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Supporting Information

Autocatalyzed three-component cyclization of polyfluoroalkyl-3-oxo esters, methyl ketones and alkyl amines: novel approach to 3-alkylamino-5-hydroxy-5-polyfluoroalkylcyclohex-2-en-1-ones

Marina V. Goryaeva,[a] Svetlana O. Kushch,[a] Olga G. Khudina,[a] Yanina V. Burgart,[a] Yulia S. Kudyakova,[a] Marina A. Ezhikova,[a] Mikhail I. Kodess,[a] Pavel A. Slepukhin,[a] Lilya Sh. Sadretdinova,[a] Nataliya P. Evstigneeva,[b] Nataliya A. Gerasimova[b] and Victor I. Saloutin*[a]

[a]Postovsky Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences, S. Kovalevskoy St. 22, 620990 Ekaterinburg, Russia. E-mail: saloutin@ios.uran.ru

[b]Ural Research Institute for Dermatology, Venereology and Immunopathology, Scherbakova St. 8, 620076 Ekaterinburg, Russia.

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General Remarks

Melting points were measured in the open capillaries with a Stuart SMP3 melting-point apparatus. The IR spectra were recorded with a diffuse reflectance attachment (DRA) on a Perkin-Elmer Spectrum One FT-IR spectrometer and with the attenuated total reflectance (ATR) accessory on a Nicolet 6700 FT-IR spectrometer in the range 400 - 4000 cm^{-1}. The ^{1}H, ^{19}F and ^{13}C NMR spectra were registered on a Bruker DRX-400, an AVANCE 500 and an AVANCE NEO 600 spectrometers using Me_4Si (^{1}H) and C_6F_6 (^{19}F) as internal standards. The ^{13}C chemical shifts were calibrated using the solvent signal DMSO-d_6 (δ_C 39.5 ppm) or $CDCl_3$ (δ_C 77.0 ppm). A signal in ^{1}H NMR spectra at δ 3.30–3.33 ppm corresponds to water in DMSO-d_6.[1] The complete assignment of ^{1}H and ^{13}C signals was based on 2D ^{1}H-^{13}C HSQC and HMBC experiments for heterocycles **4aae**, **4aah**, **4aba**, **8**, **9b**; on 2D ^{1}H-^{13}C HSQC data for compound **4abi**. The high-resolution mass spectra (HRMS) were recorded on *a Bruker maXis impact mass spectrometer* (ESI). Optical rotation values were measured with a Perkin Elmer M 341 polarimeter. All optical rotations were obtained at room temperature. High-performance liquid chromatography (HPLC) for was performed on a Knauer SmartLine 1000 instrument (for compounds **6a**, **6c**, **6d**) and an Agilent 1100 instrument with a diode array detector (for compound **6b**). The column chromatography was performed on Merck silica gel 60 (0.063–0.200 mm).

Ethyl 4,4,5,5,5-pentafluoro-3-oxopentanoate (**1c**), ethyl 4,4,5,5-tetrafluoro-3-oxopentanoate (**1d**), ethyl 4,4,5,5,6,6,6-heptafluoro-3-oxohexanoate (**1e**) were obtained according to the literature procedure.[2] Ethyl 4,4,4-trifluoro-3-oxobutanoate (**1a**), ethyl 4,4-difluoro-3-oxobutanoate (**1b**), acetone (**2a**), 2-butanone (**2b**), 2-hexanone (**2c**), cyclohexylamine (**3a**), cyclopropylamine (**3b**), octylamine (**3c**), dodecylamine (**3d**), *N*,*N*′-dimethylethylenediamine (**3e**), benzylamine(**3f**), 4-fluorobenzylamine (**g**), 3,4-dimethoxybenzylamine (**h**), furfurylamine (**3i**), pyrrolidine (**3j**), piperidine (**3k**), morpholine (**3l**), L-proline (**3m**) are commercially available (purchased from Alfa Aesar, Acros Organics, and Sigma–Aldrich).

General procedures for the synthesis of compounds 4.

Method A: To a solution of the corresponding 3-oxo ester **1** (3 mmol) and methyl ketone **2** (3 mmol) in absolute ethanol (15 mL) was added the zeolite catalyst (molecular sieves 3Å (1000 mg)). Then amine **3** (3 mmol) was added and the reaction mixture was stirred for 2–3 days at room temperature (25 °C). After the reaction was complete (TLC monitoring), the reaction mixture was filtered to separate zeolite catalyst. After evaporation of the solvent from filtrate, the residue was washed with diethyl ether and crystallized from the proper solvent (acetonitrile, acetone, hexane, ethanol, benzene).

Method B: To a mixture of the corresponding aldol **6** (3 mmol) and zeolite catalyst (molecular sieves 3Å (1000 mg)) in absolute ethanol (15 mL) was added amine **3** (3 mmol). The reaction mixture was stirred for 2–3 days at room temperature. After the reaction was complete (TLC monitoring), the reaction mixture was filtered to separate zeolite catalyst. After evaporation of the solvent from filtrate, the residue was washed with diethyl ether and crystallized from the proper solvent (acetonitrile, acetone, hexane, ethanol, benzene).

General procedure for the synthesis of compounds 5.

A mixture of the corresponding aldol **6** (3 mmol) and amine **3** (3 mmol) in 95% ethanol (15 mL) was stirred for 2–3 days at room temperature(25 °C). After the reaction was complete (TLC monitoring), the solvent was evaporated and the residue was washed with hexane and crystallized from acetonitrile.

General procedure for the synthesis of compounds 6.

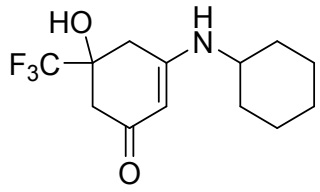
To a solution of 3-oxo ester **1** (10 mmol) and methyl ketone **2** (50 mmol) in toluene (50 mL) was added L-proline (1 mmol). The reaction mixture was kept under cooling (0 °C) for 3–5 days. After the reaction was complete (TLC monitoring), the solvent was evaporated and the residue was purified by column chromatography (eluent chloroform).

General procedures for the synthesis of compounds 9.

Method C: A mixture of the corresponding cyclohexenone **4** (1.5 mmol) and *p*-toluensulfonic acid monohydrate (1.5 mmol) in toluene (100 mL) was heated with azeotropic distillation system for removal of water for 3–4 days. After the reaction was complete (TLC monitoring), the hot solution was filtered and the filtrate was concentrated with a rotary evaporator. The residue was purified by column chromatography (eluent chloroform/diethyl ether = 1:1).

Method D: A mixture of cyclohexenone **4** (1.5 mmol) and 20% aq. sulfuric acid (30mL) was heated for 3–4 days. After the reaction was complete (TLC monitoring), the reaction mixture was cooled, poured into water (100 mL) and neutralized to pH 7 with sodium hydrogen carbonate. The mixture was extracted with chloroform (3 x 50 mL). The solvent was evaporated, and the residue was purified by column chromatography (eluent chloroform/diethyl ether = 1:1).

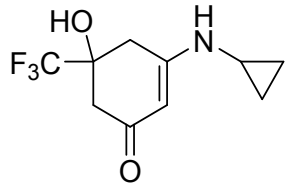
3-(Cyclohexylamino)-5-hydroxy-5-(trifluoromethyl)cyclohex-2-en-1-one (4aaa)



Isolated by crystallization (acetonitrile); Chemical Formula: $C_{13}H_{18}F_3NO_2$; White powder; M.P. 234–236°C; Yield (method A) 616 mg (74%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.10–1.23

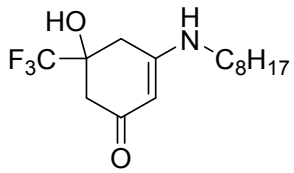
(m, 3 H, H cyclohexyl), 1.26–1.35 (m, 2 H, H cyclohexyl), 1.54–1.59 (m, 1 H, H cyclohexyl), 1.66–1.72 (m, 2 H, H cyclohexyl), 1.83–1.86 (m, 2 H, H cyclohexyl), 2.25 (dd, J = 16.3, 1.9 Hz, 1 H, H-6B), 2.46 (d, J = 16.3 Hz, 1 H, H-6A), 2.50 (d, J = 16.3 Hz, 1 H, H-4B), 2.68 (d, J = 16.3, 1 H, H-4A), 3.20 (m, 1 H, NCH), 4.93 (s, 1 H, H-2), 6.21 (s, 1 H, OH), 7.07 (d, J = 7.2 Hz, 1 H, NH) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 24.13, 24.17, 25.14, 31.42 and 31.71 (5*C cyclohexyl), 33.46 (C-4), 40.83 (C-6), 50.68 (NCH), 72.24 (q, J = 28.0 Hz, C-5), 93.33 (C-2), 125.79 (q, J = 285.7 Hz, CF_3), 158.09 (C-3), 188.94 (C-1) ppm. ^{19}F NMR (470 MHz, DMSO-d_6): δ = 80.36 (s, CF_3) ppm. DRA: v = 3274 (O–H, N–H), 3082, 2937, 2858 (C–H), 1581, 1525, 1455 (C=O, C=C), 1174–1102 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{19}F_3NO_2$ $[M + H]^+$ 278.1367; found 278.1362.

3-(Cyclopropylamino)-5-hydroxy-5-(trifluoromethyl)cyclohex-2-en-1-one (4aab)



Isolated by crystallization (acetonitrile); Chemical Formula: $C_{10}H_{12}F_3NO_2$; White powder; M.P. 217–219°C; Yield (method A) 367 mg (52%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.41–0.48 (m, 2 H, H cyclopropyl), 0.69–0.76 (m, 2 H, H cyclopropyl), 2.27 (dd, J = 16.2, 1.8 Hz, 1 H, H-6B), 2.35-2.41 (m, 2 H, H-4B and NCH), 2.47 (d, J = 16.2 Hz, 1 H, H-6A), 2.68 (d, J = 16.4 Hz, 1 H, H-4A), 5.20 (s, 1 H, H-2), 6.23 (s, 1 H, OH), 7.42 (br. s, 1 H, NH) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 6.08 and 6.34 (2*CH_2), 24.03 (NCH), 32.89 (C-4), 40.99 (C-6), 72.37 (q, J = 28.2 Hz, C-5), 95.20 (C-2), 125.78 (q, J = 285.7 Hz, CF_3), 160.41 (C-3), 189.31 (C-1) ppm. ^{19}F NMR (470 MHz, DMSO-d_6): δ = 80.32 (s, CF_3) ppm. DRA: v = 3318, 3227 (O–H, N–H), 3060, 2970, 2828 (C–H), 1602, 1573, 1506 (C=O, C=C), 1162–1100 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{13}F_3NO_2$ $[M + H]^+$ 236.0893; found 236.0895.

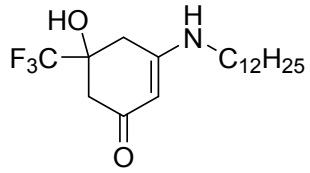
5-Hydroxy-3-(octylamino)-5-(trifluoromethyl)cyclohex-2-en-1-one (4aac)



Isolated by crystallization (acetonitrile); Chemical Formula: $C_{15}H_{24}F_3NO_2$, White powder; M.P: 150–151 °C, Yield (method A) 627 mg (68%); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.86 (t, J = 6.9 Hz, 3 H, CH_3), 1.23–1.34 (m, 10 H, 5 CH_2), 1.51 (qw, J = 7.2 Hz, 2 H, CH_2), 2.26 (dd, J = 16.2, 2.0 Hz, 1 H, H-6B), 2.46 (d, J = 16.3 Hz, 1 H, H-6A), 2.49 (d, J = 16.3 Hz, 1 H, H-4B, overlapped with DMSO signal), 2.70 (d, J = 16.3 Hz, 1 H, H-4A), 2.98 (td, J = 6.9, 5.4 Hz, 2 H,

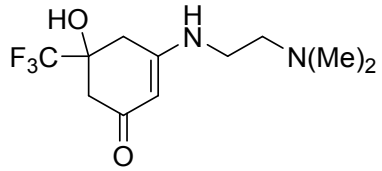
NCH_2), 4.87 (s, 1 H, H-2), 6.22 (s, 1 H, OH), 7.19 (t, J = 5.4 Hz, 1 H, NH) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 13.92 (CH_3), 22.07, 26.52, 27.65, 28.63, 28.70 and 31.22 (6*CH_2), 33.31 (C-4), 40.90 (C-6), 42.30 (NCH_2), 72.31 (q, J = 28.1 Hz, C-5), 93.30 (C-2), 125.83 (q, J = 286.0 Hz, CF_3), 159.37 (C-3), 188.99 (C-1) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = 80.36 (s, CF_3) ppm. DRA: v = 3227 (N–H, O–H), 3060, 2954, 2920, 2856 (C–H), 1594, 1552, 1520 (C=O, C=C), 1166–1103 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{25}F_3NO_2$ $[M + H]^+$ 308.1832; found 308.1830.

5-Hydroxy-3-(dodecylamino)-5-(trifluoromethyl)cyclohex-2-en-1-one (4aad)



Isolated by crystallization (acetonitrile); Chemical Formula: $C_{19}H_{32}F_3NO_2$; White powder; M.P: 135–137 °C; Yield (method A) 687 mg (63%). ^1H NMR (500 MHz, DMSO-d_6): δ = 0.86 (t, J = 6.9 Hz, 3 H, CH_3), 1.21–1.32 (m, 20 H, 10 CH_2), 1.50 (qw, J = 7.1 Hz, 2 H, CH_2), 2.26 (dd, J = 16.2, 2.0 Hz, 1 H, H-6B), 2.45 (d, J = 16.2 Hz, 1 H, H-6A), 2.49 (d, J = 16.2 Hz, 1 H, H-4B, overlapped with DMSO signal), 2.70 (d, J = 16.2 Hz, 1 H, H-4A), 2.97 (td, J = 6.9, 5.2 Hz, 2 H, NCH_2), 4.87 (s, 1 H, H-2), 6.22 (s, 1 H, OH), 7.18 (t, J = 5.2 Hz, 1 H, NH) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 13.92 (CH_3), 22.07, 26.51, 27.64, 28.69, 28.73, 28.98, 29.00, 29.03 and 31.27 (9*CH_2), 33.31 (C-4), 40.90 (C-6), 42.28 (NCH_2), 72.30 (q, J = 28.1 Hz, C-5), 93.30 (C-2), 125.82 (q, J = 285.7 Hz, CF_3), 159.34 (C-3), 188.97 (C-1) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = 80.37 (s, CF_3) ppm. DRA: v = 3341, 3240 (N–H, O–H), 3083, 2919, 2853 (C–H), 1593, 1559, 1514 (C=O, C=C), 1174–1100 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{33}F_3NO_2$ $[M + H]^+$ 364.2458; found 364.2458.

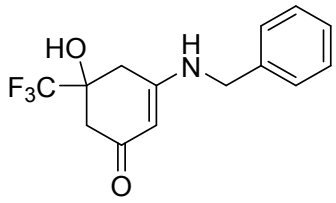
3-{[2-(Dimethylamino)ethyl]amino}-5-hydroxy-5-(trifluoromethyl)cyclohex-2-en-1-one (4aae)



Isolated by crystallization (acetonitrile); Chemical Formula: $C_{11}H_{17}F_3N_2O_2$; White powder; M.P: 186–188 °C; Yield (method A) 471 mg (59%). ^1H NMR (500 MHz, DMSO-d_6): δ = 2.16 (s, 6 H, $N(CH_3)_2$), 2.26 (dd, J = 16.2, 2.0 Hz, 1 H, H-6B), 2.40 (t, J = 6.5 Hz, 2 H, H-3'), 2.47 (d, J = 16.2 Hz, 1 H, H-6A), 2.53 (dd, J = 16.2, 2.0 Hz, 1 H, H-4B), 2.70 (d, J = 16.2 Hz, 1 H, H-4A), 3.08 (br. q, J = 6.0 Hz, 2 H, H-2'), 4.91 (s, 1 H, H-2), 6.23 (s, 1 H, OH), 7.10 (t, J = 5.3 Hz, 1 H, NH) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 33.32 (C-4), 40.43 (C-2'), 40.93 (C-6), 45.14

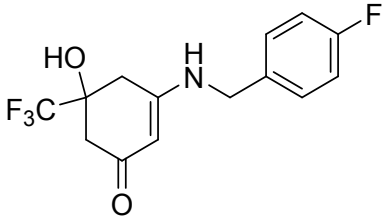
($N(CH_3)_2$), 56.67 (C-3'), 72.33 (q, J = 28.0 Hz, C-5), 93.47 (C-2), 125.82 (q, J = 285.9 Hz, CF_3), 159.37 (C-3), 189.09 (C-1) ppm. ^{19}F NMR (470 MHz, DMSO-d_6): δ = 80.38 (s, CF_3) ppm. DRA: v = 3253 (N–H, O–H), 3097, 2992, 2970, 2874, 2838 (C–H), 1609, 1555 (C=O, C=C), 1178–1099 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{18}F_3N_2O_2$ $[M + H]^+$ 267.1315; found 267.1316.

3-(Benzylamino)-5-hydroxy-5-(trifluoromethyl)cyclohex-2-en-1-one (4aaf)



Isolated by crystallization (acetonitrile); Chemical Formula: $C_{14}H_{14}F_3NO_2$; White powder; M.P: 194–195 °C; Yield (method A) 488 mg (57%). ^1H NMR (400 MHz, DMSO-d_6): δ = 2.25 (dd, J = 16.3, 1.9 Hz, 1 H, H-6B), 2.46 (d, J = 16.3 Hz, 1 H, H-6A), 2.57 (dd, J = 16.4, 1.9 Hz, 1 H, H-4B), 2.80 (d, J = 16.4 Hz, 1 H, H-4A), 4.27 (d, J = 5.8 Hz, 2 H, NCH_2), 4.90 (s, 1 H, H-2), 6.26 (s, 1 H, OH), 7.25–7.37 (m, 5 H, Ph), 7.74 (t, J = 5.8 Hz, 1 H, NH) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 33.33 (C-4), 40.90 (C-6), 45.79 (NCH_2), 72.34 (q, J = 28.1 Hz, C-5), 94.31 (C-2), 125.80 (q, J = 285.6 Hz, CF_3), 127.06 (C_p), 127.26 (C_o), 128.39 (C_m), 137.69 (C_i), 159.37 (C-3), 189.30 (C-1) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = 80.39 (s, CF_3) ppm. DRA: v = 3372, 3233 (N–H, O–H), 3076, 2919, 2869 (C–H), 1590, 1575, 1526 (C=O, C=C), 1099–1170 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{15}F_3NO_2$ $[M + H]^+$ 286.1049; found 286.1049.

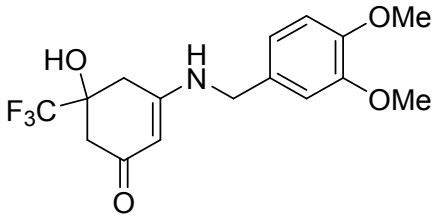
3-[(4-Fluorobenzyl)amino]-5-hydroxy-5-(trifluoromethyl)cyclohex-2-en-1-one (4aag)



Isolated by crystallization (ethanol); Chemical Formula: $C_{14}H_{13}F_4NO_2$; White powder; M.P: 182–184 °C; Yield (method A) 482 mg (53%); Yield (method B) 809 mg (89%). ^1H NMR (500 MHz, DMSO-d_6): δ = 2.26 (dd, J = 16.2, 1.9 Hz, 1 H, H-6B), 2.47 (d, J = 16.2 Hz, 1 H, H-6A), 2.56 (dd, J = 16.4, 1.9 Hz, 1 H, H-4B), 2.80 (d, J = 16.4 Hz, 1 H, H-4A), 4.25 (d, J = 5.8 Hz, 2 H, NCH_2), 4.90 (s, 1 H, H-2), 6.27 (s, 1 H, OH), 7.18 (t, J = 8.9 Hz, 2 H, Hm), 7.35 (dd, J = 8.5, 5.7 Hz, 2 H, Ho), 7.73 (t, J = 5.8 Hz, 1 H, NH) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 33.33 (C-4), 40.91 (C-6), 45.00 (NCH_2), 72.35 (q, J = 28.1 Hz, C-5), 94.37 (C-2), 115.14 (d, J = 21.7 Hz, C_m), 125.81 (q, J = 285.7 Hz, CF_3), 129.25 (d, J = 7.9 Hz, C_o), 133.90 (d, J = 2.5 Hz, C_i), 159.28 (C-3), 161.32 (d, J = 242.5 Hz, C_p), 189.39 (C-1) ppm. ^{19}F NMR (376 MHz, DMSO-d_6):

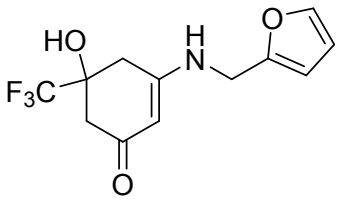
δ = 46.83 (tt, J = 8.9, 5.7 Hz, 1 F, CF), 80.37 (s, 3 F, CF_3) ppm. DRA: ν = 3321 (N–H, O–H), 3089, 2984, 2798 (C–H), 1598, 1574, 1532, 1512 (C=O, C=C), 1186–1104 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{14}F_4NO_2$ $[M + H]^+$ 304.0955; found 304.0958.

3-[(3,4-Dimethoxybenzyl)amino]-5-hydroxy-5-(trifluoromethyl)cyclohex-2-en-1-one (4aah)



Isolated by crystallization (hexane); Chemical Formula: $C_{16}H_{18}F_3NO_4$; White powder; M.P: 164–165 °C; Yield (method A) 425 mg (41%); Yield (method B) 870 mg (84%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.26 (d, J = 16.2 Hz, 1 H, H-6B), 2.46 (d, J = 16.2 Hz, 1 H, H-6A), 2.56 (d, J = 16.2 Hz, 1 H, H-4B), 2.78 (d, J = 16.2 Hz, 1 H, H-4A), 3.73 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 4.17 (d, J = 5.2 Hz, 2 H, NCH_2), 4.91 (s, 1 H, H-2), 6.25 (s, 1 H, OH), 6.83 (dd, J = 8.1 Hz, 1 H, H-6'), 6.90–6.92 (m, 2 H, H-2' and H-5'), 7.64 (t, J = 5.2 Hz, 1 H, NH) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 33.34 (C-4), 40.91 (C-6), 45.65 (NCH_2), 55.43 (OCH_3), 55.54 (OCH_3), 72.36 (q, J = 28.1 Hz, C-5), 94.29 (C-2), 111.31 (C-2'), 111.75 (C-5'), 119.46 (C-6'), 125.83 (q, J = 285.9 Hz, CF_3), 129.90 (C-1'), 147.95 (C-4'), 148.75 (C-3'), 159.28 (C-3), 189.25 (C-1) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = 80.43 (CF_3) ppm. DRA: ν = 3617, 3368, 3190 (N–H, O–H), 3016, 2970, 2840 (C-H), 1594, 1569, 1519 (C=O, C=C), 1174–1101 (C–F); HRMS (ESI): calcd. for $C_{16}H_{19}F_3NO_4$ $[M + H]^+$ 346.1261; found 346.1255.

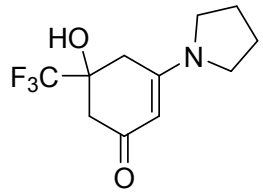
3-[(Furan-2-ylmethyl)amino]-5-hydroxy-5-(trifluoromethyl)cyclohex-2-en-1-one (4aai)



Isolated by crystallization (dichloromethane); Chemical Formula: $C_{12}H_{12}F_3NO_3$; White powder; M.P: 179–180 °C; Yield (method A) 421 mg (51%); Yield (method B) 718 mg (87%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.26 (dd, J = 16.2, 1.8 Hz, 1 H, H-6B), 2.47 (d, J = 16.2 Hz, 1 H, H-6A, overlapped with DMSO signal), 2.51 (d, J = 16.4 Hz, 1 H, H-4B, overlapped with DMSO signal), 2.73 (d, J = 16.4 Hz, 1 H, H-4A), 4.24 (d, J = 5.4 Hz, 2 H, NCH_2), 5.05 (s, 1 H, H-2), 6.25 (s, 1 H, OH), 6.37 (br. d, J = 3.2 Hz, 1 H, H-3'), 6.42 (dd, J = 3.2, 1.9 Hz, 1 H, H-4'), 7.60–7.63 (m, 2 H, H-5' and NH) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 33.22 (C-4), 39.5 (NCH_2, overlapped with DMSO signal), 40.93 (C-6), 72.34 (q, J = 28.1 Hz, C-5), 94.29 (C-2), 108.00 (C-3'), 110.48 (C4'), 125.79 (q, J = 285.5 Hz, CF_3), 142.57 (C-5'), 150.64 (C-2'), 159.11 (C-3),

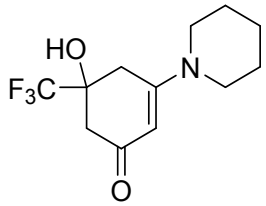
189.56 (C-1) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = 80.39 (s, CF_3) ppm. DRA: ν = 3390, 3224 (N–H, O–H), 3066, 2929, 2860 (C–H), 1639, 1616, 1524 (C=O, C=C), 1099–1165 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{13}F_3NO_3$ $[M + H]^+$ 276.0842; found 276.0845.

5-Hydroxy-3-(pyrrolidin-1-yl)-5-(trifluoromethyl)cyclohex-2-en-1-one (4aaj)



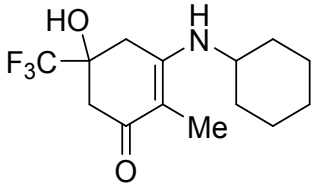
Isolated by crystallization (acetonitrile); Chemical Formula: $C_{11}H_{14}F_3NO_2$; Yelow powder; M.P. 238–240 °C; Yield (method A) 538 mg (72%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.81–1.96 (m, 4 H, CH_2), 2.25 (dd, J = 16.0, 1.8 Hz, 1 H, H-6A), 2.43 (d, J = 16.0 Hz, 1 H, H-6B), 2.67 (dd, J = 16.8, 1.8 Hz, 1 H, H-4A), 2.85 (d, J = 16.8 Hz, 1 H, H-4B), 3.09–3.24 (m, 2 H, NCH_2), 3.46 (m, 2 H, NCH_2), 4.85 (s, 1 H, H-2), 6.21 (s, 1 H, OH) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 24.28 and 24.87 (2*CH_2), 32.39 (C-4), 40.29 (C-6), 47.58 and 47.98 (NCH_2), 72.42 (q, J = 28.0 Hz, C-5), 95.78 (C-2), 125.81 (q, J = 285.7 Hz, CF_3), 157.79 (C-3), 188.10 (C-1) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = 80.39 (s, CF_3) ppm. DRA: ν = 3117, 3233 (N–H, O–H), 2935, 2904, 2873 (C–H), 1596, 1555 (C=O, C=C), 1188–1102 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{15}F_3NO_2$ $[M + H]^+$ 250.1045; found 250.1049.

5-Hydroxy-3-(piperidin-1-yl)-5-(trifluoromethyl)cyclohex-2-en-1-one (4aak)



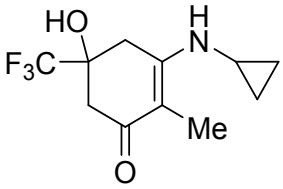
Isolated by crystallization (hexane); Chemical Formula: $C_{12}H_{16}F_3NO_2$; White powder; M.P. 187–189 °C, Yield (method A) 419 mg (53%). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 1.47–1.63 (m, 6 H, CH_2), 2.26 (dd, J = 16.0, 1.5 Hz, 1 H, H-6B), 2.46 (d, J = 16.0 Hz, 1 H, H-6A), 2.67 (dd, J = 16.5, 1.5 Hz, 1 H, H-4B), 2.72 (d, J = 16.5 Hz, 1 H, H-4A), 3.29–3.37 (m, 2 H, NCH_2, overlapped with H_2O signal), 5.16 (s, 1 H, H-2), 6.20 (s, 1 H, OH) ppm. ^{13}C NMR (151 MHz, DMSO-d_6): δ = 23.74 and 25.12 (3*CH_2), 31.68 (C-4), 40.02 (C-6), 47.26 (2*NCH_2), 72.47 (q, J = 28.0 Hz, C-5), 96.93 (C-2), 125.88 (q, J = 285.9 Hz, CF_3), 158.80 (C-3), 189.60 (C-1) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = 80.41 (s, CF_3) ppm. DRA: ν = 3141 (N–H, O–H), 2951, 2928, 2861 (C–H), 1580, 1550 (C=O, C=C), 1181–1103 (C–F); HRMS (ESI): calcd. for $C_{12}H_{17}F_3NO_2$ $[M + H]^+$ 264,1206; found 264.1208.

3-(Cyclohexylamino)-5-hydroxy-2-methyl-5-(trifluoromethyl)cyclohex-2-en-1-one (4aba)



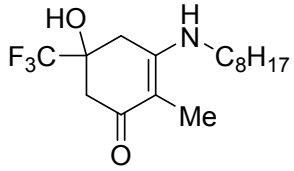
Isolated by crystallization (hexane); Chemical Formula: $C_{14}H_{20}F_3NO_2$; White powder; M.P: 223–225°C; Yield (method A) 551 mg (63%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.07 (m, 1 H, H cyclohexyl), 1.25–1.41 (m, 4 H, H cyclohexyl), 1.57–1.62 (m, 1 H, H cyclohexyl), 1.60 (s, 3 H, CH_3), 1.68–1.77 (m, 3 H, H cyclohexyl), 1.82–1.84 (m, 1 H, H cyclohexyl), 2.30 (dd, J = 16.1, 1.9 Hz, 1 H, H-6B, overlapped with DMSO signal), 2.48 (d, J= 16.1 Hz, 1 H, H-6A), 2.69 and 2.76 (AB system, J = 16.6 Hz, 2 H, H-4), 3.28-3.36 (m, 1 H, NCH, overlapped with H_2O signal), 5.94 (d, J = 9.0 Hz, 1 H, NH), 6.14 (s, 1 H, OH) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 8.23 (CH_3), 24.74, 24.78 and 24.96 (3*CH_2), 30.09 (C-4), 33.62 and 33.56 (2*CH_2), 40.14 (C-6), 51.55 (NCH), 71.63 (q, J = 27.8 Hz, C-5), 101.03 (C-2), 125.89 (q, J = 286.2 Hz, CF_3), 155.12 (C-3), 186.90 (C-1) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = 80.34 (s, CF3) ppm. DRA: v = 3203 (O–H, N–H), 2937, 2845 (C–H), 1554 (C=O, C=C), 1176–1084 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{21}F_3NO_2$ $[M + H]^+$ 292.1519; found 292.1517.

3-(Cyclopropylamino)-5-hydroxy-2-methyl-5-(trifluoromethyl)cyclohex-2-en-1-one (4abb)



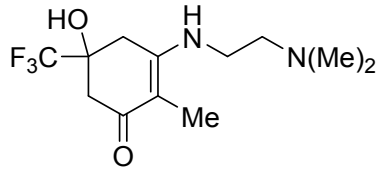
Isolated by crystallization (acetonitrile); Chemical Formula: $C_{11}H_{14}NO_2F_3$; White powder; M.P. 203–205 °C; Yield (method A) 359 mg (48%); Yield (method B) 725 mg (97%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.63 (br. s, 2 H, H cyclopropyl), 0.71 (br. s, 2 H, H cyclopropyl), 1.56 (s, 3 H, CH_3), 2.31 (d, J = 16.1 Hz, 1 H, H-6B), 2.49 (d, J = 16.1 Hz, 1 H, H-6A, overlapped with DMSO signal), 2.62 (br.s, 1 H, NCH), 2.86 (d, J = 16.6 Hz, 1 H, H-4B), 3.03 (d, J = 16.6 Hz, 1 H, H-4A), 6.17 (s, 1 H, OH), 6.66 (br. s, 1 H, NH) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 7.39 and 7.61 (2*CH_2), 8.08 (CH_3), 24.69 (NCH), 30.92 (C-4), 40.36 (C-6), 71.63 (q, J = 27.8 Hz, C-5), 101.77 (C-2), 125.91 (q, J = 285.6 Hz, CF_3), 157.72 (C-3), 187.38 (C-1) ppm. ^{19}F NMR (470 MHz, DMSO-d_6): δ = 80.21 (s, CF_3) ppm. DRA: v = 3325, 3306, 3105 (O–H, N–H), 2962, 2915 (C–H), 1585, 1538 (C=O, C=C), 1169–1075 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{15}F_3NO_2$ $[M + H]^+$ 250.1049; found 250.1050.

5-Hydroxy-2-methyl-3-(octylamino)-5-(trifluoromethyl)cyclohex-2-en-1-one (4abc)



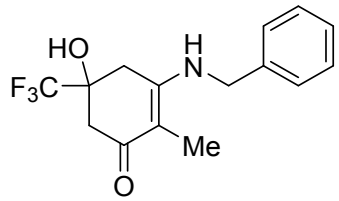
Isolated by crystallization (acetonitrile); Chemical Formula: $C_{16}H_{26}F_3NO_2$; White powder; M.P: 144–146 °C; Yield (method A) 569 mg (59%); Yield (method B) 877 mg (91%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.86 (t, J = 7.0 Hz, 3 H, CH_3), 1.23–1.30 (m, 10 H, 5 CH_2), 1.50 (qw, J = 7.2 Hz, 2 H, CH_2), 1.59 (s, 3 H, C^2-CH_3), 2.30 (dd, J = 16.0, 1.6 Hz, 1 H, H-6B), 2.47 (d, J = 16.0 Hz, 1 H, H-6A), 2.68 and 2.72 (AB system, J = 16.8 Hz, 2 H, H-4), 3.16 (td, J = 7.2, 6.2 Hz, 2 H, NCH_2), 6.14 (s, 1 H, OH), 6.42 (t, J = 6.2 Hz, 1 H, NH) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 8.11 (C^2-$\underline{C}H_3$), 13.92 (CH_3), 22.07, 26.16, 28.61 and 28.67 (4*CH_2), 29.95 (C-4), 30.30 and 31.23 (2*CH_2), 40.20 (C-6), 42.61 (NCH_2), 71.62 (q, J = 27.9 Hz, C-5), 101.02 (C-2), 125.90 (q, J = 285.9 Hz, CF_3), 156.36 (C-3), 186.69 (C-1) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = 80.23 (s, CF_3) ppm. DRA: ν = 3333 (N–H, O–H), 3064, 2927, 2851 (C–H), 1608, 1528 (C=O, C=C), 1181–1114 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{27}F_3NO_2$ $[M + H]^+$ 322.1988; found 322.1985.

3-{[2-(Dimethylamino)ethyl]amino}-5-hydroxy-2-methyl-5-(trifluoromethyl)-cyclohex-2-en-1-one (4abe)



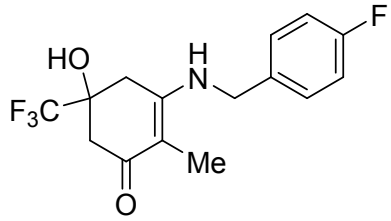
Isolated by crystallization (acetonitrile); Chemical Formula: $C_{12}H_{19}F_3N_2O_2$, White powder; M.P: 172–174 °C; Yield (method A) 538 mg (64%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.58 (s, 3 H, C^2-CH_3), 2.20 (s, 6 H, $N(CH_3)_2$), 2.31 (dd, J = 16.0, 1.8 Hz, 1 H, H-6B), 2.42 (br. t, J = 6.4 Hz, 2 H, H-3'), 2.48 (d, J = 16.0 Hz, 1 H, H-6A, overlapped with DMSO signal), 2.69 (d, J = 16.7 Hz, 1 H, H-4B), 2.79 (d, J = 16.7 Hz, 1 H, H-4A), 3.29 (q, J = 6.3 Hz, 2 H, H-2'), 6.17 (s, 1 H, OH), 6.22 (br. t, J = 6.2 Hz, 1 H, NH) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 7.83 (C^2-$\underline{C}H_3$), 30.07 (C-4), 40.21 (C-6), 40.31 (C-2'), 45.10 ($N(CH_3)_2$), 58.79 (C-3'), 71.56 (q, J = 27.9 Hz, C-5), 101.17 (C-2), 125.88 (q, J = 285.4 Hz, CF_3), 156.16 (C-3), 186.80 (C-1) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = 80.21 (s, CF_3) ppm. DRA: ν = 3321, 3219 (N–H, O–H), 2970, 2962, 2879, 2845 (C–H), 1581, 1551 (C=O, C=C), 1182–1079 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{20}F_3N_2O_2$ $[M + H]^+$ 281.1471; found 281.1471.

3-(Benzylamino)-5-hydroxy-2-methyl-5-(trifluoromethyl)cyclohex-2-en-1-one (4abf)



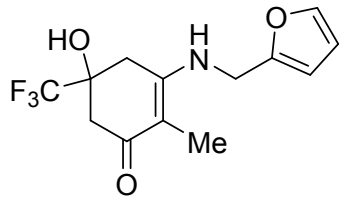
Isolated by crystallization (acetonitrile); Chemical Formula: $C_{15}H_{16}F_3NO_2$; White powder; M.P: 197–199 °C; Yield (method A) 350 mg (39%); Yield (method B) 790 mg (88%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.68 (s, 3 H, CH_3), 2.32 (dd, J = 16.1, 1.6 Hz, 1 H, H-6B), 2.48 (d, J = 16.1 Hz, 1 H, H-6A, overlapped with DMSO signal), 2.54 (d, J = 16.9 Hz, 1 H, H-4B), 2.66 (d, J = 16.9 Hz, 1 H, H-4A), 4.46 (d, J = 6.5 Hz, 2 H, NCH_2), 6.16 (s, 1 H, OH), 7.09 (t, J = 6.5 Hz, 1 H, NH), 7.24–7.29 (m, 3 H, H*o* and H*p*), 7.34–7.37 (m, 2 H, H*m*) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 8.18 (CH_3), 30.18 (C-4), 40.27 (C-6), 45.67 (NCH_2), 71.55 (q, J = 27.9 Hz, C-5), 101.84 (C-2), 125.78 (q, J = 286.4 Hz, CF_3), 126.49 (C_o), 126.91 (C_p), 128.50 (C_m), 139.71 (C_i), 156.41 (C-3), 187.15 (C-1) ppm. ^{19}F NMR (470 MHz, DMSO-d_6): δ = 80.19 (s, CF_3) ppm. DRA: ν = 3354 (N–H, O–H), 3085, 2876 (C–H), 1607, 1534 (C=O, C=C), 1130–1087 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{17}F_3NO_2$ $[M + H]^+$ 300.1203; found 300.1206.

3-[(4-Fluorobenzyl)amino]-5-hydroxy-2-methyl-5-(trifluoromethyl)cyclohex-2-en-1-one (4abg)



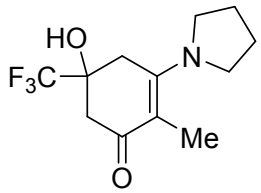
Isolated by crystallization (ethanol); Chemical Formula: $C_{15}H_{15}F_4NO_2$; White powder; M.P: 222–224 °C; Yield (method A) 409 mg (43%); Yield (method B) 895 mg (94%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.67 (s, 3 H, CH_3), 2.32 (dd, J = 16.0, 1.6 Hz, 1 H, H-6B), 2.48 (d, J = 16.0 Hz, 1 H, H-6A), 2.55 (d, J = 16.9 Hz, 1 H, H-4B), 2.64 (d, J = 16.9 Hz, 1 H, H-4A), 4.44 (d, J = 6.4 Hz, 2 H, NCH_2), 6.16 (s, 1 H, OH), 7.07 (t, J = 6.4 Hz ,1 H, NH), 7.19 (t, J = 8.9 Hz, 2 H, H*m*), 7.32 (dd, J = 8.5, 5.6 Hz, 2 H, H*o*) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 8.18 (CH_3), 30.19 (C-4), 40.20 (C-6), 44.97 (NCH_2), 71.56 (q, J = 27.8 Hz, C-5), 101.96 (C-2), 115.24 (d, J = 21.3 Hz, C_m), 125.78 (q, J = 285.7 Hz, CF_3), 128.54 (d, J = 8.1 Hz, C_o), 135.89 (d, J = 3.0 Hz, C_i), 156.26 (C-3), 161.21 (d, J = 242.5 Hz, C_p), 187.24 (C-1) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = 46.56 (tt, J = 8.9, 5.6 Hz, 1 F, CF), 80.23 (s, 3 F, CF_3) ppm. DRA: ν = 3339 (N–H, O–H), 3084, 2878, 2679 (C–H), 1605, 1526 (C=O, C=C), 1199–1087 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{16}F_4NO_2$ $[M + H]^+$ 318.1112; found 318.1109.

3-[(Furan-2-ylmethyl)amino]-5-hydroxy-2-methyl-5-(trifluoromethyl)cyclohex-2-en-1-one (4abi)



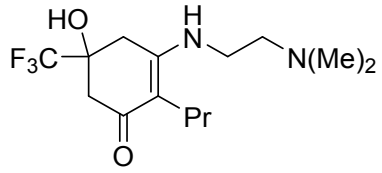
Isolated by crystallization (dichloromethane); Chemical Formula: $C_{13}H_{14}F_3NO_3$; White powder; M.P: 192–193 °C; Yield (method A) 269 mg (31%); Yield (method B) 738 mg (85%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.61 (s, 3 H, CH_3), 2.34 (d, J = 16.1 Hz, 1 H, H-6B), 2.55 (d, J = 16.1 Hz, 1 H, H-6A, overlapped with DMSO signal), 2.70 (d, J = 16.8 Hz, 1 H, H-4B), 2.81 (d, J = 16.8 Hz, 1 H, H-4A), 4.37–4.47 (m, 2 H, NCH_2), 6.18 (s, 1 H, OH), 6.26 (br. d, J = 2.7 Hz, 1 H, H-3'), 6.42 (br.t, J = 2.4 Hz, 1 H, H-4'), 6.93 (t, J = 6.2 Hz, 1 H, NH), 7.61 (br.s, 1 H, H-5') ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 8.11 (CH_3), 30.02 (C-4), 39.5 (NCH_2, overlapped with DMSO signal), 40.30 (C-6), 71.59 (q, J = 27.9 Hz, C-5), 102.14 (C-2), 106.94 (C-3'), 110.54 (C-4'), 125.84 (q, J = 286.1 Hz, CF_3), 142.42 (C-5'), 152.55 (C-2'), 156.03 (C-3), 187.42 (C-1) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = 80.24 (s, CF_3) ppm. ATR: ν = 3290, 3205 (N–H, O–H), 1607, 1524 (C=O, C=C), 1086–1176 (C–F); HRMS (ESI): calcd. for $C_{13}H_{15}F_3NO_3$ [M + H]$^+$ 290.0999; found 290.1001.

5-Hydroxy-2-methyl-3-(pyrrolidin-1-yl)-5-(trifluoromethyl)cyclohex-2-enone (4abj)



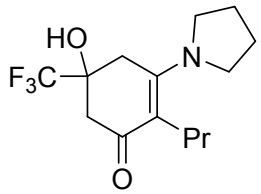
Isolated by crystallization (acetonitrile); Chemical Formula: $C_{12}H_{16}F_3NO_2$; White powder; M.P. 216–218 °C; Yield (method A) 529 mg (67%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.70–1.79 (m, 2 H, CH_2), 1.83 (s, 3 H, CH_3), 1.83–1.90 (m, 2 H, CH_2), 2.32 (dd, J = 16.0, 1.7 Hz, 1 H, H-6B), 2.48 (d, J = 16.0 Hz, 1 H, H-6A), 2.79 and 2.82 (AB system, J = 17.3 Hz, 2 H, H-4), 3.46–3.50 (m, 2 H, NCH_2), 3.53–3.58 (m, 2 H, NCH_2), 6.11 (s, 1 H, OH) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 12.00 (CH_3), 25.04 (2*CH_2), 34.03 (C-4), 40.39 (C-6), 50.92 (2*NCH_2), 70.94 (q, J = 27.9 Hz, C-5), 102.96 (C-2), 125.83 (q, J = 285.7 Hz, CF_3), 156.75 (C-3), 189.16 (C-1) ppm. ^{19}F NMR (470 MHz, DMSO-d_6): δ = 80.34 (s, CF_3) ppm. DRA: ν = 3208 (N–H, O–H), 2981, 2880, 2873 (C–H), 1581, 1535, 1516 (C=O, C=C), 1153–1094 (C–F) cm^{-1}. for $C_{12}H_{17}F_3NO_2$ [M + H]$^+$ 264.1206; found 264.1205.

3-{[2-(Dimethylamino)ethyl]amino}-5-hydroxy-2-propyl-5-(trifluoromethyl)-cyclohex-2-en-1-one (4ace)



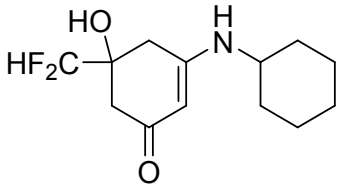
Isolated by crystallization (acetonitrile); Chemical Formula: $C_{14}H_{23}F_3N_2O_2$, White powder; M.P.: 216–218 °C; Yield (method A) 296 mg (32%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.83 (t, J = 7.4 Hz, 3 H, CH_3), 1.23 (sxt, J = 7.4, 2 H, CH_2), 2.09–2.18 (m, 2 H, CH_2), 2.18 (s, 6 H, 2 $N(CH_3)_2$), 2.30 (dd, J = 16.0, 1.8 Hz, 1 H, H-6B), 2.38 (t, J = 6.7 Hz, 2 H, H-3'), 2.47 (d, J = 16.0 Hz, 1 H, H-6A), 2.68 (dd, J = 16.8, 1.8 Hz, 1 H, H-4B), 2.78 (d, J = 16.8 Hz, 1 H, H-4A), 3.26 (q, J = 6.4 Hz, 2 H, H-2'), 6.14 (s, 1 H, OH), 6.26 (t, J = 6.0 Hz, 1 H, NH) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 13.97 (CH_3), 20.70 and 23.82 (2*CH_2), 30.04 (C-4), 40.28 (C-6 and C-2'), 44.32 ($N(CH_3)_2$), 57.96 (C-3'), 71.56 (q, J = 28.1 Hz, C-5), 107.05 (C-2), 125.88 (q, J = 285.8 Hz, CF_3), 155.58 (C-3), 187.23 (C-1) ppm.^{19}F NMR (376 MHz, DMSO-d_6): δ = 80.22 (s, CF_3) ppm. DRA: v = 3341, 3159 (N–H, O–H), 2960, 2872, 2829 (C–H), 1598, 1544 (C=O, C=C), 1186–1121 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{24}F_3N_2O_2$ $[M + H]^+$ 309.1784; found 309.1785.

5-Hydroxy-2-propyl-3-(pyrrolidin-1-yl)-5-(trifluoromethyl)cyclohex-2-en-1-one (4acj)



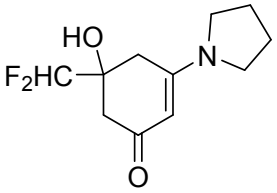
Isolated by crystallization (acetonitrile); Chemical Formula: $C_{14}H_{20}F_3NO_2$, White powder; M.P.: 185–187 °C; Yield (method A) 315 mg (36%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.83 (t, J = 7.3 Hz, 3 H, CH_3 propyl), 1.12–1.40 (m, 2 H, CH_2 propyl), 1.74–1.91 (m, 4 H, CH_2), 2.26 (m, 1 H, CH propyl), 2.32 (d, J = 16.0, 1 H, H-6B), 2.40–2.48 (m, 2 H, CH propyl and H-6A, overlapped with DMSO signal), 2.80 and 2.82 (AB system, J = 17.3 Hz, 2 H, H-4), 3.42–3.54 (m, 4 H, NCH_2), 6.09 (s, 1 H, OH) ppm. ^{13}C NMR (151 MHz, DMSO-d_6): δ = 14.04 (CH_3), 23.31 (CH_2 propyl), 25.07 (2*CH_2), 26.55 (CH_2 propyl), 34.29 (C-4), 40.55 (C-6), 50.82 (2*NCH_2), 70.90 (q, J = 27.9 Hz, C-5), 108.54 (C-2), 125.85 (q, J = 285.6 Hz, CF_3), 155.69 (C-3), 189.37 (C-1) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = 80.34 (s, CF_3) ppm. DRA: v = 3165 (N–H, O–H), 2962, 2932, 2874 (C–H), 1591, 1519 (C=O, C=C), 1158–1106 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{21}F_3NO_2$ $[M + H]^+$ 292.1519; found 292.1522.

3-(Cyclohexylamino)-5-hydroxy-5-(difluoromethyl)cyclohex-2-en-1-one (4baa)



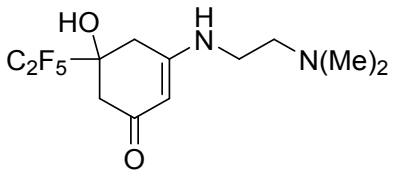
Isolated by crystallization (acetonitrile); Chemical Formula: $C_{13}H_{19}F_2NO_2$, White powder; M.P: 196–197 °C; Yield (method A) 482 mg (62%); Yield (method B) 708 mg (91%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.10–1.24 (m, 3 H, H cyclohexyl), 1.25-1.36 (m, 2 H, H cyclohexyl), 1.54–1.60 (m, 1 H, H cyclohexyl), 1.65–1.72 (m, 2 H, H cyclohexyl), 1.83–1.86 (m, 2 H, H cyclohexyl), 2.12 (dd, J = 16.4, 1.6 Hz, 1 H, H-6B), 2.30 (d, J = 16.4 Hz, 1 H, H-6A), 2.34 (d, J = 16.5 Hz, 1 H, H-4B), 2.54 (d, J = 16.5, 1 H, H-4A), 3.18 (m, 1 H, NCH), 4.89 (s, 1 H, H-2), 5.47 (s, 1 H, OH), 5.79 (t, J = 55.8 Hz, 1 H, CF_2H), 7.00 (d, J = 7.0 Hz, 1 H, NH) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 24.24, 24.29, 25.21, 31.52, and 31.79 (5*CH_2), 33.70 (C-4), 41.49 (C-6), 50.68 (NCH), 71.62 (t, C-5, J = 20.6 Hz), 93.66 (C-2), 116.78 (t, J = 246.1 Hz, CF_2H), 158.82 (C-3), 190.19 (C-1) ppm. ^{19}F NMR (470 MHz, DMSO-d_6): δ = 29.68 and 31.07 (AB system, $^2J_{FF}$ = 275.7 Hz, $^2J_{FH}$ = 55.8 Hz, CF_2H) ppm. DRA: ν = 3223 (N–H, O–H), 3062, 2933, 2857 (C–H), 1581, 1547, 1452 (C=O, C=C), 1028–1121 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{20}F_2NO_2$ $[M + H]^+$ 260.1460; found 260.1457.

5-Hydroxy-3-(pyrrolidin-1-yl)-5-(1,1-difluoromethyl)cyclohex-2-enone (4baj)



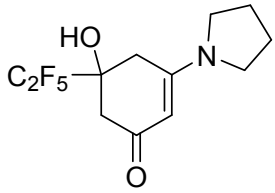
Isolated by crystallization (acetonitrile); Chemical Formula: $C_{11}H_{15}F_2NO_2$; Yelow powder; M.P. 218–220 °C; Yield (method A) 492 mg (71%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.82–1.94 (m, 4 H, CH_2), 2.12 (dd, J = 16.1, 1.8 Hz, 1 H, H-6B), 2.29 (d, J = 16.1 Hz, 1 H, H-6A), 2.54 (dd, J = 16.9, 1.8 Hz, 1 H, H-4B), 2.67 (d, J = 16.9 Hz, 1 H, H-4A), 3.09–3.22 (m, 2 H, NCH_2), 3.44 (m, 2 H, NCH_2), 4.81 (s, 1 H, H-2), 5.50 (s, 1 H, OH), 5.82 (t, J = 55.9 Hz, 1 H, CF_2H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 24.29 and 24.88 (2*CH_2), 32.59 (t, J = 3.3 Hz, C-4), 40.74 (C-6), 47.54 and 47.85 (2*NCH_2), 71.77 (t, J = 20.6 Hz, C-5), 96.16 (C-2), 116.82 (t, J = 246.5 Hz, CF_2H), 158.45 (C-3), 189.36 (C-1) ppm. ^{19}F NMR (470 MHz, DMSO-d_6): δ = 30.22 and 30.92 (AB system, $^2J_{FF}$ = 275.0 Hz, $^2J_{FH}$ = 55.9 Hz, CF_2H) ppm. DRA: ν = 3110, 3233 (N–H, O–H), 2987, 2949, 2873 (C–H), 1592, 1547, 1526 (C=O, C=C), 1124–1030 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{16}F_2NO_2$ $[M + H]^+$ 232.1137; found 232.1144.

3-{[2-(Dimethylamino)ethyl]amino}-5-hydroxy-5-(pentafluoroethyl)cyclohex-2-en-1-one (4cae)



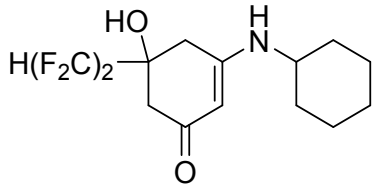
Isolated by crystallization (acetonitrile); Chemical Formula: $C_{12}H_{17}F_5N_2O_2$; White powder; M.P.: 223–224 °C with decomposition; Yield (method A) 446 mg (47%). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 2.18 (s, 6 H, $N(CH_3)_2$), 2.33 (d, J = 16.2 Hz, 1 H, H-6B), 2.42 (t, J = 6.5 Hz, 2 H, H-3'), 2.50 (d, J = 16.2 Hz, 1 H, H-6A), 2.62 (d, J = 16.3 Hz, 1 H, H-4B), 2.73 (d, J = 16.3 Hz, 1 H, H-4A), 3.08 (br. q, J = 6.0 Hz, 2 H, H-2'), 4.92 (s, 1 H, H-2), 6.35 (s, 1 H, OH), 7.14 (br t, J = 5.2 Hz, 1 H, NH) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 33.45 (C-4), 40.38 (C-2'), 40.98 (C-6), 45.07 ($N(CH_3)_2$), 56.60 (C-3'), 73.46 (q, J = 22.6 Hz, C-5), 93.40 (C-2), 114.23 (tq, J = 261.6, 34.1 Hz, CF_2), 119.22 (qt, J = 288.3, 36.6 Hz, CF_3), 159.37 (C-3), 188.83 (C-1) ppm.^{19}F NMR (376 MHz, DMSO-d_6): δ = 38.36 and 39.02 (AB system, J = 273.10 Hz, 2 F, CF_2,), 85.17 (s, 3 F, CF_3) ppm. DRA: ν = 3248 (N–H, O–H), 3090, 2992, 2880 (C–H), 1610, 1555 (C=O, C=C), 1173–1068 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{18}F_5N_2O_2$ $[M + H]^+$ 317.1283; found 317.1286.

5-Hydroxy-5-(pentafluoroethyl)-3-(pyrrolidin-1-yl)cyclohex-2-en-1-one (4caj)



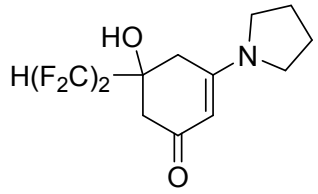
Isolated by crystallization (acetonitrile); Chemical Formula: $C_{12}H_{14}F_5NO_2$; White powder; M.P. 230–231 °C; Yield (method A) 476 mg (53%); Yield (method B) 781 mg (87%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.82–1.95 (m, 4 H, CH_2), 2.32 (br. d, J = 16.2 Hz, 1 H, H-6B), 2.47 (d, J = 16.2 Hz, 1 H, H-6A), 2.73 (d, J = 16.7, 1.7 Hz, 1 H, H-4B), 2.89 (d, J = 16.7 Hz, 1 H, H-4A), 3.10-3.25 (m, 2 H, NCH_2), 3.45–3.48 (m, 2 H, NCH_2), 4.87 (s, 1 H, H-2), 6.34 (s, 1 H, OH) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 24.23 and 24.81 (2*CH_2), 32.41 (C-4), 40.47 (C-6), 47.50 and 48.02 (2*NCH_2), 73.54 (t, J =22.8 Hz, C-5), 95.70 (C-2), 114.23 (tq, J = 261.3, 33.8 Hz, CF_2), 119.19 (qt, J = 288.2, 36.6 Hz, CF_3), 157.70 (C-3), 187.84 (C-1) ppm. ^{19}F NMR (470 MHz, DMSO-d_6): δ = 38.06 (d, J = 272.7 Hz, 1 F, CF^B), 39.41 (d, J = 272.7 Hz, 1 F, CF^A), 85.27 (s, 3 F, CF_3) ppm. DRA: ν = 3115 (N–H, O–H), 2978, 2877 (C–H), 1557 (C=O, C=C), 1211–1103 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{15}F_5NO_2$ $[M + H]^+$ 300.1018; found 300.1019.

