Supplementary Material
First highly stereocontrolled synthesis of tetrahydro *trans*-β-carboline derivatives by exploiting the influence of a cyclic amide

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Dedicated to Professor Richard R. Schmidt on the occasion of his 78th anniversary

Table of contents

Experimental Section

General. All starting materials were commercial substances. LR grade solvents and commercial reagents were used without further purification. The FT IR spectra were recorded as KBr pallet and only diagnostic and/or intense peaks are reported. Mass spectra (70 eV) were recorded on LC-MS spectrometer. The melting points were determined by using the capillary method and are uncorrected. ^{1}HNMR spectra were recorded in $CDCl_3$ and DMSO-d6 using a 400 MHz instrument. ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d6 using a 400 MHz instrument. Signals due to the solvent (^{13}C NMR) or residual protonated solvent (^{1}H NMR) served as the internal standard. The ^{1}H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); the list of coupling constants (J) corresponds to the order of multiplicity assignment. TLC analyses were performed on silica gel precoated-plates (250 μm layers). We note that our stereo chemical assignments are supported by comparisons with the literature. HPLC analysis was performed

with Waters Symmetry shield RP18 (250X4.6 mm, 5µ) column by using gradient elution and monitored at 220 nm.

Preparation of (*R*)-ethyl 2-(2-((tert-butoxycarbonyl)amino)-3-(1H-indol-3-yl)-*N*-methyl propanamido)acetate (11). A mixture of *N*-Boc-D-tryptophan (5 g, 16.4 mmol) and THF (25 mL) was cooled to -20 °C under nitrogen atmosphere. To the mixture charged *N*-methyl morpholine (1.83 g, 18 mmol) and stirred for 20 min. Thereafter, a solution of ethyl chloroformate (1.95 g, 18 mmol) in THF (2 mL) was slowly added and stirred the reaction mass for 30 min. Subsequently, a solution of sarcosine ethyl ester in THF (5 mL) was prepared by treating sarcosine ethyl ester hydrochloride (2.76 g, 18 mmol) with *N*-methyl morpholine (2 g). This solution was added to the solution of mixed anhydride in THF drop wise at -20 °C. The reaction mass was allowed to attain ambient temperature and maintained for 1 h. After completion of the reaction, solvent was removed by distillation (CAUTION: THF forms peroxides while distillation and hence PPE should be wear during concentration of THF) and to the obtained residue water and DCM were charged. After stirring, organic layer was separated and 2N HCl washings (2 X 10 mL) were given followed by bicarbonate washing (1X10 mL). The organic layer was evaporated to give compound **11** in 5.4 g, 81% yield; mp 126-128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, 3H, *J*.7.2 Hz), 1.42 (s, 9H), 2.77 (s, 3H), 3.13-3.24 (m, 2H), 3.9-4.08 (m, 2H), 4.17 (q, 2H, *J*.7.2 Hz), 4.99 (dd, 1H, *J*.7.8 Hz), 5.41-5.43 (d, 1H), 7.1-7.35 (m, 4H), 7.6 (d, 1H, *J*.7.8 Hz), 8.11 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 24.9, 25.6, 28.3, 29.3, 33.9, 36.2, 49.6, 50.8, 51.0, 61.2, 77.6, 110.2, 111.1, 118.7, 119.5, 121.9, 123.3, 136.0, 155.2, 168.9, 172.8; IR (KBr) ν 3295, 3060, 2981, 2933, 1750, 1688, 1645, 1459, 1203, 1171, 746 cm^{-1}; $[\alpha]_D^{28.4}$ = -4.65 (c 0.50, CH_3OH); HRMS (ESI) calcd for $C_{21}H_{30}N_3O_5$ $[M^+ + H]$: 404.2185; Found: 404.2171.

Preparation of (6*R*,12a*R*)-6-(benzo[d][1,3]dioxol-5-yl)-2-methyl-2,3,12,12a-tetrahydropyrazino [1',2':1,6]pyrido[3,4-b]indole-1,4(6H,7H)-dione (1c). A mixture of toluene (10 mL), compound **11** (1 g, 12.4 mmol) and compound **2** (0.36 g, 12.65 mmol) were stirred for 10 min. Trifluoroacetic acid was added slowly and the reaction mass was heated to 45-50 °C, maintained at the same temperature for 15 h and concentrated under vacuum. To the obtained residue, charged water (5 mL) and dichloromethane (5 mL) and the mixture was neutralized with saturated sodium bicarbonate solution. Organic layer was separated and concentrated below 35 °C under vacuum. Charged toluene (5 mL) to the obtained residue and the mixture was heated to reflux. After stirring for 8 h, reaction mass was cooled to ambient temperature and the product separated was filtered to give tadalafil, **1**c in 0.39 g, 50% yield; mp 301-303 °C; purity by HPLC 99.9%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.04 (s, 3H), 3.18-3.25 (m, 1H), 3.77 (dd, 1H, *J*.4.4Hz, 16.1Hz), 3.93 (d, 1H, *J*.17.7 Hz), 4.08 (d, 1H, *J*.17.7 Hz), 4.29-4.31 (m, 1H), 5.85 (s, 2H), 6.15 (s, 1H), 6.67-6.73 (m, 2H), 6.84-6.86 (m, 1H), 7.14-7.18 (m, 2H), 7.26-7.28 (m, 1H), 7.61(d, 1H, *J*.6.4), 7.9 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 33.6, 52.1, 56.2, 56.6, 101.1, 106.4, 107.4, 108.2, 111.2, 118.6, 120.0, 120.6, 122.4, 126.1, 132.8, 135.3, 136.5, 147.1, 147.8, 166.4, 166.8; IR (KBr) ν 3327, 3061, 2904, 1677, 1650, 1627, 1438,

1323, 1242, 1041, 939, 922, 746 cm^{-1}; $[\alpha]_D^{26.8}$ = 70.54 (c 0.99, $CHCl_3$); HRMS calcd for $C_{22}H_{20}N_3O_4$ $[M^+ + H]$: 390.1454; Found: 390.1454.

Preparation of (*R*)-3-((1H-indol-3-yl) methyl)-1-methyl piperazine-2, 5-dione (15). Method a. A mixture of compound **11** (2 g, 12.4 mmol) and hydrochloric acid in dioxane (20 mL, 4N) and stirred at ambient temperature for 5 h. Thereafter, reaction mass was concentrated under reduced pressure. Charged DCM and washed with saturated sodium bicarbonate solution (15 mL). Then, solvent was evaporated under reduced pressure to get the desired compound **15** in 0.9 g, 70% yield. **Method b.** A suspension of HCl salt of compound **3** (1.17 g, 4.58 mmol) in chloroform (10 mL), to that added aqueous ammonia solution (2 mL) and water (10 mL) and stirred at ambient temperature for 10 min. Organic layer was separated and solvent was evaporated under reduced pressure. The obtained residue was diluted with chloroform (10 mL) then added triethyl amine (0.394 g, 3.894 mmol) and cooled to 0 °C. Compound **5** (0.66 g, 5.84 mmol) was added and the reaction mass was stirred for 1 h. Thereafter, water (10 mL) was added to the mass below 10 °C, and organic layer was separated and washed with saturated sodium bicarbonate solution followed by water. Finally, organic layer was distilled under vacuum. To the obtained compound, methylamine (0.42 g, 13.548 mmol) in methanol (10 mL) was added and stirred for 6 h at 55 °C for completion of the reaction. Subsequently, the reaction mass was cooled to ambient temperature and separated solids were filtered. The filtrate was evaporated to get the desired compound **15** in 0.95 g, 80% yield; mp 234-236 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.46 (s, 3H), 2.98 (dd, 1H, *J*.4.4 Hz, 14.4 Hz), 3.27 (dd, 1H, *J*.3.9 Hz, 14.4 Hz), 3.36 (s, 3H), 4.1 (br s, 1H), 6.9-7.1 (m, 3H), 7.34 (d, 1H, *J*.7.9 Hz), 7.43 (d, 1H, *J*.7.9 Hz) 8.18 (br s, 1H, NH), 11.0 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6), δ 30.1, 32.8, 50.4, 55.5, 107.9, 111.3, 118.3, 118.7, 121.0, 125.0, 127.2, 136.0, 165.1, 166.3; IR (KBr) ν 3250, 3057, 2931, 1686, 1650, 1630, 1474, 1321, 1189, 1103, 1028, 738, 712 cm^{-1}; $[\alpha]_D^{28.4}$ = -133.5 (c 0.49, CH_3OH); HRMS calcd. for $C_{14}H_{16}N_3O_2$ $(M^+ + H)$ 258.1243; found $(M^+ + H)$ 258.1246.

Preparation of (6*S*,12a*R*)-6-(benzo[d][1,3]dioxol-5-yl)-2-methyl-2,3,12,12a-tetrahydropyrazino [1',2':1,6]pyrido[3,4-b]indole-1,4(6H,7H)-dione (12). Method a. A mixture of toluene (10 mL), compound **11** (1 g, 12.4 mmol) and compound **2** (0.36 g, 12.65 mmol) was stirred for 10 min. Trifluoroacetic acid was added slowly and the reaction mass was heated to reflux and maintained at the same temperature for 8 h. Thereafter, the reaction mass was cooled to ambient temperature and neutralize it with saturated sodium bicarbonate solution. Charge dichloromethane (15 mL) to the mass and stir for 10 min. Organic layer was separated and concentrated below 35 °C under vacuum and the product was purified by column chromatography to give pure *S*,*R* isomer of tadalafil, **12** in 0.7 g, 65% yield. **Method b.** A mixture of compound **15** (2 g, 7.78 mmol) and **2** (1.17 g, 7.78 mmol) is taken along with aqueous HCl (10 mL, 6N) and dioxane (10 mL) and stirred at reflux temperature for 1 h. Thereafter, reaction mass was concentrated under reduced pressure. Charged DCM and washed with saturated sodium bicarbonate solution (30 mL). Subsequently, solvent was evaporated under reduced pressure followed by purification through column chromatography using petroleum ethers: ethyl acetate (7:3) to give pure compound **12** in 2.4 g, 80% yield; mp 287-288 °C; purity

by HPLC 99.0%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.91-2.98 (m, 1H), 3.0 (s, 3H), 3.55 (dd, 1H, *J*.12 Hz, 4.4 Hz), 4.0 (s, 2H, *J*.17.7 Hz), 4.14 (d, 2H, *J*.17.6 Hz), 4.35 (dd, 1H, *J*.11.9 Hz, 4.4 Hz), 5.9 (s, 2H), 6.72 (s, 2H), 6.82 (s, 1H, Ar), 6.98 (s, 1H), 7.14-7.24 (m, 2H), 7.28 (d, 1H, *J*.7.8 Hz), 7.53 (d, 1H, *J*.7.8 Hz), 7.90 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 27.6, 33.4, 51.4, 51.8, 52.4, 101.3, 108.3, 109.0, 119.1, 111.1, 118.4, 120.0, 122.4, 122.7, 126.2, 129.7, 132.3, 136.3, 148.0, 148.1, 161.5, 165.4**;** IR (KBr) ν 3348, 3060, 2926, 1657, 1623, 1594, 1452, 1325, 1263, 1040, 934.9, 746.1 cm^{-1}; $[\alpha]_D^{28.8}$ = 265.16 (c 1.03, $CHCl_3$); HRMS calcd for $C_{22}H_{20}N_3O_4$ [M^++H]: 390.1454. Found: 390.1460.

