Electronic Supplementary Material (ESI) for RSC Advances

An Efficient Synthetic Approach for N-C Bond Formation from (*S*)-Amino Acids: An Easy Access to *cis*-2,5-Disubstituted Chiral Piperazines

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Supporting Information

Contents:

General Remarks:

All dry reactions were carried out under argon in oven-dried glassware using standard gas-light syringes, cannulas and septa. All reagents and solvents were dried prior to use according to standard methods. Commercial reagents were used without further purification unless otherwise stated. Amino acids, tosyl chloride, nosyl chloride, mesyl chloride, palladium acetate, copper acetate and LAH were purchased from Aldrich Milwaukee, WI. Organic solvents were dried by standard methods. All final products were characterized by ^{1}H, ^{13}C, IR, ESI-MS, HRMS. Analytical TLC was performed using 2.5 × 5 cm plates coated with a 0.25 mm thickness of silica gel (60F-254), visualization was accomplished with iodine and under UV lamp. Column chromatography was performed using silica gel (60–120 and 100–200 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on Brucker DPX-200 (operating at 200 MHz for ^{1}H and 50 MHz for

^{13}C) or DPX-300 (operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C) spectrometer. ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), double dublet (dd), triplet (t), quartet (q) or multiplet (m). Experiments were recorded in $CDCl_3$ at 25^{o}C. Chemical shifts are given on the δ scale and are referenced to the TMS at 0.00 expressed in parts per million (ppm) for proton. For ^{13}C NMR reference $CDCl_3$ appeared at 77.00 ppm. IR spectra were recorded on Perkin–Elmer 881 and FTIR-8210 PC Shimadzu Spectrophotometers. Mass spectra were recorded on a JEOL JMS-600H high resolution spectrometer using EI mode at 70 eV. Optical rotations were determined on an Autopol III polarimeters using a 1 dm cell at 25 ^{o}C in chloroform, methanol as the solvents, concentrations mentioned are in g/100 mL. The enantiomeric excess was determined by Lichro CART Chiradex column (250x4 mm), (*R,R*-Whelk-01) column using 5 % *iso*-propanol and 95 % acetonitrile, flow rate 0.50 mL/min as eluent at 25 °C. Retention time range is 0 to 30 min.

Experimental Procedures and Characterization Data:

General experimental procedure for the synthesis of (9a-f):

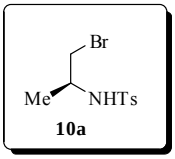
To a stirred solution of *S*-amino acids **6a-f** (1 equiv.) in MeOH (30 mL), $SOCl_2$ (1.5 equiv.) was added at 0 ^{o}C, and then the reaction mixture was stirred for 6 h. After completion of reaction, reaction mixture was concentrated *in vacuo*. The compound (1 equiv.) was dissolved in 5 mL anhydrous DCM (CH_2Cl_2) and then it was cooled at 0 ^{o}C followed by addition of *p*-toluene sulfonyl chloride (1.2 equiv.) and Et_3N (2 equiv.). Then it was continuously stirred for 2 h at rt. After completion (checked by TLC), the reaction mixture was diluted with 30 mL water. The aqueous layer was extracted with DCM (2 X 50 mL), washed with brine and dried over Na_2SO_4. The reaction mixture was concentrated *in vacuo* and purified by silica gel column chromatography. After purification, LAH reduction of ester group to give the corresponding N-tosylated aminoalcohols **9a-f** followed by Appel reaction and Mitsunobu cyclization.

General procedure for Appel reaction of N-tosyl/nosyl/mesyl/Boc protected amino alcohols:

To an ice cooled solution of N-Ts/Ns/Ms/Boc protected amino alcohols, **9a-f** (1 mmol) in dry CH_2Cl_2 (30 ml), carbon-tetrabromide (CBr_4, 1.20 mmol) and triphenylphosphine (PPh_3, 1.20 mmol) for bromination or [imidazole (4 mmol) and triphenylphosphine (PPh_3, 2 mmol) and I_2 (2

mmol) for iodination] were added. Then the whole reaction mixture was stirred for 1-2 hours at room temperature. After completion of the reaction (checked by TLC) was concentrated *in vacuo* and the crude product was purified over silica gel column chromatography to furnish corresponding N-Ts/Ns/Ms/Boc protected bromino and iodo forms **10a-f** as colourless solid and oil respectively in 68-85% yield.

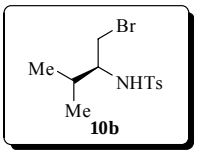
(*S*)-N-(1-bromopropan-2-yl)-4-methylbenzenesulfonamide (10a):



10a

Colorless semi-solid, yield = 73%. R_f = 0.61 (10% EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ_H 7.78 (d, *J* = 8.27 Hz, 2H), 7.31 (d, *J* = 8.00 Hz, 2H), 5.25 (d, *J* = 7.99 Hz, 1H), 3.64-3.52 (m, 1H), 3.40-3.28 (m, 2H), 2.42 (s, 3H), 1.16 (d, *J* = 6.62 Hz, 3H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 ^{o}C): δ_C 143.5, 137.4, 129.6, 126.8, 49.4, 38.7, 21.4, 19.7 ppm. IR (KBr, cm^{-1}): 3430, 3281, 2962, 2368, 2306, 1635, 1423, 1330, 1156, 1098, 934, 765, 663. Mass (ESI-MS): *m/z* 291.9 (100, $[M+1]^+$), 293.8 (96, $[M+1]^+$), 313.9 (60, $[M+Na]^+$). ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{10}H_{15}BrNO_2S$ 292.0007, found 291.9996.

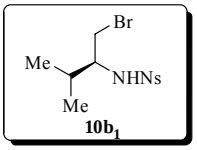
(*S*)-N-(1-bromo-3-methylbutan-2-yl)-4-methylbenzenesulfonamide (10b):



10b

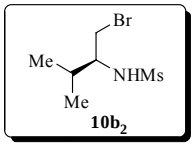
Colorless semi-solid, yield = 84%. R_f = 0.53 (10% EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ_H 7.77 (d, *J* = 8.27 Hz, 2H), 7.30 (d, *J* = 8.04 Hz, 2H), 4.77 (d, *J* = 8.96 Hz, 1H), 3.46 (dd, J_1 = 3.22, J_2 = 10.77 Hz, 1H), 3.27 (dd, J_1 = 4.73, J_2 = 10.66 Hz, 1H), 3.15-3.06 (m, 1H), 2.43 (s, 3H), 1.96-1.85 (m, 1H), 0.84 (t, *J* = 7.14 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ_C 143.6, 137.7, 129.7, 127.0, 58.9, 36.2, 30.2, 21.5, 18.9, 18.0 ppm. IR (KBr, cm^{-1}): 3430, 3286, 2959, 2377, 2306, 1638, 1423, 1329, 1150, 1092, 929, 761, 664. Mass (ESI-MS): *m/z* 320.0 (100, $[M+1]^+$), 322.1(95, $[M+1]^+$), 342.0 (60, $[M+Na]^+$). ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{12}H_{19}BrNO_2S$ 320.0320, found 320.0316.

(*S*)-N-(1-bromo-3-methylbutan-2-yl)-4-nitrobenzenesulfonamide ($10b_1$):



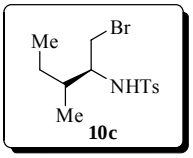
Colorless oily liquid, yield = 81%. R_f = 0.54 (10% EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ_H 8.38 (d, J = 8.76 Hz, 2H), 8.09 (d, J = 8.79 Hz, 2H), 5.03 (d, J = 9.05 Hz, 1H), 3.49 (dd, J_1 = 3.87, J_2 = 10.89 Hz, 1H), 3.34 (dd, J_1 = 4.23, J_2 = 10.86 Hz, 1H), 3.26-3.18 (m, 1H), 1.99-1.88 (m, 1H), 0.86 (dd, J_1 = 4.77, J_2 = 6.57 Hz, 6H) ppm. IR (Neat, cm^{-1}): 3439, 3284, 2959, 2372, 2316, 1636, 1423, 1324, 1156, 1098, 935, 761, 663. (ESI-MS): *m/z* 350.9 (100, $[M+1]^+$), 352.8 (90, $[M+1]^+$), 372.8(65, $[M+Na]^+$). ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{11}H_{16}BrN_2O_4S$ 351.0014, found 351.0002.

(*S*)-N-(1-bromo-3-methylbutan-2-yl)-4-methylbenzenesulfonamide ($10b_2$):



Light brownish oily liquid, yield = 71%. R_f = 0.51 (10% EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ_H 4.87 (d, J = 8.46 Hz, 1H), 3.58 (d, J = 3.99 Hz, 2H), 3.38-3.29 (m, 1H), 3.05 (s, 3H), 2.05-1.94 (m, 1H), 1.00 (t, J = 7.14 Hz, 6H) ppm. IR (Neat, cm^{-1}): 3435, 3281, 2959, 2378, 2306, 1638, 1423, 1327, 1156, 1092, 934, 761, 668. Mass (ESI-MS): *m/z* 243.9 (100, $[M+1]^+$), 245.8 (60, $[M+1]^+$), 265.9 (90, $[M+Na]^+$). ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_6H_{15}BrNO_2S$ 244.0007, found 243.9998.

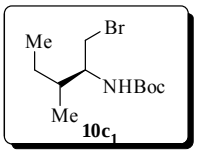
N-((*2S,3R*)-1-bromo-3-methylpentan-2-yl)-4-methylbenzenesulfonamide (10c):



Light brownish semi-solid, yield = 78%. R_f = 0.45 (10% EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ_H 7.77 (d, J = 8.25 Hz, 2H), 7.30 (d, J = 8.03 Hz, 2H), 4.97 (d, J = 8.84 Hz, 1H), 3.42 (dd, J_1 = 3.43, J_2 = 10.66 Hz, 1H), 3.27 (dd, J_1 = 4.38, J_2 = 10.52 Hz, 1H), 3.23-3.15 (m, 1H), 2.43 (s, 3H), 1.71-1.60 (m, 1H), 1.59-1.47 (m, 1H), 1.09-0.95 (m, 1H), 0.82-0.77 (m, 6H)

ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^oC): δ_C 143.5, 137.7, 129.6, 126.9, 36.7, 36.0, 24.3, 21.5, 14.9, 10.9 ppm. IR (KBr, cm^{-1}): 3442, 3282, 2955, 2376, 2316, 1632, 1423, 1324, 1156, 1092, 935, 761, 658. Mass (ESI-MS): *m/z* 335.3 (100, $[M+1]^+$), 337.2 (65, $[M+1]^+$), 356.1 (90, $[M+Na]^+$). ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{13}H_{21}BrNO_2S$ 334.0476, found 334.0472.

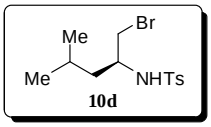
***Tert-butyl* (*2S,3R*)-1-bromo-3-methylpentan-2-ylcarbamate ($10c_1$):**



$10c_1$

Colorless oily liquid, yield = 68%. R_f = 0.62 (10% EtOAc/Hexane). ^{1}H NMR (300MHz, $CDCl_3$, 25^{o}C): δ_H 4.66 (bs, 1H), 3.57 (s, 3H), 1.65-1.52 (m, 2H), 1.45 (s, 9H), 1.23-1.08 (m, 1H), 0.90 (t, *J* = 6.42 Hz, 6H) ppm. IR (Neat, cm^{-1}): 3432, 3272, 2955, 2376, 1622, 1423, 1334, 1156, 1092, 935, 761. Mass (ESI-MS): *m/z* 280.0 (100, $[M+1]^+$), 282.0 (60, $[M+1]^+$), 302.1 (70, $[M+Na]^+$). ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{11}H_{23}BrNO_2$ 280.0912, found 280.0918.

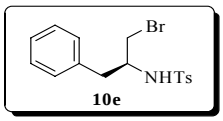
(*S*)-N-(1-bromo-4-methylpentan-2-yl)-4-methylbenzenesulfonamide (10d):



10d

Colorless semi-solid, yield = 76%. R_f = 0.50 (10% EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ_H 7.78 (d, *J* = 8.25 Hz, 2H), 7.31 (d, *J* = 7.98 Hz, 2H), 4.88 (d, *J* = 8.61 Hz, 1H), 3.53-3.43 (m, 1H), 3.39-3.28 (m, 2H), 2.43 (s, 3H), 1.59-1.46 (m, 1H), 1.38-1.33 (m, 2H), 0.83 (d, *J* = 6.57 Hz, 3H), 0.72 (d, *J* = 6.45 Hz, 3H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 ^{o}C): δ_C 143.6, 137.7, 129.7, 126.9, 51.2, 42.6, 38.6, 24.1, 22.6, 21.7, 21.5 ppm. IR (KBr, cm^{-1}): 3439, 3278, 2955, 2382, 2316, 1635, 1423, 1330, 1156, 1082, 935, 765, 663. Mass (ESI-MS): *m/z* 334.0 (100, $[M+1]^+$), 336.1 (85, $[M+1]^+$), 356.3 (90, $[M+Na]^+$). ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{13}H_{21}BrNO_2S$ 334.0476, found 334.0474.

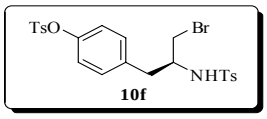
(*S*)-N-(1-bromo-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (10e):



10e

White semi-solid, yield = 81%. R_f = 0.45 (10% EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^oC): δ_H 7.63 (d, J = 8.22 Hz, 2H), 7.23-7.19 (m, 5H), 7.06-7.03 (m, 2H), 4.95 (d, J = 8.19 Hz, 1H), 3.67-3.57 (m, 1H), 3.33 (t, J = 3.06 Hz, 2H), 2.88 (dd, J_1 = 7.65, J_2 = 13.77 Hz, 1H), 2.76 (dd, J_1 = 6.45, J_2 = 13.74 Hz, 1H), 2.40 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^oC): δ_C 143.5, 137.1, 136.0, 129.7, 129.1, 128.7, 126.9, 126.8, 54.5, 39.1, 36.9, 21.5 ppm. IR (KBr, cm^{-1}): 3433, 3282, 2963, 2376, 2322, 1634, 1428, 1324, 1163, 1092, 939, 776, 668. Mass (ESI-MS): *m/z* 368.0 (100, $[M+1]^+$), 370.0 (65, $[M+1]^+$), 390.0 (30, $[M+Na]^+$). ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{16}H_{19}BrNO_2S$ 368.0320, found 368.0318.

(S)-4-(3-bromo-2-(4-methylphenylsulfonamido)propyl)phenyl-4-methylbenzenesulfonate (10f):



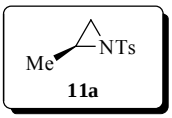
10f

Light brownish semi-solid, yield = 85%. R_f = 0.43 (10% EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^oC): δ_H 7.69 (d, J = 8.20 Hz, 2H), 7.60 (d, J = 8.20 Hz, 2H), 7.31 (d, J = 7.86 Hz, 2H), 7.24 (d, J = 8.20 Hz, 2H), 6.98 (d, J = 8.36 Hz, 2H), 6.82 (d, J = 8.44 Hz, 2H), 4.85 (d, J = 8.52 Hz, 1H), 3.59-3.57 (m, 1H), 3.30 (d, J = 3.85 Hz, 2H), 2.86 (dd, J_1 = 7.33, J_2 = 13.84 Hz, 1H), 2.73 (dd, J_1 = 6.75, J_2 = 13.84 Hz, 1H), 2.44 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ^oC): δ_C 148.5, 145.4, 143.8, 137.0, 135.2, 132.3, 130.3, 129.7, 128.4, 126.8, 122.5, 54.4, 38.7, 36.9, 21.7, 21.5 ppm. IR (KBr, cm^{-1}): 3438, 3282, 2957, 2365, 2316, 1633, 1423, 1324, 1159, 1092, 935, 764, 668. Mass (ESI-MS): *m/z* 538.0 (60, $[M+1]^+$), 540.2 (60, $[M+1]^+$), 560.2 (70, $[M+Na]^+$). ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{23}H_{25}BrNO_5S_2$ 538.0358, found 538.0363.

Procedure for the Synthesis of Chiral Aziridines (11a-e):

The chiral aziridines are prepared using our previously reported procedure.[36]

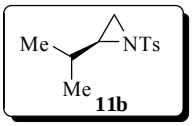
(*S*)-2-Methyl-1-tosylaziridine (11a):



11a

Colorless semi-solid, yield = 42% (overall yield after four steps). R_f = 0.51 (20% EtOAc/Hexane). $[\alpha]_D^{25}$ = -13.1 (*c* = 0.100, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ_H 7.82 (d, *J* = 8.28 Hz, 2H), 7.32 (d, *J* = 8.04 Hz, 2H), 2.88-2.74 (m, 1H), 2.59 (d, *J* = 6.96 Hz, 1H), 2.43 (s, 3H), 2.01 (d, *J* = 4.58 Hz, 1H), 1.23 (d, *J* = 5.58 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 144.3, 135.3, 129.6, 127.7, 35.7, 34.6, 21.5, 16.7 ppm. IR (KBr, cm^{-1}): 3291, 3027, 2958, 1457, 1320, 1158, 759. Mass (ESI-MS): *m/z* 212.0 (100, $[M+H]^+$), ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{10}H_{14}NO_2S$ 212.0745, found 212.0749.

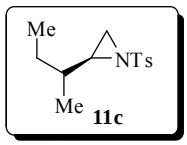
(*S*)-2-*iso*-propyl-1-tosylaziridine (11b):



11b

Colorless solid, yield = 47% (overall yield after four steps). R_f = 0.50 (15% EtOAc/Hexane). $[\alpha]_D^{25}$ = +4.4 (*c* = 0.100, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.82 (d, *J* = 7.50 Hz, 2H), 7.33 (d, *J* = 7.77 Hz, 2H), 2.60 (d, *J* = 6.96 Hz, 1H), 2.54-2.48 (m, 1H), 2.43 (s, 3H), 2.09 (d, *J* = 4.38 Hz, 1H), 1.47-1.35 (m, 1H), 0.89 (d, *J* = 6.72 Hz, 3H), 0.79 (d, *J* = 6.57 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 143.8, 135.8, 129.4, 128.1, 45.8, 32.4, 30.1, 21.6, 19.6, 19.1 ppm. IR (KBr, cm^{-1}): 3298, 3024, 2964, 1463, 1321, 1158, 758. Mass (ESI-MS): *m/z* 240.1 (90, $[M+H]^+$), ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{12}H_{18}NO_2S$ 240.1058, found 240.1061.

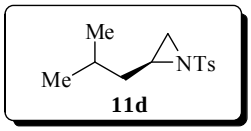
(*S*)-2-*sec*-butyl-1-tosylaziridine (11c):



11c

Colorless oily liquid, yield = 45% (overall yield after four steps). R_f = 0.52 (15% EtOAc/Hexane). $[\alpha]_D^{25}$ = +21.765 (*c* = 0.173, CH_3OH). ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.81 (d, *J* = 8.20 Hz, 2H), 7.32 (d, *J* = 7.94 Hz, 2H), 2.56 (s, 2H), 2.42 (s, 3H), 2.05 (d, *J* = 2.52, 1H), 1.40-1.31 (m, 1H), 1.16-1.07 (m, 2H), 0.87 (d, *J* = 6.40 Hz, 3H), 0.80 (d, *J* = 7.39 Hz, 3H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 144.2, 134.8, 129.4, 127.8, 44.9, 36.3, 32.4, 26.8, 21.3, 15.3, 10.6 ppm. IR (Neat, cm^{-1}): 3291, 3019, 2954, 1443, 1328, 1168, 757. Mass (ESI-MS): *m/z* 254.4 (90, $[M+H]^+$), ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{13}H_{20}NO_2S$ 254.1215, found 254.1217.

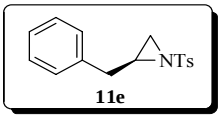
(*S*)-2-*iso*-butyl-1-tosylaziridine (11d):



11d

Colorless oily liquid, yield = 45% (overall yield after four steps). R_f = 0.50 (15% EtOAc/Hexane). $[\alpha]_D^{25}$ = +24.1 (*c* = 0.110, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ_H 7.82 (d, *J* = 8.25 Hz, 2H), 7.33 (d, *J* = 8.07 Hz, 2H), 2.82-2.74 (m, 1H), 2.62 (d, *J* = 4.66 Hz, 1H), 2.44 (s, 3H), 2.02 (d, *J* = 3.06 Hz, 1H), 1.67-1.54 (m, 1H), 1.35-1.30 (m, 2H), 0.86 (t, *J* = 3.5 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 144.3, 135.0, 129.5, 127.8, 40.3, 38.9, 33.9, 26.6, 22.6, 21.8, 21.5 ppm. IR (Neat, cm^{-1}): 3291, 3021, 2958, 1462, 1159, 764. Mass (ESI-MS): *m/z* 254.0 (70, $[M+H]^+$), ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{13}H_{20}NO_2S$ 254.1215, found 254.1219.

(*S*)-2-benzyl-1-tosylaziridine (11e):



11e

Colorless semi-solid, yield = 44% (overall yield after four steps). R_f = 0.56 (15% EtOAc/Hexane). $[\alpha]_D^{25}$ = -9.660 (*c* = 0.127, CH_3OH). ^1H NMR (200 MHz, $CDCl_3$): δ_H 7.69 (d, *J* = 8.10 Hz, 2H), 7.22 (d, *J* = 8.04 Hz, 2H), 7.16-7.14 (m, 3H), 7.06-7.03 (m, 2H), 2.97-2.91 (m, 1H), 2.84-2.78 (m, 1H), 2.73-2.66 (m, 2H), 2.44 (s, 3H), 2.12 (d, *J* = 2.94 Hz, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 144.2, 136.9, 134.8, 128.6, 128.4, 127.8, 126.4, 41.1, 37.4, 32.8, 21.5 ppm. IR (KBr, cm^{-1}): 3297, 3030, 2945, 1451, 1325, 1165, 762. Mass (ESI-MS): *m/z* 288.0 (100, $[M+H]^+$), ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{16}H_{18}NO_2S$ 288.1058, found 288.1061.

Synthesis of *cis*-2,5-disubstituted chiral piperazines (symmetrical) (12a-f) from N-tosyl halogenated amino alcohols:

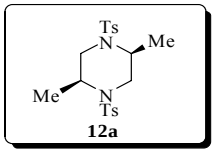
$Pd(OAc)_2$ (10 mol%), K_2CO_3 (2 mmol) and N-tosyl halogenated amino alcohols **10a-f** (1 mmol) were stirred at 110 ^oC in DMF (10 mL) for 24 h under an argon atmosphere. The progress of reaction was monitored by TLC using ethyl acetate and hexane. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (20 mL). The organic layer was washed successively with brine (1 x 3 mL) and water (3 x 5 mL). Drying (Na_2SO_4) and vaporation of the

solvent gave a residue that was purified on silica gel column chromatography using 1:9 ethyl acetate and hexane as eluent.

Synthesis of cis-2,5-disubstituted chiral piperazines (symmerical) (12a-e) from aziridines:

$Cu(OAc)_2$ (10 mol%), Cs_2CO_3 (1.2 mmol) and aziredines **10a-e** (1 mmol) were stirred preheated at 100 ^oC for 5-15 min in DMF (10 mL) under an argon atmosphere. The progress of reaction was monitored by TLC using ethyl acetate and hexane. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (20 mL). Usual workup (as described above), purified on silica gel column chromatography using 1:9 ethylacetate and hexane as eluent furnished **12a-e**.

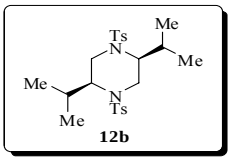
(*2S,5S*)-2,5-dimethyl-1,4-ditosylpiperazine (12a):



12a

Colorless oily liquid, yield = 57% (from **10a**), 52% (from **11a**). $[\alpha]_D^{25}$= +79.395 (*c* = 0.027, $CHCl_3$). HPLC analysis: ee > 99 (t_R = 6.046 min, *iso*-propanol/acetonitrile). R_f = 0.52 (15% EtOAc/Hexane). ^1H NMR (300 MHz, $CDCl_3$, 25 ^oC): δ_H 7.62 (d, *J* = 8.07 Hz, 4H), 7.29 (d, *J* = 7.89 Hz, 4H), 3.59-3.57 (m, 2H), 3.21 (t, *J* = 6.54 Hz, 4H), 2.43 (s, 6H), 1.20 (d, *J* = 6.39 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^oC): δ_C 143.6, 136.3, 129.8, 127.1, 51.2, 48.7, 21.5, 16.8 ppm. IR (Neat, cm^{-1}): 3452, 3241, 2960, 1633, 1460, 1342, 1158, 1094, 930, 766. Mass (ESI-MS): *m/z* 423.3 (90, $[M+1]^+$), 445.3 (80, $[M+Na]^+$), 267.2 (100, $[M-Ts]^+$), 212.1 (10, $[M-2Ts]^+$). ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{20}H_{27}N_2O_4S_2$ 423.1412, found 423.1411.

(*2S,5S*)-2,5-diisopropyl-1,4-ditosylpiperazine (12b):

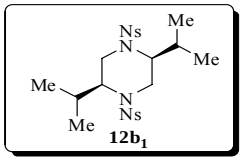


12b

Colorless oily liquid, yield = 66% (from **10b**), 76% (from **11b**). However, this reaction was performed two times on gram scale (from **10b**: 3.840 mmol, yield: 64% and 4.746 mmol, yield:

63%) and the yield varies from 63-64% and (from **11b**: 3.133 mmol, yield: 74%). $[\alpha]_D^{25}$= +78.231 (*c* = 0.110, CH_3OH). HPLC analysis: ee > 99 (t_R = 5.268 min, *iso*-propanol/acetonitrile). R_f = 0.62 (20% EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ_H 7.66 (d, *J* = 8.28 Hz, 4H), 7.28 (d, *J* = 8.04 Hz, 4H), 3.62-3.54 (m, 4H), 3.09-3.00 (m, 2H), 2.42 (s, 6H), 2.21-2.10 (m, 2H), 0.82 (dd, J_1 = 7.05, J_1 = 14.7 Hz , 12H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ_C 143.4, 137.5, 129.7, 127.0, 58.4, 40.8, 30.7, 21.5, 18.6, 15.6 ppm. IR (Neat, cm^{-1}): 3460, 3241, 2964, 1637, 1460, 1339, 1158, 1094, 929, 761. Mass (ESI-MS): *m/z* 479.1 (80, $[M+1]^+$), 501.1 (30, $[M+Na]^+$), 323.1 (35, $[M-Ts]^+$), 168.1 (50, $[M-2Ts]^+$). ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{24}H_{35}N_2O_4S_2$ 479.2038, found 479.2040.

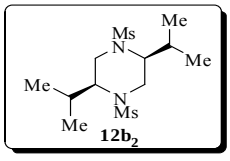
(*2S,5S*)-2,5-diisopropyl-1,4-*bis*(4-nitrophenylsulfonyl)piperazine ($12b_1$):



$12b_1$

Light brownish oily liquid, yield = 58%. R_f = 0.43 (15% EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ_H 8.36 (d, *J* = 8.79 Hz, 4H), 7.97 (d, *J* = 8.79 Hz, 4H), 3.89-3.76 (m, 4H), 3.09-2.93 (m, 2H), 2.02-1.95 (m, 2H), 0.87 (d, *J* = 6.97 Hz, 6H), 0.78 (d, *J* = 6.84 Hz, 6H). IR (Neat, cm^{-1}): 3462, 3237, 2964, 1637, 1460, 1340, 1158, 1099, 929, 761. Mass (ESI-MS): *m/z* 541.2 (100, $[M+1]^+$), 563.2 (40, $[M+Na]^+$), 354.1 (30, $[M-Ns]^+$), 168.2 (60, $[M-2Ns]^+$). ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{22}H_{29}N_4O_8S_2$ 541.1427, found 541.1424.

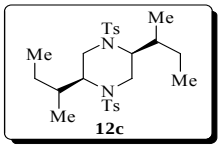
(*2S,5S*)-2,5-diisopropyl-1,4-bis(methyl-sulfonyl)piperazine ($12b_2$):



$12b_2$

Light yellowish oily liquid, yield = 51%. R_f = 0.60 (15% EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ_H 3.90-3.74 (m, 4H), 2.95 (s, 6H), 1.97-1.85 (m, 2H), 1.26-1.18 (m, 2H), 0.89 (d, *J* = 6.60 Hz, 12H). IR (Neat, cm^{-1}): 3460, 2964, 1632, 1464, 1339, 1158, 1094, 933, 766. Mass (ESI-MS): *m/z* 327.4 (80, $[M+1]^+$), 349.2 (40, $[M+Na]^+$), 247.6 (10, $[M-Ms]^+$), 168.2 (25, $[M-2Ms]^+$). ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{12}H_{27}N_2O_4S_2$ 327.1412, found 327.1414.

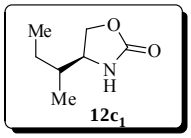
(*2S,5S*)-2,5-di-*sec*-butyl-1,4-ditosylpiperazine (12c):



12c

Colorless oily liquid, yield = 76% (from **10c**), 68% (from **11c**). $[\alpha]_D^{25}$= +91.893 (*c* = 0.140, $CHCl_3$). HPLC analysis: ee > 99 (t_R = 6.185 min, *iso*-propanol/acetonitrile). R_f = 0.58 (20% EtOAc /Hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ_H 7.66 (d, *J* = 8.22 Hz, 4H), 7.29 (d, *J* = 8.07 Hz, 4H), 3.75-3.67 (m, 2H), 3.60-3.53 (m, 2H), 3.09-3.00 (m, 2H), 2.42 (s, 6H), 1.98-1.90 (m, 2H), 1.33-1.19 (m, 2H), 1.14-0.91 (m, 2H), 0.82 (dd, J_1 = 7.29, J_2 = 33.36 Hz, 12H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25^{o}C): δ_C 143.4, 137.5, 129.7, 127.0, 57.2, 40.3, 37.9, 25.7, 21.5, 12.5, 11.9 ppm. IR (Neat, cm^{-1}): 3452, 3245, 2964, 1635, 1460, 1348, 1158, 1099, 938, 760. Mass (ESI-MS): *m/z* 507.4 (100, $[M+1]^+$), 529.2 (25, $[M+Na]^+$), 351.2 (75, $[M-Ts]^+$), 196.3 (45, $[M-2Ts]^+$). ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{26}H_{39}N_2O_4S_2$ 507.2351, found 507.2349.

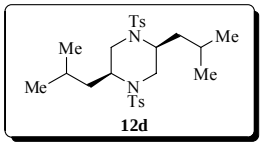
(*S*)-4-*sec*-butyloxazolidin-2-one (12c$_1$):



12c$_1$

Colorless oily liquid, yield = 70%. R_f = 0.63 (15% EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ_H 7.10 (s, 1H), 4.42 (t, *J* = 8.64 Hz, 1H), 4.12-4.07 (m, 1H), 3.74-3.67 (m, 1H), 1.59-1.44 (m, 2H), 1.20-1.07 (m, 1H), 0.94-0.86 (m, 6H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25^{o}C): δ_C 160.6, 68.2, 57.0, 38.9, 24.9, 13.6, 10.8 ppm. IR (Neat, cm^{-1}): 3357, 3072, 2371, 1653, 1526, 1299, 1175, 696. Mass (ESI-MS): *m/z* 144.1 (100, $[M+1]^+$), 166.0 (10, $[M+Na]^+$). ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_7H_{14}NO_2$ 144.1025, found 144.1021.

(*2S,5S*)-2,5-diisobutyl-1,4-ditosylpiperazine (12d):

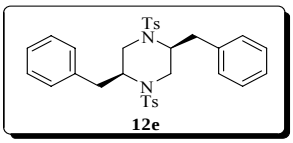


12d

Light brownish oily liquid, yield = 69% (from **10d**), 71% (from **11d**). $[\alpha]_D^{25}$= +91.406 (*c* = 0.066, $CHCl_3$). HPLC analysis: ee > 99 (t_R = 6.224 min, *iso*-propanol/acetonitrile). R_f = 0.63

(15% EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ_H 7.63 (d, J = 8.25 Hz, 4H), 7.28 (d, J = 8.04 Hz, 4H), 3.66-3.59 (m, 2H), 3.40 (dd, J_1 = 4.83, J_2 = 13.92 Hz, 2H), 3.11 (dd, J_1 = 7.74, J_2 = 13.89 Hz, 2H), 2.42 (s, 6H), 1.56-1.51 (m, 2H), 1.49-1.39 (m, 4H), 0.85 (dd, J_1 = 6.03, J_2 = 11.58 Hz, 12H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 ^{o}C): δ_C 143.5, 136.9, 129.7, 127.1, 53.6, 45.5, 40.6, 24.6, 23.5, 21.5, 21.4 ppm. IR (Neat, cm^{-1}): 3446, 3295, 2974, 2366, 1645, 1521, 1291, 1175, 768. Mass (ESI-MS): *m/z* 507.5 (90, $[M+1]^+$), 529.2 (25, $[M+Na]^+$), 351.2 (40, $[M-Ts]^+$), 196.3 (10, $[M-2Ts]^+$). ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{26}H_{39}N_2O_4S_2$ 507.2351, found 507.2356.

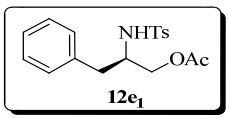
(*2S,5S*)-2,5-dibenzyl-1,4-ditosylpiperazine (12e):



12e

Light blackish oily liquid, yield = 62% (from **10e**), 56% (from **11e**). $[\alpha]_D^{25}$= +21.741 (c = 0.108, $CHCl_3$). HPLC analysis: ee > 99 (t_R = 6.556 min, *iso*-propanol/acetonitrile). R_f = 0.55 (15% EtOAc/Hexane). ^{1}H NMR (300 MHz, CDCl3, 25 ^{o}C): δ_H 7.56 (d, J = 8.15 Hz, 4H), 7.29-7.24 (m, 10H), 7.13 (d, J = 6.25 Hz, 4H), 3.77-3.74 (m, 2H), 3.26-3.12 (m, 4H), 3.03-2.90 (m, 4H), 2.42 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ_C 143.8, 137.1, 135.3, 129.8, 129.5, 128.6, 127.4, 126.8, 56.8, 43.6, 39.3, 21.5 ppm. IR (Neat, cm^{-1}): 3450, 2964, 1632, 1464, 1349, 1158, 1097, 933, 762. Mass (ESI-MS): *m/z* 575.3 (60, $[M+1]^+$), 597.2 (100, $[M+Na]^+$), 419.3 (20, $[M-Ts]^+$), 264.1 (20, $[M-2Ts]^+$). ESI-HRMS: *m/z* $[M+H]^+$ calcd $C_{32}H_{35}N_2O_4S_2$ 575.2038, found 575.2039.

(*R*)-2-(4-methylphenylsulfonamido)-3-phenylpropyl acetate (12e$_1$):

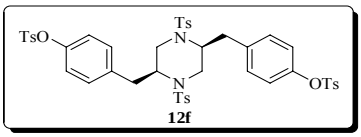


12e$_1$

Colourless semi-solid, yield = 42% (from **11e**). R_f = 0.30 (15% EtOAc/Hexane). ^{1}H NMR (300 MHz, CDCl3, 25 ^{o}C): δ_H 7.63 (d, J = 8.10 Hz, 2H), 7.23-7.19 (m, 5H), 7.02 (d, J = 4.47 Hz, 2H), 4.89 (d, J = 7.83 Hz, 1H), 4.01-3.90 (m, 2H), 3.72-3.68 (m, 1H), 2.78 (d, J = 6.78 Hz, 2H), 2.40 (s, 3H), 1.96 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ_C 170.7, 143.3, 137.5, 136.2, 129.6, 129.2, 128.6, 126.9, 126.8, 64.9, 53.8, 38.6, 21.4, 20.6 ppm. IR (Neat, cm^{-1}): 3458, 2954, 1721, 1635, 1464, 1354, 1158, 1097, 933, 762. Mass (ESI-MS): *m/z* 348.3 (60, $[M+1]^+$), 370.1

(100, $[M+Na]^+$), 192.5 (20, $[M-Ts]^+$). ESI-HRMS: *m/z* $[M+H]^+$ calcd $C_{18}H_{22}NO_4S$ 348.1270, found 348.1273.

4,4'-((2S,5S)-1,4-ditosylpiperazine-2,5-diyl)*bis*(methylene)*bis*(4,1-phenylene)*bis*(4-methyl-benzenesulfonate) (12f):



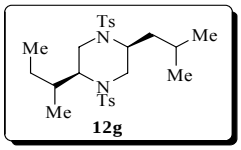
12f

Colorless oily liquid, yield = 70%. $[\alpha]_D^{25}$= +1.009 (*c* = 0.161, $CHCl_3$). HPLC analysis: ee > 99 (t_R = 7.360 min, *iso*-propanol/acetonitrile). R_f = 0.45 (20% EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25^{o}C): δ_H 7.72 (d, *J* = 8.22 Hz, 4H), 7.51 (d, *J* = 8.10 Hz, 4H), 7.33 (d, *J* = 7.95 Hz, 4H), 7.25 (d, *J* = 7.87 Hz, 4H), 7.06 (d, *J* = 8.33 Hz, 4H), 6.90 (d, *J* = 8.33 Hz, 4H), 3.65 (d, *J* = 5.22 Hz, 2H), 3.22-3.18 (m, 2H), 3.09 (dd, J_1 = 5.08, J_2 = 13.54 Hz, 2H), 3.01-2.93 (m, 2H), 2.83 (dd, J_1 = 3.39, J_2 = 13.30 Hz, 2H) 2.45 (s, 6H), 2.41 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, 25^{o}C): δ_C 148.5, 145.4, 144.1, 136.1, 134.9, 132.4, 130.7, 129.9, 129.8, 128.4, 127.3, 122.6, 56.7, 43.5, 38.7, 21.7, 21.5 ppm. IR (Neat, cm^{-1}): 3444, 3234, 2954, 1645, 1460, 1348, 1168, 1099, 938, 768. Mass (ESI-MS): *m/z* 915.3 (90, $[M+1]^+$), 937.2 (30, $[M+Na]^+$), 759.1 (35, $[M-Ts]^+$), 604.2 (50, $[M-2Ts]^+$), 425.9 (10, $[M+1]^+$),. ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{46}H_{47}N_2O_{10}S_4$ 915.2114, found 915.2102.

Synthesis of *cis*-2,5-disubstituted chiral piperazines (unsymmetrical) (12g-j) from N-tosyl halogenated amino alcohols:

$Pd(OAc)_2$ (10 mol%), K_2CO_3 (2 mmol) and N-tosyl halogenated amino alcohols **10c-f** (1 mmol) (both N-tosyl halogenated amino alcohols are 1 mmol each) were stirred at 110 ^{o}C in DMF (10 mL) for 24 h under an argon atmosphere. The progress of reaction was monitored by TLC using ethyl acetate and hexane. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (20 mL). Usual workup (as described above), purified on silica gel column chromatography using 1:9 ethylacetate and hexane as eluent gave **12g-j**.

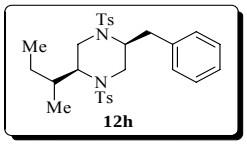
(*2S,5S*)-2-*sec*-butyl-5-isobutyl-1,4-ditosylpiperazine (12g):



12g

Colorless oily liquid, yield = 52%. $[\alpha]_D^{25}$= +64.735 (*c* = 0.106, $CHCl_3$). HPLC analysis: ee > 99 (t_R = 6.195 min, *iso*-propanol/acetonitrile). R_f = 0.60 (15% EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ_H 7.67-7.61 (m, 4H), 7.28 (d, *J* = 8.25 Hz, 4H), 3.74-3.57 (m, 3H), 3.43-3.30 (m, 1H), 3.23-2.84 (m, 2H), 2.41 (s, 6H), 2.04-1.94 (m, 2H), 1.14-0.98 (m, 2H), 0.89-0.75 (m, 14H). IR (Neat, cm^{-1}): 3352, 3072, 2956, 2368, 1643, 1530, 1278, 1145, 768. Mass (ESI-MS): *m/z* 507.3 (60, $[M+1]^+$), 529.2 (80, $[M+Na]^+$), 351.2 (35, $[M-Ts]^+$), 196.2 (10, $[M-2Ts]^+$). ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{26}H_{39}N_2O_4S_2$ 507.2351, found 507.2353.

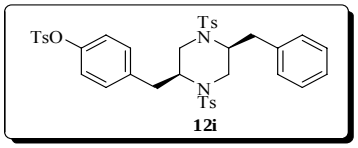
(*2S,5S*)-2-benzyl-5-sec-butyl-1,4-ditosylpiperazine (12h):



12h

Colorless oily liquid, yield = 48%. $[\alpha]_D^{25}$= +18.148 (*c* = 0.040, $CHCl_3$). HPLC analysis: ee > 99 (t_R = 5.420 min, *iso*-propanol/acetonitrile). R_f = 0.63 (15% EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ_H 7.67 (d, *J* = 8.15 Hz, 2H), 7.46 (d, *J* = 8.15 Hz, 2H), 7.32-7.20 (m, 8H), 7.05 (d, *J* = 5.73 Hz, 2H), 3.67-3.64 (m, 2H), 3.39 (dd, J_1 = 5.17, J_2 = 14.84 Hz, 1H), 3.28 (dd, J_1 = 5.72, J_2 = 14.38 Hz, 1H), 3.12-3.05 (m, 2H), 2.91 (dd, J_1 = 10.40, J_2 = 15.08 Hz, 1H), 2.67 (dd, J_1 = 9.53, J_2 = 13.34 Hz, 1H), 2.44 (s, 3H), 2.41 (s, 3H), 1.96-1.83 (m, 1H), 1.08-0.97 (m, 2H), 0.88-0.83 (m, 6H). IR (Neat, cm^{-1}): 3454, 3275, 2974, 2362, 1635, 1528, 1291, 1175, 768. Mass (ESI-MS): *m/z* 541.1 (90, $[M+1]^+$), 563.2 (60, $[M+Na]^+$), 385.2 (30, $[M-Ts]^+$), 230.1 (10, $[M-2Ts]^+$). ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{29}H_{37}N_2O_4S_2$ 541.2195, found 541.2195.