3-(Cyclohexylamino)-5-hydroxy-5-(1,1,2,2-tetrafluoroethyl)cyclohex-2-en-1-one (4daa)



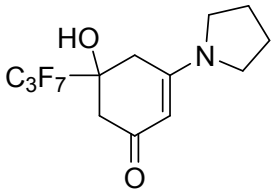
Isolated by crystallization (acetonitrile); Chemical Formula: $C_{14}H_{19}F_4NO_2$; White powder; M.P. 218–220 °C; Yield (method A) 547 mg (59%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.09–1.37 (m, 5 H, H cyclohexyl), 1.55–1.60 (m, 1 H, H cyclohexyl), 1.65–1.73 (m, 2 H, H cyclohexyl) 1.83–1.87 (m, 2 H, H cyclohexyl), 2.26 (d, J = 16.3 Hz, 1 H, H-6B), 2.41(d, J = 16.3 Hz, 1 H, H-6A), 2.51 (d, J = 16.4 Hz, 1 H, H-4B, overlapped with DMSO signal), 2.64 (d, J = 16.4, 1 H, H-4A), 3.19 (m, 1 H, NCH), 4.92 (s, 1 H, H-2), 6.17 (s, 1 H, OH), 6.55 (tt, J = 52.1, 6.2 Hz, 1 H, $(CF_2)_2H$), 7.09 (d, J = 7.3 Hz, 1 H, NH) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 24.21, 24.25, 25.20, 31.45 and 31.78 (5*CH_2), 33.50(C-4), 40.92 (C-6), 50.73 (NCH), 72.92 (t, J = 23.4 Hz, C-5), 93.41 (C-2), 109.23 (tt, J = 248.3, 30.9 Hz, CF_2H), 116.07 (tt, J = 256.4, 23.6 Hz, CF_2), 158.42 (C-3), 189.27 (C-1) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = 25.87 and 26.69 (AB system, both ddm, $^2J_{FF}$ = 301.0 Hz, $^2J_{FH}$ = 52.1 Hz, 2 F, HCF_2), 32.15 and 33.18 (AB system, both dm, J = 262.8 Hz, 2 F, CF_2) ppm. DRA: ν = 3284 (N–H, O–H), 3077, 2946, 2861 (C–H), 1585, 1538, 1452 (C=O, C=C), 1135–1074 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{20}F_4NO_2$ $[M + H]^+$ 310.1424; found 310.1425.

5-Hydroxy-3-(pyrrolidin-1-yl)-5-(1,1,2,2-tetrafluoroethyl)cyclohex-2-enone (4daj)



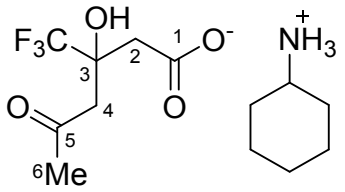
Isolated by crystallization (acetonitrile); Chemical Formula: $C_{12}H_{15}F_4NO_2$; White powder; M.P. 219–221 °C; Yield (method A) 455 mg (54%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.82–1.96 (m, 4 H, CH_2), 2.27 (br. d, J = 16.2 Hz, 1 H, H-6B), 2.38 (d, J = 16.2 Hz, 1 H, H-6A), 2.69 (br. d, J = 17.0, 1.4 Hz, 1 H, H-4B), 2.80 (d, J = 17.0 Hz, 1 H, H-4A), 3.10–3.24 (m, 2 H, NCH_2), 3.45 (m, 2 H, NCH_2), 4.85 (s, 1 H, H-2), 6.16 (s, 1 H, OH), 6.60 (tt, J = 51.9, 6.3 Hz, 1 H, $(CF_2)_2H$) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 24.28 and 24.86 (2*CH_2), 32.32 (q, J = 3.1 Hz, C-4), 40.46 (C-6), 47.54 and 47.98 (2*NCH_2), 73.05 (t, J = 23.7 Hz, C-5), 95.89 (C-2), 109.21 (tt, J = 248.7, 30.7 Hz, CF_2H), 116.06 (tt, J = 257.2, 22.9 Hz, CF_2), 158.01 (C-3), 188.48 (C-1) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = 25.72 (ddt, 1 F, HCF^B, J = 300.9, 51.9, 7.8 Hz), 27.20 (ddt, 1 F, HCF^A, J = 300.6, 51.9, 7.2 Hz), 32.81 (br. q, J = 7.5 Hz 2 F, CF_2) ppm. DRA: ν = 3228 (N–H, O–H), 3020, 2988, 2958, 2881 (C–H), 1586, 1558 (C=O, C=C), 1118–1065 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{16}F_4NO_2$ $[M + H]^+$ 282.1107; found 282.1112.

5-Hydroxy-5-(heptafluoropropyl)-3-(pyrrolidin-1-yl)cyclohex-2-en-1-one (4eaj)



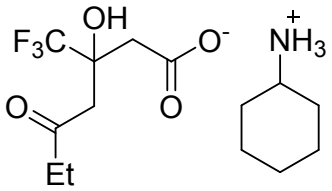
Isolated by crystallization (acetonitrile); Chemical Formula: $C_{13}H_{14}F_7NO_2$; White powder; M.P. 212 °C with decomposition; Yield (method A) 220 mg (21%). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 1.80–1.94 (m, 4 H, CH_2), 2.34 (d, J = 16.0 Hz, 1 H, H-6B), 2.49 (d, J = 16.0 Hz, 1 H, H-6A, overlapped with DMSO signal), 2.76 (d, J = 16.7 Hz, 1 H, H-4B), 2.92 (d, J = 16.7 Hz, 1 H, H-4A), 3.10–3.25 (m, 2 H, NCH_2), 3.43–3.49 (m, 2 H, NCH_2), 4.87 (s, 1 H, H-2), 6.41 (s, 1 H, OH) ppm. ^{13}C NMR (151 MHz, DMSO-d_6): δ = 24.27 and 24.86 (2*CH_2), 32.46 (C-4), 40.53 (C-6), 47.53 and 48.06 (2*NCH_2), 74.66 (q, J = 23.2 Hz, C-5), 95.71 (C-2), 110.04 (tm, J = 267.8 Hz, CF_2), 115.65 (tt, J = 261.8, 28.6 Hz, CF_2), 117.53 (qt, J = 288.1, 33.9 Hz, CF_3), 157.70 C-3), 187.80 (C-1) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = 39.47 and 39.78 (AB system, $^2J_{FF}$ = 289.9 Hz, 2 F, CF_2), 41.65 and 42.54 (AB system, $^2J_{FF}$ = 278.8 Hz, 2 F, CF_2), 82.52 (t, J = 10.3 Hz, 3 F, CF_3) ppm. DRA: v = 3094 (N–H, O–H), 2996, 2874 (C–H), 1594, 1558 (C=O, C=C), 1205–1100 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{15}F_7NO_2$ $[M + H]^+$ 350.2520; found 350.2523.

Cyclohexanaminium 3-hydroxy-5-oxo-3-(trifluoromethyl)hexanoate (5a)



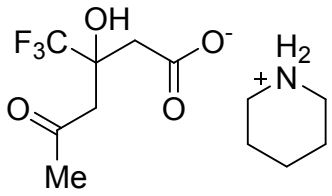
Chemical Formula: $C_{13}H_{22}F_3NO_4$; White powder; M.P. 124–126°C; Yield 620 mg (66%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.18–1.29 (m, 5 H, H cyclohexyl), 1.57 (m, 1 H, H cyclohexyl), 1.66–1.92 (m, 4 H, H cyclohexyl), 2.11 (d, J = 16.0 Hz, 1 H, H-2B), 2.17 (s, 3 H, H-6), 2.34 (d, J = 16.0 Hz, 1 H, H-2A), 2.37 (d, J = 13.0 Hz, 1 H, H-4B), 2.72 (d, J = 13.0 Hz, 1 H, H-4A), 2.92 (m, 4 H, NCH_2), 7.98 (br. s, 3 H, NH_3^+), 10.63 (br. s, 1 H, OH), ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = 81.96 (s, CF_3) ppm. DRA: v = 3252 (O–H, N–H), 3005, 2937, 2859 (C–H), 2582, 2526 (NH_3^+), 1703, 1658 (C=O), 1177–1156 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{23}F_3NO_4$ $[M + H]^+$ 314.1574; found 314.1576.

Cyclohexanaminium 3-hydroxy-5-oxo-3-(trifluoromethyl)heptanoate (5b)



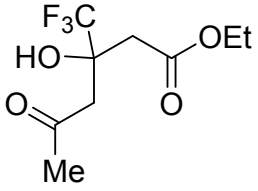
Chemical Formula: $C_{14}H_{24}F_3NO_4$; White powder; M.P. 156–158°C; Yield 766 mg (78%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.88 (t, J = 7.2 Hz, 3 H, H-7), 1.03–1.12 (m, 1 H, H cyclohexyl), 1.19–1.29 (m, 4 H, H cyclohexyl), 1.56–1.60 (m, 1 H, H cyclohexyl), 1.68–1.73 (m, 2 H, H cyclohexyl), 1.85–1.91 (m, 2 H, H cyclohexyl), 2.11 (d, J = 16.0 Hz, 1 H, H-2B), 2.34 (d, J = 13.1 Hz, 1 H, H-4B), 2.41 (dq, J = 16.0, 1.2 Hz, 1 H, H-2A), 2.56 (q, J = 7.2 Hz, 2 H, H-6), 2.73 (d, J = 13.1 Hz, 1 H, H-4A), 2.96 (m, 1 H, NCH), 8.01 (br s, 3 H, NH_3^+), 10.44 (br s, 1 H, OH) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 7.36 (C-7), 23.78, 24.59 and 30.47 (3*CH_2), 36.60 (C-2), 37.67 (C-6), 46.65 (C-4), 49.13 (NCH), 72.13 (q, J =27.2 Hz, C-3), 126.42 (q, J = 287.9 Hz, CF_3), 173.34 (C-1), 207.93 (C-5) ppm. ^{19}F NMR (470 MHz, DMSO-d_6): δ = 81.88 (s, CF_3) ppm. DRA: v = 3235 (O–H, N–H), 3036, 2977, 2859 (C–H), 1702, 1659 (C=O), 1175–1128 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{21}F_3NO_2$ $[M\text{-}H_2O + H]^+$ 292.1519; found 292.1520.

Piperidinium 3-hydroxy-5-oxo-3-(trifluoromethyl)hexanoate (5c)



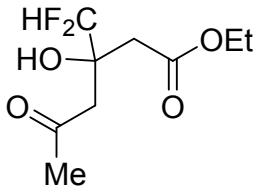
Chemical Formula: $C_{12}H_{20}F_3NO_4$; White powder; M.P. 108–109 °C; Yield 736 mg (82%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.50–1.68 (m, 6 H, CH_2), 2.14 (d, J = 17.0 Hz, 1 H, H-2B), 2.17 (s, 3 H, H-6), 2.38 (d, J = 17.0 Hz, 1 H H-2A), 2.385 (d, J = 13.0 Hz, 1 H, H-4B), 2.73 (d, J = 13.0 Hz, 1 H, H-4A), 2.97 (m, 4 H, NCH_2), 8.4–11.0 (3 H, NH_2^+ and OH), ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 21.76 and 22.24 (2*CH_2), 32.33 (C-6), 36.67 (C-2), 43.49 (2*NCH_2), 47.75 (C-4), 72.10 (q, J = 27.3 Hz, C-3), 126.34 (q, J = 287.8 Hz, CF_3), 173.30 (C-1), 205.59 (C-5) ppm. ^{19}F NMR (470 MHz, DMSO-d_6): δ = 81.95 (s, CF_3) ppm. DRA: v = 2960, 2930, 2864 (C–H), 2531, 2457 (NH_2^+), 1710, 1636 (C=O), 1192–1112 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{21}F_3NO_4$ $[M + H]^+$ 300.1417; found 300.1419.

Ethyl 3-hydroxy-5-oxo-3-(trifluoromethyl)hexanoate (6a)



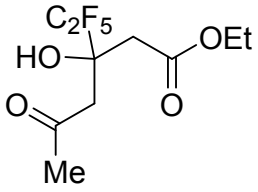
Chemical Formula: $C_9H_{13}F_3O_4$; Yellow oil, 2059 mg (85%). Spectral data correspond to the previously reported[3] $[\alpha]_D$ = +0.59 (*c* = 1.0, CH_2Cl_2). HPLC: 3.8% ee, Chiralcel ODH-3, hexane : iPrOH = 100:1, flow rate = 1.0 mL/min, T = 24 °C, UV = 220 nm, t_R = 11.25 min (major), t_R = 13.52 min (minor).

Ethyl 3-hydroxy-5-oxo-3-(difluoromethyl)hexanoate (6b)



Chemical Formula: $C_9H_{14}F_2O_4$; Yellow oil, 1390 mg (62%). $[\alpha]_D$ = +3.09 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.1 Hz, 3 H, CH_3), 2.26 (s, 3 H, H-6), 2.68 and 2.70 (AB system, *J* = 15.4 Hz, 2 H, CH_2), 2.90 (s, 2 H, CH_2), 4.17 (q, *J* = 7.1 Hz, 2 H, OCH_2), 4.96 (s, 1 H, OH), 5.86 (t, *J* = 56.0 Hz, 1 H, CF_2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.98 (CH_3), 31.92 (C-6), 38.00 (t, *J* = 2.9 Hz, C-2), 44.06 (t, *J* = 2.2 Hz, C-4), 61.13 (OCH_2), 72.88 (t, *J* =22.0 Hz, C-3), 115.86 (t, *J* = 248.5 Hz, CF_2H), 170.60 (C-1), 208.65 (C-5) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 29.84 and 30.15 (AB system, $^2J_{FF}$ = 281.5 Hz, $^2J_{FH}$ = 56.0 Hz, CF_2H) ppm. ATR: ν = 3449 (OH, NH), 2986, 2938, 2911 (C-H), 1728, 1709 (C=O), 1068-1029 (C-F) cm^{-1}. HRMS (ESI): calcd. for $C_9H_{15}F_2O_4$ $[M + H]^+$ 225.0931; found 225.0933. HPLC: 10.8% ee, Kromasil 5-Cellucoat, MeOH : H_2O = 40:60, flow rate = 0.5 mL/min, T = 24 °C, UV = 220 nm, t_R = 25.41 min (major), t_R = 27.22 min (minor).

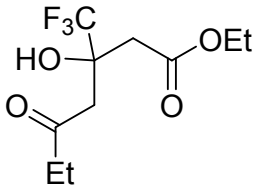
Ethyl 3-hydroxy-5-oxo-3-(pentafluoroethyl)hexanoate (6c)



Chemical Formula: $C_{10}H_{13}F_5O_4$; Yellow oil, 1717 mg (67%). $[\alpha]_D$ = - 1.48 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.1 Hz, 3 H, CH_3), 2.29 (s, 3 H, H-6), 2.83 (d, *J* = 15.5 Hz, 1 H, CH), 2.88 (dd, *J* = 15.5, 1.5 Hz, 1 H, CH), 3.02 (d, *J* = 16.4 Hz, 1 H, CH), 3.11 (d, *J* = 16.4, 1.5 Hz, 1 H, CH), 4.18 (q, *J* = 7.1 Hz, 2 H, OCH_2), 5.96 (br s, 1 H, OH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.82 (CH_3), 32.00 (C-6), 37.49 (C-2), 43.00 (C-4), 61.30 (OCH_2), 75.03 (t, *J* = 23.8 Hz, C-3), 114.21 (tq, *J* = 262.3, 35.0 Hz, CF_2), 119.02 (qt, *J* = 287.9, 36.0 Hz, CF_3), 170.44 (C-1), 208.61 (C-5) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 39.04 and 39.77 (AB system, *J* = 279.7 Hz, 2 F, CF_2), 83.75 (s, 3 F, CF_3) ppm. ATR: ν = 3366 (OH, NH), 2988, 2944, 2909 (C-H), 1731, 1713 (C=O), 1216-1146 (C-F) cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{14}F_5O_4$ $[M + H]^+$

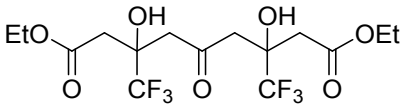
293.2072; found 293.2073. HPLC: 13.6% ee, Chirapak AD, hexane : iPrOH = 100:1, flow rate = 1.0 mL/min, T = 24 °C, UV = 220 nm, t_R = 8.85 min (minor), t_R = 10.27 min (major).

Ethyl 3-hydroxy-5-oxo-3-(trifluoromethyl)heptanoate (6d)



Chemical Formula: $C_9H_{15}F_3O_4$; Yellow oil; Yield 2396 mg (82%). $[\alpha]_D$ = -2.88 (c = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.07 (t, J = 7.2 Hz, 3 H, H-7), 1.28 (t, J = 7.2 Hz, 3 H, CH_3), 2.53–2.65 (m, 2 H, H-6), 2.76 and 2.84 (AB system, J = 15.3 Hz, 2 H, CH_2), 2.93 and 2.98 (AB system, J = 16.1 Hz, 2 H, CH_2), 4.18 (q, J = 7.2 Hz, 2 H, OCH_2), 5.82 (s, 1 H, OH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 7.15 (C-7), 13.96 (CH_3), 37.44 (C-2), 38.27 (C-6), 42.05 (C-4), 61.37 (OCH_2), 73.85 (q, J =29.1 Hz, C-3), 125.03 (q, J = 286.1 Hz, CF_3), 170.37 (C-1), 210.97 (C-5) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 79.54 (s, CF_3) ppm. ATR: ν = 3382 (O–H), 2985, 29448 (C–H), 1731, 1716 (C=O), 1173–1107 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{16}F_3O_4$ $[M + H]^+$ 257.0996; found 257.0995. HPLC: 21.8% ee, Chiralcel ODH-3, hexane : iPrOH = 50:1, flow rate = 1.0 mL/min, T = 24 °C, UV = 230 nm, t_R = 6.58 min (minor), t_R = 7.47 min (major).

Diethyl 3,7-dihydroxy-5-oxo-3,7-bis(trifluoromethyl)nonanedioate (7).

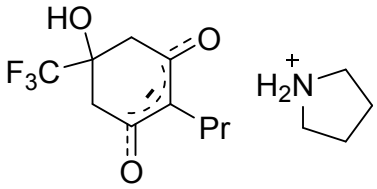


To a solution of ester **1a** (10 mmol) and methyl ketone **3a** (30 mmol) in toluene (15 mL) was added L-proline (0.1 mmol) and the reaction mixture was kept under reflux for 2 days. After the reaction was complete (TLC monitoring), the solvent was evaporated and the residue was purified by column chromatography (eluent chloroform). The first fraction contains the product **6a,** and the second fraction - the product **7**.

Chemical Formula: $C_{15}H_{20}F_6O_7$; Brown oil, 1449 mg (34%). Mixture of two diastereomers, ratio ~ 1:1. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.29 (t, J = 7.1 Hz, 6 H, CH_3), 2.75 and 2.76 (both d, J = 15.9 Hz, 2 H, 2*CH), 2.87 (d, J = 15.9 Hz, 1 H, CH), 2.92 (d, J = 15.9 Hz, 1 H, CH), 2.96 and 3.00 (both d, J = 16.0 Hz, 2 H, 2*CH), 3.13 and 3.14 (both d, J = 16.0 Hz, 2 H, 2*CH), 4.17-4.23 (m, 4 H, OCH_2), 5.56 (br.s, 2 H, OH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.94 (CH_3), 36.30 and 36.50 (C-2, 8), 45.66 and 45.76 (C-4, 6), 61.64 (OCH_2), 73.57 (q, J = 29.2 Hz, C-3, 7), 124.84 and 124.86 (both q, J = 286.0 Hz, CF_3), 170.77 and 170.83 (C-1, 9), 207.34, 206.73 (C-5) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 79.58 and 79.59 (both s, CF_3) ppm. ATR: ν = 3441, 3290

(O–H), 2990 (C–H), 1714 (C=O), 1174–1122 (C–F). HRMS (ESI): calcd. for $C_{15}H_{21}F_6O_7$ [M + H]$^+$ 427.1185; found 427.1186.

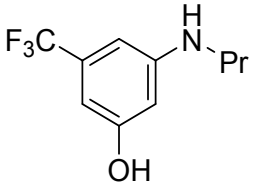
Pyrrolidinium 5-Hydroxy-2-propyl-5-(trifluoromethyl)cyclohex-1-one-3-olate (8)



To a solution of the corresponding 3-oxo ester **1a** (3 mmol) and 2-hexanone **2c** (3 mmol) in 95% ethanol (15 mL) was added pyrrolidine **3c** (3 mmol) and the reaction mixture was stirred for 2–3 days at room temperature (25 °C). After the reaction was complete (TLC monitoring), the solvent was evaporated and the residue was washed with diethyl ether and crystallized from acetonitrile.

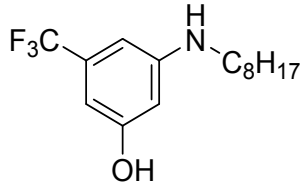
Chemical Formula: $C_{14}H_{22}F_3NO_3$; White powder; M.P. 169–170 °C; Yield (method A) 278 mg (30%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.78 (t, J = 7.3 Hz, 3 H, CH_3 propyl), 1.24 (sxt, 2 H, CH_2 propyl), 1.75–1.82 (m, 4 H, 2*CH_2), 2.07 (m, 2 H, CH_2 propyl), 2.24 (d, J = 16.3 Hz, 2 H, H-4B, H-6B), 2.45 (d, J = 16.3 Hz, 2 H, H-4A, H-6A), 2.96–3.04 (m, 4 H, NCH_2), 5.01–6.96 (NH_2 + H_2O) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 14.37 (CH_3), 21.94 (CH_2 propyl), 24.03 (CH_2), 24.64 (CH_2 propyl), 39.59 (C-4, 6), 45.09 (NCH_2), 71.76 (q, J = 27.4 Hz, C-5), 110.21 (C-2), 126.32 (q, J = 285.2 Hz, CF_3), 182.28 (C-1, 3) ppm. ^{19}F NMR (470 MHz, DMSO-d_6): δ = 80.25 (s, CF_3) ppm. DRA: ν = 3119 (NH), 2958, 2749 (C–H), 2583, 2462 (NH_2^+), 1605, 1575 (C=O), 1174–1092 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{21}F_3NO_3$ [M - H]$^+$ 308.1468; found 308.1463.

3-(Propylamino)-5-(trifluoromethyl)phenol (9a)



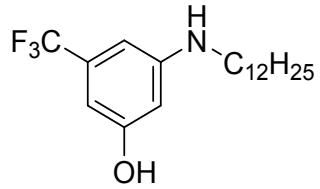
Chemical Formula: $C_{10}H_{12}F_3NO$; White powder; M.P. 65–66 °C; Yield (method C) 207 mg (63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, J = 7.4 Hz, 3 H, CH_3), 1.65 (sxt, J = 7.4 Hz, 2 H, CH_2), 3.08 (t, J = 7.3 Hz, 2 H, NCH_2), 4.88 (br. s, 2 H, NH and OH), 6.34 (br. t, J = 2.3 Hz, 1 H, H-2), 6.45 (br. t, J = 2.3 Hz, 1 H, H-6), 6.49 (br. t, J = 2.3 Hz, 1 H, H-4) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 98.57 (s, CF_3) ppm. DRA: ν = 3396, 3340 (O–H, N–H), 3074, 2966, 2879 (C–H), 1615, 1597 (C=C), 1180–1104 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{13}F_3NO$ [M + H]$^+$ 220.0944; found 220.0947.

3-(Octylamino)-5-(trifluoromethyl)phenol (9b)



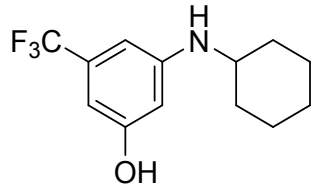
Chemical Formula: $C_{15}H_{22}F_3NO$; Brown oil; Yield (method C) 321 mg (74%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.0 Hz, 3 H, CH_3), 1.24–1.40 (m, 10 H, 5 CH_2), 1.61 (qw, J = 7.5 Hz, 2 H, CH_2), 3.09 (t, J = 7.2 Hz, 2 H, NCH_2), 4.63 (br. s, 2 H, NH and OH), 6.28 (br. s, 1 H, H-2), 6.42 (br. s, 1 H, H-6), 6.45 (br. s, 1 H, H-4) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.05 (CH_3), 22.62, 27.01, 29.02, 29.19, 29.29 and 31.77 (6*CH_2), 44.47 (NCH_2), 100.89 (q, J = 3.6 Hz, C-6), 102.72 (C-2), 103.05 (q, J = 3.9 Hz, C-4), 123.90 (q, J = 272.5 Hz, CF_3), 132.66 (q, J = 32.0 Hz, C-5), 149.15 (C-3), 156.92 (C-1) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 98.61 (s, CF_3) ppm. ATR: ν = 3412, 3348 (O–H, N–H), 2956, 2929, 2857 (C–H), 1621, 1605 (C=C), 1172–1127 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{23}F_3NO$ $[M + H]^+$ 290.1726; found 290.1727.

3-(Dodecylamino)-5-(trifluoromethyl)phenol (9c)



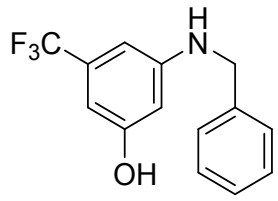
Chemical Formula: $C_{19}H_{30}F_3NO$; White powder; M.P. 59–61 °C; Yield (method D) 357 mg (69%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.85 (t, J = 6.7 Hz, 3 H, CH_3), 1.21–1.37 (m, 18 H, 9 CH_2), 1.51 (qw, J = 7.1 Hz, 2 H, CH_2), 2.95 (br. q, J = 6.3 Hz, 2 H, NCH_2), 5.94 (t, J = 5.7 Hz, 1 H, NH), 6.15-6.18 (m, 2 H, H arom), 6.28 (s, 1 H, H arom.), 9.53 (s, 1 H, OH) ppm. ^{13}C NMR (151 MHz, DMSO-d_6): δ = 13.91 (CH_3), 22.07, 26.58, 28.44, 28.69, 28.82, 28.99, 29.01, 29.04 and 31.28 (10*CH_2), 42.59 (NCH_2), 98.77 (q, J = 4.0 Hz C-4/6), 99.69 (q, J = 4.0 Hz, C-6/4), 101.13 (C-2), 124.47 (q, J = 272.1 Hz, CF_3), 130.39 (q, J = 3.7 Hz, C-5), 150.78 (C-3), 158.63 (C-1) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = 100.96 (s, CF_3) ppm. DRA: ν = 3292 (O–H, N–H), 3090, 2918, 2853 (C–H), 1609 (C=C), 1181–1127(C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{31}F_3NO$ $[M + H]^+$ 346.4502; found 346.4504.

3-(Cyclohexylamino)-5-(trifluoromethyl)phenol (9d)



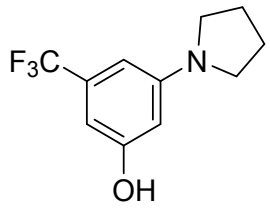
Chemical Formula: $C_{13}H_{16}F_3NO$; White powder; M.P. 93–94 °C; Yield (method C) 296 mg (76%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.11–1.41 (m, 5 H, H cyclohexyl), 1.65–1.79 (m, 3 H, H cyclohexyl), 2.00–2.05 (m, 2 H, H cyclohexyl), 3.22 (tt, J = 10.1, 3.8 Hz, 1 H, NCH), 3.5–5.2 (2 H, OH and NH), 6.18 (t, J = 2.2 Hz, 1 H, H-2), 6.33 (br. t, J = 2.2 Hz, 1 H, H-6), 6.38 (br. t, J = 2.2 Hz, 1 H, H-4) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 24.86, 25.75 and 33.18 (C cyclohexyl), 51.61 (NCH), 100.49 (q, J = 3.8 Hz, C-6), 102.04 (C-2), 102.94 (q, J = 3.9 Hz, C-4), 123.99 (q, J = 272.6 Hz, CF_3), 132.61 (q, J = 31.9 Hz, C-5), 149.08 (C-3), 156.80 (C-1) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 98.59 (s, CF_3) ppm. ATR: ν = 3270 (O–H, N–H), 3081, 2933, 2858 (C–H), 1582, 1575, 1536 (C=C), 1179–1114 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{17}F_3NO$ $[M + H]^+$ 260.1257; found 260.1257.

3-(Benzylamino)-5-(trifluoromethyl)phenol (9e)



Chemical Formula: $C_{14}H_{12}F_3NO$; Brown oil; Yield (method C) 261 mg (65%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.31 (s, 2 H, NCH_2), 4.23 and 5.02 (each br.s, 1 H, NH and OH), 6.19 (br. t, J = 2.2 Hz, 1 H, H-2), 6.39 (br. s, 1 H, H-6), 6.46 (br. s, 1 H, H-4), 7.27–7.37 (m, 5 H, C_6H_5) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 48.06 (NCH_2), 101.33 (q, J = 3.5 Hz, C-6), 102.01 (C-2), 102.75 (q, J = 3.9 Hz, C-4), 123.92 (q, J = 273.4 Hz, CF_3), 127.44 (C_o), 125.54 (C_p), 128.78 (C_m), 123.61 (q, J = 32.1 Hz, C-5), 138.36 (C_i), 149.78 (C-3), 156.82 (C-1) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 98.60 (s, CF_3) ppm. ATR: ν = 3419 (O–H, N–H), 3065, 3032, 2859 (C–H), 1622, 1606 (C=C), 1179–1114 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{13}F_3NO$ $[M + H]^+$ 268.0945; found 268.0944.

3-(Pyrrolidin-1-yl)-5-(trifluoromethyl)phenol (9f)



Chemical Formula: $C_{11}H_{12}F_3NO$; Beige powder; M.P. 143–145 °C; Yield (method C) 232 mg (67%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.97-2.04 (m, 4 H, CH_2), 3.23–3.30 (m, 4 H, NCH_2), 4.95 (br. s, 1 H, OH), 6.14 (br. t, J = 2.2 Hz, 1 H, H-2), 6.34–6.36 (m, 2 H, H-4 and H-6) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.40 (CH_2), 47.69 (NCH_2), 99.19 (q, J = 3.8 Hz, C-6), 101.05 (C-2), 101.42 (q, J = 4.0 Hz, C-4), 124.20 (q, J = 272.5 Hz, CF_3), 132.36 (q, J = 31.7 Hz, C-5),

149.27 (C-3), 156.54 (C-1) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 98.78 (s, CF_3) ppm. DRA: ν = 3163 (O–H, N–H), 3075, 2962, 2885 (C–H), 1623 (C=C), 1168-1117 (C-F) cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{13}F_3NO$ $[M + H]^+$ 232.0941; found 232.0944.

Antifungal activity assay. The following fungal strains were used: *Trichophyton rubrum* (RCPF F-1408), *Trichophyton mentagrophytes var. gypseum* (RCPF F-1425), *Trichophyton tonsurans* (RCPF F-1458), *Trichophiton violaceum* (RCPF F-1393/658), *Trichophyton mentagrophytes var. interdigitale* (RCPF F-1229), *Epidermophyton floccosum* (RCPF F-1174), *Microsporum canis* (RCPF F-1403), *Candida albicans* (RCPF Y -401/NCTC 885-653). The fungal strains were obtained from Russian Collection of Patogenic Fungi (RCPF), Kashkin Research Institute of Medical Mycology (St. Peterburg, Russia). Fungi were cultivated at 27 °C on Sabouraud Dextrose Agar (SDA) and MIC was determined by using Sabouraud Dextrose Broth (SDB). The test and standard compounds were dissolved in dimethylsulfoxide (DMSO, 1/10) and applied in different concentrations (1000–0.19 μg/mL). Dimethylsulfoxide was used as a negative control and antifungal drug Terbinafine as a positive control. The broth dilution test was performed in test tubes. The inoculum suspension, which gave the final concentration of 1 x 10^8 CFU/mL, was prepared. A growth control tube and sterility control tube were used in each test. After 14 days incubation at 27 °C, MIC was determined visually as the lowest concentration that inhibited the growth, evidenced by the absence of turbidity.

Antibacterial activity assay. Assays were performed using reference strain *Neisseria gonorrhoeae* NCTC 12700 from the National Collection of Type Cultures (NCTC, UK). Microorganisms were identified with an accuracy of 99.9% using a VITEK MS MALDI-TOF Plus analyzer (BioMerieux, France) by flight mass spectrometry of samples embedded in a matrix of bacterial proteins. The inocolum of *N. gonorrhoeae* was prepared from an overnight culture using a DensiCHEK™ Plus densitometer (BioMerieux, France), the optical density of the inoculums was 0.5 MacFarland standard, which corresponds to 1 x 10^8 CFU/mL. The inocolum dose of *N. gonorrhoeae* was 5.0 x 10^5 CFU/mL. The plates were incubated at 37 °C at a CO_2 concentration of 5.0% in a wet chamber of a MCO-15AC CO_2 incubator (Sanyo, Japan). The results were visually assessed within 24 h using a Leica MZ 16 stereomicroscope equipped with a DFC 420 digital camera and the Image Manager IM 50 software (Leica Microsystems, Germany).

The criteria for interpretation of the results were as follows: the concentrations of the tested compound in the well, in which growth retardation of *N. gonorrhoeae* colonies was observed, corresponds to the MIC of the tested compound against this strain.

The antibacterial activity of 3-aminophenols against *N. gonorrhoeae* was evaluated by the serial two-fold agar dilution method (gold standard).[4] The agar-based nutrient medium Complegon supplemented with a 1% growth additive (Russia, registration certificate number FSR 2007/00163) was used as the culture medium. The liquid state of the medium was maintained by heating (52 °C) in a WB-4 MS water bath (BioSan, Latvia). Serial two-fold agar dilutions were prepared in sterile 24-well flat-bottomed plates (Sarstedt, Germany). For each compound, at least 12 dilutions were prepared; the final concentration range was 250.0 - 0.122 μg/mL. The stock solution of the tested compounds (10 mg/mL) was prepared in DMSO; the working solution (5 mg/mL) and a series of two-fold dilutions were prepared in sterile distilled water for injection. Nine parts of the agar-based culture medium and one part of a ten-fold diluted solution of 3-aminophenol were aseptically added to plate wells and then thoroughly mixed using a TS-100 thermoshaker (BioSan, Latvia). The DMSO and water content of the culture medium was 2.5 - 0.012%, which had no effect on the growth properties of *N. gonorrhoeae*. Each series of experiments included two control experiments: the control of the growth of the culture inoculum (K+) and the control of the purity of the culture medium (K–).[41] Spectinomycin (Sigma-Aldrich, USA; 102K05447V) was used as the reference.

X-ray Analysis

The XRD analyses were accomplished on a "Xcalibur 3" diffractometer on standard procedure (graphite monochromator, ω-scans with 1° step). Empirical absorption correction was applied. Using Olex2,[5] the structure was solved with the ShelXS structure solution program using Direct Methods and refined with the ShelXL[6] refinement package using Least Squares minimization. All non-hydrogen atoms were refined in the anisotropic approximation; H-atoms of the OH- and NH-groups were localized from the electron density peaks and refined independently, H-atoms at the C-H bonds were refined in the "rider" model with dependent displacement parameters. Results of the refinement are summarized in the Table S2. CCDC – 1887247 (for **4aae**) and – 1887248 (for **8**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

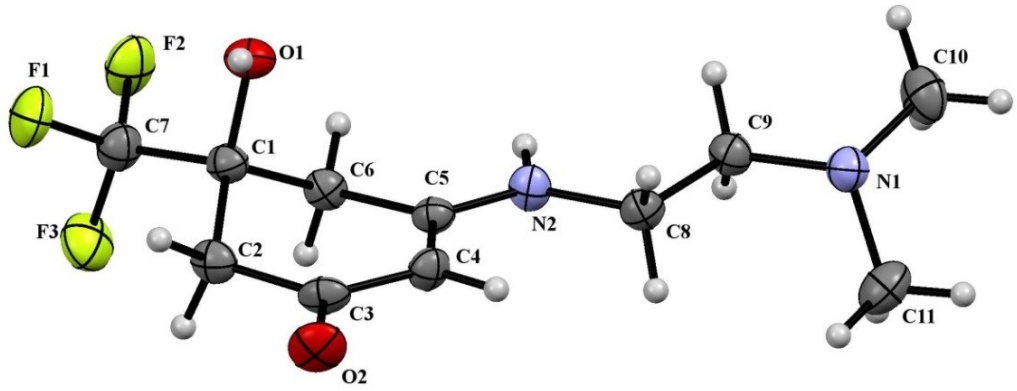


Fig. S1 ORTEP drawing of compound **4aae** showing thermal ellipsoids at the 50% probability level.

According to XRD data, the compound **4aae** is crystallized in the centrosymmetric space group. General geometry of the molecule is shown on the Fig. S1. The N(1) atom has a typical sp^3-hybridized non-planar configuration and deviated from the plane C(9)C(10)C(11) on 0.489 Å. N(2) atom is placed in the anti-periplanar configuration toward N(1) and has a conjugated with O(2)=C(3)-C(4)=C(5) moiety planar configuration. As a result, the N(2)-C(5) bond (length 1.333(3) Å) much lesser than N(2)-C(8) bond (length 1.448(3) Å). The cyclohexenyl moiety has a configuration "sofa". The atoms C(2)C(3)C(4)C(5)C(6) are deviated from its least-squared plane less than 0.05 Å, C(1) atom is deviated from its plane on the distance 0.643 Å with (pseudo) axial placed OH-group. The crystal packing is ordered by intermolecular H-bonds (Table S1). The H-bonds O(1)H…N(1) form the centrosymmetric intermolecular dimers of the molecules and N(2)H…O(2) H-bonds form a layers of the molecules, oriented along 0a axis.

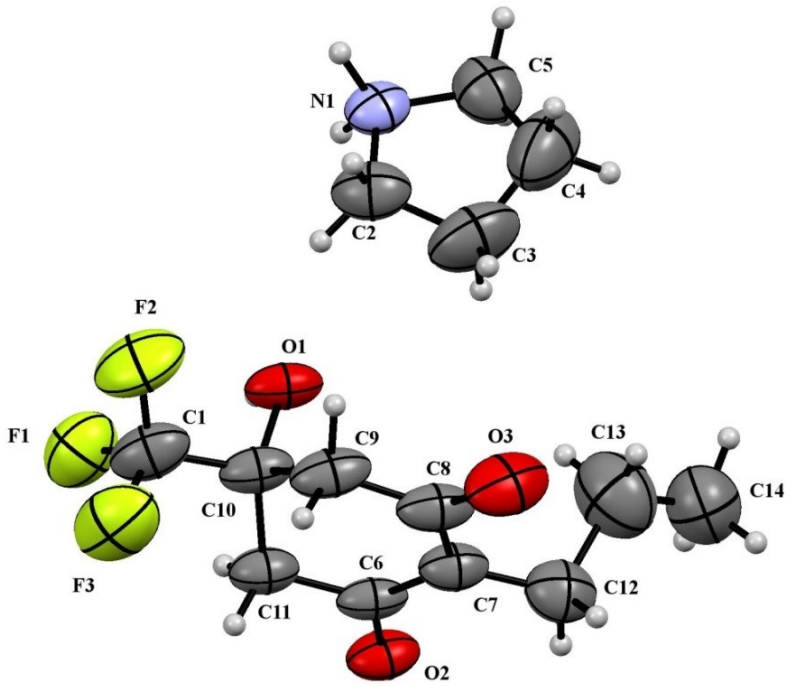


Fig. S2 ORTEP drawing of compound **8**. The disordering of the alkyl substituent is omitted for clarity**.**

According to XRD data, the compound **8** is crystallized in the centrosymmetric space group of the monoclinic system. General geometry of the molecule is shown on the Fig. S2. The alkyl substituent C_3H_7 demonstrates the strong disordering of the atomic positions and restraints for its anisotropic displacement parameters and interatomic distances were applied. The cyclohexenyl moiety has a configuration "sofa". The atoms C(6)C(7)C(8)C(9)C(11) are deviated from its least-squared plane less than 0.03 Å, C(10) atom is deviated from its plane on the distance 0.627 Å with (pseudo) axial placed OH-group. The bond C(6)-C(7) and C(7)-C(8) lengths are near in the magnitude and show strong delocalization of the charge in the carbanion. The measured C=O bonds lengths (1.255–1.275 Å) also indicate the participation of the carbonyl groups in the delocalization of the anionic charge. The asymmetry in the bond distances of the symmetrical anion may be explained by asymmetry of the intermolecular surrounding. Both H-atoms in the NH_2^+ group of the pyrrolydinic cation are bonded with anionic parts by intermolecular H-bonds (Table S1). These H-bonds form layer of the molecules along 0a axis. Additional centrosymmetric H-bonds O(1)H…O(2) form dimers from these layers providing mean motif of the crystal packing.

Table S1 Hydrogen bonds with H..A < r(A) + 2.000 Å and <DHA > 110°.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
4aae					
O1-H17	0.95(4)	1.83(4)	170(2)	2.772(3)	N1 [-x, -y+1, -z+2]
N2-H2	0.93(3)	1.89(3)	171(2)	2.817(3)	O2 [x+1, y, z]
8					
N1-H1N	0.94(4)	1.85(4)	172(2)	2.784(4)	O2 [x-1, y, z-1]
N1-H2N	1.04(3)	1.69(3)	153(3)	2.656(4)	O3 [x, y, z-1]
O1-H1	0.89(4)	1.83(4)	166(3)	2.694(4)	O2 [-x, -y+1, -z]

Table S2 Crystal data and structure refinement.

	4aae	**8**
Empirical formula	$C_{11}H_{17}F_3N_2O_2$	$C_{14}H_{22}F_3NO_3$
Formula weight	266.27	309.33
Wavelength, Å	0.71073 (MoKα)	0.71073 (MoKα)
T, K	145(2)	295(2)
Crystal system	Triclinic	Monoclinic
Space group	P-1	$P2_1/c$
a, Å	7.0958(6)	9.1257(9)
b, Å	8.4262(7)	21.064(2)
c, Å	11.3160(8)	8.9372(10)
α, °	87.424(6)	90
β, °	82.903(6)	117.891(14)
γ, °	75.668(7)	90
Volume, Å^3	650.44(9)	1518.4(3)
Z	2	4
D_{calk}, g/cm^3	1.360	1.353
μ, mm^{-1}	0.122	0.118
F(000)	280	656
Θ range for data collection	3.63 < Θ < 30.80°	3.85 < Θ < 30.93°
Reflections collected	5313	9806
Independent reflections	3488 (R_{int} = 0.0399)	4151 (R_{int} = 0.0360)
Goodness-of-fit on F^2	1.002	1.003
R_1 [I>2σ(I)]	0.0646	0.0666
wR_2 [I>2σ(I)]	0.1552	0.1804
R_1 (all data)	0.1146	0.1277
wR_2 (all data)	0.2089	0.2429
$\Delta\rho_{\bar{e}}$, ēÅ^{-3}	0.341/-0.322	0.399/-0.210

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4. Clinical and laboratory standards institute. Performance standards for antimicrobial susceptibility testing; twenty-fourth informational supplement; CLSI document M100-S24, Wayne, USA, 2014, p. 226.
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6. G.M. Sheldrick, *Acta Cryst.*, 2008, **A64**, 112.

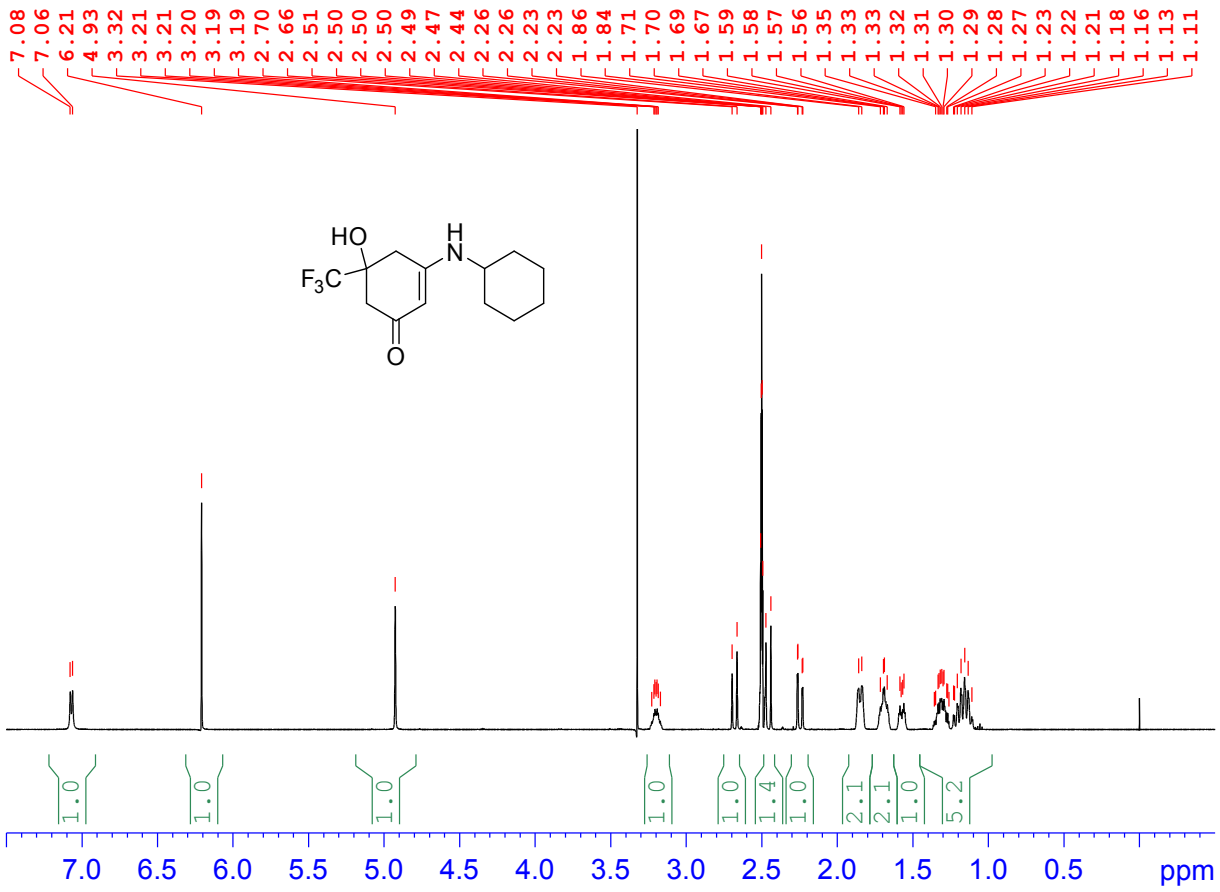

Fig. S4 ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **4aaa**.

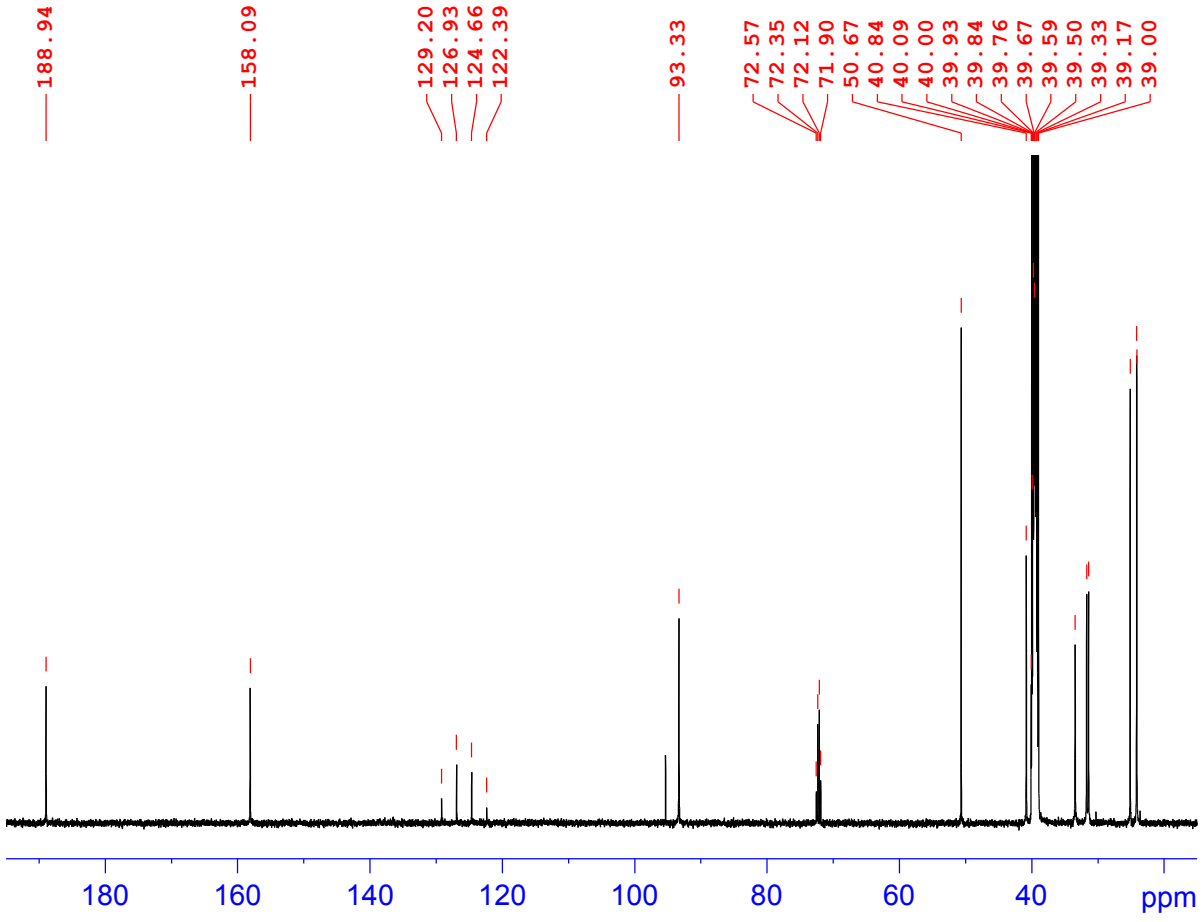

Fig. S5 ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **4aaa**.

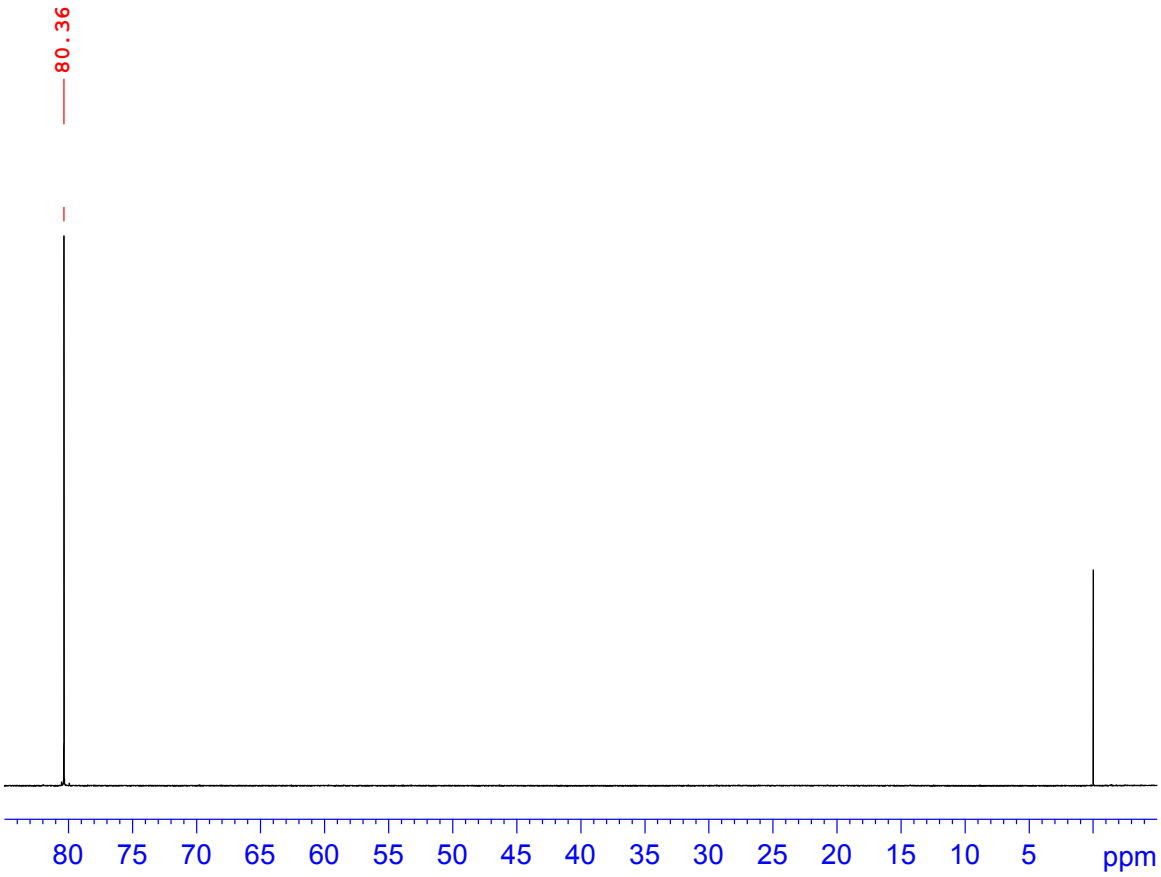

Fig. S6 ^{19}F NMR (470 MHz, DMSO-d_6) spectrum of **4aaa**.

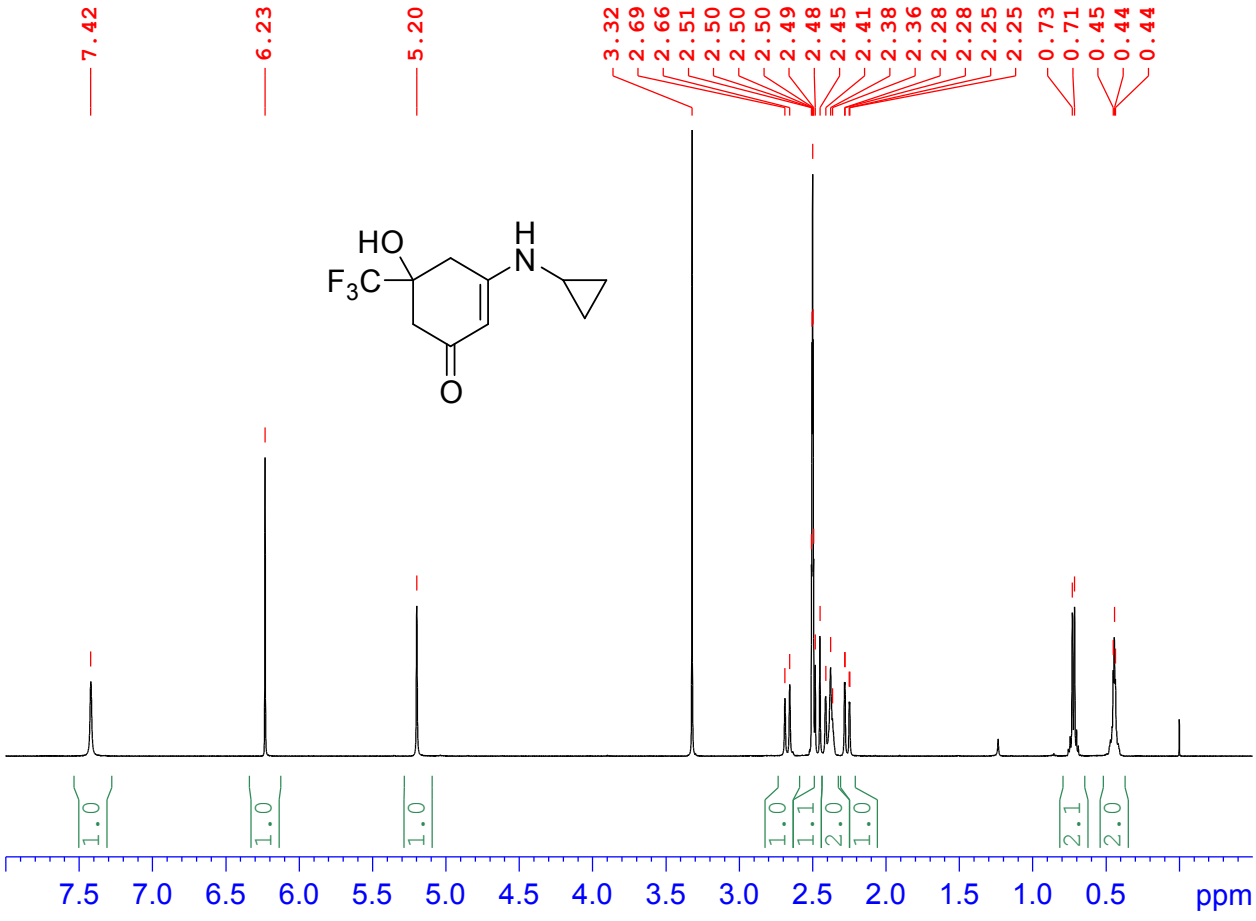

Fig. S7 ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **4aab**.