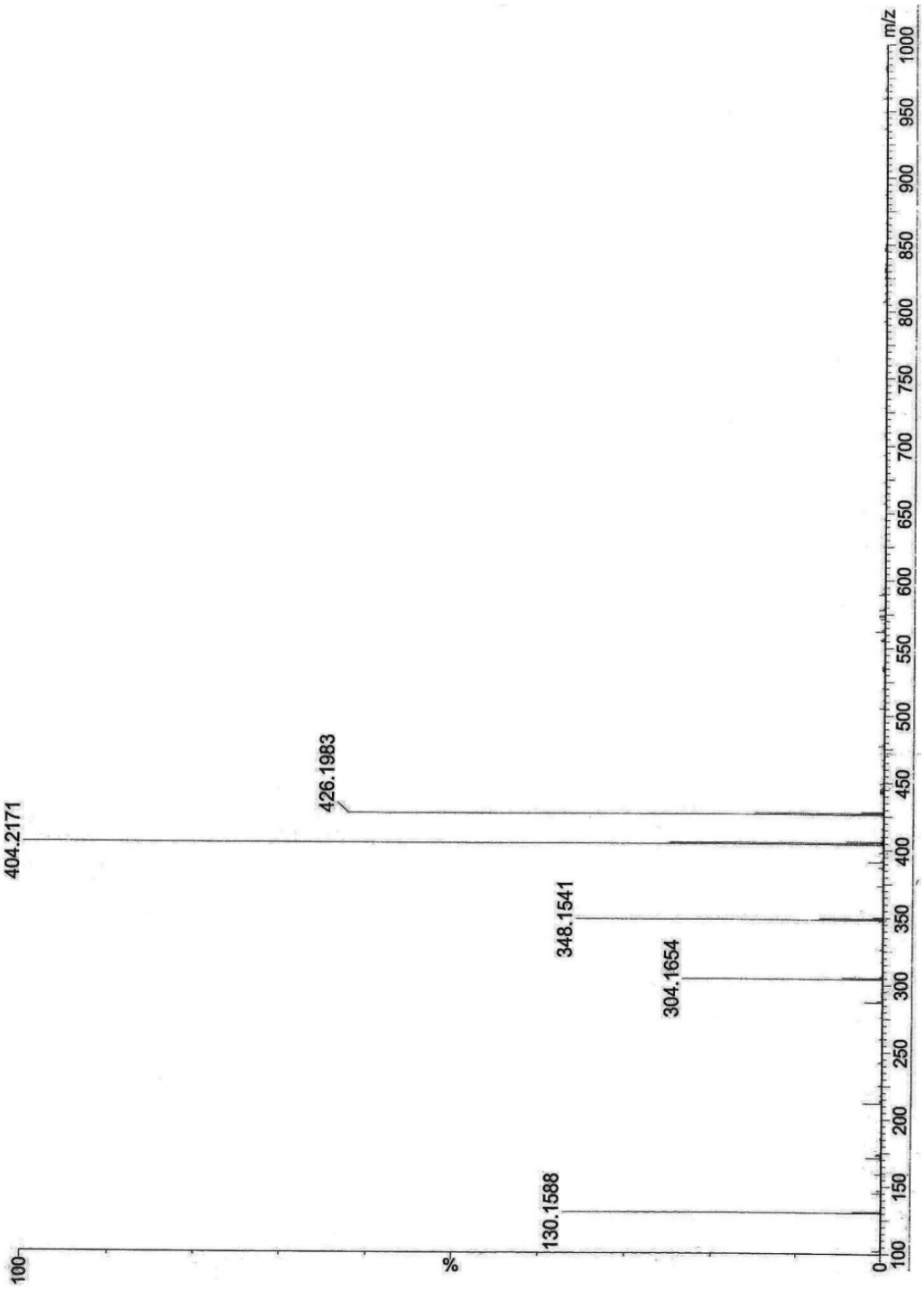
Procedure for preparation of compound 17. A mixture of compound **15** (7.78 mmol) and **16** (7.78 mmol) in aqueous HCl (10 mL, 6N) and dioxane (10 mL) is stirred at reflux temperature. After stirring for 1 h, reaction mass was concentrated under reduced pressure and DCM was charged and washed with saturated sodium bicarbonate solution (30 mL). Theraafter, solvent was evaporated under reduced pressure to get crude compound **17** followed by its purification through column chromatography using petroleum ethers: ethylacetate (7:3) to give pure compound **17** in 80-85% yield range.

(6*S*,12a*R*)-6-(2-bromophenyl)-2-methyl-2,3,12,12a-tetrahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4(6H,7H)-dione (17a). 80% Isolated yield; mp 283-284 °C; purity by HPLC 99.9%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.92-2.96 (m, 1H), 3.02 (s, 3H), 3.49 (dd, 1H, *J*.15.6 Hz, 4.3 Hz), 4.07-4.13 (m, 2H), 4.33 (dd, 1H, *J*.11.95 Hz, 4.4 Hz), 6.84 (d, 1H, *J*.9.3 Hz), 7.16-7.26 (m, 5H), 7.32 (d, 1H, *J*.7.8 Hz), 7.52 (d, 1H, *J*.7.8 Hz), 7.65 (d, 1H, *J*.9.3 Hz), 7.97 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 27.3, 29.7, 33.3, 51.4, 52.2, 53.0, 60.4, 108.7, 111.3, 118.3, 120.0, 122.7, 124.1, 126.2, 127.5, 129.8, 130.3, 131.1, 133.7, 136.3, 136.7, 163.2, 166.1; IR (KBr) ν 3305, 3057, 2930, 1668, 1655, 1621, 1453, 1328, 1041, 743.5 cm^{-1}; $[\alpha]_D^{29.6}$ = 199.78 (c 0.50, $CHCl_3$); EI-MS m/z = 422 [M^-].

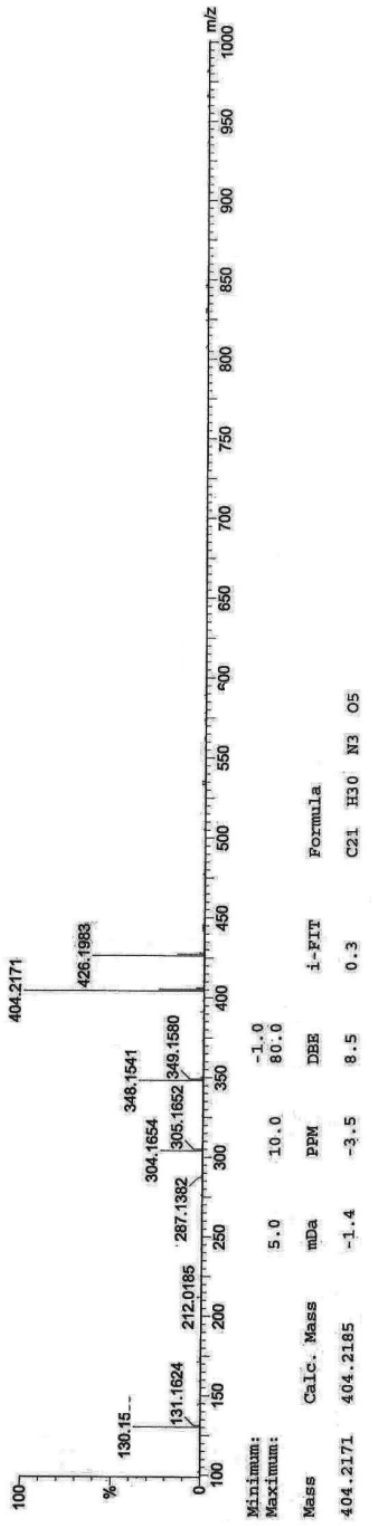
(6*S*,12a*R*)-6-(4-methoxyphenyl)-2-methyl-2,3,12,12a-tetrahydropyrazino[1',2':1,6]pyrido[3,4-b] indole-1,4(6H,7H)-dione(17b). 82% Isolated yield; mp 245-246 °C; purity by HPLC 99.0%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.92-2.96 (m, 1H), 2.99 (s, 3H), 3.56 (dd, 1H, *J*.15.5 Hz, 4.4 Hz), 3.8 (s, 3H), 3.99 (d, 1H, *J*.17.6 Hz), 4.1 (d, 1H, *J*.17.6 Hz), 4.34 (dd, 1H, *J*.11.95 Hz, 4.4 Hz), 6.84 (m, 2H), 7.0 (s, 1H), 7.16-7.23 (m, 4H), 7.31 (d, 1H, *J*.7.8 Hz), 7.52 (d, 1H, *J*.7.6 Hz), 7.86 (brs,1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 33.3, 51.3, 51.5, 52.3, 55.3, 108.7, 111.1, 114.1, 118.3, 119.8, 122.5, 126.2, 130.0, 130.5, 136.3, 159.8, 161.4, 165.4; IR (KBr) ν 3333, 3057, 2932, 1658, 1648, 1591, 1459, 1329, 1237, 1126, 1004, 745, 708 cm^{-1}; $[\alpha]_D^{29.4}$ = 202.63 (c 0.49, $CHCl_3$); EI-MS m/z = 374 [M^-].

