Supporting Information

A Novel and Practical Synthesis of Ramelteon

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Materials and Methods

Unless otherwise noted, stated reagents were commercially available and used without purification. Reactions were monitored by thin layer chromatography (TLC) using ultra violet light (UV) as the visualizing agent. Nuclear magnetic resonance spectra (NMR) were obtained using a Bruker V-400 instrument at 400 mHz for ^{1}H and 100 Hz for ^{13}C in either $CDCl_3$ or DMSO-d_6. The chemical shift were reported in δ ppm relative to TMS. The following abbreviations were used to indicate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, m = multiplet). The melting points were determined by using Buchi M-565 apparatus. Specific optical rotations were performed using Rudolph Automatic Polarimeter IV, measurement wavelength: 589 nm. HPLC was used to establish the purity of compound **1** using Dionex U3000; HPLC column: Symmetry Shield RP C18 4.6 mm × 250 mm, particle size 5 µm, 1 ml/min flow, detection at 289 nm. The enantiomeric purity of compound **13** and compound **1** was also monitored by HPLC (HPLC column: Diacel Chiralcel OD-RH 4.6 mm × 150 mm, 5 µm).

Experimental Data

Preparation of 8-Hydroxy-4,5-dibromo-(1,2,6,7-tetrahydro-8*H*-indeno[5,4-*b*]furan-8-yl)acetonitrile(11). A 500 ml flask was charged with anhydrous tetrahydrofuran (200 ml) and n-butyllithium in hexane 2.5 M (96.4 ml, 0.24mol) was added at −75 °C under a nitrogen atmosphere, followed by a solution of acetonitrile (9.881 g, 0.24 mol) in tetrahydrofuran (50 ml). After stirring for 30 min, compound **2** (20 g, 0.06 mol) was added to the resulting white suspension and stirred for 2 h at −75 °C. The yellow reaction mixture was poured into 500 ml ice−water. The aqueous mixture was extracted with 2 × 200 ml ethyl acetate, dried over $MgSO_4$, and filtered. The organic layer was evaporated under vacuum to give the crude product of **11** as a light yellow solid. It was recrystallized with toluene to give the desired product as a white solid (17.298 g, 77% yield). Mp: 174−175 °C. ^{1}H−NMR(400 MHz, DMSO-d_6): δ 2.16 (m, 1H); 2.32 (m, 1H); 2.84 (m, 2H); 3.08 (dd, J=1.6, 2H); 3.40 (m, 2H); 4.66 (m, 2H,); 5.94 (br s,1H). MS (ES+): m/z 396$(M+Na)^+$.

Preparation of (S)- 2-(1,6,7,8-Tetrahydro-2*H*-indeno[5,4-*b*] furan-8-yl)ethylamine Dibenzoyl-L-tartaric Acid(13). A solution of **11** (12 g 0.03 mol) in acetic acid (60 ml) and H_2O (60 ml) was subjected to hydrogenation in the presence of palladium 10% on carbon

(1.8 g) in a hydrogen pressure (3.0 MPa) at 60 °C for 18 h. After hydrogen absorption ceased, the catalyst was removed by filtration. The filtrate was concentrated to dryness and the residue was neutralized with 10% NaOH (aq). The mixture was extracted with 4× 30 ml ethyl acetate, dried over $MgSO_4$, and filtered. Then, dibenzoyl-L-tartaric acid (11.517 g, 0.03 mol) was added to the filtrate and stirred at room temperature for 1 h and filtered to afford a white solid of 2-(1,6,7,8-tetrahydro-2*H*-indeno[5,4-*b*]furan-8-yl)ethylamine dibenzoyl -L-tartaric acid(**12**) (16.063 g, 89% yield).

The above **12** (11.220 g, 0.02 mol) was recrystallized with acetonitrile: ethyl alcohol=5:4 to afford a white solid of (S)-2-(1,6,7,8-tetrahydro-2*H*-indeno[5,4-*b*]furan-8-yl)-ethylamine dibenzoyl-L-tartaric acid (**13**) (4.151 g, 37% yield, 98.6% ee). Mp: 1.69−171°C. ^{1}H−NMR(400 MHz, DMSO-d_6): δ 1.60 (m, 2H); 2.05 (m, 2H); 2.71 (m, 4H); 3.07 (m, 3H); 4.45 (m, 2H); 5.66 (s, 2H,); 6.54 (d, J=8, 1H); 6.89 (d, J=8, 1H); 7.50 (m, 4H); 7.63 (m,2H); 7.93 (d, J=4 4H); 8.00 (br s,2H). MS (ES+): m/z 204$(M+H)^+$. $[\alpha]_D$−115.2 (c=1.0, MeOH).

Preparation of (S)-*N*-[2-(1,6,7,8-Tetrahydro-2*H*-indeno[5,4-*b*] furan-8-yl)ethyl]propionamide(1). To a solution of **13** (4 g, 7 mmol) in tetrahydrofuran (40 ml) was added 20% NaOH (aq) (1.120 g, 28 mmol) and stirred at −10 °C. And then propionyl chloride (0.777 g, 8.4

mmol) was added dropwise at −10 °C. After that, the reaction mixture was stirred at room temperature for 2 h, and ethyl acetate (40 ml) and water (40 ml) were added. After separation, the aqueous layer was extracted with 2×30 ml ethyl acetate. The organic layer was washed with brine and dried over $MgSO_4$. The filtrate was concentrated to give a solid, which was recrystallized from ethanol and water to afford a white solid of **1**(1.570 g, 85% yield, 99.8% ee). Purity by HPLC 99.6%. Mp: 115−116 °C(113−115°C in literature [1]). ^{1}H−NMR(400 MHz, $CDCl_3$): δ 1.39 (t, 3H); 1.63 (m, 1H); 1.83 (m, 1H); 2.02 (m, 1H); 2.16 (dd, J=8, 2H); 2.28 (m, 1H); 2.78 (m, 1H); 2.83 (m, 1H); 3.14 (m, 1H); 3.22 (m, 2H); 3.33 (m, 2H); 4.54 (m, 2H); 5.38 (br s, 1H); 6.61 (d, J=8, 1H); 6.97 (d, J=8, 1H). ^{13}C−NMR(100 MHz, $CDCl_3$): δ 173.85, 159.56, 143.26, 135.92, 123.52, 122.28, 107.56, 71.26, 42.37, 38.17, 33.66, 31.88, 30.82, 29.86, 28.73, 10.01. MS (ES+): m/z 282$(M+Na)^+$. $[\alpha]_D$ −57.3(c=1.0, $CHCl_3$, −57.8 in literature [1]). Anal. ($C_{16}H_{21}NO_2$) Calc: C, 74.10; H, 8.16; N, 5.40; found: 74.09; H, 8.17; N, 5.47.