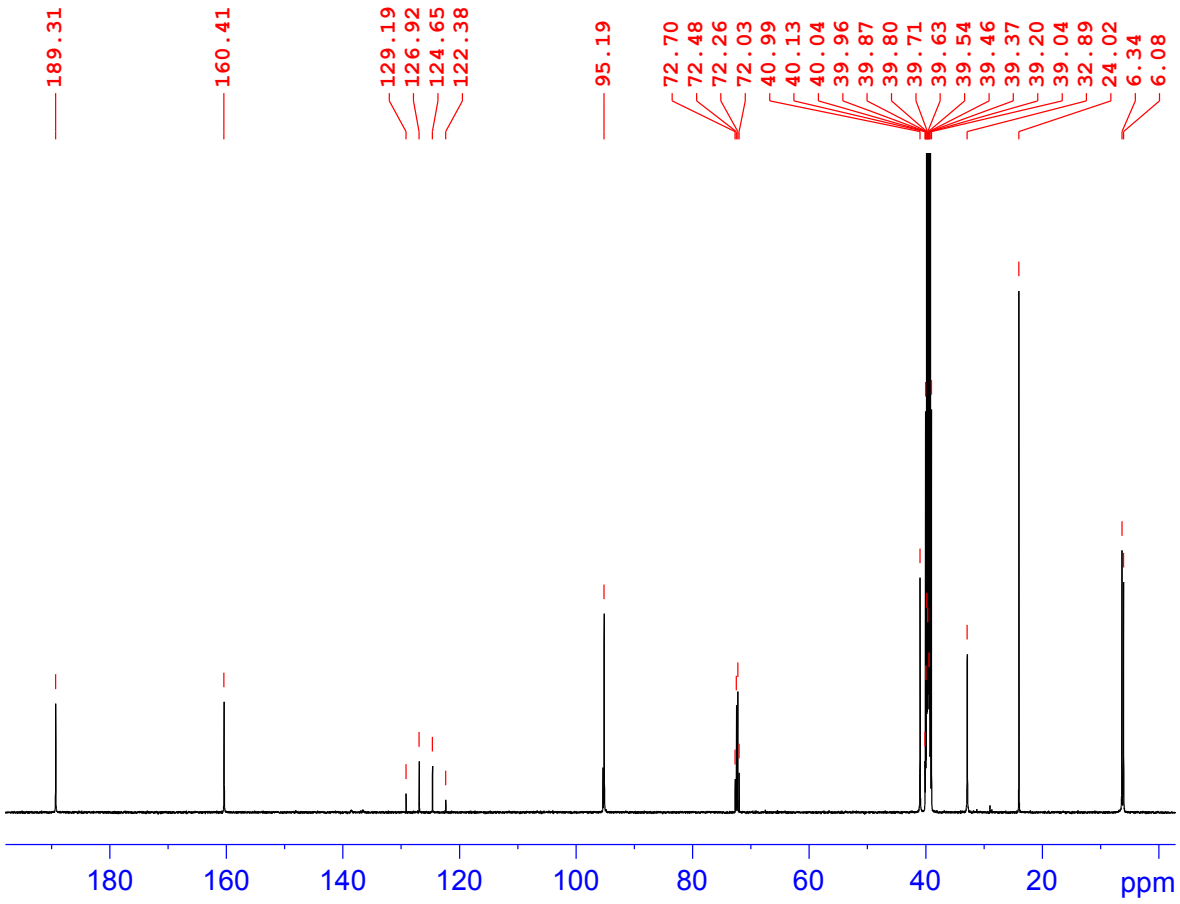

Fig. S8 ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **4aab**.

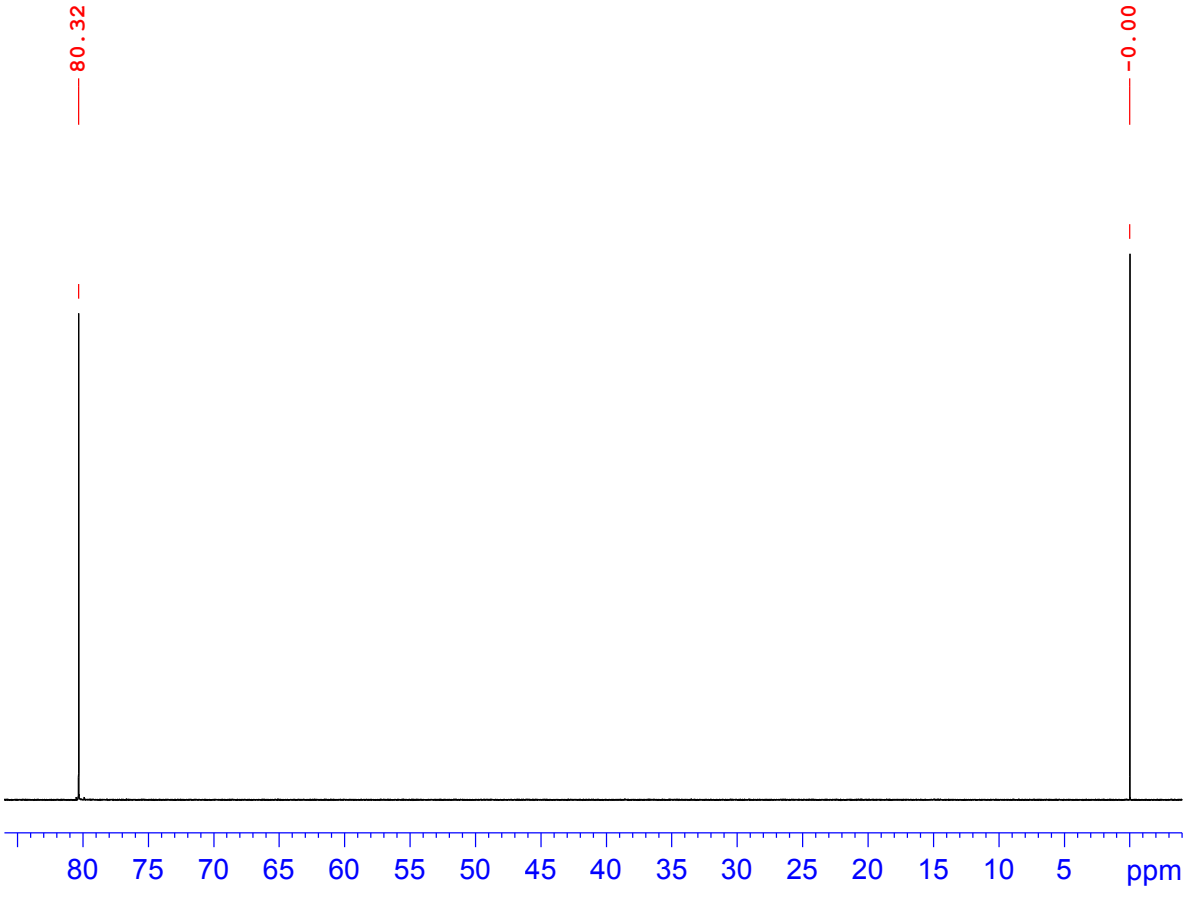

Fig. S9 ^{19}F NMR (470 MHz, DMSO-d_6) spectrum of **4aab**.

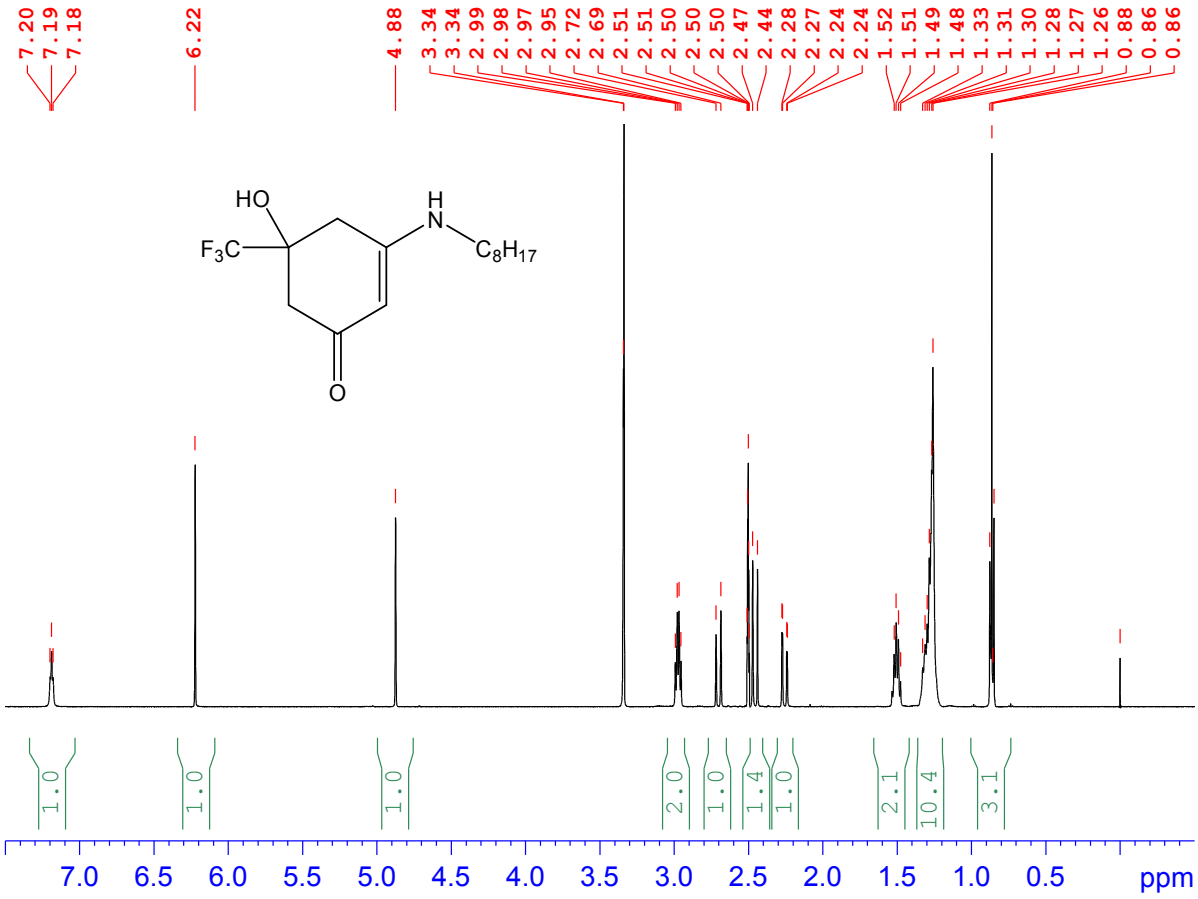

Fig. S10 ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **4aac**.

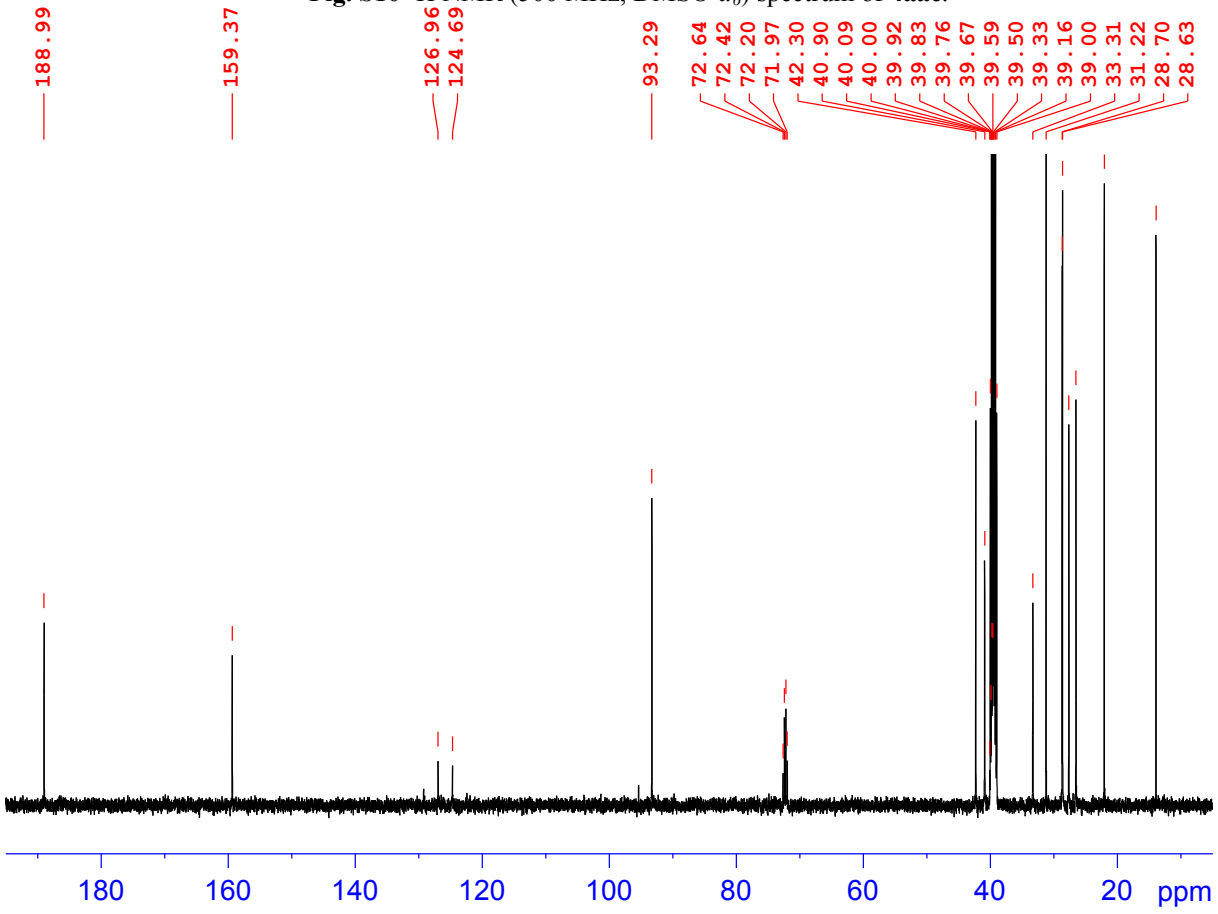

Fig. S11 ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **4aac**.

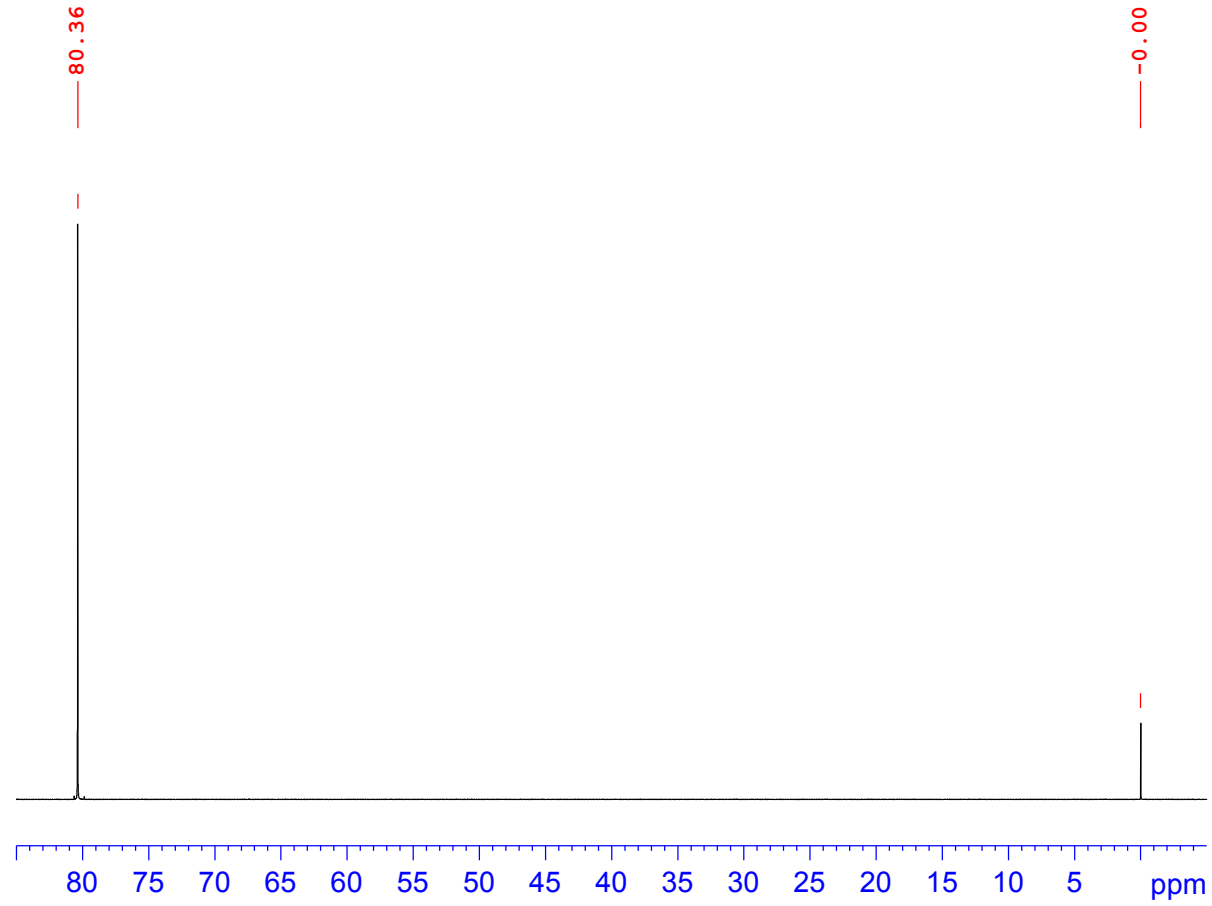

Fig. S12 ^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **4aac**.

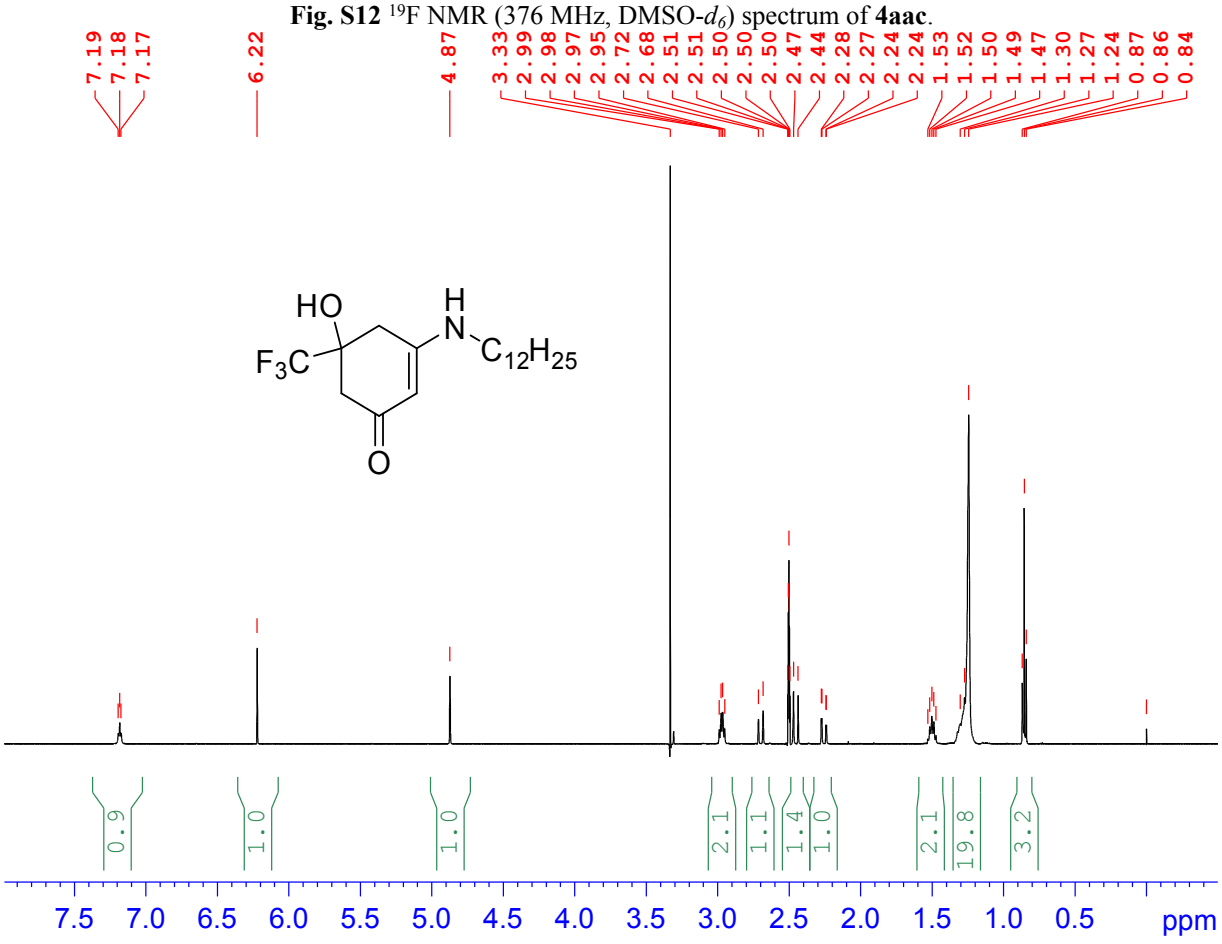

Fig. S13 ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **4aad**.

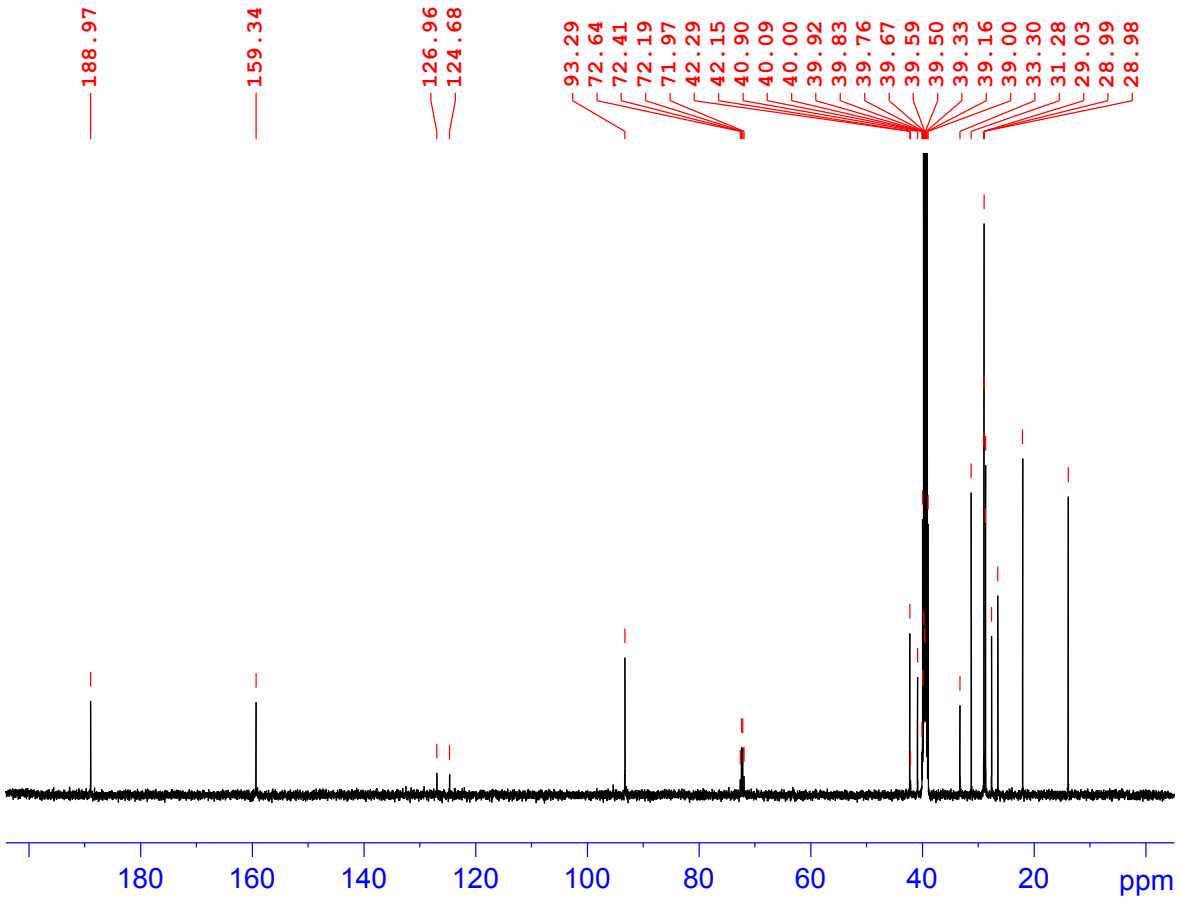

Fig. S14 ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **4aad**.

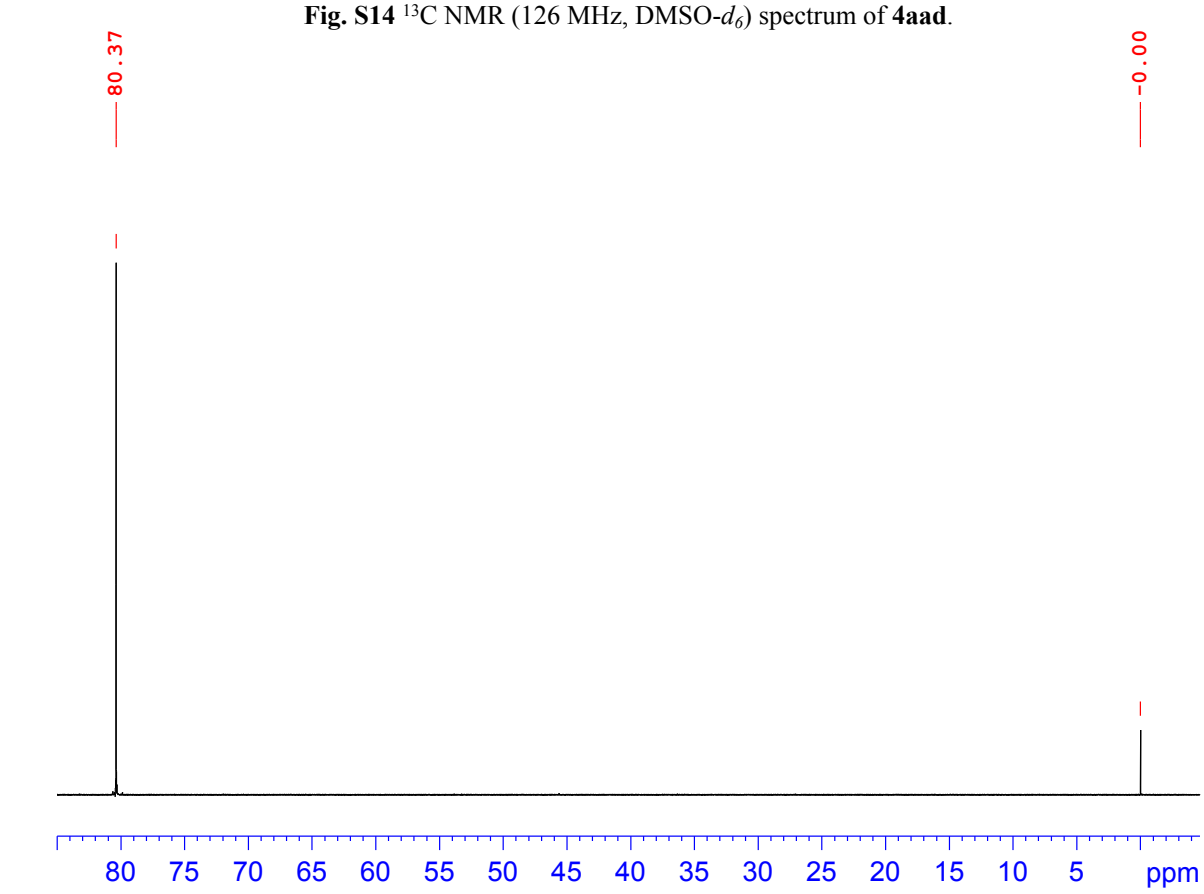

Fig. S15 ^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **4aad**.

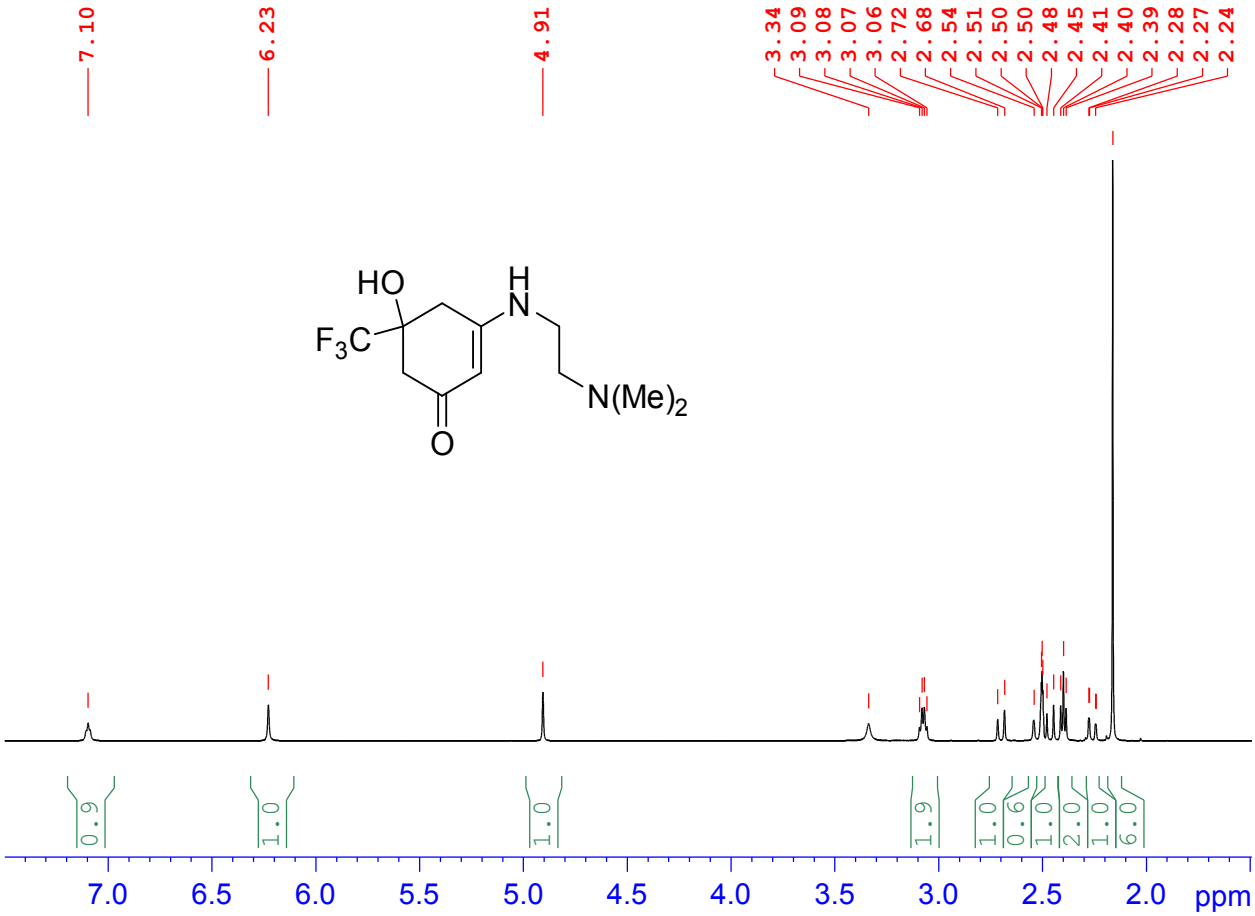

Fig. S16 ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **4aae**.

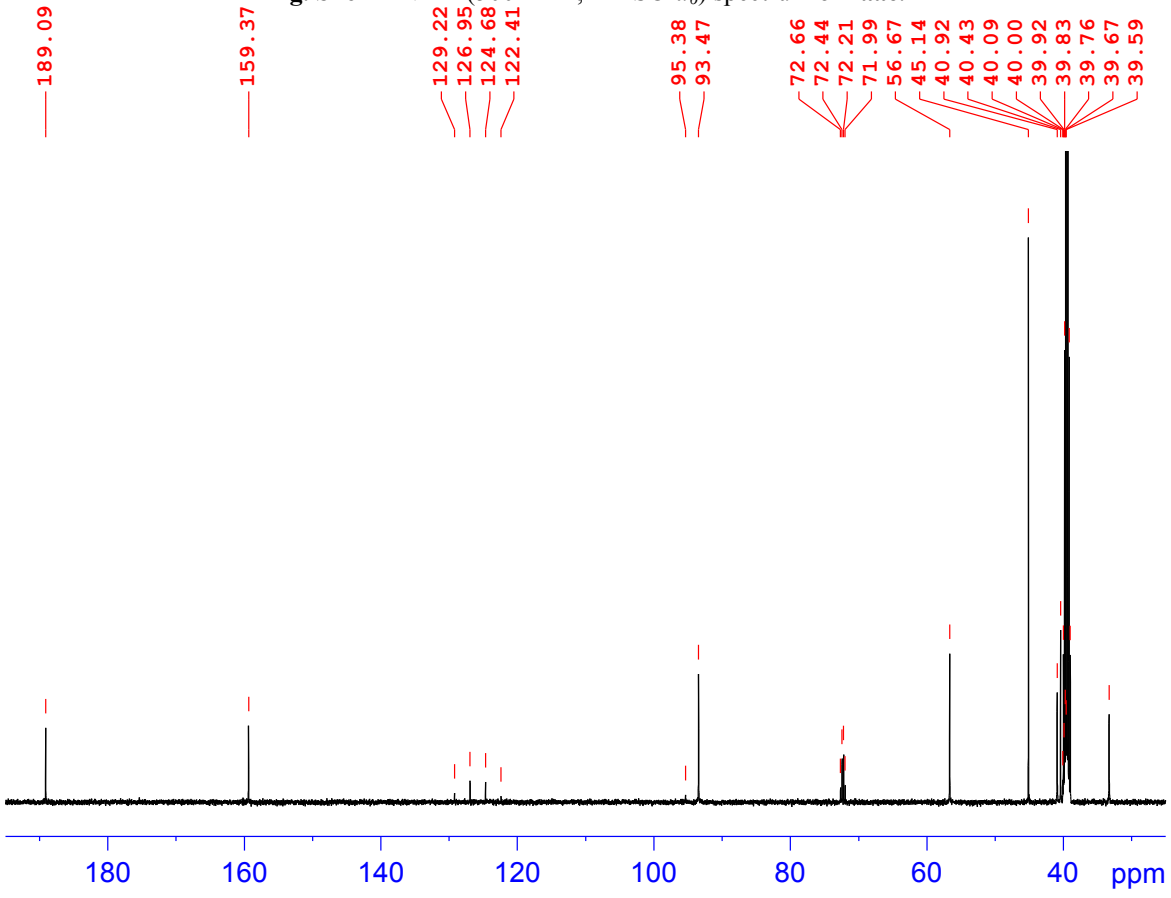

Fig. S17 ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **4aae**.

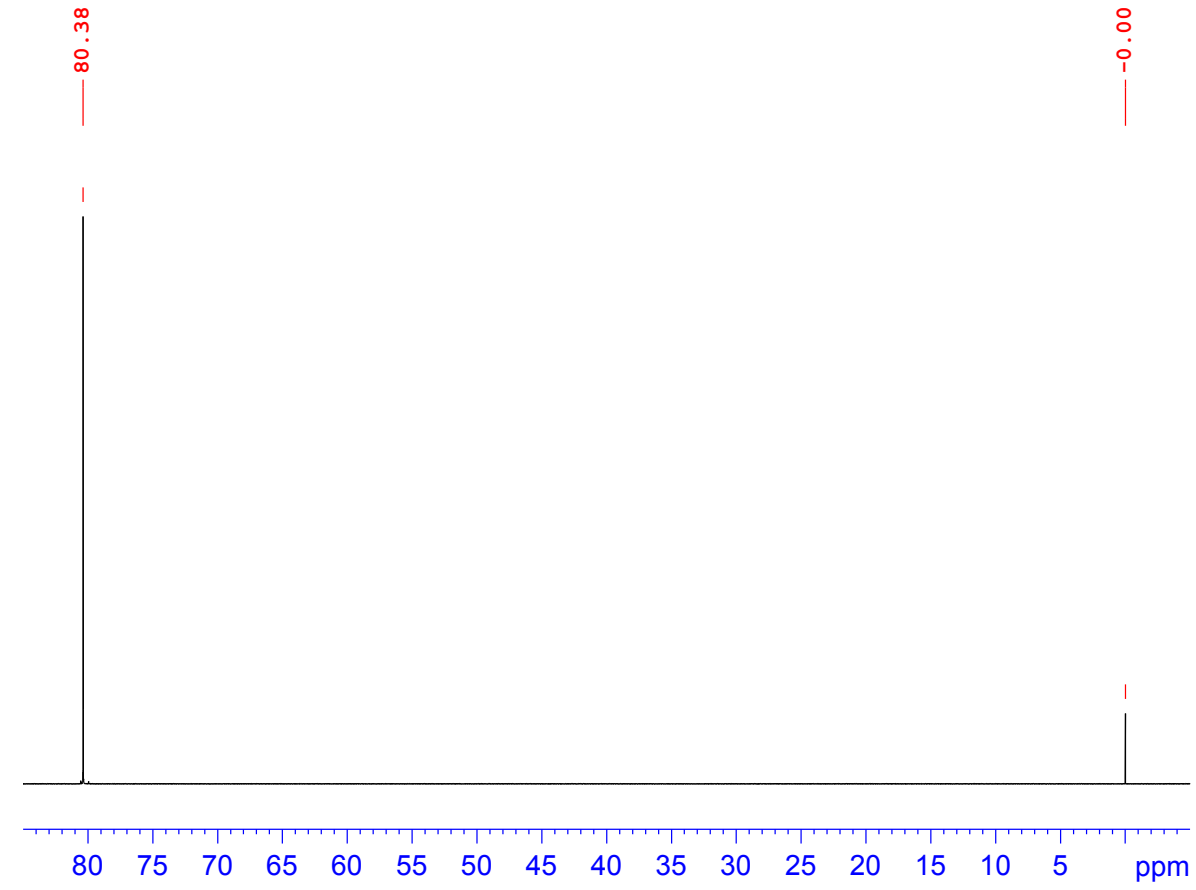

Fig. S18 ^{19}F NMR (470 MHz, DMSO-d_6) spectrum of **4aae**.

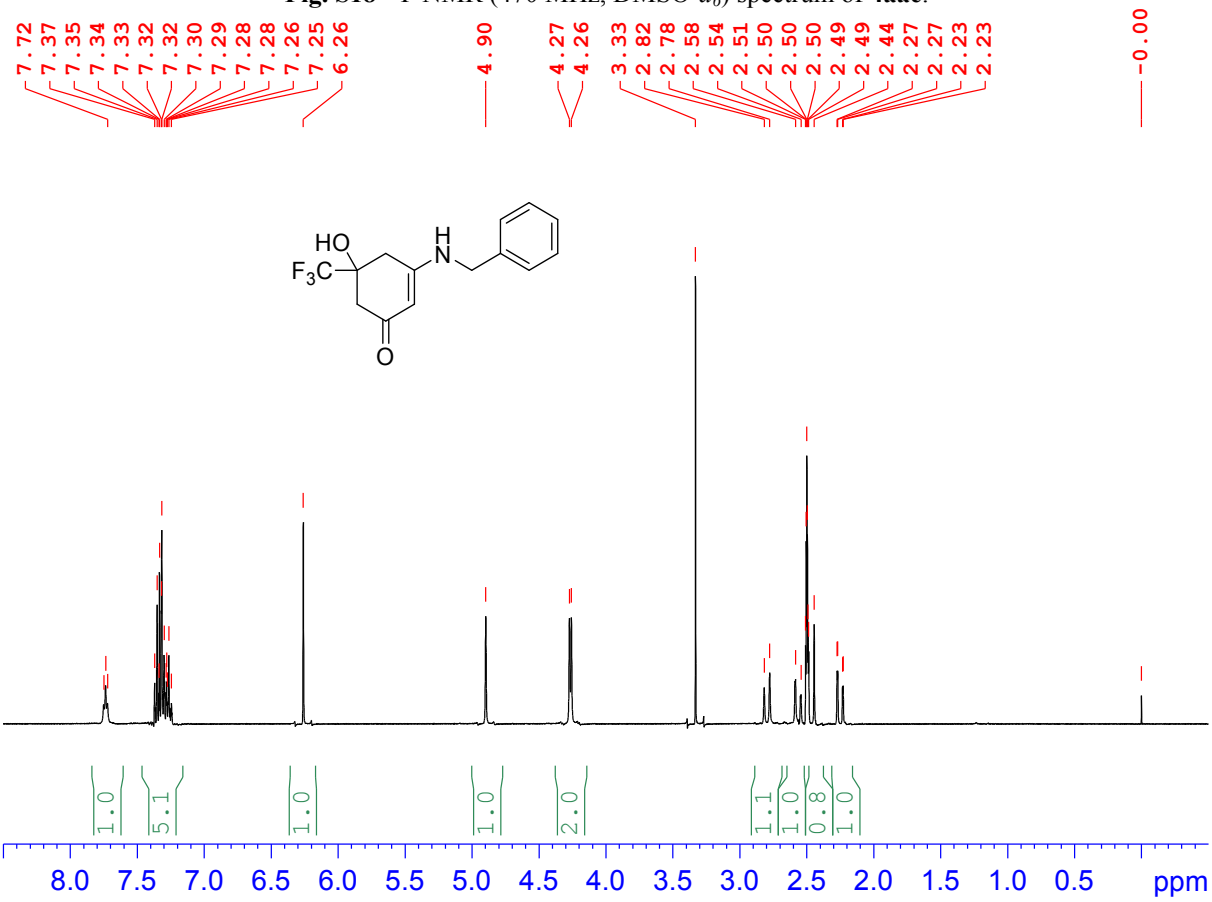

Fig. S19^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **4aaf**.

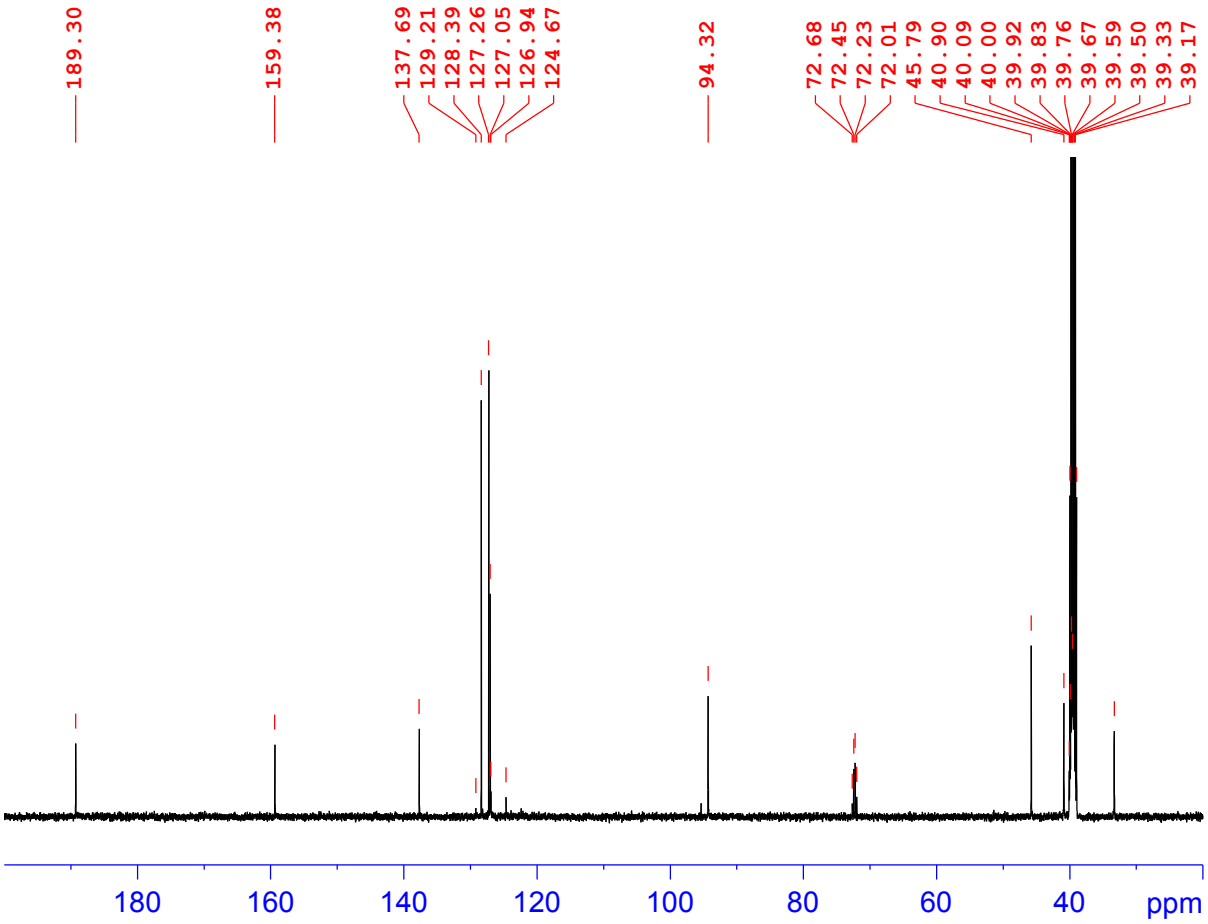

Fig. S20 ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **4aaf**.

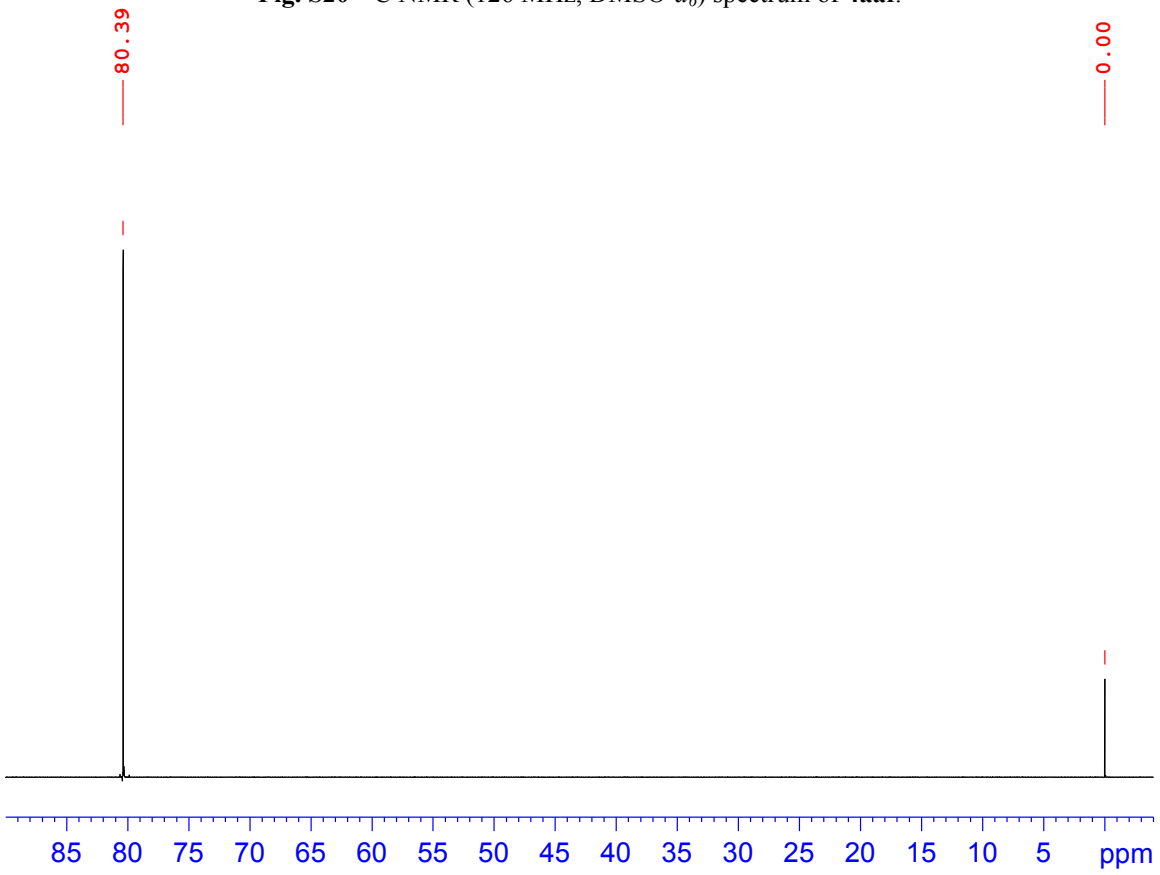

Fig. S21 ^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **4aaf**.

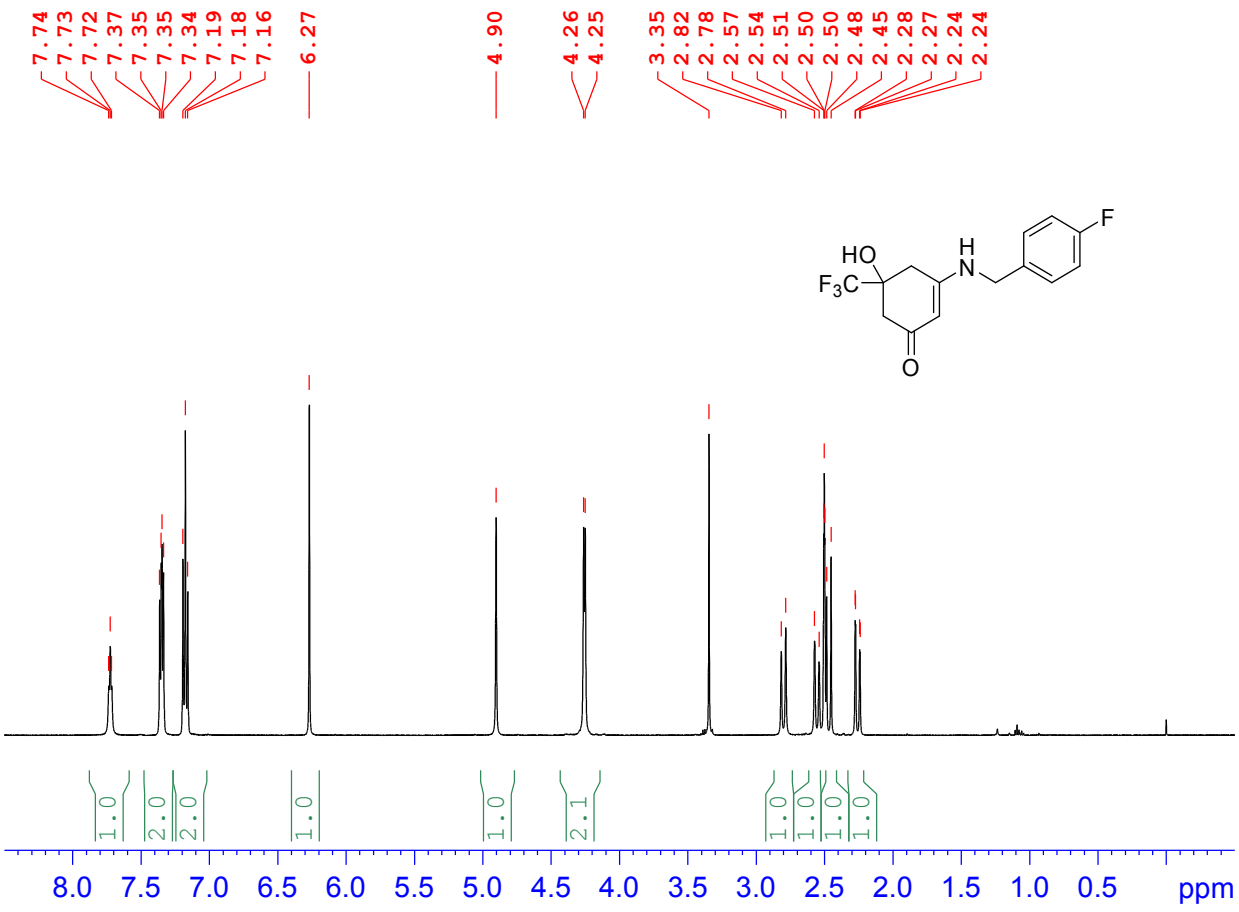

Fig. S22 [1]H NMR (500 MHz, DMSO-d_6) spectrum of **4aag**.

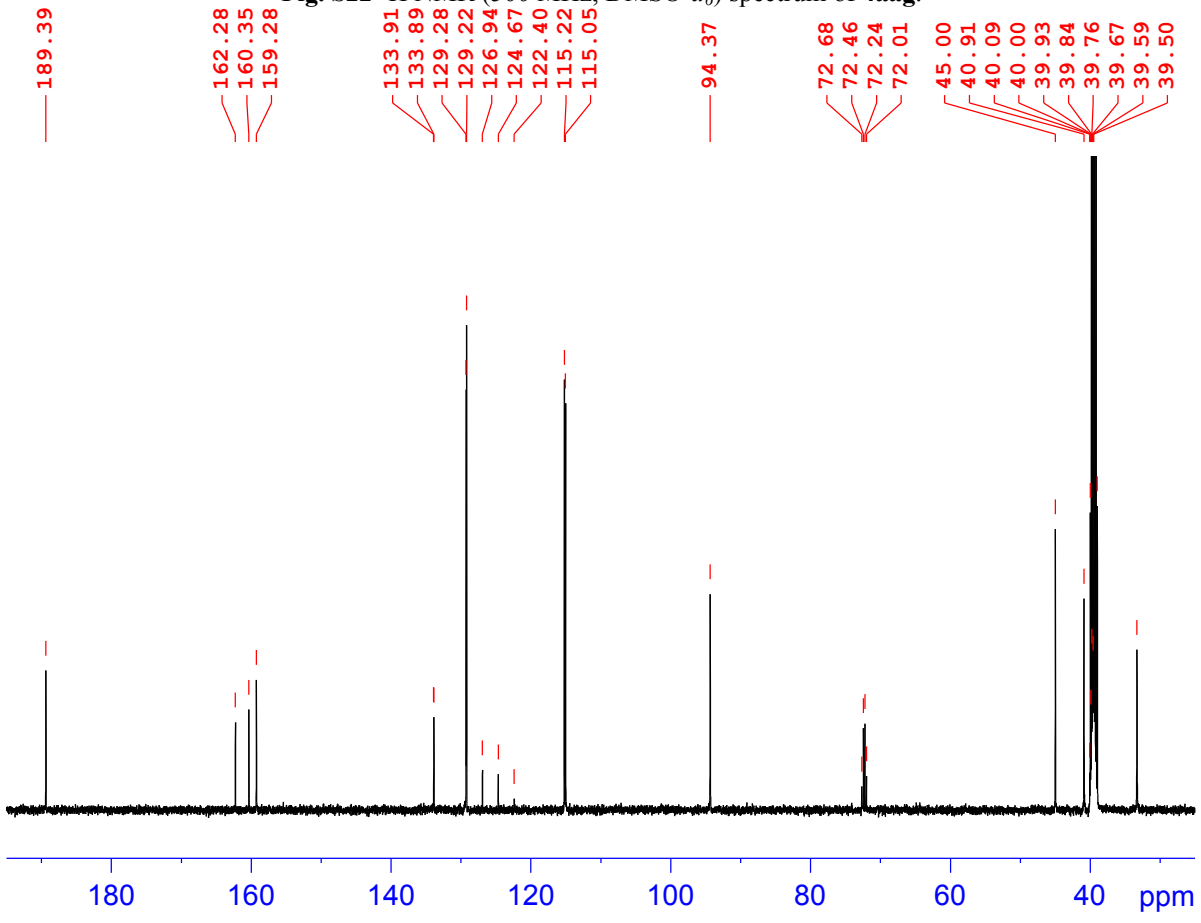

Fig. S23 [13]C NMR (126 MHz, DMSO-d_6) spectrum of **4aag**.

