Supplementary Information

Enhancement of the carbamate activation rate enabled syntheses of tetracyclic benzolactams: 8-oxoberbines and their 5- and 7-membered C-ring homologues

Hiroaki Kurouchi*

Research Foundation ITSUU Laboratory, C1232 Kanagawa Science Park R & D Building, 3-2-1 Sakado, Takatsu-ku, Kawasaki, Kanagawa 213-0012, Japan

E-mail: hurouchi@itsuu.or.jp

Table of Contents

1. Experimental Section

I. General methods

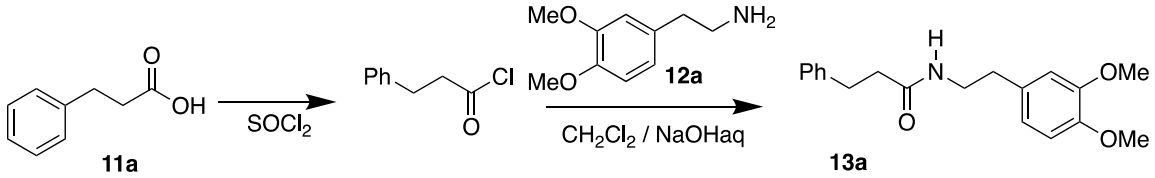
NMR spectra were recorded on a JEOL ECZ 400S spectrometer (400 MHz for ^{1}H-NMR, 100 MHz for ^{13}C-NMR). Chemical shifts were reported in ppm on the δ scale relative to tetramethylsilane (δ = 0 for ^{1}H-NMR) and $CDCl_3$ (δ = 77.0 for ^{13}C-NMR). Multiplicities are indicated as: br (broad), s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Coupling constants (J) are reported in Hertz (Hz). High-resolution mass spectra (HRMS) were recorded on a Thermo Fisher Scientific Exactive Plus. Melting points were determined with a Yanaco micro melting point apparatus Model MP-500D. Simple chemicals were analytical-grade and obtained commercially. Trifluoromethanesulfonic acid (TfOH) was purchased from Central Glass Co., Ltd., and used as received.

II. Synthesis of substrates

Compounds **4a**,[S1] **4b**,[S2] **4c**,[9] **4d**,[9] **4e**,[9] **4f**,[S3] **4g**,[S4] **4h**,[S5] **4i**,[S6] **4k**,[S7] **4m**,[S7] **4n**,[S5] **4s**,[S8] **13a**,[S9] **13b**,[S10] **13c**,[9] **13d**,[9] **13e**,[9] **13f**,[S11] **12g**,[S12] **13h**,[S12] **13i**,[S13] **13j**,[S11] **13k**,[S14] **13l**,[S15] **13m**,[S14] **13n**,[9] **13p**,[S16] **13r**,[S17] **13s**,[9] **14a**,[S18] **14b**,[S2] **14c**,[9] **14d**,[S19] **14e**,[S19] **14f**,[S20] **14g**,[S19] **14h**,[S5] **14i**,[S6] **14j**,[S15] **14k**,[S15] **14l**,[S15] **14m**,[S15] **14n**,[S21] **14p**[S16], **17**[8c] and **18**[S13] were previously reported in literatures.

Synthesis of amides 13a–t

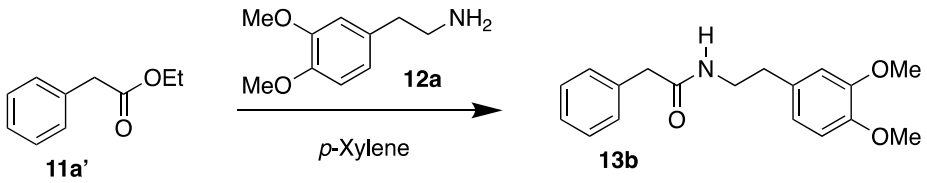
Typical procedure A: Synthesis of N-(3,4-dimethoxyphenethyl)-3-phenylpropanamide (13a)



To a mixture of 3-phenylpropanoic acid (**11a**) (4663 mg, 31.1 mmol), thionyl chloride (5.0 mL) was added at 25 °C under stirring. The mixture was stirred at 50 °C for 3 hours, then the solvent was removed under reduced pressure to afford 3-phenylpropanoyl chloride as a crude oil (4885 mg, 29.0 mmol). A part of the crude oil (1187 mg, 7.04 mmol) was dissolved in 5 mL of dichloromethane and added to a mixture of 2-(3,4-dimethoxyphenyl)ethan-1-amine (**12a**) (1825 mg, 10.1 mmol), dichloromethane (15 mL), and aqueous sodium hydroxide (4M, 10 mL) at 0 °C under vigorous stirring. The mixture was stirred at 0 °C for 10 min. The organic layer was separated by separatory funnel. Then, the organic layer was washed with aqueous hydrogen chloride (1M, 20 mL), brine (20 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure to give white solid. The solid was recrystallized from dichloromethane and hexane to afford **13a** as white solid (1920 mg, 7.99 mmol, 75% yield based on **11a**).

1H-NMR (400 MHz, $CDCl_3$) δ 7.29-7.26 (m, 2H), 7.22-7.17 (m, 3H), 6.78 (d, J = 8.0 Hz, 1H), 6.66 (d, J = 1.8 Hz, 1H), 6.62 (dd, J = 8.1, 1.8 Hz, 1H), 5.32 (brs, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.46 (dt, J = 7.0, 7.0 Hz, 2H), 2.95 (t, J = 7.7 Hz, 2H), 2.69 (t, J = 7.0 Hz, 2H), 2.43 (t, J = 7.7 Hz, 2H).

Typical procedure B: Synthesis of N-(3,4-dimethoxyphenethyl)-2-phenylacetamide (13b)



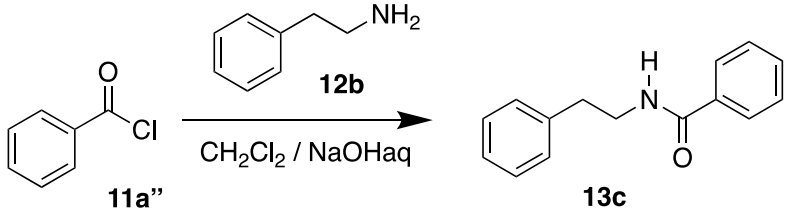
To avoid the use of phenylacetic acid, which is regulated as a methamphetamine ingredient in Japan, ethyl phenylacetate was used as a legal substitute.

A mixture of ethyl phenylacetate (**11a'**) (1640 mg, 10.0 mmol), and 2-(3,4-dimethoxyphenyl)ethan-1-amine (**12a**) (906 mg, 5.0 mmol) in *p*-xylene (3 mL) was stirred at 100 °C for 3 days. After cooling, *n*-hexane was added to obtain white precipitates. The solid was purified by silica-gel column chromatography (eluent: ethyl acetate: dichloromethane = 1:1) to afford **13b** as white solid (1065 mg, 3.56 mmol, 71% yield based on **12a**).

1H-NMR (400 MHz, $CDCl_3$) δ 7.24-7.07 (m, 5H), 6.64 (d, J = 8.0 Hz, 1H), 6.52 (s, 1H), 6.47 (d, J = 8.0 Hz, 1H), 5.44 (brs, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.43 (s, 2H), 3.36 (dt, J = 7.0, 7.0 Hz, 2H), 2.59 (t, J = 7.0 Hz, 2H).

13C-NMR (101 MHz, $CDCl_3$) δ 170.8, 148.9, 147.5, 134.7, 131.0, 129.3, 128.8, 127.1, 120.5, 111.7, 111.2, 55.8, 55.7, 43.7, 40.7, 34.9.

Typical procedure C: Synthesis of *N*-phenethylbenzamide (12c)



A solution of benzoyl chloride (**11a"**) (2902 mg, 20.64 mmol) in 10 mL of dichloromethane was added to a mixture of phenethylamine **12b** (2437 mg, 20.11 mmol), dichloromethane (15 mL), and aqueous sodium hydroxide (4M, 10 mL) at 0 °C under vigorous stirring. The mixture was stirred at 0 °C for 10 min. The organic layer was separated by separatory funnel. And the organic layer was washed with aqueous hydrogen chloride (1M, 20 mL), brine (20 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure to give white solid. The solid was recrystallized from dichloromethane and hexane to afford *N*-phenethylbenzamide **13c** as white solid (4205 mg, 18.66 mmol, 93% yield based on **12b**).

1H-NMR (400 MHz, $CDCl_3$) δ 7.70-7.67 (m, 2H), 7.50-7.45 (m, 1H), 7.42-7.38 (m, 2H), 7.35-7.31 (m, 2H), 7.26-7.23 (m, 3H), 6.16 (brs, 1H), 3.72 (dt, J = 7.0, 7.0 Hz, 2H), 2.94 (t, J = 7.0 Hz, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 167.4, 138.9, 134.6, 131.4, 128.8, 128.7, 128.5, 126.8, 126.6, 41.1, 35.7.

Compounds **13d,e,j,k,n-s** were synthesized following the procedure A using corresponding acids **11** and amines **12**. The yields were calculated based on **10.** Compounds **13i,l,m** were synthesized following the procedure B using ethyl phenylacetate **11a'** and amines **12**. The yields were calculated based on **12.** Compounds **13f–h** were synthesized following the procedure C using benzoyl chloride **11a"** and amines **12**. The yields were calculated based on **11a"**.

Synthesis of 4-methyl-N-phenethylbenzamide (13d)

91% yield (4341 mg) from 4-methylbenzoic acid (**11b**) and **12b**. Purified by recrystallization from ethyl acetate/*n*-hexane. White solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.0 Hz, 2H), 7.31 (dd, J = 7.2, 7.2 Hz, 2H), 7.25-7.17 (m, 5H), 6.27 (brs, 1H), 3.69 (dt, J = 6.9, 6.9 Hz, 2H), 2.91 (t, J = 6.9 Hz, 2H), 2.36 (s, 3H). 13C-NMR (101 MHz, $CDCl_3$) δ 167.4, 141.7, 138.9, 131.7, 129.1, 128.8, 128.6, 126.8, 126.5, 41.1, 35.7, 21.4. ESI-HRMS: Calcd for $C_{16}H_{18}NO^+$ $[M+H]^+$: 240.1383. Found: 240.1383.

Synthesis of 4-chloro-N-phenethylbenzamide (13e)
94% yield (4984 mg) from 4-chlorobenzoic acid (**11c**) and **12b**. Purified by recrystallization from ethyl acetate/*n*-hexane. White solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.62-7.60 (m, 2H), 7.33-7.17 (m, 7H), 6.57 (brs, 1H), 3.65 (dt, J = 7.0, 7.0 Hz, 2H), 2.89 (t, J = 7.0 Hz, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 166.5, 138.7, 137.5, 132.9, 128.9, 128.6, 128.6, 128.2, 126.5, 41.2, 35.5. ESI-HRMS: Calcd for $C_{15}H_{15}ClNO^+$ $[M+H]^+$: 260.0837. Found: 260.0838.

Synthesis of N-(3,4-dimethoxyphenethyl)benzamide (13f)
89% yield (1065 mg) from **11a"** and **12a**. Purified by recrystallization from ethyl acetate/*n*-hexane. White solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 7.3 Hz, 2H), 7.47-7.37 (m, 3H), 6.82 (d, J = 8.0 Hz, 1H), 6.77-6.75 (m, 2H), 6.28 (brs, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.69 (dt, J = 6.9, 6.9 Hz, 2H), 2.88 (t, J = 6.9 Hz, 2H).

Synthesis of N-(4-methylphenethyl)benzamide (13g)
81% yield (2819 mg) from **11a"** and 2-(*p*-tolyl)ethan-1-amine (**12c**). Purified by recrystallization from ethyl acetate/*n*-hexane. White solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.70-7.68 (m, 2H), 7.49-7.45 (m, 1H), 7.41-7.37 (m, 2H), 7.12 (s, 4H), 6.22 (s, 1H), 3.69 (dd, J = 12.8, 6.9 Hz, 2H), 2.88 (t, J = 7.0 Hz, 2H), 2.33 (s, 3H). 13C-NMR (101 MHz, $CDCl_3$) δ 167.4, 136.1, 135.7, 134.7, 131.3, 129.4, 128.6, 128.5, 126.8, 41.2, 35.2, 21.0.

Synthesis of N-(4-chlorophenethyl)benzamide (13h)
87% yield (4790 mg) from **11a"** and 2-(4-chlorophenyl)ethan-1-amine (**12d**). Purified by recrystallization from ethyl acetate/*n*-hexane. White solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 7.4 Hz, 2H), 7.49 (dd, J = 7.4, 7.4 Hz, 1H), 7.41 (dd, J = 7.4, 7.4 Hz, 2H), 7.30-7.26 (m, 2H), 7.16 (d, J = 8.2 Hz, 2H), 6.17 (brs, 1H), 3.69 (dt, J = 6.8, 6.8 Hz, 2H), 2.91 (t, J = 6.9 Hz, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 167.5, 137.4, 134.5, 132.4, 131.5, 130.1, 128.8, 128.6, 126.8, 41.0, 35.1.

Synthesis of N-phenethyl-2-phenylacetamide (13i)
75% yield (2745 mg) from **11a'** and **12b**. Purified by silica-gel column chromatography (eluent: ethyl acetate: n-hexane = 1:2 ~ 1:0). White solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.36-7.17 (m, 8H), 7.04-7.02 (m, 2H), 5.37 (brs, 1H), 3.55 (s, 2H), 3.46 (dt, J = 6.7, 6.7 Hz, 2H), 2.72 (t, J = 6.7 Hz, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 170.9, 138.6, 134.6, 129.5, 129.0, 128.7, 128.5, 127.3, 126.4, 43.8, 40.6, 35.4.

Synthesis of N-phenethyl-2-(p-tolyl)acetamide (13j)
92% yield (3421 mg) from 2-(*p*-tolyl)acetic acid (**11d**) and **12b**. Purified by recrystallization from ethyl acetate/*n*-hexane. White solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.25-7.17 (m, 3H), 7.12 (d, J = 7.8 Hz, 2H), 7.06-7.02 (m, 4H), 5.36 (s, 1H),

3.49 (s, 2H), 3.44 (dt, J = 6.7, 6.7 Hz, 2H), 2.71 (t, J = 6.7 Hz, 2H), 2.34 (s, 3H). 13C-NMR (101 MHz, $CDCl_3$) δ 171.1, 138.7, 136.9, 131.7, 129.6, 129.3, 128.7, 128.5, 126.3, 43.4, 40.6, 35.4, 21.0.

Synthesis of 2-(4-chlorophenyl)-N-phenethylacetamide (13k)
91% yield (3676 mg) from 2-(4-chlorophenyl)acetic acid (**11e**) and **12b**. Purified by recrystallization from ethyl acetate/*n*-hexane. White solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.28-7.18 (m, 5H), 7.09 (d, J = 8.2 Hz, 2H), 7.04-7.02 (m, 2H), 5.40 (s, 1H), 3.47 (dt, J = 6.9, 6.9 Hz, 2H), 3.46 (s, 2H), 2.73 (t, J = 6.9 Hz, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 170.2, 138.5, 133.2, 133.2, 130.6, 129.0, 128.6, 128.6, 126.5, 43.0, 40.6, 35.3.

Synthesis of N-(4-methylphenethyl)-2-phenylacetamide (13l)
74% yield (2705 mg) from **11a'** and **12c**. Purified by silica-gel column chromatography (eluent: ethyl acetate: n-hexane = 1:2 ~ 1:0). White solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 3H), 7.18-7.16 (m, 2H), 7.04 (d, J = 7.9 Hz, 2H), 6.91 (d, J = 7.9 Hz, 2H), 5.36 (s, 1H), 3.52 (s, 2H), 3.43 (dt, J = 6.9 Hz, 2H), 2.68 (t, J = 6.9 Hz, 2H), 2.31 (s, 3H). 13C-NMR (101 MHz, $CDCl_3$) δ 170.8, 135.9, 135.5, 134.8, 129.4, 129.2, 129.0, 128.5, 127.3, 43.9, 40.7, 35.0, 21.0. ESI-HRMS: Calcd for $C_{17}H_{20}NO^+$ $[M+H]^+$: 254.1540. Found: 254.1535.

Synthesis of N-(4-chlorophenethyl)-2-phenylacetamide (13m)
78% yield (3468 mg) from **11a'** and **12d**. Purified by silica-gel column chromatography (eluent: ethyl acetate: n-hexane = 1:2 ~ 1:0). White solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.35-7.27 (m, 3H), 7.20-7.15 (m, 4H), 6.94 (d, J = 8.2 Hz, 2H), 5.31 (s, 1H), 3.53 (s, 2H), 3.43 (dt, J = 6.9, 6.9 Hz, 2H), 2.69 (t, J = 6.9 Hz, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 170.9, 137.1, 134.7, 132.3, 130.0, 129.4, 129.0, 128.7, 127.4, 43.9, 40.5, 34.8.

Synthesis of N-phenethyl-3-phenylpropanamide (13n)
84% yield (6395 mg) from **11a** and **12b**. Purified by recrystallization from ethyl acetate/*n*-hexane. White solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.31-7.18 (m, 9H), 7.08 (d, J = 6.9 Hz, 2H), 5.38 (s, 1H), 3.48 (dt, J = 6.7, 6.7 Hz, 2H), 2.95 (t, J = 7.7 Hz, 2H), 2.73 (t, J = 6.7 Hz, 2H), 2.42 (t, J = 7.7 Hz, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 172.0, 140.7, 138.8, 128.7, 128.6, 128.5, 128.3, 126.4, 126.2, 40.5, 38.6, 35.6, 31.6.

Synthesis of N-phenethyl-3-(p-tolyl)propanamide (13o)
61% yield (3652 mg) from 3-(*p*-tolyl)propanoic acid (**11f**) and **12b**. Purified by recrystallization from ethyl acetate/*n*-hexane. White solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.29-7.19 (m, 3H), 7.09-7.04 (m, 6H), 5.40 (s, 1H), 3.46 (dt, J = 7.0, 7.0 Hz, 2H), 2.89 (t, J = 7.7 Hz, 2H), 2.73 (t, J = 7.0 Hz, 2H), 2.39 (t, J = 7.7 Hz, 2H), 2.31 (s, 3H). 13C-NMR (101 MHz, $CDCl_3$) δ 172.1, 138.9, 137.7, 135.7, 129.1, 128.7, 128.5, 128.2, 126.4, 40.5, 38.6, 35.6, 31.2, 21.0. ESI-HRMS: Calcd for $C_{18}H_{22}NO^+$ $[M+H]^+$: 268.1696. Found: 268.1690.

Synthesis of 3-(4-chlorophenyl)-N-phenethylpropanamide (13p)
98% yield (2891 mg) from 3-(4-chlorophenyl)propanoic acid (**11g**) and **12b**. Purified by recrystallization from ethyl acetate/*n*-hexane. White solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.30-7.20 (m, 5H), 7.10-7.07 (m, 4H), 5.41 (brs, 1H), 3.47 (dt, J = 7.0, 7.0 Hz, 2H), 2.90 (t, J = 7.5 Hz, 2H), 2.74 (t, J = 7.0 Hz, 2H), 2.38 (t, J = 7.5 Hz, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 171.6, 139.3, 138.7, 131.9, 129.7, 128.6, 128.6, 128.5, 126.5, 40.5,

38.2, 35.6, 30.9. ESI-HRMS: Calcd for $C_{17}H_{19}ClNO^+$ $[M+H]^+$: 288.1150. Found: 288.1146.

Synthesis of N-(4-methylphenethyl)-3-phenylpropanamide (13q)

87% yield (2174 mg) from **11a** and **12c**. Purified by recrystallization from ethyl acetate/*n*-hexane. White solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.29-7.16 (m, 5H), 7.08 (d, J = 7.8 Hz, 2H), 6.97 (d, J = 7.8 Hz, 2H), 5.36 (brs, 1H), 3.45 (dt, J = 6.9, 6.9 Hz, 2H), 2.93 (t, J = 7.7 Hz, 2H), 2.69 (t, J = 6.9 Hz, 2H), 2.41 (t, J = 7.7 Hz, 2H), 2.31 (s, 3H). 13C-NMR (101 MHz, $CDCl_3$) δ 171.9, 140.8, 136.0, 135.7, 129.3, 128.6, 128.5, 128.3, 126.2, 40.6, 38.5, 35.2, 31.7, 21.0. ESI-HRMS: Calcd for $C_{18}H_{22}NO^+$ $[M+H]^+$: 268.1696. Found: 268.1690.

Synthesis of N-(4-chlorophenethyl)-3-phenylpropanamide (13r)

80% yield (1705 mg) from **11a** and **12d**. Purified by recrystallization from ethyl acetate/*n*-hexane. White solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.30-7.17 (m, 7H), 6.99 (d, J = 8.2 Hz, 2H), 5.26 (s, 1H), 3.44 (dt, J = 7.0, 7.0 Hz, 2H), 2.94 (t, J = 7.5 Hz, 2H), 2.70 (t, J = 7.0 Hz, 2H), 2.42 (t, J = 7.5 Hz, 2H).

Synthesis of N-phenethyl-4-phenylbutanamide (13s)

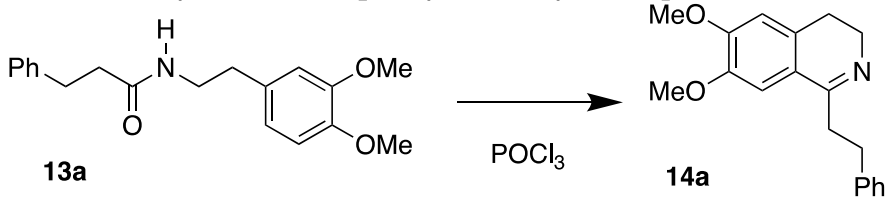
84% yield (5801 mg) from 4-phenylbutanoic acid (**11h**) and **12b**. Purified by recrystallization from ethyl acetate/*n*-hexane. White solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.33-7.13 (m, 10H), 5.56 (brs, 1H), 3.50 (dt, J = 6.8, 6.8 Hz, 2H), 2.80 (t, J = 6.8 Hz, 2H), 2.61 (t, J = 7.4 Hz, 2H), 2.13-2.09 (m, 2H), 1.97-1.90 (m, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 172.7, 141.4, 138.8, 128.7, 128.6, 128.4, 128.3, 126.4, 125.8, 40.4, 35.7, 35.5, 35.0, 27.0.

Synthesis of N-phenethyl-2,3-diphenylpropanamide (13t)

89% yield (3198 mg) from 2,3-diphenylpropanoic acid (**11i**) and **12b**. Purified by recrystallization from ethyl acetate/*n*-hexane. White solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.31-7.10 (m, 13H), 6.88-6.85 (m, 2H), 5.36 (brs, 1H), 3.57-3.45 (m, 2H), 3.38 (ddd, J = 12.8, 6.7, 1.4 Hz, 2H), 2.96 (dd, J = 12.8, 6.5 Hz, 1H), 2.65-2.56 (m, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 172.5, 139.7, 139.6, 138.8, 129.0, 128.7, 128.7, 128.5, 128.2, 128.0, 127.3, 126.3, 126.2, 55.7, 40.7, 39.5, 35.5. ESI-HRMS: Calcd for $C_{23}H_{24}NO^+$ $[M+H]^+$: 330.1853. Found: 330.1844.

Synthesis of imines 14a–t

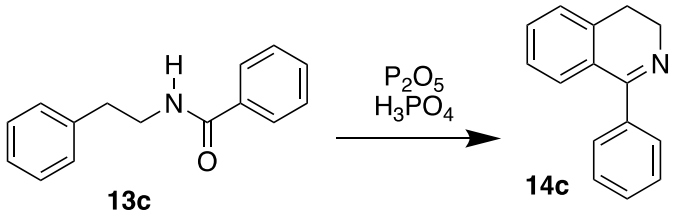
Typical procedure D: Synthesis of 1-phenyl-3,4-dihydroisoquinoline (14a)



A solution of **13a** (2504 mg, 7.99 mmol) in 10 mL of phosphoryl chloride was refluxed under stirring for 3 hr. Then, the mixture was cooled, and poured into 50 mL of ice water. The mixture was basified with aqueous sodium hydroxide (2 mol/L). The whole was extracted with ethyl acetate (50 mL x 2). The organic layer was washed with brine, dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by silica-gel column chromatography

(eluent: ethyl acetate: *n*-hexane = 1:4 ~ 2:1) to afford **14a** (1715 mg, 5.81 mmol, 73%) as white solid.
1H-NMR (400 MHz, $CDCl_3$) δ 7.32-7.17 (m, 5H), 6.99 (s, 1H), 6.79 (s, 1H), 3.96 (s, 3H), 3.86 (s, 3H), 3.75 (t, J = 7.7 Hz, 2H), 3.34-3.31 (m, 2H), 3.12-3.08 (m, 2H), 2.80 (t, J = 7.7 Hz, 2H). ESI-HRMS: Calcd for $C_{19}H_{22}NO_2^+$ $[M+H]^+$: 296.1645. Found: 296.1636.

Typical procedure E: Synthesis of 1-phenyl-3,4-dihydroisoquinoline (14c)



13c **14c**

To phosphorous pentoxide (20 g), 7 mL of phosphoric acid (70%) was slowly added under stirring to prepare polyphosphoric acid. Then, **13c** (3993 mg, 17.7 mmol) was added to the acid and the mixture was stirred at 170 °C for 1hr. Then, the mixture was cooled in ice bath and basified with 200 mL of aqueous sodium hydroxide (2 mol/L). The whole was extracted with ethyl acetate (50 mL x 3). The organic layer was washed with brine, dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:4 ~ 2:1) to afford **14c** (3155 mg, 15.22 mmol, 86%) as pale yellow oil.
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.61-7.59 (m, 2H), 7.43-7.37 (m, 4H), 7.28-7.22 (m, 3H), 3.85 (t, J = 7.3 Hz, 2H), 2.81 (t, J = 7.3 Hz, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 167.2, 139.0, 138.8, 130.6, 129.3, 128.8, 128.8, 128.1, 127.9, 127.4, 126.5, 47.6, 26.3.

Compounds **14a**, **14b**, and **14f** were synthesized following the procedure D. Compounds **14c–e, 14g–t** were synthesized following the procedure E.

Synthesis of 1-benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline (14b)
78% yield (1303 mg) from **13b**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:4 ~ 2:1). 1H-NMR (400 MHz, $CDCl_3$) δ 7.32-7.25 (m, 4H), 7.20-7.16 (m, 1H), 6.94 (s, 1H), 6.65 (s, 1H), 4.04 (s, 2H), 3.87 (s, 3H), 3.74 (t, J = 7.4 Hz, 2H), 3.72 (s, 3H), 2.65 (t, J = 7.5 Hz, 2H).
13C-NMR (101 MHz, $CDCl_3$) δ 165.3, 150.6, 147.2, 138.2, 131.8, 128.6, 128.5, 126.4, 121.6, 110.2, 109.6, 55.9, 55.9, 47.3, 43.6, 25.8.
ESI-HRMS: Calcd for $C_{18}H_{20}NO_2^+$ $[M+H]^+$: 282.1489. Found: 282.1479.

Synthesis of 1-(p-tolyl)-3,4-dihydroisoquinoline (14d)
88% yield (2576 mg) from **13d**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:4 ~ 2:1). White solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 7.8 Hz, 2H), 7.34 (dd, J = 7.3, 7.3 Hz, 1H), 7.28-7.20 (m, 5H), 3.81 (t, J = 7.2 Hz, 2H), 2.76 (t, J = 7.3 Hz, 2H), 2.38 (s, 3H). 13C-NMR (101 MHz, $CDCl_3$) δ 166.9, 139.1, 138.7, 136.0, 130.4, 130.1, 128.7, 128.6, 128.6, 128.3, 127.8, 127.2, 126.3, 47.4, 26.2, 21.2. ESI-HRMS: Calcd for $C_{16}H_{16}N^+$ $[M+H]^+$: 222.1277. Found: 222.1279.

Synthesis of 1-(4-chlorophenyl)-3,4-dihydroisoquinoline (14e)
85% yield (2953 mg) from **13e**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:4 ~ 2:1). White solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.54

(d, J = 8.2 Hz, 2H), 7.39-7.36 (m, 3H), 7.26-7.20 (m, 3H), 3.84-3.80 (m, 2H), 2.78 (t, J = 7.2 Hz, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 166.0, 138.7, 137.2, 135.2, 130.7, 130.0, 128.3, 128.2, 127.4, 127.4, 126.5, 47.5, 26.1
ESI-HRMS: Calcd for $C_{15}H_{13}ClN^+$ $[M+H]^+$: 242.0731. Found: 242.0731.

Synthesis of 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline (14f)
89% yield (712 mg) from **13f**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:4 ~ 2:1). Pale yellow oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.61-7.43 (m, 3H), 6.80 (s, 1H), 6.79 (s, 1H), 3.95 (s, 3H), 3.82 (t, J = 7.4 Hz, 2H), 3.73 (s, 3H), 2.74 (t, J = 7.4 Hz, 2H). ESI-HRMS: Calcd for $C_{17}H_{18}NO_2^+$ $[M+H]^+$: 268.1332. Found: 268.1325.

Synthesis of 7-methyl-1-phenyl-3,4-dihydroisoquinoline (14g)
81% yield (1697 mg) from **13g**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:4 ~ 2:1). Pale yellow oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.61-7.58 (m, 2H), 7.45-7.41 (m, 3H), 7.20 (d, J = 7.5 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 7.07 (s, 1H), 3.85-3.81 (m, 2H), 2.76 (t, J = 7.3 Hz, 2H), 2.29 (s, 3H). 13C-NMR (101 MHz, $CDCl_3$) δ 167.4, 139.2, 136.1, 135.8, 131.3, 129.2, 128.8, 128.7, 128.4, 128.1, 127.2, 47.9, 25.9, 21.2. ESI-HRMS: Calcd for $C_{16}H_{16}N^+$ $[M+H]^+$: 222.1277. Found: 222.1279.

Synthesis of 7-chloro-1-phenyl-3,4-dihydroisoquinoline (14h)
18% yield (376 mg) from **13h**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:4 ~ 2:1). Pale yellow oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.59-7.57 (m, 2H), 7.46-7.42 (m, 3H), 7.36 (dd, J = 8.0, 2.1 Hz, 1H), 7.25 (d, J = 2.1 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 3.87-3.83 (m, 2H), 2.77 (t, J = 7.3 Hz, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 166.1, 138.3, 137.1, 132.2, 130.5, 130.0, 129.6, 128.7, 128.6, 128.3, 127.8, 47.6, 25.7. ESI-HRMS: Calcd for $C_{15}H_{13}ClN^+$ $[M+H]^+$: 242.0731. Found: 242.0731.

Synthesis of 1-benzyl-3,4-dihydroisoquinoline (14i)
90% yield (1486 mg) from **13i**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:4 ~ 2:1). Pale yellow oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 7.5 Hz, 1H), 7.31-7.24 (m, 5H), 7.20-7.14 (m, 3H), 4.08 (s, 2H), 3.76 (t, J = 7.4 Hz, 2H), 2.71 (t, J = 7.4 Hz, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 165.8, 138.0, 137.9, 130.4, 128.8, 128.6, 128.5, 127.5, 126.8, 126.3, 125.7, 47.1, 42.9, 26.1. ESI-HRMS: Calcd for $C_{16}H_{16}N^+$ $[M+H]^+$: 222.1277. Found: 222.1273.

Synthesis of 1-(4-methylbenzyl)-3,4-dihydroisoquinoline (14j)
89% yield (1780 mg) from **13j**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:4 ~ 2:1). Pale yellow oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 7.5 Hz, 1H), 7.28-7.23 (m, 1H), 7.19-7.12 (m, 4H), 7.06 (d, J = 7.8 Hz, 2H), 4.03 (s, 2H), 3.74 (t, J = 7.4 Hz, 2H), 2.69 (t, J = 7.4 Hz, 2H), 2.27 (s, 3H). 13C-NMR (101 MHz, $CDCl_3$) δ 165.9, 138.0, 135.7, 134.7, 130.3, 129.2, 128.8, 128.5, 127.4, 126.7, 125.6, 47.1, 42.5, 26.1, 20.9. ESI-HRMS: Calcd for $C_{17}H_{18}N^+$ $[M+H]^+$: 236.1434. Found: 236.1429.

Synthesis of 1-(4-chlorobenzyl)-3,4-dihydroisoquinoline (14k)
88% yield (1981 mg) from **13k**. Purified by silica-gel column chromatography (eluent:

ethyl acetate: *n*-hexane = 1:4 ~ 2:1). Pale yellow oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 7.8 Hz, 1H), 7.30 (td, J = 7.4, 1.1 Hz, 1H), 7.25-7.15 (m, 6H), 4.03 (s, 2H), 3.74 (t, J = 7.5 Hz, 2H), 2.70 (t, J = 7.5 Hz, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 165.5, 138.0, 136.3, 132.1, 130.6, 130.0, 128.6, 128.6, 127.6, 126.8, 125.4, 47.1, 42.1, 26.0. ESI-HRMS: Calcd for $C_{16}H_{15}ClN^+$ $[M+H]^+$: 256.0888. Found: 256.0881.

Synthesis of 1-benzyl-7-methyl-3,4-dihydroisoquinoline (14l)
85% yield (1576 mg) from **13l**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:4 ~ 2:1). Pale yellow oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.31-7.24 (m, 5H), 7.19-7.15 (m, 1H), 7.09 (dd, J = 7.5, 0.7 Hz, 1H), 7.03 (d, J = 7.5 Hz, 1H), 4.06 (s, 2H), 3.72 (t, J = 7.4 Hz, 2H), 2.65 (t, J = 7.4 Hz, 2H), 2.27 (s, 3H). 13C-NMR (101 MHz, $CDCl_3$) δ 165.9, 138.0, 136.2, 134.9, 131.0, 128.7, 128.6, 128.4, 127.3, 126.2, 126.2, 47.3, 42.7, 25.7, 21.2. ESI-HRMS: Calcd for $C_{17}H_{18}N^+$ $[M+H]^+$: 236.1434. Found: 236.1428.

Synthesis of 1-benzyl-7-chloro-3,4-dihydroisoquinoline (14m)
63% yield (1512 mg) from **13m**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:4 ~ 2:1). Pale yellow oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 2.1 Hz, 1H), 7.29-7.16 (m, 6H), 7.07 (d, J = 8.0 Hz, 1H), 4.04 (s, 2H), 3.74 (t, J = 7.4 Hz, 2H), 2.65 (t, J = 7.4 Hz, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 164.8, 137.3, 136.3, 132.3, 130.3, 130.0, 128.8, 128.7, 128.6, 126.5, 125.7, 47.0, 42.7, 25.5. ESI-HRMS: Calcd for $C_{16}H_{15}ClN^+$ $[M+H]^+$: 256.0888. Found: 256.0881.

Synthesis of 1-phenethyl-3,4-dihydroisoquinoline (14n)
83% yield (1152 mg) from **13n**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:4 ~ 2:1). Pale yellow oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 7.5 Hz, 1H), 7.35 (ddd, J = 7.3, 7.3, 1.4 Hz, 1H), 7.31-7.17 (m, 7H), 3.71-3.67 (m, 2H), 3.06-2.96 (m, 4H), 2.68 (t, J = 7.4 Hz, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 166.3, 141.9, 137.8, 130.4, 129.0, 128.4, 128.4, 127.6, 126.9, 125.9, 124.8, 46.9, 37.6, 33.1, 26.1. ESI-HRMS: Calcd for $C_{17}H_{18}N^+$ $[M+H]^+$: 236.1434. Found: 236.1429.

Synthesis of 1-(4-methylphenethyl)-3,4-dihydroisoquinoline (14o)
89% yield (2919 mg) from **13o**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:4 ~ 2:1). Pale brown oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 7.8 Hz, 1H), 7.35-7.25 (m, 2H), 7.18-7.06 (m, 5H), 3.68 (t, J = 7.4 Hz, 2H), 3.03-2.92 (m, 4H), 2.67 (t, J = 7.4 Hz, 2H), 2.31 (s, 3H).
13C-NMR (101 MHz, $CDCl_3$) δ 166.4, 138.8, 137.7, 135.3, 130.3, 129.0, 128.9, 128.2, 127.5, 126.8, 124.7, 46.8, 37.7, 32.6, 26.1, 20.9.
ESI-HRMS: Calcd for $C_{18}H_{20}N^+$ $[M+H]^+$: 250.1590. Found: 250.1585.

Synthesis of 1-(4-chlorophenethyl)-3,4-dihydroisoquinoline (14p)
87% yield (1587 mg) from **13p**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:4 ~ 2:1). Pale brown oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 7.3 Hz, 1H), 7.35 (dd, J = 7.4, 7.4, 1.3 Hz, 1H), 7.31-7.27 (m, 1H), 7.25-7.14 (m, 5H), 3.68 (t, J = 7.4 Hz, 2H), 3.02-2.95 (m, 4H), 2.67 (t, J = 7.4 Hz, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 166.0, 140.3, 137.8, 131.6, 130.5, 129.8, 128.9, 128.4, 127.6, 126.9, 124.7, 46.9, 37.3, 32.3, 26.1. ESI-HRMS: Calcd for $C_{17}H_{17}ClN^+$ $[M+H]^+$: 270.1044. Found: 270.1040.

Synthesis of 7-methyl-1-phenethyl-3,4-dihydroisoquinoline (14q)

97% yield (1496 mg) from **13q**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:4 ~ 2:1). Pale brown oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.32-7.17 (m, 8H), 7.09 (d, J = 7.5 Hz, 1H), 3.68 (t, J = 7.3 Hz, 2H), 3.05-2.98 (m, 4H), 2.65 (t, J = 7.3 Hz, 2H), 2.36 (s, 3H). 13C-NMR (101 MHz, $CDCl_3$) δ 166.4, 142.1, 136.4, 134.8, 131.0, 128.9, 128.4, 128.4, 127.4, 125.9, 125.5, 47.1, 37.6, 33.0, 25.8, 21.3. ESI-HRMS: Calcd for $C_{18}H_{20}N^+$ $[M+H]^+$: 250.1590. Found: 250.1584.

Synthesis of 7-chloro-1-phenethyl-3,4-dihydroisoquinoline (14r)

27% yield (493 mg) from **13r**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:4 ~ 2:1). Pale brown oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 2.1 Hz, 1H), 7.33-7.06 (m, 7H), 3.69 (t, J = 7.4 Hz, 2H), 3.00-2.94 (m, 4H), 2.64 (t, J = 7.4 Hz, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 165.2, 141.6, 136.0, 132.5, 130.3, 129.8, 128.9, 128.4, 128.4, 126.0, 125.0, 46.8, 37.4, 32.8, 25.5. ESI-HRMS: Calcd for $C_{17}H_{17}ClN^+$ $[M+H]^+$: 270.1044. Found: 270.1039.

Synthesis of 1-(3-phenylpropyl)-3,4-dihydroisoquinoline (14s)

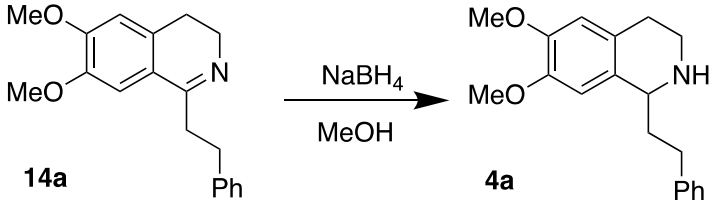
74% yield (1003 mg) from **13s**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:4 ~ 2:1). Pale yellow oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 7.5 Hz, 1H), 7.33 (ddd, J = 7.3, 7.3, 1.4 Hz, 1H), 7.28-7.25 (m, 3H), 7.17 (dd, J = 12.8, 6.9 Hz, 4H), 3.66 (t, J = 7.3 Hz, 2H), 2.77-2.65 (m, 6H), 2.03-1.96 (m, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 167.0, 142.1, 137.8, 130.3, 129.0, 128.5, 128.3, 127.5, 126.8, 125.7, 124.9, 46.9, 35.7, 35.3, 28.7, 26.2. ESI-HRMS: Calcd for $C_{18}H_{20}N^+$ $[M+H]^+$: 250.1590. Found: 250.1586.

Synthesis of 1-(1,2-diphenylethyl)-3,4-dihydroisoquinoline (14t)

85% yield (2358 mg) from **13t**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:4 ~ 2:1). Pale yellow oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 7.8 Hz, 1H), 7.24-7.09 (m, 11H), 7.02-7.00 (m, 2H), 4.43 (dd, J = 8.2, 6.3 Hz, 1H), 3.84-3.80 (m, 2H), 3.55 (dd, J = 13.3, 6.6 Hz, 1H), 3.08 (dd, J = 13.3, 8.2 Hz, 1H), 2.67-2.63 (m, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 167.1, 141.9, 140.8, 138.1, 130.0, 129.4, 129.3, 128.4, 128.1, 127.9, 127.4, 126.7, 126.5, 125.7, 125.1, 52.1, 47.0, 41.4, 26.2. ESI-HRMS: Calcd for $C_{23}H_{22}N^+$ $[M+H]^+$: 312.1747. Found: 312.1740.

Synthesis of amines 4a–t

Typical procedure F: Synthesis of 6,7-dimethoxy-1-phenethyl-1,2,3,4-tetrahydroisoquinoline (4a)



To a solution of **14a** (1157 mg, 3.92 mmol) in methanol (20 mL), sodium borohydride (393 mg, 10.4 mmol, 2.7 eq.) was added at 0 °C. The mixture was stirred at 25 °C under air for 1hr. Then the mixture was quenched with 20 mL of ice water and the whole was extracted with ethyl acetate (30 mL x 2). The organic layer was washed with brine, dried over sodium sulfate and the solvent was evaporated to give

a crude oil. The crude oil was purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:2 ~ 1:0) to afford **4a** (1144 mg, 3.84 mmol, 98% yield) as pale yellow oil.
1H-NMR (400 MHz, $CDCl_3$) δ 7.31-7.17 (m, 5H), 6.58 (s, 1H), 6.57 (s, 1H), 3.96 (dd, J = 8.9, 3.2 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.25 (dt, J = 12.4, 5.6 Hz, 1H), 3.03-2.97 (m, 1H), 2.88-2.63 (m, 4H), 2.17-1.99 (m, 2H), 1.59 (brs, 1H). 13C-NMR (101 MHz, $CDCl_3$) δ 147.2, 147.1, 142.3, 131.3, 128.3, 127.2, 125.7, 111.8, 109.1, 55.9, 55.7, 55.0, 41.0, 38.2, 32.4, 29.5. ESI-HRMS: Calcd for $C_{19}H_{24}NO_2^+$ $[M+H]^+$: 298.1802. Found: 298.1789.

Compounds **4b**–**t** were synthesized following the procedure F.

Synthesis of 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (4b)
97% yield from **14b**. Purified by silica-gel column chromatography (eluent: ethyl acetate). Pale orange sticky oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.34-7.22 (m, 5H), 6.62 (s, 1H), 6.59 (s, 1H), 4.15 (dd, J = 4.6, 4.6 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.23-3.18 (m, 2H), 2.94-2.88 (m, 2H), 2.80-2.67 (m, 2H), 1.72 (brs, 1H). 13C-NMR (101 MHz, $CDCl_3$) δ 147.4, 146.9, 139.1, 130.5, 129.3, 128.5, 127.3, 126.4, 111.7, 109.4, 56.8, 55.9, 55.7, 42.8, 40.6, 29.4. ESI-HRMS: Calcd for $C_{18}H_{22}NO_2^+$ $[M+H]^+$: 284.1645. Found: 284.1634.

Synthesis of 1-phenyl-1,2,3,4-tetrahydroisoquinoline (4c)
72% yield (1782 mg) from **14c**. Purified by silica-gel column chromatography (eluent: ethyl acetate). Pale orange sticky oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.34-7.25 (m, 5H), 7.15-7.12 (m, 2H), 7.06-7.01 (m, 1H), 6.75 (d, J = 7.8 Hz, 1H), 5.10 (s, 1H), 3.30-3.23 (m, 1H), 3.13-3.00 (m, 2H), 2.88-2.80 (m, 1H), 1.81 (brs, 1H). 13C-NMR (101 MHz, $CDCl_3$) δ 144.9, 138.3, 135.4, 129.0, 129.0, 128.4, 128.1, 127.3, 126.2, 125.6, 62.1, 42.3, 29.8.

Synthesis of 1-(p-tolyl)-1,2,3,4-tetrahydroisoquinoline (4d)
97% yield (1864 mg) from **14d**. Purified by silica-gel column chromatography (eluent: ethyl acetate). Pale brown solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.16-7.11 (m, 6H), 7.05-7.00 (m, 1H), 6.75 (d, J = 7.5 Hz, 1H), 5.07 (s, 1H), 3.30-3.25 (m, 1H), 3.12-2.99 (m, 2H), 2.84-2.79 (m, 1H), 2.34 (s, 3H), 1.82 (brs, 1H). 13C-NMR (101 MHz, $CDCl_3$) δ 141.9, 138.5, 136.9, 135.4, 129.1, 129.0, 128.8, 128.1, 126.1, 125.6, 61.8, 42.2, 29.8, 21.1. ESI-HRMS: Calcd for $C_{16}H_{18}N^+$ $[M+H]^+$: 224.1434. Found: 224.1435.

Synthesis of 1-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline (4e)
94% yield (2498 mg) from **14e**. Purified by silica-gel column chromatography (eluent: ethyl acetate). Pale orange solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.30-7.27 (m, 2H), 7.22-7.19 (m, 2H), 7.15-7.04 (m, 2H), 7.06-7.02 (m, 1H), 6.71 (d, J = 7.8 Hz, 1H), 5.07 (s, 1H), 3.28-3.22 (m, 1H), 3.12-2.99 (m, 2H), 2.84-2.79 (m, 1H), 1.83 (brs, 1H). 13C-NMR (101 MHz, $CDCl_3$) δ 143.4, 137.8, 135.4, 133.1, 130.3, 129.1, 128.5, 127.9, 126.4, 125.7, 61.4, 42.2, 29.7. ESI-HRMS: Calcd for $C_{15}H_{15}ClN^+$ $[M+H]^+$: 244.0888. Found: 244.0889.

Synthesis of 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (4f)
90% yield (397 mg) from **14f**. Purified by silica-gel column chromatography (eluent: ethyl acetate). Pale orange sticky oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.34-7.24 (m, 6H), 6.63 (s, 1H), 6.25 (s, 1H), 5.05 (s, 1H), 3.87 (s, 3H), 3.63 (s, 3H), 3.22 (dt, J = 12.0, 5.3 Hz, 1H), 3.08-3.02 (m, 1H), 2.97-2.89 (m, 1H), 2.75 (dt, J = 15.9, 4.9 Hz, 1H), 1.71 (brs,

1H). 13C-NMR (101 MHz, $CDCl_3$) δ 147.6, 147.0, 144.8, 129.8, 128.9, 128.4, 127.7, 127.3, 111.4, 111.0, 61.4, 55.8, 41.8, 29.3. ESI-HRMS: Calcd for $C_{17}H_{20}NO_2^+$ $[M+H]^+$: 270.1489. Found: 270.1480.

Synthesis of 7-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (4g)
79% yield (1392 mg) from **14g**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:2 ~ 1:0). Pale orange sticky oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.34-7.24 (m, 5H), 7.04 (d, J = 7.6 Hz, 1H), 6.96 (d, J = 7.6 Hz, 1H), 6.57 (s, 1H), 5.06 (s, 1H), 3.27-3.22 (m, 1H), 3.09-2.96 (m, 2H), 2.81-2.75 (m, 1H), 2.17 (s, 3H), 1.86 (brs, 1H). 13C-NMR (101 MHz, $CDCl_3$) δ 145.0, 137.9, 135.0, 132.4, 129.0, 128.9, 128.5, 128.4, 127.3, 127.1, 62.0, 42.2, 29.4, 21.0. ESI-HRMS: Calcd for $C_{16}H_{18}N^+$ $[M+H]^+$: 224.1434. Found: 224.1426.

Synthesis of 7-chloro-1-phenyl-1,2,3,4-tetrahydroisoquinoline (4h)
94% yield (658 mg) from **14h**. Purified by silica-gel column chromatography (eluent: ethyl acetate). Pale orange sticky oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.36-7.06 (m, 5H), 7.12-7.06 (m, 2H), 6.74 (d, J = 1.4 Hz, 1H), 5.04 (s, 1H), 3.30-3.24 (m, 1H), 3.10-2.95 (m, 2H), 2.81-2.75 (m, 1H), 1.79 (brs, 1H). 13C-NMR (101 MHz, $CDCl_3$) δ 144.0, 140.1, 133.9, 131.2, 130.4, 128.9, 128.6, 127.8, 127.7, 126.5, 62.0, 42.1, 29.2. ESI-HRMS: Calcd for $C_{15}H_{15}ClN^+$ $[M+H]^+$: 244.0888. Found: 244.0879.

Synthesis of 1-benzyl-1,2,3,4-tetrahydroisoquinoline (4i)
96% yield (701 mg) from **14i**. Purified by silica-gel column chromatography (eluent: ethyl acetate). Pale yellow sticky oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.34-7.09 (m, 9H), 4.20 (dd, J = 10.2, 3.5 Hz, 1H), 3.29-3.17 (m, 2H), 2.93-2.73 (m, 4H), 1.71 (s, 1H). 13C-NMR (101 MHz, $CDCl_3$) δ 139.1, 138.6, 135.2, 129.3, 129.3, 128.5, 126.4, 126.1, 126.1, 125.6, 57.2, 42.5, 40.6, 29.9. ESI-HRMS: Calcd for $C_{16}H_{18}N^+$ $[M+H]^+$: 224.1434. Found: 224.1431.

Synthesis of 1-(4-methylbenzyl)-1,2,3,4-tetrahydroisoquinoline (4j)
97% yield (1016 mg) from **14j**. Purified by silica-gel column chromatography (eluent: ethyl acetate). Pale yellow sticky oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 7.1 Hz, 1H), 7.21-7.08 (m, 7H), 4.16 (d, J = 10.1 Hz, 1H), 3.24-3.18 (m, 2H), 2.90-2.76 (m, 4H), 2.33 (s, 3H), 1.78 (s, 1H). 13C-NMR (101 MHz, $CDCl_3$) δ 138.7, 136.0, 135.9, 135.2, 129.2, 129.1, 126.1, 126.0, 125.6, 57.2, 42.0, 40.6, 29.9, 21.0. ESI-HRMS: Calcd for $C_{17}H_{20}N^+$ $[M+H]^+$: 238.1590. Found: 238.1585.

Synthesis of 1-(4-chlorobenzyl)-1,2,3,4-tetrahydroisoquinoline (4k)
94% yield (948 mg) from **14k**. Purified by silica-gel column chromatography (eluent: ethyl acetate). Pale orange sticky oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.27 (dt, J = 8.7, 2.2 Hz, 2H), 7.21-7.08 (m, 6H), 4.16 (dd, J = 10.1, 3.7 Hz, 1H), 3.22-3.15 (m, 2H), 2.93-2.70 (m, 4H), 1.68 (brs, 1H). 13C-NMR (101 MHz, $CDCl_3$) δ 138.3, 137.6, 135.2, 132.1, 130.6, 129.3, 128.6, 126.1, 126.0, 125.6, 57.0, 41.8, 40.6, 29.8. ESI-HRMS: Calcd for $C_{16}H_{17}ClN^+$ $[M+H]^+$: 258.1044. Found: 258.1039.

Synthesis of 1-benzyl-7-methyl-1,2,3,4-tetrahydroisoquinoline (4l)
67% yield (950 mg) from **14l**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:2 ~ 1:0). Pale yellow sticky oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.34-7.21 (m, 5H), 7.06 (s, 1H), 7.00-6.96 (m, 2H), 4.16 (dd, J = 10.3, 3.4 Hz, 1H), 3.26

(dd, J = 13.5, 3.7 Hz, 1H), 3.22-3.16 (m, 1H), 2.91-2.70 (m, 4H), 2.32 (s, 3H), 1.69 (brs, 1H). 13C-NMR (101 MHz, $CDCl_3$) δ 139.3, 138.4, 135.0, 132.1, 129.3, 129.1, 128.5, 126.9, 126.7, 126.4, 57.2, 42.5, 40.7, 29.6, 21.1. ESI-HRMS: Calcd for $C_{17}H_{20}N^+$ $[M+H]^+$: 238.1590. Found: 238.1586.

Synthesis of 1-benzyl-7-chloro-1,2,3,4-tetrahydroisoquinoline (4m)
63% yield (716 mg) from **14m**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:2 ~ 1:0). Pale orange sticky oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.35-7.01 (m, 8H), 4.14 (dd, J = 10.2, 3.5 Hz, 1H), 3.24-3.15 (m, 2H), 2.90-2.65 (m, 4H), 1.68 (brs, 1H). 13C-NMR (101 MHz, $CDCl_3$) δ 140.4, 138.6, 133.7, 131.1, 130.6, 129.2, 128.6, 126.5, 126.2, 126.1, 57.0, 42.2, 40.5, 29.4. ESI-HRMS: Calcd for $C_{16}H_{17}ClN^+$ $[M+H]^+$: 258.1044. Found: 258.1039.

Synthesis of 1-phenethyl-1,2,3,4-tetrahydroisoquinoline (4n)
91% yield (1151 mg) from **14n**. Purified by silica-gel column chromatography (eluent: ethyl acetate). Pale orange sticky oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.30-7.06 (m, 9H), 4.00 (dd, J = 8.9, 3.4 Hz, 1H), 3.25 (dt, J = 12.6, 5.6 Hz, 1H), 3.04-2.98 (m, 1H), 2.87-2.70 (m, 4H), 2.19-2.00 (m, 2H), 1.60 (brs, 1H). 13C-NMR (101 MHz, $CDCl_3$) δ 142.3, 139.5, 135.2, 129.2, 128.4, 128.4, 126.0, 125.8, 125.7, 125.7, 55.3, 40.9, 38.1, 32.4, 30.0. ESI-HRMS: Calcd for $C_{17}H_{20}N^+$ $[M+H]^+$: 238.1590. Found: 238.1584.

Synthesis of 1-(4-methylphenethyl)-1,2,3,4-tetrahydroisoquinoline (4o)
96% yield (2114 mg) from **14o**. Purified by silica-gel column chromatography (eluent: ethyl acetate). Pale yellow sticky oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.12-7.07 (m, 8H), 3.99-3.97 (m, 1H), 3.26-3.20 (m, 1H), 3.02-2.95 (m, 1H), 2.86-2.65 (m, 4H), 2.30 (s, 3H), 2.15-2.00 (m, 2H), 1.62 (brs, 1H). 13C-NMR (101 MHz, $CDCl_3$) δ 139.5, 139.1, 135.2, 135.1, 129.2, 129.0, 128.2, 126.0, 125.8, 125.7, 55.3, 40.9, 38.2, 31.9, 29.9, 20.9. ESI-HRMS: Calcd for $C_{19}H_{22}N^+$ $[M+H]^+$: 252.1747. Found: 252.1743.

Synthesis of 1-(4-chlorophenethyl)-1,2,3,4-tetrahydroisoquinoline (4p)
89% yield (1097 mg) from **14p**. Purified by silica-gel column chromatography (eluent: ethyl acetate). Pale yellow sticky oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.25-7.23 (m, 2H), 7.16-7.07 (m, 6H), 3.99 (dd, J = 8.8, 3.5 Hz, 1H), 3.24 (dt, J = 12.6, 5.7 Hz, 1H), 3.05-2.99 (m, 1H), 2.86-2.70 (m, 4H), 2.11-2.01 (m, 2H), 1.57 (brs, 1H). 13C-NMR (101 MHz, $CDCl_3$) δ 140.8, 139.3, 135.3, 131.4, 129.7, 129.3, 128.4, 126.0, 125.9, 125.8, 55.1, 40.9, 38.1, 31.7, 30.0. ESI-HRMS: Calcd for $C_{17}H_{19}ClN^+$ $[M+H]^+$: 272.1201. Found: 272.1195.

Synthesis of 7-methyl-1-phenethyl-1,2,3,4-tetrahydroisoquinoline (4q)
95% yield (1211 mg) from **14q**. Purified by silica-gel column chromatography (eluent: ethyl acetate). Pale yellow sticky oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.31-7.14 (m, 5H), 6.98-6.89 (m, 3H), 3.97 (dd, J = 9.1, 3.2 Hz, 1H), 3.24 (dt, J = 12.4, 5.6 Hz, 1H), 3.02-2.96 (m, 1H), 2.88-2.66 (m, 4H), 2.28 (s, 3H), 2.19-2.11 (m, 1H), 2.08-1.98 (m, 1H), 1.63 (brs, 1H). 13C-NMR (101 MHz, $CDCl_3$) δ 142.4, 139.3, 135.1, 132.1, 129.1, 128.4, 128.4, 126.7, 126.6, 125.7, 55.4, 41.1, 38.2, 32.5, 29.6, 21.1. ESI-HRMS: Calcd for $C_{18}H_{22}N^+$ $[M+H]^+$: 252.1747. Found: 252.1740.