(6*S*,12a*R*)-2-methyl-6-(3,4,5-trimethoxyphenyl)-2,3,12,12a-tetrahydropyrazino[1',2':1,6]pyrido [3,4-b]indole-1,4(6H,7H)-dione (17c). 85% Isolated yield; mp 239-240 °C; purity by HPLC 99.5%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.93-2.98 (m, 1H), 3.08 (s, 3H), 3.58 (dd, 1H, *J*.15.6 Hz, 4.4 Hz,), 3.7 (s, 3H), 3.8 (s, 6H), 4.01 (d, 1H, *J*.17.6 Hz), 4.15 (d, 1H, *J*.17.6 Hz), 4.4 (dd, 1H, *J*.12.2 Hz, 3.9 Hz,), 6.51 (s, 2H), 6.98 (s, 1H), 7.15-7.26 (m, 2H), 7.33 (d, 1H, *J*.7.9 Hz), 7.55 (d, 1H, *J*.7.9 Hz), 8.03 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 33.3, 51.3, 52.3, 52.8, 55.9, 60.5, 105.5, 108.5, 111.2, 118.2, 119.5, 122.3, 126.0, 134.1,

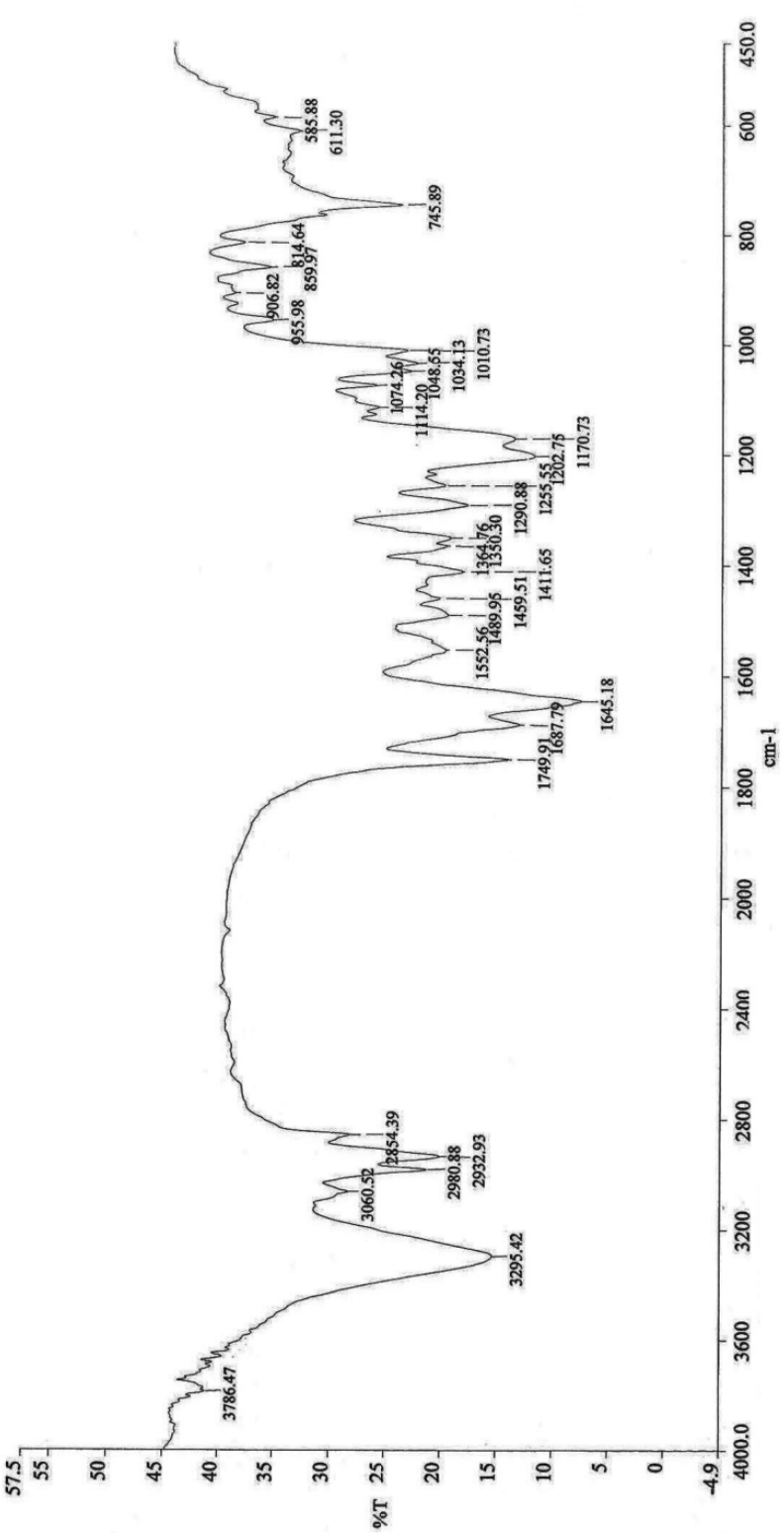
136.4, 137.4, 152.9, 161.5, 165.5; IR (KBr) ν 3266, 3058, 2925, 1655, 1464, 1329, 1248, 1175, 1158, 744 cm^{-1} $[\alpha]_D^{29.4}$: 220.19 (c 0.50, $CHCl_3$); EI-MS m/z = 434 [M^-].



