Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

Synthesis, Binding Affinity and Structure-Activity Relationships of Novel, Selective and Dual Targeting CCR2 and CCR5 Receptor Antagonists

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1. Purity data of the test compounds

compd.	purity by HPLC
6	99 %
8a	99 %
8b	99 %
8c	>97 %
8d	>95 %
8e	97 %
8f	>95 %
9a	95 %
9b	95 %
9c	99 %
9d	98 %
9e	99 %
9f	99 %
9g	>99 %
9h	96 %
9j	98 %
9k	99 %
9l	97 %
9m	98 %
9o	96 %
9p	96 %
9v	98 %
14a	95 %
14b	95 %
14d	97 %
14g	>97 %
14h	95 %

2. Experimental, Chemistry

2.1. Chemistry General

Unless otherwise noted, moisture-sensitive reactions were conducted under dry nitrogen. THF and 1,4-dioxane were dried with sodium/benzophenone and freshly distilled before use. Flash column chromatography (fc): Silica gel 60, 40–64 µm; parentheses include: eluent, R_f value. Melting point: melting point apparatus Stuart Scientific® SMP 3, uncorrected. IR: IR spectrophotometer FT-ATR-IR (Jasco®). ^{1}H NMR (400 MHz): Unity Mercury Plus 400 spectrometer (Varian®), AV400 (Bruker®), JEOL JNM-ECA-400. ^{13}C NMR (100 MHz): Unity Mercury plus 400 spectrometer (Varian®) JEOL JNM-ECA-400; δ in ppm relative to tetramethylsilane; coupling constants are given with 0.5 Hz resolution, the assignments of ^{13}C and ^{1}H NMR signals were supported by 2D NMR techniques; MS: APCI = atmospheric pressure chemical ionization, EI = electron impact, ESI = electro-spray ionization: MicroTof (Bruker Daltronics, Bremen), calibration with sodium formate clusters before measurement. HPLC method for determination of the product purity: Merck Hitachi Equipment; UV detector: L-7400; autosampler: L-7200; pump: L-7100; degasser: L-7614; Method: column: LiChrospher® 60 RP-select B (5 µm), 250x4 mm^2 column; flow rate: 1.00 mL/min; injection volume: 5.0 µL; detection at ë = 210 nm; solvents: A: water with 0.05 % (v/v) trifluoroacetic acid; B: acetonitrile with 0.05 % (v/v) trifluoroacetic acid: gradient elution: (A %): 0-4 min: 90 % , 4-29 min: gradient from 90 % to 0 %, 29-31 min: 0 %, 31-31.5 min: gradient from 0 % to 90 %, 31.5-40 min: 90 %. Thin layer chromatography (tlc): all reactions were monitored by tlc. Tlc aluminium foils (by Merck®, silica gel 60 F_{254}) were used in tlc chambers in saturated atmosphere at rt. The spots were visualized using UV light (254 nm). The reported R_f values should be taken as approximate values. The ratio of (highly volatile) solvent mixtures strongly depend on temperature and opening the tlc chamber might change the solvent composition and hence the R_f value.

2.2. Synthetic procedures

General procedure A: Suzuki-Miyaura cross-coupling

A 20 mL Schlenk flask was equipped with a Dimroth condenser, a magnetic stirring bar and closed. The flask was flame-dried *in vacuo* and filled with N_2. Under a permanent flow of N_2, amide **7** (1 eq.), $PdCl_2$(dppf) (5 mol%), base (K_2CO_3, KOAc, $NaOCH_3$) (2 eq.) and arylboronic acid (1.1-1.5 eq.) were suspended in dry dimethoxyethane (5-15 mL). The flask was sealed and heated to reflux for 12 h. After cooling to rt, the mixture was

filtered through a short silica pad (EtOAc). The filtrate was concentrated *in vacuo* to give the crude product, which was purified by fc. Recrystallization from acetonitrile afforded the final product.

2-(4-Methylphenyl)-6,7-dihydro-5*H*-benzo[7]annulene-8-carboxylic acid[37] **(6)**

A 50 mL Schlenk flask was equipped with a Dimroth condenser, a magnetic stirring bar and closed. The flask was flame-dried *in vacuo* and filled with N_2. Under a permanent flow of N_2, ester **3** (1.0 g, 3.5 mmol), $PdCl_2$(dppf) (130 mg, 0.17 mmol, 5 mol%), KOAc (700 mg, 7.0 mmol, 2 eq.) and 4-methylphenylboronic acid (525 mg, 3.85 mmol, 1.1 eq.) were suspended in dry dimethoxyethane (10 mL). The flask was sealed and heated to reflux for 12 h. After cooling down to rt, the mixture was filtered through a short silica pad (EtOAc). The filtrate was concentrated in vacuo to give the crude product as a brown oil, which was purified by fc (EtOAc : MeOH = 95:5) to yield 1.02 g (99 %) of the ester **5** as a colorless oil. The ester **5** (1.02 g, 3.48 mmol) was dissolved in MeOH (50 mL) and 5 M NaOH (50 mL) was added. The mixture was heated to reflux for 3 h. After cooling down to rt, the mixture was concentrated in vacuo and acidified with conc. HCl to give a precipitate. The solid was filtered off, washed with 1 M HCl, water, dried and recrystallized from acetonitrile to give **6** as a colorless solid. R_f = 0.42 (CH_2Cl_2 : MeOH= 95:5), mp 189-190 °C, yield 950 mg (97 %), $C_{19}H_{18}O_2$ (278.3 g/mol). Purity (HPLC): 99 %, t_R = 21.40 min. HRMS (APCI): m/z = calcd. for $C_{19}H_{19}O_2$ [MH^+] 279.1380, found 279.1381. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.92-2.17 (m, 2H, 6-C*H*$_2$), 2.40 (s, 3H, C*H*$_{3tolyl}$), 2.70 (t, *J* = 5.6 Hz, 2H, 7-C*H*$_2$), 2.89 (t, *J* = 5.6 Hz, 2H, 5-C*H*$_2$), 7.18-7.30 (m, 3H, 3-C*H*$_{phenyl}$, 5-C*H*$_{phenyl}$, 4-C*H*), 7.46 (dd, *J* = 7.8/2.1 Hz, 1H, 3-C*H*), 7.49 (d, *J* = 8.1 Hz, 2H, 2-C*H*$_{phenyl}$, 6-C*H*$_{phenyl}$), 7.57 (d, *J* = 2.0 Hz, 1H, 1-C*H*), 7.92 (s, 1H, 9-C*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 21.6 (*C*H$_{3tolyl}$), 27.6 (*C*-6), 30.6 (*C*-7), 35.4 (*C*-5), 127.2 (*C*-2$_{tolyl}$, *C*-6$_{tolyl.}$), 128.0 (*C*-3), 130.0 (*C*-3$_{tolyl.}$, *C*-5$_{tolyl}$), 130.4 (*C*-4), 132.1 (*C*-1), 132.2 (*C*-4$_{tolyl}$), 134.7 (*C*-4a), 137.6 (*C*-1$_{tolyl}$), 137.9 (C-2), 139.6 (*C*-9a), 142.3 (*C*-9), 142.6 (*C*-8), 174.3 (O=*C*-OH). FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2920, 2840 (C-H$_{alkyl}$), 2634, 2549 (COOH), 1732, 1680 (C=O).

2-(4-Methyphenyl)-*N*-{4-[*N*-methyl-*N*-(tetrahydro-2*H*-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5*H*-benzo[7]annulene-8-carboxamide[39] **(8a)**

According to general procedure A amide **7** (200 mg, 0.42 mmol), $PdCl_2$(dppf) (20 mg, 0.02 mmol, 5 mol%), K_2CO_3 (174 mg, 1.26 mmol, 3 eq.) and 4-methylphenylboronic acid

(86 mg, 0.63 mmol, 1.5 eq.) were suspended in dry dimethoxyethane (15 mL). The crude product was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give **8a** as a colorless solid. R_f = 0.28 (CH_2Cl_2 : MeOH = 95:5), mp 160-162 °C, yield 74 mg (90 %). $C_{32}H_{36}N_2O_2$ (480.6 g/mol). Purity (HPLC): 99 %, t_R = 21.31 min. HRMS (APCI): m/z = calcd. for $C_{32}H_{37}N_2O_2$ [MH^+] 481.2850, found 481.2835. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.52-1.79 (m, 4H, 3-C*H*$_{2pyran,}$ 5-C*H*$_{2pyran}$), 2.03-2.11 (m, 2H, 6-C*H*$_2$), 2.15 (s, 3H, N-C*H*$_3$), 2.33 (s, 3H, C*H*$_{3tolyl}$), 2.51-2.68 (m, 3H, 4-*H*$_{pyran,}$ 7-C*H*$_2$), 2.74-2.89 (m, 2H, 5-C*H*$_2$), 3.30 (td, *J* = 11.5/2.5 Hz, 2H, C*H*$_{2axial}$-O-C*H*$_{2axial}$), 3.52 (s, 2H, N-C*H*$_2$), 3.89-4.02 (m, 2H, C*H*$_{2equat.}$-O-C*H*$_{2equat.}$), 7.13-7.18 (m, 3H, 4-C*H,* 3-*H*$_{tolyl}$, 5-*H*$_{tolyl}$), 7.25 (d, *J* = 8.4 Hz, 2H, 3-*H*$_{phenyl}$, 5-*H*$_{phenyl}$), 7.31-7.39 (m, 2H, 3-C*H*, 9-C*H*), 7.41 (d, *J* = 8.1 Hz, 2H, 2-*H*$_{tolyl}$, 6-*H*$_{tolyl}$), 7.44 (d, *J* = 1.9 Hz, 1H, 1-C*H*), 7.50 (d, *J* = 8.5 Hz, 2H, 2-*H*$_{phenyl}$, 6-*H*$_{phenyl}$), 7.65 (s, 1H, N-*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 21.6 (*C*H$_{3tolyl}$), 28.4 (*C*-6), 29.6 (*C*-3$_{pyran,}$ *C*-5$_{pyran}$), 30.9 (*C*-7), 35.1 (*C*-5), 38.0 (N-*C*H$_3$), 57.8 (Ph-*C*H$_2$), 60.0 (*C*-4$_{pyran}$), 68.2 (*C*-2$_{pyran,}$ *C*-6$_{pyran}$), 120.5 (*C*-2$_{phenyl,}$ *C*-6$_{phenyl}$), 127.2 (*C*-2$_{tolyl,}$ *C*-6$_{tolyl}$), 127.3 (*C*-3), 129.8 (*C*-3$_{tolyl,}$ *C*-5$_{tolyl}$), 130.0 (*C*-3$_{phenyl}$, *C*-5$_{phenyl}$), 130.3 (*C*-4), 130.3 (*C*-4$_{tolyl}$), 131.1 (*C*-1), 134.7 (*C*-9), 135.1 (*C*-4a), 137.3 (*C*-4$_{phenyl}$), 137.6 (C-1$_{tolyl}$), 138.0 (C-2), 138.4 (*C*-1$_{phenyl}$), 139.6 (*C*-9a), 141.9 (*C*-8), 168.5 (O=*C*-NH). FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3298 (N-H), 2970, 2920 (C-H$_{alkyl}$), 1644 (C=O), 1095, 1014 (C-O).

N-[4-Diethylamino)phenyl]-2-(4-methylphenyl)-6,7-dihydro-5*H*-benzo[7]annulene-8-carboxamide (8b)

N^1,N^1-Diethylbenzene-1,4-diamine (60 mg, 0.36 mmol, 1 eq.) was added to a vigorously stirred mixture of acid **6** (100 mg, 0.36 mmol), triethylamine (73 mg, 0.72 mmol, 2 eq.) and HATU™ (153 mg, 0.40 mmol. 1.1 eq.) in THF (5 mL). The mixture was stirred overnight at rt. The mixture was concentrated *in vacuo* and the residue was purified by fc (EtOAc : CH_2Cl_2 = 1:2 + 5% MeOH) and recrystallized from acetonitrile to give **8b** as a colorless solid. R_f = 0.91 (MeOH : CH_2Cl_2 = 5:95), mp 153-155 °C , yield 86 mg (56 %). $C_{29}H_{32}N_2O$ (424.6 g/mol). Purity (HPLC): 99 %, t_R = 21.33 min. HRMS (EI): *m/z* = calcd. for $C_{29}H_{33}N_2O$ [MH^+] 425.2587, found 425.2608. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.15 (t, *J* = 7.2 Hz, 6H, N(CH_2C*H*$_3$)$_2$), 2.15 (quint, *J* = 6.3 Hz, 2H, 6-C*H*$_2$), 2.40 (s, 3H, C*H*$_{3tolyl}$), 2.71 (t, *J* = 6.6 Hz, 2H, 7-C*H*$_2$), 2.81-2.92 (m, 2H, 5-C*H*$_2$), 3.34 (q, *J* = 7.0 Hz, 4H, N(C*H*$_2$CH$_3$)$_2$), 6.68 (d, *J* = 9.0 Hz, 2H, 3-C*H*$_{phenyl}$, 5-C*H*$_{phenyl.}$), 7.22 (d, *J* = 7.8 Hz, 1H, 4-C*H*), 7.25 (d, *J* = 8.4 Hz, 2H, 3-C*H*$_{tolyl}$, 5-C*H*$_{tolyl}$), 7.38-7.44 (m, 4H, 3-C*H*, 9-C*H,* 2-C*H*$_{phenyl}$, 6-C*H*$_{phenyl.}$), 7.47-7.50 (m, 3H, 2-C*H*$_{tolyl}$, 6-C*H*$_{tolyl}$, 1-C*H*), 7.51 (s, 1H, N*H*). ^{13}C

NMR ($CDCl_3$): δ (ppm) = 13.0 ($N(CH_2\mathit{C}H_3)_2$), 21.6 ($\mathit{C}H_{3tolyl}$), 28.5 (*C*-6), 30.9 (*C*-7), 35.0 (*C*-5), 45.0 ($N(\mathit{C}H_2\mathit{C}H_3)_2$), 112.9 (*C*-$3_{phenyl}$, *C*-$5_{phenyl}$), 122.8 (*C*-$2_{phenyl}$, *C*-$6_{phenyl}$), 127.1 (*C*-3), 127.2 (*C*-1), 129.9 (*C*-2_{tolyl}, *C*-6_{tolyl}), 130.2 (*C*-3_{tolyl}, *C*-5_{tolyl}), 131.1 (*C*-4), 134.2 (*C*-9) 135.4 (*C*-8), 137.5 (*C*-9a), 138.1 (*C*-1_{tolyl}), 138.6 (*C*-4_{tolyl}), 139.6 (*C*-2), 141.6 (*C*-4a), 145.7 (C-4_{phenyl}), 164.9 (O=*C*-NH). A signal for the atom C-1_{phenyl} is not visible. FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3344 (N-H), 2785 (C-H_{alkyl}), 1627 (C=O).

2-(4-Methylphenyl)-*N*-{4-[4-(tetrahydro-2*H*-pyran-4-yl)piperazin-1-yl]phenyl}-6,7-dihydro-5*H*-benzo[7]annulene-8-carboxamide (8c)

4-[4-(Tetrahydro-2*H*-pyran-4-yl)piperazin-1-yl]aniline (78 mg, 0.36 mmol, 1 eq.) was added to a vigorously stirred mixture of acid **6** (100 mg, 0.36 mmol), triethylamine (110 mg, 1.08 mmol, 3 eq.) and COMU™ (232 mg, 0.54 mmol. 1.5 eq.) in acetonitrile (5 mL). The mixture was stirred overnight at rt, during which a precipitate was formed. The solid was filtered off, washed with acetonitrile and water, dried and recrystallized from acetonitrile to afford **8c** as a colorless solid. R_f = 0.34 (MeOH : CH_2Cl_2 = 5:95), mp 248-250 °C (dec.), yield 107 mg (53 %). $C_{34}H_{39}N_3O_2$ (521.7 g/mol). Purity (HPLC): >97 %, t_R = 21.05 min. HRMS (APCI): m/z = calcd. for $C_{34}H_{40}N_3O_2$ [MH^+] 522.3115, found 522.3092. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.62 (qd, *J* = 12.0/4.3 Hz, 2H, 3-C$\mathit{H}_{2pyran\text{-}axial,}$ 5-C$\mathit{H}_{2pyran\text{-}axial}$), 1.76-1.86 (m, 2H, 3-C$\mathit{H}_{2pyran\text{-}equat,}$ 5-C$\mathit{H}_{2pyran\text{-}equat}$), 2.15 (quint. m, *J* = 6.3 Hz, 2H, 6-CH_2), 2.40 (s, 3H, CH_{3tolyl}), 2.48 (tt, *J* = 10.0/2.9 Hz, 1H, 4-H_{pyran}), 2.67-2.78 (m, 6H, 7-CH_2, 3-C$\mathit{H}_{2piperazin}$, 5- C$\mathit{H}_{2piperazin}$), 2.82-2.92 (m, 2H, 5-CH_2), 3.13-3.28 (m, 4H, 2-C$\mathit{H}_{2piperazin}$, 6-C$\mathit{H}_{2piperazin}$), 3.41 (td, *J* = 11.9/1.9 Hz, 2H, CH_{2axial}-O-CH_{2axial}), 4.05 (dd, *J* = 11.5/3.9 Hz, 2H, $CH_{2equat.}$-O-$CH_{2equat.}$), 6.93 (d, *J* = 8.9 Hz, 2H, 3-CH_{phenyl}, 5-CH_{phenyl}), 7.18-7.25 (m, 3H, 4-C*H*, 3-CH_{tolyl}, 5-CH_{tolyl}), 7.40 (s, 1H, 9-C*H*), 7.43 (dd, *J* = 7.8/1.9 Hz, 1H, 3-C*H*), 7.45-7.52 (m, 5H, 1-C*H*, 2-CH_{phenyl}, 6-CH_{phenyl}, 2-CH_{tolyl}, 6-CH_{tolyl}), 7.53 (s, 1H, N*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 21.6 ($\mathit{C}H_{3tolyl}$), 28.4 (*C*-6), 30.0 (*C*-3_{pyran}, *C*-5_{pyran}), 30.9 (*C-5*), 35.0 (*C-7*), 49.5 (*C*-$2_{piper.}$, *C*-$6_{piper.}$), 50.3 (*C*-3_{piper}, *C*-5_{piper}), 61.4 (*C*-4_{pyran}), 67.9 (*C*-2_{pyran}, *C*-6_{pyran}), 117.1 (*C*-3_{phenyl}, *C*-5_{phenyl}), 121.9 (*C*-2_{phenyl}, *C*-6_{phenyl}), 127.2 (*C*-2_{tolyl}, *C*-6_{tolyl}), 129.1 (C-1_{phenyl}), 130.0 (*C*-3_{tolyl}, *C*-5_{tolyl}), 130.3 (*C*-3), 131.0 (*C*-1), 131.1 (*C*-4), 134.5 (*C*-9), 135.2 (*C*-8), 137.6 (*C*-9a), 138.0 (*C*-1_{tolyl}), 138.4 (*C*-4_{tolyl}), 139.6 (*C*-2), 141.7 (*C*-4a), 148.8 (*C*-4_{phenyl}), 168.6 (O=*C*-NH). FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3290 (N-H), 2831, 2769 (C-H_{alkyl}), 1635 (C=O).

2-(4-Methylphenyl)-*N*-{4-[*N*-(thiazol-2-yl)sulfamoyl]phenyl}-6,7-dihydro-5*H*-benzo[7]annulene-8-carboxamide (8d)

4-Amino-*N*-(1,3-thiazol-2-yl)benzenesulfonamide (Sulfathiazole) (92 mg, 0.36 mmol, 1 eq.) was added to a vigorously stirred mixture of acid **6** (100 mg, 0.36 mmol), triethylamine (75 mg, 0.72 mmol, 2 eq.) and COMU™ (171 mg, 0.4 mmol. 1.1 eq.) in acetonitrile (15 mL). The mixture was concentrated *in vacuo* and the residue was purified by fc (EtOAc : CH_2Cl_2 = 1:2 + 5% MeOH) and recrystallized from acetonitrile to afford **8d** as a colorless solid. R_f = 0.28 (MeOH : CH_2Cl_2 = 5:95), mp 222-224 °C (dec.), yield 45 mg (25 %). $C_{28}H_{25}N_3O_3S_2$ (515.6 g/mol). Purity (HPLC): >95 %, t_R = 21.48 min. HRMS (APCI): m/z = calcd. for $C_{28}H_{26}N_3O_2S_2$ [MH^+] 516.1410, found 516.1448. ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.95-2.05 (m, 2H, 6-C*H*$_2$), 2.34 (s, 3H, C*H*$_{3tolyl}$), 2.62 (t, *J* = 6.5 Hz, 2H, 7-C*H*$_2$), 2.79-2.89 (m, 2H, 5-C*H*$_2$), 6.82 (d, *J* = 4.6 Hz, 1H, 5-C*H*$_{thiazol}$), 7.23-7.31 (m, 4H, 4-C*H*$_{thiazol}$, 4-CH, 3-C*H*$_{tolyl}$, 5-C*H*$_{tolyl}$), 7.39 (s, 1H, 9-C*H*), 7.52 (dd, *J* = 7.8/2.0 Hz, 1H, 3-C*H*), 7.58 (d, *J* = 8.2 Hz, 2H, 2-C*H*$_{tolyl}$, 6-C*H*$_{tolyl}$), 7.68 (d, *J* = 2.0 Hz, 1H, 1-C*H*), 7.76 (d, *J* = 8.8 Hz, 2H, 2-C*H*$_{phenyl}$, 6-C*H*$_{phenyl}$), 7.87 (d, *J* = 8.9 Hz, 2H, 3-C*H*$_{phenyl}$, 5-C*H*$_{phenyl}$), 10.30 (s, 1H, N*H*), 12.69 (s, 1H, SO_2N*H*). ^{13}C NMR (DMSO-d_6): δ (ppm) = 20.5 (*C*H$_{3tolyl}$), 27.2 (*C*-6), 29.9 (*C*-5), 33.8 (*C*-*7*), 107.7 (*C*-5$_{thiazol}$), 119.3 (*C*-2$_{phenyl}$, *C*-6$_{phenyl}$), 126.1 (*C*-2$_{tolyl}$, *C*-6$_{tolyl}$), 126.2 (*C*-3), 126.6 (*C*-3$_{phenyl}$, *C*-5$_{phenyl}$), 129.4 (*C*-3$_{tolyl}$, *C*-5$_{tolyl}$), 129.7 (*C*-4$_{thiazol}$), 129.8 (*C*-4, *C*-1), 133.8 (*C*-9), 134.5 (*C*-9a), 136.4 (*C*-4$_{phenyl}$), 136.5 (*C*-4a), 136.9 (*C*-8), 137.8 (*C*-1$_{tolyl}$), 137.9 (*C*-4$_{tolyl}$), 140.9 (*C*-2), 142.4 (*C*-1$_{phenyl}$), 168.5 (O=*C*-NH), 179.6 (*C*-2$_{thiazol}$). FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3348 (N-H), 2773 (C-H$_{alkyl}$), 1647 (C=O) 1350, 1184 (SO_2-N).

2-(4-Methylphenyl)-*N*-(thiazol-2-yl)-6,7-dihydro-5*H*-benzo[7]annulene-8-carboxamide (8e)

2-Aminothiazole (100 mg, 1.0 mmol, 1 eq.) was added to a vigorously stirred mixture of acid **6** (280 mg, 1.0 mmol), triethylamine (203 mg, 2.0 mmol, 2 eq.) and COMU™ (471 mg, 1.1 mmol. 1.1 eq.) in acetonitrile (15 mL). The mixture was stirred overnight at rt, during which a precipitate was formed. The solid was filtered off, washed with acetonitrile and water, dried and recrystallized from acetonitrile to afford **8e** as a beige solid. R_f = 0.37 (MeOH : CH_2Cl_2 = 5:95), mp 200-202 °C (dec.), yield 297 mg (82 %). $C_{22}H_{20}N_2OS$ (360.5 g/mol). Purity (HPLC): 97 %, t_R = 22.70 min. HRMS (APCI): m/z = calcd. for $C_{22}H_{21}N_3OS$ [MH^+] 361.1369, found 361.1383. ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.11-2.27 (m, 2H, 6-C*H*$_2$), 2.39 (s, 3H, C*H*$_{3tolyl}$), 2.81 (t, *J* = 6.6 Hz, 2H, 7-C*H*$_2$), 2.89-3.00

(m, 2H, 5-CH_2), 6.83-6.91 (m, 1H, 5-C$H_{thiazol}$), 7.19-7.30 (m, 3H, 3-CH_{tolyl}, 5-CH_{tolyl}, 4-C*H*), 7.29-7.37 (m, 1H, 4-C$H_{thiazol}$), 7.37 (s, 1H, 9-C*H*), 7.42 (d, *J* = 7.8, 2H, 2-CH_{tolyl}, 6-CH_{tolyl}), 7.47 (dd, *J* = 7.8/2.0 Hz, 1H, 3-C*H*), 7.55 (broad, 1H, 1-C*H*), 12.06 (s, 1H, N*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 21.6 (*C*H_{3tolyl}), 28.2 (*C*-6), 30.9 (*C*-5), 35.3 (*C*-*7*), 113.9 (*C*-$5_{thiazol}$), 127.1 (*C*-2_{tolyl}, *C*-6_{tolyl}), 127.7 (*C*-3), 130.0 (*C*-3_{tolyl}, *C*-5_{tolyl}), 130.5 (*C*-4), 131.6 (*C*-1), 134.6 (*C*-9), 137.3 (*C*-9a), 137.3 (*C*-8), 137.7 (*C*-1_{tolyl}), 137.8 (*C*-4_{tolyl}), 137.8 (*C*-4a), 139.6 (*C*-2), 141.9 (*C*-$4_{thiazol}$), 160.5 (*C*-$2_{thiazol}$), 168.5 (O=*C*-NH). FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3205 (N-H), 2773 (C-H_{alkyl}), 1647 (C=O).

2-[(4-Methyl)phenyl]-*N*-{4-[(piperidin-1-yl)methyl]phenyl}-6,7-dihydro-5*H*-benzo[7]annulene-8-carboxamide (8f)

1-(4-Aminobenzyl)piperidine dihydrochloride (95 mg, 0.36 mmol, 1 eq.) was added to a vigorously stirred mixture of acid **6** (100 mg, 0.36 mmol), triethylamine (110 mg, 1.08 mmol, 3 eq.) and HATU™ (153 mg, 0.39 mmol. 1.1 eq.) in acetonitrile (5 mL). The mixture was stirred overnight at rt. The mixture was concentrated *in vacuo* and the residue was purified by fc (EtOAc : cyclohexane = 8:2 -› EtOAc : CH_2Cl_2 = 1:2 + 5% MeOH) and recrystallization from acetonitrile afforded **8f** as a colorless solid. R_f = 0.14 (CH_2Cl_2 : MeOH = 95:5), mp 194-196 °C, yield 140 mg (86 %). $C_{31}H_{34}N_2O$ (450.6 g/mol). Purity (HPLC): >95 %, t_R = 21.44 min. HRMS (APCI): m/z = calcd. for $C_{31}H_{35}N_2O$ [MH^+] 451.2744, found 451.2741. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.34-1.48 (m, 2H, 4-C$H_{2piperidin}$), 1.57 (m, Hz, 4H, 3-C$H_{2piperidin,}$ 5-C$H_{2piperidin}$), 2.10-2.25 (m, 2H, 6-CH_2), 2.30-2.43 (m, 7H, 2-C$H_{2piperidin,}$ 6-C$H_{2piperidin}$, CH_{3tolyl}), 2.72 (t, *J* = 6.5 Hz, 2H, 2H, 7-CH_2), 2.83-2.97 (m, 1H, 5-CH_2), 3.46 (s, 2H, Ph-CH_2-N), 7.20-7.25 (m, 3H, 4-C*H*, 3-CH_{tolyl}, 5-CH_{tolyl}), 7.31 (d, *J* = 8.5 Hz, 2H, 3-CH_{phenyl}, 5-CH_{phenyl}), 7.41 (s, 1H, 9-C*H*), 7.44 (dd, *J* = 7.9/1.9 Hz, 1H, 3-C*H*), 7.48 (d, *J* = 8.1 Hz, 2H, 2-CH_{tolyl}, 6-CH_{tolyl}), 7.51 (d, *J* = 1.8 Hz, 1H, 1-CH), 7.55 (d, *J* = 8.5 Hz, 2H, 2-CH_{phenyl}, 6-CH_{phenyl}), 7.62 (s, 1H, N*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 21.6 (*C*-4_{piper}), 24.8 (*C*-6), 26.4 (*C*-$3_{piper.}$, *C*-$5_{piper.}$), 30.9 (C-7), 32.0 (C-5), 54.8 (*C*-$2_{piper.}$, *C*-$6_{piper.}$), 63.8 (Ph-CH_2-N), 120.3 (*C*-2_{phenyl}, *C*-6_{phenyl}), 127.2 (C-2_{tolyl}, C-6_{tolyl}), 127.3 (C-3), 130.0 (*C*-3_{phenyl}, *C*-5_{phenyl}), 130.3 (C-9), 130.4 (C-3_{tolyl}, C-5_{tolyl}), 131.1 (C-1), 134.7 (C-4), 135.1 (*C*-4_{phenyl}), 137.3 (*C*-1_{tolyl}), 137.6 (*C*-4_{tolyl}), 137.9 (*C*-9a), 138.4 (*C*-4a), 139.6 (*C*-2), 141.7 (*C*-4a), 146.3 (C-1_{phenyl}), 168.4 (O=*C*-NH). FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3325 (N-H), 2931 (C-H_{alkyl}), 1643 (C=O), 1041, 1018 (C-O).

_N_-{4-[_N_-Methyl-_N_-(tetrahydro-2_H_-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5_H_-benzo[7]annulene-8-carboxamide (9a)

According to general procedure A amide **7** (83 mg, 0.17 mmol), $PdCl_2$(dppf) (16 mg, 0.02 mmol, 10 mol %), $NaOCH_3$ (20 mg, 0.35 mmol, 2 eq.) and phenylboronic acid (24 mg, 0.2 mmol, 1.1 eq.) were suspended in dry dimethoxyethane (5 mL). The crude product was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give **9a** as a colorless solid. R_f = 0.17 (CH_2Cl_2 : MeOH= 95:5), mp 165-167 °C, yield 74 mg (90 %). $C_{31}H_{34}N_2O_2$ (466.6 g/mol). Purity (HPLC): 95 %, t_R = 20.83 min. HRMS (APCI): m/z = calcd. for $C_{31}H_{35}N_2O_2$ [MH^+] 467.2693, found 467.2690. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.55-1.84 (m, 4H, 3-C$H_{2pyran,}$ 5-CH_{2pyran}), 2.11-2.22 (m, 2H, 6-CH_2), 2.23 (s, 3H, N-CH_3), 2.58-2.69 (m, 1H, 4-H_{pyran}),2.72 (t, J = 6.6 Hz, 2H, 7-CH_2), 2.84-2.96 (m, 2H, 5-CH_2), 3.37 (td, J = 11.7/2.3 Hz, 2H, CH_{2axial}-O-CH_{2axial}), 3.60 (s, 2H, Ph-CH_2-N), 4.04 (dd, J = 11.4/2.5 Hz, 2H, $CH_{2equat.}$-O-$CH_{2equat.}$), 7.25 (d, J = 7.7 Hz, 1H, 4-CH), 7.30-7.38 (m, 4H, 3-$CH_{N\text{-}phenyl}$, 5-$CH_{N\text{-}phenyl,}$ 3-CH, 9-CH), 7.37-7.47 (m, 3H, 4-$CH_{N\text{-}phenyl}$, 3-CH_{phenyl}, 5-CH_{phenyl}), 7.46 (d, J = 2.1 Hz, 1H, 1-CH), 7.54 (m, 2H, 2-$CH_{N\text{-}phenyl}$, 6-$CH_{N\text{-}phenyl,}$), 7.57-7.60 (m, 2H, 2-CH_{phenyl}, 6-CH_{phenyl}), 7.65 (s, 1H, N-H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 28.4 (_C_-6), 29.4 (_C_-7), 30.9 (_C_-3_{pyran}, _C_-5_{pyran}), 35.1 (_C_-5), 37.7 (N-_C_H_3), 57.7 (Ph-_C_H_2-N), 60.0 (_C_-4_{pyran}), 68.0 (_C_-2_{pyran}, _C_-6_{pyran}), 120.5 (_C_-$2_{N\text{-}phenyl}$, _C_-$6_{N\text{-}phenyl}$), 127.4 (C-2_{phenyl}, C-6_{phenyl}), 127.6 (_C_-3), 127.8 (C-3_{phenyl}, C-5_{phenyl}), 129.3 (_C_-$3_{N\text{-}phenyl}$, _C_-$5_{N\text{-}phenyl}$), 130.2 (C-4_{phenyl}), 130.4 (_C_-4), 131.3 (_C_-1), 134.8 (_C_-9), 135.1 (_C_-4a), 138.4 (C-2), 139.7 (C-$1_{N\text{-}phenyl}$), 140.9 (_C_-9a), 142.0 (_C_-8), 146.4 (C-1_{phenyl}), 168.5 (O=_C_-NH). A Signal for the quaternary carbon atom _C_-$4_{N\text{-}phenyl}$ is not visible. FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3302 (N-H), 2939, 2843 (C-H_{alkyl}), 1643 (C=O), 1049, 1010 (C-O).

2-(3-Methyphenyl)-_N_-{[_N_-methyl-_N_-(tetrahydro-2_H_-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5_H_-benzo[7]annulene-8-carboxamide (9b)

According to general procedure A amide **7** (100 mg, 0.21 mmol), $PdCl_2$(dppf) (10 mg, 0.01 mmol, 5 mol%), K_2CO_3 (60 mg, 0.42 mmol, 2 eq.) and 3-methylphenylboronic acid (45 mg, 0.32 mmol, 1.5 eq.) were suspended in dry dimethoxyethane (8 mL). The crude product was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give **9b** as a colorless solid. R_f = 0.24 (CH_2Cl_2 : MeOH = 95:5), mp 183-184 °C, yield 92 mg (92 %). $C_{32}H_{36}N_2O_2$ (480.6 g/mol). Purity (HPLC): 95 %, t_R = 20.89 min. HRMS (APCI): m/z = calcd. for $C_{32}H_{37}N_2O_2$ [MH^+] 481.2850, found 481.2827.^{1}H NMR ($CDCl_3$): δ (ppm) = 1.63-1.88 (m, 4H, 3-C$H_{2pyran,}$ 5-CH_{2pyran}), 2.13-2.21 (m, 2H, 6-CH_2), 2.21 (s,

3H, N-C*H*$_3$), 2.33 (s, 3H, C*H*$_{3tolyl}$), 2.57-2.70 (m, 1H, 4-H$_{pyran}$), 2.73 (t, *J* = 6.6 Hz, 2H, 7-C*H*$_2$), 2.89 (t, *J* = 5.5 Hz, 2H, 5-C*H*$_2$), 3.30 (td, *J* = 11.7/2.3 Hz, 2H, CH$_{2axial}$-O-CH$_{2axial}$), 3.57 (s, 2H, Ph-*C*H$_2$-N), 4.04 (dd, *J* = 11.9/3.6 Hz, 2H, CH$_{2equat.}$-O-CH$_{2equat.}$), 7.17 (d, *J* = 7.3 Hz, 1H, *4*-C*H*), 7.24 (d, *J* = 7.9 Hz, 1H, 6-C*H*$_{tolyl}$), 7.28-7.36 (m, 3H, 3-C*H*$_{phenyl}$, 5-C*H*$_{phenyl}$, 5-C*H*$_{tolyl}$), 7.35-7.44 (m, 3H, 2-C*H*$_{tolyl}$, 4-C*H*$_{tolyl,}$ 9-C*H*), 7.45 (dd, *J* = 7.9/2.0 Hz, 1H, 3-C*H*), 7.53 (d, *J* = 1.9 Hz, 1H, 1-C*H*), 7.56 (d, *J* = 8.4 Hz, 2H, 2-*H*$_{phenyl}$, 6-*H*$_{phenyl}$), 7.62 (s, 1H, N-*H*).^{13}C NMR ($CDCl_3$): δ (ppm) = 22.2 (*C*H$_{3tolyl}$), 28.4 (*C*-6), 29.6 (*C*-3$_{pyran}$, *C*-5$_{pyran}$), 30.9 (*C*-7), 35.1 (*C*-5), 38.0 (N-*C*H$_3$), 57.7 (Ph-*C*H$_2$-N), 60.0 (*C*-4$_{pyran}$), 68.2 (*C*-2$_{pyran}$, *C*-6$_{pyran}$), 120.5 (*C*-2$_{phenyl}$, *C*-6$_{phenyl}$), 124.5 (*C*-2$_{tolyl}$), 127.5 (*C*-3), 128.2 (*C*-4$_{tolyl}$), 128.5 (*C*-4), 129.2 (*C*-5$_{tolyl}$), 129.9 (*C*-3$_{phenyl}$, *C*-5$_{phenyl}$), 130.3 (*C*-6$_{tolyl}$), 131.3 (*C*-1), 134.7 (*C*-9), 135.1 (*C*-4a), 136.4 (*C*-3$_{tolyl}$), 137.2 (*C*-4$_{phenyl}$), 138.4 (C-2), 138.9 (C-1$_{tolyl}$), 139.8 (*C*-1$_{phenyl}$), 140.8 (*C*-9a), 141.9 (*C*-8), 168.5 (O=*C*-NH). FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3344 (N-H), 2924, 2866 (C-H$_{alkyl}$), 1647 (C=O), 1095, 1010 (C-O).

2-(2-Methyphenyl)-*N*-{4-[*N*-Methyl-*N*-(tetrahydro-2*H*-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5*H*-benzo[7]annulene-8-carboxamide (9c)

According to general procedure A amide **7** (100 mg, 0.21 mmol), $PdCl_2$(dppf) (10 mg, 0.01 mmol, 5 mol%), K_2CO_3 (60 mg, 0.42 mmol, 2 eq.) and 2-methylphenylboronic acid (45 mg, 0.32 mmol, 1.5 eq.) were suspended in dry dimethoxyethane (5 mL). The crude product was purified by fc (EtOAc : MeOH+3 % triethylamine = 95:5) and recrystallized from acetonitrile to give **9c** as a colorless solid. R_f = 0.24 (CH_2Cl_2 : MeOH = 95:5), mp 144-145 °C, yield 69 mg (68 %). $C_{32}H_{36}N_2O_2$ (480.6 g/mol). Purity (HPLC): 99 %, t_R = 21.34 min. HRMS (APCI): m/z = calcd. for $C_{32}H_{37}N_2O_2$ [MH$^+$] 481.2850, found 481.2869. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.63-1.88 (m, 4H, 3-C*H*$_{2pyran,}$ 5-C*H*$_{2pyran}$), 2.13-2.21 (m, 2H, 6-C*H*$_2$), 2.21 (s, 3H, N-C*H*$_3$), 2.28 (s, 3H, C*H*$_{3tolyl}$), 2.65 (tt, *J* = 11.2/3.9 Hz, 1H, 4-H$_{pyran}$), 2.73 (t, *J* = 6.3 Hz, 2H, 7-C*H*$_2$), 2.89 (t, *J* = 5.7 Hz, 2H, 5-C*H*$_2$), 3.36 (td, *J* = 11.6/2.3 Hz, 2H, CH$_{2axial}$-O-CH$_{2axial}$), 3.57 (s, 2H, Ph-*C*H$_2$-N), 4.04 (dd, *J* = 10.7/4.1 Hz, 2H, CH$_{2equat.}$-O-CH$_{2equat.}$), 7.18 (dd, *J* = 7.7/1.7 Hz, 1H, 3-C*H*), 7.20 (d, *J* = 7.0 Hz, 1H, 4-C*H*), 7.22 (d, *J* = 1.9 Hz, 1H, 1-C*H*), 7.23-7.30 (m, 4H, 2- ,3- ,4- ,5-C*H*$_{tolyl}$), 7.30 (d, 2H, *J* = 8.5 Hz, 3-C*H*$_{phenyl}$, 5-C*H*$_{phenyl}$), 7.35 (s, 9-C*H*), 7.55 (d, *J* = 8.5 Hz, 2H, 2-*H*$_{phenyl}$, 6-*H*$_{phenyl}$), 7.67 (s, 1H, N-*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 21.0 (*C*H$_{3tolyl}$), 28.3 (*C*-6), 29.6 (*C*-3$_{pyran}$, *C*-5$_{pyran}$), 31.0 (*C*-7), 35.2 (*C*-5), 38.0 (N-*C*H$_3$), 57.7 (Ph-*C*H$_2$-N), 60.0 (*C*-4$_{pyran}$), 68.2 (*C*-2$_{pyran}$, *C*-6$_{pyran}$), 120.4 (*C*-2$_{phenyl}$, *C*-6$_{phenyl}$), 126.3 (*C*-3), 127.8 (*C*-4), 129.4 (*C*-5$_{tolyl}$), 129.7 (*C*-6$_{tolyl}$), 129.7 (*C*-4$_{tolyl}$), 129.9 (*C*-3$_{phenyl}$, *C*-5$_{phenyl}$), 130.2 (*C*-3$_{tolyl}$), 130.1 (*C*-1), 133.4 (*C*-9),

134.6 (*C*-2_{tolyl}), 135.8 (*C*-4a), 137.2 (*C*-4_{phenyl}), 137.8 (*C*-2), 139.1 (*C*-1_{phenyl}), 140.5 (*C*-9a), 141.5 (*C*-8), 142.3 (*C*-1_{tolyl}). A signal for the carbon atom O=*C*-NH is not visible. FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3302 (N-H), 2966, 2862 (C-H_{alkyl}), 1651 (C=O), 1095, 1014 (C-O).

2-(4-Ethylphenyl)-*N*-{4-[*N*-methyl-*N*-(tetrahydro-2*H*-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5*H*-benzo[7]annulene-8-carboxamide (9d)

According to general procedure A amide **7** 100 mg, 0.21 mmol), $PdCl_2$(dppf) (8 mg, 0.01 mmol, 5 mol%), KOAc (42 mg, 0.42 mmol, 2 eq.) and 4-ethylphenylboronic acid (50 mg, 0.32 mmol, 1.5 eq.) were suspended in dry dimethoxyethane (8 mL). The crude product was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give **9d** as a colorless solid. R_f = 0.20 (CH_2Cl_2 : MeOH= 95:5), mp 154-156 °C, yield 100 mg (96 %). $C_{33}H_{38}N_2O_2$ (494.6 g/mol). Purity (HPLC): 98 %, t_R = 21.61 min. HRMS (APCI): m/z = calcd. for $C_{33}H_{39}N_2O_2$ [MH^+] 495.3006, found 495.3004. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.28 (t, *J* = 7.6 Hz, 3H, CH_2CH_3), 1.62-1.83 (m, 4H, 3-C$H_{2pyran,}$ 5-CH_{2pyran}), 2.10-2.19 (m, 2H, 6-CH_2), 2.21 (s, 3H, N-CH_3), 2.54-2.70 (m, 1H, 4-CH_{pyran}), 2.68-2.76 (m, 4H, 7-CH_2, CH_2CH_3), 2.82-2.95 (m, 2H, 5-CH_2), 3.37 (td, *J* = 11.6/2.4 Hz, 2H, CH_{2axial}-O-CH_{2axial}), 3.57 (s, 2H, Ph-CH_2-N), 4.04 (dd, *J* = 10.9/3.4 Hz, 2H, CH_{2equat}-O-CH_{2equat}), 7.23 (d, *J* = 7.9 Hz, 1H, *4*-C*H*), 7.28 (d, *J* = 8.5 Hz, 2H, 3-C$H_{ethylphenyl}$, 5-C$H_{ethylphenyl}$), 7.32 (d, *J* = 8.3 Hz, 2H, 3-CH_{phenyl}, 5-CH_{phenyl}), 7.42 (s, 1H, 9-C*H*), 7.44 (dd, *J* = 7.8/1.9 Hz, 1H, 3-C*H*), 7.51 (m, 3H, 1-CH, 2-C$H_{ethylphenyl}$ 6-C$H_{ethylphenyl}$), 7.56 (d, *J* = 8.5 Hz, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.61 (s, 1H, N-*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 16.04 (CH_2CH_3), 28.4 (*C*-6), 28.9 (CH_2CH_3), 29.6 (*C*-3_{pyran}, *C*-5_{pyran}), 30.9 (*C*-7), 35.1 (*C*-5), 38.0 (N-CH_3), 57.8 (Ph-CH_2), 60.0 (*C*-4_{pyran}), 68.2 (*C*-2_{pyran}, *C*-6_{pyran}), 120.5 (*C*-2_{phenyl}, *C*-6_{phenyl}), 127.3 (*C*-$2_{ethylphenyl}$, *C*-$6_{ethylphenyl}$), 127.3 (*C*-3), 128.8 (*C*-$3_{ethylphenyl.}$, *C*-$5_{ethylphenyl.}$), 129.9 (*C*-3_{phenyl}, *C*-5_{phenyl}), 130.3 (*C*-4), 131.2 (*C*-1), 134.8 (*C*-9), 135.1 (*C*-4a), 137.3 (*C*-4_{phenyl}), 138.2 (*C*-$4_{ethylphenyl.}$),138.4 (*C*-1_{phenyl}), 139.7 (C-2), 139.7 (*C*-9a), 141.7 (*C*-8), 143.9 (C-$1_{ethylphenyl.}$), 168.5 (O=*C*-NH). FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3332 (N-H), 2951, 2835 (C-H_{alkyl}), 1643 (C=O), 1087 (C-O).

2-(4-Butylphenyl)-*N*-{4-[*N*-methyl-*N*-(tetrahydro-2*H*-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5*H*-benzo[7]annulene-8-carboxamide (9e)

According to general procedure A amide **7** (100 mg, 0.21 mmol), $PdCl_2$(dppf) (10 mg, 0.01 mmol, 5 mol%), $NaOCH_3$ (23 mg, 0.42 mmol, 2 eq.) and 4-butylphenylboronic acid (41 mg, 0.23 mmol, 1.1 eq.) were suspended in dry dimethoxyethane (6 mL). The crude

product was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give **9e** as a colorless solid. R_f = 0.32 (CH_2Cl_2 : MeOH= 95:5), mp 134-135 °C, yield 83 mg (76 %). $C_{35}H_{42}N_2O_2$ (522.7 g/mol). Purity (HPLC): 99 %, t_R = 22.95 min. HRMS (APCI): m/z = calcd. for $C_{35}H_{43}N_2O_2$ [MH^+] 523.3319, found 523.3335. ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.95 (t, *J* = 7.3 Hz, 3H, 4-CH_{3butyl}), 1.39 (h, 2H, 3-CH_{2butyl}), 1.55-1.81 (m, 6H, 3-C$H_{2pyran,}$ 5-CH_{2pyran}, 2-CH_{2butyl}), 2.07-2.19 (m, 2H, 6-CH_2), 2.21 (s, 3H, N-CH_3), 2.58-2.70 (m, 3H, 4-C$H_{pyran,}$ 1-CH_{2butyl}), 2.71 (t, *J* = 6.5 Hz, 2H, 7-CH_2), 2.82-2.92 (m, 2H, 5-CH_2), 3.37 (td, *J* = 11.3/2.3 Hz, 2H, CH_{2axial}-O-CH_{2axial}), 3.57 (s, 2H, Ph-CH_2-N), 4.04 (dd, *J* = 11.3/4.0 Hz, 2H, CH_{2equat}-O-$CH_{2equat.}$), 7.19-7.27 (m, 3H, *4*-C*H,* 3-C$H_{butylphenyl}$, 5-C$H_{butylphenyl}$), 7.31 (d, *J* = 8.3 Hz, 2H, 3-CH_{phenyl}, 5-CH_{phenyl}), 7.41 (s, 1H, 9-C*H*), 7.44 (dd, *J* = 7.8/2.0 Hz, 1H, 3-C*H*), 7.46-7.53 (m, 3H, 1-CH, 2-C$H_{butylphenyl}$ 6-C$H_{butylphenyl}$), 7.56 (d, *J* = 8.4 Hz, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.67 (s, 1H, N-*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 14.4 (*C*-4_{butyl}), 22.9 (*C*-3_{butyl}), 28.4 (*C*-6), 29.6 (*C*-3_{pyran}, *C*-5_{pyran}), 30.9 (*C*-7), 34.1 (*C*-2_{butyl}), 35.1 (*C*-5), 35.7 (*C*-1_{butyl}), 38.0 (N-*C*H_3), 57.8 (Ph-*C*H_2-N), 60.0 (*C*-4_{pyran}), 68.2 (*C*-2_{pyran}, *C*-6_{pyran}), 120.5 (*C*-2_{phenyl}, *C*-6_{phenyl}), 127.2 (*C*-$2_{butylphenyl}$, *C*-$6_{butylphenyl}$), 127.3 (*C*-$3_{butylphenyl}$, *C*-$5_{butylphenyl.}$), 129.4 (*C*-3), 129.9 (*C*-3_{phenyl}, *C*-5_{phenyl}), 130.3 (*C*-4), 131.2 (*C*-1), 134.8 (*C*-9), 135.1 (*C*-4a), 136.3 (*C*-$1_{butylphenyl.}$), 137.3 (*C*-4_{phenyl}), 138.1 (*C*-1_{phenyl}), 138.3 (C-2), 139.6 (*C*-9a), 141.7 (*C*-8), 142.6 (*C*-$4_{butylphenyl.}$), 168.5 (O=*C*-NH). FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3352 (N-H), 2951, 2927 (C-H_{alkyl}), 1643 (C=O), 1087 (C-O).

2-(4-*tert*-Butylphenyl)-*N*-{4-[*N*-methyl-*N*-(tetrahydro-2*H*-pyran-4-yl) aminomethyl]phenyl}-6,7-dihydro-5*H*-benzo[7]annulene-8-carboxamide (9f)

According to general procedure A amide **7** (100 mg, 0.21 mmol), $PdCl_2$(dppf) (8 mg, 0.01 mmol, 5 mol%), KOAc (42 mg, 0.42 mmol, 2 eq.) and 4-*tert*-butylphenylboronic acid (45 mg, 0.25 mmol, 1.2 eq.) were suspended in dry dimethoxyethane (8 mL). The crude product was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give **9f** as a colorless solid. (R_f = 0.22, CH_2Cl_2 : MeOH= 95:5), mp 164-165 °C, yield 88 mg (79 %). $C_{35}H_{42}N_2O_2$ (522.7 g/mol). Purity (HPLC): 99 %, t_R = 22.9 min. HRMS (APCI): m/z = calcd. for $C_{35}H_{43}N_2O_2$ [MH^+] 523.3319, found 523.3335. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.36 (s, 9H, 2-CH_{3butyl}, 3-C$H_{3butyl,}$ 4-CH_{3butyl}), 1.62-1.84 (m, 4H, 3-C$H_{2pyran,}$ 5-CH_{2pyran}), 2.17 (t, *J* = 5.9 Hz, 2H, 6-CH_2), 2.21 (s, 3H, N-CH_3), 2.51-2.69 (m, 1H, 4-CH_{pyran}), 2.72 (t, *J* = 6.6 Hz, 2H, 7-CH_2), 2.84-2.94 (m, 2H, 5-CH_2), 3.37 (td, *J* = 11.5/2.3 Hz, 2H, CH_{2axial}-O-CH_{2axial}), 3.57 (s, 2H, Ph-CH_2-N), 4.04 (dd, *J* = 10.9/4.1 Hz, 2H, CH_{2equat}-O-CH_{2equat}), 7.23 (d, *J* = 7.8, 1H, 4-C*H*), 7.31 (d, *J* = 8.4 Hz, 2H, 3-CH_{phenyl}, 5-

C*H*$_{phenyl}$), 7.41-7.44 (m, 2H, 9-C*H,* 3-C*H*), 7.47 (d, *J* = 8.4 Hz, 2H, 3-C*H*$_{butylphenyl}$, 5-C*H*$_{butylphenyl}$), 7.51-7.54 (m, 3H, 1-CH, 2-C*H*$_{butylphenyl.}$ 6-C*H*$_{butylphenyl}$), 7.56 (d, *J* = 8.5 Hz, 2H, 2-*H*$_{phenyl}$, 6-*H*$_{phenyl}$), 7.62 (s, 1H, N-*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 28.4 (*C*-6), 29.6 (*C*-3$_{pyran}$, *C*-5$_{pyran}$), 30.9 (*C*-7), 31.8 (C-2$_{bytyl}$, C-3$_{butyl}$, C-4$_{butyl}$), 35.1 (*C*-5), 38.0 (N-*C*H_3), 57.8 (Ph-*C*H_2-N), 60.0 (*C*-4$_{pyran}$), 68.2 (*C*-2$_{pyran}$, *C*-6$_{pyran}$), 85.5 (C-1$_{bytyl}$),120.5 (*C*-2$_{phenyl}$, *C*-6$_{phenyl}$), 126.2 (*C*-2$_{butylphenyl}$, *C*-6$_{butylphenyl}$), 127.0 (*C*-3$_{butylphenyl}$, *C*-5$_{butylphenyl.}$), 127.4 (*C*-3), 129.9 (*C*-3$_{phenyl}$, *C*-5$_{phenyl}$), 130.3 (*C*-4), 131.2 (*C*-1), 134.8 (*C*-9), 135.1 (*C*-4a), 136.3 (*C*-1$_{butylphenyl.}$), 137.3 (*C*-4$_{phenyl}$), 137.9 (*C*-1$_{phenyl}$), 138.3 (C-2), 139.5 (*C*-9a), 141.7 (*C*-8), 150.8 (*C*-4$_{butylphenyl.}$), 168.5 (O=*C*-NH). FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3352 (N-H), 2966, 2904 (C-H$_{alkyl}$), 1651 (C=O), 1064, 1022 (C-O).

2-([1,1'-Biphenyl]-4-yl)-*N*-{4-[*N*-methyl-*N*-(tetrahydro-2*H*-pyran-4yl)-aminomethyl]phenyl}-6,7-dihydro-5*H*-benzo[7]annulene-8-carboxamide (9g)

According to general procedure A amide **7** (200 mg, 0.42 mmol), $PdCl_2$(dppf) (16 mg, 0.02 mmol, 5 mol%), KOAc (84 mg, 0.84 mmol, 2 eq.) and 1,1'-biphenylboronic acid (130 mg, 0.64 mmol, 1.5 eq.) were suspended in dry dimethoxyethane (10 mL). The crude product was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give **9g** as a colorless solid. R_f = 0.15 (CH_2Cl_2 : MeOH= 95:5), mp 203 °C, yield 205 mg (90 %). $C_{37}H_{38}N_2O_2$ (542.7 g/mol). Purity (HPLC): >99 %, t_R = 25.01 min. HRMS (APCI): m/z = calcd. for $C_{37}H_{39}N_2O_2$ [MH^+] 543.3006, found 543.3017. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.62-1.82 (m, 4H, 3-C*H*$_{2pyran,}$ 5-C*H*$_{2pyran}$), 2.13-2.18 (m, 2H, 6-C*H*$_2$), 2.21 (s, 3H, N-C*H*$_3$), 2.56-2.69 (s, 1H, 4-C*H*$_{pyran}$), 2.74 (t, *J* = 6.6 Hz, 2H, 7-C*H*$_2$), 2.85-3.08 (m, 2H, 5-C*H*$_2$), 3.37 (td, *J* = 11.6/2.4 Hz, 2H, CH$_{2axial}$-O-CH$_{2axial}$), 3.57 (s, 2H, Ph-C*H*$_2$-N), 4.04 (dd, *J* = 10.6/4.1 Hz, 2H, CH$_{2equat}$-O-CH$_{2equat}$), 7.27 (d, *J* = 8.1 Hz, 1H, *4*-C*H*), 7.31 (d, *J* = 8.4 Hz, 2H, 3-C*H*$_{phenyl}$, 5-C*H*$_{phenyl}$), 7.34-7.39 (m, 1H, 4´-C*H*$_{biphenyl}$), 7.43-7.49 (m, 3H, 9-C*H,* 3-C*H*$_{phenyl.}$, 5-C*H*$_{phenyl.}$), 7.51 (dd, *J* = 7.8/2.0 Hz, 1H, 3-C*H*), 7.53-7.61 (m, 3H, 1-CH, 2-C*H*$_{biphenyl.}$ 6-C*H*$_{biphenyl}$), 7.62-7.65 (m, 3H, 2-*H*$_{phenyl}$, 6-*H*$_{phenyl}$, N-*H*), 7.65-7.69 (m, 4H, 2´, 3´, 5´, 6´-CH$_{biphenyl}$). ^{13}C NMR ($CDCl_3$): δ (ppm) = 28.4 (*C*-6), 29.6 (*C*-3$_{pyran}$, *C*-5$_{pyran}$), 30.9 (*C*-7), 35.1 (*C*-5), 38.0 (N-*C*H_3), 57.8 (Ph-*C*H_2-N), 60.0 (*C*-4$_{pyran}$), 68.2 (*C*-2$_{pyran}$, *C*-6$_{pyran}$), 120.5 (*C*-2$_{phenyl}$, *C*-6$_{phenyl}$), 127.4 (C-4´$_{phenyl}$), 127.5 (C-3´$_{biphenyl}$, C-5´$_{biphenyl}$), 127.7 (C-3$_{biphenyl}$, C-5$_{biphenyl}$), 127.84 (*C*-3), 128.0 (*C*-2´$_{biphenyl}$, C-6´$_{biphenyl}$), 129.3 (*C*-2$_{biphenyl}$, *C*-6$_{biphenyl}$), 129.9 (*C*-3$_{phenyl}$, *C*-5$_{phenyl}$), 130.5 (*C*-4), 131.2 (*C*-1), 134.7 (*C*-9), 135.2 (*C*-4a), 137.3 (C-4$_{phenyl}$), 137.9 (*C*-1$_{phenyl}$), 138.6 (C-2), 139.2 (*C*-9a), 139.8 (*C*-4$_{biphenyl}$), 140.6 (C-1´$_{biphenyl}$), 141.1 (C-1$_{biphenyl}$), 142.1 (*C*-8), 168.3 (O=*C*-

NH). FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3344 (N-H), 2970, 2940 (C-H_{alkyl}), 1647 (C=O), 1138, 1056 (C-O).

_N_-{4-[_N_-Methyl-_N_-(tetrahydro-2_H_-pyran-4-yl)aminomethyl]phenyl}-2-(naphtalen-2-yl)-6,7-dihydro-5_H_-benzo[7]annulene-8-carboxamide (9h)

According to general procedure A amide **7** (100 mg, 0.21 mmol), $PdCl_2$(dppf) (8 mg, 0.01 mmol, 5 mol%), KOAc (40 mg, 0.42 mmol, 2 eq.) and 2-naphthylboronic acid (40 mg, 0.23 mmol, 1.1 eq.) were suspended in dry dimethoxyethane (5 mL).). The crude product was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give **9h** as a colorless solid. R_f = 0.19, CH_2Cl_2 : MeOH= 95:5), mp 172-174 °C, yield 84 mg (77 %). $C_{35}H_{36}N_2O_2$ (516.6 g/mol). Purity (HPLC): 96 %, t_R = 21.57 min. HRMS (APCI): m/z = calcd. for $C_{35}H_{37}N_2O_2$ [MH^+] 517.2850, found 517.2880. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.63-1.88 (m, 4H, 3-C$H_{2pyran,}$ 5-CH_{2pyran}), 2.15-2.20 (m, 2H, 6-CH_2), 2.21 (s, 3H, N-CH_3), 2.64 (tt, J = 11.1/4.1 Hz, 1H, 4-C$H_{pyran,}$), 2.75 (t, J = 6.6 Hz, 2H, 7-CH_2), 2.87-2.97 (m, 2H, 5-CH_2), 3.37 (td, J = 11.6/2.4 Hz, 2H, CH_{2axial}-O-CH_{2axial}), 3.57 (s, 2H, Ph-CH_2-N), 4.04 (dd, J = 10.8/4.3 Hz, 2H, CH_{2equat}-O-CH_{2equat}), 7.28-7.37 (m, 3H, *4*-C*H,* 3-CH_{phenyl}, 5-CH_{phenyl}), 7.45-7.54 (m, 3H, 9-C*H*, 6,7-C$H_{naphthyl}$), 7.55-7.61 (m, 3H, 3-CH, 2-CH_{phenyl}, 6-CH_{phenyl}), 7.63 (s, 1H, N-*H*), 7.68 (d, J = 2.0 Hz, 1H, 1-CH,), 7.74 (dd, J = 8.5/1.9 Hz, 1H, 3-C$H_{naphtyl}$), 7.82-7.98 (m, 3H, 1-C$H_{naphthyl}$, 5,8-C$H_{naphthyl}$), 8.04 (d, J = 1.8 Hz, 1H, 4-C$H_{naphthyl}$). ^{13}C NMR ($CDCl_3$): δ (ppm) = 28.4 (*C*-6), 29.6 (*C*-3_{pyran}, *C*-5_{pyran}), 30.9 (*C*-7), 35.1 (*C*-5), 38.0 (N-*C*H_3), 57.7 (Ph-*C*H_2-N), 60.0 (*C*-4_{pyran}), 68.2 (*C*-2_{pyran}, *C*-6_{pyran}), 120.5 (*C*-2_{phenyl}, *C*-6_{phenyl}), 125.8 (*C*-$3_{naphthyl}$), 126.0 (*C*-$4_{naphthyl}$), 126.4 (*C*-$7_{naphthyl}$), 126.8 (*C*-3), 127.8 (*C*-$1_{naphthyl}$), 128.1 (*C*-$5_{naphthyl}$), 128.6 (*C*-$8_{naphthyl}$), 128.9 (*C*-$6_{naphthyl}$), 129.9 (*C*-3_{phenyl}, *C*-5_{phenyl}), 130.5 (*C*-4), 131.6 (*C*-1), 133.1 (*C*-$4a_{naphthyl}$), 134.1 (*C*-$8a_{naphtyl}$), 134.7 (*C*-9), 135.3 (*C*-4a), 136.4 (*C*-$2_{naphtyl}$), 137.3 (*C*-4_{phenyl}), 138.2 (*C*-1_{phenyl}), 138.6 (C-2), 139.6 (*C*-9a), 142.1 (*C*-8), 168.5 (O=*C*-NH). FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3298 (N-H), 2970, 2940 (C-H_{alkyl}), 1645 (C=O), 1099, 1010 (C-O).

2-(2-Fluoropyridin-3-yl)-_N_-{4-[_N_-methyl-_N_-(tetrahydro-2_H_-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5_H_-benzo[7]annulene-8-carboxamide (9j)

According to general procedure A amide **7** (150 mg, 0.32 mmol), $PdCl_2$(dppf) (12 mg, 0.016 mmol, 5 mol%), KOAc (40 mg, 0.64 mmol, 2 eq.) and 2-fluoropyridine-3-ylboronic acid (68 mg, 0.48 mmol, 1.5 eq.) were suspended in dry dimethoxyethane (8 mL). The crude product was purified by fc (CH_2Cl_2: EtOAC + 5 % MeOH = 2:1) and recrystallized

from acetonitrile to give **9j** as a pale yellow solid. R_f = 0.17 (CH_2Cl_2 : MeOH= 95:5), mp 154-156 °C, yield 59 mg (60 %). $C_{30}H_{32}FN_3O_2$ (485.6 g/mol). Purity (HPLC): 98 %, t_R = 18.35 min. HRMS (APCI): m/z = calcd. for $C_{30}H_{33}FN_3O_2$ [MH^+] 486.2551, found 486.2524. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.63-1.85 (m, 4H, 3-C*H*$_{2pyran,}$ 5-C*H*$_{2pyran}$), 2.12-2.20 (m, 2H, 6-C*H*$_2$), 2.24 (s, 3H, N-C*H*$_3$), 2.64-2.81 (m, 3H, 4-C*H*$_{pyran}$, 7-C*H*$_2$), 2.84-2.96 (m, 2H, 5-C*H*$_2$), 3.37 (td, *J* = 11.7/2.2 Hz, 2H, C*H*$_{2axial}$-O-C*H*$_{2axial}$), 3.61 (s, 2H, Ph-C*H*$_2$-N), 4.04 (dd, *J* = 11.2/4.4 Hz, 2H, C*H*$_{2equat}$-O-C*H*$_{2equat}$), 7.26 (m, 1H, 4-C*H*), 7.27-7.32 (m, 2H, 9-C*H,* 5-C*H*$_{pyridine}$), 7.34 (d, *J* = 7.9 Hz, 2H, 3-C*H*$_{phenyl}$, 5-C*H*$_{phenyl}$), 7.43 (d, *J* = 7.8 Hz, 1H, 3-C*H*), 7.50 (s, 1H, 1-C*H*), 7.57 (d, *J* = 8.4 Hz, 2H, 2-*H*$_{phenyl}$, 6-*H*$_{phenyl}$), 7.69 (s, 1H, N-*H*), 7.87 (ddd, *J* = 9.7/7.4/2.0 Hz, 1H, 4-C*H*$_{pyridine}$), 8.20 (d, *J* = 4.6 Hz, 1H, 6-C*H*$_{pyridine}$). ^{13}C NMR ($CDCl_3$): δ (ppm) = 28.3 (*C*-6), 29.5 (*C*-3$_{pyran,}$ *C*-5$_{pyran}$), 30.9 (*C*-7), 35.2 (*C*-5), 37.8 (N-*C*H_3), 57.7 (Ph-*C*H_2-N), 60.0 (*C*-4$_{pyran}$), 68.0 (*C*-2$_{pyran,}$ *C*-6$_{pyran}$), 120.5 (*C*-2$_{phenyl,}$ *C*-6$_{phenyl}$), 122.3 (d, *J* = 4.3 Hz, C-3$_{pyridine}$), 123.5 (*C*-3), 129.1 (d, *J* = 2.6 Hz, C-5$_{pyridine}$), 130.1 (*C*-3$_{phenyl}$, *C*-5$_{phenyl}$), 130.4 (*C*-4), 132.4 (*C*-2), 132.7 (*C*-4$_{phenyl}$), 132.8 (*C*-1), 134.1 (*C*-9), 135.3 (*C*-4a), 139.0 (*C*-1$_{phenyl}$), 140.9 (*C*-9a), 140.9 (d, *J* = 10.7 Hz, *C*-4$_{pyridine}$), 143.3 (*C*-8), 146.8 (d, *J* = 14.6 Hz, C-6$_{pyridine}$), 162.1 (d, *J* = 238.1 Hz, C-2$_{pyridine}$), 168.4 (O=*C*-NH). FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3294 (N-H), 2943, 2924 (C-H$_{alkyl}$), 1647 (C=O), 1141, 1010 (C-O), 759, 725 (out of plane).

2-(6-Isopropoxypyridin-3-yl)-*N*-{4-[*N*-methyl-*N*-(tetrahydro-2*H*-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5*H*-benzo[7]annulene-8-carboxamide (9k)

According to general procedure A amide **7** (172 mg, 0.37 mmol), $PdCl_2$(dppf) (15 mg, 0.02 mmol, 5 mol%), KOAc (73 mg, 0.74 mmol, 2 eq.) and 6-isopropoxypyridine-3-ylboronic acid (100 mg, 0.55 mmol, 1.5 eq.) were suspended in dry dimethoxyethane (10 mL). The crude product was purified by fc (CH_2Cl_2: EtOAC + 5 % MeOH = 2:1) and recrystallized from acetonitrile to give **9k** as a colorless solid. R_f = 0.06 (CH_2Cl_2: EtOAC + 5 % MeOH = 2:1), mp 173-175 °C, yield 132 mg (67 %). $C_{33}H_{39}N_3O_3$ (525.7 g/mol). Purity (HPLC): 99 %, t_R = 19.75 min. HRMS (APCI): m/z = calcd. for $C_{33}H_{40}N_3O_3$ [MH^+] 526.3064, found 526.3077. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.38 (d, 6.2 Hz, 6H, CH(C*H*$_3$)$_2$), 1.52-1.87 (m, 4H, 3-C*H*$_{2pyran,}$ 5-C*H*$_{2pyran}$), 2.07-2.20 (m, 2H, 6-C*H*$_2$), 2.21 (s, 3H, N-C*H*$_3$), 2.58-2.69 (m, 1H, 4-C*H*$_{pyran}$), 2.72 (t, *J* = 6.6 Hz, 2H, 7-C*H*$_2$), 2.81-2.98 (m, 2H, 5-C*H*$_2$), 3.37 (td, *J* = 11.6/2.3 Hz, 2H, CH$_{2axial}$-O-CH$_{2axial}$), 3.57 (s, 2H, Ph-C*H*$_2$-N), 4.04 (dd, *J* = 11.5/4.3 Hz, 2H, CH$_{2equat}$-O-CH$_{2equat}$), 5.34 (sept., *J* = 6.2 Hz, 1H, C*H*(CH$_3$)$_2$), 6.75 (d, *J* = 8.6 Hz, 1H, 5-CH$_{pyridine}$), 7.24 (d, *J* = 8.1 Hz, 1H, 4-C*H*), 7.31 (d, *J* = 8.2 Hz, 2H, 3-

C*H*$_{phenyl}$, 5-C*H*$_{phenyl}$), 7.37 (dd, *J* = 7.9/1.8 Hz, 1H, 3-C*H*), 7.40 (s, 1H, 9-C*H*), 7.44 (s, 1H, 1-C*H*), 7.56 (d, *J* = 8.4 Hz, 2H, 2-*H*$_{phenyl}$, 6-*H*$_{phenyl}$), 7.64 (s, 1H, N-*H*), 7.75 (dd, *J* = 8.6/2.6 Hz, 1H, 4-CH$_{pyridine}$), 8.35 (d, *J* = 2.6 Hz, 1H, 2-CH$_{pyridine}$). ^{13}C NMR ($CDCl_3$): δ (ppm) = 22.6 (CH(*C*H$_3$)$_2$), 28.5 (*C*-6), 29.7 (*C*-3$_{pyran}$, *C*-5$_{pyran}$), 30.9 (*C*-7), 35.0 (*C*-5), 37.9 (N-*C*H$_3$), 57.7 (Ph-*C*H$_2$-N), 60.0 (*C*-4$_{pyran}$), 68.2 (*C*-2$_{pyran}$, *C*-6$_{pyran}$), 68.6 (*C*H(CH$_3$)$_2$), 111.9 (*C*-5$_{pyridine}$), 120.5 (*C*-2$_{phenyl}$, *C*-6$_{phenyl}$), 126.9 (*C*-3), 129.3 (*C*-2), 129.9 (*C*-3$_{phenyl}$, *C*-5$_{phenyl}$), 130.5 (*C*-4), 130.7 (*C*-1), 134.5 (*C*-9), 135.4 (*C*-4a), 136.6 (C-4$_{phenyl}$), 137.2 (C-4$_{pyridine}$), 137.7 (*C*-9a, C-3$_{pyridine}$), 138.7 (*C*-1$_{phenyl}$), 141.9 (*C*-8), 145.3 (*C*-2$_{pyridine}$), 163.4 (*C*-6$_{pyridine}$), 168.3 (O=*C*-NH). FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3321 (N-H), 2924, 2835 (C-H$_{alkyl}$), 1643 (C=O), 1114, 1049 (C-O), 709, 686 (out of plane bending).