Synthesis of 7-chloro-1-phenethyl-1,2,3,4-tetrahydroisoquinoline (4r)
99% yield (429 mg) from **14r**. Purified by silica-gel column chromatography (eluent: ethyl acetate). Pale yellow sticky oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.32-6.99 (m, 8H),

3.95 (dd, J = 9.1, 3.4 Hz, 1H), 3.23 (dt, J = 12.7, 5.6 Hz, 1H), 3.02-2.96 (m, 1H), 2.89-2.64 (m, 6H), 2.16-1.97 (m, 2H), 1.59 (brs, 1H). 13C-NMR (101 MHz, $CDCl_3$) δ 142.0, 141.3, 133.7, 131.3, 130.6, 128.4, 128.4, 126.1, 126.0, 125.9, 55.1, 40.7, 38.0, 32.3, 29.4. ESI-HRMS: Calcd for $C_{17}H_{19}ClN^+$ $[M+H]^+$: 272.1201. Found: 272.1200.

Synthesis of 1-(3-phenylpropyl)-1,2,3,4-tetrahydroisoquinoline (4s)

94% yield (941 mg) from **14s**. Purified by silica-gel column chromatography (eluent: ethyl acetate). Pale orange sticky oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.29-7.07 (m, 9H), 3.98 (d, J = 5.0 Hz, 1H), 3.23-3.18 (m, 1H), 3.00-2.94 (m, 1H), 2.85-2.62 (m, 4H), 1.91-1.75 (m, 4H), 1.61 (s, 1H). 13C-NMR (101 MHz, $CDCl_3$) δ 142.2, 139.4, 135.1, 129.2, 128.4, 128.2, 126.0, 125.8, 125.7, 125.7, 55.5, 41.0, 35.9, 35.9, 29.9, 27.9. ESI-HRMS: Calcd for $C_{18}H_{22}N^+$ $[M+H]^+$: 252.1747. Found: 252.1739.

Synthesis of Racemic mixture of (R)-1-((R)-1,2-diphenylethyl)-1,2,3,4-tetrahydroisoquinoline and (S)-1-((S)-1,2-diphenylethyl)-1,2,3,4-tetrahydroisoquinoline (4t)

90% yield (1037 mg) from **14t**. Purified by silica-gel column chromatography (eluent: ethyl acetate). White amorphous solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.22-7.03 (m, 13H), 6.95 (d, J = 7.3 Hz, 1H), 4.22 (d, J = 4.7 Hz, 1H), 3.57 (td, J = 7.7, 4.7 Hz, 1H), 3.33 (dd, J = 13.5, 7.8 Hz, 1H), 3.12-3.00 (m, 2H), 2.78-2.71 (m, 1H), 2.54 (dt, J = 16.1, 5.0 Hz, 1H), 2.42-2.34 (m, 1H), 1.47 (brs, 1H). 13C-NMR (101 MHz, $CDCl_3$) δ 140.8, 140.8, 138.1, 136.5, 129.1, 129.0, 128.9, 128.2, 127.9, 127.2, 126.4, 125.9, 125.8, 125.3, 58.2, 52.1, 41.1, 38.8, 29.9. ESI-HRMS: Calcd for $C_{23}H_{24}N^+$ $[M+H]^+$: 314.1903. Found: 314.1898.

Synthesis of dimethyl 2,2'-(carbonylbis(oxy))bis(3-nitrobenzoate) (15)

To a solution of methyl 2-hydroxy-3-nitrobenzoate (5532 mg, 28.1 mmol) and triphosgene (1459 mg, 4.92 mmol) in dry dichloromethane (50 mL) was added a dry pyridine (5.0 mL) at 0 °C. The mixture was stirred at 0 °C for 1.5 h. The reaction was quenched with aqueous HCl (1 mol/L) (40 mL). The reaction mixture was extracted with dichloromethane (50 mL). The organic phase was washed with brine (20 mL), dried over sodium sulfate, and the solvent was evaporated to give the crude solid. The crude solid was purified by recrystallization (solvent: dichloromethane and hexane) to afford **14** as white powder (5615 mg, 13.4 mmol, 95% yield).

Mp. 98–101 °C (White powder, recrystallized from dichloromethane/*n*-hexane). 1H-NMR (400 MHz, $CDCl_3$) δ 8.23 (dd, J = 7.8, 1.6 Hz, 2H), 8.17 (dd, J = 8.1, 1.5 Hz, 2H), 7.55 (dd, J = 8.1, 7.9 Hz, 2H), 4.02 (s, 6H). 13C-NMR (101 MHz, $CDCl_3$) δ 163.4, 148.6, 143.0, 142.2, 136.1, 129.0, 127.3, 126.8, 53.3. ESI-HRMS: Calcd for $C_{17}H_{12}N_2NaO_{11}^+$ $[M+Na]^+$: 443.0333. Found: 443.0323.

Synthesis of dimethyl 6,6'-(carbonylbis(oxy))bis(3-nitrobenzoate) (16)

To a solution of methyl 2-hydroxy-5-nitrobenzoate (2085 mg, 10.6 mmol) and triphosgene (593 mg, 2.00 mmol) in dry dichloromethane (40 mL) was added a dry pyridine (3.0 mL) at 0 °C. The mixture was stirred at 0 °C for 1.5 h. The reaction was quenched with aqueous HCl (1 mol/L) (40 mL). The reaction mixture was extracted with dichloromethane (50 mL). The organic phase was washed with brine (20 mL), dried over sodium sulfate, and the solvent was evaporated to give the crude solid. The crude solid was purified by recrystallization (solvent: dichloromethane) to afford **15** as

white powder (1947 mg, 4.63 mmol, 88% yield).
Mp. 185–187 °C (Colorless needles, recrystallized from dichloromethane). 1H-NMR (400 MHz, DMSO-d_6) δ 8.70 (d, J = 2.7 Hz, 2H), 8.61 (dd, J = 8.9, 2.7 Hz, 2H), 7.80 (d, J = 8.9 Hz, 2H), 3.95 (s, 6H). 13C-NMR (101 MHz, DMSO-d_6) δ 162.7, 153.2, 149.2, 145.7, 129.6, 126.8, 125.3, 123.8, 53.3. ESI-HRMS: Calcd for $C_{17}H_{12}N_2NaO_{11}^+$ $[M+Na]^+$: 443.0333. Found: 443.0324.

Synthesis of tetramethyl 2,2'-(carbonylbis(oxy))diisophthalate(17)

A mixture of 2-hydroxyisophthalaldehyde (465 mg, 3.10 mmol), sodium hydroxide (1305 mg, 32.6 mmol) and silver(I) oxide (1438 mg, 6.21 mmol) in water (12mL) was heated at 60 °C for 10 min. The solution was filtered. Then pH was lowered to 1 by adding HCl. The whole was extracted with ethyl acetate (50 mL). The organic layer was washed with brine, dried over sulfate and the solvent was evaporated to afford dimethyl 2-hydroxyisophthalate as white solid (525 mg, 2.88 mmol, 93% yield). The NMR spectra are in accord with previous report.[S22]
1H-NMR (400 MHz, methanol-d_4) δ 8.10 (d, J = 7.8 Hz, 2H), 6.98 (dd, J = 7.8, 7.8 Hz, 1H). 13C-NMR (101 MHz, methanol-d_4) δ 171.1, 163.3, 137.7, 119.5, 117.8.

Dimethyl 2-hydroxyisophthalate was synthesized according to previously reported procedure from 2-hydroxyisophthalic acid (89% yield).[S23]

To a solution of dimethyl 2-hydroxyisophthalate (325 mg, 1.54 mmol) and triphosgene (78 mg, 0.26 mmol) in dry dichloromethane (2 mL) was added a dry pyridine (0.50 mL) at 0 °C. The mixture was stirred at 25 °C for 20 h. The reaction was quenched with aqueous HCl (1 mol/L) (40 mL). The reaction mixture was extracted with dichloromethane (30 mL). The organic phase was washed with brine (10 mL), dried over sodium sulfate, and the solvent was evaporated to give the crude solid. The crude solid was purified by silica-gel column chromatography (eluent: ethyl acetate:*n*-hexane = 1:4 ~ 1:2) to afford **17** as white powder (213 mg, 0.48 mmol, 62% yield).
Mp. 129–130 °C (White powder, recrystallized from dichloromethane/*n*-hexane). 1H-NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 7.8 Hz, 4H), 7.41 (dd, J = 7.8, 7.8 Hz, 2H), 3.96 (s, 12H). 13C-NMR (101 MHz, $CDCl_3$) δ 164.6, 150.2, 148.8, 135.1, 126.3, 125.8, 52.7. ESI-HRMS: Calcd for $C_{21}H_{18}NaO_{11}^+$ $[M+Na]^+$: 469.0741. Found: 469.0720.

Synthesis of substrate 2-(methoxycarbonyl)phenyl 6,7-dimethoxy-1-phenethyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (1a)

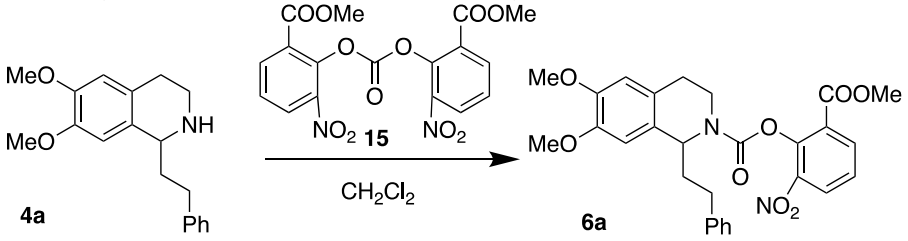
Dimethyl 2,2'-(carbonylbis(oxy))dibenzoate (**18**) was synthesized according to previously reported procedure.[8c]
White solid. 1H-NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, J = 7.8, 1.6 Hz, 2H), 7.63-7.59 (m, 2H), 7.40-7.34 (m, 4H), 3.95 (s, 6H).

A solution of **18** (336 mg, 1.02 mmol) and **4a** (360 mg, 1.21 mmol, 1.2 eq.) in tetrahydrofuran (5.0 mL) was stirred at 25 °C for 15 h. The solvent was evaporated under reduced pressure to give a crude oil. The crude oil was purified by silica-gel column chromatography (eluent: ethyl acetate:*n*-hexane = 1:4 ~ 1:2) to afford **1a** as colorless sticky oil (446 mg, 0.939 mmol, 78% yield).
Colorless sticky oil. 1H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A:B = 6:4 ratio at 25 °C), δ 7.96 (dd, J = 8.0, 1.6 Hz, 1H, rotamer A and B), 7.51 (td, J = 8.0, 1.6 Hz, 1H, rotamer A and B), 7.23-7.28 (m, 5H, rotamer A and B), 7.14-7.18 (m, 2H, rotamer A and B), 6.64 (s, 1H, rotamer A and B), 6.59 (s, 0.4H, rotamer B), 6.57 (s, 0.6H, rotamer A), 5.34 (s, 0.4H,

rotamer B), 5.23 (s, 0.6H, rotamer A), 4.24-4.33 (m, 1H, rotamer A and B), 3.81-3.89 (m, 6H, rotamer A and B), 3.73 (s, 1.8H, rotamer A), 3.54-3.61 (m, 0.6H, rotamer A), 3.54 (m, 1.2 H, rotamer B), 3.39 (m, 0.4H, rotamer B), 2.71-3.11 (m, 4H, rotamer A and B), 2.09-2.27 (m, 2H, rotamer A and B). 13C-NMR (101 MHz, $CDCl_3$) two rotamers with respect to the amide bond were observed, δ 165.46, 165.24, 153.84, 151.18, 150.82, 148.08, 147.80, 142.02, 141.76, 133.33, 131.66, 131.51, 129.71, 129.47, 128.34, 126.16, 125.93, 125.77, 125.34, 124.10, 124.00, 111.89, 110.59, 110.35, 56.13, 55.99, 55.26, 55.06, 51.86, 39.12, 38.70, 38.47, 32.82, 32.70, 28.14, 27.70. ESI-HRMS: Calcd for $C_{28}H_{29}NNaO_6^+$ $[M+Na]^+$: 498.1887. Found: .498.1874.

Synthesis of substrates 6a–t

Typical Procedure F: Synthesis of 2-(methoxycarbonyl)-6-nitrophenyl 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (6a)



A solution of **15** (1427 mg, 3.40 mmol) and **4a** (1144 mg, 3.84 mmol, 1.1 eq.) in dichloromethane (10.0 mL) was stirred at 25 °C for 5 min. The solvent was evaporated under reduced pressure to give a crude oil. The crude oil was dissolved in ethyl acetate (50 mL) and washed with 10 mL of aqueous tripotassium phosphate (0.5 mol/L) two times, and then washed with brine once. The organic layer was dried over sodium sulfate. The solvent was evaporated under reduced pressure to give a crude oil. The crude oil was purified by silica-gel column chromatography (eluent: ethyl acetate:*n*-hexane = 1:4 ~ 1:1) to afford **6a** as pale yellow sticky oil (1425 mg, 2.74 mmol, 81% yield).

1H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A:B = 6:4 ratio at 25 °C), δ 8.22 (dd, J = 8.0, 1.6 Hz, 1H, rotamer A and B), 8.19-8.14 (m, 1H, rotamer A and B), 7.46-7.40 (m, 1H, rotamer A and B), 7.36-7.26 (m, 5H, rotamer A and B), 6.73 (s, 1H, rotamer A and B), 6.54 (s, 1H, rotamer A and B), 6.48 (s, 0.4H, rotamer B), 6.40 (s, 0.6H, rotamer A), 4.25-4.13 (m, 1H, rotamer A and B), 3.91 (s, 3H, rotamer A and B), 3.77 (s, 3H, rotamer A and B), 3.62 (s, 1.8H, rotamer A), 3.50 (s, 1H, rotamer B), 3.44-3.37 (m, 1H, rotamer A and B), 3.28-3.03 (m, 1.4H, rotamer A and B), 2.80-2.72 (m, 1H, rotamer A and B). 13C-NMR (101 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ 164.2, 164.0, 152.0, 151.4, 148.2, 148.2, 147.5, 144.5, 144.3, 143.8, 141.8, 141.5, 136.3, 136.2, 129.0, 129.0, 128.6, 128.6, 128.3, 128.3, 127.7, 127.3, 126.8, 126.8, 126.3, 126.1, 125.7, 125.6, 111.3, 111.2, 111.1, 110.8, 58.4, 57.8, 55.9, 55.9, 52.5, 52.4, 38.9, 38.5, 28.1, 27.5. ESI-HRMS: Calcd for $C_{26}H_{24}N_2NaO_8^+$ $[M+Na]^+$: 515.1425. Found: 515.1404.

Compounds **6b–t** were synthesized following the procedure F.

Synthesis of 2-(methoxycarbonyl)-6-nitrophenyl 1-benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (6b)

92% yield (466 mg) from **4b**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:5 ~ 1:2). Pale yellow sticky oil. 1H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately

A:B = 6:4 ratio at 25 °C), δ 8.26-8.15 (m, 2H, rotamer A and B), 7.47-7.41 (m, 1H, rotamer A and B), 7.26-7.17 (m, 3H, rotamer A and B), 7.12-7.07 (m, 2H, rotamer A and B), 6.63, (s, 0.6H, rotamer A), 6.62 (s, 0.4H, rotamer B), 6.12 (s, 0.6H, rotamer A), 6.04 (s, 0.4H, rotamer B), 5.41 (dd, J = 8.7, 3.9 Hz, 0.4H, rotamer B), 5.26 (dd, J = 8.1, 5.1 Hz, 0.6H, rotamer A), 4.09-3.96 (m, 1H, rotamer A and B), 3.87 (s, 3H, rotamer A and B), 3.80 (s, 1.8H, rotamer A), 3.70 (s, 1.2H, rotamer B), 3.67-3.61 (m, 0.6H, rotamer A), 3.58 (s, 1.8H, rotamer A), 3.54 (s, 1.2H, rotamer B), 3.49 (dd, J = 13.0, 3.9 Hz, 0.4H, rotamer B), 3.39-3.28 (m, 1H, rotamer A and B), 3.17-3.04 (m, 1H, rotamer A and B), 2.99-2.84 (m, 1H, rotamer A and B), 2.71-2.63 (m, 1H, rotamer A and B).

13C-NMR (101 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ 182.0, 163.9, 163.7, 151.9, 151.9, 147.8, 146.8, 146.7, 144.7, 144.6, 143.9, 143.8, 137.8, 137.7, 136.2, 136.0, 130.1, 130.0, 129.1, 129.0, 128.3, 128.2, 128.0, 127.4, 127.2, 127.1, 127.0, 126.5, 126.5, 126.0, 125.9, 125.6, 125.5, 111.1, 111.0, 110.5, 110.5, 57.2, 55.8, 55.8, 55.6, 55.5, 52.6, 43.1, 42.5, 40.5, 40.3, 28.0, 27.7.

ESI-HRMS: Calcd for $C_{27}H_{26}N_2NaO_8^+$ $[M+Na]^+$: 529.1581. Found: 529.1572.

Synthesis of 2-(methoxycarbonyl)-6-nitrophenyl 1-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (6c)

76% yield (132 mg) from **4c**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:5 ~ 1:2). Pale yellow sticky oil. 1H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A:B = 6:4 ratio at 25 °C), δ 8.21 (d, J = 7.8 Hz, 1H, rotamer A and B), 8.17-8.14 (m, 1H, rotamer A and B), 7.46-7.40 (m, 1H, rotamer A and B), 7.34-7.19 (m, 8H, rotamer A and B), 7.10 (d, J = 7.3 Hz, 1H, rotamer A and B), 6.55 (s, 0.4H, rotamer B), 6.46 (s, 0.6H, rotamer A), 4.24-4.11 (m, 1H, rotamer A and B), 3.61 (s, 1.8H, rotamer A), 3.56-3.49 (m, 0.6H, rotamer A), 3.46 (s, 1.2H, rotamer B), 3.38-3.31 (m, 0.4H, rotamer B), 3.23-3.07 (m, 1H, rotamer A and B), 2.89-2.80 (m, 1H, rotamer A and B). 13C-NMR (101 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ 163.9, 152.1, 151.6, 144.5, 143.8, 141.7, 141.4, 136.3, 136.2, 134.8, 134.7, 134.6, 129.1, 129.0, 129.0, 128.8, 128.5, 128.4, 128.4, 128.4, 128.3, 127.6, 127.6, 127.3, 127.2, 126.2, 125.7, 125.6, 58.9, 58.3, 52.5, 52.4, 39.3, 39.0, 28.5, 27.9. ESI-HRMS: Calcd for $C_{24}H_{20}N_2NaO_6^+$ $[M+Na]^+$: 455.1213. Found: 455.1194.

Synthesis of 2-(methoxycarbonyl)-6-nitrophenyl 1-(p-tolyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (6d)

83% yield (556 mg) from **4d**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:5 ~ 1:2). Pale yellow sticky oil. 1H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A:B = 6:4 ratio at 25 °C), δ 8.20 (dd, J = 7.8, 1.6 Hz, 1H, rotamer A and B), 8.16-8.12 (m, 1H, rotamer A and B), 7.46-7.40 (m, 1H, rotamer A and B), 7.25-7.08 (m, 8H, rotamer A and B), 6.53 (s, 0.4H, rotamer B), 6.43 (s, 0.6H, rotamer A), 4.22-4.18 (m, 1H, rotamer A and B), 3.62 (s, 1.8H, rotamer A), 3.54-3.48 (m, 0.6H, rotamer A), 3.46 (s, 1.2H, rotamer B), 3.37-3.30 (m, 0.4H, rotamer B), 3.26-3.06 (m, 1H, rotamer A and B), 2.88-2.79 (m, 1H, rotamer A and B), 2.33 (s, 1.2H, rotamer B), 2.31 (s, 1.8H, rotamer A). 13C-NMR (101 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ 164.2, 163.9, 152.0, 151.6, 144.5, 144.3, 143.8, 138.8, 138.4, 137.3, 137.3, 136.3, 136.1, 134.9, 134.8, 134.6, 129.0, 128.9, 128.8, 128.5, 128.4, 128.3, 127.3, 127.2, 127.1, 126.1, 125.6, 125.5, 58.6, 58.0, 52.5, 52.3, 39.2, 38.8, 28.5, 27.9, 21.0. ESI-HRMS: Calcd for $C_{25}H_{22}N_2NaO_6^+$ $[M+Na]^+$: 469.1370. Found: 469.1350.

Synthesis of 2-(methoxycarbonyl)-6-nitrophenyl 1-(4-chlorophenyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (6e)

75% yield (534 mg) from **4e**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:5 ~ 1:2). Pale yellow sticky oil. 1H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A:B = 6:4 ratio at 25 °C), 1H-NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, J = 8.0, 1.6 Hz, 1H, rotamer A and B), 8.16 (ddd, J = 8.0, 4.7, 1.6 Hz, 1H, rotamer A and B), 7.46-7.40 (m, 1H, rotamer A and B), 7.33-7.20 (m, 7H, rotamer A and B), 7.08 (d, J = 7.3 Hz, 1H, rotamer A and B), 6.52 (s, 0.4H, rotamer B), 6.41 (s, 0.6H, rotamer A), 4.23-4.10 (m, 1H, rotamer A and B), 3.67 (s, 1.8H, rotamer A), 3.53-3.46 (m, 0.6H, rotamer A), 3.50 (s, 1.2H, rotamer A), 3.34-3.27 (m, 0.4H, rotamer B), 3.21-3.06 (m, 1H, rotamer A and B), 2.88-2.79 (m, 1H, rotamer A and B).

13C-NMR (101 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ 164.0, 163.7, 152.2, 151.5, 144.5, 144.2, 143.7, 140.3, 140.0, 136.3, 136.1, 134.7, 134.3, 134.1, 133.6, 133.5, 129.8, 129.7, 129.2, 129.1, 129.0, 128.9, 128.5, 128.4, 128.4, 128.2, 127.5, 127.4, 127.2, 127.1, 126.4, 125.8, 125.7, 58.3, 57.6, 52.5, 52.4, 39.4, 39.0, 28.4, 27.8.

ESI-HRMS: Calcd for $C_{24}H_{19}ClN_2NaO_6^+$ $[M+Na]^+$: 489.0824. Found: 489.0804.

Synthesis of 2-(methoxycarbonyl)-6-nitrophenyl 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (6f)

81% yield (500 mg) from **4f**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:5 ~ 1:2). Pale yellow sticky oil. 1H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A:B = 6:4 ratio at 25 °C), δ 8.22 (dd, J = 8.0, 1.6 Hz, 1H, rotamer A and B), 8.19-8.14 (m, 1H, rotamer A and B), 7.46-7.40 (m, 1H, rotamer A and B), 7.36-7.26 (m, 5H, rotamer A and B), 6.73 (s, 1H, rotamer A and B), 6.54 (s, 1H, rotamer A and B), 6.48 (s, 0.4H, rotamer B), 6.40 (s, 0.6H, rotamer A), 4.25-4.13 (m, 1H, rotamer A and B), 3.91 (s, 3H, rotamer A and B), 3.77 (s, 3H, rotamer A and B), 3.62 (s, 1.8H, rotamer A), 3.50 (s, 1H, rotamer B), 3.44-3.37 (m, 1H, rotamer A and B), 3.28-3.03 (m, 1.4H, rotamer A and B), 2.80-2.72 (m, 1H, rotamer A and B).

13C-NMR (101 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ 164.2, 164.0, 152.0, 151.4, 148.2, 148.2, 147.5, 144.5, 144.3, 143.8, 141.8, 141.5, 136.3, 136.2, 129.0, 129.0, 128.6, 128.6, 128.3, 128.3, 127.7, 127.3, 126.8, 126.8, 126.3, 126.1, 125.7, 125.6, 111.3, 111.2, 111.1, 110.8, 58.4, 57.8, 55.9, 55.9, 52.5, 52.4, 38.9, 38.5, 28.1, 27.5.

ESI-HRMS: Calcd for $C_{26}H_{24}N_2NaO_8^+$ $[M+Na]^+$: 515.1425. Found: 515.1404.

Synthesis of 2-(methoxycarbonyl)-6-nitrophenyl 7-methyl-1-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (6g)

89% yield (948 mg) from **4g**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:5 ~ 1:2). Pale yellow sticky oil. 1H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A:B = 6:4 ratio at 25 °C), δ 8.22 (dd, J = 7.8, 1.4 Hz, 1H, rotamer A and B), 8.19-8.14 (m, 1H, rotamer A and B), 7.46-7.40 (m, 1H, rotamer A and B), 7.37-7.26 (m, 5H, rotamer A and B), 7.14 (d, J = 7.8 Hz, 1H, rotamer A and B), 7.07 (d, J = 8.0 Hz, 1H, rotamer A and B), 6.91 (s, 1H, rotamer A and B), 6.50 (s, 0.4H, rotamer B), 6.41 (s, 0.6H, rotamer A), 4.22-4.10 (m, 1H, rotamer A and B), 3.60 (s, 1.8H, rotamer A), 3.53-

3.49 (m, 0.6H, rotamer A), 3.46 (s, 1.2H, rotamer B), 3.36-3.29 (m, 0.4H, rotamer B), 3.18-3.03 (m, 1H, rotamer A and B), 2.87-2.77 (m, 1H, rotamer A and B), 2.30 (s, 3H, rotamer A and B). 13C-NMR (101 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ 164.3, 164.0, 152.1, 151.6, 144.5, 144.3, 143.8, 141.9, 141.5, 136.3, 136.2, 135.8, 135.8, 134.5, 134.4, 131.6, 129.0, 129.0, 128.9, 128.7, 128.7, 128.5, 128.5, 128.3, 128.3, 128.2, 128.1, 127.6, 127.6, 127.4, 127.4, 125.7, 125.6, 58.9, 58.3, 52.5, 52.4, 39.4, 39.0, 28.1, 27.5, 21.0.ESI-HRMS: Calcd for $C_{25}H_{22}N_2NaO_6^+$ $[M+Na]^+$: 469.1370. Found: 469.1350.

Synthesis of 2-(methoxycarbonyl)-6-nitrophenyl 7-chloro-1-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (6h)

89% yield (616 mg) from **4h**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:5 ~ 1:2). Pale yellow sticky oil. 1H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A:B = 6:4 ratio at 25 °C), δ 8.21 (d, J = 7.8 Hz, 1H, rotamer A and B), 8.16 (dd, J = 7.0, 7.0 Hz, 1H, rotamer A and B), 7.45-7.40 (m, 1H, rotamer A and B), 7.38-7.18 (m, 7H, rotamer A and B), 7.10 (s, 1H, rotamer A and B), 6.52 (s, 0.4H, rotamer B), 6.43 (s, 0.6H, rotamer A), 4.24-4.13 (m, 1H, rotamer A and B), 3.62 (s, 1.8H, rotamer A), 3.54 (s, 1.2H, rotamer B), 3.51-3.44 (m, 0.6H, rotamer A), 3.35-3.28 (m,0.40H, rotamer B), 3.20-3.03 (m, 1H, rotamer A and B), 2.85-2.78 (m, 1H, rotamer A and B).

13C-NMR (101 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ 164.0, 163.8, 152.0, 151.5, 144.4, 144.3, 143.7, 141.0, 140.8, 136.5, 136.3, 136.2, 133.3, 133.2, 131.9, 131.9, 130.4, 130.2, 129.1, 129.0, 128.5, 128.4, 128.4, 128.3, 128.0, 127.9, 127.5, 127.5, 127.2, 125.8, 125.7, 58.6, 57.9, 52.5, 52.4, 38.9, 38.6, 28.0, 27.4.

ESI-HRMS: Calcd for $C_{24}H_{19}ClN_2NaO_6^+$ $[M+Na]^+$: 489.0824. Found: 489.0805.

Synthesis of 2-(methoxycarbonyl)-6-nitrophenyl 1-benzyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (6i)

75% yield (333 mg) from **4i**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:5 ~ 1:2). Pale yellow sticky oil. 1H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A:B = 6:4 ratio at 25 °C), δ 8.21-8.08 (m, 2H, rotamer A and B), 7.41-7.34 (m, 1H, rotamer A and B), 7.24-7.01 (m, 8H, rotamer A and B), 6.87-6.82 (m, 1H, rotamer A and B), 5.51 (dd, J = 7.5, 4.3 Hz, 0.4H, rotamer B), 5.37 (dd, J = 6.3, 6.3 Hz, 0.6H, rotamer A), 4.03-3.96 (m, 0.6H, rotamer A), 3.88-3.83 (m, 0.4H, rotamer B), 3.76 (s, 1.8H, rotamer A), 3.65 (s, 1.2H, rotamer B), 3.65-3.58 (m, 0.6H, rotamer A), 3.43 (dd, J = 13.3, 4.1 Hz, 0.4H, rotamer B), 3.33-3.13 (m, 2H, rotamer A and B), 3.00-2.92 (m, 0.6H, rotamer A), 2.90-2.82 (m, 0.4H, rotamer B), 2.68-2.57 (m, 1H, rotamer A and B). 13C-NMR (101 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ 163.7, 163.5, 152.0, 151.9, 144.5, 144.4, 143.8, 143.7, 137.4, 137.3, 136.0, 135.8, 135.5, 135.2, 134.3, 134.1, 129.8, 129.7, 128.9, 128.8, 128.4, 128.3, 128.1, 128.1, 127.3, 127.3, 127.0, 126.9, 126.8, 126.4, 126.4, 125.9, 125.9, 125.5, 125.4, 57.5, 57.4, 52.5, 43.0, 42.4, 40.6, 40.5, 28.2, 27.9. ESI-HRMS: Calcd for $C_{25}H_{22}N_2NaO_6^+$ $[M+Na]^+$: 469.1370. Found: 469.1360.

Synthesis of 2-(methoxycarbonyl)-6-nitrophenyl 1-(4-methylbenzyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (6j)

87% yield (397 mg) from **4j**. Purified by silica-gel column chromatography (eluent:

ethyl acetate: *n*-hexane = 1:5 ~ 1:2). Pale yellow sticky oil. 1H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A:B = 6:4 ratio at 25 °C), δ 8.22-8.10 (m, 2H, rotamer A and B), 7.43-7.36 (m, 1H, rotamer A and B), 7.23-6.84 (m, 8H, rotamer A and B), 5.48 (dd, J = 7.3, 4.3 Hz, 0.4H, rotamer B), 5.34 (dd, J = 6.2, 6.2 Hz, 0.6H, rotamer A), 4.03-3.97 (m, 0.6H, rotamer A), 3.91-3.85 (m, 0.4H, rotamer B), 3.77 (s, 1.8H, rotamer A), 3.65 (s, 1.2H, rotamer B), 3.63-3.58 (m, 0.6H, rotamer A), 3.40-3.09 (m, 2H, rotamer A and B), 3.00-2.84 (m, 1H, rotamer A and B), 2.70-2.59 (m, 1H, rotamer A and B), 2.29 (s, 1.2H, rotamer B), 2.29 (s, 1.8H, rotamer A). 13C-NMR (101 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ 163.8, 163.6, 152.0, 151.9, 144.6, 144.5, 143.9, 143.8, 136.1, 136.0, 135.9, 135.7, 135.4, 134.4, 134.3, 134.2, 134.2, 129.7, 129.6, 129.0, 128.9, 128.9, 128.8, 128.5, 128.3, 127.4, 127.4, 127.1, 127.0, 126.9, 126.8, 126.0, 125.9, 125.6, 125.4, 57.6, 57.5, 52.5, 42.6, 42.1, 40.6, 28.3, 28.0, 21.0. ESI-HRMS: Calcd for $C_{26}H_{24}N_2NaO_6^+$ $[M+Na]^+$: 483.1526. Found: 483.1517.

Synthesis of 2-(methoxycarbonyl)-6-nitrophenyl 1-(4-chlorobenzyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (6k)

87% yield (415 mg) from **4k**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:5 ~ 1:2). Pale yellow sticky oil. 1H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A:B = 6:4 ratio at 25 °C), δ 8.23-8.18 (m, 1H, rotamer A and B, rotamer A and B), 8.14 (ddd, J = 8.1, 8.1, 1.6 Hz, 1H, rotamer A and B), 7.44-7.38 (m, 1H, rotamer A and B, rotamer A and B), 7.24-7.12 (m, 5H, rotamer A and B), 7.02-6.86 (m, 3H, rotamer A and B), 5.48 (dd, J = 7.1, 4.6 Hz, 0.4H, rotamer B), 5.33 (dd, J = 6.2, 6.2 Hz, 0.6H, rotamer A), 4.01-3.95 (m, 0.6H, rotamer A), 3.89-3.83 (m, 0.4H, rotamer B), 3.79 (s, 1.8H, rotamer A), 3.67 (s, 1.2H, rotamer B), 3.64-3.57 (m, 0.6H, rotamer A), 3.37 (dd, J = 13.5, 4.3 Hz, 0.4H, rotamer B), 3.31-3.11 (m, 2H, rotamer A and B), 3.00-2.83 (m, 1H, rotamer A and B), 2.68-2.57 (m, 1H, rotamer A and B). 13C-NMR (101 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ 163.6, 163.4, 152.0, 144.6, 144.5, 143.9, 143.7, 136.1, 135.9, 135.9, 135.3, 134.9, 134.4, 134.2, 132.4, 132.3, 131.2, 131.1, 129.0, 128.9, 128.6, 128.4, 128.3, 128.2, 127.3, 127.2, 127.1, 127.0, 127.0, 126.9, 126.1, 126.1, 125.6, 125.5, 57.3, 52.5, 42.3, 41.8, 40.6, 28.3, 27.9. ESI-HRMS: Calcd for $C_{25}H_{21}ClN_2NaO_6^+$ $[M+Na]^+$: 503.0980. Found: 503.0971.

Synthesis of 2-(methoxycarbonyl)-6-nitrophenyl 1-benzyl-7-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (6l)

82% yield (388 mg) from **4l**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:5 ~ 1:2). Pale yellow sticky oil. 1H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A:B = 6:4 ratio at 25 °C), δ 8.19-8.06 (m, 2H, rotamer A and B), 7.39-7.32 (m, 1H, rotamer A and B), 7.24-6.98 (m, 7H, rotamer A and B), 6.67 (s, 0.6H, rotamer A), 6.61 (s, 0.4H, rotamer B), 5.46 (dd, J = 7.4, 4.5 Hz, 0.4H, rotamer B), 5.32 (dd, J = 6.3, 6.3 Hz, 0.6H, rotamer A), 4.03-3.97 (m, 0.6H, rotamer A), 3.87-3.83 (m, 0.4H, rotamer B), 3.74 (s, 1.8H, rotamer A), 3.64 (s, 1.2H, rotamer B), 3.61-3.55 (m, 0.6H, rotamer A), 3.41 (dd, J = 13.3, 4.3 Hz, 0.4H, rotamer B), 3.30-3.12 (m, 2H, rotamer A and B), 2.96-2.88 (m, 0.6H, rotamer A), 2.85-2.78 (m, 0.4H, rotamer B), 2.61-2.50 (m, 1H, rotamer A and B), 2.23 (s, 1.8H, rotamer A), 2.22 (s, 1.2H, rotamer B).

13C-NMR (101 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ 163.7, 163.5, 152.0, 151.8, 144.4, 143.8, 143.7, 137.4, 137.4, 135.9, 135.8,

135.4, 135.3, 135.2, 134.9, 131.2, 131.0, 129.8, 129.7, 128.9, 128.8, 128.2, 128.1, 128.0, 127.8, 127.6, 127.6, 127.0, 126.9, 126.4, 126.3, 125.5, 125.4, 57.5, 57.4, 52.4, 42.9, 42.4, 40.6, 40.5, 27.8, 27.4, 20.9.
ESI-HRMS: Calcd for $C_{26}H_{24}N_2NaO_6^+$ $[M+Na]^+$: 483.1526. Found: 483.1516.

Synthesis of 2-(methoxycarbonyl)-6-nitrophenyl 1-benzyl-7-chloro-3,4-dihydroisoquinoline-2(1H)-carboxylate (6m)

71% yield (350 mg) from **4m**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:5 ~ 1:2). Pale yellow sticky oil. 1H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A:B = 6:4 ratio at 25 °C), δ 8.23-8.11 (m, 2H, rotamer A and B), 7.44-7.37 (m, 1H, rotamer A and B), 7.26-7.03 (m, 7H, rotamer A and B), 6.86 (d, J = 1.4 Hz, 0.6H, rotamer A), 6.81 (d, J = 1.4 Hz, 0.4H, rotamer B), 5.48 (dd, J = 7.3, 4.3 Hz, 0.4H, rotamer B), 5.33 (dd, J = 6.2, 6.2 Hz, 0.6H, rotamer A), 4.05-3.99 (m, 0.6H, rotamer A), 3.92-3.86 (m, 0.4H, rotamer B), 3.77 (s, 1.8H, rotamer A), 3.70 (s, 1.2H, rotamer B), 3.58-3.52 (m, 1H, rotamer A), 3.40 (dd, J = 13.4, 4.2 Hz, 0.4H, rotamer B), 3.28-3.13 (m, 2H, rotamer A and B), 2.97-2.89 (m, 0.6H, rotamer A), 2.86-2.79 (m, 0.4H, rotamer B), 2.61-2.50 (m, 1H, rotamer A and B). 13C-NMR (101 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ 163.6, 163.5, 151.9, 151.8, 144.5, 143.7, 143.7, 137.3, 137.0, 136.9, 136.8, 136.1, 135.9, 132.9, 132.7, 131.5, 131.4, 129.8, 129.7, 129.7, 129.0, 128.9, 128.3, 128.2, 127.2, 127.2, 127.1, 127.0, 126.9, 126.8, 126.7, 126.6, 125.7, 125.5, 57.1, 57.0, 52.5, 42.7, 42.2, 40.2, 27.7, 27.4. ESI-HRMS: Calcd for $C_{25}H_{21}ClN_2NaO_6^+$ $[M+Na]^+$: 503.0980. Found: 503.0971.

Synthesis of 2-(methoxycarbonyl)-6-nitrophenyl 1-phenethyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (6n)

78% yield (534 mg) from **4n**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:5 ~ 1:2). Pale yellow sticky oil. 1H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A:B = 6:4 ratio at 25 °C), δ 8.20-8.11 (m, 2H, rotamer A and B), 7.38 (dd, J = 7.9, 7.9 Hz, 1H, rotamer A and B), 7.26-7.09 (m, 9H, rotamer A and B), 5.36 (dd, J = 7.9, 5.4 Hz, 0.4H, rotamer B), 5.28 (dd, J = 9.4, 4.1 Hz, 0.6H, rotamer A), 4.34-4.31 (m, 0.6H, rotamer A), 4.19-4.16 (m, 0.4H, rotamer B), 3.77 (s, 1.8H, rotamer A), 3.66-3.59 (m, 0.6H, rotamer A), 3.53-3.45 (m, 0.4H, rotamer B), 3.49 (s, 1.2H, rotamer B), 3.22-3.14 (m, 0.6H, rotamer A), 3.10-3.02 (m, 0.4H, rotamer B), 2.88-2.78 (m, 3H, rotamer A and B), 2.34-2.08 (m, 2H, rotamer A and B). 13C-NMR (101 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ 164.0, 163.6, 152.1, 144.6, 144.2, 143.8, 143.8, 141.8, 141.6, 136.9, 136.1, 135.9, 133.7, 133.6, 129.0, 128.9, 128.8, 128.3, 128.3, 127.2, 127.1, 126.9, 126.8, 126.7, 126.2, 126.2, 125.8, 125.7, 125.6, 125.5, 56.1, 55.5, 52.6, 52.4, 39.2, 39.1, 38.6, 38.4, 32.4, 32.4, 28.5, 27.9. ESI-HRMS: Calcd for $C_{26}H_{24}N_2NaO_6^+$ $[M+Na]^+$: 483.1527. Found: 483.1517.

Synthesis of 2-(methoxycarbonyl)-6-nitrophenyl 1-(4-methylphenethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (6o)

82% yield (797 mg) from **4o**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:5 ~ 1:2). Pale yellow amorphous solid. 1H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A:B = 6:4 ratio at 25 °C), δ 8.18-8.09 (m, 2H, rotamer A and B), 7.37 (dd, J = 8.1 Hz, 1H, rotamer A and B), 7.24-7.03 (m, 8H, rotamer A and B), 5.34 (dd, J

= 7.7, 5.5 Hz, 0.4H, rotamer B), 5.27 (dd, J = 9.3, 4.1 Hz, 0.6H, rotamer A), 4.34-4.30 (m, 0.6H, rotamer A), 4.18-4.14 (m, 0.4H, rotamer B), 3.77 (s, 1.8H, rotamer A), 3.65-3.58 (m, 0.6H, rotamer A), 3.49 (s, 1.2H, rotamr B), 3.53-3.45 (m, 0.4H, rotamer B), 3.21-3.13 (m, 0.6H, rotamer A), 3.09-3.01 (m, 0.4H, rotamer B), 2.88-2.74 (m, 3H, rotamer A and B), 2.32-2.06 (m, 2H, rotamer A and B), 2.28 (s, 1.8H, rotamer A), 2.26 (s, 1.2H, rotamer B). 13C-NMR (101 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ 164.0, 163.6, 152.1, 152.0, 144.6, 144.2, 143.7, 138.6, 138.4, 137.0, 136.1, 135.9, 135.1, 135.1, 133.7, 133.6, 128.9, 128.9, 128.8, 128.2, 128.1, 127.1, 127.1, 126.8, 126.8, 126.6, 126.2, 126.2, 125.5, 125.5, 56.0, 55.5, 52.5, 52.3, 39.1, 38.7, 38.6, 32.0, 31.9, 28.5, 27.9, 20.9. ESI-HRMS: Calcd for $C_{27}H_{26}N_2NaO_6^+$ $[M+Na]^+$: 497.1683. Found: 497.1672.

Synthesis of 2-(methoxycarbonyl)-6-nitrophenyl 1-(4-chlorophenethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (6p)

86% yield (433 mg) from **4p**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:5 ~ 1:2). Pale yellow sticky oil. 1H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A:B = 7:3 ratio at 25 °C), δ 8.21-8.11 (m, 2H, rotamer A and B), 7.40 (dd, J = 8.0, 8.0 Hz, 1H, rotamer A and B), 7.23-7.06 (m, 8H, rotamer A and B), 5.34 (dd, J = 8.5, 5.3 Hz, 0.3H, rotamer B), 5.25 (dd, J = 9.8, 4.3 Hz, 0.7H, rotamer A), 4.32 (ddd, J = 13.4, 5.4, 3.9 Hz, 0.7H, rotamer A), 4.20-4.14 (m, 0.3H, rotamer B), 3.77 (s, 2.1H, rotamer A), 3.64-3.57 (m, 0.7H, rotamer A and B), 3.50 (s, 0.9H, rotamer B), 3.50-3.44 (m, 0.3H, rotamer A and B), 3.22-3.14 (m, 0.7H, rotamer A), 3.10-3.02 (m, 0.3H, rotamer B), 2.90-2.74 (m, 3H, rotamer A and B), 2.32-2.03 (m, 2H, rotamer A and B). 13C-NMR (101 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ 163.9, 163.5, 152.1, 152.1, 144.7, 144.2, 143.8, 143.7, 140.2, 140.0, 136.7, 136.7, 136.2, 136.0, 133.8, 133.6, 131.4, 131.4, 129.8, 129.6, 129.0, 128.9, 128.9, 128.3, 127.1, 127.0, 127.0, 126.8, 126.3, 126.3, 125.6, 125.5, 55.9, 55.2, 52.6, 52.3, 39.2, 38.5, 38.3, 31.8, 31.6, 28.5, 27.9. ESI-HRMS: Calcd for $C_{26}H_{23}ClN_2NaO_6^+$ $[M+Na]^+$: 517.1137. Found: 517.1125.

Synthesis of 2-(methoxycarbonyl)-6-nitrophenyl 7-methyl-1-phenethyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (6q)

83% yield (467 mg) from **4q**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:5 ~ 1:2). Pale yellow sticky oil. 1H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A:B = 6:4 ratio at 25 °C), δ 8.17-8.08 (m, 2H, rotamer A and B), 7.35 (dd, J = 8.0, 8.0 Hz, 1H, rotamer A and B), 7.26-6.90 (m, 8H, rotamer A and B), 5.32 (dd, J = 8.2, 5.3 Hz, 0.4H, rotamer B), 5.24 (dd, J = 9.6, 4.1 Hz, 0.6H, rotamer A), 4.33-4.30 (m, 0.6H, rotamer A), 4.18-4.15 (m, 0.4H, rotamer B), 3.76 (s, 1.8H, rotamer A), 3.63-3.56 (m, 1H, rotamer A), 3.49 (S, 1.2H, rotamer B) 3.49-3.42 (m, 0.4H, rotamer B), 3.17-3.09 (m, 0.6H, rotamer A), 3.05-2.97 (m, 0.4H, rotamer B), 2.93-2.78 (m, 3H, rotamer A and B), 2.31 (s, 1.2H, rotamer B), 2.28 (s, 1.8H, rotamer A), 2.28-2.10 (m, 2H, rotamer A and B). 13C-NMR (101 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ 164.0, 163.6, 152.0, 144.6, 144.2, 143.8, 143.7, 141.8, 141.6, 136.7, 136.0, 135.8, 135.6, 135.5, 130.6, 130.4, 128.8, 128.7, 128.6, 128.3, 128.2, 127.7, 127.5, 127.2, 127.1, 125.7, 125.6, 125.5, 125.4, 56.1, 55.5, 52.5, 52.3, 39.2, 38.5, 38.4, 32.4, 32.3, 28.1, 27.5, 20.9. ESI-HRMS: Calcd for $C_{27}H_{26}N_2NaO_6^+$ $[M+Na]^+$: 497.1683. Found: 497.1672.

Synthesis of 2-(methoxycarbonyl)-6-nitrophenyl 7-chloro-1-phenethyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (6r)

68% yield (412 mg) from **4r**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:5 ~ 1:2). Pale yellow sticky oil. 1H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A:B = 6:4 ratio at 25 °C), δ 8.22-8.14 (m, 2H, rotamer A and B), 7.41 (dd, J = 8.1, 8.1 Hz, 1H, rotamer A and B), 7.29-7.03 (m, 8H, rotamer A and B), 5.34 (dd, J = 8.9, 5.0 Hz, 0.4H, rotamer B), 5.25 (dd, J = 10.1, 4.3 Hz, 0.6H, rotamer A), 4.35 (ddd, J = 13.6, 5.5, 3.2 Hz, 0.6H, rotamer A), 4.21 (ddd, J = 13.3, 5.5, 3.7 Hz, 0.4H, rotamer B), 3.80 (s, 1.8H, rotamer A), 3.60-3.53 (m, 0.6H, rotamer A), 3.58 (s, 1.2H, rotamer B), 3.47-3.40 (m, 0.4H, rotamer B), 3.19-3.10 (m, 0.6H, rotamer A), 3.07-2.99 (m, 0.4H, rotamer B), 2.92-2.77 (m, 3H, rotamer A and B), 2.32-2.06 (m, 2H, rotamer A and B). 13C-NMR (101 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ 163.8, 163.5, 152.1, 144.7, 144.3, 143.7, 141.5, 141.3, 138.8, 138.7, 136.2, 136.0, 132.3, 132.1, 131.8, 130.4, 130.2, 129.8, 129.0, 128.4, 128.3, 128.3, 127.1, 127.1, 127.0, 126.9, 126.7, 125.9, 125.9, 125.7, 125.6, 55.8, 55.1, 52.6, 52.5, 38.8, 38.8, 38.5, 38.4, 32.4, 32.3, 28.0, 27.4. ESI-HRMS: Calcd for $C_{26}H_{23}ClN_2NaO_6^+$ $[M+Na]^+$: 517.1137. Found: 517.1127.

Synthesis of 2-(methoxycarbonyl)-6-nitrophenyl 1-(3-phenylpropyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (6s)

76% yield (546 mg) from **4s**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:5 ~ 1:2). Pale yellow sticky oil. 1H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A:B = 6:4 ratio at 25 °C), δ 8.18-8.14 (m, 1H, rotamer A and B), 8.10 (dq, J = 8.2, 1.6 Hz, 1H, rotamer A and B), 7.36 (dd, J = 8.1, 8.1 Hz, 1H, rotamer A and B), 7.26-7.12 (m, 8H, rotamer A and B), 7.10-7.05 (m, 1H, rotamer A and B), 5.31-5.27 (m, 0.4H, rotamer B), 5.23 (dd, J = 9.5, 3.5 Hz, 0.6H, rotamer A), 4.26 (ddd, J = 13.4, 5.4, 3.8 Hz, 0.6H, rotamer A), 4.12 (ddd, J = 13.2, 5.6, 3.7 Hz, 0.4H, rotamer B), 3.67 (s, 1.8H, rotamer A), 3.54-3.47 (m, 0.6H, rotamer A), 3.43 (s, 1.2H, rotamer B), 3.39-3.32 (m, 0.4H, rotamer B), 3.19-3.10 (m, 0.6H, rotamer A), 3.07-2.98 (m, 0.4H, rotamer B), 2.88-2.62 (m, 3H, rotamer A and B), 2.02-1.78 (m, 4H, rotamer A and B). 13C-NMR (101 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ 164.0, 163.6, 152.1, 152.0, 144.6, 144.2, 143.8, 143.7, 142.1, 141.9, 137.2, 137.2, 136.1, 135.9, 133.6, 133.5, 128.9, 128.8, 128.8, 128.4, 128.4, 128.2, 128.1, 127.2, 127.1, 127.0, 126.8, 126.7, 126.6, 126.1, 125.6, 125.6, 125.5, 125.4, 56.1, 55.3, 52.5, 52.3, 38.9, 38.8, 36.1, 36.0, 35.4, 35.3, 28.4, 27.8, 27.5. ESI-HRMS: Calcd for $C_{27}H_{26}N_2NaO_6^+$ $[M+Na]^+$: 497.1683. Found: 497.1679.

Synthesis of 2-(methoxycarbonyl)-6-nitrophenyl (R)-1-((R)-1,2-diphenylethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate and 2-(methoxycarbonyl)-6-nitrophenyl (S)-1-((S)-1,2-diphenylethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (6t)

90% yield (486 mg) from **4t**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:5 ~ 1:2). Pale yellow sticky oil. 1H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A:B = 8:2 ratio at 25 °C), δ 8.14-8.05 (m, 2H, rotamer A and B), 7.35-7.06 (m, 15H, rotamer A and B), 5.64 (s, 0.2H, rotamer B), 5.56 (s, 1H, rotamer A), 3.90-3.16 (m, 7H, rotamer A and B), 2.89-2.69 (m, 2H, rotamer A and B), 2.48-2.39 (m, 1H, rotamer A and B). 13C-NMR (101 MHz, $CDCl_3$), two rotamers with respect to the amide bond

were observed, δ 163.9, 163.5, 152.9, 152.7, 144.5, 143.9, 143.7, 140.4, 140.1, 139.8, 139.5, 136.0, 135.8, 135.6, 134.5, 134.4, 129.2, 128.9, 128.8, 128.5, 128.1, 127.9, 127.6, 127.4, 126.9, 126.8, 126.7, 126.6, 125.9, 125.7, 125.6, 125.4, 59.6, 59.1, 54.7, 54.0, 52.4, 52.2, 40.8, 40.3, 38.3, 38.1, 27.9, 27.4. ESI-HRMS: Calcd for $C_{32}H_{28}N_2NaO_6^+$ $[M+Na]^+$: 559.1839. Found: 559.1832.

Synthesis of 2-(methoxycarbonyl)-4-nitrophenyl 6,7-dimethoxy-1-phenethyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (7a)

A solution of **16** (645 mg, 1.53 mmol) and **4a** (523 mg, 1.76 mmol, 1.2 eq.) in tetrahydrofuran (4.0 mL) was stirred at 25 ºC for 15 h. The solvent was evaporated under reduced pressure to give a crude oil. The crude oil was purified by silica-gel column chromatography (eluent: ethyl acetate:*n*-hexane = 1:4 ~ 1:1) to afford **7a** as colorless sticky oil (717 mg, 1.38 mmol, 90% yield).

1H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A:B = 6:4 ratio at 25 °C), δ 8.83 (d, J = 2.3 Hz, 1H, rotamer A and B), 8.38 (dd, J = 8.6, 2.9 Hz, 1H, rotamer A and B), 7.38-7.18 (m, 6H, rotamer A and B), 6.66 (s, 1H, rotamer A and B), 6.61 (s, 0.4H, rotamer B), 6.56 (s, 0.6H, rotamer A), 5.33 (dd, J = 8.5, 4.8 Hz, 0.4H, rotamer B), 5.20 (dd, J = 4.5, 4.5 Hz, 0.6H, rotamer A), 4.34-4.29 (m, 0.6H, rotamer A), 4.25-4.22 (m, 0.4H, rotamer B), 3.87 (s, 3H, rotamer A and B), 3.86 (s, 1.2H, rotamer B), 3.83 (s, 1.8H, rotamer A), 3.80 (s, 1.8H, rotamer A), 3.65 (s, 0.4H, rotamer B), 3.61-3.58 (m, 0.6H, rotamer A), 3.47-3.40 (m, 0.4H, rotamer B), 3.14-2.75 (m, 4H, rotamer A and B), 2.32-2.10 (m, 2H, rotamer A and B). 13C-NMR (101 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ 163.4, 163.2, 155.7, 155.3, 152.6, 152.5, 147.9, 147.8, 147.5, 144.7, 144.6, 141.6, 141.3, 128.9, 128.6, 128.4, 128.3, 128.2, 128.2, 128.0, 127.2, 127.0, 126.0, 125.8, 125.6, 125.4, 125.2, 125.0, 124.9, 111.5, 111.3, 109.9, 109.7, 55.9, 55.8, 55.4, 55.2, 52.6, 52.5, 39.1, 38.6, 38.4, 38.2, 32.6, 32.5, 28.0, 27.5.ESI-HRMS: Calcd for $C_{28}H_{28}N_2NaO_8^+$ $[M+Na]^+$: 543.1738. Found: 543.1729.

Synthesis of dimethyl 4-((6,7-dimethoxy-1-phenethyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)oxy)isophthalate (8a)

Tetramethyl 4,4'-(carbonylbis(oxy))diisophthalate (**19**) was synthesized accorting to previously reported procedure.

1H-NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 2.1 Hz, 2H), 8.28 (dd, J = 8.5, 2.3 Hz, 2H), 7.49 (d, J = 8.5 Hz, 2H), 3.98 (s, 6H), 3.96 (s, 6H).

A solution of **19** (650 mg, 1.46 mmol) and **4a** (454 mg, 1.53 mmol, 1.1 eq.) in tetrahydrofuran (5.0 mL) was stirred at 25 ºC for 5 h. The solvent was evaporated under reduced pressure to give a crude oil. The crude oil was purified by silica-gel column chromatography (eluent: ethyl acetate:*n*-hexane = 1:4 ~ 1:1) to afford **8a** as colorless sticky oil (755 mg, 1.41 mmol, 97% yield).

1H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A:B = 6:4 ratio at 25 °C), δ 8.65 (s, 1H, rotamer A and B), 8.20 (dd, J = 8.3, 1.7 Hz, 1H, rotamer A and B), 7.28-7.24 (m, 5H, rotamer A and B), 7.17-7.16 (m, 1H, rotamer A and B), 6.65 (s, 1H, rotamer A and B), 6.62 (s, 0.4H, rotamer B), 6.57 (s, 0.6H, rotamer A), 5.35 (q, J = 4.6 Hz, 0.4H, rotamer B), 5.22 (q, J = 4.7 Hz, 0.6H, rotamer A), 4.33 (td, J = 8.5, 4.7 Hz, 0.6H, rotamer A), 4.24 (dt, J = 10.4, 2.6 Hz, 0.4H, rotamer B), 3.90 (s, 3H, rotamer A and B), 3.85 (s, 4.2H, rotamer A and B), 3.81 (s, 1.8H, rotamer A), 3.76 (s, 1.8H, rotamer A), 3.66-3.56 (m, 0.6H, rotamer A), 3.59 (s, 1.2H, , rotamer B), 3.44-3.37 (m, 0.4H, rotamer B), 3.13-2.72 (m, 4H,

rotamer A and B), 2.34-2.08 (m, 2H, rotamer A and B). 13C-NMR (101 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ 165.3, 164.4, 164.2, 154.4, 153.9, 152.9, 152.8, 147.7, 147.6, 147.3, 141.6, 141.3, 134.2, 133.0, 132.8, 129.0, 128.7, 128.2, 128.1, 127.3, 127.2, 125.7, 125.6, 125.4, 124.1, 124.0, 123.9, 123.8, 111.3, 111.2, 109.8, 109.5, 55.7, 55.6, 55.0, 54.8, 52.0, 52.0, 51.9, 38.8, 38.3, 38.2, 38.1, 32.5, 32.4, 27.8, 27.4. ESI-HRMS: Calcd for $C_{30}H_{31}NNaO_8^+$ $[M+Na]^+$: 556.1942. Found: 556.1935.

