SUPPLEMENTARY MATERIALS

Radiolabelling of 1,4-substituted 3-[^{18}F]fluoropiperidines and its application to new radiotracers for the NR2B NMDA receptors visualization

Radouane Koudih,[a,b,c] Gwénaëlle Gilbert,[a,b,c] Martine Dhilly,[a,b,c] Ahmed Abbas,[d] Louisa Barré,[a,b,c] Danièle Debruyne[a,b,c] and Franck Sobrio*[a,b,c]

[a] *CEA, I2BM, LDM-TEP, UMR 6302 ISTCT, GIP Cyceron, BP5229, F-14074 Caen, France. Fax: +33 2 3147 0225; Tel: +33 2 3147 0264; E-mail: sobrio@cyceron.fr*
[b] *Université de Caen Basse-Normandie, UMR 6302 ISTCT, LDM-TEP, GIP Cyceron, F-14074 Caen, France*
[c] *CNRS, UMR 6302 ISTCT, LDM-TEP, GIP Cyceron, F-14074 Caen, France*
[d] *INSERM U1077, GIP Cyceron, F-14074 Caen, France*

Content

1. Synthetic procedures

1.1. Materials and reagents

Reagents and solvents used, unless stated otherwise, were of commercially available reagents grade quality and were used without further purification. Nuclear magnetic resonance spectra ^{1}H, ^{11}C and ^{19}F NMR were recorded on a Brucker DRX 400, at 400 MHz, 100.6 MHz and 376.4 MHz respectively. ^{1}H NMR spectra were referenced internally on $CDCl_3$ (^{1}H 7.26) and ^{13}C NMR spectra were referenced internally on $CDCl_3$ (^{13}C 77.20). Coupling constants (J) are expressed in hertz (Hz) and coupling patterns are abbreviated as: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), dd (doublet of doublet) and dt (doublet of triplet). IR spectra were recorded on a Thermo Scientific Nicolet 380 FT-IR spectrometer. Flash chromatography purifications were performed on Macherey-Nagel silica gel 60 M (0.04-0.063 mm). Thin Layer Chromatography (TLC) was run on pre-coated aluminium plates of silica gel $60F_{254}$ (Merck) and Rf were established either using either an UV-lamp at 254 nm either by ninhydrin or phosphomolybdic acid hydrate spray reagent. Radioactive TLC was measured using an Instant Imager® Packard apparatus. Melting points were determined on a Barnstead Electrothermal IA 9100 melting point apparatus and are uncorrected. HPLC analyses were performed using a Waters 600 pump and controller, a Waters 717 plus autosampler and a Waters 996 photodiode arrays detector (210-380 nm) coupled with a NaI probe radioactive detector (Novelec, France). Purity was determined by HPLC on an analytical column CC 250/4 Nucleodur C-18 ISIS, Macherey-Nagel, 5µm; 1 mL/min at 220 nm and at 235 nm and the purities of compounds were found to be at least 98%. [^{18}F]-fluoride was produced by the $^{18}O(p,n)^{18}F$ nuclear reaction using the Cyclone 18/9 (IBA) cyclotron at the Cyceron PET Center. Irradiation occurred on target filled with ^{18}O-enriched water (97%, Eurisotop).

1.2. (±)-cis-1-Benzyl-4-(hydroxymethyl)piperidin-3-ol (4).

To (±)-*cis*-1-benzyl-4-(acetyloxymethyl)piperidin-3-yl acetate[22,23] (2.1 g, 6.88 mmol) was added NaOH in methanol (40 mL, 2N). The reaction mixture was stirred at room temperature for 15 h, then diluted with brine (40 mL) and extracted with EtOAc (4 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give **4** (1.43 g, 94%) as yellow crystals. mp: 81-83°C. ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.24-7.19 (m, 5H); 3.86 (s, 1H); 3.59 (d, ^{3}J=4.8 Hz, 2H); 3.44 (s, 2H); 2.89-2.79 (m, 4H); 2.06 (dd, ^{2}J=11.6 Hz, ^{3}J=1.2 Hz, 1H); 1.90 (ddd, ^{3}J=3.2 Hz, ^{3}J=12.8 Hz, ^{2}J=12.4 Hz, 1H); 1.66-1.63 (m, 1H); 1.46-1.35 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.9; 129.0; 128.2; 127.1 ; 67.0; 64.9; 62.6; 59.6; 52.8; 41.3; 22.9. ν_{max}/cm^{-1} 3344, 2920, 1012. HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{13}H_{20}NO_2$ 222.1494; found 222.1502.

1.3. (±)-*cis*-4-(Hydroxymethyl)piperidin-3-ol (5).

To a solution of **4** (2.0 g, 9.04 mmol) in methanol (60 mL), was added palladium (10%) on activated carbon catalyst (500 mg). The reaction mixture was stirred under H_2 atmosphere (1.5 bars) at room temperature for 6 h. The mixture was filtered off then concentrated under reduced pressure to give **5** (1.18 g, 99%) as a white solid. mp: 128-129°C. ^{1}H NMR (400 MHz, CD_3OD) δ 4.01 (s, 1H); 3.65 (dd, ^{3}J=7.2 Hz, ^{2}J=10.8 Hz, 1H); 3.48 (dd, ^{3}J=6 Hz, ^{2}J=10.8 Hz, 1H); 3.15-3.25 (m, 2H); 2.8 (dd, ^{2}J=13.6 Hz, ^{3}J=1.6 Hz, 1H); 2.70 (ddd, ^{3}J=3.6 Hz, ^{3}J=12.8 Hz, ^{2}J=12.8 Hz, 1H); 1.77-1.66 (m, 2H); 1.55-1.52 (m, 1H). ^{13}C NMR (100.6

MHz, CD_3OD) δ 65.0; 64.7; 52.3; 45.8; 42.8; 23.4. ν_{max}/cm^{-1} 3260, 2859, 1541, 1054. HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_6H_{14}NO_2$ 132.1025; found 132.1031.

1.4. (±)-*cis*-*tert*-Butyl 1-[4-(hydroxymethyl)piperidin-3-ol-1-yl] carboxylate (6).

To a solution of **5** (837 mg, 6.38 mmol) in DMF (30 mL), was added di-*tert*-butyl dicarbonate (2.78 g, 12.76 mmol). The reaction mixture was stirred for 48h at room temperature, then diluted with brine (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (CH_2Cl_2 / MeOH, 95:5) gave **6** as a colourless oil (1.18 g, 80%). ^1H NMR (400 MHz, CD_3OD) δ 4.0-3.97 (m, 2H); 3.80 (br s, 1H); 3.52 (ABX, dd, ^3J=6.8 Hz, ^2J=10.8 Hz, 1H); 3.38 (ABX, dd, ^3J=6.4 Hz, ^2J=10.8 Hz, 1H); 2.87-2.57 (m, 2H); 1.58-1.56 (m, 1H); 1.48 (dddd, ^3J=12.8 Hz, ^3J=12.8 Hz, ^2J =12.8 Hz, ^3J=4.4 Hz, 1H); 1.35-1.32 (m, 10H). ^{13}C NMR (100.6 MHz, CD_3OD) δ 156.1; 80.0; 67.3; 65.1; 50.1; 44.0, 41.4; 28.4; 22.4. ν_{max}/cm^{-1} 3383, 2923, 1662, 1365, 1162, 1052. MS (ESI) *m/z* 232 ($[M+H]^+$, 68); 176 (100). HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{11}H_{22}NO_4$ 232.1549; found 232.1544.

1.5. (±)-*cis*-1-Benzoyl-4-(hydroxymethyl)piperidin-3-ol (7).

To a solution of **5** (360 mg, 2.7 mmol) and Et_3N (1.56 mL, 11.2 mmol) in DMF (7 mL), was added benzoyl chloride (357 µL, 3.08 mmol) under nitrogen atmosphere. The mixture was stirred overnight at 80°C. The reaction mixture was diluted with brine (10 mL) and extracted with EtOAc (4 x 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (CH_2Cl_2 / MeOH, 99:1) gave **7** as a brown oil (370 mg, 56%). ^1H NMR (500 MHz, CD_3OD, rotamers 40/60) δ 7.38-7.33 (m, 5H); 4.60-4.57 (m, 1H); 3.99 (br s, 0.4H); 3.74 (br s, 0.6H); 3.70-3.66 (m, 1H); 3.55-3.49 (m, 1H); 3.40-3.36 (m, 1H); 3.13-3.10 (dd, ^2J=14.3 Hz, ^3J=1.08 Hz, 0.6H); 2.99-2.90 (m, 0.4H); 2.86-2.83 (m, 0.4H); 2.75-2.74 (m, 0.6H); 1.75-1.71 (m, 1H); 1.55-1.49 (m, 1.6H); 1.40-1.30 (m, 0.4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.8; 137.5 and 137.3; 130.9 and 130.8; 129.7 and 129.5; 128.6; 127.7; 66.1 and 66.0; 64.3 and 64.3; 55.4; 43.8; 43.4; 24.3; 23.5. ν_{max}/cm^{-1} 3351, 2920, 1596, 1442, 1084. MS (ESI) *m/z* 236 ($[M+H]^+$, 70); 218 (33); 114 (25); 105 (100). HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{13}H_{18}NO_3$ 236.1287; found 236.1294.

1.6. (±)-*cis*-1-Butyl-4-(hydroxymethyl)piperidin-3-ol (8).

To a solution of **5** (147 mg, 1.12 mmol) in anhydrous DMF (2 mL) was added, *n*-butyl bromide (184 mg, 1.34 mmol) and potassium carbonate (619 mg, 4.47 mmol). The reaction mixture was stirred overnight at 70°C. After cooling to room temperature, water was added (3 mL) and the reaction mixture was extracted with EtOAc (3 x 3 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give **8** (115 mg, 55%) as a brown solid. mp: 101-103°C. ^1H NMR (400 MHz,$CDCl_3$) δ 3.88 (s, 1H); 3.66 (dd, ^3J=4 Hz, ^2J=10.8 Hz, 1H); 3.60 (dd, ^3J=5.8 Hz, ^2J=10.8 Hz, 1H); 2.89-2.81 (m, 2H); 2.30-2.24 (m, 2H); 2.02 (dd, ^2J=11.4 Hz, ^3J=1.2 Hz, 1H); 1.93-1.88 (m, 1H); 1.75-1.65 (m, 1H); 1.44-1.21 (m, 6H); 0.84 (t, ^3J=7.2 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 67.2; 65.2; 59.6; 57.7; 53.1; 41.2; 28.6; 22.6; 20.5; 13.9. ν_{max}/cm^{-1} 3351, 2929, 1029. HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{10}H_{22}NO_2$ 188.1651; found 188.1644.

1.7. (±)-*cis*-*tert*-Butyl 4-(trityloxymethyl)piperidin-3-ol-1-yl carboxylate (9).

To a solution of **6** (281 mg, 1.21 mmol) in anhydrous pyridine (6.5 mL) was added, triphenylmethyl chloride (400 mg, 1.44 mmol) and a catalytic amount of DMAP. The reaction mixture was heated at 110 °C for 10 h. After cooling to room temperature, water was added (5

mL) and the reaction mixture was extracted with EtOAc (4 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (9/1, heptane/EtOAc) gave **6** (281 mg, 1.21 mmol) as a white solid (460 mg, 80%). mp: 139-141°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.34 (m, 6H); 7.32-7.13 (m, 9H); 4.02-3.94 (m, 3H); 3.16-3.12 (m, 1H); 3.06-3.02 (m, 1H); 2.80-2.77 (m, 1H); 2.67-2.61 (m, 1H); 2.01 (br s, 1H); 1.73-1.69 (m, 1H); 1.59-1.53 (m, 1H); 1.37-1.35 (m, 10H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.9; 143.9; 128.6; 127.9; 127.0; 86.7; 79.7; 66.3; 64.9; 50.2; 43.4; 40.7; 28.4; 23.2. ν_{max}/cm^{-1} 3461, 2978, 1665, 1434, 1166, 1064. HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{30}H_{35}NO_4Na$ 496.2464; found 496.2471.

1.8. (±)-*cis*-1-Benzoyl-4-(trityloxymethyl)piperidin-3-ol (10).

Following the procedure for the preparation of **9**, the compound **10** was obtained from **7** (442 mg, 1.88 mmol) as a brown oil (640 mg, 71%). ^{1}H NMR (500 MHz, CD_3OD, rotamers) δ 7.34-7.10 (m, 20 H); 4.59-4.52 (m, 1H); 4.07 (s, 0.5H); 3.83 (s, 0.5H); 3.66-3.64 (m, 1H); 3.20-3.08 (m, 1.5H); 2.97-2.96 (m, 0.5H); 2.90-2.84 (m, 1.5H); 2.73-2.72 (m, 0.5H); 1.88-1.86 (m, 1H); 1.49-1.18 (m, 3H). ^{13}C NMR (125 MHz, CD_3OD, rotamers) δ 173.7 and 173.5; 145.6; 137.5 and 137.3; 130.8 and 130.7; 129.9; 129.6 and 129.5; 128.8 and 128.6; 128.1 and 127.8; 87.6; 66.3 and 66.2; 65.8 and 65.7; 55.5; 43.4; 42.2 and 42.1; 24.8; 24.1 and 24.0. ν_{max}/cm^{-1} 3428, 1052, 1024. MS (ESI) *m/z* 478 ($[M+H]^+$, 25); 243 (100). HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{32}H_{32}NO_3$ 478.2382; found 478.2369.

1.9. (±)-*cis*-1-Butyl-4-(trityloxymethyl)piperidin-3-ol (11).

Following the procedure for the preparation of **9**, the compound **11** was obtained from **8** (100 mg, 0.53 mmol) as a brown oil (130 mg, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, ^{3}J=1.1 Hz, 6H); 7.32-7.23 (m, 9H); 3.97 (s, 1H); 3.26-3.22 (m, 1H); 3.26-3.22 (m, 1H); 3.04-2.98 (m, 2H); 2.90-2.84 (m, 1H); 2.39-2.33 (m, 2H); 2.13-2.10 (m, 1H); 2.03-1.94 (m, 1H); 1.68-1.64 (m, 1H); 1.57-1.34 (m, 6H); 0.92 (t, ^{3}J=7.2 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.3; 128.7; 127.7; 126.9; 86.4; 65.9; 65.0; 59.7; 57.8; 53.3; 40.9; 28.9; 23.9; 20.5; 14.0. ν_{max}/cm^{-1} 2929, 1447, 1099, 1065. MS (ESI) *m/z* 430 ($[M+H]^+$, 11); 243 (100). HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{29}H_{36}NO_2$ 430.2746; found 430.2751.

1.10. (±)-*cis*-1-Benzyl-4-(trityloxymethyl)piperidin-3-ol (12).

Following the procedure for the preparation of **9**, the compound **12** was obtained from **4** (200 mg, 0.9 mmol) as a white powder (256 mg, 61%). mp: 175-177°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, ^{3}J=1.1 Hz, 6H); 7.23-7.12 (m, 14H); 3.89 (s, 1H); 3.45 (s, 2H); 3.15 (dd, ^{2}J=8.8 Hz, ^{3}J=7.56 Hz, 1H); 2.93-2.90 (m, 2H); 2.79-2.76 (m, 1H); 2.67 (br s, 1H); 2.11-2.09 (m, 1H); 1.97-1.90 (m, 1H); 1.61-1.58 (m, 1H); 1.46-1.39 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.3; 129.2; 128.7; 128.4; 127.7; 127.4; 126.9; 86.3; 65.8; 64.8; 62.5; 59.5; 52.9; 40.8; 23.6. ν_{max}/cm^{-1} 3020, 2910, 1447, 1072. HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{32}H_{34}NO_2$ 464.2590; found 464.2597.

1.11. (±)-*cis*-*tert*-Butyl 4-(trityloxymethyl)-3-(methylsulfonyl) oxypiperidin-1-yl carboxylate (13).

To a solution of **9** (265 mg, 0.56 mmol) in dry pyridine (6 mL), was added silver trifluoromethanesulfonate (285 mg, 1.1 mmol) under nitrogen atmosphere at 0°C, followed by the addition of methanesulfonyl chloride (202 mg, 1.1 mmol). The reaction mixture was stirred at 0°C for 1 h, then further 2 h at room temperature. The reaction mixture was diluted with water (6 mL) and extracted with EtOAc (4 x 8 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (CH_2Cl_2 / MeOH, 98:2) gave **13** as a white solid (255 mg, 82%). mp= 129-

131°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.17 (m, 15 H); 5.10-4.86 (m, 1H); 4.56-4.51 (m, 1H); 4.21-4.19 (m, 1H); 3.10-2.86 (m, 4H); 2.56 (s, 3H); 1.93-1.90 (m, 1H); 1.40-1.37 (m, 11H). ν_{max}/cm^{-1} 2930, 1681, 1445, 1174, 1067. HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{31}H_{37}NO_6SNa$ 574.2239; found 574.2233 HPLC purity: H_2O / MeCN; 80:20; t_R: 9.5 min.

1.12. (±)-*cis*-1-Benzoyl-4-(trityloxymethyl)-3-(methylsulfonyl) oxypiperidine (14).

Following the procedure for the preparation of **13**, the compound **14** was obtained from **10** (200 mg, 0.42 mmol) as a yellow viscous oil (220 mg, 94%). ^{1}H NMR (400 MHz, CD_3OD, rotamers) δ 7.43-7.24 (m, 20 H); 5.18-5.07 (m, 1H); 4.76-4.65 (m, 0.5H); 4.11-4.08 (m, 0.5H); 3.73-3.70 (m, 0.5H); 3.43-3.39 (m, 0.5H); 3.15-2.57 (m, 7H); 2.20-2.15 (m, 1H); 1.62-1.43 (m, 2H). ν_{max}/cm^{-1} 3016, 2931, 1599, 1444, 1170, 1077. HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{33}H_{33}NO_5SNa$ 578.1977; found 578.1968. HPLC purity: H_2O / MeCN; 80:20; t_R: 5.8 min.

1.13. (±)-*cis*-1-Butyl-4-(trityloxymethyl)-3-(methylsulfonyl)oxypiperidine (15).

Following the procedure for the preparation of **13**, the compound **15** was obtained from **11** (120 mg, 0.27 mmol) as a brown viscous oil (93 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.32 (m, 6H); 7.25-7.17 (m, 9H); 4.97 (br s, 1H); 3.29-3.26 (m, 1H); 3.14-2.99 (m, 2H); 2.84-2.82 (m, 1H); 2.66 (s, 3H); 2.32-2.20 (m, 2H); 2.10-2.03 (m, 1H); 1.94-1.92 (m, 1H); 1.78-1.76 (m, 1H); 1.55-1.34 (m, 4H); 1.25-1.20 (m, 2H); 0.82 (t, ^{3}J=7.3 Hz, 3H). ν_{max}/cm^{-1} 2961, 1448, 1153, 1066, 1037. MS (ESI) *m/z* 508 ($[M+H]^+$, 3); 430 (35); 243 (100). HPLC purity: H_2O / MeCN / TFA; 50:50:0.1; t_R: 10.8 min.

1.14. (±)-*cis*-1-Benzyl-4-(trityloxymethyl)-3-(methylsulfonyl)oxypiperidine (16).

Following the procedure for the preparation of **13**, the compound **16** was obtained from **12** (90 mg, 0.194 mmol) as a brown solid (103 mg, 98%). mp: 71-73°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.44 (m, 6H); 7.36-7.27 (m, 14H); 5.08 (br s, 1H); 3.59 (d, AB, ^{2}J=13.2 Hz, 2H); 3.37-3.34 (m, 1H); 3.20-3.12 (m, 2H); 2.96-2.93 (m, 1H); 2.69 (s, 3H); 2.28-2.22 (m, 1H); 2.15-2.09 (m, 1H); 1.90-1.88 (m, 1H); 1.63-1.47 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.8; 137.7; 129.1; 128.6; 128.2; 127.9; 127.2; 127.1; 86.8; 63.6; 62.5; 56.6; 53.4; 52.4; 40.2; 38.6; 23.7. ν_{max}/cm^{-1} 3055, 1448, 1173, 1038. MS (ESI) *m/z* 542 ($[M+H]^+$, 2); 464 (6); 243 (100). HPLC purity: H_2O / MeCN / TFA; 50:50:0.1; t_R: 12.4 min.

1.15. (±)-*cis*-*tert*-Butyl 1-[3-fluoro-4-(hydroxymethyl)piperidin-1-yl] carboxylate (*cis*-*17*) and (±)-*trans*-*tert*-butyl 1-[3-fluoro-4-(hydroxymethyl)piperidin-1-yl] carboxylate (*trans*-17).

A solution of 9-BBN (0.5 M in THF, 44.65 mL, 22.32 mmol) was added under nitrogen atmosphere to a solution of *tert*-butyl 1-[3-fluoro-4-methylenepiperidin-1-yl] carboxylate[a] (3.2 g, 14.88 mmol) in THF (55 mL). The resulting solution was refluxed for 2 h. After cooling to 0°C, NaOH 3N (25 mL) was added and the mixture was stirred for 5 min. Then, H_2O_2 (25 mL) was added and the stirring was hold for 10 min. The reaction was quenched with water (50 mL) and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (CH_2Cl_2 / AcOEt, 9:1) permitted to obtain *cis*-**17** (1.7 g, 49%) and *trans*-**17** (1.5 g, 43%) as colorless oils. *Cis*-**17**: ^{1}H NMR δ (400 MHz, $CDCl_3$) 4.74 (d, $^2J_{H-F}$=48 Hz, 1H); 4.36-4.04 (m, 2H); 3.67-3.62 (m, 1H); 3.56-3.52 (m, 1H); 2.82-2.59 (m, 2H); 1.76-1.54 (m, 3H); 1.39 (s, 9H). ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 155.2 (CO); 86.1 (d, $^1J_{C-}$

$_F$=176 Hz, CH); 79.8 (C); 63.2 (d, $^4J_{C-F}$=3.3 Hz, CH_2); 49.0 (CH_2); 42.6 (CH_2); 41.8 (d, $^3J_{C-F}$=19.8 Hz, CH); 28.4 (CH_3); 22.4 (CH_2). ^{19}F NMR δ (376.5 MHz, $CDCl_3$) -203.4. MSMS (ESI) *m/z* 234 ($[M+H]^+$, 45); 178 (100). HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{11}H_{21}FNO_3$ 234.1505, found 234.1517. HPLC purity: H_2O / MeCN; 60:40; t_R: 8.7 min. *Trans*-**17**: ^{1}H NMR δ (400 MHz, $CDCl_3$) 4.39-4.21 (m, 2H); 3.97-3.95 (m, 1H); 3.70 (ABX, dd, ^{3}J=4.3 Hz, ^{2}J=10.8 Hz, 1H); 3.60 (ABX, dd, ^{3}J=5.2 Hz, ^{2}J=10.8 Hz, 1H); 2.68-2.62 (m, 2H); 1.77-1.69 (m, 2H); 1.38-1.25 (m, 10H). ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 154.5 (CO); 88.0 (d, $^1J_{C-F}$=176 Hz, CH); 80.2 (C); 63.3 (d, $^4J_{C-F}$=2.2 Hz, CH_2); 48.0 (CH_2); 44.0 (d, $^3J_{C-F}$=16 Hz, CH); 41.0 (CH_2); 28.5 (CH_3); 26.2 (CH_2). ^{19}F NMR δ (376.5 MHz, $CDCl_3$) -186.8 (d, $^2J_{H-F}$=49 Hz). HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{11}H_{21}FNO_3$ 234.1505, found 234.1510. HPLC purity: H_2O / MeCN; 60:40; t_R: 10.7 min.

1.16. (±)-*cis*-3-fluoro-4-(hydroxymethyl)piperidine hydrochloride (*cis*-18).

Following the procedure for the preparation of *trans*-**18**, the compound *cis*-**18** was obtained from *cis*-**17** (240 mg, 1.03 mmol) as a yellow oil (174 mg, 99%). ^{1}H NMR (400 MHz, CD_3OD) δ 4.76 (d, $^2J_{H-F}$=49.6 Hz, 1H); 3.61 (ABX, dd, ^{3}J=8.4 Hz, ^{2}J=10.8 Hz, 1H); 3.46-3.42 (m, 1H); 3.27-3.20 (m, 1H); 3.09-3.04 (m, 1H); 2.80-2.76 (dd, ^{2}J=14.3 Hz, ^{3}J=1.08 Hz, 1H); 2.70-2.59 (m, 1H); 1.86-1.71 (m, 1H); 1.53-1.44 (m, 2H). ^{13}C NMR (100.6 MHz, CD_3OD) δ 87.5 (d, $^1J_{C-F}$=171.3 Hz); 63.8 (d, $^4J_{C-F}$=3.5 Hz); 50.2 (d, $^3J_{C-F}$=21 Hz); 45.8; 42.9 (d, $^3J_{C-F}$=19.7 Hz); 24.8. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -205.8. MS (ESI) *m/z* 134 ($[M+H]^+$, 100); 116 (100); 114 (37); 96 (66). HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_6H_{13}FNO$ 134.0981; found 134.0986.

1.17. (±)-*trans*-3-fluoro-4-(hydroxymethyl)piperidine hydrochloride (*trans*-18).

HCl gas was bubbled through a solution of *trans*-**17** (540 mg, 2.31 mmol) in EtOAc (3 mL) for about 45 min. The solvent was then removed under reduced pressure and the chlorhydrate *trans*-**18** was obtained as a yellow oil (390 mg, 99%). ^{1}H NMR (400 MHz, CD_3OD) δ 4.93-4.75 (m, 1H); 3.72 (d, ^{3}J=4.8 Hz, 2H); 3.61-3.52 (m, 1H); 3.37-3.32 (m, 1H); 3.26-3.19 (m, 1H); 3.13-3.06 (m, 1H); 2.17-2.06 (m, 2H); 1.82-1.78 (m, 1H). ^{13}C NMR (100.6 MHz, CD_3OD) δ 86.0 (d, $^1J_{C-F}$=173.6 Hz); 61.4 (d, $^4J_{C-F}$=6 Hz); 45.9 (d, $^3J_{C-F}$=28.4 Hz); 43.1; 41.5 (d, $^3J_{C-F}$=18.4 Hz); 22.9 (d, $^4J_{C-F}$=5.4 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -189.3 (d, $^2J_{H-F}$=169.3 Hz). ν_{max}/cm^{-1} 3363, 1042. HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_6H_{13}FNO$ 134.0981; found 134.0986.

1.18. (±)-*cis*-1-Benzyl-3-fluoro-4-(hydroxymethyl)piperidine (*cis*-19).

To a solution of *cis*-**18** (1.2 g, 7.11 mmol), Et_3N (4 mL, 28.44 mmol) in DMF (15 mL), was added benzyl bromide (1.01 mL, 8.53 mmol). The reaction mixture was stirred overnight at 80°C. After cooling to RT, the reaction mixture was diluted with water (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over MgSO4, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (CH_2Cl_2 / MeOH, 98:2) led to *cis*-**19** (1.2 g, 73%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.29 (m, 5H); 4.86 (d, $^2J_{H-F}$=48 Hz, 1H); 3.79 (ABX, dd, ^{3}J=7.7 Hz, ^{2}J=10.7 Hz, 1H); 3.70-3.30 (m, 4H); 3.30-3.23 (m, 1H); 3.03-2.98 (m, 1H); 2.25-2.09 (m, 2H); 1.77-1.56 (m, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.7; 129.1; 128.2; 127.1; 87.1 (d, $^1J_{C-F}$=174 Hz); 63.5 (d, $^4J_{C-F}$=4.4 Hz); 62.72; 56.5 (d, $^3J_{C-F}$=19.1 Hz); 52.3; 41.4 (d, $^3J_{C-F}$=19.4 Hz); 23.2. ^{19}F NMR

(376.5 MHz, $CDCl_3$) δ -199.3. ν_{max}/cm^{-1} 3318, 2921, 1453, 1070, 1012. HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{13}H_{19}FNO$ 224.1451; found 224.1459.