2-(4-Fluorophenyl)-*N*-{[*N*-methyl-*N*-(tetrahydro-2*H*-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5*H*-benzo[7]annulene-8-carboxamide (9l)

According to general procedure A amide **7** (57 mg, 0.12 mmol), $PdCl_2$(dppf) (10 mg, 0.01 mmol, 10 mol%), $NaOCH_3$ (14 mg, 0.24 mmol, 2 eq.) and 4-fluorophenylboronic acid (19 mg, 0.13 mmol, 1.1 eq.) were suspended in dry dimethoxyethane (5 mL). The crude product was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give **9l** as a colorless solid. R_f = 0.25 (CH_2Cl_2 : MeOH = 95:5), mp 192 °C, yield 38 mg (65 %). $C_{31}H_{33}FN_2O_2$ (484.6 g/mol). Purity (HPLC): 97 %, t_R = 20.78 min. HRMS (APCI): m/z = calcd. for $C_{31}H_{34}FN_2O_2$ [MH$^+$] 485.2599, found 485.2598. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.59-1.84 (m, 4H, 3-C*H*$_{2pyran,}$ 5-C*H*$_{2pyran}$), 2.10-2.22 (m, 2H, 6-C*H*$_2$), 2.24 (s, 3H, N-C*H*$_3$), 2.64-2.77 (m, 3H, 4-C*H*$_{pyran,}$7-C*H*$_2$), 2.82-2.95 (m, 2H, 5-C*H*$_2$), 3.37 (td, *J* = 11.7/2.1 Hz, 2H, CH$_{2axial}$-O-CH$_{2axial}$), 3.61 (s, 2H, Ph-C*H*$_2$-N), 4.04 (dd, *J* = 11.0/3.9 Hz, 2H, CH$_{2equat}$-O-CH$_{2equat}$), 7.09 (m, 2H, 3-C*H*$_{F\text{-}phen}$, 5-C*H*$_{F\text{-}phen}$), 7.24 (d, *J* = 7.8 Hz, 1H, *4*-C*H*), 7.34 (d, *J* = 8.1 Hz, 2H, 3-C*H*$_{phenyl}$, 5-C*H*$_{phenyl}$), 7.40 (dd, *J* = 7.8/2.0 Hz, 1H, 3-C*H*), 7.42 (s, 1H, 9-C*H*), 7.48 (d, *J* = 1.8 Hz, 1H, 1-C*H,*) 7.51-7.55 (m, 2H, 2-C*H*$_{F\text{-}phen}$, 6-C*H*$_{F\text{-}phen}$), 7.57 (d, *J* = 8.4 Hz, 2H, 2-C*H*$_{phenyl}$, 6-C*H*$_{phenyl}$), 7.64 (s, 1H, N-*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 27.7 (*C*-6), 28.9 (*C*-3$_{pyran}$, *C*-5$_{pyran}$), 30.3 (*C*-7), 34.4 (*C*-5), 37.2 (N-*C*H$_3$), 57.1 (Ph-*C*H$_2$-N), 59.4 (*C*-4$_{pyran}$), 67.4 (*C*-2$_{pyran}$, *C*-6$_{pyran}$), 115.5 (d, *J* = 21.5 Hz, *C*-3$_{F\text{-}phen}$, *C*-5$_{F\text{-}phen}$), 119.8 (*C*-2$_{phenyl}$, *C*-6$_{phenyl}$), 126.7 (*C*-3), 128.3 (d, *J* = 8.0 Hz, *C*-2$_{F\text{-}phen}$, *C*-6$_{F\text{-}phen}$), 129.4 (*C*-3$_{phenyl}$, *C*-5$_{phenyl}$), 129.8 (*C*-4), 130.5 (*C*-1), 134.0 (*C*-9a), 134.6 (*C*-4$_{phenyl}$), 135.5 (*C*-9), 135.9 (*C*-4a), 136.3 (d, *J* = 3.1 Hz, *C*-1$_{F\text{-}phen}$), 137.9 (*C*-2), 138.1 (*C*-1$_{phenyl}$), 141.3 (*C*-8), 162.3 (d, *J* = 248.6 Hz, C-4$_{F\text{-}phen}$), 167.7 (O=*C*-NH).

FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3298 (N-H), 2939, 2924 (C-H_{alkyl}), 1647 (C=O), 1141, 1010 (C-O).

2-(4-Fluoro-3-methylphenyl)-*N*-{4-[*N*-methyl-*N*-(tetrahydro-2*H*-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5*H*-benzo[7]annulene-8-carboxamide (9m)

According to general procedure A amide **7** (65 mg, 0.14 mmol), $PdCl_2$(dppf) (12 mg, 0.01 mmol, 10 mol%), K_2CO_3 (59 mg, 0.42 mmol, 3 eq.) and 4-fluoro-3-methylphenylboronic acid (24 mg, 0.15 mmol, 1.1 eq.) were suspended in dry dimethoxyethane (5 mL). The crude product was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give **9m** as a colorless solid. R_f = 0.33, CH_2Cl_2 : MeOH = 95:5), mp 161-162 °C (dec.) yield 48 mg (70 %). $C_{32}H_{35}FN_2O_2$ (498.6 g/mol). Purity (HPLC): 98 %, t_R = 21.48 min. HRMS (APCI): m/z = calcd. for $C_{32}H_{36}FN_2O_2$ [MH^+] 499.2755, found 499.2773. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.61-1.90 (m, 4H, 3-C$H_{2pyran,}$ 5-CH_{2pyran}), 2.10-2.22 (m, 2H, 6-CH_2), 2.28 (s, 3H, N-CH_3), 2.34 (s, 3H, $CH_{3F\text{-}phen.}$), 2.72 (t, *J* = 6.2 Hz, 2H, 7-CH_2), 2.74-2.81 (m, 1H, 4-CH_{pyran}), 2.84-2.93 (m, 2H, 5-CH_2), 3.37 (td, *J* = 11.7/2.0 Hz, 2H, CH_{2axial}-O-CH_{2axial}), 3.67 (s, 2H, Ph-CH_2-N), 4.05 (dd, *J* = 11.2/3.9 Hz, 2H, CH_{2equat}-O-CH_{2equat}), 7.06 (m, 5-C$H_{F\text{-}phen}$), 7.23 (d, *J* = 7.7 Hz, 1H, *4*-C*H*), 7.30-7.37 (m, 2H, 2-C$H_{F\text{-}phen}$, 3-C*H*), 7.36 (d, *J* = 8.6 Hz, 2H, 3-CH_{phenyl}, 5-CH_{phenyl}), 7.40 (m, 1H, 6-C$H_{F\text{-}phen}$), 7.42 (s, 1H, 9-C*H*), 7.48 (d, *J* = 1.8 Hz, 1H, 1-C*H*), 7.58 (d, *J* = 8.4 Hz, 2H, 2-CH_{phenyl}, 6-CH_{phenyl}), 7.66 (s, 1H, N-*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 14.56 (d, *J* = 3.2 Hz, $CH_{3F\text{-}phen}$), 27.7 (*C*-6), 28.3 (*C*-$3_{pyran,}$ *C*-5_{pyran}), 30.3 (*C*-7), 34.4 (*C*-5), 36.5 (N-*C*H_3), 56.7 (Ph-*C*H_2-N), 59.8 (*C*-4_{pyran}), 67.1 (*C*-$2_{pyran,}$ *C*-6_{pyran}), 115.1 (d, *J* = 21.5 Hz, *C*-$5_{F\text{-}phen}$), 120.0 (*C*-$2_{phenyl,}$ *C*-6_{phenyl}), 125.5 (d, *J* = 8.2 Hz, *C*-$6_{F\text{-}phen}$), 126.7 (*C*-3), 129.8 (*C*-4), 129.8 (d, *J* = 5.2 Hz, *C*-$2_{F\text{-}phen}$),130.0 (*C*-3_{phenyl}, *C*-5_{phenyl}), 130.5 (*C*-1), 134.4 (d, *J* = 18.8 Hz, *C*-$3_{F\text{-}phen}$), 134.0 (*C*-9a), 134.6 (*C*-4_{phenyl}), 135.9 (*C*-9), 136.0 (d, *J* = 3.7 Hz, *C*-$1_{F\text{-}phen.}$), 136.3 (*C*-4a), 137.7 (*C*-2), 138.3 (*C*-1_{phenyl}), 141.2 (*C*-8), 160.9 (d, *J* = 245.2 Hz, C-$4_{F\text{-}phen}$), 167.8 (O=*C*-NH). FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3286 (N-H), 2924, 2843 (C-H_{alkyl}), 1651 (C=O), 1138, 1006 (C-O).

2-(4-Hydroxy-3-methylphenyl)-*N*-{4-[*N*-methyl-*N*-(tetrahydro-2*H*-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5*H*-benzo[7]annulene-8-carboxamide (9o)

According to general procedure A amide **7** (162 mg, 0.34 mmol), $PdCl_2$(dppf) (14 mg, 0.017 mmol, 5 mol%), $NaOCH_3$ (38 mg, 0.68 mmol, 2 eq.) and 4-hydroxy-3-methylphenylboronic acid (90 mg, 0.38 mmol, 1.1 eq.) were suspended in dry

dimethoxyethane (7 mL). The crude product was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give **9o** as a colorless solid. R_f = 0.11 (CH_2Cl_2 : EtOAc + 5 % MeOH= 2:1), mp 192 °C , yield 128 mg (76 %).

$C_{32}H_{36}N_2O_3$ (496.6 g/mol). Purity (HPLC): 96 %, t_R = 19.32 min. HRMS (APCI): m/z = calcd. for $C_{32}H_{37}N_2O_3$ [MH^+] 497.2799, found 497.2778. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.55-1.73 (m, 4H, 3-C*H*$_{2pyran,}$ 5-C*H*$_{2pyran}$), 2.03-2.12 (m, 2H, 6-C*H*$_2$), 2.14 (s, 3H, C*H*$_{3hydroxyphen.}$), 2.25 (s, 3H, N-C*H*$_3$), 2.51-2.62 (m, 1H, 4-C*H*$_{pyran,}$), 2.65 (t, *J* = 6.5 Hz, 2H, 7-C*H*$_2$), 2.76-2.86 (m, 2H, 5-C*H*$_2$), 3.37 (td, *J* = 11.6/2.4 Hz, 2H, CH_{2axial}-O-CH_{2axial}), 3.50 (s, 2H, Ph-C*H*$_2$-N), 3.97 (dd, *J* = 10.9/4.3 Hz, 2H, CH_{2equat}-O-CH_{2equat}), 6.76 (d, *J* = 8.2 Hz, 1H, 5-C*H*$_{hydroxyphen}$), 7.13 (d, *J* = 7.9 Hz, 1H, 4-C*H*), 7.22 (d, *J* = 2.2 Hz, 1H, 2-C*H*$_{hydroxyphen}$), 7.24 (d, *J* = 8.3 Hz, 2H, 3-C*H*$_{phenyl}$, 5-C*H*$_{phenyl}$), 7.29 (m, 1H, 6-C*H*$_{hydroxyphen}$), 7.30-7.36 (m, 2H, 9-C*H,* 3-C*H*), 7.40 (d, *J* = 2.0 Hz, 1H, 1-C*H*), 7.49 (d, *J* = 8.4 Hz, 2H, 2-C*H*$_{phenyl}$, 6-C*H*$_{phenyl}$), 7.56 (s, 1H, N-*H*). ^{13}C NMR (DMSO-d_6): δ (ppm) = 16.2 ($CH_{3HO-phen}$), 27.5 (*C*-6), 28.9 (*C*-3$_{pyran}$, *C*-5$_{pyran}$), 30.2 (*C*-7), 34.0 (*C*-5), 37.1 (N-*C*H_3), 56.7 (Ph-*C*H_2-N), 58.9 (*C*-4$_{pyran}$), 66.7 (*C*-2$_{pyran}$, *C*-6$_{pyran}$), 109.3 (*C*-5$_{HO-phen}$), 115.0 (*C*-6$_{HO-phen}$), 119.9 (*C*-2$_{phenyl}$, *C*-6$_{phenyl}$), 124.3 (*C*-3), 124.7 (*C*-3$_{HO-phen}$), 125.5 (*C*-2$_{HO-phen}$), 128.7 (*C*-3$_{phenyl}$, *C*-5$_{phenyl}$), 129.5 (*C*-4), 129.8 (*C*-1), 130.2 (*C*-9a), 131.4, 133.4 (*C*-4$_{phenyl}$), 134.7 (*C*-9), 134.9 (*C*-4a), 137.9 (*C*-2), 138.1 (*C*-1$_{HO-phen}$), 138.2 (*C*-1$_{phenyl}$), 140.0 (*C*-8), 155.2 (*C*-4$_{HO-phen}$), 168.3 (O=*C*-NH). FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3352 (N-H), 2927, 2846 (C-H_{alkyl}), 1647 (C=O), 1161, 1083 (C-O), 810, 671 (out of plane bending).

2-[4-(Hydroxymethyl)phenyl]-*N*-{4-[*N*-methyl-*N*-(tetrahydro-2*H*-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5*H*-benzo[7]annulene-8-carboxamide (9p)

According to general procedure A amide **7** (100 mg, 0.21 mmol), $PdCl_2$(dppf) (15 mg, 0.02 mmol, 10 mol%), $NaOCH_3$ (23 mg, 0.42 mmol, 2 eq.) and 4-(hydroxymethyl)phenylboronic acid (35 mg, 0.23 mmol, 1.1 eq.) were suspended in dry dimethoxyethane (6 mL). The crude product was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give **9p** as a colorless solid. R_f = 0.08 (CH_2Cl_2 : MeOH = 95:5), mp 210 °C (dec.), yield 53 mg (51 %).

$C_{32}H_{36}N_2O_2$ (496.6 g/mol). Purity (HPLC): 96 %, t_R = 18.37 min. HRMS (APCI): m/z = calcd. for $C_{32}H_{37}N_2O_3$ [MH^+] 497.2799, found 497.2798. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.57-1.86 (m, 4H, 3-C*H*$_{2pyran,}$ 5-C*H*$_{2pyran}$), 2.10-2.22 (m, 2H, 6-C*H*$_2$), 2.23 (s, 3H, N-C*H*$_3$), 2.62-2.71 (m, 1H, 4-C*H*$_{pyran}$), 2.71-2.77 (m, 2H, 7-C*H*$_2$), 2.84-2.93 (m, 2H, 5-C*H*$_2$), 3.37 (td, *J* = 11.7/4.4 Hz, 2H, CH_{2axial}-O-CH_{2axial}), 3.60 (s, 2H, Ph-C*H*$_2$-N), 4.04 (dd, *J* =

11.0/3.9 Hz, 2H, CH_{2equat}-O-CH_{2equat}), 4.75 (s, 2H, CH_2OH), 7.25 (d, *J* = 7.8 Hz, 1H, 4-C*H*), 7.33 (d, *J* = 8.0 Hz, 2H, 3-CH_{phenyl}, 5-CH_{phenyl}), 7.42 (s, 1H, 9-C*H*), 7.43-7.47 (m, 3H, 3-C*H,* 3-C$H_{hydroxymethylphen}$, 5-C$H_{hydroxymethylphen}$), 7.53 (d, *J* = 2.0 Hz, 1H, 1-C*H*) 7.56 (d, *J* 7.5 Hz, 2H, 2-C$H_{hydroxymethylphen}$, 6-C$H_{hydroxymethylphen}$), 7.58 (d, *J* = 8.1 Hz, 2H, 2-CH_{phenyl}, 6-CH_{phenyl}), 7.66 (s, 1H, N-*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 28.1 (*C*-6), 29.3 (*C*-3_{pyran}, *C*-5_{pyran}), 30.6 (*C*-7), 34.7 (*C*-5), 37.7 (N-*C*H_3), 57.4 (Ph-*C*H_2-N), 59.7 (*C*-4_{pyran}), 65.2 (*C*H_2OH), 67.8 (*C*-2_{pyran}, *C*-6_{pyran}), 120.2 (*C*-2_{phenyl}, *C*-6_{phenyl}), 127.1 (*C*-3), 127.2 (*C*-$2_{hydroxymethylphen}$, *C*-$6_{hydroxymethylphen}$), 127.6 (*C*-$3_{hydroxymethylphen}$, *C*-$5_{hydroxymethylphen}$), 129.6 (*C*-3_{phenyl}, *C*-5_{phenyl}), 130.1 (*C*-4), 130.9 (*C*-1), 134.4 (*C*-9a), 134.8 (*C*-4_{phenyl}), 135.8 (*C*-9), 138.2 (*C*-2), 138.9 (*C*-1_{phenyl}), 139.9 (*C*-8), 141.7 (*C*-$4_{hydroxymethylphen}$), 148.8 (*C*-$1_{hydroxymethylphen}$). Signals for quaternary carbon atoms O=*C*-NH and *C*-4a are not visible.

2-(5-Formylthiophen-2-yl)-*N*-{4-[(methyl-*N*-(tetrahydro-2*H*-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5*H*-benzo[7]annulene-8-carboxamide (9v)

According to general procedure A amide **7** (60 mg, 0.13 mmol), $PdCl_2$(dppf) (10 mg, 0.01 mmol, 10 mol%), $NaOCH_3$ (14 mg, 0.25 mmol, 2 eq.) and 5-formylthiophen-2-ylboronic acid (50 mg, 0.32 mmol, 1.5 eq.) were suspended in dry dimethoxyethane (5 mL). The crude product was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give **9v** as an orange solid. R_f = 0.23 (CH_2Cl_2 : MeOH= 95:5), mp 168-169 °C, yield 43 mg (86 %). $C_{30}H_{32}N_2O_3S$ (500.6 g/mol). Purity (HPLC): 98 %, t_R = 19.66 min. HRMS (APCI): m/z = calcd. for $C_{30}H_{33}N_2O_3S$ [MH^+] 501.2206, found 501.2223. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.63-1.85 (m, 4H, 3-C$H_{2pyran,}$ 5-CH_{2pyran}), 2.09-2.22 (m, 2H, 6-CH_2), 2.25 (s, 3H, N-CH_3), 2.63-2.81(m, 3H, 4-C$H_{pyran,}$ 7-CH_2), 2.82-2.95 (m, 2H, 5-CH_2), 3.37 (td, *J* = 11.7/2.2 Hz, 2H, CH_{2axial}-O-CH_{2axial}), 3.63 (s, 2H, Ph-CH_2-N), 4.05 (dd, *J* = 11.6/4.1 Hz, 2H, CH_{2equat}-O-CH_{2equat}), 7.23-7.26 (m, 1H, 4-C*H*), 7.26 (s, 1H, 9-C*H*), 7.36 (d, *J* = 7.4 Hz, 2H, 3-C$H_{phenyl.}$, 5-CH_{phenyl}), 7.39 (d, *J* = 4.1 Hz, 1H, 4-CH_{thioph}), 7.52 (dd, *J* = 7.8/2.0 Hz, 1H, 3-C*H*), 7.58 (d, *J* = 8.6 Hz, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.61 (d, *J* = 1.9 Hz, 1H, 1-CH), 7.67 (s, 1H, N-*H*), 7.74 (d, *J* = 3.9 Hz, 1H, 3-CH_{thioph}), 9.89 (s, 1H, C*H*O). ^{13}C NMR ($CDCl_3$): δ (ppm) = 28.3 (*C*-6), 29.2 (*C*-3_{pyran}, *C*-5_{pyran}), 30.9 (*C*-7), 35.2 (*C*-5), 37.5 (N-*C*H_3), 57.5 (Ph-*C*H_2-N), 60.1 (*C*-4_{pyran}), 67.9 (*C*-2_{pyran}, *C*-6_{pyran}), 120.6 (*C*-2_{phenyl}, *C*-6_{phenyl}), 126.6 (*C*-3), 130.3 (*C*-3_{phenyl}, *C*-5_{phenyl}), 130.3 (*C*-4), 130.7 (*C*-$3_{thioph.}$), 131.6 (*C*-1), 133.8 (*C*-9), 135.4 (*C*-4a), 138.0 (*C*-$4_{thioph.}$, *C*-4_{phenyl}), 139.4 (*C*-1_{phenyl}), 138.0 (*C*-2), 139.4 (*C*-9a), 142.7 (*C*-8), 144.4 (*C*-2_{thioph}), 154.1 (*C*-5_{thioph}), 168.3 (O=*C*-NH), 183.2 (H*C*=O). FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3290 (N-H), 2924, 2843 (C-H_{alkyl}),

2789 (H-CO), 1647 (HC=O), 1593 (C=C_{aryl}), 1141, 1010 (C-O), 767, 667 out of plane bending.

2-(4-Methylphenyl)-*N*-{4-[*N*-methyl-*N*-(tetrahydro-2*H*-pyran-4-yl)aminomethyl]-phenyl}-7,8-dihydro-6*H*-[7]annuleno[*b*]thiophene-5-carboxamide (14a)

N-(4-Aminophenyl)-*N*-methyltetrahydro-2*H*-pyran-4-amin (78 mg, 0.35 mmol, 1 eq.) was added to a vigorously stirred mixture of acid **13a**[40](100 mg, 0.35 mmol), triethylamine (71 mg, 0.70 mmol, 2 eq.) and HATU™ (150 mg, 0.38 mmol. 1.1 eq.) in THF (5 mL). The mixture was stirred overnight at rt. The mixture was concentrated *in vacuo* and the residue was purified by fc (EtOAc : CH_2Cl_2 = 1:2 + 5% MeOH) and recrystallized from acetonitrile to give **14a** as a yellow solid. R_f = 0.13 (MeOH : CH_2Cl_2 = 5:95), mp 201 °C, yield 136 mg (80 %). $C_{30}H_{34}N_2O_2S$ (486.6 g/mol). Purity (HPLC): 95 %, t_R = 22.85 min. HRMS (APCI): m/z = calcd. for $C_{30}H_{35}N_2O_2S$ [MH^+] 487.2414, found 487.2381. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.55-1.83 (m, 4H, 3-C*H*$_{2pyran,}$ 5-C*H*$_{2pyran}$), 2.13 (quint, *J* = 5.1 Hz, 2H, 7-C*H*$_2$), 2.21 (s, 3H, N-C*H*$_3$), 2.36 (s, 3H, CH_{3tolyl}), 2.64 (tt, *J* = 10.9/3.5 Hz, 1H, 4-H_{pyran}), 2.84 (t, *J* = 5.8 Hz, 2H, 6-C*H*$_2$), 3.11 (t, *J* = 5.6 Hz, 2H, 8-C*H*$_2$), 3.37 (td, *J* = 11.6/2.3 Hz, 2H, CH_{2axial}-O-CH_{2axial}), 3.57 (s, 2H, Ph-C*H*$_2$-N), 4.04 (dd, *J* = 11.4/4.4 Hz, 2H, CH_{2equat}-O-CH_{2equat}), 7.07 (s, 1H, 3-C*H*), 7.14-7.24 (m, 3H, 3-C*H*$_{tolyl}$, 5-C*H*$_{tolyl,}$ 4-C*H*), 7.30 (d, *J* = 8.2 Hz, 2H, 3-C*H*$_{phenyl}$, 5-C*H*$_{phenyl}$), 7.42 (d, *J* = 8.1 Hz, 2H, 2-C*H*$_{tolyl}$, 6-C*H*$_{tolyl}$), 7.49-7.57 (m, 3H, 2-C*H*$_{phenyl}$, 6-C*H*$_{phenyl}$, N*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 21.6 (*C*H_{3tolyl}), 24.6 (*C*-7), 29.6 (*C*-3$_{pyran}$, *C*-5$_{pyran}$), 31.1 (*C*-8, *C*-6), 37.9 (N-*C*H_3), 57.7 (*C*-4$_{pyran}$), 59.9 (Ph-*C*H_2-N), 68.2 (*C*-2$_{pyran}$, *C*-6$_{pyran}$), 120.4 (*C*-2$_{phenyl}$, *C*-6$_{phenyl}$), 125.8 (*C*-2$_{tolyl}$, *C*-6$_{tolyl}$), 127.1 (*C*-3), 127.7 (*C*-4), 129.9 (*C*-3$_{phenyl}$, *C*-5$_{phenyl}$), 130.0 (*C*-3$_{tolyl}$, *C*-5$_{tolyl}$), 131.5 (C-1$_{tolyl}$), 133.8 (*C*-4$_{phenyl}$), 136.4 (*C*-1$_{phenyl}$), 137.7 (*C*-2), 137.8 (*C*-3a), 140.8 (*C*-5), 143.7 (*C*-8a), 146.3 (*C*-4$_{tolyl}$), 168.7 (O=*C*-NH). FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3309 (N-H), 2839 (C-H_{alkyl}), 1627 (C=O).

2-(4-Methylphenyl)-*N*-[2-(tetrahydro-2*H*-pyran-4-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-7,8-dihydro-6*H*-[7]annuleno[*b*]thiophene-5-carboxamide (14b)

2-(Tetrahydro-2*H*-pyran-4-yl)-1,2,3,4-tetrahydroisoquinolin-7-amine (82 mg, 0.35 mmol, 1 eq.) was added to a vigorously stirred mixture of acid **13a**[40] (100 mg, 0.35 mmol), triethylamine (71 mg, 0.70 mmol, 2 eq.) and HATU™ (150 mg, 0.38 mmol. 1.1 eq.) in THF (5 mL). The mixture was stirred overnight at rt. The mixture was concentrated *in vacuo* and the residue was purified by fc (EtOAc : CH_2Cl_2 = 1:2 + 5 % MeOH)) and

recrystallized from acetonitrile to give **14b** as a yellow solid. R_f = 0.34 (MeOH : CH_2Cl_2 = 5:95), mp 215°C (dec.), yield 120 mg (69 %). $C_{31}H_{34}N_2O_2S$ (498.6 g/mol). Purity (HPLC): 95 %, t_R = 20.90 min. HRMS (APCI): m/z = calcd. for $C_{31}H_{35}N_2O_2S$ [MH^+] 499.2414, found 499.2389. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.69 (dq, *J* = 12.1/4.2 Hz, 2H, 3-C*H*$_{2pyran-equat,}$ 5-C*H*$_{2pyran-equat}$), 1.81-1.90 (m, 2H, 3-C*H*$_{2pyran-axial,}$ 5-C*H*$_{2pyran-axial}$), 2.11 (quint., *J* = 5.9 Hz, 2H, 7-C*H*$_2$), 2.36 (s, 3H, CH_{3tolyl}), 2.65 (tt, *J* = 11.1/3.8 Hz, 1H, 4-H_{pyran}), 2.77-2.90 (m, 6H, 6-C*H*$_2$, 3-C*H*$_{2isoqu}$, 4-C*H*$_{2isoqu}$), 3.09 (t, *J* = 5.3 Hz, 2H, 8-C*H*$_2$), 3.42 (t, *J* = 12.1 Hz, 2H, CH_{2axial}-O-CH_{2axial}), 3.77 (s, 2H, 1-C*H*$_{2isoqu}$), 4.06 (dd, *J* = 11.8/4.0 Hz, 2H, CH_{2equat}-O-CH_{2equat}), 7.05-7.08 (m, 2H, 3-C*H*, 5-C*H*$_{isoqu}$), 7.14-7.24 (m, 3H, 3-C*H*$_{tolyl}$, 5-C*H*$_{tolyl}$, 4-C*H*), 7.21 (dd, *J* = 8.2/2.2 Hz, 1H, 6-C*H*$_{isoqu}$), 7.41 (d, *J* = 7.7 Hz, 2H, 2-C*H*$_{tolyl}$, 6-C*H*$_{tolyl}$), 7.43 (d, *J* = 2.2 Hz, 1H, 8-C*H*$_{isoqu}$), 7.55 (s, 1H, N*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 21.7 (*C*H_{3tolyl}), 24.6 (*C*-7), 29.4 (C-4$_{isoqu}$), 30.0 (*C*-3$_{pyran}$, *C*-5$_{pyran}$), 31.1 (*C*-8, *C*-6), 47.0 (C-3$_{isoqu}$), 52.5 (*C*-1$_{isoqu}$), 60.7 (*C*-4$_{pyran}$), 67.9 (*C*-2$_{pyran}$, *C*-6$_{pyran}$), 118.6 (*C*-8$_{isoqu.}$), 118.7 (*C*-6$_{isoqu}$), 125.8 (*C*-2$_{tolyl}$, *C*-6$_{tolyl}$), 127.1 (*C*-3), 127.6 (*C*-4), 129.6 (*C*-5$_{isoqu}$), 130.0 (*C*-3$_{tolyl}$, *C*-5$_{tolyl}$), 131.0 (*C*-1$_{tolyl}$), 131.5 (*C*-4a$_{isoqu}$), 133.9 (*C*-8a$_{isoqu}$), 136.2 (*C*-4$_{tolyl}$), 136.2 (*C*-2), 136.4 (*C*-5), 137.8 (*C*-3a), 140.5 (*C*-7$_{isoqu}$), 143.7 (*C*-8a), 168.7 (O=*C*-NH). FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3290 (N-H), 2943 (C-H_{alkyl}), 1627 (C=O).

***N*-{4-[*N*-Methyl-*N*-(tetrahydro-2*H*-pyran-4-yl)aminomethyl]phenyl}-2-(3-methylphenyl)-7,8-dihydro-6*H*-[7]annuleno[*b*]thiophene-5-carboxamide (14d)**

N-(4-Aminophenyl)-*N*-methyltetrahydro-2H-pyran-4-amin (78 mg, 0.35 mmol, 1 eq.) was added to a vigorously stirred mixture of acid **13b**[40](100 mg, 0.35 mmol), triethylamine (71 mg, 0.70 mmol, 2 eq.) and HATU™ (150 mg, 0.38 mmol. 1.1 eq.) in THF (5 mL). The mixture was stirred overnight at rt. The mixture was concentrated *in vacuo* and the residue was purified by fc (EtOAc : CH_2Cl_2 = 1:2 + 5% MeOH) and recrystallized from acetonitrile to give **14d** as a yellow solid. R_f = 0.17 (EtOAc : CH_2Cl_2 + 5 % MeOH = 1:2), mp 189 °C, yield 128 mg (74 %). $C_{30}H_{34}N_2O_2S$ (486.6 g/mol). Purity (HPLC): 97 %, t_R = 20.94 min. HRMS (APCI): m/z = calcd. for $C_{30}H_{35}N_2O_2S$ [MH^+] 487.2414, found 487.2395. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.60-1.82 (m, 4H, 3-C*H*$_{2pyran,}$ 5-C*H*$_{2pyran}$), 2.14 (quint, *J* = 6.2 Hz, 2H, 7-C*H*$_2$), 2.21 (s, 3H, N-C*H*$_3$), 2.38 (s, 3H, CH_{3tolyl}), 2.64 (tt, *J* = 11.2/4.0 Hz, 1H, 4-H_{pyran}), 2.84 (t, *J* = 5.5 Hz, 2H, 6-C*H*$_2$), 3.13 (t, *J* = 5.7 Hz, 2H, 8-C*H*$_2$), 3.37 (td, *J* = 11.5/2.3 Hz, 2H, CH_{2axial}-O-CH_{2axial}), 3.57 (s, 2H, Ph-C*H*$_2$-N), 4.04 (dd, *J* = 11.2/3.4 Hz, 2H, CH_{2equat}-O-CH_{2equat}), 7.10 (d, *J* = 7.5 Hz, 1H, 4-C*H*$_{tolyl}$), 7.11 (s, 1H, 3-C*H*), 7.20 (s, 1H, 4-C*H*), 7.27-7.28 (m, 1H, 5-C*H*$_{tolyl}$), 7.30 (d, *J* = 8.3 Hz, 2H, 3-

C*H*$_{phenyl}$, 5-C*H*$_{phenyl}$), 7.34 (m, 2H, 2-C*H*$_{tolyl}$, 6-C*H*$_{tolyl}$), 7.48-7.57 (m, 3H, 2-C*H*$_{phenyl}$, 6-C*H*$_{phenyl}$, N*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 21.7 (*C*H$_{3tolyl}$), 24.4 (*C*-7), 29.4 (*C*-3$_{pyran}$, *C*-5$_{pyran}$), 30.9 (*C*-8, *C*-6), 37.7 (N-*C*H$_3$), 57.5 (*C*-4$_{pyran}$), 59.7 (Ph-*C*H$_2$-N), 67.9 (*C*-2$_{pyran}$, *C*-6$_{pyran}$), 120.1 (*C*-2$_{phenyl}$, *C*-6$_{phenyl}$), 122.8 (*C*-2$_{tolyl}$), 126.4 (*C*-6$_{tolyl}$), 127.3 (*C*-3), 127.4 (*C*-4), 127.8 (*C*-1$_{phenyl}$), 128.5 (*C*-4$_{tolyl}$), 129.0 (*C*-5$_{tolyl}$), 129.6 (*C*-3$_{phenyl}$, *C*-5$_{phenyl}$), 133.6 (*C*-3$_{tolyl}$), 133.9 (*C*-1$_{tolyl}$), 136.2 (*C*-2), 140.5 (*C*-3a), 144.7 (*C*-8a), 147.9 (*C*-5), 168.5 (O=*C*-NH). A signal for the carbon atom *C*-4$_{phenyl}$ is not visible. FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3305 (N-H), 2939, 2862 (C-H$_{alkyl}$), 1643 (C=O), 1053, 1010 (C-O).

2-(4-Butylphenyl)-*N*-[4-(piperidin-1-ylmethyl)phenyl]-7,8-dihydro-6*H*-[7]annuleno[*b*]thiophene-5-carboxamide (14g)

1-(4-Aminobenzyl)piperidine dihydrochloride (79 mg, 0.30 mmol, 1 eq.) was added to a vigorously stirred mixture of acid **13c**[40] (100 mg, 0.30 mmol), triethylamine (61 mg, 0.60 mmol, 2 eq.) and HATU™ (130 mg, 0.33 mmol. 1.1 eq.) in acetonitrile (5 mL). The mixture was stirred overnight at rt. The mixture was stirred overnight at rt during which a precipitate was formed. The solid was filtered off, washed with acetonitrile and recrystallized from acetonitrile to give **14g** as a colorless solid. R_f = 0.11 (CH_2Cl_2 : MeOH = 95:5), mp 185-188 °C, yield 132 mg (88 %). $C_{32}H_{38}N_2OS$ (498.7 g/mol). Purity (HPLC): >97 %, t_R = 23.67 min. HRMS (APCI): m/z = calcd. for $C_{32}H_{39}N_2OS$ [MH$^+$] 499.2778, found 499.2803. ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.94 (t, *J* = 7.4 Hz, 3H, 4-C*H*$_{3n\text{-}butyl}$), 1.29-1.47 (m, 4H, 3-C*H*$_{2n\text{-}butyl}$, 4-C*H*$_{2piperidin}$), 1.50-1.71 (m, 6H, 3-C*H*$_{2piperidin}$, 5-C*H*$_{2piperidin}$, 2-C*H*$_{2n\text{-}butyl}$), 2.13 (quint, *J* = 5.4 Hz, 2H, 7-C*H*$_2$), 2.36 (m, 4H, 2-C*H*$_{2piperidin}$, 6-C*H*$_{2piperidin}$), 2.61 (t, *J* = 7.7 Hz, 2H, 1-C*H*$_{2n\text{-}butyl}$), 2.84 (t, *J* = 5.7 Hz, 2H, 6-C*H*$_2$), 3.11 (t, *J* = 5.7 Hz, 2H, 8-C*H*$_2$), 3.45 (s, 2H, Ph-C*H*$_2$-N), 7.07 (s, 1H, 3-C*H*), 7.15-7.20 (m, 3H, 4-C*H*, 3-C*H*$_{butylphen}$, 5-C*H*$_{butylphen}$), 7.29 (d, *J* = 8.5 Hz, 2H, 3-C*H*$_{phenyl}$, 5-C*H*$_{phenyl}$), 7.43 (d, *J* = 8.2 Hz, 2H, 2-C*H*$_{butylphen}$, 6-C*H*$_{butylphen}$), 7.52 (d, *J* = 8.5 Hz, 2H, 2-C*H*$_{phenyl}$, 6-C*H*$_{phenyl}$), 7.54 (s, 1H, N*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 14.1 (*C*-4$_{butyl}$), 22.5 (*C*-4$_{piperidin}$), 24.3 (*C*-3$_{butyl}$), 24.5 (*C*-7), 26.1 (*C*-3$_{piperidin}$, *C*-5$_{piperidin}$), 30.8 (*C-8*, *C-6*), 33.7 (*C*-2$_{butyl}$), 35.5 (*C*-1$_{butyl}$), 54.5 (*C*-2$_{piperidin}$, *C*-6$_{piperidin}$), 63.5 (Ph-*C*H$_2$-N), 119.9 (*C*-2$_{phenyl}$, *C*-6$_{phenyl}$), 125.5 (*C*-3$_{butylphen}$, *C*-5$_{butylphen}$), 126.8 (*C*-2$_{butylphen}$, *C*-6$_{butylphen}$), 127.4 (*C*-3), 129.1 (*C*-4), 130.0 (*C*-3$_{phenyl}$, *C*-5$_{phenyl}$), 131.3 (C-1$_{butylphen}$), 133.5 (*C*-4$_{phenyl}$), 134.7 (*C*-1$_{phenyl}$), 136.1 (*C*-2), 137.0 (*C*-3a), 140.5 (*C*-5), 142.6 (*C*-8a), 143.4 (*C*-4$_{butylphen}$), 168.4 (O=*C*-NH). FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3325 (N-H), 2931 (C-H$_{alkyl}$), 1643 (C=O), 1041, 1018 (C-O).

2-(4-*tert*-Butylphenyl)-*N*-{4-[*N*-methyl-*N*-(tetrahydro-2*H*-pyran-4-yl)aminomethyl]phenyl}-7,8-dihydro-6*H*-[7]annuleno[*b*]thiophene-5-carboxamide (14h)

N-(4-Aminophenyl)-*N*-methyltetrahydro-2H-pyran-4-amin (66 mg, 0.30 mmol, 1 eq.) was added to a vigorously stirred mixture of acid **13d**[40](100 mg, 0.30 mmol), triethylamine (61 mg, 0.60 mmol, 2 eq.) and HATU™ (128 mg, 0.33 mmol. 1.1 eq.) in THF (5 mL). The mixture was stirred overnight at rt. The mixture was concentrated *in vacuo* and the residue was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give **14h** as pale yellow solid. R_f = 0.28 (MeOH : CH_2Cl_2 = 5:95), mp 209 °C, yield 123 mg (77 %). $C_{33}H_{40}N_2O_2S$ (528.7 g/mol). Purity (HPLC): 95 %, t_R = 22.66 min. HRMS (APCI): m/z = calcd. for $C_{33}H_{41}N_2O_2S$ [MH^+] 529.2883, found 529.2927. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.34 (s, 9H, $C(CH_3)_3$), 1.55-1.81 (m, 4H, 3-CH_{2pyran}, 5-CH_{2pyran}), 2.13 (quint., *J* = 5.3 Hz, 2H, 7-CH_2), 2.20 (s, 3H, N-CH_3), 2.64 (tt, *J* = 11.2/4.1 Hz, 1H, 4-H_{pyran}), 2.83 (t, *J* = 5.7 Hz, 2H, 6-CH_2), 3.11 (t, *J* = 5.7 Hz, 2H, 8-CH_2), 3.37 (td, *J* = 11.6/2.3 Hz, 2H, CH_{2axial}-O-CH_{2axial}), 3.56 (s, 2H, Ph-CH_2-N), 4.04 (dd, *J* = 11.3/4.9 Hz, 2H, CH_{2equat}-O-CH_{2equat}), 7.07 (s, 1H, 3-C*H*), 7.19 (s, 1H, 4-C*H*), 7.30 (d, *J* = 8.6 Hz, 2H, 3-CH_{phenyl}, 5-CH_{phenyl}), 7.39 (d, *J* = 8.3 Hz, 2H, 3-C$H_{butylphen}$, 5-C$H_{butylphen}$), 7.46 (d, *J* = 8.4 Hz, 2H, 2-C$H_{butylphen}$, 6-C$H_{butylphen}$), 7.53 (d, *J* = 8.5 Hz, 2H, 2-CH_{phenyl}, 6-CH_{phenyl}), 7.59 (s, 1H, N*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 24.6 (*C*-7), 29.7 (*C*-3_{pyran}, *C*-5_{pyran}), 31.1 (*C*-8), 31.1 (*C*-6), 31.7 ($C(CH_3)_3$), 35.0 ($C(CH_3)_3$), 38.0 (N-CH_3), 57.8 (*C*-4_{pyran}), 60.0 (Ph-CH_2-N), 68.2 (*C*-2_{pyran}, *C*-6_{pyran}), 120.4 (*C*-2_{phenyl}, *C*-6_{phenyl}), 125.7 (*C*-$3_{butylphen}$, *C*-$5_{butylphen}$), 126.3 (*C*-$2_{butylphen}$, *C*-$6_{butylphen}$) 127.2 (*C*-3), 127.7 (*C*-4), 129.9 (*C*-3_{phenyl}, *C*-5_{phenyl}), 131.5 (C-$1_{butylphen}$), 133.9 (*C*-4_{phenyl}), 136.2 (*C*-1_{phenyl}), 136.4 (*C*-2), 137.4 (*C*-3a), 140.7 (*C*-5), 143.8 (*C*-8a), 151.1 (*C*-$4_{butylphen}$), 168.8 (O=*C*-NH). FT-IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3251 (N-H), 2966 (C-H_{alkyl}), 1651 (C=O), 1597 (C=C), 1053, 1014 (C-O).

3. Experimental Pharmacology

σ receptor assays

Materials

The guinea pig brains and rat liver for the σ_1 and σ_2 receptor binding assays were commercially available (Harlan-Winkelmann, Borchen, Germany). Centrifuges: Cooling centrifuge model Rotina 35R (Hettich, Tuttlingen, Germany) and High-speed cooling centrifuge model Sorvall RC-5C plus (Thermo Fisher Scientific, Langenselbold, Germany). Multiplates: standard 96-well multiplates (Diagonal, Muenster, Germany).

Shaker: self-made device with adjustable temperature and tumbling speed (scientific workshop of the institute). Vortexer: Vortex Genie 2 (Thermo Fisher Scientific, Langenselbold, Germany). Harvester: MicroBeta FilterMate-96 Harvester. Filter: Printed Filtermat Typ A and B. Scintillator: Meltilex (Typ A or B) solid state scintillator. Scintillation analyzer: MicroBeta Trilux (all Perkin Elmer LAS, Rodgau-Jügesheim, Germany). Chemicals and reagents were purchased from different commercial sources and of analytical grade.

Preparation of membrane homogenates from guinea pig brain

5 guinea pig brains were homogenized with the potter (500-800 rpm, 10 up-and-down strokes) in 6 volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1200 x *g* for 10 min at 4 °C. The supernatant was separated and centrifuged at 23,500 x *g* for 20 min at 4 °C. The pellet was resuspended in 5-6 volumes of buffer (50 mM TRIS, pH 7.4) and centrifuged again at 23,500 x *g* (20 min, 4 °C). This procedure was repeated twice. The final pellet was resuspended in 5-6 volumes of buffer and frozen (−80 °C) in 1.5 mL portions containing about 1.5 mg protein/mL.

Preparation of membrane homogenates from rat liver

Two rat livers were cut into small pieces and homogenized with the potter (500-800 rpm, 10 up-and-down strokes) in 6 volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1,200 x *g* for 10 min at 4 °C. The supernatant was separated and centrifuged at 31,000 x *g* for 20 min at 4 °C. The pellet was resuspended in 5-6 volumes of buffer (50 mM TRIS, pH 8.0) and incubated at room temperature for 30 min. After the incubation, the suspension was centrifuged again at 31,000 x *g* for 20 min at 4 °C. The final pellet was resuspended in 5-6 volumes of buffer and stored at -80 °C in 1.5 mL portions containing about 2 mg protein/mL.

Protein determination

The protein concentration was determined by the method of Bradford,[52] modified by Stoscheck.[53] The Bradford solution was prepared by dissolving 5 mg of Coomassie Brilliant Blue G 250 in 2.5 mL of EtOH (95 %, v/v). 10 mL deionized water and 5 mL phosphoric acid (85%, m/v) were added to this solution, the mixture was stirred and filled to a total volume of 50.0 mL with deionized water. The calibration was carried out using bovine serum albumin as a standard in 9 concentrations (0.1, 0.2, 0.4, 0.6, 0.8,

1.0, 1.5, 2.0 and 4.0 mg /mL). In a 96 well standard multiplate, 10 µL of the calibration solution or 10 µL of the membrane receptor preparation were mixed with 190 µL of the Bradford solution, respectively. After 5 min, the UV absorption of the protein-dye complex at λ = 595 nm was measured with a platereader (Tecan Genios, Tecan, Crailsheim, Germany).

General protocol for the binding assays

The test compound solutions were prepared by dissolving approximately 10 µmol (usually 2-4 mg) of test compound in DMSO so that a 10 mM stock solution was obtained. To obtain the required test solutions for the assay, the DMSO stock solution was diluted with the respective assay buffer. The filtermats were presoaked in 0.5% aqueous polyethylenimine solution for 2 h at room temperature before use. All binding experiments were carried out in duplicates in 96-well multiplates. The concentrations given are the final concentrations in the assay. Generally, the assays were performed by addition of 50 µL of the respective assay buffer, 50 µL test compound solution in various concentrations (10^{-5}, 10^{-6}, 10^{-7}, 10^{-8}, 10^{-9} and 10^{-10} mol/L), 50 µL of corresponding radioligand solution and 50 µL of the respective receptor preparation into each well of the multiplate (total volume 200 µL). The receptor preparation was always added last. During the incubation, the multiplates were shaken at a speed of 500-600 rpm at the specified temperature. Unless otherwise noted, the assays were terminated after 120 min by rapid filtration using the harvester. During the filtration each well was washed five times with 300 µL of water. Subsequently, the filtermats were dried at 95 °C. The solid scintillator was melted on the dried filtermats at a temperature of 95 °C for 5 min. After solidifying of the scintillator at room temperature, the trapped radioactivity in the filtermats was measured with the scintillation analyzer. Each position on the filtermat corresponding to one well of the multiplate was measured for 5 min with the [^{3}H]-counting protocol. The overall counting efficiency was 20%. The IC_{50} values were calculated with the program GraphPad Prism® 3.0 (GraphPad Software, San Diego, CA, USA) by non-linear regression analysis. Subsequently, the IC_{50} values were transformed into K_i values using the equation of Cheng and Prusoff.

Protocol for the determination of σ_1 affinity

The assay was performed with the radioligand [^{3}H](+)-Pentazocine (0.81 GBq/µmol (22.0 Ci/mmol); Perkin Elmer). The thawed membrane preparation of guinea pig brain

cortex (about 100 µg of protein) was incubated with various concentrations of test compounds, 2 nM [^{3}H](+)-Pentazocine, and TRIS buffer (50 mM, pH 7.4) at 37 °C. The non-specific binding was determined with 10 µM unlabeled (+)-Pentazocine. The K_d value of (+)-pentazocine is 2.9 nM.[54]The nonspecific binding was determined in the presence of a large excess of non-tritiated (+)-pentazocine. K_i values of the reference compounds (+)-pentazocine, ditolylguanidine (DTG), haloperidol and rimcazol were determined and compared with literature data to verify the *in-vitro* assay.

	(+)-pentazocine	ditolylguanidine	haloperidol	rimcazole
$K_i \pm$ SEM [nM] /literature)	2.1 ± 0.1[54]	107 ± 21[55]	1.8 ± 0.09[55]	2380 ± 812[56]
$K_i \pm$ SEM [nM] (recorded)	5.4 ± 0.5 (n = 17)	71 ± 8 (n = 15)	6.6 ± 0.9 (n = 14)	1746 ± 609 (n = 6)

σ_1 Affinities of reference compounds (literature and own data).

Protocol for the determination of σ_2 affinity

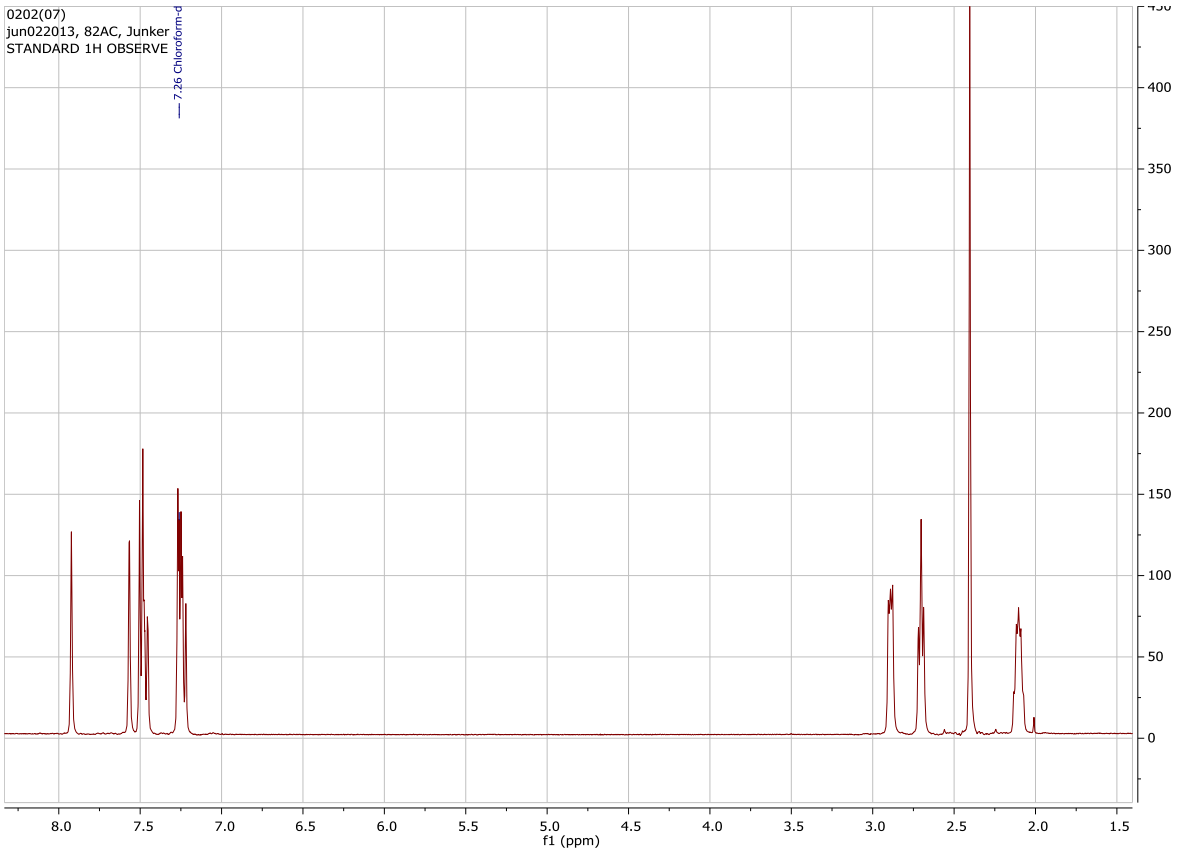
The assays were performed with the radioligand [^{3}H]DTG (specific activity 1.85 GBq/µmol (50 Ci/mmol); ARC, St. Louis, MO, USA). The thawed membrane preparation of rat liver (about 100 µg of protein) was incubated with various concentrations of the test compound, 3 nM [^{3}H]DTG and buffer containing (+)-pentazocine (500 nM (+)-pentazocine in 50 mM TRIS, pH 8.0) at room temperature. The non-specific binding was determined with 10 µM non-labeled DTG. The K_d value of [^{3}H]DTG is 17.9 nM.[55] Excess of unlabeled DTG (D) was used to determine the nonspecific binding. K_i values of reference compounds haloperidol, ditolylguanidine (DTG), ifenprodil and rimcazol were determined and compared with literature data to verify the *in vitro* assay.

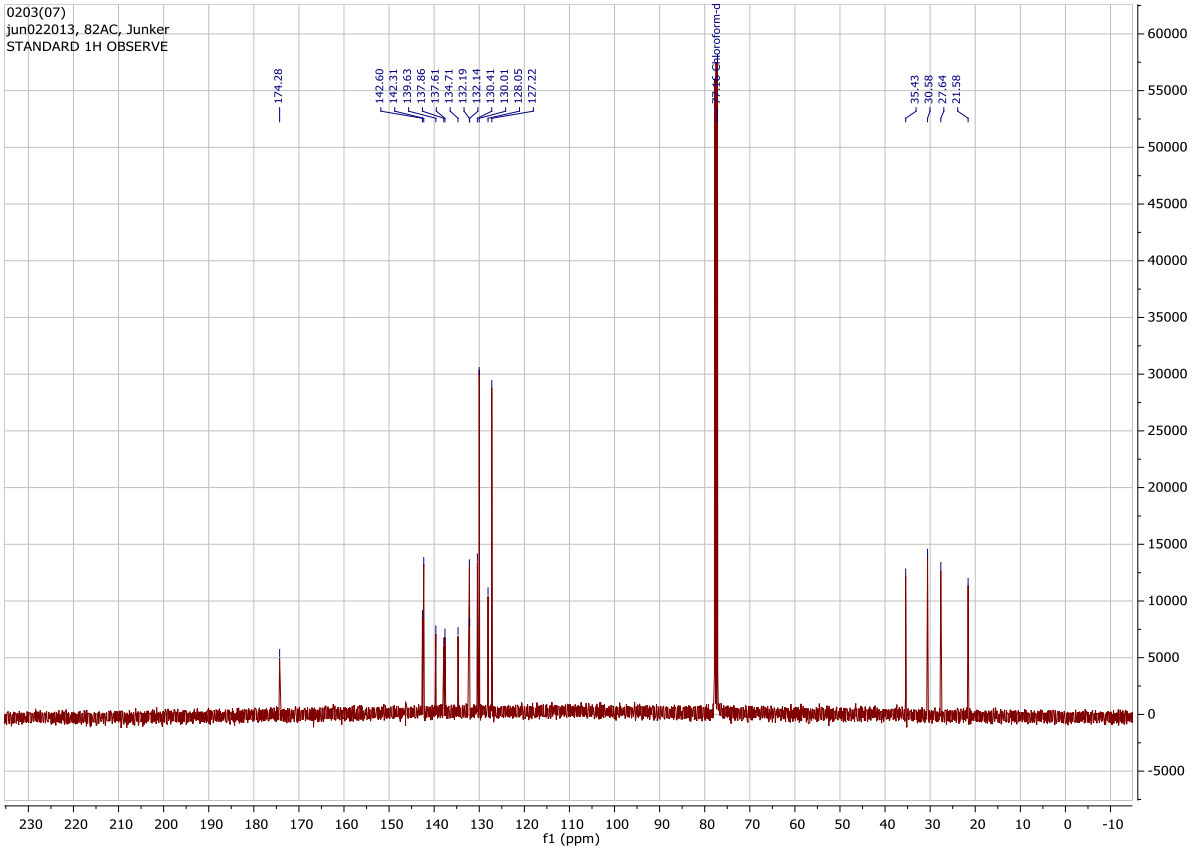
	haloperidol	ditolylguanidine	ifenprodil
$K_i \pm$ SEM [nM] (literature)	22 ± 8.5[55]	40 ± 2.6[57]	6.25 ± 0.38[58]
$K_i \pm$ SEM [nM] (recorded)	125 ± 33 (n = 7)	54 ± 8 (n = 15)	60 ± 16 (n = 5)

σ_2 Affinities of reference compounds (literature and own data).

4. ^{1}H and ^{13}C and gHSQC NMR spectra, HPLC analysis and MS spectra

2-(4-Methylphenyl)-6,7-dihydro-5H-benzo[7]annulene-8-carboxylic acid[37] (***6***)

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jun022013, 82AC, Junker
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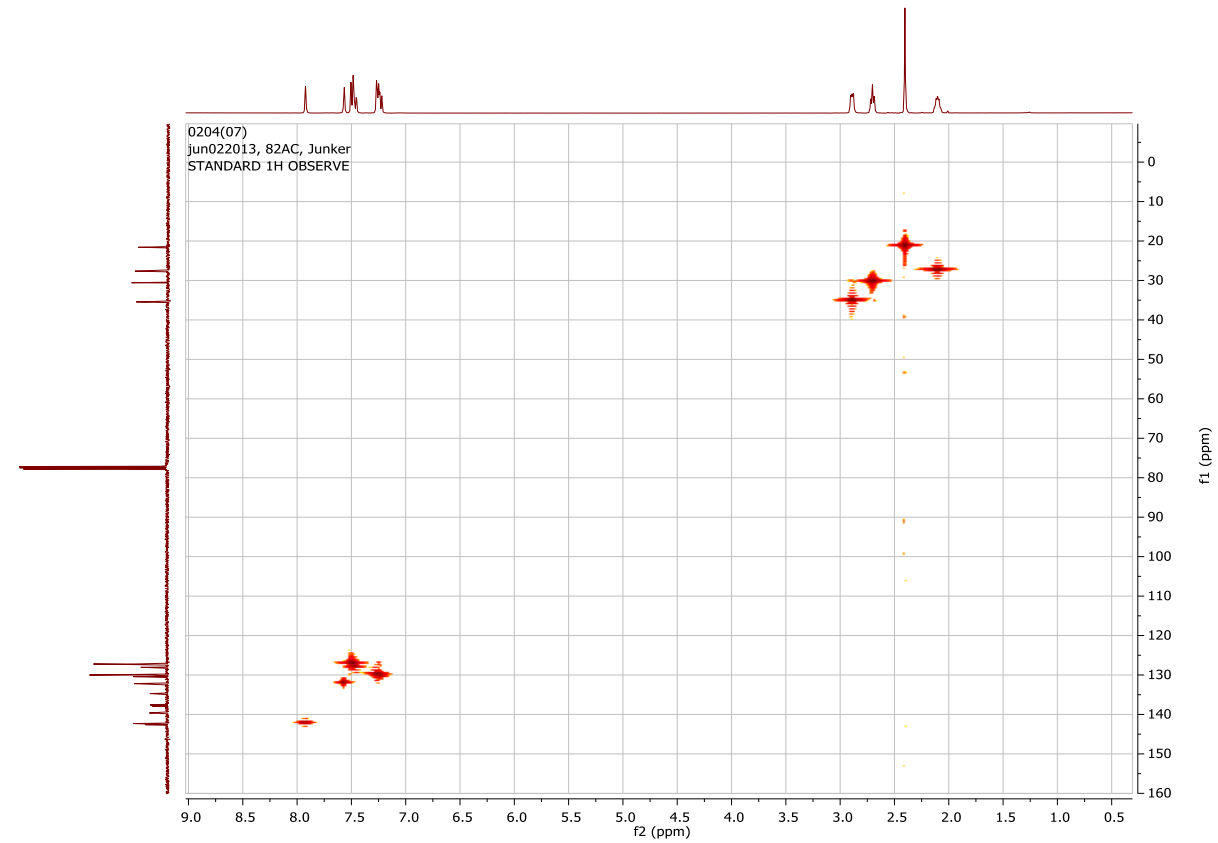
f1 (ppm)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jun022013, 82AC, Junker
STANDARD 1H OBSERVE
f2 (ppm)
f1 (ppm)

HPLC

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Reported: 24.08.12 11:19
Processed: 24.08.12 11:19

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Injection from this vial: 1 of 1

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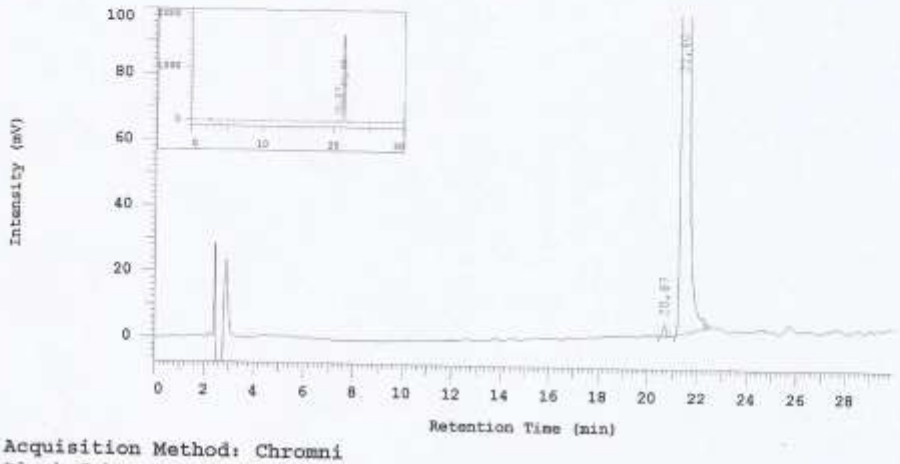
Chrom Type: HPLC Channel : 1



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Column Type: 010
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Developed by: Jens
Solvent B: ACN + 0,05%TFA

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Peak rejection level: 0

Generic Display Report

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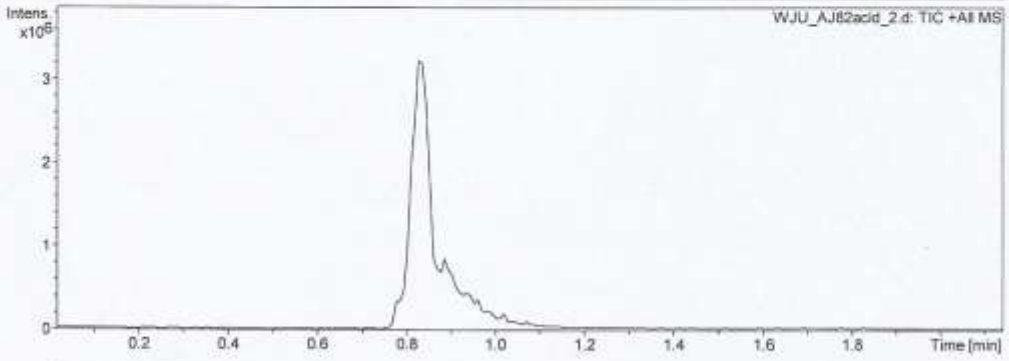

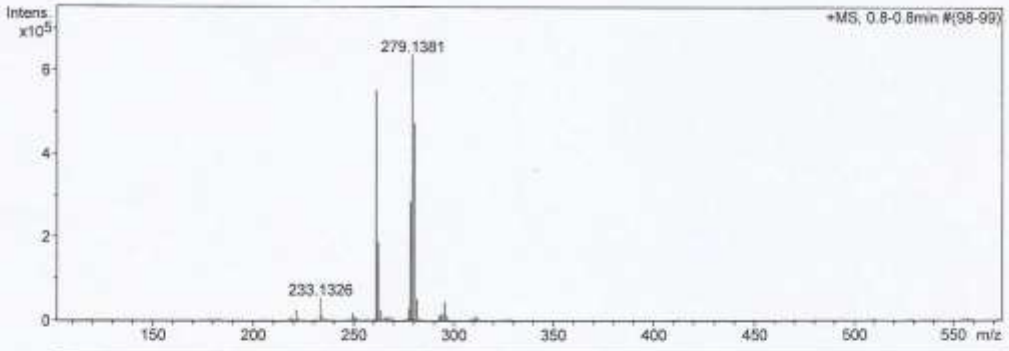

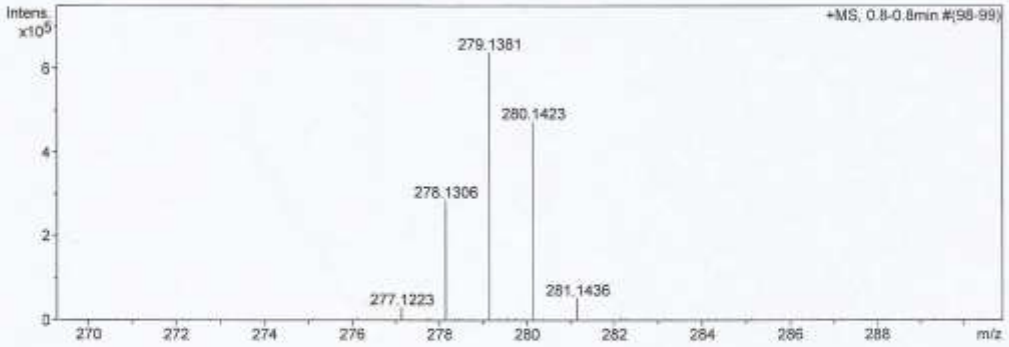

Mass Spectrum SmartFormula Report

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Acquisition Parameter

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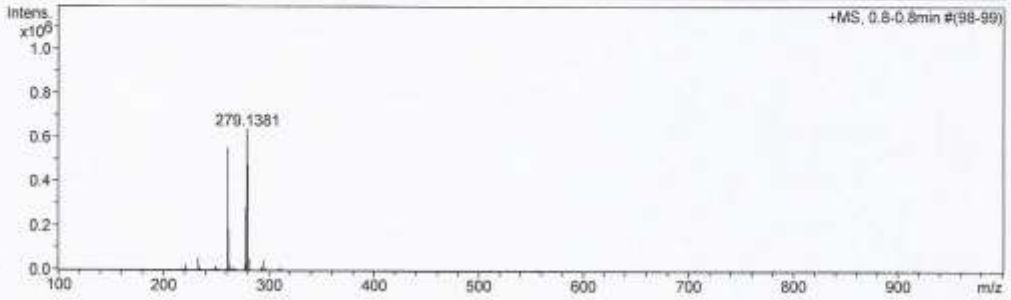

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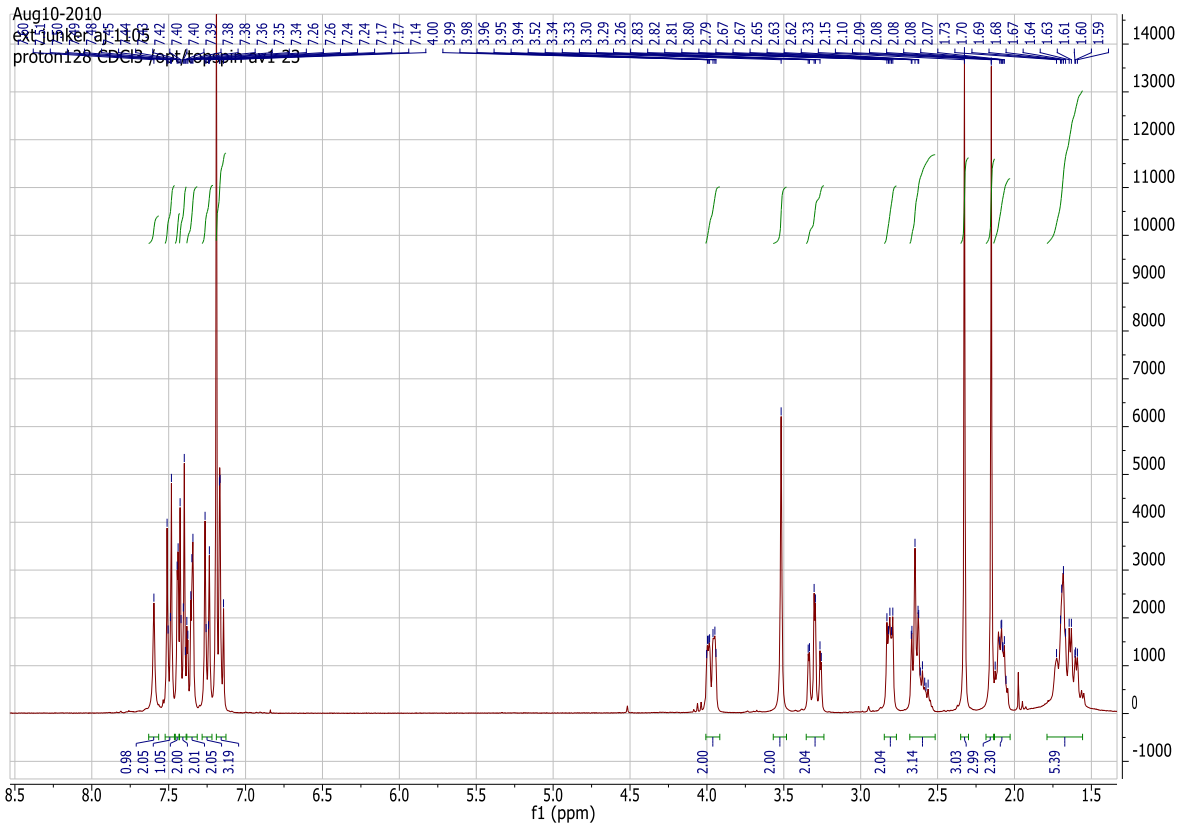
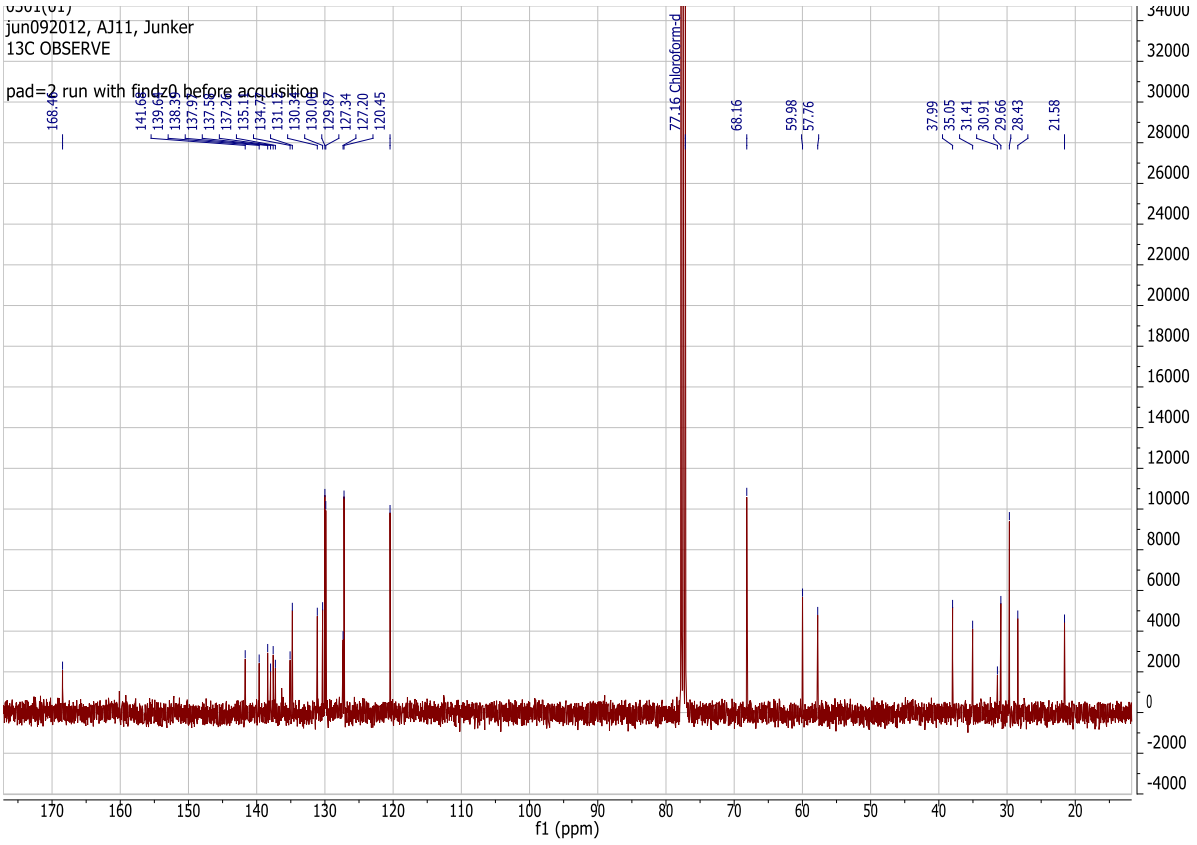
	2	C 15 H 15 N 6	3.16	279.1353	-2.9	-10.3	323.2	11.5	even	ok
	3	C 14 H 19 N 2 O 4	0.11	279.1339	-4.2	-15.1	337.6	6.5	even	ok
	4	C 13 H 19 N 4 O 3	0.00	279.1452	7.0	25.1	339.7	6.5	even	ok
	5	C 10 H 15 N 8 O 2	0.00	279.1312	-6.9	-24.7	350.2	7.5	even	ok
	6	C 9 H 15 N 10 O	0.01	279.1425	4.3	15.5	352.5	7.5	even	ok
	7	C 12 H 23 O 7	0.00	279.1438	5.7	20.4	354.2	1.5	even	ok
	8	C 8 H 19 N 6 O 5	0.01	279.1411	3.0	10.7	366.9	2.5	even	ok

