Electronic Supplementary Material (ESI) for ChemComm.

Supplementary Information

Diprotonative stabilization of carbocationic intermediate: ring-opening reaction of tetrahydroisoquinoline backbone for triarylmethane synthesis

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

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1. Experimental Section

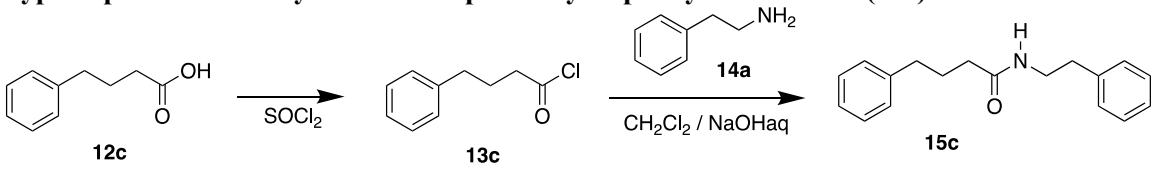
I. General methods

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 **9**,[S1] **11**,[S2] **14b**,[S3] **15b**,[S4] **15c**,[S5] **15e**,[S6] **15f**,[S7] **15g**,[S8] **15k**,[S9] **16**,[S10] **17k**,[S11] **18b**,[S12] **18c**,[S13] **18e**,[S14] **18k**,[S15] **15l**,[S16] **15m**,[S17] **15n**,[S16] **15o**,[S16] **15p**,[S16] **15q**,[S18] **15r**,[S19] **15s**,[S19] **17l**,[S20] **17m**,[S21] **17n**,[S20] **17o**,[S20] **17p**,[S22] **17q**,[S23] **17s**,[S23] **18l**,[S24] **18m**,[S24] and **18n**[S24] were previously reported in literatures.

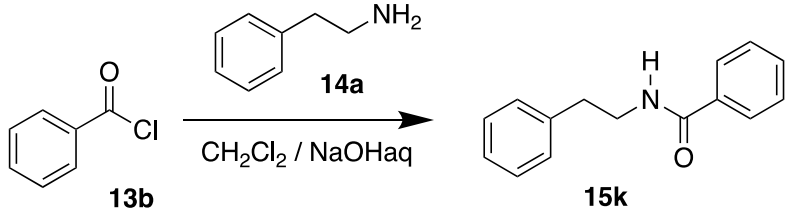
Typical procedure A: Synthesis of *N*-phenethyl-4-phenylbutanamide (15c)



To a mixture of 4-phenylbutylic acid (**12c**) (6514 mg, 39.7 mmol), thionyl chloride (5.0 mL) was added at 25 ºC under stirring. The mixture was stirred at room 50 ºC for 3 hours, then the solvent was removed under reduced pressure to afford 4-phenylbutanoyl chloride (**13c**) as a crude oil (7302 mg). A part of the crude oil (4474 mg) was dissolved in 5 mL of dichloromethane and added to a mixture of phenethylamine (**14a**) (3612 mg, 29.8 mmol), dichloromethane (15 mL), and aqueous sodium hydroxide (4M, 10 mL) at 0 ºC under vigorous stirring. The mixture was stirred at 0 ºC 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 **15c** as white solid (5801 mg, 21.7 mmol, 89% yield based on **12c**).

^{1}H-NMR (400 MHz, Chloroform-d) δ 7.33-7.13 (m, 10H), 5.56 (brs, 1H), 3.50 (dt, J = 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). ^{13}C-NMR (101 MHz, Chloroform-d) 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.

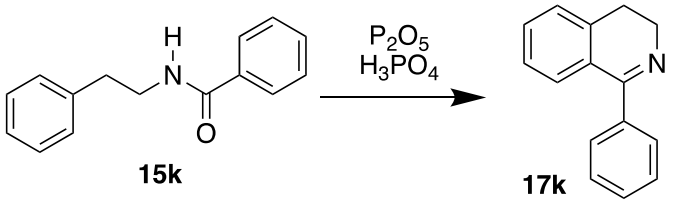
Typical procedure A-2: Synthesis of *N*-phenethylbenzamide (15k)



A solution of benzoyl chloride (**13b**) (2902 mg, 20.64 mmol) in 10 mL of dichloromethane was added to a mixture of **14a** (2437 mg, 20.11 mmol), dichloromethane (15 mL),

and aqueous sodium hydroxide (4M, 10 mL) at 0 ºC under vigorous stirring. The mixture was stirred at 0 ºC 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 **15k** as white solid (4205 mg, 18.66 mmol, 93%).
^{1}H-NMR (400 MHz, Chloroform-d) 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). ^{13}C-NMR (101 MHz, Chloroform-d) δ 167.4, 138.9, 134.6, 131.4, 128.8, 128.7, 128.5, 126.8, 126.6, 41.1, 35.7.

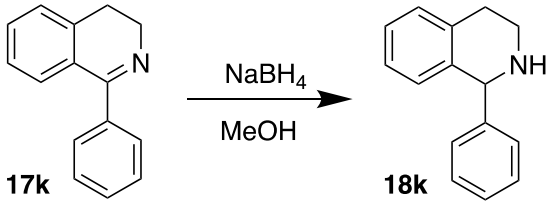
Typical procedure B: Synthesis of 1-phenyl-3,4-dihydroisoquinoline (17k)



15k **17k**

To phosphorous pentoxide (20 g), 7 mL of phosphoric acid (70%) was slowly added under stirring to prepare polyphosphoric acid. Then, **15k** was added to the acid and the mixture was stirred at 170 ºC for 1hr. Then, the mixture was cooled in ice bath and basified with 200 mL of aqueous sodium hydroxide (2M). 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 **17k** (3155 mg, 15.22 mmol, 86%) as pale yellow oil.
^{1}H-NMR (400 MHz, Chloroform-d) 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, Chloroform-d) 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.

Typical procedure C: Synthesis of 1-phenyl-1,2,3,4-tetrahydroisoquinoline (18k)

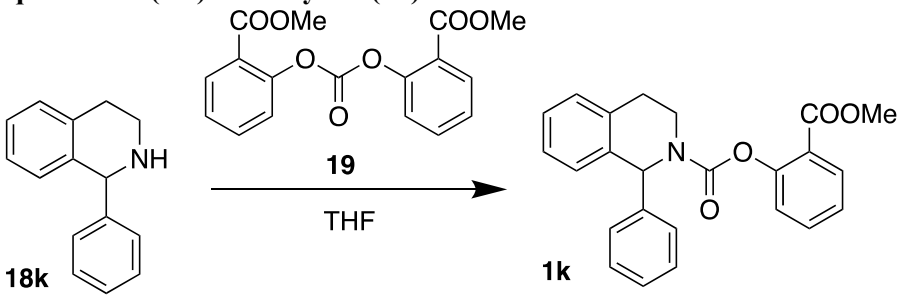


17k **18k**

To a solution of **17k** (1015 mg, 4.89 mmol) in methanol (15 mL), sodium borohydride (437 mg, 11.6 mmol, 2.4 eq.) was added at 0 ºC. The mixture was stirred at 25 ºC 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 **18k** (978 mg, 4.67 mmol, 96% yield) as white solid.
^{1}H-NMR (400 MHz, Chloroform-d) 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). ^{13}C-NMR (101 MHz, Chloroform-d) 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.

Typical procedure D: Synthesis of 2-(methoxycarbonyl)phenyl 1-phenyl-3,4-

dihydroisoquinoline-2(1*H*)-carboxylate (1k)

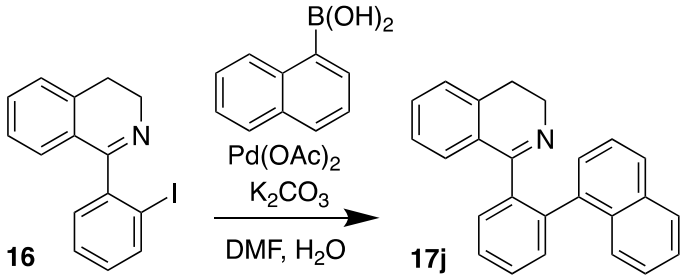


Dimethyl 2,2'-(carbonylbis(oxy))dibenzoate (**19**) was synthesized following previously reported procedure.[12a]

A solution of **19** (1484 mg, 4.49 mmol) and **18k** (1040 mg, 4.97 mmol, 1.1 eq.) in tetrahydrofuran (5.0 mL) was stirred at 50 ºC for 3 days. 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 **1k** as colorless sticky oil (1627 mg, 4.20 mmol, 94% yield).

^{1}H-NMR (400 MHz, DMSO-d6, 120 ºC) δ 7.85 (dd, J = 7.5, 1.4 Hz, 1H), 7.60-7.56 (m, 1H), 7.34-7.15 (m, 11H), 6.36 (s, 1H), 4.06-4.01 (m, 1H), 3.56 (s, 3H), 3.53-3.50 (m, 1H), 3.04-3.01 (m, 1H), 2.86-2.84 (m, 1H). ^{13}C-NMR (101 MHz, DMSO-d6, 120 ºC) δ 165.0, 153.1, 150.5, 142.3, 135.4, 134.8, 133.4, 130.8, 128.7, 128.3, 128.2, 127.8, 127.3, 127.2, 126.2, 125.5, 124.3, 124.0, 58.3, 51.6, 39.5, 27.8. ESI-HRMS: Calcd for $C_{24}H_{21}NNaO_4^+$ $[M+Na]^+$: 410.1363. Found: 410.1351.

Typical procedure E: Suzuki coupling reaction of 1-(2-iodophenyl)-3,4-dihydroisoquinoline (16)

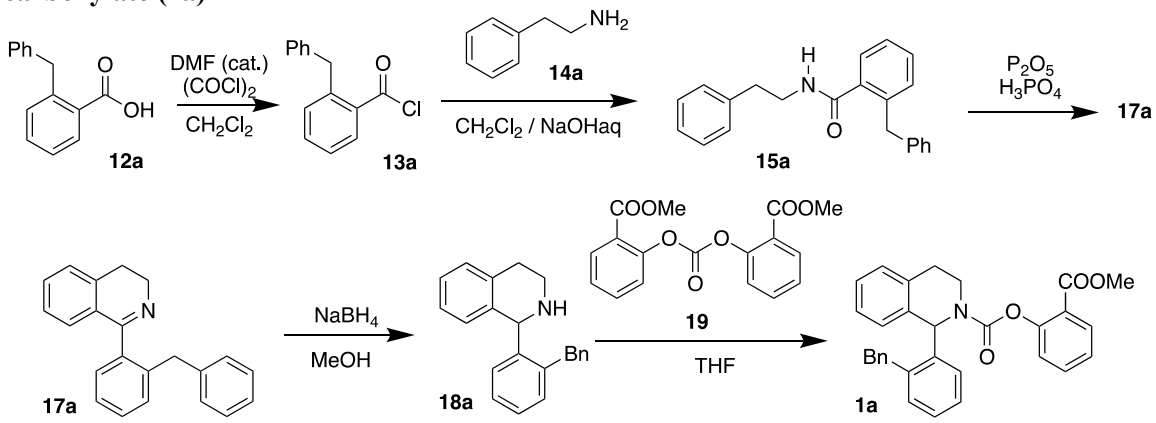


The coupling reaction was conducted following a protocol reported by Moteki and Takacs.[S25]

To a round-bottom flask equipped with a reflux condenser and a magnetic stir bar was added 1-(2-iodophenyl)-3,4-dihydroisoquinoline (1001 mg, 3.00 mmol), 1-naphtyl boronic acid (873 mg, 5.07 mmol), potassium carbonate (1376 mg, 9.96 mmol) and palladium acetate (25 mg, 0.11 mmol). The mixture of DMF (10 mL) and water (10 mL) was added and stirred at 100 ºC for 3 hours. Afterwards, the mixture was extracted with ethyl acetate (50 mL x 2). The organic layer was washed with brine (30 mL), dried over sodium sulfate, and concentrated under reduced pressure using rotary evaporator. The residue was purified by silica-gel chromatography to give 1-(2-(naphthalen-1-yl)phenyl)-3,4-dihydroisoquinoline (**17 j**) as pale brown sticky oil (512 mg, 1.54 mmol, 51% yield).

^{1}H-NMR (400 MHz, Chloroform-d) δ 7.75-7.73 (m, 1H), 7.67-7.65 (m, 2H), 7.56-7.51 (m, 3H), 7.48-7.45 (m, 1H), 7.36-7.29 (m, 2H), 7.24-7.15 (m, 2H), 6.92 (dd, J = 7.3, 7.3 Hz, 1H), 6.82 (d, J = 7.3 Hz, 1H), 6.76-6.72 (m, 2H), 3.56-3.48 (m, 2H), 2.32-2.25 (m, 1H), 2.02 (brs, 1H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 168.2, 140.1, 139.3, 138.5, 137.1, 133.3, 131.6, 131.0, 129.8, 129.5, 129.4, 128.4, 128.0, 127.8, 127.8, 127.4, 127.0, 126.9, 126.2, 125.8, 125.4, 125.4, 124.5, 77.3, 77.0, 76.7, 47.6, 25.7. ESI-HRMS: Calcd for $C_{25}H_{20}N^+$ $[M+H]^+$: 334.1590. Found: 334.1581.

Synthesis of 2-(methoxycarbonyl)phenyl 1-(2-benzylphenyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1a)



To a mixture of 2-benzylbenzoic acid (**12a**) (2141 mg, 10.1 mmol), N,N-dimethyl formamide (50 µL) in dichloromethane (20 mL), oxalyl chloride (1.30 mL, 15.1 mmol) was slowly added at 0 ºC under stirring. The mixture was stirred at room temperature for 3 hours, then the solvent was removed under reduced pressure to afford 2-benzylbenzoyl chloride (**13a**) as a crude oil. The crude oil was dissolved in 10 mL of dichloromethane and added to a mixture of phenethylamine (**14a**) (2437 mg, 20.1 mmol), dichloromethane (15 mL), and aqueous sodium hydroxide (4M, 10 mL) at 0 ºC under vigorous stirring. The mixture was stirred at 0 ºC 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 **15a** as white solid (4205 mg, 18.7 mmol, 93%).
^{1}H-NMR (400 MHz, Chloroform-d) 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). ^{13}C-NMR (101 MHz, Chloroform-d) δ 167.4, 138.9, 134.6, 131.4, 128.8, 128.7, 128.5, 126.8, 126.6, 41.1, 35.7.

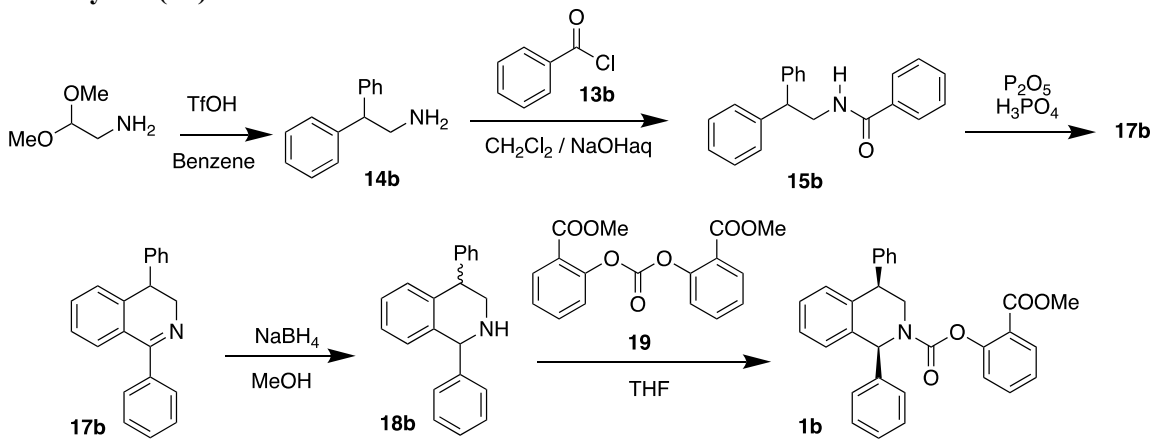
Compound 1-(2-benzylphenyl)-3,4-dihydroisoquinoline (**17a**) was synthesized following the procedure B. 67% yield from **15a**.
Pale brown oil. ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.33-7.22 (m, 4H), 7.19-7.05 (m, 6H), 6.98 (d, J = 7.1 Hz, 2H), 6.85 (d, J = 7.3 Hz, 1H), 3.89 (s, 2H), 3.85 (t, J = 7.4 Hz, 2H), 2.73 (t, J = 7.4 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 167.8, 140.5, 139.1, 138.9, 137.4, 130.6, 130.1, 129.6, 129.1, 129.0, 128.5, 128.1, 127.2, 127.2, 126.7, 126.1, 125.8, 47.5, 39.1, 25.8. ESI-HRMS: Calcd for $C_{22}H_{20}N^{+}$ $[M+H]^{+}$: 298.1590. Found: 298.1583.

Compound 1-(2-benzylphenyl)-1,2,3,4-tetrahydroisoquinoline (**18a**) was synthesized following the procedure C. 81% yield from **17a**.
Colorless oil. ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.28-7.07 (m, 11H), 7.04 (d, J = 7.5 Hz, 1H), 6.99-6.95 (m, 1H), 6.57 (d, J = 7.8 Hz, 1H), 5.33 (s, 1H), 4.24 (d, J = 15.6 Hz, 1H), 4.13 (d, J = 15.6 Hz, 1H), 3.19-3.14 (m, 1H), 3.05-2.90 (m, 2H), 2.78-2.73 (m, 1H), 1.59 (brs, 1H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 143.0, 141.4, 139.3, 138.7, 135.6, 130.8, 130.3, 128.9, 128.7, 128.5, 127.8, 127.3, 126.7, 126.0, 125.6, 58.3, 42.6, 39.0, 29.8. ESI-HRMS: Calcd for $C_{22}H_{22}N^{+}$ $[M+H]^{+}$: 300.1747. Found: 300.1740.

Compound **1a** was synthesized following the procedure D. 89% yield from **18a**.
White amorphous solid. ^{1}H-NMR (400 MHz, DMSO-d6, 140 ºC) δ 7.83 (d, J = 7.8 Hz, 1H), 7.57-7.52 (m, 1H), 7.30 (dd, J = 7.7, 7.7 Hz, 1H), 7.26-7.10 (m, 10H), 7.06 (d, J = 8.2 Hz, 1H), 7.00 (dd, J = 7.4, 7.4 Hz, 1H), 6.86 (d, J = 7.8 Hz, 1H), 6.60 (s, 1H), 6.51 (d, J = 7.8 Hz, 1H), 4.54 (d, J = 15.8 Hz, 1H), 4.23-4.13 (m, 2H), 3.50 (s, 3H), 3.50-3.42 (m, 1H), 3.20-3.13 (m, 1H), 2.95-2.91 (m, 1H). ^{13}C-NMR (101 MHz, DMSO-d6, 140 ºC) δ 164.2, 152.2, 149.6, 140.4, 139.9, 139.2, 135.2,

133.9, 132.5, 130.0, 130.0, 129.3, 128.2, 128.0, 127.5, 126.8, 126.8, 126.0, 125.3, 125.2, 125.1, 124.7, 123.6, 123.0, 54.4, 50.7, 37.6, 37.0, 27.0. ESI-HRMS: Calcd for $C_{31}H_{27}NNaO_4^+$ $[M+Na]^+$: 500.1832. Found: 500.1823.

Synthesis of cis-2-(methoxycarbonyl)phenyl 1,4-diphenyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (1b)



The synthesis of **14b** was conducted following a protocol reported by Klumpp et al.[S3] 96% yield.

White solid. ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.36-7.18 (m, 10H), 3.98 (t, J = 7.8 Hz, 1H), 3.32 (d, J = 7.8 Hz, 2H), 1.23 (brs, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 142.8, 128.6, 128.1, 126.5, 55.2, 47.0.

A solution of benzoyl chloride (**13b**) (1595 mg, 11.35 mmol) in 10 mL of dichloromethane was added to a mixture of **14b** (1877 mg, 9.51 mmol), dichloromethane (10 mL), and aqueous sodium hydroxide (1M, 20 mL) at 0 ºC under vigorous stirring. The mixture was stirred at 0 ºC 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-(2,2-diphenylethyl)benzamide **15b** as cotton-like crystal (2392 mg, 7.94 mmol, 83%).

^{1}H-NMR (400 MHz, Chloroform-d) δ 7.58-7.56 (m, 2H), 7.43 (dd, J = 7.3, 7.3 Hz, 1H), 7.35-7.21 (m, 12H), 6.14 (brs, 1H), 4.32 (t, J = 7.9 Hz, 1H), 4.08 (dd, J = 7.9, 5.8 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 167.5, 141.8, 134.5, 131.3, 128.7, 128.5, 128.0, 126.9, 126.7, 50.5, 44.2.

Compound 1,4-diphenyl-3,4-dihydroisoquinoline (**17b**) was synthesized following the procedure B. 61% yield from **15b**. ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.63-7.61 (m, 2H), 7.45-7.41 (m, 3H), 7.37-7.32 (m, 4H), 7.29-7.25 (m, 4H), 6.99 (d, J = 7.3 Hz, 1H), 4.24-4.13 (m, 2H), 4.01 (dd, J = 14.5, 10.6 Hz, 1H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 167.5, 141.5, 141.0, 138.9, 131.0, 129.3, 128.7, 128.7, 128.7, 128.5, 128.2, 128.0, 127.2, 127.0, 126.7, 54.5, 42.3.

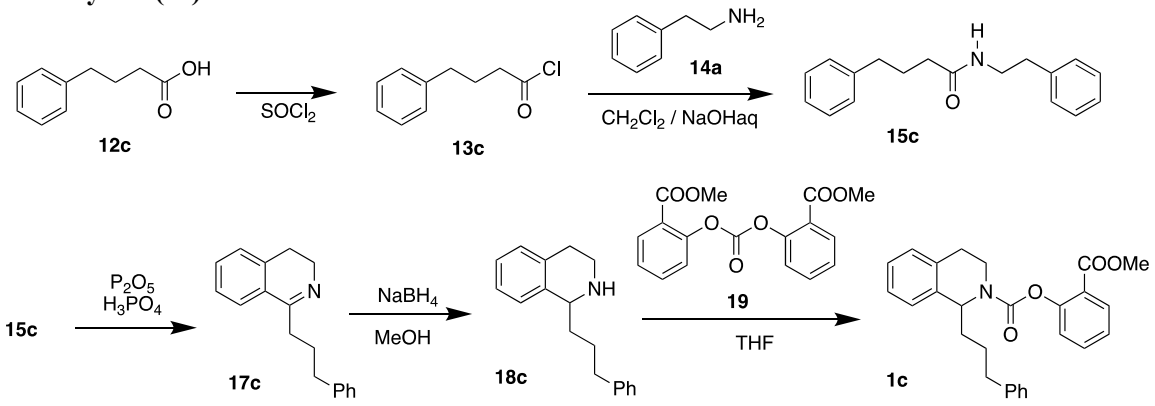
Compound 1,4-diphenyl-1,2,3,4-tetrahydroisoquinoline (**18b**) was synthesized following the procedure C. 96% yield from **17b**. The compound **18b** is the mixture of cis-1,4-diphenyl-1,2,3,4-tetrahydroisoquinoline (**18b-*cis***) and trans-1,4-diphenyl-1,2,3,4-tetrahydroisoquinoline (**18b-*trans***). The ratio was approximately 65 : 35 (determined by ^{1}H-NMR). The 1H and ^{13}C-NMR spectra were the same as previous reported spectra by Mashima et al.[S12] The product was used without further purification.

^{1}H-NMR (400 MHz, Chloroform-d) δ 7.35-6.78 (m, 14H, **18b-*cis*** and **18b-*trans***), 5.25 (s, 0.35H, **18b-*trans***), 5.18 (s, 0.65H, **18b-*cis***), 4.32 (dd, J = 8.6, 5.6 Hz, 0.35H, **18b-*trans***), 4.17 (t, J = 4.8 Hz, 0.65H, **18b-*cis***), 3.48 (dd, J = 12.3, 5.5 Hz, 0.35H, **18b-*trans***), 3.39 (dd, J = 12.8, 5.0 Hz, 0.65H, **18b-*cis***), 3.23 (dd, J = 12.6, 4.8 Hz, 0.65H, **18b-*cis***), 3.13 (dd, J = 12.3, 8.7 Hz, 0.35H, **18b-*trans***), 1.96 (brs, 1H, **18b-*cis*** and **18b-*trans***). ^{13}C-NMR (101 MHz, Chloroform-d) peaks of the

mixture. δ 145.5, 144.7, 144.5, 144.4, 138.7, 138.6, 138.5, 137.7, 130.3, 129.6, 129.0, 129.0, 128.5, 128.3, 128.0, 127.8, 127.5, 127.4, 126.6, 126.5, 126.4, 126.3, 126.2, 125.9, 62.6, 62.0, 51.4, 49.8, 46.1, 44.9

A solution of **19** (593 mg, 1.80 mmol) and **18b** (520 mg, mixture of **18b-*cis*** (1.1 mmol) and **18b-*trans*** (0.64 mmol)) in tetrahydrofuran (4.0 mL) was stirred at 50 ºC for 1 day. 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 **1b** as white amorphous solid (427 mg, 0.921 mmol, 78% yield based on **18b-*cis***). The reaction of **18b-*trans*** was relatively slow that the resultant product was not isolated.
^{1}H-NMR (400 MHz, DMSO-d6, 120 ºC) δ 7.77 (d, J = 7.5 Hz, 1H), 7.53-7.49 (ddd, J = 7.8, 7.8, 0.8 Hz, 1H), 7.32-7.03 (m, 15H), 6.79 (d, J = 7.1 Hz, 1H), 6.44 (s, 1H), 4.35 (dd, J = 11.3, 6.0 Hz, 1H), 4.18 (dd, J = 13.5, 6.0 Hz, 1H), 3.45 (s, 3H), 3.16 (dd, J = 13.5, 11.3 Hz, 1H). ^{13}C-NMR (101 MHz, DMSO-d6, 120 ºC) δ 164.3, 151.9, 149.7, 141.4, 141.3, 137.7, 133.9, 132.8, 130.2, 128.6, 128.1, 127.8, 127.8, 127.7, 127.0, 126.6, 126.4, 125.6, 124.9, 123.5, 123.4, 57.6, 51.0, 44.4, 43.8. ESI-HRMS: Calcd for $C_{30}H_{25}NNaO_4^+$ $[M+Na]^+$: 486.1676. Found: 486.1667.

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



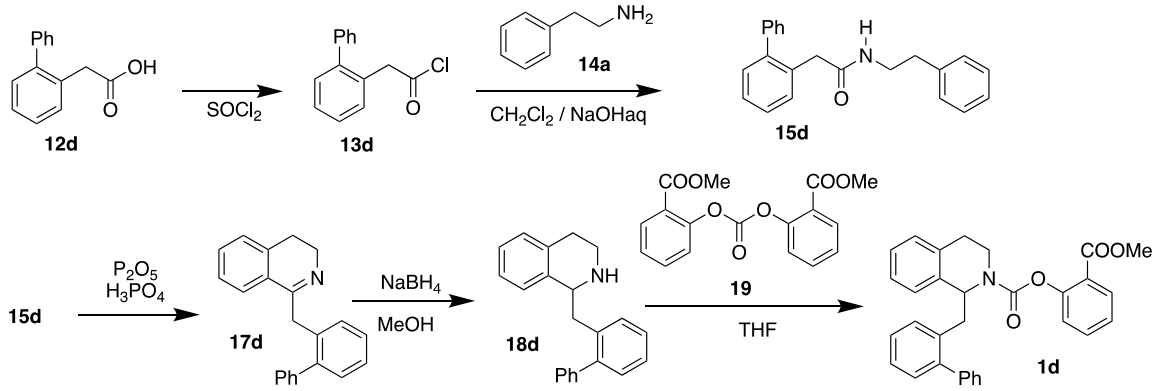
The synthesis of **15c** is shown in procedure A. Compound 1-(3-phenylpropyl)-3,4-dihydroisoquinoline (**17c)** was synthesized following the procedure B. 74% yield from **15c**. ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.39 (d, J = 7.5 Hz, 1H), 7.33 (ddd, J = 7.3, 7.3, 1.4 Hz, 1H), 7.28-7.25 (m, 3H), 7.17 (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). ^{13}C-NMR (101 MHz, Chloroform-d) 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.

Compound 1-(3-phenylpropyl)-1,2,3,4-tetrahydroisoquinoline (**18c**) was synthesized following the procedure C. 94% yield from **17c**. ^{1}H-NMR (400 MHz, Chloroform-d) 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). ^{13}C-NMR (101 MHz, Chloroform-d) 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.

Compound **1c** was synthesized following the procedure C. 88% yield from **18c**.
Colorless oil. ^{1}H-NMR (400 MHz, Chloroform-d), two rotamers (A and B) with respect to the amide bond were observed (approximately A : B = 6 : 4 ratio at 25 ºC), δ 7.96 (d, J = 7.1 Hz, 1H), 7.49-7.55 (m, 1H), 7.08-7.29 (m, 11H), 5.36 (d, J = 7.1 Hz, 0.4H, rotamer B), 5.23-5.26 (m, 0.6H, rotamer A), 4.27 (m, 0.6H, rotamer A), 4.16-4.22 (m, 0.4H, rotamer B), 3.65 (s, 1.8H, rotamer A), 3.51-3.58 (m, 0.6H, rotamer A), 3.44 (s, 1.2H, rotamer B), 3.30-3.37 (m, 0.4H, rotamer B), 2.99-3.15 (m, 1H), 2.62-2.88 (m, 3H), 1.82-2.02 (m, 4H). ^{13}C-NMR (101 MHz, Chloroform-d), two rotamers with respect to the amide bond were observed, δ ^{13}C-NMR (101 MHz, Chloroform-d) δ 165.55, 165.28, 153.85, 151.09, 150.71, 142.26, 142.00, 137.78, 137.58, 133.96, 133.82, 133.46,

131.78, 131.55, 129.05, 128.77, 128.50, 128.41, 128.33, 128.23, 127.21, 126.96, 126.72, 126.60, 126.17, 125.80, 125.65, 125.53, 125.41, 124.15, 124.04, 123.91, 55.53, 55.15, 51.93, 51.76, 38.94, 38.22, 36.32, 36.16, 35.51, 28.51, 28.05, 27.94, 27.87. ESI-HRMS: Calcd for $C_{27}H_{27}NNaO_4^+$ $[M+Na]^+$: 452.1832. Found: 452.1821.

Synthesis of 2-(methoxycarbonyl)phenyl 1-([1,1'-biphenyl]-2-ylmethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1d)



Compound 2-([1,1'-biphenyl]-2-yl)-N-phenethylacetamide (**15d**) was synthesized following the procedure A. 96% yield from **12d**.

Mp. 103 - 105 ºC (colorless needles, recrystallized from ethyl acetate/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.37-7.17 (m, 10H), 7.15-7.12 (m, 2H), 7.03-7.01 (m, 2H), 5.27 (brs, 1H), 3.48 (s, 2H), 3.40 (dt, J = 6.7, 6.7 Hz, 2H), 2.68 (t, J = 6.7 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 170.9, 142.4, 140.7, 138.6, 132.3, 130.5, 130.5, 128.9, 128.6, 128.6, 128.3, 127.9, 127.3, 127.2, 126.4, 41.2, 40.5, 35.3. ESI-HRMS: Calcd for $C_{22}H_{21}NNaO^+$ $[M+Na]^+$: 338.1515. Found: 338.1505.

Compound 1-([1,1'-biphenyl]-2-ylmethyl)-3,4-dihydroisoquinoline (**17d**) was synthesized following the procedure B. 38% yield from **15d**.

Pale yellow oil. ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.43-7.21 (m, 10H), 7.11 (d, J = 7.5 Hz, 1H), 7.06 (dd, J = 7.8, 7.8 Hz, 1H), 6.99 (d, J = 7.8 Hz, 1H), 4.04 (s, 2H), 3.70 (t, J = 7.4 Hz, 2H), 2.65 (t, J = 7.4 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.3, 141.8, 141.5, 137.8, 135.3, 130.2, 130.1, 129.3, 129.2, 128.8, 128.2, 127.4, 127.3, 127.0, 126.6, 126.4, 125.4, 47.2, 40.2, 26.1. ESI-HRMS: Calcd for $C_{22}H_{20}N^+$ $[M+H]^+$: 298.1590. Found: 298.1583.

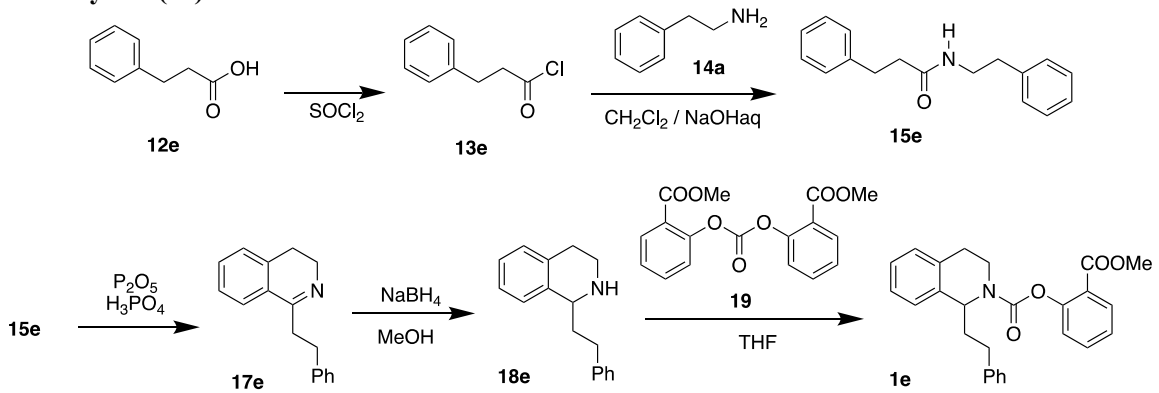
Compound 1-([1,1'-biphenyl]-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline (**18d**) was synthesized following the procedure C. 93% yield from **17d**.

Pale yellow sticky oil. ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.58-7.42 (m, 9H), 7.22-7.14 (m, 3H), 6.77 (d, J = 7.5 Hz, 1H), 4.05 (dd, J = 10.5, 3.2 Hz, 1H), 3.44 (dd, J = 13.8, 3.2 Hz, 1H), 3.13-3.05 (m, 2H), 2.94-2.82 (m, 3H), 1.78 (brs, 1H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 142.4, 141.5, 138.6, 136.8, 134.7, 130.2, 130.1, 129.1, 128.8, 128.0, 127.3, 126.8, 126.3, 126.2, 125.7, 125.3, 56.1, 39.6, 39.1, 29.6. ESI-HRMS: Calcd for $C_{22}H_{22}N^+$ $[M+H]^+$: 300.1747. Found: 300.1739.

Compound **1d** was synthesized following the procedure D. 79% yield from **18d**.

White amorphous solid. ^{1}H-NMR (400 MHz, DMSO-d6, 150 ºC) δ 7.79 (dd, J = 7.8, 1.6 Hz, 1H), 7.53-7.49 (m, 1H), 7.37-7.25 (m, 7H), 7.17-7.10 (m, 5H), 7.04-7.00 (m, 1H), 6.77 (brs, 1H), 6.55 (d, J = 7.8 Hz, 1H), 5.27 (t, J = 6.9 Hz, 1H), 3.95-3.91 (m, 1H), 3.53 (s, 3H), 3.35 (brs, 1H), 3.21-3.13 (m, 2H), 2.91-2.83 (m, 1H), 2.68 (dt, J = 16.2, 4.7 Hz, 1H). ^{13}C-NMR (101 MHz, DMSO-d6, 150 ºC) δ 164.1, 151.8, 149.6, 141.9, 140.7, 135.8, 134.9, 133.3, 132.1, 129.8, 129.7, 128.7, 128.2, 127.7, 127.1, 126.3, 125.9, 125.9, 125.7, 125.4, 125.0, 124.3, 123.3, 122.9, 55.9, 50.6, 38.1, 38.0, 26.7. ESI-HRMS: Calcd for $C_{31}H_{27}NNaO_4^+$ $[M+Na]^+$: 500.1832. Found: 500.1825.

Synthesis of 2-(methoxycarbonyl)phenyl 1-phenethyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (1e)



Compound N-phenethyl-3-phenylpropanamide (**15e**) was synthesized following the procedure A. 84% yield from **12e**.

^{1}H-NMR (400 MHz, Chloroform-d) 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). ^{13}C-NMR (101 MHz, Chloroform-d) 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.

Compound 1-phenethyl-3,4-dihydroisoquinoline (**17e**) was synthesized following the procedure B. 75% yield from **15e**.

^{1}H-NMR (400 MHz, Chloroform-d) 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). ^{13}C-NMR (101 MHz, Chloroform-d) 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.

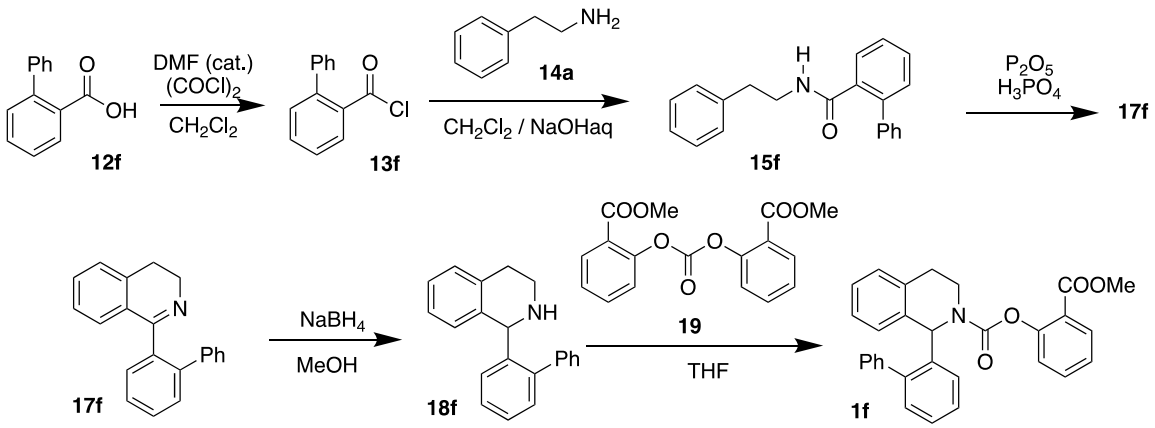
Compound 1-phenethyl-1,2,3,4-tetrahydroisoquinoline (**18e**) was synthesized following the procedure C. 96% yield from **17e**.

^{1}H-NMR (400 MHz, Chloroform-d) 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). ^{13}C-NMR (101 MHz, Chloroform-d) δ 142.3, 139.5, 135.2, 129.2, 128.4, 128.4, 126.0, 125.8, 125.7, 55.3, 40.9, 38.1, 32.4, 30.0.

Compound **1e** was synthesized following the procedure D. 81% yield from **18e**.

Colorless sticky oil. ^{1}H-NMR (400 MHz, Chloroform-d), two rotamers (A and B) with respect to the amide bond were observed (approximately A : B = 6 : 4 ratio at 25 ºC), δ 7.96 (d, J = 8.0 Hz, 1H), 7.50 (td, J = 8.0, 1.6 Hz, 1H), 7.20-7.27 (m, 5H), 7.07-7.18 (m, 6H), 5.42 (dd, J = 9.1, 5.0 Hz, 0.4H, rotamer B), 5.30 (q, J = 4.7 Hz, 0.6H, rotamer A), 4.21-4.32 (m, 1H), 3.70 (s, 1.8H, rotamer A), 3.58-3.65 (m, 0.6H, rotamer A), 3.47 (s, 1.2H, rotamer B), 3.38-3.47 (m, 0.4H), 3.01-3.16 (m, 1H), 2.78-2.91 (m, 3H), 2.00-2.30 (m, 2H). ^{13}C-NMR (101 MHz, Chloroform-d), two rotamers with respect to the amide bond were observed, δ 165.36, 165.10, 153.79, 150.98, 150.59, 141.83, 141.50, 137.32, 137.17, 133.84, 133.72, 133.36, 131.63, 131.41, 128.94, 128.65, 128.27, 128.24, 128.19, 127.09, 126.82, 126.68, 126.55, 126.08, 125.79, 125.62, 125.41, 125.31, 123.99, 123.87, 123.76, 55.48, 55.26, 51.85, 51.66, 38.99, 38.59, 38.45, 38.29, 32.67, 32.53, 28.39, 27.93. ESI-HRMS: Calcd for $C_{26}H_{25}NNaO_4^{+}$ $[M+Na]^{+}$: 438.1675. Found: 438.1664.

Synthesis of 2-(methoxycarbonyl)phenyl 1-([1,1'-biphenyl]-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1f)



To a mixture of 2-phenylbenzoic acid (**12f**) (2000 mg, 10.1 mmol), N,N-dimethyl formamide (30 μL) in dichloromethane (20 mL), oxalyl chloride (1.30 mL, 15.1 mmol) was slowly added at 0 ºC under stirring. The mixture was stirred at room temperature for 5 hours, then the solvent was removed under reduced pressure to afford 2-phenylbenzoyl chloride (**13f**) as a crude oil. The crude oil was dissolved in 10 mL of dichloromethane and added to a mixture of phenethylamine (**14a**) (1333 mg, 11.0 mmol), dichloromethane (15 mL), and aqueous sodium hydroxide (1M, 20 mL) at 0 ºC under vigorous stirring. The mixture was stirred at 0 ºC 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-phenethyl-[1,1'-biphenyl]-2-carboxamide (**15f**) as white solid (2840 mg, 9.42 mmol, 94%).

^{1}H-NMR (400 MHz, Chloroform-d) δ 7.59 (dd, J = 7.4, 1.0 Hz, 1H), 7.44-7.31 (m, 8H), 7.22-7.12 (m, 3H), 6.89 (d, J = 6.9 Hz, 2H), 5.39 (brs, 1H), 3.40 (dt, J = 6.8 Hz, 2H), 2.48 (t, J = 6.8 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 169.4, 140.0, 139.2, 138.4, 135.7, 130.0, 129.8, 128.6, 128.5, 128.4, 128.4, 128.4, 127.6, 127.4, 126.2, 40.7, 34.9.

Compound 1-([1,1'-biphenyl]-2-yl)-3,4-dihydroisoquinoline (**17f**) was synthesized following the procedure B. 51% yield from **15f**.

^{1}H-NMR (400 MHz, DMSO-d6) δ 7.42 (dd, J = 7.8, 7.8 Hz, 1H), 7.36-7.28 (m, 3H), 7.12 (d, J = 7.3 Hz, 2H), 7.08-7.03 (m, 3H), 6.99-6.95 (m, 2H), 6.88 (dd J = 7.5, 7.5 Hz, 1H), 6.55 (d, J = 7.5 Hz, 1H), 3.54 (t, J = 7.0 Hz, 2H), 2.51 (t, J = 7.4 Hz, 2H). ^{13}C-NMR (101 MHz, DMSO-d6, 100 ºC) δ 166.7, 140.3, 139.9, 137.9, 136.6, 129.9, 129.1, 129.1, 128.9, 128.4, 128.2, 127.3, 126.8, 126.5, 126.4, 126.0, 125.9, 46.8, 24.8. ESI-HRMS: Calcd for $C_{21}H_{18}N^{+}$ $[M+H]^{+}$: 284.1434. Found: 284.1427.

Compound 1-([1,1'-biphenyl]-2-yl)-1,2,3,4-tetrahydroisoquinoline (**18f**) was synthesized following the procedure C. 72% yield from **17f**.

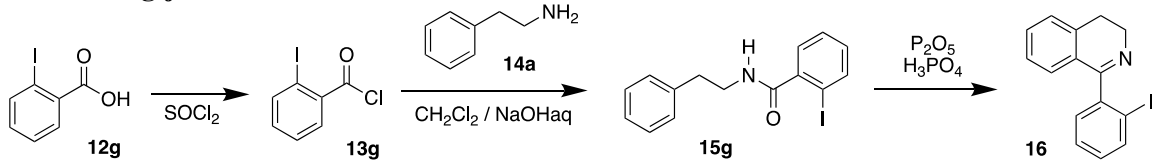
^{1}H-NMR (400 MHz, Chloroform-d) δ 7.46-7.25 (m, 8H), 7.17 (d, J = 6.9 Hz, 1H), 7.13-7.09 (m, 2H), 7.04-7.00 (m, 1H), 6.70 (d, J = 7.5 Hz, 1H), 5.24 (s, 1H), 3.28-3.23 (m, 1H), 3.07-2.91 (m, 2H), 2.76-2.71 (m, 1H), 1.71 (brs, 1H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 142.4, 141.2, 139.5, 135.6, 129.8, 129.6, 129.2, 128.9, 128.2, 128.1, 127.7, 127.1, 126.9, 126.0, 125.6, 57.8, 42.9, 29.9. ESI-HRMS: Calcd for $C_{21}H_{20}N^{+}$ $[M+H]^{+}$: 286.1590. Found: 286.1581.

Compound **1f** was synthesized following the procedure D. 80% yield from **18f**.

White amorphous solid. ^{1}H-NMR (400 MHz, DMSO-d6, 100 ºC) δ 7.73 (dd, J = 7.8, 1.6 Hz, 1H), 7.47 (td, J = 7.8, 1.4 Hz, 1H), 7.37-7.35 (m, 2H), 7.29-7.10 (m, 10H), 7.03 (t, J = 7.4 Hz, 1H), 6.83 (d, J = 7.5 Hz, 1H), 6.74 (d, J = 7.5 Hz, 1H), 6.41 (s, 1H), 4.04 (dt, J = 13.2, 4.9 Hz, 1H), 3.54-3.47 (m, 1H), 3.42 (s, 3H), 2.93-2.89 (m, 2H). ^{13}C-NMR (101 MHz, DMSO-d6, 100 ºC) δ 164.3, 152.3, 149.6, 141.1, 140.7, 140.2, 135.8, 134.3, 132.6, 130.1, 130.0, 128.6, 128.1, 127.8, 127.4, 127.0, 127.0, 126.7, 126.3, 126.2, 125.6, 124.8, 123.5, 123.3, 55.1, 51.0, 39.6, 27.7. ESI-HRMS: Calcd

for $C_{30}H_{25}NNaO_4^+$ [M+Na]$^+$: 486.1676. Found: 486.1669.

Synthesis of 1-(2-iodophenyl)-3,4-dihydroisoquinoline (16), a common intermediate of substrate 1g-j



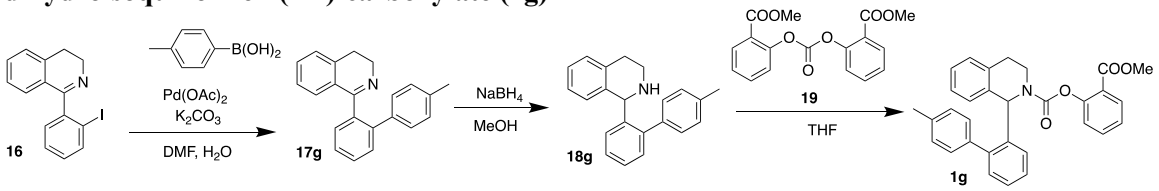
Compound 2-iodo-N-phenethylbenzamide (**15g**) was synthesized following the procedure A. 94% yield from **12g**.

^{1}H-NMR (400 MHz, Chloroform-d) δ 7.83 (dd, J = 8.0, 0.7 Hz, 1H), 7.36-7.22 (m, 7H), 7.09-7.05 (m, 1H), 5.77 (brs, 1H), 3.74 (dt, J = 6.8 Hz, 2H), 2.97 (t, J = 6.8 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 169.3, 142.3, 139.9, 138.6, 131.0, 128.9, 128.7, 128.1, 128.1, 126.6, 92.4, 41.1, 35.4.

Compound 1-(2-iodophenyl)-3,4-dihydroisoquinoline (**16**) was synthesized following the procedure B. 88% yield from **15g**.

^{1}H-NMR (400 MHz, Chloroform-d) δ 7.88 (d, J = 7.8 Hz, 1H), 7.44 (dd, J = 7.4, 7.4 Hz, 1H), 7.39-7.35 (m, 2H), 7.27-7.25 (m, 1H), 7.17 (dd, J = 7.4, 7.4 Hz, 1H), 7.11 (ddd, J = 7.8, 1.5 Hz, 1H), 6.86 (d, J = 7.5 Hz, 1H), 3.96 (brs, 2H), 2.88 (brs, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 169.2, 143.9, 139.1, 137.6, 130.9, 129.8, 129.5, 128.4, 128.2, 127.4, 127.0, 126.8, 96.3, 77.3, 77.0, 76.7, 47.7, 25.9.

Synthesis of 2-(methoxycarbonyl)phenyl 1-(4'-methyl-[1,1'-biphenyl]-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1g)



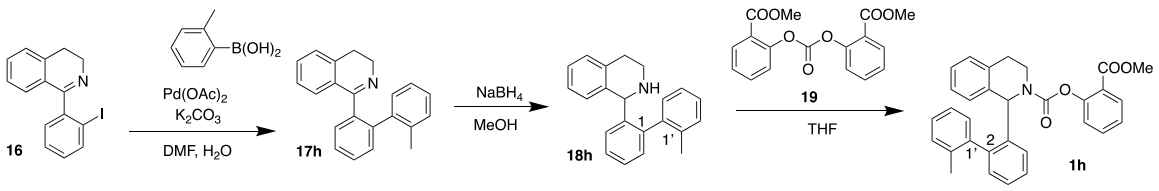
Compound 1-(4'-methyl-[1,1'-biphenyl]-2-yl)-1,2,3,4-tetrahydroisoquinoline (**18g**) was synthesized following the procedure E and procedure C. The intermediate **17g** was not isolated. 63% yield for 2 steps from **16**.

Colorless sticky oil. ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.34 (d, J = 8.0 Hz, 2H), 7.28-7.20 (m, 5H), 7.16-7.14 (m, 1H), 7.09-7.07 (m, 2H), 7.03-6.98 (m, 1H), 6.69 (d, J = 7.5 Hz, 1H), 5.26 (s, 1H), 3.27-3.22 (m, 1H), 3.06-2.91 (m, 2H), 2.75-2.70 (m, 1H), 2.38 (s, 3H), 1.75 (brs, 1H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 142.5, 142.3, 139.5, 138.2, 136.7, 135.6, 129.9, 129.5, 129.1, 128.9, 128.8, 128.1, 127.5, 126.9, 125.9, 125.6, 57.7, 42.8, 29.9, 21.1.

Compound **1g** was synthesized following the procedure D. 87% yield from **18g**.

White amorphous solid. ^{1}H-NMR (400 MHz, DMSO-d6, 140 ºC) δ 7.77 (d, J = 7.8 Hz, 1H), 7.49 (dd, J = 7.8, 7.8 Hz, 1H), 7.29-7.05 (m, 12H), 6.86-6.83 (m, 2H), 6.51 (s, 1H), 4.12-4.09 (m, 1H), 3.55-3.50 (m, 1H), 3.47 (s, 3H), 3.02-2.89 (m, 2H), 2.21 (s, 3H). ^{13}C-NMR (101 MHz, DMSO-d6, 140 ºC) δ 163.8, 151.7, 149.2, 140.8, 139.7, 137.3, 135.5, 135.1, 133.8, 131.8, 129.5, 129.5, 128.0, 127.6, 127.5, 127.4, 126.6, 126.2, 126.0, 125.6, 125.0, 124.0, 123.0, 122.9, 54.8, 50.3, 39.0, 27.2, 19.4. ESI-HRMS: Calcd for $C_{31}H_{27}NNaO_4^+$ [M+Na]$^+$: 500.1832. Found: 500.1819.

Synthesis of 2-(methoxycarbonyl)phenyl 1-(2'-methyl-[1,1'-biphenyl]-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1h)



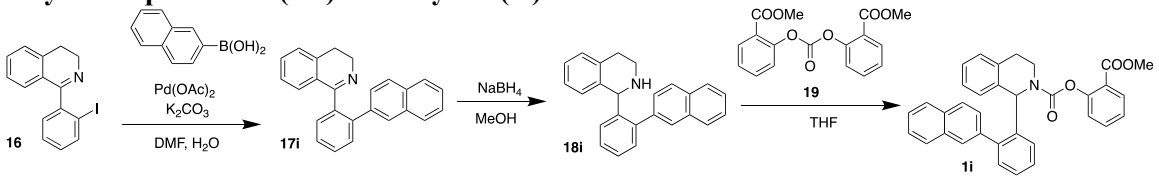
Compound 1-(2'-methyl-[1,1'-biphenyl]-2-yl)-1,2,3,4-tetrahydroisoquinoline (**18h**) was synthesized following the procedure E and procedure C. The intermediate **17h** was not isolated. 53% yield for 2 steps from **16**.

Colorless sticky oil. ^{1}H-NMR (400 MHz, Chloroform-d) two rotamers with respect to the C1-C1' bond rotation were observed, δ 7.31-7.01 (m, 11H), 6.75 (d, J = 8.6 Hz, 0.5H), 6.72 (d, J = 8.6 Hz, 0.5H), 4.97 (s, 0.5H), 4.88 (s, 0.5H), 3.25-3.14 (m, 1H), 3.04-2.82 (m, 2H), 2.76-2.68 (m, 1H), 2.24 (s, 1.5H), 2.16 (s, 1.5H), 1.67 (brs, 1H). ^{13}C-NMR (101 MHz, Chloroform-d) two rotamers with respect to the C1-C1' bond rotation were observed, δ 142.9, 142.8, 141.8, 141.5, 140.6, 140.5, 139.3, 138.5, 136.1, 135.9, 135.8, 135.5, 130.1, 130.0, 129.8, 129.7, 129.6, 129.5, 129.4, 128.9, 128.9, 128.1, 127.9, 127.7, 127.5, 127.4, 127.4, 126.8, 126.8, 126.0, 125.9, 125.5, 125.5, 58.0, 42.8, 41.9, 29.8, 20.5, 20.4. ESI-HRMS: Calcd for $C_{22}H_{22}N^{+}$ $[M+H]^{+}$: 300.1747. Found: 300.1738.

Compound **1h** was synthesized following the procedure D. 72% yield from **18h**.

White amorphous solid. ^{1}H-NMR (400 MHz, DMSO-d6, 140 ºC) two rotamers with respect to the C2–C1' bond were observed (approximately 1 : 1 ratio at 140 ºC) δ 7.77 (d, J = 7.5 Hz, 0.5H), 7.71 (d, J = 7.5 Hz, 0.5H), 7.51 (s, 1H), 7.30-6.97 (m, 12.5H), 6.92-6.87 (m, 1H), 6.56 (d, J = 7.1 Hz, 0.5H), 6.36 (s, 0.5H), 6.25 (s, 0.5H), 4.02-3.98 (m, 0.5H), 3.87-3.83 (m, 0.5H), 3.52 (s, 1.5H), 3.48-3.36 (m, 1H), 3.39 (s, 1.5H), 3.02-2.78 (m, 2H), 1.98 (s, 3H). ^{13}C-NMR (101 MHz, DMSO-d6, 140 ºC) two rotamers with respect to the C2–C1' bond were observed, δ 164.2, 164.2, 152.0, 151.7, 149.5, 149.4, 141.0, 140.1, 139.9, 139.8, 139.3, 138.9, 135.4, 135.3, 134.8, 134.3, 132.2, 132.0, 130.1, 129.9, 129.8, 129.7, 129.3, 129.2, 129.1, 128.8, 128.5, 128.2, 128.0, 127.7, 127.3, 126.6, 126.5, 126.4, 126.2, 126.2, 126.1, 125.1, 124.5, 124.4, 124.3, 123.4, 123.2, 123.2, 56.7, 55.6, 50.7, 50.5, 38.2, 26.9, 26.6, 18.8. ESI-HRMS: Calcd for $C_{31}H_{27}NNaO_4^{+}$ $[M+Na]^{+}$: 500.1832. Found: 500.1821.

Synthesis of 2-(methoxycarbonyl)phenyl 1-(2-(naphthalen-2-yl)phenyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1i)



Compound 1-(2-(naphthalen-2-yl)phenyl)-3,4-dihydroisoquinoline (**17i**) was synthesized following the procedure E. 84% yield from **16**.

^{1}H-NMR (400 MHz, Chloroform-d) δ 7.78 (s, 1H), 7.70-7.68 (m, 2H), 7.60 (d, J = 8.5 Hz, 1H), 7.56-7.52 (m, 3H), 7.50-7.44 (m, 1H), 7.42-7.35 (m, 3H), 7.05 (dd, J = 7.5, 7.5 Hz, 1H), 6.96-6.91 (m, 2H), 6.86 (d, J = 7.5 Hz, 1H), 3.78 (brs, 2H), 2.63 (t, J = 7.4 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 168.5, 140.8, 138.6, 138.5, 137.2, 133.0, 132.1, 130.2, 130.1, 129.7, 129.7, 128.9, 127.9, 127.8, 127.4, 127.4, 127.2, 127.2, 126.9, 126.8, 126.3, 125.9, 125.6, 47.7, 25.8. ESI-HRMS: Calcd for $C_{25}H_{20}N^{+}$ $[M+H]^{+}$: 334.1590. Found: 334.1581.

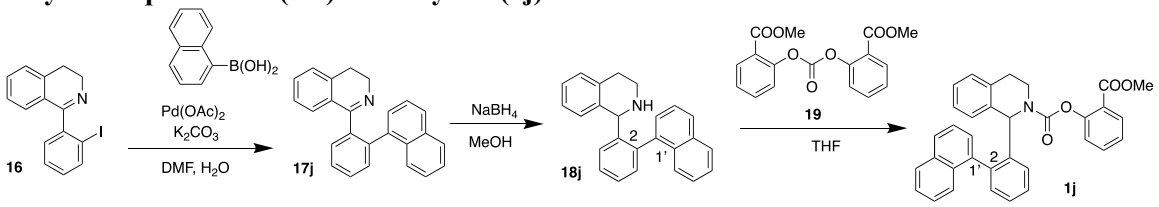
Compound 1-(2-(naphthalen-2-yl)phenyl)-1,2,3,4-tetrahydroisoquinoline (**18i**) was synthesized following the procedure C. 94% yield from **17i**.

^{1}H-NMR (400 MHz, Chloroform-d) δ 7.89-7.84 (m, 4H), 7.59 (dd, J = 8.5, 1.6 Hz, 1H), 7.52-7.47 (m, 2H), 7.39-7.35 (m, 1H), 7.34-7.29 (m, 2H), 7.24-7.20 (m, 1H), 7.12-7.02 (m, 3H), 6.77 (d, J = 7.5 Hz, 1H), 5.29 (s, 1H), 3.27-3.22 (m, 1H), 3.03-2.88 (m, 2H), 2.72-2.67 (m, 1H), 1.77 (brs, 1H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 142.6, 142.3, 139.4, 138.8, 135.6, 133.2, 132.4, 130.1,

129.7, 128.9, 128.1, 128.1, 128.0, 127.9, 127.7, 127.7, 127.7, 127.0, 126.3, 126.0, 126.0, 125.7, 58.0, 42.9, 29.9. ESI-HRMS: Calcd for $C_{25}H_{22}N^+$ $[M+H]^+$: 336.1747. Found: 336.1739.

Compound **1i** was synthesized following the procedure D. 84% yield from **18i**. Colorless oil. ^{1}H-NMR (400 MHz, DMSO-d6, 150 ºC) δ 7.91 (s, 1H), 7.82 (d, J = 8.5 Hz, 2H), 7.71-7.74 (m, 2H), 7.59 (d, J = 8.5 Hz, 1H), 7.44 (m, 2H), 7.27-7.38 (m, 5H), 7.17-7.22 (m, 3H), 7.11 (t, J = 7.2 Hz, 1H), 6.94 (d, J = 7.8 Hz, 1H), 6.57 (m, 2H), 4.09-4.14 (m, 1H), 3.52-3.55 (m, 1H), 3.45 (s, 3H), 2.88-3.04 (m, 2H). ^{13}C-NMR (101 MHz, DMSO-d6, 150 ºC) δ 164.0, 152.0, 149.3, 141.0, 140.0, 138.1, 135.7, 134.1, 132.2, 132.0, 131.4, 130.1, 129.7, 127.9, 127.1, 127.0, 126.9, 126.8, 126.7, 126.6, 126.4, 125.9, 125.3, 125.2, 124.9, 124.2, 123.1, 122.9, 55.3, 50.5, 39.2, 27.4. ESI-HRMS: Calcd for $C_{34}H_{27}NNaO_5^+$ $[M+Na]^+$: 536.1832. Found: 536.1825.

Synthesis of 2-(methoxycarbonyl)phenyl 1-(2-(naphthalen-1-yl)phenyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1j)

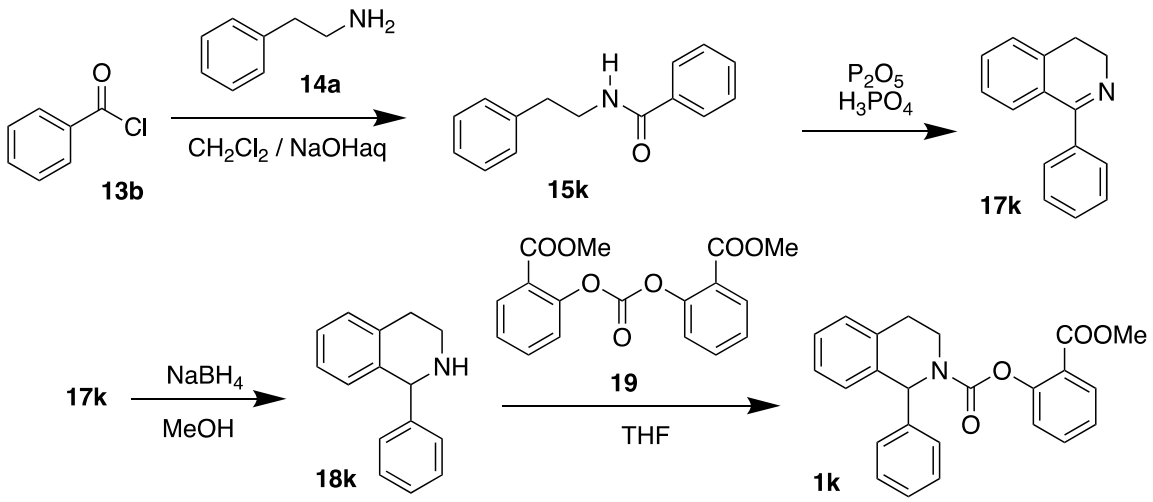


The synthetic scheme of **17j** is shown in procedure E.

Compound **18j** was synthesized following the procedure D. 93% yield from **17j**. ^{1}H-NMR (400 MHz, DMSO-d6, 120 ºC) two rotamers with respect to the C2-C1' bond were observed (approximately 1 : 1 ratio at 120 ºC), δ 7.86-7.78 (m, 2H), 7.52-7.30 (m, 5H), 7.26-7.20 (m, 2H), 7.16-7.11 (m, 1.5H), 7.00-6.97 (m, 0.5H), 6.90-6.77 (m, 3H), 6.54 (d, J = 7.3 Hz, 0.5H), 6.47 (d, J = 7.5 Hz, 0.5H), 4.59 (s, 0.5H), 4.55 (s, 0.5H), 2.99-2.91 (m, 1H), 2.74-2.65 (m, 1H), 2.59-2.53 (m, 0.5H), 2.49-2.41 (m, 1.5H), 1.94 (brs, 1H). ^{13}C-NMR (101 MHz, DMSO-d6, 25 ºC) two rotamers with respect to the C2-C1' bond were observed, δ 144.1, 143.9, 139.6, 139.5, 139.4, 138.9, 138.6, 137.9, 135.7, 135.2, 133.2, 132.9, 132.0, 131.9, 130.2, 130.0, 129.7, 129.2, 128.8, 128.7, 128.3, 128.1, 128.0, 127.6, 127.5, 127.5, 127.4, 127.2, 126.9, 126.4, 126.3, 126.0, 125.9, 125.7, 125.6, 125.5, 125.4, 125.3, 125.2, 57.8, 57.3, 42.5, 41.5, 29.3, 29.2. ESI-HRMS: Calcd for $C_{25}H_{22}N^+$ $[M+H]^+$: 336.1747. Found: 336.1739.

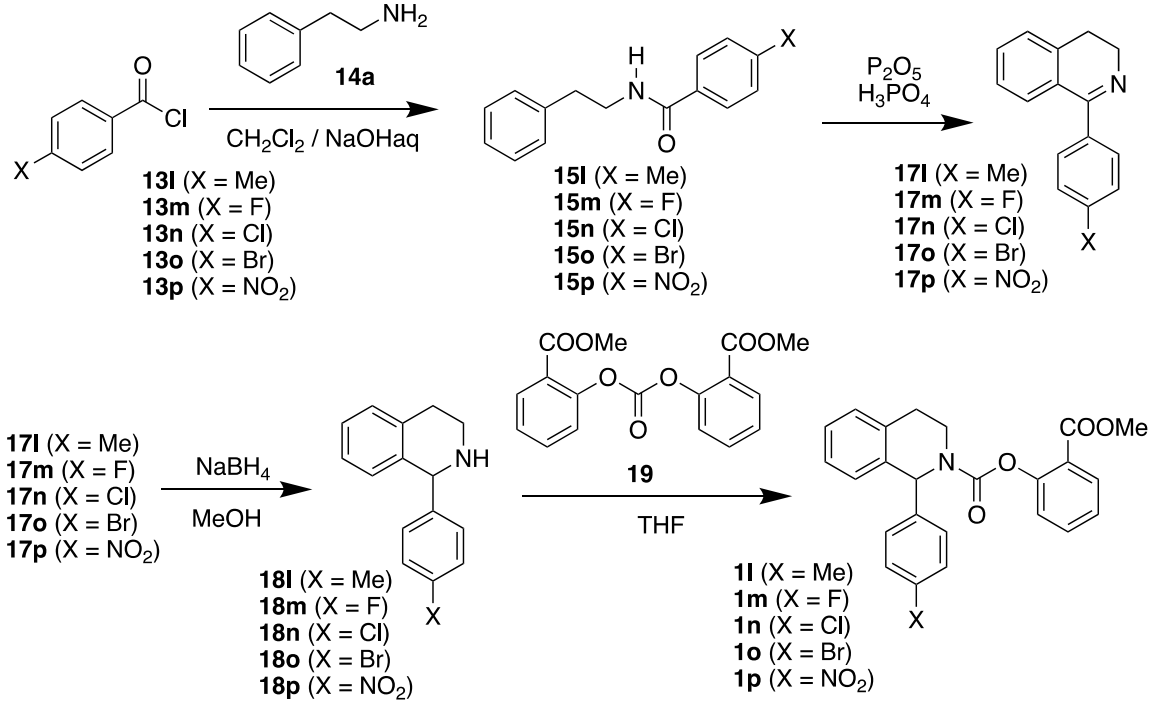
Compound **1j** was synthesized following the procedure D. 87% yield from **18j**. White amorphous solid. ^{1}H-NMR (400 MHz, DMSO-d6, 120 ºC) two rotamers with respect to the C2–C1' bond were observed (approximately 1 : 1 ratio at 120 ºC) δ 7.89-7.74 (m, 2.5H), 7.62 (dd, J = 7.8, 1.4 Hz, 0.5H), 7.58-7.54 (m, 0.5H), 7.50-7.10 (m, 12H), 6.96-6.87 (m, 1.5H), 6.61 (d, J = 7.8 Hz, 0.5H), 6.50 (s, 0.5H), 6.18 (s, 0.5H), 6.02 (d, J = 7.3 Hz, 0.5H), 3.93-3.83 (m, 1H), 3.45 (s, 1.5H), 3.42-3.36 (m, 1H), 3.33 (s, 1.5H), 2.96 (m, 1H), 2.88-2.79 (m, 1H). ^{13}C-NMR (101 MHz, DMSO-d6, 120 ºC) two rotamers with respect to the C2–C1' bond were observed (approximately 1 : 1 ratio at 120 ºC) δ 164.1, 151.8, 151.3, 149.5, 149.0, 140.4, 139.7, 139.1, 137.8, 137.5, 135.4, 135.3, 134.4, 134.1, 133.0, 132.8, 132.3, 131.8, 131.5, 130.9, 129.9, 129.6, 129.1, 128.7, 128.1, 128.0, 127.5, 127.3, 127.2, 127.0, 126.9, 126.7, 126.6, 126.4, 126.3, 126.2, 126.1, 125.4, 125.2, 124.9, 124.8, 124.6, 124.5, 124.4, 124.2, 123.3, 123.2, 123.0, 122.9, 56.1, 55.3, 50.7, 50.5, 38.6, 37.9, 26.9, 26.6. ESI-HRMS: Calcd for $C_{34}H_{27}NNaO_5^+$ $[M+Na]^+$: 536.1832. Found: 536.1822.

Synthesis of 2-(methoxycarbonyl)phenyl 1-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (1k)



The synthetic procedure of *N*-phenethylbenzamide (**15k**) is shown in the procedure A-2. The synthetic procedure of 1-phenyl-3,4-dihydroisoquinoline (**17k**) is shown in the procedure B. The synthetic procedure of 1-phenyl-1,2,3,4-tetrahydroisoquinoline (**18k**) is shown in the procedure C. The synthetic procedure of **1k** is shown in the procedure D.

Synthetic route of substrate 1l-p



Synthesis of 2-(methoxycarbonyl)phenyl 1-(p-tolyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1l)

Compound **15l** was synthesized following the procedure A-2. 91% yield from **13l** and **14a**.

White solid. ^{1}H-NMR (400 MHz, Chloroform-d) 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). ^{13}C-NMR (101 MHz, Chloroform-d) 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.

Compound **17l** was synthesized following the procedure B. 88% yield from **15l**.

White solid. ^{1}H-NMR (400 MHz, Chloroform-d) 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). ^{13}C-NMR (101 MHz, Chloroform-d) 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.

Compound **18l** was synthesized following the procedure C. 79% yield from **17l**.

Pale yellow solid. ^{1}H-NMR (400 MHz, Chloroform-d) 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). ^{13}C-NMR (101 MHz, Chloroform-d) 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.

Compound **1l** was synthesized following the procedure D. 78% yield from **18l** and **19**.

Colorless sticky oil. ^{1}H-NMR (400 MHz, Chloroform-d, 55 ºC) δ 7.95 (d, J = 7.8 Hz, 1H), 7.48 (dd, J = 7.8, 7.8 Hz, 1H), 7.26-7.14 (m, 7H), 7.10-7.06 (m, 3H), 6.47 (brs, 1H), 4.21 (brs, 1H), 3.56 (s, 3H), 3.47 (brs, 1H), 3.13 (brs, 1H), 2.83 (d, J = 16.0 Hz, 1H), 2.31 (s, 3H). ^{13}C-NMR (101 MHz, Chloroform-d, 55 ºC) δ 165.4, 153.6, 151.0, 139.4, 137.1, 135.5, 134.9, 133.3, 131.6, 128.9, 128.8, 128.5, 128.5, 127.0, 126.1, 125.4, 124.2, 124.1, 58.0, 51.7, 38.8, 28.4, 20.9. ESI-HRMS: Calcd for $C_{25}H_{23}NNaO_4^{+}$ $[M+Na]^{+}$: 424.1519. Found: 424.1508.

Synthesis of 2-(methoxycarbonyl)phenyl 1-(4-fluorophenyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1m)

Compound **15m** was synthesized following the procedure A-2. 95% yield from **13m**. White solid. ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.71-7.67 (m, 2H), 7.30 (dd, J = 7.3, 7.3 Hz, 2H), 7.25-7.19 (m, 3H), 7.06-7.01 (m, 2H), 6.44 (brs, 1H), 3.67 (dt, J = 7.0, 7.0 Hz, 2H), 2.91 (t, J = 7.0 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.4, 164.5 (d, J = 251.4 Hz), 138.8, 130.7 (d, J = 3.9 Hz), 129.1 (d, J = 8.7 Hz), 128.7, 128.6, 126.5, 115.4 (d, J = 21.2 Hz), 41.2, 35.6. ESI-HRMS: Calcd for $C_{15}H_{15}FNO^{+}$ $[M+H]^{+}$: 244.1132. Found: 244.1129.

Compound **17m** was synthesized following the procedure B. 89% yield from **15m**. Pale yellow oil. ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.60 (ddd, J = 11.9, 5.3, 3.2 Hz, 2H), 7.41-7.37 (m, 1H), 7.28-7.22 (m, 3H), 7.13-7.07 (m, 2H), 3.85-3.81 (m, 2H), 2.79 (t, J = 7.3 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.2, 163.5 (d, J = 248.5 Hz), 138.8, 135.0 (d, J = 2.9 Hz), 130.7,130.6 (d, J = 8.7 Hz), 128.5, 127.6, 127.4, 126.6, 115.0 (d, J = 22.2 Hz), 47.5, 26.2. ESI-HRMS: Calcd for $C_{15}H_{13}FN^{+}$ $[M+H]^{+}$: 226.1027. Found: 226.1024.

Compound **18m** was synthesized following the procedure C. 88% yield from **17m**. White solid. ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.26-7.22 (m, 2H), 7.14 (d, J = 4.1 Hz, 2H), 7.06-6.97 (m, 3H), 6.72 (d, J = 7.8 Hz, 1H), 5.08 (s, 1H), 3.28-3.23 (m, 1H), 3.12-3.00 (m, 2H), 2.83-2.78 (m, 1H), 1.85 (brs, 1H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 162.1 (d, J = 245.6 Hz), 140.7, 138.1, 135.4, 130.5 (d, J = 8.7 Hz), 129.1, 127.9, 126.3, 125.7, 115.2 (d, J = 21.2 Hz), 61.4, 42.3, 29.7. ESI-HRMS: Calcd for $C_{15}H_{15}FN^{+}$ $[M+H]^{+}$: 228.1183. Found: 228.1182.

Compound **1m** was synthesized following the procedure D. 93% yield from **18m**. Colorless sticky oil. ^{1}H-NMR (400 MHz, Chloroform-d, 55 ºC) δ 7.97 (dd, J = 7.8, 1.6 Hz, 1H), 7.54-7.50 (m, 1H), 7.37-7.14 (m, 8H), 7.06 (d, J = 7.5 Hz, 1H), 7.00-6.96 (m, 2H), 6.47 (brs, 1H), 4.25 (brs, 1H), 3.59 (s, 3H), 3.46 (brs, 1H), 3.15 (brs, 1H), 2.84 (dt, J = 16.2, 3.8 Hz, 1H). ^{13}C-NMR (101 MHz, Chloroform-d, 55 ºC) δ 165.4, 162.3 (d, J = 245.6 Hz), 153.9, 151.0, 138.3, 135.2, 135.0, 133.5, 131.7, 130.3 (d, J = 7.7 Hz), 129.0, 128.5, 127.3, 126.4, 125.6, 124.1, 124.1, 115.1 (d, J = 21.2 Hz), 57.6, 51.8, 38.9, 28.5. ESI-HRMS: Calcd for $C_{24}H_{20}FNNaO_4^{+}$ $[M+Na]^{+}$: 428.1268. Found: 428.1258.

Synthesis of 2-(methoxycarbonyl)phenyl 1-(4-chlorophenyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1n)

Compound **15n** was synthesized following the procedure A-2. 94% yield from **13n**. White solid. ^{1}H-NMR (400 MHz, Chloroform-d) 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). ^{13}C-NMR (101 MHz, Chloroform-d) 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.

Compound **17n** was synthesized following the procedure B. 85% yield from **15n**. White solid. ^{1}H-NMR (400 MHz, Chloroform-d) 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). ^{13}C-NMR (101 MHz, Chloroform-d) 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.

Compound **18n** was synthesized following the procedure C. 94% yield from **17n**. White solid. ^{1}H-NMR (400 MHz, Chloroform-d) 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). ^{13}C-NMR (101 MHz, Chloroform-d) 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.

Compound **1n** was synthesized following the procedure D. 95% yield from **18n**. Colorless sticky oil. ^{1}H-NMR (400 MHz, Chloroform-d, 55 ºC) δ 7.96 (dd, J = 7.8, 1.6 Hz, 1H),

7.51-7.47 (m, 1H), 7.26-7.16 (m, 8H), 7.14 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 7.5 Hz, 1H), 6.44 (brs, 1H), 4.21 (brs, 1H), 3.59 (s, 3H), 3.47 (brs, 1H), 3.12 (brs, 1H), 2.82 (dt, J = 16.2, 3.9 Hz, 1H). ^{13}C-NMR (101 MHz, Chloroform-d, 55 ºC) δ 165.2, 153.7, 150.9, 140.8, 134.9, 134.8, 133.4, 133.4, 131.6, 129.8, 128.9, 128.4, 128.4, 127.3, 126.3, 125.5, 124.0, 124.0, 57.5, 51.7, 39.1, 28.3. ESI-HRMS: Calcd for $C_{24}H_{20}ClNNaO_4^+$ $[M+Na]^+$: 444.0973. Found: 444.0968.

Synthesis of 2-(methoxycarbonyl)phenyl 1-(4-bromophenyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1o)

Compound **15o** was synthesized following the procedure A. 77% yield from **13o**.
White solid. ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.56-7.52 (m, 4H), 7.33 (dd, J = 7.2, 7.2 Hz, 2H), 7.27-7.22 (m, 3H), 6.10 (brs, 1H), 3.71 (dt, J = 6.8, 6.8 Hz, 2H), 2.93 (t, J = 6.8 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.5, 138.7, 133.5, 131.8, 128.8, 128.8, 128.4, 126.7, 126.1, 41.2, 35.6. ESI-HRMS: Calcd for $C_{15}H_{15}BrNO^+$ $[M+H]^+$: 304.0332. Found: 304.0334.

Compound **17o** was synthesized following the procedure B. 82% yield from **15o**.
White solid. ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.58-7.55 (m, 2H), 7.50-7.47 (m, 2H), 7.40 (ddd, J = 7.3, 7.4, 1.5 Hz, 1H), 7.28-7.21 (m, 3H), 3.85-3.82 (m, 2H), 2.80 (t, J = 7.3 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.3, 138.8, 137.9, 131.3, 130.9, 130.4, 128.4, 127.6, 127.5, 126.6, 123.6, 47.7, 26.2. ESI-HRMS: Calcd for $C_{15}H_{13}BrN^+$ $[M+H]^+$: 286.0226. Found: 286.0228.

Compound **18o** was synthesized following the procedure C. 95% yield from **17o**.
Pale yellow oil. ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.43 (d, J = 8.5 Hz, 2H), 715-7.13 (m, 4H), 7.05-7.01 (m, 1H), 6.70 (d, J = 7.8 Hz, 1H), 5.05 (s, 1H), 3.26-3.21 (m, 1H), 3.11-2.98 (m, 2H), 2.83-2.78 (m, 1H), 1.90 (brs, 1H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 143.9, 137.7, 135.4, 131.4, 130.7, 129.1, 127.9, 126.4, 125.7, 121.2, 61.4, 42.2, 29.6. ESI-HRMS: Calcd for $C_{15}H_{15}BrN^+$ $[M+H]^+$: 288.0383. Found: 288.0383.

Compound **1o** was synthesized following the procedure D. 76% yield from **18o**.
Colorless sticky oil. ^{1}H-NMR (400 MHz, Chloroform-d, 55 ºC) δ 7.96 (d, J = 7.8 Hz, 1H), 7.52-7.48 (m, 1H), 7.42 (d, J = 8.0 Hz, 2H), 7.31-7.19 (m, 6H), 7.14 (d, J = 8.2 Hz, 1H), 7.09-7.05 (m, 1H), 6.43 (brs, 1H), 4.21 (brs, 1H), 3.60 (s, 3H), 3.46 (brs, 1H), 3.13 (brs, 1H), 2.83 (dt, J = 16.1, 3.8 Hz, 1H). ^{13}C-NMR (101 MHz, Chloroform-d, 55 ºC) δ 165.3, 153.8, 151.0, 141.4, 135.0, 134.8, 133.4, 131.7, 131.4, 130.3, 129.0, 128.4, 127.4, 126.4, 125.5, 124.1, 124.1, 121.7, 57.8, 51.8, 39.2, 28.4. ESI-HRMS: Calcd for $C_{24}H_{20}BrNNaO_4^+$ $[M+Na]^+$: 488.0468. Found: 488.0460.

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

Compound **15p** was synthesized following the procedure A-2. 81% yield from **13p**.
White solid. ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.25-8.22 (m, 2H), 7.84-7.81 (m, 2H), 7.35-7.22 (m, 5H), 6.30 (brs, 1H), 3.74 (dt, J = 6.8, 6.8 Hz, 2H), 2.96 (t, J = 6.8 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 165.4, 149.5, 140.2, 138.4, 128.8, 128.7, 128.0, 126.8, 123.8, 41.3, 35.4. ESI-HRMS: Calcd for $C_{15}H_{15}N_2O_3^+$ $[M+H]^+$: 271.1077. Found: 271.1076.

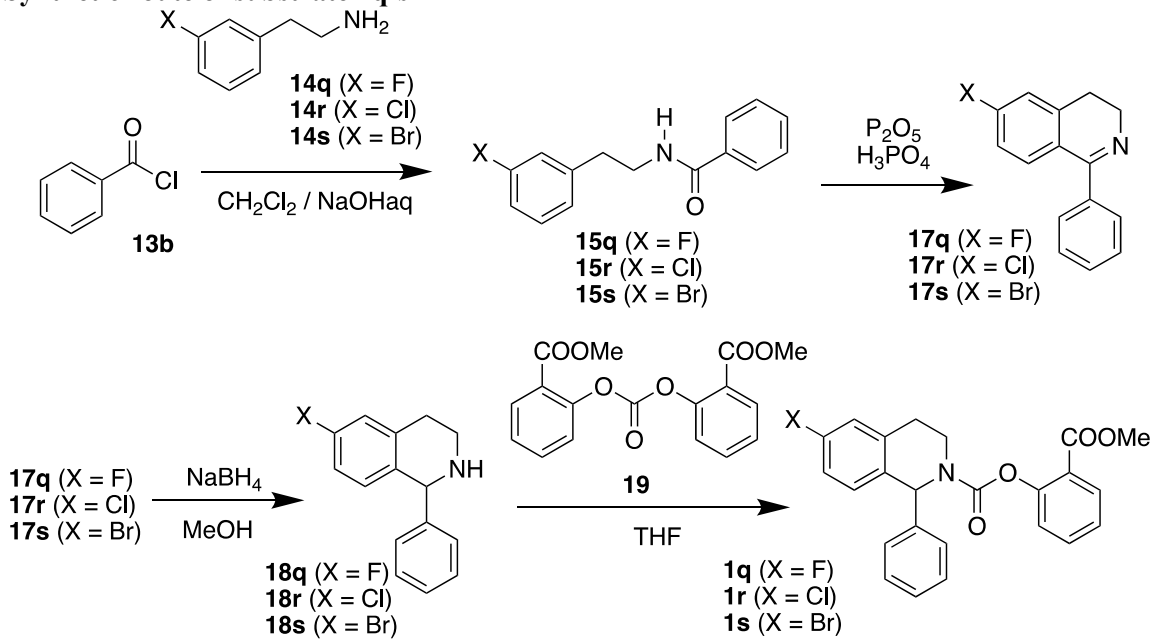
Compound **17p** was synthesized following the procedure B. 85% yield from **15p**.
White solid. ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.27 (d, J = 8.7 Hz, 2H), 7.78 (d, J = 8.7 Hz, 2H), 7.43 (dd, J = 7.4, 7.4 Hz, 1H), 7.32-7.26 (m, 2H), 7.16 (d, J = 7.8 Hz, 1H), 3.90 (t, J = 7.4 Hz, 2H), 2.83 (t, J = 7.4 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 165.4, 148.1, 144.9, 138.4, 131.1, 129.6, 127.8, 127.6, 127.0, 126.7, 123.2, 47.8, 25.9. ESI-HRMS: Calcd for $C_{15}H_{13}N_2O_2^+$ $[M+H]^+$: 253.0972. Found: 253.0971.

Compound **18p** was synthesized following the procedure C. 84% yield from **17p**.
Mp. 102 - 103 ºC (colorless needles, recrystallized from ethyl acetate/*n*-hexane)^{1}H-NMR (400 MHz, Chloroform-d) δ 8.18 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 3.9 Hz, 2H), 7.08-7.04 (m, 1H), 6.67 (d, J = 7.5 Hz, 1H), 5.21 (s, 1H), 3.27-3.22 (m, 1H), 3.15-3.01 (m, 2H), 2.87-2.81 (m, 1H), 1.92 (brs, 1H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 152.3, 147.3, 136.7, 135.4, 129.9, 129.4, 127.8, 126.8, 125.9, 123.6, 61.3, 42.0, 29.5. ESI-HRMS: Calcd for

$C_{15}H_{15}N_2O_2^+$ [M+H]$^+$: 255.1128. Found: 255.1128.

Compound **1p** was synthesized following the procedure D. 84% yield from **18p**. Pale yellow sticky oil. ^{1}H-NMR (400 MHz, Chloroform-d, 55 ºC) δ 8.14 (d, J = 8.5 Hz, 2H), 7.98 (dd, J = 7.9, 1.5 Hz, 1H), 7.54-7.50 (m, 3H), 7.31-7.22 (m, 4H), 7.15 (d, J = 8.2 Hz, 1H), 7.09 (d, J = 7.5 Hz, 1H), 6.50 (brs, 1H), 4.23-4.20 (m, 1H), 3.67 (s, 3H), 3.58 (brs, 1H), 3.17-3.10 (m, 1H), 2.85 (dt, J = 16.2, 4.7 Hz, 1H). ^{13}C-NMR (101 MHz, Chloroform-d, 55 ºC) δ 165.1, 154.2, 151.0, 149.4, 147.5, 135.1, 134.2, 133.5, 131.7, 129.2, 129.1, 128.3, 127.9, 126.7, 125.7, 124.0, 123.9, 123.5, 58.0, 51.8, 39.9, 39.8, 28.4. ESI-HRMS: Calcd for $C_{24}H_{20}N_2NaO_6^+$ [M+Na]$^+$: 455.1213. Found: 455.1207.

Synthetic route of substrate 1q-s



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

Compound **15q** was synthesized following the procedure A-2. 94% yield from **13q**. White solid. ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.72-7.70 (m, 2H), 7.45 (dd, J = 7.4, 7.4 Hz, 1H), 7.36 (dd, J = 7.5, 7.5 Hz, 2H), 7.26-7.21 (m, 1H), 6.97-6.88 (m, 3H), 6.67 (brs, 1H), 3.65 (dt, J = 6.8, 6.8 Hz, 2H), 2.89 (t, J = 6.8 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 167.6, 162.8 (d, J = 245.6 Hz), 141.4 (d, J = 6.7 Hz), 134.4, 131.3, 130.0 (d, J = 8.7 Hz), 128.4, 126.8, 124.4, 124.3, 115.5 (d, J = 20.2 Hz), 113.3 (d, J = 21.2 Hz), 40.9, 35.3. ESI-HRMS: Calcd for $C_{15}H_{15}FNO^+$ [M+H]$^+$: 244.1132. Found: 244.1130.

Compound **17q** was synthesized following the procedure B. 74% yield from **15q**. Pale yellow oil. ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.58-7.56 (m, 2H), 7.45-7.40 (m, 3H), 7.26 (dd, J = 8.6, 5.6 Hz, 1H), 6.98 (dd, J = 8.6, 2.5 Hz, 1H), 6.91 (ddd, J = 8.6, 8.6, 2.6 Hz, 1H), 3.86-3.82 (m, 2H), 2.80 (t, J = 7.3 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.3, 163.6 (d, J = 252.4 Hz), 141.8 (d, J = 8.7 Hz), 138.8, 130.1 (d, J = 8.7 Hz), 129.4, 128.7, 128.2, 125.3, 114.4 (d, J = 21.2 Hz), 113.3 (d, J = 22.2 Hz), 47.3, 26.5. ESI-HRMS: Calcd for $C_{15}H_{13}FN^+$ [M+H]$^+$: 226.1027. Found: 226.1027.

Compound **18q** was synthesized following the procedure C. 83% yield from **17q**. Mp. 88 - 90 ºC (colorless needles, recrystallized from ethyl acetate/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.25-7.22 (m, 2H), 7.14 (d, J = 3.9 Hz, 2H), 7.06-6.97 (m, 3H), 6.72 (d, J = 7.5 Hz, 1H), 5.09 (s, 1H), 3.29-3.24 (m, 1H), 3.13-3.00 (m, 2H), 2.84-2.79 (m, 1H), 1.82 (brs, 1H).

^{13}C-NMR (101 MHz, Chloroform-d) δ 162.1 (d, J = 245.6 Hz), 140.7, 138.1, 135.4, 130.5 (d, J = 7.7 Hz), 129.1, 128.0, 126.4, 125.7, 115.2 (d, J = 21.2 Hz), 61.4, 42.3, 29.7. ESI-HRMS: Calcd for $C_{15}H_{15}FN^+$ [M+H]$^+$: 228.1183. Found: 228.1184.

Compound **1q** was synthesized following the procedure D. 81% yield from **18q**.
Colorless sticky oil. ^{1}H-NMR (400 MHz, Chloroform-d, 55 °C) δ 7.97-7.95 (dd, J = 7.6, 1.2 Hz, 1H), 7.51-7.47 (m, 1H), 7.29-7.22 (m, 6H), 7.15 (d, J = 8.0 Hz, 1H), 7.03 (dd, J = 8.0, 5.9 Hz, 1H), 6.94-6.86 (m, 2H), 6.49 (brs, 1H), 4.22 (brs, 1H), 3.56 (s, 3H), 3.43 (brs, 1H), 3.12 (brs, 1H), 2.80 (d, J = 16.2 Hz, 1H). ^{13}C-NMR (101 MHz, Chloroform-d, 55 ºC) δ 165.2, 161.6 (d, J = 246.6 Hz), 153.5, 150.9, 142.0, 137.1 (d, J = 6.7 Hz), 133.3, 131.6, 130.9, 130.0 (d, J = 7.7 Hz), 128.4, 128.3, 127.5, 125.4, 124.0, 115.1 (d, J = 20.2 Hz), 113.4 (d, J = 22.2 Hz), 57.7, 51.7, 38.3, 28.5. ESI-HRMS: Calcd for $C_{24}H_{20}FNNaO_4^+$ [M+Na]$^+$: 428.1268. Found: 428.1259.

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

Compound **15r** was synthesized following the procedure A-2. 91% yield from **13r**.
White solid. ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.72-7.70 (m, 2H), 7.46 (dd, J = 7.4, 7.4 Hz, 1H), 7.37 (dd, J = 7.4, 7.4 Hz, 2H), 7.26-7.20 (m, 3H), 7.08-7.06 (m, 1H), 6.57 (brs, 1H), 3.65 (dt, J = 6.8, 6.8 Hz, 2H), 2.88 (t, J = 6.8 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 167.6, 140.9, 134.4, 134.3, 131.4, 129.8, 128.8, 128.5, 126.9, 126.8, 126.6, 40.9, 35.3. ESI-HRMS: Calcd for $C_{15}H_{15}ClNO^+$ [M+H]$^+$:260.0837. Found: 260.0835.

Compound **17r** was synthesized following the procedure B. 61% yield from **15r**.
Pale yellow oil. ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.58-7.55 (m, 2H), 7.45-7.39 (m, 3H), 7.26 (s, 1H), 7.23-7.18 (m, 2H), 3.86-3.82 (m, 2H), 2.78 (t, J = 7.3 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.3, 140.7, 138.5, 136.3, 129.5, 129.2, 128.6, 128.2, 127.5, 127.1, 126.7, 47.4, 26.2. ESI-HRMS: Calcd for $C_{15}H_{13}ClN^+$ [M+H]$^+$: 242.0731. Found: 242.0732.

Compound **18r** was synthesized following the procedure C. The product was purified by recrystallization instead of silica-gel column chromatography. 67% yield from **17r**.
Mp. 59 - 61 ºC (colorless needles, recrystallized from ethyl acetate/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.34-7.22 (m, 5H), 7.14 (d, J = 2.1 Hz, 1H), 6.99 (dd, J = 8.3, 2.2 Hz, 1H), 6.67 (d, J = 8.2 Hz, 1H), 5.03 (s, 1H), 3.28-3.24 (m, 1H), 3.09-2.97 (m, 2H), 2.81-2.76 (m, 1H), 1.89 (brs, 1H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 144.3, 137.3, 136.8, 131.8, 129.5, 128.8, 128.7, 128.5, 127.5, 125.8, 61.7, 42.0, 29.7. ESI-HRMS: Calcd for $C_{15}H_{15}ClN^+$ [M+H]$^+$: 244.0888. Found: 244.0888.