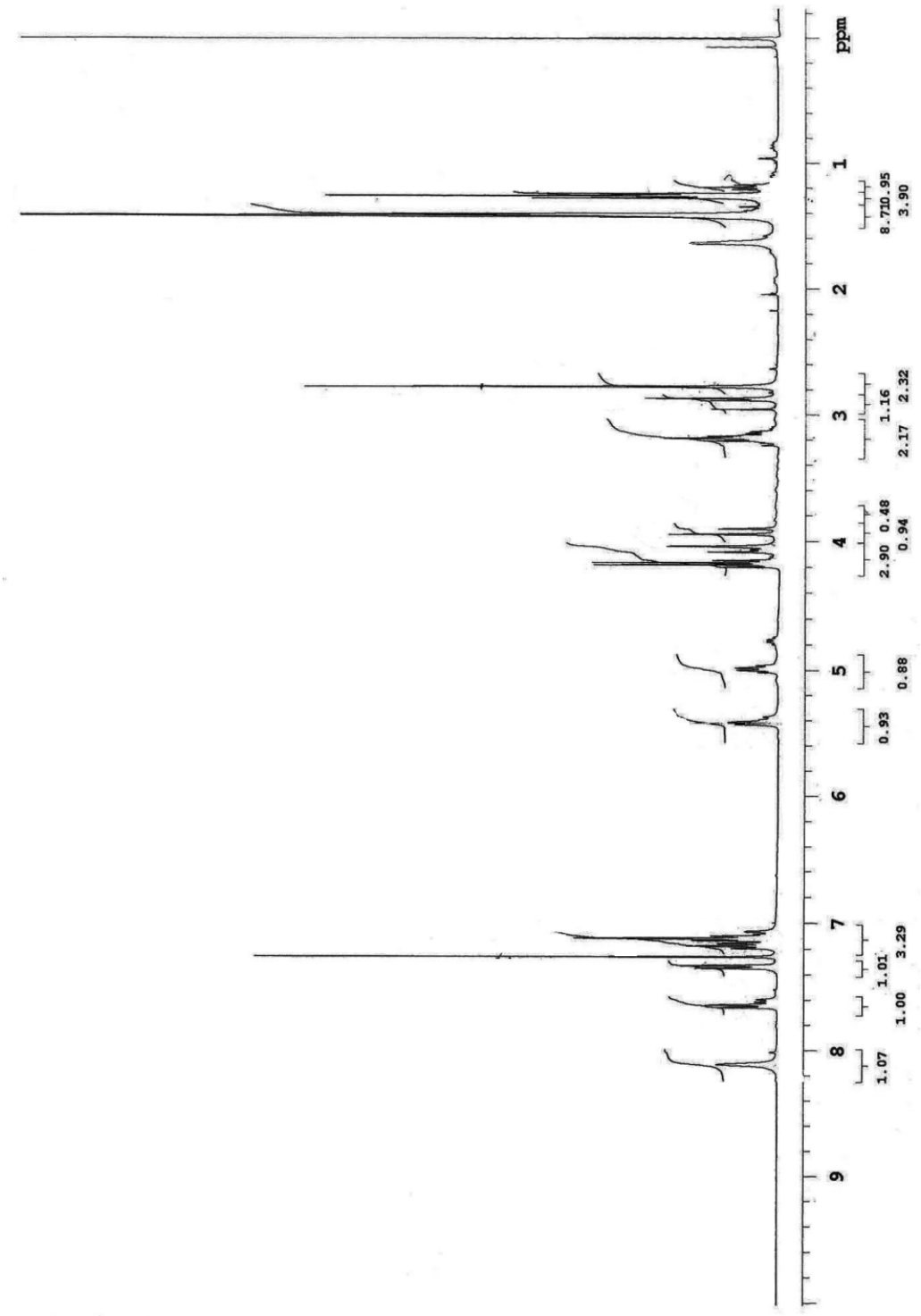
Mass Spectrum of compound 11



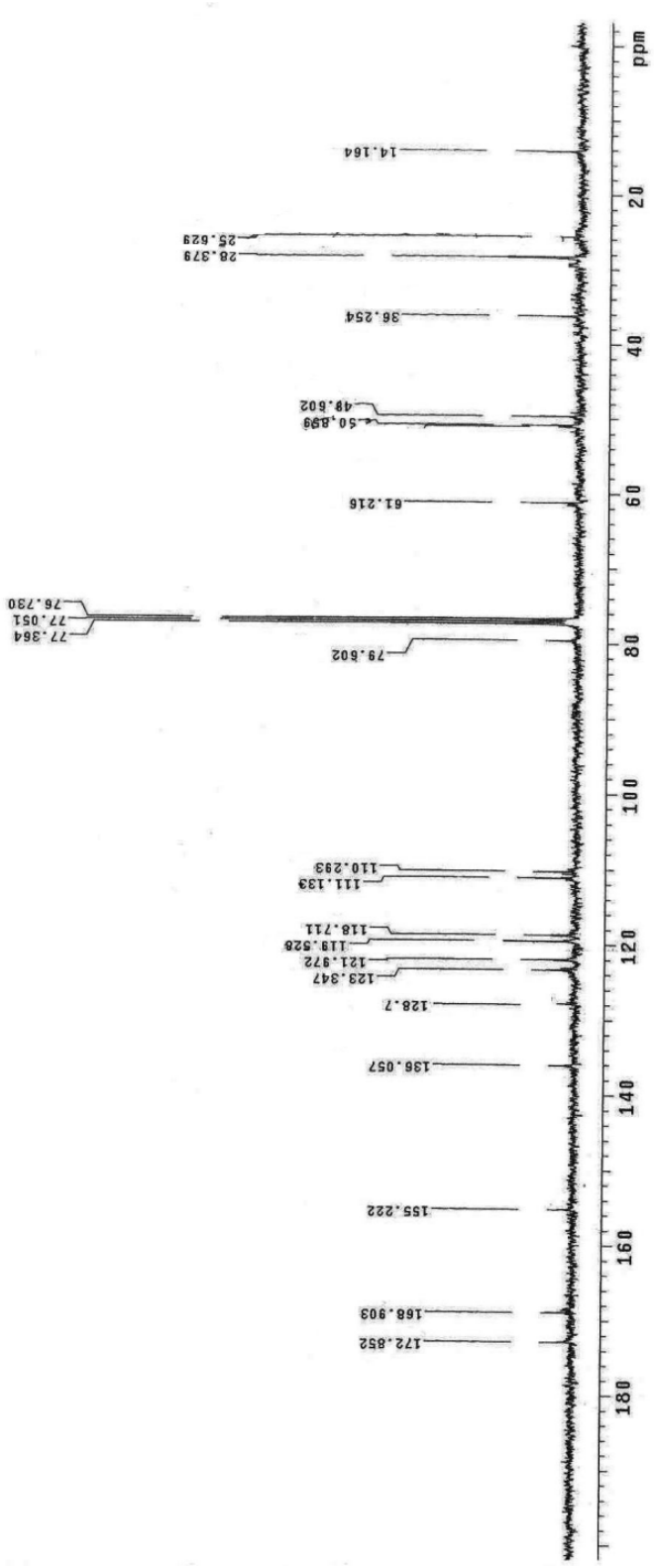
HRMS Spectrum of compound 11



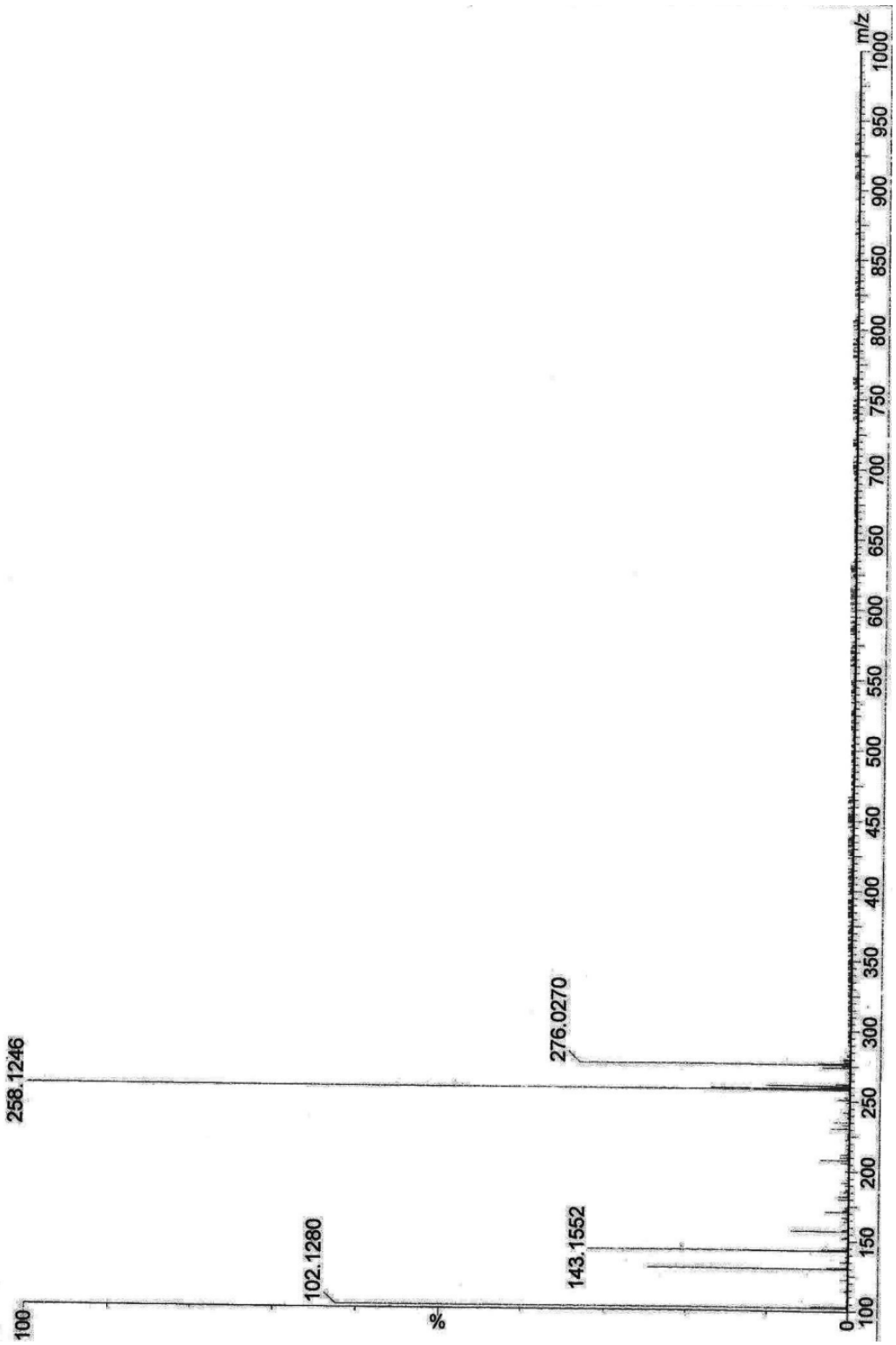
IR Spectrum of compound 11



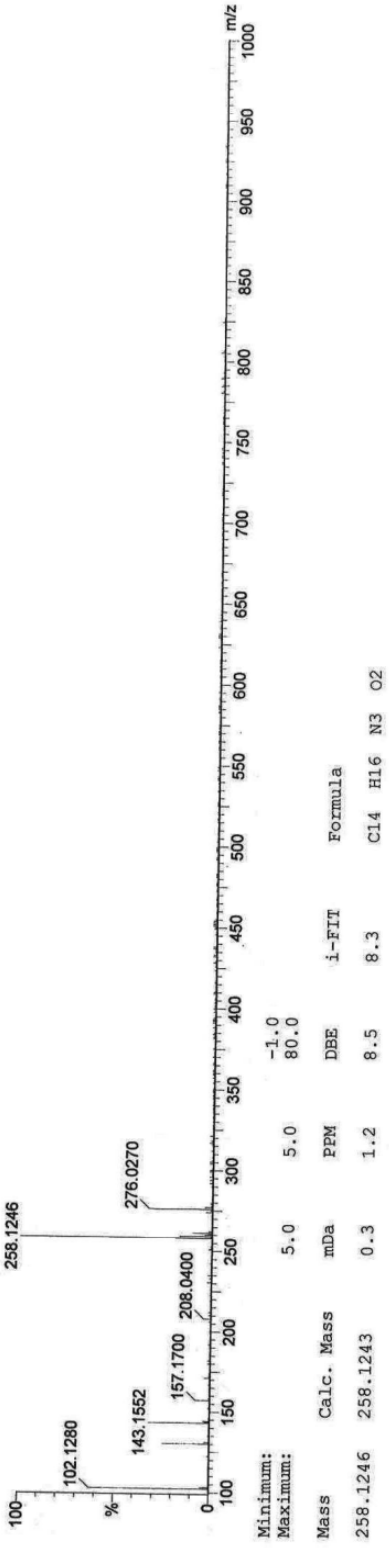
[1]H NMR Spectrum of compound 11



