NOVEL RING TRANSFORMATION OF URACILS TO 2-OXAZOLIDINONES

Yoshiaki Kitamura,[1]* Yuki Nagaya,[2] Yuto Ohshima,[1] Daiki Kato,[1] Asuki Ohguchi,[1] Hiroshi Katagiri,[3] Masato Ikeda,[1,2,4] and Yukio Kitade[1,5]

[1] Department of Chemistry and Biomolecular Science, Faculty of Engineering, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan

[2] United Graduate School of Drug Discovery and Medical Information Sciences, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan

[3] Graduate School of Science and Engineering, Yamagata University, 4-3-16 Jonan, Yonezawa, Yamagata 992-8510, Japan

[4] Gifu Center for Highly Advanced Integration of Nanosciences and Life Sciences (G-CHAIN), Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan

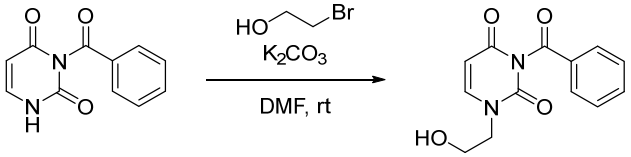
[5] Department of Applied Chemistry, Faculty of Engineering, Aichi Institute of Technology, 1247 Yachigusa, Yakusa-cho, Toyota, Aichi 470-0392, Japan

Experimental Section

General Methods. All reactions were carried out under an argon atmosphere, unless otherwise noted. All reagents and solvents were purchased from commercial vendors and used without further purification, unless indicated otherwise. ^{1}H and ^{13}C NMR spectra were recorded on a JNM ECS-400 spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). Chemical shifts (δ) were expressed in parts per million and internally referenced (7.26 ppm for $CDCl_3$ or 2.49 ppm for DMSO-d_6 for ^{1}H NMR and 77.0 ppm for $CDCl_3$ or 39.5 ppm for DMSO-d_6 for ^{13}C NMR). Electrospray ionization (ESI) mass spectra were taken on a JMS T100LP instrument or a Waters Xevo Q-Tof mass spectrometer. Flash column chromatography was performed using silica gel 60N [spherical neutral (63-210 μm)] from Kanto Chemical Co., Inc. or silica gel PSQ 100B from Fuji Silysia Chemical Co., Ltd.

Synthesis of 1a–1p

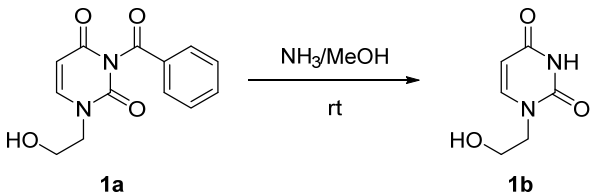
N^{1}-(2-Hydroxyethyl)-*N*^{3}-benzoyluracil (1a)



S1 **1a**

2-Bromoethanol (3.10 mL, 43.7 mmol) was added to a suspension of *N*^{3}-benzoyluracil (**S1**)[1] (2.16 g, 9.99 mmol) and K_2CO_3 (4.15 g, 30.0 mmol) in DMF (20 mL) at 0 °C, and the mixture was stirred at room temperature for 2 d. The resulting precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was diluted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 1:1~0:1) to give **1a** as a colorless solid (2.60 g, quant). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, J = 7.4 Hz, 2H), 7.79 (d, J = 8.0 Hz, 1H), 7.78 (t, J = 7.4 Hz, 1H), 7.60 (t, J = 7.4 Hz, 2H), 5.81 (d, J = 8.0 Hz, 1H), 5.04 (t, J = 5.4 Hz, 1H), 3.80 (t, J = 5.4 Hz, 2H), 3.60 (t, J = 5.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.8, 162.5, 149.6, 147.7, 135.5, 131.2, 130.2, 129.5, 99.9, 58.3, 50.8; HRMS (ESI) *m/z* Calcd for $[M(C_{13}H_{12}N_2O_4) + Na]^+$: 283.0695. Found: 283.0663.

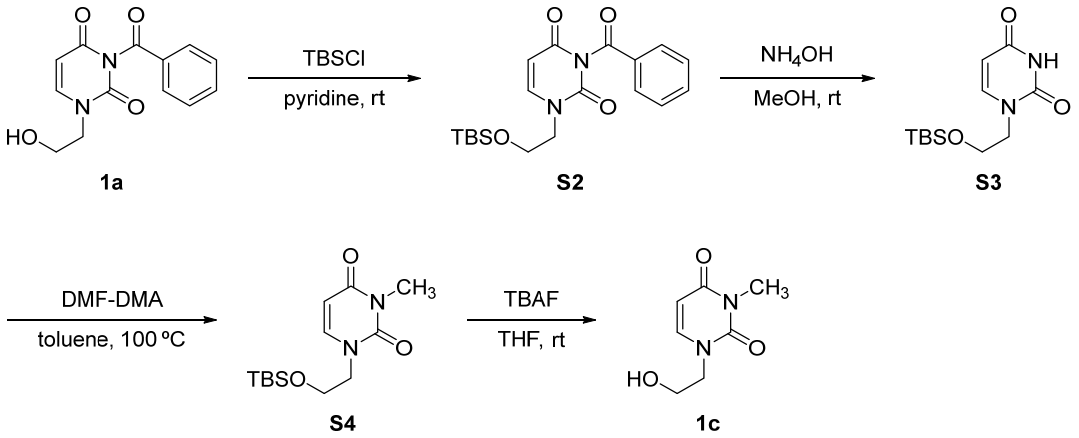
N^{1}-(2-Hydroxyethyl)uracil (1b)



1a **1b**

A mixture of **1a** (524 mg, 2.0 mmol) and 16% ammonia in methanol (10 mL) was stirred at room temperature for 4 d in a sealed tube. The mixture was concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 12:1) to give **1b** as a colorless solid (303 mg, 96%).^{1}H NMR (400 MHz, DMSO-d_6) δ 11.2 (s, 1H), 7.52 (dd, J = 7.4 Hz, 1.2 Hz, 1H), 5.49 (d, J = 7.4 Hz, 1H), 4.88 (dt, J = 5.2 Hz, 1.2 H, 1H), 3.69 (t, J = 5.2 Hz, 2H), 3.54 (q, J = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.9, 151.0, 146.7, 100.1, 58.6, 50.2; HRMS (ESI) *m/z* Calcd for [M($C_6H_8N_2O_3$) + H]$^+$: 157.0613. Found: 157.0594.

***N*^{1}-(2-Hydroxyethyl)-*N*^{3}-methyluracil (1c)**



***N*^{3}-Benzoyl-*N*^{1}-(2-*tert*-butyldimethylsilyloxyethyl)uracil (S2)**

TBDMSCl (1.71 g, 11.3 mmol) was added to a solution of **1a** (1.5 g, 5.60 mmol) in pyridine (25 mL) at 0 °C, and the mixture was stirred at room temperature for 24 h. The mixture was partitioned between EtOAc and H_2O. The organic layer was wash with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 1:1) to give **S2** as a colorless solid (2.10 g, quant). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.0 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H), 7.49 (t, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 1H), 5.77 (d, J = 8.0 Hz, 1H), 3.91–3.83 (m, 4H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 162.6, 149.7, 146.0, 135.0, 131.5, 130.4, 129.1, 100.8, 60.7, 51.4, 25.8, 18.1, −5.6; HRMS (ESI) *m/z* Calcd for [M($C_{19}H_{26}N_2O_4Si$) + H]$^+$: 375.1740. Found: 375.1732.

***N*^{1}-(2-*tert*-Butyldimethylsilyloxyethyl)uracil (S3)**

NH_4OH (28% solution in H_2O, 8.0 mL, 214 mmol) was added to a solution of **S2** (564 mg, 1.51 mmol) in MeOH (30 mL) at 0 °C, and the mixture was stirred at room temperature for 13 h. The mixture was concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 40:1) to give **S3** as a colorless solid (372 mg, 91%).^{1}H NMR (400 MHz, DMSO-d_6) δ 11.2 (s, 1H), 7.53 (d, J = 7.9 Hz, 1H), 5.50 (dd, J = 7.9 Hz, 1H), 3.77–3.71 (m, 4H), 0.82 (s, 9H), −0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 150.8, 146.3, 101.0, 60.8,

51.0, 25.7, 18.1, −5.6; HRMS (ESI) *m/z* Calcd for [M($C_{12}H_{22}N_2O_3$) + H]$^+$: 271.1478. Found: 271.1466.

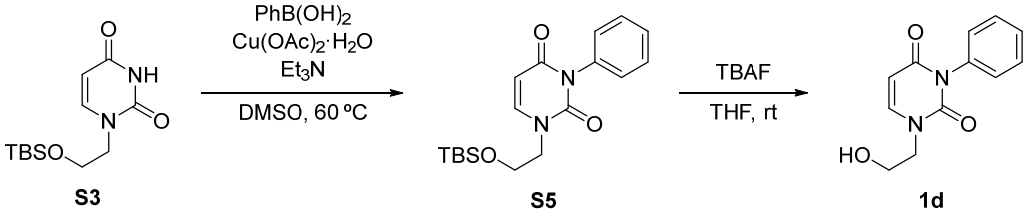
N^1-(2-*tert*-Butyldimethylsilyloxyethyl)-N^3-methyluracil (S4)

N,*N*-Dimethylformamide dimethyl acetal (200 µL, 1.50 mmol) was added to a suspension of **S3** (271 mg, 1.0 mmol) in toluene (1.4 mL) at 0 °C, and the mixture was heated at 100 °C for 19 h. The mixture was partitioned between EtOAc and H_2O. The organic layer was wash with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 50:1) to give **S4** as a colorless solid (297 mg, quant). This was used in the next step without further purification.

N^1-(2-Hydroxyethyl)-N^3-methyluracil (1c)

TBAF (1 M solution in THF, 1.1 mL, 1.12 mmol) was added to a solution of **S4** (131 mg, 460 µmol) in THF (15 mL) at 0 °C, and the mixture was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 15:1) to give **1c** as a colorless solid (69.6 mg, 89%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.57 (d, J = 8.2 Hz, 1H), 5.64 (d, J = 8.2 Hz, 1H), 4.88 (t, J = 5.6 Hz, 1H), 3.76 (t, J = 5.6 Hz, 2H), 3.56 (q, J = 5.6 Hz, 2H), 3.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 151.9, 143.6, 100.8, 60.6, 52.2, 27.8; HRMS (ESI) *m/z* Calcd for [M($C_7H_{10}N_2O_3$) + Na]$^+$: 193.0589. Found: 193.0570.

N^1-(2-Hydroxyethyl)-N^3-phenyluracil (1d)



N^1-(2-*tert*-Butyldimethylsilyloxyethyl)-N^3-phenyluracil (S5)

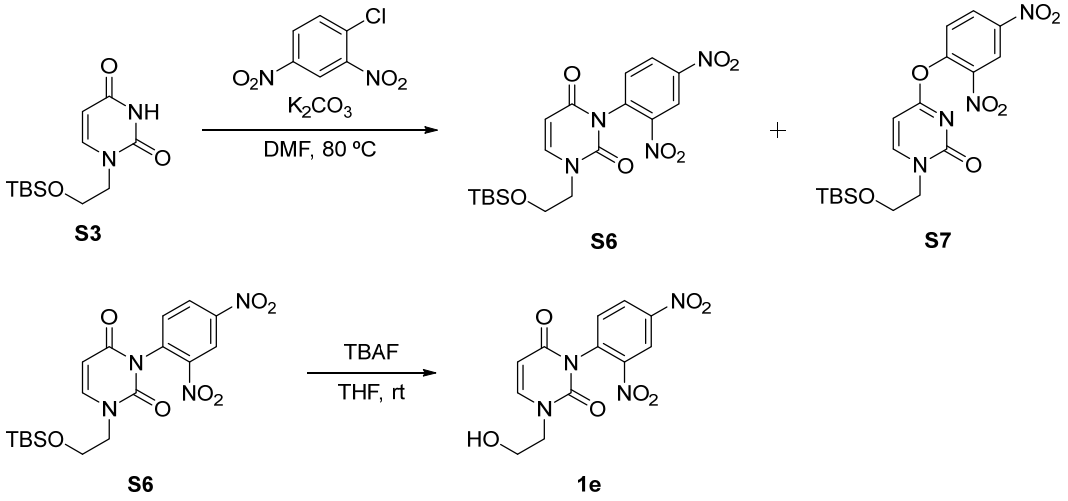
A mixture of **S3** (267 mg, 990 µmol), $Cu(OAc)_2 \cdot H_2O$ (206 mg, 1.0 mmol), phenylboronic acid (244 mg, 2.0 mmol), Et_3N (300 µL, 2.16 mmol) and DMSO (2 mL) was heated at 60 °C for 4 d. The mixture was partitioned between EtOAc and H_2O. The organic layer was wash with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 20:1) to give **S5** as a pale amber solid (126 mg, 37%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 (d, J = 8.2 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 7.39 (m, 1H), 7.14 (d, J = 7.5 Hz, 2H), 5.77 (d, J = 8.2 Hz, 1H), 3.85 (t, J = 5.0 Hz, 1H), 3.78 (t, J = 5.0 Hz, 2H), 0.85 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 151.5, 144.8, 135.1, 129.4, 128.7, 128.2, 101.0, 60.6, 52.2, 25.8, 18.1, −5.6; HRMS (ESI) *m/z* Calcd for [M($C_{18}H_{26}N_2O_3Si$) + H]$^+$:

375.1740. Found: 375.1732.

N^1-(2-Hydroxyethyl)-N^3-phenyluracil (1d)

TBAF (1 M solution in THF, 850 μL, 850 μmol) was added to a solution of **S5** (118 mg, 340 μmol) in THF (12 mL) at 0 °C, and the mixture was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 10:1) to give **1c** as a pale amber solid (76.1 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (t, J = 7.6 Hz, 2H), 7.43 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.22 (t, J = 7.6 Hz, 2H), 5.83 (d, J = 8.0 Hz, 1H), 3.92–3.85 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 152.0, 144.3, 134.9, 129.4, 128.8, 128.2, 101.6, 60.8, 52.0; HRMS (ESI) *m/z* Calcd for [M($C_{12}H_{12}N_2O_3$) + Na]$^+$: 255.0746. Found: 255.0730.

N^1-(2-Hydroxyethyl)-N^3-phenyluracil (1e)



N^1-(2-*tert*-Butyldimethylsilyloxyethyl)-N^3-(2,4-dinitrophenyl)uracil (S6)

N^1-(2-*tert*-Butyldimethylsilyloxyethyl)-O^4-(2,4-dinitrophenyl)uracil (S7)

K_2CO_3 (345 mg, 2.50 mmol) was added to a solution of **S3** (280 mg, 1.0 mmol) in DMF (7 mL). 2,4-dinitrochlorobenzene (512 mg, 2.50 mmol) was added, and the resulting mixture was heated at 80 °C for 2.5 h. The mixture was partitioned between EtOAc and H_2O. The organic layer was wash with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 4:1~1:1) to give **S6** as a pale yellow solid (288 mg, 64%) and **S7** as a colorless solid (140 mg, 31%).

S6: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (d, J = 2.4 Hz, 1H), 8.59 (dd, J = 8.6 Hz, 2.4 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.41 (d, J = 8.6 Hz, 1H), 5.84 (d, J = 8.4 Hz, 1H), 3.98–3.80 (m, 4H), 0.91 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 150.3, 147.7, 146.0, 134.6, 133.3, 128.3, 121.3, 100.6, 60.7, 52.1, 25.8, 18.1, −5.6; HRMS (ESI) *m/z* Calcd for [M($C_{18}H_{24}N_4O_7Si$) + Na]$^+$: 459.1312. Found: 459.1308.

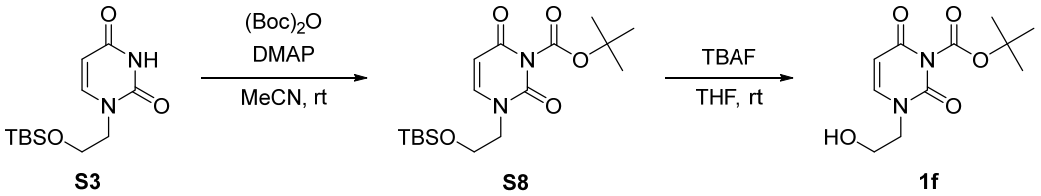
S7: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (d, J = 2.4 Hz, 1H), 8.53 (dd, J = 8.8 Hz, 2.4 Hz,

1H), 7.75 (d, J = 7.2 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 6.20 (d, J = 7.2 Hz, 1H), 4.00 (t, J = 4.7 Hz, 2H), 3.87 (t, J = 4.7 Hz, 2H), 0.87 (s, 9H), −0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 154.9, 151.5, 149.5, 145.1, 129.1, 127.2, 122.0, 93.3, 60.1, 53.1, 25.8, 18.1, −5.7; HRMS (ESI) *m/z* Calcd for [M($C_{18}H_{24}N_4O_7Si$) + Na]$^+$: 459.1312. Found: 459.1308.

N^3-(2,4-Dinitrophenyl)-N^1-(2-hydroxyethyl)uracil (1e)

TBAF (1 M solution in THF, 1.25 mL, 1.25 mmol) was added to a solution of **S6** (193 mg, 440 μmol) in THF (17 mL) at 0 °C, and the mixture was stirred at room temperature for 8 h. The mixture was concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 30:1~10:1) to give **1e** as a pale yellow solid (85.1 mg, 61%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (d, J = 2.8 Hz, 1H), 8.69 (dd, J = 8.8 Hz, 2.8 Hz, 1H), 8.30 (s, 1H), 7.97 (d, J = 8.8 Hz, 2H), 7.81 (d, J = 8.2 Hz, 2H), 5.87 (d, J = 8.2 Hz, 1H), 4.99 (t, J = 5.4 Hz, 1H), 3.86–3.81 (m, 2H), 3.62–3.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 150.6, 145.6, 134.6, 133.4, 129.0, 128.4, 128.2, 121.4, 101.3, 60.5, 51.9; HRMS (ESI) *m/z* Calcd for [M($C_{12}H_{10}N_4O_7$) + Na]$^+$: 345.0447. Found: 345.0458.

N^3-*tert*-Butoxycalbonyl-N^1-(2-hydroxyethyl)uracil (1f)



N^3-*tert*-Butoxycalbonyl-N^1-(2-*tert*-butyldimethylsilyloxyethyl)uracil (S8)

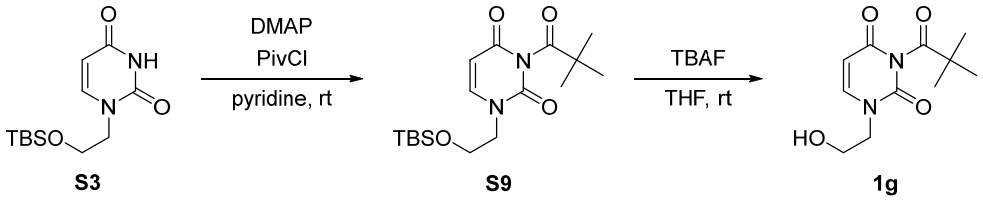
$(Boc)_2O$ (230 μL, 1.0 mmol) was added to a solution of **S3** (134 mg, 500 μmol) and DMAP (122 mg, 1.0 mmol) in MeCN (2.4 mL) at 0 °C, and the mixture was stirred at room temperature for 16 h. After MeOH was added the reaction mixture, the mixture was diluted with CH_2Cl_2. The organic layer was wash with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 3:1) to give **S8** as a colorless solid (175 mg, 95%). This was used in the next step without further purification.

N^3-*tert*-Butoxycalbonyl-N^1-(2-hydroxyethyl)uracil (1f)

Triethylamine trihydrofluoride (200 μL, 1.2 mmol) was added to a solution of **S8** (75.0 mg, 200 μmol) in THF (3 mL) at 0 °C, and the mixture was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 30:1) to give **1f** as a colorless solid (47.0 mg, 89%).^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (d, J = 8.0 Hz, 2H), 5.71 (d, J = 8.0 Hz, 1H), 4.99 (t, J = 5.1 Hz, 1H), 3.76 (t, J = 5.1 Hz, 2H), 3.57 (q, J

= 5.1 Hz, 2H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 149.2, 147.8, 145.4, 101.0, 87.0, 60.4, 51.4, 27.4; HRMS (ESI) *m/z* Calcd for [M($C_{11}H_{16}N_2O_5$) + Na]$^+$: 279.0957. Found: 279.0966.

<u>*N*^{1}-(2-Hydroxyethyl)-*N*^{3}-pivaloyluracil (1g)</u>



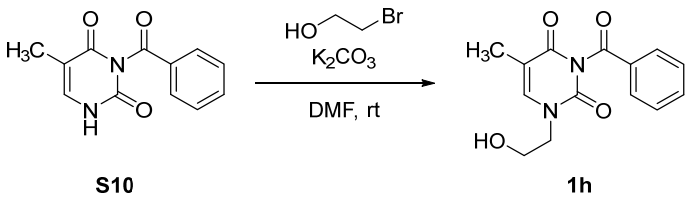
***N*^{1}-(2-*tert*-Butyldimethylsilyloxyethyl)-*N*^{3}-pivaloyluracil (S9)**

Pivaloyl chloride (660 µL, 5.36 mmol) was added to a solution of **S3** (731 mg, 2.06 mmol) and DMAP (164 mg, 1.34 mmol) in pyridine (5.3 mL) at 0 °C, and the mixture was stirred at room temperature for 30 h. The mixture was partitioned between EtOAc and H_2O. The organic layer was wash with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 3:1) to give **S9** as a colorless solid (627 mg, 66%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 (d, J = 8.2 Hz, 1H), 5.75 (d, J = 8.2 Hz, 1H), 3.86–3.82 (m, 2H), 3.77–3.75 (m, 2H), 1.21 (s, 9H), 0.82 (s, 9H), −0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 150.8, 146.4, 100.9, 60.8, 51.1, 40.2, 27.1, 26.5, 25.8, 18.1, −5.6; HRMS (ESI) *m/z* Calcd for [M($C_{17}H_{30}N_2O_4Si$) + Na]$^+$: 377.1873. Found: 377.1890.

***N*^{1}-(2-Hydroxyethyl)-*N*^{3}-pivaloyluracil (1g)**

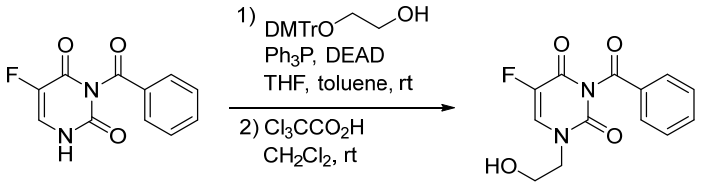
Triethylamine trihydrofluoride (130 µL, 800 µmol) was added to a solution of **S9** (45.3 mg, 130 µmol) in THF (1.5 mL) at 0 °C, and the mixture was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure, and the residue was diluted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 10:1) to give **1g** as a colorless solid (19.4 mg, 63%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 8.4 Hz, 1H), 5.69 (d, J = 8.4 Hz, 1H), 4.00–3.80 (m, 4H), 2.24 (t, J = 5.2 Hz, 1H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.7, 162.5, 149.9, 145.3, 101.4, 60.6, 51.1, 43.9, 27.3; HRMS (ESI) *m/z* Calcd for [M($C_{11}H_{16}N_2O_4$) + Na]$^+$: 263.1008. Found: 263.0997.

<u>*N*^{3}-Benzoyl-*N*^{1}-(2-hydroxyethyl)thymine (1h)</u>



2-Bromoethanol (1.80 mL, 25.4 mmol) was added to a suspension of N^3-benzoylthymine (**S10**)[2] (1.16 g, 5.04 mmol) and K_2CO_3 (2.07 g, 15.0 mmol) in DMF (10 mL) at 0 °C, and the mixture was stirred at room temperature for 2 d. The resulting precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was diluted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 1:1~0:1) to give **1h** as a colorless solid (1.30 g, 94%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (d, J = 7.6 Hz, 2H), 7.70 (tt, J = 7.6 Hz, 1.3 Hz, 1H), 7.70 (d, J = 1.0 Hz, 1H), 7.59 (t, J = 7.6 Hz, 2H), 5.00 (t, J = 5.4 Hz, 1H), 3.76 (t, J = 5.4 Hz, 2H), 3.60 (q, J = 5.4 Hz, 2H), 1.83 (d, J = 1.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 163.3, 150.3, 141.5, 135.0, 131.6, 130.4, 129.2, 110.2, 60.8, 51.0, 12.3; HRMS (ESI) *m/z* Calcd for [M($C_{14}H_{14}N_2O_4$) + Na]$^+$: 297.0851. Found: 297.0837.

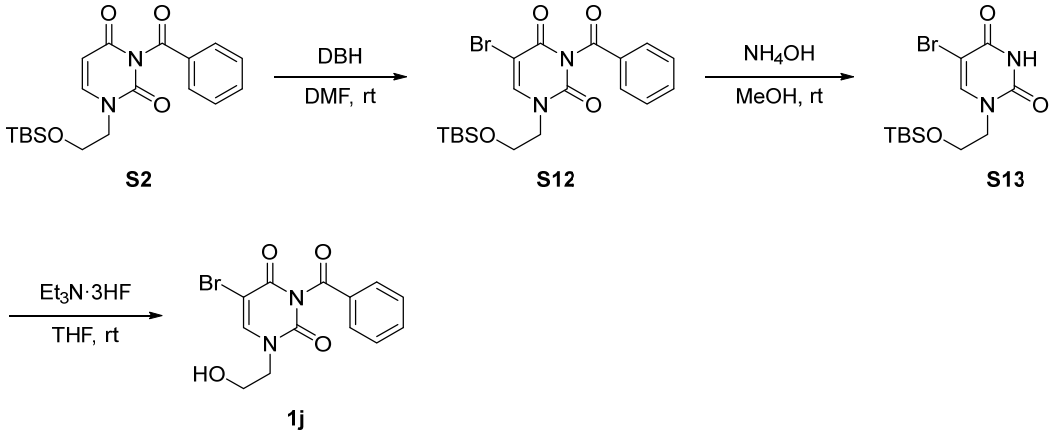
N^3-Benzoyl-5-fluoro-N^1-(2-hydroxyethyl)uracil (1i)



S11 **1i**

A solution of DEAD (2.2 M solution in toluene, 1.48 mL, 3.75 mmol) in THF (6.5 mL) was added to a mixture of N^3-benzoyl-5-fluorouracil (**S11**)[3] (761 mg, 3.25 mmol), 2-(4,4′-dimethoxytrityloxy)ethanol[4] (1.09 g, 3.0 mmol), Ph_3P (980 mg, 3.75 mmol) and THF (32.5 mL), and the mixture was stirred at room temperature for 20 h. The mixture was partitioned between EtOAc and H_2O. The organic layer was wash with saturated NH_4Cl aqueous solution and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 3:1~1:1) to give crude N^3-benzoyl-N^1-[2-(4,4′-dimethoxytrityloxy)ethyl]uracil. A solution of trichloroacetic acid (5.11 g, 31.3 mmol) in CH_2Cl_2 (18 mL) was added to a solution of the crude mixture in CH_2Cl_2 (16 mL) at 0 °C, and the mixture was stirred at room temperature for 2 h. After saturated $NaHCO_3$ aqueous solution was added the reaction mixture, the mixture was diluted with CH_2Cl_2. The organic layer was wash with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 1:1) to give **1i** as a colorless solid (609 mg, 70%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (d, J = 6.8 Hz, 1H), 8.03 (d, J = 7.6 Hz, 1H), 7.80 (t, J = 7.6 Hz, 2H), 7.61 (t, J = 7.6 Hz, 2H), 5.04 (t, J = 5.6 Hz, 1H), 3.77 (t, J = 5.6 Hz, 2H), 3.67 (q, J = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.4, 156.3 (d, J = 27.6 Hz), 148.2, 138.8 (d, J = 279 Hz), 135.8, 132.3 (d, J = 33.3 Hz), 130.8, 130.6, 129.6, 58.2, 50.9; HRMS (ESI) *m/z* Calcd for [M($C_{13}H_{11}FN_2O_4$) + Na]$^+$: 301.0601. Found: 301.0585.

N^3-Benzoyl-N^1-(2-hydroxyethyl)-5-phenyluracil (1j)



N^3-Benzoyl-5-bromo-N^1-(2-*tert*-butyldimethylsilyloxyethyl)uracil (S12)

1,3-Dibromo-5,5-dimethylhydantoin (118 mg, 410 μmol) was added to a solution of **S2** (250 mg, 670 μmol) in DMF (1.6 mL), and the mixture was stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure, and the residue was diluted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 2:1) to give **S12** as a colorless solid (284 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, J = 8.2 Hz, 1.2 Hz, 2H), 7.75 (s, 1H), 7.66 (tt, J = 8.2 Hz, 1.2 Hz, 1H), 7.49 (t, J = 8.2 Hz, 2H), 3.93–3.90 (m, 2H), 3.86–3.83 (m, 2H), 0.92 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 158.4, 149.1, 145.5, 135.2, 131.1, 130.5, 129.2, 94.9, 60.7, 51.3, 25.8, 18.1, −5.6; HRMS (ESI) *m/z* Calcd for $[M(C_{19}H_{25}BrN_2O_4Si) + H]^+$: 453.0845. Found: 453.0839.