Compound **1r** was synthesized following the procedure D. 73% yield from **18r**.
Colorless sticky oil. ^{1}H-NMR (400 MHz, Chloroform-d, 55 ºC) δ 7.95 (d, J = 7.5 Hz, 1H), 7.47 (dd, J = 7.5, 7.5 Hz, 1H), 7.28-7.23 (m, 7H), 7.14 (d, J = 7.5 Hz, 2H), 6.99 (d, J = 8.2 Hz, 1H), 6.48 (brs, 1H), 4.22 (brs, 1H), 3.56 (s, 3H), 3.41 (brs, 1H), 3.11 (brs, 1H), 2.78 (d, J = 16.2 Hz, 1H). ^{13}C-NMR (101 MHz, Chloroform-d, 55 ºC) δ 165.1, 153.5, 150.8, 141.7, 136.8, 133.7, 133.3, 132.7, 131.5, 129.7, 128.6, 128.4, 128.3, 127.6, 126.4, 125.4, 123.9, 57.7, 51.6, 38.3, 28.2. ESI-HRMS: Calcd for $C_{24}H_{20}ClNNaO_4^+$ [M+Na]$^+$: 444.0973. Found: 444.0966.

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

Compound **15s** was synthesized following the procedure A-2. 88% yield from **13s**.
White solid. ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.70 (d, J = 7.3 Hz, 2H), 7.48 (dd, J = 7.3, 7.3 Hz, 1H), 7.42-7.36 (m, 4H), 7.20-7.14 (m, 2H), 6.29 (brs, 1H), 3.68 (dt, J = 6.8, 6.8 Hz, 2H), 2.90 (t, J = 6.8 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 167.5, 141.3, 134.5, 131.8, 131.5, 130.2, 129.7, 128.6, 127.4, 126.8, 122.7, 40.9, 35.4. ESI-HRMS: Calcd for $C_{15}H_{15}BrNO^+$ [M+H]$^+$: 304.0332. Found: 304.0334.

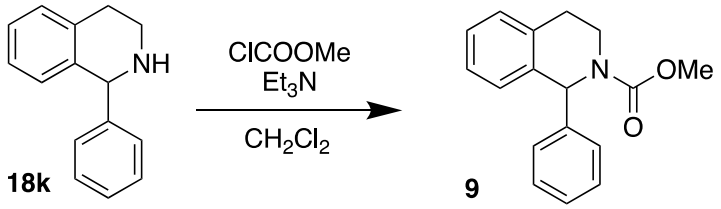
Compound **17s** was synthesized following the procedure B. 62% yield from **15s**.
Pale yellow oil. ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.58-7.56 (m, 2H), 7.45-7.37 (m, 5H), 7.13

(d, J = 8.2 Hz, 1H), 3.86-3.82 (m, 2H), 2.78 (t, J = 7.3 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.5, 140.9, 138.5, 130.4, 129.7, 129.5, 129.4, 128.6, 128.2, 127.5, 124.8, 47.4, 26.1. ESI-HRMS: Calcd for $C_{15}H_{13}BrN^+$ $[M+H]^+$: 286.0226. Found: 286.0229.

Compound **18s** was synthesized following the procedure C. 88% yield from **17s**.
Mp. 73 - 74 ºC (colorless needles, recrystallized from *n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.32-7.21 (m, 6H), 7.11 (dd, J = 8.2, 1.8 Hz, 1H), 6.59 (d, J = 8.2 Hz, 1H), 4.98 (s, 1H), 3.23-3.17 (m, 1H), 3.05-2.96 (m, 2H), 2.79-2.72 (m, 1H), 1.91 (brs, 1H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 144.1, 137.6, 137.3, 131.5, 129.7, 128.7, 128.6, 128.4, 127.4, 119.8, 61.6, 41.9, 29.5. ESI-HRMS: Calcd for $C_{15}H_{15}BrN^+$ $[M+H]^+$: 288.0383. Found: 288.0385.

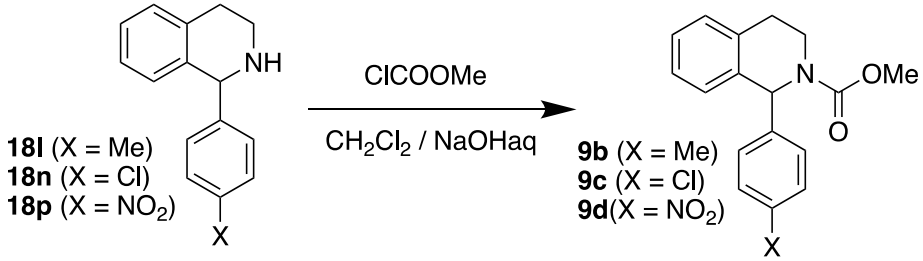
Compound **1s** was synthesized following the procedure D. 94% yield from **18s**.
Colorless sticky oil. ^{1}H-NMR (400 MHz, Chloroform-d, 55 ºC) δ 7.96 (d, J = 7.8 Hz, 1H), 7.50 (dd, J = 7.8, 7.8 Hz, 1H), 7.40 (s, 1H), 7.32-7.23 (m, 7H), 7.14 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 8.2 Hz, 1H), 6.46 (brs, 1H), 4.23 (d, J = 9.8 Hz, 1H), 3.58 (s, 3H), 3.39 (brs, 1H), 3.13 (brs, 1H), 2.83-2.79 (m, 1H). ^{13}C-NMR (101 MHz, Chloroform-d, 55 ºC) δ 165.2, 153.5, 150.9, 141.8, 137.3, 134.4, 133.4, 131.7, 131.6, 130.1, 129.4, 128.5, 128.4, 127.7, 125.5, 124.0, 124.0, 120.9, 77.3, 77.0, 76.7, 57.9, 51.7, 38.4, 28.3. ESI-HRMS: Calcd for $C_{24}H_{20}BrNNaO_4^+$ $[M+Na]^+$: 488.0468. Found: 488.0462.

Synthesis of methyl 1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (9), a model substrate



A solution of methyl chloroformate (258 mg, 2.73 mmol) in 5 mL of dichloromethane was added to a mixture of **18k** (525 mg, 2.51 mmol), dichloromethane (5 mL), and triethylamine (0.50 mL) at -78 ºC under stirring. The mixture was stirred at 25 ºC for 1hr. The reaction mixture was diluted with dichloromethane (20 mL) and quenched with water. 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 crude oil. The oil was purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1 : 4 ~ 1 : 1) to afford **9** (569 mg, 2.13 mmol, 85% yield) as colorless sticky oil.
^{1}H-NMR (400 MHz, Chloroform-d) δ 7.28-7.13 (m, 8H), 7.04 (d, J = 7.3 Hz, 1H), 6.37 (brs, 1H), 4.03 (brs, 1H), 3.75 (s, 3H), 3.30-3.23 (m, 1H), 3.01-2.93 (m, 1H), 2.74 (dt, J = 16.2, 4.1 Hz, 1H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 156.0, 142.6, 135.5, 135.0, 128.9, 128.5, 128.3, 128.2, 127.3, 127.0, 126.1, 57.8, 52.6, 38.3, 28.4.

Synthesis of substrate 9b-d



Synthesys of methyl 1-(p-tolyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (9b)

A solution of methyl chloroformate (100 mg, 1.06 mmol) in 2 mL of dichloromethane was added to a mixture of **18l** (221 mg, 0.990 mmol), dichloromethane (10 mL) and aqueous sodium

hydroxide (4M, 1 mL) at 0 ºC under vigorous stirring. The mixture was stirred at 0 ºC 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 crude oil. The solid was purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1 : 10 ~ 1 : 2) to afford **9b** (235 mg, 0.836 mmol, 84% yield) as colorless sticky oil.
^{1}H-NMR (400 MHz, Chloroform-d), two rotamers (A and B) with respect to the amide bond were observed (approximately A : B = 1 : 1 ratio at 25 ºC), δ 7.20-7.01 (m, 8H), 6.42 (brs, 0.5H), 6.27 (brs, 0.5H), 4.09 (brs, 0.5H), 3.99 (brs, 0.5H), 3.74 (s, 3H), 3.27-3.20 (m, 1H), 2.96 (s, 1H), 2.73 (dt, J = 16.2, 3.7 Hz, 1H), 2.29 (s, 3H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 155.8, 139.6, 136.9, 135.4, 134.8, 128.8, 128.3, 128.2, 128.8, 126.8, 125.9, 77.3, 77.0, 76.7, 57.3, 52.5, 37.8, 28.3, 20.9. ESI-HRMS: Calcd for $C_{18}H_{19}NNaO_2^+$ $[M+Na]^+$: 304.1308. Found: 304.1305.

Synthesis of methyl 1-(4-chlorophenyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (9c)

The compound **9c** was synthesized according to the synthetic procedure of **9b**. 74% yield from **18n**.
Colorless sticky oil. ^{1}H-NMR (400 MHz, Chloroform-d), two rotamers (A and B) with respect to the amide bond were observed (approximately A : B = 1 : 1 ratio at 25 ºC), δ 7.28-7.10 (m, 7H), 7.05-7.00 (m, 1H), 6.39 (brs, 0.5H), 6.28 (brs, 0.5H), 4.00 (brs, 1H), 3.76 (s, 3H), 3.24-3.17 (m, 1H), 3.01-2.93 (m, 1H), 2.74 (dt, J = 16.2, 3.9 Hz, 1H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 155.9, 141.0, 134.8, 134.7, 133.2, 129.6, 128.9, 128.3, 128.3, 127.1, 126.1, 57.0, 52.7, 38.0, 28.3. ESI-HRMS: Calcd for $C_{17}H_{16}ClNNaO_2^+$ $[M+Na]^+$: 324.0762. Found: 324.0758.

Synthesis of methyl 1-(4-nitrophenyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (9d)

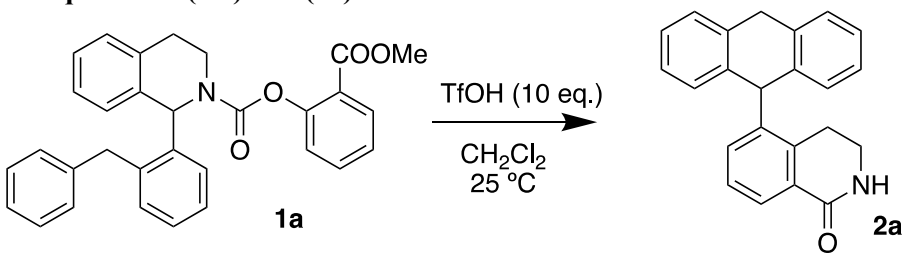
The compound **9d** was synthesized according to the synthetic procedure of **9b**. 84% yield from **18p**.
Colorless sticky oil. ^{1}H-NMR (400 MHz, Chloroform-d, 55 ºC) δ 8.13 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 7.3 Hz, 2H), 7.28-7.19 (m, 3H), 7.04 (d, J = 7.3 Hz, 1H), 6.47 (brs, 1H), 4.01 (brs, 1H), 3.78 (s, 3H), 3.31-3.24 (m, 1H), 3.03-2.95 (m, 1H), 2.78 (dt, J = 16.2, 4.3 Hz, 1H). ^{13}C-NMR (101 MHz, Chloroform-d, 55 ºC) δ 156.0, 149.7, 147.1, 134.9, 133.9, 129.0, 129.0, 128.2, 127.6, 126.5, 123.4, 57.2, 52.9, 38.7, 28.2. ESI-HRMS: Calcd for $C_{17}H_{16}N_2NaO_4^+$ $[M+Na]^+$: 335.1002. Found: 335.1001.

Synthesis of methyl dimethylcarbamate (11)

To a mixture of dimethylamine in tetrahydrofuran (2M, 10 mL) and diethylether (10 mL), methylchloroformate (0.60 mL, 7.8 mmol) was added at -78 ºC under stirring. The mixture was stirred at 0 ºC for 5 min. The reaction mixture was quenched with water, and the organic layer was separated by separatory funnel. Then, the organic layer was dried over sodium sulfate. The solvent was removed under reduced pressure to give **11** as colorless oil (258 mg, 2.5 mmol, 32% yield).
^{1}H-NMR (400 MHz, Chloroform-d) δ 3.69 (s, 3H), 2.91 (s, 6H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 157.1, 52.5, 36.4, 35.8

III. Acid-promoted reaction of substrates

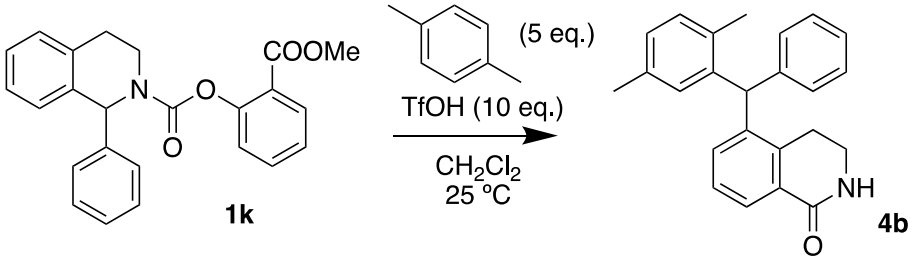
Typical procedure F (Intramolecular reaction): Synthesis of 5-(9,10-dihydroanthracen-9-yl)-3,4-dihydroisoquinolin-1(2H)-one (2a)



To a solution of **1a** (144 mg, 0.302 mmol) in dry dichloromethane (1.5 mL), trifluoromethanesulfonic acid (0.27 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 25 ºC under argon atmosphere for 30 min. Then the mixture was quenched with 10 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil. The crude product was purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1 : 4 ~ 1 : 0) to afford **2a** (95.4 mg, 0.293 mmol, 97% yield) as white solid.

Mp. 237 - 239 ºC (white solid, recrystallized from CH_2Cl_2/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.13 (dd, J = 6.9, 2.3 Hz, 1H), 7.46-7.40 (m, 2H), 7.36 (d, J = 7.5 Hz, 2H), 7.25-7.22 (dd, J = 7.5, 7.5 Hz, 2H), 7.10 (dd, J = 7.5, 7.5 Hz, 2H), 6.81 (d, J = 7.8 Hz, 2H), 6.44 (brs, 1H), 5.28 (s, 1H), 4.19-4.08 (m, 2H), 3.19 (td, J = 6.5, 2.7 Hz, 2H), 2.37 (t, J = 6.5 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.4, 139.9, 138.5, 138.3, 136.6, 136.2, 134.8, 127.7, 127.4, 127.2, 127.0, 126.6, 126.4, 48.5, 39.5, 35.7, 26.3. ESI-HRMS: Calcd for $C_{23}H_{19}NNaO^+$ $[M+Na]^+$: 348.1359. Found: 348.1350.

Typical procedure G (Intermolecular reaction): Synthesis of 5-((2,5-dimethylphenyl)(phenyl)methyl)-3,4-dihydroisoquinolin-1(2H)-one (4b)



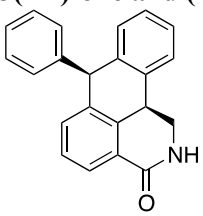
To a solution of **1k** (237 mg, 0.496 mmol) and *p*-xylene (266 mg, 2.51 mmol, 5 eq.) in dry dichloromethane (2.5 mL), trifluoromethanesulfonic acid (0.44 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 25 ºC under argon atmosphere for 30 min. Then the mixture was quenched with 10 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil. The crude product was purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1 : 4 ~ 1 : 0) to afford **4b** (146 mg, 0.428 mmol, 86% yield) as white solid.

Mp. 196 - 198 ºC (white solid, recrystallized from EtOAc/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.01 (d, J = 7.5 Hz, 1H), 7.31-7.21 (m, 4H), 7.06 (d, J = 7.8 Hz, 1H), 7.01 (d, J = 7.3 Hz, 2H), 6.97 (d, J = 7.5 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 6.68 (s, 1H), 6.48 (s, 1H), 5.67 (s, 1H), 3.43-3.38 (m, 2H), 2.80-2.67 (m, 2H), 2.19 (s, 3H), 2.11 (s, 3H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.7, 142.1, 141.0, 140.7, 137.7, 135.4, 133.2, 133.1, 130.4, 129.8, 129.7, 129.4, 128.5, 127.3, 126.5, 126.5, 126.4, 50.2, 39.6, 24.8, 21.2, 19.2. ESI-HRMS: Calcd for $C_{24}H_{23}NNaO^+$ $[M+Na]^+$: 364.1672. Found: 364.1662.

Synthesis of 7-phenyl-7,11b-dihydro-1H-dibenzo[de,h]isoquinolin-3(2H)-one (2b)

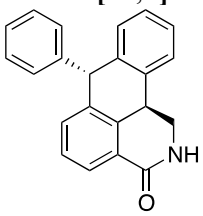
Synthesized following the procedure F. The product **2b** was obtained as mixture of *cis* and *trans* isomers (96 mg, 0.31 mmol, 87% yield, *cis* : *trans* = 1:1.4) from **1b**. The *cis*/*trans* isomers were separated by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1 : 1 ~ 1 : 0) after the calculation of the yield.

2b-*cis* (racemic mixture of (7S,11bR)-7-phenyl-7,11b-dihydro-1H-dibenzo[de,h]isoquinolin-3(2H)-one and (7R,11bS)-7-phenyl-7,11b-dihydro-1H-dibenzo[de,h]isoquinolin-3(2H)-one)



Mp. 248 - 250 ºC (white solid, recrystallized from $CHCl_3$/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.06 (d, J = 7.3 Hz, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.52-7.46 (m, 1H), 7.47 (dd, J = 7.5 Hz, 7.3 Hz, 1H), 7.35-7.28 (m, 3H), 7.21-7.16 (m, 2H), 7.09-7.12 (m, 1H), 6.98 (d, J = 7.3 Hz, 2H), 6.41 (brs, 1H), 5.40 (s, 1H), 4.34 (dd, J = 12.4, 6.3 Hz, 1H), 4.27-4.22 (m, 1H), 3.68 (t, J = 12.4 Hz, 1H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.4, 144.1, 138.9, 138.0, 136.6, 134.4, 132.6, 129.2, 128.7, 128.1, 127.6, 127.6, 127.3, 127.2, 126.8, 126.5, 124.7, 50.9, 44.5, 34.9. ESI-HRMS: Calcd for $C_{22}H_{17}NNaO^+$ $[M+Na]^+$: 334.1202. Found: 334.1196.

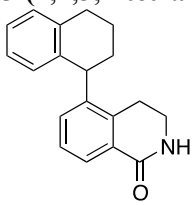
2b-*trans* (racemic mixture of (7S,11bS)-7-phenyl-7,11b-dihydro-1H-dibenzo[de,h]isoquinolin-3(2H)-one and (7R,11bR)-7-phenyl-7,11b-dihydro-1H-dibenzo[de,h]isoquinolin-3(2H)-one)



Mp. 251 - 254 ºC (white solid, recrystallized from EtOAc/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.05 (d, J = 7.5 Hz, 1H), 7.41-7.45 (m, 2H), 7.38-7.34 (m, 2H), 7.30-7.22 (m, 4H), 7.17 (dd, J = 7.5, 7.5 Hz, 1H), 7.01 (d, J = 7.8 Hz, 1H), 6.91 (brs, 1H), 6.87 (d, J = 8.0 Hz, 1H), 5.07 (d, J = 3.2 Hz, 1H), 4.40-4.30 (m, 2H), 3.80 (t, J = 11.5 Hz, 1H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.5, 143.6, 139.1, 138.2, 135.7, 133.4, 132.6, 130.8, 129.2, 128.9, 127.7, 127.1, 127.0, 127.0, 126.8, 126.5, 124.4, 48.9, 44.8, 35.0. ESI-HRMS: Calcd for $C_{22}H_{17}NNaO^+$ $[M+Na]^+$: 334.1202. Found: 334.1195.

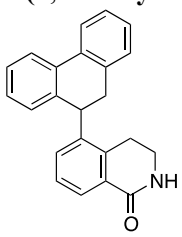
Compounds **2c-j** were synthesized following the procedure F.

5-(1,2,3,4-tetrahydronaphthalen-1-yl)-3,4-dihydroisoquinolin-1(2H)-one (2c)



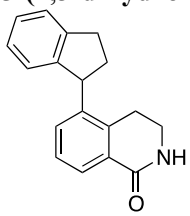
63% yield from **1c**. Mp. 172 - 174 ºC (white solid, recrystallized from CH_2Cl_2/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.98 (d, J = 7.7 Hz, 1H), 7.22 (dd, J = 7.7, 7.7 Hz, 1H), 7.10 (brs, 1H), 7.09-7.15 (m, 2H), 7.05-7.00 (m, 2H), 6.75 (d, J = 7.7 Hz, 1H), 4.35 (t, J = 6.4 Hz, 1H), 3.58-3.48 (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). ^{13}C-NMR (101 MHz, Chloroform-d) 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 .

5-(9,10-dihydrophenanthren-9-yl)-3,4-dihydroisoquinolin-1(2H)-one (2d)



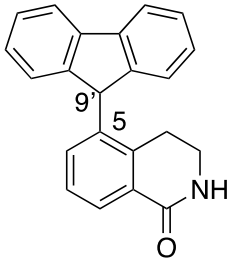
16% yield from **1d**. Mp. 208 - 210 ºC (white solid, recrystallized from EtOAc/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.05 (dd, J = 6.0, 3.0 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.37-7.15 (m, 7H), 6.76 (d, J = 7.5 Hz, 1H), 6.63 (brs, 1H), 4.41 (dd, J = 11.5, 5.0 Hz, 1H), 3.54 (td, J = 6.5, 2.7 Hz, 2H), 3.24 (dd, J = 14.8, 11.5 Hz, 1H), 3.09-2.96 (m, 3H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.6, 139.5, 138.9, 137.5, 135.8, 134.8, 134.2, 132.0, 129.6, 128.3, 127.8, 127.8, 127.4, 127.3, 127.0, 126.8, 124.1, 123.8, 40.7, 39.8, 35.8, 25.1. ESI-HRMS: Calcd for $C_{23}H_{19}NNaO^+$ $[M+Na]^+$: 348.1359. Found: 348.1351.

5-(2,3-dihydro-1H-inden-1-yl)-3,4-dihydroisoquinolin-1(2H)-one (2e)



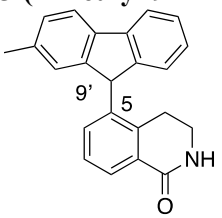
36% yield from **1e**. Mp. 160 - 162 ºC (colorless powder, recrystallized from CH_2Cl_2/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.00 (d, J = 7.4 Hz, 1H), 7.33 (d, J = 7.4 Hz, 1H), 7.13-7.28 (m, 4H), 7.00 (brs, 1H), 6.97 (d, J = 7.4 Hz, 1H), 4.60 (t, J = 8.1 Hz, 1H), 3.60 (brs, 2H), 2.95-3.09 (m, 4H), 2.57-2.62 (m, 1H), 1.97 (m, 1H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.90, 145.55, 144.40, 141.93, 137.08, 131.63, 129.26, 126.81, 126.76, 126.49, 126.29, 124.72, 124.56, 47.26, 39.74, 35.19, 31.50, 24.98. ESI-HRMS: Calcd for $C_{18}H_{17}NNaO^+$ $[M+Na]^+$: 286.1202. Found: 286.1198.

5-(9H-fluoren-9-yl)-3,4-dihydroisoquinolin-1(2H)-one (2f)



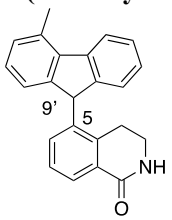
95% yield from **1f**. Mp. 228 - 233 ºC (colorless amorphous powder, recrystallized from p-Xylene). ^{1}H-NMR (400 MHz, Chloroform-d), two rotamers with respect to the C-C bond rotation between C5 and C9' were observed (approximately A : B = 1 : 1 ratio at 25 ºC), δ 8.09 (d, J = 7.1 Hz, 0.5H, rotamer A), 8.00 (d, J = 7.3 Hz, 0.5H, rotamer B), 7.85-7.80 (m, 2.5H, rotamer A and B), 7.49-7.39 (m, 2.5H, rotamer A and B), 7.29-7.20 (m, 4H, rotamer A and B), 7.08 (t, J = 7.8 Hz, 0.5H, rotamer B), 6.59 (d, J = 8.0 Hz, 0.5H, rotamer B), 6.23 (brs, 0.5H, rotamer B), 5.77 (brs, 0.5H, rotamer A), 5.37 (s, 0.5H, rotamer B), 5.08 (s, 0.5H, rotamer A), 3.78 (td, J = 6.5, 2.7 Hz, 1H, rotamer B), 3.51 (t, J = 6.5 Hz, 1H, rotamer B), 2.90 (td, J = 6.5, 2.9 Hz, 1H, rotamer A), 1.60 (t, J = 6.5Hz, 1H, rotamer A). ^{13}C-NMR (101 MHz, Chloroform-d), two rotamers with respect to the C-C bond rotation between C5 and C9' were observed, δ ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.4, 166.0, 147.6, 146.6, 141.2, 140.5, 138.8, 138.4, 137.3, 137.1, 136.4, 131.8, 130.5, 129.5, 127.5, 127.3, 127.2, 126.8, 124.9, 124.7, 120.2, 120.2, 55.5, 49.3, 40.2, 39.3, 25.9, 24.0. ESI-HRMS: Calcd for $C_{22}H_{17}NNaO^{+}$ $[M+Na]^{+}$: 334.1202. Found: 334.1193.

5-(2-methyl-9H-fluoren-9-yl)-3,4-dihydroisoquinolin-1(2H)-one (2g)



86% yield from **1g**. White amorphous solid. ^{1}H-NMR (400 MHz, Chloroform-d), two rotamers with respect to the C-C bond rotation between C5 and C9' were observed (approximately 1 : 1 ratio at 25 ºC), δ 8.09 (d, J = 7.8 Hz, 0.5H), 7.99 (d, J = 7.5 Hz, 0.5H), 7.79-7.70 (m, 2.5H), 7.46 (dd, J = 7.7, 7.7 Hz, 0.5H), 7.39-7.36 (m, 1H), 7.25-7.17 (m, 3H), 7.10-7.01 (m, 1.5H), 6.77 (brs, 0.5H), 6.59 (d, J = 7.8 Hz, 0.5H), 6.21 (brs, 0.5H), 5.32 (s, 0.5H), 5.02 (s, 0.5H), 3.77 (t, J = 6.3 Hz, 1H), 3.49 (t, J = 6.3 Hz, 1H), 2.90 (t, J = 6.2 Hz, 1H), 2.35 (s, 3H), 1.62 (t, J = 6.2 Hz, 1H). ^{13}C-NMR (101 MHz, Chloroform-d), two rotamers with respect to the C-C bond rotation between C5 and C9' were observed, δ 166.9, 166.5, 147.8, 147.4, 146.7, 146.3, 141.2, 140.5, 138.9, 138.4, 137.8, 137.4, 137.3, 137.2, 136.1, 131.6, 130.5, 129.5, 128.3, 128.2, 127.3, 127.3, 127.2, 127.1, 126.9, 126.9, 126.8, 126.6, 125.5, 125.1, 124.8, 124.5, 119.8, 119.7, 119.7, 119.7, 55.2, 49.0, 39.9, 39.0, 25.7, 23.8, 21.5, 21.5. ESI-HRMS: Calcd for $C_{23}H_{19}NNaO^{+}$ $[M+Na]^{+}$: 348.1359. Found: 348.1352.

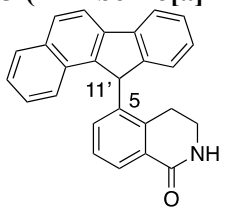
5-(4-methyl-9H-fluoren-9-yl)-3,4-dihydroisoquinolin-1(2H)-one (2h)



75% yield from **1h**. Mp. 217 - 219 ºC (white solid, recrystallized from EtOAc/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d), two rotamers with respect to the C-C bond rotation between C5 and C9'

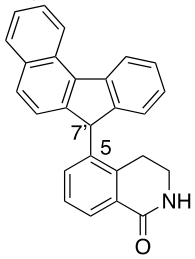
were observed (approximately 1 : 1 ratio at 25 ºC), δ 8.07 (d, J = 7.8 Hz, 1H), 7.97-7.94 (m, 1.5H), 7.77 (d, J = 7.3 Hz, 1H), 7.46-7.35 (m, 2H), 7.27-7.12 (m, 4H), 7.07-7.02 (m, 1.5H), 6.69 (brs, 0.5H), 6.55 (d, J = 7.5 Hz, 0.5H), 5.32 (s, 0.5H), 5.01 (s, 0.5H), 3.75 (td, J = 6.3, 3.8 Hz, 1H), 3.46 (t, J = 6.3 Hz, 1H), 2.88 (td, J = 6.4, 2.5 Hz, 1H), 2.77 (s, 3H), 1.57 (t, J = 6.5 Hz, 1H). ^{13}C-NMR (101 MHz, Chloroform-d), two rotamers with respect to the C-C bond rotation between C5 and C9' were observed, δ 166.8, 166.4, 148.0, 146.9, 142.1, 141.4, 139.1, 138.4, 138.4, 137.5, 137.2, 136.3, 133.2, 131.7, 130.5, 129.7, 129.7, 129.5, 127.3, 127.3, 127.3, 127.1, 127.1, 126.9, 126.7, 126.6, 124.8, 124.5, 123.2, 122.3, 122.0, 55.4, 49.1, 40.0, 39.1, 25.7, 23.9, 21.0, 21.0. ESI-HRMS: Calcd for $C_{23}H_{19}NNaO^+$ $[M+Na]^+$: 348.1359. Found: 348.1351.

5-(11H-benzo[a]fluoren-11-yl)-3,4-dihydroisoquinolin-1(2H)-one (2i)



91% yield from **1i**. Mp. 255 - 257 ºC (white solid, recrystallized from *p*-xylene). ^{1}H-NMR (400 MHz, Chloroform-d), two rotamers with respect to the C-C bond rotation between C5 and C11' were observed (approximately 1 : 1 ratio at 25 ºC), δ 8.12 (dd, J = 7.8, 1.1 Hz, 0.5H), 8.06 (d, J = 7.8 Hz, 0.5H), 8.00-7.86 (m, 4.5H), 7.58 (t, J = 7.5 Hz, 1H), 7.46-7.20 (m, 5.5H), 6.96 (dd, J = 7.8, 7.8 Hz, 0.5H), 6.45 (dd, J = 7.8, 1.4 Hz, 0.5H), 6.37 (brs, 0.5H), 5.74 (brs, 0.5H), 5.61 (s, 0.5H), 5.38 (s, 0.5H), 3.88-3.85 (m, 1H), 3.66 (t, J = 6.4 Hz, 1H), 2.83-2.73 (m, 1H), 1.55 (t, J = 6.6 Hz, 1H). ^{13}C-NMR (101 MHz, Chloroform-d), two rotamers with respect to the C-C bond rotation between C5 and C11' were observed, δ 166.5, 166.0, 148.5, 146.8, 142.6, 141.6, 141.2, 141.0, 139.6, 138.7, 138.4, 138.4, 138.2, 136.3, 136.0, 133.6, 133.3, 131.3, 130.6, 130.5, 129.9, 129.8, 129.2, 129.1, 128.9, 127.6, 127.5, 127.5, 127.3, 127.2, 127.1, 126.7, 125.6, 125.4, 124.6, 124.3, 124.1, 123.7, 120.1, 119.8, 118.7, 118.6, 55.5, 48.7, 40.3, 39.2, 26.1, 23.4. ESI-HRMS: Calcd for $C_{26}H_{19}NNaO^+$ $[M+Na]^+$: 384.1359. Found: 384.1350.

5-(7H-benzo[de]anthracen-7-yl)-3,4-dihydroisoquinolin-1(2H)-one (2j)

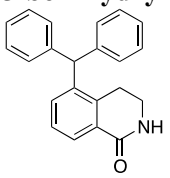


93% yield from **1j**. Mp. 184 - 188 ºC (white solid, recrystallized from EtOAc/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d), two rotamers with respect to the C-C bond rotation between C5 and C7' were observed (approximately A : B = 1 : 1 ratio at 25 ºC), δ 8.80 (d, J = 8.5 Hz, 1H, rotamer A and B), 8.44-8.41 (m, 1H, rotamer A and B), 8.10 (dd, J = 7.8, 0.9 Hz, 0.5H, rotamer A), 7.99-7.93 (m, 1.5H, , rotamer A and B), 7.85 (d, J = 7.8 Hz, 0.5H, rotamer A), 7.79-7.75 (m, 1H, rotamer A and B), 7.72-7.66 (m, 1H, rotamer A and B), 7.58-7.47 (m, 2.5H, rotamer A and B), 7.37-7.25 (m, 3H, rotamer A and B), 7.02 (dd, J = 7.7, 7.7 Hz, 0.5H, rotamer B), 6.85 (brs, 0.5H, rotamer B), 6.51 (dd, J = 7.8, 1.4 Hz, 0.5H, rotamer B), 6.18 (brs, 0.5H, rotamer A), 5.40 (s, 0.5H, rotamer B), 5.10 (s, 0.5H, rotamer A), 3.78 (td, J = 6.4, 2.7 Hz, 1H, rotamer B), 3.52 (t, J = 6.5 Hz, 1H, rotamer B), 2.83-2.78 (m, 1H, rotamer A), 1.57-1.52 (m, 1H, rotamer A). ^{13}C-NMR (101 MHz, Chloroform-d), two rotamers with respect to the C-C bond rotation between C5 and C7' were observed, δ 166.6, 166.1, 148.9, 147.6, 146.5, 145.5, 142.2, 141.5, 138.5, 138.2, 137.4, 136.7, 136.6, 135.8, 135.0,

133.7, 133.7, 131.7, 130.5, 129.6, 129.5, 129.5, 129.4, 129.3, 128.6, 127.6, 127.5, 127.3, 127.2, 126.9, 126.8, 126.6, 126.5, 125.5, 125.4, 124.8, 124.6, 123.9, 123.8, 123.2, 122.8, 122.4, 55.9, 49.6, 40.1, 39.2, 25.9, 23.7. ESI-HRMS: Calcd for $C_{26}H_{19}NNaO^+$ $[M+Na]^+$: 384.1359. Found: 384.1349.

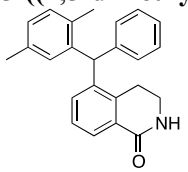
Compounds **4a-k** were synthesized following the procedure G. The amount of nucleophiles are specified for each compound.

5-benzhydryl-3,4-dihydroisoquinolin-1(2H)-one (4a)



71% yield from **1k** and **3a** (57 equiv.). The reaction was conducted without dichloromethane solvent. Mp. 205 - 207 ºC (white solid, recrystallized from EtOAc/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.02 (d, J = 7.5 Hz, 1H), 7.31-7.22 (m, 7H), 7.04 (d, J = 7.3 Hz, 4H), 6.97 (d, J = 7.8 Hz, 1H), 6.17 (brs, 1H), 5.68 (s, 1H), 3.42 (td, J = 6.5, 2.7 Hz, 2H), 2.80 (t, J = 6.5 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.5, 142.7, 140.9, 137.7, 133.3, 129.5, 128.5, 126.6, 126.5, 53.3, 39.6, 25.1. ESI-HRMS: Calcd for $C_{22}H_{19}NNaO^{+}$ $[M+Na]^{+}$: 336.1359. Found: 336.1351.

5-((2,5-dimethylphenyl)(phenyl)methyl)-3,4-dihydroisoquinolin-1(2H)-one (4b)

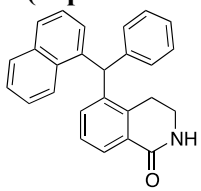


86% yield from **1k** and **3b** (5 equiv.). Mp. 196 - 198 ºC (white solid, recrystallized from EtOAc/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.01 (d, J = 7.5 Hz, 1H), 7.31-7.21 (m, 4H), 7.06 (d, J = 7.8 Hz, 1H), 7.01 (d, J = 7.3 Hz, 2H), 6.97 (d, J = 7.5 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 6.68 (s, 1H), 6.48 (s, 1H), 5.67 (s, 1H), 3.43-3.38 (m, 2H), 2.80-2.67 (m, 2H), 2.19 (s, 3H), 2.11 (s, 3H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.7, 142.1, 141.0, 140.7, 137.7, 135.4, 133.2, 133.1, 130.4, 129.8, 129.7, 129.4, 128.5, 127.3, 126.5, 126.5, 126.4, 50.2, 39.6, 24.8, 21.2, 19.2. ESI-HRMS: Calcd for $C_{24}H_{23}NNaO^{+}$ $[M+Na]^{+}$: 364.1672. Found: 364.1662.

Mixture of 5-(naphthalen-1-yl(phenyl)methyl)-3,4-dihydroisoquinolin-1(2H)-one (4c-*α*) and 5-(naphthalen-2-yl(phenyl)methyl)-3,4-dihydroisoquinolin-1(2H)-one (4c-*β*)

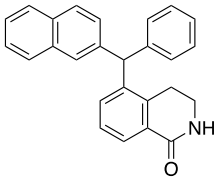
73% from **1k** and **3c** (2 equiv.). **4c-*α* : 4c-*β*** = 2 : 3 based on ^{1}H-NMR integration value. The mixture was separated by using recycling HPLC (LC-Forte/R equipped with YMC-Pack SIL, Ethyl acetate : *n*-hexane = 80 : 20, 25 mL/min) after the calculation of the yield.

5-(naphthalen-1-yl(phenyl)methyl)-3,4-dihydroisoquinolin-1(2H)-one (4c-*α*)



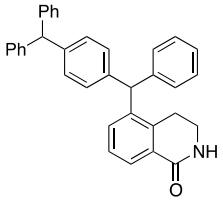
White amorphous solid. ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.03 (d, J = 7.5 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.47-7.18 (m, 7H), 7.08 (d, J = 6.9 Hz, 2H), 6.92 (d, J = 7.8 Hz, 1H), 6.85 (d, J = 7.1 Hz, 1H), 6.31 (s, 1H), 6.29 (brs, 1H), 3.42-3.35 (m, 2H), 2.86-2.70 (m, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.5, 142.3, 141.0, 138.7, 137.5, 134.0, 133.5, 131.6, 129.7, 129.6, 128.9, 128.7, 127.7, 127.4, 126.8, 126.7, 126.6, 126.4, 125.6, 125.3, 123.8, 49.8, 39.7, 25.0. ESI-HRMS: Calcd for $C_{26}H_{21}NNaO^{+}$ $[M+Na]^{+}$: 386.1515. Found: 386.1507.

5-(naphthalen-2-yl(phenyl)methyl)-3,4-dihydroisoquinolin-1(2H)-one (4c-*β*)



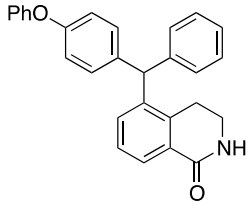
White amorphous solid. ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.04 (d, J = 7.5 Hz, 1H), 7.82-7.76 (m, 2H), 7.69-7.67 (m, 1H), 7.50-7.42 (m, 2H), 7.36 (s, 1H), 7.32-7.22 (m, 5H), 7.07 (d, J = 7.5 Hz, 2H), 7.01 (d, J = 7.8 Hz, 1H), 6.77 (brs, 1H), 5.83 (s, 1H), 3.45-3.39 (m, 2H), 2.87-2.76 (m, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.6, 142.5, 140.7, 140.3, 137.8, 133.5, 133.3, 132.2, 129.6, 129.6, 128.6, 128.2, 127.9, 127.8, 127.8, 127.5, 126.7, 126.6, 126.5, 126.1, 125.8, 53.4, 39.6, 25.1. ESI-HRMS: Calcd for $C_{26}H_{21}NNaO^{+}$ $[M+Na]^{+}$: 386.1515. Found: 386.1507.

5-((4-benzhydrylphenyl)(phenyl)methyl)-3,4-dihydroisoquinolin-1(2H)-one (4d)



55% yield from **1k** and **3d** (5 equiv.). White amorphous solid. ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.00 (d, J = 7.5 Hz, 1H), 7.29-7.18 (m, 10H), 7.11 (d, J = 7.3 Hz, 4H), 7.04 (d, J = 6.2 Hz, 4H), 6.99 (d, J = 7.8 Hz, 1H), 6.94 (d, J = 8.0 Hz, 2H), 6.55 (s, 1H), 5.64 (s, 1H), 5.52 (s, 1H), 3.41 (brs, 2H), 2.83-2.74 (m, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.6, 143.8, 143.8, 142.7, 142.1, 141.0, 140.6, 137.6, 133.3, 129.5, 129.4, 129.4, 128.5, 128.3, 126.6, 126.5, 126.4, 126.3, 56.5, 52.9, 39.6, 25.1. ESI-HRMS: Calcd for $C_{35}H_{29}NNaO^{+}$ $[M+Na]^{+}$: 502.2141. Found: 502.2133.

5-((4-phenoxyphenyl)(phenyl)methyl)-3,4-dihydroisoquinolin-1(2H)-one (4e)

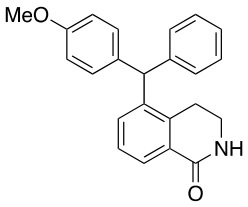


57% yield from **1k** and **3e** (2 equiv.). White amorphous solid. ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.02 (dd, J = 7.7, 0.8 Hz, 1H), 7.35-7.22 (m, 6H), 7.11-6.97 (m, 8H), 6.94-6.92 (m, 2H), 6.82 (brs, 1H), 5.66 (s, 1H), 3.43 (td, J = 6.6, 2.7 Hz, 2H), 2.86-2.74 (m, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.6, 156.9, 155.9, 142.7, 140.9, 137.7, 137.4, 133.2, 130.7, 129.7, 129.6, 129.4, 128.5, 126.6, 126.6, 126.5, 123.3, 118.9, 118.6, 52.6, 39.5, 25.1. ESI-HRMS: Calcd for $C_{28}H_{23}NNaO_{2}^{+}$ $[M+Na]^{+}$: 428.1621. Found: 428.1610.

Mixture of 5-((4-methoxyphenyl)(phenyl)methyl)-3,4-dihydroisoquinolin-1(2*H*)-one (4f-*p*) and 5-((2-methoxyphenyl)(phenyl)methyl)-3,4-dihydroisoquinolin-1(2*H*)-one (4f-*o*)

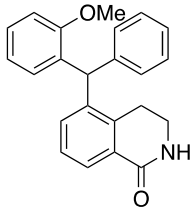
82% from **1k** and **4f** (2 equiv.). **4f-p** : **4f-o** = 7 : 1 based on ^{1}H-NMR integration value. The mixture was separated by using recycling HPLC (LC-Forte/R equipped with YMC-Pack SIL, Ethyl acetate : *n*-hexane = 80 : 20, 25 mL/min) after the calculation of the yield.

5-((4-methoxyphenyl)(phenyl)methyl)-3,4-dihydroisoquinolin-1(2*H*)-one (4f-*p*)



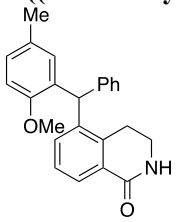
Mp. 167 - 169 ºC (white powder, recrystallized from CH_2Cl_2/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.01 (d, J = 7.8 Hz, 1H), 7.31-7.21 (m, 4H), 7.03 (d, J = 7.1 Hz, 2H), 6.97 (d, J = 8.0 Hz, 1H), 6.94 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 6.17 (brs, 1H), 5.62 (s, 1H), 3.79 (s, 3H), 3.42 (td, J = 6.6, 2.6 Hz, 2H), 2.80 (t, J = 6.6 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.4, 158.2, 143.1, 141.2, 137.6, 134.8, 133.3, 130.4, 129.4, 128.5, 126.6, 126.5, 126.5, 113.9, 55.2, 52.5, 39.7, 25.1. ESI-HRMS: Calcd for $C_{23}H_{21}NNaO_2^+$ $[M+Na]^+$: 367.1464 . Found: 367.1448.

5-((2-methoxyphenyl)(phenyl)methyl)-3,4-dihydroisoquinolin-1(2*H*)-one (4f-*o*)



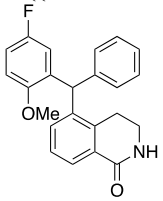
Mp. 202 - 204 ºC (white powder, recrystallized from CH_2Cl_2/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.00 (d, J = 7.5 Hz, 1H), 7.30-7.20 (m, 5H), 7.03 (d, J = 7.3 Hz, 2H), 6.96 (d, J = 7.5 Hz, 1H), 6.89-6.84 (m, 2H), 6.72 (dd, J = 7.5, 1.4 Hz, 1H), 5.99 (s, 1H), 5.95 (brs, 1H), 3.70 (s, 3H), 3.42 (td, J = 6.6, 2.7 Hz, 2H), 2.80 (t, J = 6.6 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 156.8, 142.5, 141.1, 137.8, 133.0, 131.5, 130.3, 129.5, 128.4, 127.9, 126.4, 126.3, 120.4, 110.6, 55.6, 46.2, 39.7, 24.8. ESI-HRMS: Calcd for $C_{23}H_{21}NNaO_2^+$ $[M+Na]^+$: 367.1464 . Found: 367.1451.

5-((2-methoxy-5-methylphenyl)(phenyl)methyl)-3,4-dihydroisoquinolin-1(2*H*)-one (4g)



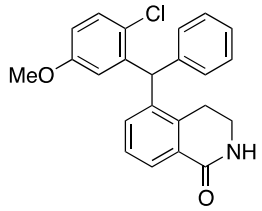
72% yield from **1k** and **3g** (2 equiv.). Mp. 202 - 205 ºC (white powder, recrystallized from CH_2Cl_2/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.00 (d, J = 7.3 Hz, 1H), 7.30-7.21 (m, 4H), 7.04-7.02 (m, 3H), 6.97 (d, J = 7.8 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 6.51 (d, J = 2.1 Hz, 1H), 5.96 (s, 1H), 5.88 (brs, 1H), 3.66 (s, 3H), 3.42 (td, J = 6.6, 2.7 Hz, 2H), 2.80 (t, J = 6.6 Hz, 2H), 2.18 (s, 3H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.9, 154.7, 142.6, 141.1, 137.8, 132.8, 131.2, 130.8, 129.6, 129.5, 129.3, 128.3, 128.1, 126.3, 126.2, 126.1, 110.7, 55.8, 46.1, 39.6, 24.8, 20.7. ESI-HRMS: Calcd for $C_{24}H_{23}NNaO_2^+$ $[M+Na]^+$: 380.1621. Found: 380.1610.

5-((5-fluoro-2-methoxyphenyl)(phenyl)methyl)-3,4-dihydroisoquinolin-1(2*H*)-one (4h)



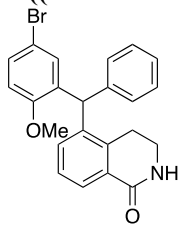
45% yield from **1k** and **3h** (5 equiv.). 15 eq. of TfOH was used. Mp. 166 - 168 ºC (white solid, recrystallized from CH_2Cl_2/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.01 (d, J = 7.8 Hz, 1H), 7.31-7.22 (m, 4H), 7.02 (d, J = 7.1 Hz, 2H), 6.96-6.89 (m, 2H), 6.81 (dd, J = 9.0, 4.5 Hz, 1H), 6.46 (dd, J = 9.5, 3.1 Hz, 1H), 6.27 (brs, 1H), 5.95 (s, 1H), 3.67 (s, 3H), 3.43 (td, J = 6.6, 2.8 Hz, 2H), 2.86-2.73 (m, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.5, 157.0 (d, J = 237.9 Hz), 153.0 (d, J = 1.9 Hz), 141.8, 140.4, 137.7, 133.5 (d, J = 6.7 Hz), 132.6, 129.5, 129.4, 128.6, 126.7, 126.6, 126.5, 117.3 (d, J = 24.1 Hz), 113.7 (d, J = 22.2 Hz), 111.6 (d, J = 8.7 Hz), 56.2, 46.4, 39.7, 24.9. ESI-HRMS: Calcd for $C_{23}H_{20}FNNaO_2^+$ [M+Na]$^+$: 384.1370. Found: 384.1361.

5-((2-chloro-5-methoxyphenyl)(phenyl)methyl)-3,4-dihydroisoquinolin-1(2H)-one (4i)



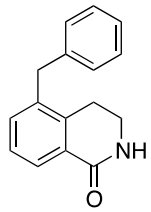
64% yield from **1k** and **3i** (5 equiv.). 15 eq. of TfOH was used. Mp. 202 - 205 ºC (white solid, recrystallized from CH_2Cl_2/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.01 (dd, J = 7.5, 0.9 Hz, 1H), 7.31-7.22 (m, 4H), 7.20 (dd, J = 8.7, 2.6 Hz, 1H), 7.02 (d, J = 7.1 Hz, 2H), 6.95 (dd, J = 7.5, 0.9 Hz, 1H), 6.80 (d, J = 8.7 Hz, 1H), 6.69 (d, J = 2.6 Hz, 1H), 6.50 (brs, 1H), 5.93 (s, 1H), 3.68 (s, 3H), 3.43 (td, J = 6.6, 2.8 Hz, 2H), 2.85-2.72 (m, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.7, 155.4, 141.6, 140.2, 137.7, 133.5, 132.6, 130.0, 129.5, 129.4, 128.5, 127.6, 126.7, 126.5, 126.4, 125.5, 111.8, 55.9, 46.2, 39.6, 24.8. ESI-HRMS: Calcd for $C_{23}H_{20}ClNNaO_2^+$ [M+Na]$^+$: 400.1075. Found: 400.1065.

5-((5-bromo-2-methoxyphenyl)(phenyl)methyl)-3,4-dihydroisoquinolin-1(2*H*)-one (4j)



79% yield from **1k** and **3j** (5 equiv.). 15 eq. of TfOH was used. White amorphous solid. ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.00 (d, J = 7.4 Hz, 1H), 7.35-7.17 (m, 5H), 7.14 (brs, 1H), 7.00 (d, J = 7.1 Hz, 2H), 6.94 (d, J = 7.4 Hz, 1H), 6.81 (d, J = 2.5 Hz, 1H), 6.75 (d, J = 8.9 Hz, 1H), 5.92 (s, 1H), 3.66 (s, 3H), 3.42-3.39 (m, 2H), 2.83-2.69 (m, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.8, 155.9, 141.5, 140.1, 137.7, 134.0, 132.7, 132.7, 130.6, 129.4, 129.3, 128.5, 126.6, 126.5, 126.4, 112.9, 112.3, 55.8, 46.1, 39.5, 24.7. ESI-HRMS: Calcd for $C_{23}H_{20}BrNNaO_2^+$ [M+Na]$^+$: 444.0569. Found: 444.0561.

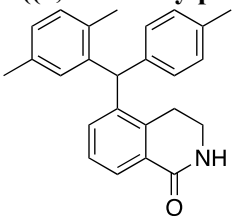
5-benzyl-3,4-dihydroisoquinolin-1(2H)-one (4k)



72% yield from **1k** and **3k** (2 equiv.). Mp. 167 - 169 ºC (colorless plates, recrystallized from CH_2Cl_2/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.04-8.02 (m, 1H), 7.34-7.26 (m, 4H),

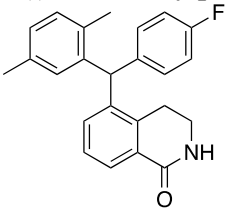
7.20 (dd, J = 7.3, 7.3 Hz, 1H), 7.08 (d, J = 7.3 Hz, 2H), 6.38 (brs, 1H), 4.05 (s, 2H), 3.48 (td, J = 6.6, 2.8 Hz, 2H), 2.84 (t, J = 6.6 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.5, 139.6, 137.7, 137.3, 134.1, 129.5, 128.6, 128.4, 126.8, 126.7, 126.3, 39.7, 39.0, 25.1. ESI-HRMS: Calcd for $C_{16}H_{15}NNaO^+$ $[M+Na]^+$: 260.1046. Found: 260.1041.

5-((2,5-dimethylphenyl)(p-tolyl)methyl)-3,4-dihydroisoquinolin-1(2H)-one (4l)



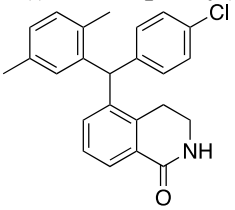
70% yield from **1l** and **3b** (5 equiv.). Mp. 187 - 189 ºC (colorless needles, recrystallized from ethyl dichloromethane/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.00 (d, J = 7.5 Hz, 1H), 7.22 (dd, J = 7.8, 7.8 Hz, 1H), 7.10-7.04 (m, 3H), 6.97-6.88 (m, 4H), 6.70 (brs, 1H), 6.49 (s, 1H), 5.62 (s, 1H), 3.41-3.38 (m, 2H), 2.76-2.70 (m, 2H), 2.33 (s, 3H), 2.19 (s, 3H), 2.10 (s, 3H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.8, 141.2, 140.9, 138.9, 137.7, 136.0, 135.3, 133.1, 133.0, 130.4, 129.7, 129.5, 129.4, 129.2, 127.2, 126.4, 126.3, 49.8, 39.6, 24.8, 21.2, 21.0, 19.1. ESI-HRMS: Calcd for $C_{25}H_{25}NNaO^+$ $[M+Na]^+$: 378.1828. Found: 378.1823.

5-((2,5-dimethylphenyl)(4-fluorophenyl)methyl)-3,4-dihydroisoquinolin-1(2H)-one (4m)



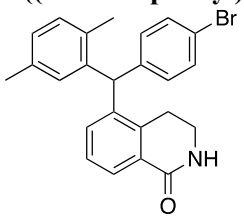
87% yield from **1m** and **3b** (5 equiv.). White amorphous solid. ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.01 (d, J = 7.5 Hz, 1H), 7.37 (brs, 1H), 7.23 (dd, J = 7.5, 7.5 Hz, 1H), 7.06 (d, J = 7.5 Hz, 1H), 6.98 (d, J = 6.9 Hz, 5H), 6.89 (d, J = 7.5 Hz, 1H), 6.46 (s, 1H), 5.65 (s, 1H), 3.42 (brs, 2H), 2.74-2.70 (m, 2H), 2.19 (s, 3H), 2.10 (s, 3H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.9, 161.5 (d, J = 245.6 Hz), 140.8, 140.5, 137.8 (d, J = 2.9 Hz), 137.6, 135.4, 133.0, 132.9, 131.0 (d, J = 8.7 Hz), 130.5, 129.6, 129.6, 127.4, 126.5, 126.4, 115.3 (d, J = 21.2 Hz), 49.4, 39.4, 24.7, 21.1, 19.1. ESI-HRMS: Calcd for $C_{24}H_{22}FNNaO^+$ $[M+Na]^+$: 382.1577. Found: 382.1567.

5-((4-chlorophenyl)(2,5-dimethylphenyl)methyl)-3,4-dihydroisoquinolin-1(2H)-one (4n)



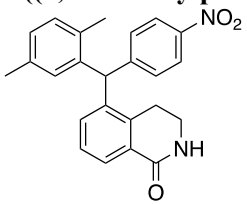
83% yield from **1n** and **3b** (5 equiv.). Mp. 222 - 225 ºC (white solid, recrystallized from ethyl acetate/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.01 (d, J = 5.9 Hz, 1H), 7.40 (brs, 1H), 7.27-7.21 (m, 3H), 7.06 (d, J = 7.5 Hz, 1H), 6.98-6.94 (m, 3H), 6.89 (d, J = 7.8 Hz, 1H), 6.45 (s, 1H), 5.64 (s, 1H), 3.41 (brs, 2H), 2.71 (brs, 2H), 2.19 (s, 3H), 2.10 (s, 3H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.8, 140.7, 140.4, 140.2, 137.6, 135.5, 133.0, 133.0, 132.3, 130.9, 130.5, 129.6, 129.6, 128.6, 127.5, 126.5, 126.5, 49.5, 39.4, 24.7, 21.1, 19.1. ESI-HRMS: Calcd for $C_{24}H_{22}ClNNaO^+$ $[M+Na]^+$: 398.1282. Found: 398.1271.

5-((4-bromophenyl)(2,5-dimethylphenyl)methyl)-3,4-dihydroisoquinolin-1(2H)-one (4o)



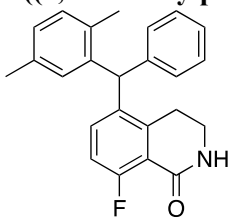
79% yield from **1o** and **3b** (5 equiv.). Mp. 241 - 243 ºC (white powder, recrystallized from ethyl acetate/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.04-8.02 (m, 1H), 7.42 (d, J = 8.5 Hz, 2H), 7.27-7.23 (m, 2H), 7.07 (d, J = 7.8 Hz, 1H), 6.98 (d, J = 7.5 Hz, 1H), 6.90-6.87 (m, 3H), 6.45 (s, 1H), 6.40 (brs, 1H), 5.61 (s, 1H), 3.44-3.39 (m, 2H), 2.78-2.66 (m, 2H), 2.19 (s, 3H), 2.10 (s, 3H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.4, 141.3, 140.4, 140.1, 137.6, 135.6, 133.0, 133.0, 131.7, 131.4, 130.6, 129.7, 129.6, 127.6, 126.7, 126.7, 120.6, 49.7, 39.6, 24.9, 21.2, 19.1. ESI-HRMS: Calcd for $C_{24}H_{22}BrNNaO^{+}$ $[M+Na]^{+}$: 442.0777. Found: 442.0770.

5-((2,5-dimethylphenyl)(4-nitrophenyl)methyl)-3,4-dihydroisoquinolin-1(2H)-one (4p)



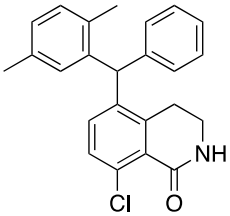
53% yield from **1p** and **3b** (5 equiv.). The reaction mixture was stirred at 2 hours instead of 30 min in general procedure. Mp. 226 - 228 ºC (white powder, recrystallized from ethyl acetate/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d) δ 8.17 (d, J = 8.5 Hz, 2H), 8.06 (d, J = 7.5 Hz, 1H), 7.27 (dd, J = 7.5, 7.5 Hz, 1H), 7.20 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 7.5 Hz, 1H), 7.02 (d, J = 7.5 Hz, 1H), 6.85 (d, J = 7.5 Hz, 1H), 6.44 (s, 1H), 6.43 (s, 1H), 5.77 (s, 1H), 3.44 (s, 2H), 2.72 (t, J = 6.5 Hz, 2H), 2.20 (s, 3H), 2.11 (s, 3H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.2, 150.1, 146.8, 139.5, 139.2, 137.5, 135.9, 133.0, 133.0, 130.8, 130.5, 129.8, 129.6, 128.0, 127.1, 126.9, 123.8, 50.0, 39.6, 24.9, 21.2, 19.1. ESI-HRMS: Calcd for $C_{24}H_{22}N_2NaO_3^{+}$ $[M+Na]^{+}$: 409.1522. Found: 409.1518.

5-((2,5-dimethylphenyl)(phenyl)methyl)-8-fluoro-3,4-dihydroisoquinolin-1(2H)-one (4q)



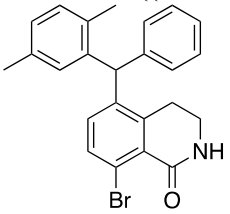
73% yield from **1q** and **3b** (2 equiv.). Mp. 192 - 195 ºC (white powder, recrystallized from dichloromethane/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.31-7.22 (m, 4H), 7.06 (d, J = 7.5 Hz, 1H), 7.00-6.83 (m, 5H), 6.46 (s, 1H), 5.60 (s, 1H), 3.35 (s, 2H), 2.76-2.63 (m, 2H), 2.19 (s, 3H), 2.10 (s, 3H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 164.2, 161.0 (d, J = 260.1 Hz), 141.8, 140.7, 140.5, 136.3 (d, J = 3.9 Hz), 135.5, 134.2 (d, J = 9.6 Hz), 133.0, 130.5, 129.6, 129.5, 128.6, 127.5, 126.7, 117.7 (d, J = 5.8 Hz), 115.0 (d, J = 22.2 Hz), 50.0, 39.2, 25.8, 21.2, 19.1. ESI-HRMS: Calcd for $C_{24}H_{22}FNNaO^{+}$ $[M+Na]^{+}$: 382.1577. Found: 382.1564.

8-chloro-5-((2,5-dimethylphenyl)(phenyl)methyl)-3,4-dihydroisoquinolin-1(2H)-one (4r)



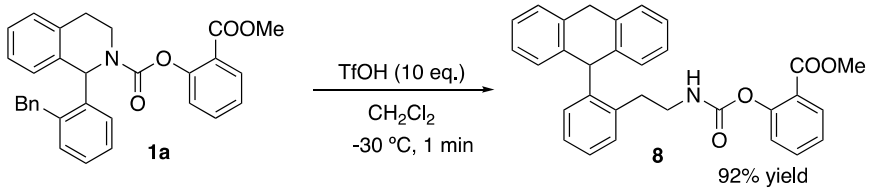
68% yield from **1r** and **3b** (2 equiv.). White amorphous solid. ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.31-7.24 (m, 4H), 7.06 (d, J = 7.5 Hz, 1H), 6.989-6.98 (m, 3H), 6.80 (brs, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.46 (s, 1H), 5.59 (s, 1H), 3.31-3.30 (m, 2H), 2.77-2.63 (m, 2H), 2.19 (s, 3H), 2.10 (s, 3H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 164.5, 141.6, 141.0, 140.5, 139.6, 135.5, 133.0, 133.0, 130.5, 130.0, 130.0, 129.7, 129.6, 128.6, 127.6, 127.1, 126.7, 50.2, 39.1, 26.5, 21.2, 19.1. ESI-HRMS: Calcd for $C_{24}H_{22}ClNNaO^{+}$ $[M+Na]^{+}$: 398.1282. Found: 398.1267.

8-bromo-5-((2,5-dimethylphenyl)(phenyl)methyl)-3,4-dihydroisoquinolin-1(2H)-one (4s)



63% yield from **1s** and **3b** (2 equiv.). Mp. 200 - 203 ºC (white powder, recrystallized from ethyl acetate/*n*-hexane). ^{1}H-NMR (400 MHz, Chloroform-d) δ 7.48 (d, J = 8.5 Hz, 1H), 7.31-7.22 (m, 3H), 7.07-6.97 (m, 4H), 6.68 (d, J = 8.5 Hz, 1H), 6.47 (s, 1H), 6.01 (brs, 1H), 5.58 (s, 1H), 3.31-3.27 (m, 2H), 2.79-2.66 (m, 2H), 2.19 (s, 3H), 2.09 (s, 3H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 164.3, 141.5, 141.1, 140.4, 140.3, 135.6, 133.6, 133.2, 133.0, 130.6, 129.7, 129.6, 128.6, 128.4, 127.6, 126.8, 120.9, 50.3, 39.1, 26.6, 21.2, 19.2. ESI-HRMS: Calcd for $C_{24}H_{22}BrNNaO^{+}$ $[M+Na]^{+}$: 442.0777. Found: 442.0768.

Isolation of methyl 2-(((2-(9,10-dihydroanthracen-9-yl)phenethyl)carbamoyl)oxy)benzoate (8)

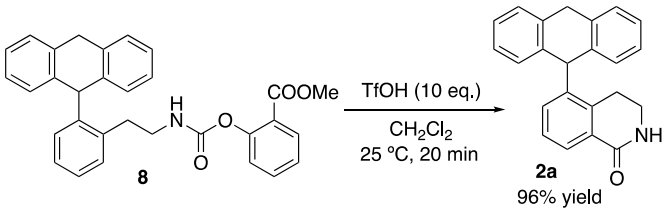


To a solution of **1a** (52.7 mg, 0.110 mmol) in dry dichloromethane (0.55 mL), trifluoromethanesulfonic acid (0.10 mL, 10 eq.) was added at -30 ºC. The mixture was stirred at -30 ºC under argon atmosphere for 1 min. Then the mixture was quenched with diisopropylethylamine (1.0 mL, 5.7 mmol) in dichloromethane (3 mL) cooled at -32 ºC, then ice water (10 mL). The whole was extracted with dichloromethane (30 mL x 2). The organic layer was washed with aqueous hydrogen chloride (1M, 10 mL), and dried over sodium sulfate. The solvent was removed under reduced pressure to give a crude oil. The crude product was purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1 : 1) to afford **8** (48.4 mg, 0.101 mmol, 92% yield) as colorless oil.

^{1}H-NMR (400 MHz, Chloroform-d, 50 ºC) δ 7.91 (d, J = 7.5 Hz, 1H), 7.46 (ddd, J = 7.8, 7.8, 1.4 Hz, 1H), 7.37-7.03 (m, 12H), 6.85 (d, J = 7.8 Hz, 2H), 5.35 (s, 1H), 4.89 (brs, 1H), 4.22-4.10 (m, 2H), 3.71 (s, 3H), 3.27 (dt, J = 6.8 Hz, 2H), 2.76 (t, J = 6.8 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d, 25 ºC) δ 165.3, 154.2, 150.5, 142.0, 139.4, 137.6, 134.9, 133.5, 132.2, 131.4, 130.5, 127.8, 127.5, 127.2, 127.1, 126.3, 126.2, 125.5, 124.0, 123.9, 52.0, 46.8, 41.9, 35.6, 33.2. ESI-

HRMS: Calcd for $C_{31}H_{27}NNaO_4^+$ [M+Na]$^+$: 500.1832. Found: 500.1819.

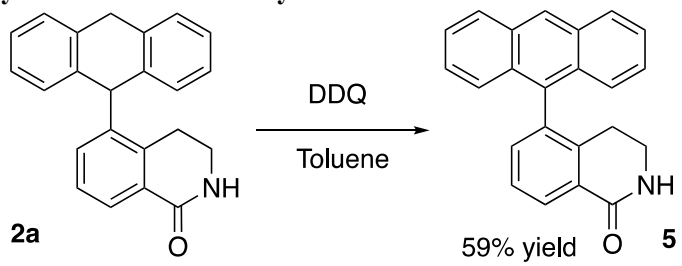
Reaction of 8 in typical reaction condition



To a solution of **8** (31.5 mg, 0.0660 mmol) in dry dichloromethane (0.33 mL), trifluoromethanesulfonic acid (0.06 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 25 ºC under argon atmosphere for 20 min. Then the mixture was quenched with ice water (10 mL). The whole was extracted with dichloromethane (20 mL x 2). The organic layer was dried over sodium sulfate. The solvent was removed under reduced pressure to give a crude oil. The crude product was purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1 : 1) to afford **2a** (20.7 mg, 0.0636 mmol, 96% yield).

IV. Derivatization of triarylmethane compounds

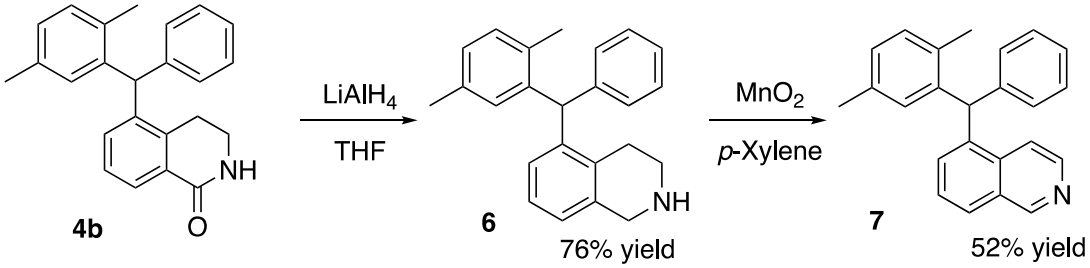
1. Oxidation of dihydroanthracene moiety



A mixture of **2a** (68.0 mg, 0.209 mmol), 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (102 mg, 0.449 mmol) in toluene (5.0 mL) was stirred at 100 ºC for 3 hours. Then the solution was cooled to r.t., and filtered through celite. The filtrate was purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 4 : 1 ~ 1 : 0) to afford **5** (40.0 mg, 0.124 mmol, 92% yield) as pale brown solid.

^{1}H-NMR (400 MHz, Chloroform-d) δ 8.54 (s, 1H), 8.30 (dd, J = 7.8, 1.1 Hz, 1H), 8.09-8.06 (m, 2H), 7.57 (dd, J = 7.8, 7.8 Hz, 1H), 7.50-7.46 (m, 5H), 7.39-7.35 (m, 2H), 6.37 (brs, 1H), 3.34 (td, J = 6.6, 2.7 Hz, 2H), 2.39 (t, J = 6.6 Hz, 2H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 166.4, 138.8, 136.8, 135.1, 134.0, 131.3, 130.1, 129.5, 128.6, 127.8, 127.1, 127.0, 126.0, 125.9, 125.3, 40.0, 25.8. ESI-HRMS: Calcd for $C_{23}H_{17}NO^{+}$ $[M+Na]^{+}$: 346.1202. Found: 346.1189.

2. Transformation of dihydroisoquinolone to isoquinoline



To a solution of **4b** (145 mg, 0.424 mmol) in dry tetrahydrofuran (5.0 mL) was added lithium aluminum hydride solution in tetrahydrofuran (2.5 M, 1.0 mL) at room temperature. The solution was stirred at 50 ºC for 2 hours. The reaction was quenched with sodium sulfate decahydrate (5 g) and filtered through celite. The filtrate was evaporated under reduced pressure to afford **6** as white amorphous solid (105 mg, 0.321 mmol, 76%). The product was used without further purification.

^{1}H-NMR (400 MHz, Chloroform-d) δ 7.26-7.17 (m, 3H), 7.04-6.99 (m, 4H), 6.93 (d, J = 7.8 Hz, 1H), 6.88 (d, J = 7.5 Hz, 1H), 6.61 (d, J = 7.5 Hz, 1H), 6.55 (s, 1H), 5.61 (s, 1H), 4.01 (s, 2H), 3.08-3.03 (m, 2H), 2.62-2.49 (m, 2H), 2.18 (s, 3H), 2.11 (s, 3H), 1.70 (brs, 1H). ^{13}C-NMR (101 MHz, Chloroform-d) δ 142.7, 142.2, 141.5, 136.1, 135.0, 133.3, 133.1, 130.1, 129.8, 129.7, 128.2, 127.4, 127.0, 126.1, 125.1, 124.5, 49.5, 49.0, 44.1, 26.0, 21.2, 19.1. ESI-HRMS: Calcd for $C_{24}H_{26}N^{+}$ $[M+H]^{+}$: 328.2060. Found: 328.2046.

A mixture of **6** (22.8 mg, 0.0696 mmol), MnO_2 (386 mg) in p-xylene (4.0 mL) was stirred under reflux for 30 hours. Then the solution was cooled to r.t., diluted by ethyl acetate (20 mL), and filtered through celite. The filtrate was evaporated under reduced pressure and the residue was purified by silica-gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1 : 1 ~ 4 : 1) to afford **7** (11.7 mg, 0.0362 mmol, 52% yield) as white amorphous solid.

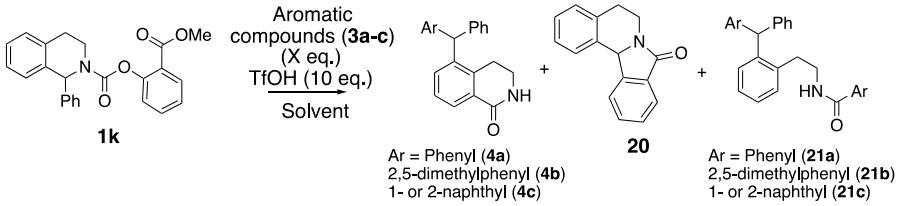
^{1}H-NMR (400 MHz, Chloroform-d) δ 9.25 (s, 1H), 8.43 (d, J = 6.2 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.60 (d, J = 6.2 Hz, 1H), 7.48 (dd, J = 7.8, 7.8 Hz, 1H), 7.32-7.22 (m, 4H), 7.12-7.05 (m, 4H), 6.97 (d, J = 7.5 Hz, 1H), 6.50 (s, 1H), 6.20 (s, 1H), 2.17 (s, 3H), 2.15 (s, 3H). ^{13}C-NMR (101 MHz,

Chloroform-d) δ 153.2, 143.4, 142.3, 141.2, 139.3, 135.3, 134.7, 133.1, 131.2, 130.5, 130.0, 129.8, 129.1, 128.5, 127.4, 126.7, 126.7, 126.6, 117.1, 49.6, 21.2, 19.3. ESI-HRMS: Calcd for $C_{24}H_{22}N^+$ $[M+H]^+$: 324.1747 . Found: 324.1735.

2. Optimization of the intermolecular reaction

For optimization of the intermolecular reaction, we initially investigated the reaction of **1k** with three different aromatic compounds (Table S1). In the presence of excess amount of benzene (**3a**), triarylmethane product **4a** was obtained in 71% yield (Entry 1). On the other hand, intramolecular reaction also proceeded to afford **20** as a byproduct. Enhancement of reactivity of **3** showed more efficient installation of aromatic ring to **1k**. With 2 equivalents of *p*-xylene (**3b**), triarylmethane product **4b** was obtained in 69% yield (Entry 2), and increase of the aromatic ring to 5 equivalents afforded high yield of 86% (Entry 3). However, the relationship between the amount of **3b** and the yield of **4b** was not simple. The use of 40 equivalents of **3b** caused intermolecular reaction of **3b** with the carbamate group to afford **21c** (Entry 4). The same trend was also found in the reaction of **1k** with naphthalene (**3c**) (Entry 5-8). The yield of product **4c** (mixture of isomers) reached maximum value under the condition that 2 equivalents of **3c** were used. The use of more naphthalene caused side reaction to produce more **21c**. The results above indicate that the target product can be obtained in reasonable yield when 2 to 5 equivalents of **3** is used, if **3** is more reactive than benzene.

Table S1. Optimization of the intermolecular reaction



Entry	Aromatic compounds (**3**)	X (eq.)	Solvent	Yield (%)[a] **3**	**20**	**21**
1	Benzene (**3a**)	57	None	71	16	0
2	p-Xylene (**3b**)	2	CH_2Cl_2	69	10	0
3	p-Xylene (**3b**)	5	CH_2Cl_2	86	3	0
4	p-Xylene (**3b**)	40	None	78	0	14
5	naphthalene (**3c**)	1	CH_2Cl_2	56[b]	8	0
6	naphthalene (**3c**)	1.5	CH_2Cl_2	66[b]	4	1[c]
7	naphthalene (**3c**)	2	CH_2Cl_2	73[b]	4	5[c]
8	naphthalene (**3c**)	5	CH_2Cl_2	70[b]	0	11[c]

[a] Isolation yield. [b] Mixture of products of 1- or 2-substituted naphthalene. [c] Mixture of products of 1- or 2-substituted naphthalene.

3. Direct NMR measurement of cationic species

The NMR spectra of **9a-d** in various acids were measured. The spectrum of **11** in TfOH was also measured to ascertain that the compound **9a-d** is protonated even in weaker acids, TFA and $MeSO_3H$.

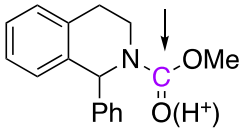
Substrate **11** (ca. 20 mg) was dissolved in TfOH (0.7 mL) in round-bottom flask at -10 ºC under argon atmosphere, and transferred to NMR tube filled with argon. Substrate **9a-d** (ca. 25 mg) were dissolved in $MeSO_3H$ (0.7 mL), TfOH (0.7 mL) or TfOH/SbF_5 (ca. 9 : 1 (w/w)) in round-bottom flask at -10 ºC under argon atmosphere, and transferred to NMR tube filled with argon. NMR spectra of all the samples are recorded on a JEOL ECZ 400S spectrometer (400 MHz for ^{1}H-NMR, 100 MHz for ^{13}C-NMR) at 0 ºC without locking.

Basically, the chemical shifts of TFA (12.3 ppm for ^{1}H and 162.6, 114.5 ppm for ^{13}C) and TfOH (10.7 ppm for ^{1}H and 118.2 ppm for ^{13}C) were used as internal standard of the NMR measurement of **9a-d** and **11**. The chemical shifts of TFA and TfOH were obtained using Chloroform-d (0.03% TMS) sealed in glass tube as external standard (tetramethylsilane for ^{1}H-NMR and $CDCl_3$ for ^{13}C-NMR). The chemical shift of **9a** in $MeSO_3H$ was corrected using Chloroform-d (0.03% TMS) as external standard.

While **9a-c** afforded dicationic open-ring structure in superacid media, open form of **9d** was not observed, but ring-closed form was observed. The compound **9d** was unstable in TfOH/SbF_5 (ca. 9 : 1 (w/w)) and the NMR spectra afforded complex chart so it was not put here.

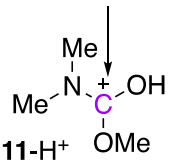
Based on the comparison of carbonyl peak of **11** in TfOH and **9a** in TFA and $MeSO_3H$, it was strongly indicated that the **9a** is protonated in these weaker acids.

156.0 ppm ($CDCl_3$)
159.4 ppm (TFA)
159.1 ppm ($MeSO_3H$)



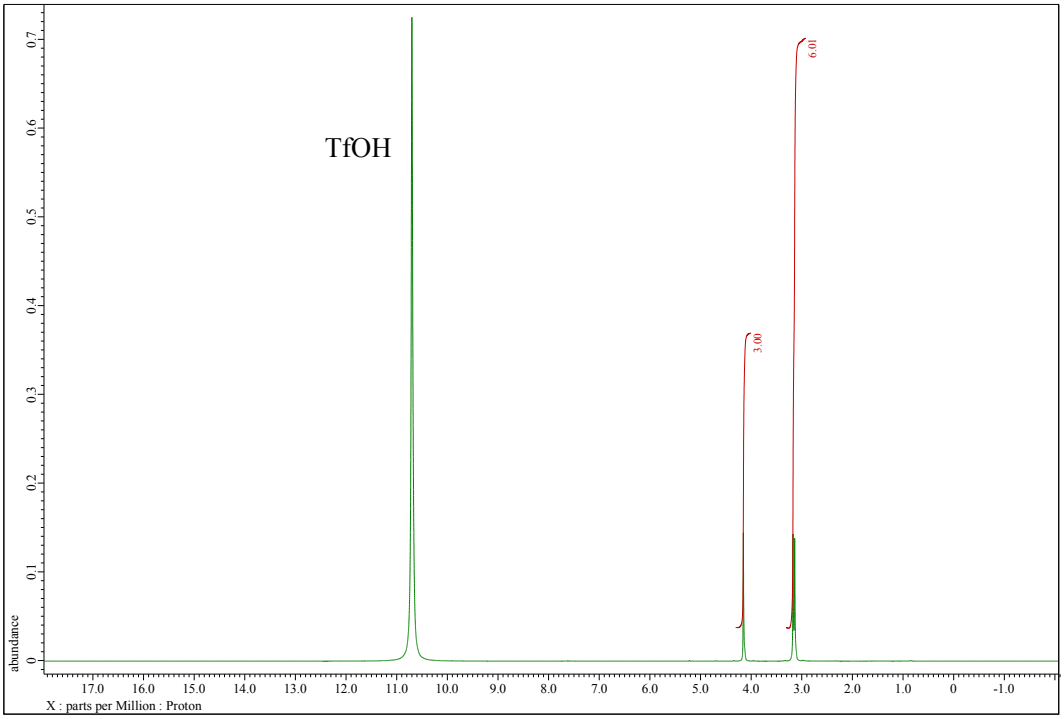
9a-H$^+$-Closed

159.5 ppm

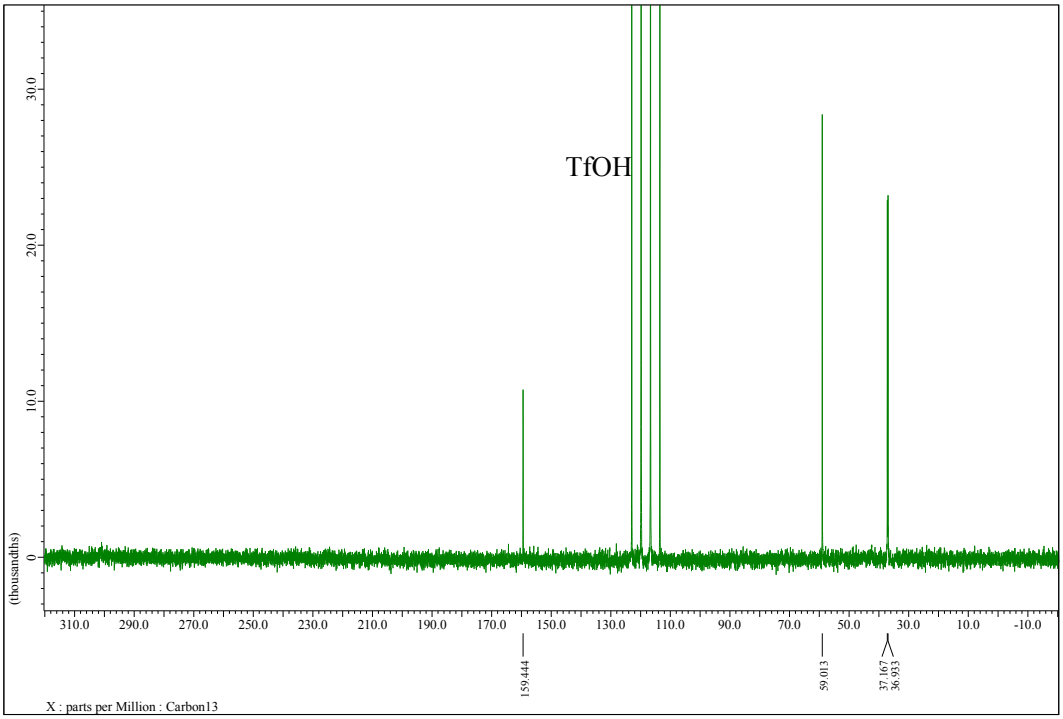


11-H$^+$

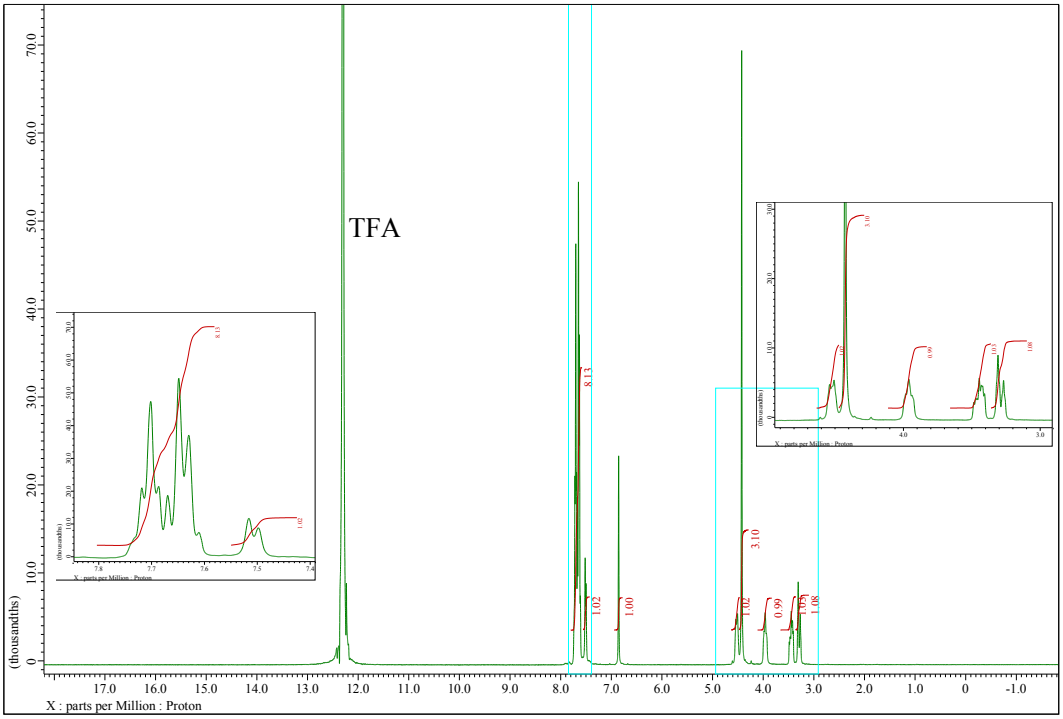
11 in TfOH (^{1}H-NMR)



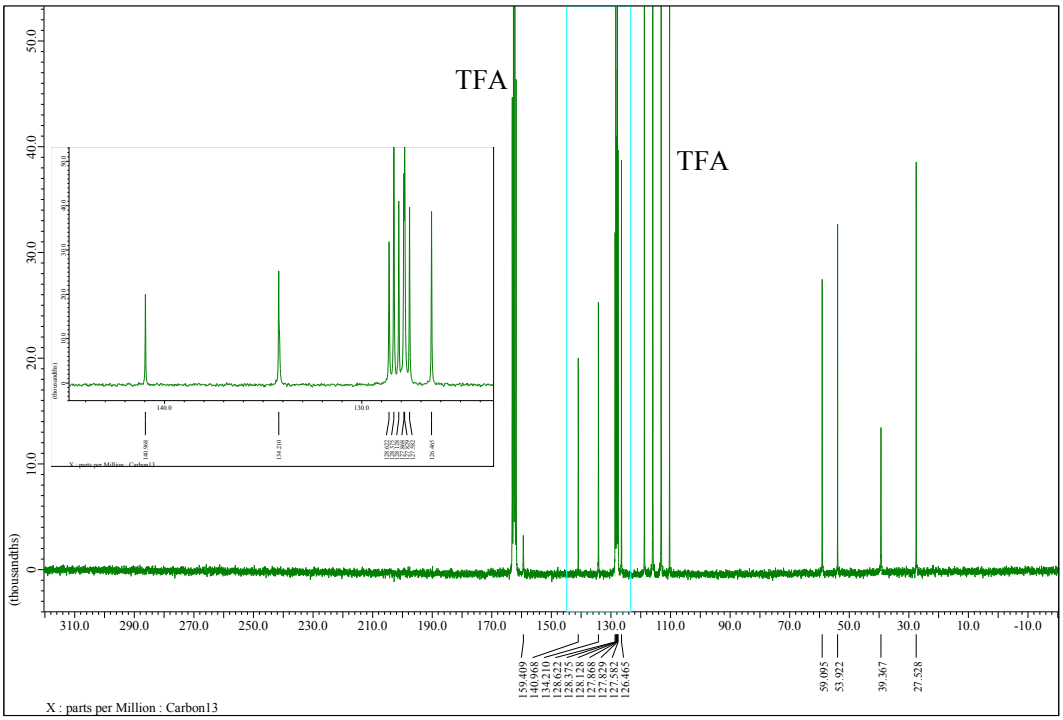
11 in TfOH (^{13}C-NMR)



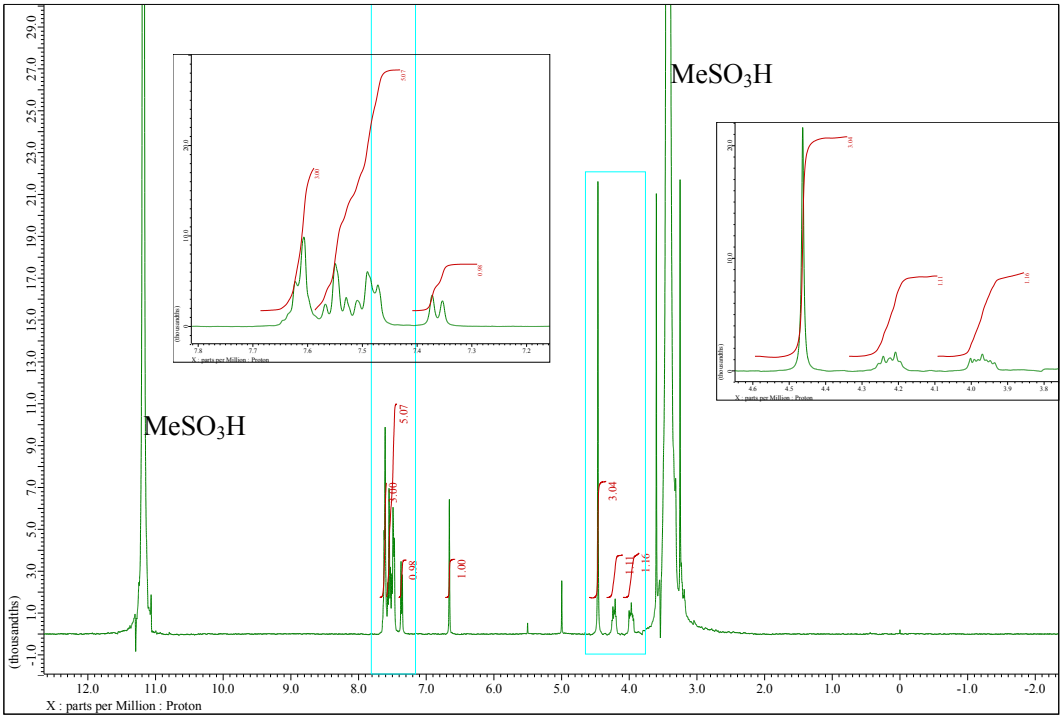
9a in TFA (^{1}H-NMR)



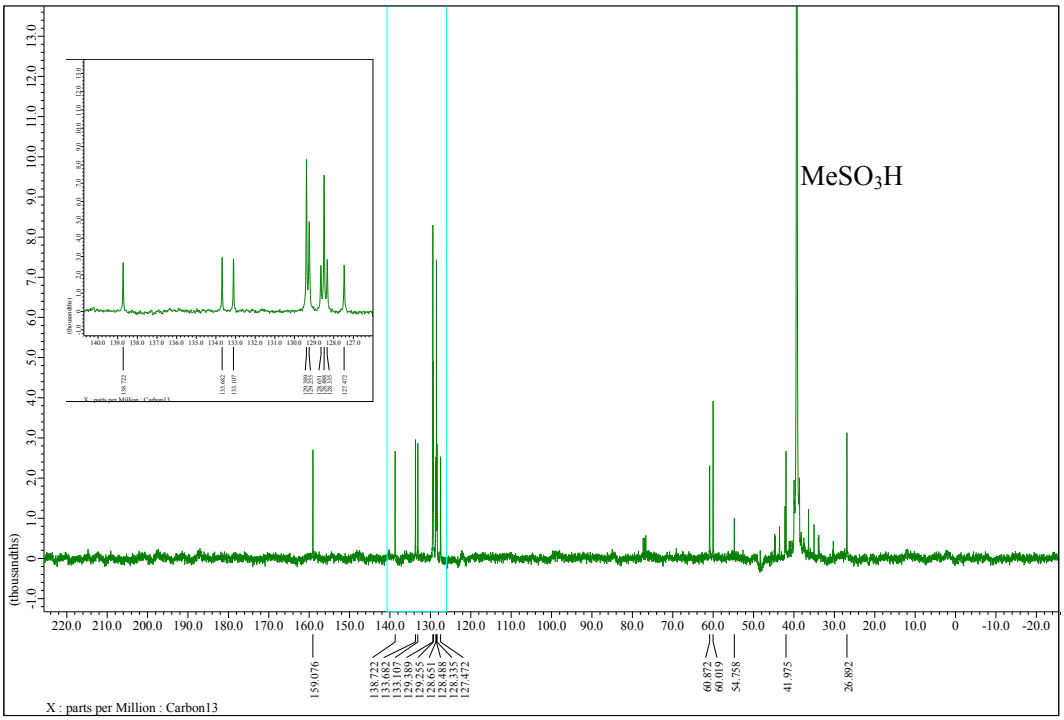
9a in TFA (^{13}C-NMR)



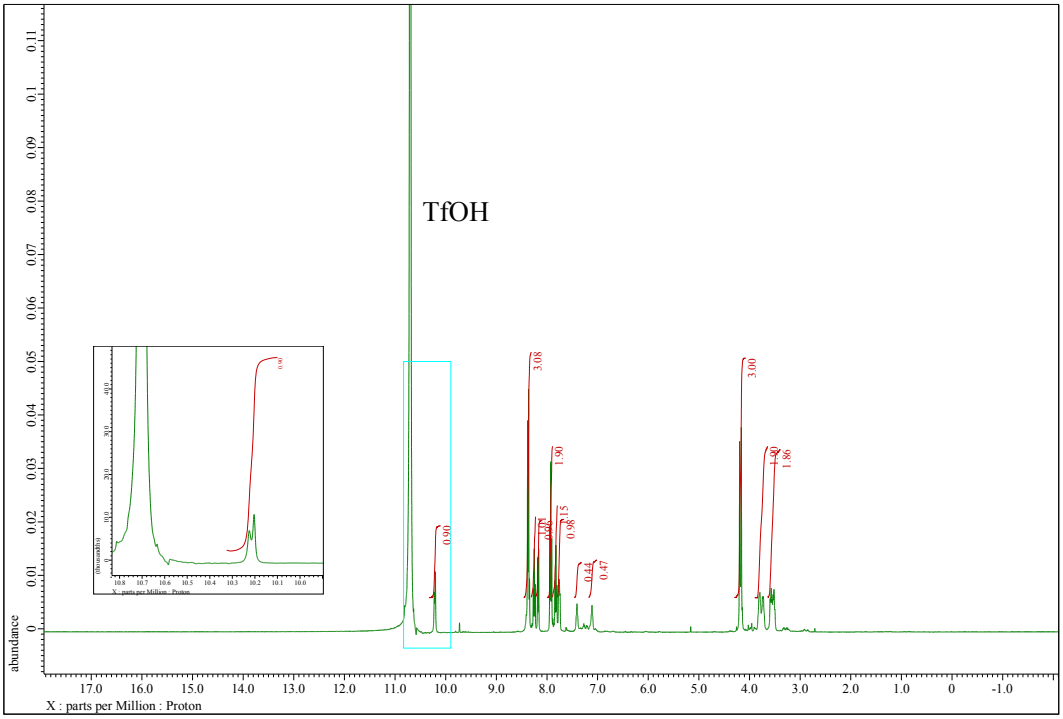
9a in $MeSO_3H$ (^{1}H-NMR)