2-(4-Methyphenyl)-N-{4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide[39] (***8a***)





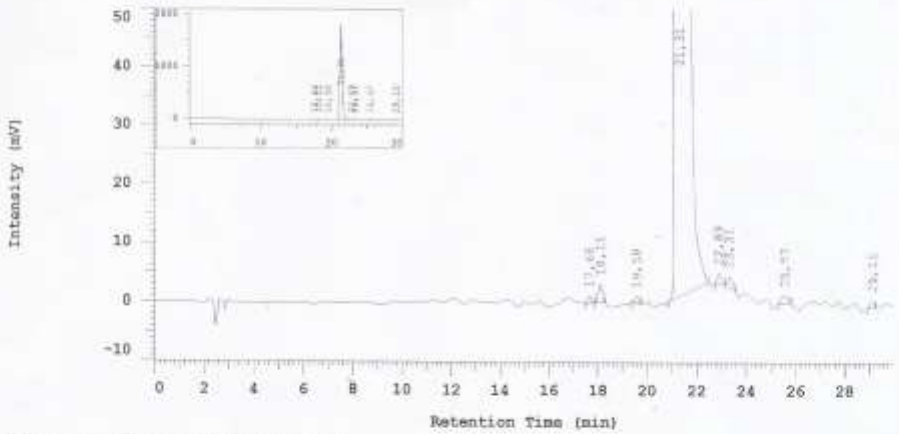
HPLC

Analyzed: 27.10.10 21:41
Reported: 28.10.10 16:22
Processed: 28.10.10 16:22

Data Path: D:\WIN32APP\HSM\Chromni\DATA\2304\
Application: Chromni
Series:2304

Sample Name: AJ1106
Vial Number: 6
Vial Type: UNK
Injection from this vial: 1 of 1
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

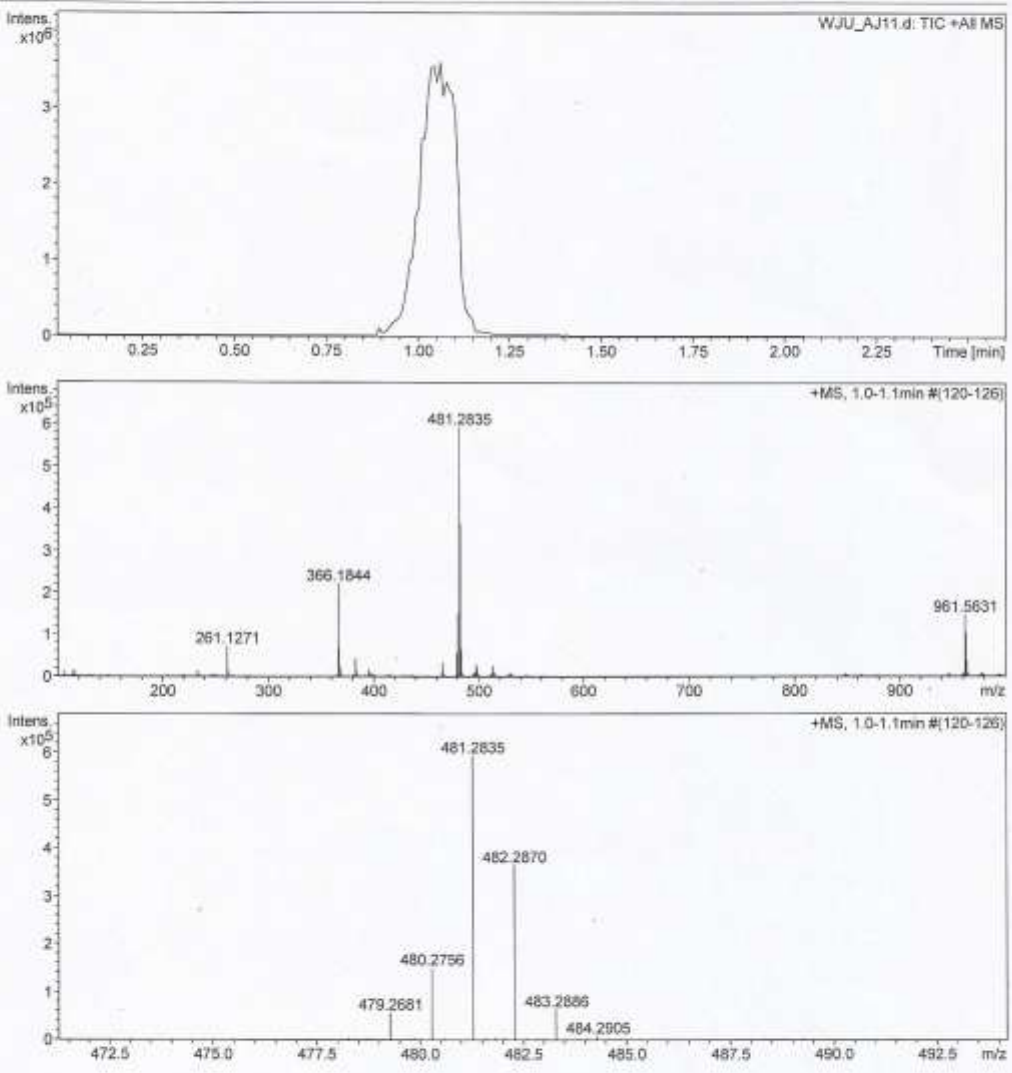
No.	RT	Area	Conc 1	BC
1	17,66	13404	0,039	BB
2	18,11	36545	0,108	BB
3	19,58	11382	0,033	BB
4	21,31	33844163	99,601	MC
5	22,89	19358	0,057	MC
6	23,31	20396	0,060	MC
7	25,57	22792	0,067	BB
8	29,15	11760	0,035	BB
		33979800	100,000	

Peak rejection level: 0

Generic Display Report

Analysis Info

Analysis Name	E:\Meiners\12_09\WJU_AJ11.d	Acquisition Date	9/4/2012 11:44:15 AM
Method	APCI_directprobe_positiv.m	Operator	Sendker
Sample Name	AJ11	Instrument	micrOTOF-Q II
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		



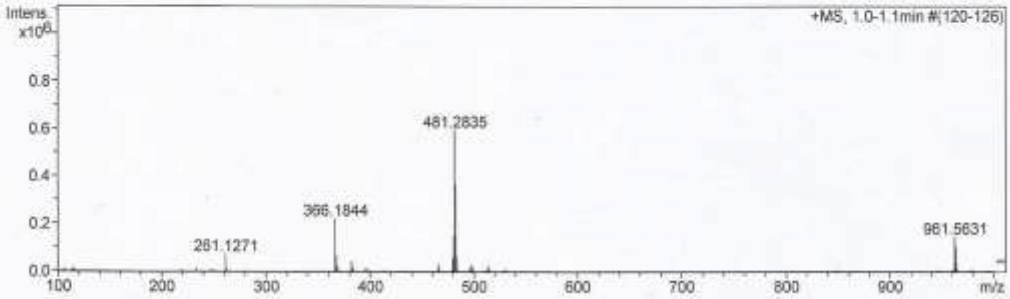
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	E:\Meiners\12_09\WJU_AJ11.d	Acquisition Date	9/4/2012 11:44:15 AM
Method	APCI_directprobe_positiv.m	Operator	Sendker
Sample Name	AJ11	Instrument / Ser#	micrOTOF-Q II 10252
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		

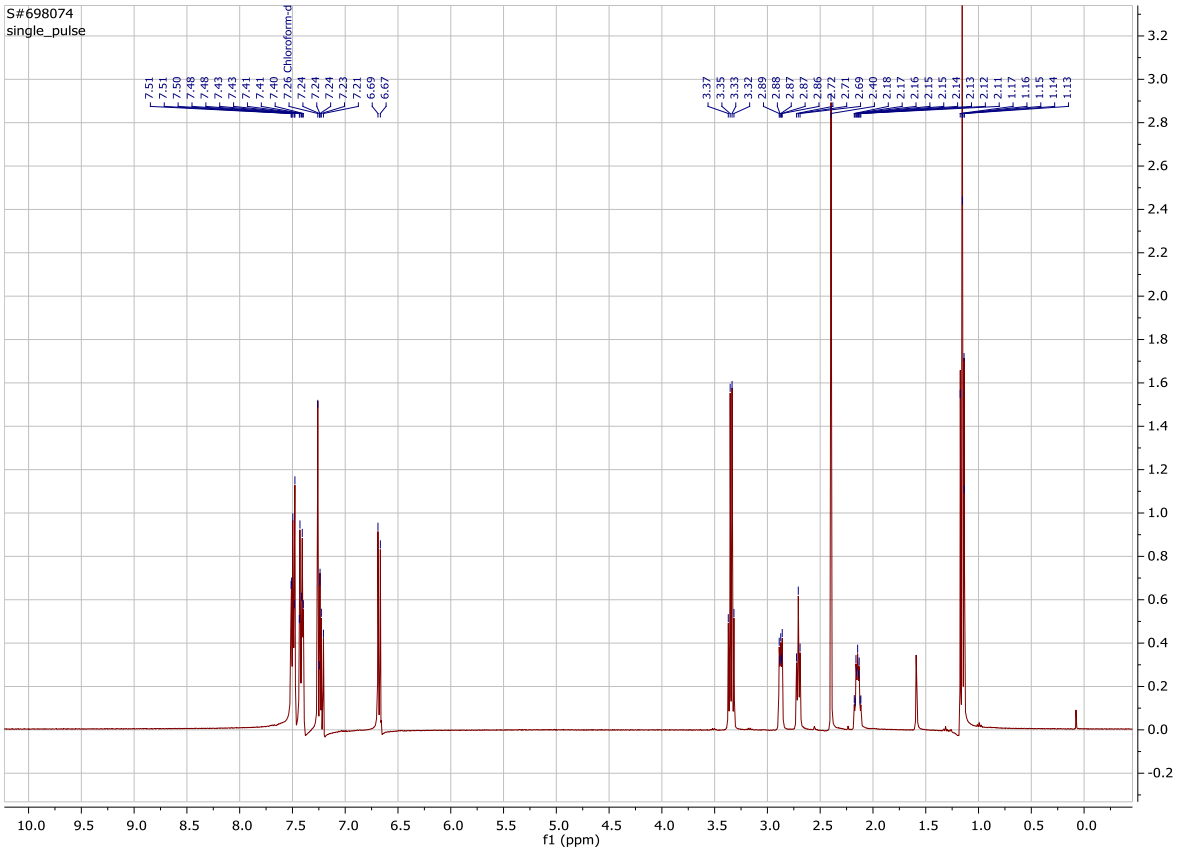
Acquisition Parameter

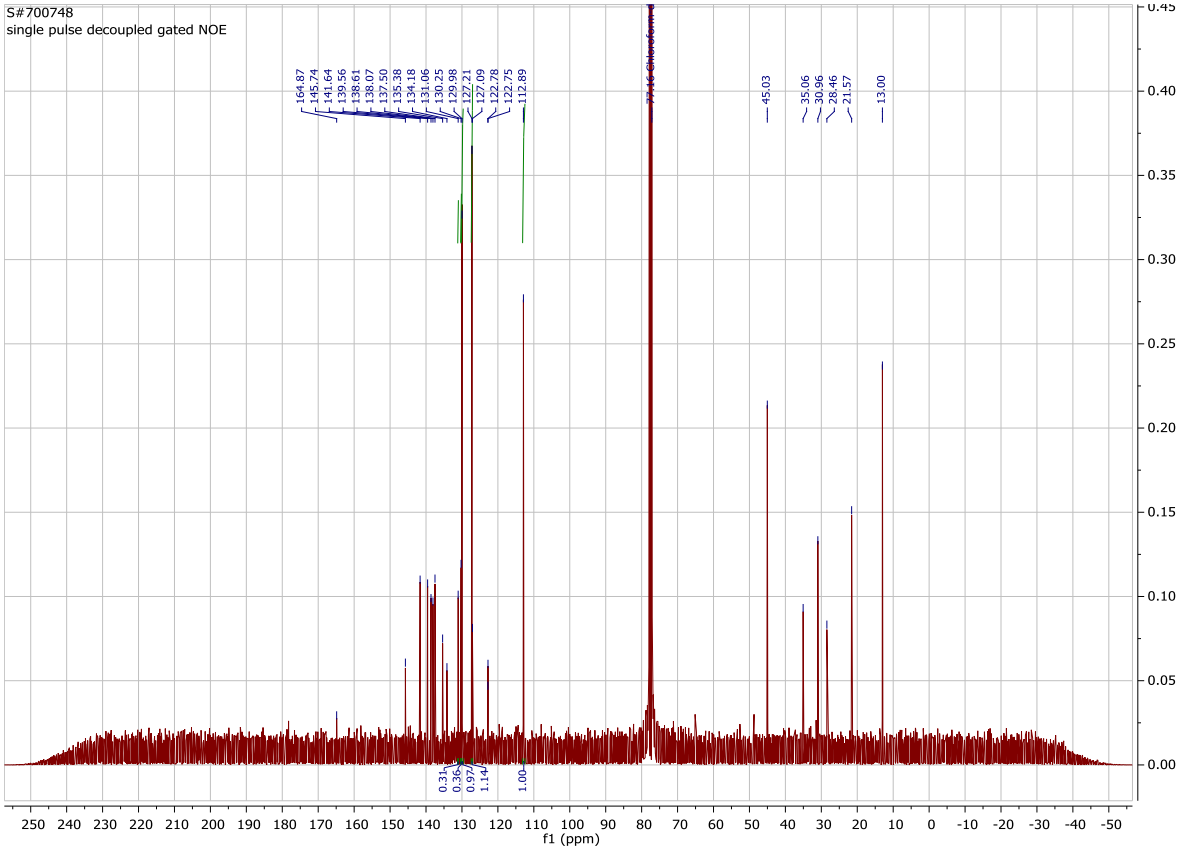
Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.7 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	3.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
481.2835	1	C 32 H 37 N 2 O 2	100.00	481.2850	1.5	3.1	128.7	15.5	even	ok
	2	C 28 H 33 N 8	59.81	481.2823	-1.2	-2.5	140.4	16.5	even	ok
	3	C 27 H 37 N 4 O 4	10.10	481.2809	-2.5	-5.3	152.7	11.5	even	ok
	4	C 26 H 41 O 8	1.11	481.2796	-3.9	-8.0	165.0	6.5	even	ok
	5	C 20 H 41 N 4 O 9	0.29	481.2868	3.3	6.9	190.6	2.5	even	ok
	6	C 21 H 37 N 8 O 5	0.02	481.2881	4.7	9.7	206.0	7.5	even	ok
	7	C 17 H 33 N 14 O 3	0.08	481.2855	2.0	4.1	219.3	8.5	even	ok
	8	C 16 H 37 N 10 O 7	0.05	481.2841	0.7	1.4	233.3	3.5	even	ok
	9	C 13 H 29 N 20 O	0.04	481.2828	-0.7	-1.4	234.9	9.5	even	ok
	10	C 12 H 33 N 16 O 5	0.01	481.2814	-2.0	-4.2	246.5	4.5	even	ok

*N-[4-Diethylamino)phenyl]-2-(4-methylphenyl)-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (**8b**)*





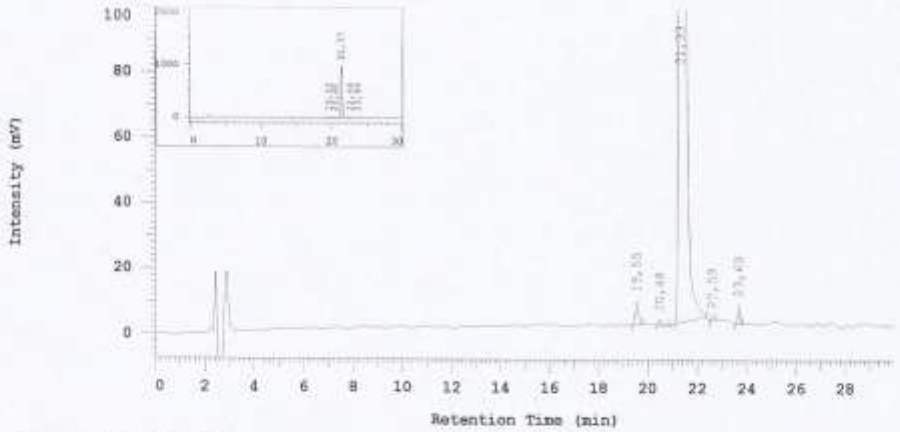
HPLC

Analyzed: 01.08.12 22:37
Reported: 02.08.12 14:55
Processed: 02.08.12 14:55

Data Path: D:\WIN32APP\HSM\Chromni\DATA\5043\
Application: Chromni
Series:5043

Sample Name: AJ452
Vial Number: 7
Injection from this vial: 1 of 1
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

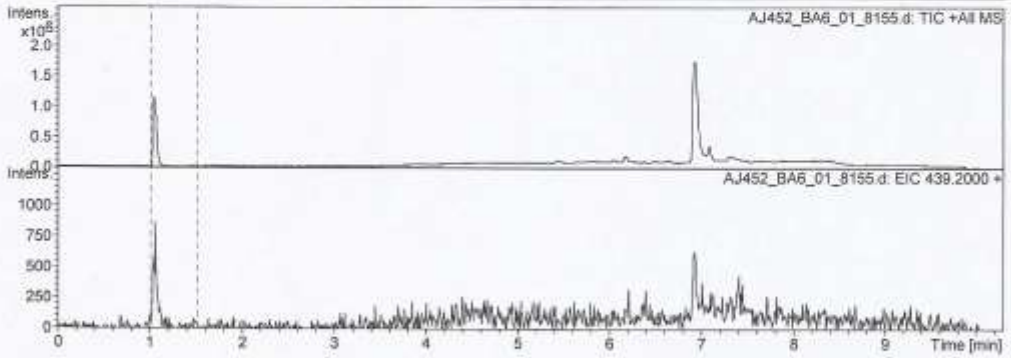
No.	RT	Area	Conc 1	BC
1	19,55	64778	0,532	BB
2	20,48	22029	0,181	BB
3	21,33	12052269	98,927	MC
4	22,59	7661	0,063	BB
5	23,69	36226	0,297	BB
		12182963	100,000	

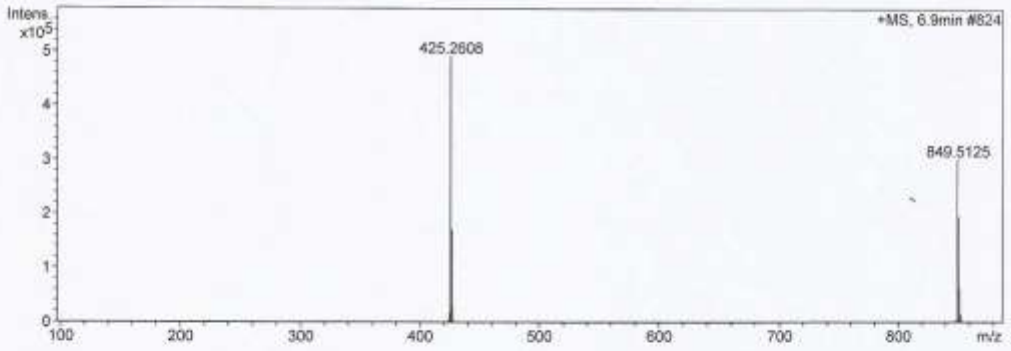
Peak rejection level: 0

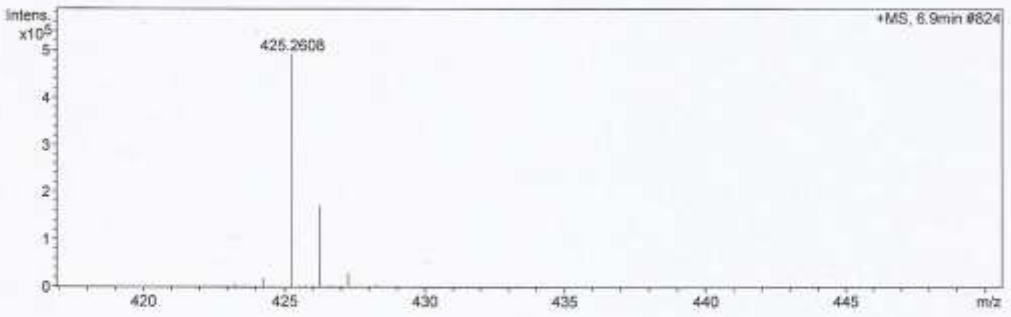
Generic Display Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\LC-MS\2012_09_10\AJ452_BA6_01_8155.d	Acquisition Date	9/10/2012 2:18:35 PM
Method	tune_low_lcms_routine_positiv_10min.m	Operator	Sendker
Sample Name	AJ452	Instrument	micrOTOF-Q II
Comment	Junker LCMS_EI+ Kalibration mit Li-Formate		







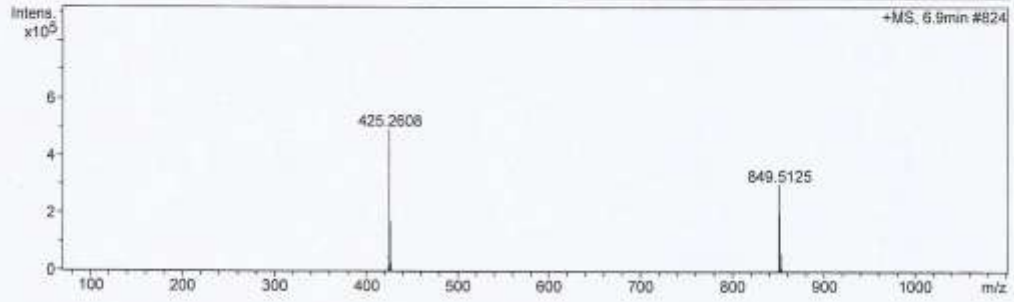
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\LC-MS\2012_09_10\AJ452_BA6_01_8155.d	Acquisition Date	9/10/2012 2:18:35 PM
Method	tune_low_lcms_routine_positiv_10min.m	Operator	Sendker
Sample Name	AJ452	Instrument / Ser#	micrOTOF-Q II 10252
Comment	Junker LCMS_EI+ Kalibration mit Li-Formate		

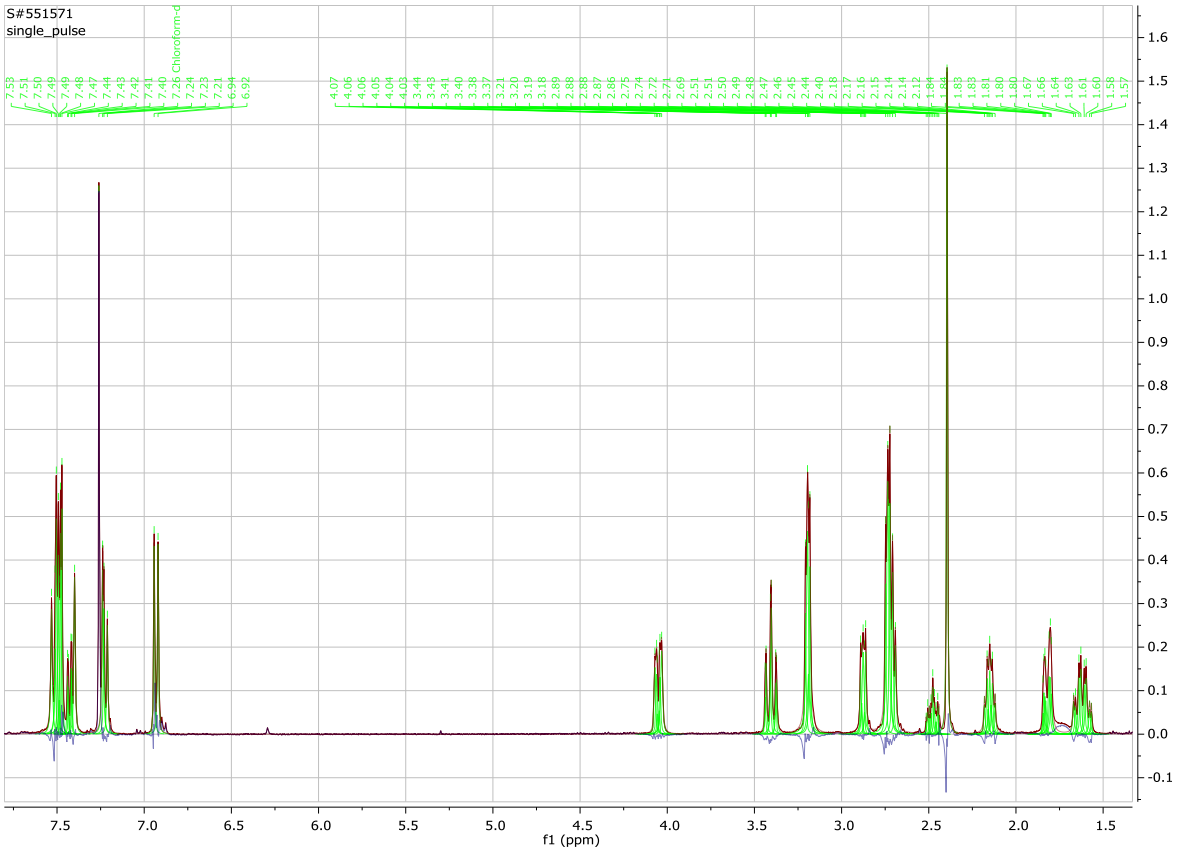
Acquisition Parameter

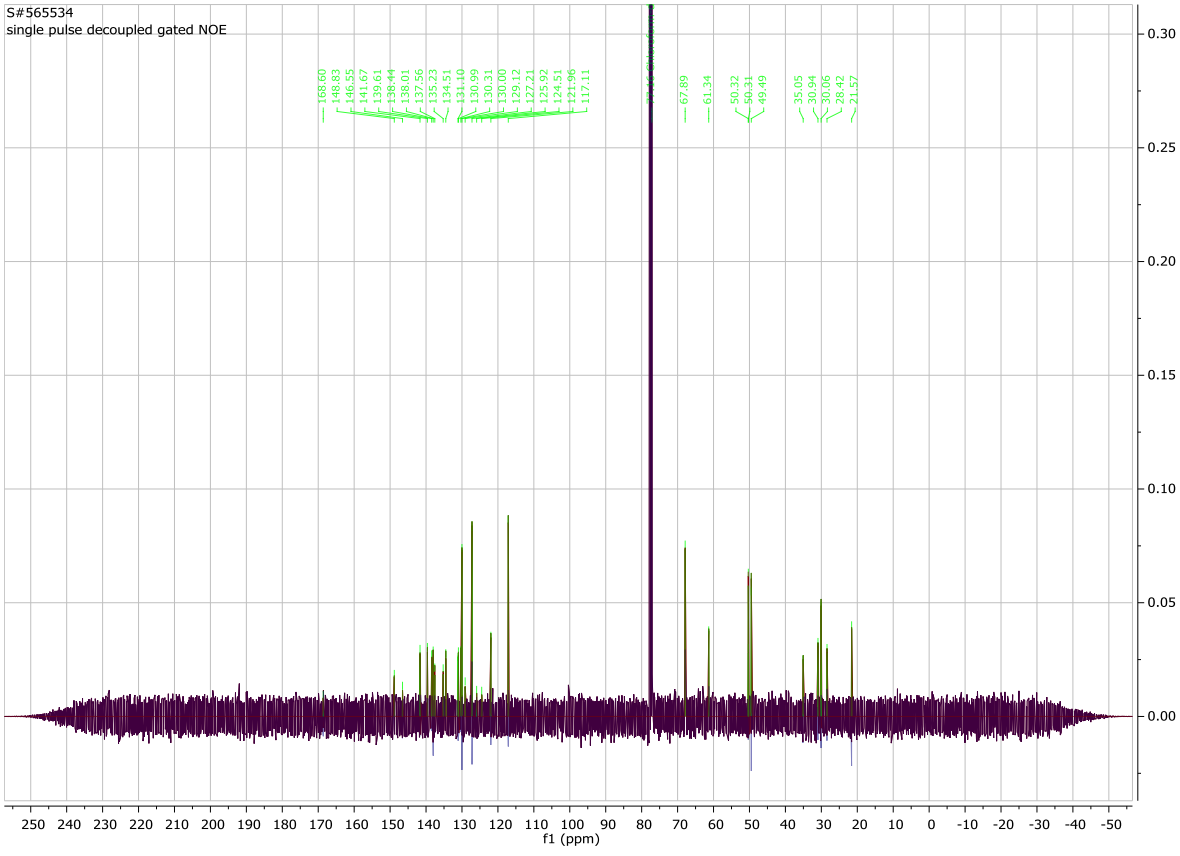
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	2.0 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	9.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	300.0 Vpp	Set Divert Valve	Waste



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
425.2608	1	C 29 H 33 N 2 O	100.00	425.2587	-2.1	-4.9	10.7	14.5	even	ok

*2-(4-Methylphenyl)-N-{4-[4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl]phenyl}-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (**8c**)*





HPLC

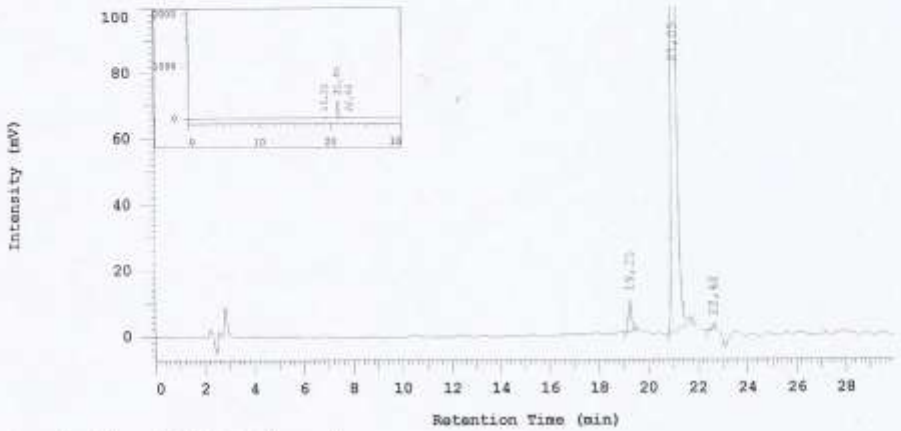
Analyzed: 02.08.12 04:09

Reported: 02.08.12 15:02
Processed: 02.08.12 15:02

Data Path: D:\WIN32APP\HSM\Chromni\DATA\5051\
Application: Chromni
Sample Name: AJ42201
Injection from this vial: 1 of 1

Series:5051
Vial Number: 13
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

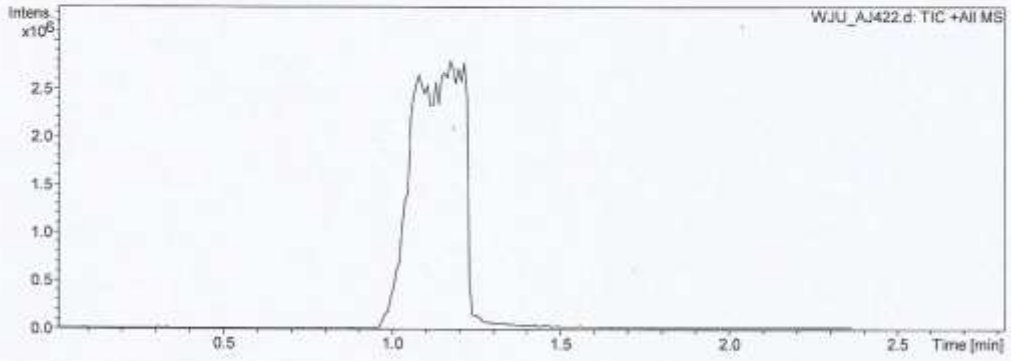
No.	RT	Area	Conc 1	BC
1	19,25	83624	2,320	BB
2	21,05	3510477	97,392	BB
3	22,62	10386	0,288	BB
		3604487	100,000	

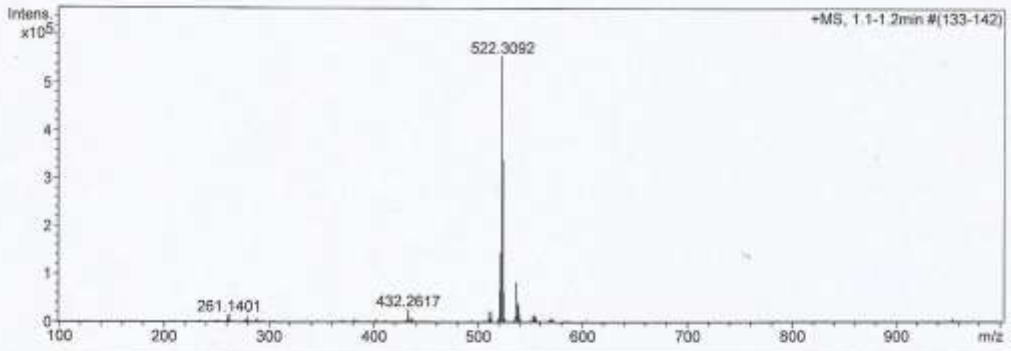
Peak rejection level: 0

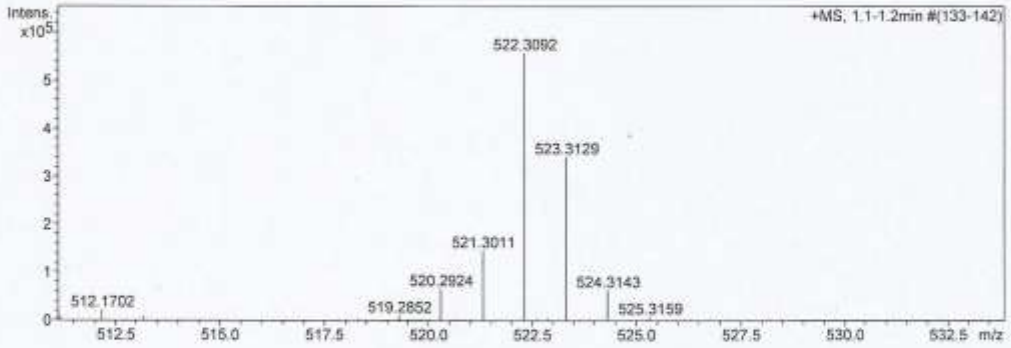
Generic Display Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\APCI\12_08\WJU_AJ422.d	Acquisition Date	8/29/2012 9:41:13 AM
Method	APCI_directprobe_positiv.m	Operator	Meiners
Sample Name	AJ422	Instrument	micrOTOF-Q II
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		







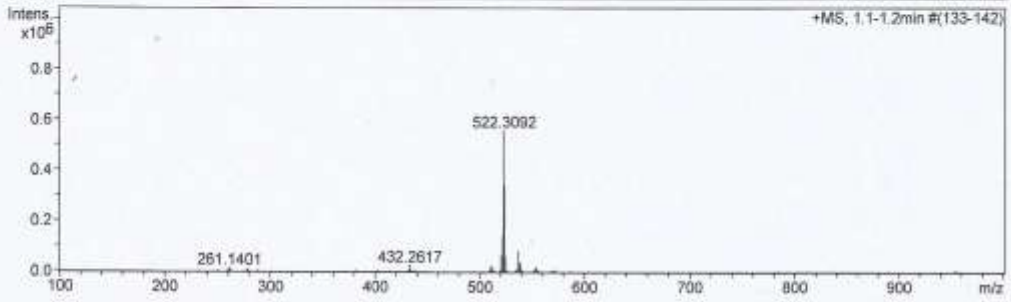
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\APCI\12_08\WJU_AJ422.d	Acquisition Date	8/29/2012 9:41:13 AM
Method	APCI_directprobe_positiv.m	Operator	Meiners
Sample Name	AJ422	Instrument / Ser#	micrOTOF-Q II 10252
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		

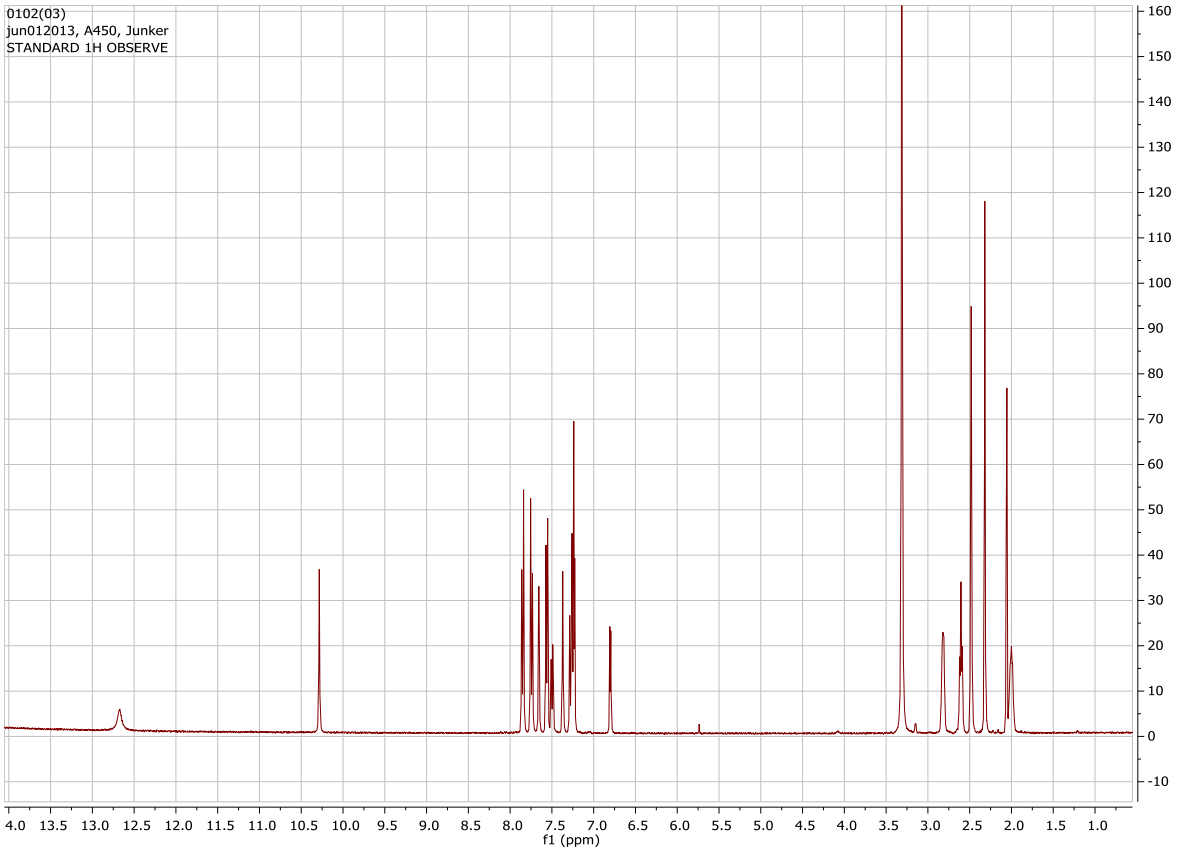
Acquisition Parameter

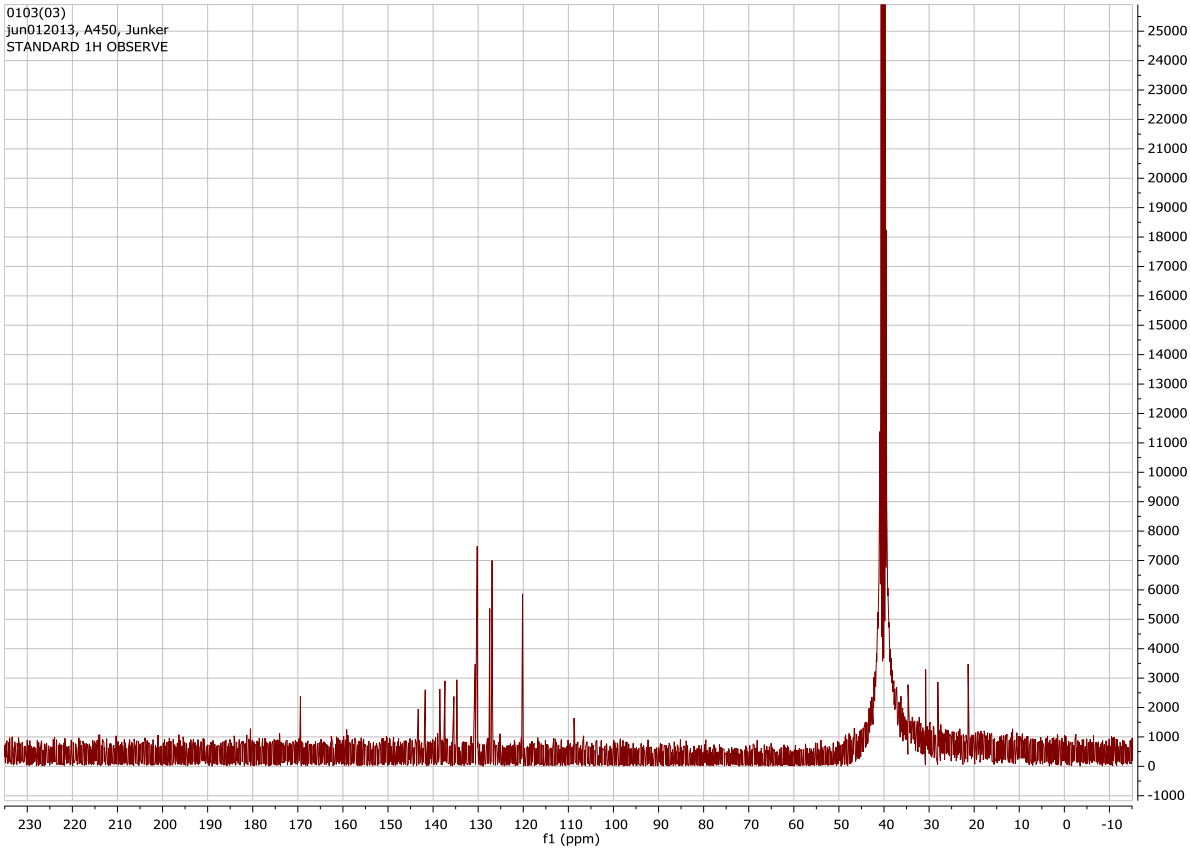
Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.7 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	3.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste

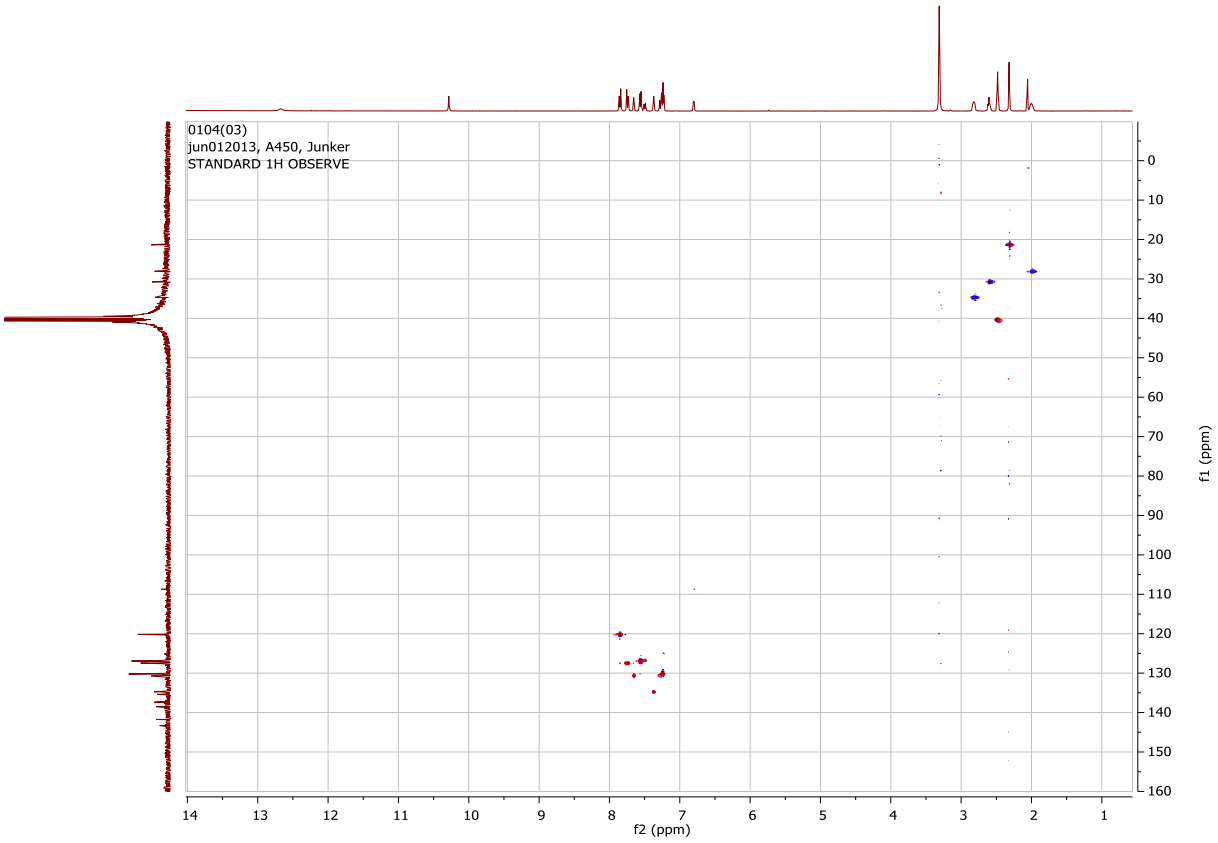


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
522.3092	1	C 34 H 40 N 3 O 2	55.11	522.3115	2.3	4.4	114.7	16.5	even	ok
	2	C 30 H 36 N 9	100.00	522.3088	-0.4	-0.7	126.4	17.5	even	ok
	3	C 29 H 40 N 5 O 4	22.17	522.3075	-1.7	-3.3	138.8	12.5	even	ok
	4	C 28 H 44 N O 8	3.28	522.3061	-3.0	-5.8	151.2	7.5	even	ok
	5	C 17 H 44 N 7 O 11	0.70	522.3093	0.1	0.3	198.4	-0.5	even	ok
	6	C 19 H 36 N 15 O 3	0.08	522.3120	2.8	5.4	203.6	9.5	even	ok
	7	C 15 H 32 N 21 O	0.13	522.3093	0.1	0.3	217.3	10.5	even	ok
	8	C 18 H 40 N 11 O 7	0.06	522.3107	1.5	2.8	217.5	4.5	even	ok
	9	C 14 H 36 N 17 O 5	0.02	522.3080	-1.2	-2.3	230.8	5.5	even	ok

*2-(4-Methylphenyl)-N-{4-[N-(thiazol-2-yl)sulfamoyl]phenyl}-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (**8d**)*






0104(03)
jun012013, A450, Junker
STANDARD 1H OBSERVE
f2 (ppm)
f1 (ppm)

HPLC

Analyzed: 01.08.12 20:33

Reported: 02.08.12 14:52
Processed: 02.08.12 14:52

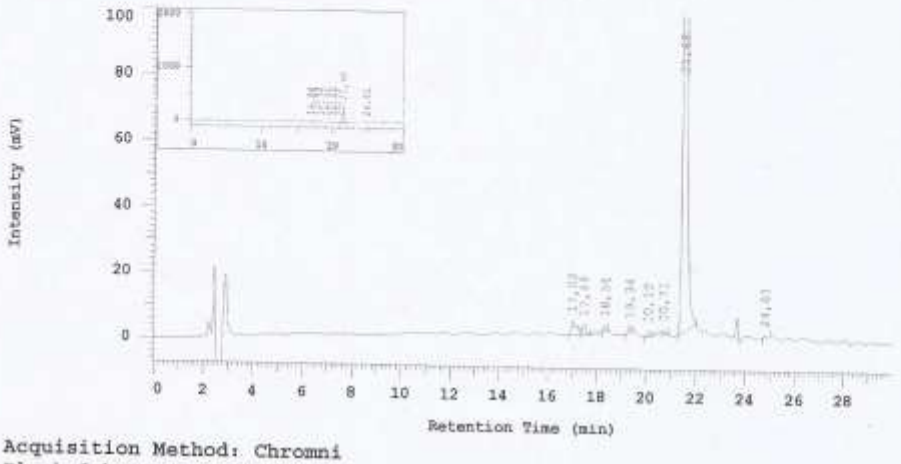
Data Path: D:\WIN32APP\HSM\Chromni\DATA\5040\
Application: Chromni

Sample Name: AJ450

Injection from this vial: 1 of 1

Series:5040
Vial Number: 4
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

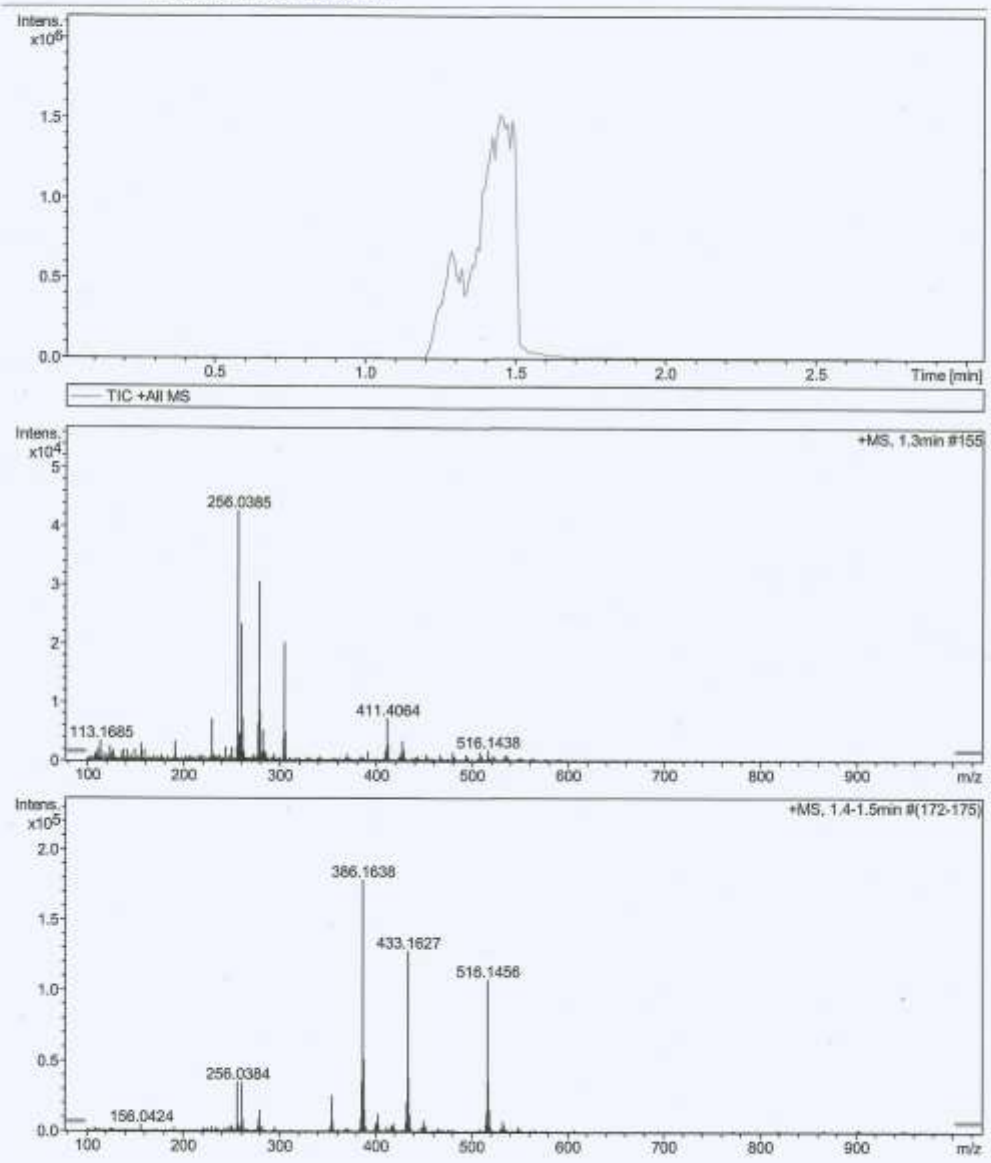
No.	RT	Area	Conc 1	BC
1	17,02	59365	1,998	BB
2	17,49	31310	1,054	BB
3	18,34	14160	0,477	BB
4	19,34	16394	0,552	BB
5	20,10	12356	0,416	BB
6	20,71	7961	0,268	BB
7	21,48	2829381	95,236	BB
8	24,81	0	0,000	
		2970927	100,000	

Peak rejection level: 0

Generic Display Report

Analysis Info

Analysis Name	\\pz-ms\PZ\PharmChemie\Routine\APCI\12_08\WJU_AJ45001.d	Acquisition Date	02.08.2012 11:16:38
Method	APCI_directprobe_positiv.m	Operator	Meiners
Sample Name	AJ45001	Instrument	micrOTOF-Q II
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		



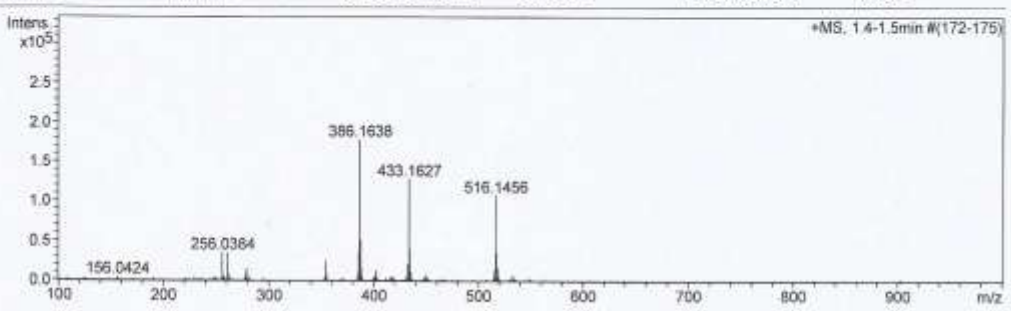
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\APCI\12_08\WJU_AJ45001.d	Acquisition Date	8/2/2012 11:16:38 AM
Method	APCI_directprobe_positiv.m	Operator	Meiners
Sample Name	AJ45001	Instrument / Ser#	micrOTOF-Q II 10252
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		

Acquisition Parameter

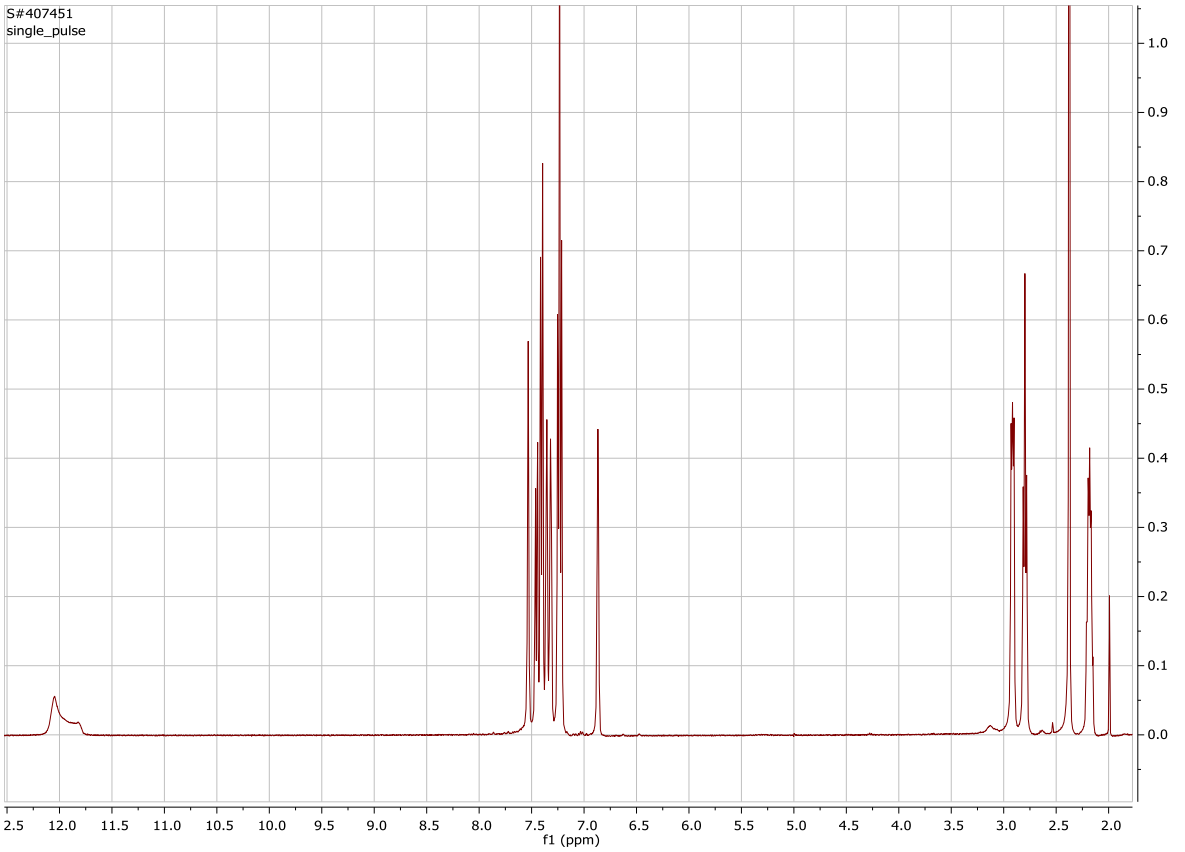
Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.7 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	3.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste

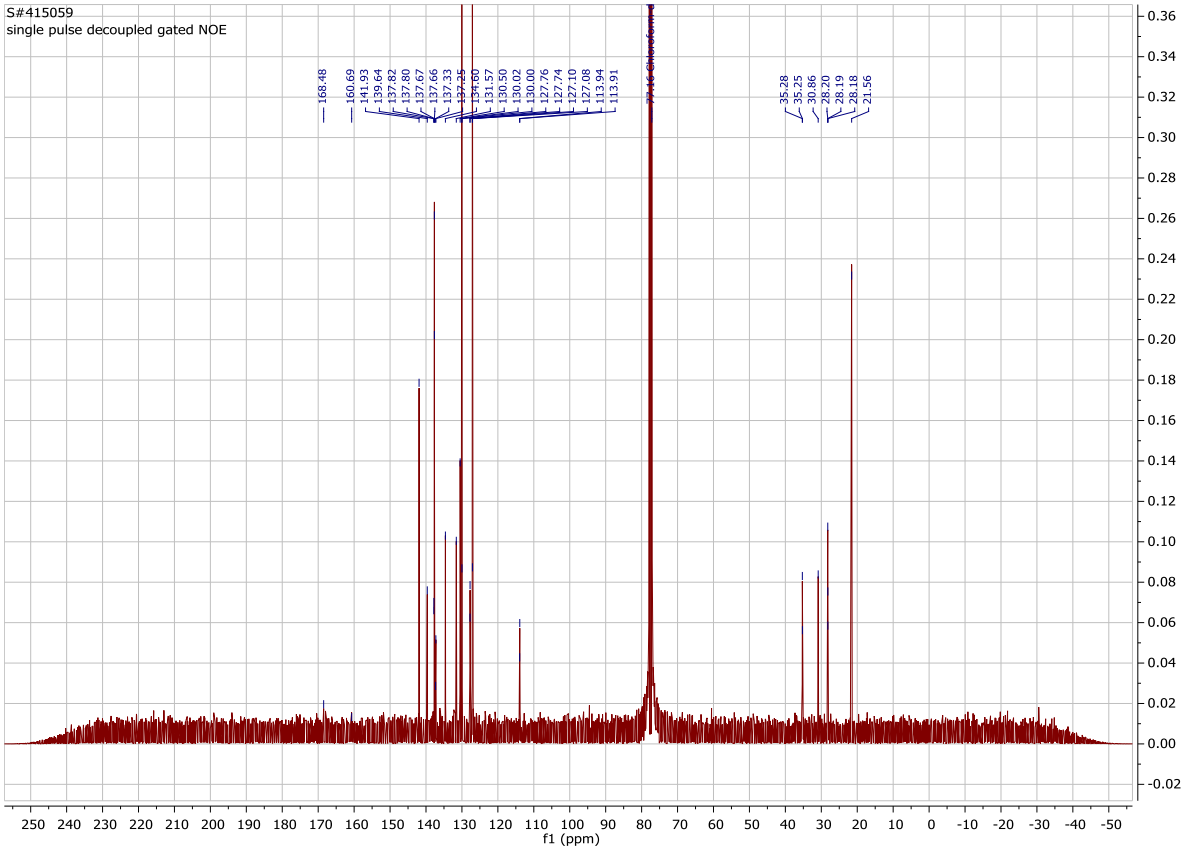


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
516.1456	1	C 28 H 26 N 3 O 3 S 2	4.02	516.1410	-4.6	-9.0	1.7	17.5	even	ok
	2	C 27 H 26 N 5 O 2 S 2	0.18	516.1522	6.6	12.8	2.4	17.5	even	ok
	3	C 24 H 22 N 9 O S 2	0.04	516.1383	-7.3	-14.2	12.4	18.5	even	ok
	4	C 26 H 30 N O 6 S 2	1.31	516.1509	5.3	10.2	14.1	12.5	even	ok
	5	C 23 H 22 N 11 S 2	7.77	516.1496	3.9	7.6	14.2	18.5	even	ok
	6	C 25 H 30 N 3 O 3 S 3	72.93	516.1444	-1.3	-2.4	20.0	12.5	even	ok
	7	C 33 H 26 N O S 2	100.00	516.1450	-0.6	-1.2	22.2	21.5	even	ok
	8	C 23 H 26 N 5 O 5 S 2	0.00	516.1370	-8.7	-16.8	23.5	13.5	even	ok
	9	C 30 H 30 N O S 3	20.81	516.1484	2.8	5.4	24.5	16.5	even	ok
	10	C 23 H 34 N O 6 S 3	0.00	516.1543	8.6	16.7	27.1	7.5	even	ok
	11	C 27 H 34 N O S 4	0.20	516.1518	6.1	11.9	37.0	11.5	even	ok
	12	C 24 H 30 N 5 S 4	0.01	516.1379	-7.8	-15.1	37.4	12.5	even	ok

2-(4-Methylphenyl)-N-(thiazol-2-yl)-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide

(8e)





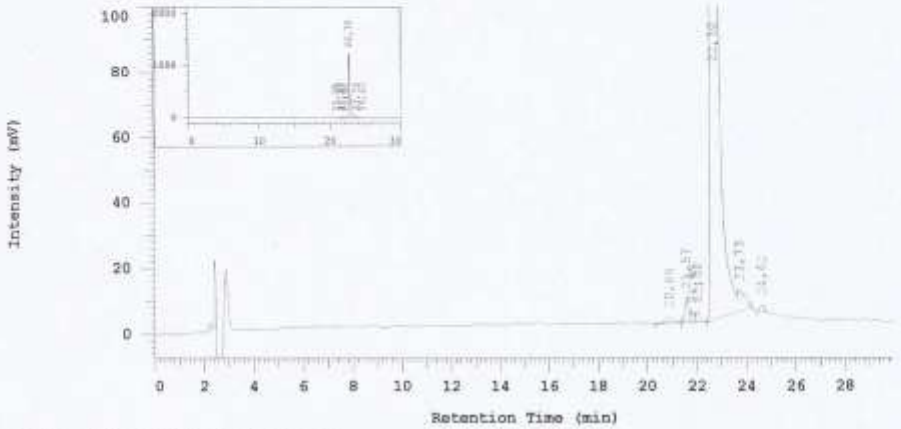
HPLC

Analyzed: 01.08.12 21:14
Reported: 02.08.12 14:53
Processed: 02.08.12 14:53

Data Path: D:\WIN32APP\HSM\Chromni\DATA\5041\
Application: Chromni
Sample Name: AJ451
Injection from this vial: 1 of 1

Series:5041
Vial Number: 5
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

No.	RT	Area	Conc 1	BC
1	20,88	29614	0,225	BB
2	21,57	73226	0,557	BV
3	21,81	30315	0,231	VV
4	22,02	39341	0,299	VB
5	22,70	12816108	97,547	BV
6	23,73	132491	1,008	MC
7	24,62	17280	0,132	BB
		13138375	100,000	

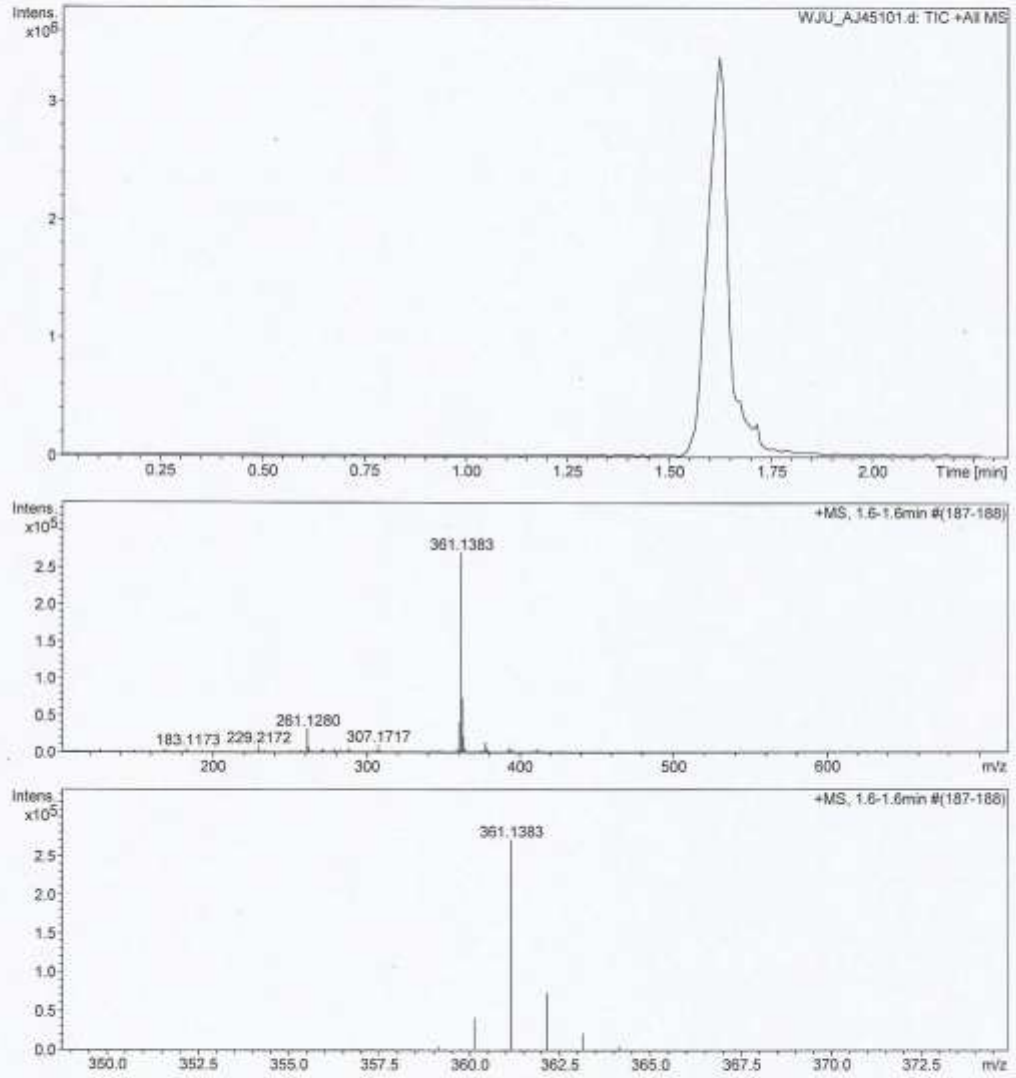
Peak rejection level: 0

361,1375 0.8 mDa

Generic Display Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\APCI\12_08\WJU_AJ45101.d	Acquisition Date	8/2/2012 9:12:36 AM
Method	APCI_directprobe_positiv.m	Operator	Meiners
Sample Name	AJ45101	Instrument	micrOTOF-Q II
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		