5-Bromo-N^1-(2-*tert*-butyldimethylsilyloxyethyl)uracil (S13)

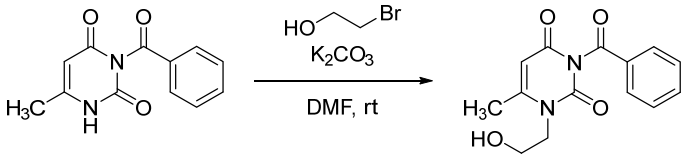
NH_4OH (28% solution in H_2O, 3.0 mL, 77.0 mmol) was added to a solution of **S12** (216 mg, 480 μmol) in MeOH (40 mL) at 0 °C, and the mixture was stirred at room temperature for 12 h. The mixture was concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 30:1) to give **S13** as a colorless solid (157 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.65 (s, 1H), 3.89–3.87 (m, 2H), 3.83–3.80 (m, 2H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 150.0, 145.8, 95.1, 60.7, 51.0, 25.7, 18.1, −5.7; HRMS (ESI) *m/z* Calcd for $[M(C_{12}H_{21}BrN_2O_3Si) + H]^+$: 349.0583. Found: 349.0566.

N^3-Benzoyl-5-bromo-N^1-(2-hydroxyethyl)uracil (1j)

Triethylamine trihydrofluoride (200 μL, 1.20 mmol) was added to a solution of **S13** (96.1 mg, 210 μmol) in THF (2.5 mL) at 0 °C, and the mixture was stirred at room temperature for 3 h. The mixture was concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 15:1) to give **1j** as a colorless solid (65.7 mg, 91%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 8.01 (d,

J = 7.8 Hz, 1H), 7.80 (t, J = 7.8 Hz, 2H), 7.60 (t, J = 7.8 Hz, 2H), 5.05 (t, J = 5.4 Hz, 1H), 3.82 (t, J = 5.4 Hz, 2H), 3.60 (q, J = 5.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.7, 158.5, 149.0, 147.2, 135.7, 130.7, 130.5, 129.6, 93.3, 58.2, 51.2; HRMS (ESI) *m/z* Calcd for [M($C_{13}H_{11}BrN_2O_4$) + Na]$^+$: 360.9800. Found: 360.9779.

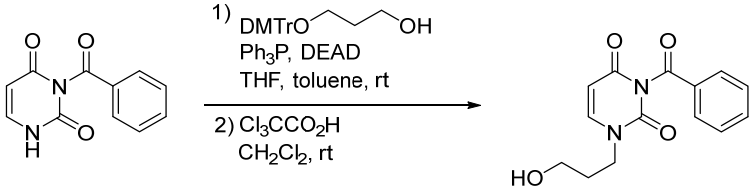
N^3-Benzoyl-N^1-(2-hydroxyethyl)-6-methyluracil (1k)



S14 **1k**

2-Bromoethanol (270 μL, 3.75 mmol) was added to a suspension of N^3-benzoyl-6-methyluracil (**S14**)[5] (173 mg, 750 μmol) and K_2CO_3 (311 mg, 2.25 mmol) in DMF (1.5 mL) at 0 °C, and the mixture was stirred at room temperature for 4 d. The resulting precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was diluted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 50:1) to give **1k** as a colorless solid (149 mg, 50%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (d, J = 7.6 Hz, 2H), 7.77 (t, J = 7.6 Hz, 1H), 7.59 (t, J = 7.6 Hz, 2H), 5.76 (s, 1H), 5.09 (t, J = 5.6 Hz, 1H), 3.85 (t, J = 5.6 Hz, 2H), 3.59 (q, J = 5.6 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.8, 161.1, 156.7, 150.1, 135.4, 131.3, 130.2, 129.5, 100.4, 58.3, 46.7, 20.2; HRMS (ESI) *m/z* Calcd for [M($C_{14}H_{14}N_2O_4$) + Na]$^+$: 297.0851. Found: 297.0833.

N^3-Benzoyl-N^1-(3-hydroxypropyl)uracil (1m)

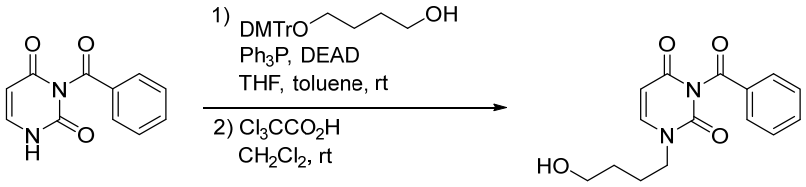


S1 **1m**

A solution of DEAD (2.2 M solution in toluene, 1.8 mL, 3.96 mmol) in THF (5 mL) was added to a mixture of **S1** (563 mg, 2.60 mmol), 3-(4,4′-dimethoxytrityloxy)propanol[6] (789 mg, 2.08 mmol) prepared from 1,3-propanediol, Ph_3P (1.07 g, 4.08 mmol) and THF (5 mL), and the mixture was stirred at room temperature for 26 h. The mixture was partitioned between EtOAc and H_2O. The organic layer was wash with saturated NH_4Cl aqueous solution and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 3:1~1:1) to give crude N^3-benzoyl-N^1-[3-(4,4′-dimethoxytrityloxy)propyl]uracil. A solution of trichloroacetic acid (1.60 g, 9.79 mmol) in CH_2Cl_2 (5 mL) was added to a solution of the crude mixture in CH_2Cl_2 (10 mL) at 0 °C, and the mixture was stirred at

room temperature for 5 h. After saturated $NaHCO_3$ aqueous solution was added the reaction mixture, the mixture was diluted with CH_2Cl_2. The organic layer was wash with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/MeOH, 1:0~10:1) to give **1m** as a pale colorless solid (312 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.6 Hz, 2H), 7.66 (t, J = 7.6 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.33 (d, J = 7.8 Hz, 1H), 5.84 (d, J = 7.8 Hz, 1H), 3.95 (t, J = 6.3 Hz, 2H), 3.71–3.67 (m, 2H), 2.08 (brs, 1H), 1.94 (quint, 6.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 162.5, 150.3, 144.7, 135.2, 131.3, 130.4, 129.2, 102.1, 58.4, 46.0, 31.1; HRMS (ESI) *m/z* Calcd for [M($C_{14}H_{14}N_2O_4$) + Na]$^+$: 297.0851. Found: 298.0863.

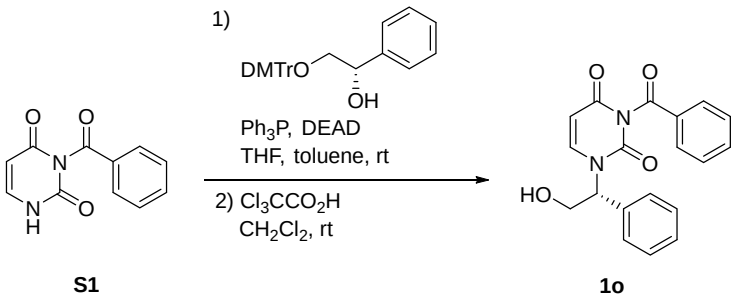
N^3-Benzoyl-N^1-(4-hydroxybutyl)uracil (1n)



S1 **1n**

A solution of DEAD (2.2 M solution in toluene, 1.80 mL, 3.96 mmol) in THF (5 mL) was added to a mixture of **S1** (436 mg, 2.02 mmol), 4-(4,4′-dimethoxytrityloxy)butanol[7] (1.08 g, 2.75 mmol) prepared from 1,4-butanediol, Ph_3P (1.07 g, 4.08 mmol) and THF (15 mL), and the mixture was stirred at room temperature for 24 h. The mixture was partitioned between EtOAc and H_2O. The organic layer was wash with saturated NH_4Cl aqueous solution and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 2:1~1:1) to give crude N^3-benzoyl-N^1-[4-(4,4′-dimethoxytrityloxy)butyl]uracil. A solution of trichloroacetic acid (1.65 g, 10.1 mmol) in CH_2Cl_2 (5 mL) was added to a solution of the crude mixture in CH_2Cl_2 (15 mL) at 0 °C, and the mixture was stirred at room temperature for 19 h. After saturated $NaHCO_3$ aqueous solution was added the reaction mixture, the mixture was diluted with CH_2Cl_2. The organic layer was wash with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/MeOH, 1:0~5:1) to give **1n** as a colorless oil (199 mg, 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 7.9 Hz, 2H), 7.65 (t, J = 7.9 Hz, 1H), 7.49 (t, J = 7.9 Hz, 2H), 7.30 (d, J = 8.2 Hz, 1H), 5.79 (d, J = 8.2 Hz, 1H), 3.79 (t, J = 7.5 Hz, 2H), 3.65 (t, J = 6.4 Hz, 2H), 1.97 (brs, 1H), 1.81 (quint, 7.5 Hz, 2H), 1.61–1.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 162.5, 149.8, 144.3, 135.1, 131.4, 130.4, 129.2, 102.0, 61.9, 49.0, 28.9, 25.7; HRMS (ESI) *m/z* Calcd for [M($C_{15}H_{16}N_2O_4$) + Na]$^+$: 311.1008. Found: 311.0984.

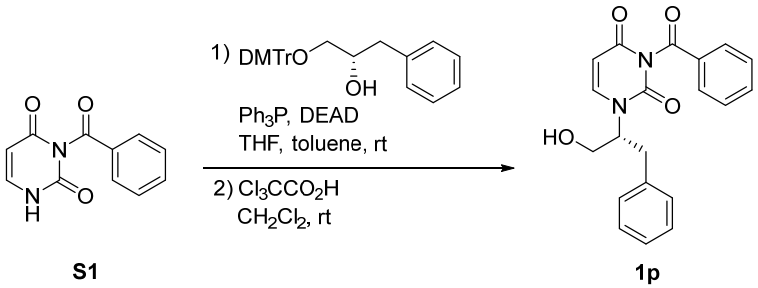
(*R*)-N^3-Benzoyl-N^1-(2-hydroxy-1-phenylethyl)uracil (1o)



S1 **1o**

A solution of DEAD (2.2 M solution in toluene, 2.30 mL, 5.06 mmol) in THF (5 mL) was added to a mixture of **S1** (544 mg, 2.52 mmol), (*S*)-2-(4,4′-dimethoxytrityloxy)-1-phenylethanol[8] (1.42 g, 3.22 mmol) prepared from (*S*)-phenylglycol, Ph_3P (1.31 g, 5.00 mmol) and THF (8 mL), and the mixture was stirred at room temperature for 12 h. The mixture was partitioned between EtOAc and H_2O. The organic layer was wash with saturated NH_4Cl aqueous solution and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 5:1~2:1) to give crude (*R*)-N^3-benzoyl-N^1-[2-(4,4′-dimethoxytrityloxy)-1-phenylethyl]uracil. A solution of trichloroacetic acid (1.54 g, 9.43 mmol) in CH_2Cl_2 (5 mL) was added to a solution of the crude mixture in CH_2Cl_2 (5 mL) at 0 °C, and the mixture was stirred at room temperature for 13 h. Trichloroacetic acid (1.07 g, 6.57 mmol) was added added to the reaction mixture at 0 °C, and the mixture was stirred an additional 2 h. After saturated $NaHCO_3$ aqueous solution was added the reaction mixture, the mixture was diluted with CH_2Cl_2. The organic layer was wash with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 2:1~1:1) to give **1o** as a colorless solid (364 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 7.8 Hz, 2H), 7.66 (t, J = 7.8 Hz, 1H), 7.50 (t, J = 7.8 Hz, 2H), 7.46–7.36 (m, 6H), 5.84 (t, J = 7.5 Hz, 1H), 5.77 (d, J = 8.4 Hz, 1H), 4.27 (t, J = 5.8 Hz, 2H), 2.10 (t, J = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 162.2, 150.7, 142.6, 135.4, 135.2, 131.3, 130.5, 129.3, 129.2, 128.9, 127.8, 101.9, 62.2, 59.8; HRMS (ESI) *m/z* Calcd for $[M(C_{19}H_{16}N_2O_4) + Na]^+$: 359.1008. Found: 359.0981.

(*R*)-N^3-Benzoyl-N^1-(2-hydroxy-1-benzylethyl)uracil (1p)



S1 **1p**

A solution of DEAD (2.2 M solution in toluene, 1.0 mL, 2.20 mmol) in THF (5 mL) was added to a mixture of **S1** (476 mg, 2.20 mmol), (*S*)-2-(4,4′-dimethoxytrityloxy)-1-benzylethanol[9] (1.28 g, 2.81 mmol) prepared from (*S*)-3-phenyl-1,2-propanediol, Ph_3P (1.17 g, 4.88 mmol) and THF (10 mL), and the mixture was stirred at room temperature for 12 h. The mixture was partitioned between EtOAc and H_2O. The organic layer was wash with saturated NH_4Cl aqueous solution and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 5:1~2:1) to give crude (*R*)-N^3-benzoyl-N^1-[2-(4,4′-dimethoxytrityloxy)-1-benzylethyl]uracil. A solution of trichloroacetic acid (1.39 g, 8.51 mmol) in CH_2Cl_2 (3 mL) was added to a solution of the crude mixture in CH_2Cl_2 (5 mL) at 0 °C, and the mixture was stirred at room temperature for 2.5 h. After saturated $NaHCO_3$ aqueous solution was added the reaction mixture, the mixture was diluted with CH_2Cl_2. The organic layer was wash with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 2:1~1:1) to give **1p** as a colorless solid (280 mg, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 7.6 Hz, 2H), 7.64 (t, J = 7.6 Hz, 1H), 7.48–7.44 (m, 3H), 7.36–7.28 (m, 3H), 7.21 (dd, J = 7.6 Hz, 1.2 Hz, 1H), 5.73 (d, J = 8.0 Hz, 1H), 4.82 (s, 1H), 3.96 (d, J = 4.8 Hz, 2H), 3.15–3.13 (m, 2H), 2.02 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.8, 161.5, 149.9, 137.1, 135.4, 130.9, 130.6, 129.9, 129.5, 129.1, 128.5, 126.6, 100.5, 79.2, 61.5, 34.8; HRMS (ESI) *m/z* Calcd for $[M(C_{20}H_{18}N_2O_4) + Na]^+$: 373.1164. Found: 373.1182.

X-ray crystallographic structure determination for 2a (*cis-trans*)

X-ray diffraction data for **2a (*cis-trans*)** was collected using a Rigaku Saturn 724 CCD diffractometer with Mo-Ka radiation (l = 0.71075 Å) at 93 K. Single crystals (size: 0.30 × 0.30 × 0.10 mm^3) of **2a (*cis-trans*)** ($C_{13}H_{12}N_2O_4$, Mw = 260.25) suitable for X-ray analysis were grown by the recrystallization of a solution of **2a** in EtOAc at ambient temperature. The unit cell was triclinic with the space group *P*1. Lattice constants with $Z = 4$, $\rho_{calcd} = 1.466$ g/cm^3, $\mu = 1.11$ cm^{-1}, $F(000) = 544$, $\theta_{max} = 27.494^o$ were $a = 7.9714(3)$, $b = 11.0019(4)$, $c = 14.4661(7)$ Å, $\alpha = 75.579(3)°$, $\beta = 86.190(4)^o$, $\gamma = 73.693(3)°$, and $V = 1179.27(9)$ $Å^3$. A total of 15,904 reflections were collected, of which 5,379 reflections were independent ($R_{int} = 0.0290$). The structure was refined to final $R_1 = 0.0490$ for 4,747 data [$I > 2\sigma(I)$] with 349 parameters and $wR_2 = 0.1164$ for all data, GOF = 1.086, and residual electron density max./min. = 0.435/–0.175 $e \cdot Å^{-3}$. The ORTEP diagram is shown in Fig. S1, and the crystal data and structure refinement are listed in Table S1. Data collection, cell refinement, and data reduction were conducted using the CrystalClear-SM Expert 2.0 software[10]. The structure was solved by direct methods using the program SHELXT[11] and refined by full-matrix least-squares methods on F^2 using SHELXL2014[12]. All materials for publication were prepared by Yadokari-XG 2009 software[13]. All non-hydrogen atoms were refined anisotropically. Tables of positional and thermal parameters, bond lengths and angles, torsion angles and Fig.s may be found from the Cambridge Crystallographic Centre by referencing CCDC number 1976179.

Table S1 Crystal data and structure refinement parameters for **2a (*cis-trans*)**

Empirical formula	$C_{13}H_{12}N_2O_4$	
Formula weight	260.25	
Temperature	93 K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P*1	
Unit cell dimensions	*a* = 7.9714(3) Å	*α* = 75.579(3)º
	b = 11.0019(4) Å	*β* = 86.190(4)º
	c = 14.4661(7) Å	*γ* = 73.693(3)º
Volume	1179.27(9) Å^3	
Z	4	
Density (calculated)	1.466 g/cm^{-3}	
Absorption coefficient	0.111 mm^{-1}	
F(000)	544	
Crystal size	0.30 × 0.30 × 0.10 mm^3	
Theta range for data collection	2.662 to 27.494º	
Index ranges	$-10 \le h \le 10$, $-14 \le k \le 14$, $-18 \le l \le 18$	
Reflections collected	15904	
Independent reflections	5379 [*R*(int) = 0.0290]	
Completeness to theta = 25.242º	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmissions	1.00000 and 0.74123	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	5379/0/349	
Goodness-of-fit on F^2	1.086	
Final *R* indices [$I > 2\text{sigma}(I)$]	R_1 = 0.0490, wR_2 = 0.1118	
R indices (all data)	R_1 = 0.0569, wR_2 = 0.1164	
Largest diff. peak and hole	0.435 and –0.175 e·Å^{-3}	

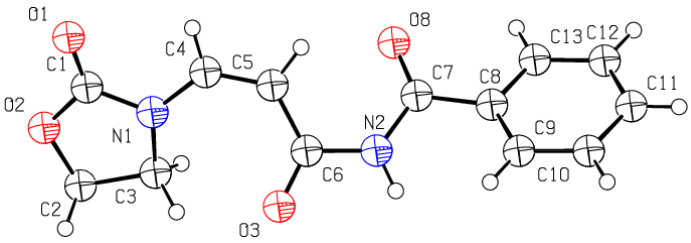


Fig. S1 ORTEP diagram of **2a (*cis-trans*)** with thermal ellipsoids at 50% probability.

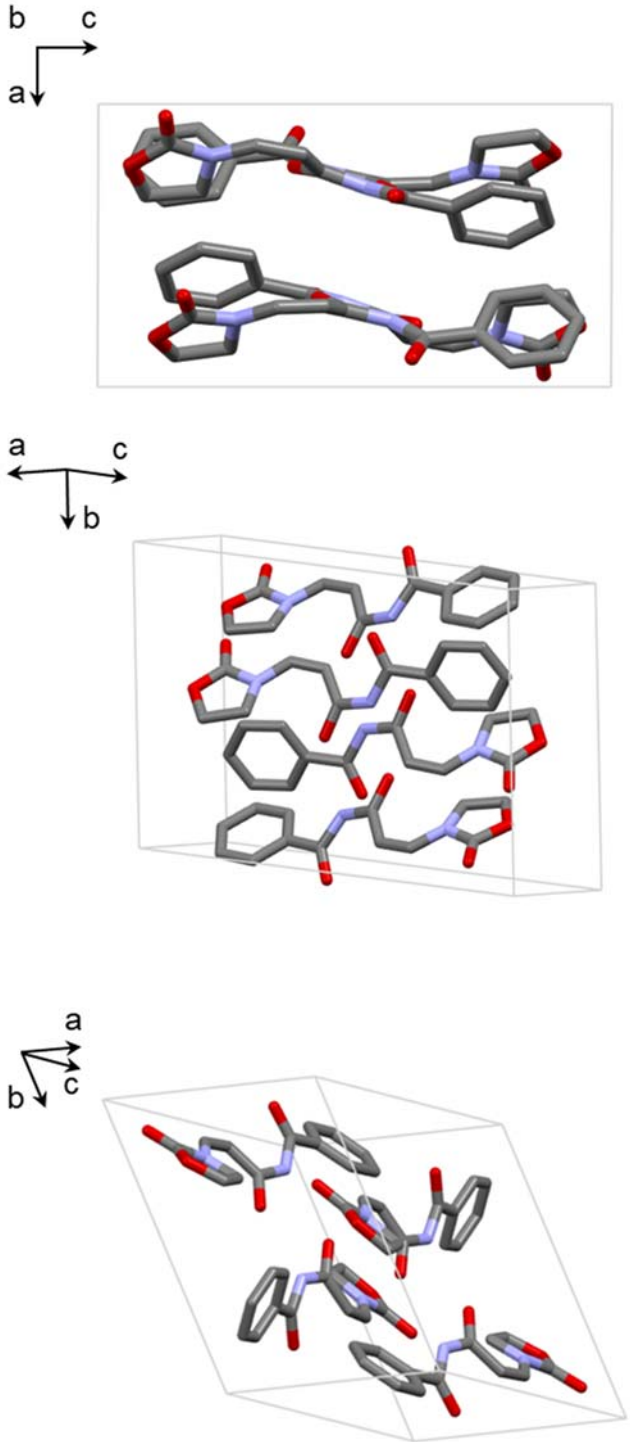


Fig. S2 Packing structure of **2a (*cis-trans*)**.

X-ray crystallographic structure determination for 2a (*trans-trans*)

X-ray diffraction data for **2a (*trans-trans*)** was collected using a Rigaku Saturn 724 CCD diffractometer with Mo-Ka radiation (l = 0.71073 Å) at 93 K. Single crystals (size: 0.35 × 0.10 × 0.10 mm^3) of **2a (*trans-trans*)** ($C_{13}H_{12}N_2O_4$, Mw = 260.25) suitable for X-ray analysis were grown by the recrystallization of a solution of **2a** in MeOH at ambient temperature. The unit cell was orthorhombic with the space group *Pbca*. Lattice constants with $Z = 8$, $\rho_{calcd} = 1.498$ g/cm^3, $\mu = 1.13$ cm^{-1}, $F(000) = 1088$, $\theta_{max} = 27.496^o$ were a = 13.6835(3), b = 7.93170(10), c = 21.2615(4) Å, $\alpha = 90°$, $\beta = 90^o$, $\gamma = 90°$, and V = 2307.58(7) $Å^3$. A total of 30,030 reflections were collected, of which 2,657 reflections were independent ($R_{int} = 0.0399$). The structure was refined to final $R_1 = 0.0361$ for 2,484 data [$I > 2\sigma(I)$] with 176 parameters and $wR_2 = 0.0907$ for all data, GOF = 1.026, and residual electron density max./min. = 0.372/–0.169 e·$Å^{-3}$. The ORTEP diagram is shown in Fig. S3, and the crystal data and structure refinement are listed in Table S2. Data collection, cell refinement, and data reduction were conducted using the CrystalClear-SM Expert 2.0 software[10]. The structure was solved by direct methods using the program SHELXT[11] and refined by full-matrix least-squares methods on F^2 using SHELXL2014[12]. All materials for publication were prepared by Yadokari-XG 2009 software[13]. All non-hydrogen atoms were refined anisotropically. Tables of positional and thermal parameters, bond lengths and angles, torsion angles and Fig.s may be found from the Cambridge Crystallographic Centre by referencing CCDC number 1976180.

Table S2 Crystal data and structure refinement parameters for **2a (*trans-trans*)**

Empirical formula	$C_{13}H_{12}N_2O_4$	
Formula weight	260.25	
Temperature	93 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	*Pbca*	
Unit cell dimensions	a = 13.6835(3) Å	α = 90º
	b = 7.93170(10) Å	β = 90º
	c = 21.2615(4) Å	γ = 90º
Volume	2307.58(7) Å^3	
Z	8	
Density (calculated)	1.498 g/cm^{-3}	
Absorption coefficient	0.113 mm^{-1}	
F(000)	1088	
Crystal size	0.35 × 0.10 × 0.10 mm^3	
Theta range for data collection	2.426 to 27.496º	
Index ranges	$-17 \le h \le 17$, $-10 \le k \le 10$, $-27 \le l \le 27$	
Reflections collected	30030	
Independent reflections	2657 [R(int) = 0.0399]	
Completeness to theta = 25.242º	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmissions	1.00000 and 0.93972	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	2657/0/176	
Goodness-of-fit on F^2	1.026	
Final R indices [I > 2sigma(I)]	R_1 = 0.0361, wR_2 = 0.0890	
R indices (all data)	R_1 = 0.0385, wR_2 = 0.0907	
Largest diff. peak and hole	0.372 and –0.169 e·Å^{-3}	

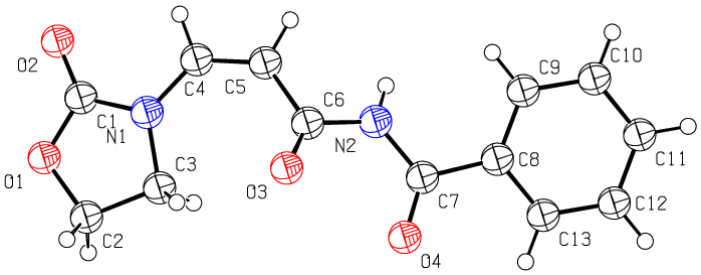


Fig. S3 ORTEP diagram of **2a (*trans-trans*)** with thermal ellipsoids at 50% probability.

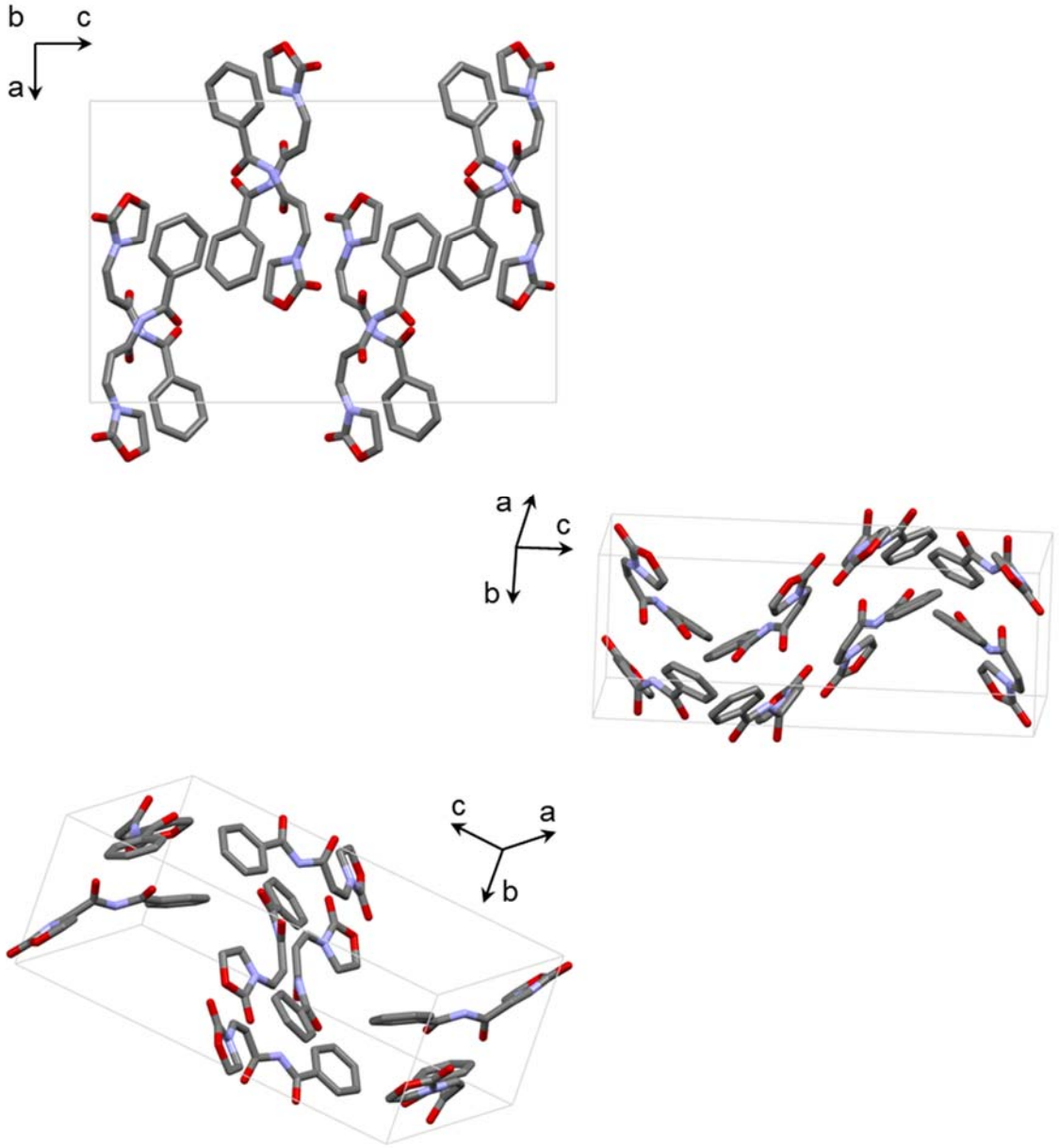


Fig. S4 Packing structure of **2a (*trans-trans*)**.