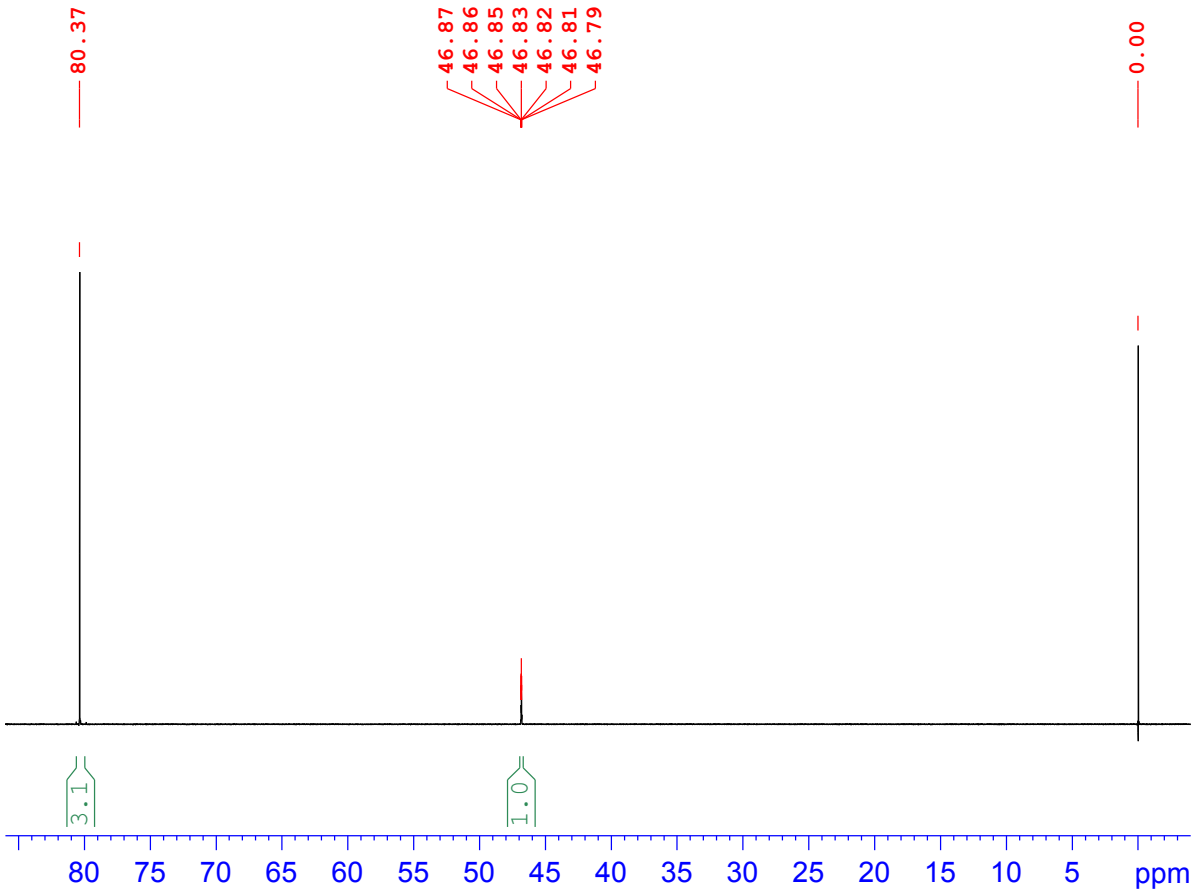

Fig. S24 ^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **4aag**.

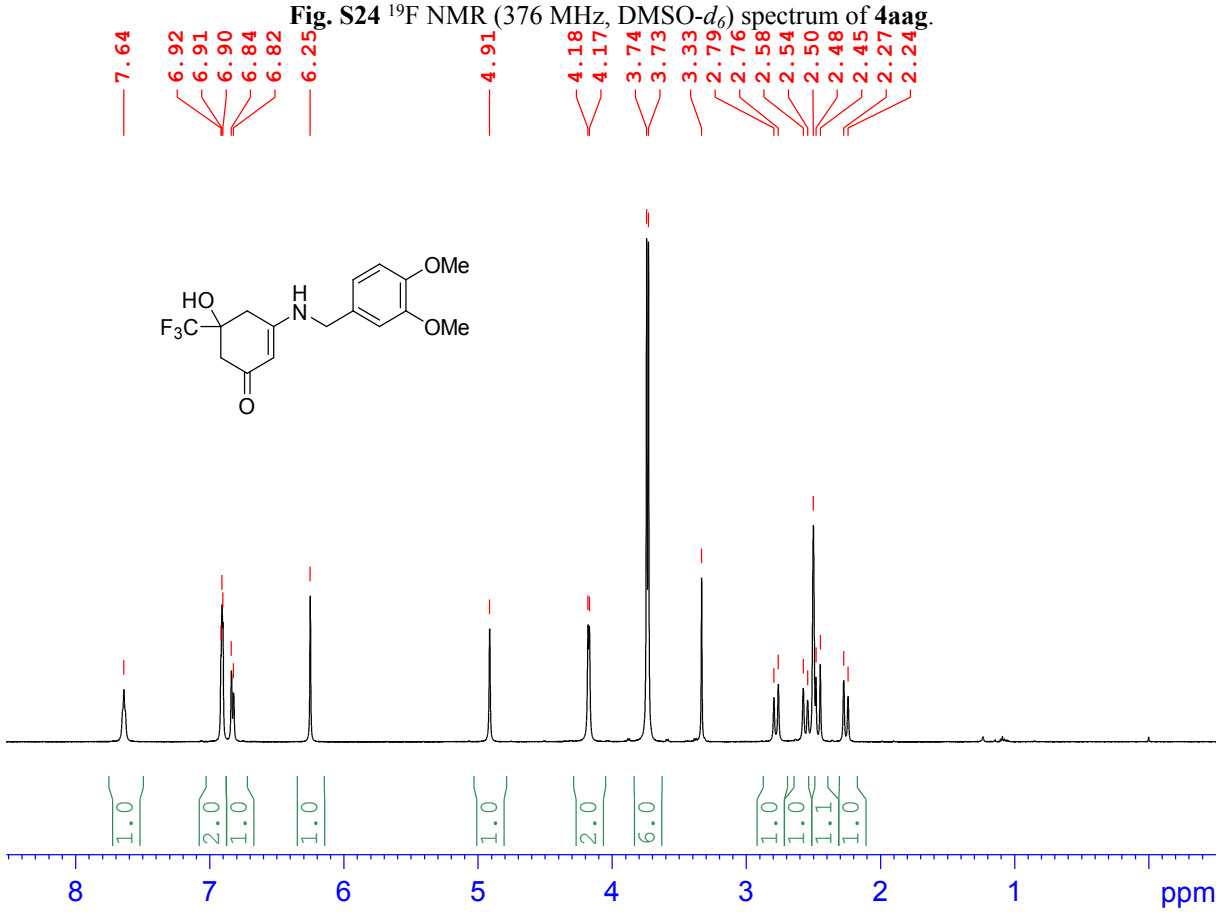

Fig. S25 ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **4aah**.

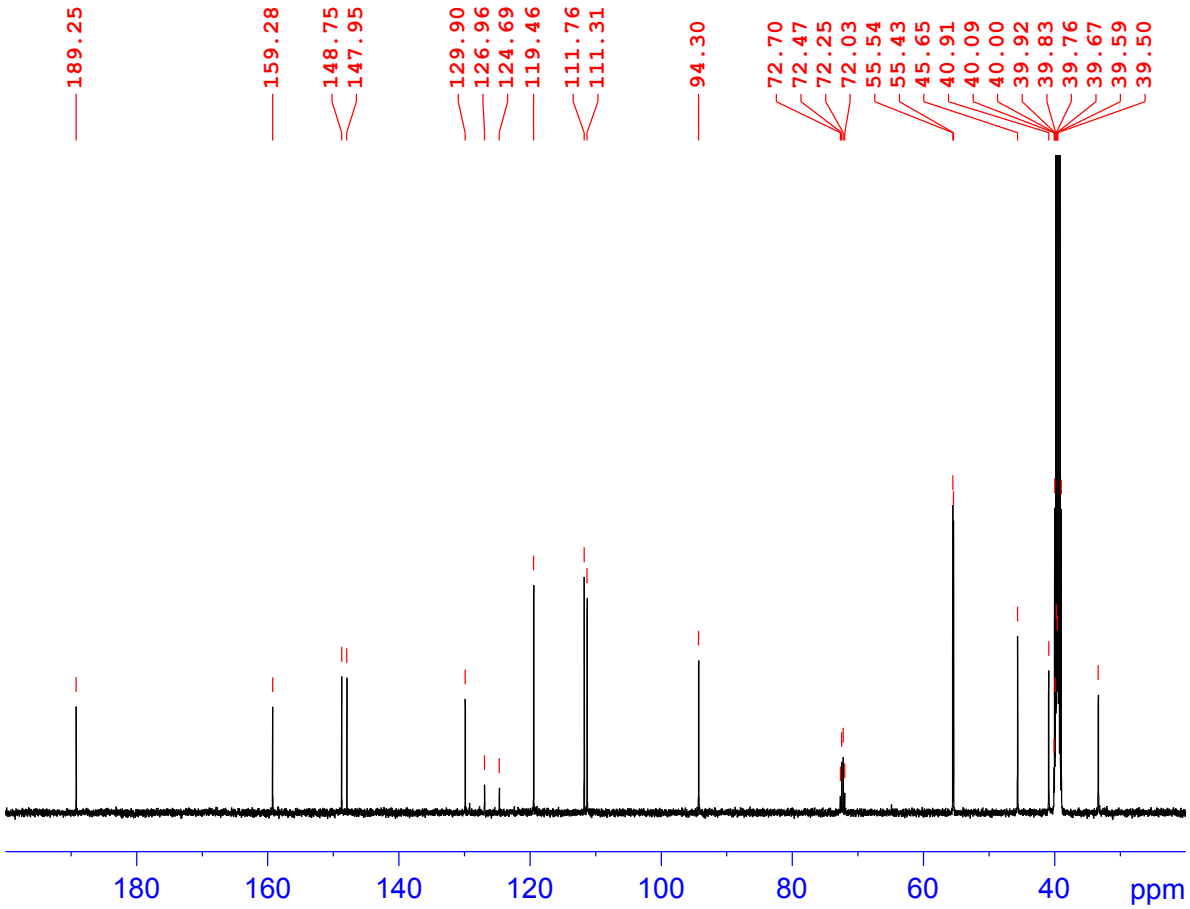

Fig. S26 ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **4aah**.

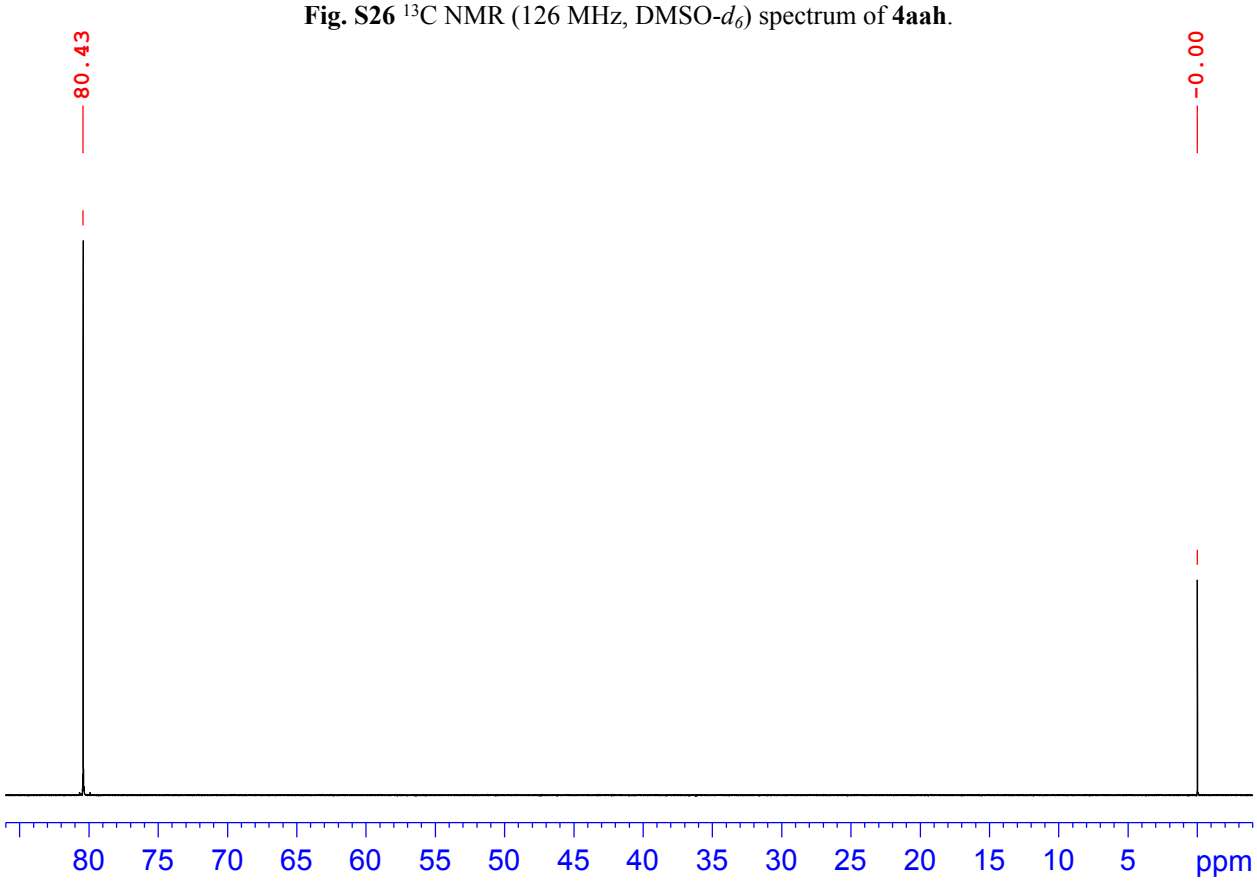

Fig. S27 ^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **4aah**.

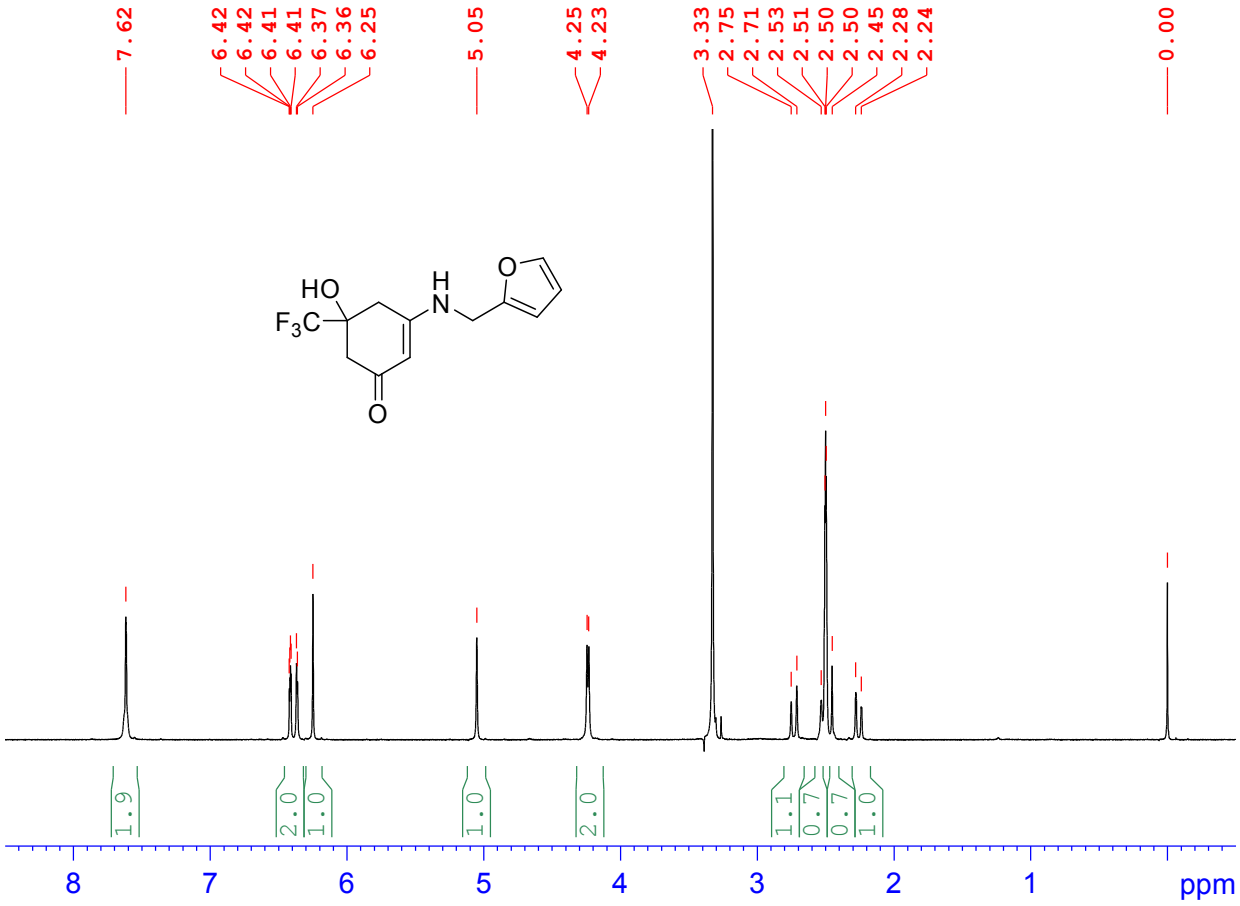

Fig. S28 ^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **4aai**.

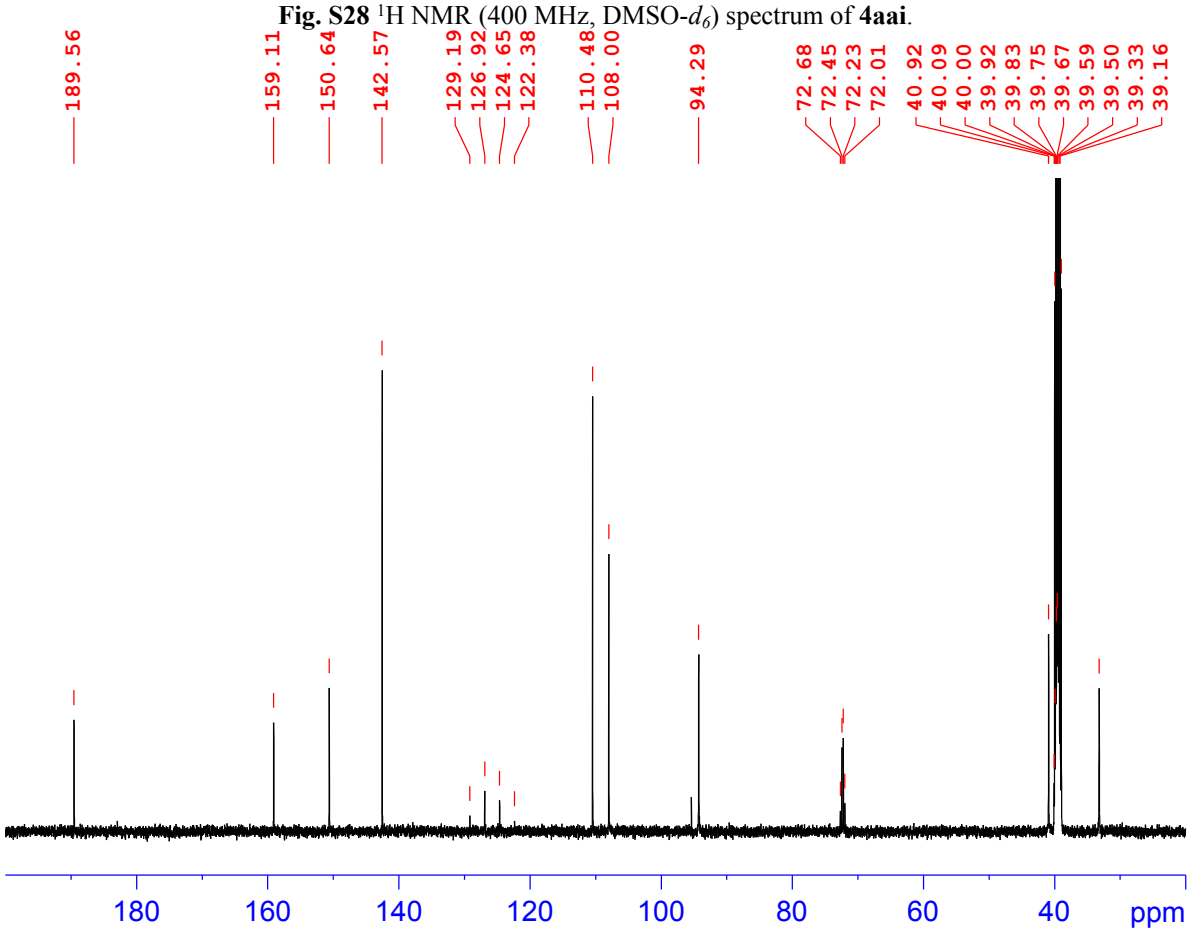

Fig. S29 ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **4aai**.

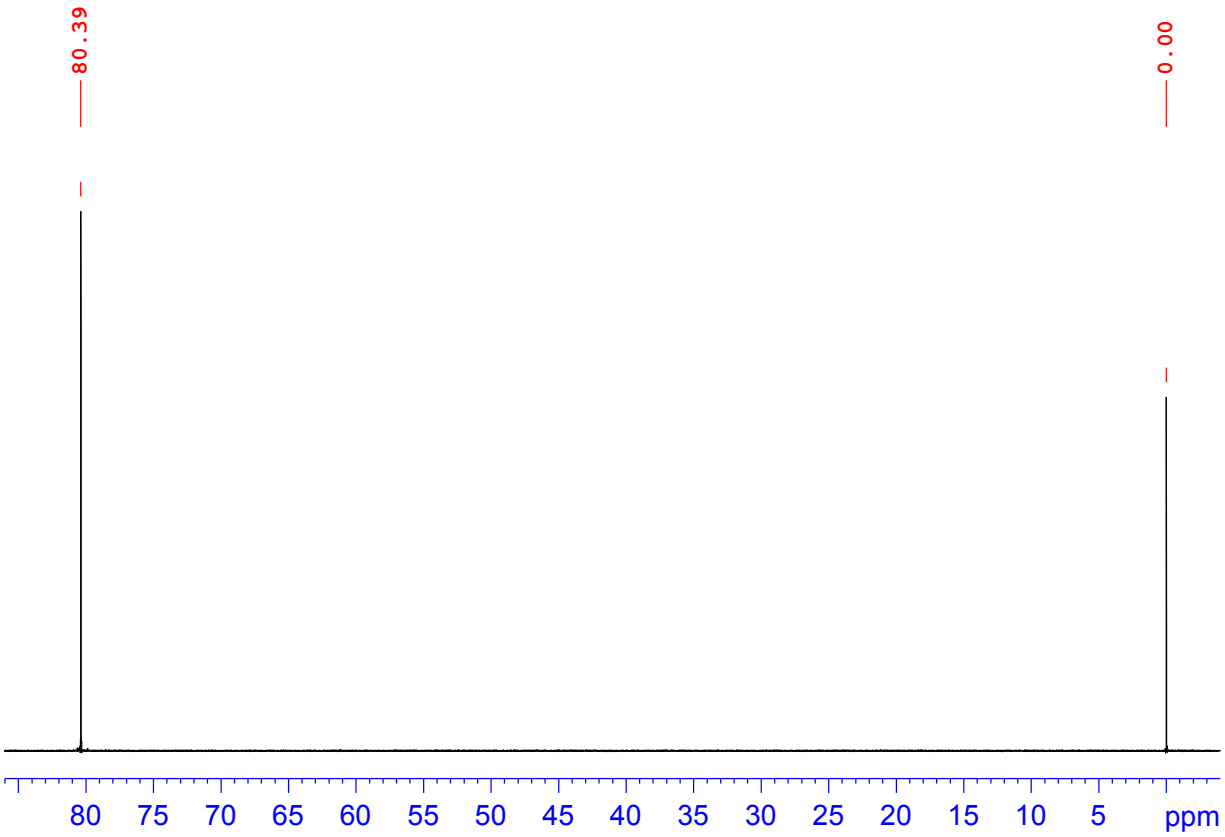

Fig. S30 ^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **4aai**.

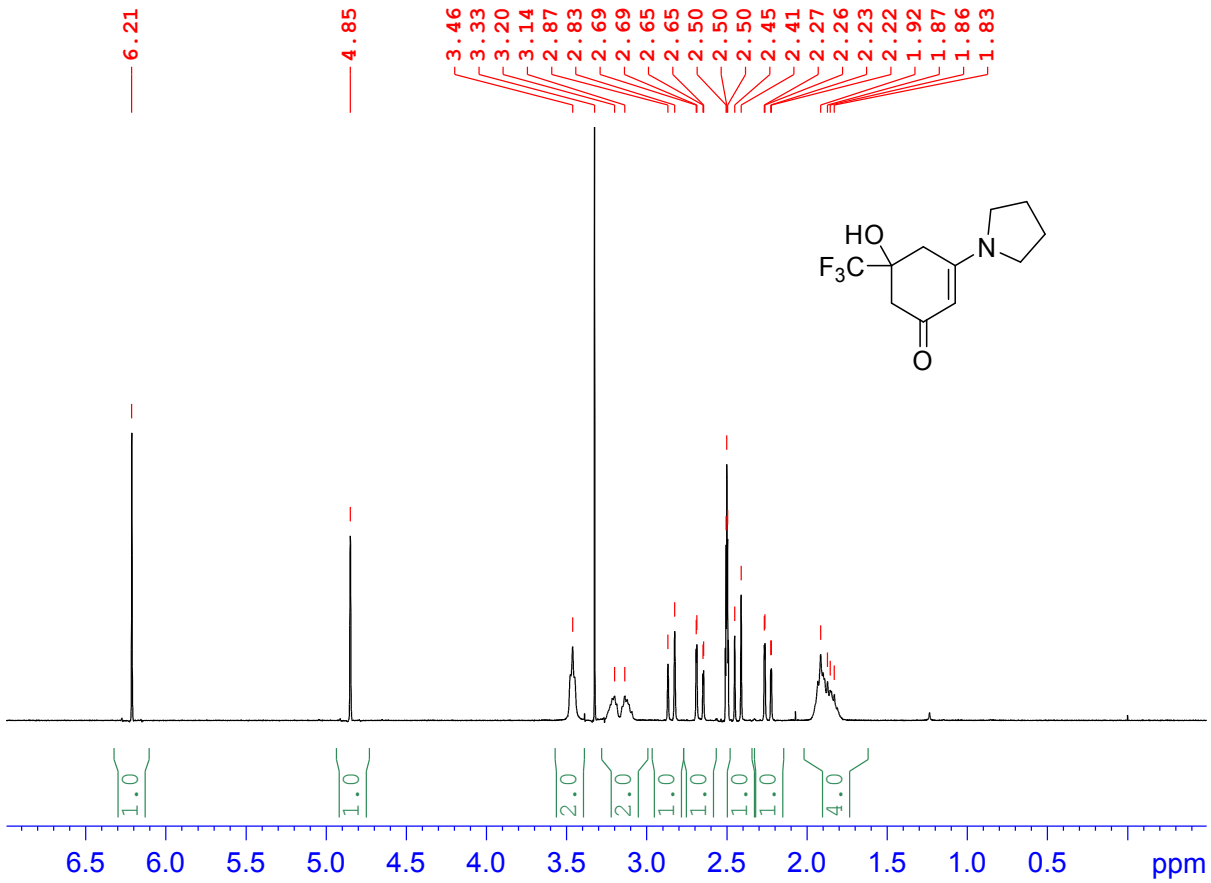

Fig. S31 ^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **4aaj**.

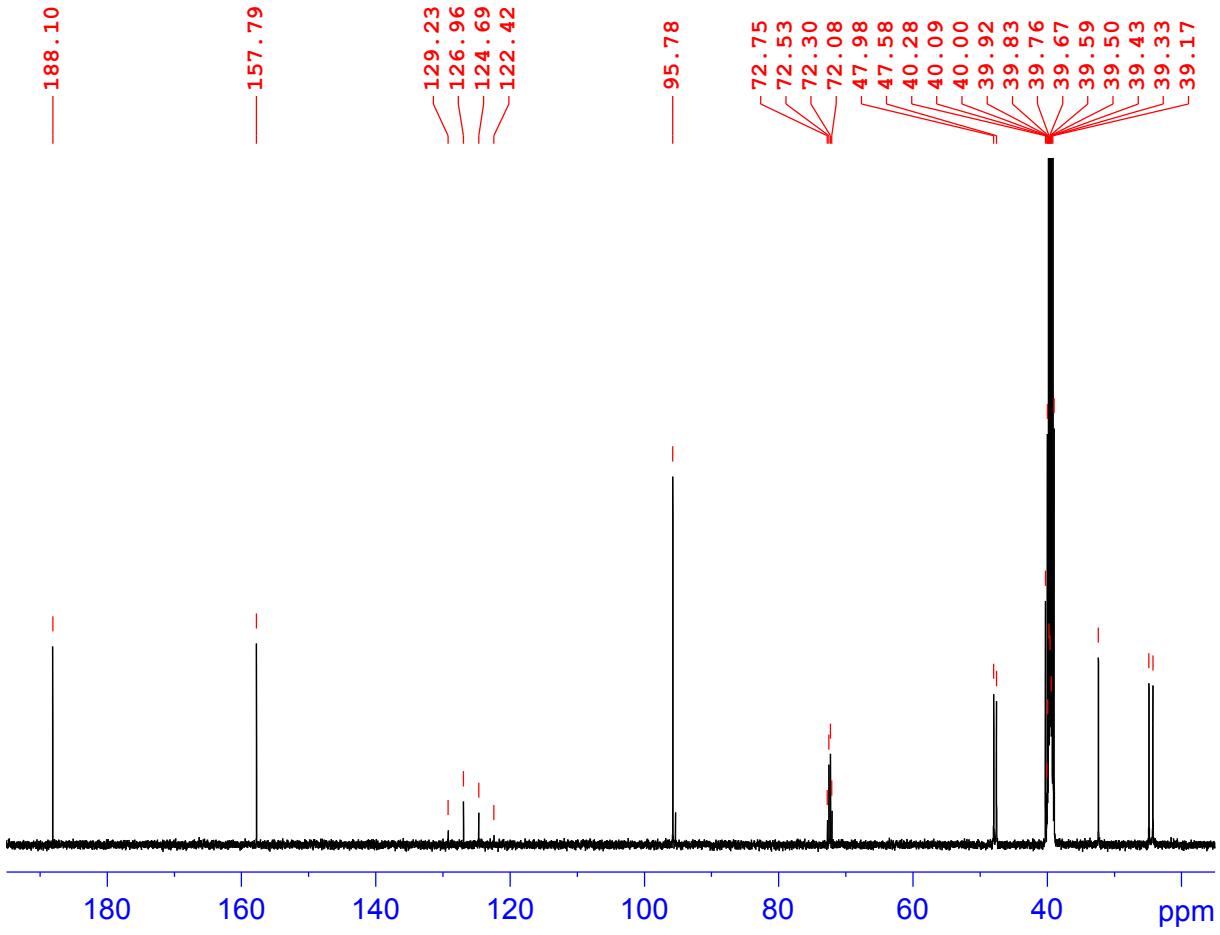

Fig. S32 ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **4aaj**.

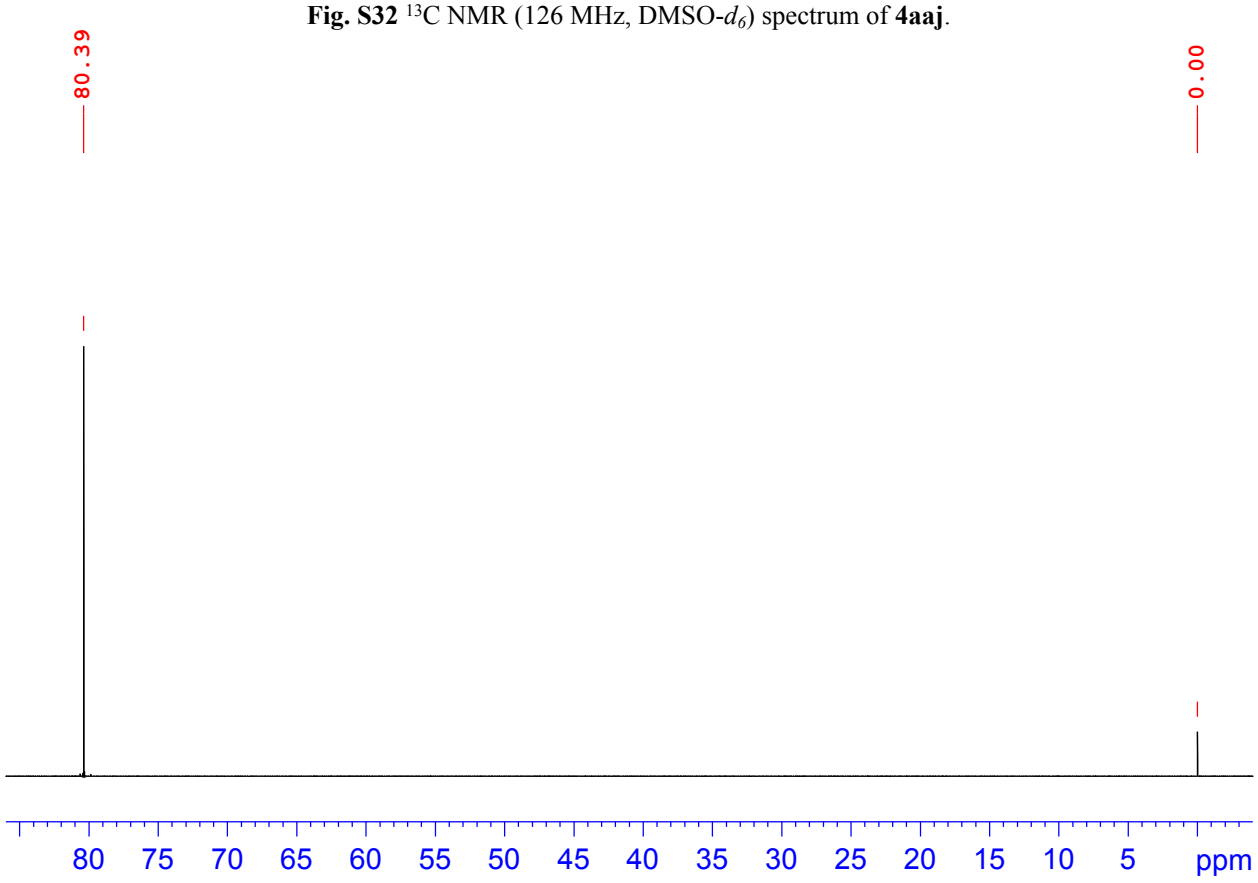

Fig. S33 ^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **4aaj**.

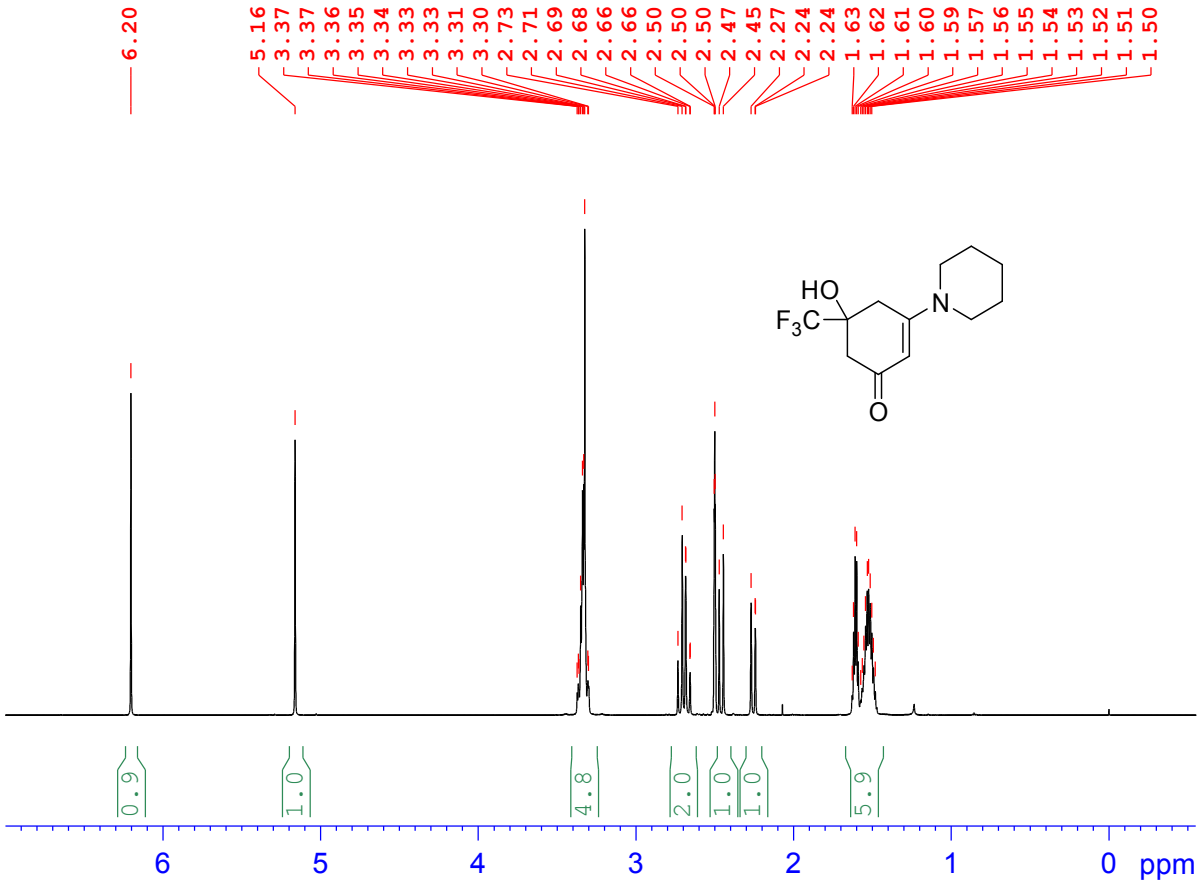

Fig. S34 ^{1}H NMR (600 MHz, DMSO-d_6) spectrum of **4aak**.

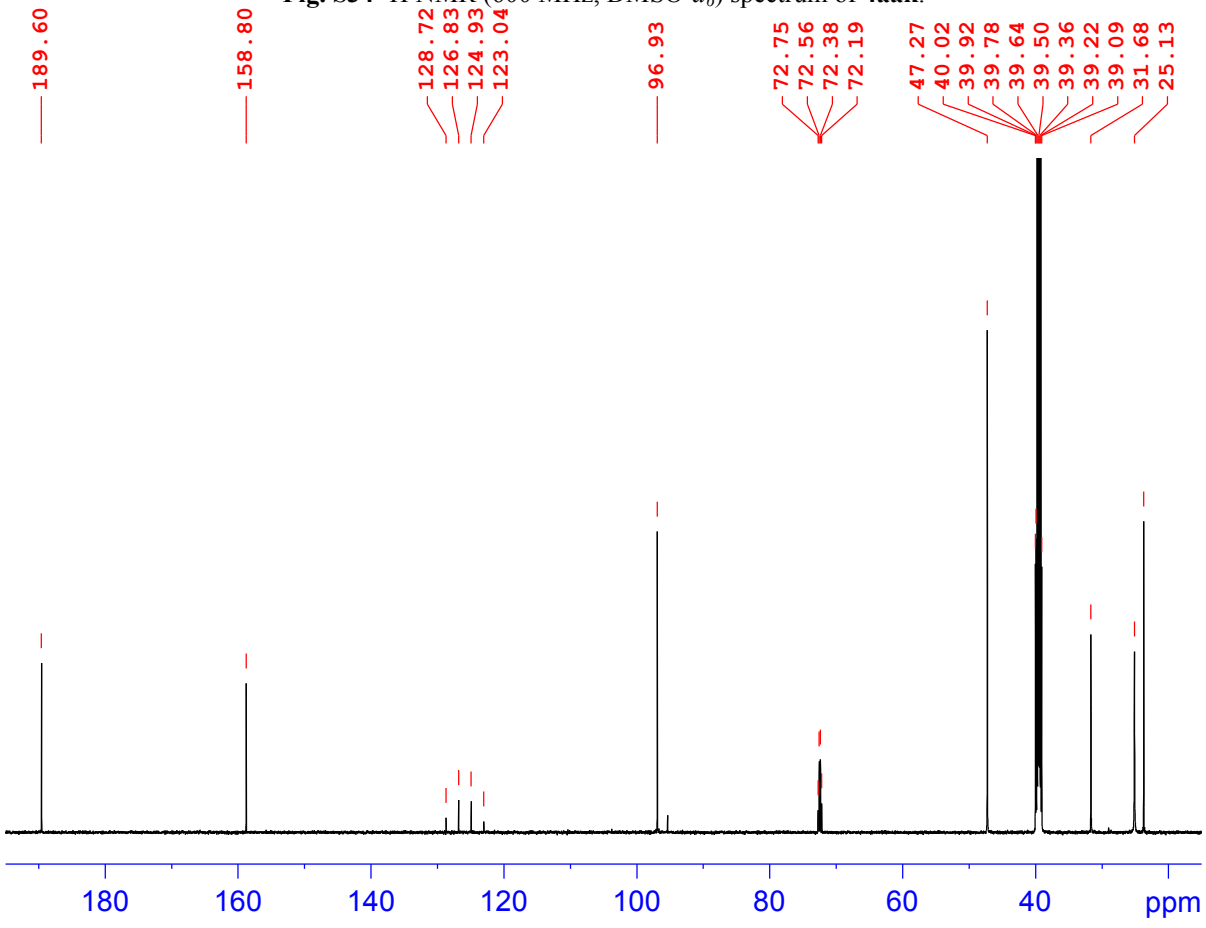

Fig. S35 ^{13}C NMR (151 MHz, DMSO-d_6) spectrum of **4aak**.

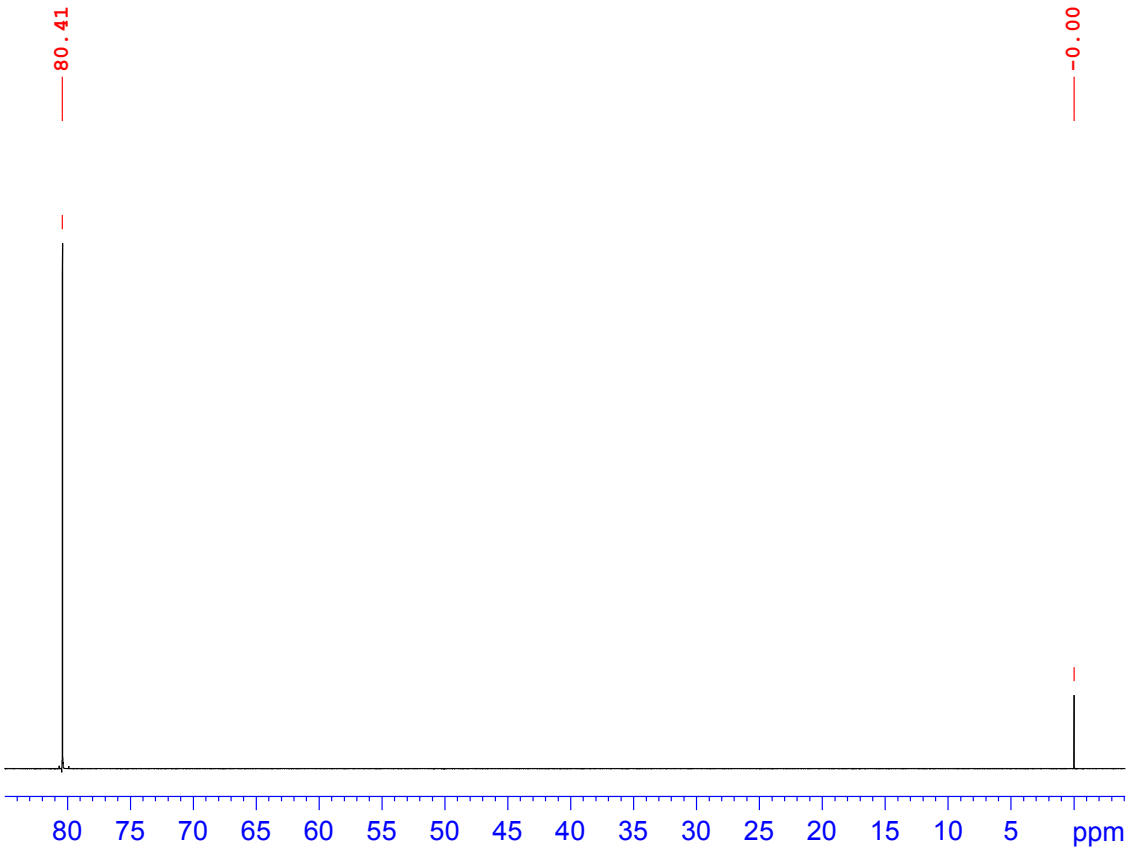

Fig. S36 ^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **4aak**.

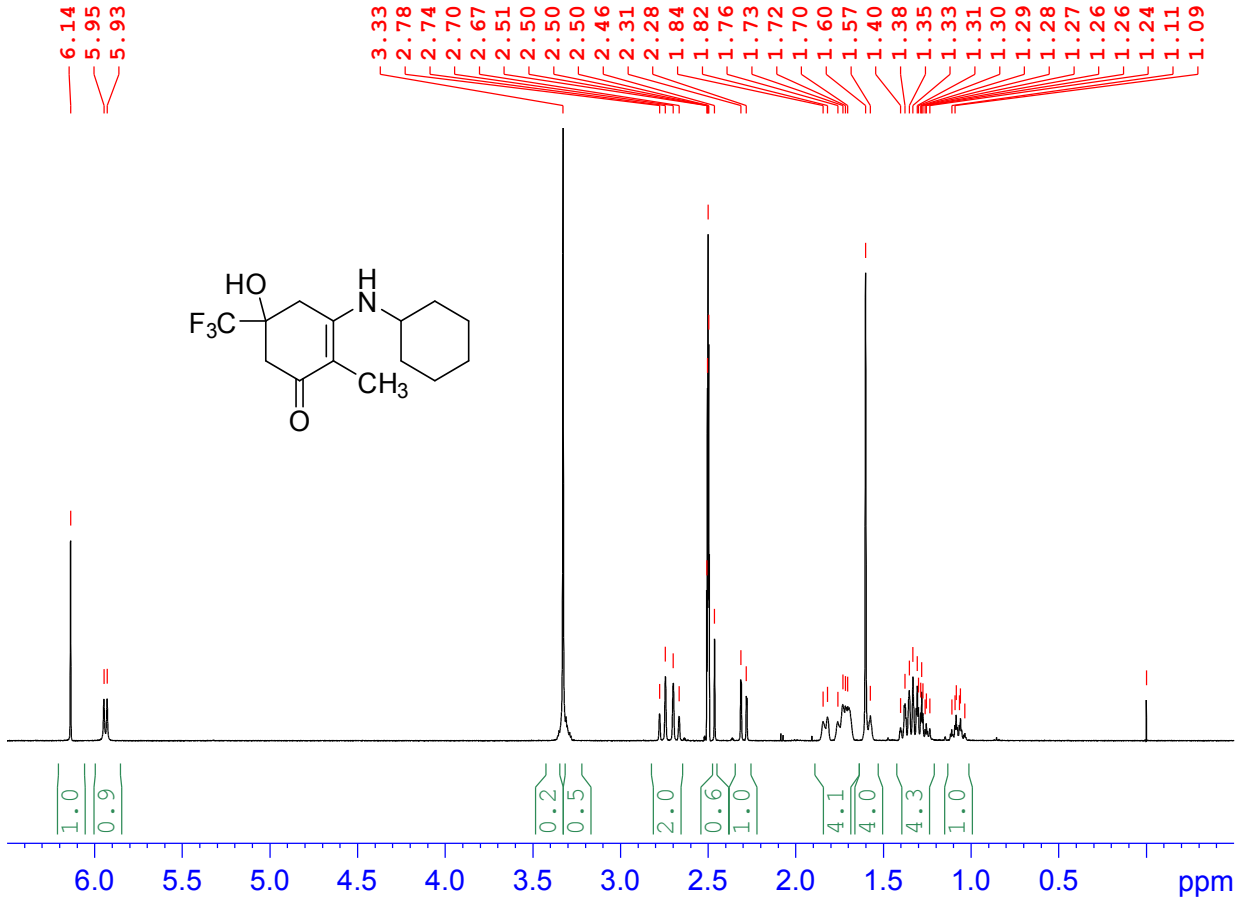

Fig. S37 ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **4aba**.

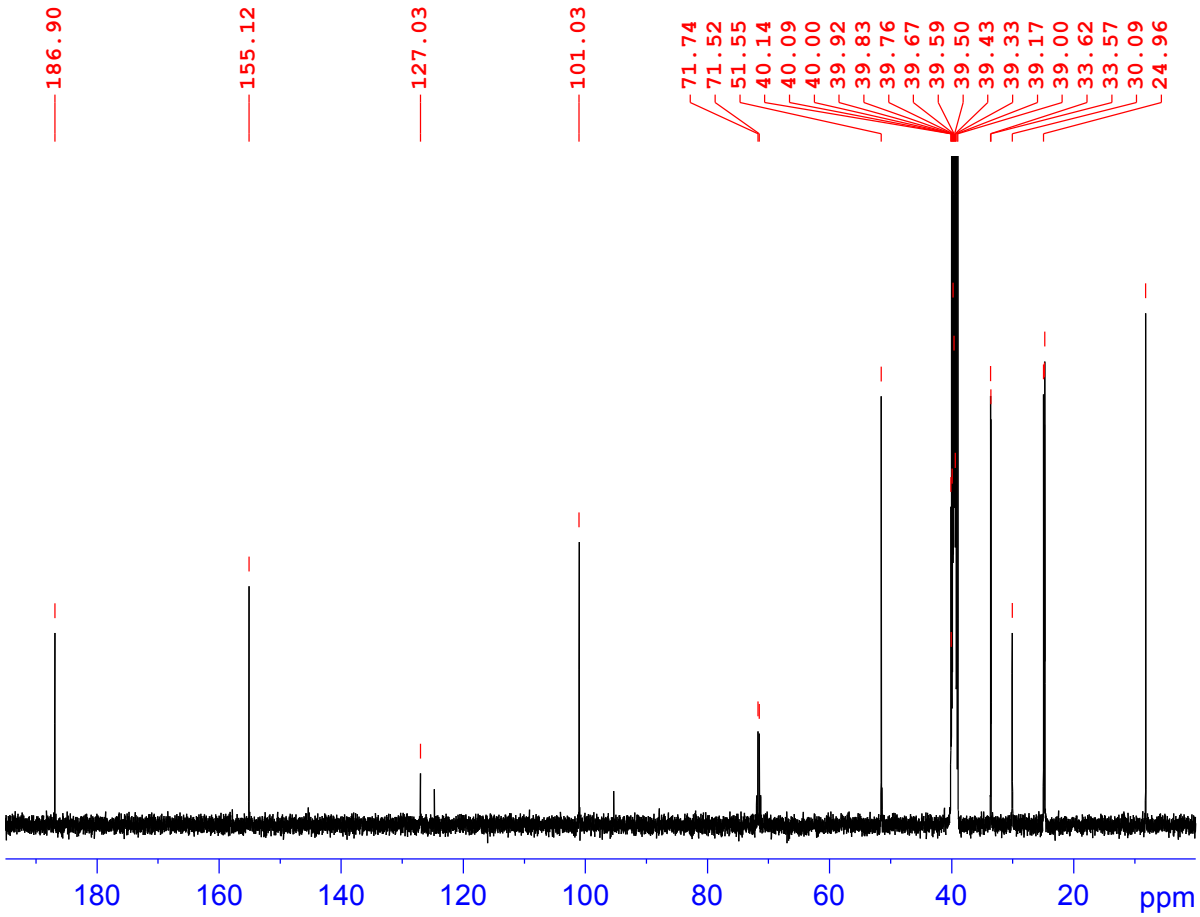

Fig. S38 ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **4aba**.

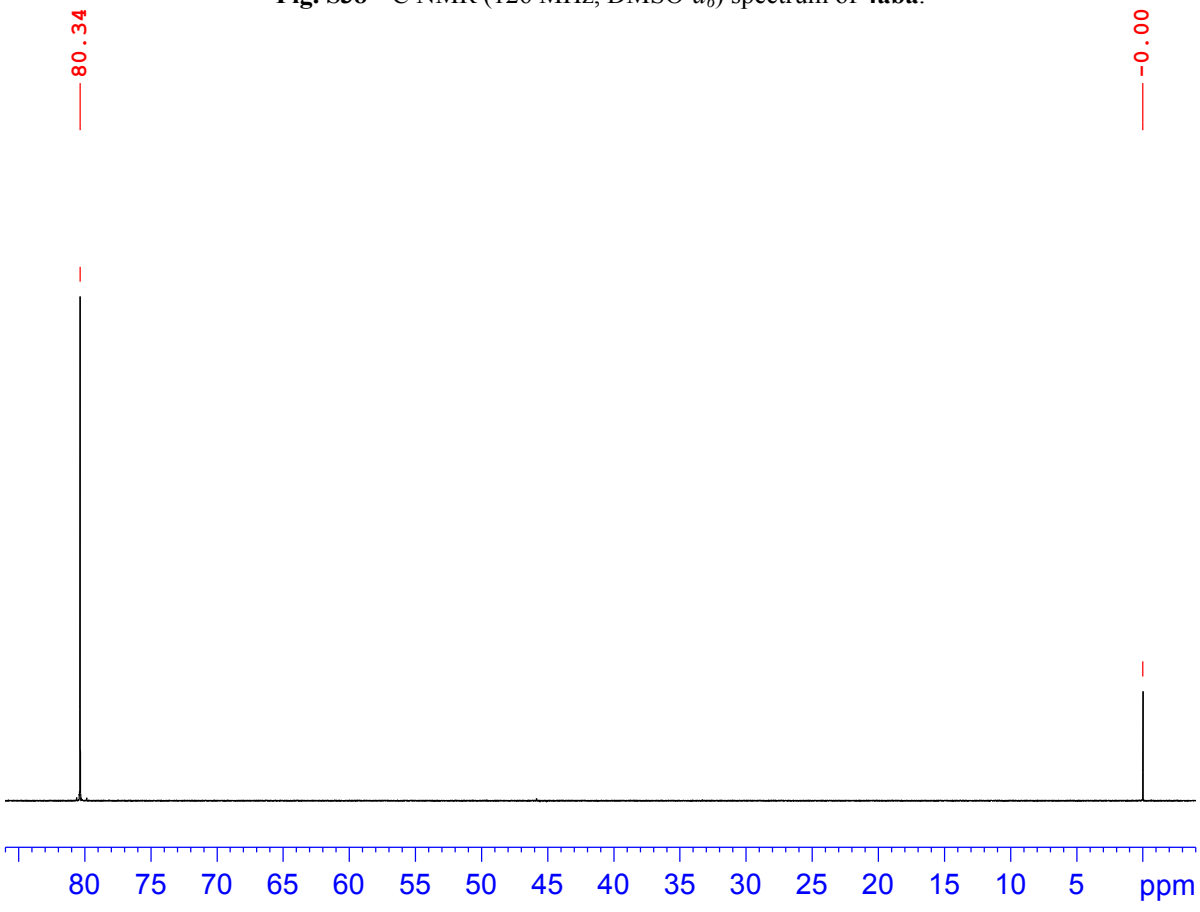

Fig. S39 ^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **4aba**.

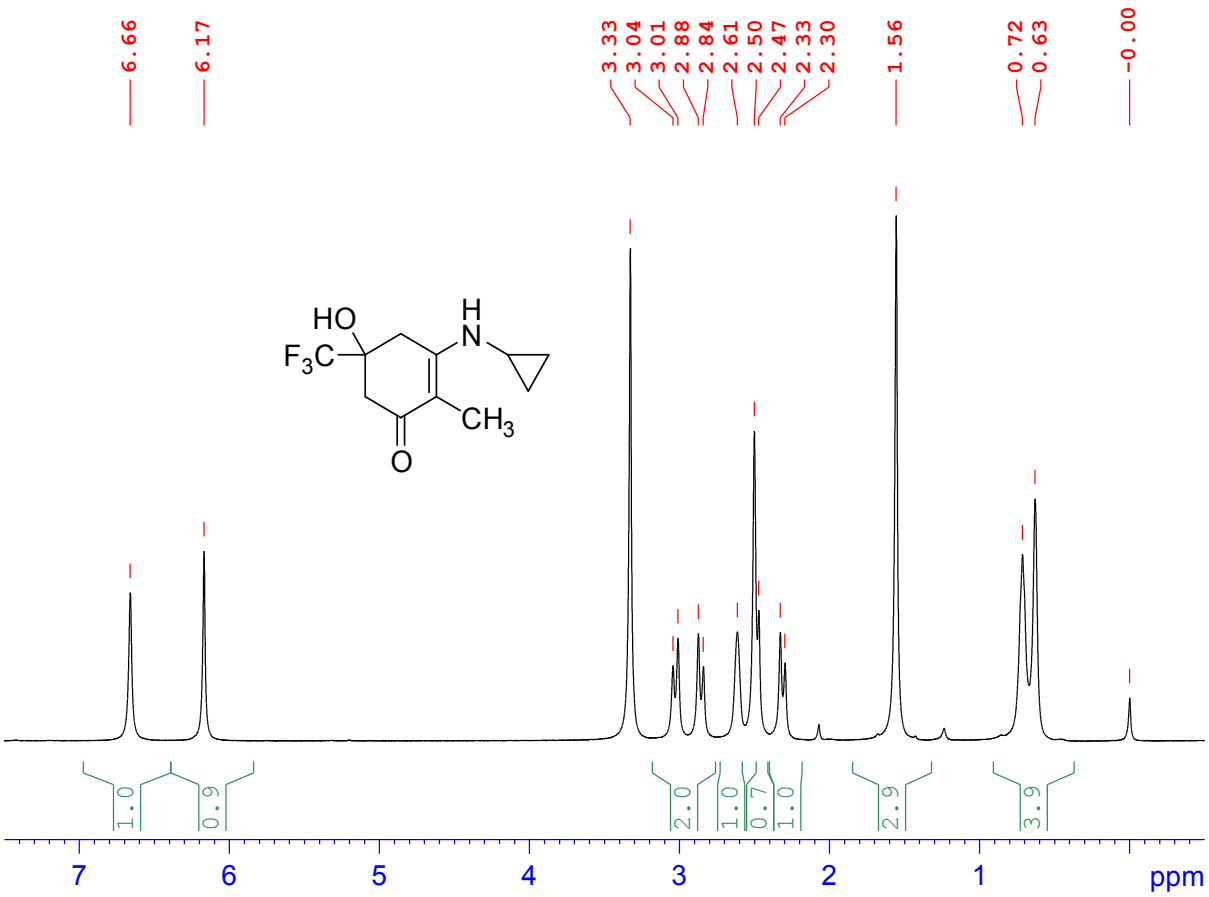

Fig. S40 ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **4abb**.