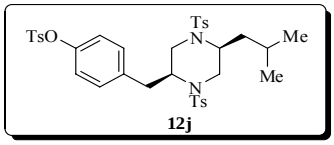
4-(((2S,5S)-5-benzyl-1,4-ditosylpiperazin-2-yl)methyl)phenyl 4-methylbenzenesulfonate (12i):



12i

Colorless oily liquid, yield = 51%. $[\alpha]_D^{25}$= +3.946 (*c* = 0.140, $CHCl_3$). HPLC analysis: ee > 99 (t_R = 5.741 min, *iso*-propanol/acetonitrile). R_f = 0.44 (20% EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ_H 7.72 (d, *J* = 7.16 Hz, 2H), 7.53 (d, *J* = 7.30 Hz, 3H), 7.33-7.25 (m, 10H), 7.11-7.05 (m, 4H), 6.90 (d, *J* = 7.42 Hz, 2H), 3.69 (s, 2H), 3.29-2.91 (m, 7H), 2.44 (s, 3H), 2.41 (s, 3H), 1.96-1.83 (m, 1H), 2.02 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ_C 148.5, 145.4, 144.0, 143.9, 137.0, 136.2, 135.2, 135.1, 132.4, 130.7, 129.9, 129.8, 129.5, 128.7, 128.5, 127.4, 127.3, 126.8, 122.6, 56.8, 56.7, 39.3, 38.7, 31.9, 31.6, 21.7, 21.5 ppm. IR (Neat, cm^{-1}): 3439, 3230, 2964, 1643, 1460, 1348, 1161, 1099, 938, 760. Mass (ESI-MS): *m/z* 745.2 (100, $[M+1]^+$), 767.2 (60, $[M+Na]^+$), 589.3 (10, $[M-Ts]^+$), 434.5 (30, $[M-2Ts]^+$). ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{39}H_{40}N_2O_7S_3$ 745.1998, found 745.2073.

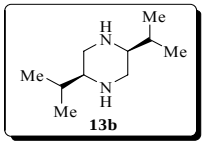
4-(((2S,5S)-5-isobutyl-1,4-ditosylpiperazin-2-yl)methyl)phenyl 4-methylbenzenesulfonate (12j):



12j

Colorless oily liquid, yield = 47%. $[\alpha]_D^{25}$= -13.952 (*c* = 0.102, $CHCl_3$). R_f = 0.42 (20% EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ_H 7.91-7.81 (m, 1H), 7.74-7.71 (m, 3H), 7.66-7.63 (m, 2H), 7.51-7.48 (m, 1H), 7.35-7.24 (m, 7H), 7.06-7.03 (m, 1H), 6.92-6.90 (m., 1H), 4.01-3.79 (m, 2H), 3.63-3.62 (m, 1H), 3.48-3.44 (m, 1H), 3.30-3.04 (m, 4H), 2.91-2.83 (m, 1H), 2.46 (s, 3H), 2.45 (s, 3H), 2.44 (s, 3H), 2.06-2.05 (m, 1H), 1.68-1.55 (m, 4H), 0.88-0.85 (m, 6H). IR (Neat, cm^{-1}): 3442, 3245, 2968, 1635, 1460, 1341, 1158, 1090, 935, 760. Mass (ESI-MS): *m/z* 711.2 (70, $[M+1]^+$), 733.2 (40, $[M+Na]^+$), 555.4 (25, $[M-Ts]^+$), 400.1 (10, $[M-2Ts]^+$). ESI-HRMS: *m/z* $[M+H]^+$ calcd $C_{36}H_{43}N_2O_7S_3$ 711.2232, found 711.2230.

Experimental procedure for the synthesis of (*2S,5S*)-2,5-diisopropylpiperazine (13b):



13b

Finely chopped sodium metal (87 mg, 3.760 mmol) and naphthalene (531mg, 4.136 mmol) were dissolved in 10 mL dry THF and stirred for 2h, until a dark green colour was appeared. The

desired THF solution of **12b** (90 mg, 0.188 mmol) was cooled to -78 ^{o}C and then Na-napthalenide solution was added dropwise to the reaction mixture via a syringe, until a dark green colour was persisted and stirred for 15 min at -78 ^{o}C. It was quenched by adding 1-2 drops water to discharge the green colour and usual work-up followed by column chromatography. Light brown oily liquid, yield = 64%. R_f = 0.46 (15% methanol/chloroform). $[\alpha]_D^{25}$ = +18.243 (*c* = 0.030, CH_3OH). HPLC analysis: ee > 99 (t_R = 5.549 min, *iso*-propanol/acetonitrile). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 4.76 (s, 2H), 3.21 (d, *J* = 12.12 Hz, 2H), 3.02-2.96 (m, 2H), 2.85 (s, 2H), 2.03 (s, 2H), 0.98 (d, *J* = 6.48, 6H), 0.95 (d, *J* = 6.27, 6H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 58.5, 43.3, 27.4, 19.0, 18.7 ppm. IR (Neat, cm^{-1}): 3298, 3024, 2964, 1463, 1321, 1158, 758. Mass (ESI-MS): *m/z* 171.2 (90, $[M+H]^+$). ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{10}H_{23}N_2$ 171.1861, found 171.1860.

Supporting Information
An Efficient Synthetic Approach for N-C Bond Formation from (*S*)-Amino Acids: An Easy Access to *cis*-2,5-Disubstituted Chiral Piperazines

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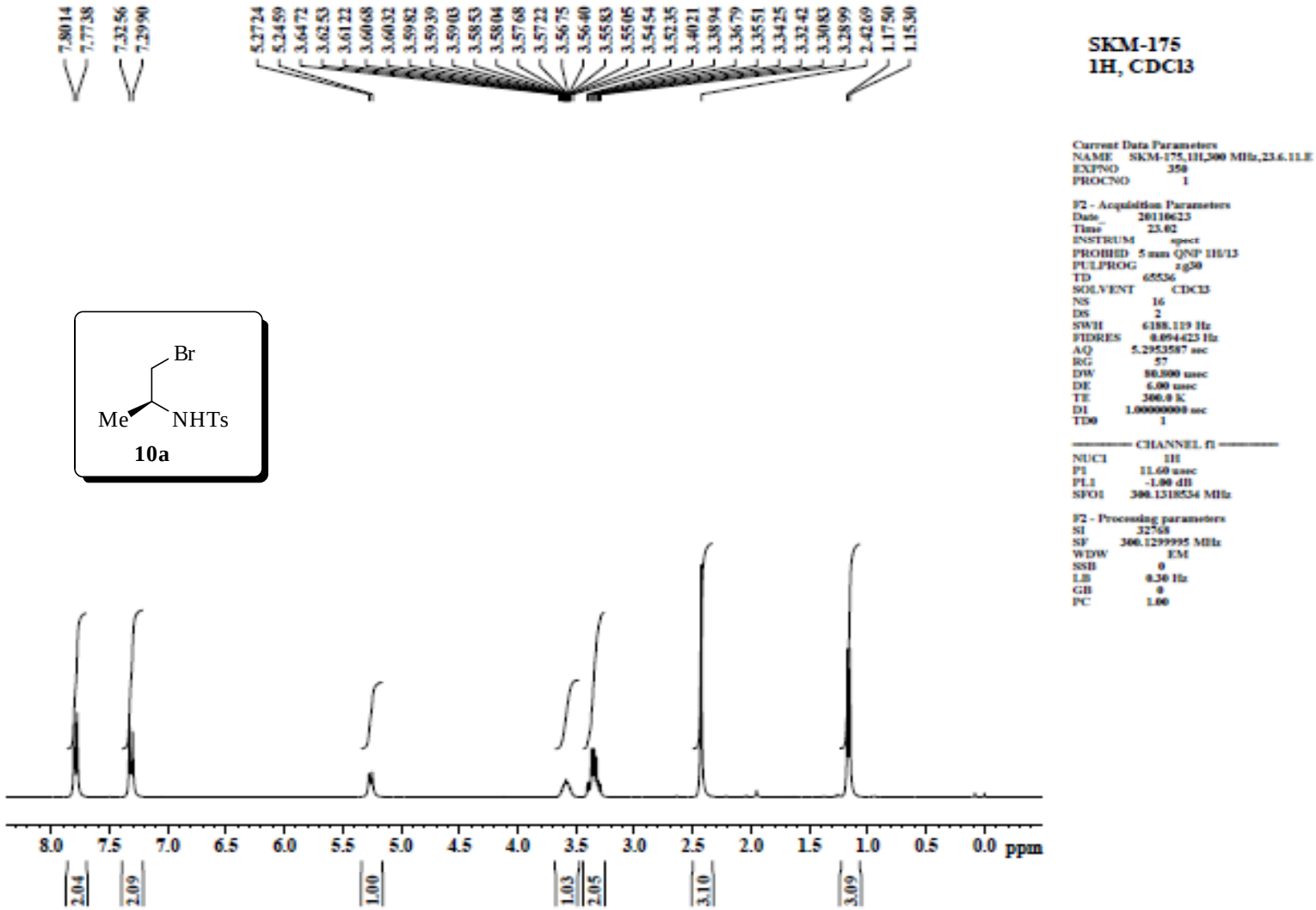