^{1}H and ^{13}C NMR spectra of compounds

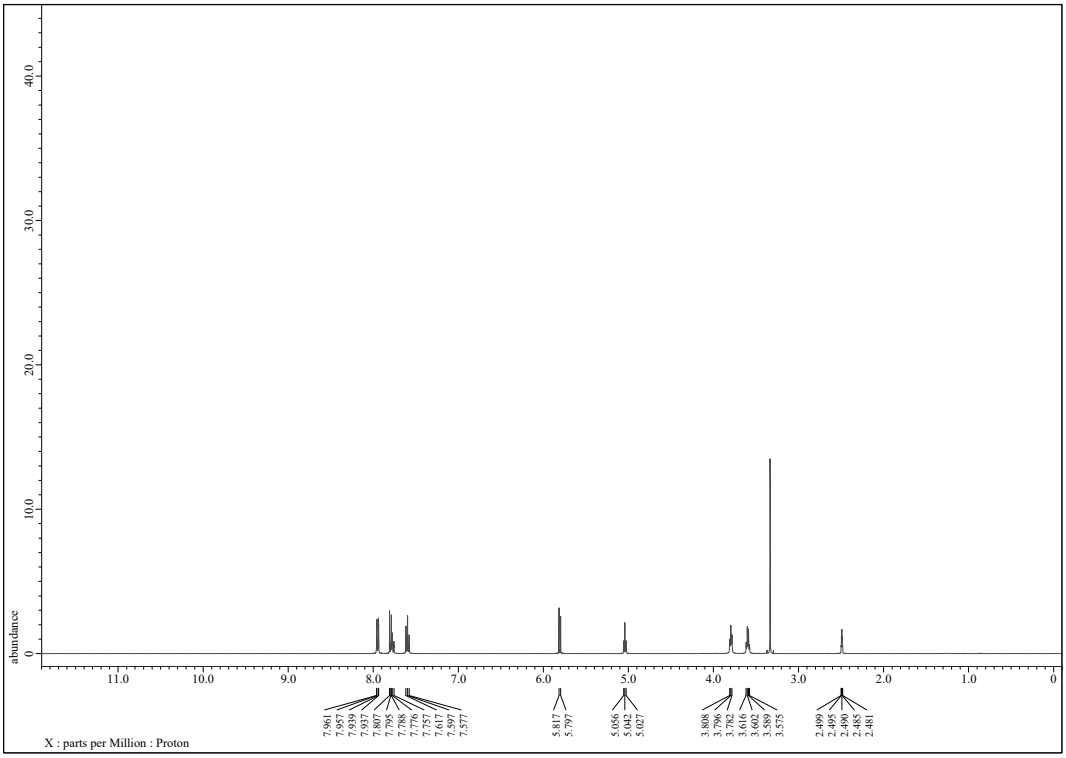


Fig. S5 ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of **1a**.

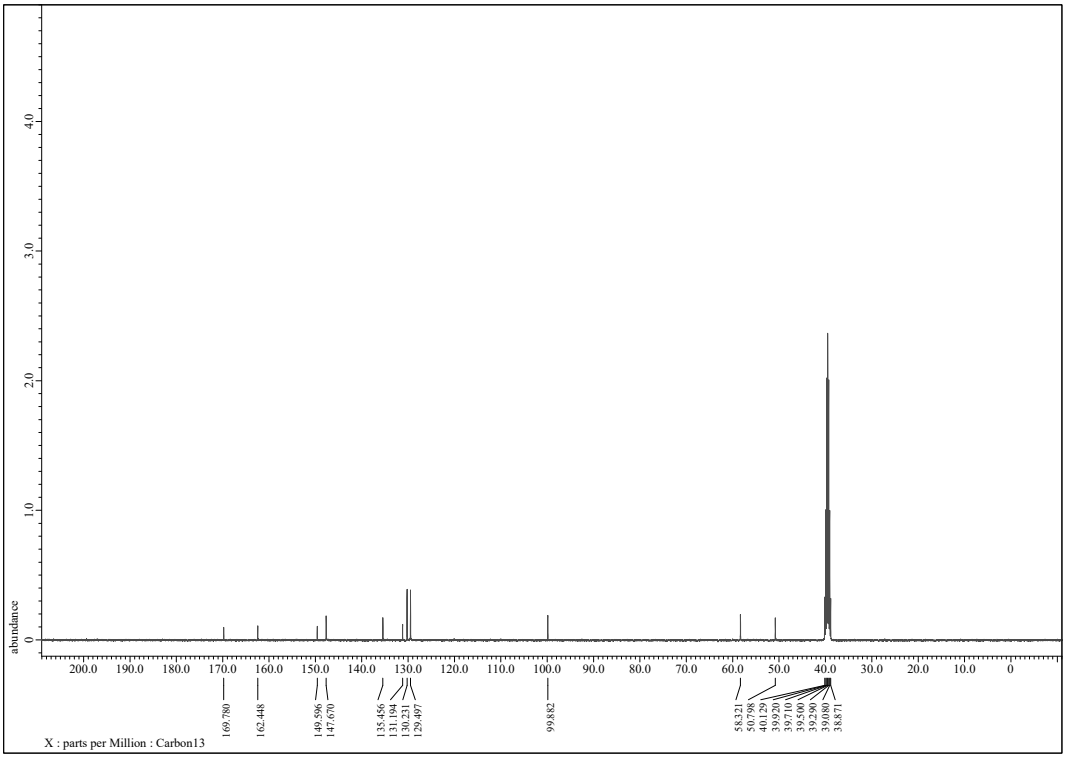


Fig. S6 ^{13}C NMR spectrum (100 MHz, DMSO-d_6) of **1a**.

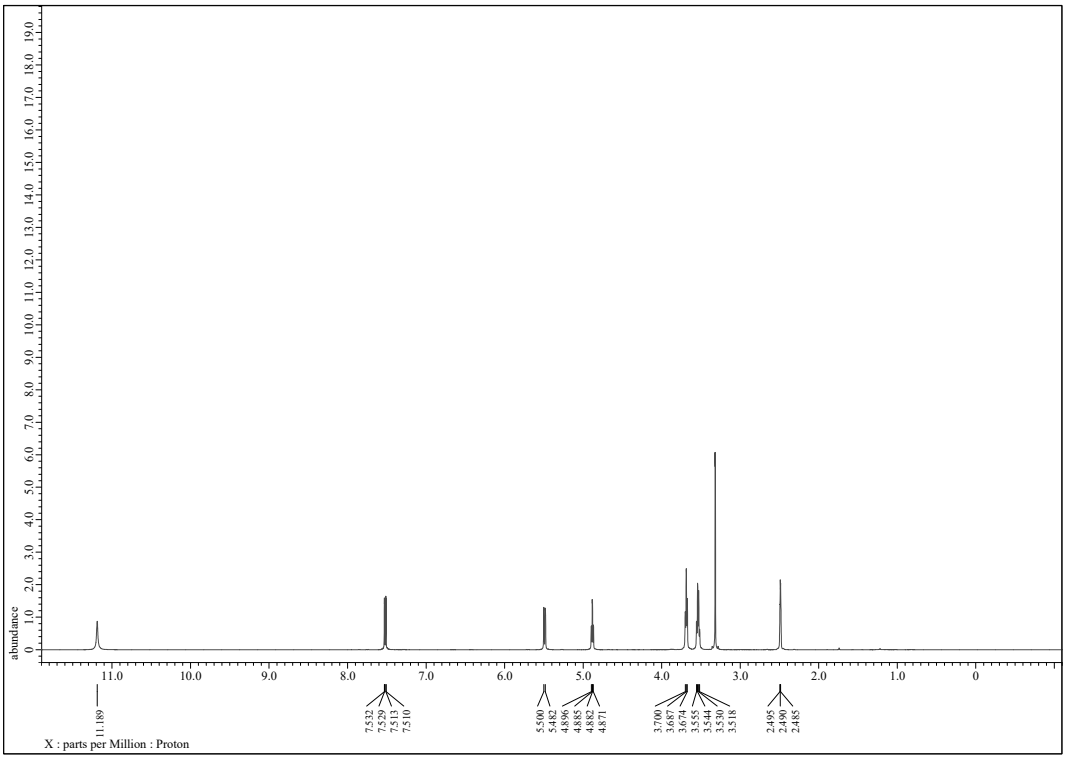


Fig. S7 ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of **1b**.

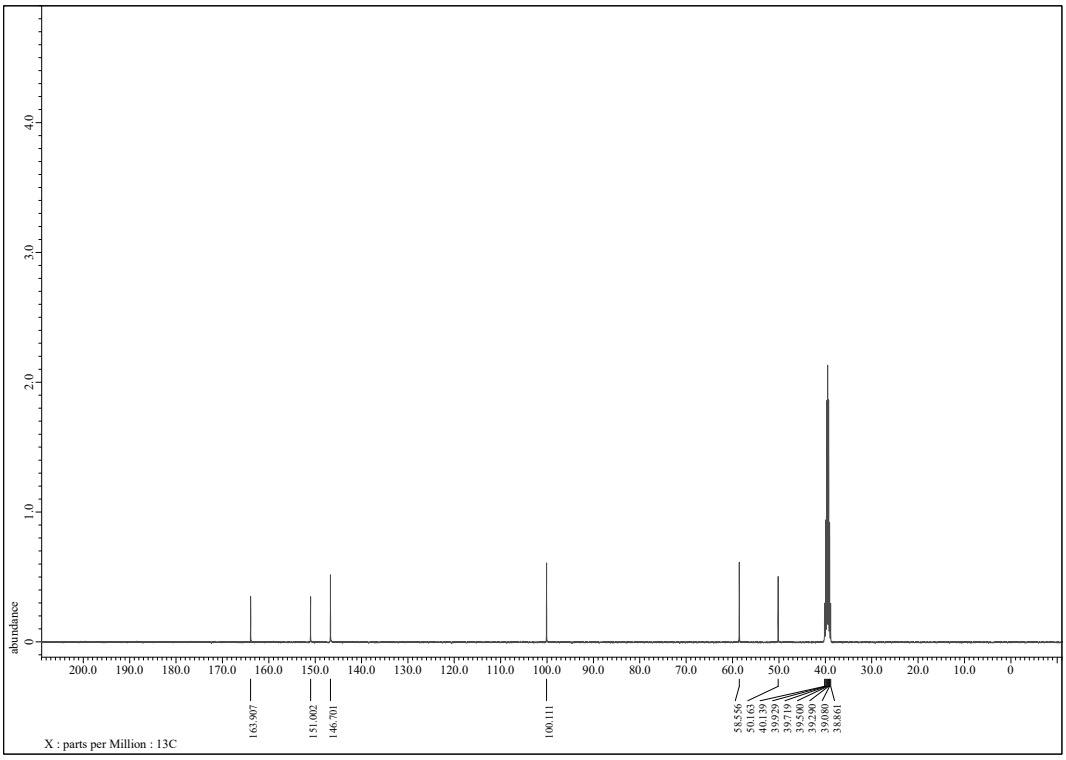


Fig. S8 ^{13}C NMR spectrum (100 MHz, DMSO-d_6) of **1b**.

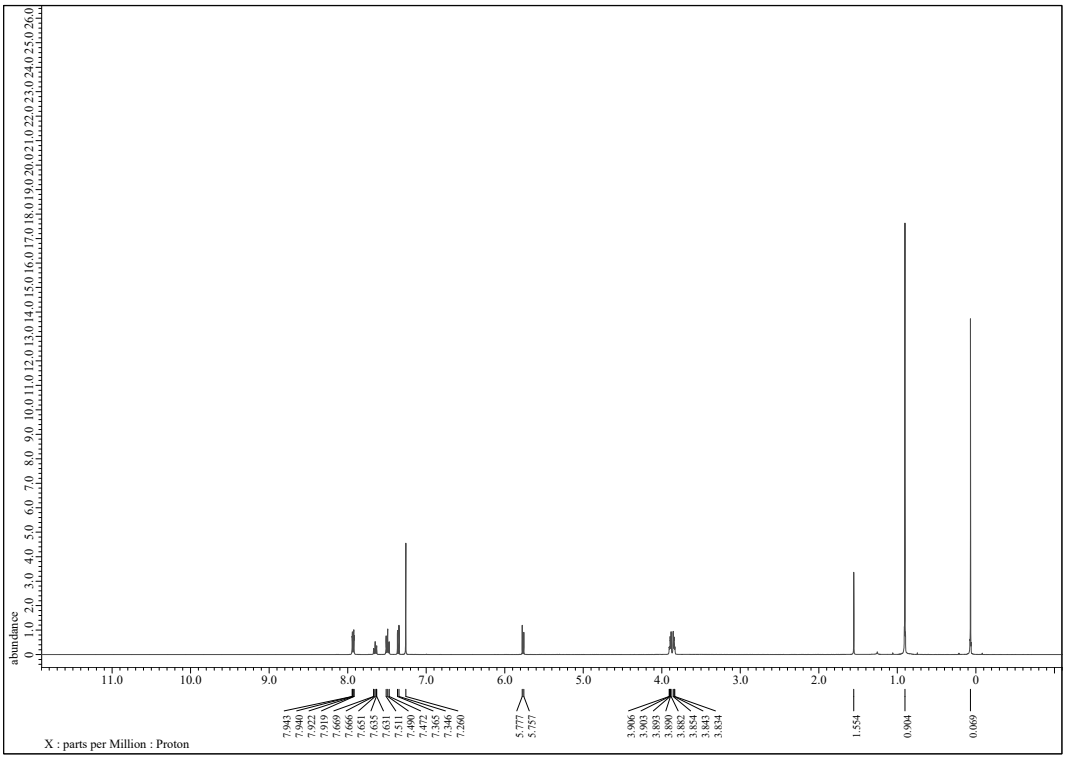


Fig. S9 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **S2**.

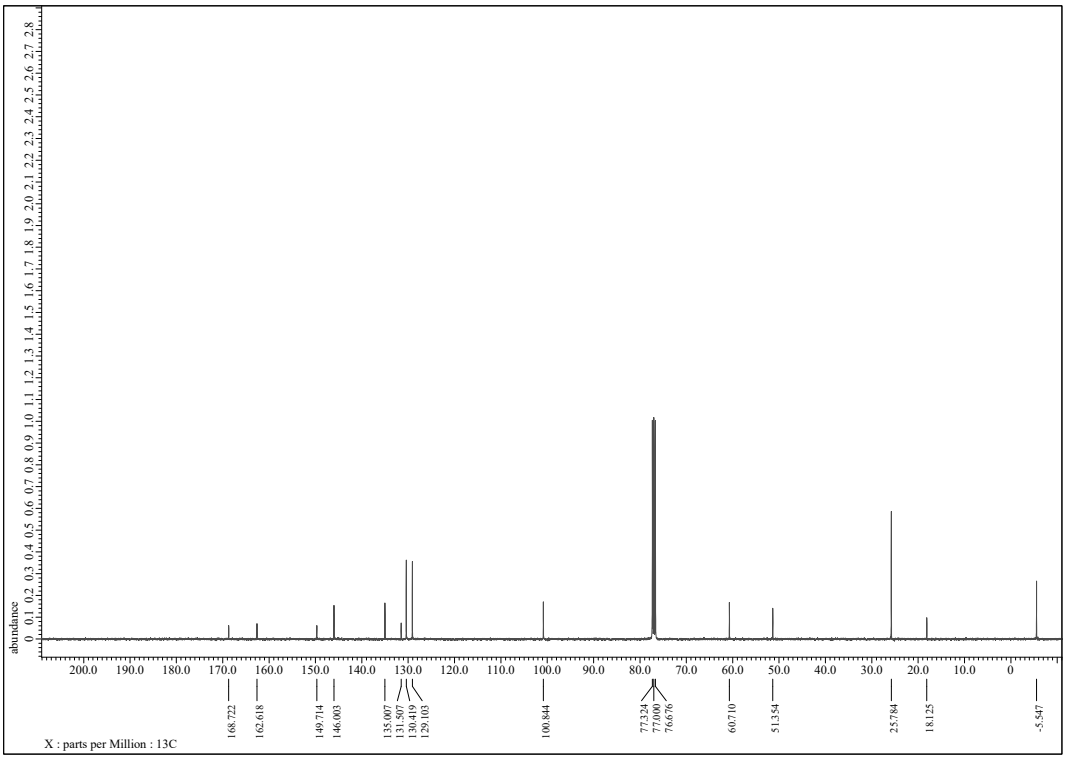


Fig. S10 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **S2**.

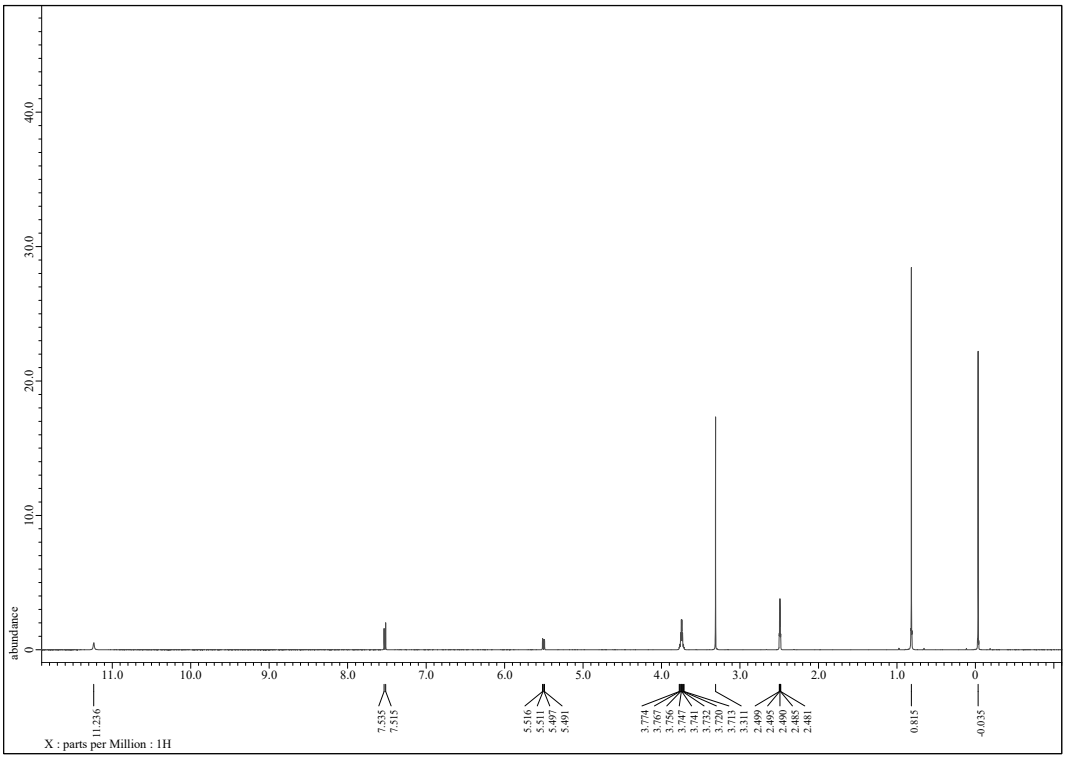


Fig. S11 ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of **S3**.

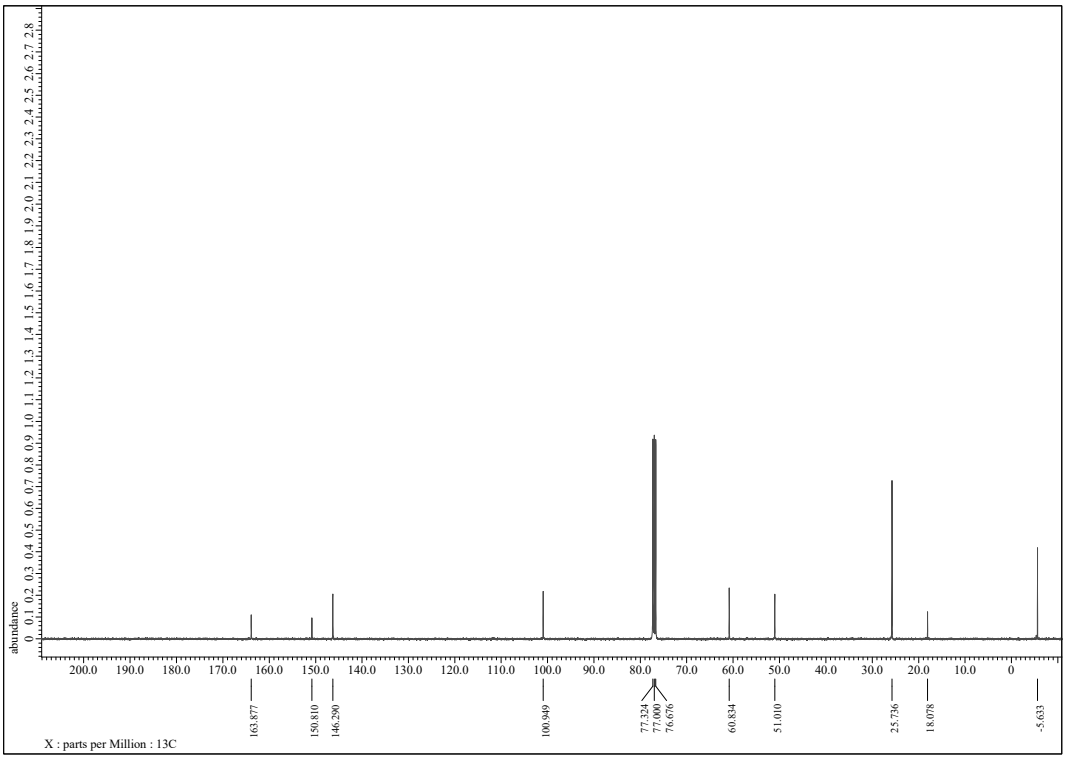


Fig. S12 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **S3**.

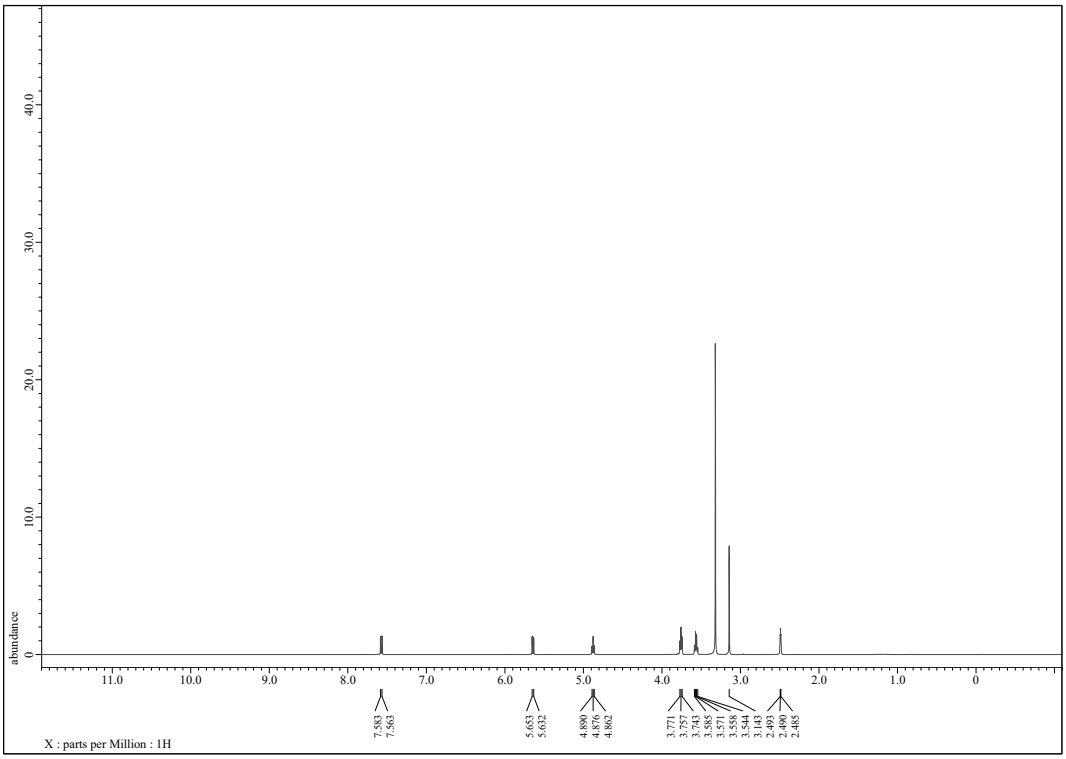


Fig. S13 ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of **1c**.

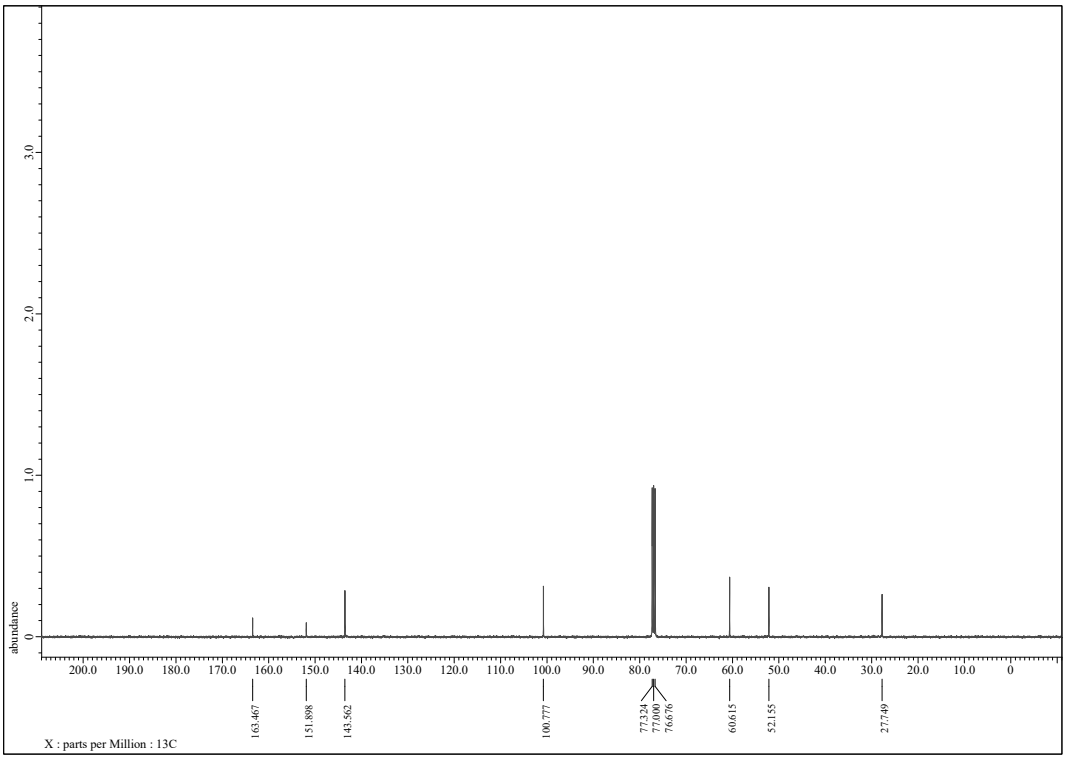


Fig. S14 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **1c**.

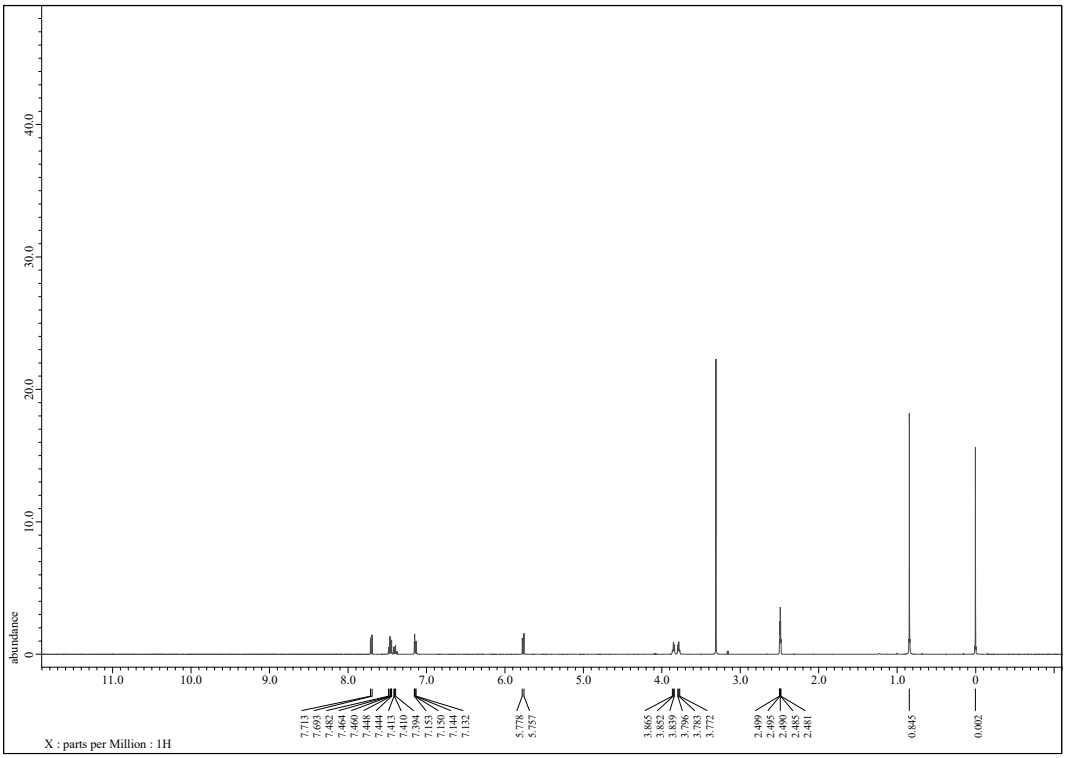


Fig. S15 ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of **S5**.

