SUPPORTING INFORMATION

for

Synthesis of aminomethylated 4-fluoropiperidines and 3-fluoropyrrolidines

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Synthetic procedures and spectroscopic data for all new compounds 6 - 8, 10, 17 -20.

***tert*-Butyl 4-bromomethyl-4-fluoropiperidine-1-carboxylate (6).** To a solution of 1-*tert*-butyl 4-methylenepiperidine **5** (1.5 g, 7.6 mmol) in dry CH_2Cl_2 (40 mL) was added $Et_3N.3HF$ (3.1 mL, 2.5 equiv) with a syringe at 0°C. Subsequently, NBS (2.03 g, 1.5 equiv) was added at 0°C and the mixture was stirred at room temperature for 3 h. After the reaction was completed, the mixture was poured in aq. 0.5 M NaOH (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed twice with aq. 0.5 M NaOH and brine. After drying over $MgSO_4$ and filtration of the solids, the solvent was evaporated in vacuo, yielding 1-*tert*-butyl 4-bromomethyl-4-fluoropiperidine-1-carboxylate **6** (2.06 g), sufficiently pure for further use in the next step. Yield: 92%. Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (9H, s), 1.49-1.77 (2H, m), 1.91-2.01 (2H, m), 3.06 (2H, t(br), J = 12.1 Hz), 3.46 (2H, d, J = 17.6 Hz), 3.99 (2H, s(br)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.5, 33.4 (d, J = 20.8 Hz), 38.8 (d, J = 25.4Hz), 39.4, 79.9, 91.6 (d, J = 177.7 Hz), 154.6. ^{19}F NMR (282 MHz, $CDCl_3$): δ -162.4 (1F, m). IR (ATR, cm^{-1}): ν 1683, 1420, 1366, 1246. GC-MS (EI): m/z (%): 295/297 (M^+, 2), 240 (34), 222 (24), 194/196 (9), 177 (11), 116 (12), 96 (26), 57 (100). Anal. Calcd. for $C_{11}H_{19}BrFNO_2$: C: 44.61; H: 6.47; N: 4.73. Found: C: 45.20; H: 7.01; N: 4.35.

***tert*-Butyl 4-azidomethyl-4-fluoropiperidine-1-carboxylate (7).** To a solution of piperidine **6** (1.27 g, 4.3 mmol) in DMSO (10 mL) was added NaN_3 (0.33 g, 5 mmol, 1.2 equiv) and NaI (0.76 g, 5 mmol, 1.2 equiv). The solution was heated to 130°C for 16 h and after cooling to room temperature, the reaction mixture was poured in water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. After filtration of the solids and evaporation of the solvents under reduced pressure, the resulting oil was subjected to flash silica gel chromatography (EtOAc/hexane 1:9) to give piperidine **7** (1.0 g) as a colourless oil. Yield 91%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (9H, s), 1.47-1.67 (2H, m), 1.84-1.97 (2H, m), 3.08 (2H, t(br), J = 12.4 Hz), 3.32 (2H, d, J = 20.4 Hz), 3.96 (2H, s(br)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.7, 32.5 (d, J = 20.8 Hz), 39.4 (s(br)), 58.5 (d, J = 23.1 Hz), 80.1, 94.1 (d, J = 175.4 Hz), 154.8. ^{19}F NMR (282 MHz, $CDCl_3$): δ -160.9 (1F, m). IR (ATR, cm^{-1}): ν 2923, 2102, 1701, 1465, 1156. LC-MS (ES+): m/z (%): 244 ($M+H^+$- CH_3, 100).

***tert*-Butyl 4-aminomethyl-4-fluoropiperidine-1-carboxylate (8)**. To a solution of 4-azidomethyl-4-fluoropiperidine **7** (0.25 g, 0.97 mmol) in freshly distilled methanol (3 mL) was added Pd/C (0.05 g, 20 w%). The solution was stirred at room temperature under hydrogen atmosphere (4.6 bar). After reaction for 16 h, the solution was filtered and the solids were washed with diethyl ether. After evaporation of the solvent of the filtrate, the crude mixture was redissolved in 5 mL of diethyl ether and extracted with aq. 2M HCl (3 x 5 mL). The combined aqueous layers were neutralized to pH 7 using aq. 2M NaOH and extracted with EtOAc (3 x 10 mL). After drying of the extract over $MgSO_4$, filtration and evaporation of the solvent, 4-aminomethyl-4-fluoropiperidine **8** (0.15 g) was obtained as a colourless oil. Yield 67%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (9H, s), 1.47-1.69 (2H, m), 1.82-1.90 (2H, m), 2.79 (2H, d, J = 20.4 Hz), 3.08 (2H, t(br), J = 12.1 Hz), 3.94 (2H, s(br)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.6, 32.4 (d, J = 20.8 Hz), 39.7 (s(br)), 50.6 (d, J = 23.1 Hz), 79.8, 94.5 (d, J = 170.8 Hz), 154.9. ^{19}F NMR (282 MHz, $CDCl_3$): δ -170.8 to -170.4 (1F, m). IR (NaCl, cm^{-1}): ν 3400, 1690, 1423, 1158. GC-MS (EI): m/z (%): 232 (M^+, 1), 175 (9), 159 (23), 155 (34), 111 (18), 96 (13), 82 (15), 70 (16), 57 (100). Anal. Calcd. for $C_{11}H_{21}FN_2O_2$: C: 56.87; H: 9.11; N: 12.06. Found: C: 57.40; H: 9.69; N: 12.32.

1-*t*-Butoxycarbonyl-4-cyano-4-fluoropiperidine (10). In a dry bulb of 25 mL provided with a Claisen connecting tube under nitrogen atmosphere, a solution of 1-*t*-butoxycarbonyl-3-cyanopiperidine **9** (0.21 g, 1 mmol) and diisopropylamine (0.12 g, 1.2 mmol, 1.2 equiv) in dry THF (10 mL) was stirred at 0°C. After 1 minute, BuLi (0.5 mL of a

2.5 M solution in hexane, 1.2 equiv) was added with a syringe. The solution was stirred during 45 minutes, and NFSI (0.38 g, 1.2 mmol, 1.2 equiv, dissolved in 5 mL of THF) was added with a syringe, still at 0°C. After stirring for 2 h while the temperature had risen till room temperature, the mixture was poured in H_2O (15 mL) and extraction was performed with diethyl ether (3 x 10 mL). The combined organic fractions were washed with brine followed by 0.5 M NaOH, and after drying ($MgSO_4$), filtration and evaporation of the solvent, the crude 1-*t*-butoxycarbonyl-4-cyano-4-fluoropiperidine **10** was obtained. Purification was performed using column chromatography on silica gel, yielding white crystals (0.05 g). Flash chromatography (hexane/EtOAc 90:10, Rf = 0.34). Yield: 22%. Mp 74.6 – 76.1°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (9H, s, $C(CH_3)_3$); 1.98-2.21 (4H, m, $(CH_2)_2CF$); 3.58 (4H, t, J = 5.8 Hz, $(CH_2)_2N$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3 (3 x CCH_3); 34.8 (d, J = 20.8 Hz, $(CH_2)_2CF$); 32.3 (s (br), $(CH_2)_2N$); 80.6 ($C(CH_3)_3$); 86.4 (d, J = 184.6 Hz, CF); 117.4 (d, J = 34.6 Hz, CN); 128.4 and 129.8 (2 x CH_2N); 154.2 (C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ -153.33 (s(br)). IR (KBr, cm^{-1}): ν 3256; 1679 (C=O); 1429. GC-MS (EI): m/z (%): 228 (M+, 1); 173 (15); 155 (45); 128 (16); 57 (100); 41(25). Anal. Calcd. for $C_{11}H_{17}FN_2O_2$: C: 57.9; H: 7.5; N: 12.3. Found: C: 58.6; H: 7.9; N: 12.0.

3-Bromomethyl-1-*tert*-butoxycarbonyl-3-fluoropyrrolidine (17). The synthetic procedure for compound **17** is analogous to the synthesis of compound **6**. Purification was performed by flash silica gel chromatography (hexane/ethyl acetate: 75/25; Rf: 0.29). Yield: 68%. Light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (9H, s, $C(CH_3)_3$); 1.94-2.30 (2H, m, NCH_2CH_2); 3.41-3.81 (6H, m, $CH_2NCH_2CFCH_2Br$). ^{19}F NMR (282 MHz, $CDCl_3$): δ -149.48 to -150.33 (1F, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.9, 33.5 (d, J = 28.8 Hz), 34.2 and 34.9 (d, J = 22.5 Hz),* 44.0 and 44.4, * 54.4 and 54.6 (d, J = 23.1 Hz),* 79.2, 99.6 and 100.4 (d, J = 182.9 Hz),* 153.5 and 153.6.* [* Different signals due to *N*-Boc rotamers]. IR (ATR, cm^{-1}): ν 1688; 1402; 1365; 1169; 1147; 1119. MS (ES+): m/z (%): 267/269 ($M+H^+$-CH_3, 100); 226/228 (45). Anal. Calcd. for $C_{10}H_{17}BrFNO_2$: C: 42.57; H: 6.07; N: 4.96. Found: C: 43.22; H: 6.41; N: 4.68.

3-Acetoxymethyl-1-*tert*-butoxycarbonyl-3-fluoropyrrolidine (18). To a solution of 3-bromomethyl-1-*tert*-butoxycarbonyl-3-fluoropyrrolidine **17** (1.20 g, 4.25 mmol) in dry DMF (15 mL) was added NaOAc (0.70 g, 8.53 mmol; 2 equiv) and sodium iodide (0.13 g, 0.87 mmol; 0.2 equiv). After heating at 120°C under stirring for 48 h, the reaction mixture was cooled down and poured in 35 mL of water. The mixture was extracted with diethyl ether (3 x 20 mL) and the extracts were washed with brine (3 x 20 mL) and dried over $MgSO_4$.

After filtration and evaporation of the solvent, 3-acetoxymethyl-3-fluoro-1-*tert*-butoxycarbonylpyrrolidine **18** (0.90 g, 3.44 mmol) was obtained as a yellow oil. Yield: 81%. A sample of compound **18** was purified for analytical purposes via flash silica gel chromatography (hexane/ethyl acetate: 85/15. Rf: 0.07). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (9H, s), 1.78-2.17 (2H, m), 2.03 (3H, s, rotamer 1), 2.05 (3H, s, rotamer 2), 3.28-3.68 (4H, m), 4.11-4.30 (2H, m). ^{19}F NMR (282 MHz, $CDCl_3$): δ -156.06 to -156.74 (1F, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5, 28.2, 32.7 and 33.5 (d, J = 23.1 Hz),* 43.7 and 44.1,* 53.1 and 53.4 (d, J = 24.8 Hz),* 55.1 (d, J = 25.4 Hz), 79.6, 99.8 and 100.6 (d, J = 180.6 Hz),* 153.9 and 154.0,* 170.2. [* Different signals due to *N*-Boc rotamers]. IR (ATR, cm^{-1}): ν 1748; 1694; 1407; 1366; 1235; 1164. GC-MS (EI): m/z (%): 261 (M^+, 0.6); 206 (18); 188 (39); 146 (22); 102 (23); 57 ($C_4H_9^+$, 100); 43 (29). Anal. Calcd. for $C_{12}H_{20}FNO_4$: C: 55.16; H: 7.72; N: 5.36. Found: C: 55.53; H: 8.11; N: 4.99.

3-Azidomethyl-1-*tert*-butoxycarbonyl-3-fluoropyrrolidine (19). To a solution of 3-bromomethyl-1-*tert*-butoxycarbonyl-3-fluoropyrrolidine **17** (3.40 g, 12.05 mmol) in dimethylsulfoxide (50 mL) was added sodium azide (0.94 g, 14.46 mmol; 1.2 equiv) and sodium iodide (2.17 g, 14.46 mmol; 1.2 equiv). After stirring for 2.5 h at 130°C, the reaction mixture was cooled down, poured in 50 mL of water, and extracted with CH_2Cl_2 (3 x 20 mL). After washing with brine (3 x 20 mL), drying over $MgSO_4$, filtration and evaporation of the solvent, 3-azidomethyl-1-*tert*-butoxycarbonyl-3-fluoropyrrolidine **19** (2.35 g, 9.62 mmol) was obtained as a yellow oil. Yield: 80%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (9H, s), 1.83-2.28 (2H, m), 3.34-3.77 (6H, m). ^{19}F NMR (282 MHz, $CDCl_3$): δ -153.10 to -153.74 (1F, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.2, 33.3 and 33.9 (d, J = 23.1 Hz),* 43.8 and 44.2,* 53.0 and 53.8 (d, J = 25.4 Hz),* 54.6 (d, J = 25.4), 79.6, 101.4 and 102.3 (d, J = 181.2 Hz),* 153.9. [* Different signals due to *N*-Boc rotamers]. IR (ATR, cm^{-1}): ν 2102; 1686; 1403; 1365; 1156; 1123. MS (ES+): m/z (%): 230 ($M+H^+$-CH_3, 100); 189 (55).

tert-Butyl 4-aminomethyl-4-fluoropyrrolidine-1-carboxylate (20a). The synthesis of pyrrolidine **20a** from 3-methylenepyrrolidine **16** proceeds analogous to the synthesis of piperidine **8** starting from 4-methylenepiperidine **5**. Pyrrolidine **20a** occurred as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (9H, s), 1.66 (2H, s(br)), 1.77-2.23 (2H, m), 2.91-3.09 (2H, m), 3.32-3.73 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3, 33.2 and 33.9 (d, J = 23.1 Hz),* 44.0 and 44.5,* 46.7 (d, J = 25.4 Hz), 53.8 and 54.1 (d, J = 28.9 Hz),* 79.5, 103.1 and 104.0 (d, J = 176.0 Hz),* 154.2. ^{19}F NMR (282 MHz, $CDCl_3$): δ -157,6 to -158,4 (1F, m). [* Different signals due to *N*-Boc rotamers]. IR (ATR, cm^{-1}): ν 3379, 1686, 1406, 1365, 1169,

1117. GC-MS (EI): m/z (%): 198 (M^+-HF, 4), 145 (M^+- $C(CH_3)_3$, 40), 142 (M^+-F-$C(CH_3)_3$, 59), 125 (37), 57 (100). Anal. Calcd. for $C_{10}H_{19}FN_2O_2$: C: 55.03; H: 8.77; N: 12.83. Found: C: 55.10; H: 9.31; N: 12.65.