Synthesis of dimethyl 2-((6,7-dimethoxy-1-phenethyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)oxy)isophthalate (9a)

A solution of **17** (190 mg, 0.426 mmol) and **4a** (149 mg, 0.501 mmol, 1.2 eq.) in tetrahydrofuran (2.0 mL) was stirred at 50 °C for 10 h. The solvent was evaporated under reduced pressure to give a crude oil. The crude oil was purified by silica-gel column chromatography (eluent: ethyl acetate:*n*-hexane = 1:4 ~ 1:1) to afford **9a** as white solid (187 mg, 0.351 mmol, 82% yield).

Mp. 156–158 °C (Colorless cubes, recrystallized from dichloromethane/*n*-hexane). 1H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A : B = 6 : 4 ratio at 25 °C), δ 8.13 (m, 2H), 7.35 (m, 1H), 7.27 (m, 4H), 7.19-7.15 (m, 1H), 6.65 (s, 0.6H), 6.60 (s, 0.4H), 6.57 (s, 1H), 5.34 (m, 0.4H), 5.24 (m, 0.6H), 4.40 (m, 0.6H), 4.27 (m, 0.4H), 3.87 (s, 3H), 3.85 (s, 1.2H), 3.83 (s, 1.8H), 3.77 (s, 3.6H), 3.64-3.58 (m, 0.6H), 3.58 (s, 2.4H), 3.47-3.40 (m, 0.4H), 3.18-3.10 (m, 0.6H), 3.04-2.72 (m, 3.4H), 2.32-2.08 (m, 2H). 13C-NMR (101 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ 165.1, 164.8, 153.3, 150.8, 150.1, 147.8, 147.7, 147.5, 147.4, 142.1, 142.0, 135.5, 135.5, 129.4, 129.4, 128.4, 128.3, 126.0, 125.8, 125.7, 125.3, 125.2, 111.4, 111.4, 110.0, 109.7, 56.0, 55.9, 55.9, 55.4, 54.9, 52.3, 52.2, 38.9, 38.6, 38.6, 32.7, 32.5, 28.1, 27.6. ESI-HRMS: Calcd for $C_{30}H_{31}NNaO_8^+$ $[M+Na]^+$: 556.1942. Found: 556.1923.

Synthesis of 6,7-dimethoxy-1-phenethyl-3,4-dihydroisoquinoline-2(1H)-carbonyl chloride (10a)

To a solution of **4a** (915 mg, 3.1mmol) and triphosgene (431 mg, 1.45 mmol, 1.4 eq.) in dry dichloromethane (15 mL) was added a dry pyridine (2.0 mL) at -78 °C. The mixture was stirred at -78 °C to 25 °C for 1 h. The reaction was quenched with aqueous HCl (1 mol/L) (20 mL). The reaction mixture was extracted with dichloromethane (50 mL). The organic phase was washed with brine (20 mL), dried over sodium sulfate, and the solvent was evaporated to give the crude solid. The crude solid was purified by silica-gel column chromatography (eluent: ethyl acetate:*n*-hexane = 1:10) to afford **10a** as pale yellow oil (797 mg, 2.21 mmol, 72% yield).

1H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A : B = 6 : 4 ratio at 25 °C), δ 7.31-7.25 (m, 2H, rotamer A and B), 7.22-7.17 (m, 3H, rotamer A and B), 6.61 (s, 1H, rotamer A and B), 6.56 (s, 0.4H, rotamer B), 6.51 (s, 0.6H, rotamer A), 5.35-5.27 (m, 1H, rotamer A and B), 4.32-4.28 (m, 0.4H, rotamer B), 4.23 (q, J = 4.5 Hz, 1H, rotamer A), 3.85 (s, 3.6H, rotamer A), 3.82 (s, 2.4H, rotamer B), 3.61-3.54 (m, 0.6H, rotamer A), 3.44-3.37 (m, 0.4H, rotamer B), 3.04-2.93 (m, 1.6H, rotamer B), 2.87-2.68 (m, 2.4H, rotamer A), 2.26-2.08 (m, 2H, rotamer A and B). 13C-NMR (101 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ 149.1, 148.8, 147.9, 147.8, 147.5, 147.4, 141.0, 140.8, 128.5, 128.5, 128.2, 128.2, 128.0, 127.8, 126.2, 126.1, 125.0, 124.8, 111.0, 110.9, 109.3,

109.2, 59.4, 57.3, 56.0, 55.9, 55.8, 43.0, 40.7, 38.5, 38.1, 32.6, 32.5, 28.1, 27.5. ESI-HRMS: Calcd for $C_{20}H_{23}NO_3$+ [M+H]+: 360.1361. Found: 360.1356.

III. Acid-promoted reaction of substrates: Screening of the reaction condition

Compounds **2**,[8c] **3a**,[7i] and **5**[8c] were previously reported in literatures.

Reaction of 1a (Table 1, Entry 1 in main text)

A solution of **1a** (117 mg, 0.246 mmol) in trifluoroacetic acid (0.91 mL, 50 eq.) was stirred at 25 °C under argon atmosphere for 24 hrs. Then the mixture was quenched with 10 mL of ice water. The whole was extracted with 50 mL of dichloromethane by separatory funnel. The organic layer was dried over sodium sulfate and the solvent was evaporated to give a recovery of **1a** (112 mg, 0.235 mmol, 96% yield).

Reaction of 1a (Table 1, Entry 2 in main text)

To a solution of **1a** (79 mg, 0.17 mmol) in dry dichloromethane (0.88 mL), trifluoromethanesulfonic acid (0.020 mL, 1.4 eq.) was added at 0 °C. The mixture was stirred at 25 °C under argon atmosphere for 18 hr. Then the mixture was quenched with of ice water. The whole was extracted with 20 mL of dichloromethane twice by separatory funnel. The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil (69 mg) which contained methyl salicylate (52% yield), **1a** (25% yield) and protonated **4a** (48% yield). The ratio was determined by ^{1}H-NMR.

Reaction of 1a (Table 1, Entry 3 in main text)

To a solution of **1a** (289 mg, 0.607 mmol) in dry dichloromethane (3.1 mL), trifluoromethanesulfonic acid (0.53 mL, 10 eq.) was added at 0 °C. The mixture was stirred at 25 °C under argon atmosphere for 1 hr. Then the mixture was quenched with of ice water. The whole was extracted with 20 mL of dichloromethane twice by separatory funnel. The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil. The crude oil was purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0) to afford 6,7-dimethoxy-3,4-dihydroisoquinolin-1(2H)-one (**2**) (98.5 mg, 0.475 mmol, 78% yield), and 2,3-dimethoxy-5,6,14,14a-tetrahydrobenzo[5,6]azepino[2,1-a]isoquinolin-8(13H)-one (**3a**) (4.3 mg, 0.013 mmol, 2% yield).

Product **2**: 1H-NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 6.81 (brs, 1H), 6.68 (s, 1H), 3.93 (s, 3H), 3.93 (s, 3H), 3.56 (td, J = 6.7, 2.9 Hz, 2H), 2.93 (t, J = 6.7 Hz, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 166.55, 152.07, 147.95, 132.61, 121.37, 110.05, 109.52, 56.03, 55.97, 40.35, 27.92. ESI-HRMS: Calcd for $C_{11}H_{13}NNaO_3^+$ $[M+Na]^+$: 230.0788. Found: 230.0785.

Product **3a**: White solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, J = 7.4, 1.3 Hz, 1H), 7.43 (ddd, J = 7.4, 7.4, 1.4 Hz, 1H), 7.38-7.35 (m, 1H), 7.22 (d, J = 7.3 Hz, 1H), 6.70 (s, 1H), 6.47 (s, 1H), 4.45 (dd, J = 12.3, 5.3 Hz, 1H), 4.02-3.96 (m, 1H), 3.87 (s, 3H), 3.87-3.82 (m, 1H), 3.78 (s, 3H), 3.01 (td, J = 12.8, 8.2 Hz, 1H), 2.91-2.88 (m, 2H), 2.77 (dd, J = 13.6, 6.3 Hz, 1H), 2.25-2.11 (m, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 170.5, 147.8, 147.7, 137.3, 136.2, 130.9, 128.7, 128.2, 127.7, 127.2, 127.2, 111.3, 109.2, 56.0, 55.9, 55.1, 39.6, 39.1, 30.8, 28.5. ESI-HRMS: Calcd for $C_{13}H_{19}NNaO_4^+$ $[M+Na]^+$: 346.1414. Found: 346.1404.

Reaction of 1a (Table 1, Entry 4 in main text)

A solution of **1a** (109 mg, 0.228 mmol) in trifluoromethanesulfonic acid (1.0 mL, 50 eq.) was stirred at 25 ºC under argon atmosphere for 1 hr. Then the mixture was quenched with 30 mL of ice water. The whole was extracted with 20 mL of dichloromethane twice by separatory funnel. The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil. The crude oil was purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0) to afford **2** (30 mg, 0.14 mmol, 63% yield).

Reaction of 1a (Table 1, Entry 5 in main text)

A solution of **1a** (270 mg, 0.569 mmol) in trifluoromethanesulfonic acid (3.2 mL, 50 eq.) was stirred at 0 ºC under argon atmosphere for 5 min. Then the mixture was quenched with 10 mL of ice water. The whole was extracted with 50 mL of dichloromethane twice by separatory funnel. The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil. The crude oil was purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:1) to afford methyl 2-(((3,4-dimethoxyphenethyl)carbamoyl)oxy)benzoate (**5**) (130 mg, 0.362 mmol, 64% yield). Trace amount of **2** was detected by ^{1}H-NMR measurement of crude oil.

Product **5**: 1H-NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, J = 7.8, 1.6 Hz, 1H), 7.54 (ddd, J = 7.8, 7.8, 1.4 Hz, 1H), 7.31-7.27 (m, 1H), 7.15 (d, J = 8.2 Hz, 1H), 6.84-6.79 (m, 3H), 5.38 (t, J = 5.9 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 3.51 (dt, J = 6.8, 6.8 Hz, 2H), 2.85 (t, J = 7.1 Hz, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 165.2, 154.3, 150.4, 148.6, 147.3, 133.6, 131.3, 131.0, 125.5, 124.0, 123.6, 120.5, 111.6, 110.9, 55.7, 55.6, 52.1, 42.6, 35.4.

Reaction of 6a (Table 1, Entry 8 in main text) (Typical procedure G)

To a solution of **4a** (200 mg, 0.384 mmol) in dry dichloromethane (1.9 mL), trifluoromethanesulfonic acid (0.34 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 0 ºC under argon atmosphere for 5 min. Then the mixture was diluted with 20 mL of dichloromethane and quenched with 10 mL of ice water. The organic layer was separated by separatory funnel. The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil. The crude oil was purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0) to afford **2** (15 mg, 0.072 mmol, 19% yield) and **3a** (96 mg, 0.30 mmol, 77% yield).

Reaction of 6a (Table 1, comment (d) in main text, 1.3 mmol scale)

To a solution of **6a** (664 mg, 1.28 mmol) in dry dichloromethane (6.4 mL), trifluoromethanesulfonic acid (1.2 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 0 ºC under argon atmosphere for 5 min. Then the mixture was diluted with 20 mL of dichloromethane and quenched with 10 mL of ice water. The organic layer was separated by separatory funnel. The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil. The crude oil was purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0) to afford **2** (42 mg, 0.20 mmol, 16% yield) and **3a** (315 mg, 0.974 mmol, 76% yield).

Reaction of 7a (Table 1, Entry 10 in main text)

To a solution of **7a** (252 mg, 0.484 mmol) in dry dichloromethane (2.4 mL),

trifluoromethanesulfonic acid (0.43 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 0 ºC under argon atmosphere for 5 min. Then the mixture was diluted with 20 mL of dichloromethane and quenched with 10 mL of ice water. The organic layer was separated by separatory funnel. The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil. The crude oil was purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0) to afford **2** (54 mg, 0.259 mmol, 53% yield) and **3a** (38 mg, 0.12 mmol, 24% yield).

Reaction of 8a (Table 1, Entry 11 in main text)

To a solution of **8a** (189 mg, 0.354 mmol) in dry dichloromethane (1.8 mL), trifluoromethanesulfonic acid (0.32 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 0 ºC under argon atmosphere for 10 min. Then the mixture was diluted with 20 mL of dichloromethane and quenched with 10 mL of ice water. The organic layer was separated by separatory funnel. The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil. The crude oil was purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0) to afford **2** (32 mg, 0.15 mmol, 44% yield) and **3a** (55 mg, 0.17 mmol, 48% yield).

Reaction of 9a (Table 1, Entry 11 in main text)

To a solution of **9a** (110 mg, 0.206 mmol) in dry dichloromethane (1.0 mL), trifluoromethanesulfonic acid (0.18 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 0 ºC under argon atmosphere for 5 min. Then the mixture was diluted with 20 mL of dichloromethane and quenched with 10 mL of ice water. The organic layer was separated by separatory funnel. The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil. The crude oil was purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0) to afford **2** (10 mg, 0.049 mmol, 24% yield) and **3a** (39 mg, 0.12 mmol, 58% yield).

Reaction of 10a (Table 1, Entry 13 in main text)

To a solution of **10a** (114 mg, 0.317 mmol) in dry benzene (2.0 mL), aluminium trichloride (60 mg, 0.374 mmol, 1.18 eq.) was added at 25 ºC. The mixture was refluxed under argon atmosphere for 20 hrs. Then the mixture was cooled to 25 °C and quenched with 10 mL of ice water. The organic layer was extracted with dichloromethane (20 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil. The crude oil was purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:4 ~ 4:1) to afford **3a** (26 mg, 0.080 mmol, 25% yield) and demethylated products (total 19% yield).

IV. Acid-promoted reaction of substrates: Substrate scope of the reaction

All reactions of this section were conducted following the procedure G.

Compounds **3b**,[S24] **3c**,[S25] **3f**,[S26] **3i**,[3a] **3n**,[7i] **3o**,[7i] and **3q**[7i] and **9**[9] were previously reported in literatures.

Synthesis of 2,3-dimethoxy-13,13a-dihydro-5H-isoquinolino[3,2-a]isoquinolin-8(6H)-one (3b)

89% yield (56 mg) from **6b**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0). White amorphous solid. 1H-NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 7.4 Hz, 1H), 7.46 (t, J = 7.4 Hz, 1H), 7.39 (t, J = 7.4 Hz, 1H), 7.26 (d, J = 7.4 Hz, 1H), 6.72 (s, 1H), 6.70 (s, 1H), 4.97-5.05 (m, 1H), 4.87 (dd, J = 13.3, 3.3 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.22 (dd, J = 15.6, 3.3 Hz, 1H), 2.92-3.02 (m, 3H), 2.73-2.82 (m, 1H). 13C-NMR (101 MHz, $CDCl_3$) δ 164.60, 148.03, 147.96, 137.27, 131.76, 129.08, 128.56, 127.64, 127.30, 126.82, 111.47, 108.86, 56.15, 55.92, 54.98, 38.71, 38.10, 29.19. ESI-HRMS: Calcd for $C_{19}H_{19}NNaO_3^+$ $[M+Na]^+$: 332.1257. Found: 332.1252.

Synthesis of 5,6-dihydroisoindolo[1,2-a]isoquinolin-8(12bH)-one (3c)

78% yield (52 mg) from **6c**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0). White amorphous solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.87-7.84 (m, 2H), 7.61-7.57 (m, 2H), 7.47 (dd, J = 7.5, 7.5 Hz, 1H), 7.28-7.16 (m, 3H), 5.64 (s, 1H), 4.41 (ddd, J = 12.9, 5.7, 4.7 Hz, 1H), 3.47 (ddd, J = 12.9, 9.6, 4.8 Hz, 1H), 3.08-3.00 (m, 1H), 2.86 (dt, J = 15.8, 4.7 Hz, 1H)
13C-NMR (101 MHz, $CDCl_3$) δ 167.8, 144.1, 134.6, 134.2, 132.7, 131.4, 129.1, 128.3, 127.3, 126.6, 125.1, 123.7, 123.4, 59.0, 38.0, 29.3
ESI-HRMS: Calcd for $C_{16}H_{13}NNaO^+$ $[M+Na]^+$: 258.0889. Found: 258.0882.

Synthesis of 10-methyl-5,12b-dihydroisoindolo[1,2-a]isoquinolin-8(6H)-one (3d)

96% yield (64 mg) from **6d**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0). Colorless sticky oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 7.8 Hz, 1H), 7.67 (s, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.28-7.17 (m, 3H), 5.62 (s, 1H), 4.41 (m, 1H), 3.51-3.44 (m, 1H), 3.09-3.01 (m, 1H), 2.87 (m, 1H), 2.43 (s, 3H). 13C-NMR (101 MHz, $CDCl_3$) δ 168.0, 141.4, 138.5, 134.7, 134.6, 132.9, 132.4, 129.2, 127.3, 126.6, 125.2, 124.0, 123.1, 58.9, 38.1, 29.4, 21.2. ESI-HRMS: Calcd for $C_{17}H_{15}NNaO^+$ $[M+Na]^+$: 272.1046. Found: 272.1032.

Synthesis of 10-chloro-5,12b-dihydroisoindolo[1,2-a]isoquinolin-8(6H)-one (3e)

74% yield (48 mg) from **6e**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0). White amorphous solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 1.8 Hz, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.59-7.55 (m, 2H), 7.31-7.20 (m, 3H), 5.66 (s, 1H), 4.44-4.39 (m, 1H), 3.54-3.47 (m, 1H), 3.12-3.04 (m, 1H), 2.90 (dt, J = 15.9, 4.6 Hz, 1H). 13C-NMR (101 MHz, $CDCl_3$) δ 166.5, 142.3, 134.9, 134.6, 134.6, 133.8, 131.6, 129.4, 127.6, 126.8, 125.0, 124.7, 124.0, 58.9, 38.3, 29.3. ESI-HRMS: Calcd for $C_{16}H_{13}ClNO^+$ $[M+H]^+$: 270.0680. Found: 270.0669.

Synthesis of 2,3-dimethoxy-5,6-dihydroisoindolo[1,2-a]isoquinolin-8(12bH)-one (3f)

74% yield (95 mg) from **6f**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0). White amorphous solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.50 (t, J = 7.4 Hz, 1H), 7.13 (s, 1H), 6.67 (s, 1H), 5.63 (s, 1H), 4.51 (m, 1H), 3.95 (s, 3H), 3.86 (s, 3H), 3.38-3.45 (m, 1H), 2.97-3.05 (m,

1H), 2.78 (dt, J = 15.8, 3.8 Hz, 1H). 13C-NMR (101 MHz, $CDCl_3$) δ 167.83, 147.96, 147.52, 144.47, 132.50, 131.51, 128.34, 126.63, 125.70, 123.77, 122.91, 111.55, 108.13, 58.82, 55.97, 55.76, 38.03, 28.93. ESI-HRMS: Calcd for $C_{18}H_{17}NNaO_3^+$ $[M+Na]^+$: 318.1101. Found: 318.1090.

Synthesis of 2-methyl-5,12b-dihydroisoindolo[1,2-a]isoquinolin-8(6H)-one (3g)

74% yield (175 mg) from **6g**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0). Pale yellow amorphous solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 7.8 Hz, 2H), 7.61 (td, J = 7.5, 0.9 Hz, 1H), 7.49 (dd, J = 7.8, 7.5 Hz, 1H), 7.42 (s, 1H), 7.06 (m, 2H), 5.63 (s, 1H), 4.42 (m, 1H), 3.50-3.43 (m, 1H), 3.01 (m, 1H), 2.87-2.82 (m, 1H), 2.36 (s, 3H). 13C-NMR (101 MHz, $CDCl_3$) δ 167.9, 144.2, 136.3, 134.1, 132.8, 131.7, 131.4, 129.1, 128.4, 128.2, 125.7, 123.8, 123.4, 59.1, 38.3, 29.0, 21.2. ESI-HRMS: Calcd for $C_{17}H_{16}NO^+$ $[M+H]^+$: 250.1227. Found: 250.1215.

Synthesis of 2-chloro-5,12b-dihydroisoindolo[1,2-a]isoquinolin-8(6H)-one (3h)

97% yield (57 mg) from **6h**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0). Colorless oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 7.5 Hz, 1H), 7.85 (d, J = 7.5 Hz, 1H), 7.65 (ddd, J = 7.5, 7.5, 0.9 Hz, 1H), 7.57 (s, 1H), 7.52 (dd, J = 7.5, 7.5 Hz, 1H), 7.21 (dd, J = 8.2, 1.8 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H), 5.62 (s, 1H), 4.40 (dt, J = 13.0, 5.3 Hz, 1H), 3.53-3.47 (m, 1H), 3.07-2.99 (m, 1H), 2.87 (dt, J = 16.0, 4.8 Hz, 1H). 13C-NMR (101 MHz, $CDCl_3$) δ 167.9, 143.4, 135.8, 133.2, 132.4, 132.4, 131.9, 130.5, 128.8, 127.6, 125.2, 124.0, 123.4, 58.9, 38.1, 28.8. ESI-HRMS: Calcd for $C_{16}H_{13}ClNO^+$ $[M+H]^+$: 270.0680. Found: 270.0669.

Synthesis of 5,6,13,13a-tetrahydro-8H-isoquinolino[3,2-a]isoquinolin-8-one (3i)

88% yield (78 mg) from **6i**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0). White amorphous solid. 1H-NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, J = 7.7, 1.0 Hz, 1H), 7.45 (ddd, J = 7.5, 7.4, 1.4 Hz, 1H), 7.37 (dd, J = 7.7, 7.5 Hz, 1H), 7.28-7.20 (m, 5H), 4.97 (td, J = 5.5, 2.9 Hz, 1H), 4.92 (dd, J = 13.5, 3.7 Hz, 1H), 3.24 (dd, J = 15.8, 3.7 Hz, 1H), 3.03-2.95 (m, 3H), 2.89-2.83 (m, 1H).
13C-NMR (101 MHz, $CDCl_3$) δ 164.4, 137.2, 135.8, 134.9, 131.7, 128.9, 128.9, 128.4, 127.2, 126.8, 126.7, 126.6, 125.8, 55.1, 38.6, 37.7, 29.6.
ESI-HRMS: Calcd for $C_{17}H_{16}NO^+$ $[M+H]^+$: 250.1227. Found: 250.1216.

Synthesis of 10-methyl-5,6,13,13a-tetrahydro-8H-isoquinolino[3,2-a]isoquinolin-8-one (3j)

91% yield (74 mg) from **6j**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0). White amorphous solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.30-7.20 (m, 5H), 7.14 (d, J = 7.5 Hz, 1H), 5.02-4.94 (m, 1H), 4.89 (dd, J = 13.5, 3.7 Hz, 1H), 3.20 (dd, J = 15.6, 3.7 Hz, 1H), 3.05-2.84 (m, 4H), 2.39 (s, 3H). 13C-NMR (101 MHz, $CDCl_3$) δ 164.7, 137.0, 136.0, 135.0, 134.3, 132.5, 128.9, 128.8, 128.7, 126.7, 126.7, 126.6, 125.9, 55.3, 38.6, 37.4, 29.7, 21.0. ESI-HRMS: Calcd for $C_{18}H_{17}NNaO^+$ $[M+Na]^+$: 286.1202. Found: 286.1196.

Synthesis of 10-chloro-5,6,13,13a-tetrahydro-8H-isoquinolino[3,2-a]isoquinolin-8-one (3k)

92% yield (76 mg) from **6k**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0). White amorphous solid. 1H-NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 1.8 Hz, 1H), 7.42 (dd, J = 8.0, 2.1 Hz, 1H), 7.31-7.19 (m, 5H), 4.97-4.90 (m,

2H), 3.24 (dd, J = 15.8, 3.4 Hz, 1H), 3.06-2.86 (m, 4H). 13C-NMR (101 MHz, $CDCl_3$) δ 163.4, 135.6, 135.5, 134.9, 133.4, 131.7, 130.6, 129.0, 128.5, 128.4, 127.0, 126.8, 125.9, 55.1, 38.8, 37.2, 29.6. ESI-HRMS: Calcd for $C_{17}H_{14}ClNNaO^+$ $[M+Na]^+$: 306.0656. Found: 306.0649.

Synthesis of 2-methyl-5,6,13,13a-tetrahydro-8H-isoquinolino[3,2-a]isoquinolin-8-one (3l)

98% yield (115 mg) from **6l**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0). White amorphous solid. 1H-NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, J = 7.6, 0.9 Hz, 1H), 7.44 (dd, J = 7.6, 7.4, 1.3 Hz, 1H), 7.36 (dd, J = 7.6, 7.4 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 7.10-7.03 (m, 3H), 5.01-4.93 (m, 1H), 4.87 (dd, J = 13.5, 3.5 Hz, 1H), 3.23 (dd, J = 15.8, 3.5 Hz, 1H), 3.01-2.92 (m, 3H), 2.84-2.78 (m, 1H), 2.36 (s, 3H). 13C-NMR (101 MHz, $CDCl_3$) δ 164.4, 137.3, 136.2, 135.6, 131.8, 131.6, 129.0, 128.7, 128.4, 127.6, 127.1, 126.8, 126.3, 55.1, 38.7, 37.8, 29.2, 21.1. ESI-HRMS: Calcd for $C_{18}H_{17}NNaO^+$ $[M+Na]^+$: 286.1202. Found: 286.1195.

Synthesis of 2-chloro-5,6,13,13a-tetrahydro-8H-isoquinolino[3,2-a]isoquinolin-8-one (3m)

96% yield (72 mg) from **6m**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0). White amorphous solid. 1H-NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 7.5 Hz, 1H), 7.47 (dd, J = 7.5, 7.5, 1.2 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 7.27 (s, 1H), 7.26 (d, J = 7.5 Hz, 1H), 7.21 (dd, J = 8.1, 1.9 Hz, 1H), 7.16 (d, J = 8.1 Hz, 1H), 5.03-4.96 (m, 1H), 4.90 (dd, J = 13.4, 3.6 Hz, 1H), 3.24 (dd, J = 15.8, 3.6 Hz, 1H), 3.06-2.80 (m, 4H). 13C-NMR (101 MHz, $CDCl_3$) δ 164.5, 137.7, 136.9, 133.6, 132.4, 131.9, 130.3, 128.8, 128.6, 127.4, 127.1, 126.9, 126.0, 54.9, 38.5, 37.6, 29.2. ESI-HRMS: Calcd for $C_{17}H_{15}ClNO^+$ $[M+H]^+$: 284.0837. Found: 284.0831.

Synthesis of 5,6,14,14a-tetrahydrobenzo[5,6]azepino[2,1-a]isoquinolin-8(13H)-one (3n)

92% yield (92 mg) from **6n**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0). White amorphous solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, J = 7.4, 1.4 Hz, 1H), 7.43 (ddd, J = 7.4, 7.4, 1.4 Hz, 1H), 7.35-7.39 (m, 1H), 7.14-7.23 (m, 4H), 6.98 (d, J = 7.1 Hz, 1H), 4.51 (dd, J = 12.2, 5.4 Hz, 1H), 3.91-3.95 (m, 2H), 2.96-3.06 (m, 3H), 2.77 (dd, J = 13.7, 6.2 Hz, 1H), 2.09-2.27 (m, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 170.5, 137.3, 135.9, 135.9, 135.1, 130.8, 128.6, 128.2, 128.1, 127.0, 126.9, 126.5, 126.0, 55.4, 39.7, 39.3, 30.7, 28.8. ESI-HRMS: Calcd for $C_{18}H_{17}NNaO^+$ $[M+Na]^+$: 286.1202. Found: 286.1198.

Synthesis of 10-methyl-5,13,14,14a-tetrahydrobenzo[5,6]azepino[2,1-a]isoquinolin-8(6H)-one (3o)

87% yield (84 mg) from **6o**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0). Colorless sticky oil. 1H-NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.23-7.08 (m, 5H), 6.94 (d, J = 7.1 Hz, 1H), 4.50 (dd, J = 12.2, 5.4 Hz, 1H), 3.92-3.89 (m, 2H), 2.98-2.91 (m, 3H), 2.72 (dd, J = 13.8, 6.3 Hz, 1H), 2.37 (s, 3H), 2.19-2.08 (m, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 170.7, 136.7, 136.0, 135.7, 135.1, 134.2, 131.5, 129.1, 128.2, 128.1, 126.8, 126.5, 125.9, 55.4, 39.7, 39.4, 30.3, 28.8, 20.9. ESI-HRMS: Calcd for $C_{19}H_{20}NO^+$ $[M+Na]^+$: 278.1540. Found: 278.1533.

Synthesis of 10-chloro-5,13,14,14a-tetrahydrobenzo[5,6]azepino[2,1-a]isoquinolin-8(6H)-one (3p)

57% yield (49 mg) from **6p**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0). White amorphous solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 2.3 Hz, 1H), 7.38 (dd, J = 8.2, 2.3 Hz, 1H), 7.21-7.14 (m, 4H), 6.97 (d, J = 7.1 Hz, 1H), 4.48 (dd, J = 12.1, 5.5 Hz, 1H), 3.95-3.86 (m, 2H), 3.00-2.91 (m, 3H), 2.76 (dd, J = 13.8, 6.1 Hz, 1H), 2.21-2.10 (m, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 169.1, 137.5, 135.7, 135.6, 135.0, 133.0, 130.8, 129.7, 128.8, 128.3, 127.1, 126.7, 126.0, 55.4, 39.9, 39.1, 30.2, 28.8. ESI-HRMS: Calcd for $C_{18}H_{17}ClNO^+$ $[M+H]^+$: 298.0993. Found: 298.0988.

Synthesis of 2-methyl-5,6,14,14a-tetrahydrobenzo[5,6]azepino[2,1-a]isoquinolin-8(13H)-one (3q)

77% yield (91 mg) from **6q**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0). White amorphous solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, J = 7.5, 1.0 Hz, 1H), 7.41 (td, J = 7.5, 1.0 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.08 (d, J = 7.8 Hz, 1H), 6.99 (d, J = 7.8 Hz, 1H), 6.78 (s, 1H), 4.46 (dd, J = 12.5, 5.6 Hz, 1H), 3.85-3.95 (m, 2H), 3.00 (m, 1H), 2.91 (t, J = 5.6 Hz, 2H), 2.75 (dd, J = 6.7, 6.7 Hz, 1H), 2.25 (s, 3H), 2.07-2.22 (m, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 170.49, 137.29, 136.11, 136.02, 135.74, 131.99, 130.81, 128.58, 128.10, 128.06, 127.64, 127.04, 126.57, 55.42, 39.90, 39.32, 30.77, 28.41, 20.92. ESI-HRMS: Calcd for $C_{19}H_{19}NNaO^+$ $[M+Na]^+$: 300.1359. Found: 300.1348.

Synthesis of 2-chloro-5,6,14,14a-tetrahydrobenzo[5,6]azepino[2,1-a]isoquinolin-8(13H)-one (3r)

92% yield (106 mg) from **6r**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0). White amorphous solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, J = 7.5, 1.4 Hz, 1H), 7.43 (ddd, J = 7.5, 7.3, 1.5 Hz, 1H), 7.36 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H), 7.21 (d, J = 7.3 Hz, 1H), 7.18-7.12 (m, 2H), 6.99 (d, J = 1.6 Hz, 1H), 4.48 (dd, J = 12.3, 5.5 Hz, 1H), 4.01-3.83 (m, 2H), 3.05-2.91 (m, 3H), 2.78 (dd, J = 13.7, 6.2 Hz, 1H), 2.24-2.11 (m, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 170.5, 137.8, 137.1, 135.8, 133.6, 132.2, 131.1, 129.7, 128.7, 128.3, 127.3, 127.1, 126.1, 55.1, 39.4, 39.1, 30.7, 28.5. ESI-HRMS: Calcd for $C_{18}H_{17}ClNO^+$ $[M+H]^+$: 298.0993. Found: 298.0988.

Synthesis of 7,8,12b,13,14,15-hexahydro-5H-benzo[6,7]azocino[2,1-a]isoquinolin-5-one (3s) and 3s'

Compound **3s**: 8% yield (10 mg) from **6s**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0). White amorphous solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.39-7.36 (m, 2H), 7.24-7.21 (m, 2H), 7.13-7.11 (m, 3H), 6.89-6.87 (m, 1H), 4.92 (dd, J = 12.7, 4.5 Hz, 1H), 4.59 (d, J = 9.6 Hz, 1H), 3.21 (td, J = 12.7, 3.7 Hz, 1H), 3.11-3.03 (m, 1H), 2.92-2.78 (m, 3H), 2.24-1.99 (m, 3H), 1.81-1.77 (m, 1H). 13C-NMR (101 MHz, $CDCl_3$) δ 169.8, 139.9, 138.1, 135.3, 134.3, 130.4, 129.3, 129.0, 127.8, 127.1, 126.6, 126.5, 126.2, 56.8, 36.1, 35.6, 32.4, 28.6, 28.5. ESI-HRMS: Calcd for $C_{19}H_{19}NNaO^+$ $[M+Na]^+$: 300.1359 . Found: 300.1357.

Compound **3s'**: 83% yield (106 mg) from **6s**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0). White amorphous solid. 1H-NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 7.7 Hz, 1H), 7.69 (brs, 1H), 7.22 (dd, J = 7.7, 7.7 Hz, 1H), 7.09-7.15 (m, 2H), 7.05-7.00 (m, 2H), 6.75 (d, J = 7.7 Hz, 1H), 4.35 (t, J =

6.4 Hz, 1H), 3.58-3.48 (m, 2H), 3.07-3.00 (m, 1H), 2.97-2.82 (m, 3H), 2.15-2.09 (m, 1H), 1.93-1.86 (m, 1H), 1.84-1.74 (m, 2H). 13C-NMR (101 MHz, $CDCl_3$) δ 167.1, 143.7, 138.8, 137.4, 136.8, 133.4, 129.5, 129.4, 129.0, 126.4, 126.0, 125.9, 125.8, 41.8, 39.5, 31.2, 29.5, 24.8, 21.0. ESI-HRMS: Calcd for $C_{19}H_{19}NNaO^+$ $[M+Na]^+$: 300.1359 . Found: 300.1357 .

Synthesis of 13-benzyl-5,6,13,13a-tetrahydro-8H-isoquinolino[3,2-a]isoquinolin-8-one (3t)

76% yield (86 mg) from **6t**. Purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3 ~ 1:0). White amorphous solid. 1H-NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 7.8 Hz, 1H), 7.37-7.17 (m, 7H), 7.11-6.99 (m, 5H), 4.91-4.85 (m, 1H), 4.66 (s, 1H), 3.82 (t, J = 7.9 Hz, 1H), 3.33-3.23 (m, 2H), 3.09 (d, J = 8.0 Hz, 2H), 2.80-2.73 (m, 1H). 13C-NMR (101 MHz, $CDCl_3$) δ 164.4, 139.9, 138.9, 137.2, 136.0, 132.0, 129.5, 129.2, 128.6, 128.5, 127.9, 127.5, 127.2, 127.1, 126.7, 125.8, 122.8, 58.3, 43.3, 42.8, 40.7, 27.4. ESI-HRMS: Calcd for $C_{24}H_{21}NNaO^+$ $[M+Na]^+$: 362.1515. Found: 362.1504.

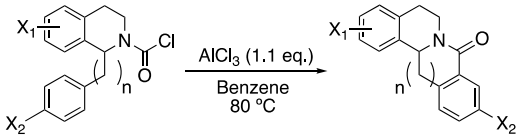
2. Substrate scope of the previously reported method

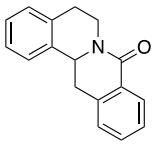
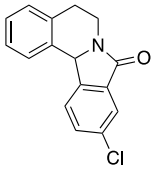
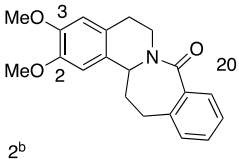
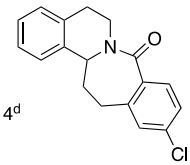
Historically, a similar synthetic approach to 8-oxoberbines has been already reported by Stambach and Jung.[4a] They only demonstrated 6-membered ring formation. Generally, 6-membered ring-formation is much easier than formation of the other ring-size compounds, and it is unclear that the method is also applicable to other substrates. In order to compare the applicability of our method and the previously proposed method, we examined the substrate scope briefly (Table S1).

The literature example of 6-membered ring-formation was reproduced (Entry 1). The reaction actually proceeded much faster than the reaction time described in the literature. On the other hand, 7-membered ring formation with the methoxy-substituted substrate was not as successful, as described in Table 1 of the main text as we mentioned in Table 1 of the main sentence, demethylation and polymerization occurred to afford the desired product in 25% yield (Entry 2). Demethylation of the methoxy groups in this condition was also discribed in the original literature. Introduction of a chloro group to the reactant retarded the reaction (Entry 3 and 4). Elongation of the reaction time caused polymerization of the reactants and the yield decreased significantly, compared with our method (74% and 57% yields for the product of Entry 3 and 4, respectively).

We initially anticipated that benzene, which was used as solvent in the previous method, could react with a reactive intermediate and forms benzoyl amine product, because carbamoyl cation can be used for the intermolecular reaction with benzene.[8d] But such compound was not observed in this case. Although it is unclear, we consider that the reactive intermediate of this Lewis-acid promoted reaction is somewhat different from the carbamoyl cation produced in strong Brønsted acid, owing to the difference of the reactivity.

Table S1. Substrate scope of $AlCl_3$-promoted reaction



Entry	Product	Time	Yield	Entry	Product	Time	Yield
1		40 min 3 hr	71% 76%[a] (crude yield)	3[c]		65 hr	18%
2[b]		20 hr	25%	4[d]		45 hr 48 hr	0%[d] 0%[e]

a) Literature yield. (ref 4a) b) Demethylated products were obtained in 11% (3-demethylated) and 7% (2-demethylated) yields respectively. c) The reactant was recovered in 37% yield. d) The reactant was recovered approximately in 74% yield. e) Excess amount of $AlCl_3$ (3 eq.) was used. Complex mixture of polymerized product was obtained after consumption of the reactant.

3. Computational Study

3-A. General Methods

The DFT calculations of structures, energies, and frequencies employed default procedures in Gaussian16 program[S27] unless otherwise noted. Complete structures and energetics are provided in sections below. All absolute energies are in Hartrees. All relative energies are presented in kcal/mol. The transition state structures were validated with frequency calculations and then intrinsic reaction coordinate (IRC) calculation.

3-B. Geometry optimization of relatively simple structure

For the geometry calculation, all possible conformations were generated by careful modeling on GaussView,[S28] referring to previously examined geometries.[8c,d] Then, the conformers were optimized to local minimum and their frequencies were calculated at using M06-2X functional and 6-31G* basis sets. The solvent effect was modeled using polarizable continuum model. For these DFT-optimized geometries, single-point energies were calculated at PCM(CH_2Cl_2)-M06-2X/6-311+G** level of theory, the thermal corrections at the PCM(CH_2Cl_2)-M06-2X/6-31G* level were incremented to obtain the Gibbs free energies at 1 atm, 298 K. The conformation having the minimum Gibbs free energy was defined as the global minimum energy conformation.

3-C. Information of the optimized geometries.

PCM(CH_2Cl_2)-M06-2X/6-31G* level of theory

SM-1'

Number of imaginary frequency = 0
Zero-point correction= 0.247169(a.u.)
Thermal correction to Energy= 0.262633
Thermal correction to Enthalpy= 0.263577
Thermal correction to Gibbs Free Energy= 0.204162
Sum of electronic and zero-point Energies= -782.526778
Sum of electronic and thermal Energies= -782.511314
Sum of electronic and thermal Enthalpies= -782.510369
Sum of electronic and thermal Free Energies= -782.569785
Electronic Energy = -782.773947
Charge = 1 Multiplicity = 1

C	-2.165609	2.395814	-0.194811
C	-0.821509	2.759473	-0.20504
C	0.169374	1.782832	-0.269936
C	-0.1996	0.448976	-0.297178
C	-1.540234	0.057968	-0.273839
C	-2.521801	1.053261	-0.236552
H	-2.936729	3.156547	-0.15578
H	-0.536886	3.805446	-0.177044
H	1.220266	2.047144	-0.314854
H	-3.564891	0.757636	-0.225492
C	-1.946889	-1.368673	-0.227283
O	0.836699	-0.488417	-0.493013
C	1.447613	-1.007874	0.570876
O	0.754099	-1.481222	1.54562
N	2.748713	-1.053853	0.570177
C	3.572508	-0.419741	-0.463364
H	4.266146	0.266128	0.026304
H	4.134051	-1.197063	-0.98466
H	2.946488	0.118006	-1.169776
C	3.479107	-1.754196	1.631657
H	4.180877	-2.445588	1.162591
H	4.028452	-1.019165	2.222935
H	2.782544	-2.298028	2.263733
O	-3.07683	-1.611278	-0.840883
O	-1.312627	-2.245266	0.358373
H	-0.167904	-1.784662	1.175584
C	-3.577257	-2.961597	-0.760454
H	-4.519661	-2.948011	-1.300902
H	-2.86628	-3.642111	-1.228826
H	-3.726057	-3.235121	0.284307

SM-6'

Number of imaginary frequency = 0
Zero-point correction= 0.250356(a.u.)
Thermal correction to Energy= 0.268362
Thermal correction to Enthalpy= 0.269306
Thermal correction to Gibbs Free Energy= 0.204174
Sum of electronic and zero-point Energies= -986.939848
Sum of electronic and thermal Energies= -986.921842
Sum of electronic and thermal Enthalpies= -986.920898
Sum of electronic and thermal Free Energies= -986.986030
Electronic Energy = -987.190204
Charge = 1 Multiplicity = 1

C	-1.68412	2.837227	-0.151627
C	-0.300126	2.786533	-0.04448
C	0.33733	1.55345	-0.021114
C	-0.380144	0.361124	-0.11147
C	-1.770219	0.416998	-0.203279
C	-2.413506	1.657656	-0.229637
H	-2.190955	3.794405	-0.167921
H	0.300245	3.686178	0.02319
H	-3.494794	1.68139	-0.305025
C	-2.585331	-0.830629	-0.187788
O	0.29535	-0.841246	-0.31666
C	0.674247	-1.59379	0.720073
O	-0.085557	-1.680042	1.761526
N	1.780773	-2.260328	0.619386
C	2.735269	-2.070486	-0.477989
H	3.684958	-1.744108	-0.050454
H	2.864457	-3.027601	-0.985763
H	2.367272	-1.324568	-1.175297
C	2.179815	-3.212136	1.663047
H	2.517608	-4.126019	1.173363

H	2.999153	-2.777059	2.238836
H	1.335525	-3.423806	2.313438
O	-3.664147	-0.754504	-0.922499
O	-2.294152	-1.810963	0.487688
H	-1.054997	-1.657534	1.445541
C	-4.549737	-1.89389	-0.881864
H	-5.382951	-1.629033	-1.526607
H	-4.02652	-2.773277	-1.257096
H	-4.881064	-2.061451	0.143112
N	1.793515	1.545702	0.134473
O	2.408269	2.498539	-0.292661
O	2.289802	0.593513	0.716058

SM-7'

Number of imaginary frequency = 0

Zero-point correction=	0.249423(a.u.)
Thermal correction to Energy=	0.267772
Thermal correction to Enthalpy=	0.268717
Thermal correction to Gibbs Free Energy=	0.201327
Sum of electronic and zero-point Energies=	-986.944829
Sum of electronic and thermal Energies=	-986.926479
Sum of electronic and thermal Enthalpies=	-986.925535
Sum of electronic and thermal Free Energies=	-986.992924
Electronic Energy =	-987.194252

Charge = 1 Multiplicity = 1

C	2.166334	-2.698668	0.429631
C	0.897012	-3.221024	0.229189
C	-0.130803	-2.350374	-0.110596
C	0.131827	-0.991976	-0.210904
C	1.41115	-0.470436	0.005463
C	2.448218	-1.3483	0.315709
H	0.724247	-4.28577	0.323726
H	-1.128593	-2.722749	-0.311431
H	3.454034	-0.980832	0.478689
C	1.691103	0.991771	-0.026303
O	-0.911813	-0.18232	-0.681956
C	-1.747229	0.398415	0.182782
O	-1.288281	0.960725	1.246524
N	-3.014502	0.405172	-0.104169
C	-3.589092	-0.328318	-1.237089
H	-4.39649	-0.95711	-0.858043
H	-3.990648	0.394449	-1.94963
H	-2.830509	-0.938913	-1.718513
C	-3.964059	1.16962	0.713846
H	-4.60138	1.743166	0.039858
H	-4.573107	0.471567	1.291086
H	-3.424618	1.836973	1.38043
O	2.880253	1.280644	-0.480997
O	0.898262	1.84055	0.370684
H	-0.343144	1.323007	1.043936
C	3.256011	2.675283	-0.463142
H	4.273489	2.699167	-0.842506
H	2.581841	3.239257	-1.107601
H	3.205752	3.052083	0.558411
N	3.263868	-3.616878	0.775424
O	2.994607	-4.798264	0.872682
O	4.367349	-3.134288	0.941723

INT-1'

Number of imaginary frequency = 0

Zero-point correction=	0.247768(a.u.)
Thermal correction to Energy=	0.263585
Thermal correction to Enthalpy=	0.264529
Thermal correction to Gibbs Free Energy=	0.203997
Sum of electronic and zero-point Energies=	-782.513405
Sum of electronic and thermal Energies=	-782.497588
Sum of electronic and thermal Enthalpies=	-782.496644
Sum of electronic and thermal Free Energies=	-782.557176
Electronic Energy =	-782.761173

Charge = 1 Multiplicity = 1

C	2.465018	2.489699	-0.05689
C	1.198471	3.070354	0.050972
C	0.051408	2.291295	0.156272
C	0.171081	0.909002	0.147778
C	1.439983	0.305014	0.044994
C	2.586723	1.113328	-0.055434
H	3.348044	3.112589	-0.134113
H	1.100069	4.150576	0.059501
H	-0.926499	2.746464	0.239406
H	3.559502	0.641212	-0.126863
C	1.602701	-1.137417	0.04647
O	-0.915729	0.080119	0.310912
C	-2.111266	0.365422	-0.392968
O	-2.132433	1.177397	-1.284404
N	-3.107181	-0.393738	0.076685
C	-2.965233	-1.356054	1.16352
H	-3.934197	-1.452716	1.656054
H	-2.66895	-2.340547	0.784042
H	-2.239824	-1.00579	1.895878
C	-4.386546	-0.371798	-0.623043
H	-4.600666	-1.363932	-1.031063
H	-5.179722	-0.092162	0.074728
H	-4.338354	0.353817	-1.431966
O	2.779903	-1.611903	-0.110871
O	0.640898	-1.978344	0.19857
H	-0.21769	-1.497295	0.308052
C	2.97361	-3.053695	-0.110404
H	4.04041	-3.183354	-0.261068
H	2.654039	-3.453605	0.850769
H	2.398577	-3.487792	-0.927062

INT-6'

Number of imaginary frequency = 0

Zero-point correction=	0.250493(a.u.)
Thermal correction to Energy=	0.268837
Thermal correction to Enthalpy=	0.269782
Thermal correction to Gibbs Free Energy=	0.203395
Sum of electronic and zero-point Energies=	-986.925653
Sum of electronic and thermal Energies=	-986.907308
Sum of electronic and thermal Enthalpies=	-986.906364
Sum of electronic and thermal Free Energies=	-986.972751
Electronic Energy =	-987.176145

Charge = 1 Multiplicity = 1

C	-1.951496	2.686915	0.37868
C	-0.568697	2.834816	0.331992
C	0.244226	1.736758	0.086868
C	-0.287899	0.456816	-0.077038
C	-1.687354	0.315997	-0.022368
C	-2.508872	1.434583	0.191402
H	-2.584049	3.54805	0.553348
H	-0.100109	3.802549	0.46965
H	-3.583864	1.300504	0.214551
C	-2.321485	-0.988561	-0.18754
O	0.467436	-0.652604	-0.302113
C	1.58852	-0.866892	0.567335
O	1.627095	-0.311634	1.636631
N	2.430877	-1.732824	0.015588
C	2.344635	-2.189913	-1.36883
H	3.360735	-2.370135	-1.723222
H	1.775176	-3.121766	-1.441388
H	1.88841	-1.42264	-1.991866
C	3.558159	-2.207262	0.811747
H	3.585065	-3.298939	0.778086
H	4.491941	-1.809078	0.405849
H	3.435493	-1.874525	1.840356
O	-3.591021	-1.047167	-0.082815
O	-1.692476	-2.078749	-0.43768
H	-0.718407	-1.916127	-0.4986
C	-4.266052	-2.326732	-0.263519
H	-5.318248	-2.095858	-0.134134
H	-4.055259	-2.695057	-1.26633
H	-3.909827	-3.021437	0.495494
N	1.684771	1.983509	-0.039811
O	2.143374	2.920805	0.577351
O	2.316899	1.256264	-0.786981

INT-7'

Number of imaginary frequency = 0

Zero-point correction=	0.250331(a.u.)
Thermal correction to Energy=	0.268828
Thermal correction to Enthalpy=	0.269773
Thermal correction to Gibbs Free Energy=	0.201993

Sum of electronic and zero-point Energies= -986.930724
Sum of electronic and thermal Energies= -986.912227
Sum of electronic and thermal Enthalpies= -986.911283
Sum of electronic and thermal Free Energies= -986.979063
Electronic Energy = -987.181055
Charge = 1 Multiplicity = 1

C	2.404569	-0.897795	-0.132474
C	1.537639	-1.983851	-0.231184
C	0.170288	-1.76523	-0.260346
C	-0.315876	-0.46174	-0.187294
C	0.573382	0.629336	-0.092157
C	1.95495	0.401942	-0.066666
H	1.940245	-2.98772	-0.291346
H	2.655442	1.225066	0.001861
C	0.102437	2.007507	-0.014567
O	-1.648378	-0.177726	-0.27381
C	-2.581958	-1.010843	0.411435
O	-2.209501	-1.776627	1.263618
N	-3.816021	-0.761228	-0.028071
C	-4.137887	0.179581	-1.096733
H	-3.347148	0.198115	-1.844798
H	-5.057213	-0.16042	-1.575981
H	-4.305238	1.186427	-0.698617
C	-4.938033	-1.389877	0.662246
H	-5.600932	-0.615922	1.058536
H	-5.494443	-2.016957	-0.038709
H	-4.558636	-2.00059	1.478565
O	0.973799	2.925354	0.138586
O	-1.130048	2.35762	-0.09131
H	-1.713083	1.566761	-0.206062
C	0.543913	4.316528	0.213599
H	1.464209	4.875467	0.346784
H	0.044298	4.579488	-0.717503
H	-0.123615	4.430859	1.066202
H	-0.518112	-2.595556	-0.337797
N	3.853106	-1.142924	-0.104508
O	4.58483	-0.174349	-0.030363
O	4.224466	-2.299133	-0.156921

TS-1'

Number of imaginary frequency = 1
Zero-point correction= 0.245261(a.u.)
Thermal correction to Energy= 0.261230
Thermal correction to Enthalpy= 0.262174
Thermal correction to Gibbs Free Energy= 0.201125
Sum of electronic and zero-point Energies= -782.483125
Sum of electronic and thermal Energies= -782.467157
Sum of electronic and thermal Enthalpies= -782.466213
Sum of electronic and thermal Free Energies= -782.527262
Electronic Energy = -782.728387
Charge = 1 Multiplicity = 1

C	2.554859	2.472378	-0.095463
C	1.346631	3.01596	0.345834
C	0.271782	2.195333	0.665293
C	0.404519	0.815555	0.539566
C	1.613788	0.252325	0.095145
C	2.685482	1.096704	-0.215119
H	3.38865	3.120515	-0.339734
H	1.240458	4.091103	0.445948
H	-0.667489	2.606339	1.019741
H	3.617783	0.655592	-0.549324
C	1.722555	-1.21804	-0.0129
O	-0.671628	0.03132	0.85252
C	-2.364683	0.435106	-0.520154
O	-1.869046	1.196996	-1.22164
N	-3.229802	-0.352488	-0.02241
C	-3.194945	-0.988359	1.313823
H	-4.22823	-1.031275	1.656016
H	-2.7896	-1.996027	1.211741
H	-2.596959	-0.389612	1.99258
C	-4.394408	-0.676936	-0.897773
H	-4.443191	-1.7625	-0.980493
H	-5.289457	-0.277352	-0.422067
H	-4.252492	-0.231254	-1.880652
O	2.890709	-1.643797	-0.454833
O	0.807222	-1.982462	0.283274
H	-0.3667	-0.917046	0.761193
C	3.042719	-3.067899	-0.565422
H	4.054457	-3.222328	-0.931796
H	2.907569	-3.532485	0.412047
H	2.309662	-3.465948	-1.268179

TS-6'

Number of imaginary frequency = 1
Zero-point correction= 0.247487(a.u.)
Thermal correction to Energy= 0.265835
Thermal correction to Enthalpy= 0.266779
Thermal correction to Gibbs Free Energy= 0.200021
Sum of electronic and zero-point Energies= -986.904965
Sum of electronic and thermal Energies= -986.886618
Sum of electronic and thermal Enthalpies= -986.885674
Sum of electronic and thermal Free Energies= -986.952431
Electronic Energy = -987.152453
Charge = 1 Multiplicity = 1

C	-1.950123	2.747214	0.530131
C	-0.595614	2.923388	0.286272
C	0.194935	1.842163	-0.093036
C	-0.355765	0.564271	-0.242178
C	-1.731682	0.399131	-0.002088
C	-2.516505	1.487377	0.378585
H	-2.559664	3.590259	0.830828
H	-0.127232	3.89528	0.382911
H	-3.574907	1.331494	0.553316
C	-2.317054	-0.950524	-0.192519
O	0.395813	-0.505157	-0.62412
C	1.692708	-0.991734	0.771606
O	1.302441	-0.53291	1.760341
N	2.506782	-1.738211	0.118745
C	2.635491	-1.820793	-1.347829
H	3.671574	-2.089005	-1.54993
H	1.971426	-2.596836	-1.731867
H	2.410077	-0.854887	-1.789576
C	3.437937	-2.554314	0.938192
H	3.343616	-3.590733	0.6133
H	4.451552	-2.187515	0.773861
H	3.17105	-2.468872	1.989988
O	-3.596105	-1.029914	0.068916
O	-1.644169	-1.91032	-0.572368
H	-0.273715	-1.283943	-0.729074
C	-4.211476	-2.319903	-0.123538
H	-5.257394	-2.177061	0.133079
H	-4.100095	-2.625048	-1.164158
H	-3.742016	-3.050787	0.534977
N	1.610137	2.104605	-0.351657
O	1.949089	3.258924	-0.500884
O	2.380472	1.154436	-0.401601

TS-7'

Number of imaginary frequency = 1
Zero-point correction= 0.247889(a.u.)
Thermal correction to Energy= 0.266385
Thermal correction to Enthalpy= 0.267329
Thermal correction to Gibbs Free Energy= 0.199271
Sum of electronic and zero-point Energies= -986.905338
Sum of electronic and thermal Energies= -986.886842
Sum of electronic and thermal Enthalpies= -986.885897
Sum of electronic and thermal Free Energies= -986.953956
Electronic Energy = -987.153226
Charge = 1 Multiplicity = 1

C	2.504449	-0.97054	-0.040539
C	1.635608	-1.993446	-0.409439
C	0.308056	-1.689338	-0.663694
C	-0.125781	-0.37108	-0.54081
C	0.761535	0.654469	-0.165413
C	2.096304	0.345838	0.082113
H	2.004247	-3.007853	-0.497336
H	2.799974	1.118865	0.365179
C	0.250848	2.042256	-0.061042
O	-1.436914	-0.090221	-0.793507
C	-2.713481	-1.084129	0.488286
O	-2.00475	-1.617255	1.225337
N	-3.849222	-0.736976	0.016968

C	-4.121999	-0.051347	-1.262818
H	-3.356244	-0.30058	-1.989943
H	-5.089802	-0.416148	-1.604301
H	-4.171368	1.024833	-1.0895
C	-5.025085	-1.041827	0.880876
H	-5.555802	-0.105156	1.0527
H	-5.654297	-1.756376	0.350812
H	-4.688465	-1.461878	1.826621
O	1.149193	2.920816	0.314285
O	-0.917702	2.33166	-0.309926
H	-1.534397	0.915185	-0.699527
C	0.701387	4.285787	0.421327
H	1.5759	4.849692	0.734074
H	0.339284	4.629623	-0.547872
H	-0.094327	4.353205	1.16367
H	-0.392979	-2.459014	-0.965077
N	3.90939	-1.298348	0.225044
O	4.65437	-0.385916	0.531968
O	4.244858	-2.46398	0.123142

PD-1'

Number of imaginary frequency = 0

Zero-point correction=	0.245304(a.u.)
Thermal correction to Energy=	0.262405
Thermal correction to Enthalpy=	0.263349
Thermal correction to Gibbs Free Energy=	0.198882
Sum of electronic and zero-point Energies=	-782.484275
Sum of electronic and thermal Energies=	-782.467174
Sum of electronic and thermal Enthalpies=	-782.466229
Sum of electronic and thermal Free Energies=	-782.530696
Electronic Energy =	-782.729579

Charge = 1 Multiplicity = 1

C	2.506035	2.448722	-0.056336
C	1.261409	2.945016	0.342629
C	0.208666	2.085004	0.62001
C	0.388142	0.705955	0.497406
C	1.637457	0.193539	0.099623
C	2.687929	1.080359	-0.172242
H	3.323498	3.127751	-0.269974
H	1.111779	4.015396	0.441511
H	-0.75726	2.461066	0.94253
H	3.646327	0.673662	-0.474952
C	1.810648	-1.269135	-0.013527
O	-0.671171	-0.098062	0.768179
C	-2.671653	0.461265	-0.699434
O	-2.041022	1.170216	-1.33477
N	-3.471347	-0.304954	-0.096838
C	-3.480513	-0.471	1.380964
H	-4.504294	-0.292901	1.708217
H	-3.170887	-1.493396	1.597554
H	-2.79382	0.237508	1.833424
C	-4.478378	-1.066758	-0.891322
H	-4.352525	-2.11934	-0.639929
H	-5.464863	-0.705559	-0.602387
H	-4.307809	-0.907261	-1.954286
O	3.023863	-1.640245	-0.393078
O	0.918347	-2.077912	0.221349
H	-0.36272	-1.033852	0.67047
C	3.239956	-3.053699	-0.509079
H	4.275956	-3.163889	-0.820259
H	3.07074	-3.537384	0.453939
H	2.564373	-3.474697	-1.255022

PD-6'

Number of imaginary frequency = 0

Zero-point correction=	0.248599(a.u.)
Thermal correction to Energy=	0.267824
Thermal correction to Enthalpy=	0.268768
Thermal correction to Gibbs Free Energy=	0.200014
Sum of electronic and zero-point Energies=	-986.908868
Sum of electronic and thermal Energies=	-986.889643
Sum of electronic and thermal Enthalpies=	-986.888698
Sum of electronic and thermal Free Energies=	-986.957453
Electronic Energy =	-987.157466

Charge = 1 Multiplicity = 1

C	-1.922911	2.654516	0.647192
C	-0.58303	2.778545	0.316515
C	0.12295	1.684165	-0.178084
C	-0.492652	0.434718	-0.376336
C	-1.863939	0.332682	-0.048353
C	-2.556723	1.431801	0.458665
H	-2.46721	3.502729	1.043113
H	-0.057185	3.71788	0.438094
H	-3.6065	1.314109	0.70202
C	-2.547091	-0.965621	-0.266449
O	0.190584	-0.604987	-0.870432
C	2.033658	-1.084486	0.933035
O	1.390236	-0.551039	1.713407
N	2.816822	-1.800222	0.249544
C	2.997178	-1.732909	-1.222969
H	3.989629	-1.322719	-1.409858
H	2.923092	-2.755913	-1.591414
H	2.226883	-1.102641	-1.652546
C	3.676111	-2.765912	0.999149
H	3.413511	-3.767282	0.660066
H	4.711635	-2.52523	0.760398
H	3.500306	-2.666412	2.068902
O	-3.815532	-0.966904	0.092598
O	-1.986076	-1.94865	-0.738146
H	-0.459893	-1.352402	-0.983411
C	-4.52691	-2.200306	-0.107003
H	-5.539123	-2.007306	0.238671
H	-4.519729	-2.464068	-1.165116
H	-4.060471	-2.994883	0.476482
N	1.526203	1.905803	-0.50456
O	1.881572	3.045432	-0.723032
O	2.291258	0.946538	-0.534788

PD-7'

Number of imaginary frequency = 0

Zero-point correction=	0.248336(a.u.)
Thermal correction to Energy=	0.267888
Thermal correction to Enthalpy=	0.268832
Thermal correction to Gibbs Free Energy=	0.198344
Sum of electronic and zero-point Energies=	-986.909154
Sum of electronic and thermal Energies=	-986.889603
Sum of electronic and thermal Enthalpies=	-986.888659
Sum of electronic and thermal Free Energies=	-986.959147
Electronic Energy =	-987.157491

Charge = 1 Multiplicity = 1

C	2.471317	-0.806143	-0.191206
C	1.59361	-1.818357	-0.581788
C	0.259241	-1.515195	-0.766693
C	-0.19966	-0.207665	-0.557688
C	0.704011	0.805611	-0.171246
C	2.050361	0.494863	0.011358
H	1.966718	-2.823131	-0.737055
H	2.756318	1.260495	0.308131
C	0.200791	2.184378	0.027249
O	-1.510289	0.032623	-0.734522
C	-3.091654	-1.528605	0.650742
O	-2.185673	-2.01038	1.150701
N	-4.139729	-1.038086	0.154885
C	-4.296076	-0.849627	-1.313876
H	-3.39902	-1.192369	-1.822584
H	-5.166866	-1.429553	-1.617881
H	-4.448063	0.215019	-1.490767
C	-5.266267	-0.644253	1.049849
H	-5.432136	0.423496	0.911288
H	-6.137476	-1.223846	0.747442
H	-5.004251	-0.858819	2.084158
O	1.134218	3.046793	0.382796
O	-0.974375	2.494912	-0.126994
H	-1.662334	1.000696	-0.580102
C	0.698436	4.402252	0.577238
H	1.590988	4.954209	0.860421
H	0.277301	4.79198	-0.350268
H	-0.050961	4.44062	1.368724
H	-0.446967	-2.275402	-1.081708
N	3.882608	-1.129551	0.007269
O	4.631504	-0.229991	0.346853
O	4.231282	-2.282918	-0.177084

4-D. Information of the single point calculation for each optimized geometry.