Figure 1: ^{1}H -NMR Spectrum of **10a.**

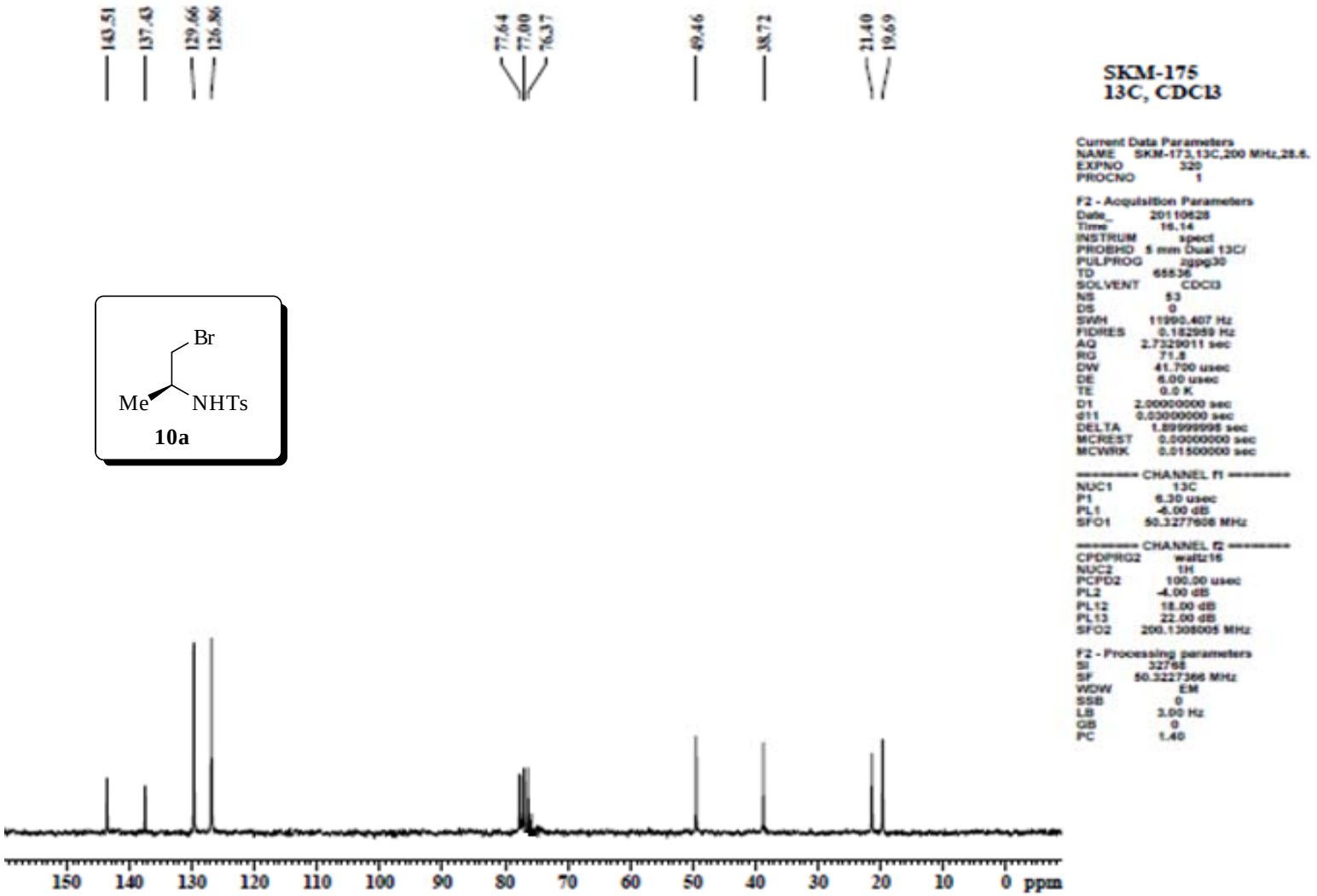

Figure 2: ^{13}C -NMR Spectrum of **10a.**

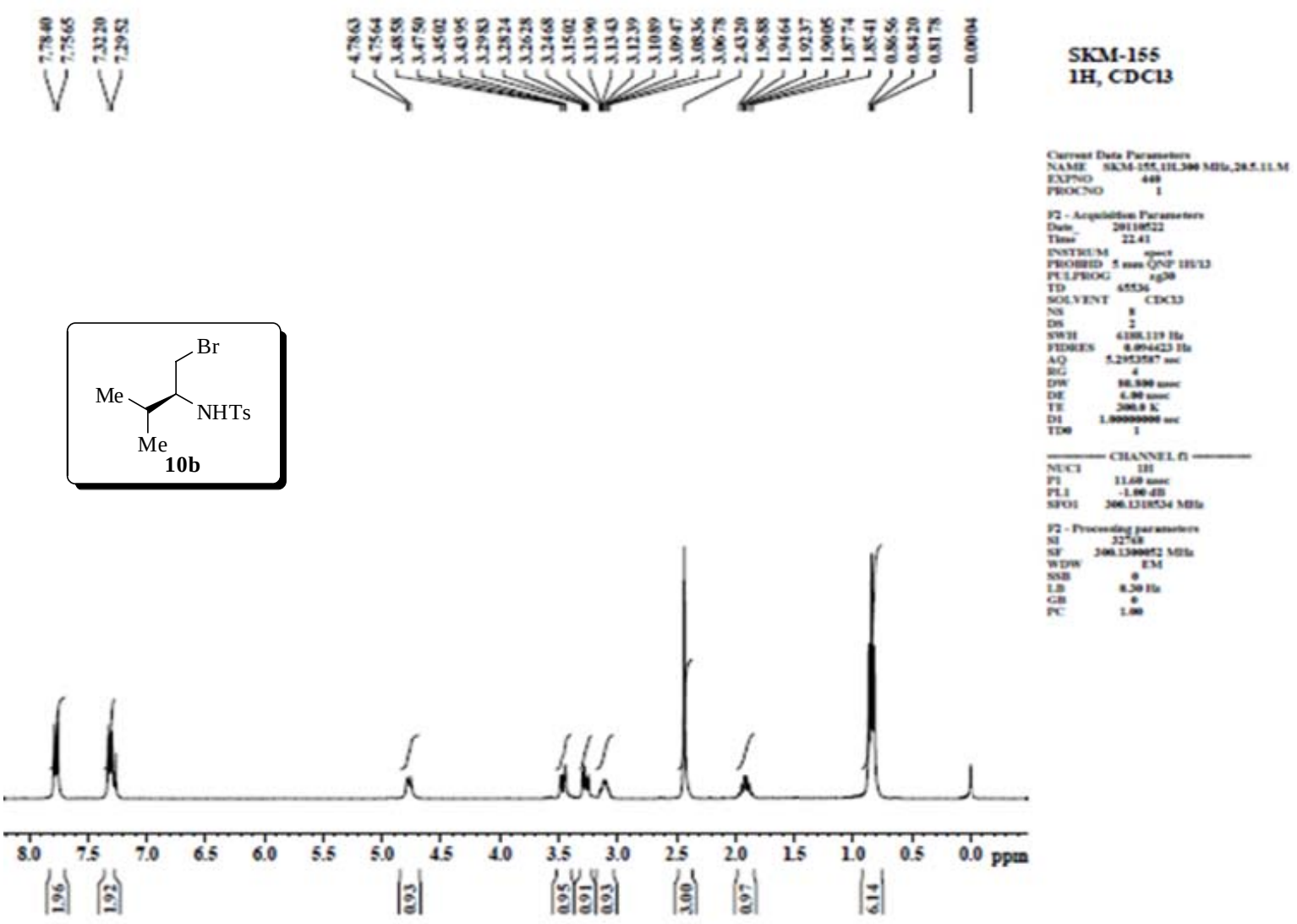

Figure 3: ^{1}H -NMR Spectrum of **10b.**

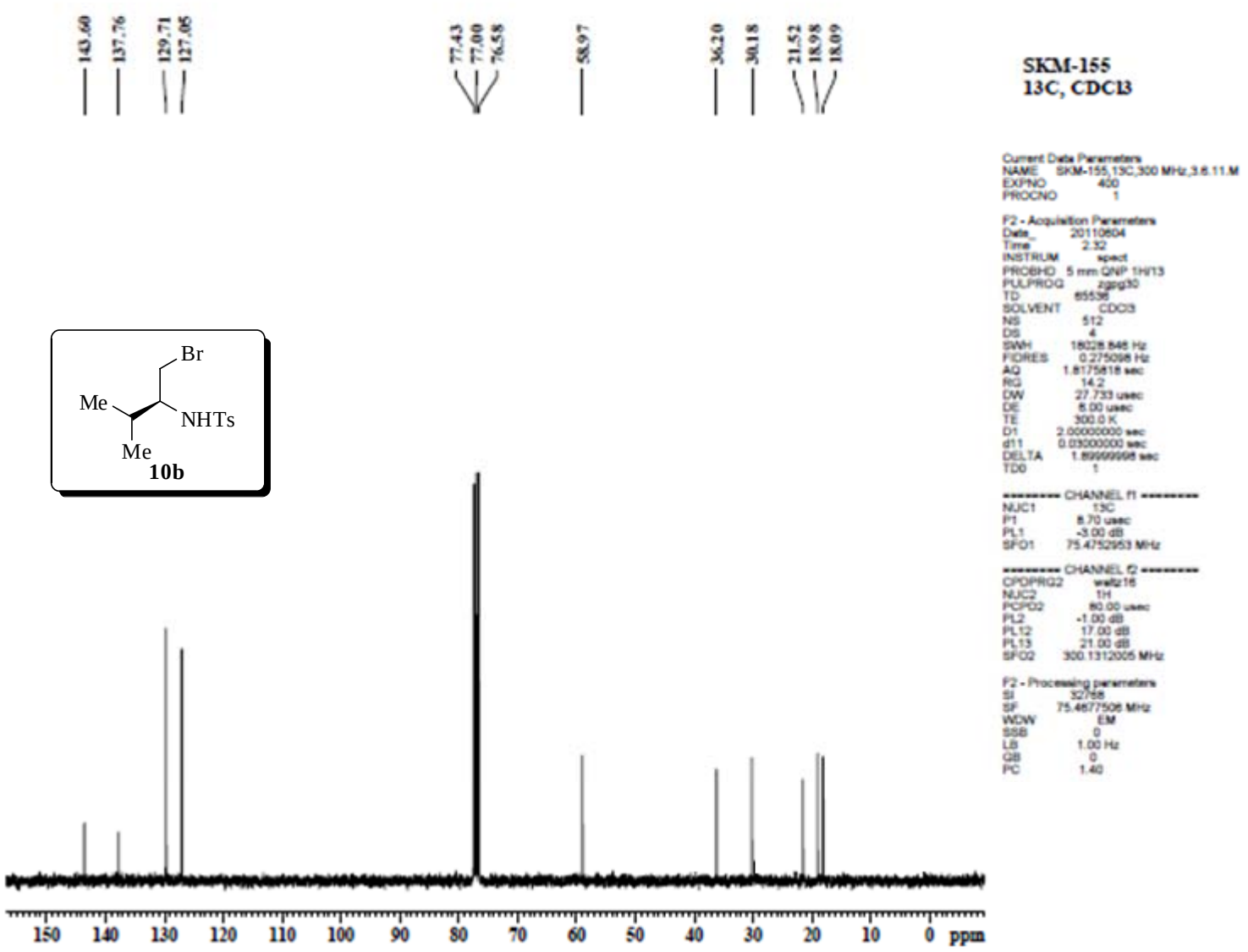

Figure 4: ^{13}C -NMR Spectrum of **10b.**

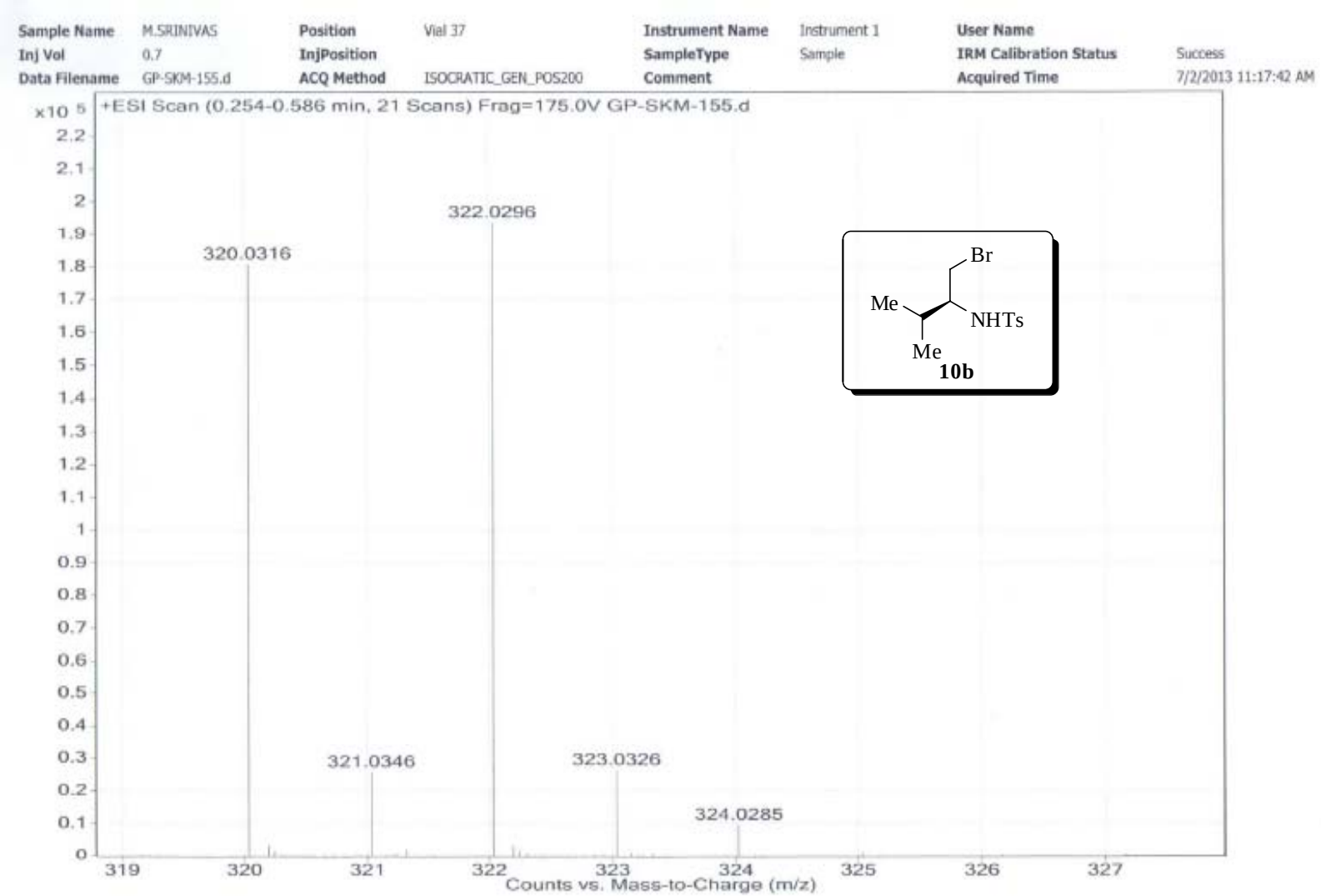

Figure 5: HRMS -Spectrum of **10b.**

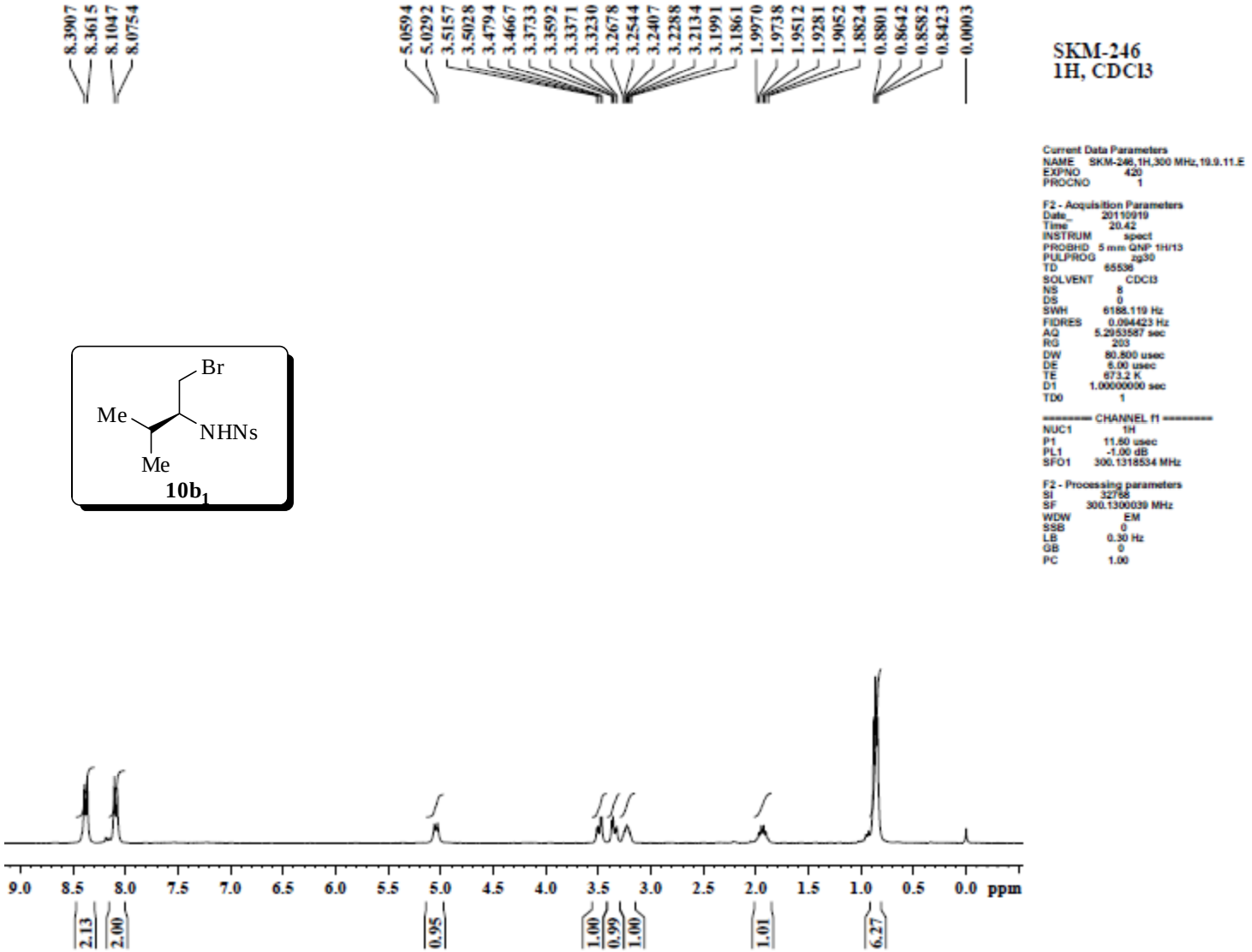

Figure 6: ^{1}H -NMR Spectrum of **10b1.**

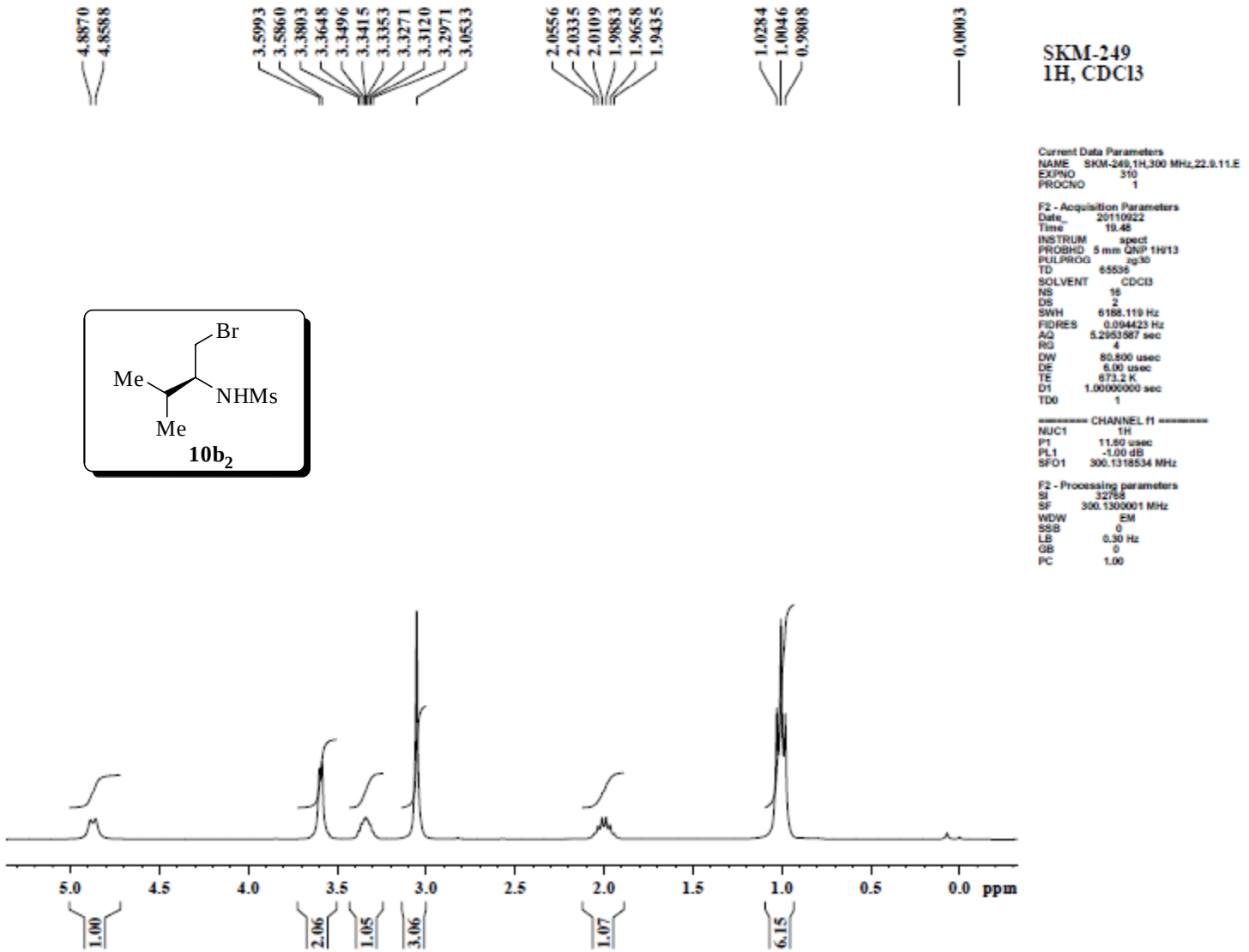

Figure 7: ^{1}H -NMR Spectrum of **10b2.**

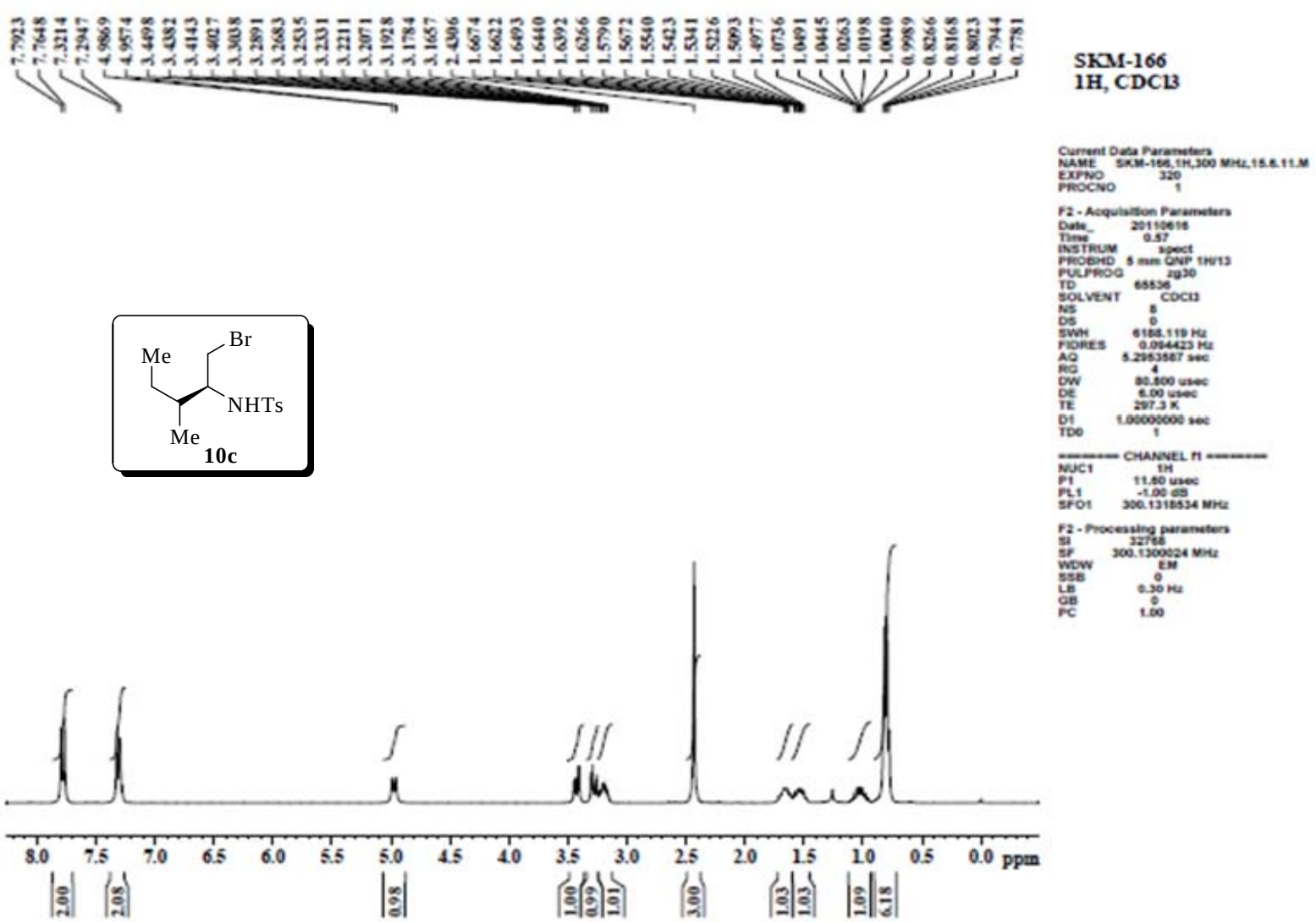

Figure 8: ^{1}H -NMR Spectrum of **10c.**

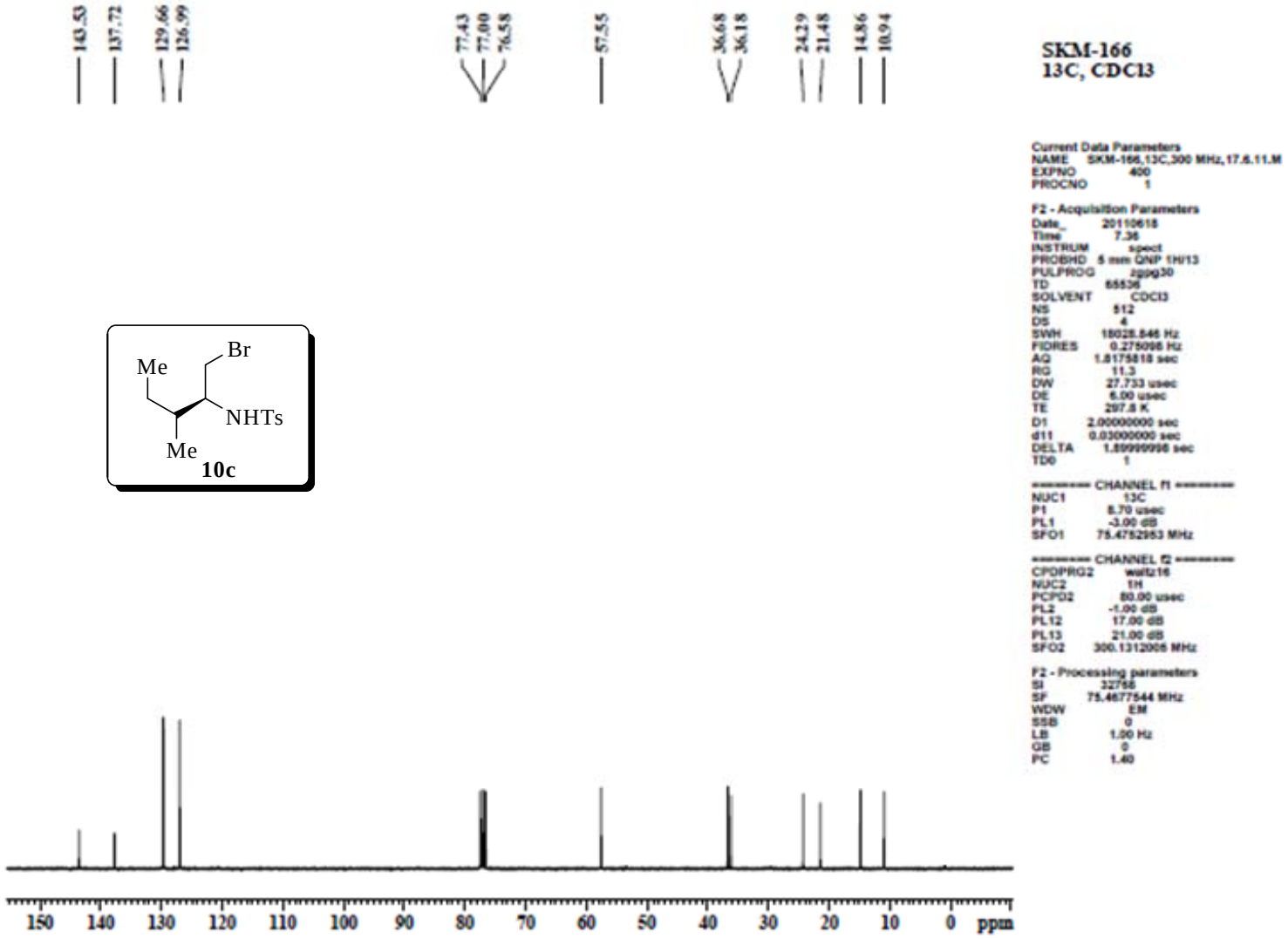

Figure 9: ^{13}C -NMR Spectrum of **10c.**

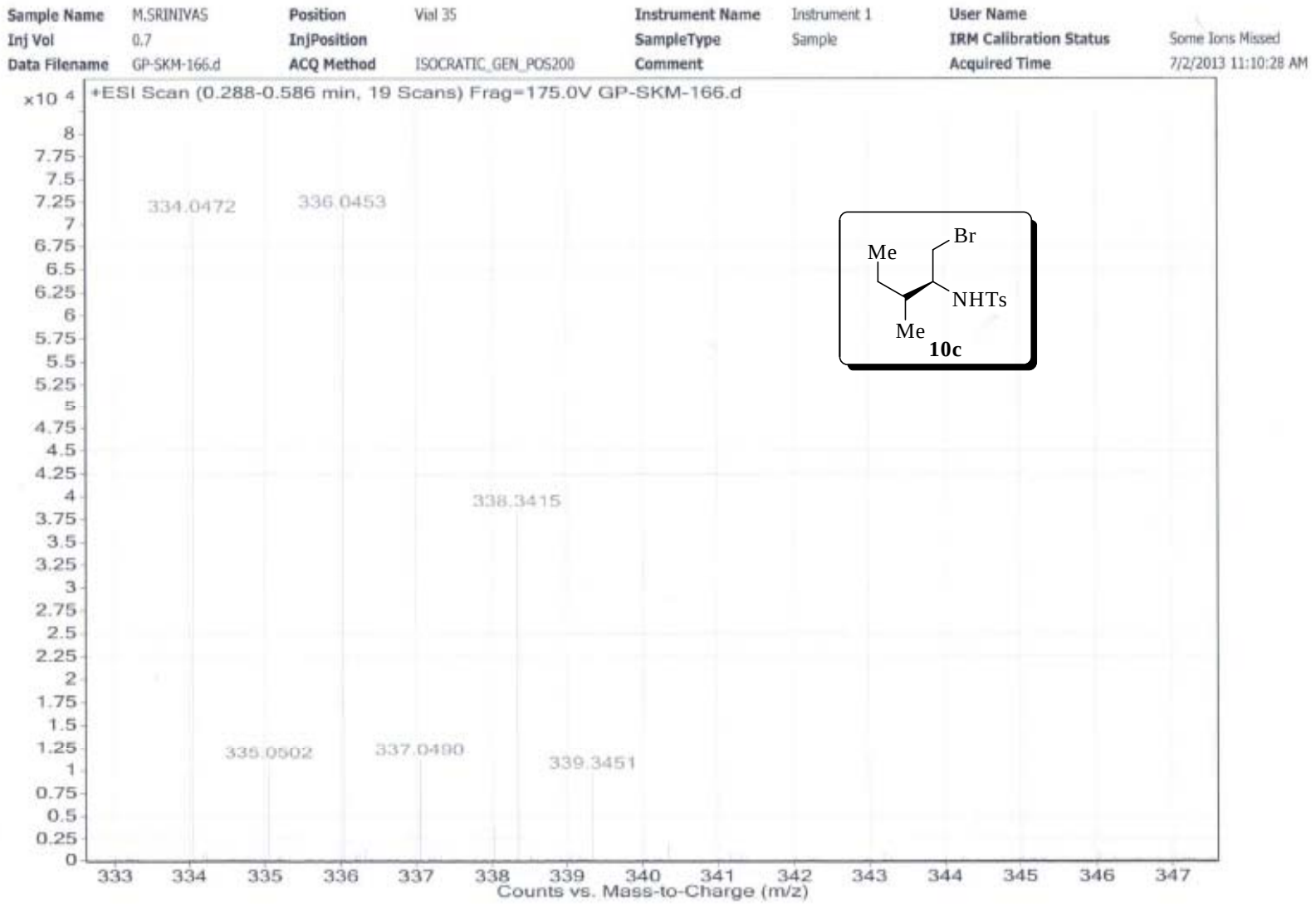

Figure 10: HRMS -Spectrum of **10c.**

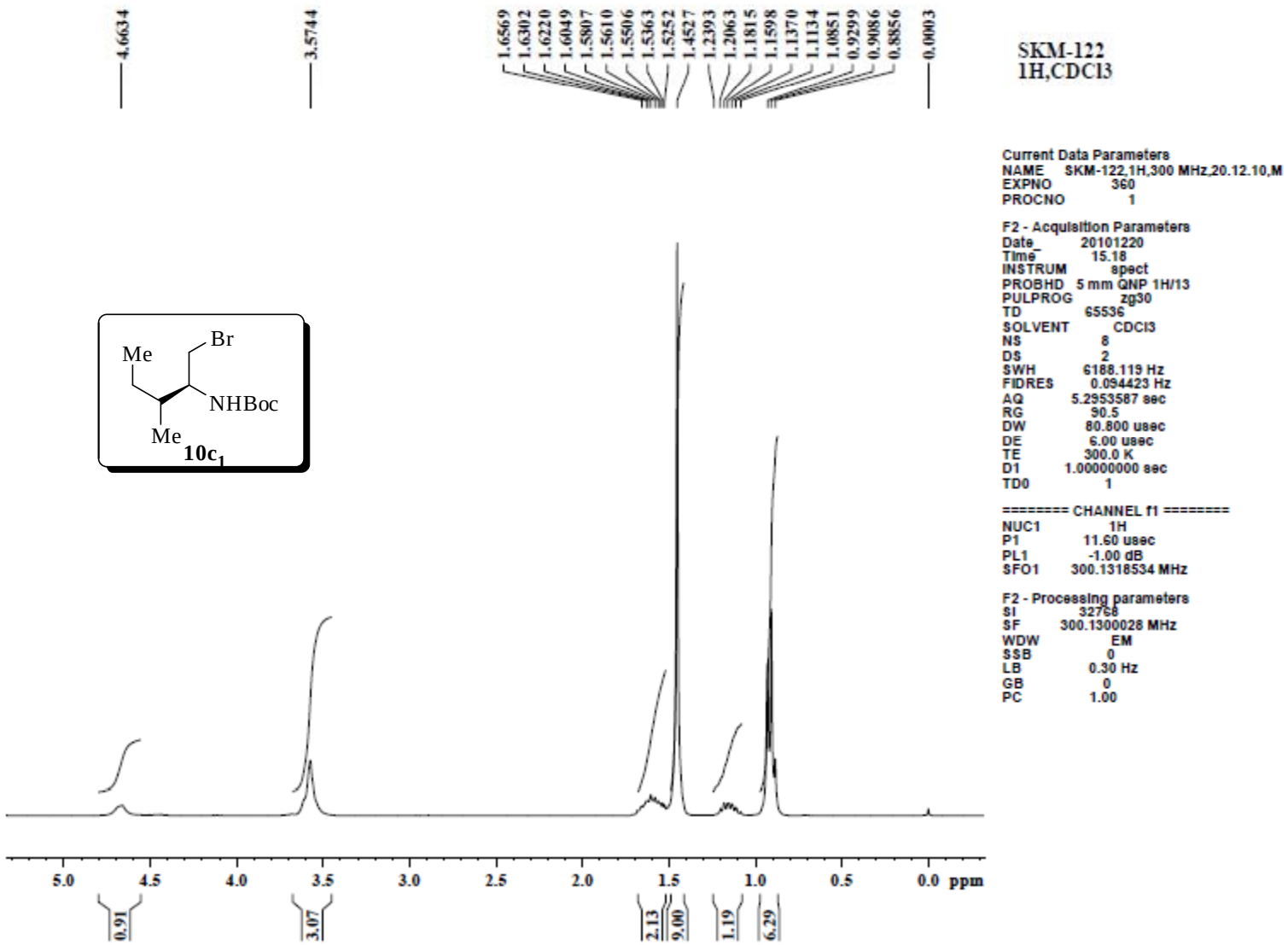

Figure 11: ^{1}H -NMR Spectrum of **10c1.**

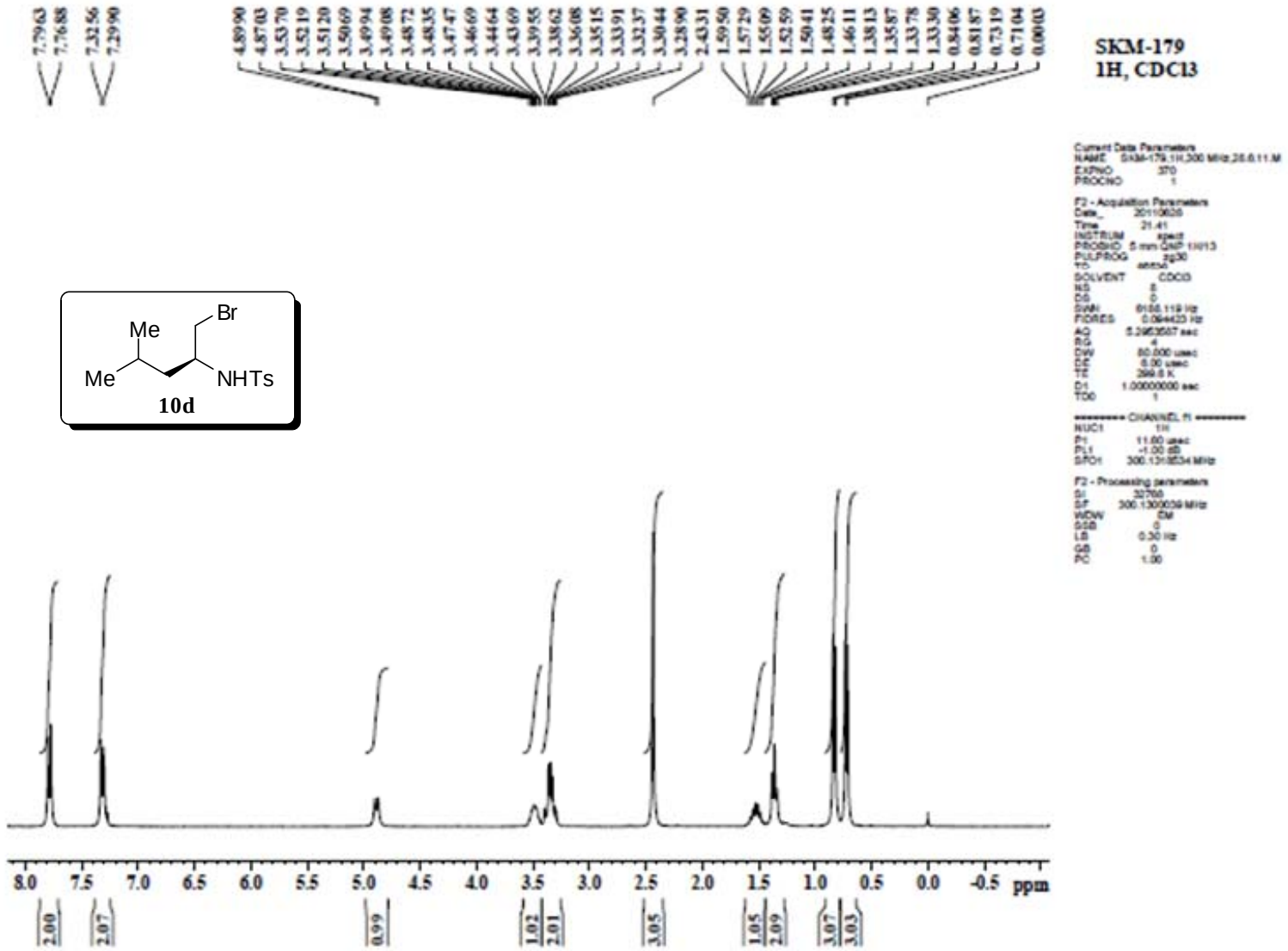

Figure 12: ^{1}H -NMR Spectrum of **10d.**

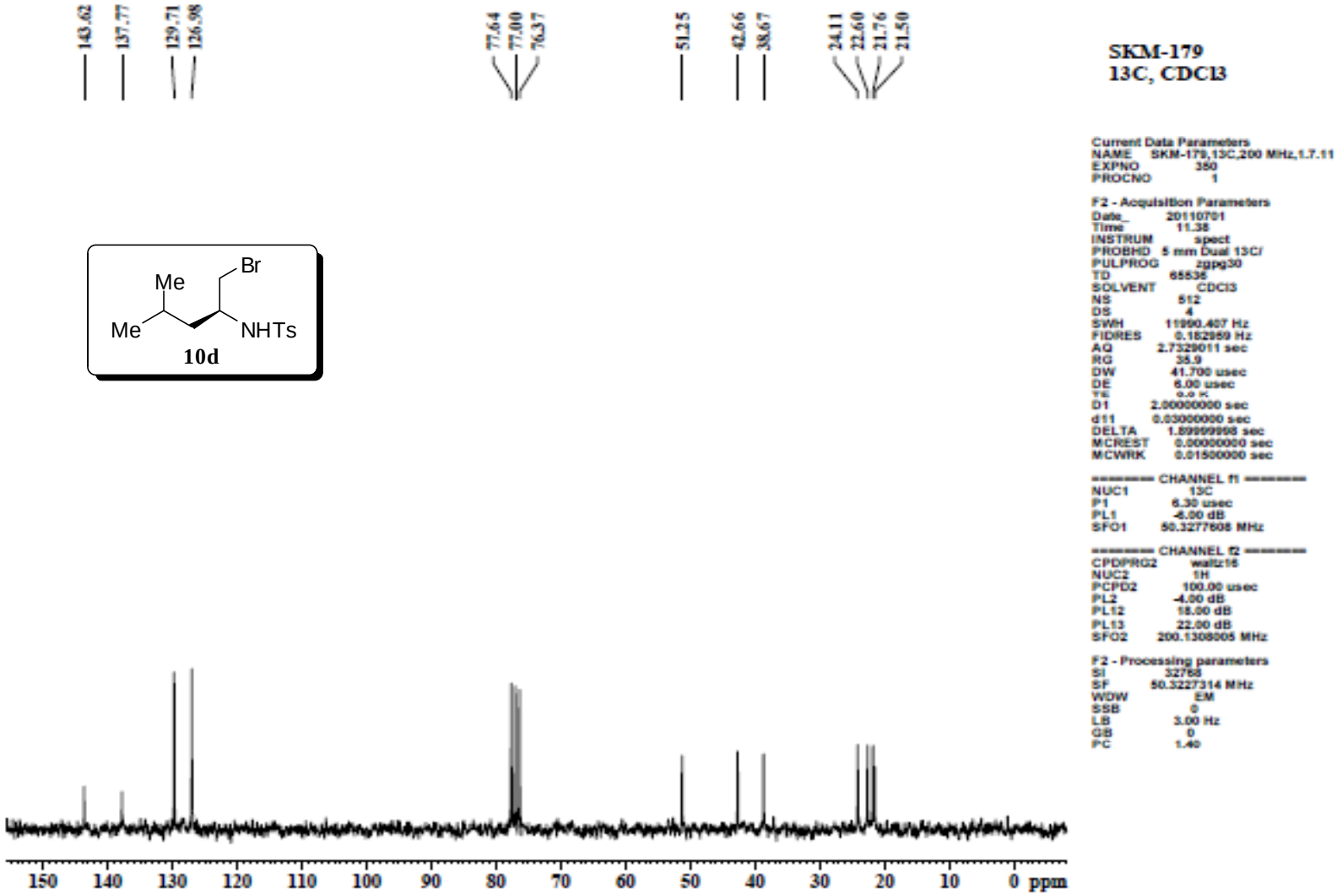

Figure 13: ^{13}C -NMR Spectrum of **10d.**