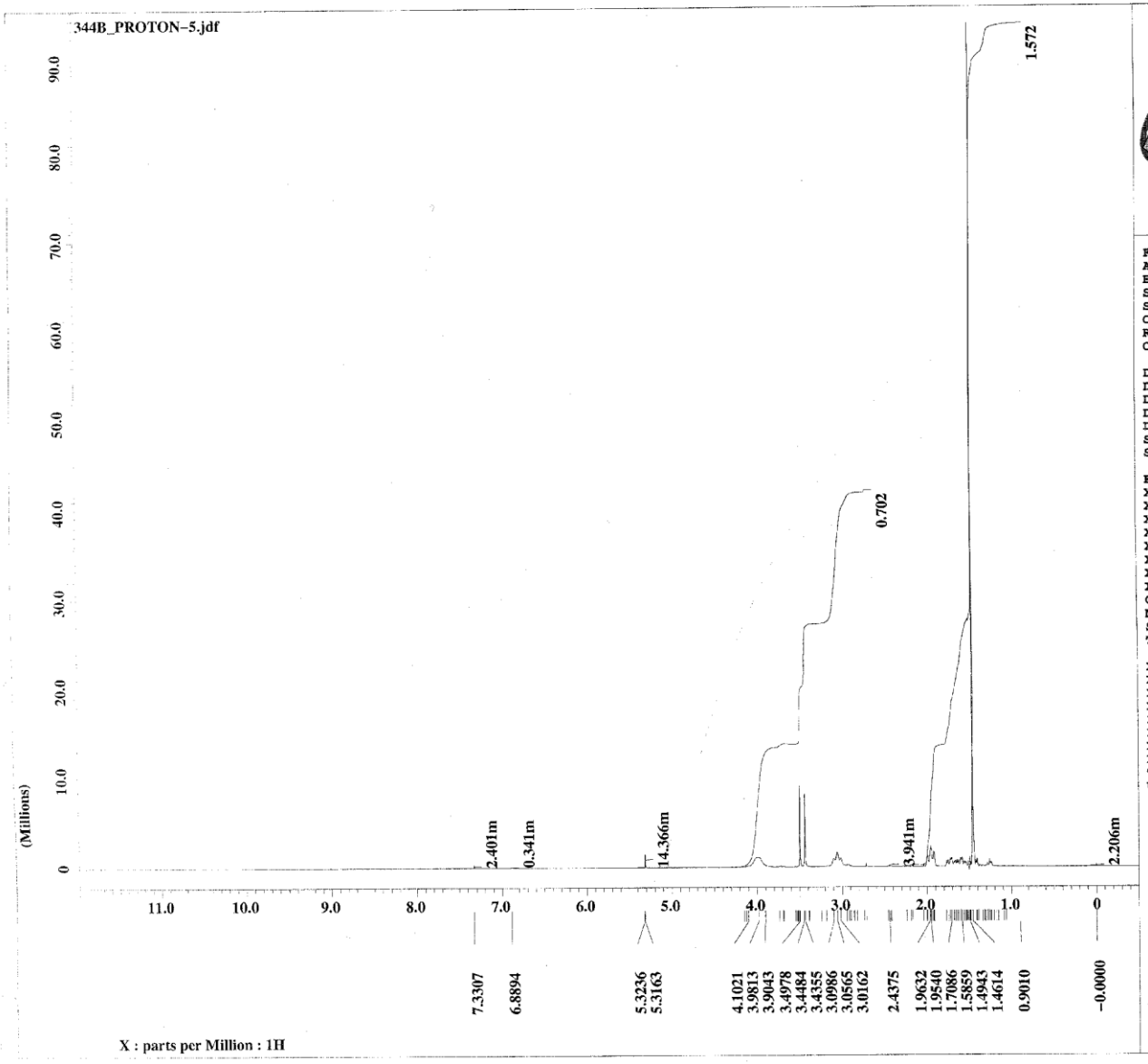
3-(*N*-Acetyl)aminomethyl-1-*tert*-butoxycarbonyl-3-fluoropyrrolidine (20b). 3-aminomethyl-1-*tert*-butoxycarbonyl-3-fluoropyrrolidine **20a** (0.10 g, 0.46 mmol) was dissolved in acetic anhydride (2 mL). After stirring for 16 h, the excess of acetic anhydride was evaporated yielding 3-(*N*-acetyl)aminomethyl-1-*tert*-butoxycarbonyl-3-fluoropyrrolidine **20b** (0.11 g, 0.42 mmol). Yield: 91%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (9H, s), 1.88-2.20 (2H, m), 2.03 (3H, s, rotamer 1), 2.05 (3H, s, rotamer 2), 3.32-3.68 (6H, m), 6.52 (1H, s(br)). ^{19}F NMR (282 MHz, $CDCl_3$): δ -153.70 to -154.45 (1F, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.9, 28.3, 33.3 and 34.0 (d, J = 21.9 Hz),* 43.3 (d, J = 23.1 Hz), 43.9 and 44.4,* 53.7 and 54.0 (d, J = 26.6 Hz),* 79.7, 102.1 and 103.0 (d, J = 177.7 Hz),* 154.1 and 154.2,* 170.5. [* Different signals due to *N*-Boc rotamers]. IR (ATR, cm^{-1}): ν 3307; 1661; 1407; 1366; 1162; 1130; 730. MS (ES+): m/z (%): 205 (88); 189 ($M+2H^+$-$OC(CH_3)_3$, 100). Anal. Calcd. for $C_{12}H_{21}FN_2O_3$: C: 55.37; H: 8.13; N: 10.76. Found: C: 55.04; H: 8.52; N: 10.37.

3-(*N*-Benzyloxycarbonyl)aminomethyl-1-*tert*-butoxycarbonyl-3-fluoropyrrolidine (20c). To a solution of 3-aminomethyl-1-*tert*-butoxycarbonyl-3-fluoropyrrolidine **20a** (100 mg, 0.46 mmol) in dry THF (5 mL) was added benzyl chloroformate (78 mg, 0.46 mmol, 1 equiv) at 0°C. After stirring for 4.5 h at rt, the reaction mixture was poured in aq. 1 M NaOH (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo* yielding 3-(*N*-benzyloxycarbonyl)aminomethyl-1-*tert*-butoxycarbonyl-3-fluoropyrrolidine **20c** as a yellow oil. Yield: 62%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1,46 (9H, s), 1.86-2.18 (2H, m), 3.31-3.71 (6H, m), 5.12 (2H, s(br)), 5.25 (1H, s(br)), 7.32-7.40 (5H, m). ^{19}F NMR (282 MHz, $CDCl_3$): δ -154.46 to -155.28 (1F, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.4, 33.3 and 33.9 (d, J = 22.5 Hz),* 43.9 and 44.4,* 45.3 (d, J = 23.1 Hz), 53.6 and 53.9 (d, J = 26.0 Hz),* 67.0, 79.7, 102.0 and 102.9 (d, J = 178.8 Hz),* 128.1 (2 x CHarom), 128.2, 128.5 (2 x CHarom), 136.1, 154.15, 156.5. [* Different signals due to *N*-Boc rotamers]. IR (ATR, cm^{-1}): ν 3319; 1681; 1409; 1366; 1253; 1154; 1134; 731. MS (ES-): 351 ($M-H^+$, 100). Anal. Calcd. for $C_{18}H_{25}FN_2O_4$: C: 61.35; H: 7.15; N: 7.95. Found: C: 61.49; H: 7.57; N: 7.44.

3-(*N*-Acetyl)aminomethyl-1-benzyl-3-fluoropyrrolidine (20d). To a solution of 3-(*N*-acetyl)aminomethyl-3-fluoropyrrolidiniumtrifluoracetate (0.50 g, 1.82 mmol) and triethylamine (1 mL, 7.28 mmol, 4 equiv) in CH_2Cl_2 (25 mL) was added benzyl bromide (0.27

mL, 2.18 mmol, 1.2 equiv). After stirring at rt for 5h, the mixture was poured in aq. sat. Na_2CO_3 (50 mL) and extracted with dichloromethane (3 x 10 mL). After drying over $MgSO_4$, filtration and evaporation of the solvent, the obtained crude oil was purified via flash silica gel chromatography (CH_2Cl_2/MeOH: 95/5; Rf: 0,18) yielding 3-(*N*-acetyl)aminomethyl-1-benzyl-3-fluoropyrrolidine **20d** (0.18 g, 0.72 mmol) as a yellow oil. Yield: 40%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.92, 1.84-2.13 (2H, m), 2.46-2.83 (4H, m), 3.49 (2H, dd, J_1 = 22.0 Hz, J_2 = 6.1 Hz), 3.53 (1H, d, J = 13.0 Hz), 3.61 (1H, d, J = 13.0 Hz), 6.02 (1H, s, NH), 7.15-7.25 (5H, m). ^{19}F NMR (282 MHz, $CDCl_3$): δ -142.51 to -143.03 (1F, septet, J = 24.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.1, 34.9 (d, J = 23.0 Hz), 45.3 (d, J = 24.2 Hz), 52.5, 59.8, 62.1 (d, J = 24.3 Hz), 103.3 (d, J = 178.8 Hz), 127.1, 128.3 (2 x CHarom), 128.6 (2 x CHarom), 137.9, 170.4. IR (ATR, cm^{-1}): ν 3286; 1652; 1553; 1376; 1111; 736; 699. GC-MS **(**EI): m/z (%): 249 (M-H$^+$, 1.4), 230 (69), 172 (77), 158 (30), 91 ($C_7H_7^+$, 100). Anal. Calcd. for $C_{14}H_{19}FN_2O$: C: 67.18; H: 7.65; N: 11.19. Found: C: 67.75; H: 8.00; N: 11.04.

3-Ammoniomethyl-3-fluoropyrrolidinium bis(trifluoroacetate) 20e. To a solution of *tert*-butyl 3-aminomethyl-3-fluoropyrrolidine-1-carboxylate **20a** (0.62 g) in CH_2Cl_2 (25 mL) was added trifluoroacetic acid (4.35 mL, 56.8 mmol, 20 equiv) at 0°C. After stirring the mixture under dry atmosphere for 7 h at 0°C, the solvent and the excess of TFA was evaporated under reduced pressure. The obtained residue was recrystallized from EtOH to yield 3-ammoniomethyl-3-fluoropyrrolidinium bis(trifluoroacetate) **20e** (0.51 g). Yield: (52%). Mp 169 °C. ^{1}H NMR (300 MHz, D_2O): δ 2.25 (1H, ddt, J = 36.9 Hz, J = 14.9 Hz, J = 10.0 Hz), 2.42-2.58 (1H, m), 3.40-3.65 (5H, m), 3.74 (1H, ddd, J = 18.2 Hz, J = 13.8 Hz, J = 2.2 Hz). ^{13}C NMR (75 MHz, D_2O): δ 33.3 (d, J = 23.1 Hz), 42.2 (d, J = 23.1 Hz), 44.3, 52.5 (d, J = 25.4 Hz), 100.0 (d, J = 181.1 Hz), 116.5 (q, J = 291.9 Hz), 163.1 (q, J = 35.8 Hz). ^{19}F NMR (282 MHz, D_2O): δ -75.4 (6F, s), -154.6 to -155.0 (1F, m). IR (ATR, cm^{-1}): ν 3024, 1667, 1186, 1145, 1126. MS (ES+): m/z (%): 433 (100); 199 (M+H$^+$, 20). Anal. Calcd. for $C_9H_{13}F_7N_2O_4$, C: 31.2%; H: 3.8%; N: 8.1%. Found C: 31.0%, H: 3.3%; N: 7.8%.



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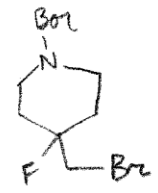