Preparation of 8-Hydroxy -(1,2,6,7-tetrahydro-8*H*-indeno[5,4-*b*]furan-8-yl)acetonitrile(15). A solution of **11** (2 g, 0.005 mol) in acetic acid (10 ml) and H_2O (10 ml) was subjected to hydrogenation in the presence of palladium 10% on carbon (1.8 g) while hydrogen was bubbled into the reaction mixture at 60 °C for 18 h. Then, the catalyst was removed by filtration. The filtrate

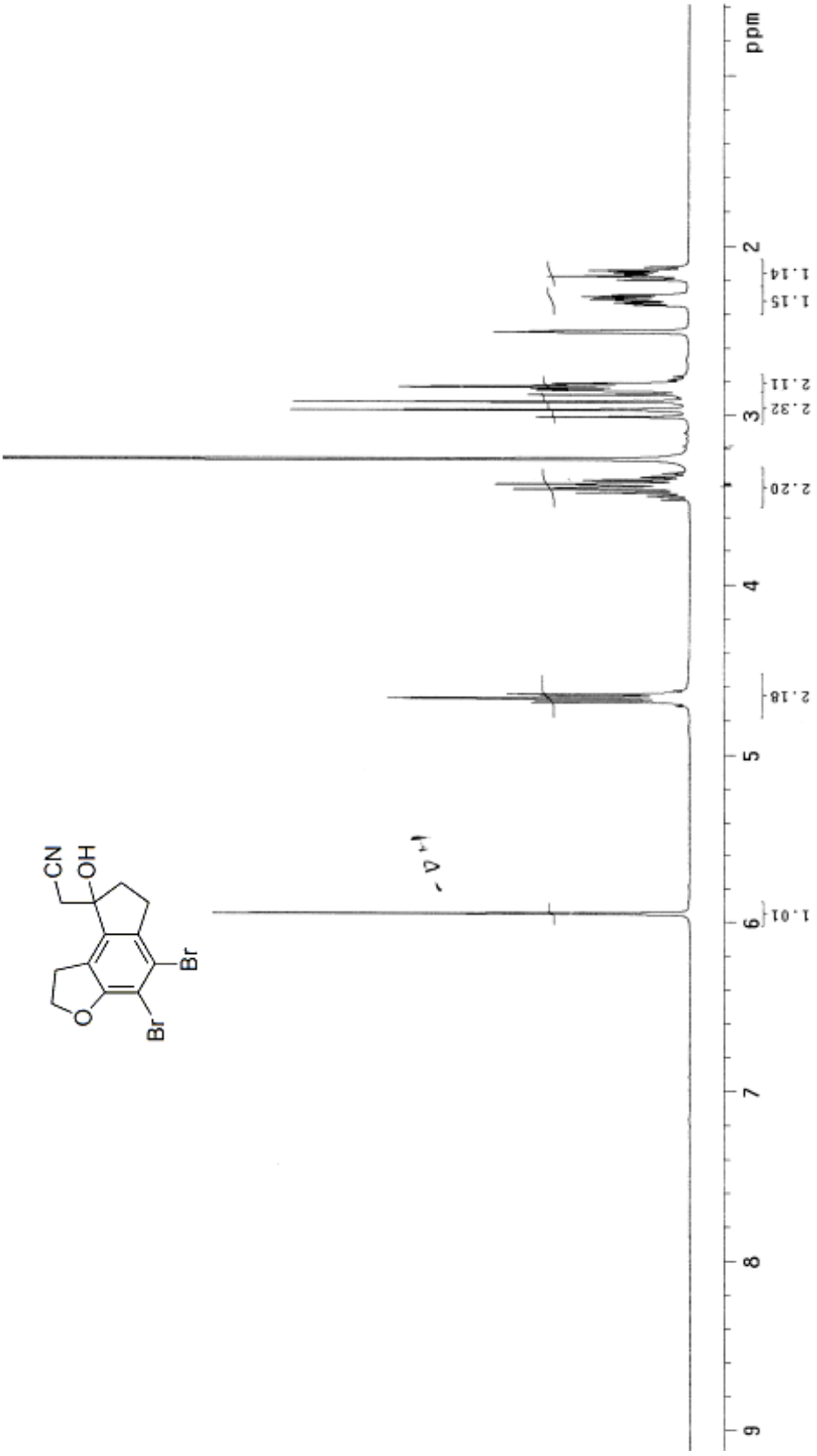
was concentrated into dryness. Water was added into the residue and then extracted with 3×10 ml ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. After concentration, the residue was separated by column chromatography with ethyl acetate−hexanes 1:9, and compound **15** was obtained as a white solid (0.813 g 77% yield). Mp: 122−123 °C. ^{1}H−NMR(400 MHz, $CDCl_3$): δ 2.21 (m, 1H); 2.52 (m, 1H); 2.80 (dd, J=16, 2H); 2.91 (m, 2H), 3.32 (m, 2H); 4.57 (m, 2H); 6.73 (d, J=8, 1H); 6.97 (d, J=8, 1H). MS (ES+): m/z 238$(M+Na)^+$.

Preparation of 2-(1,2,6,7-Tetrahydro-8*H*-indeno[5,4-*b*]furan-8-ylidene)acetonitrile(9). A solution of **11** (2 g, 0.005 mol) in acetic acid (10 ml) and H_2O (10 ml) was subjected to hydrogenation in the presence of palladium 10% on carbon (1.8 g) in a hydrogen pressure of 0.5 MPa at 60 °C for 18 h. Then, the catalyst was removed by filtration. The filtrate was concentrated to dryness. Water was added into the residue and then extracted with 3×10 ml ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. After column chromatography with 5% ethyl acetate in hexanes, compound **9** was obtained as a yellow solid (0.354 g, 34% yield). Mp: 149−150°C (146−151°C in literature [2]). ^{1}H−NMR(400 MHz, $CDCl_3$): δ 3.03 (t, 2H); 3.11 (m, 2H); 3.30 (t, 2H); 4.66 (t, 2H); 5.44 (t, 1H); 6.85 (d, J=8,