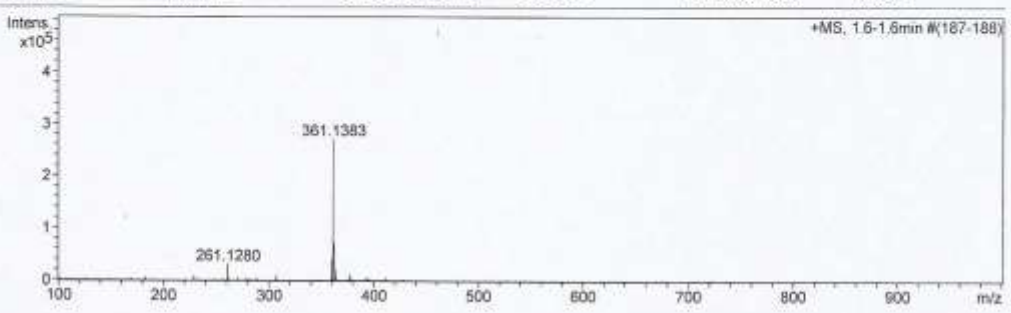
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\APCI\12_08\WJU_AJ45101.d	Acquisition Date	8/2/2012 9:12:36 AM
Method	APCI_directprobe_positiv.m	Operator	Meiners
Sample Name	AJ45101	Instrument / Ser#	micrOTOF-Q II 10252
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		

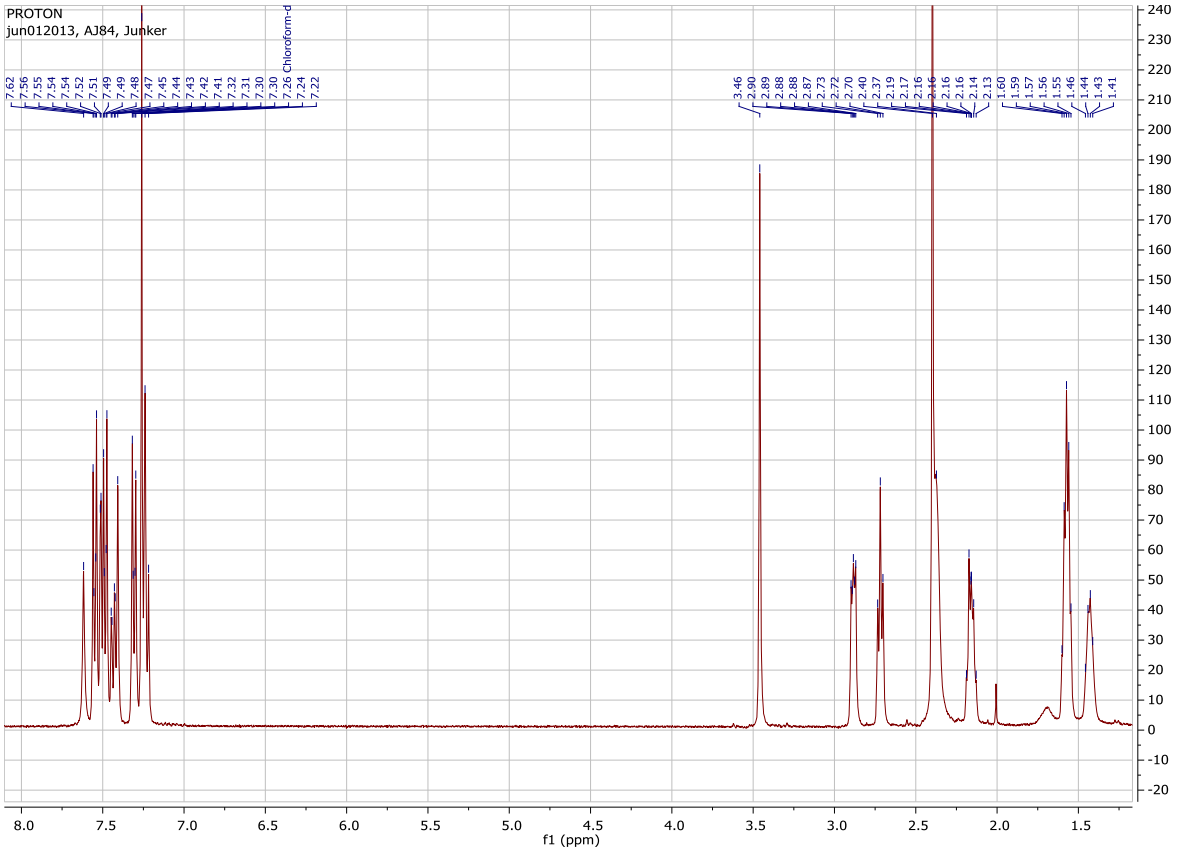
Acquisition Parameter

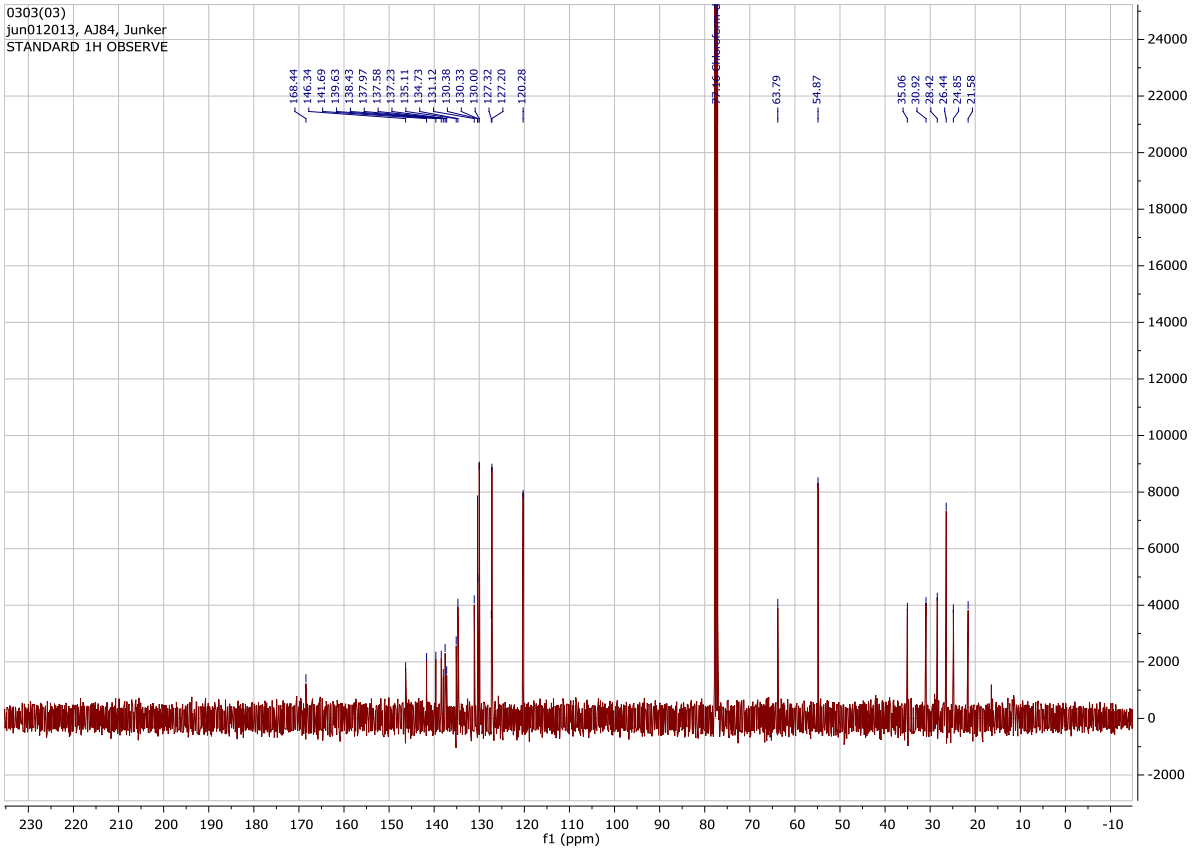
Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.7 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	3.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste

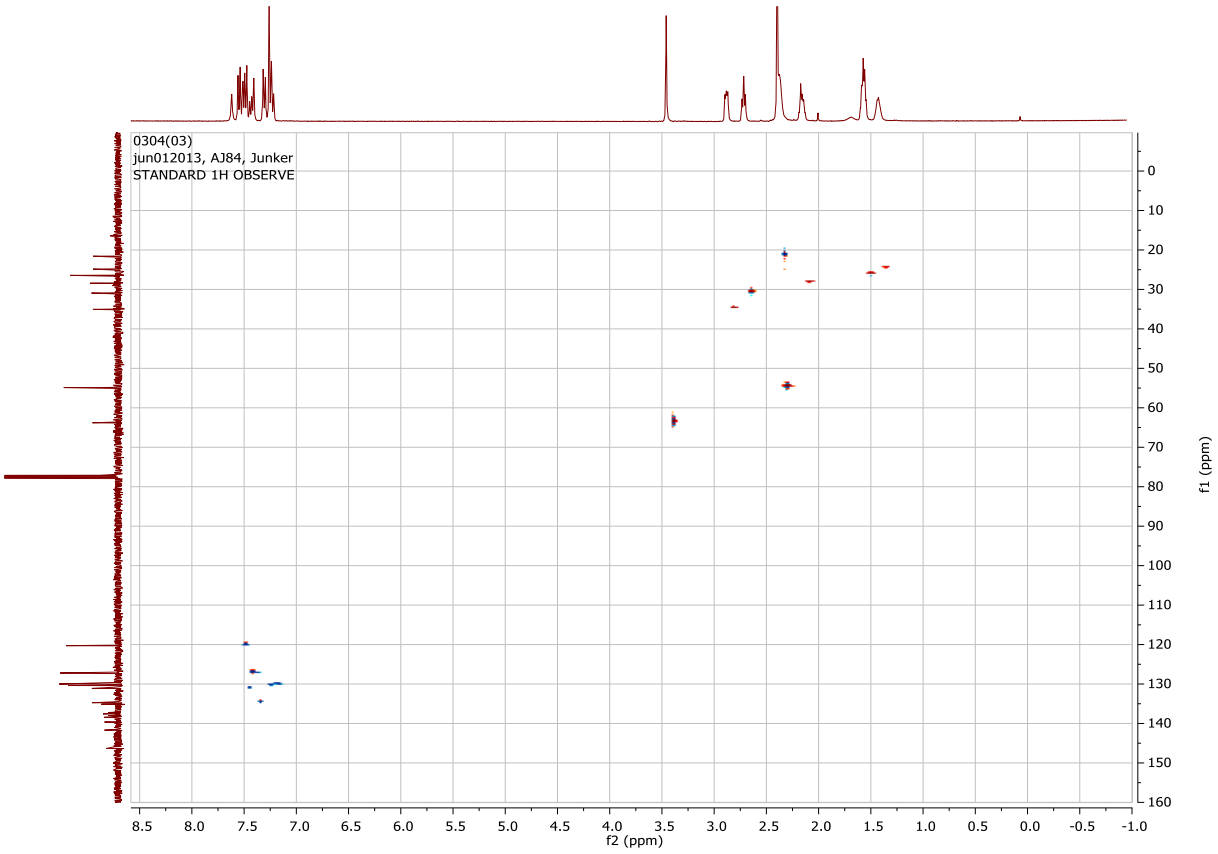


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
361.1383	1	C 22 H 21 N 2 O S	100.00	361.1369	-1.4	-3.8	7.7	13.5	even	ok
	2	C 19 H 25 N 2 O S 2	43.54	361.1403	2.0	5.5	27.1	8.5	even	ok

*2-[(4-Methyl)phenyl]-N-{4-[(piperidin-1-yl)methyl]phenyl}-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (**8f**)*






0304(03)
jun012013, AJ84, Junker
STANDARD 1H OBSERVE
f2 (ppm)
f1 (ppm)

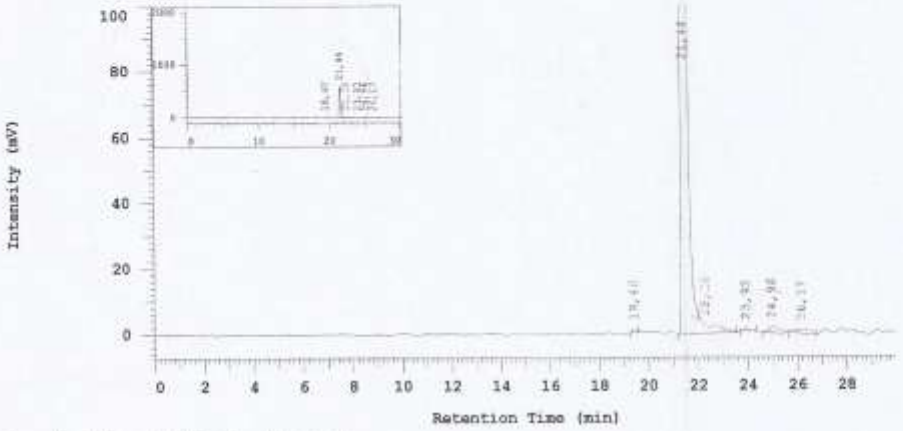
HPLC

Analyzed: 24.01.13 05:53
Reported: 25.01.13 10:18
Processed: 25.01.13 10:18

Data Path: D:\WIN32APP\HSM\Chromni\DATA\5856\
Application: Chromni
Sample Name: AJ84
Injection from this vial: 1 of 1

Series:5856
Vial Number: 15
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

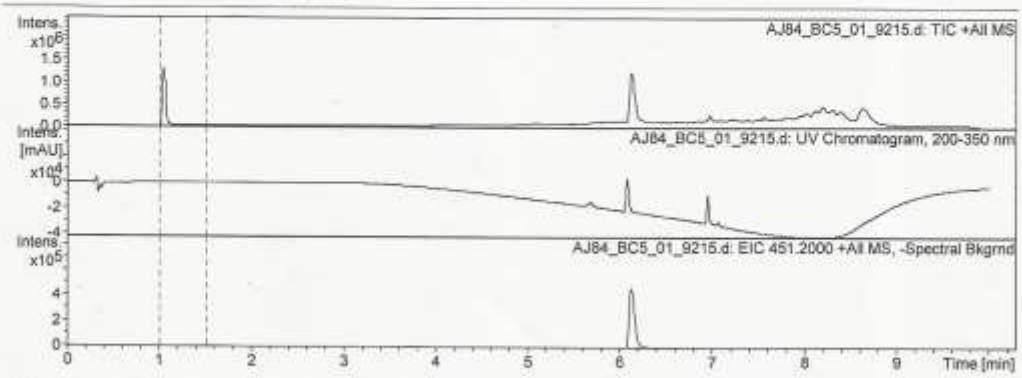
No.	RT	Area	Conc 1	BC
1	19,40	11066	0,159	BB
2	21,44	6638365	95,646	MC
3	22,28	172954	2,492	MC
4	23,92	16415	0,237	MC
5	24,96	52086	0,750	MC
6	26,17	49657	0,715	BB
		6940543	100,000	

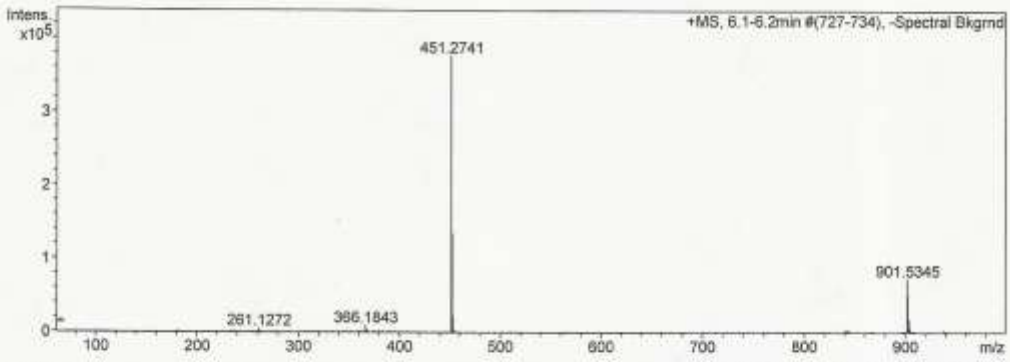
Peak rejection level: 0

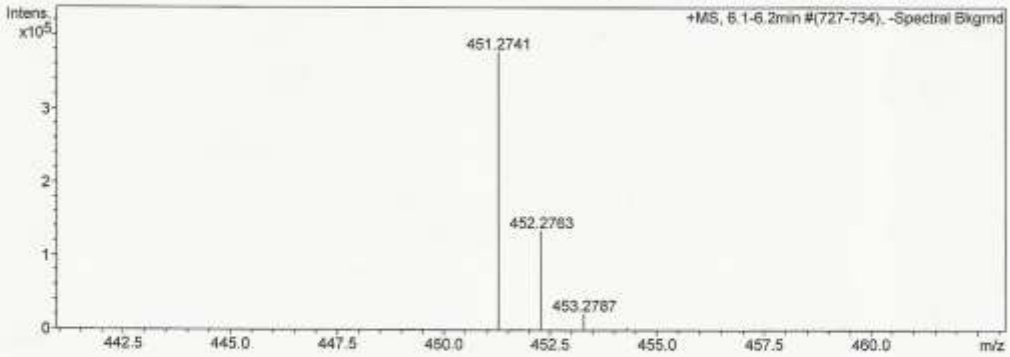
Generic Display Report

Analysis Info

Analysis Name	E:\Meiners\2013_01_14\AJ84_BC5_01_9215.d	Acquisition Date	1/14/2013 6:11:02 PM
Method	tune_low_lcms_routine_positiv_10min.m	Operator	Meiners
Sample Name	AJ84	Instrument	micrOTOF-Q II
Comment	Junker Kalibration mit LI-Formate		







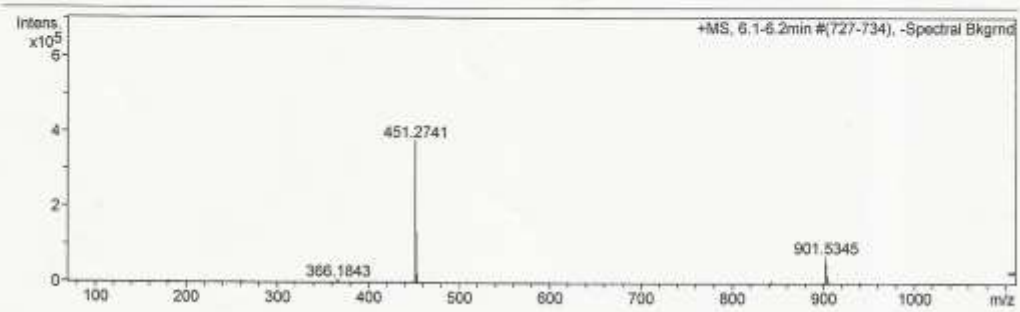
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	E:\Meiners\2013_01_14\AJ84_BC5_01_9215.d	Acquisition Date	1/14/2013 6:11:02 PM
Method	tune_low_lcms_routine_positiv_10min.m	Operator	Meiners
Sample Name	AJ84	Instrument / Ser#	micrOTOF-Q II 10252
Comment	Junker Kalibration mit Li-Formate		

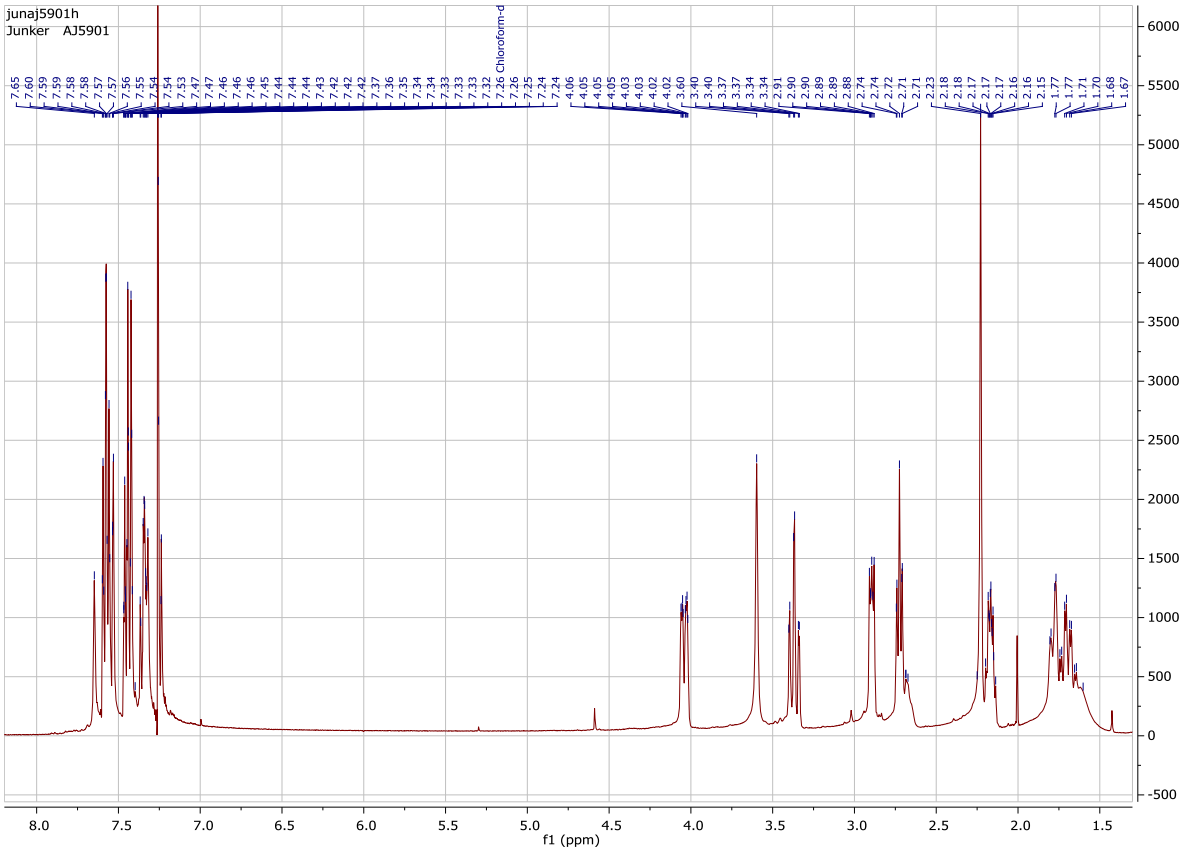
Acquisition Parameter

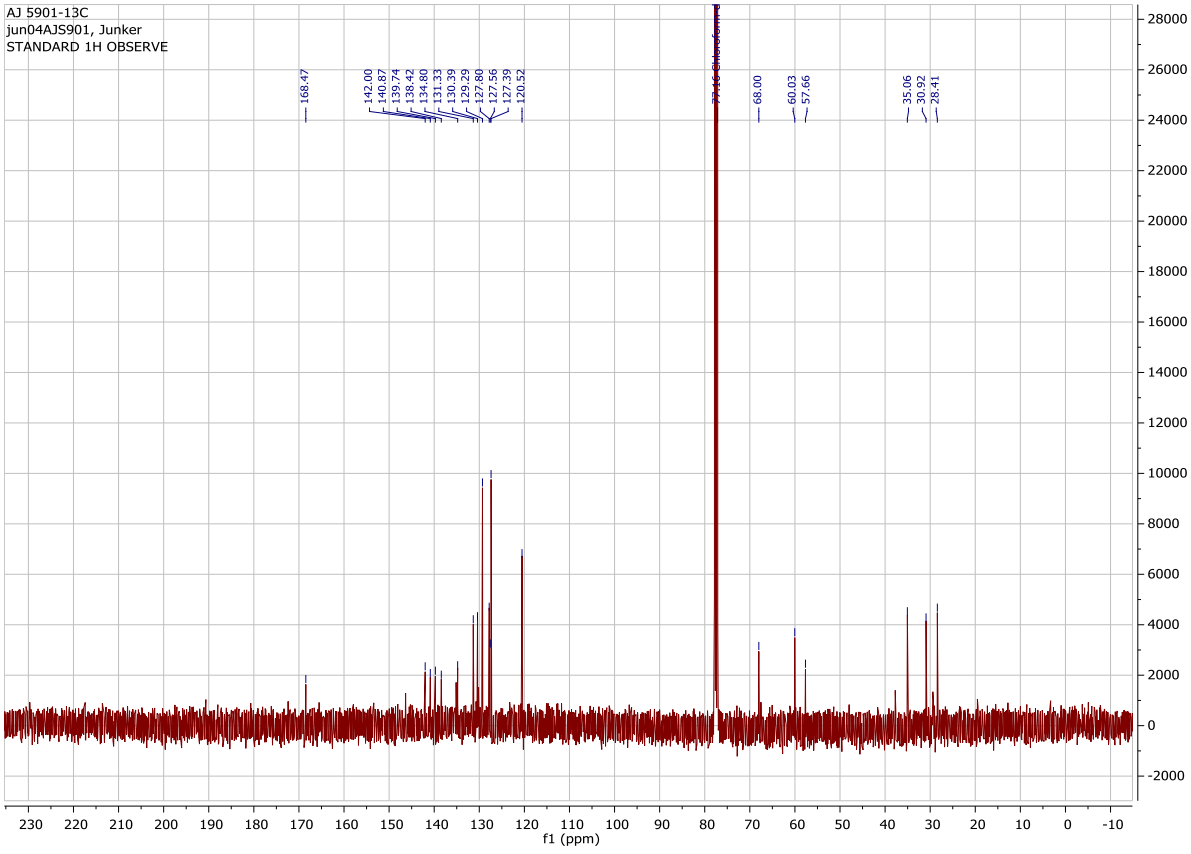
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	2.0 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	9.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	300.0 Vpp	Set Divert Valve	Waste



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
451.2741	1	C 31 H 35 N 2 O	100.00	451.2744	0.3	0.7	4.8	15.5	even	ok
	2	C 28 H 35 N 4 O 3	4.05	451.2704	-3.7	-8.2	32.7	11.5	even	ok

*N-{4-[N-Methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (**9a**)*





HPLC

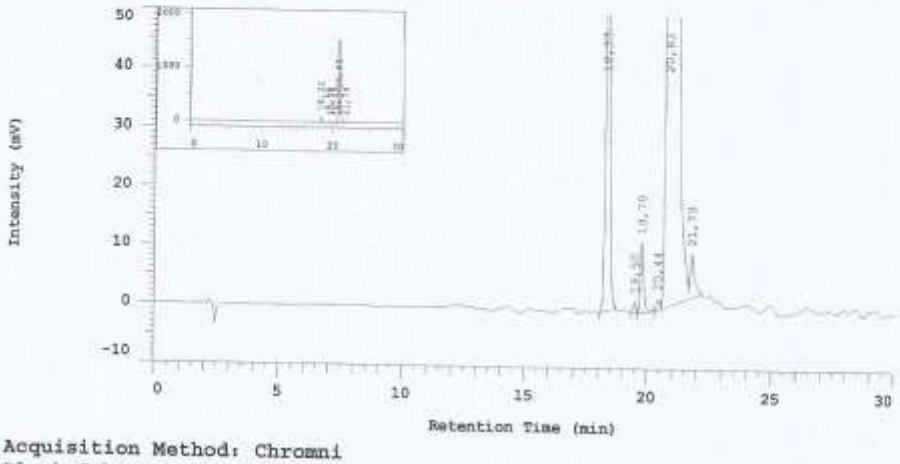
Analyzed: 20.04.11 03:13

Reported: 20.04.11 14:14
Processed: 20.04.11 14:14

Data Path: D:\WIN32APP\HSM\Chromni\DATA\2992\
Application: Chromni
Sample Name: AJ5901
Injection from this vial: 1 of 1

Series:2992
Vial Number: 12
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Solvent A: Wasser + 0,05%TFA

Developed by: Jens
Solvent B: ACN + 0,05%TFA

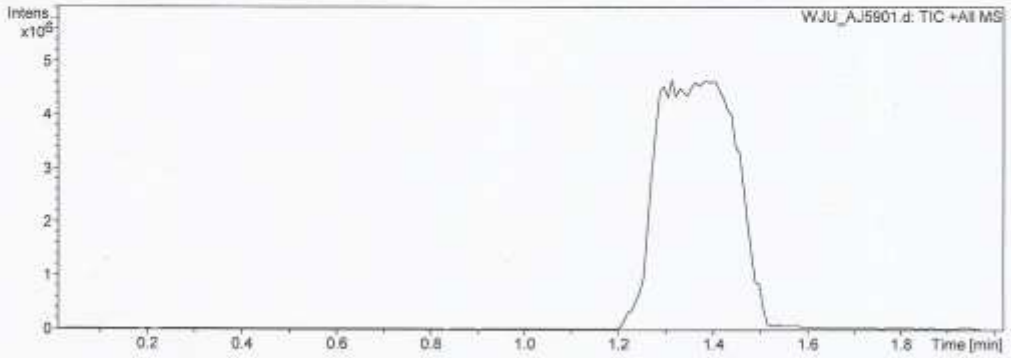
No.	RT	Area	Conc 1	BC
1	18,33	949394	3,832	BB
2	19,50	12954	0,052	BB
3	19,78	107892	0,435	BB
4	20,44	13457	0,054	MC
5	20,83	23602756	95,260	MC
6	21,79	90764	0,366	MC
		24777217	100,000	

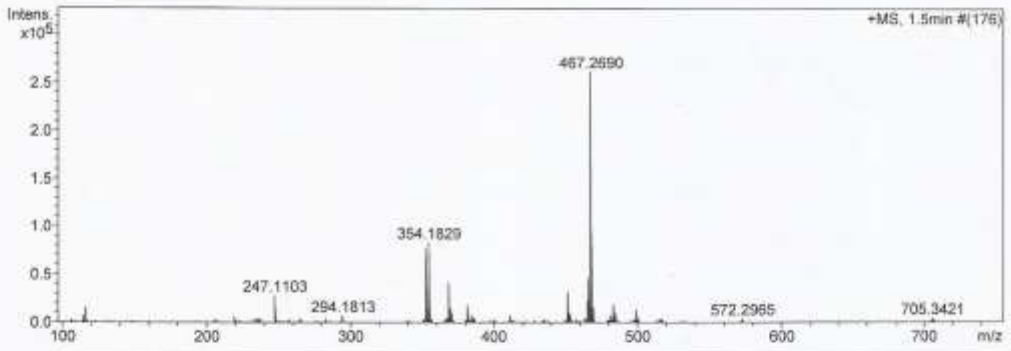
Peak rejection level: 0

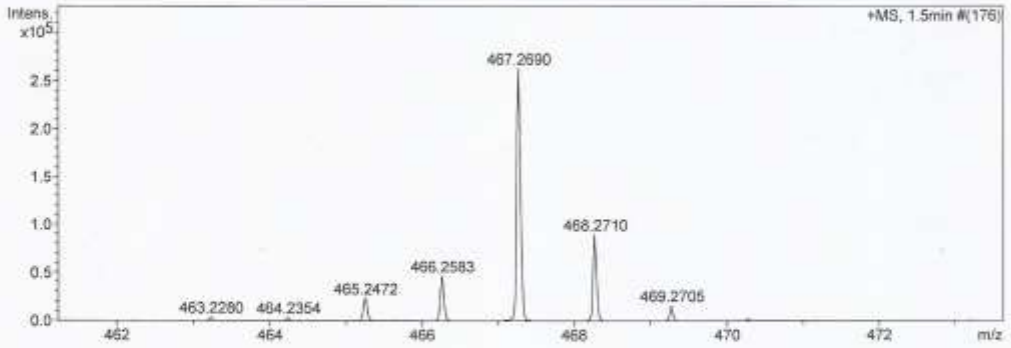
Generic Display Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\2011_5\WJU_AJ5901.d	Acquisition Date	5/2/2011 2:35:53 PM
Method	APCI_directprobe_default.m	Operator	Meiners
Sample Name	AJ5901	Instrument	micrOTOF-Q II
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		







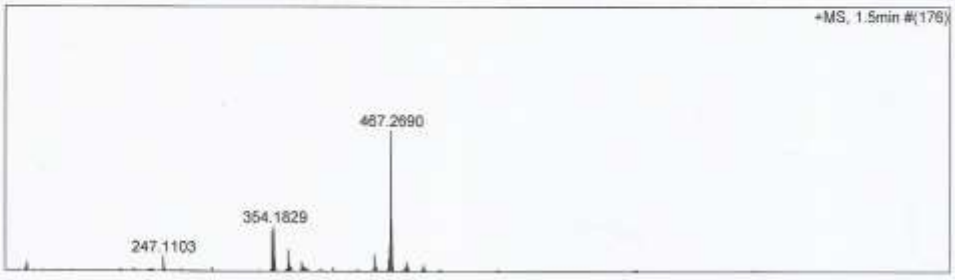
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\2011_5\WJU_AJ5901.d	Acquisition Date	5/2/2011 2:35:53 PM
Method	APCI_directprobe_default.m	Operator	Meiners
Sample Name	AJ5901	Instrument / Ser#	micrOTOF-Q II 10252
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		

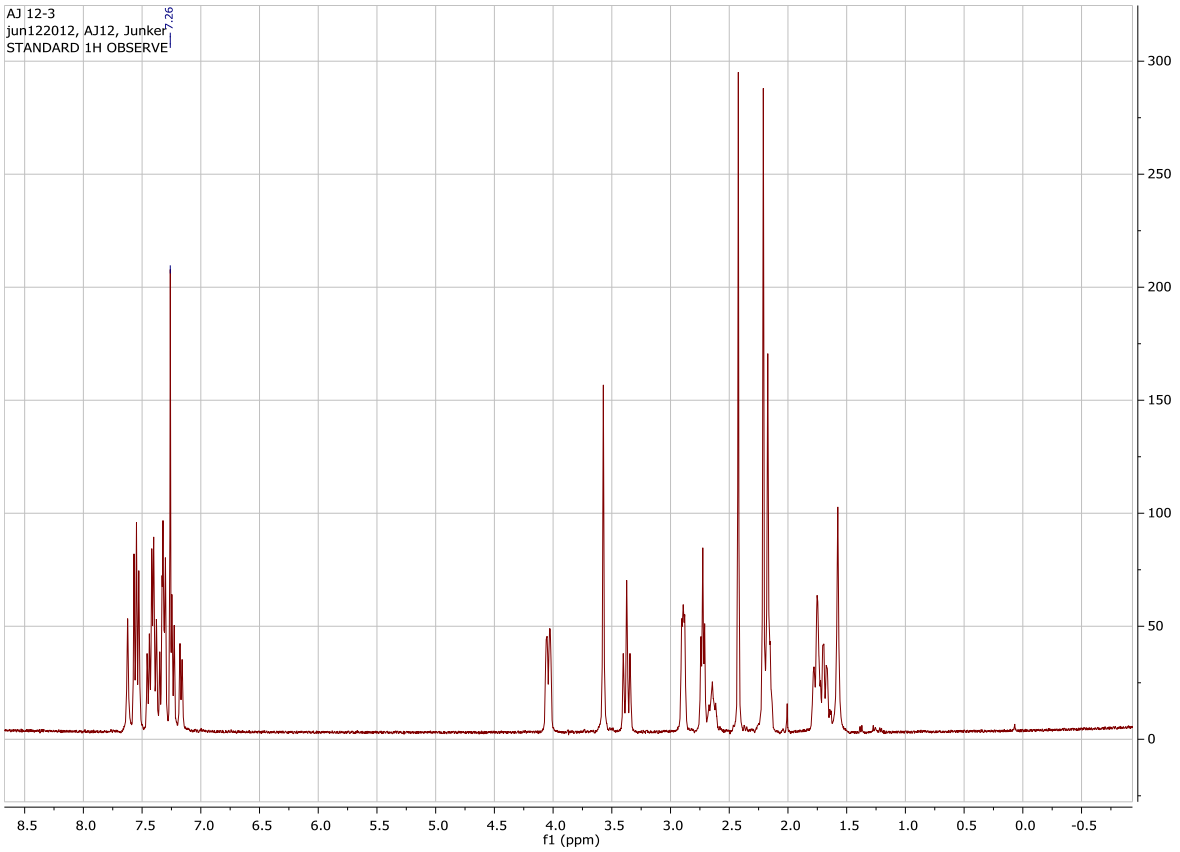
Acquisition Parameter

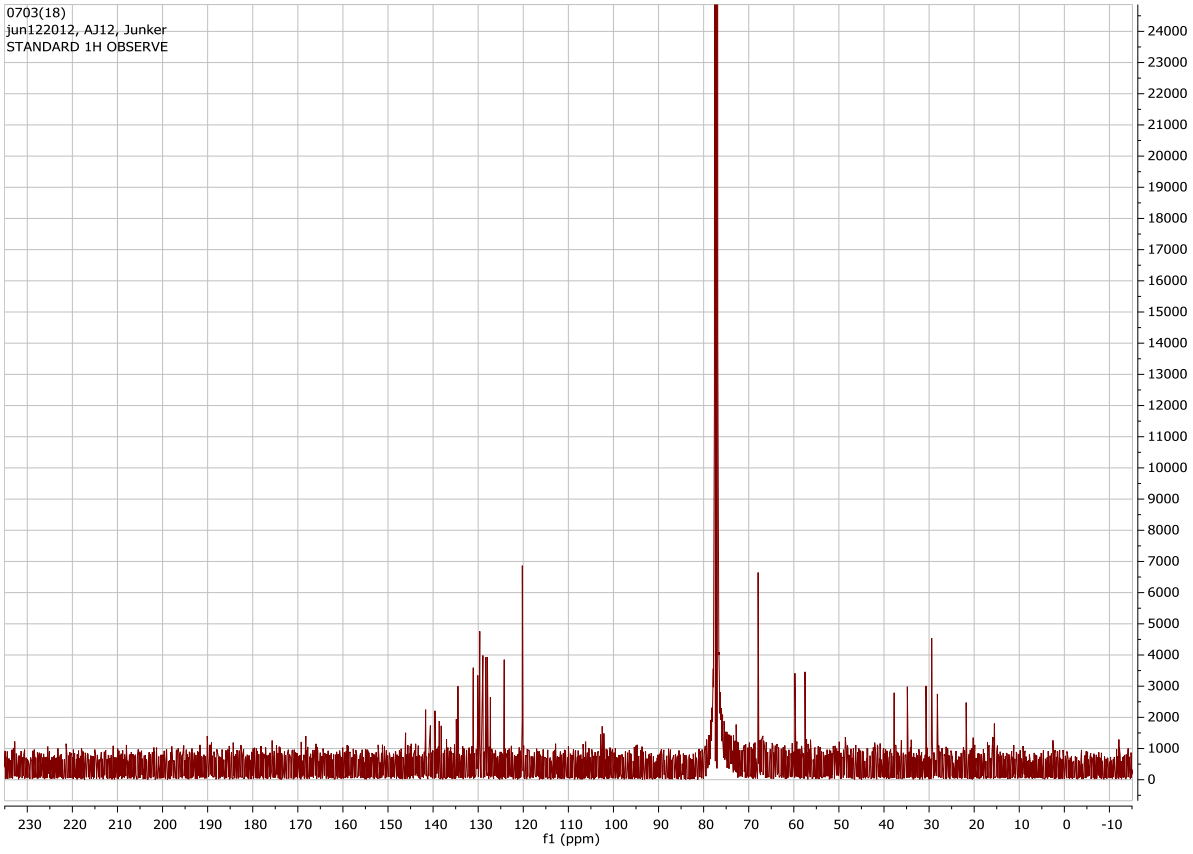
Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.7 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	3.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste

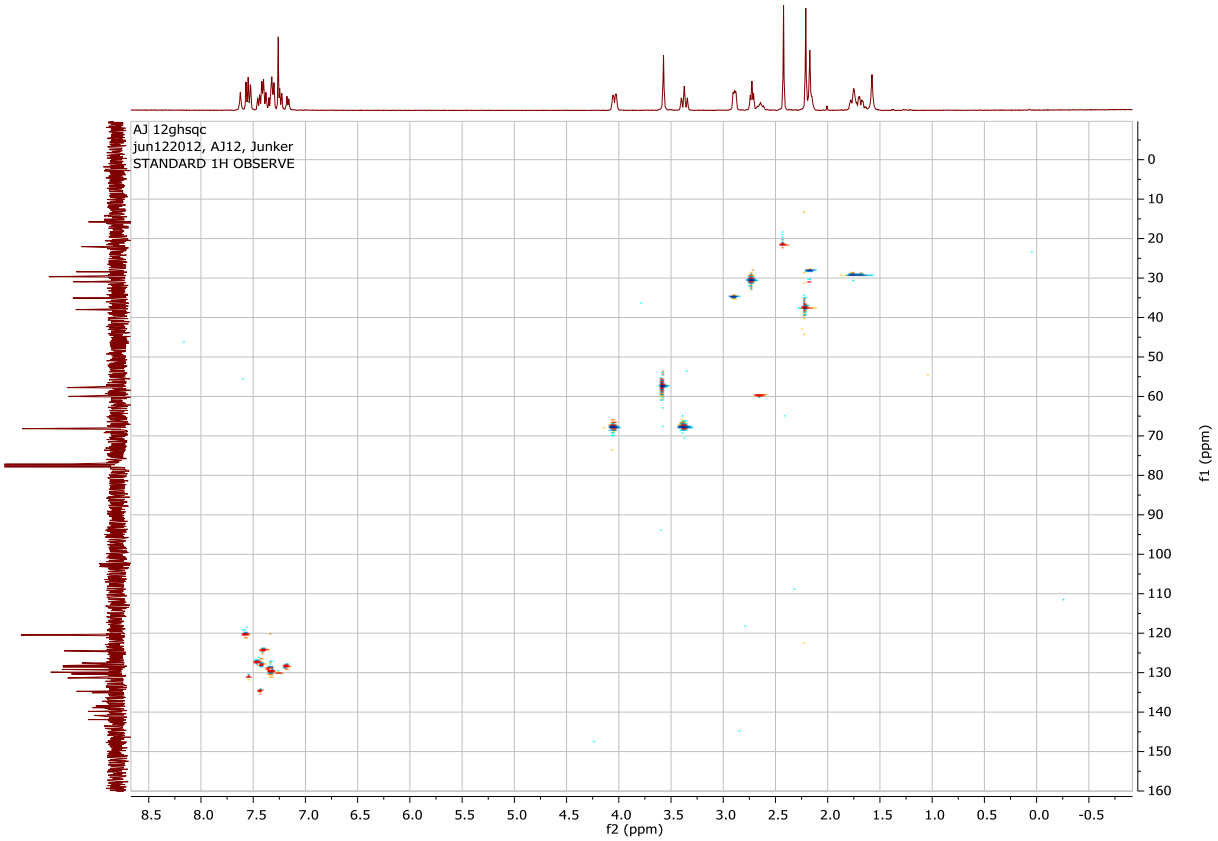


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
467.2690	1	C 31 H 35 N 2 O 2	100.00	467.2693	0.3	0.6	2.0	15.5	even	ok
	2	C 27 H 31 N 8	22.03	467.2666	-2.4	-5.2	10.5	16.5	even	ok
	3	C 26 H 35 N 4 O 4	4.32	467.2653	-3.7	-8.0	25.5	11.5	even	ok

*2-(3-Methyphenyl)-N-{[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (**9b**)*






AJ 12ghsqc
jun122012, AJ12, Junker
STANDARD 1H OBSERVE
f2 (ppm)
f1 (ppm)

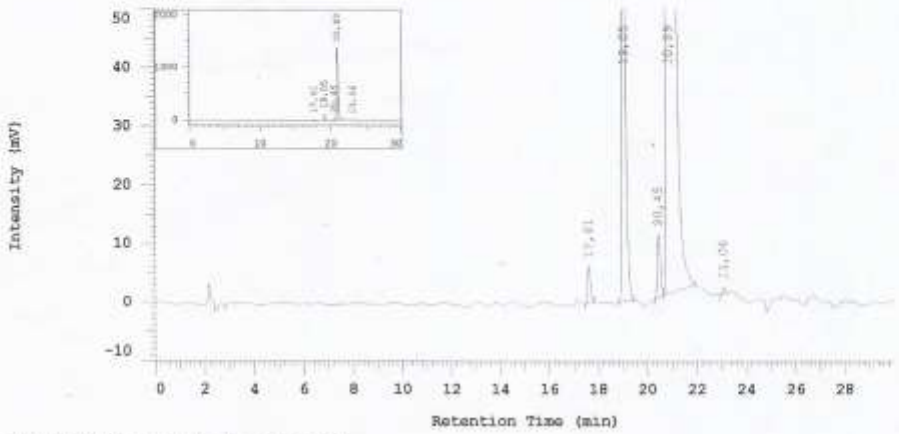
HPLC

Analyzed: 01.09.10 22:12
Reported: 02.09.10 17:20
Processed: 02.09.10 17:20

Data Path: D:\WIN32APP\HSM\Chromni\DATA\2046\
Application: Chromni
Series:2046

Sample Name: AJ1201
Vial Number: 6
Vial Type: UNK
Injection from this vial: 1 of 1
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

No.	RT	Area	Conc 1	BC
1	17,61	49941	0,261	BB
2	19,05	898693	4,694	MC
3	20,45	87954	0,459	MC
4	20,89	18104659	94,553	MC
5	23,06	6310	0,033	BB
		19147557	100,000	

Peak rejection level: 0

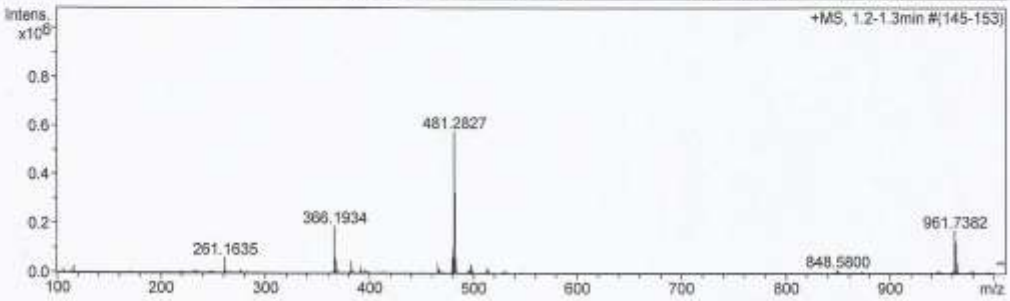
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	E:\Meiners\12_09\WJU_AJ12.d	Acquisition Date	9/7/2012 9:16:48 AM
Method	APCI_directprobe_positiv.m	Operator	Sendker
Sample Name	AJ12	Instrument / Ser#	micrOTOF-Q II 10252
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		

Acquisition Parameter

Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.7 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	3.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste

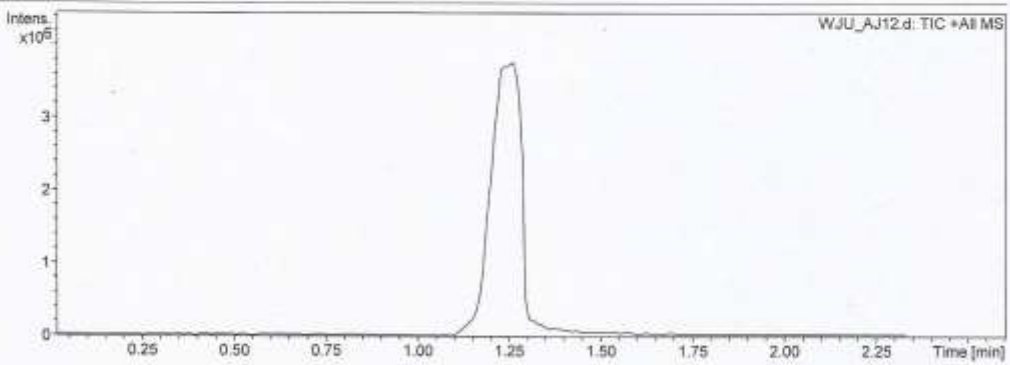


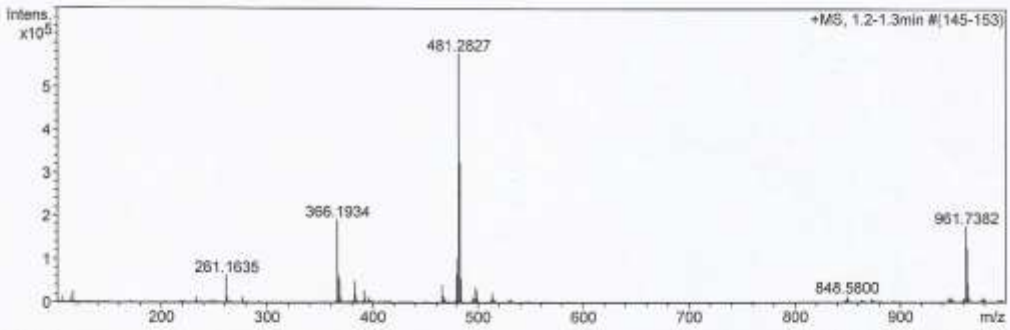
Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
481.2827	1	C 32 H 37 N 2 O 2	57.09	481.2850	2.2	4.7	102.4	15.5	even	ok
	2	C 28 H 33 N 8	100.00	481.2823	-0.4	-0.9	114.0	16.5	even	ok
	3	C 27 H 37 N 4 O 4	23.08	481.2809	-1.8	-3.7	126.3	11.5	even	ok
	4	C 26 H 41 O 8	3.54	481.2796	-3.1	-6.5	138.7	6.5	even	ok
	5	C 23 H 33 N 10 O 2	0.20	481.2782	-4.5	-9.3	159.2	12.5	even	ok
	6	C 20 H 41 N 4 O 9	0.22	481.2868	4.1	8.5	164.3	2.5	even	ok
	7	C 17 H 33 N 14 O 3	0.14	481.2855	2.7	5.7	188.9	8.5	even	ok
	8	C 16 H 37 N 10 O 7	0.13	481.2841	1.4	2.9	202.8	3.5	even	ok
	9	C 13 H 29 N 20 O	0.23	481.2828	0.1	0.1	204.5	9.5	even	ok
	10	C 12 H 33 N 16 O 5	0.04	481.2814	-1.3	-2.7	216.0	4.5	even	ok

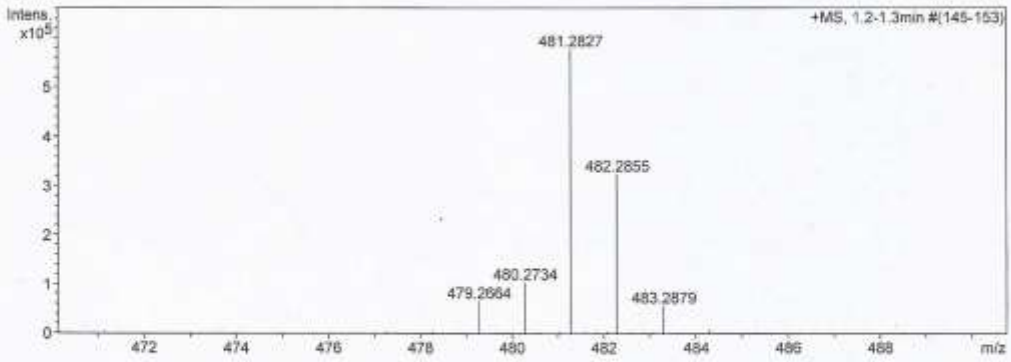
Generic Display Report

Analysis Info

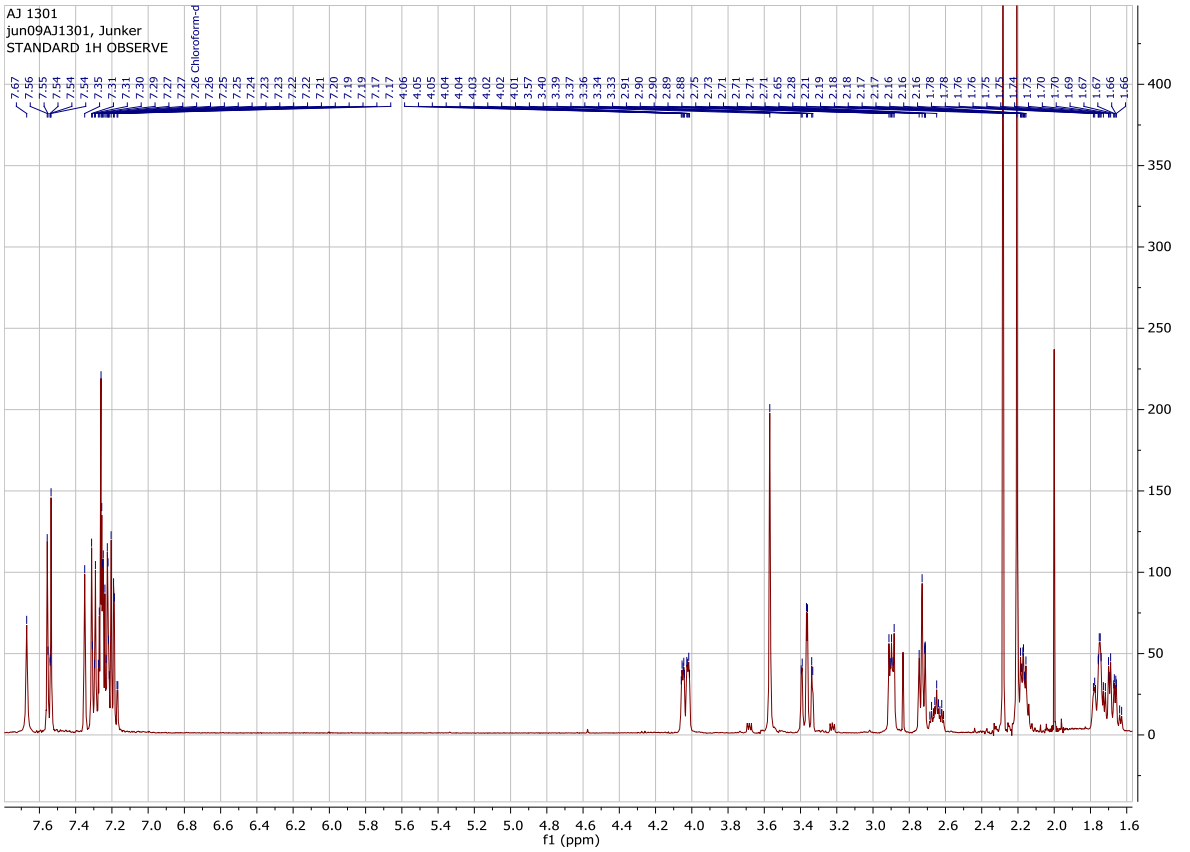
Analysis Name	E:\Meiners\12_09\WJU_AJ12.d	Acquisition Date	9/7/2012 9:16:48 AM
Method	APCI_directprobe_positiv.m	Operator	Sendker
Sample Name	AJ12	Instrument	micrOTOF-Q II
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		

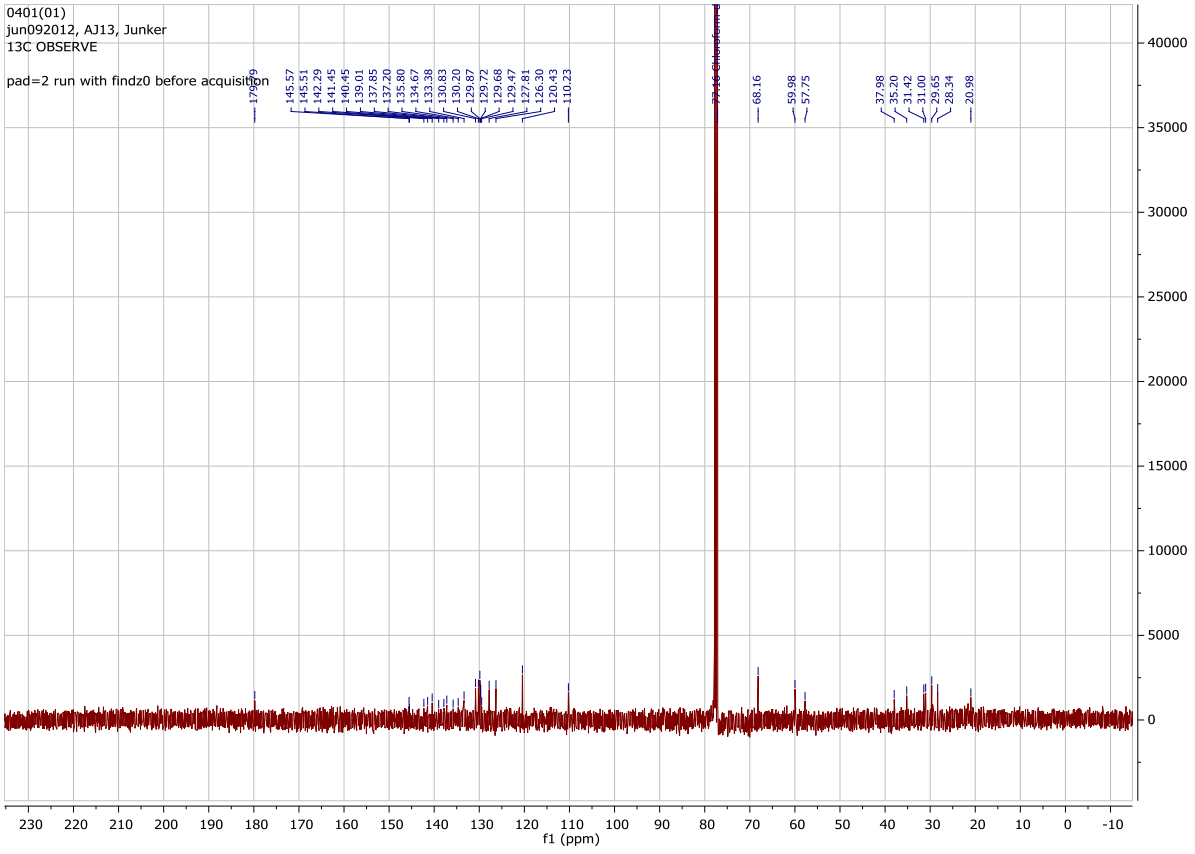






*2-(2-Methyphenyl)-N-{4-[N-Methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (**9c**)*





HPLC

Analyzed: 21.10.10 03:58

Reported: 21.10.10 13:45
Processed: 21.10.10 13:45

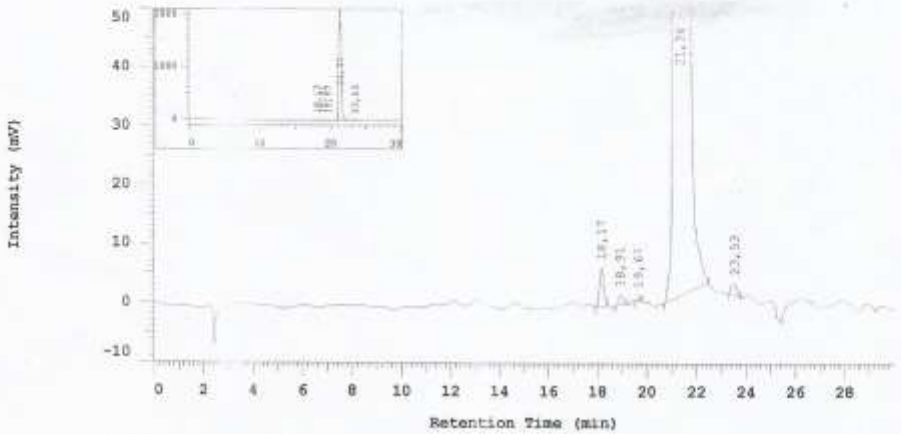
Data Path: D:\WIN32APP\HSM\Chromni\DATA\2286\
Application: Chromni

Sample Name: AJ1301

Injection from this vial: 1 of 1

Series:2286
Vial Number: 12
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

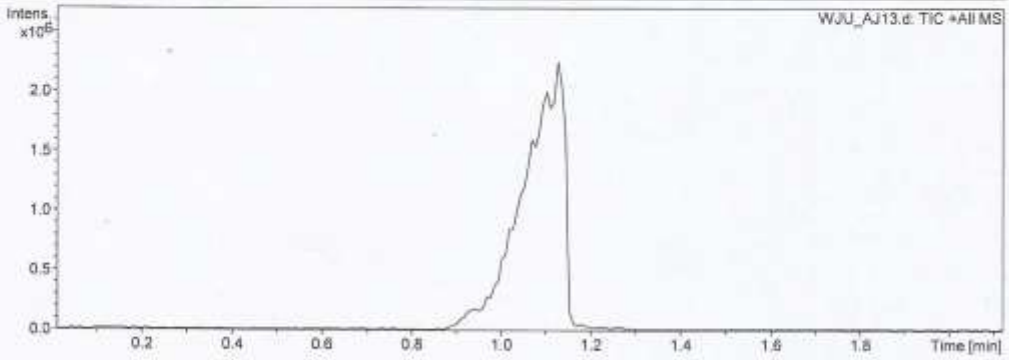
No.	RT	Area	Conc 1	BC
1	18,17	76388	0,157	MC
2	18,91	20994	0,043	MC
3	19,67	6971	0,014	BB
4	21,34	48466825	99,725	MC
5	23,53	29471	0,061	MC
		48600649	100,000	

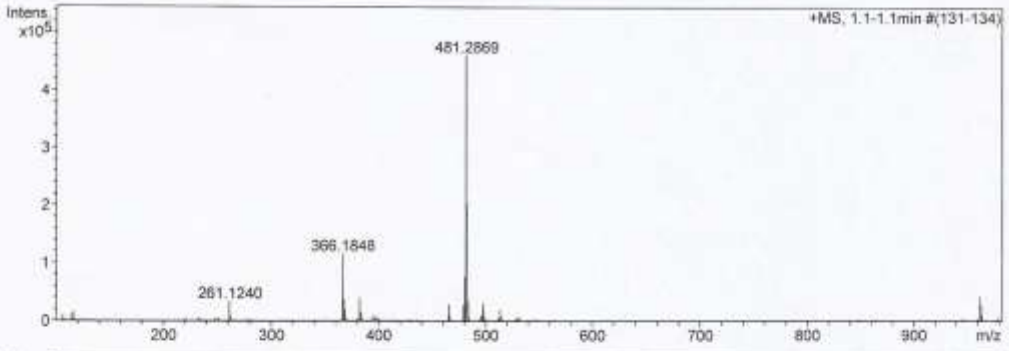
Peak rejection level: 0

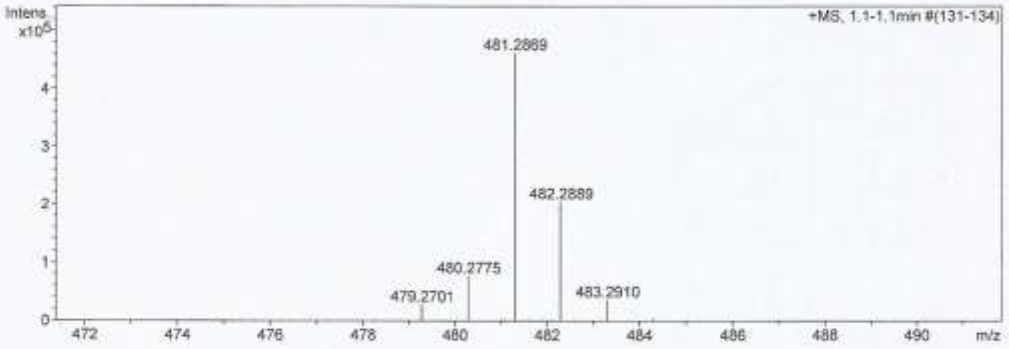
Generic Display Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\APCI\12_09\WJU_AJ13.d	Acquisition Date	9/10/2012 8:30:48 AM
Method	APCI_directprobe_positiv.m	Operator	Sendker
Sample Name	AJ13	Instrument	micrOTOF-Q II
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		







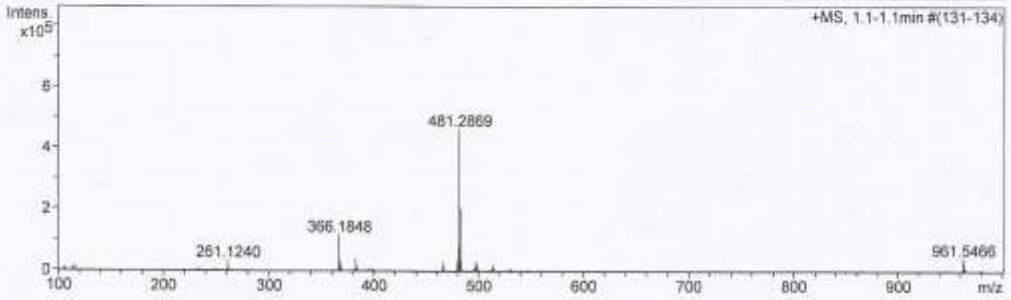
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\APCI\12_09\WJU_AJ13.d	Acquisition Date	9/10/2012 8:30:48 AM
Method	APCI_directprobe_positiv.m	Operator	Sendker
Sample Name	AJ13	Instrument / Ser#	micrOTOF-Q II 10252
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		

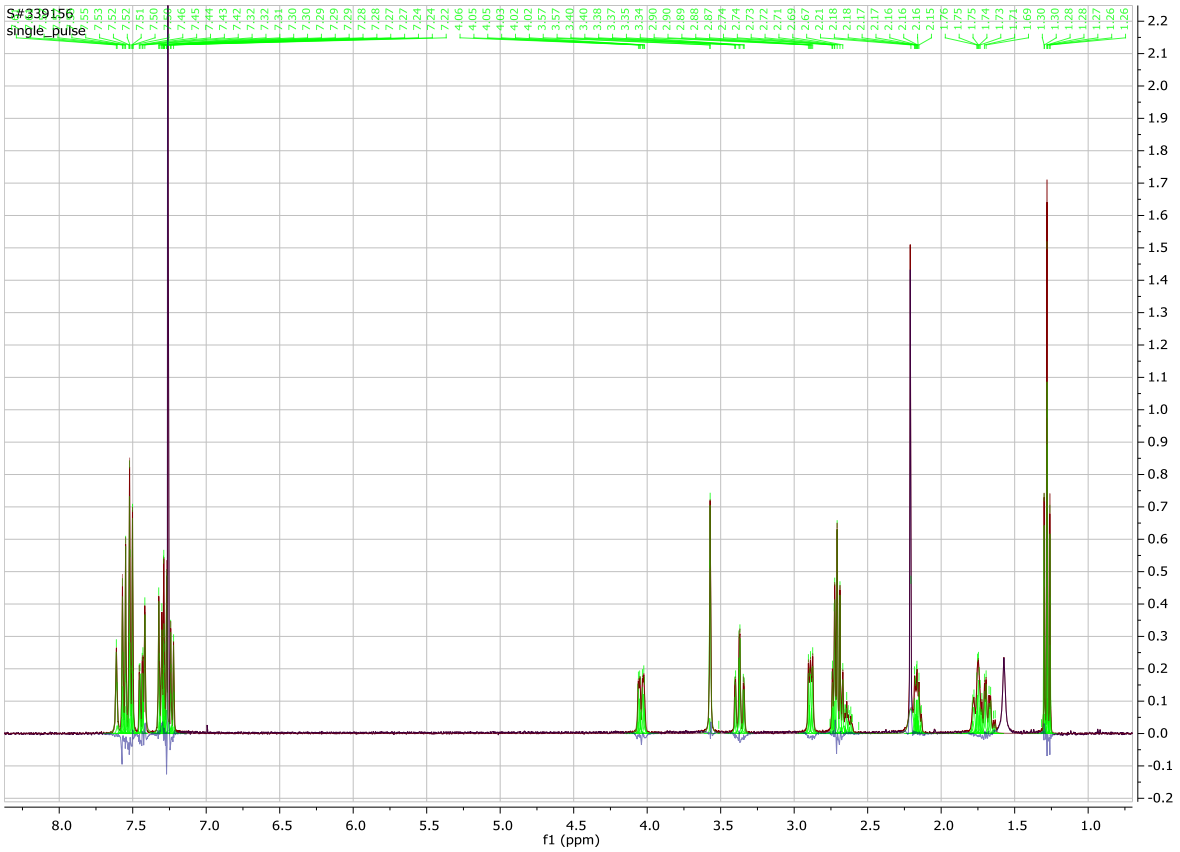
Acquisition Parameter

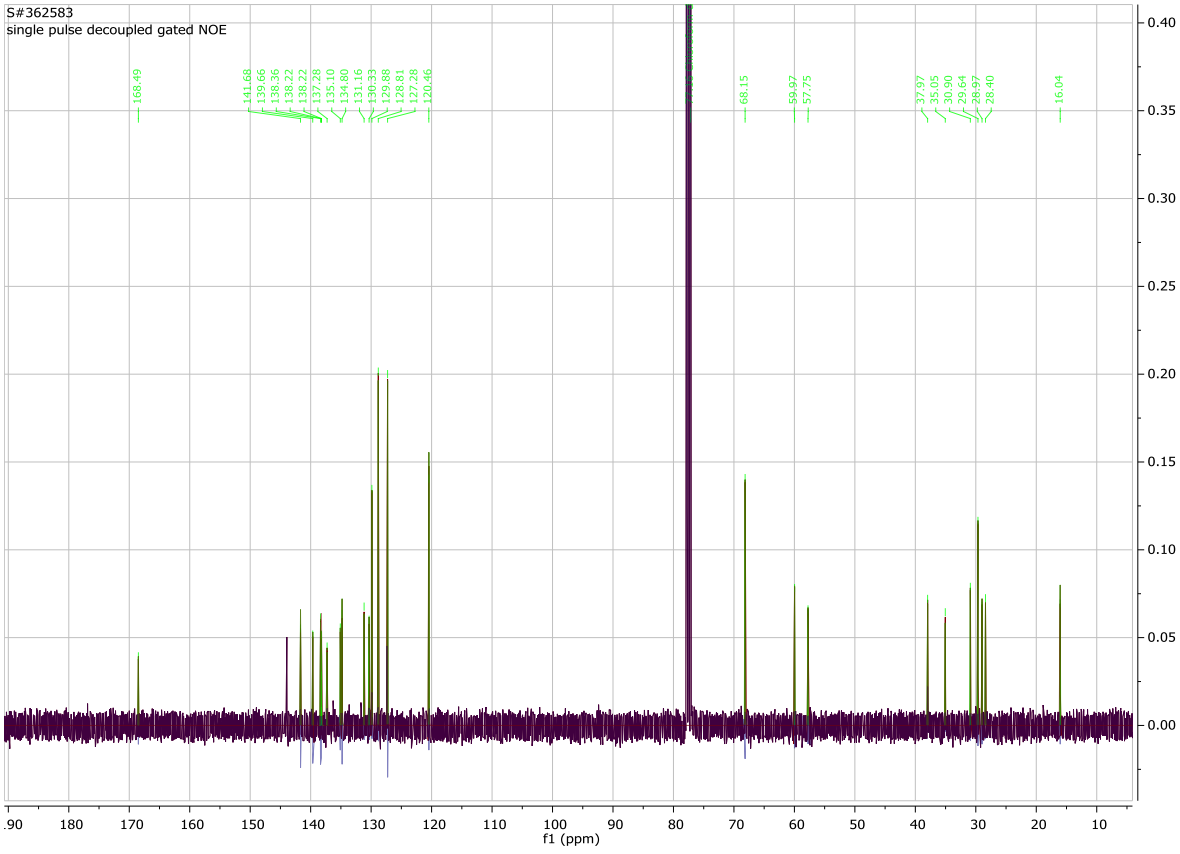
Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.7 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	3.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
481.2869	1	C 37 H 37	100.00	481.2890	2.1	4.3	18.7	19.5	even	ok
	2	C 32 H 37 N 2 O 2	61.61	481.2850	-2.0	-4.1	42.2	15.5	even	ok
	3	C 25 H 41 N 2 O 7	2.53	481.2908	3.9	8.1	80.4	6.5	even	ok
	4	C 22 H 33 N 12 O	6.04	481.2895	2.6	5.3	92.3	12.5	even	ok
	5	C 20 H 41 N 4 O 9	16.85	481.2868	-0.1	-0.2	104.1	2.5	even	ok
	6	C 21 H 37 N 8 O 5	8.55	481.2881	1.2	2.6	106.1	7.5	even	ok
	7	C 17 H 33 N 14 O 3	3.73	481.2855	-1.4	-3.0	119.4	8.5	even	ok
	8	C 16 H 37 N 10 O 7	0.59	481.2841	-2.8	-5.8	133.3	3.5	even	ok