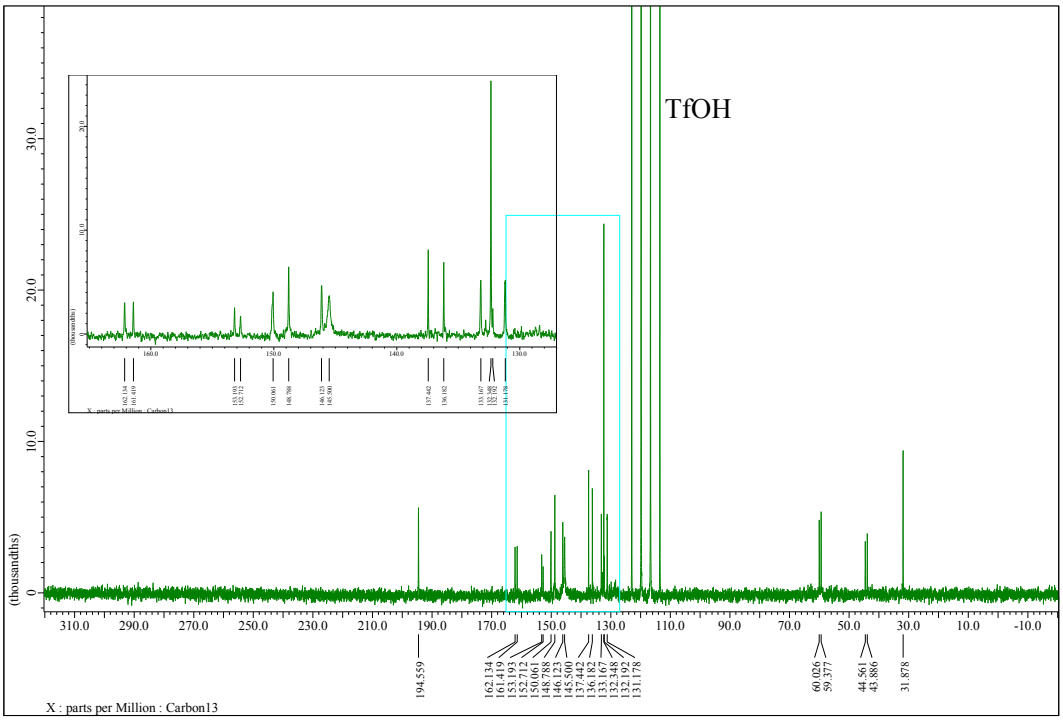
9a in $MeSO_3H$ (^{13}C-NMR)



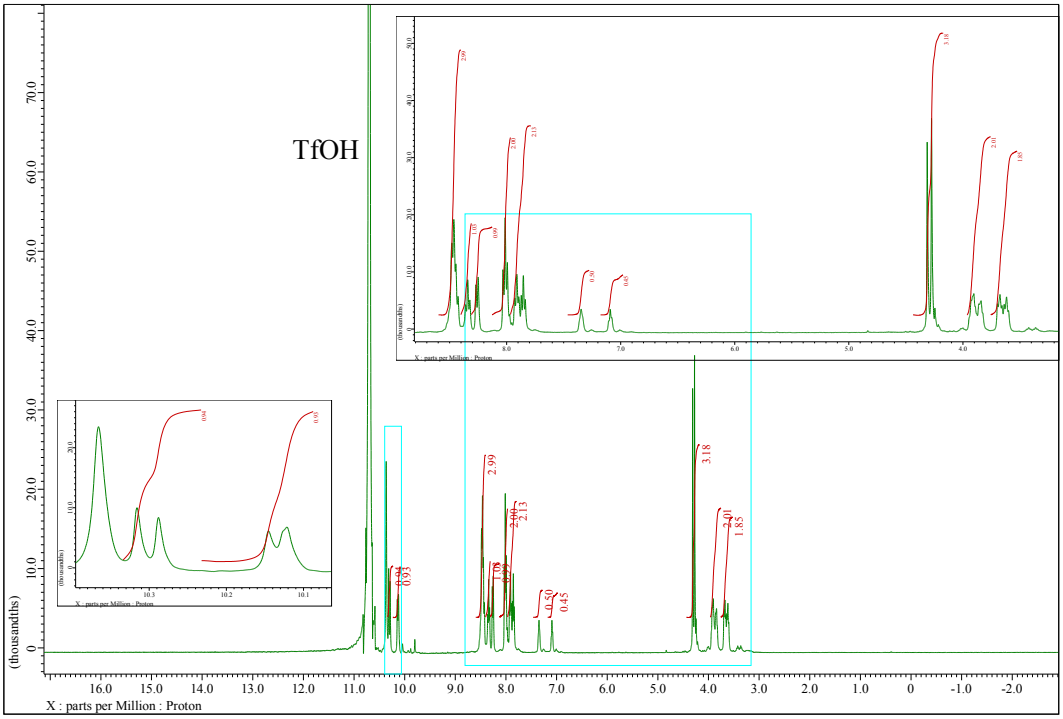
9a in TfOH (^{1}H-NMR)



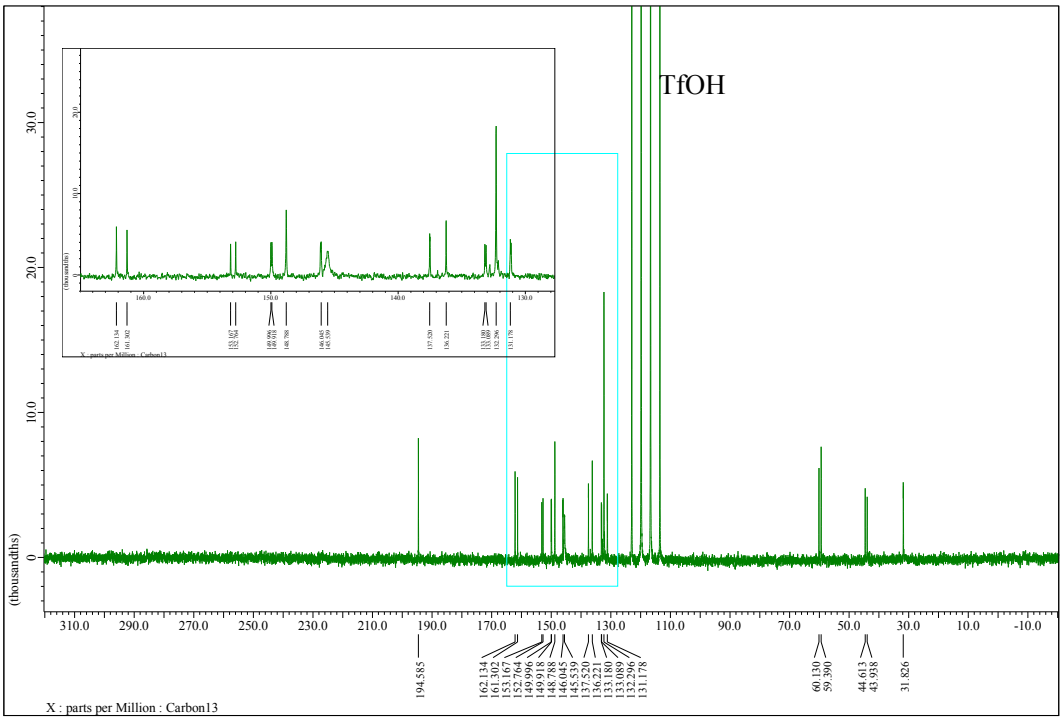
9a in TfOH (^{13}C-NMR)



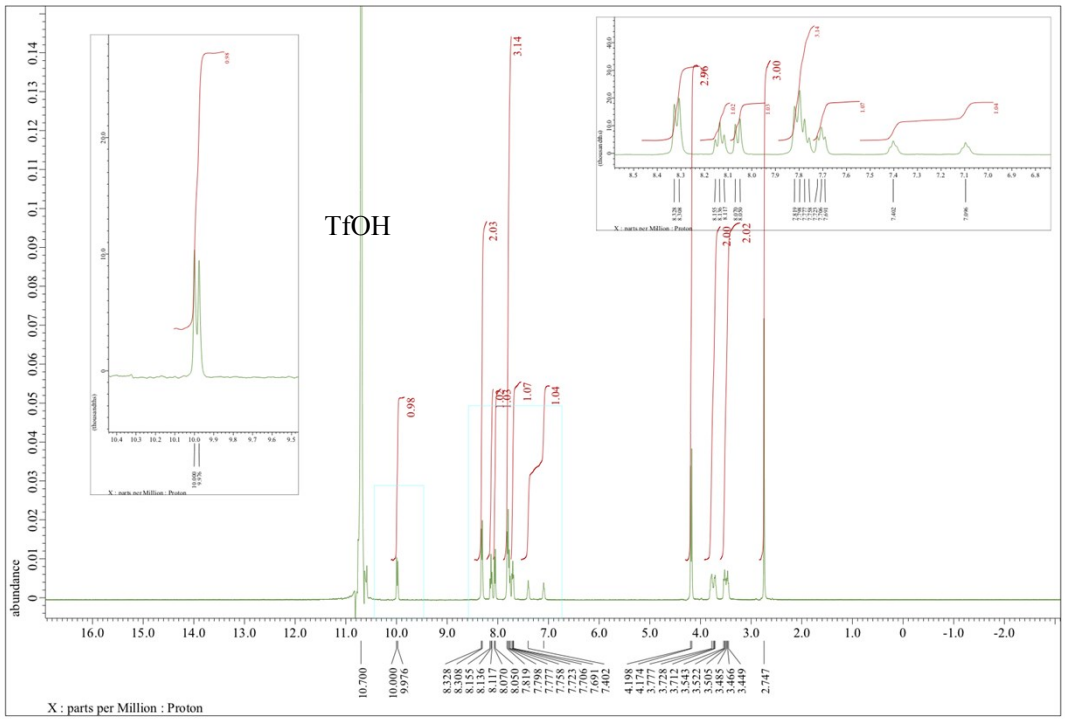
9a in TfOH/SbF_5 (9:1 w/w) (^{1}H-NMR)



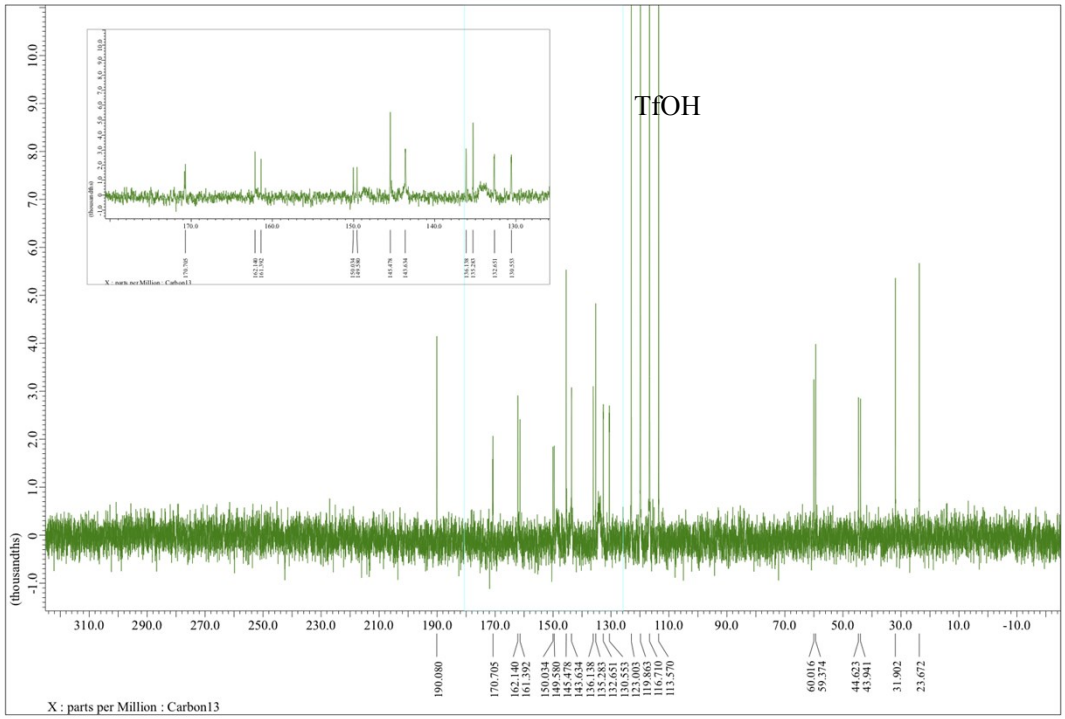
9a in TfOH/SbF_5 (9:1 w/w) (^{13}C-NMR)



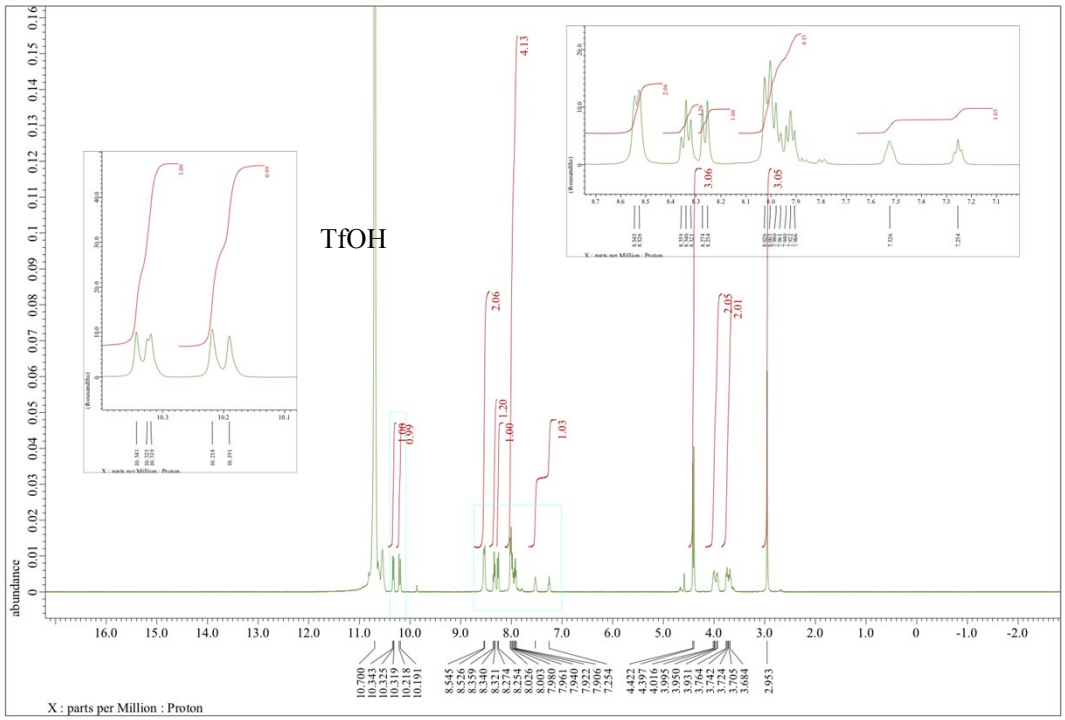
9b in TfOH (^{1}H-NMR)



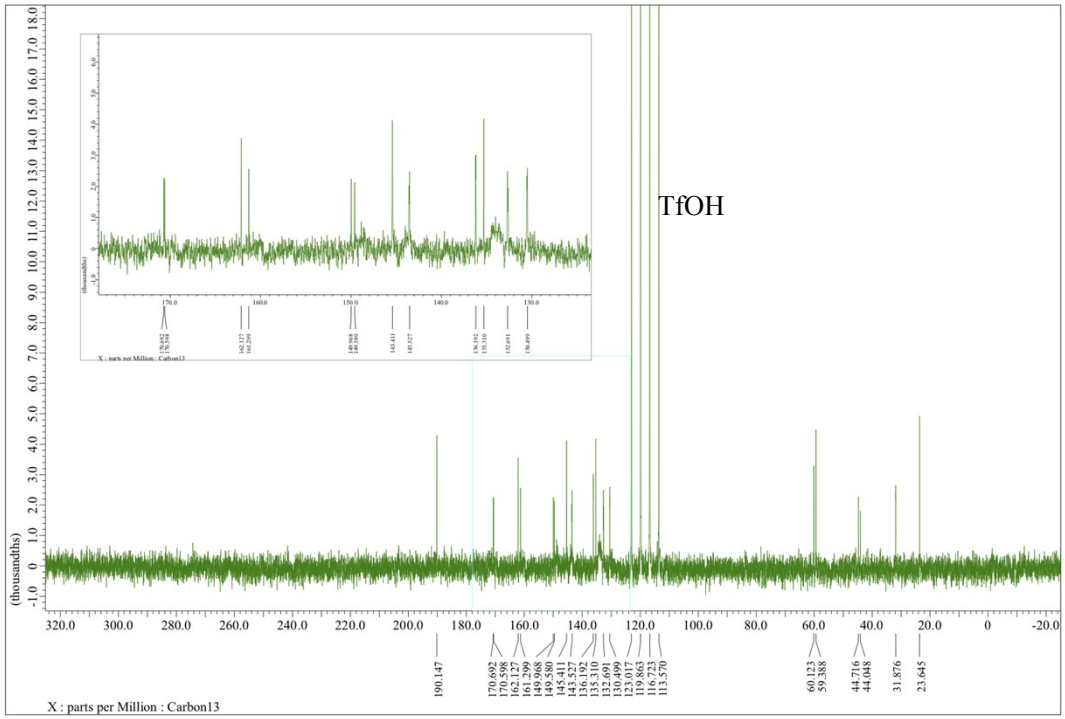
9b in TfOH (^{13}C-NMR)



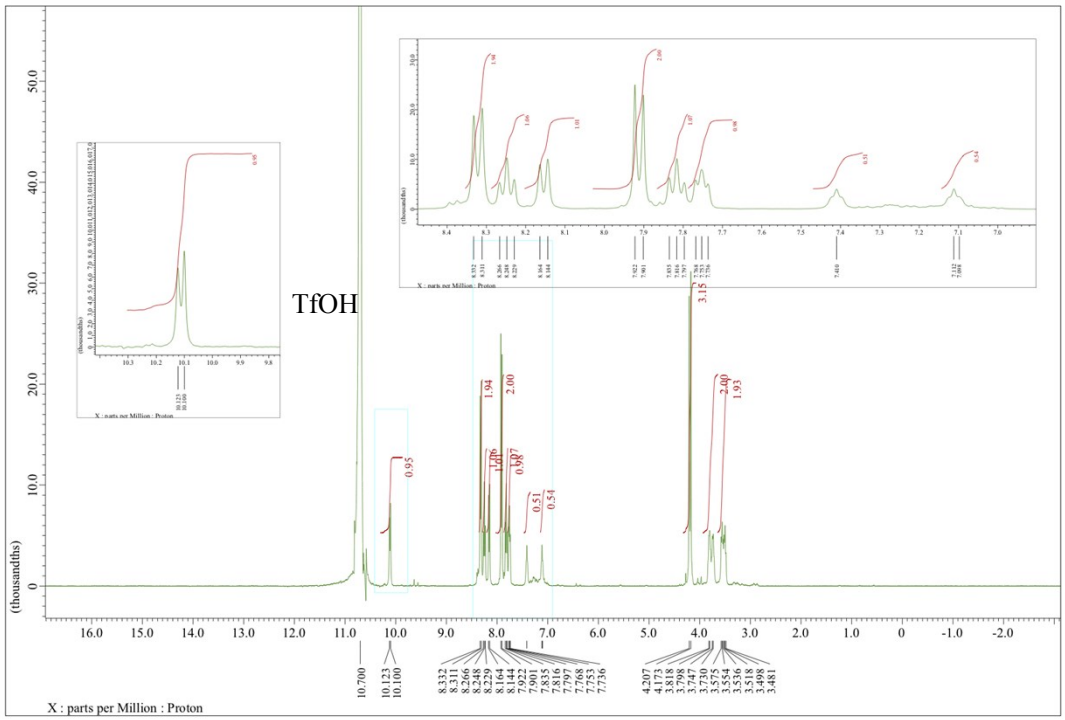
9b in TfOH/SbF_5 (9:1 w/w) (^{1}H-NMR)



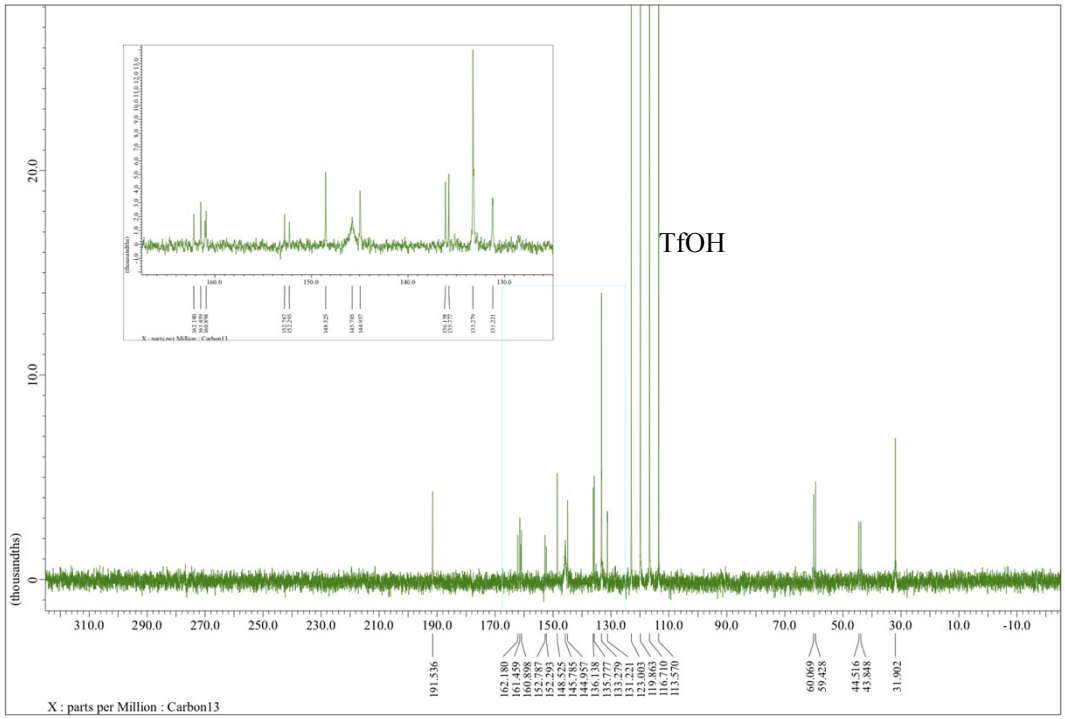
9b in TfOH/SbF_5 (9:1 w/w) (^{13}C-NMR)



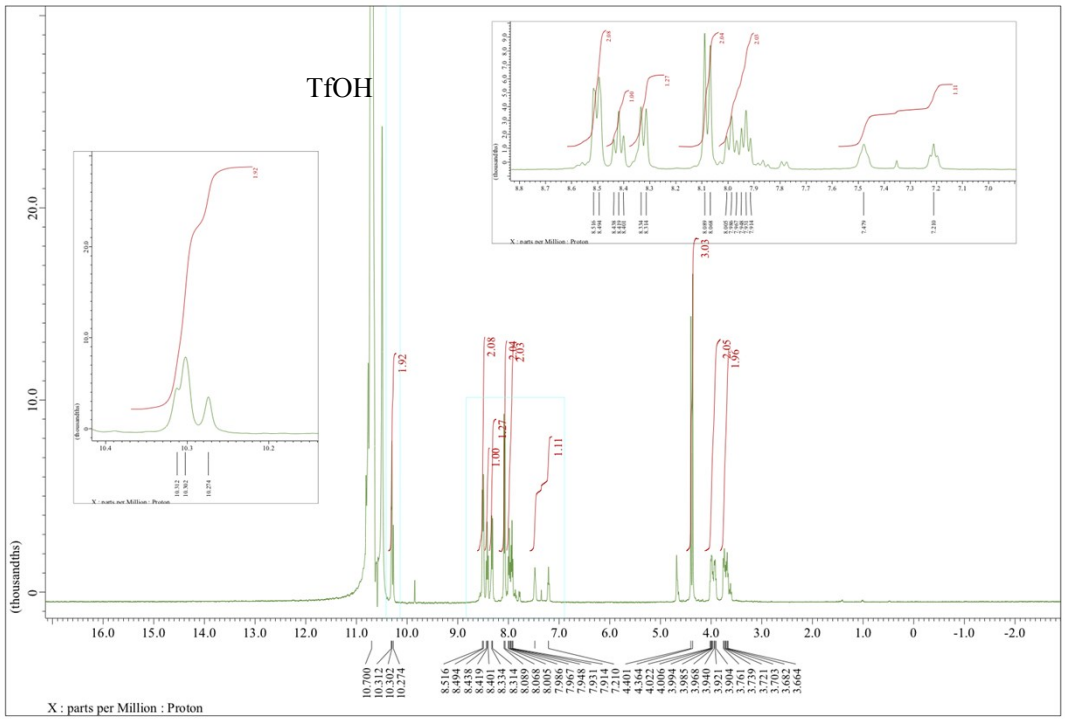
9c in TfOH (^{1}H-NMR)



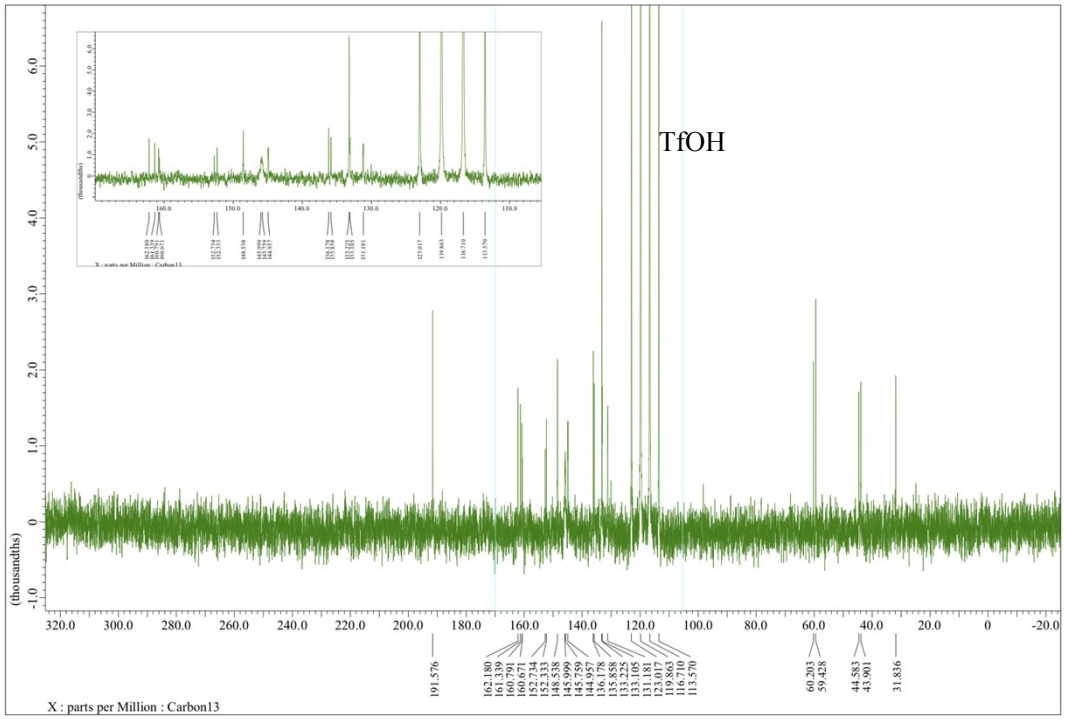
9c in TfOH (^{13}C-NMR)



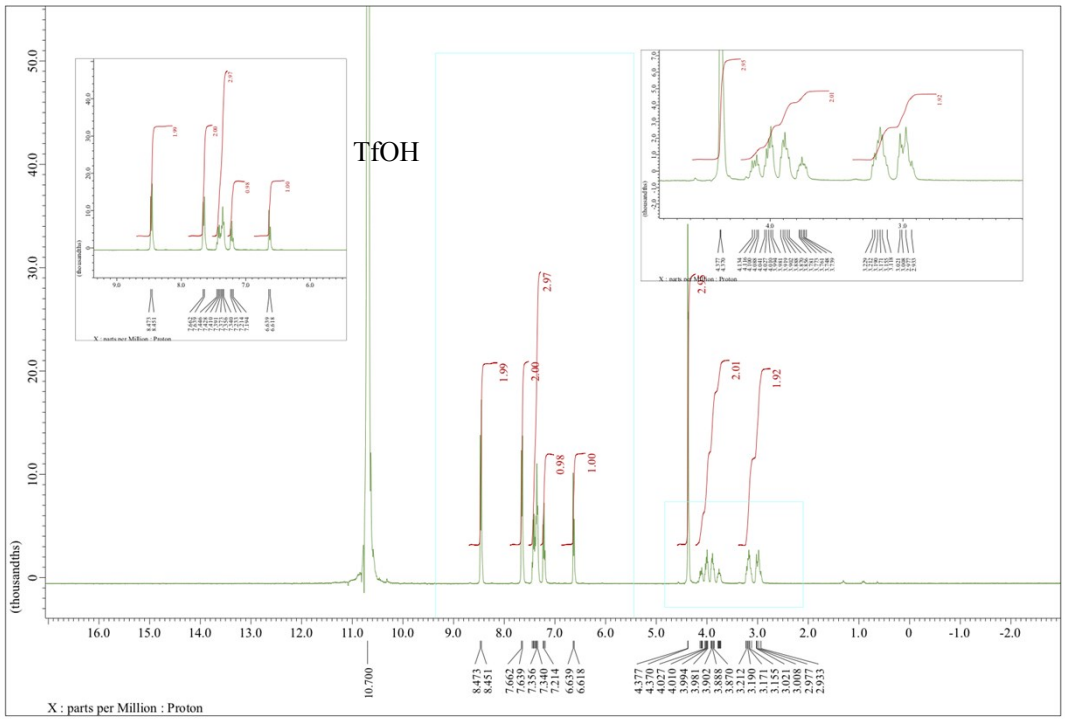
9c in TfOH/SbF_5 (9:1 w/w) (^{1}H-NMR)



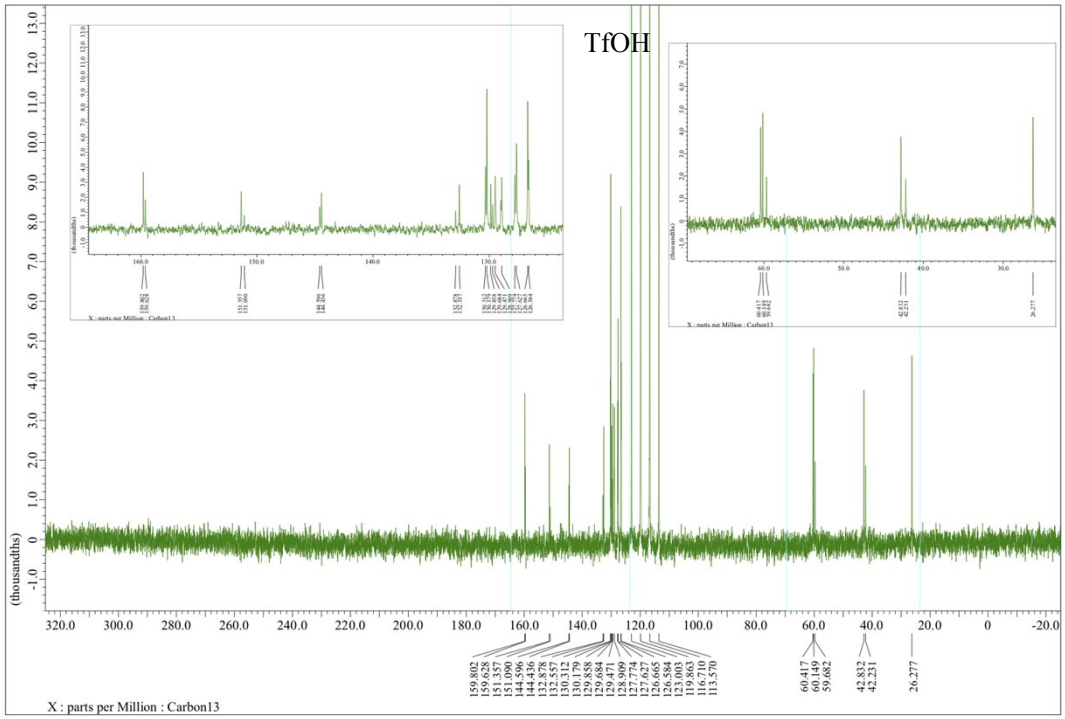
9c in TfOH/SbF_5 (9:1 w/w) (^{13}C-NMR)



9d in TfOH (^{1}H-NMR)



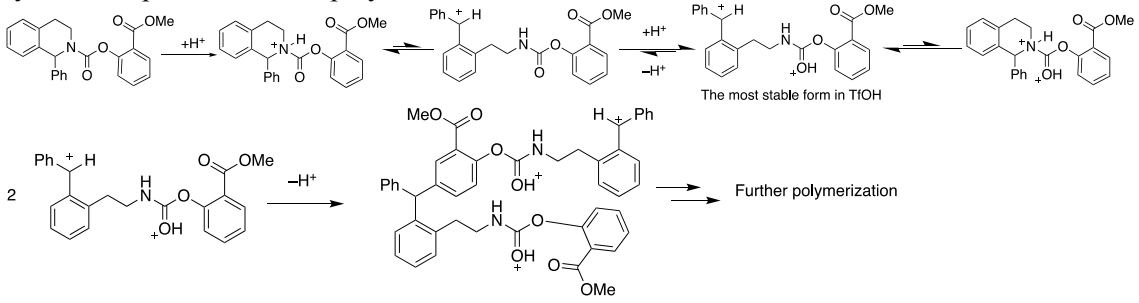
9d in TfOH (^{13}C-NMR)



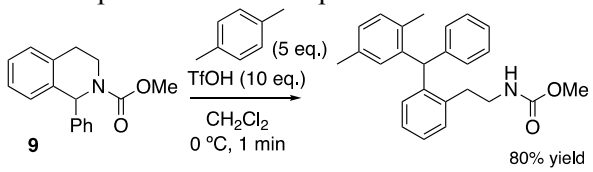
Response to reviewer:

One of reviewers asked me the reason why **1** was not used for the observation of dication, and the reaction of **9** affords the same product as **1** or not.

The reason why I used **9** instead of **1**: This is because **1** has additional Ar = 2-MeOOCC6H4 group which can react with ring-opened carbocation. It affords NMR spectra of complex mixture. Because the ring-opened carbocation is more stable than the ring-closed carbocation, it becomes major species in the reaction system. In the absence of nucleophile, it is observable by NMR. But in the presence of nucleophiles such as **3** in Table 2 or intramolecular nucleophile of substrate as shown in Table 1, the dication can be trapped by nucleophiles and triarylmethanes are to be generated. But in the absence of **3** and in the presence of methyl salicylate moiety, methyl salicylate moiety probably reacted with the dication and made the system complex mixture of polymers.

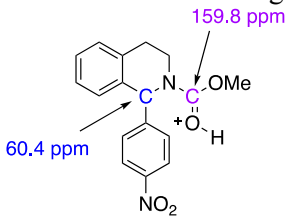


The reaction of **9** with nucleophiles: Partially yes. As discussed in (7), the Ar = 2-MeOOCC6H4 is essential for forming dihydroisoquinolone. Because methoxy group is poor leaving group. So, the triarylmethane moiety can be synthesized, but further cyclization does not occur even if the reaction mixture was left at room temperature. In order to activate the methyl carbamate group in TfOH, it requires heating condition at 70 ºC.[S26] But in such condition, the triarylmethane groups decompose to afford complex mixture.

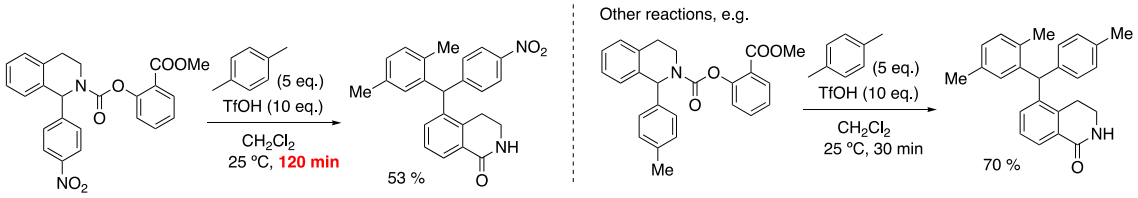


And other referees suggested me to measure more substrates in superacid to measure dications. One of the referees suggested that the change of the structure might change the timing of the formation of dication and stability of the resultant dication.

As the referee mentioned, the timing of the formation of the ring-opened dication was changed by introducing a nitro group. The expected ring-opened dication was not observed, but a ring-closed cation was observed in TfOH instead. Because the substrate is unstable in the $TfOH/SbF_5$ system, the degree of protonation on the nitro group could not be detected.



A related substrate could afford the target product. This clearly shows that the C-N bond scission process did occur for the substrate. This reaction took 2 hours to consume the substrate, while regular reactions completely consumed the substrates within 30 min. It indicates that C-N bond scission of this substrate is so slow that the succeeding reactions were retarded.



4. Computational Study

4-A. General Methods

PM7 and 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 program suite *ConfProg* used for conformation search is a series of component programs written as Python3 programs. A program "optimize" of TINKER program[S28] was used to conduct optimization and energy calculation at each cycles of Monte Carlo multiple minimum (MCMM) method. A full description of ConfProg including listings of the subprograms are written in a later section. Some MM3 force field parameters of TINKER were complemented by the author.

The transition state structures were validated with frequency calculations and then intrinsic reaction coordinate (IRC) calculation. Basically, IRC calculation afforded desired pathway between reactant and product, but sometimes caused error and stopped before normal termination. In such a case of IRC calculation failure, the transition state structure was moved along its transition vector by "irc=(forward,calcfc,stepsize=2)" or "irc=(reverse,calcfc,stepsize=2)" option, and the obtained geometry was optimized using "opt=calcall" option to check the validity of transition state geometry.

4-B. Geometry optimization of relatively simple structure

For the geometry calculation of **PD**, **INT4**, **INT5**, **TS-FC2**, **9-2H$^+$-Open** and **9-2H$^+$-Closed**, possible conformations were generated by manual modeling on GaussView,[S29] then the conformers were optimized to local minimum and their frequencies were calculated at PCM(CH_2Cl_2)-M06-2X/6-31G* level. For these DFT-optimized geometries, single-point energies were calculated at SMD(CH_2Cl_2)-M06-2X/jul-cc-pVTZ 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. Because of higher degree of freedom, other structures needed automated conformation search shown below.

4-C. Conformation search and optimization of the structure of ground states

The geometry of **SM-O**, **SM-N**, **INT-1**, **INT-3**, and **INT-1-Dication** of Figure 4 were calculated by the procedure shown below.

In the first step of the conformation search, 5000 steps of the MCMM method calculation were run using a *ConfProg* suite we developed. The source code is shown in the next chapter. The probability of acceptance of new structure is modified during Metropolis-Hasting algorithm of MCMM process to obtain as many candidate structures as possible using limited calculation resource.

In this process, the first geometry ($\boldsymbol{R}_1^{\text{nonoptimize}}$) was prepared arbitrary and optimized at MM3 force field by "*optimize*" program of TINKER program suite to obtain optimized geometry ($\boldsymbol{R}_1^{\text{optimized}}$). And new geometry of $n+1^{\text{th}}$ cycle ($\boldsymbol{R}_{n+1}^{\text{nonoptimize}}$) was generated by random rotation of the torsional angle of previously accepted geometry ($\boldsymbol{R}_n^{\text{optimized}}$), and then the geometry was optimized at MM3 force field by the "*optimize*" program to obtain optimized geometry ($\boldsymbol{R}_{n+1}^{\text{optimized}}$) and its potential energy (E_n). The probability to accept the new structure (P_{accept}) was calculated as follows.

$$P_{\text{accept}} = \exp\{-\beta(E_{n+1} - E_n)/S\}$$

The variable E_n is potential energy of $\boldsymbol{R}_n^{\text{optimized}}$, and E_{n+1} is a potential energy of $\boldsymbol{R}_{n+1}^{\text{optimized}}$. The constant β is inverse temperature. In order to accept wide range of structures, the index is divided

by sampling bias *S*, which was set to 100. The new geometry was accepted when

$$P_{\text{accept}} > Rand$$

The variable *Rand* is a random number between 0 and 1. Because this conformation search process is conducted to obtain as many candidate structures as possible, the emergence rate of geometries are not in accord with free energy. Generally, about 500 conformations were obtained at this process.

All the obtained geometries were further optimized at PM7 level of theory by Gaussian16 program in gas phase. After getting rid of duplicated geometries, 100 geometries from the lowest energy were chosen. Geometry optimization and frequency calculation were conducted for them at PCM(CH_2Cl_2)-M06-2X/6-31G* level by Gaussian16 program. For the DFT-optimized geometries, single-point energies were calculated at SMD(CH_2Cl_2)-M06-2X/jul-cc-pVTZ 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.

4-D. Conformation search and optimization of the structure of transition states

The transition state geometry of **TS-CN**, **TS-FC**, **TS-CO**, and **TS1-FC-Dication** of Figure 4 were calculated by the procedure shown below.

In the first step of the conformation search, 5000 steps of the MCMM method calculation were run using the *ConfProg* suite. To obtain as many candidate structures as possible using limited calculation resource, the probability of acceptance of new structure is modified during Metropolis-Hasting algorithm of MCMM process.

In this process, the first geometry ($\boldsymbol{R}_1^{\text{nonoptimize}}$) was prepared arbitrary and optimized at MM3 force field by "*optimize*" program of TINKER program suite to obtain optimized geometry ($\boldsymbol{R}_1^{\text{optimized}}$). The length of the bonds, which are to be cleaved, are set to 1.8 Å during the optimization. And new geometry of $n+1^{\text{th}}$ cycle ($\boldsymbol{R}_{n+1}^{\text{nonoptimize}}$) is generated by random rotation of the torsional angle of previously accepted geometry ($\boldsymbol{R}_n^{\text{optimized}}$), and then the geometry was optimized at MM3 force field by the "*optimize*" program to obtain optimized geometry ($\boldsymbol{R}_{n+1}^{\text{optimized}}$) and its potential energy (E_n). The length of the bonds under dissociation of formation are also set to 1.8 Å during the optimization. The probability (P_{accept}) was calculated as follows.

$$P_{\text{accept}} = \exp\{-\beta(E_{n+1} - E_n)/S\}$$

The variable E_n is potential energy of $\boldsymbol{R}_n^{\text{optimized}}$, and E_{n+1} is potential energy of $\boldsymbol{R}_{n+1}^{\text{optimized}}$. The constant β is inverse temperature. In order to accept wide range of structures, the index is divided by sampling bias *S*, which was set to 100. The new geometry was accepted when

$$P_{\text{accept}} > Rand$$

The variable *Rand* is a random number between 0 and 1. Because this conformation search process is conducted to obtain as many candidate structures as possible, the emergence rate of geometries are not in accord with free energy. Generally, about 1000 conformations were obtained at this process.

All the obtained geometries were further optimized at PM7 level of theory by Gaussian16 program in gas phase, fixing the length of bonds under dissociation or formation. Because of poor convergence of the default SCF calculation algorithm, "scf=xqc" option was used. After getting rid of duplicated geometries, 100 geometries from the lowest energy were chosen. The potential energy surfaces of the TS candidates were scanned using "opt=modredundant" option and extended by

0.05 Å for 9 times. The geometries at energy maximum of each scan calculation were chosen, and geometry optimization and frequency calculation of the transition state geometries were conducted for them at PCM(CH_2Cl_2)-M06-2X/6-31G* level by Gaussian16 program. For the DFT-optimized geometries, single-point energies were calculated at SMD(CH_2Cl_2)-M06-2X/jul-cc-pVTZ 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.

4-E. Information of the optimized geometries.

SM-O

```
 Number of imaginary frequency = 0
Zero-point       correction=       0.530013
(Hartree/Particle)
Thermal correction to Energy= 0.559410
Thermal correction to Enthalpy= 0.560354
Thermal correction to Gibbs Free Energy=
0.469173
Sum of electronic and zero-point Energies=
-1552.524367
Sum of electronic and thermal Energies= -
1552.494971
Sum of electronic and thermal Enthalpies= -
1552.494027
Sum of electronic and thermal Free Energies=
-1552.585208
 Electronic Energy = -1553.05438076

   E (Thermal)          CV            S
351.035   KCal/Mol       117.369   Cal/Mol-K
191.907 Cal/Mol-K

 Charge = 1 Multiplicity = 1
 C,0,-2.853208,2.545108,-0.891330
 C,0,-2.334710,1.660112,0.058340
 C,0,-2.477669,1.926846,1.425385
 C,0,-3.148576,3.091687,1.811886
 C,0,-3.666618,3.969640,0.868065
 C,0,-3.517436,3.697677,-0.492296
 C,0,-1.893291,1.017822,2.490678
 C,0,-1.434223,-0.325779,1.928229
 C,0,-1.640897,0.399585,-0.428490
 C,0,0.555661,0.027451,0.606931
 O,0,1.288205,-0.230508,1.628704
 O,0,1.136962,0.361526,-0.552060
 N,0,-0.741680,-0.051736,0.659418
 C,0,-2.590642,-0.731111,-0.831917
 C,0,-2.093741,-1.897879,-1.444525
 C,0,-3.964171,-0.604019,-0.608503
 C,0,-2.998569,-2.893949,-1.818824
 C,0,-4.850098,-1.610533,-0.983088
 C,0,-4.365548,-2.761029,-1.594208
 C,0,-0.583100,-3.350729,0.593109
 C,0,1.500989,-2.782134,-0.462253
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 C,0,2.198463,-3.344395,0.604545
 C,0,1.506166,-3.904658,1.675909
 C,0,1.889709,1.557640,-0.559927
 C,0,1.206984,2.740564,-0.787364
 C,0,3.280876,1.518835,-0.453201
 C,0,1.931663,3.924217,-0.911054
 C,0,3.992554,2.711783,-0.610256
 C,0,3.321748,3.908981,-0.831298
 C,0,4.008910,0.268926,-0.118174
 O,0,3.572871,-0.607269,0.625305
 O,0,5.196932,0.195875,-0.666019
 C,0,5.991125,-0.957643,-0.324925
 C,0,0.101991,-2.778289,-0.482520
 C,0,-0.620926,-2.151645,-1.669419
 H,0,-2.739285,2.316959,-1.948593
 H,0,-3.261702,3.305694,2.871559
 H,0,-1.037353,1.519515,2.958447
 H,0,-2.628585,0.842798,3.281525
 H,0,-0.758404,-0.854904,2.597963
 H,0,-2.277902,-0.977036,1.689069
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 H,0,-3.915533,4.380119,-1.235790
 H,0,-4.185517,4.866285,1.191079
 H,0,-4.350891,0.295231,-0.140639
 H,0,-2.614780,-3.794100,-2.292310
 H,0,-5.912404,-1.488907,-0.799124
 H,0,-5.044725,-3.551599,-1.896595
 H,0,-1.669764,-3.361182,0.596673
 H,0,2.048734,-2.331657,-1.287601
 H,0,-0.437012,-4.340864,2.494378
 H,0,3.283744,-3.326196,0.604692
 H,0,2.047800,-4.335975,2.511684
 H,0,0.124442,2.733551,-0.875113
 H,0,1.403180,4.855334,-1.083075
 H,0,5.074169,2.688705,-0.539442
 H,0,3.884451,4.829123,-0.939294
 H,0,5.489858,-1.860652,-0.675168
 H,0,6.937878,-0.813896,-0.838247
 H,0,6.131133,-1.001297,0.755391
 H,0,-0.099228,-1.230247,-1.953219
 H,0,-0.516323,-2.823148,-2.529576
 H,0,2.261891,-0.387237,1.309692
```

SM-N

```
 Number of imaginary frequency = 0
Zero-point correction= 0.532535
(Hartree/Particle)
Thermal correction to Energy= 0.561844
Thermal correction to Enthalpy= 0.562788
Thermal correction to Gibbs Free Energy=
0.472705
Sum of electronic and zero-point Energies=
-1552.520885
Sum of electronic and thermal Energies= -
1552.491575
Sum of electronic and thermal Enthalpies=
-1552.490631
Sum of electronic and thermal Free
Energies= -1552.580715
 Electronic Energy = -1553.05341960

   E (Thermal)          CV            S
352.563 KCal/Mol   117.469 Cal/Mol-K
189.597 Cal/Mol-K

 Charge = 1 Multiplicity = 1
 C,0,3.715346,-1.706318,-1.232965
 C,0,2.895294,-1.282653,-0.181406
 C,0,3.041090,-1.835026,1.092290
 C,0,4.015354,-2.820763,1.288613
 C,0,4.831472,-3.238181,0.247286
```

C,0,4.682243,-2.677605,-1.023065
C,0,2.157630,-1.433653,2.251055
C,0,1.255369,-0.243675,1.957325
C,0,1.903608,-0.183372,-0.480630
C,0,-0.179027,-1.360639,0.232457
O,0,-0.220327,-2.375499,0.842025
O,0,-0.860443,-0.990310,-0.849755
C,0,2.466606,1.226944,-0.490367
C,0,1.773382,2.259249,-1.151080
C,0,3.679381,1.498120,0.149769
C,0,2.327671,3.542216,-1.139827
C,0,4.208841,2.783835,0.157174
C,0,3.529041,3.810213,-0.491685
C,0,-0.736738,2.944218,0.253495
C,0,-2.032159,1.844262,-1.451969
C,0,-1.910235,3.211457,0.964025
C,0,-3.199884,2.117240,-0.750530
C,0,-3.142553,2.814118,0.458723
C,0,-2.137852,-1.537175,-1.024516
C,0,-2.355087,-2.296591,-2.158045
C,0,-3.158112,-1.226591,-0.117920
C,0,-3.638632,-2.779559,-2.404517
C,0,-4.436193,-1.725814,-0.386382
C,0,-4.675535,-2.496162,-1.519254
C,0,-2.899665,-0.397987,1.095404
O,0,-1.796514,-0.034967,1.468842
O,0,-4.009311,-0.112762,1.759676
C,0,-3.832410,0.576727,3.005920
C,0,-0.787057,2.274219,-0.972024
C,0,0.444228,2.057966,-1.845120
N,0,0.755189,-0.244982,0.536139
H,0,3.591004,-1.261428,-2.217019
H,0,4.126580,-3.258512,2.277151
H,0,1.553181,-2.292270,2.552083
H,0,2.778555,-1.163253,3.110854
H,0,0.368820,-0.223604,2.590717
H,0,1.787907,0.704776,2.054001
H,0,1.430816,-0.390252,-1.443626
H,0,5.313803,-3.001144,-1.843471
H,0,5.583183,-4.001055,0.421574
H,0,4.219003,0.691026,0.636106
H,0,1.800832,4.342475,-1.653003
H,0,5.150634,2.977533,0.659236
H,0,3.935350,4.816352,-0.500872
H,0,0.217135,3.286701,0.646897
H,0,-2.080930,1.305353,-2.395897
H,0,-1.853708,3.744376,1.908489
H,0,-4.156214,1.785138,-1.144114
H,0,-4.056110,3.037766,1.001655
H,0,-1.527572,-2.496929,-2.829123
H,0,-3.822779,-3.378807,-3.289511
H,0,-5.240149,-1.500278,0.304036
H,0,-5.673364,-2.874450,-1.710598
H,0,-3.281129,1.503577,2.845367
H,0,-4.836864,0.776990,3.371161
H,0,-3.286529,-0.060945,3.703482
H,0,0.373811,1.067449,-2.308114
H,0,0.387833,2.769667,-2.676898
H,0,0.170837,0.602809,0.416752

TS-CN

Number of imaginary frequency = 1
Zero-point correction= 0.529775
(Hartree/Particle)
Thermal correction to Energy= 0.559350
Thermal correction to Enthalpy= 0.560294
Thermal correction to Gibbs Free Energy=
0.468303
Sum of electronic and zero-point Energies=
-1552.498913
Sum of electronic and thermal Energies= -
1552.469338
Sum of electronic and thermal Enthalpies=
-1552.468393
Sum of electronic and thermal Free
Energies= -1552.560385
Electronic Energy = -1553.02868785

E (Thermal) CV S
350.998 KCal/Mol 117.504 Cal/Mol-K
193.612 Cal/Mol-K

Charge = 1 Multiplicity = 1
C,0,-3.225914,-0.632075,-2.368601
C,0,-2.774050,-0.881229,-1.051696
C,0,-2.877020,-2.190444,-0.506584
C,0,-3.372786,-3.211248,-1.312628
C,0,-3.808968,-2.950897,-2.608741
C,0,-3.748570,-1.657764,-3.134087
C,0,-2.336802,-2.491193,0.857349
C,0,-0.807035,-2.313180,0.894182
C,0,-2.300038,0.178712,-0.207951
C,0,0.517362,-0.634448,-0.280397
O,0,0.638029,-1.231998,-1.317892
O,0,1.197782,0.487087,0.064034
C,0,-1.783148,1.442158,-0.644255
C,0,-1.867785,2.576216,0.214426
C,0,-1.165604,1.561796,-1.910886
C,0,-1.411806,3.797178,-0.269307
C,0,-0.716026,2.790022,-2.364341
C,0,-0.858326,3.911231,-1.546188
C,0,-0.184139,1.832176,2.598055
C,0,-2.128602,0.577852,3.263961
C,0,0.620650,0.996356,3.370594
C,0,-1.325733,-0.266008,4.031972
C,0,0.053083,-0.062380,4.081787
C,0,2.390373,0.740345,-0.595089
C,0,2.511652,1.978261,-1.206382
C,0,3.453692,-0.173778,-0.578525
C,0,3.702918,2.318365,-1.840353
C,0,4.636775,0.183681,-1.234407
C,0,4.763302,1.416001,-1.864528
C,0,3.367364,-1.462241,0.170295
O,0,2.466735,-1.776324,0.922335
O,0,4.421939,-2.245682,-0.058151
C,0,4.429084,-3.489310,0.651317
C,0,-1.565219,1.625265,2.528493
C,0,-2.424074,2.491659,1.622448
N,0,-0.414872,-0.918316,0.701521
H,0,-3.227502,0.381061,-2.753301
H,0,-3.427623,-4.220415,-0.916528
H,0,-2.784356,-1.848180,1.625644
H,0,-2.568073,-3.523916,1.128496
H,0,-0.421919,-2.643573,1.862340
H,0,-0.340344,-2.908974,0.108319
H,0,-2.571462,0.104909,0.838746
H,0,-4.120207,-1.454240,-4.131939
H,0,-4.212954,-3.759070,-3.209894
H,0,-1.010154,0.672189,-2.512452
H,0,-1.487196,4.677682,0.361067
H,0,-0.242436,2.872928,-3.336125
H,0,-0.513842,4.880600,-1.892743
H,0,0.269612,2.631627,2.017626
H,0,-3.203815,0.413707,3.227088
H,0,1.693334,1.158531,3.399460
H,0,-1.777495,-1.082735,4.586117
H,0,0.681704,-0.723156,4.669514
H,0,1.668047,2.658198,-1.170197
H,0,3.797506,3.288008,-2.317835
H,0,5.464191,-0.515758,-1.231689
H,0,5.690827,1.674436,-2.363210
H,0,5.342052,-3.995190,0.345423

H,0,4.429804,-3.308044,1.727470
H,0,3.551390,-4.079190,0.382148
H,0,-3.449989,2.108622,1.610089
H,0,-2.479638,3.506647,2.028208
H,0,-0.228899,-0.409635,1.565295

INT-1

Number of imaginary frequency = 0
Zero-point correction= 0.529538
(Hartree/Particle)
Thermal correction to Energy= 0.559946
Thermal correction to Enthalpy= 0.560890
Thermal correction to Gibbs Free Energy=
0.467230
Sum of electronic and zero-point Energies=
-1552.500441
Sum of electronic and thermal Energies= -
1552.470033
Sum of electronic and thermal Enthalpies=
-1552.469089
Sum of electronic and thermal Free
Energies= -1552.562749
Electronic Energy = -1553.02997913

E (Thermal) CV S
351.372 KCal/Mol 119.923 Cal/Mol-K
197.124 Cal/Mol-K

Charge = 1 Multiplicity = 1
C,0,-2.065458,-1.900894,-2.600208
C,0,-2.109540,-1.637444,-1.204385
C,0,-2.136783,-2.725388,-0.278764
C,0,-2.044111,-4.018816,-0.783014
C,0,-1.980523,-4.255121,-2.153867
C,0,-2.009116,-3.196186,-3.068315
C,0,-2.134381,-2.511389,1.205556
C,0,-0.751977,-2.073247,1.733197
C,0,-2.176672,-0.311440,-0.710083
C,0,0.604391,-0.554894,0.388394
O,0,0.949752,-1.362029,-0.444333
O,0,1.081614,0.720689,0.479852
C,0,-1.728700,0.869280,-1.360078
C,0,-2.256099,2.135904,-0.958137
C,0,-0.746956,0.805293,-2.382577
C,0,-1.867404,3.259993,-1.674197
C,0,-0.372136,1.944799,-3.069582
C,0,-0.955128,3.167140,-2.729525
C,0,-1.323326,2.485926,1.885115
C,0,-3.168210,1.034855,2.421098
C,0,-0.712558,2.157195,3.093708
C,0,-2.553595,0.691592,3.625405
C,0,-1.323049,1.252697,3.965250
C,0,2.252072,1.034479,-0.182469
C,0,2.226415,2.185776,-0.956904
C,0,3.429478,0.287510,-0.037963
C,0,3.374091,2.594105,-1.628856
C,0,4.566897,0.703199,-0.737916
C,0,4.543972,1.844418,-1.531084
C,0,3.510394,-0.868233,0.902271
O,0,2.745897,-1.071390,1.821626
O,0,4.558179,-1.653366,0.641010
C,0,4.732013,-2.757321,1.535326
C,0,-2.557240,1.929054,1.537091
C,0,-3.210543,2.279144,0.209053
N,0,-0.371742,-0.733953,1.317847
H,0,-2.153821,-1.076537,-3.298627
H,0,-2.031773,-4.856240,-0.092581
H,0,-2.876679,-1.767146,1.515878
H,0,-2.397100,-3.450902,1.698711
H,0,-0.778360,-2.086598,2.825350
H,0,0.015107,-2.774239,1.395309
H,0,-2.655986,-0.178342,0.253281
H,0,-2.004663,-3.392581,-4.134192
H,0,-1.930798,-5.276832,-2.516677
H,0,-0.248349,-0.138407,-2.577138
H,0,-2.277423,4.228751,-1.406510
H,0,0.386022,1.892649,-3.842723
H,0,-0.672035,4.067082,-3.266649
H,0,-0.829808,3.172768,1.201966
H,0,-4.133886,0.602928,2.165517
H,0,0.247113,2.595345,3.348363
H,0,-3.037986,-0.010172,4.297099
H,0,-0.841884,0.988124,4.901161
H,0,1.299780,2.745922,-1.017137
H,0,3.349445,3.496045,-2.231714
H,0,5.478233,0.125347,-0.636342
H,0,5.439065,2.153704,-2.059357
H,0,5.617715,-3.282530,1.184699
H,0,4.875033,-2.397251,2.555620
H,0,3.857184,-3.408864,1.499739
H,0,-4.100885,1.659481,0.059454
H,0,-3.560351,3.315852,0.237072
H,0,-0.451556,0.007157,2.009016

TS-FC1

Number of imaginary frequency = 1
Zero-point correction= 0.528513
(Hartree/Particle)
Thermal correction to Energy= 0.558308
Thermal correction to Enthalpy= 0.559252
Thermal correction to Gibbs Free Energy=
0.467908
Sum of electronic and zero-point Energies=
-1552.491511
Sum of electronic and thermal Energies= -
1552.461716
Sum of electronic and thermal Enthalpies=
-1552.460772
Sum of electronic and thermal Free
Energies= -1552.552116
Electronic Energy = -1553.02002396

E (Thermal) CV S
350.343 KCal/Mol 118.510 Cal/Mol-K
192.249 Cal/Mol-K

Charge = 1 Multiplicity = 1
C,0,3.501526,-0.497525,-1.142435
C,0,2.261276,-0.865094,-0.564774
C,0,1.977180,-2.235699,-0.311558
C,0,2.957148,-3.178829,-0.638432
C,0,4.168180,-2.798918,-1.201356
C,0,4.444174,-1.449834,-1.463040
C,0,0.642399,-2.741160,0.173206
C,0,1.303178,0.144379,-0.235534
C,0,-1.872398,-1.184503,-1.442217
O,0,-2.262088,-0.216896,-2.062174
O,0,-2.523812,-1.710657,-0.365764
N,0,-0.745145,-1.883360,-1.712020
C,0,1.329733,1.530265,-0.759171
C,0,2.169161,2.549195,-0.287903
C,0,0.400202,1.794241,-1.777415
C,0,2.090308,3.809461,-0.882830
C,0,0.355320,3.048147,-2.374214
C,0,1.205827,4.057784,-1.927056
C,0,3.847929,0.155689,1.932578
C,0,1.499704,0.715159,1.941853
C,0,1.207464,-0.493760,2.608414
C,0,2.220044,-1.397593,2.863518
C,0,-3.716495,-1.112979,0.006184
C,0,-4.861964,-1.886312,-0.110243
C,0,-3.774619,0.193010,0.506529

C,0,-6.090714,-1.361663,0.280274
C,0,-5.020129,0.710953,0.874651
C,0,-6.171920,-0.059942,0.768513
C,0,-2.542155,1.004158,0.699977
O,0,-1.424156,0.545538,0.841440
O,0,-2.799248,2.308453,0.747661
C,0,-1.680215,3.160164,1.021296
C,0,2.835367,1.064054,1.635673
C,0,3.113059,2.336044,0.885622
C,0,-0.295976,-3.071742,-1.004779
C,0,3.540792,-1.070383,2.514613
H,0,3.694103,0.552544,-1.344260
H,0,2.757192,-4.230582,-0.454604
H,0,0.801744,-3.658604,0.748431
H,0,0.128954,-2.035427,0.831591
H,0,-0.272885,-1.601684,-2.560883
H,0,0.305908,-0.194098,0.024427
H,0,5.386807,-1.160543,-1.913671
H,0,4.905292,-3.557098,-1.446184
H,0,-0.294510,1.019067,-2.091380
H,0,2.723732,4.608400,-0.507093
H,0,-0.360087,3.241000,-3.166465
H,0,1.161239,5.046266,-2.372335
H,0,4.875009,0.388538,1.668039
H,0,0.701221,1.437758,1.799925
H,0,0.178594,-0.708240,2.880957
H,0,2.003590,-2.351960,3.331967
H,0,-4.773654,-2.890678,-0.509559
H,0,-6.984448,-1.970594,0.193895
H,0,-5.071110,1.724148,1.256478
H,0,-7.128489,0.354033,1.067581
H,0,-1.277363,2.938945,2.012328
H,0,-0.904645,3.021973,0.264571
H,0,-2.071688,4.174567,0.989021
H,0,3.012853,3.194168,1.561295
H,0,4.152278,2.337694,0.536619
H,0,-1.168368,-3.606614,-0.627609
H,0,0.212724,-3.717572,-1.724161
H,0,4.336153,-1.784018,2.706258

INT2

Number of imaginary frequency = 0
Zero-point correction= 0.529691
(Hartree/Particle)
Thermal correction to Energy= 0.559746
Thermal correction to Enthalpy= 0.560690
Thermal correction to Gibbs Free Energy=
0.468528
Sum of electronic and zero-point Energies=
-1552.494016
Sum of electronic and thermal Energies= -
1552.463961
Sum of electronic and thermal Enthalpies=
-1552.463017
Sum of electronic and thermal Free
Energies= -1552.555180
Electronic Energy = -1553.02370719

E (Thermal) CV S
351.246 KCal/Mol 119.353 Cal/Mol-K
193.972 Cal/Mol-K

Charge = 1 Multiplicity = 1
C,0,3.485836,-0.635089,-0.975905
C,0,2.225593,-0.951908,-0.447592
C,0,1.842420,-2.304017,-0.357165
C,0,2.742506,-3.285994,-0.791575
C,0,3.988082,-2.959532,-1.310149
C,0,4.362249,-1.620431,-1.406752
C,0,0.486327,-2.780022,0.118116
C,0,1.312283,0.159025,0.013369
C,0,-1.926753,-1.091596,-1.420618
O,0,-2.239522,-0.056072,-1.972190
O,0,-2.617651,-1.631031,-0.370999
N,0,-0.871231,-1.867485,-1.747328
C,0,1.431378,1.468133,-0.734779
C,0,2.275228,2.493629,-0.298512
C,0,0.639368,1.660946,-1.871212
C,0,2.324975,3.695527,-1.007373
C,0,0.698352,2.858260,-2.575406
C,0,1.545414,3.878338,-2.143530
C,0,3.849639,0.252783,2.206710
C,0,1.488145,0.561297,1.634147
C,0,1.165699,-0.602337,2.445899
C,0,2.157513,-1.368920,2.985939
C,0,-3.783362,-0.994876,0.019090
C,0,-4.960694,-1.718163,-0.105253
C,0,-3.788694,0.304026,0.538082
C,0,-6.165379,-1.148478,0.297581
C,0,-5.009391,0.871647,0.912710
C,0,-6.192314,0.149485,0.801839
C,0,-2.522773,1.059045,0.740244
O,0,-1.450507,0.550180,1.008767
O,0,-2.700470,2.372879,0.641394
C,0,-1.544158,3.183494,0.880755
C,0,2.861824,1.044929,1.657505
C,0,3.143721,2.319480,0.937637
C,0,-0.461282,-3.078943,-1.053821
C,0,3.498172,-0.946456,2.832261
H,0,3.777427,0.408162,-1.065326
H,0,2.448225,-4.330471,-0.719310
H,0,0.615733,-3.698514,0.700523
H,0,-0.018938,-2.060242,0.767092
H,0,-0.334456,-1.544953,-2.541190
H,0,0.272596,-0.160367,-0.016160
H,0,5.328711,-1.345522,-1.815959
H,0,4.662694,-3.743814,-1.638161
H,0,-0.055175,0.884887,-2.181010
H,0,2.977925,4.491639,-0.659452
H,0,0.070899,3.000603,-3.449048
H,0,1.588647,4.818684,-2.683216
H,0,4.891529,0.548200,2.145468
H,0,0.723449,1.340635,1.701434
H,0,0.115653,-0.853340,2.563631
H,0,1.937631,-2.274196,3.539350
H,0,-4.916121,-2.718583,-0.521493
H,0,-7.083737,-1.718836,0.205933
H,0,-5.016775,1.882966,1.303854
H,0,-7.130628,0.598687,1.107915
H,0,-1.174213,3.018376,1.895425
H,0,-0.762908,2.947467,0.153963
H,0,-1.878932,4.211615,0.761828
H,0,2.935767,3.145139,1.634362
H,0,4.207481,2.385784,0.685887
H,0,-1.354007,-3.588696,-0.689625
H,0,0.026520,-3.730017,-1.783351
H,0,4.289267,-1.570230,3.238722

INT3

Number of imaginary frequency = 0
Zero-point correction= 0.529750
(Hartree/Particle)
Thermal correction to Energy= 0.559325
Thermal correction to Enthalpy= 0.560269
Thermal correction to Gibbs Free Energy=
0.468263
Sum of electronic and zero-point Energies=
-1552.533607
Sum of electronic and thermal Energies= -
1552.504032
Sum of electronic and thermal Enthalpies=
-1552.503087

Sum of electronic and thermal Free Energies= -1552.595094
Electronic Energy = -1553.06335675

E (Thermal) CV S
350.982 KCal/Mol 117.850 Cal/Mol-K 193.644 Cal/Mol-K

Charge = 1 Multiplicity = 1
C,0,0.989943,2.317304,-1.291774
C,0,1.573813,1.343694,-0.473769
C,0,1.293688,1.363625,0.906214
C,0,0.447338,2.355768,1.411376
C,0,-0.135295,3.311813,0.584930
C,0,0.138400,3.291275,-0.778574
C,0,1.840641,0.333074,1.872070
C,0,2.483889,0.304575,-1.138290
C,0,-1.344400,-0.490962,1.237191
O,0,-1.870290,0.342057,2.055654
O,0,-1.951966,-0.809781,0.098659
N,0,-0.188631,-1.048037,1.462395
C,0,1.873350,-1.085700,-1.080077
C,0,2.505040,-2.158969,-0.445085
C,0,0.619500,-1.282294,-1.674078
C,0,1.841501,-3.391731,-0.367186
C,0,-0.021471,-2.513008,-1.615031
C,0,0.587241,-3.574197,-0.938909
C,0,3.922070,0.376563,-0.649962
C,0,5.915335,-0.582808,0.311774
C,0,6.596212,0.614827,0.147993
C,0,5.938643,1.709519,-0.416987
C,0,-3.328920,-1.103127,0.088039
C,0,-3.665015,-2.444004,0.167862
C,0,-4.290998,-0.117446,-0.144164
C,0,-5.000135,-2.817407,0.036396
C,0,-5.622834,-0.514157,-0.301479
C,0,-5.977491,-1.854038,-0.201448
C,0,-3.954286,1.327389,-0.181974
O,0,-3.101159,1.855947,0.531538
O,0,-4.676385,2.014527,-1.028063
C,0,-4.445434,3.438459,-1.060320
C,0,4.577654,-0.717085,-0.080986
C,0,3.881452,-2.035361,0.162199
C,0,0.745084,-0.558112,2.482672
C,0,4.614216,1.583748,-0.809855
H,0,1.208902,2.306728,-2.356740
H,0,0.240303,2.375560,2.479329
H,0,2.588110,-0.293540,1.392529
H,0,2.345313,0.831380,2.707327
H,0,0.115513,-1.757554,0.794571
H,0,2.509157,0.582508,-2.200113
H,0,-0.301294,4.030586,-1.440858
H,0,-0.794588,4.064718,1.004795
H,0,0.133089,-0.442423,-2.164969
H,0,2.328965,-4.218366,0.144071
H,0,-0.996823,-2.641091,-2.074085
H,0,0.092591,-4.537743,-0.869674
H,0,6.420420,-1.438345,0.754288
H,0,7.633113,0.698125,0.457892
H,0,6.458775,2.652713,-0.550894
H,0,-2.878383,-3.176889,0.313740
H,0,-5.269980,-3.865341,0.106481
H,0,-6.375092,0.243744,-0.489356
H,0,-7.015462,-2.145464,-0.313862
H,0,-3.406733,3.632038,-1.329214
H,0,-5.125306,3.819510,-1.817145
H,0,-4.664705,3.866146,-0.081776
H,0,4.508413,-2.850255,-0.219936
H,0,3.813026,-2.210009,1.246348
H,0,0.153498,-0.012664,3.217754
H,0,1.182466,-1.429097,2.973966
H,0,4.094558,2.432077,-1.249945
H,0,-2.471414,1.009858,1.513795

TS-CO
Number of imaginary frequency = 1
Zero-point correction= 0.527623 (Hartree/Particle)
Thermal correction to Energy= 0.557666
Thermal correction to Enthalpy= 0.558610
Thermal correction to Gibbs Free Energy= 0.464947
Sum of electronic and zero-point Energies= -1552.494891
Sum of electronic and thermal Energies= -1552.464847
Sum of electronic and thermal Enthalpies= -1552.463903
Sum of electronic and thermal Free Energies= -1552.557567
Electronic Energy = -1553.02251327

E (Thermal) CV S
349.941 KCal/Mol 118.878 Cal/Mol-K 197.131 Cal/Mol-K

Charge = 1 Multiplicity = 1
C,0,5.234233,-0.695769,0.651675
C,0,3.923465,-0.458997,0.235456
C,0,3.487970,-1.010203,-0.985597
C,0,4.376606,-1.773840,-1.744819
C,0,5.680884,-2.007178,-1.315559
C,0,6.111617,-1.464877,-0.110063
C,0,2.074457,-0.826274,-1.496222
C,0,3.014795,0.398784,1.103762
C,0,-1.107550,-1.639452,-1.646879
O,0,-1.722904,-1.543868,-2.609888
O,0,-2.392079,-1.080351,-0.049569
N,0,-0.122875,-1.841218,-0.862938
C,0,1.802349,-0.374074,1.621731
C,0,0.643093,0.320467,1.998692
C,0,1.835140,-1.764853,1.761619
C,0,-0.481706,-0.389885,2.423272
C,0,0.717905,-2.468453,2.212413
C,0,-0.455245,-1.780040,2.525184
C,0,2.612736,1.709592,0.422701
C,0,1.111029,3.598745,0.247740
C,0,1.886342,4.142414,-0.771491
C,0,3.032914,3.472460,-1.191432
C,0,-2.864308,0.196917,-0.215792
C,0,-1.940021,1.225931,-0.372518
C,0,-4.242652,0.462405,-0.240767
C,0,-2.394834,2.525573,-0.560035
C,0,-4.678479,1.780298,-0.419468
C,0,-3.762189,2.808788,-0.580979
C,0,-5.190738,-0.661815,-0.080162
O,0,-4.828224,-1.825315,0.075975
O,0,-6.460108,-0.308748,-0.120269
C,0,-7.416301,-1.371199,0.030439
C,0,1.465117,2.389645,0.850608
C,0,0.643044,1.827957,1.983899
C,0,1.246211,-2.122811,-1.390166
C,0,3.391075,2.266232,-0.596444
H,0,5.573554,-0.267238,1.591046
H,0,4.040509,-2.186492,-2.693593
H,0,1.565007,-0.036848,-0.941518
H,0,2.095963,-0.503892,-2.541812
H,0,-0.286639,-1.757686,0.148174
H,0,3.600919,0.680786,1.991818
H,0,7.125694,-1.633030,0.237855
H,0,6.354031,-2.603144,-1.923284
H,0,2.742750,-2.305931,1.508913

H,0,-1.386385,0.155834,2.679930
H,0,0.762339,-3.548672,2.308367
H,0,-1.338816,-2.318624,2.852178
H,0,0.226687,4.124956,0.599489
H,0,1.599934,5.083255,-1.230593
H,0,3.650353,3.886957,-1.981983
H,0,-0.875706,1.004948,-0.340870
H,0,-1.670651,3.322738,-0.694377
H,0,-5.744016,1.979844,-0.434320
H,0,-4.106995,3.826170,-0.724951
H,0,-7.291276,-2.098557,-0.772513
H,0,-7.278801,-1.858784,0.996216
H,0,-8.390379,-0.892327,-0.027581
H,0,1.063040,2.179800,2.937975
H,0,-0.382608,2.209834,1.941782
H,0,1.672631,-2.833312,-0.682190
H,0,1.130866,-2.626322,-2.350672
H,0,4.286136,1.749860,-0.929917
H,0,-3.193259,-1.678291,0.042197

INT4

Number of imaginary frequency = 0
Zero-point correction= 0.376668
(Hartree/Particle)
Thermal correction to Energy= 0.396228
Thermal correction to Enthalpy= 0.397172
Thermal correction to Gibbs Free Energy=
0.329023
Sum of electronic and zero-point Energies=
-1017.487202
Sum of electronic and thermal Energies= -
1017.467642
Sum of electronic and thermal Enthalpies=
-1017.466697
Sum of electronic and thermal Free
Energies= -1017.534847
Electronic Energy = -1017.86386968

E (Thermal)	CV	S
248.637 KCal/Mol	80.116 Cal/Mol-K	143.433 Cal/Mol-K

Charge = 1 Multiplicity = 1
C,0,-0.551368,1.108877,-0.609417
C,0,-1.026811,1.128614,0.746085
C,0,-1.873180,2.202552,1.160664
C,0,-2.387837,3.107459,0.252303
C,0,-2.040983,2.970704,-1.090497
C,0,-0.462753,0.242426,1.838131
C,0,0.548316,0.169395,-1.088177
C,0,-2.777141,0.086696,0.394473
O,0,-3.508325,0.428649,-0.449771
N,0,-2.599085,-0.809969,1.323931
C,0,0.199394,-1.292400,-0.864292
C,0,1.055978,-2.172647,-0.200267
C,0,-1.020498,-1.765816,-1.367454
C,0,0.657534,-3.504574,-0.025679
C,0,-1.411138,-3.084660,-1.182312
C,0,-0.565483,-3.960777,-0.498751
C,0,1.892271,0.602858,-0.510385
C,0,3.973569,0.173582,0.627309
C,0,4.358907,1.496378,0.468088
C,0,3.508459,2.386953,-0.189131
C,0,2.743990,-0.290281,0.142226
C,0,2.392054,-1.742418,0.350210
C,0,-1.330494,-1.020447,2.024038
C,0,2.287599,1.937771,-0.670463
H,0,-2.145147,2.259973,2.211320
H,0,0.564843,-0.047327,1.616866
H,0,-0.446190,0.811493,2.768855
H,0,-3.308415,-1.541092,1.356374
H,0,0.608064,0.318455,-2.174472
H,0,-2.463446,3.645795,-1.827968
H,0,-3.062100,3.891604,0.575370
H,0,-1.669919,-1.082494,-1.912730
H,0,1.325018,-4.185742,0.496516
H,0,-2.362192,-3.430528,-1.574149
H,0,-0.855448,-4.995387,-0.346577
H,0,4.632704,-0.526317,1.135404
H,0,5.316490,1.834028,0.851328
H,0,3.797343,3.424047,-0.325249
H,0,3.175725,-2.365904,-0.098915
H,0,2.424398,-1.969392,1.424839
H,0,-1.553327,-1.203680,3.074834
H,0,-0.857260,-1.906772,1.595478
H,0,1.625018,2.630601,-1.183253
C,0,-1.115061,2.004539,-1.504237
H,0,-0.817898,1.970522,-2.548006

TS-FC2

Number of imaginary frequency = 1
Zero-point correction= 0.376226
(Hartree/Particle)
Thermal correction to Energy= 0.394921
Thermal correction to Enthalpy= 0.395865
Thermal correction to Gibbs Free Energy=
0.329736
Sum of electronic and zero-point Energies=
-1017.482238
Sum of electronic and thermal Energies= -
1017.463543
Sum of electronic and thermal Enthalpies=
-1017.462599
Sum of electronic and thermal Free
Energies= -1017.528728
Electronic Energy = -1017.85846404

E (Thermal)	CV	S
247.816 KCal/Mol	77.939 Cal/Mol-K	139.179 Cal/Mol-K

Charge = 1 Multiplicity = 1
C,0,0.686925,-0.812472,-0.953946
C,0,1.209948,-1.031195,0.335557
C,0,2.547738,-1.534691,0.466992
C,0,3.261064,-2.014243,-0.674911
C,0,2.730725,-1.811346,-1.917135
C,0,0.517482,-0.641933,1.610766
C,0,-0.663101,-0.151706,-1.165422
C,0,3.053669,0.249100,0.707499
O,0,3.720635,0.751429,-0.129476
N,0,2.592899,0.606227,1.892600
C,0,-0.618895,1.322998,-0.755253
C,0,-1.795632,1.965350,-0.353367
C,0,0.575414,2.050086,-0.799059
C,0,-1.748663,3.306322,0.033723
C,0,0.611627,3.388352,-0.420101
C,0,-0.554460,4.018479,0.007609
C,0,-1.791501,-0.923795,-0.482692
C,0,-3.979409,-0.957097,0.538818
C,0,-3.873280,-2.325398,0.762318
C,0,-2.728835,-3.002692,0.347988
C,0,-2.953245,-0.249476,-0.090286
C,0,-3.107342,1.222180,-0.380929
C,0,1.560567,-0.137832,2.617462
C,0,-1.697205,-2.302967,-0.270062
H,0,2.852770,-1.921719,1.438621
H,0,-0.232218,0.128169,1.422712
H,0,-0.002383,-1.517136,2.018704
H,0,2.929890,1.495944,2.250109
H,0,-0.861251,-0.179228,-2.247002
H,0,3.260984,-2.120361,-2.810409

H,0,4.232152,-2.475505,-0.535966
H,0,1.490504,1.576786,-1.143999
H,0,-2.665233,3.793966,0.355483
H,0,1.549244,3.933625,-0.460665
H,0,-0.535377,5.059644,0.313313
H,0,-4.872456,-0.422804,0.852555
H,0,-4.679456,-2.860355,1.254001
H,0,-2.636214,-4.072354,0.506082
H,0,-3.554507,1.338399,-1.379374
H,0,-3.813712,1.674576,0.321794
H,0,2.021080,-0.948427,3.188807
H,0,1.102111,0.550446,3.325413
H,0,-0.809685,-2.841727,-0.591386
C,0,1.462791,-1.196778,-2.040868
H,0,1.070086,-1.022448,-3.039382

INT5

Number of imaginary frequency = 0
Zero-point correction= 0.376045 (Hartree/Particle)
Thermal correction to Energy= 0.395211
Thermal correction to Enthalpy= 0.396155
Thermal correction to Gibbs Free Energy= 0.327847
Sum of electronic and zero-point Energies= -1017.485916
Sum of electronic and thermal Energies= -1017.466750
Sum of electronic and thermal Enthalpies= -1017.465805
Sum of electronic and thermal Free Energies= -1017.534114
Electronic Energy = -1017.86196069

E (Thermal)	CV	S
247.999 KCal/Mol	79.032 Cal/Mol-K	143.768 Cal/Mol-K

Charge = 1 Multiplicity = 1
C,0,0.628312,-0.322801,-1.171431
C,0,1.369500,-0.343510,0.006826
C,0,2.806593,-0.684082,-0.032674
C,0,3.444544,-0.844233,-1.342133
C,0,2.697083,-0.814518,-2.476074
C,0,0.797697,-0.035061,1.351555
C,0,-0.869879,-0.060700,-1.189044
C,0,3.685319,0.126256,0.979337
O,0,4.794939,0.505522,0.671820
N,0,3.070595,0.313417,2.157706
C,0,-1.207618,1.338339,-0.673919
C,0,-2.440854,1.579481,-0.060922
C,0,-0.309476,2.398157,-0.842867
C,0,-2.735589,2.863229,0.405708
C,0,-0.614035,3.674403,-0.383054
C,0,-1.831808,3.907545,0.252842
C,0,-1.634891,-1.174380,-0.470163
C,0,-3.557342,-1.924374,0.783381
C,0,-3.053396,-3.218857,0.819860
C,0,-1.839263,-3.500275,0.197468
C,0,-2.865322,-0.898029,0.135021
C,0,-3.467121,0.481648,0.054983
C,0,1.790460,-0.304627,2.476592
C,0,-1.138260,-2.482741,-0.440180
H,0,2.825485,-1.712408,0.409874
H,0,0.531950,1.032612,1.340415
H,0,-0.138213,-0.582825,1.506679
H,0,3.602642,0.786779,2.878380
H,0,-1.178776,-0.094152,-2.244055
H,0,3.142264,-0.962074,-3.452297
H,0,4.517252,-1.005279,-1.357573
H,0,0.644180,2.228402,-1.335561
H,0,-3.691555,3.038870,0.892196
H,0,0.098430,4.481438,-0.519375
H,0,-2.076050,4.897635,0.624067
H,0,-4.506728,-1.697485,1.261473
H,0,-3.604255,-4.003386,1.328602
H,0,-1.436032,-4.507717,0.209001
H,0,-4.125992,0.525097,-0.824790
H,0,-4.111549,0.660394,0.921507
H,0,1.910453,-1.383527,2.635562
H,0,1.427004,0.128384,3.407375
H,0,-0.192763,-2.717502,-0.921039
C,0,1.308725,-0.562572,-2.372239
H,0,0.728302,-0.541129,-3.292184

PD

Number of imaginary frequency = 0
Zero-point correction= 0.379582 (Hartree/Particle)
Thermal correction to Energy= 0.398266
Thermal correction to Enthalpy= 0.399210
Thermal correction to Gibbs Free Energy= 0.332785
Sum of electronic and zero-point Energies= -1017.543717
Sum of electronic and thermal Energies= -1017.525033
Sum of electronic and thermal Enthalpies= -1017.524088
Sum of electronic and thermal Free Energies= -1017.590513
Electronic Energy = -1017.92329851

E (Thermal)	CV	S
249.916 KCal/Mol	78.267 Cal/Mol-K	139.803 Cal/Mol-K

Charge = 1 Multiplicity = 1
C,0,-0.630898,0.090329,1.247187
C,0,-1.441299,0.077652,0.103003
C,0,-2.837248,0.073152,0.269553
C,0,-3.439138,0.094114,1.533239
C,0,-2.628739,0.105576,2.655360
C,0,-0.900346,0.123711,-1.308202
C,0,0.882540,0.066185,1.154361
C,0,-3.680432,0.046719,-0.921596
N,0,-3.185582,-0.269905,-2.085689
C,0,1.459116,1.294692,0.449920
C,0,2.774413,1.237297,-0.027694
C,0,0.734095,2.480775,0.311640
C,0,3.328006,2.349222,-0.662465
C,0,1.295938,3.589982,-0.315649
C,0,2.595569,3.523304,-0.810753
C,0,1.414142,-1.236092,0.548573
C,0,3.244313,-2.437607,-0.476686
C,0,2.469257,-3.591366,-0.543032
C,0,1.165667,-3.572288,-0.054173
C,0,2.731039,-1.262207,0.072272
C,0,3.580016,-0.020258,0.186887
C,0,-1.779441,-0.690739,-2.240749
C,0,0.643625,-2.400443,0.488031
H,0,-0.862386,1.167523,-1.645277
H,0,0.117362,-0.266565,-1.358464
H,0,-3.789146,-0.297951,-2.903253
H,0,1.260028,0.098724,2.188154
H,0,-3.067136,0.114422,3.646699
H,0,-4.519541,0.089256,1.621247
H,0,-0.280160,2.543127,0.696676
H,0,4.345854,2.291283,-1.039345
H,0,0.717047,4.502584,-0.416730
H,0,3.038142,4.381232,-1.306969

H,0,4.263901,-2.444102,-0.853322
H,0,2.880827,-4.499067,-0.972890
H,0,0.552410,-4.467056,-0.093748
H,0,4.021011,0.012697,1.194931
H,0,4.418973,-0.063379,-0.514130
H,0,-1.717736,-1.760426,-2.015195
H,0,-1.510402,-0.531610,-3.283993
H,0,-0.374354,-2.397336,0.866917
C,0,-1.242331,0.099759,2.502848
H,0,-0.612400,0.101049,3.388026
O,0,-4.941023,0.349503,-0.751545
H,0,-5.482233,0.270090,-1.558391

methyl salicylate

Number of imaginary frequency = 0
Zero-point correction= 0.150509 (Hartree/Particle)
Thermal correction to Energy= 0.159952
Thermal correction to Enthalpy= 0.160896
Thermal correction to Gibbs Free Energy= 0.115550
Sum of electronic and zero-point Energies= -534.990972
Sum of electronic and thermal Energies= -534.981529
Sum of electronic and thermal Enthalpies= -534.980585
Sum of electronic and thermal Free Energies= -535.025931
Electronic Energy = -535.141480384

E (Thermal)	CV	S
100.371 KCal/Mol	35.670 Cal/Mol-K	95.439 Cal/Mol-K

Charge = 0 Multiplicity = 1
C,0,1.095419,0.929125,-0.000012
C,0,0.163089,-0.129443,0.000002
C,0,0.622136,-1.455923,0.000012
C,0,1.976356,-1.737888,0.000009
C,0,2.895038,-0.680593,-0.000000
C,0,2.465265,0.635425,-0.000008
H,0,-0.108463,-2.257207,0.000043
H,0,2.321875,-2.765488,0.000021
H,0,3.960238,-0.890818,0.000016
H,0,3.166078,1.463323,-0.000016
O,0,0.738308,2.224777,-0.000055
H,0,-0.243499,2.265921,-0.000143
C,0,-1.278258,0.183680,0.000045
O,0,-2.062761,-0.890483,-0.000019
O,0,-1.732433,1.321716,0.000119
C,0,-3.471408,-0.631337,-0.000060
H,0,-3.947487,-1.609343,-0.000060
H,0,-3.749750,-0.066362,0.891017
H,0,-3.749717,-0.066387,-0.891152

9-2H$^+$-Open

Number of imaginary frequency = 0
Zero-point correction= 0.334681 (Hartree/Particle)
Thermal correction to Energy= 0.352796
Thermal correction to Enthalpy= 0.353741
Thermal correction to Gibbs Free Energy= 0.285856
Sum of electronic and zero-point Energies= -863.358465
Sum of electronic and thermal Energies= -863.340349
Sum of electronic and thermal Enthalpies= -863.339405
Sum of electronic and thermal Free Energies= -863.407290
Electronic Energy = -863.693145956

E (Thermal)	CV	S
221.383 KCal/Mol	69.761 Cal/Mol-K	142.875 Cal/Mol-K

Charge = 2 Multiplicity = 1
C,0,2.135054,2.158412,-0.123854
C,0,1.136748,1.185789,-0.405215
C,0,-0.232266,1.590853,-0.506079
C,0,-0.546141,2.917547,-0.248455
C,0,0.448132,3.851087,0.051361
C,0,1.793244,3.476671,0.098565
C,0,-1.354720,0.619229,-0.774520
C,0,-1.758649,-0.117128,0.511818
C,0,1.502089,-0.158088,-0.663867
C,0,-4.145673,-0.558588,0.288330
O,0,-4.332246,0.712937,0.490042
O,0,-5.199138,-1.283286,0.108710
C,0,2.658595,-0.847847,-0.238790
C,0,3.447053,-0.438585,0.871121
C,0,4.156809,-2.723037,-0.611074
C,0,4.574897,-1.156909,1.212878
C,0,4.937410,-2.283853,0.463985
N,0,-2.913233,-0.998870,0.286369
H,0,3.179668,1.872063,-0.164461
H,0,-1.583159,3.235738,-0.290008
H,0,-2.216826,1.181090,-1.143882
H,0,-1.093794,-0.109091,-1.548127
H,0,-0.951618,-0.750542,0.884288
H,0,-2.022946,0.593083,1.297701
H,0,0.822262,-0.742670,-1.282126
H,0,2.562705,4.216120,0.286473
H,0,0.170522,4.885344,0.226765
H,0,3.126132,0.395520,1.485042
H,0,4.443196,-3.608067,-1.167055
H,0,5.169034,-0.861851,2.069920
H,0,5.826890,-2.841608,0.739213
H,0,-2.744153,-1.979599,0.091810
H,0,-5.285442,0.927521,0.507993
C,0,3.010744,-2.029339,-0.945036
H,0,2.387680,-2.356359,-1.772168
C,0,-5.081589,-2.713713,-0.085017
H,0,-4.602181,-3.159138,0.787793
H,0,-6.104675,-3.065044,-0.175606
H,0,-4.530029,-2.912639,-1.005065

9-2H$^+$-Closed

Number of imaginary frequency = 0
Zero-point correction= 0.337662 (Hartree/Particle)
Thermal correction to Energy= 0.354332
Thermal correction to Enthalpy= 0.355276
Thermal correction to Gibbs Free Energy= 0.293571
Sum of electronic and zero-point Energies= -863.324536
Sum of electronic and thermal Energies= -863.307866
Sum of electronic and thermal Enthalpies= -863.306922
Sum of electronic and thermal Free Energies= -863.368627
Electronic Energy = -863.662198359

E (Thermal)	CV	S
222.347 KCal/Mol	67.108 Cal/Mol-K	129.869 Cal/Mol-K

```
Charge = 2 Multiplicity = 1
C,0,-2.097405,1.676513,-0.176760
C,0,-1.658450,0.355530,-0.263146
C,0,-2.576924,-0.705688,-0.253808
C,0,-3.934685,-0.434899,-0.127347
C,0,-4.374687,0.884657,-0.040645
C,0,-3.461229,1.935744,-0.071623
C,0,-2.018318,-2.096836,-0.360416
C,0,-0.940087,-2.327590,0.691170
C,0,-0.215994,-0.013174,-0.439214
C,0,1.434843,-1.582618,0.554309
O,0,2.215664,-1.210792,1.480262
O,0,1.673537,-2.251417,-0.476163
C,0,3.013214,-2.771254,-0.826298
H,0,-1.388012,2.496049,-0.211508
H,0,-4.647191,-1.253930,-0.106266
H,0,-2.790144,-2.851397,-0.190566
H,0,-1.604590,-2.280161,-1.358869
H,0,-1.351519,-2.338503,1.698921
H,0,-0.377896,-3.243196,0.511827
H,0,-0.064872,-0.581558,-1.361805
H,0,2.850380,-3.271086,-1.774762
H,0,3.685873,-1.922425,-0.936174
H,0,3.314874,-3.475473,-0.052672
H,0,-3.808639,2.961334,-0.013464
H,0,-5.435840,1.092062,0.047982
H,0,3.164028,-1.464949,1.406665
C,0,0.841478,1.035537,-0.268498
C,0,1.801959,1.206018,-1.269517
C,0,0.901734,1.810896,0.897877
C,0,2.804829,2.160648,-1.115379
H,0,1.754656,0.611609,-2.178313
C,0,1.910868,2.753311,1.050680
H,0,0.154775,1.698190,1.681623
C,0,2.859358,2.931084,0.042398
H,0,3.539222,2.300761,-1.900929
H,0,1.952279,3.355189,1.951723
H,0,3.640810,3.673946,0.162286
H,0,0.009927,-0.654684,1.592529
N,0,0.077893,-1.151627,0.693754
```

4-F. Single-point calculation of the geometries

The single-point energies were calculation at SMD(CH_2Cl_2)-M06-2X/jul-cc-pVTZ level. The values are summarized in Table S2.