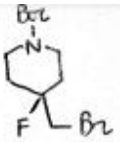

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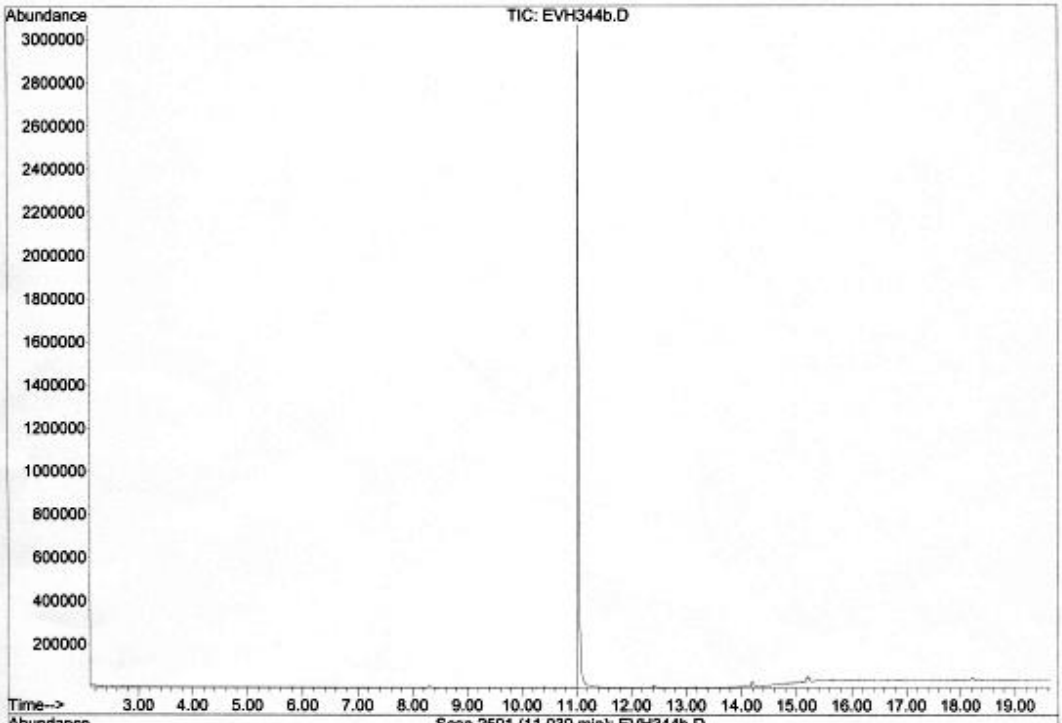
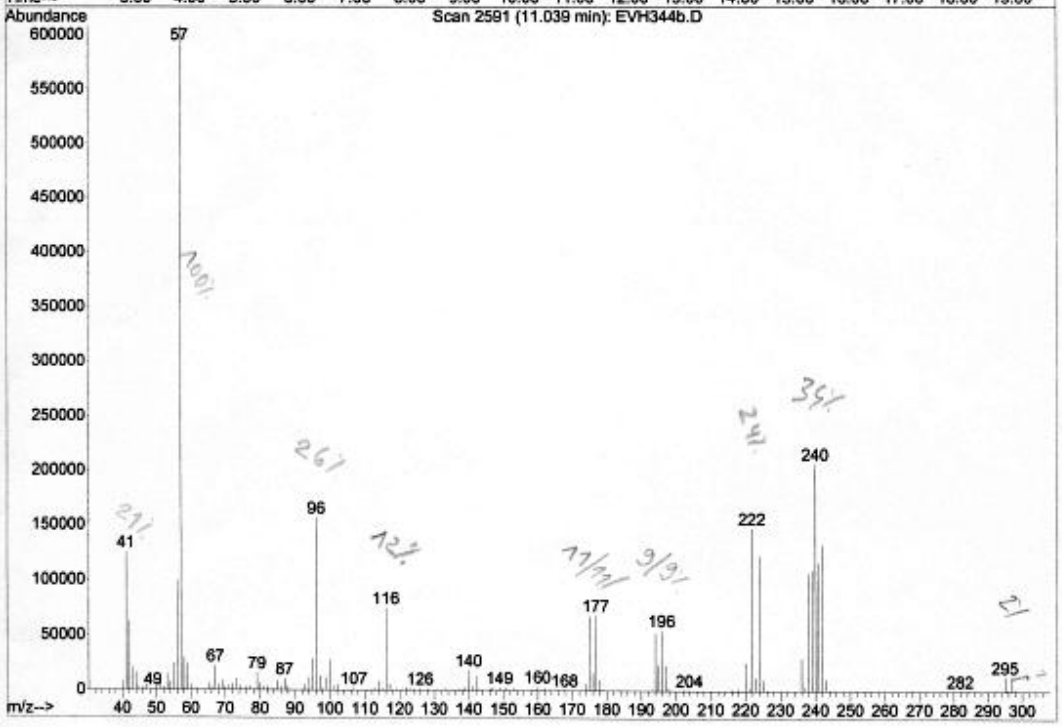
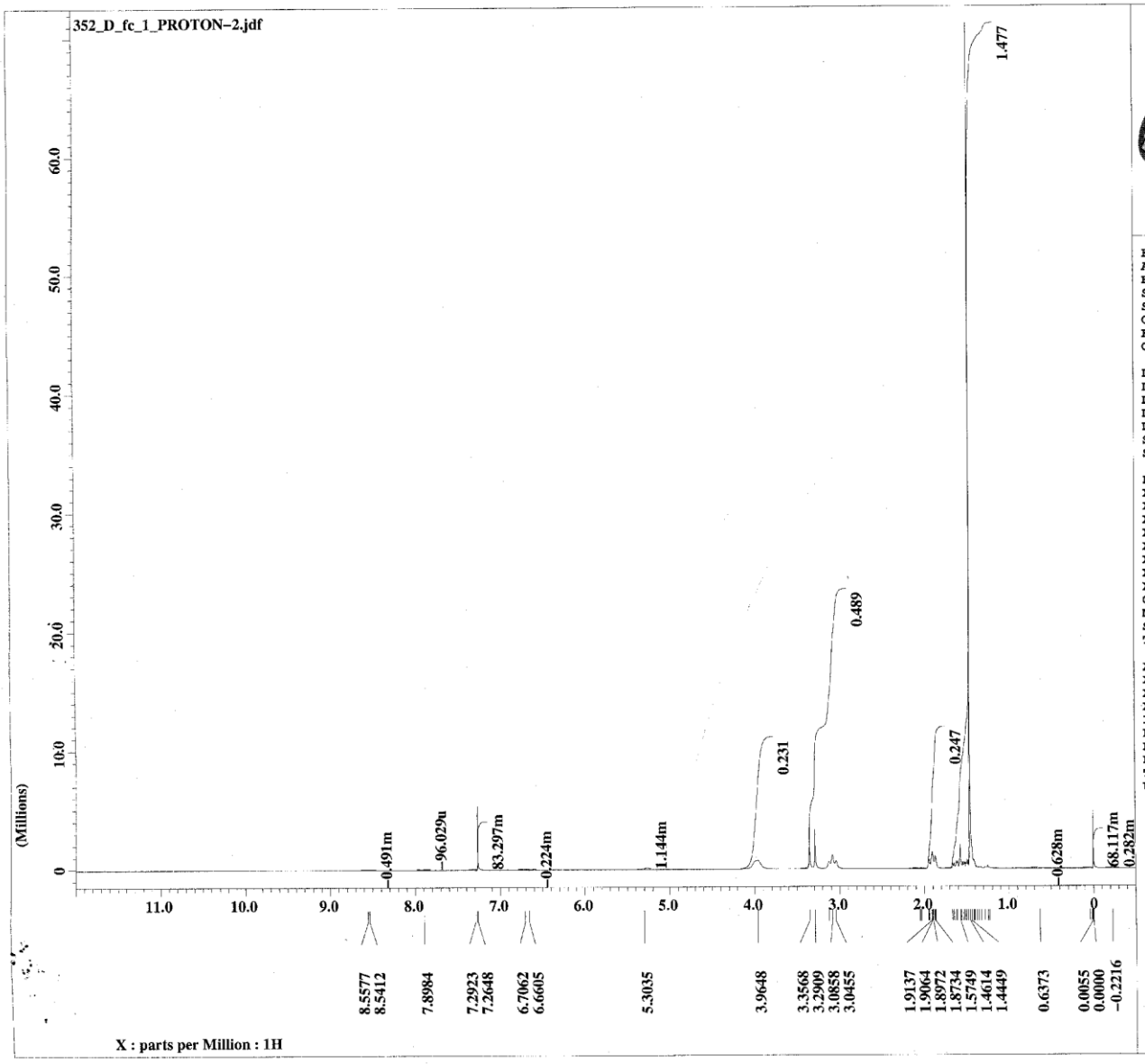
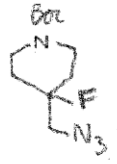




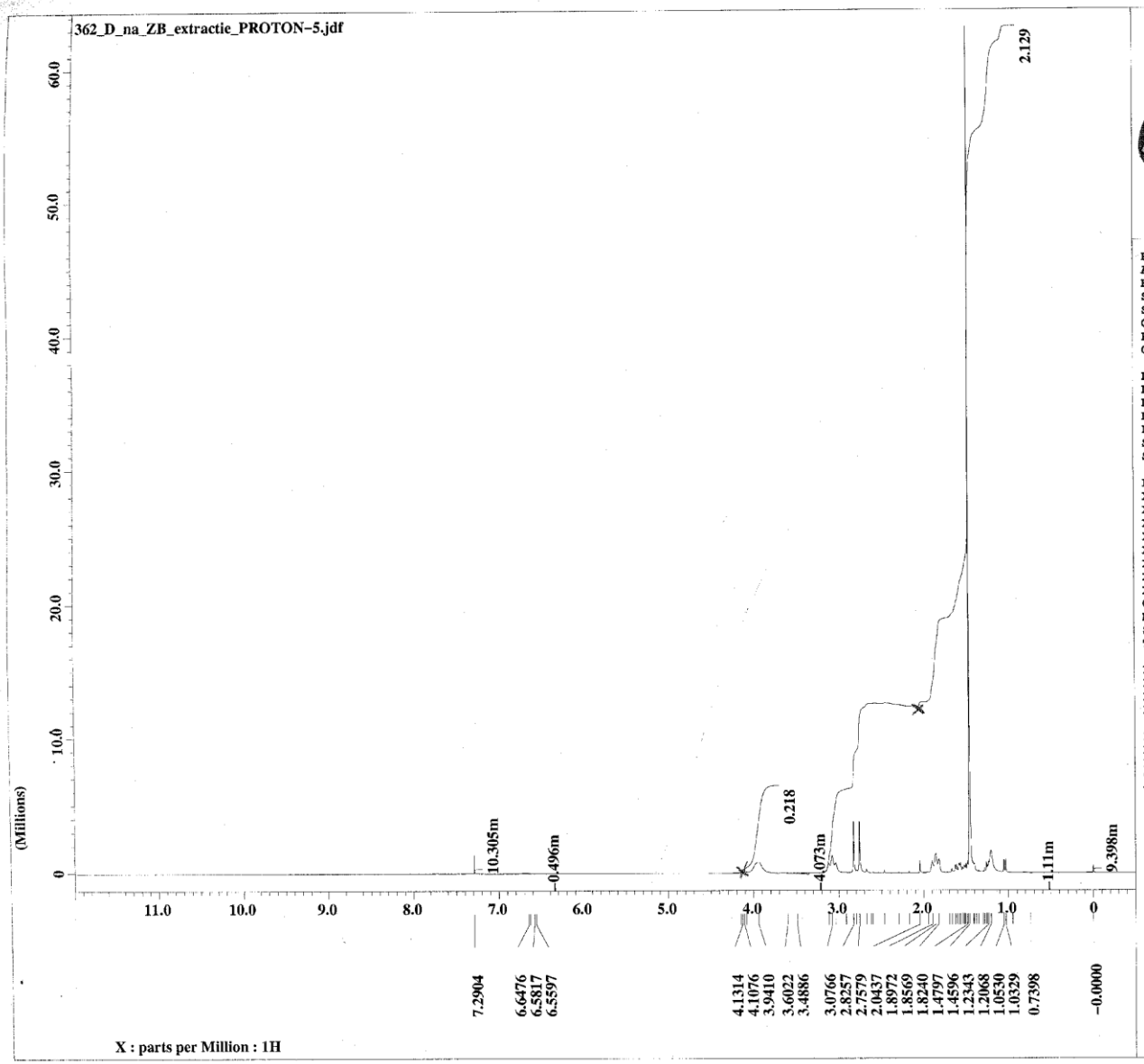


JEOL

Filename	= 352_D_fc_1_PROTON-2.j
Author	= delta3
Experiment	= single_pulse.exp
Sample_id	= EVH/352_D_fc_1
Solvent	= CHLOROFORM-D
Creation_time	= 28-APR-2008 15:10:14
Revision_time	= 28-APR-2008 15:40:03
Current_time	= 28-APR-2008 15:40:03
Data_format	= 1D COMPLEX
Dim_size	= 8192
Dim_title	= 1H
Dim_units	= [ppm]
Dimensions	= X
Site	= Eclipse+ 300
Spectrometer	= DELTA_NMR
Field_strength	= 7.0586013[T] (300[MHz
X_acq_duration	= 1.8169856[s]
X_domain	= 1H
X_freq	= 300.52965592[MHz]
X_offset	= 5[ppm]
X_points	= 8192
X_prescans	= 0
X_resolution	= 0.55036209[Hz]
X_sweep	= 4.50856628[kHz]
Clipped	= FALSE
Mod_return	= 1
Scans	= 16
Total_scans	= 16
X_90_width	= 11.3[us]
X_acq_time	= 1.8169856[s]
X_angle	= 90[deg]
X_pulse	= 11.3[us]
Initial_wait	= 1[s]
Phase_preset	= 3[us]
Recvr_gain	= 16
Relaxation_delay	= 5[s]
Temp_get	= 21.1[dC]
Unblank_time	= 2[us]

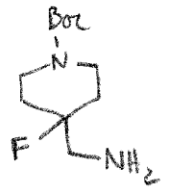


7



JEOL

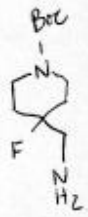
Filename	= 362_D_na_ZB_extractie
Author	= delta3
Experiment	= single_pulse.exp
Sample_id	= EVH/362_D_na_ZB_extra
Solvent	= CHLOROFORM-D
Creation_time	= 4-MAY-2008 11:53:17
Revision_time	= 4-MAY-2008 12:22:48
Current_time	= 4-MAY-2008 12:22:48
Data_format	= 1D COMPLEX
Dim_size	= 8192
Dim_title	= 1H
Dim_units	= [ppm]
Dimensions	= X
Site	= Eclipse+ 300
Spectrometer	= DELTA_NMR
Field_strength	= 7.0586013[T] (300[MHz
X_acq_duration	= 1.8169856[s]
X_domain	= 1H
X_freq	= 300.52965592[MHz]
X_offset	= 5[ppm]
X_points	= 8192
X_prescans	= 0
X_resolution	= 0.55036209[Hz]
X_sweep	= 4.50856628[kHz]
Clipped	= FALSE
Mod_return	= 1
Scans	= 16
Total_scans	= 16
X_90_width	= 11.3[us]
X_acq_time	= 1.8169856[s]
X_angle	= 90[deg]
X_pulse	= 11.3[us]
Initial_wait	= 1[s]
Phase_preset	= 3[us]
Recvr_gain	= 10
Relaxation_delay	= 5[s]
Temp_get	= 19.9[dC]
Unblank_time	= 2[us]