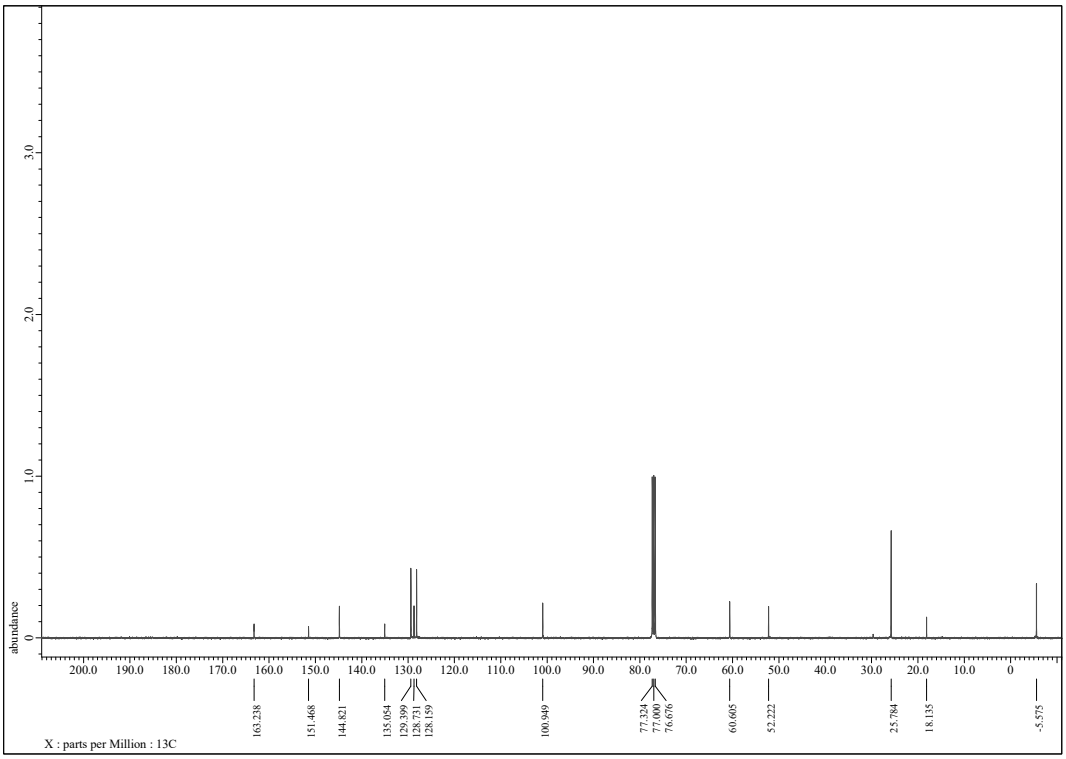


Fig. S16 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **S5**.

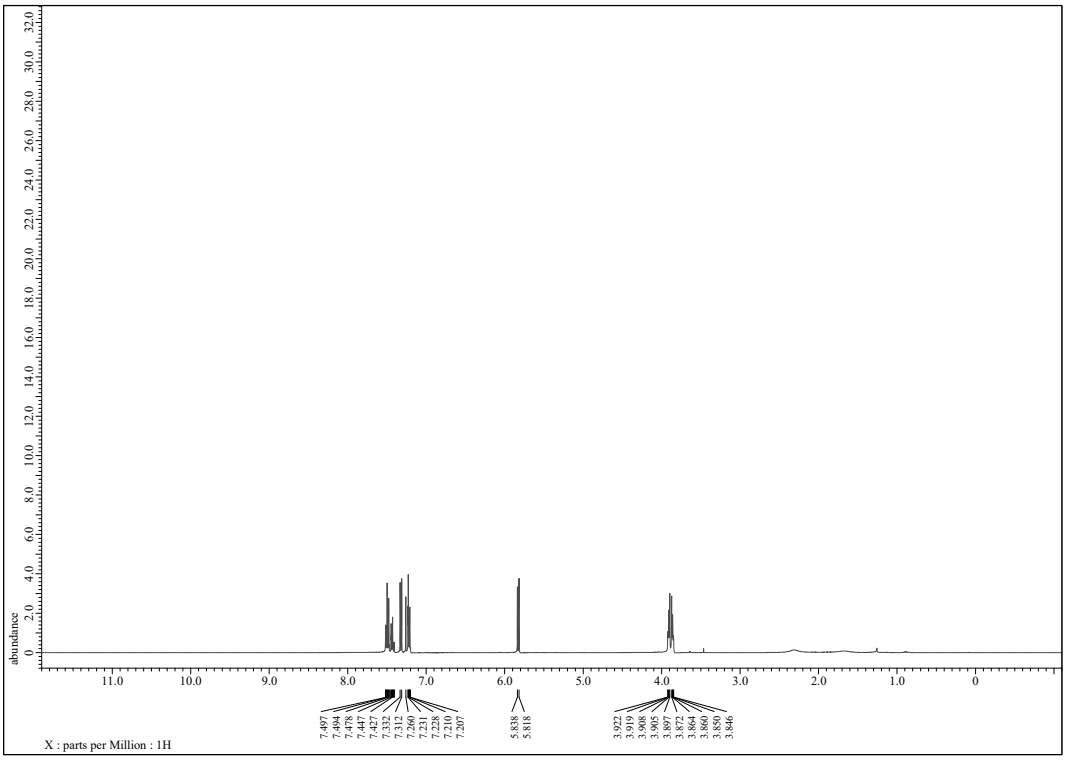


Fig. S17 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **1d**.

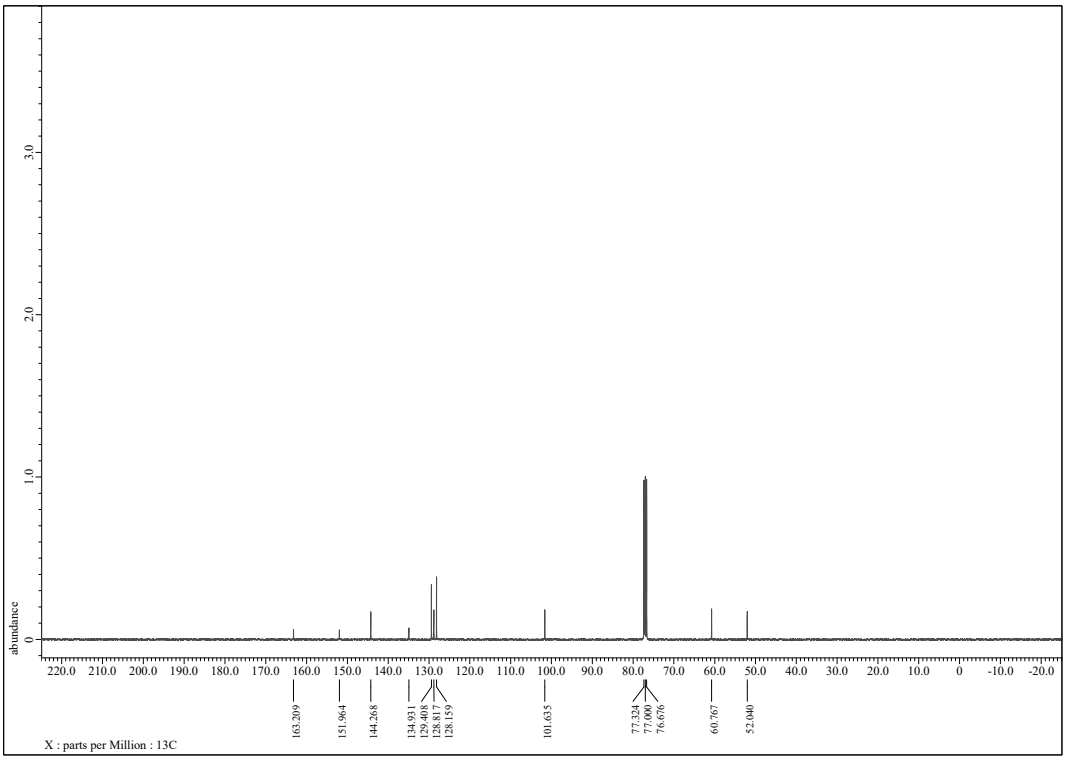


Fig. S18 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **1d**.

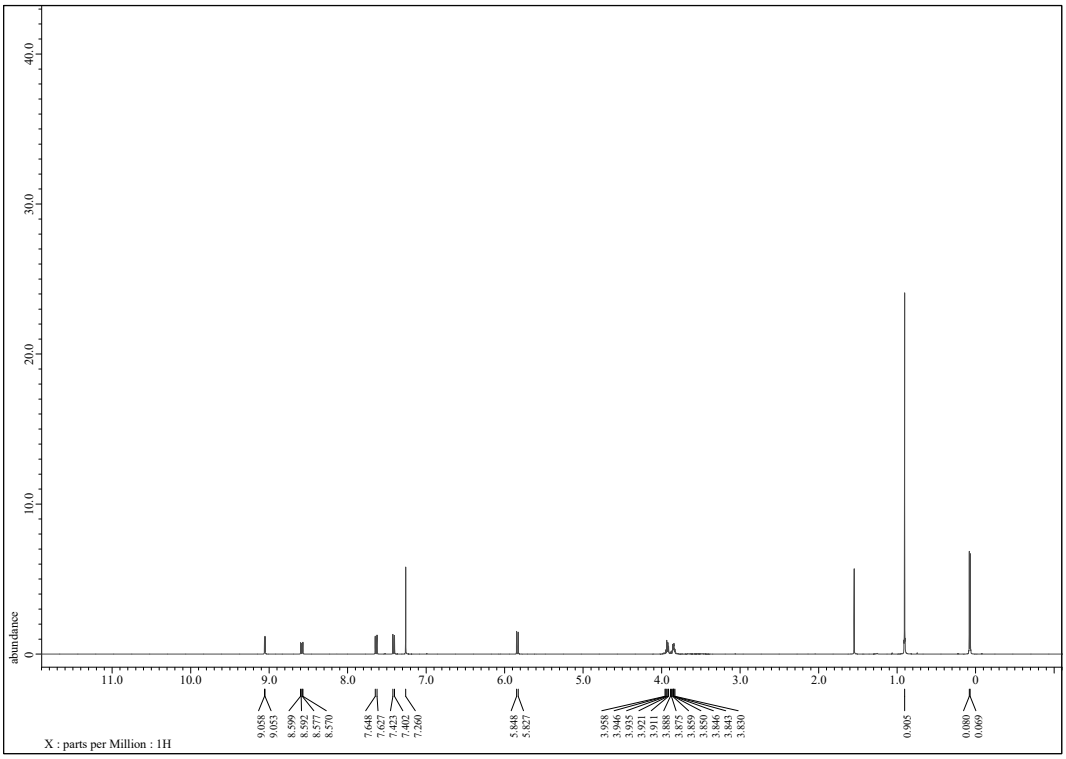


Fig. S19 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **S6**.

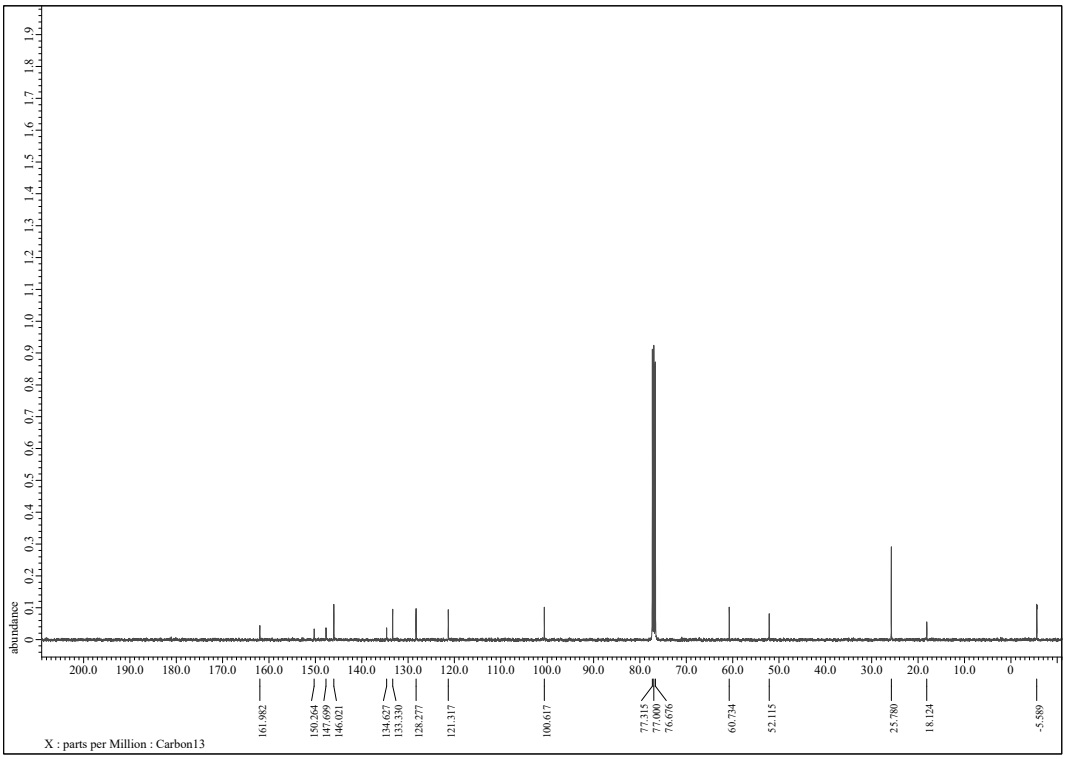


Fig. S20 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **S6**.

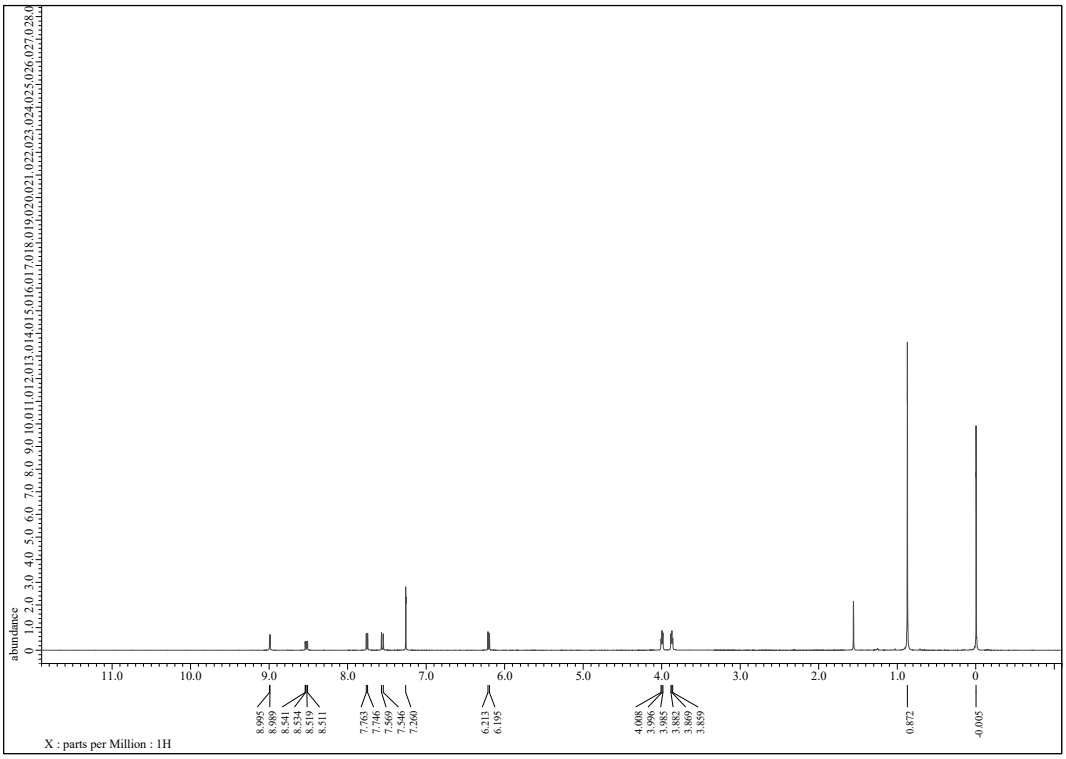


Fig. S21 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **S7**.

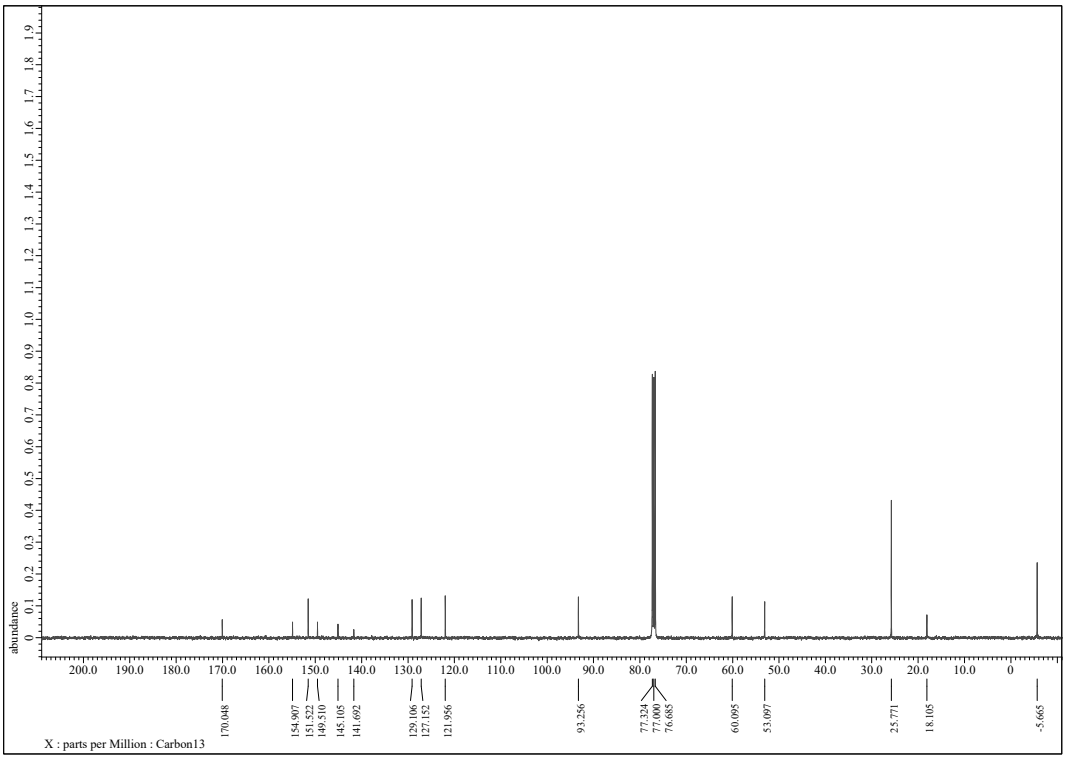


Fig. S22 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **S7**.

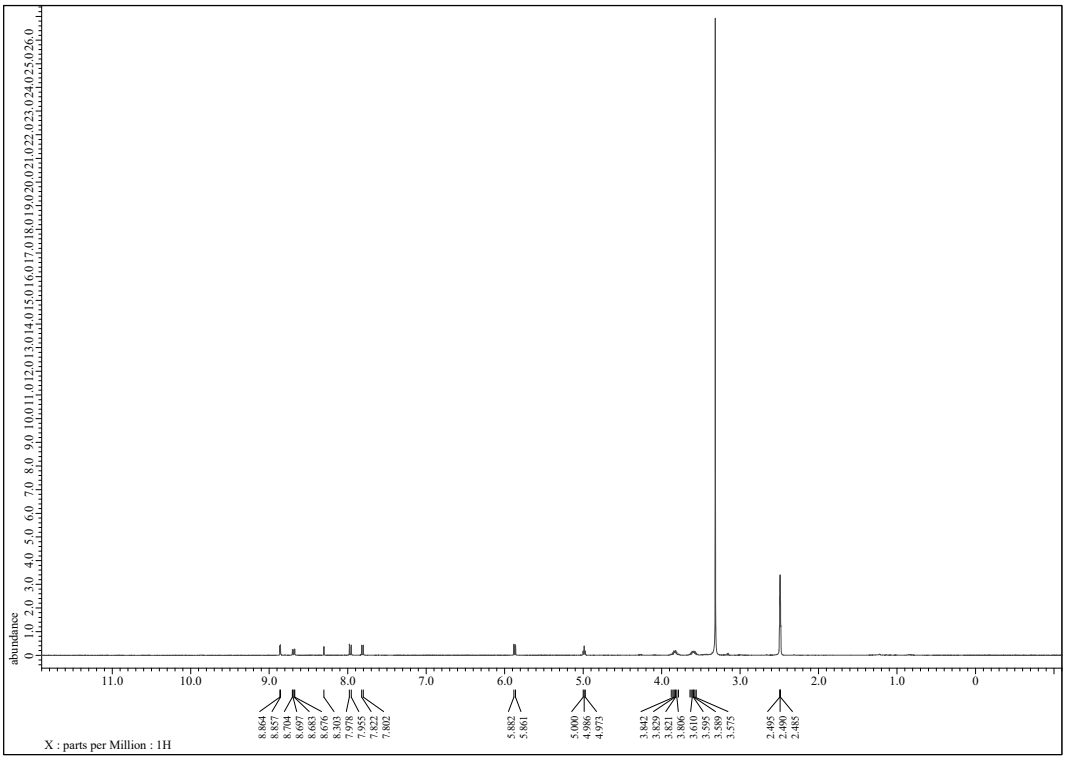


Fig. S23 ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of **1e**.

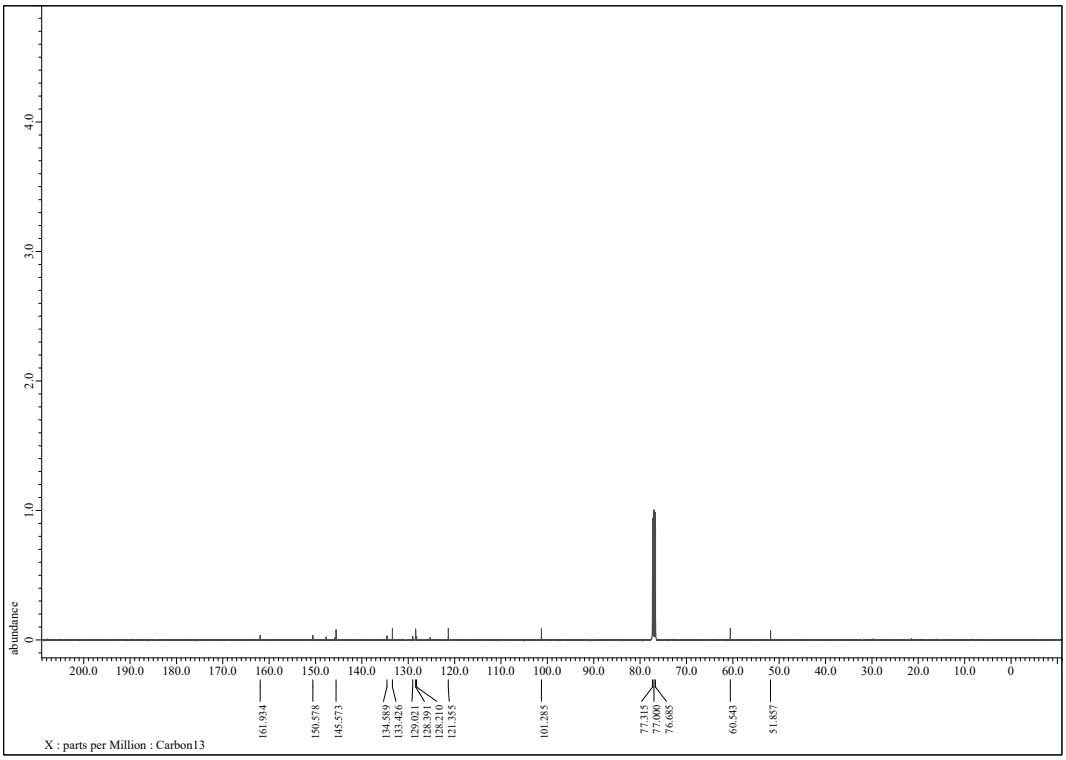


Fig. S24 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **1e**.

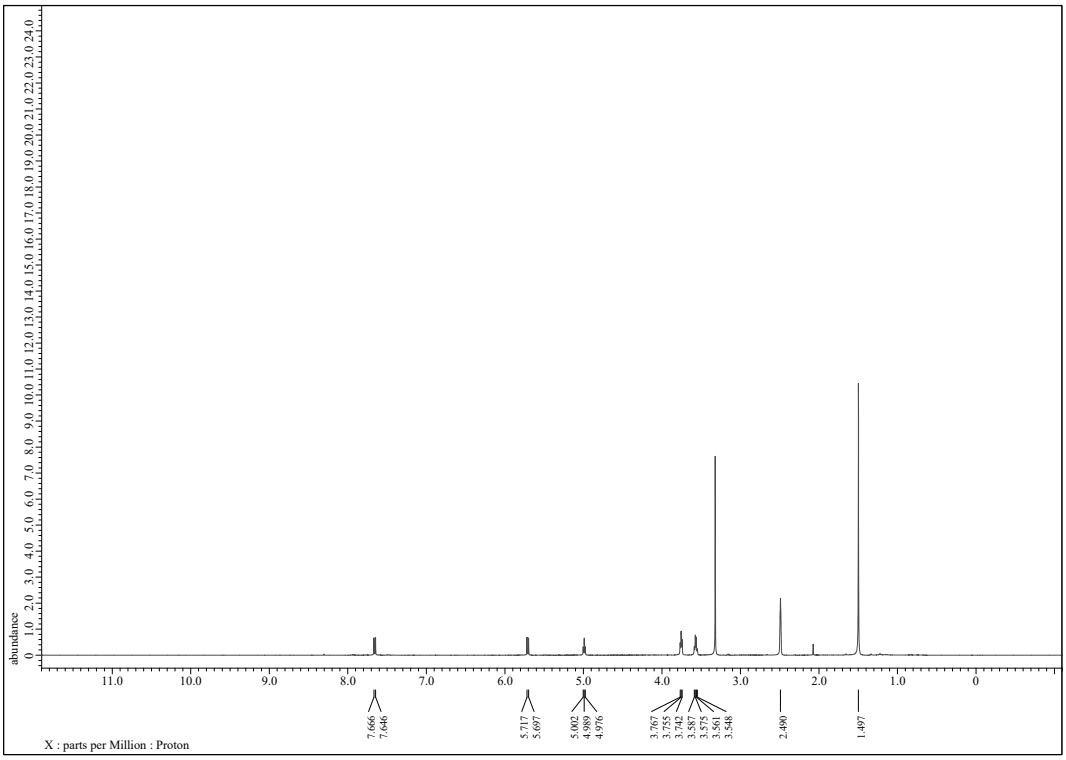


Fig. S25 ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of **1f**.

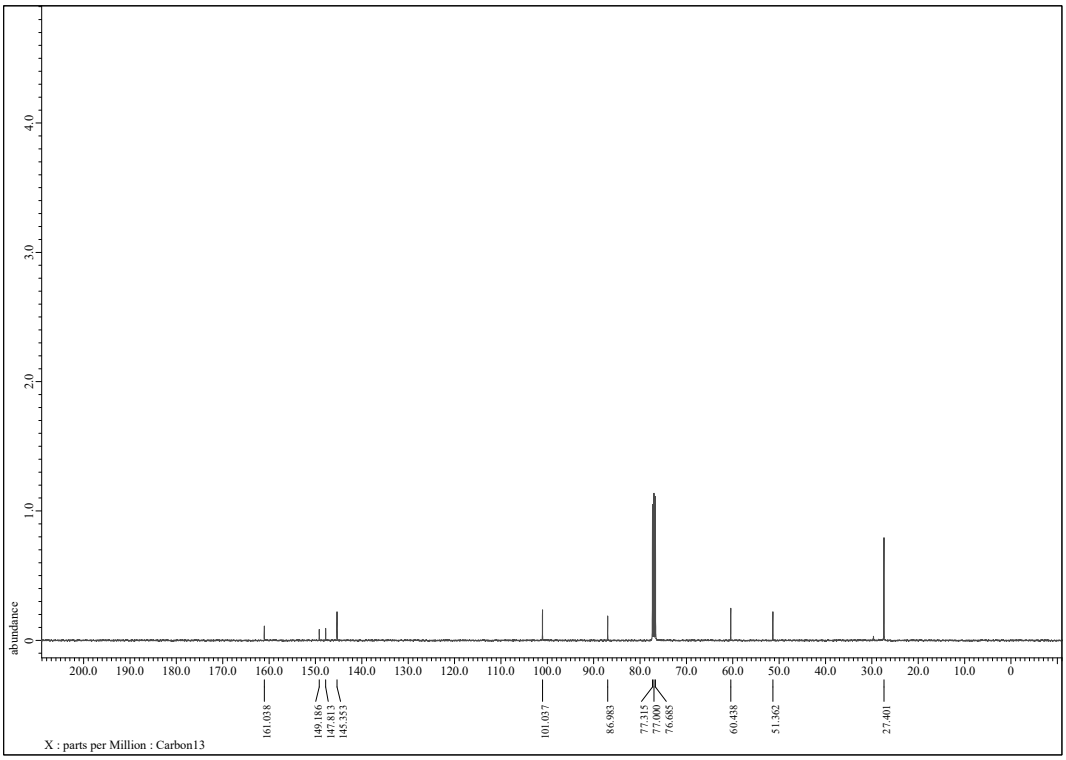


Fig. S26 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **1f**.