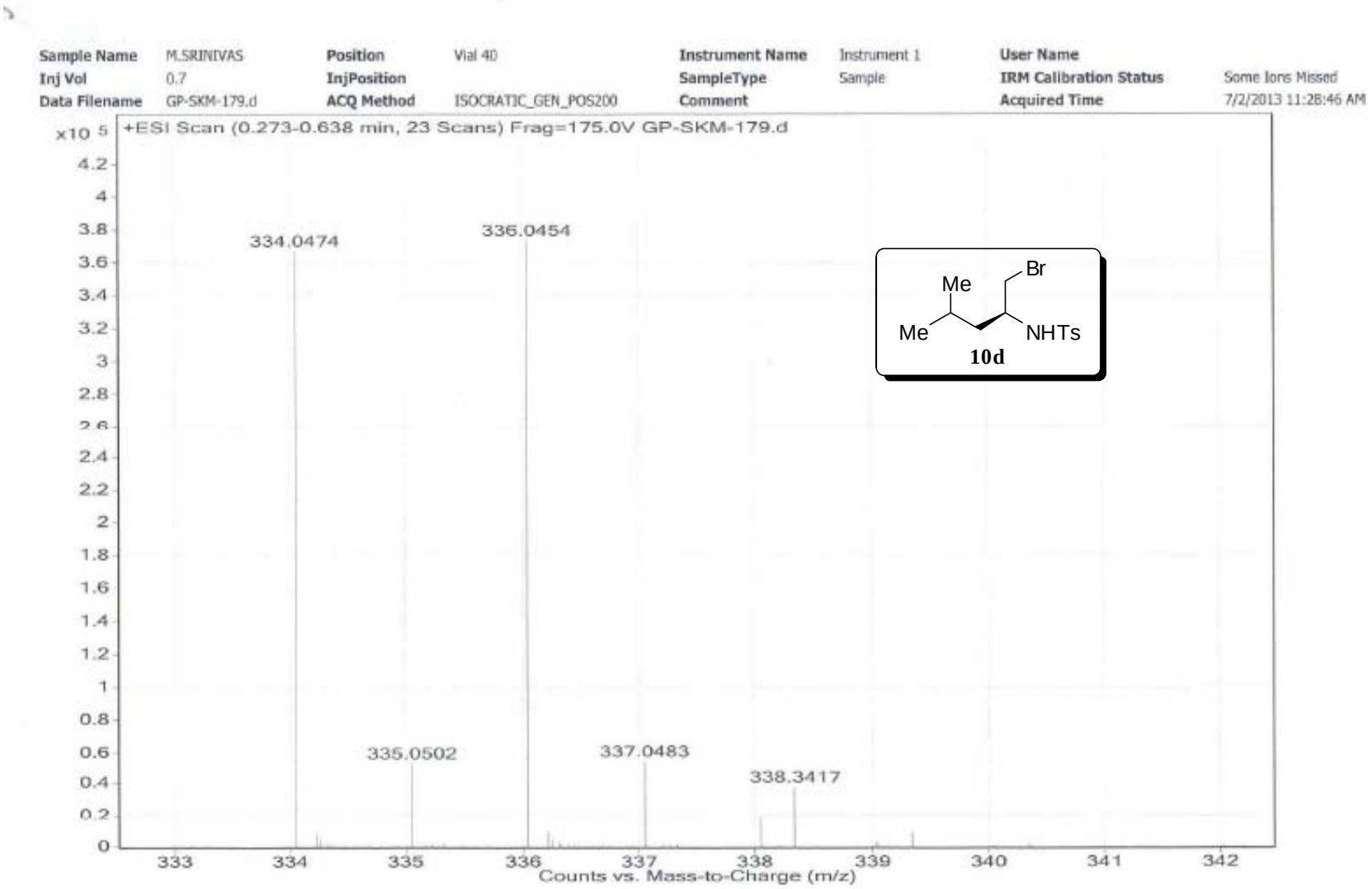

Figure 14: HRMS -Spectrum of **10d.**

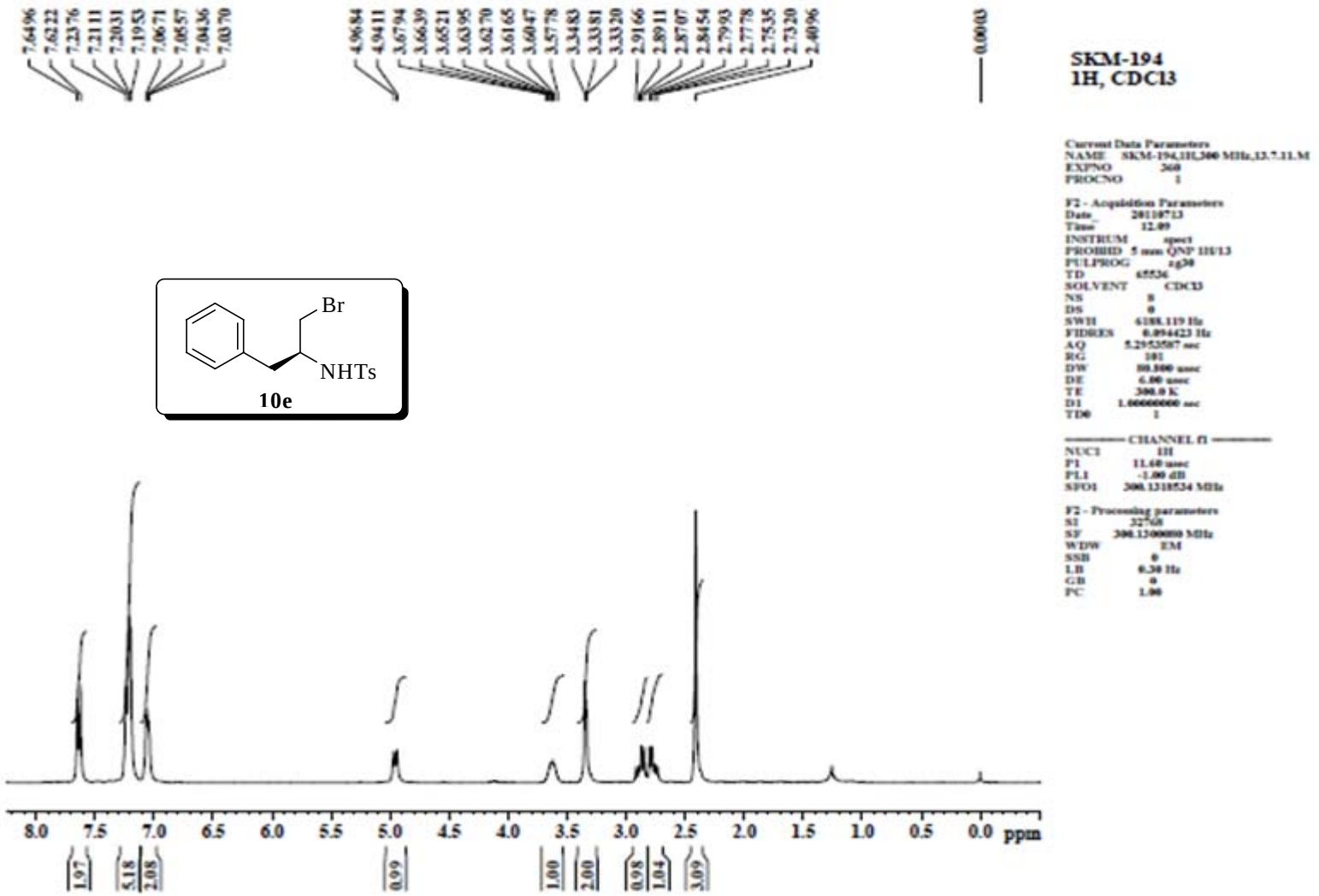

Figure 15: ^{1}H -NMR Spectrum of **10e.**

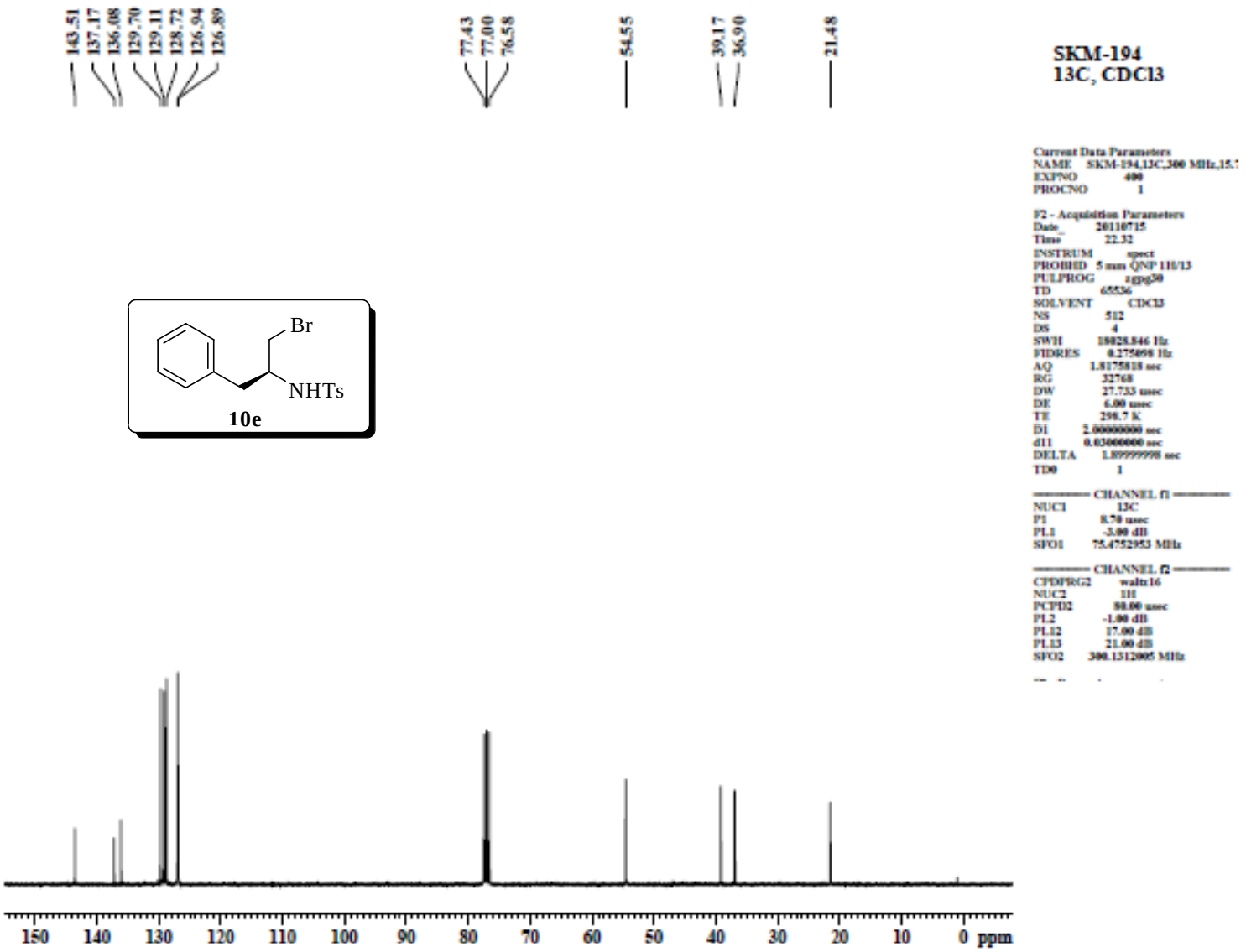

Figure 16: ^{13}C -NMR Spectrum of **10e.**

Figure 17: HRMS -Spectrum of **10e.**

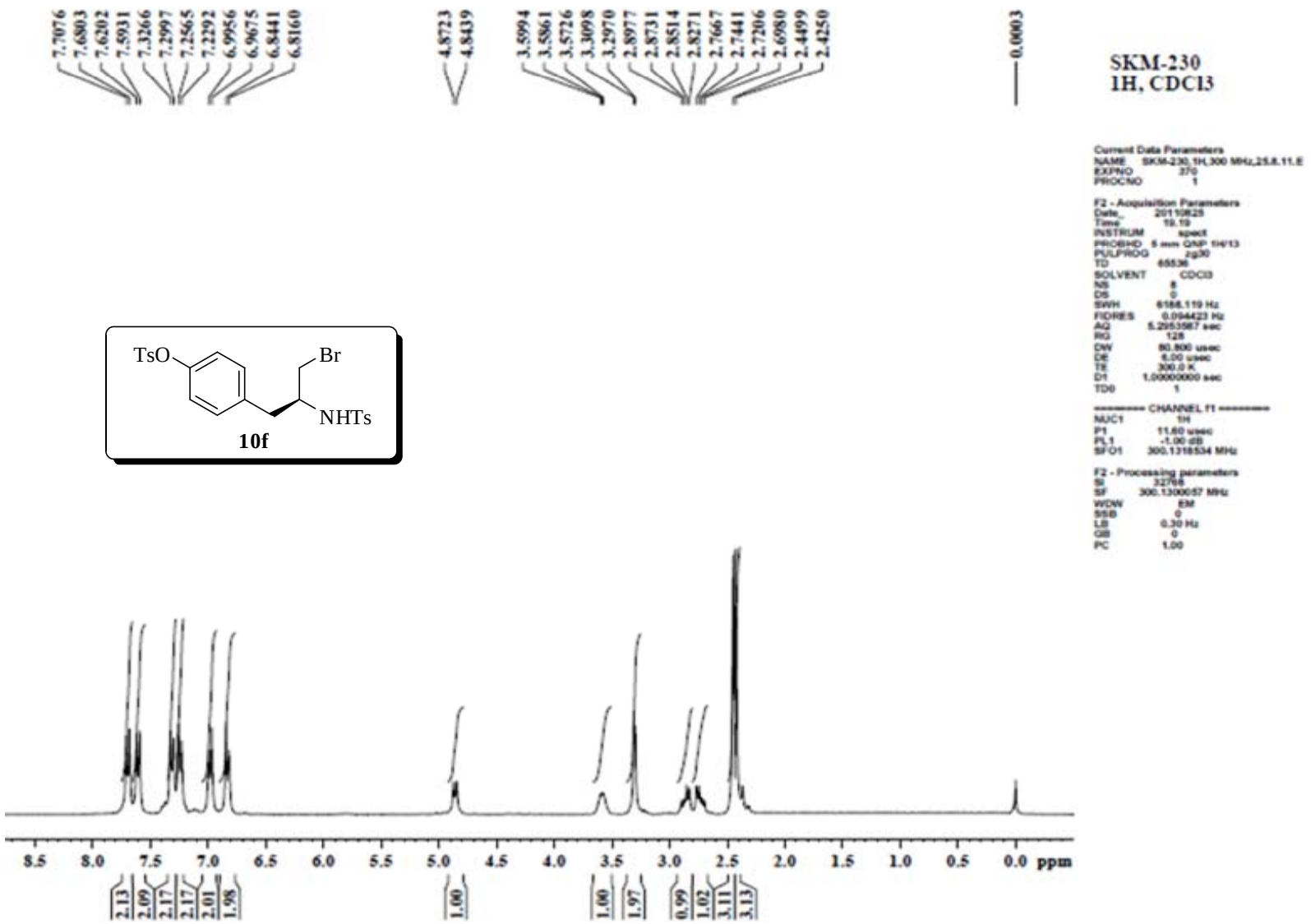

Figure 18: ^{1}H -NMR Spectrum of **10f.**

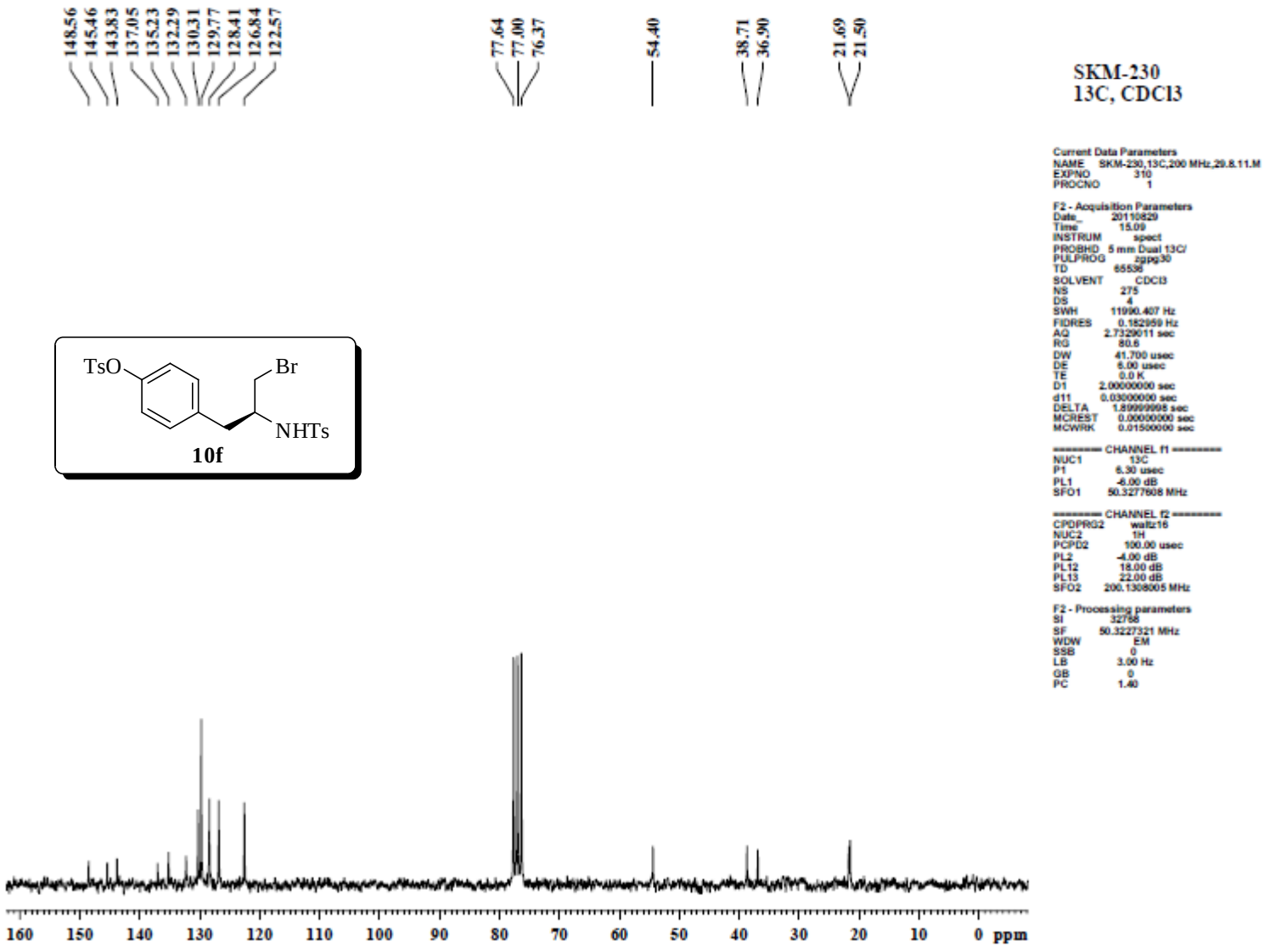

Figure 19: ^{13}C -NMR Spectrum of **10f.**

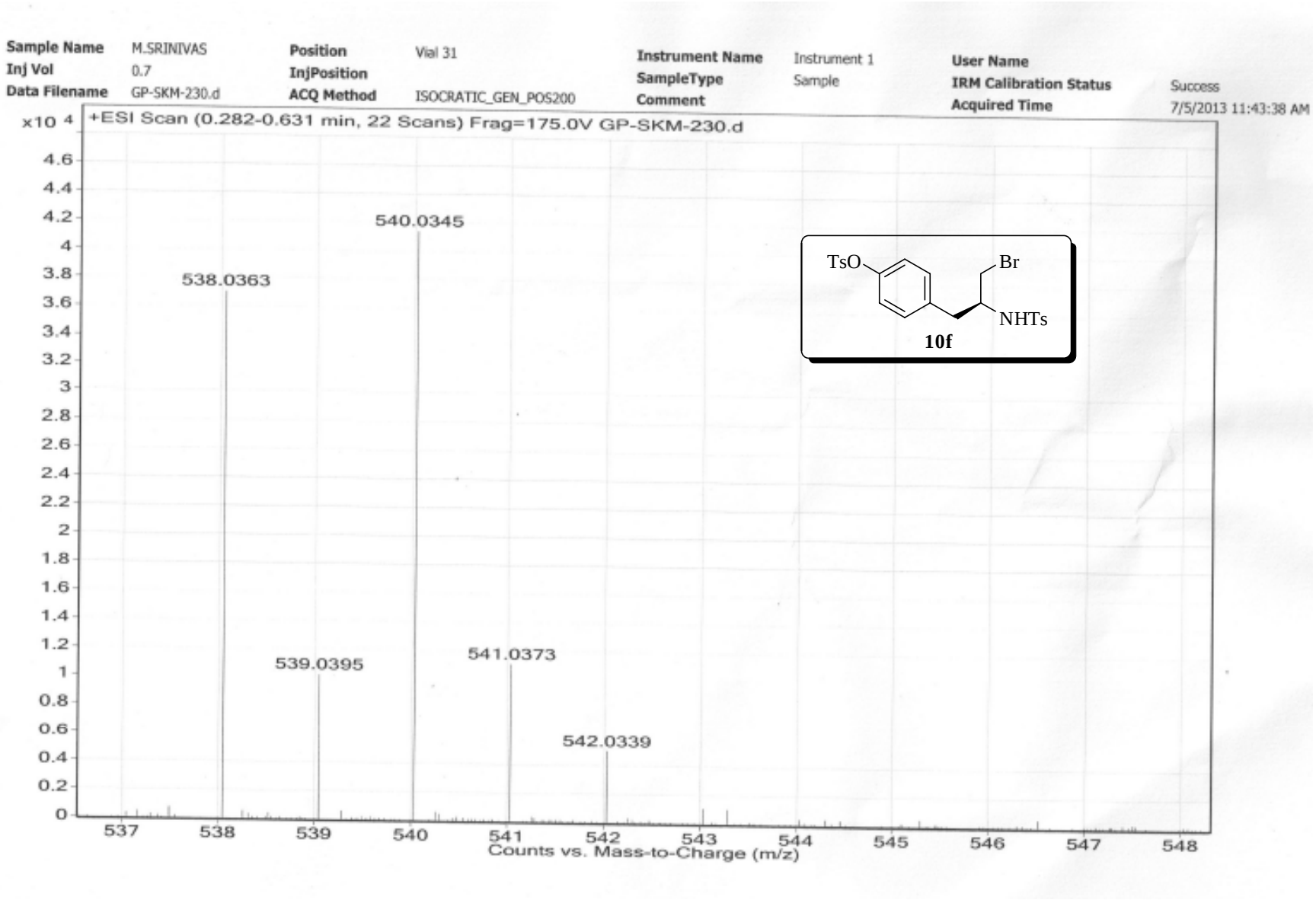

Figure 20: HRMS -Spectrum of **10f.**

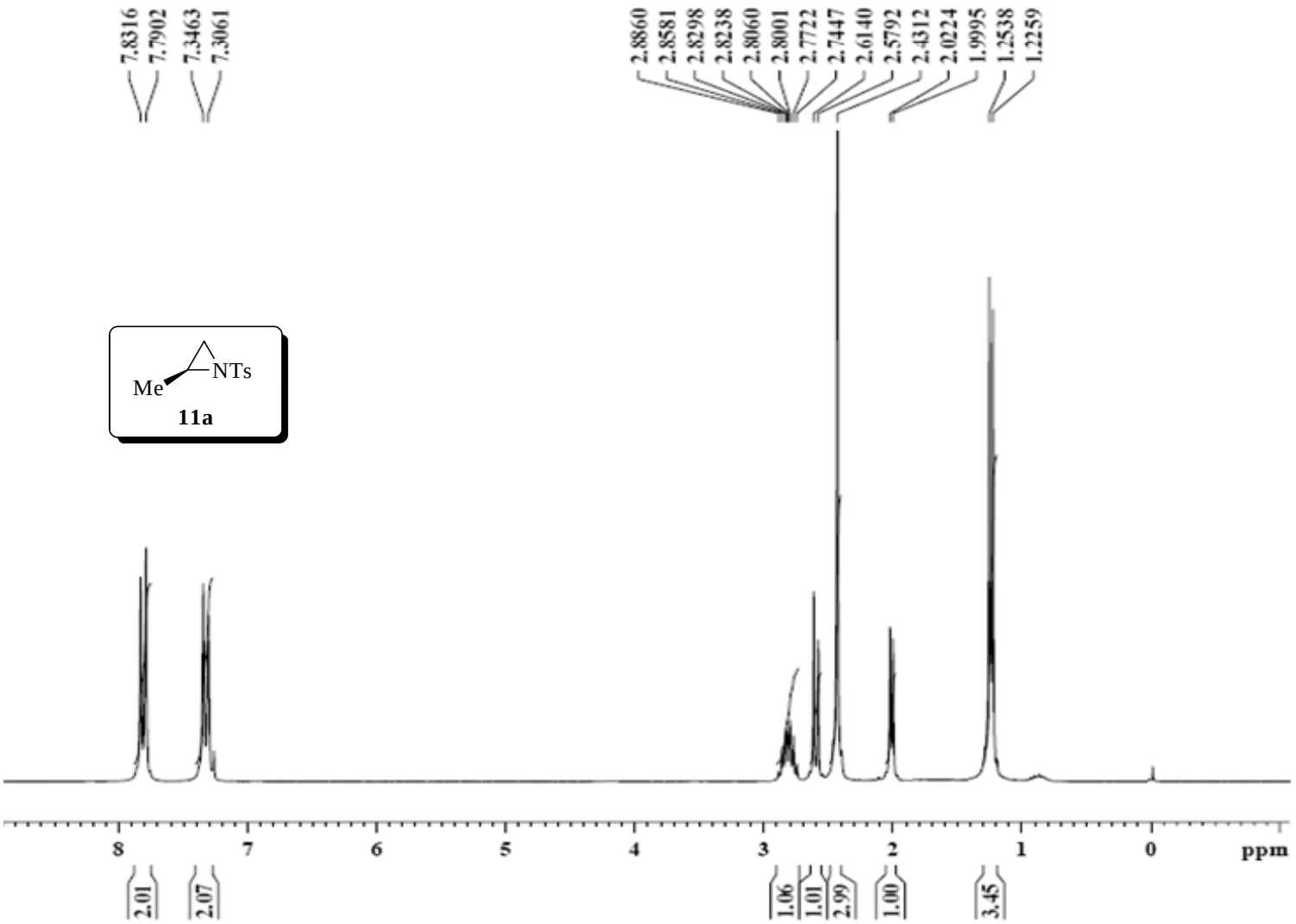

Figure 21: ^{1}H -NMR Spectrum of **11a.**

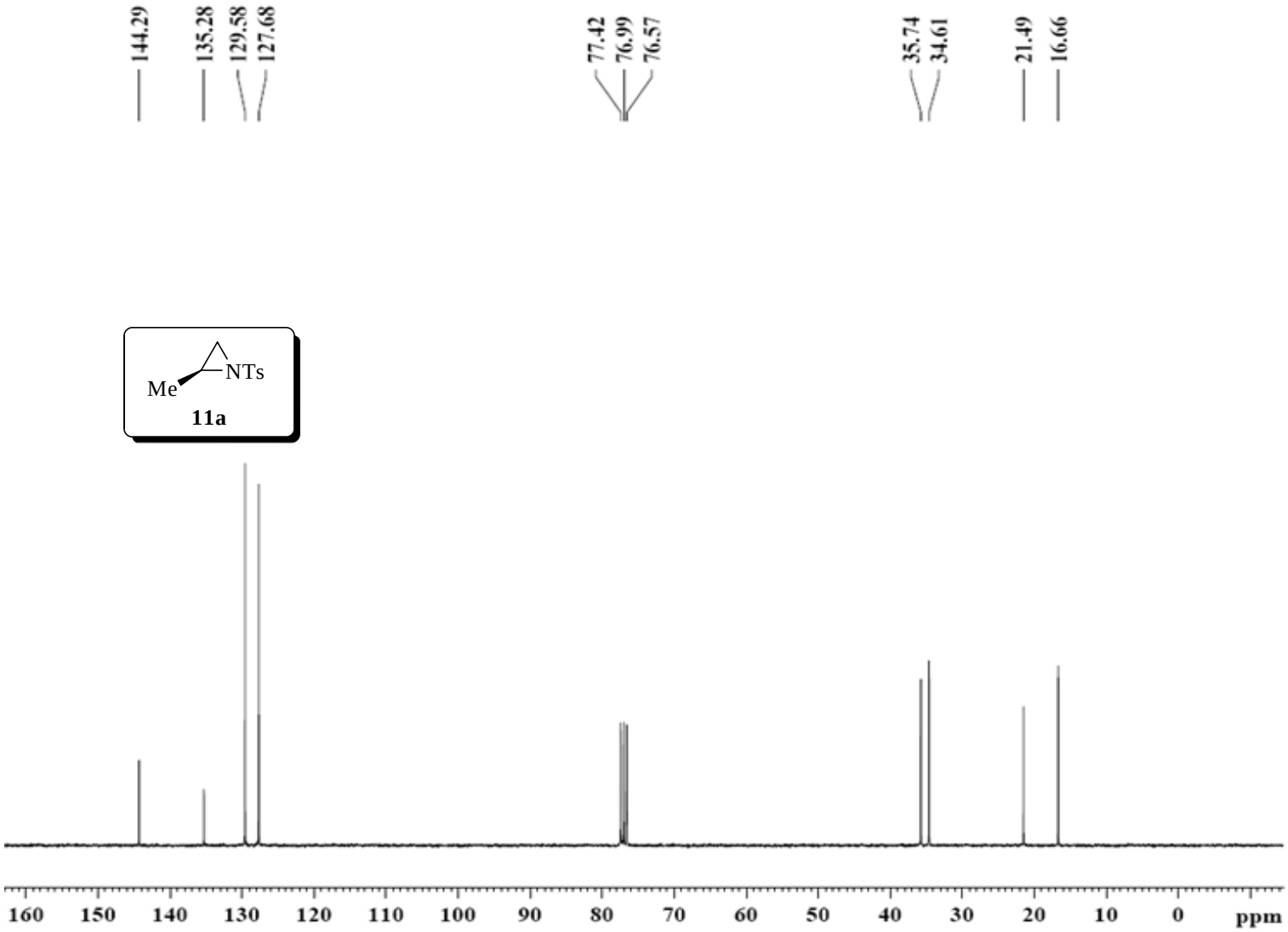

Figure 22: ^{13}C -NMR Spectrum of **11a.**

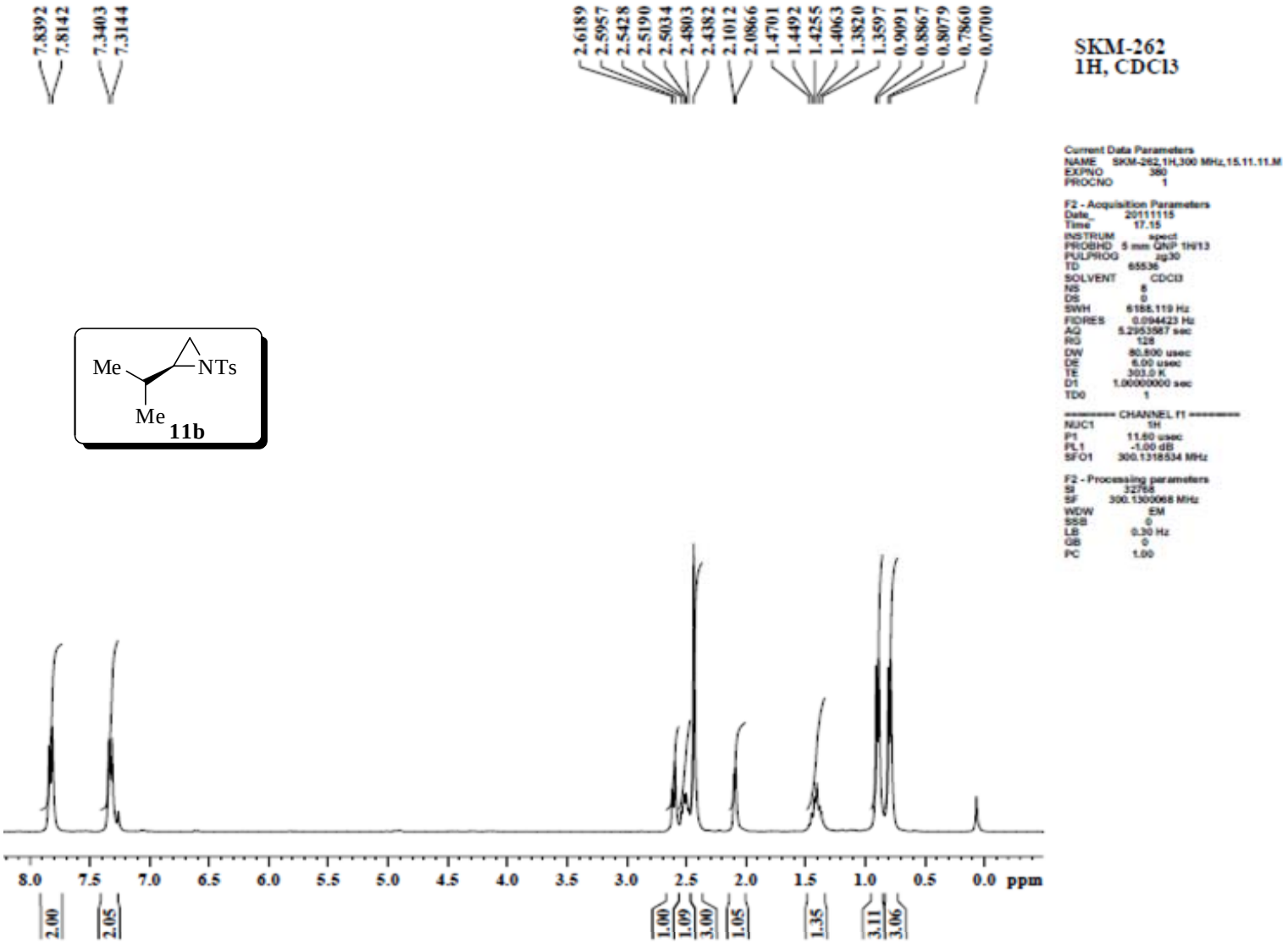

Figure 23: ^{1}H -NMR Spectrum of **11b.**

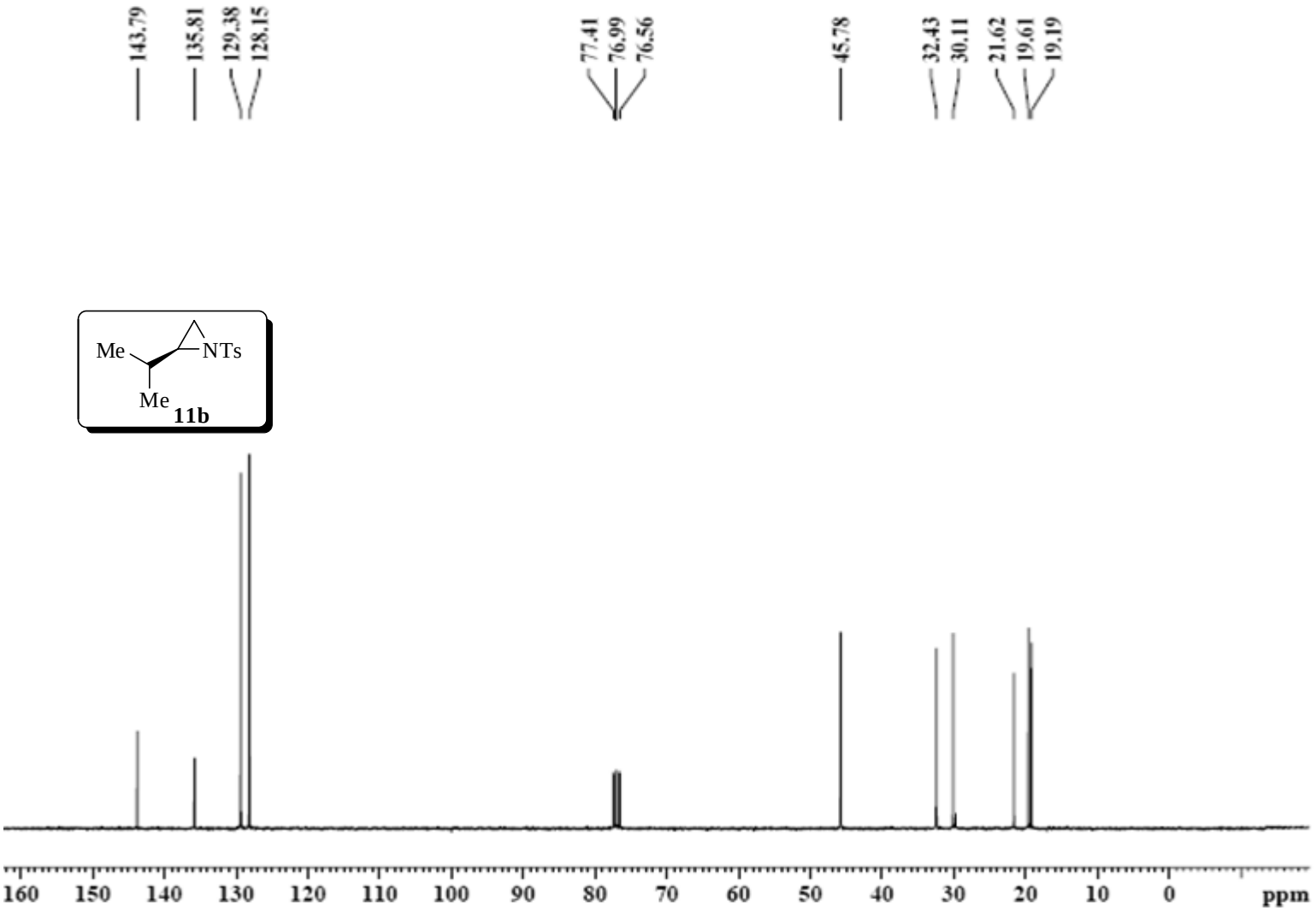

Figure 24: ^{13}C -NMR Spectrum of **11b.**

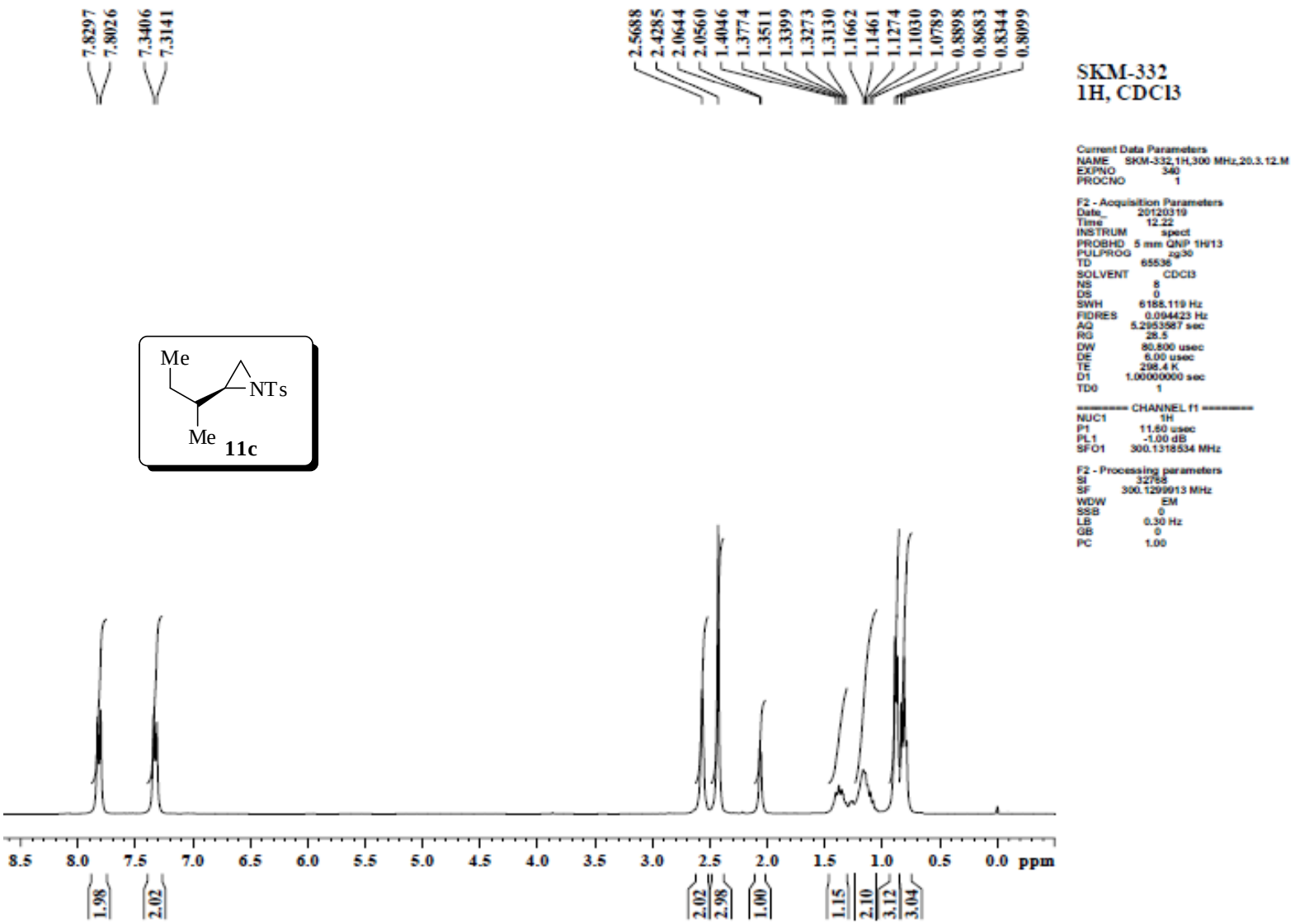

Figure 25: ^{1}H -NMR Spectrum of **11c.**

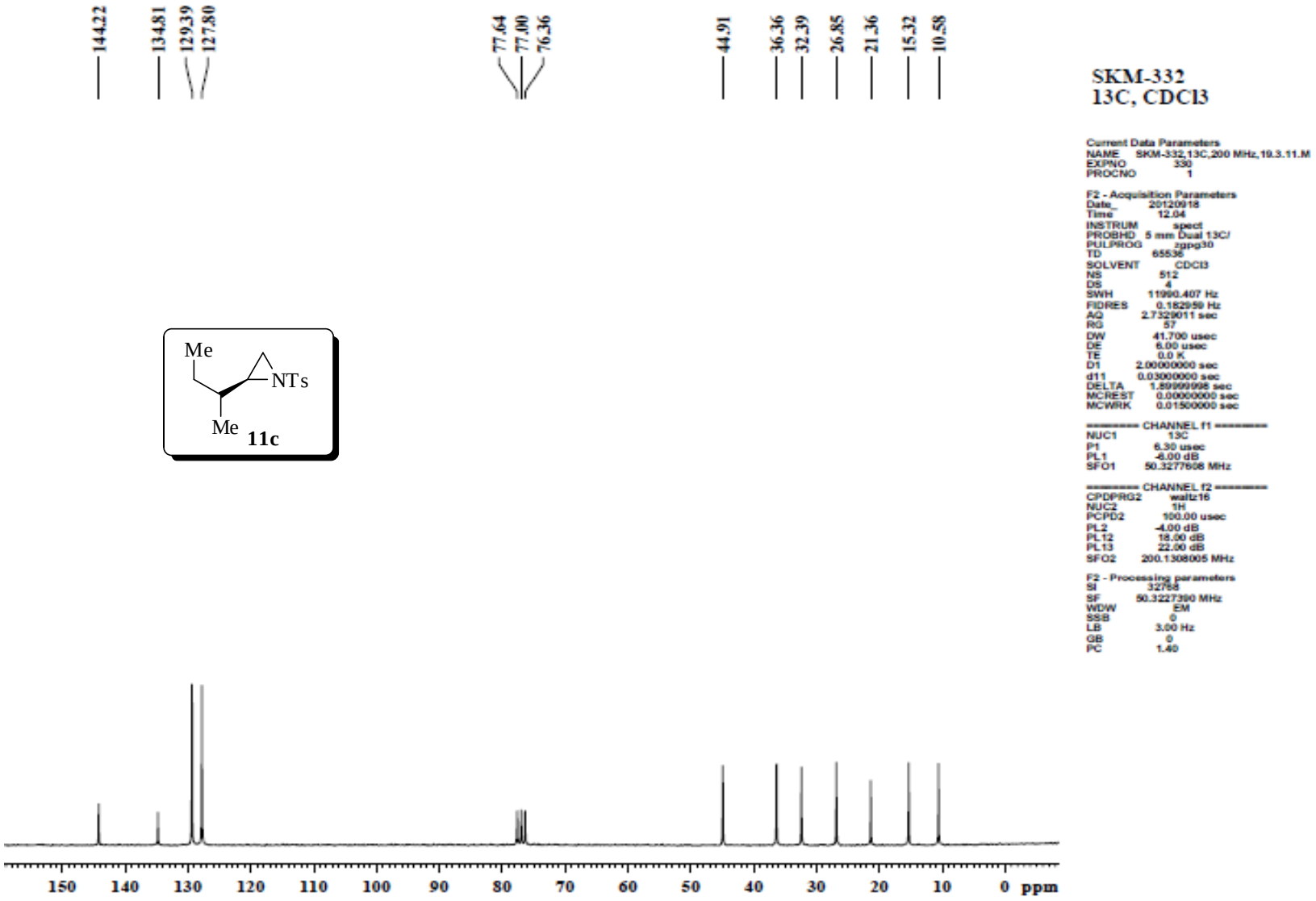

Figure 26: ^{13}C -NMR Spectrum of **11e.**