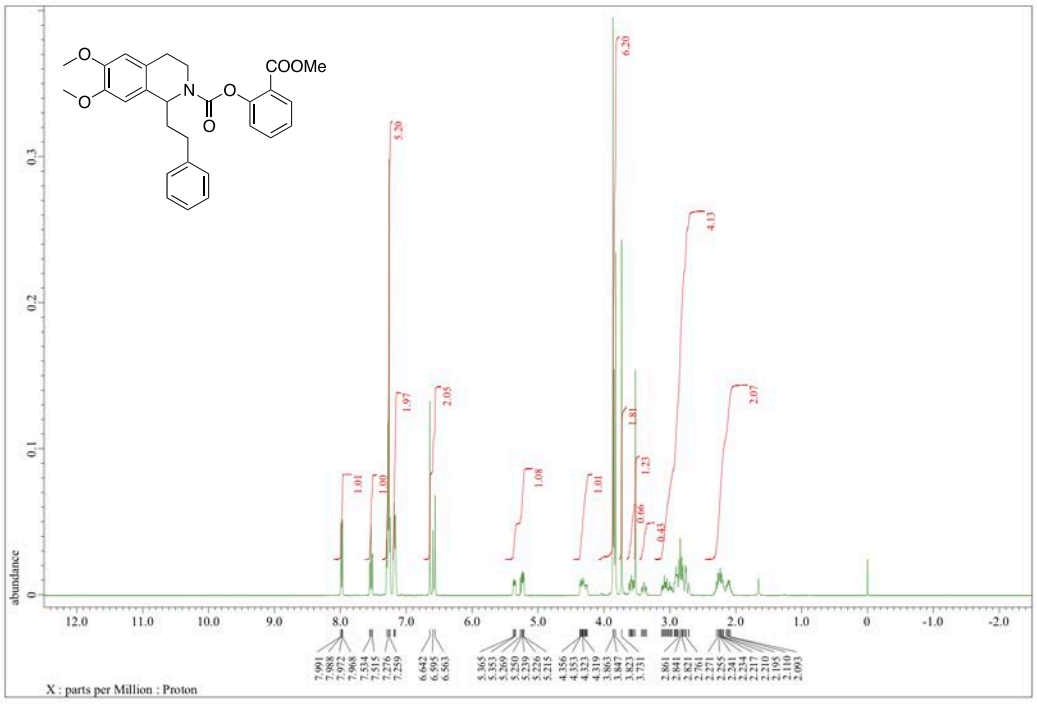
PCM(CH_2Cl_2)-M06-2X/6-3111G** level of theory (unit: a.u.)

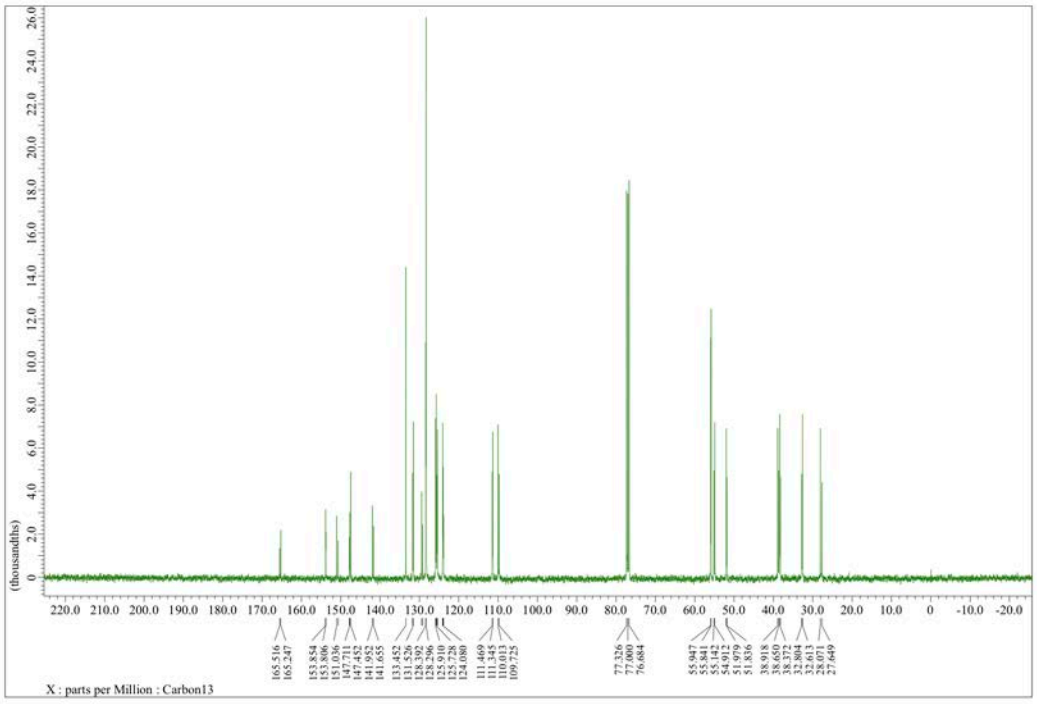
SM-1': E(RM062X) = -782.997416831
SM-6': E(RM062X) = -987.476263947
SM-7': E(RM062X) = -987.480885316
INT-1': E(RM062X) = -782.985498754
INT-6': E(RM062X) = -987.463776360
INT-7': E(RM062X) = -987.468730404
TS-1': E(RM062X) = -782.958351497
TS-6': E(RM062X) = -987.443209595
TS-7': E(RM062X) = -987.445580789
PD-1': E(RM062X) = -782.961221363
PD-6': E(RM062X) = -987.450747281
PD-7': E(RM062X) = -987.452392616

4. NMR spectra of new compounds

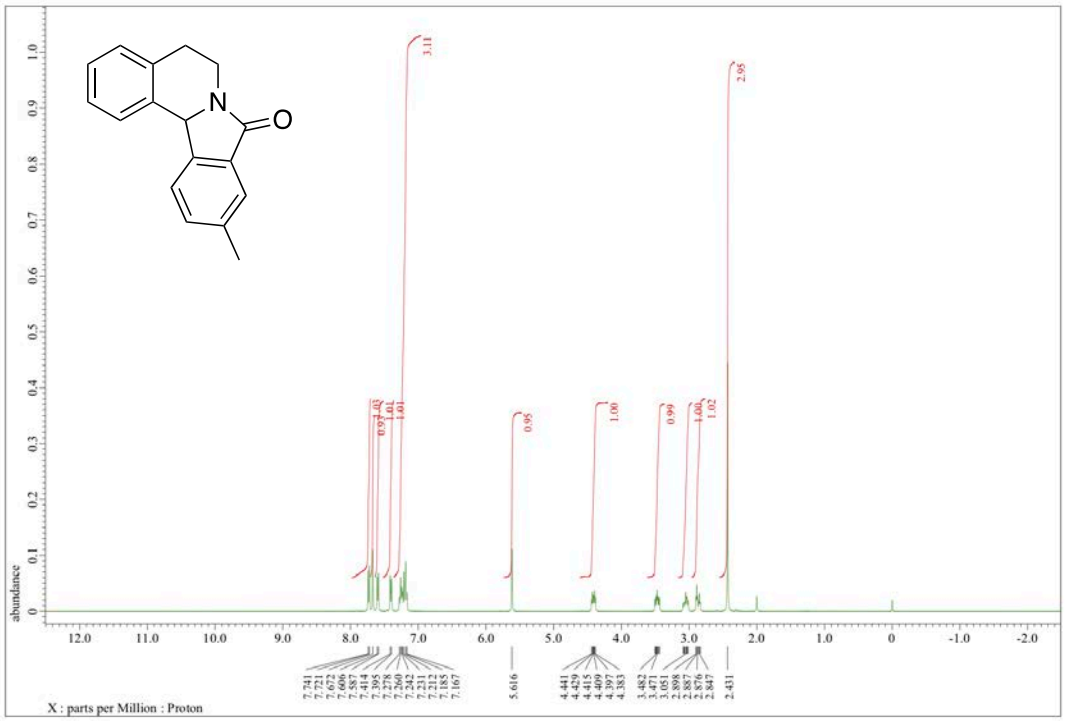
^{1}H NMR (400 MHz) and ^{13}C NMR (100MHz) spectra are shown in this section.

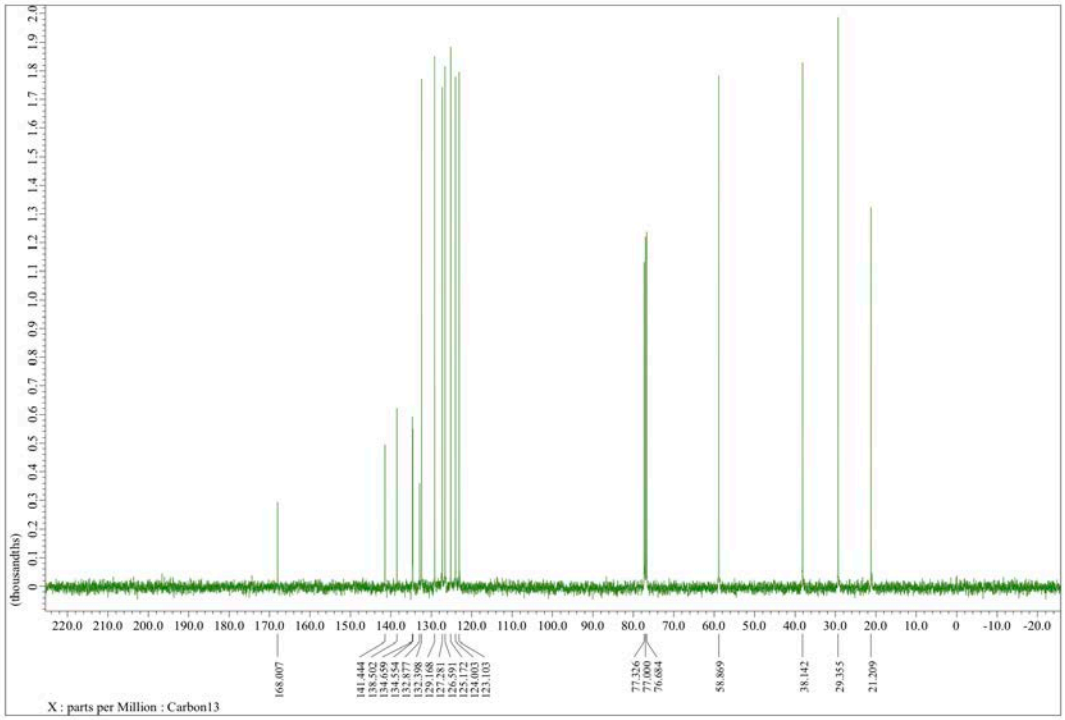
1a (Solvent: $CDCl_3$)



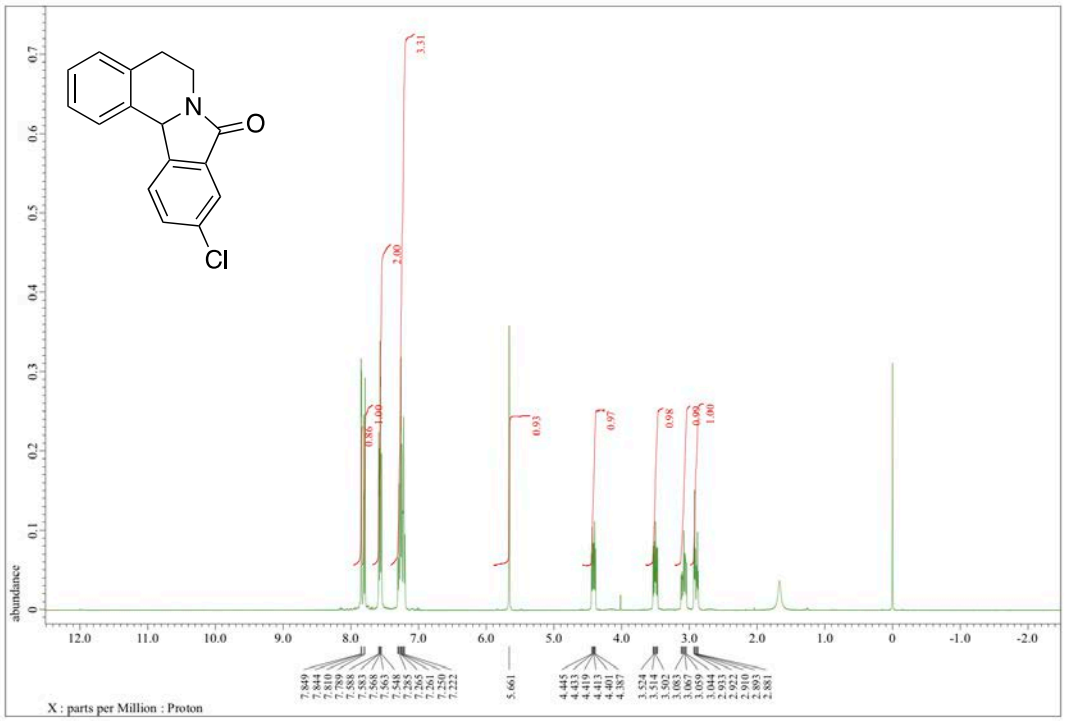


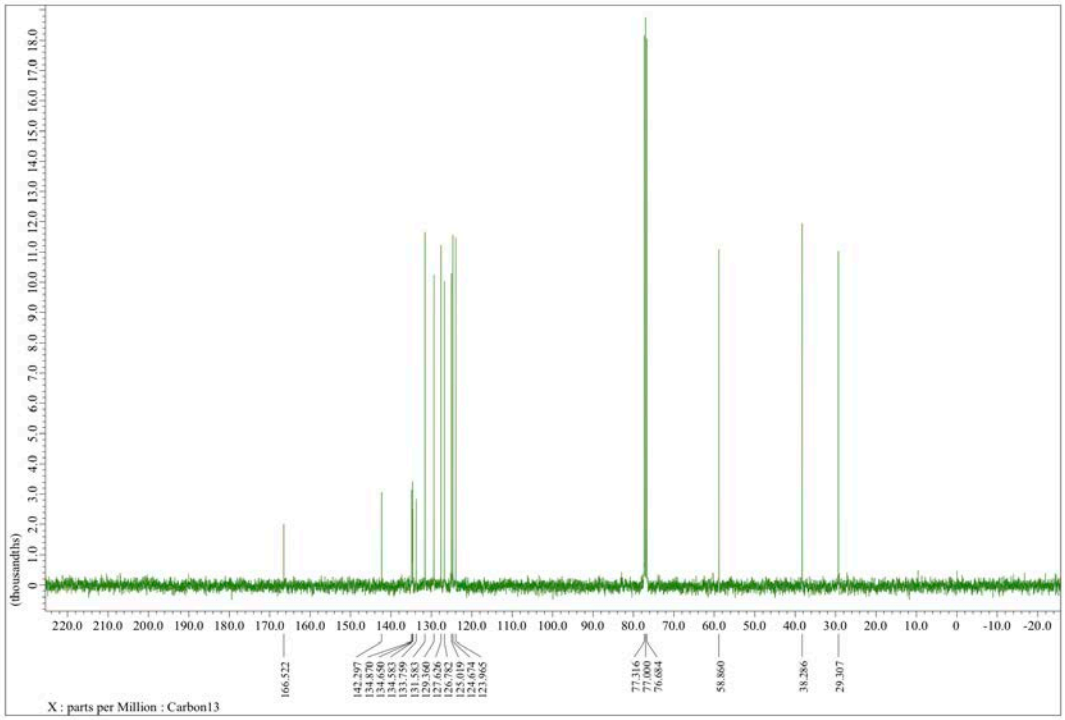
3d (Solvent: $CDCl_3$)



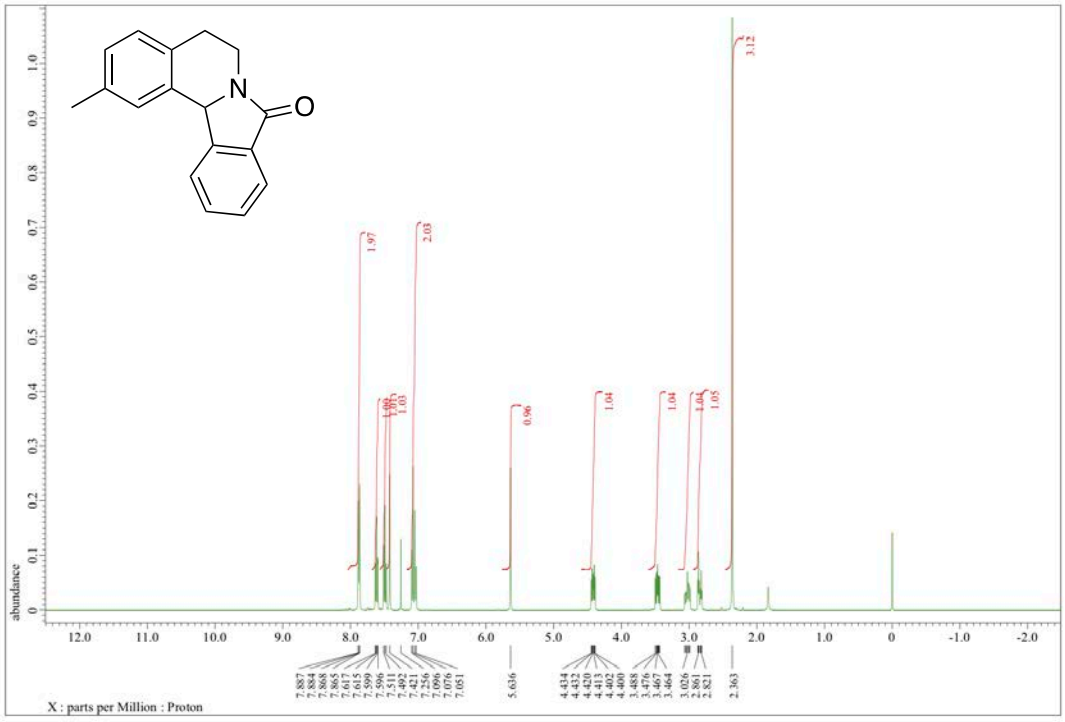


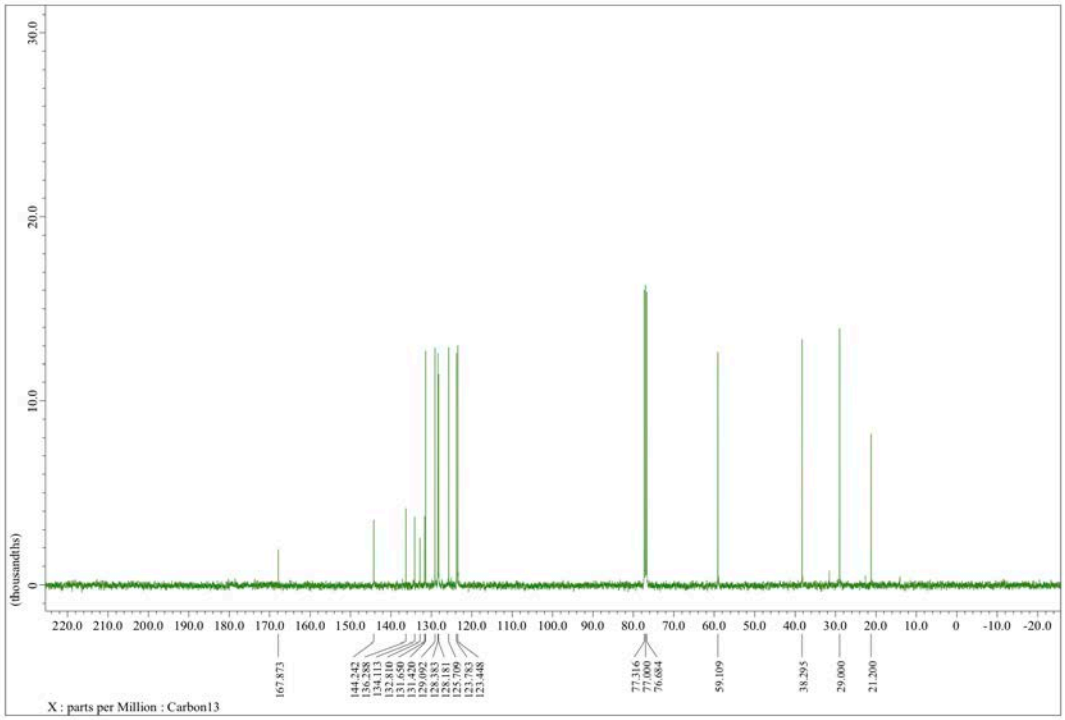
3e (Solvent: $CDCl_3$)



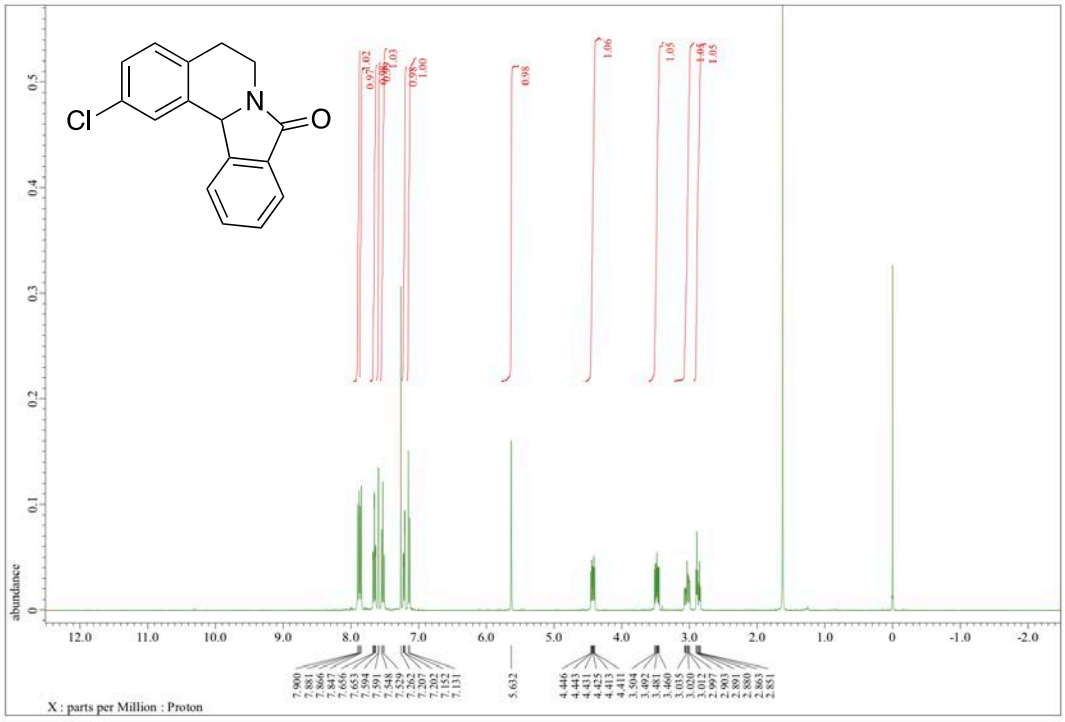


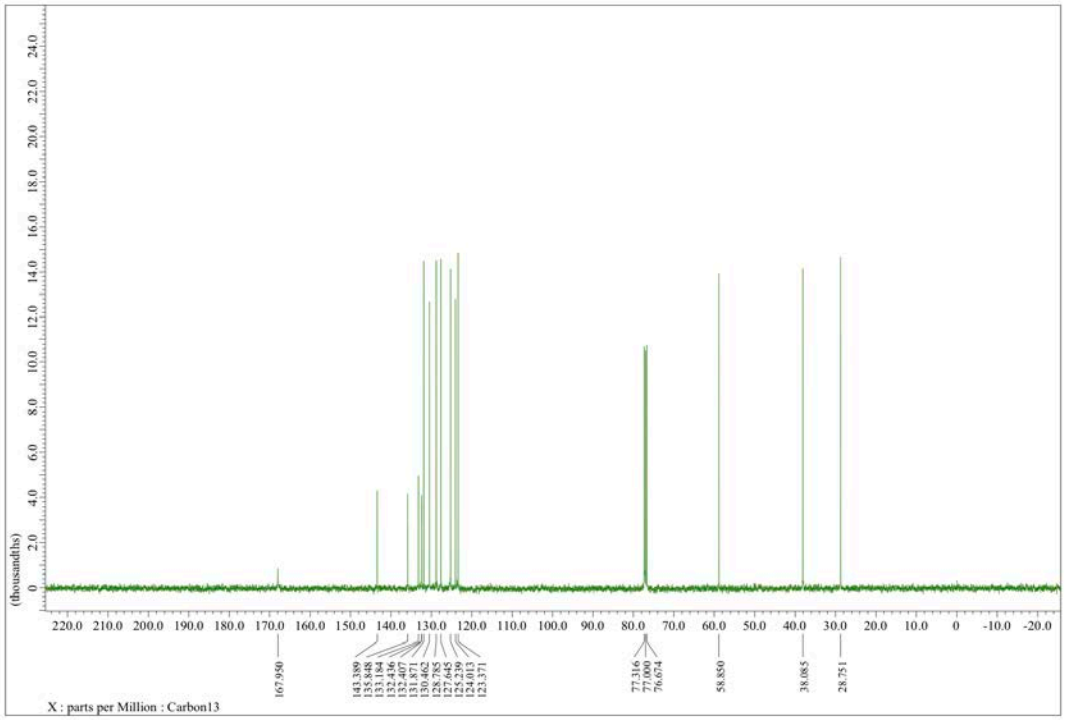
3g (Solvent: $CDCl_3$)



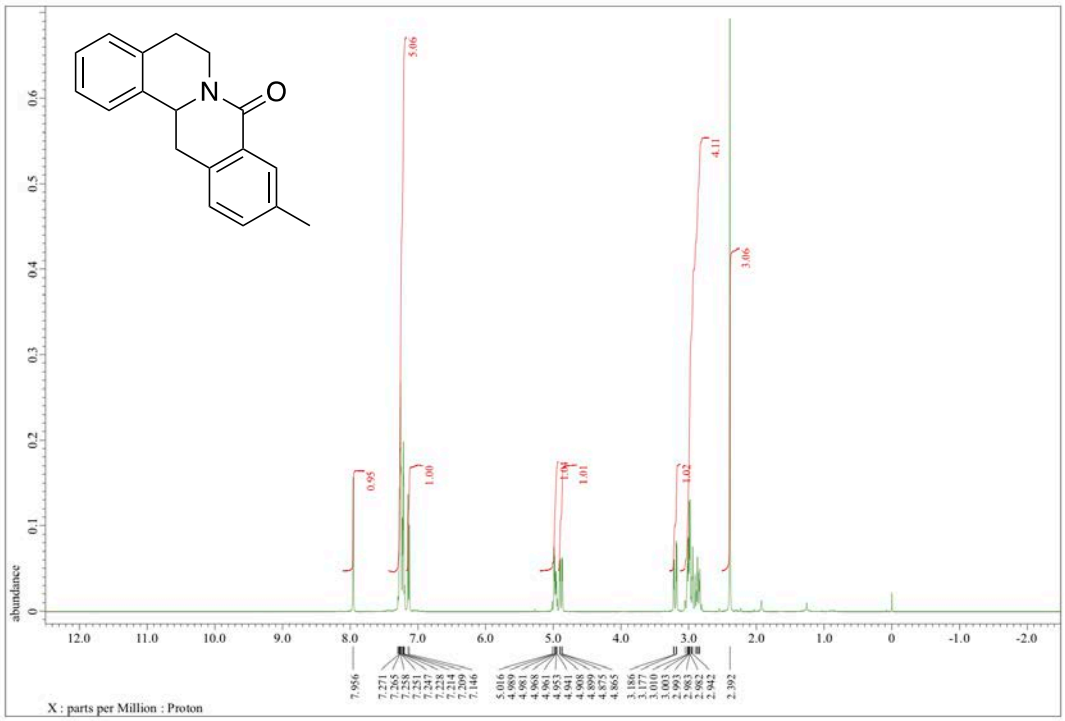


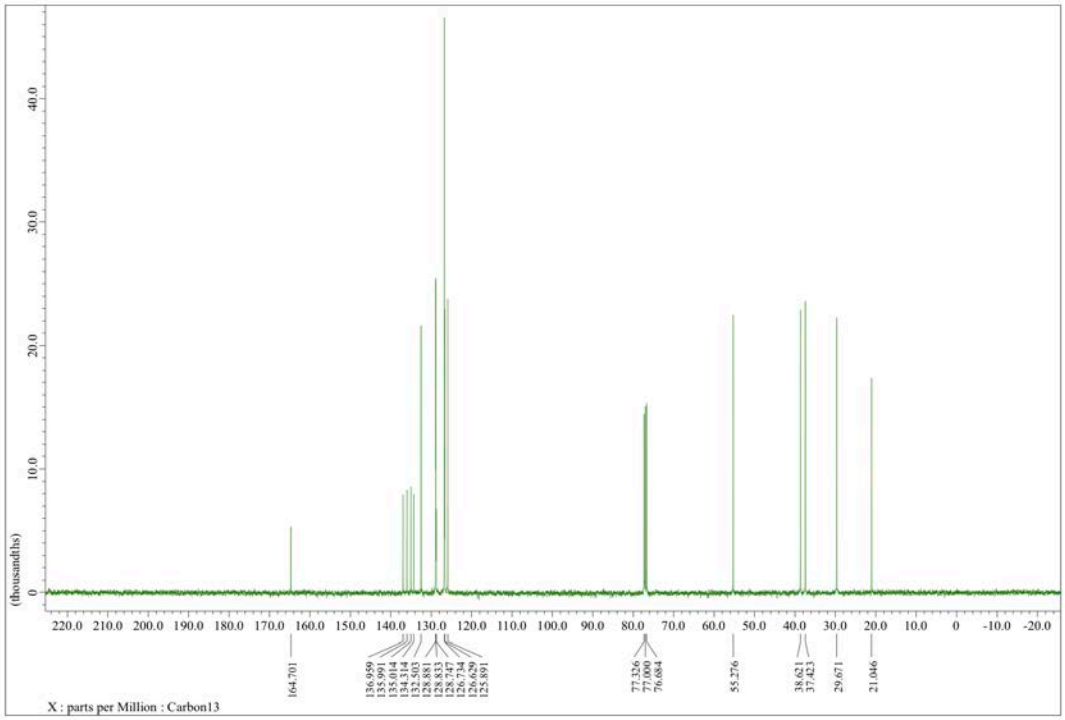
3h (Solvent: $CDCl_3$)



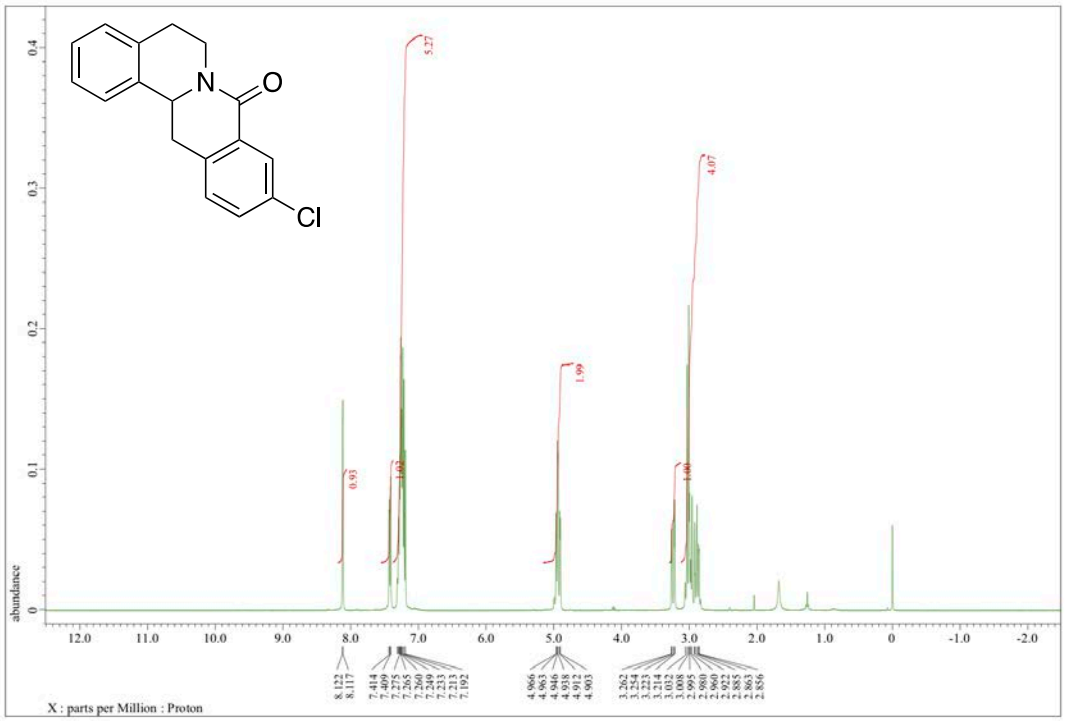


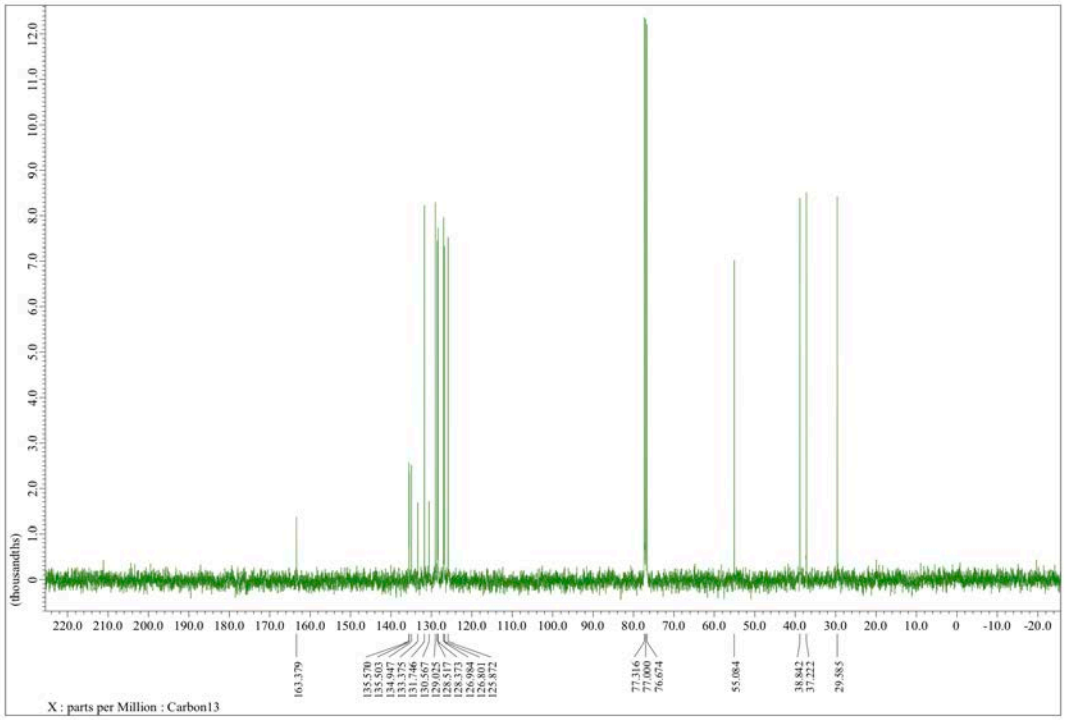
3j (Solvent: $CDCl_3$)



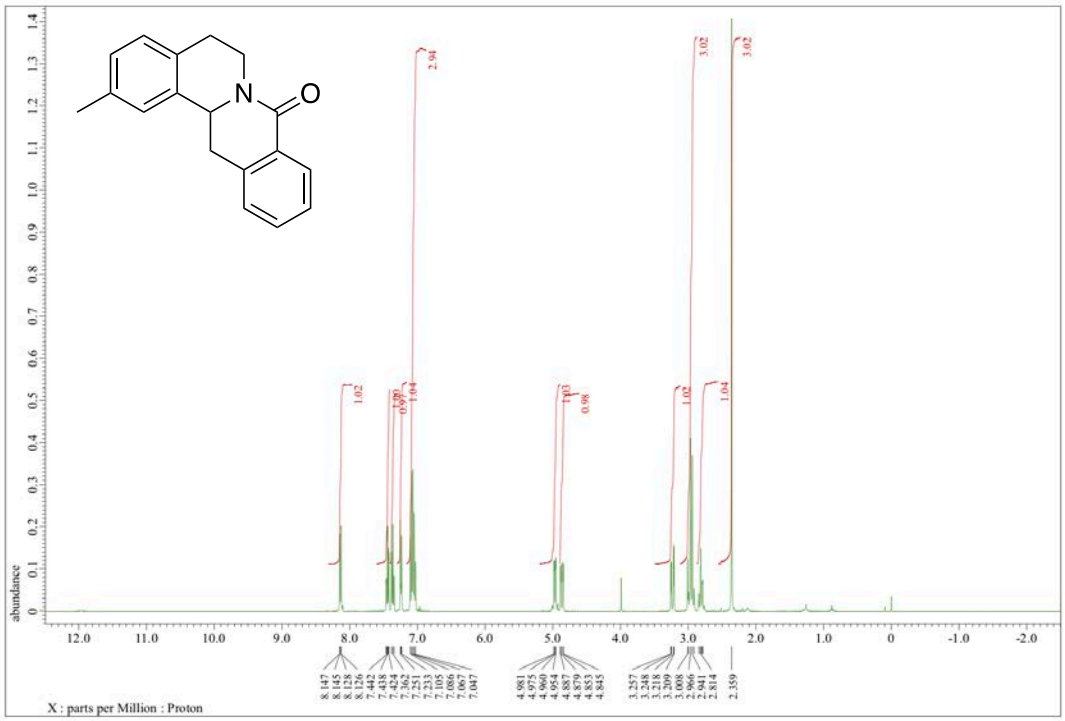


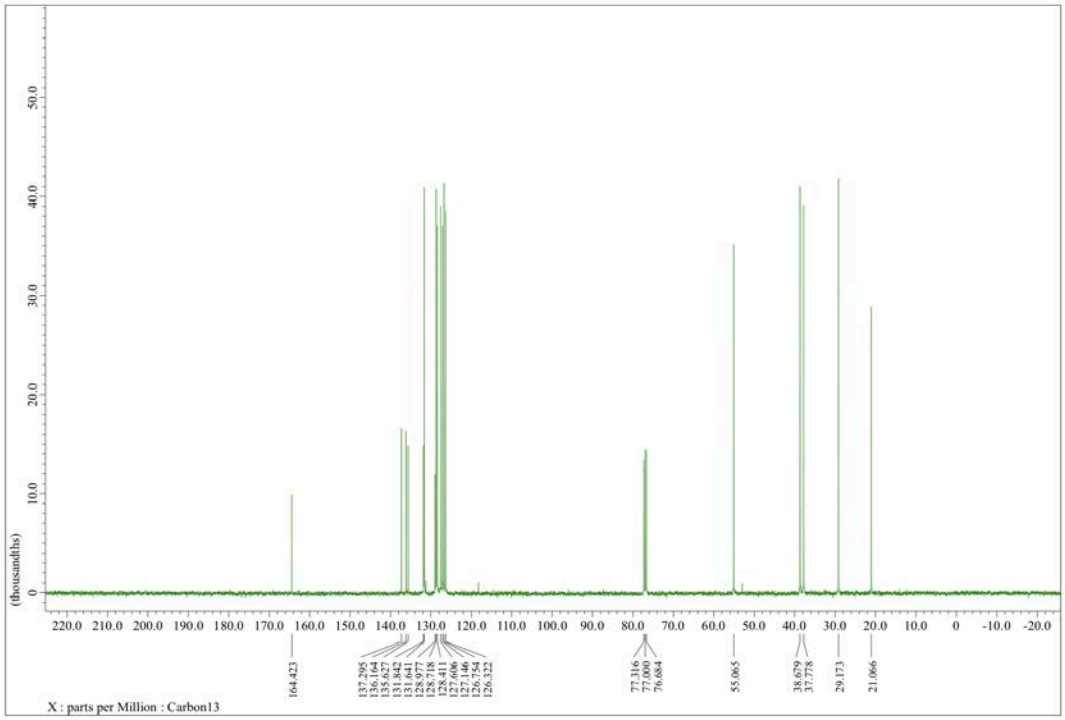
3k (Solvent: $CDCl_3$)



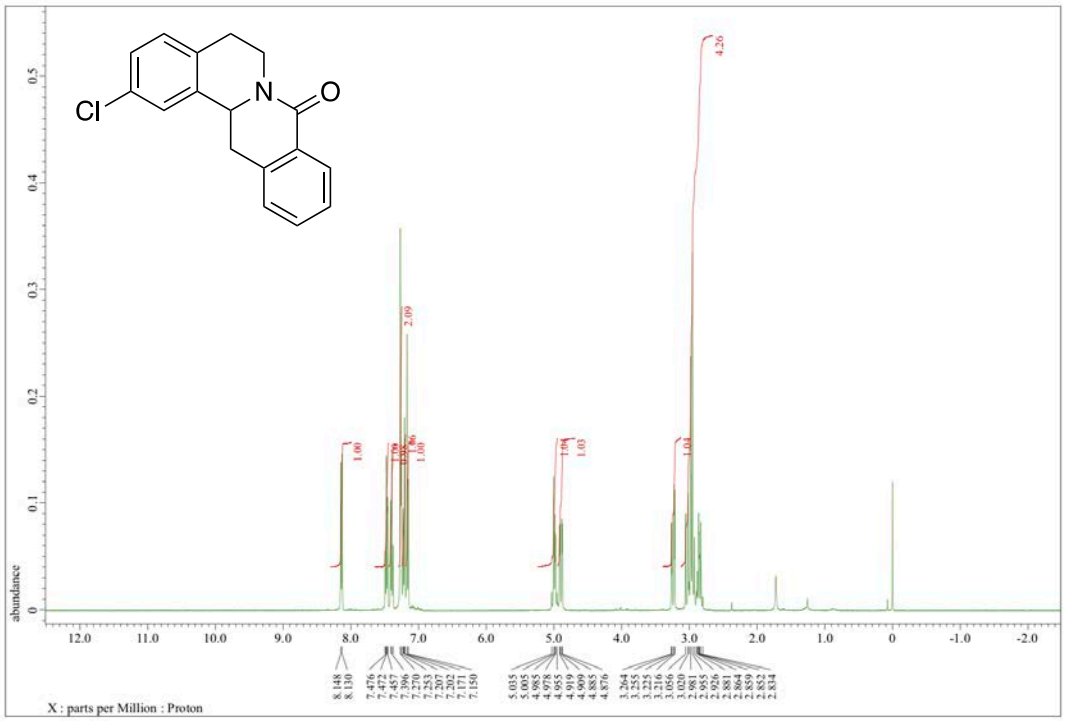


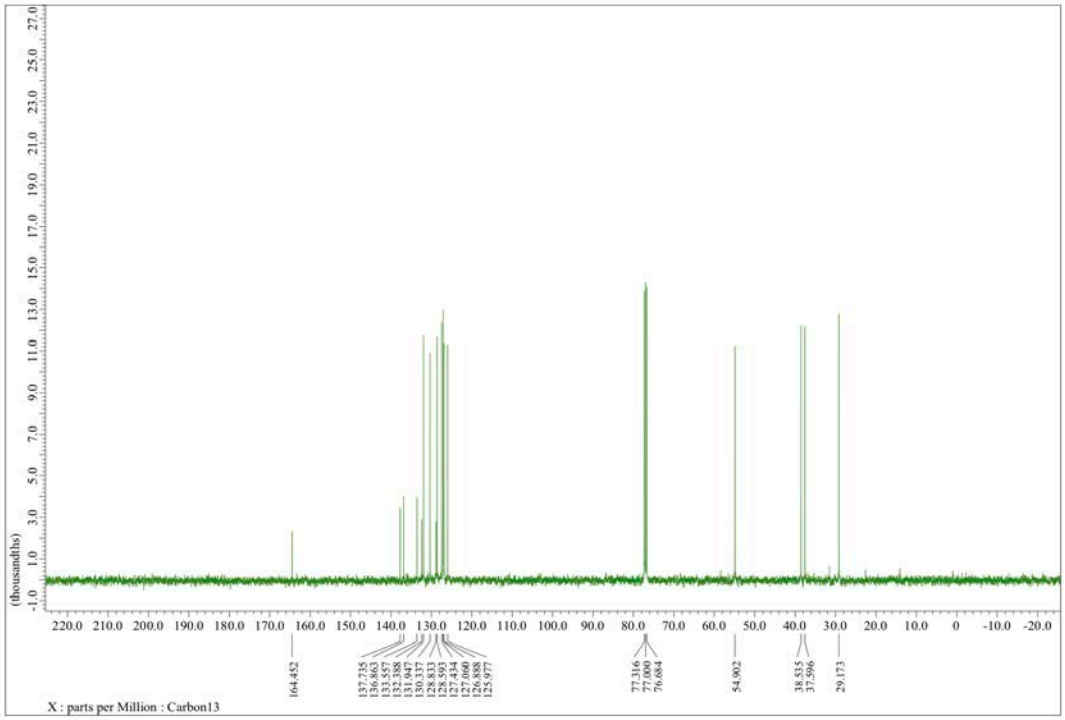
3l (Solvent: $CDCl_3$)



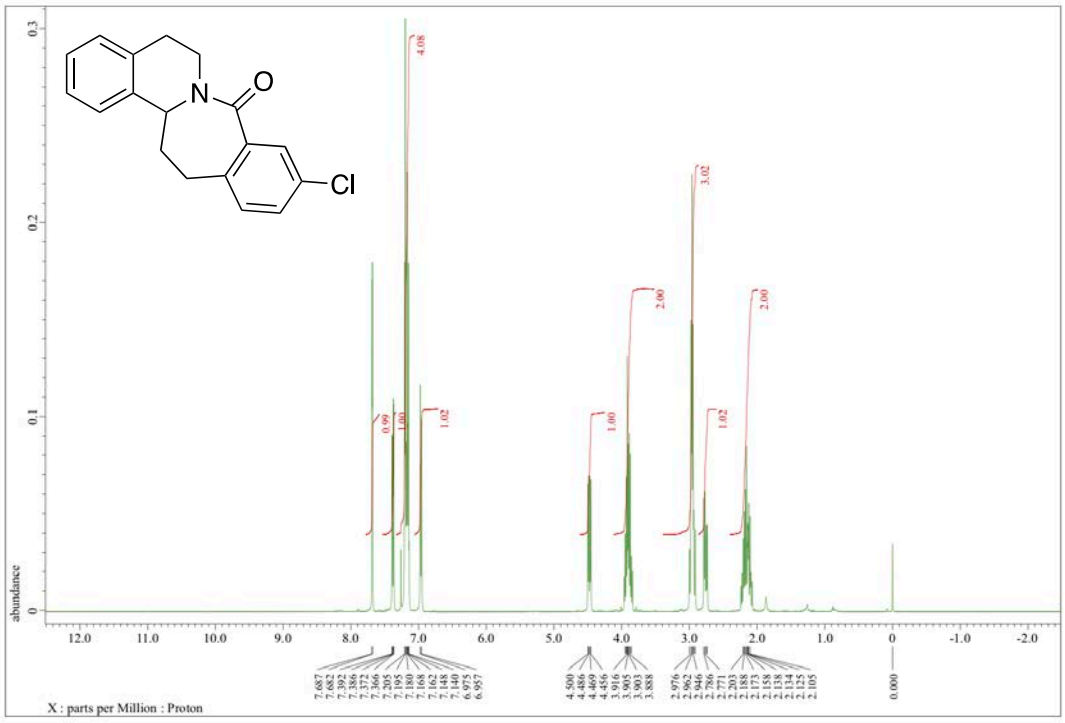


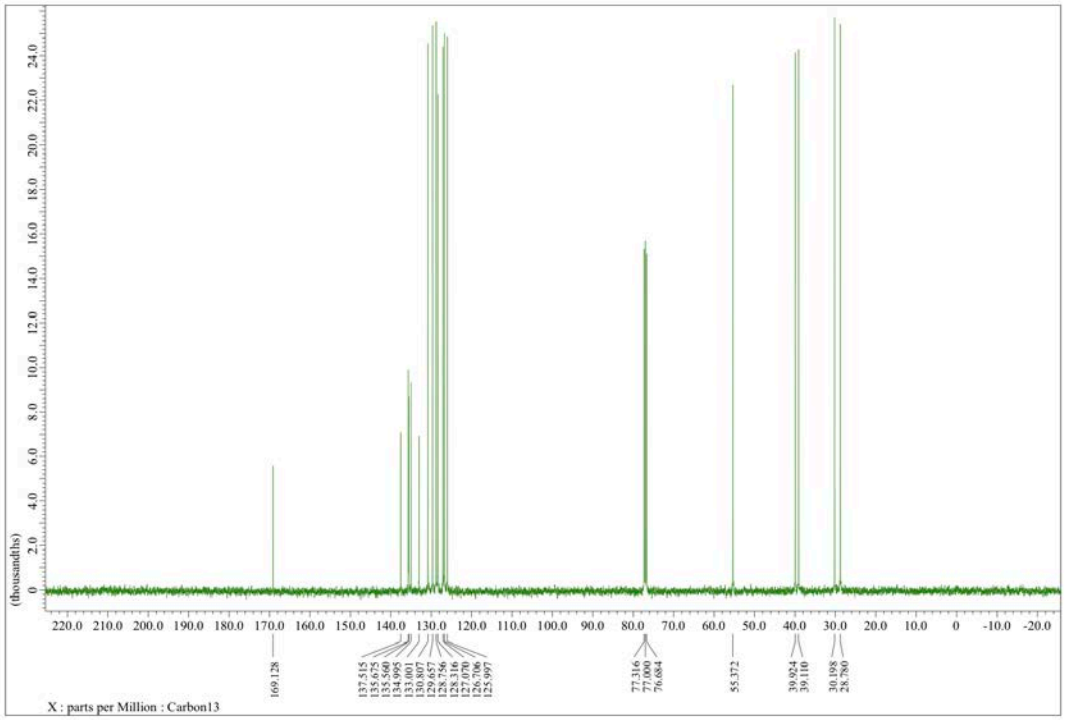
3m (Solvent: $CDCl_3$)