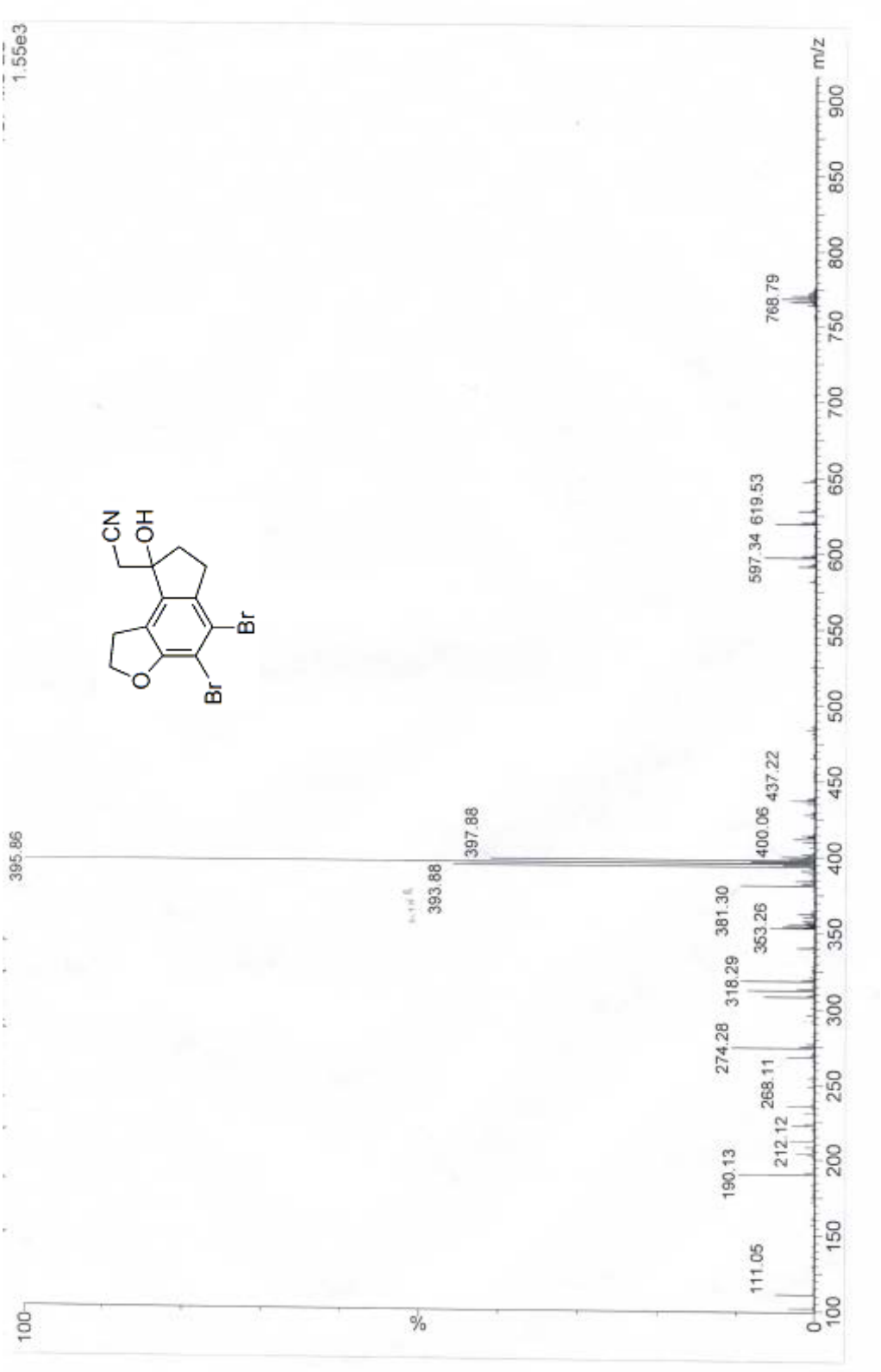
1H); 7.10 (d, J=8, 1H). MS (ES+):m/z 198$(M+H)^+$.

Preparation of 2,2'-Bis(1,2,6,7-tetrahydro-8*H*-indeno[5,4-*b*]furan-8-yl)-diethylamine (17). A solution of **11** (2 g, 0.005 mol) in acetic acid (10 ml) and CH_3OH (10 ml) was subjected to hydrogenation in the presence of palladium 10% on carbon (1.8 g, 15 wt %) in a hydrogen atmosphere (3.0 MPa) at 60 °C for 18 h. Then, the catalyst was removed by filtration. The filtrate was concentrated to dryness. Water was added into the residue. The mixture was neutralized with 10 wt % NaOH (aq), extracted with 4×30 ml ethyl acetate, dried over $MgSO_4$, and filtered. After that, compound **17** was separated by column chromatography (5% methanol in dichloromethane) as a white solid (0.259 g). Mp: 225−227 °C. ^{1}H−NMR(400 MHz, $CDCl_3$): δ 1.69 (m, 2H); 1.99 (m, 2H); 2.24 (m, 2H); 2.40 (m, 2H); 2.82 (m, 8H); 3.09 (m, 4H); 3.28 (m, 2H); 4.50 (m, 4H); 6.58 (d, J=8, 2H); 6.90 (d, J=8, 2H); 9.68 (br s, 1H). MS (ES+):m/z 390$(M+H)^+$.