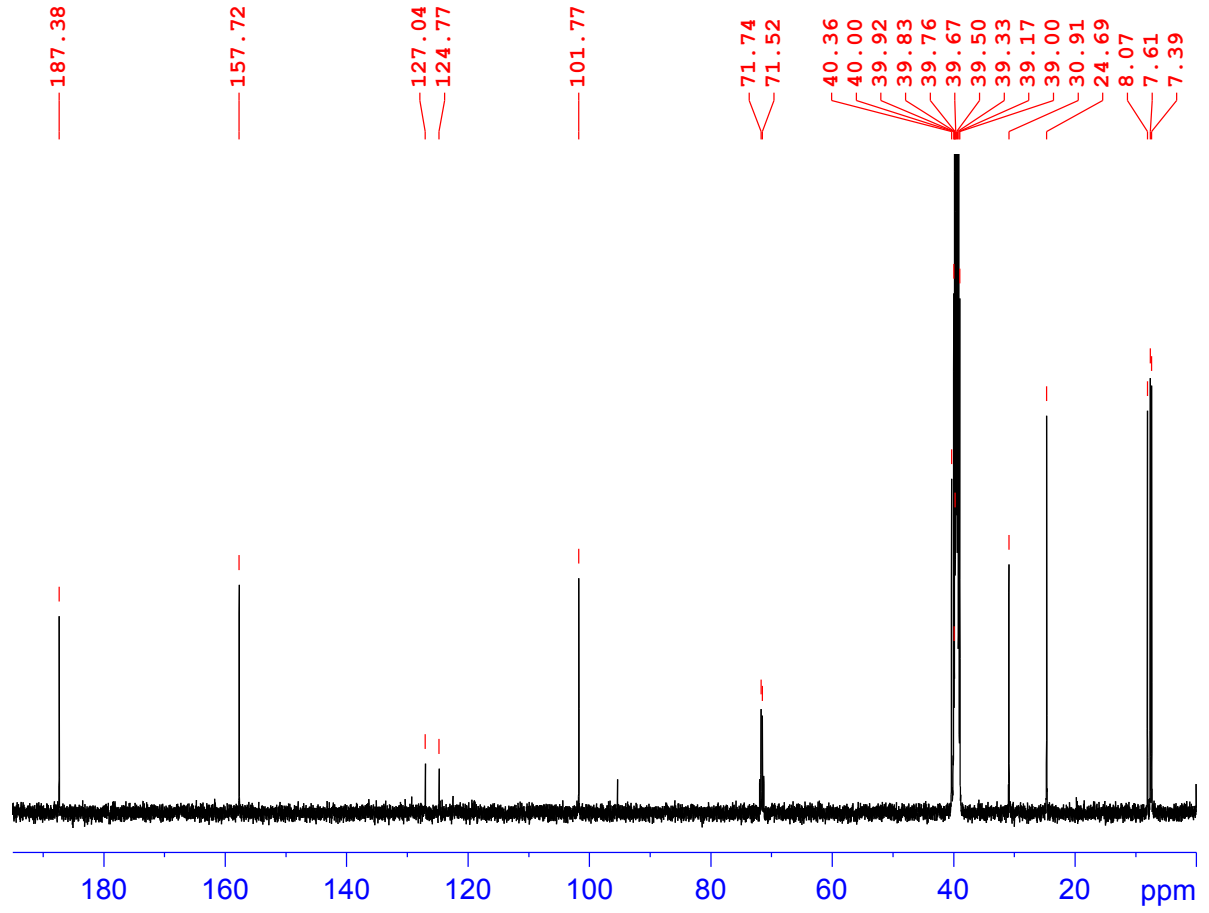

Fig. S41 ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **4abb**.

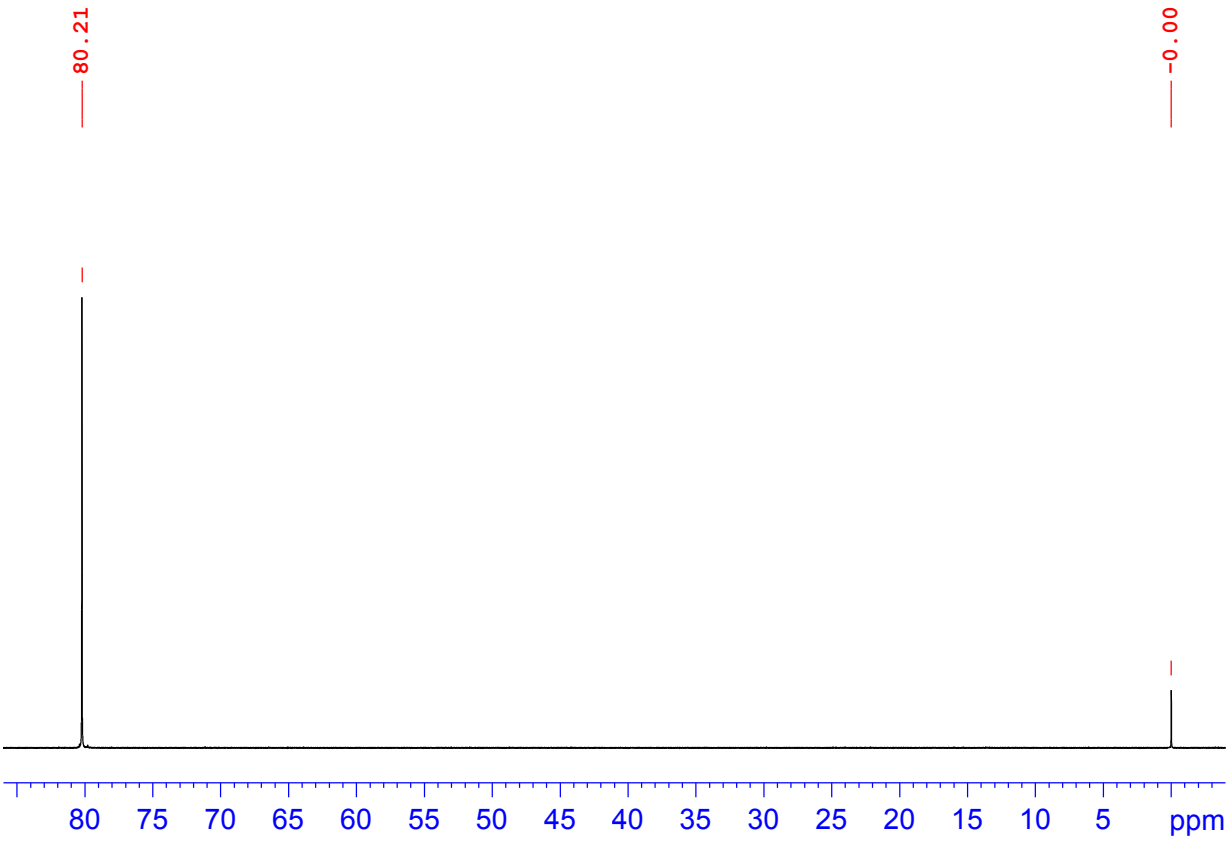

Fig. S42 ^{19}F NMR (470 MHz, DMSO-d_6) spectrum of **4abb**.

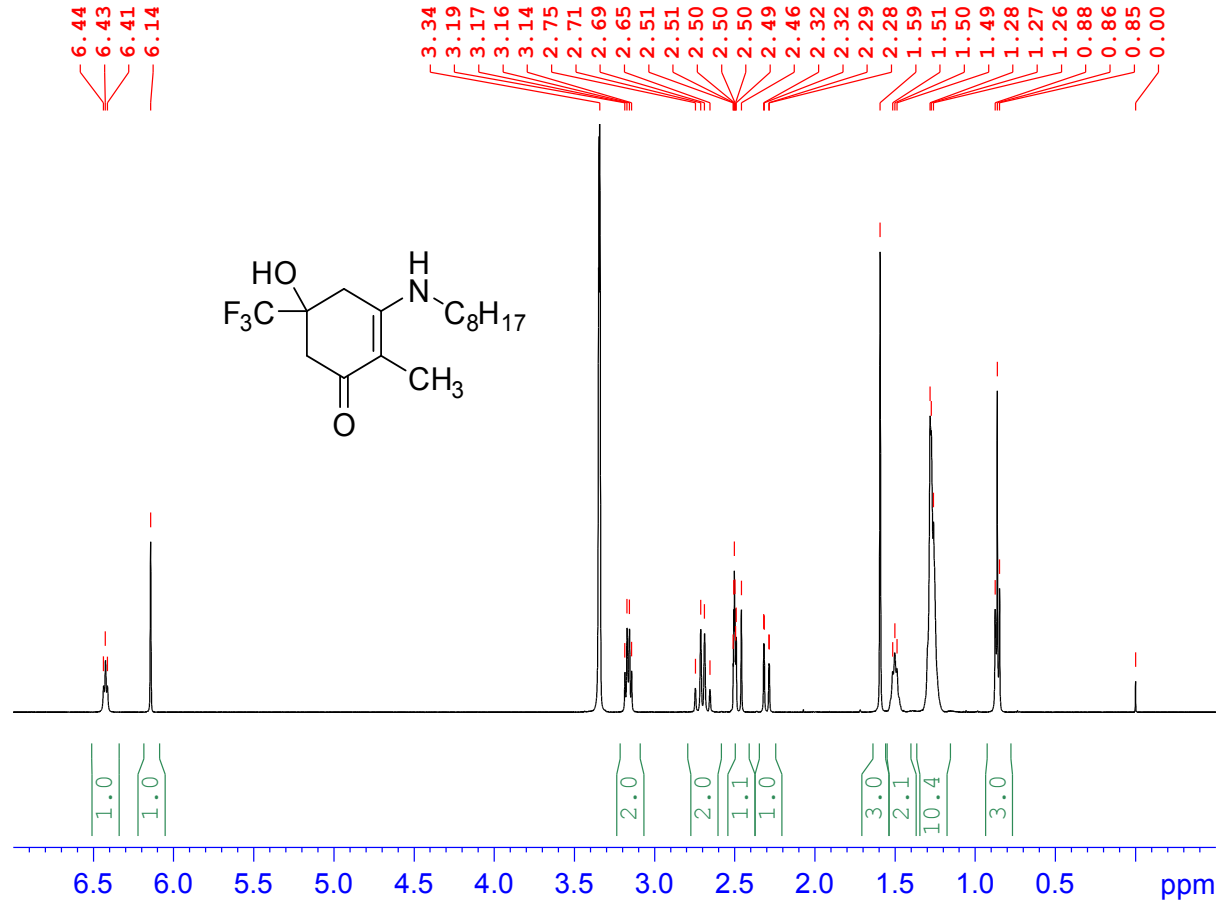

Fig. S43 ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **4abc**.

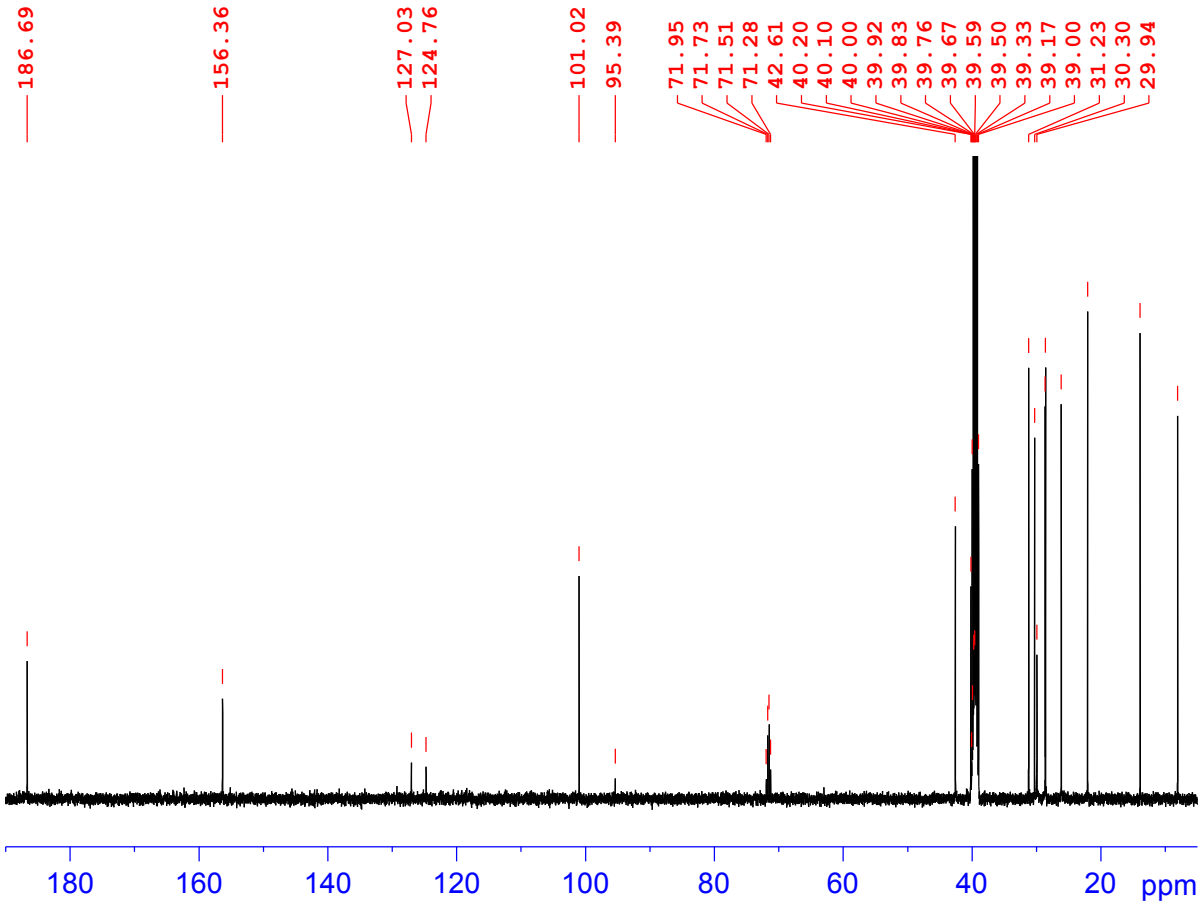

Fig. S44 ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **4abc**.

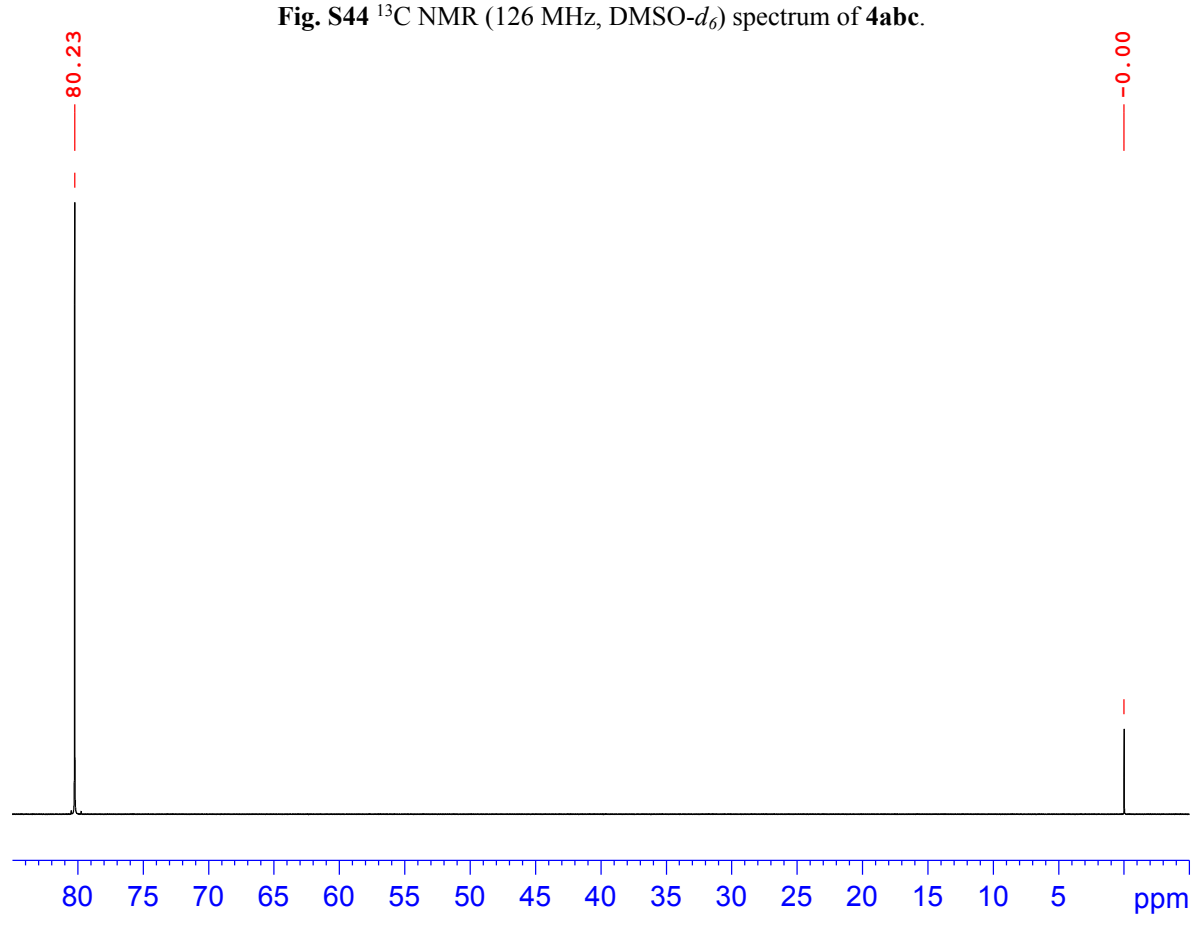

Fig. S45 ^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **4abc**.

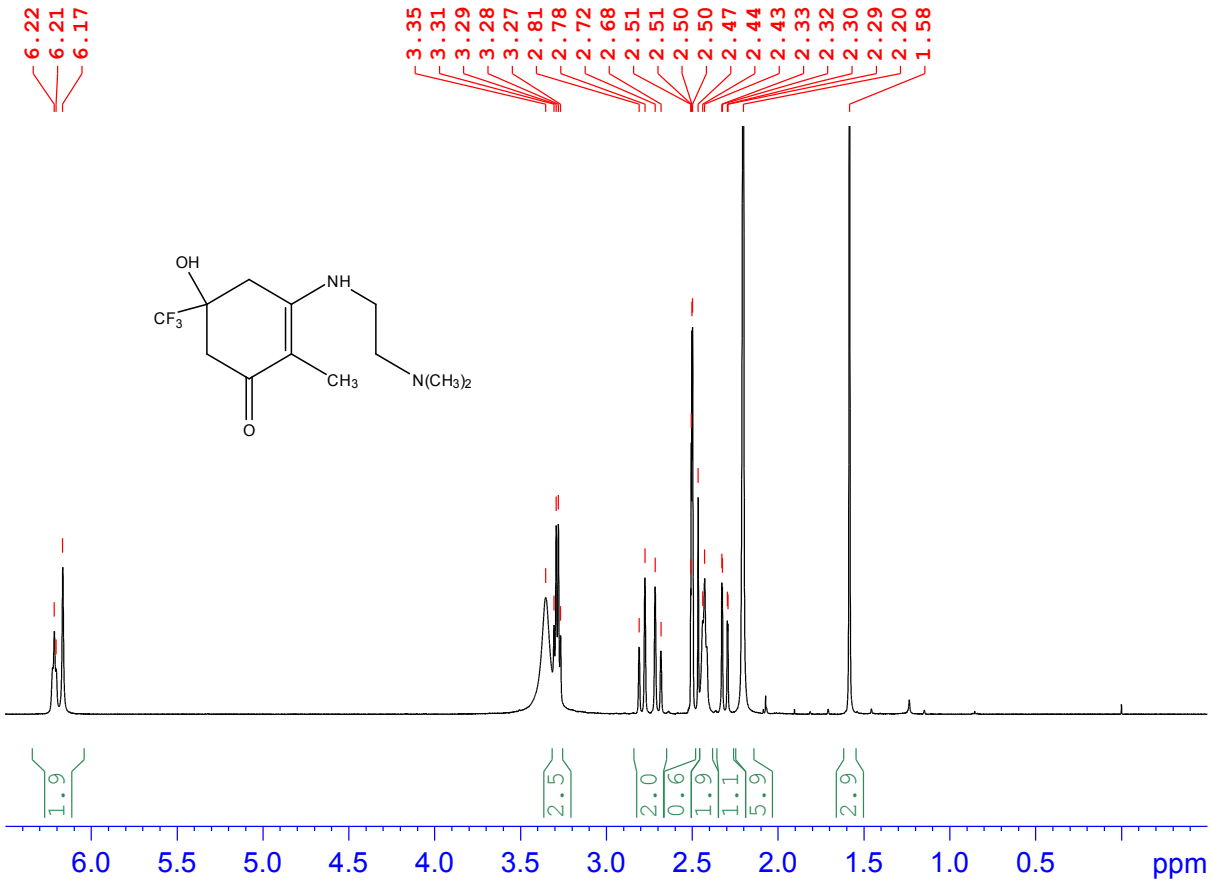

Fig. S46 ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **4abe**.

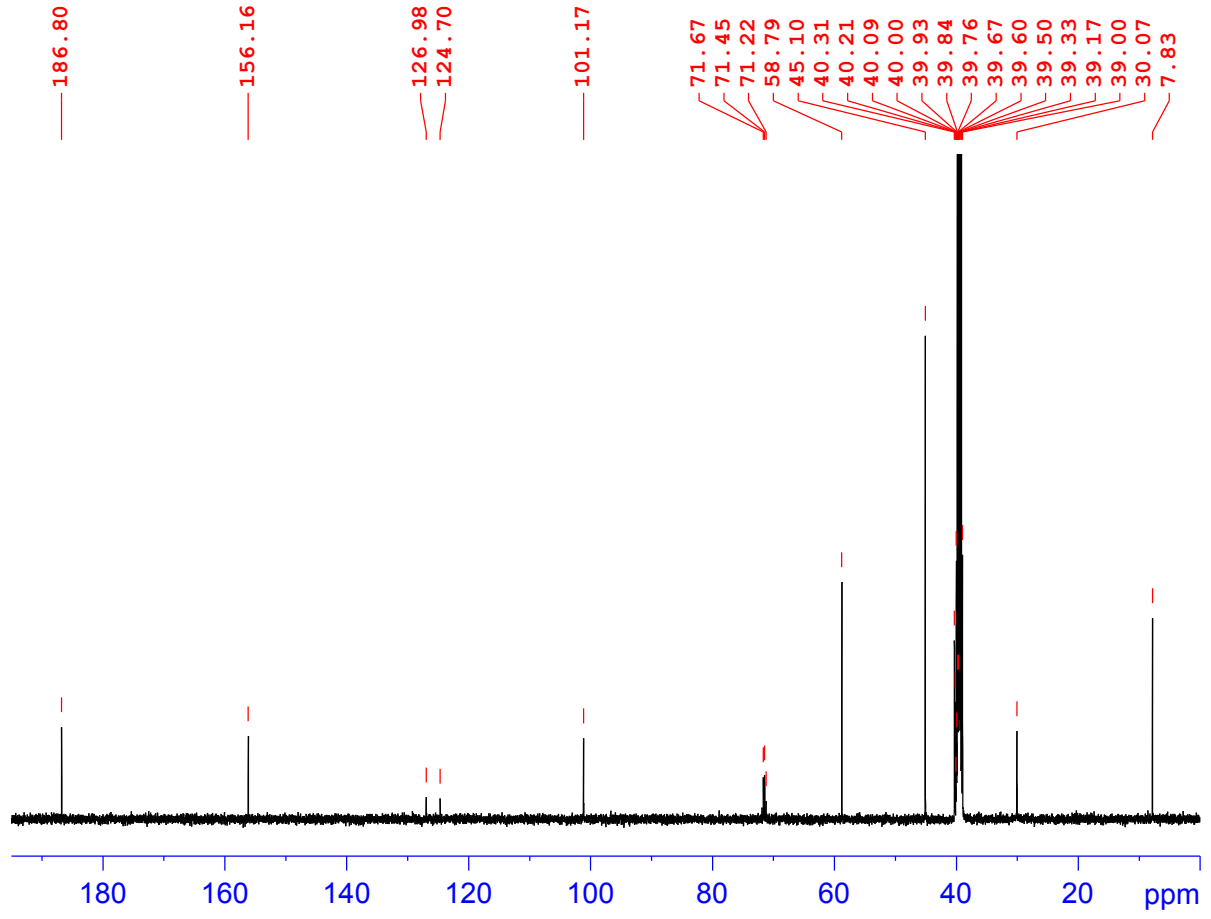

Fig. S47 ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **4abe**.

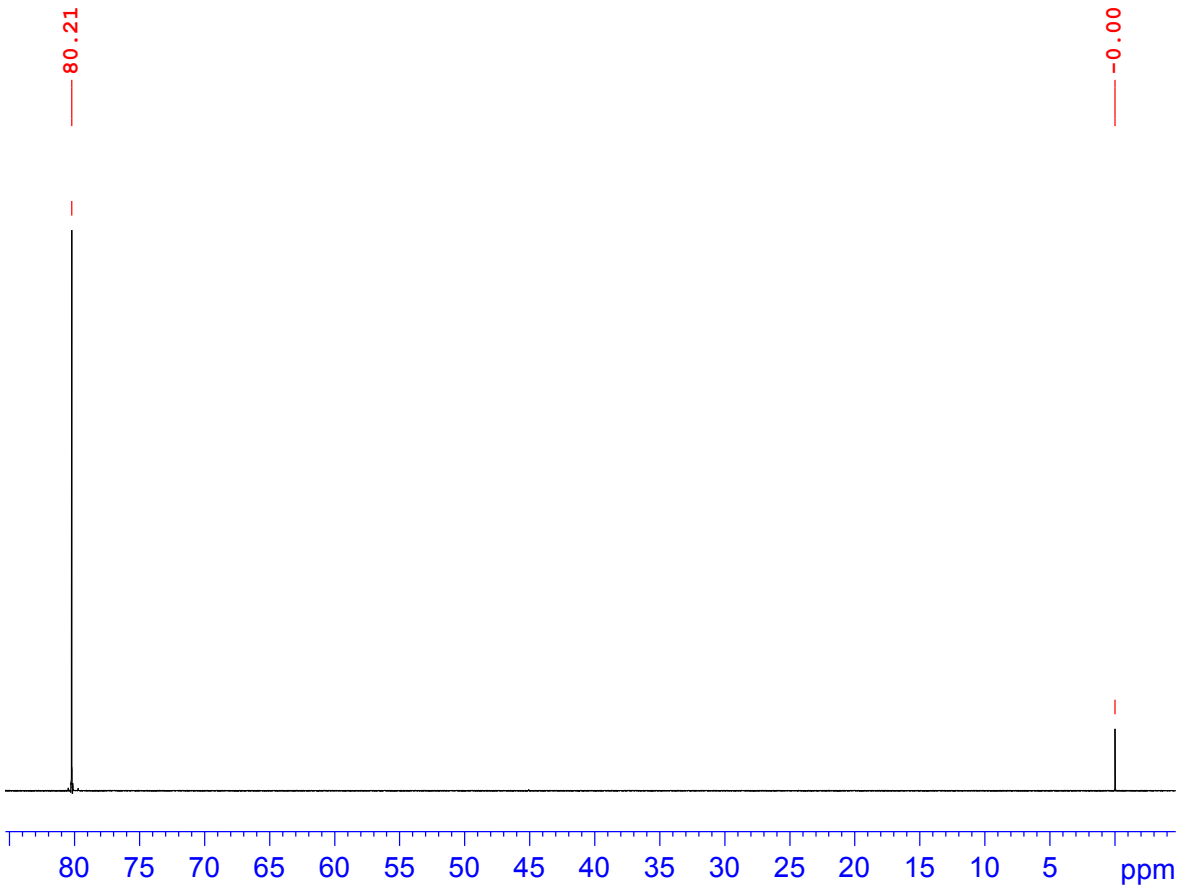

Fig. S48 ^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **4abe**.

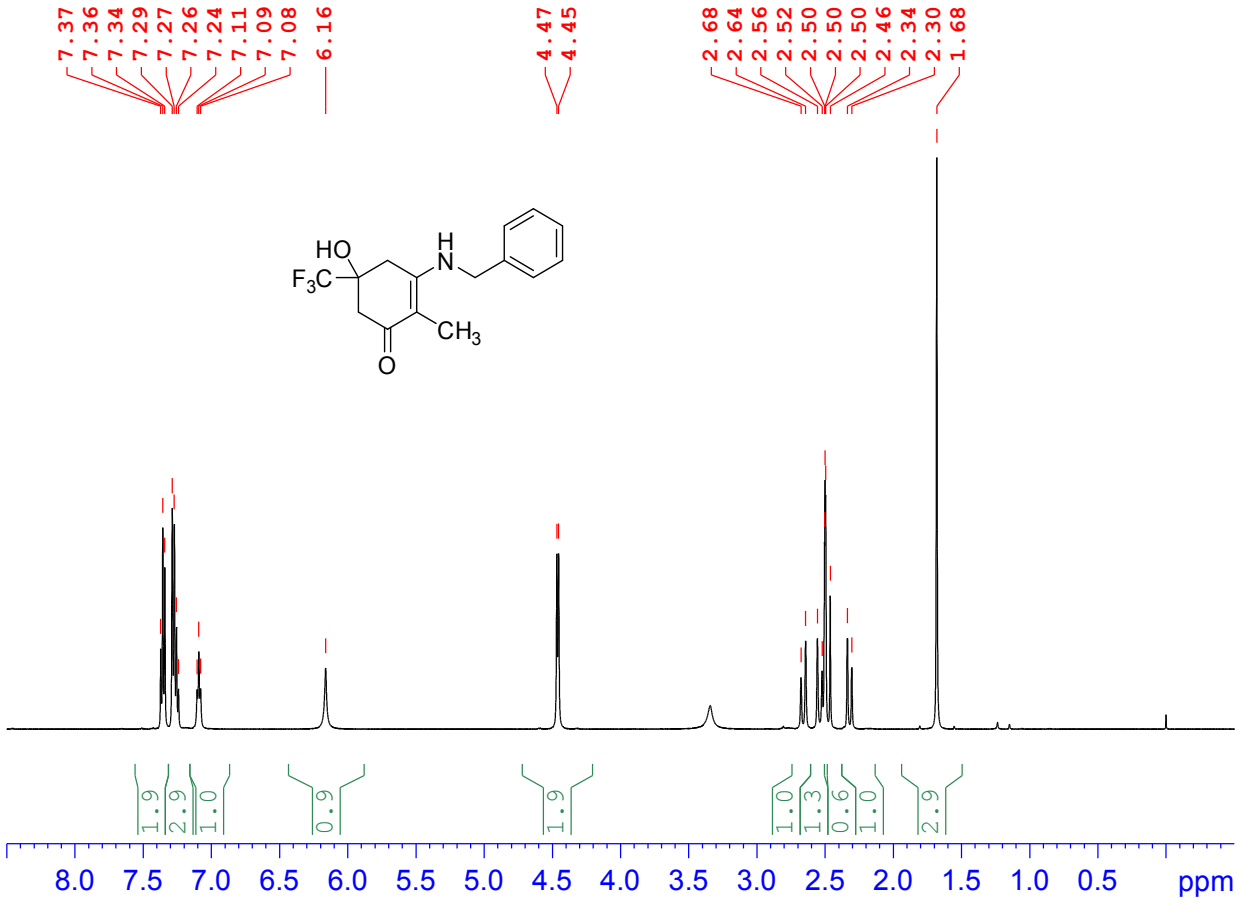

Figure S49 ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **4abf**.

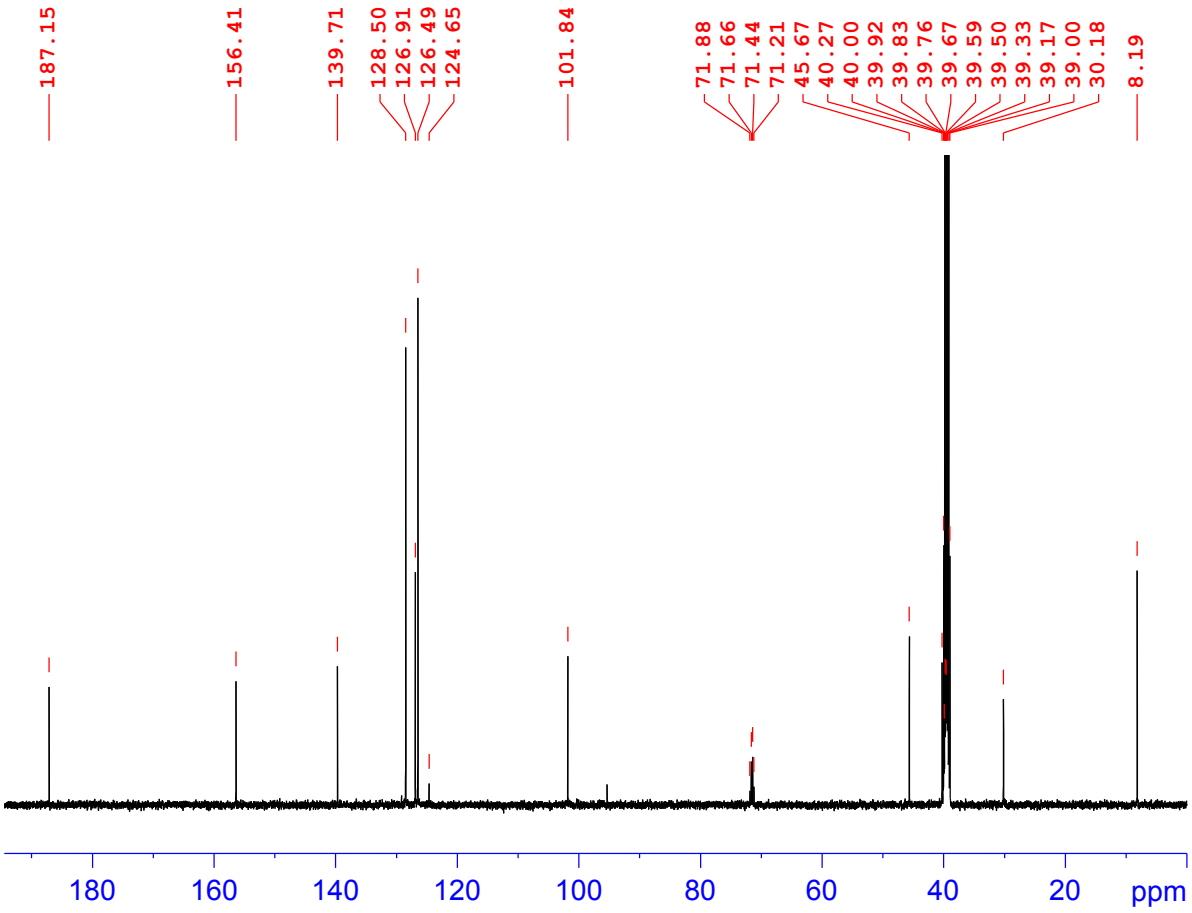

Fig. S50 ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **4abf**.

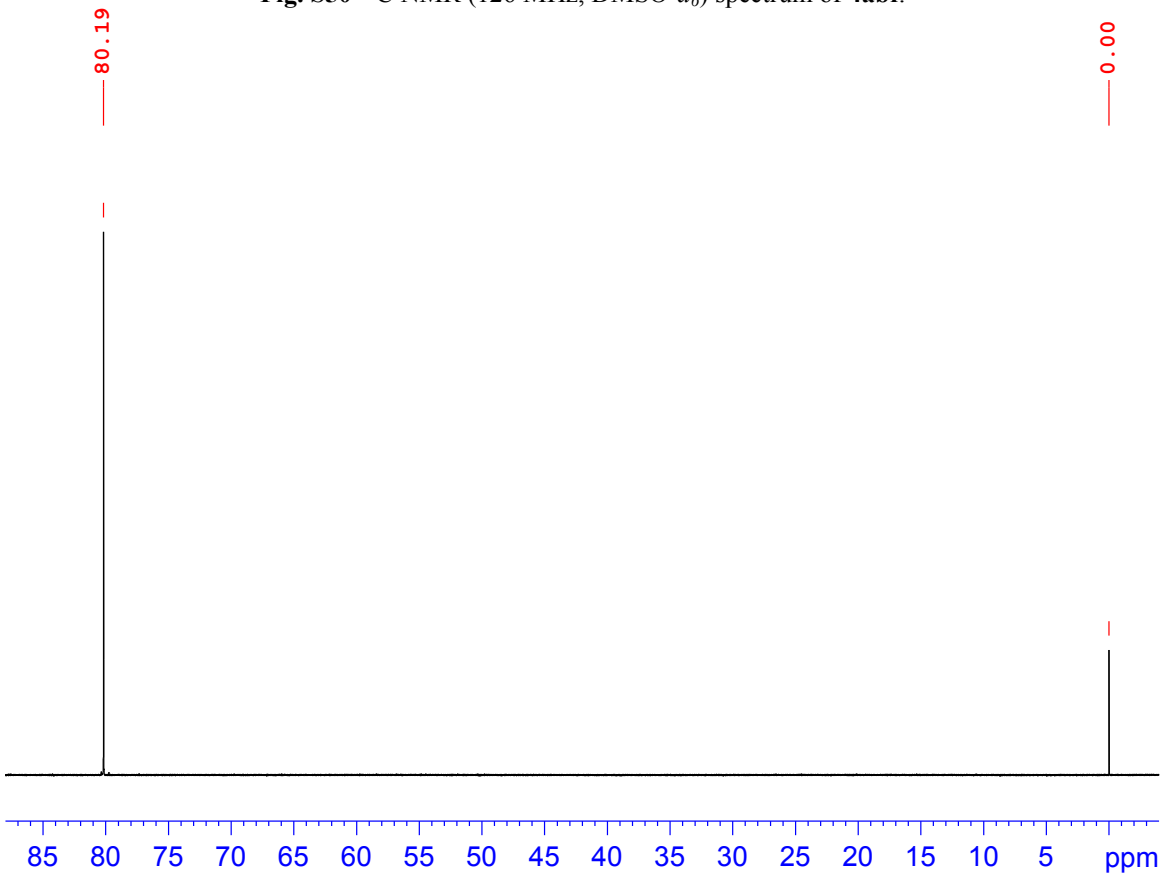

Fig. S51 ^{19}F NMR (470 MHz, DMSO-d_6) spectrum of **4abf**.

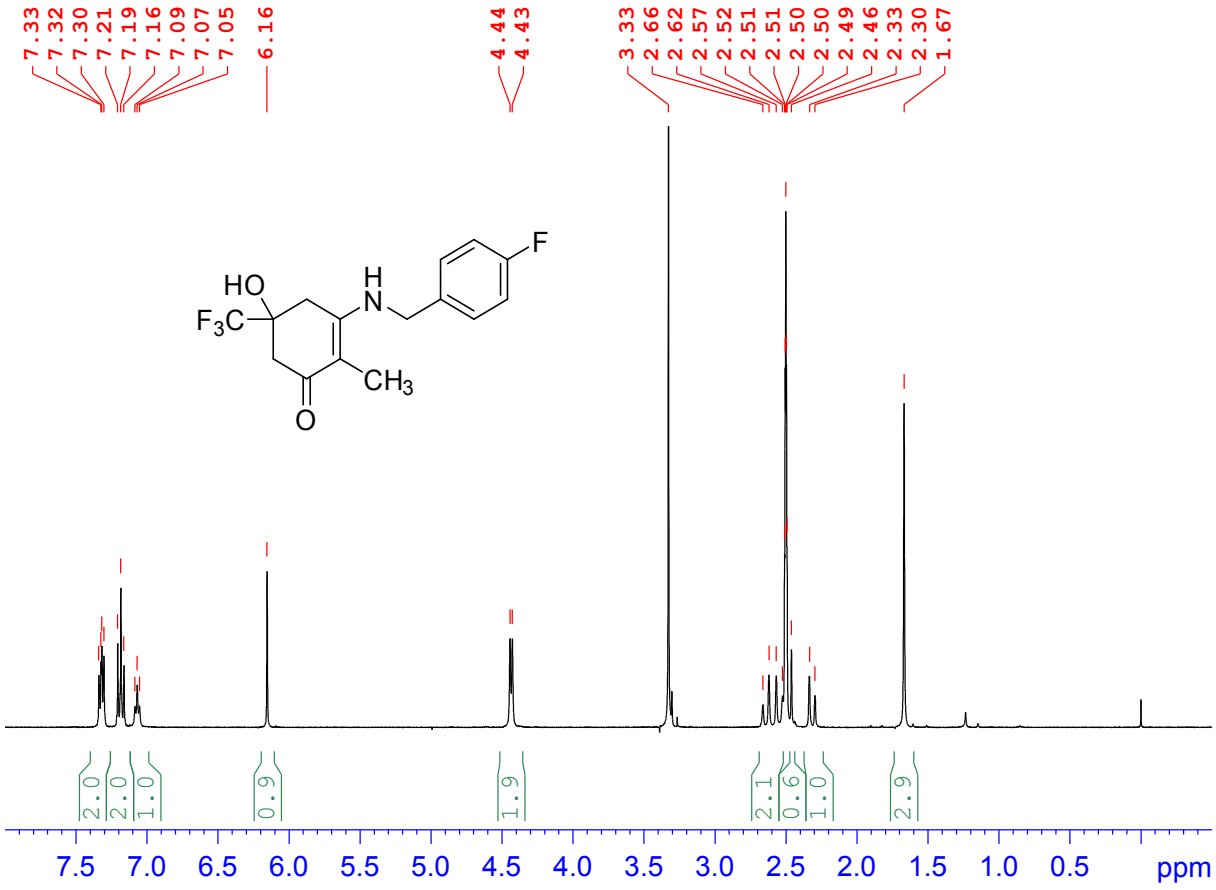

Fig. S52 ^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **4abg**.

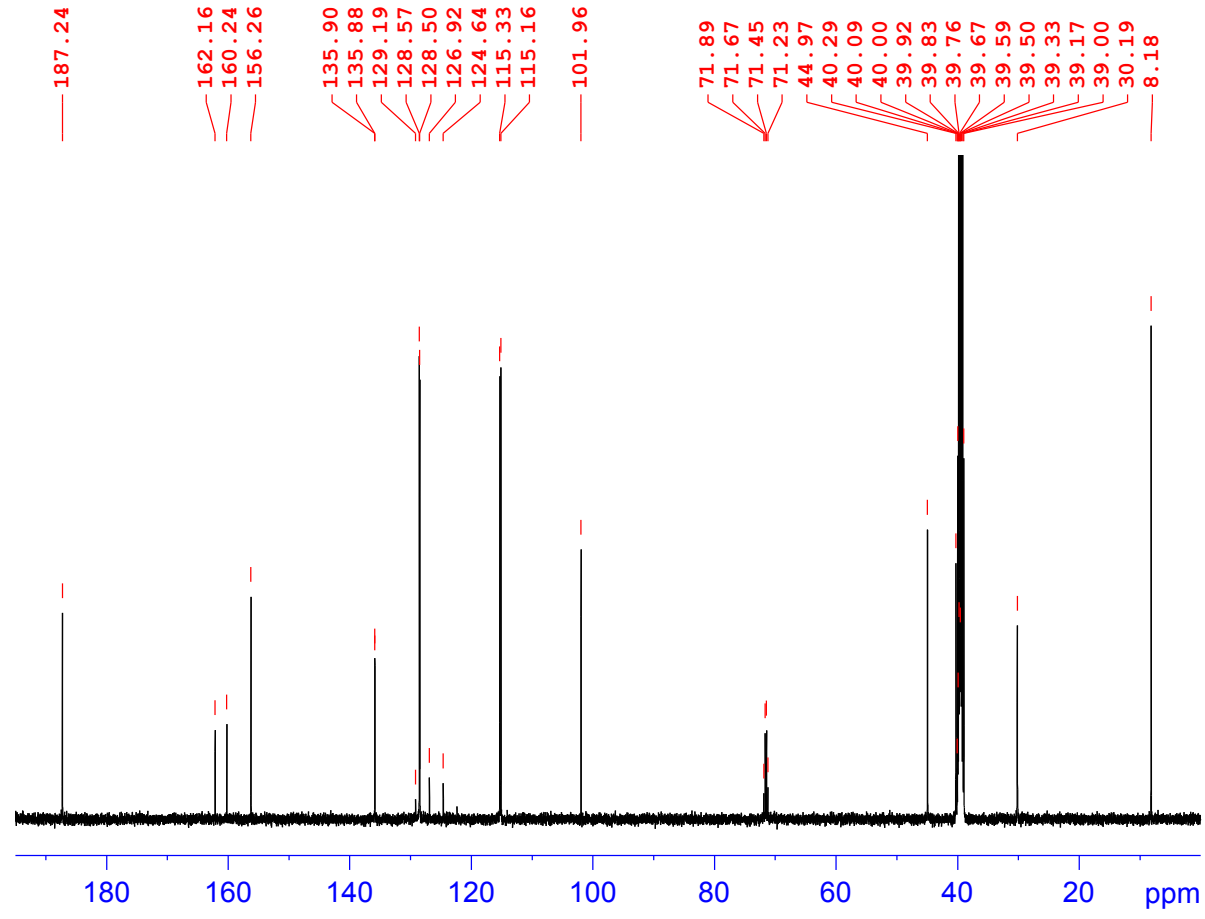

Fig. S53 ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **4abg**.

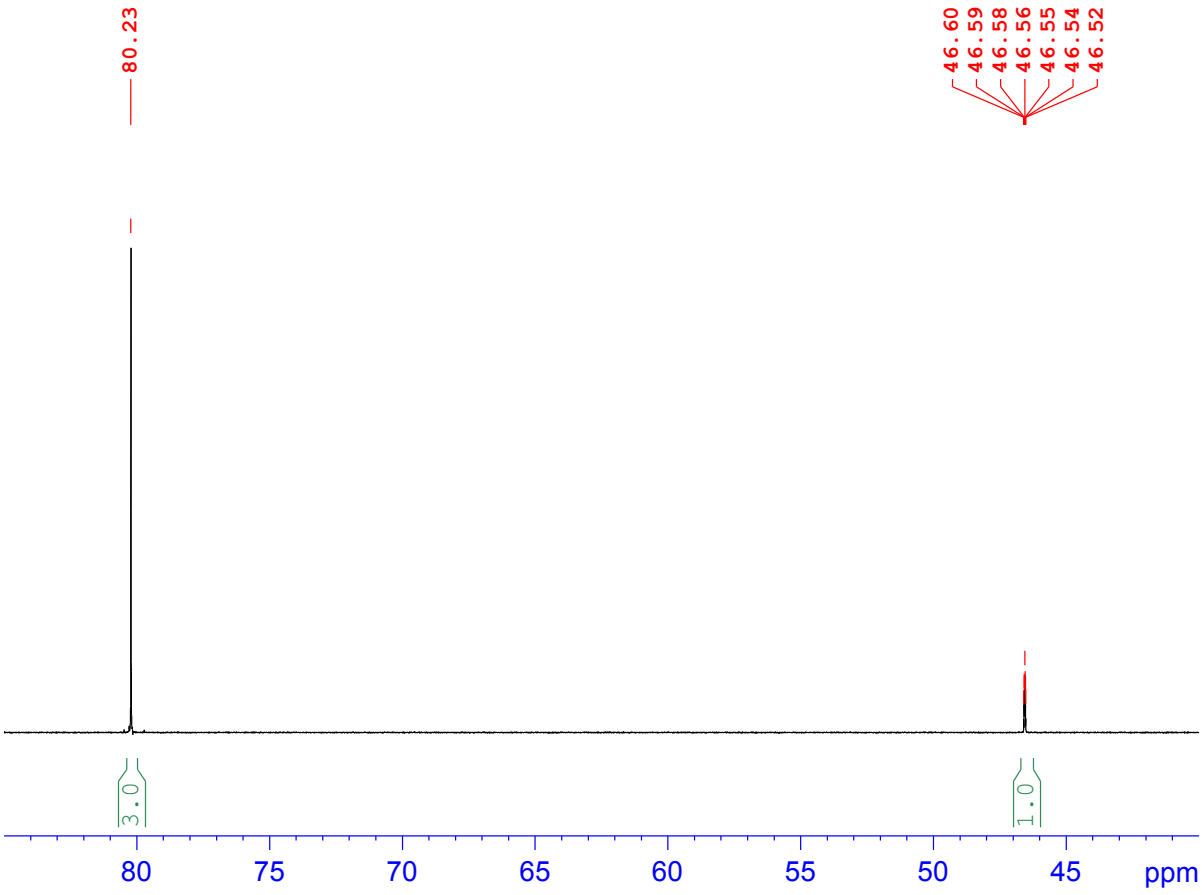

Fig. S54 ^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **4abg**.

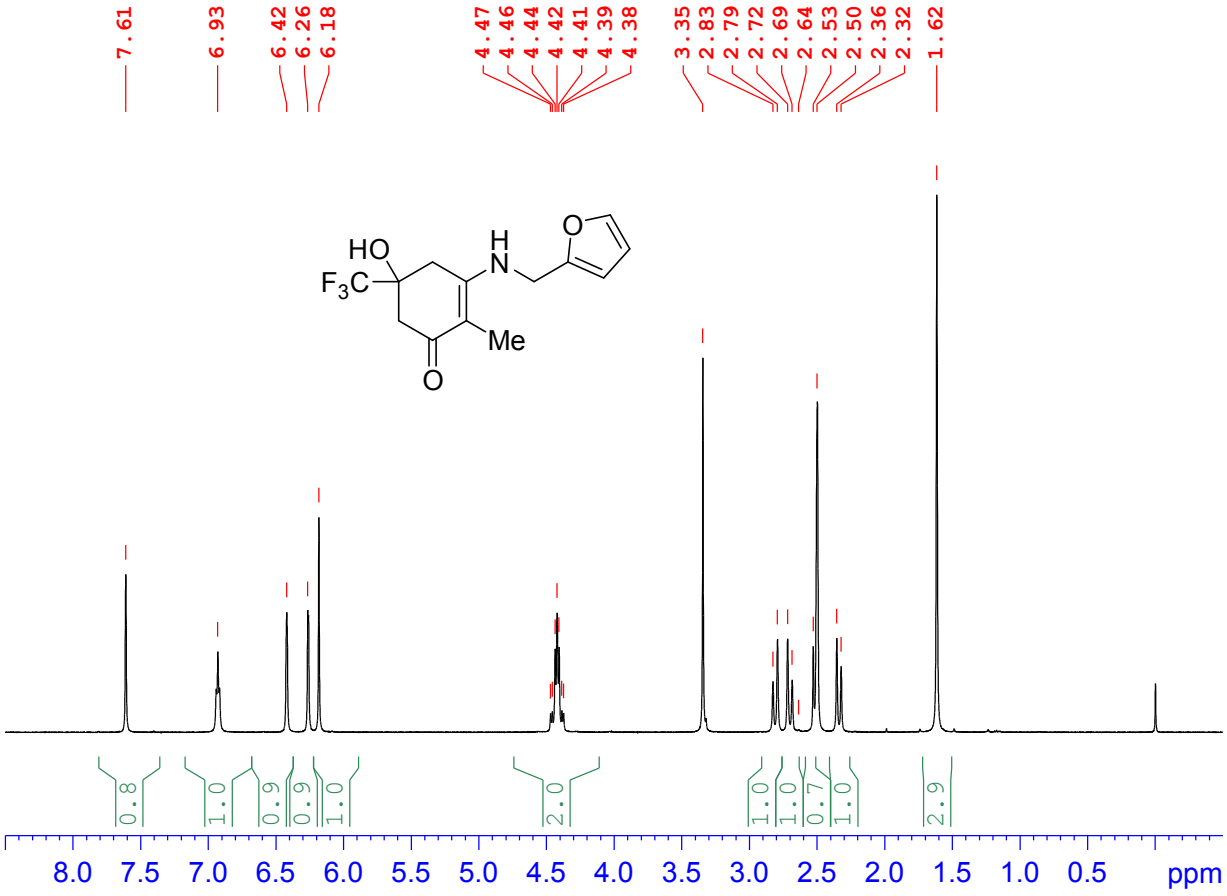

Fig. S55 ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **4abi**.

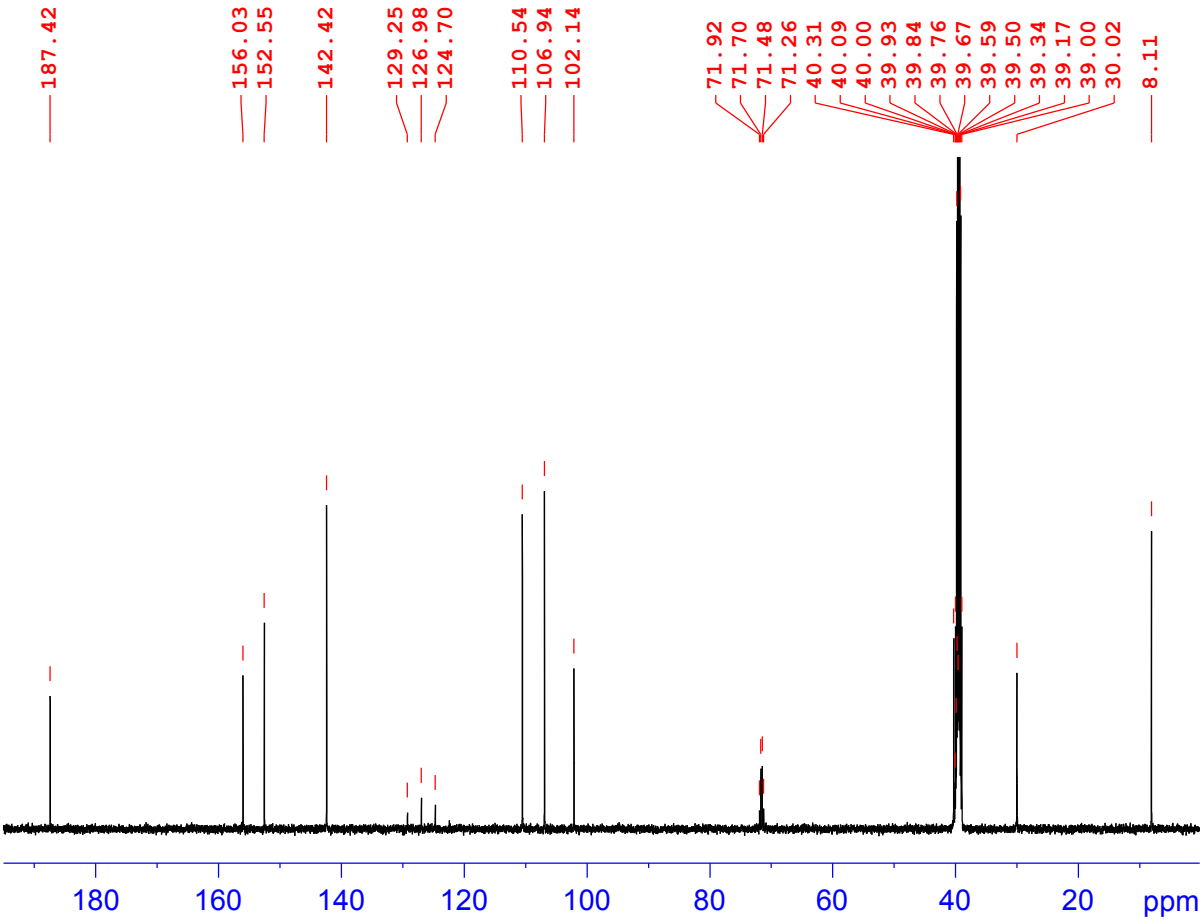

Fig. S56 ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **4abi**.