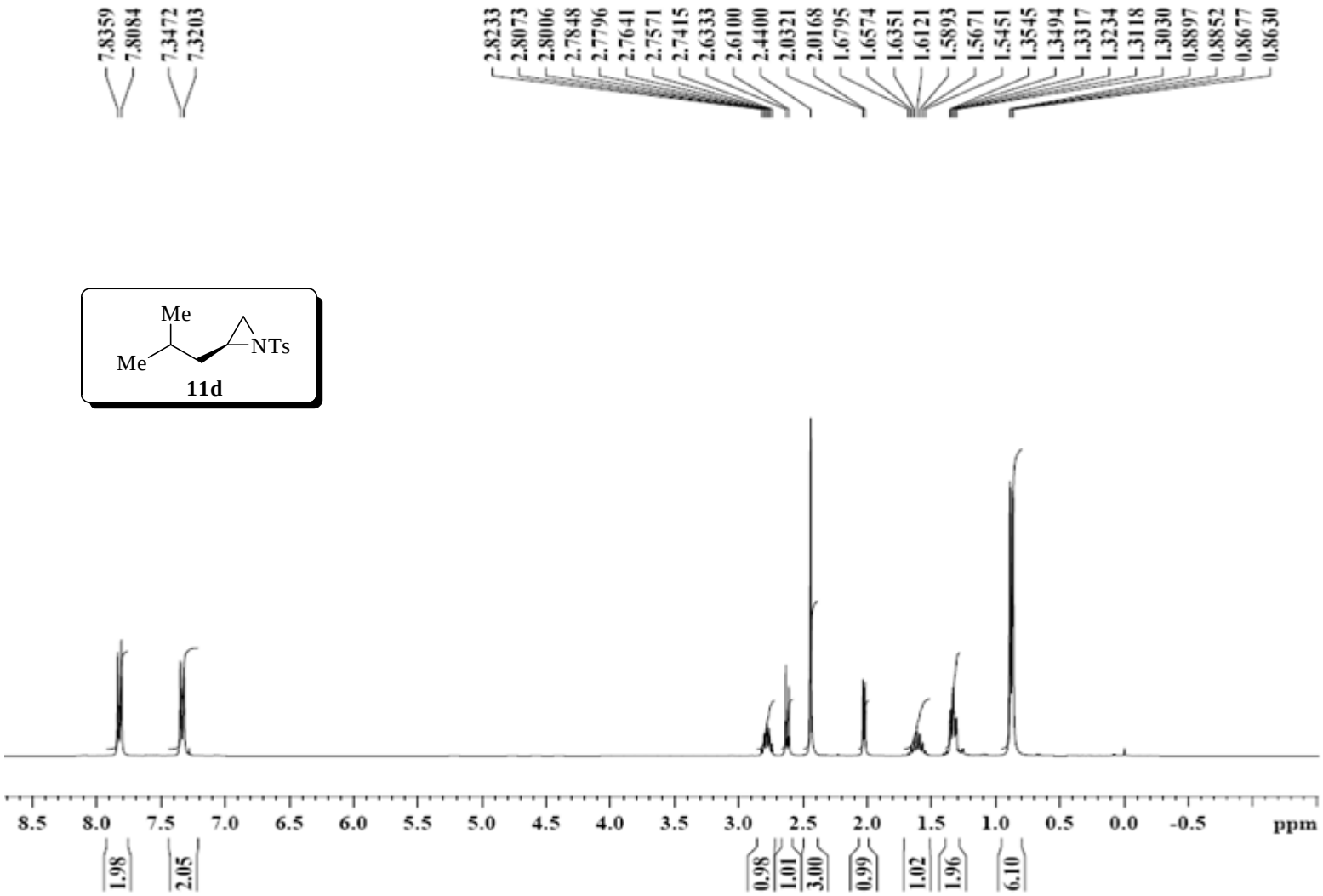

Figure 27: ^{1}H -NMR Spectrum of **11d.**

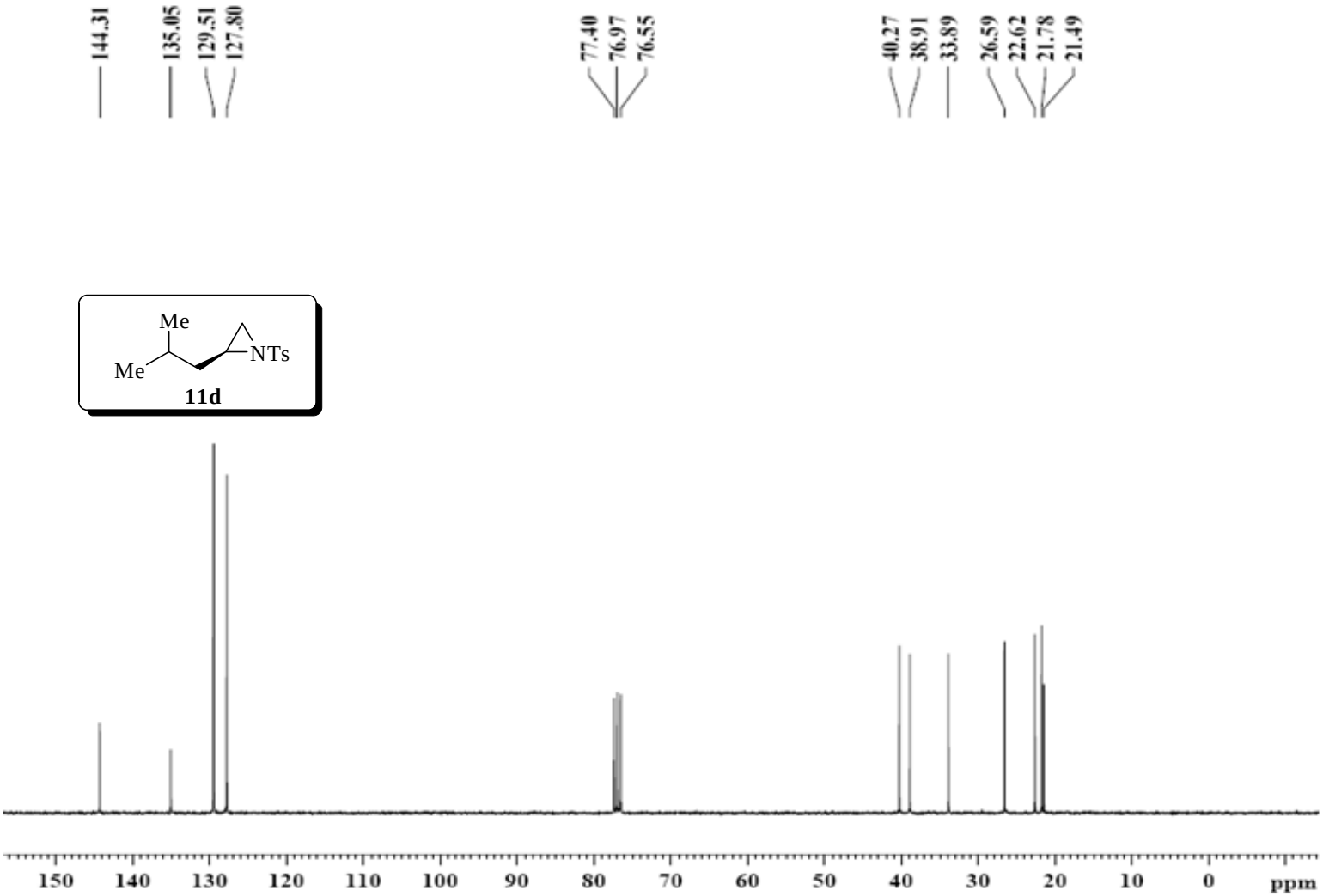

Figure 28: ^{13}C -NMR Spectrum of **11d.**

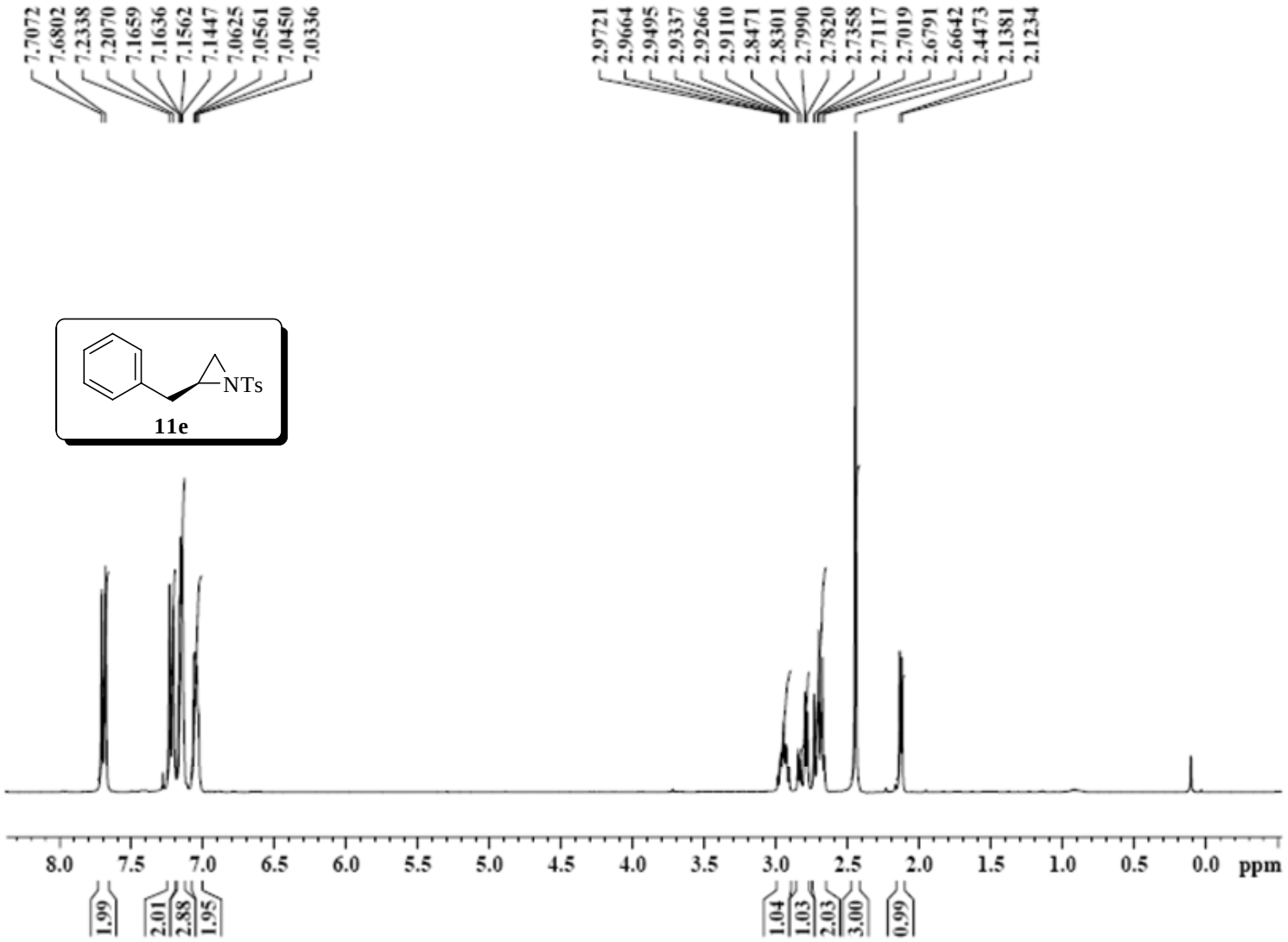

Figure 29: ^{1}H -NMR Spectrum of **11e.**

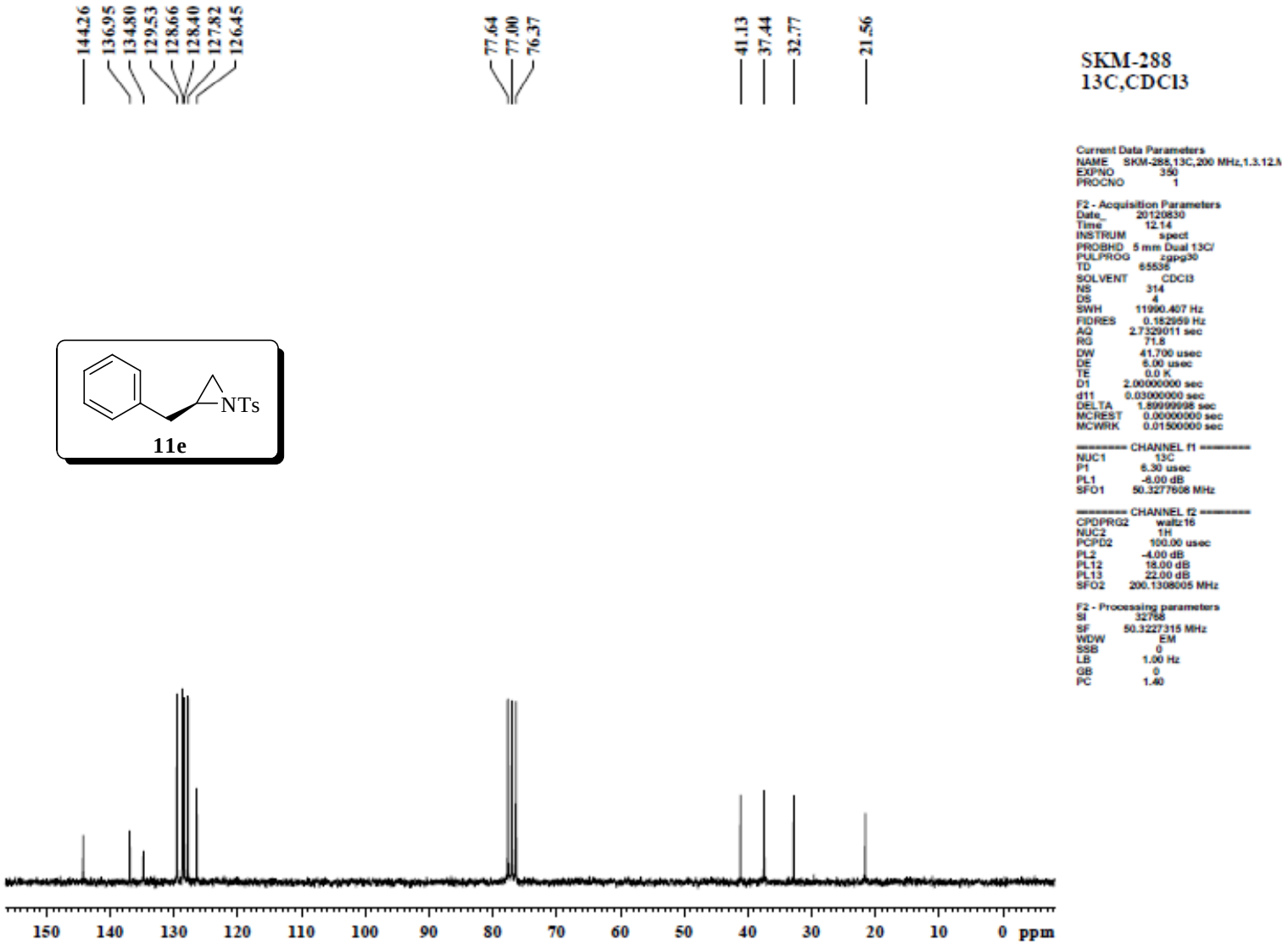

Figure 30: ^{13}C -NMR Spectrum of **11e.**

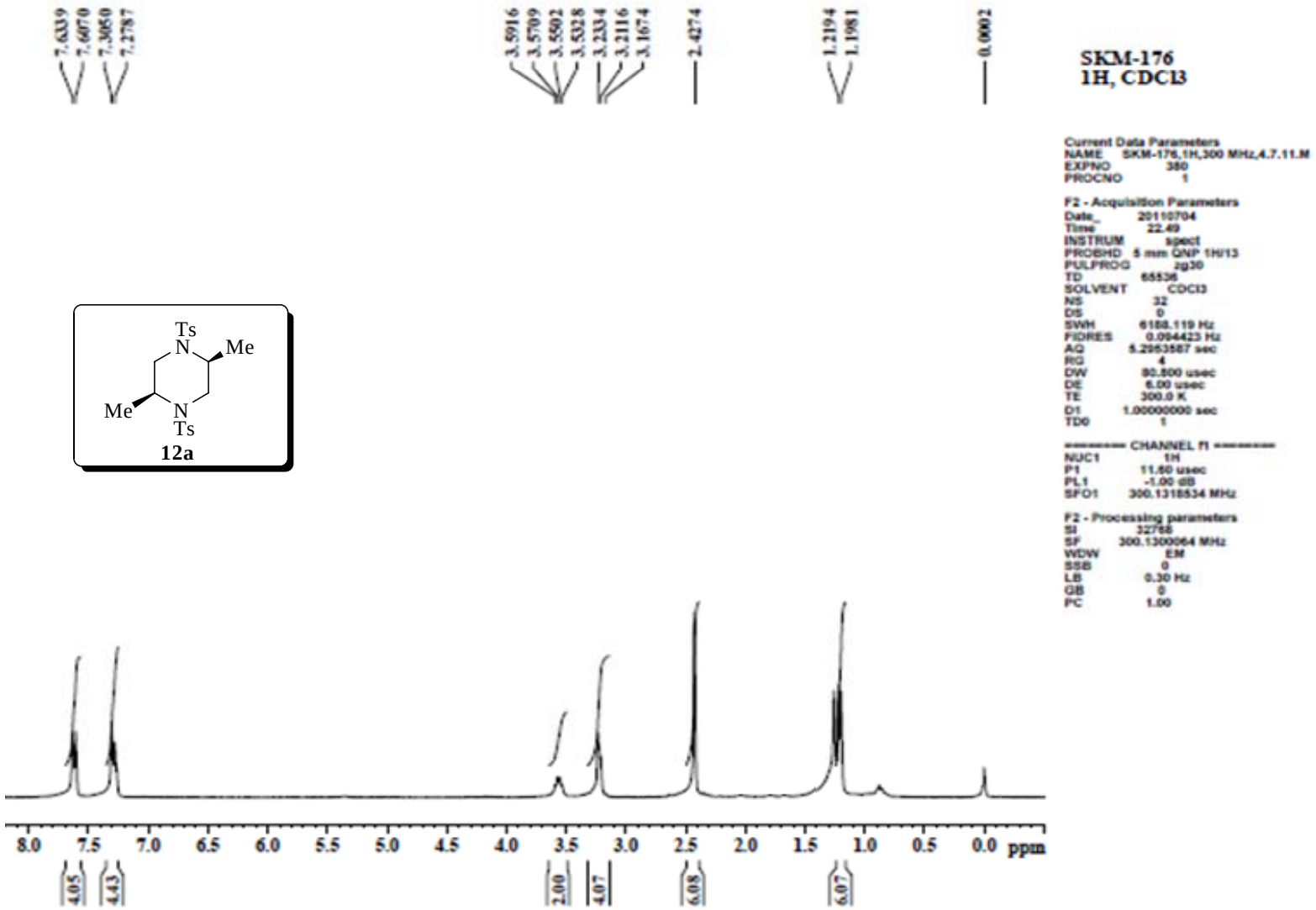

Figure 31: ^{1}H -NMR Spectrum of **12a.**

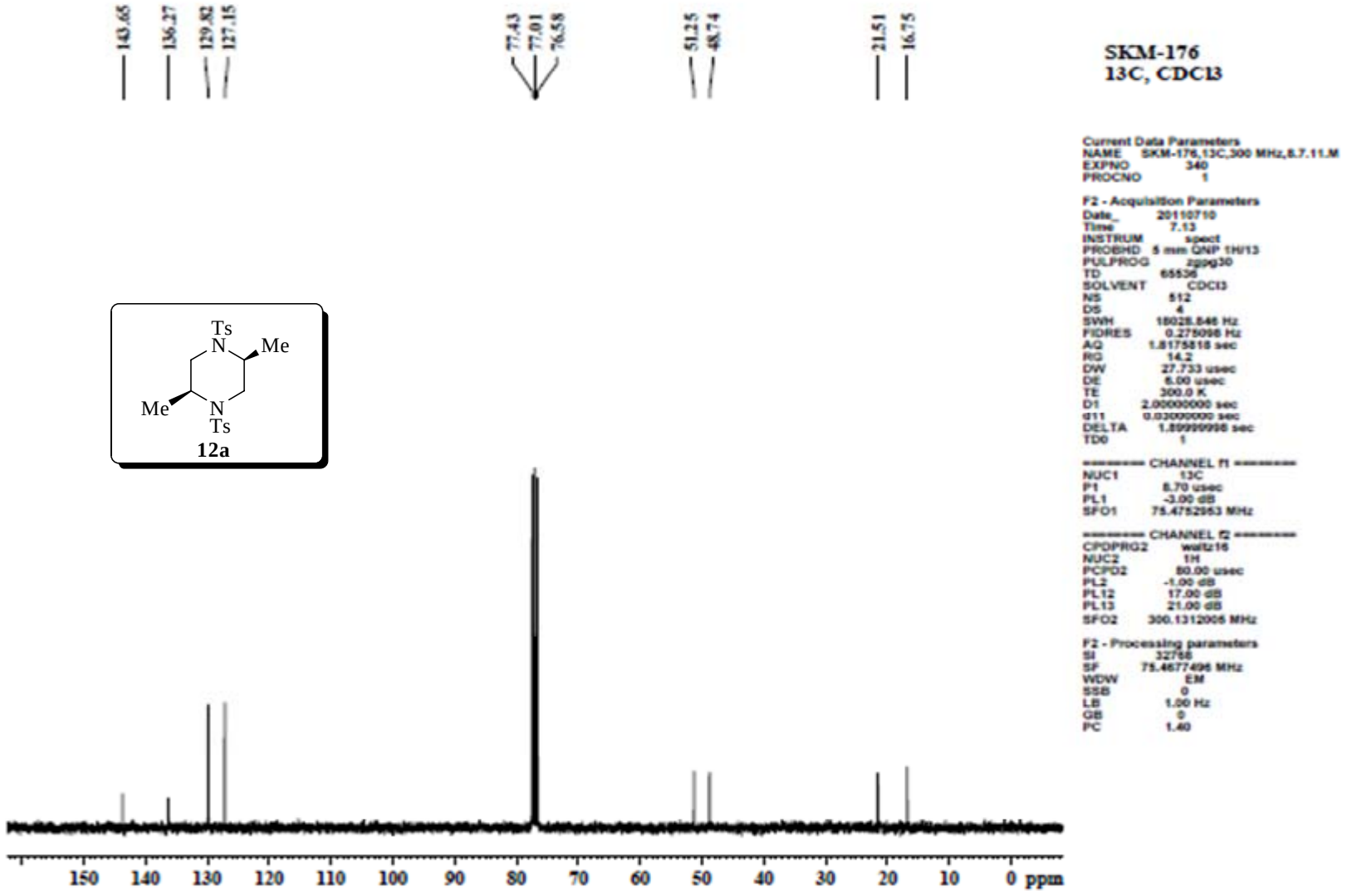

Figure 32: ^{13}C -NMR Spectrum of **12a.**

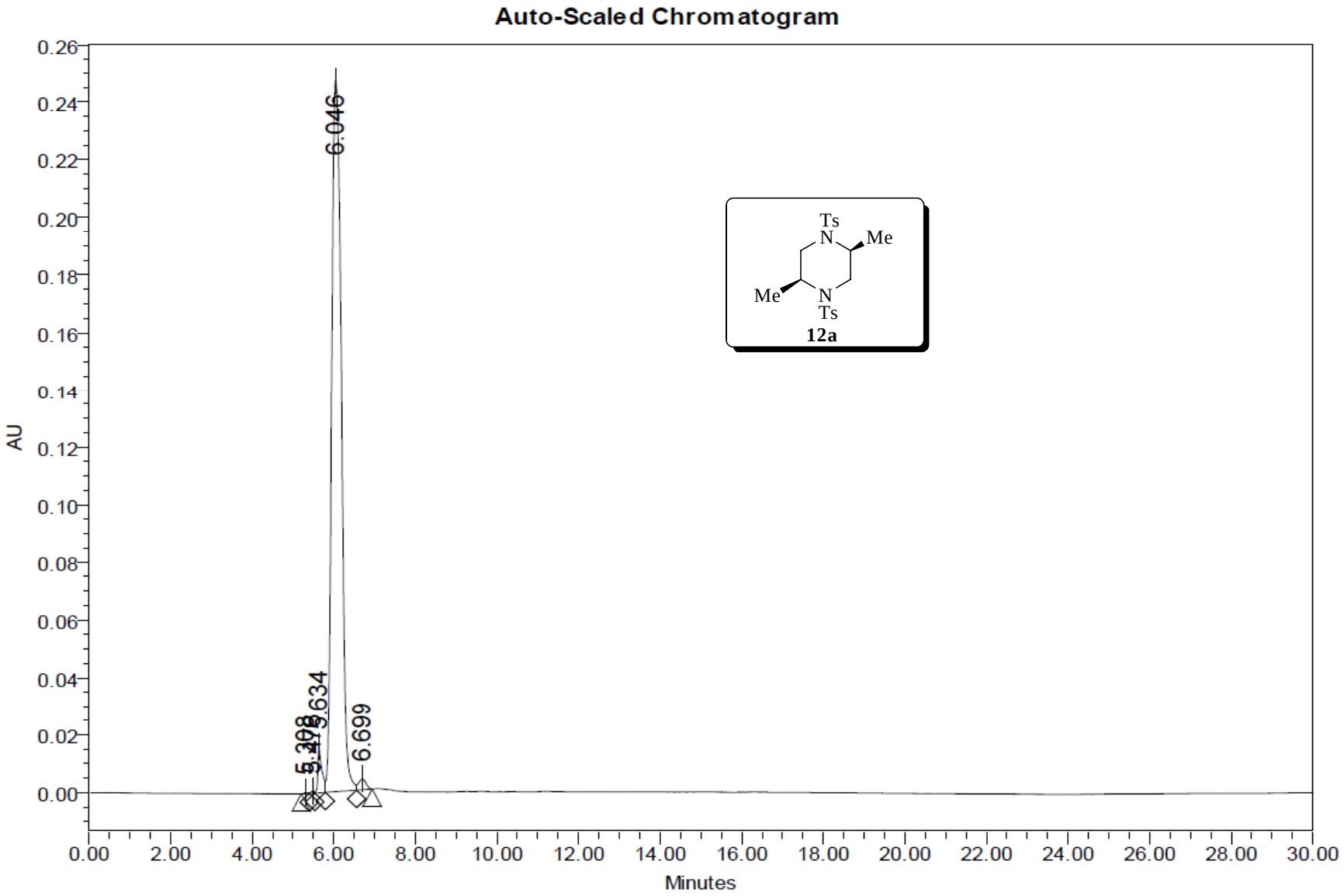

Figure 33: HPLC Spectrum of **12a.**

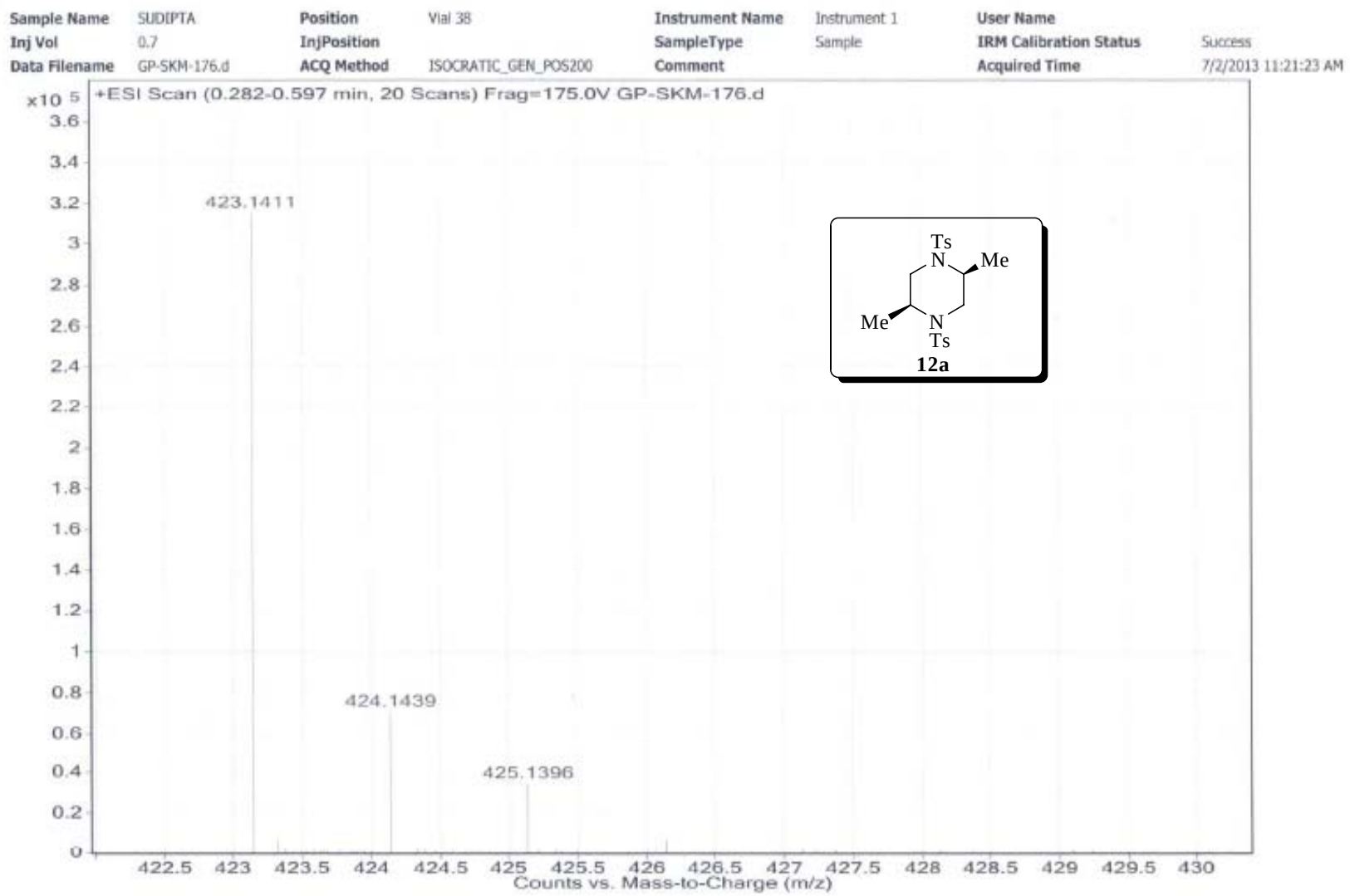

Figure 34: HRMS -Spectrum of **12a.**

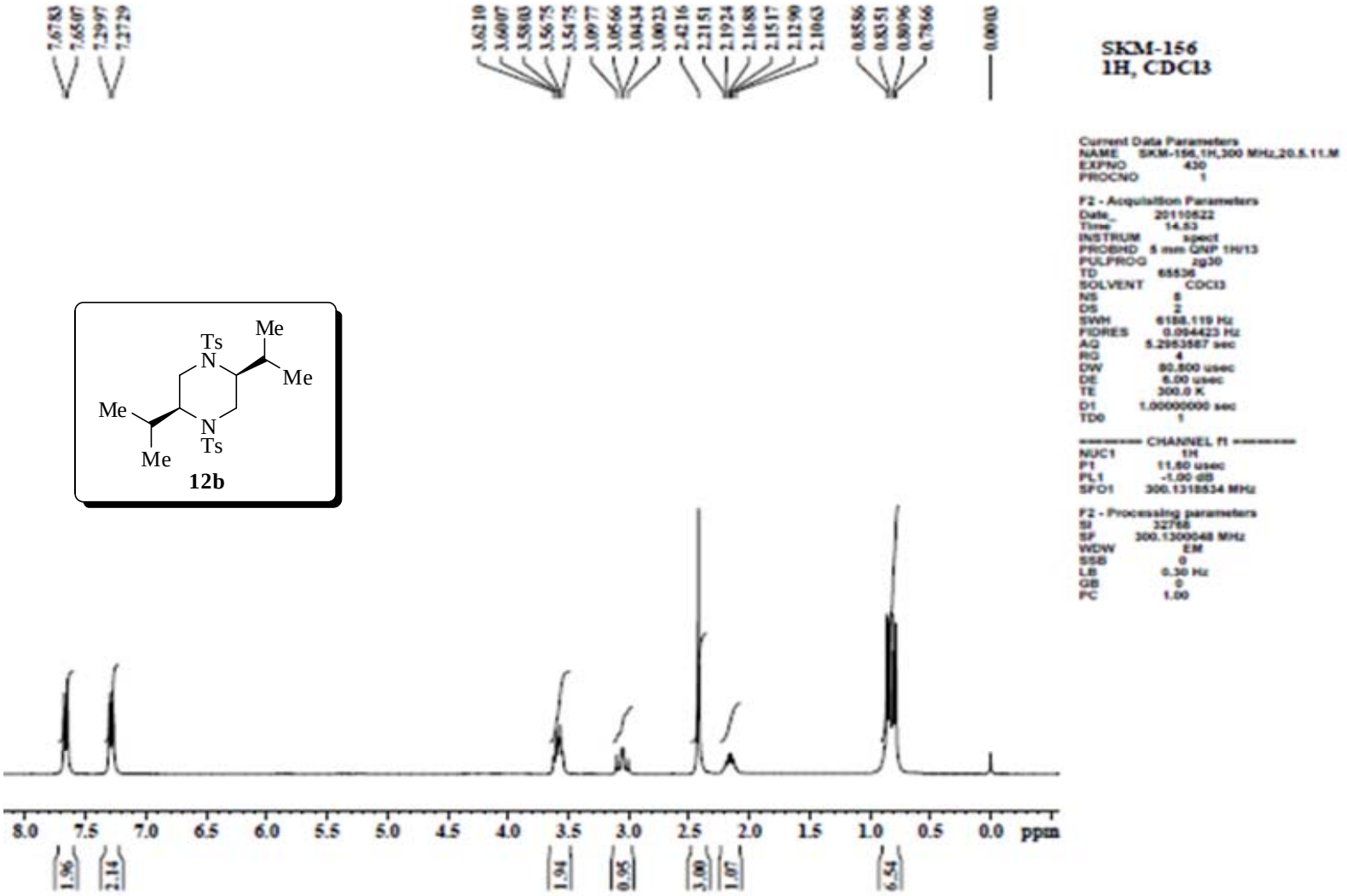

Figure 35: ^{1}H -NMR Spectrum of **12b.**

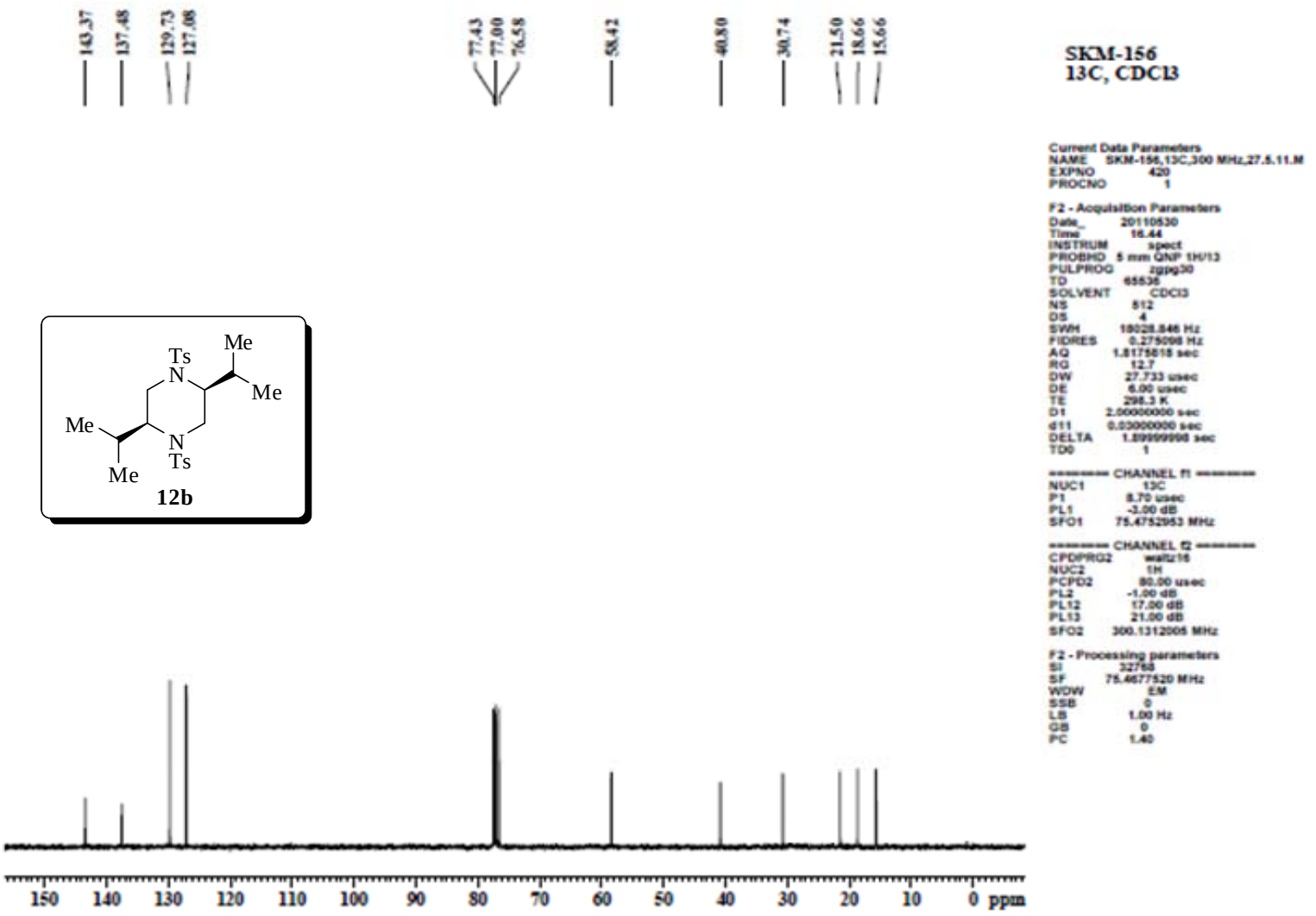

Figure 36: ^{13}C -NMR Spectrum of **12b.**

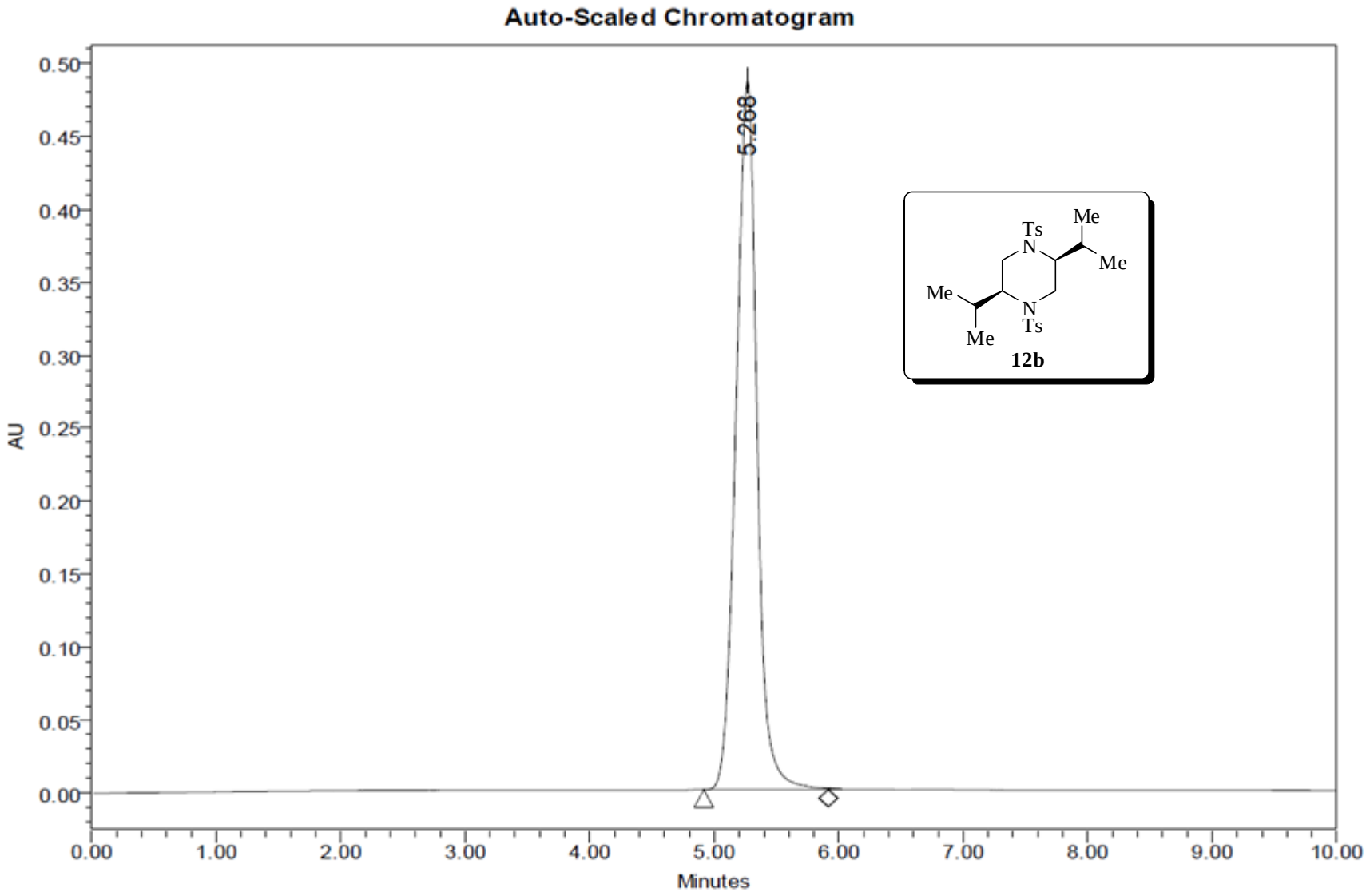

Figure 37: HPLC -Spectrum of **12b.**

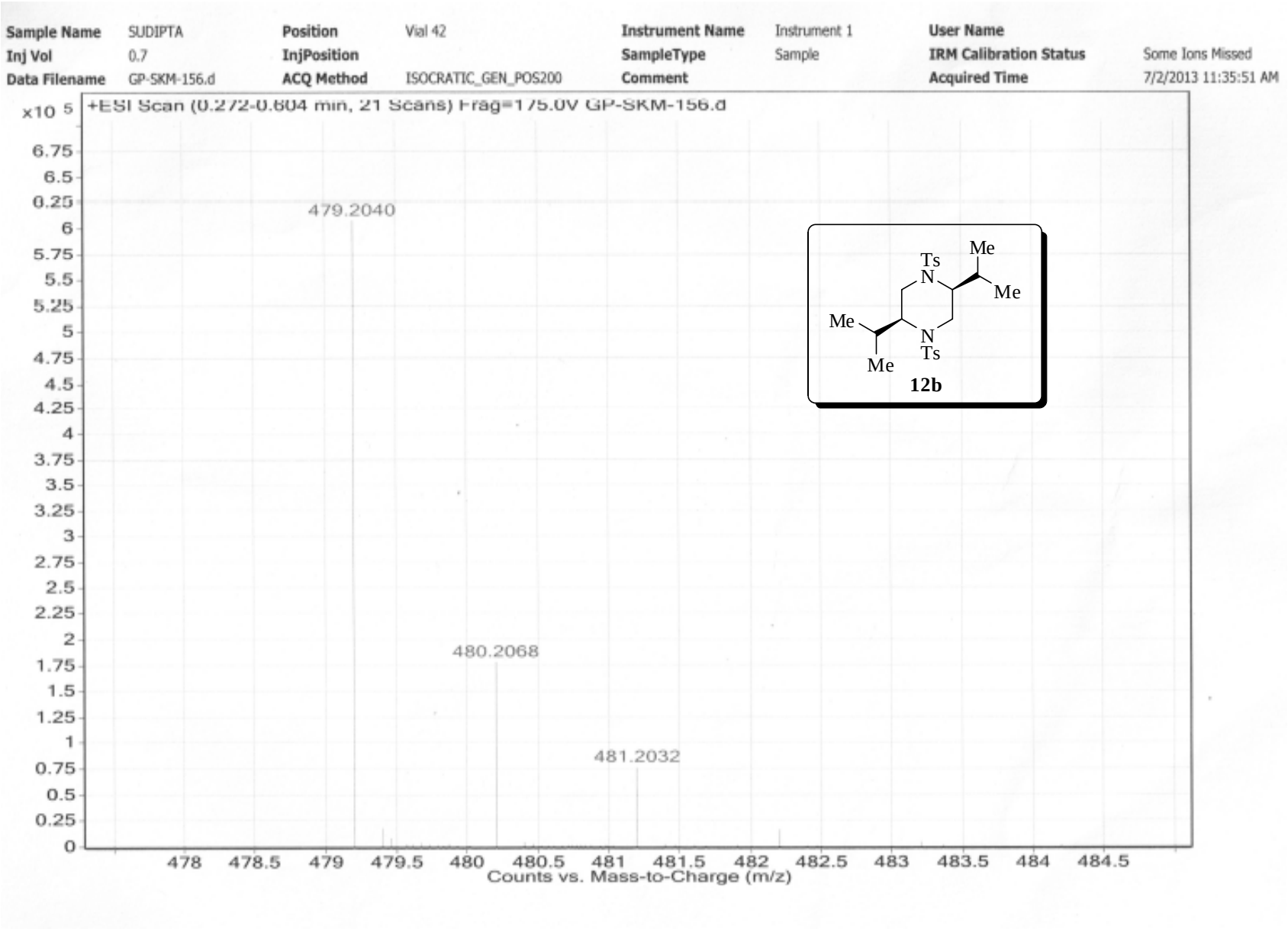

Figure 38: HRMS -Spectrum of **12b.**

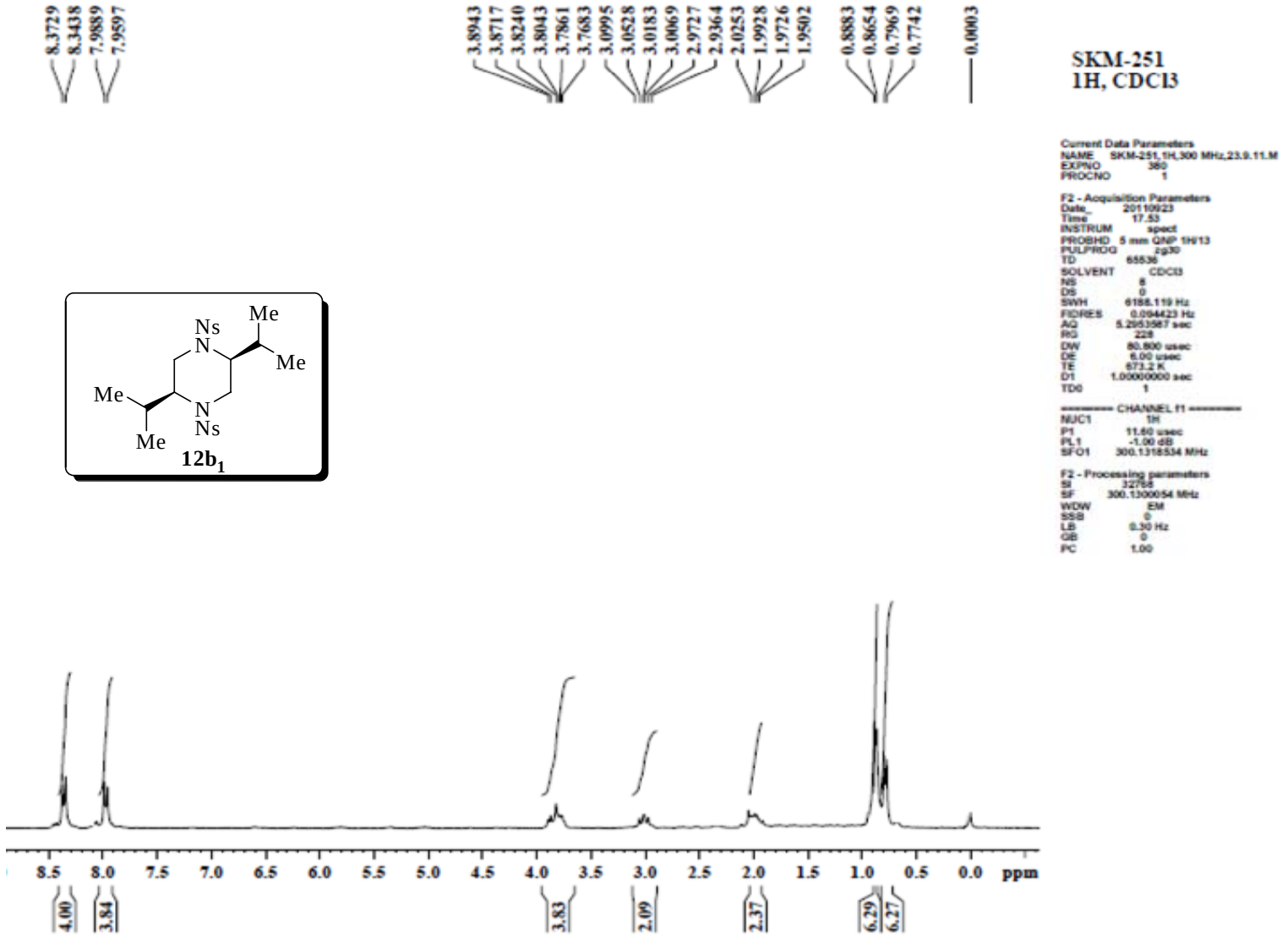