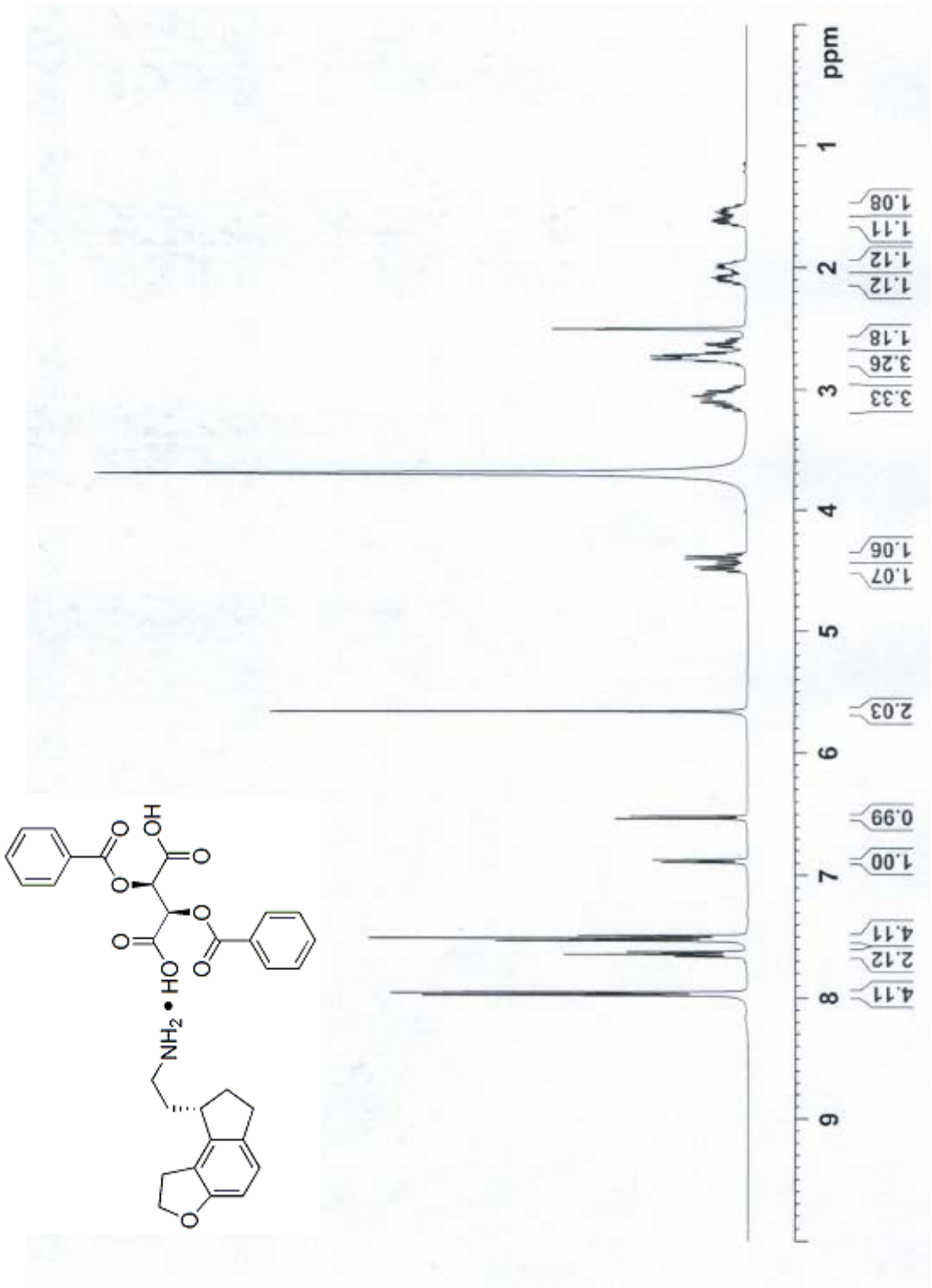
Spectroscopic Data



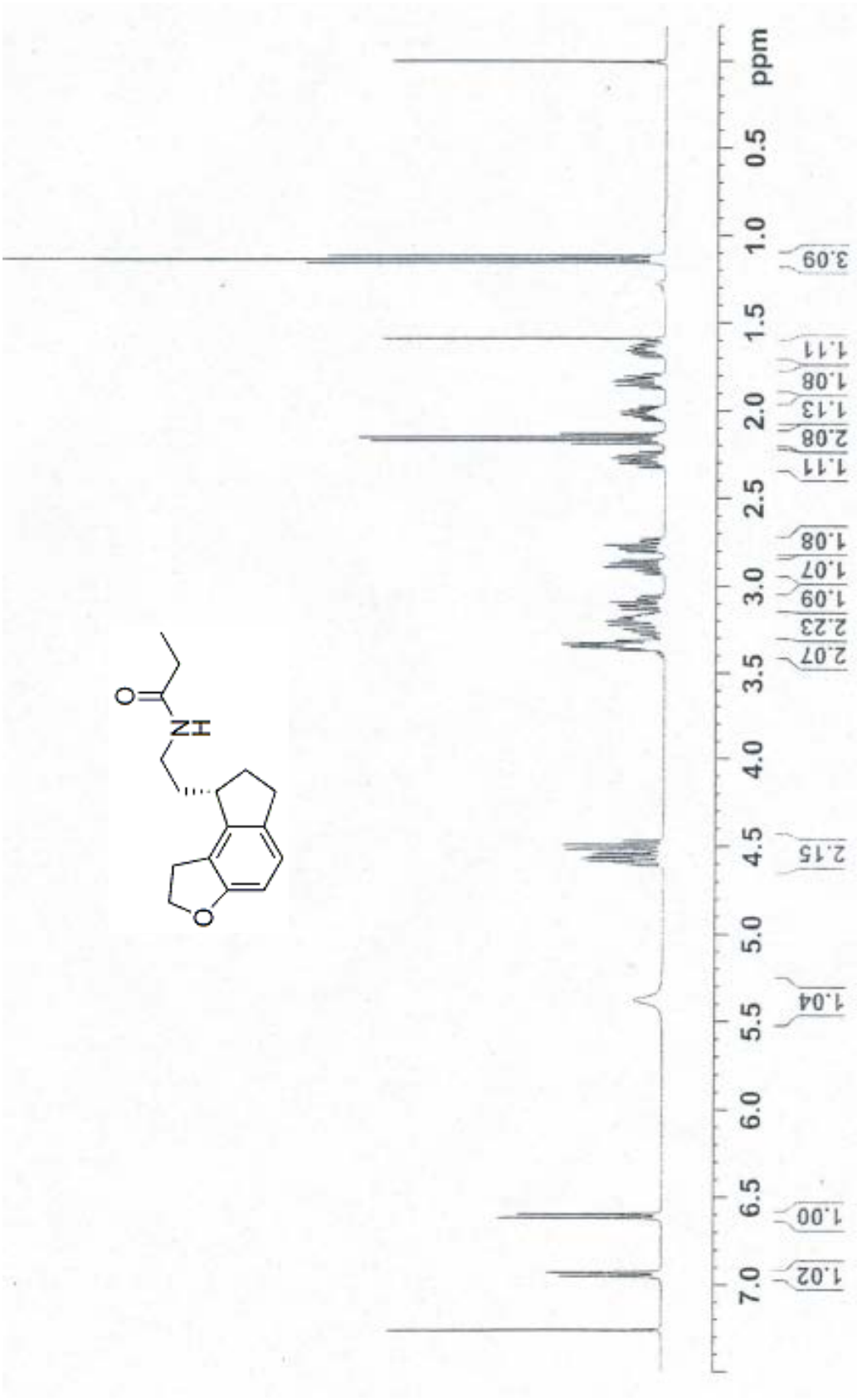
^{1}H NMR (400 MHz, DMSO-d_6) of compound **11**