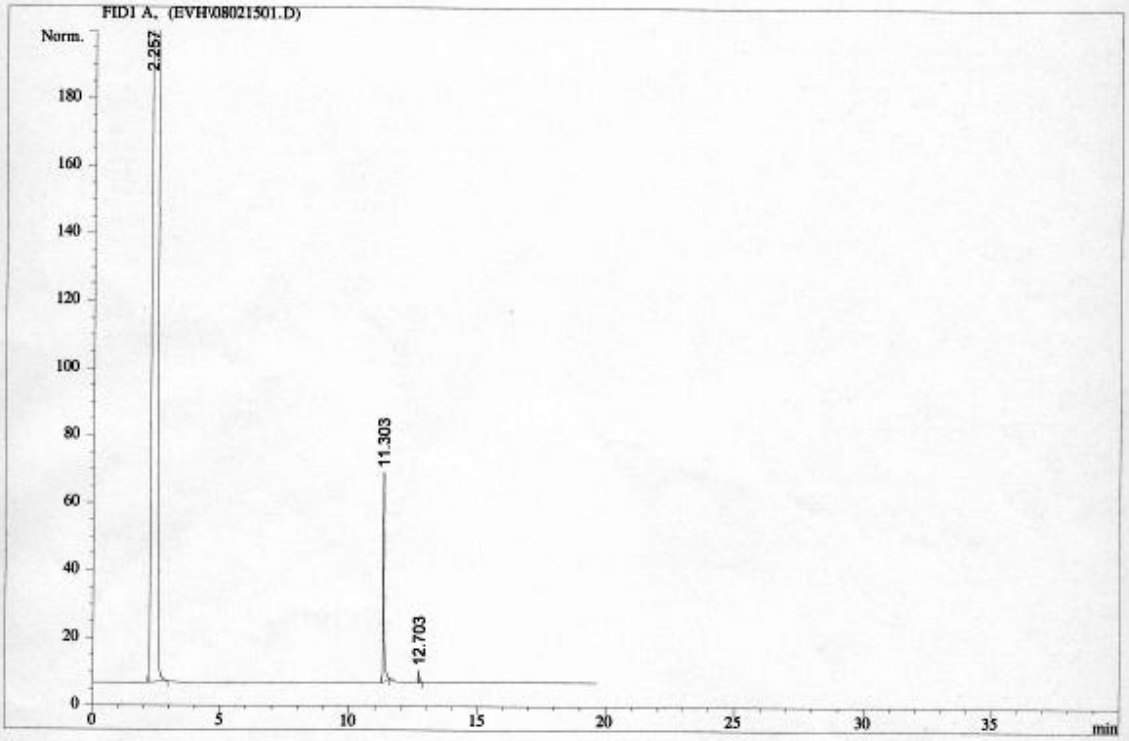


Data File D:\HPCHEM\1\DATA\EVH\08021501.D Sample Name: EVH

8

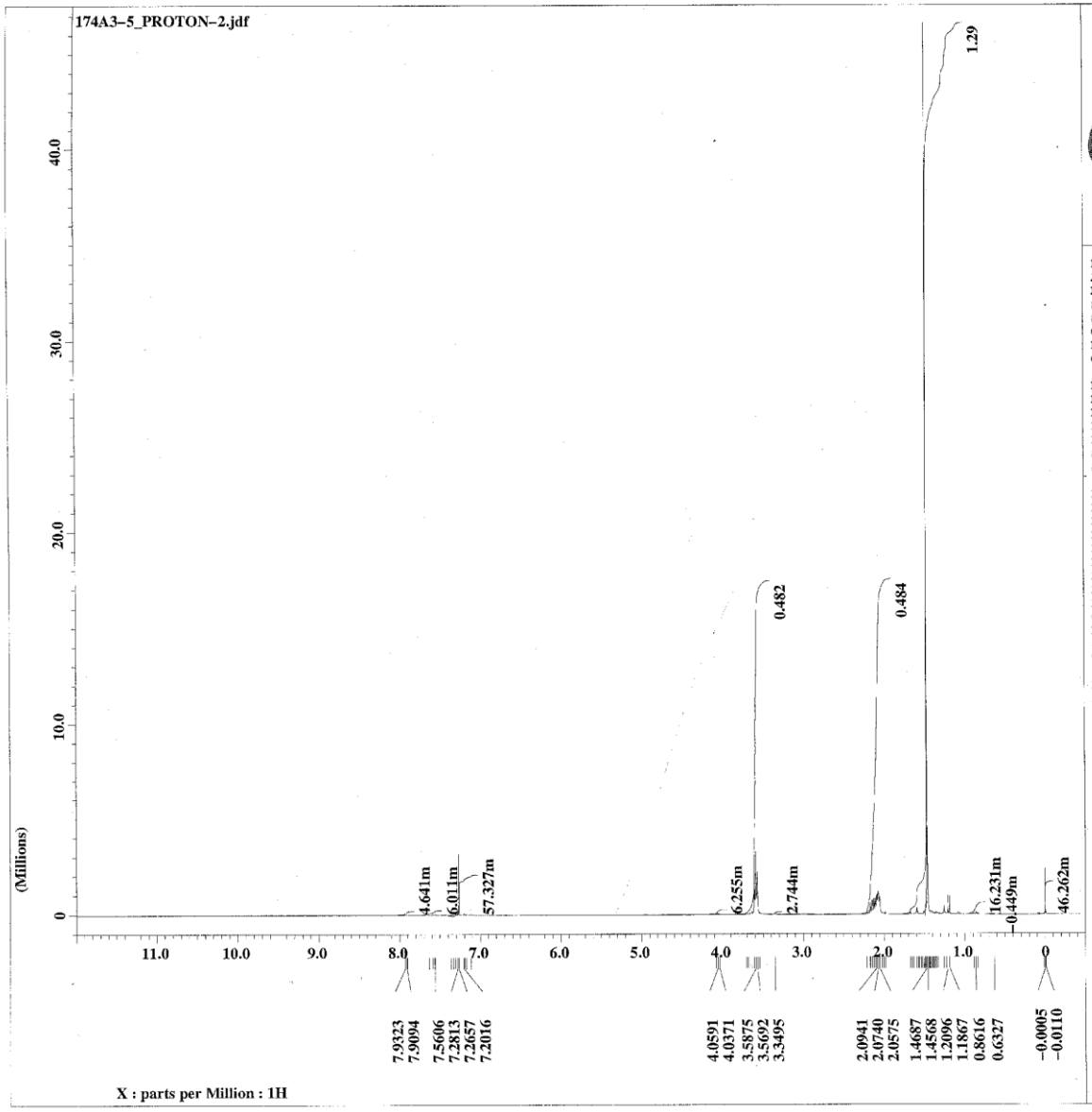
```
Injection Date  : 5/9/08 1:29:26 PM          Seq. Line :   2
Sample Name     : EVH 362                      Vial :  20
Acq. Operator   : EVH                          Inj :   1
                                           Inj Volume : 1 µl

Acq. Method     : D:\HPCHEM\1\METHODS\SYNTS1A.M
Last changed    : 2/12/08 1:33:54 PM by vvh
Analysis Method : D:\HPCHEM\1\METHODS\STERVV1A.M
Last changed    : 5/9/08 1:25:49 PM by EVH
                  (modified after loading)
METHOD FOR STEROL DETERMINATION
```





Area Percent Report

```
Sorted By             :      Signal
Calib. Data Modified  :      5/10/00 10:31:33 AM
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: FID1 A,
```



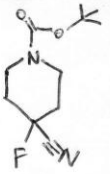
JEOL

```
Filename          = 174A3-5_PROTON-2.jdf
Author            = delta2
Experiment        = single_pulse.exp
Sample_id         = EVH/174A3-5
Solvent           = CHLOROFORM-D
Creation_time     = 24-AUG-2006 13:51:10
Revision_time     = 24-AUG-2006 14:12:21
Current_time      = 24-AUG-2006 14:12:21

Data_format       = 1D COMPLEX
Dim_size          = 16384
Dim_title         = 1H
Dim_units         = [ppm]
Dimensions        = X
Site              = Eclipse+ 300
Spectrometer      = DELTA_NMR

Field_strength    = 7.0586013[T] (300[MHz
X_acq_duration    = 3.6339712[s]
X_domain          = 1H
X_freq            = 300.52965592[MHz]
X_offset          = 5[ppm]
X_points          = 16384
X_prescans        = 0
X_resolution      = 0.27518105[Hz]
X_sweep           = 4.50856628[kHz]
Clipped           = FALSE
Mod_return        = 1
Scans             = 16
Total_scans       = 16

X_90_width        = 11.5[us]
X_acq_time        = 3.6339712[s]
X_angle           = 45[deg]
X_pulse           = 5.75[us]
Initial_wait      = 1[s]
Phase_preset      = 3[us]
Recvr_gain        = 17
Relaxation_delay  = 1[s]
Temp_get          = 20.2[dC]
Unblank_time      = 2[us]
```

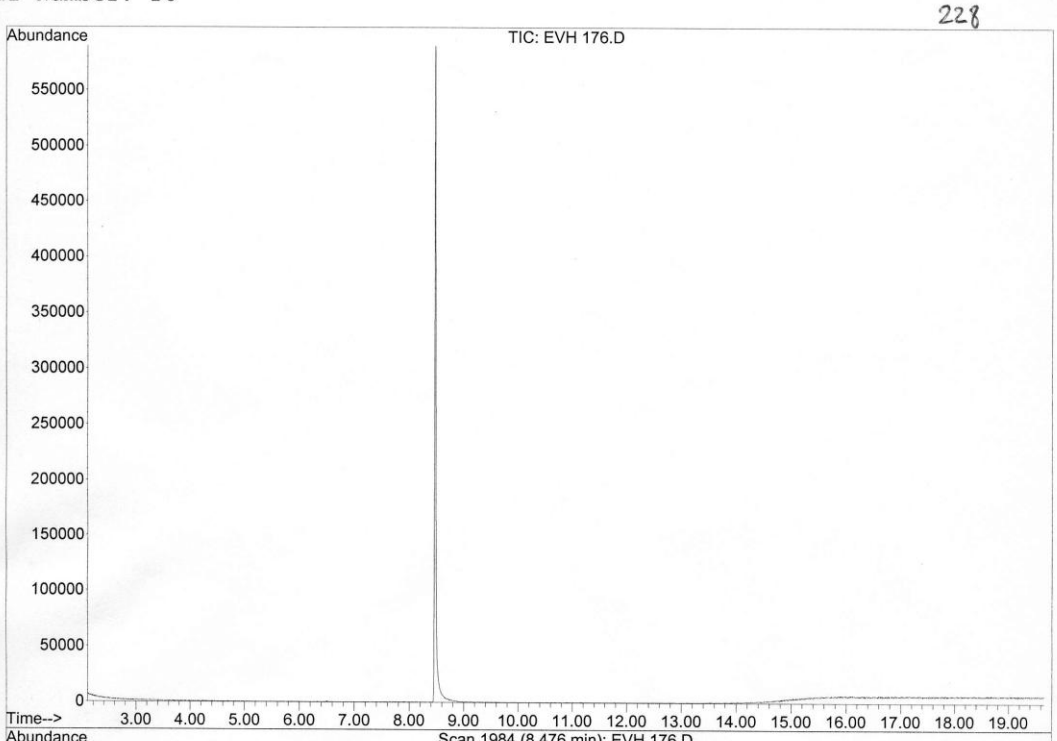
10

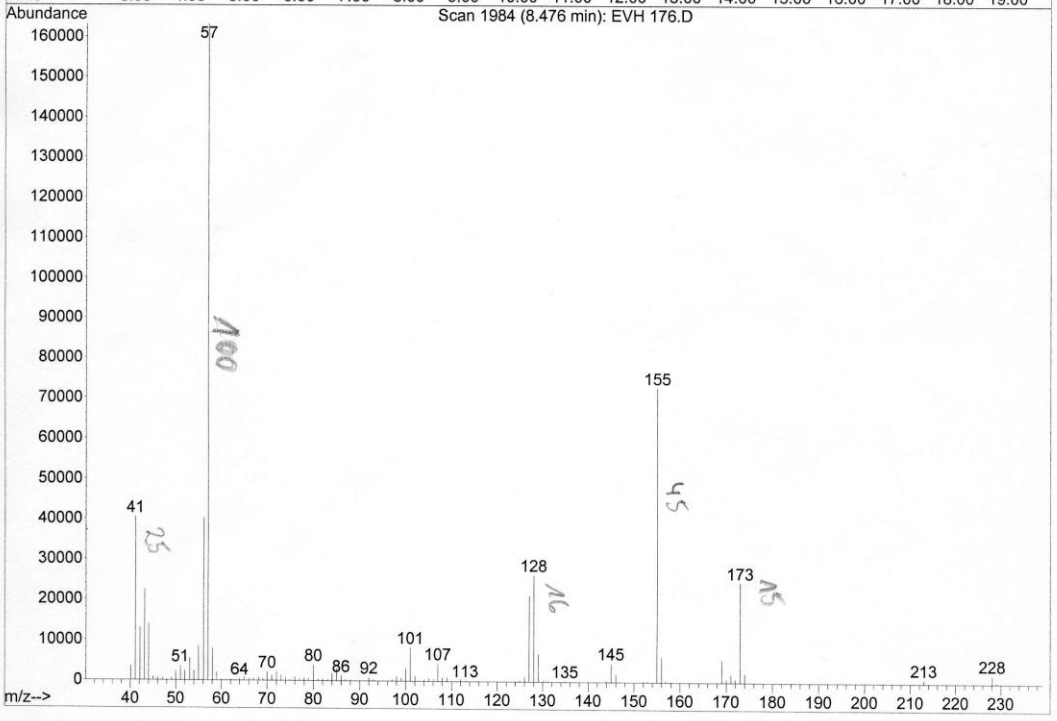
10

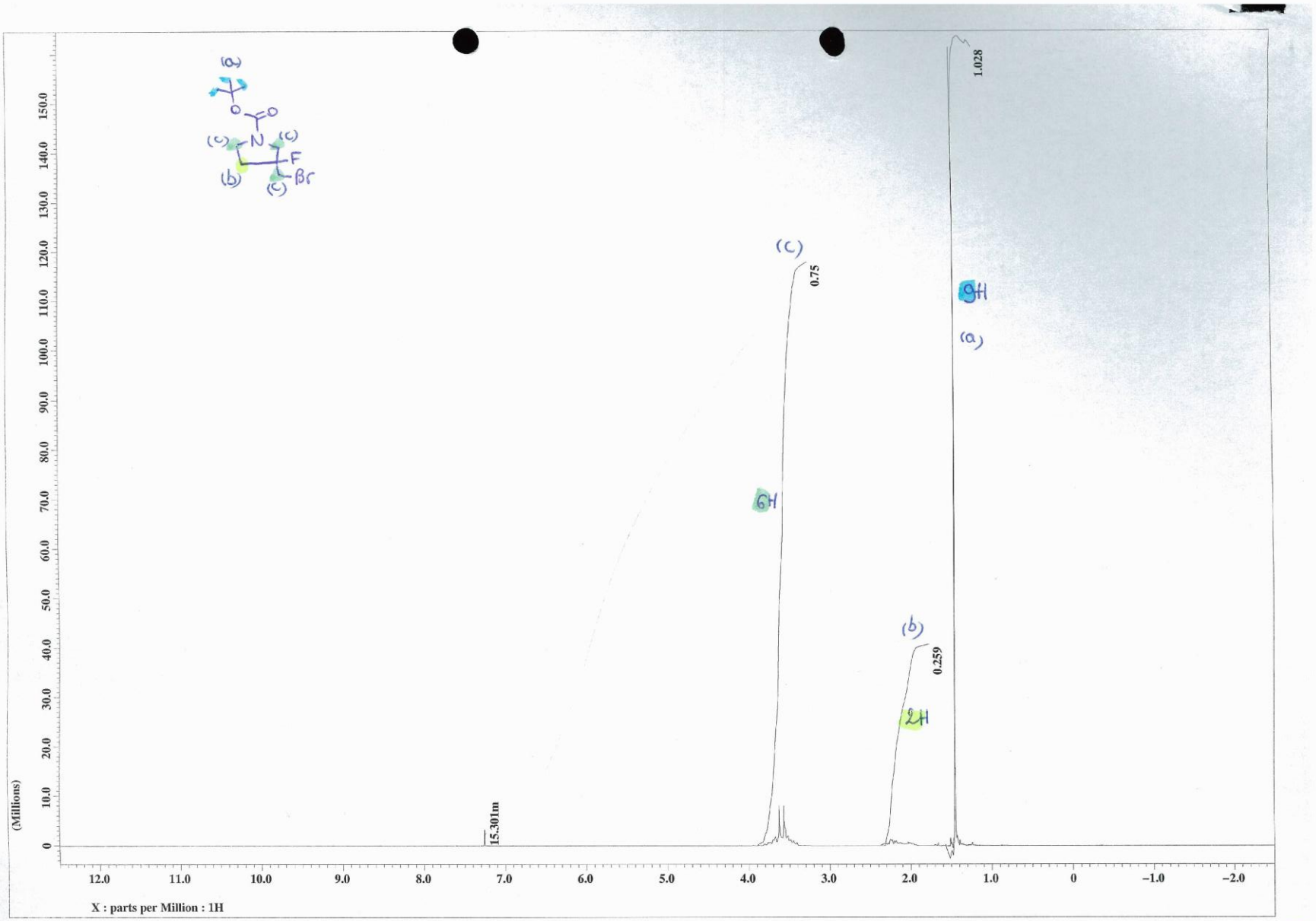
File :C:\MSDChem\1\DATA\EVH 176.D
Operator : FVL
Acquired : 14 Sep 2006 19:15 using AcqMethod Synthese.M
Instrument : Instrument #1
Sample Name:
Misc Info :
Vial Number: 16