Figure 39: ^{1}H -NMR Spectrum of **12b1.**

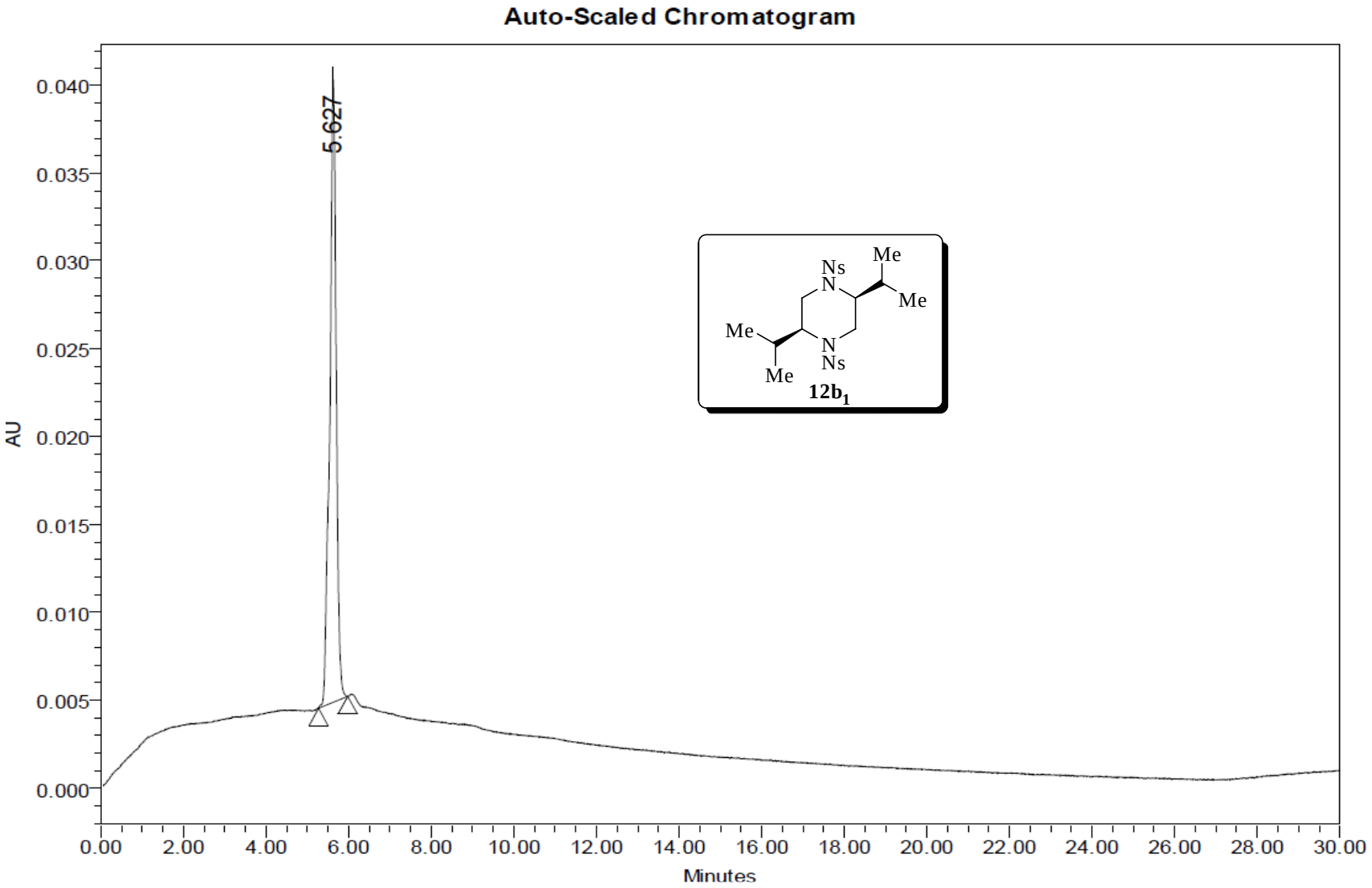

Figure 40: HPLC -Spectrum of **12b1.**

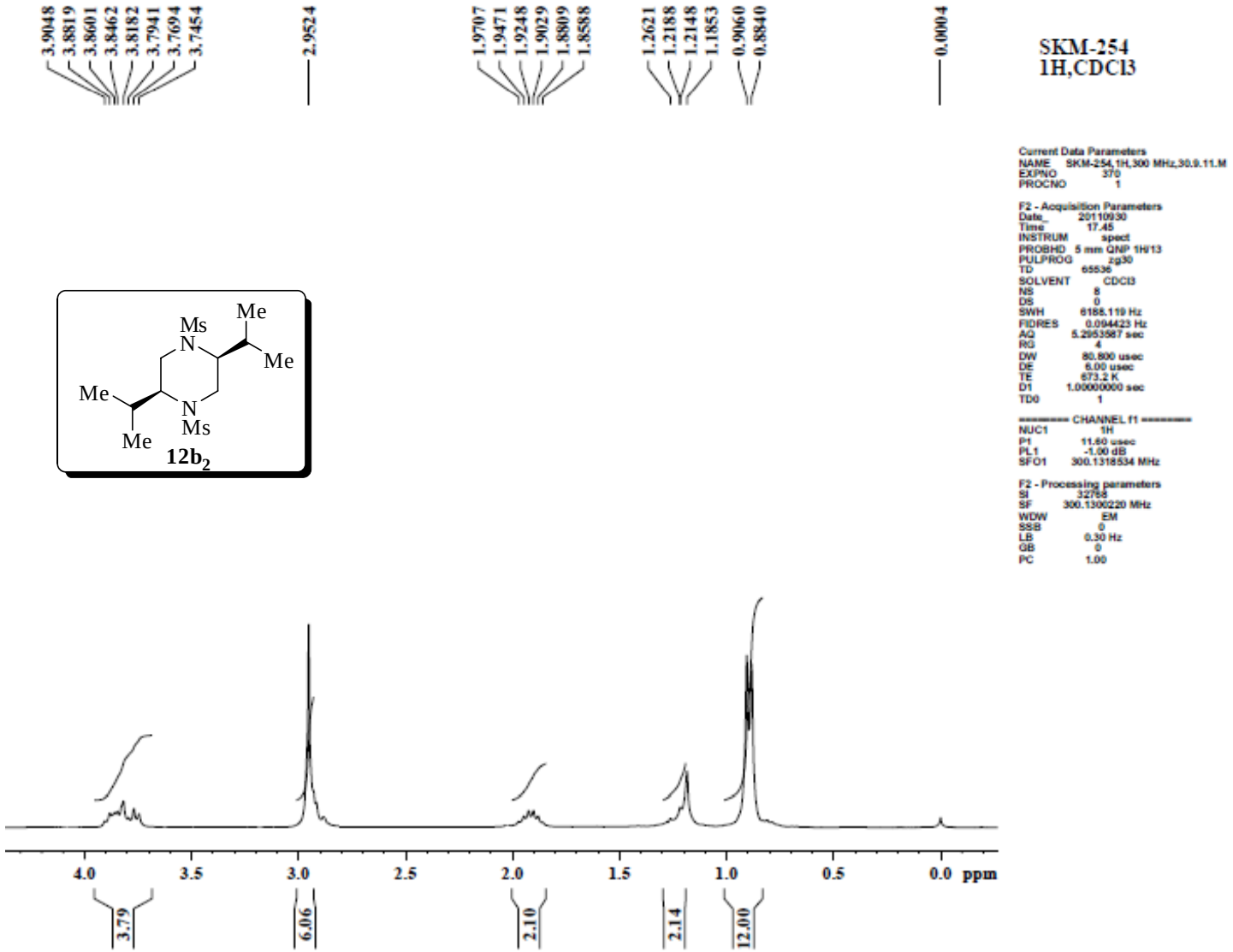

Figure 41: ^{1}H -NMR Spectrum of **12b2.**

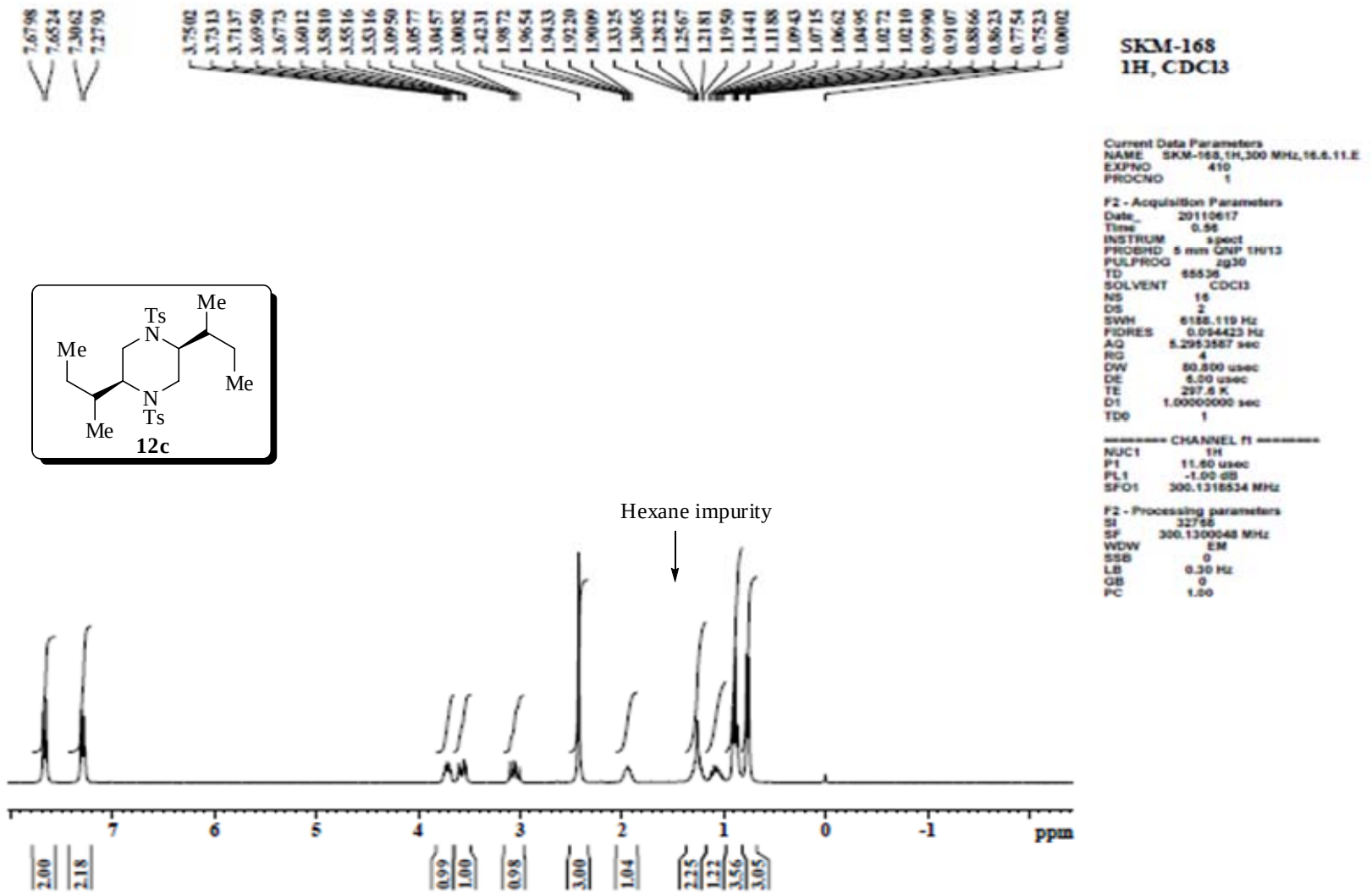

Figure 42: ^{1}H -NMR Spectrum of **12c.**

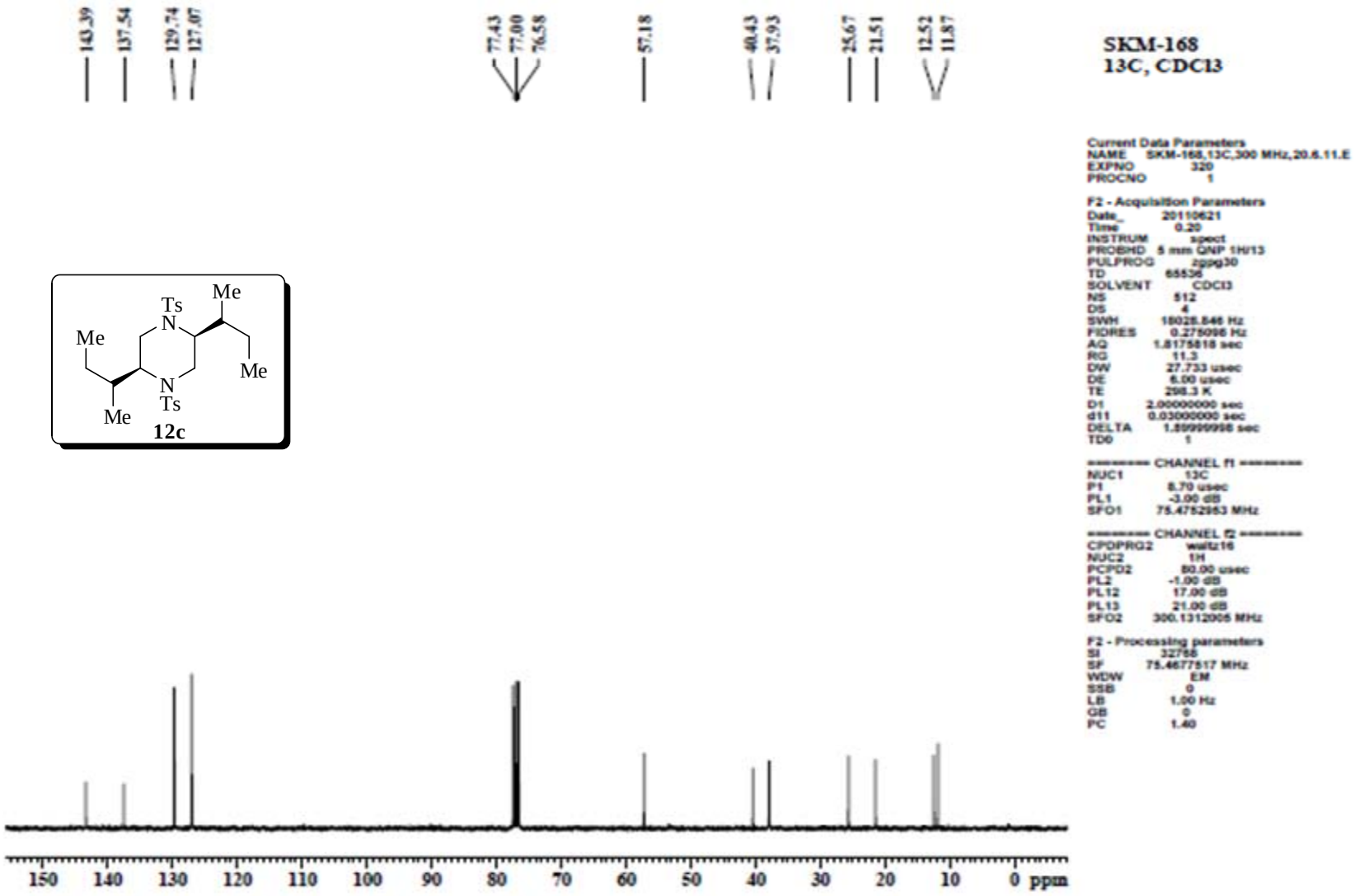

Figure 43: ^{13}C -NMR Spectrum of **12c.**

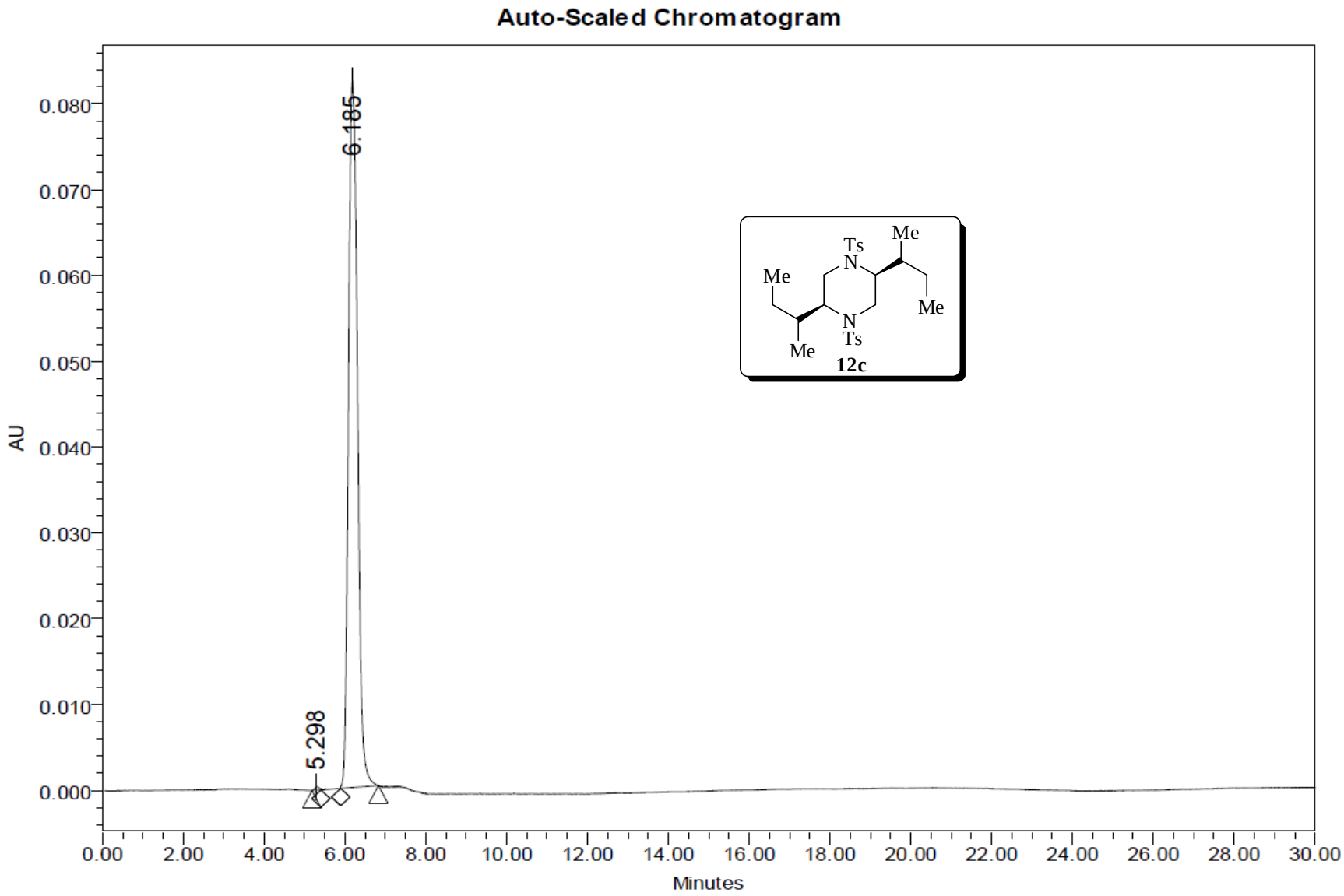

Figure 44: HPLC -Spectrum of **12c.**

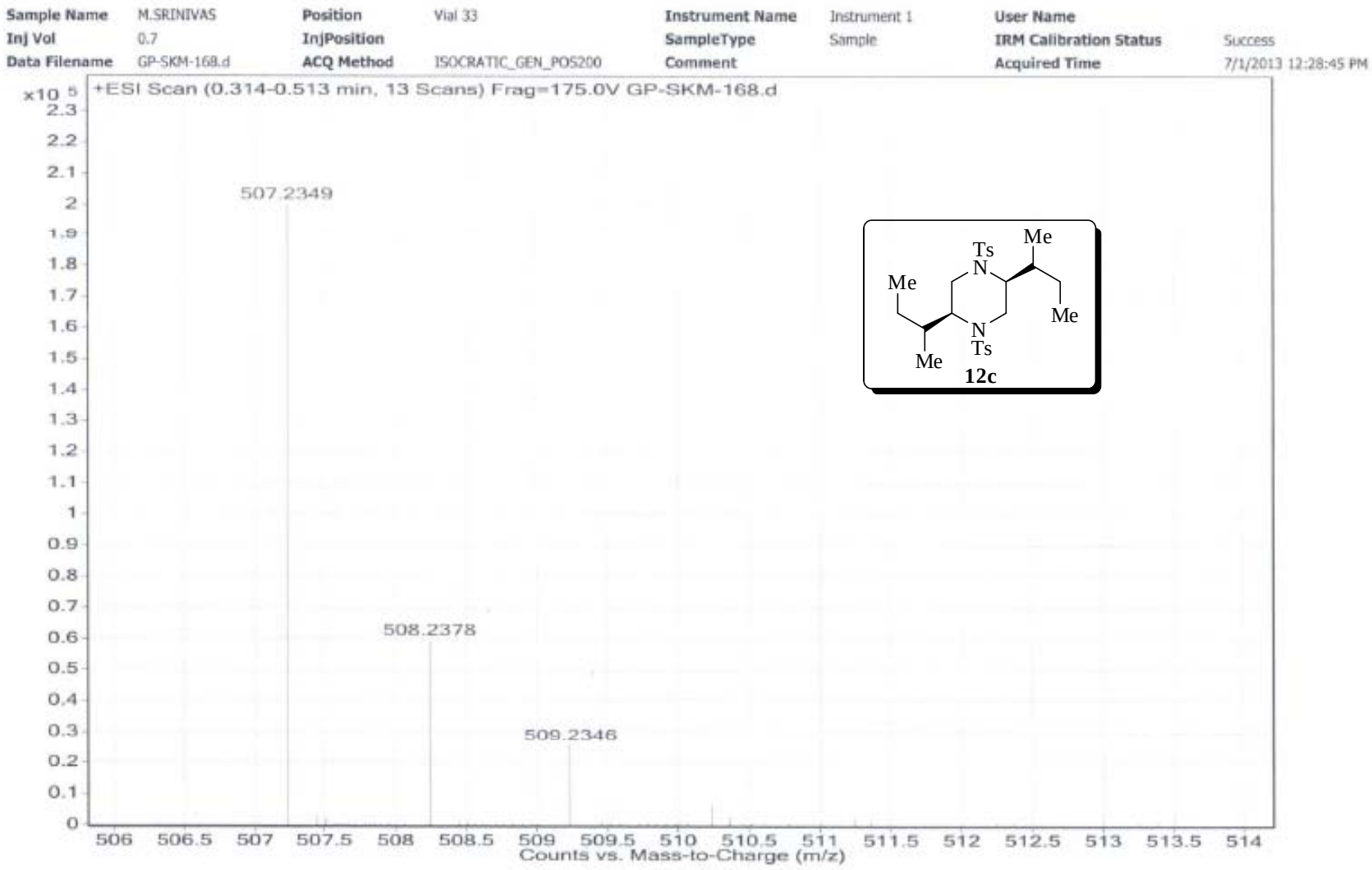

Figure 45: HRMS -Spectrum of **12c.**

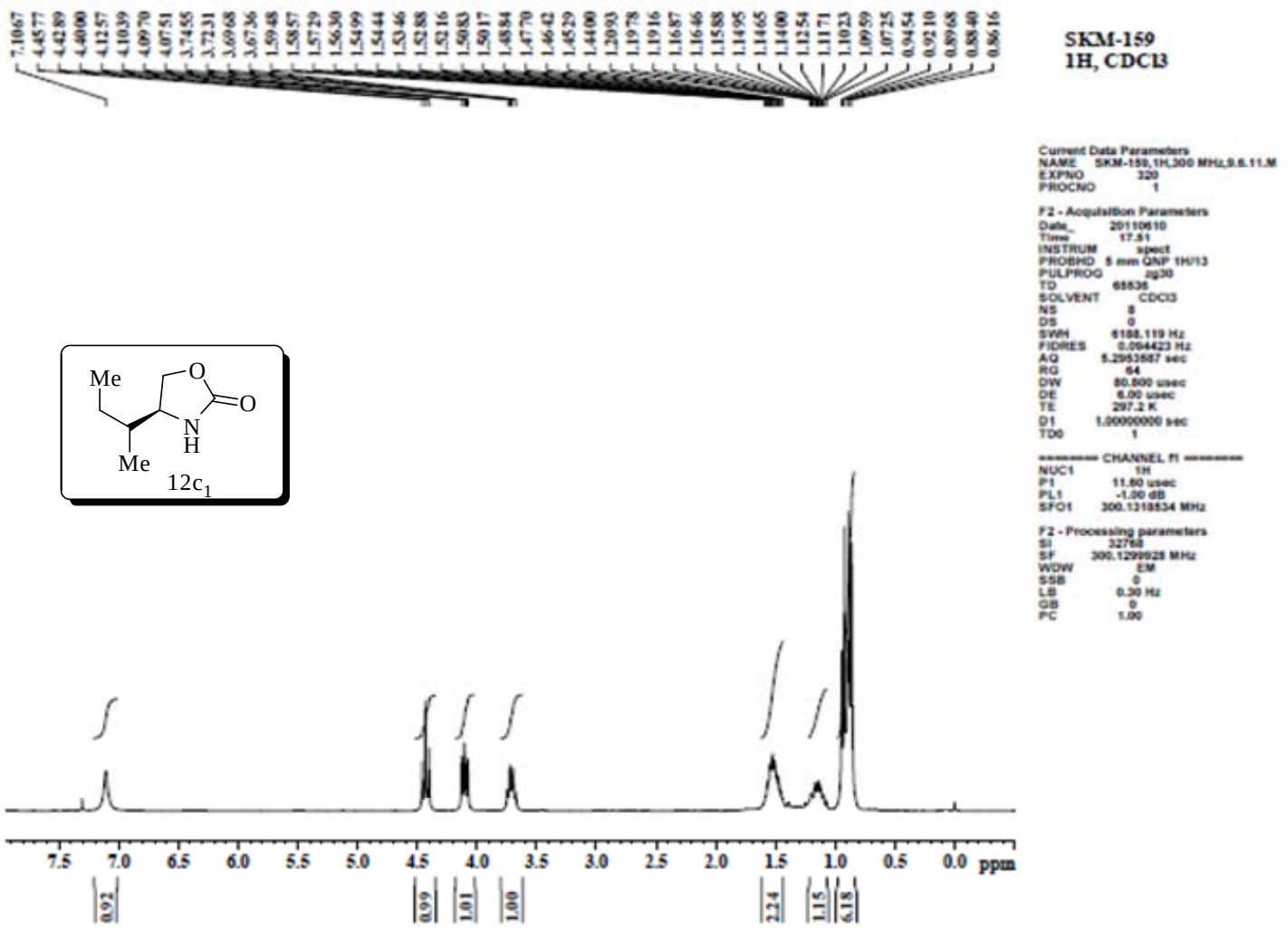

Figure 46: ^{1}H -NMR Spectrum of **12c1.**

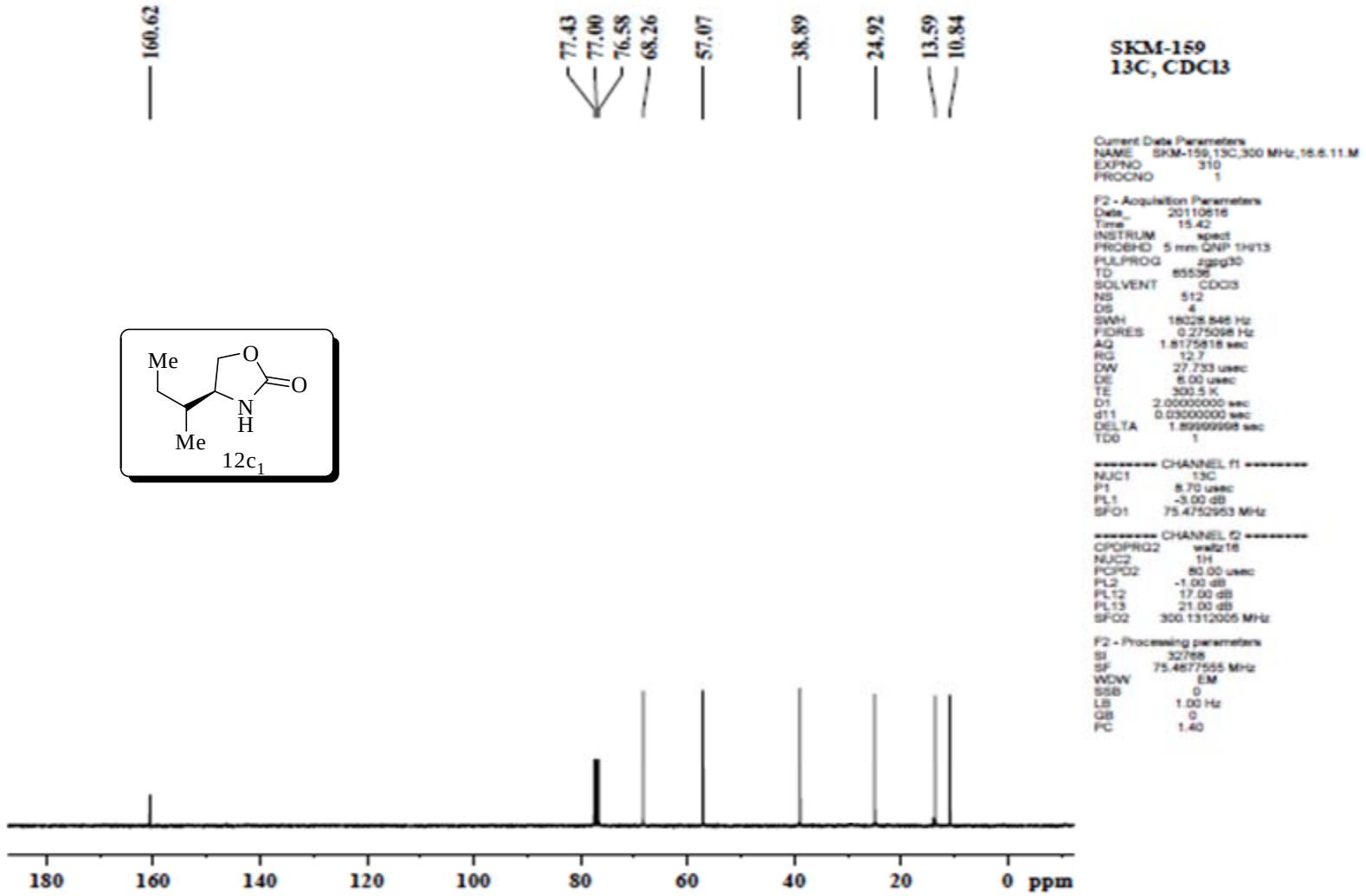

Figure 47: ^{13}C -NMR Spectrum of **12c1.**

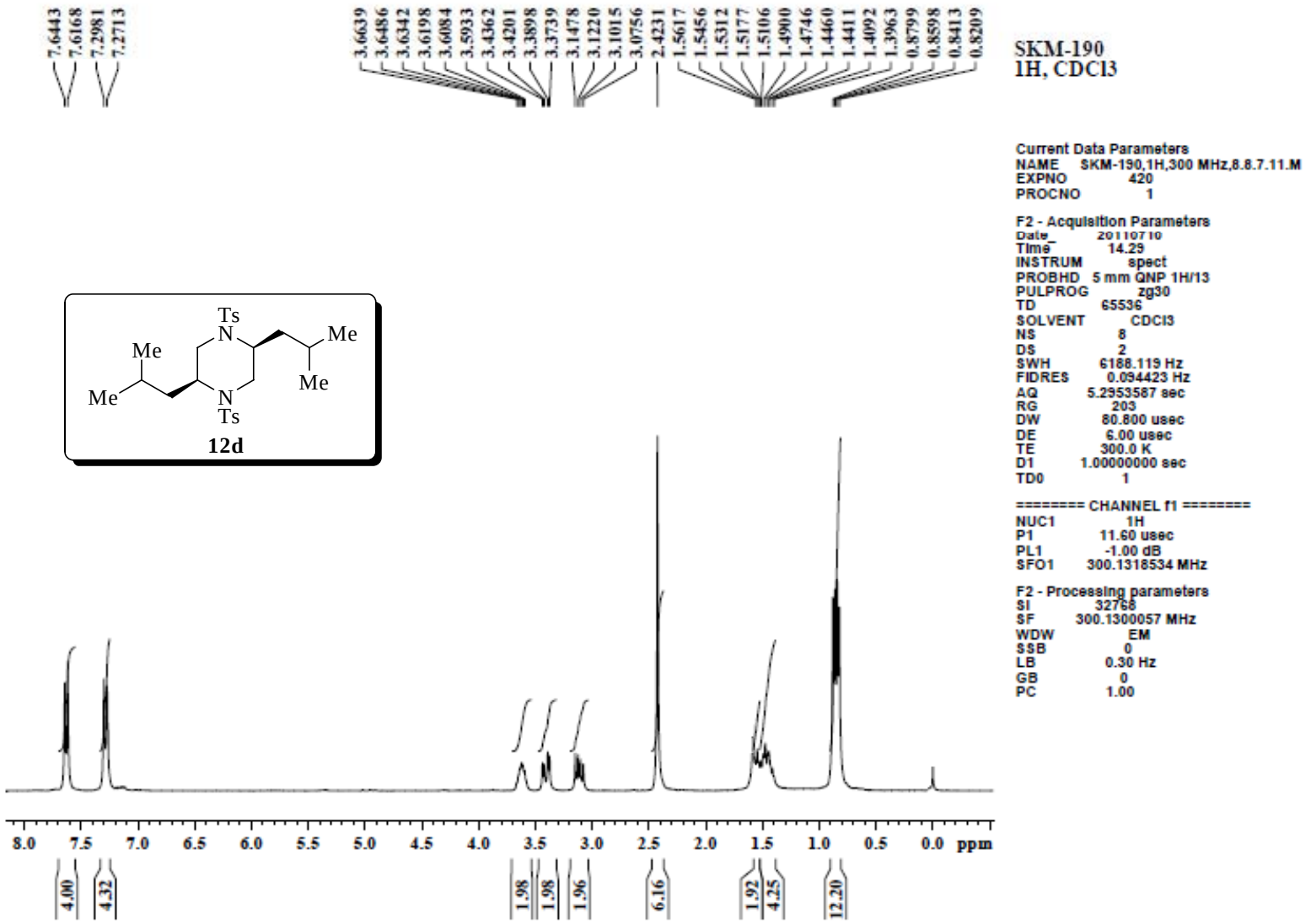

Figure 48: ^{1}H -NMR Spectrum of **12d.**

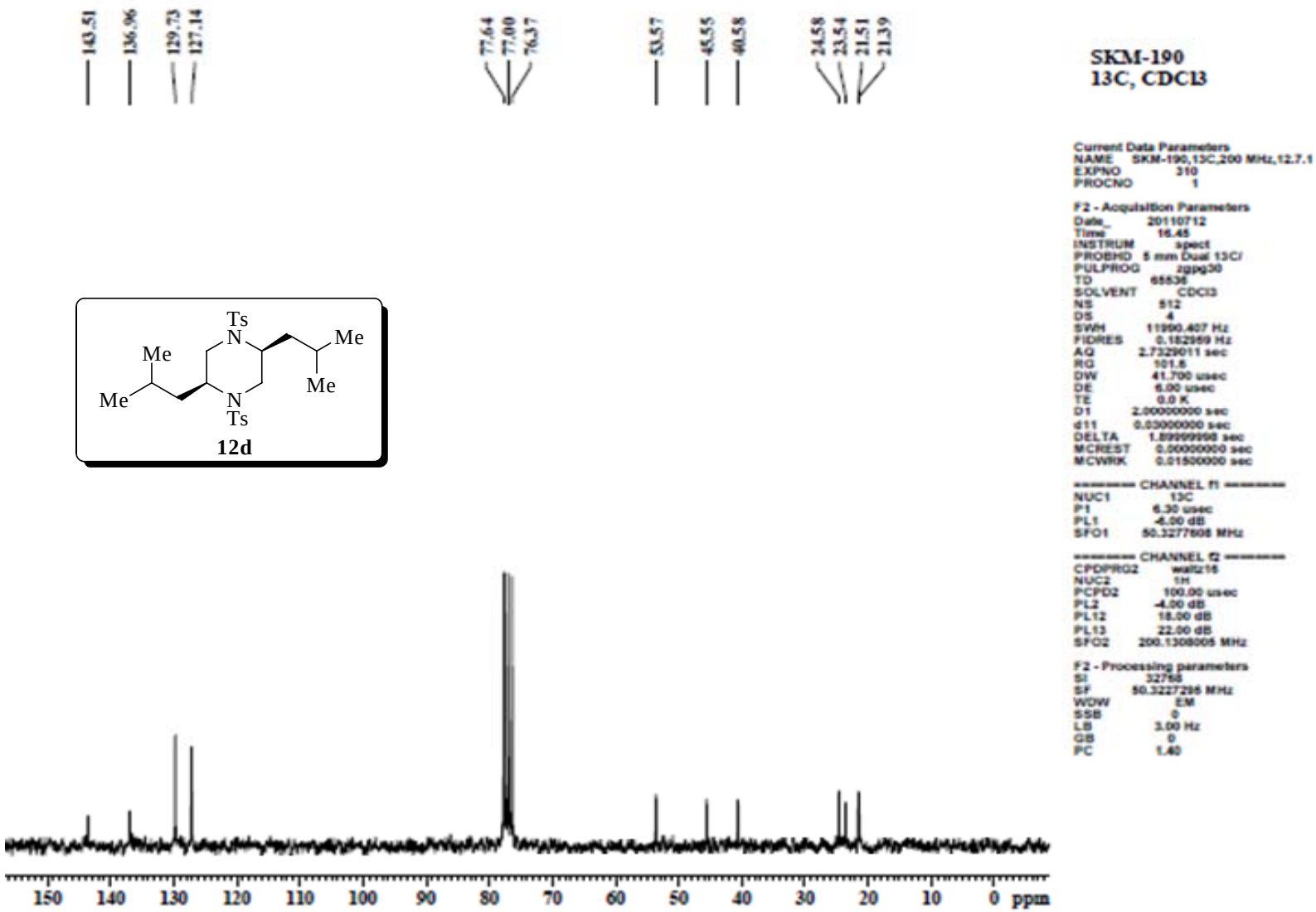

Figure 49: ^{13}C -NMR Spectrum of **11c.**

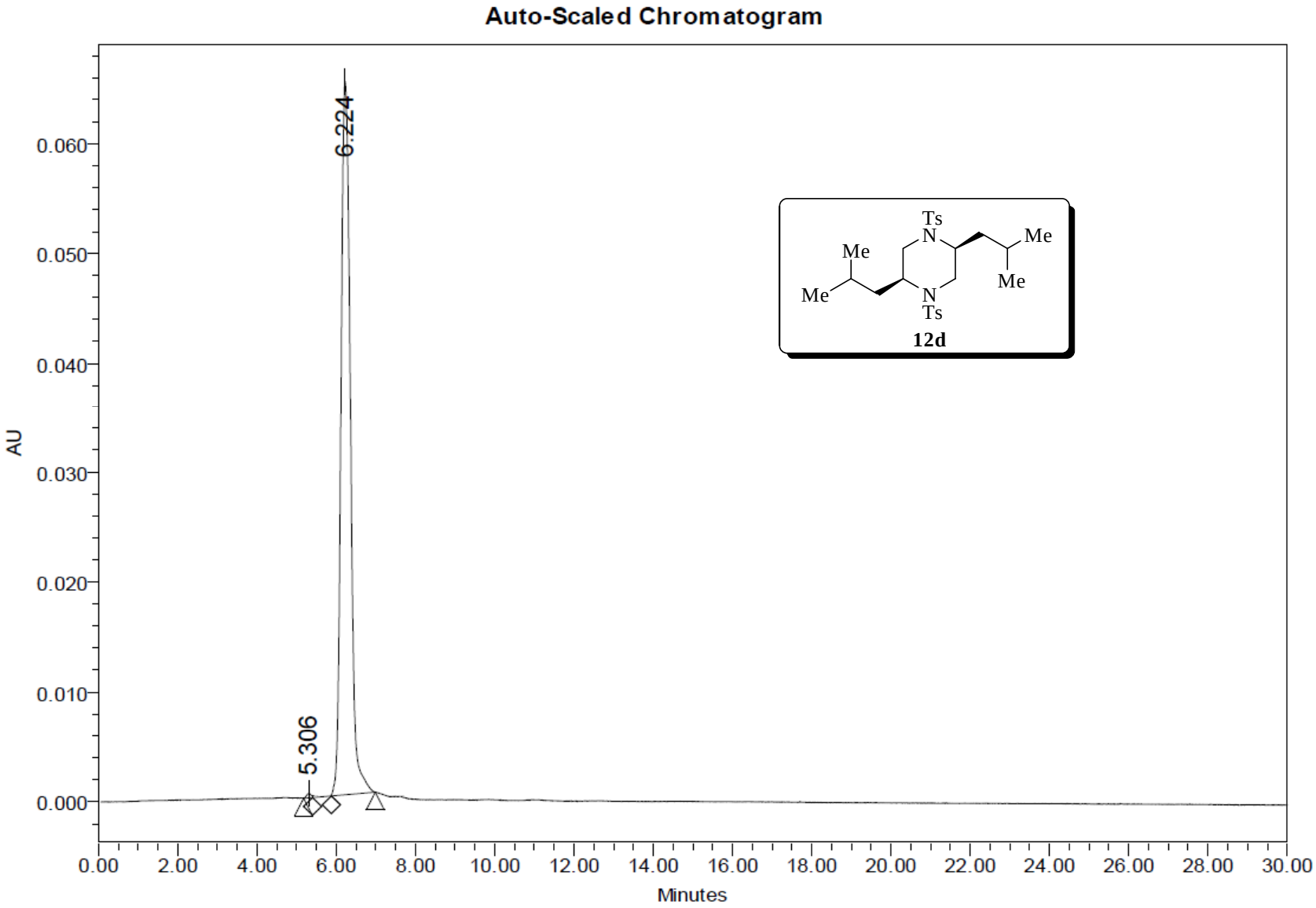

Figure 50: HPLC -Spectrum of **12d.**

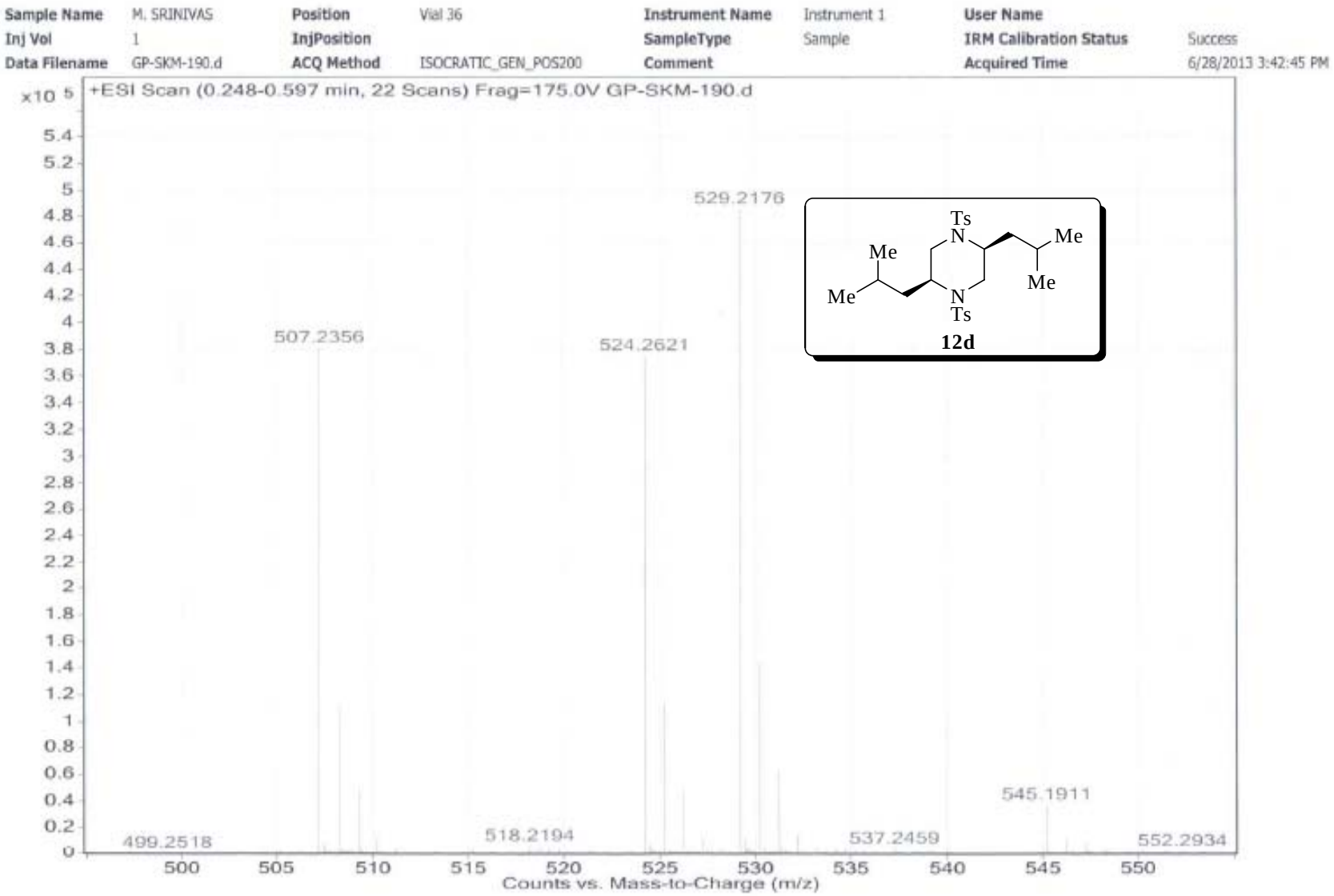

Figure 51: HRMS -Spectrum of **12d.**