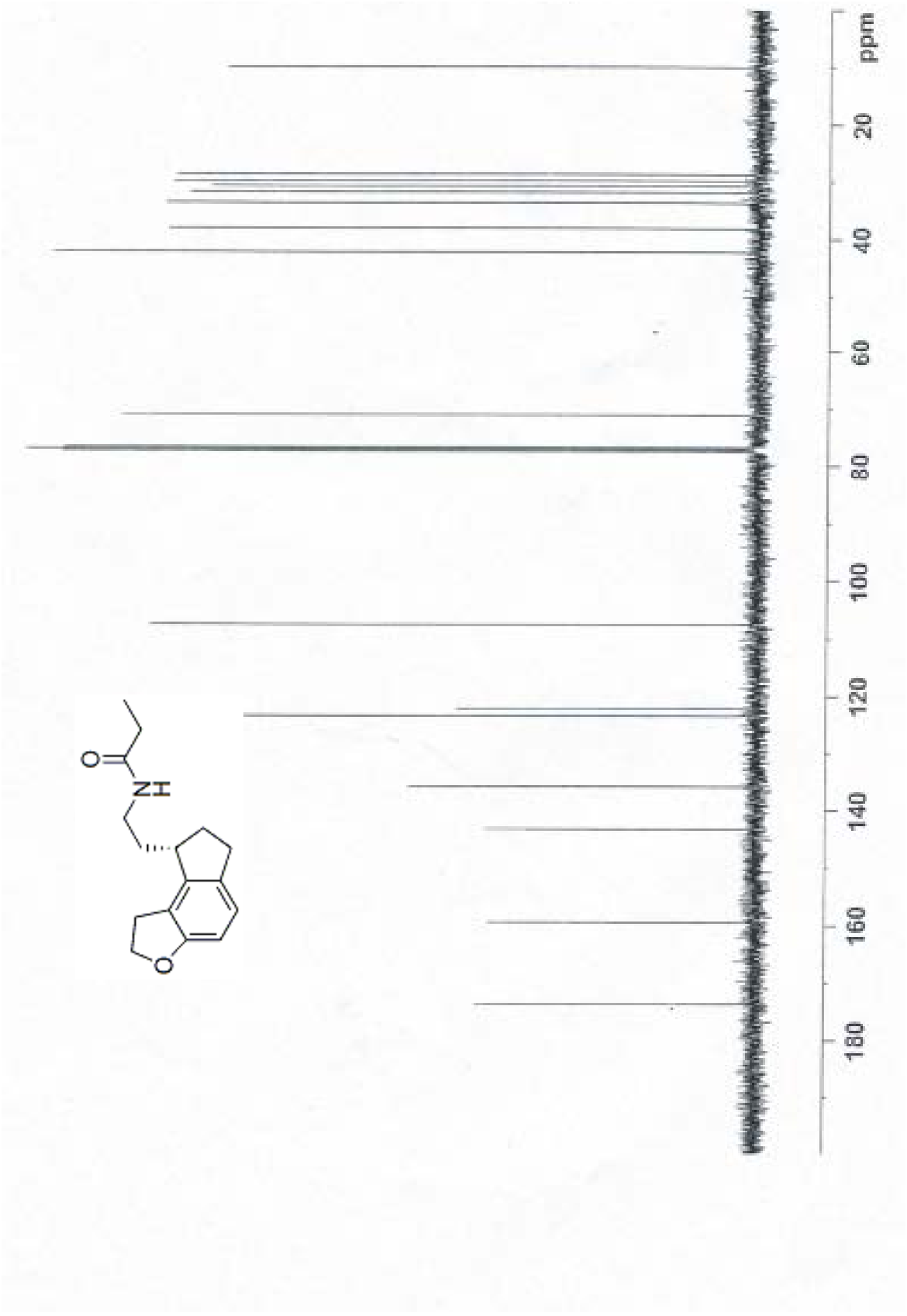
MS (ES+): m/z 396$(M+Na)^+$ (calculated for $C_{14}H_{13}Br_2NO$ 373)



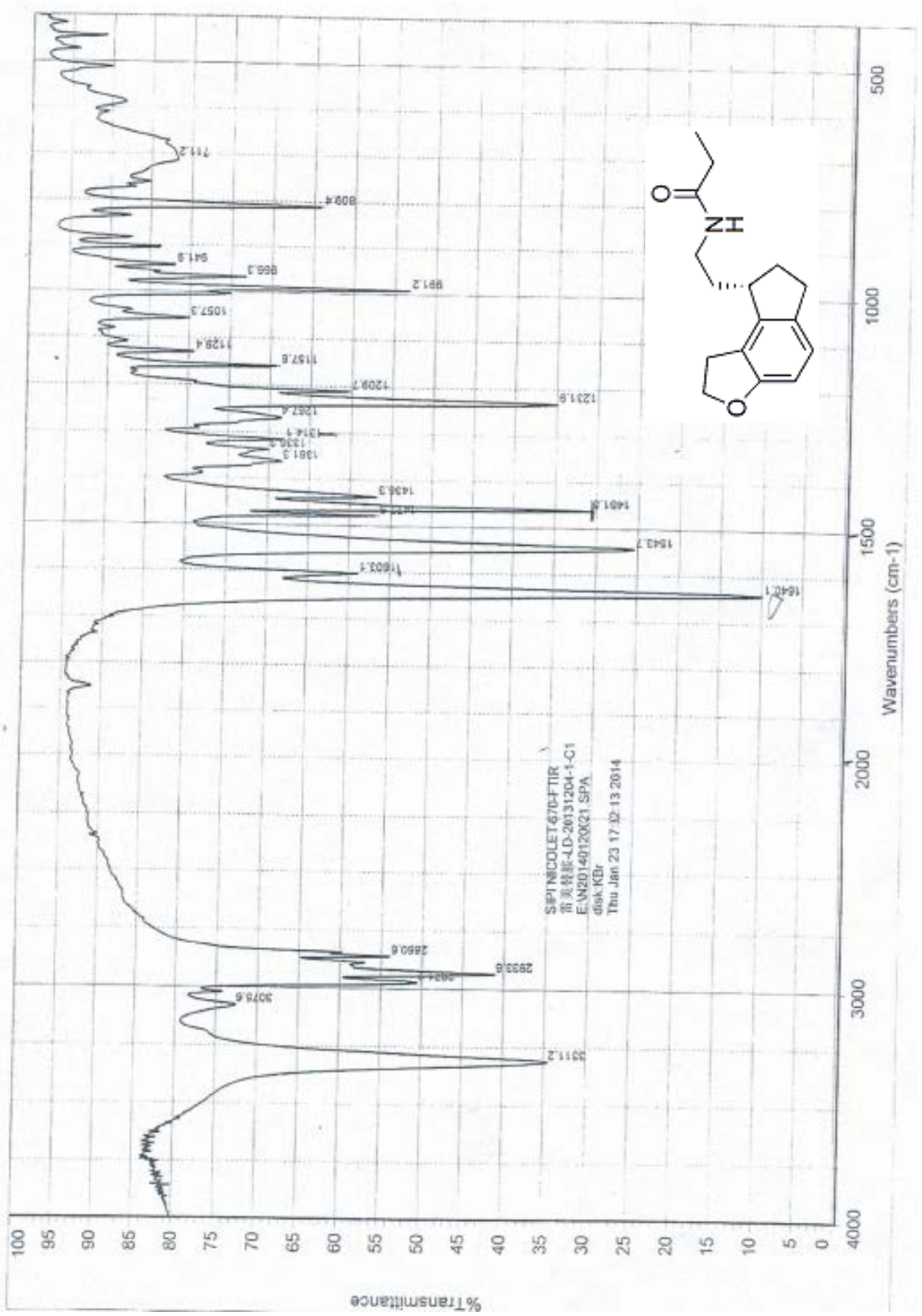
^{1}H NMR (400 MHz, DMSO-d_6 + D_2O) of compound **13**