1.19. (±)-*trans*-1-Benzyl-3-fluoro-4-(hydroxymethyl)piperidine (*trans*-19).

Following the procedure for the preparation of *cis*-**19**, the compound *trans*-**19** was obtained from *trans*-**18** (114 mg, 0.86 mmol) as a yellow oil (110 mg, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.30 (m, 5H); 4.61-4.44 (ddt, $^2J_{H-F}$=48 Hz, ^{3}J=4.8 Hz, ^{3}J=9.8 Hz, ^{3}J=9.8 Hz, 1H); 3.86 (ABX, dd, ^{3}J=4.8 Hz, ^{2}J=10.8 Hz, 1H); 3.71 (ABX, dd, ^{3}J=5.3 Hz, ^{2}J=10.8 Hz, 1H); 3.64 (d, AB, ^{2}J=13.2 Hz, 2H); 3.25-3.20 (m, 1H); 2.91-2.87 (m, 1H); 2.12-2.01 (m, 2H); 1.82-1.65 (m, 2H); 1.52-1.46 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.8; 129.0; 128.3; 127.2; 90.9 (d, $^1J_{C-F}$=171.5 Hz); 64.4; 62.6; 57.0 (d, $^3J_{C-F}$=26 Hz); 52.4; 44.2 (d, $^3J_{C-F}$=16 Hz); 26.2 (d, $^4J_{C-F}$=9.1 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -185.7 (d, $^2J_{H-F}$=45 Hz). ν_{max}/cm^{-1} 3318, 2921, 1453, 1070, 1012. HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{13}H_{19}FNO$ 224.1451; found 224.1459.

1.20. (±)-*cis*-1-Benzoyl-3-fluoro-4-(hydroxymethyl)piperidine (*cis*-20).

Following the procedure for the preparation of **7**, the compound *cis*-**20** was obtained from *cis*-**18** (126 mg, 0.75 mmol) as a white solid (154 mg, 87%). mp: 178-180°C. ^{1}H NMR (400 MHz, CD_3OD, rotamers 60/40) δ 7.49-7.41 (m, 5H); 5.09-4.75 (m, 2H); 4.34-4.32 (m, 1H); 4.17-4.15 (m, 0.4H); 4.08-4.02 (m, 0.6H); 384-3.80 (m, 0.4H); 3.55-3.54 (m, 0.6H); 3.14-2.90 (m, 2H); 2.38-2.29 (m, 1H); 1.79-1.67 (m, 1.6H); 1.28-1.11 (m, 0.4H). ^{13}C NMR (100.6 MHz, CD_3OD, rotamers) δ 167.7; 162.5; 134.3; 131.3 and 131.1; 130.5; 129.6; 128.4 and 127.9; 127.7 and 122.2; 88.3 (d, $^1J_{C-F}$=171 Hz); 65.9; 52.3 (d, $^3J_{C-F}$=23 Hz); 42.7; 40.1 (d, $^3J_{C-F}$=20.1 Hz); 23.8. ^{19}F NMR (376.5 MHz, CD_3OD) δ -204.7 . ν_{max}/cm^{-1} 3364, 2930, 1612, 1462, 1073, 1024.

1.21. (±)-*trans*-1-Benzoyl-3-fluoro-4-(hydroxymethyl)piperidine (*trans*-20).

Following the procedure for the preparation of **7**, the compound *trans*-**20** was obtained from *trans*-**18** (261 mg, 1.55 mmol) as a brown oil (80 mg, 22%). ^{1}H NMR (500 MHz, CD_3OD, rotamers 55/45) δ 7.38-7.32 (m, 5H); 4.62-4.60 (m, 0.5H); 4.43-4.27 (m, 1.5H); 3.73-3.71 (m, 0.5H); 3.60-3.57 (m, 2.5H); 3.20-2.94 (m, 2H); 1.88-1.83 (m, 1.5H); 1.72-1.69 (m, 0.5H); 1.47-1.44 (m, 0.5H); 1.35-1.33 (m, 0.5H). ^{13}C NMR (125.7 MHz, CD_3OD, rotamers) δ 172.9; 136.7; 131.3; 129.8; 127.9; 88.6 and 88.1(d, $^1J_{C-F}$=174 Hz); 62.0; 51.3 and 46.1 (d, $^3J_{C-F}$=29 Hz); 48.0 and 42.0; 45.2 and 44.6 (d, $^3J_{C-F}$=18 Hz); 27.6 and 26.1. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -188.1. ν_{max}/cm^{-1} 3364, 2930, 1612, 1462, 1073, 1024. HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{13}H_{17}FNO_2$ 238.1243; found 238.1254.

1.22. (±)-*cis*-1-Butyl-3-fluoro-4-(hydroxymethyl)piperidine (*cis*-21).

Following the procedure for the preparation of **8**, the compound *cis*-**21** was obtained from *cis*-**18** (174 mg, 1.03 mmol) as a brown oil (72 mg, 54%). ^{1}H NMR (400 MHz, CD_3OD) δ 4.9-4.8 (m, 1H); 3.63 (ABX, dd, ^{3}J=7.9 Hz, ^{2}J=10.8 Hz, 1H); 3.50-3.46 (m, 1H); 3.33-3.26 (m, 1H); 3.02-2.98 (m, 1H); 2.43-2.34 (m, 2H); 2.21-2.18 (m, 2H); 1.72-1.50 (m, 5H); 1.55-1.31 (dt, ^{3}J=14.8 Hz, ^{3}J=7.4 Hz, 2H); 0.96 (t, ^{3}J=7.4 Hz, 3H). ^{13}C NMR (100.6 MHz, CD_3OD) δ 87.8 (d, $^1J_{C-F}$=174 Hz); 63.3; 59.5; 57.6; 53.9; 42.9 (d, $^3J_{C-F}$=19.1 Hz); 29.3; 24.0; 21.8; 14.3. ^{19}F NMR (376.5 MHz, CD_3OD) δ -201.1. ν_{max}/cm^{-1} 3347, 2935, 1029. HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{10}H_{21}FNO$ 190.1607; found 190.1599.

1.23. (±)-*trans*-1-Butyl-3-fluoro-4-(hydroxymethyl)piperidine (*trans*-21).

Following the procedure for the preparation of **8**, the compound *trans*-**21** was obtained from *trans*-**18** (194 mg, 1.15 mmol) as a brown oil (168 mg, 77%). ^{1}H NMR (400 MHz, CD_3OD) δ 4.40 (ddt, $^{2}J_{H-F}$=49 Hz, ^{3}J=4.8 Hz, ^{3}J=16.6 Hz, ^{3}J=16.6 Hz, 1H); 4.27 (ABX, dd, ^{3}J=3.6 Hz, ^{2}J=11.1 Hz, 1H); 4.10 (ABX, dd, ^{3}J=5.7 Hz, ^{2}J=11.1 Hz, 1H); 3.23-3.20 (m, 1H); 2.91-2.88 (m, 1H); 2.44-2.42 (m, 2H); 2.07-1.98 (m, 2H); 1.84-1.82 (m, 2H); 1.55-1.31 (m, 5H); 0.96 (t, ^{3}J=7.3 Hz, 3H). ^{13}C NMR (100.6 MHz, CD_3OD) δ 89.5 (d, $^{1}J_{C-F}$=174 Hz); 65.2; 59.1; 58.1 (d, $^{3}J_{C-F}$=26.1 Hz); 53.4; 42.6 (d, $^{3}J_{C-F}$=17.1 Hz); 29.7; 27.0 (d, $^{4}J_{C-F}$=8.3 Hz); 21.7; 14.3. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -188.2 (d, $^{2}J_{H-F}$=52 Hz). ν_{max}/cm^{-1} 3347, 2935, 1029. HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{10}H_{21}FNO$ 190.1607; found 190.1598.

1.24. (±)-*cis*-1-Benzyl-3-fluoro-4-(trityloxymethyl)piperidine (*cis*-22).

Following the procedure for the preparation of **9**, the compound *cis*-**22** was obtained from *cis*-**19** (25 mg, 0.11 mmol) as a brown oil (20 mg, 39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, ^{3}J=7.08 Hz, 6H); 7.32-7.22 (m, 14H); 4.92 (d, $^{2}J_{H-F}$=48.6 Hz, 1H); 3.46 (d, AB, ^{2}J=13.2 Hz, 2H); 3.18-3.10 (m, 2H); 2.95-2.92 (m, 1H); 2.84-2.81 (m, 1H); 2.12-1.93 (m, 2H); 1.71-1.43 (m, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.2; 137.7; 129;2; 128.7; 128.2; 127.8; 127.1; 126.9; 87.6 (d, $^{1}J_{C-F}$=175.7 Hz); 86.4; 63.6 (d, $^{4}J_{C-F}$=3.7 Hz); 62.7; 56.6 (d, $^{3}J_{C-F}$=19.0 Hz); 52.5; 40.0 (d, $^{3}J_{C-F}$=19.6 Hz); 23.7. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -198.7. HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{32}H_{33}NOF$ 466.2546; found 466.2531. HPLC purity: H_2O / MeCN / TFA; 50:50:0.1; t_R: 13.1 min.

1.25. (±)-*trans*-Benzyl 3-fluoro-4-(trityloxymethyl)piperidine (*trans*-22).

Following the procedure for the preparation of **9**, the compound *trans*-**22** was obtained from *trans*-**19** (88 mg, 0.37 mmol) as a colourless oil (70 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.46 (m, 6H); 7.39-7.25 (m, 14H); 4.56 (ddt, $^{2}J_{H-F}$=49.3 Hz, ^{3}J=4.8 Hz, ^{3}J=9.8 Hz, ^{3}J=9.8 Hz, 1H); 3.60 (d, AB, ^{2}J=13.1 Hz, 2H); 3.33-3.30 (m, 1H); 3.19-1.15 (m, 2H); 2.87-2.84 (m, 1H); 2.08-1.93 (m, 3H); 1.85-1.72 (m, 1H); 1.61-1.59 (m, 1H). ^{13}C NMR (100.6 MHz, CD_3OD) δ 145.5; 138.3; 130.6; 129.8; 129.3; 128.7; 128.5; 128.0; 89.7 (d, $^{1}J_{C-F}$=173 Hz); 87.6; 63.8 (d, $^{4}J_{C-F}$=33.1 Hz); 58.0 (d, $^{3}J_{C-F}$=26.1 Hz); 54.8; 53.6; 43.9 (d, $^{3}J_{C-F}$=17.1 Hz); 27.8 (d, $^{4}J_{C-F}$=9 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -185.8 (d, $^{2}J_{H-F}$=48.9 Hz). ν_{max}/cm^{-1} 3028, 2922, 1447, 1178, 1076, 1015. HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{32}H_{33}NOF$ 466.2546; found 466.2538. HPLC purity: H_2O / MeCN / TFA; 50:50:0.1; t_R: 17.2 min.

1.26. (±)-*cis*-1-Benzoyl-3-fluoro-4-(trityloxymethyl)piperidine (*cis*-23).

Following the procedure for the preparation of **9**, the compound *cis*-**23** was obtained from *cis*-**20** (60 mg, 0.25 mmol) as a white solid (70 mg, 58%). mp: 49-51°C. ^{1}H NMR (400 MHz, CD_3OD, rotamers) δ 7.47-7.25 (m, 20 H); 5.17-4.71 (m, 2H); 4.06-3.72 (m, 1H); 3.76-2.84 (m, 4H); 2.13-2.05 (m, 1H); 1.61-1.47 (m, 2H). ^{13}C NMR (100.6 MHz, CD_3OD, rotamers) δ 173.6 and 173.3; 145.6 and 145.4; 137.0 and 136.8; 131.0; 129.8 and 129.6; 128.9; 128.4 and 128.2; 127.8; 88.5 (d, $^{1}J_{C-F}$=176 Hz); 87.8; 64.6; 52.5; 48.3 and 47.6; 46.9; 42.9; 41.4; 24.7 and 23.9. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -203.9. ν_{max}/cm^{-1} 3056, 2927, 1630, 1446, 1155, 1070. HRMS (ESI, $[M + Na]^+$) calcd. for $C_{32}H_{30}NO_2FNa$ 502.2158; found 502.2163. HPLC purity: H_2O / MeCN; 80:20; t_R: 7.9 min.

1.27. (±)-*trans*-1-Benzoyl-3-fluoro-4-(trityloxymethyl)piperidine (*trans*-23).

Following the procedure for the preparation of **9**, the compound *trans*-**23** was obtained from *trans*-**20** (146 mg, 0.61 mmol) as a white solid (189 mg, 64%). mp: 141-143°C. ^{1}H NMR (400

MHz, $CDCl_3$, rotamers) δ 7.47-7.25 (m, 20 H); 4.8-4.1 (m, 2H); 3.74-3.55 (m, 1H); 3.22-2.93 (m, 4H); 1.96-1.82 (m, 2H); 1.56-1.42 (m, 1H). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -185.8. HRMS (ESI, $[M+Na]^+$) *m/z* calcd. for $C_{32}H_{30}NO_2FNa$ 502.2158; found 502.2162. HPLC purity: H_2O / MeCN; 80:20; t_R: 9.1 min.

1.28. (±)-*cis*-1-Butyl-3-fluoro-4-(trityloxymethyl)piperidine (*cis*-24).

Following the procedure for the preparation of 12, the compound *cis*-**24** was obtained from *cis*-**21** (45 mg, 0.23 mmol) as a brown oil (79 mg, 79%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, ^3J=7.4 Hz, 6H); 7.23-7.12 (m, 9H); 4.86 (d, $^2J_{H-F}$=48.3 Hz, 1H); 3.21-2.15 (m, 2H); 2.97-2.86 (m, 2H); 2.35-2.25 (m, 2H); 2.05-1.93 (m, 1H); 1.65-1.47 (m, 1H); 1.46-1.39 (m, 3H); 1.26-1.18 (m, 4H); 0.83 (t, ^3J=7.3 Hz, 3H). ^{13}C NMR (100.6 MHz, CD_3OD) δ 145.4; 129.8; 129.3; 128.8; 128.6; 128.1; 88.0 (d, $^1J_{C-F}$=173.4 Hz); 87.9; 64.6; 59.1; 57.0 (d, $^3J_{C-F}$=19.1 Hz); 53.6; 40.4 (d, $^3J_{C-F}$=20.1 Hz); 28.5; 23.7; 21.5; 14.2. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -198.0. ν_{max}/cm^{-1} 3058, 2929, 1447, 1077, 1019. HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{29}H_{35}NOF$ 432.2703; found 432.2690. HPLC purity: H_2O / MeCN / TFA; 50:50:0.1; t_R: 13.5 min.

1.29. (±)-*trans*-1-Butyl-3-fluoro-4-(trityloxymethyl)piperidine (*trans*-24).

Following the procedure for the preparation of **9**, the compound *trans*-**24** was obtained from *trans*-**21** (160 mg, 0.84 mmol) as a brown oil (147 mg, 40%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, ^3J=7.4 Hz, 6H); 7.36-7.25 (m, 9H); 4.56 (ddt, $^2J_{H-F}$=49.3 Hz, ^3J=4.9 Hz, ^3J=9.8 Hz, ^3J=9.8 Hz, 1H); 3.32-3.18 (m, 3H); 2.90-2.87 (m, 1H); 2.43-2.41 (m, 2H); 2.0-1.94 (m, 2H); 1.77-1.70 (m, 1H); 1.64-1.50 (m, 4H); 1.39-1.35 (m, 2H); 0.97 (t, ^3J=7.3 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.2; 128.7; 127.7; 126.9; 89.4 (d, $^1J_{C-F}$=173.4 Hz); 86.3; 63.2; 58.2; 57.4 (d, $^3J_{C-F}$=25.6 Hz); 52.9; 42.8 (d, $^3J_{C-F}$=16.6 Hz); 29.1; 27.1 (d, $^4J_{C-F}$=8.7 Hz); 20.7; 14.0. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -185.6 (d, $^2J_{H-F}$=47.4 Hz). ν_{max}/cm^{-1} 3058, 2929, 1447, 1077, 1019. HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{29}H_{35}NOF$ 432.2703; found 432.2690. HPLC purity: H_2O / MeCN / TFA; 50:50:0.1; t_R: 13.1 min.

1.30. (±)-*cis*-*tert*-Butyl-3-fluoro-4-(trityloxymethyl)piperidin-1-yl carboxylate (*cis*-25).

Following the procedure for the preparation of 12, the compound *cis*-**25** was obtained from *cis*-**17** (133 mg, 0.57 mmol) as a yellow oil (85 mg, 31%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.34 (m, 6H); 7.24-7.13 (m, 9H); 4.83 (d, $^2J_{H-F}$=48.0 Hz, 1H); 4.33-4.14 (m, 2H); 3.16-3.11 (m, 1H); 2.95-2.60 (m, 3H); 1.83-1.69 (m, 1H); 1.5-1.37 (m, 11H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155;2; 144.0; 128.7; 127.8; 127.0; 86.5; 86.3 (d, $^1J_{C-F}$=177.3 Hz); 79.7; 63.5; 54.4; 52.9; 40.4 (d, $^3J_{C-F}$=19.9 Hz); 28.4; 22.9. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -202.7. ν_{max}/cm^{-1} 3058, 2928, 1689, 1447, 1168, 1069. HRMS (ESI, $[M+Na]^+$) *m/z* calcd. for $C_{30}H_{34}FNO_3Na$ 498.2420; found 498. 2399. HPLC purity: H_2O / MeCN; 80:20; t_R: 13.5 min.

1.31. (±)-*trans*-*tert*-Butyl-3-fluoro-4-(trityloxymethyl)piperidin-1-yl carboxylate (*trans*-25).

Following the procedure for the preparation of 12, the compound *trans*-**25** was obtained from *trans*-**17** (180 mg, 0.77 mmol) as a yellow viscous oil (100 mg, 27%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.34 (m, 6H); 7.20-7.13 (m, 9H); 4.44-4.27 (m, 1H); 4.15 (br s, 1H); 3.86 (br s, 1H); 3.18-3.09 (m, 1H); 2.69-2.63 (m, 2H); 1.82-1.77 (m, 2H); 1.50-1.39 (m, 11H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.6; 144.0; 128.7; 127.8; 127.0; 87.7 (d, $^1J_{C-F}$=177.3 Hz); 86.5; 80.1; 62.7 (d, $^4J_{C-F}$=2.4 Hz); 48.0; 44.0; 42.5 (d, $^3J_{C-F}$=19.9 Hz); 28.4; 24.9. ^{19}F NMR (376.5 MHz,

$CDCl_3$) δ -186.5. HRMS (ESI, $[M+Na]^+$) *m/z* calcd. for $C_{30}H_{34}FNO_3Na$ 498. 2420; found 498.2407. HPLC purity: H_2O / MeCN; 80:20; t_R: 18.9 min.

1.32. (±)-*cis*-*tert*-Butyl 1-[4-(pyrimidin-2-ylamino)methylpiperidin-3-ol-1-yl] carboxylate (*cis*-26).

A mixture of (±)-*cis*-*tert*-butyl 1-[4-(azidomethyl)piperidin-3-ol-1-yl]carboxylate[a] (690 mg, 2.69 mmol) and 10% palladium on carbon (200 mg) in methanol (40 mL) was stirred under H_2 atmosphere (1.2 bars) at room temperature for 7 h. The reaction mixture was filtered off then concentrated to give the intermediate amine as a yellow oil (610 mg, 99%). The intermediate amine (305 mg, 1.32 mmol) was dissolved in *tert*-amyl alcohol (4 mL), then 2-chloro-pyrimidine (226 mg, 1.98 mmol) and *N*,*N*-di-*iso*propylethylamine (DIPEA) (2ml) were added under nitrogen atmosphere. The reaction mixture was stirred 48 hours at 90°C, then diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (CH_2Cl_2 / MeOH, 99:1) afforded *cis*-**26** as yellow crystals (210 mg, 51%). mp: 125-127°C. Elem. analysis found: C, 57.34; H, 8.30; N, 17.57% calcd. for $C_{15}H_{24}N_4O_3.0.2H_2O$: C, 57.74; H, 7.88; N, 17.95%. ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.18 (d, ^{3}J=4.8 Hz, 2H); 6.46 (m, 1H); 4.20-4.10 (m, 2H); 3.70 (bs, 1H); 3.57-3.49 (m, 1H); 3.14-3.10 (m, 1H); 2.73-2.63 (m, 2H); 1.65-1.59 (m, 2H); 1.39 (s, 9H); 1.28-1.26 (m, 1H). ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 162.7; 158.1; 154.6; 110.5; 79.4; 63.8; 49.6; 43.3; 43.2; 41.5; 28.4; 23.8. HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{15}H_{25}N_4O_3$ 309.1927, found 309.1924. HPLC purity: H_2O / MeCN; 70:30; t_R: 9.8 min.

1.33. (±)-*trans*-*tert*-Butyl 1-[4-(pyrimidin-2-ylamino)methylpiperidin-3-ol-1-yl] carboxylate (*trans*-26).

Following the procedure for the preparation of *cis*-**26**, the compound *trans*-**26** was obtained from (±)-*trans*-*tert*-butyl 1-[4-(azidomethyl)piperidin-3-ol-1-yl]carboxylate[a] (670 mg, 2.6 mmol) as yellow crystals (495 mg, 61%). mp: 114-116°C. ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.18 (d, ^{3}J=4.8 Hz, 2H); 6.50 (t, ^{3}J=4.8 Hz, 2H); 4.17-3.94 (m, 3H); 3.19-3.05 (m, 2H); 2.59-2.46 (m, 2H); 1.55-1.39 (m, 12H). ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 162.8; 158.1; 154.6; 110.7; 79.7; 67.1; 49.1; 45.4; 43.2; 43.0; 28.4; 27.9. HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{15}H_{25}N_4O_3$ 309.1927, found 309.1919. HPLC purity: H_2O / MeCN; 60:40; t_R: 5.1 min.

1.34. (±)-*cis*(*trans*-Phenylcyclopropyl)[4-(pyrimidin-2-ylamino)methylpiperidin-3-ol-1-yl]methanone (27).

HCl gas was bubbled through a solution of *cis*-**26** (240 mg, 0.67 mmol) in EtOAc (3 mL) for 45 min. The reaction mixture was concentrated under reduced pressure and the crude amine hydrochloride was dissolved in dry DMF (4 mL) and Et_3N (187 µL, 1.34 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (155 mg, 0.80 mmol), 1-hydroxy-7-azabenzotriazole (110 mg, 0.80 mmol) and *trans*-2-phenylcyclopropane-1-carboxylic acid (131 mg, 0.80 mmol) were added. The reaction mixture was stirred overnight at 70°C. After cooling to RT, the reaction mixture was diluted with water (5 mL) and extracted with EtOAc (4 x 5 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and purified by chromatography on silica gel (CH_2Cl_2 / MeOH, 98:2) led to **27** as a yellow oil (160 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, ^{3}J=4.8 Hz, 2H); 7.33-7.13 (m, 5H); 6.59 (t, ^{3}J=4.8 Hz, 1H); 5.80-5.75 (m, 1H); 4.76-4.55 (m, 1H); 4.31-4.25 (m, 1H); 3.93-3.80

(m, 1H); 3.68-3.62 (m, 1H); 3.20-3.13 (m, 2H); 2.75-2.40 (m, 2H); 2.20-2.07 (m, 1H); 1.85-1.28 (m, 6H). ν_{max}/cm^{-1} 3331, 2971, 1592, 1044. MS (ESI) *m/z* 353 ($[M+H]^+$, 96); 335 (100); 209 (80); 191 (100); 145 (43). HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{20}H_{25}N_4O_2$ 353.1978; found 353.1972.

1.35. (±)-*cis*-4-Methylbenzyl 1-[4-(pyrimidin-2-ylamino)methylpiperidin-3-ol-1-yl] carboxylate (*cis*-28).

HCl gas was bubbled through a solution of *cis*-**26** (560 mg, 1.81 mmol) in EtOAc (3 mL) for about 45 min. The mixture was then concentrated under reduced pressure and the crude amine hydrochloride was dissolved in dry DMF (5 mL). DIPEA (710 mg, 5.43 mmol) was added and the resulting solution was stirred for 30 min. To a solution of *N,N'*-disuccinimidyl carbonate (926 mg, 3.62 mmol) in dry acetonitrile (10 mL), was added 4-methylbenzyl alcohol (441 mg, 3.54 mmol) in dry CH_2Cl_2 (10 mL) and a catalytic amount of DMAP. The reaction mixture was stirred overnight at room temperature. The solution was then added to the amine hydrochloride previous prepared and stirred for two days at room temperature. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc (4 x 15 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and purified by chromatography on silica gel (CH_2Cl_2 / MeOH, 98:2) led to *cis*-**28** as a yellow oil (466 mg, 72%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.15 (d, ^{3}J=4.8 Hz, 2H); 7.17 (d, ^{3}J=8 Hz, 2H); 7.06 (d, ^{3}J=8 Hz, 2H); 6.44 (t, ^{3}J=4.8 Hz, 1H); 5.83 (bs, 1H); 5.15-4.98 (m, 2H); 4.30-4.20 (m, 2H); 3.73-3.66 (m, 1H); 3.53-3.47 (m ,1H); 3.12-3.11 (m, 1H); 2.76-2.69 (m, 2H); 2.25 (s, 3H); 1.65-1.64 (m, 2H); 1.27 (bs, 1H). ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 162.7; 158.1; 156.2; 137.6; 134.0; 129.1; 128.0; 110.6; 67.0; 63.6; 49.7; 43.8; 43.2; 41.5; 23.7; 21.2.). ν_{max}/cm^{-1} 3247, 1681, 1368, 1223. MSMS (ESI) *m/z* 357 ($[M+H]^+$, 100); 313 (55); 295 (30) ; 105 (50). HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{19}H_{25}N_4O_3$ 357.1927, found 357.1928.

1.36. (±)-*trans*-4-Methylbenzyl 1-[4-(pyrimidin-2-ylamino)methylpiperidin-3-ol-1-yl] carboxylate (*trans*-28).

Following the procedure for the preparation of *cis*-**28**, the compound *trans*-**28** was obtained from *trans*-**26** (250 mg, 0.81mmol) as a yellow oil (160 mg, 55%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.30 (d, ^{3}J=4.8 Hz, 2H); 7.27 (d, ^{3}J=8 Hz, 2H); 7.18 (d, ^{3}J=8 Hz, 2H); 6.60 (t, ^{3}J=4.8 Hz, 1H); 5.62 (bs, 1H); 5.1 (bs, 2H); 4.15-4.08 (m, 3H); 3.28 (bs, 1H); 3.19-3.15 (m, 1H); 2.78-2.67 (m, 2H); 2.38 (s, 3H); 1.63-1.58 (m, 3H). ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 162.8; 158.1; 155.2; 137.8; 133.6; 129.1; 128.1; 110.9; 67.1; 66.9; 49.2; 45.5; 43.7; 42.8; 27.8; 23.2. HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{19}H_{25}N_4O_3$ 357.1927, found 357.1920. HPLC purity: H_2O / MeCN; 60:40; t_R: 9.4 min.