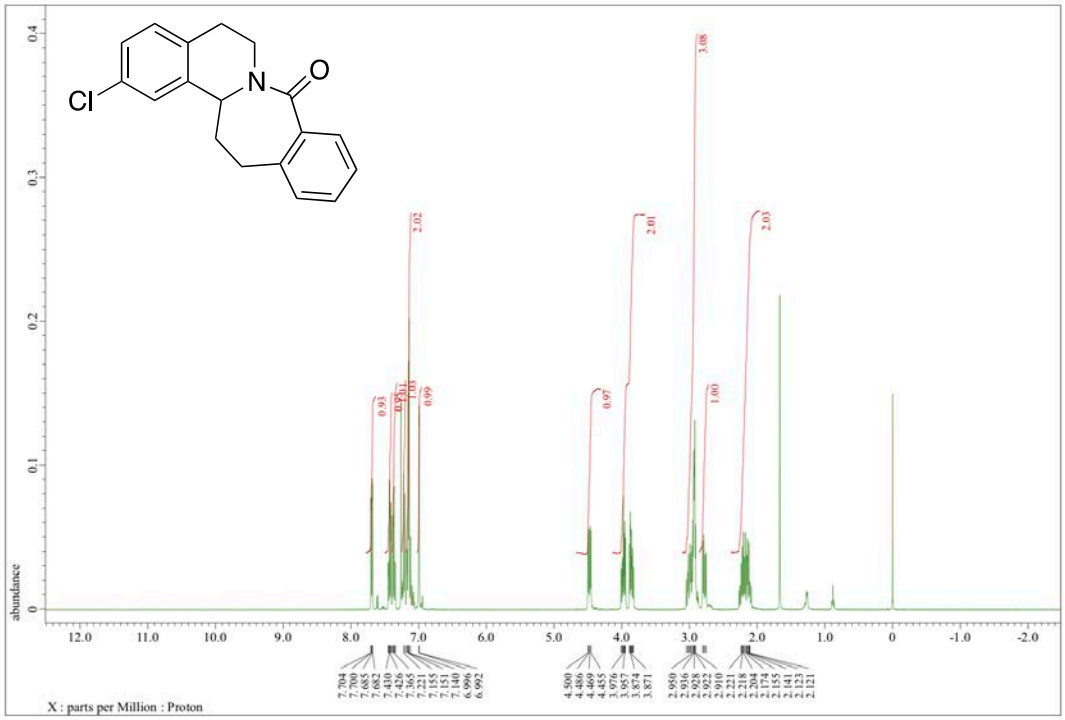


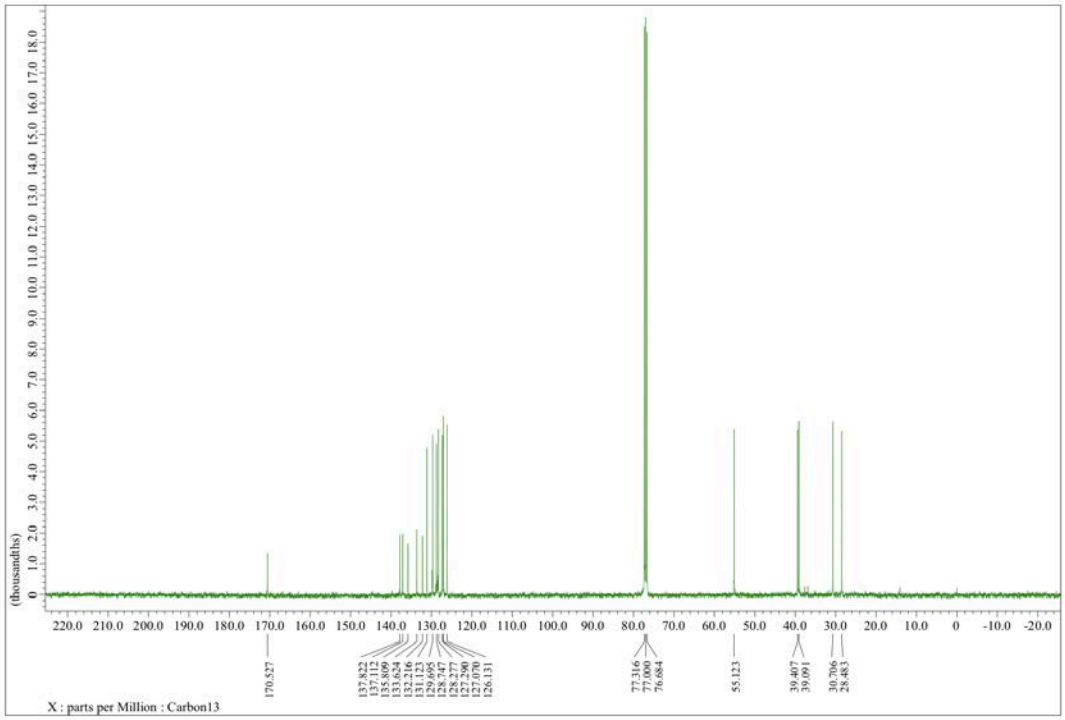
3p (Solvent: $CDCl_3$)



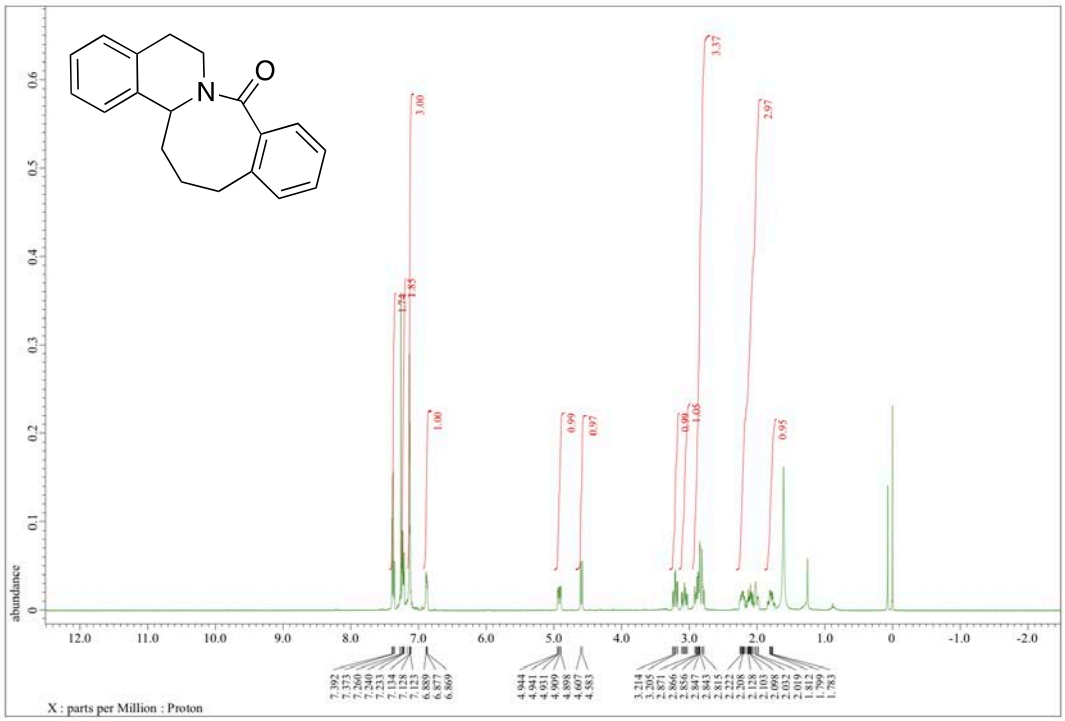


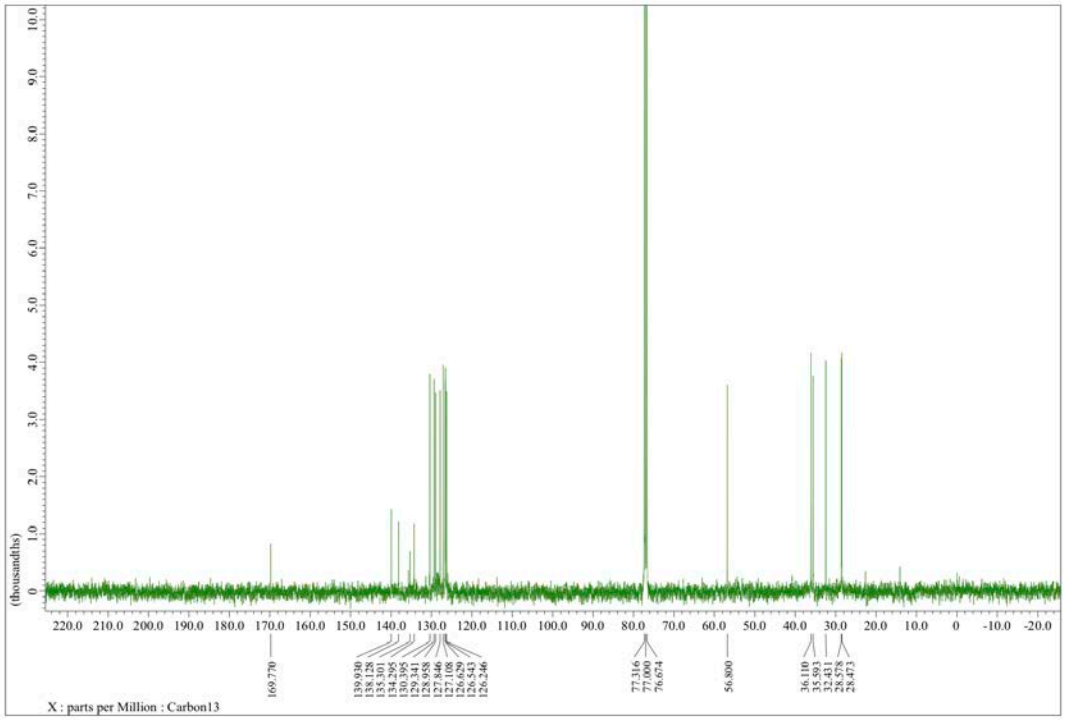
3r (Solvent: $CDCl_3$)



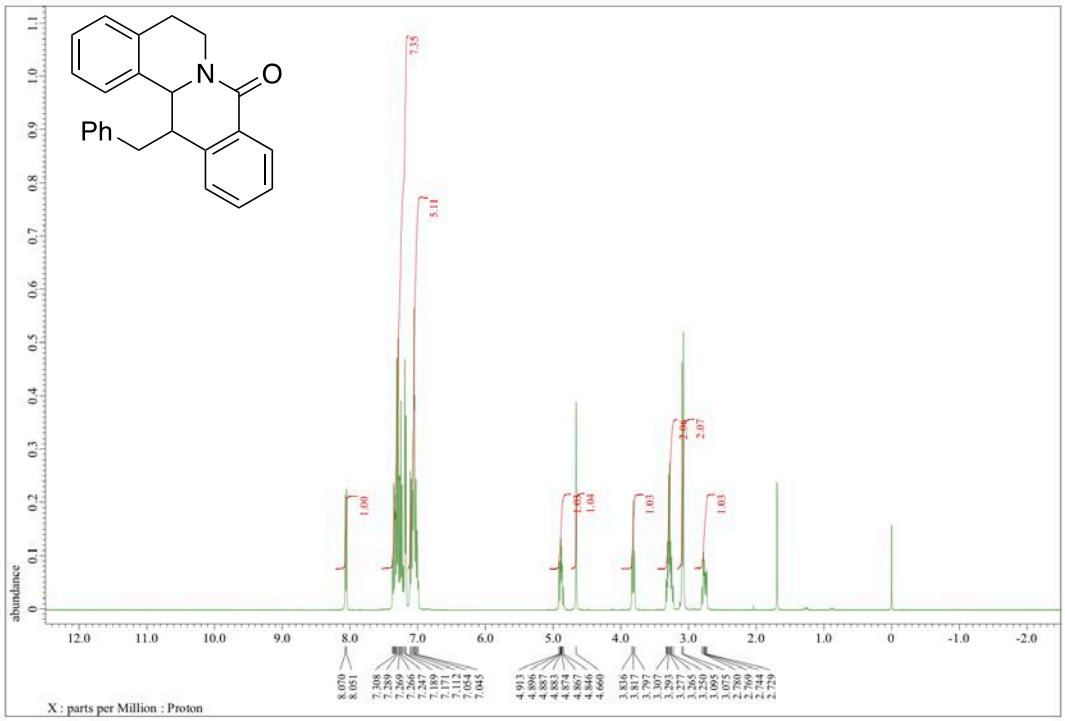


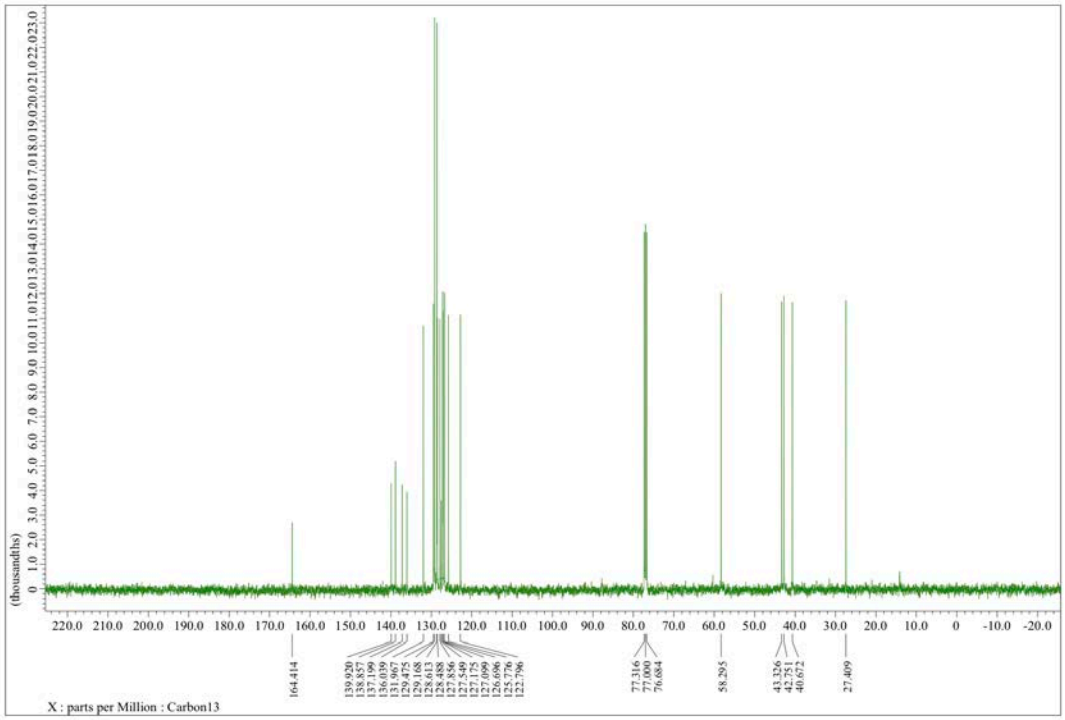
3s (Solvent: $CDCl_3$)



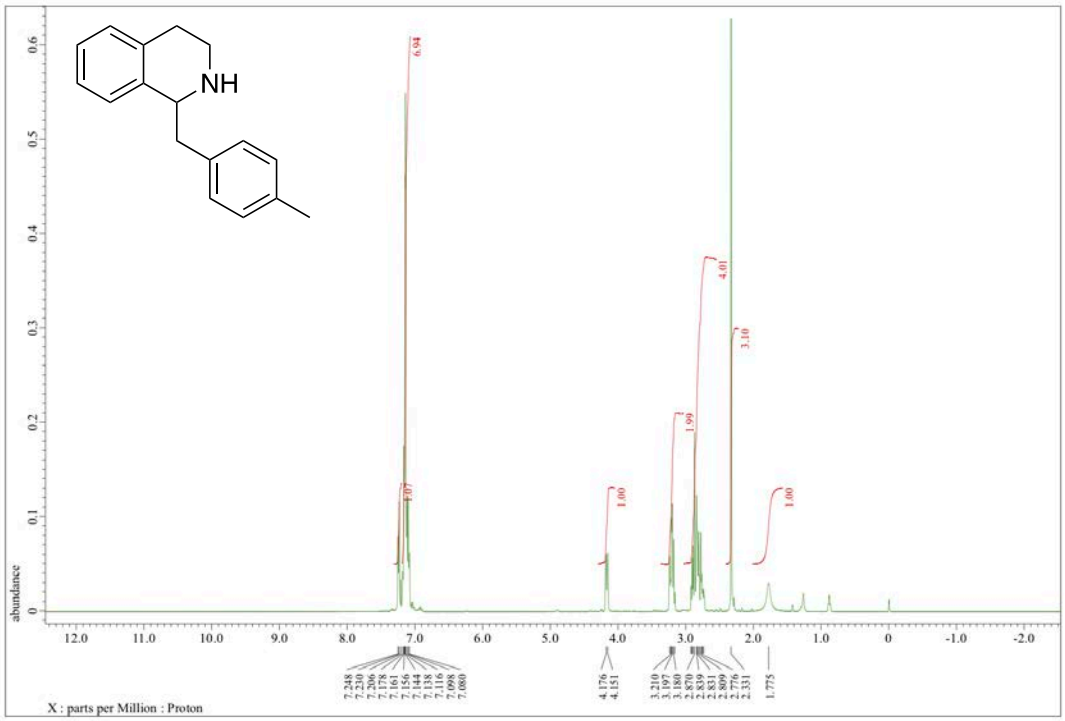


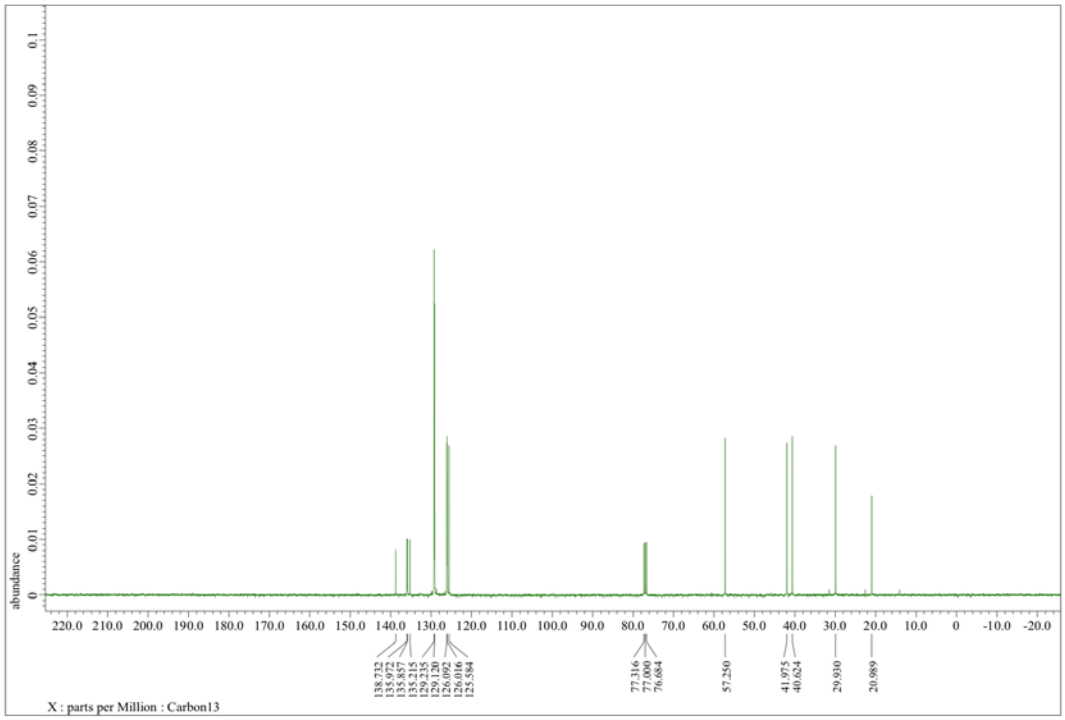
3t (Solvent: $CDCl_3$)



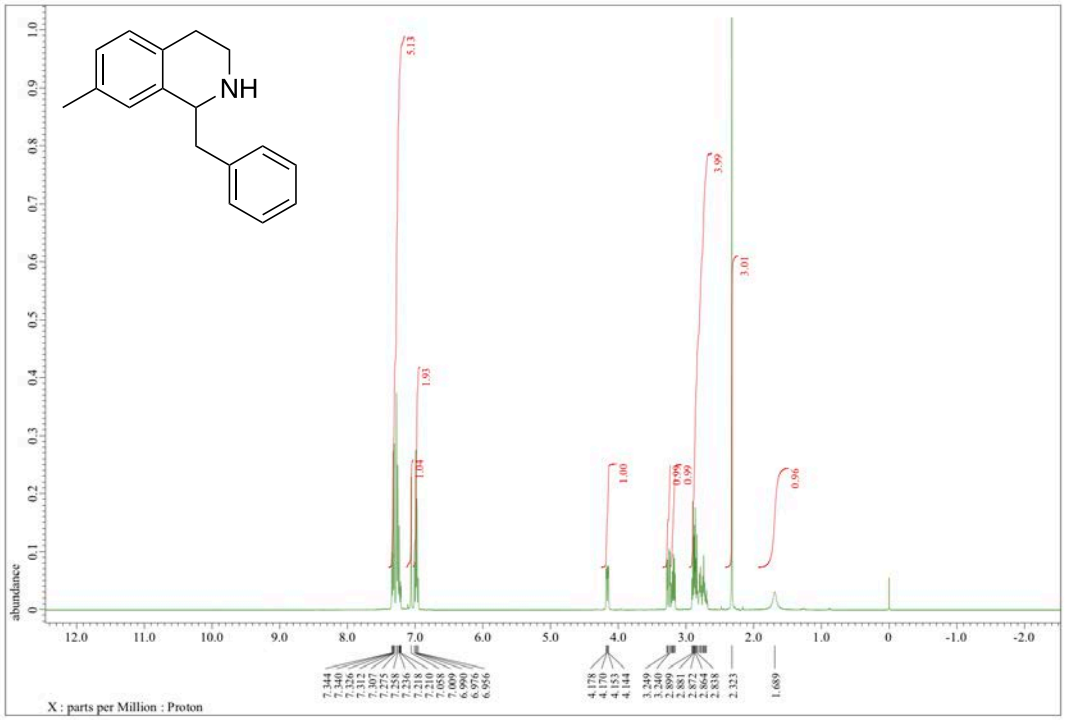


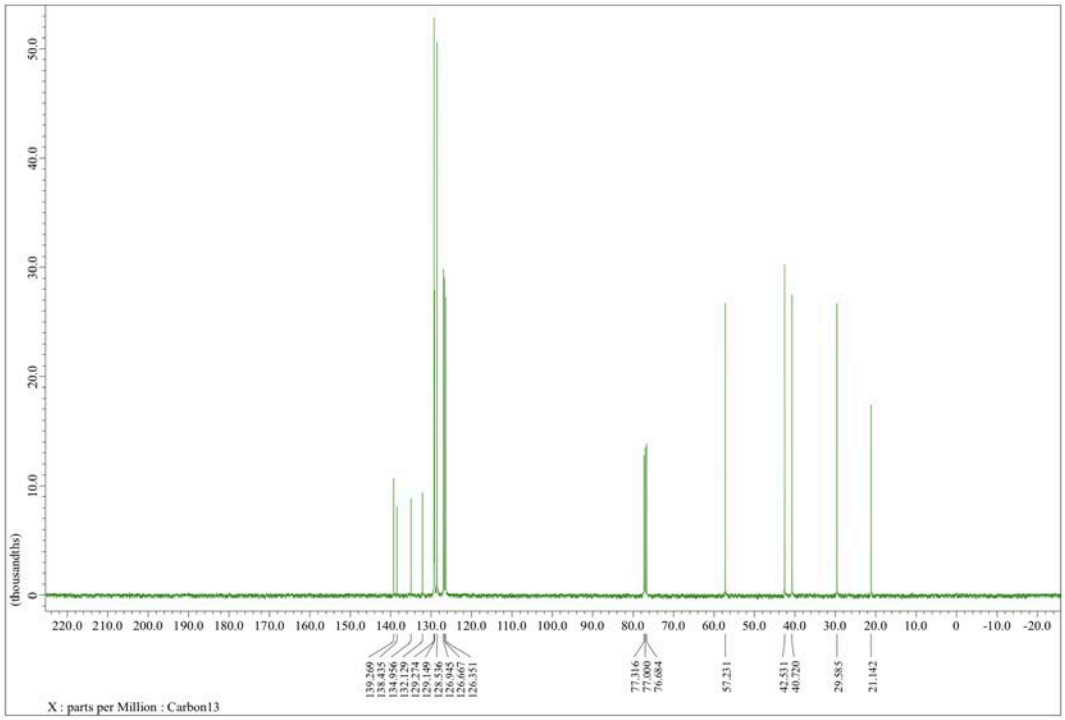
4j (Solvent: $CDCl_3$)



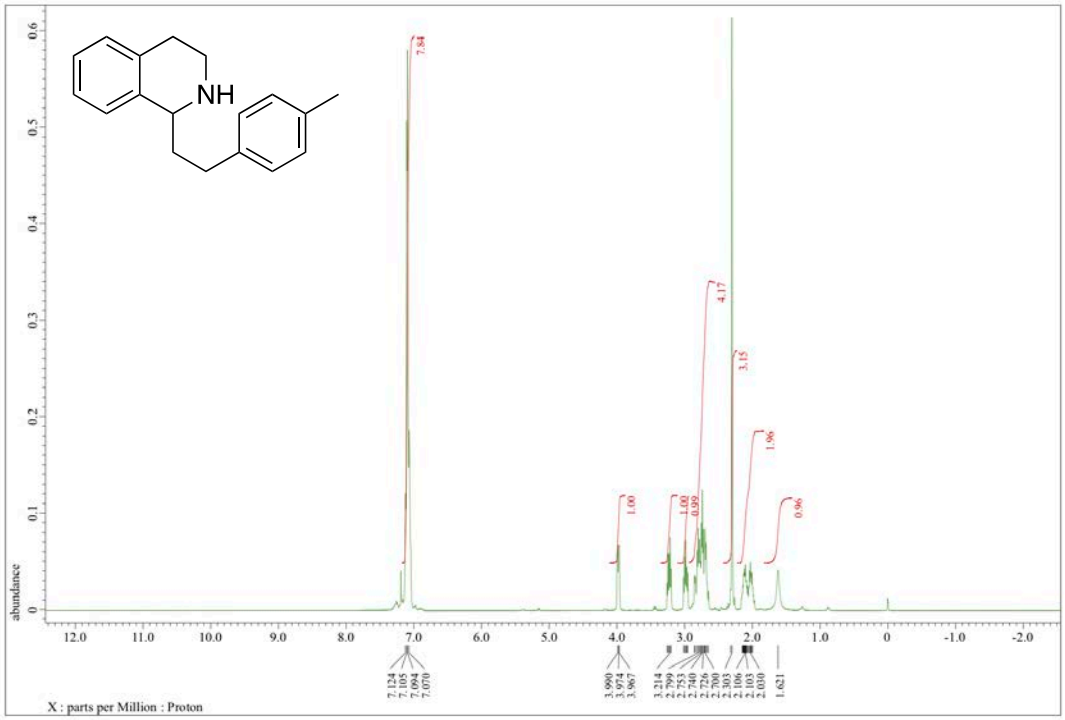


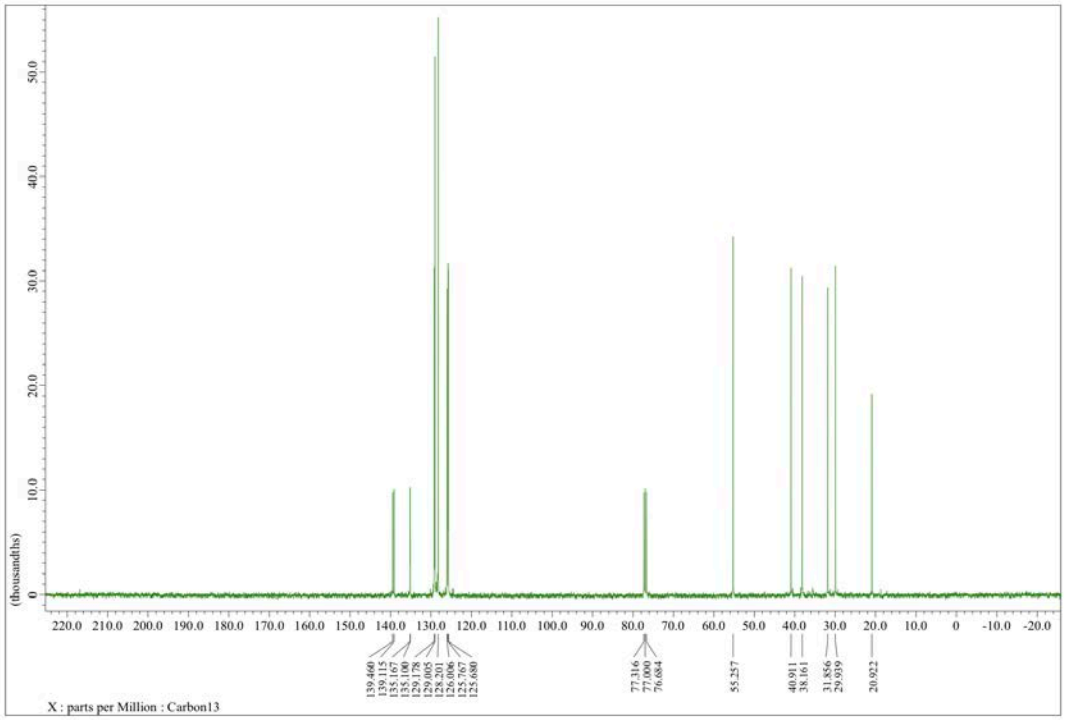
4l (Solvent: $CDCl_3$)



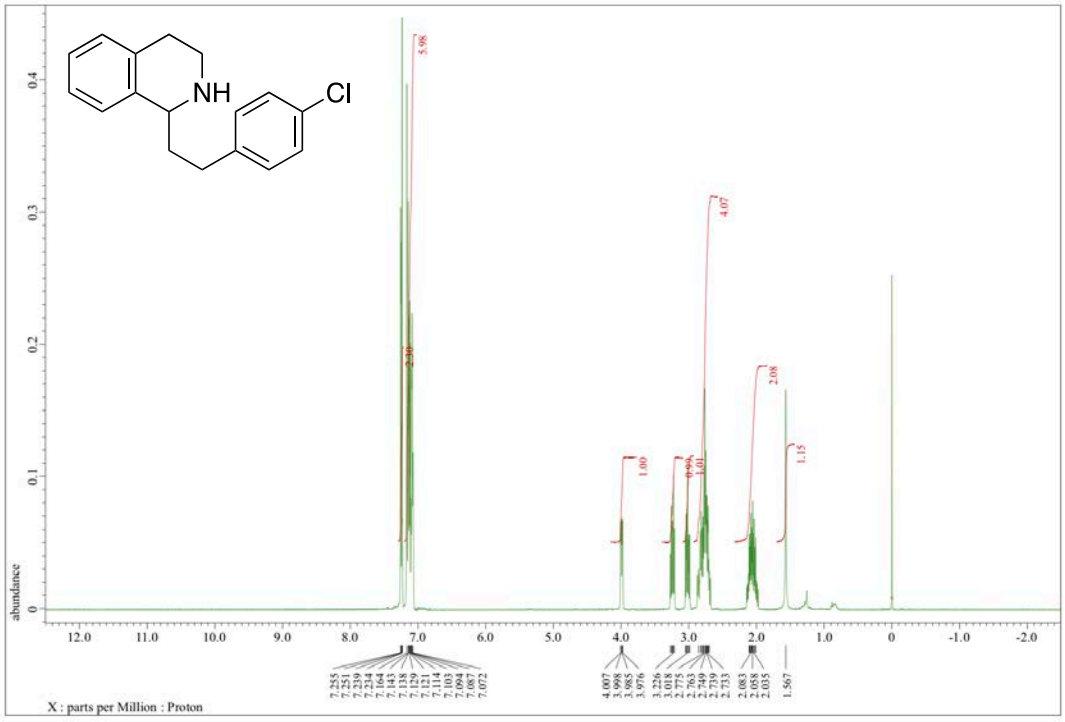


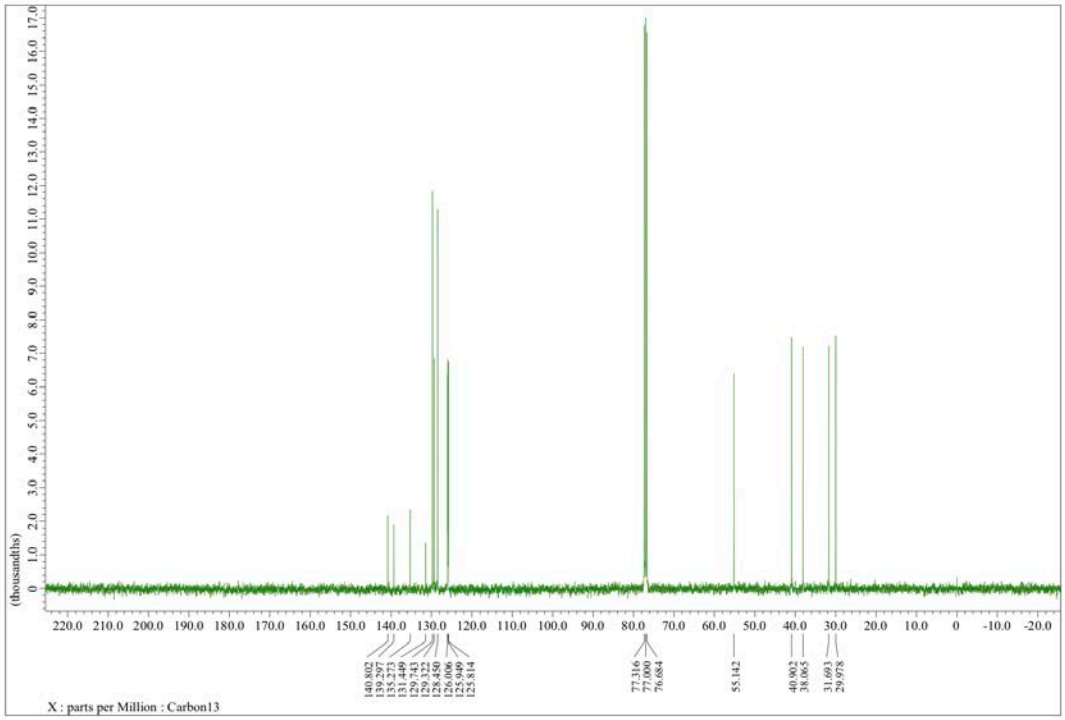
4o (Solvent: $CDCl_3$)



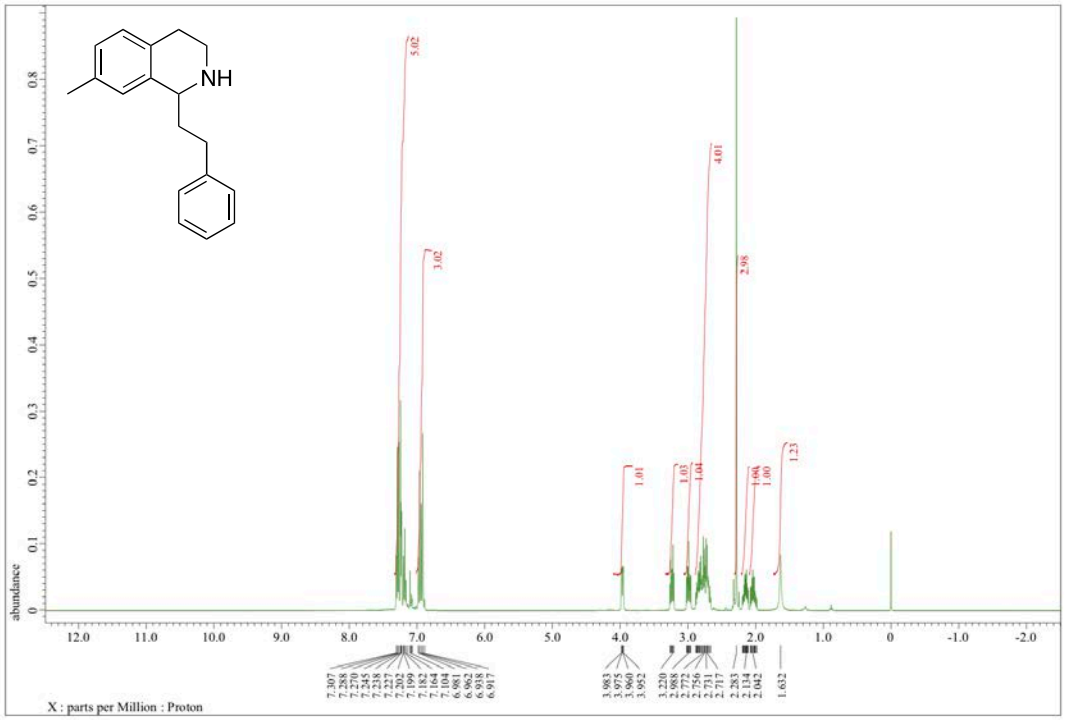


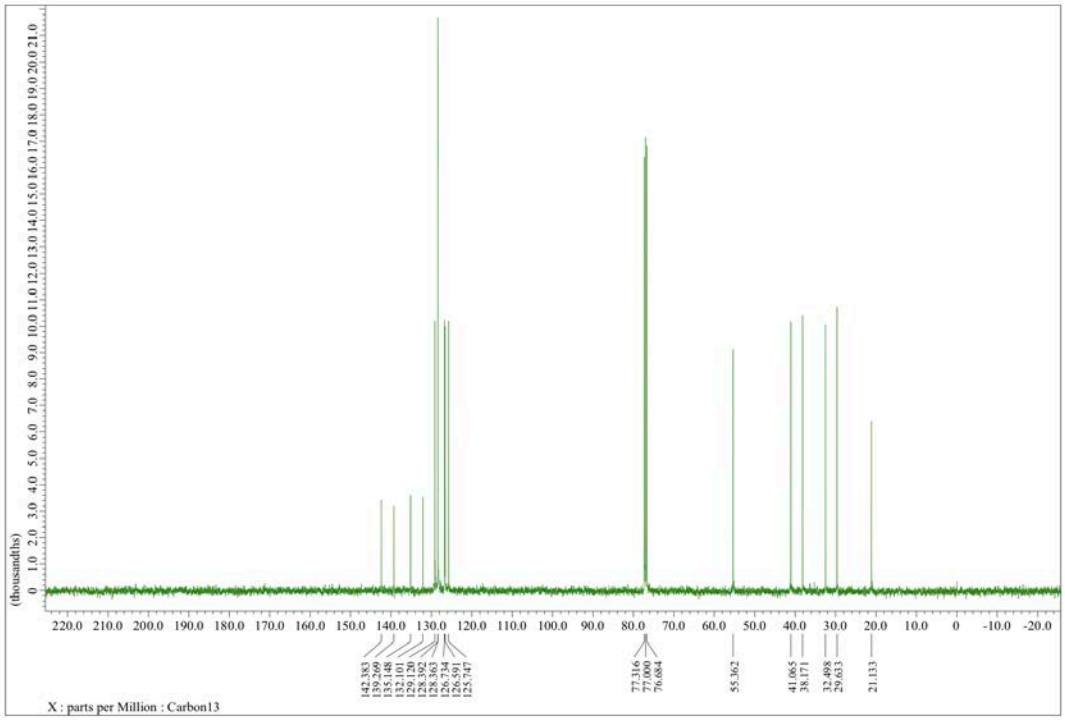
4p (Solvent: $CDCl_3$)



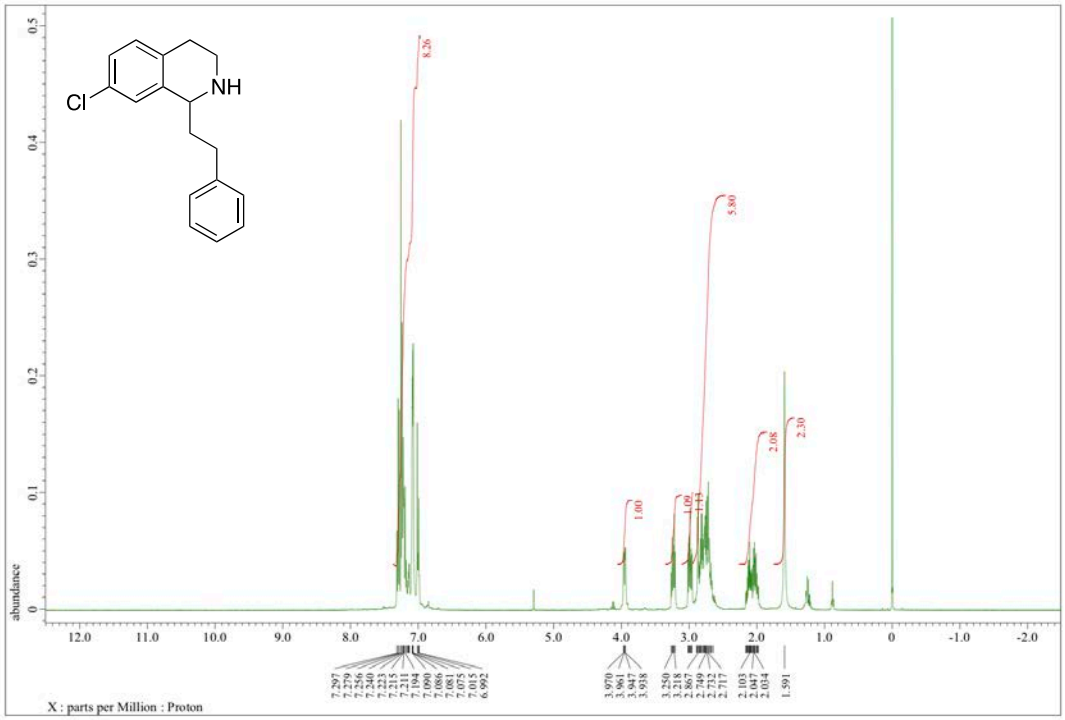


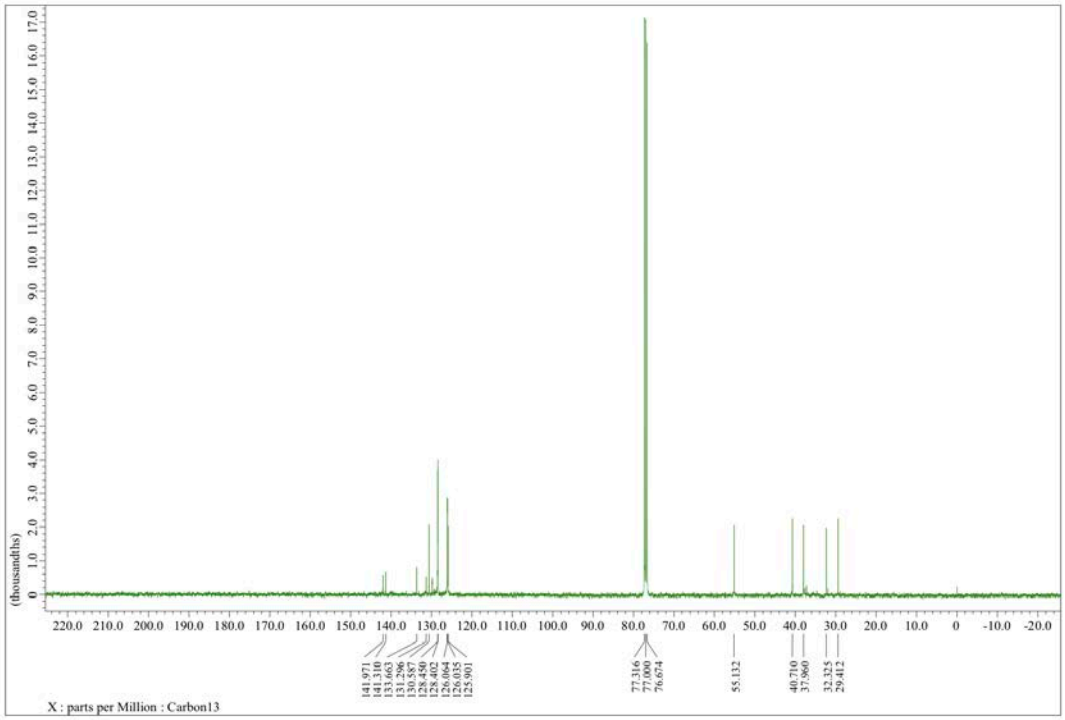
4q (Solvent: $CDCl_3$)



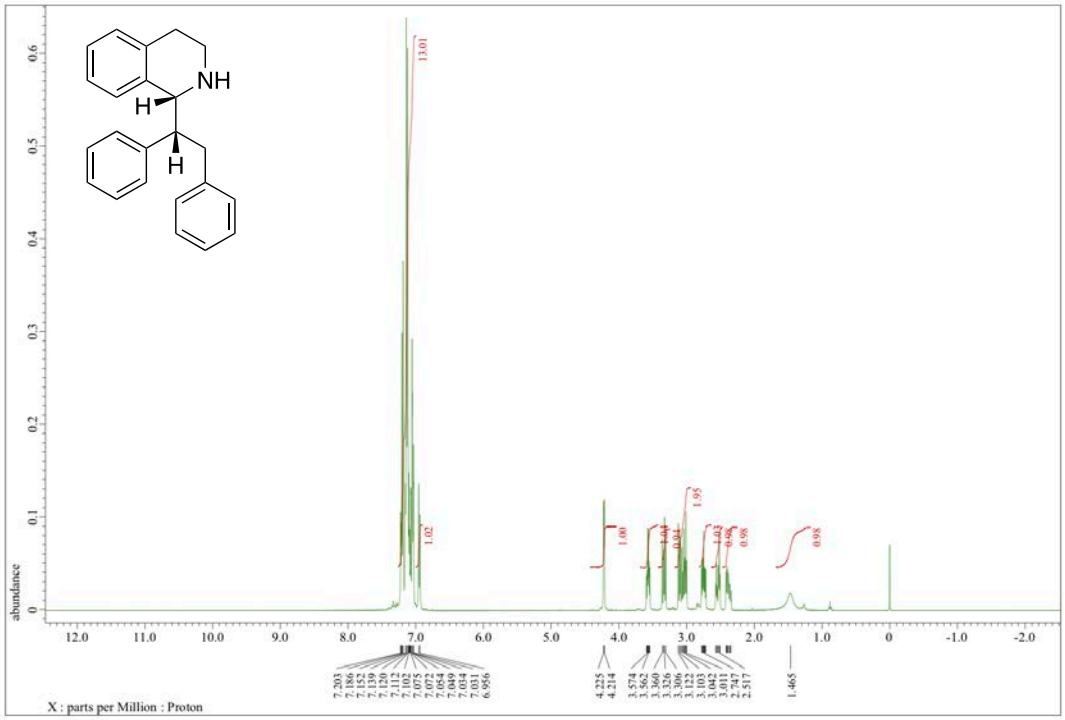


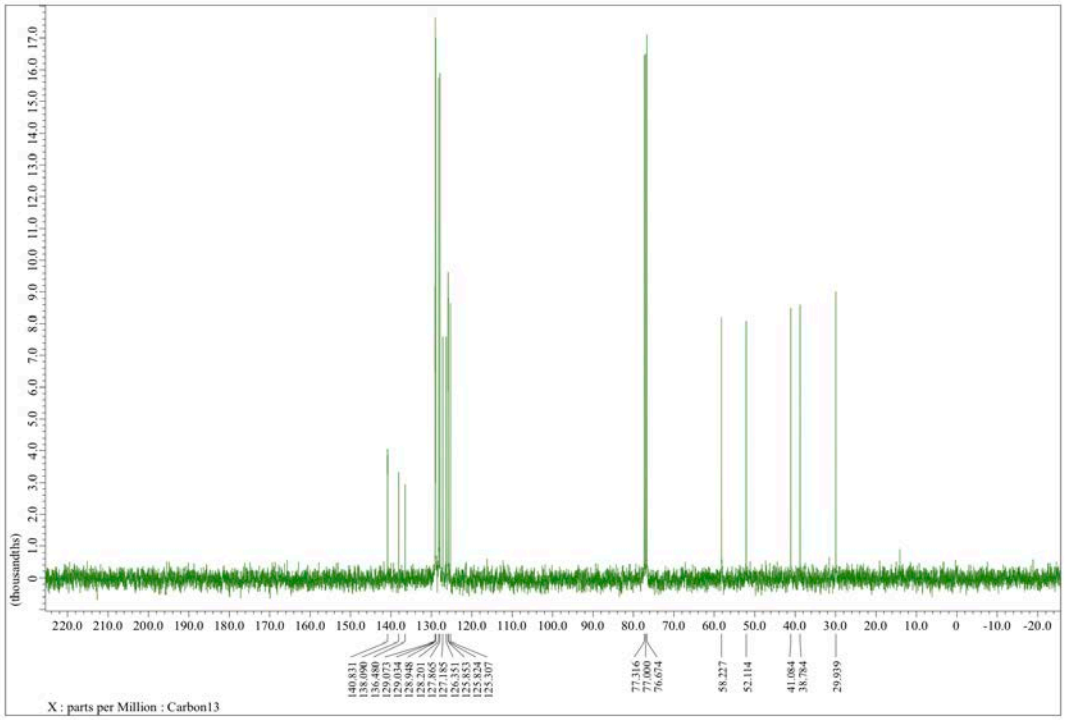
4r (Solvent: $CDCl_3$)



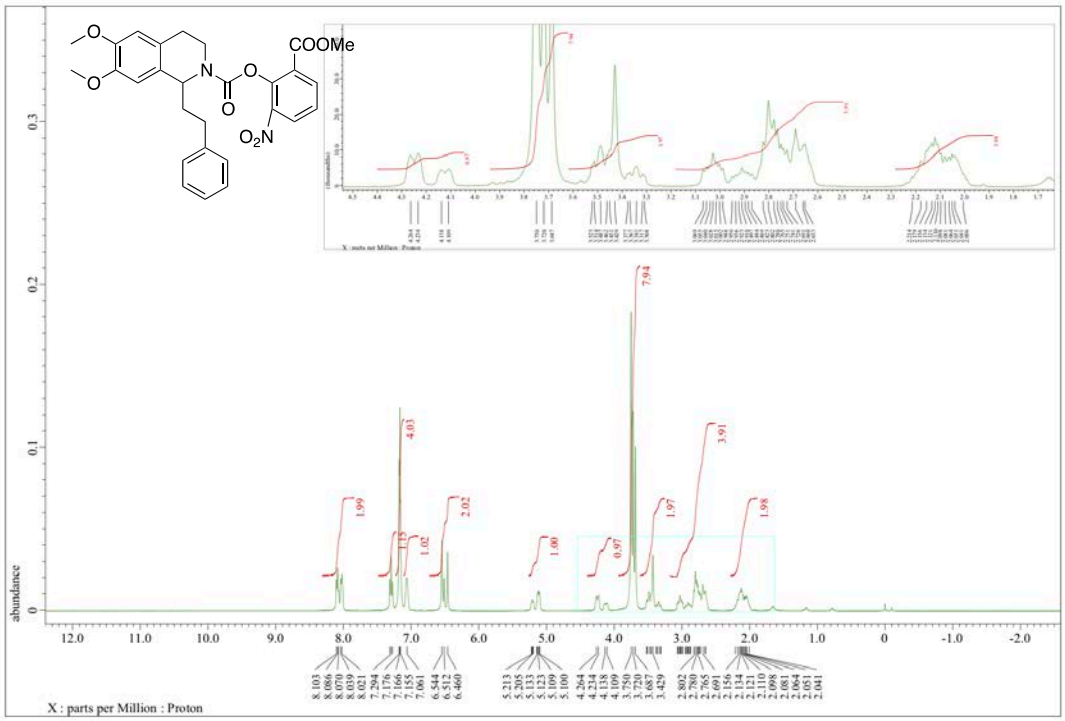


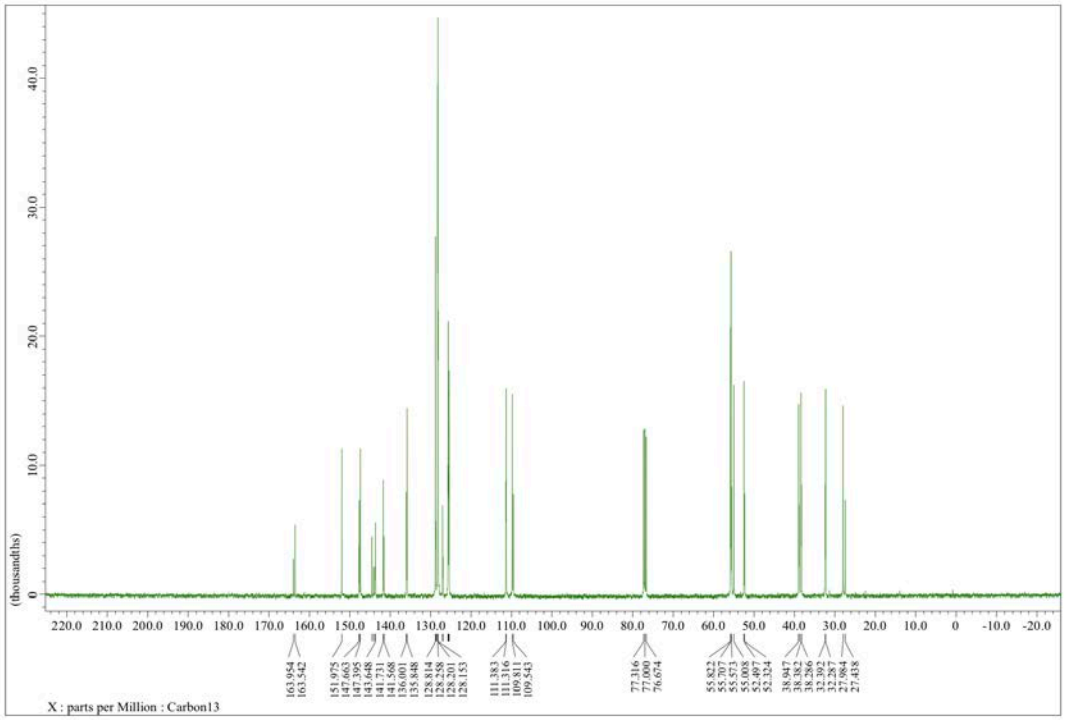
4t (Solvent: $CDCl_3$)



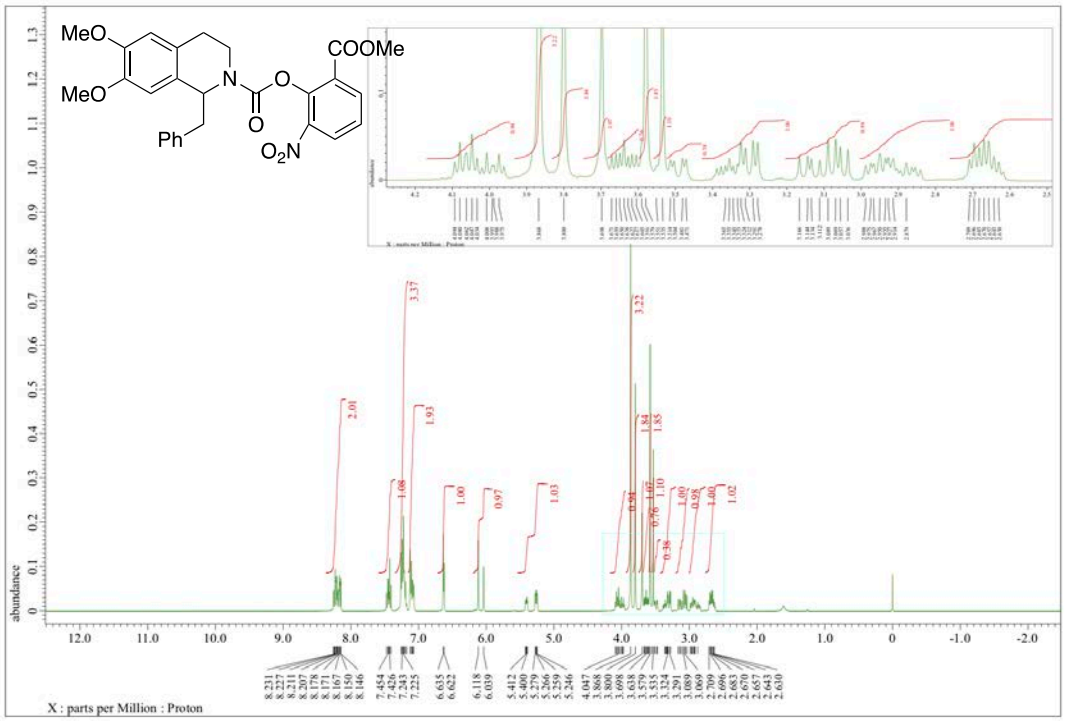


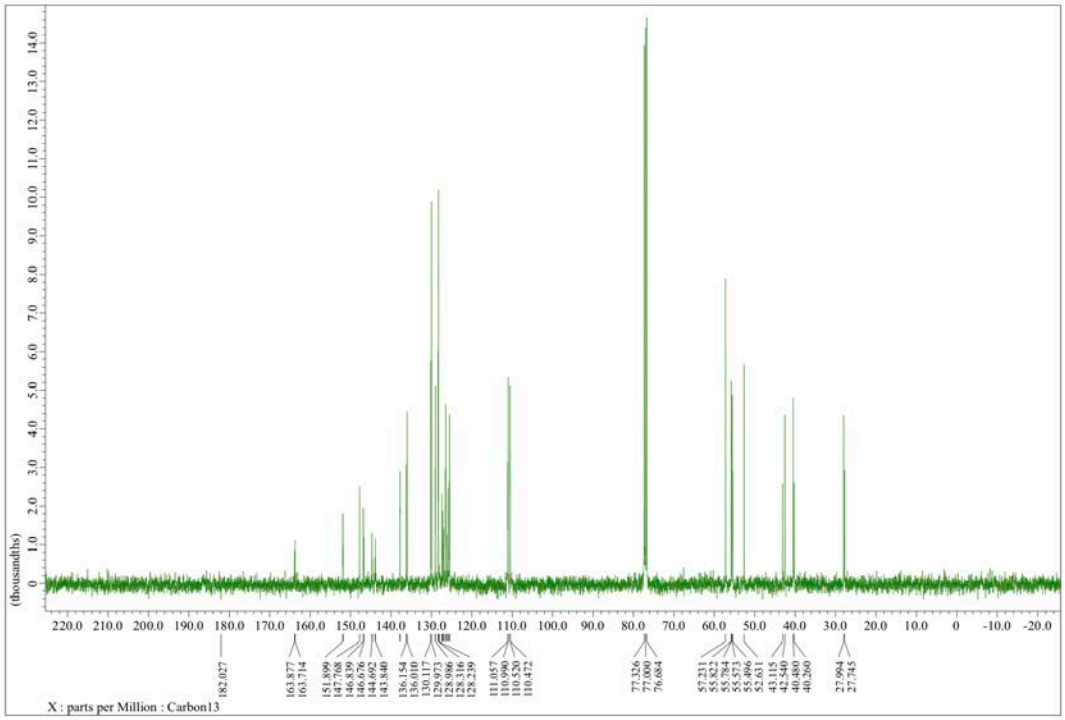
6a (Solvent: $CDCl_3$)