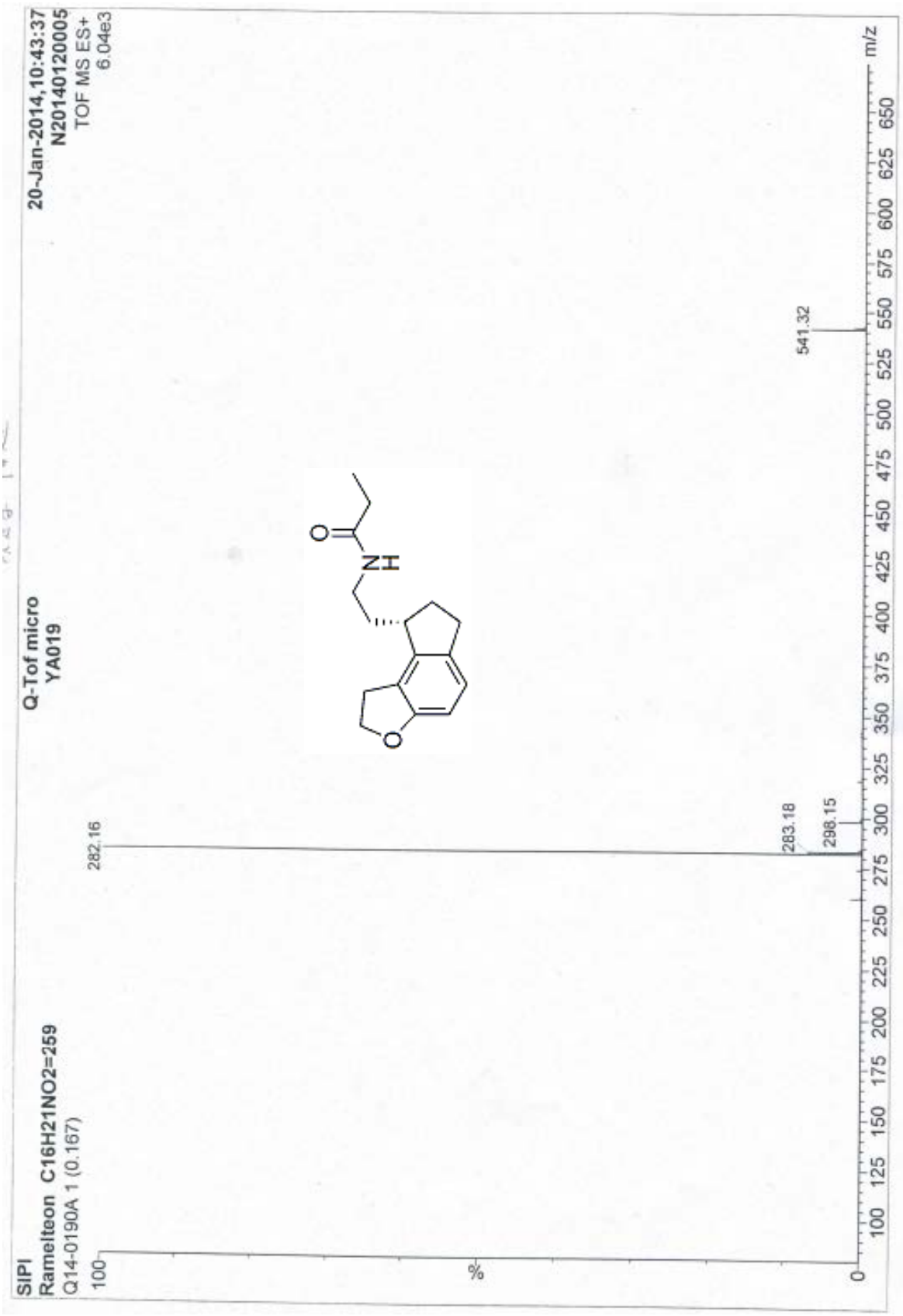
^{1}H NMR (400 MHz, $CDCl_3$) of compound **1**



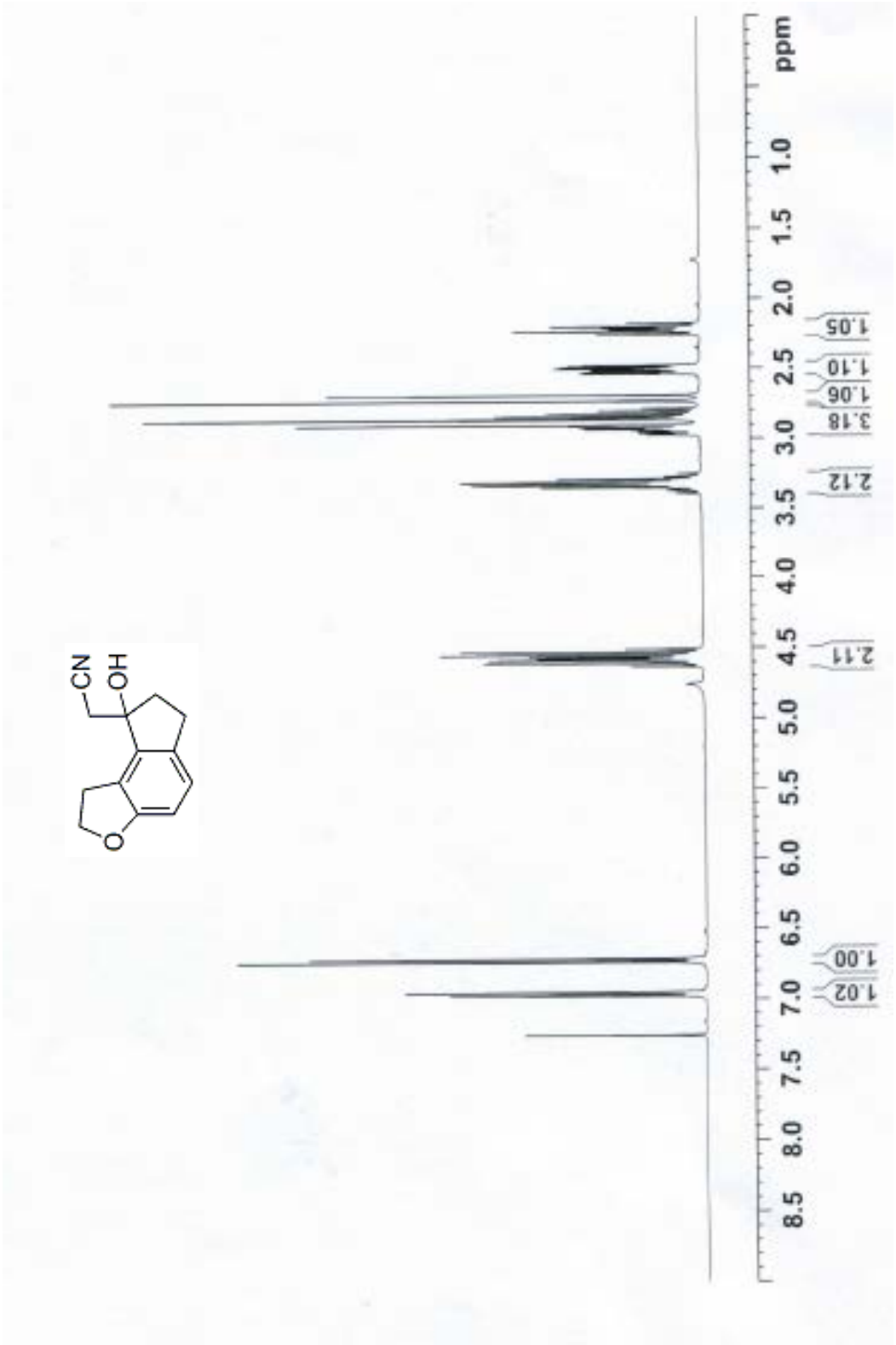
^{13}C NMR (100 MHz, $CDCl_3$) of compound **1**