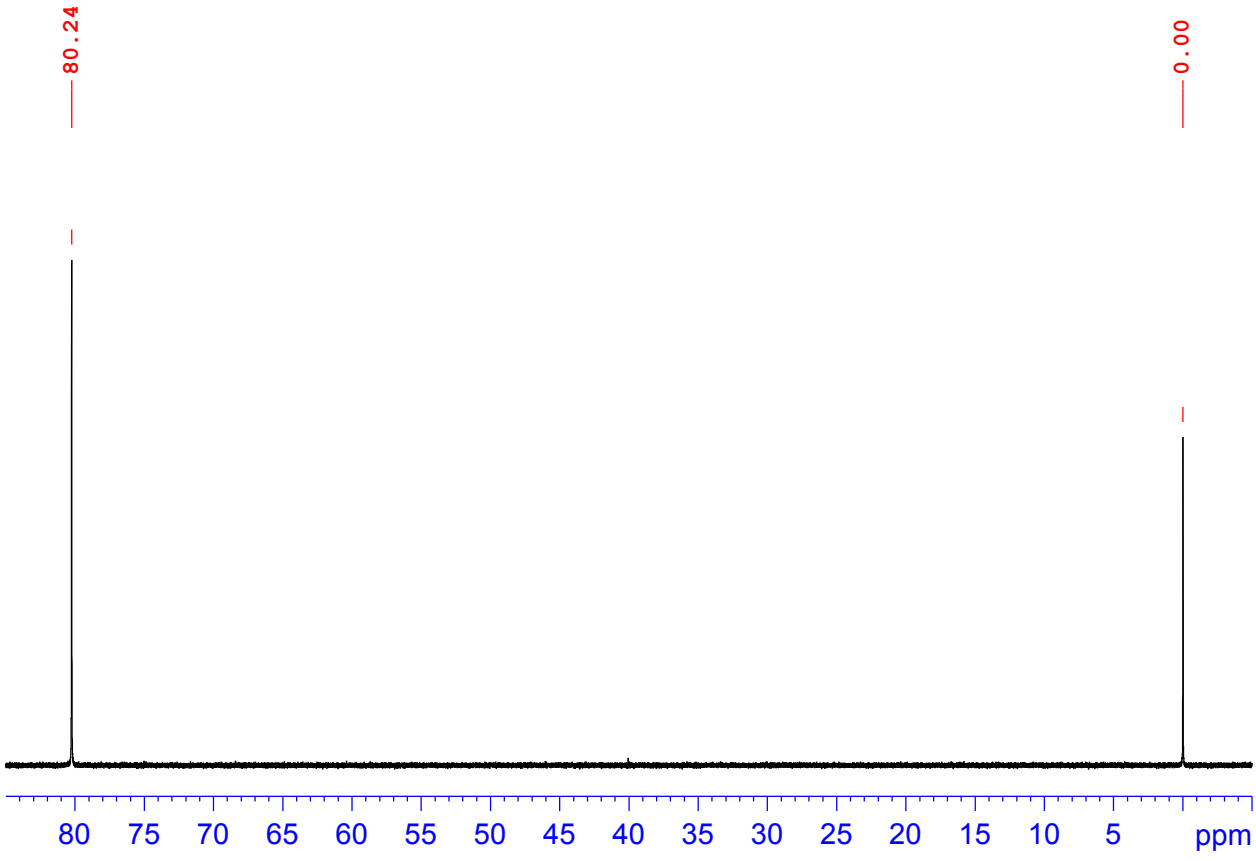

Fig. S57 ^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **4abi**.

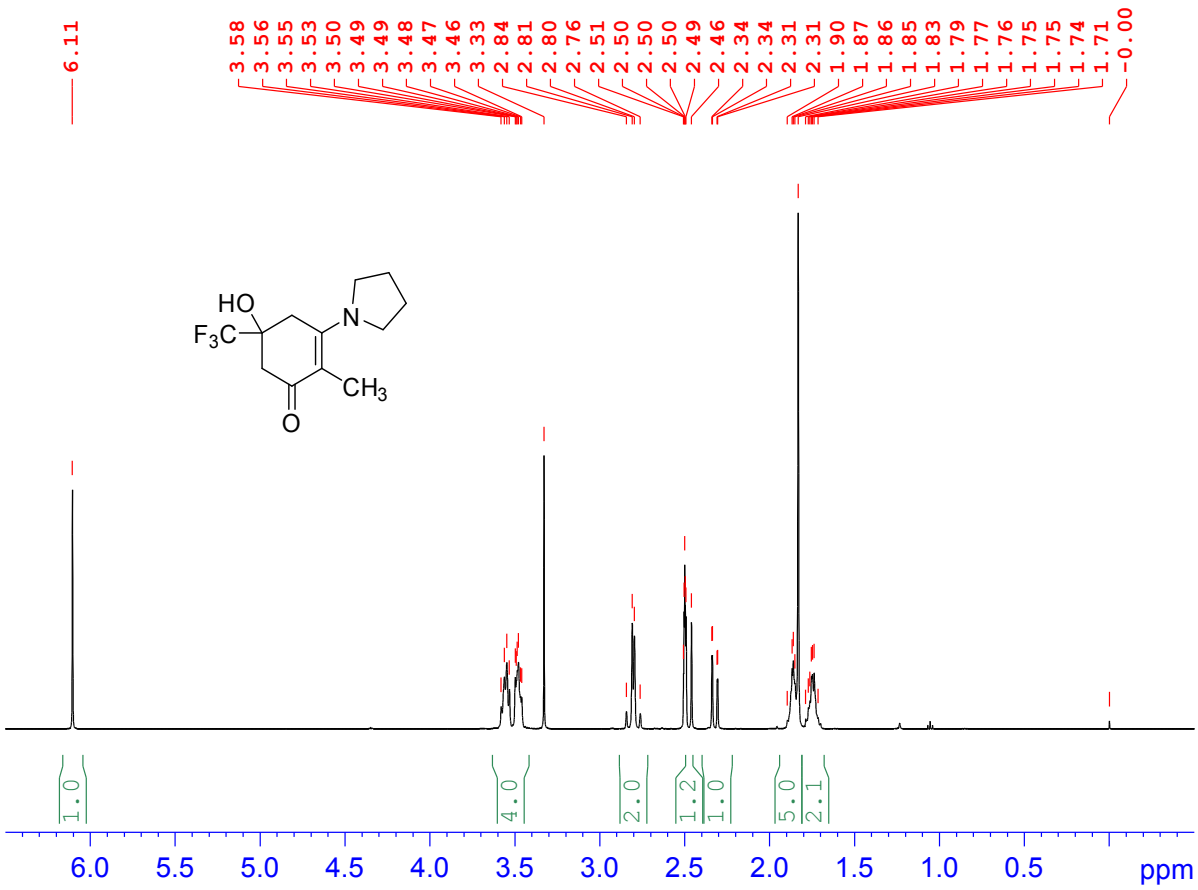

Fig. S581 ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **4abj**.

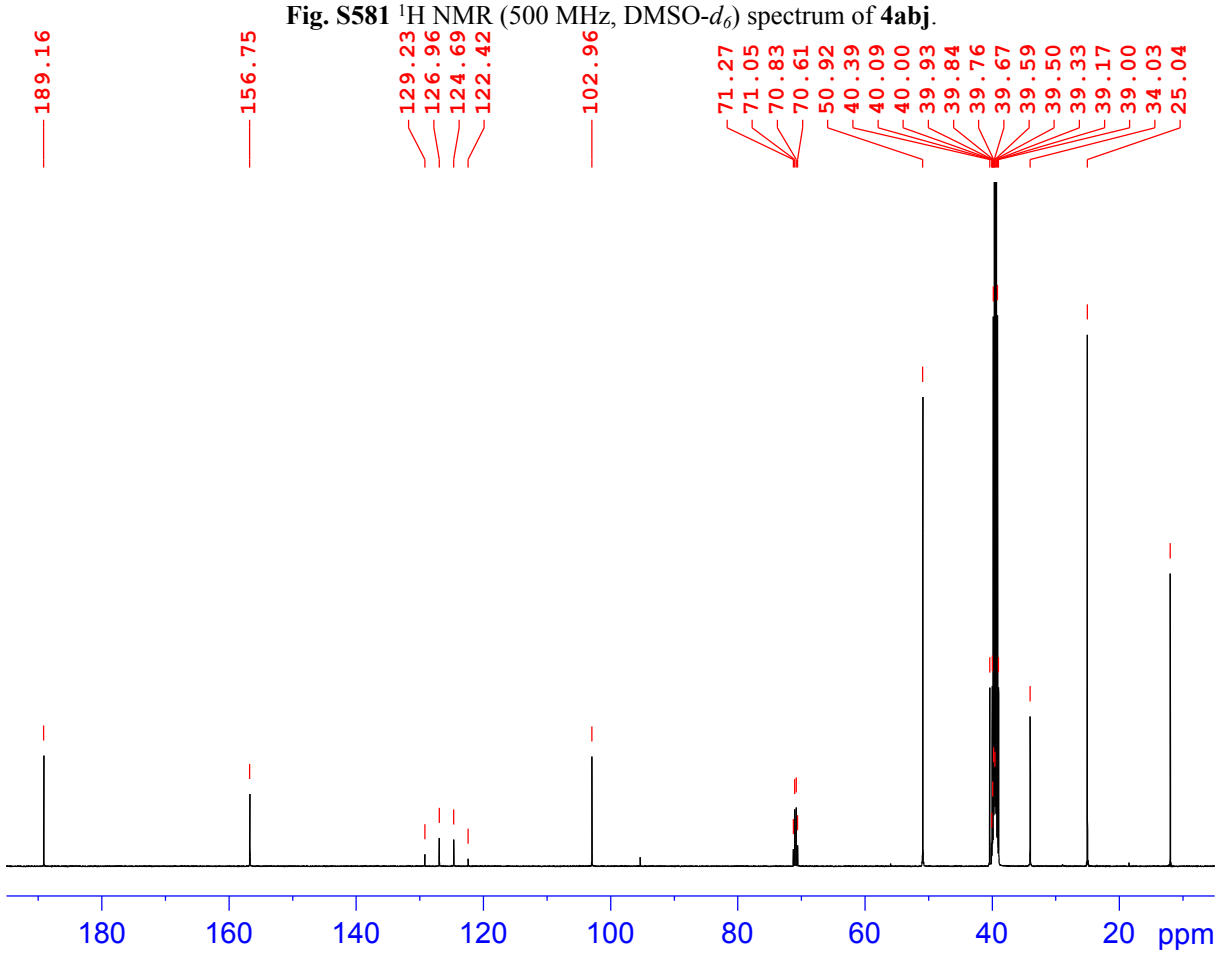

Fig. S59 ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **4abj**.

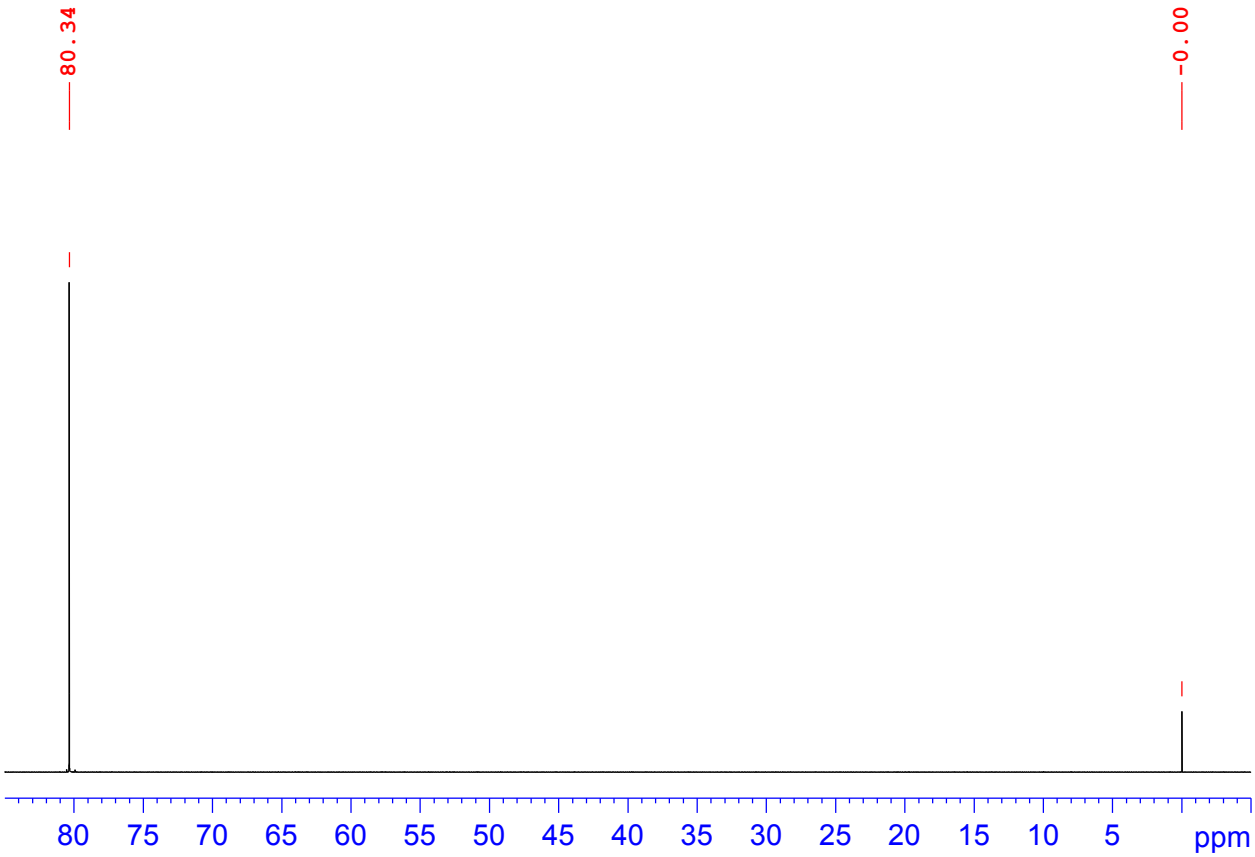

Fig. S60 ^{19}F NMR (470 MHz, DMSO-d_6) spectrum of **4abj**.

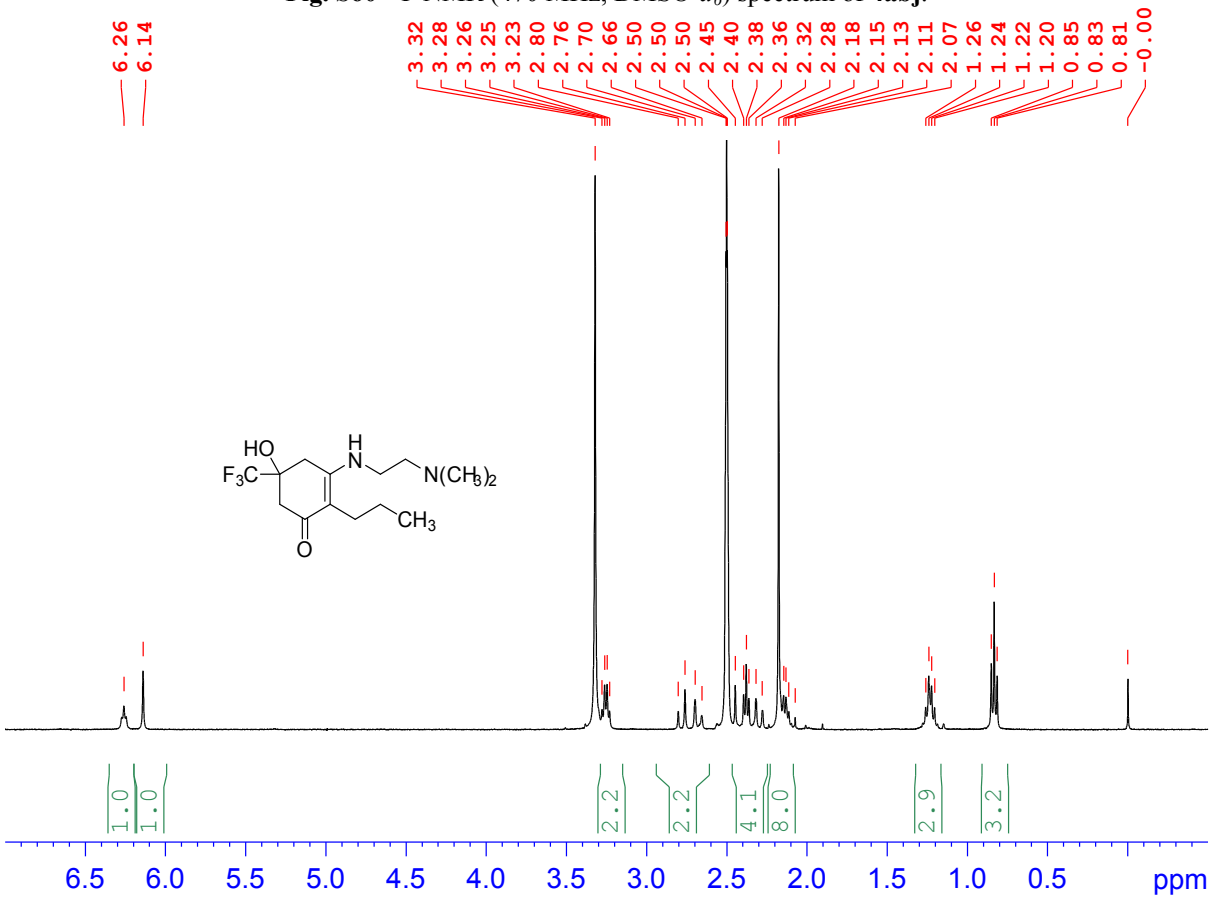

Fig. S61 ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **4ace**.

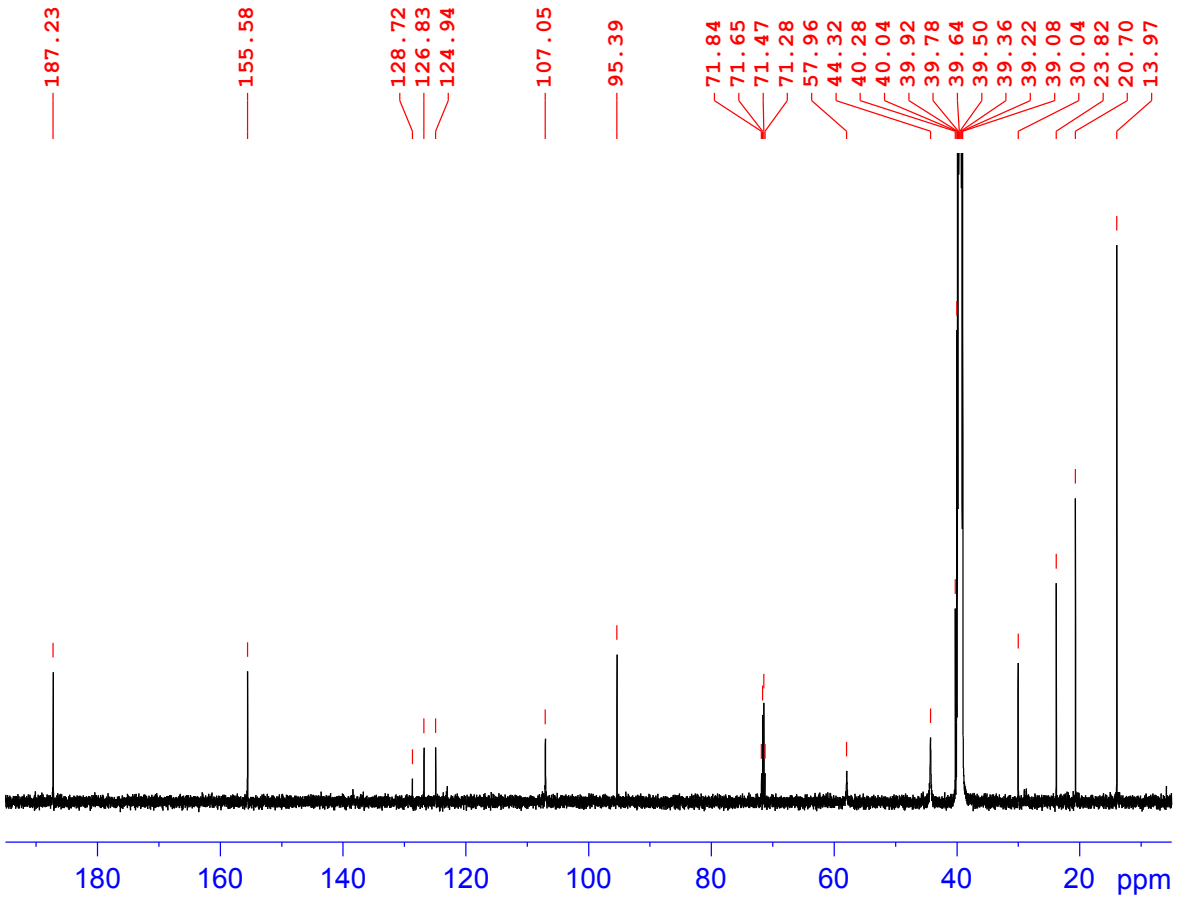

Fig. S62 ^{13}C NMR (151 MHz, DMSO-d_6) spectrum of **4ace**.

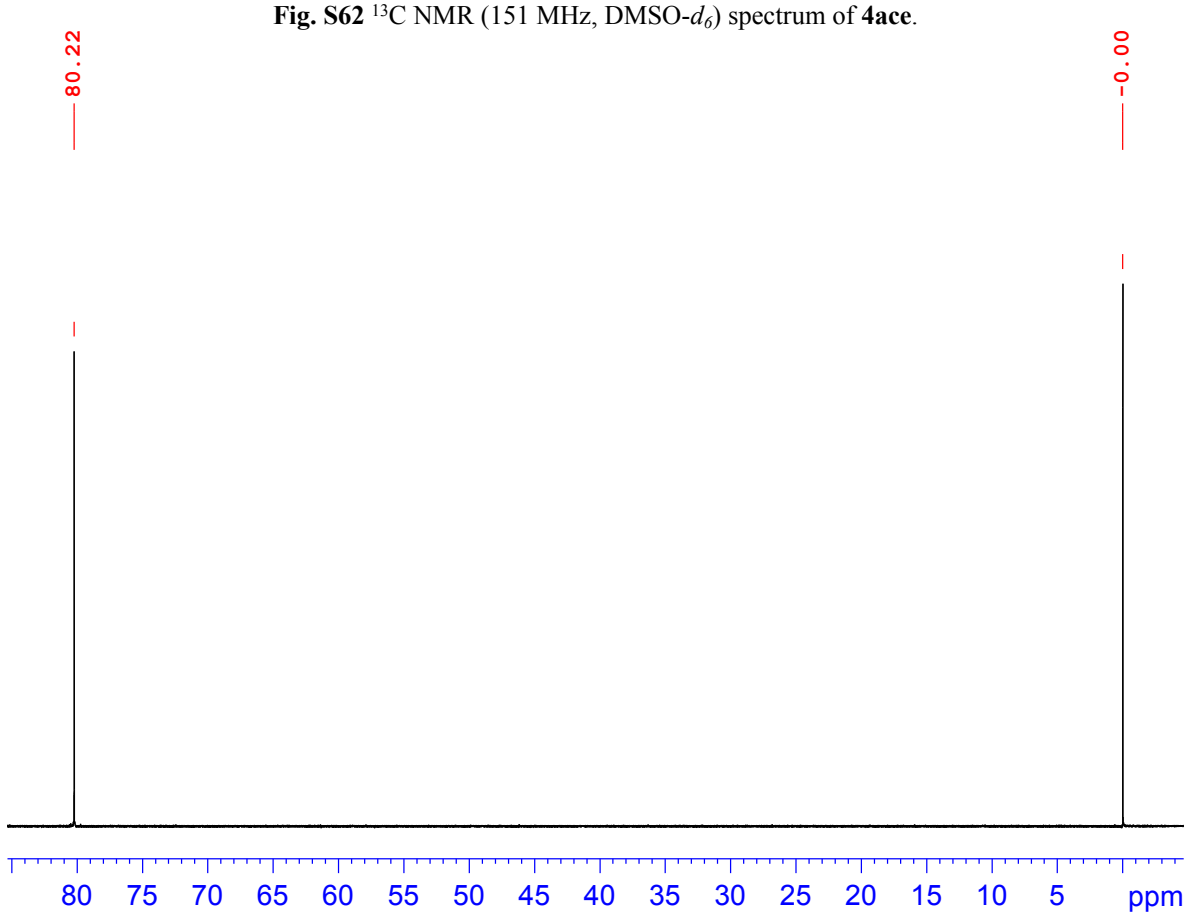

Fig. S63 ^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **4ace**.

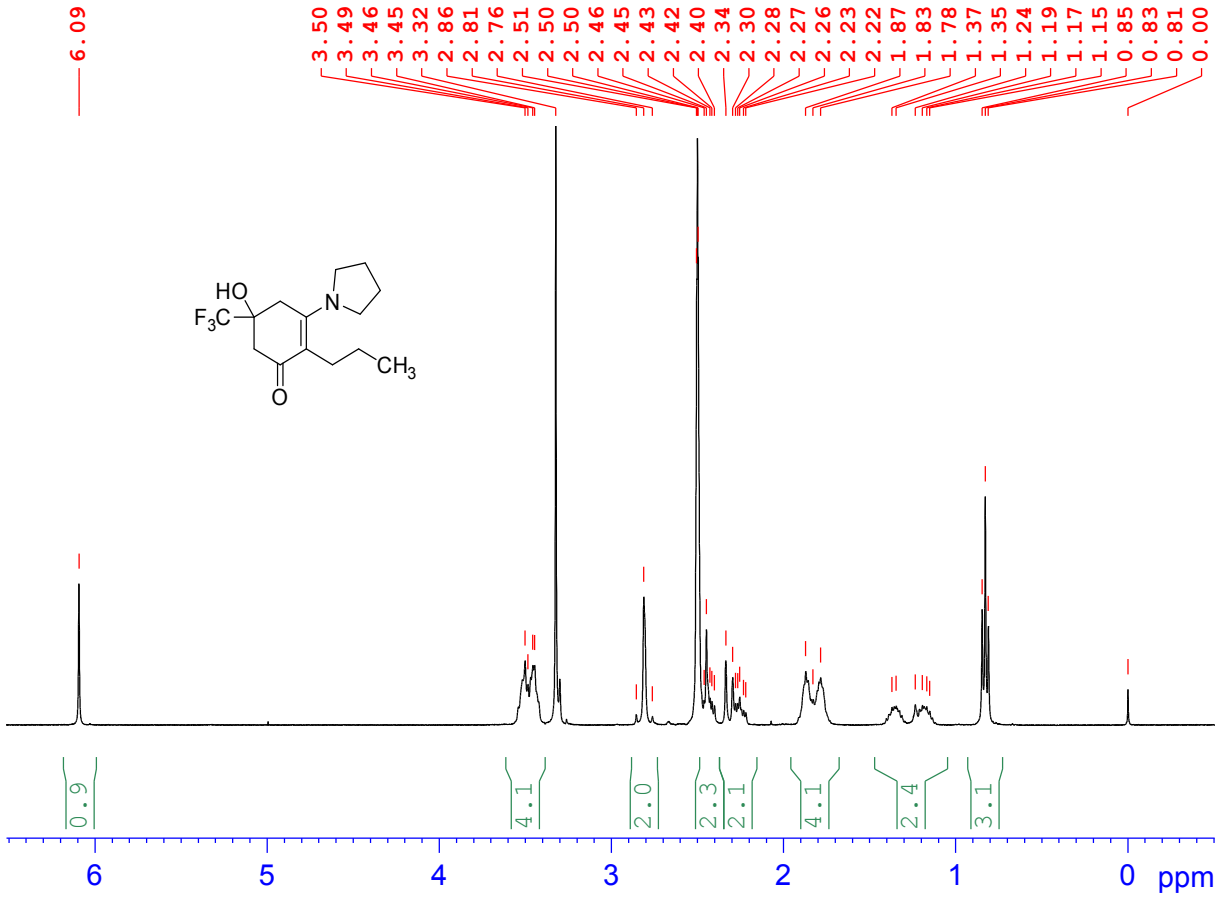

Fig. S64 ^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **4acj**.

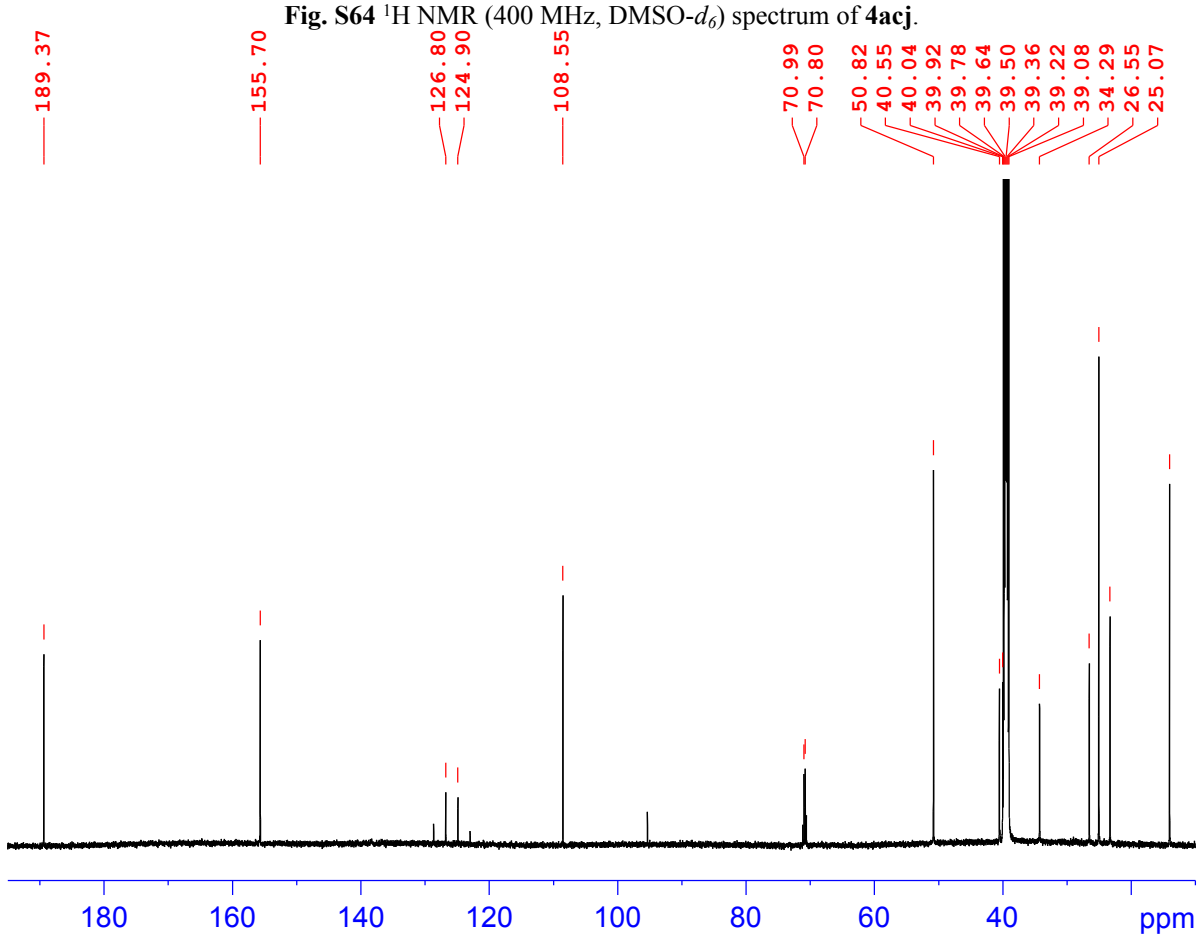

Fig. S65 ^{13}C NMR (151 MHz, DMSO-d_6) spectrum of **4acj**.

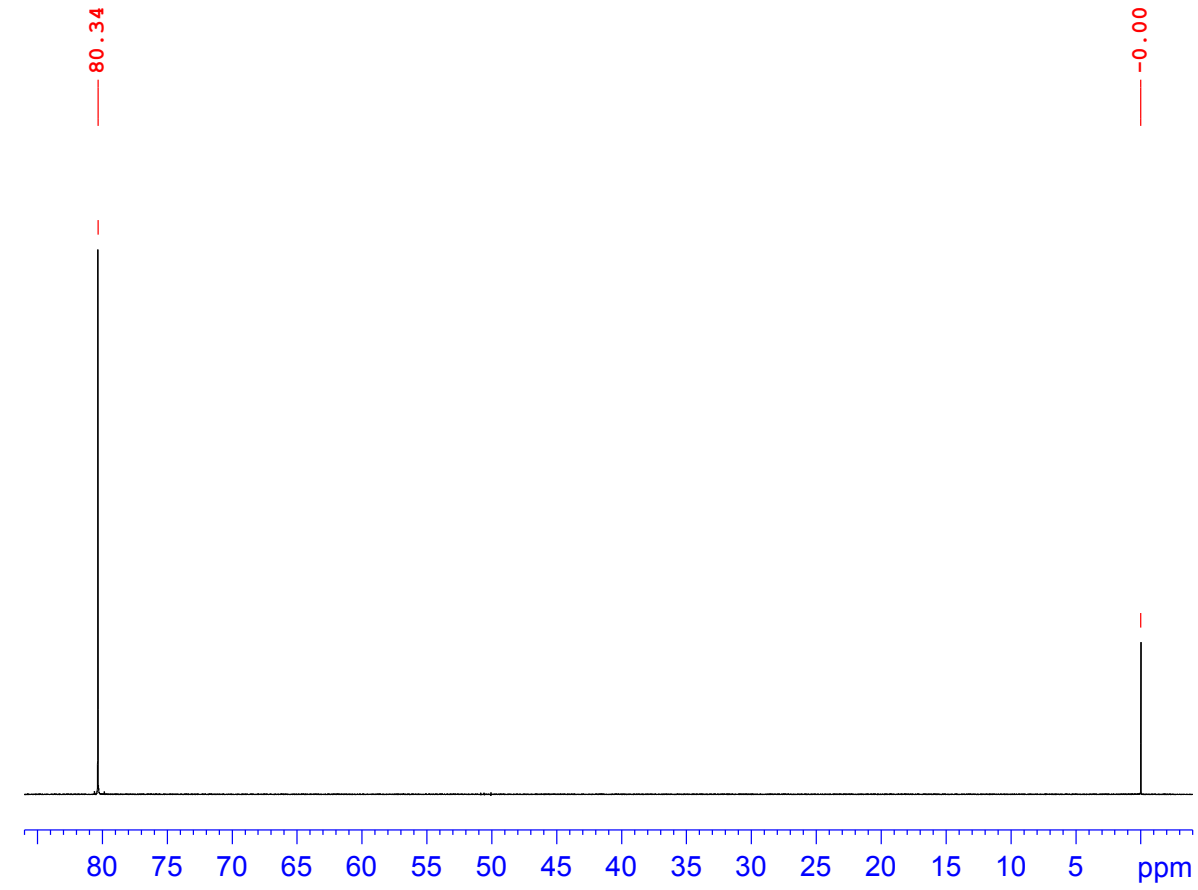

Fig. S66 ^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **4acj**.

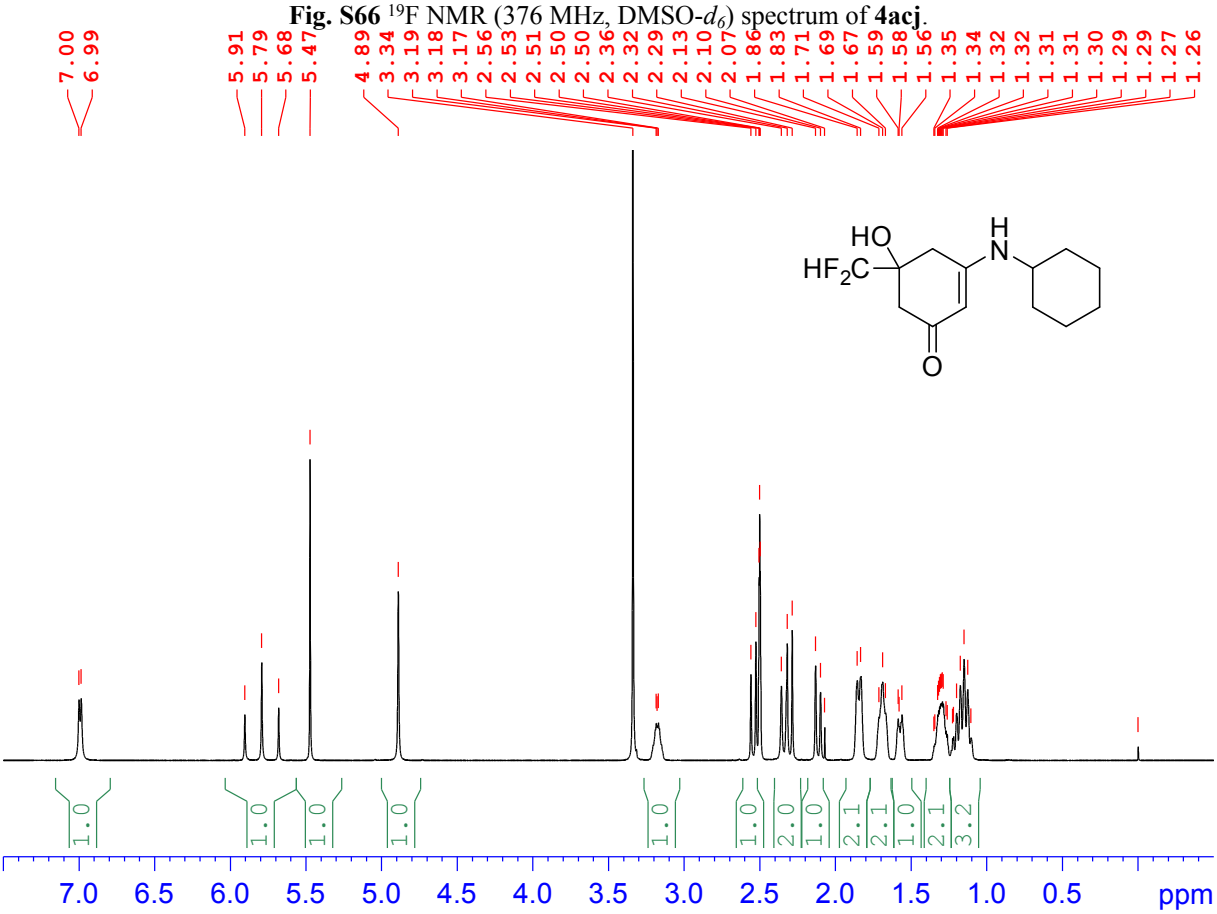

Fig. S67 ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **4baa**.

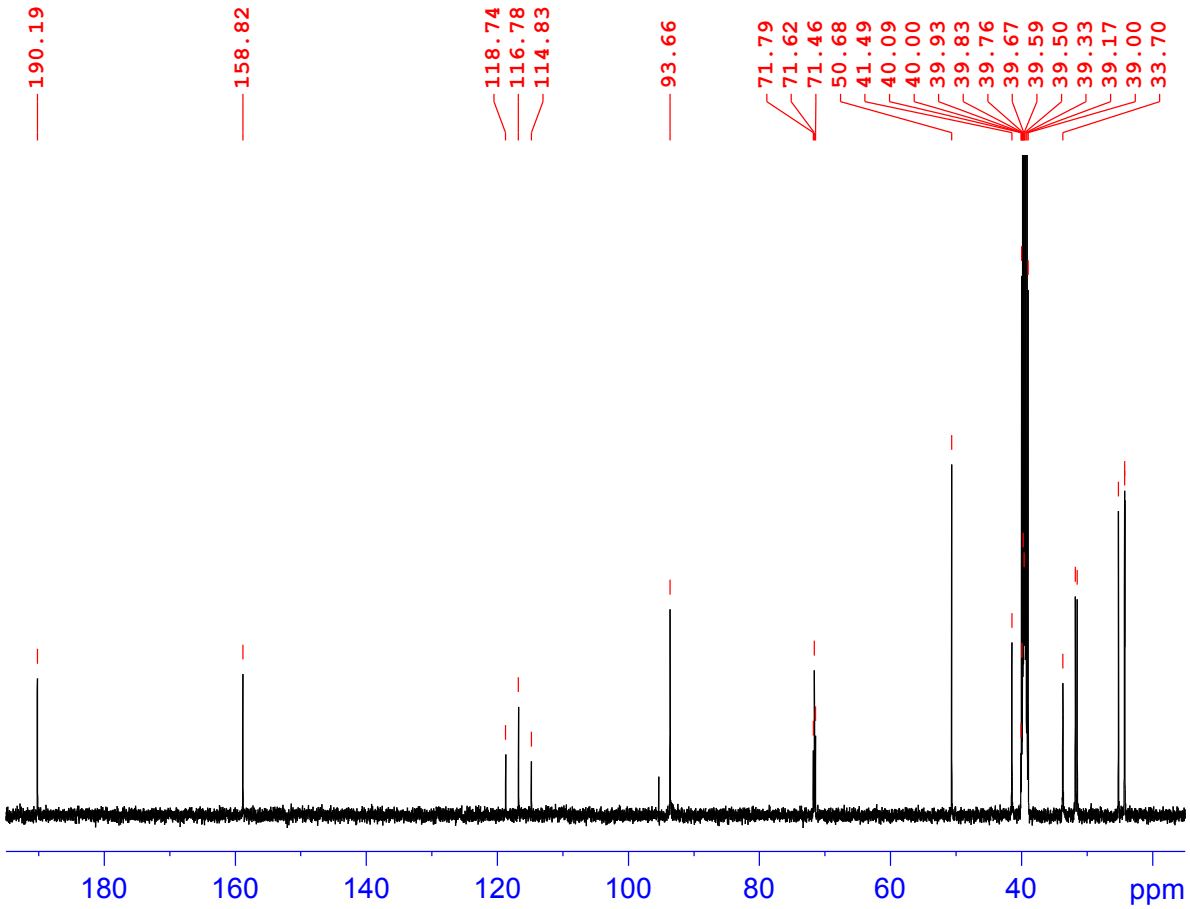

Fig. S68 ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **4baa**.

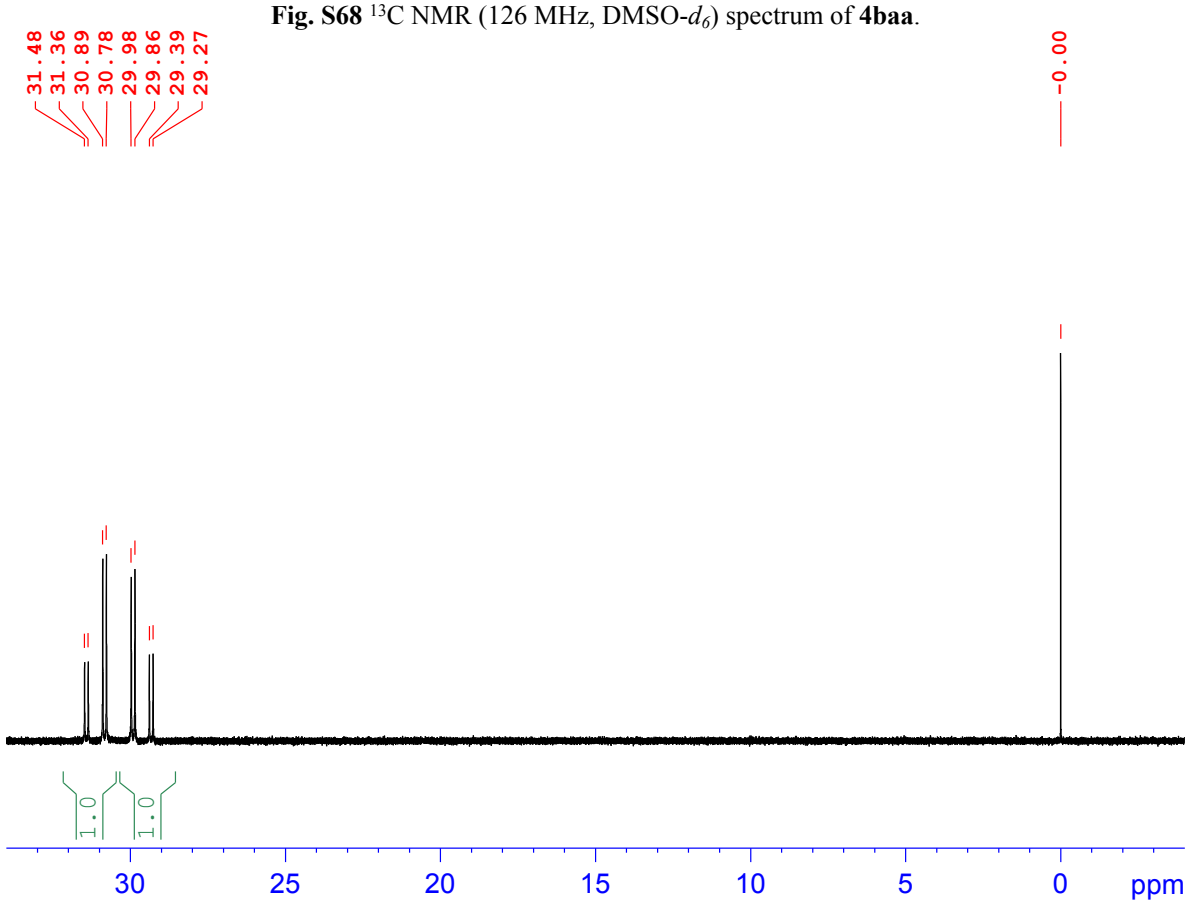

Fig. S69 ^{19}F NMR (470 MHz, DMSO-d_6) spectrum of **4baa**.

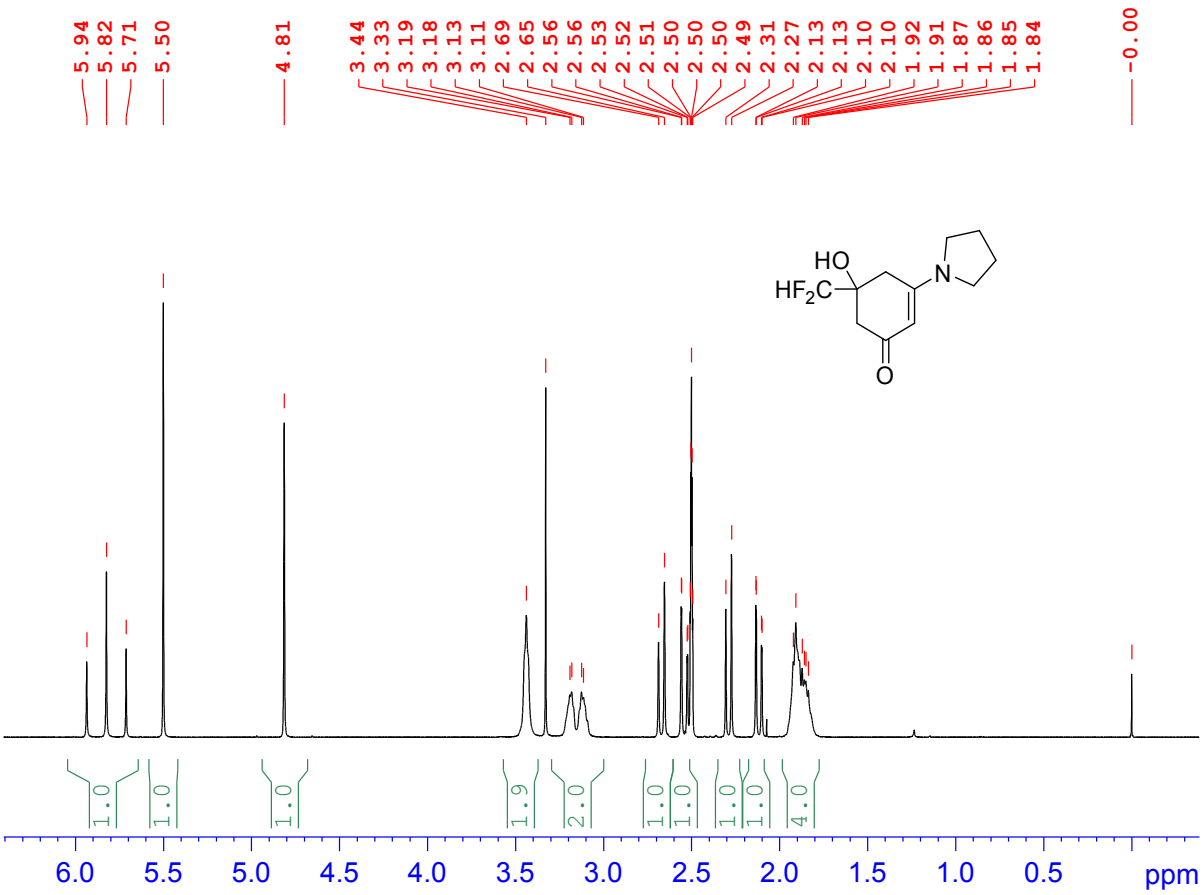

Fig. S70 ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **4baj**.

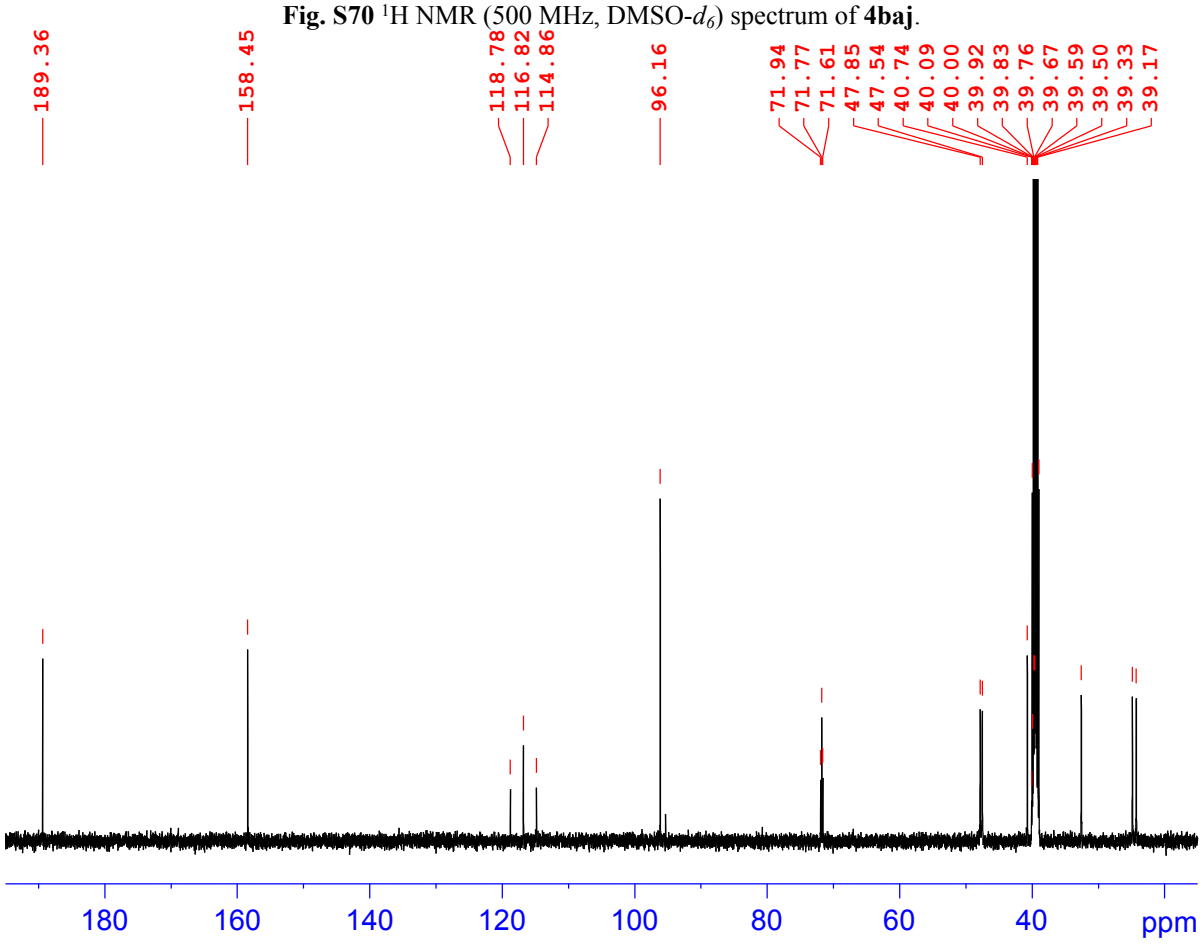

Fig. S71 ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **4baj**.

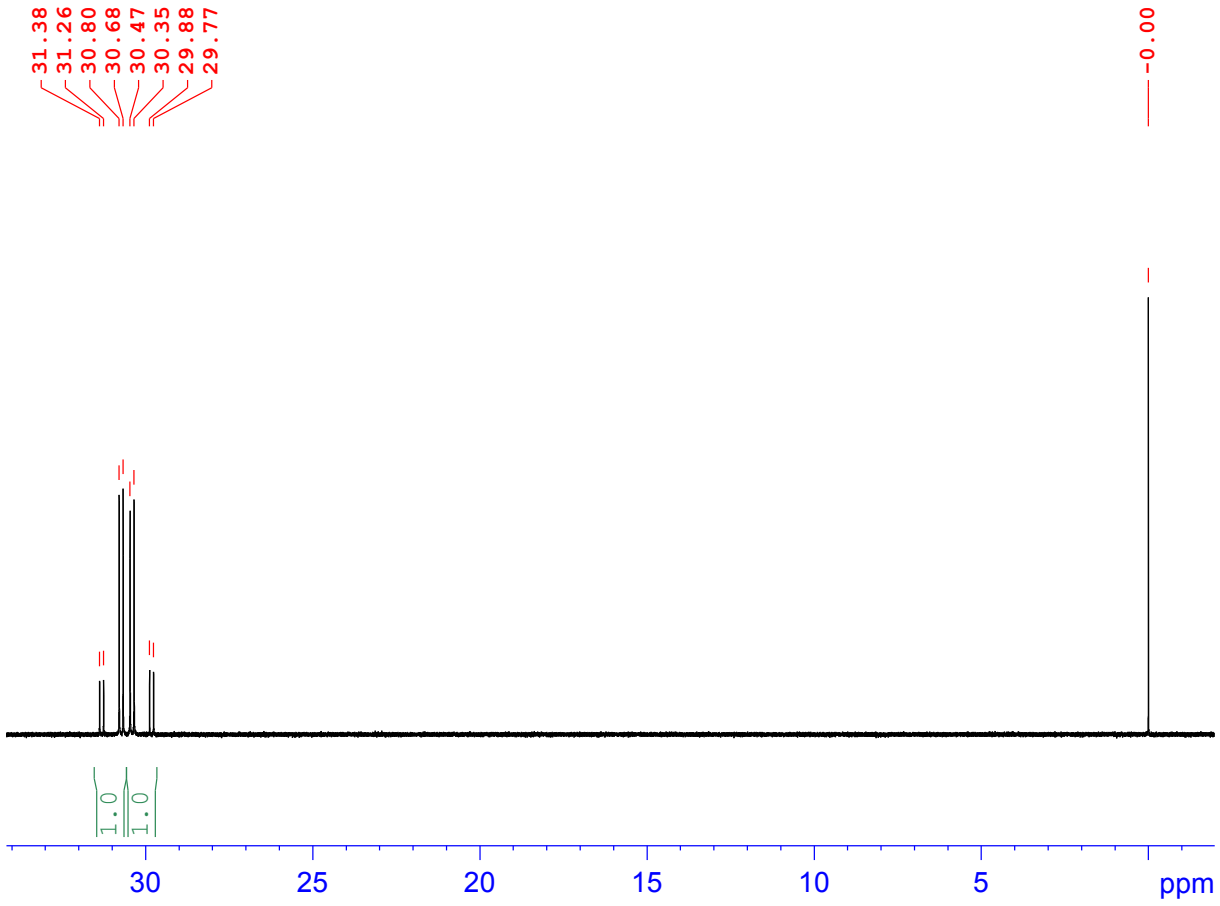

Fig. S72 ^{19}F NMR (470 MHz, DMSO-d_6) spectrum of **4baj**.