1.37. (±)-*cis*(*trans*-Phenylcyclopropyl)[4-(pyrimidin-2-ylamino)methyl-3-(methylsulfonyl)oxypiperidine-1-yl]methanone (29).

To a solution of **27** (47 mg, 0.13 mmol) in dry pyridine (2 mL), was added silver trifluoromethanesulfonate (68 mg, 0.26 mmol) under nitrogen atmosphere at 0°C, followed by the addition of methanesulfonyl chloride (48 mg, 0.26 mmol). The reaction mixture was stirred at 0°C for 1 h, then further 2 h at room temperature. The reaction mixture was diluted with water (4 mL) and extracted with EtOAc (4 x 2 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (CH_2Cl_2 / MeOH, 98:2) gave **29** as a yellow oil (53 mg, 92%). ^{1}H NMR (400

MHz, $CDCl_3$, rotamers) δ 8.19 (m, 2H); 7.33-7.13 (m, 5H); 6.59 (t, ^{3}J=4.8 Hz, 1H); 5.63-5.57 (m, 1H); 5.0-4.96 (m, 1.5H); 4.72-4.70 (m, 0.5H); 4.57-4.51 (m, 0.5H); 4.14 (br s, 0.5H); 3.53-3.49 (m, 1H); 3.19-3.05 (m, 4H); 2.66-2.55 (m, 2H); 2.41-1.93 (m, 3H); 1.58-1.18 (m, 4H). ν_{max}/cm^{-1} 3426, 2930, 1586, 1455, 1168, 1077. MS (ESI) *m/z* 355 ([M+H]$^+$, 12); 335 (100); 191 (10). HRMS (ESI, [M+H]$^+$) *m/z* calcd. for $C_{21}H_{27}N_4O_4S$ 431.1753; found 431.1768. HPLC purity: H_2O / MeOH; 55:45; t_R: 9.9 min.

1.38. (±)-*cis*-4-Methylbenzyl 1-[4-(pyrimidin-2-yl)aminomethyl-3-(methylsulfonyl)hydroxypiperidin-1-yl] carboxylate (*cis*-30).

To a solution of *cis*-**28** (85 mg, 0.238 mmol) in dry pyridine (2 mL), was added silver trifluoromethanesulfonate (123 mg, 0.47 mmol) under nitrogen atmosphere at 0°C, followed by the addition of methanesulfonyl chloride (87 mg, 1.03 mmol). The reaction mixture was stirred at 0°C for 1 h, then further 1 h at room temperature. The reaction mixture was diluted with water (2 mL) and extracted with EtOAc (4 x 3 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (CH_2Cl_2 / MeOH, 98:2) gave *cis*-**30** as yellow crystals (73 mg, 70%). mp: 107-109°C. Elem. analysis found: C, 54.73; H, 6.18; N, 12.93% calcd. for $C_{20}H_{26}N_4O_5S$: C, 55.28; H, 6.03; N, 12.89%. ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.18 (d, ^{3}J=4.8 Hz, 2H); 7.18 (m, 2H); 7.10 (m, 2H); 6.45 (t, ^{3}J=4.8 Hz, 1H); 5.65 (bs, 1H); 5.14-4.86 (m, 3H); 4.54-4.41 (m, 1H); 4.31-4.16 (m, 1H); 3.54-3.47 (m, 1H); 3.11 (bs, 1H); 2.97-2.66 (m, 5H); 2.27 (s, 3H); 2.11 (bs, 1H); 1.51-1.45 (m, 2H). ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 162.1; 158.1; 156.2; 138.0; 134.0; 129.1; 128.0; 110.8; 74.9; 67.3; 47.6; 43.5; 42.4; 38.7; 38.1; 23.7; 21.2. HRMS (ESI, [M+H]$^+$) *m/z* calcd. for $C_{20}H_{27}N_4O_5S$ 435.1702, found 435.1683. HPLC purity: H_2O / MeCN; 60:40; t_R: 10.4 min.

1.39. (±)-*trans*-4-Methylbenzyl 1-[4-(pyrimidin-2-ylamino)methyl-3-(methylsulfonyl)hydroxypiperidin-1-yl] carboxylate (*trans*-30).

Following the procedure for the preparation of *cis*-**30**, the compound *trans*-**30** was obtained from *trans*-**28** (50 mg, 0.14 mmol) as an yellow oil (60 mg, 98%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.18 (d, ^{3}J=4.8 Hz, 2H); 7.17 (d, ^{3}J=8 Hz, 2H); 7.08 (d, ^{3}J=8 Hz, 2H); 6.45 (t, ^{3}J=4.8 Hz, 1H); 5.40 (bs, 1H); 5.01 (bs, 2H); 4.46-4.45 (m, 1H); 4.33-4.29 (m, 1H); 3.92 (bs, 1H); 3.69 (bs, 1H); 3.45-3.38 (m, 1H); 3.03-2.79 (m , 5H); 2.27 (s, 3H); 1.95-1.93 (m, 1H); 1.87-1.83 (m, 1H); 1.36-1.33 (m, 1H). ν_{max}/cm^{-1} 3272, 3023, 2923, 1695, 1367, 1170. MSMS (ESI) *m/z* 359 ([M+H]$^+$, 100); 339 (10); 295 (45) ; 105 (50). HRMS (ESI, [M+H]$^+$) *m/z* calcd. for $C_{20}H_{27}N_4O_5S$ 435.1702, found 435.1696. HPLC purity: H_2O / MeCN; 60:40; t_R: 12.9 min.

1.40. (±)-*cis*-*tert*-Butyl 1-[4-(pyrimidin-2-yl)aminomethyl-3-(methylsulfonyl)oxypiperidin-1-yl] carboxylate (*cis*-31).

Following the procedure for the preparation of **16**, the compound **31** was obtained from **26** (160 mg, 0.51 mmol) as a brown viscous oil (168 mg, 97%). mp: 110-112°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, ^3_r=4.8 Hz, 2H); 6.46 (t, ^{3}J=4.8 Hz, 1H); 4.9 (br s, 1H); 4.47 (m, 1H); 4.2 (m, 1H); 3.5 (m, 1H); 3.15 (m, 1H); 3.04 (br s, 3H); 2.73-2.63 (m, 2H); 2.12-2.07(m, 1H); 1.5-1.39 (m, 11H). ^{13}C NMR (100.6 MHz, CD_3OD) δ 163.3 ; 159.3 ; 156.6 ; 111.6 ; 81.0 ; 77.3 ; 48.1 ; 45.0 ; 43.7 ; 40.0 ; 38.2 ; 28.6 ; 24.9. ν_{max}/cm^{-1} 2940, 1676, 1352, 1160. HRMS (ESI, [M+H]$^+$) *m/z* calcd. for $C_{16}H_{27}N_4O_5S$: 387.1702; found : 387.1716. HPLC purity: H_2O / MeOH; 60:40; t_R: 8.3 min.

1.41. (±)-*cis*-*tert*-Butyl 1-[3-fluoro-4-(pyrimidin-2-ylamino)methylpiperidin-1-yl] carboxylate (*cis*-32).

Following the procedure for the preparation of *cis*-**26**, the compound *cis*-**32** was obtained from (±)-*cis*-*tert*-butyl 1-[3-fluoro-4-(azidomethyl)piperidin-1-yl]carboxylate[a] (818 mg, 3.17 mmol) as a yellow solid (457 mg, 46%). mp: 131-133°C. ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.20 (d, ^{3}J=4.7 Hz, 2H); 6.46 (t, ^{3}J=4.8 Hz, 1H); 5.76 (bs, 1H); 4.67 (d, $^{2}J_{H-F}$=48 Hz, 1H); 4.33-4.18 (m, 2H); 3.43-3.31 (m, 2H); 2.79-2.64 (m, 2H); 2.09-1.84 (m, 1H); 1.56-1.50 (m, 2H); 1.39 (s, 9H). ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 162.5; 158.1; 155.2; 110.7; 86.6 (d, $^{2}J_{C-F}$=176 Hz); 79.8; 48.2; 42.9; 42.7 (d,$^{4}J_{C-F}$=3.3 Hz); 38.7 (d, $^{3}J_{C-F=}$19.9 Hz); 28.4; 23.7. ^{19}F NMR δ (376.5 MHz, $CDCl_3$) -203.2 (d, $^{2}J_{H-F}$=30 Hz). HPLC purity : H_2O / MeCN; 60:40; t_R: 15.4 min.

1.42. (±)-*trans*-*tert*-Butyl 1-[3-fluoro-4-(pyrimidin-2-ylamino)methylpiperidin-1-yl] carboxylate *(trans*-32).

Following the procedure for the preparation of *cis*-**26**, the compound *trans*-**32** was obtained from (±)-*trans*-*tert*-butyl 1-[3-fluoro-4-(azidomethyl)piperidin-1-yl]carboxylate[a] (789 mg, 3.06 mmol) as a yellow solid (574 mg, 60%). mp: 124-126°C. Elem. analysis found: C, 58.39; H, 8.08; N, 17.79% calcd. for $C_{15}H_{23}FN_4O_2$: C, 58.05; H, 7.47; N, 18.05%. ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.20 (d, ^{3}J=4.7 Hz, 2H); 6.46 (t, ^{3}J=4.7 Hz, 1H); 5.43 (bs, 1H); 4.33-4.17 (m, 2H); 3.9 (bs, 1H); 3.63-3.42 (m, 2H); 2.73-2.63 (m, 2H); 1.92-1.78 (m, 2H); 1.38 (s, 9H); 1.33-1.25 (m, 1H). ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 162.5; 158.0; 154.4; 110.7; 90.1 (d, $^{2}J_{C-F}$=176 Hz); 80.1; 47.0; 43.1 (d,$^{4}J_{C-F}$=2.2 Hz); 43.0; 42.2 (d, $^{3}J_{C-F=}$16.6 Hz); 28.3; 27.2. ^{19}F NMR δ (376.5 MHz, $CDCl_3$) -185.8 (d, $^{2}J_{H-F}$=48.8 Hz). HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{15}H_{24}FN_4O_2$ 311.1883, found 311.1873. HPLC purity: H_2O / MeCN; 60:40; t_R: 12.7 min.

1.43. (±)-*trans*(*trans*-Phenylcyclopropyl)[3-fluoro-4-(pyrimidin-2-ylamino)methylpiperidin-1-yl]methanone (33).

Following the procedure for the preparation of **27**, the compound **33** was obtained from *trans*-**32** (47 mg, 0.15 mmol) as a yellow oil (20 mg, 38%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.25 (d, ^{3}J=4.8 Hz, 2H); 7.29-7.12 (m, 5H); 6.59 (t, ^{3}J=4.8 Hz, 1H); 4.48-4.01 (m, 3H); 3.72-3.69 (m, 1H); 3.45-3.01 (m, 3H); 2.38-2.36 (m, 1H); 2.18-2.10 (m, 2H); 1.96-1.82 (m, 1H); 1.54-1.53 (m, 1H); 1.35-1.33 (m, 2H). ν_{max}/cm^{-1} 3332, 2972, 1589, 1047. HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{20}H_{24}FN_4O$: 355.1934; found : 355.1934. HPLC purity: H_2O / MeOH; 55:45; t_R: 12.5 min.

1.44. (±)-*cis*-4-Methylbenzyl 1-[3-fluoro-4-(pyrimidin-2-ylamino)methylpiperidin-1-yl] carboxylate (*cis*-3).

Following the procedure for the preparation of *cis*-**28**, the compound *cis*-**3** was obtained from *cis*-**32** (160 mg, 0.516 mmol) as a yellow solid (65 mg, 35%). mp: 131-133°C. ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.18 (d, ^{3}J=4.8 Hz, 2H); 7.17 (d, ^{3}J=8.4 Hz, 2H); 7.08 (d, ^{3}J=7.8 Hz, 2H); 6.45 (t, ^{3}J=4.8 Hz, 1H); 5.77 (bs, 1H); 5.02-5.01 (m, 2H); 4.79-4.17 (m, 3H); 3.44-3.29 (m, 2H); 2.85-2.67 (m, 2H); 2.27 (s, 3H); 2.02-1.89 (m, 1H); 1.54 (bs, 2H). ^{19}F NMR δ (376.5 MHz, $CDCl_3$) -203.1. HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{19}H_{24}FN_4O_2$ 359.1883, found 359.1887. HPLC purity: H_2O / MeCN; 55:45; t_R: 12.6 min.

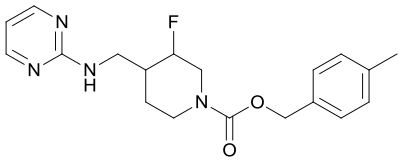
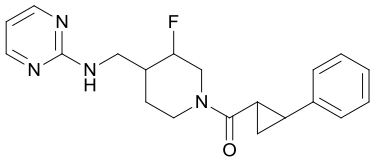
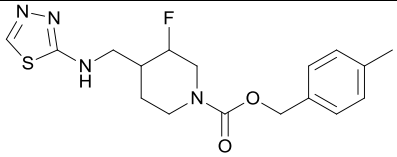
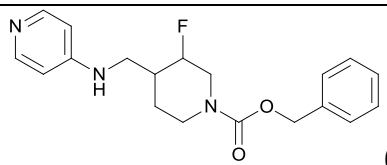
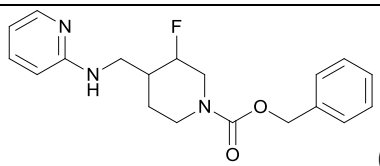
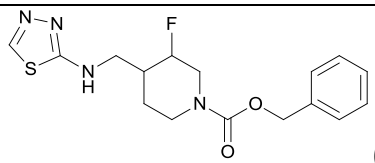
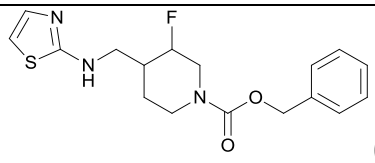
1.45. (±)-*trans*-4-Methylbenzyl 1-[3-fluoro-4-(pyrimidin-2-ylamino)methylpiperidin-1-yl] carboxylate (*trans*-3).

Following the procedure for the preparation of *cis*-**28**, the compound *trans*-**3** was obtained from *trans*-**32** (164 mg, 0.52 mmol) as a yellow oil (72 mg, 38%). Elem. analysis found C, 63.86; H=6.85%; N, 15.54 calcd. for $C_{19}H_{23}FN_4O_2$: C, 63.67; H, 6.47; N, 15.63%. ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.18 (d, ^{3}J=4.8 Hz, 2H); 7.18 (d, ^{3}J=7.9 Hz, 2H); 7.09 (d, ^{3}J=7.9 Hz, 2H); 6.44 (t, ^{3}J=4.8 Hz, 1H); 5.5 (bs, 1H); 5.0 (s, 2H); 4.32-4.20 (m, 2H); 3.96 (bs, 1H); 3.63-3.57 (m, 1H); 3.47-3.40 (m, 1H); 2.82-2.70 (m, 2H); 2.27 (s, 3H); 1.93-1.79 (m, 2H); 1.26-1.23 (m, 1H). ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 162.5; 158.0; 155.1; 138.0; 133.4; 129.2; 128.2; 110.7; 89.8 (d, $^2J_{C-F}$=178 Hz); 67.4; 47.0 (d,$^3J_{C-F}$=29.9 Hz); 43.0; 42.1; 42.0; 27.0; 21.2 . ^{19}F NMR δ (376.5 MHz, $CDCl_3$) -185.8 (d, $^2J_{H-F}$=47.8 Hz). HRMS (ESI, $[M+H]^+$) *m/z* calcd. for $C_{19}H_{24}FN_4O_2$ 359.1883, found 359.1874. HPLC purity: H_2O / MeCN; 55:45; t_R: 14.3 min.

[a] R. Koudih, G. Gilbert, M. Dhilly, A. Abbas, L. Barré, D. Debruyne, and F. Sobrio, *Eur. J. Med. Chem.*, 2012, **53**, 408-415.

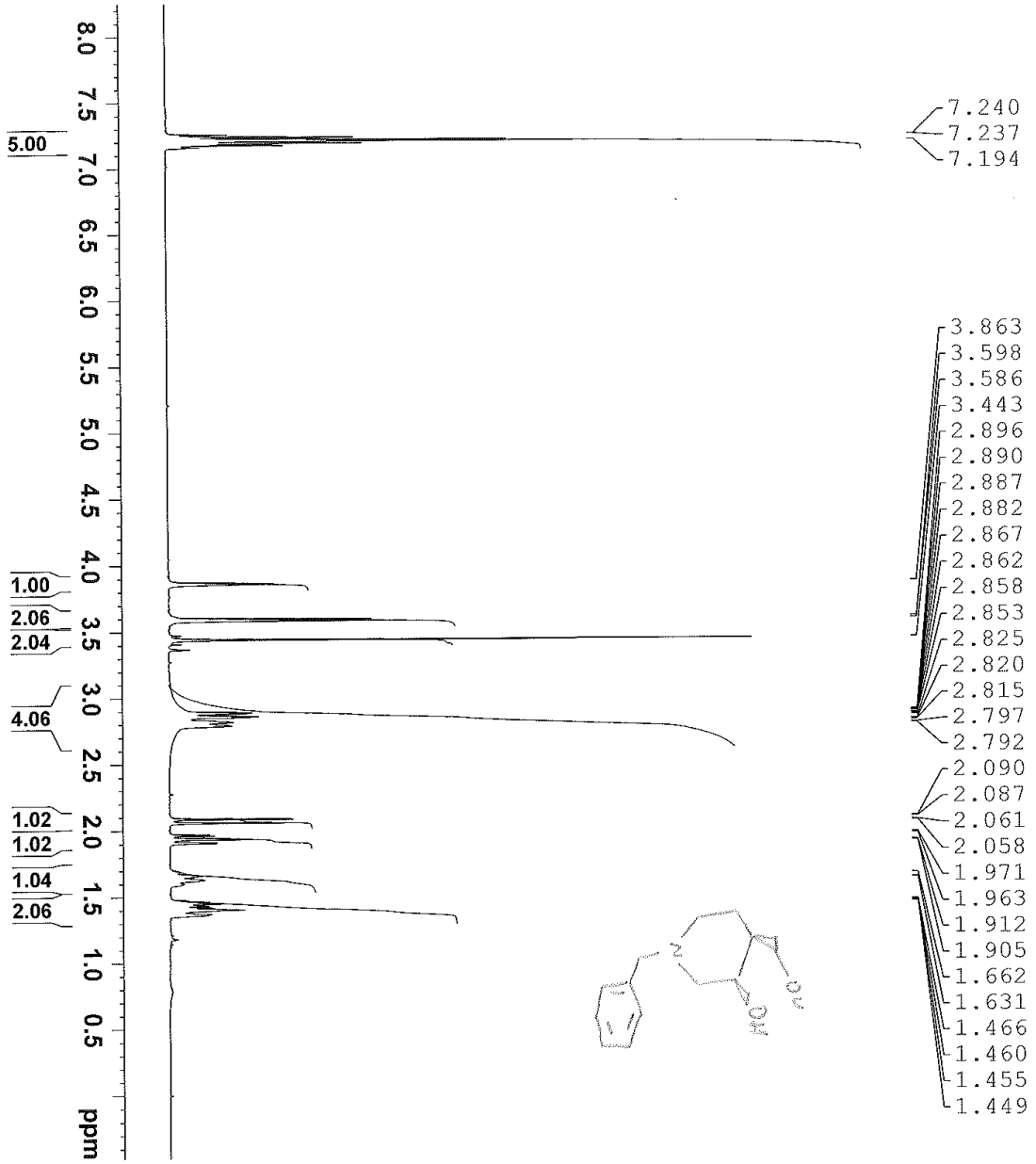
2. *In silico* calculated pharmacological properties

Software: Chemsilico Predictor, Chemsilico LLC, Tewksbury, MA, USA.

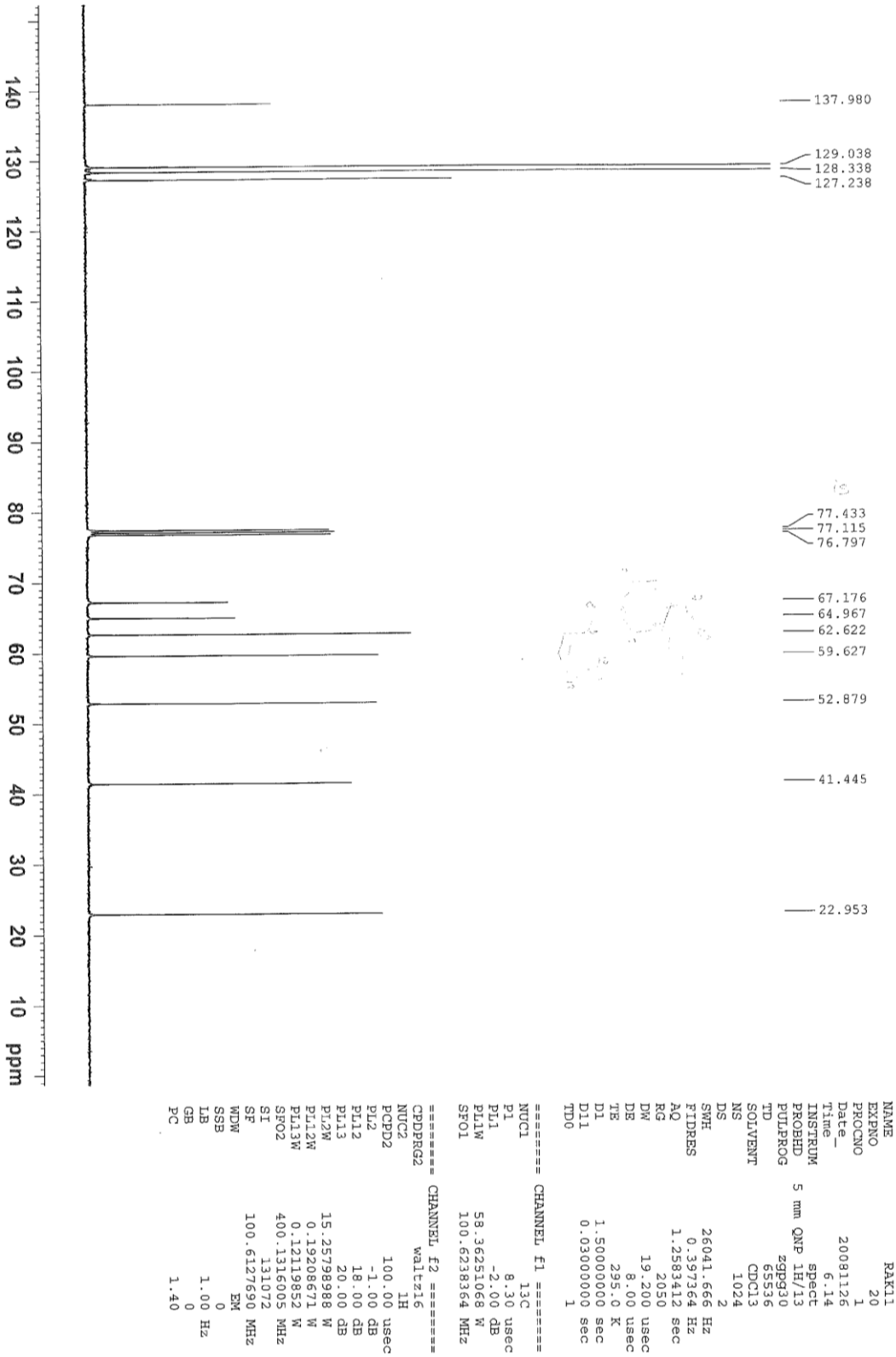
Ligand (reference)	CSLogD7.4: $clogD_{7.4}$	CSPB: Protein binding (%)	CSBBB: Log (Brain / Blood)	Brain / Blood ratio
 **3** (27, 21)	2.77 ± 1.03	69.2 ± 13.2	-0.35 ± 0.22	0.45
 33 (27)	2.19 ± 0.94	47.7 ± 14.9	0.18 ± 0.17	1.51
 (27)	2.74 ± 0.9	84.4 ± 9.1	-0.91 ± 0.25	0.12
 (10)	3.03 ± 0.86	58.8 ± 15.7	0.09 ± 0.17	1.23
 (10)	3.00 ± 0.87	76.5 ± 9.5	0.14 ± 0.2	1.38
 (10)	2.27 ± 0.91	64.9 ± 11.3	-0.68 ± 0.19	0.21
 (10)	2.46 ± 0.71	65.35 ± 10.1	-0.25 ± 0.16	0.56

3. NMR Spectra

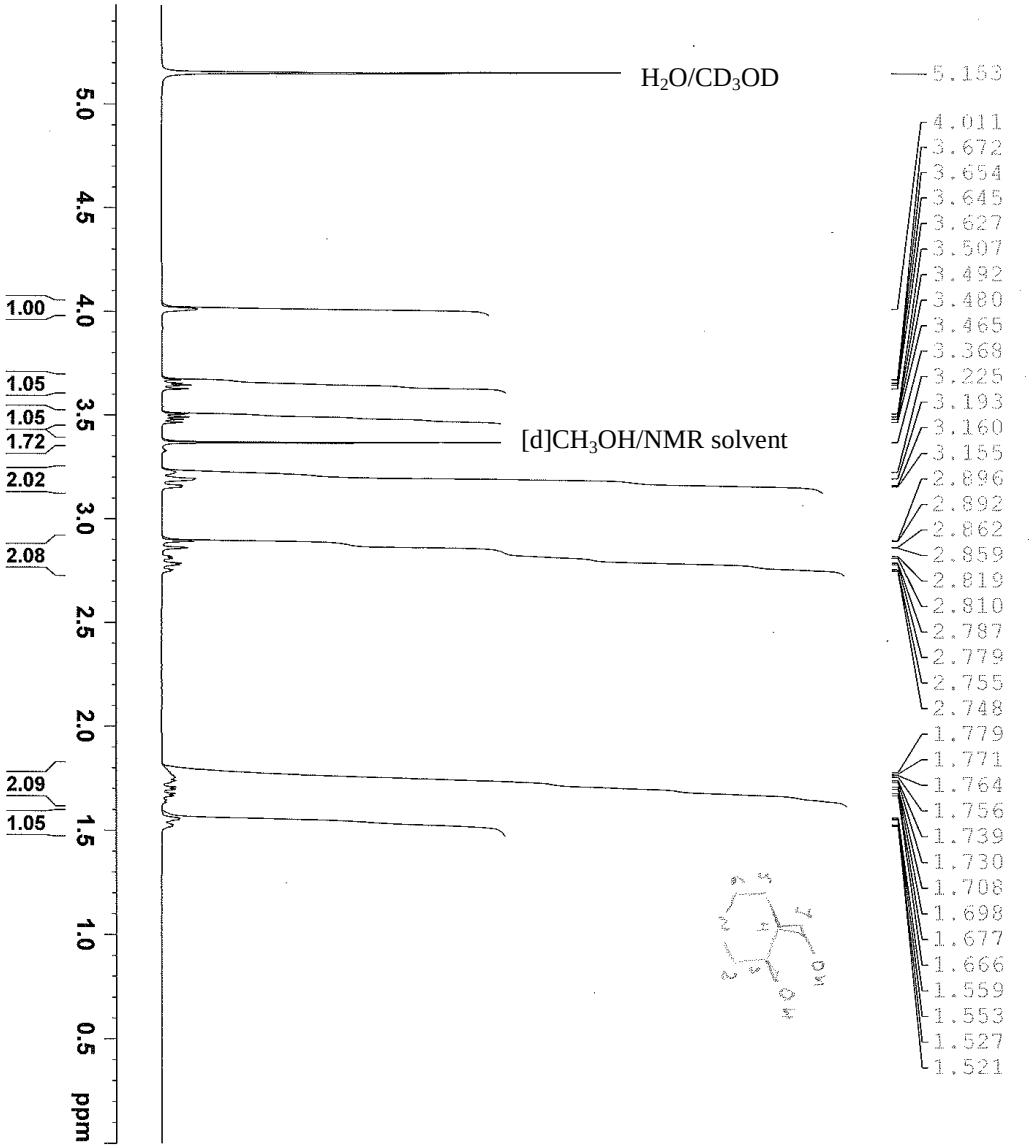
Compound **4**.



