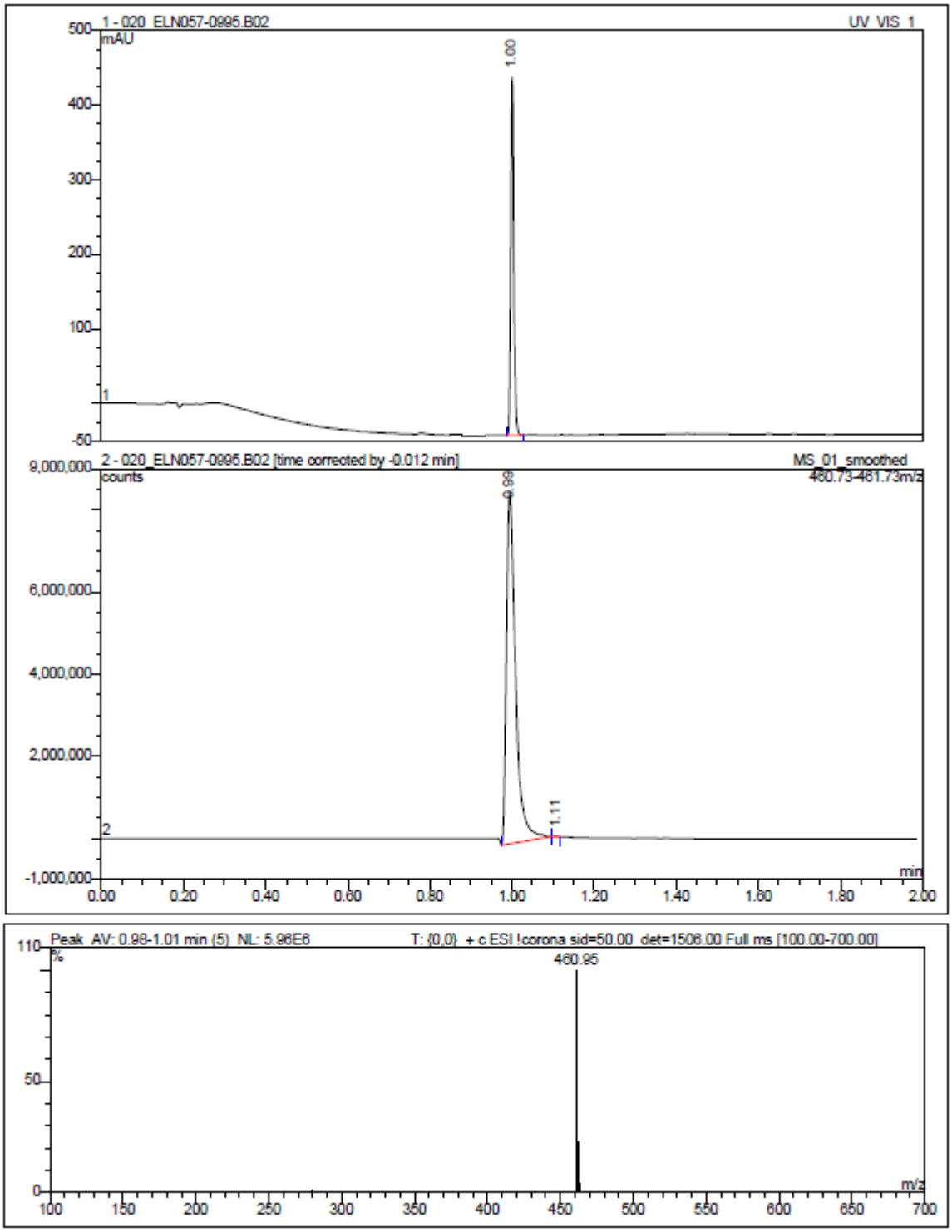
Compound **11g**:



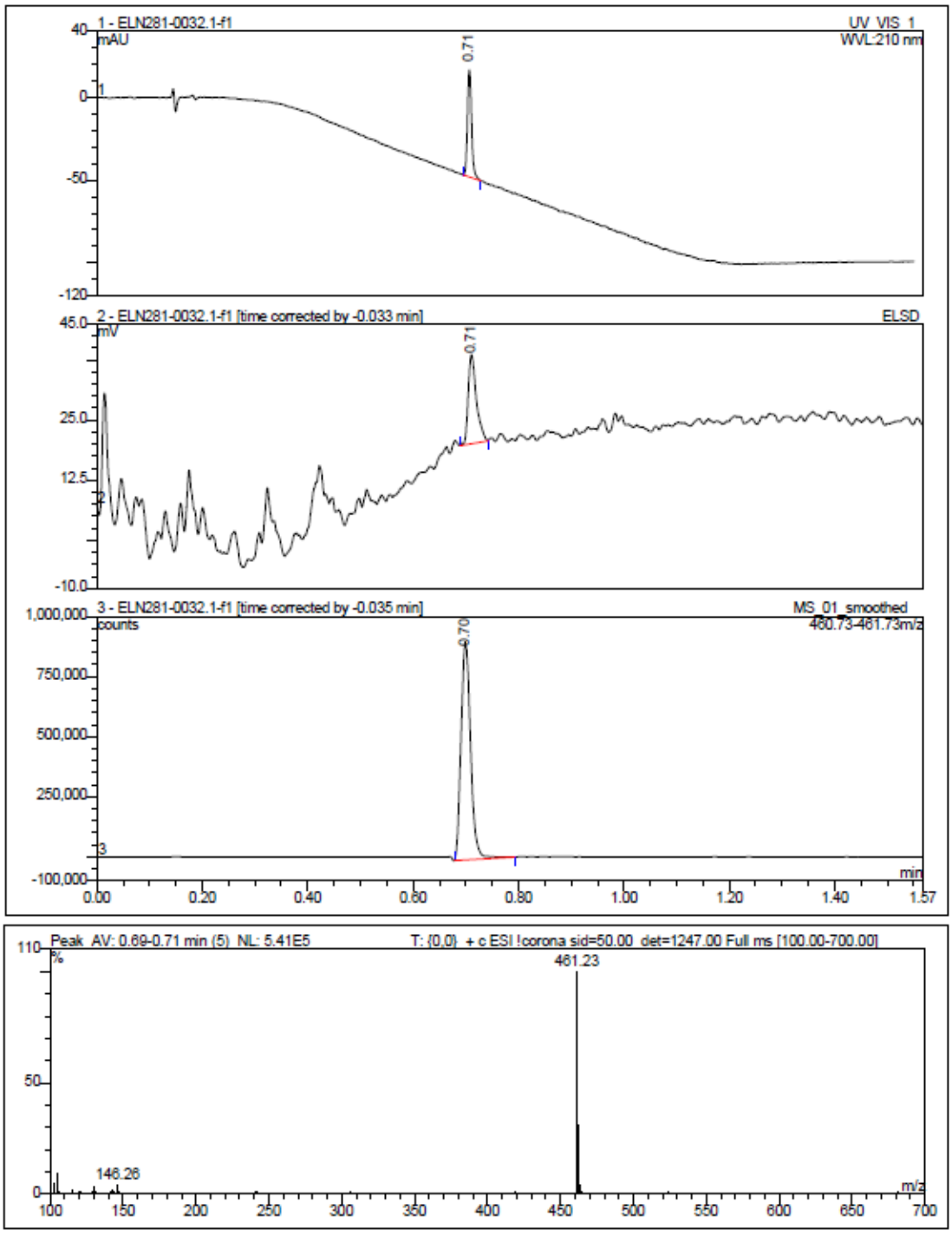
Compound **11h**:



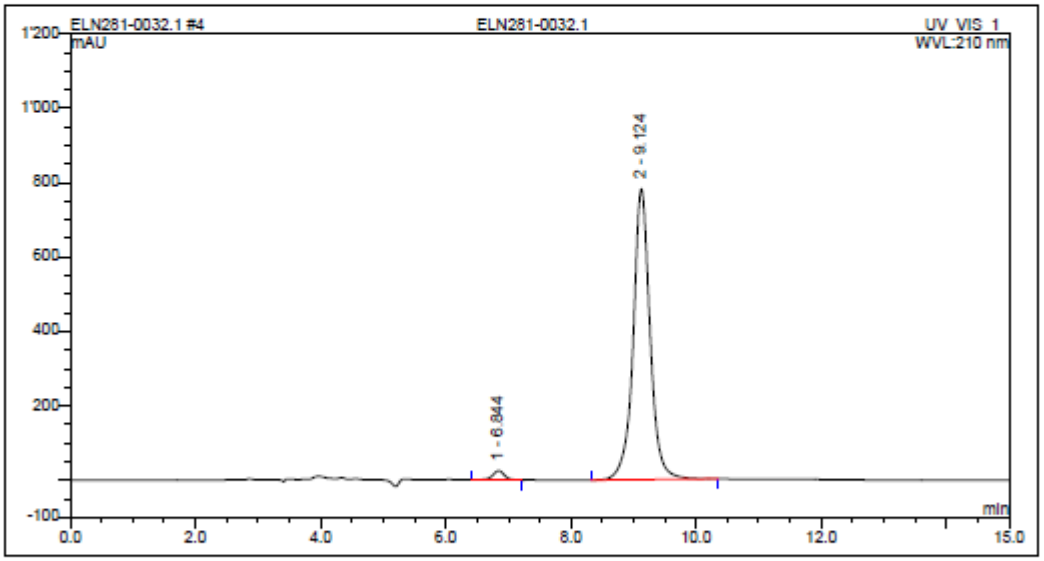
Compound **11i**:



Compound **(*R*,*R*)-11i**:

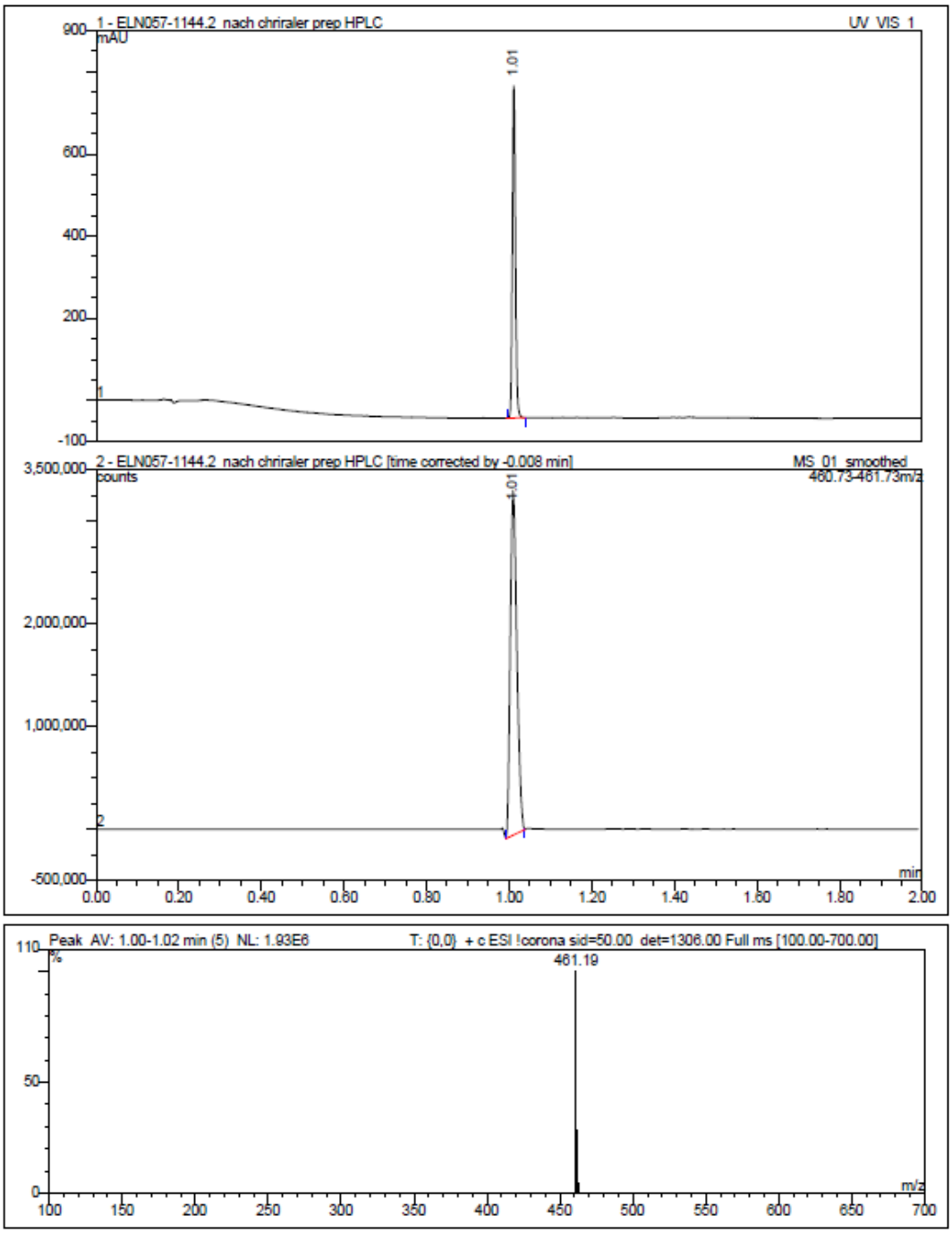


Sample ID:	b446957a-20dd-11e5-ac35-001e2abd2a4c		
Sample Name:	ELN281-0032.1	*Date:*	02.07.15
Sample Number:	4		
Time Base:	CHIRALLC04		
Datasource Name:	HPLC003_local		
Sequence Name:	ELN281-0032.1		
Sequence Dir:	Data\CHIRALLC04\erharmi1\CXCR7		
Quantif. Method:	default		
Injection Volume:	5.00 ul *Comment:* 1mg/ml Heptane/EtOH 1:1		
Eluent A:	30.0 % Heptane 0.05% DEA		
Eluent B:	70.0 % Ethanol 0.05% DEA		
Flow:	0.800 ml/min		
Column:	(R,R) Whelk-01 250x4.6mm ID,5um		
Serial number:	100487		
Temperature:	25.0 °C		
Detection:	210 nm		

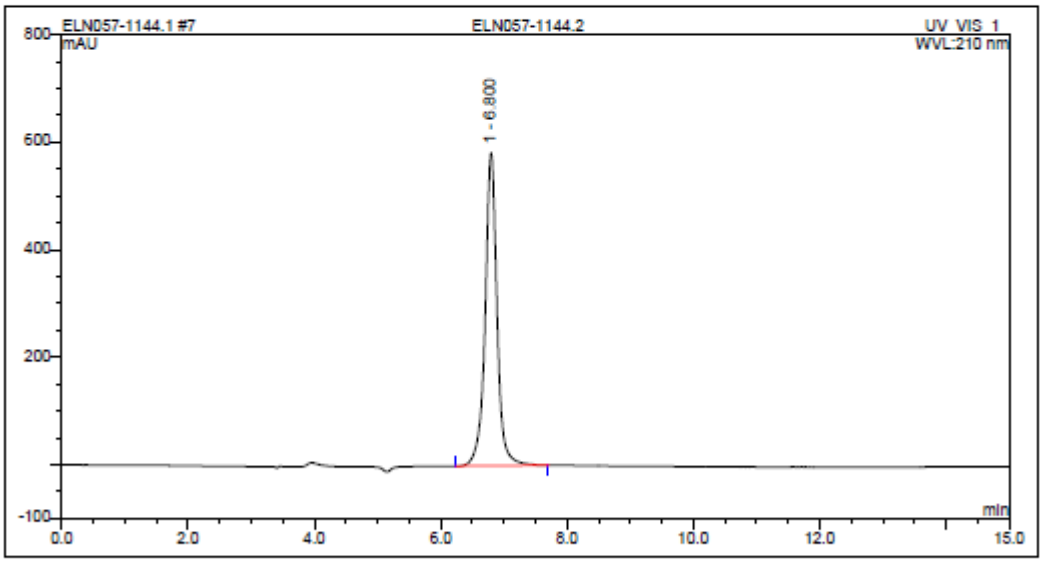


Peak No. UV_VIS_1	Ret.Time UV_VIS_1 min	Height UV_VIS_1 mAU	Rel.Area UV_VIS_1 %	Area UV_VIS_1 mAU*min	Resolution UV_VIS_1	Asymmetry UV_VIS_1	Plates UV_VIS_1
1	6.8	25	2.1	5.354	5.9	0.9	7251
2	9.1	781	97.9	244.917	n.a.	1.0	6397
Total:			100.0	250.3			

Compound **(*S*,*S*)-11i**:



Sample ID:	9c585f7c-3b68-11e5-ac35-001e2abd2a4c		
Sample Name:	ELN057-1144.2	*Date:*	05.08.15
Sample Number:	7		
Time Base:	CHIRALLC04		
Datasource Name:	HPLC003_local		
Sequence Name:	ELN057-1144.1		
Sequence Dir:	Data\CHIRALLC04\erharmi1\CXCR7		
Quantif. Method:	default		
Injection Volume:	2.50 ul *Comment:* 1.2mg/ml Heptane/EtOH 1:1		
Eluent A:	30.0 % Heptane 0.05% DEA		
Eluent B:	70.0 % Ethanol 0.05% DEA		
Flow:	0.800 ml/min		
Column:	(R,R) Whelk-01 250x4.6mm ID,5um		
Serial number:	100487		
Temperature:	25.0 °C		
Detection:	210 nm		

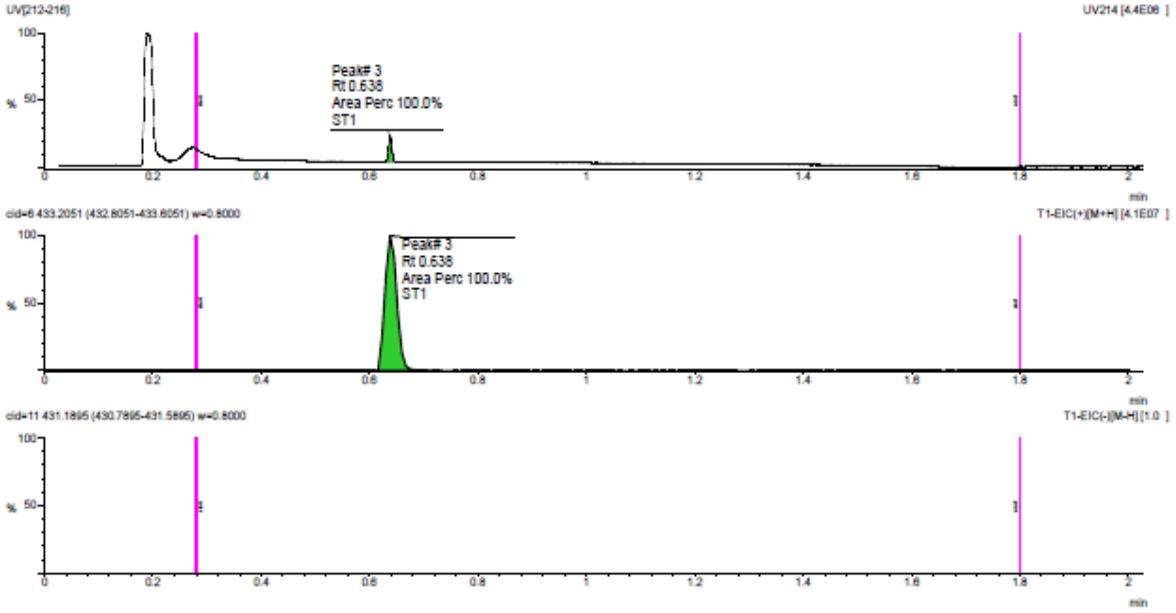


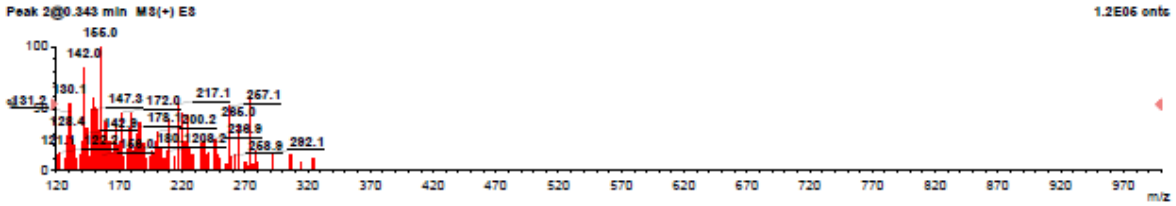
Peak No. UV_VIS_1	Ret.Time UV_VIS_1 min	Height UV_VIS_1 mAU	Rel.Area UV_VIS_1 %	Area UV_VIS_1 mAU*min	Resolution UV_VIS_1	Asymmetry UV_VIS_1	Plates UV_VIS_1
1	6.8	582	100.0	127.438	n.a.	1.0	7525
Total:			100.0	127.4			

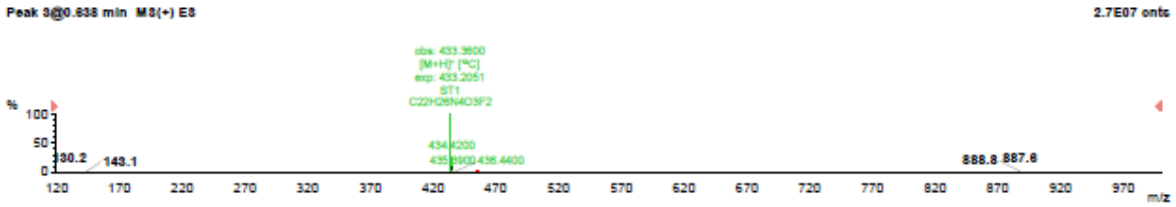
Compound **11j**:

Sample Name: LCMSP384-20200528-1_A05 **ACT No:** ACT-747599 **ELN Nr:** ELN026-1219.A04
Instrument: ICHALW-DL00021-SQD **Acquisition time:** 5/28/2020 9:18 AM

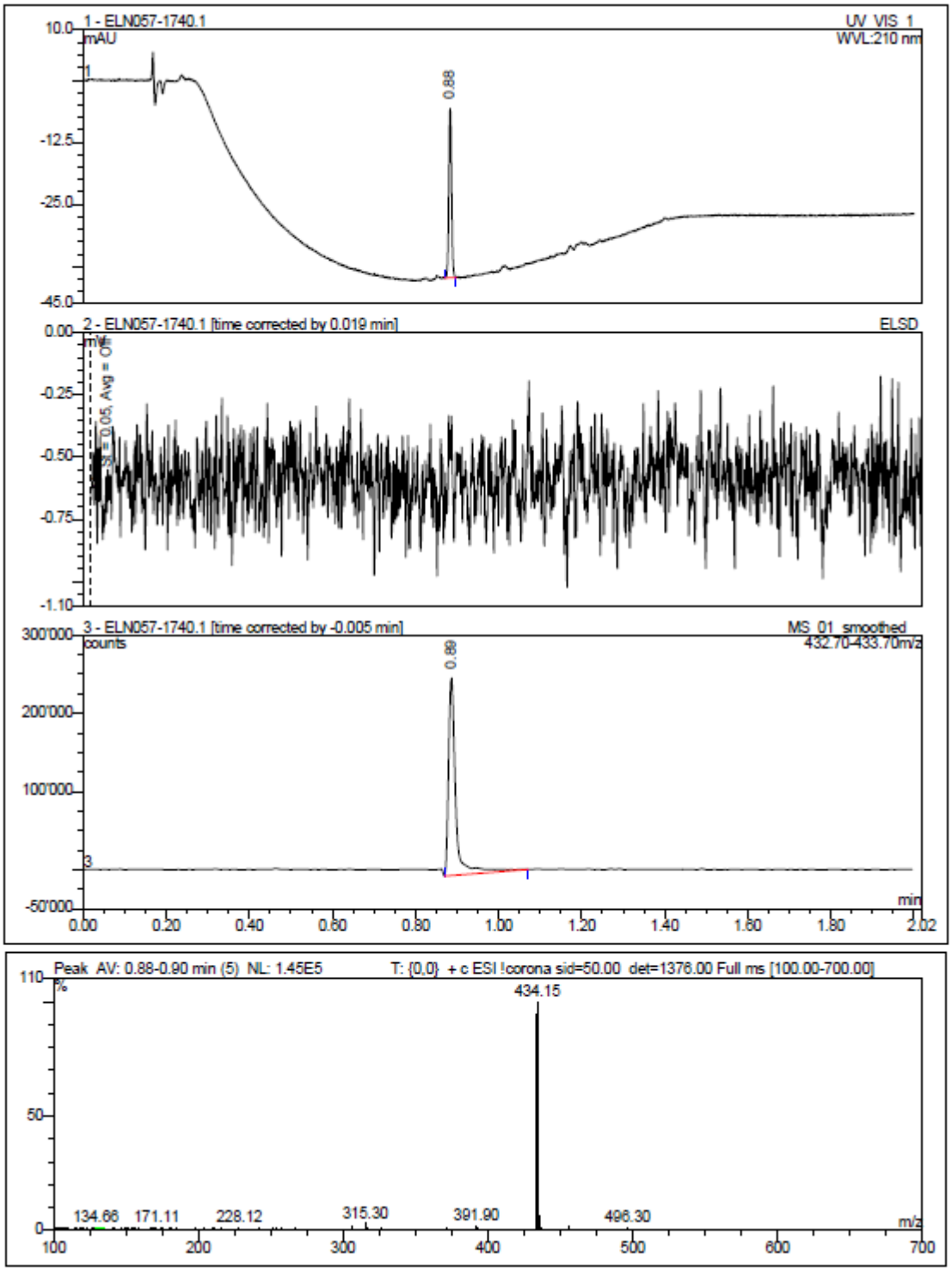
Expression	Result
Auto-Comments	
Auto-Summary	GOOD
Purity	100.0000
Target Mass	433.4000
Target RT	0.6380



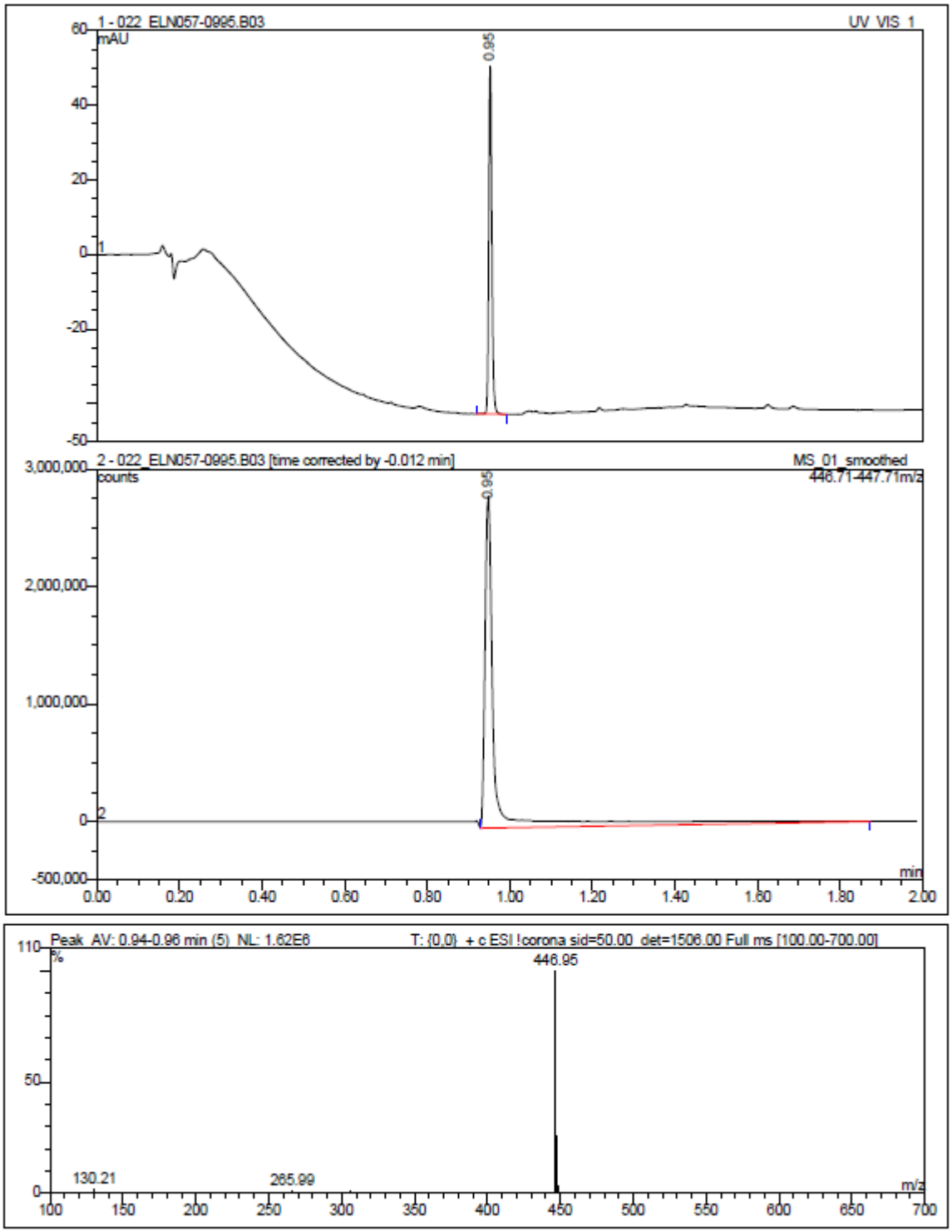




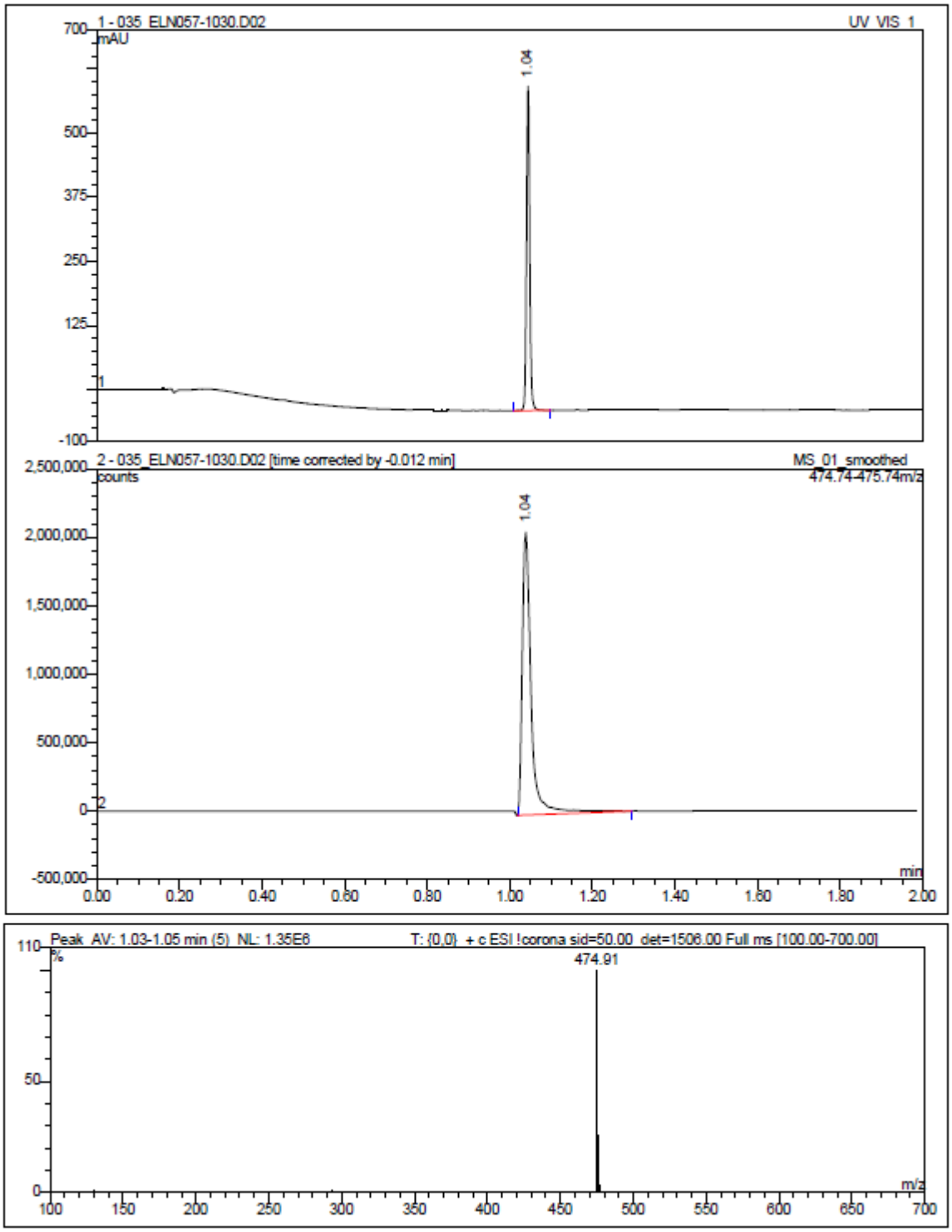
Compound **20a**:



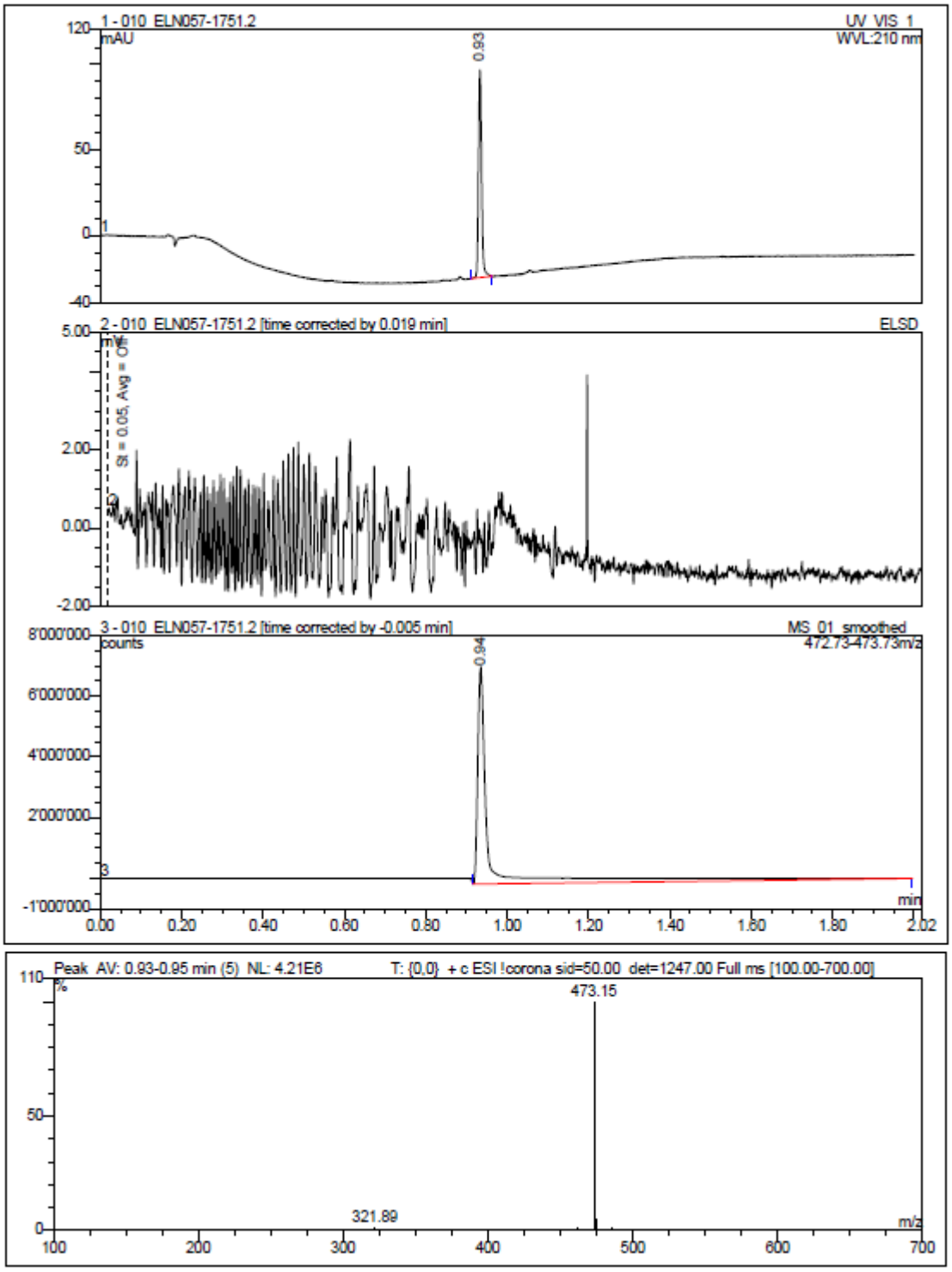
Compound **20b**:



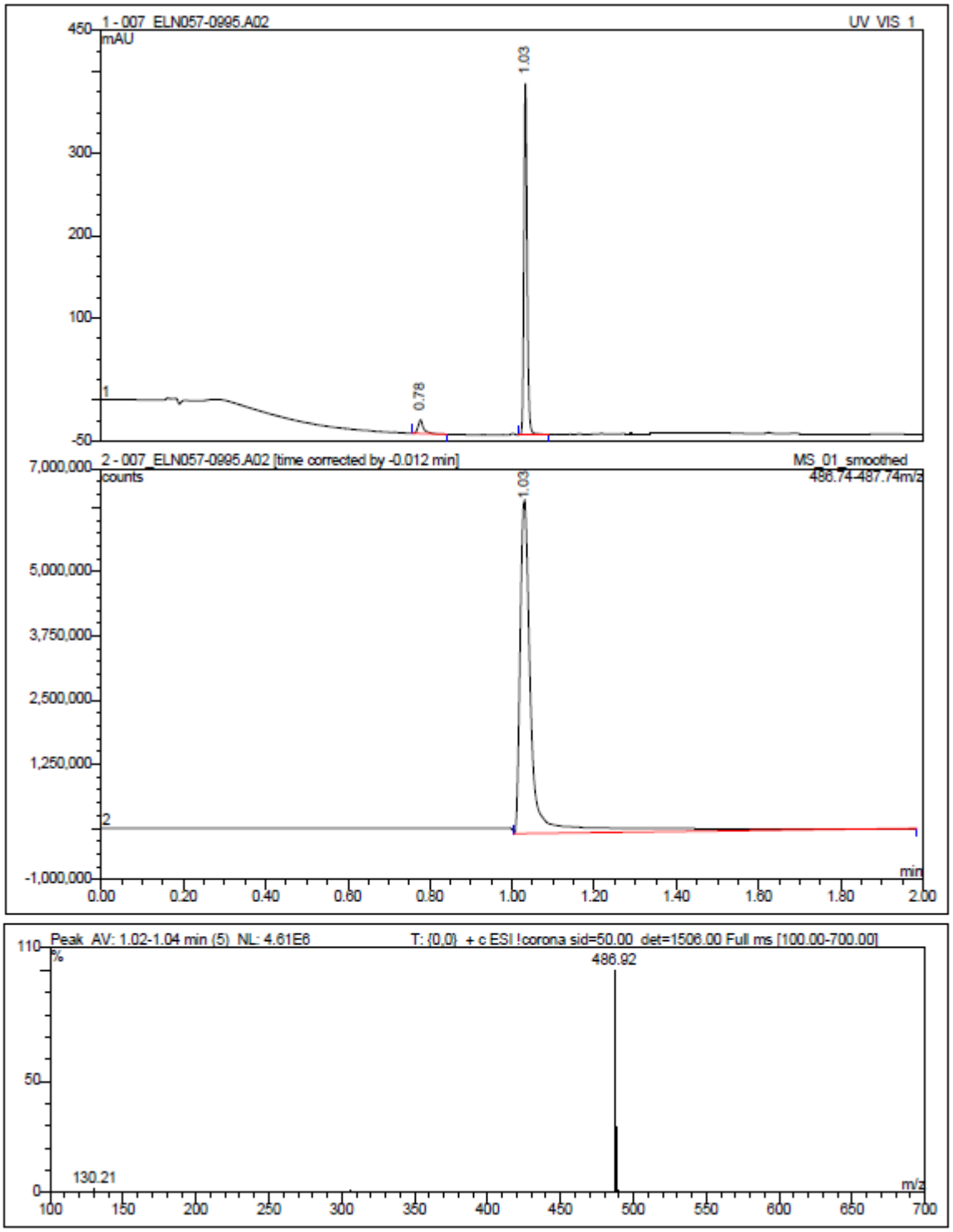
Compound **20c**:



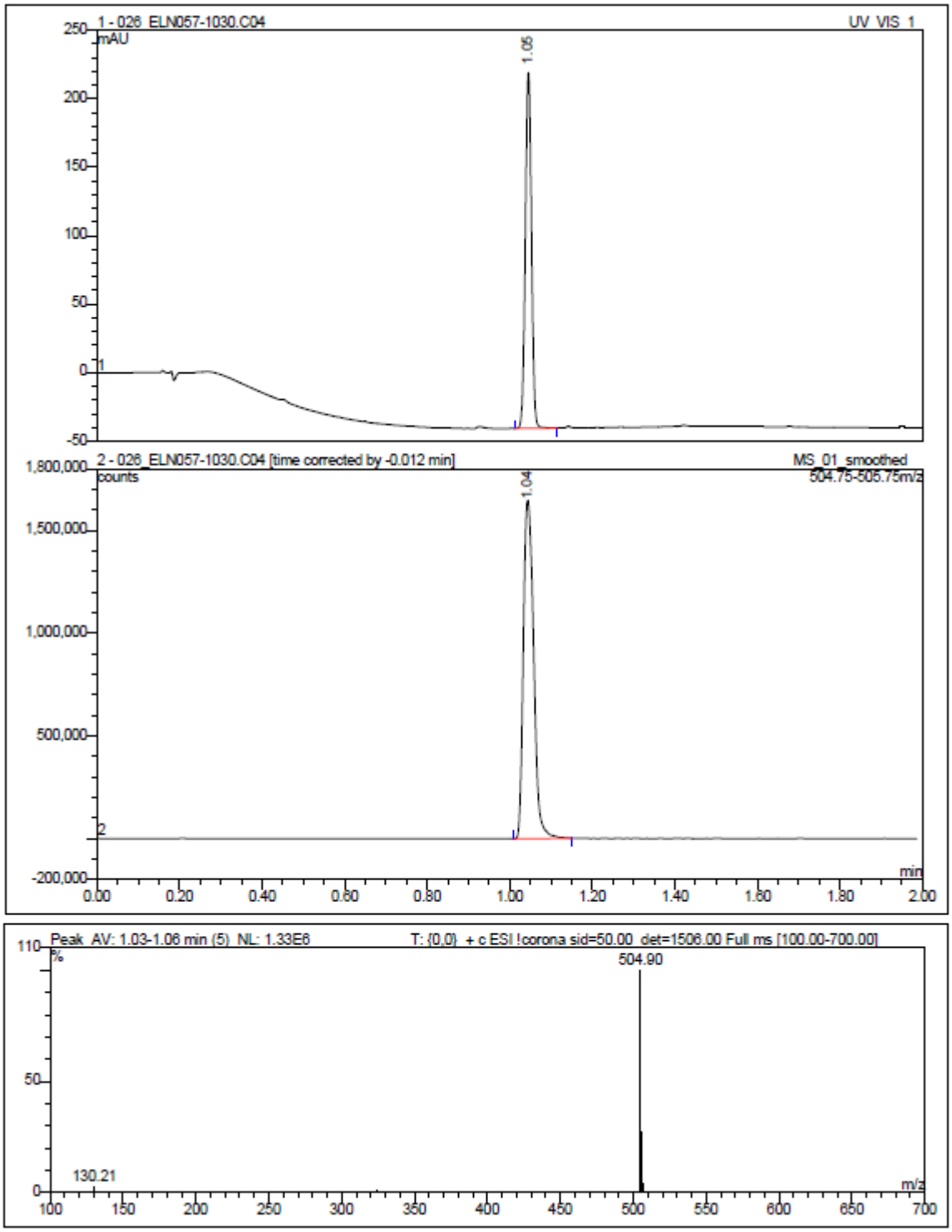
Compound **20d**:



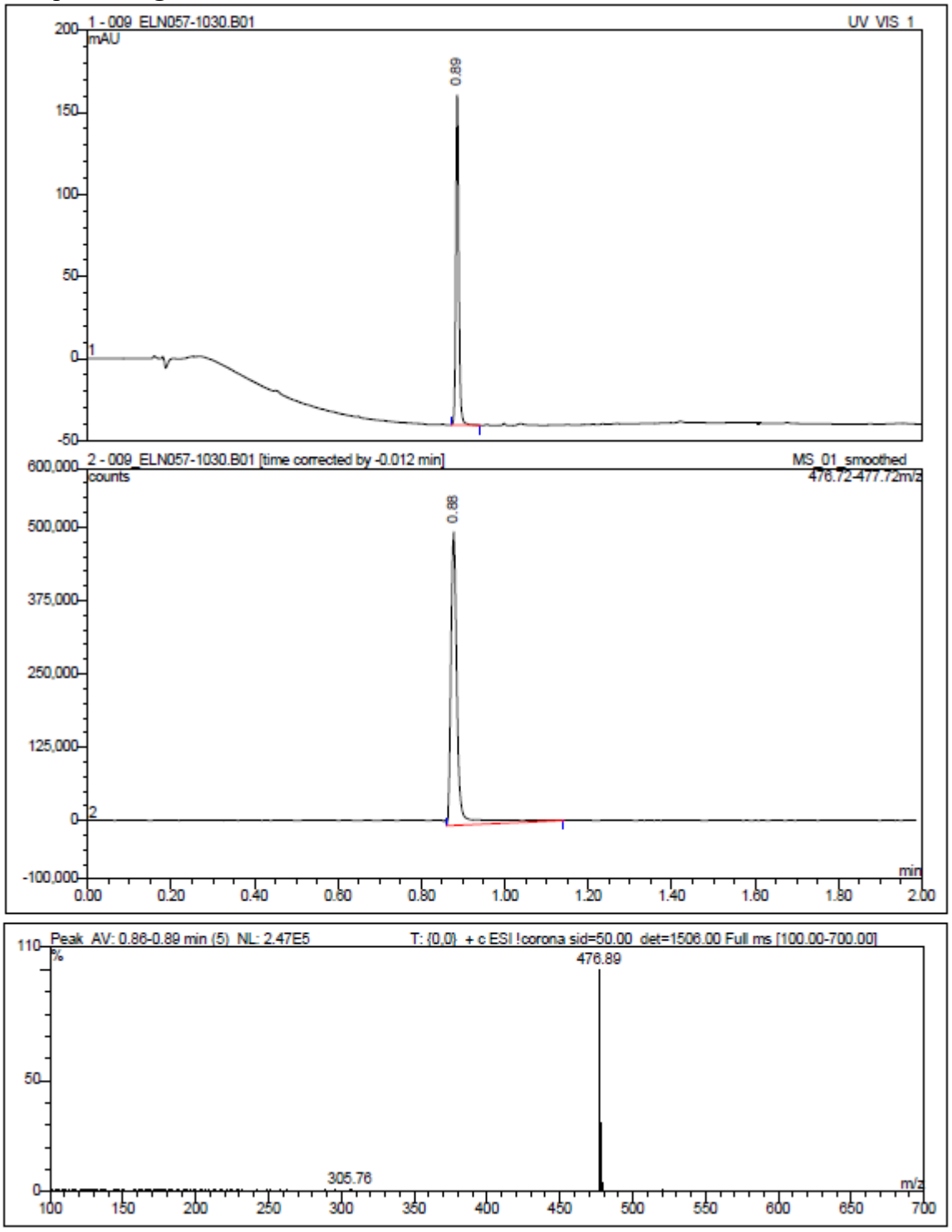
Compound **20e**:



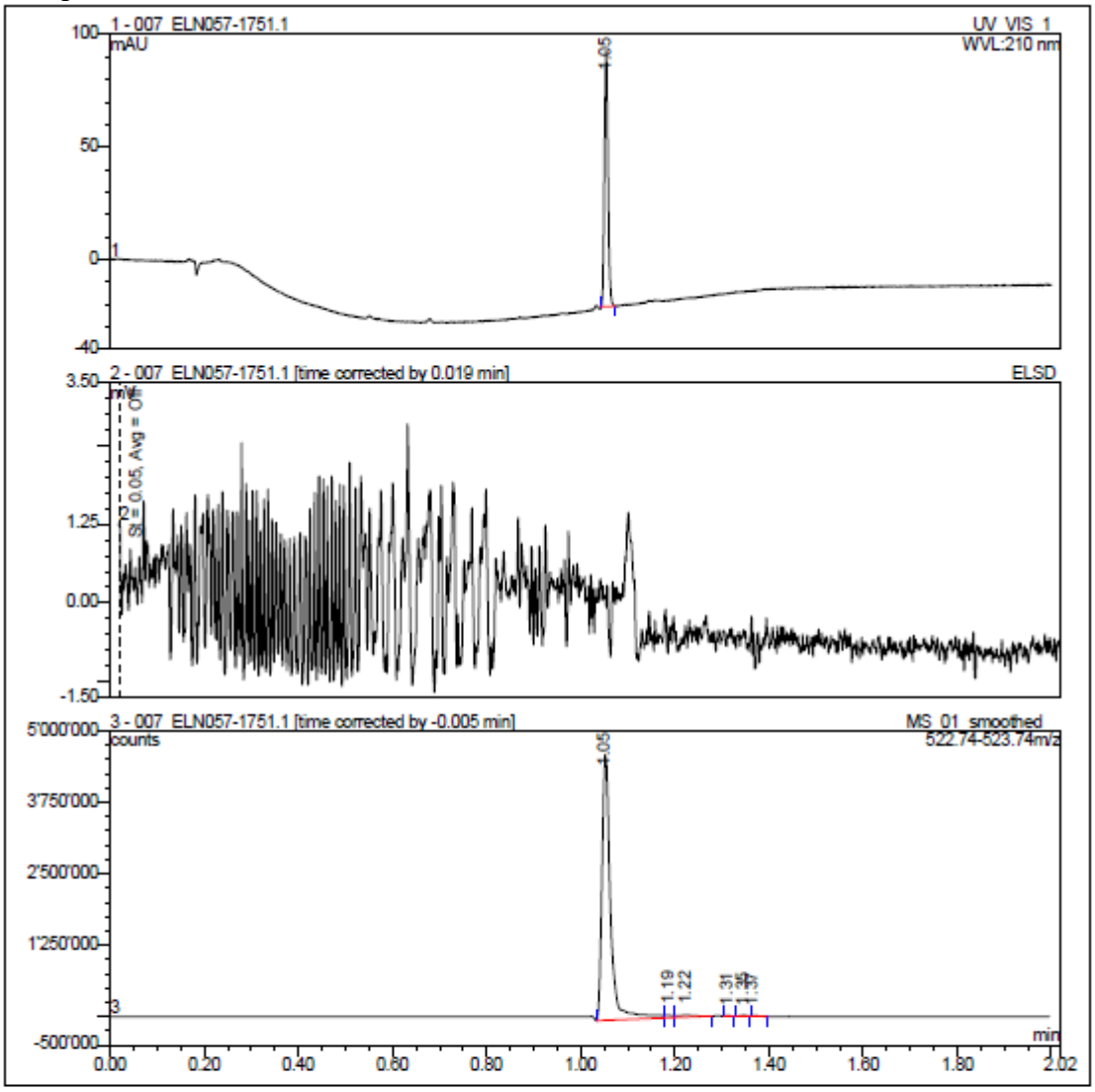
Compound **20f**:

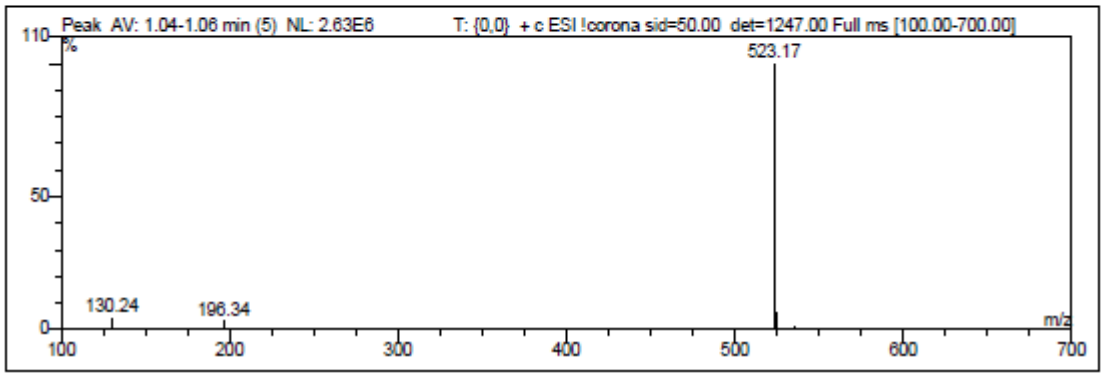


Compound **20g**:

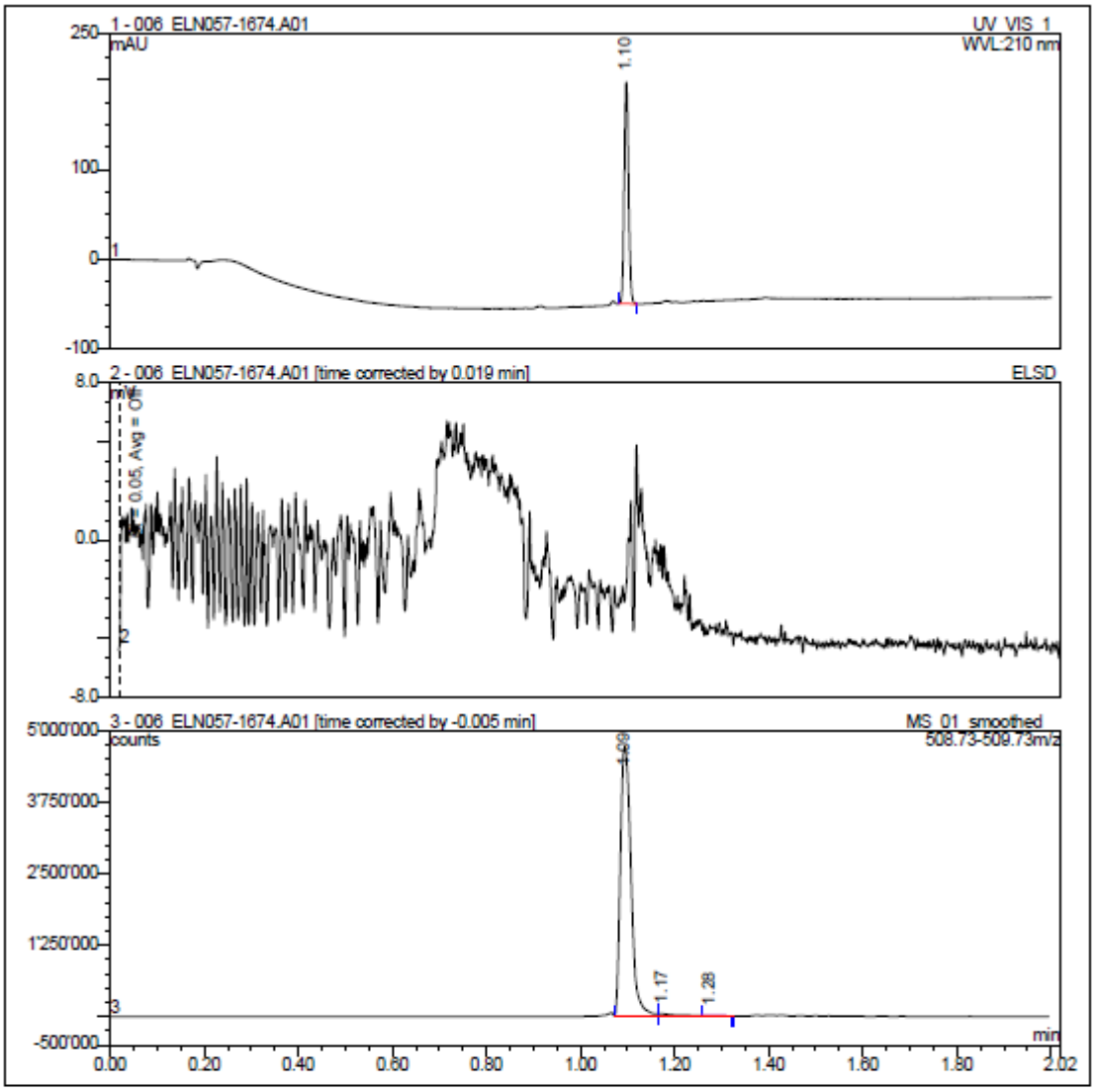


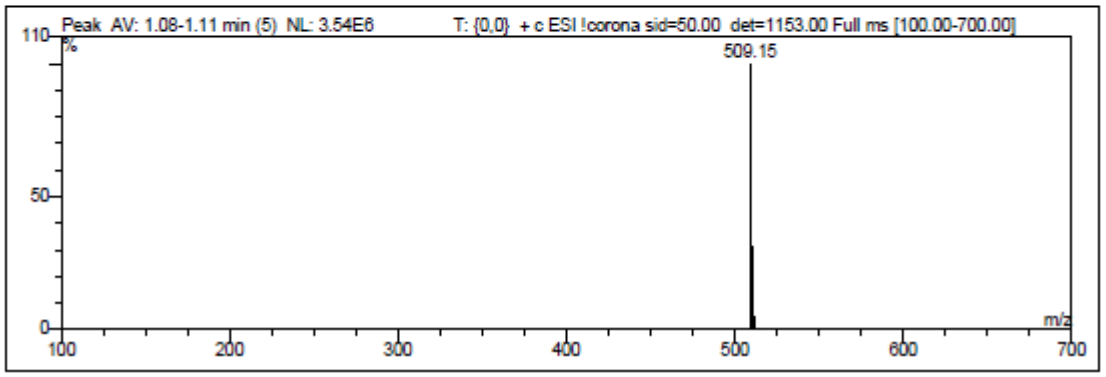
Compound **20h**:



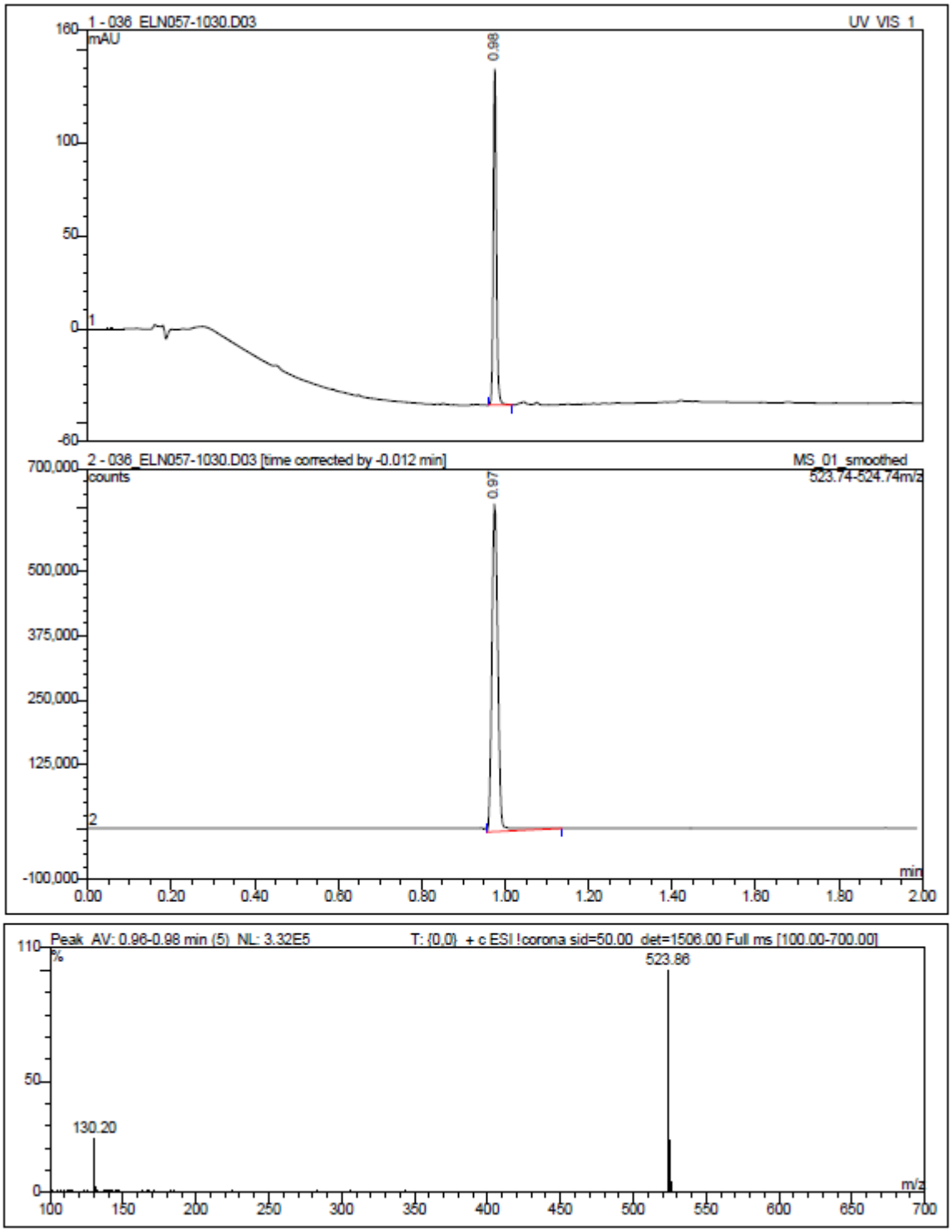


Compound **20i**:

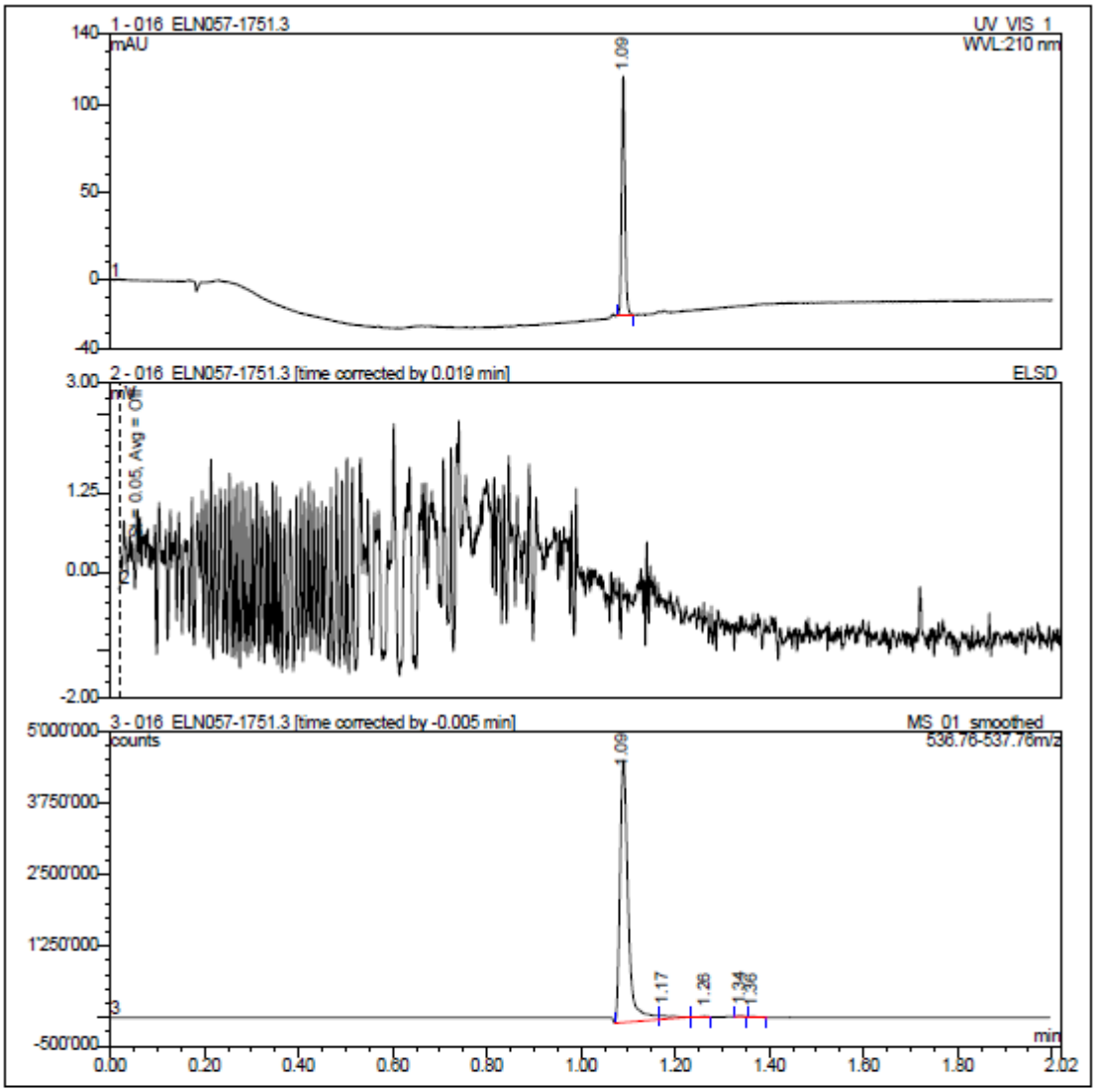


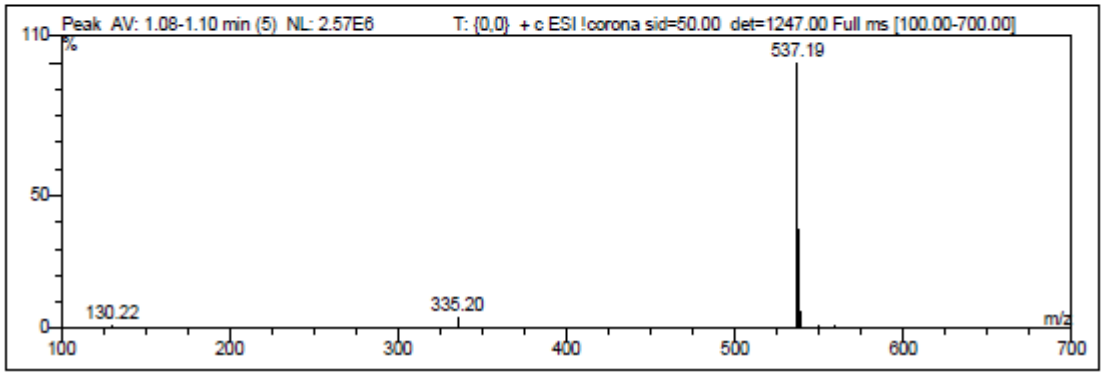


Compound **20j**:

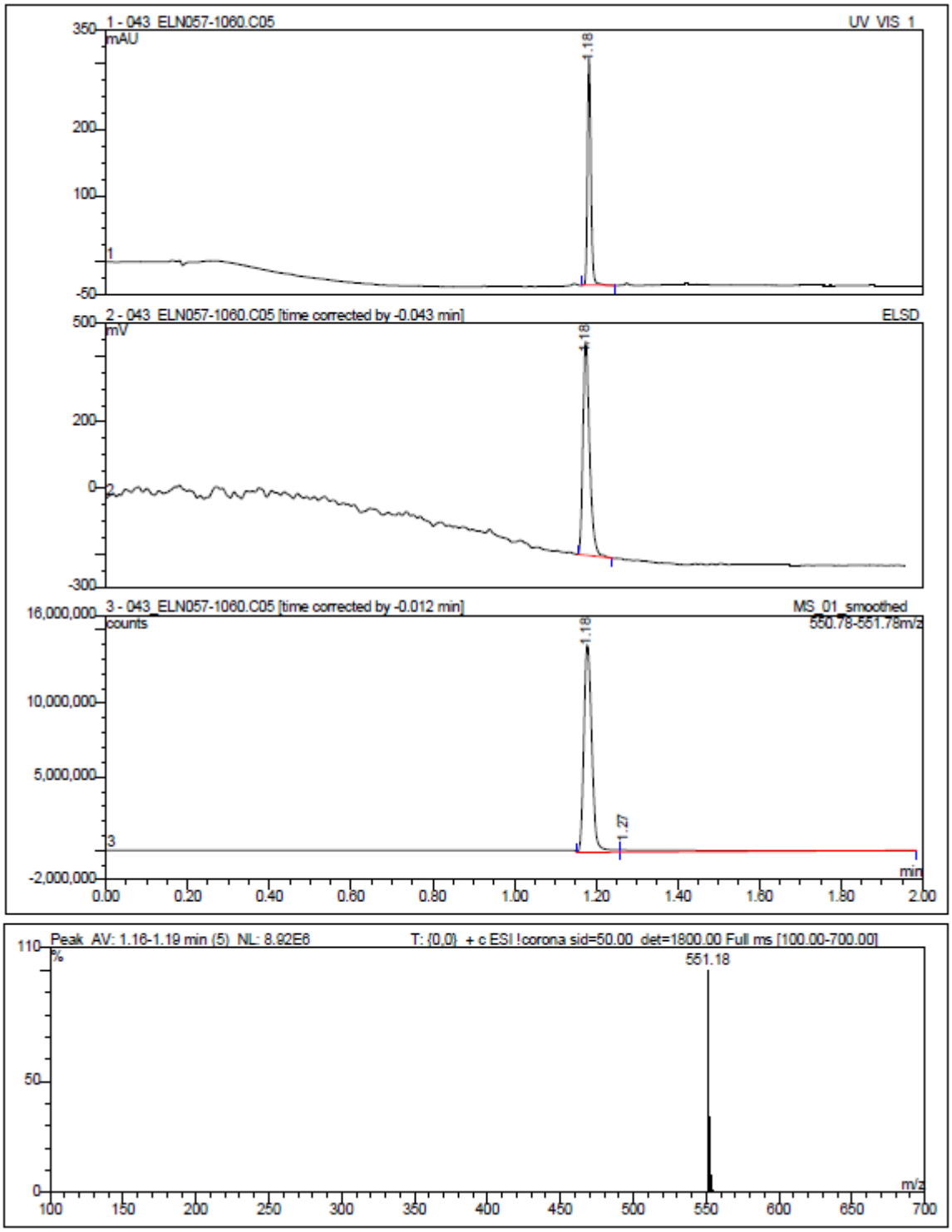


Compound **20k**:





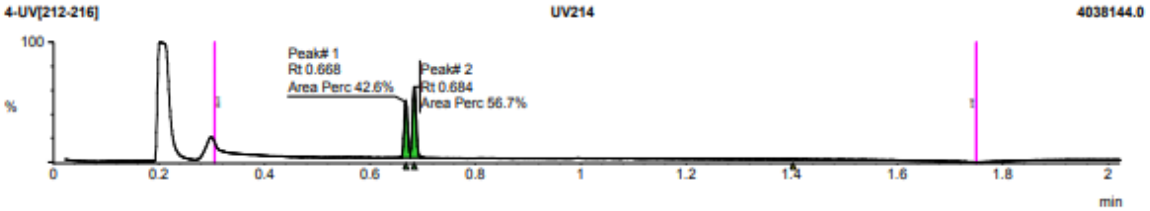
Compound **20l**:

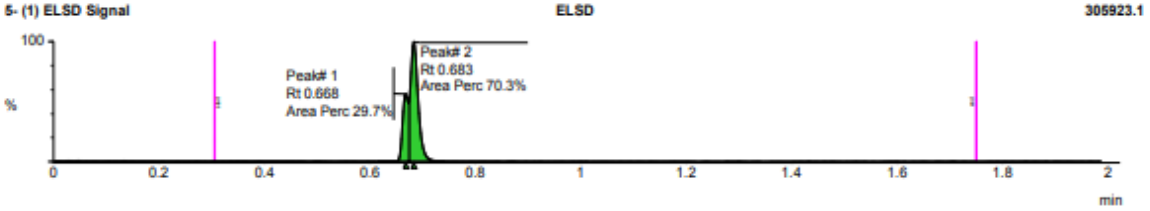


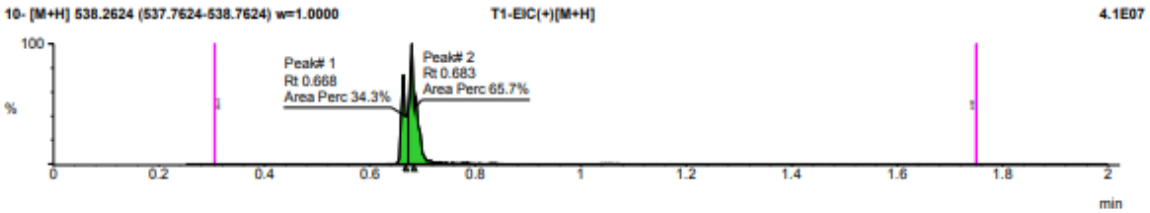
Compound **20m**:

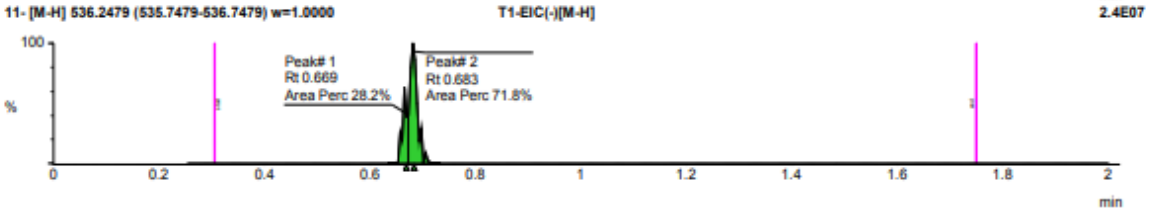
Sample Name: LCMS96-20150114-3_A03 **ACT No:** ACT-797084 **ELN Nr:** ELN057-1060.A12
Location: 4:3 **Instrument:** ACQ-SQD#B09SQD437W **Acquisition time:** 1/14/2015 6:44 PM

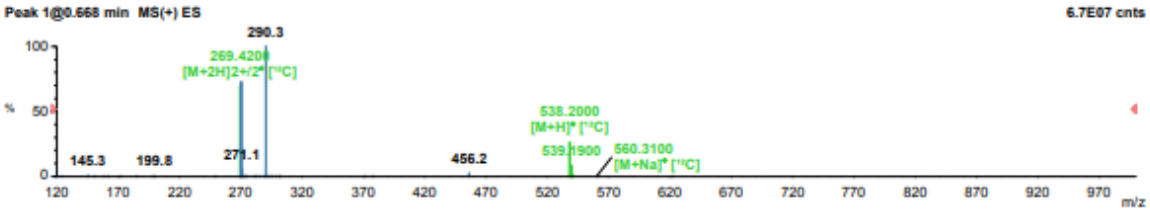
Expression	Result
Auto-Comments	Possible Isomers Present.
Auto-Summary	GOOD
Purity	99.3000
Target Mass	269.4000

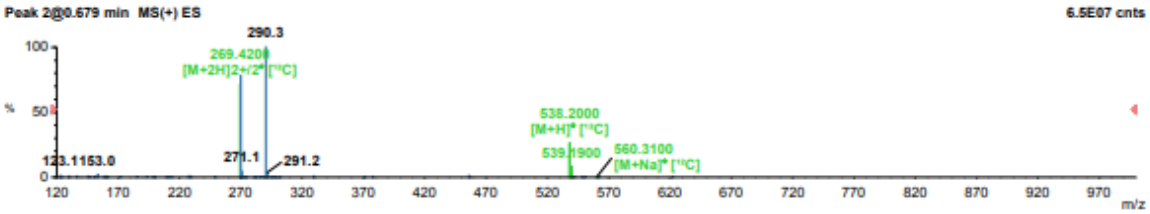




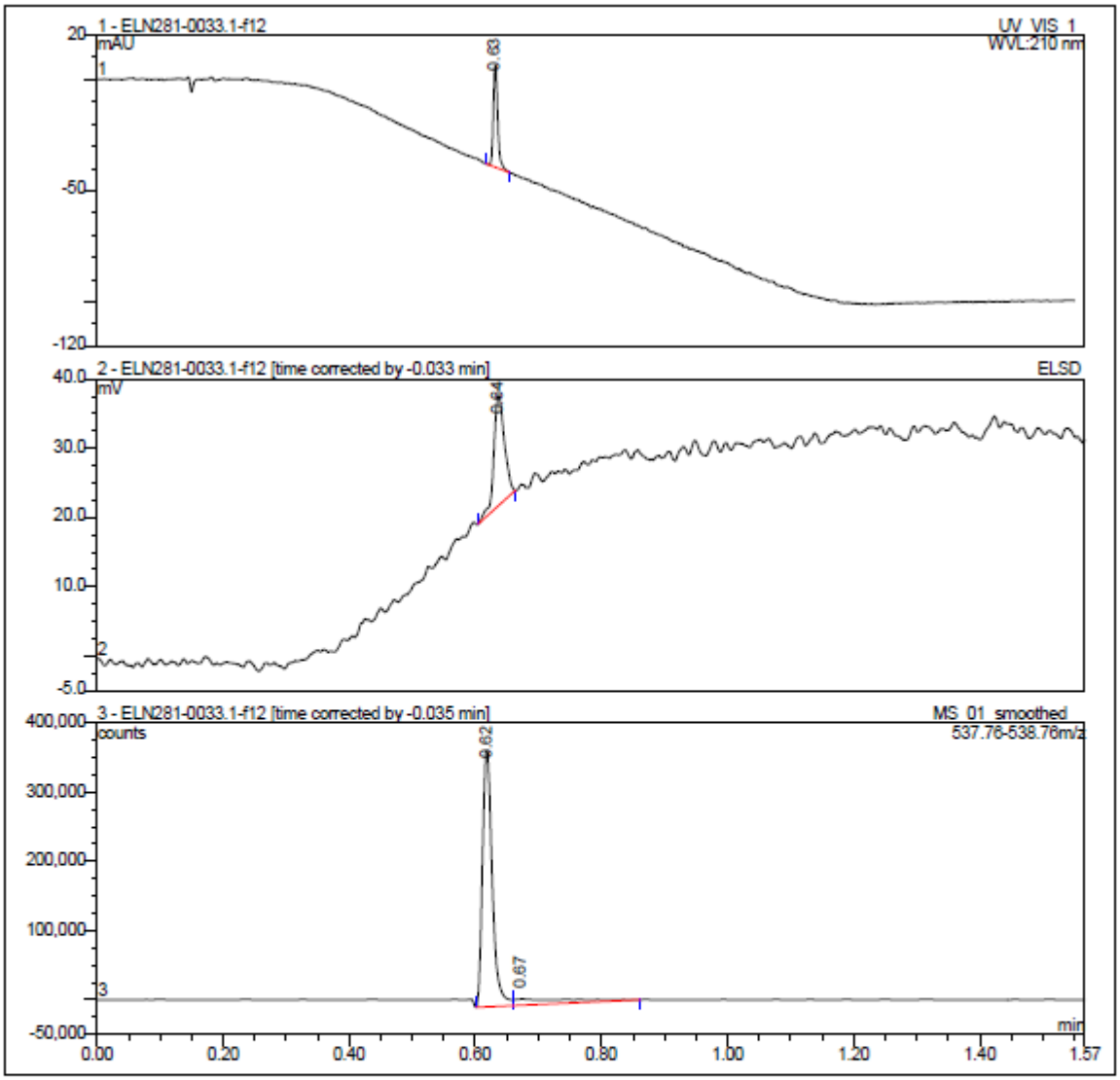


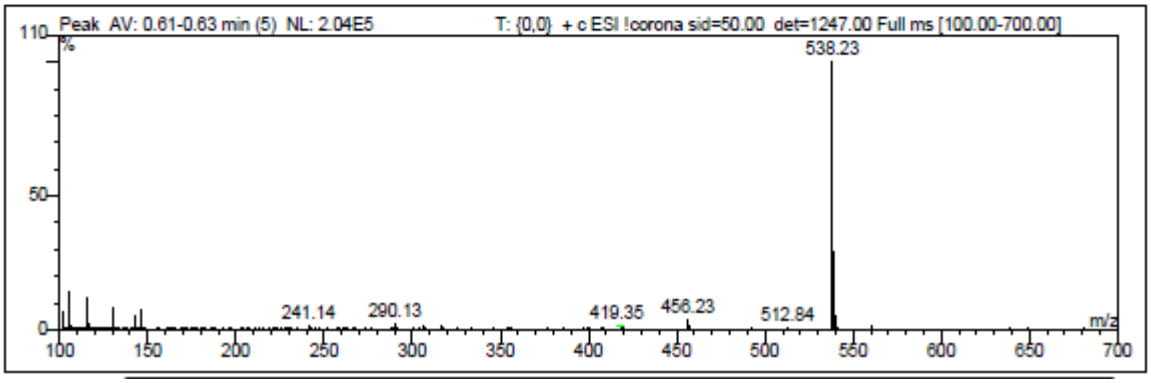




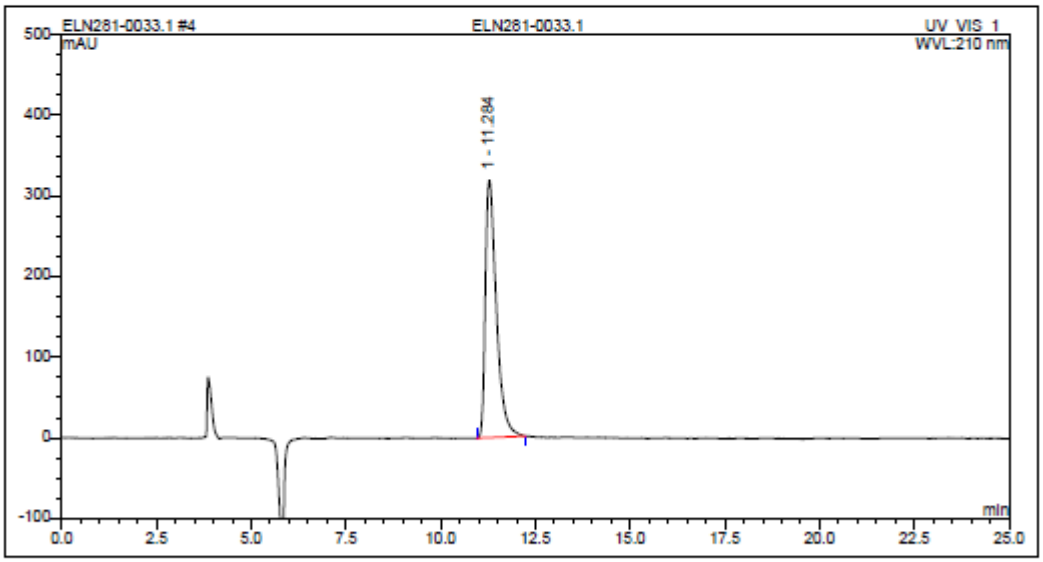


Compound **20n**:



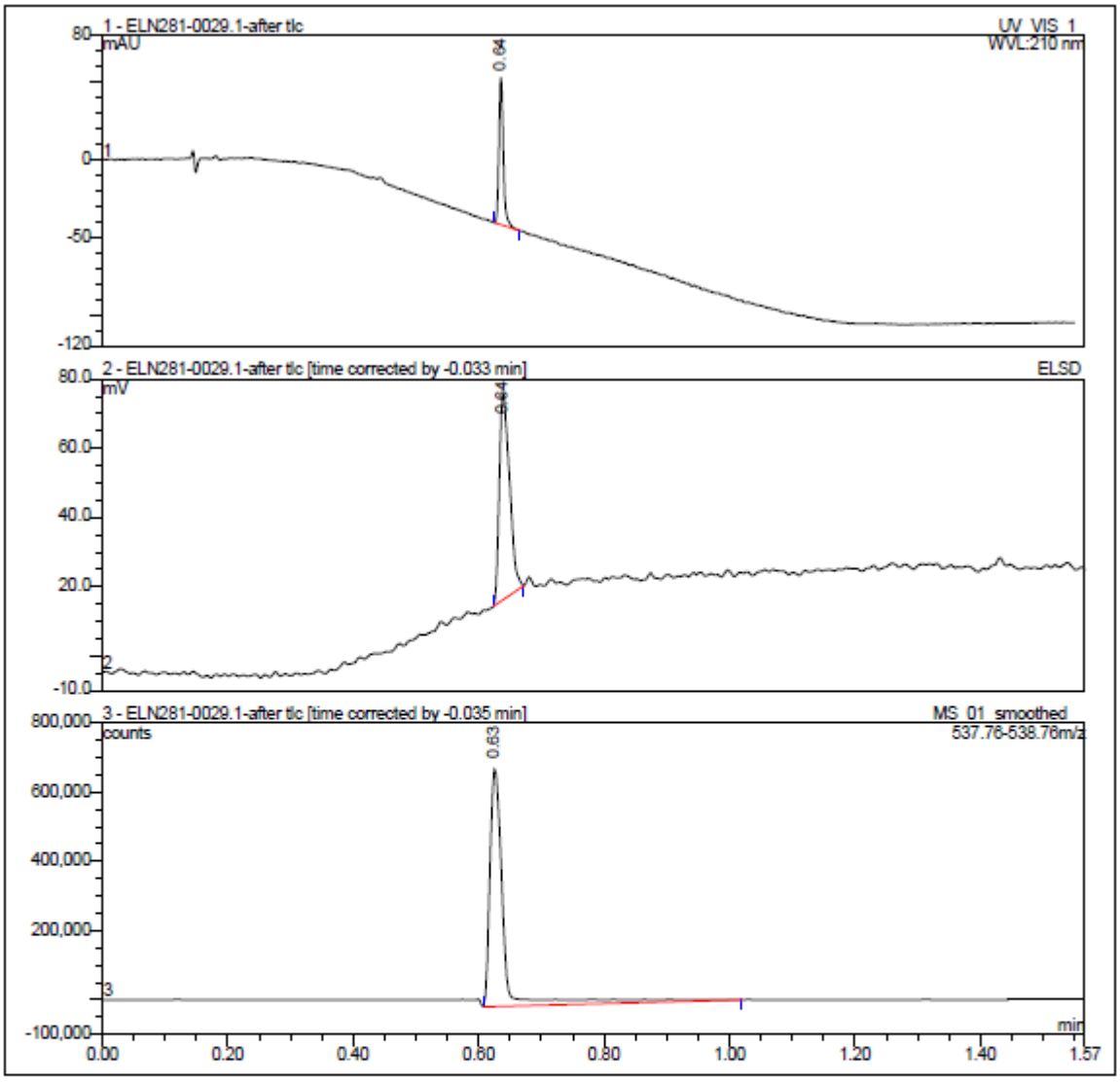


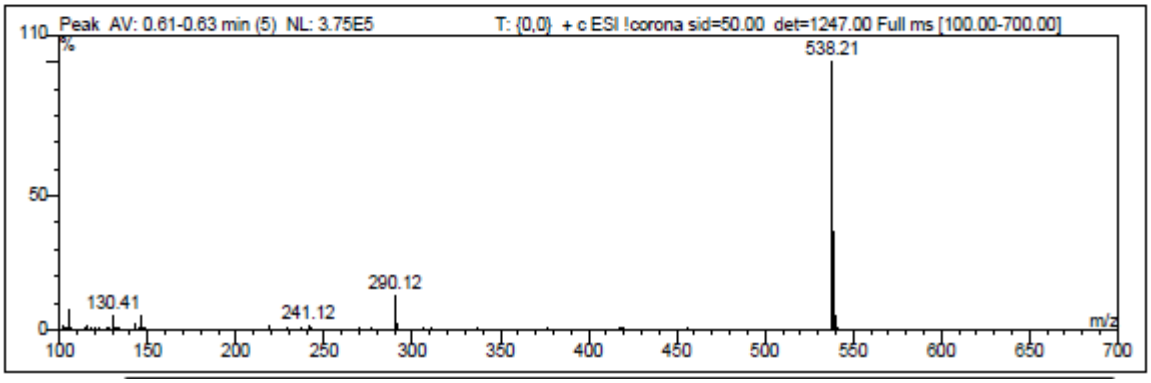
Sample ID:	322471f3-20d3-11e5-ba0c-0022191a3ba4		
Sample Name:	ELN281-0033.1	*Date:*	02.07.15
Sample Number:	4		
Time Base:	U3000		
Datasource Name:	LCMSCHEM03_local		
Sequence Name:	ELN281-0033.1		
Sequence Dir:	Data\erharmi1\Samples\CXCR7		
Quantif. Method:	default		
Injection Volume:	4.00 ul	*Comment:*	1mg/mL Heptan/Ethanol 1:1
Eluent A:	90.0 %	Heptane 0.05% DEA	
Eluent B:	10.0 %	Ethanol 0.05% DEA	
Flow:	0.800	ml/min	
Column:	Chiralpak IB 250x4.6mm ID, 5um		
Serial number:	IB00CE-LI036		
Temperature:	25.0	°C	
Detection:	210	nm	