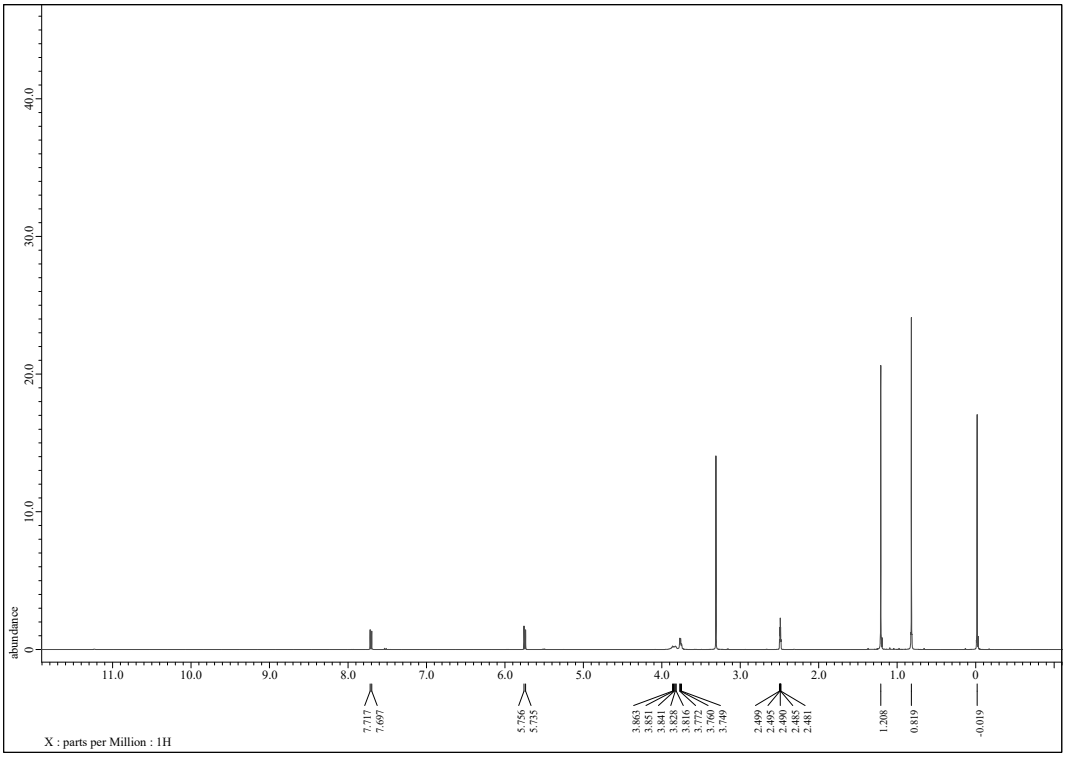


Fig. S27 ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of **S9**.

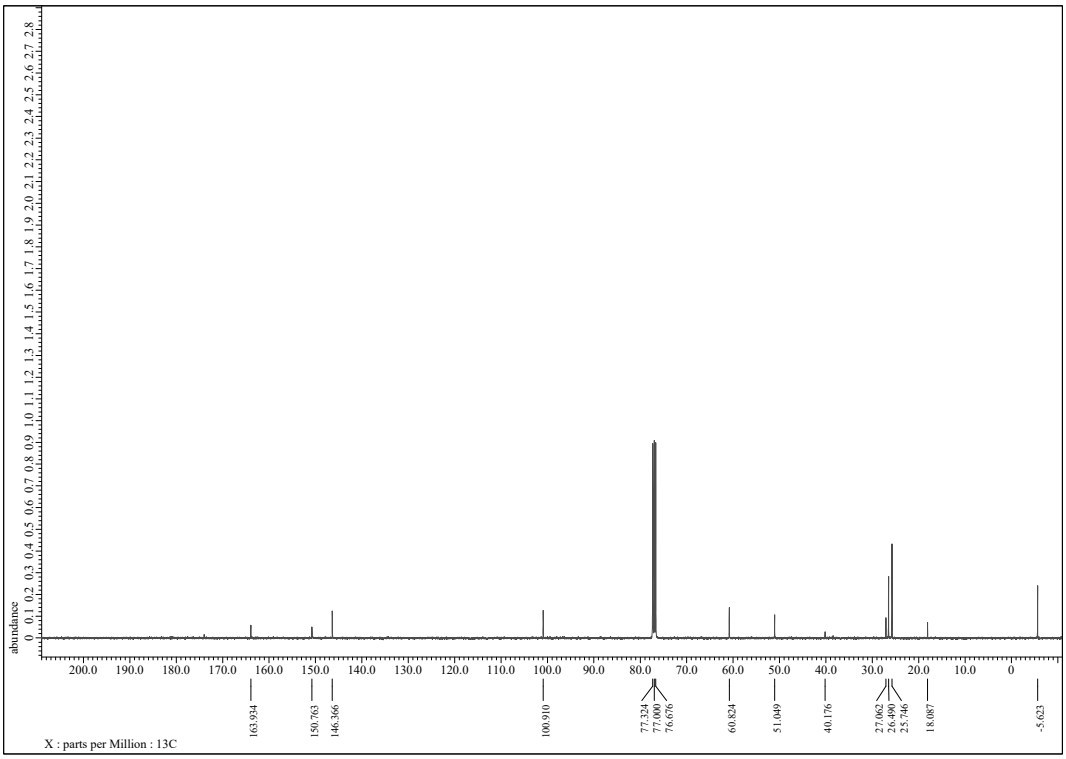


Fig. S28 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **S9**.

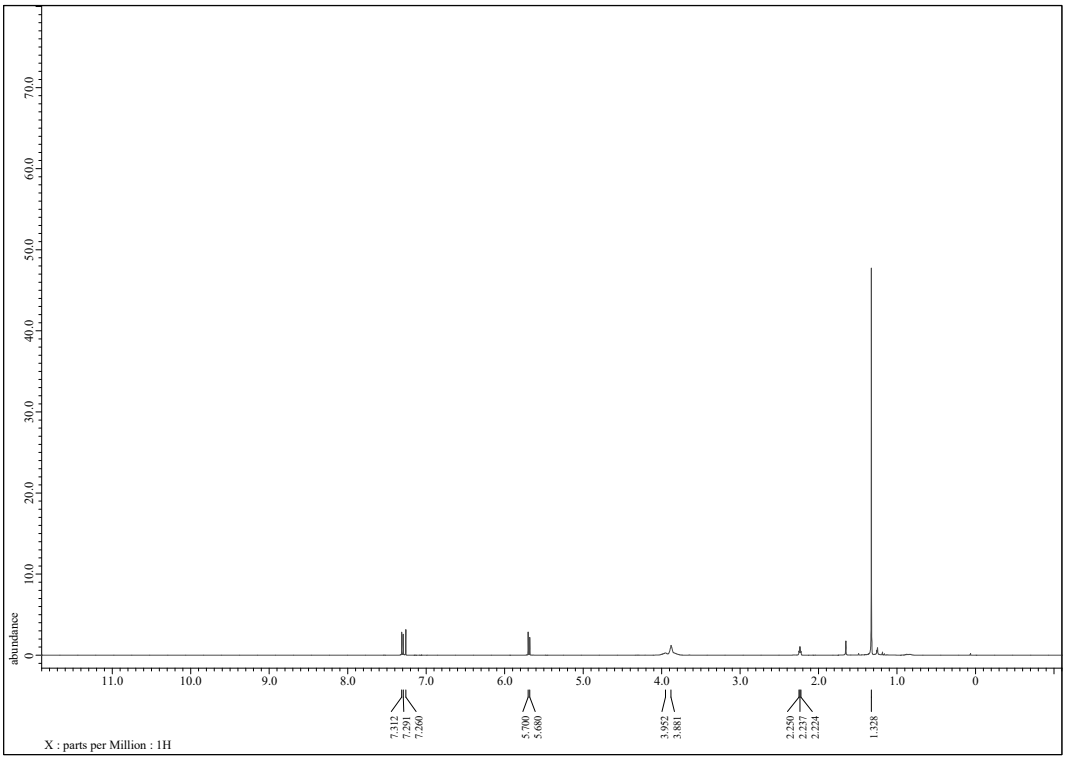


Fig. S29 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **1g**.

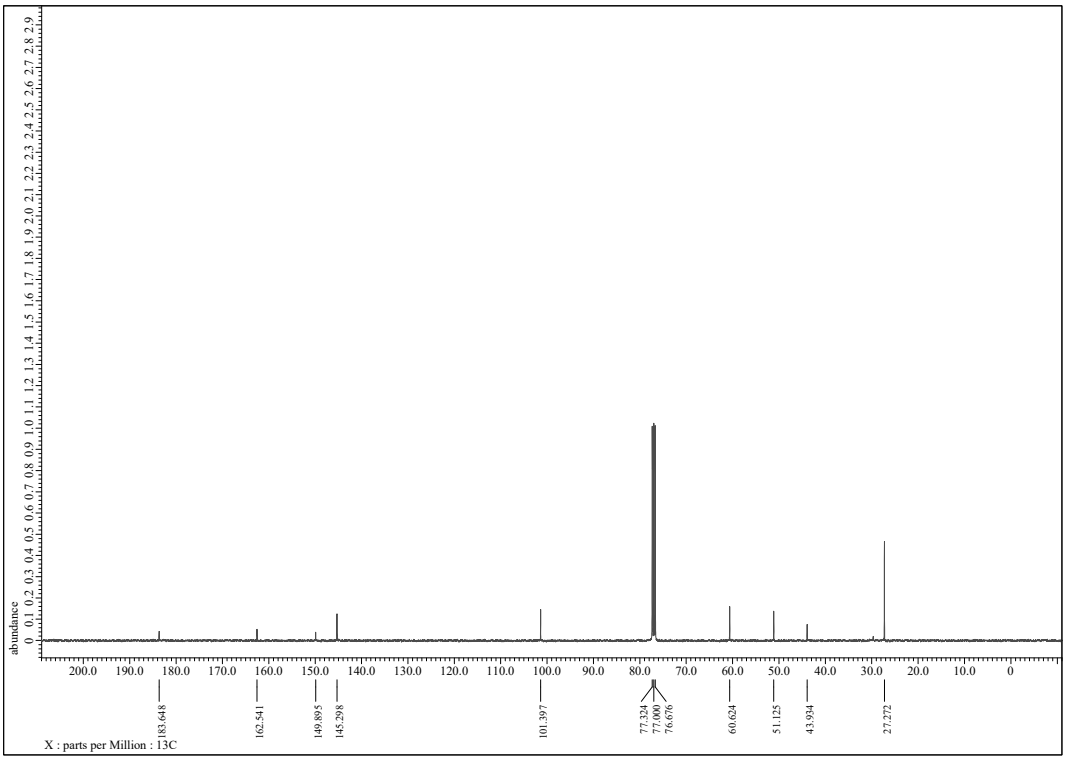


Fig. S30 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **1g**.

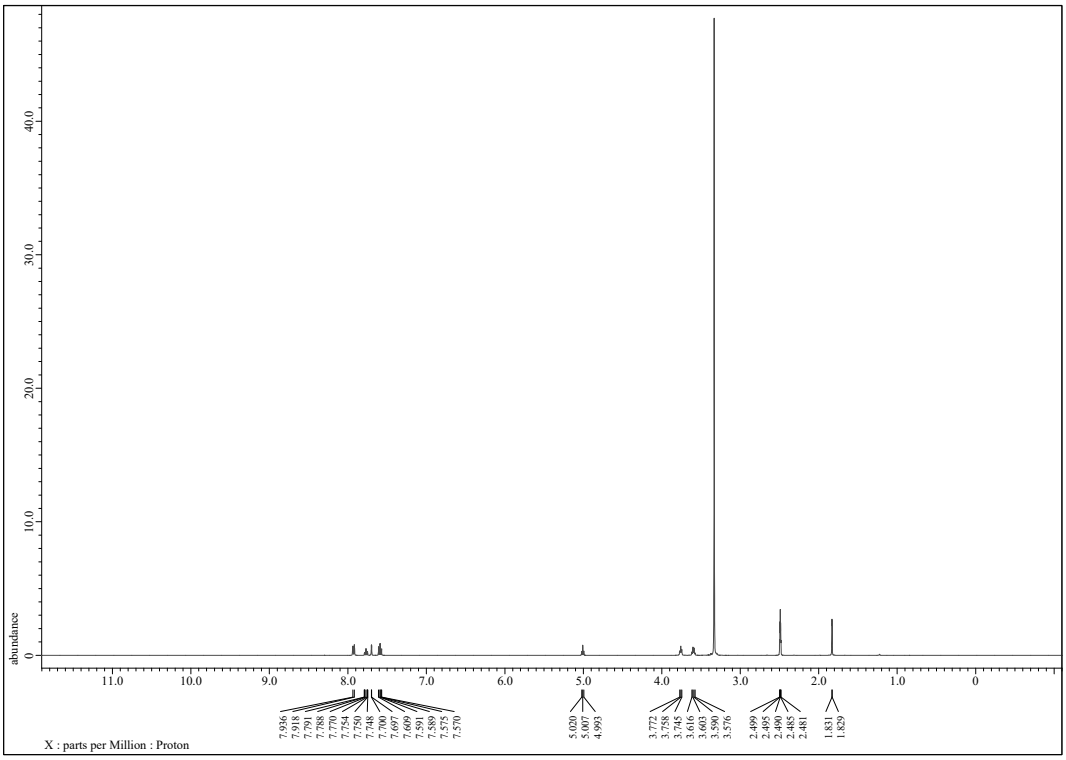


Fig. S31 ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of **1h**.

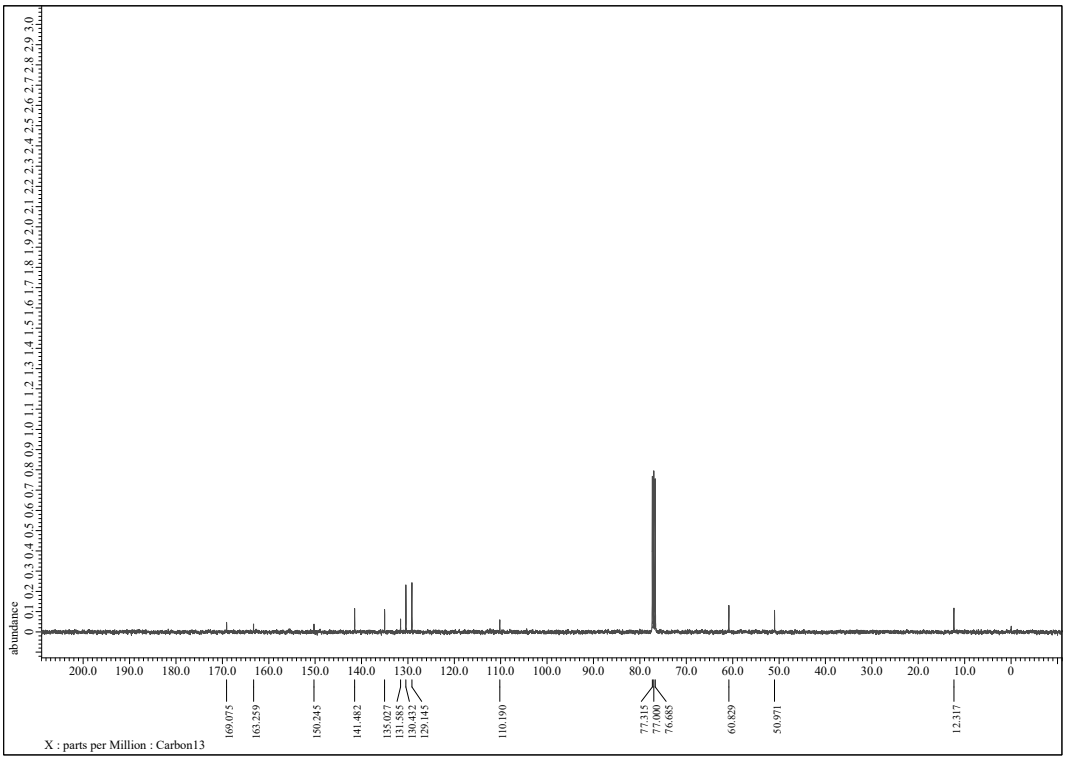


Fig. S32 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **1h**.

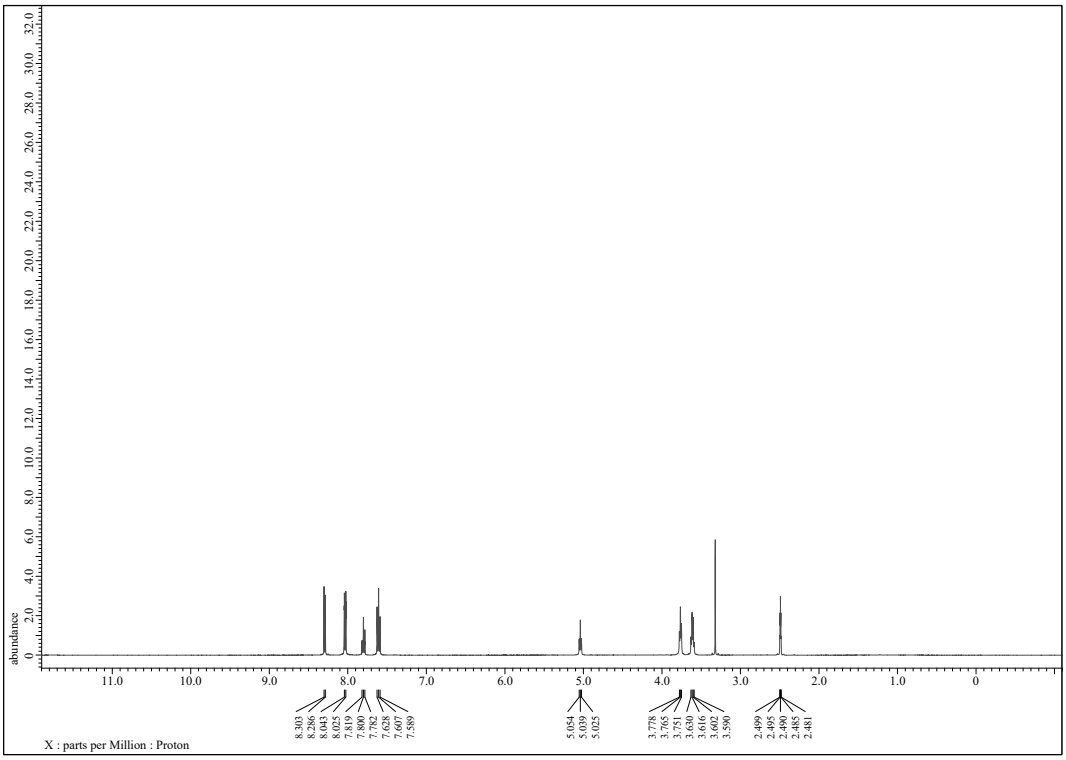


Fig. S33 ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of **1i**.

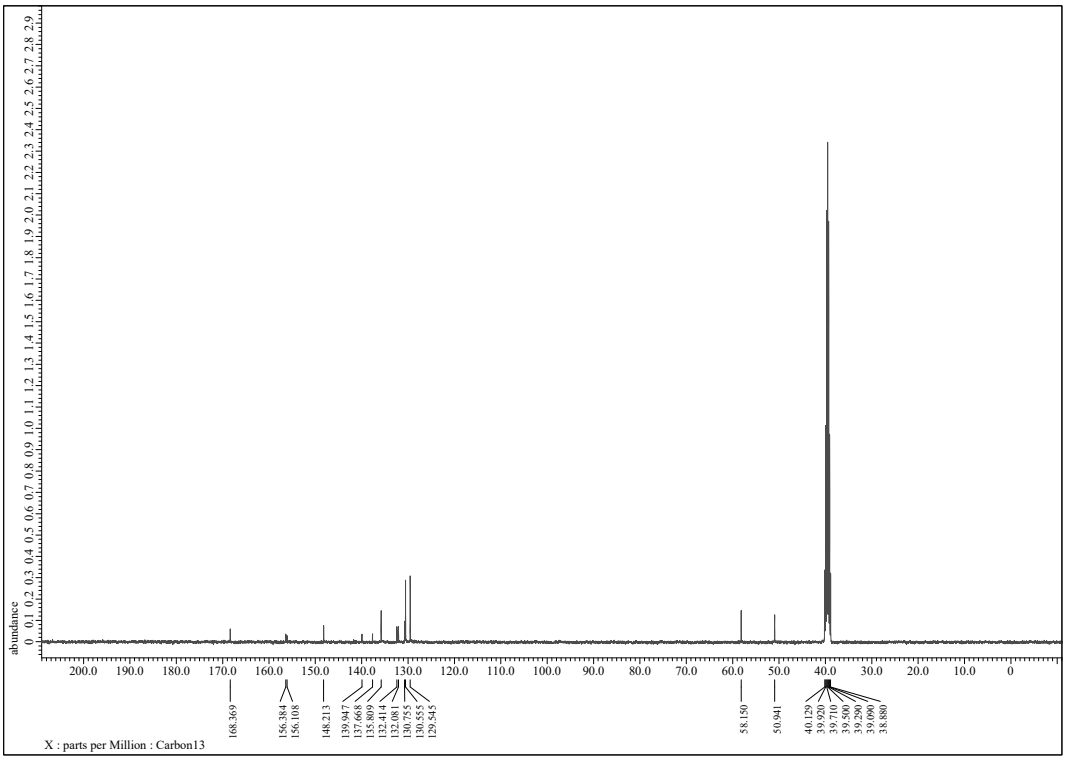


Fig. S34 ^{13}C NMR spectrum (100 MHz, DMSO-d_6) of **1i**.

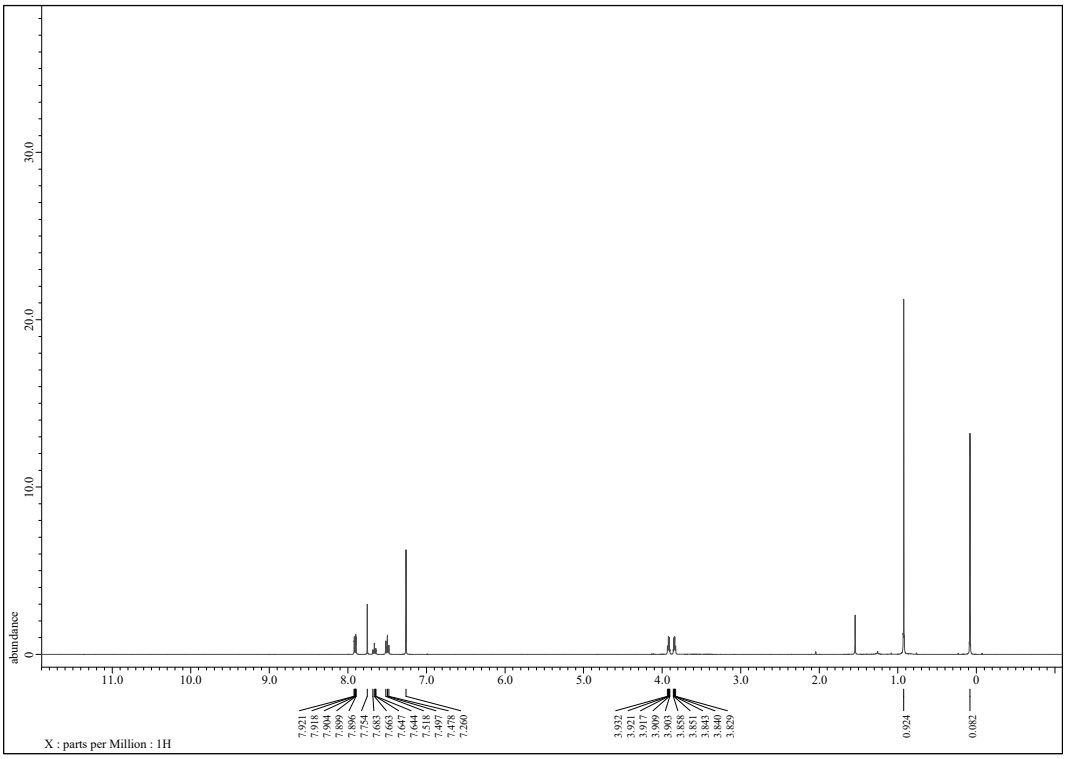


Fig. S35 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **S12**.

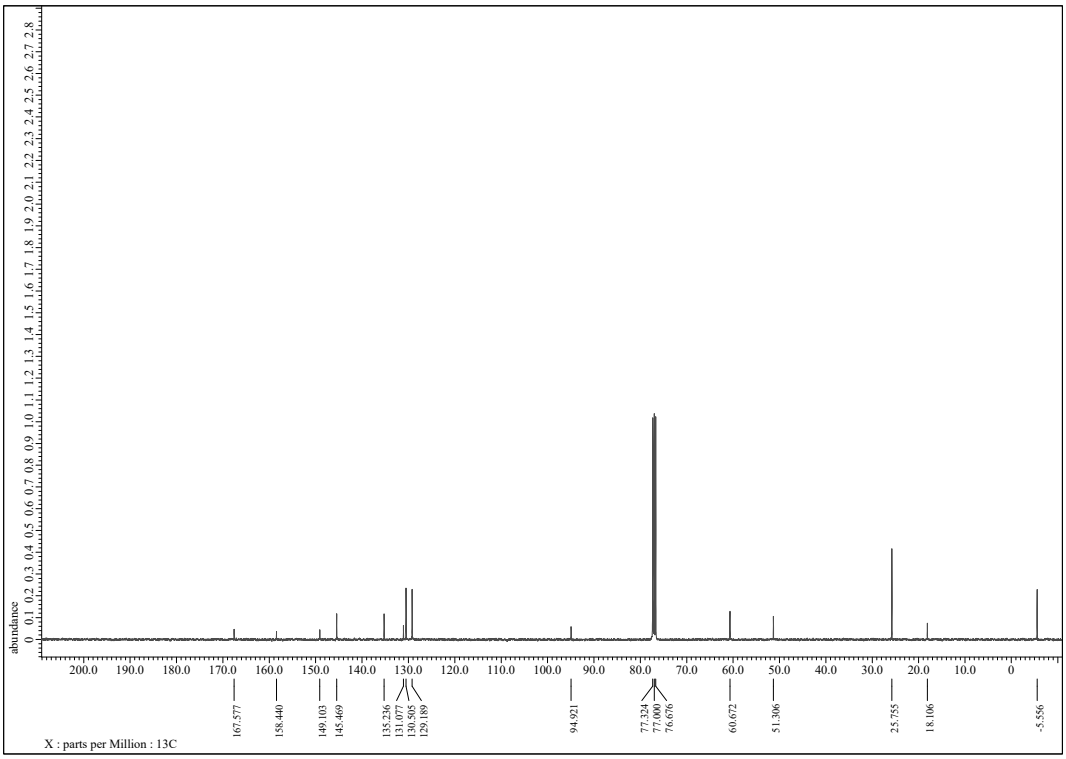


Fig. S36 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **S12**.

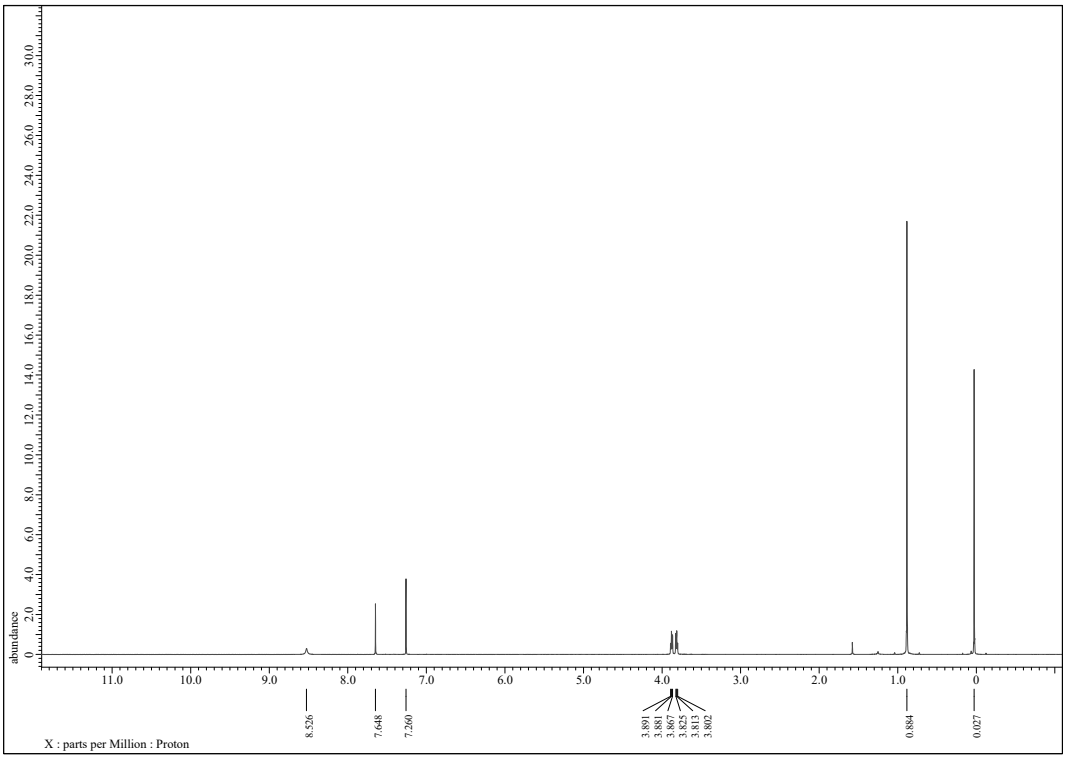


Fig. S37 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **S13**.