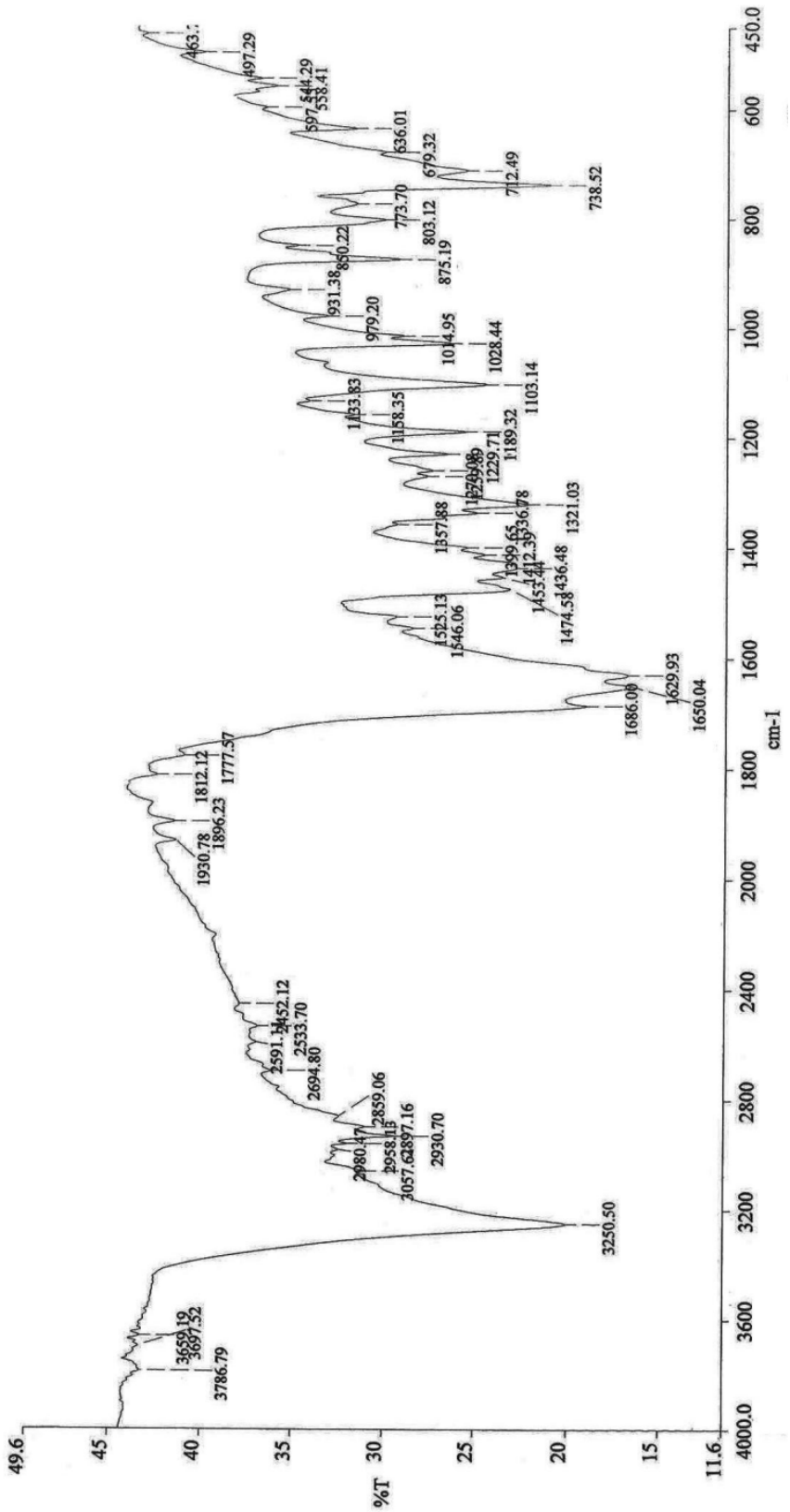
^{13}C NMR Spectrum of compound 11



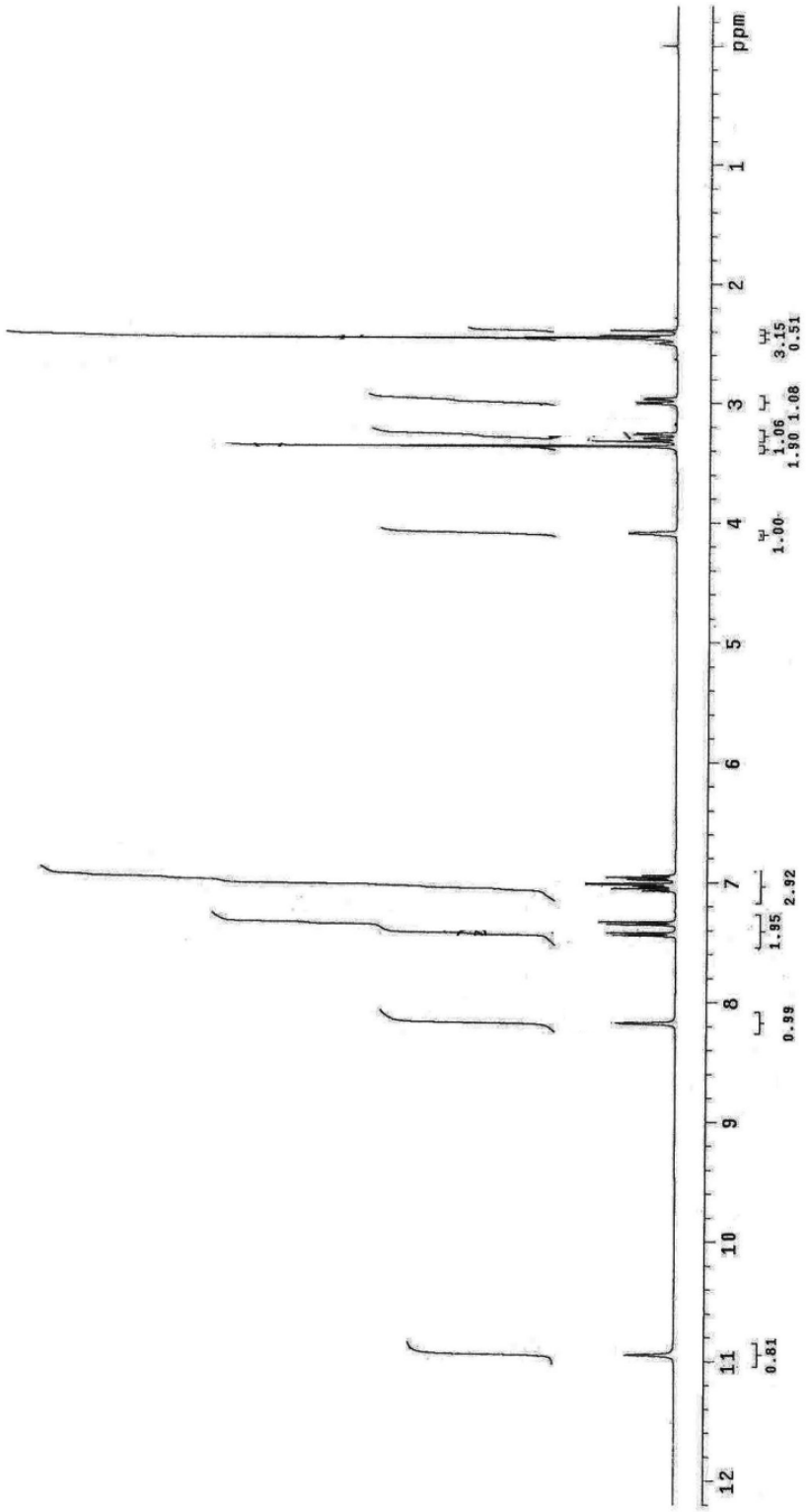
Mass Spectrum of compound 15



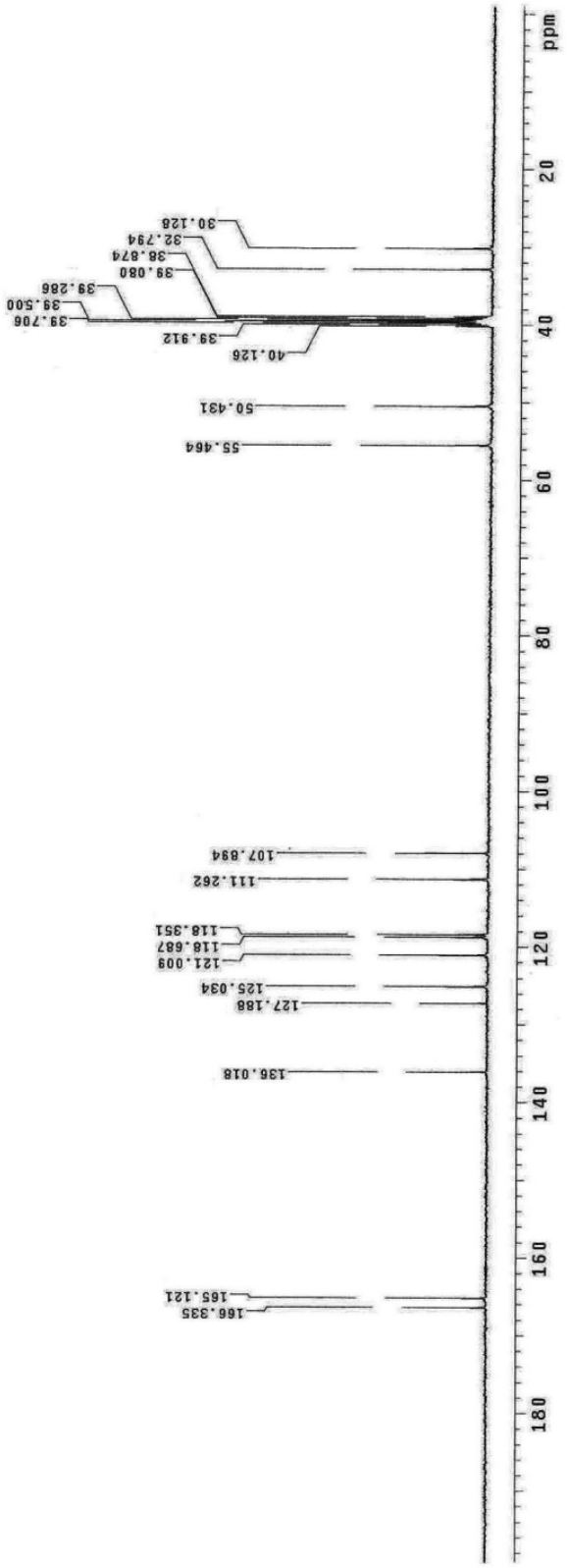
HRMS Spectrum of compound 15



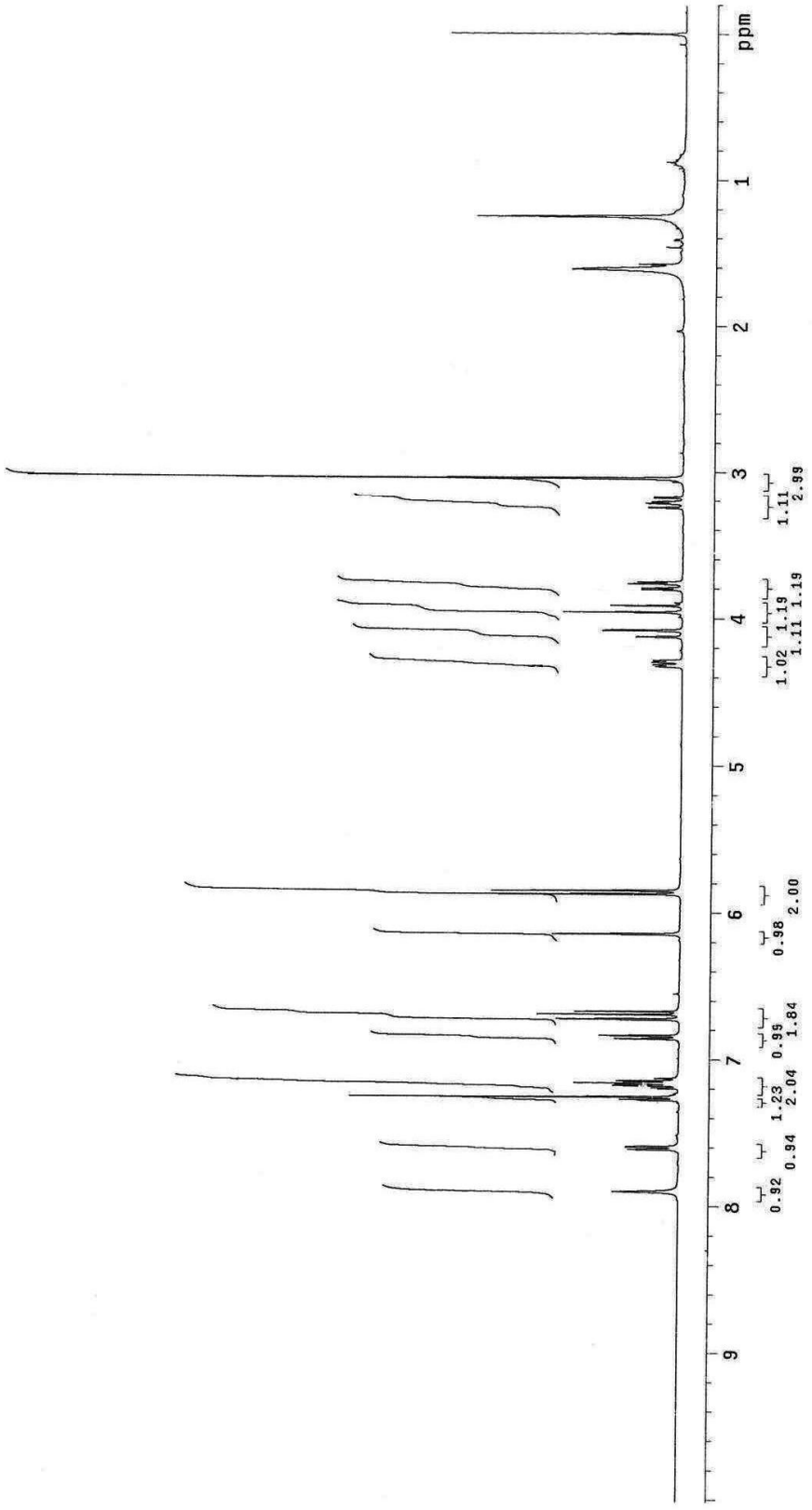