*2-(4-Ethylphenyl)-N-{4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (**9d**)*





HPLC

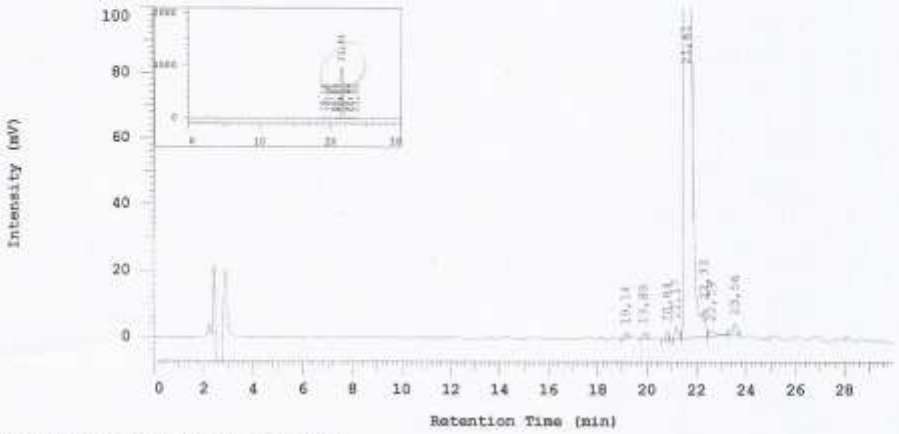
Analyzed: 05.07.12 03:21
Reported: 05.07.12 15:46
Processed: 05.07.12 15:45

Data Path: D:\WIN32APP\HSM\Chromni\DATA\4971\
Application: Chromni
Series:4971

Sample Name: AJ7501
Vial Number: 13
Vial Type: UNK
Volume: 5,0 ul

Injection from this vial: 1 of 1

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: KG 97.1
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

No.	RT	Area	Conc 1	BC
1	19,14	12781	0,106	MC
2	19,88	14479	0,121	BB
3	20,84	19943	0,166	MC
4	21,17	34405	0,287	MC
5	21,61	11771381	98,081	MC
6	22,33	66843	0,557	MC
7	22,59	35122	0,293	MC
8	23,56	46779	0,390	MC
		12001733	100,000	

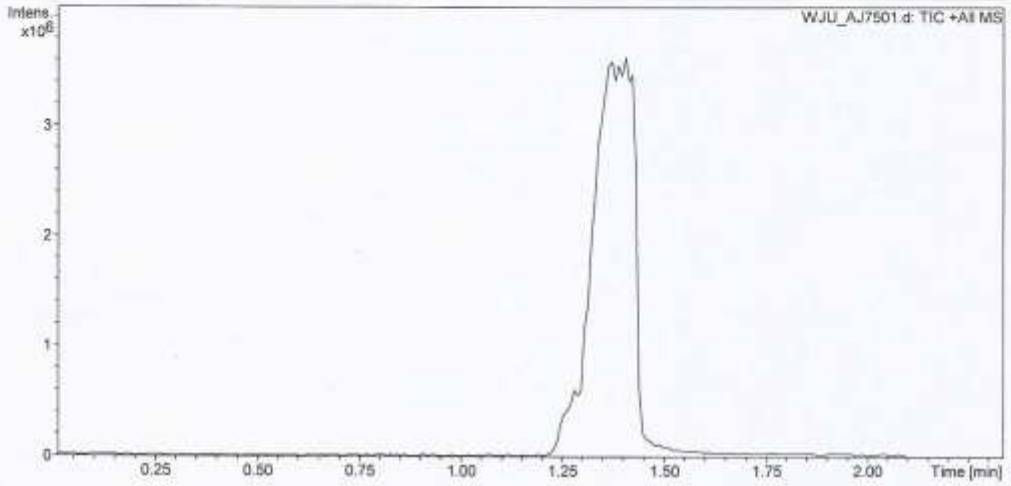
Peak rejection level: 0

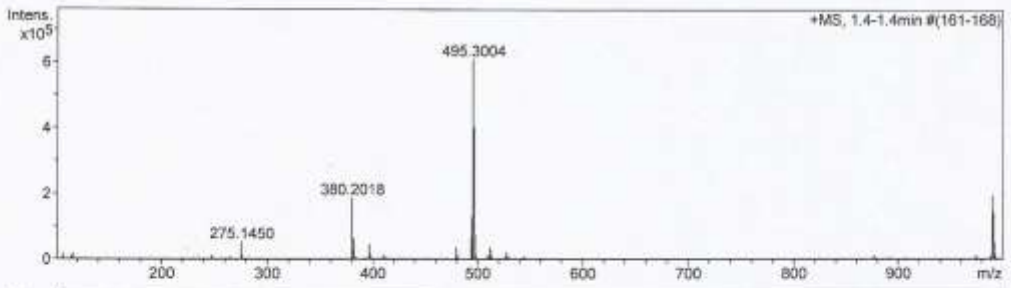
495.3012 0.8 mDa

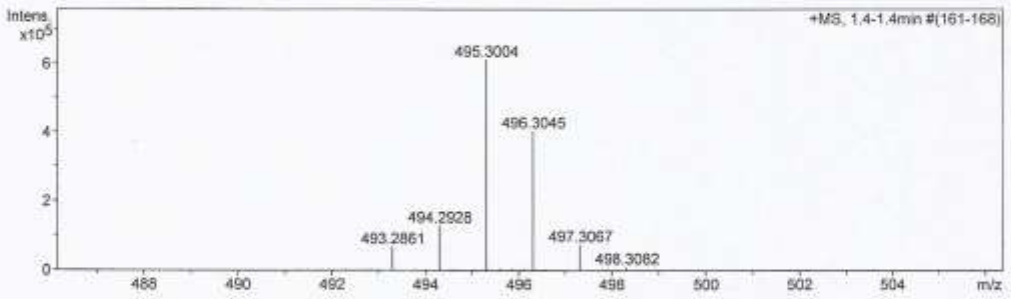
Generic Display Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\APCI\12_08\WJU_AJ7501.d	Acquisition Date	8/2/2012 9:37:48 AM
Method	APCI_directprobe_positiv.m	Operator	Meiners
Sample Name	AJ7501	Instrument	micrOTOF-Q II
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		







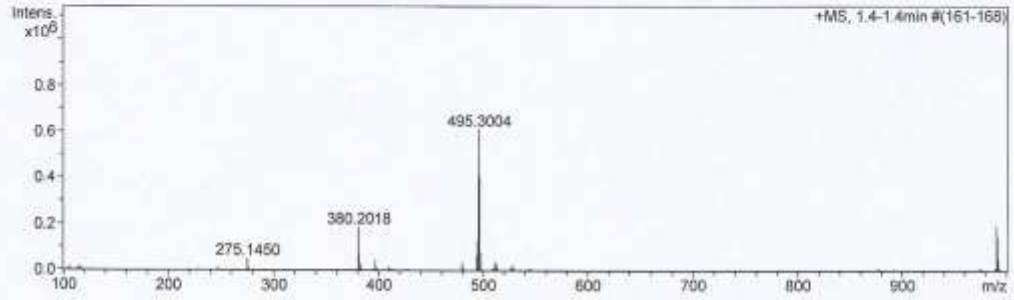
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\APCI\12_08\WJU_AJ7501.d	Acquisition Date	8/2/2012 9:37:48 AM
Method	APCI_directprobe_positiv.m	Operator	Meiners
Sample Name	AJ7501	Instrument / Ser#	micrOTOF-Q II 10252
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		

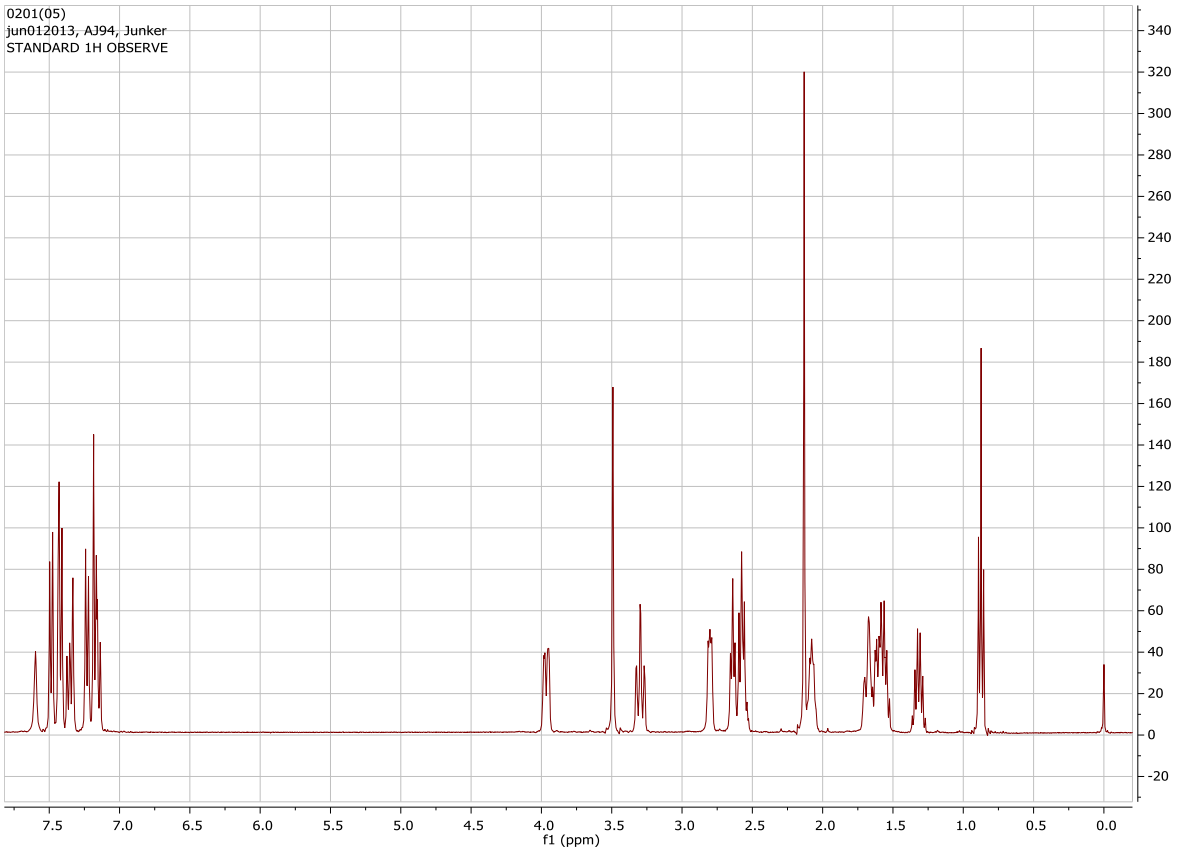
Acquisition Parameter

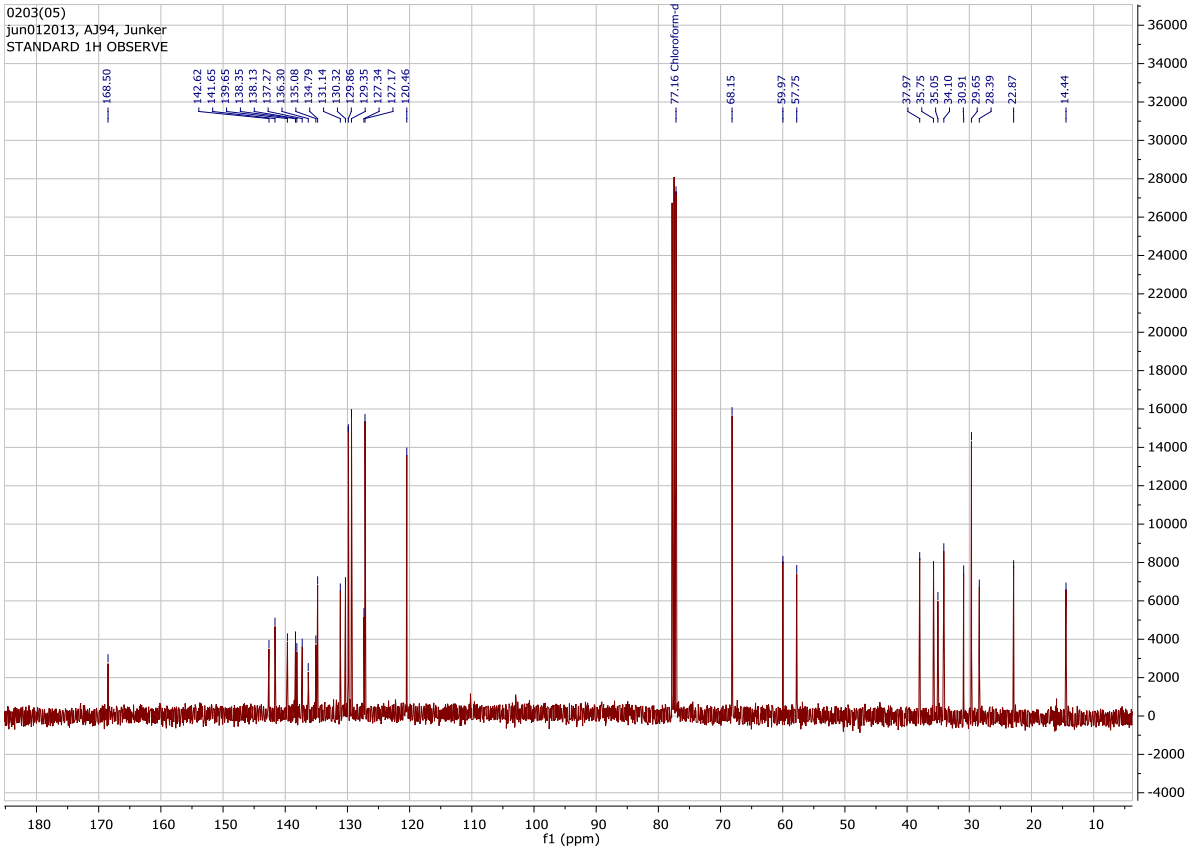
Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.7 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	3.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste

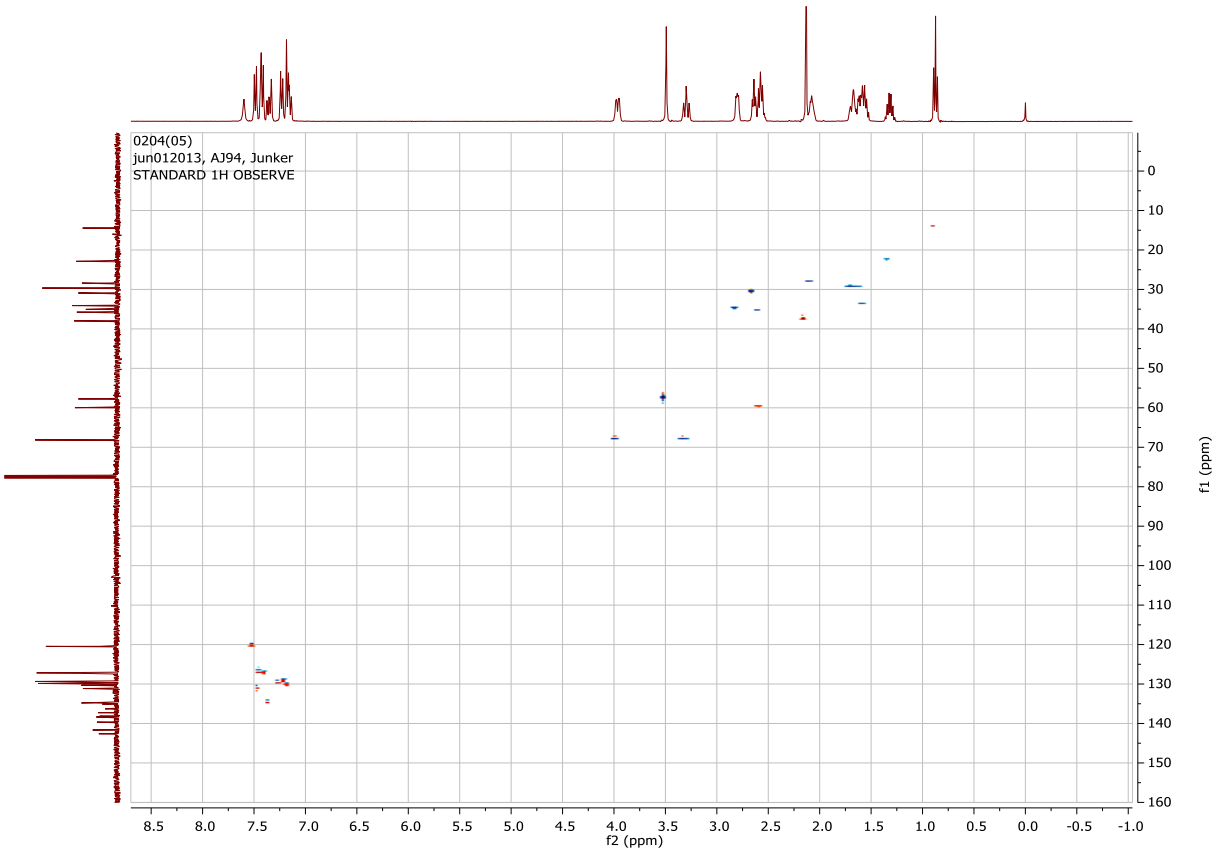


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
495.3004	1	C 33 H 39 N 2 O 2	100.00	495.3006	0.2	0.4	147.0	15.5	even	ok
	2	C 29 H 35 N 8	10.59	495.2979	-2.5	-5.0	158.7	16.5	even	ok
	3	C 28 H 39 N 4 O 4	1.15	495.2966	-3.8	-7.7	171.0	11.5	even	ok
	4	C 21 H 43 N 4 O 9	0.29	495.3025	2.0	4.1	209.0	2.5	even	ok
	5	C 22 H 39 N 8 O 5	0.02	495.3038	3.4	6.8	227.2	7.5	even	ok
	6	C 18 H 35 N 14 O 3	0.04	495.3011	0.7	1.4	240.6	8.5	even	ok
	7	C 14 H 31 N 20 O	0.00	495.2984	-2.0	-4.0	254.3	9.5	even	ok
	8	C 17 H 39 N 10 O 7	0.01	495.2998	-0.6	-1.3	254.5	3.5	even	ok
	9	C 13 H 35 N 16 O 5	0.00	495.2971	-3.3	-6.7	267.8	4.5	even	ok

*2-(4-Butylphenyl)-N-{4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (**9e**)*






0204(05)
jun012013, AJ94, Junker
STANDARD 1H OBSERVE
f2 (ppm)
f1 (ppm)

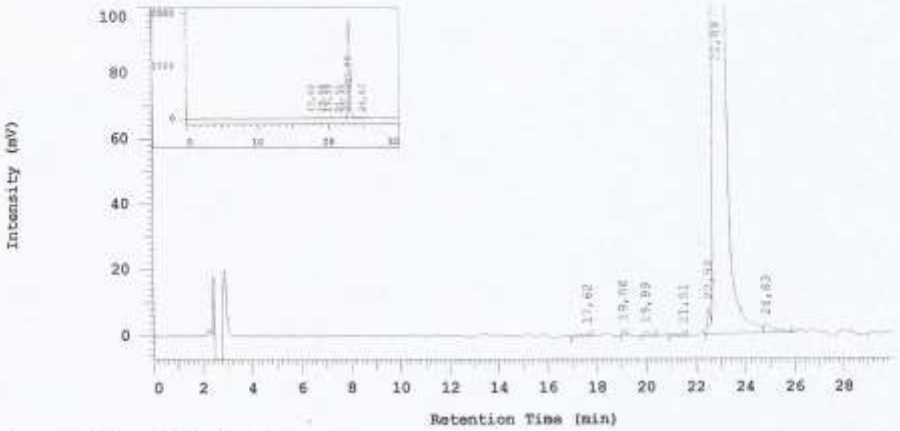
HPLC

Analyzed: 05.07.12 09:34
Reported: 05.07.12 15:57
Processed: 05.07.12 15:57

Data Path: D:\WIN32APP\HSM\Chromni\DATA\4980\
Application: Chromni
Sample Name: AJ9401
Injection from this vial: 1 of 1

Series:4980
Vial Number: 20
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

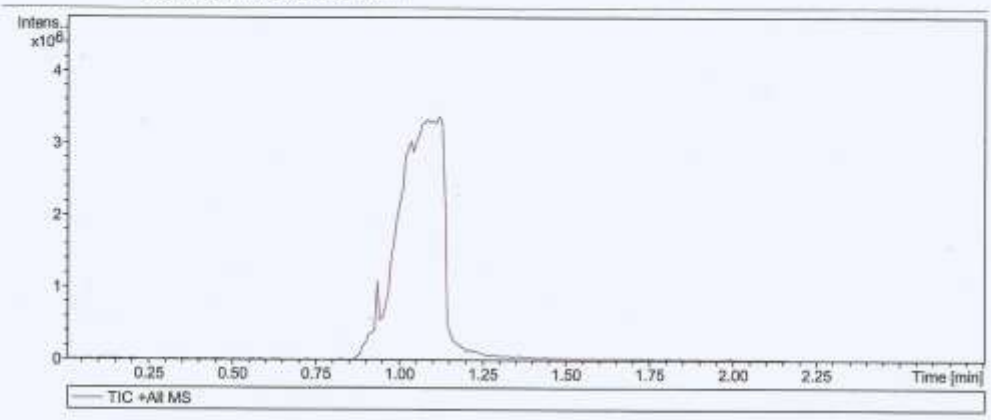
No.	RT	Area	Conc 1	BC
1	17,62	18416	0,055	MC
2	19,06	14108	0,042	MC
3	19,99	16006	0,048	MC
4	21,51	17645	0,053	MC
5	22,52	63872	0,191	MC
6	22,89	33270307	99,395	MC
7	24,83	72535	0,217	MC
		33472889	100,000	

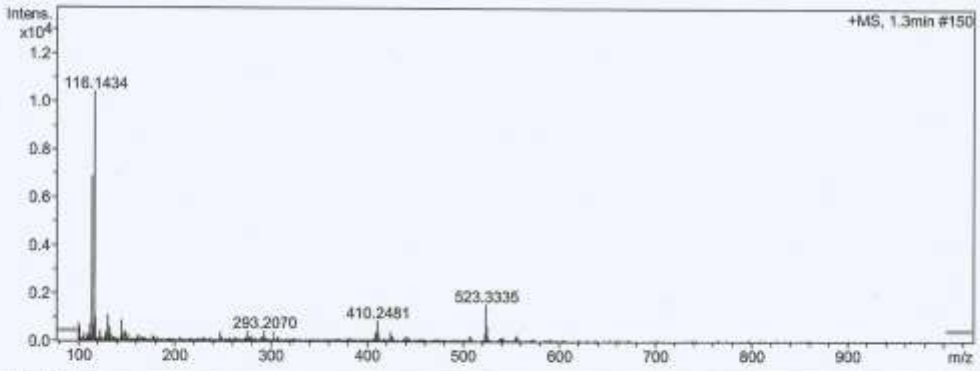
Peak rejection level: 0

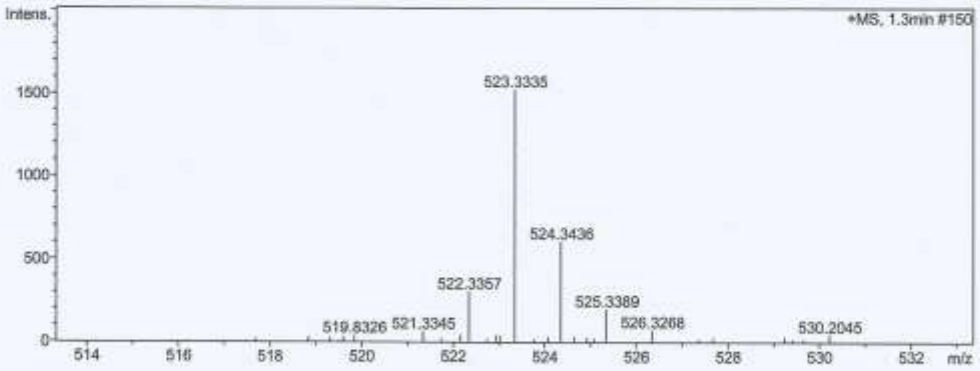
Generic Display Report

Analysis Info

Analysis Name	\\pz-ms\PZ\PharmChemie\Routine\APCI\12_08\WJU_AJ9401.d	Acquisition Date	02.08.2012 11:40:36
Method	APCI_directprobe_positiv.m	Operator	Meiners
Sample Name	AJ9401	Instrument	micrOTOF-Q II
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		







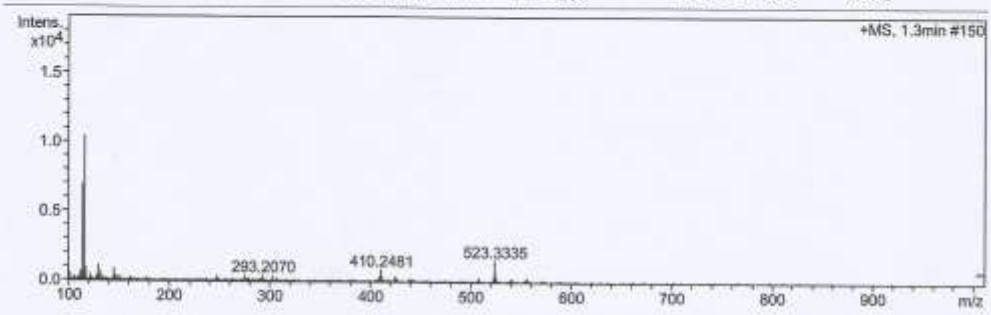
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	\\pz-ms\PZ\PharmChemie\Routine\APCI\12_08\WJU_AJ9401.d	Acquisition Date	02.08.2012 11:40:36
Method	APCI_directprobe_positiv.m	Operator	Meiners
Sample Name	AJ9401	Instrument / Ser#	micrOTOF-Q II 10252
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		

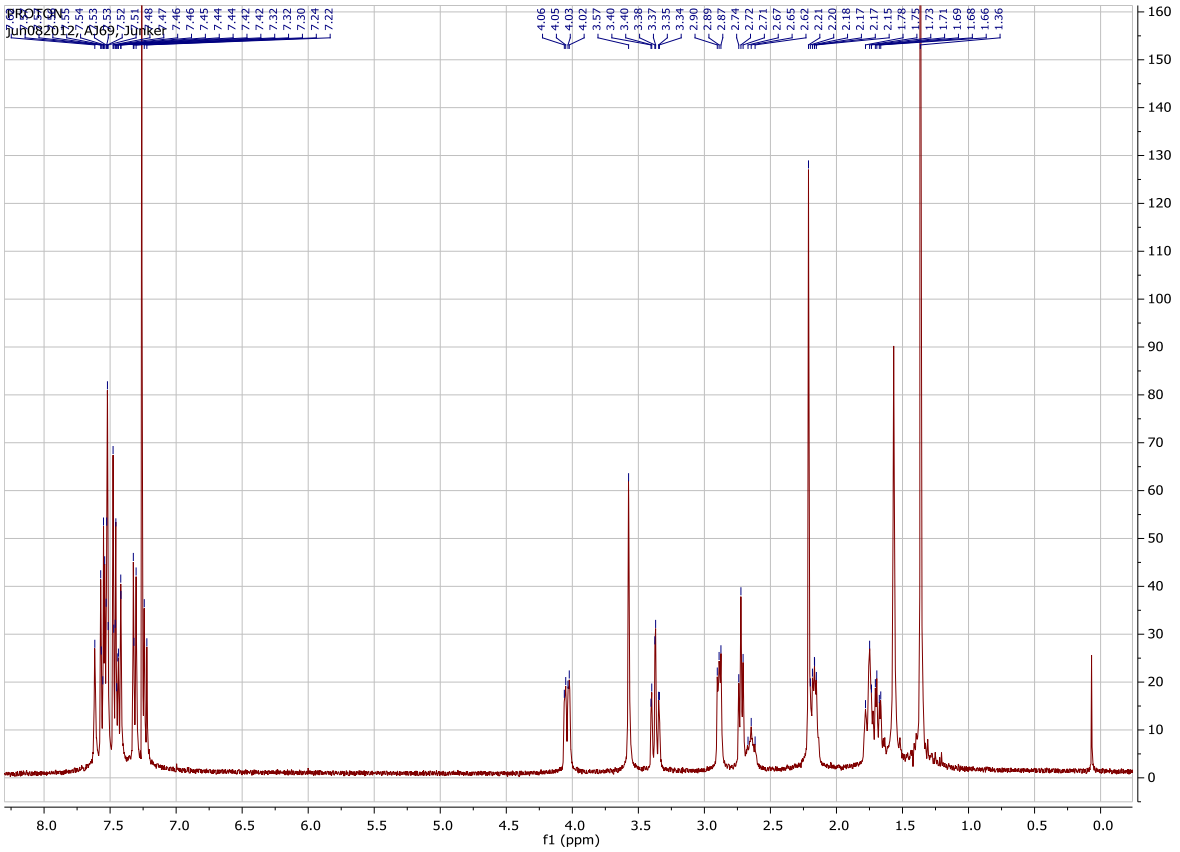
Acquisition Parameter

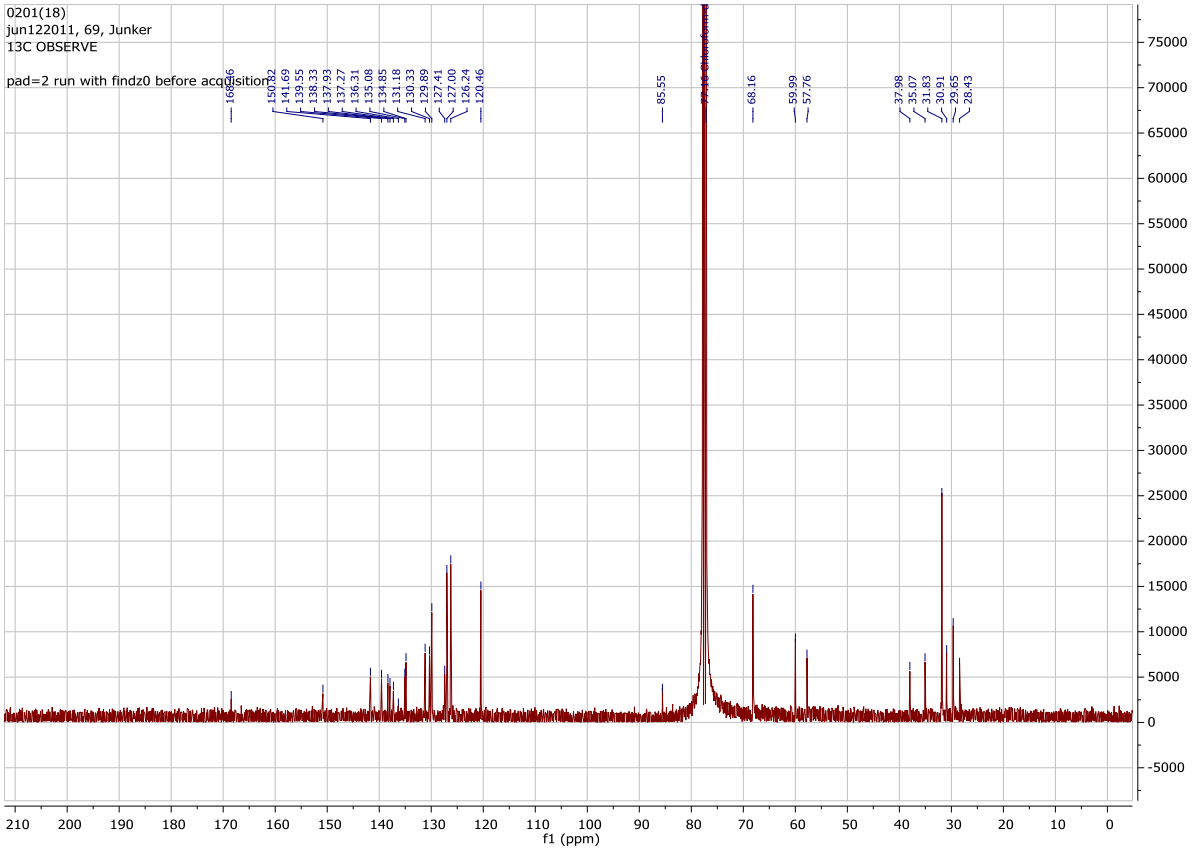
Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.7 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	3.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
149.0563	1	C 5 H 5 N 6	100.00	149.0570	0.7	4.6	14.0	6.5	even	ok
523.3335	1	C 35 H 43 N 2 O 2	100.00	523.3319	-1.6	-3.1	30.4	15.5	even	ok
	2	C 40 H 43	54.46	523.3359	2.4	4.6	31.5	19.5	even	ok
	3	C 31 H 39 N 8	6.00	523.3292	-4.3	-8.3	38.7	16.5	even	ok
	4	C 28 H 47 N 2 O 7	4.11	523.3378	4.2	8.1	54.9	6.5	even	ok
525.3389	1	C 26 H 41 N 10 O 2	58.82	525.3408	1.9	3.6	18.1	11.5	even	ok

*2-(4-tert-Butylphenyl)N-{4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (**9f**)*





HPLC

Analyzed: 11.08.11 01:52

Reported: 11.08.11 09:20
Processed: 11.08.11 09:20

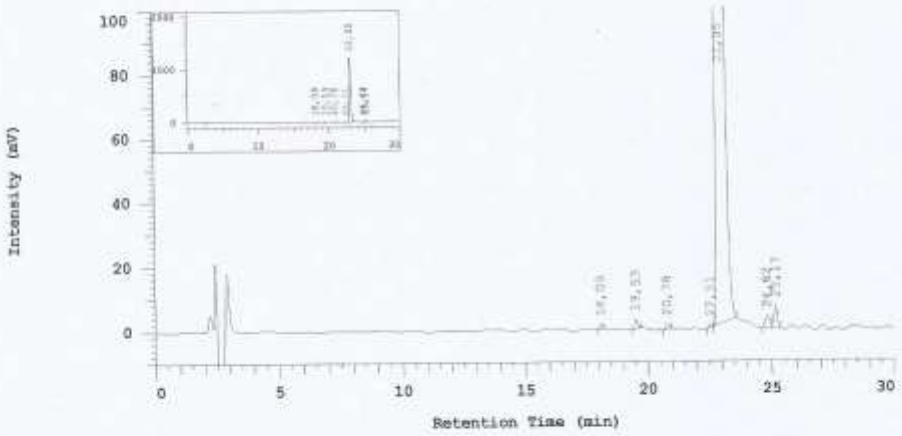
Data Path: D:\WIN32APP\HSM\Chromni\DATA\3443\
Application: Chromni

Sample Name: AJ6902

Injection from this vial: 1 of 1

Series:3443
Vial Number: 12
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

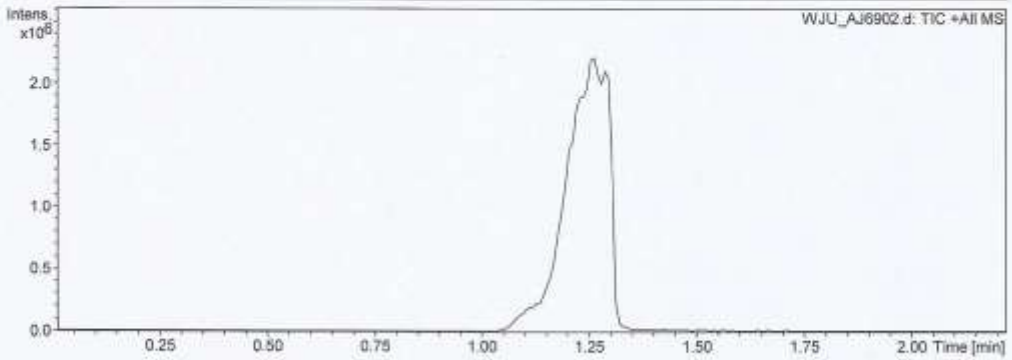
No.	RT	Area	Conc 1	BC
1	18,09	10374	0,060	BB
2	19,53	26270	0,153	BB
3	20,78	14834	0,086	BB
4	22,51	5954	0,035	MC
5	22,95	17024297	99,002	BB
6	24,82	47769	0,278	MC
7	25,17	66435	0,386	MC
		17195933	100,000	

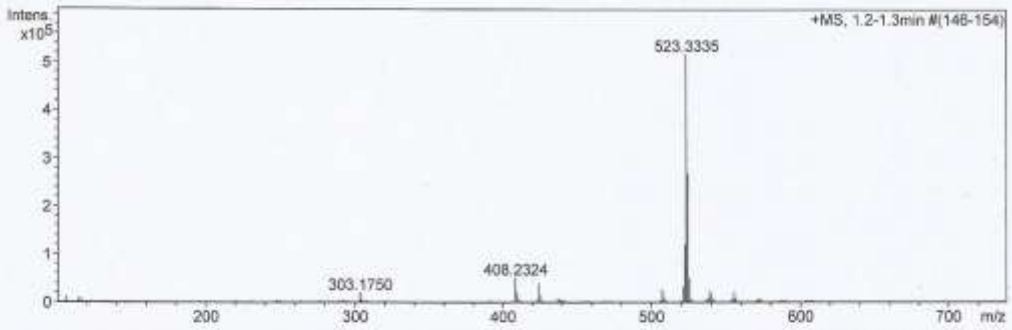
Peak rejection level: 0

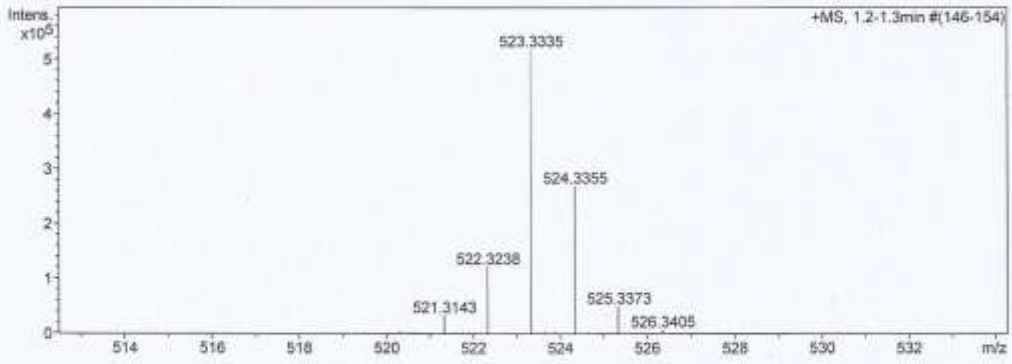
Generic Display Report

Analysis Info

Analysis Name	E:\Meiners\12_09\WJU_AJ6902.d	Acquisition Date	9/4/2012 11:32:37 AM
Method	APCI_directprobe_positiv.m	Operator	Sendker
Sample Name	AJ6902	Instrument	micrOTOF-Q II
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		







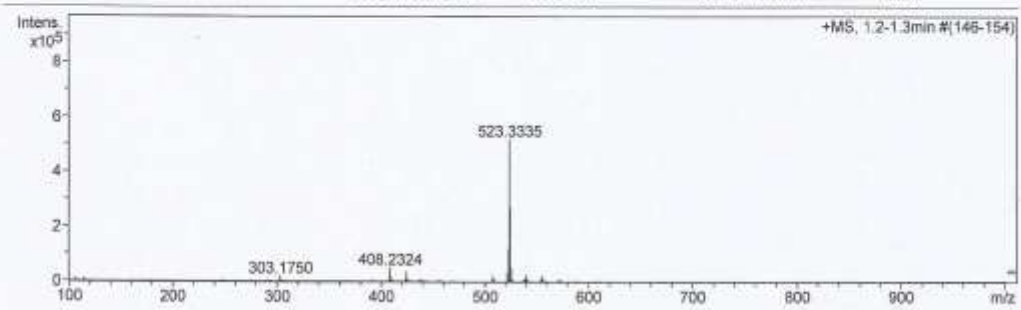
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	E:\Meiners\12_09\WJU_AJ6902.d	Acquisition Date	9/4/2012 11:32:37 AM
Method	APCI_directprobe_positiv.m	Operator	Sendker
Sample Name	AJ6902	Instrument / Ser#	micrOTOF-Q II 10252
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		

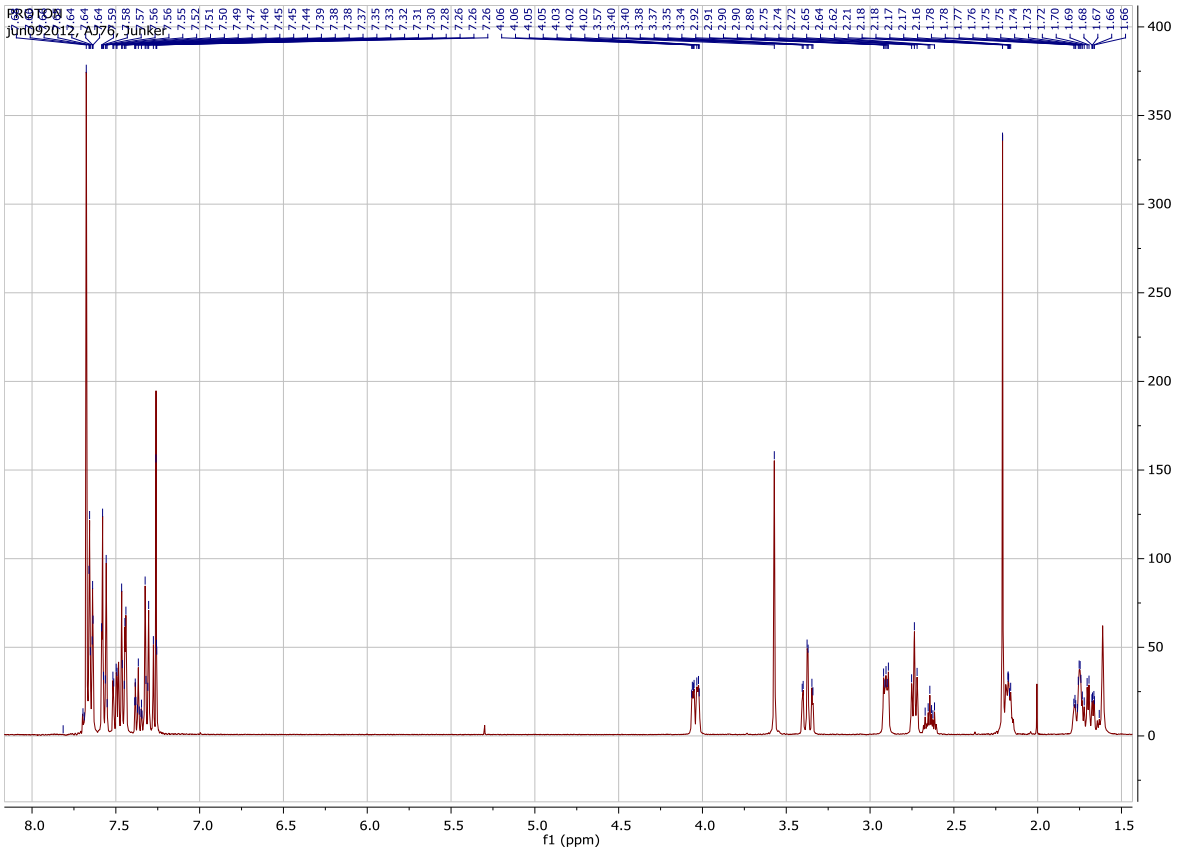
Acquisition Parameter

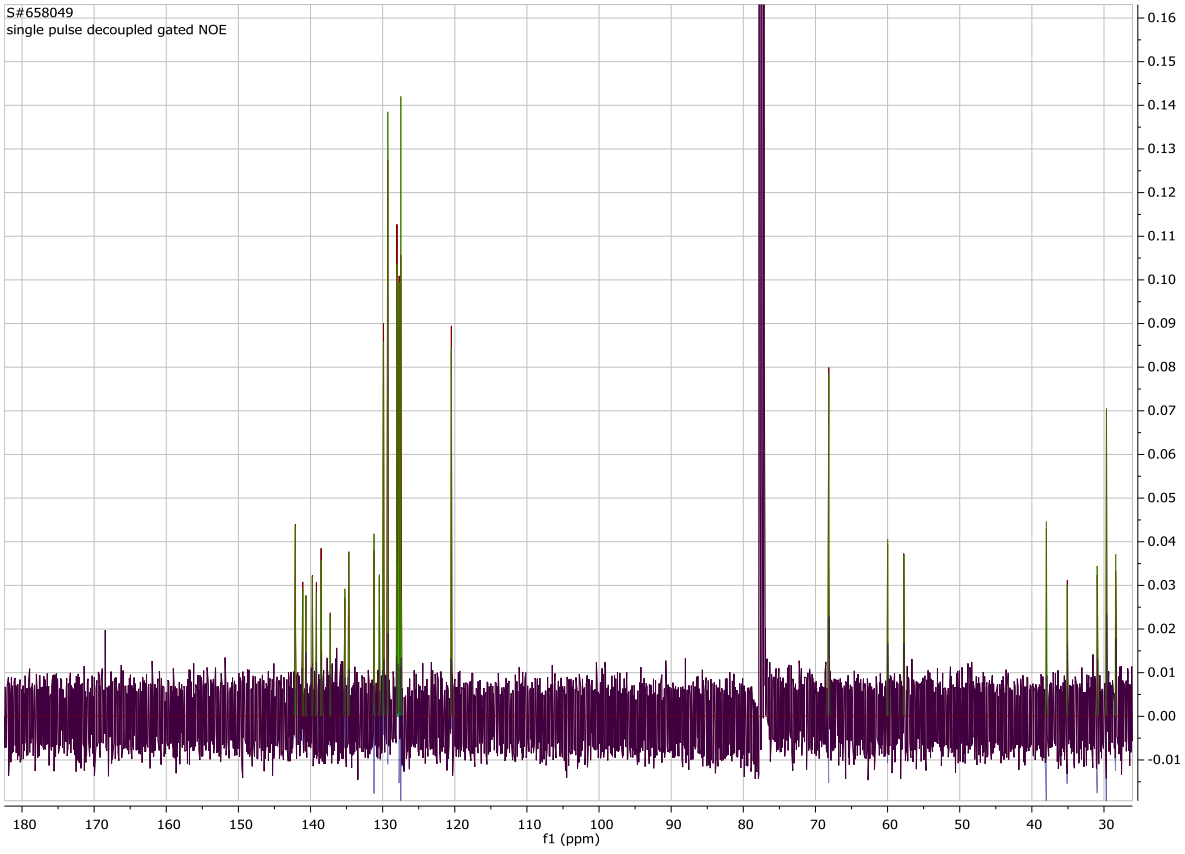
Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.7 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	3.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
523.3335	1	C 40 H 43	100.00	523.3359	2.4	4.6	40.6	19.5	even	ok
	2	C 35 H 43 N 2 O 2	89.82	523.3319	-1.6	-3.0	64.4	15.5	even	ok
	3	C 31 H 39 N 8	4.44	523.3292	-4.3	-8.2	76.1	16.5	even	ok
	4	C 28 H 47 N 2 O 7	1.38	523.3378	4.3	8.2	102.8	6.5	even	ok
	5	C 25 H 39 N 12 O	2.76	523.3364	2.9	5.6	118.2	12.5	even	ok
	6	C 23 H 47 N 4 O 9	10.87	523.3338	0.3	0.5	126.6	2.5	even	ok
	7	C 24 H 43 N 8 O 5	3.76	523.3351	1.6	3.0	132.0	7.5	even	ok
	8	C 20 H 39 N 14 O 3	2.27	523.3324	-1.1	-2.1	145.5	8.5	even	ok
	9	C 16 H 35 N 20 O	0.09	523.3297	-3.8	-7.2	159.3	9.5	even	ok
	10	C 19 H 43 N 10 O 7	0.34	523.3311	-2.4	-4.6	159.4	3.5	even	ok

*2-([1,1'-Biphenyl]-4-yl)-N-{4-[N-methyl-N-(tetrahydro-2H-pyran-4yl)aminomethyl]phenyl}-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (**9g**)*





HPLC

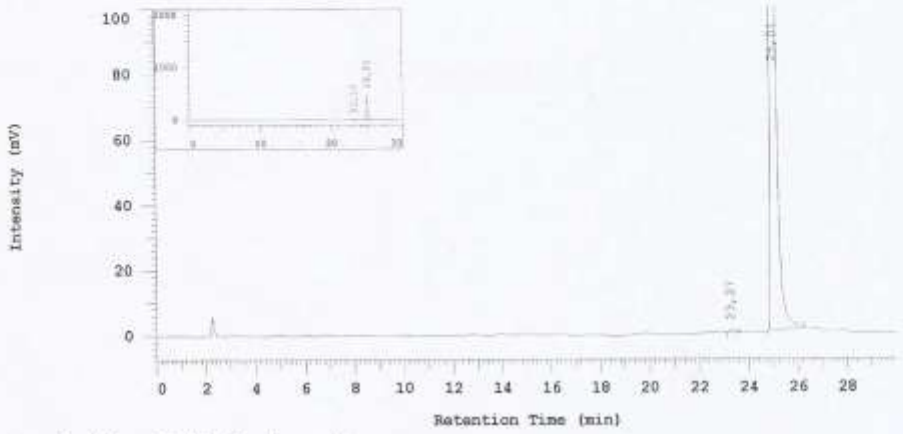
Analyzed: 12.09.12 22:57

Reported: 13.09.12 10:08
Processed: 13.09.12 10:08

Data Path: D:\WIN32APP\HSM\Chromni\DATA\5233\
Application: Chromni
Sample Name: AJ7602
Injection from this vial: 1 of 1

Series:5233
Vial Number: 7
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

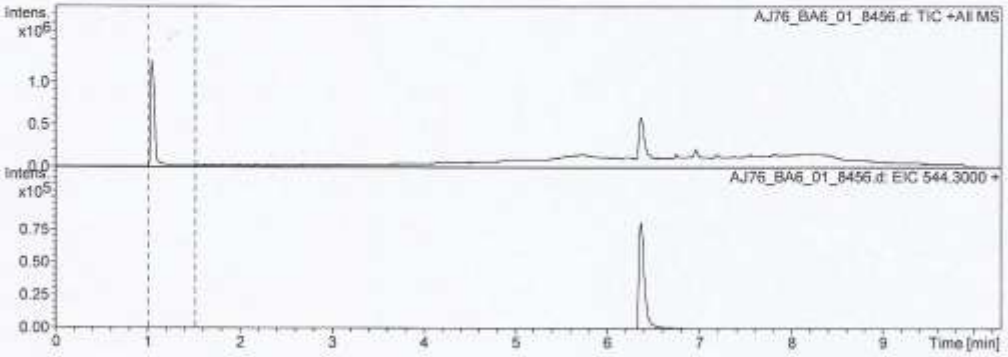
No.	RT	Area	Conc 1	BC
1	23,27	14208	0,267	BB
2	25,01	5311184	99,733	MC
		5325392	100,000	

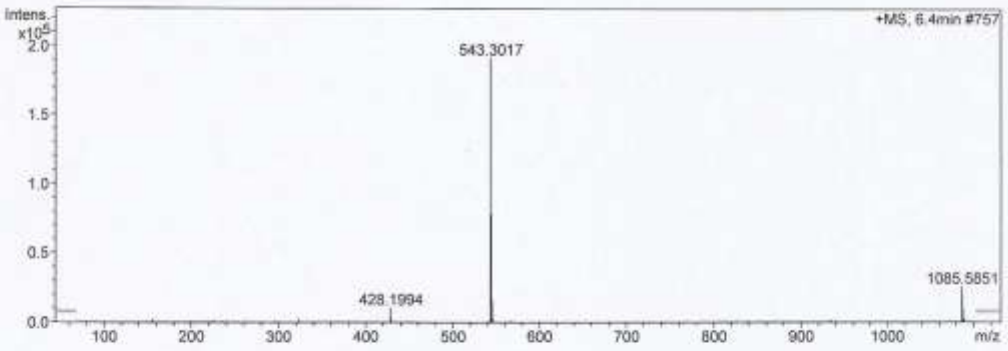
Peak rejection level: 0

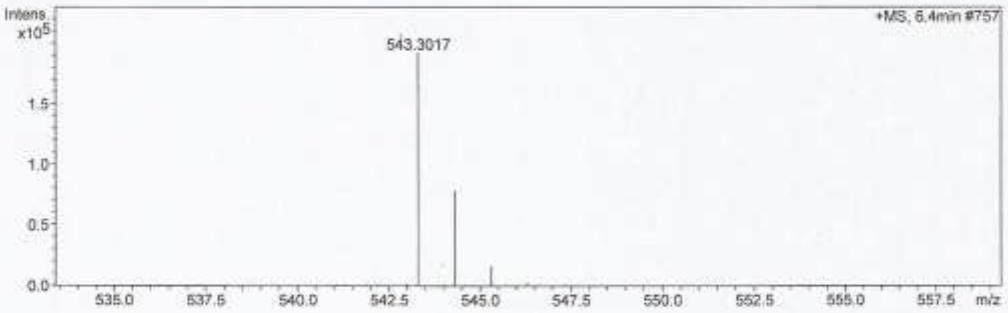
Generic Display Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\LC-MS\2012_10_22\AJ76_BA6_01_8456.d	Acquisition Date	10/22/2012 3:34:21 PM
Method	tune_low_lcms_routine_positiv_10min.m	Operator	Meiners
Sample Name	AJ76	Instrument	micrOTOF-Q II
Comment	Junker LCMS-ESI+ Kalibration mit Li-Formate		







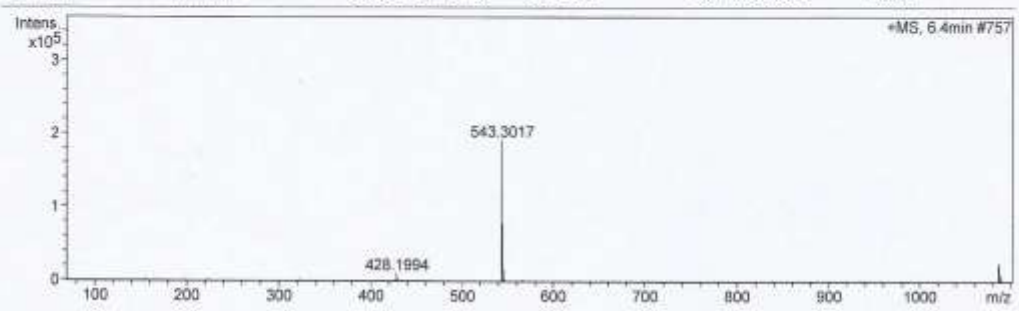
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\LC-MS\2012_10_22\AJ76_BA6_01_8456.d	Acquisition Date	10/22/2012 3:34:21 PM
Method	tune_low_lcms_routine_positiv_10min.m	Operator	Meiners
Sample Name	AJ76	Instrument / Ser#	micrOTOF-Q II 10252
Comment	Junker LCMS-ESI+ Kalibration mit Li-Formate		

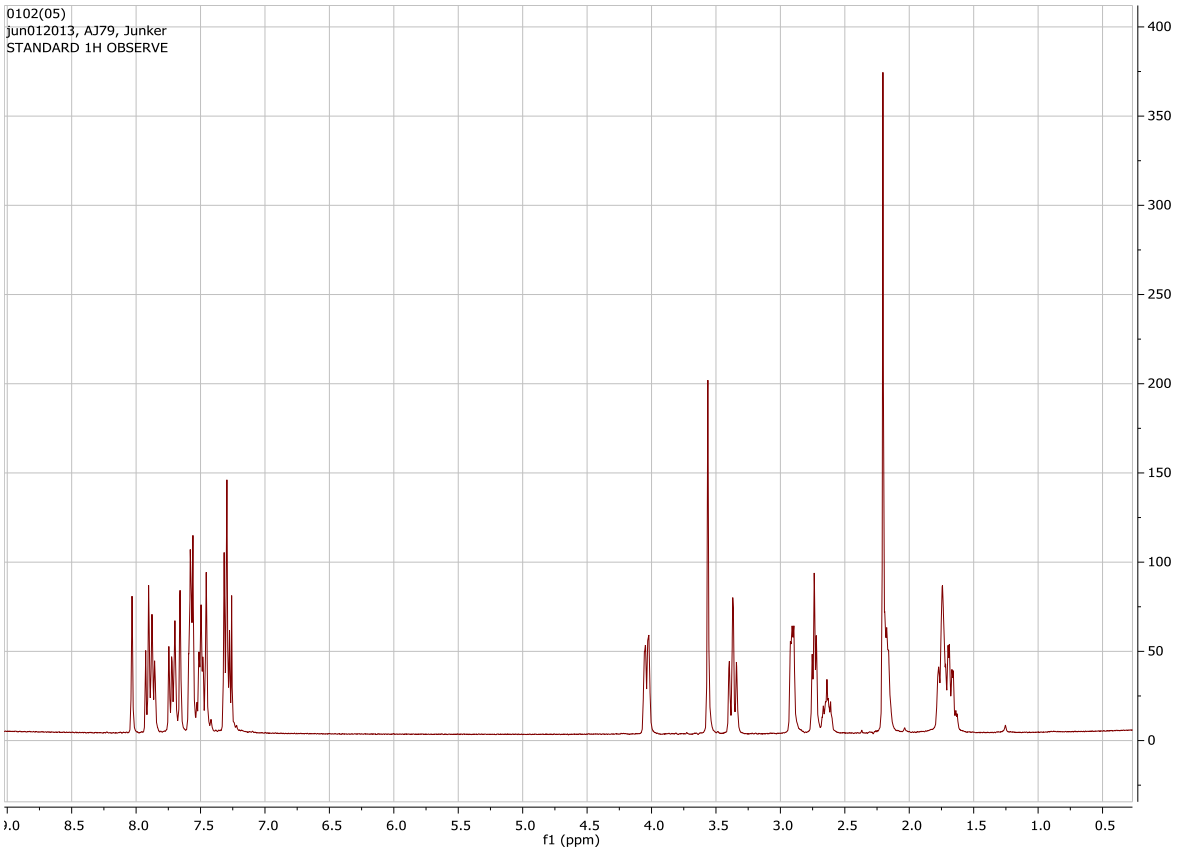
Acquisition Parameter

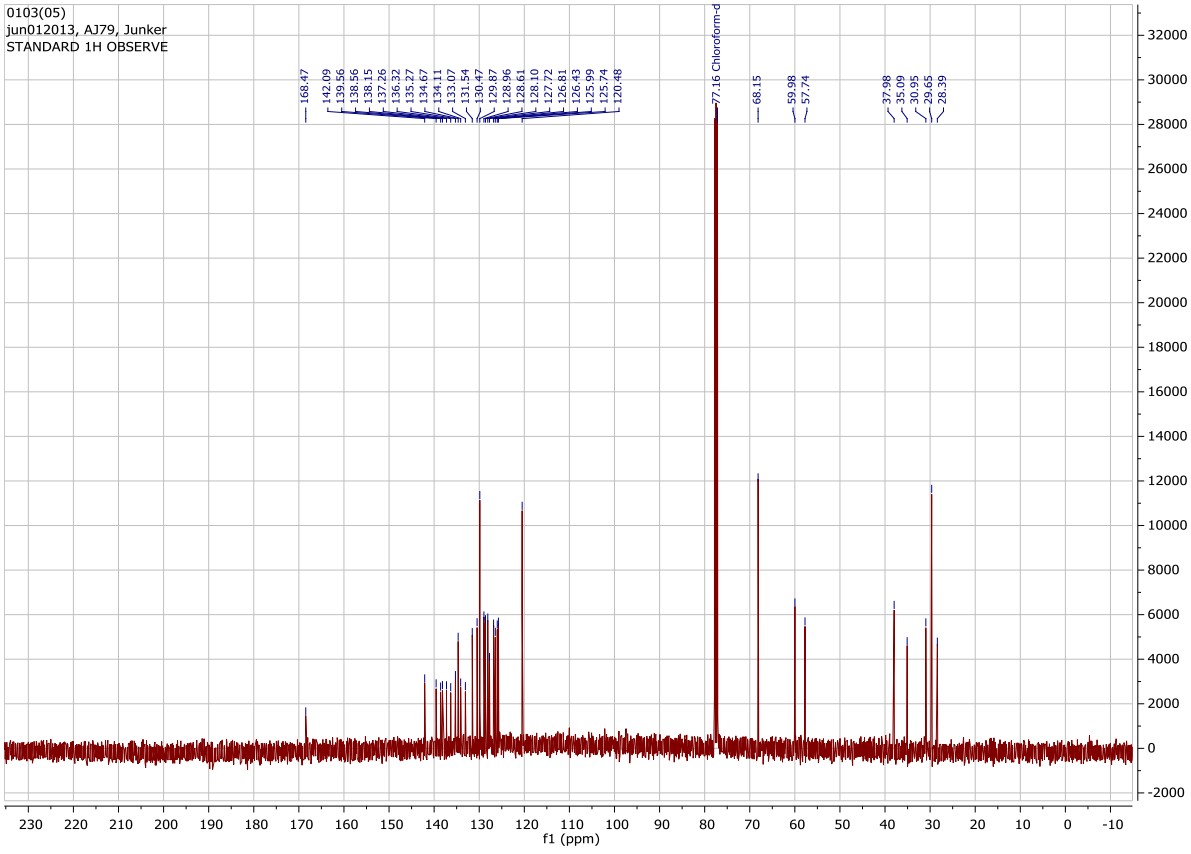
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	2.0 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	9.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	300.0 Vpp	Set Divert Valve	Waste

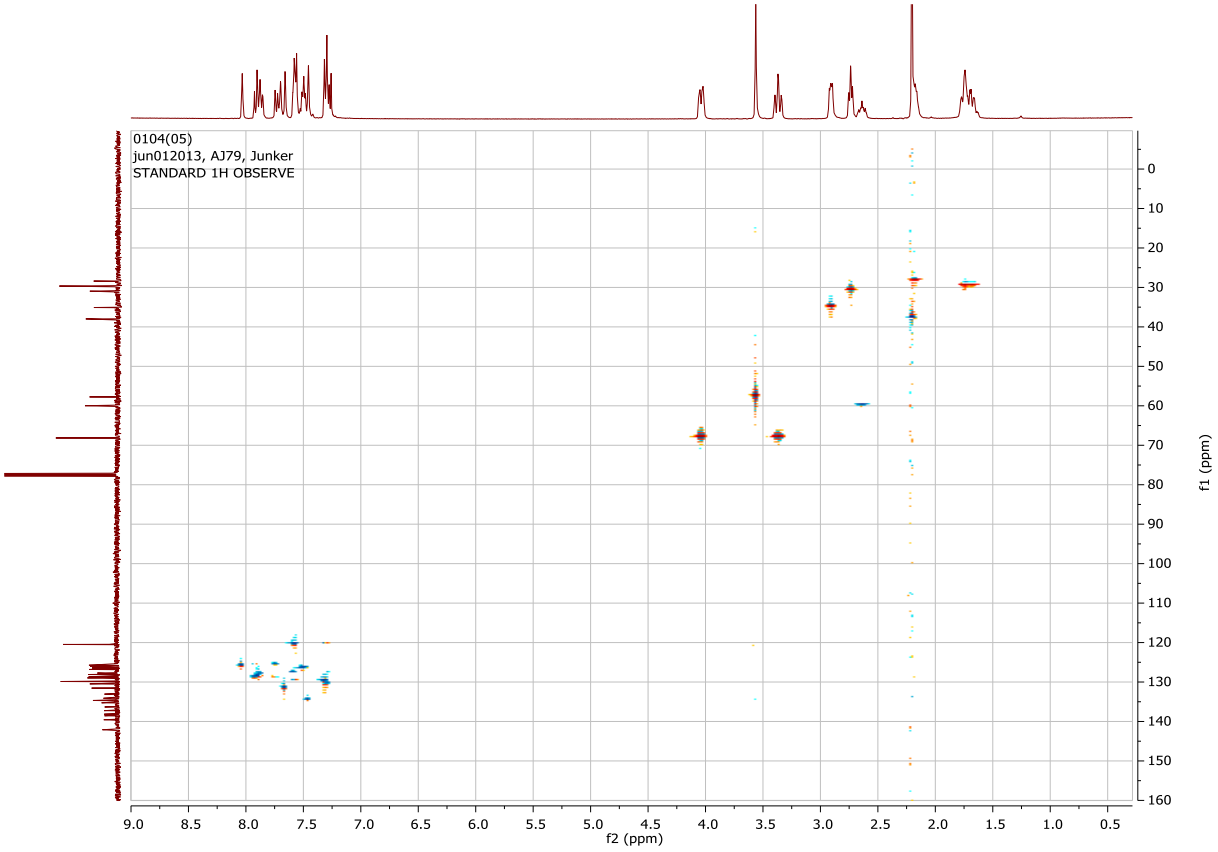


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
543.3017	1	C 37 H 39 N 2 O 2	100.00	543.3006	-1.1	-1.9	3.9	19.5	even	ok
	2	C 33 H 35 N 8	9.39	543.2979	-3.7	-6.9	9.1	20.5	even	ok
	3	C 42 H 39	14.04	543.3046	3.0	5.5	28.1	23.5	even	ok
	4	C 30 H 43 N 2 O 7	1.35	543.3065	4.8	8.9	35.6	10.5	even	ok

*N-{4-[N-Methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl}-2-(naphtalen-2-yl)-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (**9h**)*






0104(05)
jun012013, AJ79, Junker
STANDARD 1H OBSERVE
f2 (ppm)
f1 (ppm)

HPLC

Analyzed: 05.07.12 06:07

Reported: 05.07.12 15:50
Processed: 05.07.12 15:50

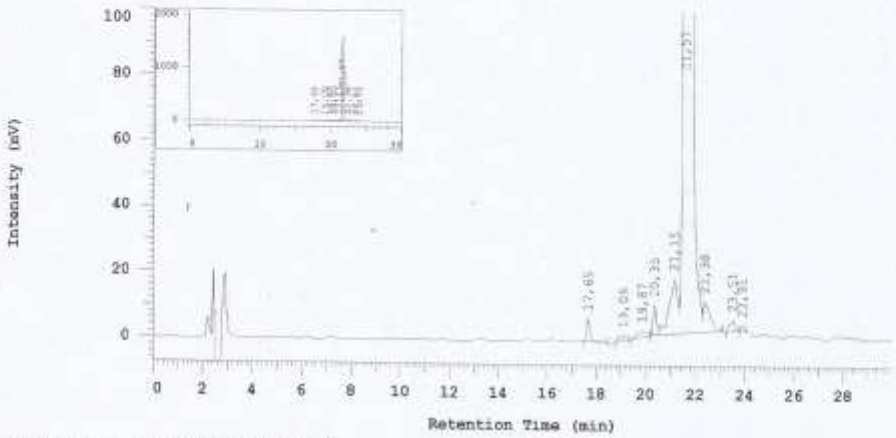
Data Path: D:\WIN32APP\HSM\Chromni\DATA\4975\
Application: Chromni

Sample Name: AJ7901

Injection from this vial: 1 of 1

Series:4975
Vial Number: 16
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

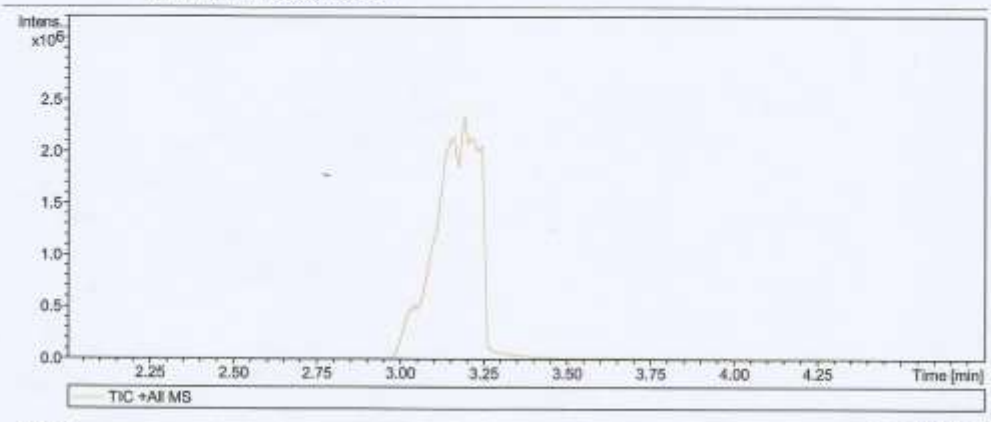
No.	RT	Area	Conc 1	BC
1	17,65	69519	0,309	MC
2	19,09	29553	0,132	BB
3	19,87	46234	0,206	MC
4	20,35	85375	0,380	MC
5	21,15	380256	1,692	MC
6	21,57	21616632	96,199	MC
7	22,38	179392	0,798	MC
8	23,51	51409	0,229	MC
9	23,91	12416	0,055	MC
		22470786	100,000	