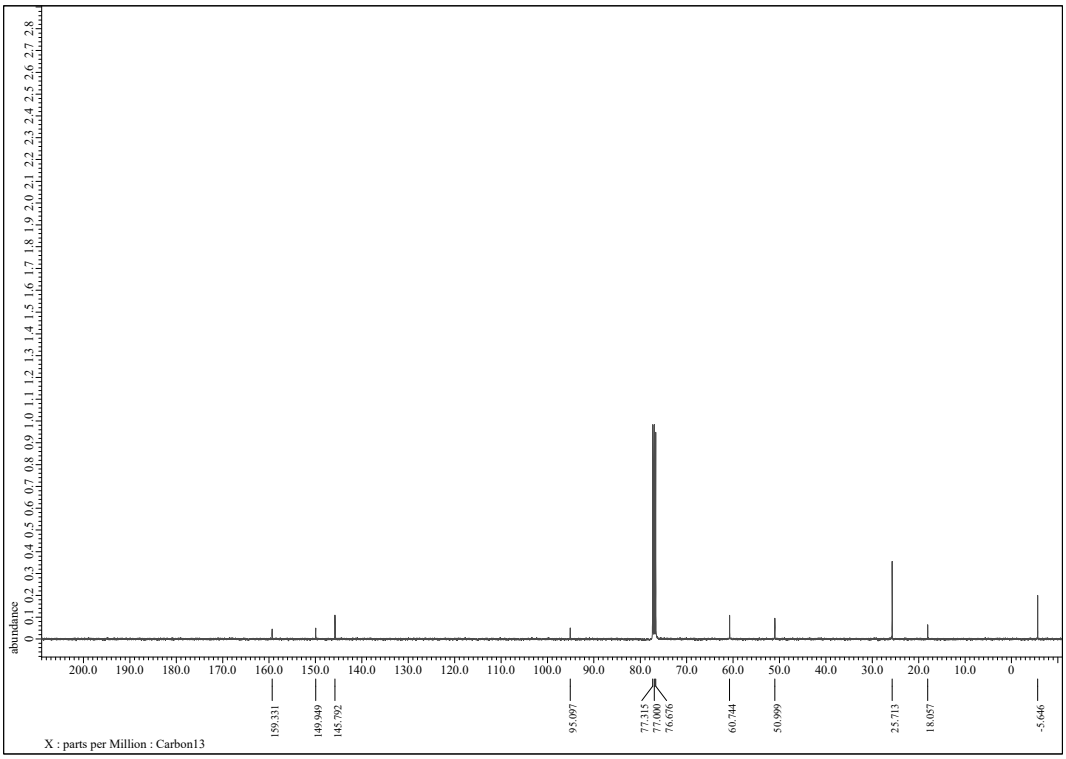


Fig. S38 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **S13**.

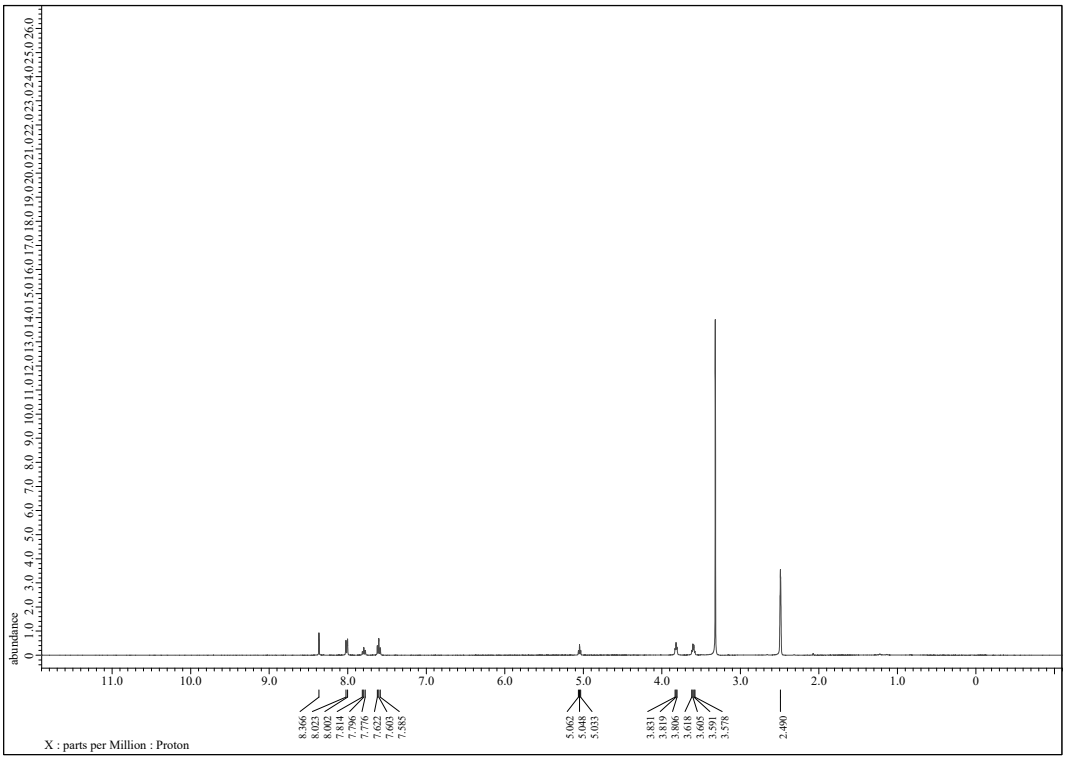


Fig. S39 ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of **1j**.

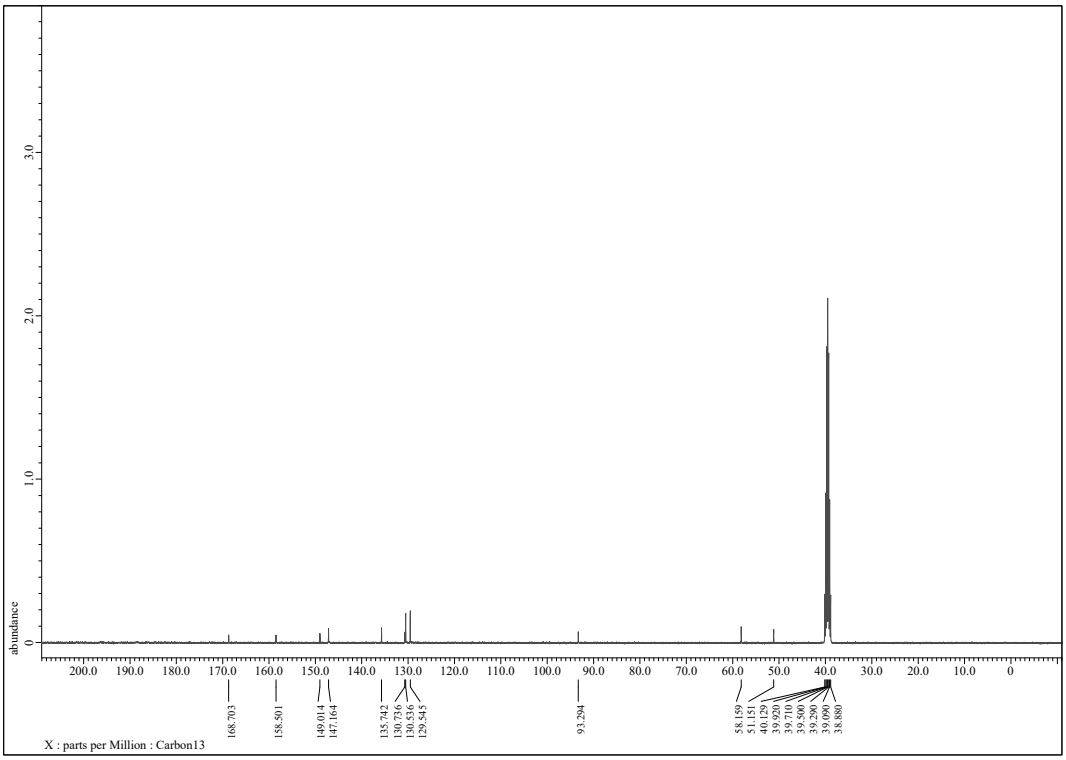


Fig. S40 ^{13}C NMR spectrum (100 MHz, DMSO-d_6) of **1j**.

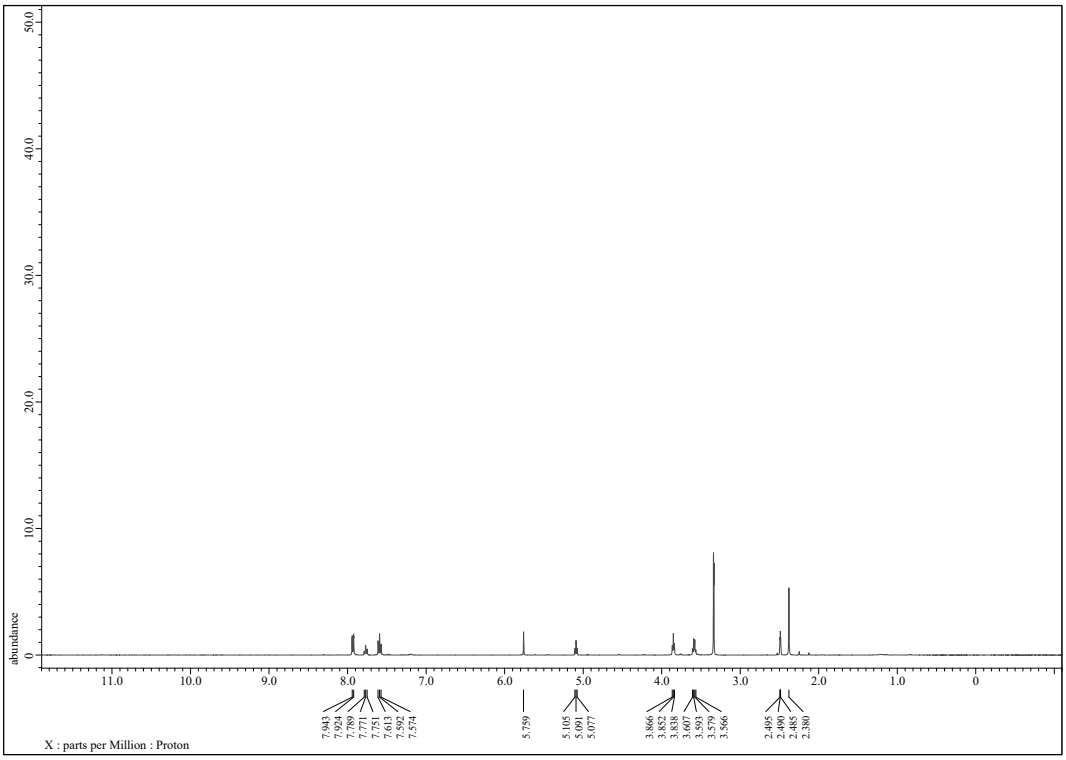


Fig. S41 ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of **1k**.

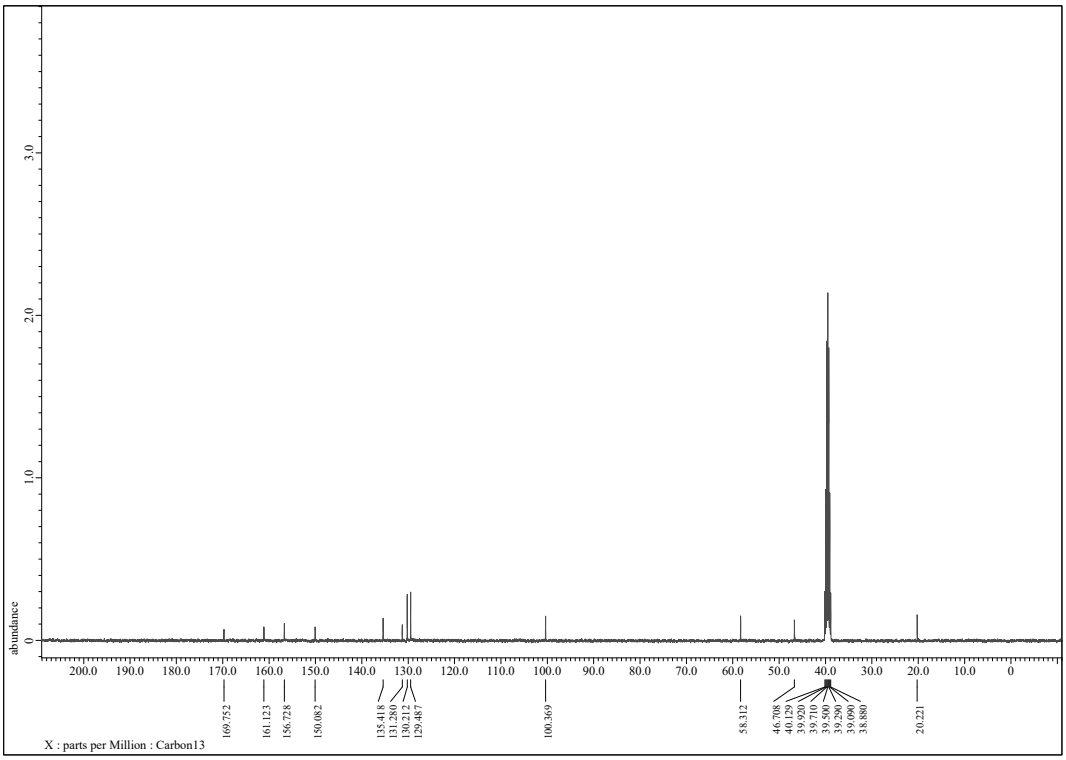


Fig. S42 ^{13}C NMR spectrum (100 MHz, DMSO-d_6) of **1k**.

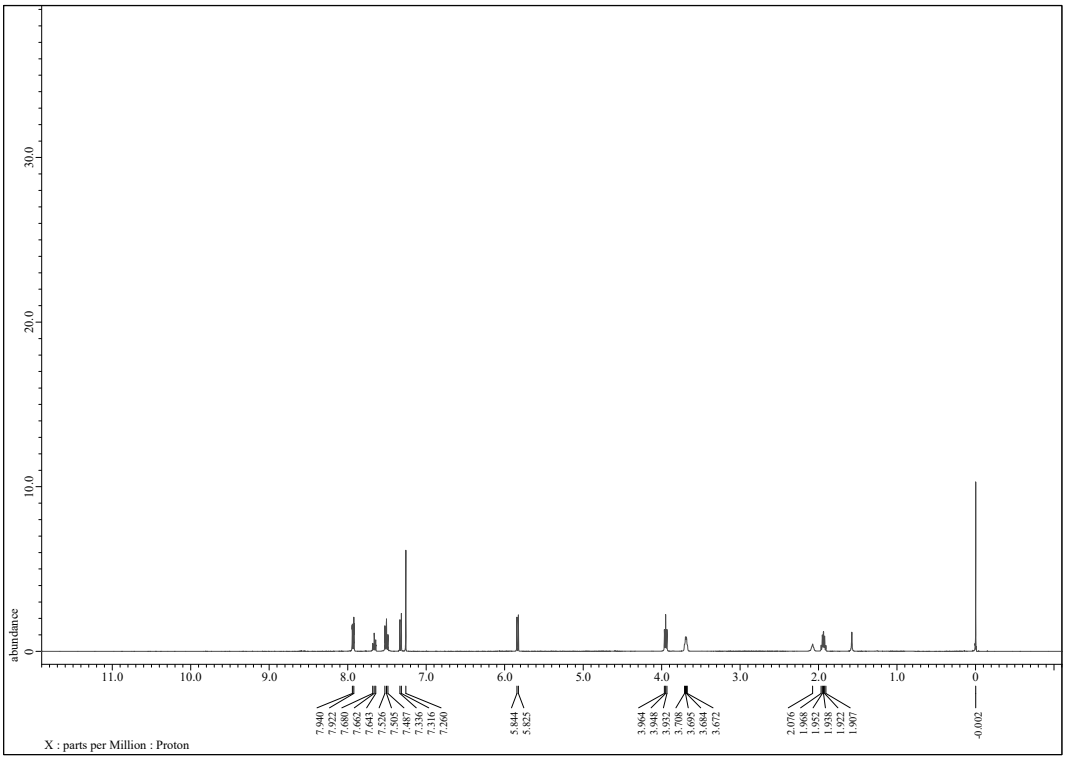


Fig. S43 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **1m**.

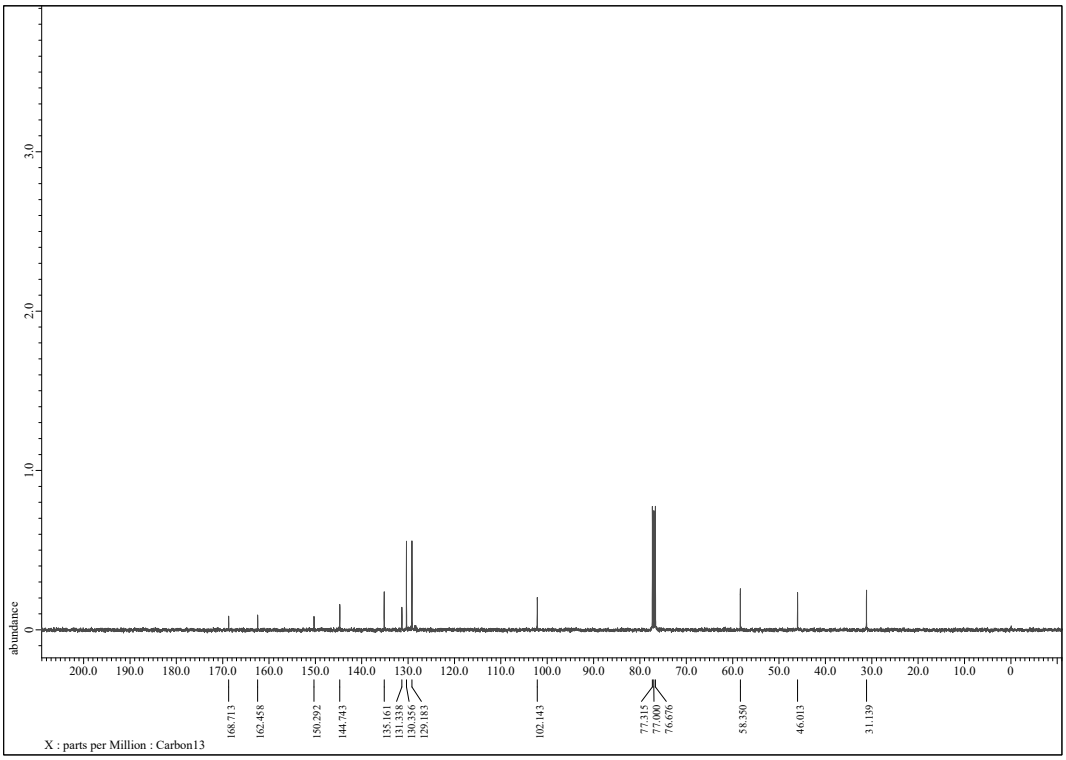


Fig. S44 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **1m**.

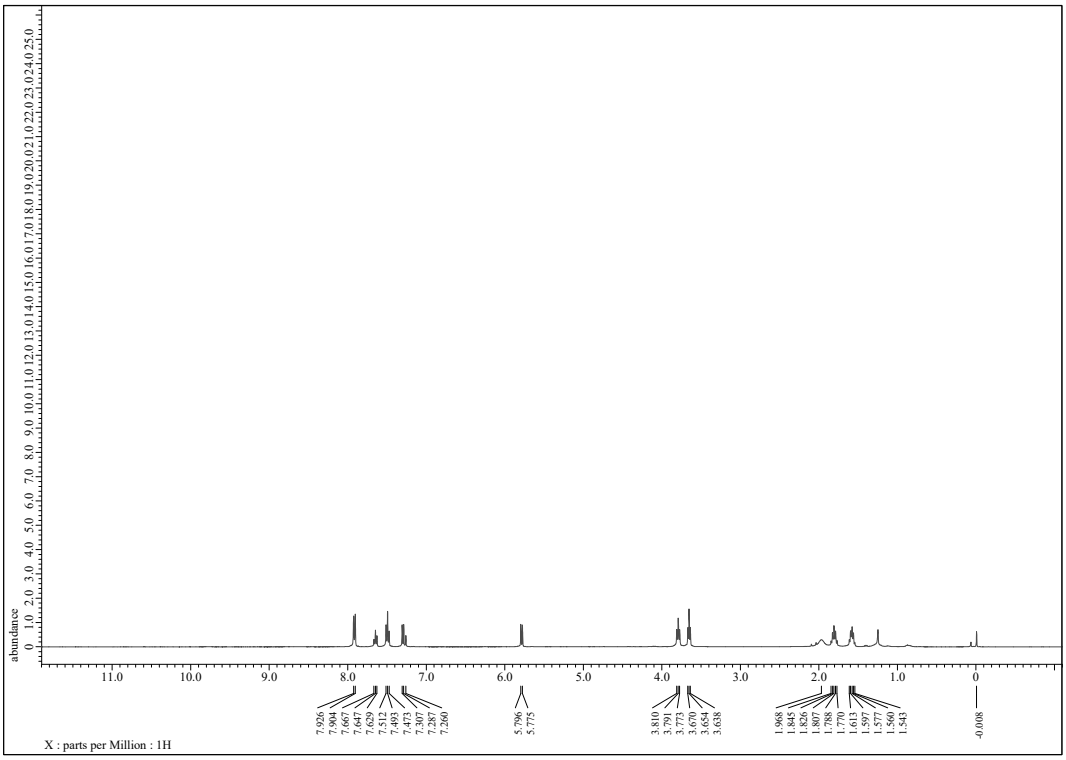


Fig. S45 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **1n**.

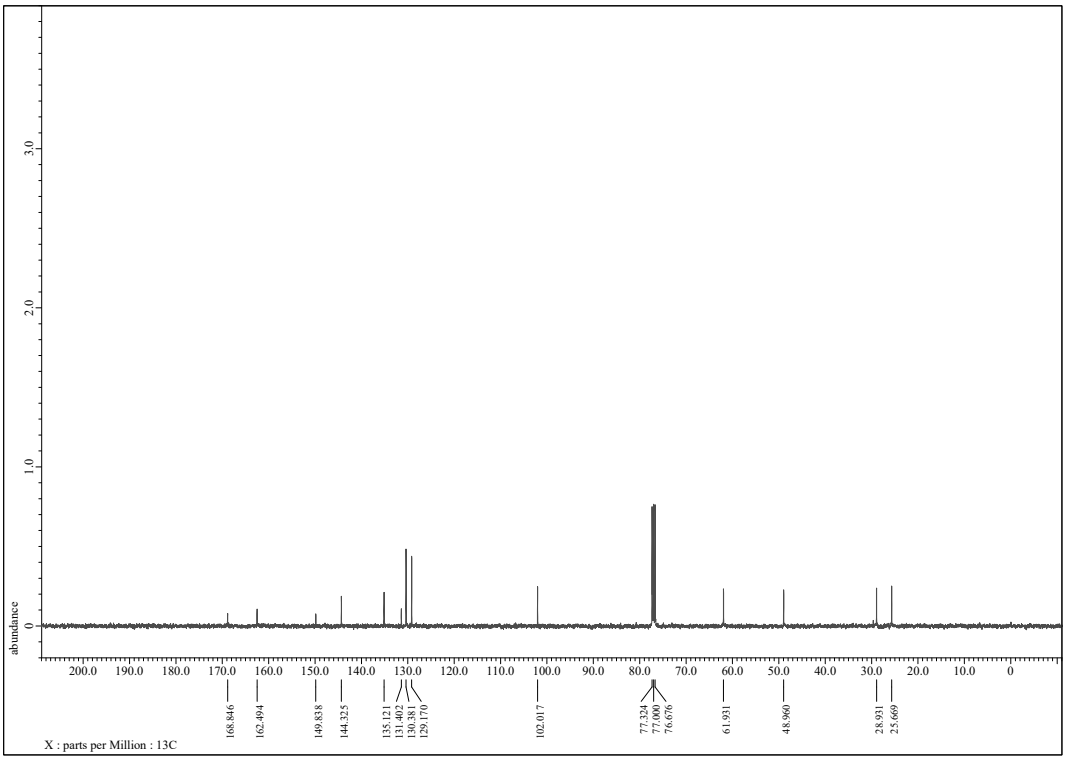


Fig. S46 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **1n**.

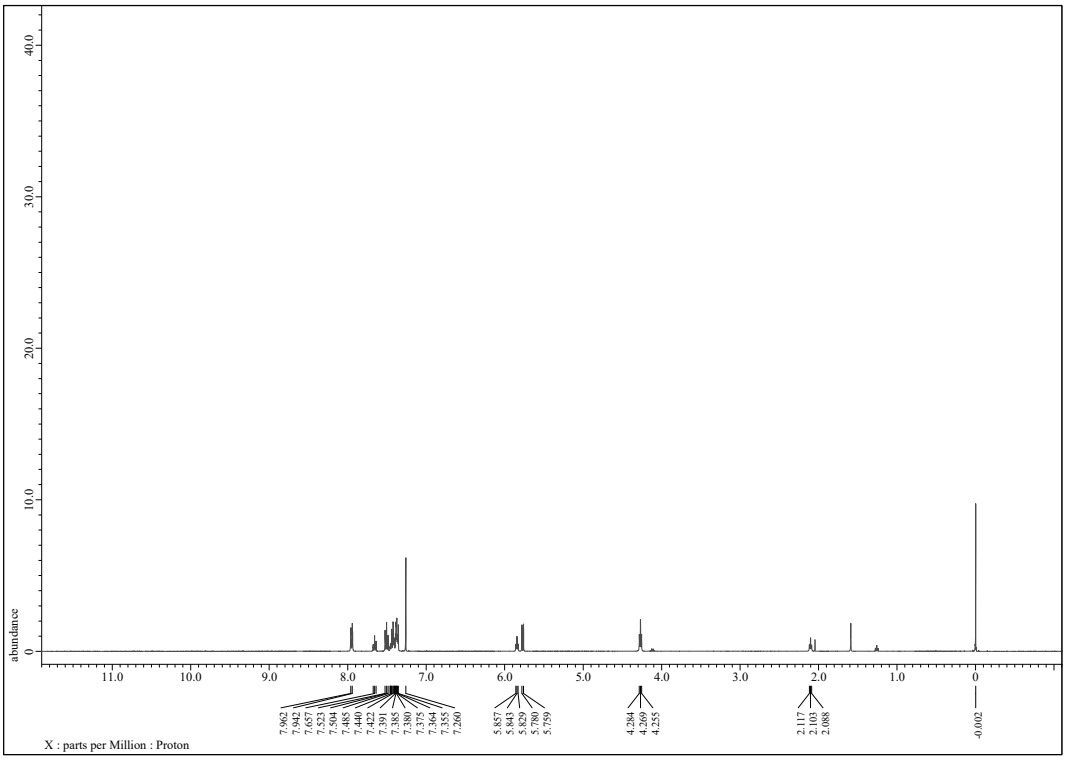


Fig. S47 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **1o**.