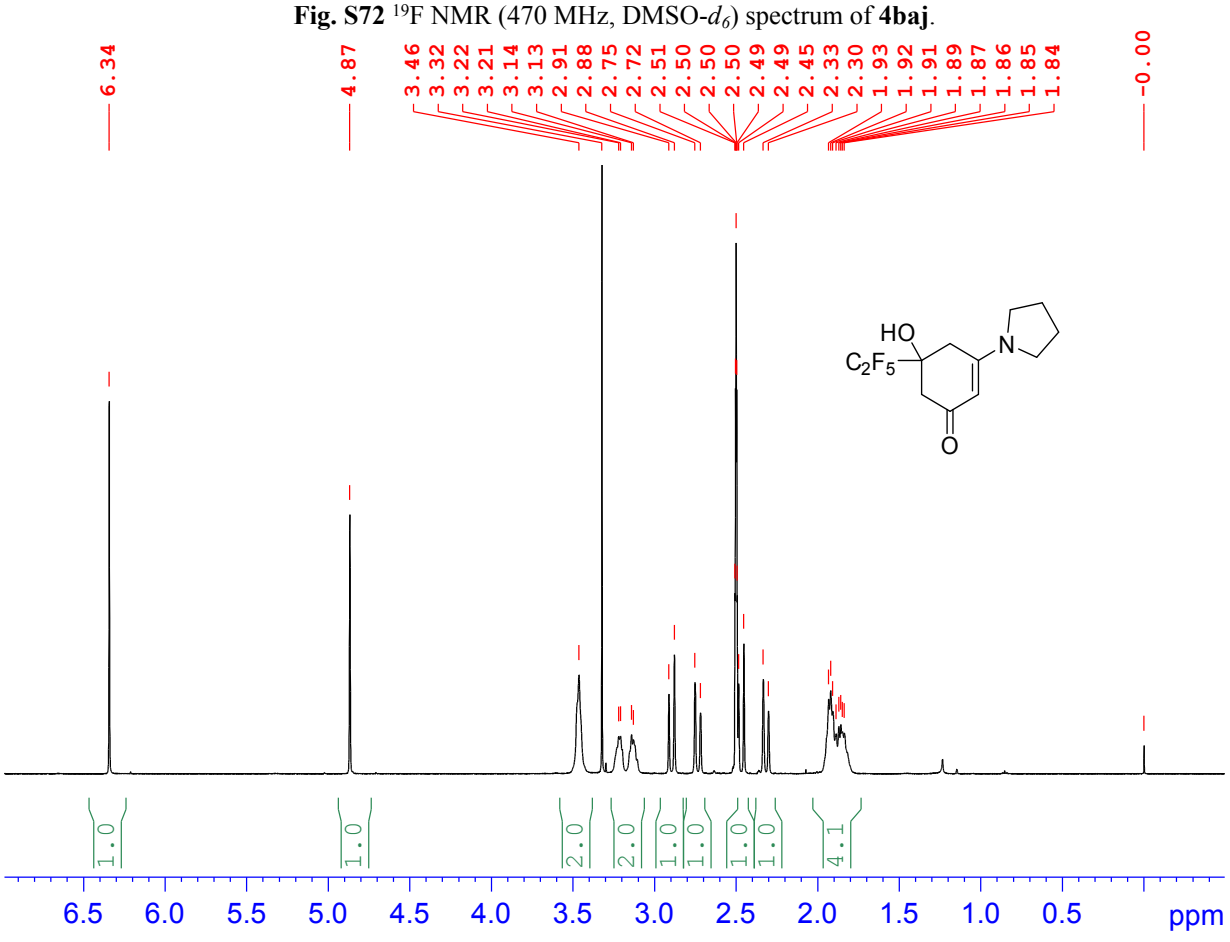

Fig. S73 ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **4caj**.

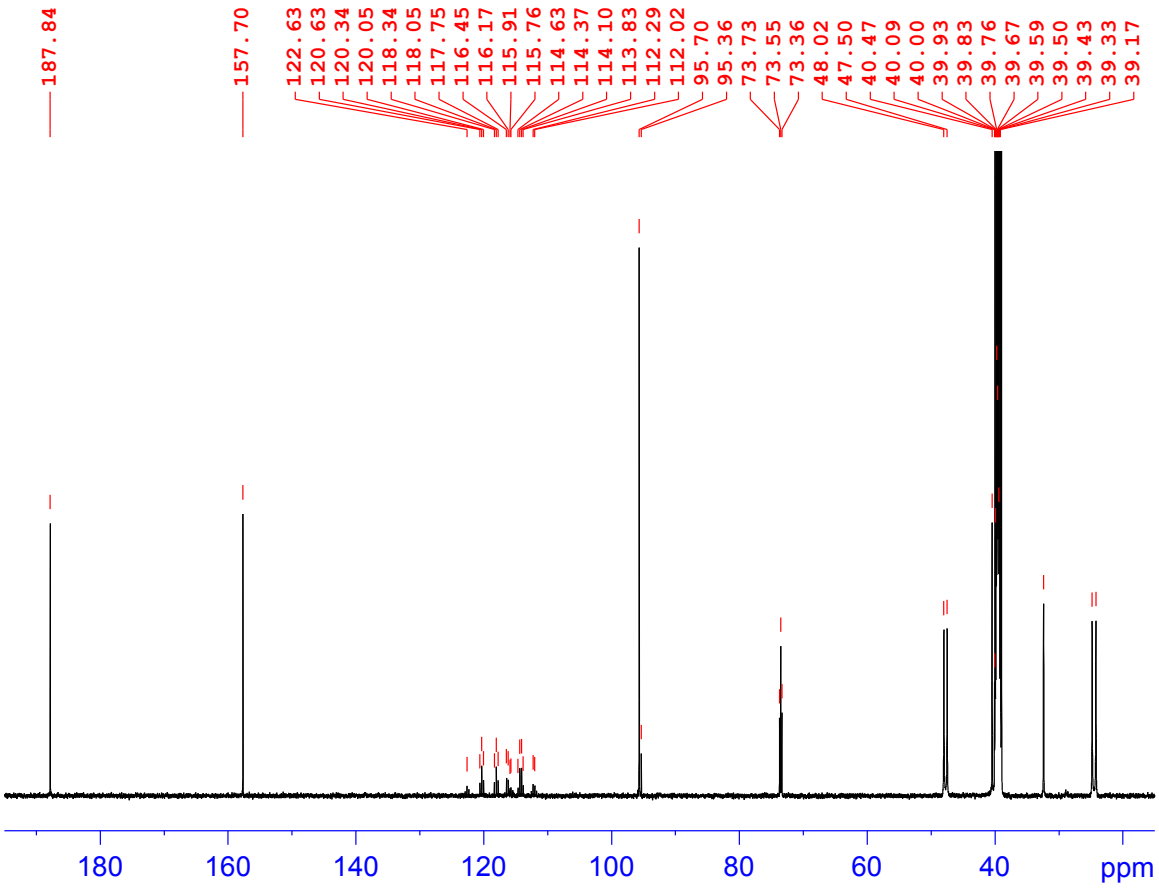

Fig. S74 ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **4caj**.

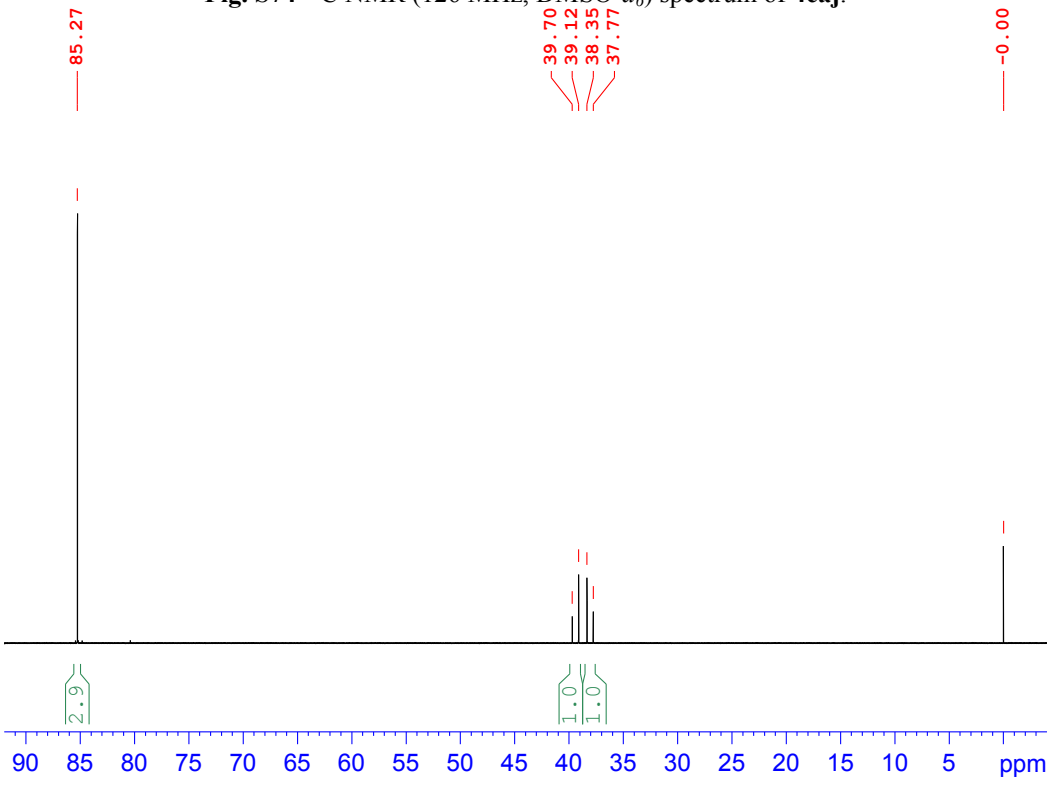

Fig. S75 ^{19}F NMR (470 MHz, DMSO-d_6) spectrum of **4caj**.

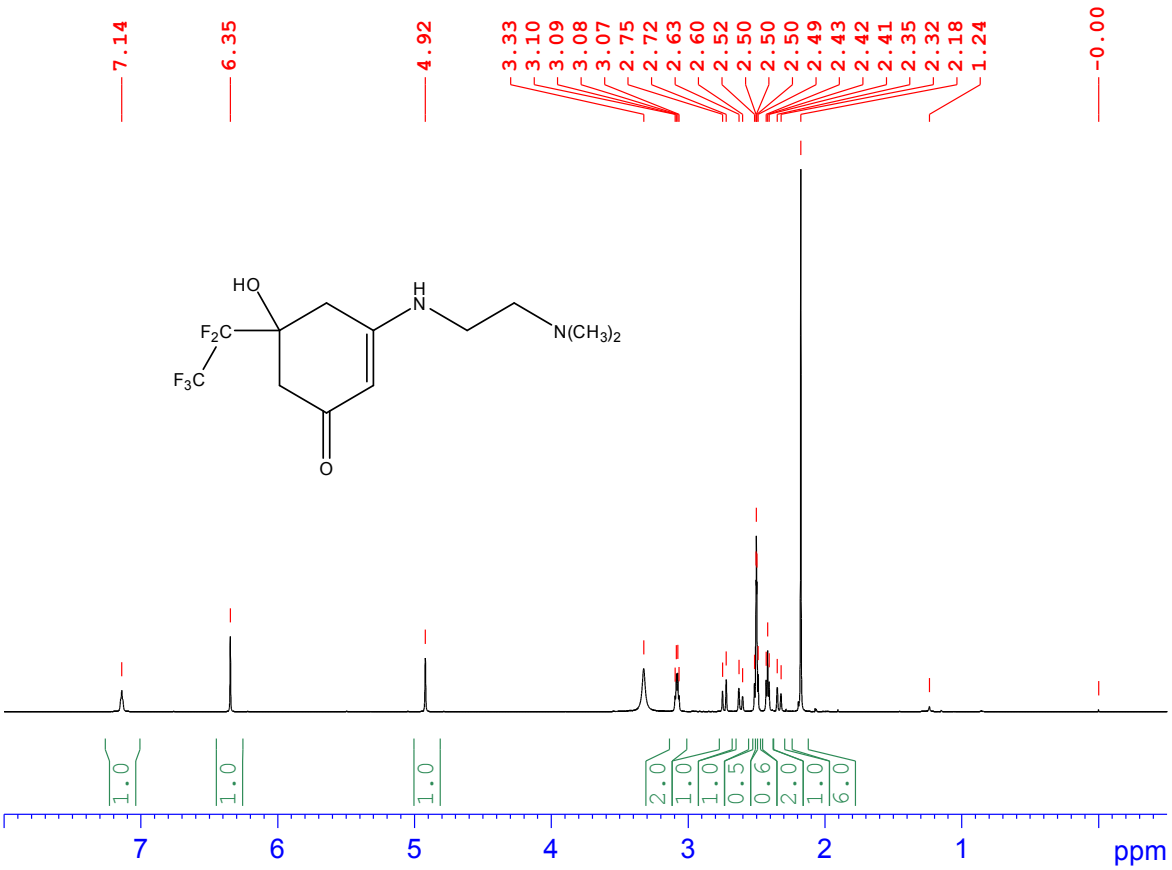

Fig. S276 ^{1}H NMR (600 MHz, DMSO-d_6) spectrum of **4cae.**

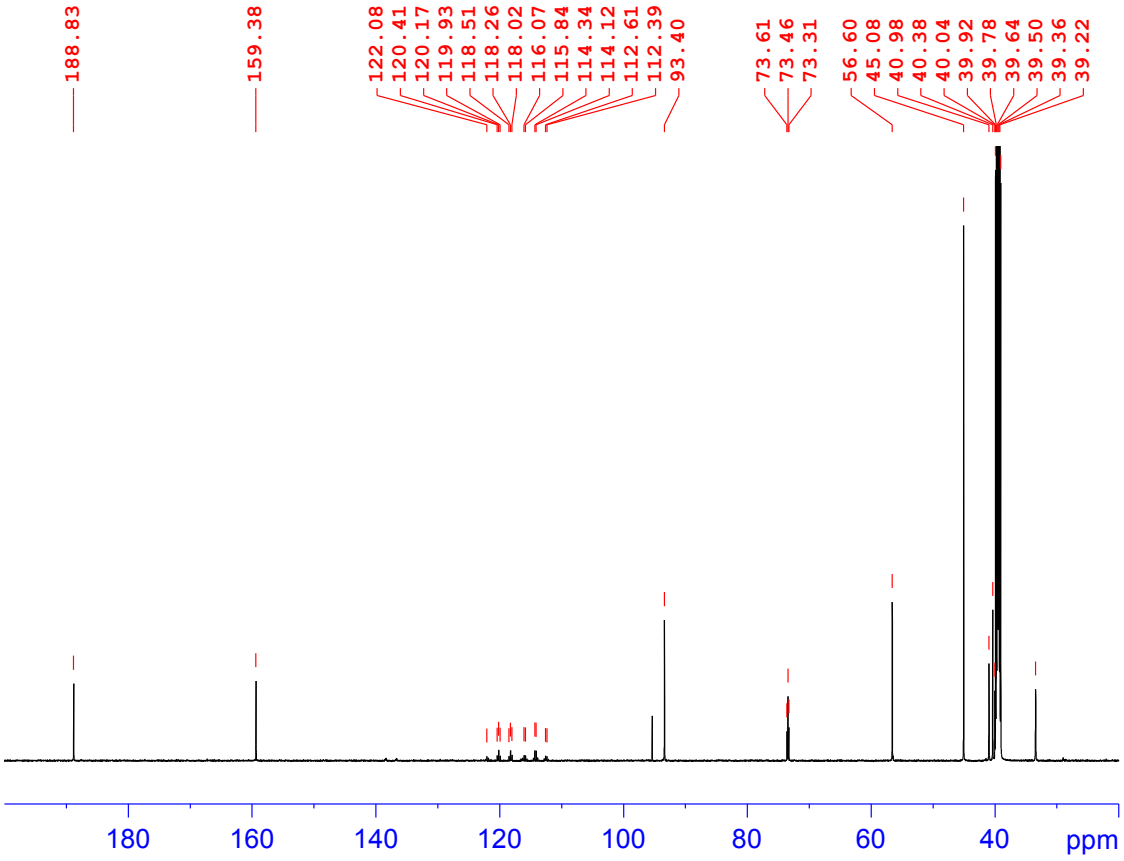

Fig. S77 ^{13}C NMR (151 MHz, DMSO-d_6) spectrum of **4cae**.

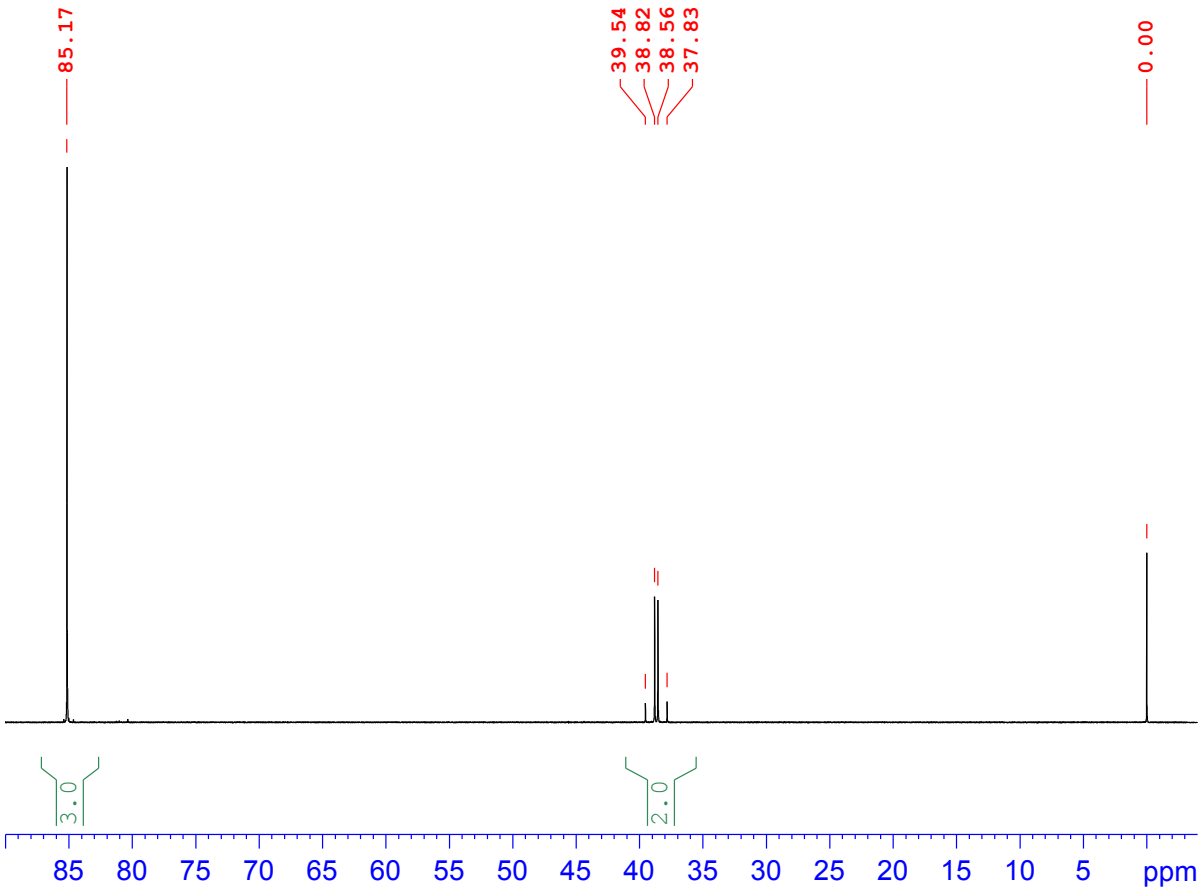

Fig. S78 ^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **4cae**.

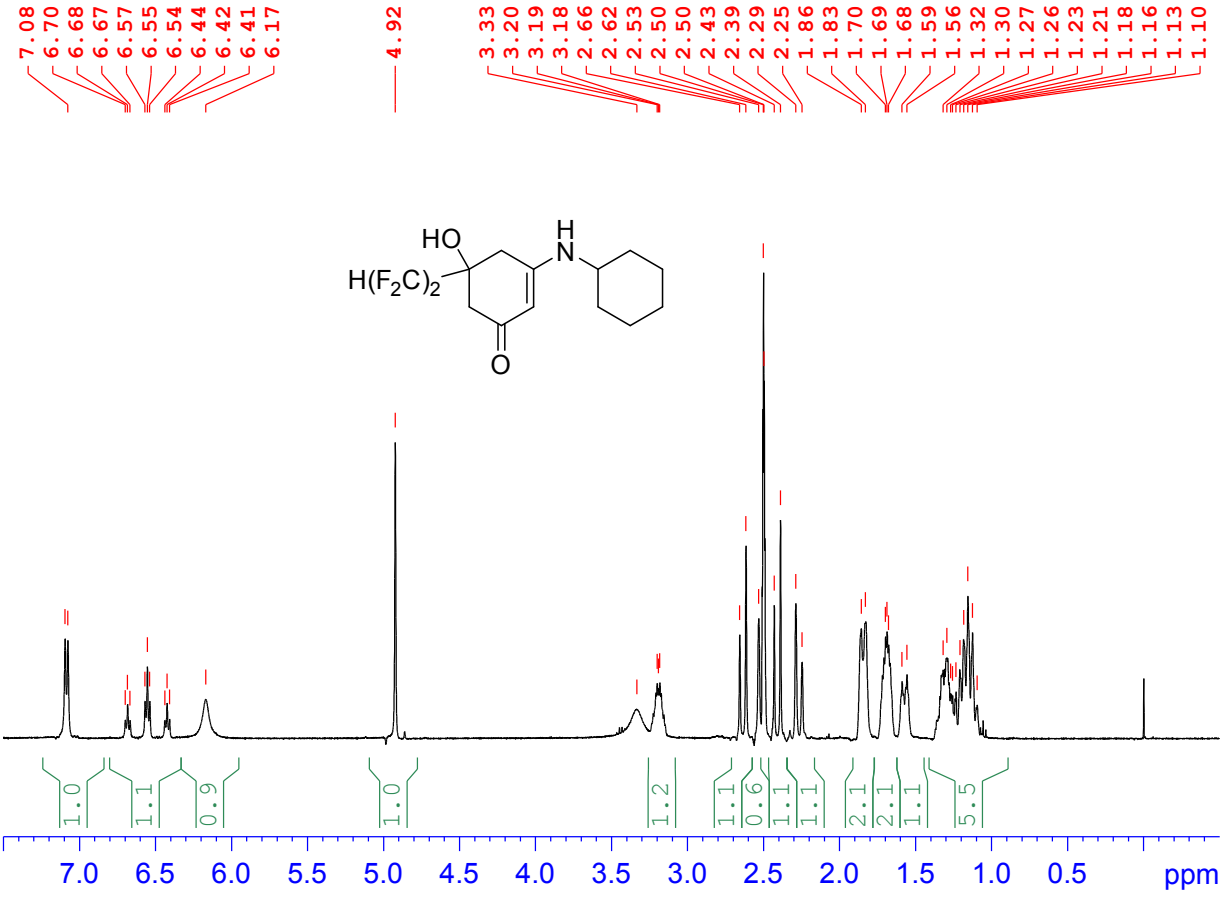

Fig. S79 ^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **4daa**.

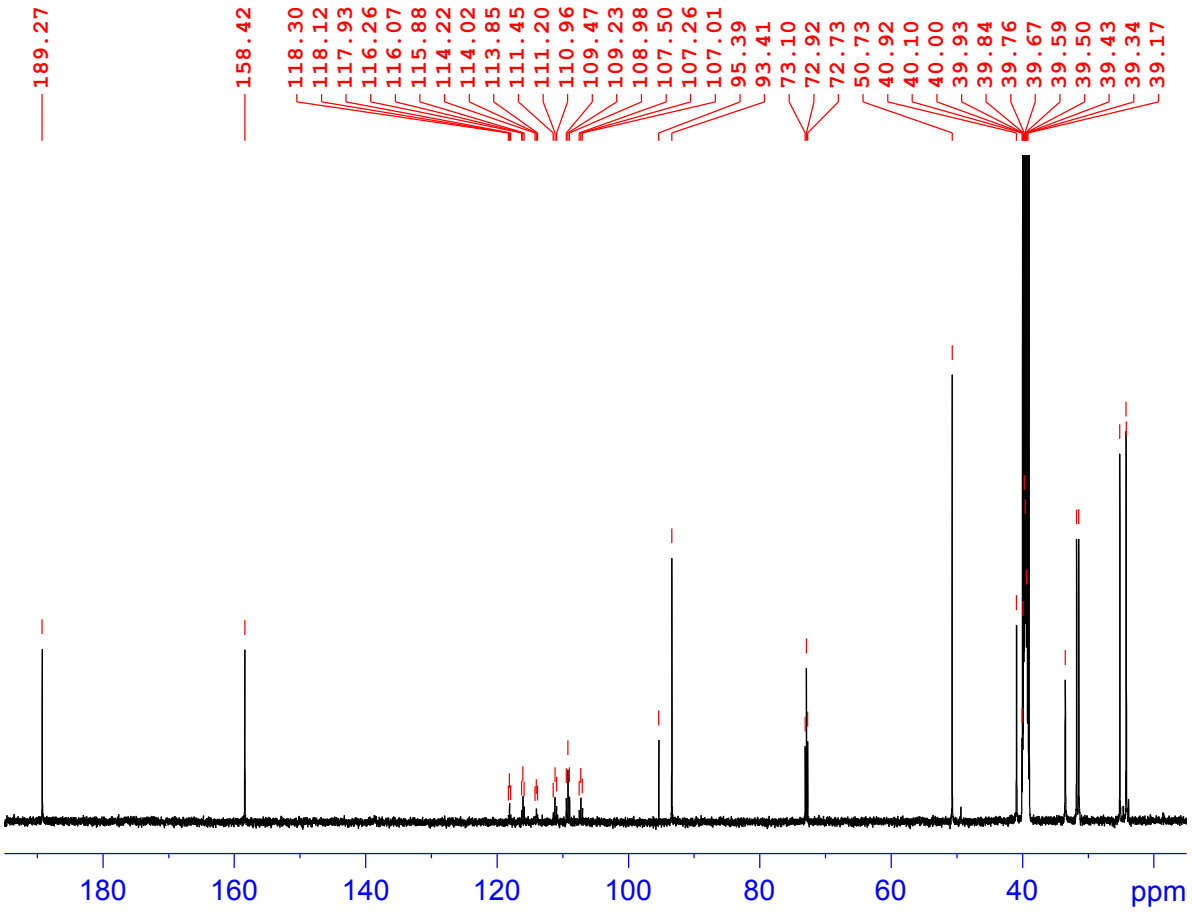

Fig. S80 ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **4daa**.

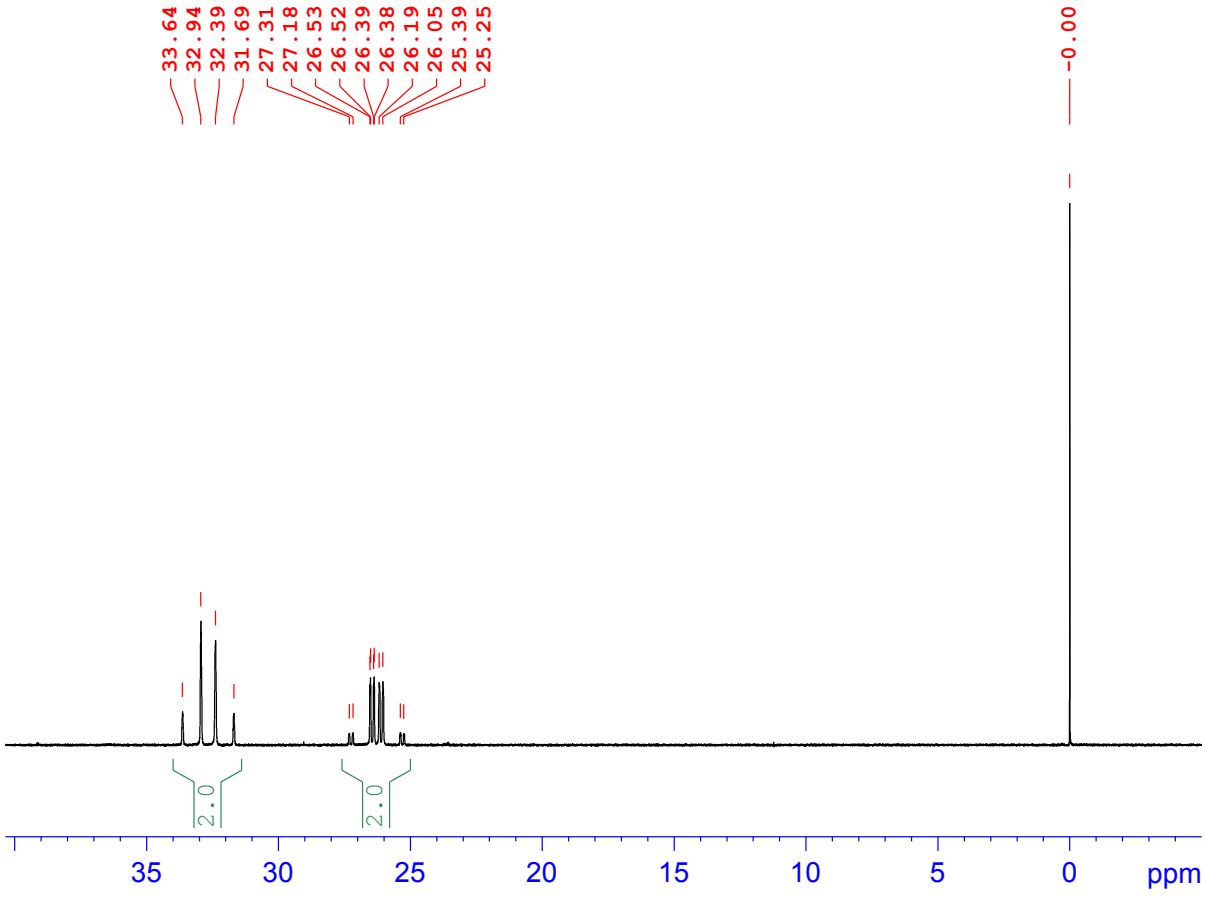

Fig. S81 ^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **4daa**.

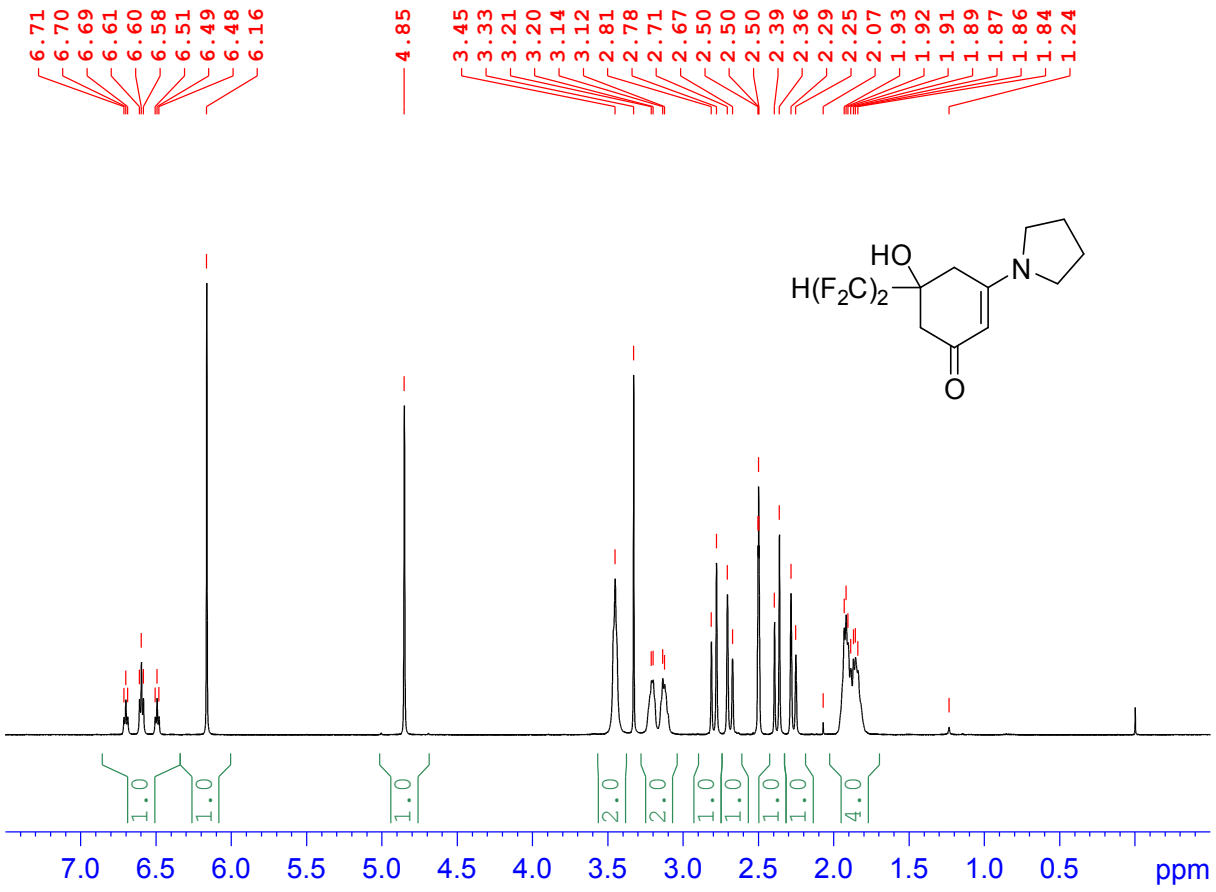

Fig. S82 ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **4daj**.

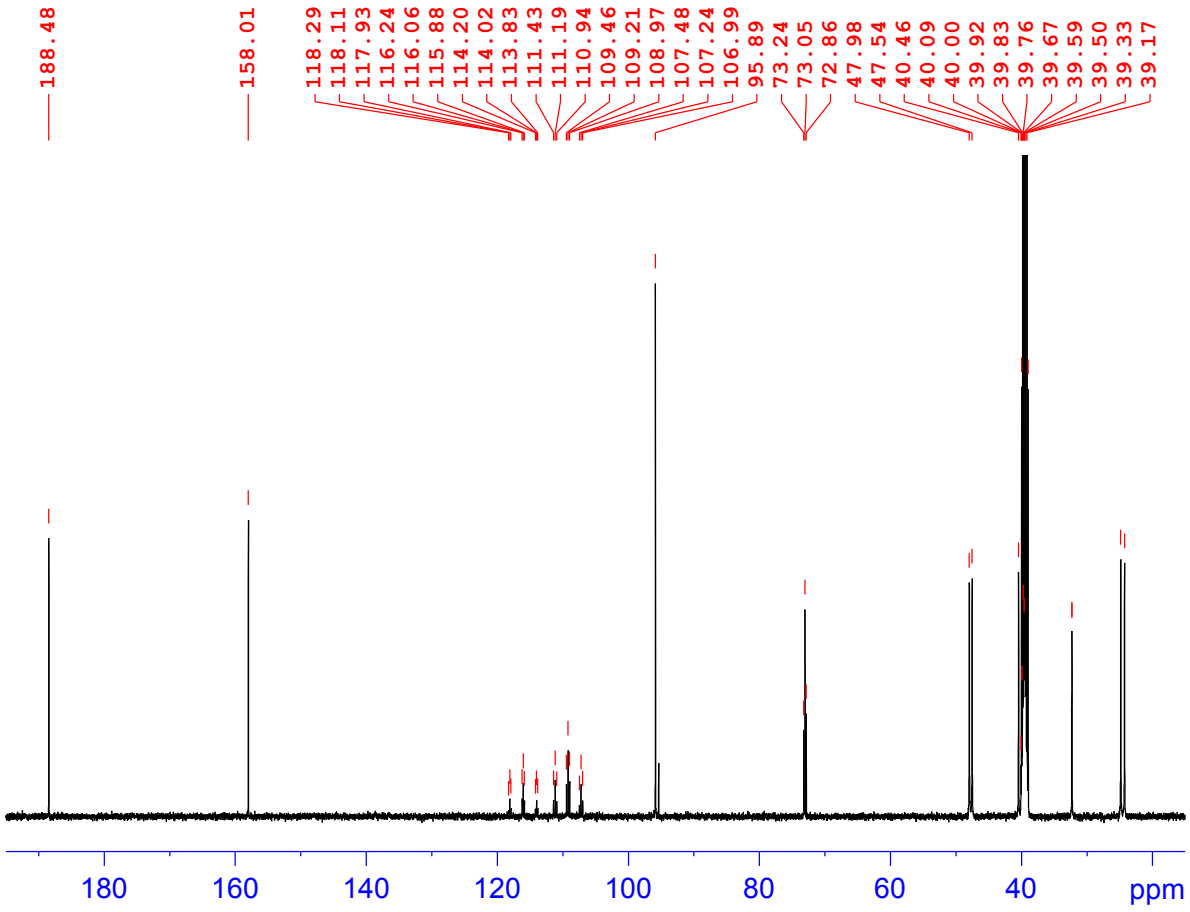

Fig. S83 ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **4daj**.

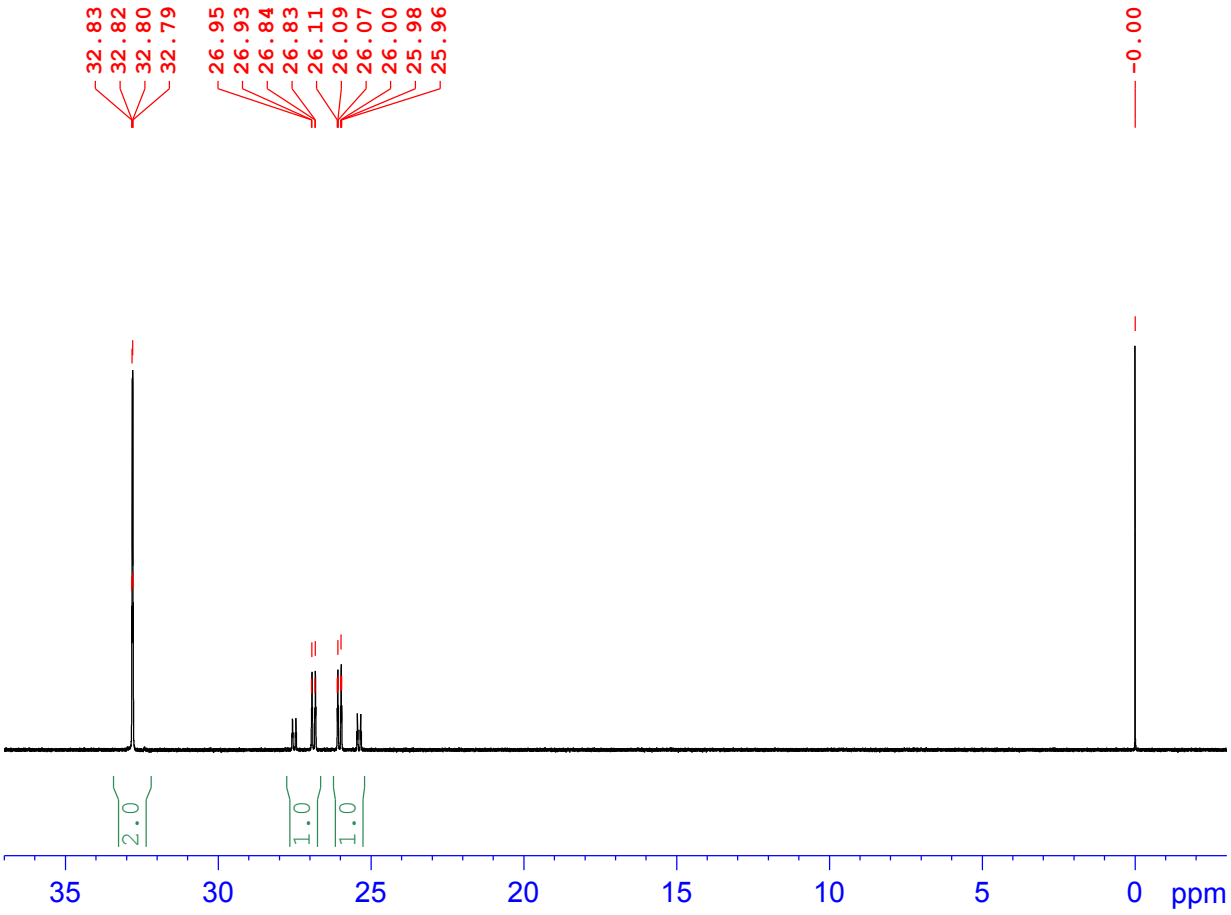

Fig. S84 ^{19}F NMR (470 MHz, DMSO-d_6) spectrum of **4daj**.

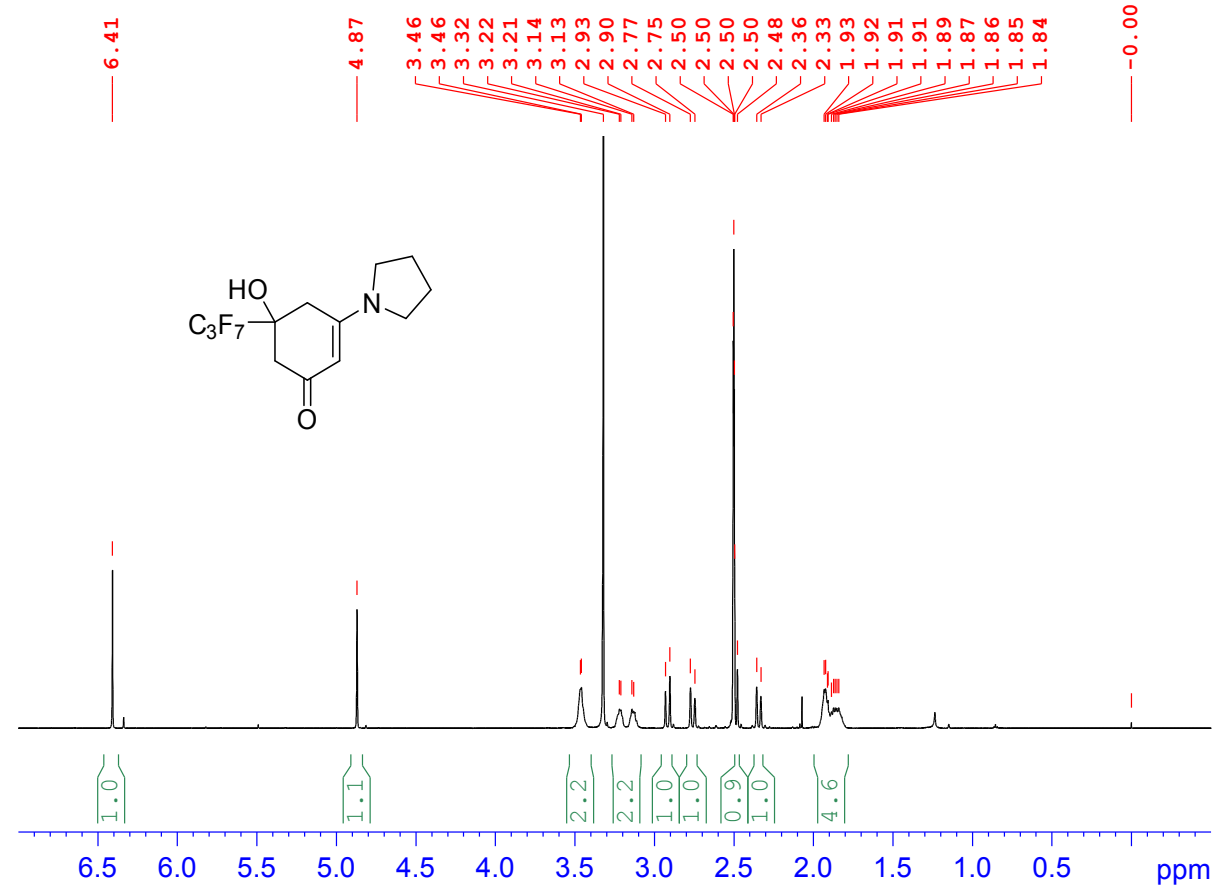

Fig. S85 ^{1}H NMR (600 MHz, DMSO-d_6) spectrum of **4eaj**.

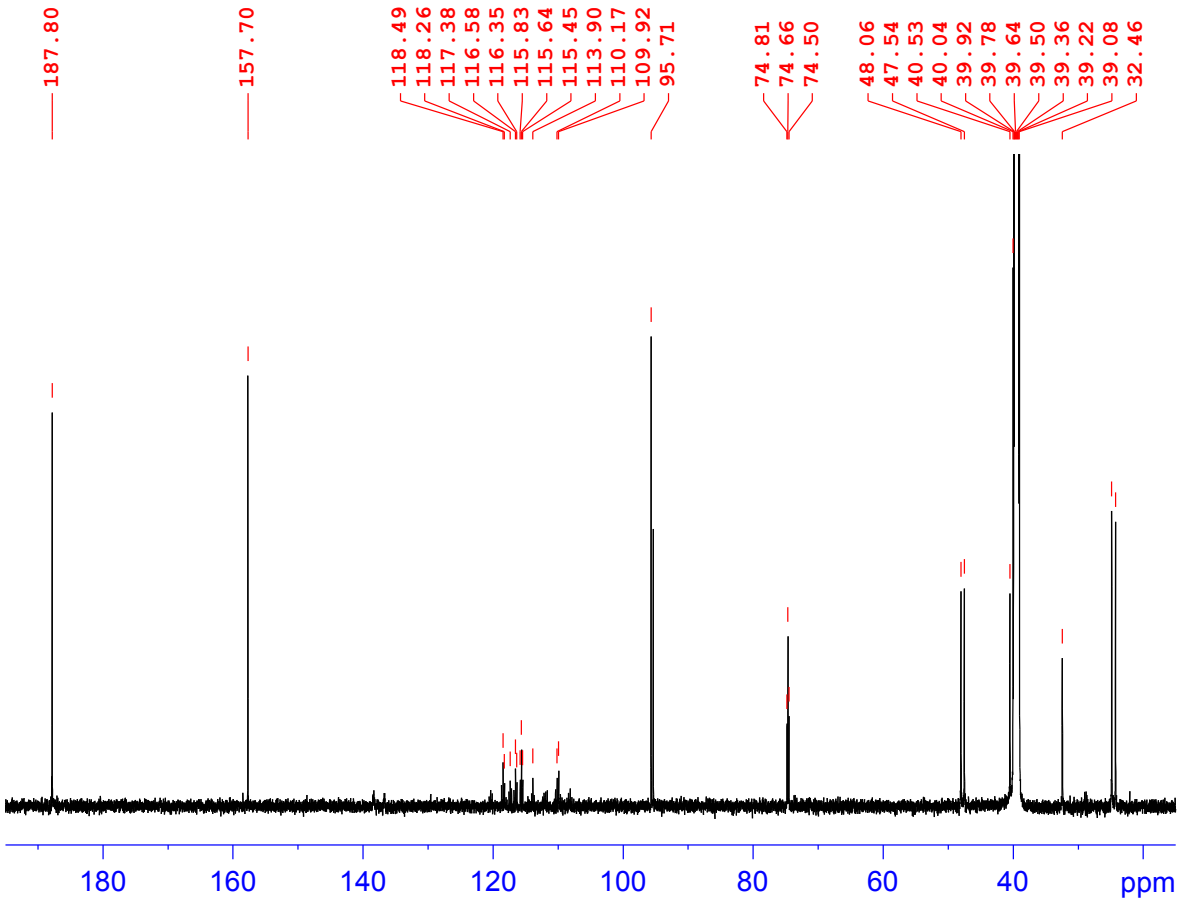

Fig. S86 ^{13}C NMR (151 MHz, DMSO-d_6) spectrum of **4eaj**.

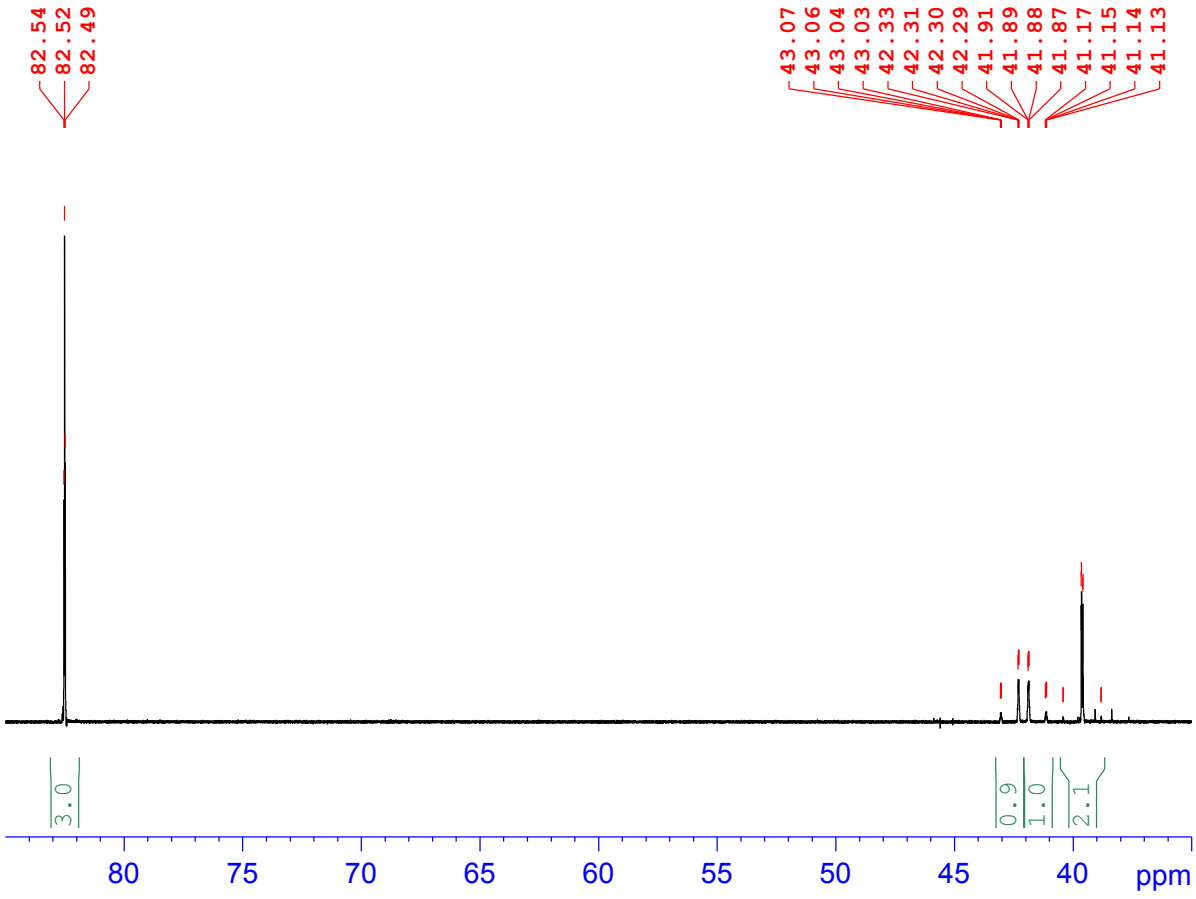

Fig. S87 ^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **4eaj**.

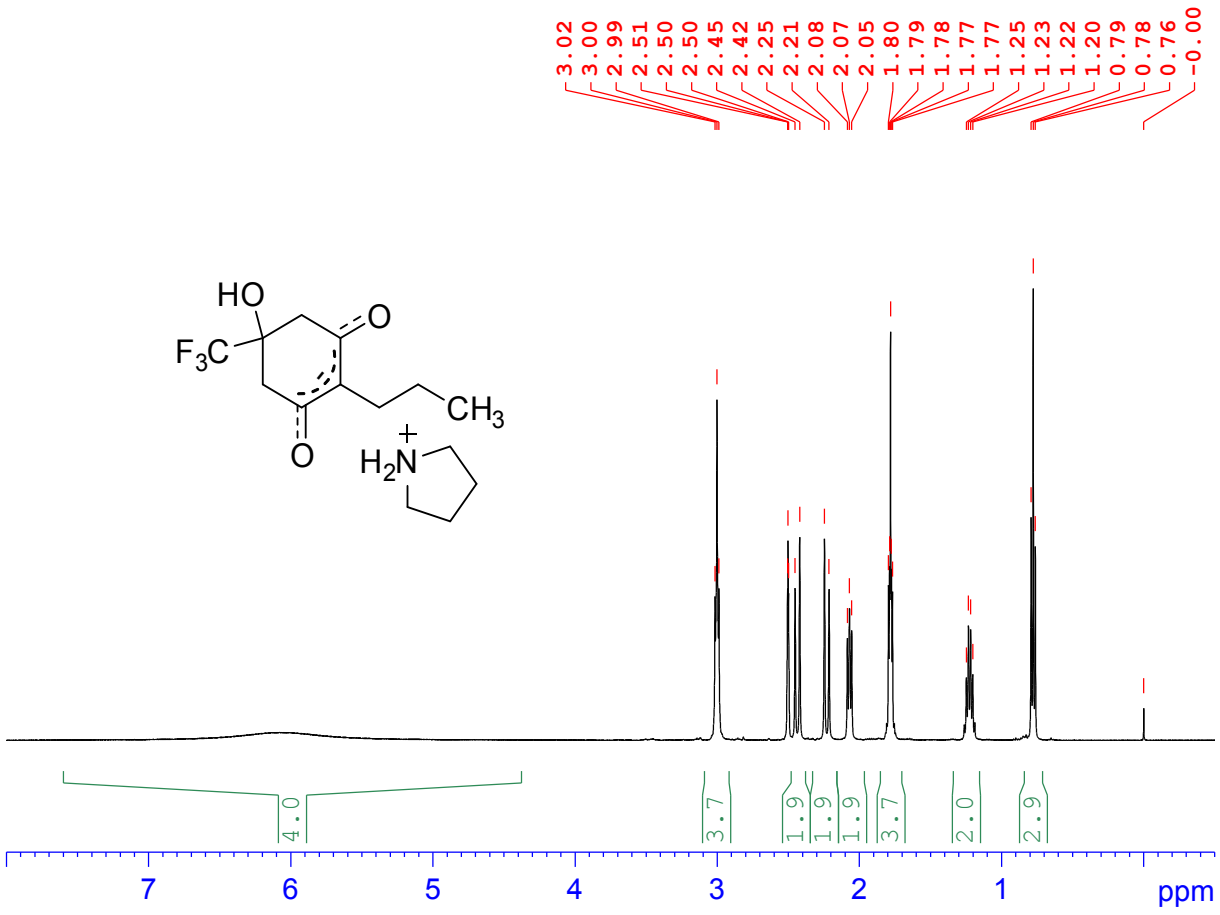

Fig. S88 ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **8**.

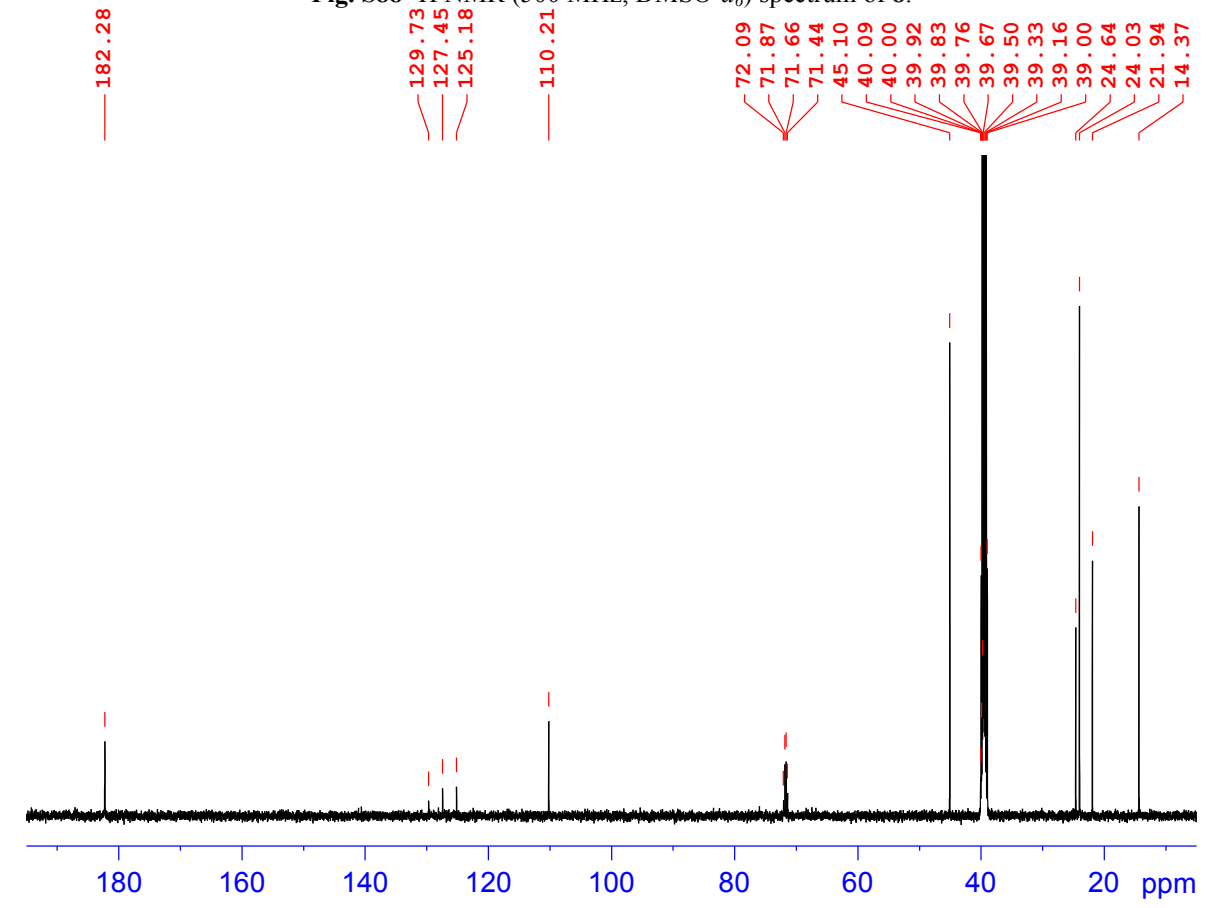

Fig. S89 ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **8**.