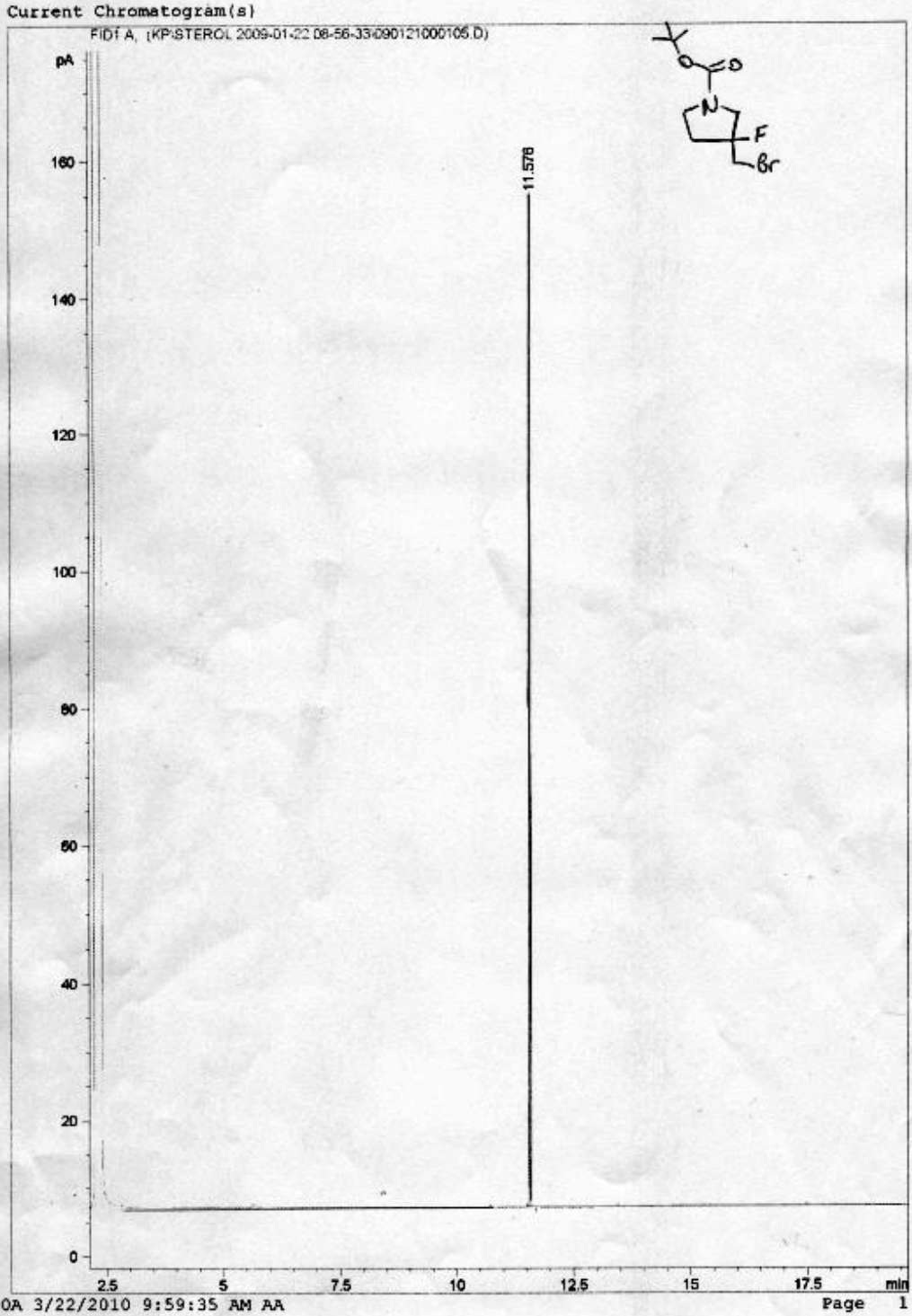
228

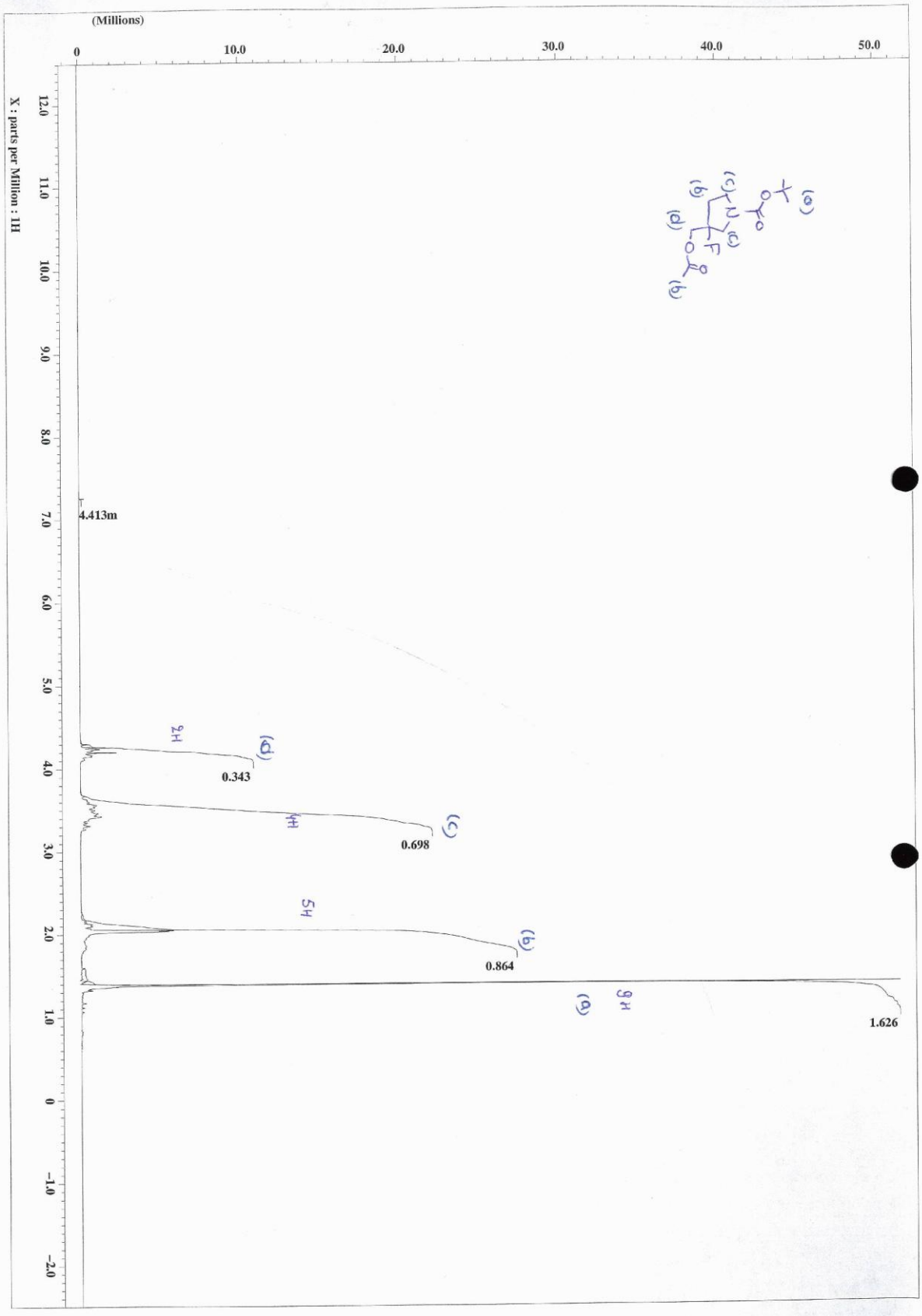




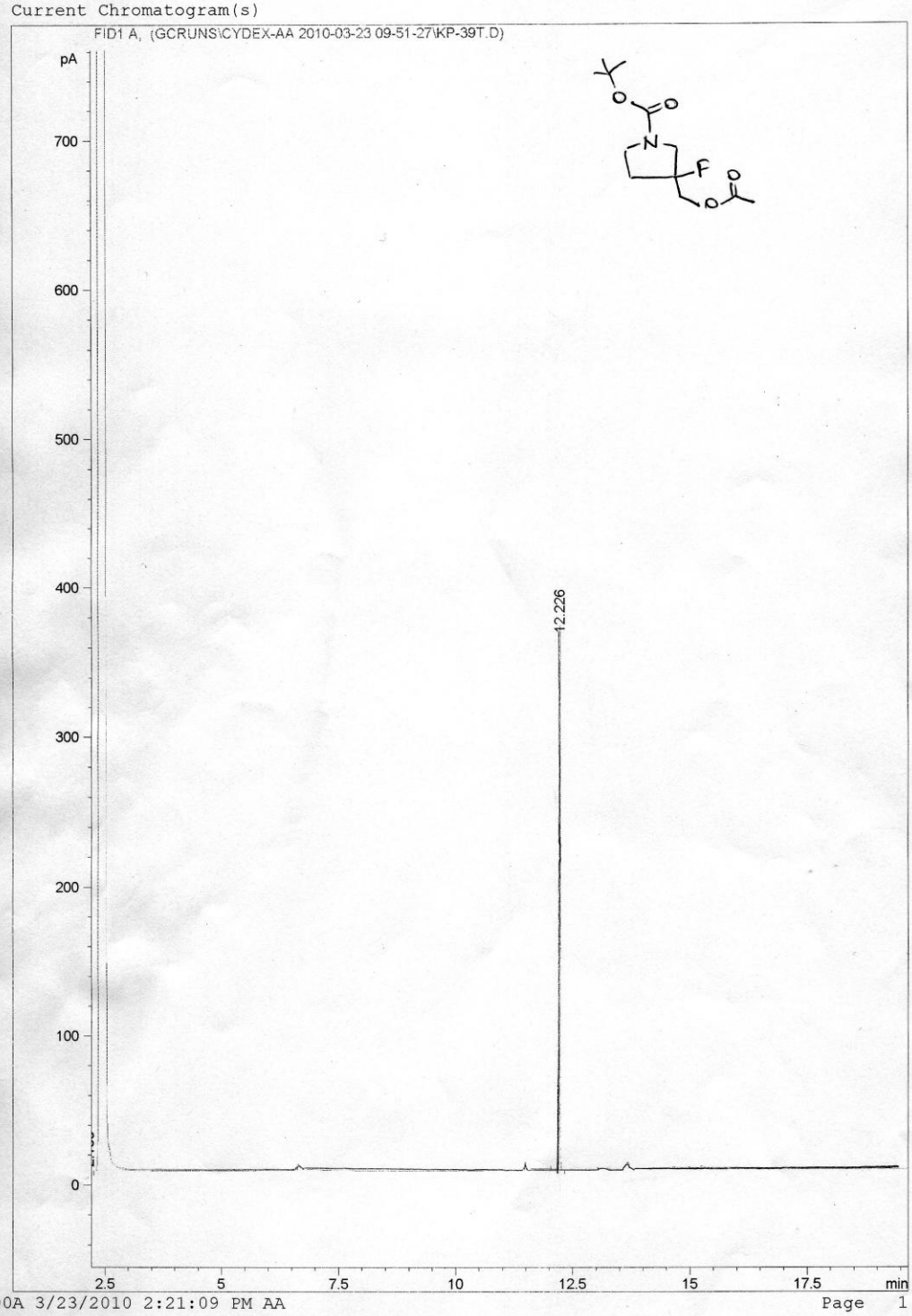

(a)
(c)
(c)
N
F
(b)
(c)
Br
1.028
(c)
0.75
9H
(a)
6H
(b)
0.259
2H
15.301m
(Millions)
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
−1.0
−2.0
X : parts per Million : 1H

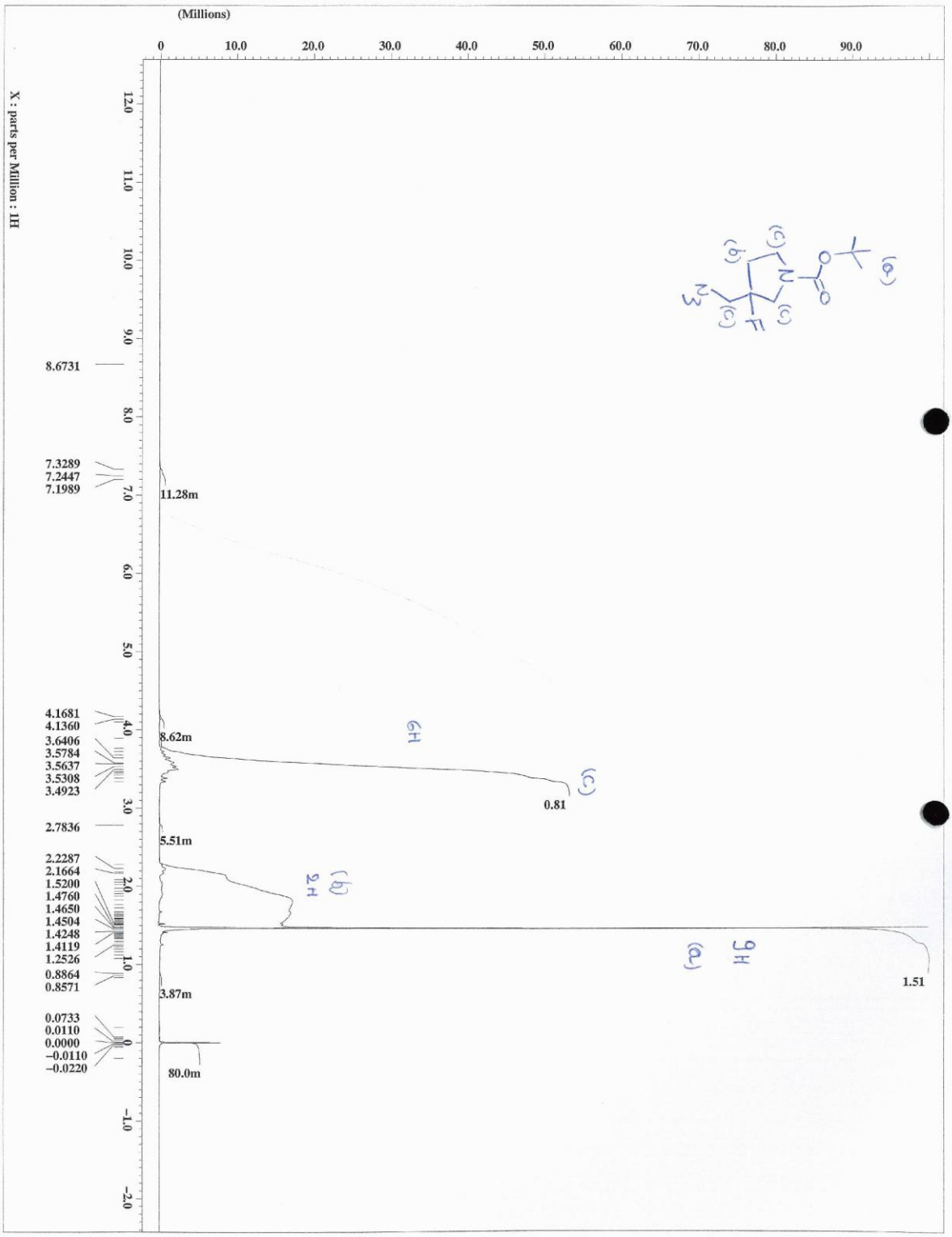
Current Chromatogram(s)