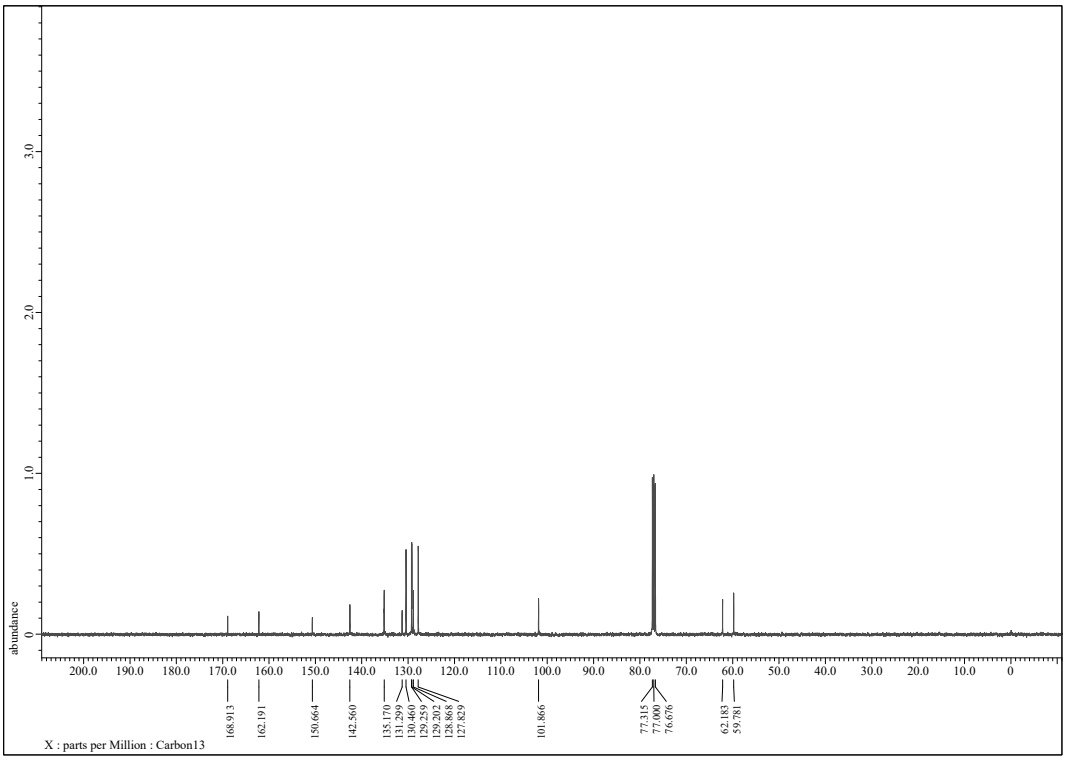


Fig. S48 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **1o**.

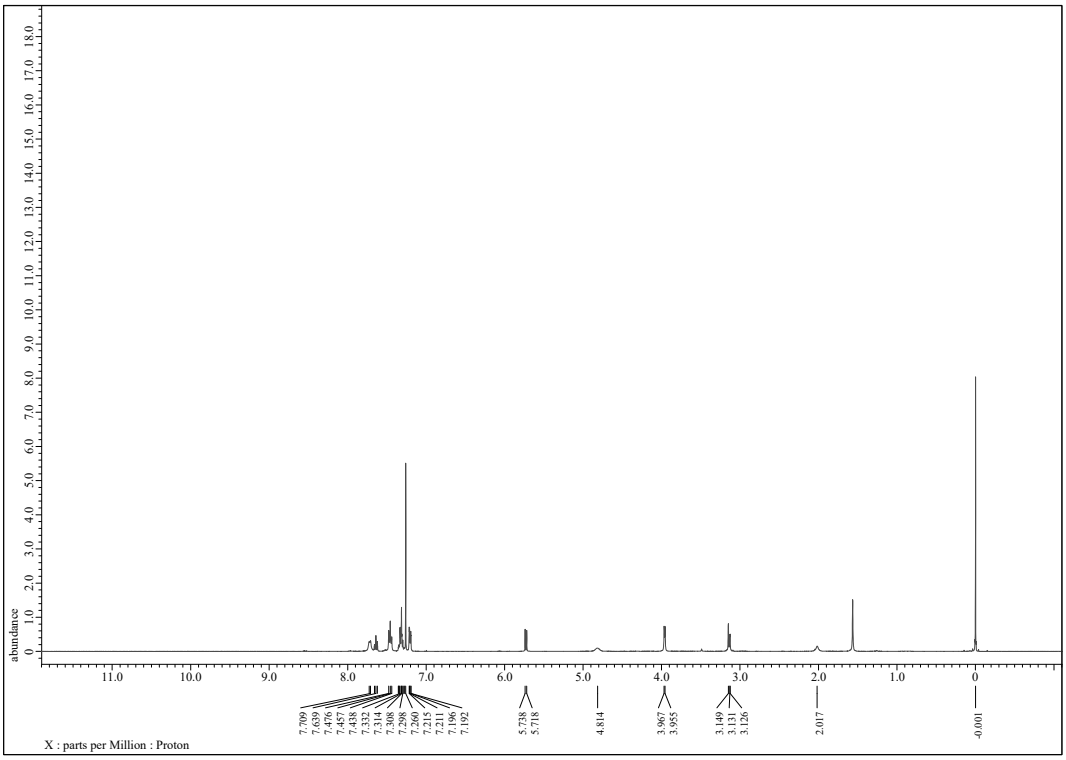


Fig. S49 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **1p**.

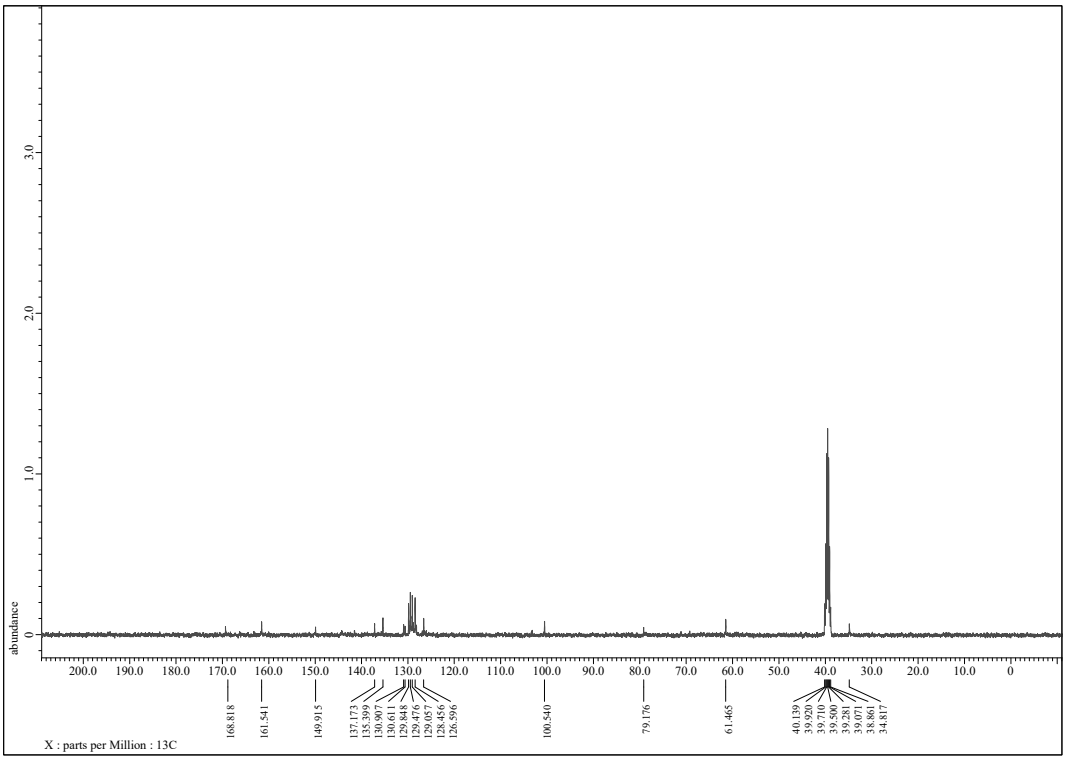


Fig. S50 ^{13}C NMR spectrum (100 MHz, DMSO-d_6) of **1p**.

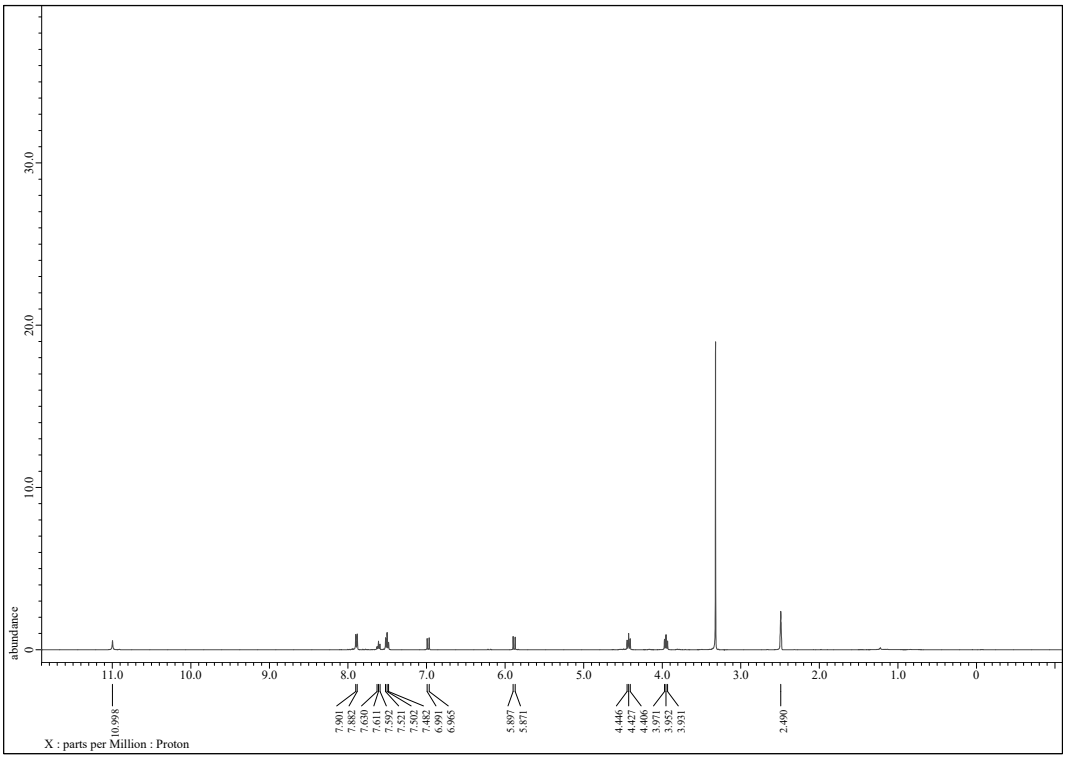


Fig. S51 ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of **2a**.

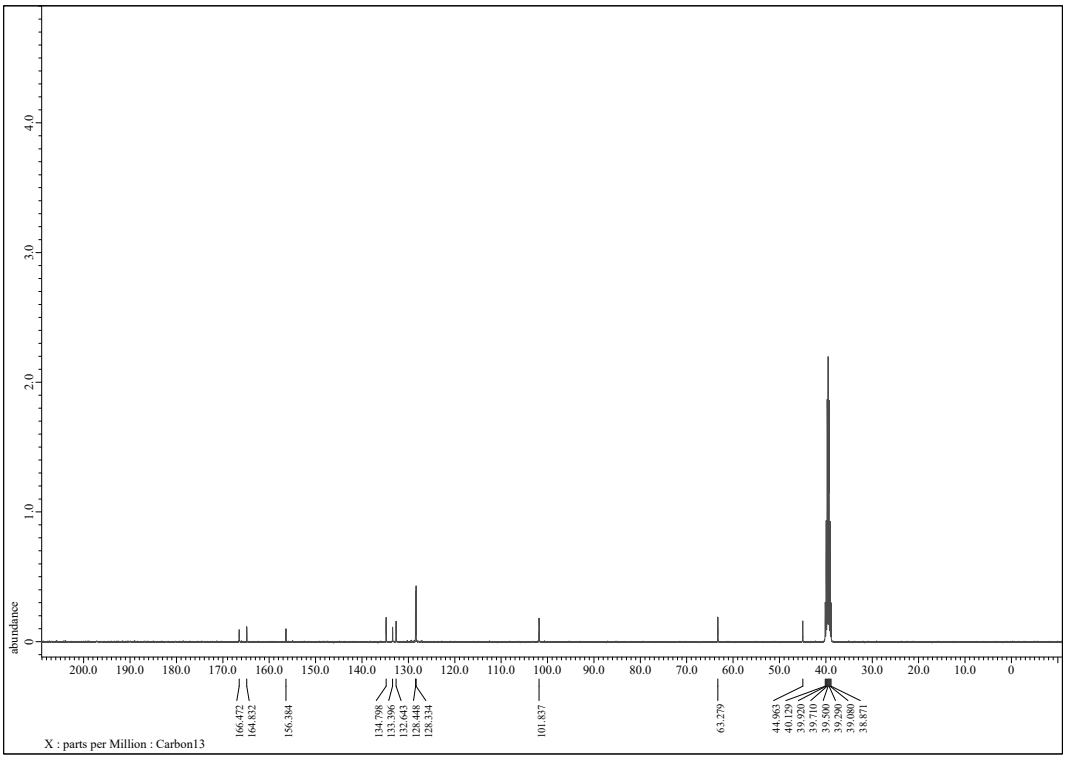


Fig. S52 ^{13}C NMR spectrum (100 MHz, DMSO-d_6) of **2a**.

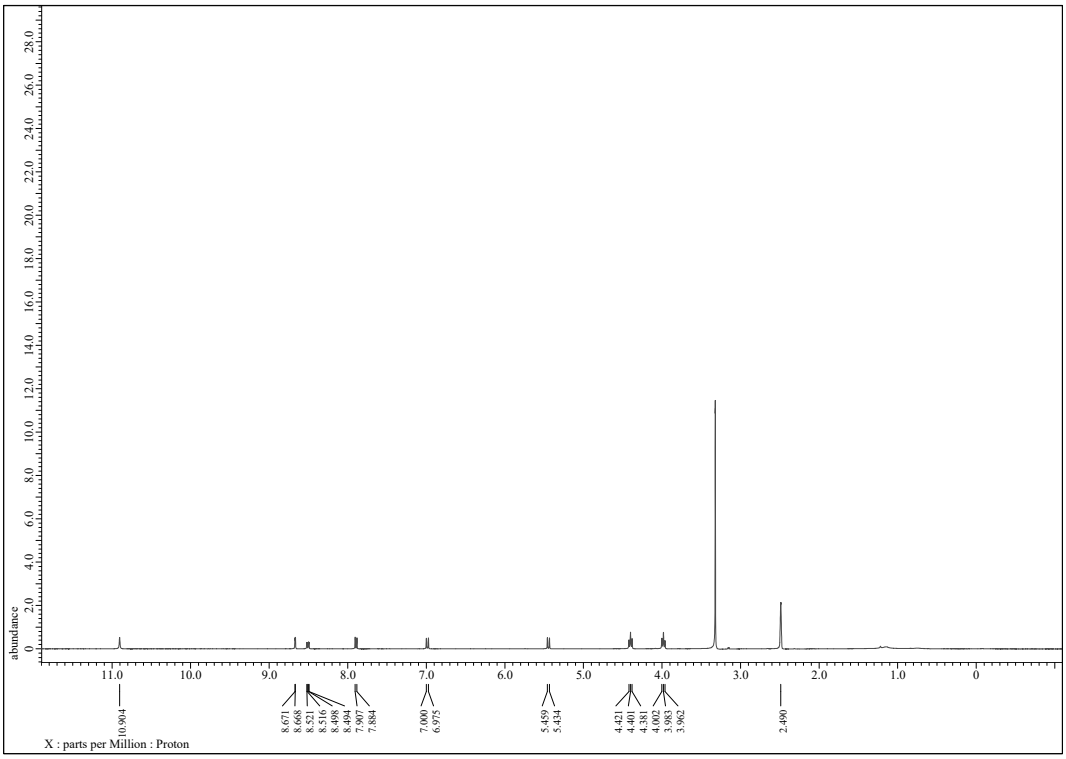


Fig. S53 ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of **2e**.

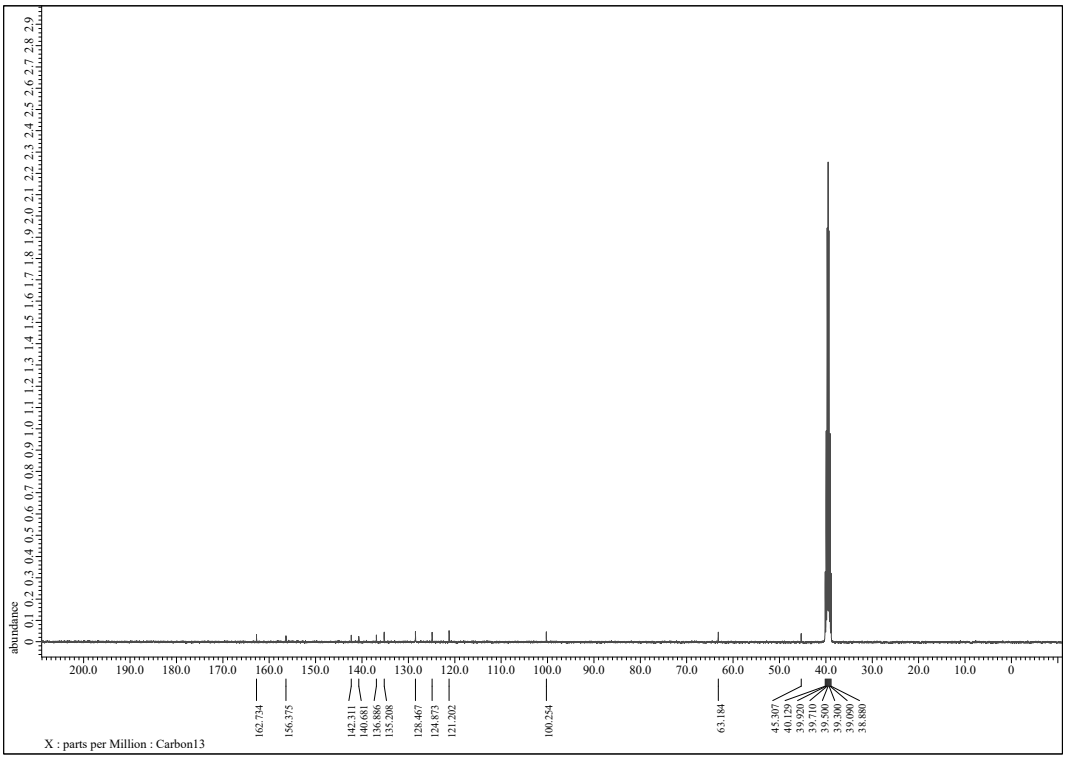


Fig. S54 ^{13}C NMR spectrum (100 MHz, DMSO-d_6) of **2e**.

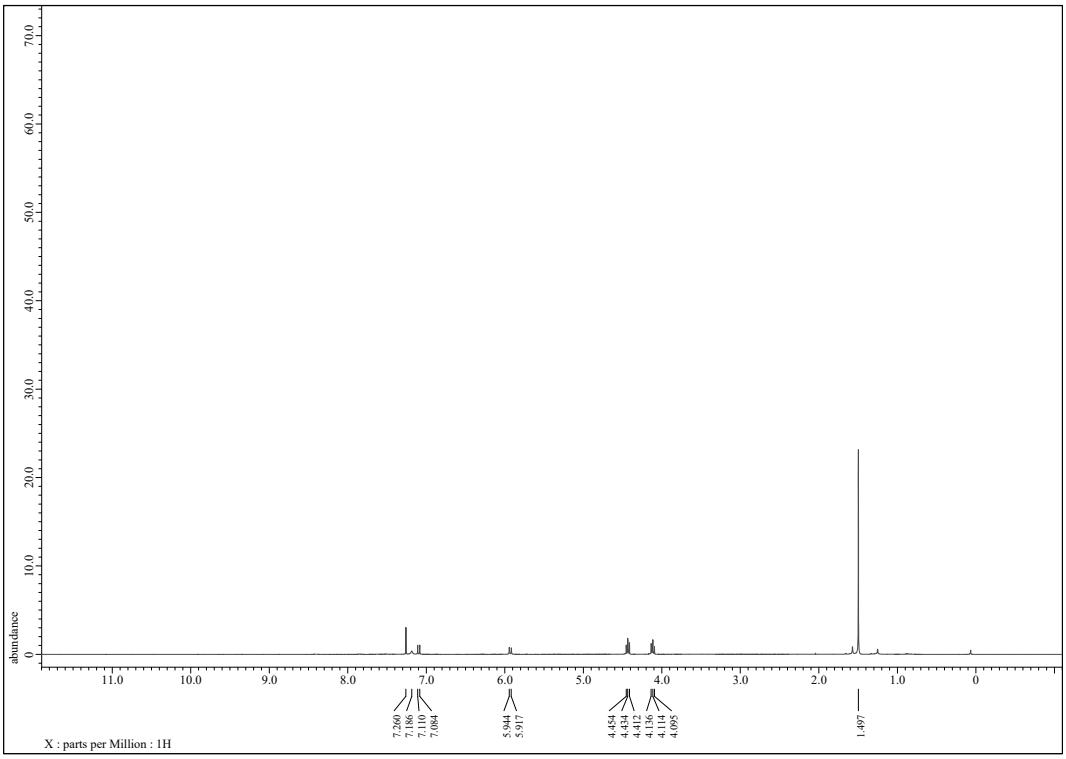


Fig. S55 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2f**.

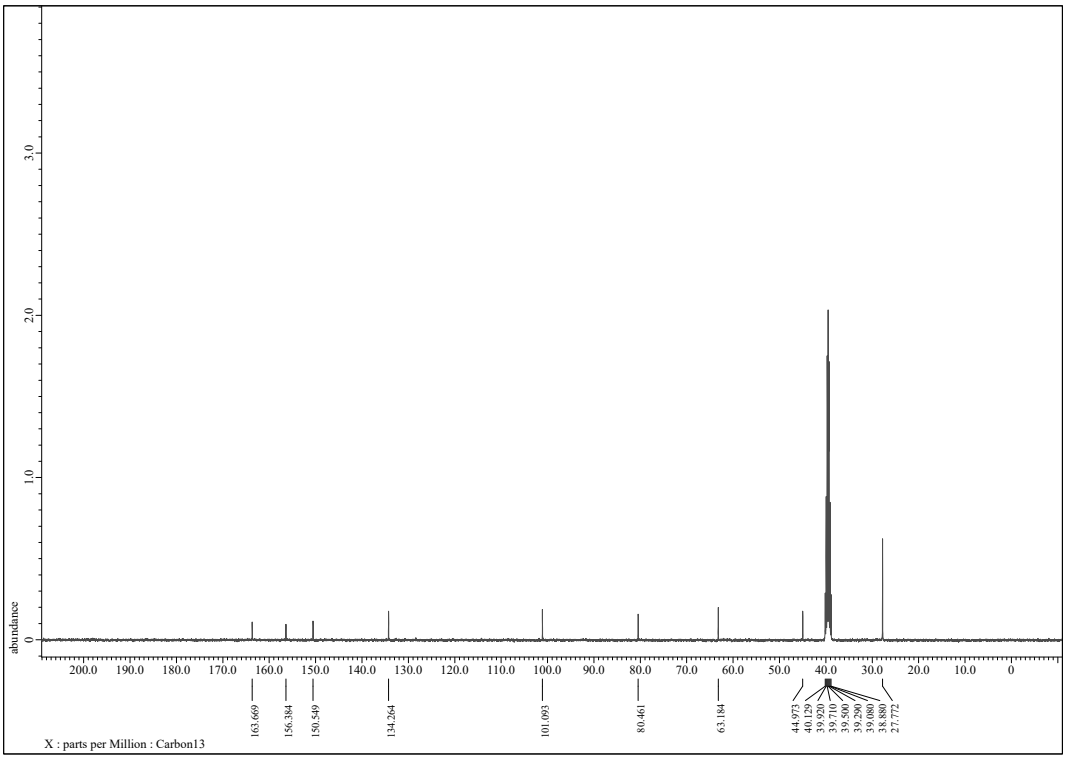


Fig. S56 ^{13}C NMR spectrum (100 MHz, DMSO-d_6) of **2f**.

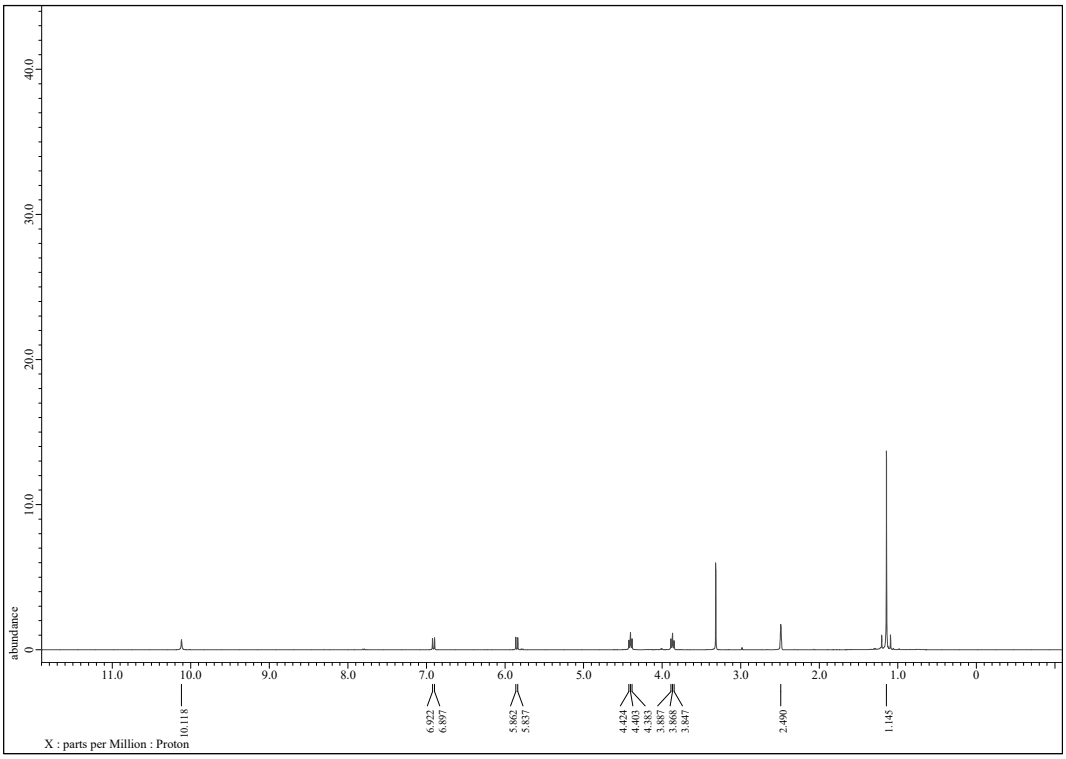


Fig. S57 ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of **2g**.

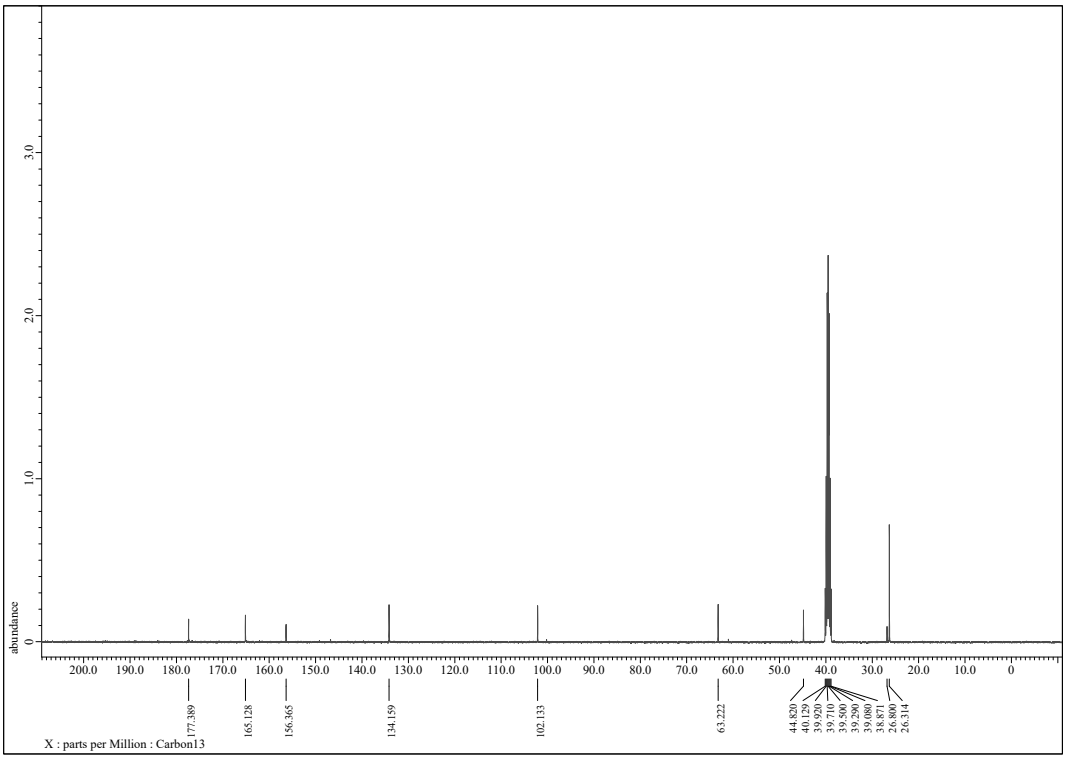


Fig. S58 ^{13}C NMR spectrum (100 MHz, DMSO-d_6) of **2g**.