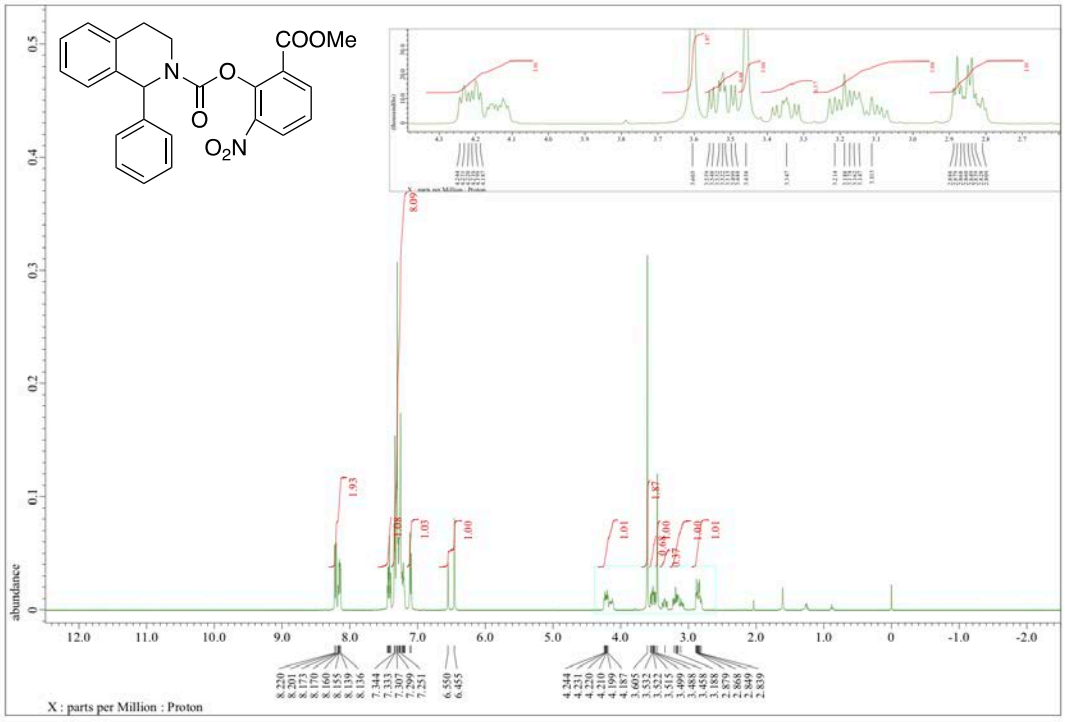


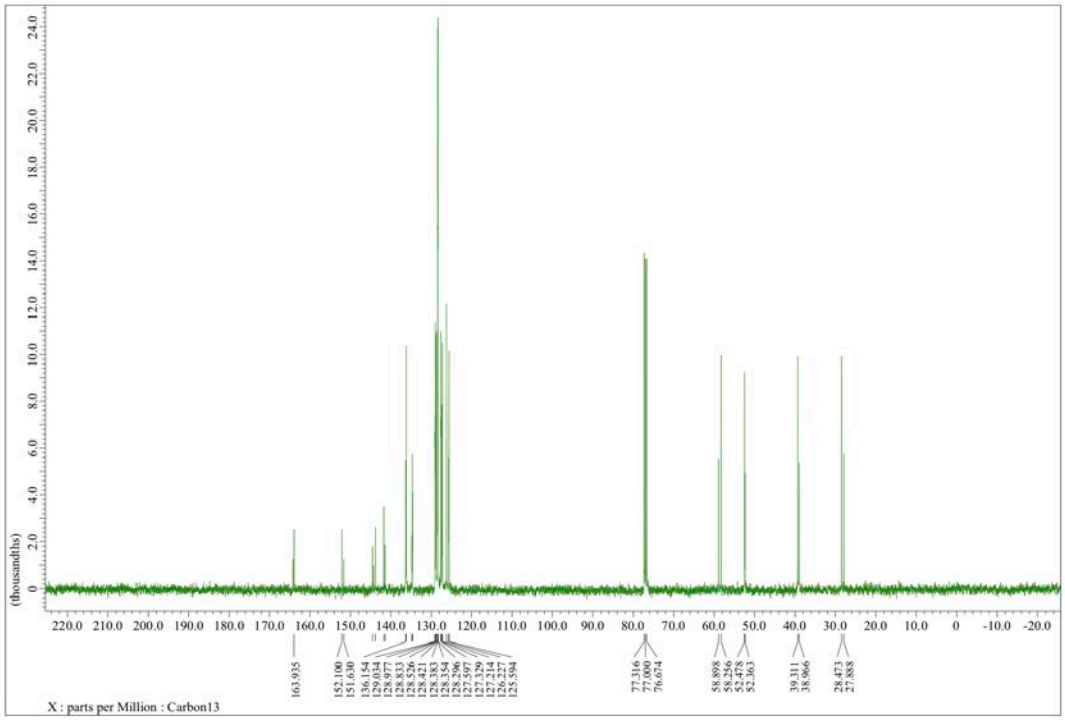
6b (Solvent: $CDCl_3$)



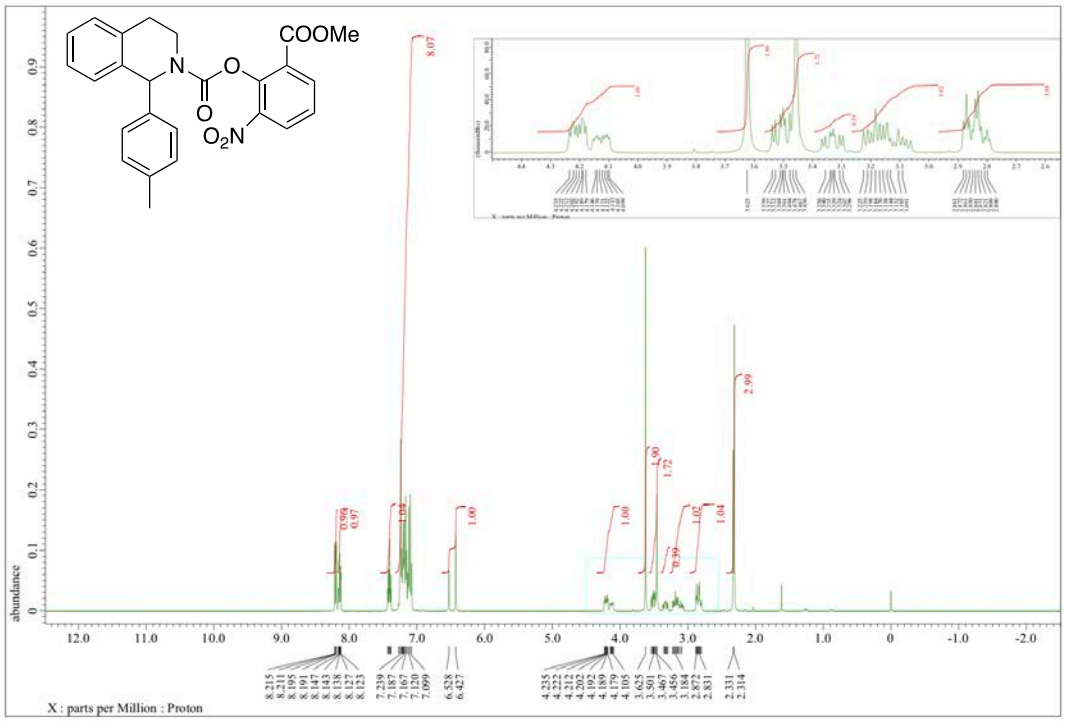


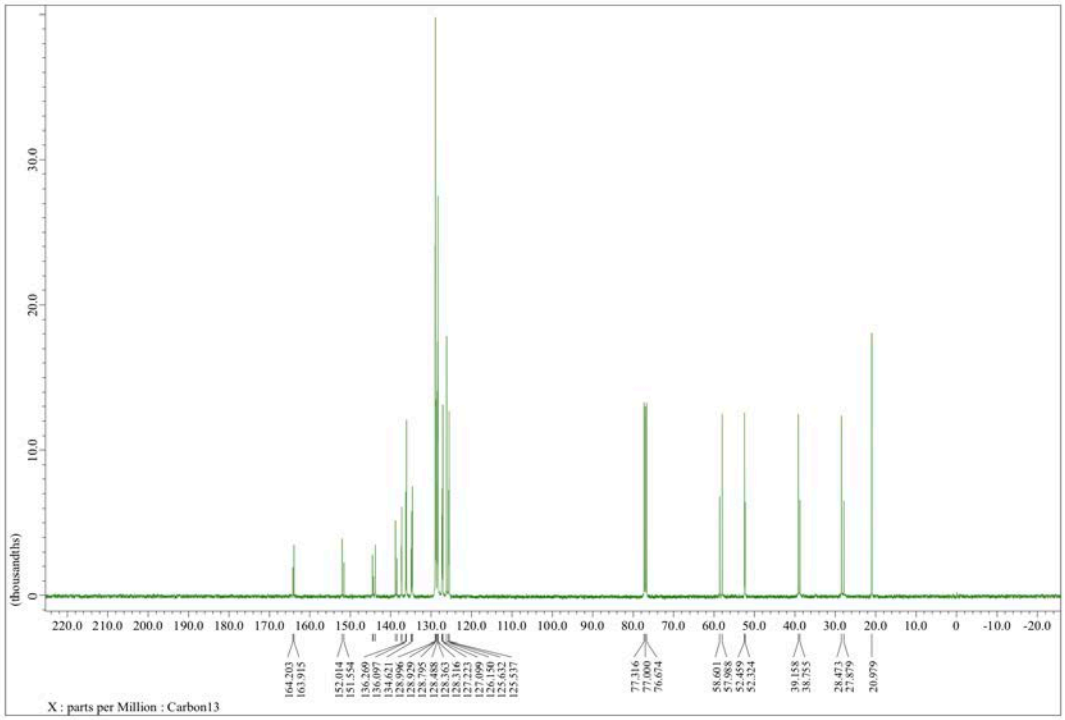
6c (Solvent: $CDCl_3$)



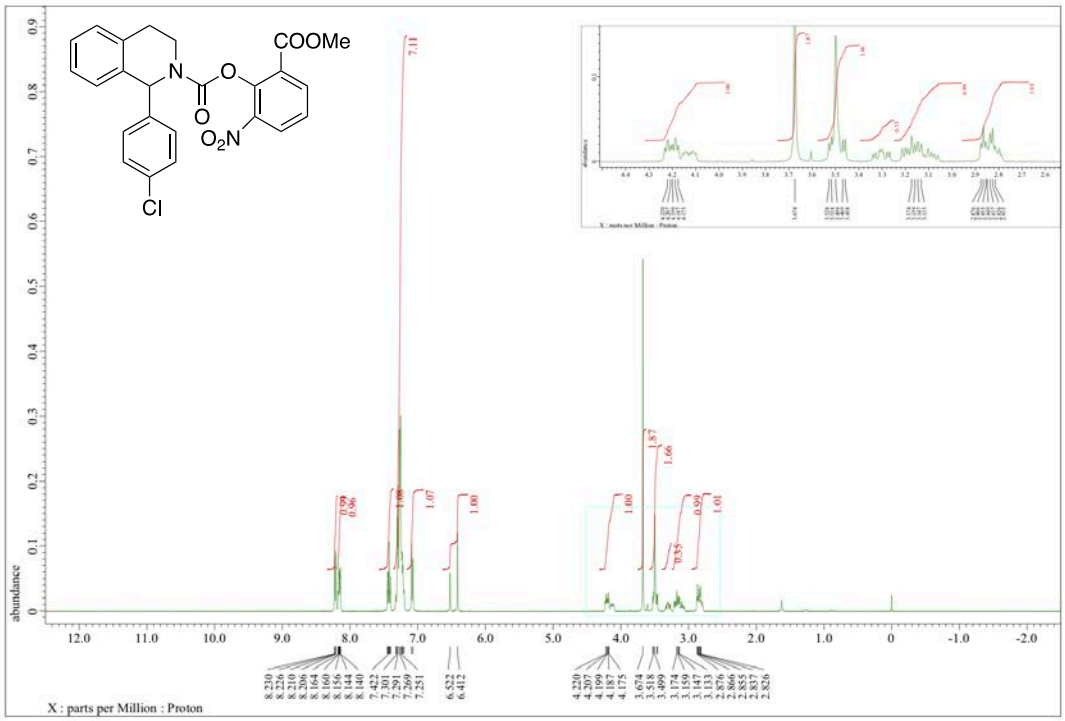


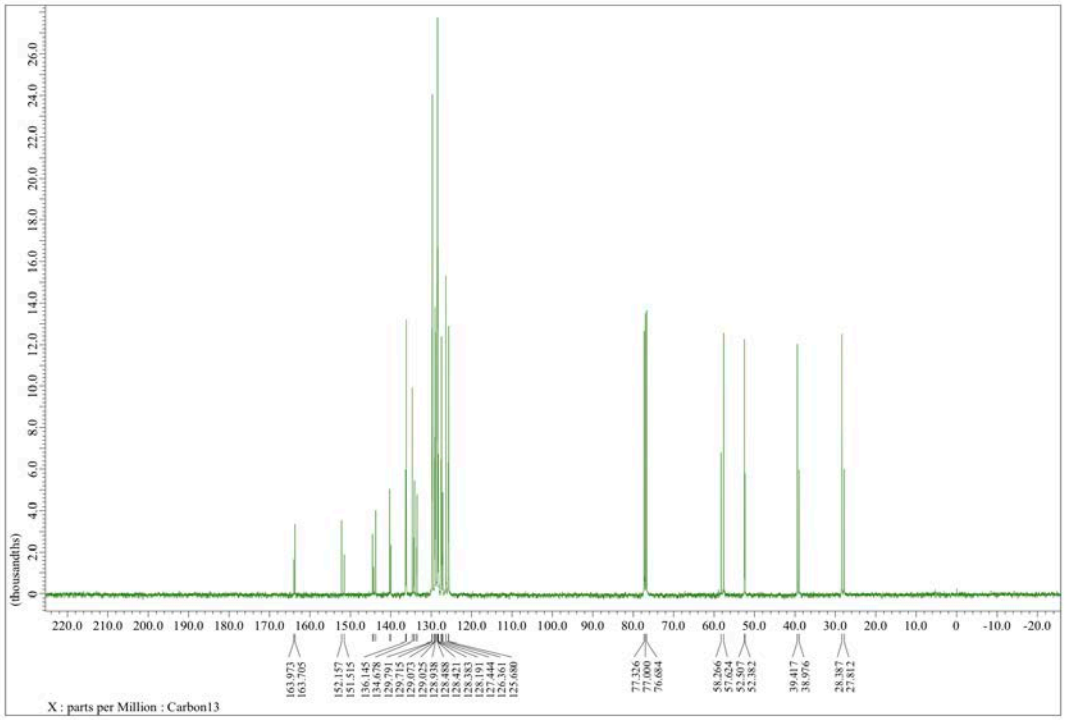
6d (Solvent: $CDCl_3$)



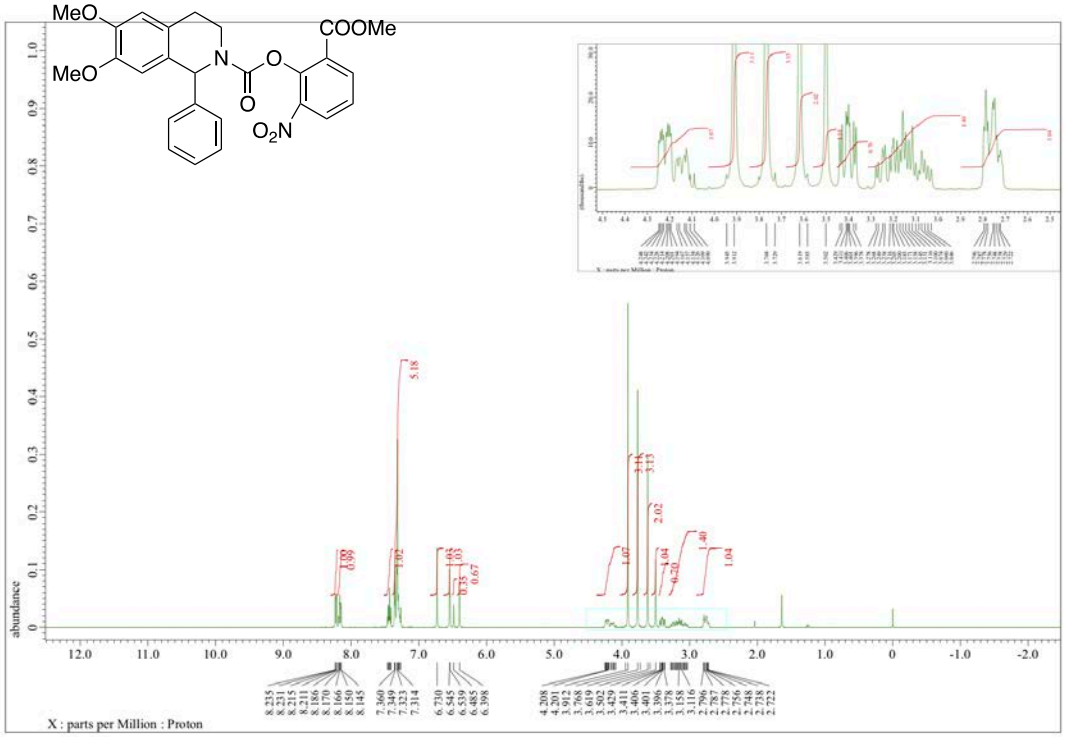


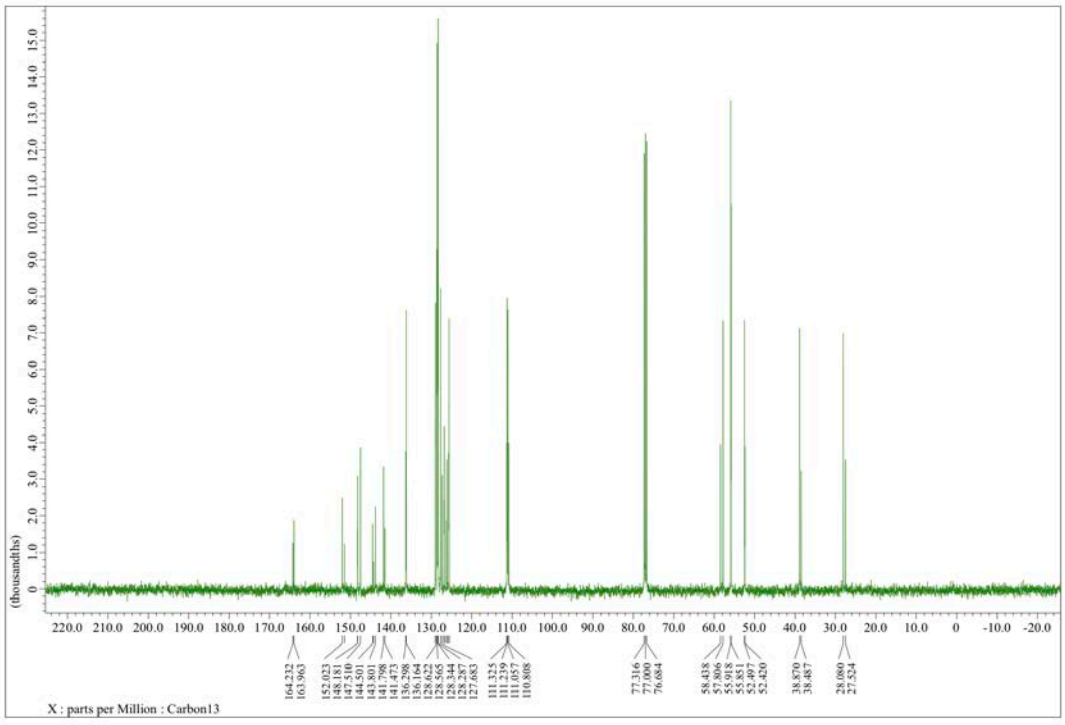
6e (Solvent: $CDCl_3$)



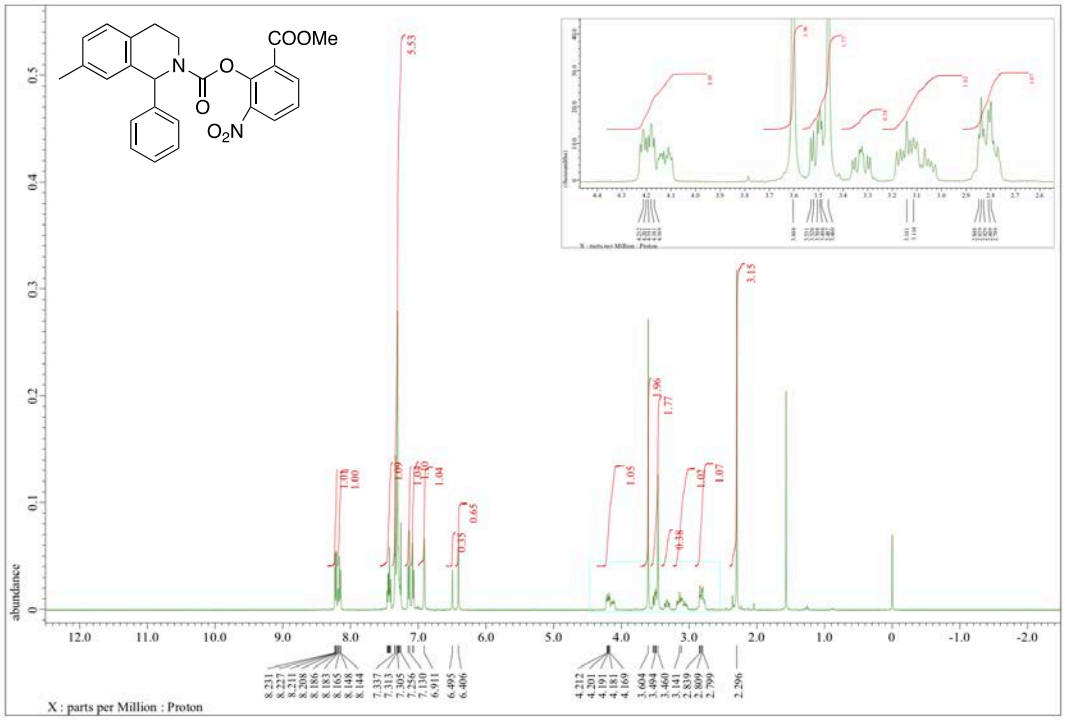


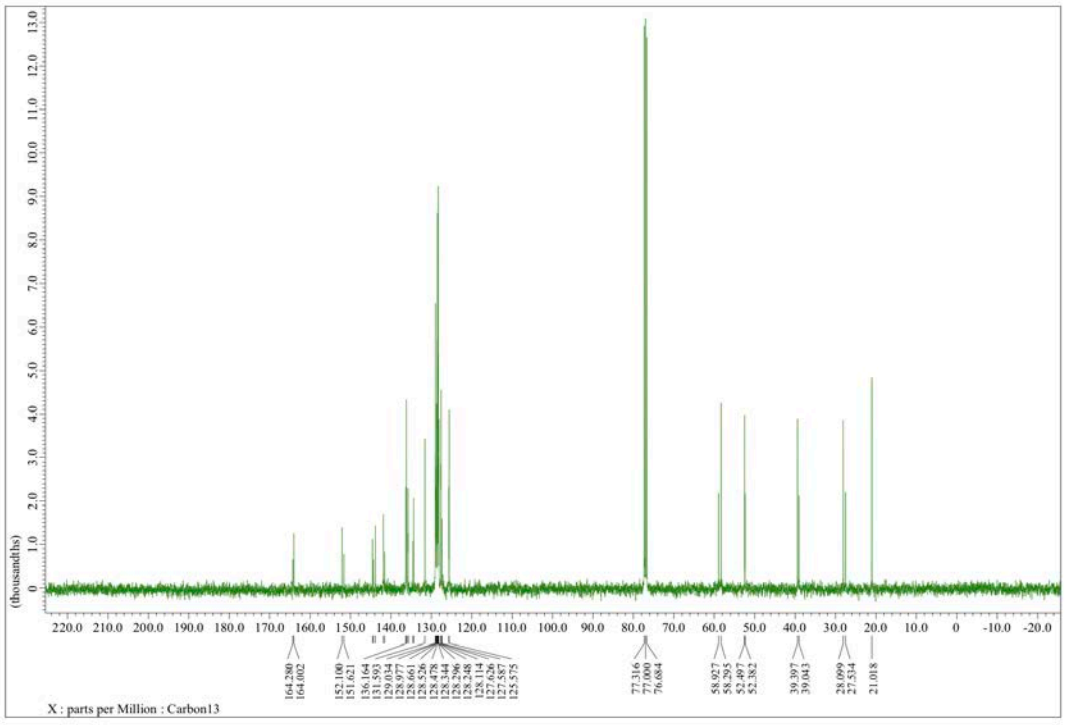
6f (Solvent: $CDCl_3$)



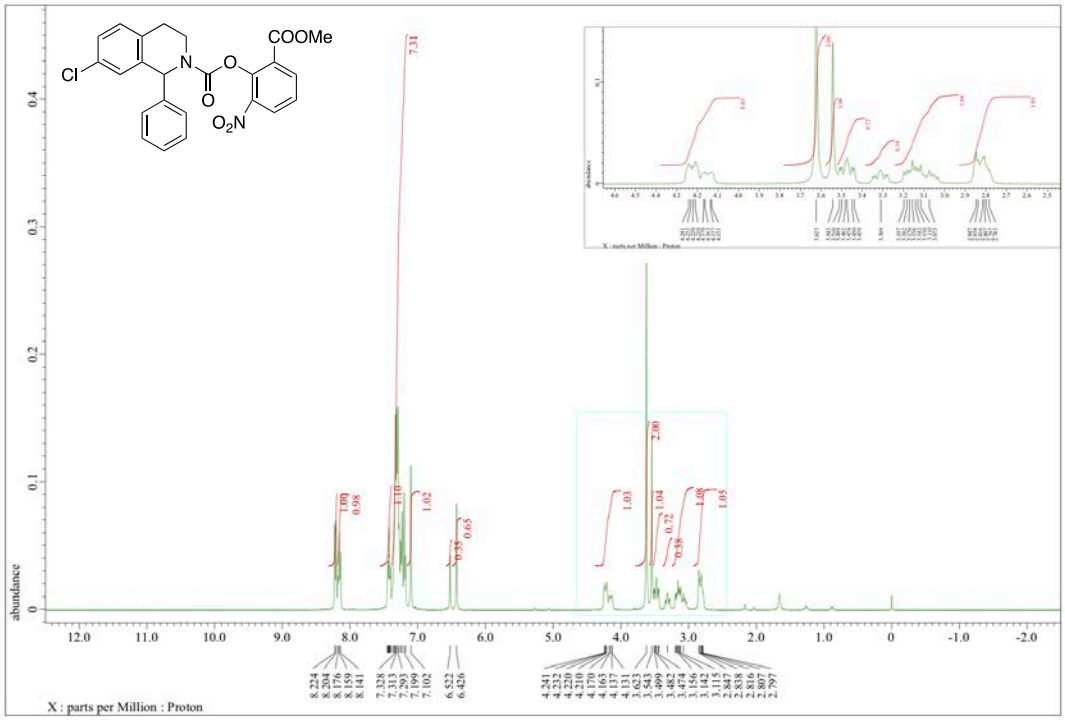


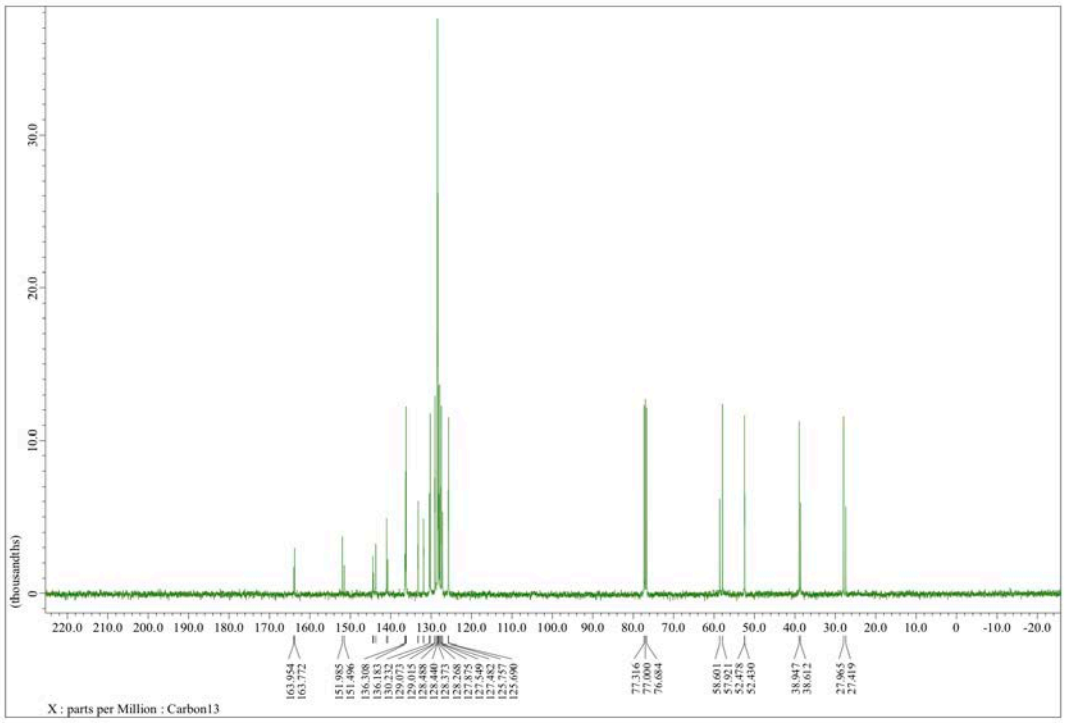
6g (Solvent: $CDCl_3$)



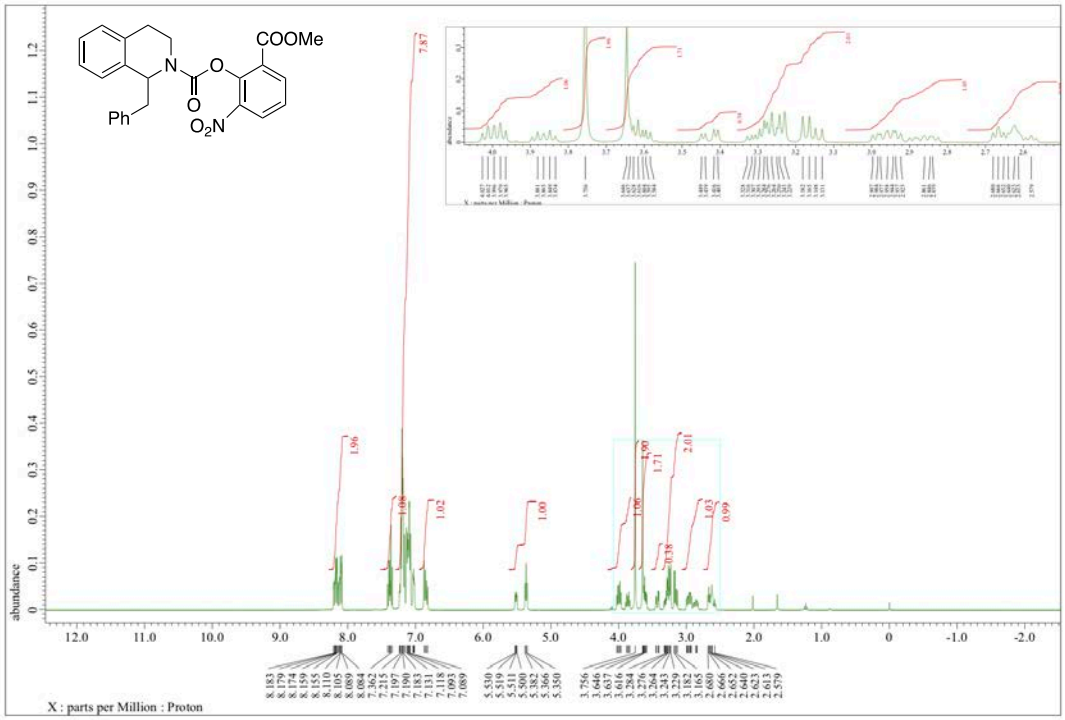


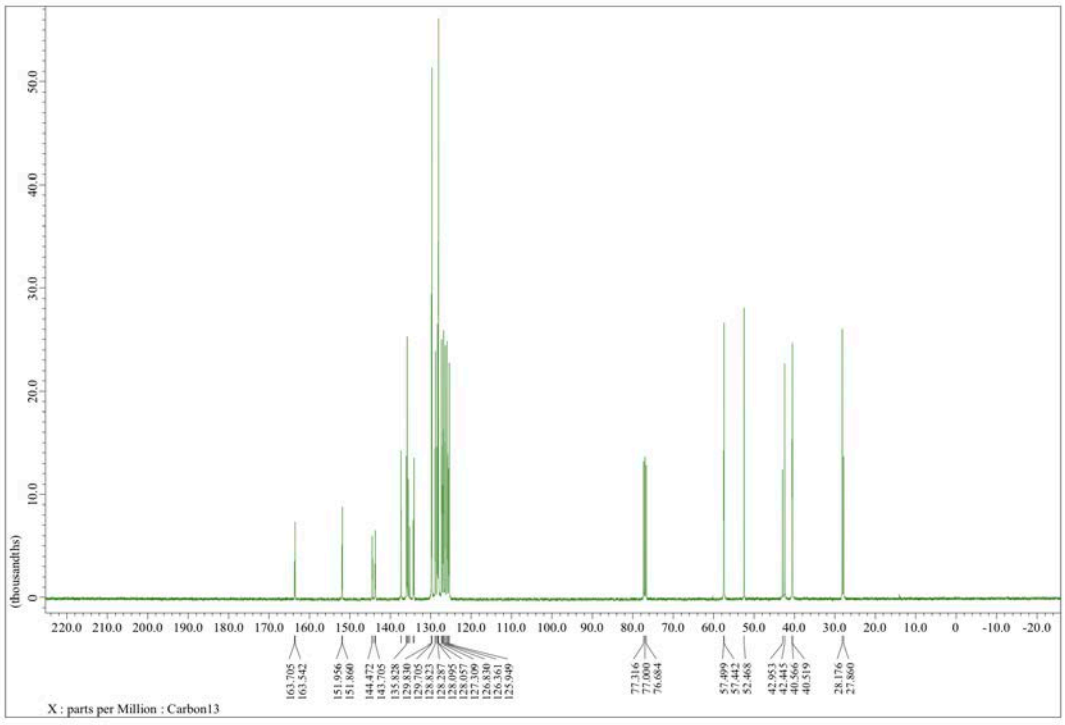
6h (Solvent: $CDCl_3$)



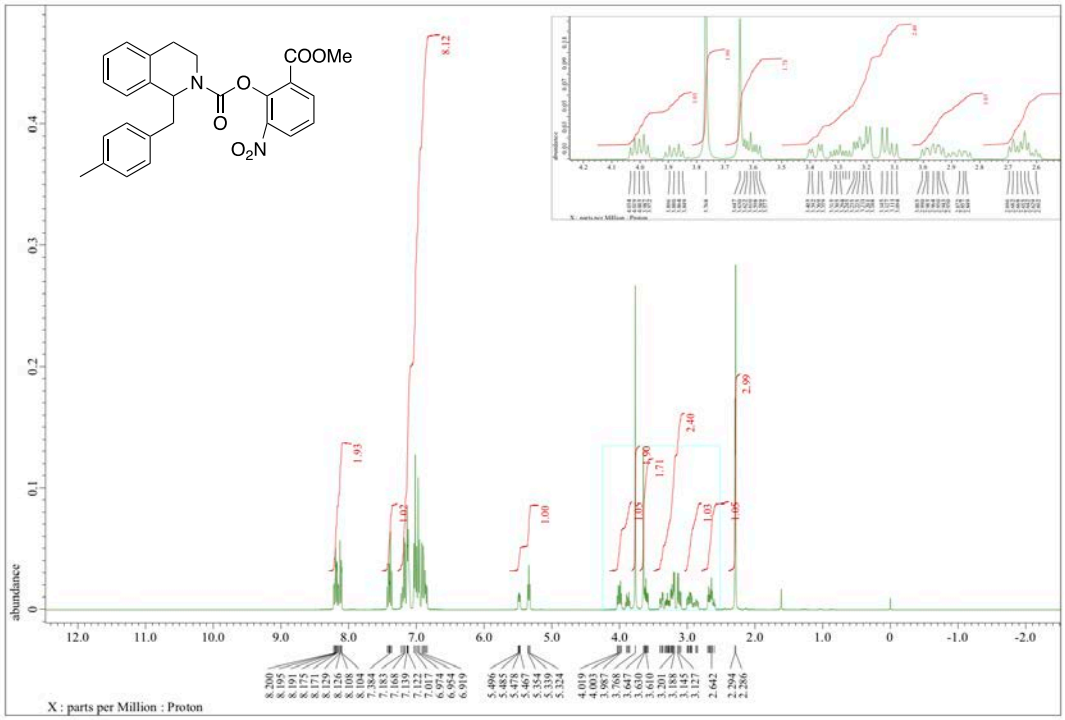


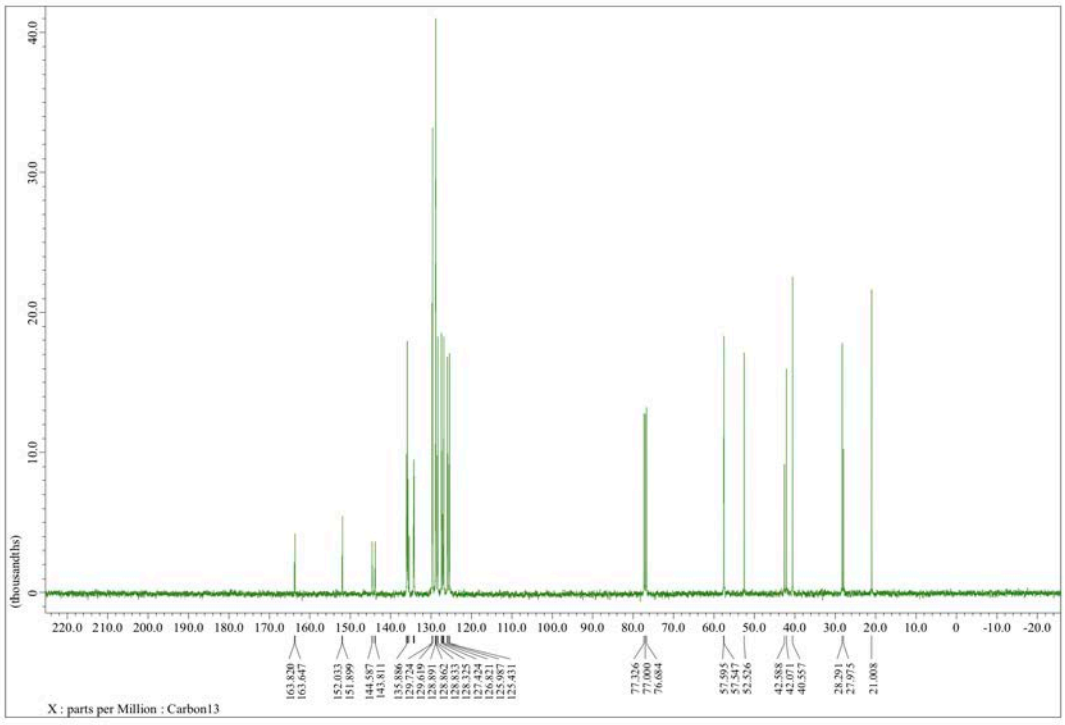
6i (Solvent: $CDCl_3$)



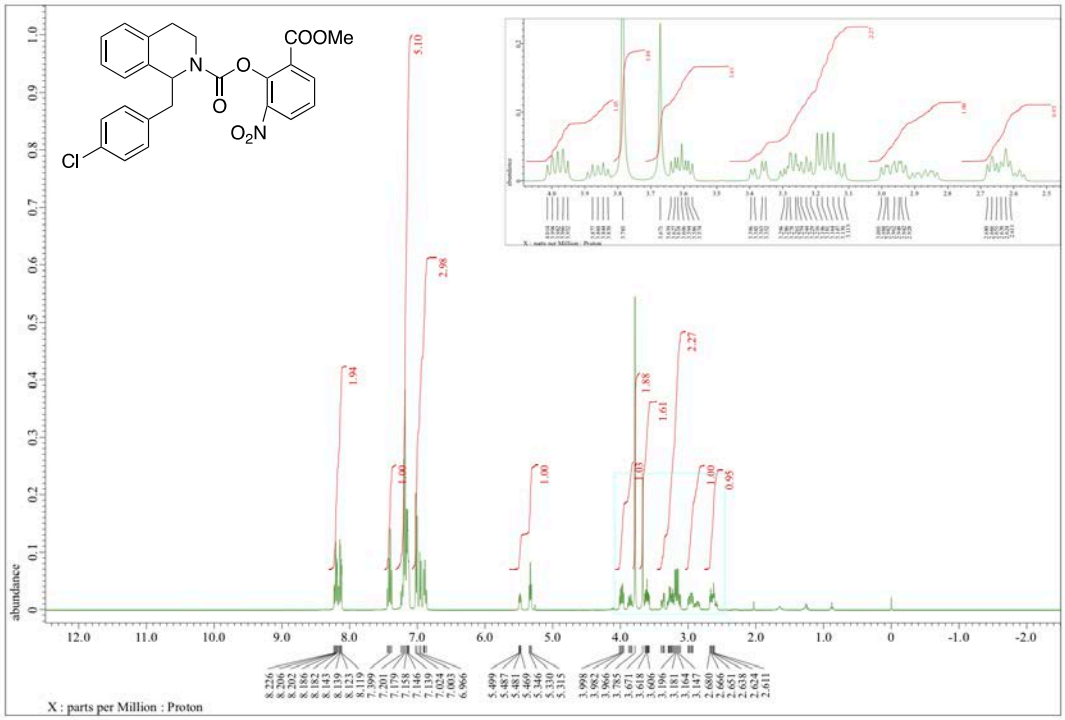


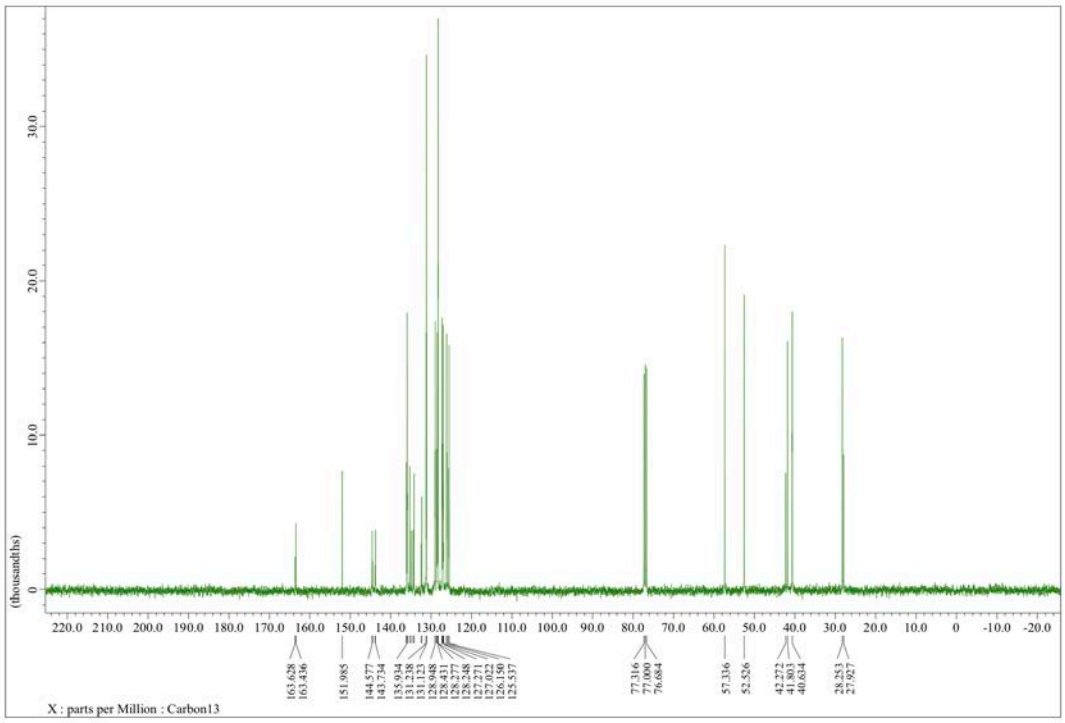
6j (Solvent: $CDCl_3$)



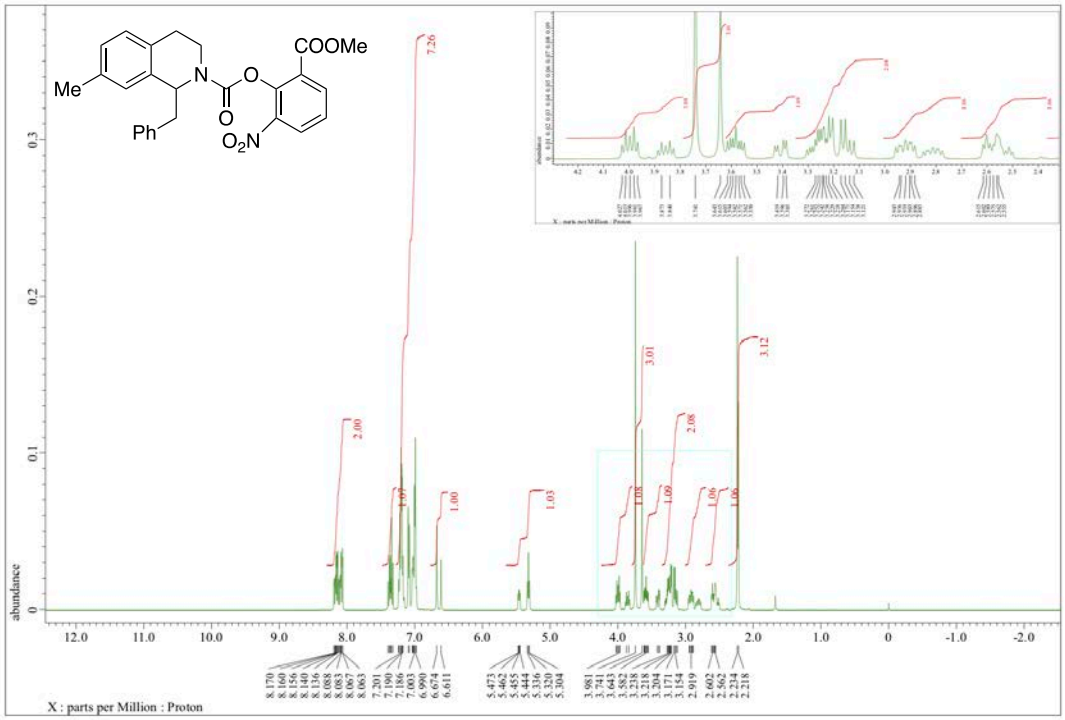


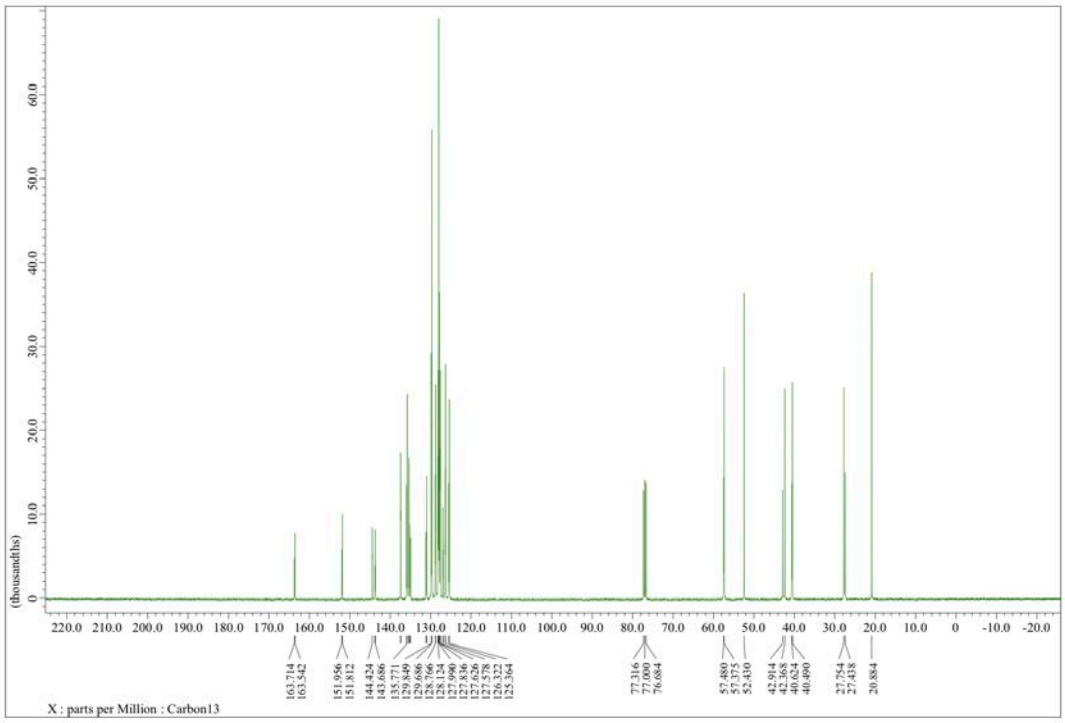
6k (Solvent: $CDCl_3$)



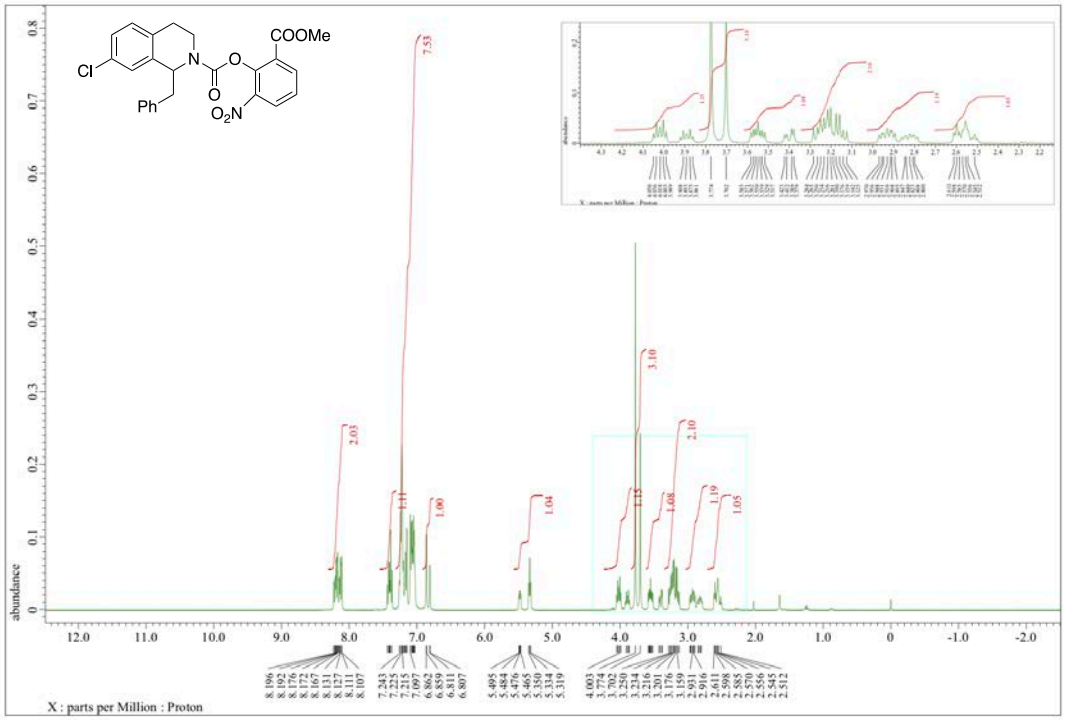


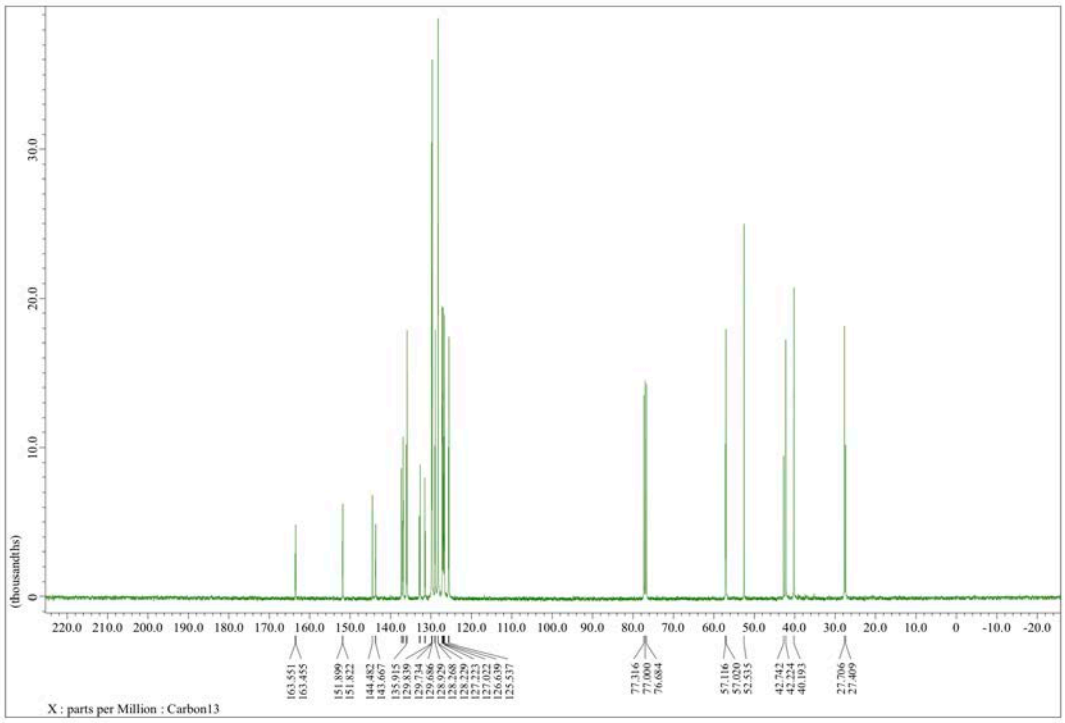
6l (Solvent: $CDCl_3$)