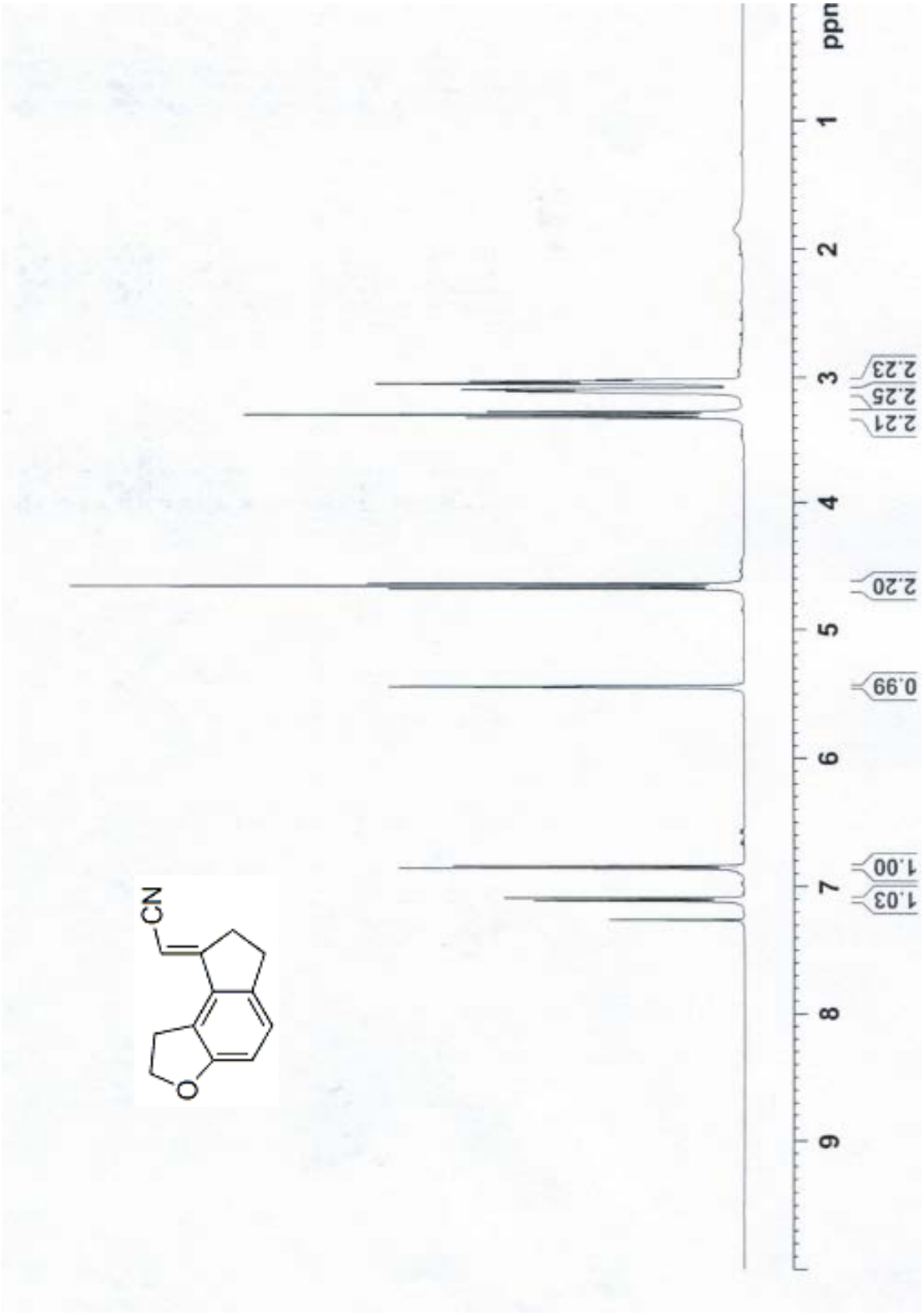
IR (KBr) (cm^{-1}) of compound **1**



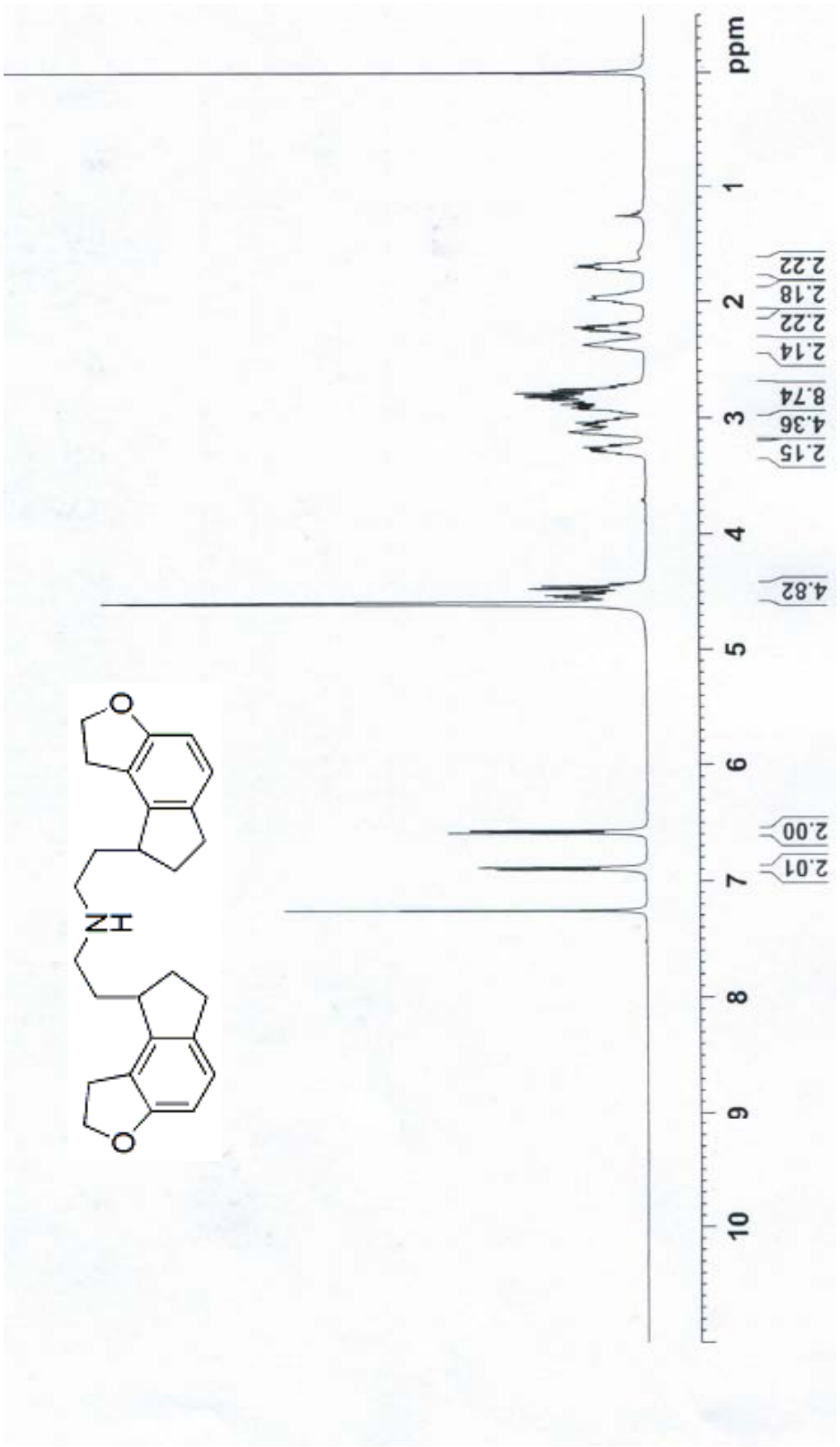
MS (ES+): m/z 282$(M+Na)^+$ (calculated for $C_{16}H_{21}NO_2$ 259)



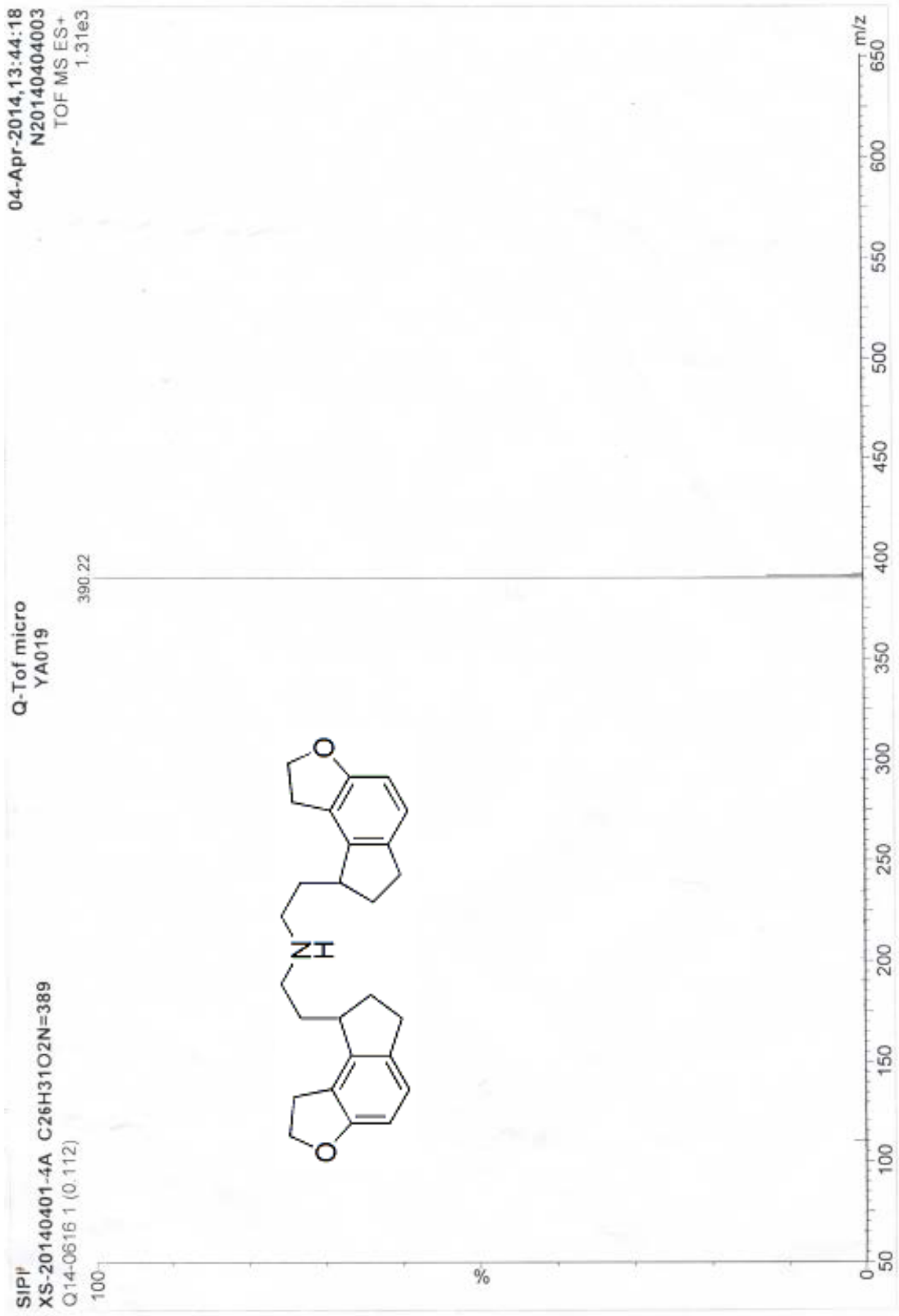
^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) of compound **15**



^{1}H NMR (400 MHz, $CDCl_3$) of compound **9**



^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) of compound **17**



MS (ES+): m/z 390$(M+H)^+$ (calculated for $C_{26}H_{31}NO_2$ 389)

References

(1) Uchikawa, O.; Fukatsu, K.; Tokunoh, R.; Kawada, M.; Matsumoto, K.; Imai, Y.; Hinuma, S.; Kato, K.; Nishikawa, H.; Hirai, K.; Miyamoto M.; Ohkawa, S. J. Med. Chem. 2002, 45, 4222-4239.

(2) Yamano, T.; Yamashita, M.; Adachi, M.; Tanaka, M.; Matsumoto, K.; Kawada, M.; Uchikawa, O.; Fukatsu, K.; Ohkawa, S. *Tetrahedron: Asymmetry*. **2006**, 17, 184-190.