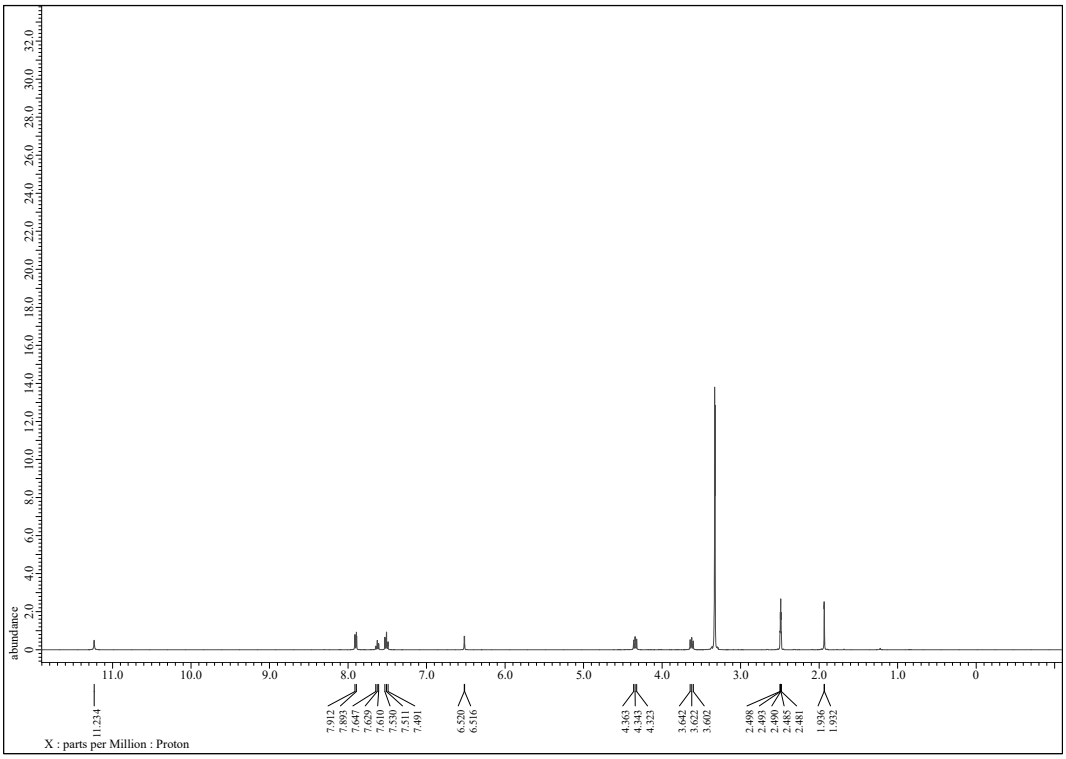


Fig. S59 ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of **2h**.

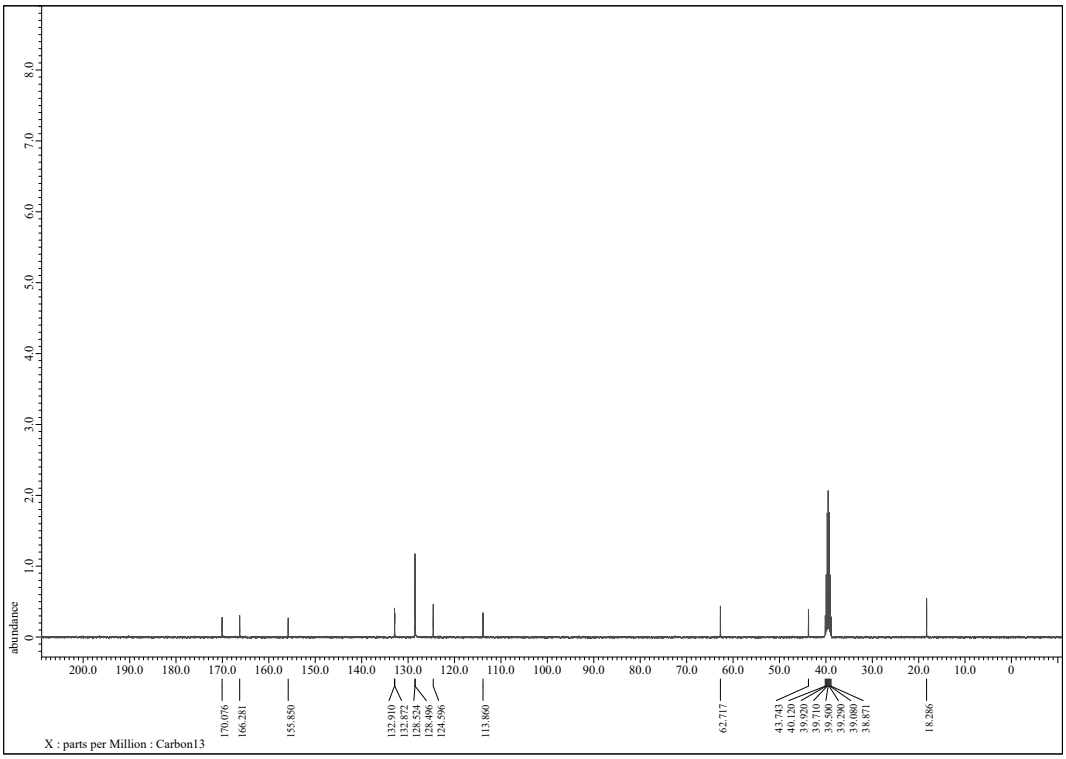


Fig. S60 ^{13}C NMR spectrum (100 MHz, DMSO-d_6) of **2h**.

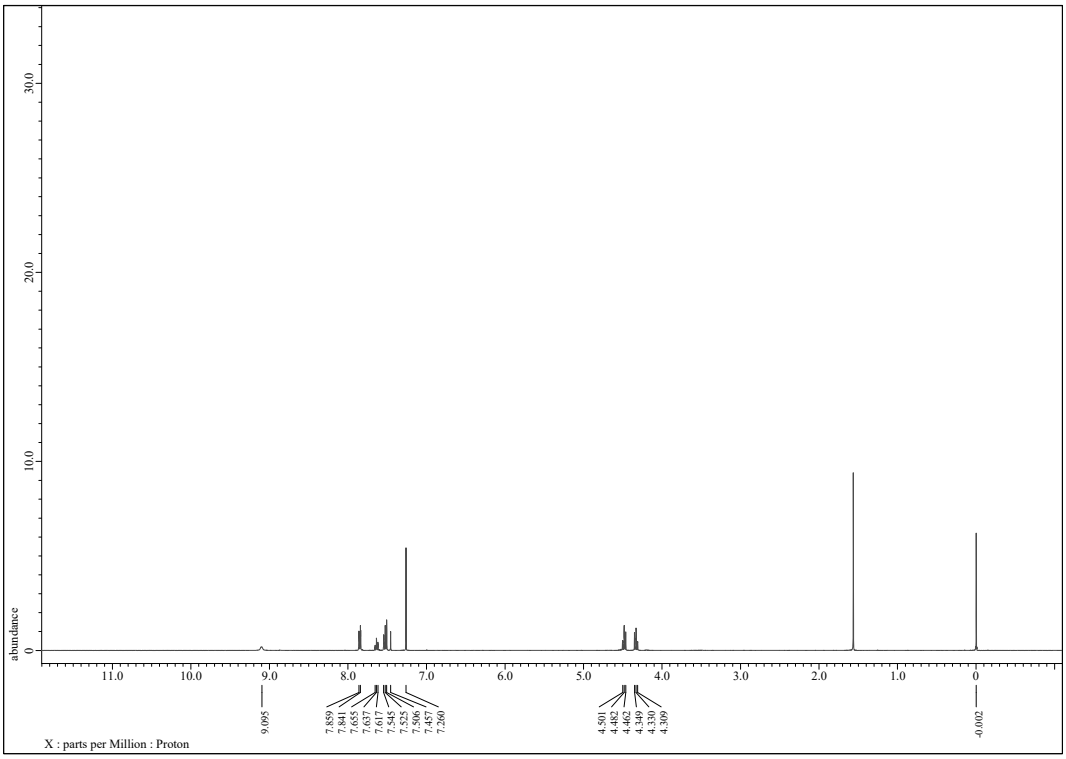


Fig. S61 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2i**.

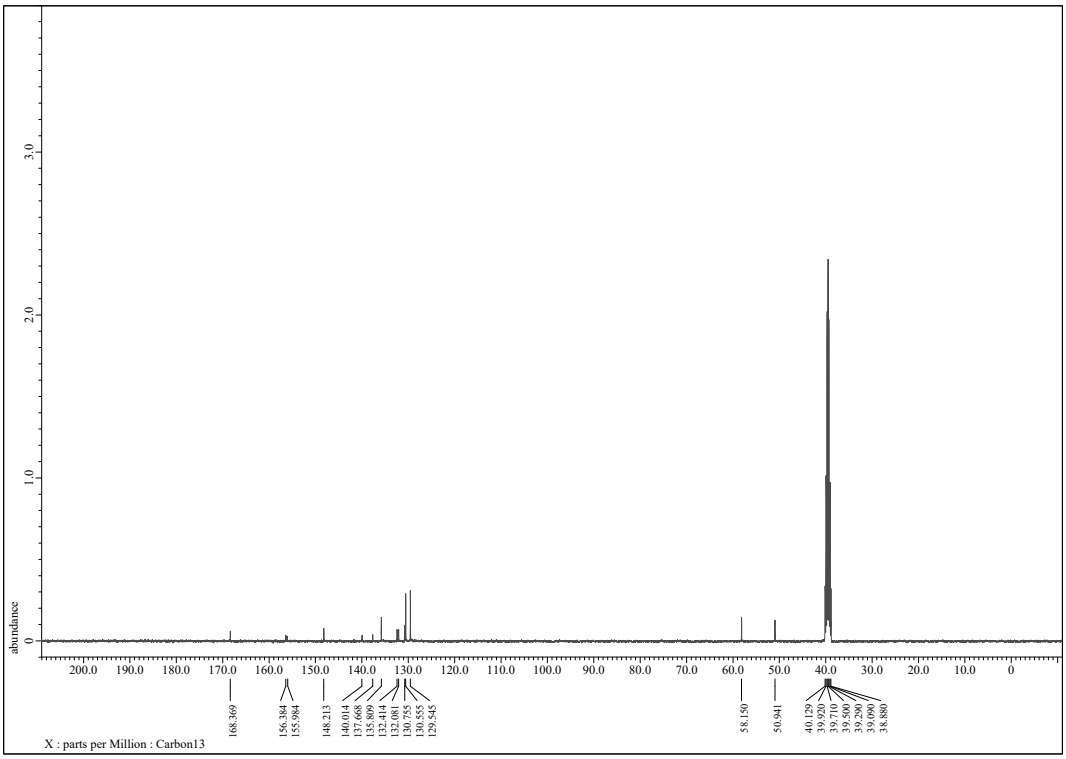


Fig. S62 ^{13}C NMR spectrum (100 MHz, DMSO-d_6) of **2i**.

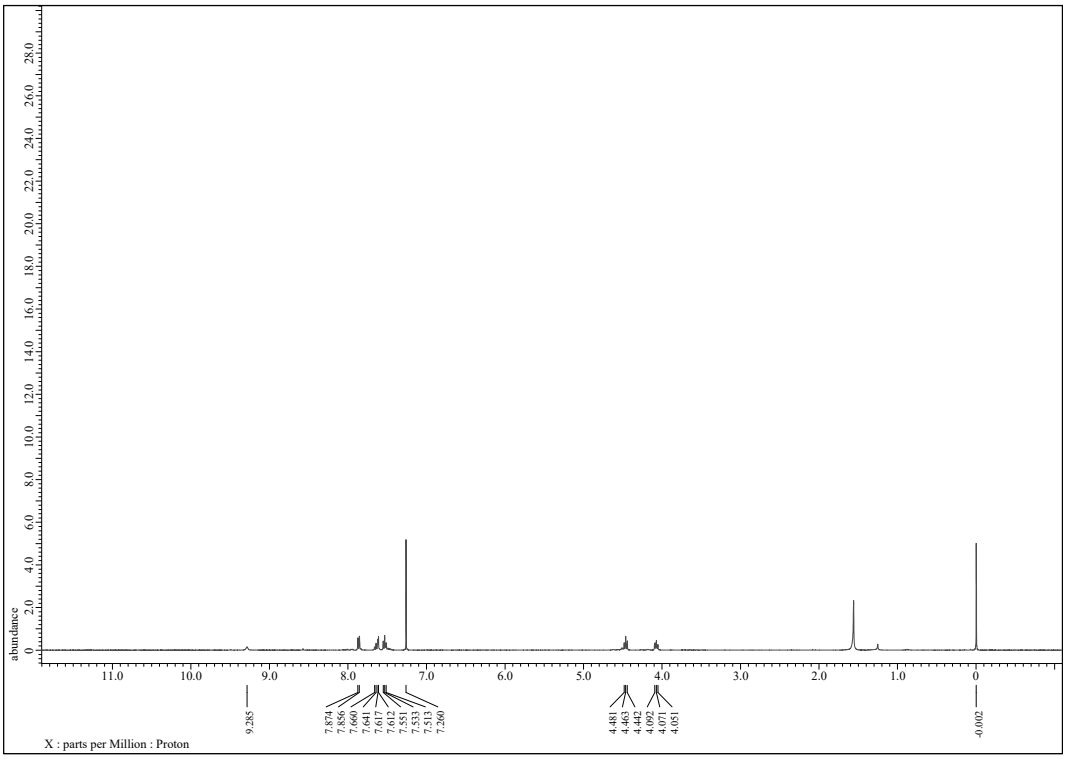


Fig. S63 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2j**.

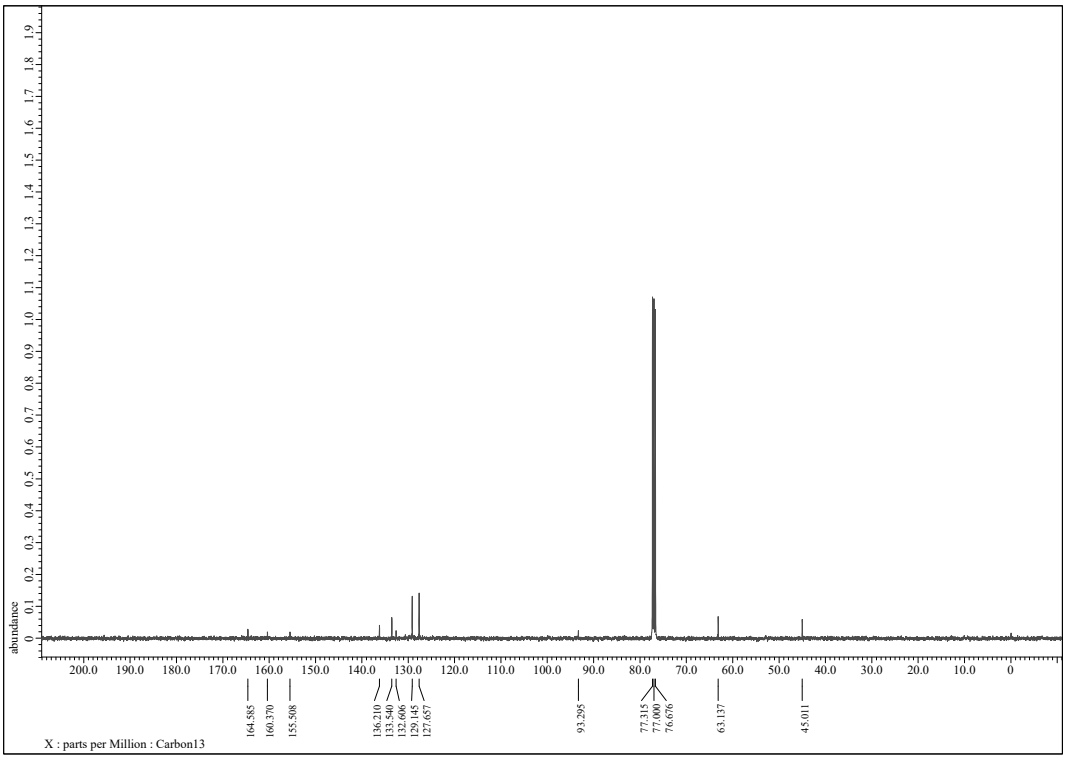


Fig. S64 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **2j**.

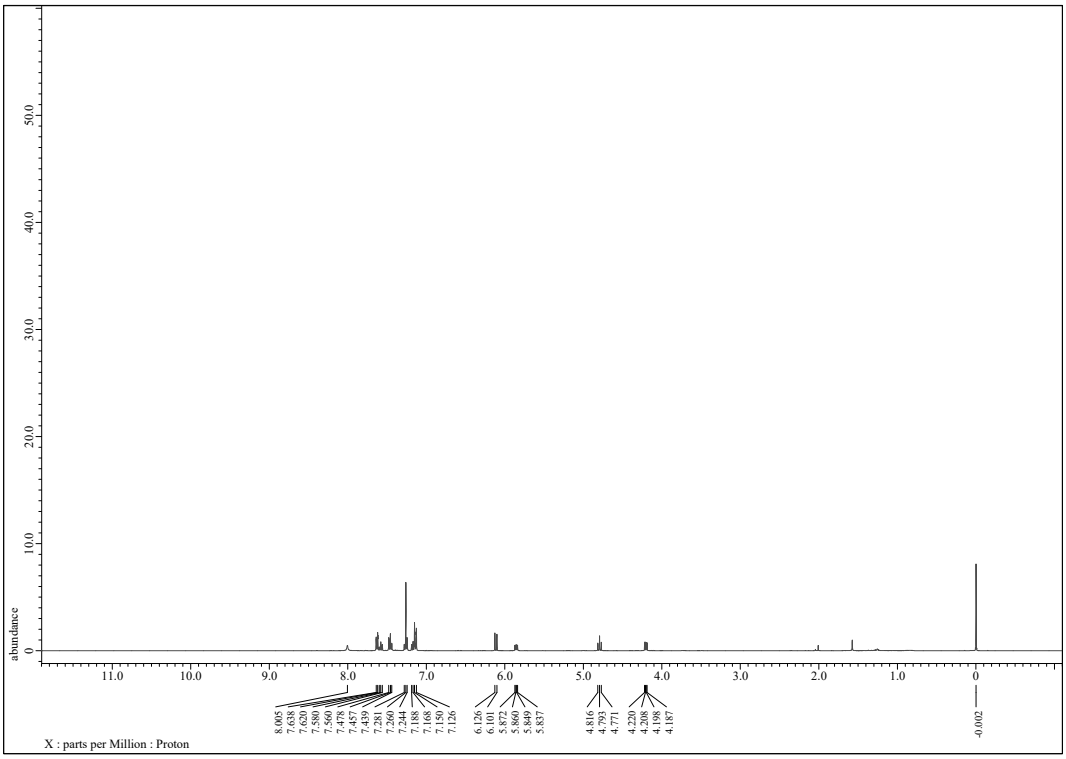


Fig. S65 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2o**.

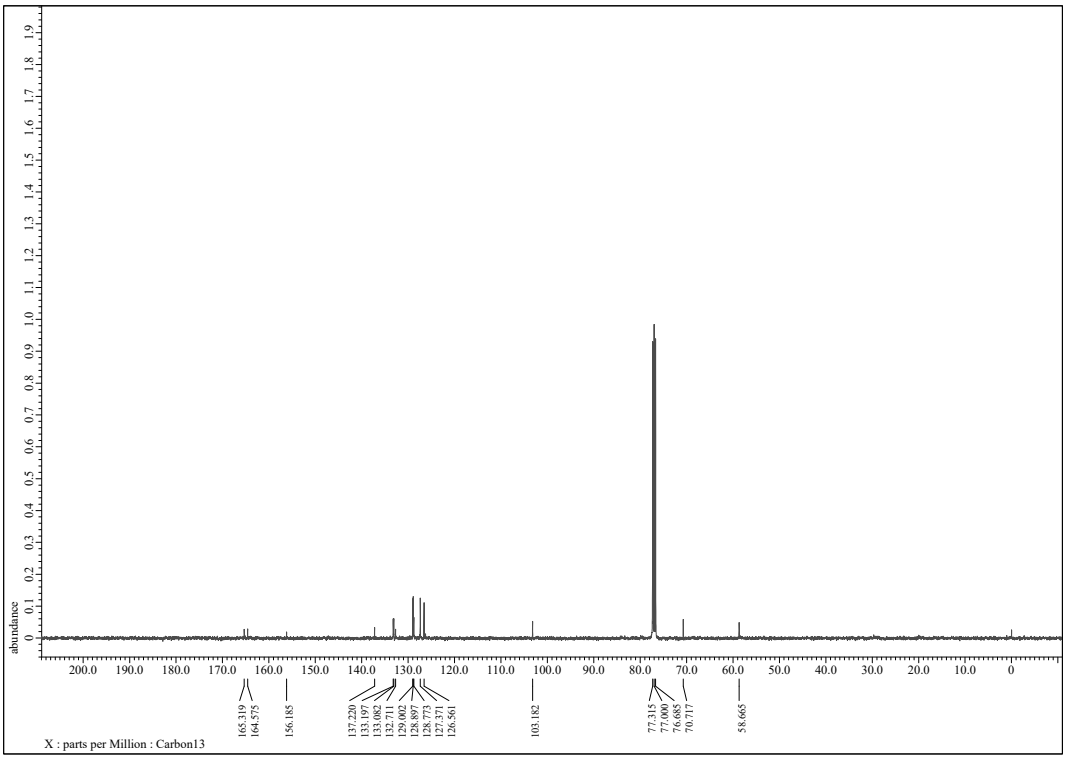


Fig. S66 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **2o**.

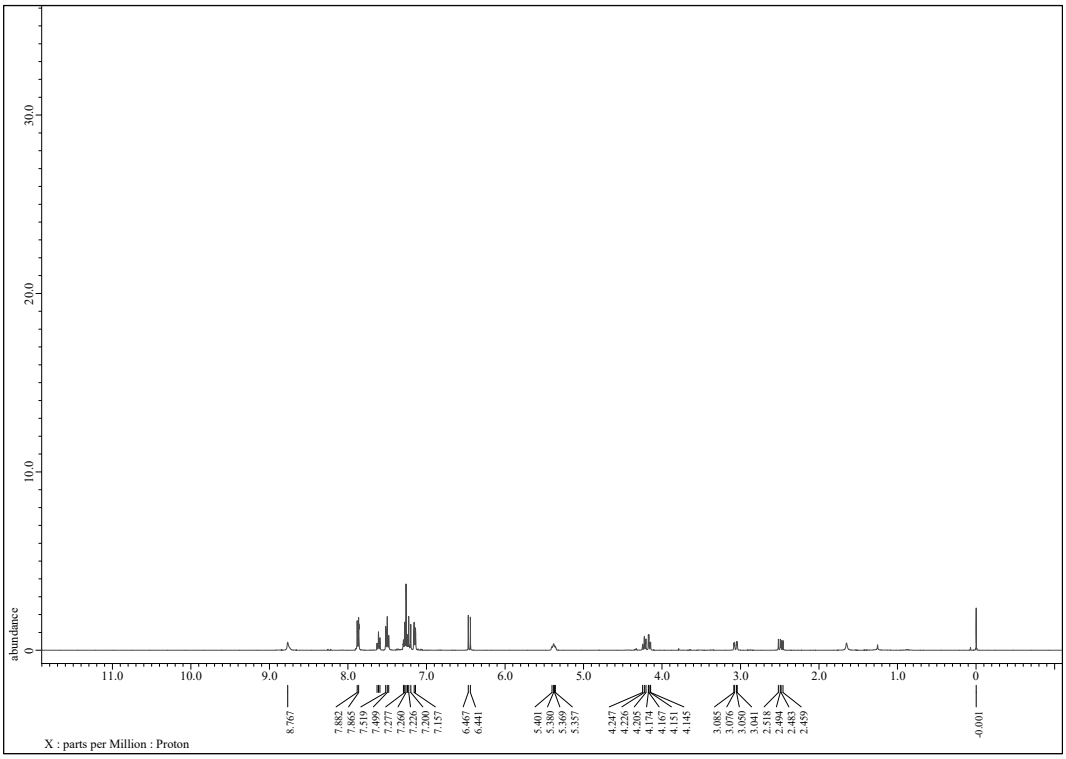


Fig. S67 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2p**.

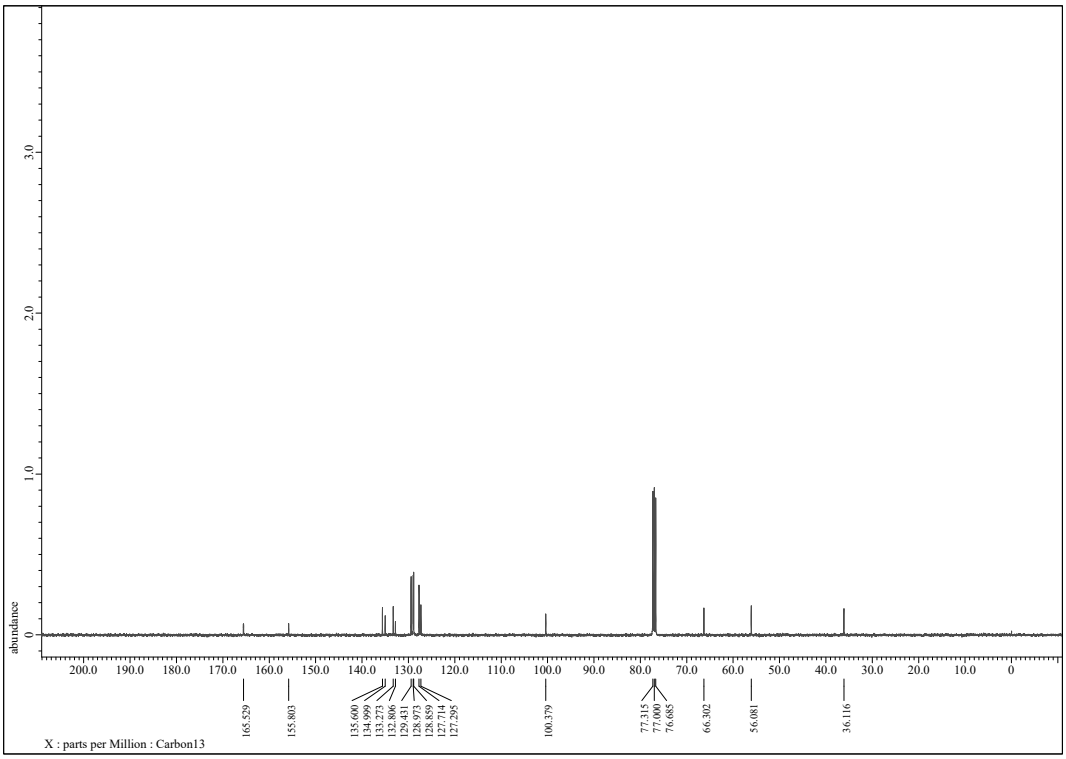


Fig. S68 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of **2p**.

References

1. C. Nguyen, G. F. Ruda, A. Schipani, G. Kasinathan, I. Leal, A. Musso-Buendia, M. Kaiser, R. Brun, L. M. Ruiz-Pérez, B.-L. Sahlberg, N. G. Johansson, D. González-Pacanowska, and I. H. Gilbert, *J. Med. Chem.*, 2006, **49**, 4183.
2. T. Coppola, M. Varra, G. Oliviero, A. Galeone, G. D'Isa, L. Mayol, E. Morelli, M.-R. Bucci, V. Vellecco, G. Cirino, and N. Borbone, *Bioorg. Med. Chem.*, 2008, **16**, 8244.
3. T. Kametani, K. Kigasawa, M. Hiiragi, K. Wakisaka, S. Haga, Y. Nagamatsu, H. Sugi, K. Fukawa, O. Irino, T. Yamamoto, N. Nishimura, and A. Taguchi, *J. Med. Chem.*, 1980, **23**, 1324.
4. F. Ferreira, A. Meyer, J.-J. Vasseur, and F. Morvan, *J. Org. Chem.*, 2005, **70**, 9198.
5. A. Ozerov, M. Novikov, A. Khandazhinskaya, and P. Solyev, *Heterocycles*, 2017, **94**, 912.
6. H. Masuda, N. Watanabe, H. Naruoka, S. Nagata, K. Takagaki, T. Wada, and J. Yano, *Bioorg. Med. Chem.*, 2010, **18**, 8277.
7. Y.-C. Chang, J. Herath, T. H.-H. Wang, and C. S. Chow, *Bioorg. Med. Chem.*, 2008, **16**, 2676.
8. C. Bolm, A. Seger, and M. Felder, *Tetrahedron Lett.*, 1993, **34**, 8079.
9. P. Lin and A. Ganesan, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 511.
10. *CrystalClear-SM Expert*: Rigaku Corporation, Tokyo, Japan, 2011.
11. *SHELXT*: G. M. Sheldrick, *Acta Cryst.*, 2008, A**64**, 112.
12. *SHELXL2014*: G. M. Sheldrick, *Acta Cryst.*, 2015, C**71**, 3.
13. (a) *Yadokari–XG*: K. Wakita, Software for crystal structure analyses, 2001. (b) *Yadokari–XG 2009*: C. Kabuto, S. Akine, T. Nemoto, and E. Kwon, Release of software for crystal structure analyses; *J. Cryst. Soc. Jpn.*, 2009, **51**, 218.