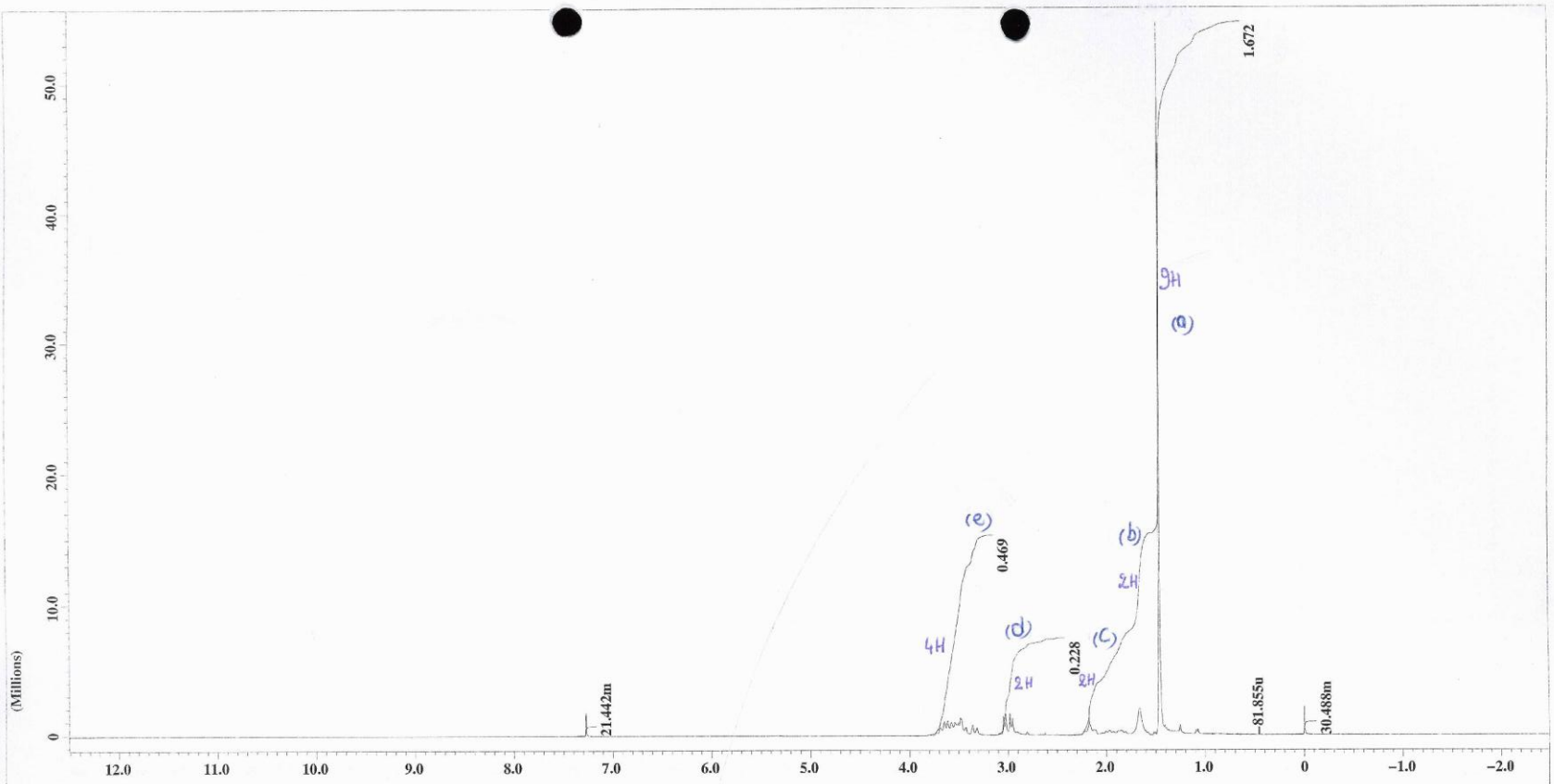



(Millions)
0
10.0
20.0
30.0
40.0
50.0
X : parts per Million : 1H
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
-1.0
-2.0
4.413m
0.343
0.698
0.864
1.626
2H
4H
5H
9H
(a)
(b)
(c)
(d)
(e)
(f)
(g)

Current Chromatogram(s)

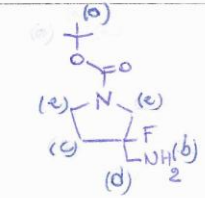



(Millions)
0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
X : parts per Million : 1H
8.6731
7.3289
7.2447
7.1989
4.1681
4.1360
3.6406
3.5784
3.5637
3.5308
3.4923
2.7836
2.2287
2.1664
1.5200
1.4760
1.4650
1.4504
1.4248
1.4119
1.2526
0.8864
0.8571
0.0733
0.0110
0.0000
−0.0110
−0.0220
11.28m
8.62m
5.51m
3.87m
80.0m
6H
0.81
(c)
2H
(b)
9H
(a)
1.51
(c)
(b)
(c)
(c)
N
N3
F
O
O
(a)



X : parts per Million : 1H

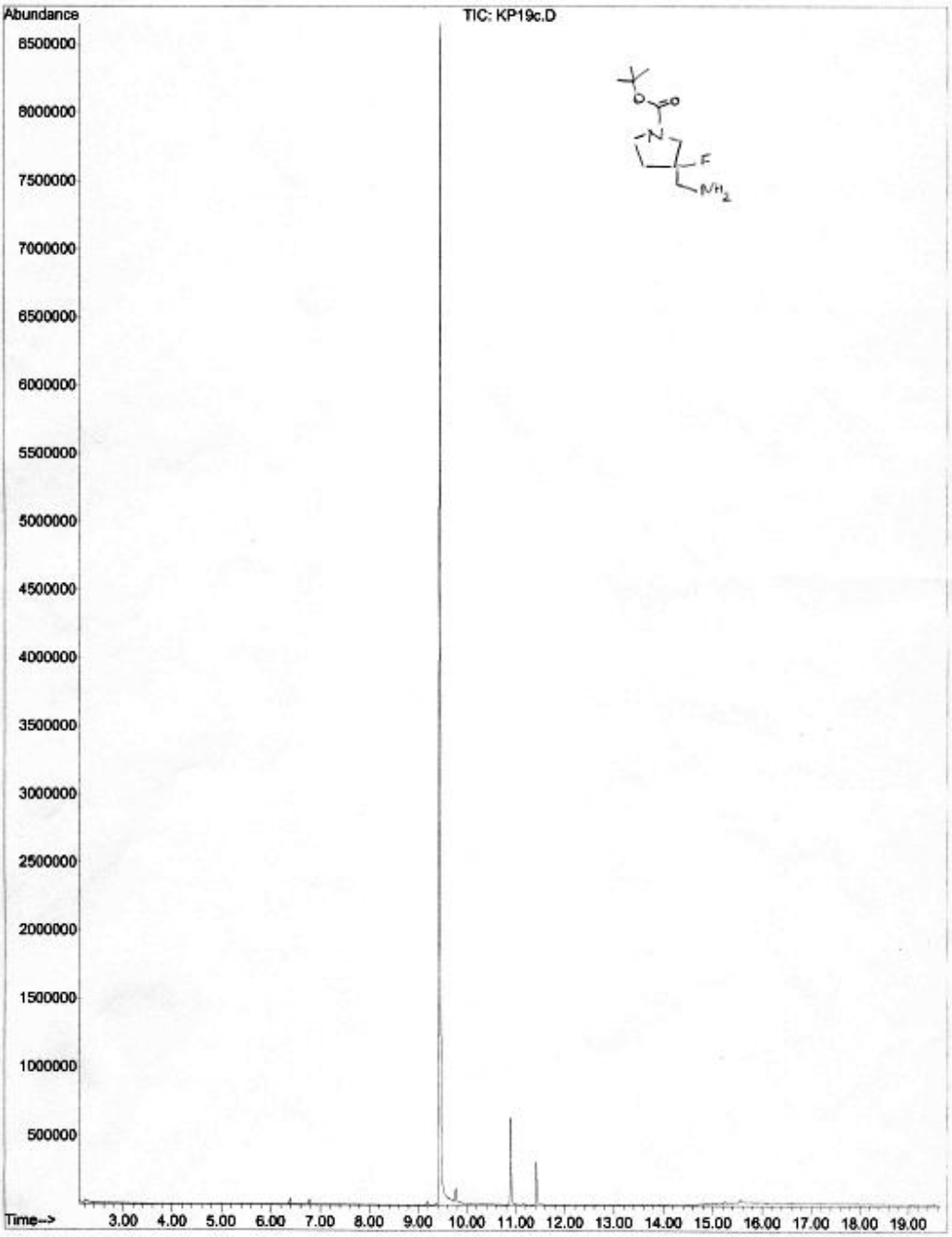
Filename	= 19c_PROTON-3.jdf	Field_strength	= 7.0586013[T] (300[MHz	Initial_wait	= 1[s]
Author	= delta3	X_acq_duration	= 1.8169856[s]	Phase_preset	= 3[us]
Experiment	= single_pulse.exp	X_domain	= 1H	Recvr_gain	= 15
Sample_id	= KP/19c	X_freq	= 300.52965592[MHz]	Relaxation_delay	= 5[s]
Solvent	= CHLOROFORM-D	X_offset	= 5[ppm]	Temp_get	= 20.6[dC]
Creation_time	= 14-OCT-2008 16:38:26	X_points	= 8192	Unblank_time	= 2[us]
Revision_time	= 14-OCT-2008 16:59:46	X_prescans	= 0		
Current_time	= 27-OCT-2008 11:35:24	X_resolution	= 0.55036209[Hz]		
		X_sweep	= 4.50856628[kHz]		
Content	= na 4h30	Clipped	= FALSE		
Data_format	= 1D COMPLEX	Mod_return	= 1		
Dim_size	= 8192	Scans	= 16		
Dim_title	= 1H	Total_scans	= 16		
Dim_units	= [ppm]				
Dimensions	= X	X_90_width	= 11.3[us]		
Site	= Eclipse+ 300	X_acq_time	= 1.8169856[s]		
Spectrometer	= DELTA_NMR	X_angle	= 90[deg]		
		X_pulse	= 11.3[us]		

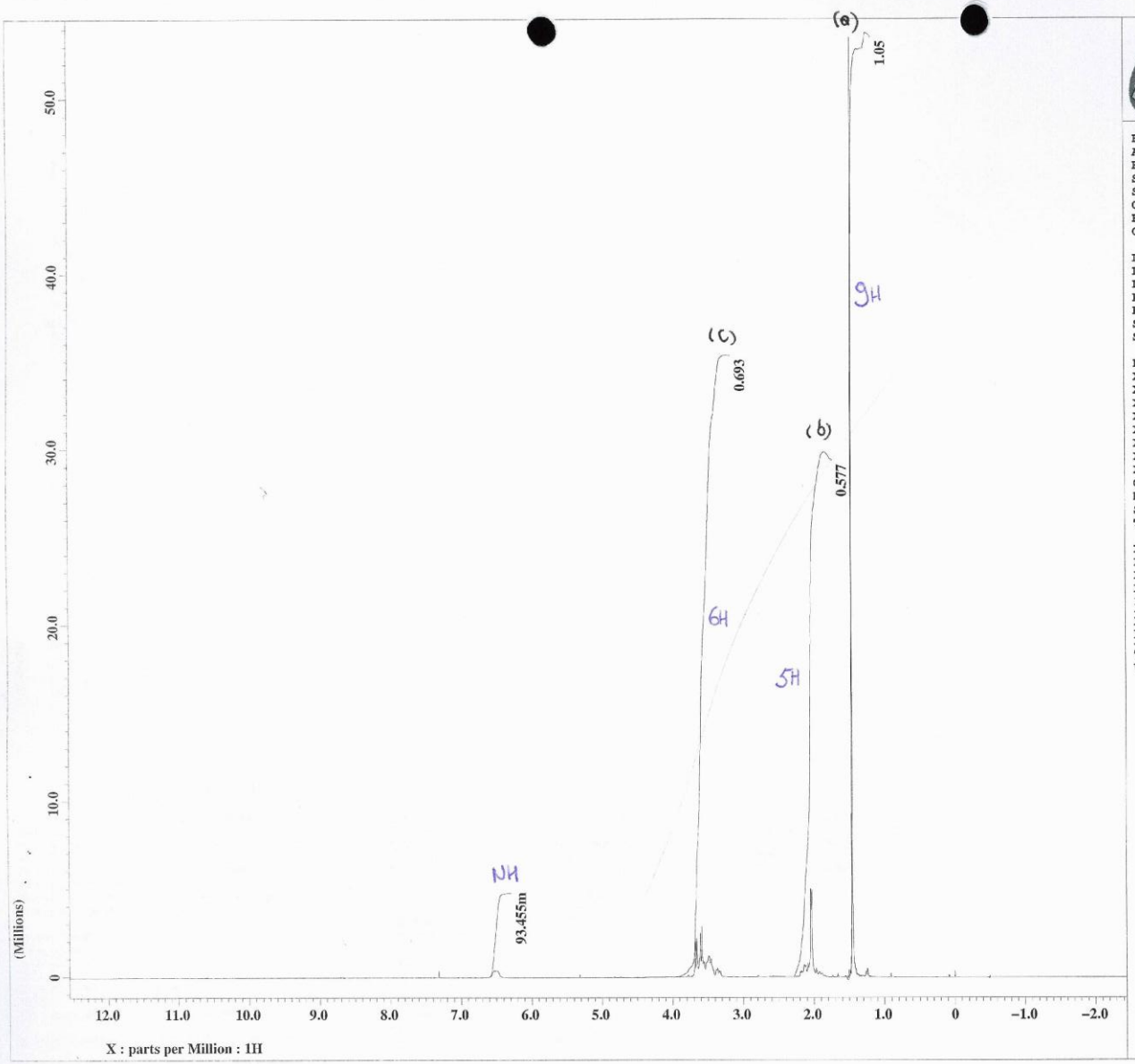


20a

20a

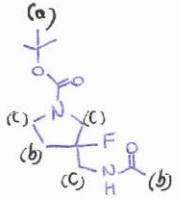
File :D:\GCMS-data\synthese\KP19c.D
Operator : AA
Acquired : 20 Oct 2008 13:51 using AcqMethod Synthese.M
Instrument : Instrument #1
Sample Name:
Misc Info :
Vial Number: 7