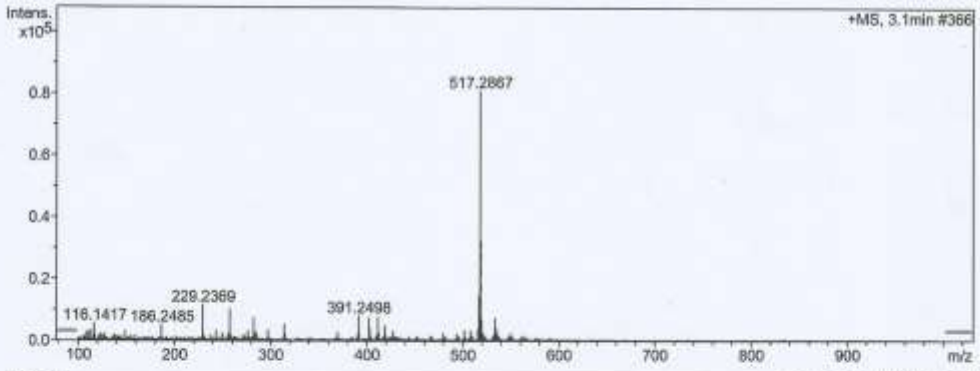
Peak rejection level: 0

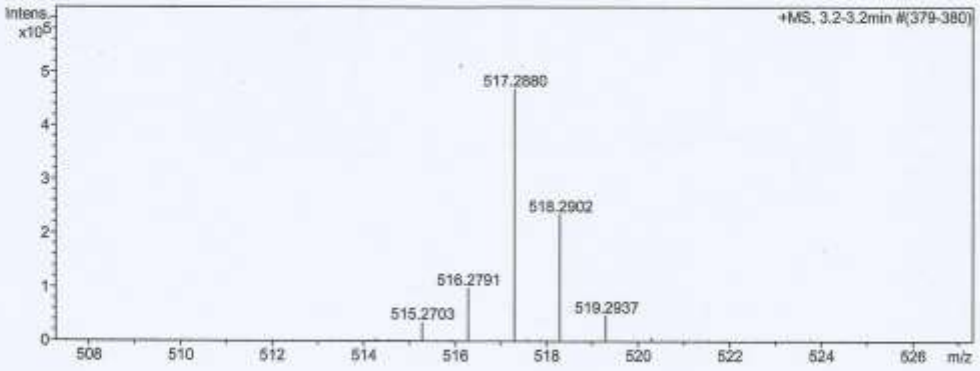
Generic Display Report

Analysis Info

Analysis Name	\\pz-ms\PZ\PharmChemie\Routine\APCI\12_08\WJU_AJ7901.d	Acquisition Date	02.08.2012 10:53:37
Method	APCI_directprobe_positiv.m	Operator	Meiners
Sample Name	AJ7901	Instrument	micrOTOF-Q II
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		







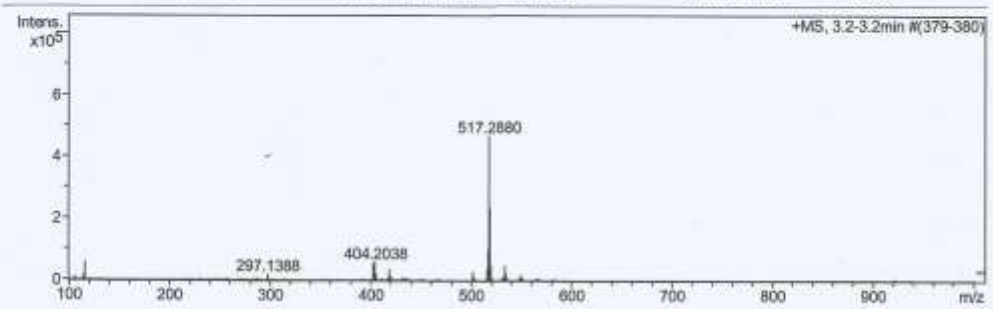
Mass Spectrum SmartFormula Report

Analysis Info

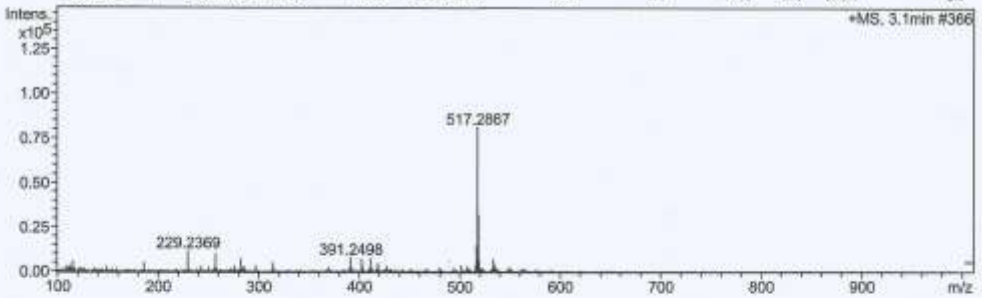
Analysis Name	\\pz-ms\PZ\PharmChemie\Routine\APCI\12_08\WJU_AJ7901.d	Acquisition Date	02.08.2012 10:53:37
Method	APCI_directprobe_positiv.m	Operator	Meiners
Sample Name	AJ7901	Instrument / Ser#	micrOTOF-Q II 10252
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		

Acquisition Parameter

Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.7 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	3.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste

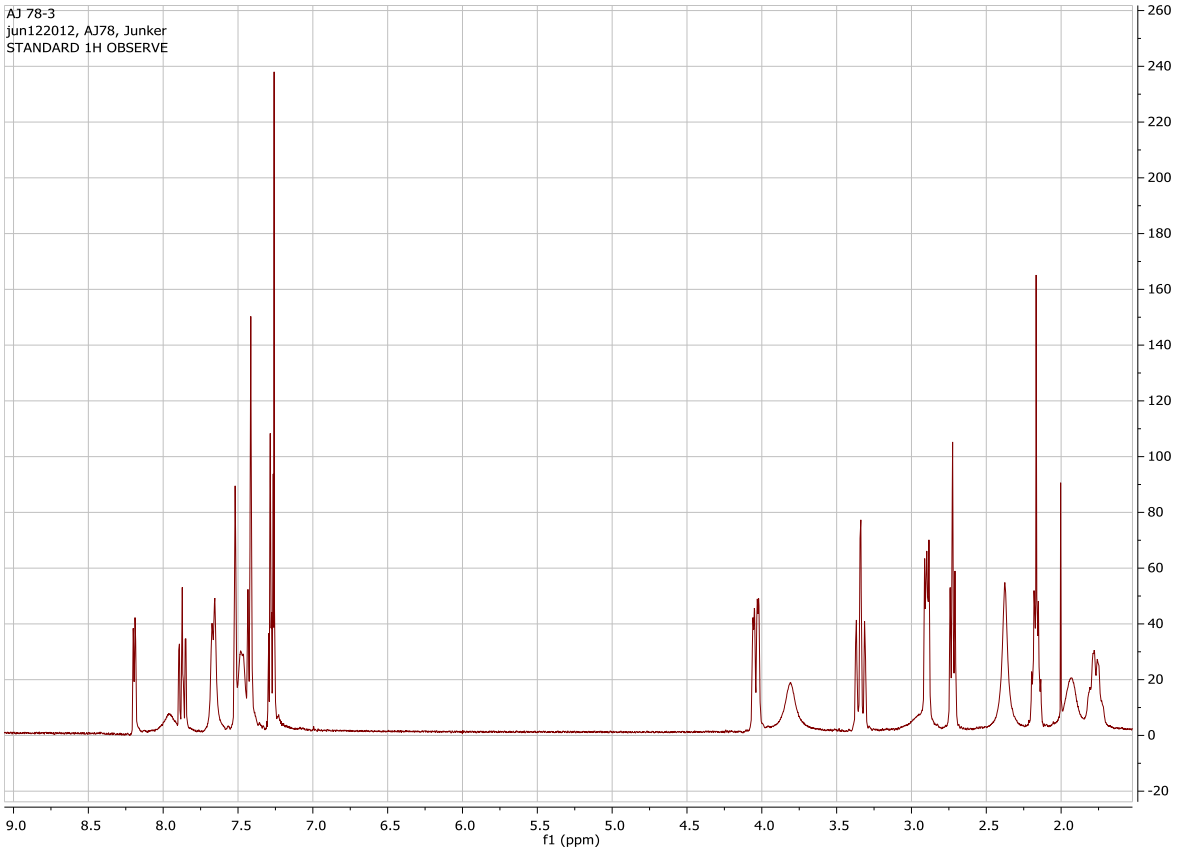


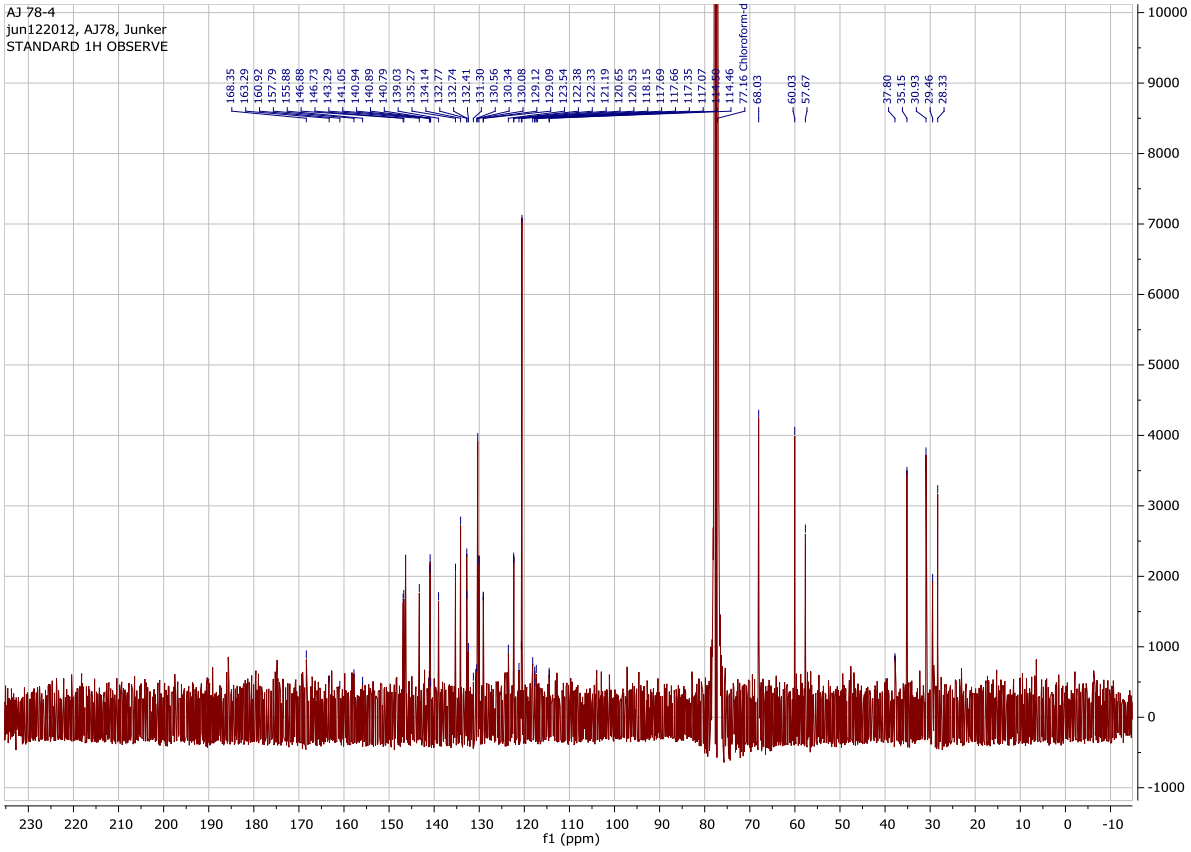
Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
297.1388	1	C 21 H 17 N 2	100.00	297.1386	-0.2	-0.6	6.1	14.5	even	ok
518.2902	1	C 16 H 40 N 9 O 10	94.69	518.2893	-0.9	-1.8	10.7	1.5	even	ok
551.2854	1	C 30 H 39 N 4 O 6	76.07	551.2864	1.0	1.9	17.6	13.5	even	ok

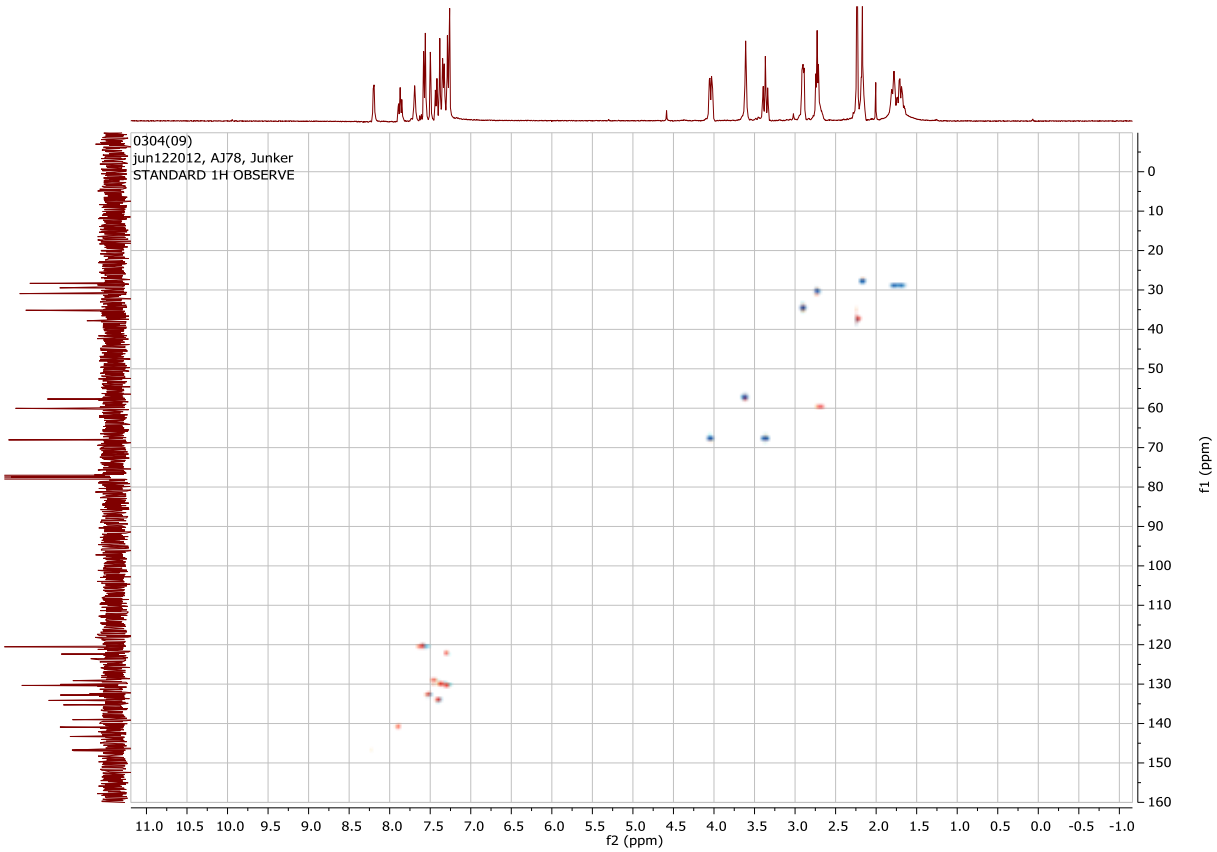


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
315.1602	1	C 5 H 15 N 16 O	100.00	315.1609	0.7	2.3	11.9	6.5	even	ok
391.2498	1	C 24 H 31 N 4 O	100.00	391.2492	-0.5	-1.4	4.0	11.5	even	ok
	2	C 23 H 35 O 5	37.61	391.2479	-1.9	-4.8	12.9	6.5	even	ok
411.3985	1	C 30 H 51	100.00	411.3985	-1.0	-2.4	16.0	5.5	even	ok
517.2867	1	C 35 H 37 N 2 O 2	100.00	517.2850	-1.7	-3.4	3.5	18.5	even	ok

*2-(2-Fluoropyridin-3-yl)-N-{4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (**9j**)*




AJ 78-4
jun122012, AJ78, Junker
STANDARD 1H OBSERVE
168.35
163.29
160.92
157.79
155.88
146.88
146.73
143.29
141.05
140.94
140.89
140.79
139.03
135.27
134.14
132.77
132.74
132.41
131.30
130.56
130.34
130.08
129.12
129.09
123.54
122.38
122.33
121.19
120.65
120.53
118.15
117.69
117.66
117.35
117.07
114.50
114.46
77.16 Chloroform-d
68.03
60.03
57.67
37.80
35.15
30.93
29.46
28.33
f1 (ppm)


0304(09)
jun122012, AJ78, Junker
STANDARD 1H OBSERVE
f2 (ppm)
f1 (ppm)

HPLC

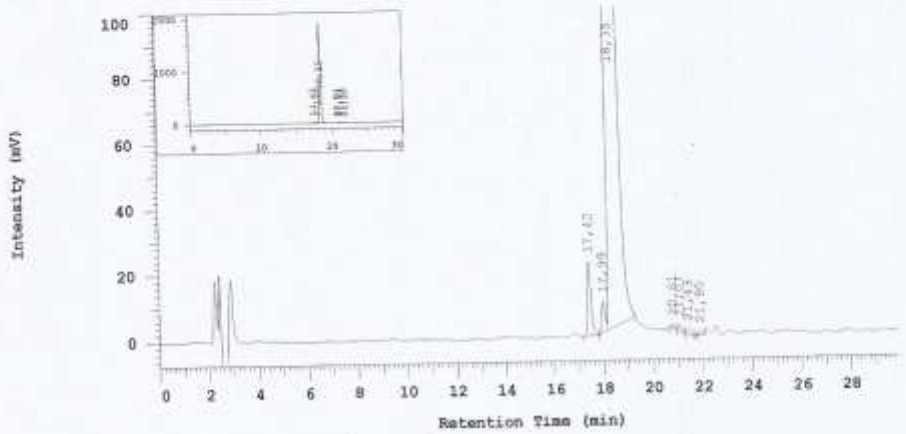
Analyzed: 29.11.12 09:45

Reported: 30.11.12 09:18
Processed: 30.11.12 09:18

Data Path: D:\WIN32APP\HSM\Chromni\DATA\5605\
Application: Chromni
Sample Name: AJ78
Injection from this vial: 1 of 1

Series:5605
Vial Number: 23
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

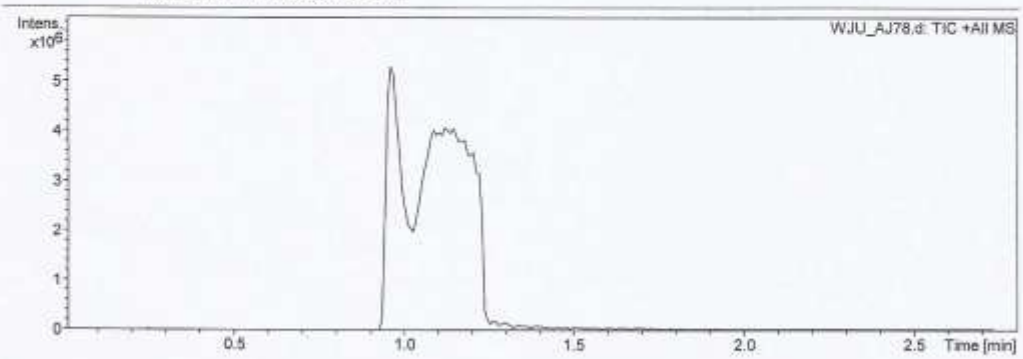
No.	RT	Area	Conc 1	BC
1	17,42	212460	0,687	BB
2	17,99	82817	0,268	BV
3	18,35	30571654	98,846	VB
4	20,81	10723	0,035	BB
5	21,07	14352	0,046	BB
6	21,43	24293	0,079	BB
7	21,90	12166	0,039	BB
		30928465	100,000	

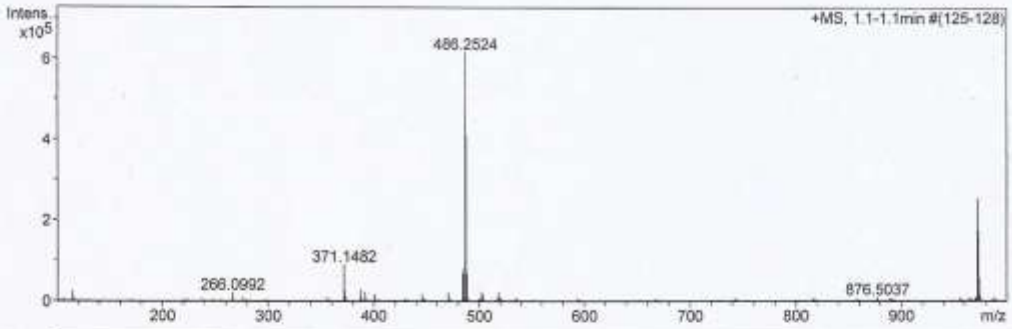
Peak rejection level: 0

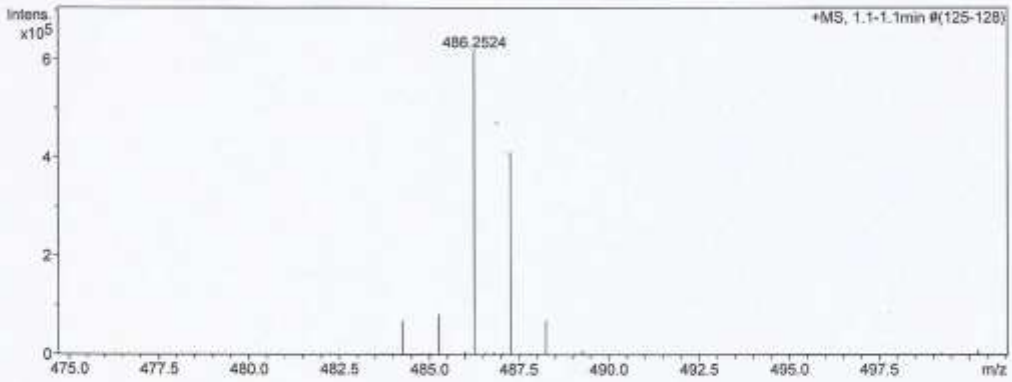
Generic Display Report

Analysis Info

Analysis Name	E:\Meiners\12_12\WJU_AJ78.d	Acquisition Date	12/10/2012 8:55:51 AM
Method	APCI_directprobe_positiv.m	Operator	Meiners
Sample Name	AJ78	Instrument	micrOTOF-Q II
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		







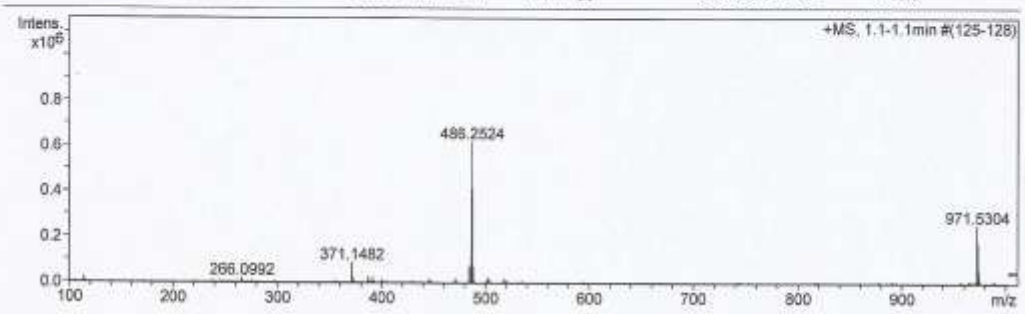
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	E:\Meiners\12_12\WJU_AJ78.d	Acquisition Date	12/10/2012 8:55:51 AM
Method	APCI_directprobe_positiv.m	Operator	Meiners
Sample Name	AJ78	Instrument / Ser#	micrOTOF-Q II 10252
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		

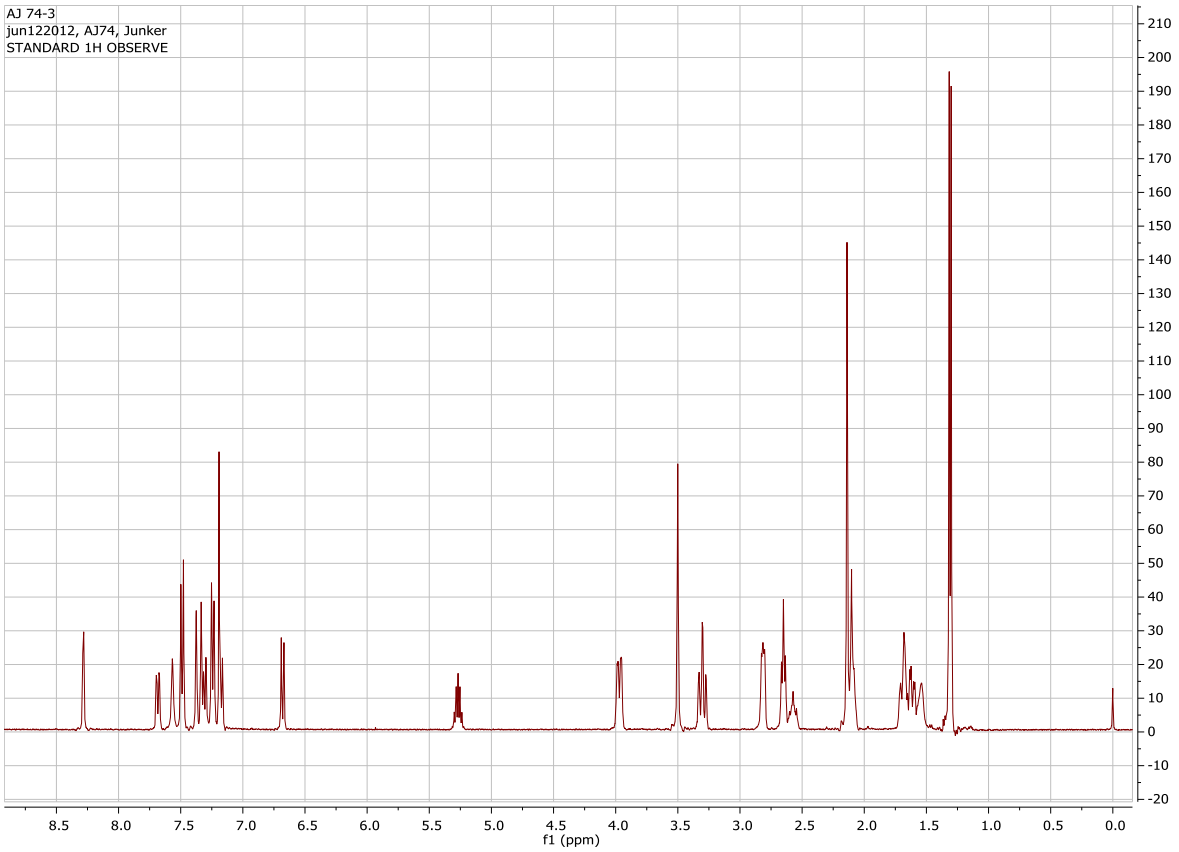
Acquisition Parameter

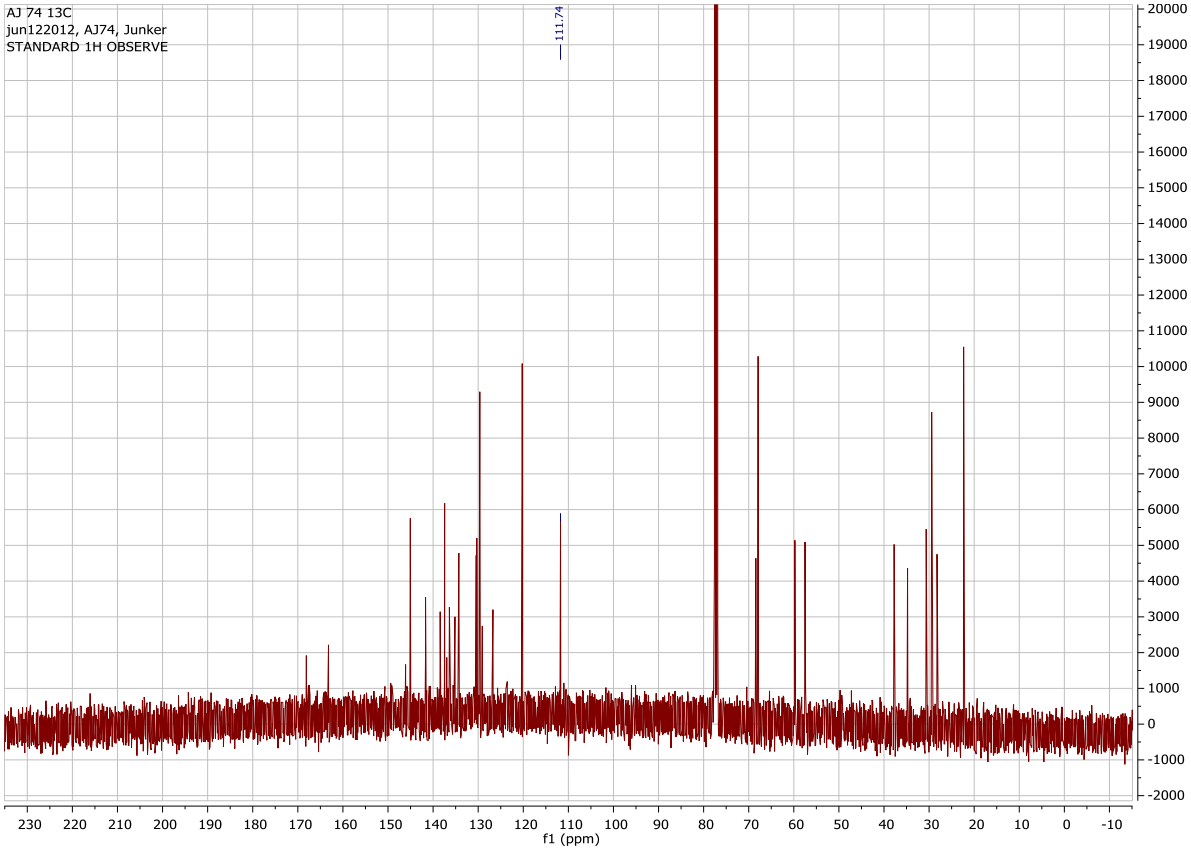
Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.7 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	3.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste

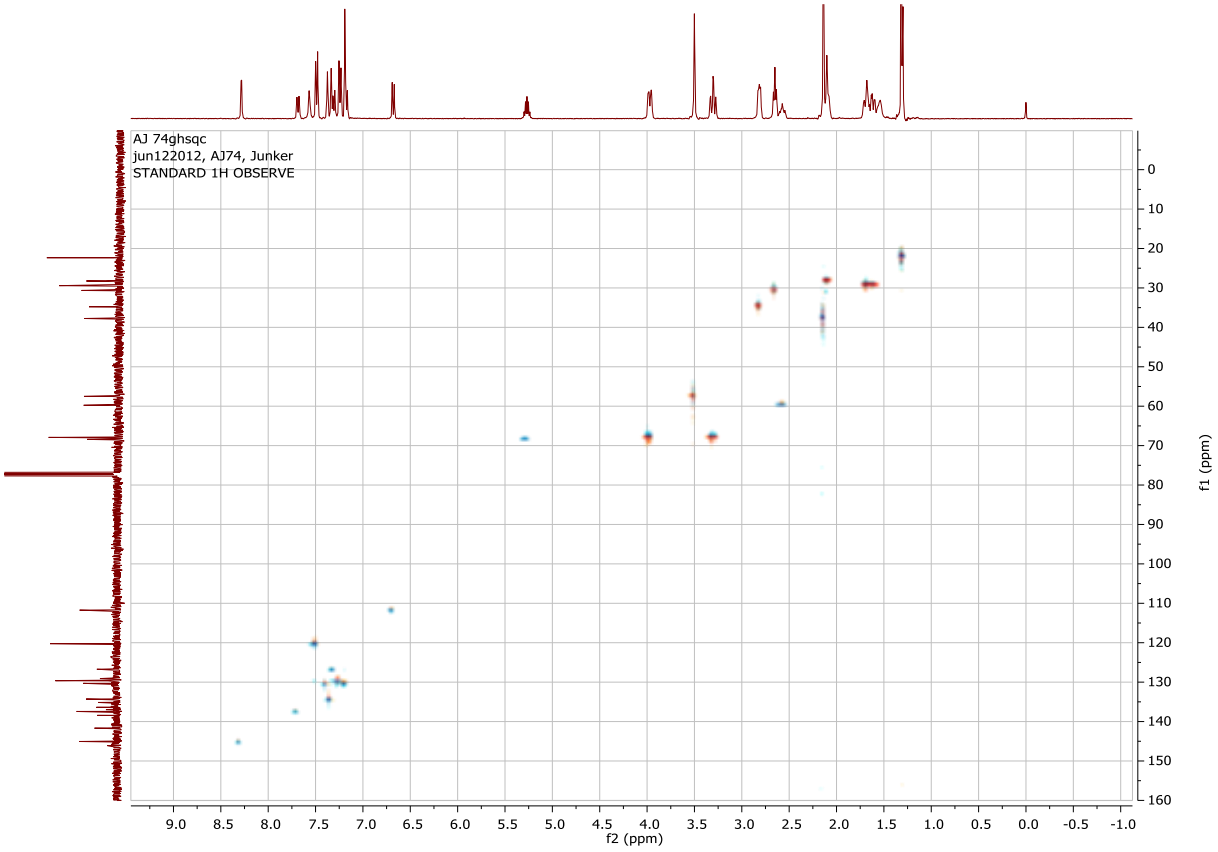


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
486.2524	1	C 30 H 33 F N 3 O 2	46.16	486.2551	2.7	5.5	163.7	15.5	even	ok
	2	C 28 H 32 F 4 N 3	100.00	486.2527	0.3	0.5	175.4	12.5	even	ok
	3	C 27 H 34 F 2 N 3 O 3	4.18	486.2563	3.8	7.9	180.3	11.5	even	ok
	4	C 24 H 37 F N O 8	2.87	486.2498	-2.7	-5.5	199.9	6.5	even	ok
	5	C 26 H 29 F N 9	10.64	486.2524	0.0	0.0	204.4	16.5	even	ok
	6	C 26 H 31 F 3 N 5 O	0.08	486.2475	-4.9	-10.1	211.1	12.5	even	ok
	7	C 21 H 38 F 2 N O 9	1.66	486.2509	-1.5	-3.1	216.4	2.5	even	ok
	8	C 25 H 33 F N 5 O 4	1.84	486.2511	-1.3	-2.7	216.6	11.5	even	ok
	9	C 25 H 33 F 5 N 3 O	1.09	486.2538	1.4	2.9	221.8	8.5	even	ok
	10	C 23 H 30 F 2 N 9 O	1.05	486.2536	1.2	2.4	223.8	12.5	even	ok
	11	C 18 H 37 F N 5 O 9	0.04	486.2570	4.5	9.4	225.5	2.5	even	ok
	12	C 24 H 35 F 3 N 3 O 4	0.02	486.2574	5.0	10.2	227.3	7.5	even	ok
	13	C 23 H 32 F 4 N 5 O 2	0.06	486.2487	-3.8	-7.8	230.0	8.5	even	ok
	14	C 21 H 29 F N 11 O 2	0.04	486.2484	-4.0	-8.2	231.9	12.5	even	ok
	15	C 22 H 34 F 2 N 5 O 5	0.56	486.2523	-0.2	-0.4	235.7	7.5	even	ok
	16	C 20 H 31 F 3 N 9 O 2	0.09	486.2547	2.3	4.7	240.6	8.5	even	ok
	17	C 22 H 34 F 6 N 3 O 2	0.07	486.2550	2.5	5.2	240.7	4.5	even	ok
	18	C 20 H 33 F 5 N 5 O 3	0.03	486.2498	-2.6	-5.4	249.0	4.5	even	ok
	19	C 18 H 30 F 2 N 11 O 3	0.02	486.2496	-2.9	-5.9	251.0	8.5	even	ok
	20	C 20 H 33 F 9 N 3	0.09	486.2525	0.1	0.2	254.0	1.5	even	ok
	21	C 19 H 35 F 3 N 5 O 6	0.05	486.2534	1.0	2.0	254.6	3.5	even	ok
	22	C 16 H 27 F 3 N 15	0.07	486.2520	-0.4	-0.8	255.7	9.5	even	ok
	23	C 18 H 30 F 6 N 9	0.07	486.2523	-0.1	-0.3	256.0	5.5	even	ok
	24	C 17 H 32 F 4 N 9 O 3	0.00	486.2559	3.4	7.1	259.5	4.5	even	ok
	25	C 19 H 35 F 7 N 3 O 3	0.00	486.2561	3.7	7.6	259.6	0.5	even	ok
	26	C 15 H 29 F N 15 O 3	0.00	486.2556	3.2	6.6	261.5	8.5	even	ok
	27	C 17 H 34 F 2 N 7 O 7	0.00	486.2482	-4.2	-8.6	262.9	3.5	even	ok
	28	C 19 H 37 F 5 N O 7	0.00	486.2485	-4.0	-8.2	263.0	-0.5	even	ok
	29	C 15 H 31 F 3 N 11 O 4	0.01	486.2507	-1.7	-3.5	267.8	4.5	even	ok
	30	C 17 H 34 F 6 N 5 O 4	0.01	486.2510	-1.5	-3.1	267.8	0.5	even	ok
	31	C 15 H 31 F 7 N 9 O	0.01	486.2534	1.0	2.0	273.0	1.5	even	ok
	32	C 14 H 33 F N 11 O 7	0.00	486.2543	1.9	3.8	273.4	3.5	even	ok

*2-(6-Isopropoxypyridin-3-yl)-N-{4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (**9k**)*






AJ 74ghsqc
jun122012, AJ74, Junker
STANDARD 1H OBSERVE
f2 (ppm)
f1 (ppm)

HPLC

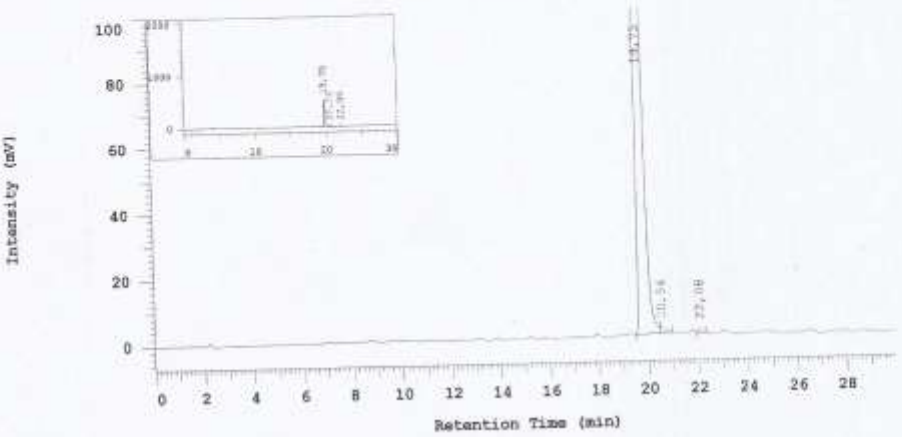
Analyzed: 05.12.12 22:31

Reported: 06.12.12 09:19
Processed: 06.12.12 09:19

Data Path: D:\WIN32APP\HSM\Chromni\DATA\5629\
Application: Chromni
Sample Name: AJ74
Injection from this vial: 1 of 1

Series:5629
Vial Number: 7
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

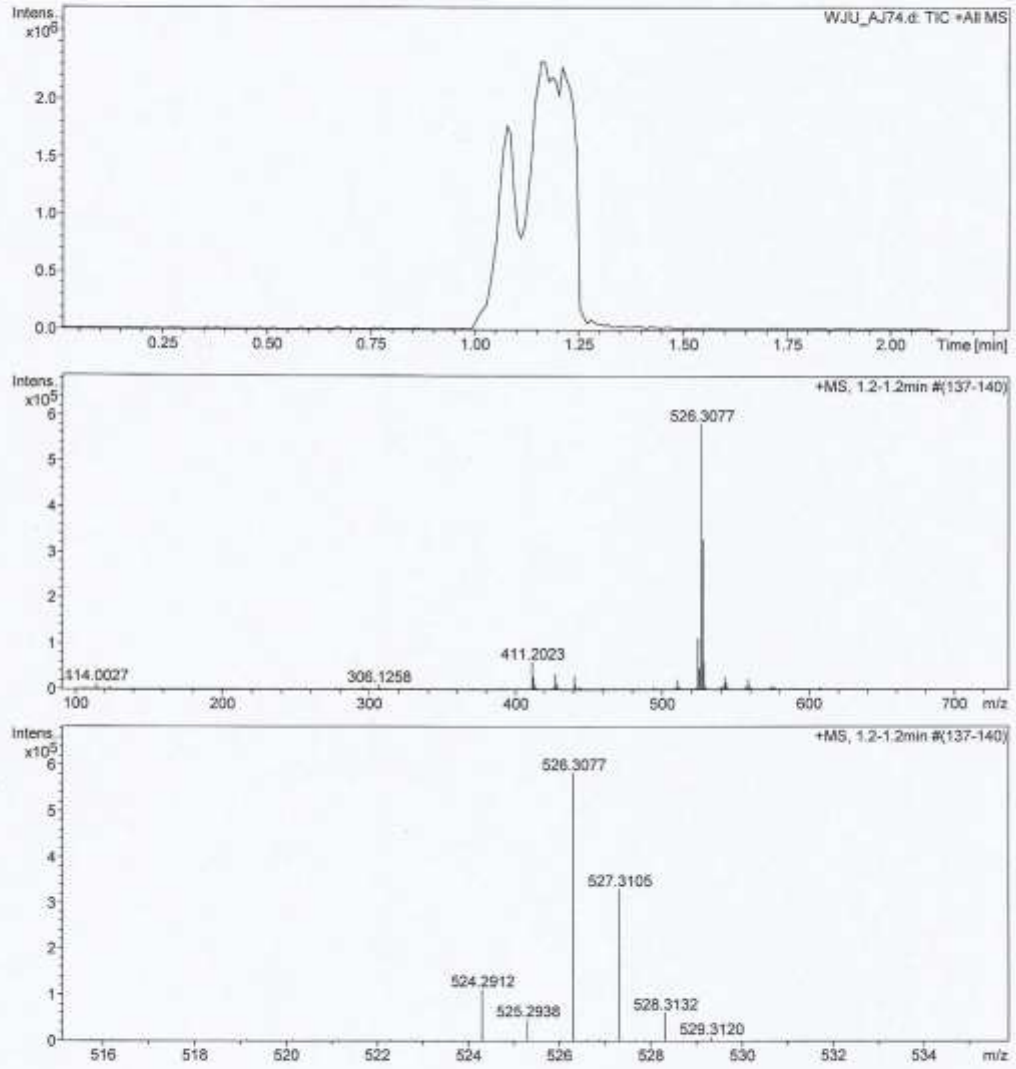
No.	RT	Area	Conc 1	BC
1	19,75	6214690	99,369	MC
2	20,54	24206	0,387	MC
3	22,08	15226	0,243	MC
		6254122	100,000	

Peak rejection level: 0

Generic Display Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\APCI\12_12\WJU_AJ74.d	Acquisition Date	12/18/2012 9:28:57 AM
Method	APCI_directprobe_positiv.m	Operator	Meiners
Sample Name	AJ74	Instrument	micrOTOF-Q II
Comment	JUnker APCI-Direkt Kalibration mit Fettsaeureestern		



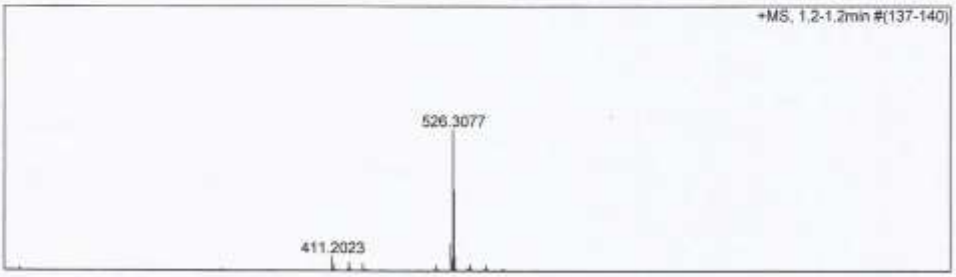
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\APCI\12_12\WJU_AJ74.d	Acquisition Date	12/18/2012 9:28:57 AM
Method	APCI_directprobe_positiv.m	Operator	Meiners
Sample Name	AJ74	Instrument / Ser#	micrOTOF-Q II 10252
Comment	JUnker APCI-Direkt Kalibration mit Fettsaeureestern		

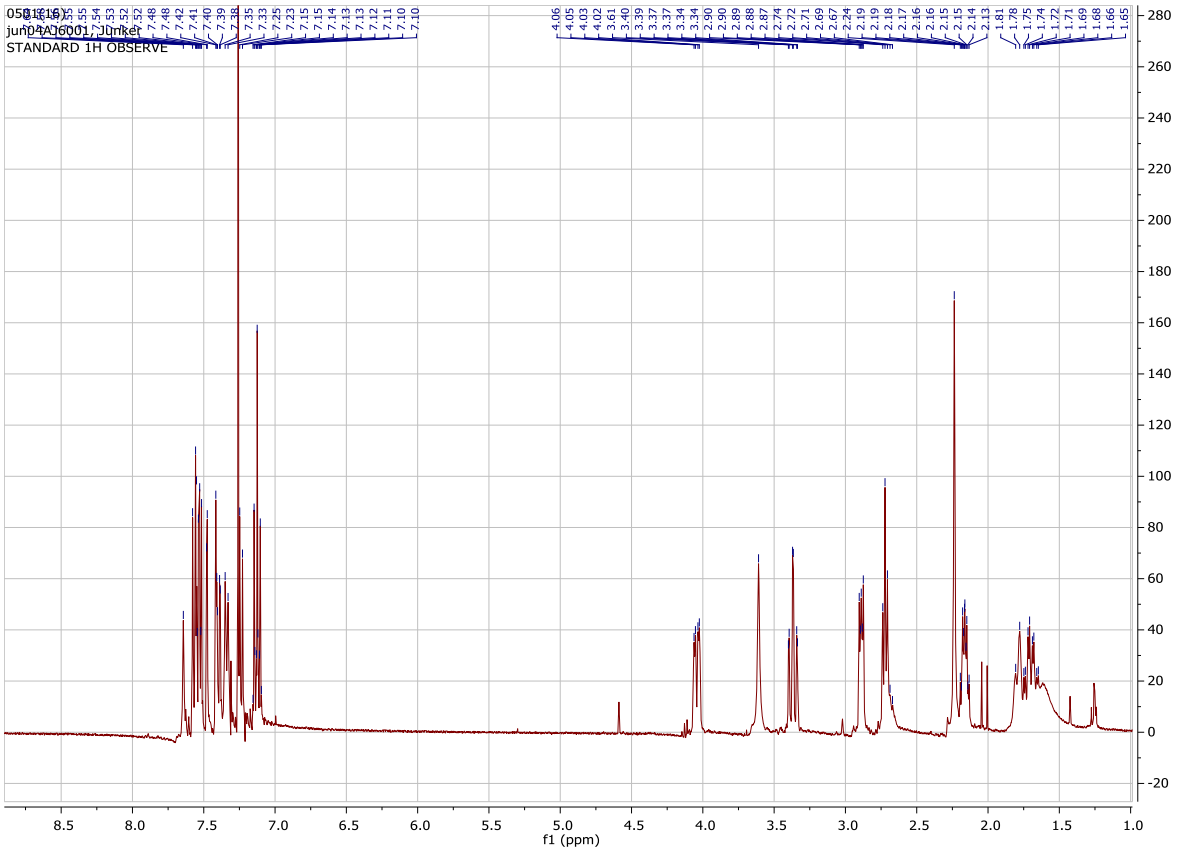
Acquisition Parameter

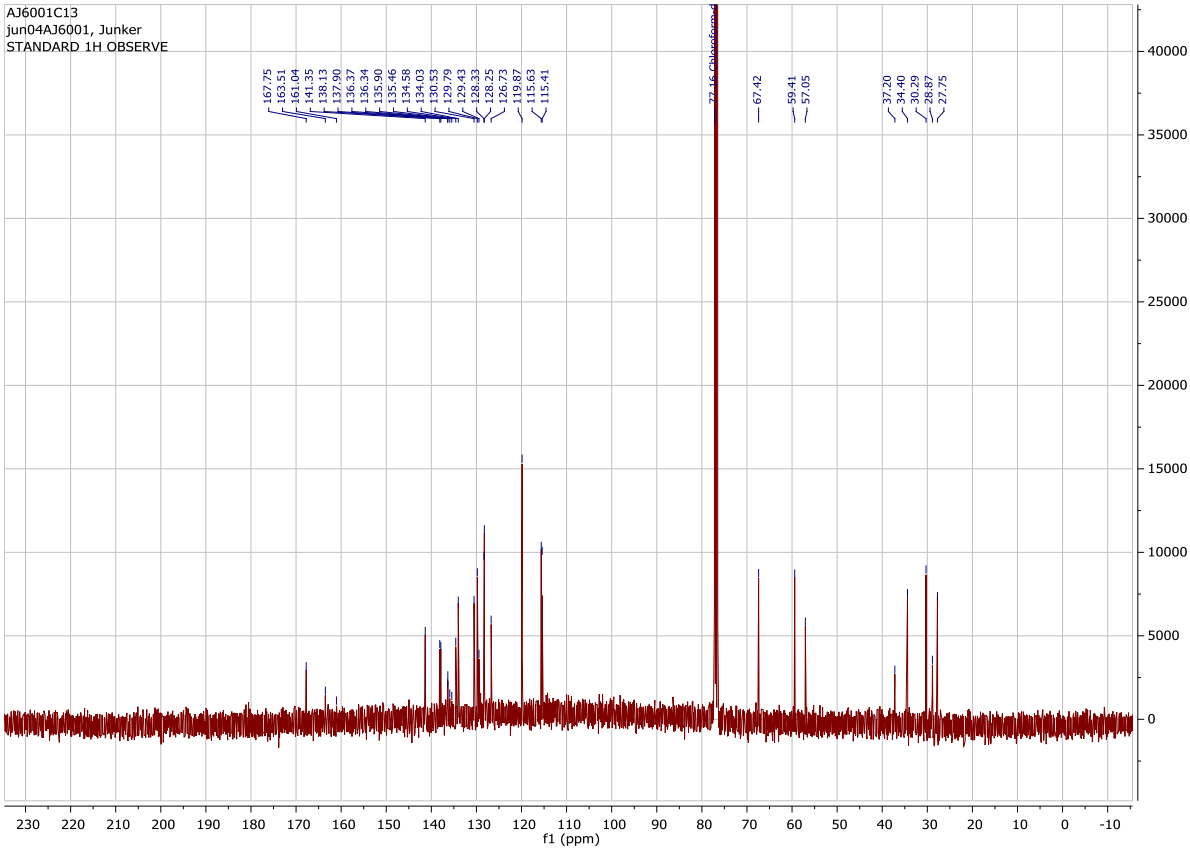
Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.7 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	3.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
526.3077	1	C 38 H 40 N O	85.35	526.3104	2.8	5.3	73.8	19.5	even	ok
	2	C 33 H 40 N 3 O 3	100.00	526.3064	-1.2	-2.4	97.8	15.5	even	ok
	3	C 29 H 36 N 9 O	5.18	526.3037	-3.9	-7.5	109.7	16.5	even	ok
	4	C 26 H 44 N 3 O 8	0.49	526.3123	4.6	8.8	136.1	5.5	even	ok
	5	C 23 H 36 N 13 O 2	0.66	526.3109	3.3	6.2	156.4	12.5	even	ok
	6	C 21 H 44 N 5 O 10	4.49	526.3083	0.6	1.2	157.9	2.5	even	ok
	7	C 19 H 32 N 19	1.91	526.3083	0.6	1.1	170.0	13.5	even	ok
	8	C 22 H 40 N 9 O 6	0.80	526.3096	1.9	3.7	170.5	7.5	even	ok
	9	C 18 H 36 N 15 O 4	0.62	526.3069	-0.7	-1.4	183.9	8.5	even	ok
	10	C 14 H 32 N 21 O 2	0.03	526.3042	-3.4	-6.5	197.3	9.5	even	ok
	11	C 17 H 40 N 11 O 8	0.08	526.3056	-2.1	-3.9	197.8	3.5	even	ok
	12	C 13 H 36 N 17 O 6	0.00	526.3029	-4.8	-9.1	211.1	4.5	even	ok

*2-(4-Fluorophenyl)-N-{[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (**9l**)*



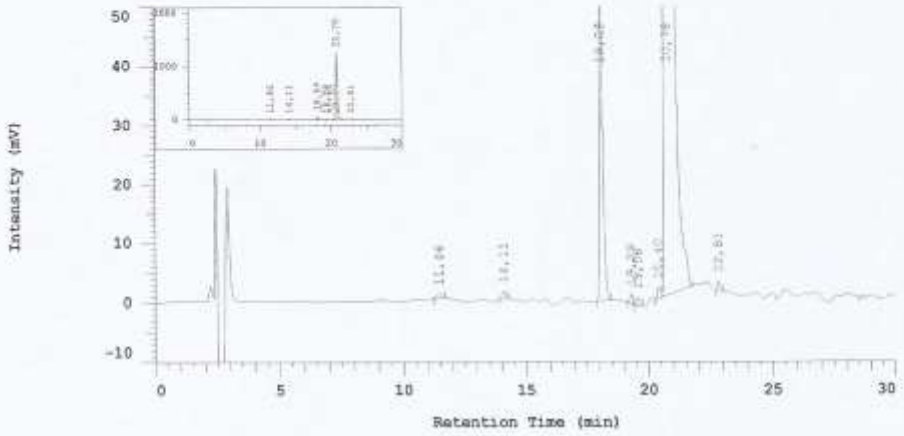


HPLC

Analyzed: 07.04.11 00:01
Reported: 08.04.11 08:04
Processed: 08.04.11 08:04

Data Path: D:\WIN32APP\HSM\Chromni\DATA\2932\
Application: Chromni
Series:2932
Sample Name: AJ6001
Vial Number: 8
Injection from this vial: 1 of 1
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

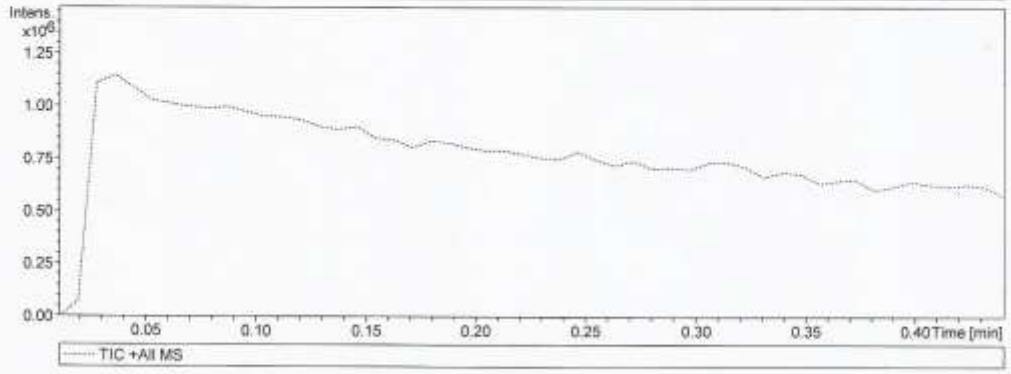
No.	RT	Area	Conc 1	BC
1	11,46	9825	0,056	MC
2	14,11	13863	0,080	MC
3	18,09	476322	2,736	MC
4	19,29	10713	0,062	BB
5	19,56	12243	0,070	MC
6	20,40	16915	0,097	MC
7	20,78	16857190	96,819	BB
8	22,81	14032	0,081	MC
		17411103	100,000	

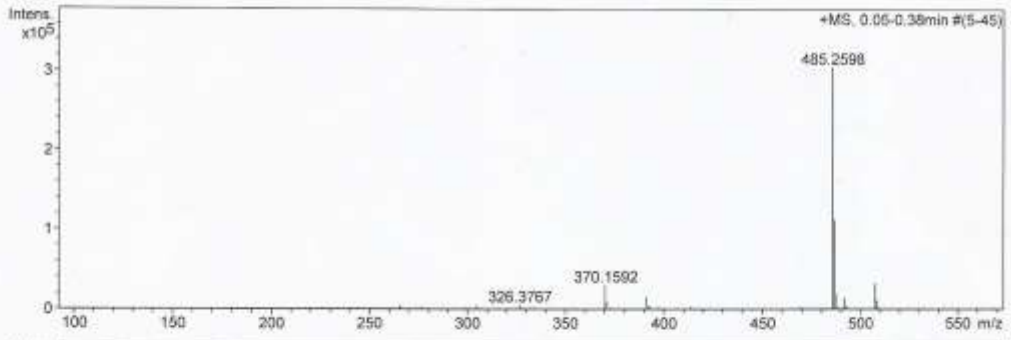
Peak rejection level: 0

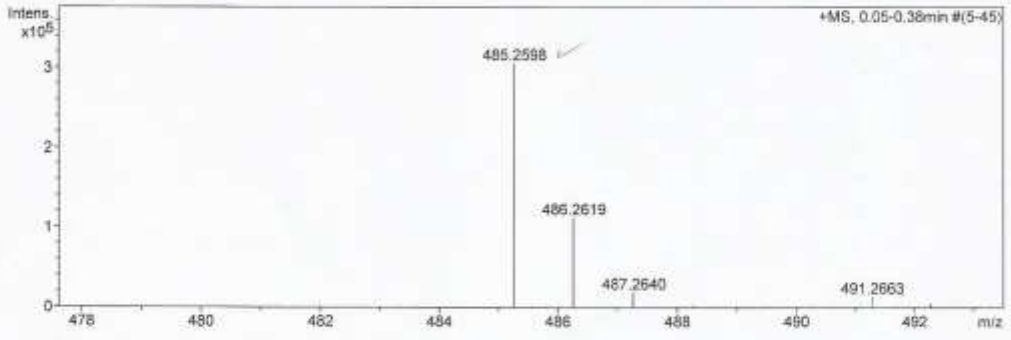
Generic Display Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\2011_4\WJU_AJ6001.d	Acquisition Date	4/18/2011 7:46:36 AM
Method	Kurz_pos_MS_low.m	Operator	Meiners
Sample Name	AJ6001	Instrument	micrOTOF-Q II
Comment	Junker ESI-Direkt Kalibration mit LI-Formate		







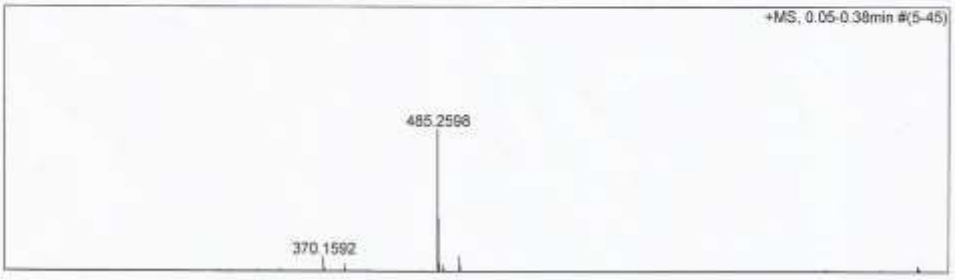
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\2011_4\WJU_AJ6001.d	Acquisition Date	4/18/2011 7:46:36 AM
Method	Kurz_pos_MS_low.m	Operator	Meiners
Sample Name	AJ6001	Instrument / Ser#	micrOTOF-Q II 10252
Comment	Junker ESI-Direkt Kalibration mit LI-Formate		

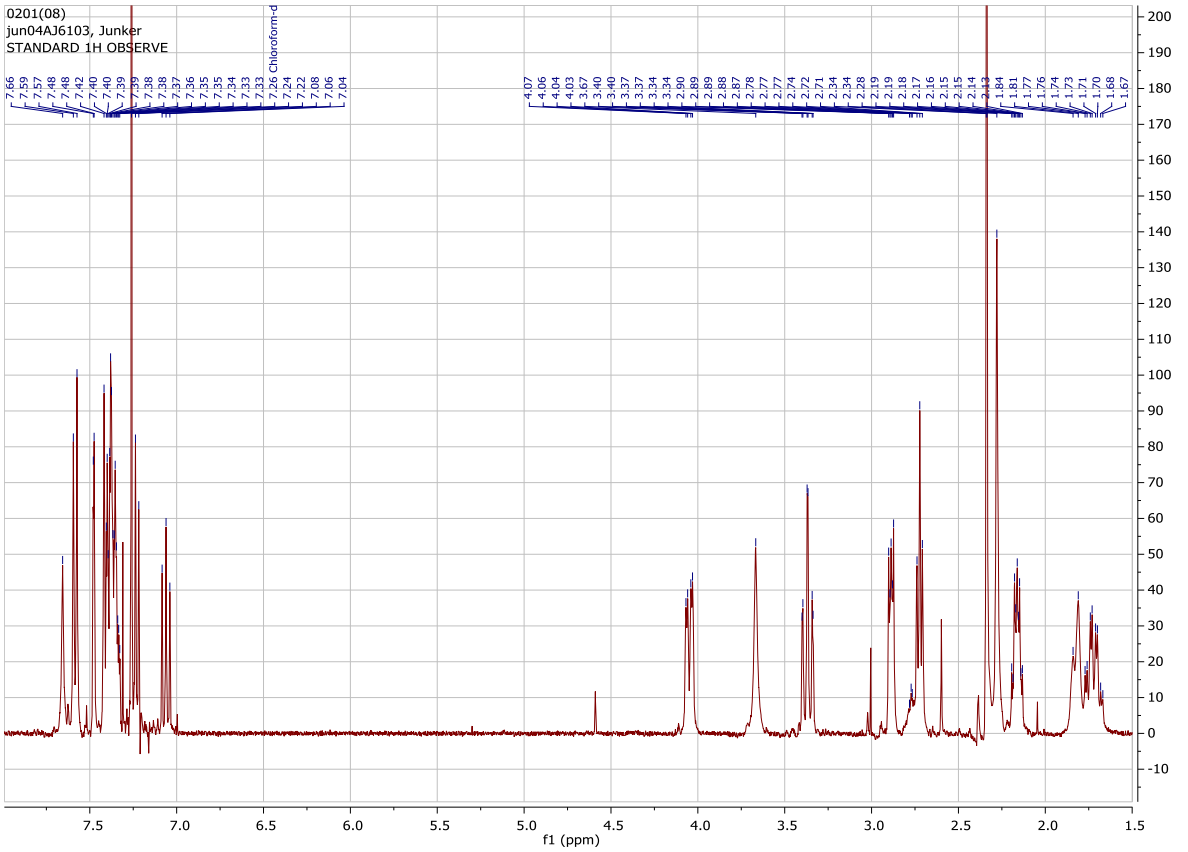
Acquisition Parameter

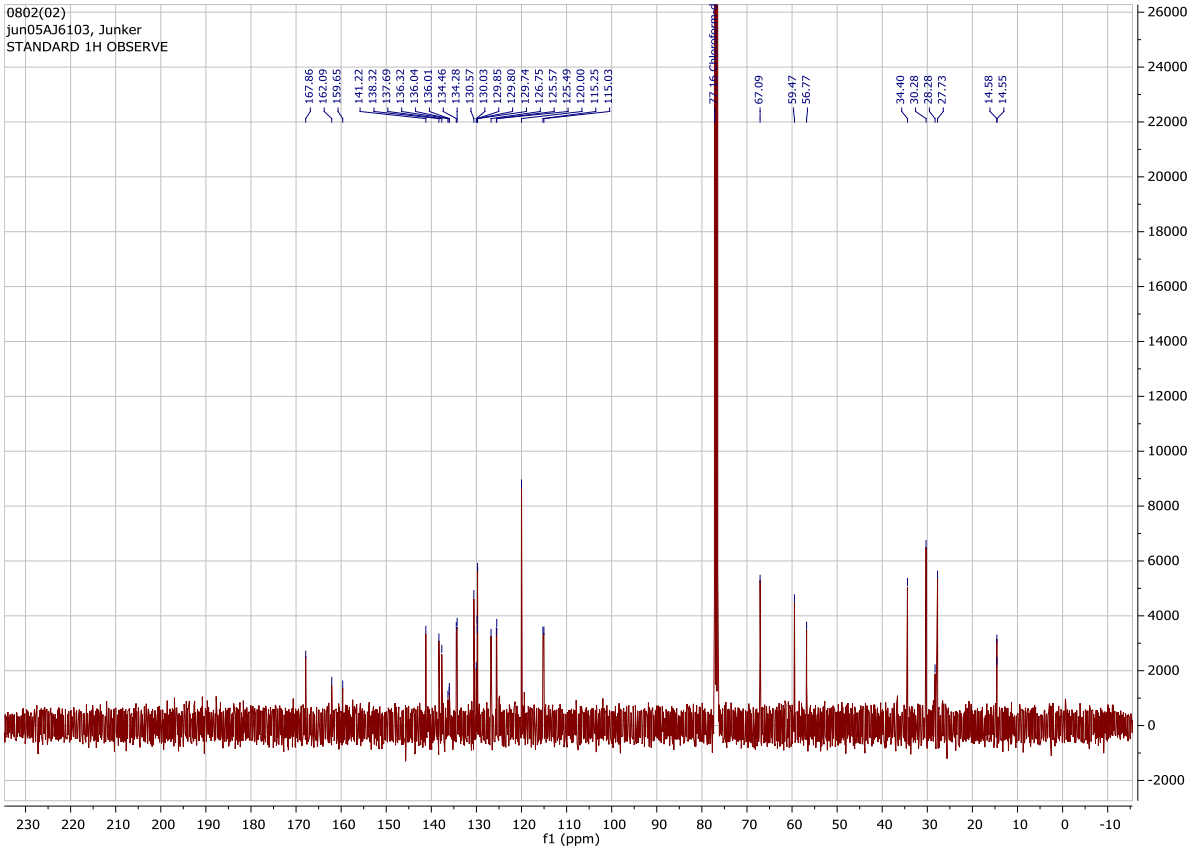
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	5.0 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	220 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	9.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	500.0 Vpp	Set Divert Valve	Waste



Meas. m/z	#	Formula	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule	I
485.2598	1	C 31 H 34 F N 2 O 2	485.2599	0.1	0.2	9.9	15.5	even	ok	304884

*2-(4-Fluoro-3-methylphenyl)-N-{4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (**9m**)*





HPLC

Analyzed: 06.04.11 22:38

Reported: 08.04.11 07:59
Processed: 08.04.11 07:59

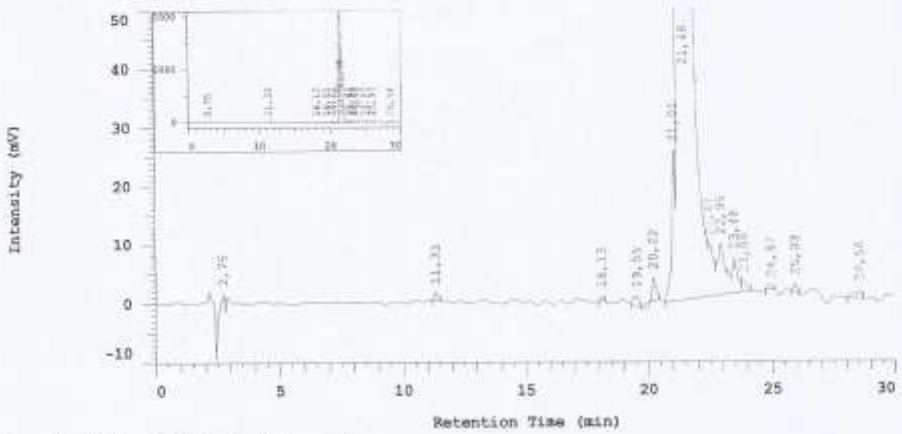
Data Path: D:\WIN32APP\HSM\Chromni\DATA\2930\
Application: Chromni

Series:2930
Vial Number: 7
Vial Type: UNK
Volume: 5,0 ul

Sample Name: AJ6103

Injection from this vial: 1 of 1

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

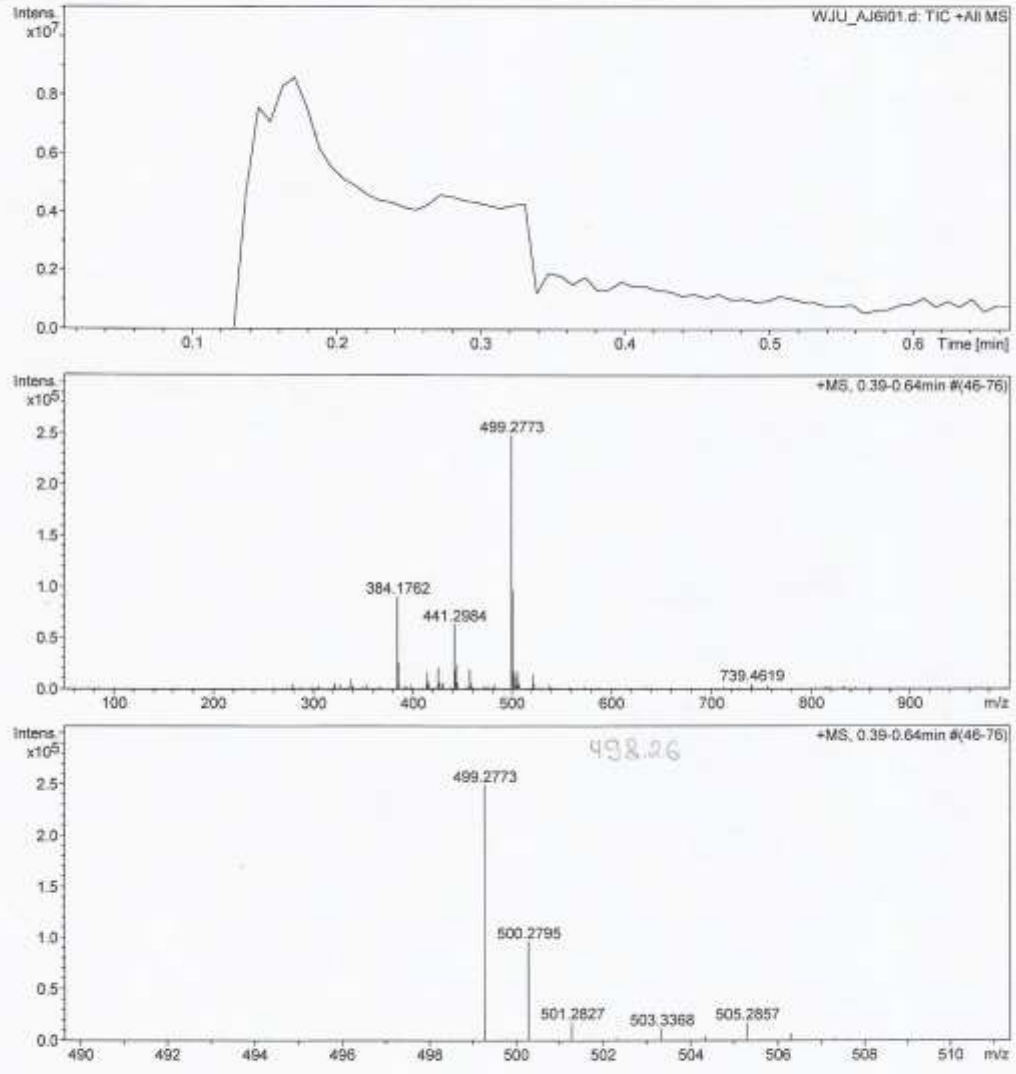
No.	RT	Area	Conc 1	BC
1	2,75	0	0,000	
2	11,33	13420	0,027	MC
3	18,13	7228	0,015	MC
4	19,55	27104	0,054	MC
5	20,22	40302	0,081	MC
6	21,05	235918	0,474	MC
7	21,48	48993769	98,441	MC
8	22,47	122196	0,246	MC
9	22,95	167799	0,337	MC
10	23,48	84561	0,170	MC
11	23,88	25720	0,052	MC
12	24,97	10467	0,021	BB
13	25,93	14890	0,030	MC
14	28,56	26122	0,052	BB
		49769496	100,000	