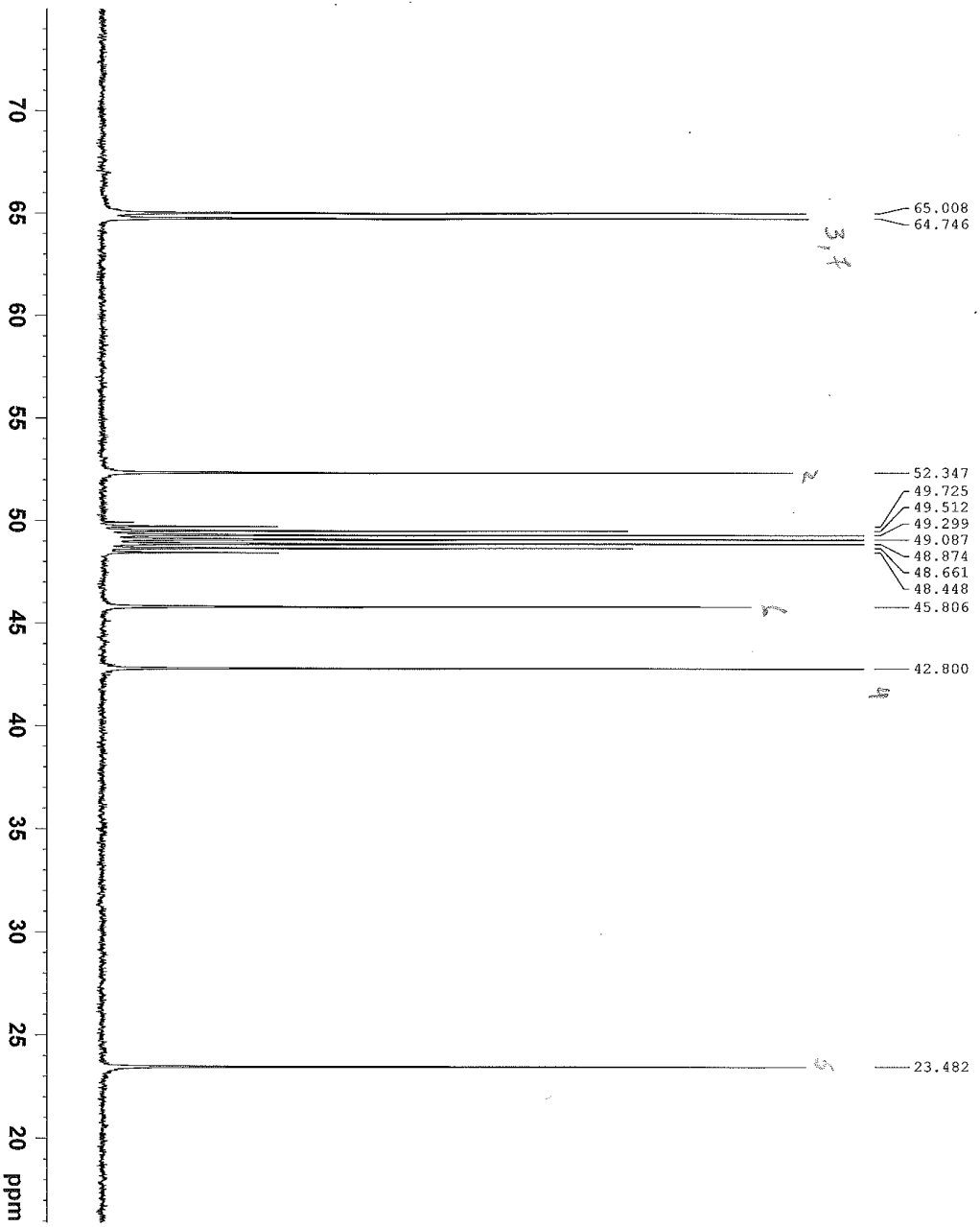

```
NAME                    RAK11
EXPNO                      10
PROCNO                      1
Date_                20081120
Time_                   13.28
INSTRUM                 spect
PROBHD     5 mm QNP 1H/13
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                        64
DW                  60.800 usec
DE                   8.00 usec
TE                   295.0 K
D1                  1.00000000 sec
TD0                        1

========== CHANNEL f1 ========
NUC1                      1H
P1                     11.00 usec
PL1                    -1.00 dB
PL1W                15.25798988 W
SFO1               400.1324710 MHz
SI                        32768
SF                 400.1300402 MHz
WDW                        EM
SSB                         0
LB                   0.30 Hz
GB                          0
PC                       1.00
```


137.980
129.038
128.338
127.238
77.433
77.115
76.797
67.176
64.967
62.622
59.627
52.879
41.445
22.953
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm
NAME RAK11
EXPNO 20
PROCNO 1
Date_ 20091126
Time_ 6.14
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 2
SWH 26041.666 Hz
FIDRES 0.397364 Hz
AQ 1.2583412 sec
RG 2050
DW 19.200 usec
DE 8.00 usec
TE 295.0 K
D1 1.50000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 8.30 usec
PL1 -2.00 dB
PL1W 58.36251068 W
SFO1 100.6238364 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -1.00 dB
PL12 18.00 dB
PL13 20.00 dB
PL2W 15.25798988 W
PL12W 0.19208671 W
PL13W 0.12119852 W
SFO2 400.1316005 MHz
SI 131072
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Compound **5**.

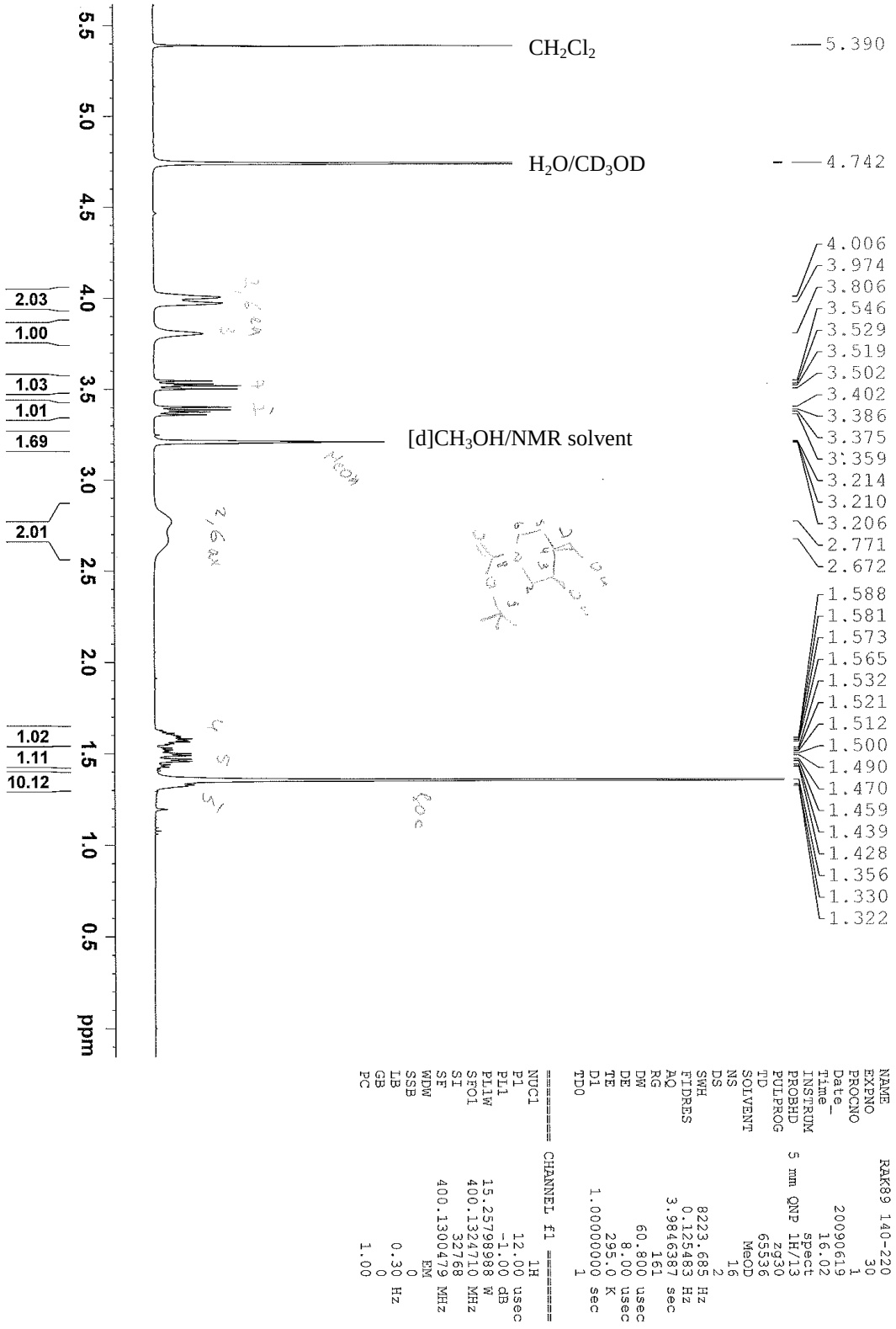


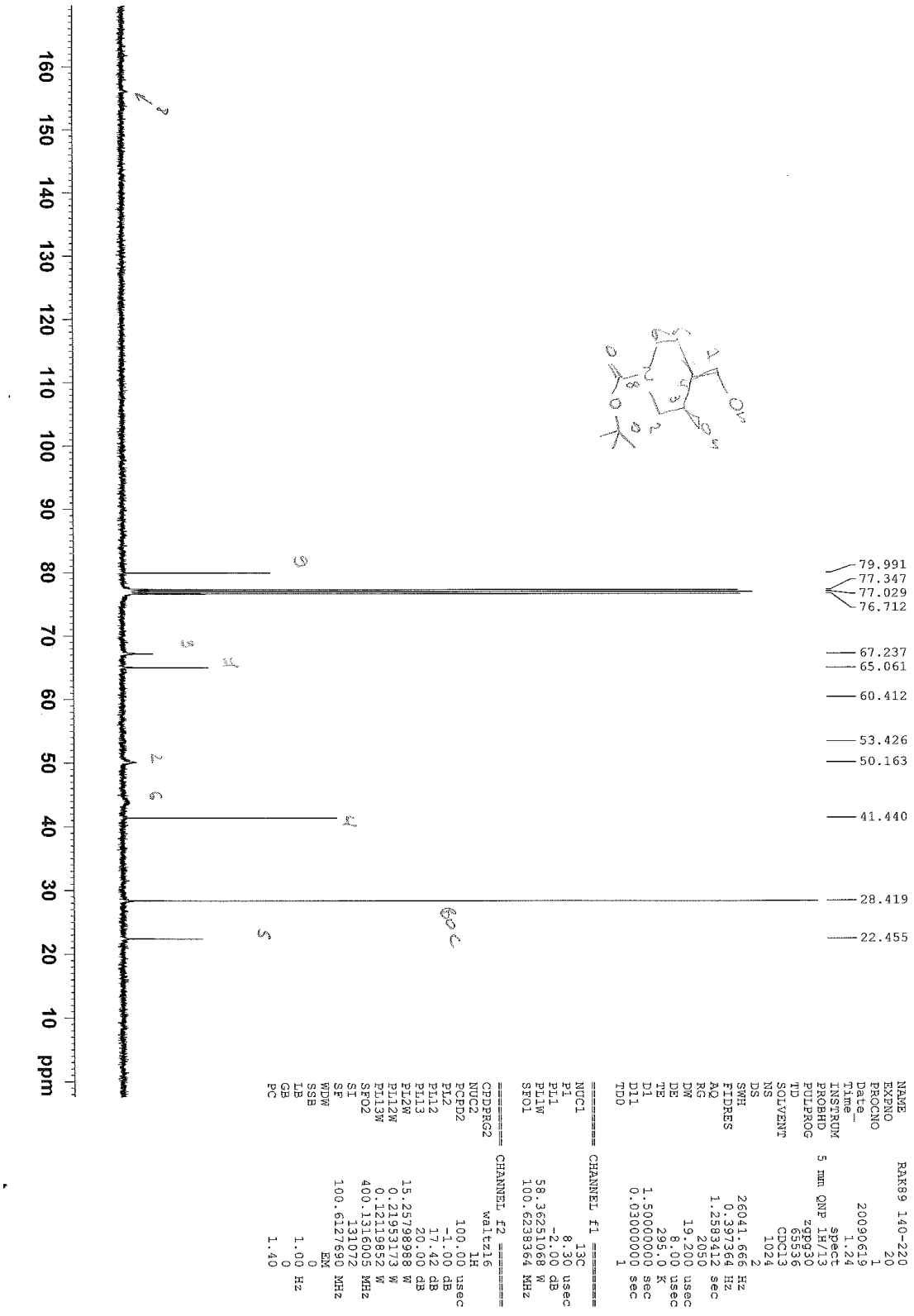

```
NAME                  RAK14 1-5
EXPNO                    40
PROCNO                    1
Date_              20081204
Time_                 12.30
INSTRUM               spect
PROBHD     5 mm QNP 1H/13
PULPROG               zg30
TD                   65536
SOLVENT               MeOD
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                      12.7
DW                    60.800 usec
DE                     8.00 usec
TE                    295.0 K
D1                 1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                     1H
P1                    11.00 usec
PL1                   -1.00 dB
PL1W           15.25798988 W
SFO1           400.1324710 MHz
SI                    32768
SF             400.1300000 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```



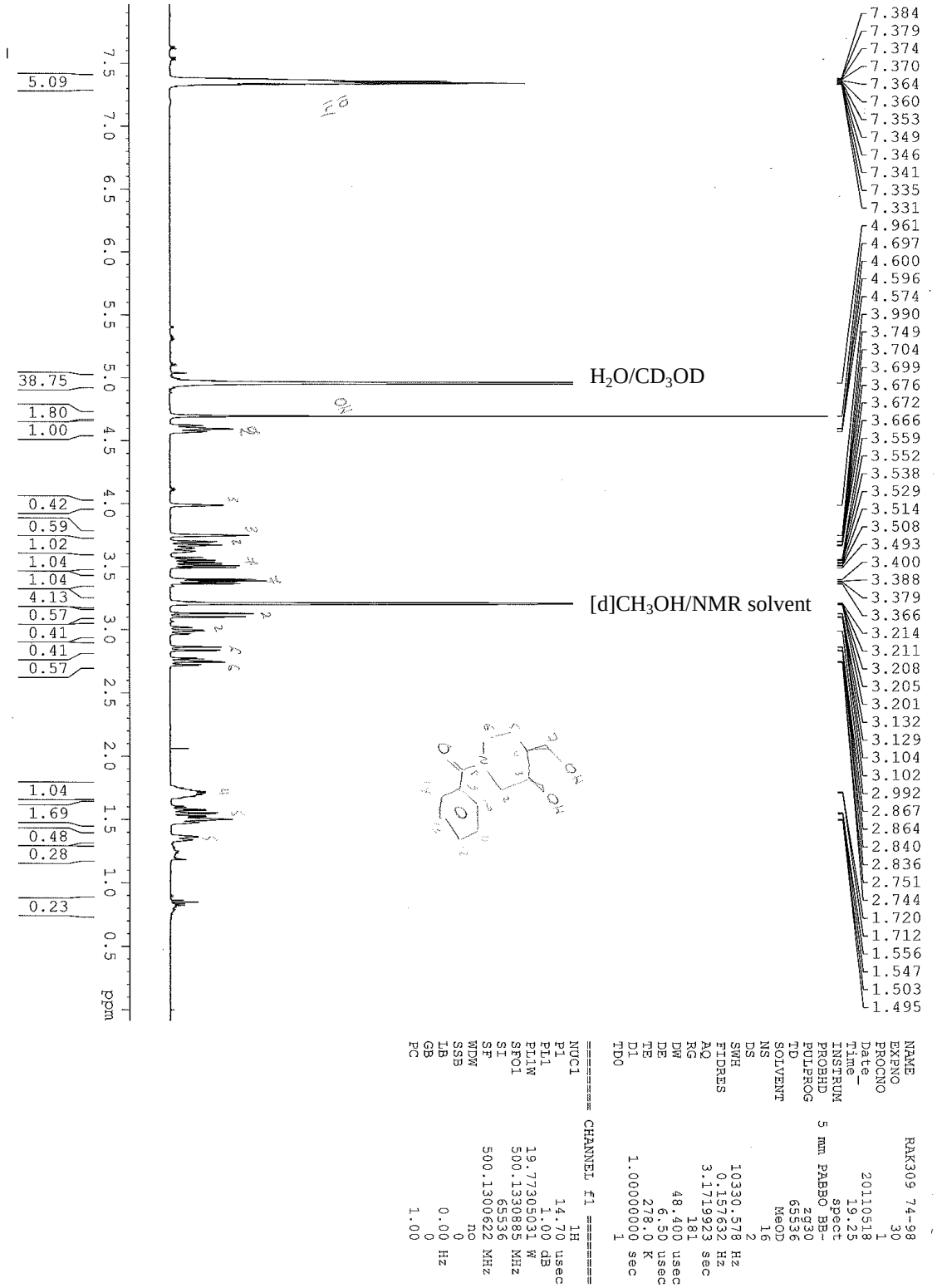

```
NAME                                                    RAK14 1-5
EXPNO                                                        51
PROCNO                                                        1
Date_                                               20081207
Time_                                                   12.37
INSTRUM                                                  spect
PROBHD                                 5 mm QNP  1H/1
PULPROG                                                 zgpg30
TD                                                      65536
SOLVENT                                                  MeOD
NS                                                       1024
DS                                                          2
SWH                                                 26041.666 Hz
FIDRES                                                0.397364 Hz
AQ                                                    1.2583412 sec
RG                                                       2050
DW                                                     19.200 usec
DE                                                      8.00 usec
TE                                                     295.0 K
D1                                                     1.50000000 sec
D11                                                    0.03000000 sec
TD0                                                          1

======== CHANNEL f1 ========
NUC1                                                       13C
P1                                                      8.30 usec
PL1                                                    -2.00 dB
PL1W                                                58.36251068 W
SFO1                                               100.6238364 MHz

======== CHANNEL f2 ========
CPDPRG2                                                waltz16
NUC2                                                       1H
PCPD2                                                 100.00 usec
PL2                                                    -1.00 dB
PL12                                                   18.00 dB
PL13                                                   20.00 dB
PL2W                                                15.25798988 W
PL12W                                                0.19208671 W
PL13W                                                0.12119852 W
SFO2                                               400.1316005 MHz
SI                                                      131072
SF                                                 100.6126261 MHz
WDW                                                        EM
SSB                                                         0
LB                                                       1.00 Hz
GB                                                          0
PC                                                       1.40
```

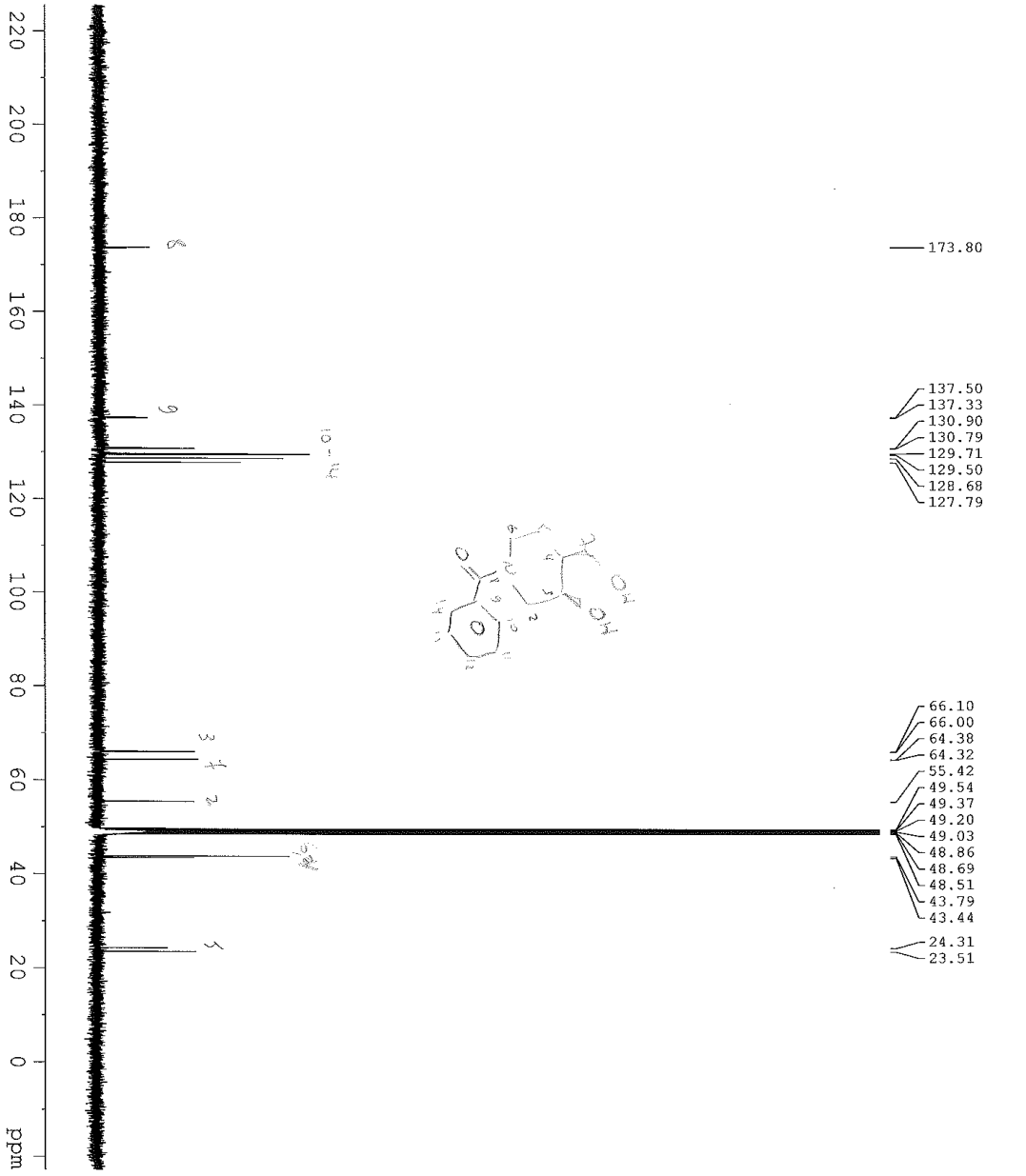
Compound **6**.




160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
79.991
77.347
77.029
76.712
67.237
65.061
60.412
53.426
50.163
41.440
28.419
22.455
NAME RAK89 140-220
EXPNO 20
PROCNO 1
Date_ 20090619
Time_ 1.24
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 2
SWH 26041.666 Hz
FIDRES 0.397364 Hz
AQ 1.2583412 sec
RG 2050
DW 19.200 usec
DE 8.00 usec
TE 295.0 K
D1 1.50000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 8.30 usec
PL1 -2.00 dB
PL1W 58.36251068 W
SFO1 100.6238364 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -1.00 dB
PL12 17.42 dB
PL13 20.00 dB
PL2W 15.25798988 W
PL12W 0.21953173 W
PL13W 0.12119852 W
SFO2 400.1316005 MHz
SI 131072
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

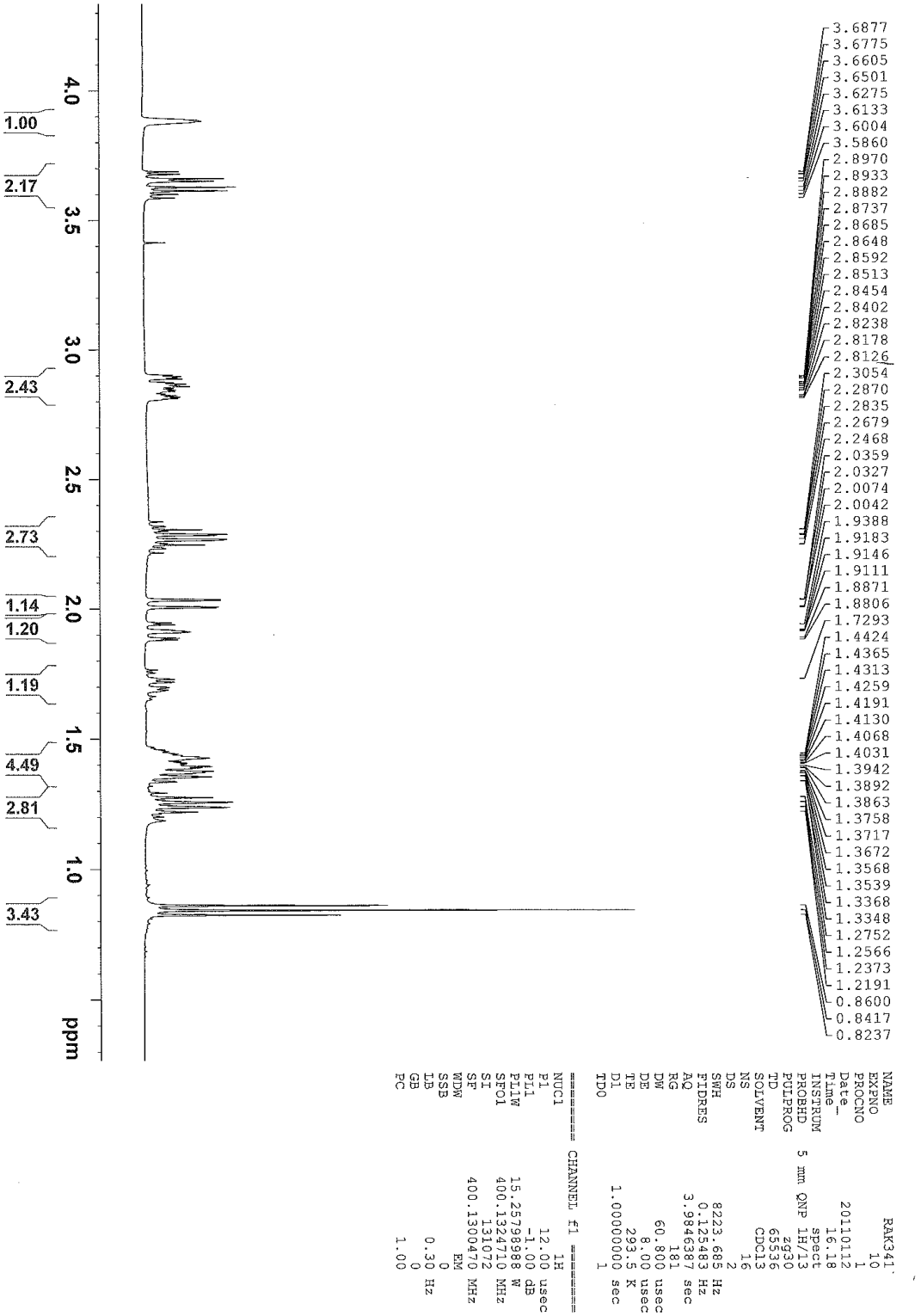
Compound **7**.

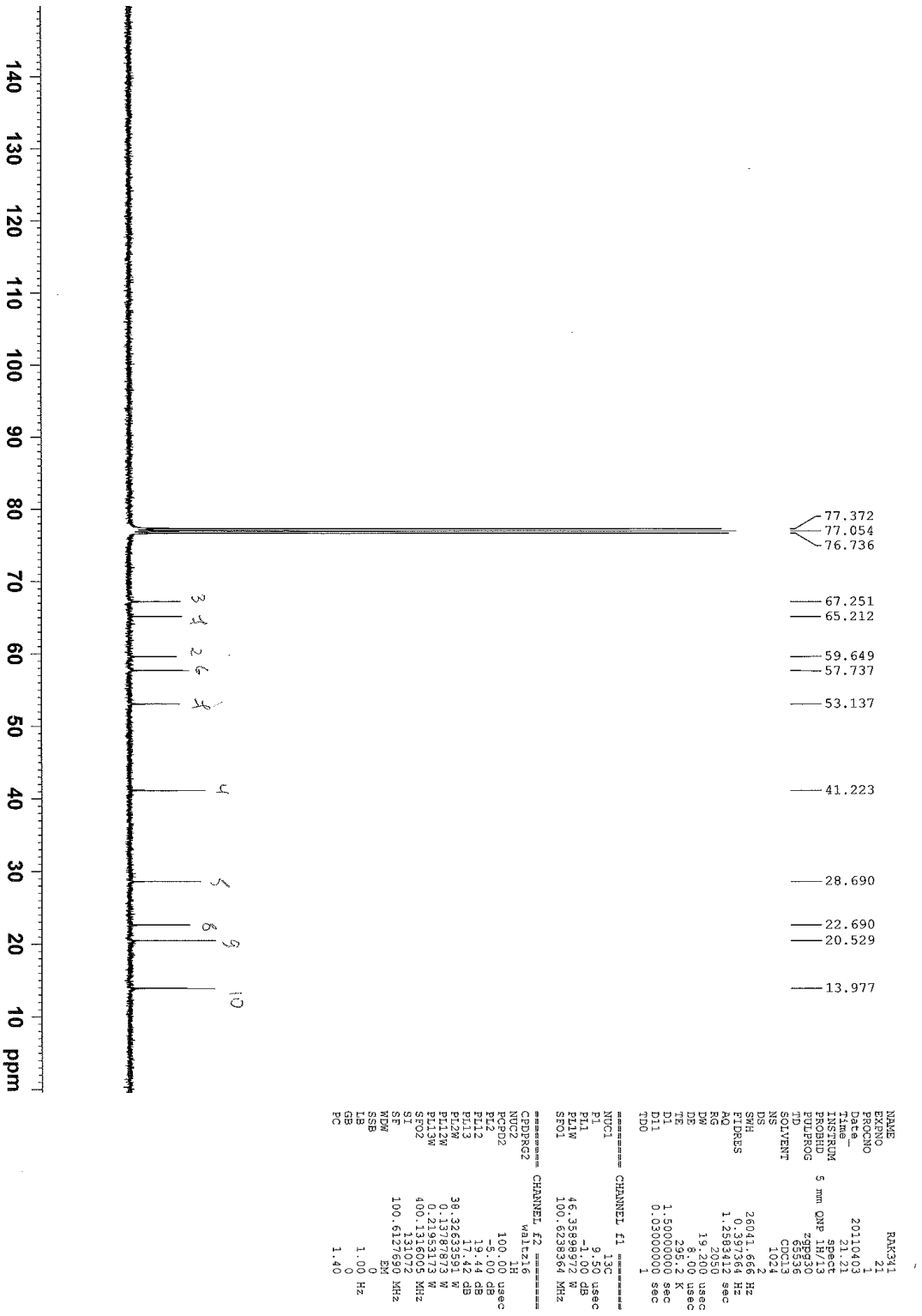

H2O/CD3OD
[d]CH3OH/NMR solvent
5.09
38.75
1.80
1.00
0.42
0.59
1.02
1.04
1.04
4.13
0.57
0.41
0.41
0.57
1.04
1.69
0.48
0.28
0.23
ppm
NAME RAK309 74-98
EXPNO 30
PROCNO 1
Date_ 20110518
Time_ 19.25
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT MeOD
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 181
DW 48.400 usec
DE 6.50 usec
TE 278.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.70 usec
PL1 1.00 dB
PL1W 19.77305031 W
SFO1 500.1330885 MHz
SI 65536
SF 500.1300622 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00



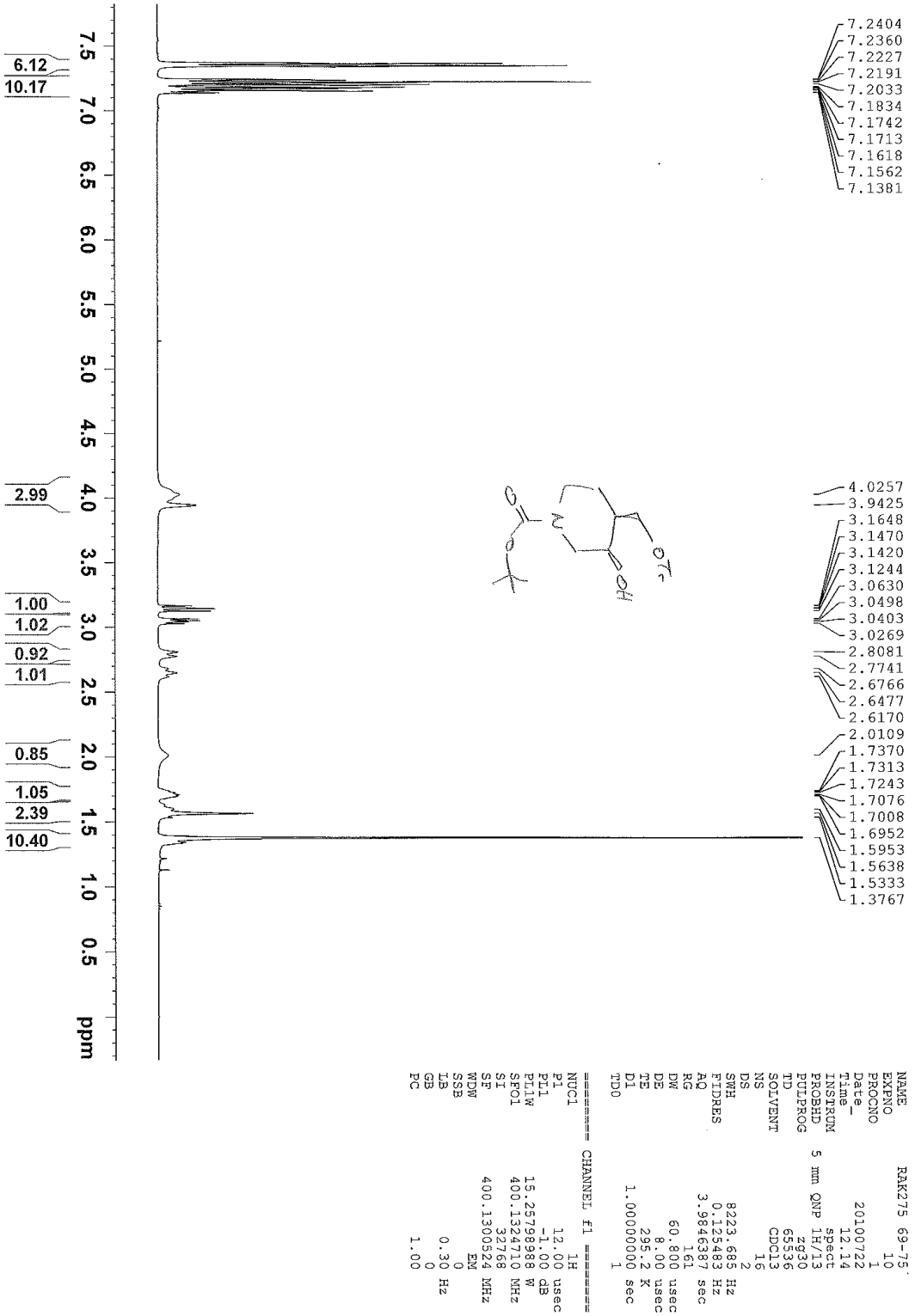