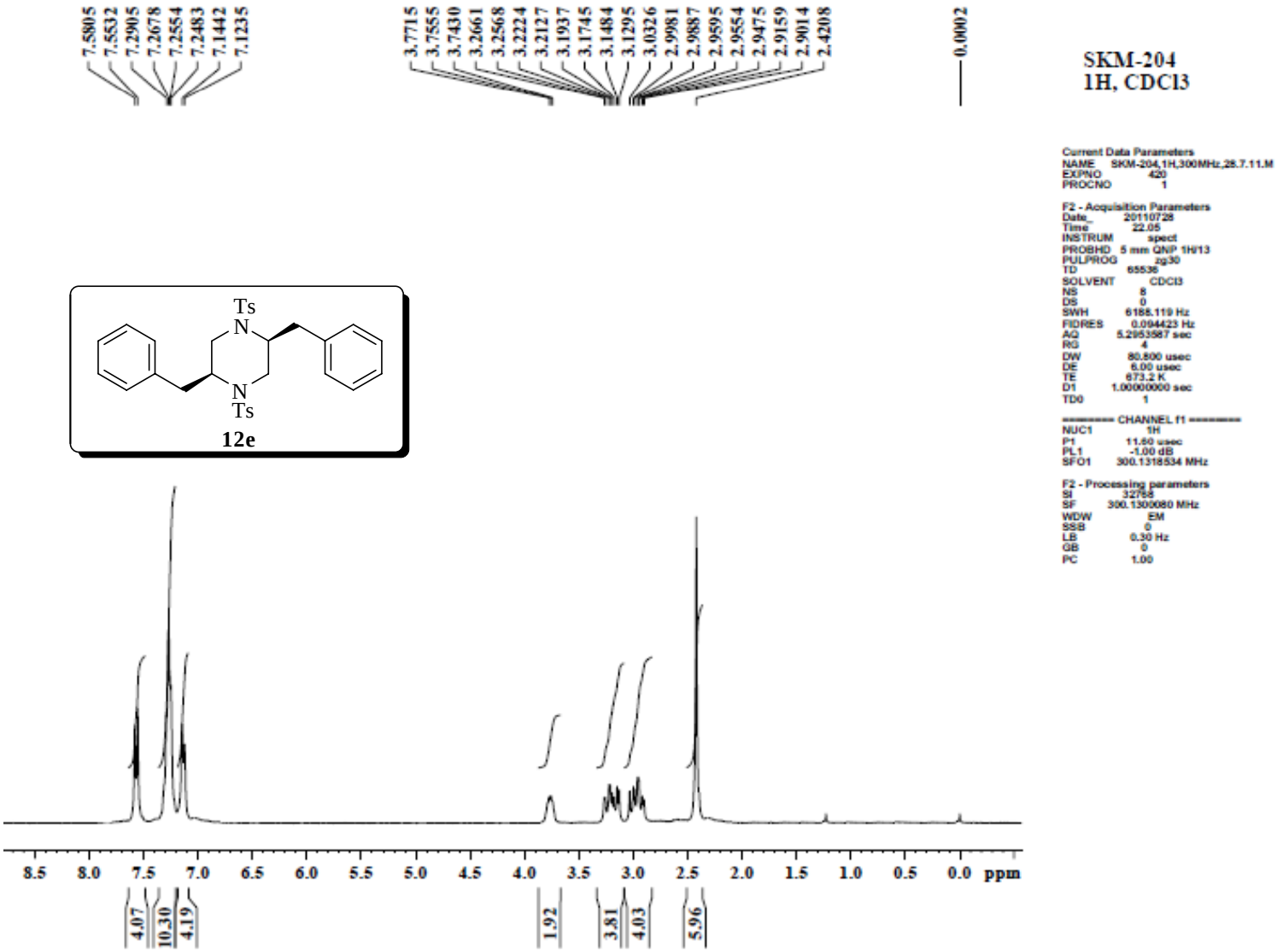

Figure 52: ^{1}H -NMR Spectrum of **12e.**

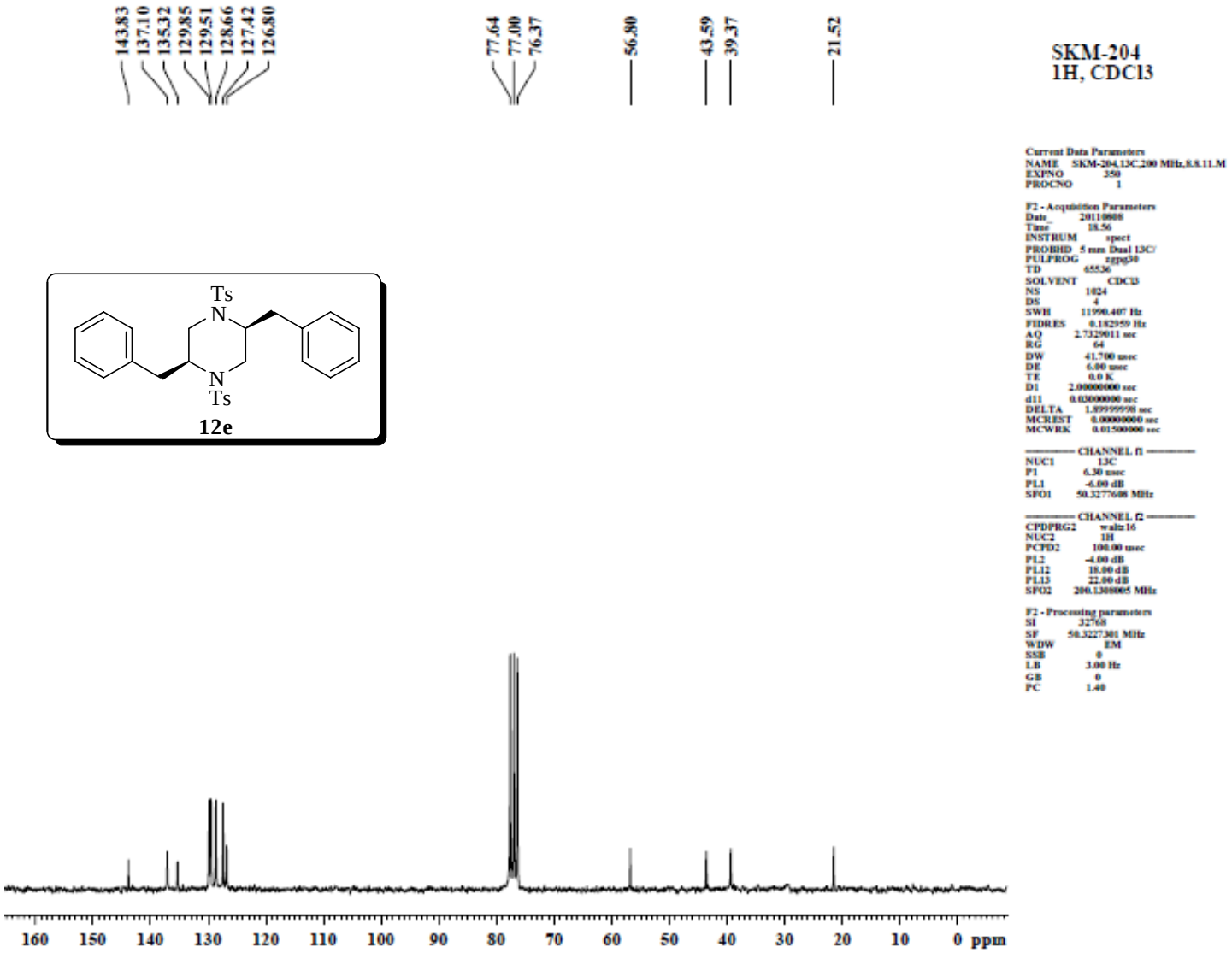

Figure 53: ^{13}C -NMR Spectrum of **12e.**

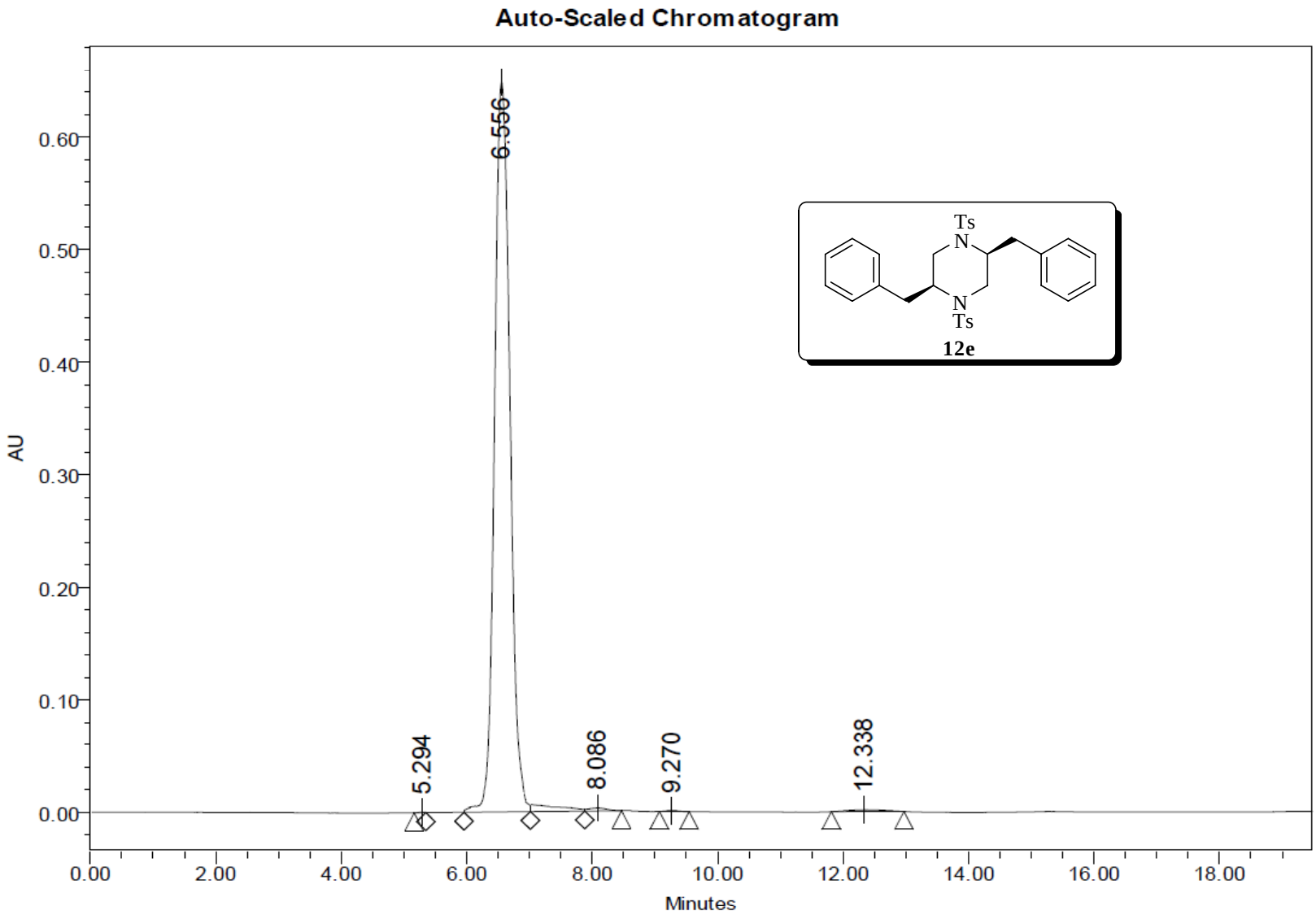

Figure 54: HPLC -Spectrum of **12e.**

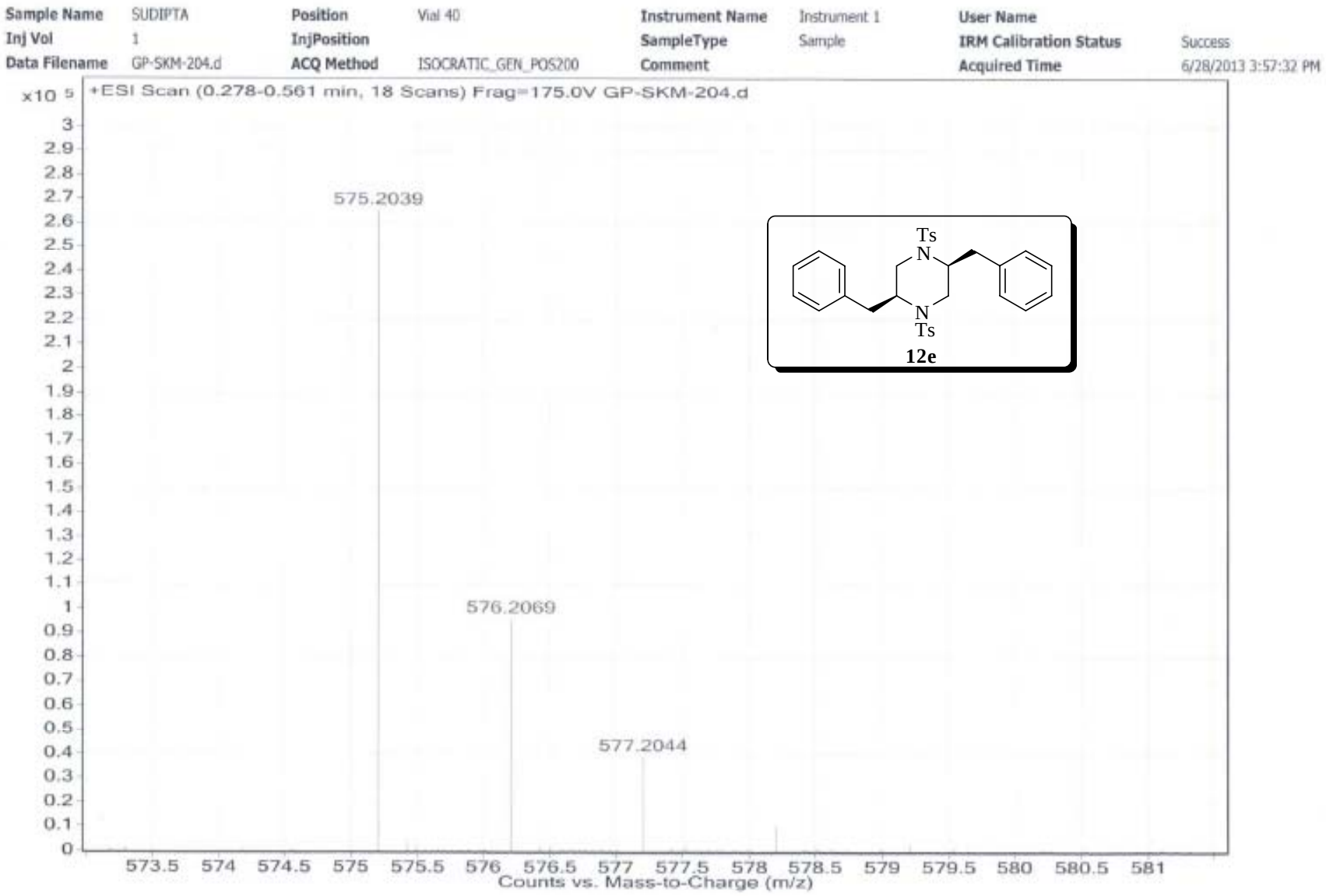

Figure 55: HRMS -Spectrum of **12e.**

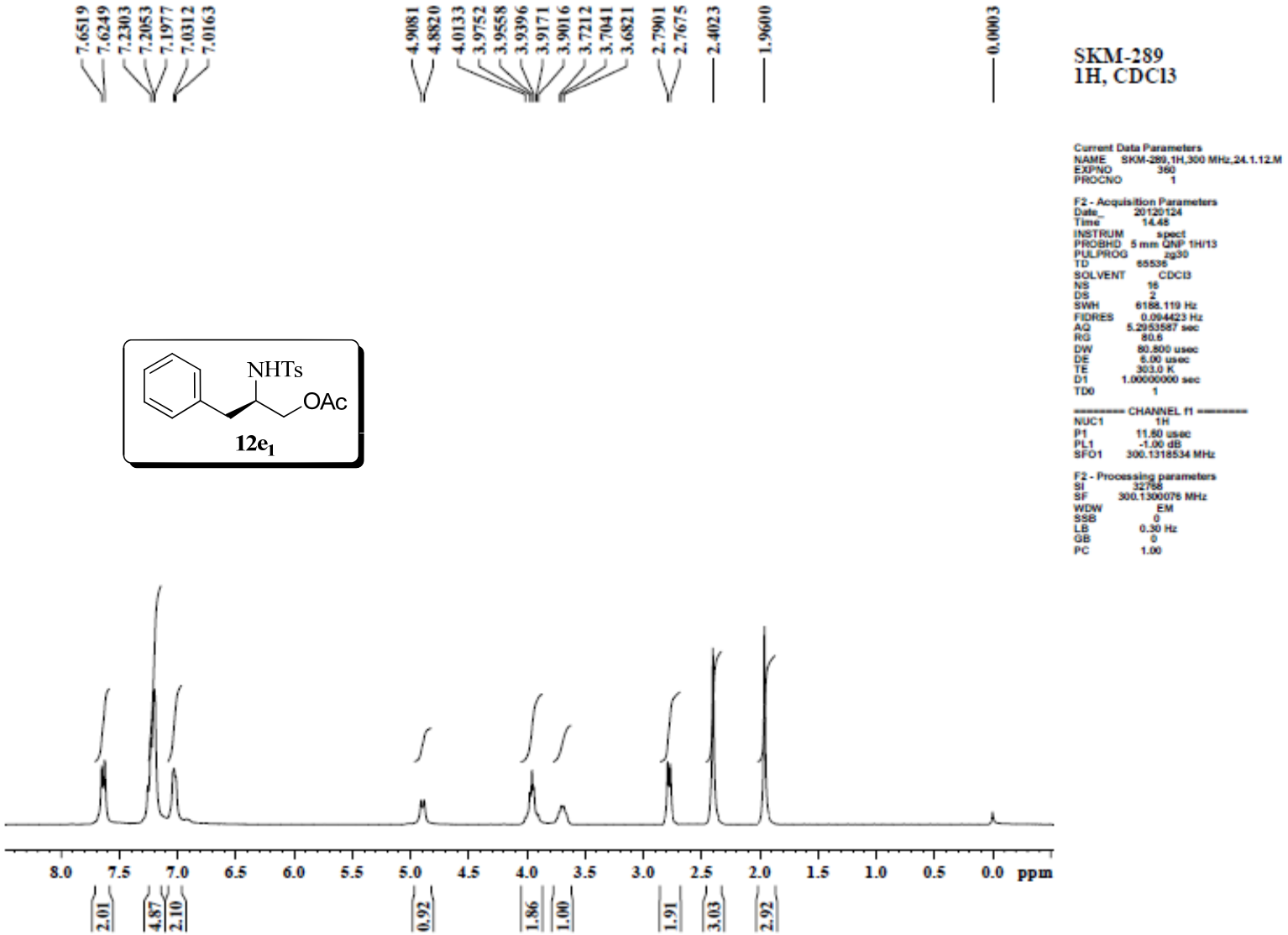

Figure 56: ^{1}H -NMR Spectrum of **12e1.**

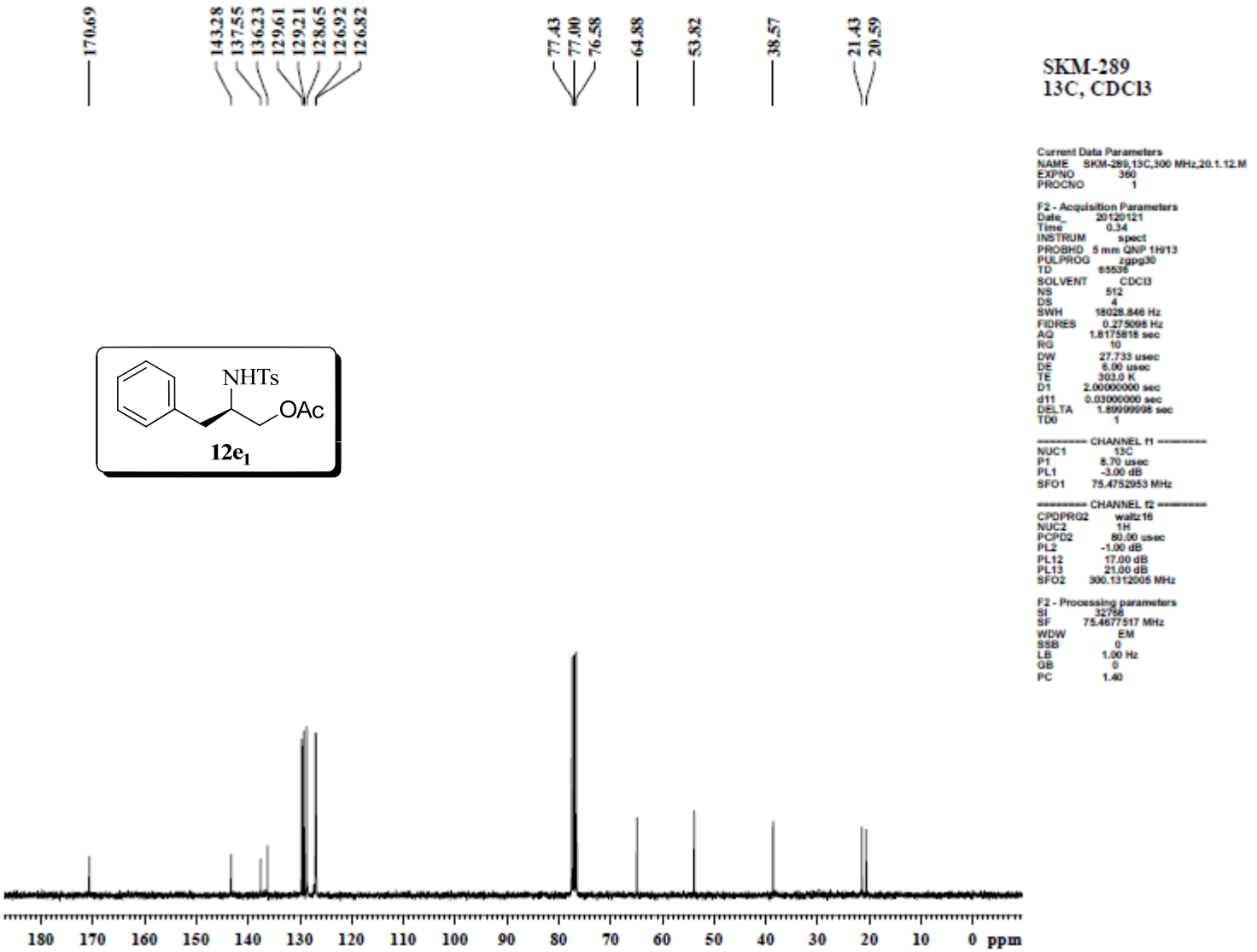

Figure 57: ^{13}C -NMR Spectrum of **12e1.**

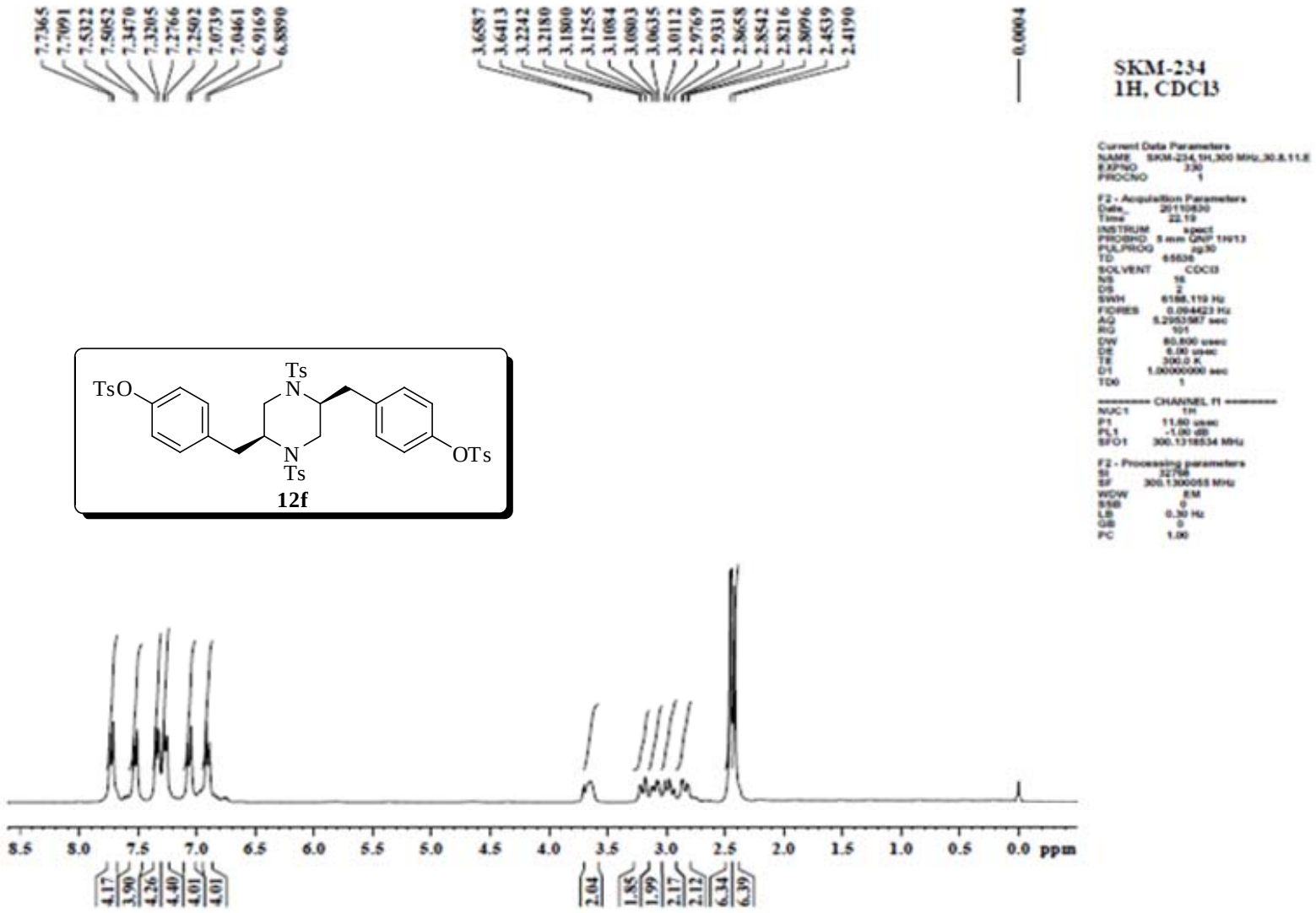

Figure 58: ^{1}H -NMR Spectrum of **12f.**

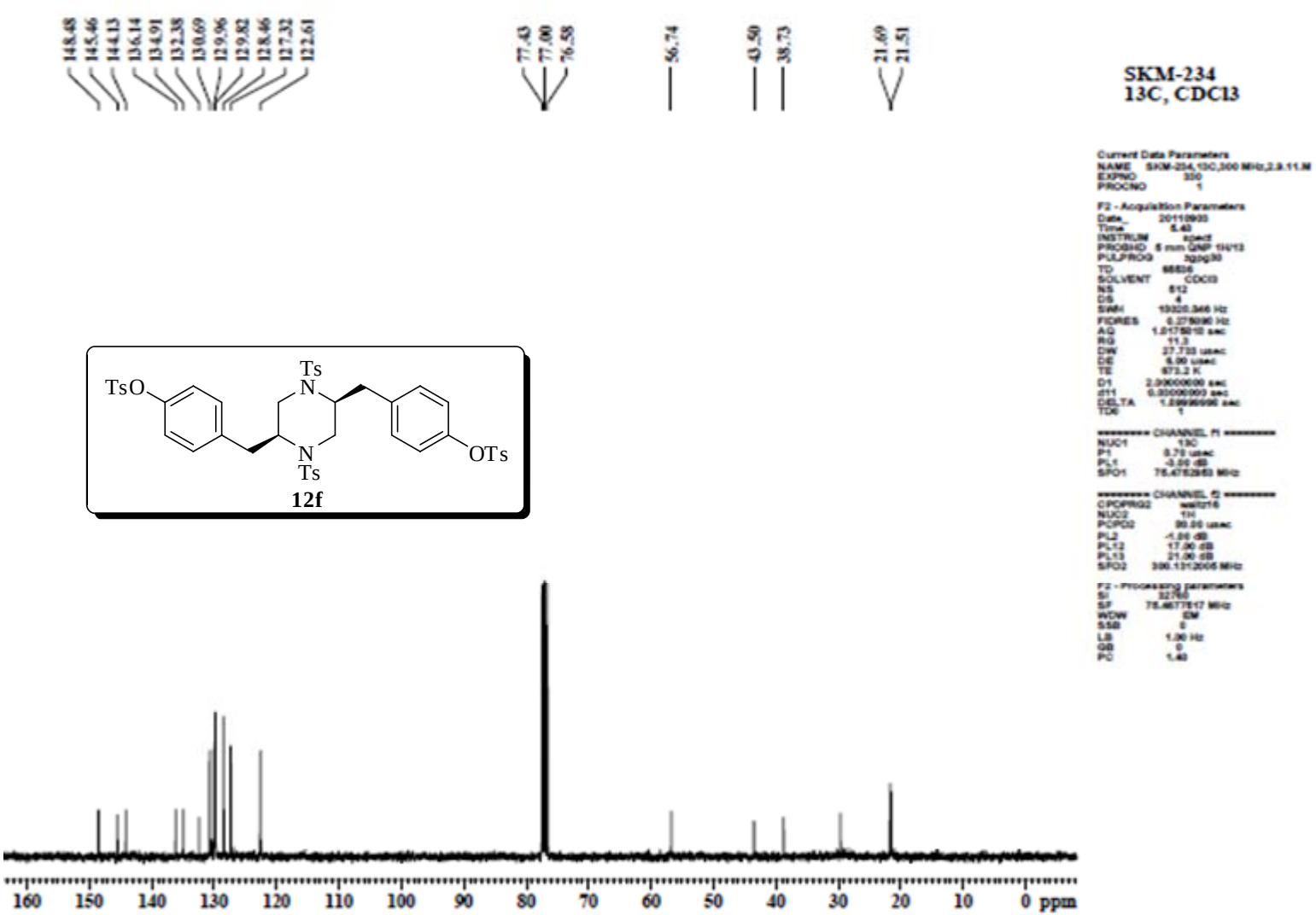

Figure 59: ^{13}C -NMR Spectrum of **12f.**

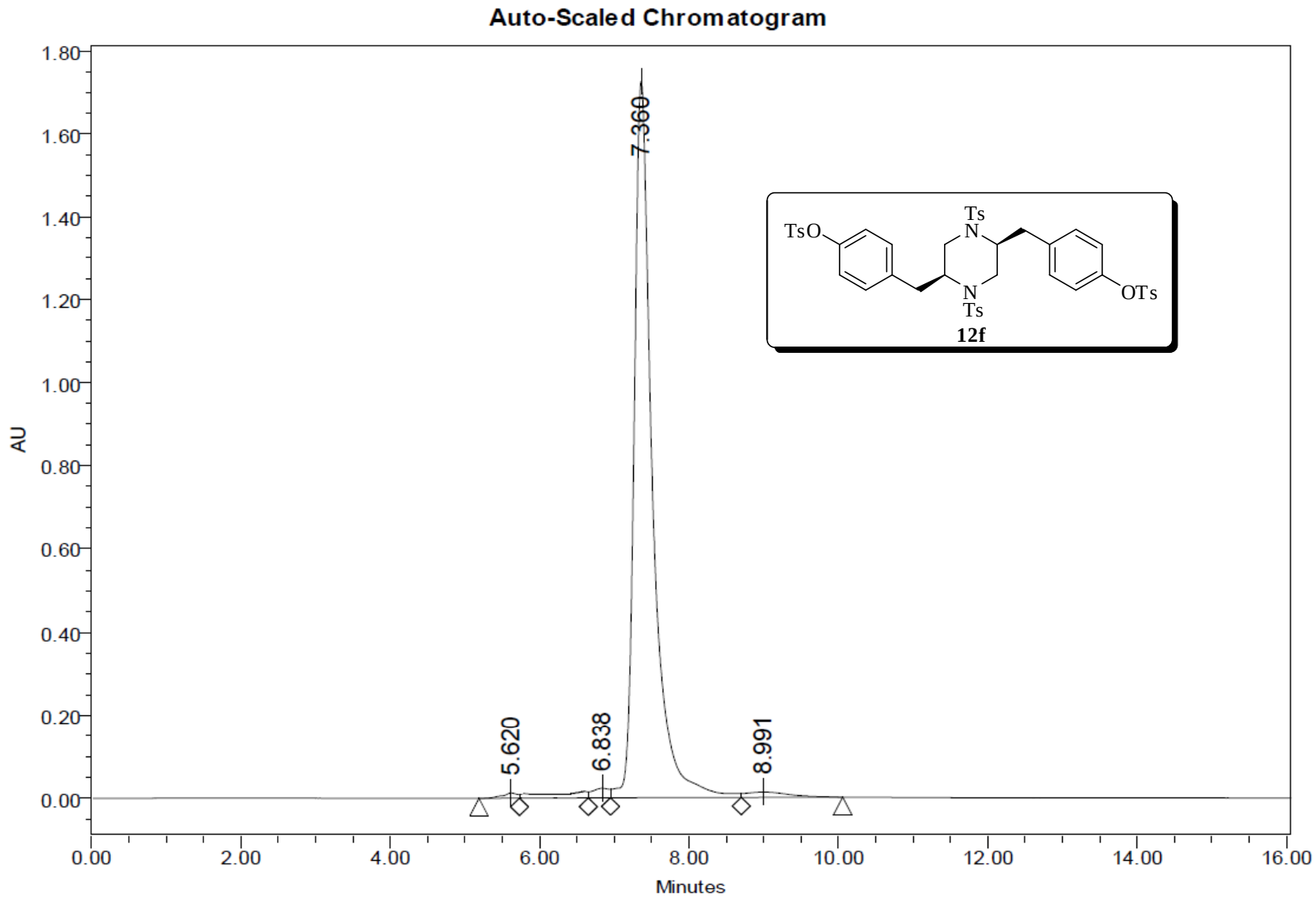

Figure 60: HPLC -Spectrum of **12f.**

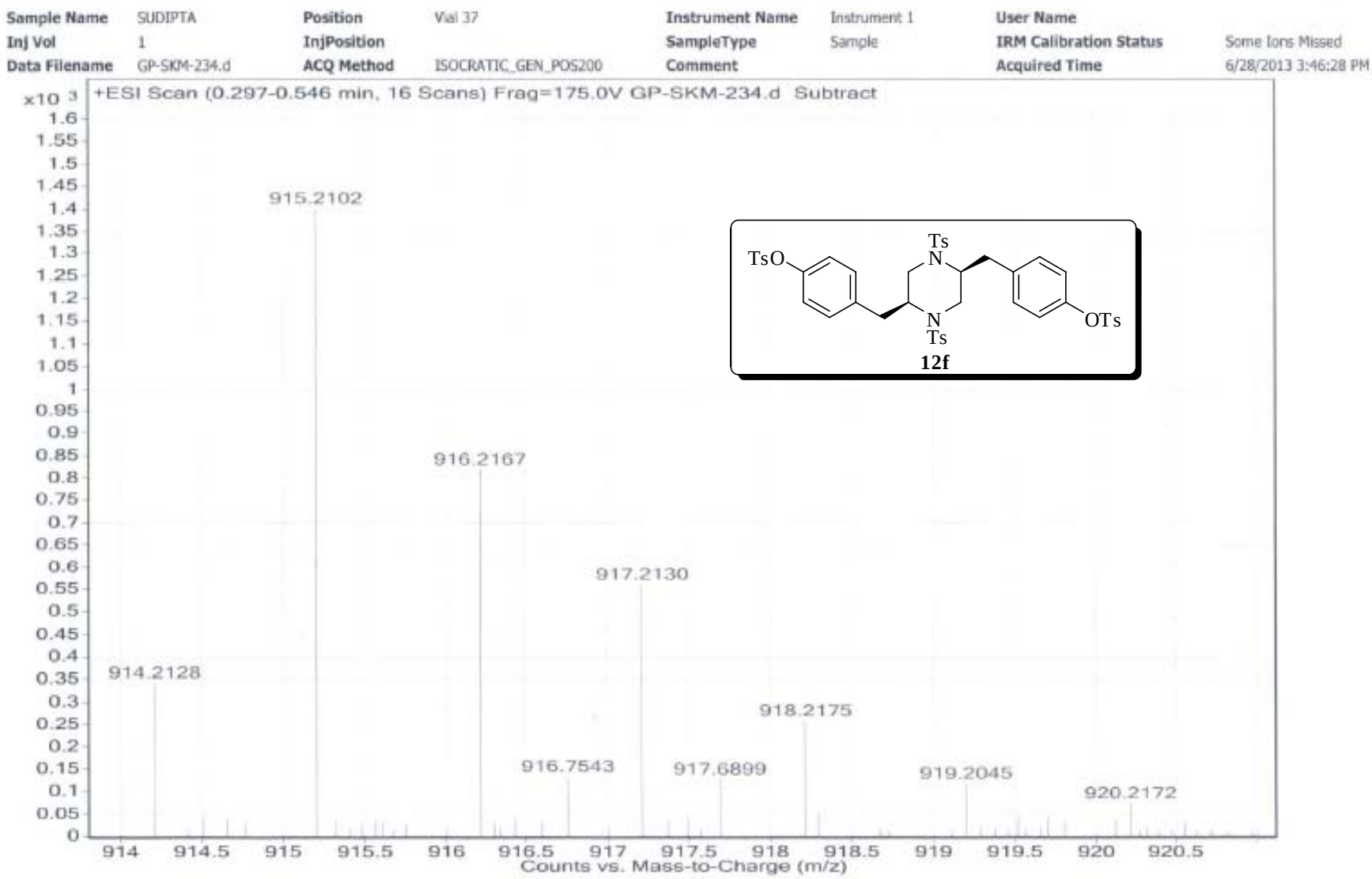

Figure 61: HRMS -Spectrum of **12f.**

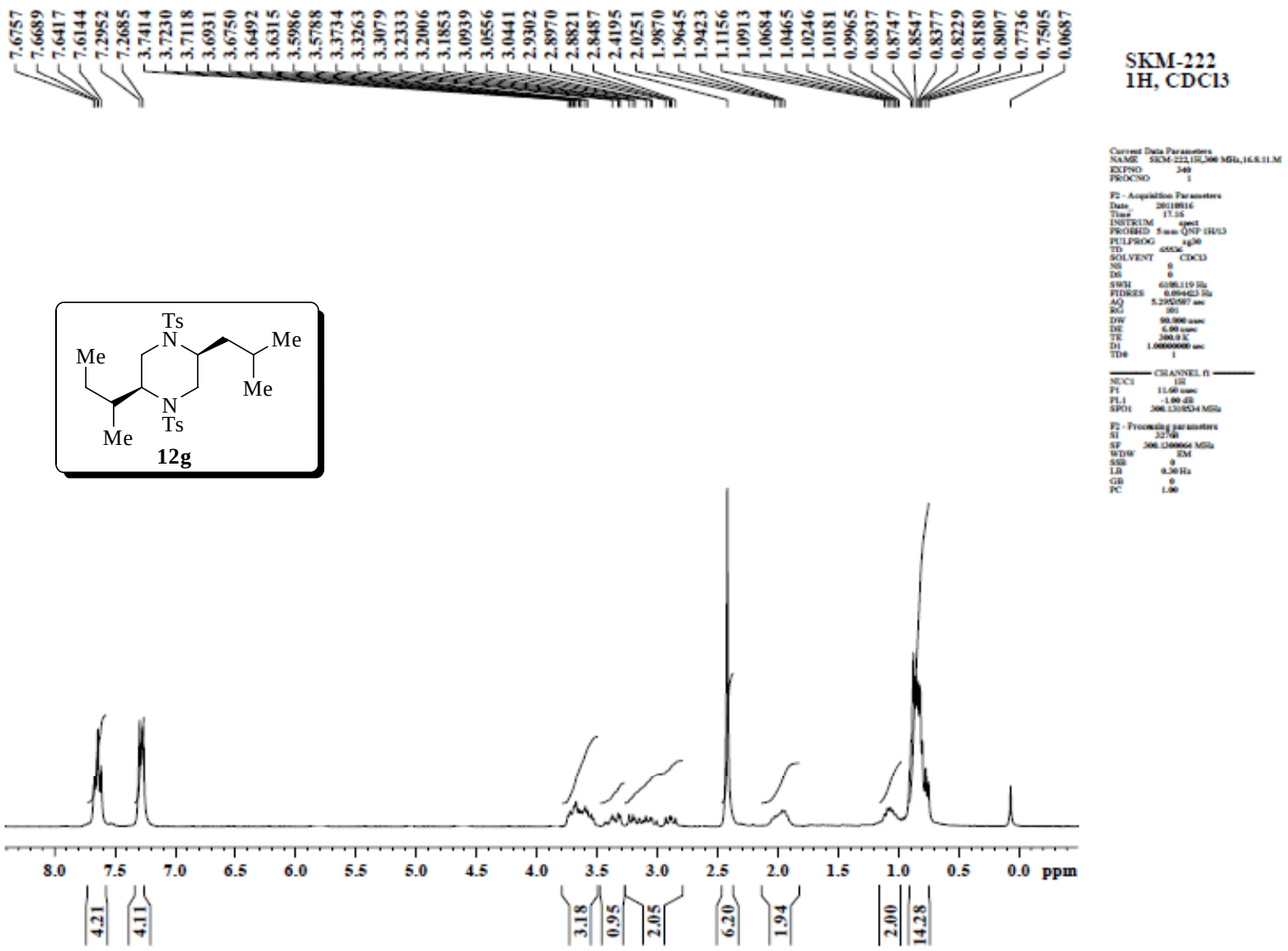

Figure 62: ^{1}H -NMR Spectrum of **12g.**

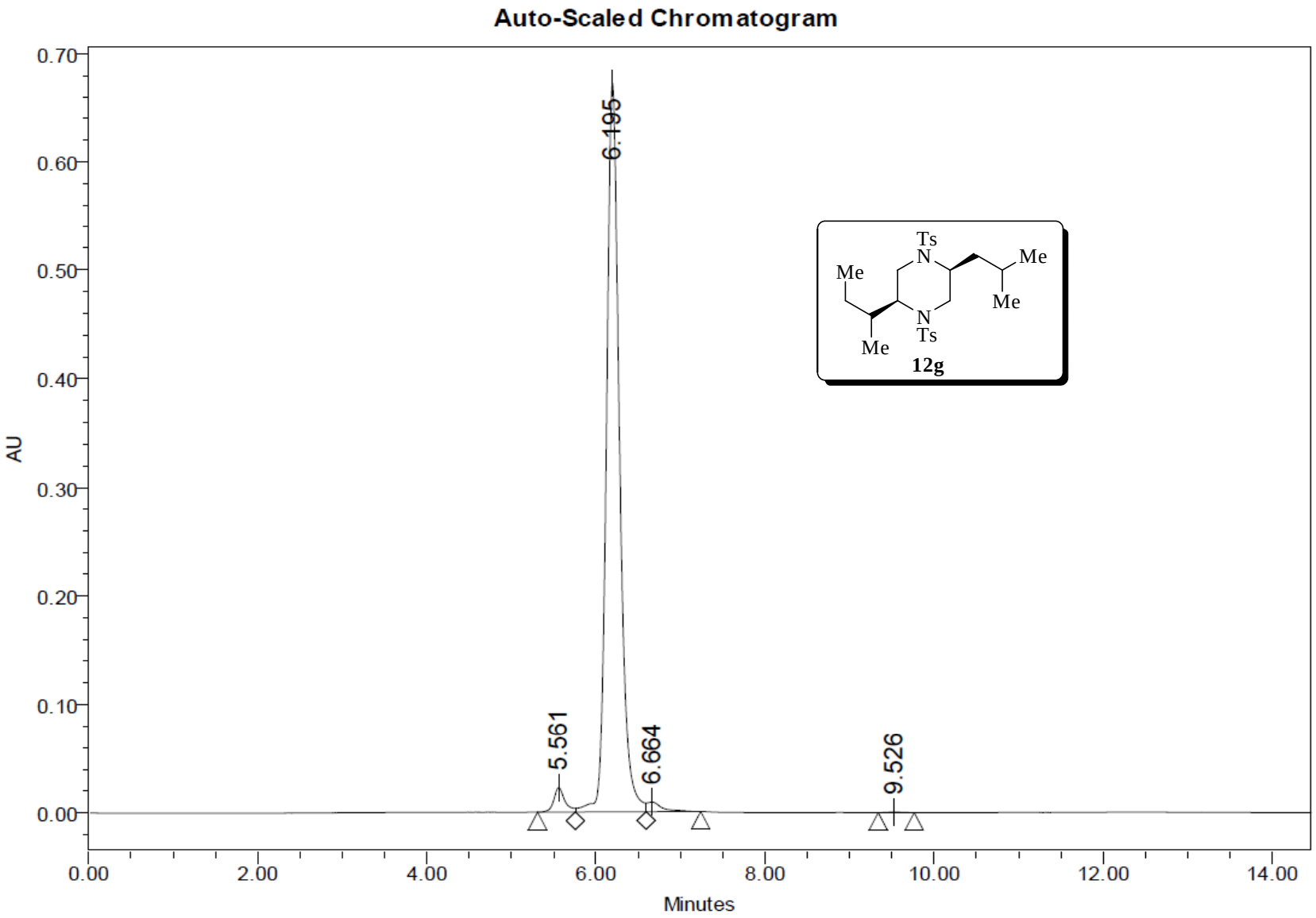

Figure 63: HPLC -Spectrum of **12g.**

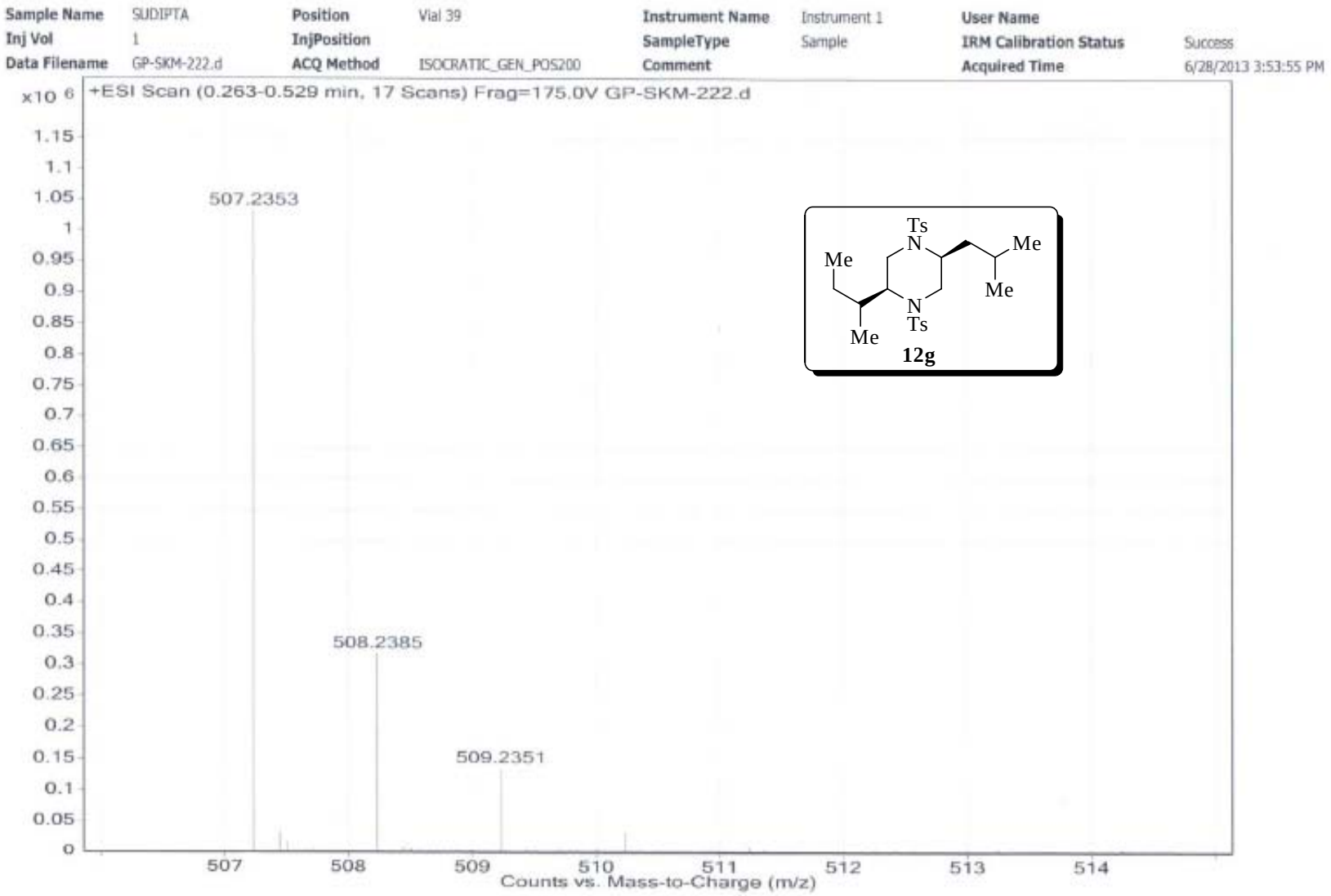