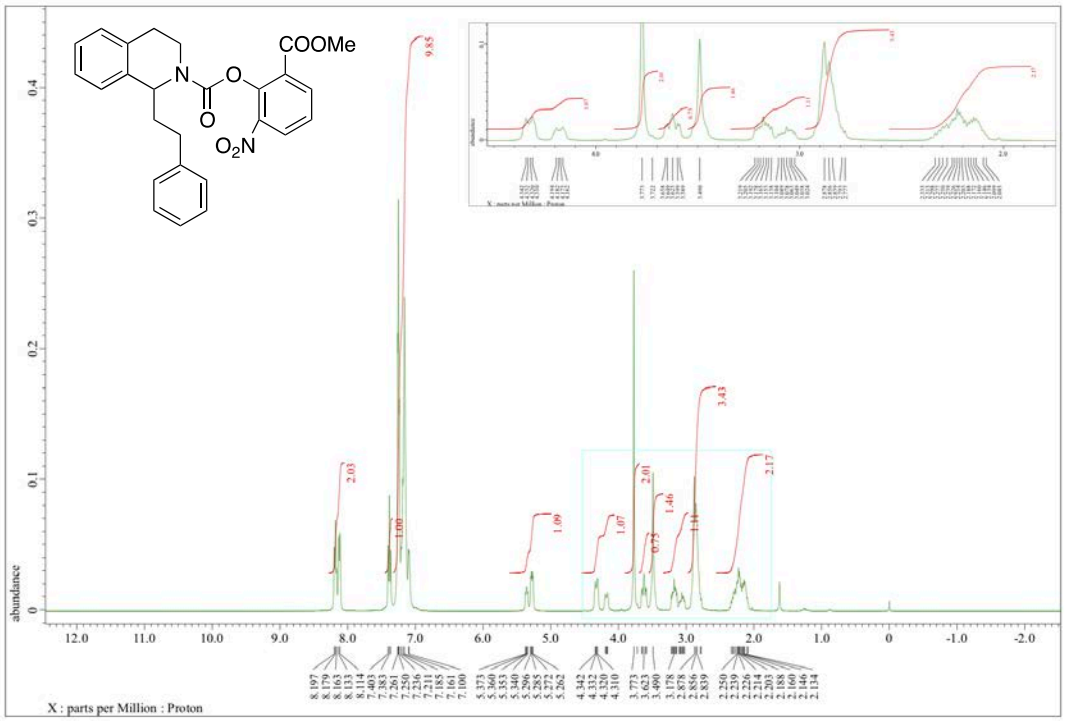


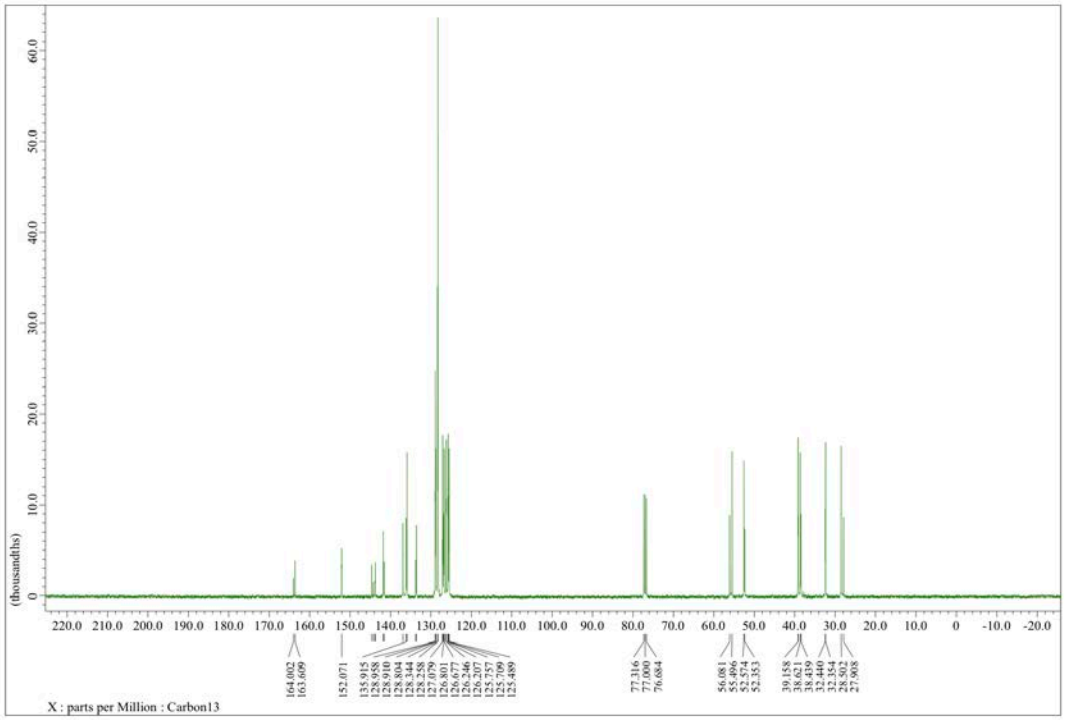
6m (Solvent: $CDCl_3$)



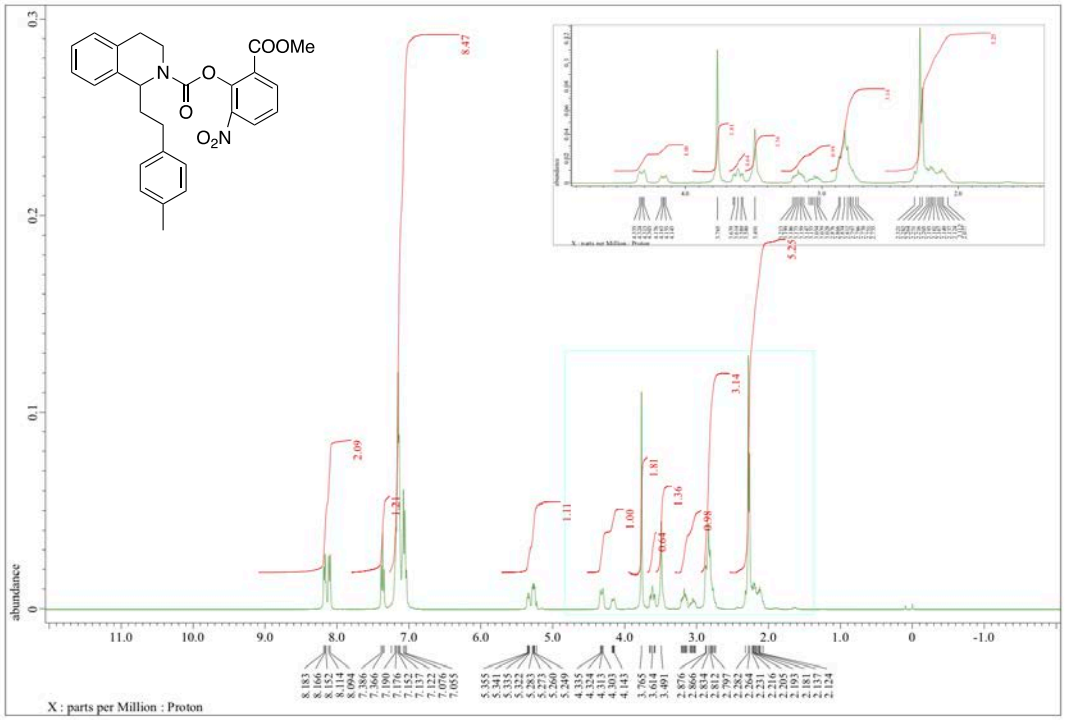


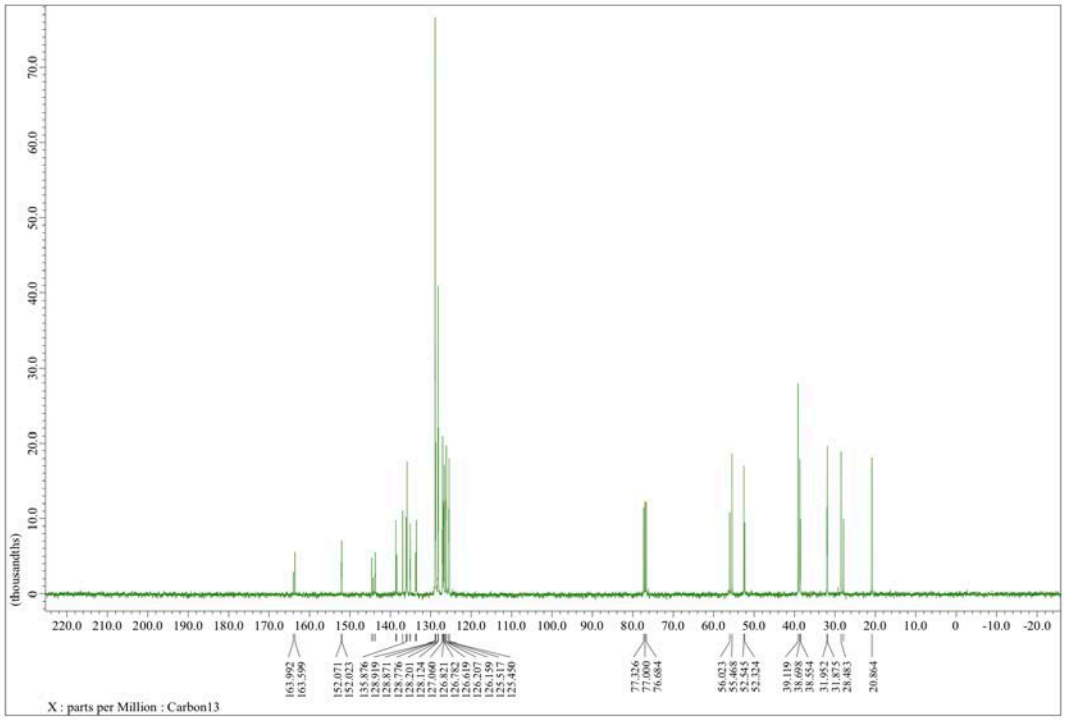
6n (Solvent: $CDCl_3$)



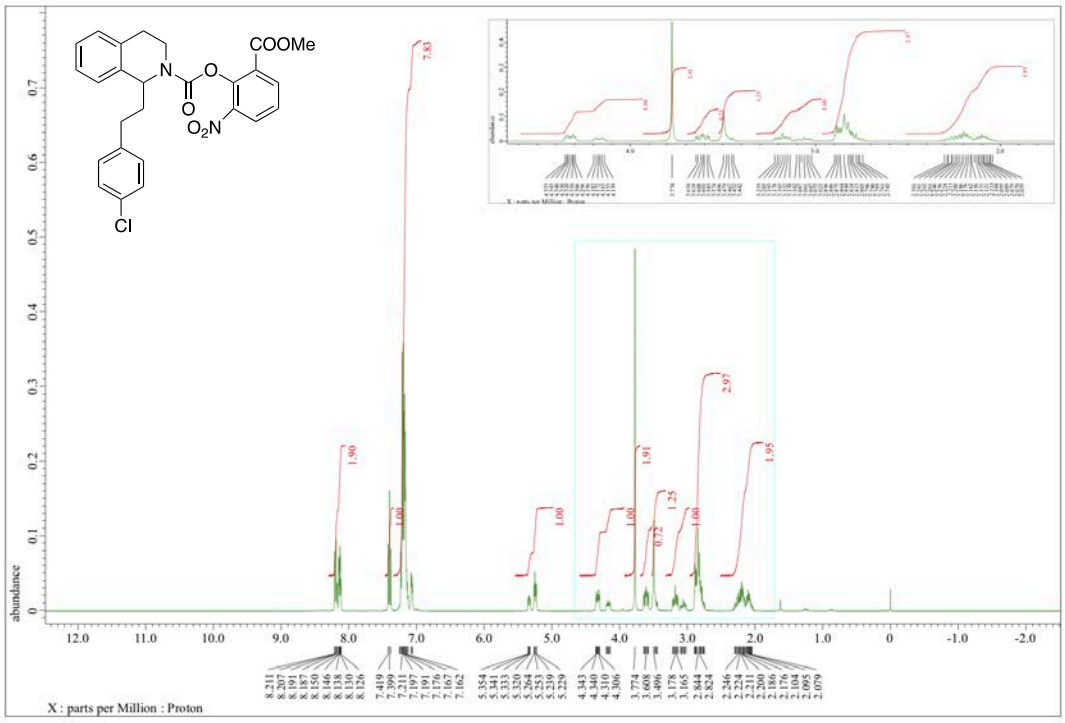


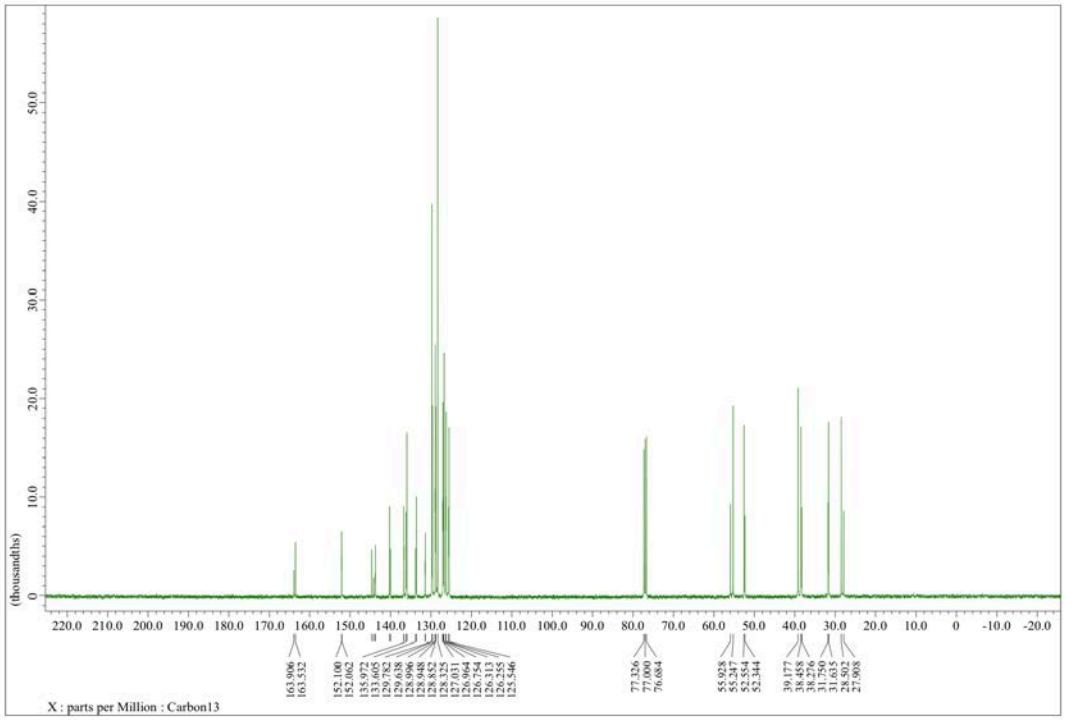
6o (Solvent: $CDCl_3$)



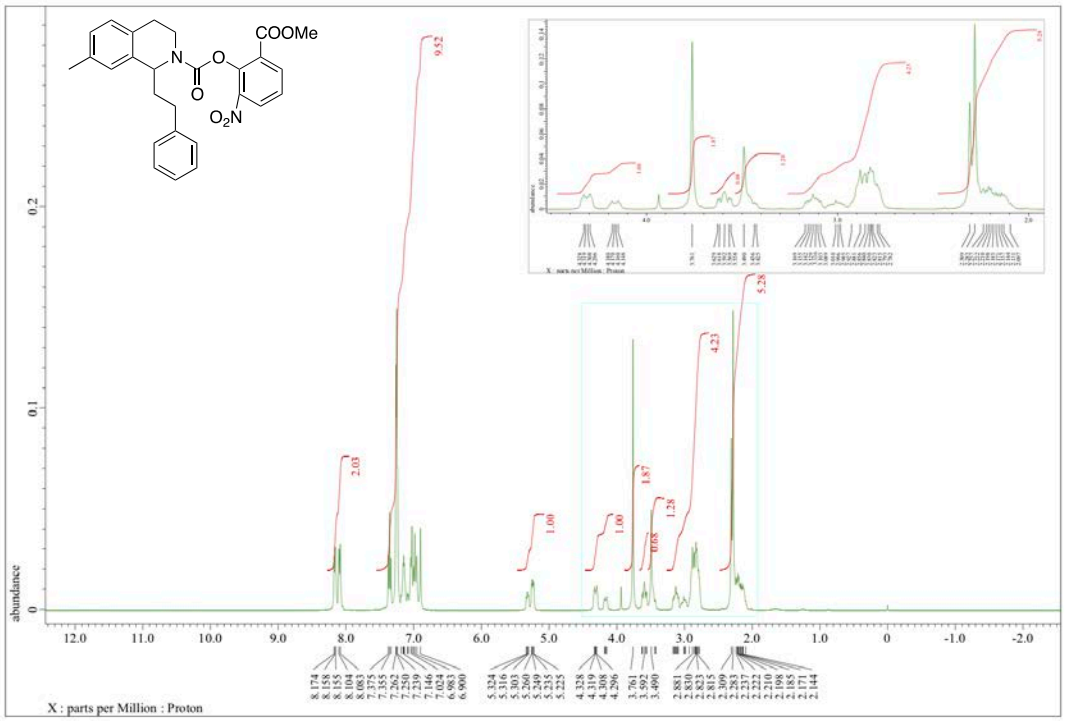


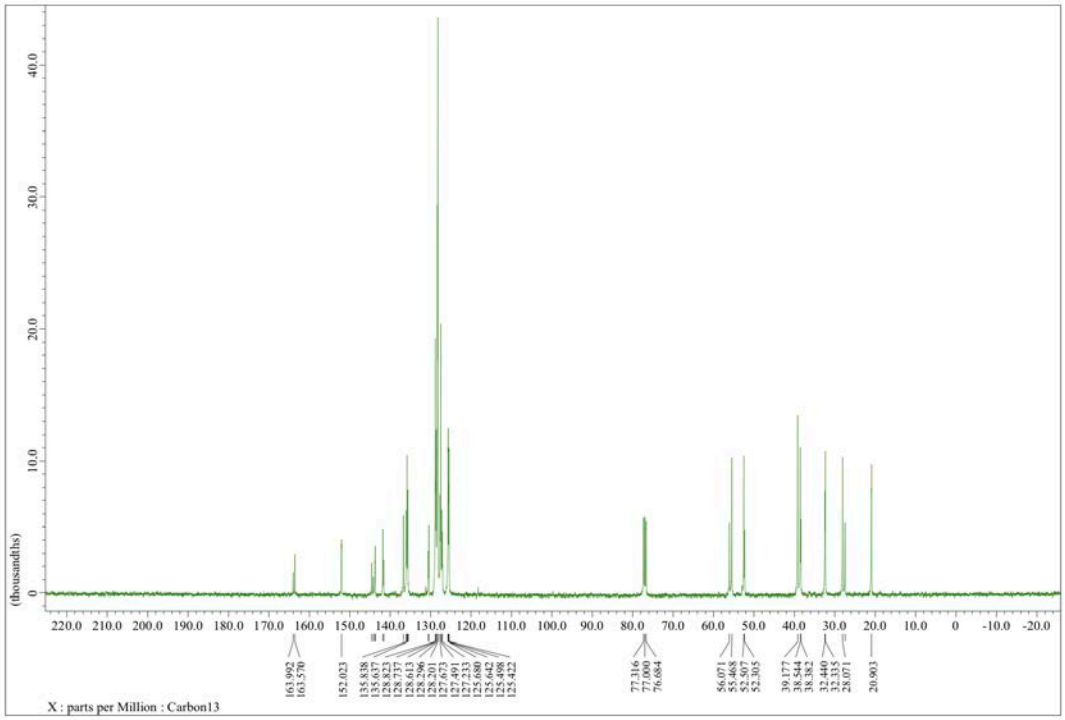
6p (Solvent: $CDCl_3$)



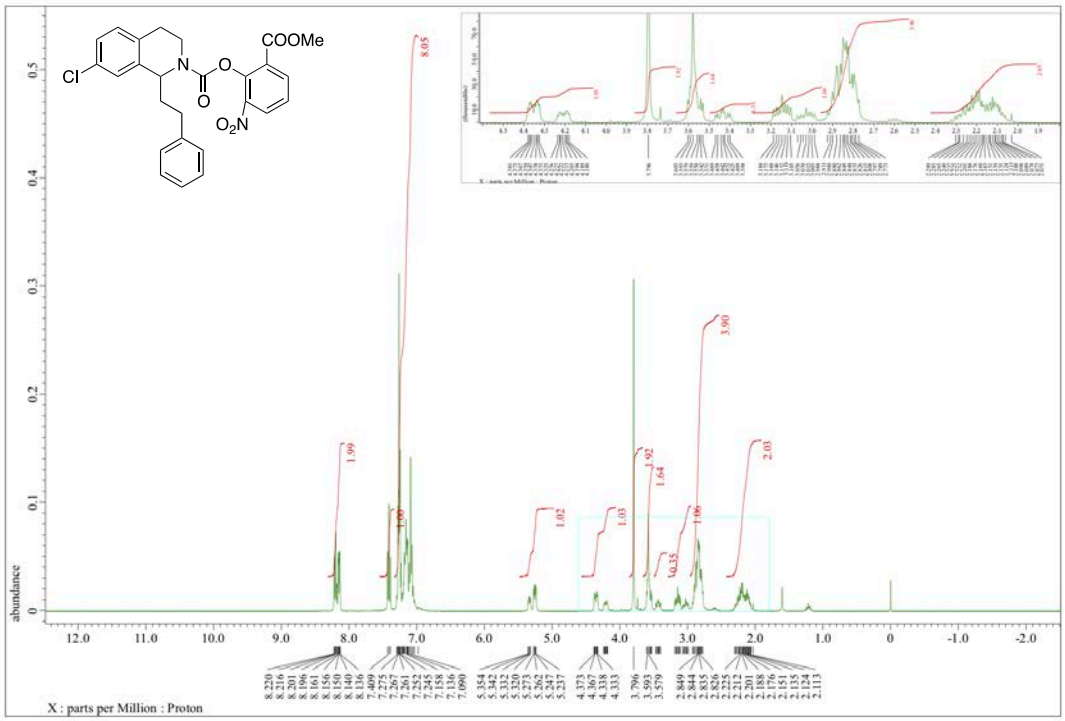


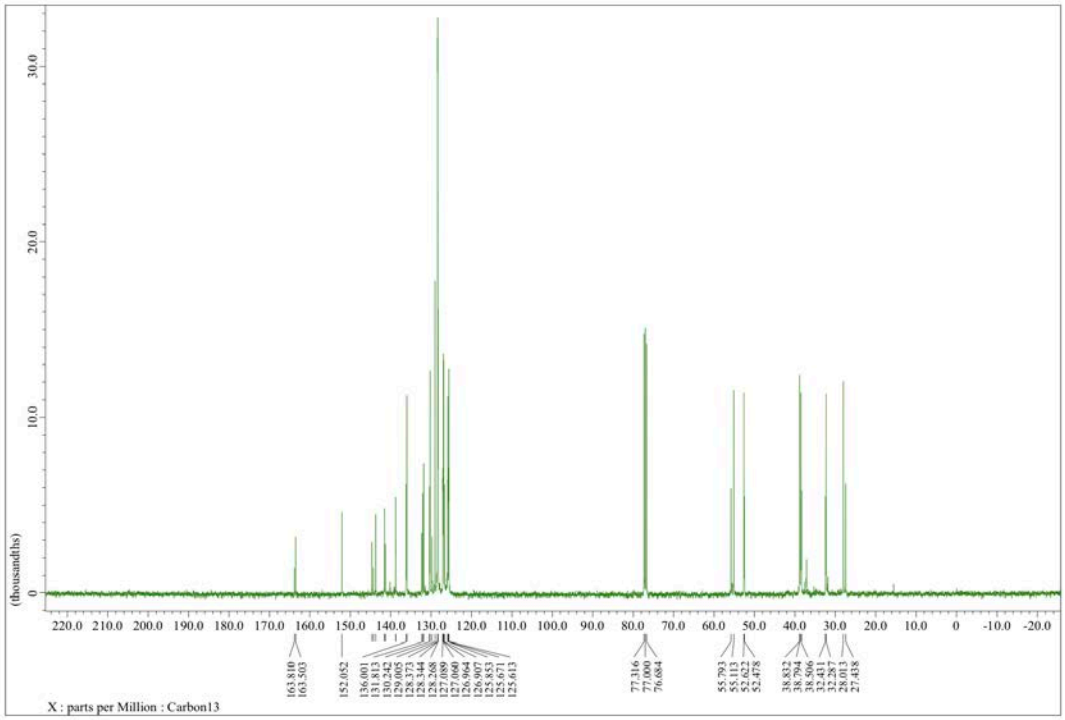
6q (Solvent: $CDCl_3$)



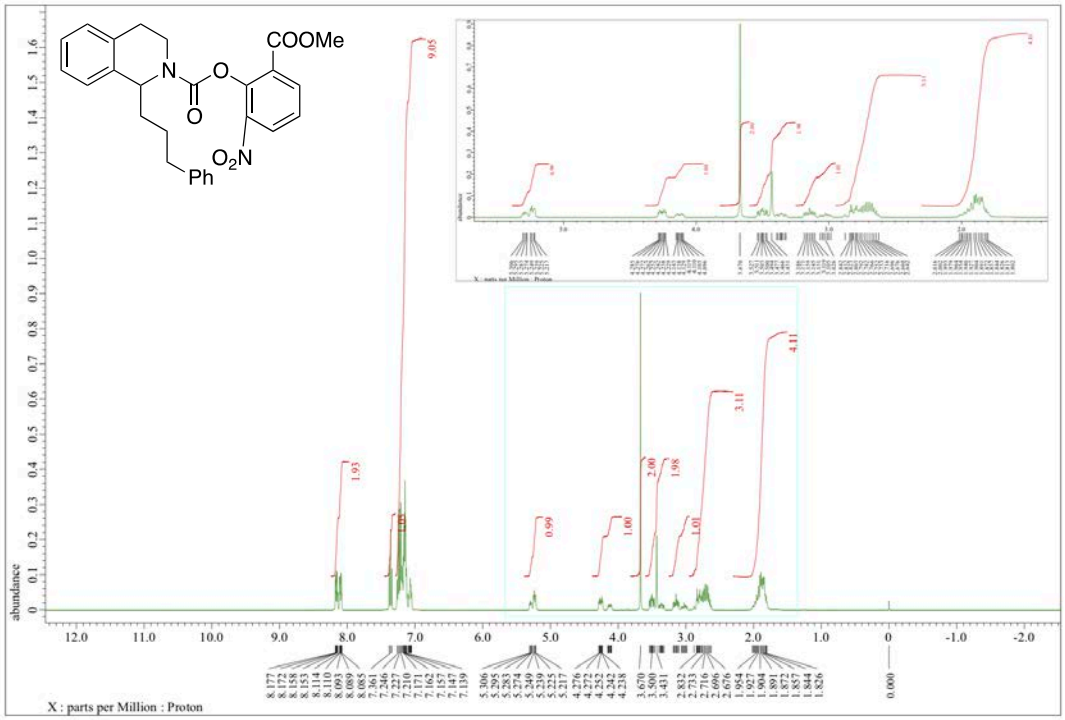


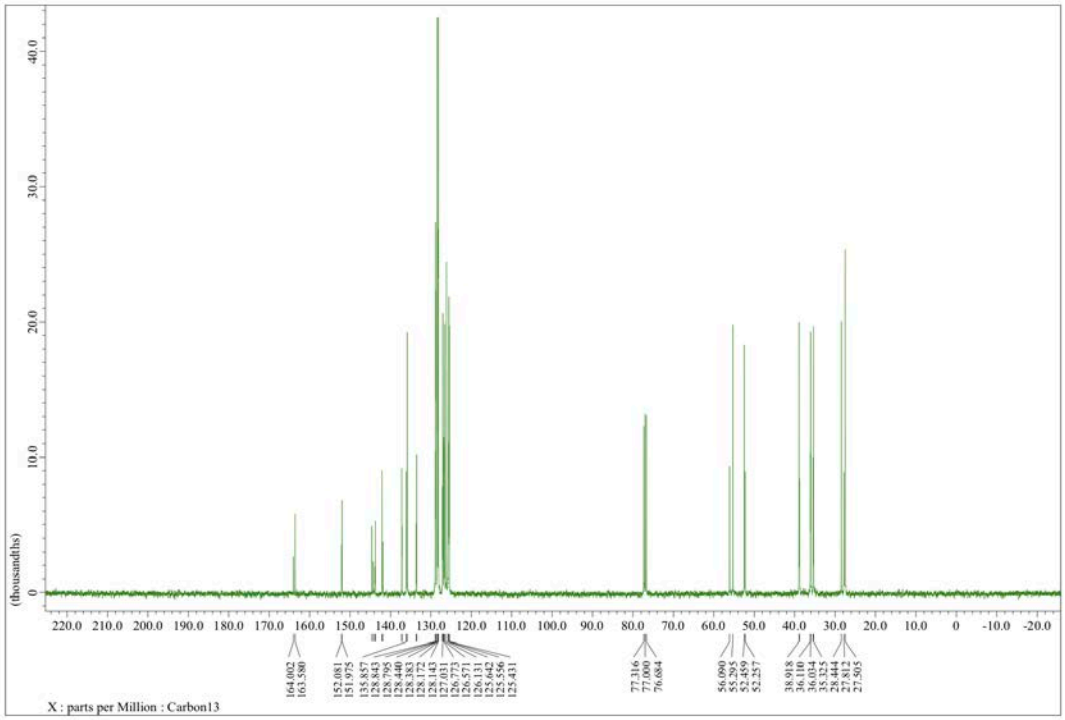
6r (Solvent: $CDCl_3$)



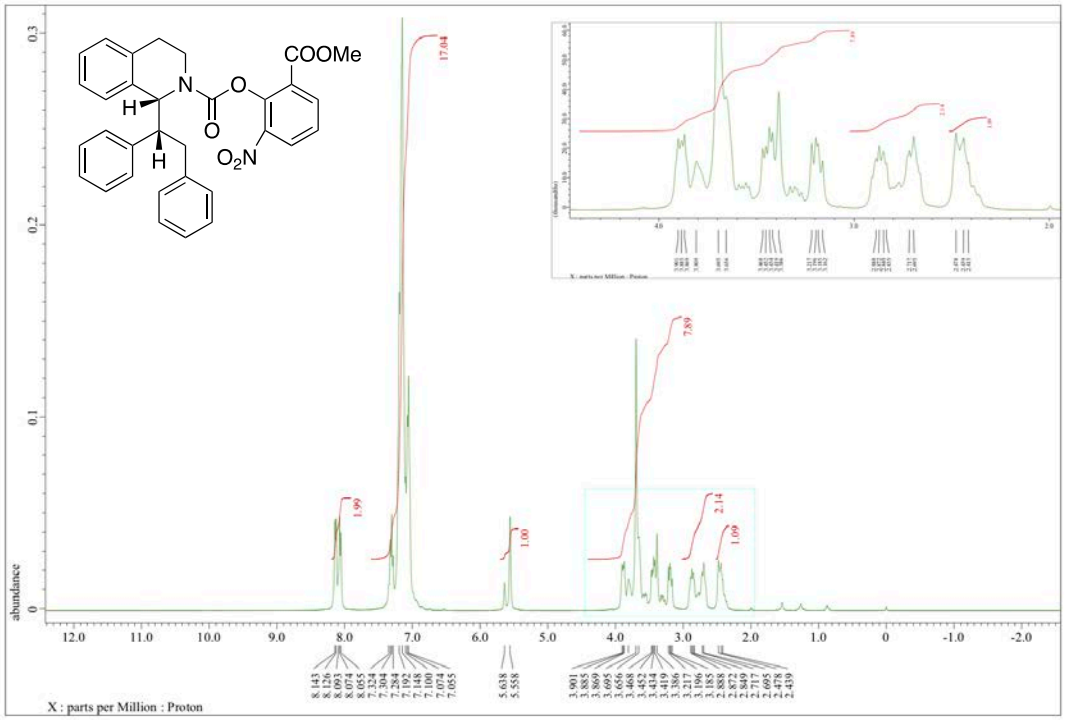


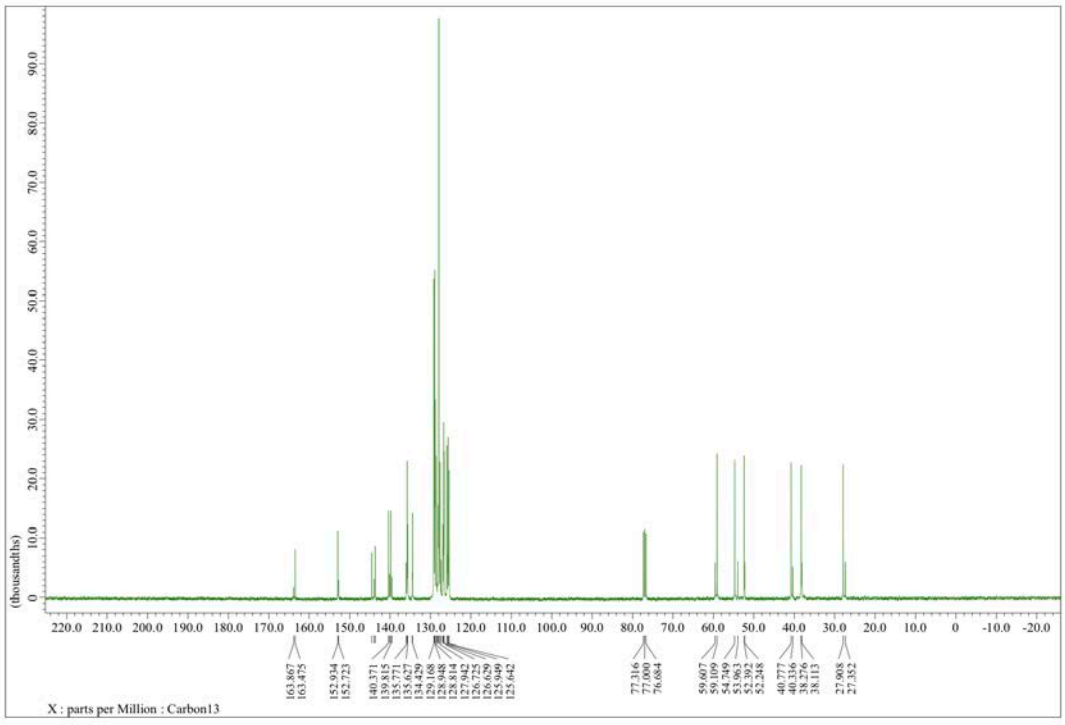
6s (Solvent: $CDCl_3$)



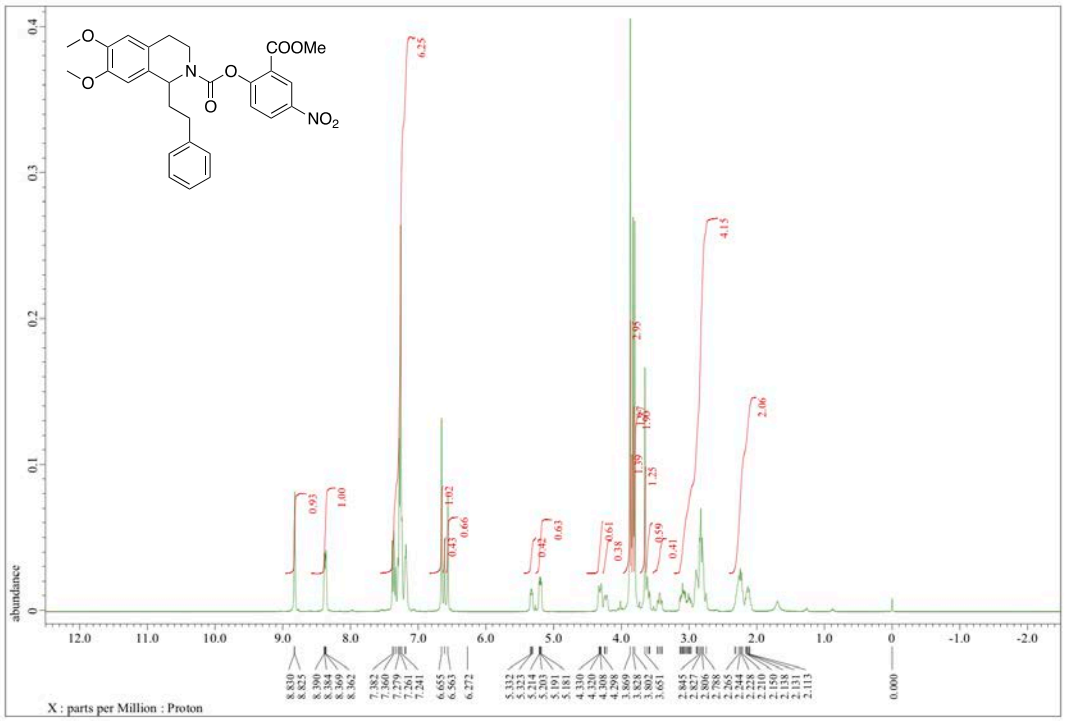


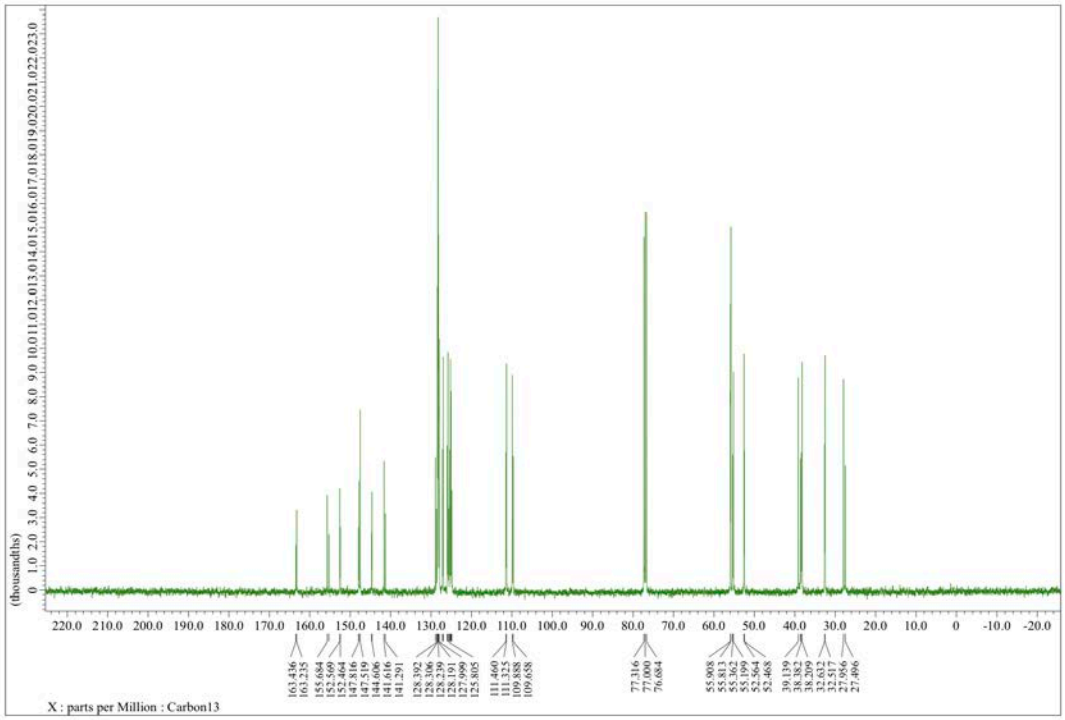
6t (Solvent: $CDCl_3$)



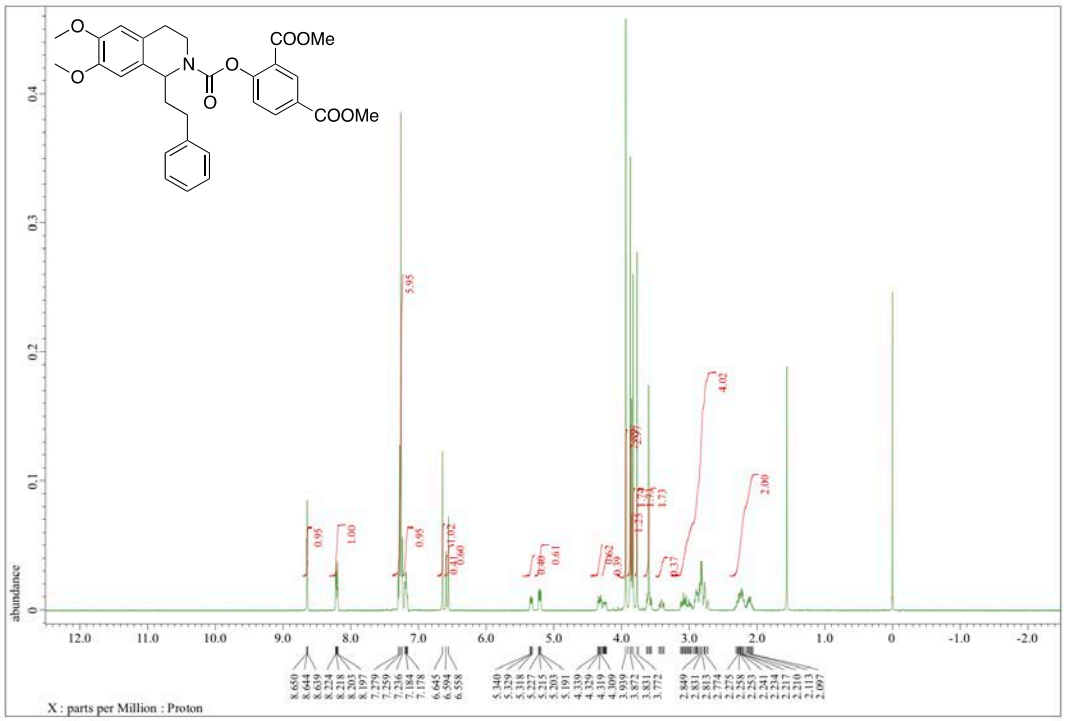


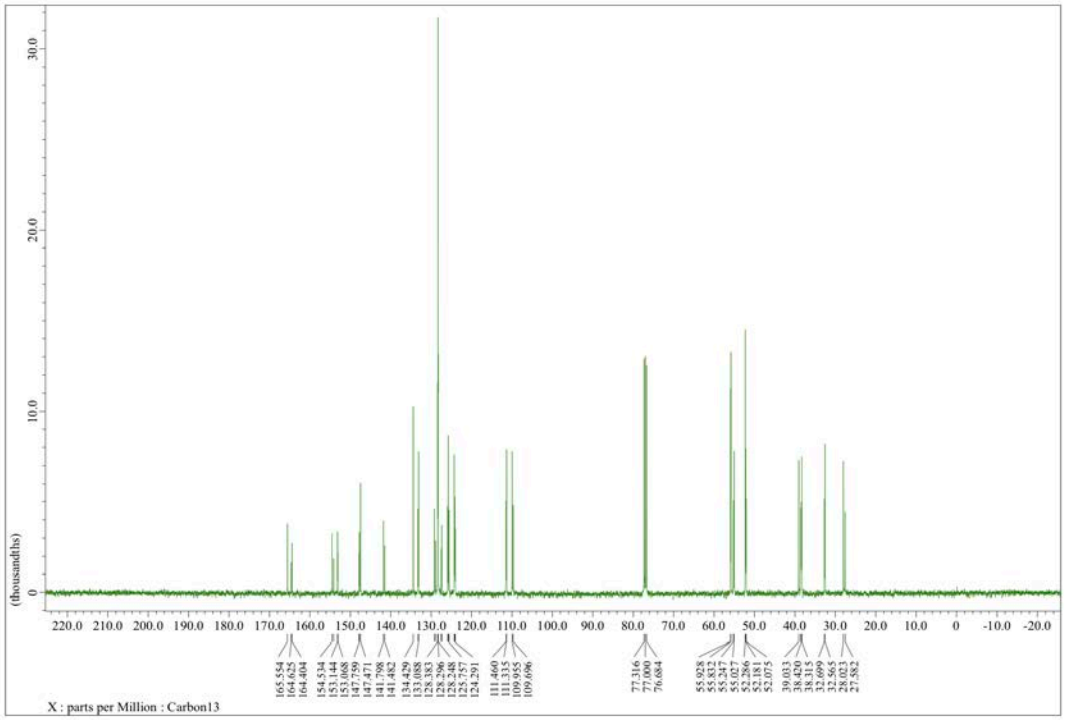
7a (Solvent: $CDCl_3$)



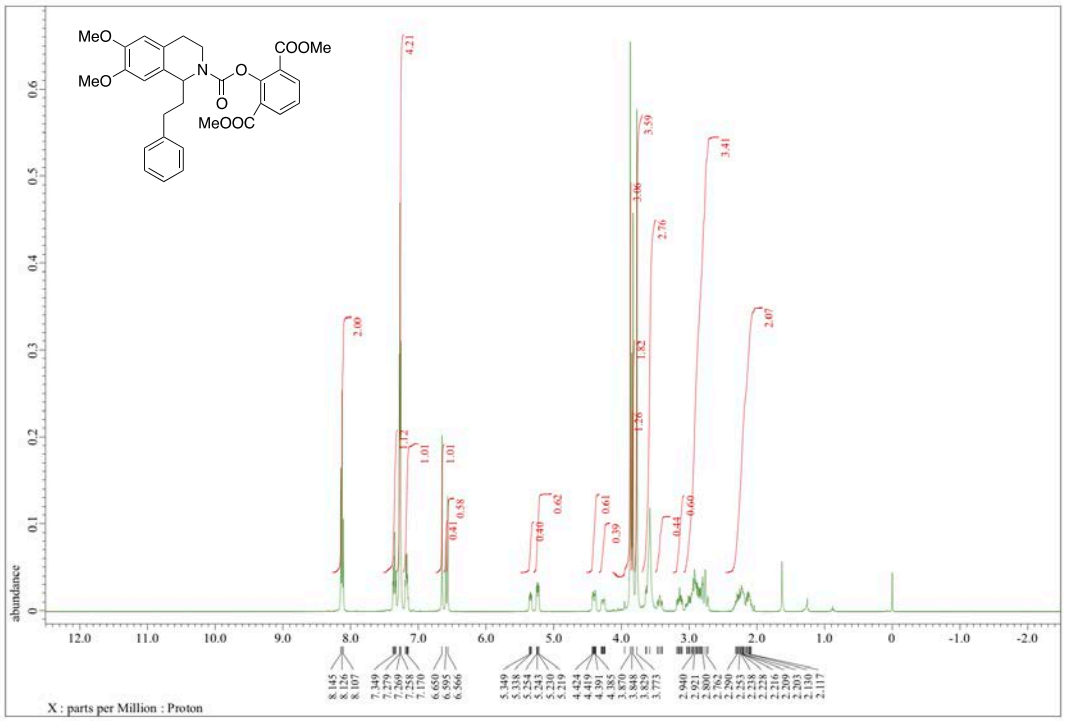


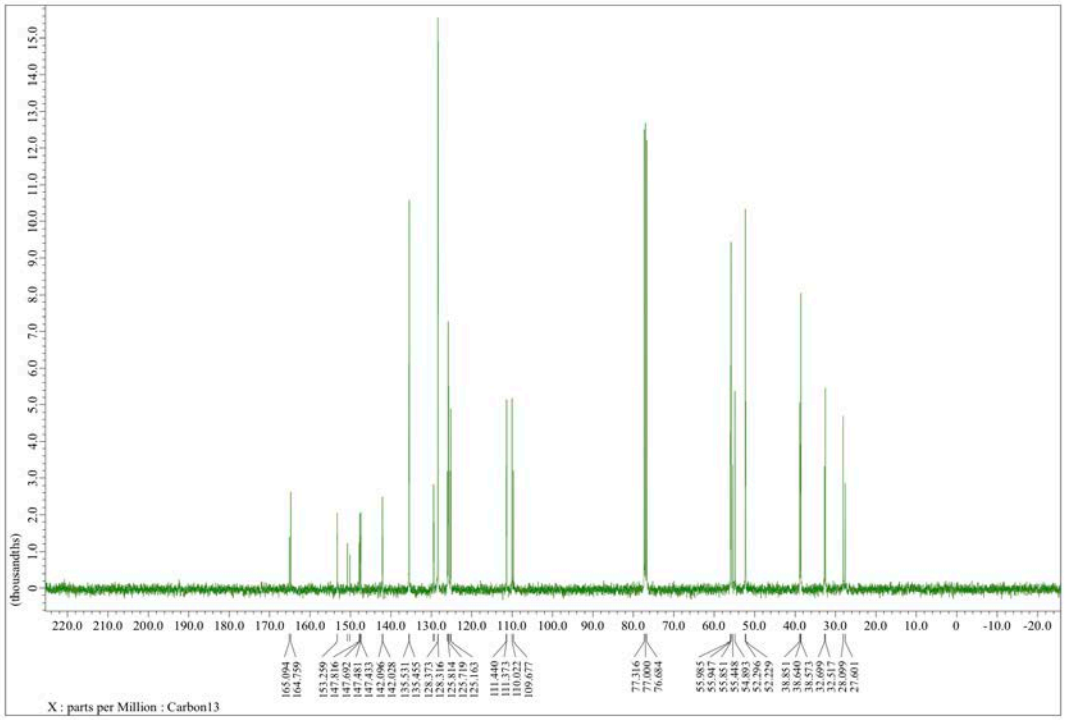
8a (Solvent: $CDCl_3$)



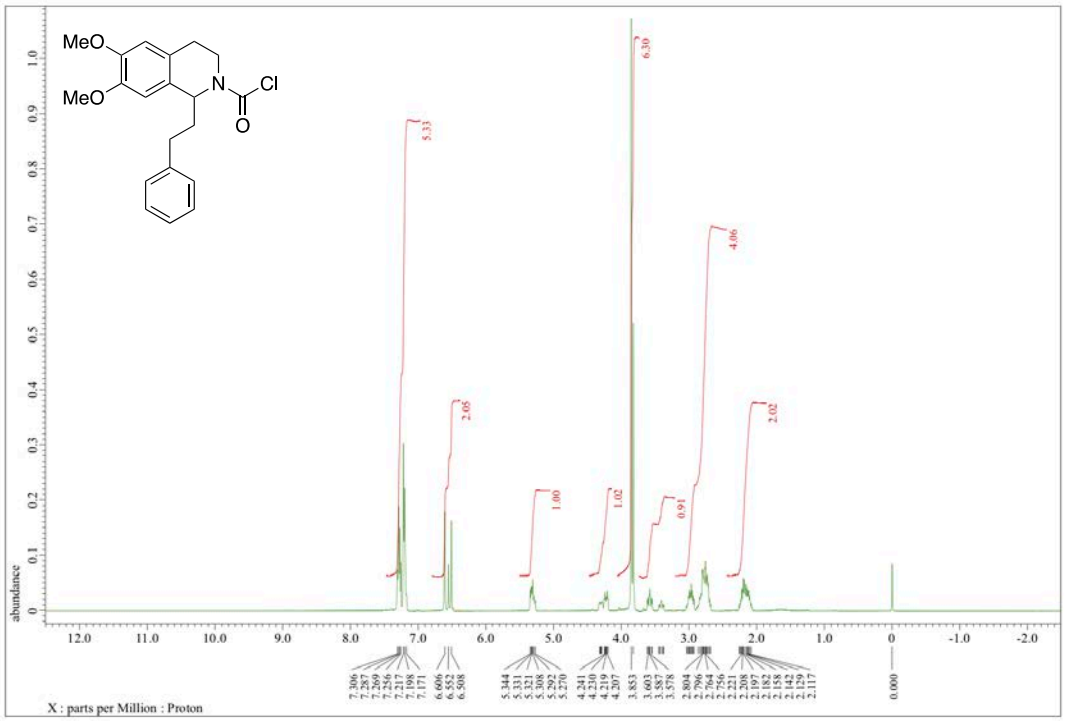


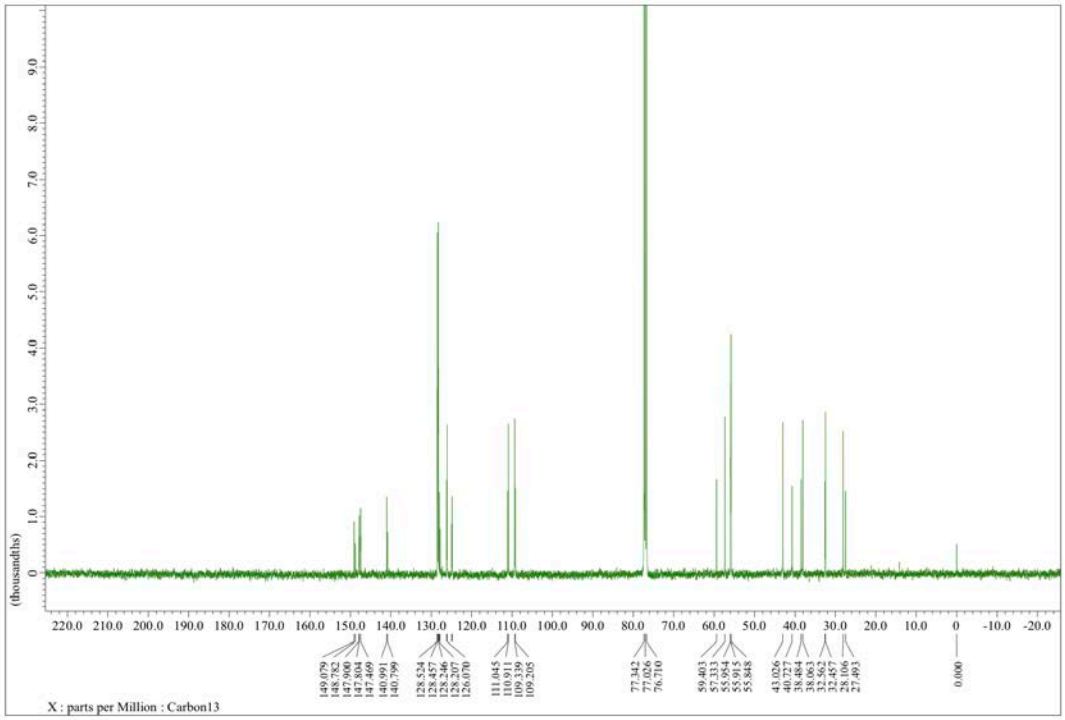
9a (Solvent: $CDCl_3$)