```
NAME                 RAK309 74-98
EXPNO                        31
PROCNO                        1
Date_               20110518
Time_                   19.28
INSTRUM                  spect
PROBHD     5 mm PABBO BB-
PULPROG                 zgpg30
TD                       65536
SOLVENT                   MeOD
NS                        1824
DS                           2
SWH                  31250.000 Hz
FIDRES                0.476837 Hz
AQ                    1.0486259 sec
RG                        1820
DW                      16.000 usec
DE                       8.00 usec
TE                      279.0 K
D1                    1.00000000 sec
D11                   0.03000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                       13C
P1                       10.50 usec
PL1                       1.50 dB
PL1W                64.32036591 W
SFO1                125.7703648 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                    80.00 usec
PL2                       1.00 dB
PL12                     15.72 dB
PL13                     15.72 dB
PL2W                19.77305031 W
PL12W                0.66691983 W
PL13W                0.66691983 W
SFO2               500.1316005 MHz
SI                       131072
SF                 125.7576104 MHz
WDW                        EM
SSB                         0
LB                       1.00 Hz
GB                          0
PC                       1.40
```

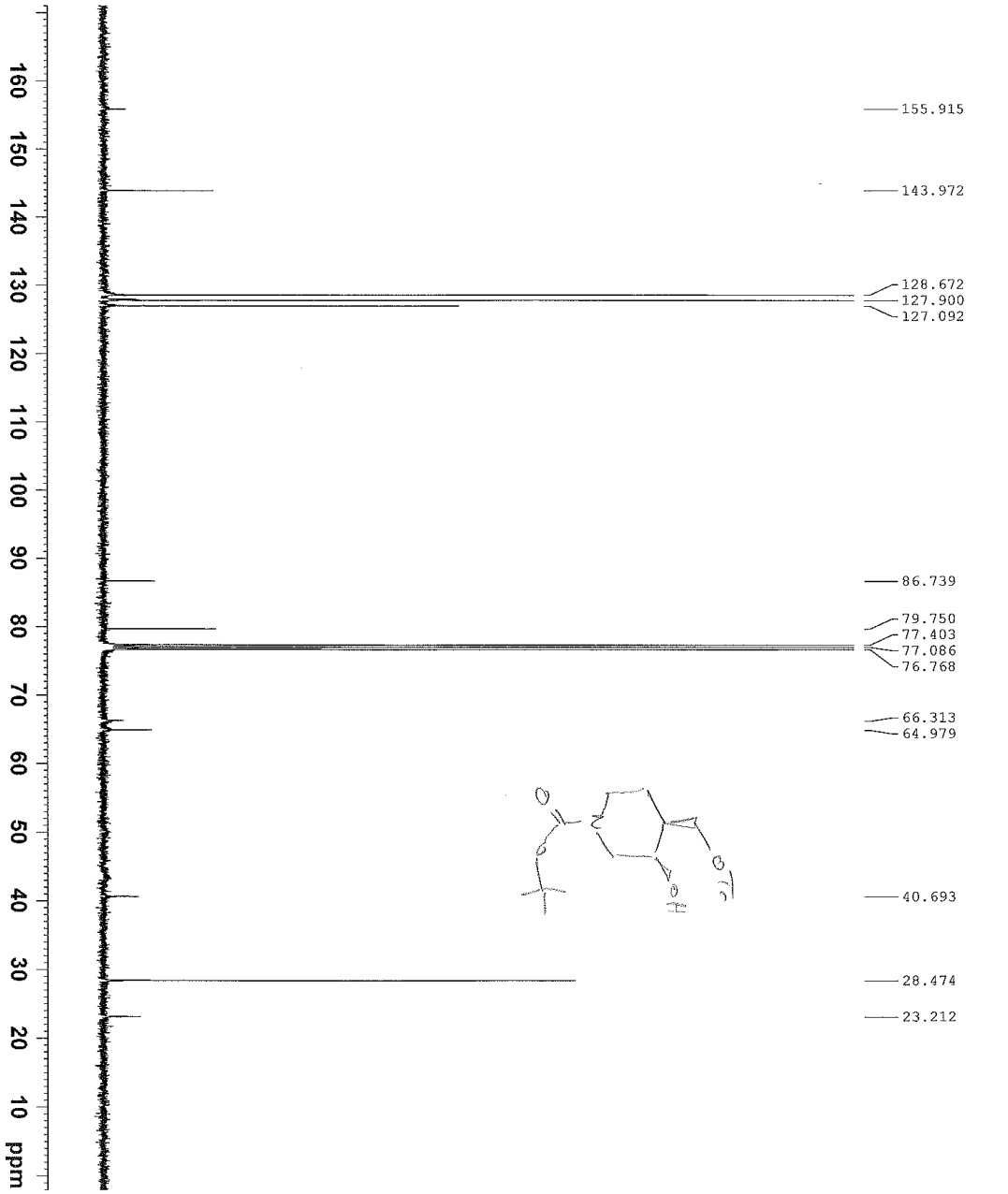
Compound **8**.


4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
2.17
2.43
2.73
1.14
1.20
1.19
4.49
2.81
3.43
3.6877
3.6775
3.6605
3.6501
3.6275
3.6133
3.6004
3.5860
2.8970
2.8933
2.8882
2.8737
2.8685
2.8648
2.8592
2.8513
2.8454
2.8402
2.8238
2.8178
2.8126
2.3054
2.2870
2.2835
2.2679
2.2468
2.0359
2.0327
2.0074
2.0042
1.9388
1.9183
1.9146
1.9111
1.8871
1.8806
1.7293
1.4424
1.4365
1.4313
1.4259
1.4191
1.4130
1.4068
1.4031
1.3942
1.3892
1.3863
1.3758
1.3717
1.3672
1.3568
1.3539
1.3368
1.3348
1.2752
1.2566
1.2373
1.2191
0.8600
0.8417
0.8237
NAME RAM341
EXPNO 10
PROCNO 1
Date_ 20110112
Time_ 16.18
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 181
DW 60.800 usec
DE 8.00 usec
TE 293.5 K
D1 1.00000000 sec
TD0 1
========== CHANNEL f1 ==========
NUC1 1H
P1 12.00 usec
PL1 -1.00 dB
PL1W 15.25798988 W
SFO1 400.1324710 MHz
SI 131072
SF 400.1300470 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00


140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
77.372
77.054
76.736
67.251
65.212
59.649
57.737
53.137
41.223
28.690
22.690
20.529
13.977
1 2 3 4 5 6 7 8 9 10
NAME RAK341
EXPNO 21
PROCNO 1
Date_ 20110403
Time_ 21.21
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 2
SWH 26041.666 Hz
FIDRES 0.397364 Hz
AQ 1.2583412 sec
RG 2050
DW 19.200 usec
DE 8.00 usec
TE 295.2 K
D1 1.50000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.50 usec
PL1 -1.00 dB
PL1W 46.35898972 W
SFO1 100.6238364 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -5.00 dB
PL12 19.44 dB
PL13 17.42 dB
PL2W 38.32633591 W
PL12W 0.13787873 W
PL13W 0.21953173 W
SFO2 400.1316005 MHz
SI 131072
SF 100.6127650 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

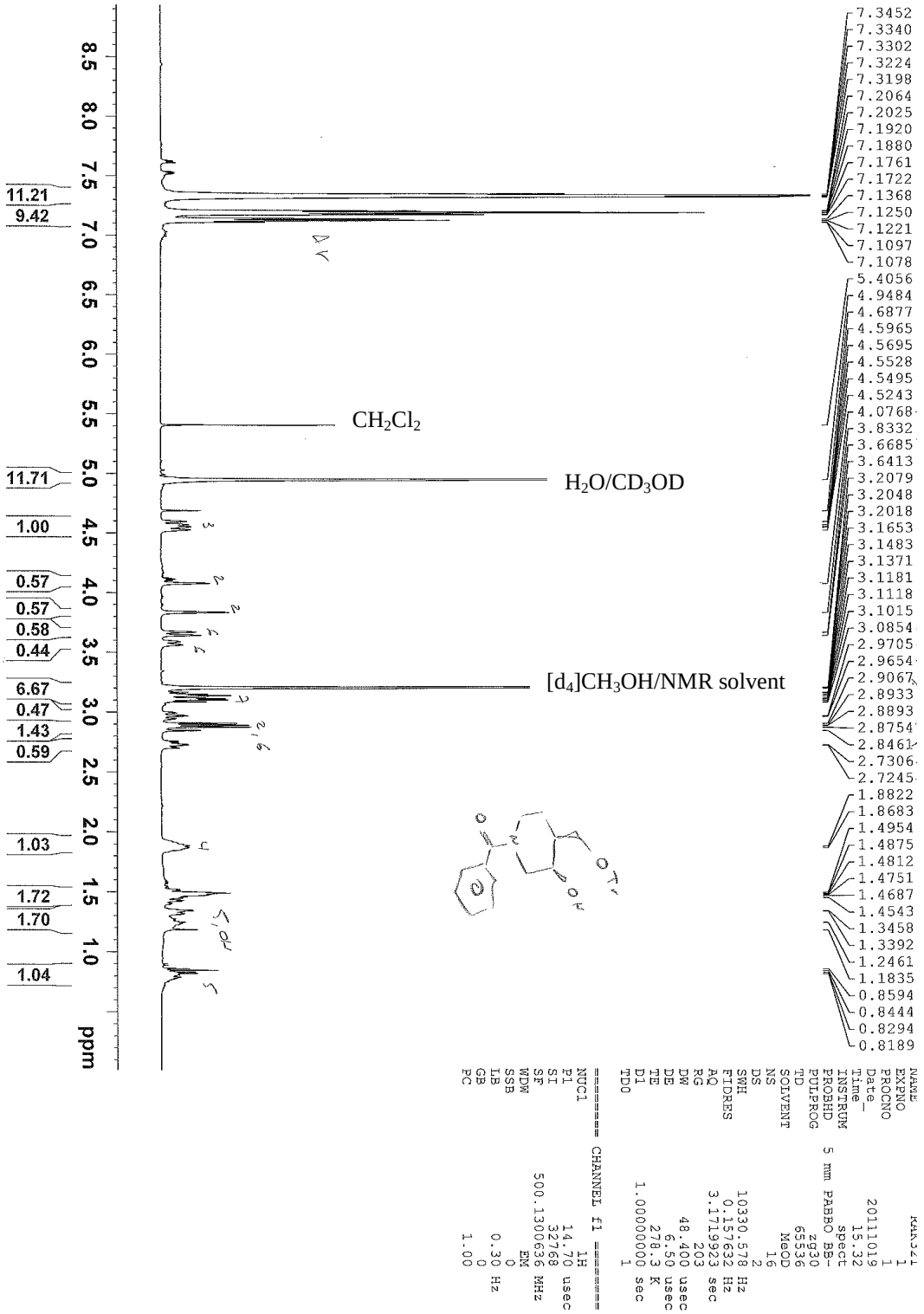
Compound **9**.

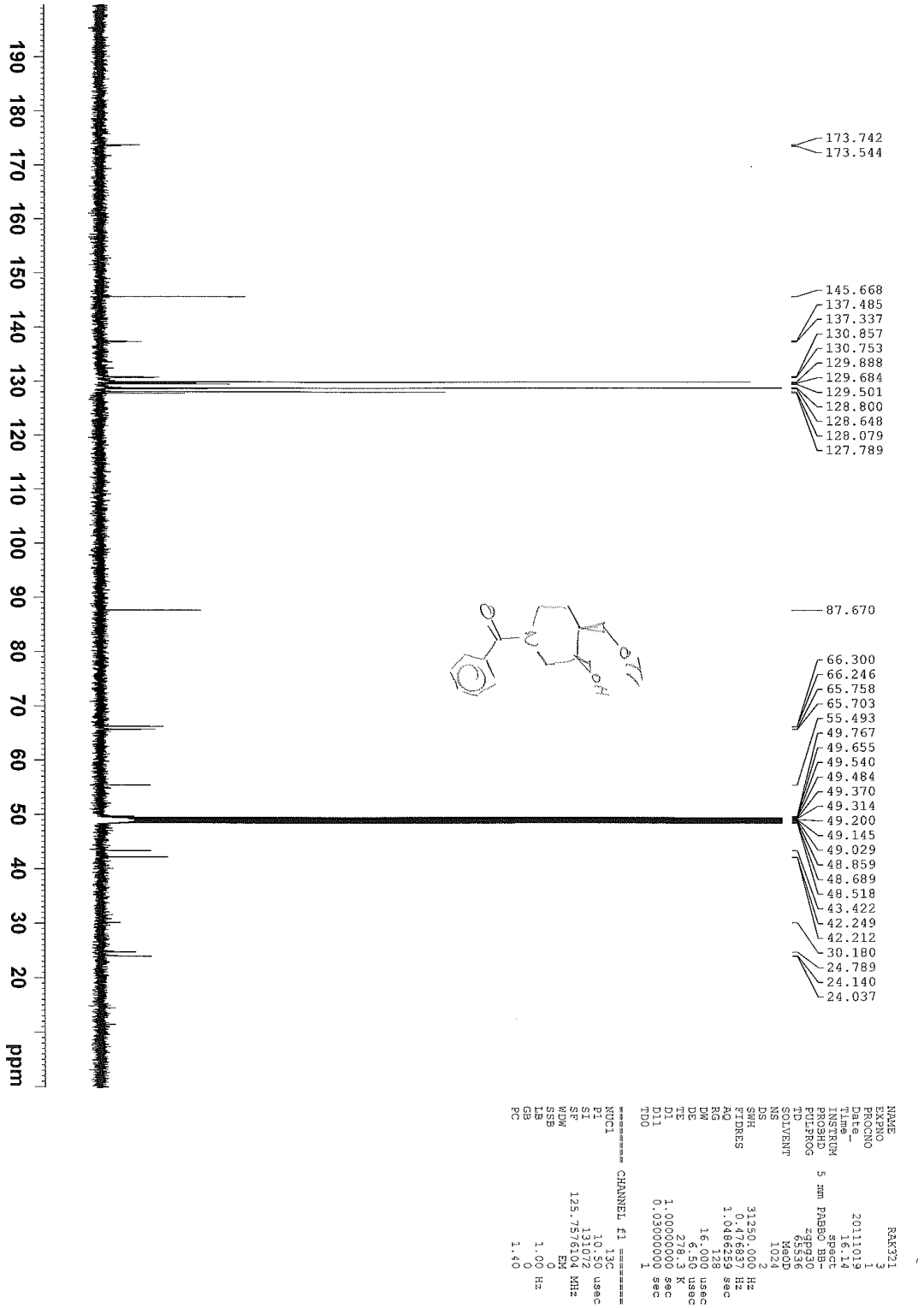




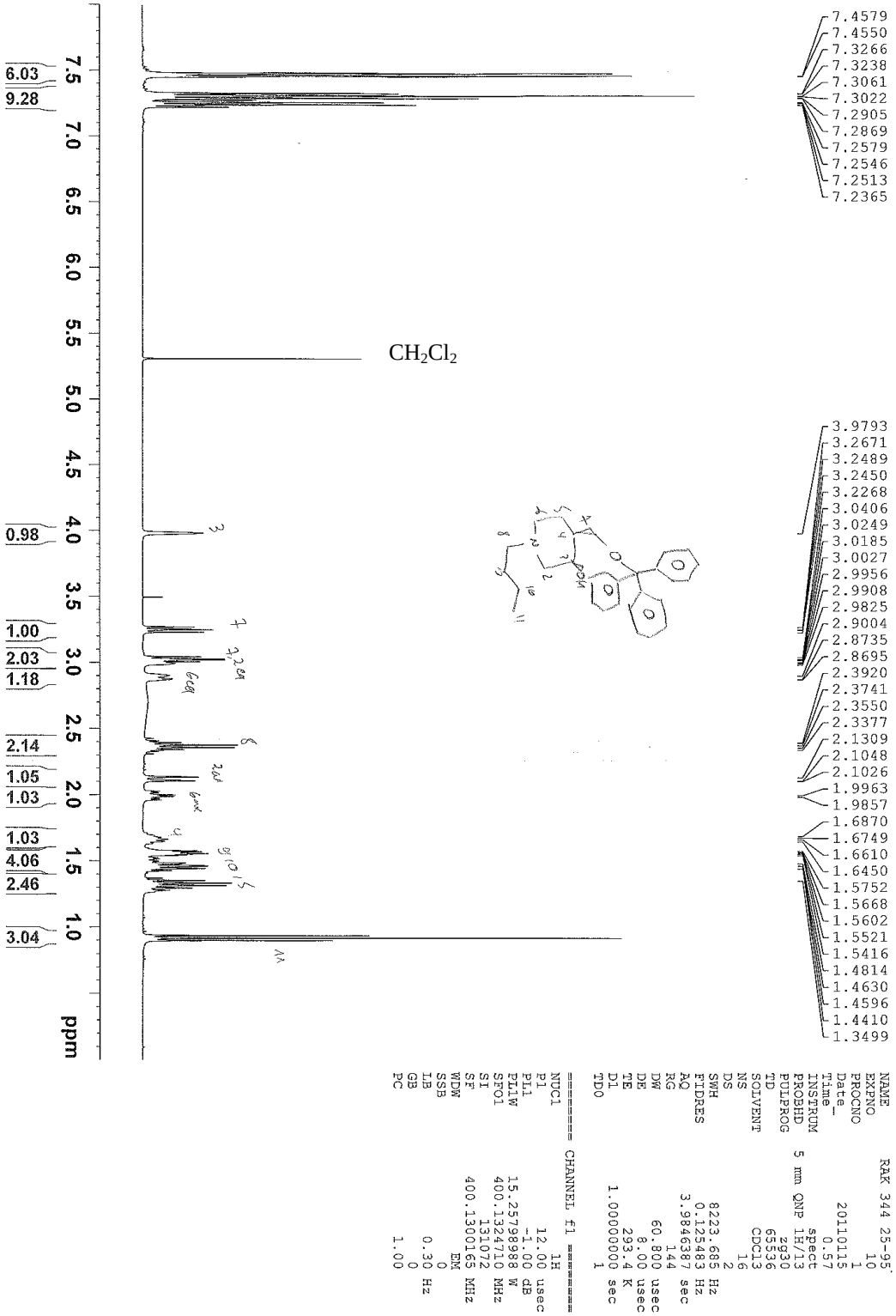

```
NAME                 RAK275 69-74
EXPNO                        11
PROCNO                        1
Date_              20101031
Time               0.29
INSTRUM            spect
PROBHD     5 mm QNP 1H/13
PULPROG            zgpg30
TD                 65536
SOLVENT            CDCl3
NS                 1024
DS                 2
SWH                26041.666 Hz
FIDRES             0.397364 Hz
AQ                 1.2583412 sec
RG                 2050
DW                 19.200 usec
DE                 8.00 usec
TE                 292.6 K
D1                 1.50000000 sec
D11                0.03000000 sec
TD0                1

====== CHANNEL f1 ======
NUC1               13C
P1                 8.20 usec
PL1                -2.00 dB
PL1W               58.36251068 W
SFO1               100.6238364 MHz