Figure 64: HPLC -Spectrum of **12g.**

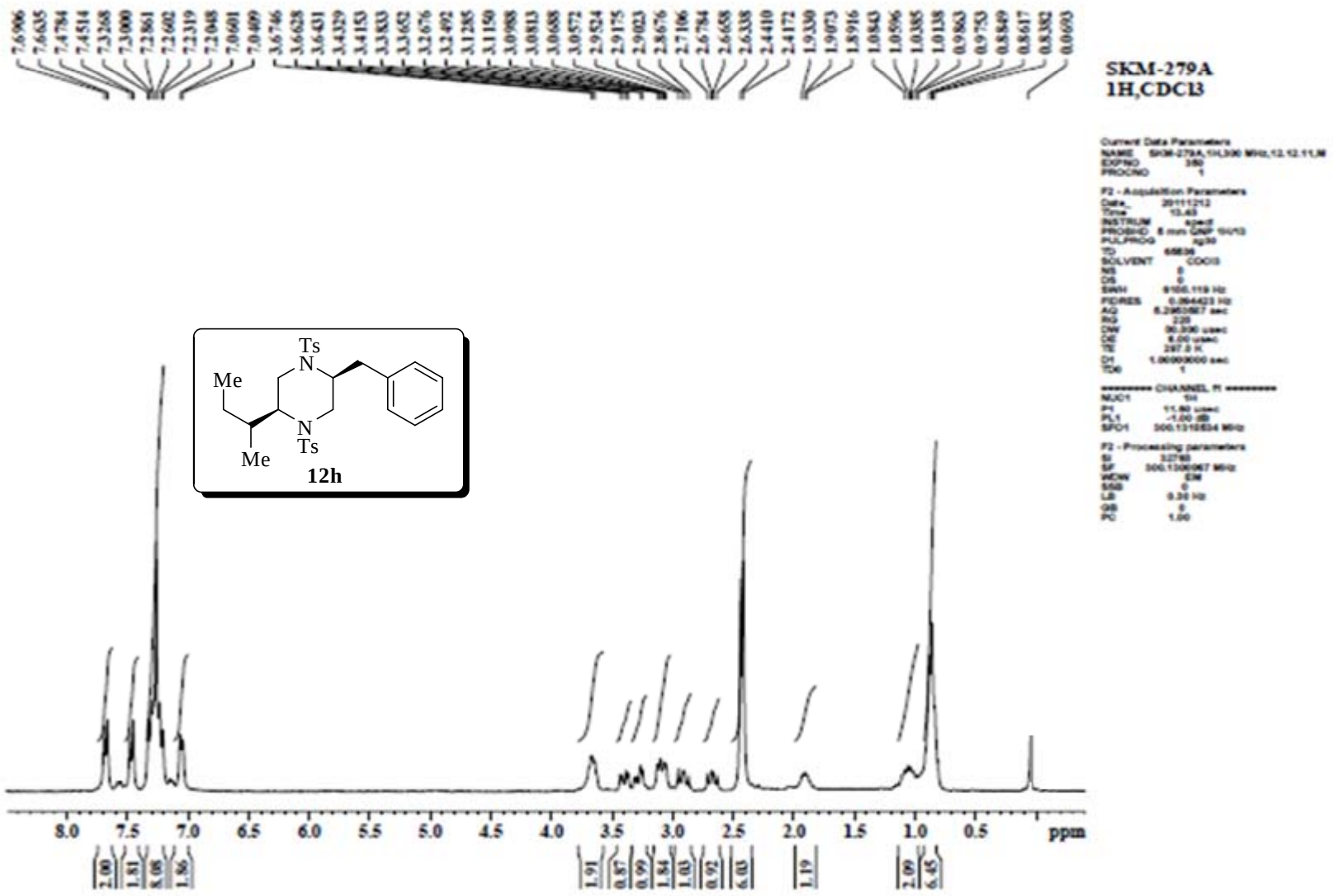

Figure 65: ^{1}H -NMR Spectrum of **12h.**

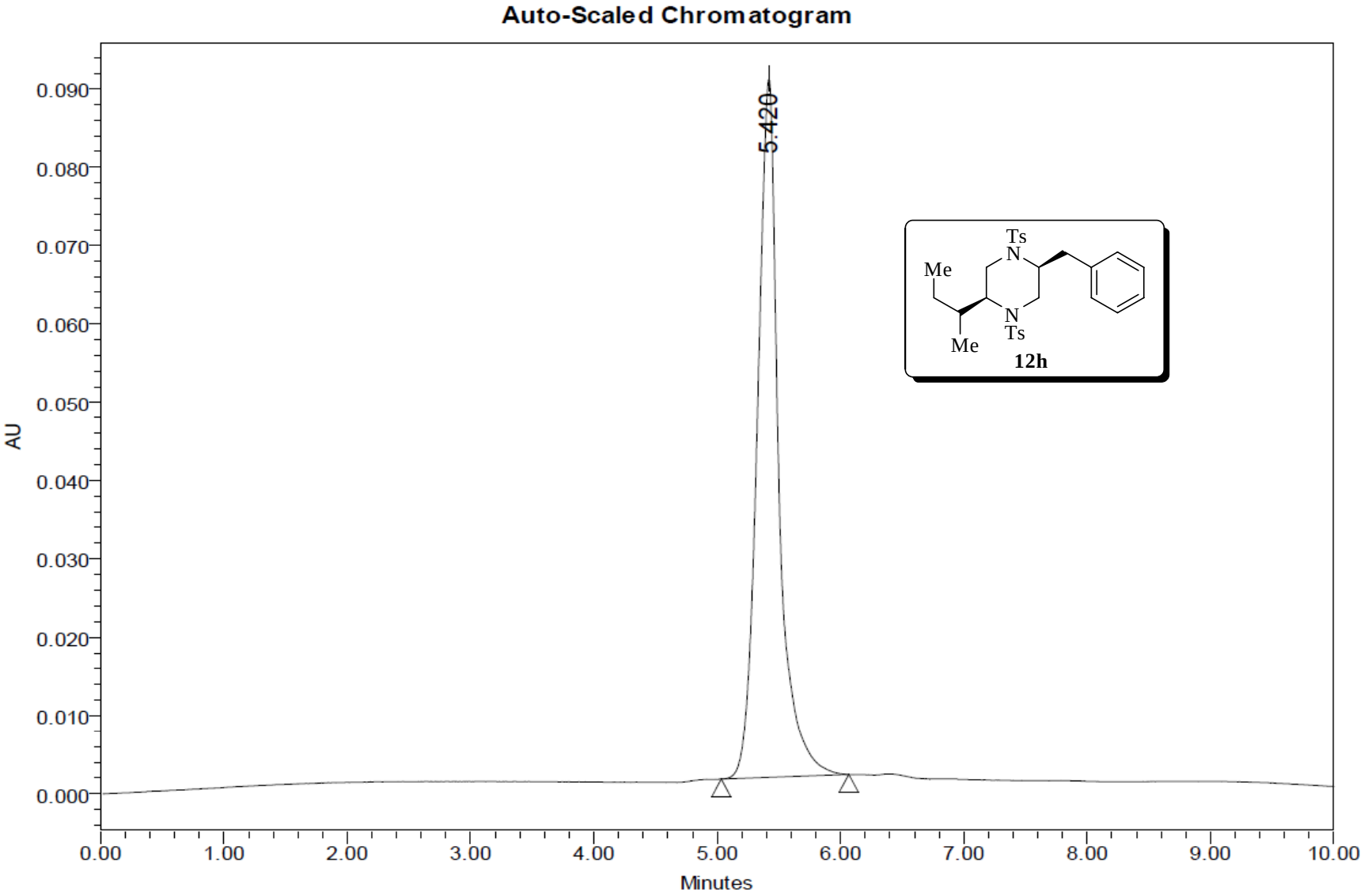

Figure 66: HPLC -Spectrum of **12h.**

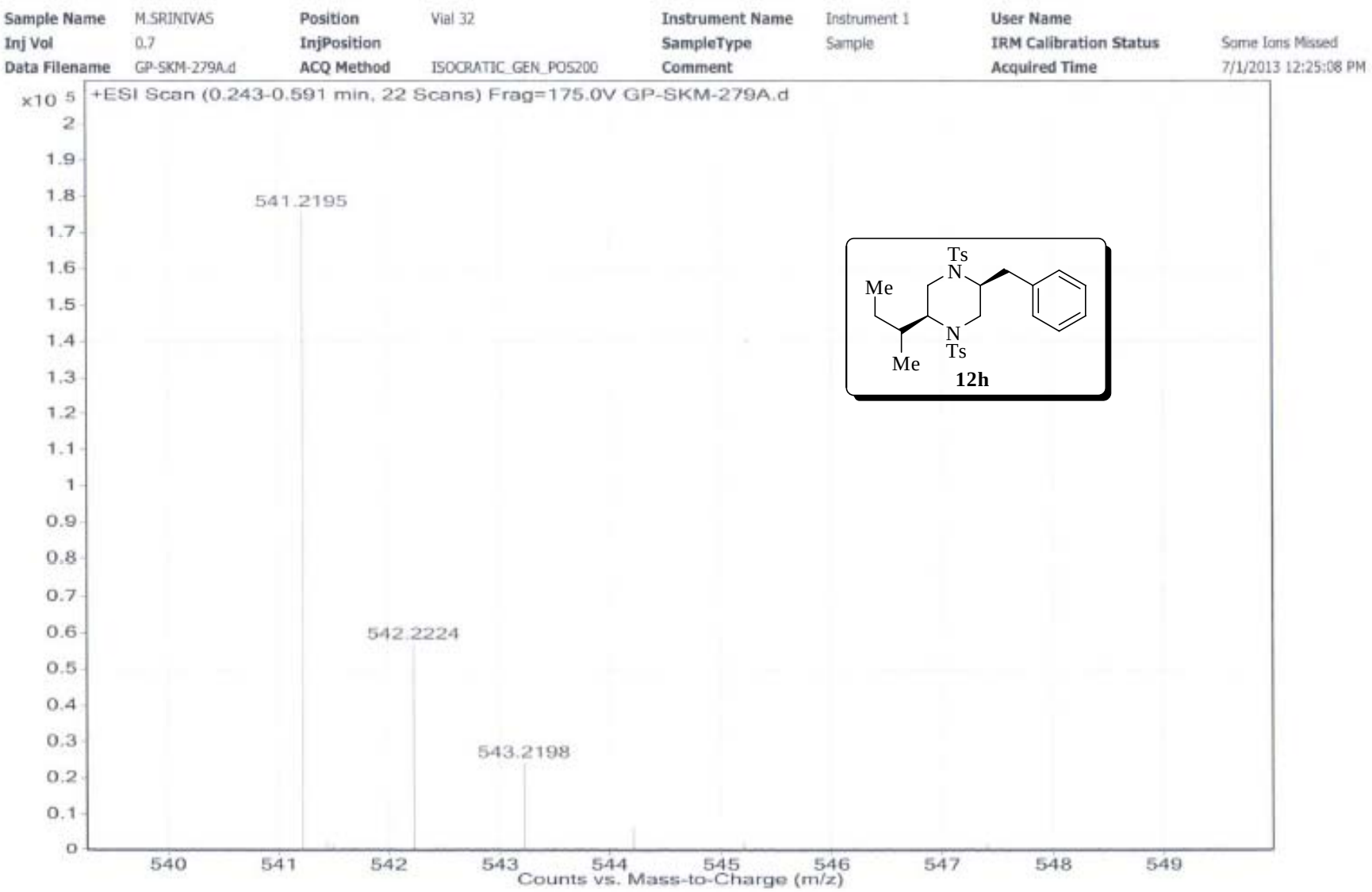

Figure 67: HPLC -Spectrum of **12h.**

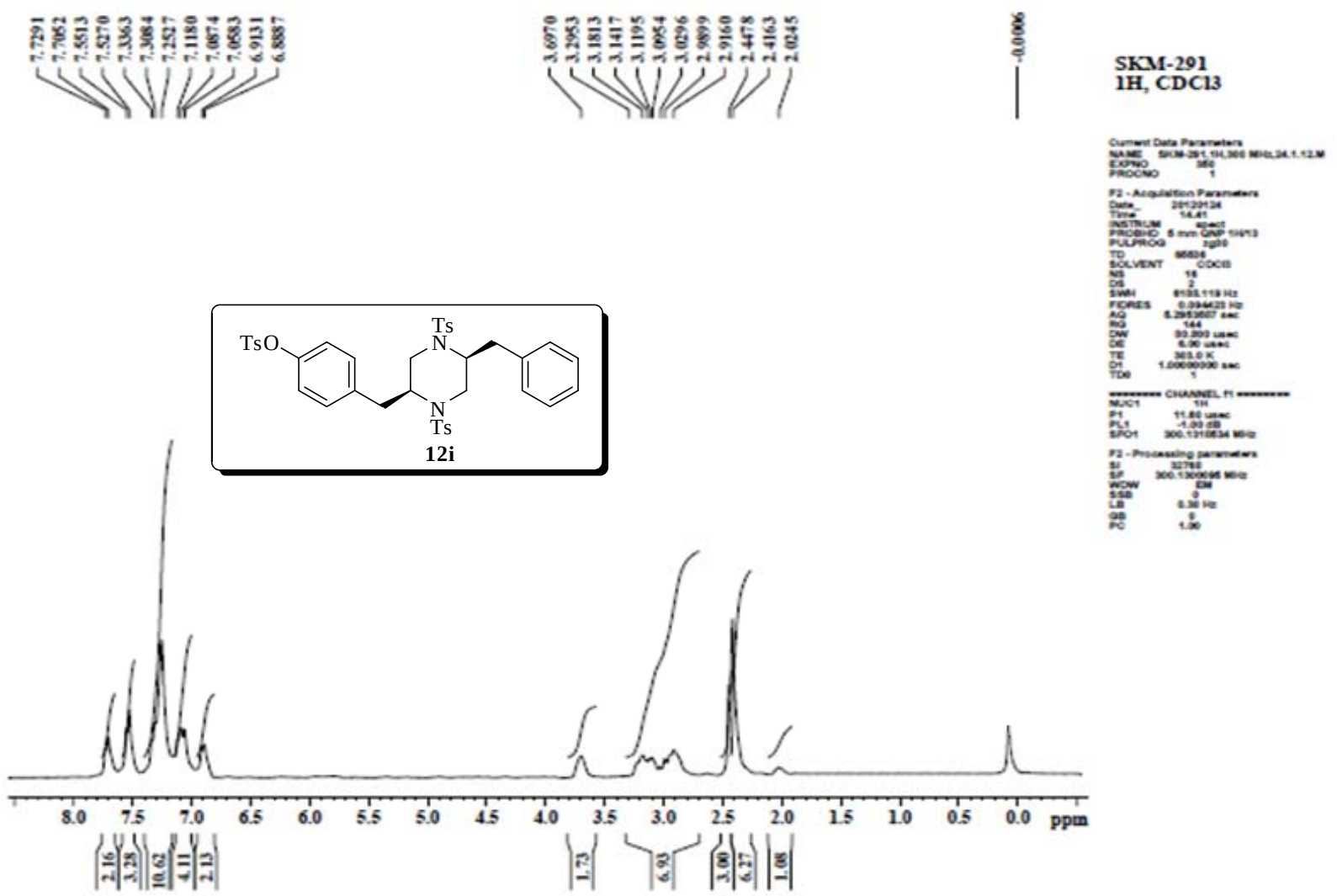

Figure 68: ^{1}H -NMR Spectrum of **12i.**

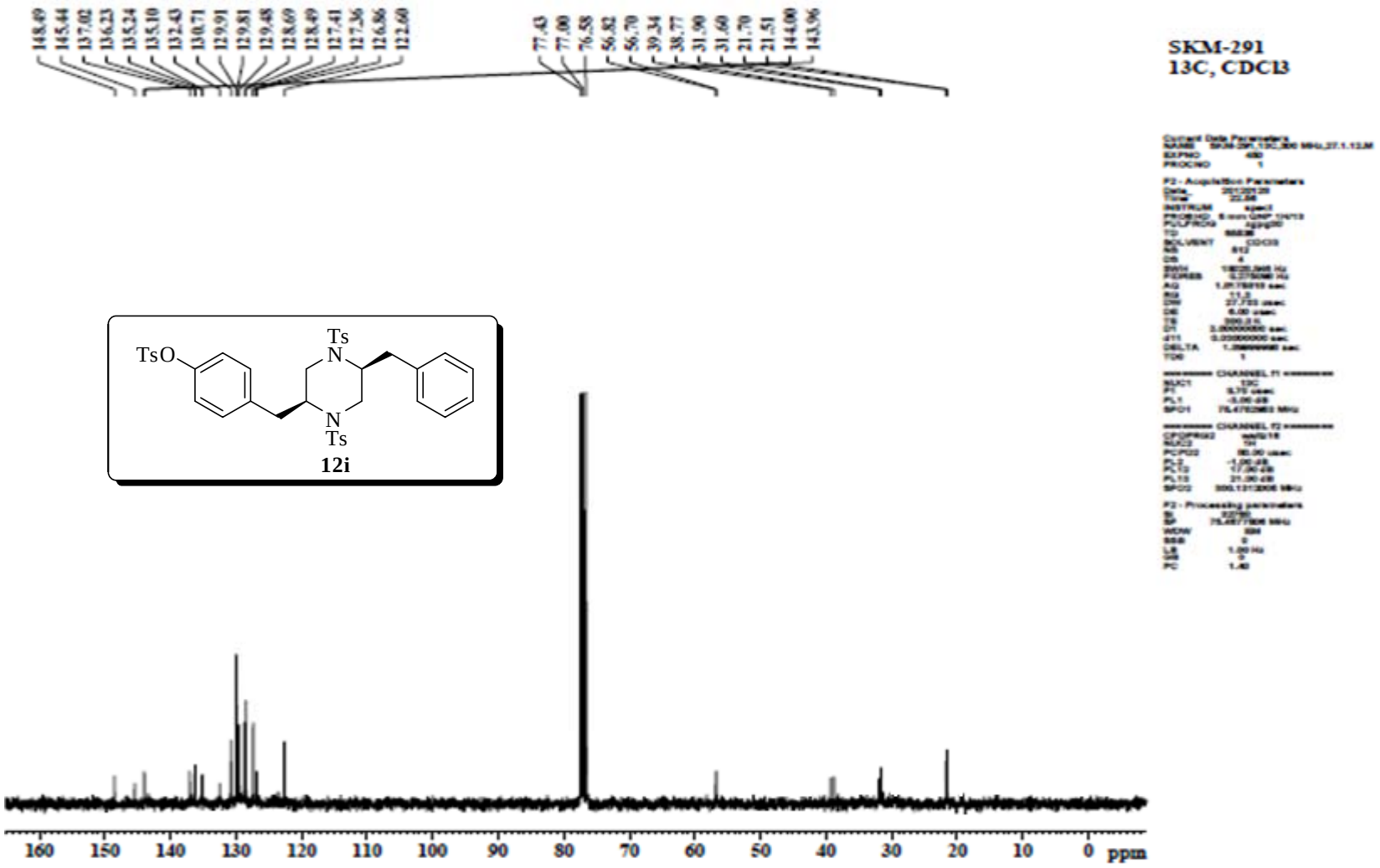

Figure 69: ^{13}C -NMR Spectrum of **12i.**

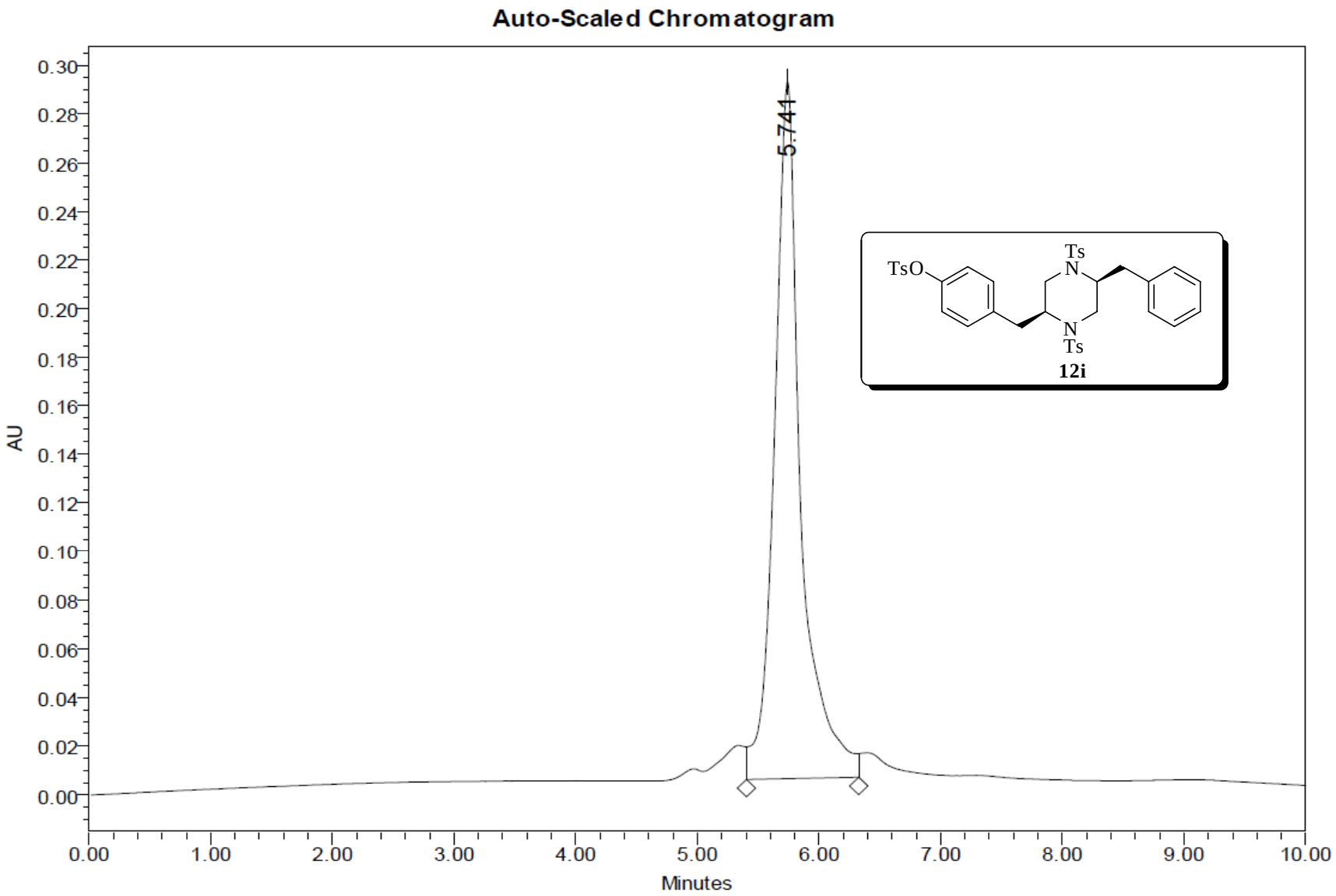

Figure 70: HPLC -Spectrum of **12i.**

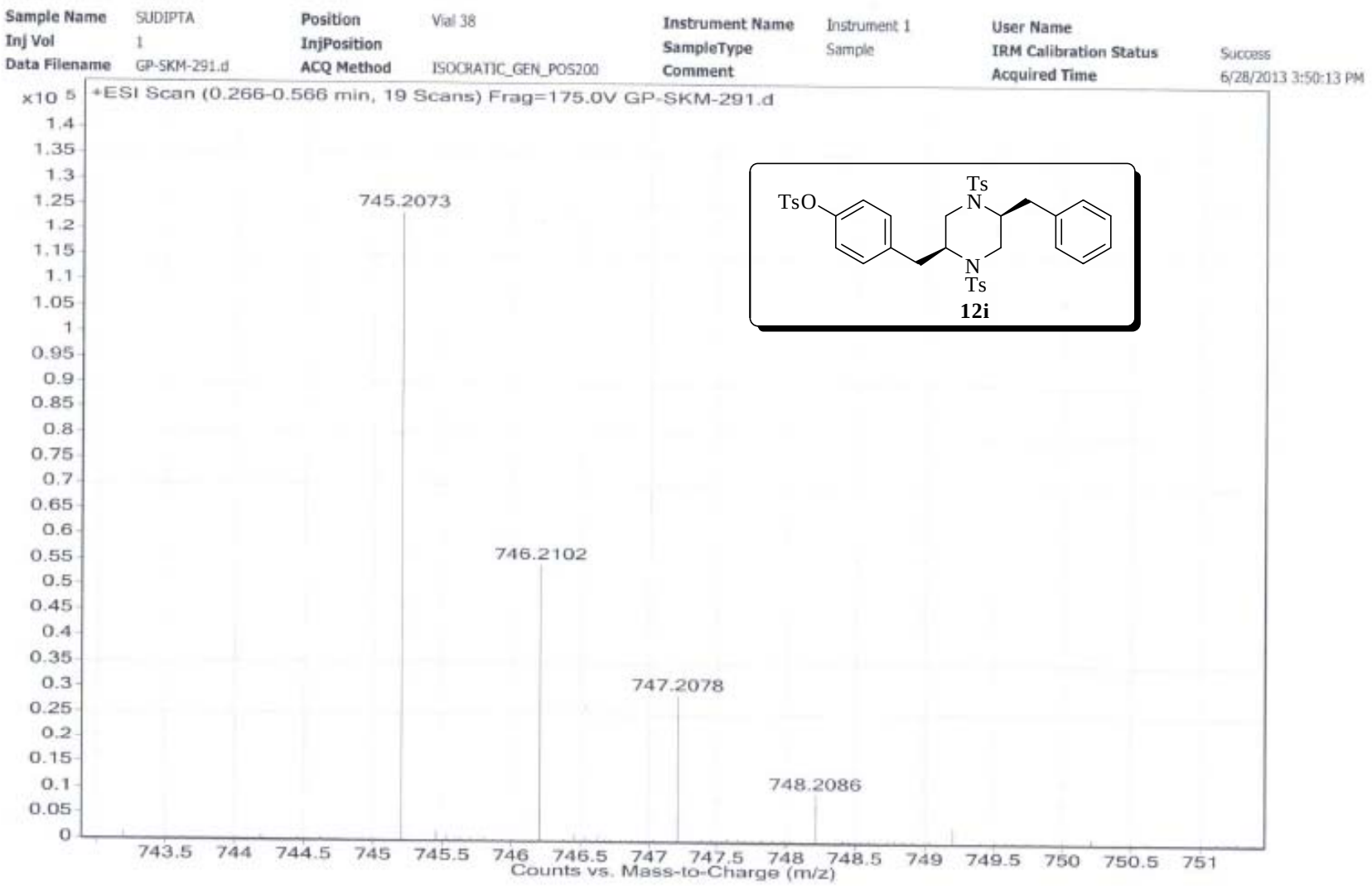

Figure 71: HRMS -Spectrum of **12i.**

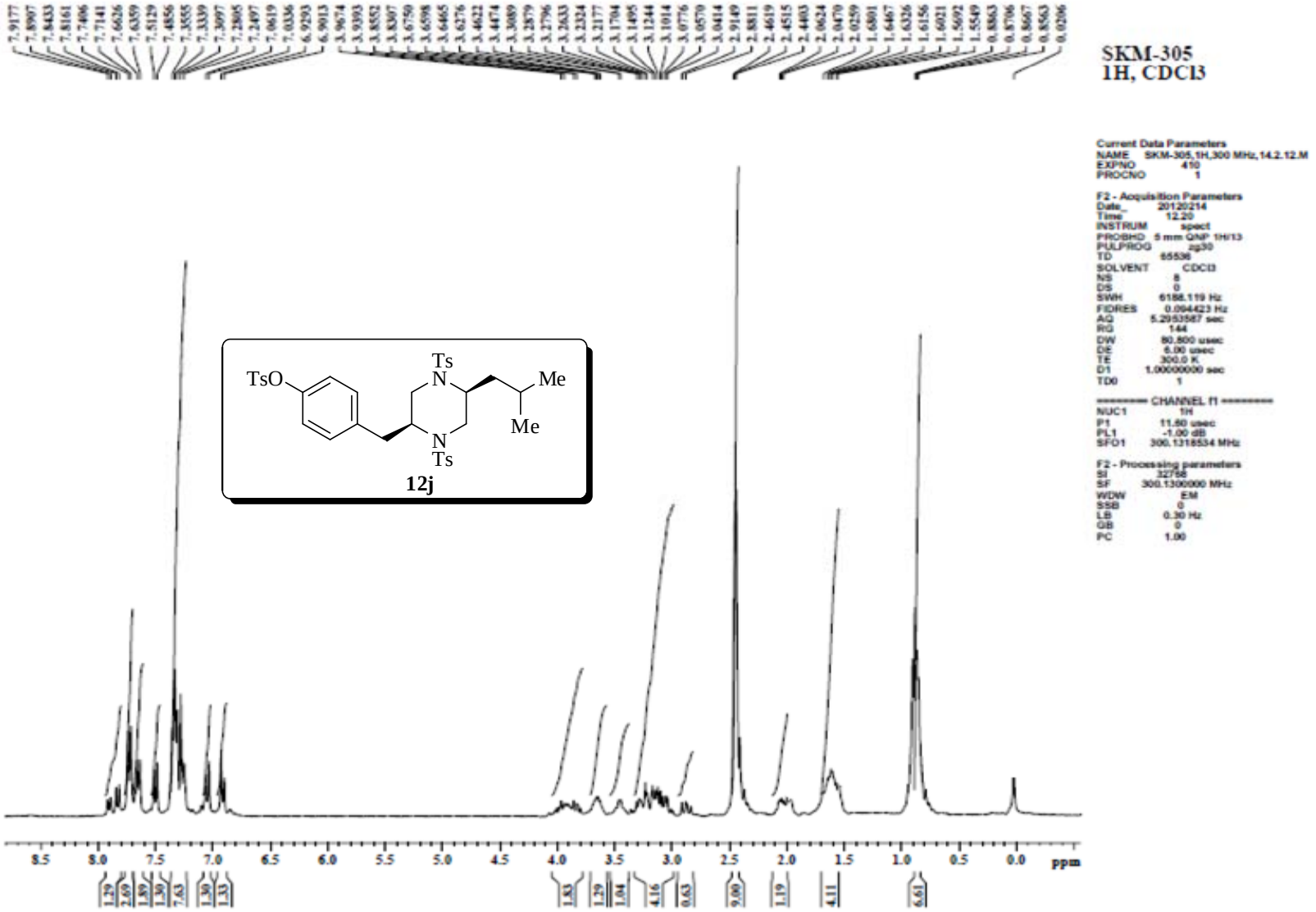

Figure 72: ^{1}H -NMR Spectrum of **12j.**

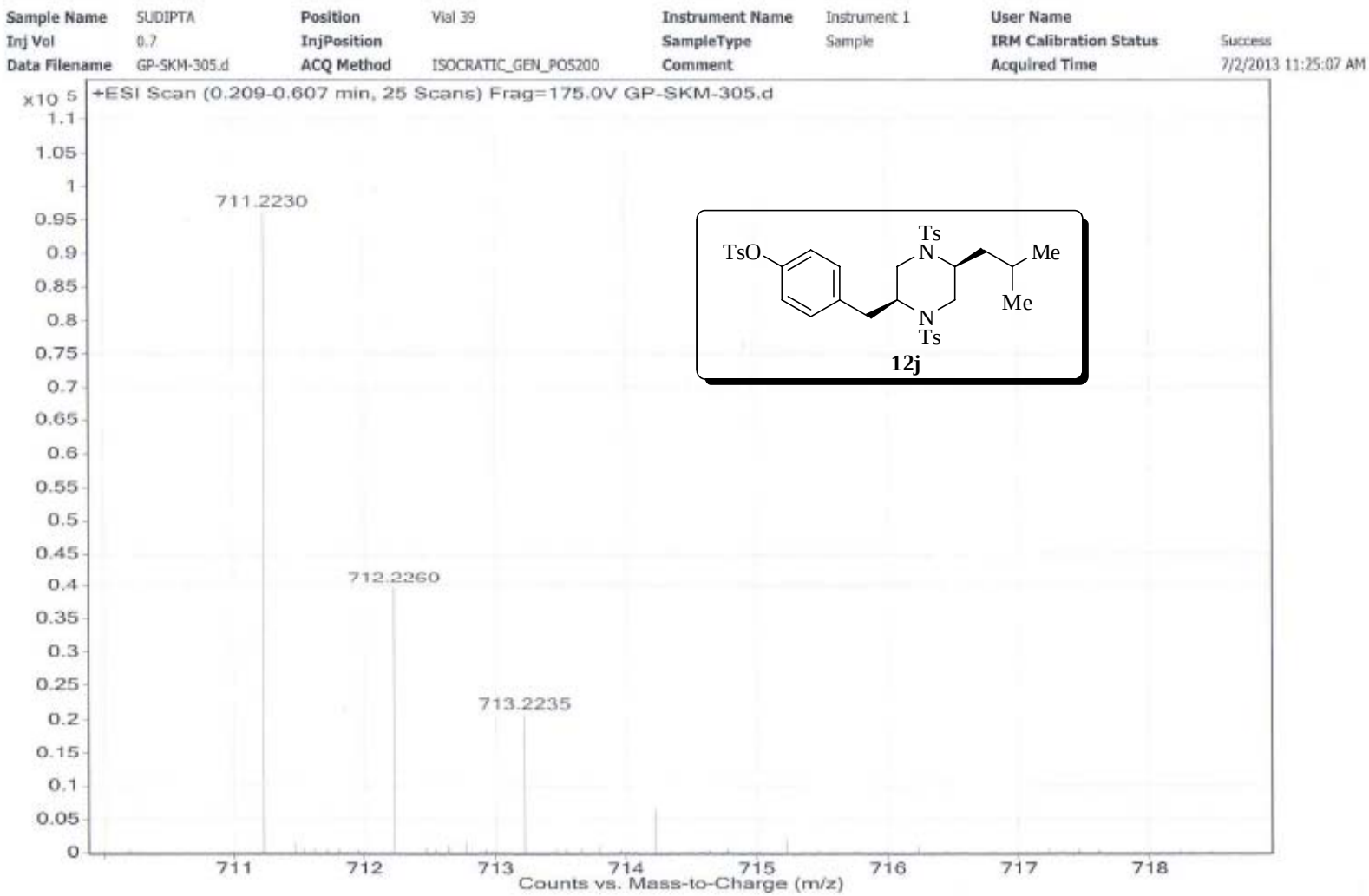

Figure 73: HRMS -Spectrum of **12j.**

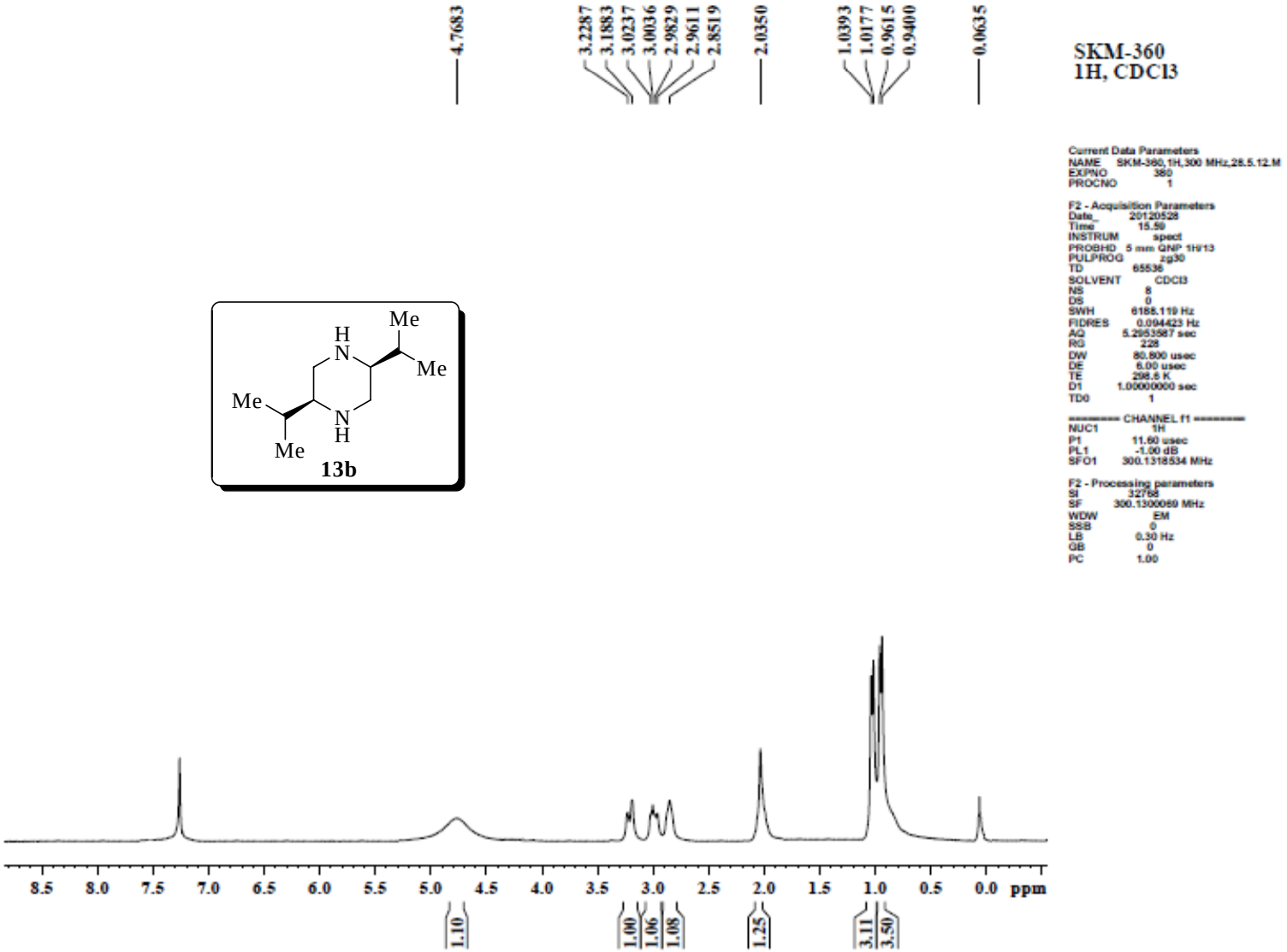

Figure 74: ^{1}H -NMR Spectrum of **13b.**

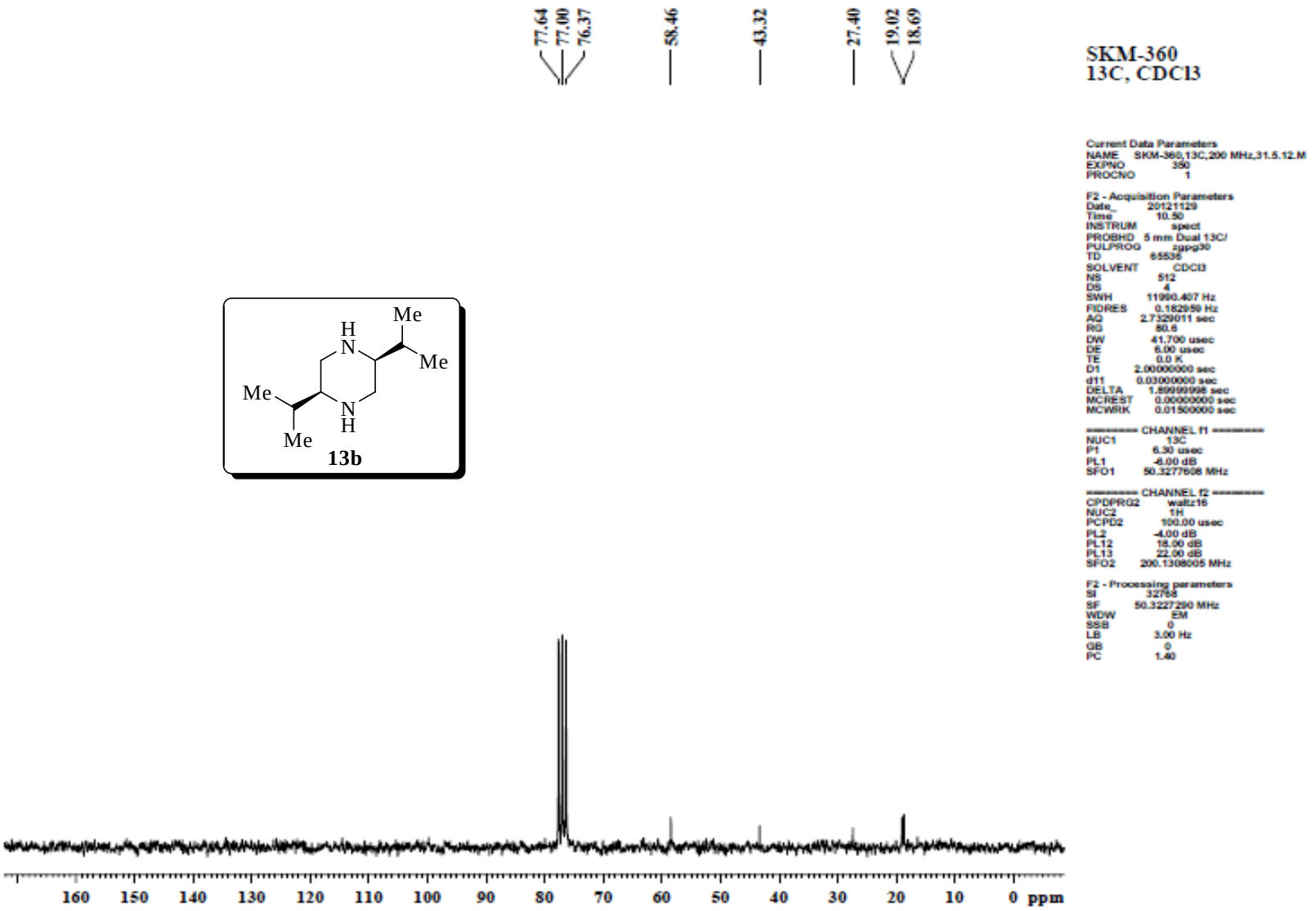

Figure 75: ^{13}C -NMR Spectrum of **13b.**

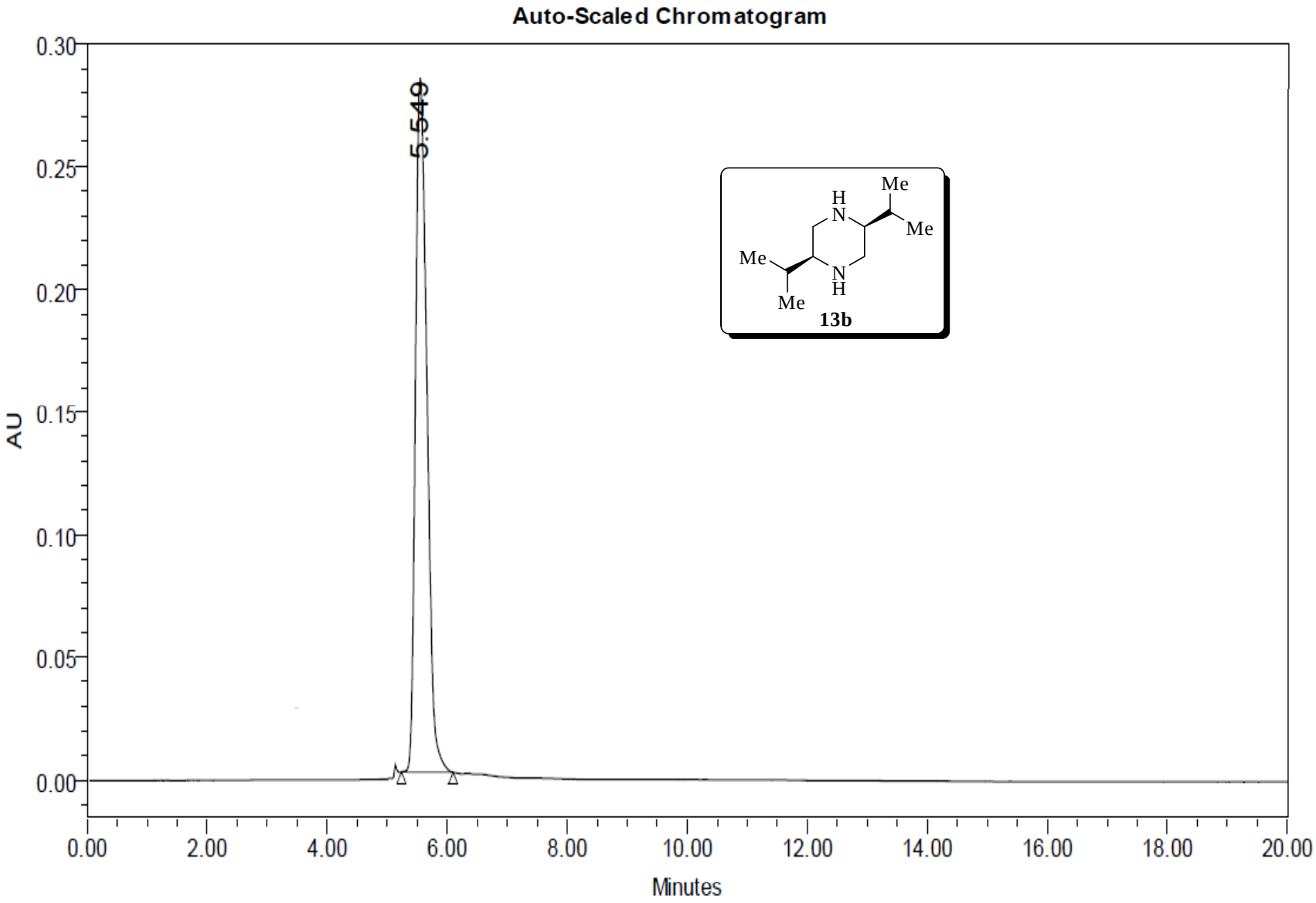

Figure 76: HPLC -Spectrum of **13b.**