Peak rejection level: 0

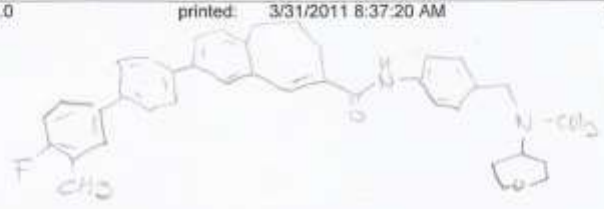
Generic Display Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\2011_3\WJU_AJ6I01.d	Acquisition Date	3/31/2011 8:32:06 AM
Method	Kurz_pos_MS_low.m	Operator	Meiners
Sample Name	AJ6I01	Instrument	micrOTOF-Q II
Comment	Junker ESI-Direkt Kalibration mit Li-Formate		



Bruker Compass DataAnalysis 4.0 printed: 3/31/2011 8:37:20 AM Page 1 of 1



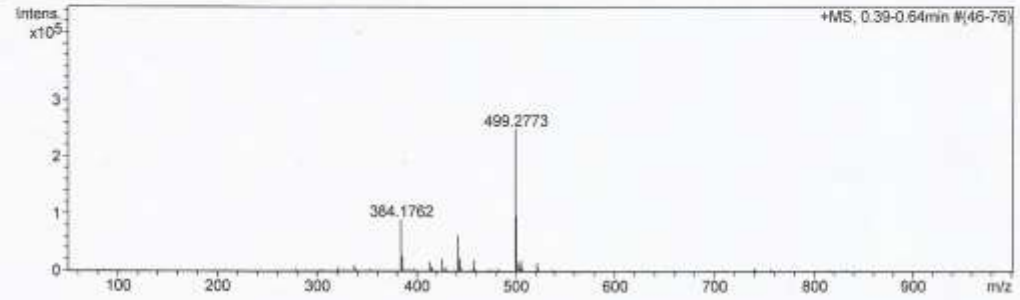
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\2011_3\WJU_AJ6I01.d	Acquisition Date	3/31/2011 8:32:06 AM
Method	Kurz_pos_MS_low.m	Operator	Meiners
Sample Name	AJ6I01	Instrument / Ser#	micrOTOF-Q II 10252
Comment	Junker ESI-Direkt Kalibration mit Li-Formate		

Acquisition Parameter

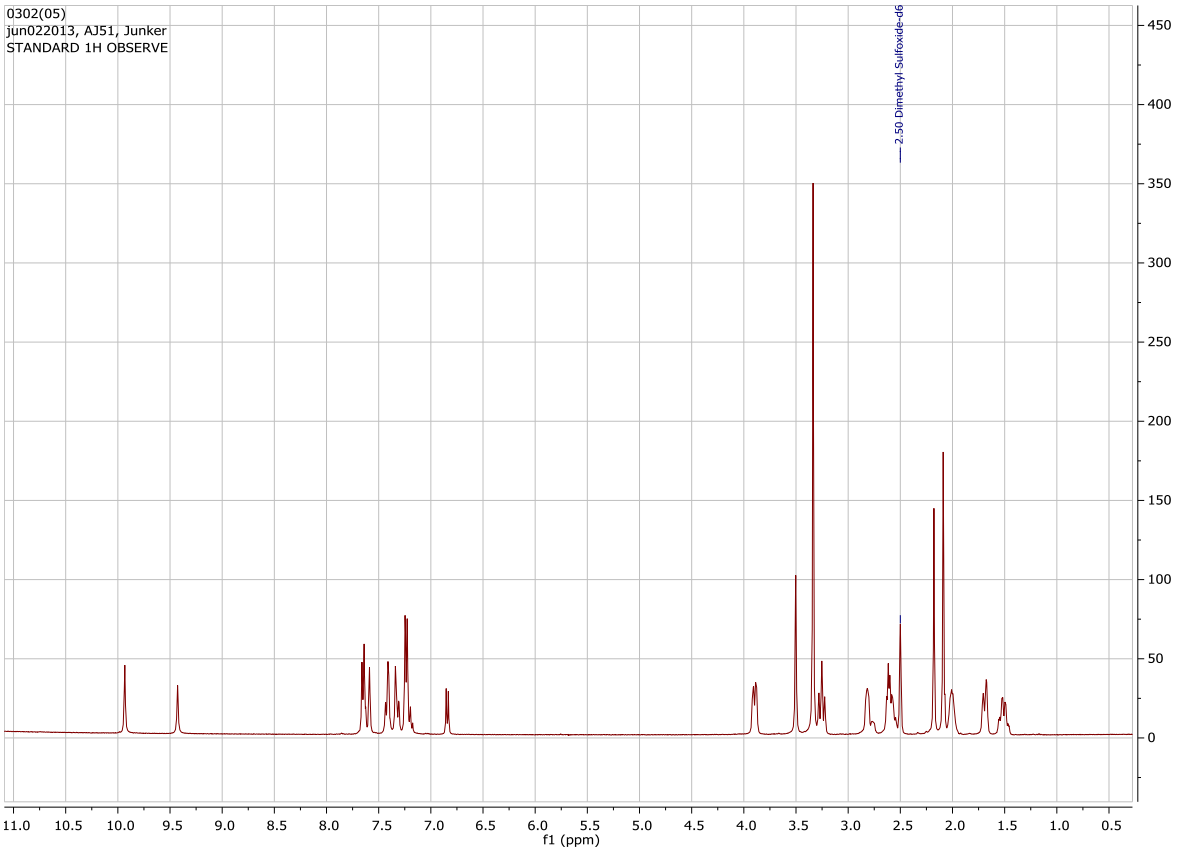
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	5.0 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	220 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	9.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	500.0 Vpp	Set Divert Valve	Waste

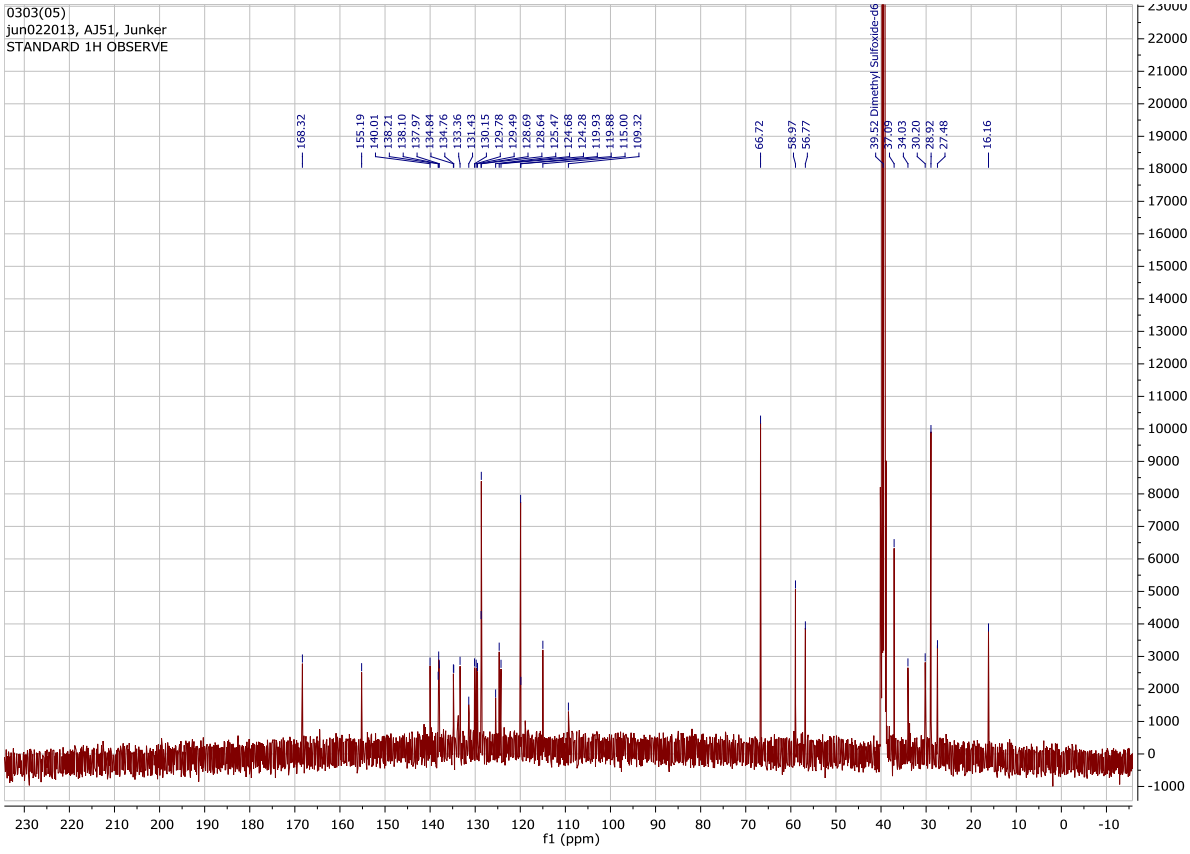


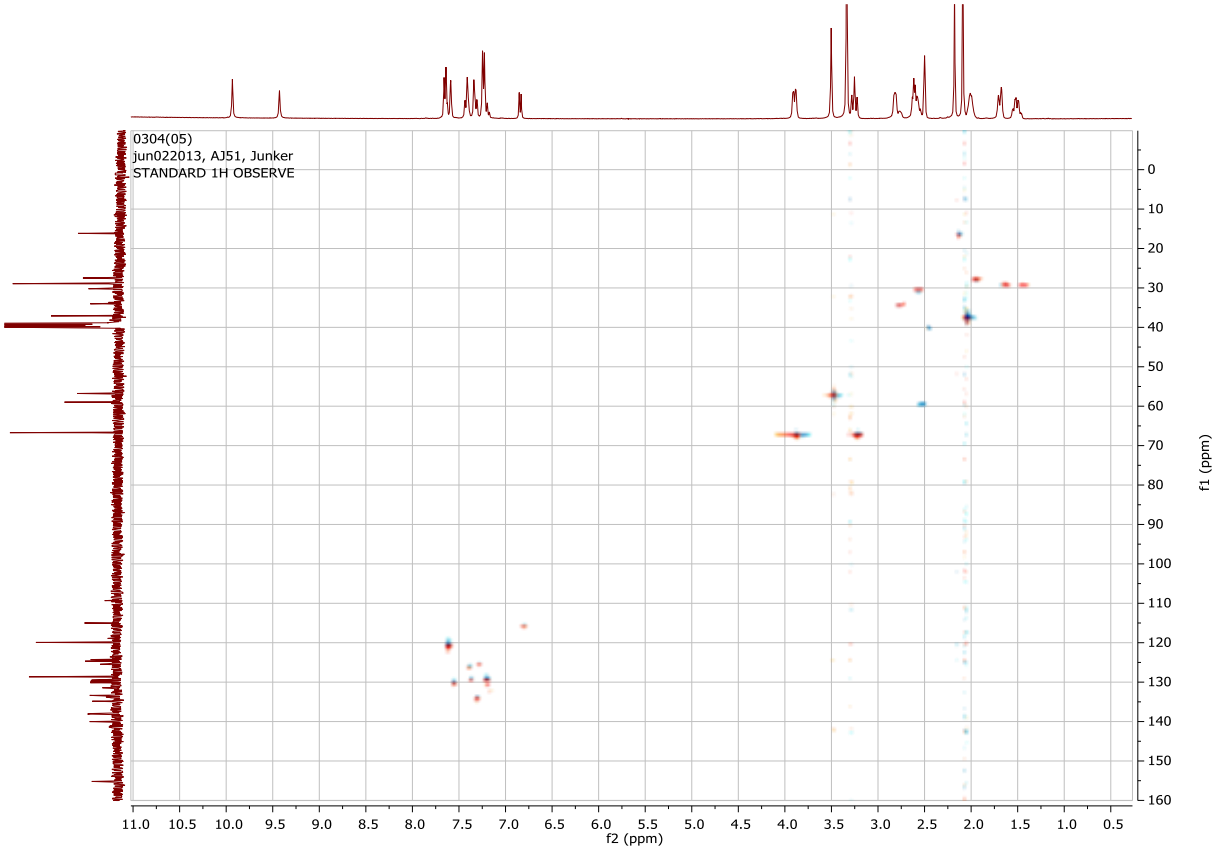
Meas. m/z	#	Formula	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule	I
499.2773	1	C 34 H 37 F 2 O	499.2807	3.4	6.9	6.9	15.5	even	ok	248084
	2	C 37 H 36 F	499.2796	2.3	4.6	10.6	19.5	even	ok	
	3	C 32 H 36 F N 2 O 2	499.2755	-1.7	-3.4	14.1	15.5	even	ok	

± 5mDa = 50ppm

*2-(4-Hydroxy-3-methylphenyl)-N-{4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (**9o**)*






0304(05)
jun022013, AJ51, Junker
STANDARD 1H OBSERVE
f2 (ppm)
f1 (ppm)

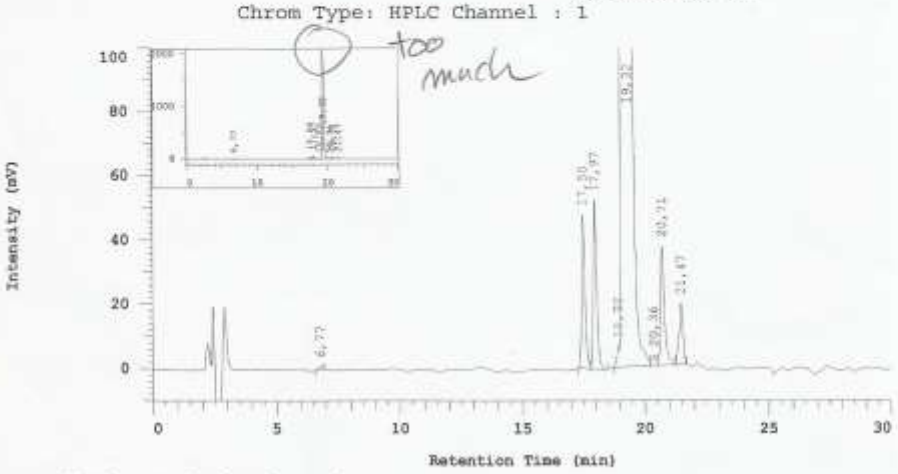
HPLC

Analyzed: 04.08.11 03:37
Reported: 04.08.11 13:46
Processed: 04.08.11 13:46

Data Path: D:\WIN32APP\HSM\Chromni\DATA\3414\
Application: Chromni
Series:3414

Sample Name: AJ5101
Vial Number: 12
Vial Type: UNK
Injection from this vial: 1 of 1
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

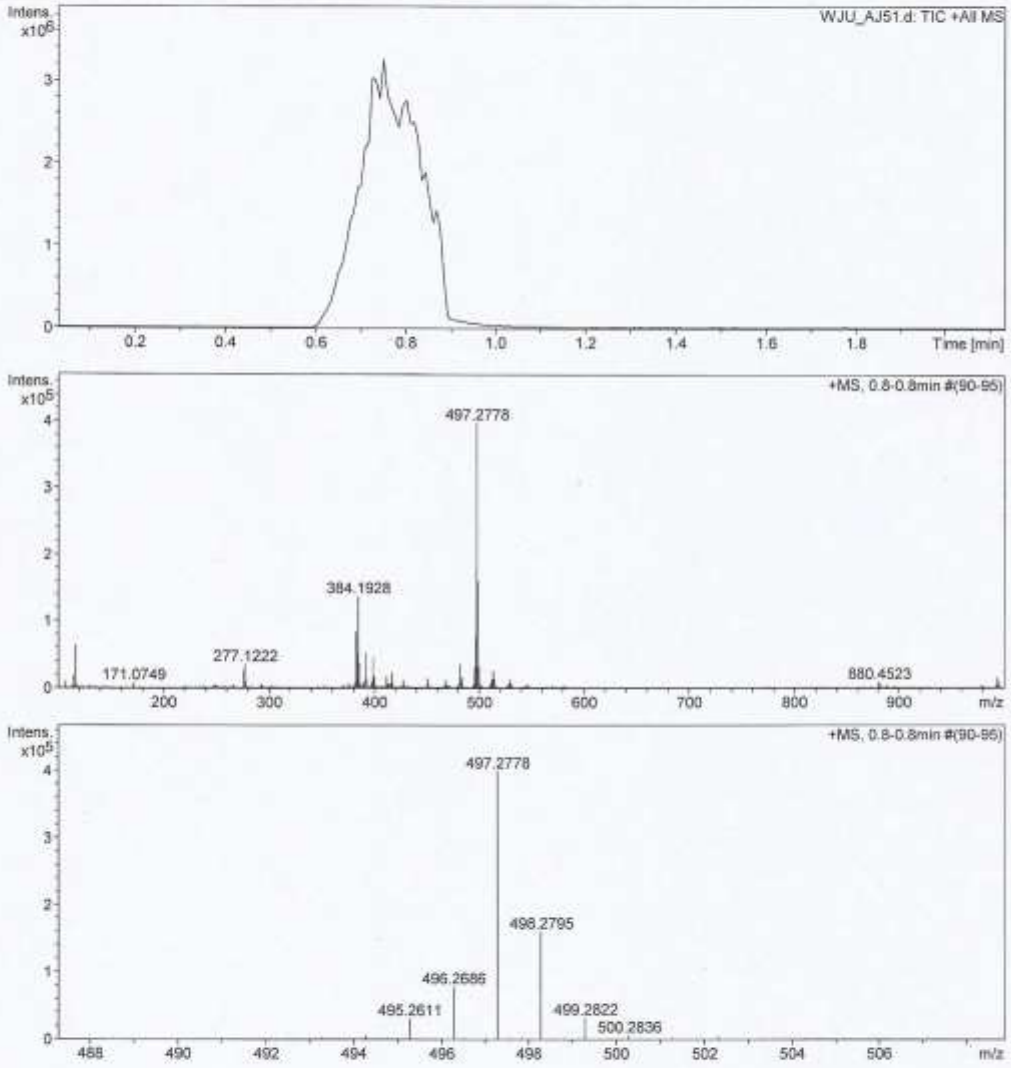
No.	RT	Area	Conc 1	BC
1	6,77	11420	0,028	MC
2	17,50	437070	1,063	BV
3	17,97	485438	1,181	VB
4	18,92	50137	0,122	MC
5	19,32	39483280	96,045	MC
6	20,36	36383	0,089	MC
7	20,71	398976	0,971	MC
8	21,47	206541	0,502	MC
		41109245	100,000	

Peak rejection level: 0

Generic Display Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\APCI\12_09\WJU_AJ51.d	Acquisition Date	9/11/2012 9:34:38 AM
Method	APCI_directprobe_positiv.m	Operator	Sendker
Sample Name	AJ51	Instrument	micrOTOF-Q II
Comment	Junker APCI-Direkt Kalibrationn mit Fettsaeureestern		



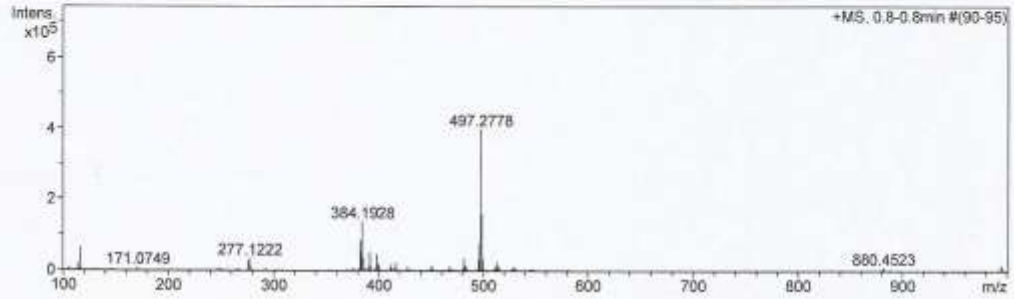
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\APCI\12_09\WJU_AJ51.d	Acquisition Date	9/11/2012 9:34:38 AM
Method	APCI_directprobe_positiv.m	Operator	Sendker
Sample Name	AJ51	Instrument / Ser#	micrOTOF-Q II 10252
Comment	Junker APCI-Direkt Kalibrationn mit Fettsaeureestern		

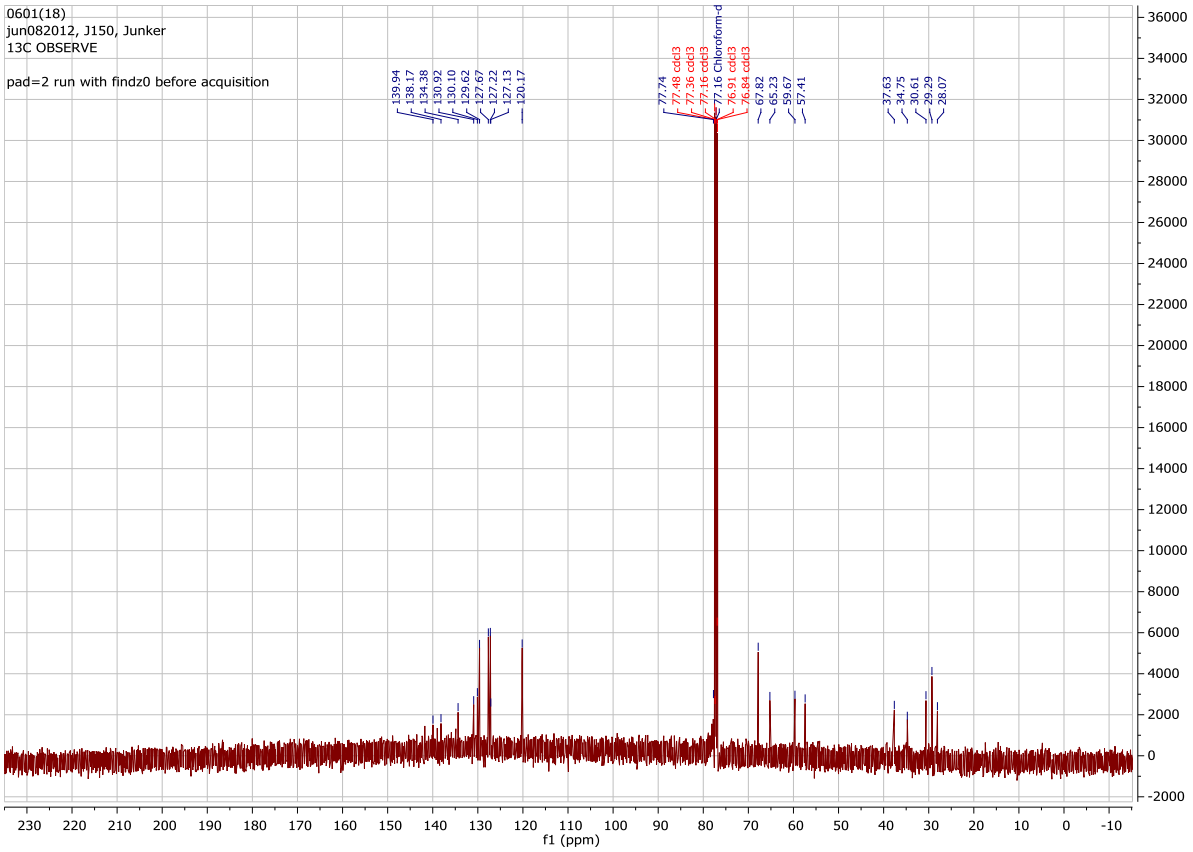
Acquisition Parameter

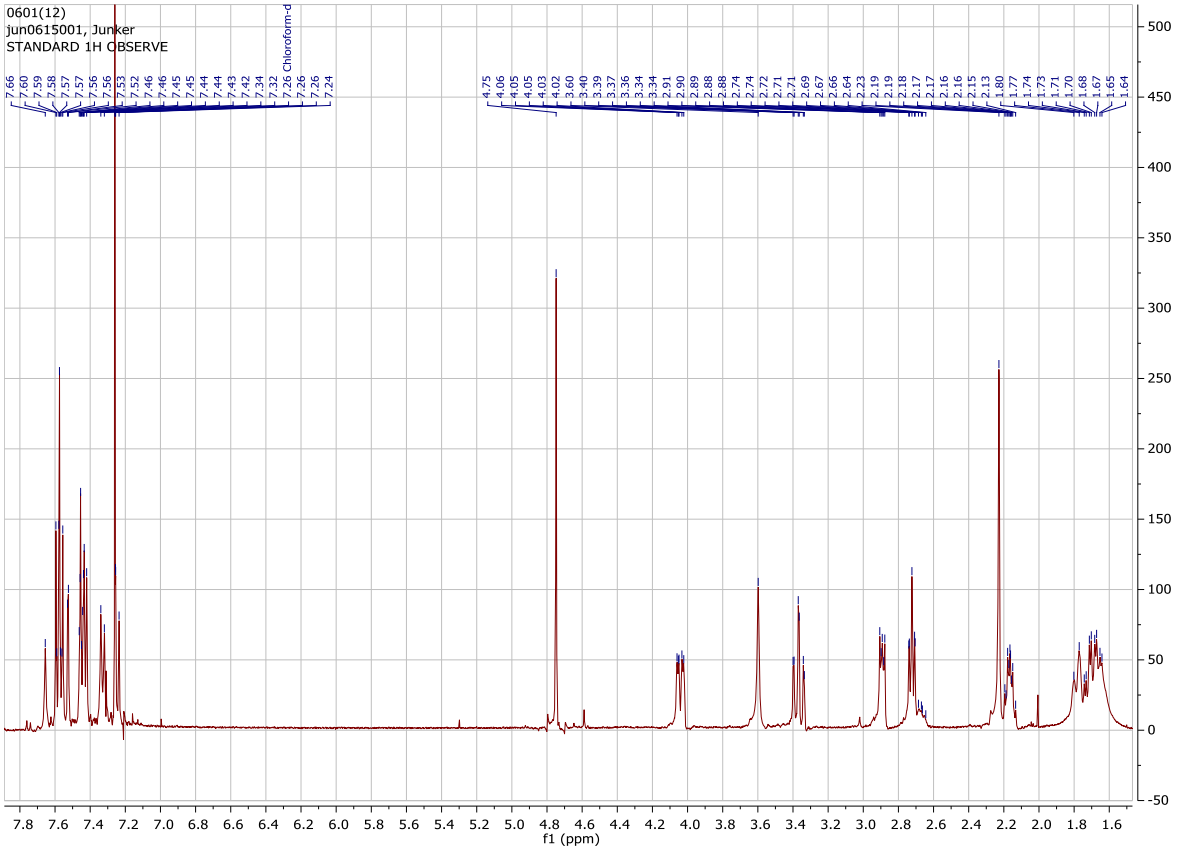
Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.7 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	3.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
497.2778	1	C 37 H 37 O	1.10	497.2839	6.1	12.3	2.9	19.5	even	ok
	2	C 34 H 33 N 4	0.04	497.2700	-7.8	-15.7	8.4	20.5	even	ok
	3	C 32 H 37 N 2 O 3	100.00	497.2799	2.1	4.2	22.2	15.5	even	ok

*2-[4-(Hydroxymethyl)phenyl]-N-{4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (**9p**)*



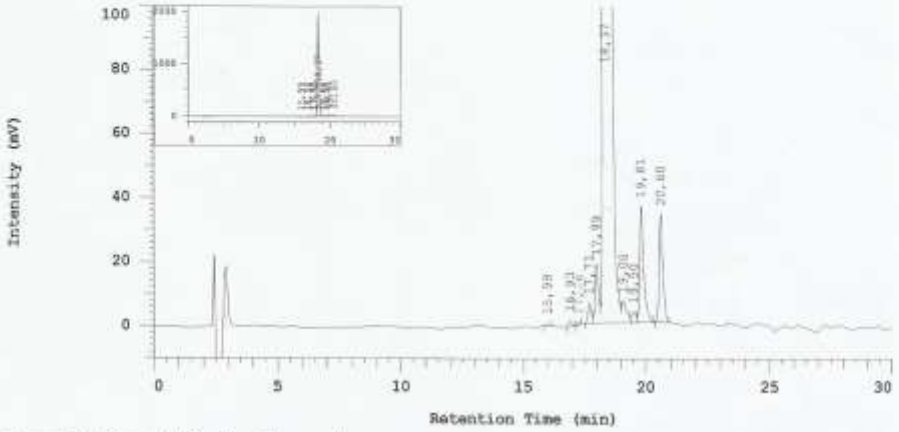


HPLC

Analyzed: 04.08.11 05:42
Reported: 04.08.11 13:50
Processed: 04.08.11 13:50

Data Path: D:\WIN32APP\HSM\Chromni\DATA\3417\
Application: Chromni
Series:3417
Sample Name: AJ15001
Vial Number: 14
Injection from this vial: 1 of 1
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

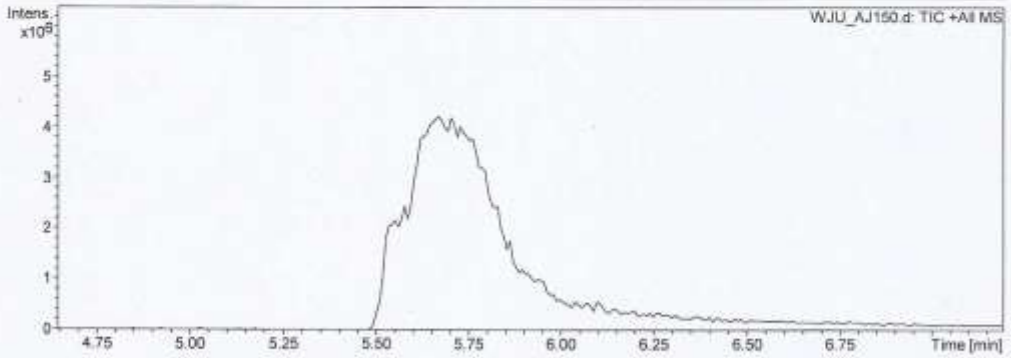
No.	RT	Area	Conc 1	BC
1	15,99	7672	0,028	MC
2	16,93	16812	0,061	MC
3	17,26	5207	0,019	MC
4	17,71	57119	0,209	MC
5	17,99	173110	0,632	MC
6	18,37	26258558	95,867	MC
7	19,08	89935	0,328	MC
8	19,50	34927	0,128	MC
9	19,81	411366	1,502	MC
10	20,60	335801	1,226	MC
		27390507	100,000	

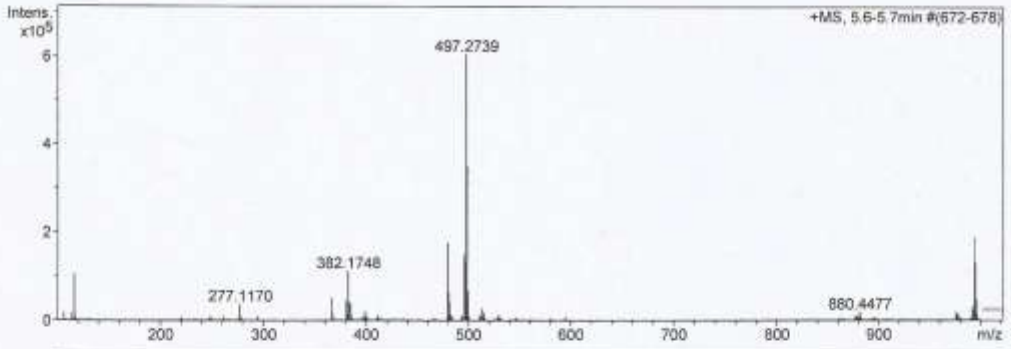
Peak rejection level: 0

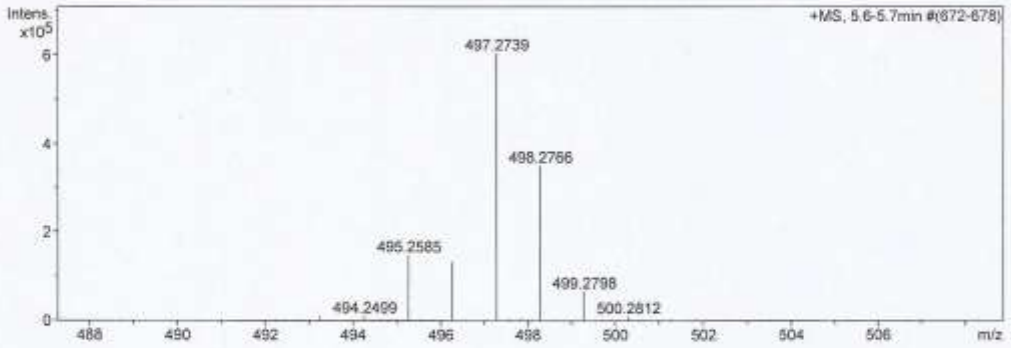
Generic Display Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\APCI\12_09\WJU_AJ150.d	Acquisition Date	9/11/2012 9:41:50 AM
Method	APCI_directprobe_positiv.m	Operator	Sendker
Sample Name	AJ150	Instrument	micrOTOF-Q II
Comment	Junker APCI-Direkt Kalibrationn mit Fettsaeureestern		







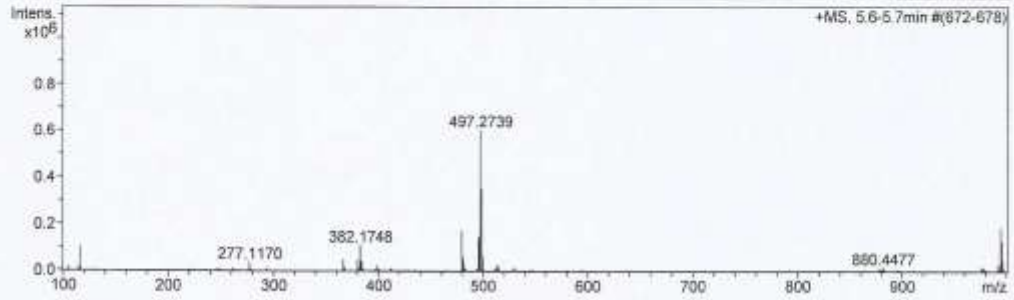
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\APCI\12_09\WJU_AJ150.d	Acquisition Date	9/11/2012 9:41:50 AM
Method	APCI_directprobe_positiv.m	Operator	Sendker
Sample Name	AJ150	Instrument / Ser#	micrOTOF-Q II 10252
Comment	Junker APCI-Direkt Kalibrationn mit Fettsaeureestern		

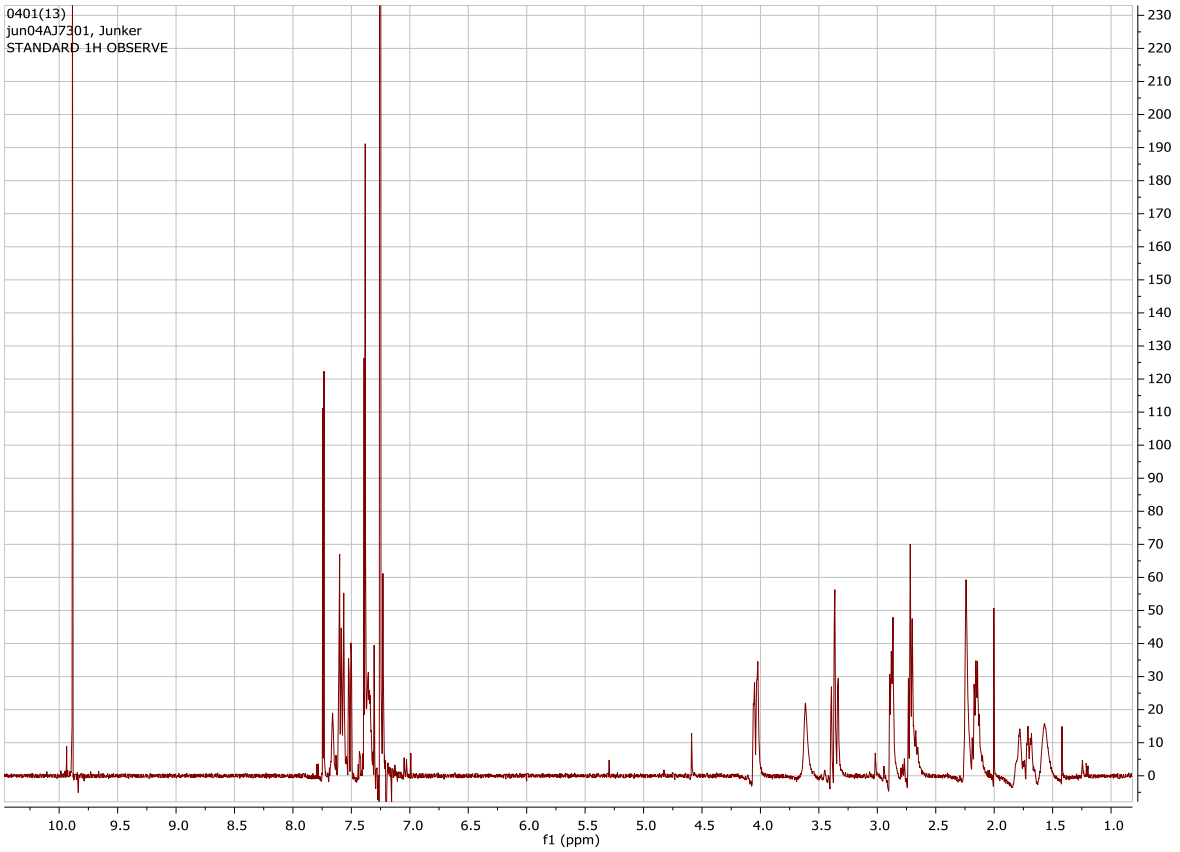
Acquisition Parameter

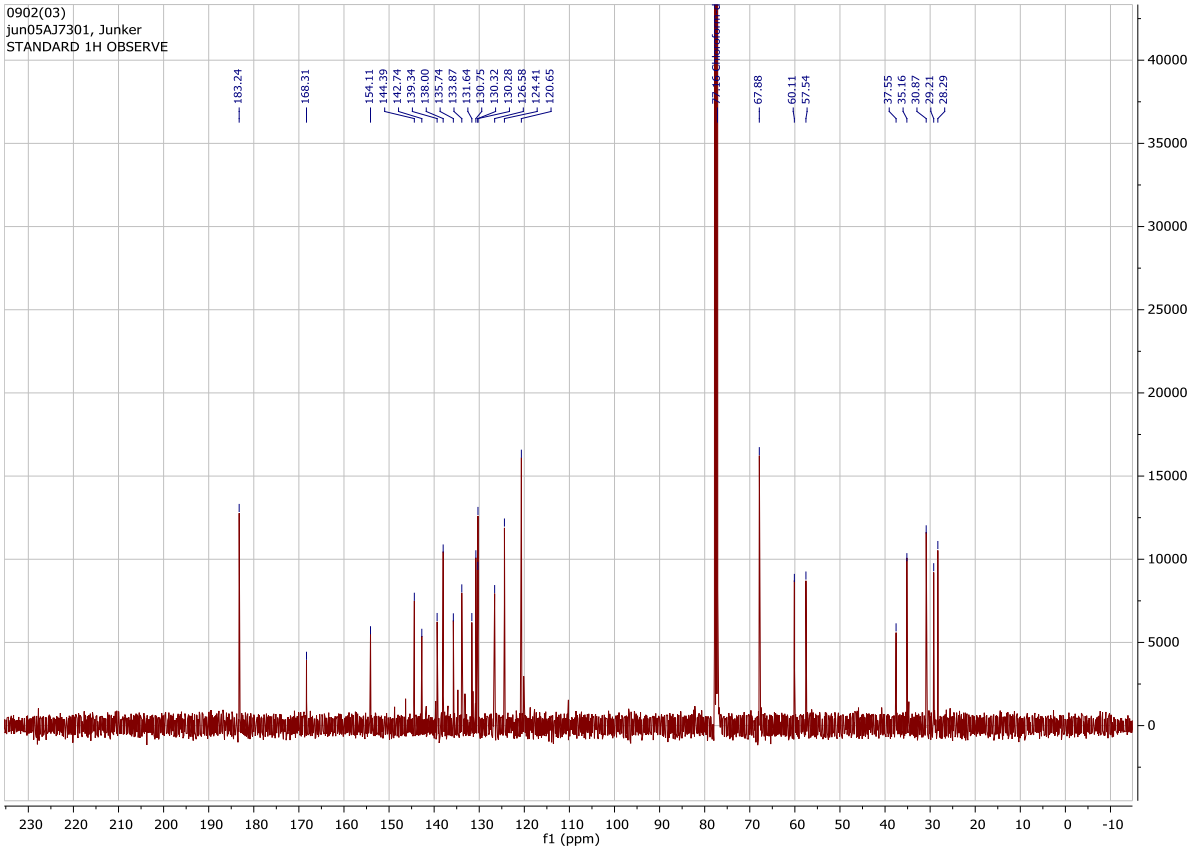
Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.7 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	3.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
497.2739	1	C 34 H 33 N 4	100.00	497.2700	-4.0	-8.0	97.9	20.5	even	ok
	2	C 33 H 37 O 4	9.17	497.2686	-5.3	-10.7	110.3	15.5	even	ok
	3	C 32 H 37 N 2 O 3	3.23	497.2799	5.9	11.9	112.3	15.5	even	ok

*2-(5-Formylthiophen-2-yl)-N-{4-[(methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (**9v**)*





HPLC

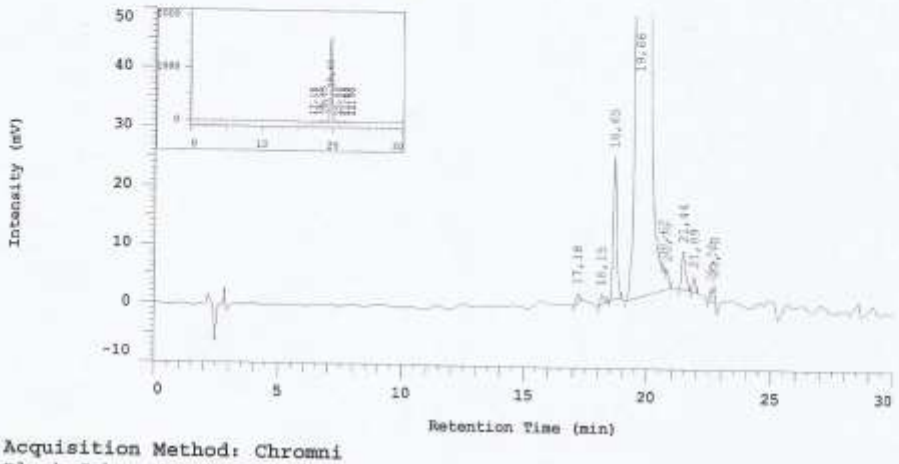
Analyzed: 14.04.11 01:25

Reported: 14.04.11 14:02
Processed: 14.04.11 14:02

Data Path: D:\WIN32APP\HSM\Chromni\DATA\2964\
Application: Chromni
Sample Name: AJ7301
Injection from this vial: 1 of 1

Series:2964
Vial Number: 10
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Solvent A: Wasser + 0,05%TFA

Developed by: Jens
Solvent B: ACN + 0,05%TFA

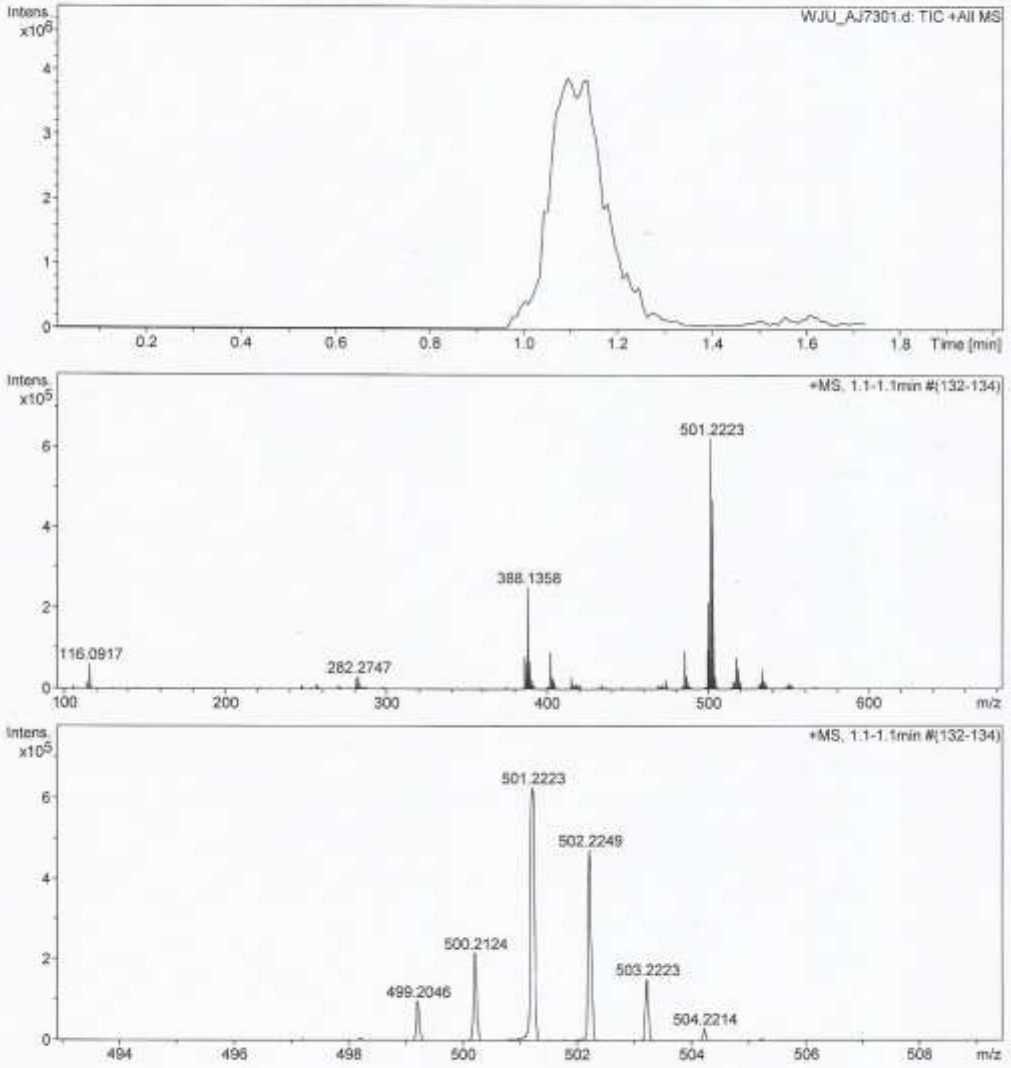
No.	RT	Area	Conc 1	BC
1	17,18	12357	0,044	MC
2	18,15	15586	0,056	MC
3	18,65	229788	0,822	MC
4	19,66	27517846	98,442	MC
5	20,62	28816	0,103	MC
6	20,78	26502	0,095	MC
7	21,44	72029	0,258	MC
8	21,89	21067	0,075	MC
9	22,55	13198	0,047	MC
10	22,70	16295	0,058	MC
		27953484	100,000	

Peak rejection level: 0

Generic Display Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\2011_5\WJU_AJ7301.d	Acquisition Date	5/2/2011 2:41:29 PM
Method	APCI_directprobe_default.m	Operator	Meiners
Sample Name	AJ7301	Instrument	micrOTOF-Q II
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestem		



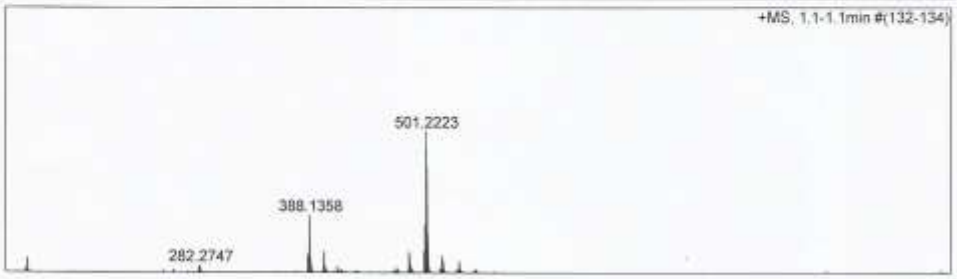
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\2011_5\WJU_AJ7301.d	Acquisition Date	5/2/2011 2:41:29 PM
Method	APCI_directprobe_default.m	Operator	Meiners
Sample Name	AJ7301	Instrument / Ser#	micrOTOF-Q II 10252
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		

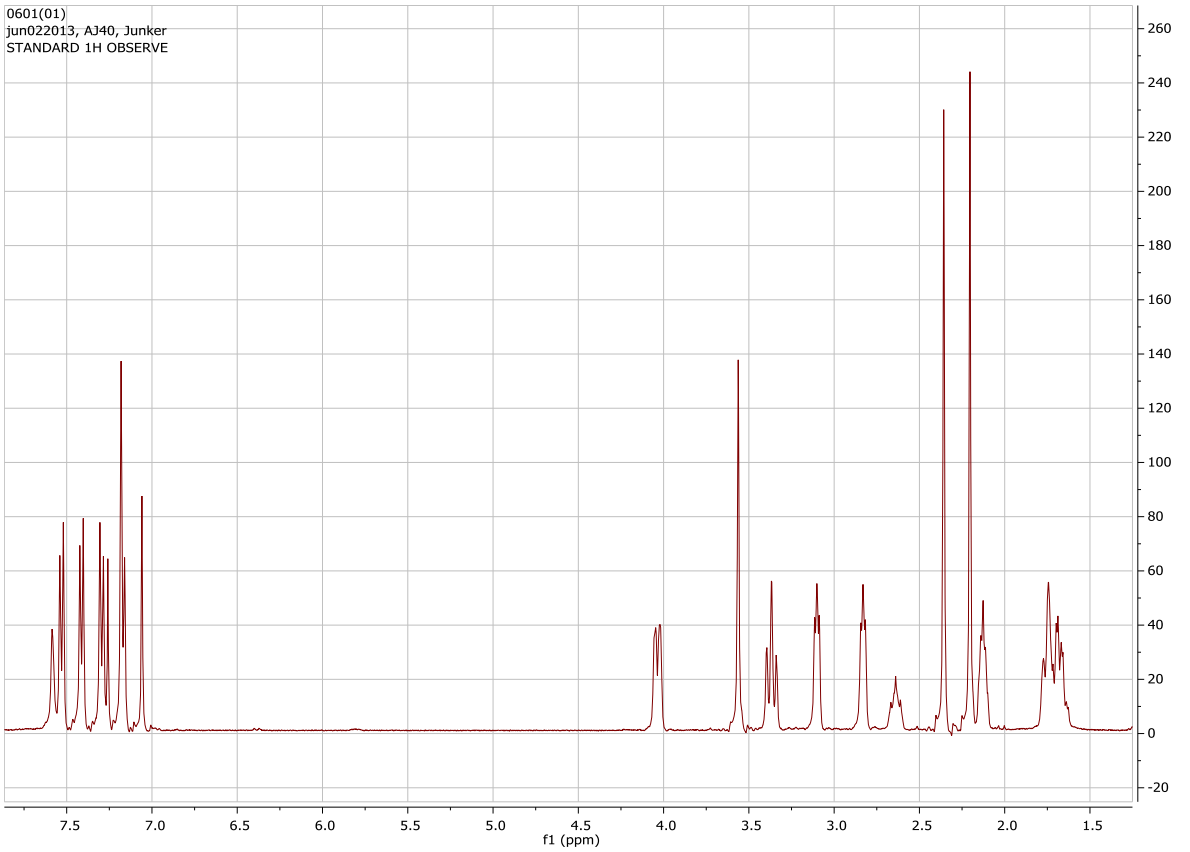
Acquisition Parameter

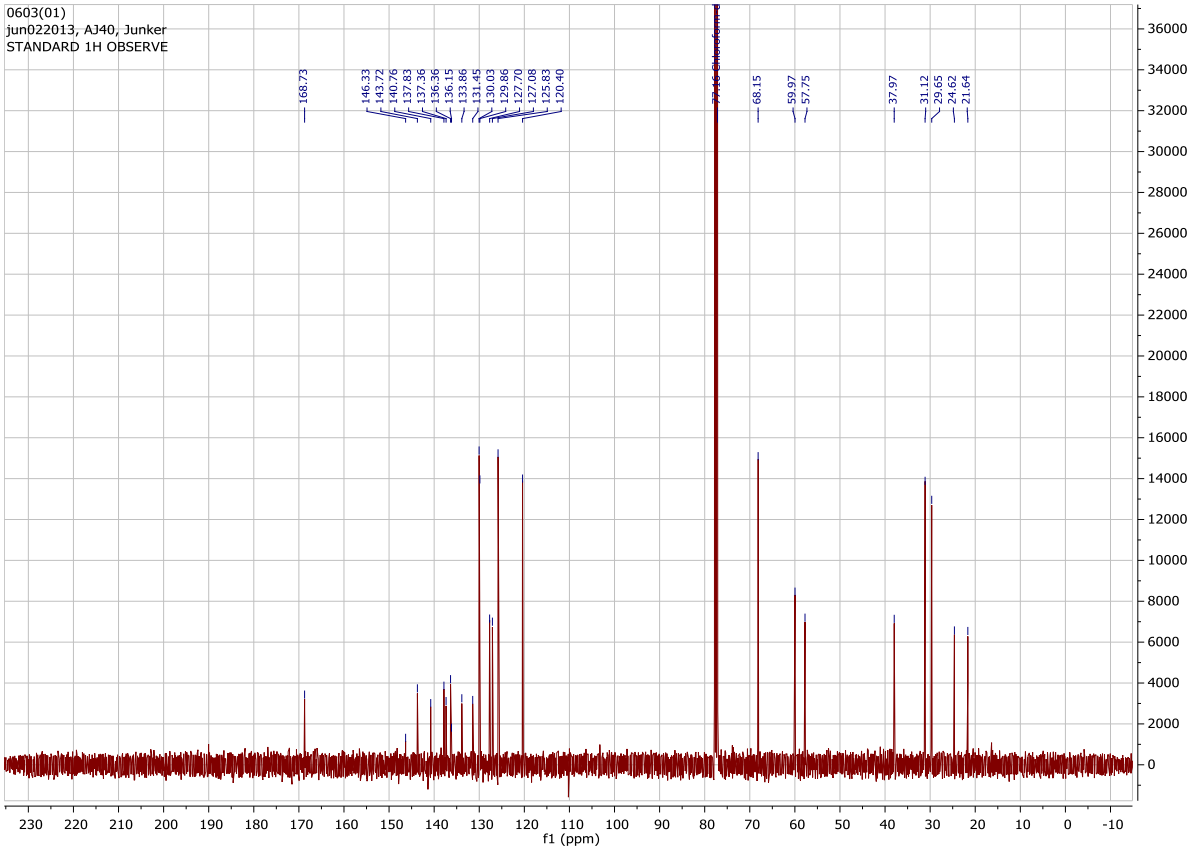
Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.7 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	3.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste

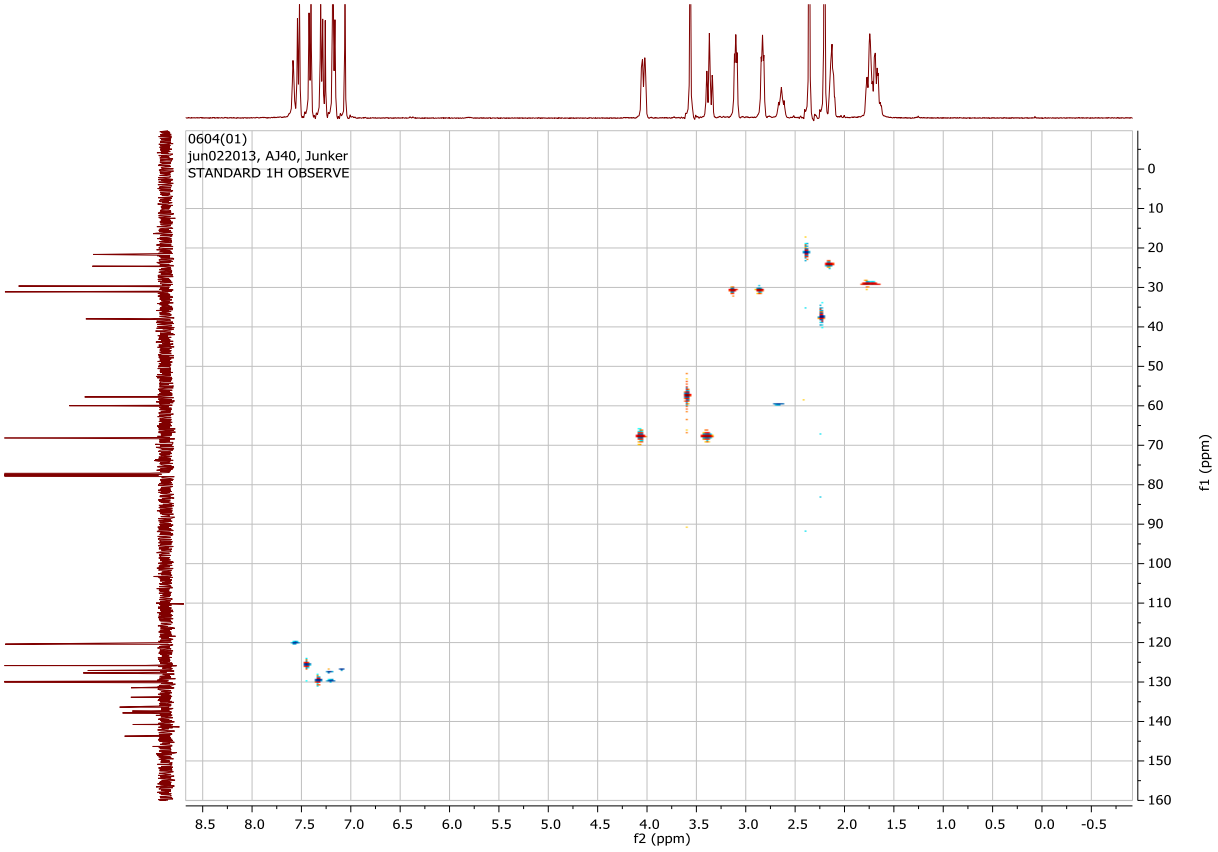


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
501.2223	1	C 35 H 33 O S	100.00	501.2247	2.4	4.7	192.9	19.5	even	ok
	2	C 30 H 33 N 2 O 3 S	21.82	501.2206	-1.7	-3.3	216.8	15.5	even	ok

*2-(4-Methylphenyl)-N-{4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl}-7,8-dihydro-6H-[7]annuleno[b]thiophene-5-carboxamide (**14a**)*






0604(01)
jun022013, AJ40, Junker
STANDARD 1H OBSERVE
f2 (ppm)
f1 (ppm)

HPLC

Analyzed: 06.02.13 19:20

Reported: 12.02.13 17:36
Processed: 12.02.13 17:36

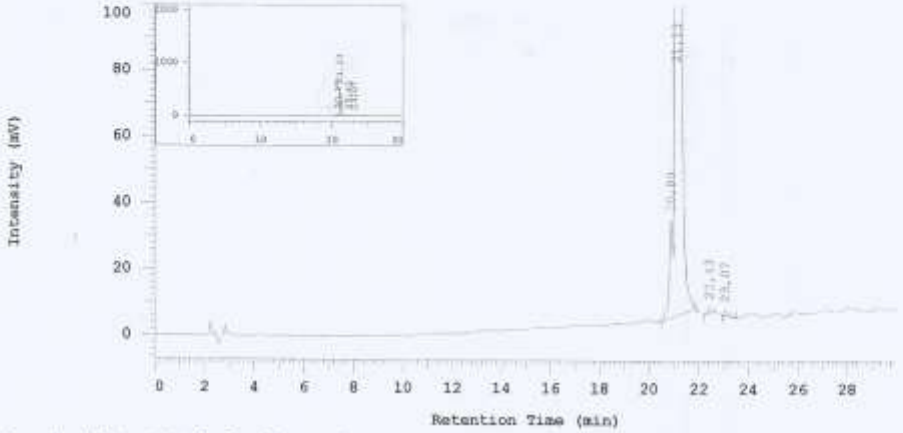
Data Path: D:\WIN32APP\HSM\Chromni\DATA\5913\
Application: Chromni

Sample Name: AJ40

Injection from this vial: 1 of 1

Series:5913
Vial Number: 2
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

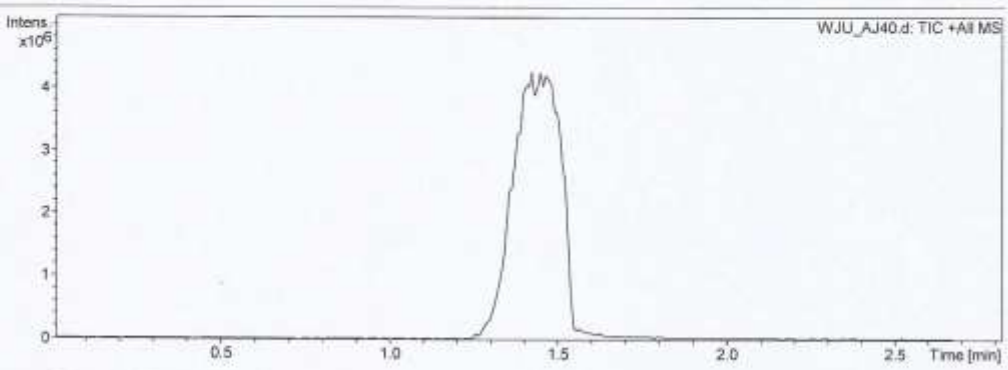
No.	RT	Area	Conc 1	BC
1	20,89	271402	4,285	MC
2	21,13	6026153	95,148	MC
3	22,43	14036	0,222	BB
4	23,07	21881	0,345	MC
		6333472	100,000	

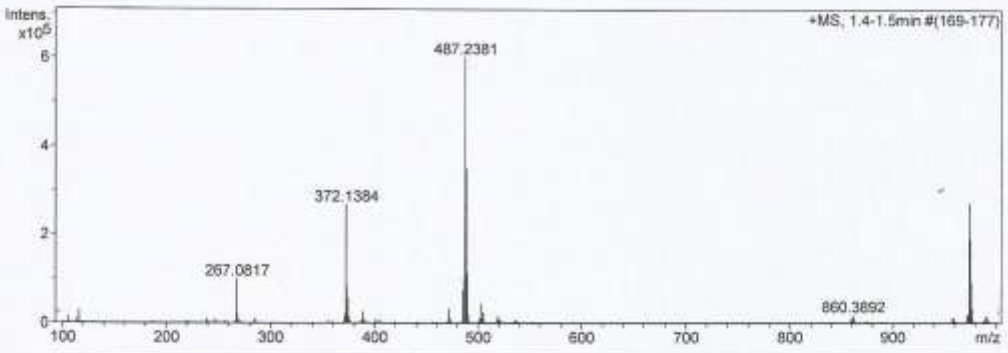
Peak rejection level: 0

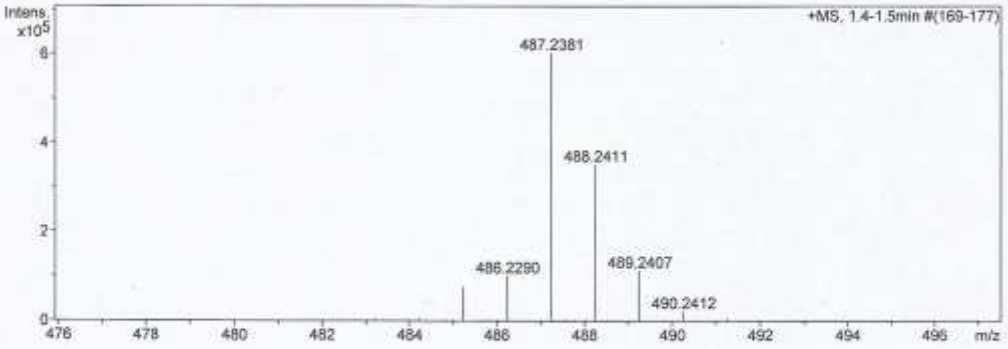
Generic Display Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\APCI\12_08\WJU_AJ40.d	Acquisition Date	8/29/2012 9:35:27 AM
Method	APCI_directprobe_positiv.m	Operator	Meiners
Sample Name	AJ40	Instrument	micrOTOF-Q II
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		







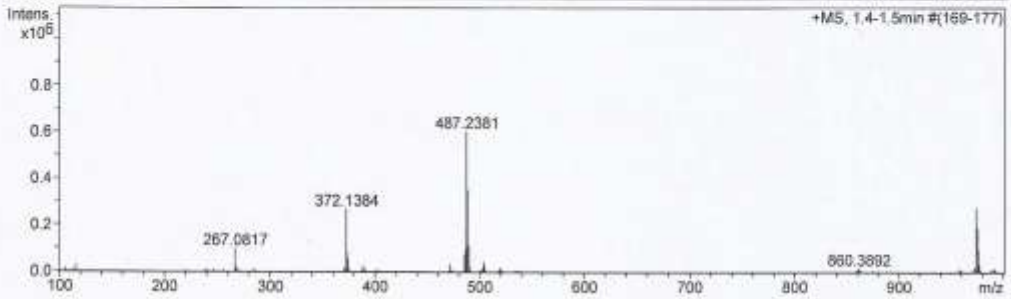
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\APCI\12_08\WJU_AJ40.d	Acquisition Date	8/29/2012 9:35:27 AM
Method	APCI_directprobe_positiv.m	Operator	Meiners
Sample Name	AJ40	Instrument / Ser#	micrOTOF-Q II 10252
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		