JEOL

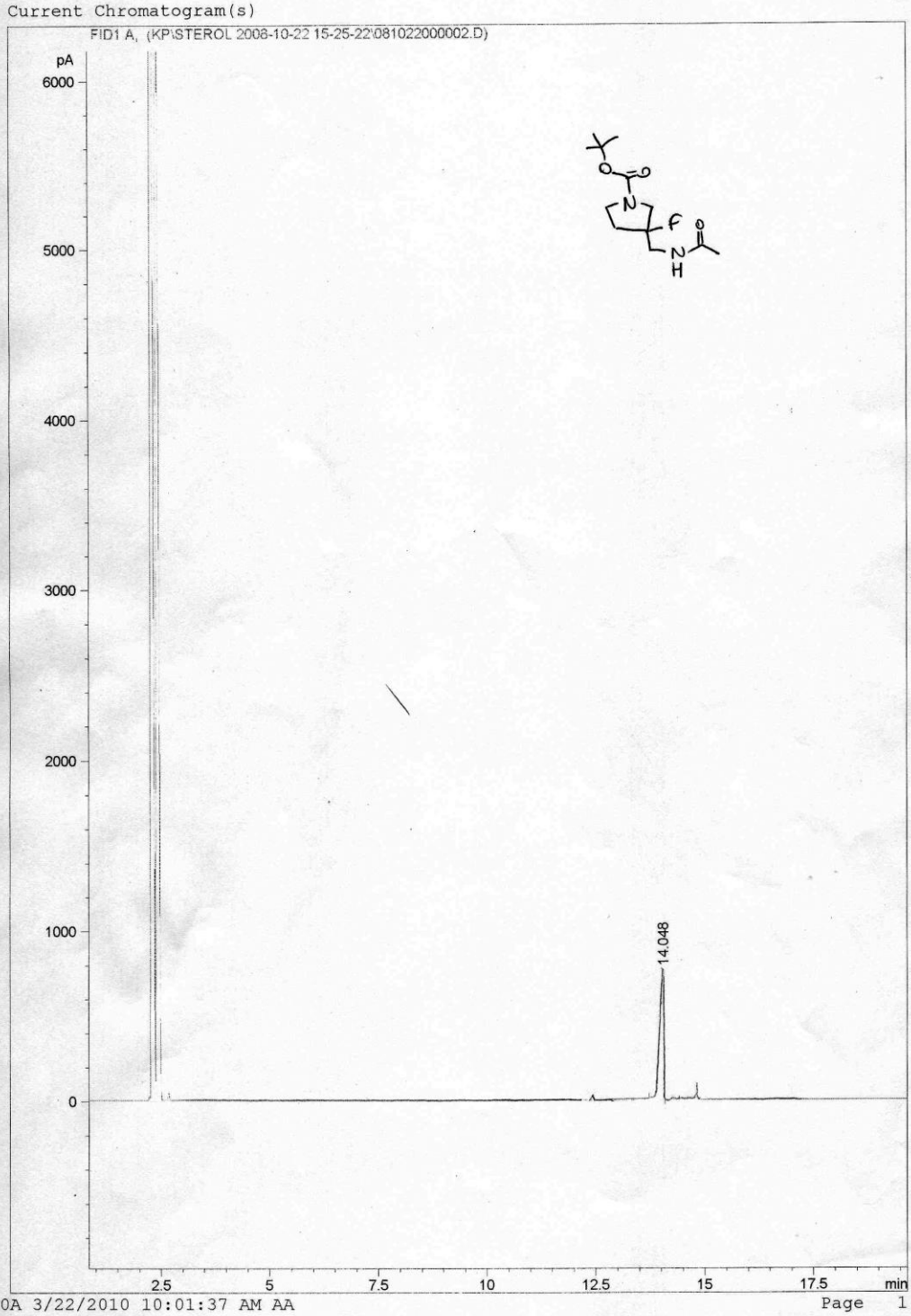
Filename	= 21a_PROTON-7.jdf
Author	= delta3
Experiment	= single_pulse.exp
Sample_id	= KP/21a
Solvent	= CHLOROFORM-D
Creation_time	= 7-NOV-2008 16:35:59
Revision_time	= 12-NOV-2008 14:08:52
Current_time	= 12-NOV-2008 14:09:02
Data_format	= 1D COMPLEX
Dim_size	= 8192
Dim_title	= 1H
Dim_units	= [ppm]
Dimensions	= X
Site	= Eclipse+ 300
Spectrometer	= DELTA_NMR
Field_strength	= 7.0586013[T] (300[MHz
X_acq_duration	= 1.8169856[s]
X_domain	= 1H
X_freq	= 300.52965592[MHz]
X_offset	= 5[ppm]
X_points	= 8192
X_prescans	= 0
X_resolution	= 0.55036209[Hz]
X_sweep	= 4.50856628[kHz]
Clipped	= FALSE
Mod_return	= 1
Scans	= 16
Total_scans	= 16
X_90_width	= 11.3[us]
X_acq_time	= 1.8169856[s]
X_angle	= 90[deg]
X_pulse	= 11.3[us]
Initial_wait	= 1[s]
Phase_preset	= 3[us]
Recvr_gain	= 8
Relaxation_delay	= 5[s]
Temp_get	= 20.1[dC]
Unblank_time	= 2[us]

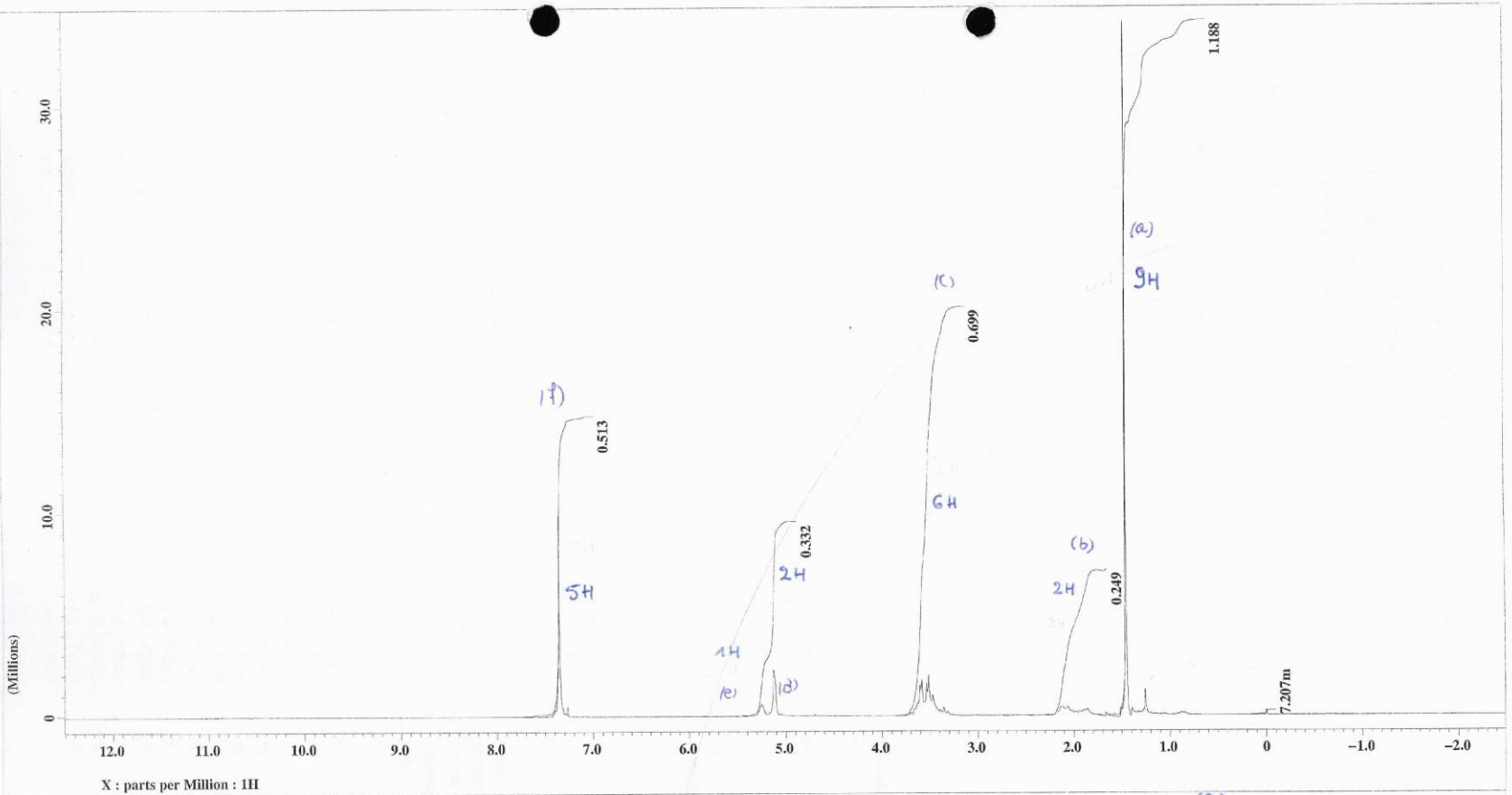


2ab

20b

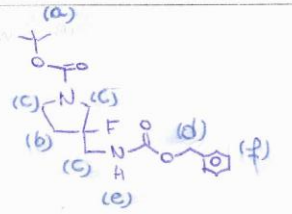
Current Chromatogram(s)





X : parts per Million : 1H

Filename	= 22b_FC_fr18-26_PROTON	Field_strength	= 7.0586013[T] (300[MHz	Initial_wait	= 1[s]
Author	= delta3	X_acq_duration	= 1.8169856[s]	Phase_preset	= 3[us]
Experiment	= single_pulse.exp	X_domain	= 1H	Recvr_gain	= 10
Sample_id	= KP/22b_FC_fr18-26	X_freq	= 300.52965592[MHz]	Relaxation_delay	= 5[s]
Solvent	= CHLOROFORM-D	X_offset	= 5[ppm]	Temp_get	= 19.3[dC]
Creation_time	= 29-OCT-2008 15:27:54	X_points	= 8192	Unblank_time	= 2[us]
Revision_time	= 30-OCT-2008 14:56:38	X_prescans	= 0		
Current_time	= 30-OCT-2008 14:56:52	X_resolution	= 0.55036209[Hz]		
		X_sweep	= 4.50856628[kHz]		
Content	= 30 mg	Clipped	= FALSE		
Data_format	= 1D COMPLEX	Mod_return	= 1		
Dim_size	= 8192	Scans	= 16		
Dim_title	= 1H	Total_scans	= 16		
Dim_units	= [ppm]				
Dimensions	= X	X_90_width	= 11.3[us]		
Site	= Eclipse+ 300	X_acq_time	= 1.8169856[s]		
Spectrometer	= DELTA_NMR	X_angle	= 90[deg]		
		X_pulse	= 11.3[us]		



20c

Print of window 38: Current Chromatogram(s)

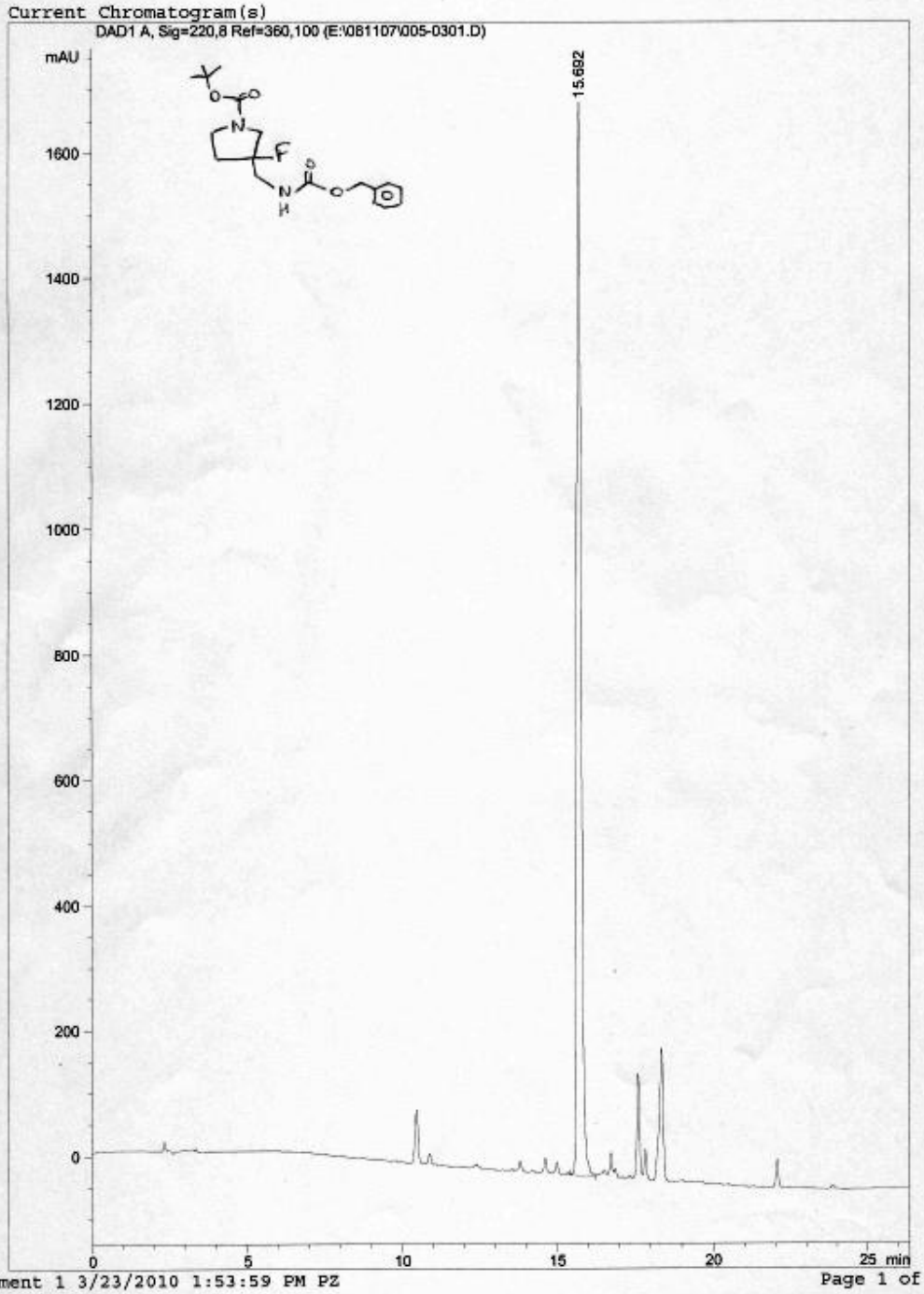
Injection Date : 11/7/2008 1:25:54 PM
Sample Name : KP/22b
Acq. Operator : PZ