IR Spectrum of compound 15



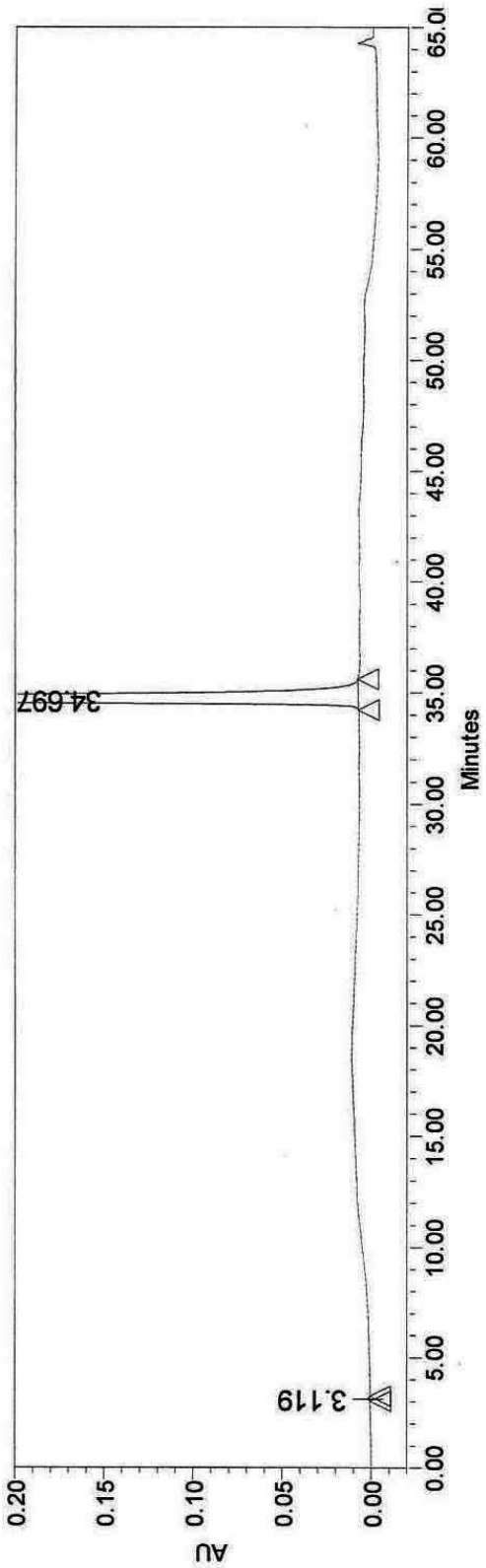
^{1}H NMR Spectrum of compound 15



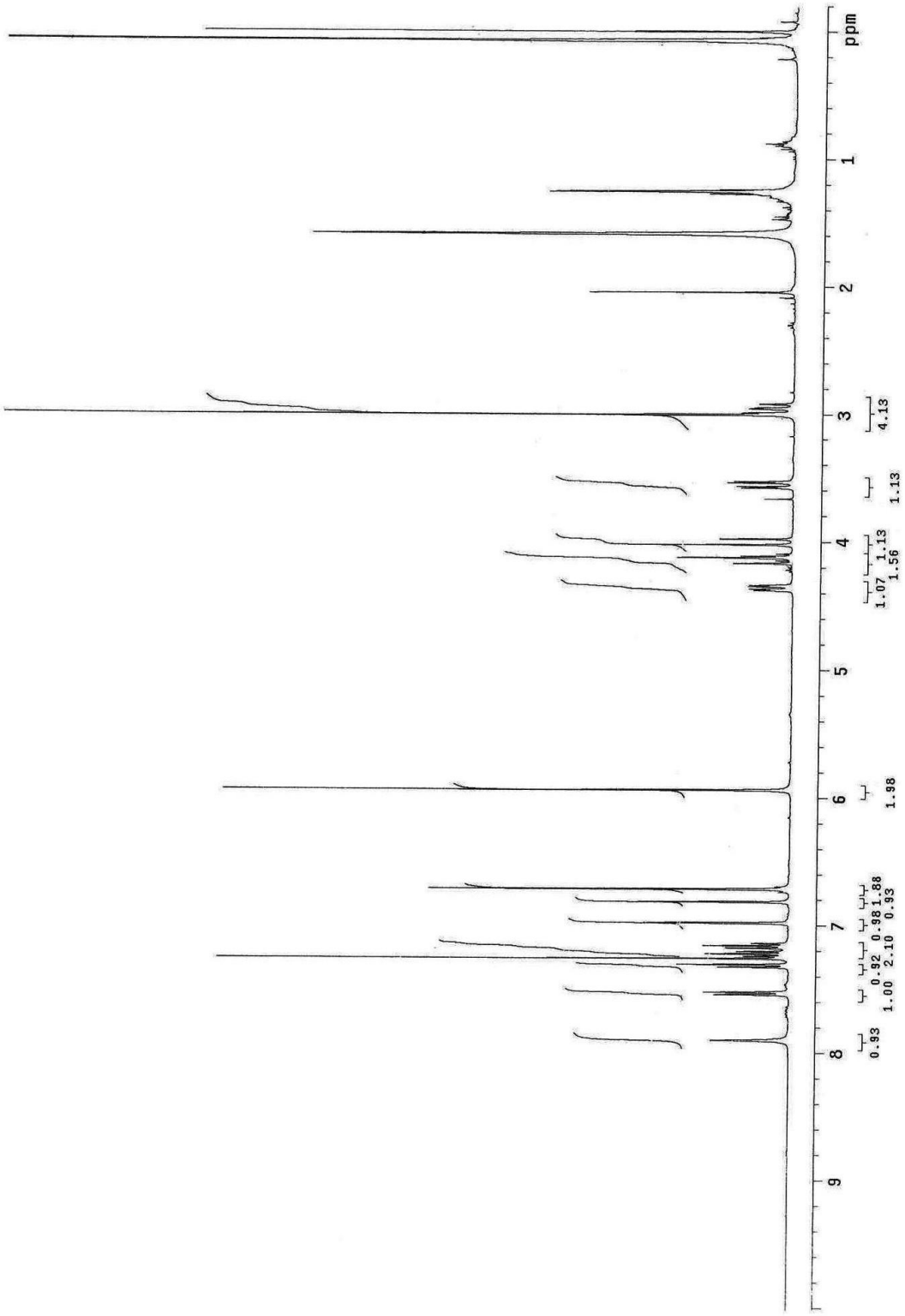
^{13}C NMR Spectrum of compound 15



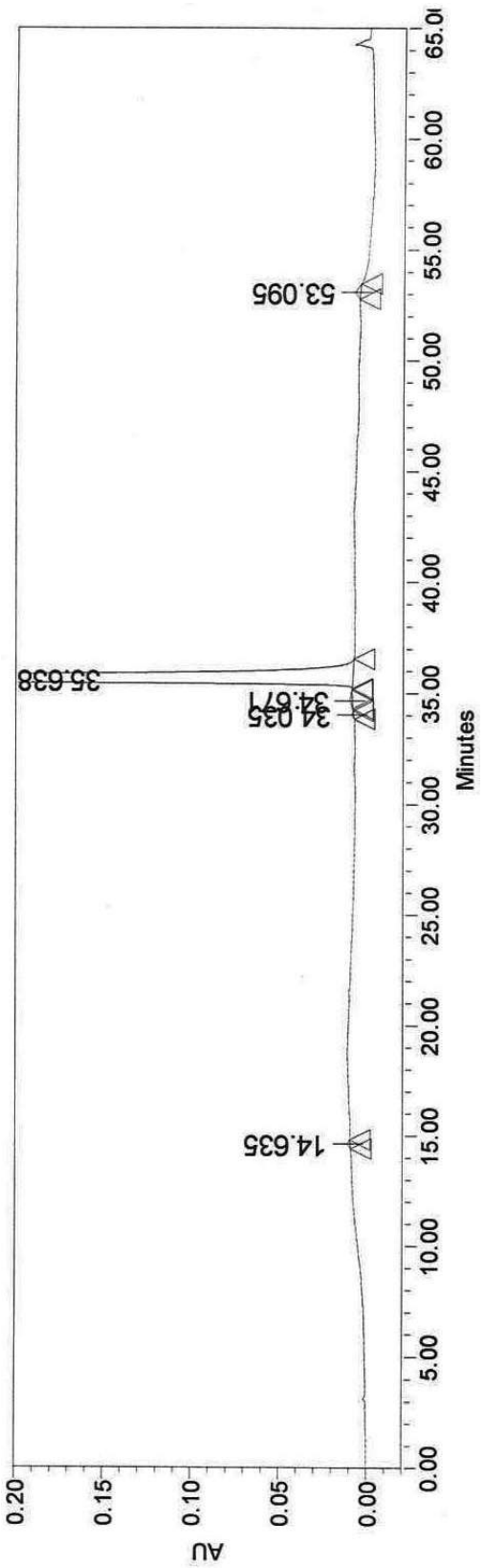
^{1}H NMR Spectrum of compound 1c