Table S2

Structure name	Electronic Energy (a.u.)
SM-O	-1553.65982602
SM-N	-1553.65491532
TS-CN	-1553.63331737
INT-1	-1553.63603454
TS-FC1	-1553.62292367
INT-2	-1553.62839364
INT-3	-1553.67129888
TS-CO	-1553.63318177
INT-4	-1018.25624232
TS-FC2	-1018.25356502
INT-5	-1018.25975109
PD	-1018.32174329
Methylsalicylate	-535.36646675
INT-1-Dication	-1554.04245449
TS-FC1-Dication	-1554.02275347
INT-2-Dication	-1554.02685125
9-2H+-Open	-864.054320933
9-2H+-Closed	-864.025636310

5. Source code and an instruction of conformation search program *ConfProg*

ConfProg is a Python program suite for conformation search of organic molecules. Monte Carlo multiple minimum (MCMM) search algorithm[S30] is employed. Python3.4 is needed to run this program. The source code and brief instruction are shown below. For minimization of the molecular geometry, TINKER program (https://dasher.wustl.edu/tinker/)[S28] is called after generation of new candidate structure. Thus, TINKER programs should be downloaded and located properly to use ConfProg program.

The directory composition of ConfProg is shown below. This program requires two input files to run. The *parameters.py* file is one of the input files, which controls conformation search process. Initial geometry of the conformation search is prepared as *inputcoordinates*.

Composition of the directory of Confprog suite:

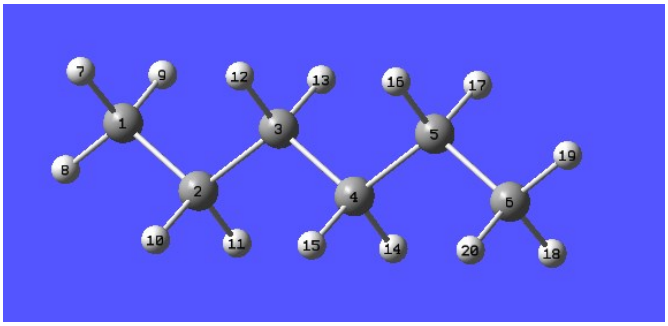
```
(Any directory name)/
 ├ ConfProg/
 |  └ Confprog.py       ••• Main program
 |  └ monte.py          ••• A module for MCMM
 |  └ rotator.py        ••• A module for rotation of molecule
 |  └ tinkermanager.py  ••• A module to run "optimize" of TINKER
 |  └ atomdefine.py     ••• A module for define topology and type of atoms
 |  └ initprocess.py    ••• A module to initialize the process
 |  └ printer.py        ••• A module to create gaussian input files
 |  └ rulechk.py        ••• A module to check rule for accepting new geometry
 |  └ parameters.py     ••• Input file 1
 |  └ tinkerbin/
 |    └ optimize        ••• *A program of TINKER program suite
 |    └ params/
 |       └mm3.prm       ••• *A parameter file to run "optimize" program
 └ Rundir/
    └ inputcoordinates   ••• Input file 2
    └ settings.key       ••• *Setting file of TINKER calculation
```

*Components of TINKER program suite

To run this program, prepare directories above and type "python3 ../ConfProg/Confprog.py" in *Rundir* directory. Then, input file for TINKER calculation "*input.xyz"* and input file for defining single bonds of a molecule "*Rotbondinfo*" will be created automatically. After that MCMM process starts. A "*confcache*" directory will be created in the *Rundir* directory, in which accepted geometries are to be contained. After the calculation, "*MCMCresult*" directory will be created and input file of Gaussian16 calculation will be saved in it.

Example input files: Conformation search of n-hexane.

In this example, conformation of n-hexane is calculated. Conformation search will be repeated for 200 cycles at MM3 level. Gaussian16 input file for further optimization will be generated in Rundir/MCMCresult directory. The result is saved as *mcmclogfile* in Rundir/. This calculation will afford 18 different conformers.



parameters.py:

```
################################ parameters.py ################################
# Caution, this file should be written in programming syntax of python3
####################    input parameters below   ##############################
temp                 = 298.15
rotbondnum            = 2
rotbondrange          = [15,180] # this must be integer and list type.
tinker_input_file      = "input.xyz"
tinker_temp_input_file  = "temp.xyz"
tinker_temp_output_file = "temp_output.xyz"
keyword_file          = "settings.key"
searchcycle_num        = 200
samplingbias          = 10     # controls boltzmann factor

        #### recommended values for conformation sampling ####
        # rotbondnum     = 2 ~ 4
        # rotbondrange    = [0 ~ 15,60 ~ 90]
        # searchcycle_num = 100 (small molecule) ~ 10000 (large)
        # samplingbias    = 100~1000
        #     (if it is small, most of unstable structures will be rejected)

########################### Here define path ###################################
confprogpath          = "/(Absolute path to the ConfProg on users computer)/ConfProg/"
gaussianpath          = ""

############## Here define the theory and proc, mem to use ####################
prefix1               = "Gaussiancalc"
modredundant1          = "OFF" # ON or OFF. Use capital

nproc1                = 1  # number of processors for gaussian calculation
mem1                  = 2  # memory, unit:GB for gaussian calculation
num_of_comfile         = "auto"  # optdft1 calculation is done for this number of molecules
                              # this parameters is needed to run gaussrun.py
                              # input the value after MCMC process or input "auto"
num_of_logfile         = "auto" # gaussanal.py reads this number of molecules
                             # if not in special case, use "auto"
num_of_proc            = 16  # Total processors used in parallel computing.
optdft1               = "HF/3-21G"
option1               = "opt=calcall scf=xqc freq"
restriction1           = " "

###############################################################################

                       # Special section

###############################################################################
################################  acceptrule  #################################
###############################################################################
```

```
# For example, acceptrule = [[ 1,  2,"Longer",3.0]] means a structure of which
#                          int int  str   float
# 1,2 bond distance is shorter than 3.0 will be rejected
# you must use it so as to retain cis and trans structure of alkene
# regular C*-C-C-C* 's C*C* distance: trans:3.91, cis: 3.11
# regular C*-C-C-H* 's C*H* distance: trans:3.49, cis: 2.59
#acceptrule           = [[8,11,"S",3.2]]

##############################################################################
############################## Atomchange Section ############################
##############################################################################
# Here we change 'prefix1(Number).com' file. You must input 2 parameters below
Atomchange              = [""] # "A"="add","E"="erase","R"="replace"
charge_spin_changed      = [0,0] # list of two integers
############################### Atomadd Section ##############################
added_atom              = "None" # must be string
added_to                = 0 # must be integer.
length                  = 0.00 # must be float
vector                  = [0,0] # list of two integers.
############################## Atomerase Section #############################
erased_atom             = "None" # must be integer.
############################# Atomreplace Section ############################
replaced_atom           = "None" ## must be integer.
replaced_to             = "None"

##############################################################################
################## Transition Vector/ Structure analysis section ###############
##############################################################################
atoms_of_interest        = [0,0]
```

inputcoordinates

(1st line: number of atoms, 2nd line: spin and charge, 3rd line~: atom symbol & coordinate)

```
20
0 1
 C              -3.60366706   -0.64174893    0.00000000
 H              -3.24701263   -1.65055894    0.00000000
 H              -3.24699422   -0.13735074   -0.87365150
 H              -4.67366706   -0.64173575    0.00000000
 C              -3.09032484    0.08420734    1.25740497
 H              -2.02032486    0.08402477    1.25750243
 H              -3.44681989    1.09307367    1.25730739
 C              -3.60389650   -0.64158719    2.51480962
 H              -3.24743173   -1.65046422    2.51488831
 H              -4.67389647   -0.64137309    2.51473063
 C              -3.09051078    0.08433909    3.77221415
 H              -3.44696965    1.09321821    3.77213080
 H              -2.02051081    0.08411875    3.77229702
 C              -3.60409093   -0.64144943    5.02961880
 H              -3.24763191   -1.65032850    5.02970119
 H              -4.67409090   -0.64122924    5.02953611
 C              -3.09070542    0.08447699    6.28702332
 H              -3.44716586    1.09335555    6.28694077
 H              -3.44754213   -0.41980566    7.16067461
 H              -2.02070544    0.08425832    6.28710541
```

input.xyz

```
20  initialstructure
 1   C    -3.603667   -0.641749    0.000000    1      2   7   8   9
 2   C    -3.090325    0.084207    1.257405    1      1   3  10  11
 3   C    -3.603896   -0.641587    2.514810    1      2   4  12  13
 4   C    -3.090511    0.084339    3.772214    1      3   5  14  15
 5   C    -3.604091   -0.641449    5.029619    1      4   6  16  17
 6   C    -3.090705    0.084477    6.287023    1      5  18  19  20
 7   H    -3.247013   -1.650559    0.000000    5      1
 8   H    -3.246994   -0.137351   -0.873652    5      1
 9   H    -4.673667   -0.641736    0.000000    5      1
10   H    -2.020325    0.084025    1.257502    5      2
11   H    -3.446820    1.093074    1.257307    5      2
12   H    -3.247432   -1.650464    2.514888    5      3
13   H    -4.673896   -0.641373    2.514731    5      3
14   H    -3.446970    1.093218    3.772131    5      4
15   H    -2.020511    0.084119    3.772297    5      4
16   H    -3.247632   -1.650329    5.029701    5      5
17   H    -4.674091   -0.641229    5.029536    5      5
18   H    -3.447166    1.093356    6.286941    5      6
19   H    -3.447542   -0.419806    7.160675    5      6
20   H    -2.020705    0.084258    6.287105    5      6
```

Rotbondinfo

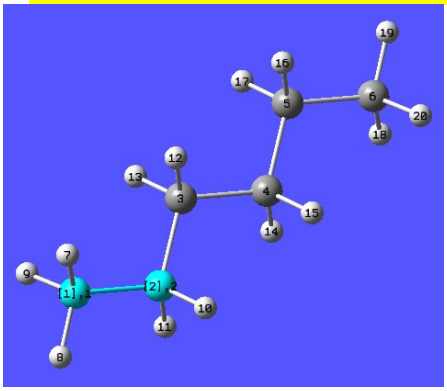
```
1 2
1 7 8 9
2 3 4 5 6 10 11 12 13 14 15 16 17 18 19 20
2 3
1 2 7 8 9 10 11
3 4 5 6 12 13 14 15 16 17 18 19 20
3 4
1 2 3 7 8 9 10 11 12 13
4 5 6 14 15 16 17 18 19 20
4 5
1 2 3 4 7 8 9 10 11 12 13 14 15
5 6 16 17 18 19 20
5 6
1 2 3 4 5 7 8 9 10 11 12 13 14 15 16 17
6 18 19 20
```

* In the *Rotbondinfo* file, torsional rotation parameters are specified in this manner:
line 1: *atom1a atom2a* : atoms of a bond, which is to be rotated
line 2: *atom1a-1 atom1a-2 atom1a-3 ....* : atoms rotated together with atom1a
line 3: *atom2a-1 atom2a-2 atom2a-3 ....* : atoms rotated together with atom2a
line 4: *atom1b atom2b* : atoms of a bond, which is to be rotated
line 5: *atom1b-1 atom1b-2 atom1b-3 ....* : atoms rotated together with atom1a
line 6: *atom2b-1 atom2b-2 atom2b-3 ....* : atoms rotated together with atom2a
line 7: ...
...
...

In the first 3 lines of the example, a bond consists of atom number 1 and atom number 2 is set for rotation.

The first 3 lines:

```
1 2     # axis of bond rotation is defined here
1 7 8 9 # atoms 7-9 rotates around the blue bond below
2 3 4 5 6 10 11 12 13 14 15 16 17 18 19 20 # atoms 3-6,10-20 rotates in the same way
```



Source codes:

```
################################       Confprog.py       ##############################
#
#                       Main program of this conformational search program suite
#
#       written by Hiroaki Kurouchi
#
#############################################################################################

import os
import numpy as np
import math
import copy
import linecache
import rotator
import subprocess
import parameters
import initprocess
import tinkermanager
import printer
import shutil
import monte
import atomdefine
import datetime

### Here we read parameter name ###
tinker_input_file = parameters.tinker_input_file
tinker_temp_output_file = parameters.tinker_temp_output_file

keyword_file = parameters.keyword_file
temp = parameters.temp
rotbondnum = parameters.rotbondnum
rotbondrange = parameters.rotbondrange
outputfilename = tinker_input_file + "_2"

searchcycle_num = parameters.searchcycle_num
potential_energy_of_accepted_structure = []

confprogpath = parameters.confprogpath
runningdirpath = os.getcwd()
try:
        acceptrule = parameters.acceptrule
        for i in range(len(acceptrule)):
                acceptrule[i][0] -= 1
                acceptrule[i][1] -= 1

except:
        acceptrule = [[0]]

prefix1             = parameters.prefix1
nproc1               = parameters.nproc1
mem1                  = parameters.mem1
optdft1              = parameters.optdft1
option1              = parameters.option1
restriction1     = parameters.restriction1
modredundant1 = parameters.modredundant1


### Main process ###
if __name__ == '__main__':
        # Read input file, get information of the molecule.
        charge_spin,Coordinates_list,¥
        atomarray,Adjacency_matrix,Adjacency_list,¥
        atomtype,Rotbondinfo ¥
        = initprocess.initialprocessing(runningdirpath)
        try:
                os.remove("./mcmclogfile")
        except:
                pass
```

```
with open('./mcmclogfile', mode='w') as logwrite:
	logwrite.write(
	"---------- Conformation Analysis Program Confprog.py ---------- ¥n" +
                            "Start Time: "+str(datetime.datetime.today()) + "¥n")
# Check whether initialprocess is done and the first structure is generated.
if confprogpath[len(confprogpath)-1] != "/":
	confprogpath = confprogpath + "/"
with open('./mcmclogfile', mode='a') as logwrite:
	logwrite.write(
	"¥n---------- parameters.py ----------¥n")
subprocess.call("cat "+ confprogpath + "parameters.py >> ./mcmclogfile ",shell=True)
with open('./mcmclogfile', mode='a') as logwrite:
	logwrite.write(
	"¥n---------- inputcoordinates ----------¥n")
subprocess.call("cat "+ runningdirpath + "/inputcoordinates    >> ./mcmclogfile ",shell=True)
with open('./mcmclogfile', mode='a') as logwrite:
	logwrite.write(
	"¥n¥n---------- settings.key ----------¥n¥n")
subprocess.call("cat "+ runningdirpath + "/settings.key    >> ./mcmclogfile ",shell=True)
if os.path.exists(runningdirpath+"/"+tinker_input_file) == False:
	####### Here we are checking whether initialprocessing was already done or not
	print(runningdirpath+"/"+tinker_input_file,"does not exist, run initprocess")
	with open('./mcmclogfile', mode='a') as logwrite:
		logwrite.write(
		str(runningdirpath) +"/"+ str(tinker_input_file) + "does not exist, run initprocess ¥n")
	subprocess.call("python3 " + confprogpath + "initprocess.py",shell=True)

# Adjacency_list and Adjacency_matrix are reread from input file
atoms,coordinates,atomtype,connectivity = tinkermanager.tinkeroutputreader(tinker_input_file)
Rotbondinfo = initprocess.Rotbondinforeader()
with open('./mcmclogfile', mode='a') as logwrite:
	logwrite.write(
	"¥n---------- Rotbondinfo ----------¥n")
subprocess.call("cat "+ runningdirpath + "/Rotbondinfo >> ./mcmclogfile ",shell=True)
with open('./mcmclogfile', mode='a') as logwrite:
	logwrite.write(
	"¥n---------- "
	+ str(tinker_input_file)+" ----------¥n")
subprocess.call("cat " + runningdirpath + "/" + tinker_input_file + "    >> ./mcmclogfile ",shell=True)

# See if it has cache folder of the previous calculation.
# Erase it for current process
try:
	shutil.rmtree("./confcache")
except:
	pass
os.mkdir("./confcache")

# Then run the first process.
# The result must be saved because it is the first accepted structure.
tinkeroptpath = [confprogpath,"tinkerbin/optimize"]
tinkeroptpath = "".join(tinkeroptpath)
try:
	os.remove(outputfilename)
except:
	pass

potE =    tinkermanager.tinkeropt(tinker_input_file,keyword_file,tinkeroptpath)
potential_energy_of_accepted_structure.append(potE)
dummy1,coordinates,dummy2,dummy3 = tinkermanager.tinkeroutputreader(outputfilename)
os.rename(outputfilename,tinker_temp_output_file) #!!!caution!!! relative path?
shutil.move(tinker_temp_output_file,"./confcache/acceptedstr"+str(0))

# Here we start conformation sampling by metropolis algorithm
with open('./mcmclogfile', mode='a') as logwrite:
	logwrite.write(
	"¥n---------- MCMC Iteration ---------- ¥n")
accepted_coordinates,potential_energy_of_accepted_structure,accepted_number = ¥
monte.metropolis(coordinates,rotbondrange,rotbondnum,Rotbondinfo,atomarray,atomtype,
		Adjacency_list,tinker_input_file,tinker_temp_output_file,outputfilename,
```

```
                keyword_file,tinkeroptpath,potential_energy_of_accepted_structure,
                searchcycle_num,acceptrule)

    # Here we sort and print the result
    # the potential_energy_of_accepted_structure is returned as ndarray
    potential_energy_of_accepted_structure = np.array(potential_energy_of_accepted_structure)
    order = np.argsort(potential_energy_of_accepted_structure)
    #accepted_number_ordered = (accepted_number[order])
    try:
        shutil.rmtree("./MCMCresult")
    except:
        pass
    os.mkdir("./MCMCresult")
    potE_of_accepted_structure_ordered = (potential_energy_of_accepted_structure[order])
    accepted_coordinates_ordered = copy.copy(accepted_coordinates)
    accepted_number_ordered = copy.copy(accepted_number)
    for i in range(len(order)):
        accepted_coordinates_ordered[i] = accepted_coordinates[order[i]]
        accepted_number_ordered[i]      = accepted_number[order[i]]

    for i in range(len(accepted_coordinates_ordered)):
        printer.gaussian_inputmaker(accepted_coordinates_ordered[i],atomarray,optdft1,option1,
                                    charge_spin,comment="potential energy = "+str(potE_of_accepted_structure_ordered[i]),
                                    inputfilename="./MCMCresult/"+str(prefix1)+str(i)+".com",
                                    nproc=int(nproc1),mem=int(mem1),
                                    restriction=str(restriction1),modredundant=str(modredundant1))

    with open('./mcmclogfile', mode='a') as logwrite:
        logwrite.write("¥n    MCMC Finish Time: "+str(datetime.datetime.today()) + "¥n")
        logwrite.write("      filename                    potE          num of accepted¥n" +
                       "                                      kcal/mol              time")
        for i in range(len(order)):
            logwrite.write("¥n    gaussinput"+str(i)+".com          " +
                           str(potE_of_accepted_structure_ordered[i]) + "                " +
                           str(accepted_number_ordered[i]))



################################### monte.py ###################################
#
#                       Main program for Monte-Carlo method
#
#    written by Hiroaki Kurouchi
#
################################################################################

import numpy as np
import math
import copy
import linecache
import os
import rotator
import subprocess
import parameters
import initprocess
import tinkermanager
import printer
import shutil
import atomdefine
import rulechk

kb = 1.380648e-23
beta = 1 / (kb * parameters.temp)
beta_per_mol = beta / (6.022e23)
samplingbias = parameters.samplingbias
borderenergy = 100000.0

def metropolis(coordinates,rotbondrange,rotbondnum,Rotbondinfo,atomarray,atomtype,Adjacency_list,
                tinker_input_file,tinker_temp_output_file,outputfilename,
                keyword_file,tinkeroptpath,potential_energy_of_accepted_structure,
```

```
                searchcycle_num,restriction):

    coordinates = rotator.coordinate_rot(coordinates)
    Adjacency_matrix = atomdefine.Adjacency_converter_LtoM(Adjacency_list)
    initial_rel_chirality_list = atomdefine.relative_chirality_check(atomarray,Adjacency_list,
                                                                     Adjacency_matrix,coordinates)
    previousE = potential_energy_of_accepted_structure[0]
    number_of_mcmc_cycle = 0
    accepted_coordinates = []
    accepted_number = [1] # if conf0 is accepted 3 times and conf1 is 4 times, conf2 is 1, then [3,4,1]
    accepted_coordinates.append(coordinates)
    montereject = 0
    confbreak   = 0
    distance_check = 0
    while number_of_mcmc_cycle <= searchcycle_num:
        new_or_not = 0
        number_of_mcmc_cycle += 1
        print("¥nnumber_of_mcmc_cycle",number_of_mcmc_cycle)
        with open('./mcmclogfile', mode='a') as logwrite:
            logwrite.write("¥n number_of_mcmc_cycle: "+str(number_of_mcmc_cycle) +"¥n")
        newcoordinates = rotator.randomrot(coordinates,rotbondrange,rotbondnum,Rotbondinfo)
        #print("newcoordinates before opt",newcoordinates)
        printer.xyzmaker(atomarray,newcoordinates,atomtype,Adjacency_list,tinker_input_file)
        try:
            os.remove(outputfilename)
        except:
            pass
        try:
            potE =  tinkermanager.tinkeropt(tinker_input_file,keyword_file,tinkeroptpath)
        except:
            potE = borderenergy
        print("potE",potE,"previousE",previousE)
# Added 01/23/2020
        if potE == 0.0:
            potE = borderenergy
            with open('./mcmclogfile', mode='a') as logwrite:
                logwrite.write("¥nThe potE was changed from 0.0 to borderenergy("+
                               str(borderenergy)+")  because of the failure of optimization¥n")
            if os.path.exists(outputfilename) == True:
                os.remove(outputfilename)
#
        if potE < borderenergy:
### Added 12/17/2019
            if os.path.exists(outputfilename) == True:
                dummy1,newcoordinates,dummy2,dummy3 = tinkermanager.tinkeroutputreader(outputfilename)
                if np.sum(newcoordinates) == 0.0:
                    potE = borderenergy
            else:
                potE = borderenergy
###
        #print("newcoordinates right after opt",newcoordinates)
        newcoordinates = rotator.coordinate_rot(newcoordinates)
        #print("newcoordinates before check",newcoordinates)
        rel_chirality_list = atomdefine.relative_chirality_check(atomarray,Adjacency_list,Adjacency_matrix,newcoordinates)
        #print("initial_rel_chirality_list",initial_rel_chirality_list)
        #print("rel_chirality_list",rel_chirality_list)
        if potential_energy_of_accepted_structure[0] < 0:
            potential_energy_of_accepted_structure[0] = 0
        distance_check = rulechk.distchk(newcoordinates,restriction)
        if np.abs(potE-potential_energy_of_accepted_structure[0]) > 1000:
            print("Caution. The energy of the candidate structure exceeded 1000 kcal/mol and rejected")
            with open('./mcmclogfile', mode='a') as logwrite:
                logwrite.write("    potE: "+str(potE)+"    Caution. The energy of the candidate structure exceeded 1000 kcal/mol
and rejected ¥n"+
                               "    The difference is "+str(potE-potential_energy_of_accepted_structure[0])+"¥n")
        elif initial_rel_chirality_list != rel_chirality_list:
            confbreak += 1
            print("Caution. Diastereomer is generated and rejected")
            with open('./mcmclogfile', mode='a') as logwrite:
                logwrite.write("    Caution. Diastereomer is generated and rejected ¥n")
```

```
            elif distance_check == 1:
                confbreak += 1
                print("Caution. Distance-regulation is broken and rejected")
                with open('./mcmclogfile', mode='a') as logwrite:
                    logwrite.write("    Caution. Distance-regulation is broken and rejected ¥n")
            else:
                # Here the structure is to be selected on the ground of the Metropolis algorithm
                random = np.random.rand()
                print("potE",potE,"previousE",previousE)
                boltzman_factor = np.exp(-beta_per_mol * 1000 * 4.184 * (potE - previousE) / samplingbias)
                print("boltzman_factor: ",boltzman_factor)
                with open('./mcmclogfile', mode='a') as logwrite:
                    logwrite.write("    potE: "+str(potE)+" previousE: "+str(previousE)+"¥n")
                    logwrite.write("    boltzman_factor: "+str(boltzman_factor)+"¥n")
                if boltzman_factor > random and potE < borderenergy:
                    accepted_number,new_or_not = strcheck(accepted_number,accepted_coordinates,newcoordinates,atomtype)
                    if new_or_not == 1:       # In the case of NEW conformation
                        potential_energy_of_accepted_structure.append(potE)
                        accepted_number.append(int(1))
                        accepted_coordinates.append(newcoordinates)
                        os.rename(outputfilename,tinker_temp_output_file)
                        shutil.move(tinker_temp_output_file,"./confcache/acceptedstr"+str(len(accepted_coordinates)-1))
                    print("the structure was accepted in the process of Metropolis algorithm")
                    print("new_or_not",new_or_not)
                    print("accepted_number",accepted_number)
                    print(potential_energy_of_accepted_structure,"¥n")
                    with open('./mcmclogfile', mode='a') as logwrite:
                        logwrite.write("    the structure was accepted in the process of Metropolis algorithm ¥n"+
                                       "    new_or_not: "+ str(new_or_not) + " at the cycle number of " +
str(number_of_mcmc_cycle) + "¥n"+
                                       "")
#                                      "    accepted_number: "+ str(accepted_number) + "¥n")
                    previousE = potE
                    coordinates = copy.copy(newcoordinates)
                else:
                    monтereject += 1
                    print("rejected in the process of stochastic selection of Metropolis algorithm")
                    with open('./mcmclogfile', mode='a') as logwrite:
                        logwrite.write("    rejected in the process of stochastic selection of Metropolis algorithm ¥n")

        print("¥n Monte Carlo method finished")
        print(confbreak," structures are broken and rejected")
        print(montereject," structures are rejected    in the process of stochastic selection of Metropolis algorithm")
        print("Totally, ",len(accepted_number)," conformers are found.")
        with open('./mcmclogfile', mode='a') as logwrite:
            logwrite.write("¥n----------Monte Carlo method finished----------¥n    " +
                           str(confbreak) + " structures are broken and rejected¥n    " +
                           str(montereject) + " structures are rejected    in the process of stochastic selection of Metropolis algorithm
¥n    " +
                           "Totally, " + str(len(accepted_number)) + " conformers are found.")
        return accepted_coordinates,potential_energy_of_accepted_structure,accepted_number

    def strcheck(accepted_number,accepted_coordinates,newcoordinates,atomtype):
        new_or_not = 1
        #print("strcheck started, length of accepted coordinates",len(accepted_coordinates))
        newcoordinates_copy = copy.deepcopy(newcoordinates)
        coordinates_mirror = copy.deepcopy(newcoordinates)
        coordinates_mirror[:,2] = -coordinates_mirror[:,2]
        accepted_coordinates_copy = copy.deepcopy(accepted_coordinates) # When copy.copy(accepted_coordinates) is used, been
overridden.
        for i in range(len(accepted_coordinates)):
            for j in range(len(atomtype)):
                if atomtype[j] == 5 or atomtype[j] == 45: # normal alkyl hydrogen or ammonium
                    accepted_coordinates_copy[i][j]    = [0.0001,0.0001,0.0001]
                    newcoordinates_copy[j] = [0.0001,0.0001,0.0001]
                    coordinates_mirror[j] = [0.0001,0.0001,0.0001]

            diff    = (accepted_coordinates_copy[i].T[:,accepted_coordinates_copy[i].T[0].argsort()].T
                       - newcoordinates_copy.T[:,newcoordinates_copy.T[0].argsort()].T )
            diff2 = ( accepted_coordinates_copy[i].T[:,accepted_coordinates_copy[i].T[0].argsort()].T
```

```
                        - coordinates_mirror.T[:,coordinates_mirror.T[0].argsort()].T )
            #print("accepted_coordinates[i]",accepted_coordinates[i],"newcoordinates",newcoordinates,"diff",diff)
            print("deviatiton",np.sum(np.power(diff,2)),"deviation_mirror",np.sum(np.power(diff2,2)))
#             with open('./mcmclogfile', mode='a') as logwrite:
#                   logwrite.write("deviatiton: " + str(np.sum(np.power(diff,2))) + "    deviation_mirror: "+
str(np.sum(np.power(diff2,2))))
            if np.sum(np.power(diff,2)) < 0.1 or np.sum(np.power(diff2,2)) < 0.1:
                  new_or_not = 0
                  accepted_number[i] += 1
                  print("the same structure as conformer number ", i)
                  with open('./mcmclogfile', mode='a') as logwrite:
                        logwrite.write("    the same structure as conformer number " + str(i) + "¥n")
                  break

      return accepted_number,new_or_not

################################### rotator.py ###################################
#
#                                 A Module for rotating atom fragments
#
#     written by Hiroaki Kurouchi
#
##################################################################################

import numpy as np
import math
import copy
import random

# A module which rotates a coordinate to a position of which atom0 is at O
# atom1 is at X axys and atom2 is at XY plane.
def setter(coordinates):
      # First, move the atom0 to the original point
      newcoordinates = copy.copy(coordinates)
      for i in range(len(coordinates)):
            for j in range(3):
                  newcoordinates[i][j] += -coordinates[0][j]

      # Next, rotate the molecule to fit the atom1 of it to X axis.
      r_xyz = np.linalg.norm(newcoordinates[1])
      r_xy    = np.linalg.norm(newcoordinates[1][0:2])
      sint    = newcoordinates[1][1] / r_xy
      cost    = newcoordinates[1][0] / r_xy
      rot_mat_yx = np.array([[ cost, sint, 0],
                                    [-sint, cost, 0],
                                    [       0,       0, 1]])

      sinp    = r_xy / r_xyz
      cosp    = newcoordinates[1][2] / r_xyz
      rot_mat_zx = np.array([[ sinp, 0, cosp],
                                    [       0, 1,       0],
                                    [-cosp, 0, sinp]])

      newcoordinates = (np.dot(rot_mat_zx,np.dot(rot_mat_yx,newcoordinates.T))).T

      # Finally, rotate the molecule to let atom on XY plane
      r_yz    = (newcoordinates[2][2] ** 2 + newcoordinates[2][1] ** 2) ** 0.5
      sinq    = newcoordinates[2][2] / r_yz
      cosq    = newcoordinates[2][1] / r_yz
      rot_mat_yz = np.array([[ 1,       0,       0],
                                    [ 0, cosq, sinq],
                                    [ 0,-sinq, cosq]])

      newcoordinates = (np.dot(rot_mat_yz,newcoordinates.T)).T

      return newcoordinates

# Rotate the molecule so as to set atom1 on O and atom2 on X axis
def setter_bond(coordinates,atom1,atom2):
      # First, move the atom1 to the original point
```

```
    newcoordinates = copy.copy(coordinates)
    for i in range(len(coordinates)):
        for j in range(3):
            newcoordinates[i][j] += -coordinates[atom1][j]

    # Next, rotate the molecule to fit the atom2 of it to X axis.
    r_xyz = (newcoordinates[atom2][0] ** 2 + newcoordinates[atom2][1] ** 2 +
             newcoordinates[atom2][2] ** 2) ** 0.5
    r_xy  = (newcoordinates[atom2][0] ** 2 + newcoordinates[atom2][1] ** 2) ** 0.5
    sint  = newcoordinates[atom2][1] / r_xy
    cost  = newcoordinates[atom2][0] / r_xy
    rot_mat_yx = np.array([[ cost, sint, 0],
                           [-sint, cost, 0],
                           [    0,    0, 1]])

    sinp  = r_xy / r_xyz
    cosp  = newcoordinates[atom2][2] / r_xyz
    rot_mat_zx = np.array([[ sinp, 0, cosp],
                           [    0, 1,    0],
                           [-cosp, 0, sinp]])

    newcoordinates = np.dot(rot_mat_zx,np.dot(rot_mat_yx,newcoordinates.T)).T

    return newcoordinates

# Rotate around X axis
def rotator_x(coordinates,angle):
    rot_mat_yz = np.array([[ 1,                0,                0],
                           [ 0, np.cos(angle),-np.sin(angle)],
                           [ 0, np.sin(angle), np.cos(angle)]])
    newcoordinates = (np.dot(rot_mat_yz,coordinates.T)).T

    return newcoordinates

# Rotate the molecule around a bond
def rotatebond(Rotbondinfo,rotbondnum,coordinates,angle1,angle2):
    newcoordinates = setter_bond(coordinates,Rotbondinfo[rotbondnum][0][0],Rotbondinfo[rotbondnum][0][1])
    # Make coordinates to rotate
    rotcoord = []
    for i in range(1,3):
        rotcoord.append(np.zeros([len(Rotbondinfo[rotbondnum][i]),3]))

    angle = [float(angle1),float(angle2)]
    # Rotate fragments !!! Caution, kono 4 gyou de hamatte 2jikan kieta !!!
    for i in range(2):
        for j in range(len(rotcoord[i])):
            newcoordinates[Rotbondinfo[rotbondnum][i+1][j]] =    ¥
            rotator_x(newcoordinates[Rotbondinfo[rotbondnum][i+1][j]],angle[i])

    return newcoordinates

# This function choose several bonds and rotates.
def randomrot(coordinates,rotbondrange,rotbondnum,Rotbondinfo):
    for i in range(rotbondnum):
        angle1 = np.pi * float(np.random.randint(rotbondrange[0],rotbondrange[1]))/ 180
        angle2 = np.pi * float(np.random.randint(rotbondrange[0],rotbondrange[1]))/ 180

        if np.random.rand() > 0.5:
            angle1 = -angle1
        else:
            angle2 = -angle2

        coordinates = rotatebond(Rotbondinfo,
                                 np.random.choice(range(len(Rotbondinfo))),
                                 coordinates,angle1,angle2)

    return coordinates

# atom0 = O, atom1 on X axis and atom2 on xy plane
def coordinate_rot(coordinates):
```

```
    coordinates = setter_bond(coordinates,0,1)
    r_yz = np.linalg.norm(coordinates[2][1:3])
    cost = coordinates[2][1] / r_yz
    sint = coordinates[2][2] / r_yz
    rot_mat_yz = np.array([[ 1,    0,    0],
                           [ 0, cost, sint],
                           [ 0,-sint, cost]])
    coordinates = (np.dot(rot_mat_yz,coordinates.T)).T

    return coordinates


################################ tinkermanager.py ##############################
#
#           A program to manage TINKER as an optimization module.
#
#    written by Hiroaki Kurouchi
#
################################################################################

import numpy as np
import math
import copy
import linecache
import os
import initprocess
import rotator
import subprocess
import sys

# function to read tinker output file of MM3 calculation
def tinkeroutputreader(tinker_output_file):
    atomnum          = int(linecache.getline(tinker_output_file,1).split()[0])
    coordinates      = np.zeros([atomnum,3])
    atoms            = ["Null" for i in range(atomnum)]
    connectivity     = [[] for i in range(atomnum)]
    atomtype         = [int(0) for i in range(atomnum)]
    for line in range(1,atomnum + 1):
        lineinfo    = linecache.getline(tinker_output_file,line+1).split()
        atoms[line-1] = str(lineinfo[1])
        for i in range(3):
            coordinates[line-1][i] = float(lineinfo[i+2])
        atomtype[line-1] = int(lineinfo[5])
        for i in range(6,len(lineinfo)):
            connectivity[line-1].append(lineinfo[i])

#    print("tinkeroutputreader coordinates")
#    print(coordinates)

    linecache.clearcache()

    return atoms,coordinates,atomtype,connectivity

# This function start optimization, but does not check the validity of the structure
def tinkeropt(tinker_input_file,keyword_file,tinkeroptpath,RMSgrad=0.001):
    result = 0
    tinkerinput = [tinkeroptpath," ",tinker_input_file,' -k ',keyword_file," ",str(RMSgrad)]
#    print(tinkerinput,"tinkerinput")
    potE = 0 # potential energy
    try:
        try:
##### Section for Python3.5 or later
            """
            result = subprocess.run(" ".join(tinkerinput),shell=True,universal_newlines=True,
                                    stdout=subprocess.PIPE,stderr=subprocess.PIPE,timeout=10)

            if result.returncode != 0:
                print("failed in the TINKER OPTIMIZATION process error, see tinkermanager.py Error1")
                sys.exit()
            for line in result.stdout.splitlines():
```

```
                    try:
                        if line.split()[1] == "Function":
                            potE = float(line.split()[4])
                    except:
                        pass
                """
#####Section for Python3.4 or before
#"""
                result = subprocess.check_output(" ".join(tinkerinput),shell=True,
                                                 timeout=120)
                for line in result.splitlines():
                    try:
                        if "Function" in str(line.split()[1]):
                            potE = float(line.split()[4])
                    except:
                        pass
#"""
            except:
                potE = 0.0
                print("Optimization failed, see tinkermanager.py Error 2")
                with open('./mcmclogfile', mode='a') as logwrite:
                    logwrite.write(" Optimization failed, potE was set to 100000.0. See tinkermanager.py Error 2¥n")

        except:
            print("failed in the TINKER OPTIMIZATION process error, see tinkermanager.py    Error3")
            sys.exit()

        return potE


##############################       atomdefine.py       ##############################
#
#       written by Hiroaki Kurouchi
#
#############################################################################

import numpy as np
import math
import copy

# Set atom sets
period1 = {'H','He'}
period2 = {'Li','B','C','N','O','F','Ne'}
period3 = {'Na','Mg','Al','Si','P','S','Cl'}
period4 = {'K','Ca','Ti','Br'}
period5 = {'Zr','Sn','Sb','I'}

# A function to measure a distance of atoms
def distance(atom1,atom2):
        distance_sq = 0.0
        for i in range(3):
            distance_sq += (atom1[i]-atom2[i])**2
        distance = distance_sq ** 0.5

        return distance

# A function to divide heavy atoms and hydrogen atoms
def classify(atoms,coordinates):
        Hydrogen_num = 0
        for atomnum in range(len(atoms)):
            if atoms[atomnum] == 'H':
                Hydrogen_num    += 1

        Heavy_num                   = len(atoms) - Hydrogen_num
        Heavy_atoms                 = [i for i in range(Heavy_num)]
        Heavy_coord       = np.zeros([Heavy_num,      3])
        Hydrogen_coord = np.zeros([Hydrogen_num,3])
        Heavy_atomcount           = 0
        Hydrogen_atomcount      = 0
        for atomnum in range(len(atoms)):
```

```
            if atoms[atomnum] == 'H':
                Hydrogen_coord[Hydrogen_atomcount] = coordinates[atomnum]
                Hydrogen_atomcount += 1
            else:
                Heavy_atoms[Heavy_atomcount]      = atoms[atomnum]
                Heavy_coord[Heavy_atomcount] = coordinates[atomnum]
                Heavy_atomcount                   += 1

    return Heavy_atoms,Heavy_coord,Hydrogen_coord

# A function to define connection of atoms
# The "Singlebonds" is a matrix which only contains single bonds
def definebonds(Heavy_atoms,Heavy_coord,Hydrogen_coord):
    atomarray     = copy.copy(Heavy_atoms)
    coordinates = np.r_[Heavy_coord,Hydrogen_coord]
    for i in range(len(Hydrogen_coord)):
        atomarray.append("H")

    Adjacency_matrix = np.zeros([len(Heavy_coord)+len(Hydrogen_coord),
                                 len(Heavy_coord)+len(Hydrogen_coord)])
    Singlebonds      = copy.copy(Adjacency_matrix)
    BondLength       = 0.0
    for i in range(len(Adjacency_matrix)):
        for j in range(i+1,len(Adjacency_matrix)):
            BondLength = distance(coordinates[i],coordinates[j])
            if (atomarray[i] in period2 and atomarray[j] in period2):
                if   BondLength - 2.1 < 0: # So as to calculate TS
                    Adjacency_matrix[i][j] = Adjacency_matrix[j][i] = 1
                    if BondLength -1.3 > 0:
                    # If necessary, change the borderline
                        Singlebonds[i][j] = Singlebonds[j][i] = 1

            elif (atomarray[i] in period2 and atomarray[j] in period3)¥
               or (atomarray[j] in period2 and atomarray[i] in period3):
                if BondLength - 2.2 < 0:
                    Adjacency_matrix[i][j] = Adjacency_matrix[j][i] = 1
                    Singlebonds[i][j] = Singlebonds[j][i] = 1

            elif (atomarray[i] in period2 and atomarray[j] in period4)¥
               or (atomarray[j] in period2 and atomarray[i] in period4):
                if BondLength - 2.5 < 0:
                    Adjacency_matrix[i][j] = Adjacency_matrix[j][i] = 1
                    Singlebonds[i][j] = Singlebonds[j][i] = 1

            elif (atomarray[i] in period2 and atomarray[j] in period5)¥
               or (atomarray[j] in period2 and atomarray[i] in period5):
                if BondLength - 2.8 < 0:
                    Adjacency_matrix[i][j] = Adjacency_matrix[j][i] = 1
                    Singlebonds[i][j] = Singlebonds[j][i] = 1

            elif (atomarray[i] not in period1 and atomarray[j] == "H"):
                if   BondLength - 1.6 < 0:
                    Adjacency_matrix[i][j] = Adjacency_matrix[j][i] = 1

    return atomarray,Adjacency_matrix,Singlebonds

# Check whether the molecule is connected graph or not, based on graph theory
def connectcheck(Adjacency_matrix,n=0):
    graph_distance     = [n]
    addedatoms         = [n]
    newdistancelist    = [n]
    nextdistancelist = []
    while len(newdistancelist) > 0:
        for i in newdistancelist:
            for j in range(len(Adjacency_matrix)):
                if (Adjacency_matrix[i][j] == 1) and (j not in addedatoms):
                    addedatoms.append(j)
                    nextdistancelist.append(j)

        graph_distance.append(nextdistancelist)
```

```
            newdistancelist = copy.copy(nextdistancelist)
            nextdistancelist = []

        allset = set([i for i in range(len(Adjacency_matrix))])
        setA   = set(addedatoms)
        setB   = allset.difference(setA)

        return graph_distance,setA,setB

# Here we make an adjacent matrix which solely contains information of ring conectivity
def ringmatrixmaker(Adjacency_matrix):
        Adjacency_list = Adjacency_converter_MtoL(Adjacency_matrix)
        Ring_matrix = copy.copy(Adjacency_matrix)
        for i in range(len(Adjacency_matrix)):
                for j in Adjacency_list[i]:
                        if j > i:
                                Bond_erased_Adjacency_matrix = copy.copy(Adjacency_matrix)
                                Bond_erased_Adjacency_matrix[i][j] = 0
                                Bond_erased_Adjacency_matrix[j][i] = 0
                                graph_distance,setA,setB = connectcheck(Bond_erased_Adjacency_matrix,n=0)
                                if len(setB) > 0:
                                        Ring_matrix[i][j] = Ring_matrix[j][i] = 0

        return Ring_matrix

# Here we define atoms those are to be moved in the Monte Calro method
# The bonds defined in Singlebonds are regarded as bonds to be rotated.
def rotatomlist(atomarray,Ring_matrix,Adjacency_matrix,Singlebonds):
        Rotbondinfo = []
        Adjacency_list = Adjacency_converter_MtoL(Adjacency_matrix)
        bondnum = np.sum(Adjacency_matrix,axis=0)
        for i in range(len(Singlebonds)):
                for j in range(i,len(Singlebonds)):
                        if Singlebonds[i][j] == 1 and bondnum[j] != 1:
                                Rotbondinfo.append([[i,j]])

        # Add atom data connected to atoms adjacent to atoms of bond"k"
        #
        for k in range(len(Rotbondinfo)):
                for atomnum in range(2):
                        # make a list Rotbondinfo[k][atomnum+1]
                        Rotbondinfo[k].append([])
                        # Rotbondinfo[k][0][atomnum] is a atomnumber of atom of interest.
                        # Then pickup atoms adjacent to Rotbondinfo[k][atomnum] as l
                        #
                        if Ring_matrix[Rotbondinfo[k][0][0]][Rotbondinfo[k][0][1]] == 0:
                                Adjacency_matrix_k = copy.copy(Adjacency_matrix)
                                Adjacency_matrix_k[Rotbondinfo[k][0][0]][Rotbondinfo[k][0][1]] = ¥
                                Adjacency_matrix_k[Rotbondinfo[k][0][1]][Rotbondinfo[k][0][0]]  = 0
                                graph_distance,setA,setB =  connectcheck(Adjacency_matrix_k,Rotbondinfo[k][0][atomnum])
                                Rotbondinfo[k][atomnum+1].extend(list(setA))

                        elif Ring_matrix[Rotbondinfo[k][0][0]][Rotbondinfo[k][0][1]] == 1:
                                for l in Adjacency_list[Rotbondinfo[k][0][atomnum]]:
                                        Rotbondinfo[k][atomnum+1].append(l)
                                        if l not in Rotbondinfo[k][0]:
                                                if Ring_matrix[Rotbondinfo[k][0][atomnum]][l] == 0:
                                                        Adjacency_matrix_l = copy.copy(Adjacency_matrix)
                                                        Adjacency_matrix_l[Rotbondinfo[k][0][0]][Rotbondinfo[k][0][1]] = ¥
                                                        Adjacency_matrix_l[Rotbondinfo[k][0][1]][Rotbondinfo[k][0][0]] = ¥
                                                        Adjacency_matrix_l[Rotbondinfo[k][0][atomnum]][l] = ¥
                                                        Adjacency_matrix_l[l][Rotbondinfo[k][0][atomnum]] = 0
                                                        graph_distance,setA,setB =  connectcheck(Adjacency_matrix_l,l)
                                                        Rotbondinfo[k][atomnum+1].extend(list(setA))

                                                elif Ring_matrix[Rotbondinfo[k][0][atomnum]][l] == 1:
                                                        for m in Adjacency_list[l]:
                                                                if m not in Rotbondinfo[k][0]:
                                                                        if Ring_matrix[l][m] == 0:
                                                                                Adjacency_matrix_m = copy.copy(Adjacency_matrix)
```

```
                                                Adjacency_matrix_m[Rotbondinfo[k][0][0]][Rotbondinfo[k][0][1]] = ¥
                                                Adjacency_matrix_m[Rotbondinfo[k][0][1]][Rotbondinfo[k][0][0]] = ¥
                                                Adjacency_matrix_m[l][m] = ¥
                                                Adjacency_matrix_m[m][l] = ¥
                                                Adjacency_matrix_m[Rotbondinfo[k][0][atomnum]][m] = ¥
                                                Adjacency_matrix_m[m][Rotbondinfo[k][0][atomnum]] = 0
                                                graph_distance,setA,setB =    connectcheck(Adjacency_matrix_m,m)
                                                Rotbondinfo[k][atomnum+1].extend(list(setA))

                                    else:
                                        print("Ring_matrix is weird, check the program")

                        Rotbondinfo[k][atomnum+1] = list(set(Rotbondinfo[k][atomnum+1]))
                        Rotbondinfo[k][atomnum+1].sort()

        return Rotbondinfo

# Here we check ring sizes
def ringsizedefine(Ring_matrix):
        ringsizelist    = [[] for i in range(len(Ring_matrix))]
        Ring_list       = Adjacency_converter_MtoL(Ring_matrix)
        for i in range(len(Ring_list)):
                New_Ring_matrix = copy.copy(Ring_matrix)
                for j in Ring_list[i]:
                        New_Ring_matrix[i][j] = New_Ring_matrix[j][i] = 0

                New_Ring_list   = Adjacency_converter_MtoL(New_Ring_matrix)
                for j in range(len(Ring_list[i])):
                        for k in range(j+1,len(Ring_list[i])):
                                ringsize = 2
                                passed     = [Ring_list[i][j]]
                                nowonsearch = New_Ring_list[Ring_list[i][j]]
                                nextsearch = []
                                findflag = 0
                                while findflag == 0 and len(nowonsearch) >0:
                                        ringsize += 1
                                        for l in nowonsearch:
                                                for m in range(len(New_Ring_list[l])):
                                                        if New_Ring_list[l][m] not in passed:
                                                                nextsearch.append(New_Ring_list[l][m])

                                        if Ring_list[i][k] in nowonsearch:
                                                findflag = 1
                                                ringsizelist[i].append(ringsize)

                                        passed.extend(nowonsearch)
                                        nowonsearch = copy.copy(nextsearch)
                                        nextsearch    = []

        return ringsizelist

# Here we check whether the atom is in aromatic ring or not
# by making ring matrix which only contains sp2 carbon and heteroatoms
def aromatic_check(Ring_matrix,Adjacency_matrix,atomarray):
        bondnum = np.sum(Adjacency_matrix,axis=0)
        aromatic_matrix = copy.copy(Ring_matrix)
        for i in range(len(atomarray)):
                if atomarray[i] == "C" and bondnum[i] != 3:
                        for j in range(len(atomarray)):
                                aromatic_matrix[i][j] = aromatic_matrix[j][i] = 0

        aromaticlist = ringsizedefine(aromatic_matrix)

        return aromaticlist


# A function to convert matrix to list
def Adjacency_converter_MtoL(Adjacency_matrix):
        listtoadd = []
        Adjacency_list = []
```

```
    for i in range(len(Adjacency_matrix)):
        listtoadd = []
        for j in range(len(Adjacency_matrix)):
            if Adjacency_matrix[i][j] == 1:
                listtoadd.append(j)
        Adjacency_list.append(listtoadd)

    return Adjacency_list

# A function to convert list to matrix
def Adjacency_converter_LtoM(Adjacency_list):
    Adjacency_matrix = np.zeros([len(Adjacency_list),len(Adjacency_list)])
    for i in range(len(Adjacency_list)):
        for j in Adjacency_list[i]:
            Adjacency_matrix[i][j] = 1

    return Adjacency_matrix

# A function to make Rotbondinfo into Rotbond_list
def Rotbondinfo_to_Rotbond_list(Rotbondinfo,atomnum):
    Rotbond_list = [[] for i in range(atomnum)]
    for i in range(len(Rotbondinfo)):
        Rotbond_list[Rotbondinfo[i][0][0]].append(Rotbondinfo[i][0][1])
        Rotbond_list[Rotbondinfo[i][0][1]].append(Rotbondinfo[i][0][0])

    return Rotbond_list

# A function to define chirality. not R nor S, but based on an original rule just for checking whether the
# chirality is retained or not
def relative_chirality_check(atomarray,Adjacency_list,Adjacency_matrix,coordinates):
    relative_chirality_list = [0 for i in range(len(atomarray))]
    bondnum = np.sum(Adjacency_matrix,axis=0)
    for i in range(len(atomarray)):
        if (atomarray[i] == "C") and (bondnum[i] == 4):
            V = np.zeros([4,3])
            for j in range(4):
                V[j] = coordinates[Adjacency_list[i][j]] - coordinates[i]

            r_xyz = np.linalg.norm(V[0])
            r_xy  = np.linalg.norm(V[0][0:2])
            sint  = V[0][1] / r_xy
            cost  = V[0][0] / r_xy
            sinp  = r_xy    / r_xyz
            cosp  = V[0][2] / r_xyz
            rot_mat_yx = np.array([[ cost, sint, 0],
                                   [-sint, cost, 0],
                                   [    0,    0, 1]])
            rot_mat_zx = np.array([[ sinp, 0, cosp],
                                   [    0, 1,    0],
                                   [-cosp, 0, sinp]])
            V = np.dot(rot_mat_zx,np.dot(rot_mat_yx,V.T) ).T
            for j in range(1,4):
                V[j][0] = 0
            if np.cross(V[1],V[2])[0] > 0:
                relative_chirality_list[i] = 1
            else:
                relative_chirality_list[i] = -1

#       print("relative_chirality_list",relative_chirality_list)
    return relative_chirality_list

# Here we will attribute MM3 atom numbers to each atom
def mm3define(atomarray,Adjacency_matrix,Adjacency_list,Ring_matrix,ringsizelist,aromaticlist):
    atomtype    = [0 for i in range(len(atomarray))]
    Carray      = []
    Oarray      = []
    Narray      = []
    Harray      = []
    Sarray      = []
    Parray      = []
```

```
Barray          = []
Otherarray    = []
for i in range(len(atomarray)):
    if atomarray[i] == "C":
        Carray.append(i)
    elif atomarray[i] == "O":
        Oarray.append(i)
    elif atomarray[i] == "N":
        Narray.append(i)
    elif atomarray[i] == "H":
        Harray.append(i)
    elif atomarray[i] == "S":
        Sarray.append(i)
    elif atomarray[i] == "P":
        Parray.append(i)
    elif atomarray[i] == "B":
        Barray.append(i)
    else:
        Otherarray.append(i)

bondnum = np.sum(Adjacency_matrix,axis=0)

# Here we allocate the MM3 atom property numbers to each atoms
# C atom:
#     bond number = 4 : sp3
#                   3 : sp2
#                   2 : sp
CarbonylC = [3,58,67]
for i in Carray:
    carbonylflag = 0
    for j in Adjacency_list[i]:
        if atomarray[j] == "O" and bondnum[j] == 1:
            carbonylflag = 1

    if bondnum[i] == 4:
        if 4 in ringsizelist[i]:
            atomtype[i] = 56 # Cyclobutane
        elif 3 in ringsizelist[i]:
            atomtype[i] = 22 # Cyclopropane
        else:
            atomtype[i] = 1    # Alkane

    elif bondnum[i] == 3:
        if carbonylflag == 1:
            if 4 in ringsizelist[i]:
                atomtype[i] = 58 # Cyclobutanone
            elif 3 in ringsizelist[i]:
                atomtype[i] = 67 # Cyclopropanone
            else:
                atomtype[i] = 3    # Carbonyl

        elif len(aromaticlist[i]) > 0:
            atomtype[i] = 50 # It will be changed to "2" in initprocess.py
                             # because benzene parameters are not defined in TINKER

        else:
            if 4 in ringsizelist[i]:
                atomtype[i] = 57 # Cyclobutene
            elif 3 in ringsizelist[i]:
                atomtype[i] = 38 # Cyclopropene
            else:
                atomtype[i] = 2    # Alkene

    elif bondnum[i] == 2:
        alleneflag = 1
        for j in Adjacency_list[i]:
            if bondnum[j] != 3 or atomarray[j] != "C":
                alleneflag = alleneflag * 0

        if carbonylflag == 1:
```

```
                    atomtype[i] = 106 # Ketene
                elif alleneflag == 1:
                    atomtype[i] = 68    # Allene
                else:
                    atomtype[i] = 4     # Alkyne

        # O atom:
        #     bond number = 2 : sp3
        #                   1 : sp2
        # Carbonyl oxygen is not assigned to special oxygens like amide, ester etc.
        # Ketonium(70), Carboxylate(47) etc. also are not to be asssigned automatically.
        # If you want to use these mm3 parameters, modify input file manually or modify this program
        for i in Oarray:
            nitroxyflag = 0
            for j in Adjacency_list[i]:
                if atomarray[j] == "N":
                    nitroxyflag = 1

            if bondnum[i] == 2:
                anhydrideflag = 1
                for j in Adjacency_list[i]:
                    if atomtype[j] not in CarbonylC:
                        anhydrideflag = anhydrideflag * 0

                carbonylflag = 0
                for j in range(len(Adjacency_list[i])):
                    if atomtype[Adjacency_list[i][j]] in CarbonylC:
                        carbonylflag += 10
                    elif atomarray[Adjacency_list[i][j]] == "H":
                        carbonylflag += 1
                    elif atomarray[Adjacency_list[i][j]] == "C":
                        carbonylflag += 6

                if 3 in ringsizelist[i]:
                    atomtype[i] = 49    # Epoxy
                elif nitroxyflag == 1:
                    atomtype[i] = 145 # Hydroxyamine
                elif anhydrideflag == 1:
                    atomtype[i] = 149 # Anhydride(Delocalized)
                                      # if you want to use Localized version, use 148
#                 elif carbonylflag == 11 or carbonylflag == 16:
#                     atomtype[i] = 75    # Acid or Ester R-CO-'O'-R
                elif 5 in aromaticlist[i]:
                    atomtype[i] = 41    # Furan
                elif atomtype[i] == 0:
                    atomtype[i] = 6     # Ether

            if bondnum[i] == 1:
                if nitroxyflag == 1:
                    atomtype[i] = 69    # Amine oxide
                else:
                    atomtype[i] = 7     # Carbonyl

        # N atom:
        #     bond number = 4 : sp3(ammonium)
        #                   3 : sp3
        #                   2 : sp2
        #                   1 : sp
        for i in Narray:
            nitroxynum = 0
            for j in Adjacency_list[i]:
                if atomtype[j] == 69:
                    nitroxynum += 1

            if bondnum[i] == 4:
                atomtype[i] = 39    # Ammonium

            if bondnum[i] == 3:
                if nitroxynum == 2:
                    atomtype[i] = 46    # Nitro
```

```
                else:
                    atomtype[i] = 8      # sp3 amine

                # Here we assign the atom to specific functional groups
                for j in Adjacency_list[i]:
                    if atomarray[j] == "O" and bondnum[j] == 2:
                        atomtype[i] = 146    # Hydroxyamine
                    elif atomarray[j] == "N" and bondnum[j] == 3:
                        atomtype[i] = 150    # Hydrazine
#                     elif atomtype[j] in CarbonylC:
#                         atomtype[i] = 151    # Amide
                    elif atomtype[j] in CarbonylC:
                        atomtype[i] = 9    # Amide
                    elif atomarray[j] == "S":
                        atomtype[i] = 155    # Sulfonamide
                    elif atomarray[j] == "Li":
                        atomtype[i] = 164    # Lithiumamide
                    elif 5 in aromaticlist[i]:
                        atomtype[i] = 40      # Pyrrole

            if bondnum[i] == 2:
                atomtype[i] = 9 # sp2 nitrogen
                # Here we assign the atom to specific functional groups
                nitrogensp2 = 1
                for j in Adjacency_list[i]:
                    if atomarray[j] == "C" and bondnum[j] == 3:
                        nitrogensp2 = nitrogensp2 * 2
                    if atomarray[j] == "N" and bondnum[j] == 2:
                        nitrogensp2 = nitrogensp2 * 3
                    if atomarray[j] == "O" and bondnum[j] == 2:
                        nitrogensp2 = nitrogensp2 * 5
                if nitrogensp2 == 2 or nitrogensp2 == 4:
                    atomtype[i] = 72    # Imine(Localized)
                elif nitrogensp2 == 3 or nitrogensp2 == 6:
                    atomtype[i] = 107 # Azo
                elif nitrogensp2 == 10:
                    atomtype[i] = 108 # Oxime
                elif 6 in aromaticlist[i]:
                    atomtype[i] = 37    # Pyridine

            if bondnum[i] == 1:
                atomtype[i] = 10

        # H atom:
        #     bond number = 1 : s
        for i in Harray:
            # Here we start from enol/phenol check
            ### Caution, carbocation is also recognized as enol carbon ###
            if atomarray[Adjacency_list[i][0]] == "O":
                for j in Adjacency_list[Adjacency_list[i][0]]:
                    if bondnum[j] == 3 and atomarray[j] == "C":
                        atomtype[i] = 73    # Phenol or Enol

            if atomtype[Adjacency_list[i][0]] == 75:
                atomtype[i] = 24    # Carboxylic acid
            elif atomtype[Adjacency_list[i][0]] == 151:
                atomtype[i] = 28    # Amide
            elif atomtype[Adjacency_list[i][0]] == 39:
                atomtype[i] = 48    # Ammonium
            elif atomtype[Adjacency_list[i][0]] == 4:
                atomtype[i] = 124 # Acetylene
            elif atomarray[Adjacency_list[i][0]] == "O" and atomtype[i] == 0:
                atomtype[i] = 21    # Alcohol
            elif atomarray[Adjacency_list[i][0]] == "N" and atomtype[i] == 0:
                atomtype[i] = 23    # Amine or Imine
            elif atomarray[Adjacency_list[i][0]] == "S":
                atomtype[i] = 44    # Thiol

            if atomtype[i] == 0:
                atomtype[i] = 5    # Other Hydrogen
```

```
# S atom:
# Thiophene and Polysulfide are not defined automatically. Set the param by yourself
for i in Sarray:
	if bondnum[i] == 4:
		atomtype[i] = 18    # Sulfone

	if bondnum[i] == 3:
		for j in Adjacency_list[i]:
			if atomarray[j] == "O" and bondnum[j] == 1:
				atomtype[i] = 17    # Sulfoxide
		if atomtype[i] == 0:
			atomtype[i] = 16 # Sulfonium ion R3S+

	if bondnum[i] == 2:
		for j in Adjacency_list[i]:
			if atomarray[j] == "S":
				atomtype[i] = 104    # Disulfide -S-S-
		if atomtype[i] == 0:
			atomtype[i] = 15 # Sulfide -S-

	if bondnum[i] == 1:
		atomtype[i] = 74    # Thiocarbonyl

# P atom:
for i in Parray:
	if bondnum[i] == 4:
		for j in Adjacency_list[i]:
			if atomarray[j] == "O" and bondnum[j] == 1:
				atomtype[i] = 153    # Phosphate
		if atomtype[i] == 0:
			atomtype[i] = 60 # Phosphorous(V)

	if bondnum[i] == 3:
		atomtype[i] = 25 # Phosphine

# B atom:
for i in Barray:
	if bondnum[i] == 4:
		atomtype[i] = 27 # Borate

	if bondnum[i] == 3:
		atomtype[i] = 26 # Borane

# Define Other atoms:
for i in Otherarray:
	if atomarray[i] == "F":
		atomtype[i] = 11
	if atomarray[i] == "Cl":
		atomtype[i] = 12
	if atomarray[i] == "Br":
		atomtype[i] = 13
	if atomarray[i] == "I":
		atomtype[i] = 14
	if atomarray[i] == "Si":
		atomtype[i] = 19
	if atomarray[i] == "Ge":
		atomtype[i] = 31
	if atomarray[i] == "Sn":
		atomtype[i] = 32
	if atomarray[i] == "Pb":
		atomtype[i] = 33
	if atomarray[i] == "Se":
		atomtype[i] = 34
	if atomarray[i] == "Te":
		atomtype[i] = 35
	if atomarray[i] == "D":
		atomtype[i] = 36
	if atomarray[i] == "He":
		atomtype[i] = 51
```

```
    if atomarray[i] == "Ne":
        atomtype[i] = 52
    if atomarray[i] == "Ar":
        atomtype[i] = 53
    if atomarray[i] == "Kr":
        atomtype[i] = 54
    if atomarray[i] == "Xe":
        atomtype[i] = 55
    if atomarray[i] == "Mg":
        atomtype[i] = 59
    if atomarray[i] == "Fe":
        if bondnum[i] ==2:
            atomtype[i] = 61 # Fe(II)
        if bondnum[i] ==3:
            atomtype[i] = 62 # Fe(III)
    if atomarray[i] == "Ni":
        if bondnum[i] ==2:
            atomtype[i] = 63 # Ni(II)
        if bondnum[i] ==3:
            atomtype[i] = 64 # Ni(III)
    if atomarray[i] == "Co":
        if bondnum[i] ==2:
            atomtype[i] = 65 # Co(II)
        if bondnum[i] ==3:
            atomtype[i] = 66 # Co(III)
    if atomarray[i] == "Ca":
        atomtype[i] = 125
    if atomarray[i] == "Sr":
        atomtype[i] = 126
    if atomarray[i] == "Ba":
        atomtype[i] = 127
    if atomarray[i] == "La":
        atomtype[i] = 128
    if atomarray[i] == "Ce":
        atomtype[i] = 129
    if atomarray[i] == "Pr":
        atomtype[i] = 130
    if atomarray[i] == "Nd":
        atomtype[i] = 131
    if atomarray[i] == "Pm":
        atomtype[i] = 132
    if atomarray[i] == "Sm":
        atomtype[i] = 133
    if atomarray[i] == "Eu":
        atomtype[i] = 134
    if atomarray[i] == "Gd":
        atomtype[i] = 135
    if atomarray[i] == "Tb":
        atomtype[i] = 136
    if atomarray[i] == "Dy":
        atomtype[i] = 137
    if atomarray[i] == "Ho":
        atomtype[i] = 138
    if atomarray[i] == "Er":
        atomtype[i] = 139
    if atomarray[i] == "Tm":
        atomtype[i] = 140
    if atomarray[i] == "Yb":
        atomtype[i] = 141
    if atomarray[i] == "Lu":
        atomtype[i] = 142
    if atomarray[i] == "Li":
        atomtype[i] = 163

return atomtype
```

```
################################       initprocess.py       ##############################
#
#    Initiallization program which converts gaussian input file to MM3 input form
#    Reads input files and finally returns inputfiles
#
#       written by Hiroaki Kurouchi
#
#############################################################################################

import math
import copy
import linecache
import numpy as np
import random
import atomdefine
import os
import printer
import parameters

### read parameters###
tinker_input_file = parameters.tinker_input_file

######################

# A function for reading input files.
# The input file must be named "inputcoordinates".
# The first line of "inputcoordinates" is number of atoms.
# The second line of "inputcoordinates" is charge and multiplicity. e.g. 0 1
# From the third line, the atom symbol and the coordinate are to be
# input following the gaussian input file rule.
def inputreader(runningdirpath):
    charge_spin = [0,0]
    atomnum     = int(linecache.getline(runningdirpath+'/inputcoordinates',1))
    atoms       = [i for i in range(atomnum)]
    raw_coordinates = np.zeros([atomnum,3])

    lineinfo = linecache.getline(runningdirpath+'/inputcoordinates',2).split()
    for i in range(2):
        charge_spin[i] = int(lineinfo[i])

    for line in range(3,atomnum+3):
        lineinfo = linecache.getline(runningdirpath+'/inputcoordinates',line).split()
        atoms[line-3] = str(lineinfo[0])
        for i in range(3):
            raw_coordinates[line-3][i] = float(lineinfo[i+1])

    linecache.clearcache()
    return charge_spin,atoms,raw_coordinates

def Rotbondinforeader():
    linenum = sum(1 for line in open("Rotbondinfo"))
    Rotbondinfo = [[] for i in range(int(linenum / 3))]
    for i in range(1,linenum + 1):
        lineinfo = linecache.getline("Rotbondinfo",i).split()
        for j in range(len(lineinfo)):
            lineinfo[j] = int(lineinfo[j]) - 1
        Rotbondinfo[int((i-1)/3)].append(lineinfo)

    linecache.clearcache()
    return Rotbondinfo

def initialprocessing(runningdirpath):
    charge_spin,atoms,raw_coordinates ¥
        = inputreader(runningdirpath)
    Heavy_atoms,Heavy_coord,Hydrogen_coord    ¥
        = atomdefine.classify(atoms,raw_coordinates)
    atomarray,Adjacency_matrix,Singlebonds    ¥
        = atomdefine.definebonds(Heavy_atoms,Heavy_coord,Hydrogen_coord)
    Adjacency_list ¥
```

```
        = atomdefine.Adjacency_converter_MtoL(Adjacency_matrix)
    Ring_matrix ¥
        = atomdefine.ringmatrixmaker(Adjacency_matrix)
    ringsizelist ¥
        = atomdefine.ringsizedefine(Ring_matrix)
    aromaticlist    ¥
        = atomdefine.aromatic_check(Ring_matrix,Adjacency_matrix,atomarray)
    atomtype        ¥
        = atomdefine.mm3define(atomarray,Adjacency_matrix,Adjacency_list,¥
                                        Ring_matrix,ringsizelist,aromaticlist)

    # Here we change Singlebonds information so as not to treat benzene C=C bond as singlebond
    for i in range(len(Singlebonds)):
        if atomtype[i] == 50:
            for j in range(len(Singlebonds[i])):
                if atomtype[j] == 50:
                    Singlebonds[i][j] = 0

    Rotbondinfo ¥
        = atomdefine.rotatomlist(atomarray,Ring_matrix,Adjacency_matrix,Singlebonds)

    #Here if atomtype = 50(benzene), atomtype = 2
    for i in range(len(atomtype)):
        if atomtype[i] == 50:
            atomtype[i] = 2

    HecL = Heavy_coord.tolist()
    HycL = Hydrogen_coord.tolist()
    Coordinates_list = HecL + HycL # Coordinates_list is not ndarray

    return charge_spin,Coordinates_list,¥
            atomarray,Adjacency_matrix,Adjacency_list,¥
            atomtype,Rotbondinfo


if __name__ == '__main__':
    runningdirpath = os.getcwd()+"/"

    charge_spin,Coordinates_list,¥
    atomarray,Adjacency_matrix,Adjacency_list,¥
    atomtype,Rotbondinfo = initialprocessing(runningdirpath)

    printer.xyzmaker(atomarray,Coordinates_list,atomtype,Adjacency_list,tinker_input_file)
    printer.rotbondprinter(Rotbondinfo,"Rotbondinfo")
    Rotbond_list = atomdefine.Rotbondinfo_to_Rotbond_list(Rotbondinfo,len(atomarray))
    printer.xyzmaker(atomarray,Coordinates_list,atomtype,Rotbond_list,tinker_input_file+"_rotate")


################################### printer.py ################################
#
# A program to output coordinates (xyzmaker), rotation bond list (listfilemaker)
#
#       written by Hiroaki Kurouchi
#
###############################################################################

import os

def xyzmaker(atomarray,Coordinates_list,atomtype,Adjacency_list,initstr="str1.xyz"):
    try:
        os.remove(initstr)
    except:
        pass
    f = open(initstr,'w')
    f.write(str(len(atomarray)))
    f.write("    initialstructure¥n")
    for i in range(len(atomarray)):
        if i < 9:
            f.write(" ")
        f.write(str(i + 1))
```

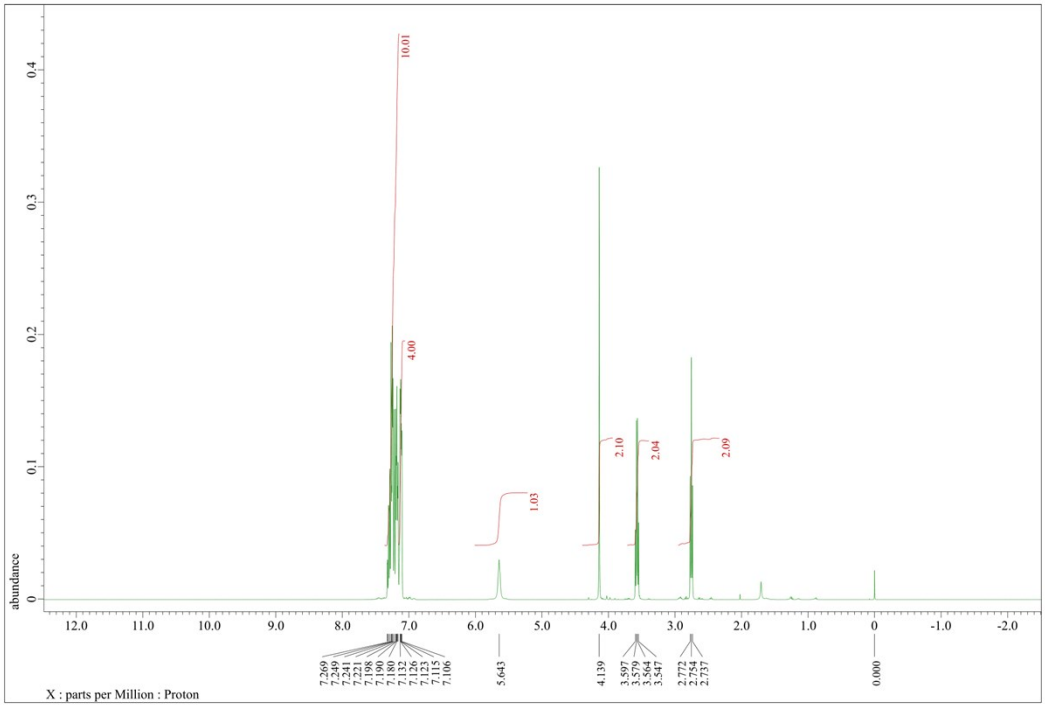
```
            f.write("      ")
            f.write(str(atomarray[i]))
            if len(str(atomarray[i])) == 1:
                f.write(" ")
            f.write("      ")
            for j in range(3):
                if Coordinates_list[i][j] >= 0:
                    f.write(" ")
                f.write(str("{0:8f}".format(Coordinates_list[i][j])))
                f.write("      ")

            if len(str(atomtype[i])) == 1:
                f.write(" ")
            f.write(str(atomtype[i]))
            f.write("           ")
            for j in range(len(Adjacency_list[i])):
                if    Adjacency_list[i][j] <9:
                    f.write(" ")
                f.write(str(1 + Adjacency_list[i][j]))
                f.write("    ")
            f.write("¥n")
        f.write("¥n")
        f.flush()
        f.close()

        return 0

# this function can be used only for 3-dim list
def rotbondprinter(listvar,listname):
        try:
            os.remove(listname)
        except:
            pass
        f = open(listname,'w')
        for i in range(len(listvar)):
            for j in range(len(listvar[i])):
                for k in range(len(listvar[i][j])):
                    f.write(str(int(listvar[i][j][k]) + 1))
                    f.write(" ")
                f.write("¥n")
        f.flush()
        f.close()

        return 0

# This module prints a coordinate as a gaussian input file
def gaussian_inputmaker(coordinates,atomarray,optdft,option1,charge_spin,
                                    comment="komento",inputfilename="g09.com",nproc=8,mem=8,
                                    restriction="",modredundant="OFF"):
        try:
            os.remove(inputfilename)
        except:
            pass
        #print(coordinates)
        f = open(inputfilename,'w')
        f.write("%nproc=")
        f.write(str(nproc))
        f.write("¥n")
        f.write("%mem=")
        f.write(str(mem))
        f.write("gb ¥n")
        f.write("#p ")
        f.write(option1)
        f.write(" ")
        f.write(optdft)
        f.write("¥n¥n")
        f.write(str(comment))
        f.write("¥n¥n")
        f.write(str(charge_spin[0])+" "+str(charge_spin[1])+"¥n")
        for i in range(len(atomarray)):
```

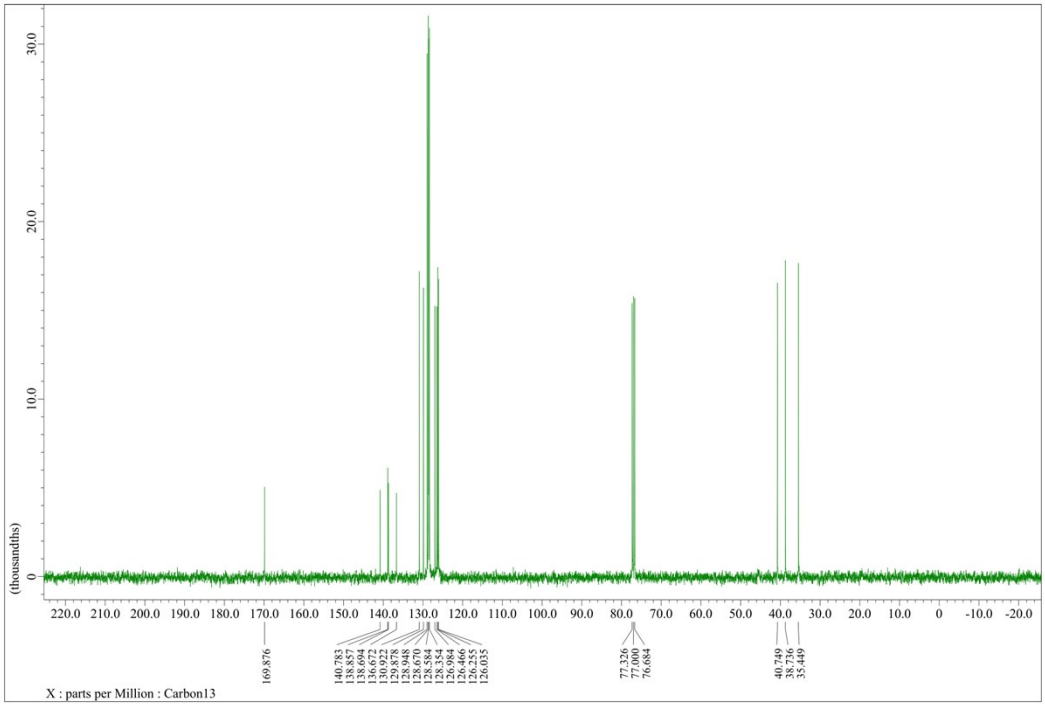
```
            f.write(str(atomarray[i]))
            if len(str(atomarray[i])) == 1:
                f.write(" ")
            f.write("      ")
            for j in range(3):
                if coordinates[i][j] >= 0:
                    f.write(" ")
                f.write(str("{0:8f}".format(coordinates[i][j])))
                f.write("    ")
            f.write("¥n")
        f.write("¥n")
        if modredundant == "ON":
            f.write(str(restriction))
            f.write("¥n¥n")
        f.flush()
        f.close()

        return 0


################################       rulechk.py       ##############################
#
#       written by Hiroaki Kurouchi
#
#############################################################################

import numpy as np
import math
import copy

# A function to measure a distance of atoms
# atom1 and atom2 are 3-dimentional array
def distance(atom1,atom2):
        distance_sq = 0.0
        for i in range(3):
            distance_sq += (atom1[i]-atom2[i])**2
        distance = distance_sq ** 0.5

        return distance

# A function to check weather the candidate structure doesn't violate the rule
def distchk(newcoordinates,acceptrule):
        distance_check = 0 # 0 is "no problem :)"
        if not acceptrule[0][0] == 0:
            for i in range(len(acceptrule)):
                bond_length = distance(newcoordinates[int(acceptrule[i][0])],
                                       newcoordinates[int(acceptrule[i][1])])
                if acceptrule[i][2].upper() == "L" or acceptrule[i][2].upper() == "LONGER":
                    if bond_length < float(acceptrule[i][3]):
                        distance_check = 1
                elif acceptrule[i][2].upper() == "S" or acceptrule[i][2].upper() == "SHORTER":
                    if bond_length > float(acceptrule[i][3]):
                        distance_check = 1

        return distance_check
```

*Caution
Confprog program suite is provided "as is" and without any warranty express or implied. The user assumes all risks of using these programs.