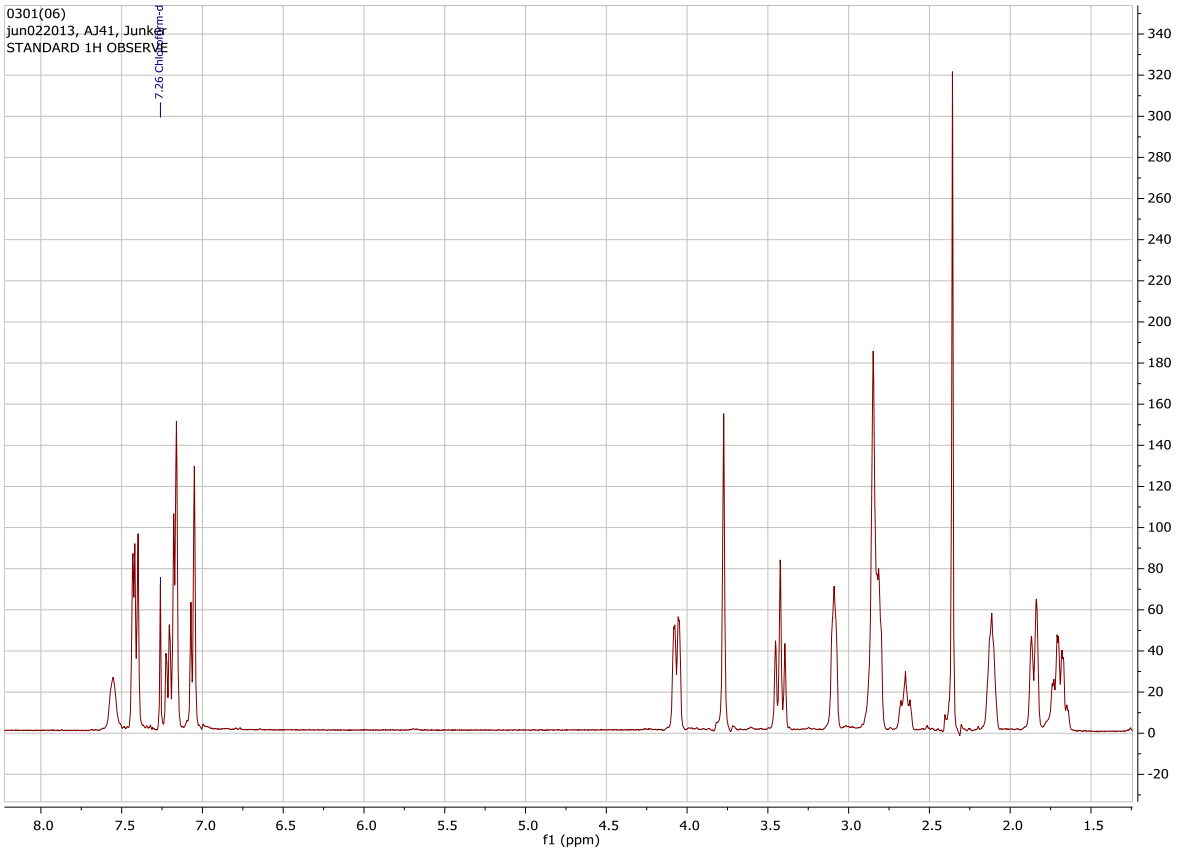
Acquisition Parameter

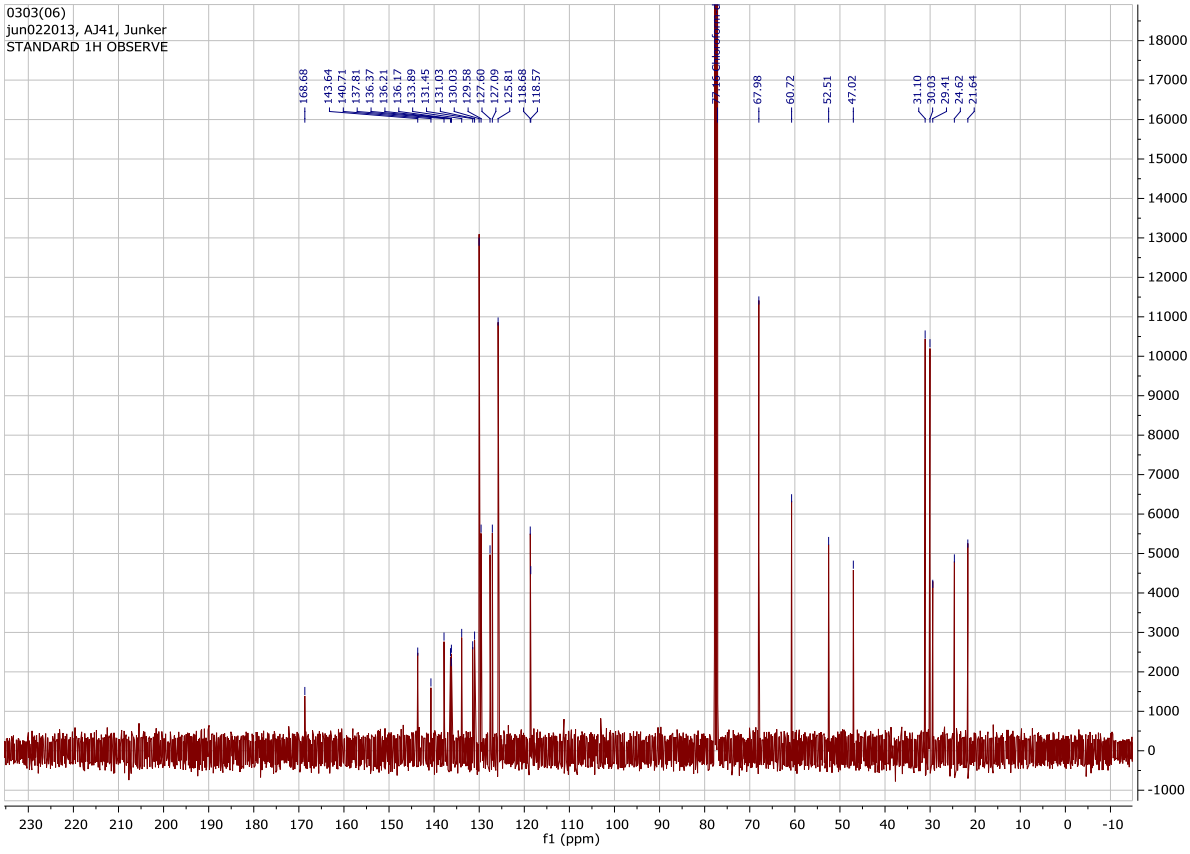
Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.7 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	3.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste

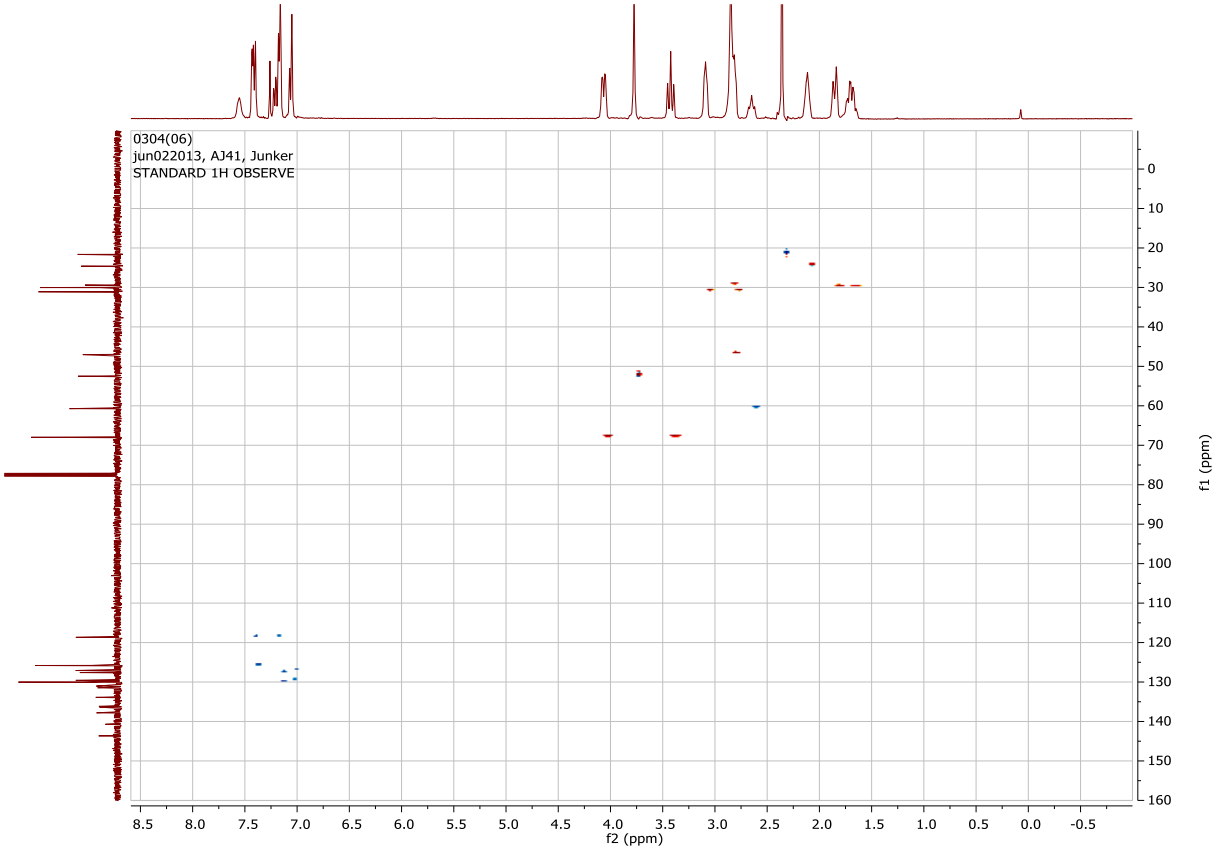


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
487.2381	1	C 30 H 35 N 2 O 2 S	20.76	487.2414	3.2	6.7	125.9	14.5	even	ok
	2	C 25 H 43 O 3 S 3	100.00	487.2369	-1.2	-2.6	126.8	4.5	even	ok
	3	C 21 H 39 N 6 O S 3	5.22	487.2342	-3.9	-8.1	136.6	5.5	even	ok
	4	C 26 H 31 N 8 S	75.20	487.2387	0.6	1.1	138.1	15.5	even	ok
	5	C 22 H 47 O 3 S 4	26.36	487.2403	2.1	4.4	138.9	-0.5	even	ok
	6	C 23 H 35 N 8 S 2	3.16	487.2421	3.9	8.1	144.6	10.5	even	ok
	7	C 18 H 43 N 6 O S 4	40.67	487.2376	-0.6	-1.2	147.8	0.5	even	ok
	8	C 25 H 35 N 4 O 4 S	31.90	487.2374	-0.8	-1.6	149.8	10.5	even	ok
	9	C 22 H 39 N 4 O 4 S 2	5.55	487.2407	2.6	5.3	156.9	5.5	even	ok
	10	C 15 H 39 N 10 O 2 S 3	2.47	487.2414	3.3	6.7	159.1	1.5	even	ok
	11	C 24 H 39 O 8 S	5.95	487.2360	-2.1	-4.3	161.7	5.5	even	ok
	12	C 21 H 31 N 10 O 2 S	1.70	487.2347	-3.5	-7.1	161.8	11.5	even	ok
	13	C 18 H 35 N 10 O 2 S 2	12.21	487.2380	-0.1	-0.2	168.4	6.5	even	ok
	14	C 21 H 43 O 8 S 2	6.35	487.2394	1.3	2.6	169.2	0.5	even	ok
	15	C 14 H 31 N 16 S 2	0.88	487.2354	-2.8	-5.7	180.0	7.5	even	ok
	16	C 17 H 39 N 6 O 6 S 2	2.42	487.2387	-1.4	-2.9	180.6	1.5	even	ok
	17	C 15 H 31 N 14 O 3 S	0.18	487.2419	3.7	7.7	187.3	7.5	even	ok
	18	C 14 H 35 N 10 O 7 S	0.27	487.2405	2.4	4.9	198.9	2.5	even	ok
	19	C 11 H 27 N 20 O S	0.58	487.2392	1.1	2.2	201.0	8.5	even	ok

*2-(4-Methylphenyl)-N-[2-(tetrahydro-2H-pyran-4-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-7,8-dihydro-6H-[7]annuleno[b]thiophene-5-carboxamide (**14b**)*






0304(06)
jun022013, AJ41, Junker
STANDARD 1H OBSERVE
f2 (ppm)
f1 (ppm)

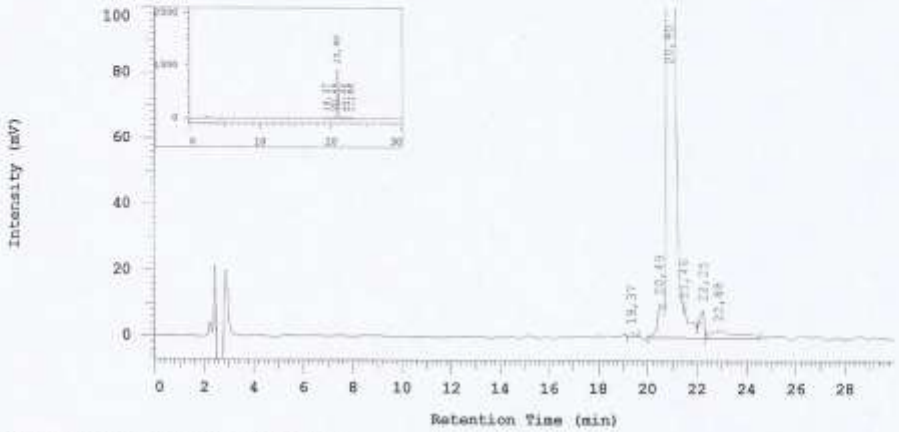
HPLC

Analyzed: 18.07.12 22:04
Reported: 19.07.12 13:28
Processed: 19.07.12 13:28

Data Path: D:\WIN32APP\HSM\Chromni\DATA\5000\
Application: Chromni
Series:5000

Sample Name: AJ4101
Vial Number: 4
Vial Type: UNK
Injection from this vial: 1 of 1
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

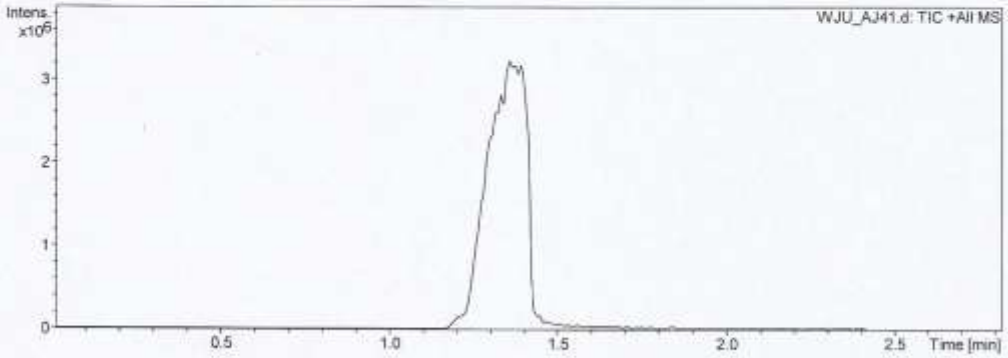
No.	RT	Area	Conc 1	BC
1	19,37	16512	0,130	MC
2	20,49	178338	1,408	MC
3	20,90	12013283	94,848 ✓	MC
4	21,48	166125	1,312	MC
5	22,25	117703	0,929	MC
6	22,88	173882	1,373	MC
		12665843	100,000	

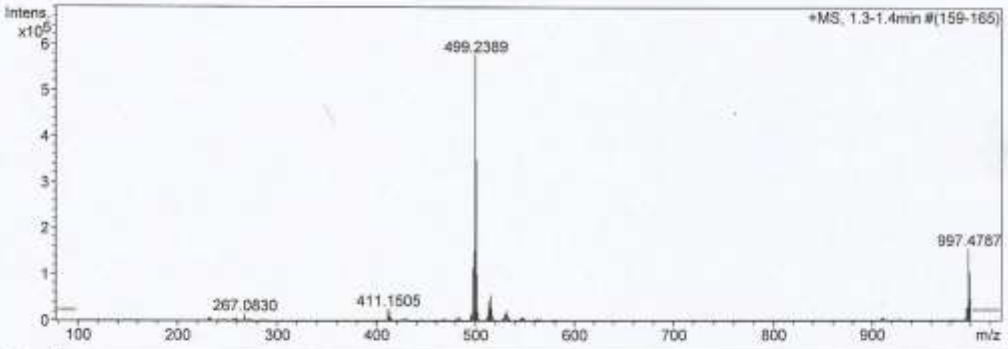
Peak rejection level: 0

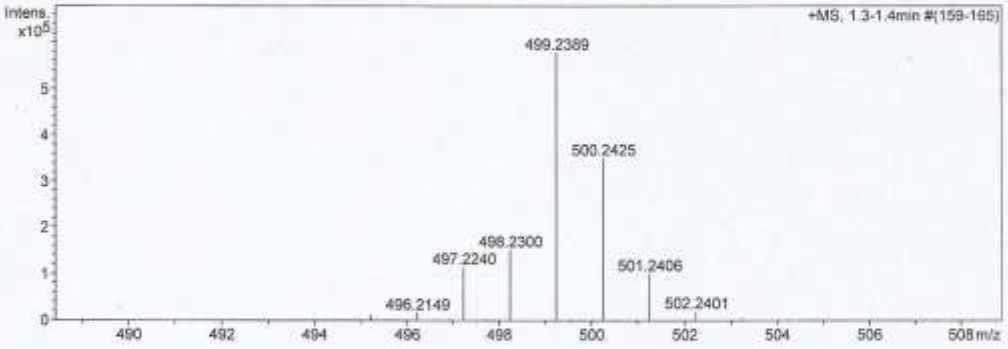
Generic Display Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\APCI\12_08\WJU_AJ41.d	Acquisition Date	8/29/2012 9:25:00 AM
Method	APCI_directprobe_positiv.m	Operator	Meiners
Sample Name	AJ41	Instrument	micrOTOF-Q II
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		







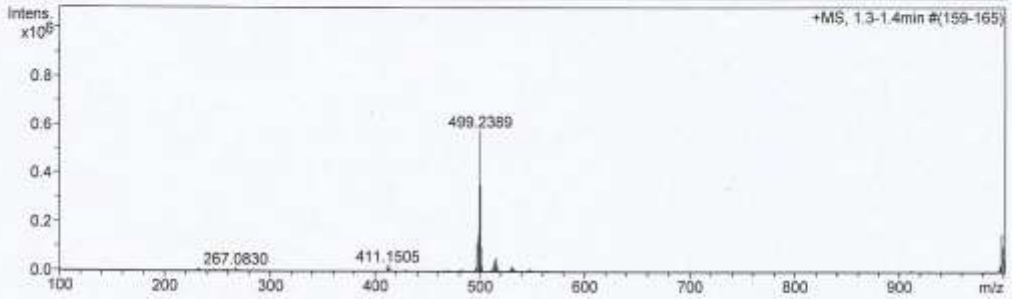
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\APCI\12_08\WJU_AJ41.d	Acquisition Date	8/29/2012 9:25:00 AM
Method	APCI_directprobe_positiv.m	Operator	Meiners
Sample Name	AJ41	Instrument / Ser#	micrOTOF-Q II 10252
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		

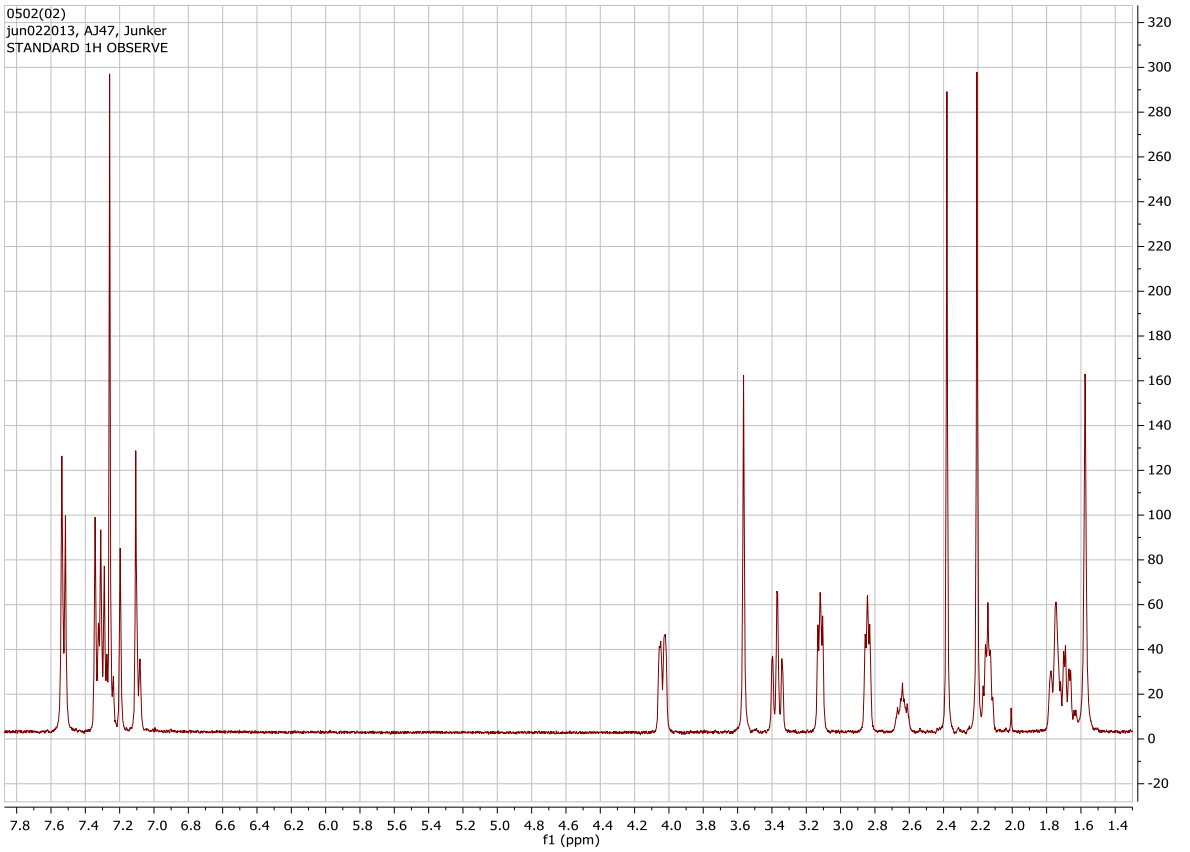
Acquisition Parameter

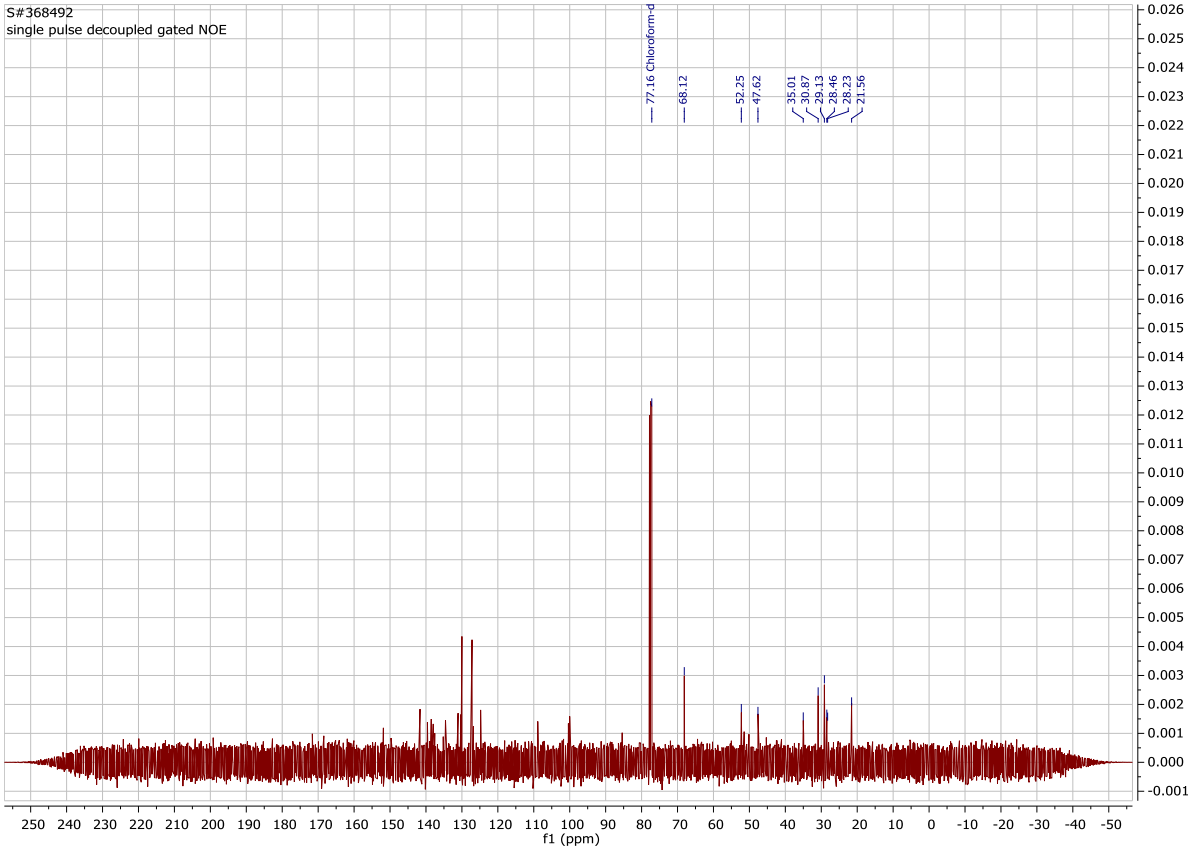
Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.7 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	3.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste

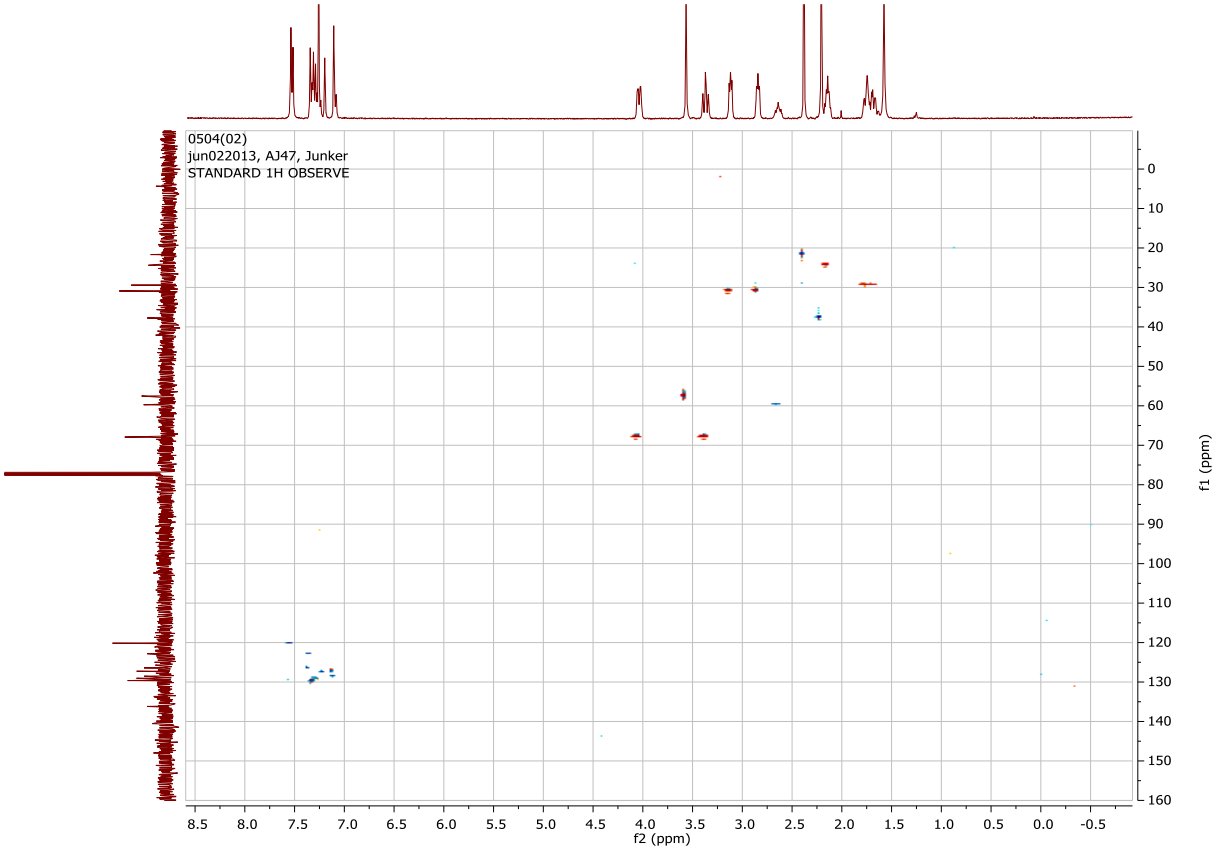


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
499.2389	1	C 31 H 35 N 2 O 2 S	49.01	499.2414	2.5	4.9	129.6	15.5	even	ok
	2	C 26 H 43 O 3 S 3	58.43	499.2369	-2.0	-4.1	132.7	5.5	even	ok
	3	C 27 H 31 N 8 S	100.00	499.2387	-0.2	-0.4	141.5	16.5	even	ok
	4	C 23 H 47 O 3 S 4	42.39	499.2403	1.3	2.7	145.6	0.5	even	ok
	5	C 24 H 35 N 8 S 2	7.51	499.2421	3.2	6.3	149.6	11.5	even	ok
	6	C 26 H 35 N 4 O 4 S	21.76	499.2374	-1.6	-3.1	153.7	11.5	even	ok
	7	C 19 H 43 N 6 O S 4	24.27	499.2376	-1.3	-2.7	154.2	1.5	even	ok
	8	C 23 H 39 N 4 O 4 S 2	10.24	499.2407	1.8	3.6	162.0	6.5	even	ok
	9	C 16 H 39 N 10 O 2 S 3	5.00	499.2414	2.5	5.0	164.5	2.5	even	ok
	10	C 25 H 39 O 8 S	3.19	499.2360	-2.9	-5.8	165.8	6.5	even	ok
	11	C 19 H 35 N 10 O 2 S 2	8.22	499.2380	-0.9	-1.7	173.4	7.5	even	ok
	12	C 12 H 35 N 16 S 3	10.75	499.2387	-0.2	-0.4	174.2	3.5	even	ok
	13	C 22 H 43 O 8 S 2	9.27	499.2394	0.5	1.0	174.4	1.5	even	ok
	14	C 15 H 31 N 16 S 2	0.39	499.2354	-3.6	-7.1	184.8	8.5	even	ok
	15	C 18 H 39 N 6 O 6 S 2	1.30	499.2367	-2.2	-4.4	185.7	2.5	even	ok
	16	C 16 H 31 N 14 O 3 S	0.43	499.2419	3.0	5.9	191.2	8.5	even	ok
	17	C 15 H 35 N 10 O 7 S	0.46	499.2405	1.6	3.3	203.0	3.5	even	ok
	18	C 12 H 27 N 20 O S	0.88	499.2392	0.3	0.6	204.8	9.5	even	ok
	19	C 11 H 31 N 16 O 5 S	0.25	499.2379	-1.1	-2.1	214.6	4.5	even	ok

*N-{4-[N-Methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl}-2-(3-methylphenyl)-7,8-dihydro-6H-[7]annuleno[b]thiophene-5-carboxamide (**14d**)*






0504(02)
jun022013, AJ47, Junker
STANDARD 1H OBSERVE
f2 (ppm)
f1 (ppm)

HPLC

Analyzed: 19.07.12 00:08

Reported: 19.07.12 13:32
Processed: 19.07.12 13:32

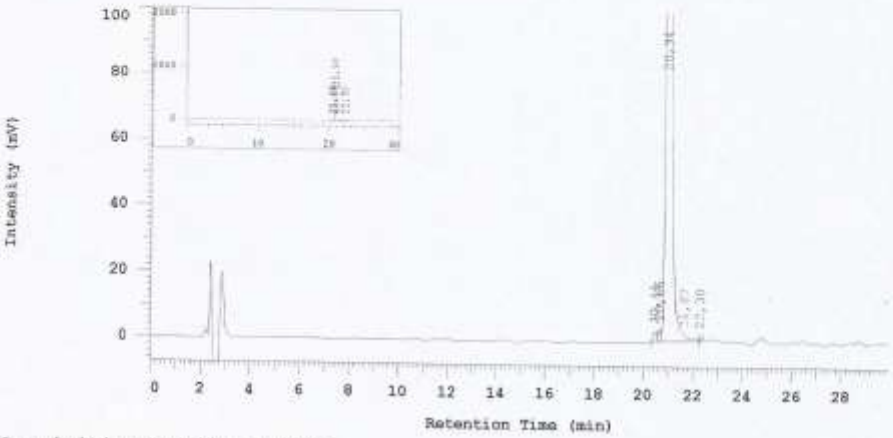
Data Path: D:\WIN32APP\HSM\Chromni\DATA\5003\
Application: Chromni

Sample Name: AJ4701

Injection from this vial: 1 of 1

Series:5003
Vial Number: 7
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

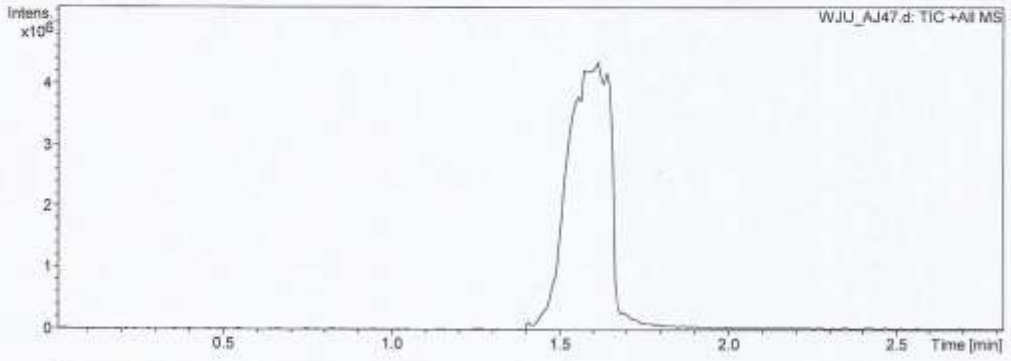
No.	RT	Area	Conc 1	BC
1	20,46	25001	0,408	MC
2	20,66	30570	0,499	MC
3	20,94	5933442	96,905	MC
4	21,67	128176	2,093	MC
5	22,30	5741	0,094	MC
		6122930	100,000	

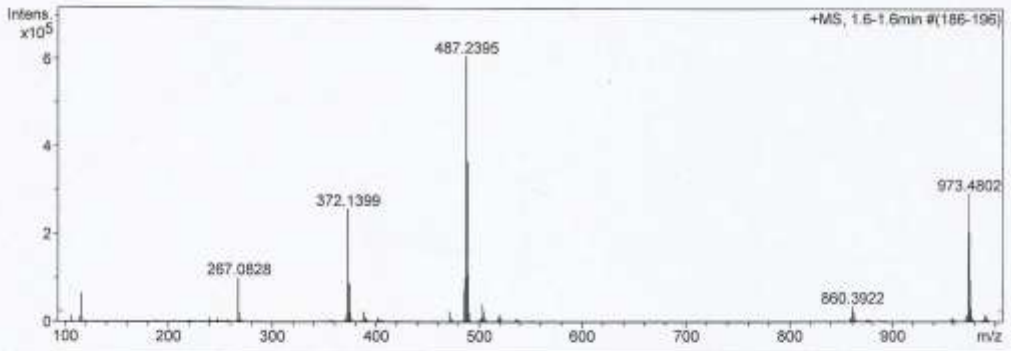
Peak rejection level: 0

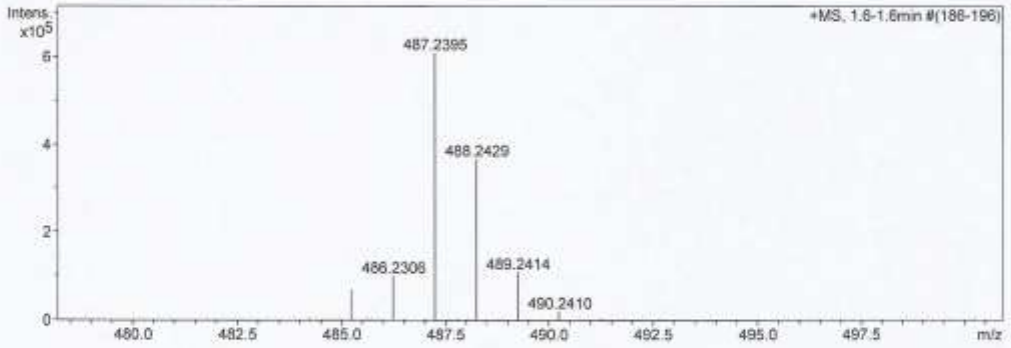
Generic Display Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\APCI\12_08\WJU_AJ47.d	Acquisition Date	8/29/2012 8:37:55 AM
Method	APCI_directprobe_positiv.m	Operator	Meiners
Sample Name	AJ47	Instrument	micrOTOF-Q II
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		







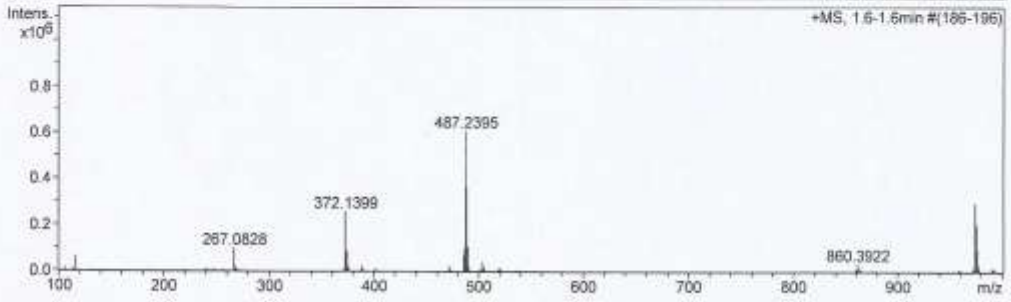
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\IPMC\PharmChemie\Routine\APCI\12_08\WJU_AJ47.d	Acquisition Date	8/29/2012 8:37:55 AM
Method	APCI_directprobe_positiv.m	Operator	Meiners
Sample Name	AJ47	Instrument / Ser#	micrOTOF-Q II 10252
Comment	Junker APCI-Direkt Kalibration mit Fettsaeureestern		

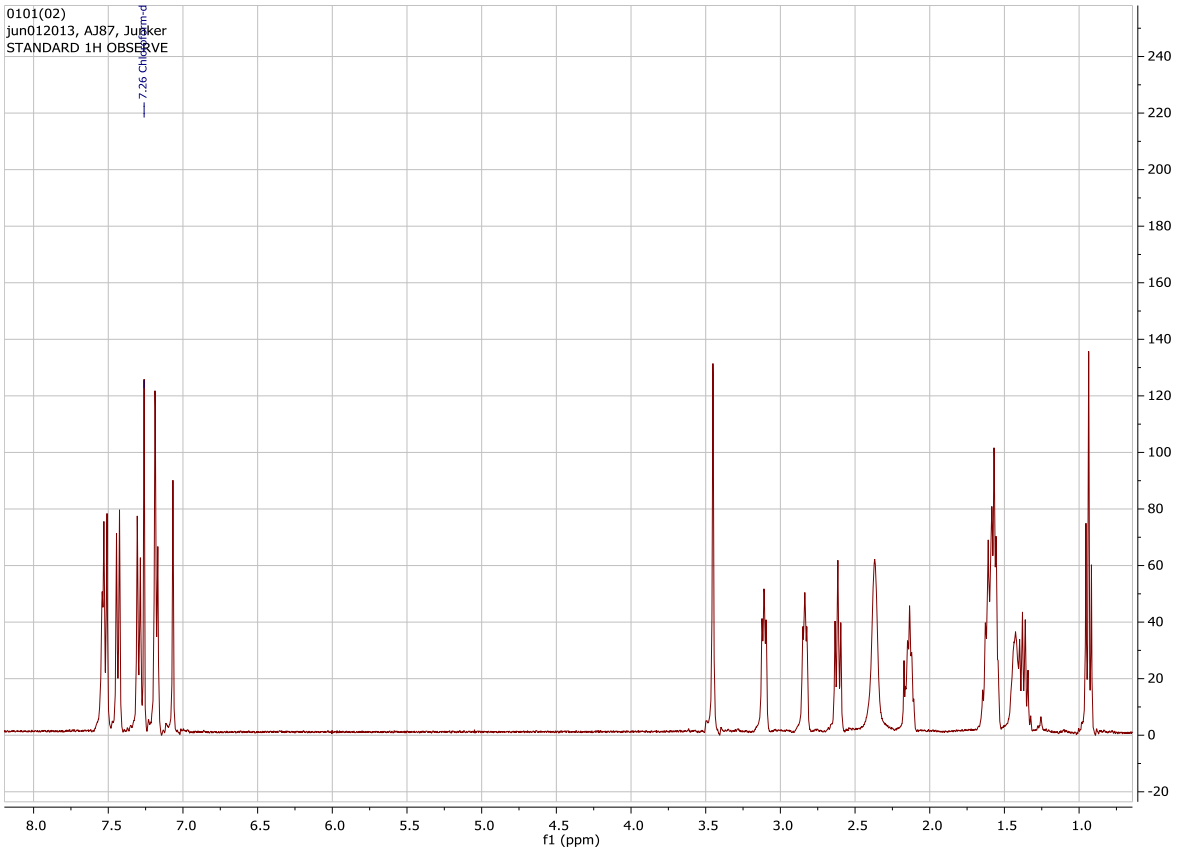
Acquisition Parameter

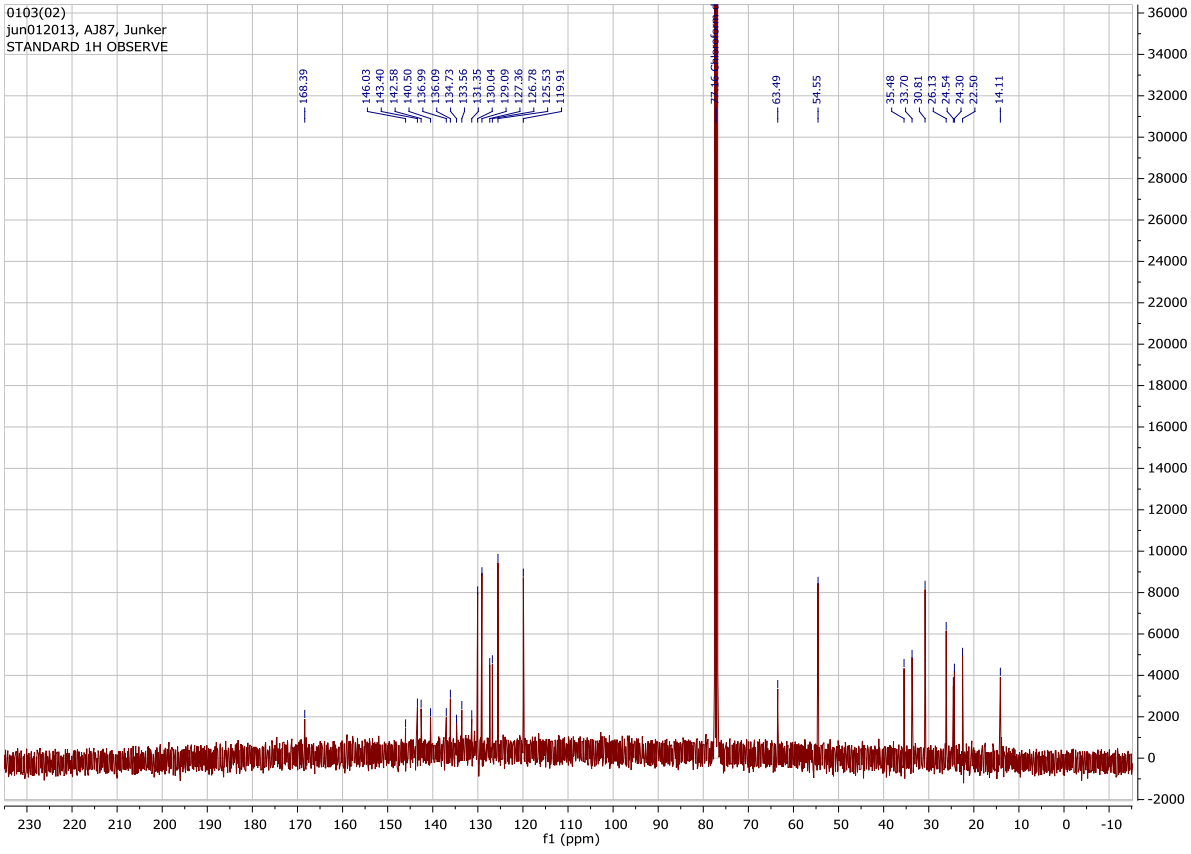
Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.7 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	3.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste

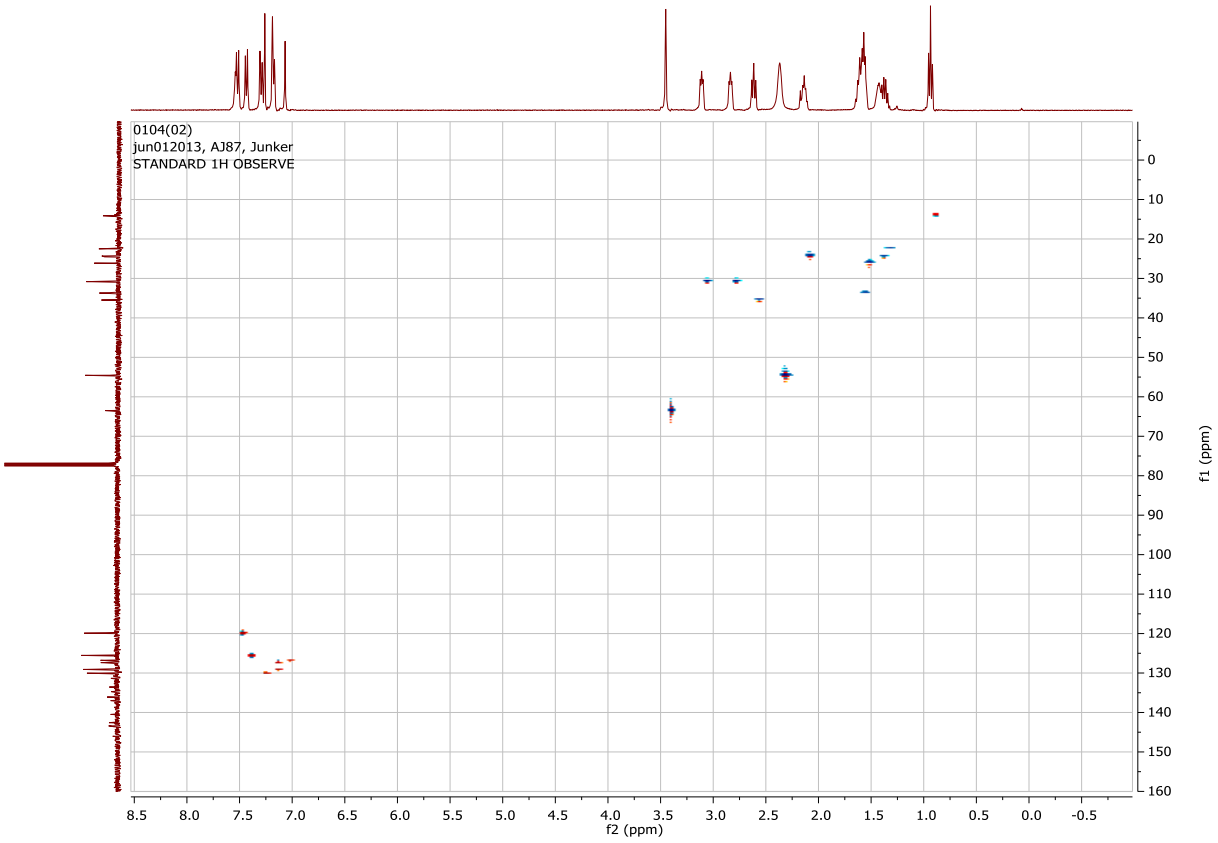


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
487.2395	1	C 30 H 35 N 2 O 2 S	100.00	487.2414	1.9	3.8	134.4	14.5	even	ok
	2	C 25 H 43 O 3 S 3	48.64	487.2369	-2.6	-5.4	135.9	4.5	even	ok
	3	C 26 H 31 N 6 S	90.65	487.2387	-0.8	-1.7	146.5	15.5	even	ok
	4	C 22 H 47 O 3 S 4	84.91	487.2403	0.7	1.5	148.3	-0.5	even	ok
	5	C 23 H 35 N 6 S 2	16.68	487.2421	2.5	5.2	154.0	10.5	even	ok
	6	C 18 H 43 N 6 O S 4	21.86	487.2376	-1.9	-4.0	157.1	0.5	even	ok
	7	C 19 H 43 N 4 O 4 S 3	1.36	487.2441	4.6	9.4	158.2	0.5	even	ok
	8	C 25 H 35 N 4 O 4 S	16.80	487.2374	-2.2	-4.4	158.5	10.5	even	ok
	9	C 22 H 39 N 4 O 4 S 2	19.00	487.2407	1.2	2.5	166.3	5.5	even	ok
	10	C 15 H 39 N 10 O 2 S 3	10.64	487.2414	1.9	3.9	167.9	1.5	even	ok
	11	C 21 H 31 N 10 O 2 S	0.40	487.2347	-4.9	-10.0	170.3	11.5	even	ok
	12	C 24 H 39 O 6 S	2.05	487.2360	-3.5	-7.2	170.5	5.5	even	ok
	13	C 18 H 35 N 10 O 2 S 2	6.86	487.2380	-1.5	-3.0	177.7	6.5	even	ok
	14	C 21 H 43 O 6 S 2	13.17	487.2394	-0.1	-0.3	178.7	0.5	even	ok
	15	C 14 H 31 N 16 S 2	0.23	487.2354	-4.2	-8.6	189.2	7.5	even	ok
	16	C 17 H 39 N 6 O 6 S 2	0.91	487.2367	-2.8	-5.8	190.0	1.5	even	ok
	17	C 15 H 31 N 14 O 3 S	0.84	487.2419	2.4	4.8	195.9	7.5	even	ok
	18	C 18 H 39 N 4 O 9 S	0.22	487.2432	3.7	7.6	196.0	1.5	even	ok
	19	C 14 H 35 N 10 O 7 S	0.79	487.2405	1.0	2.1	207.6	2.5	even	ok
	20	C 11 H 27 N 20 O S	0.95	487.2392	-0.3	-0.7	209.5	8.5	even	ok

*2-(4-Butylphenyl)-N-[4-(piperidin-1-ylmethyl)phenyl]-7,8-dihydro-6H-[7]annuleno[b]thiophene-5-carboxamide (**14g**)*






0104(02)
jun012013, AJ87, Junker
STANDARD 1H OBSERVE
f2 (ppm)
f1 (ppm)

HPLC

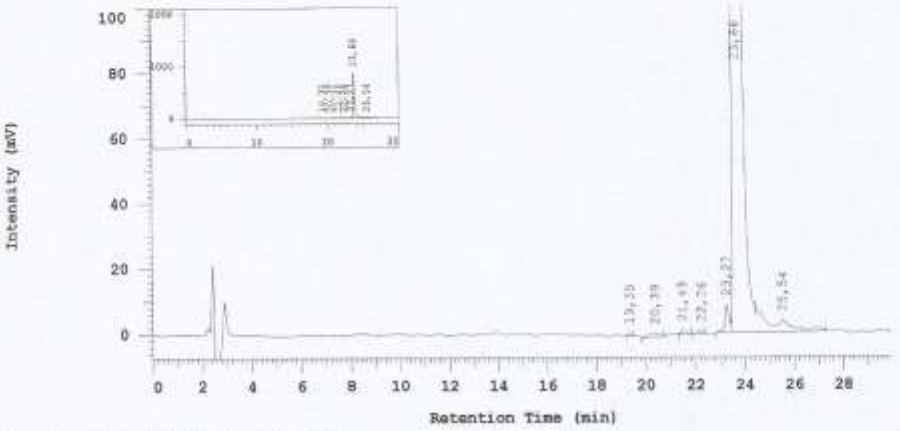
Analyzed: 10.01.13 03:21

Reported: 10.01.13 10:18
Processed: 10.01.13 10:17

Data Path: D:\WIN32APP\HSM\Chromni\DATA\5799\
Application: Chromni
Sample Name: AJ 87
Injection from this vial: 1 of 1

Series:5799
Vial Number: 8
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

No.	RT	Area	Conc 1	BC
1	19,35	8348	0,058	MC
2	20,39	29633	0,206	MC
3	21,49	15280	0,106	BB
4	22,26	14512	0,101	MC
5	23,27	97290	0,675	MC
6	23,66	13896507	96,435	MC
7	25,54	348676	2,420	MC
		14410246	100,000	

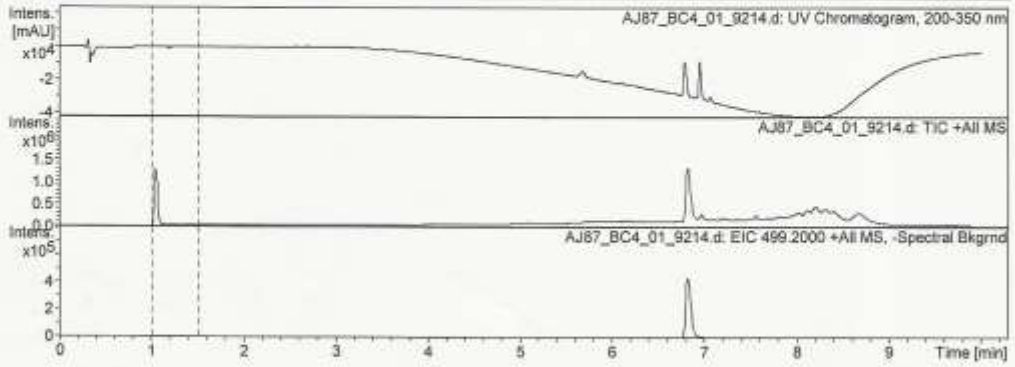
Peak rejection level: 0

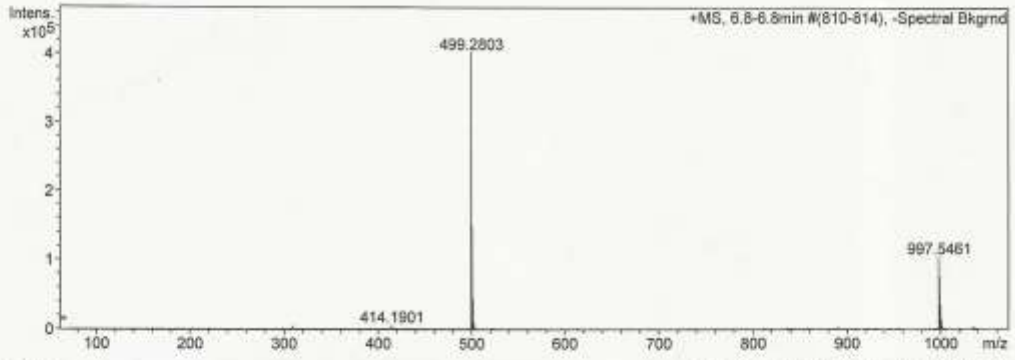
→ NMR

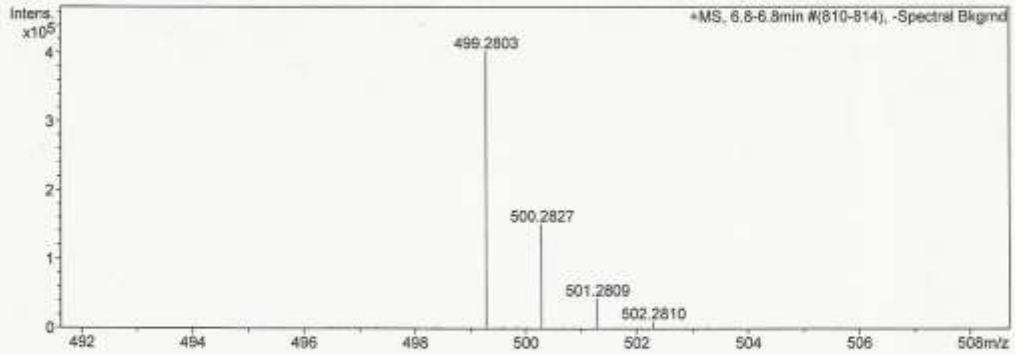
Generic Display Report

Analysis Info

Analysis Name	E:\Meiners\2013_01_14\AJ87_BC4_01_9214.d	Acquisition Date	1/14/2013 5:59:35 PM
Method	tune_low_lcms_routine_positiv_10min.m	Operator	Meiners
Sample Name	AJ87	Instrument	micrOTOF-Q II
Comment	Junker Kalibration mit Li-Formate		







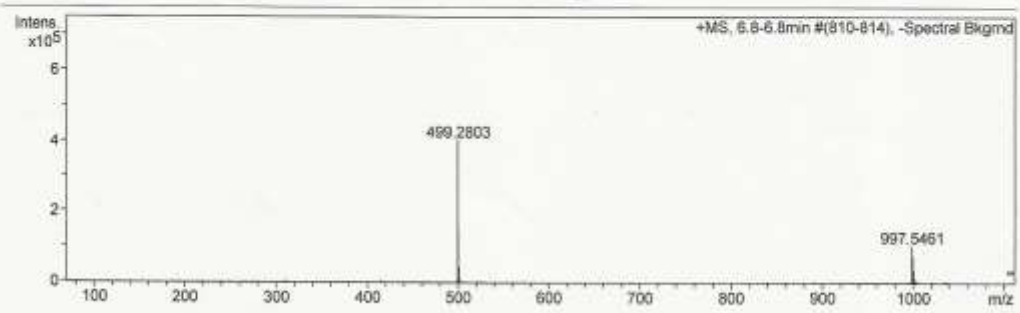
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	E:\Meiners\2013_01_14\AJ87_BC4_01_9214.d	Acquisition Date	1/14/2013 5:59:35 PM
Method	tune_low_lcms_routine_positiv_10min.m	Operator	Meiners
Sample Name	AJ87	Instrument / Ser#	micrOTOF-Q II 10252
Comment	Junker Kalibration mit Li-Formate		

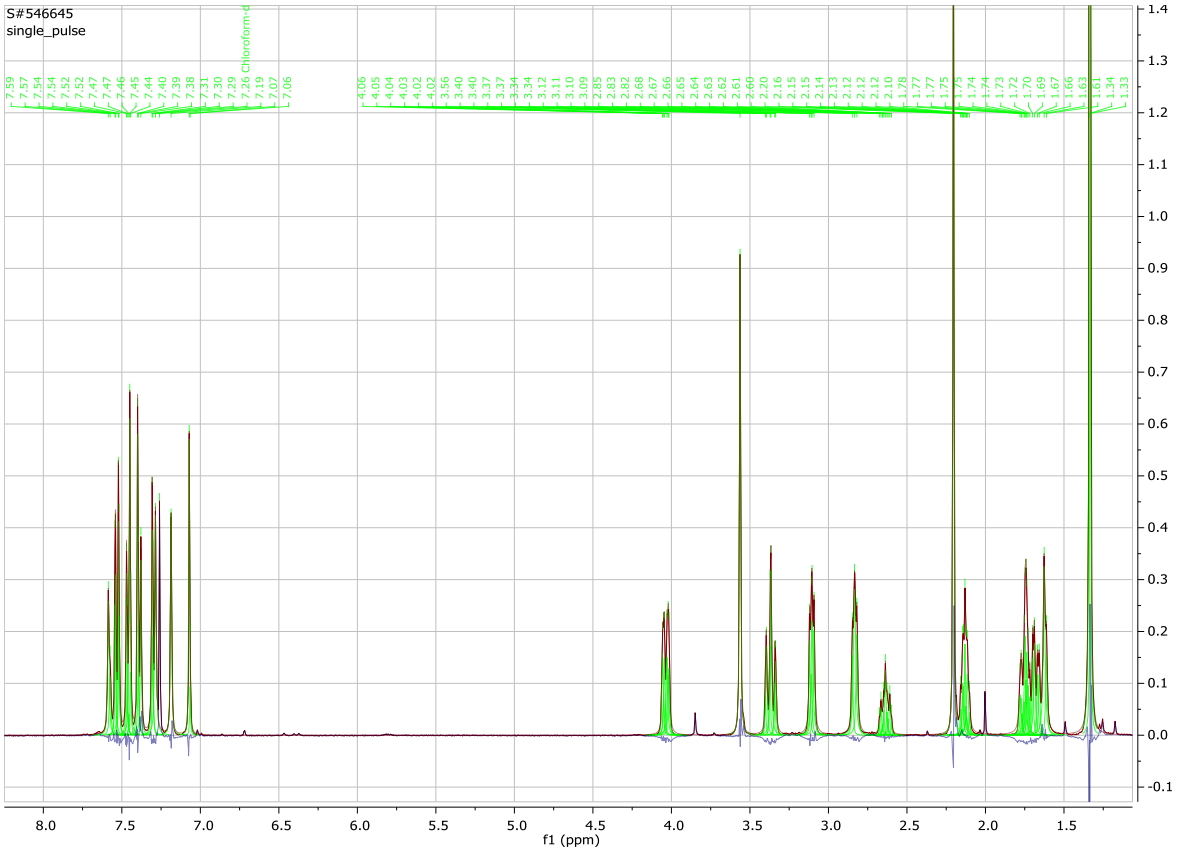
Acquisition Parameter

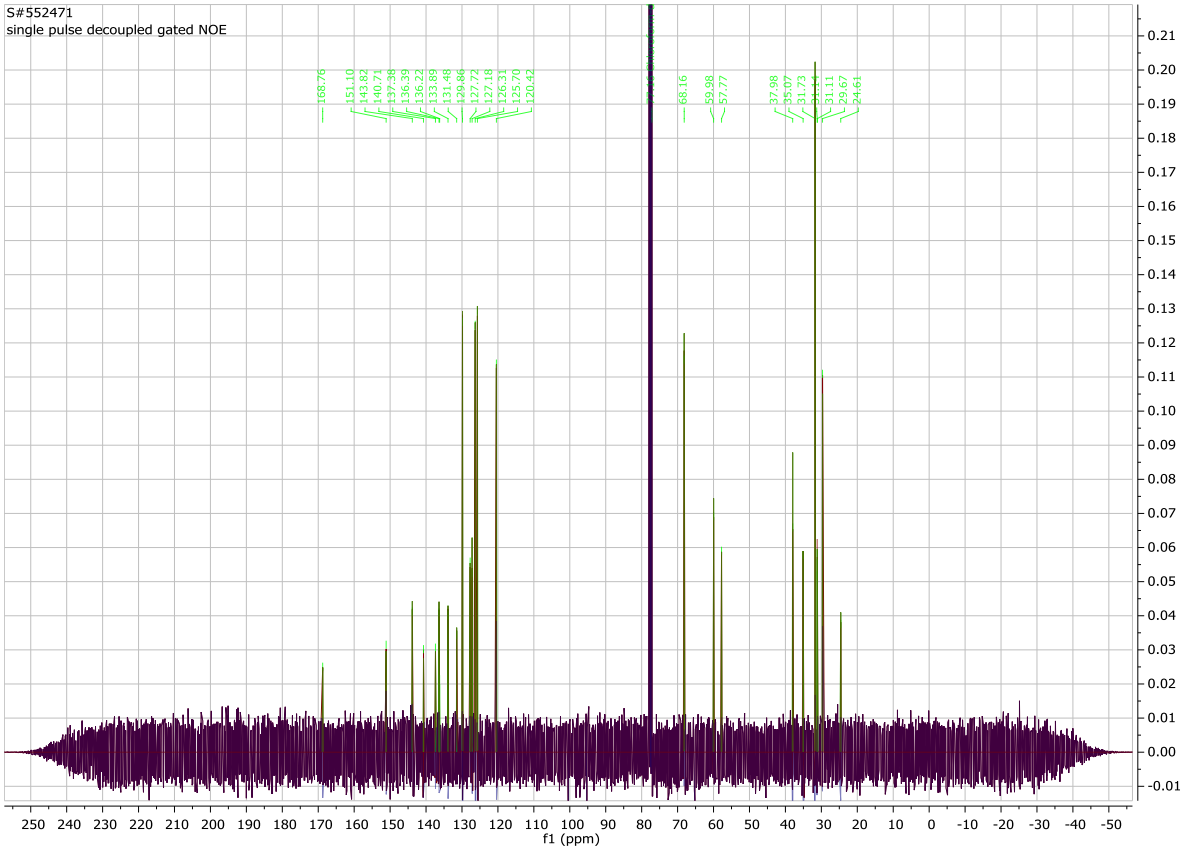
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	2.0 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	9.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	300.0 Vpp	Set Divert Valve	Waste



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
499.2803	1	C 32 H 39 N 2 O S	44.52	499.2778	-2.5	-5.1	4.3	14.5	even	ok
	2	C 29 H 43 N 2 O S 2	100.00	499.2811	0.8	1.7	23.7	9.5	even	ok

*2-(4-tert-Butylphenyl)-N-{4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl}-7,8-dihydro-6H-[7]annuleno[b]thiophene-5-carboxamide (**14h**)*





HPLC

Analyzed: 19.07.12 01:31

Reported: 19.07.12 13:34
Processed: 19.07.12 13:34

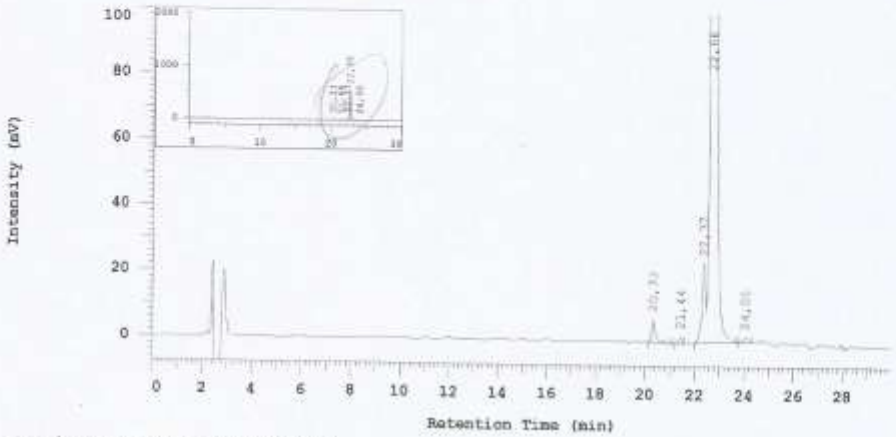
Data Path: D:\WIN32APP\HSM\Chromni\DATA\5005\
Application: Chromni

Sample Name: AJ7001

Injection from this vial: 1 of 1

Series:5005
Vial Number: 8
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1



Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

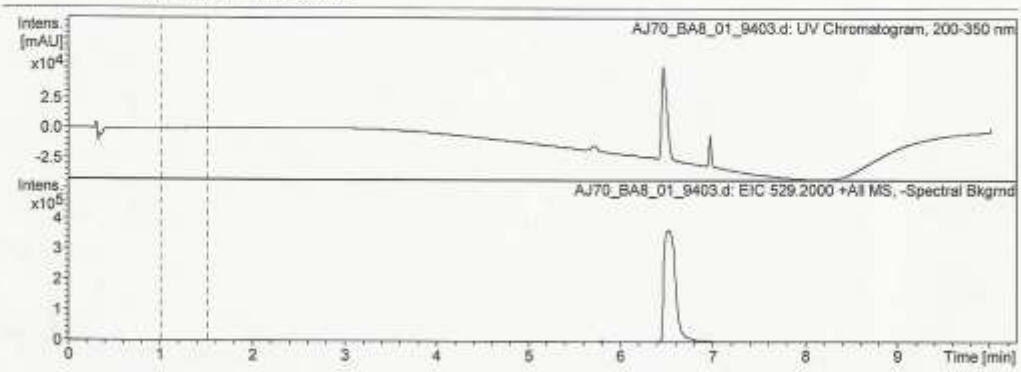
No.	RT	Area	Conc 1	BC
1	20,33	75324	1,001	BB
2	21,44	17628	0,234	MC
3	22,37	240727	3,198	MC
4	22,66	7172172	95,281	MC
5	24,05	21550	0,286	MC
		7527401	100,000	

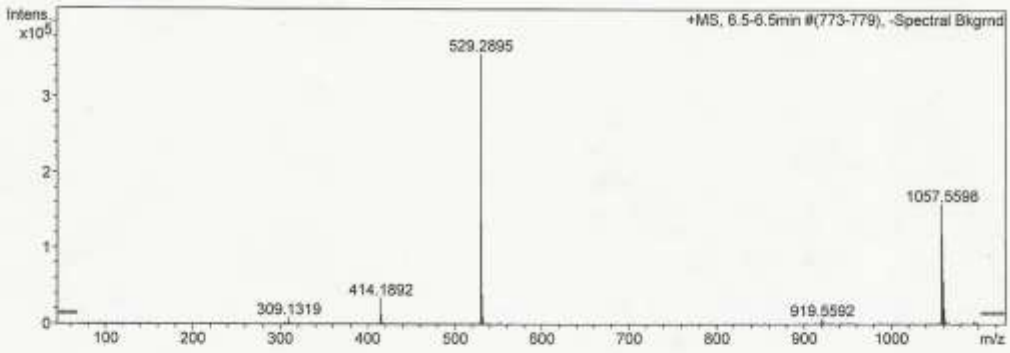
Peak rejection level: 0

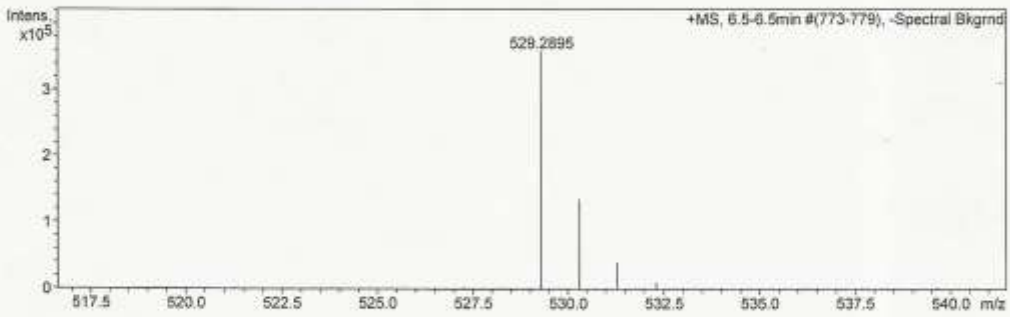
Generic Display Report

Analysis Info

Analysis Name	E:\Meiners\2013_01_28\AJ70_BA8_01_9403.d	Acquisition Date	1/28/2013 3:27:48 PM
Method	tune_low_lcms_routine_positiv_10min.m	Operator	Meiners
Sample Name	AJ70	Instrument	micrOTOF-Q II
Comment	Junker LCMS-ESI+ Kalibration mit LI-Formate		







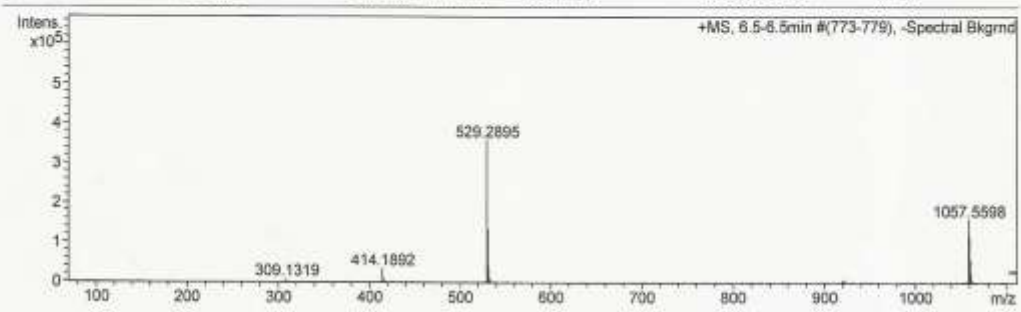
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	E:\Meiners\2013_01_28\AJ70_BA8_01_9403.d	Acquisition Date	1/28/2013 3:27:48 PM
Method	tune_low_lcms_routine_positiv_10min.m	Operator	Meiners
Sample Name	AJ70	Instrument / Ser#	micrOTOF-Q II 10252
Comment	Junker LCMS-ESI+ Kalibration mit Li-Formate		

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	2.0 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	9.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	300.0 Vpp	Set Divert Valve	Waste



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
529.2895	1	C 33 H 41 N 2 O 2 S	100.00	529.2883	-1.2	-2.3	4.9	14.5	even	ok
	2	C 29 H 37 N 8 S	8.80	529.2856	-3.9	-7.4	8.9	15.5	even	ok
	3	C 30 H 45 N 2 O 2 S 2	35.88	529.2917	2.2	4.1	23.0	9.5	even	ok
	4	C 38 H 41 S	19.48	529.2923	2.8	5.3	25.1	18.5	even	ok