====== CHANNEL f2 ======
CPDPRG2            waltz16
NUC2               1H
PCPD2              100.00 usec
PL2                -1.00 dB
PL12               17.42 dB
PL13               17.42 dB
PL2W               15.25798988 W
PL12W              0.21953173 W
PL13W              0.21953173 W
SFO2               400.1316005 MHz
SI                 131072
SF                 100.6127690 MHz
WDW                EM
SSB                0
LB                 1.00 Hz
GB                 0
PC                 1.40
```

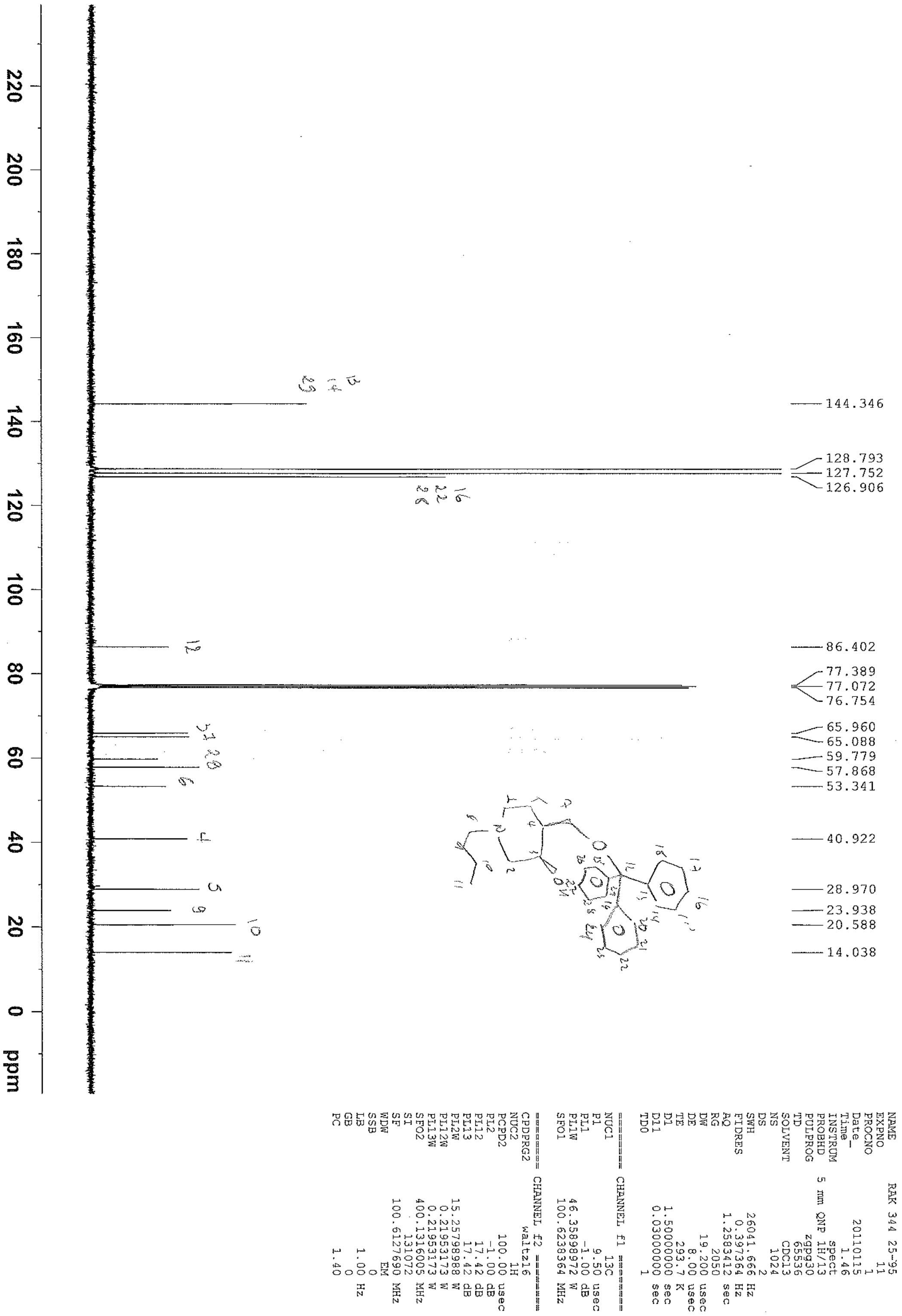
Compound **10**.



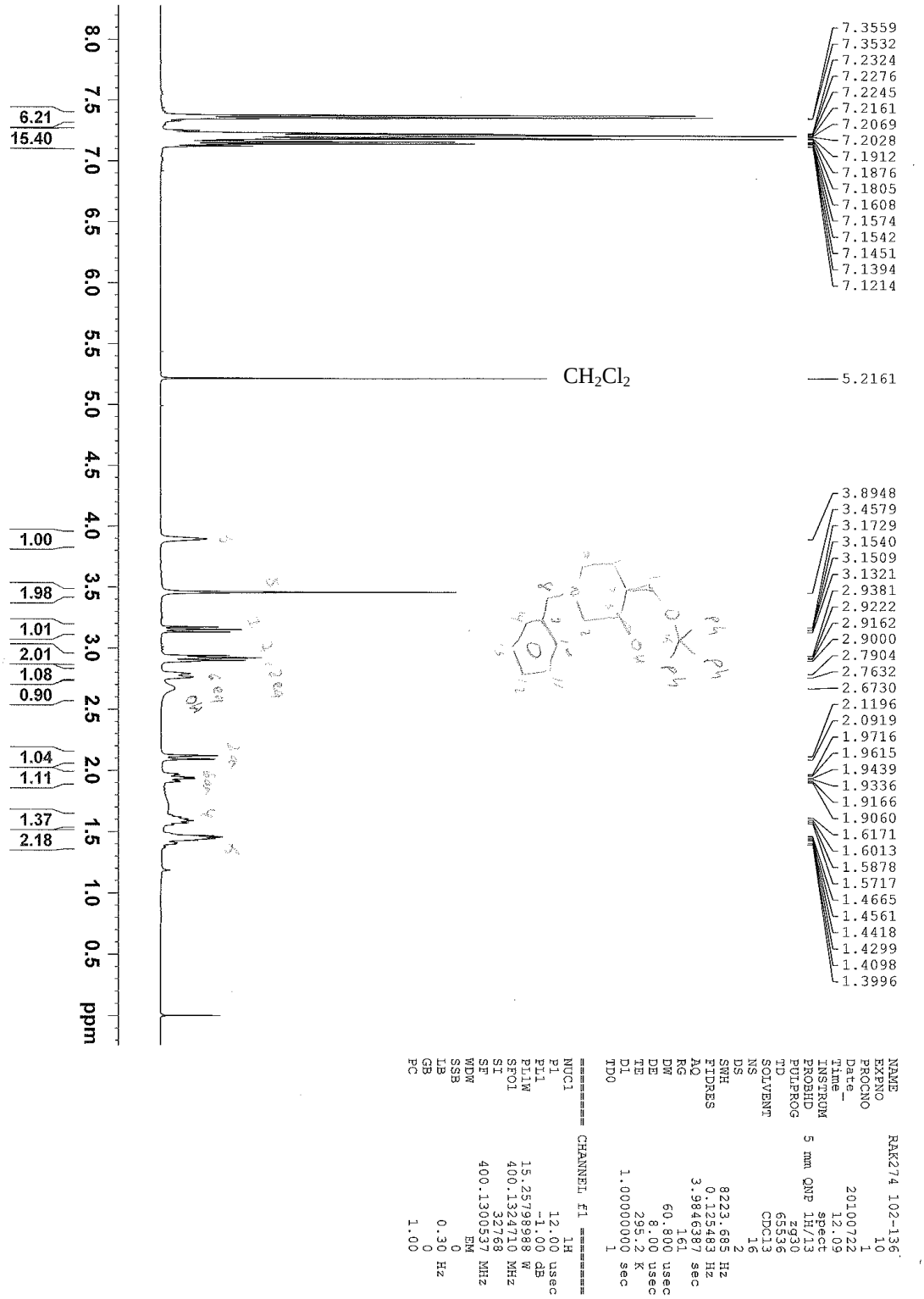

ppm
173.742
173.544
145.668
137.485
137.337
130.857
130.753
129.888
129.684
129.501
128.800
128.648
128.079
127.789
87.670
66.300
66.246
65.758
65.703
55.493
49.767
49.655
49.540
49.484
49.370
49.314
49.200
49.145
49.029
48.859
48.689
48.518
43.422
42.249
42.212
30.180
24.789
24.140
24.037
NAME RAF321
EXPNO 3
PROCNO 1
Date_ 20111019
Time 16.14
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT MeOD
NS 1024
DS 2
SWH 31250.000 Hz
FIDRES 0.476837 Hz
AQ 1.0486259 sec
RG 128
DW 16.000 usec
DE 6.50 usec
TE 278.3 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
CHANNEL f1
NUC1 13C
P1 10.50 usec
SI 131072
SF 125.7576104 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

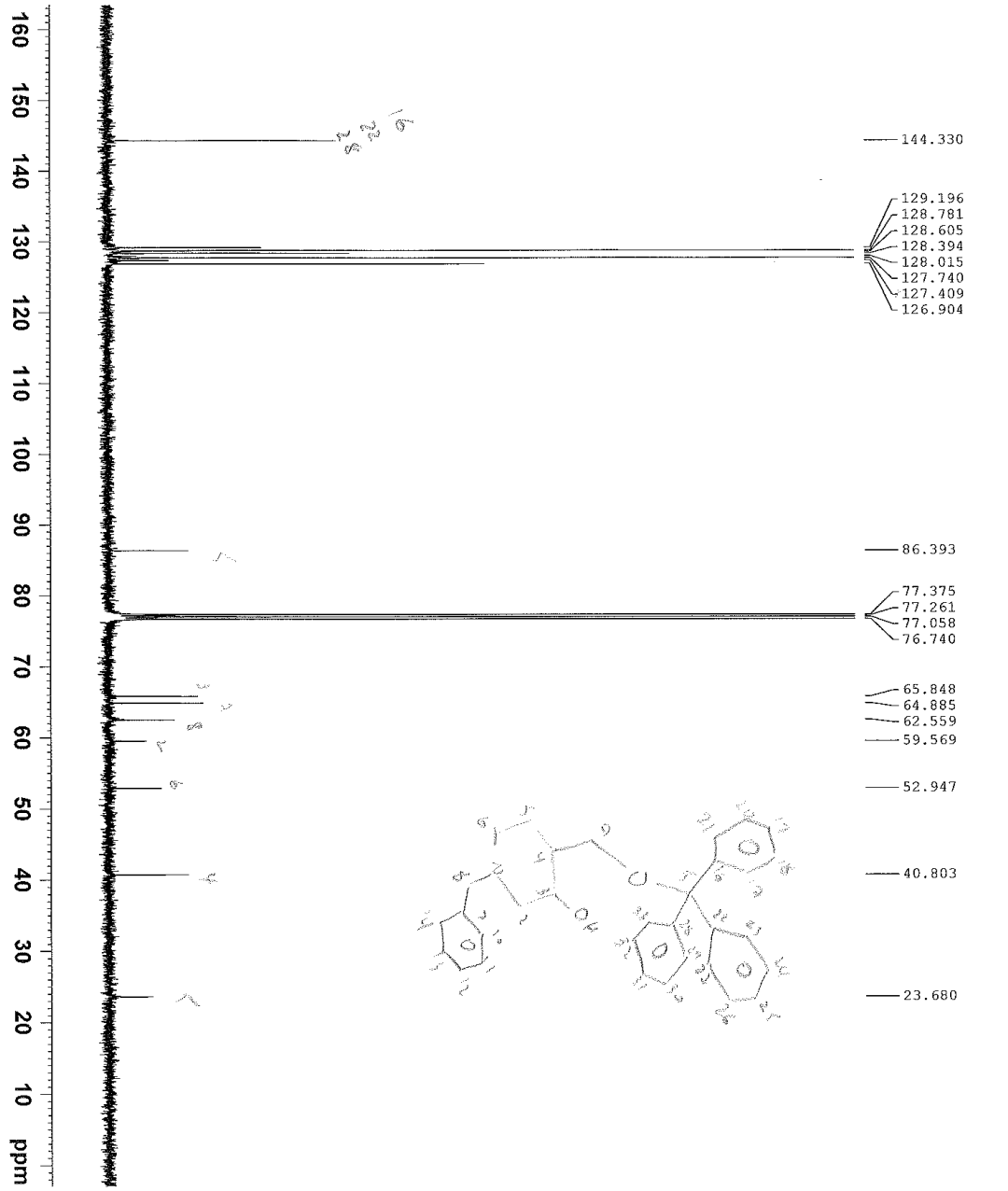
Compound **11**.


7.4579
7.4550
7.3266
7.3238
7.3061
7.3022
7.2905
7.2869
7.2579
7.2546
7.2513
7.2365
CH2Cl2
3.9793
3.2671
3.2489
3.2450
3.2268
3.0406
3.0249
3.0185
3.0027
2.9956
2.9908
2.9825
2.9004
2.8735
2.8695
2.3920
2.3741
2.3550
2.3377
2.1309
2.1048
2.1026
1.9963
1.9857
1.6870
1.6749
1.6610
1.6450
1.5752
1.5668
1.5602
1.5521
1.5416
1.4814
1.4630
1.4596
1.4410
1.3499
6.03
9.28
0.98
1.00
2.03
1.18
2.14
1.05
1.03
1.03
4.06
2.46
3.04
ppm
NAME RAK 344 25-95
EXPNO 10
PROCNO 1
Date_ 20110115
Time_ 0.57
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 144
DW 60.800 usec
DE 8.00 usec
TE 293.4 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 -1.00 dB
PL1W 15.25798988 W
SFO1 400.1324710 MHz
SI 131072
SF 400.1300165 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00


220
200
180
160
140
120
100
80
60
40
20
0
ppm
144.346
128.793
127.752
126.906
86.402
77.389
77.072
76.754
65.960
65.088
59.779
57.868
53.341
40.922
28.970
23.938
20.588
14.038
NAME RAK 344 25-95
EXPNO 11
PROCNO 1
Date_ 20110115
Time 1.46
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 2
SWH 26041.666 Hz
FIDRES 0.397364 Hz
AQ 1.2583412 sec
RG 2050
DW 19.200 usec
DE 8.00 usec
TE 293.7 K
D1 1.50000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.50 usec
PL1 -1.00 dB
PL1W 46.35898972 W
SFO1 100.6238364 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -1.00 dB
PL12 17.42 dB
PL13 17.42 dB
PL2W 15.25798988 W
PL12W 0.21953173 W
PL13W 0.21953173 W
SFO2 400.1316005 MHz
SI 131072
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

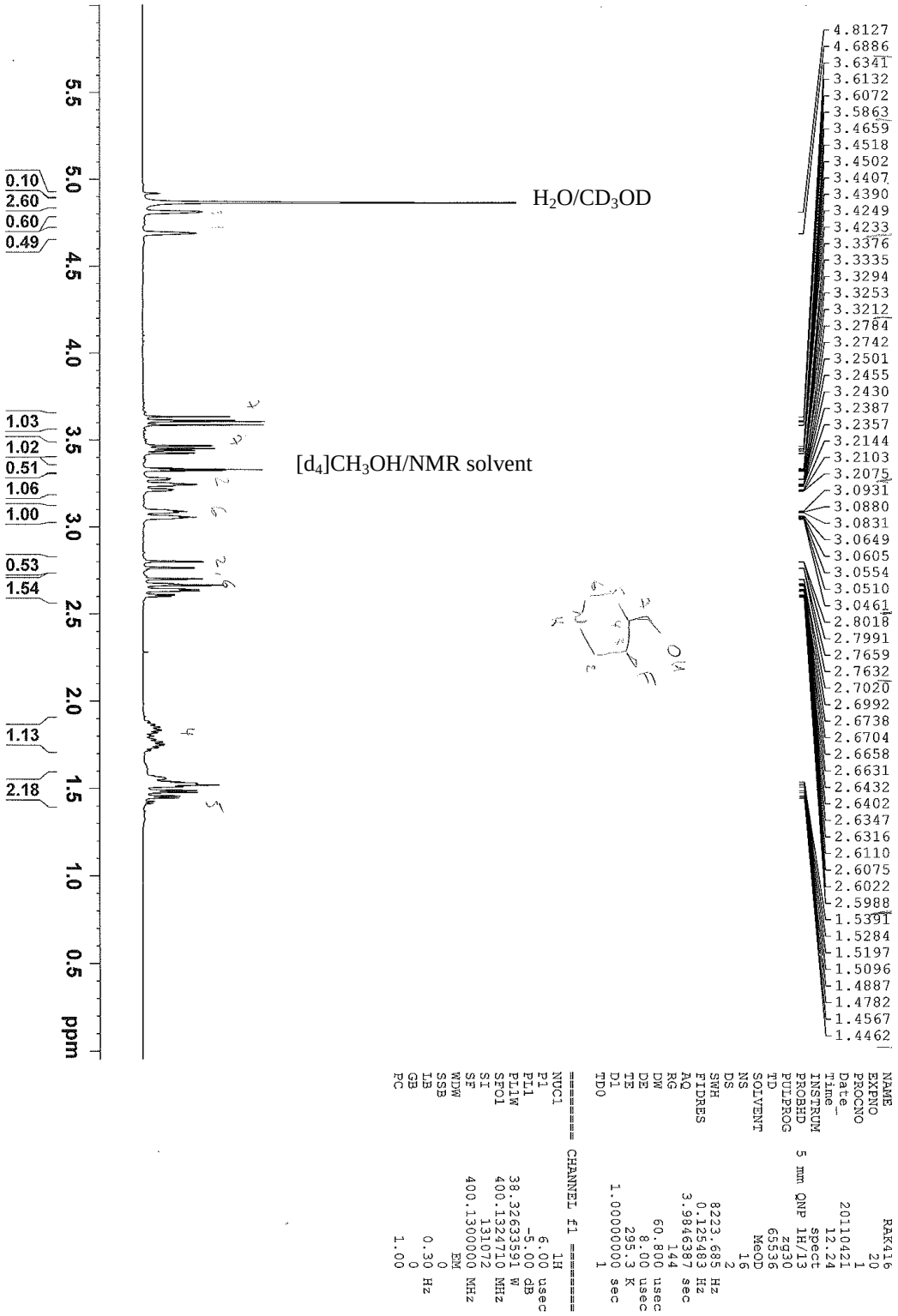
Compound **12**.

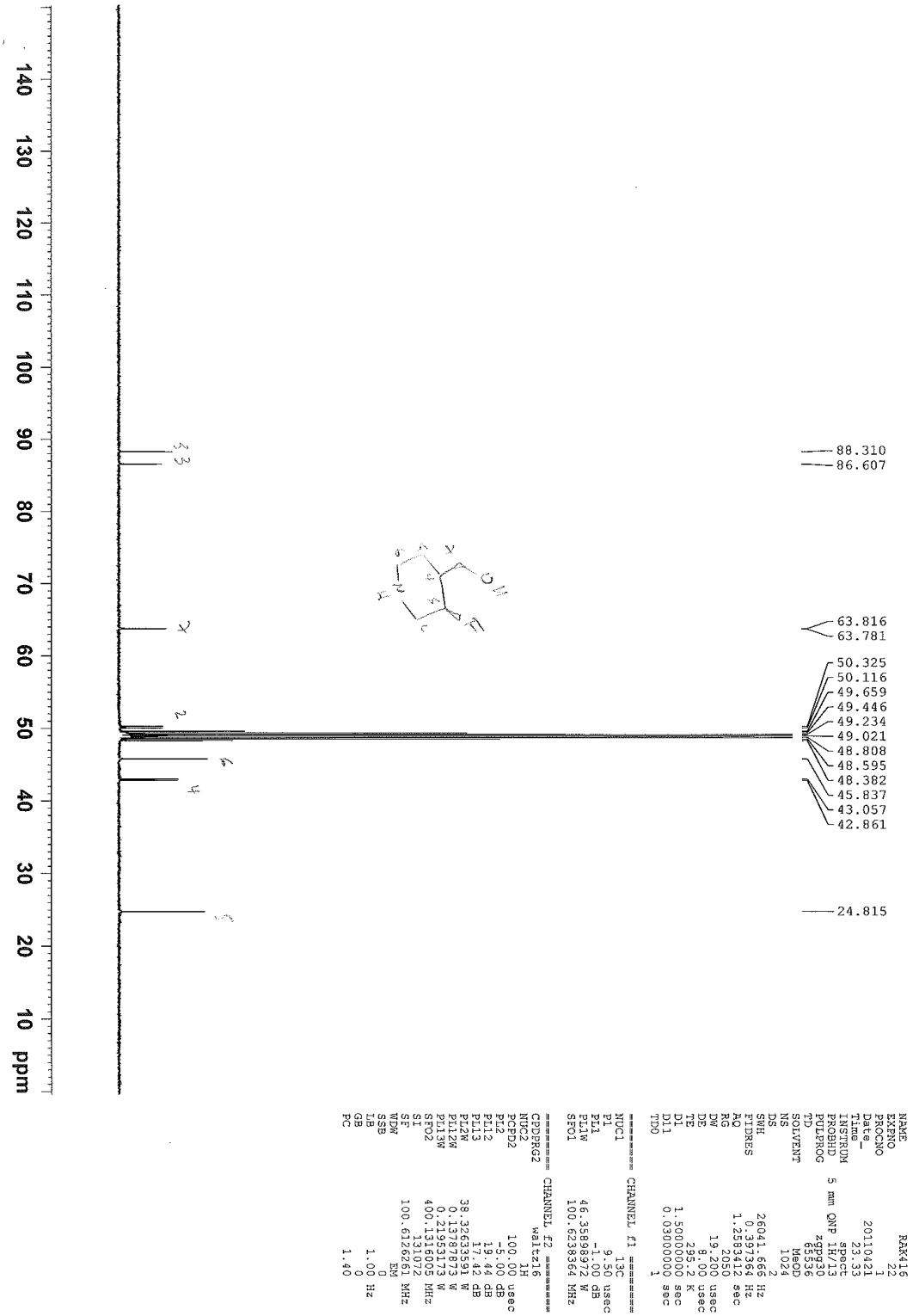

7.3559
7.3532
7.2324
7.2276
7.2245
7.2161
7.2069
7.2028
7.1912
7.1876
7.1805
7.1608
7.1574
7.1542
7.1451
7.1394
7.1214
CH2Cl2
5.2161
3.8948
3.4579
3.1729
3.1540
3.1509
3.1321
2.9381
2.9222
2.9162
2.9000
2.7904
2.7632
2.6730
2.1196
2.0919
1.9716
1.9615
1.9439
1.9336
1.9166
1.9060
1.6171
1.6013
1.5878
1.5717
1.4665
1.4561
1.4418
1.4299
1.4098
1.3996
6.21
15.40
1.00
1.98
1.01
2.01
1.08
0.90
1.04
1.11
1.37
2.18
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
NAME RAK274 102-136
EXPNO 10
PROCNO 1
Date_ 20100722
Time_ 12.09
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 161
DW 60.800 usec
DE 8.00 usec
TE 295.2 K
D1 1.00000000 sec
TD0 1
========== CHANNEL f1 ==========
NUC1 1H
P1 12.00 usec
PL1 -1.00 dB
PL1W 15.25798988 W
SFO1 400.1324710 MHz
SI 32768
SF 400.1300537 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



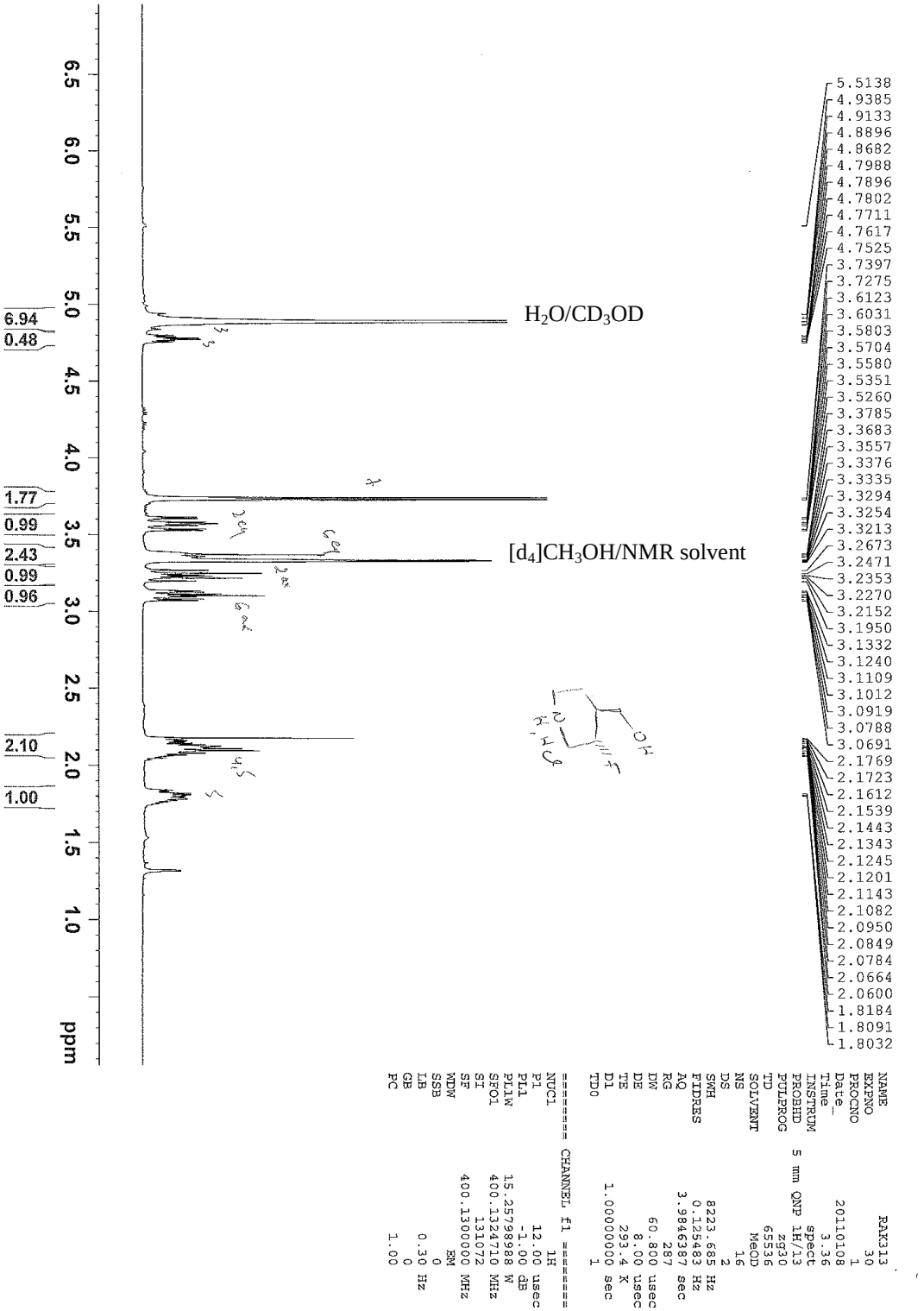