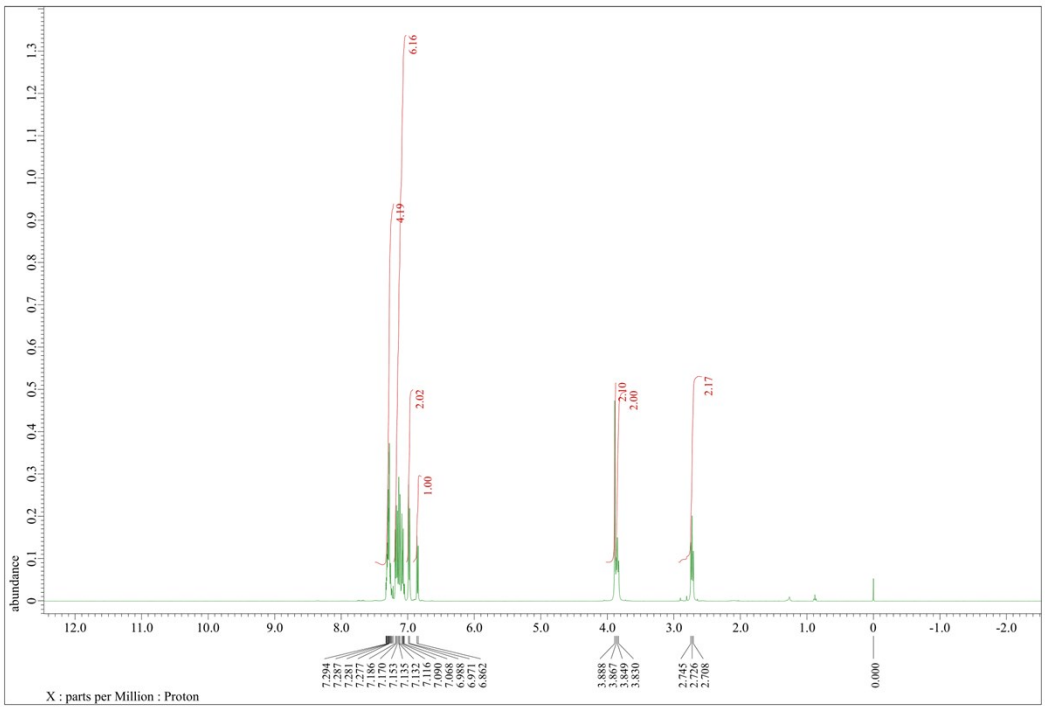
6. **NMR spectra of new compounds**

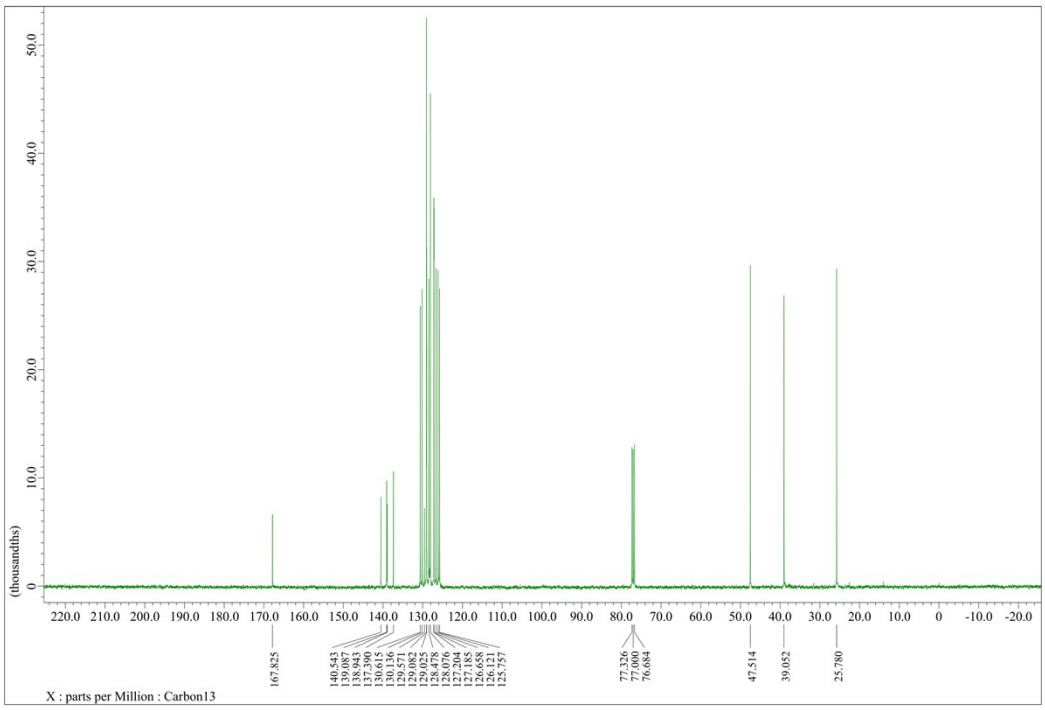
15a (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C), water (1.6 ppm for ^{1}H)



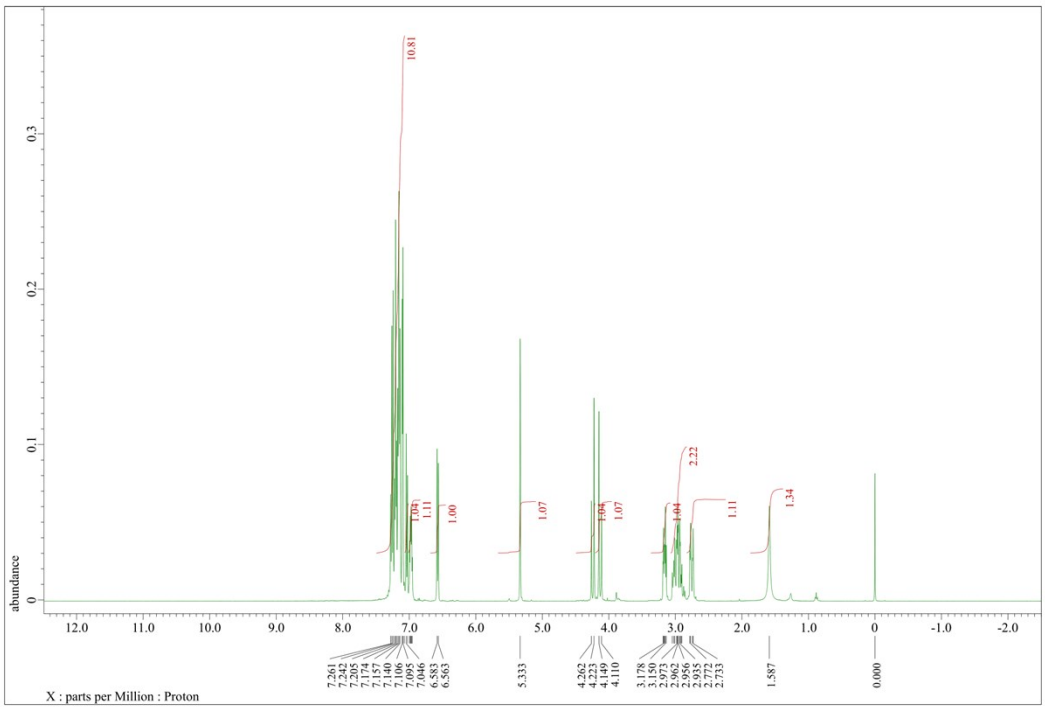

(thousandths)
30.0
20.0
10.0
0
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
169.876
140.783
138.857
136.644
136.672
130.922
129.878
128.948
128.670
128.584
128.354
126.984
126.466
126.255
126.035
77.326
77.000
76.684
40.749
38.736
35.449
X : parts per Million : Carbon13

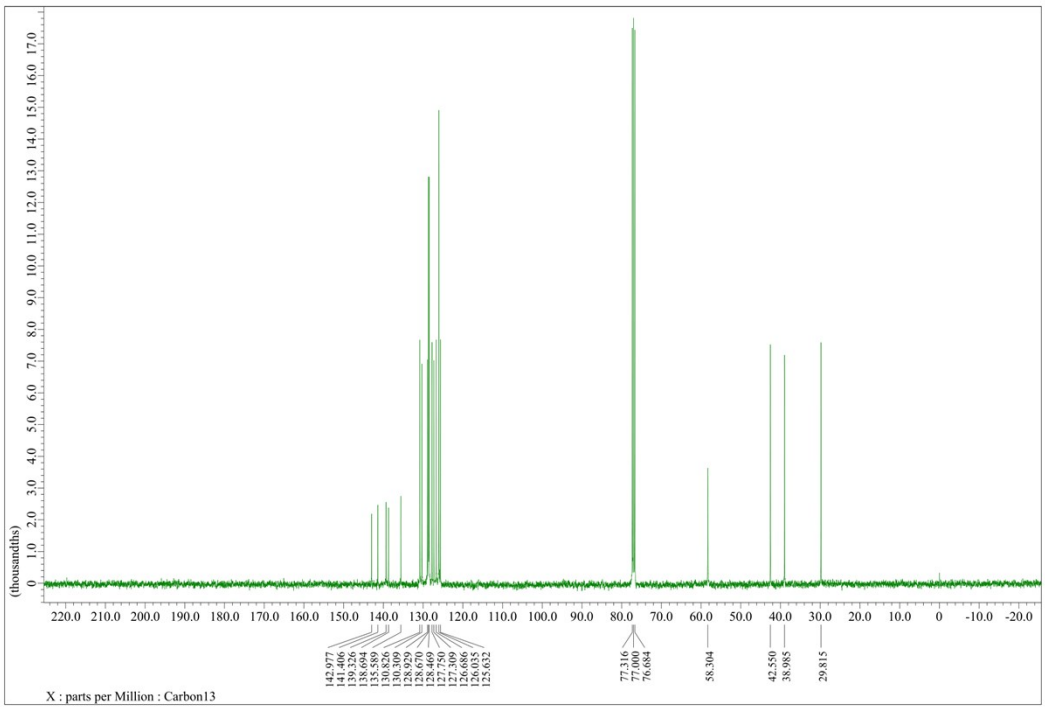
17a (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



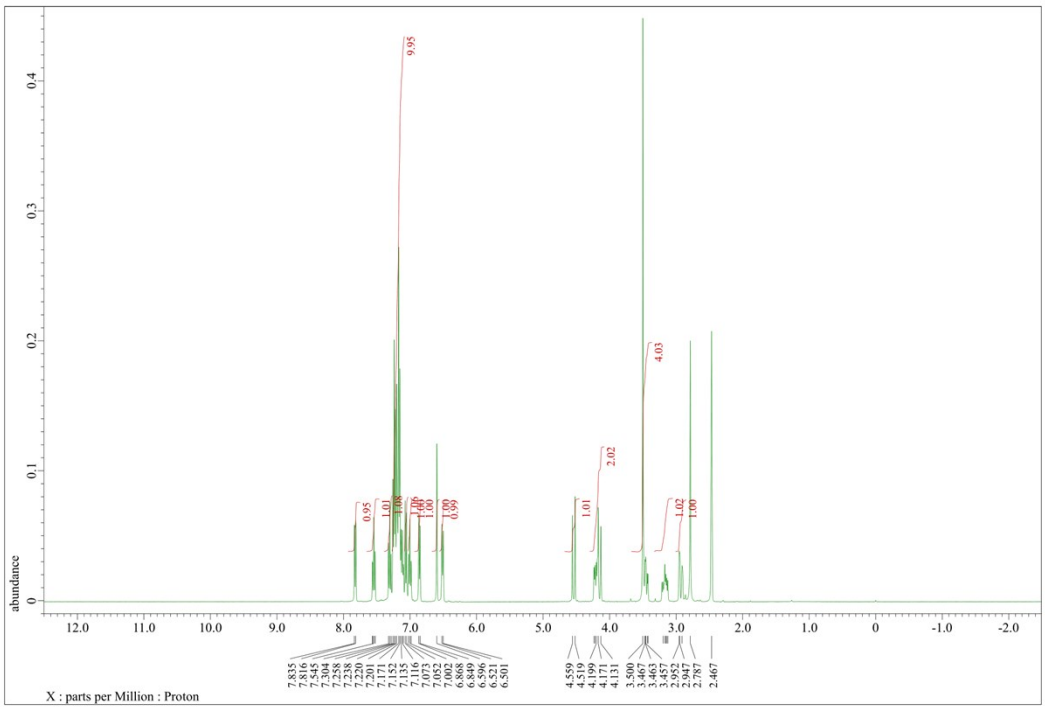


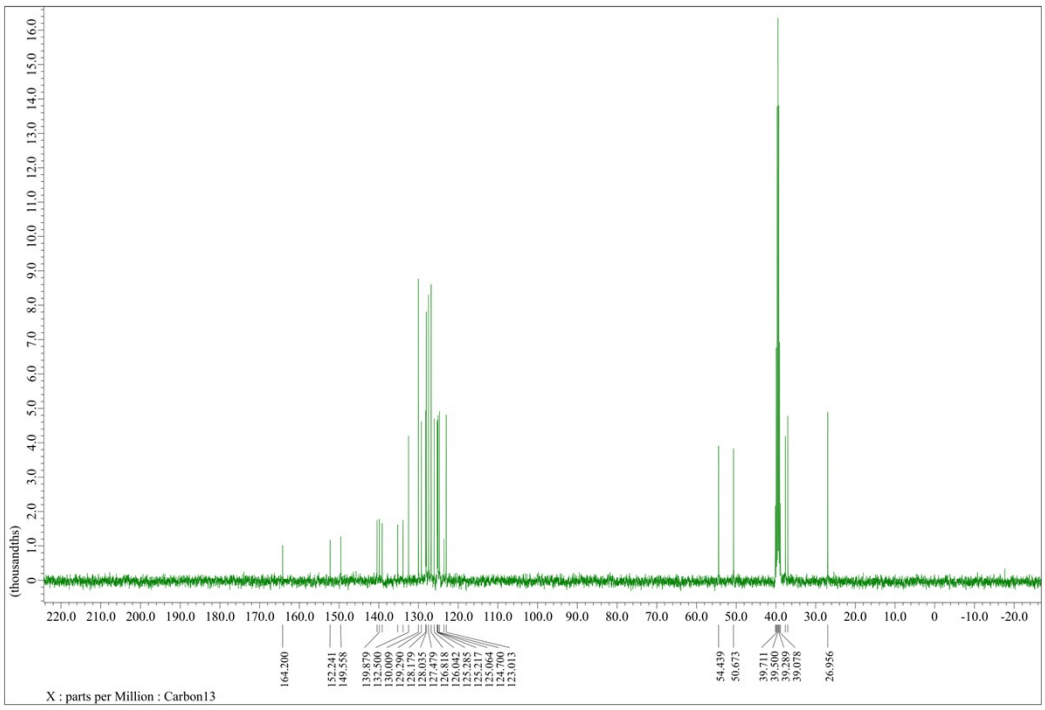
18a (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



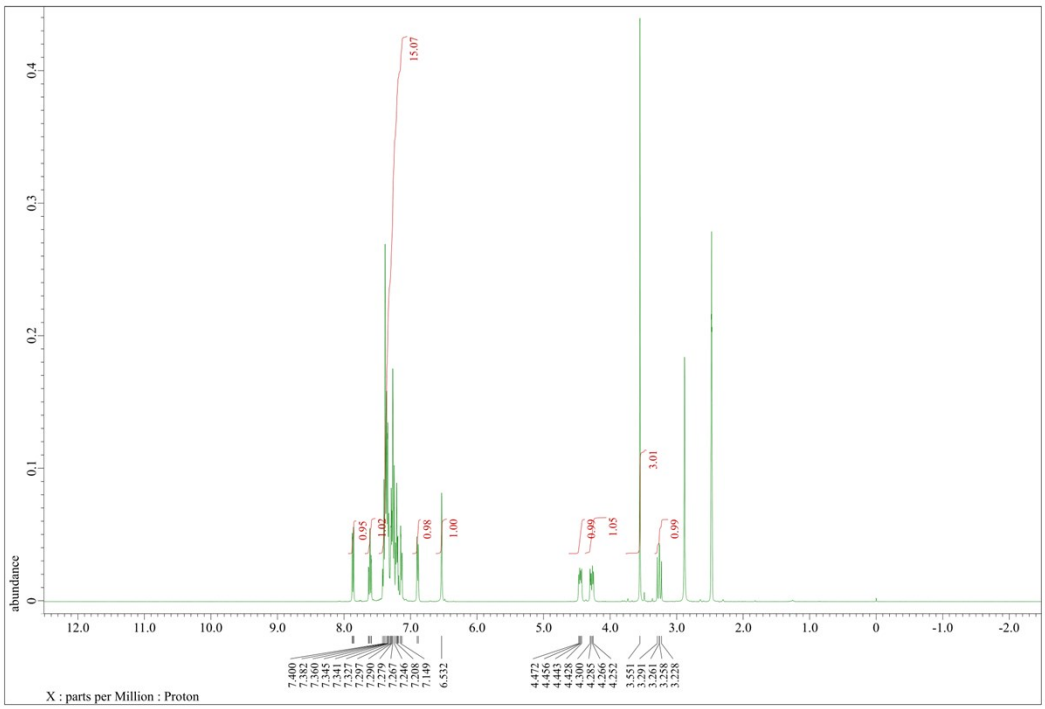


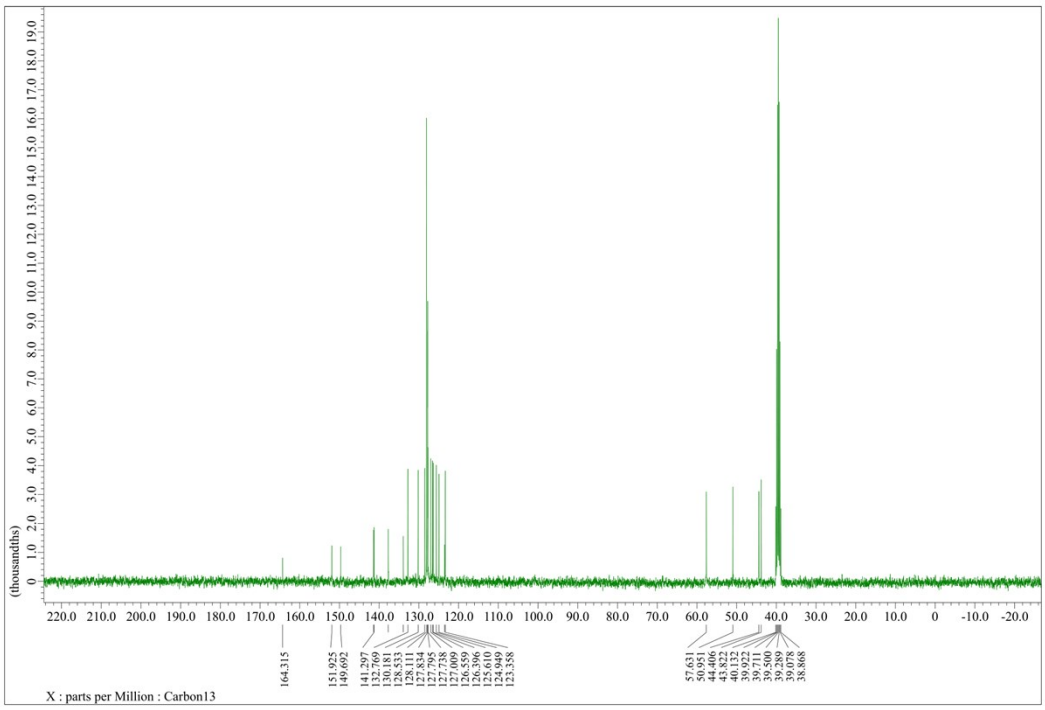
1a (Solvent: DMSO-d_6, 140 °C)
Solvent peak: DMSO (2.5 ppm for ^{1}H, 39.5 ppm for ^{13}C), water (2.8 ppm for ^{1}H)



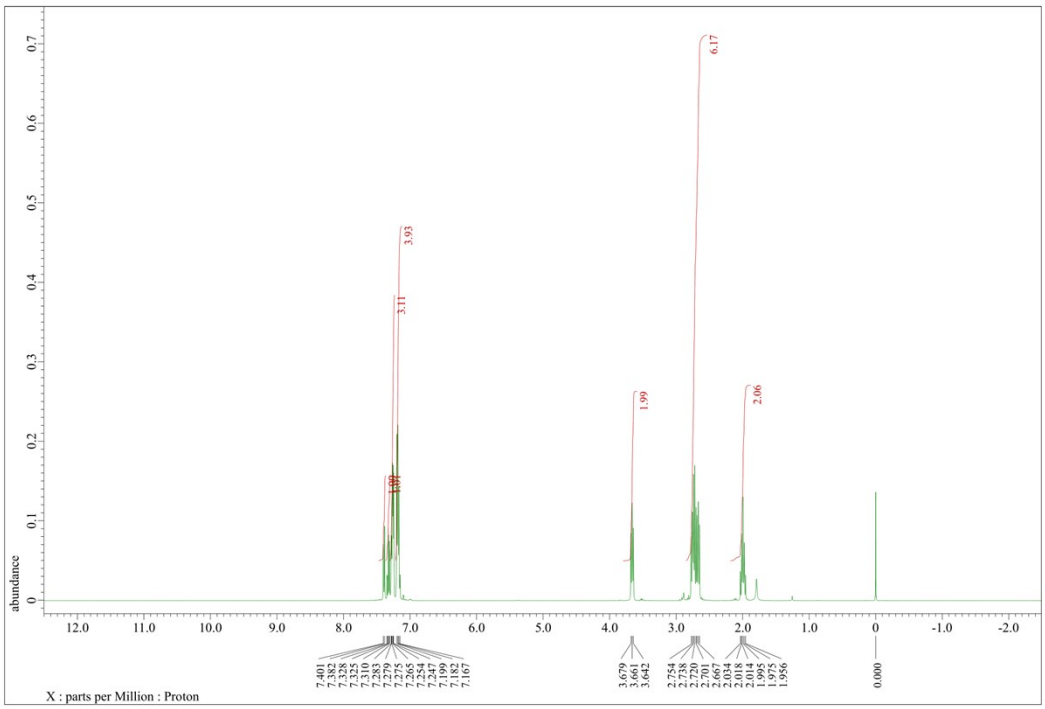


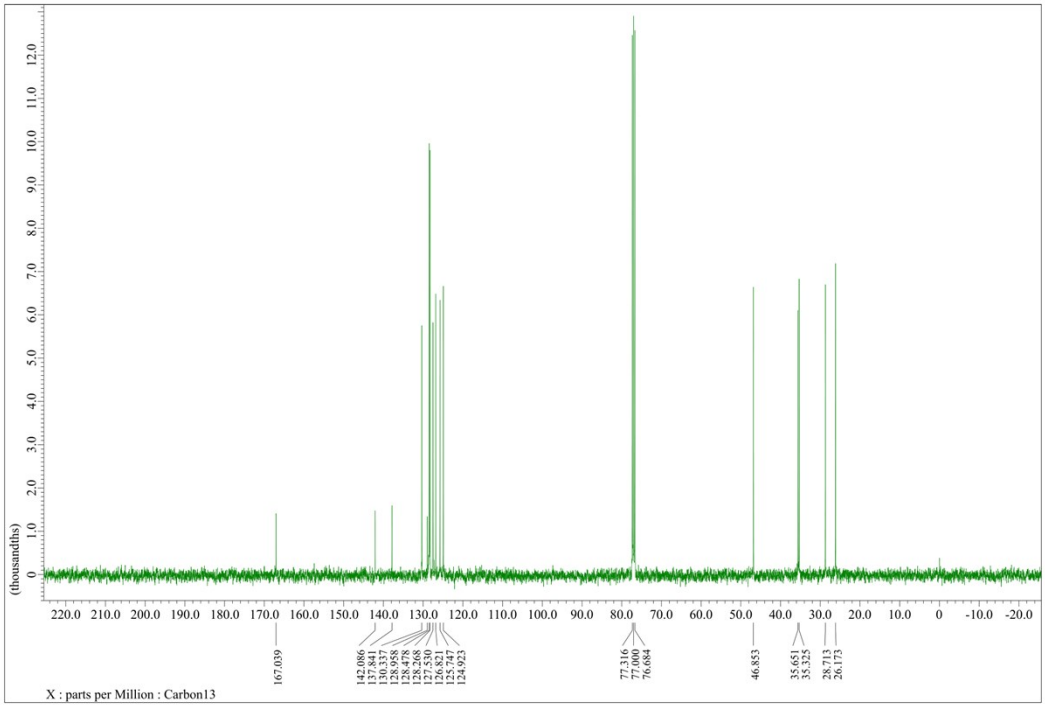
1b (Solvent: DMSO-d_6, 120 °C)
Solvent peak: DMSO (2.5 ppm for ^{1}H, 39.5 ppm for ^{13}C), water (2.8 ppm for ^{1}H)



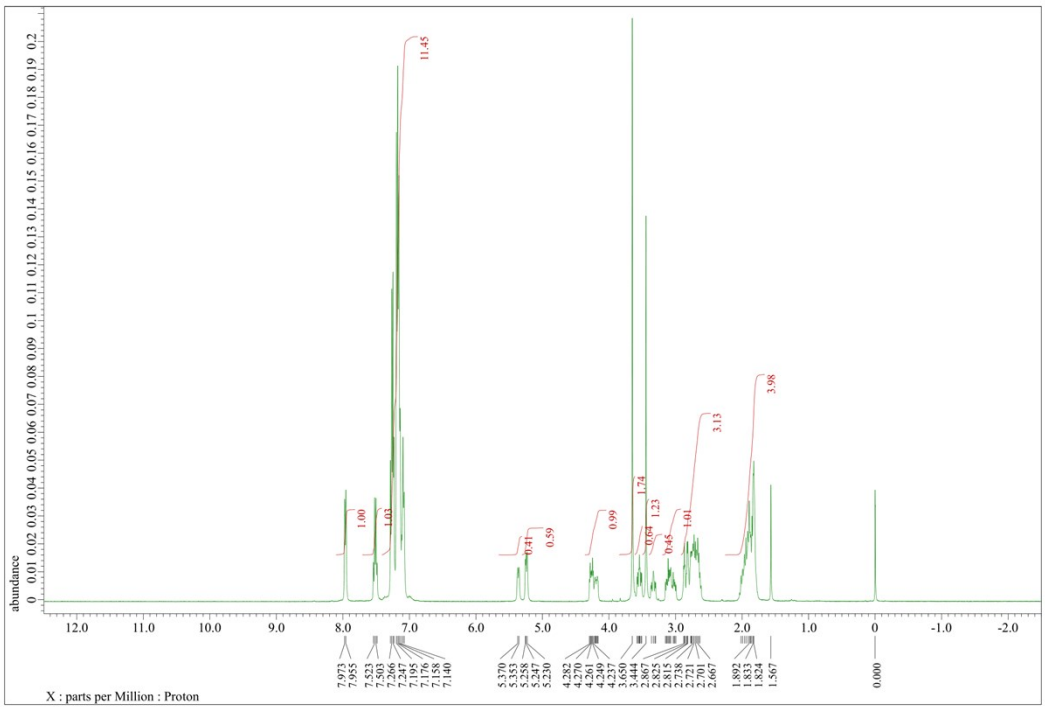


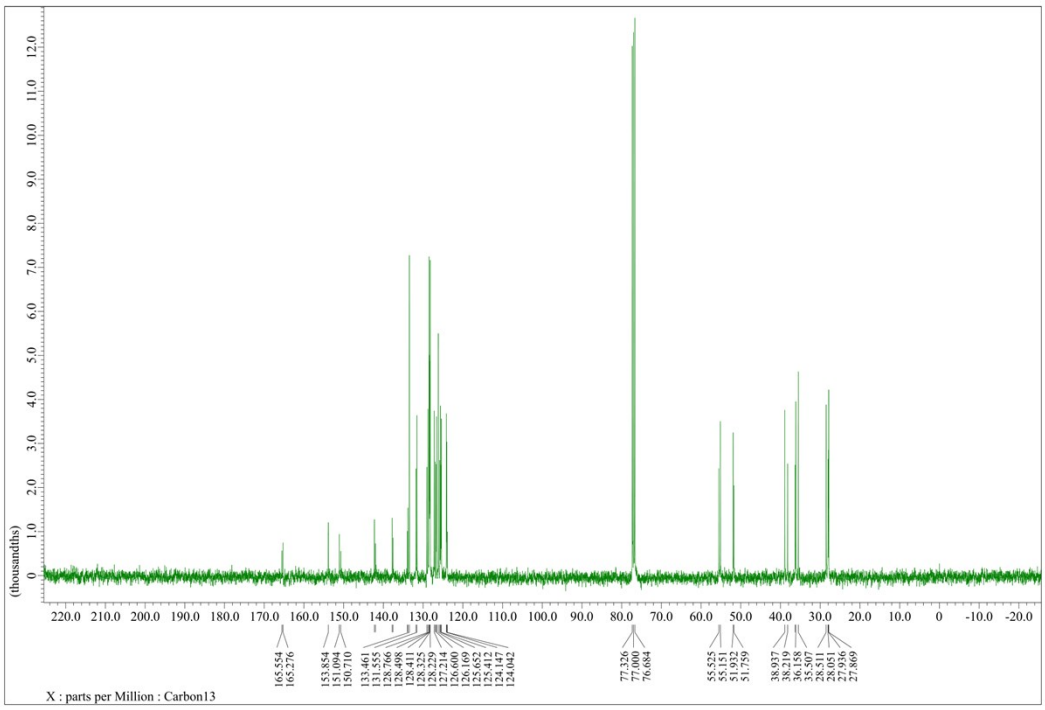
17c (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



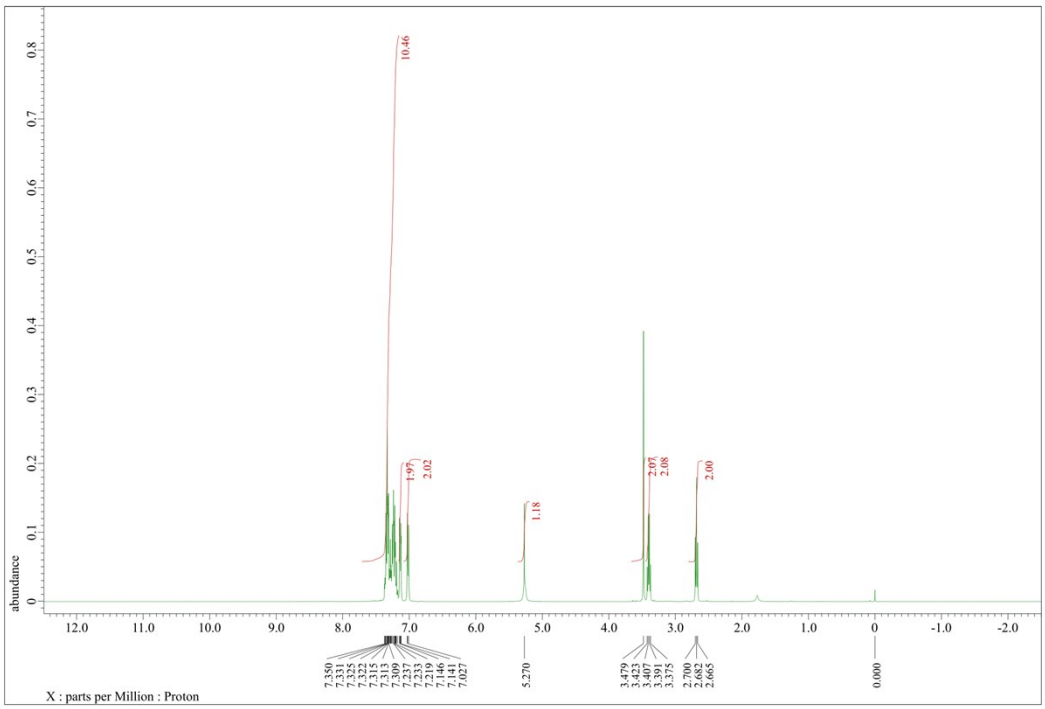


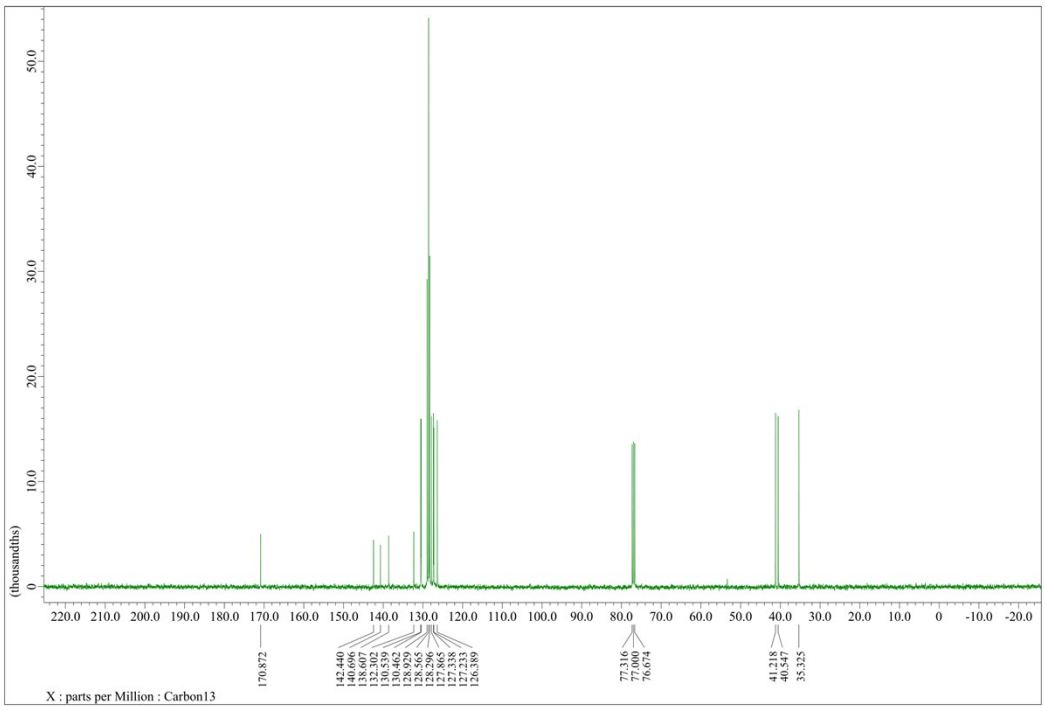
1c (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C), water (1.6 ppm for ^{1}H)



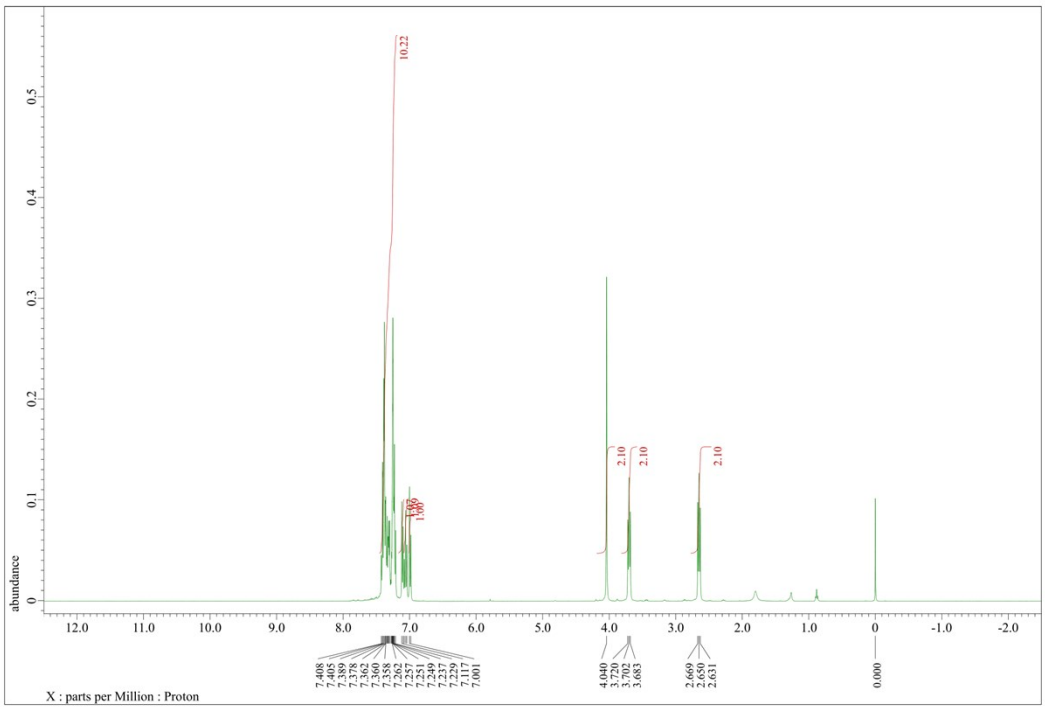


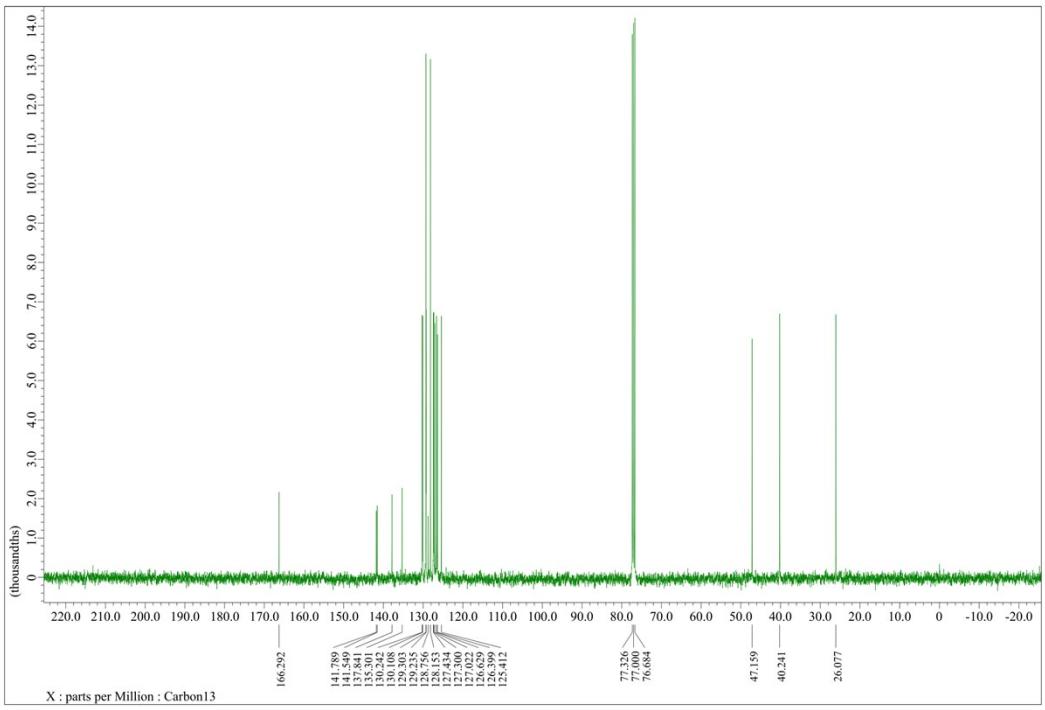
15d (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



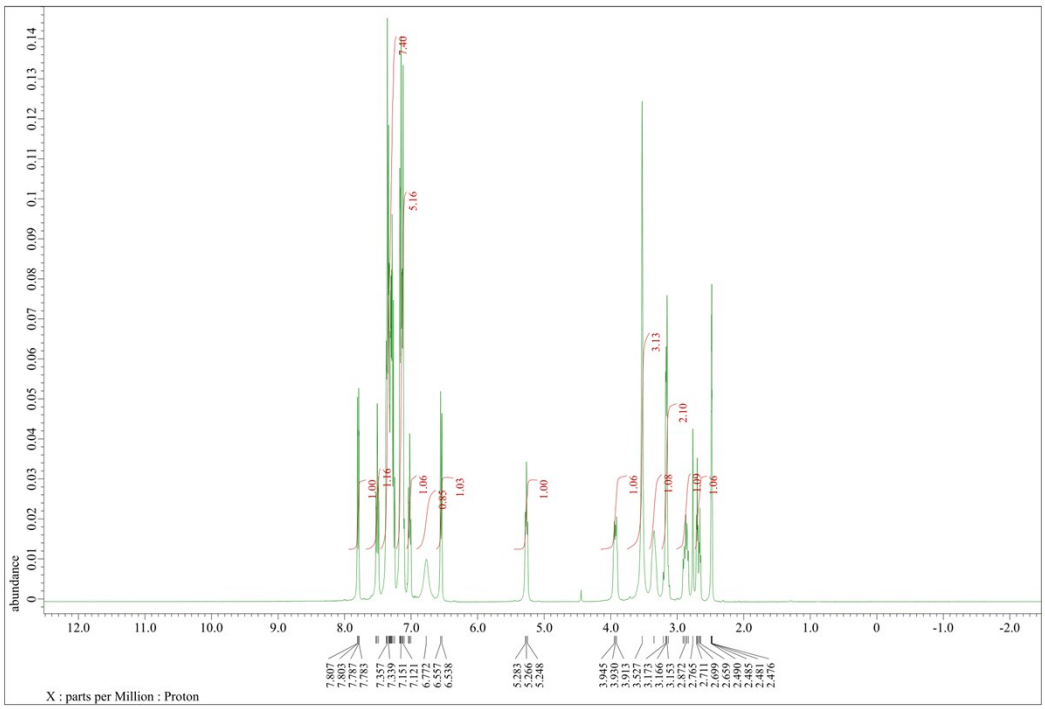


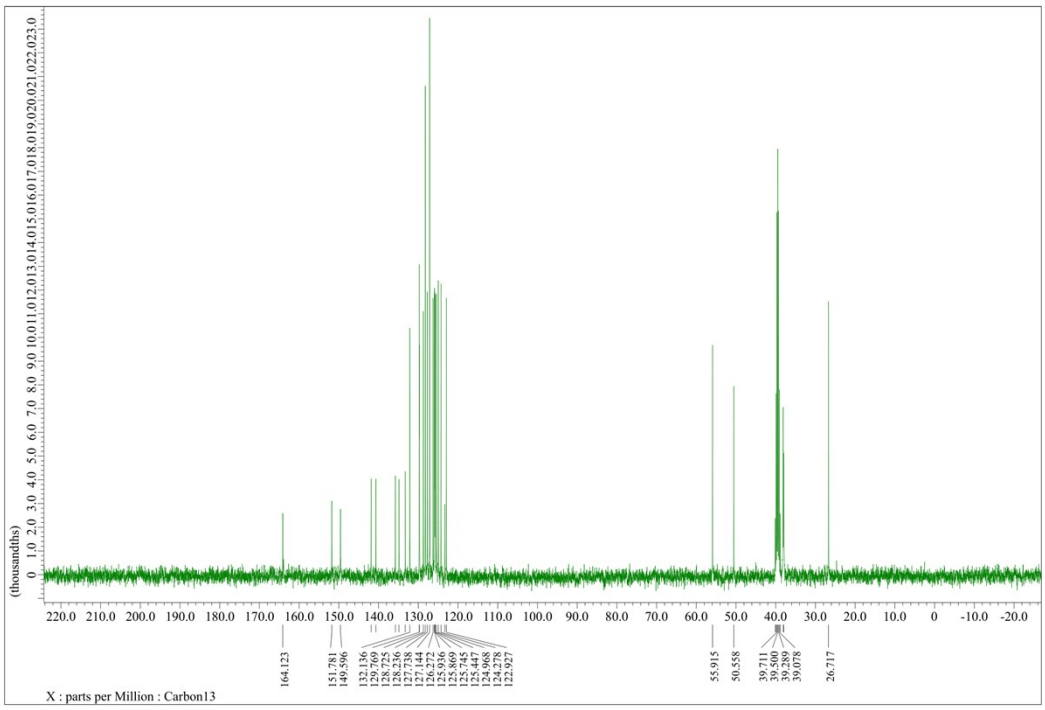
17d (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



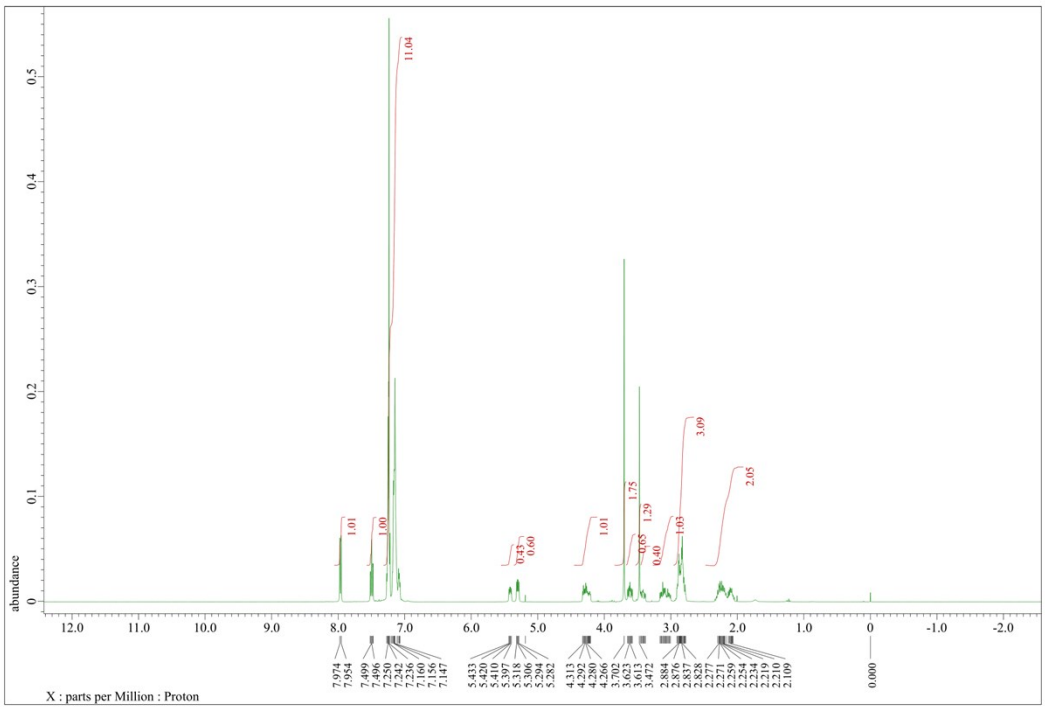


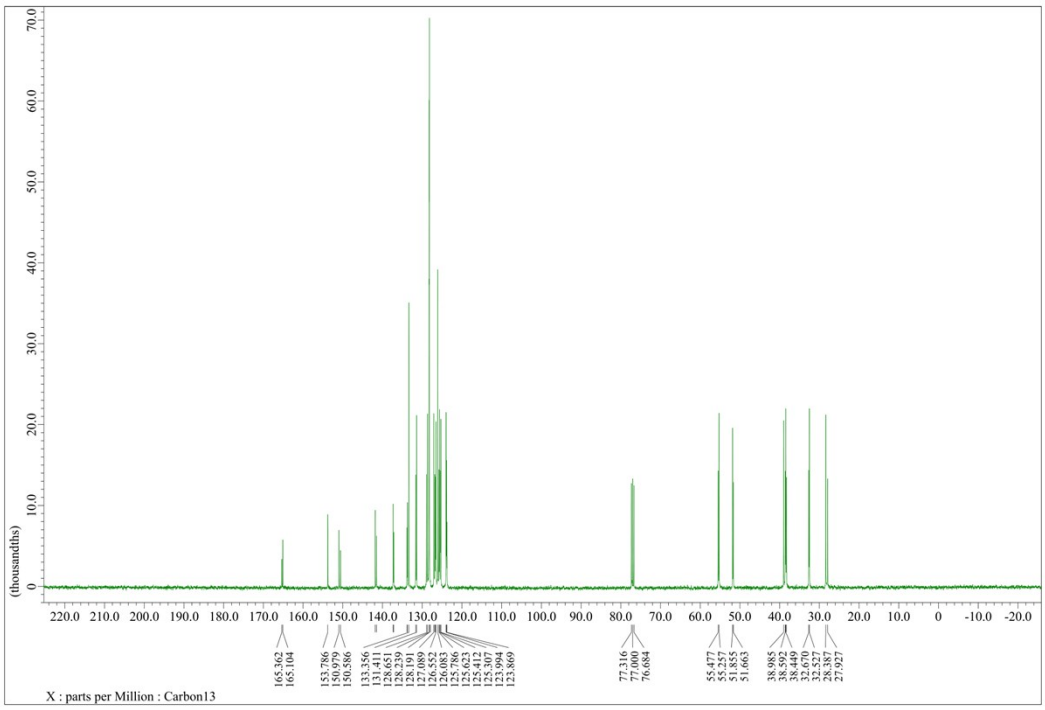
1d (Solvent: DMSO-d_6, 150 °C)
Solvent peak: DMSO (2.5 ppm for ^{1}H, 39.5 ppm for ^{13}C), water (2.8 ppm for ^{1}H)



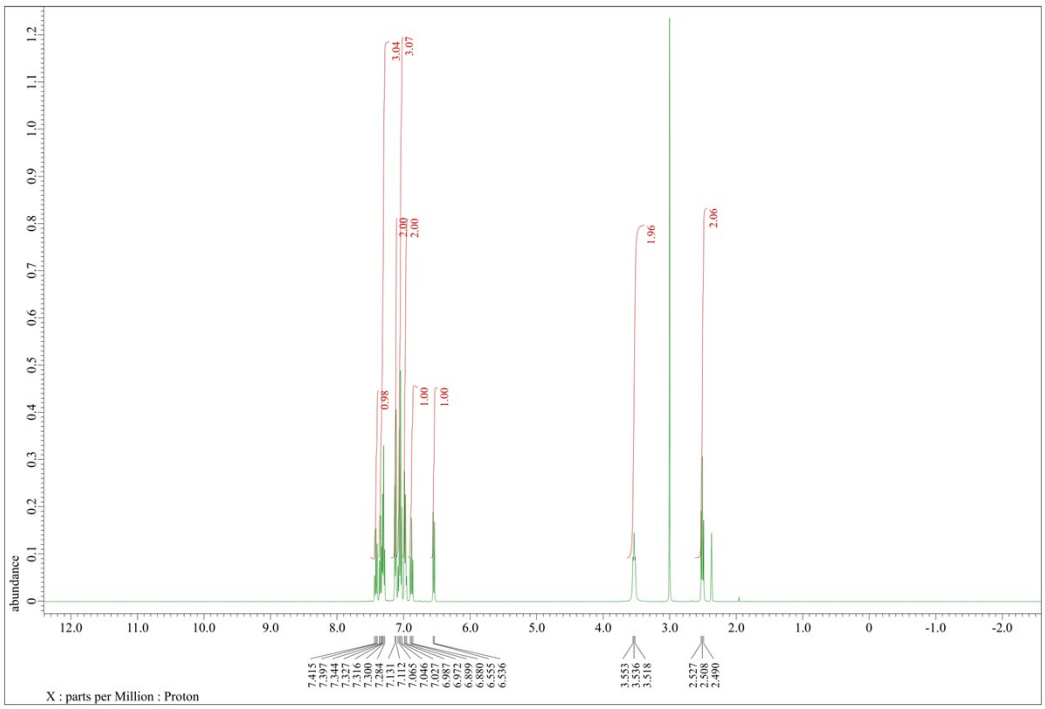


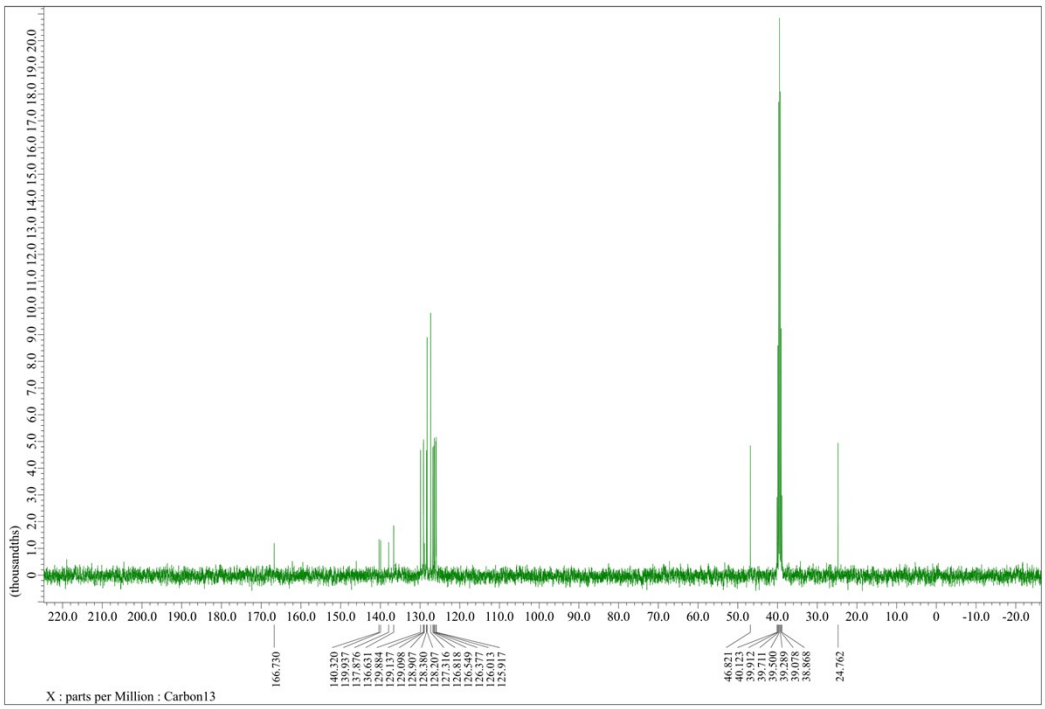
1e (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



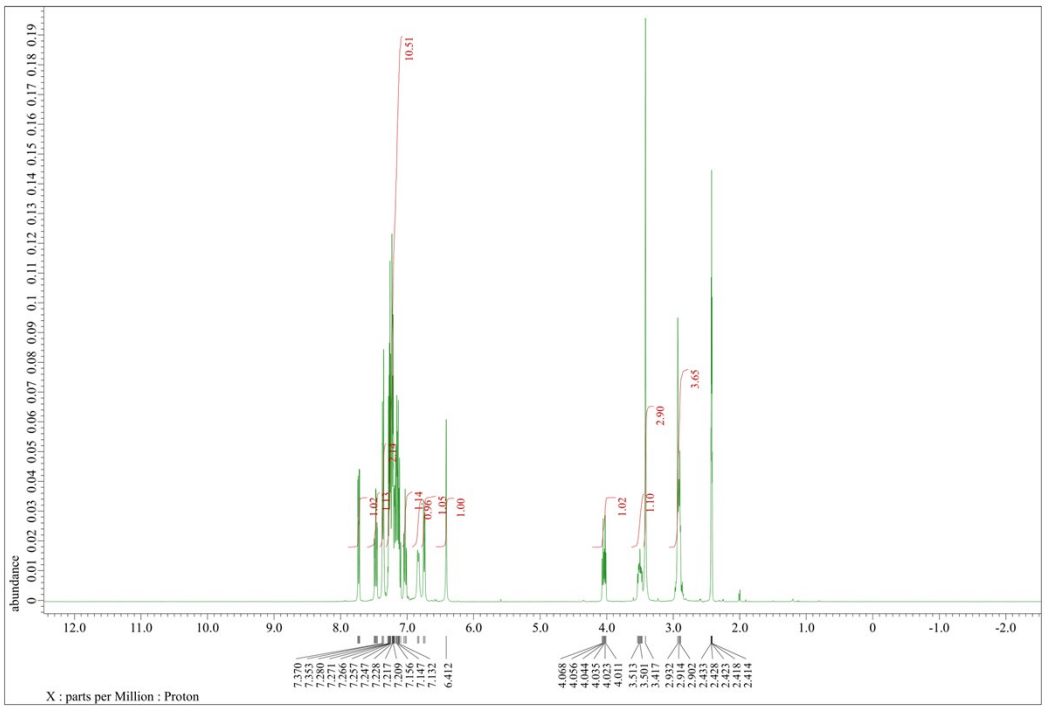


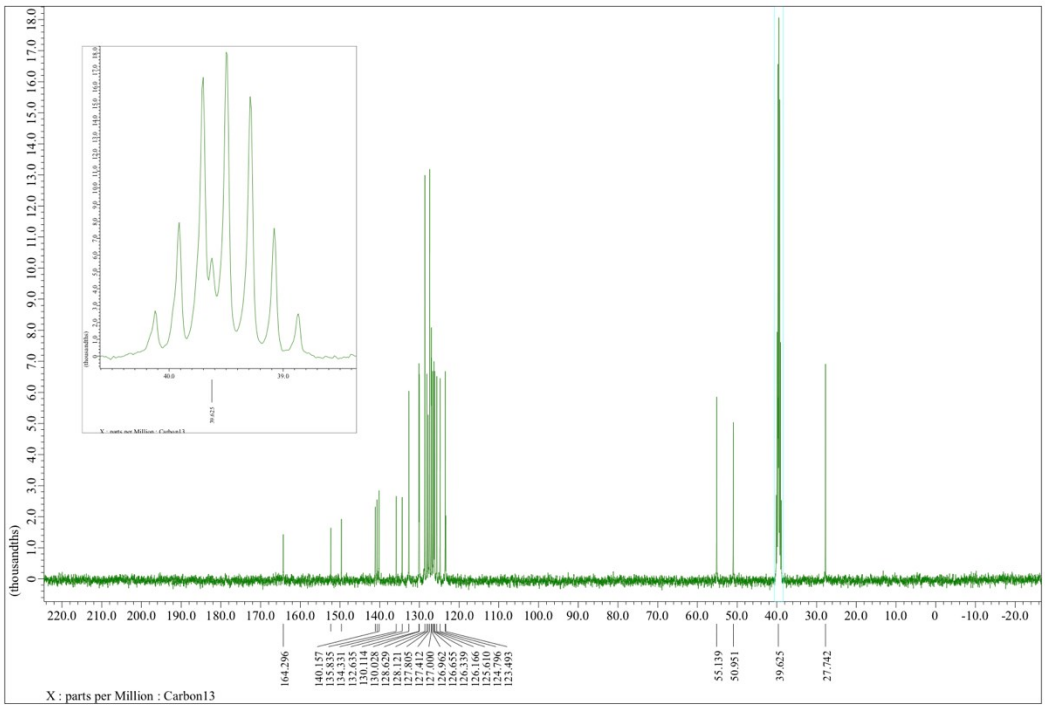
17f (Solvent: DMSO-d_6, 100 °C)
Solvent peak: DMSO (2.4 ppm for ^{1}H, 39.5 ppm for ^{13}C), water (3.0 ppm for ^{1}H)



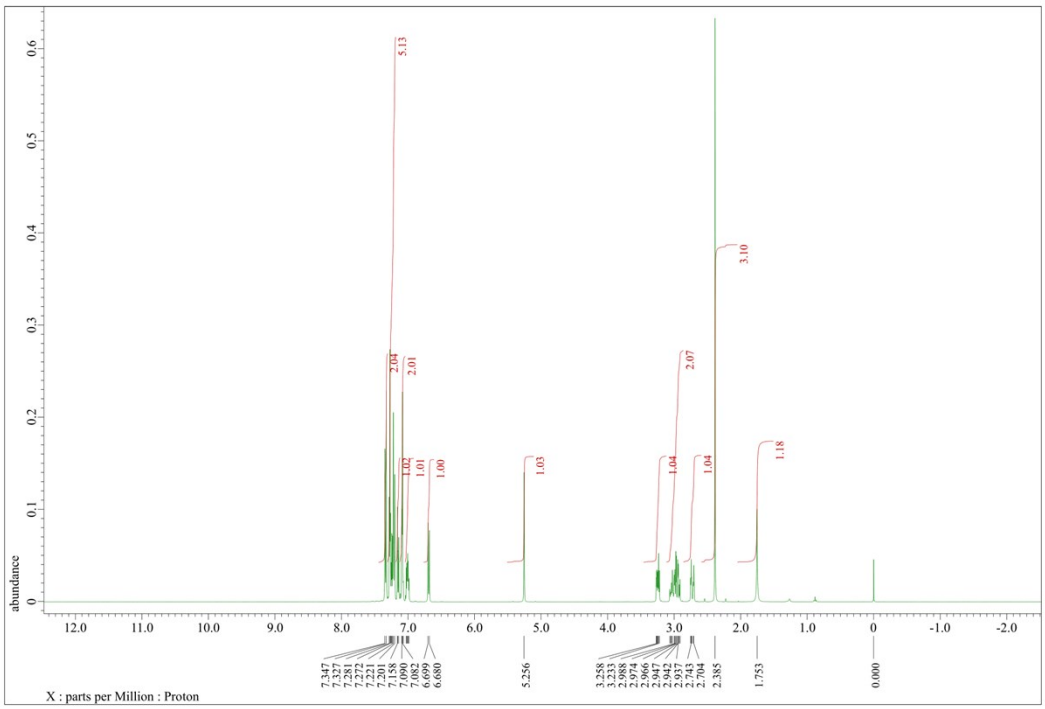


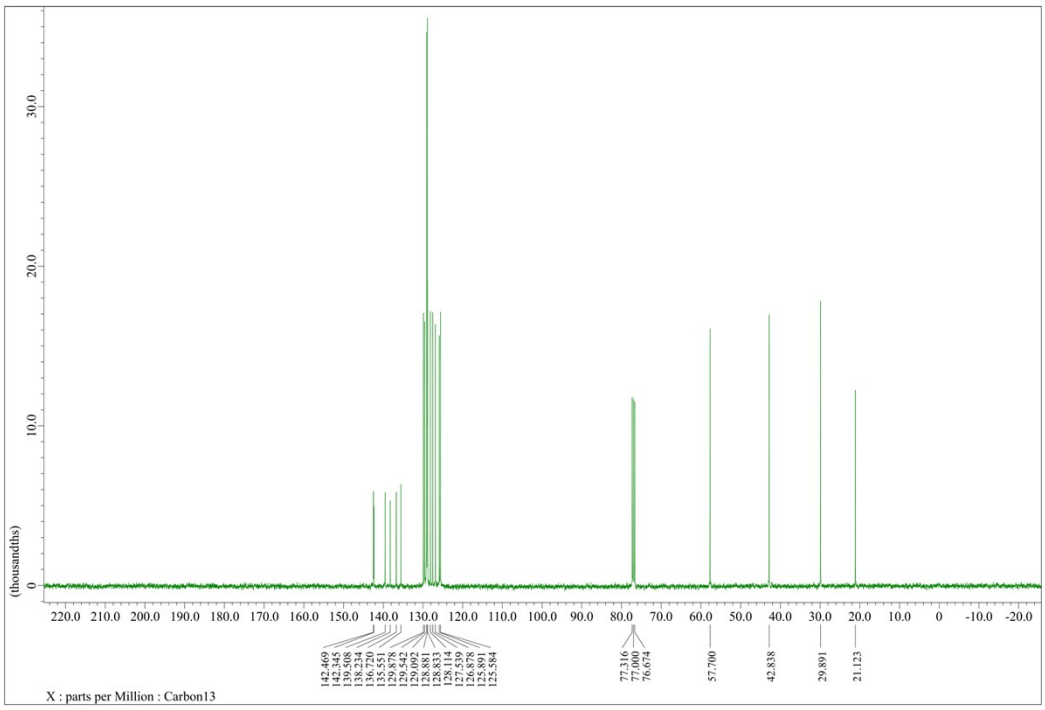
1f (Solvent: DMSO-d_6, 150 °C)
Solvent peak: DMSO (2.4 ppm for ^{1}H, 39.5 ppm for ^{13}C), water (2.9 ppm for ^{1}H)



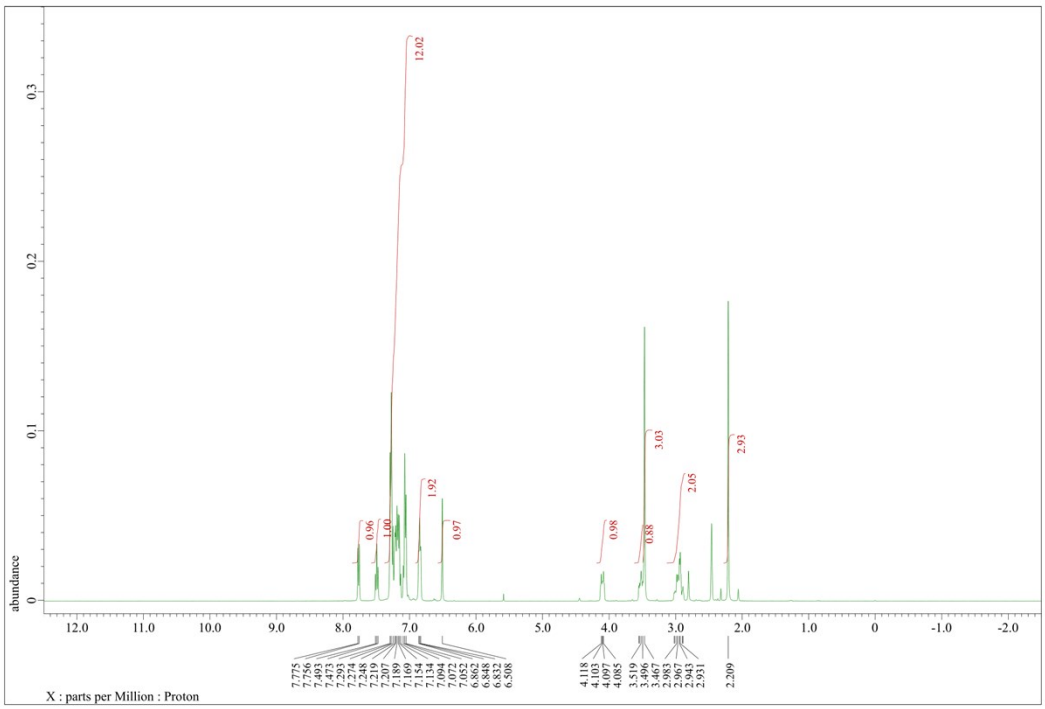


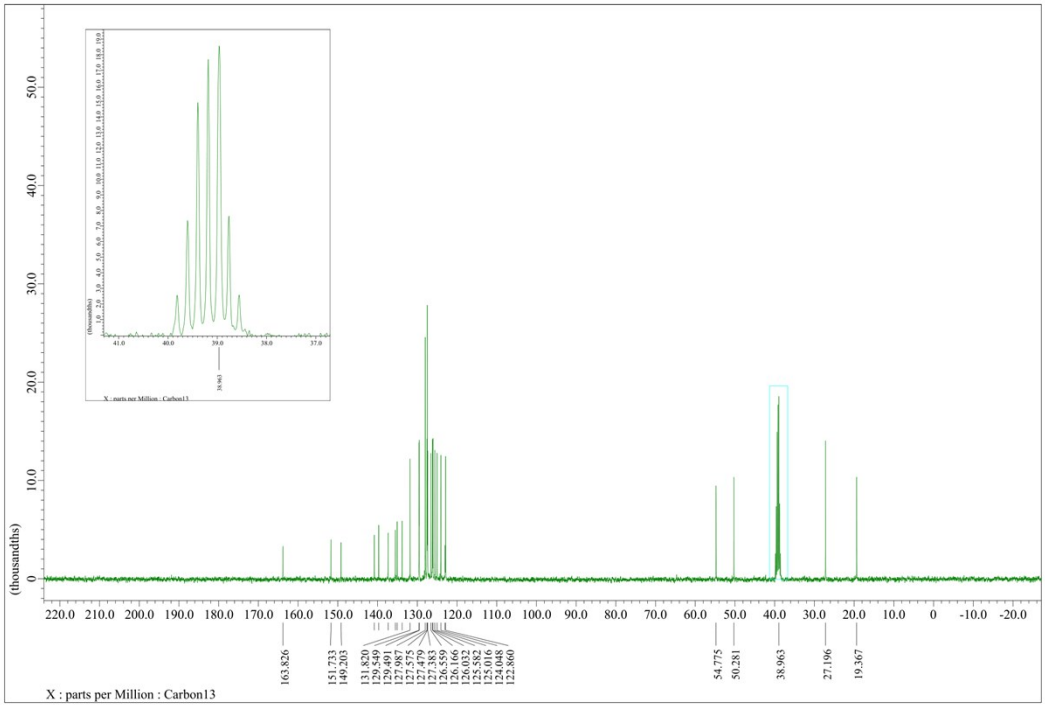
18g (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



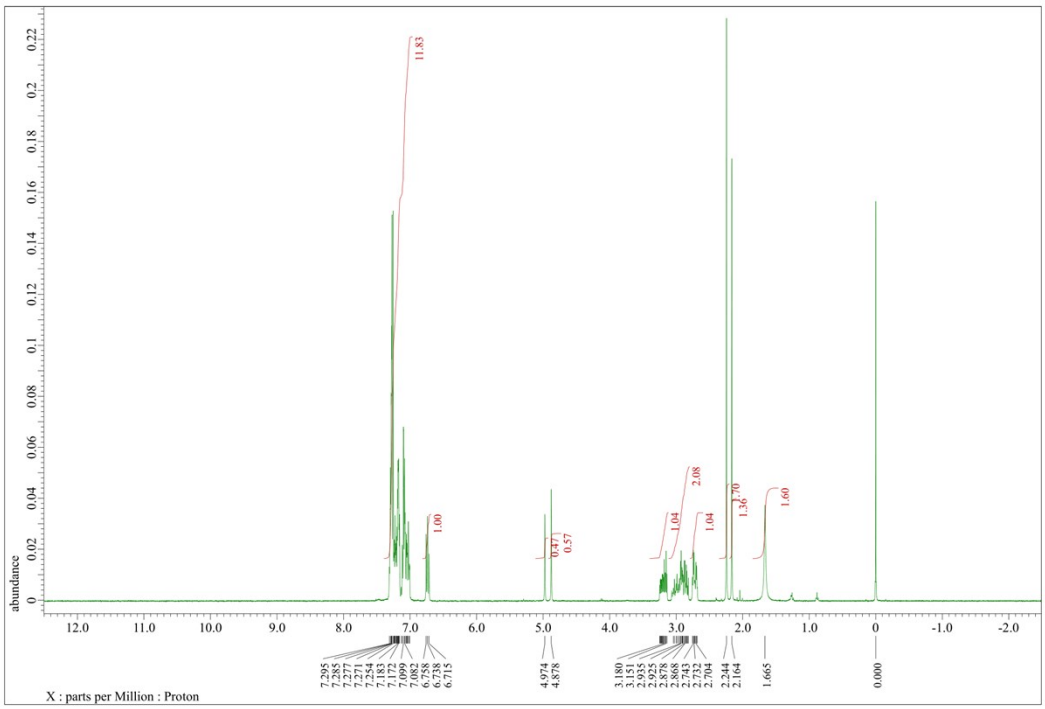


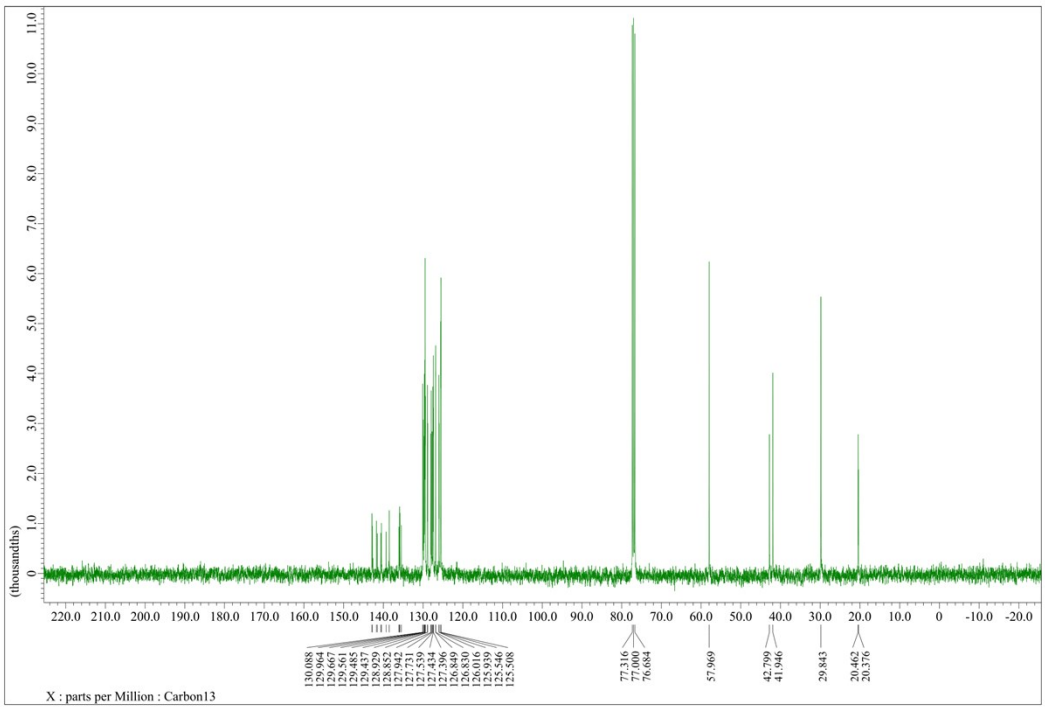
1g (Solvent: DMSO-d_6, 140 °C)
Solvent peak: DMSO (2.5 ppm for ^{1}H, 39.5 ppm for ^{13}C), water (2.8 ppm for ^{1}H)



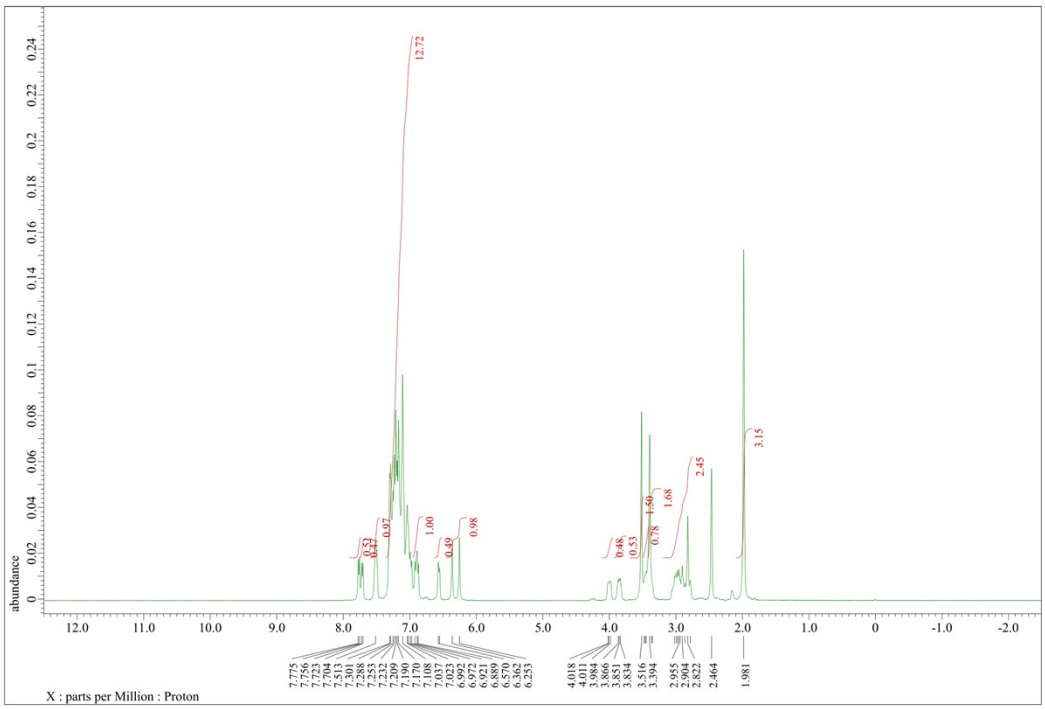


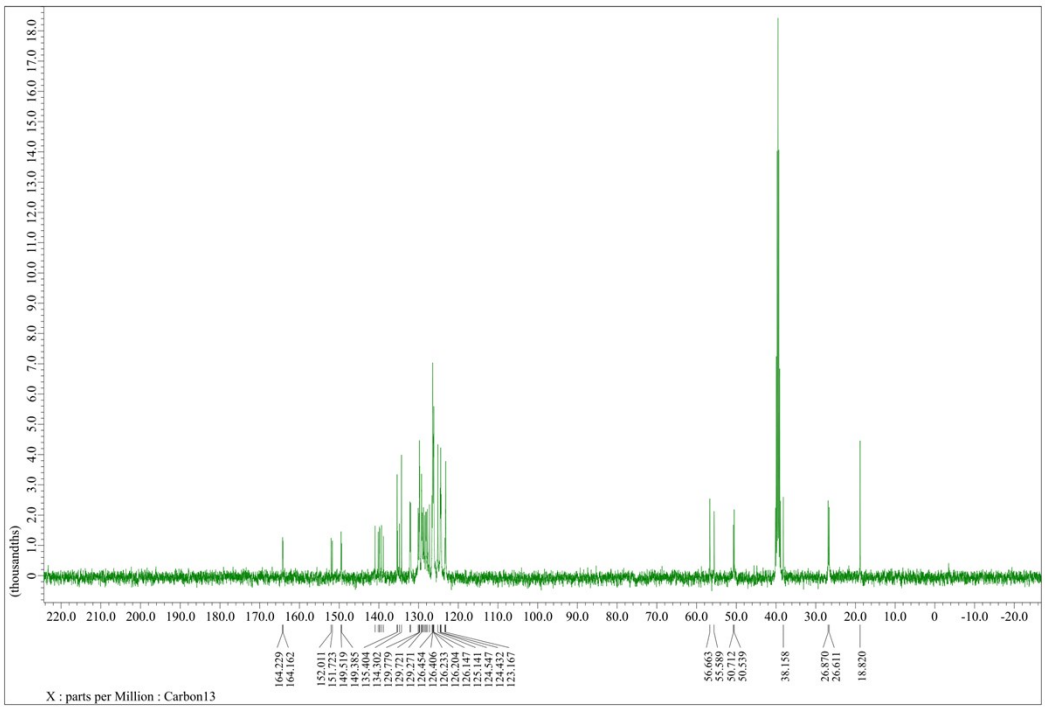
18h (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



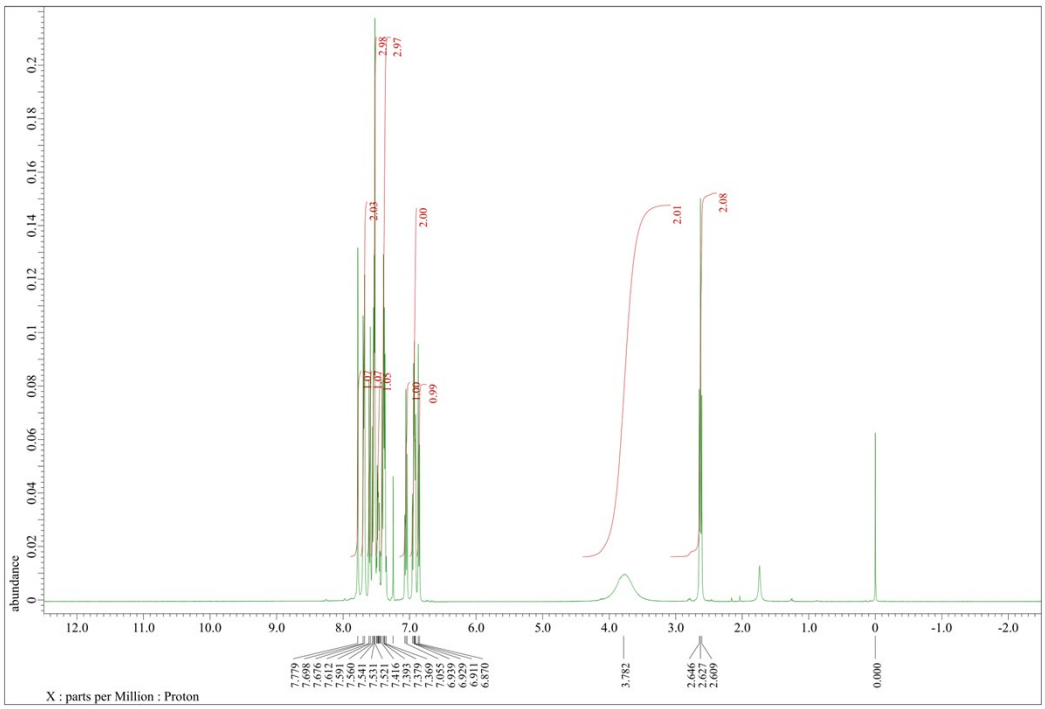


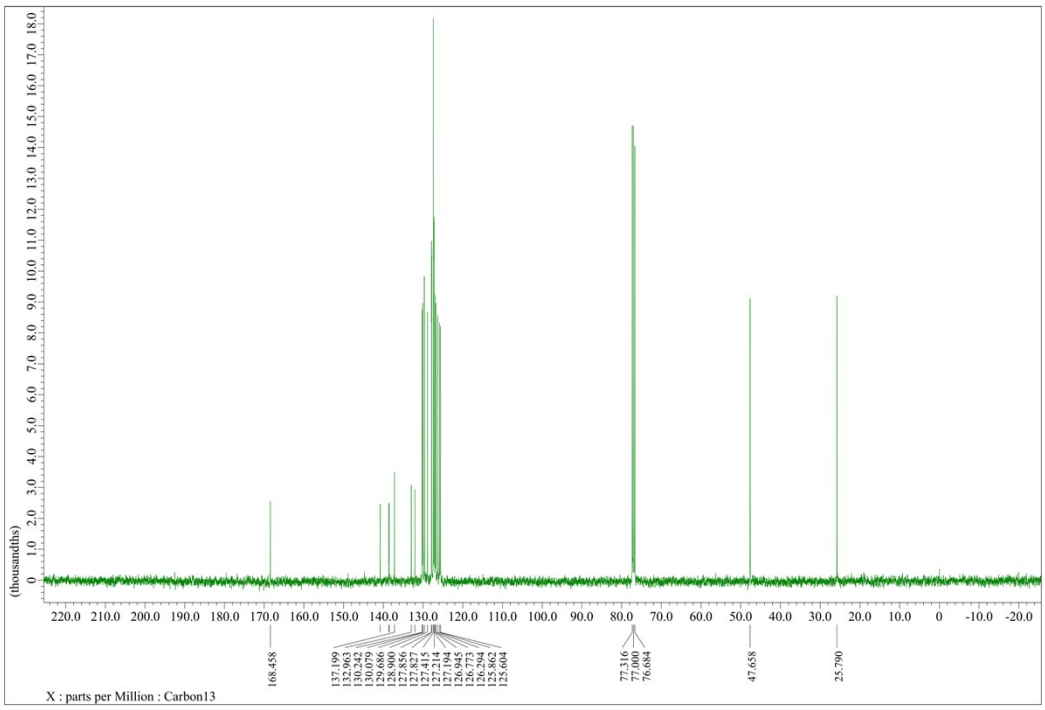
1h (Solvent: DMSO-d_6, 140 °C)
Solvent peak: DMSO (2.5 ppm for ^{1}H, 39.5 ppm for ^{13}C), water (2.8 ppm for ^{1}H)



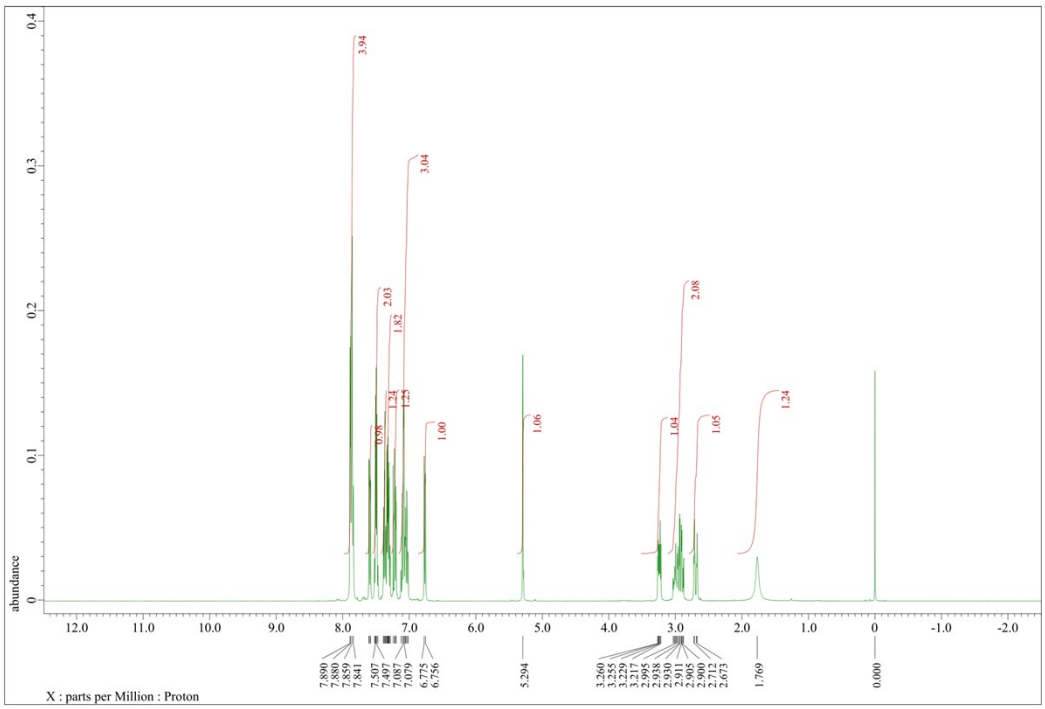


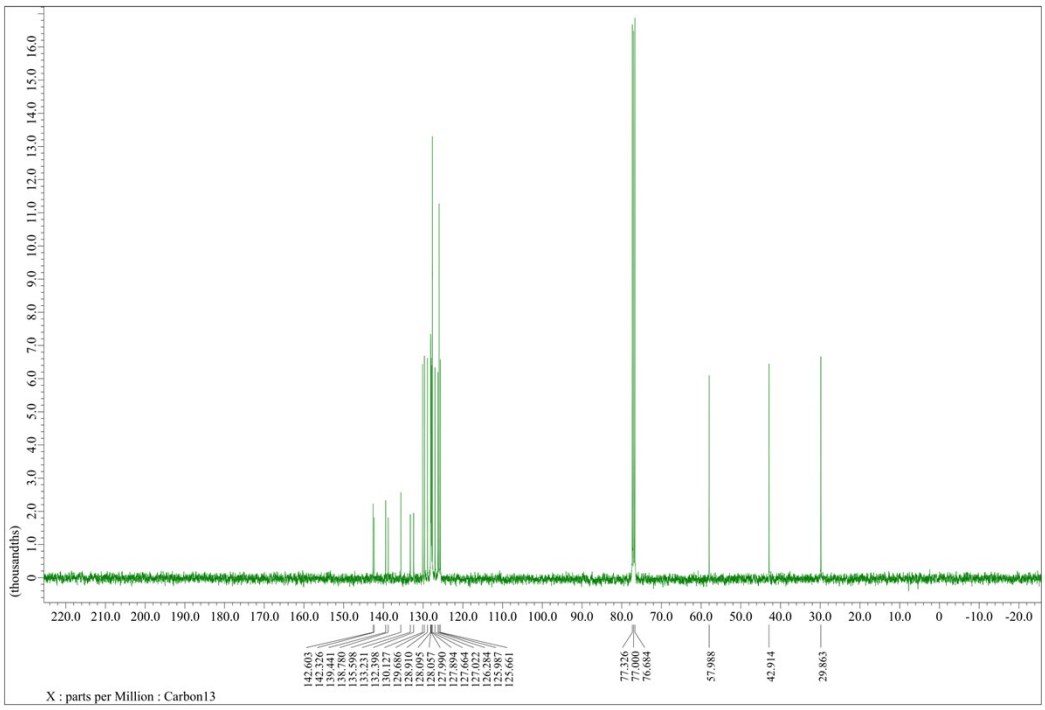
17i (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C), water (1.6 ppm for ^{1}H)



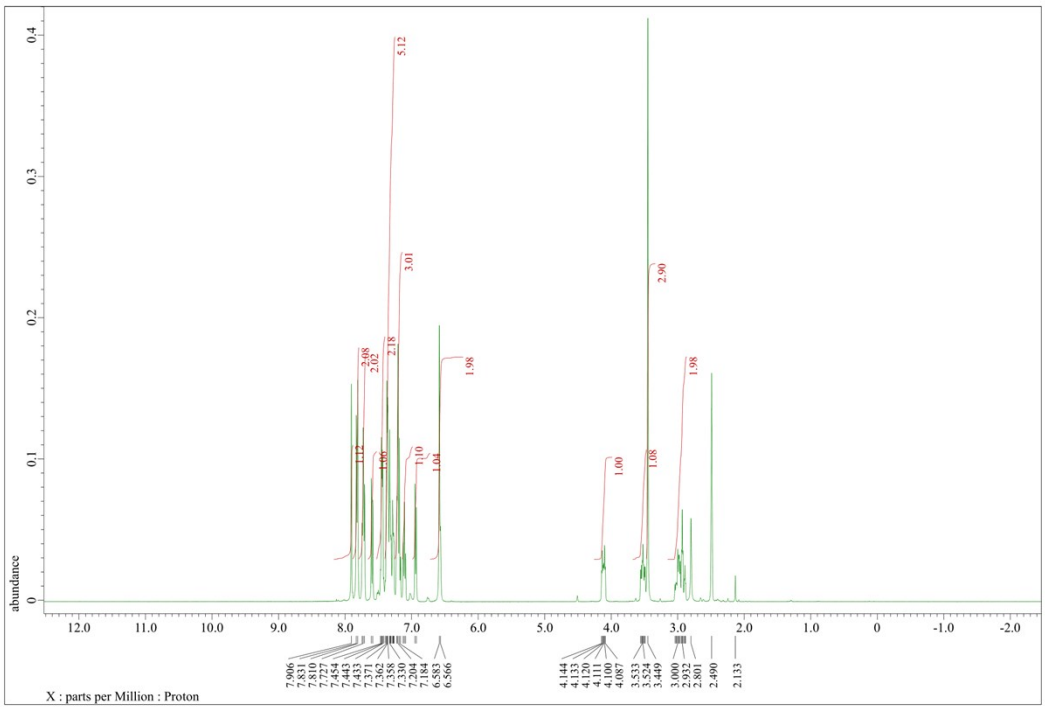


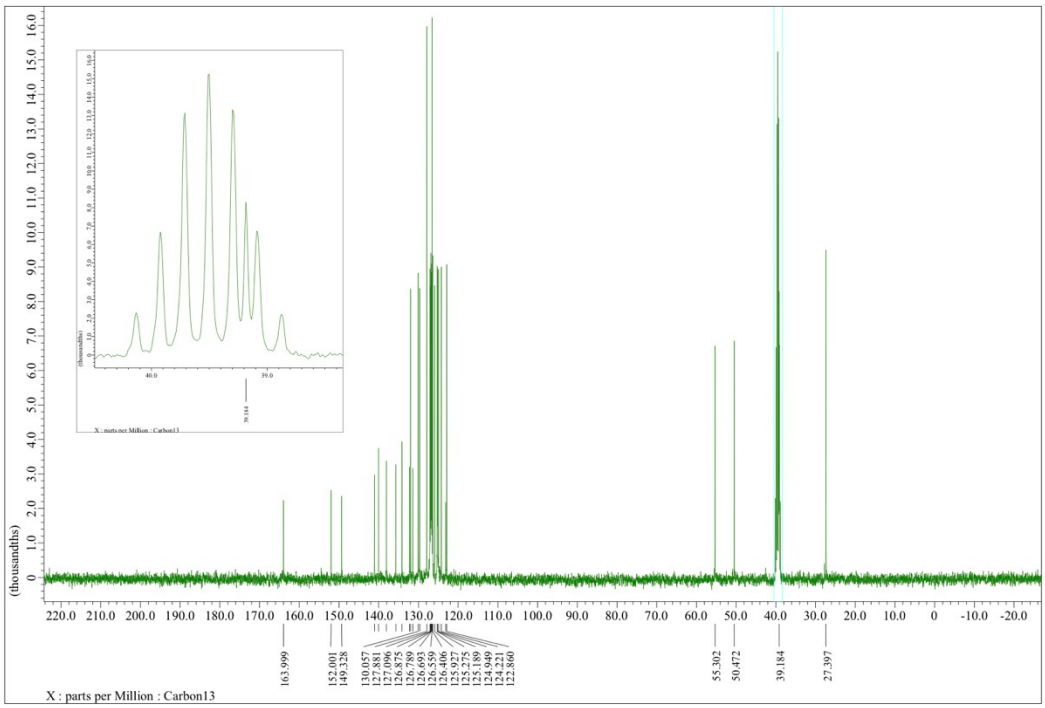
18i (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



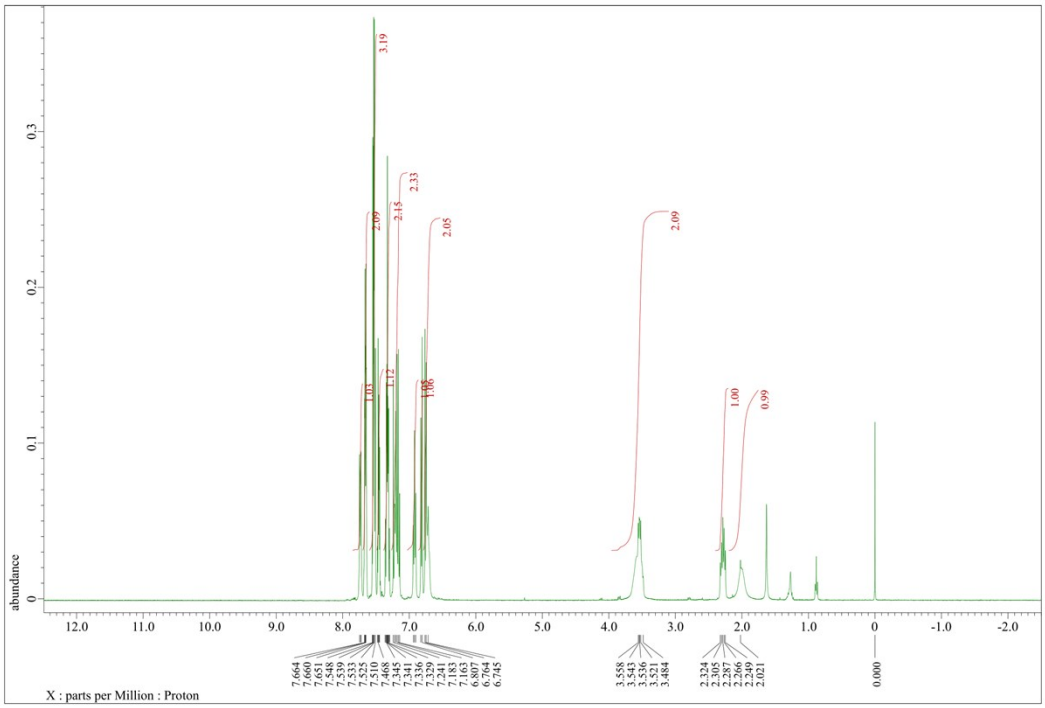


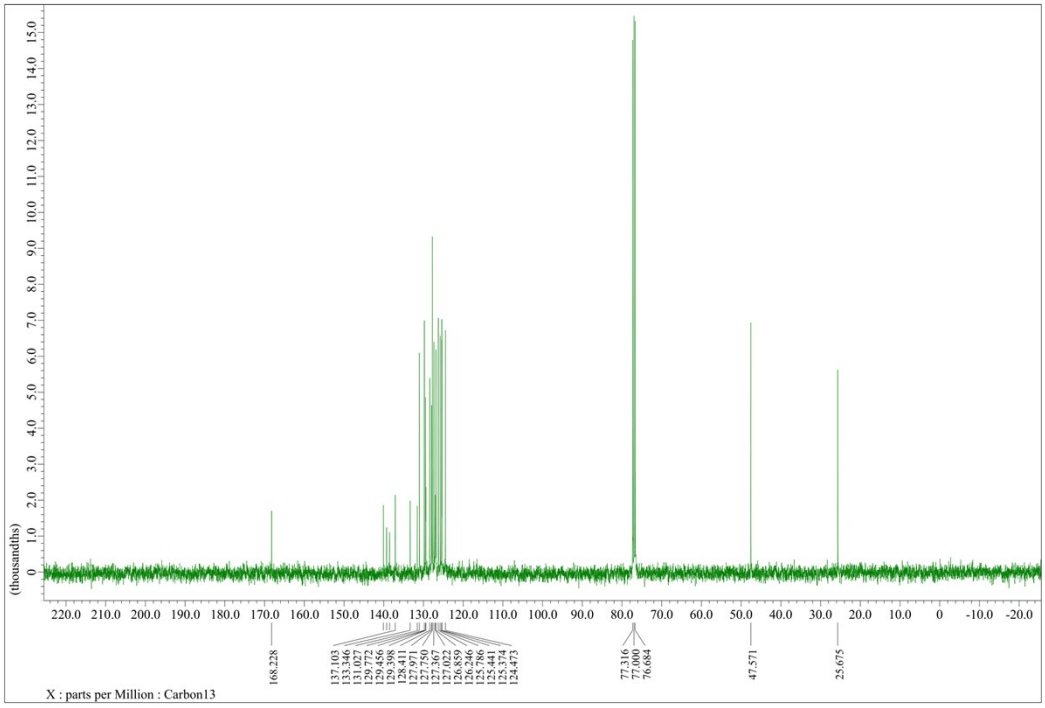
1i (Solvent: DMSO-d_6, 150 °C)
Solvent peak: DMSO (2.5 ppm for ^{1}H, 39.5 ppm for ^{13}C), water (2.8 ppm for ^{1}H)



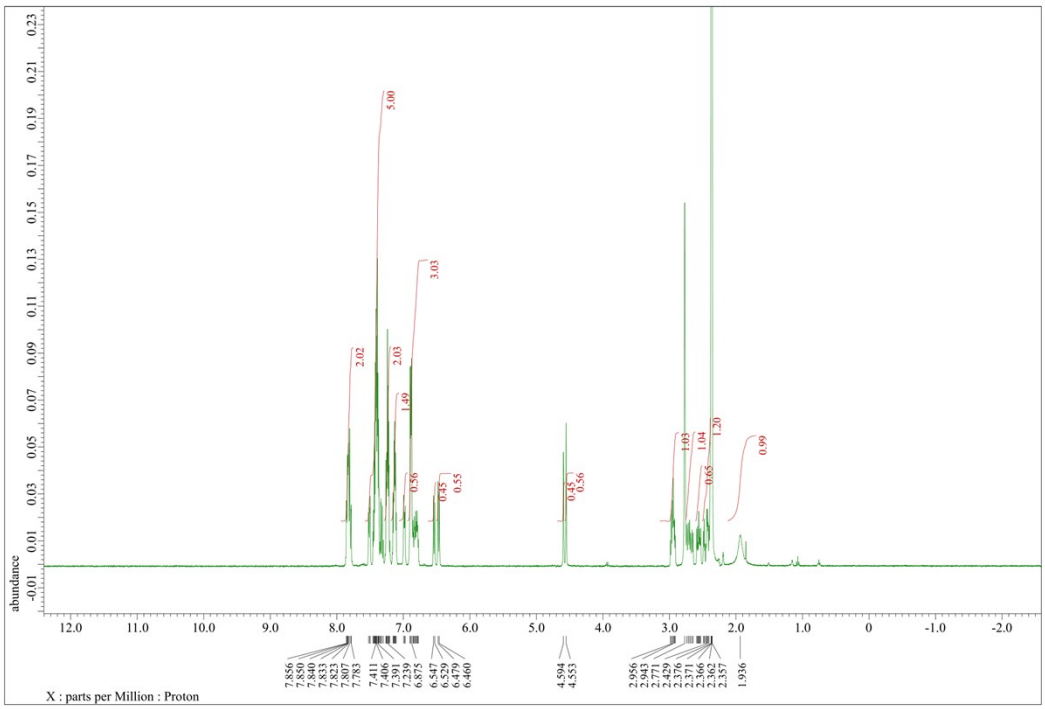


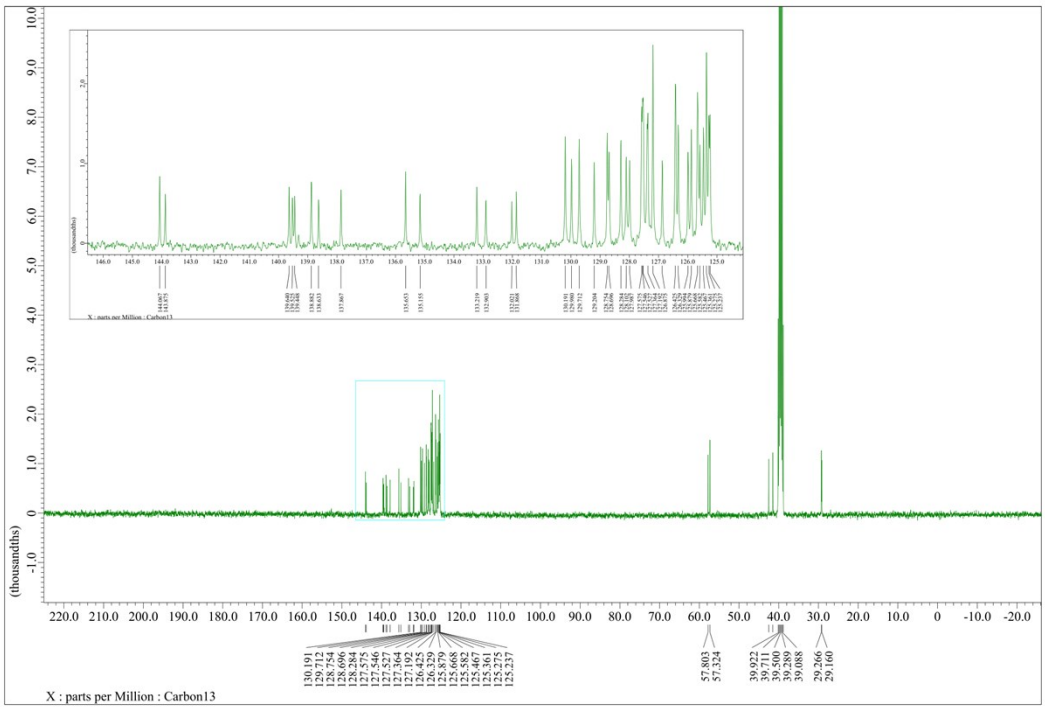
17j (Solvent: $CDCl_3$), water (1.6 ppm for ^1H)



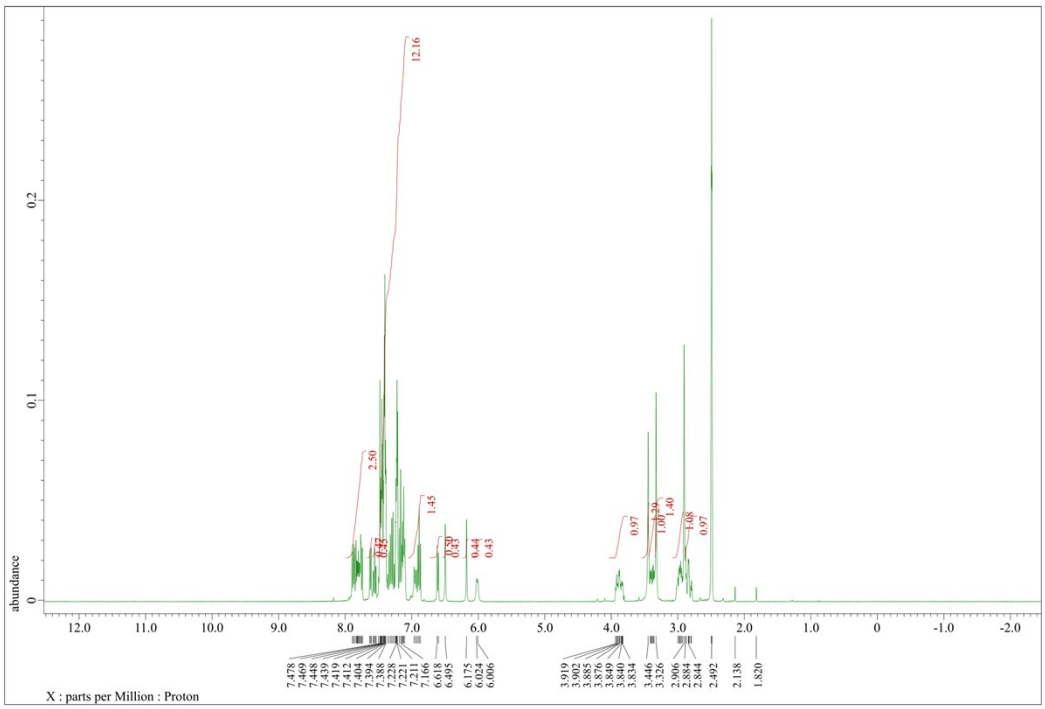


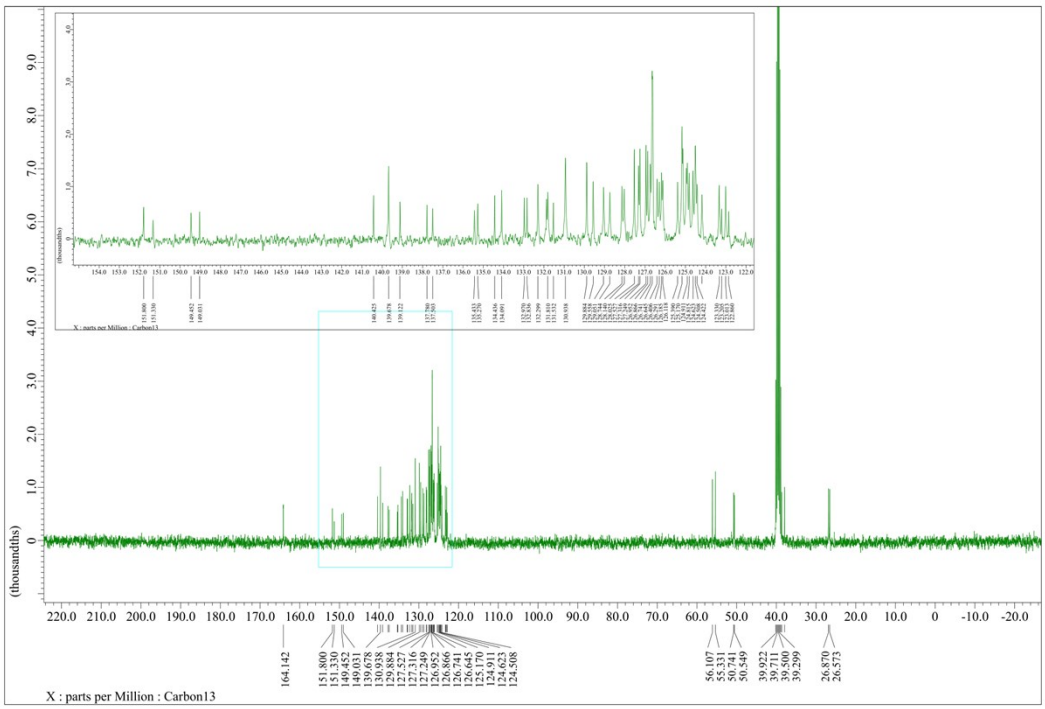
18j (Solvent: DMSO-d_6)
Solvent peak: DMSO (2.4 ppm for ^{1}H, 39.5 ppm for ^{13}C), water (2.8 ppm for ^{1}H)