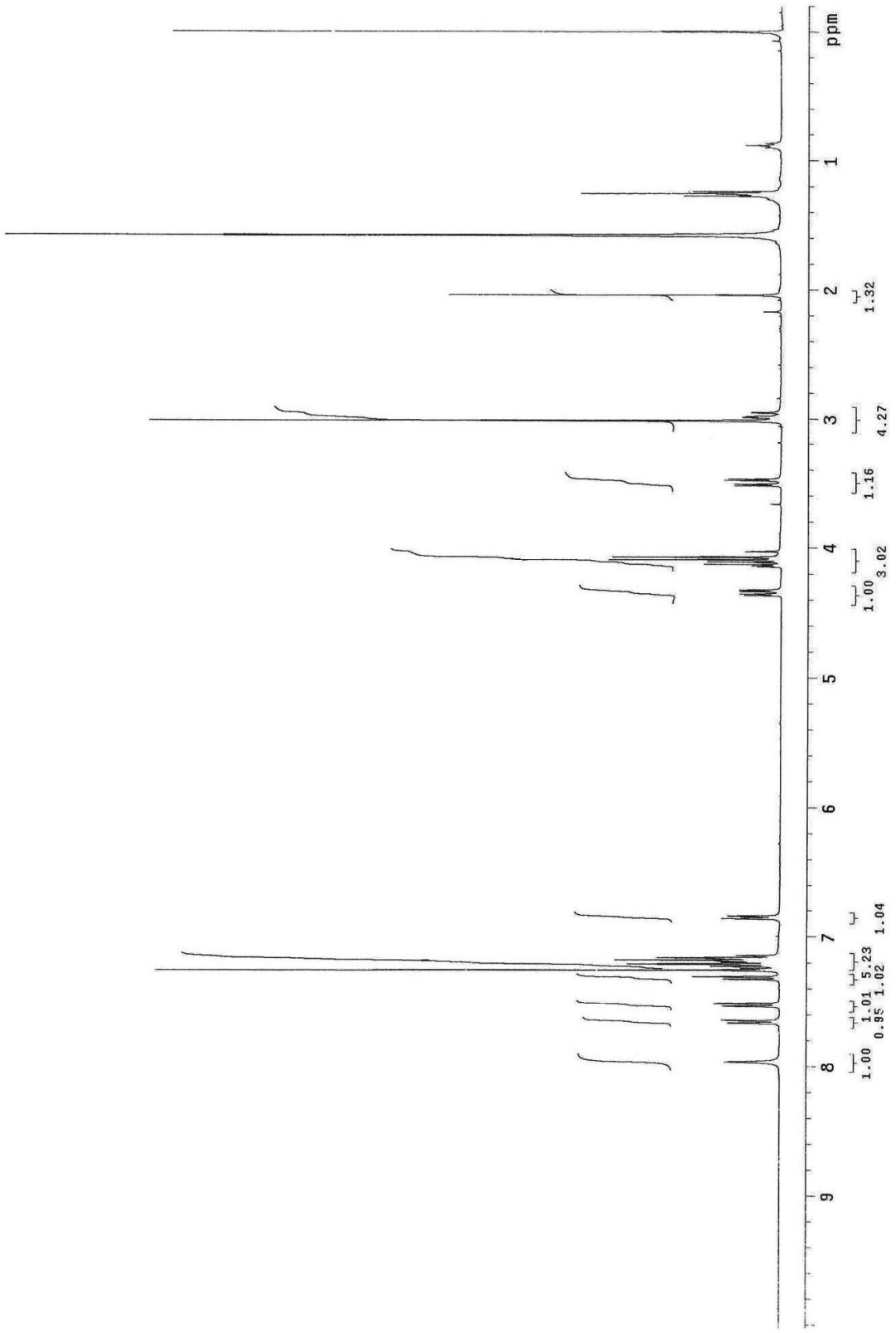
HPLC Chromatogram of compound 1c



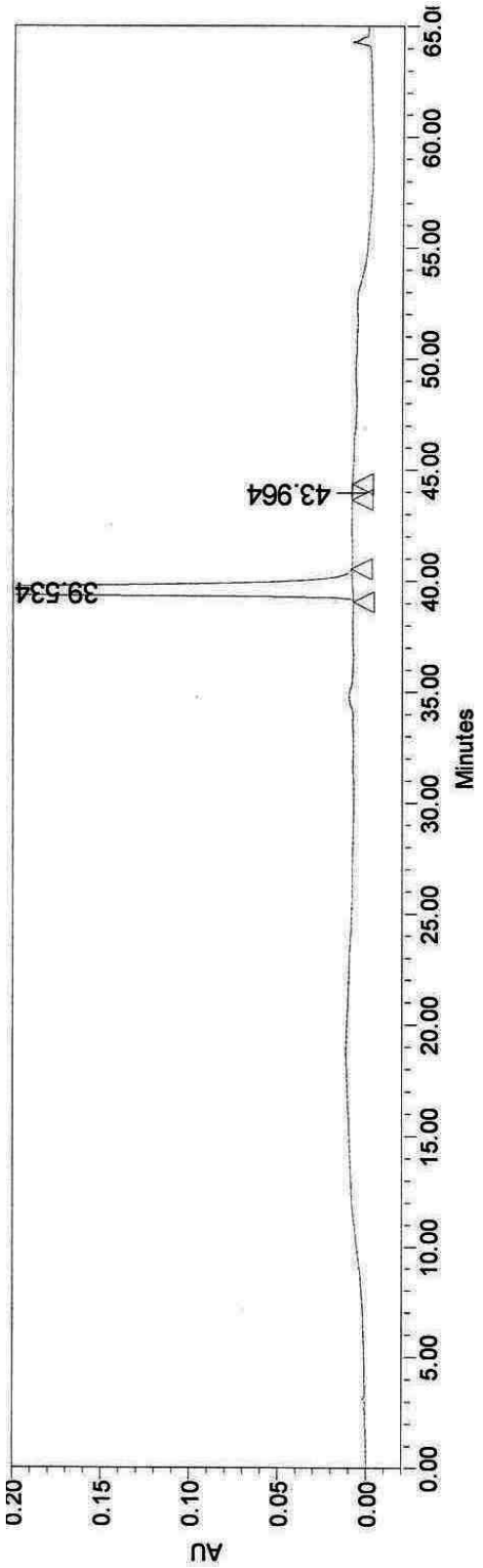
[1]H NMR Spectrum of compound 12



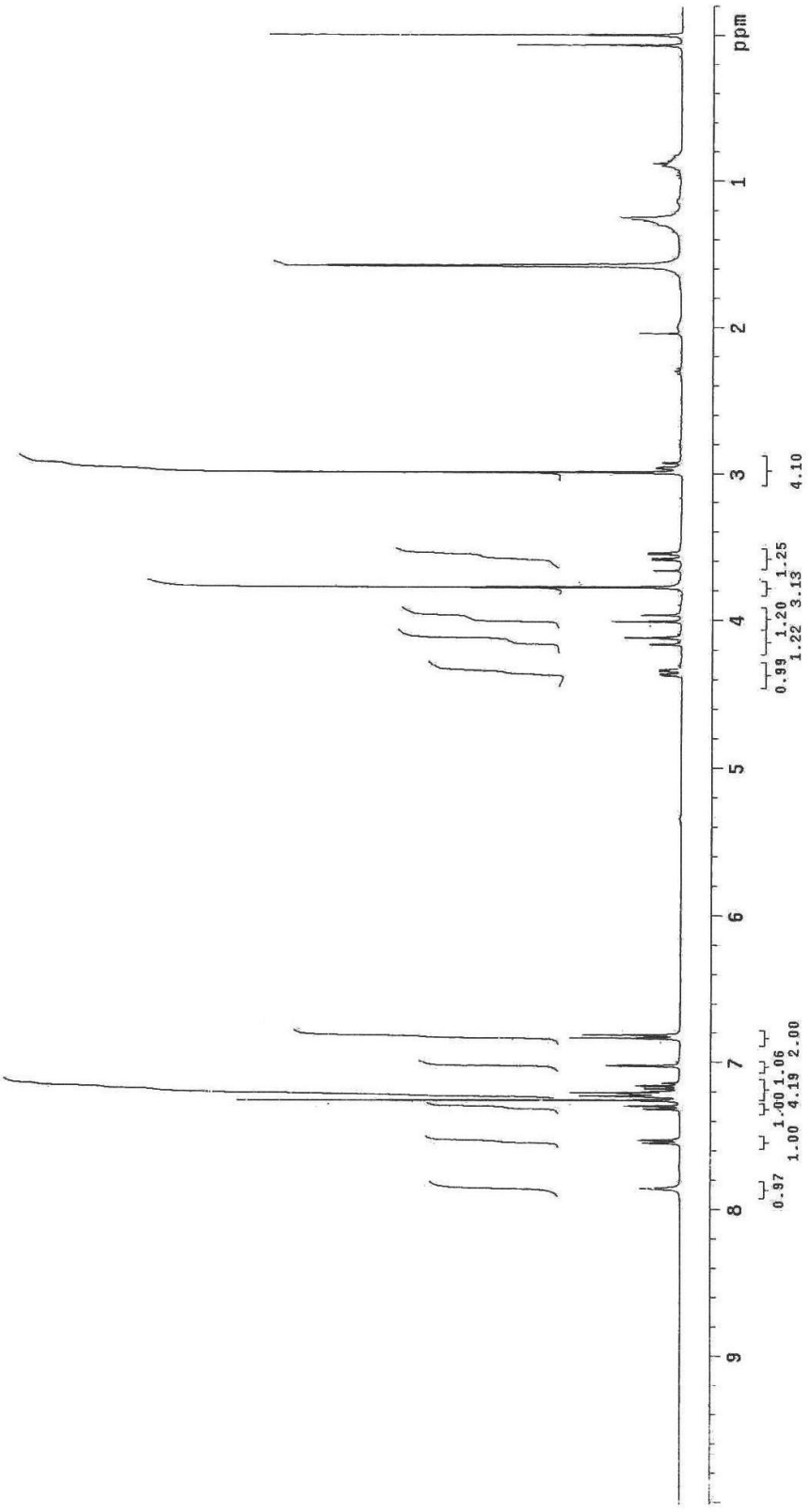
HPLC Chromatogram of compound 12



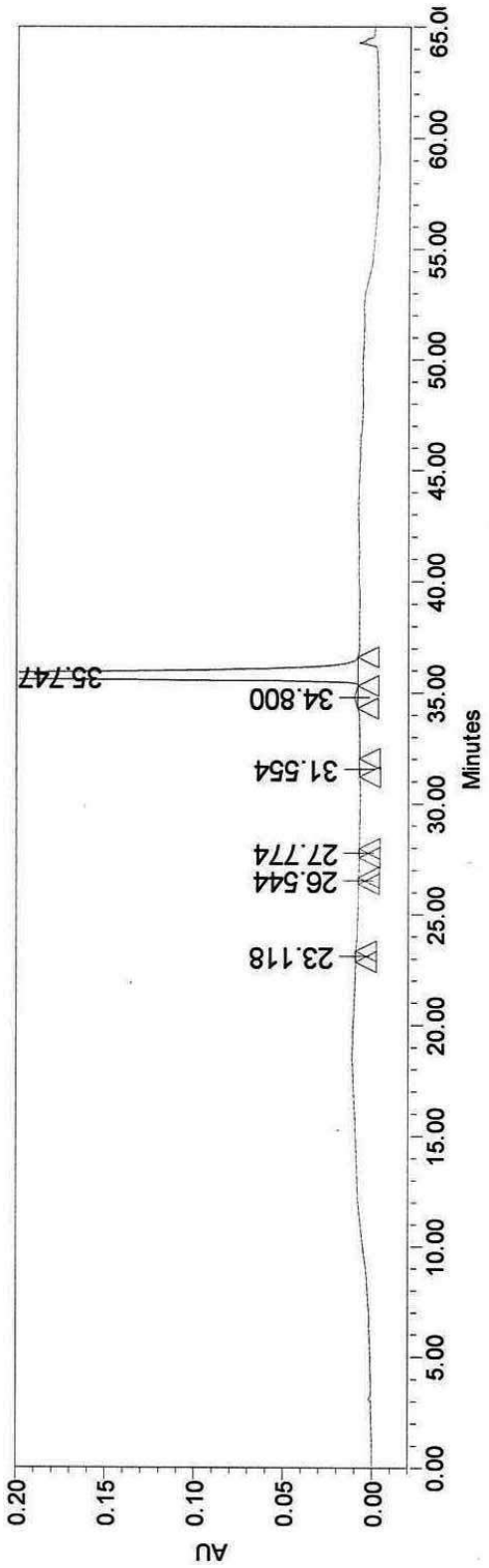
^{1}H NMR Spectrum of compound 17a