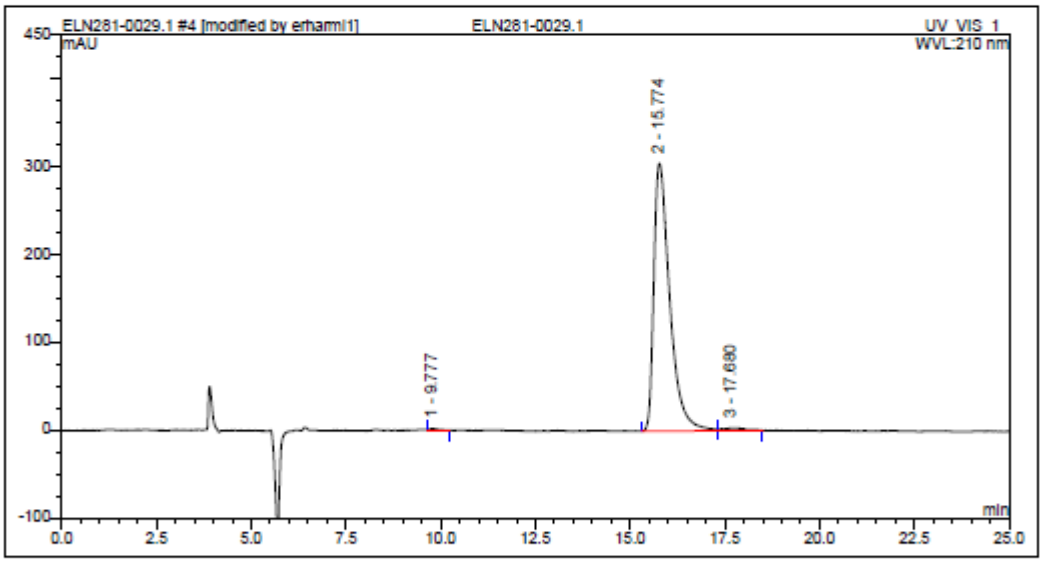
Peak No. UV_VIS_1	Ret.Time UV_VIS_1 min	Height UV_VIS_1 mAU	Rel.Area UV_VIS_1 %	Area UV_VIS_1 mAU*min	Resolution UV_VIS_1	Asymmetry UV_VIS_1	Plates UV_VIS_1
1	11.3	319	100.0	107.963	n.a.	1.7	7759
Total:			100.0	108.0			

Compound **20o**:



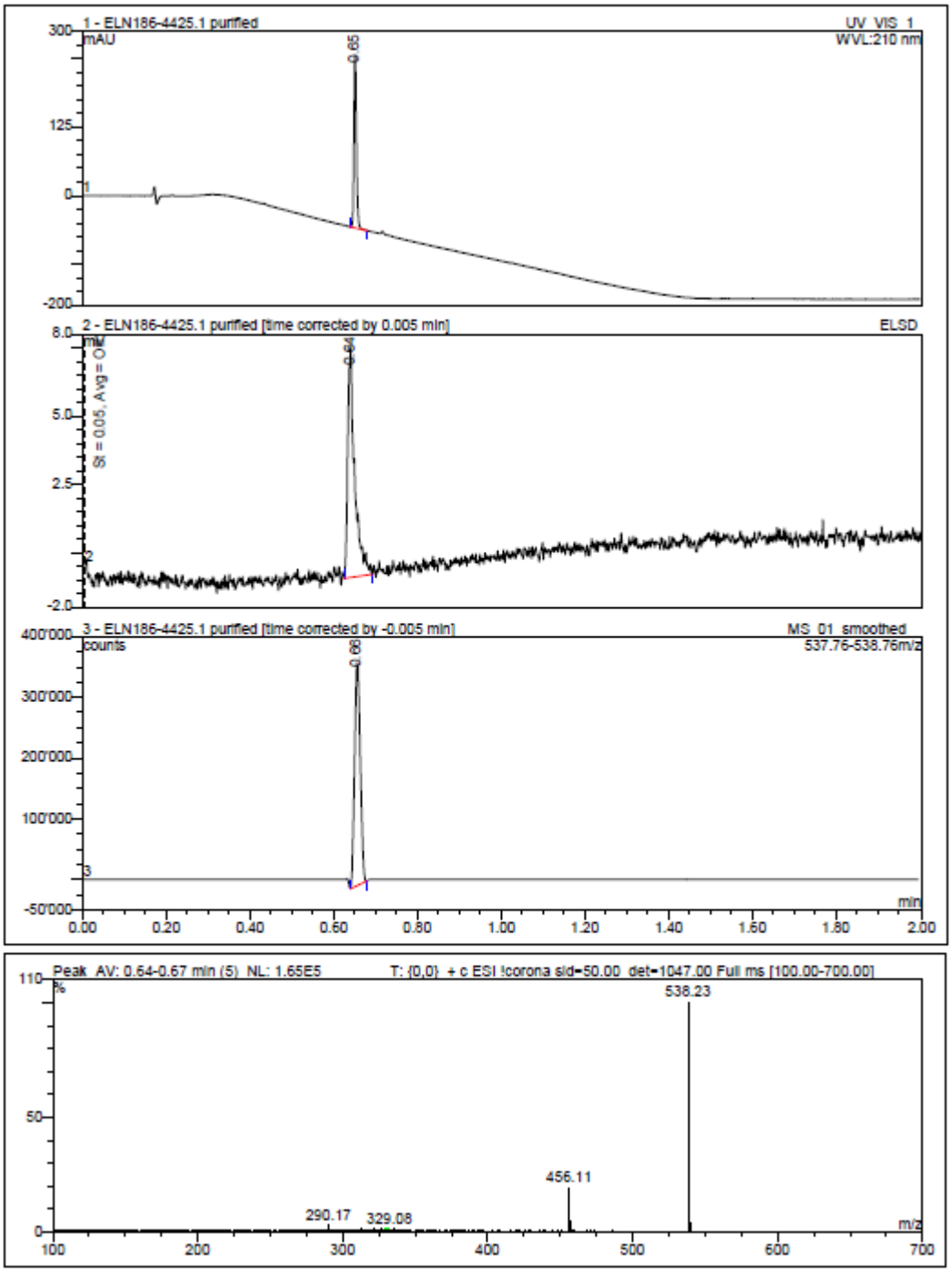


Sample ID:	b0cd9997-1981-11e5-ba0c-0022191a3ba4		
Sample Name:	ELN281-0029.1	*Date:*	23.06.15
Sample Number:	4		
Time Base:	U3000		
Datasource Name:	LCMSCHEM03_local		
Sequence Name:	ELN281-0029.1		
Sequence Dir:	Data\erharmi1\Samples\CXCR7		
Quantif. Method:	default		
Injection Volume:	5.00 ul	*Comment:*	1mg/mL Heptan/Ethanol 3:1
Eluent A:	90.0 %	Heptane 0.05% DEA	
Eluent B:	10.0 %	Ethanol 0.05% DEA	
Flow:	0.800	ml/min	
Column:	Chiralpak IB 250x4.6mm ID, 5um		
Serial number:	IB00CE-LI036		
Temperature:	25.0	°C	
Detection:	210	nm	

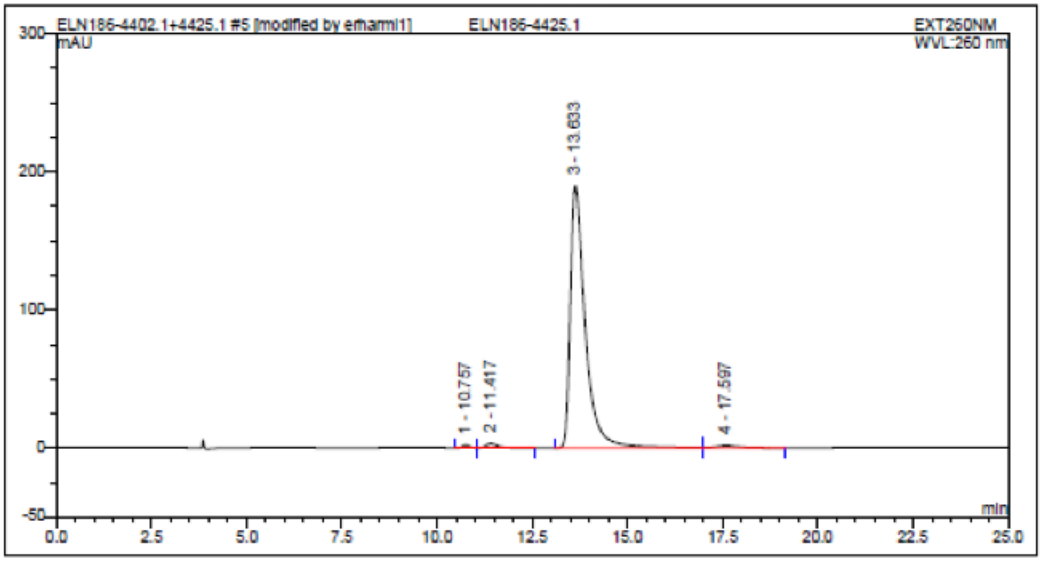


Peak No. UV_VIS_1	Ret.Time UV_VIS_1 min	Height UV_VIS_1 mAU	Rel.Area UV_VIS_1 %	Area UV_VIS_1 mAU*min	Resolution UV_VIS_1	Asymmetry UV_VIS_1	Plates UV_VIS_1
1	9.8	2	0.4	0.612	10.2	n.a.	7675
2	15.8	304	98.2	148.244	n.a.	1.8	7460
3	17.7	3	1.4	2.167	n.a.	n.a.	n.a.
Total:			100.0	151.0			

Compound **20p**:

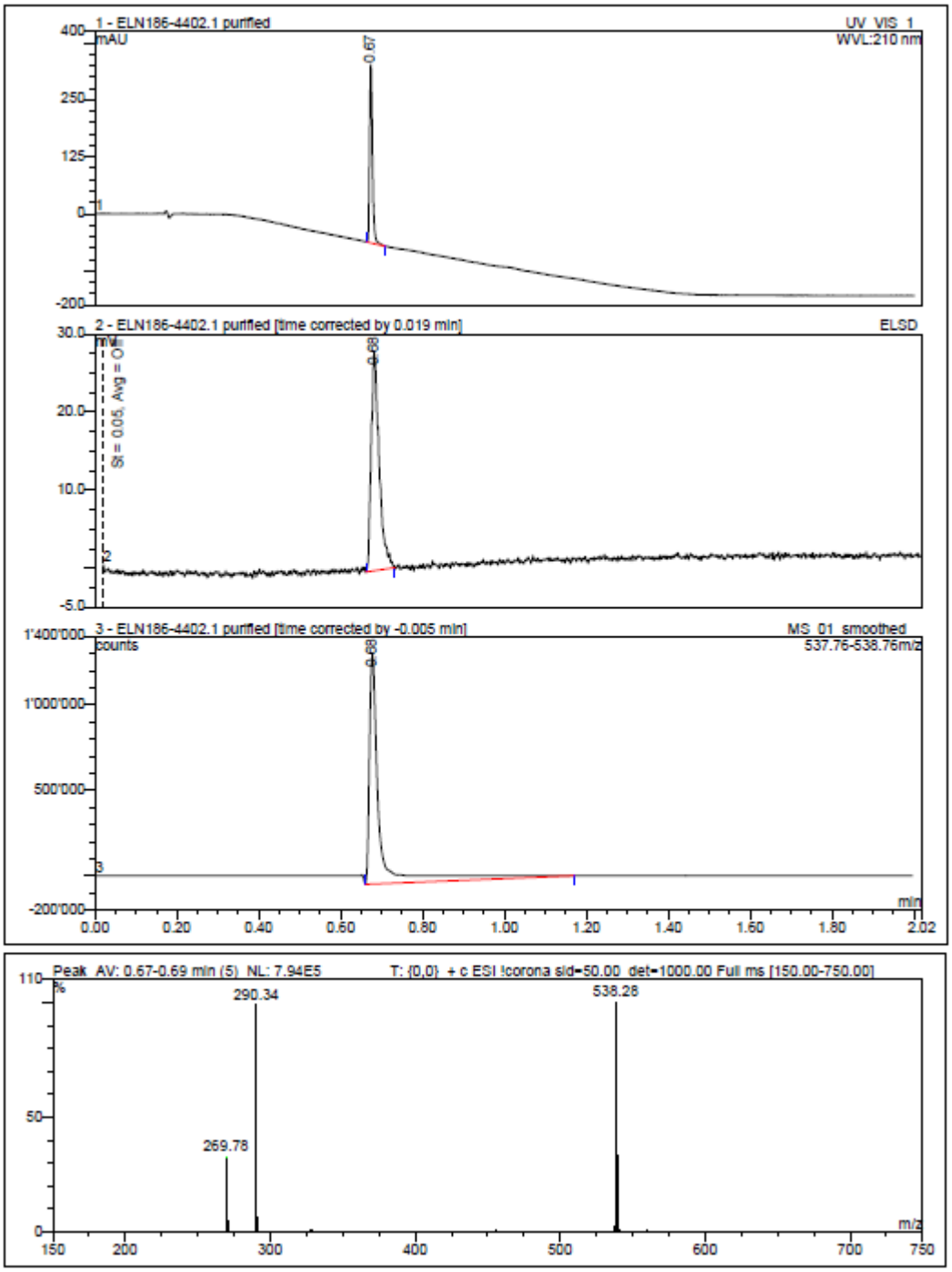


Sample ID:	048242ea-679b-11ea-a9dc-4ccc6a34d1c7		
Sample Name:	ELN186-4425.1	*Date:*	16.03.20
Sample Number:	5		
Time Base:	U3000		
Datasource Name:	LCMSCHEM03_local		
Sequence Name:	ELN186-4402.1+4425.1		
Sequence Dir:	Data\erharmi1\Samples\		
Quantif. Method:	default		
Injection Volume:	2.50 ul *Comment:*	1mg/mL Heptan/Ethanol 1:1	
Eluent A:	90.0 %	Heptane 0.05% DEA	
Eluent B:	10.0 %	Ethanol 0.05% DEA	
Flow:	0.800	ml/min	
Column:	Chiralpak IB 250x4.6mm ID, 5um		
Serial number:	IB00CE-LI036		
Temperature:	25.0	°C	
Detection:	260	nm	

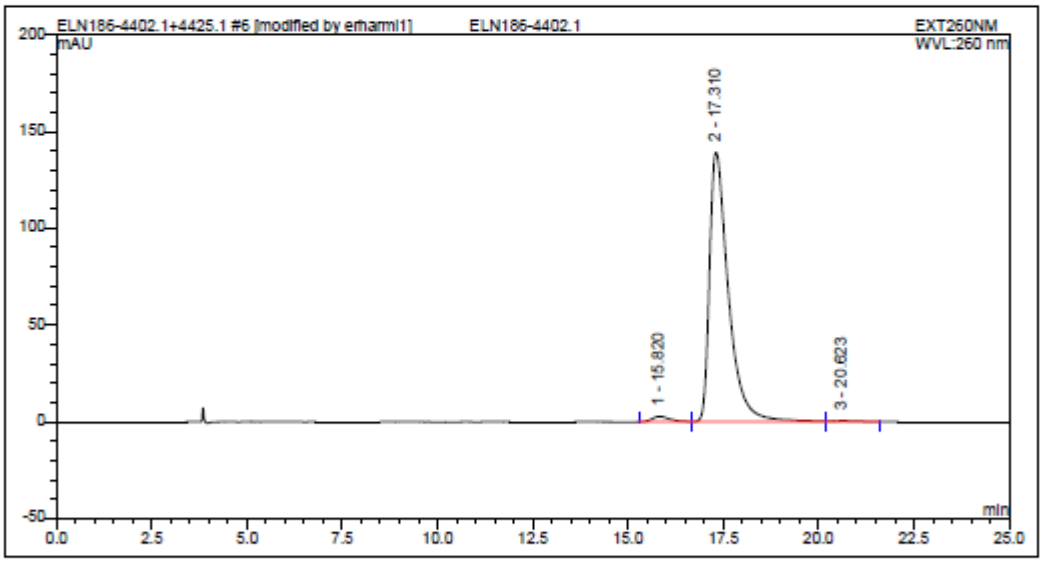


Peak No. EXT260NM	Ret.Time EXT260NM min	Height EXT260NM mAU	Rel.Area EXT260NM %	Area EXT260NM mAU*min	Resolution EXT260NM	Asymmetry EXT260NM	Plates EXT260NM
1	10.8	2	0.6	0.549	1.5	n.a.	16378
2	11.4	3	1.5	1.310	3.6	1.4	6486
3	13.6	190	96.5	87.114	4.8	1.9	6947
4	17.6	2	1.4	1.302	n.a.	n.a.	4873
Total:			100.0	90.3			

Compound **20q**:

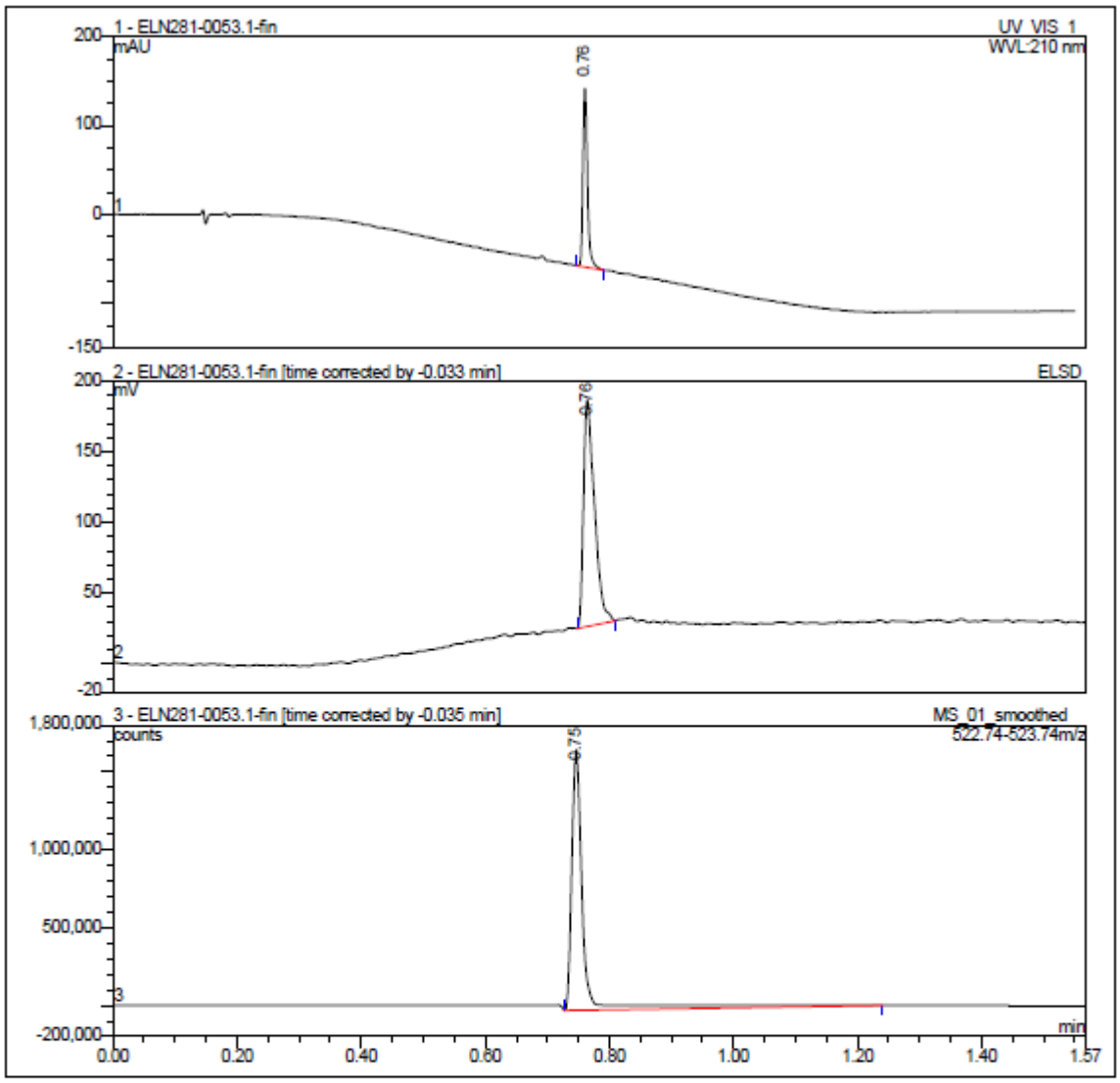


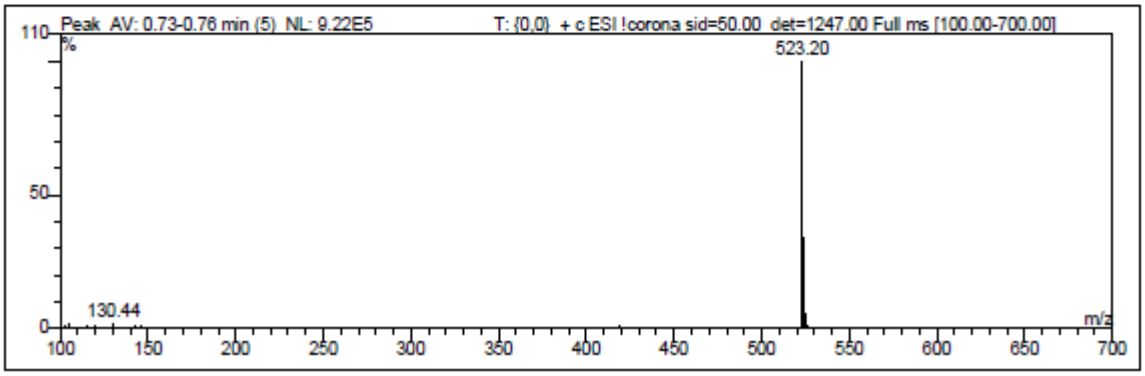
Sample ID:	da238cdf-679e-11ea-a9dc-4ccc6a34d1c7		
Sample Name:	ELN186-4402.1	*Date:*	16.03.20
Sample Number:	6		
Time Base:	U3000		
Datasource Name:	LCMSCHEM03_local		
Sequence Name:	ELN186-4402.1+4425.1		
Sequence Dir:	Data\erharmi1\Samples		
Quantif. Method:	default		
Injection Volume:	3.00 ul *Comment:* 1mg/mL Heptan/Ethanol 1:1		
Eluent A:	90.0 % Heptane 0.05% DEA		
Eluent B:	10.0 % Ethanol 0.05% DEA		
Flow:	0.800 ml/min		
Column:	Chiralpak IB 250x4.6mm ID, 5um		
Serial number:	IB00CE-LI036		
Temperature:	25.0 °C		
Detection:	260 nm		



Peak No. EXT260NM	Ret.Time EXT260NM min	Height EXT260NM mAU	Rel.Area EXT260NM %	Area EXT260NM mAU*min	Resolution EXT260NM	Asymmetry EXT260NM	Plates EXT260NM
1	15.8	3	1.8	1.500	1.8	1.5	6162
2	17.3	139	97.8	80.085	n.a.	1.8	6693
3	20.6	0	0.4	0.332	n.a.	n.a.	n.a.
Total:			100.0	81.9			

Compound **21a**:

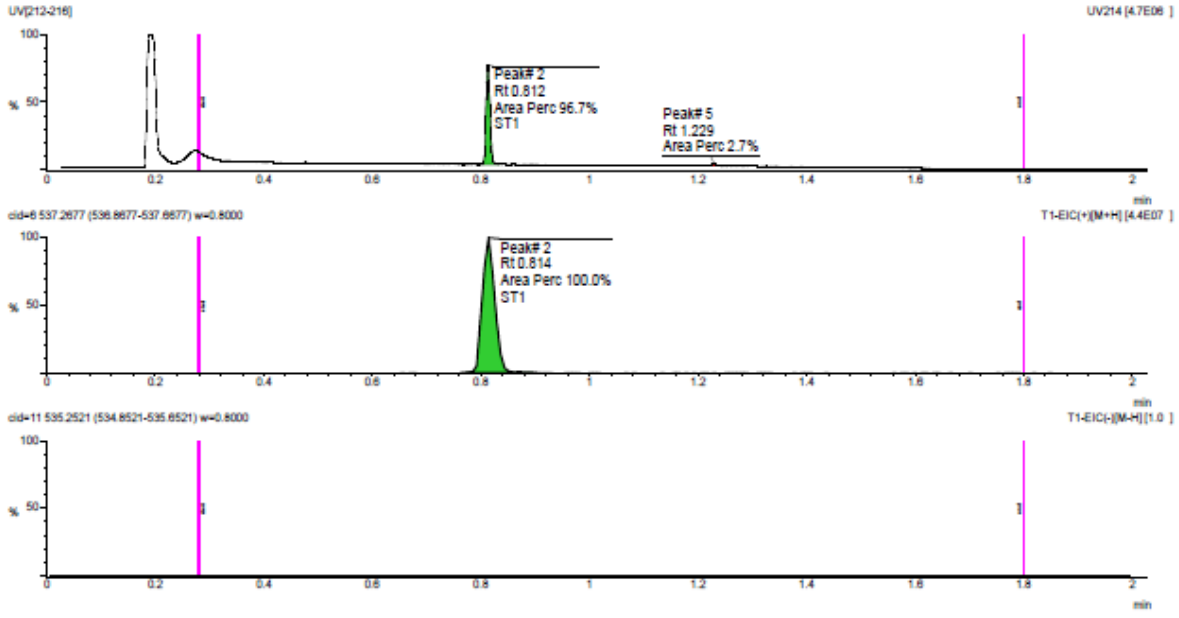


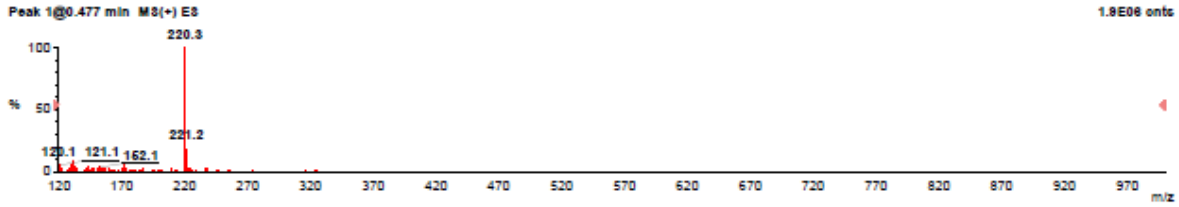


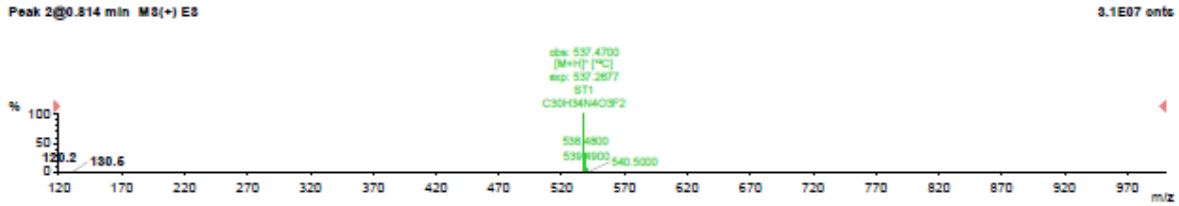
Compound **21b**:

Sample Name: LCMSP384-20200430-1_M05 **ACT No:** ACT-1003-6905 **ELN Nr:** ELN281-0048.1
Instrument: ICHALW-DL00021-SQD **Acquisition time:** 5/4/2020 3:24 PM

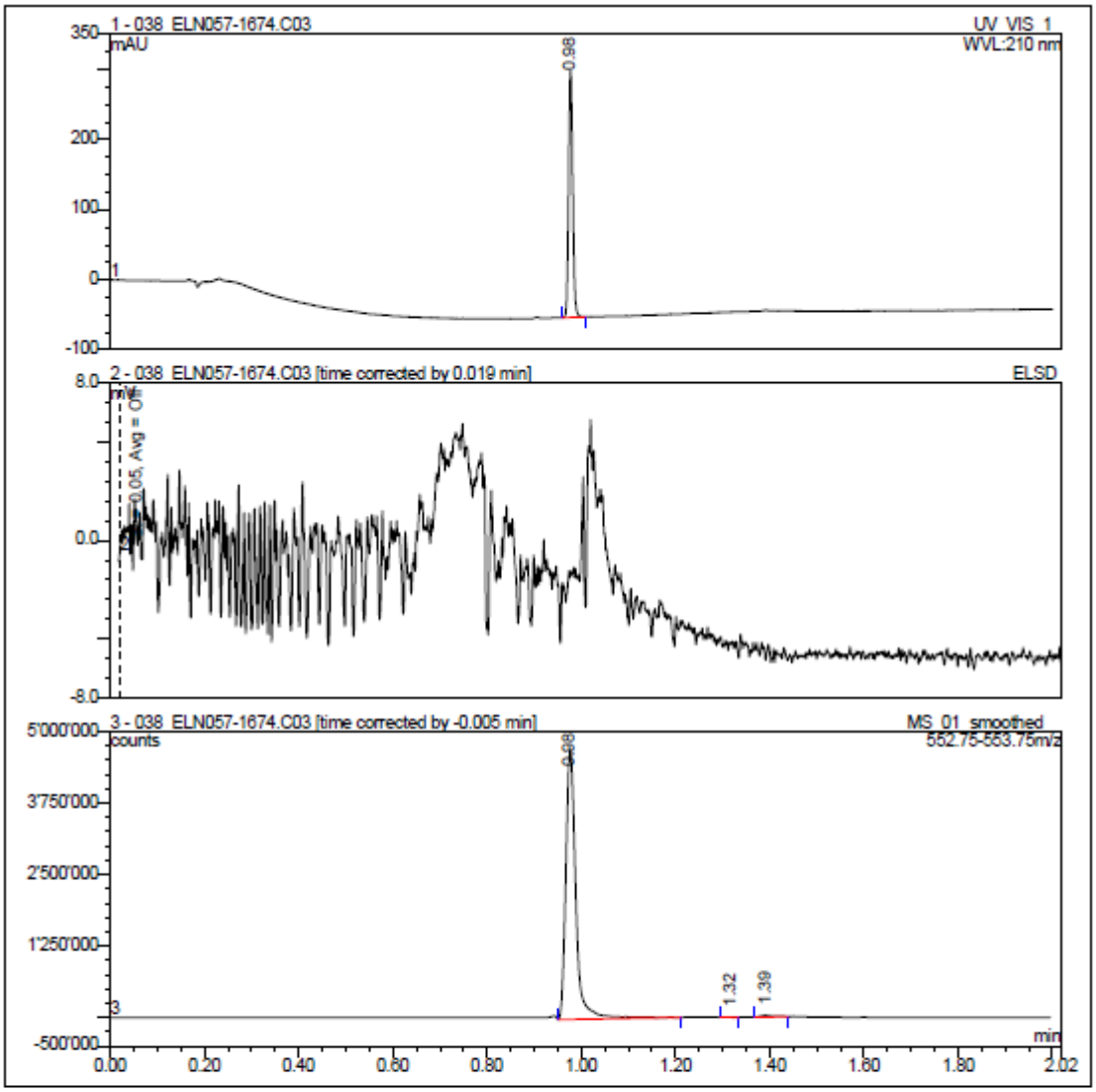
Expression	Result
Auto-Comments	
Auto-Summary	GOOD
Purity	96.7000
Target Mass	537.5000
Target RT	0.8120