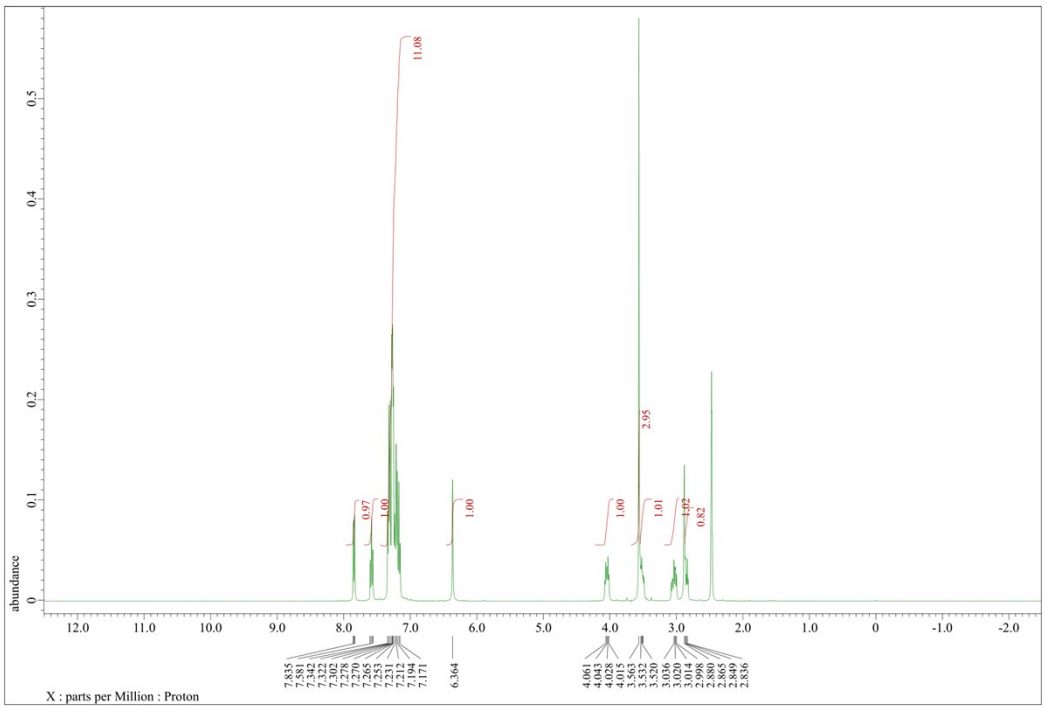


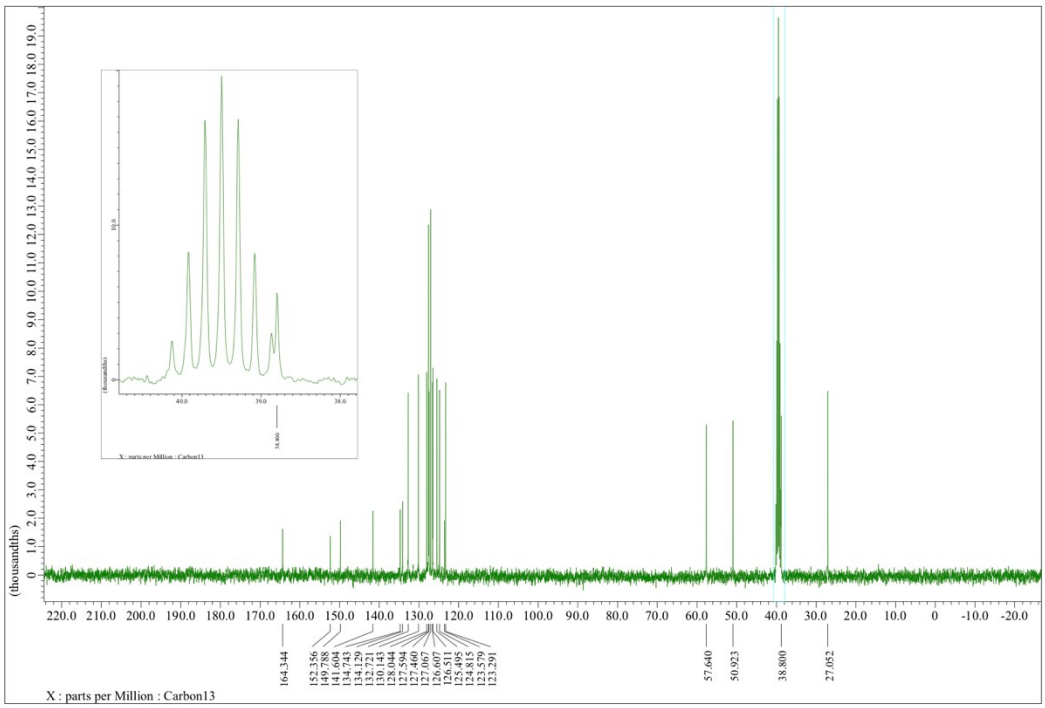
1j (Solvent: DMSO-d_6, 120 °C)
Solvent peak: DMSO (2.5 ppm for ^{1}H, 39.5 ppm for ^{13}C), water (2.8 ppm for ^{1}H)



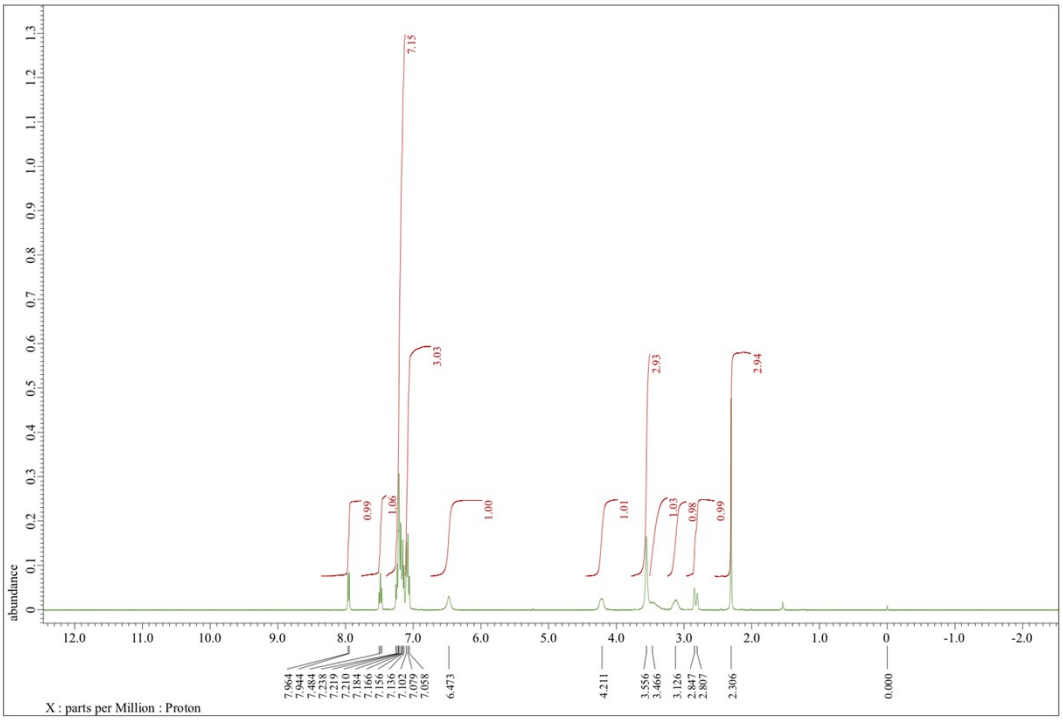


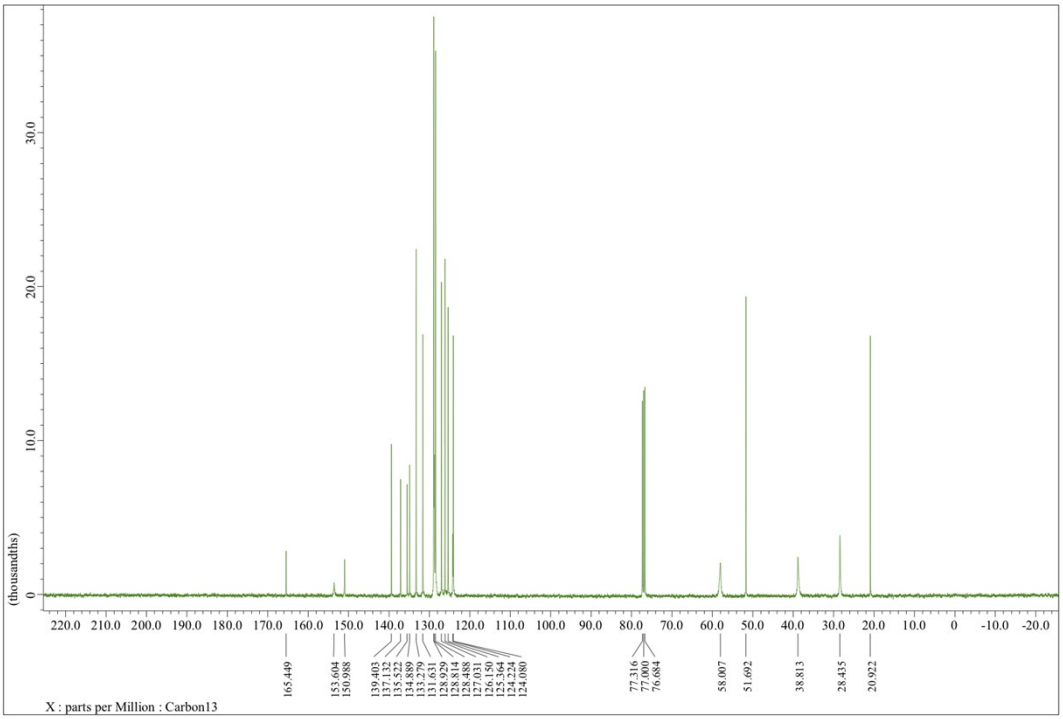
1k (Solvent: DMSO-d_6, 120 °C)
Solvent peak: DMSO (2.5 ppm for ^{1}H, 39.5 ppm for ^{13}C), water (2.8 ppm for ^{1}H)



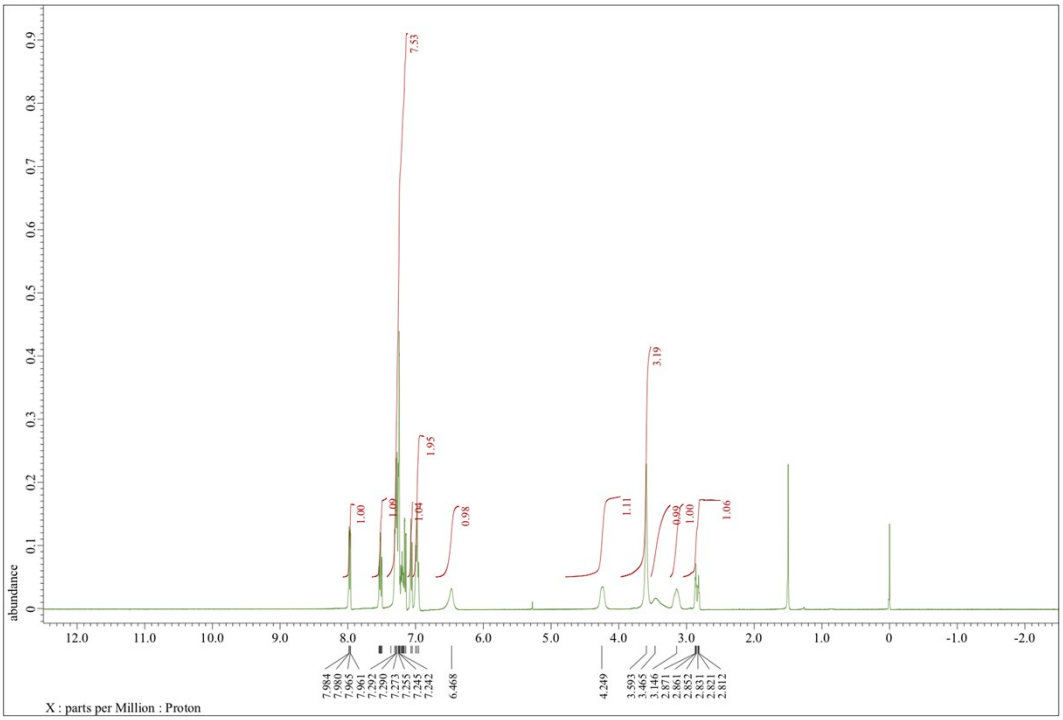


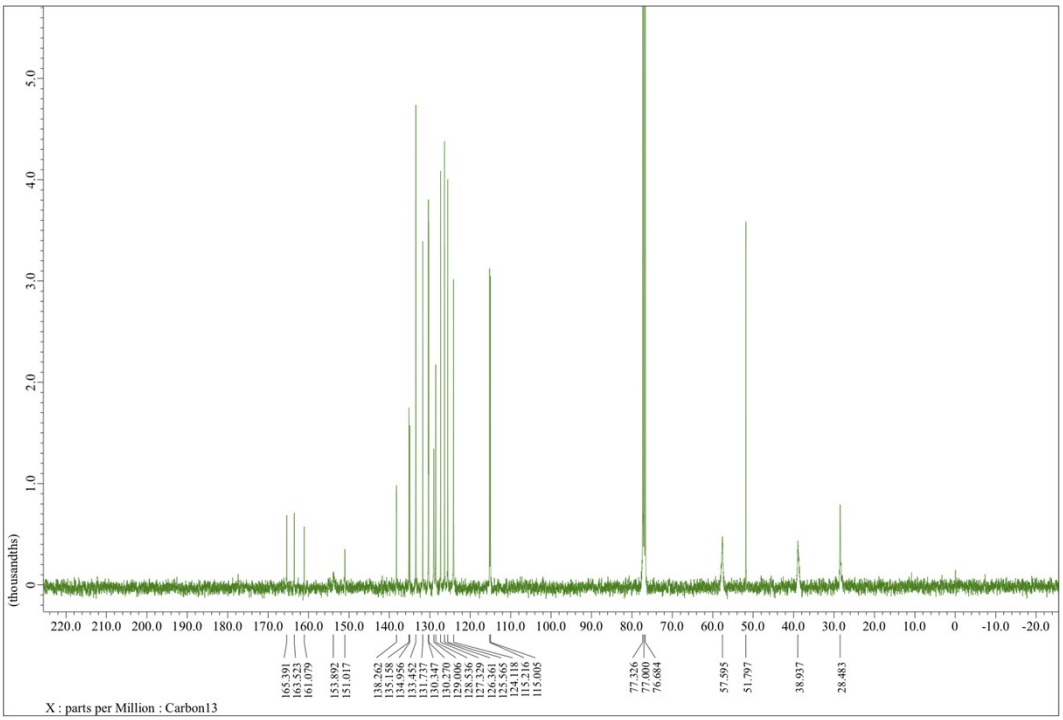
1l (Solvent: $CDCl_3$, 55 ºC)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



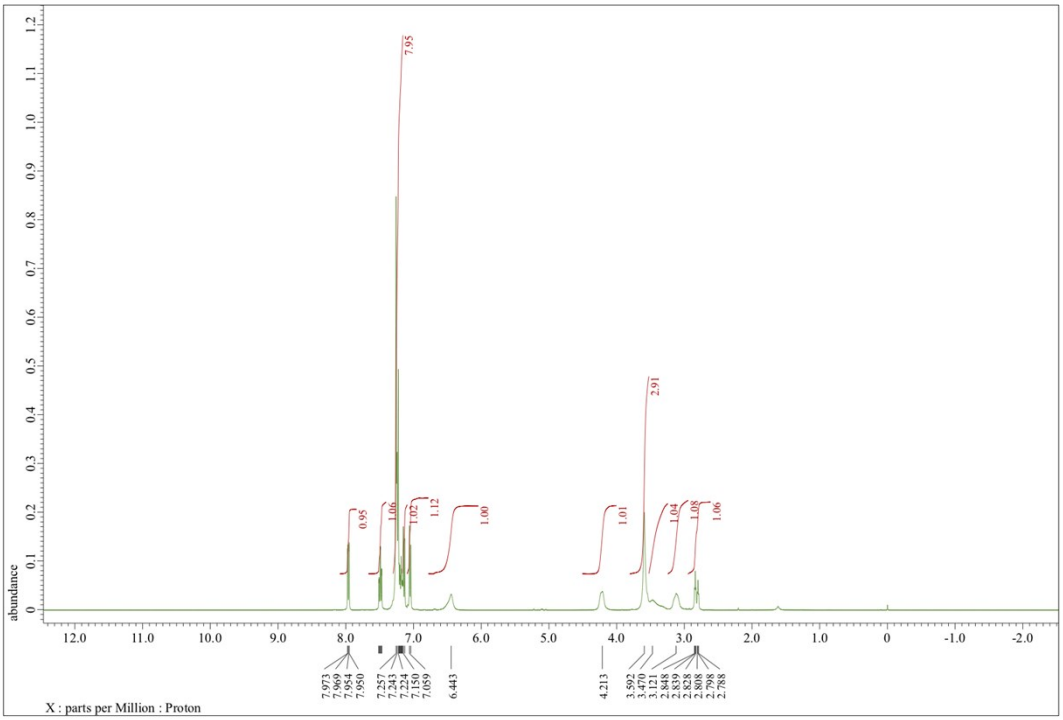


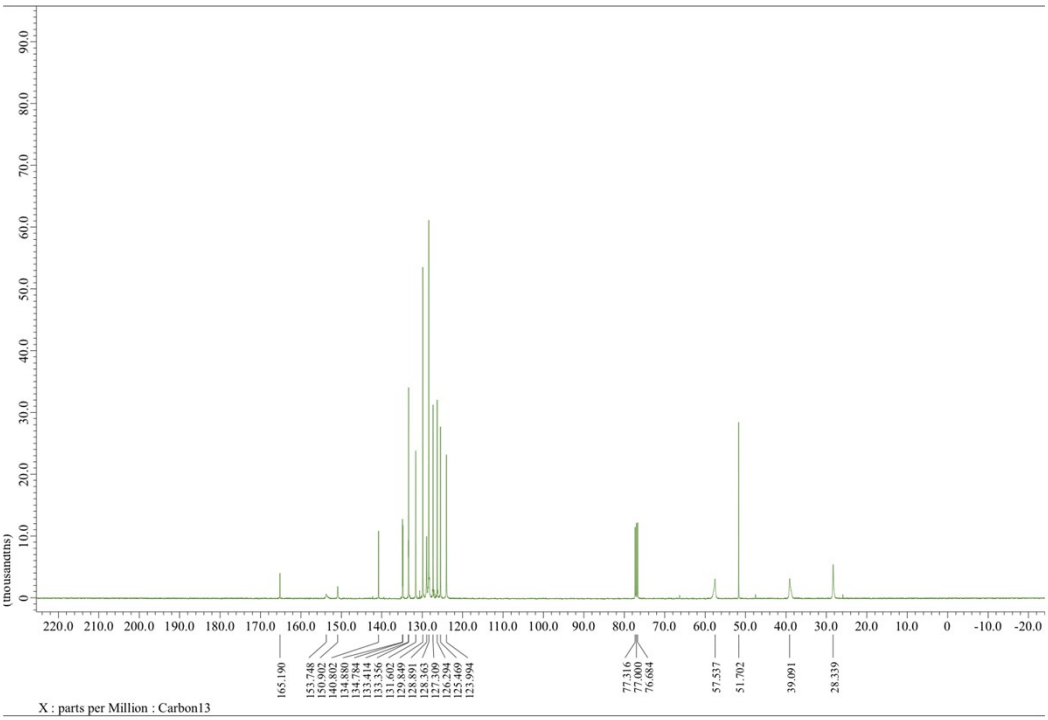
1m (Solvent: $CDCl_3$, 55 ºC)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



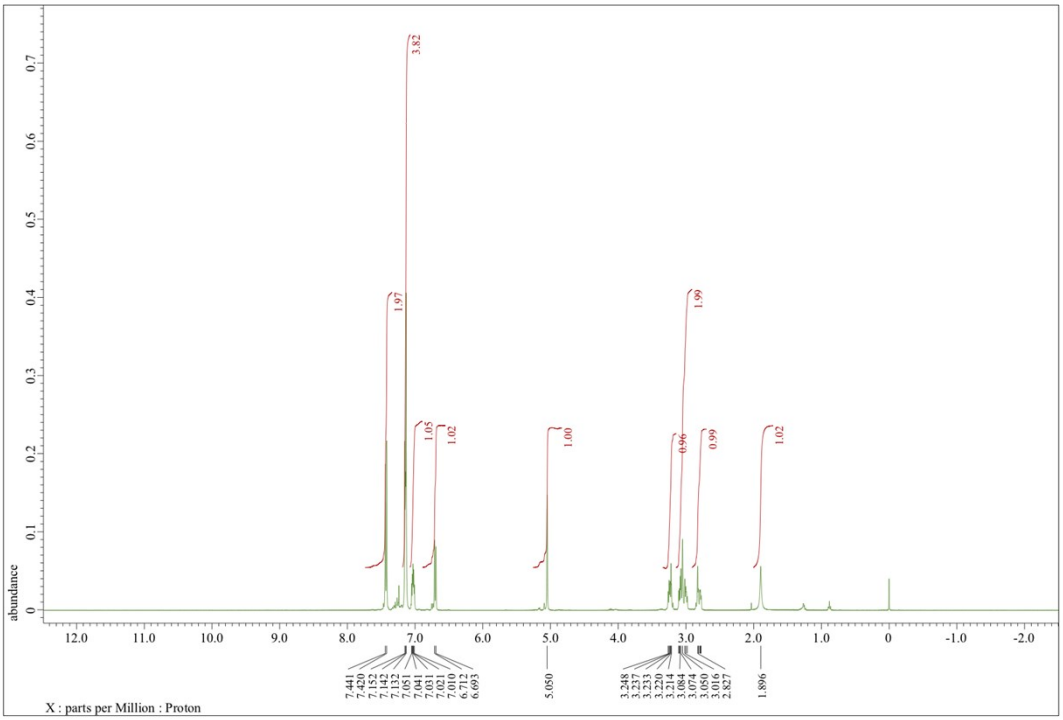


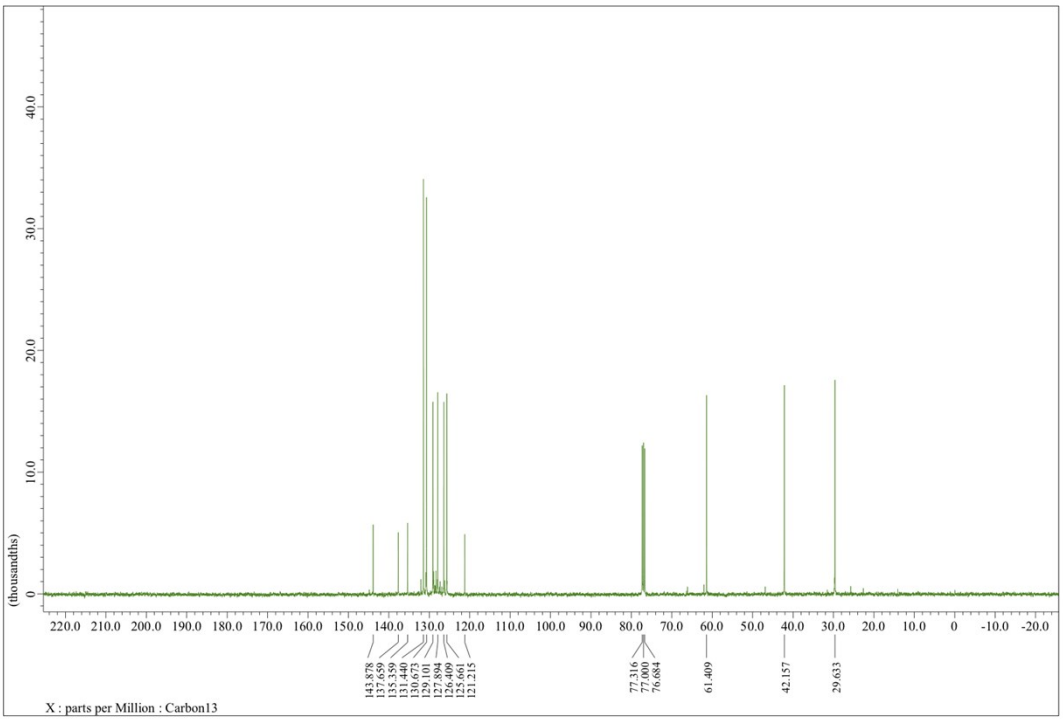
1n (Solvent: $CDCl_3$, 55 ºC)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



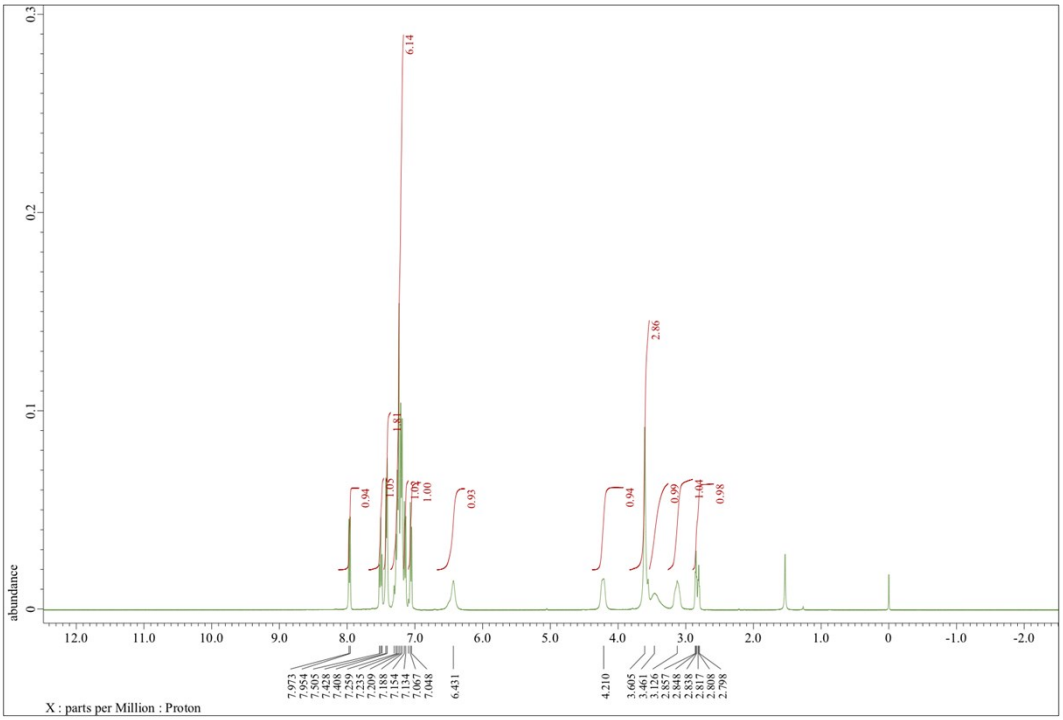


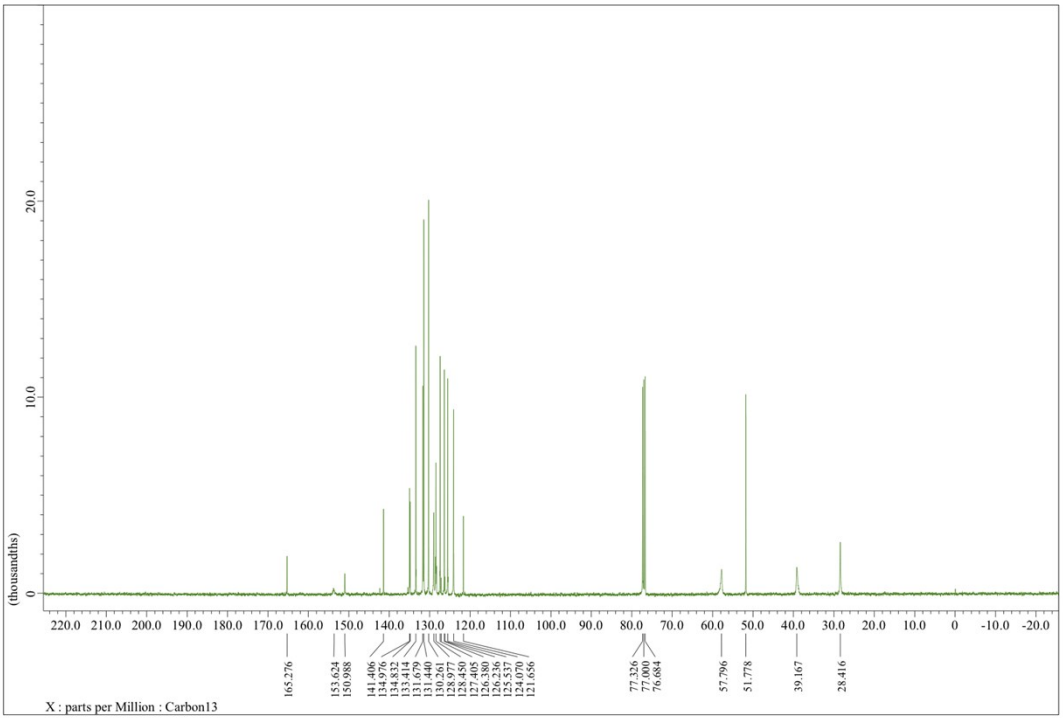
18o (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



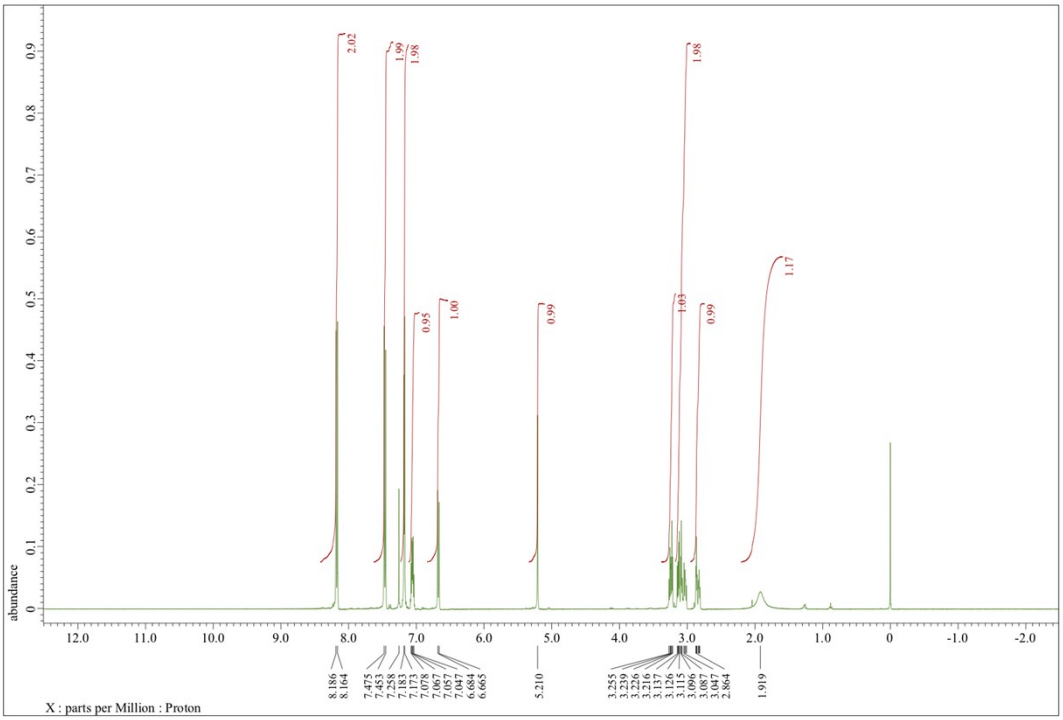


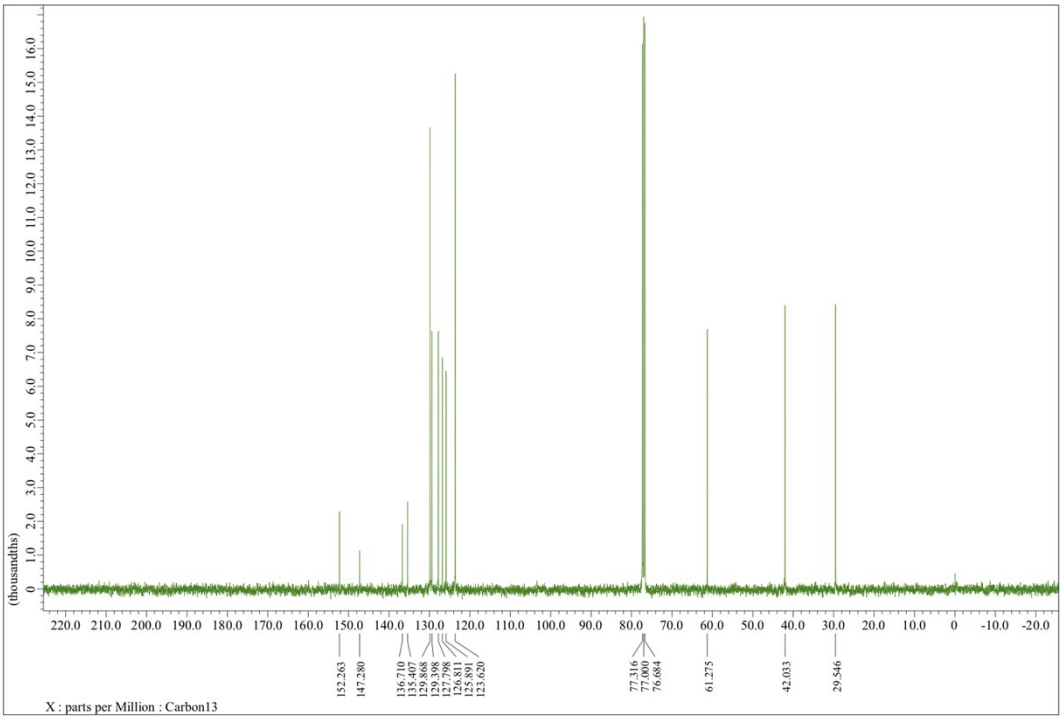
1o (Solvent: $CDCl_3$, 55 ºC)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



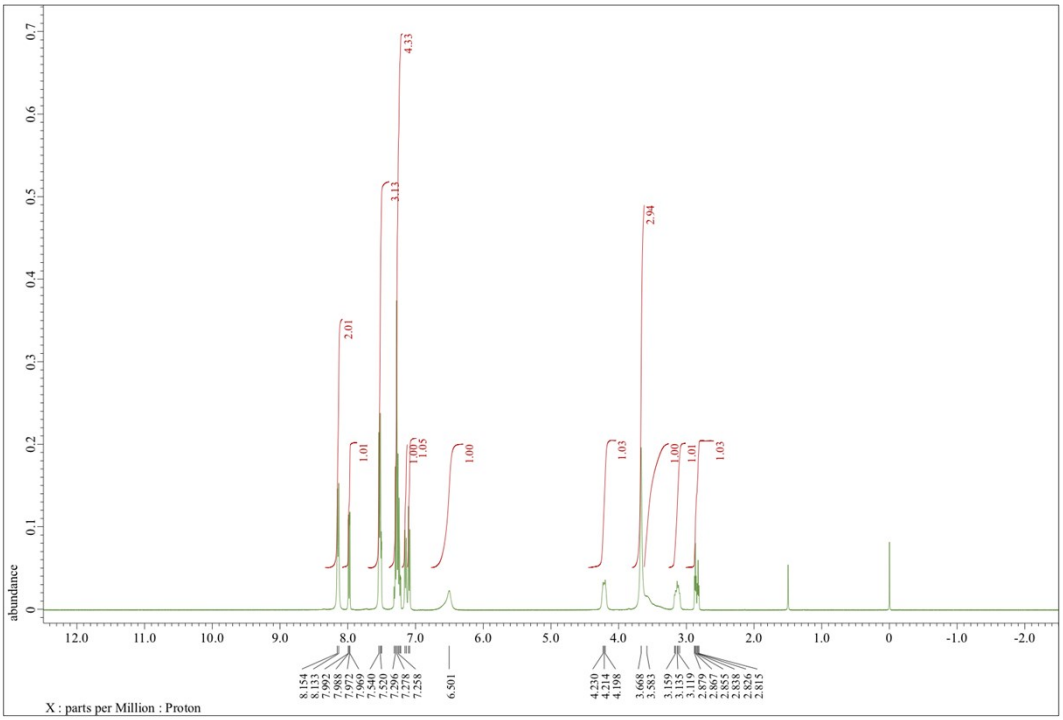


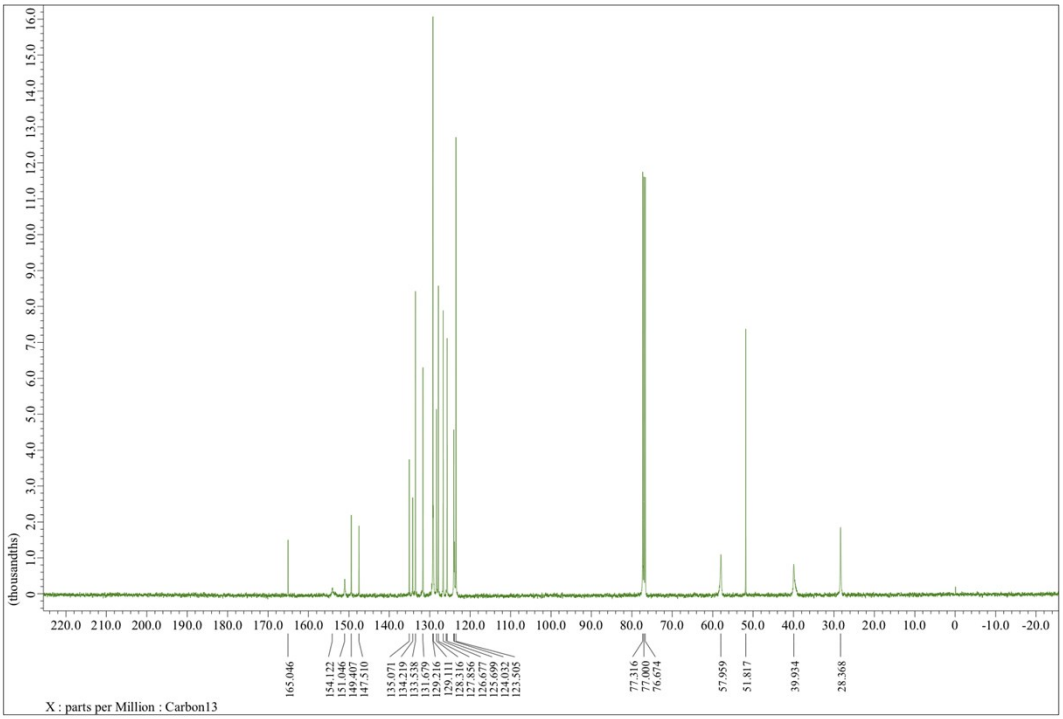
18p (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



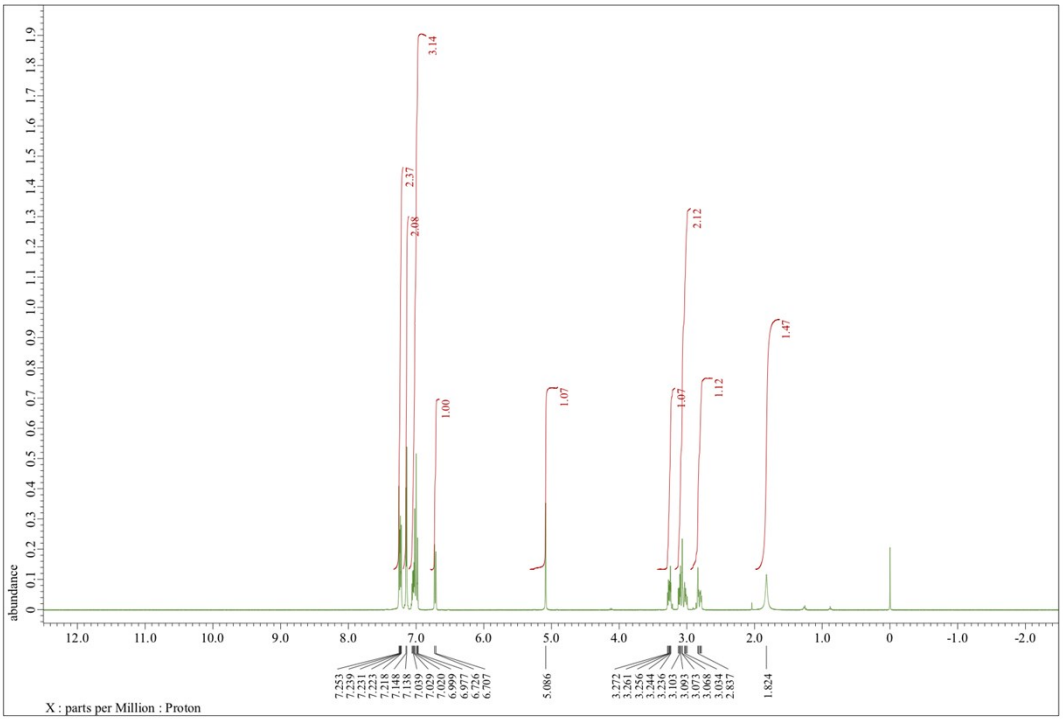


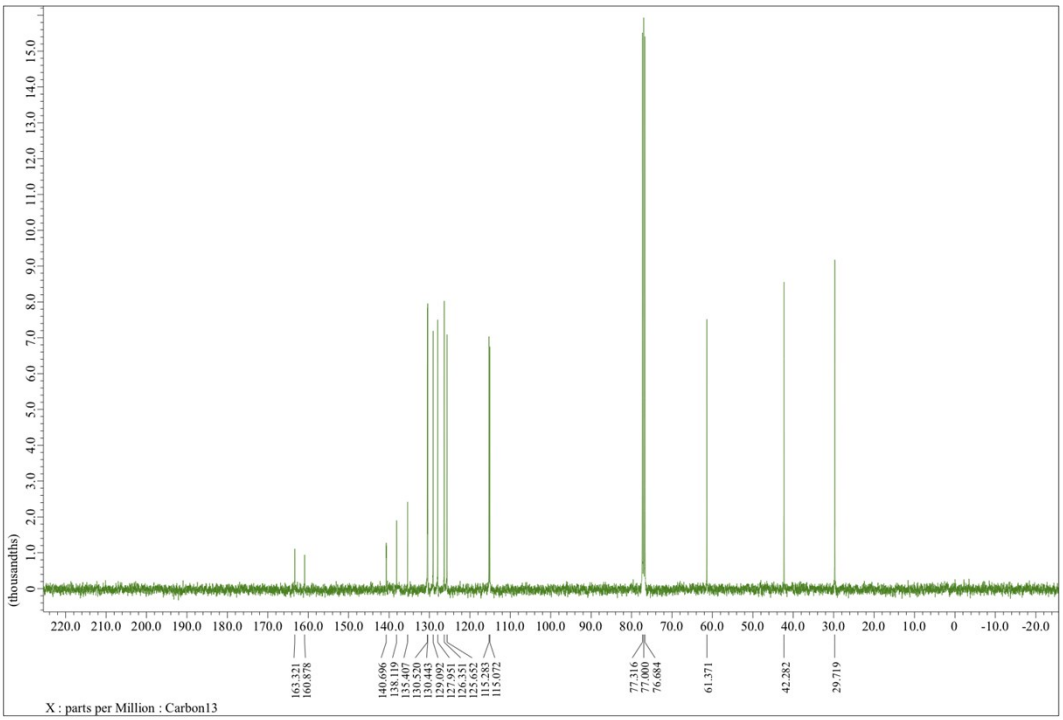
1p (Solvent: $CDCl_3$, 55 ºC)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



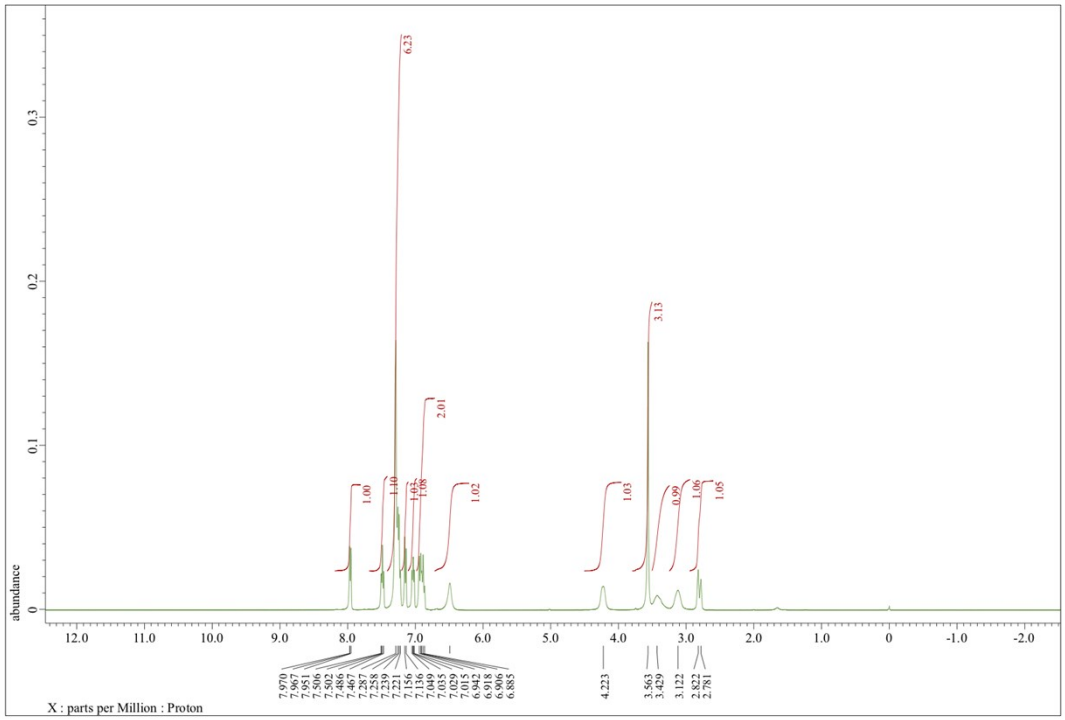


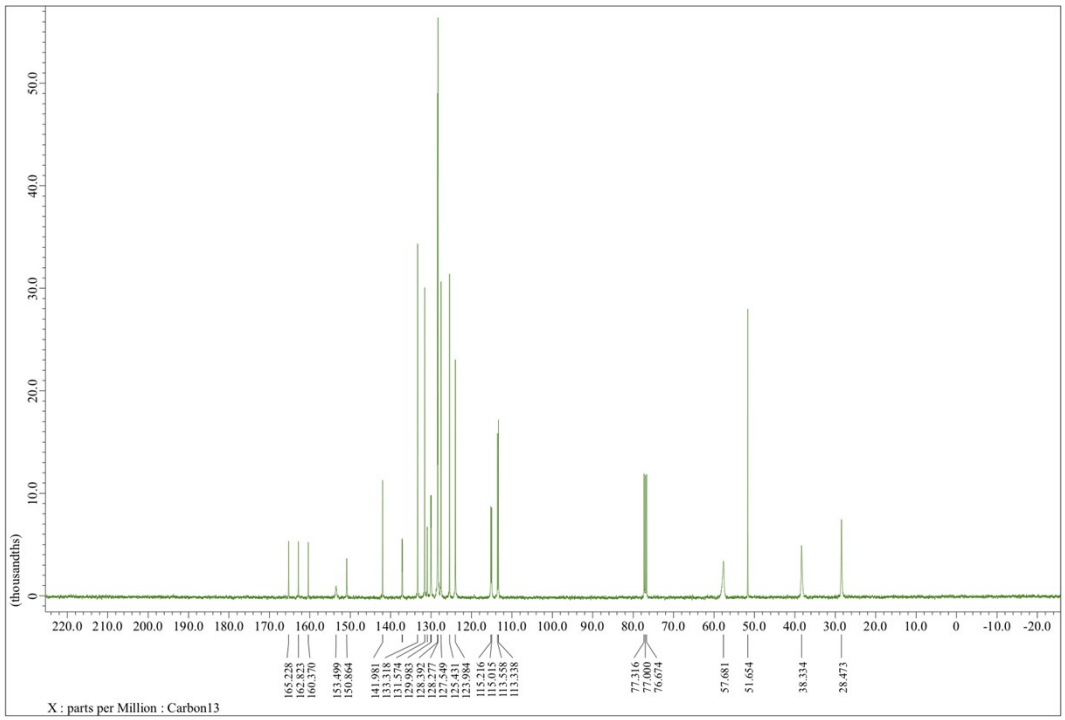
18q (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



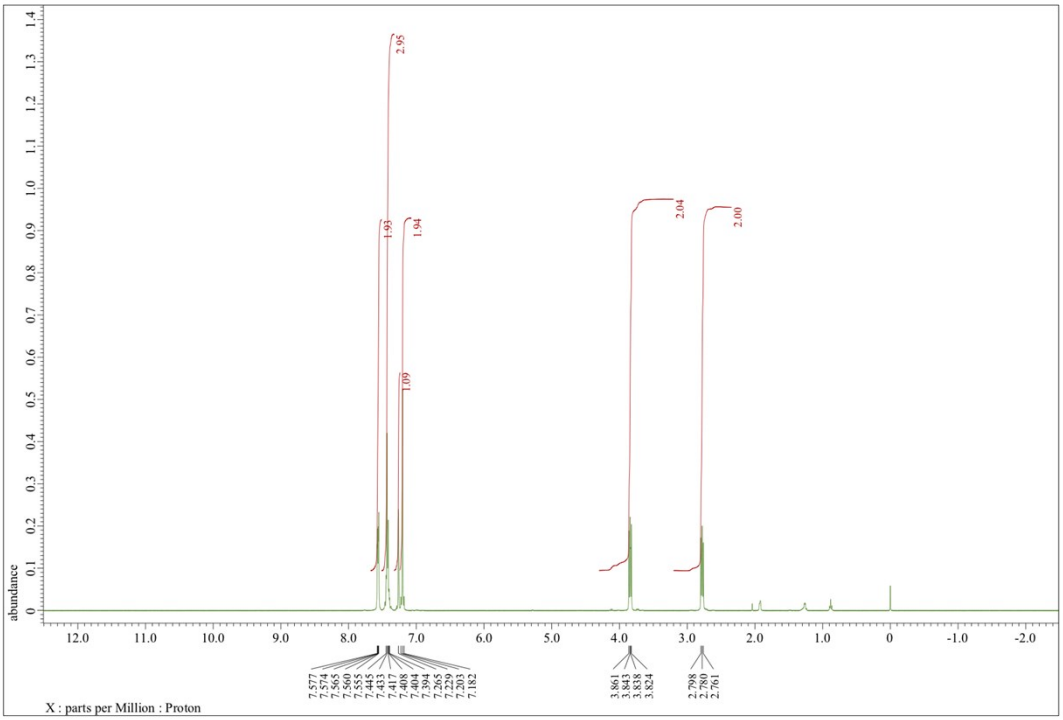


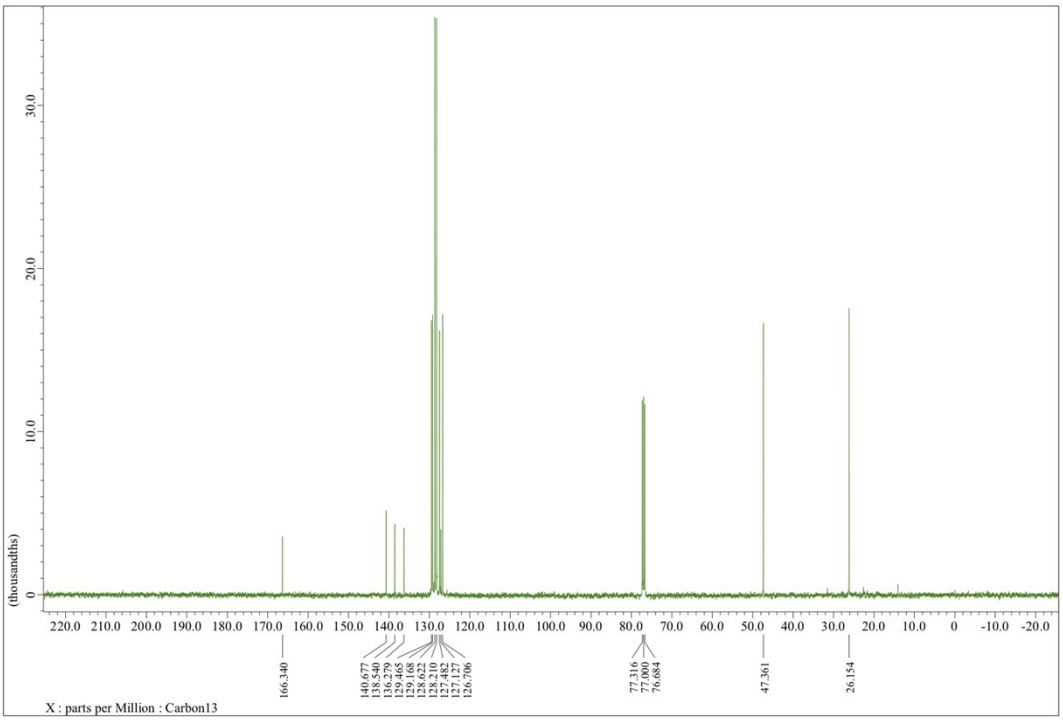
1q (Solvent: $CDCl_3$, 55 ºC)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



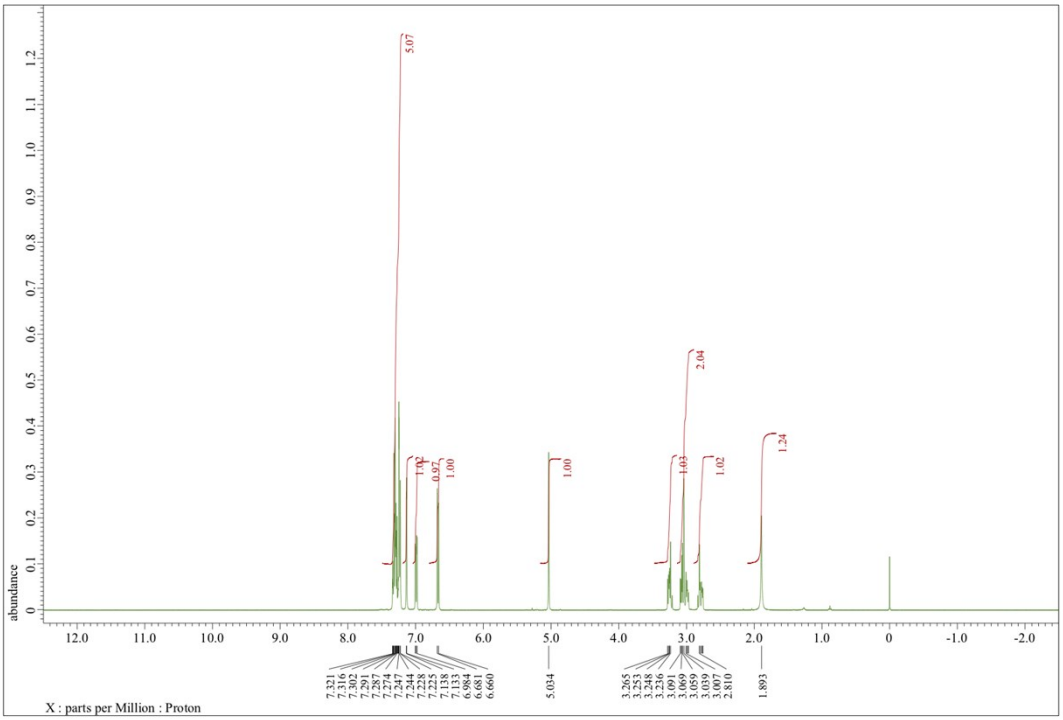


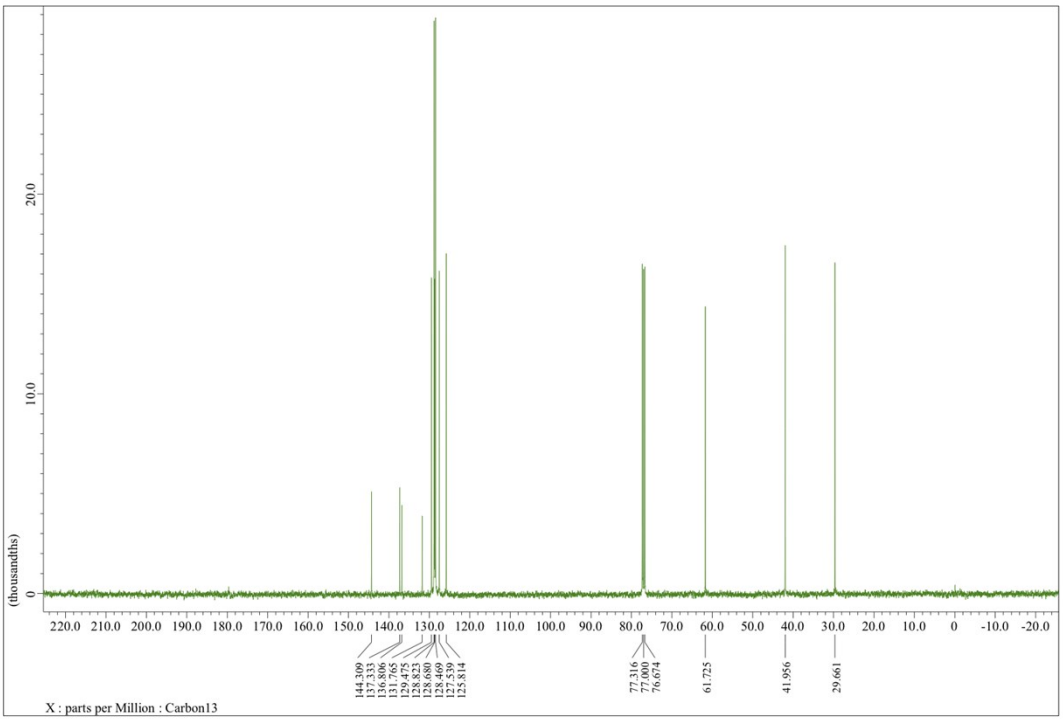
17r (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



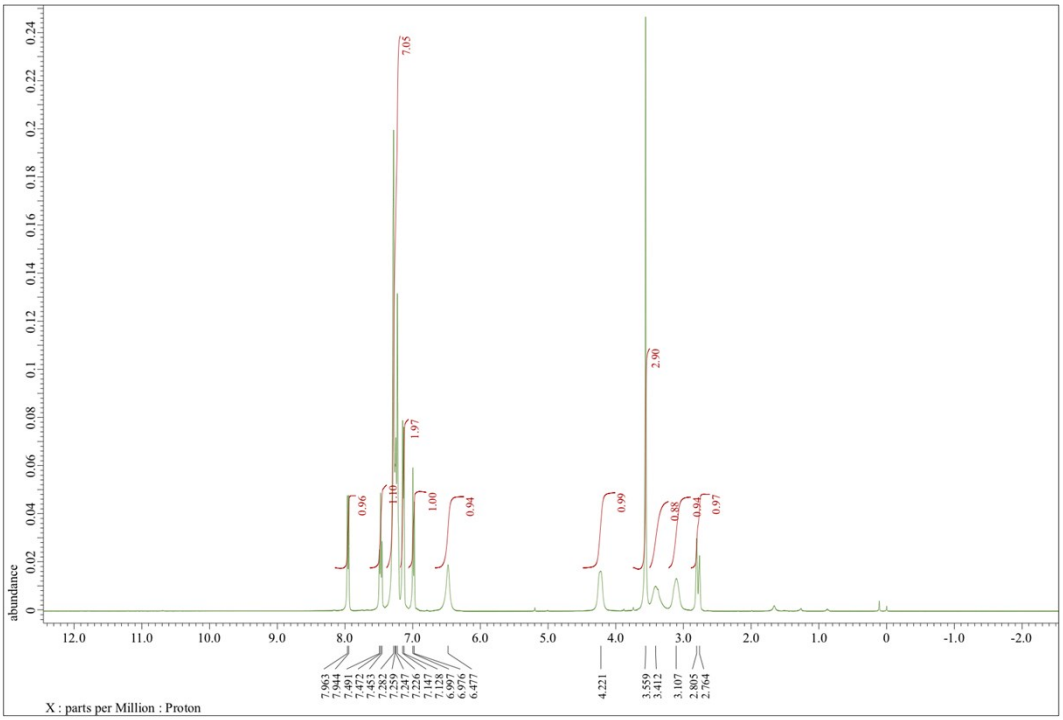


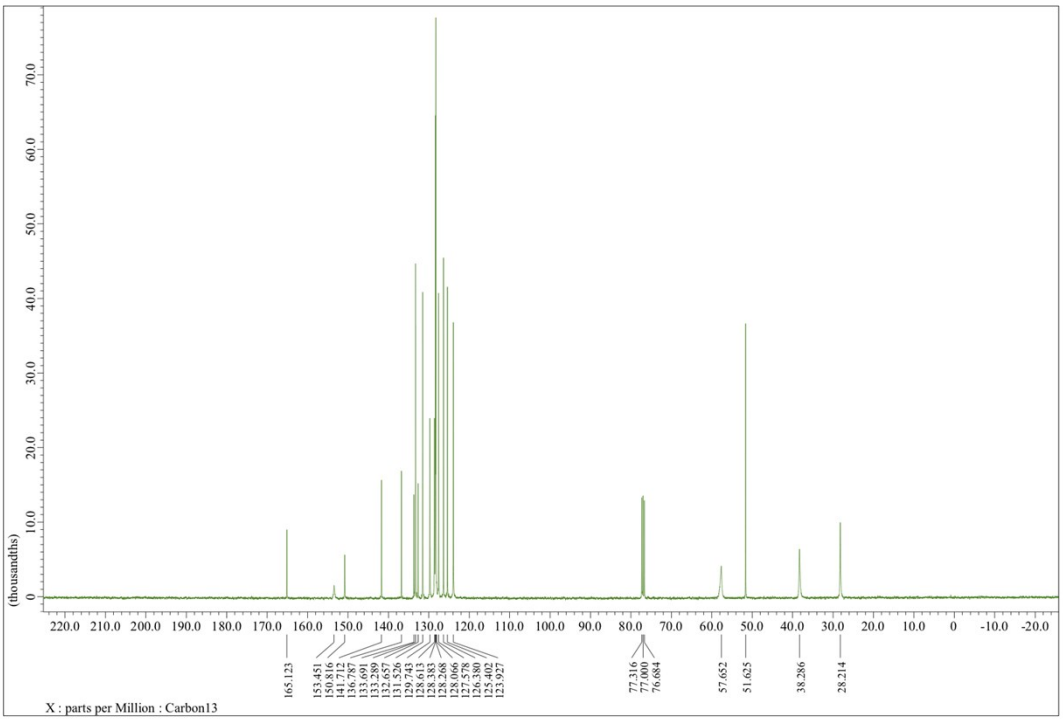
18r (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



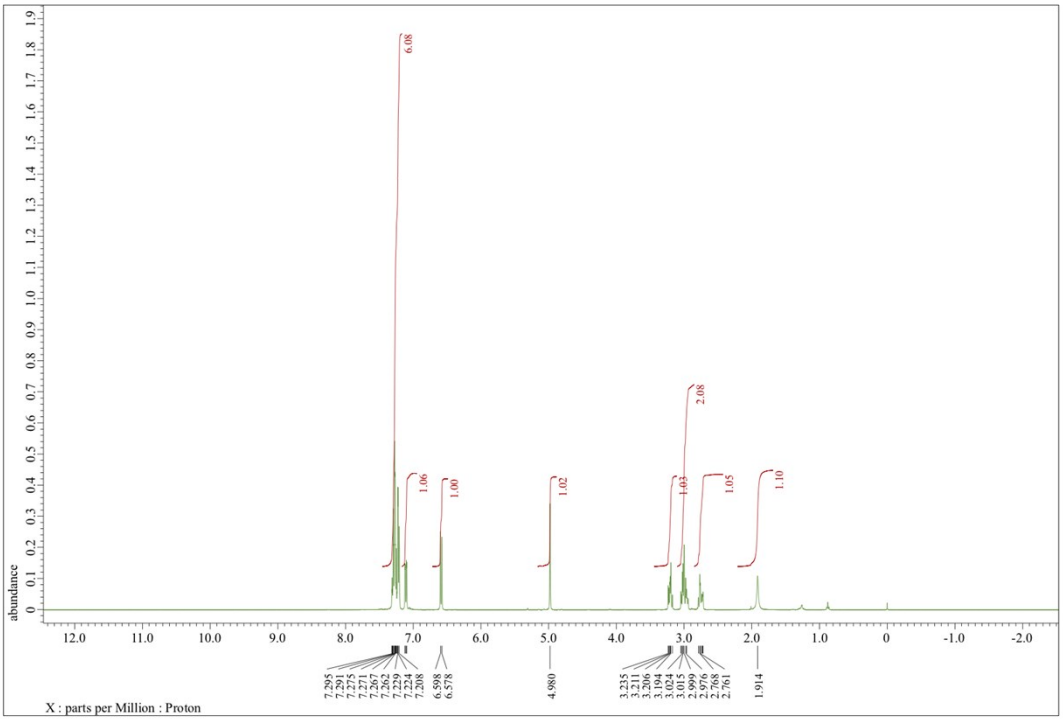


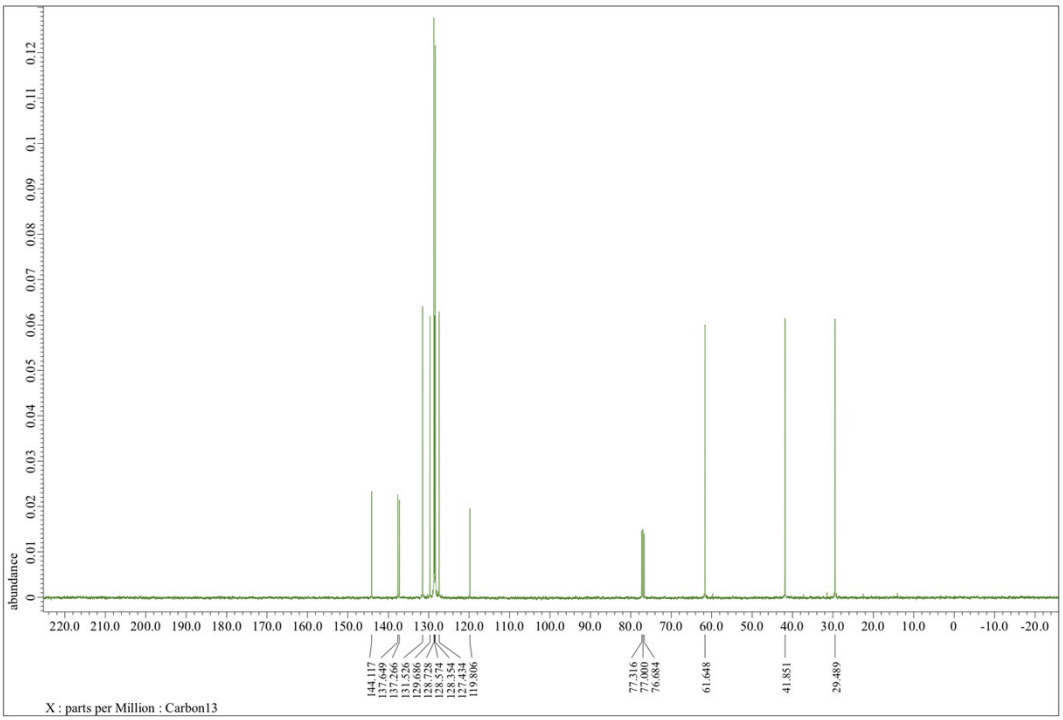
1r (Solvent: $CDCl_3$, 55 ºC)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



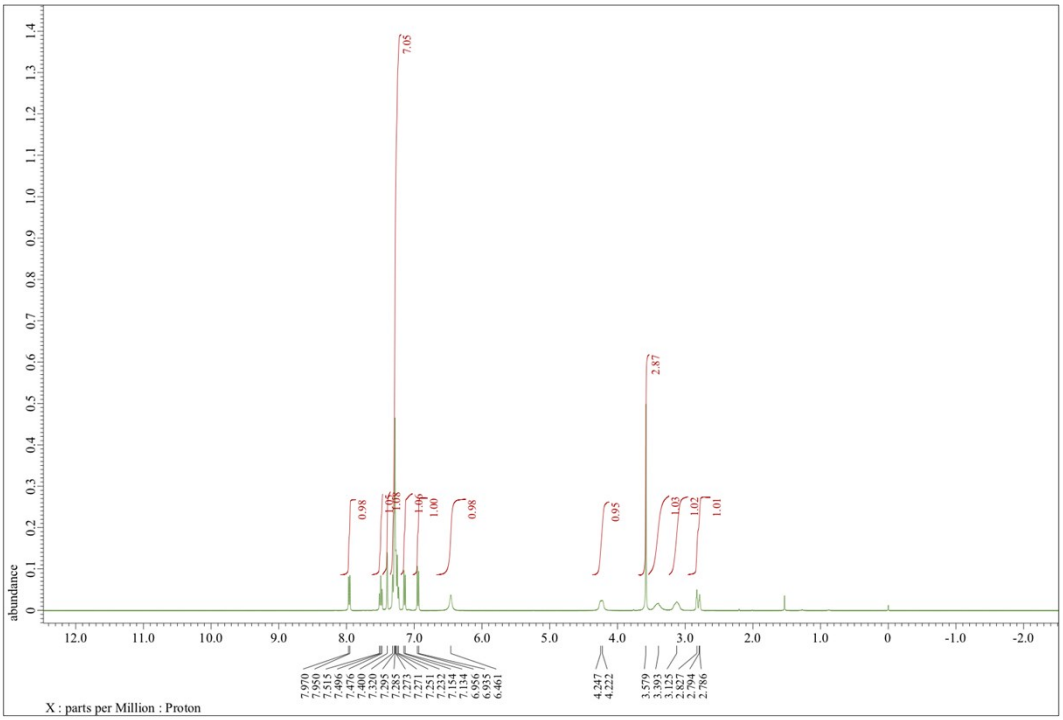


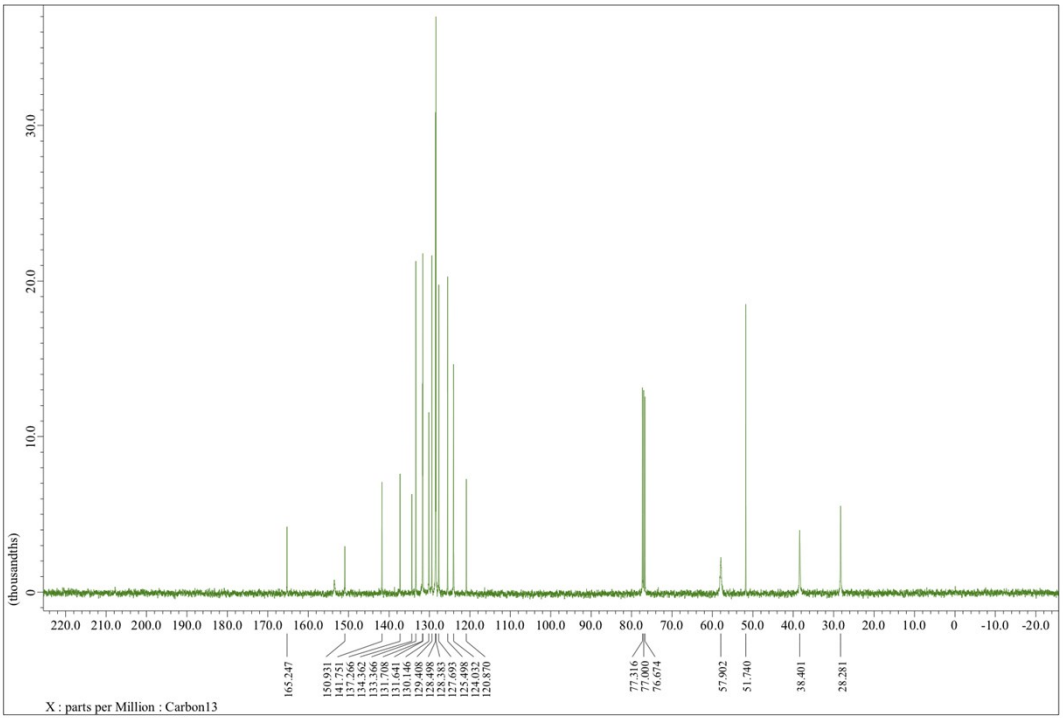
18s (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



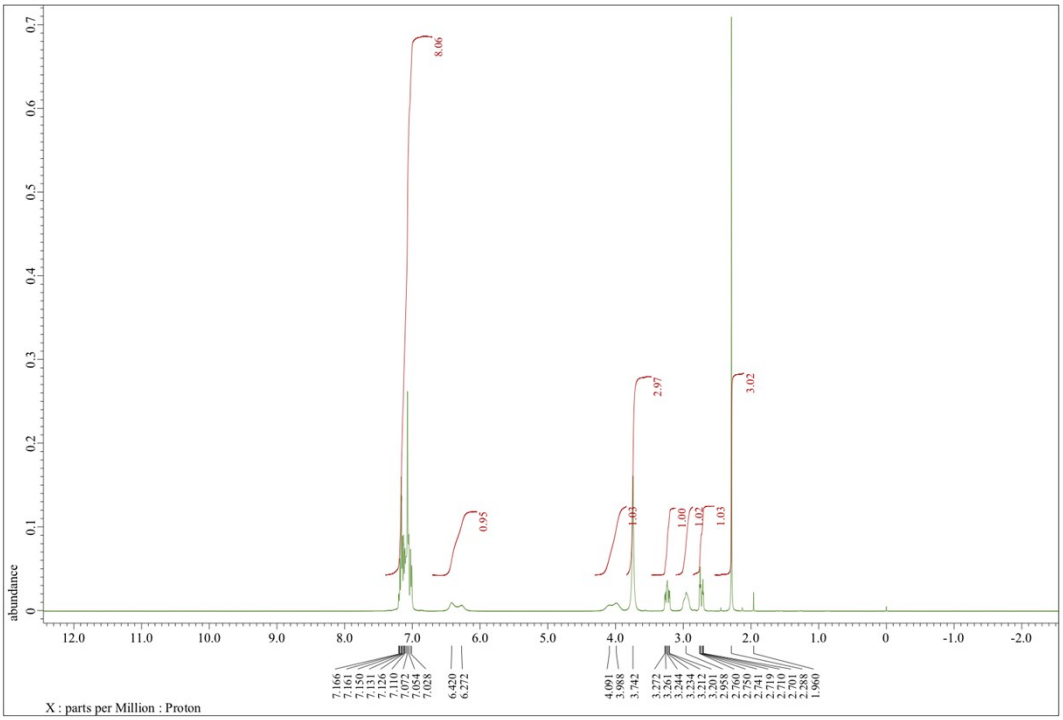


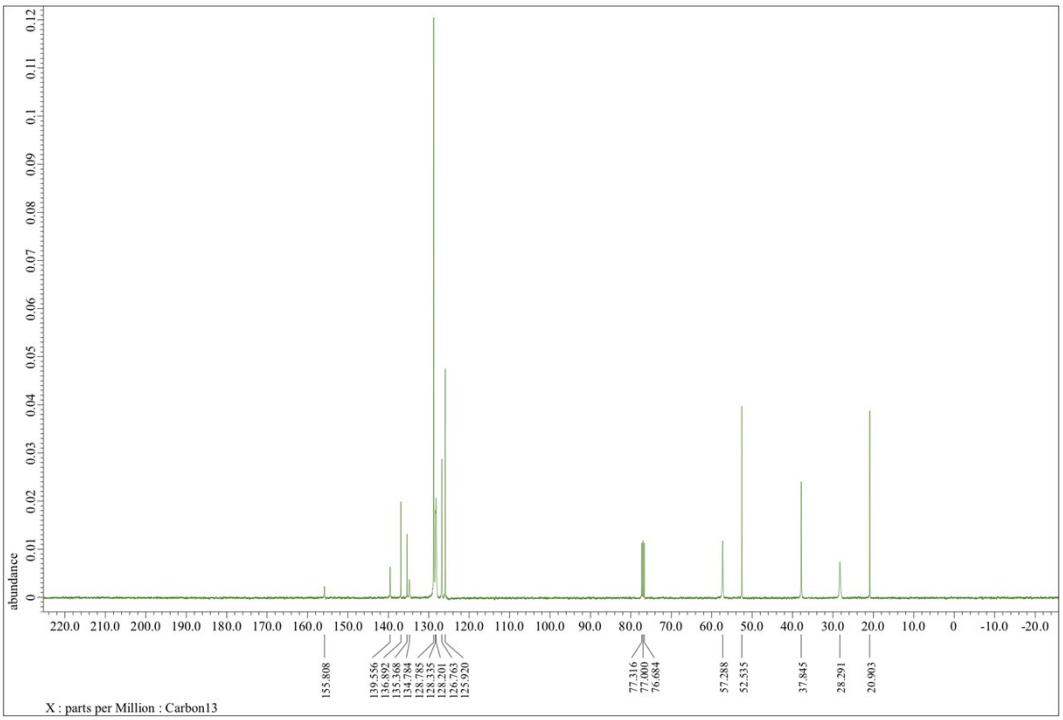
1s (Solvent: $CDCl_3$, 55 ºC)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



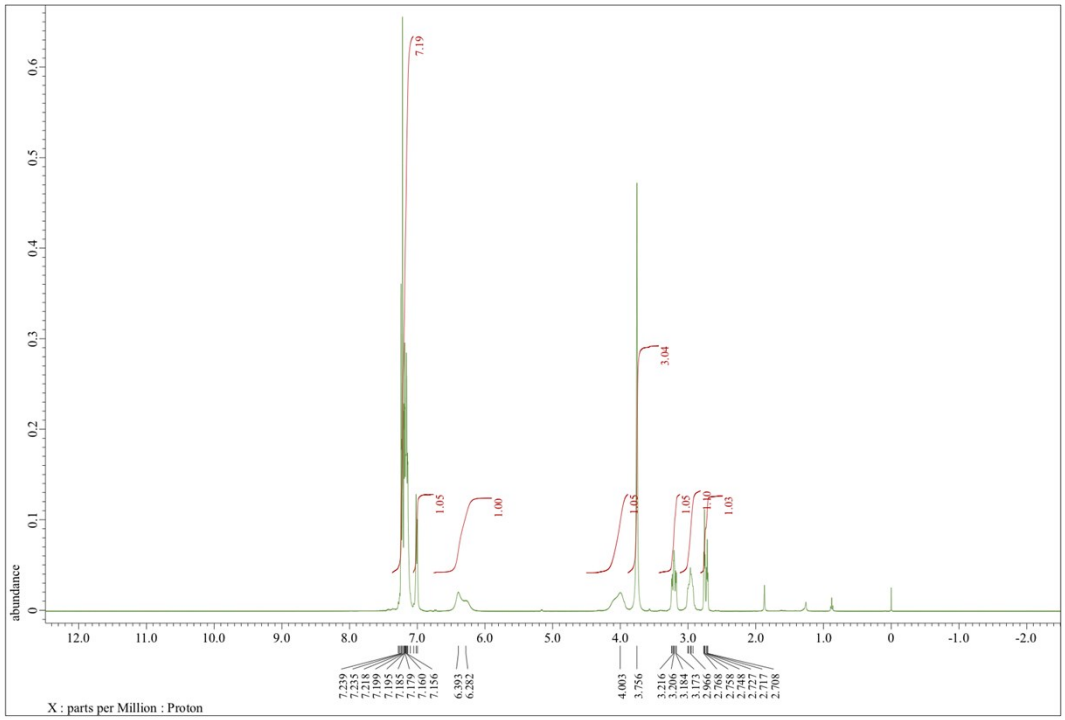


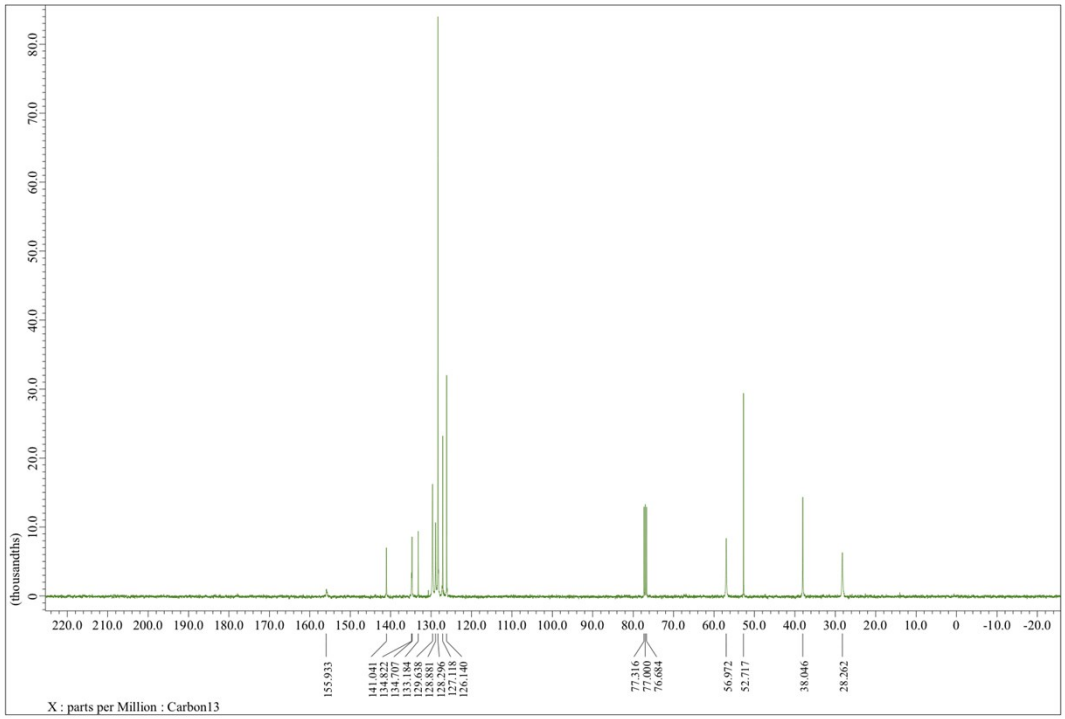
9b (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



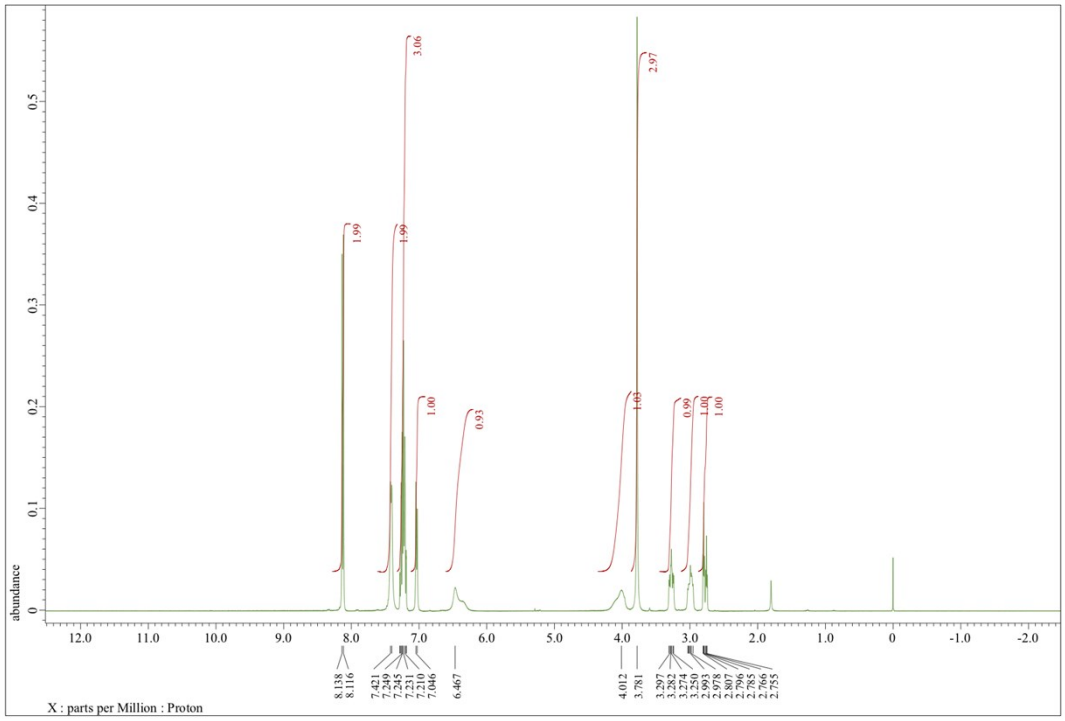


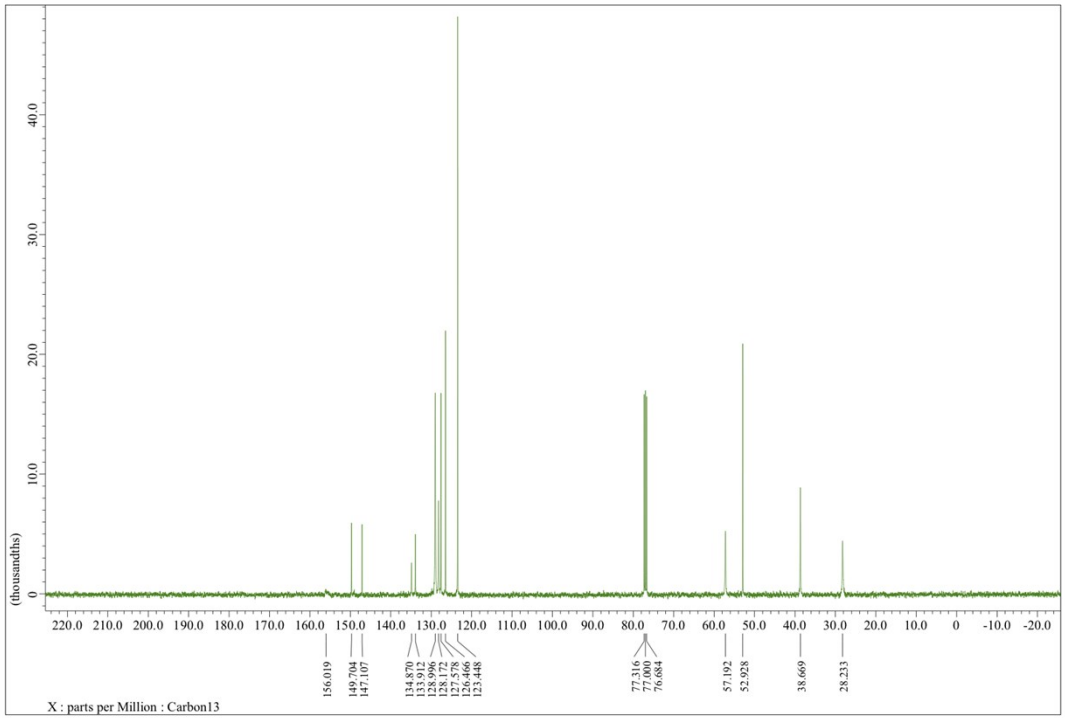
9c (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



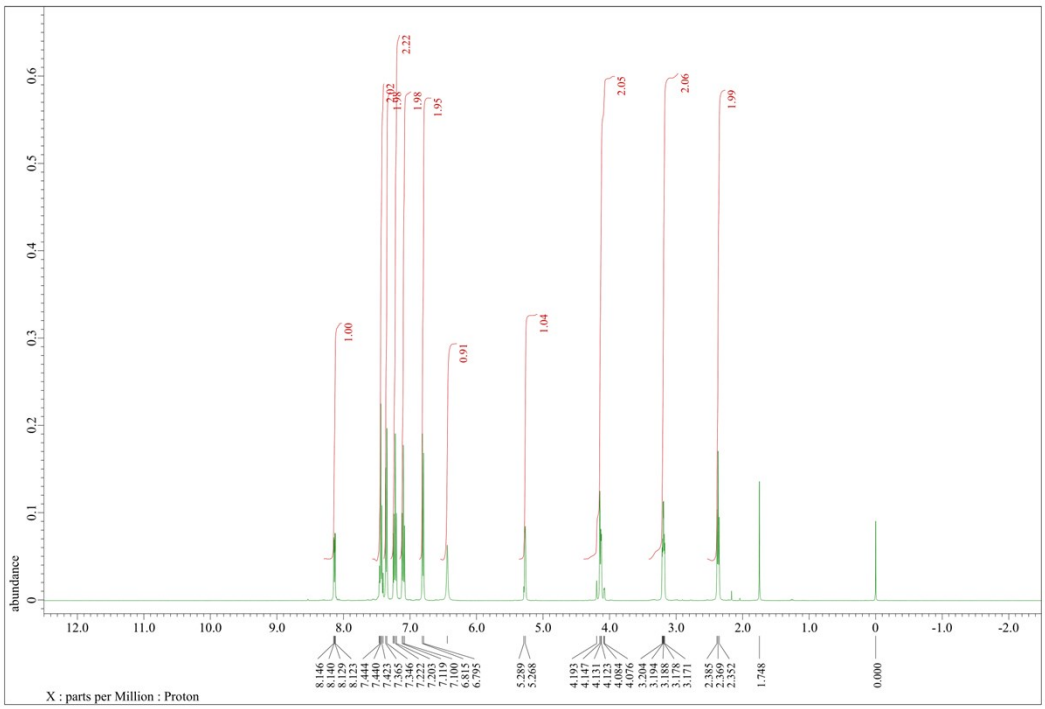


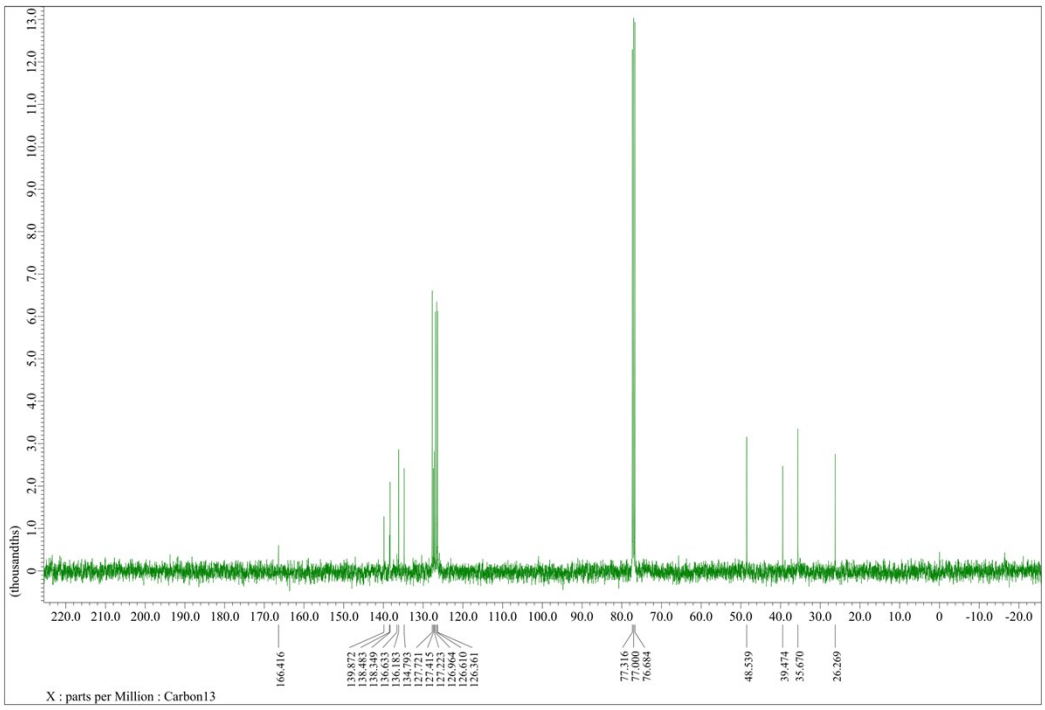
9d (Solvent: $CDCl_3$, 55 ºC)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