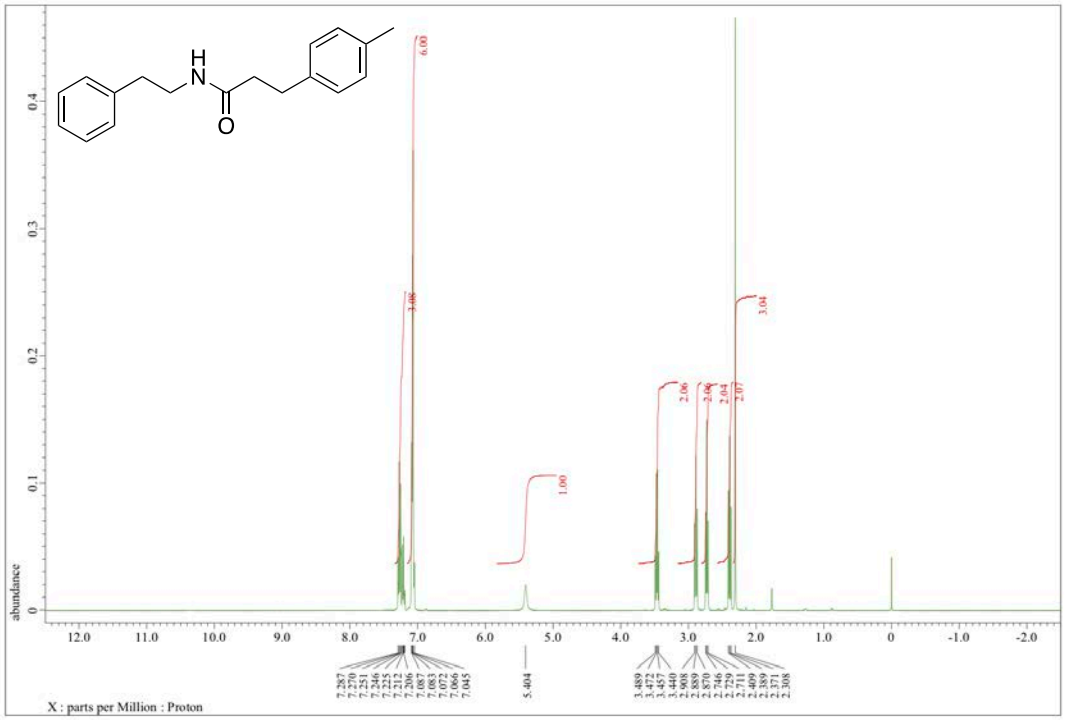


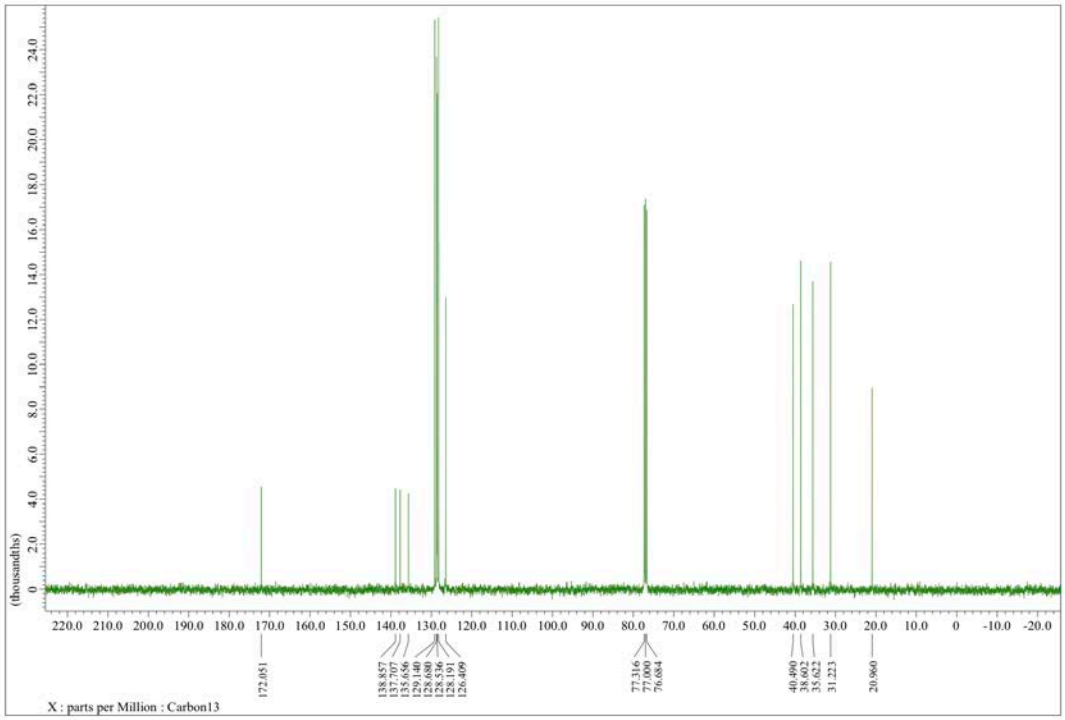
10a (Solvent: $CDCl_3$)



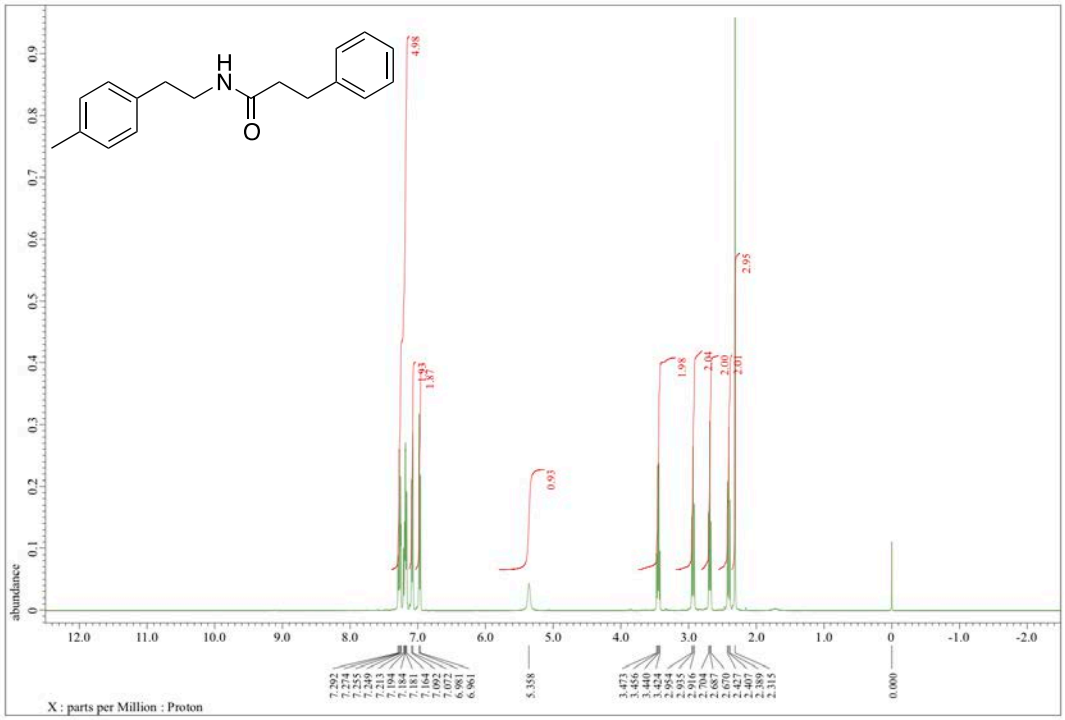


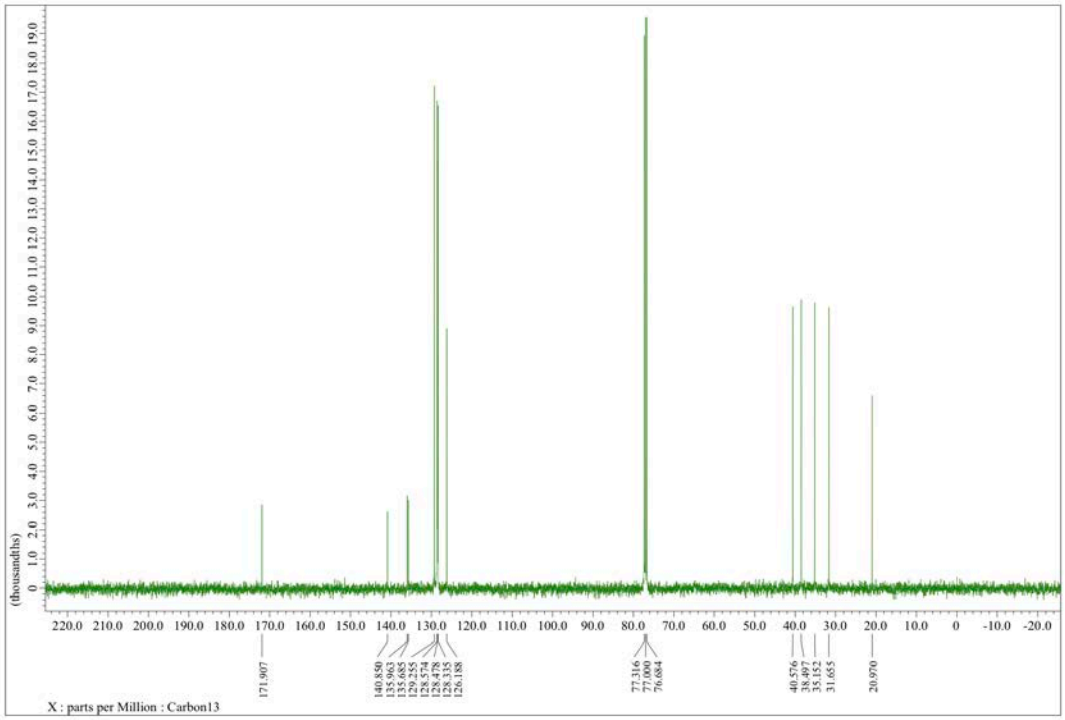
13o (Solvent: $CDCl_3$)



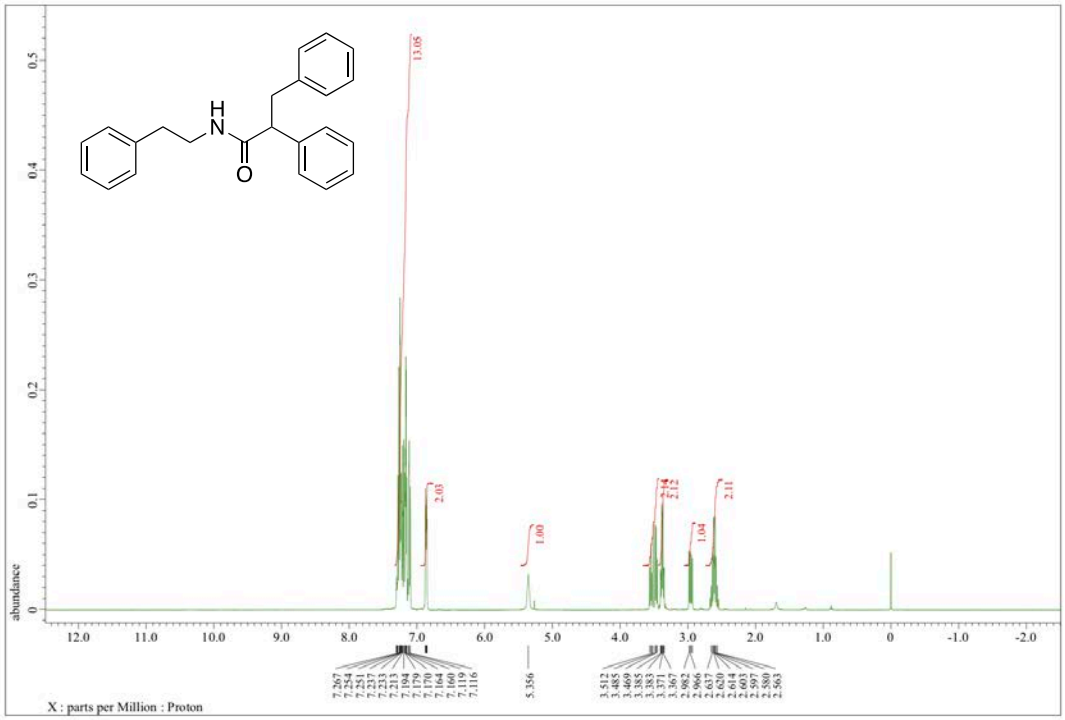


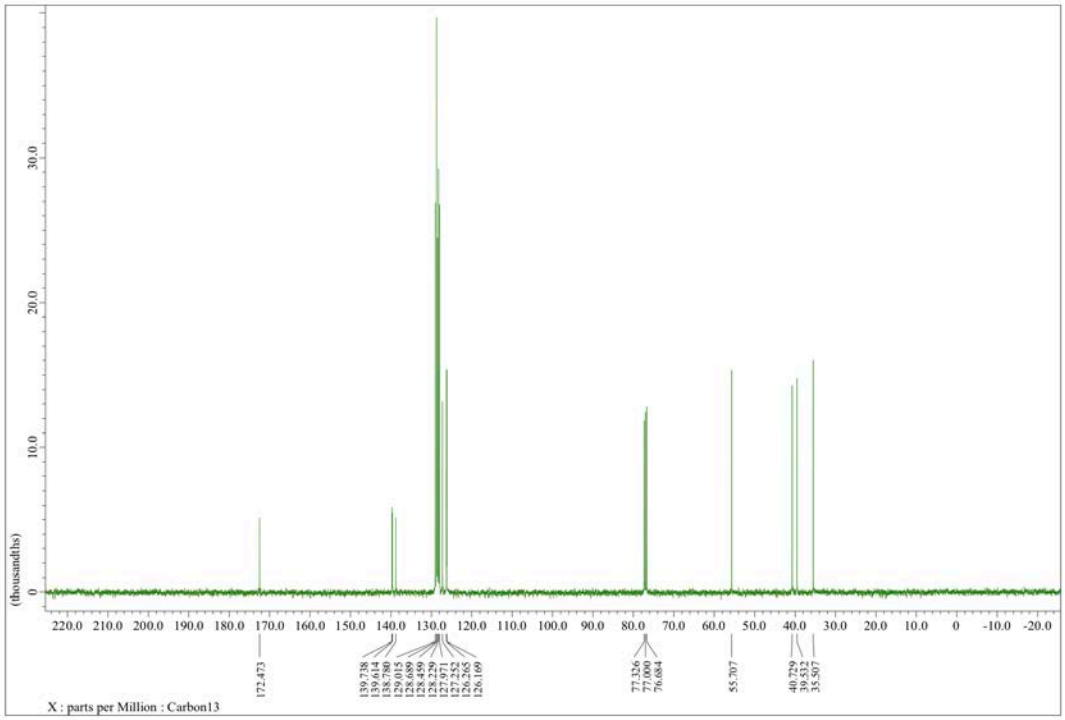
13q (Solvent: $CDCl_3$)



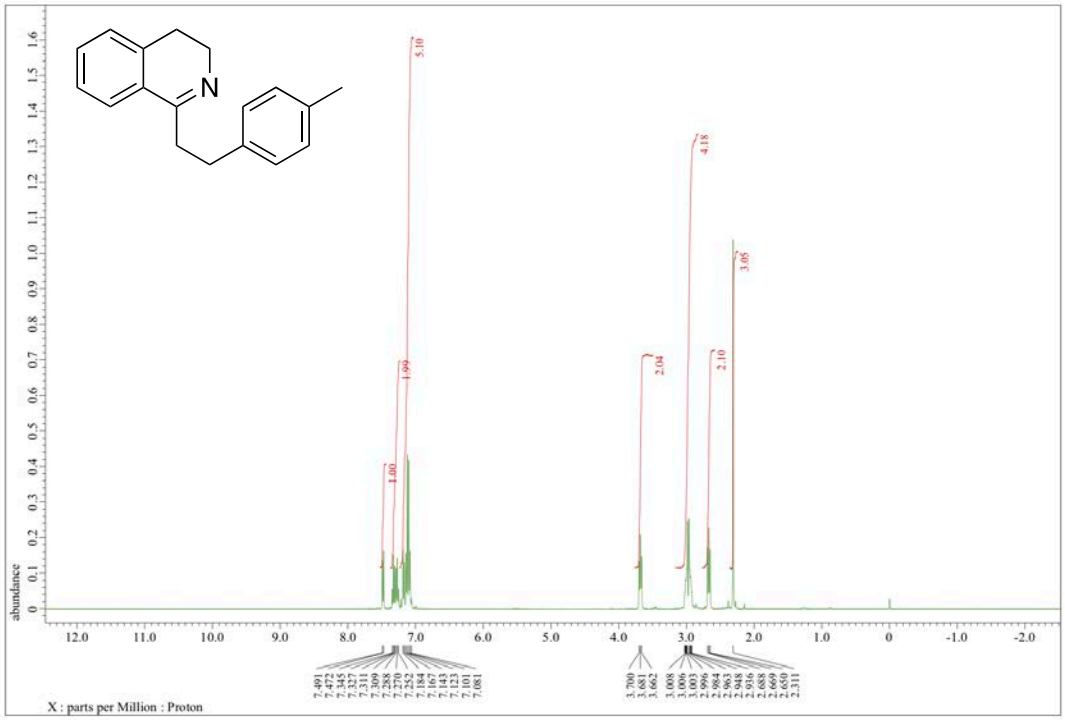


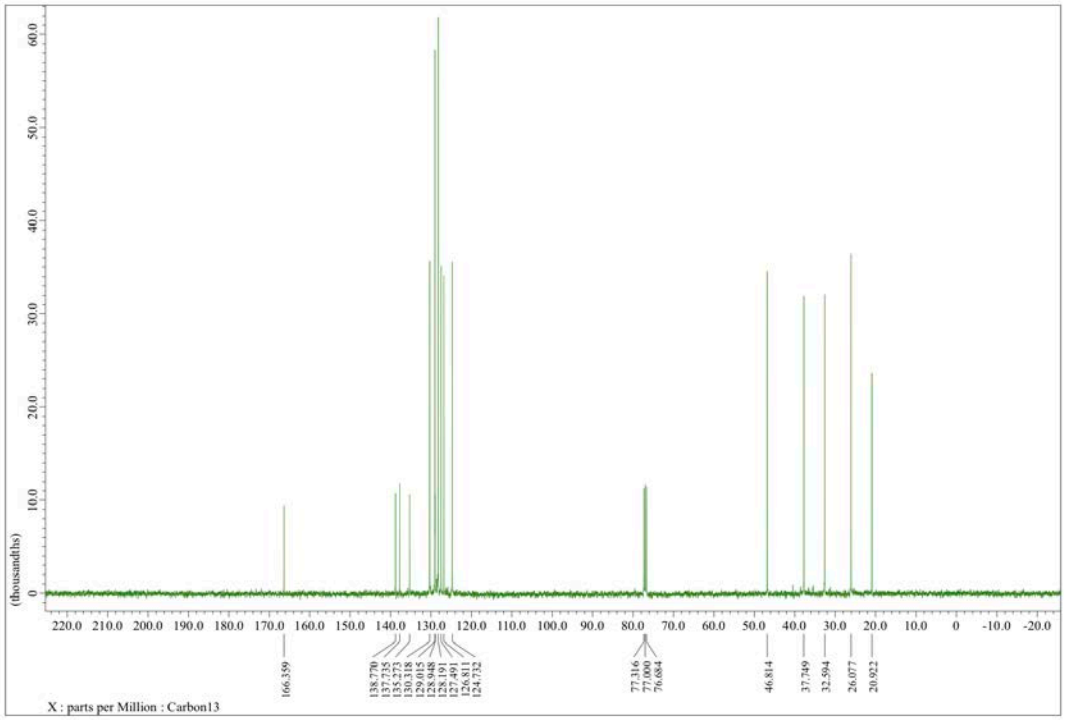
13t (Solvent: $CDCl_3$)



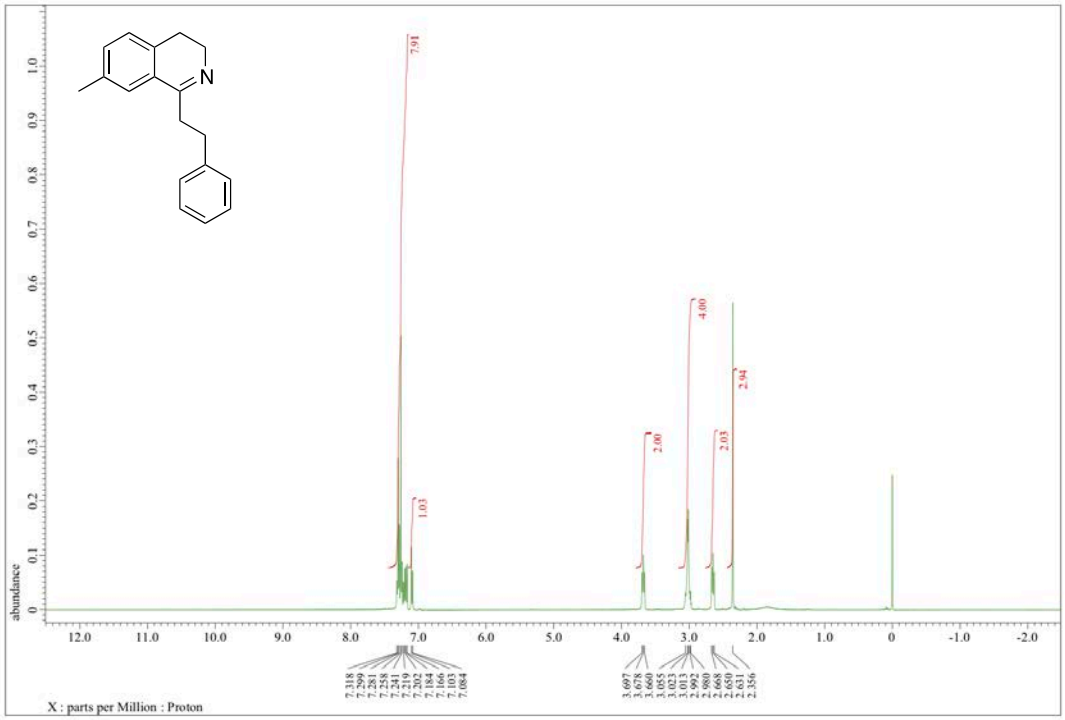


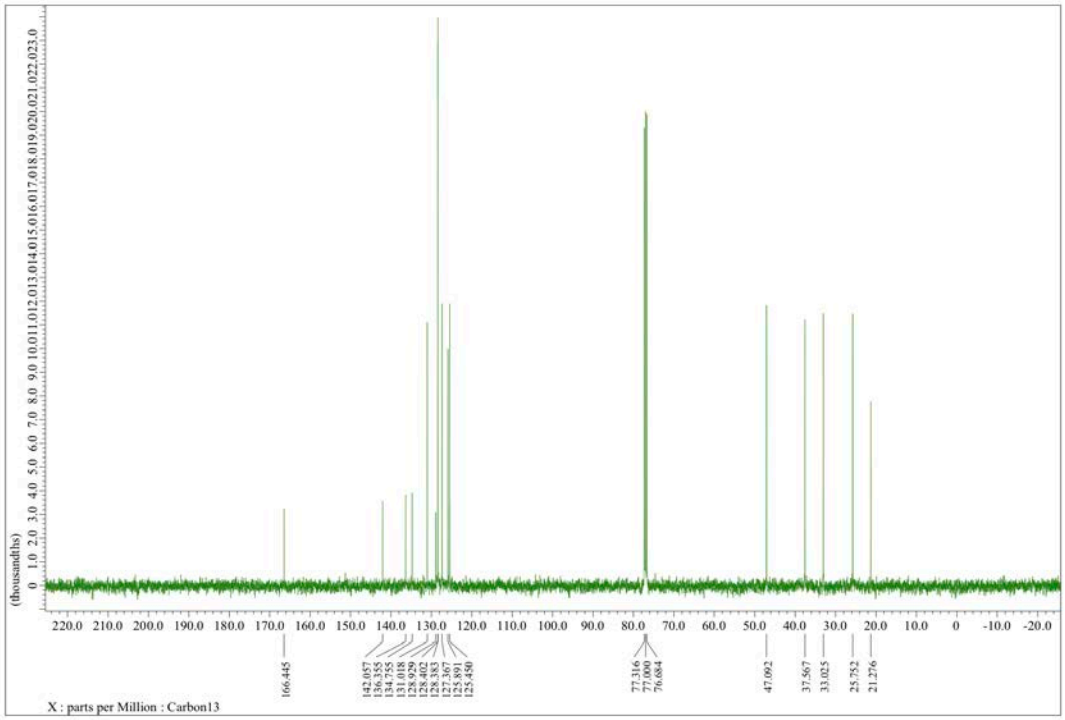
14o (Solvent: $CDCl_3$)



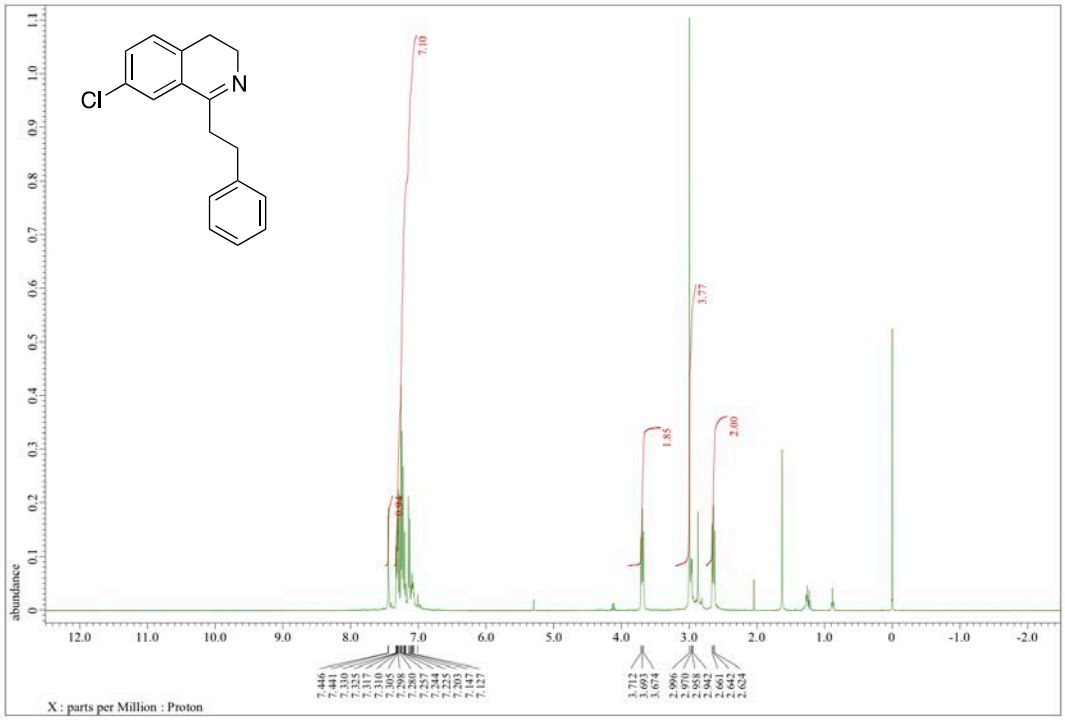


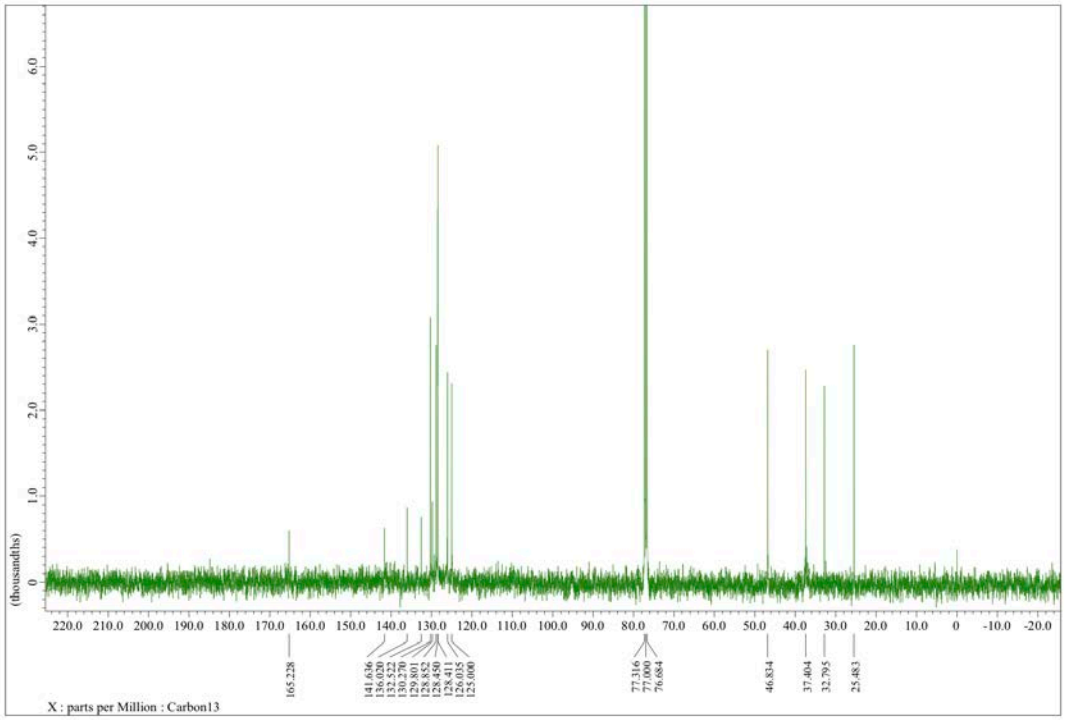
14q (Solvent: $CDCl_3$)



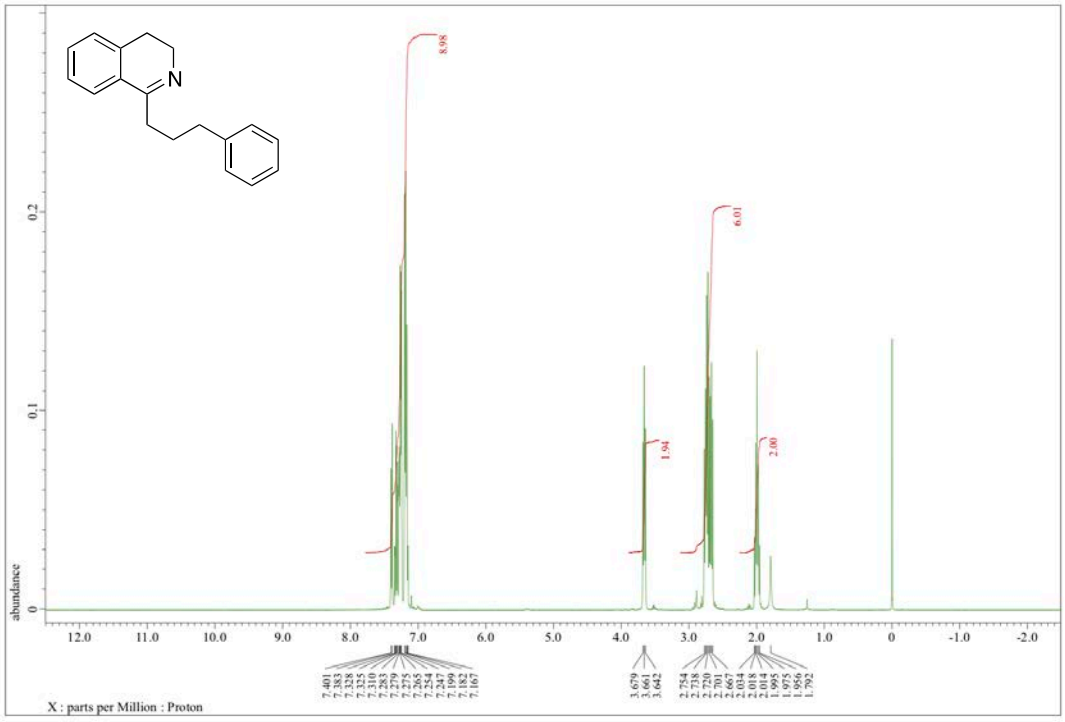


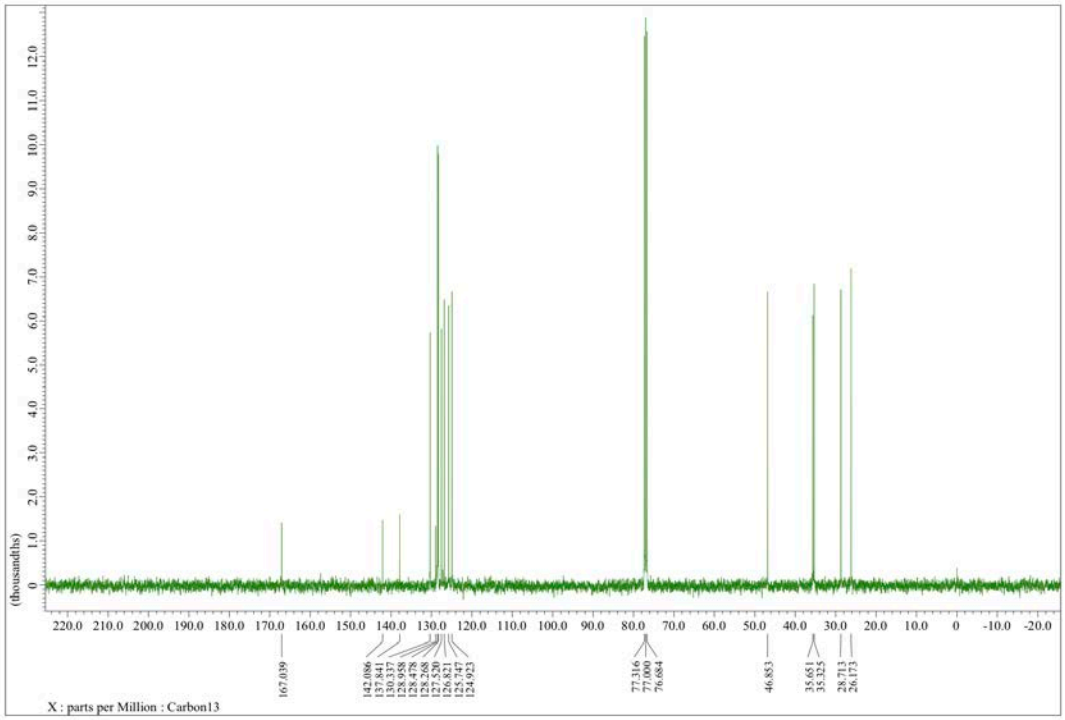
14r (Solvent: $CDCl_3$)



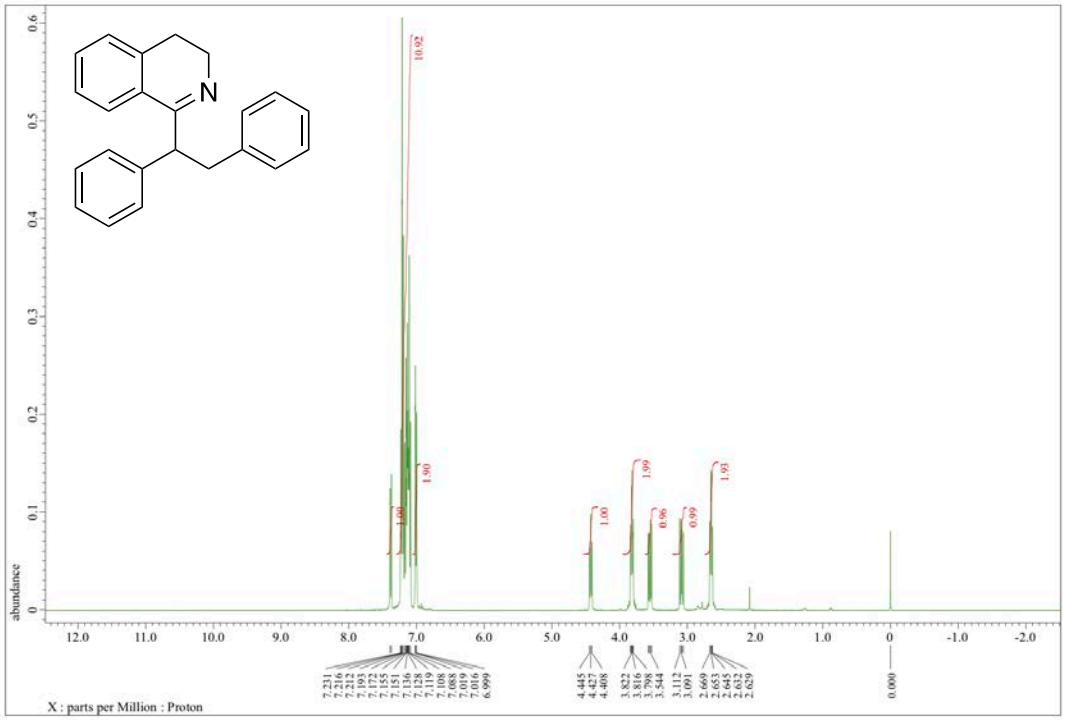


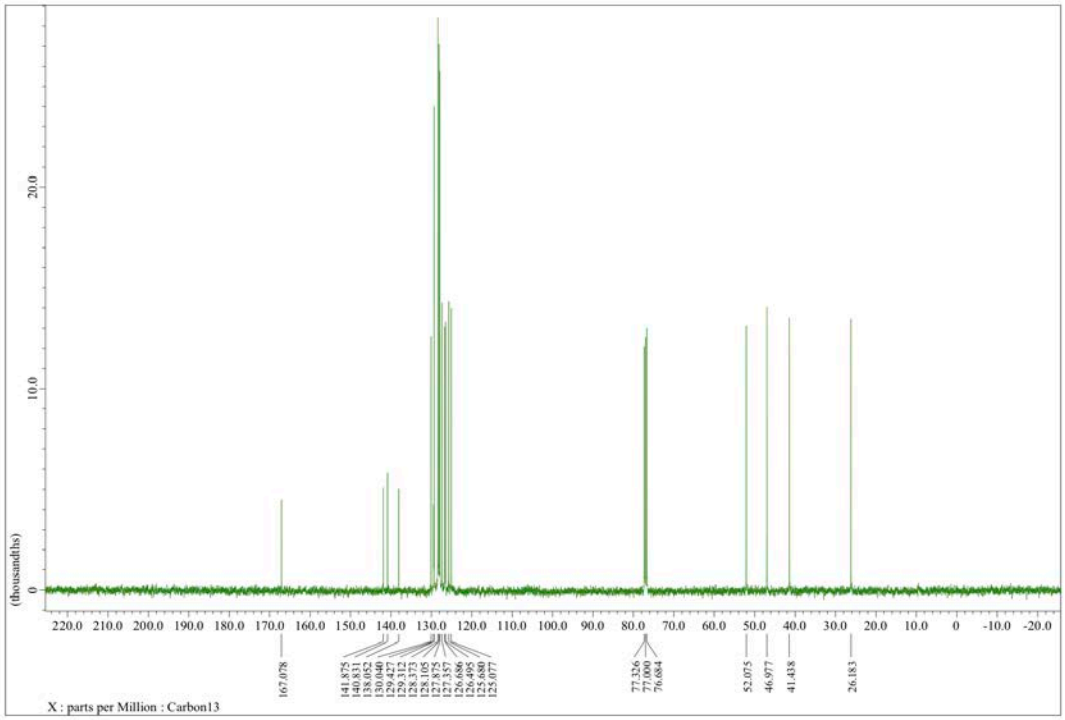
14s (Solvent: $CDCl_3$)



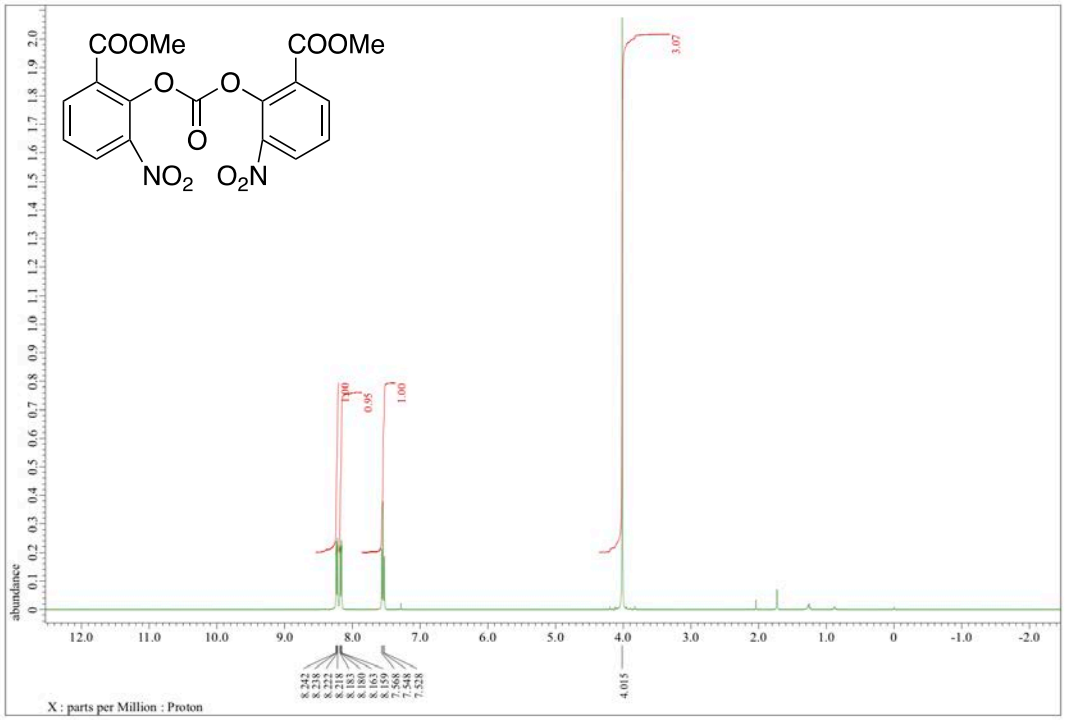


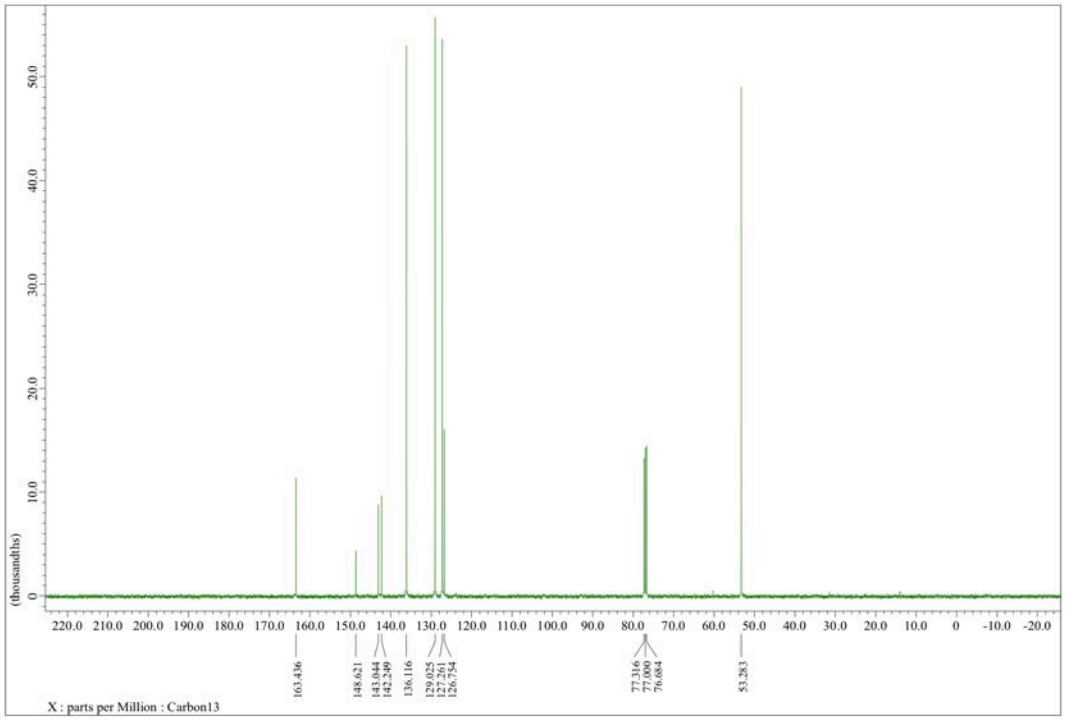
14t (Solvent: $CDCl_3$)



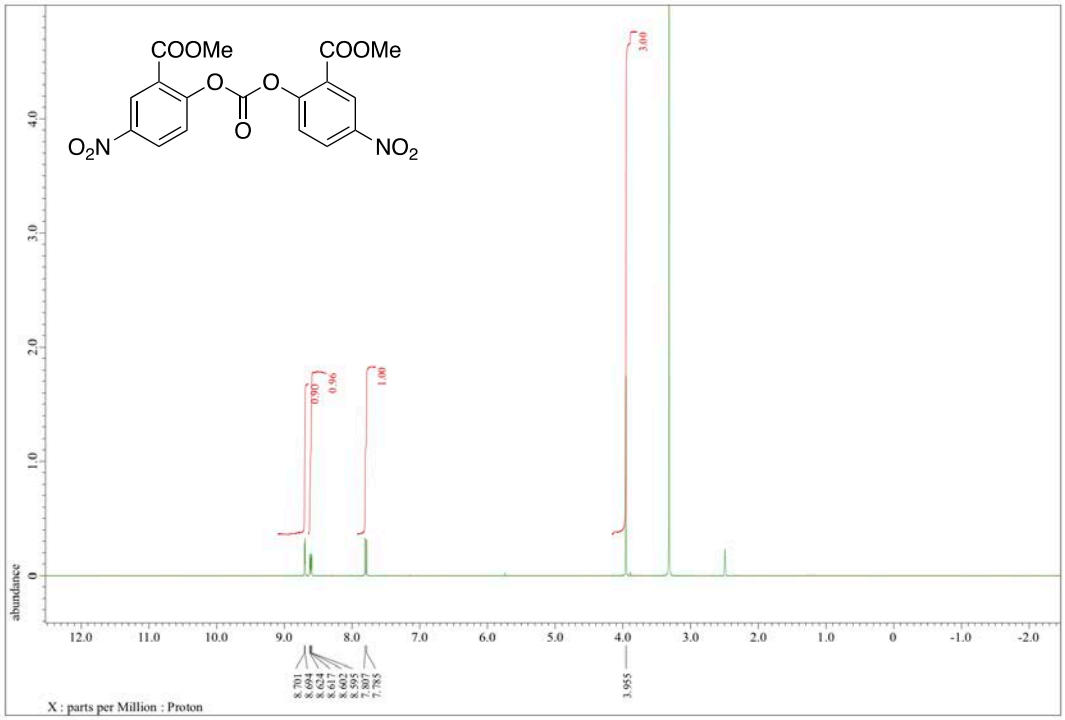


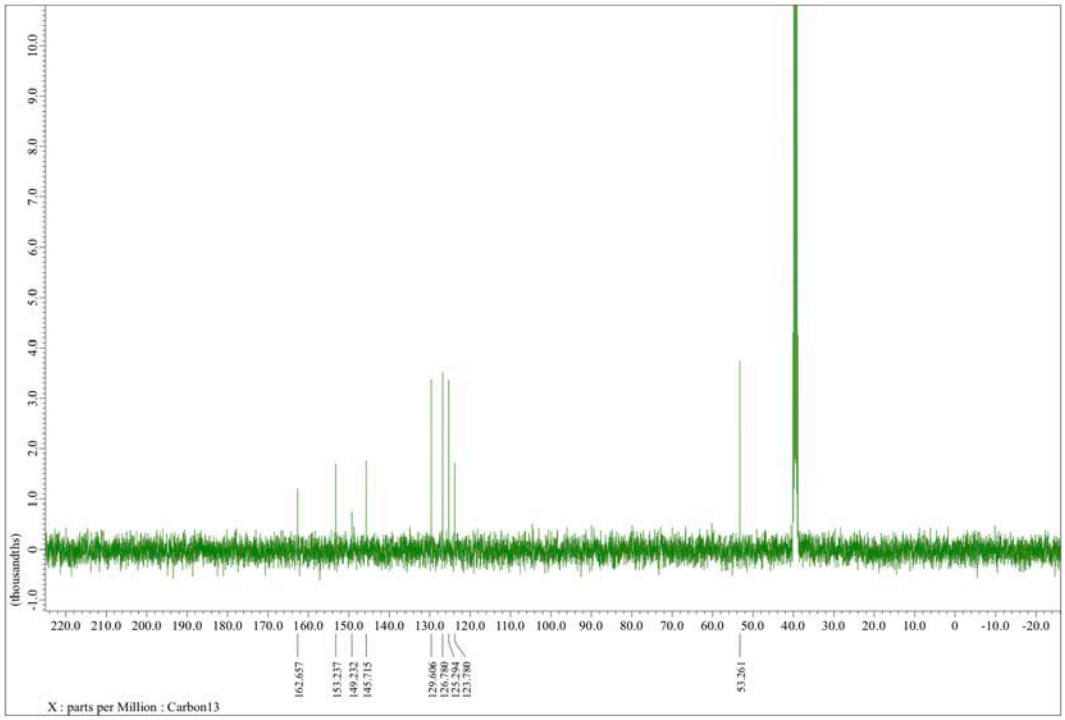
15 (Solvent: $CDCl_3$)



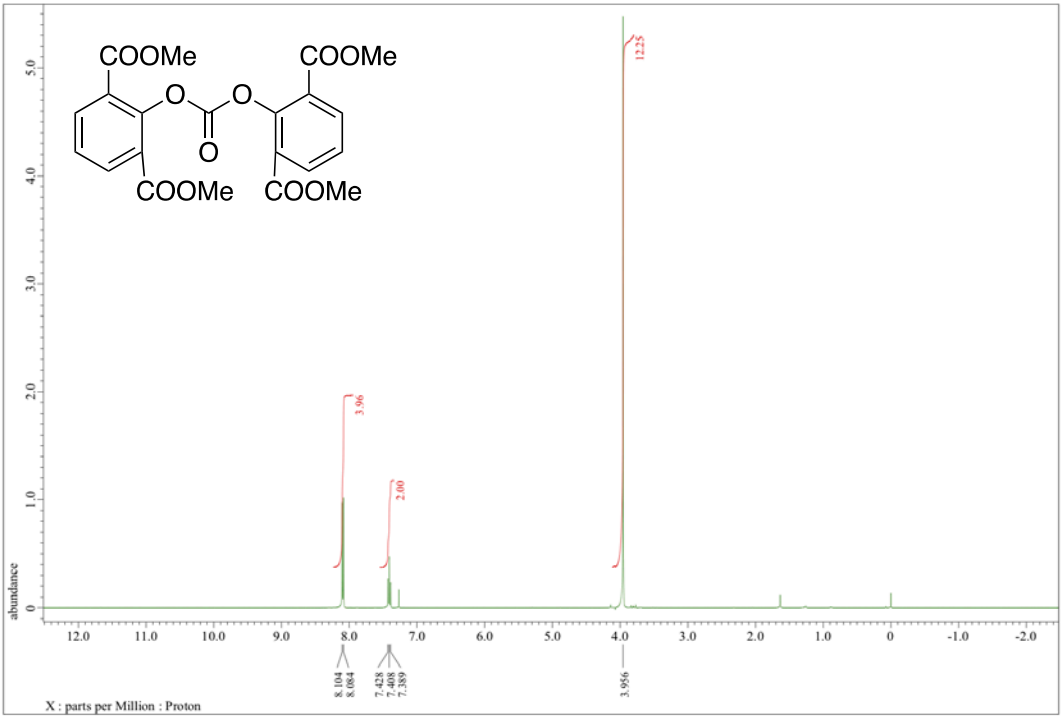


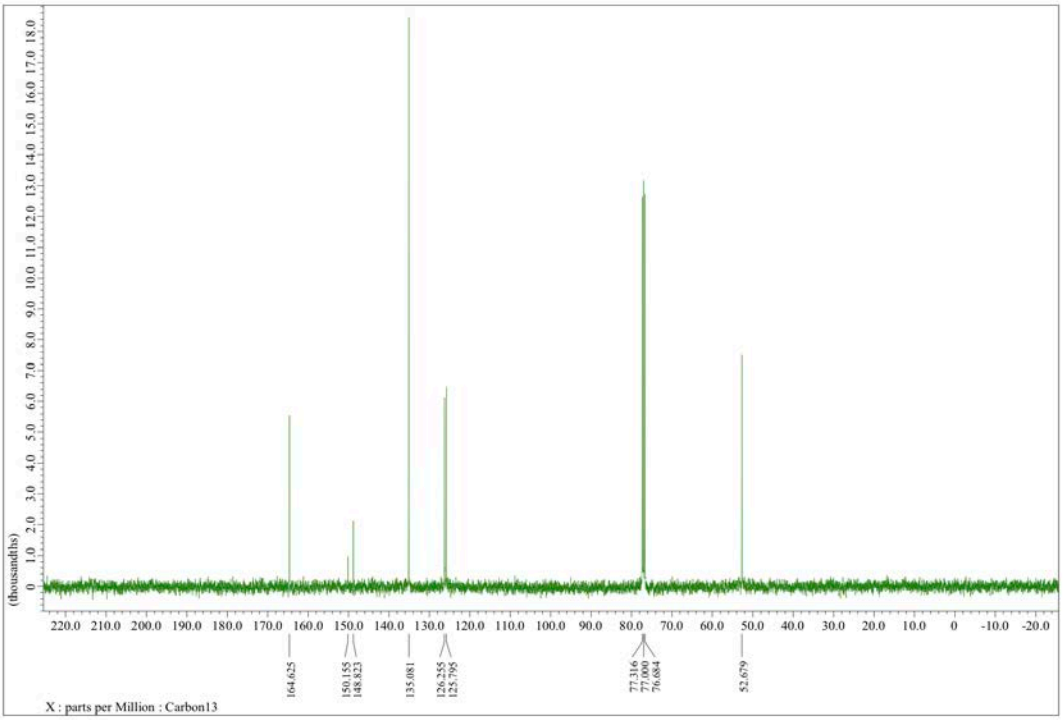
16 (Solvent: DMSO-d_6)





17 (Solvent: $CDCl_3$)





5. References

S1 Meyers, A. I.; Hellring, S.; Hoeve, W. T., *Tetrahedron Lett.* **1981**, *22*, 5115–5118.

S2 Evanno, L.; Ormala, J.; Pihko, P. M., *Chem Eur J.* **2009**, *15*, 12963–12967.

S3 Awuah, E.; Capretta, A. *J Org. Chem.* **2010**, *75*, 5627–5634.

S4 Georgiev, V. S.; Carlson, R. P.; Inwegen, R. G. V.; Khandwala A. *J. Med. Chem.* **1979**, *22,* 348–352.

S5 Feng, G.; Ji, Y.; Liu, H.; Shi, L.; Zhou, Y., *Tetrahedron Lett.* **2016**, *57*, 747–749.

S6 Kawai, Hiroshi; Kotake, Yaichiro; Ohta, Shigeru, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1669–1671.

S7 Bel, P.; Mandelbaum, A. *Org. Mass Spec.* **1980**, *15*, 568–572.

S8 Yamaguchi, R.; Tanaka, M.; Matsuda T.; Fujita, K. *Chem. Commun.* **1999**, 2213–2214.

S9 Puerto Galvis, C. E.; Kouznetsov, V. V., *J. Org. Chem.* **2019**, *84*, 15294–15308.

S10 Gabriel, C. M.; Keener, M.; Gallou, F.; Lipshutz, B. H., *Org. Lett.* **2015**, 17, 3968–3971.

S11 Xu, X.; Feng, H.; Huang, L.; Liu, X., *J. Org. Chem.* **2018**, *83*, 7962–7969.

S12 Chen, L.; Wu, M., *Synthesis*, **2019**, *51,* 1595–1602.

S13 Álvarez-Pérez, A.; Esteruelas, M. A.; Izquierdo, S.; Varela, J. A.; Saá, C., *Org. Lett.* **2019**, *21*, 5346–5350.

S14 Gruen, A.; Milen, M.; Foeldesi, T.; Abranyi-Balogh, P.; Drahos, L.; Keglevich, G., *Synthetic Commun.* **2013**, *43*, 1491–1498.

S15 Martin, N. H.; Jefford C. W., *Helv. Chim. Acta* **1982**, *65*, 762–774.

S16 Tute, M. S.; Brammer, K. W.; Kaye, B.; Broadbentb R. W. *J. Med. Chem.* **1970** *13*, 44–48.

S17 McDonald, C. E.; Ramsey, J. D.; McAtee, C. C.; Mauck, J. R.; Hale, E. M.; Cumens, J. A., *J. Org. Chem.* **2016**, *81*, 5903–5914.

S18 Santangelo Freel, R. M.; Ogden, K. K.; Strong, K. L.; Khatri, A.; Chepiga, K. M.; Jensen, H. S.; Traynelis, S. F.; Liotta, D. C., *J. Med. Chem.* **2013**, *56*, 5351–5381.

S19 Min, L.; Yang, W.; Weng, Y.; Zheng, W.; Wang, X.; Hu, Y. *Org. Lett.* **2019**, *21*, 2574–2577.

S20 Valpuesta, M.; Ariza, M.; Díaz A.; Suau R., *Eur J. Org. Chem.* **2010**, *23*, 4393–4401.

S21 Caronna G. ; Palazzo S., *Gazz. Chim. Ital.*, **1963**, *93*, 198–203.

S22 Estelle G.; Augustin L.; Roselyne R.; Gilles L.; Marion J.; Sébastien L.; Sabine B.-B.; Célia G.; Laure-Lise C.; Jean-Pierre D.; Alexandre M., *Org. Lett.* **2019**, *21*, 1999-2003.

S23 Xin P.; Tan, S.; Wang, Y.; Sun, Y.; Wang, Y.; Xu Y.; Chen, C.-P. *Chem. Commun.*, **2017**, *53*, 625-628.

S24 Rodríguez, G; Castedo, L.; Domínguez, D.; Saá, C.; Adam W.; Saha-Möller, C. R., *J. Org. Chem.* **1999**, *64*, 877–883.

S25 Castro-Castillo, V.; Suárez-Rozas, C.; Pabón, A.; Pérez, E. G.; Cassels B. K.; Blair, S. *Bioorganic Med. Chem. Lett.* **2013**, *23*, 327–329.

S26 Othman, R. B.; Affani, R.; Tranchant, M. J.; Antoniotti, S.; Dalla V.; Duñach, E. *Angew. Chem. Int. Ed.* **2010**, *49*, 776–780.

S27 Gaussian 16, Revision B.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.;

Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2016.

S28 GaussView, Version 6, Dennington, Roy; Keith, Todd A.; Millam, John M. Semichem Inc., Shawnee Mission, KS, 2016.