```
NAME                 RAK274 102-136
EXPNO                        21
PROCNO                        1
Date_                  20100916
Time                      21.33
INSTRUM                    spect
PROBHD          5 mm QNP 1H/13
PULPROG                 zgpg30
TD                       65536
SOLVENT                  CDCl3
NS                        1024
DS                           2
SWH                  26041.666 Hz
FIDRES                0.397364 Hz
AQ                    1.2583412 sec
RG                         2050
DW                       19.200 usec
DE                        8.00 usec
TE                       295.2 K
D1                    1.50000000 sec
D11                   0.03000000 sec
TD0                          1
======== CHANNEL f1 ========
NUC1                        13C
P1                         8.20 usec
PL1                       -2.00 dB
PL1W                58.36251068 W
SFO1               100.6238364 MHz
======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                   100.00 usec
PL2                       -1.00 dB
PL12                      17.42 dB
PL13                      17.42 dB
PL2W                15.25799988 W
PL12W                0.21953173 W
PL13W                0.21953173 W
SFO2               400.1316005 MHz
SI                       131072
SF                 100.6127690 MHz
WDW                         EM
SSB                          0
LB                        1.00 Hz
GB                           0
PC                        1.40
```

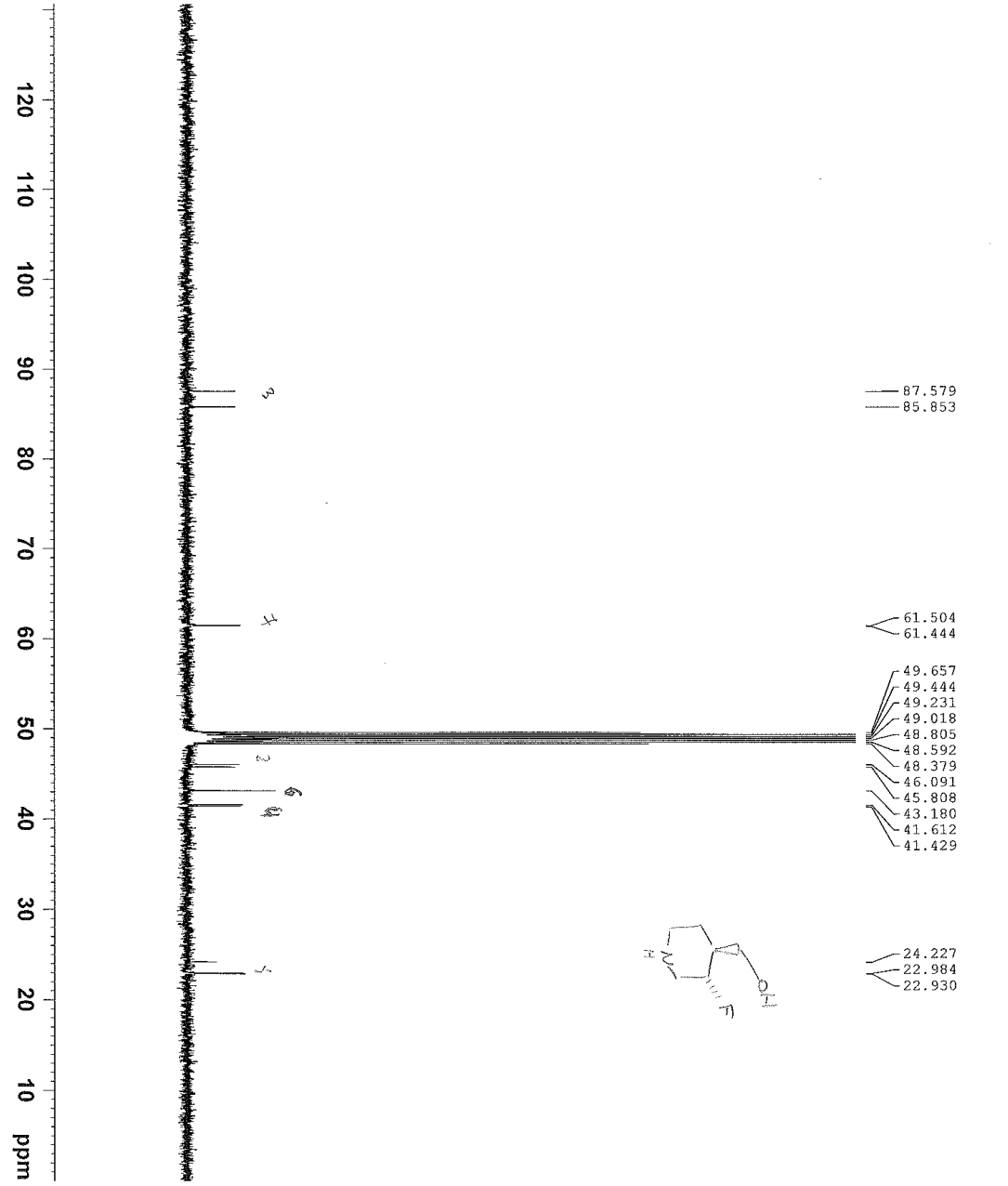
Compound *cis*-**18**.




88.310
86.607
63.816
63.781
50.325
50.116
49.659
49.446
49.234
49.021
48.808
48.595
48.382
45.837
43.057
42.861
24.815
140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
NAME RAK416
EXPNO 22
PROCNO 1
Date_ 20110421
Time 23.33
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zgpg30
TD 65536
SOLVENT MeOD
NS 1024
DS 2
SWH 26041.666 Hz
FIDRES 0.397364 Hz
AQ 1.2583412 sec
RG 2050
DW 19.200 usec
DE 8.00 usec
TE 295.2 K
D1 1.50000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.50 usec
PL1 -1.00 dB
PL1W 46.35898972 W
SFO1 100.6238364 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -5.00 dB
PL12 19.44 dB
PL13 17.42 dB
PL2W 38.32633591 W
PL12W 0.13787873 W
PL13W 0.21953173 W
SFO2 400.1316005 MHz
SI 131072
SF 100.6126261 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

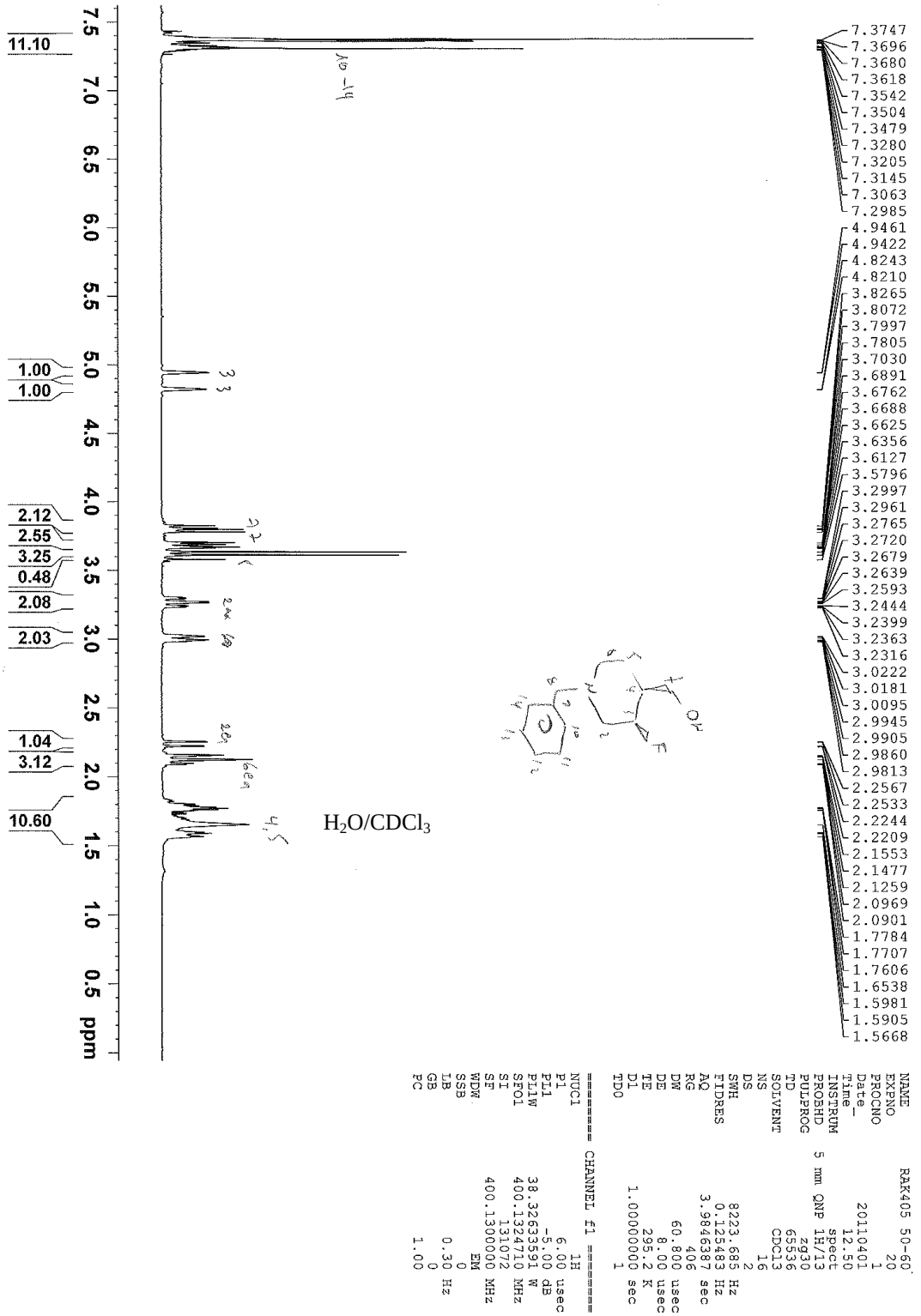
Compound *trans*-**18**.

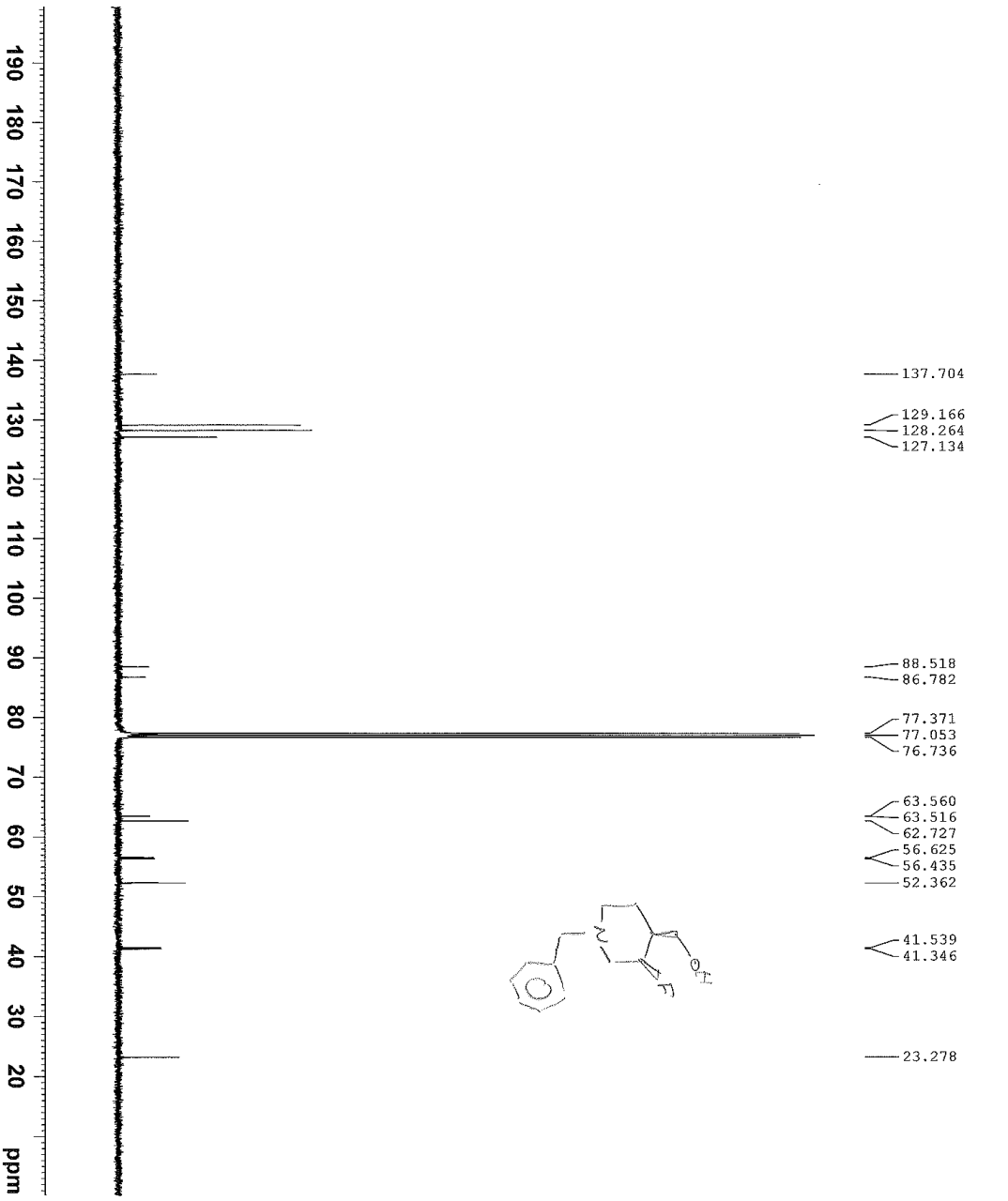





```
NAME                                                    RAK313
EXPNO                                                       31
PROCNO                                                       1
Date_                                             20110108
Time_                                                  4.25
INSTRUM                                                spect
PROBHD                                  5 mm QNP 1H/13
PULPROG                                            zgpg30
TD                                                  65536
SOLVENT                                              MeOD
NS                                                    1024
DS                                                       2
SWH                                            26041.666 Hz
FIDRES                                          0.397364 Hz
AQ                                             1.2583412 sec
RG                                                    2050
DW                                              19.200 usec
DE                                               8.00 usec
TE                                              293.9 K
D1                                              1.50000000 sec
D11                                             0.03000000 sec
TD0                                                      1

======== CHANNEL f1 ========
NUC1                                                   13C
P1                                                    9.50 usec
PL1                                                -1.00 dB
PL1W                                    46.35898972 W
SFO1                                    100.6238364 MHz

======== CHANNEL f2 ========
CPDPRG2                                            waltz16
NUC2                                                   1H
PCPD2                                             100.00 usec
PL2                                                -1.00 dB
PL12                                               17.42 dB
PL13                                               17.42 dB
PL2W                                    15.25799988 W
PL12W                                   0.21953173 W
PL13W                                   0.21953173 W
SFO2                                    400.1316005 MHz
SI                                                  131072
SF                                      100.6126261 MHz
WDW                                                    EM
SSB                                                     0
LB                                               1.00 Hz
GB                                                      0
PC                                                   1.40
```

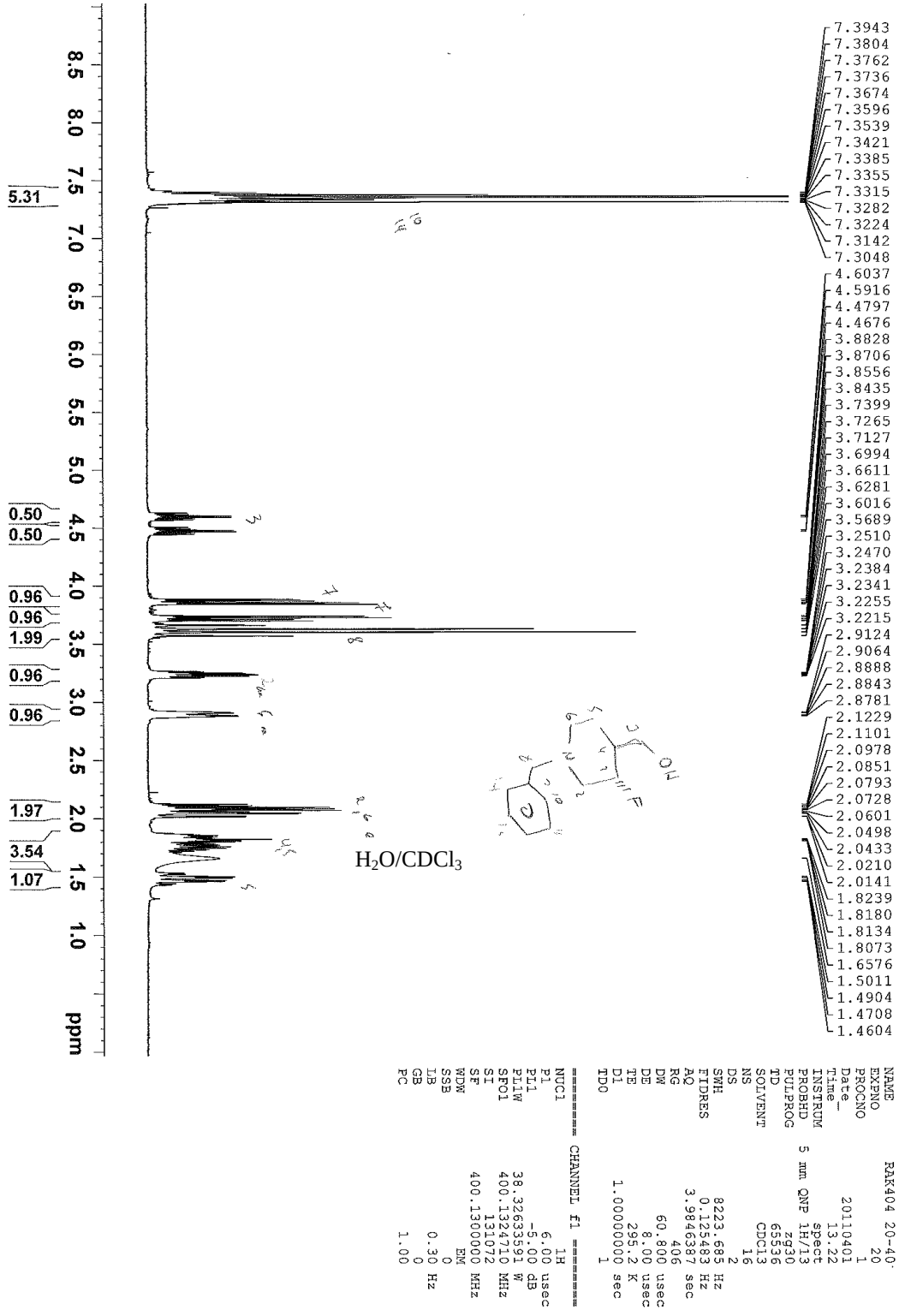
Compound *cis*-**19**.

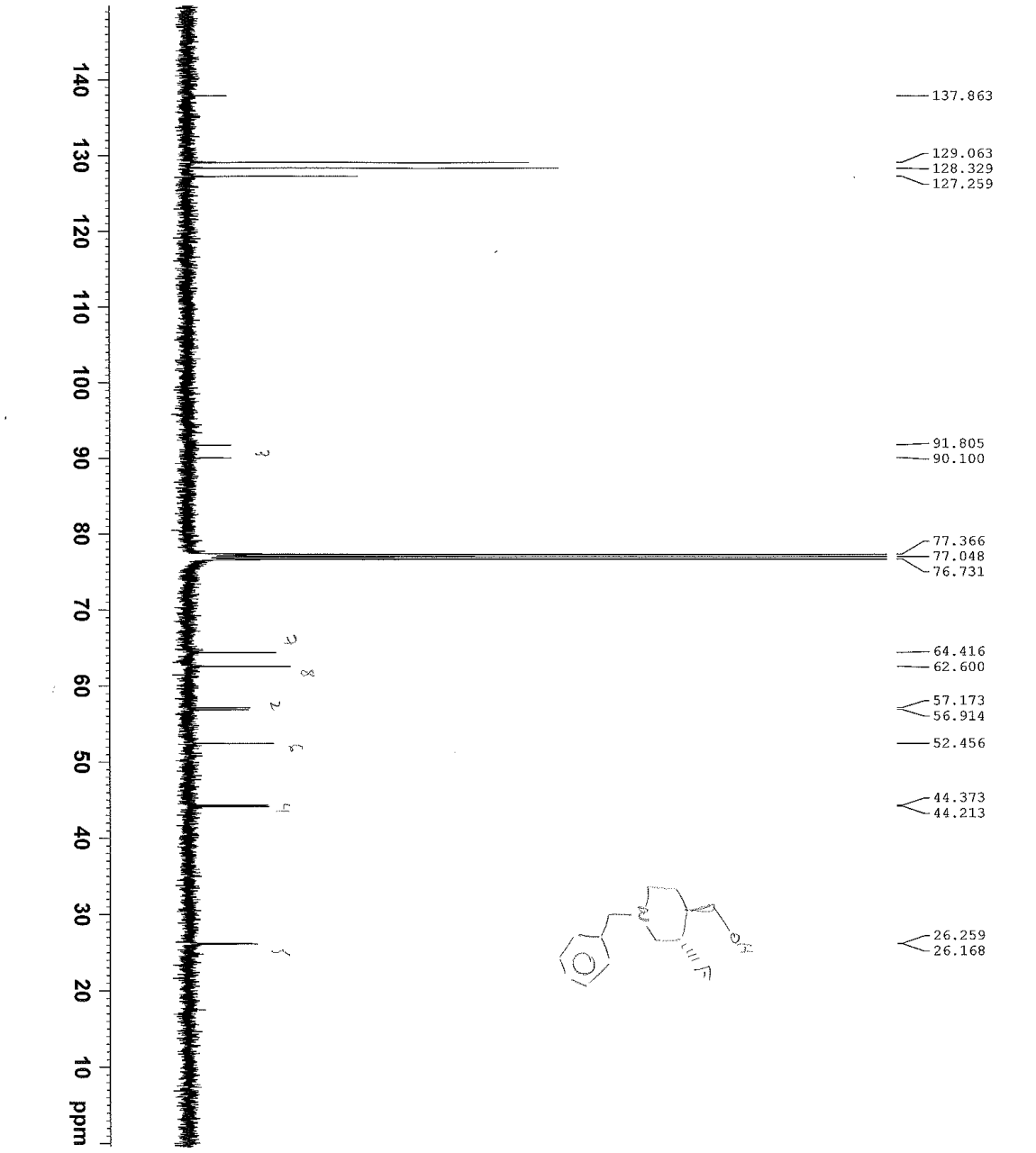