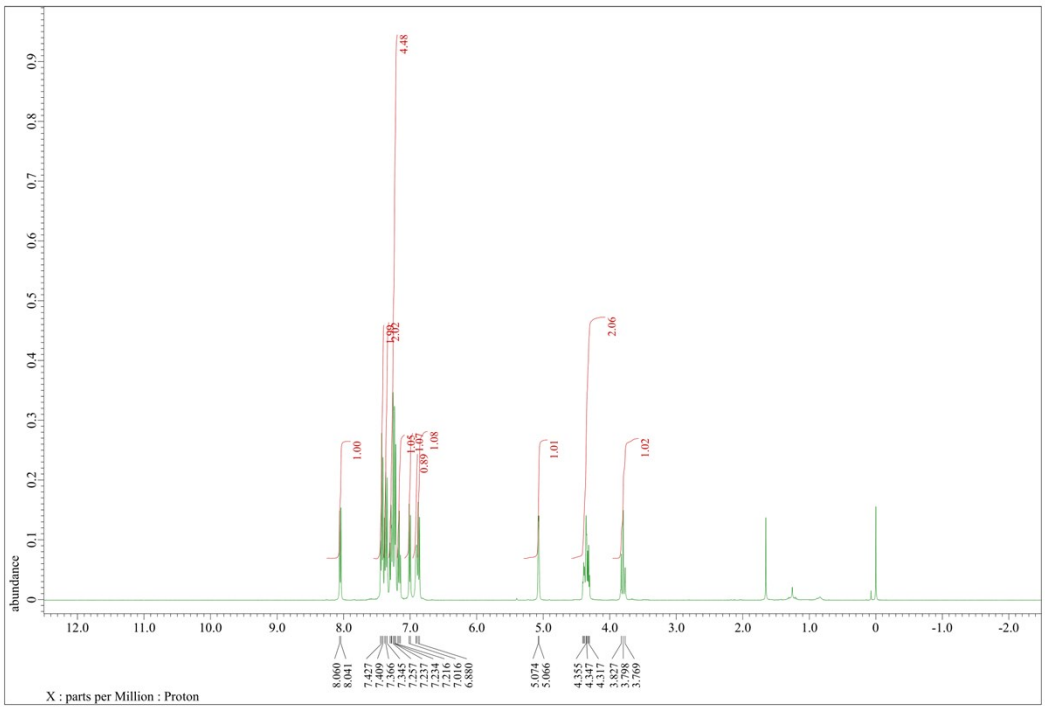


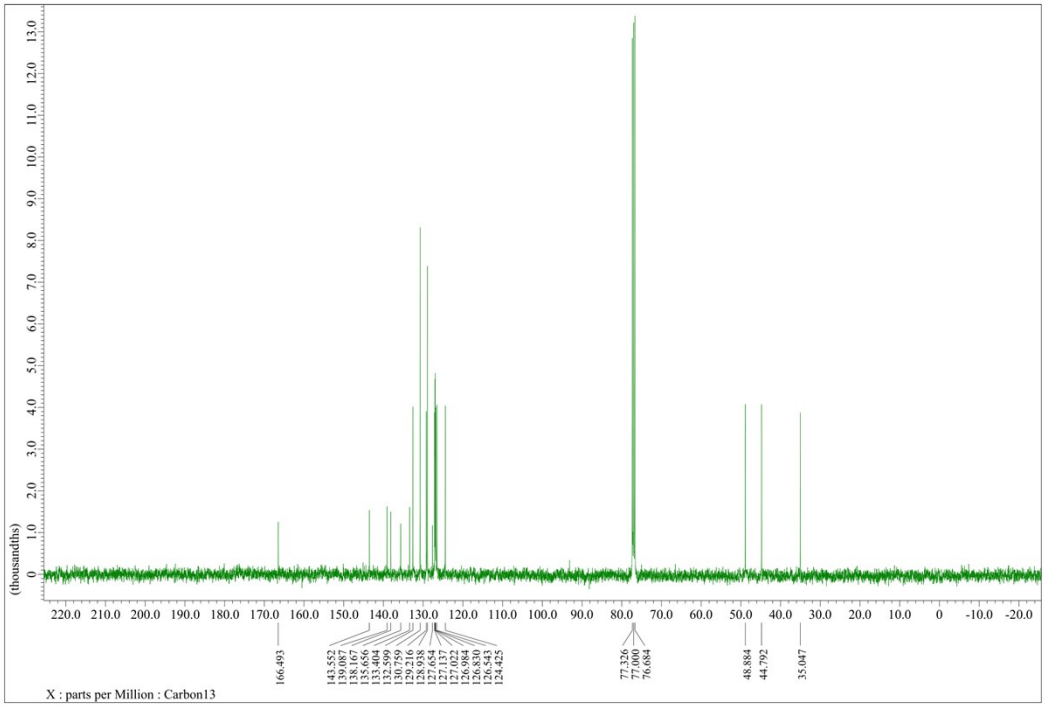
2a (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C), water (1.7 ppm for ^{1}H)



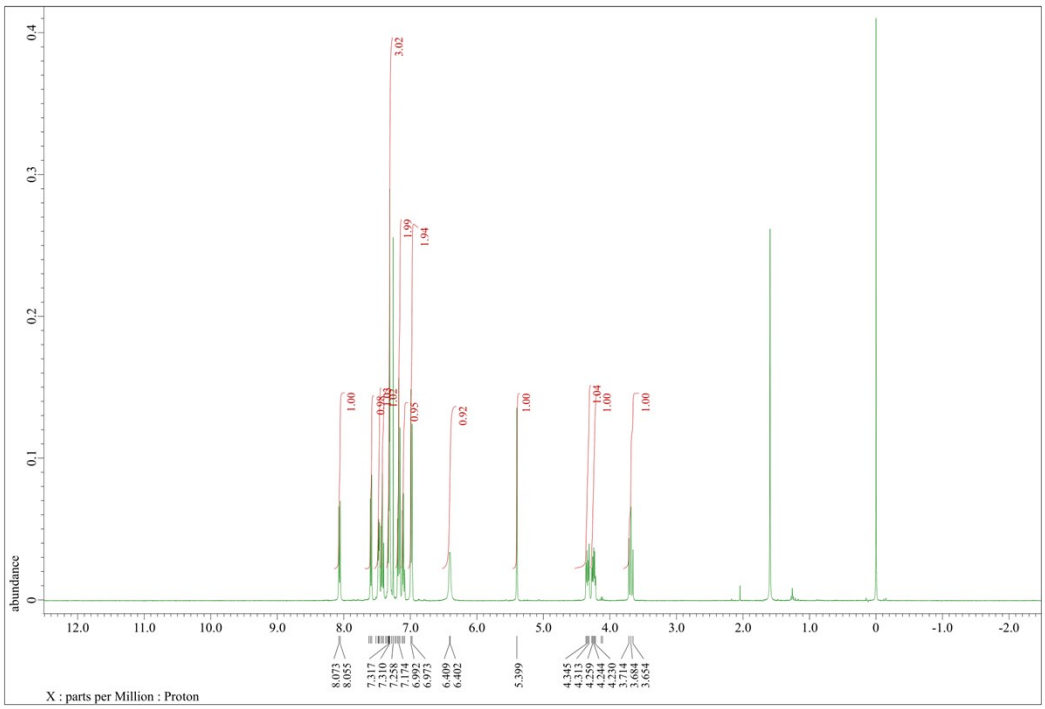


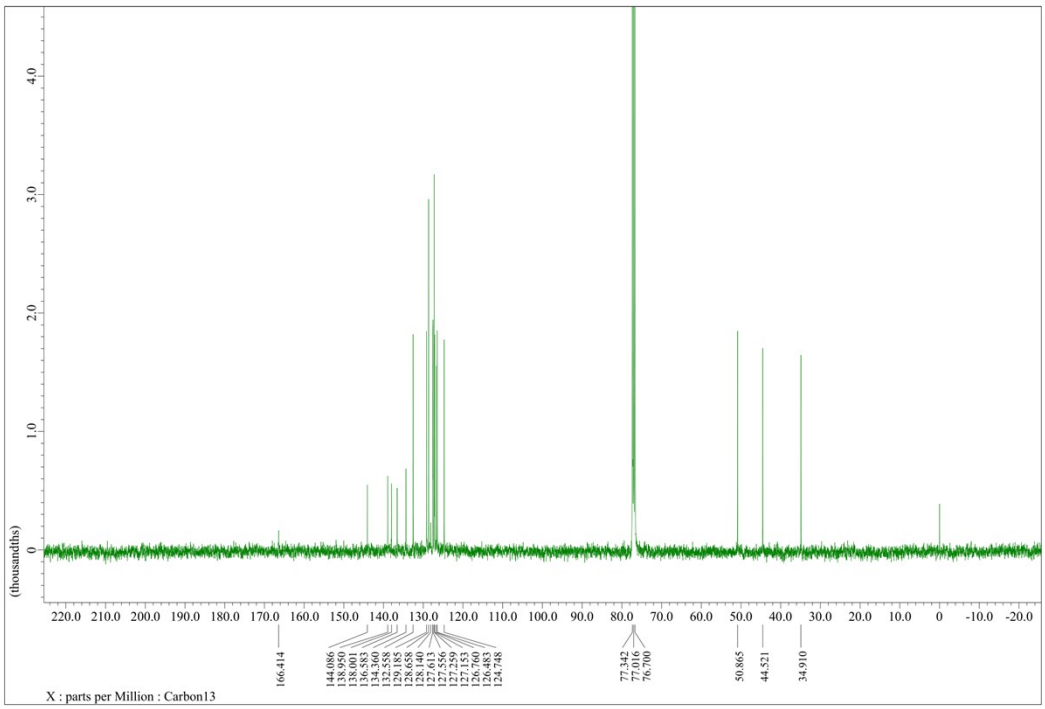
2b-cis (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C), water (1.6 ppm for ^{1}H)



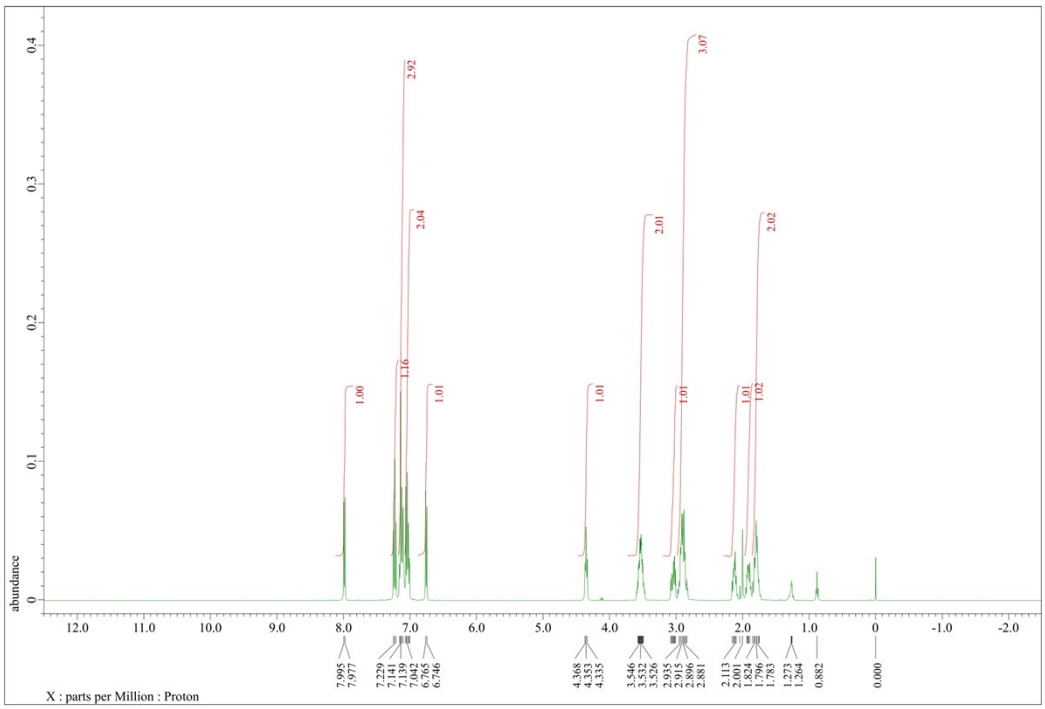


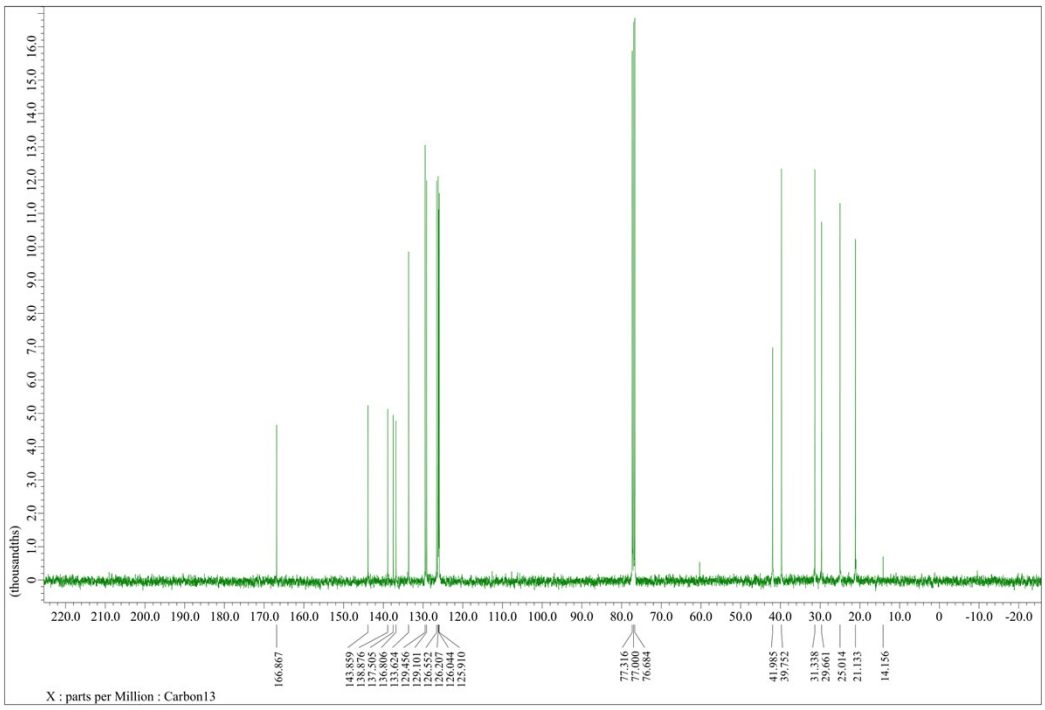
2b-trans (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C), water (1.6 ppm for ^{1}H)



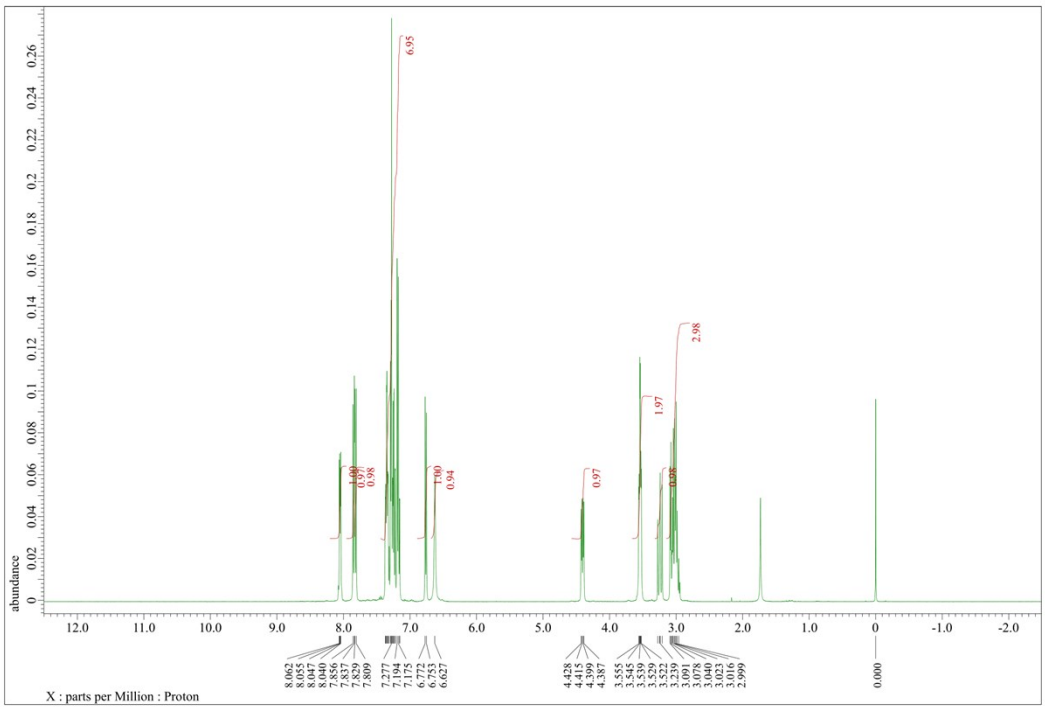


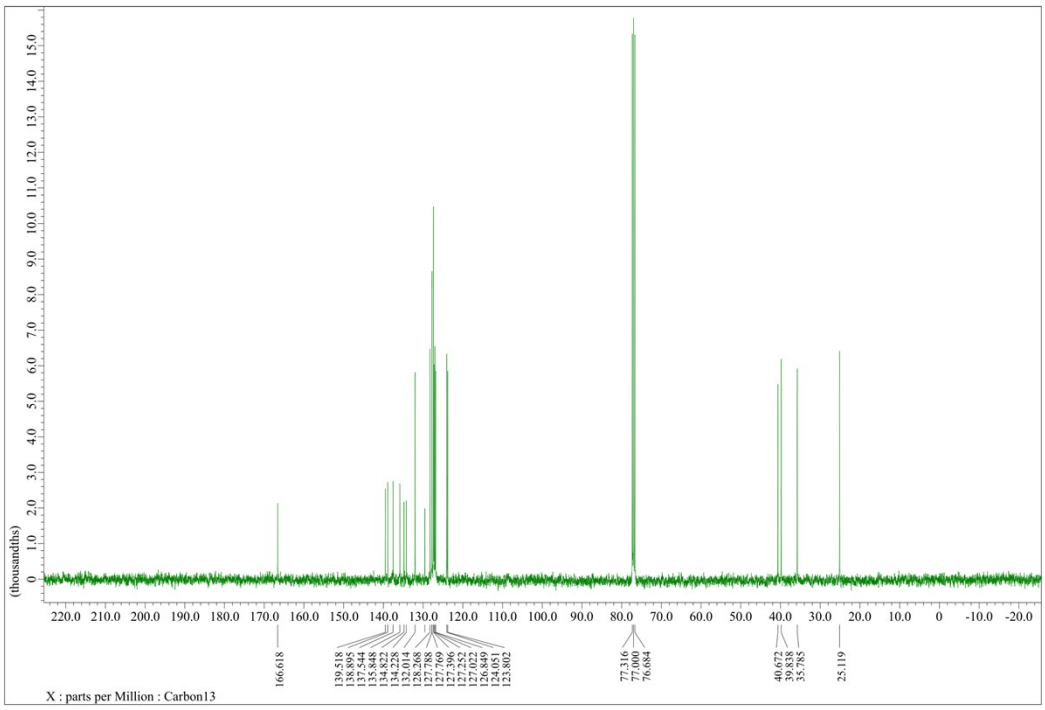
2c (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



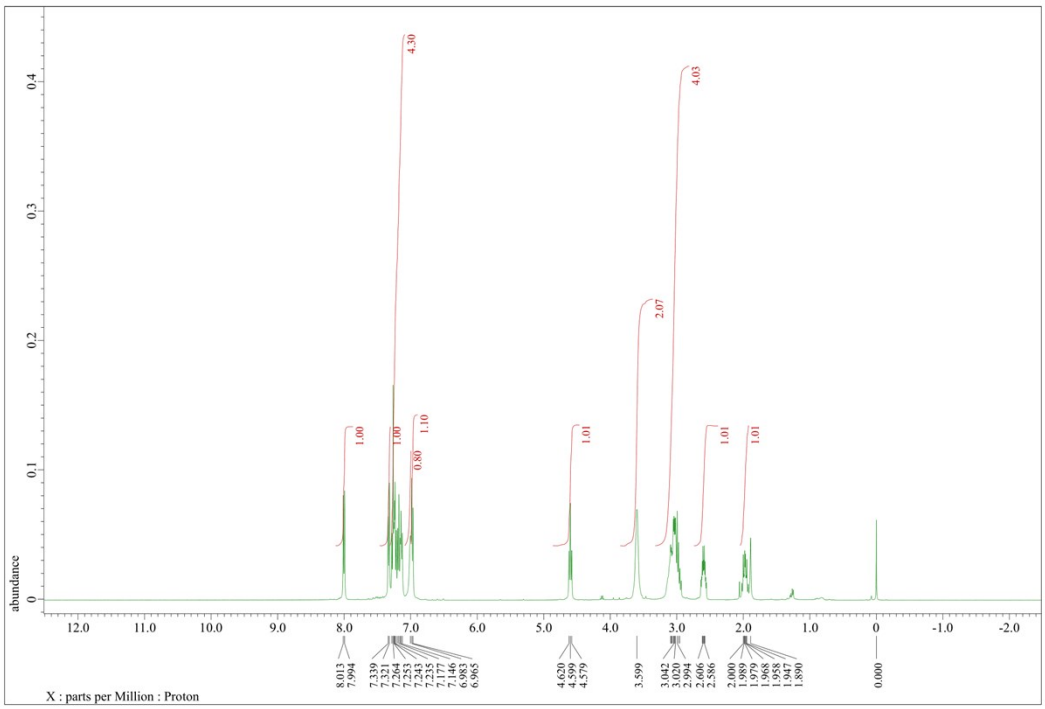


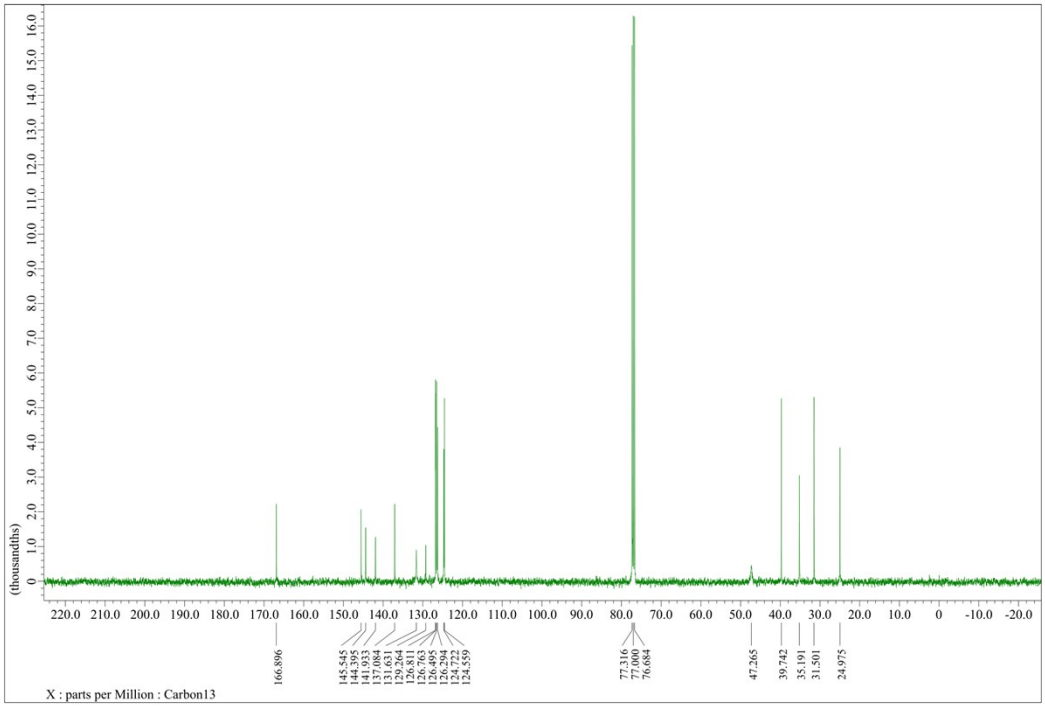
2d (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C), water (1.6 ppm for ^{1}H)



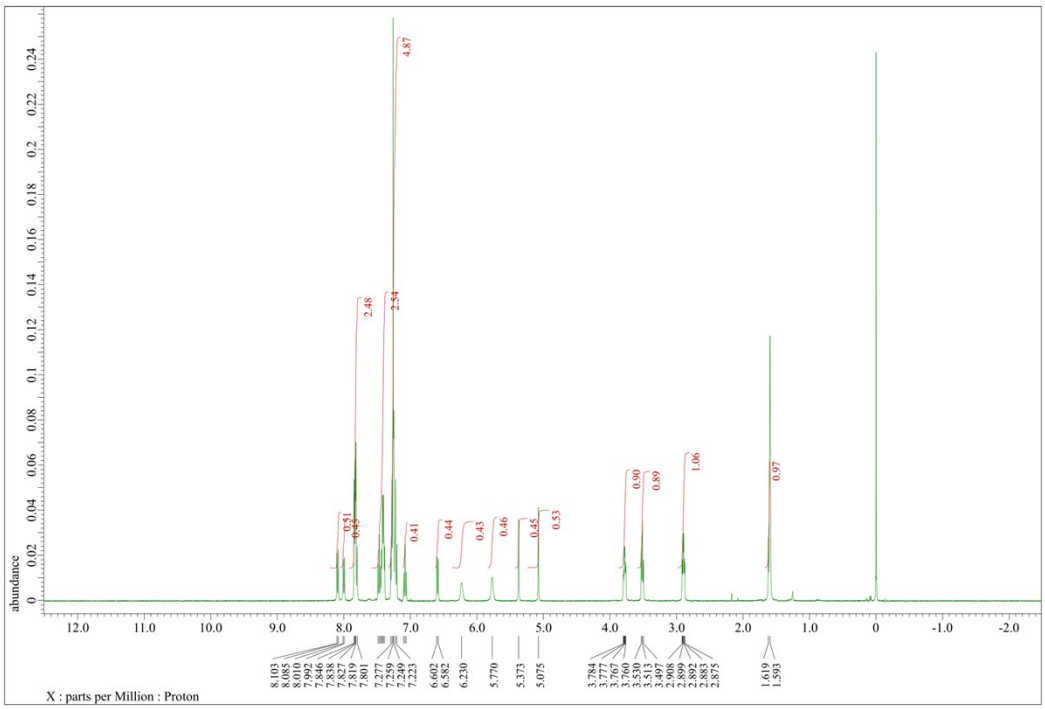


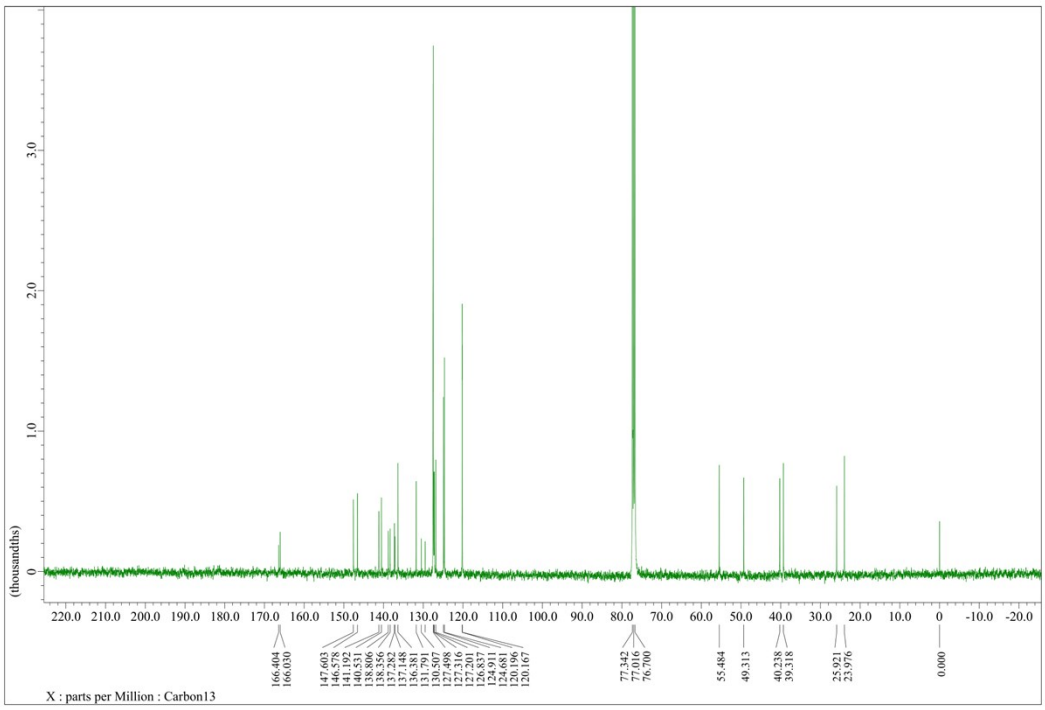
2e (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



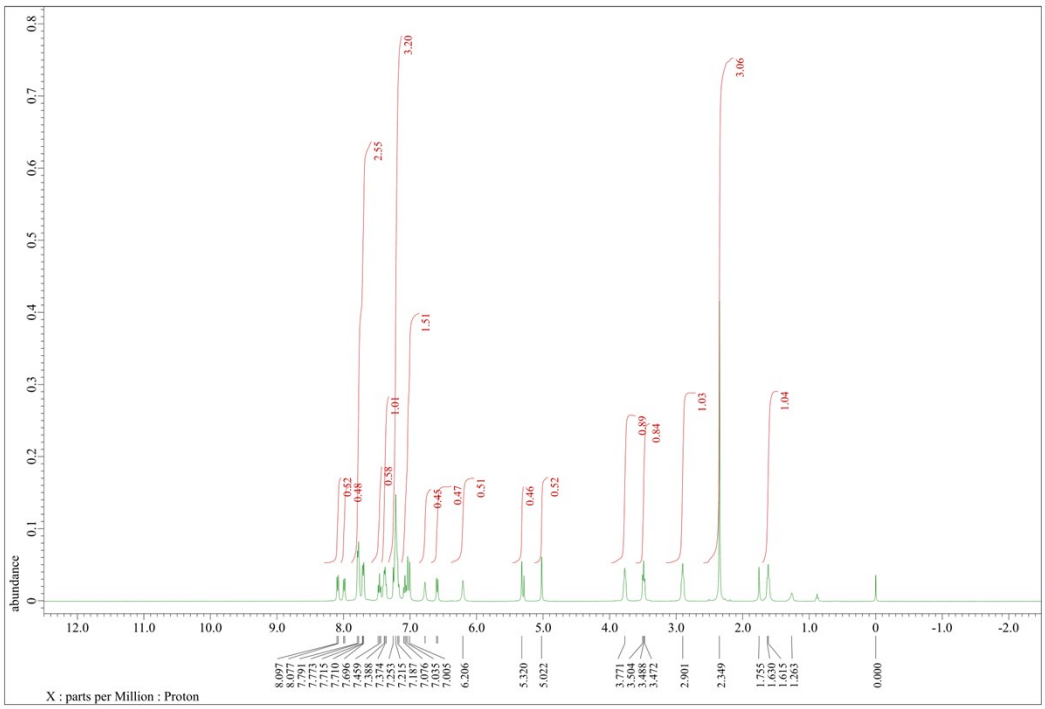


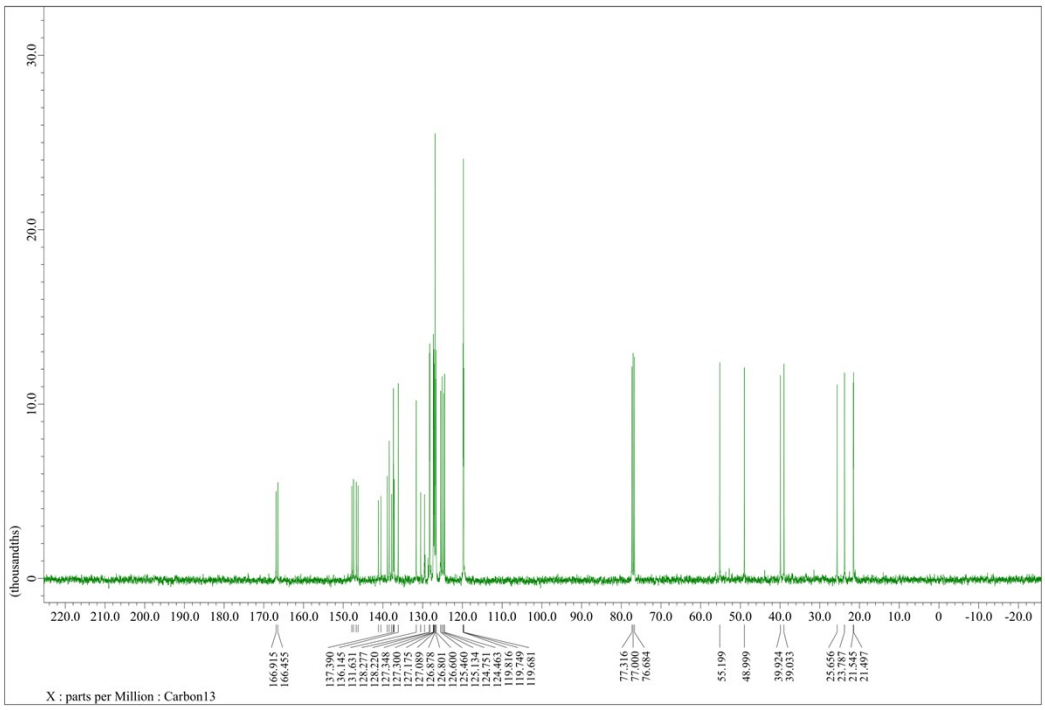
2f (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



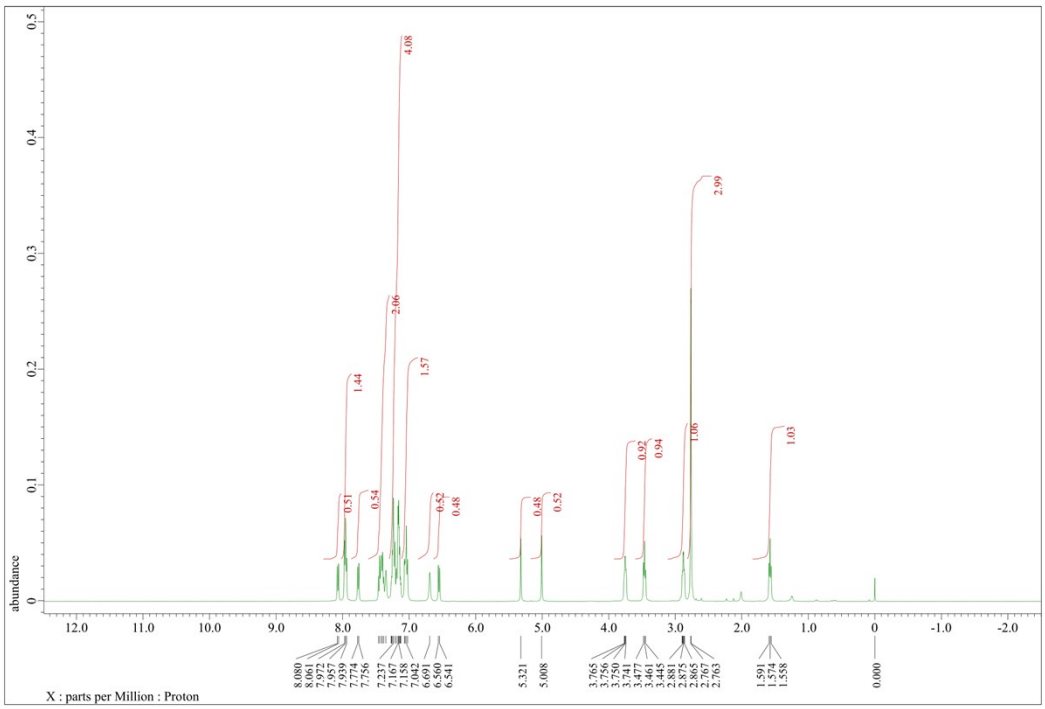


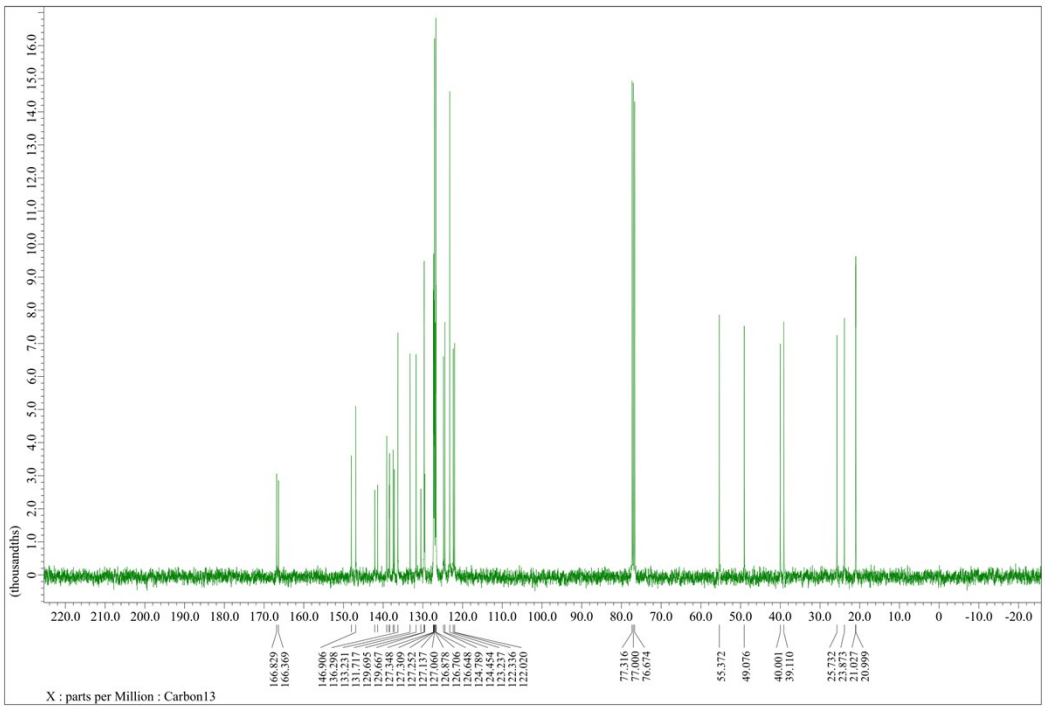
2g (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C), water (1.7 ppm for ^{1}H)



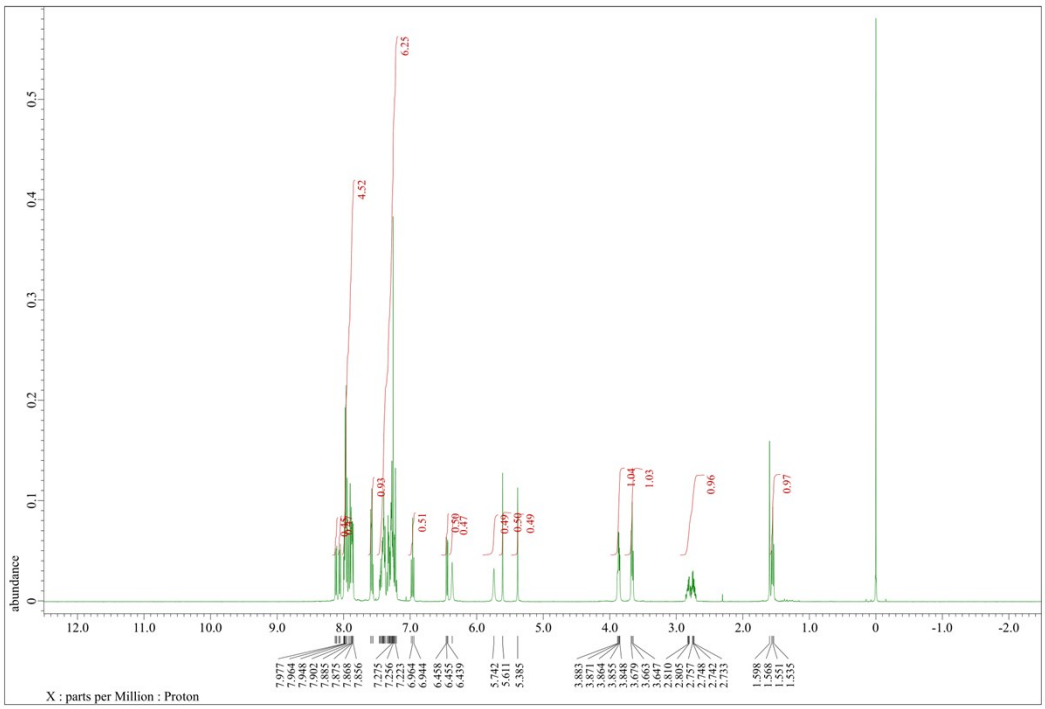


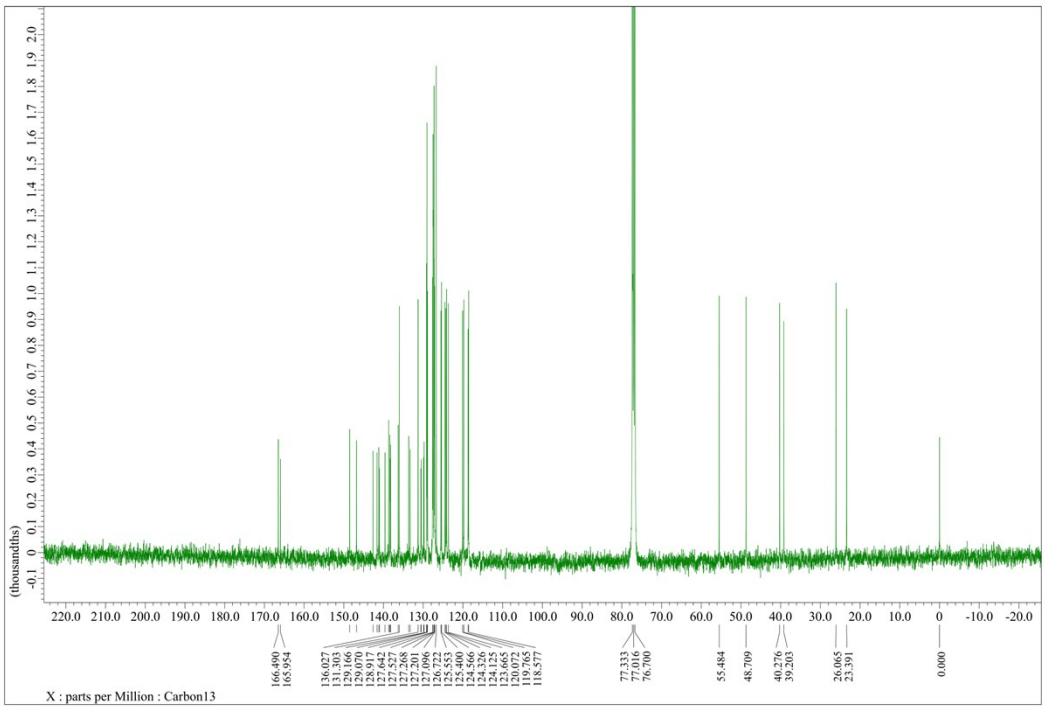
2h (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



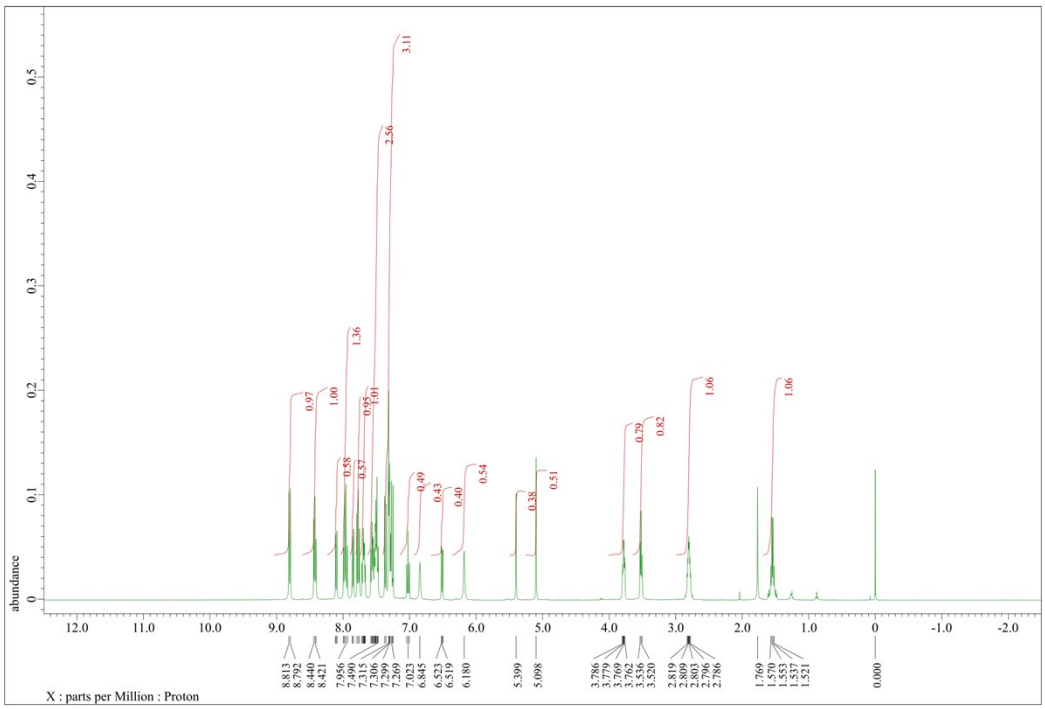


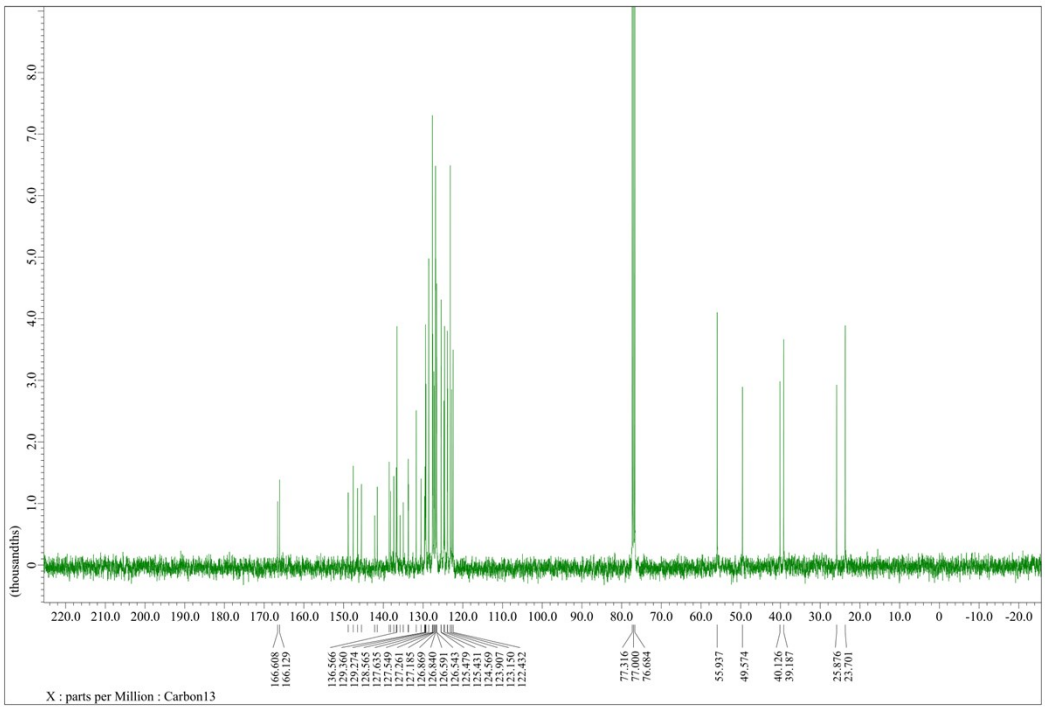
2i (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



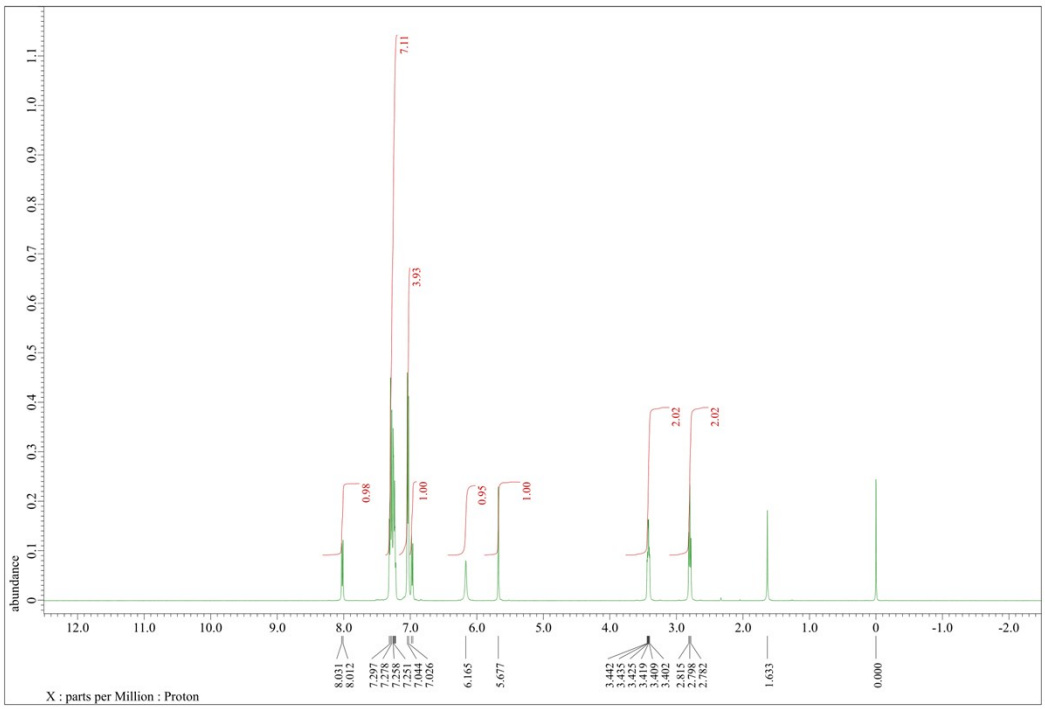


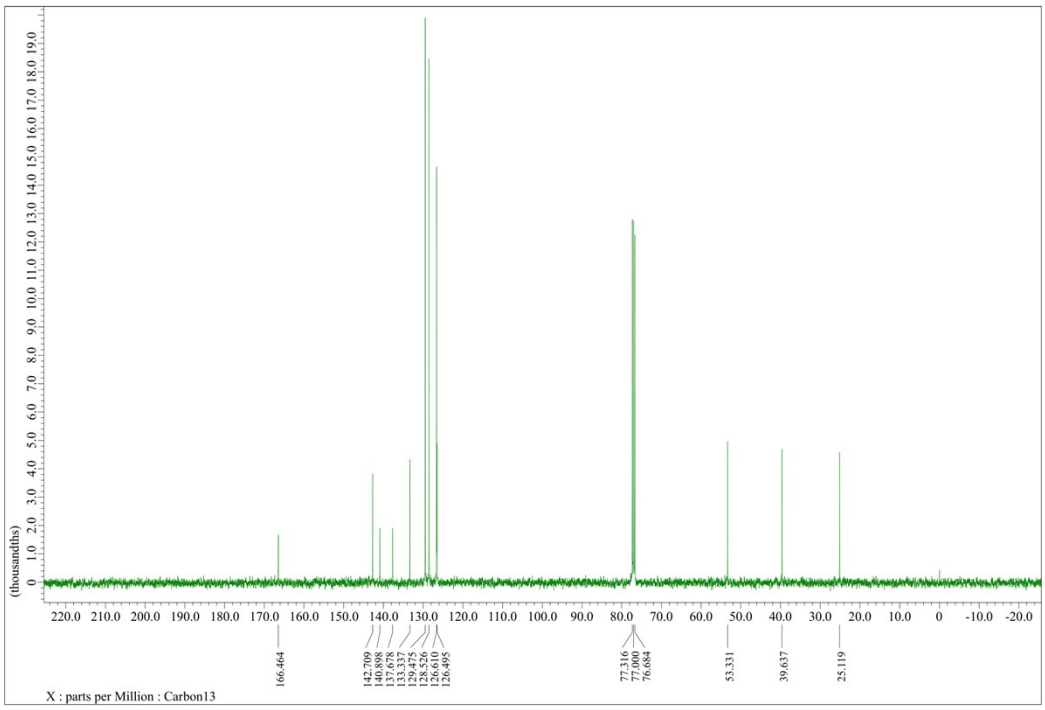
2j (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C), water (1.8 ppm for ^{1}H)



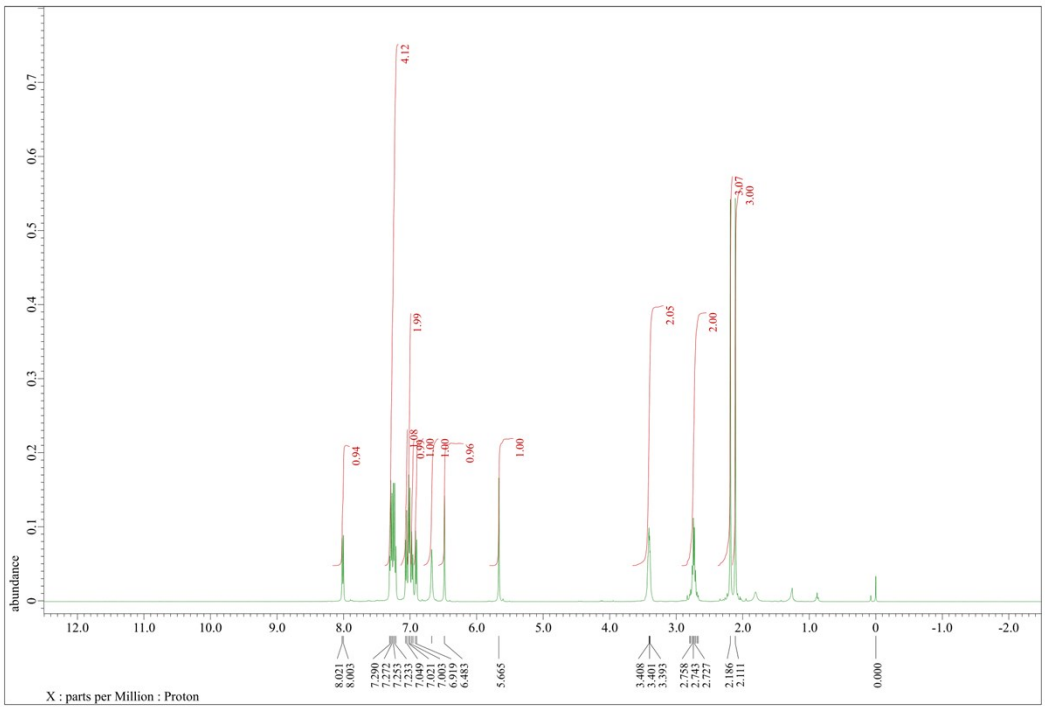


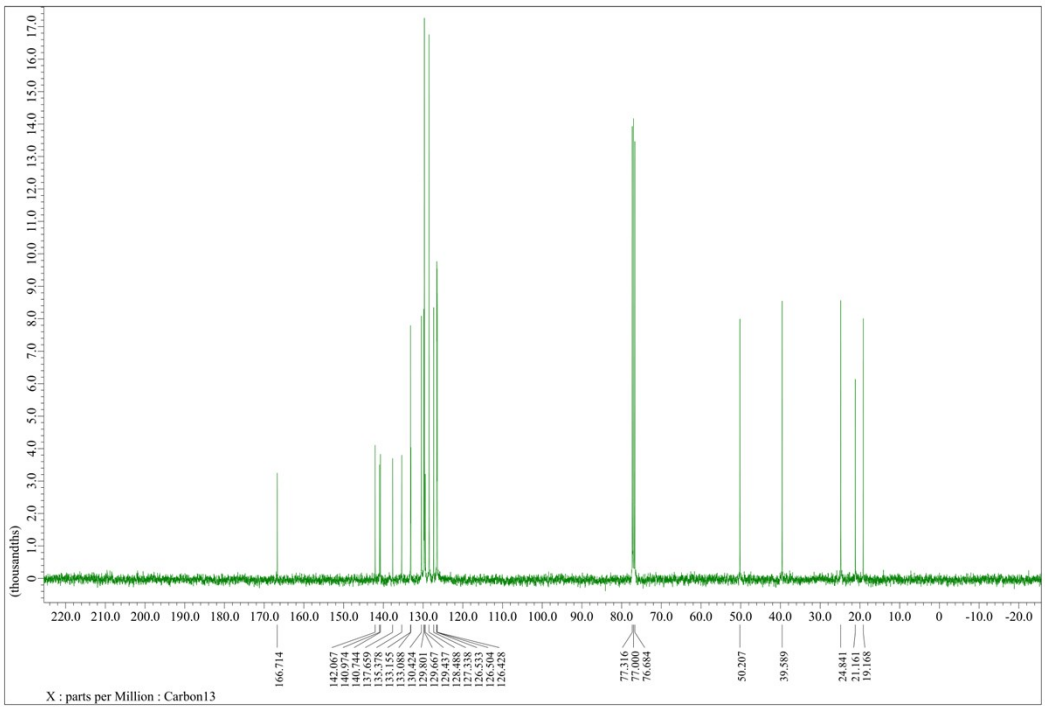
4a (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C), water (1.6 ppm for ^{1}H)



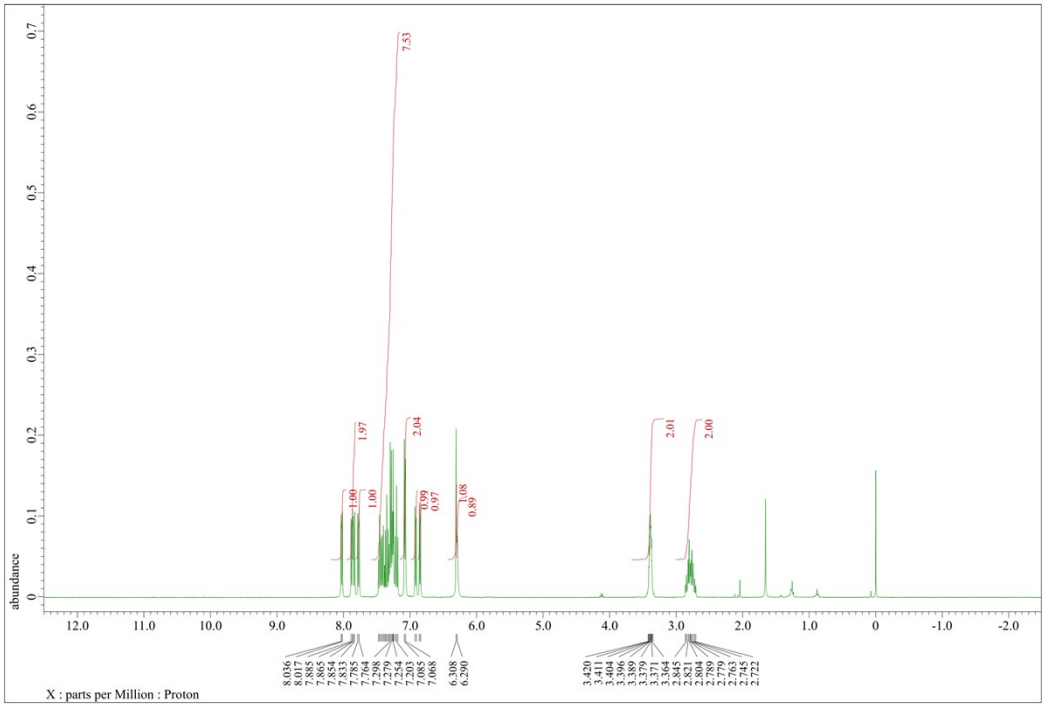


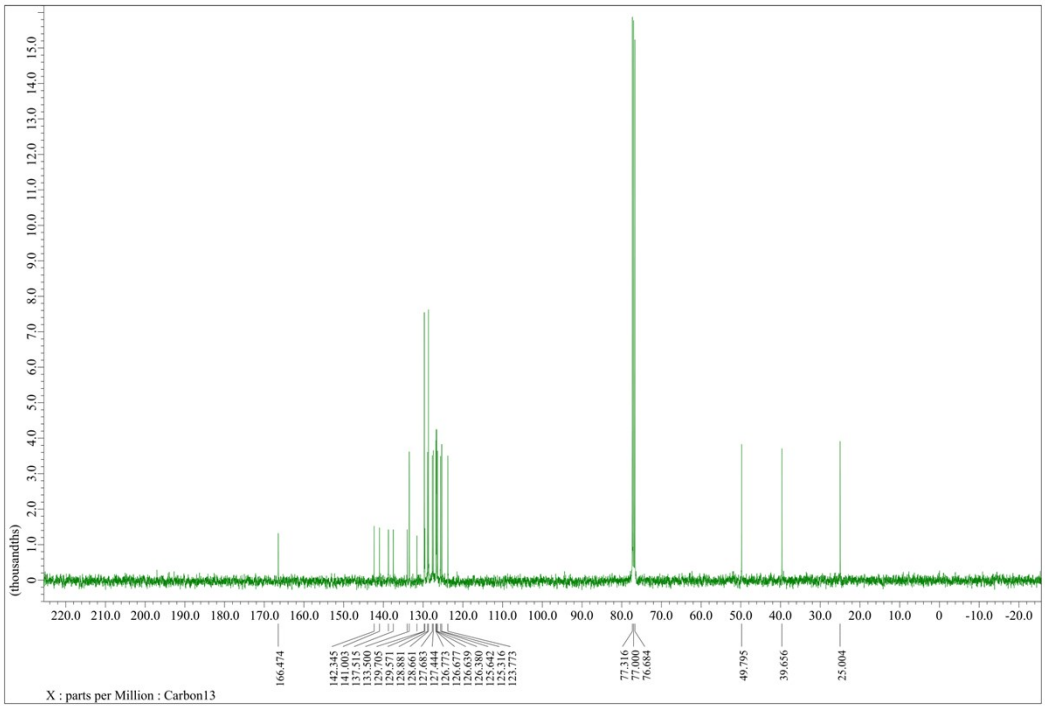
4b (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



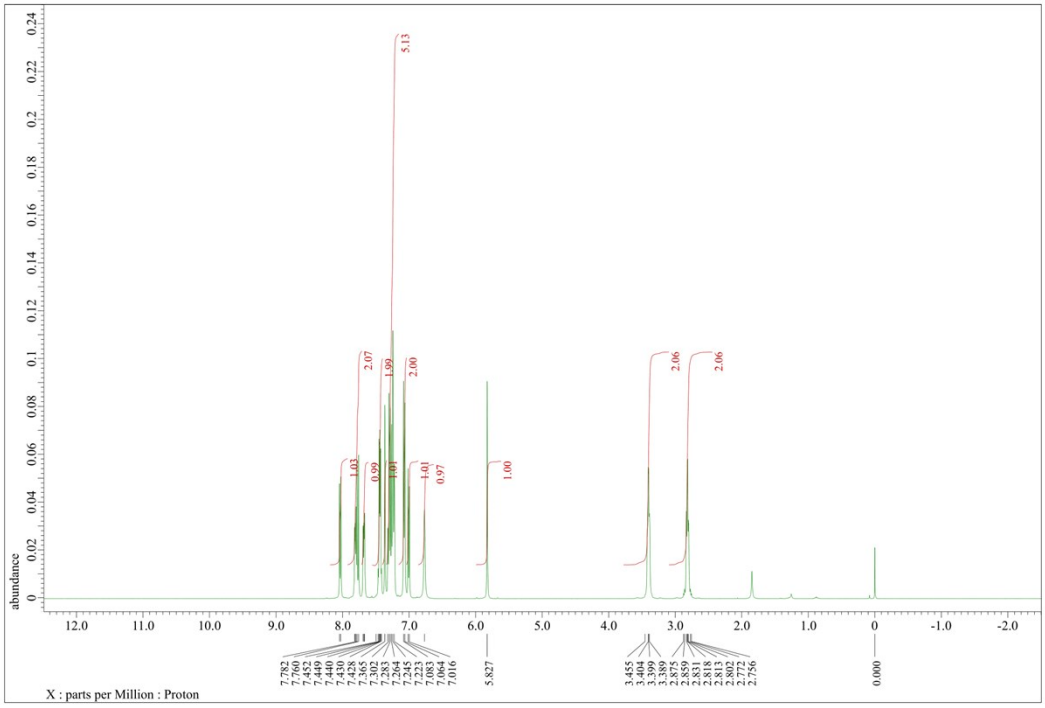


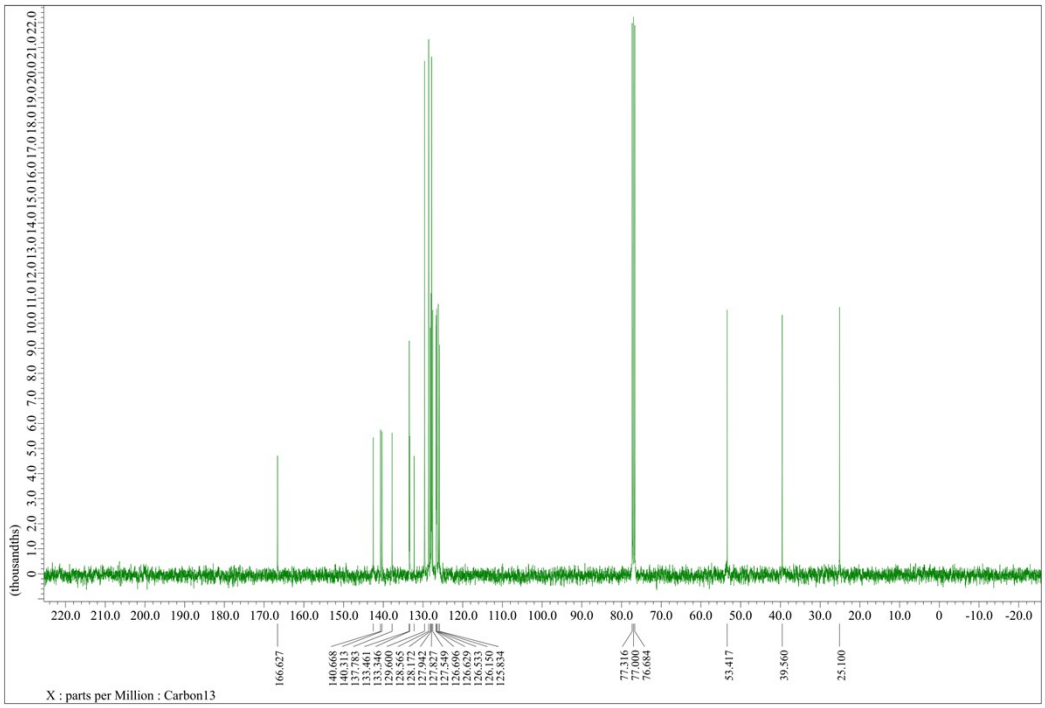
4c-*α* (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C), water (1.6 ppm for ^{1}H)



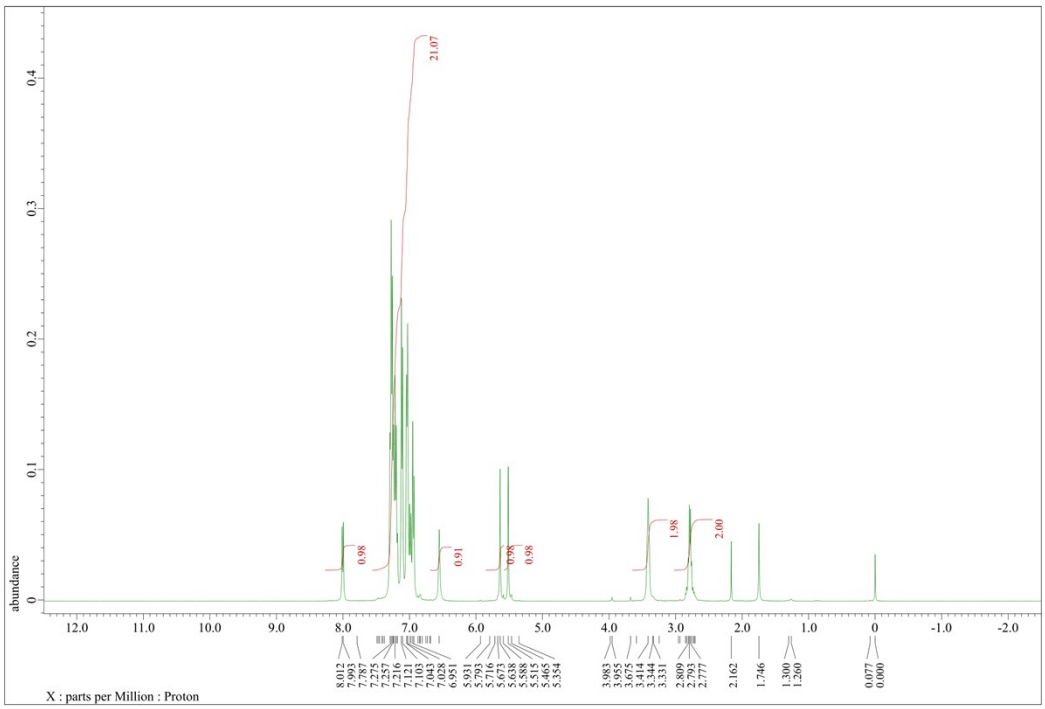


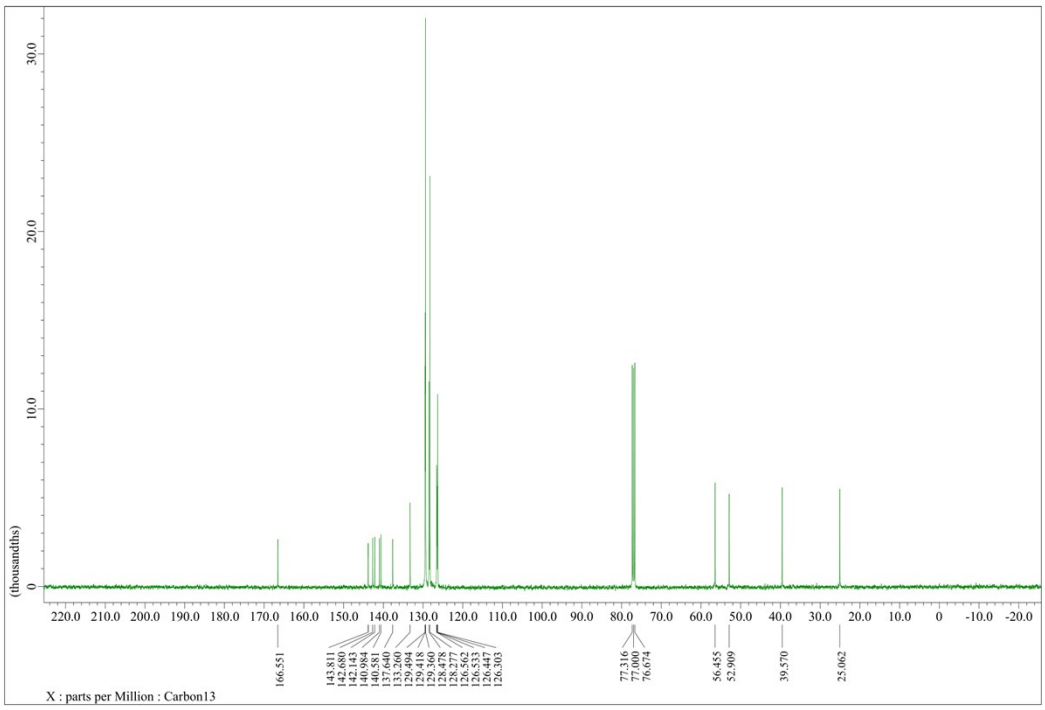
4c-*β* (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C), water (1.8 ppm for ^{1}H)



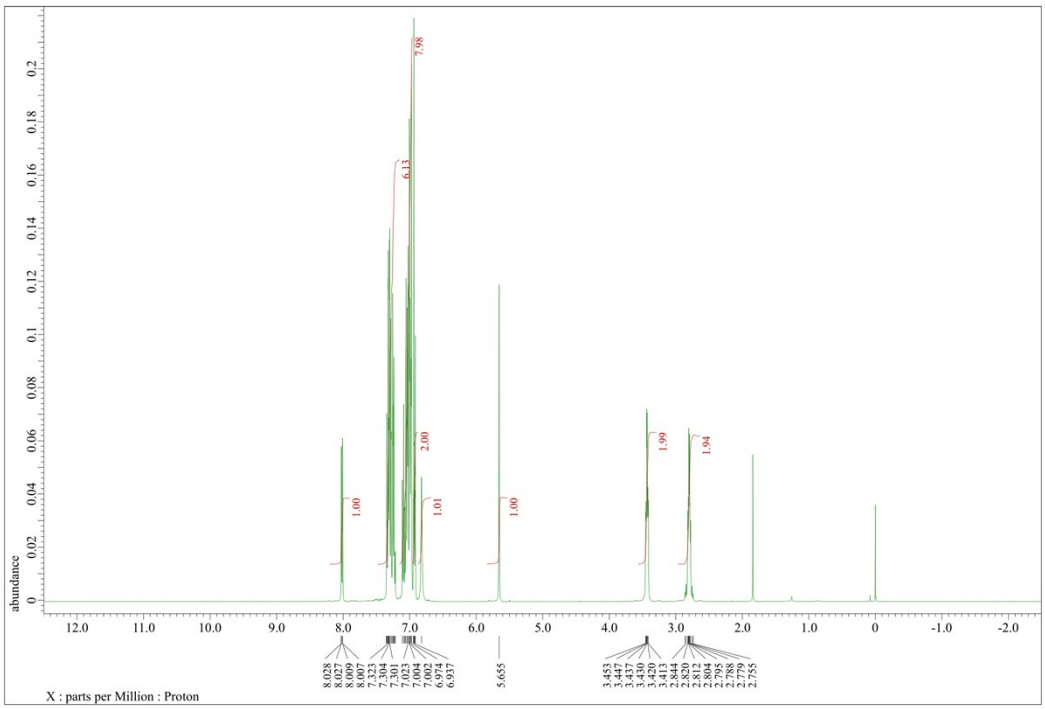


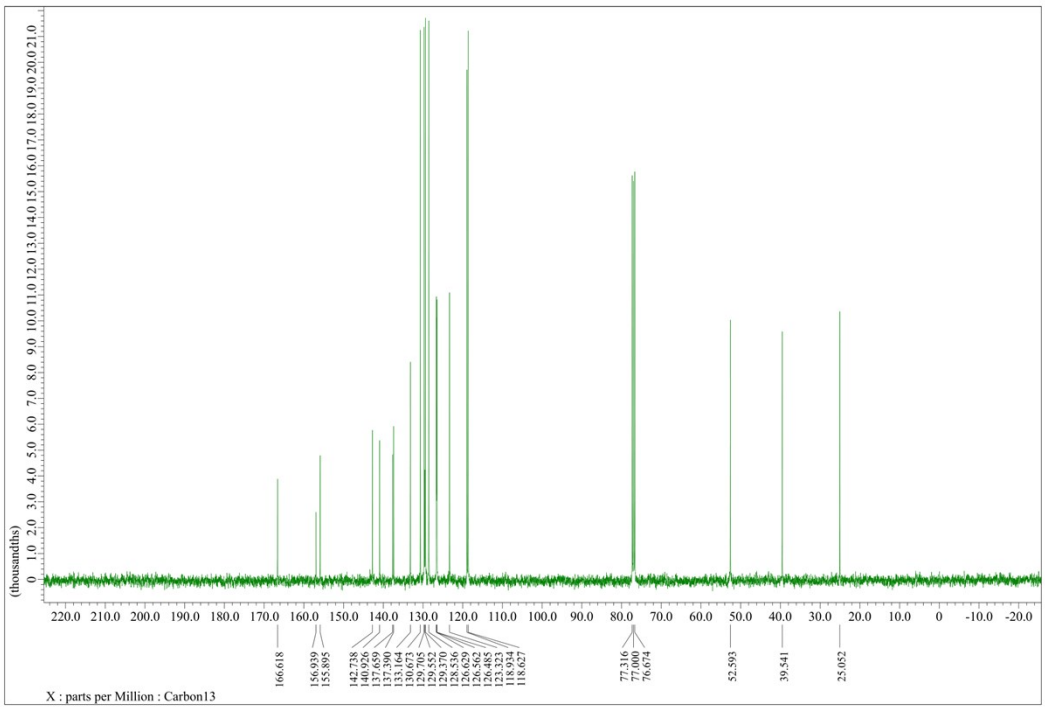
4d (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C), water (1.7 ppm for ^{1}H)



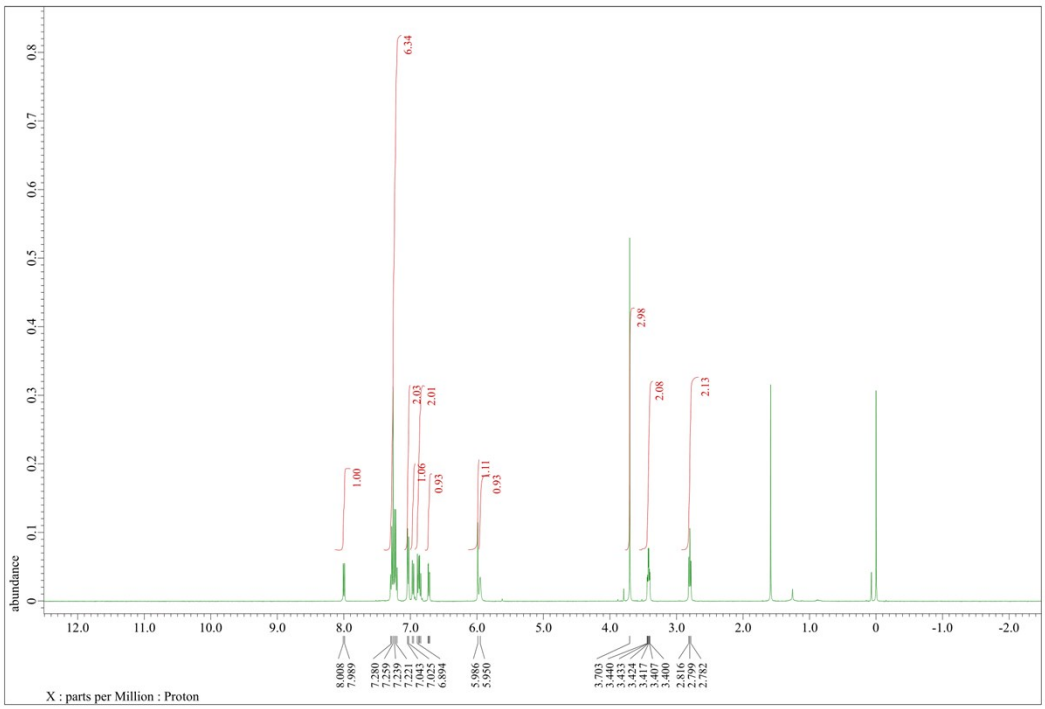


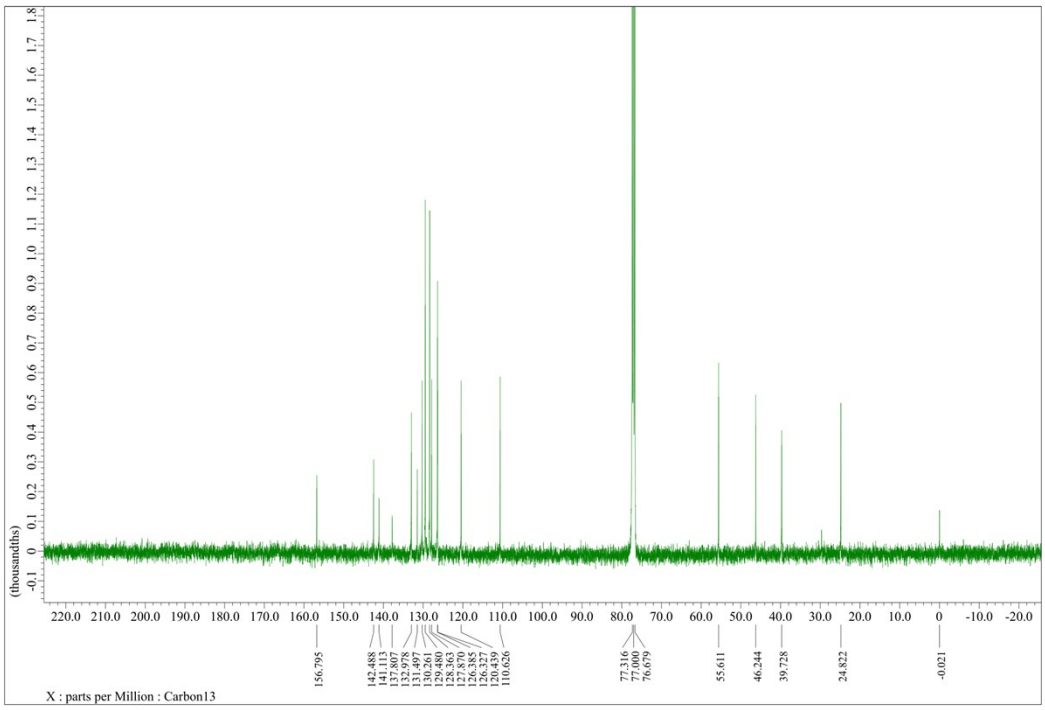
4e (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C), water (1.8 ppm for ^{1}H)



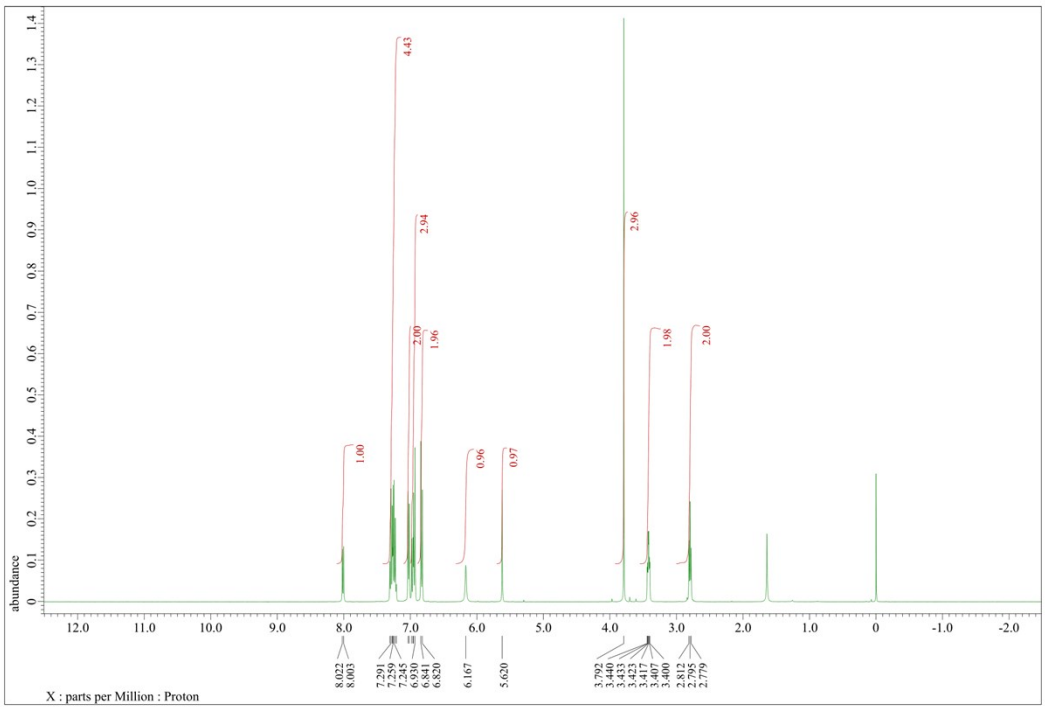


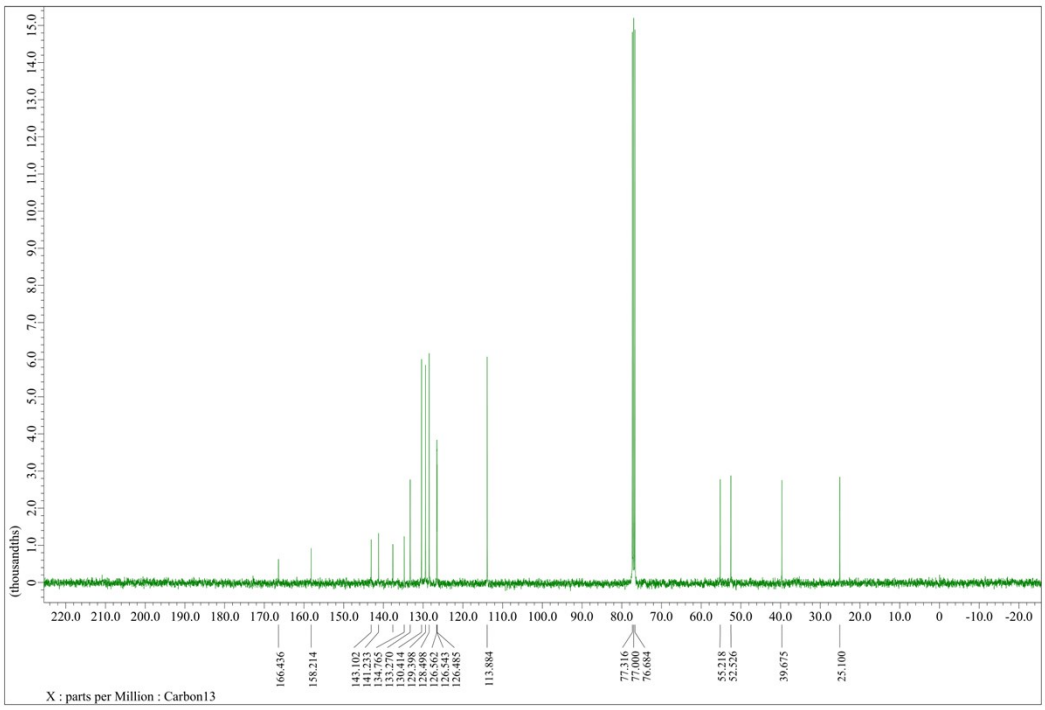
4f-*o* (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C), water (1.6 ppm for ^{1}H)



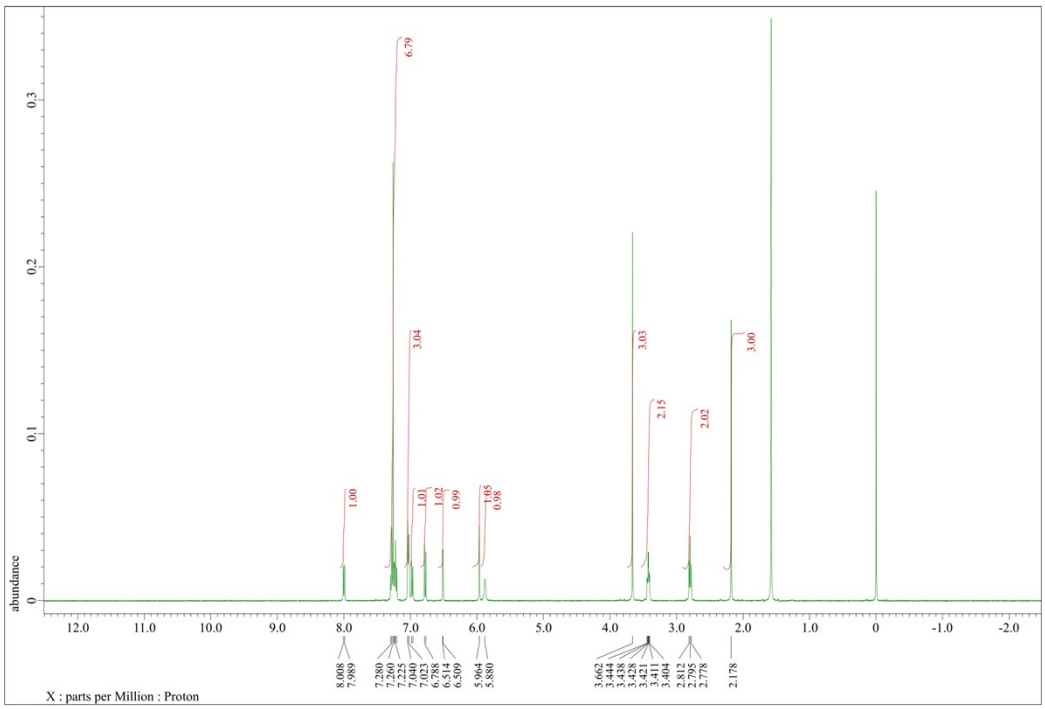


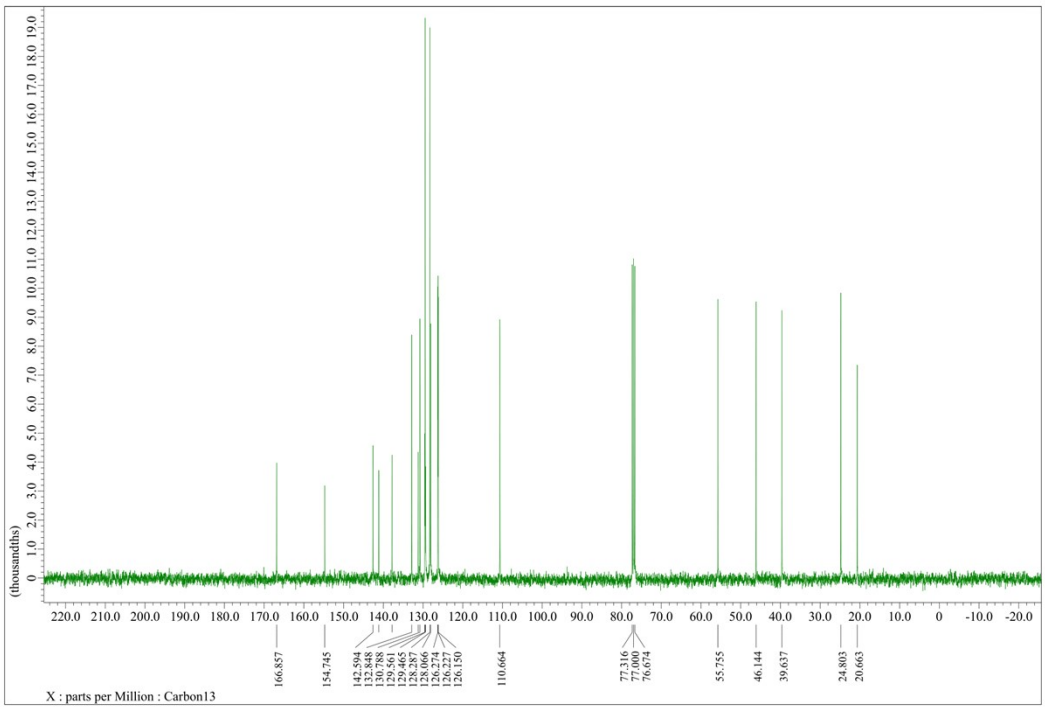
4f-*p* (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C), water (1.6 ppm for ^{1}H)