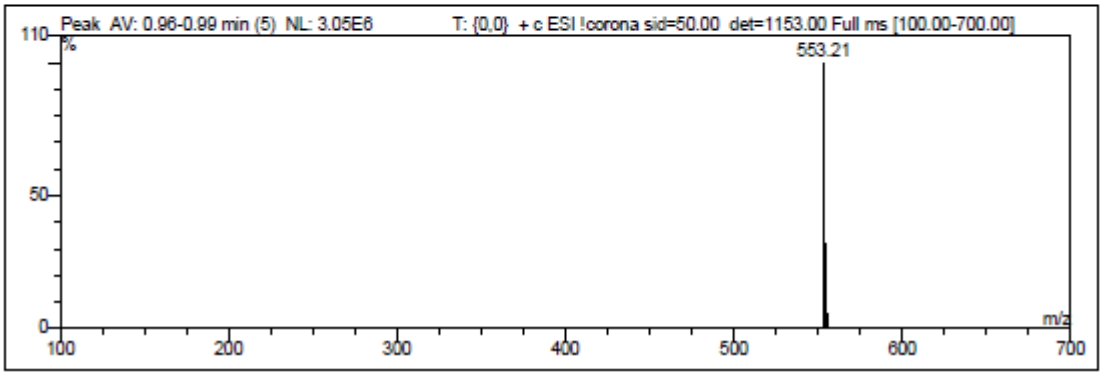




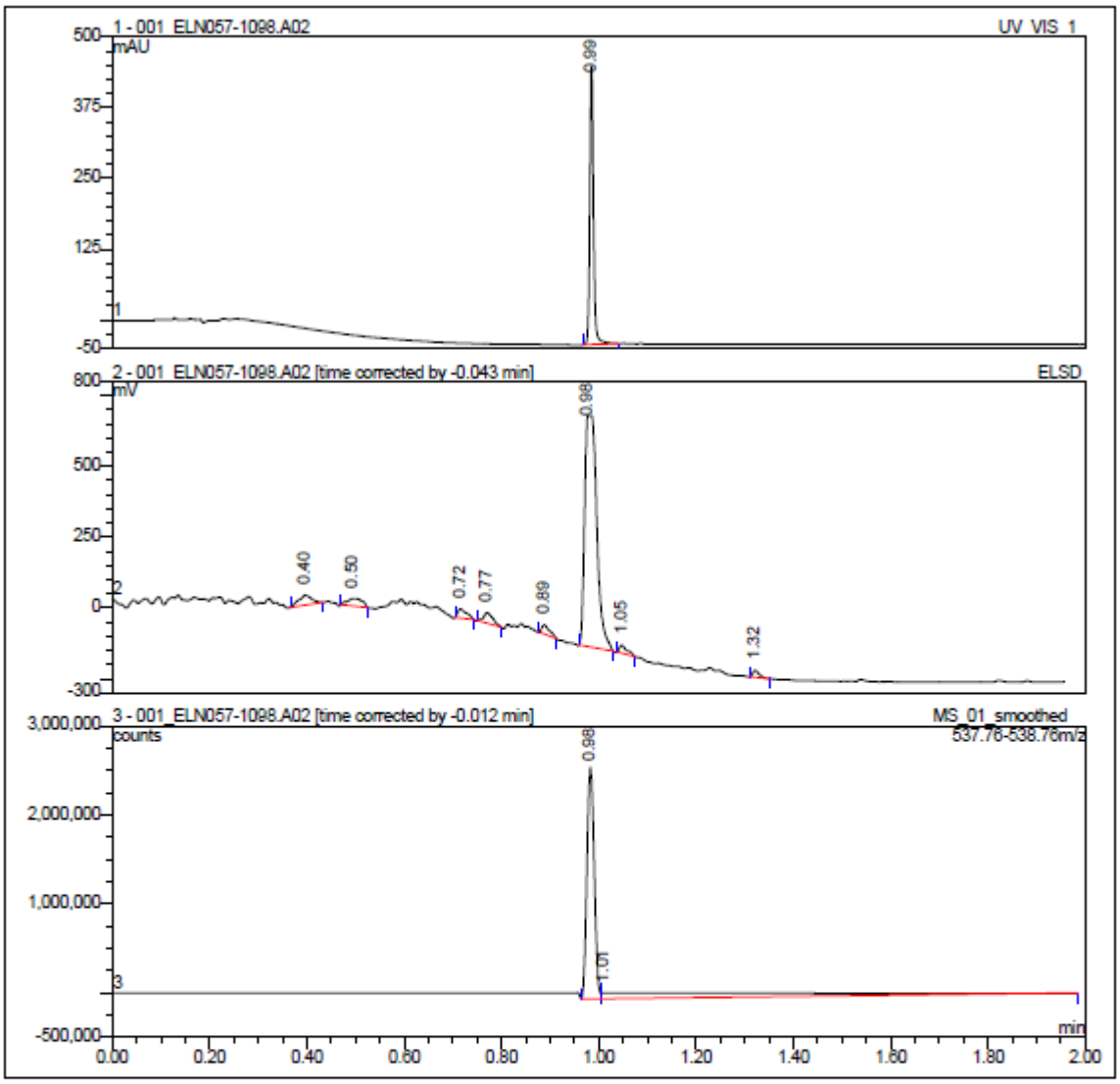


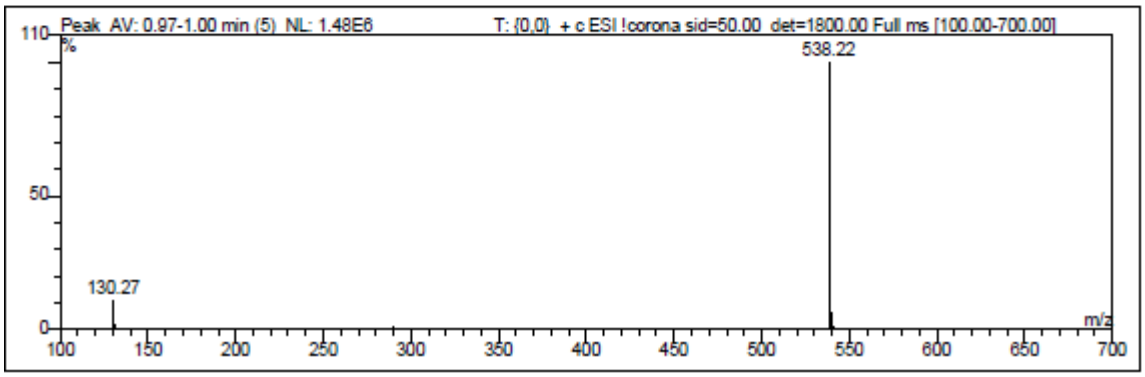
Compound **21c**:



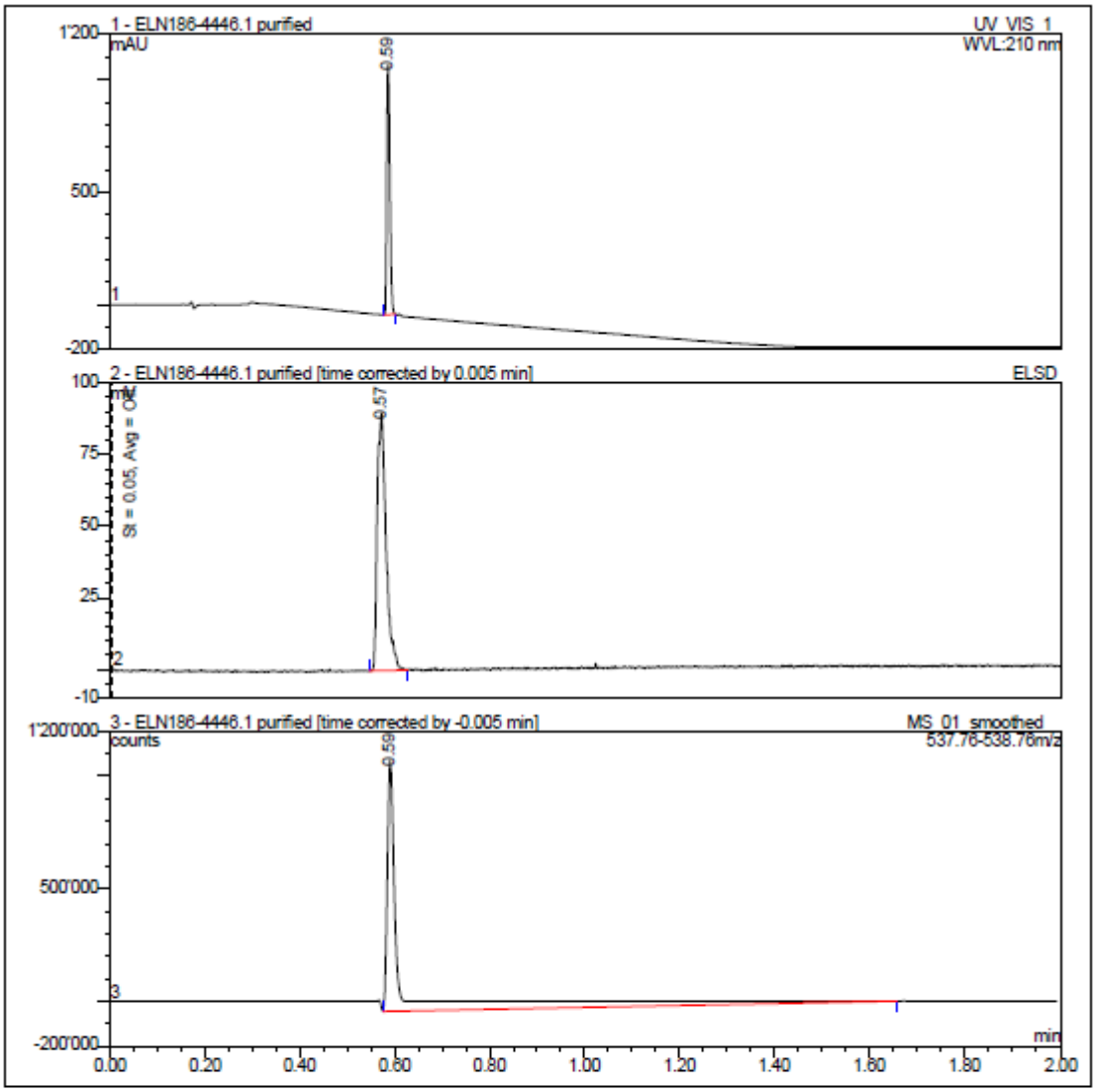


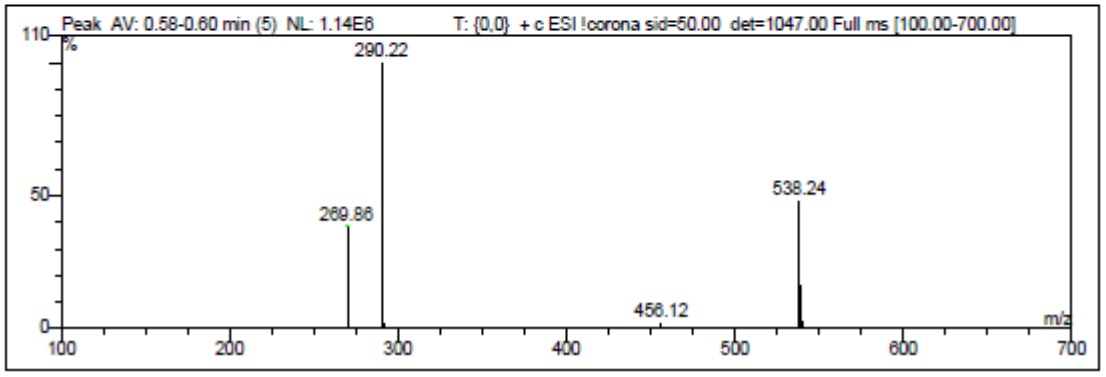
Compound **21d**:



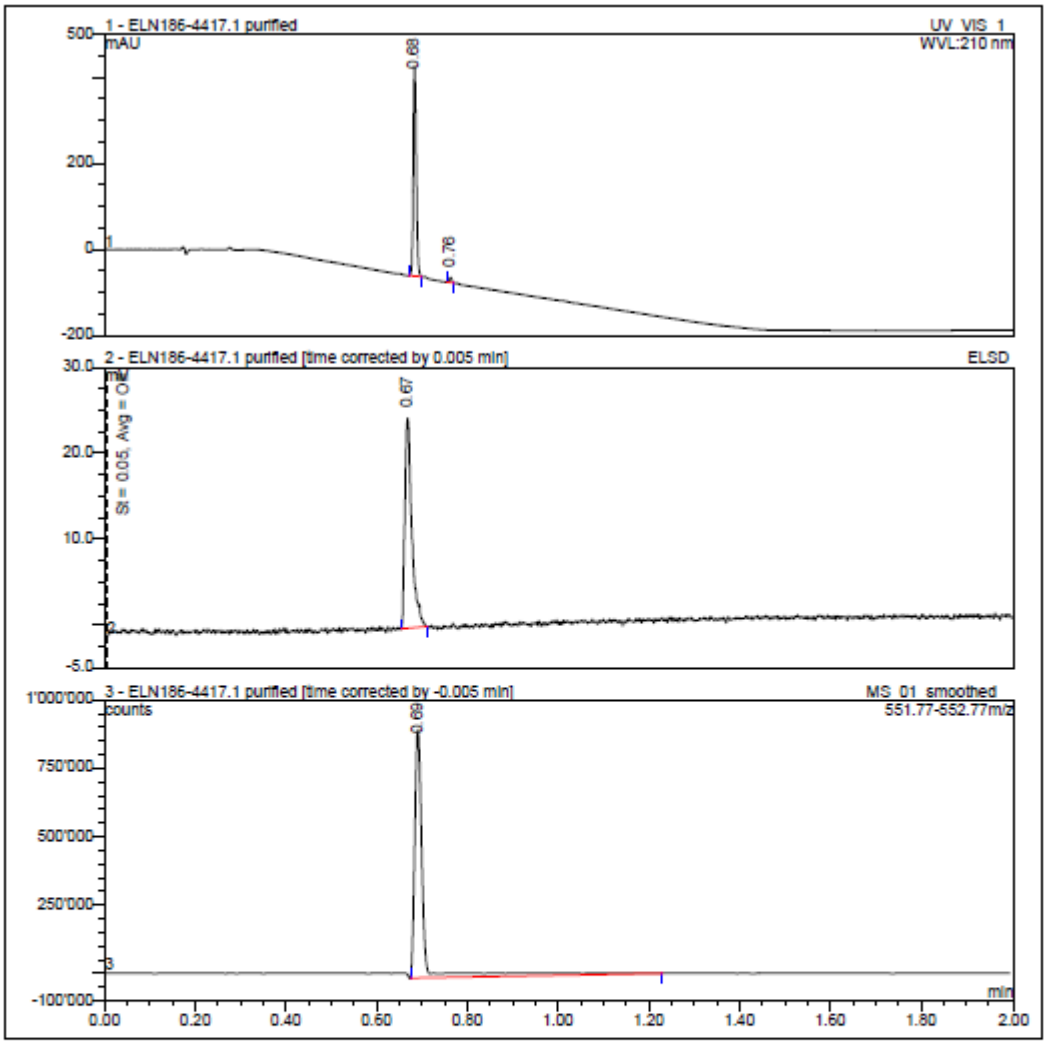


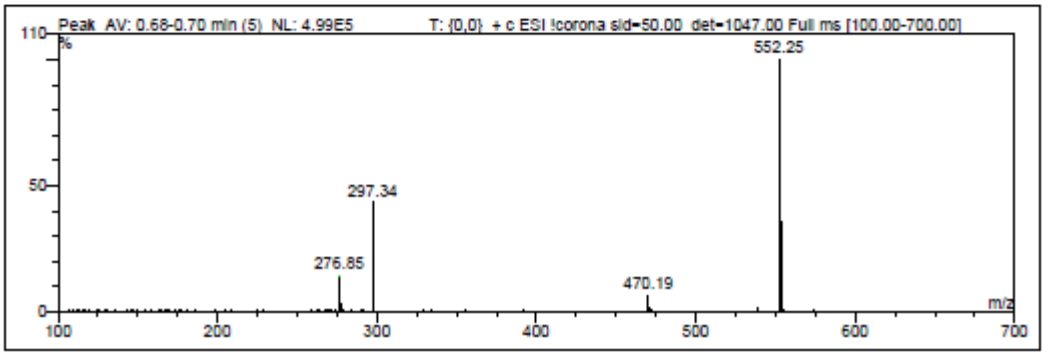
Compound **21d**:





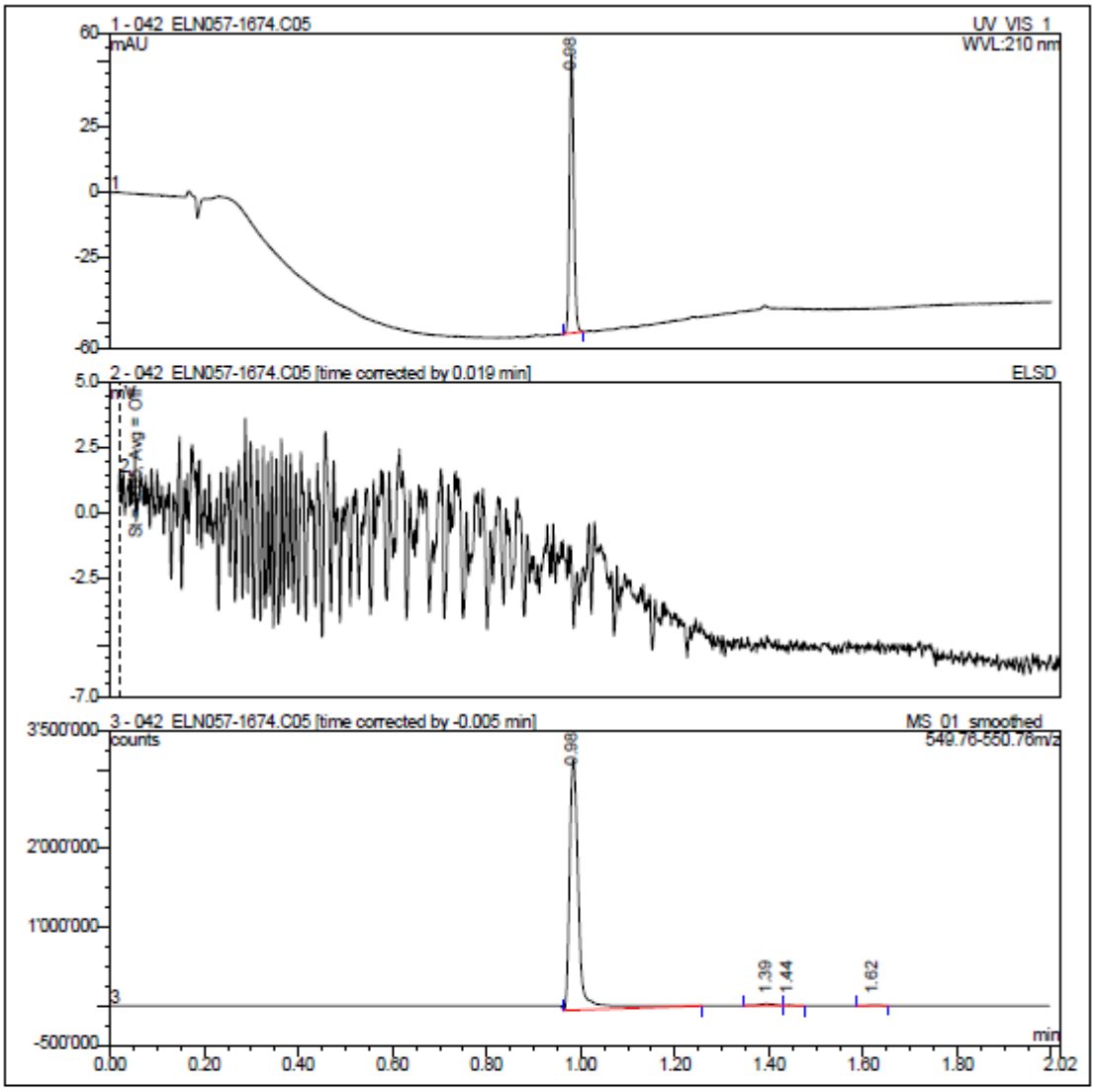
Compound **21e**:

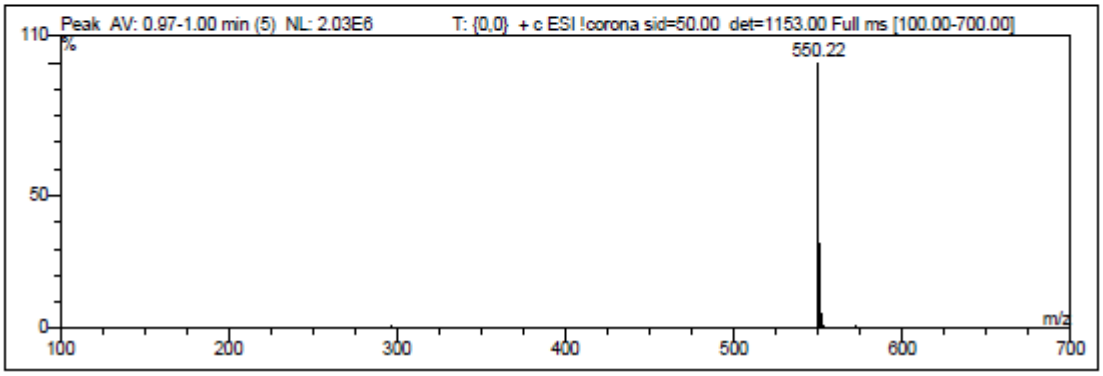




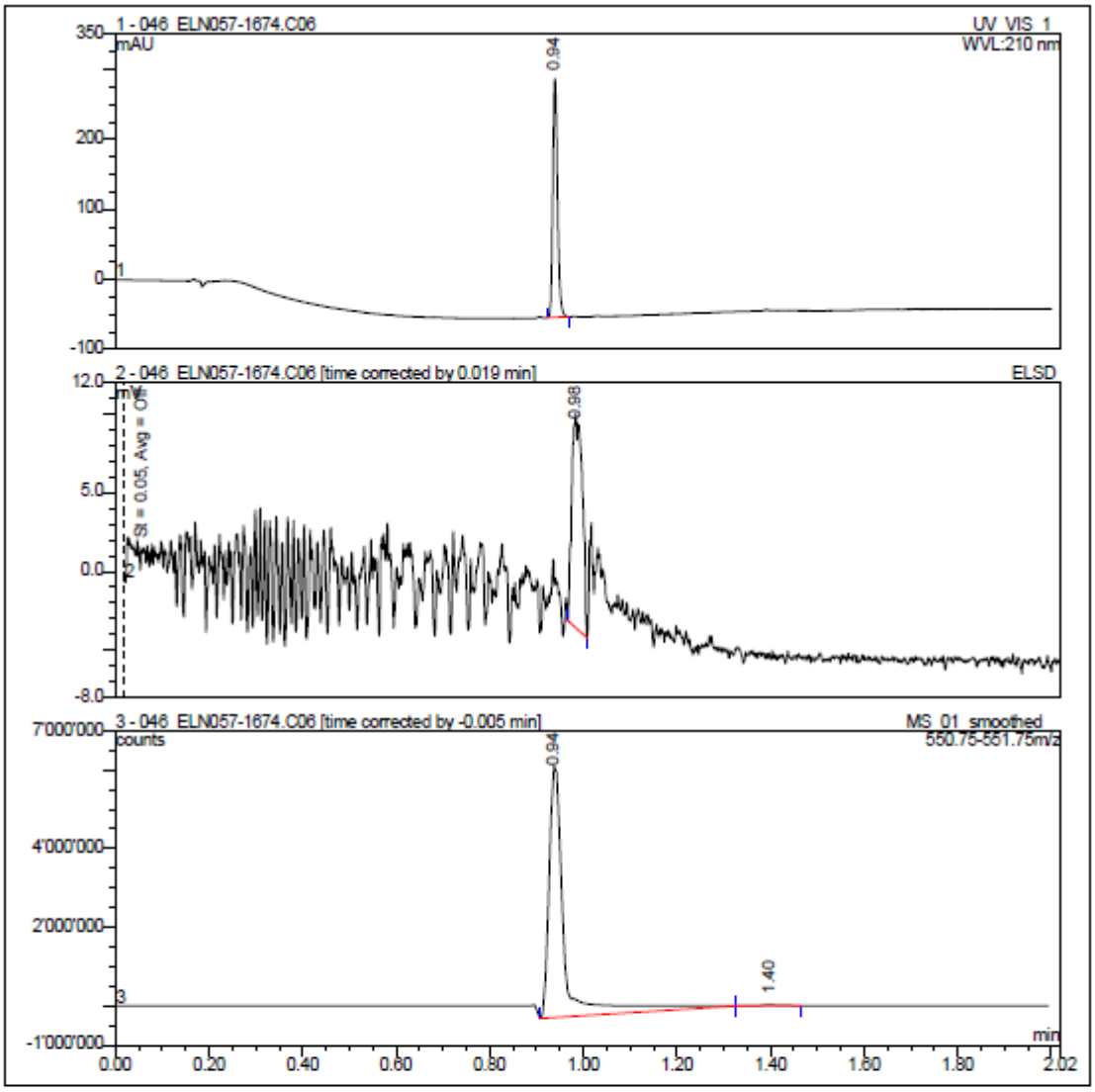
Peak No. UV_VIS_1	Ret.Time UV_VIS_1 min	Area UV_VIS_1	Rel.Area UV_VIS_1 %	Mass 01 UV_VIS_1 amu	Mass 02 UV_VIS_1 amu	Mass 03 UV_VIS_1 amu	UV Match UV_VIS_1
1	0.68	3821	98.1	552.25	297.34	553.24	999
2	0.76	73	1.9	473.38	107.47	104.04	995
Total:			100.0				

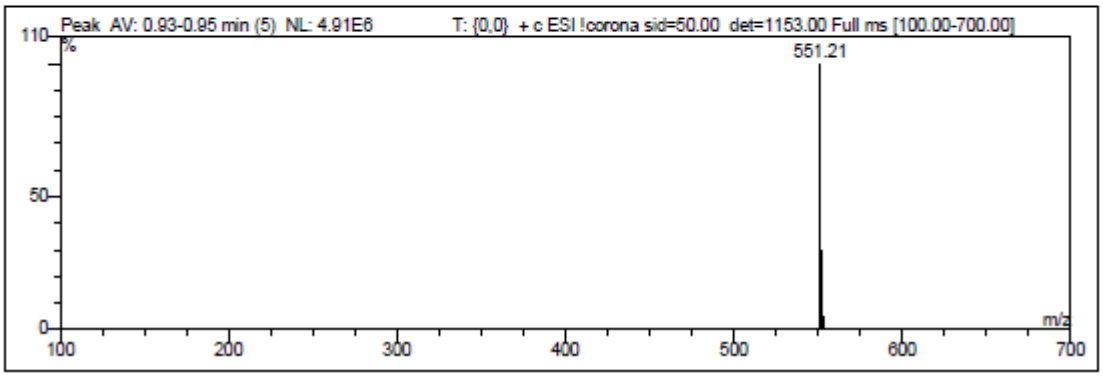
Compound **21f**:



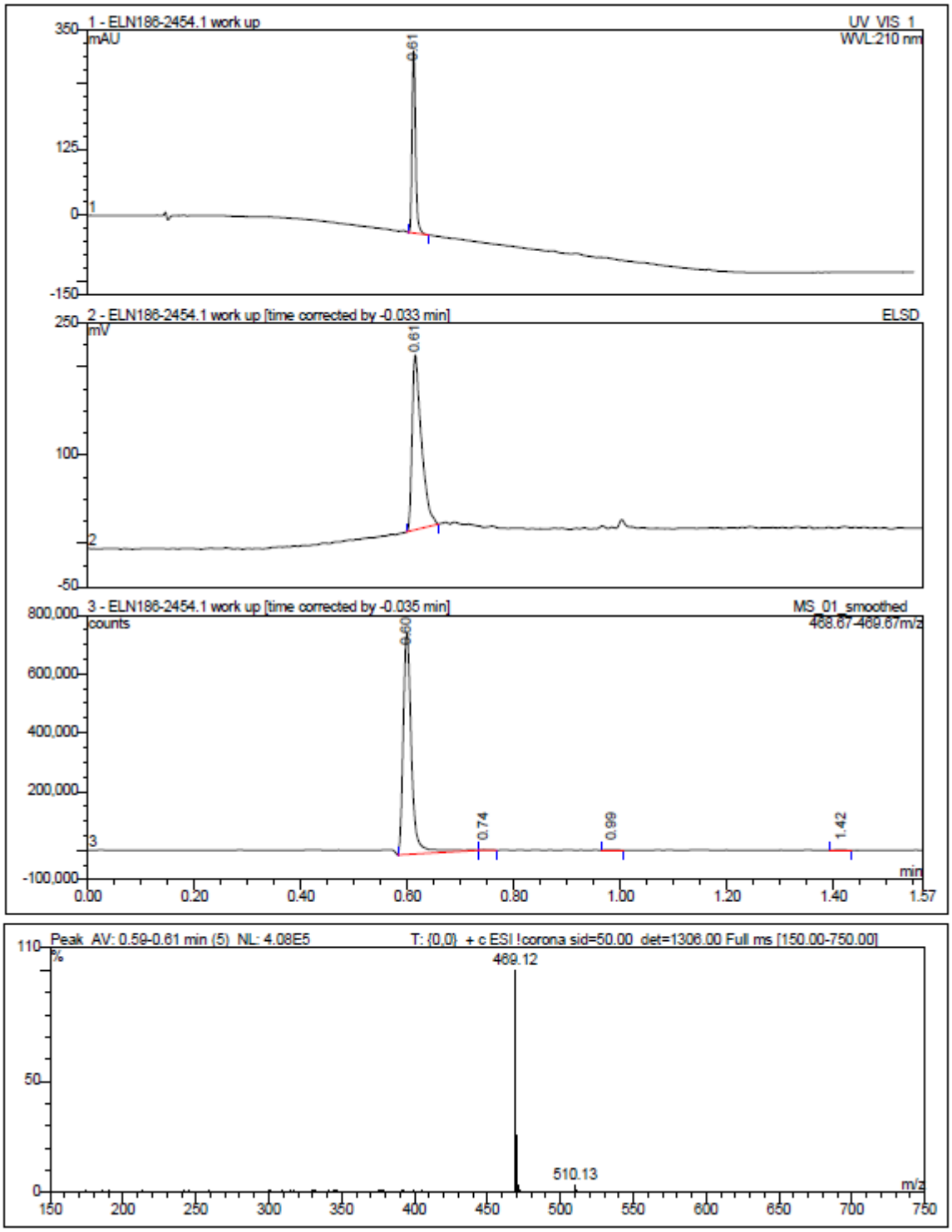


Compound **21g**:

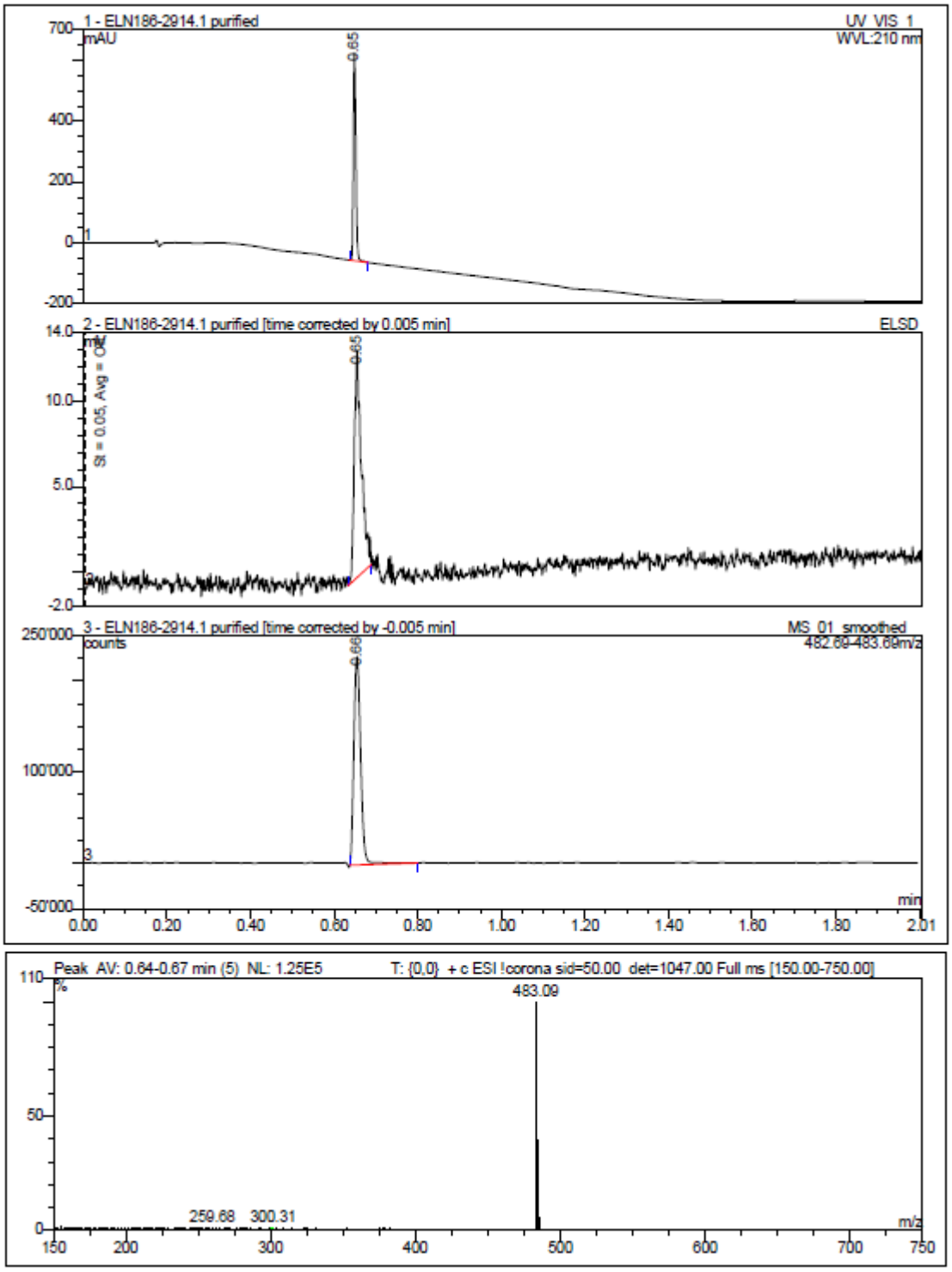




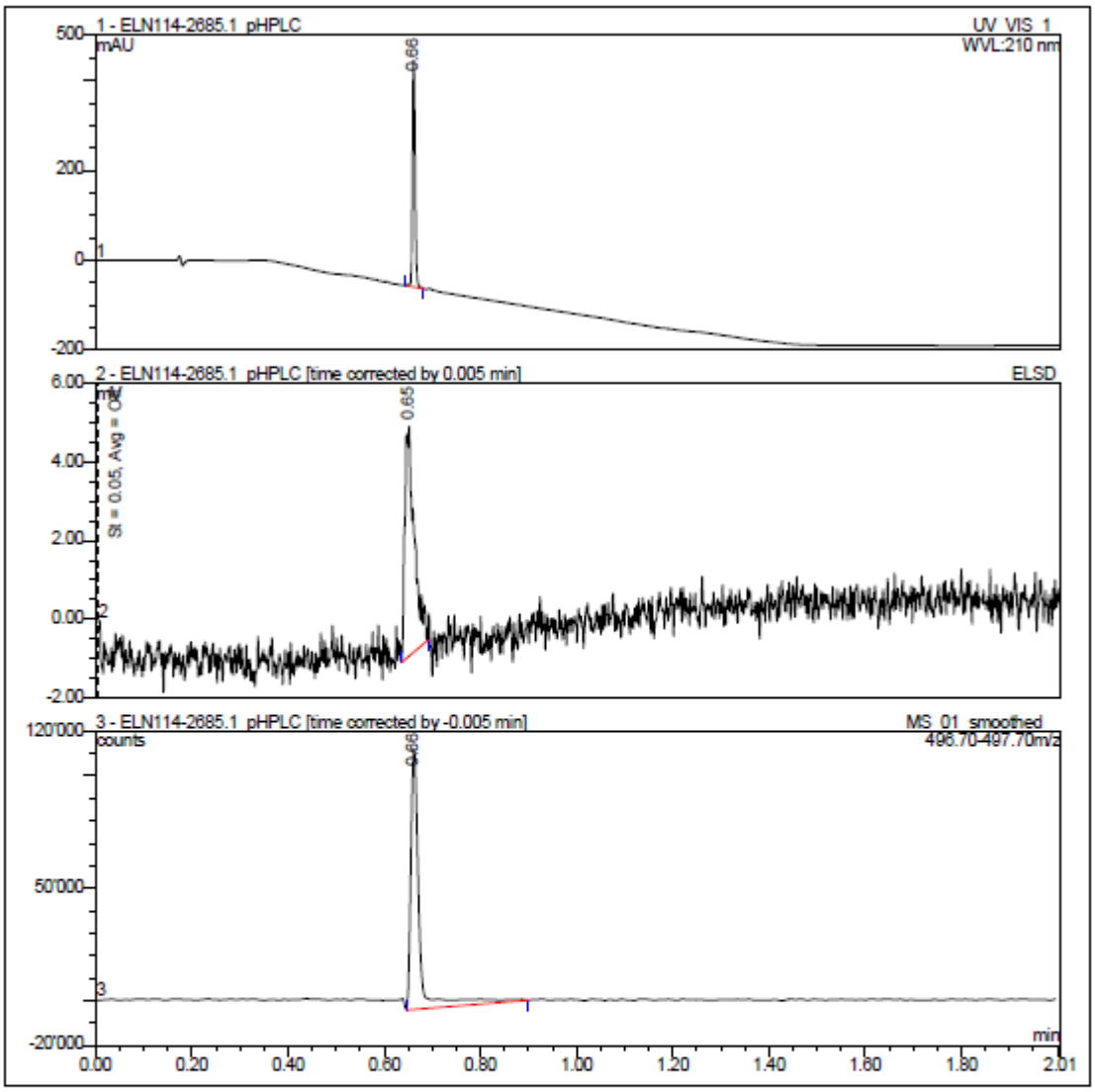
Compound **27**:

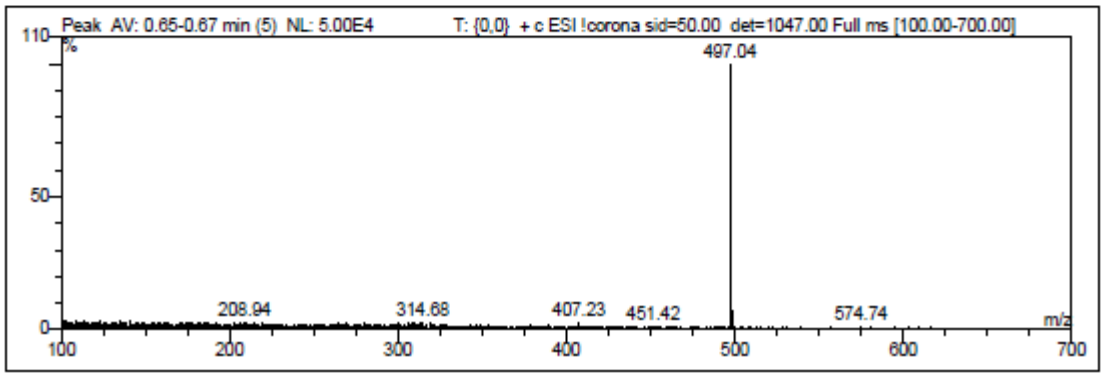

1 - ELN186-2454.1 work up
UV_VIS_1
mAU
WVL:210 nm
0.61
2 - ELN186-2454.1 work up [time corrected by -0.033 min]
ELSD
mV
3 - ELN186-2454.1 work up [time corrected by -0.035 min]
MS_01_smoothed
counts
468.67-469.67m/z
0.74
0.99
1.42
min
Peak AV: 0.59-0.61 min (5) NL: 4.08E5
T: {0,0} + c ESI !corona sid=50.00 det=1306.00 Full ms [150.00-750.00]
469.12
510.13
m/z

Compound **28a**:

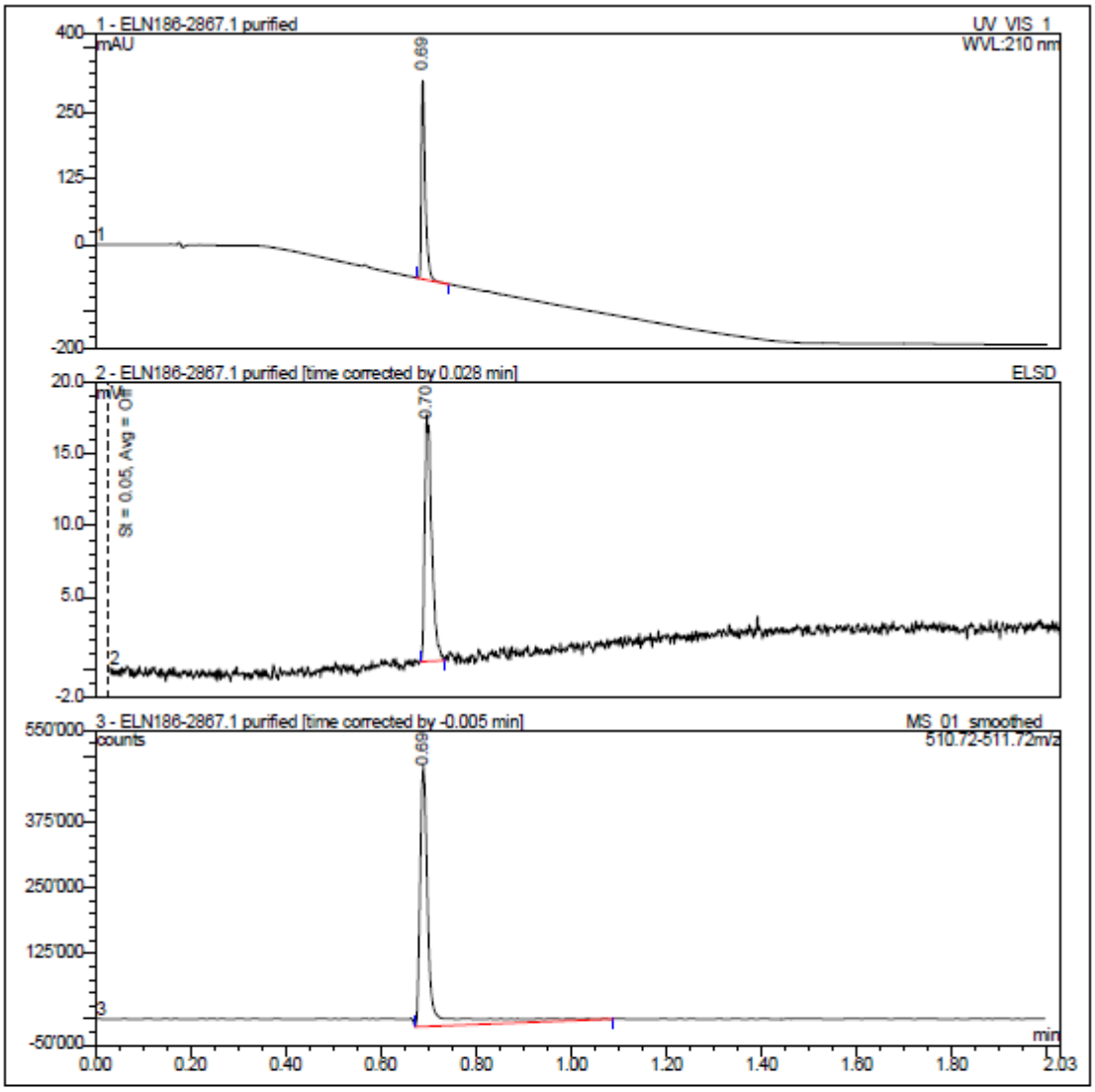


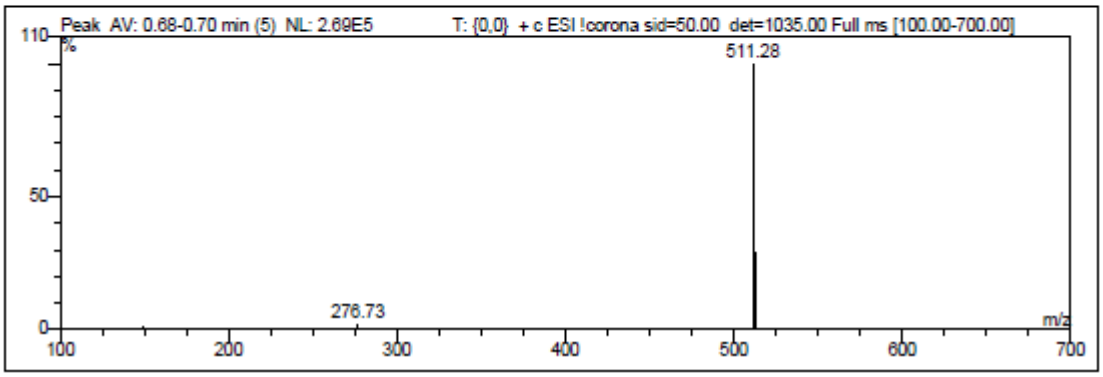
Compound **28b**:



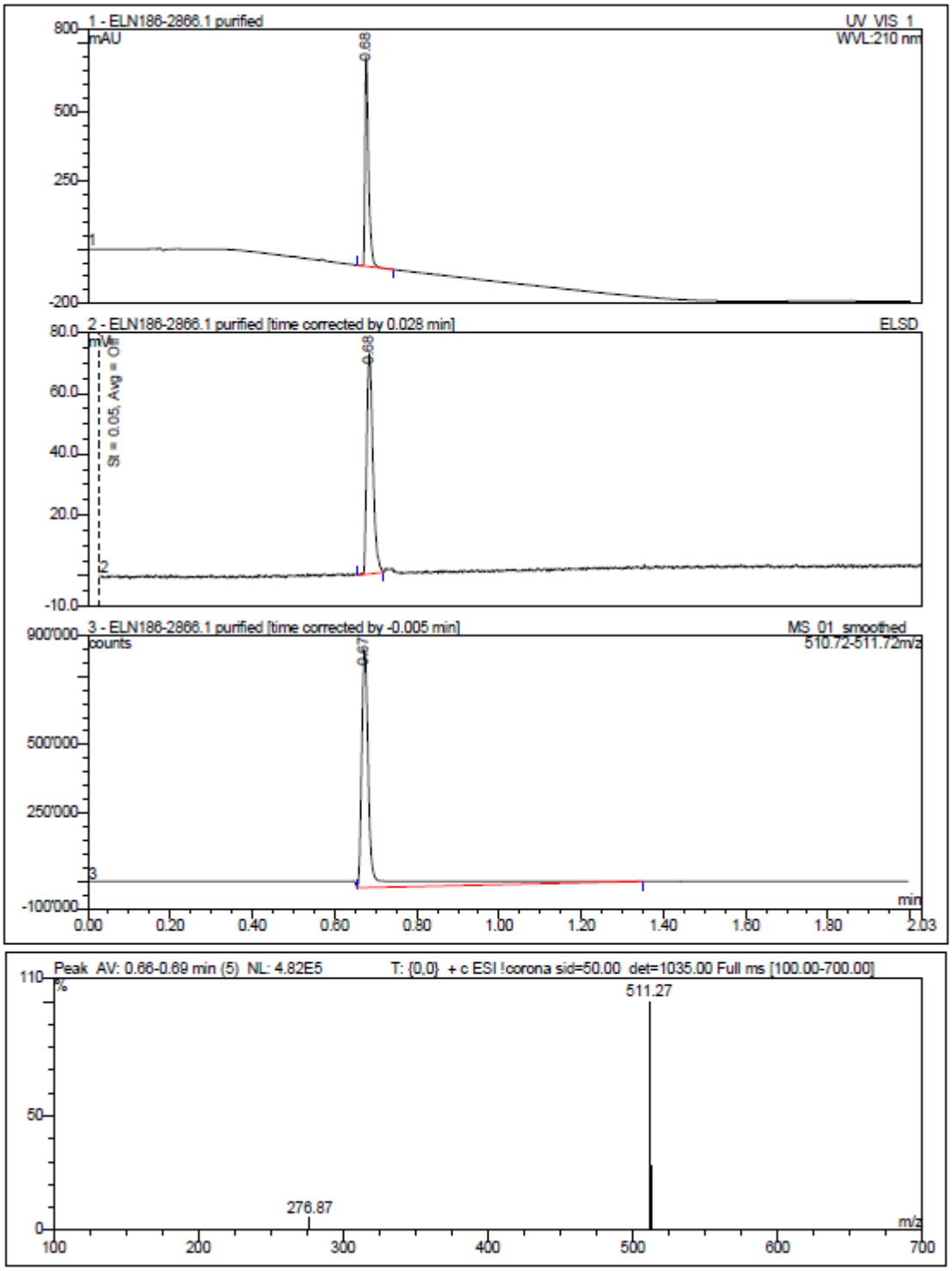


Compound **28c**:

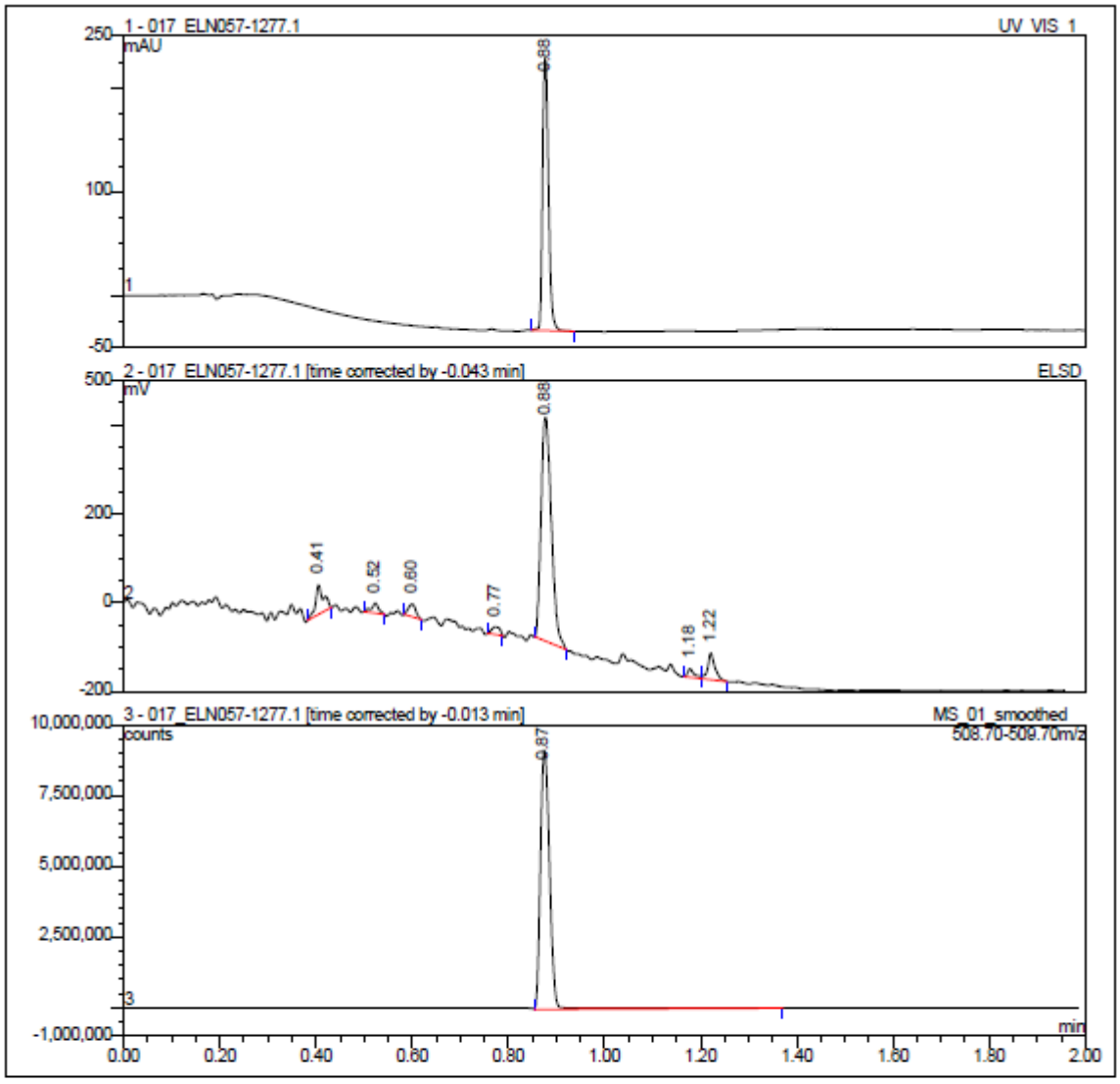


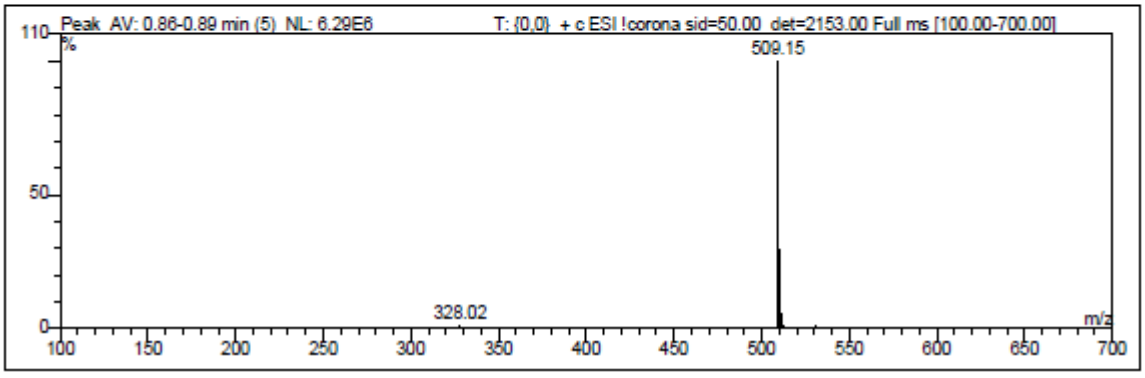


Compound **28d**:



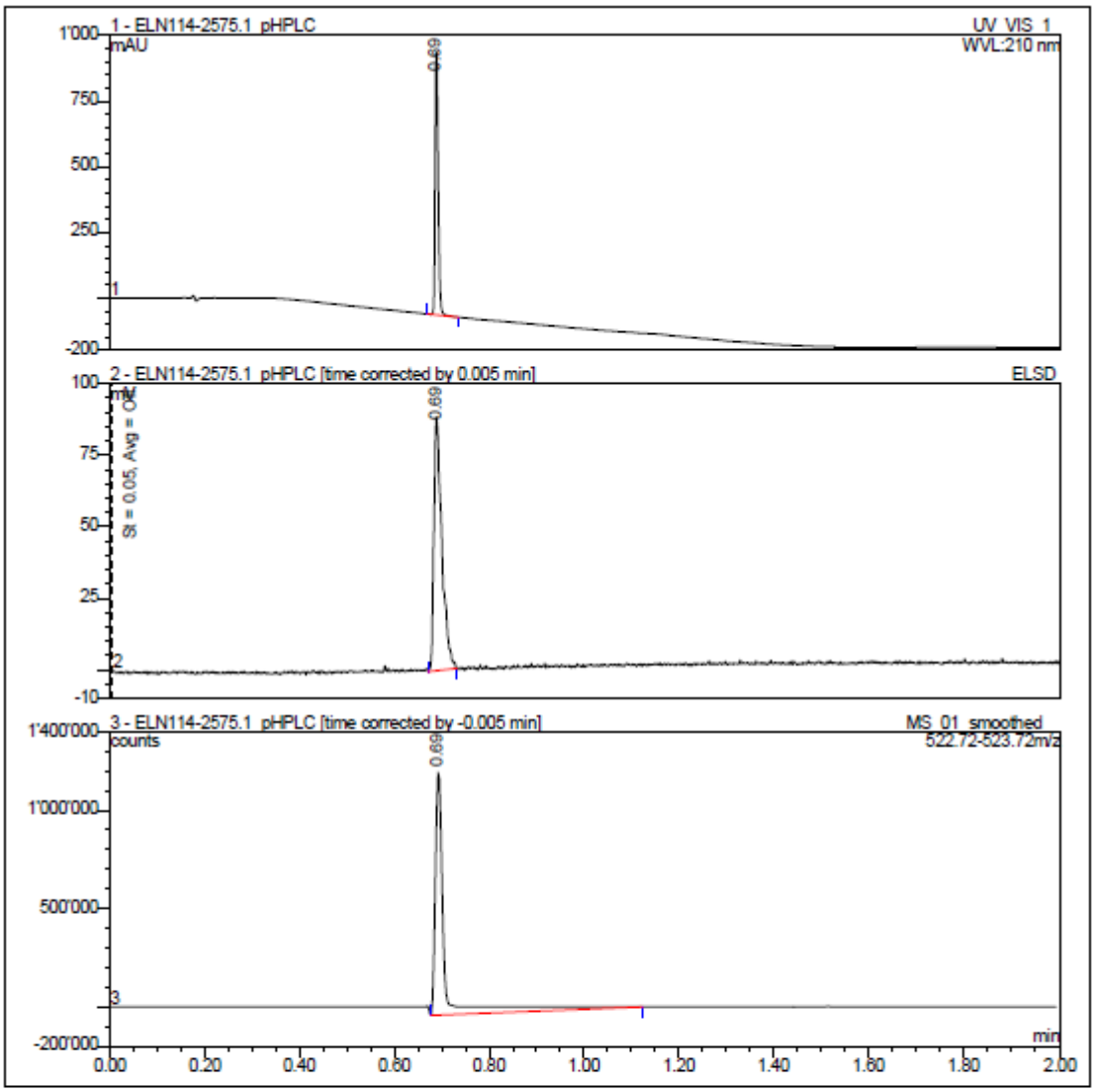
Compound **28e**:

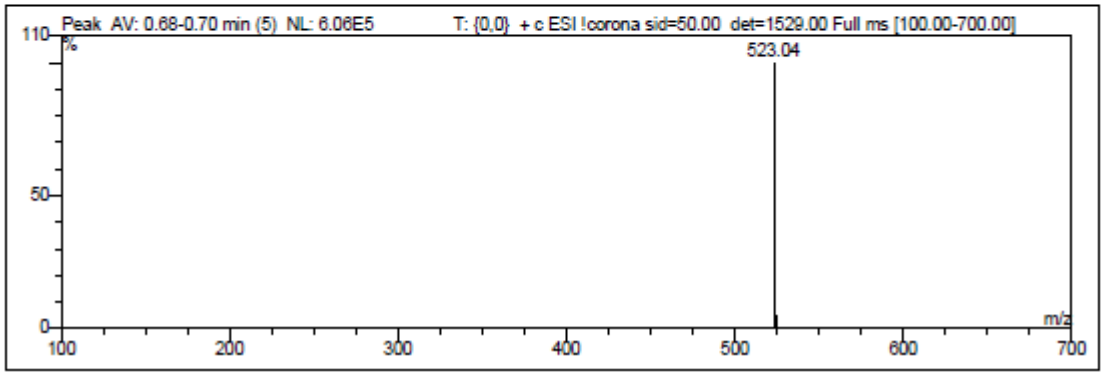




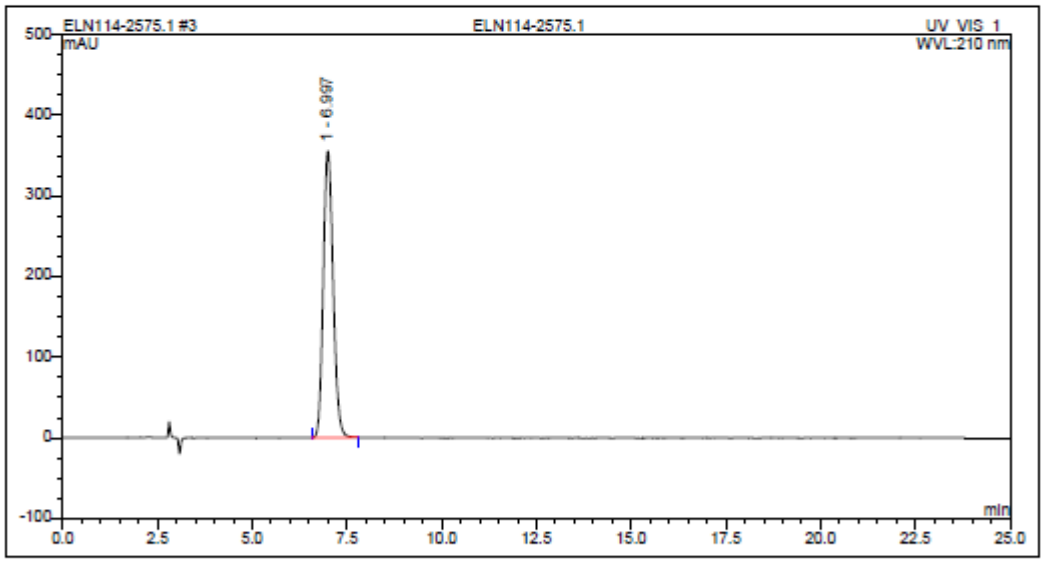
Compound **28f**

Method A



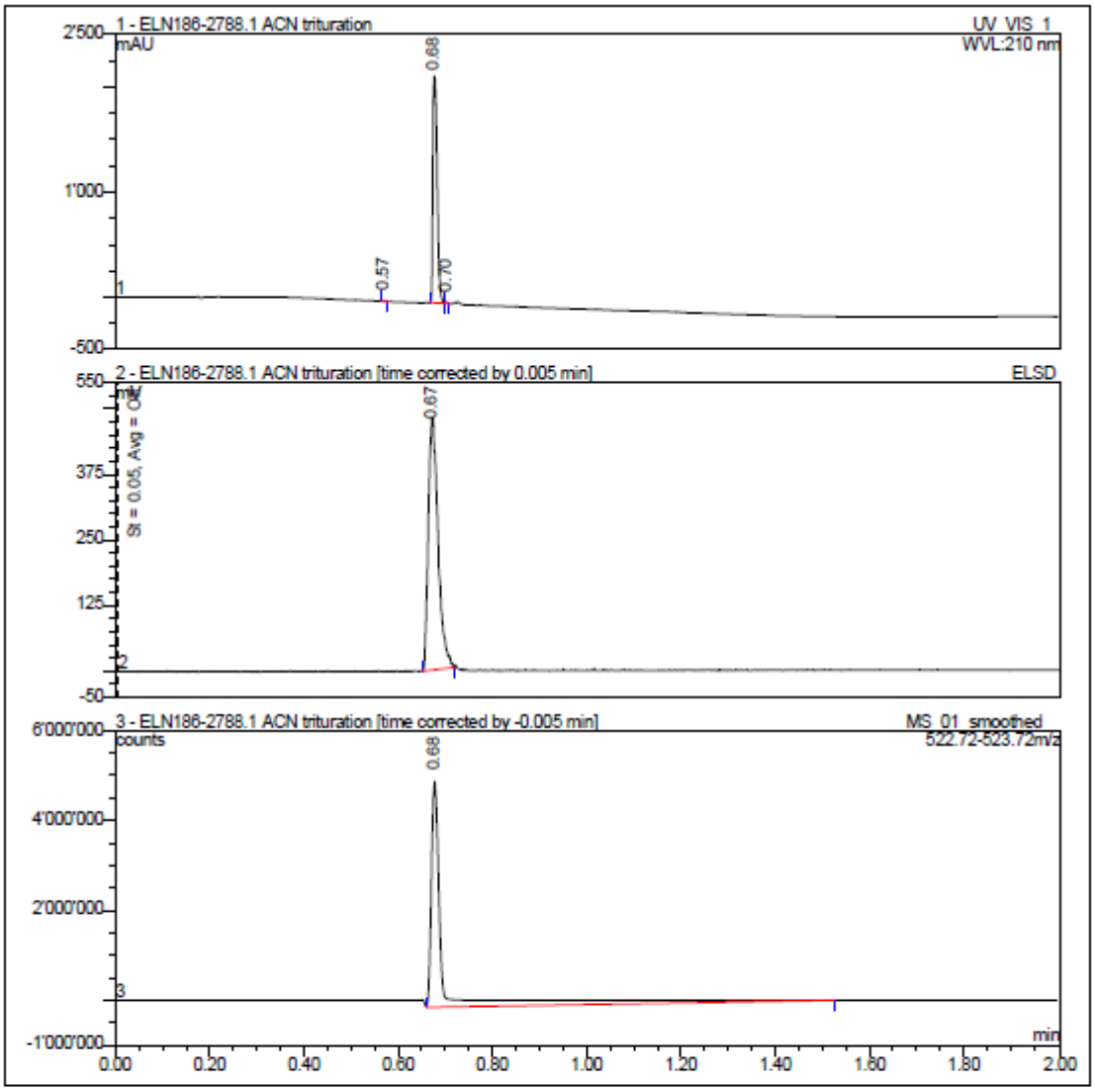


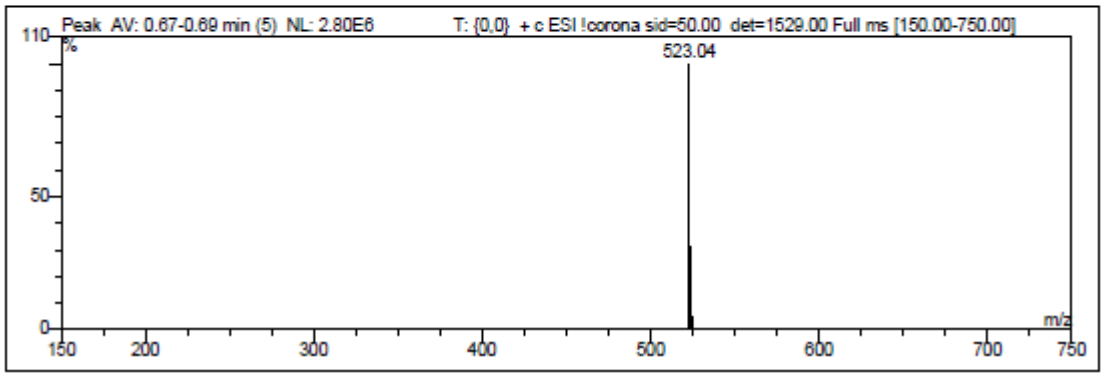
Sample ID:	78d6da9a-9f8c-11e6-ba18-0022191a3ba4		
Sample Name:	ELN114-2575.1	*Date:*	31.10.16
Sample Number:	3		
Time Base:	U3000		
Datasource Name:	LCMSCHEM03_local		
Sequence Name:	ELN114-2575.1		
Sequence Dir:	Data\erharmi1\Samples\CXCR7		
Quantif. Method:	default		
Injection Volume:	2.00 ul *Comment:* 1.2mg/mL EtOH		
Eluent A:	10.0 % Heptane 0.05% DEA		
Eluent B:	90.0 % Ethanol 0.05% DEA		
Flow:	1.200 ml/min		
Column:	Chiralpak IC 250x4.6mm ID, 5um		
Serial number:	IC00CE-OC010		
Temperature:	25.0 °C		
Detection:	210 nm		



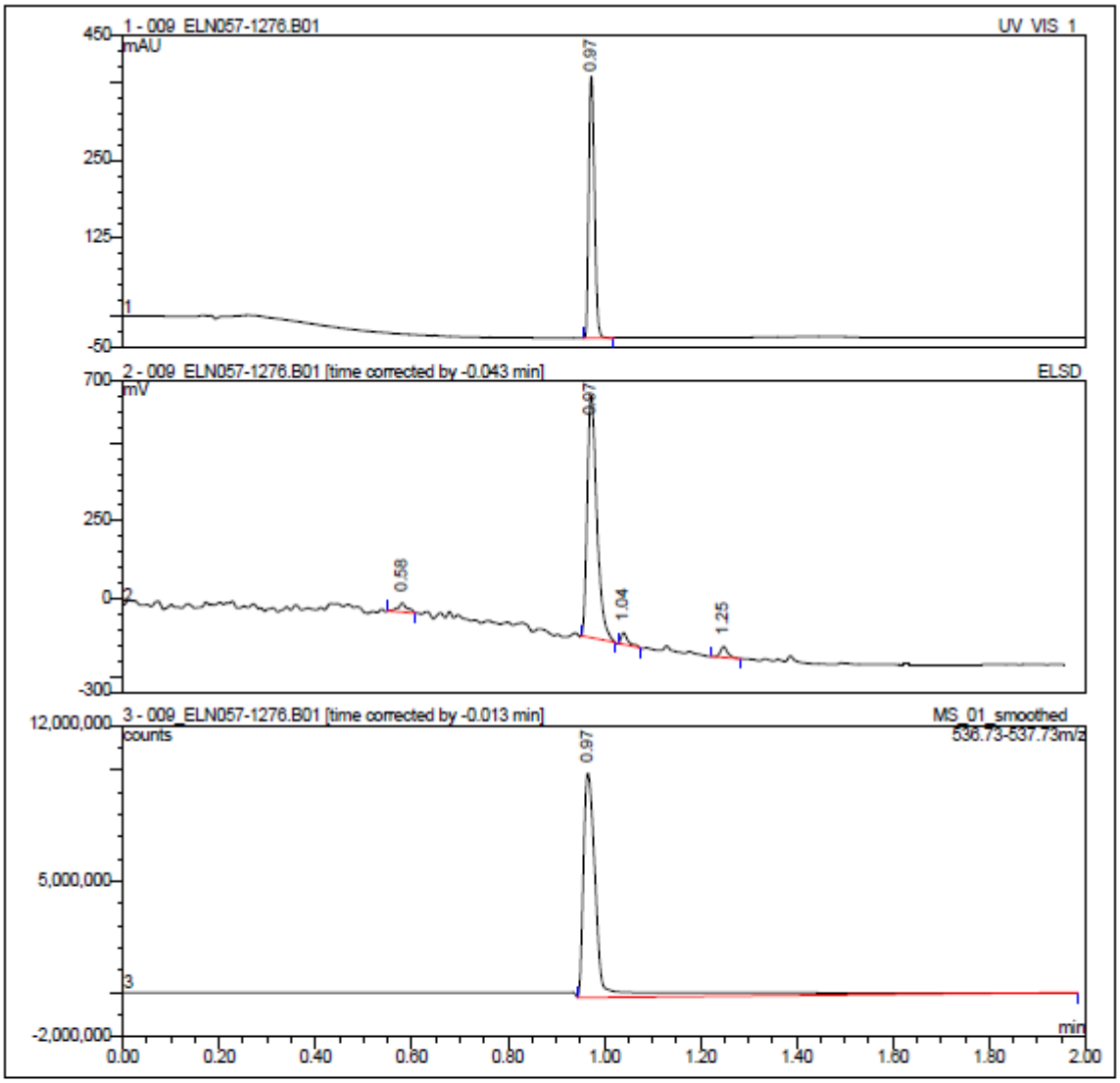
Peak No. UV_VIS_1	Ret.Time UV_VIS_1 min	Height UV_VIS_1 mAU	Rel.Area UV_VIS_1 %	Area UV_VIS_1 mAU*min	Resolution UV_VIS_1	Asymmetry UV_VIS_1	Plates UV_VIS_1
1	7.0	355	100.0	107.276	n.a.	1.1	3463
Total:			100.0	107.3			

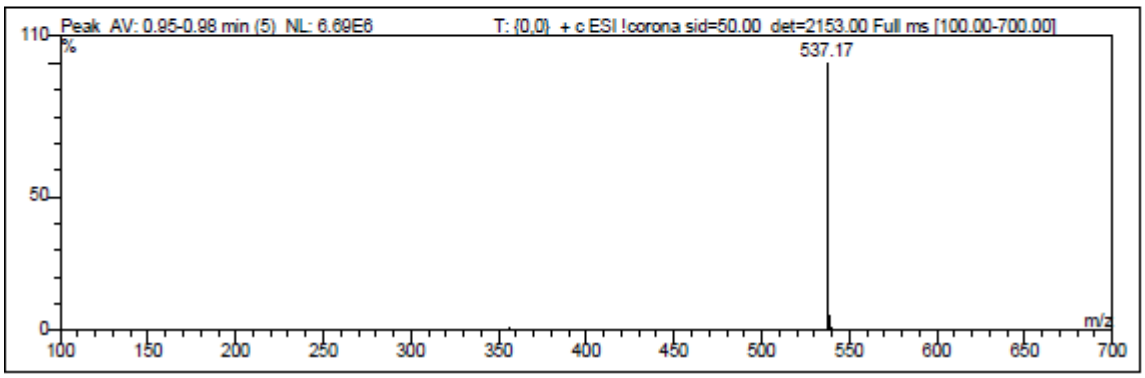
Compound **28g**:



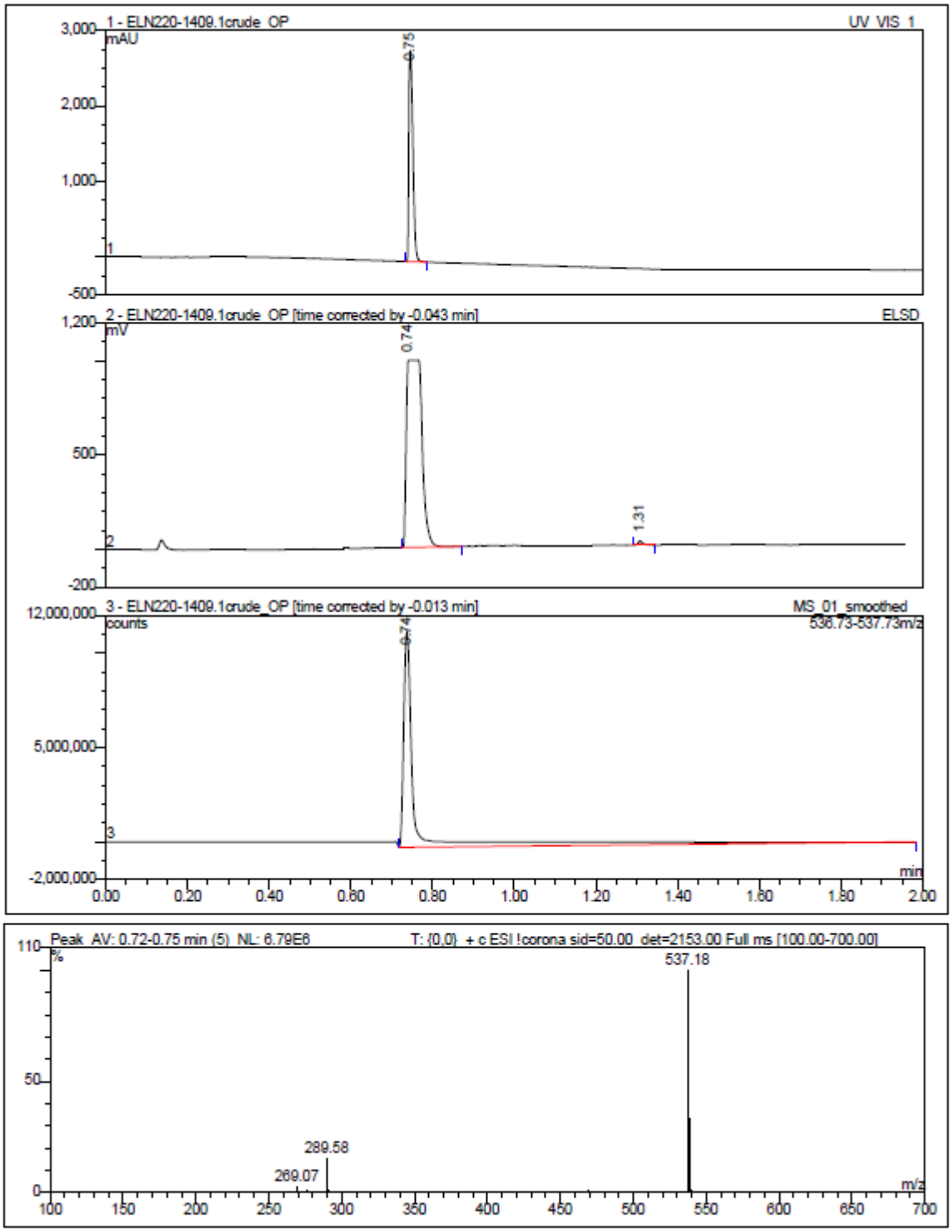


Compound **28h**:

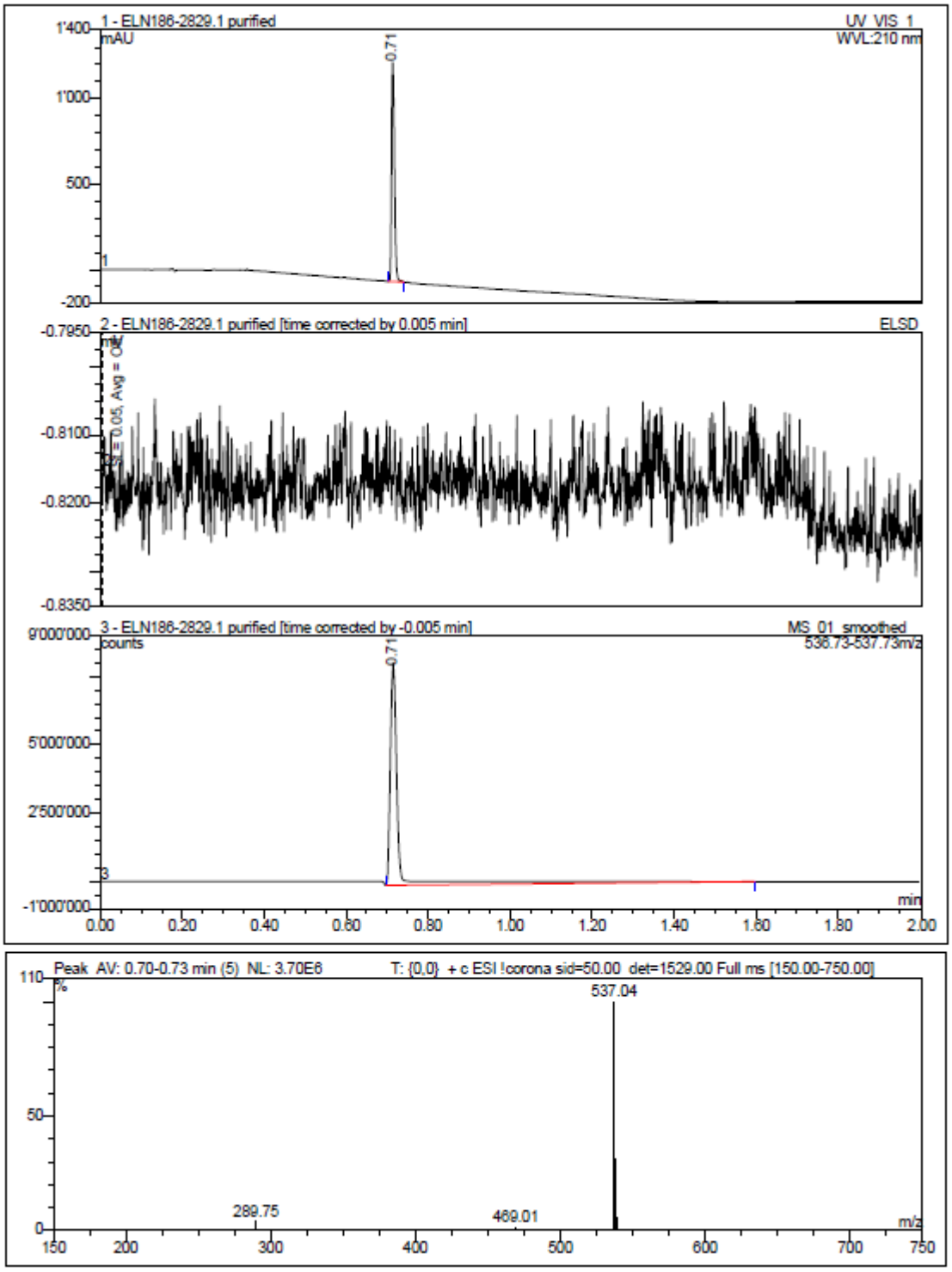




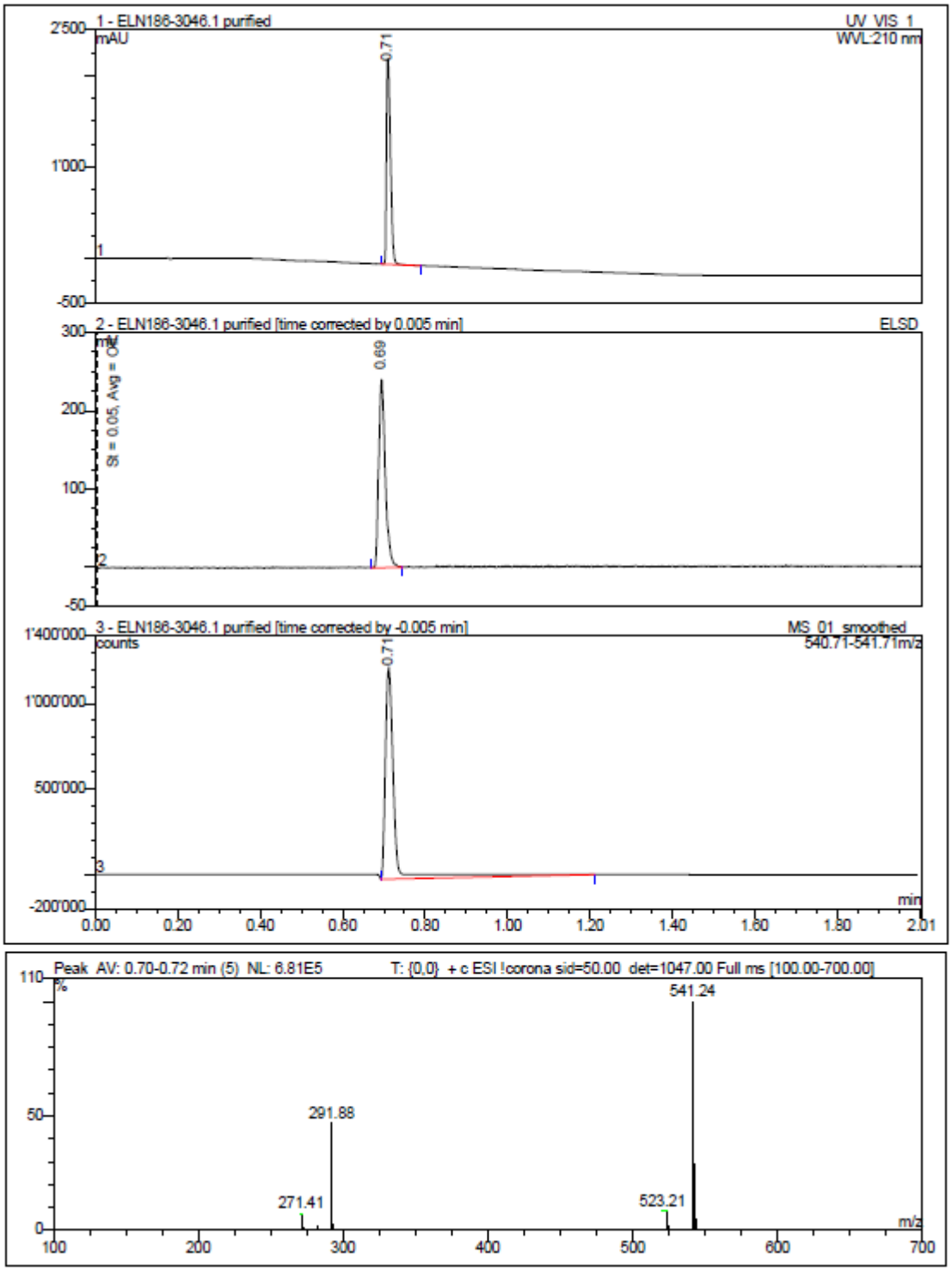
Compound **28i**:



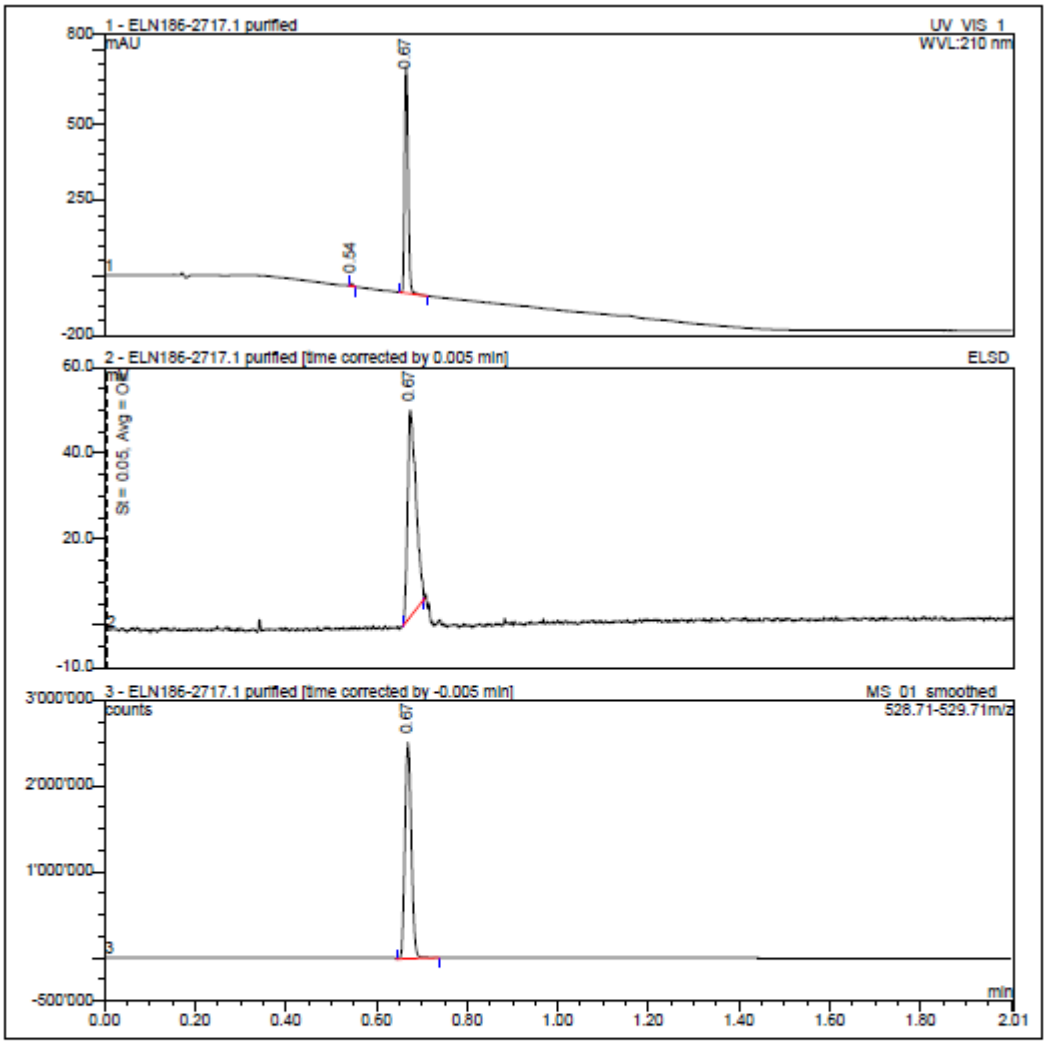
Compound **28j**:

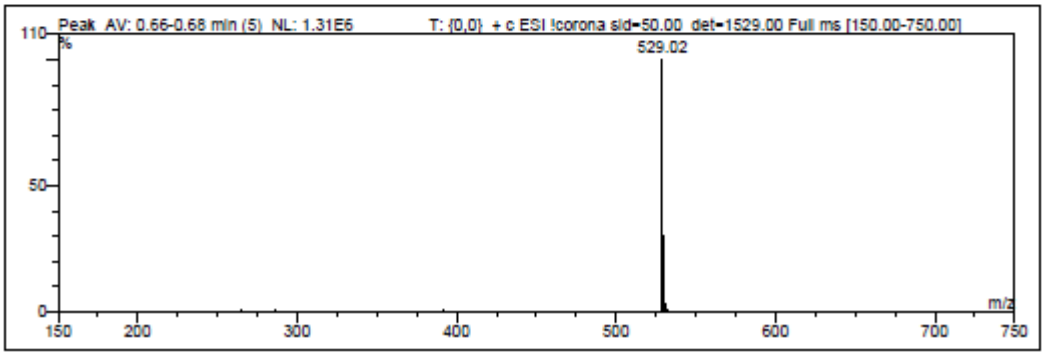


Compound **28k**:

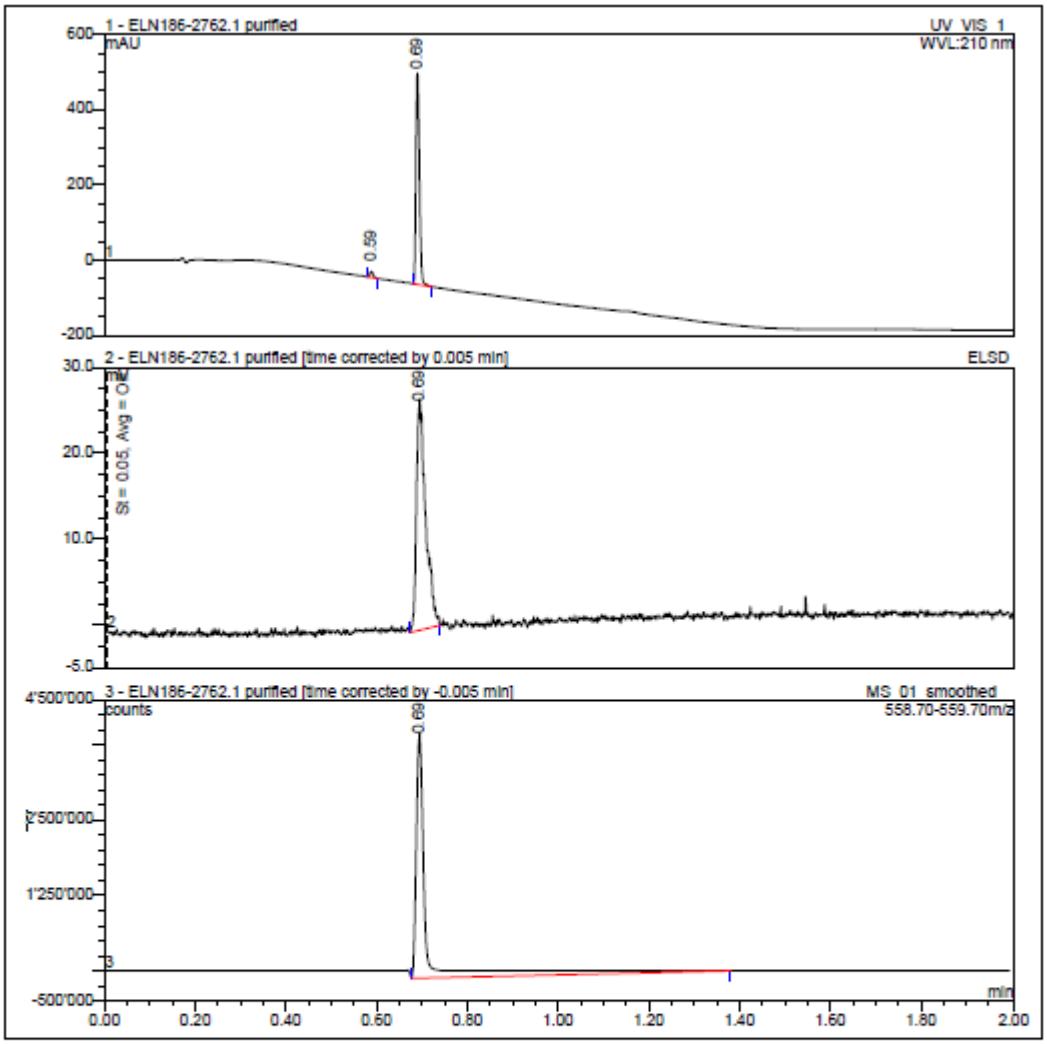


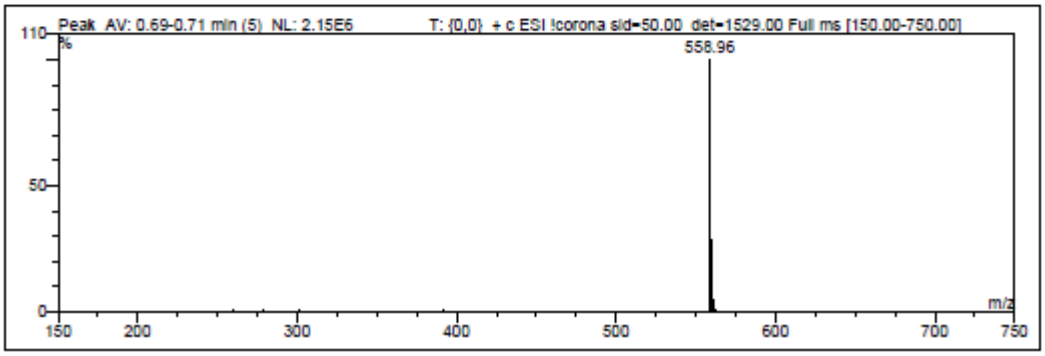
Compound **28l**:





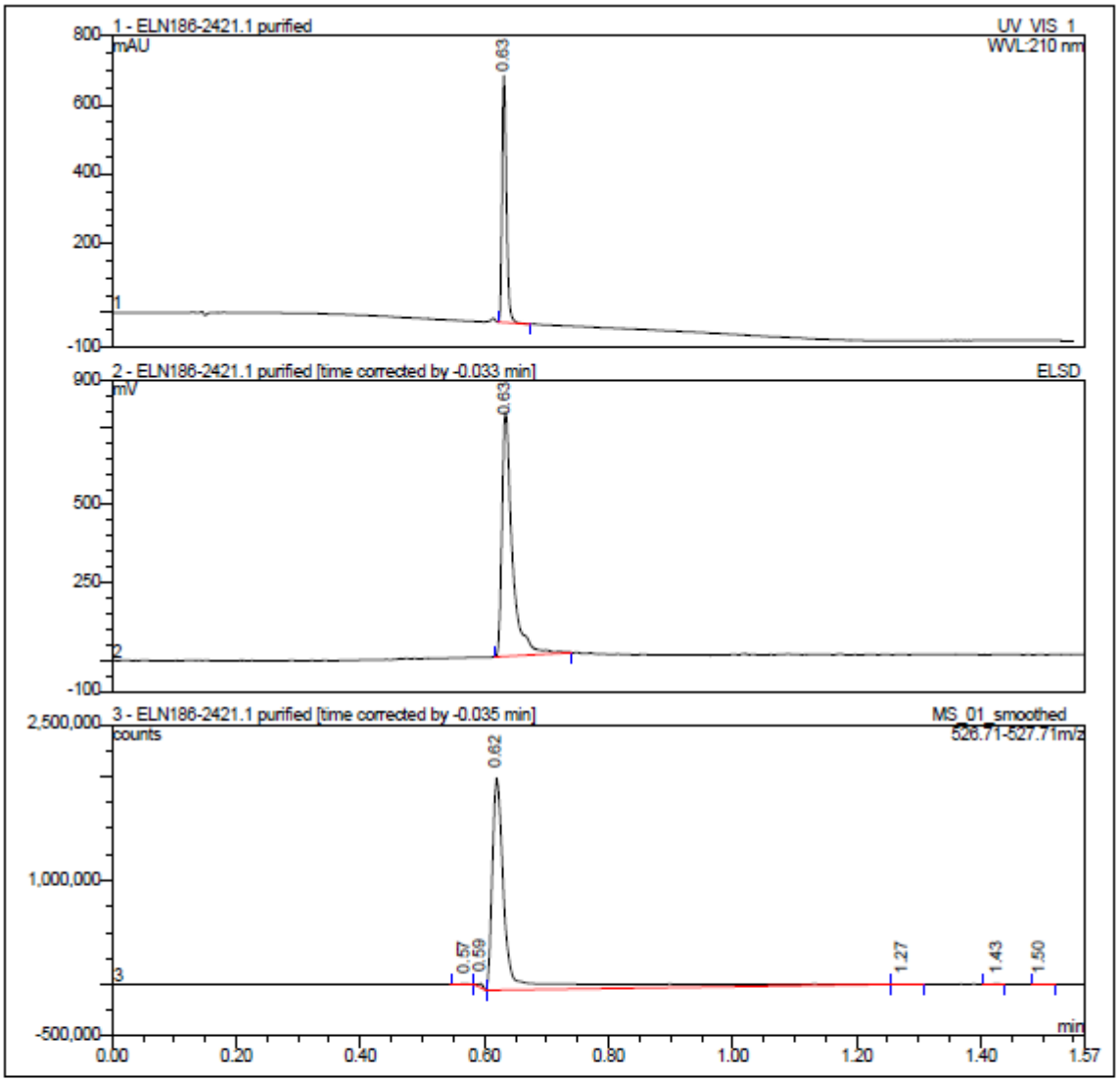
Compound **28m:**

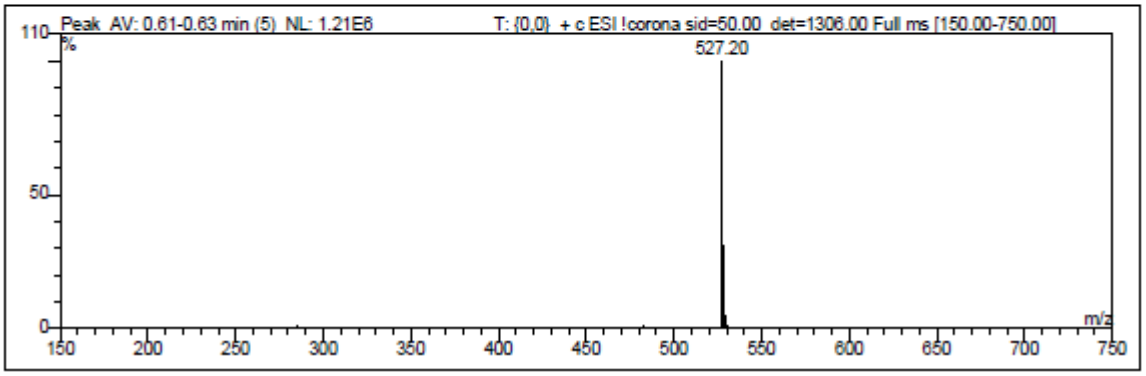




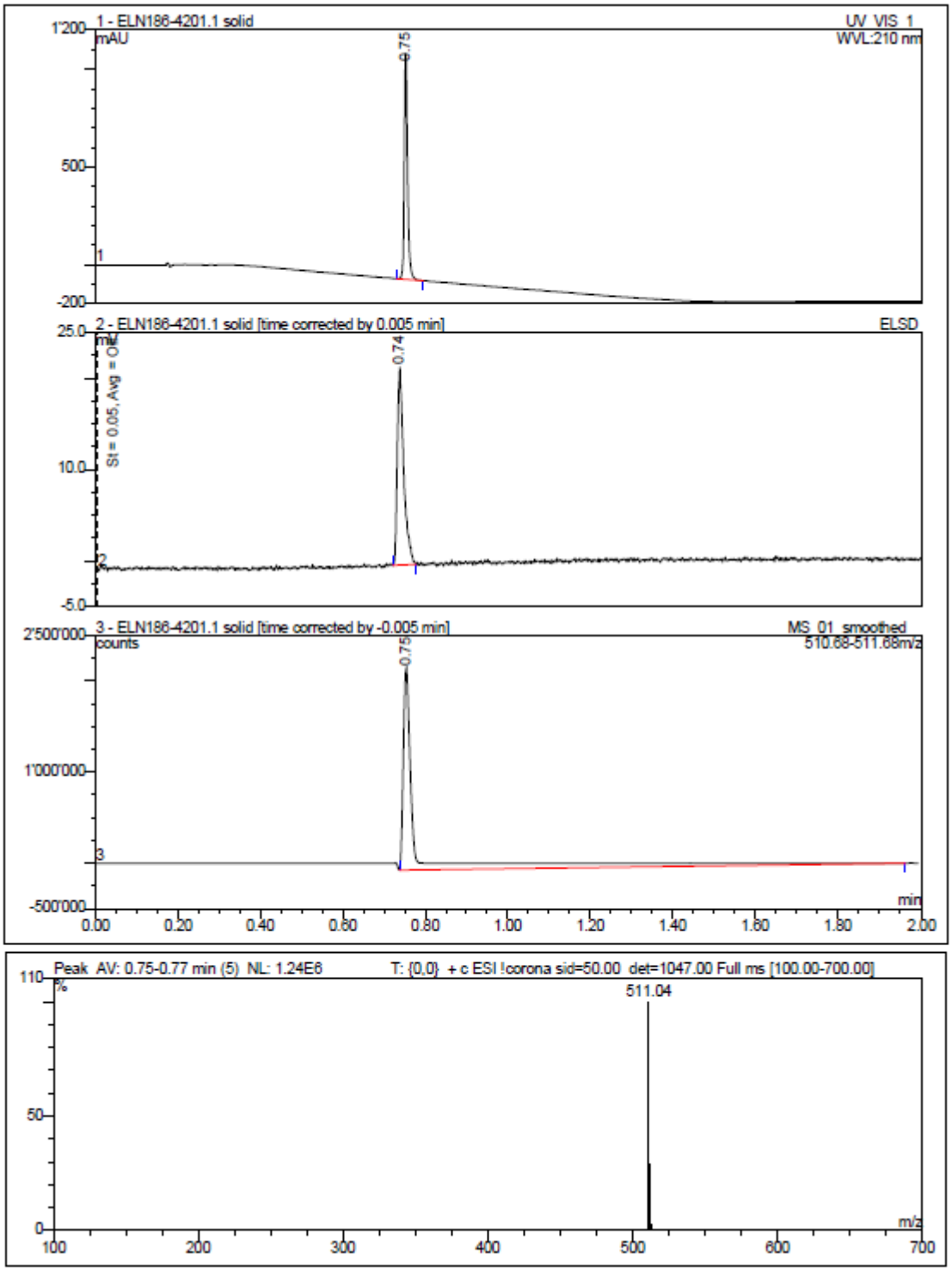
Peak No. UV_VIS_2	Ret.Time UV_VIS_2 min	Area UV_VIS_2	Rel.Area UV_VIS_2 %	Mass 01 UV_VIS_2 amu	Mass 02 UV_VIS_2 amu	Mass 03 UV_VIS_2 amu	UV Match UV_VIS_2
1	0.59	81	2.1	560.96	561.96	391.17	999
2	0.69	3679	97.9	558.96	559.98	560.95	1000
Total:			100.0				

Compound **28n**:

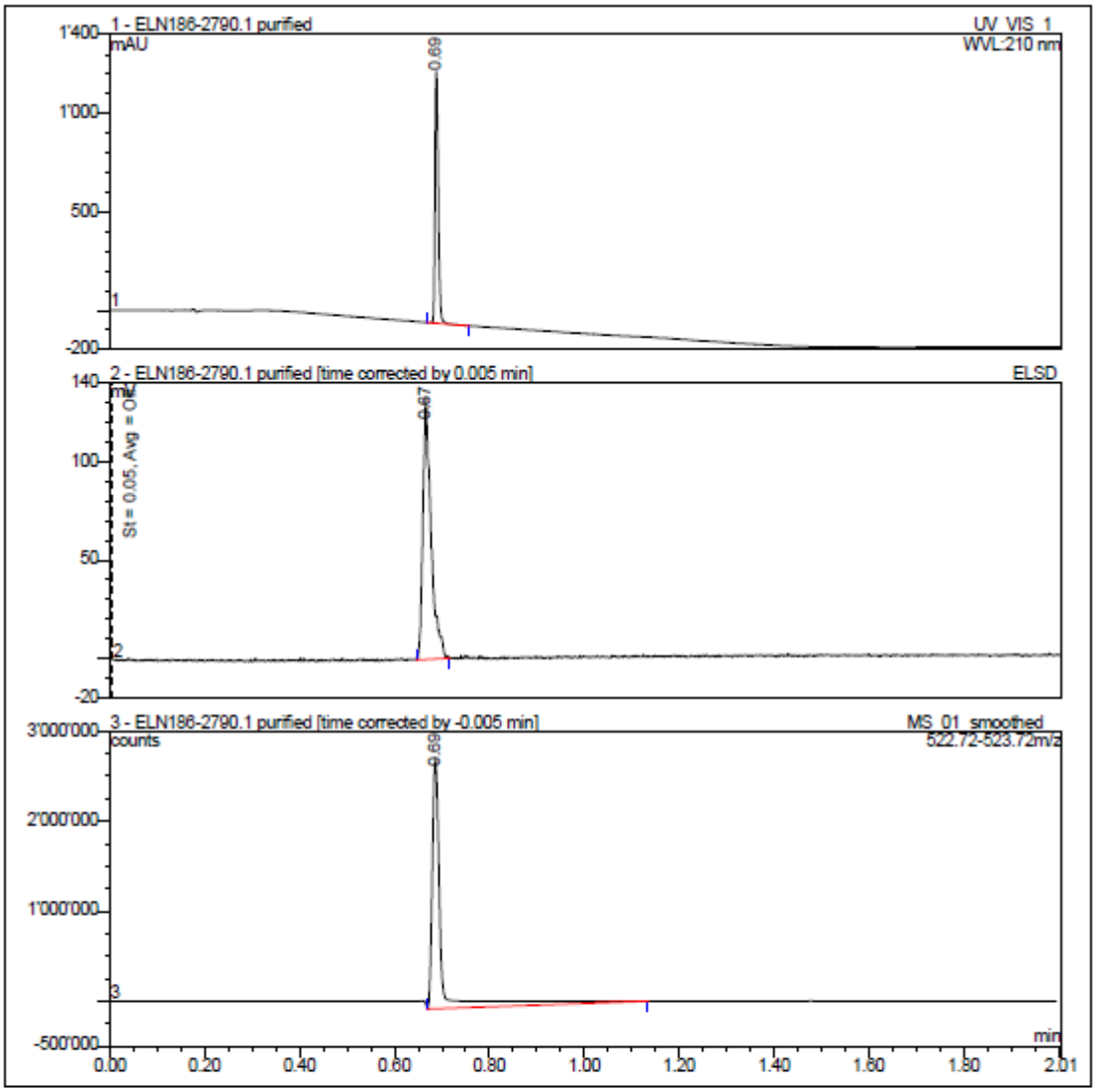


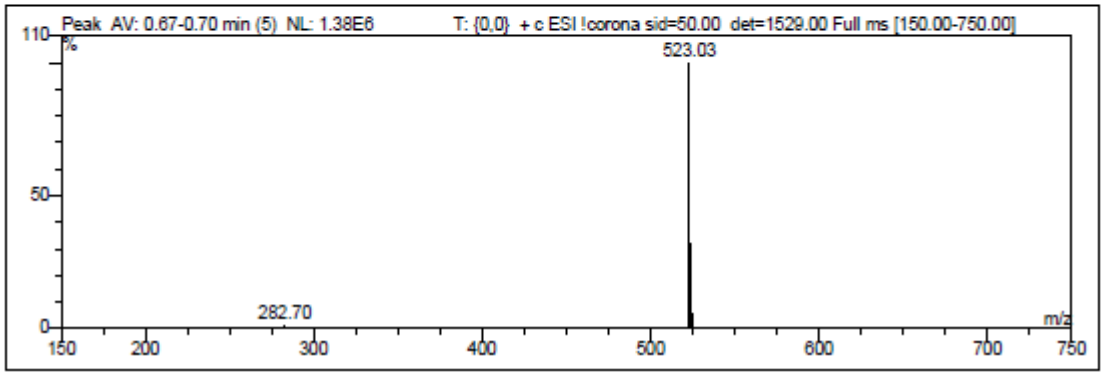


Compound **28o**:

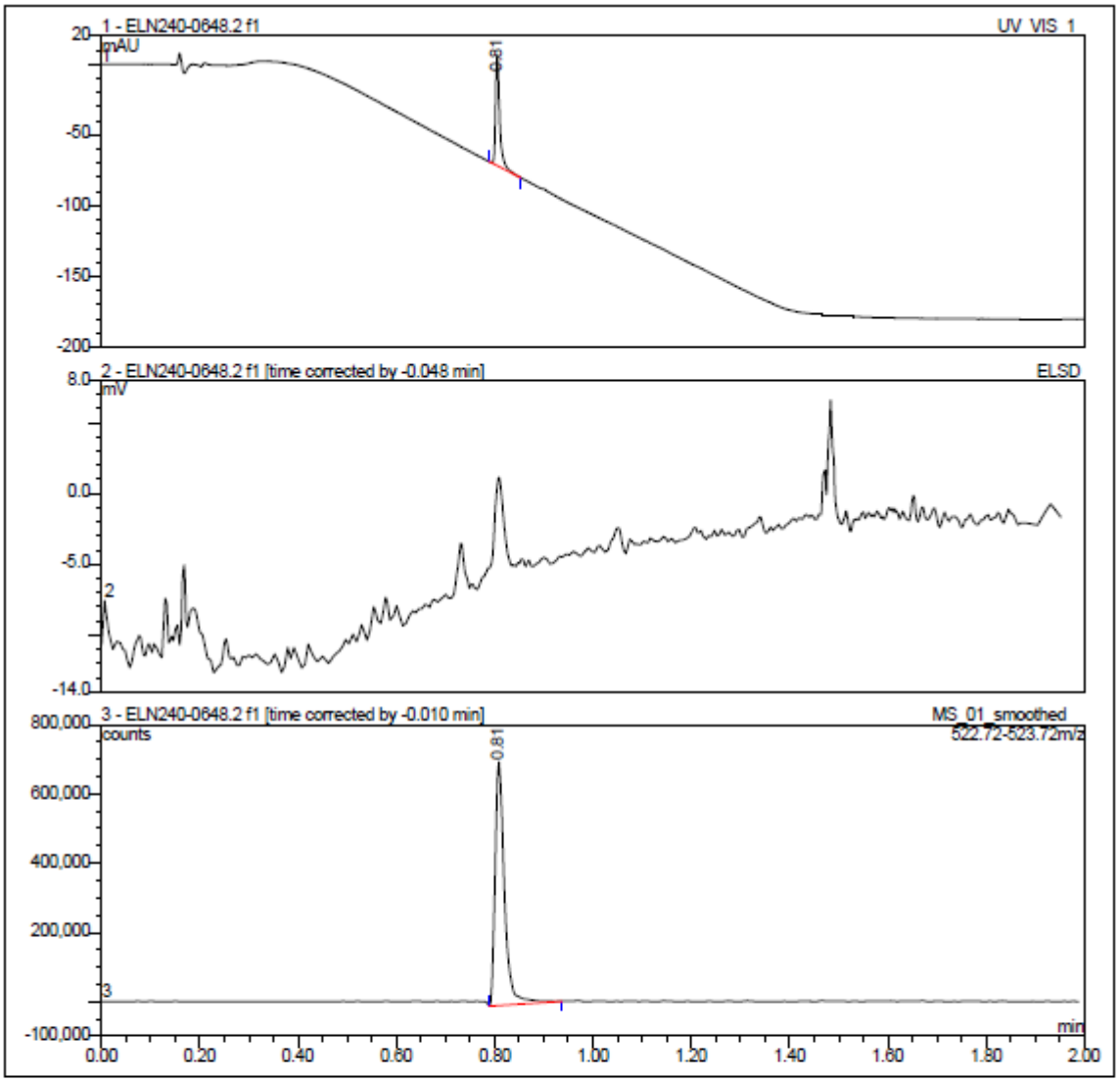


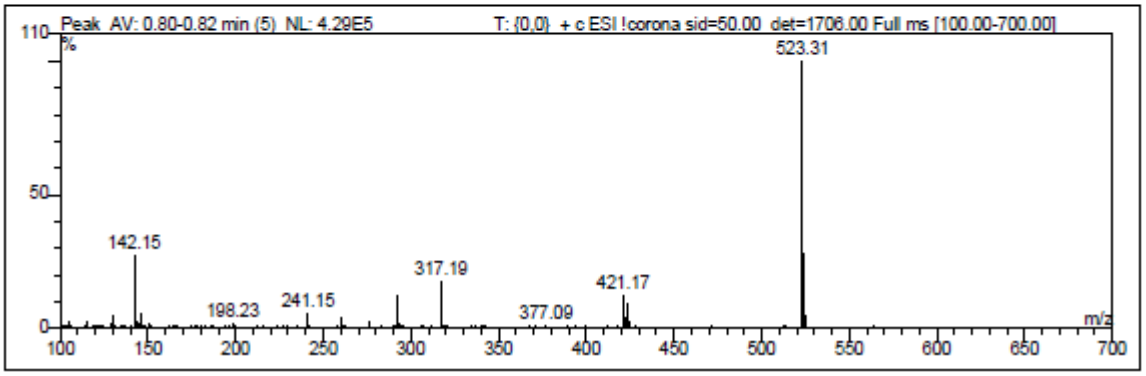
Compound **29**:


1 - ELN186-2790.1 purified
UV_VIS_1
mAU
WVL:210 nm
0.69
2 - ELN186-2790.1 purified [time corrected by 0.005 min]
ELSD
St = 0.05, Avg = 0.0
0.67
3 - ELN186-2790.1 purified [time corrected by -0.005 min]
MS_01_smoothed
counts
522.72-523.72m/z
0.69
min

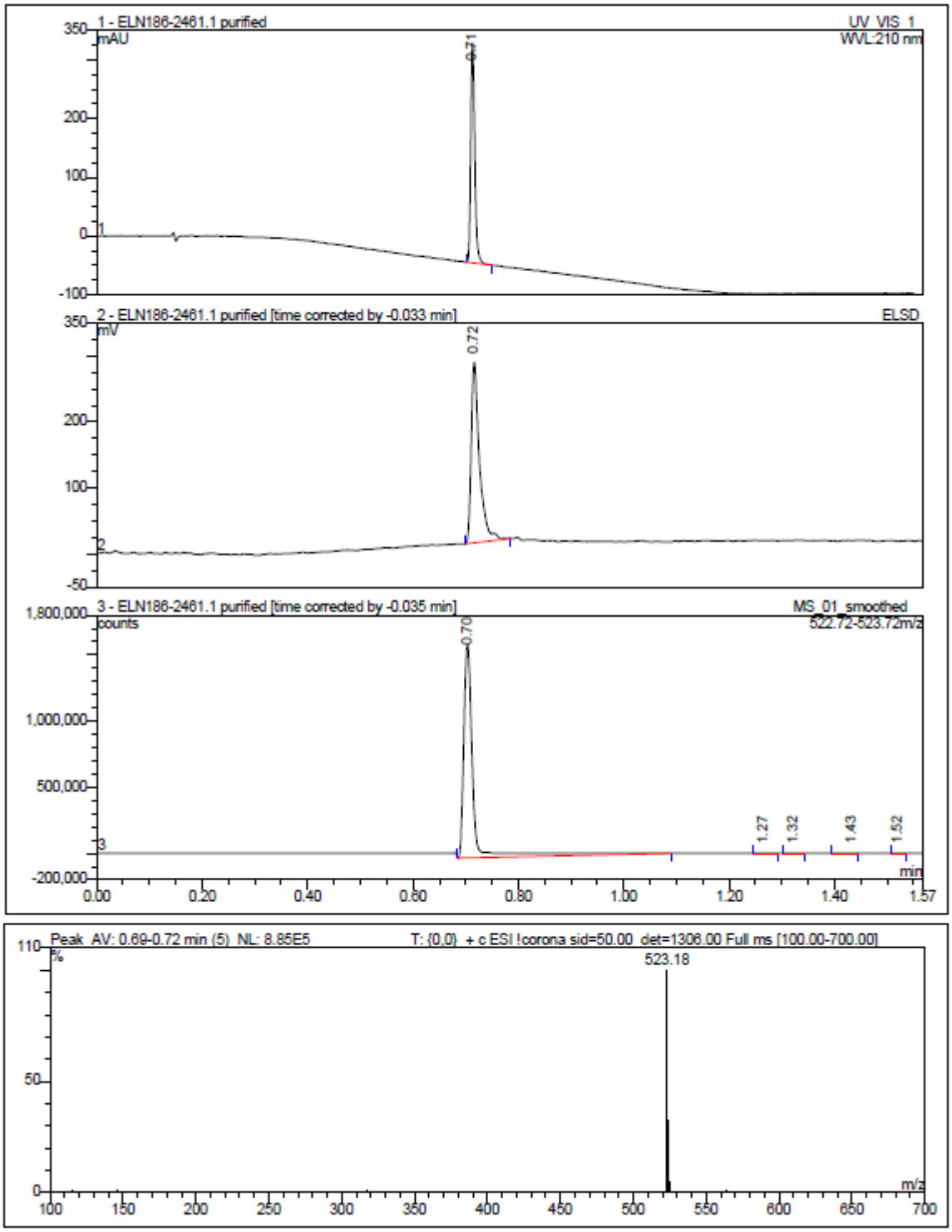

Peak AV: 0.67-0.70 min (5) NL: 1.38E6
T: {0,0} + c ESI !corona sid=50.00 det=1529.00 Full ms [150.00-750.00]
%
523.03
282.70
m/z

Compound **30**:


1 - ELN240-0648.2 f1
UV VIS 1
mAU
0.81
2 - ELN240-0648.2 f1 [time corrected by -0.048 min]
ELSD
mV
3 - ELN240-0648.2 f1 [time corrected by -0.010 min]
MS_01_smoothed
counts
522.72-523.72m/z
min


Peak AV: 0.80-0.82 min (5) NL: 4.29E5
T: {0,0} + c ESI !corona sid=50.00 det=1706.00 Full ms [100.00-700.00]
%
523.31
142.15
198.23
241.15
317.19
377.09
421.17
m/z

Compound **31**:


1 - ELN186-2461.1 purified
UV_VIS_1
mAU
WVL:210 nm
0.71
2 - ELN186-2461.1 purified [time corrected by -0.033 min]
ELSD
mV
0.72
3 - ELN186-2461.1 purified [time corrected by -0.035 min]
MS_01_smoothed
counts
522.72-523.72m/z
0.70
1.27
1.32
1.43
1.52
min
Peak AV: 0.69-0.72 min (5) NL: 8.85E5
T: {0,0} + c ESI !corona sid=50.00 det=1306.00 Full ms [100.00-700.00]
%
523.18
m/z