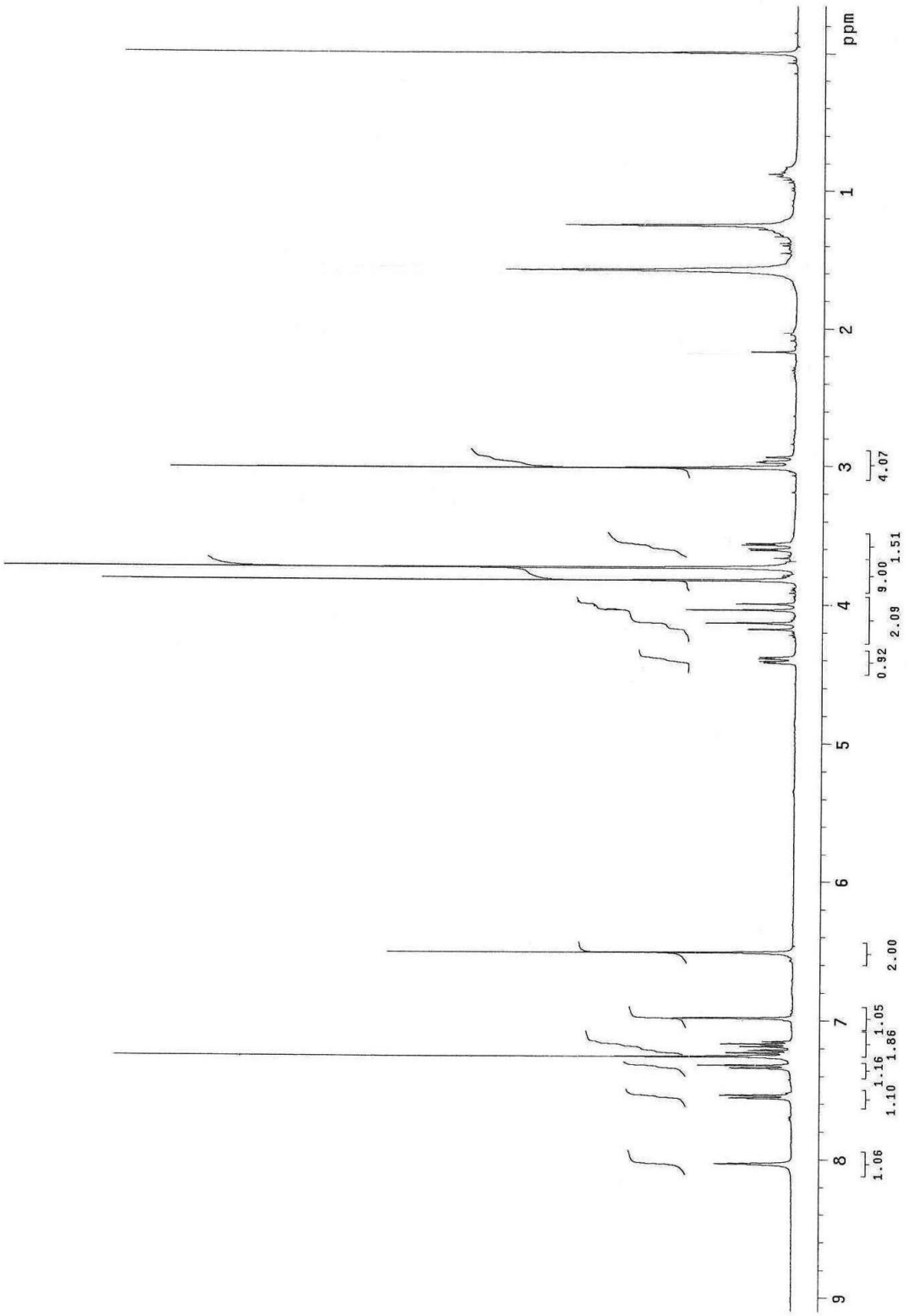
HPLC Chromatogram of compound 17a



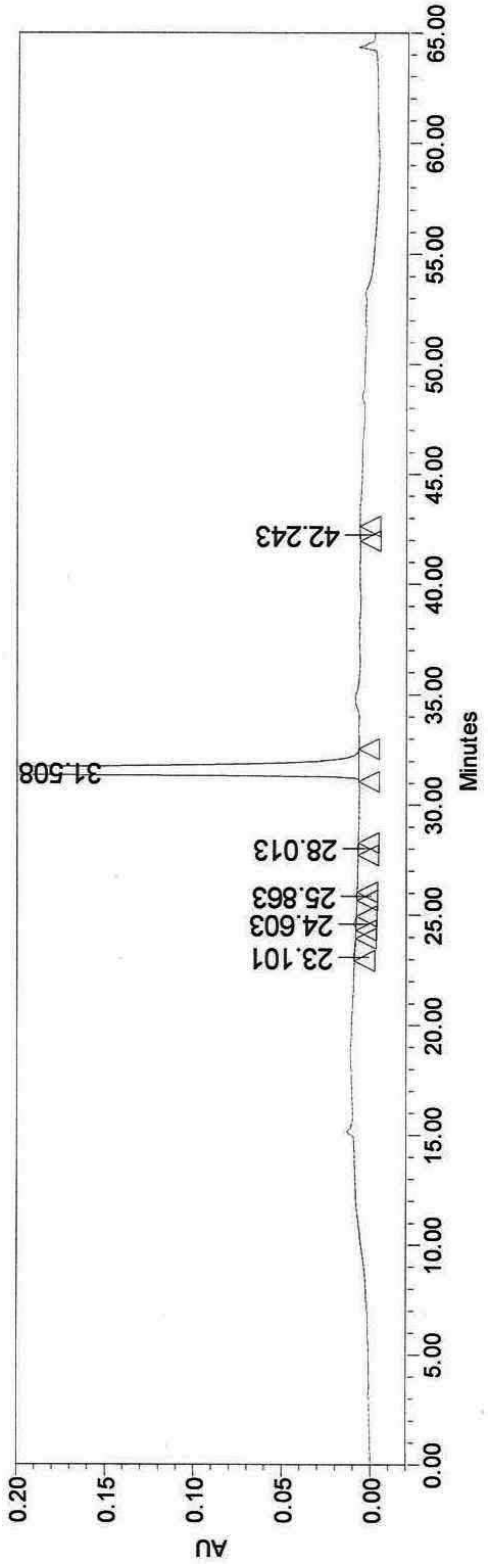
^{1}H NMR Spectrum of compound 17b



HPLC Chromatogram of compound 17b



^{1}H NMR Spectrum of compound 17c



HPLC Chromatogram of compound 17c