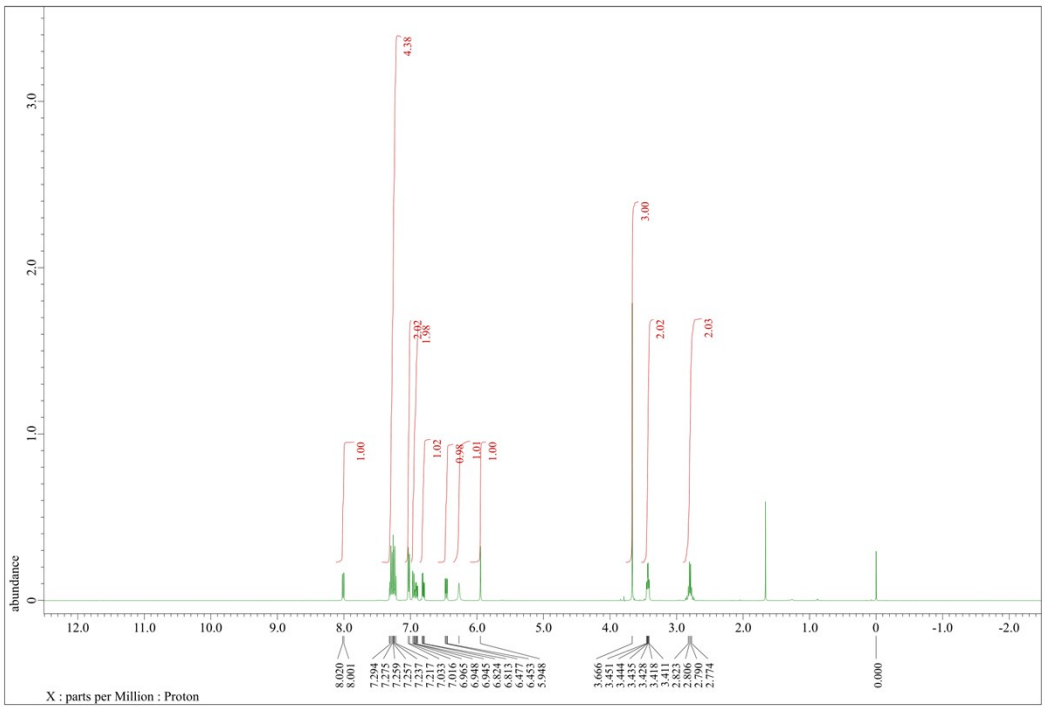


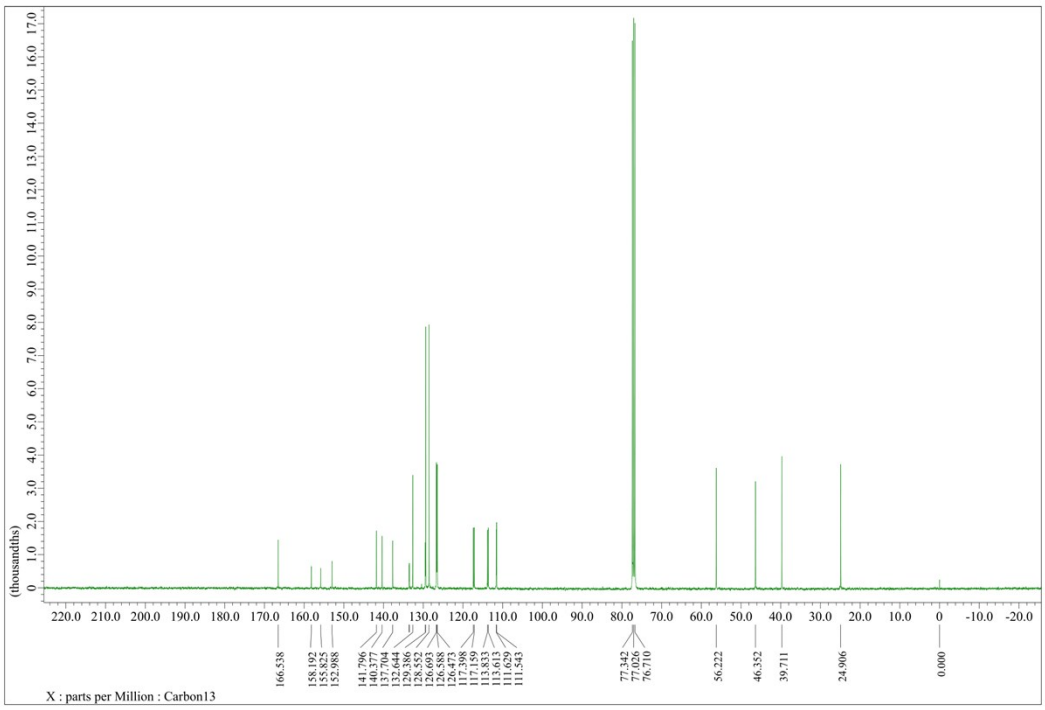
4g (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C), water (1.6 ppm for ^{1}H)



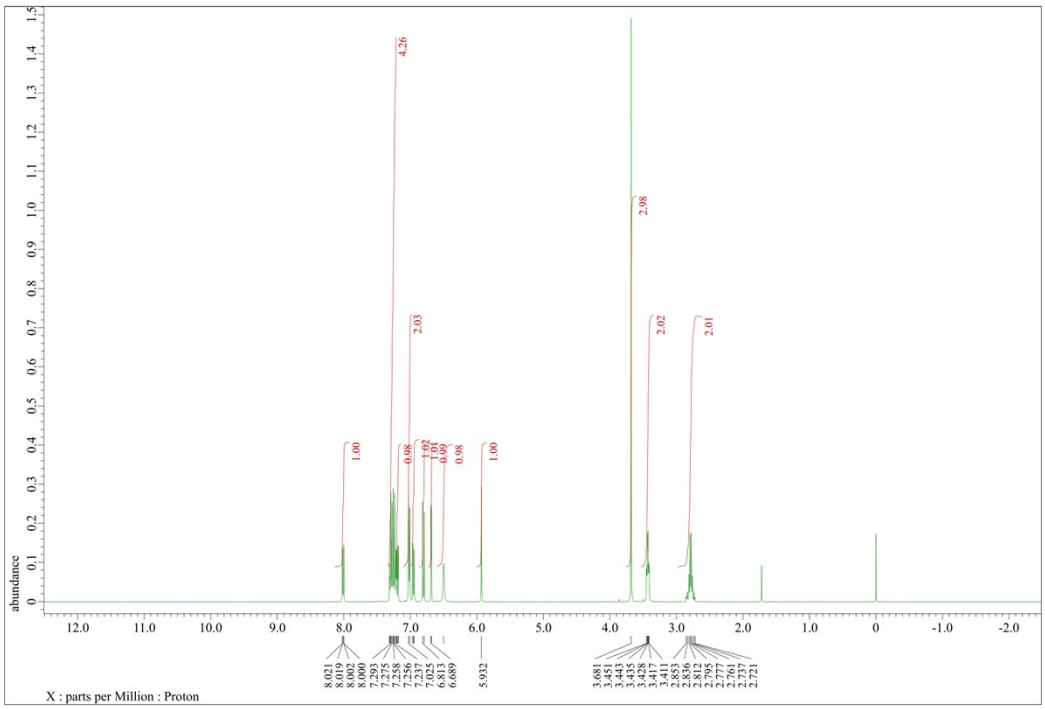


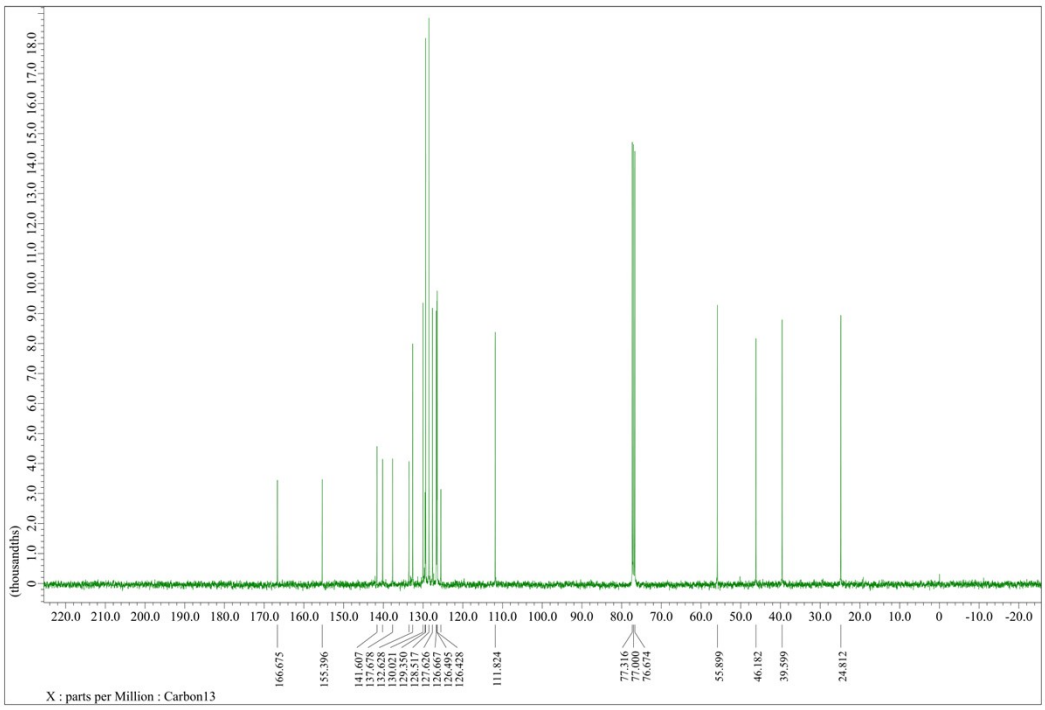
4h (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C), water (1.6 ppm for ^{1}H)



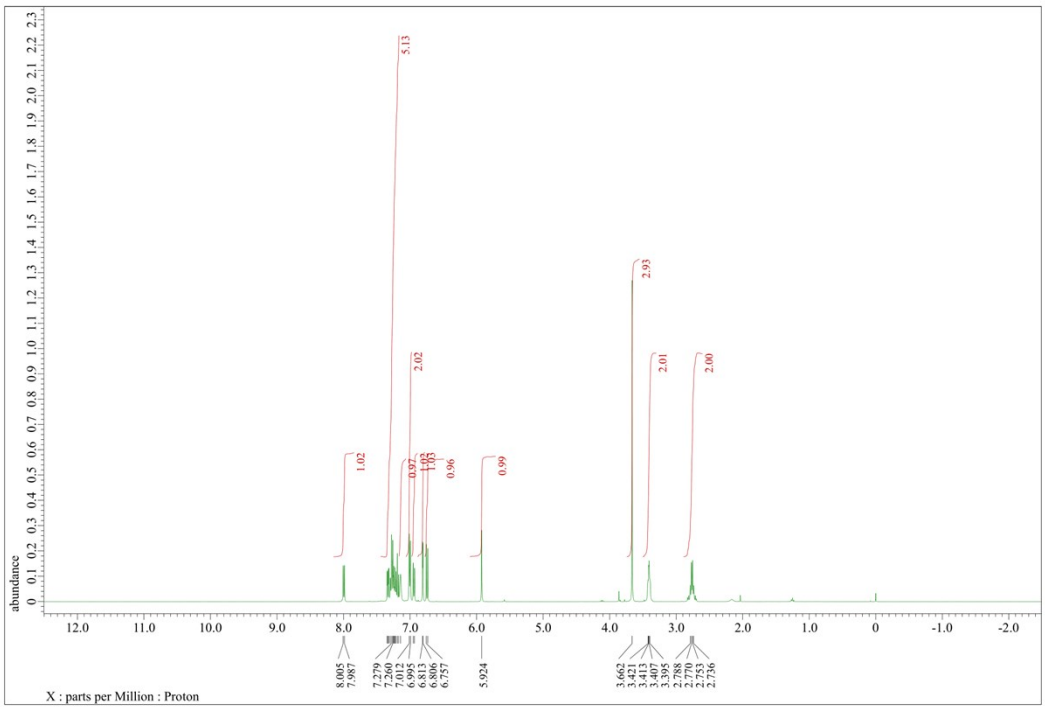


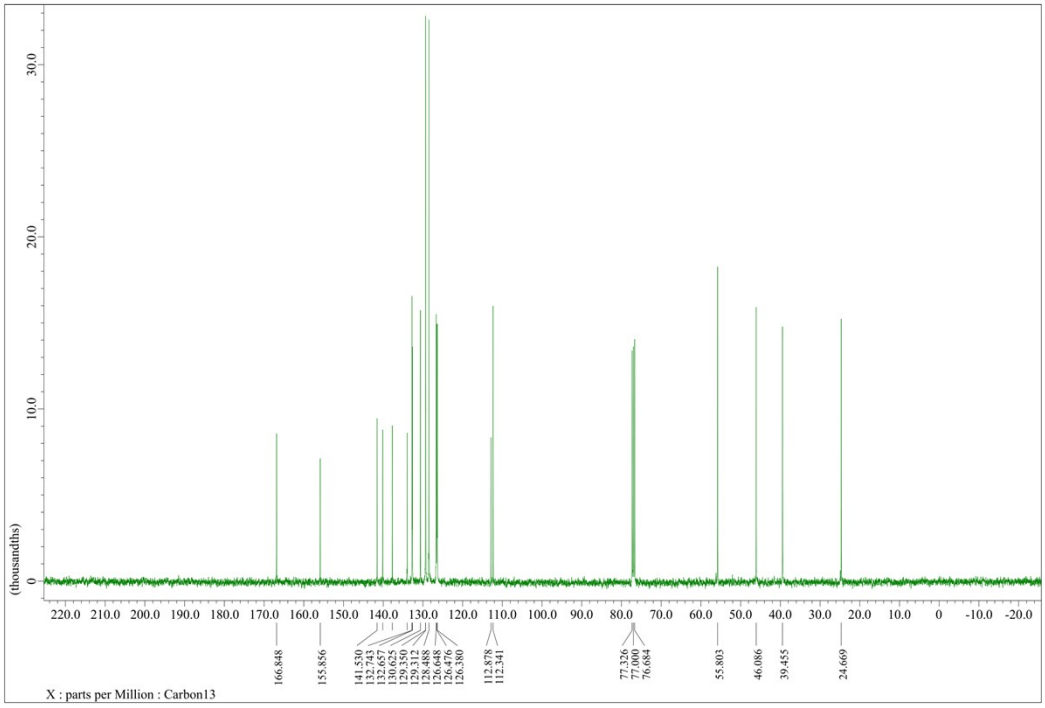
4i (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C), water (1.6 ppm for ^{1}H)



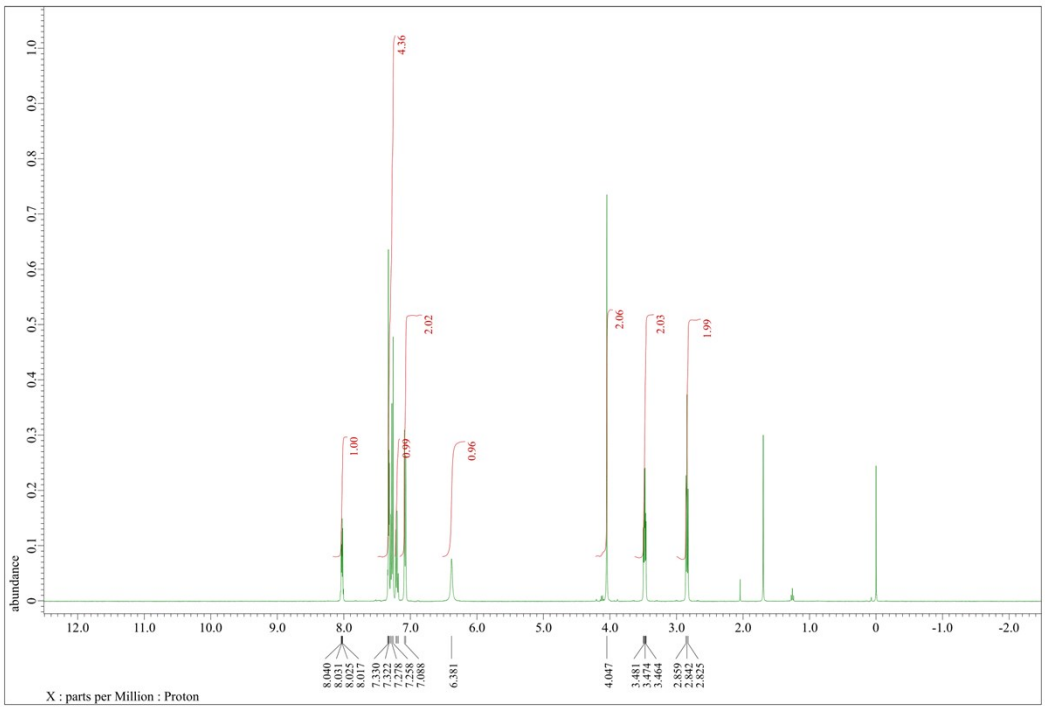


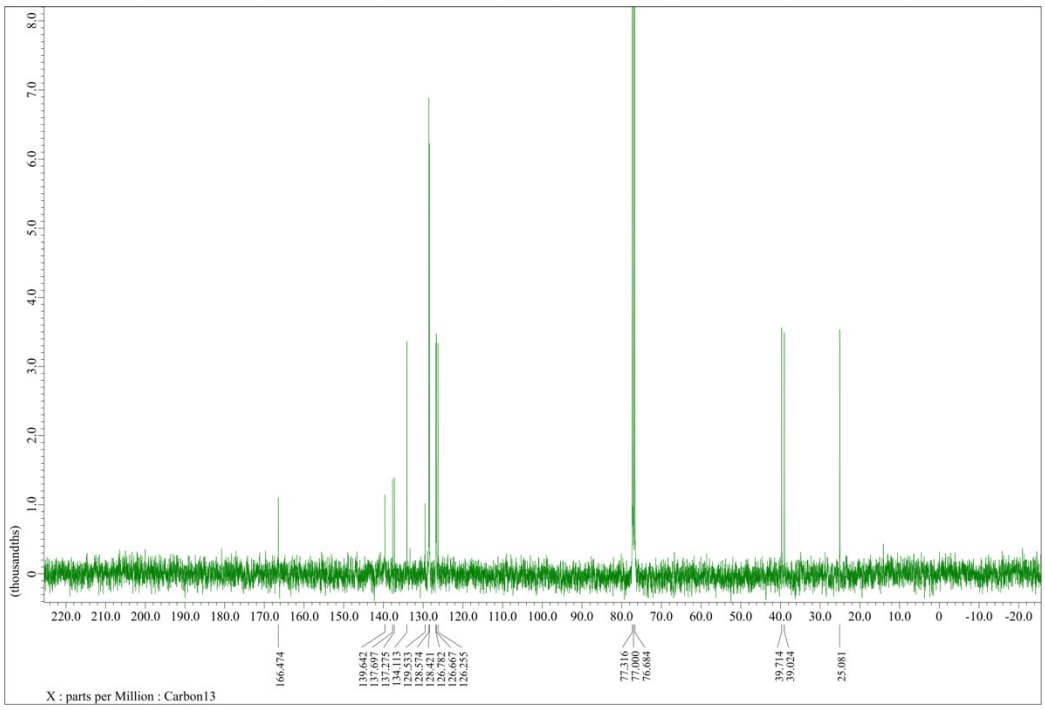
4j (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



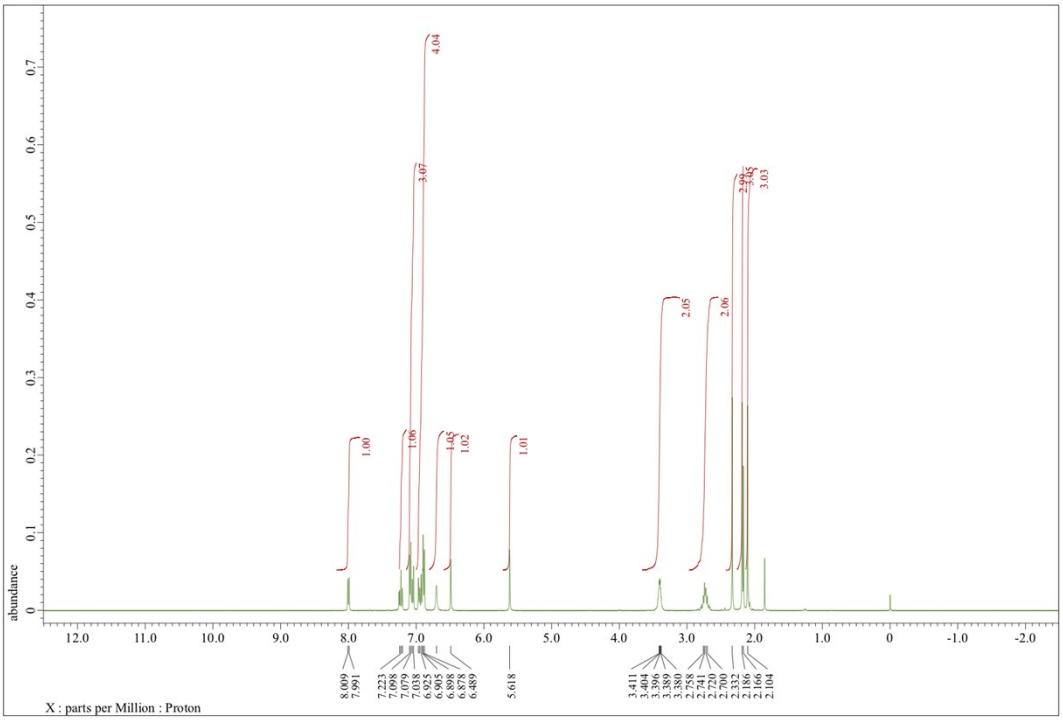


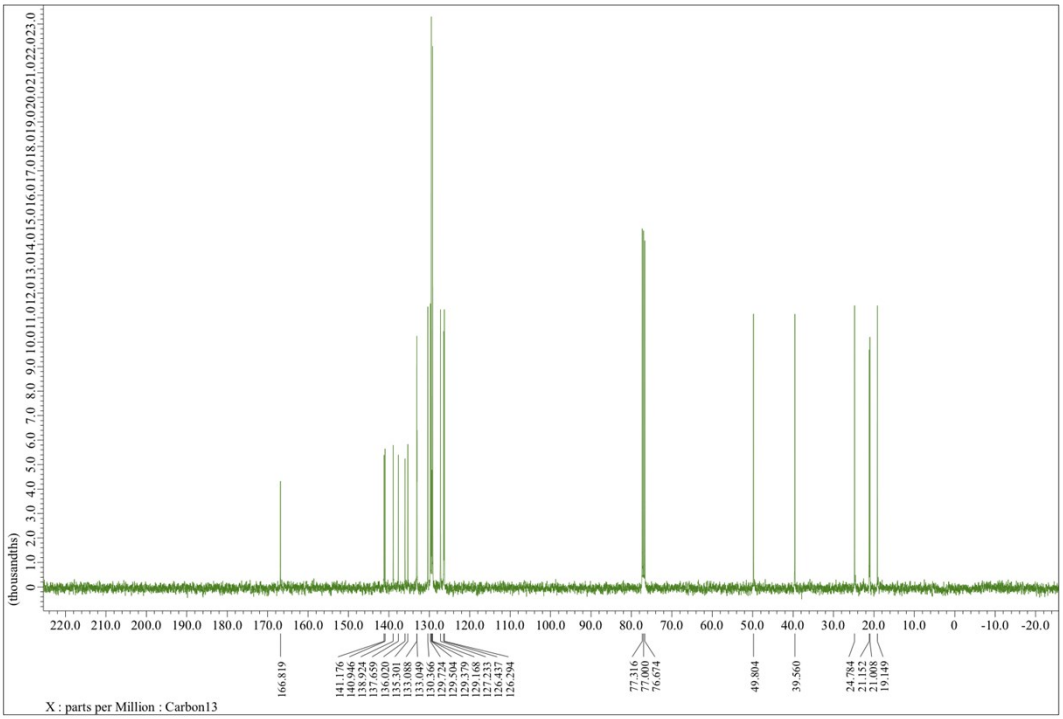
4k (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C), water (1.6 ppm for ^{1}H)



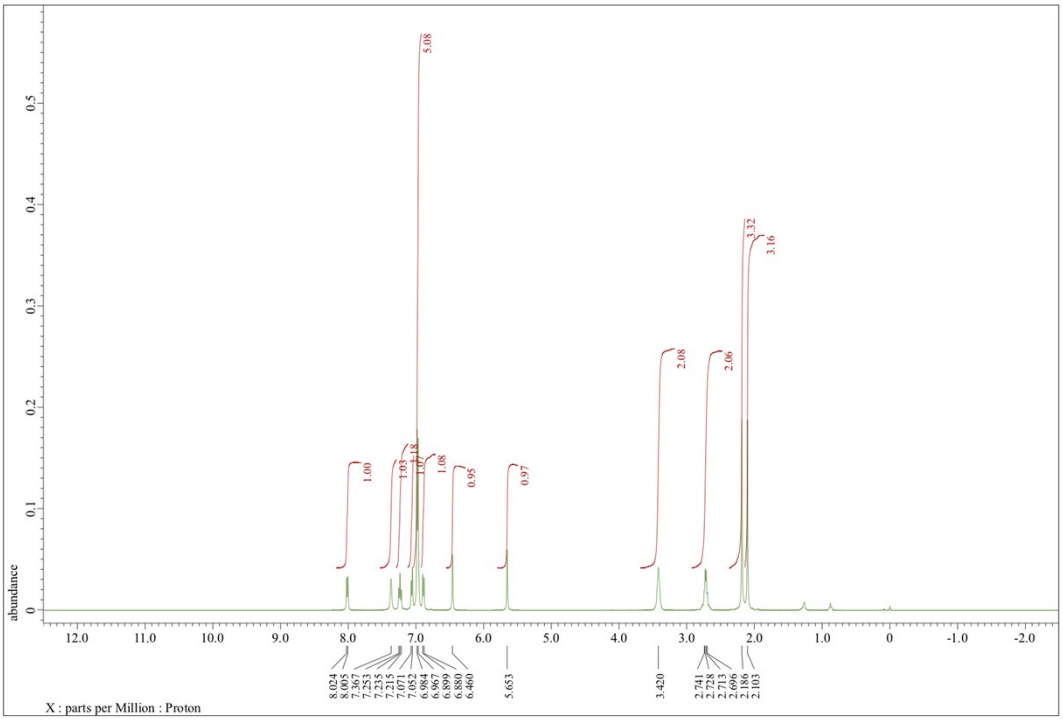


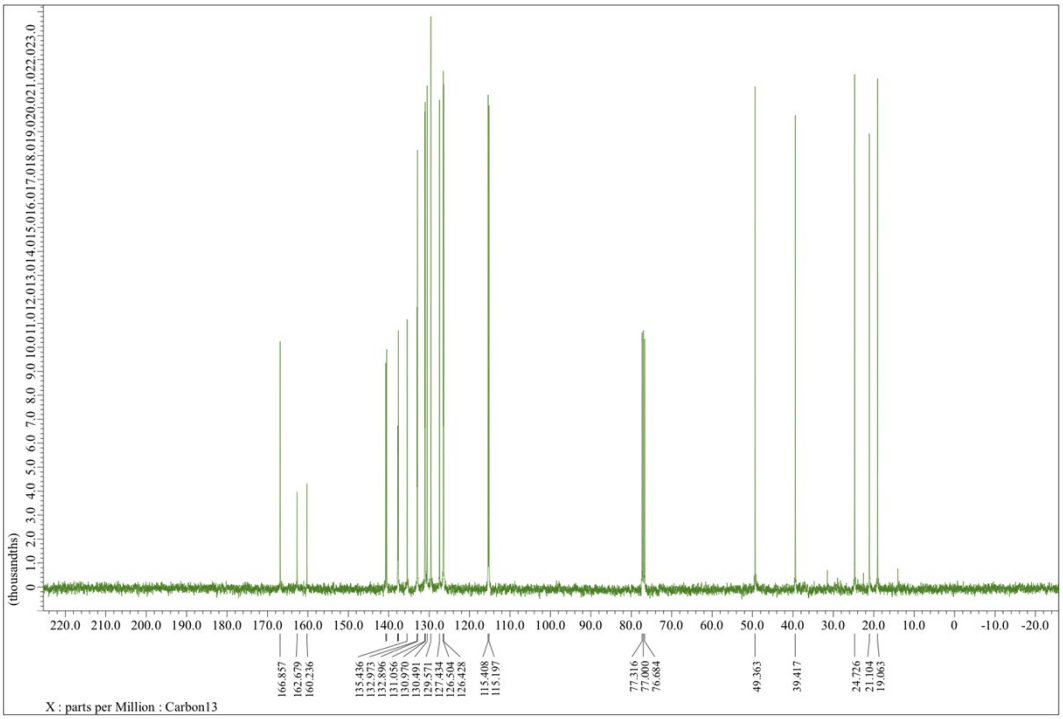
4l (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



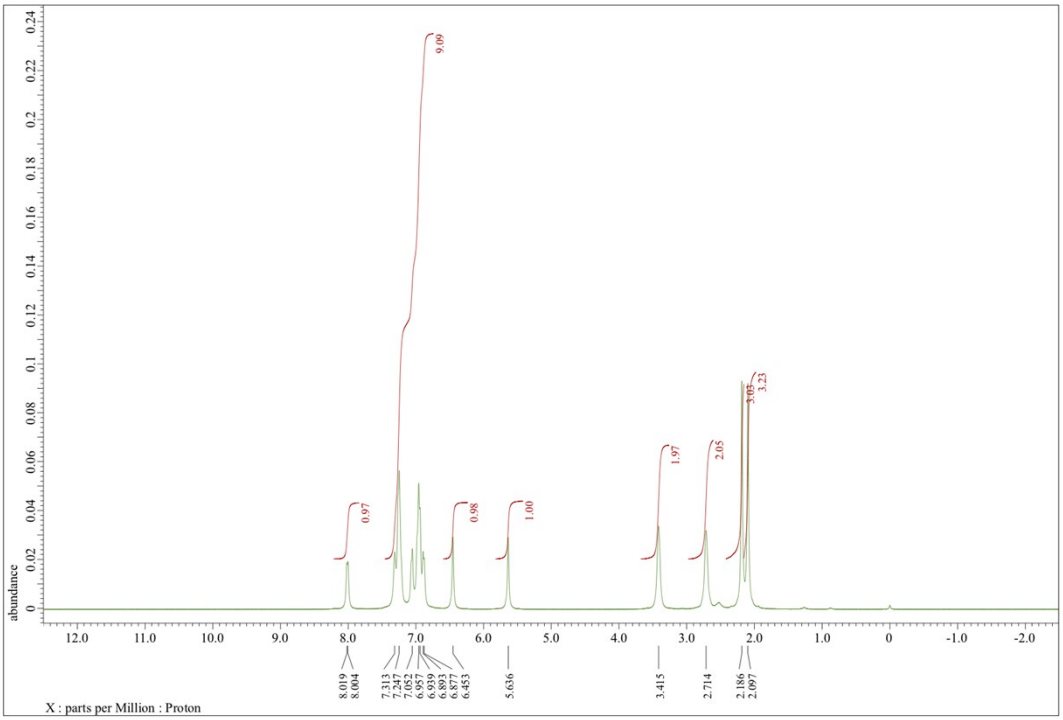


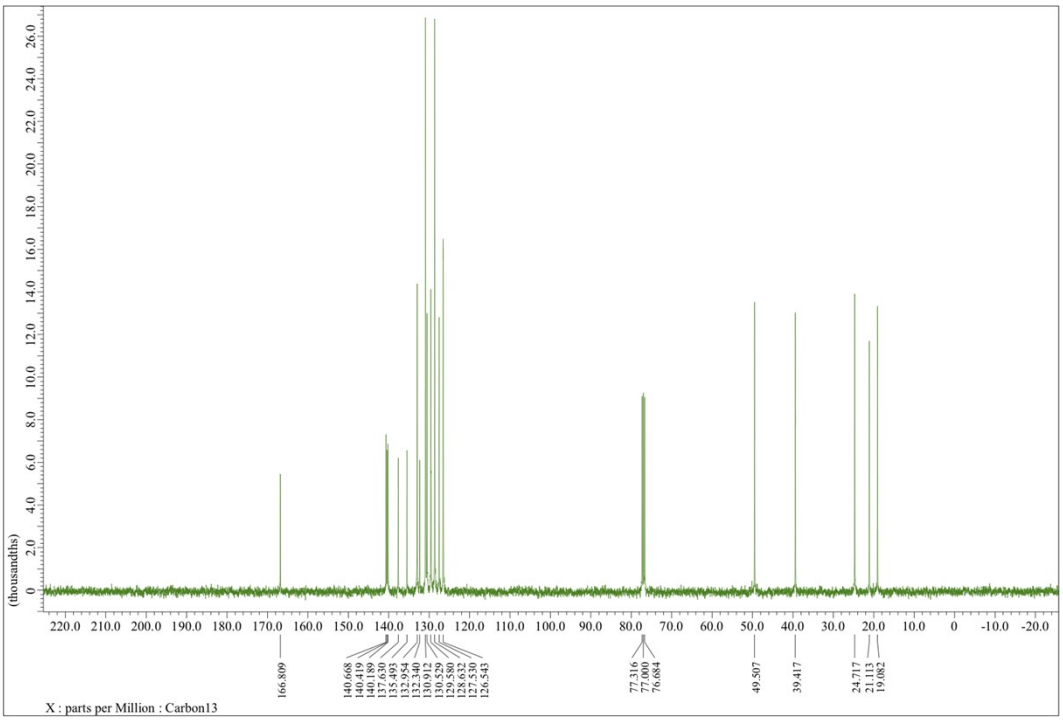
4m (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



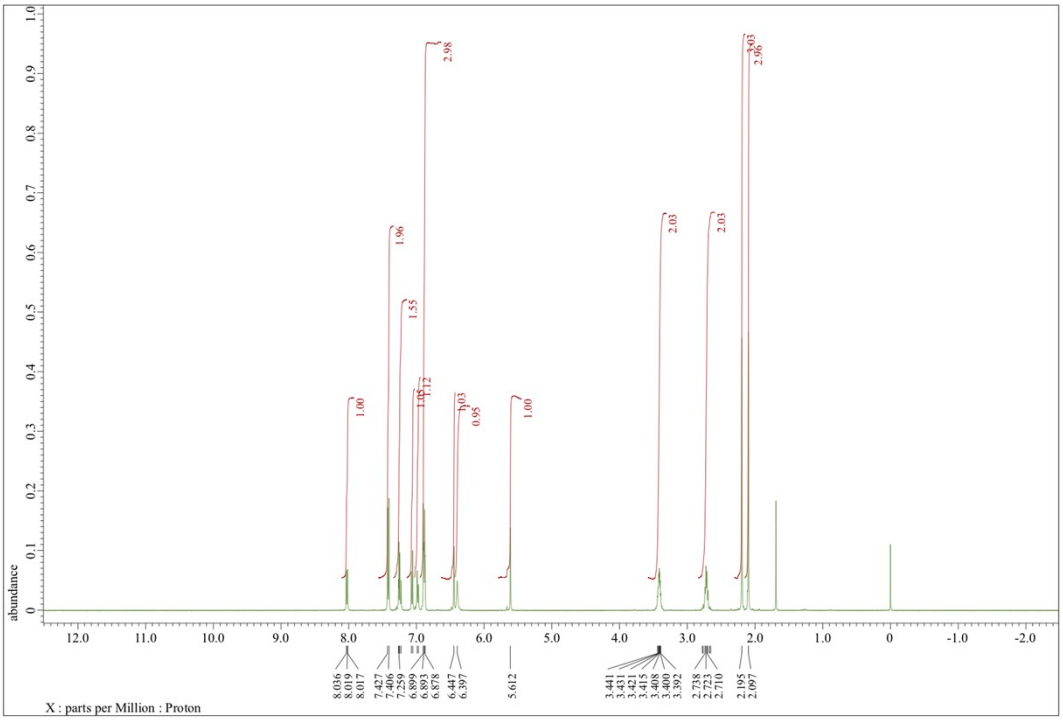


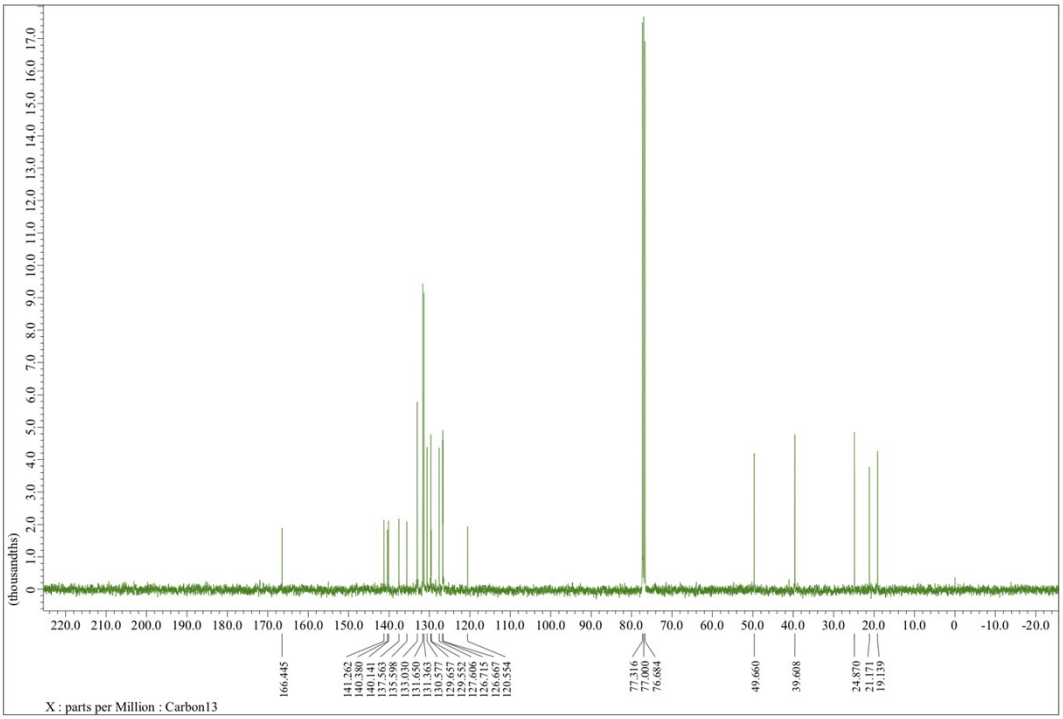
4n (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



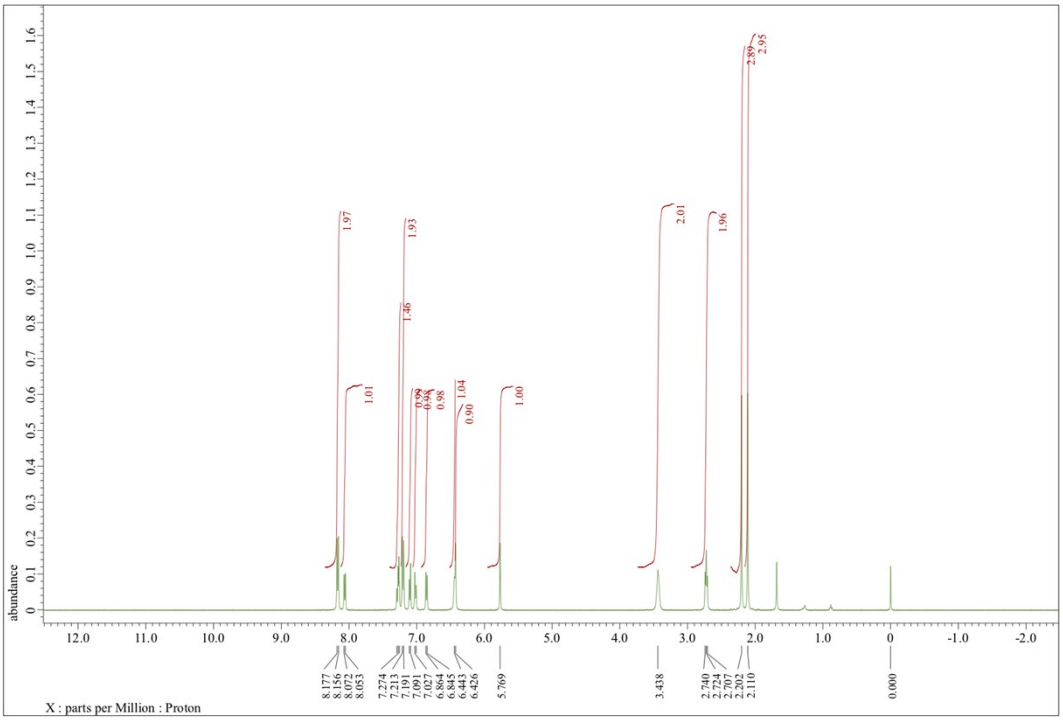


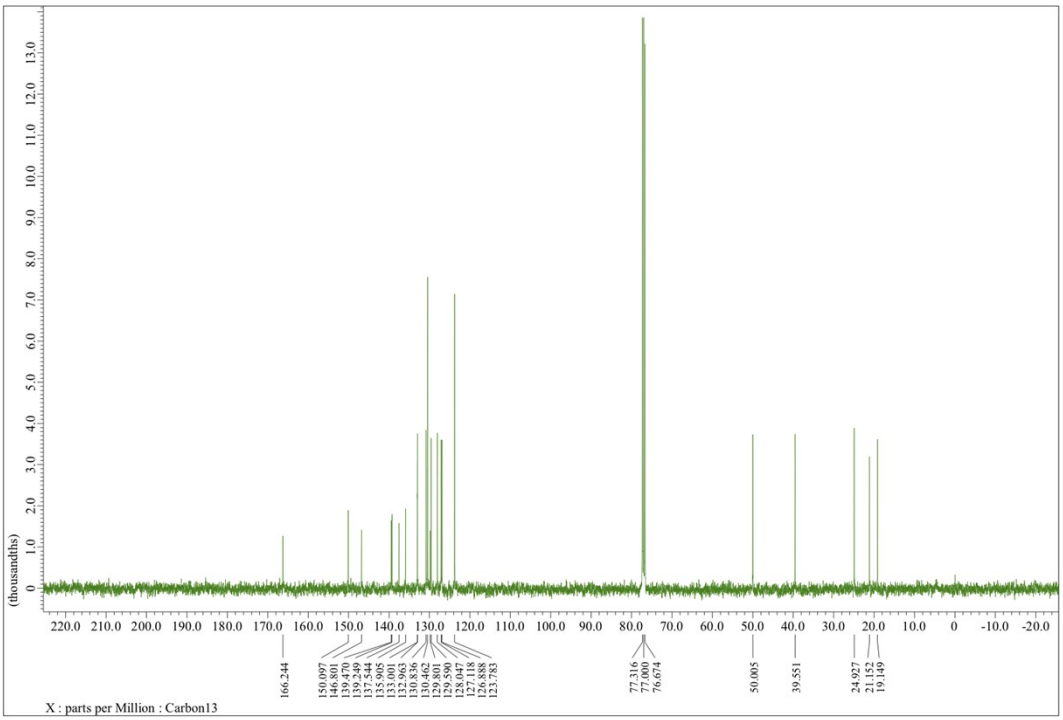
4o (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



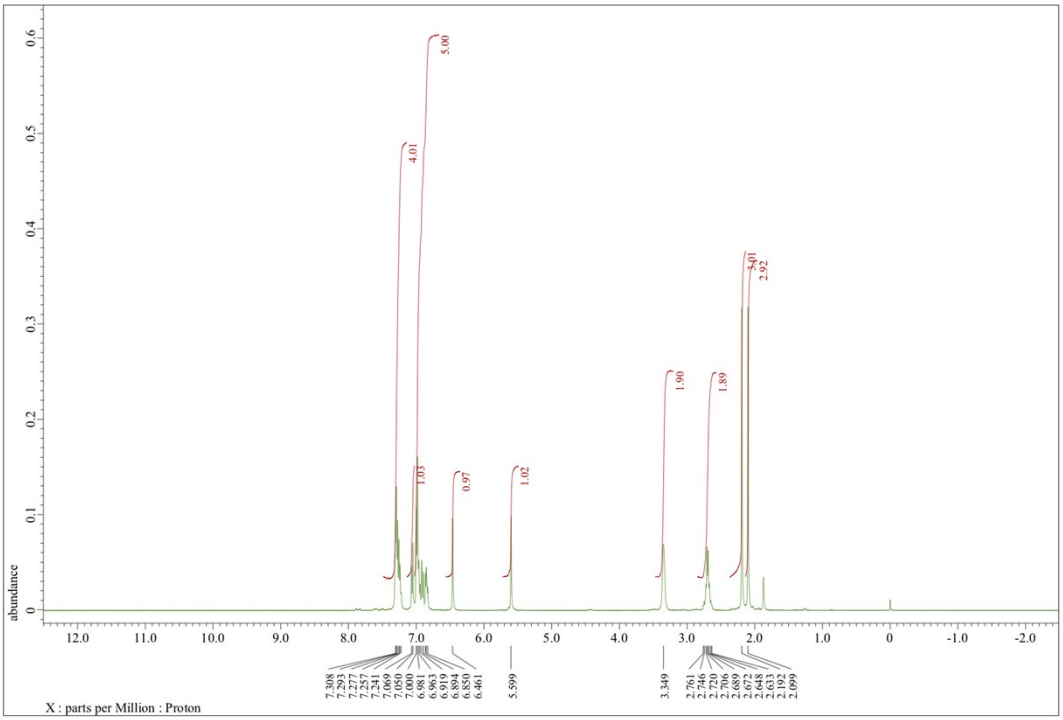


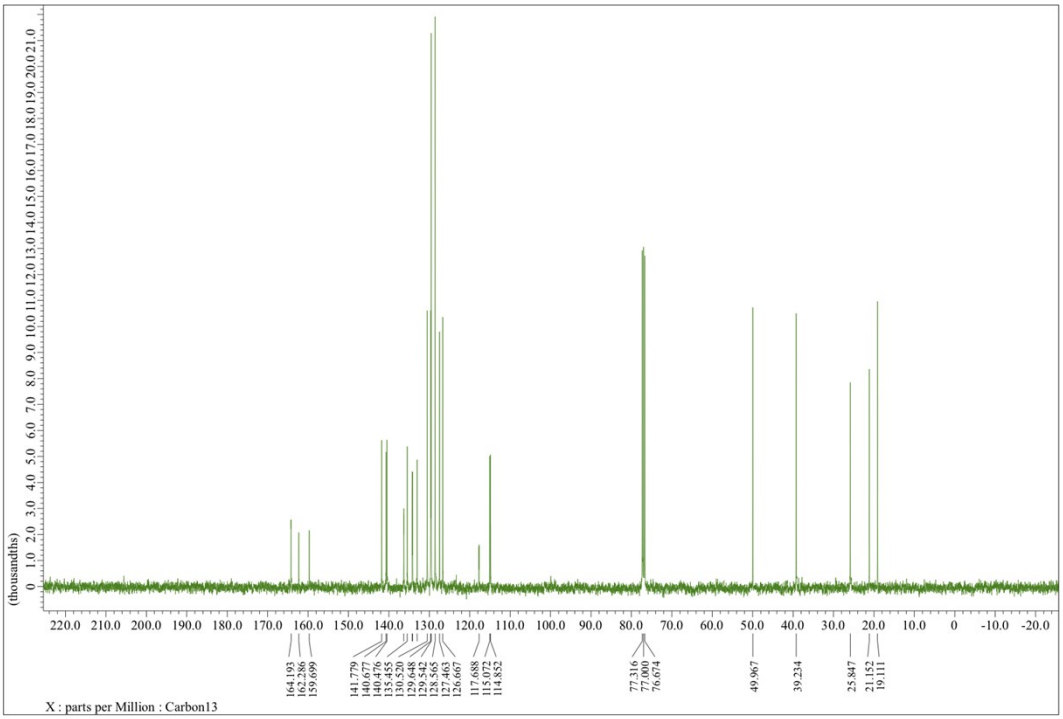
4p (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



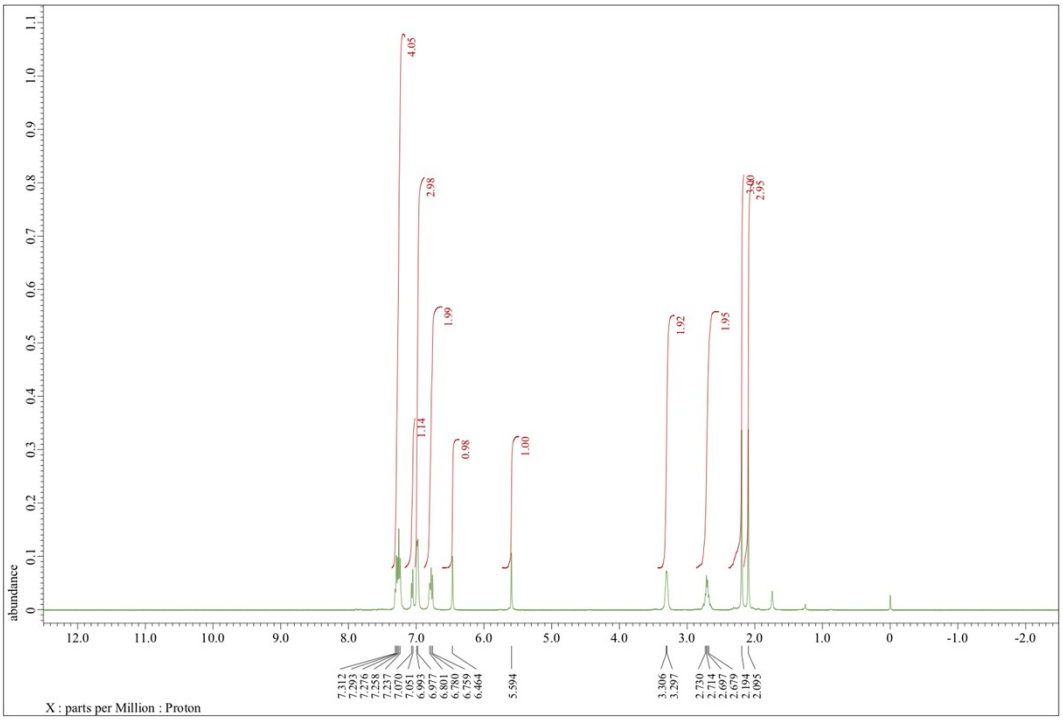


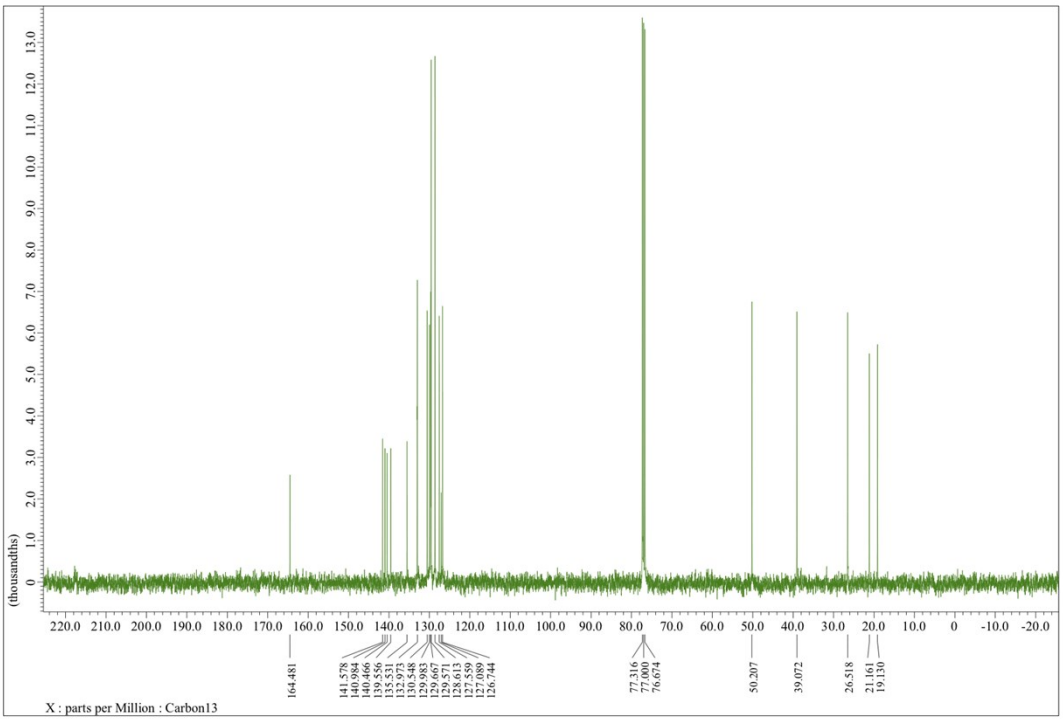
4q (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



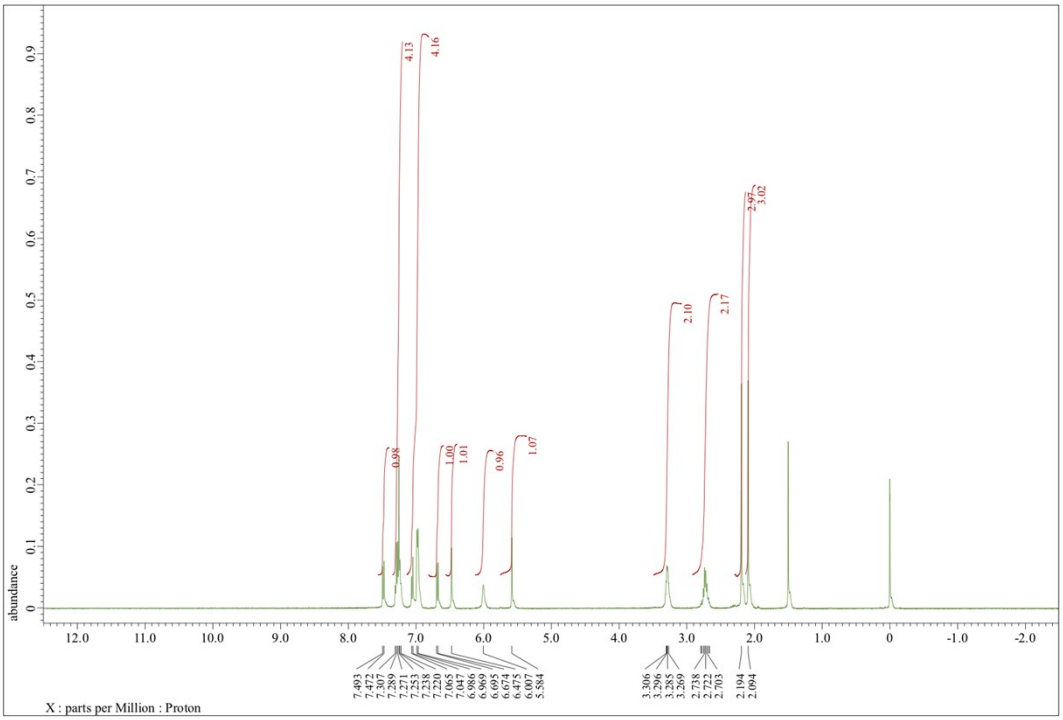


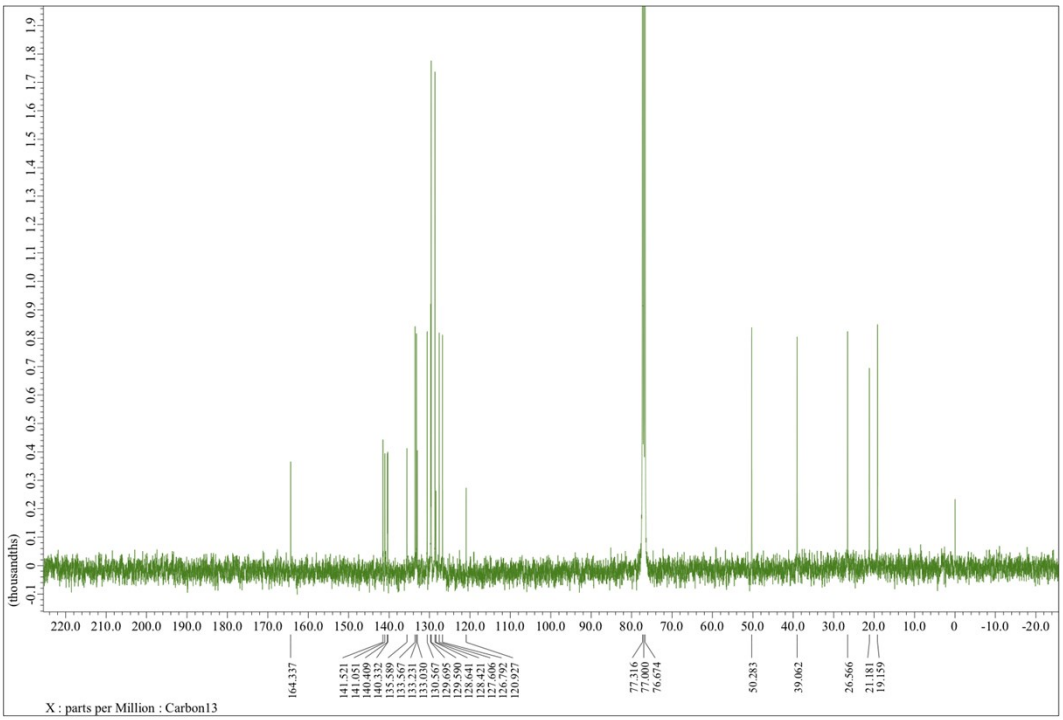
4r (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



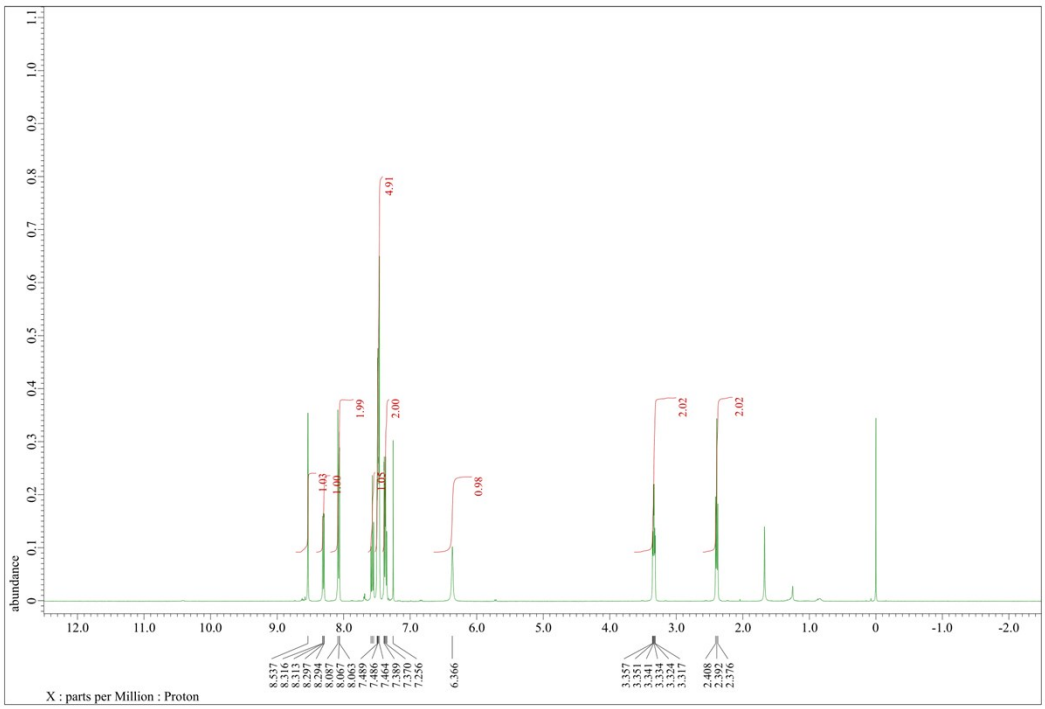


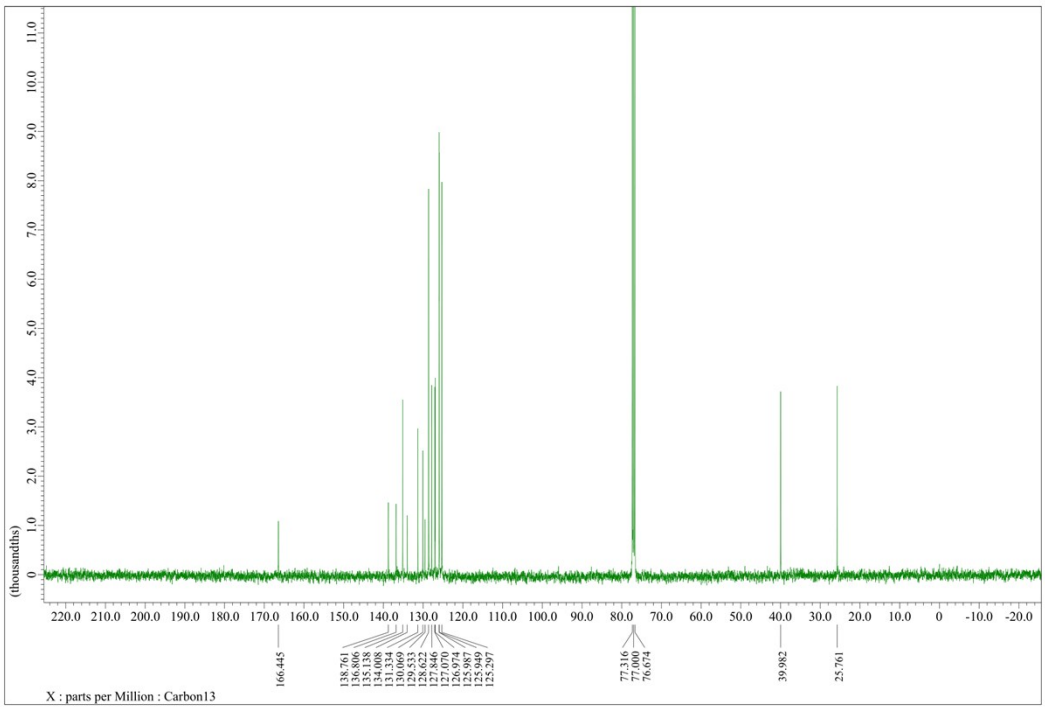
4s (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C)



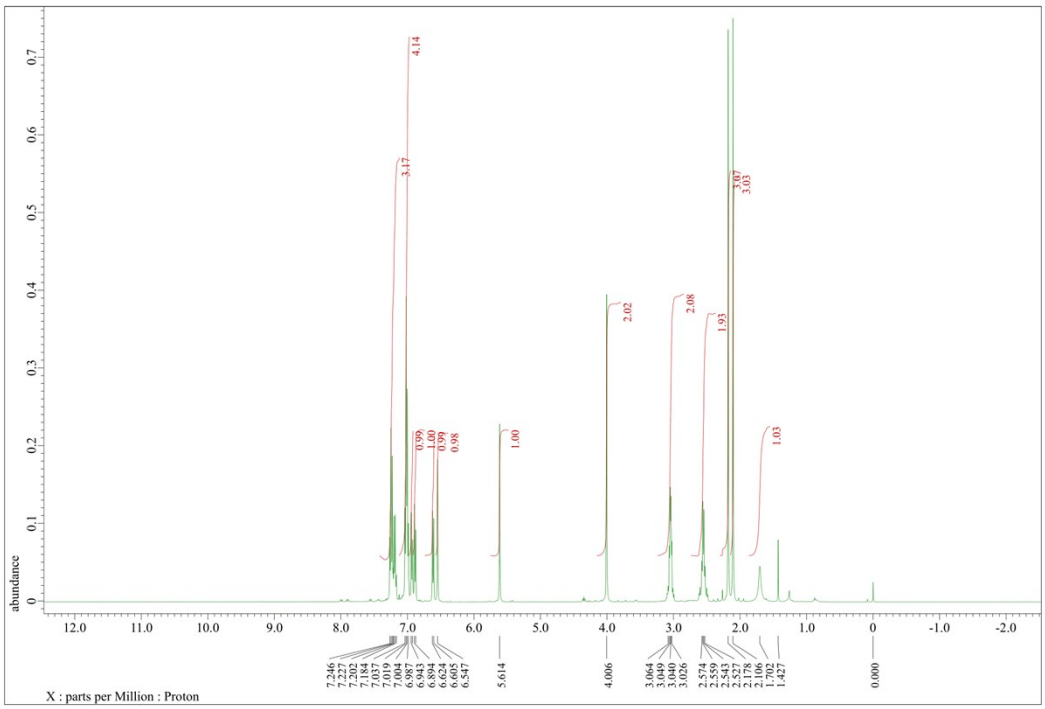


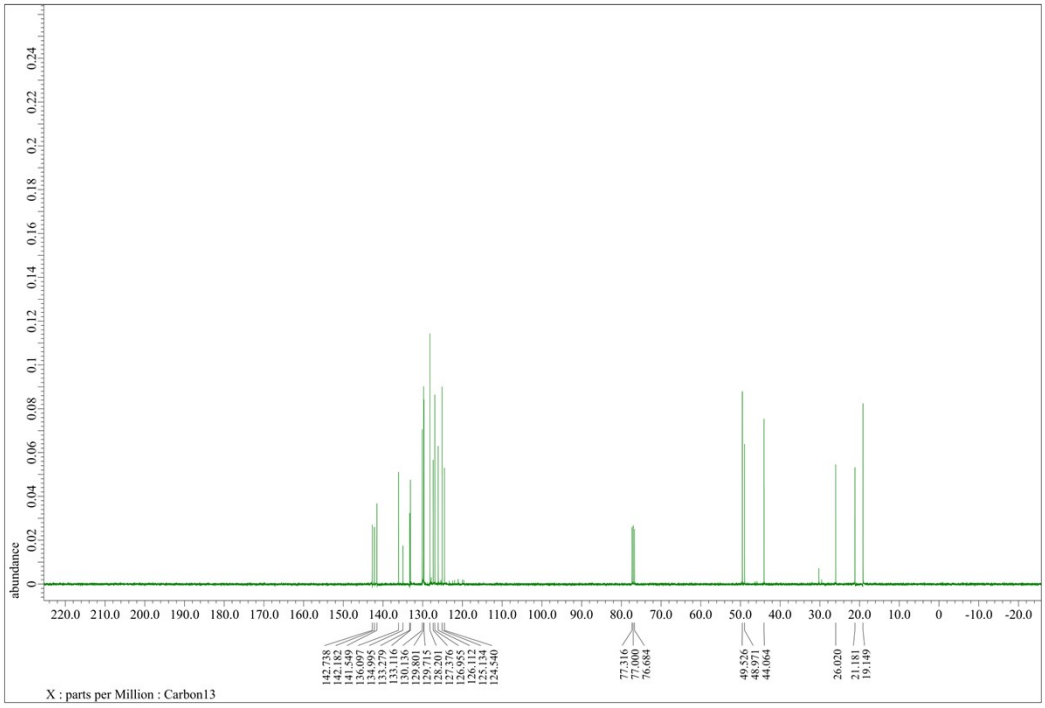
5 (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C), water (1.6 ppm for ^{1}H)



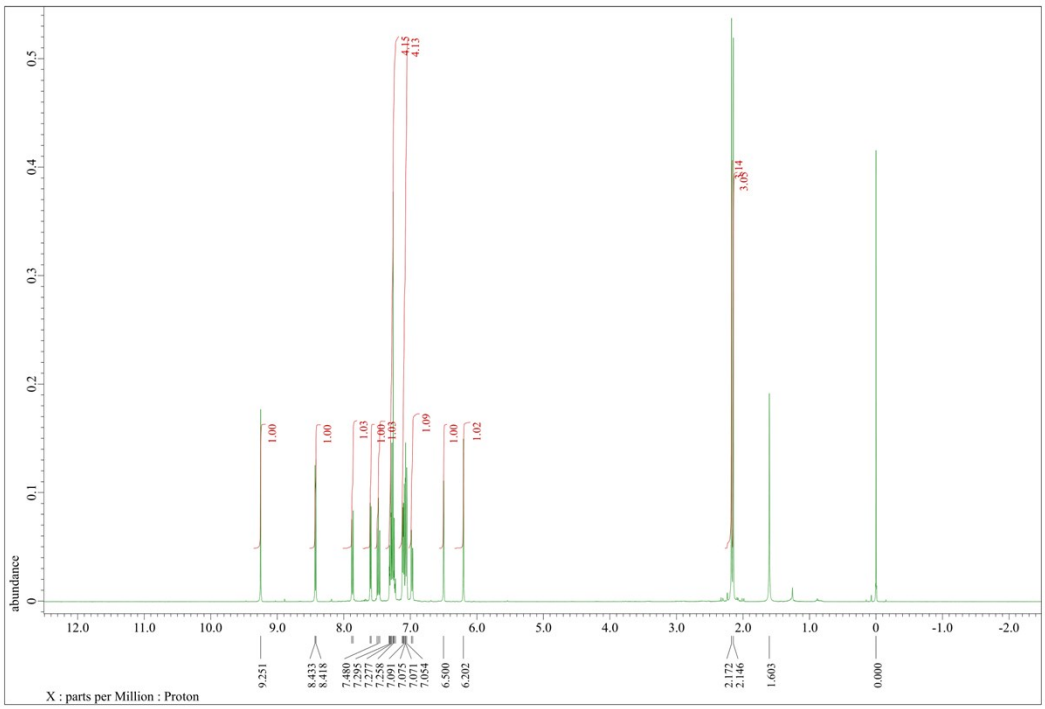


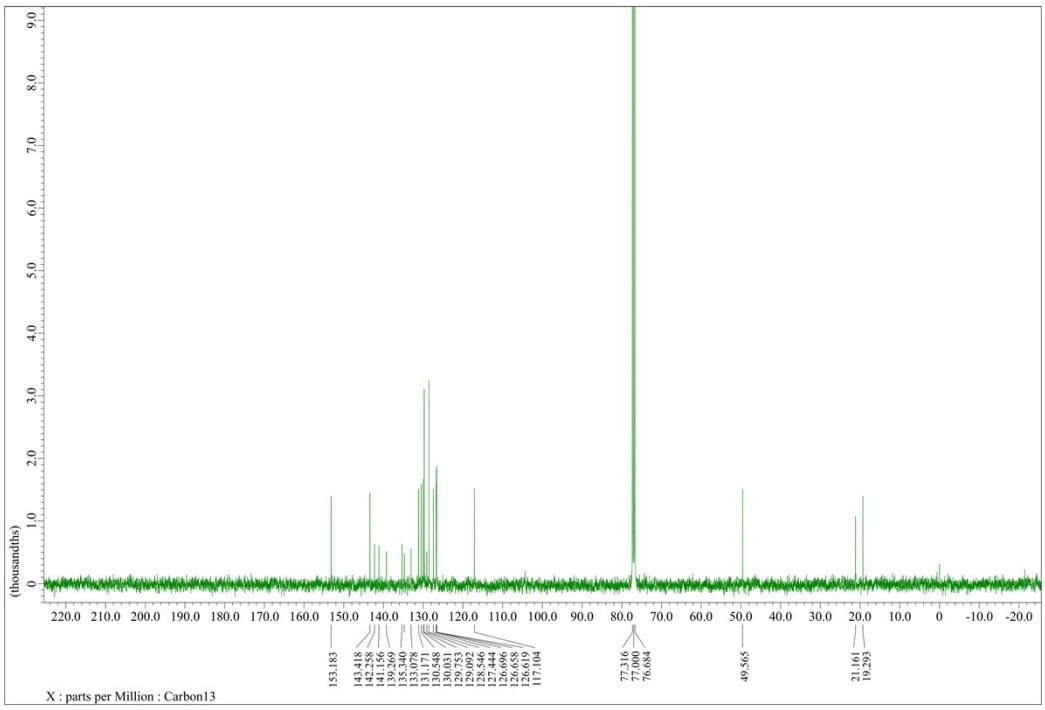
6 (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C), water (1.4 ppm for ^{1}H)



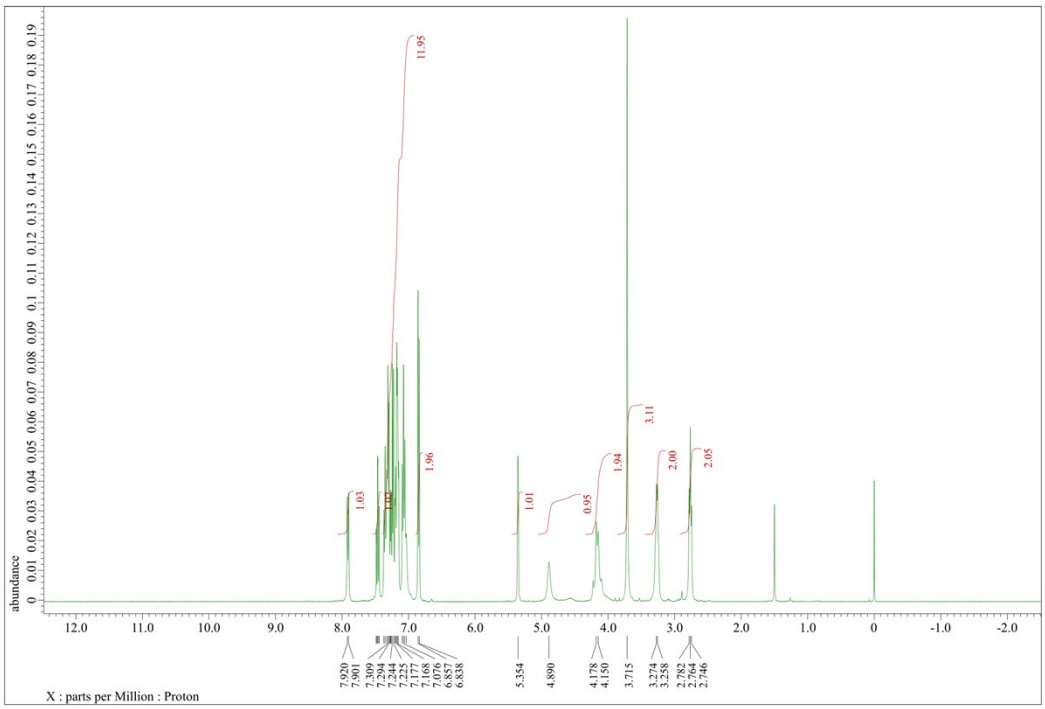


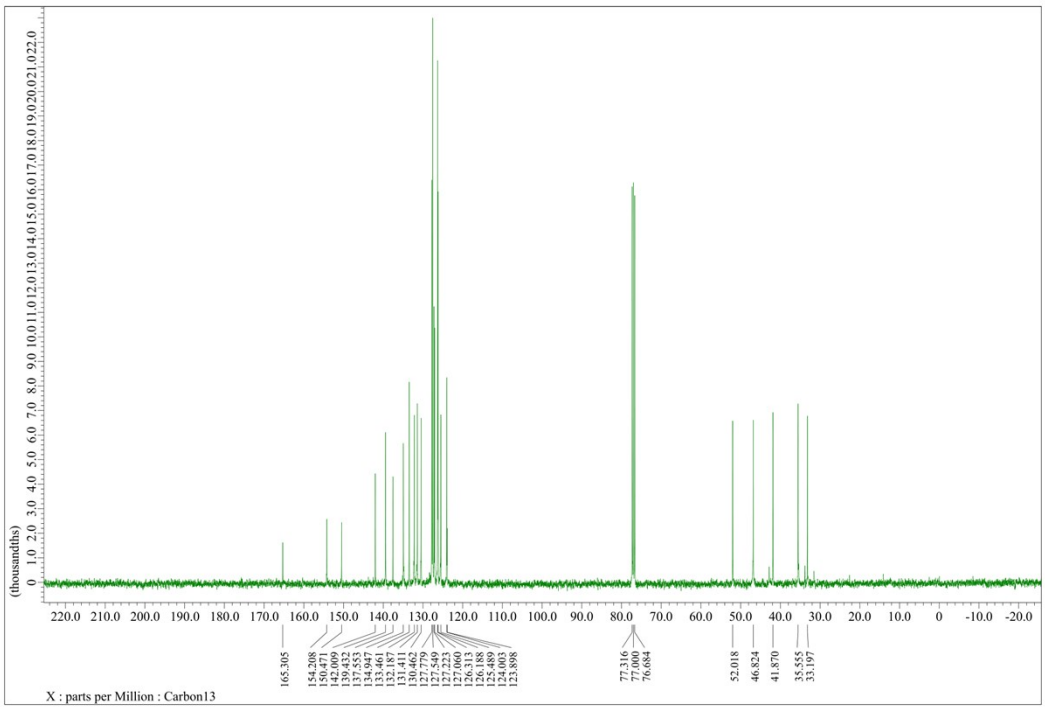
7 (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C), water (1.6 ppm for ^{1}H)





8 (Solvent: $CDCl_3$)
Solvent peak: $CDCl_3$ (77.0 ppm for ^{13}C), water (1.5 ppm for ^{1}H)





7. Detailed description of the mechanistic study

Here we additionally explain the reaction mechanism, because the discussion in the main text required some knowledge of statistical theory and the discussion might be insufficient for clear understanding. Because of the difficulty in estimating the free energy difference between monocationic and dicationic species, we supplementary employed experimental analysis to interpret the DFT-calculation result in the main text. This type of discussion is not regularly seen, because the protonation degree of the reaction system does not change in many cases.

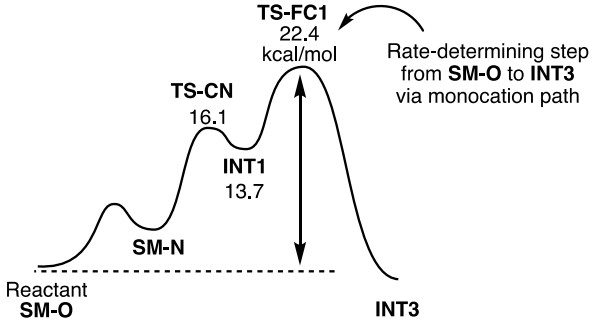
Two out of three referees directed questions at the validity of dicationic mechanism. They suggested that the monocationic pathway is more plausible than the dicationic pathway because the free energy barrier between **TS-FC1** and **INT-1** (8.7 kcal/mol) is lower than the free energy barrier between **TS-FC1-Dication** and **INT1-Dication** (10.8 kcal/mol). Therefore, we will explain the way how we interpreted the DFT-obtained energies considering experimental results in details below.

7-1. The validity of the dicationic pathway

As with typical reaction diagrams, Figure 3 should be interpreted based on statistical mechanics and related theories such as transition state theory.[18] We would like to emphasize that the diagram is used to *exclude the possibility of a monocationic pathway to form "**INT3**" via "**TS-FC1**"*. The details are explained in (A), (B), and (C) below. The validity of the dicationic pathway is discussed in (D).

(A) Interpretation of the energy profile based on statistical theory

If we assume that the reaction proceeds via a monocationic pathway, the reaction rate of the formation of **INT3** can be estimated based on transition state theory. Using transition state theory, *the reaction rate is not determined by the free energy difference between **INT-1** and **TS-FC1** (22.4 - 13.7 = 8.7 kcal/mol), but by the difference between **SM-O** and **TS-FC1** (22.4 kcal/mol)*. Simply comparing the energy barrier of the cyclization step of the monocation (8.7 kcal/mol) and dication (10.8 kcal/mol) is insufficient and can lead to misunderstanding.



Calculating the reaction rate: Note that **SM-O** and **INT-1** are in fast equilibrium because **TS-CN** has a lower free energy of 16.1 kcal/mol than **TS-FC1**. Because the Gibbs free energy of **SM-O** is much lower than **INT-1**, the concentration of **INT-1** is very low; the relative ratio can be estimated to be **INT-1:SM-O** = 9.0 x 10^{-11}:1 using the Boltzmann distribution (or canonical ensemble) at 298.15 K.

For a unimolecular reaction system, the reaction rate (k) can be estimated using transition state theory:

$$k = \kappa \frac{k_B T}{h} exp\left(-\frac{\Delta G^{\ddagger}}{RT}\right)$$

where k_B is the Boltzmann constant, T is temperature, h is the Planck constant, R is the gas constant, and $\Delta G^{\ddagger}$ is the activation free energy. As is the case in the typical use of transition state theory, the transmission coefficient κ is assumed to be 1 because the tunneling effect is negligible

in this system. Because this is a unimolecular reaction, the reaction rate can be calculated as shown below. In order to calculate the reaction rate from **INT-1**, the relative ratio of **INT-1** (9×10^{-11}) should be multiplied by the reaction rate needed to pass through the energy barrier of 8.7 kcal/mol.

$$k = 9.0 \times 10^{-11} \times \frac{k_B T}{h} exp\left(-\frac{8.7}{RT}\right)$$

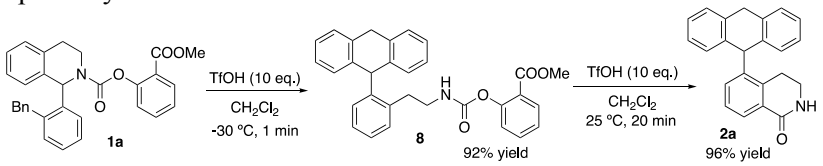
$$= \frac{k_B T}{h} exp\left(-\frac{22.4}{RT}\right) = 2.3 \times 10^{-4}\,(s^{-1})$$

This value determines the *upper limit** of the reaction rate constant. In other words, the half-life of this reaction is estimated to be longer than 0.8 hours, so it would take 4 hours for >95% conversion of the reactant. This reaction rate is much longer than the experimental reaction time (<30 min).

*Because we cannot ignore the possibility that some unexpected conformation or aggregated form of substrate is as stable as **SM-O**, which increases the partition function of the whole system and decreases the substantial reaction rate through **TS-FC1**.

(B) Experimental support for eliminating the monocationic pathway

Furthermore, the reaction shown in Scheme 4 strongly supports the absence of a monocationic pathway.



Scheme 4 in the main text

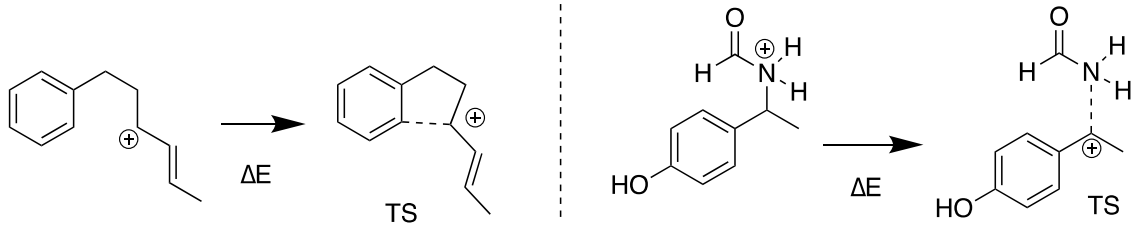
This reaction is not only used for the isolation of intermediate **8**, *but also for estimating the activation free energy*. This was stated in the main text: "*The rate of the reaction, with a half-life presumed to be shorter than ~10 s at -30 °C, indicated that the energy barrier from substrate **1a** to **8** is less than 16 kcal/mol based on Eyring's absolute rate theory.*" This value was calculated using the deformed Eyring equation.

$$\Delta G^{\ddagger} < RT \ln \frac{k_B T}{kh}$$

Because the estimated activation free energy (~16 kcal/mol) value is much lower than the DFT-calculated value (22.4 kcal/mol), *the monocationic pathway is not plausible*. This was explicitly described in the main text: *"The calculated monocationic pathway via **TS-FC1** has an energy barrier of 22.4 kcal/mol, which is the highest barrier in the entire process. When compared with the experimental results shown in Scheme 4, the DFT-calculated energy barrier is overestimated by more than 6 kcal/mol."*

(C) Validity of the M06-2X functional

Before doing the calculation, a benchmark test of the functionals of the DFT calculation was conducted to check the validity of the choice of functionals. The activation electronic energy of the model reactions shown below was calculated at the CCSD(T)-F12/aug-cc-pVDZ level of theory first using Molpro program,[S31] which is very high-cost but chemically accurate theory. Various functionals were then compared with this reliable result. See the table below.



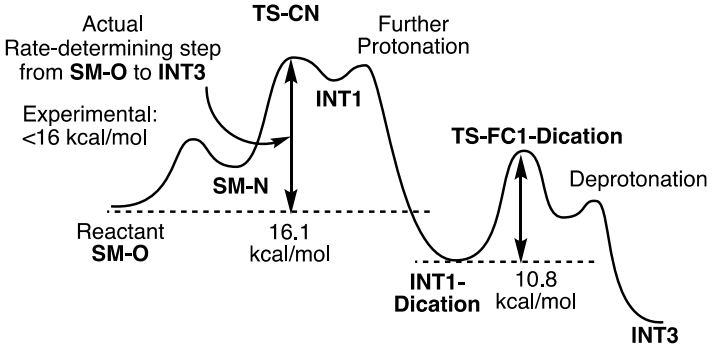
Root mean square error between DFT and CCSD(T)-F12 (kcal/mol). The geometry was obtained using the M06-2X/6-31G* level of theory. The 6-31G* basis set was used for all DFT calculations.					
apfd	b3lyp	b3lyp-d3	cam-b3lyp	cam-b3lyp-d3	m06
3.4	5.2	5.4	2.4	2.3	4.1
m06-2x	m06-hf	m06-l	m11	m11-l	wb97xd
0.3	4.5	6.8	0.9	5.0	1.3

Although other functionals resulted in a large deviation from the CCSD(T)-F12 level of theory, the M06-2X and M11 functionals afforded very accurate activation electronic energies. Therefore, the error of the DFT calculation result is small enough that the DFT calculations can be used for quantitative discussion. In the real system calculation, larger basis sets such as jul-cc-pVTZ were employed to include the effect of larger orbitals and to minimize the basis set superposition error.

(D) Evidence for the dicationic pathway

Based on the results shown above, we proposed a more reasonable pathway in which the rate-determining step has a reasonable energy barrier which fits with the experimental results. Considering the dicationic pathway, the rate-determining step of the conversion from **SM-O** to **INT3** is through **TS-CN**, which has a free energy barrier of 16.1 kcal/mol.

It was previously determined that the ring-opened dication is more stable in free energy than the ring-closed monocation under superacid conditions (see response to observation 3 of referee 1). In other words, the free energy of **INT-Dication** is lower than **SM-O** to some degree. In addition, the free energy difference between **TS-FC1-Dication** and **INT1-Dication** is only 10.8 kcal/mol. Thus, the rate-determining step of this reaction is the CN-bond dissociation step. This is consistent with the experimentally estimated free energy barrier. As is often the case with general proton transfer reactions, the proton transfer is expected to be extremely fast.[S32] Therefore, the protonation processes can be assumed not to be rate-determining steps.



7-2. The reason why I used INT1-Dication as "another standard"

In Figure 3, "Another standard" means that the energy of **INT1-Dication** is to be used as a standard to show the relative energy of the other dicationic species. We set the **INT1-Dication** as "another standard" because the free energy change of the protonation process is hard to

calculate by contemporary computational theory, so it was not possible to calculate the relative energy difference between **SM-O** and **INT1-Dication**; however, it had already been experimentally determined that **INT-Dication** has a lower free energy than **SM-O**.

One might think that the free energy difference in the protonation process could be calculated using this model:

$$S + TfOH \rightarrow SH^+ + TfO^-$$

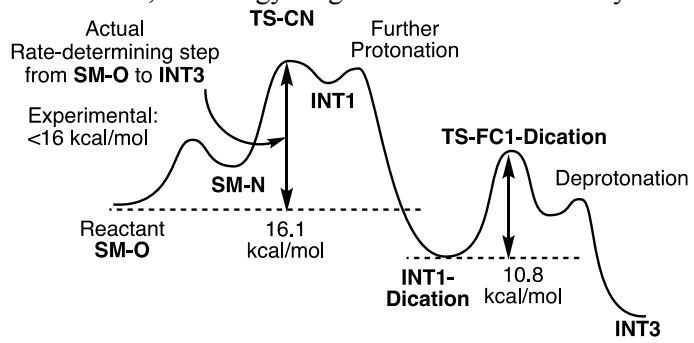
$$\Delta G_{system} = G_{SH+} + G_{TfO-} - G_S - G_{TfOH}$$

where S is the substrate. Unfortunately, *this model is incorrect*.

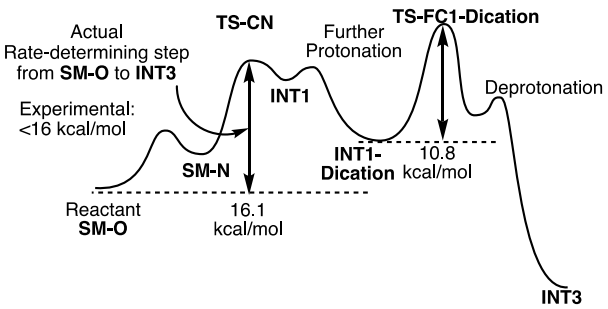
In protonation processes, a substrate receives a proton from an acid molecule, and the resultant counter anion is *solvated* by other acid molecules. In order to estimate the free energy difference between monocationic and dicationic species, the solvation energy should be properly calculated. A reviewer asked me to use the same computational method and unify the energy standard, but the calculation requires, however, a very accurate molecular dynamics simulation such as ab-initio molecular dynamics, which requires unrealistic computational time.

Fortunately, the computational problem can be overcome experimentally. The state of the substrate was measured directly (shown in Figure 2), and it was found that the triflic acid is strong enough to further protonate the ring-opened monocation to form dication **9-2H$^+$-Open**. In addition, no monocation **9-H$^+$-Closed** was observed. This indicates that the ring-opened dication is the most stable species in the reaction system in the presence of triflic acid. Therefore, it is reasonable to assume that **INT1-Dication** is thermodynamically the most stable species in the system before the formation of **INT3,** and it is difficult for the molecule to return to **SM-O**. This was discussed in the main text: *"As previously seen in the NMR studies, the carbamate substrate forms a stabilized dication. The open dication **INT1-Dication** is expected to be more stable in free energy than **SM-O** in the presence of excess TfOH. The reaction rate of the Friedel-Crafts cyclization should therefore be assumed from the energy barrier between **INT-1-Dication** and **TS-FC1-Dication**, which is 10.8 kcal/mol. The barrier of the dicationic pathway is consistent with the experimental reaction rate. After the dicationic cyclization, deprotonation of **INT2-Dication** immediately proceeds to afford monocationic **INT3** because the dihydroanthracene moiety cannot be fully protonated in TfOH."*

Based on the discussion above, the energy diagram can be described by the figure below.



If the **INT-Dication** had a much higher free energy than **SM-O** in the superacid system, the diagram should have been drawn like below to make **TS-FC1-Dication** as the rate-determining step:



However, this possibility was eliminated by direct NMR observation of Figure 2 as have been discussed above.

8. Other supplementary information in reply to reviewers

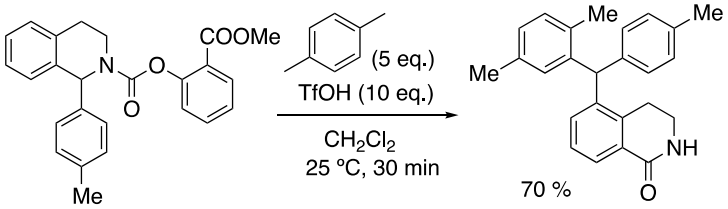
In the reviewing process of this paper, we received miscellaneous questions or comments those cannot be categorized in the sections above nor necessary to be written in the main text. The question and reply are pasted below.

Question 1:

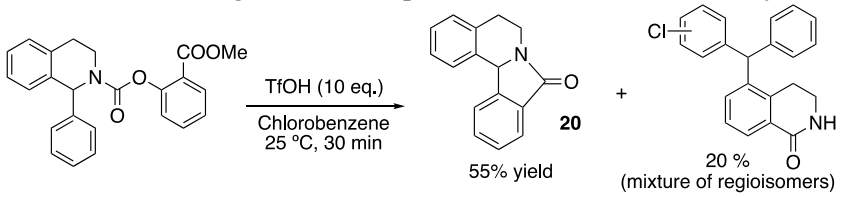
In Table 2, is there any competition could occur? If the tethered Ph group replaced with electronic-rich Ar group? Or using 3 with electronic-deficient arene.

Response 1:

Substitution of the Ph group with the relatively electron-rich *p*-tolyl group did not result in any significant side reactions.



The lower the electron density of **3**, the higher the generation of byproduct **20**. Therefore, **3** should be more electron-rich than benzene **3a**, which was also required to be large excess amount to afford product **4a,** to obtain the target product in high yield. Probably because the dication and the monocation are in equilibrium, activation of the carbamate can proceed to afford **20** from the monocation, although the desired product was obtained in a low yield of 20%.

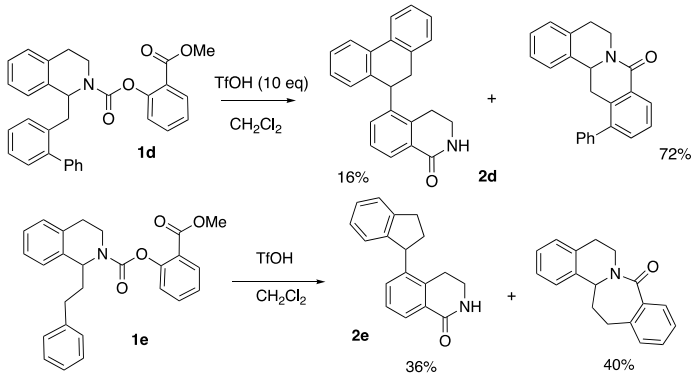


Question 2:

Is there any byproduct for 2d and 2e?

Response 2:

Yes, activation of the carbamate group competes with C-N bond scission and byproducts were formed.



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