```
NAME                                    RAK405 50-60
EXPNO                                           22
PROCNO                                           1
Date_                                     20110403
Time_                                        18.45
INSTRUM                                      spect
PROBHD                      5 mm QNP 1H/13
PULPROG                                   zgpg30
TD                                         65536
SOLVENT                                    CDCl3
NS                                          1024
DS                                             2
SWH                                    26041.666 Hz
FIDRES                                  0.397364 Hz
AQ                                      1.2583412 sec
RG                                           2050
DW                                       19.200 usec
DE                                        8.00 usec
TE                                         295.2 K
D1                                     1.50000000 sec
D11                                    0.03000000 sec
TD0                                             1
======== CHANNEL f1 ========
NUC1                                          13C
P1                                         9.50 usec
PL1                                        -1.00 dB
PL1W                        46.35896972 W
SFO1                        100.6238364 MHz
======== CHANNEL f2 ========
CPDPRG2                                    waltz16
NUC2                                          1H
PCPD2                                    100.00 usec
PL2                                        -5.00 dB
PL12                                       19.44 dB
PL13                                       17.42 dB
PL2W                        38.32633591 W
PL12W                       0.13787873 W
PL13W                       0.21953173 W
SFO2                        400.1316005 MHz
SI                                         131072
SF                          100.6127690 MHz
WDW                                           EM
SSB                                            0
LB                                          1.00 Hz
GB                                             0
PC                                          1.40
```

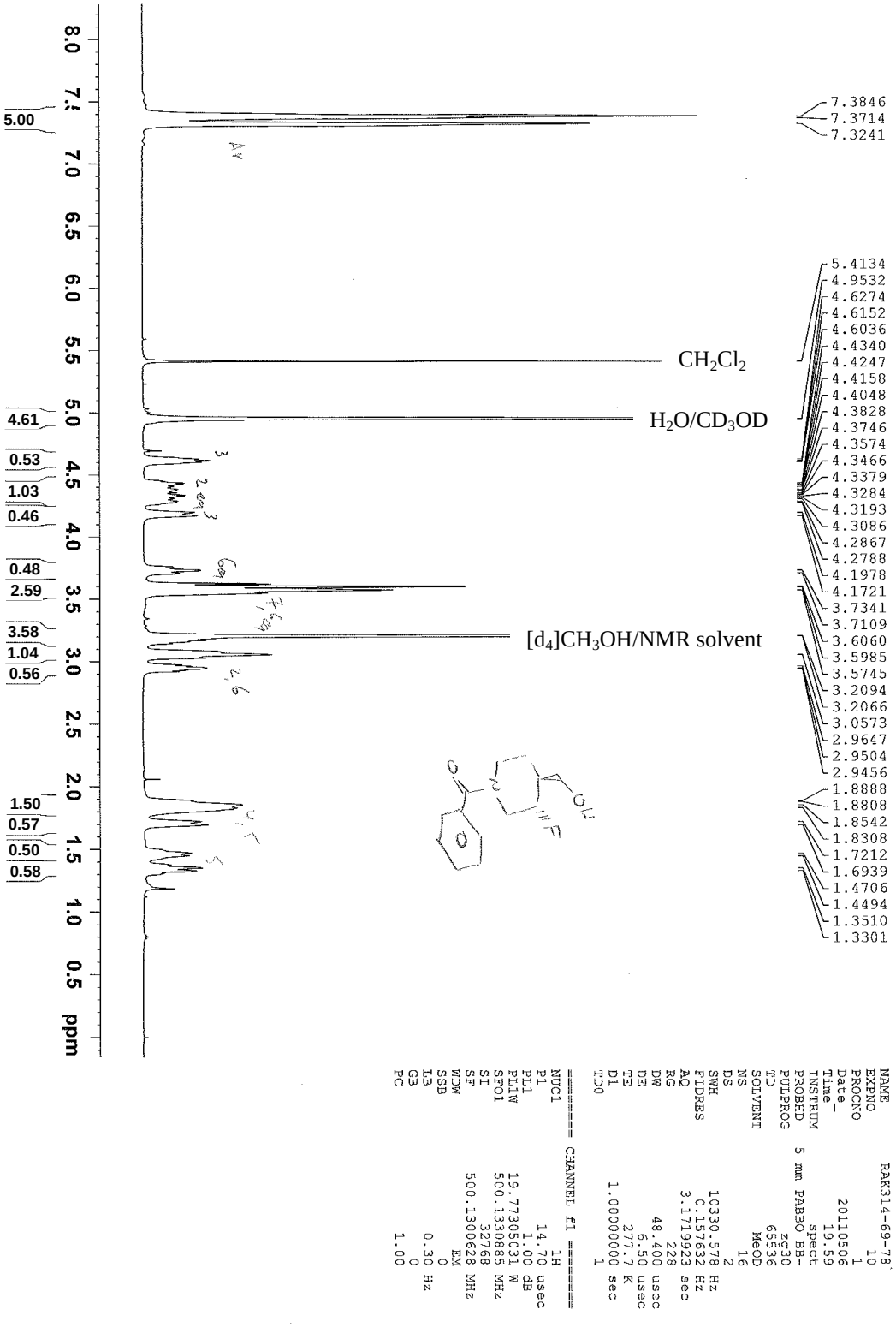
Compound *trans*-**19**.

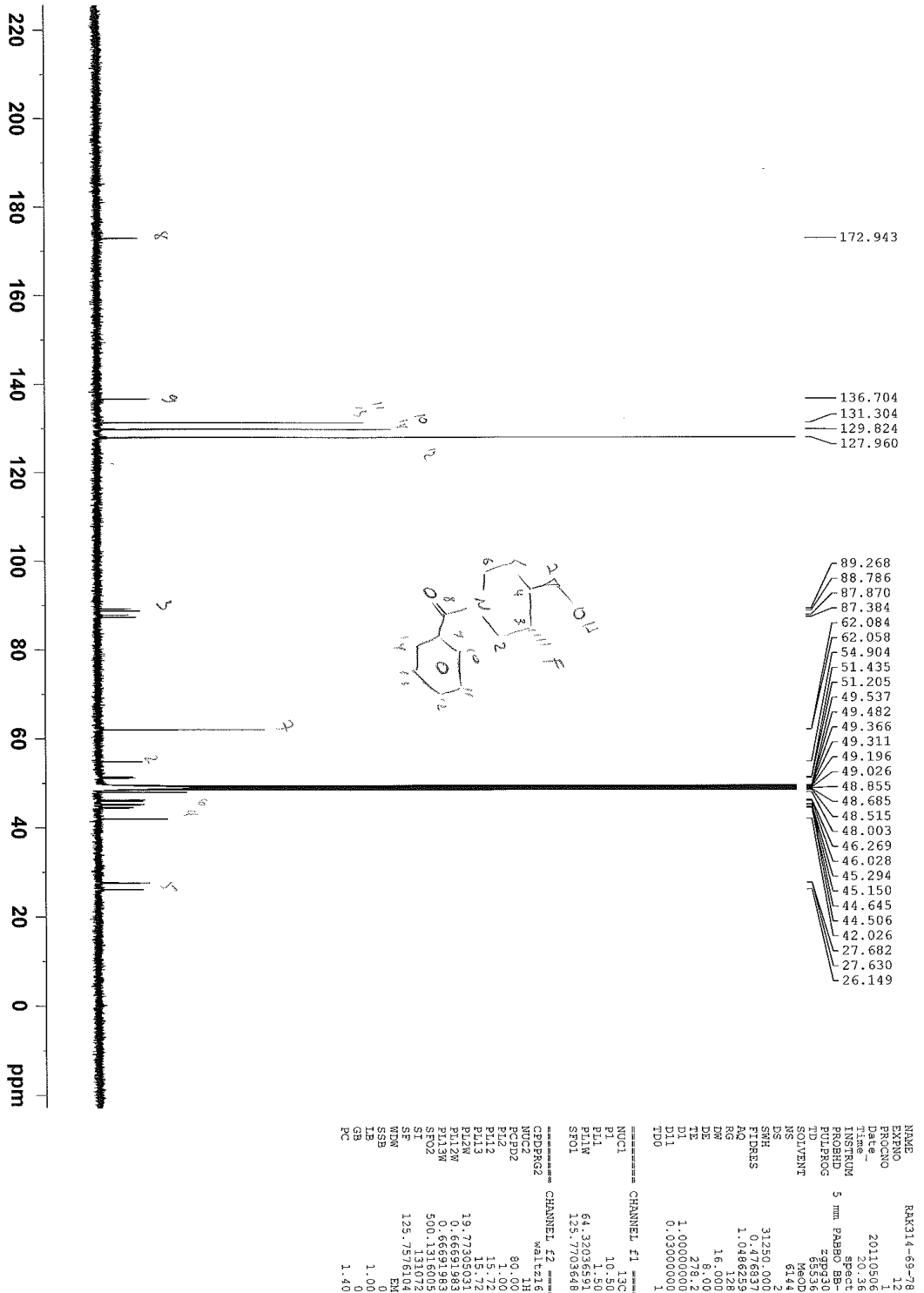




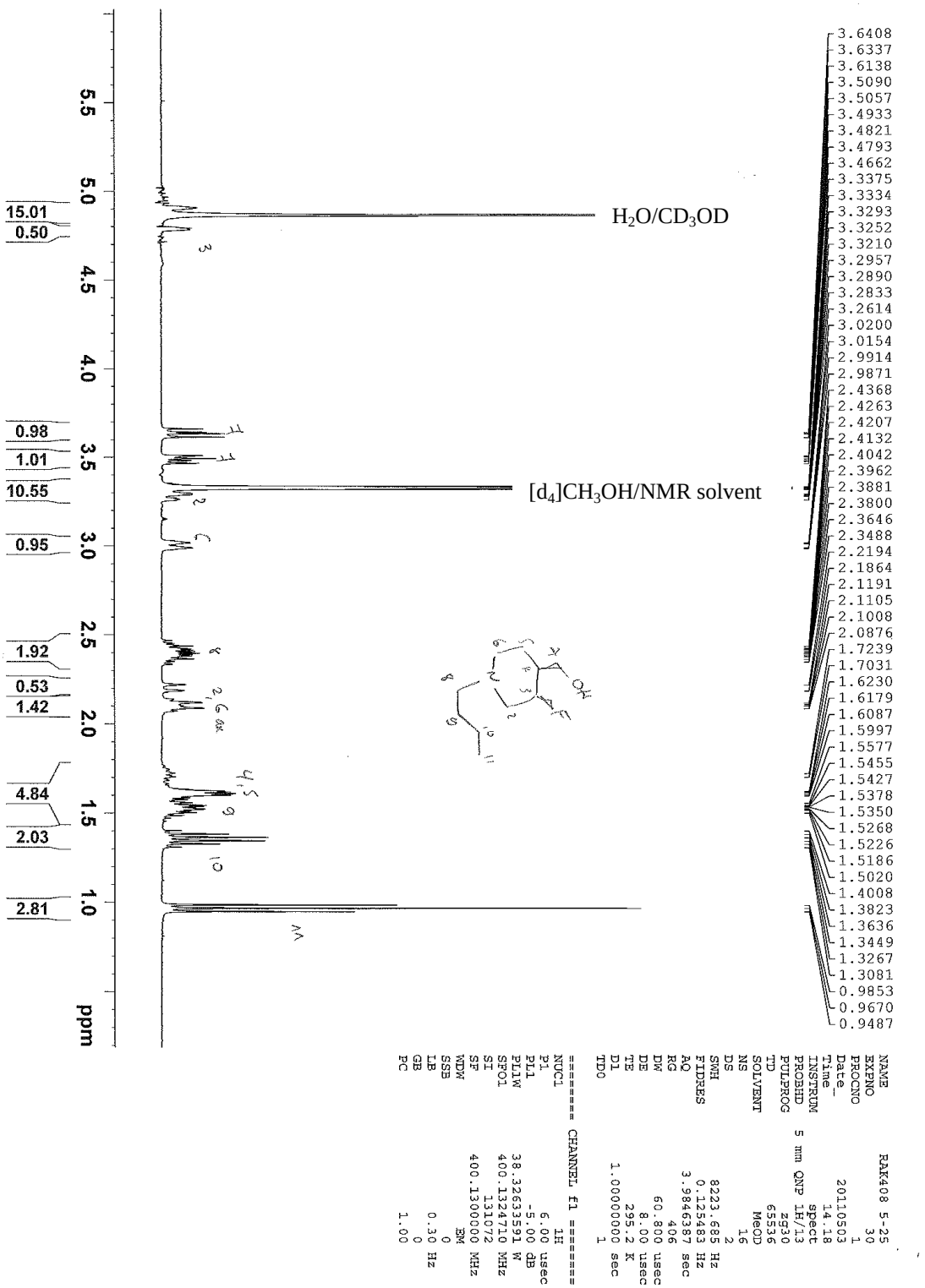

```
NAME                                  RAK404 20-40
EXPNO                                         22
PROCNO                                         1
Date_                                   20110403
Time                                       20.29
INSTRUM                                    spect
PROBHD                      5 mm QNP 1H/13
PULPROG                                  zgpg30
TD                                        65536
SOLVENT                                   CDCl3
NS                                         1024
DS                                            2
SWH                                   26041.666 Hz
FIDRES                                    0.397364 Hz
AQ                                    1.2583412 sec
RG                                         2050
DW                                       19.200 usec
DE                                        8.00 usec
TE                                       295.2 K
D1                                    1.50000000 sec
D11                                   0.03000000 sec
TD0                                           1
======== CHANNEL f1 ========
NUC1                                        13C
P1                                         9.50 usec
PL1                                       -1.00 dB
PL1W                                 46.35898972 W
SFO1                                100.6238364 MHz
======== CHANNEL f2 ========
CPDPRG2                                   waltz16
NUC2                                        1H
PCPD2                                    100.00 usec
PL2                                       -5.00 dB
PL12                                      19.44 dB
PL13                                      17.42 dB
PL2W                                 38.32633591 W
PL12W                                 0.13787873 W
PL13W                                 0.21953173 W
SFO2                                400.1316005 MHz
SI                                         131072
SF                                  100.6127690 MHz
WDW                                           EM
SSB                                            0
LB                                          1.00 Hz
GB                                             0
PC                                          1.40
```

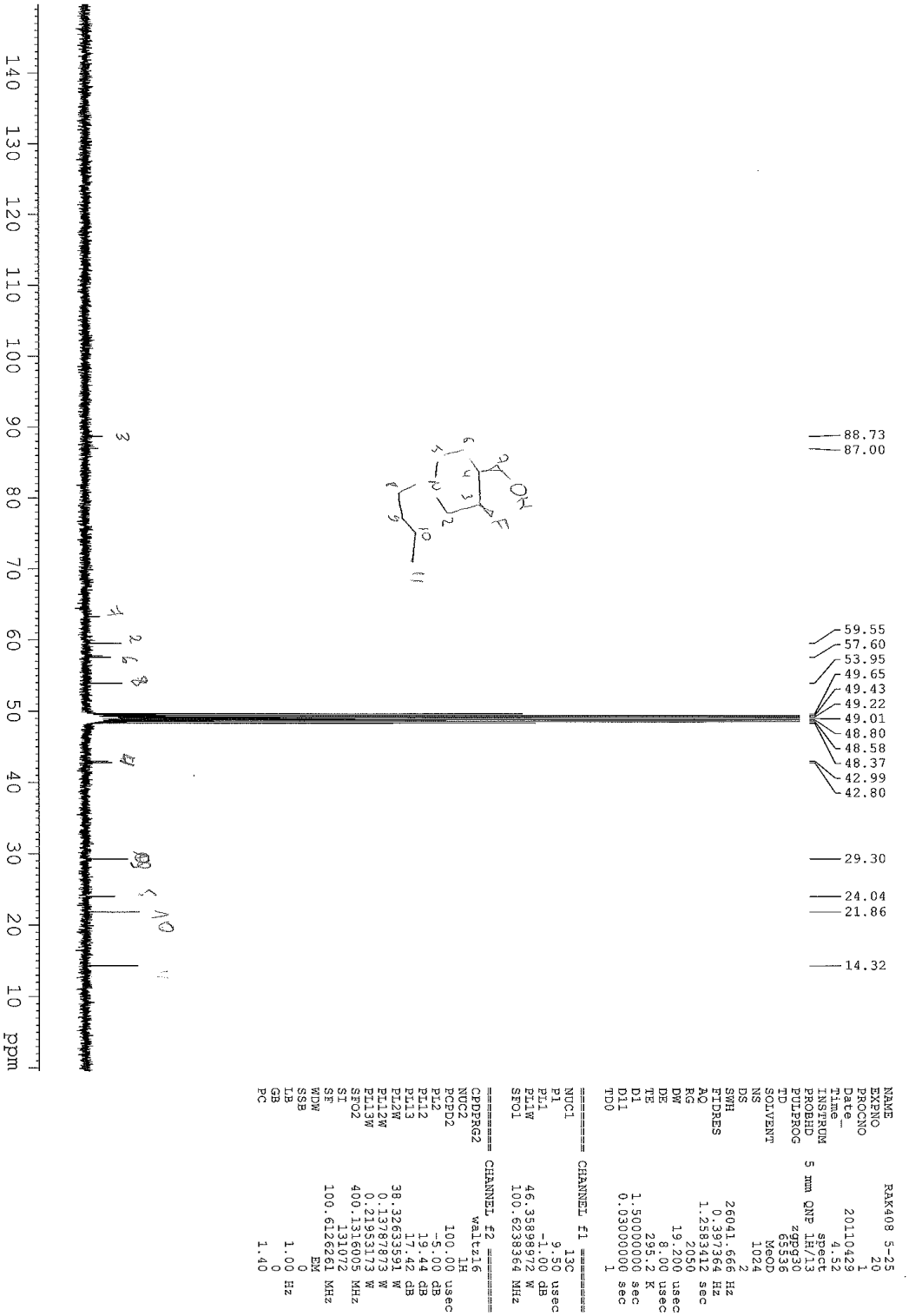
Compound *trans*-**20**.



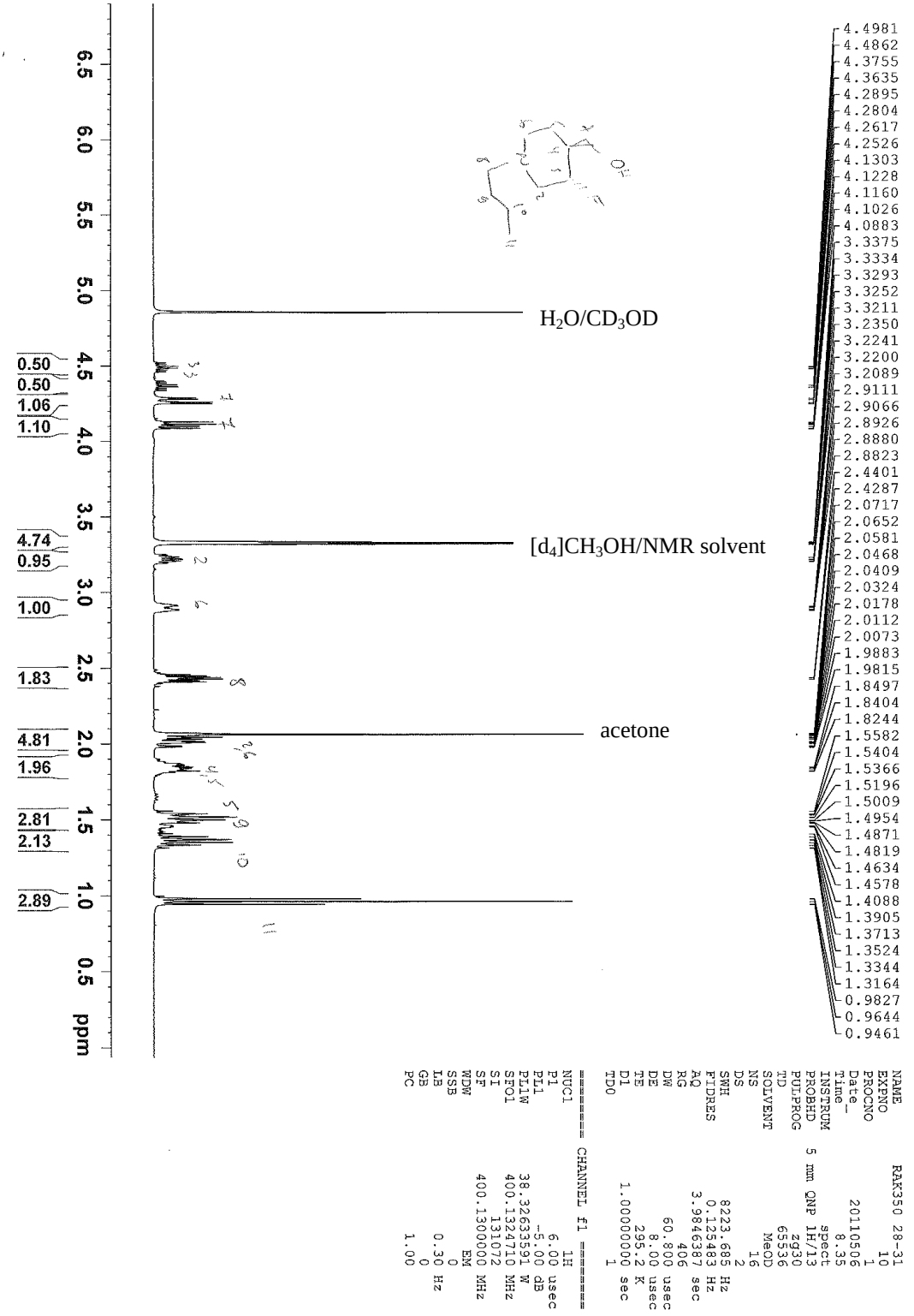

220
200
180
160
140
120
100
80
60
40
20
0
ppm
172.943
136.704
131.304
129.824
127.960
89.268
88.786
87.870
87.384
62.084
62.058
54.904
51.435
51.205
49.537
49.482
49.366
49.311
49.196
49.026
48.855
48.685
48.515
48.003
46.269
46.028
45.294
45.150
44.645
44.506
42.026
27.682
27.630
26.149
NAME RAK314-69-78
EXPNO 12
PROCNO 1
Date_ 20110506
Time_ 20.36
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT MeOD
NS 6144
DS 2
SWH 31250.000 Hz
FIDRES 0.476837 Hz
AQ 1.0486259 sec
RG 128
DW 16.000 usec
DE 8.00 usec
TE 278.2 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 10.50 usec
PL1 1.50 dB
PL1W 64.32036591 W
SFO1 125.7703648 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PL2 1.00 dB
PL12 15.72 dB
PL13 15.72 dB
PL2W 19.77305031 W
PL12W 0.66691983 W
PL13W 0.66691983 W
SFO2 500.1316005 MHz
SI 131072
SF 125.7576104 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

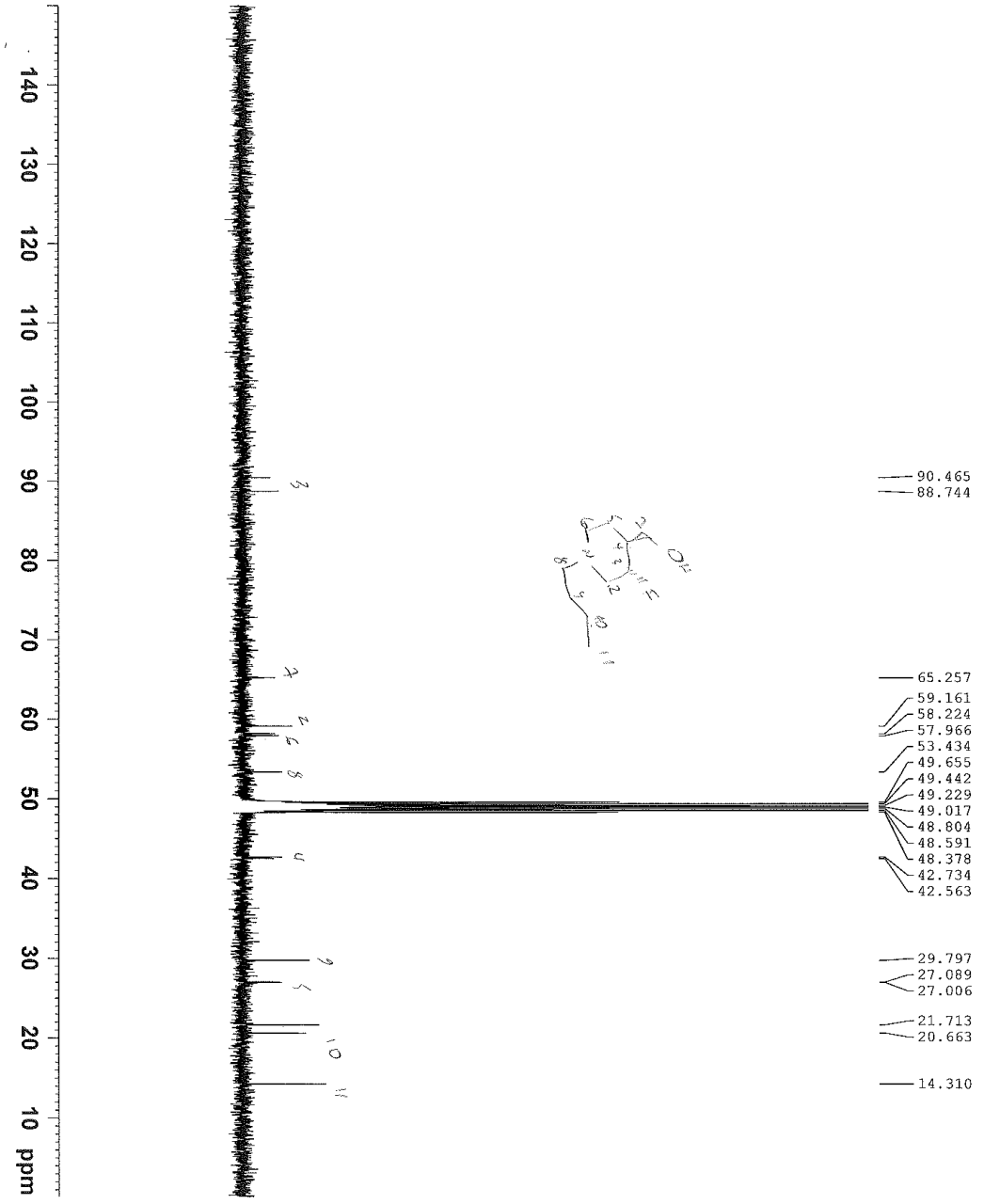
Compound *cis*-**21**.




88.73
87.00
59.55
57.60
53.95
49.65
49.43
49.22
49.01
48.80
48.58
48.37
42.99
42.80
29.30
24.04
21.86
14.32
140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
NAME RAK408 5-25
EXPNO 20
PROCNO 1
Date_ 20110429
Time_ 4.52
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zgpg30
TD 65536
SOLVENT MeOD
NS 1024
DS 2
SWH 26041.666 Hz
FIDRES 0.397364 Hz
AQ 1.2583412 sec
RG 2050
DW 19.200 usec
DE 8.00 usec
TE 295.2 K
D1 1.50000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.50 usec
PL1 -1.00 dB
PL1W 46.35898972 W
SFO1 100.6238364 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -5.00 dB
PL12 19.44 dB
PL13 17.42 dB
PL2W 38.32633591 W
PL12W 0.13787873 W
PL13W 0.21953173 W
SFO2 400.1316005 MHz
SI 131072
SF 100.6126261 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

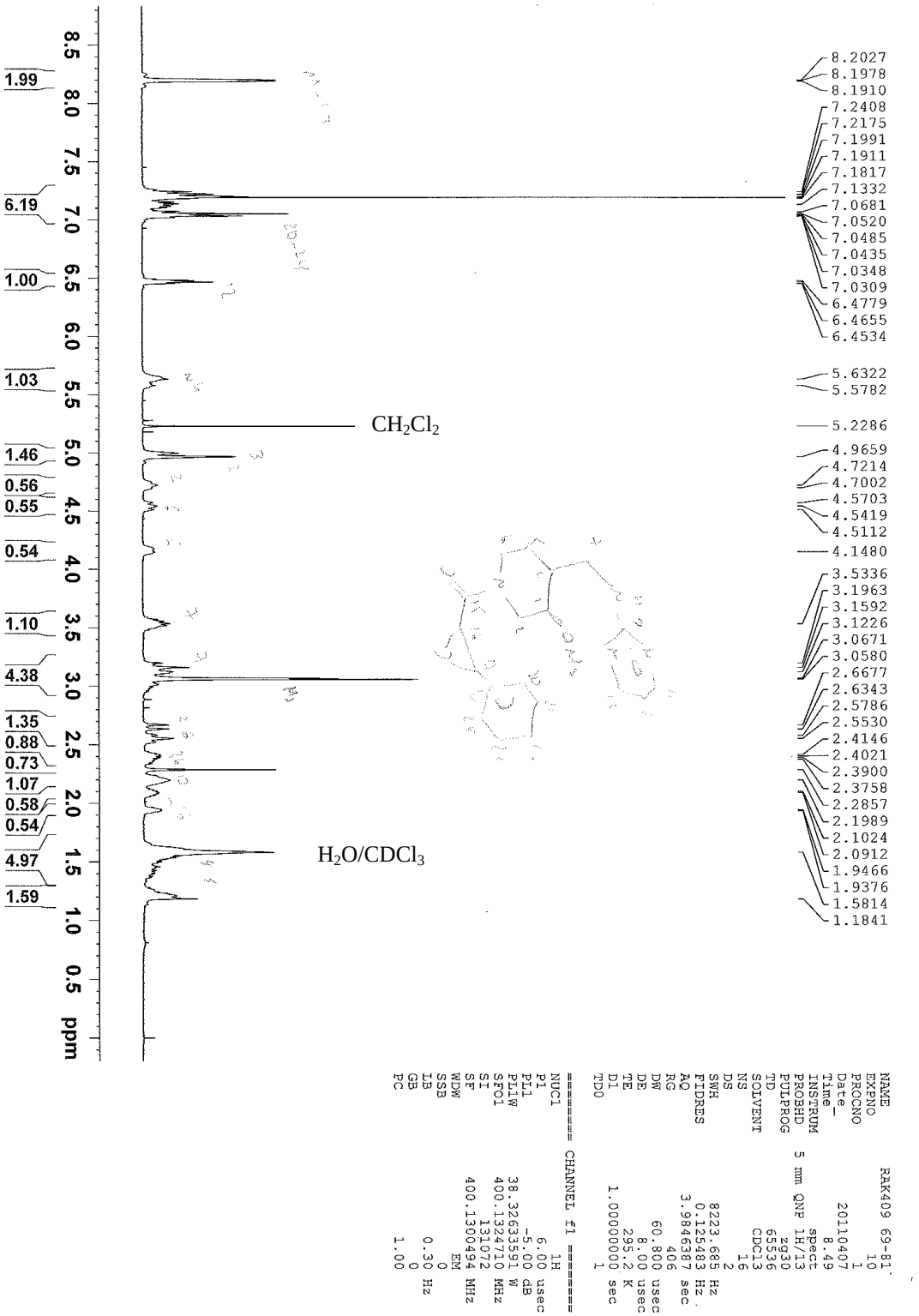
Compound *trans*-**21**.





NAME RAK350
EXPNO 21
PROCNO 1
Date_ 20111014
Time 7.14
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zgpg30
TD 65536
SOLVENT MeOD
NS 1024
DS 2
SWH 26041.666 Hz
FIDRES 0.397364 Hz
AQ 1.2583412 sec
RG 2050
DW 19.200 usec
DE 8.00 usec
TE 295.2 K
D1 1.50000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.50 usec
PL1 -1.00 dB
PL1W 46.35898972 W
SFO1 100.6239364 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -5.00 dB
PL12 19.44 dB
PL13 17.42 dB
PL2W 38.32633591 W
PL12W 0.13787873 W
PL13W 0.21953173 W
SFO2 400.1316005 MHz
SI 131072
SF 100.6126261 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Compound **29**.


8.2027
8.1978
8.1910
7.2408
7.2175
7.1991
7.1911
7.1817
7.1332
7.0681
7.0520
7.0485
7.0435
7.0348
7.0309
6.4779
6.4655
6.4534
5.6322
5.5782
5.2286
4.9659
4.7214
4.7002
4.5703
4.5419
4.5112
4.1480
3.5336
3.1963
3.1592
3.1226
3.0671
3.0580
2.6677
2.6343
2.5786
2.5530
2.4146
2.4021
2.3900
2.3758
2.2857
2.1989
2.1024
2.0912
1.9466
1.9376
1.5814
1.1841
CH2Cl2
H2O/CDCl3
1.99
6.19
1.00
1.03
1.46
0.56
0.55
0.54
1.10
4.38
1.35
0.88
0.73
1.07
0.58
0.54
4.97
1.59
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
NAME RAK409 69-81
EXPNO 10
PROCNO 1
Date_ 20110407
Time_ 8.49
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 406
DW 60.800 usec
DE 8.00 usec
TE 295.2 K
D1 1.00000000 sec
TD0 1
========== CHANNEL f1 ==========
NUC1 1H
P1 6.00 usec
PL1 -5.00 dB
PL1W 38.32633591 W
SFO1 400.1324710 MHz
SI 131072
SF 400.1300494 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00