Seq. Line : 3
Location : Vial 5
Inj : 1
Inj Volume : 20 µl

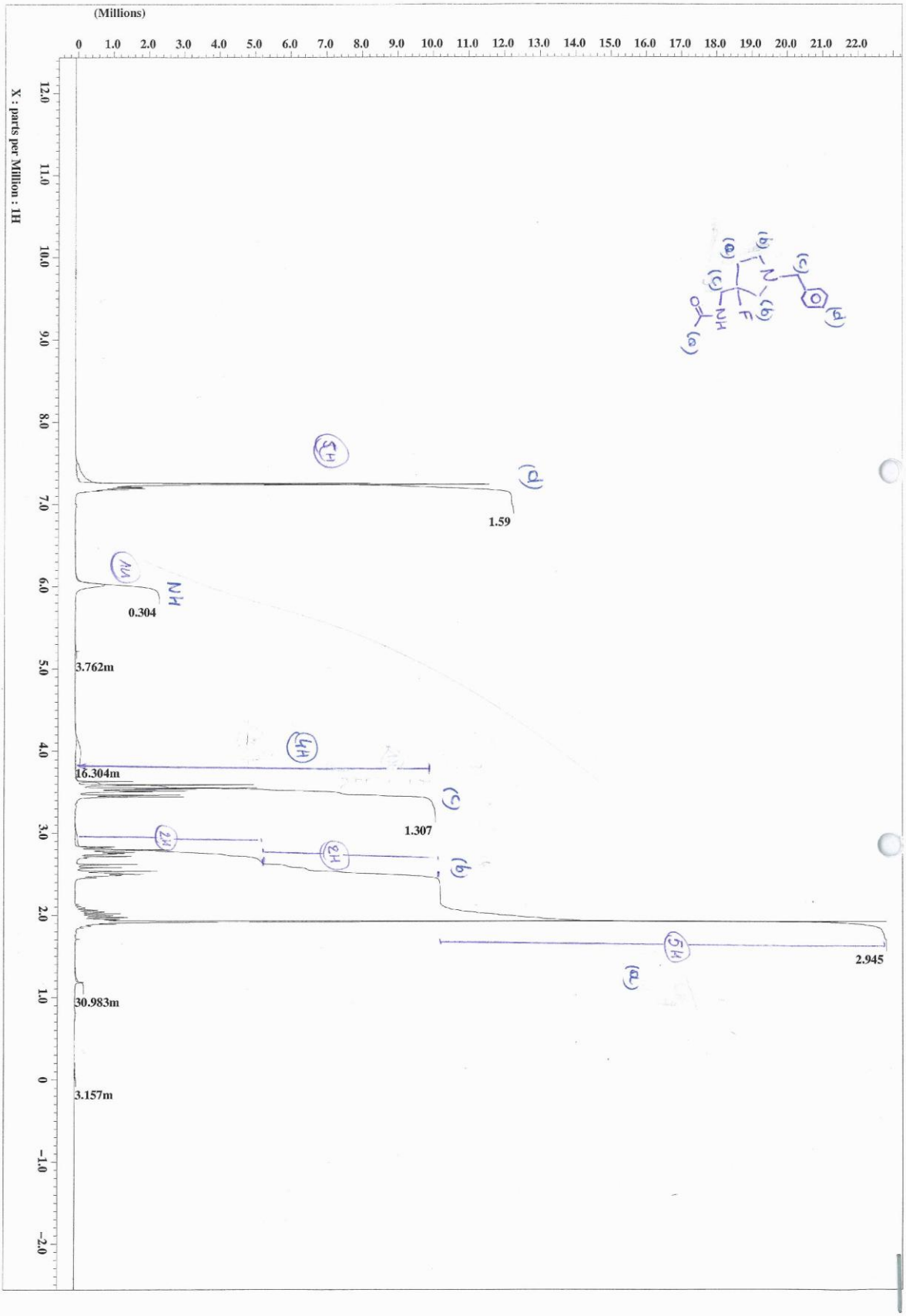
2oc

Acq. Method : D:\1\METHODS\RPLMSYAC.M
Last changed : 8/1/2008 2:46:54 PM by PZ
Analysis Method : D:\1\METHODS\RPSYACLF.M
Last changed : 3/18/2009 9:49:58 AM by vvh
methode RP-LCMS voor synthesestalen

Current Chromatogram(s)

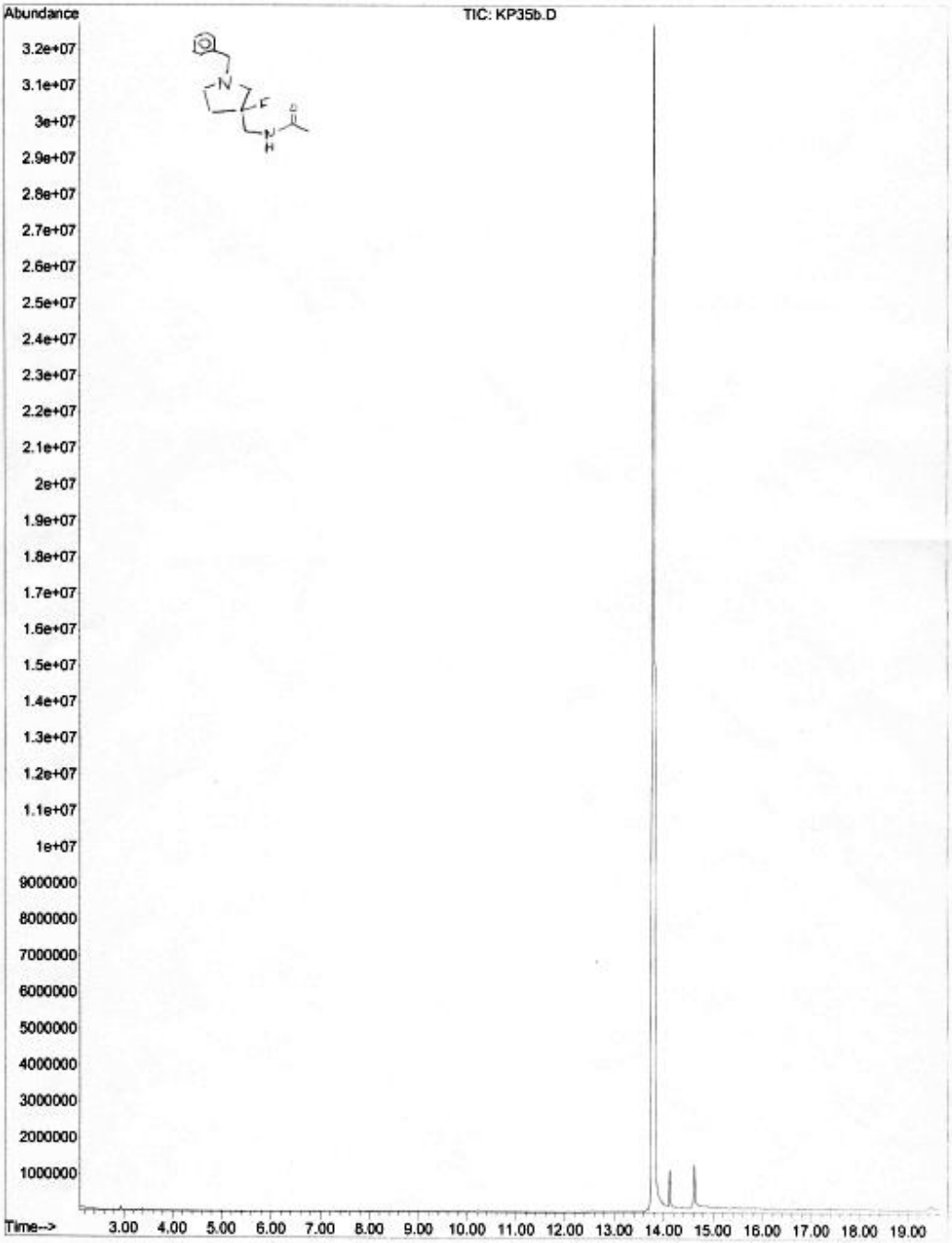


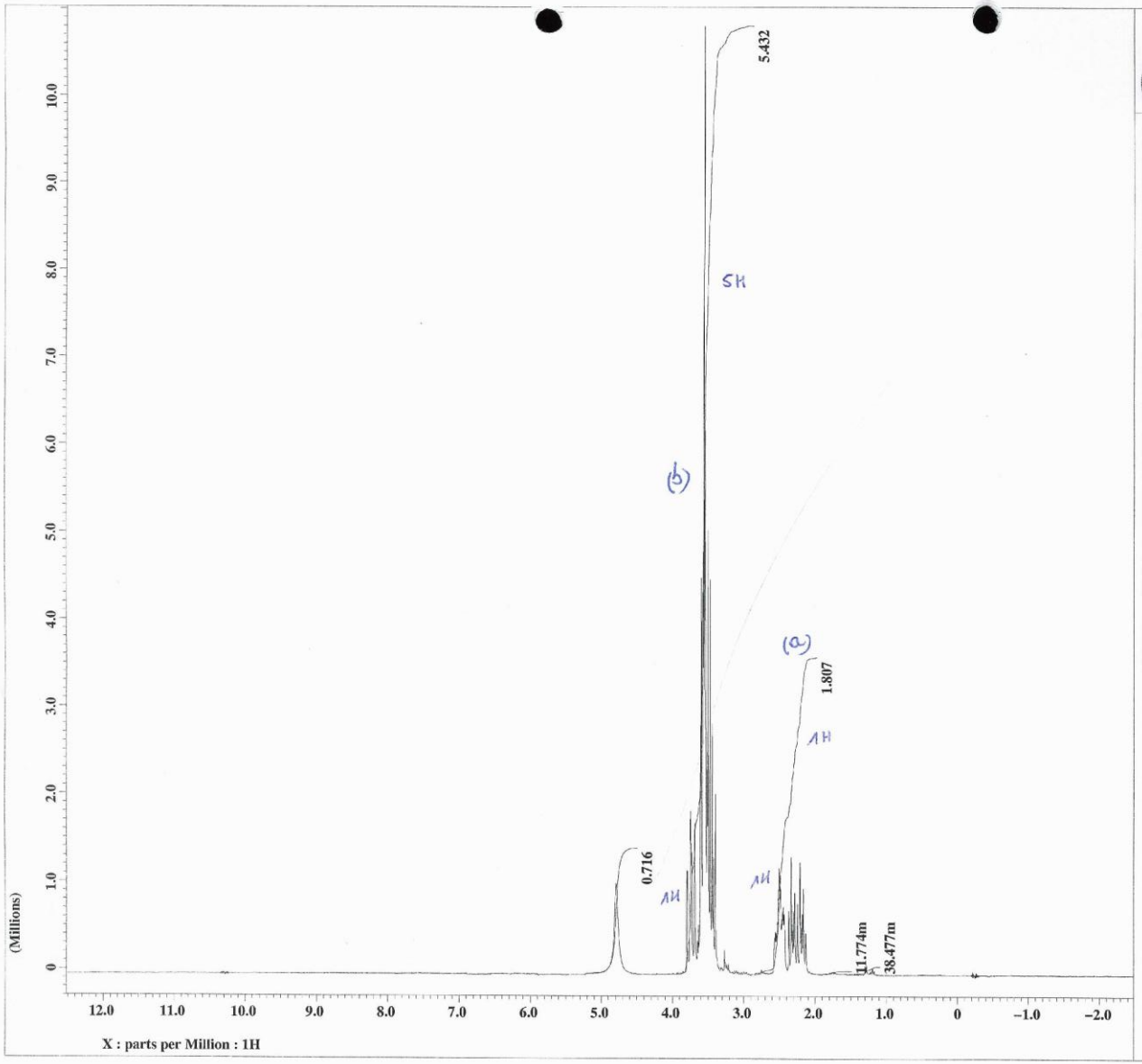
Instrument 1 3/23/2010 1:53:59 PM PZ


(Millions)
X : parts per Million : 1H
1.59
0.304
3.762m
16.304m
1.307
30.983m
3.157m
2.945
NH

2o d

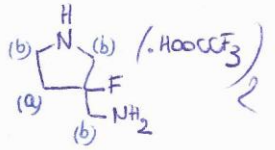
File :D:\GCMS-data\synthese\KP35b.D
Operator : AA
Acquired : 10 Feb 2009 13:41 using AcqMethod Synthese.M
Instrument : Instrument #1
Sample Name:
Misc Info :
Vial Number: 7





JEOL

Filename	= 32_PROTON-22.jdf
Author	= delta3
Experiment	= single_pulse.exp
Sample_id	= KP/32
Solvent	= D2O
Creation_time	= 13-FEB-2009 01:23:46
Revision_time	= 20-FEB-2009 18:01:31
Current_time	= 20-FEB-2009 18:01:37
Data_format	= 1D COMPLEX
Dim_size	= 8192
Dim_title	= 1H
Dim_units	= [ppm]
Dimensions	= X
Site	= Eclipse+ 300
Spectrometer	= DELTA_NMR
Field_strength	= 7.0586013[T] (300[MHz
X_acq_duration	= 1.8169856[s]
X_domain	= 1H
X_freq	= 300.52965592[MHz]
X_offset	= 5[ppm]
X_points	= 8192
X_prescans	= 0
X_resolution	= 0.55036209[Hz]
X_sweep	= 4.50856628[kHz]
Clipped	= FALSE
Mod_return	= 1
Scans	= 16
Total_scans	= 16
X_90_width	= 11.3[us]
X_acq_time	= 1.8169856[s]
X_angle	= 90[deg]
X_pulse	= 11.3[us]
Initial_wait	= 1[s]
Phase_preset	= 3[us]
Recvr_gain	= 11
Relaxation_delay	= 5[s]
Temp_get	= 399.7[dC]
Unblank_time	= 2[us]



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