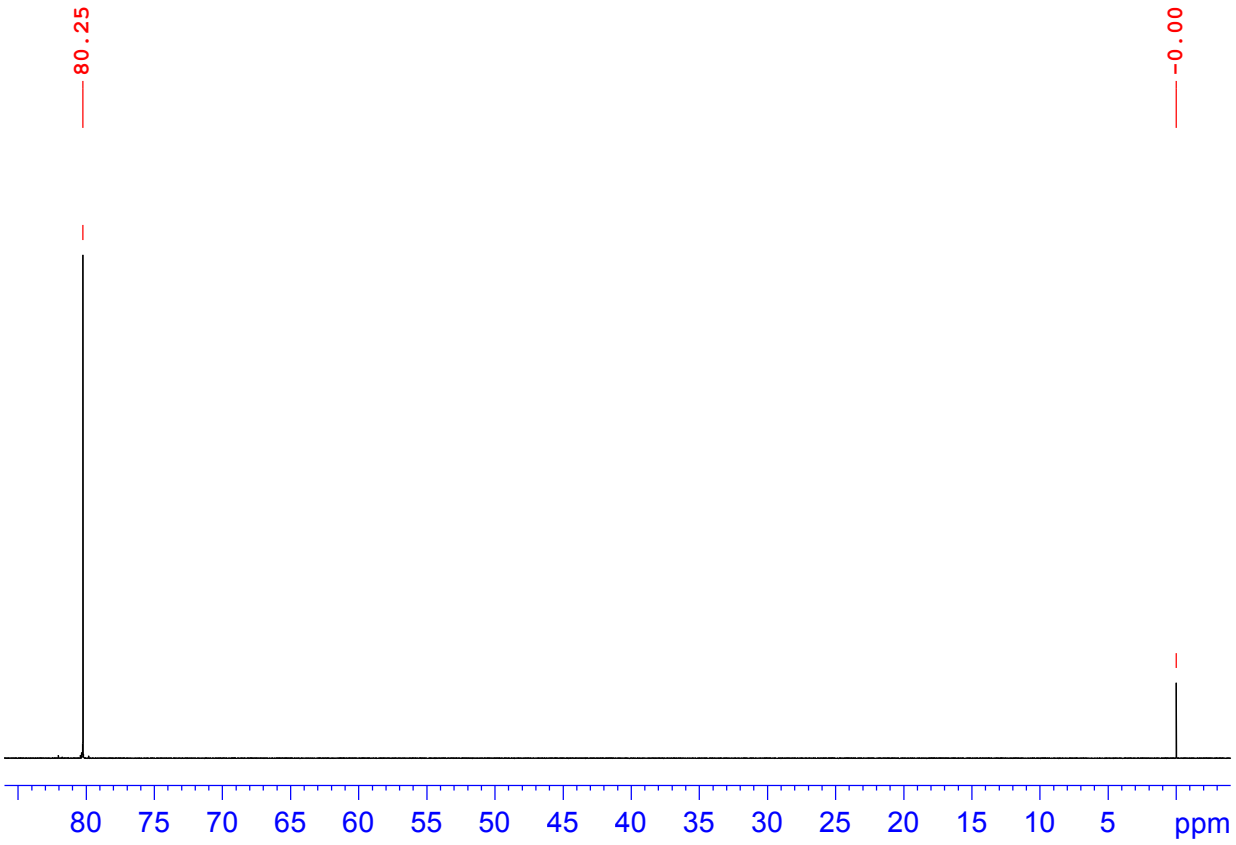

Fig. S90 ^{19}F NMR (470 MHz, DMSO-d_6) spectrum of **8**.

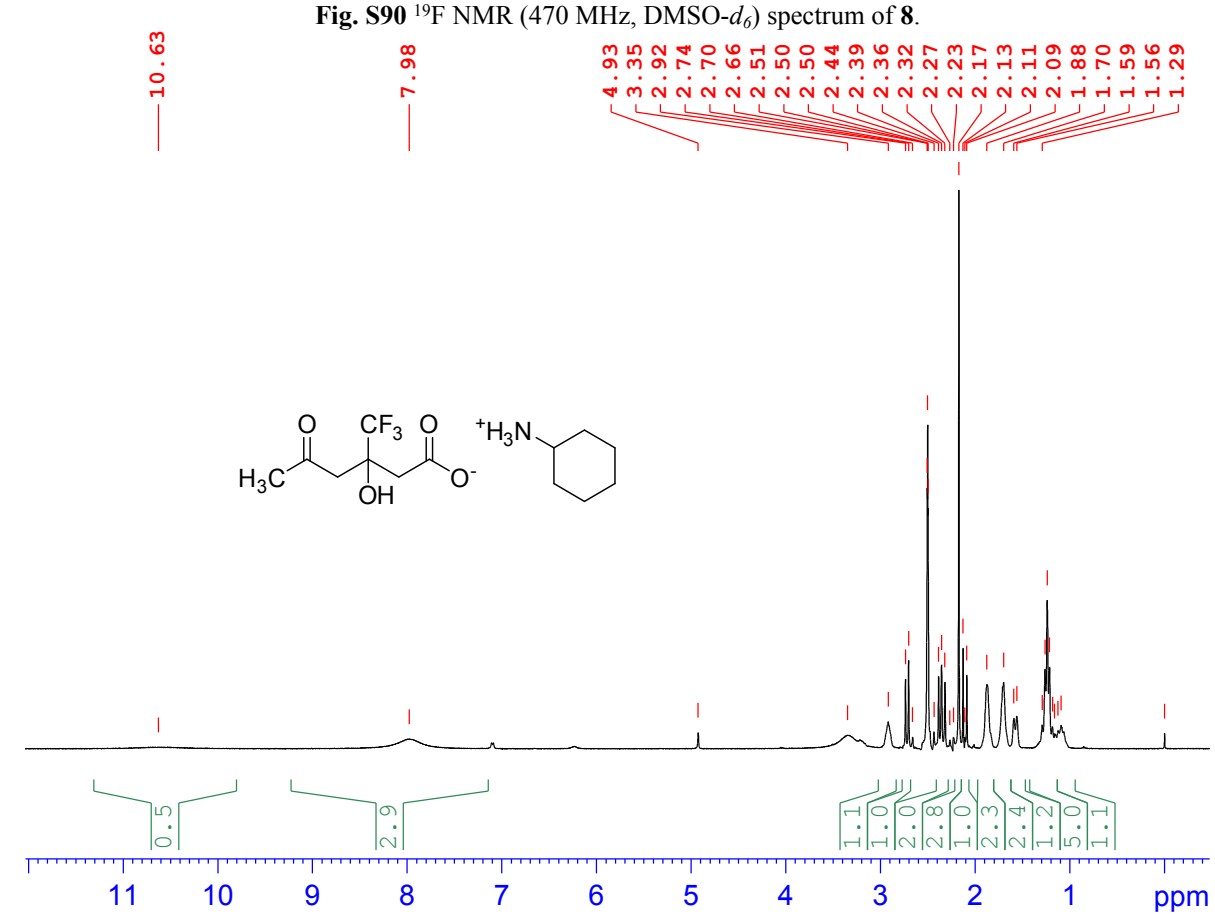

Fig. S91 ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **5a** (impurity of **4aaa** is about 13%).

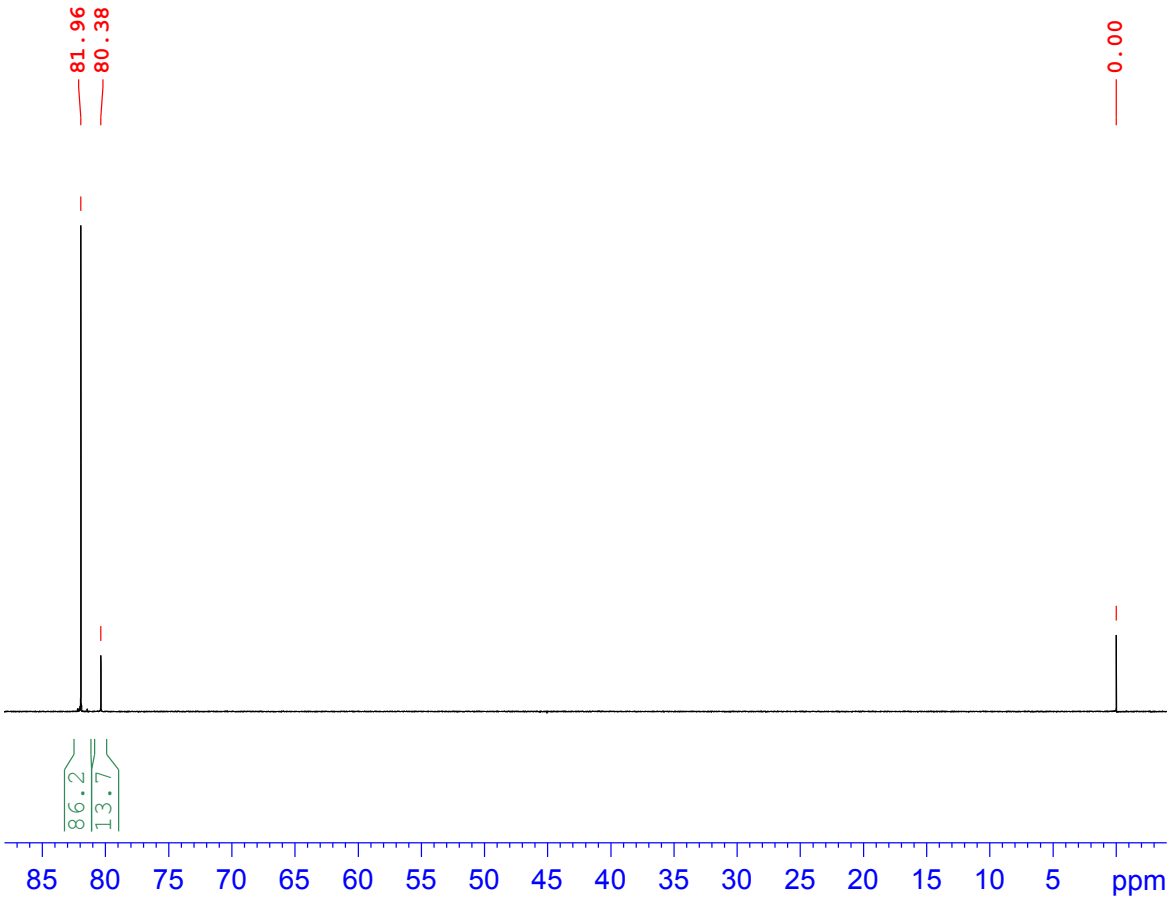

Figure S92 ^{19}F NMR (470 MHz, DMSO-d_6) spectrum of **5a** (impurity of **4aaa** is about 13%).

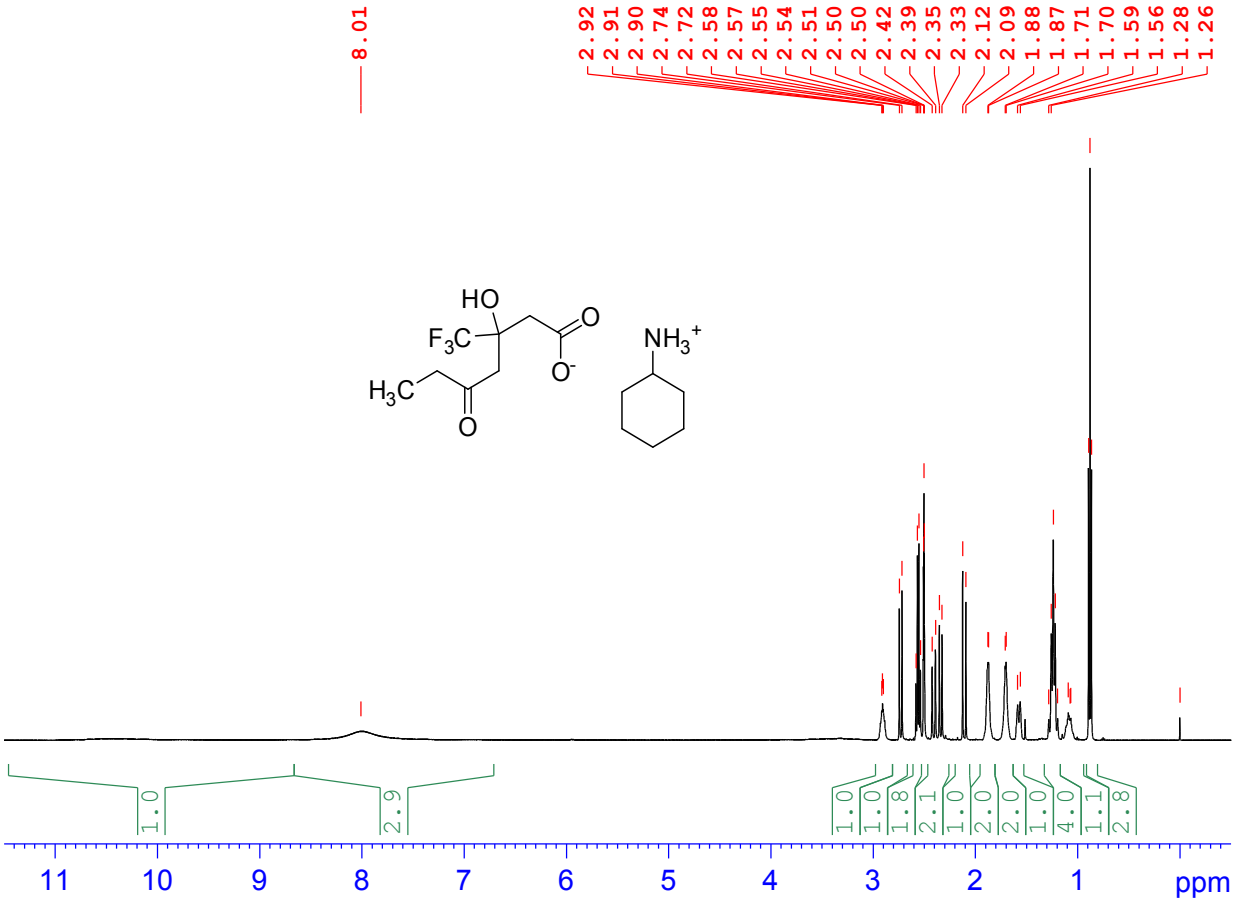

Fig. S93 ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **5b**.

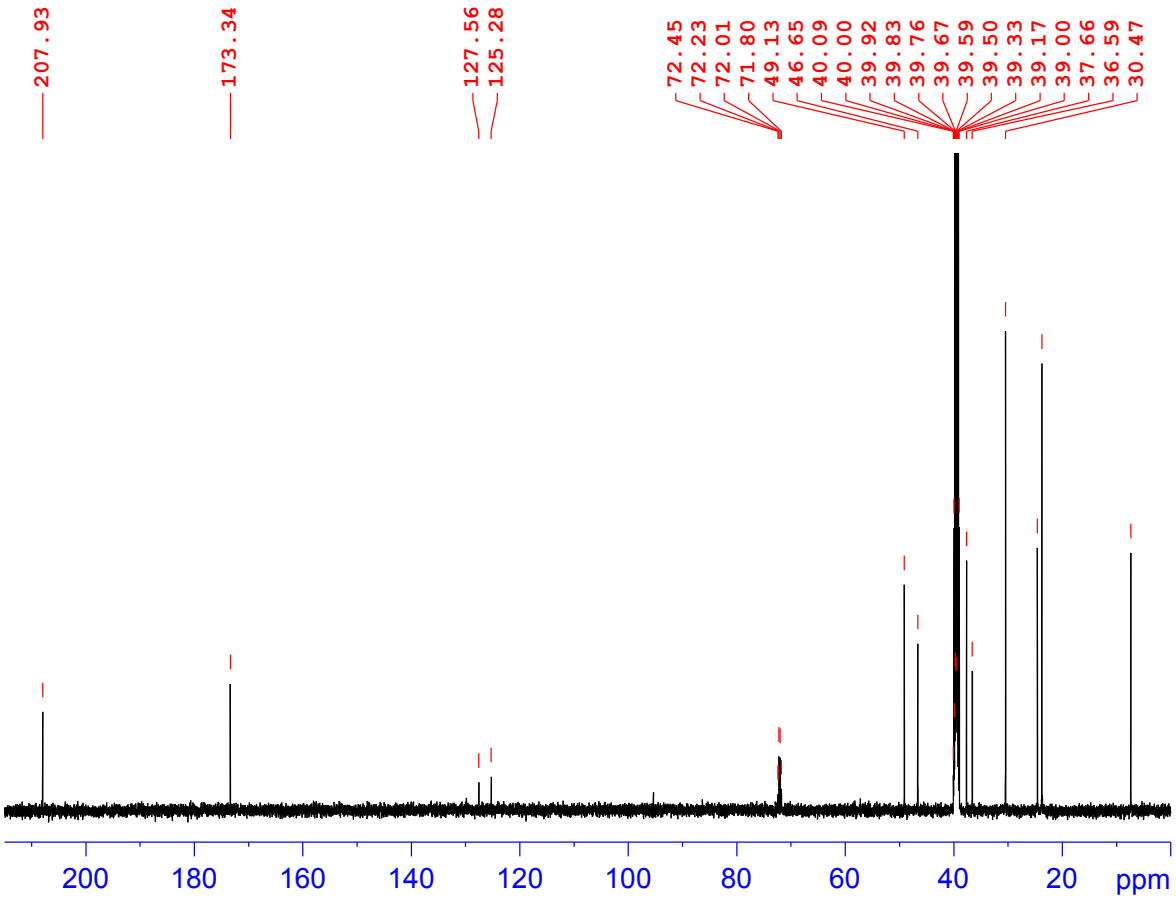

Fig. S94 ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **5b**.

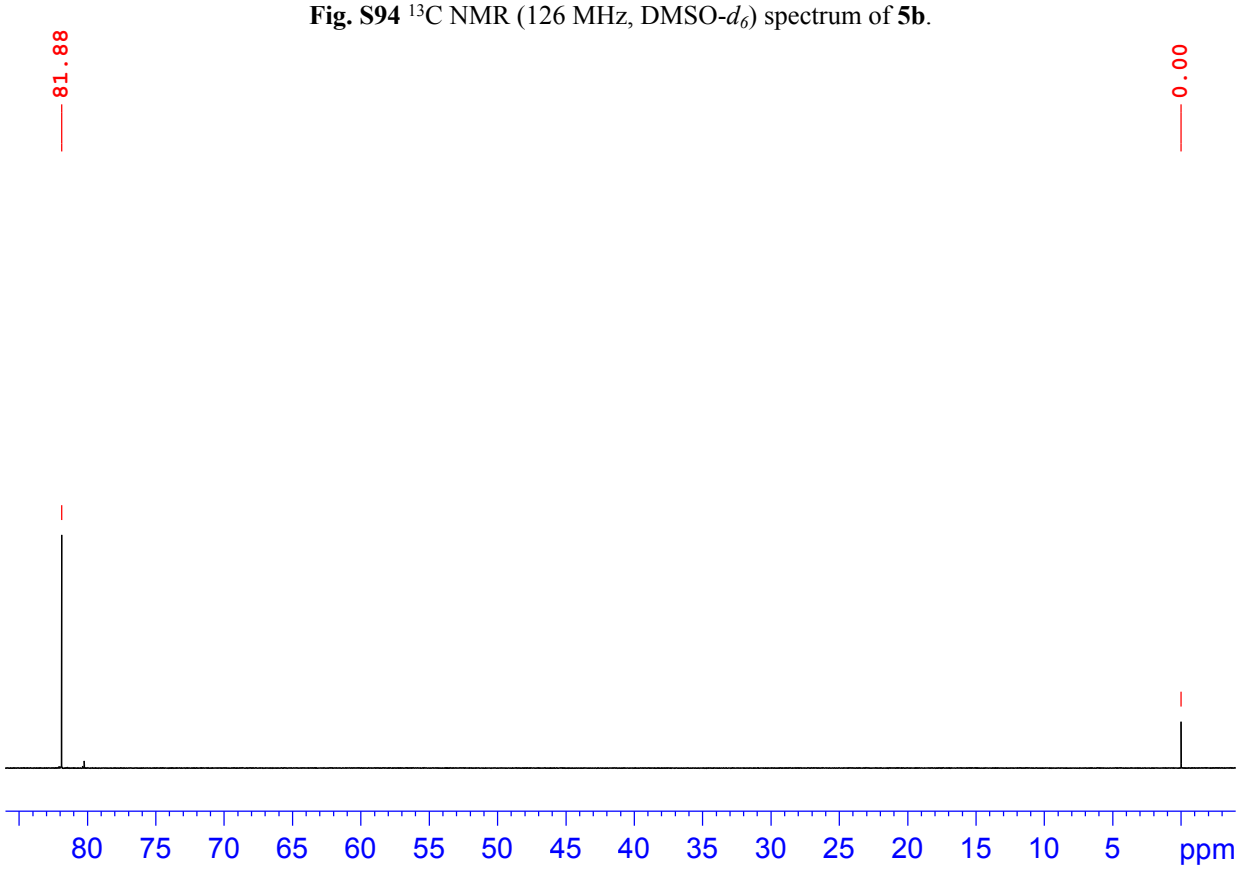

Fig. S95 ^{19}F NMR (470 MHz, DMSO-d_6) spectrum of **5b**.

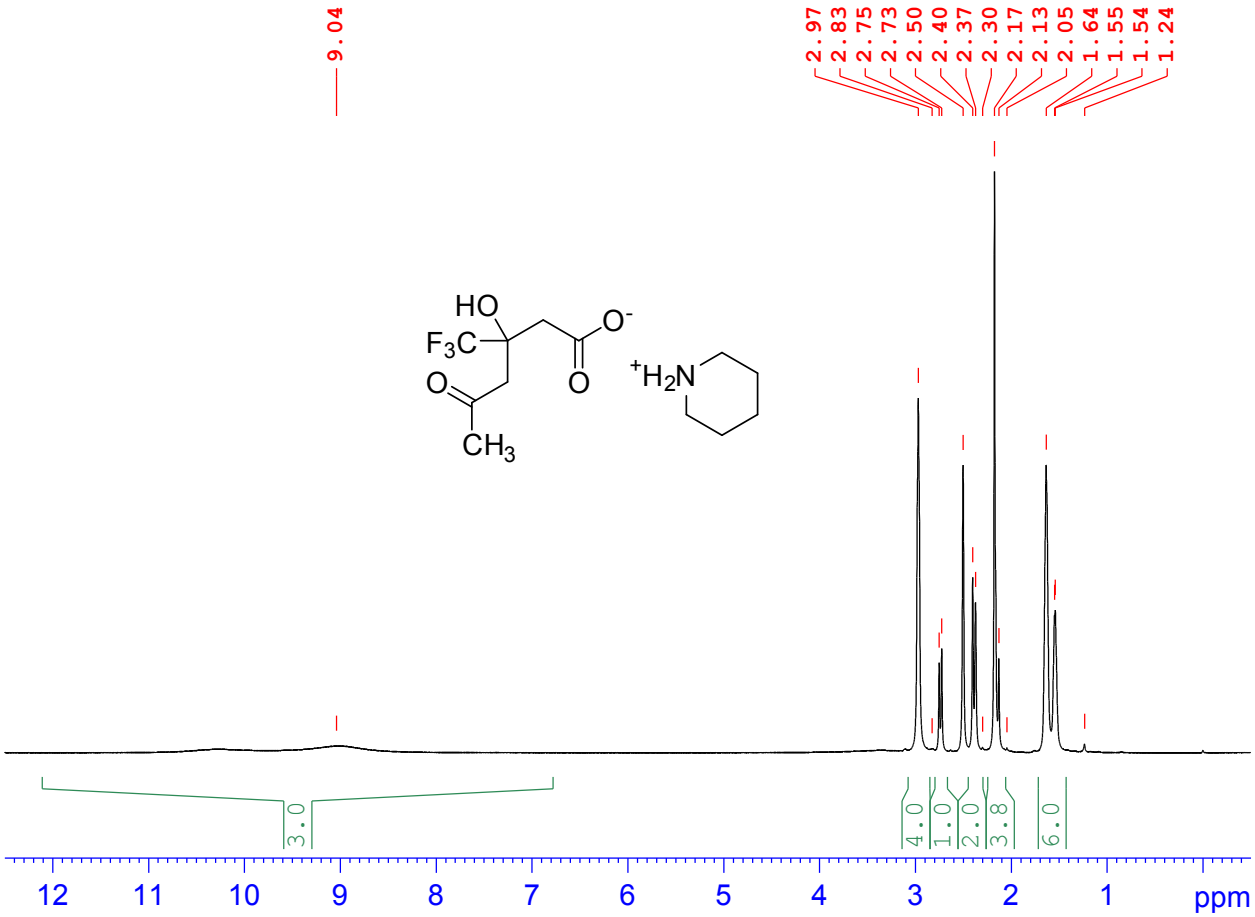

Figure S96 ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **5c**.

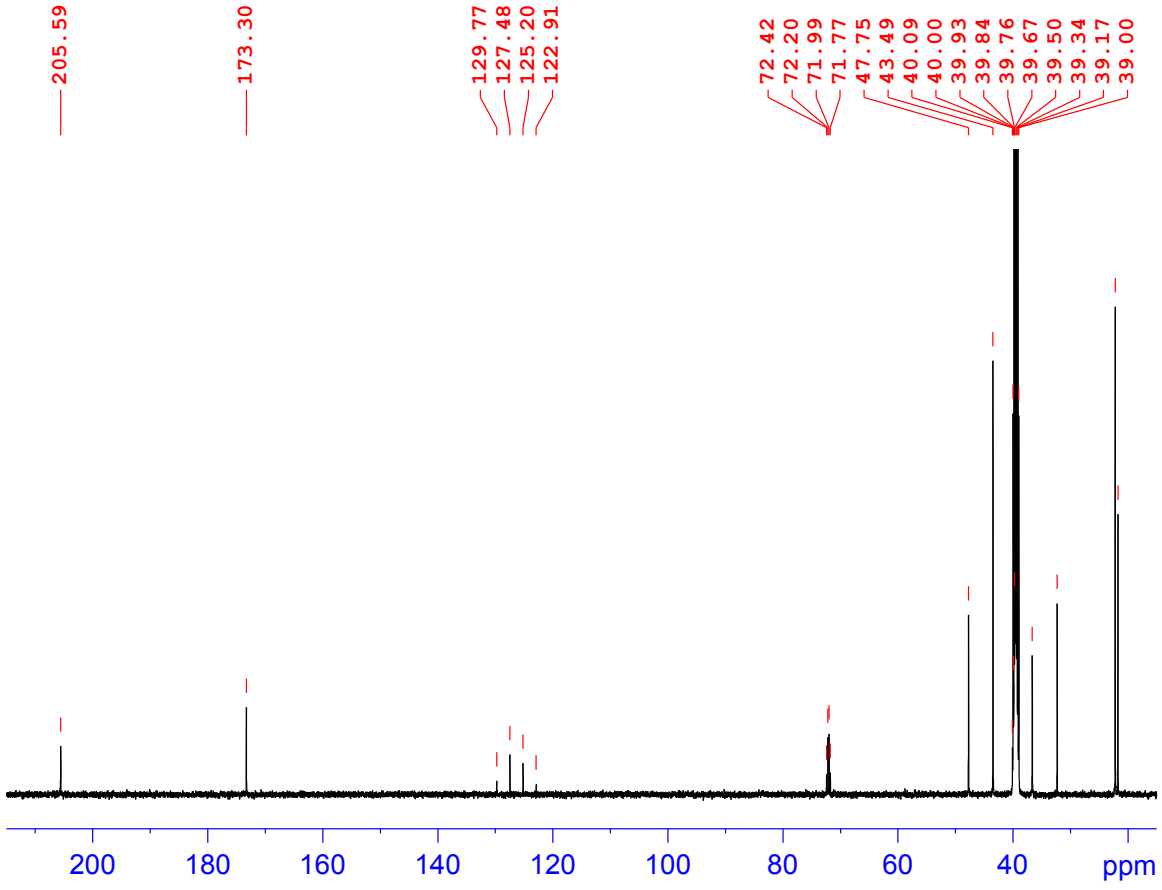

Fig. S97 ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **5c**.

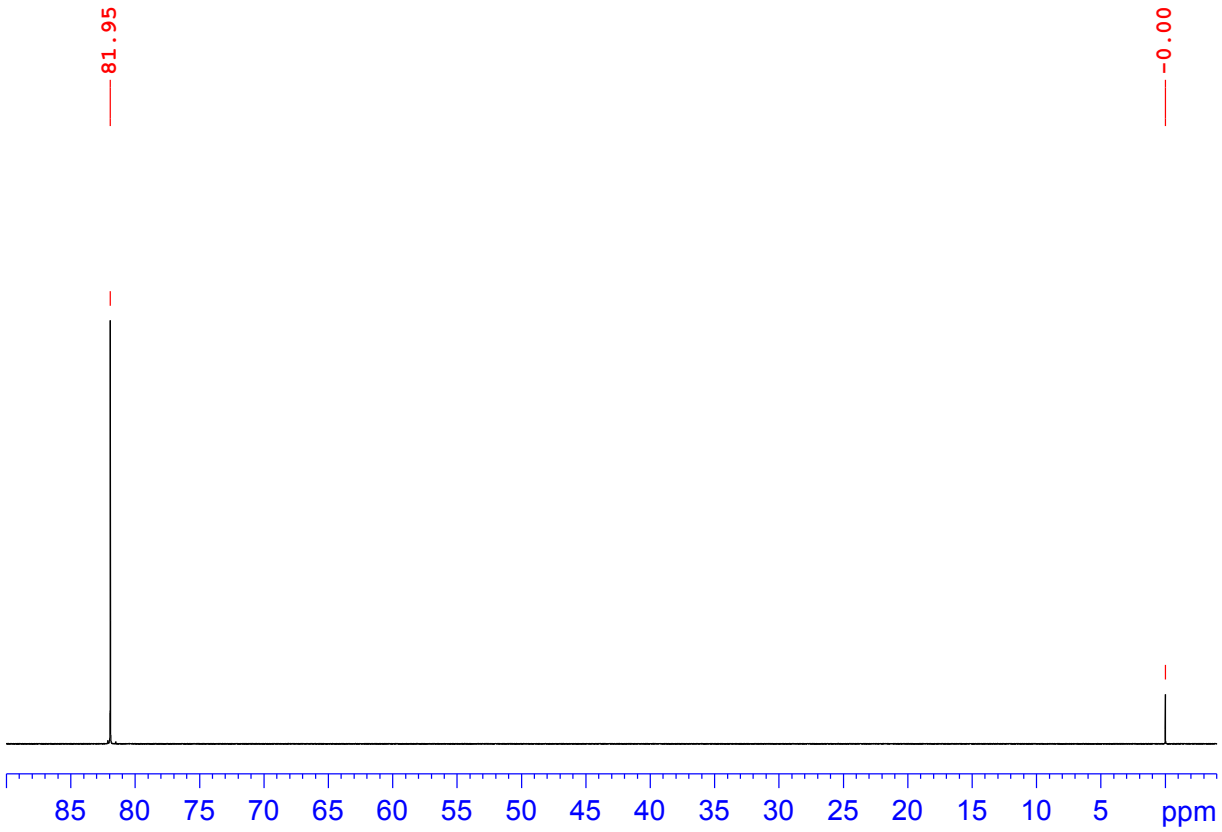

Fig. S98 ^{19}F NMR (470 MHz, DMSO-d_6) spectrum of **5c**.

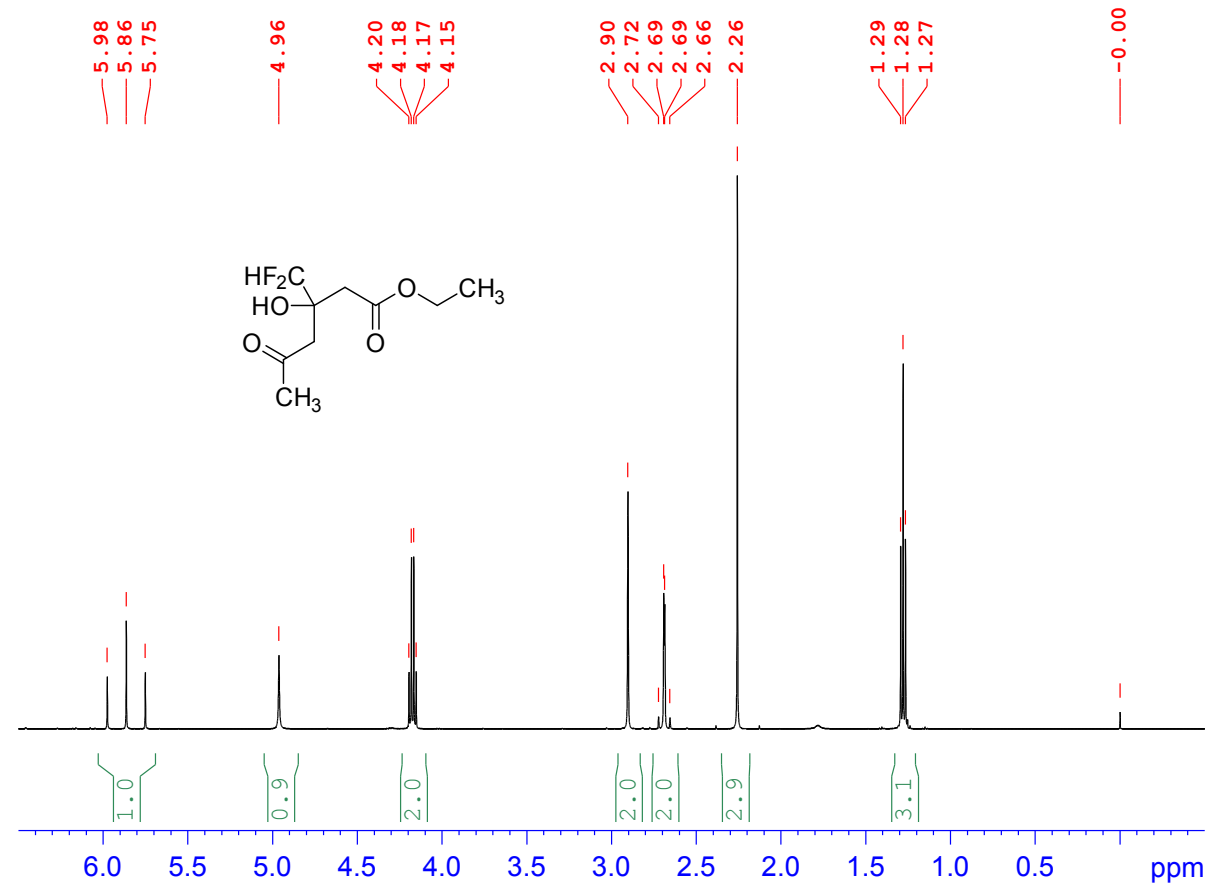

Fig. S99 ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **6b**.

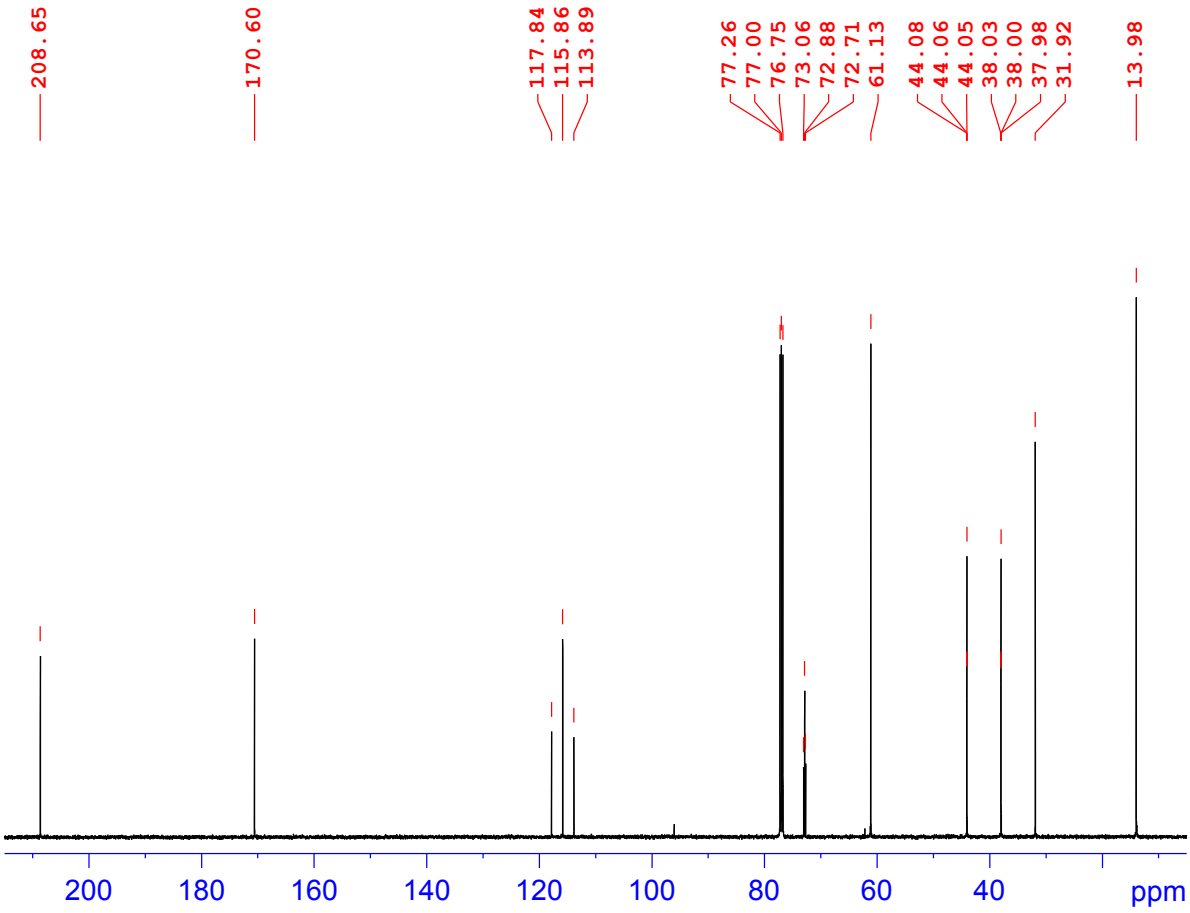

Fig. S100 ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of **6b**.

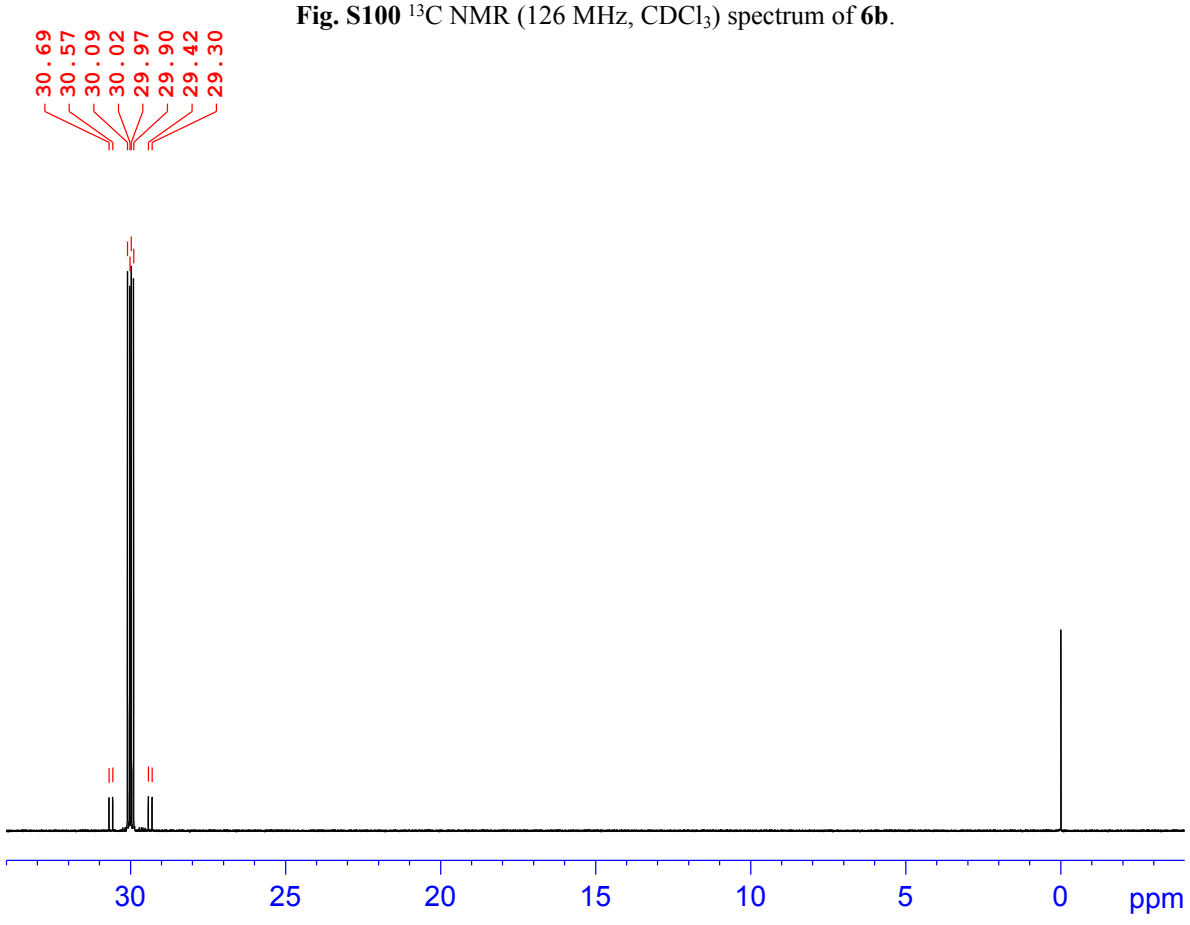

Fig. S101 ^{19}F NMR (470 MHz, $CDCl_3$) spectrum of **6b**.

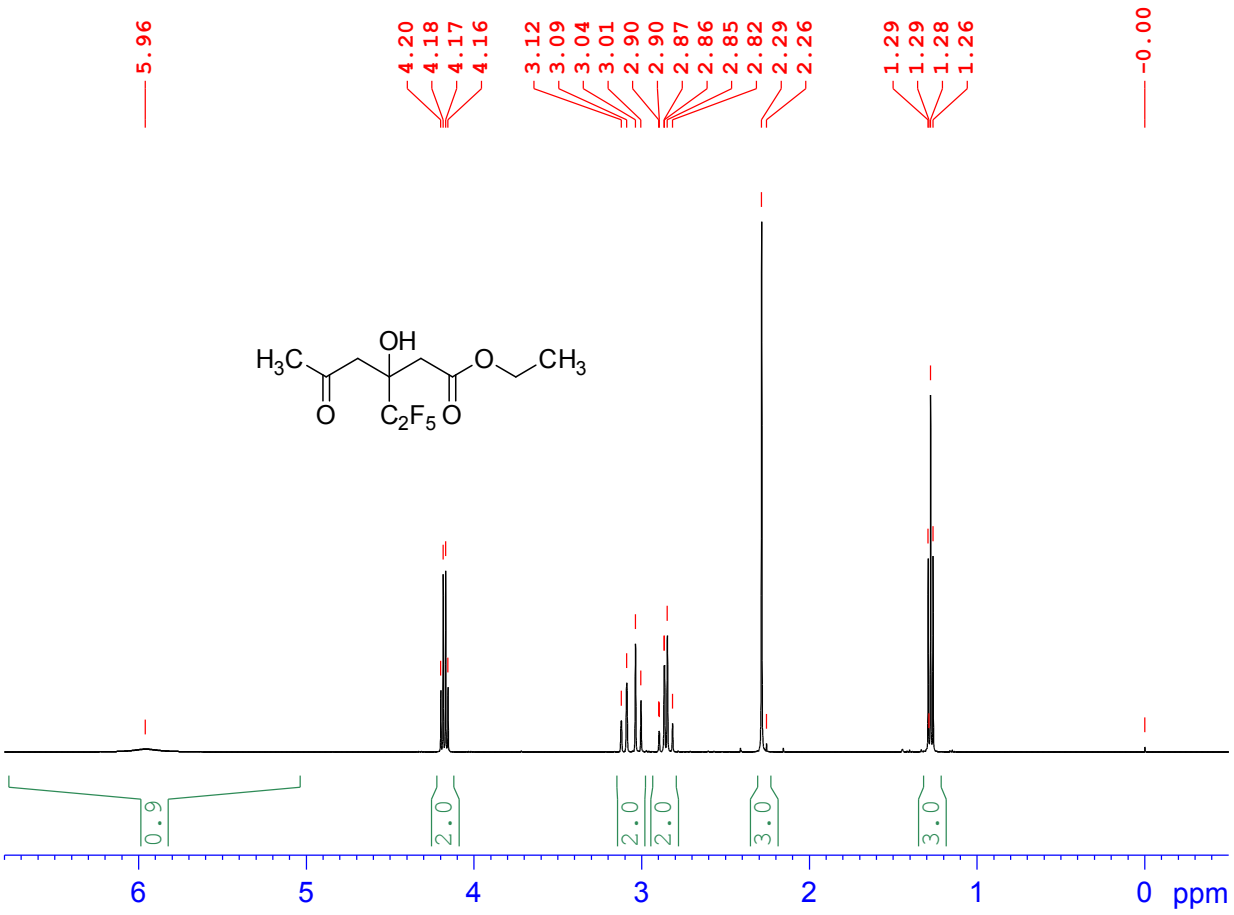

Fig. S102 ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **6c**.

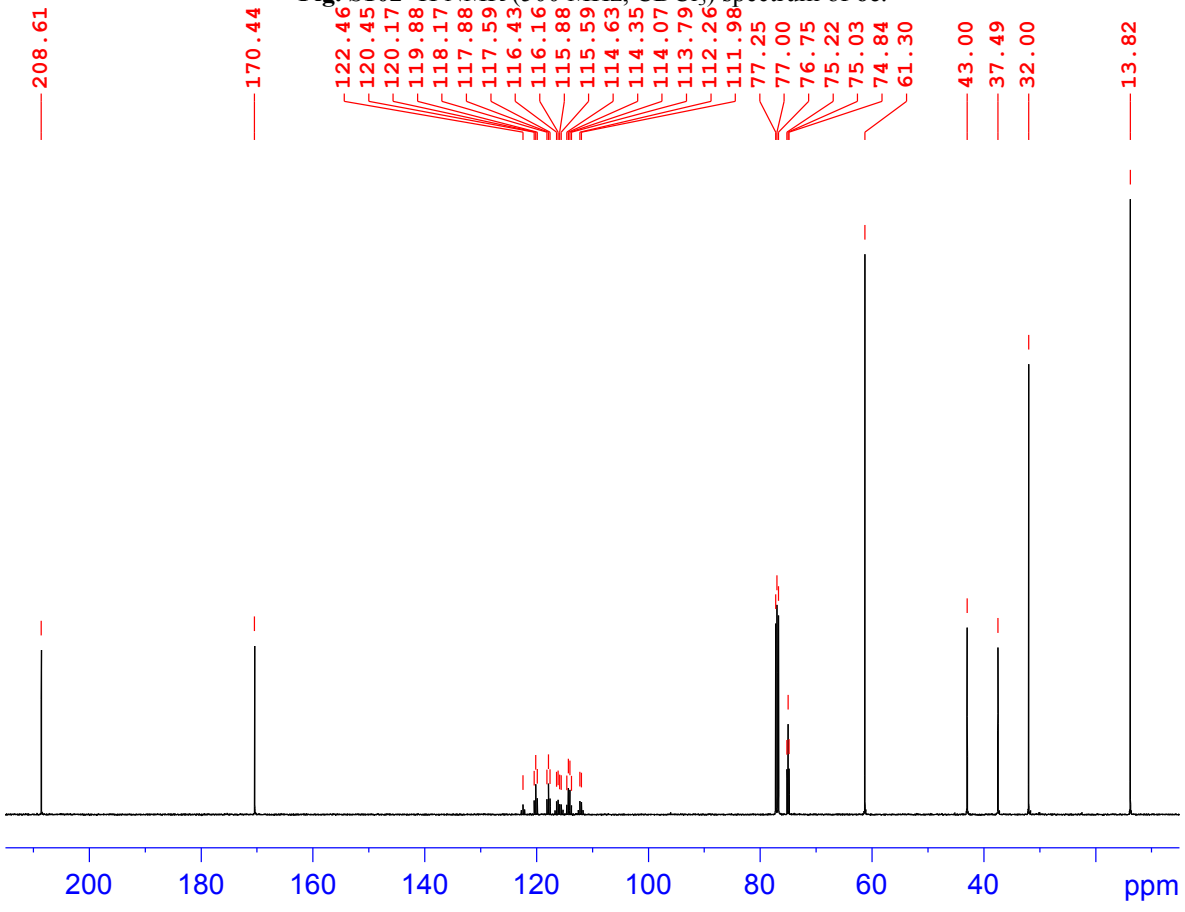

Fig. S 103 ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of **6c**.

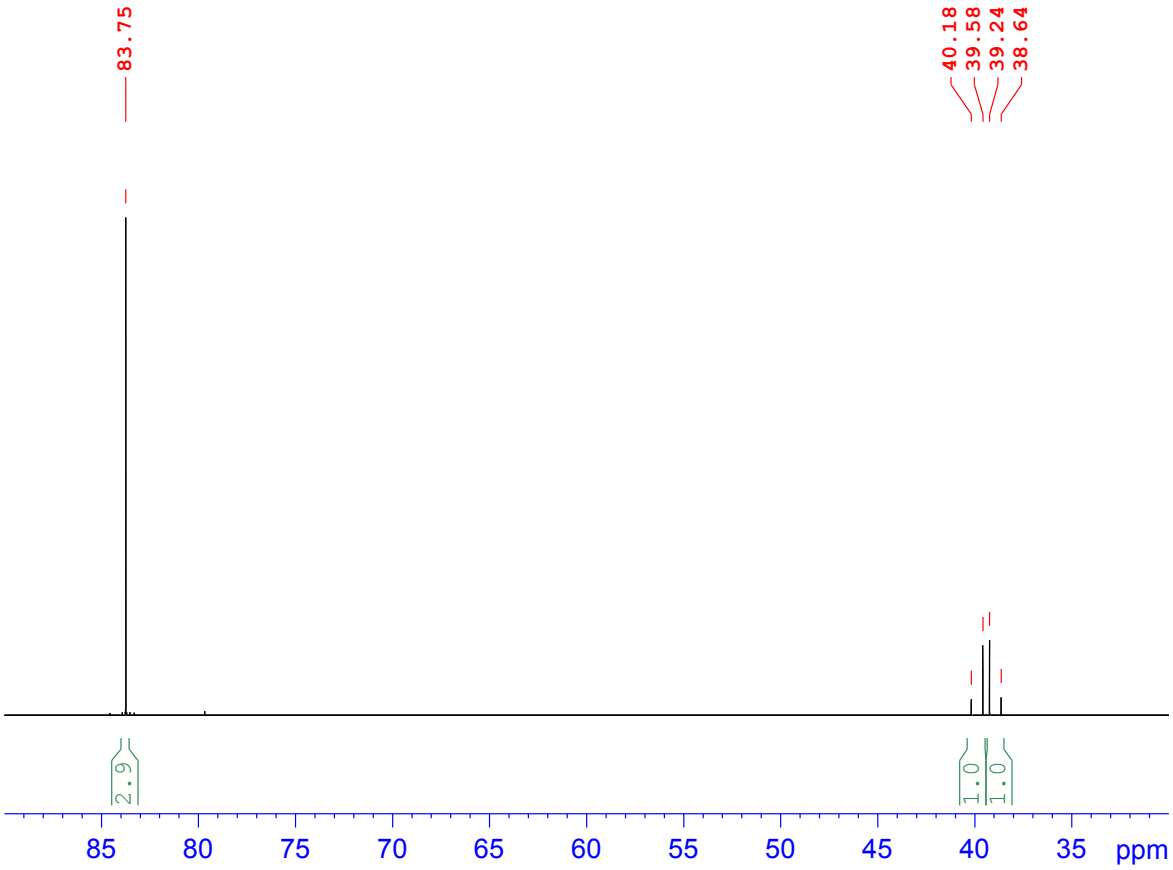

Fig. S104 ^{19}F NMR (470 MHz, $CDCl_3$) spectrum of **6c**.

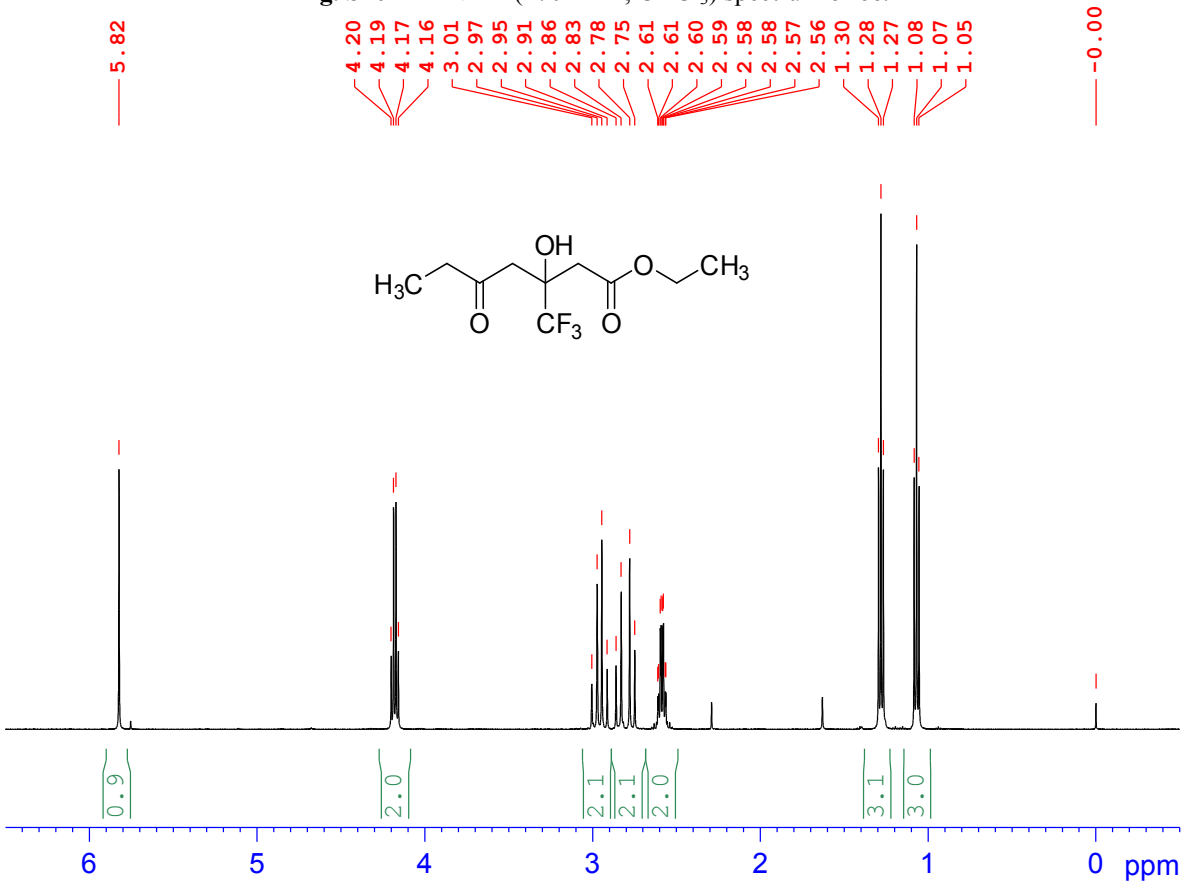

Fig. S105 ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **6d**.

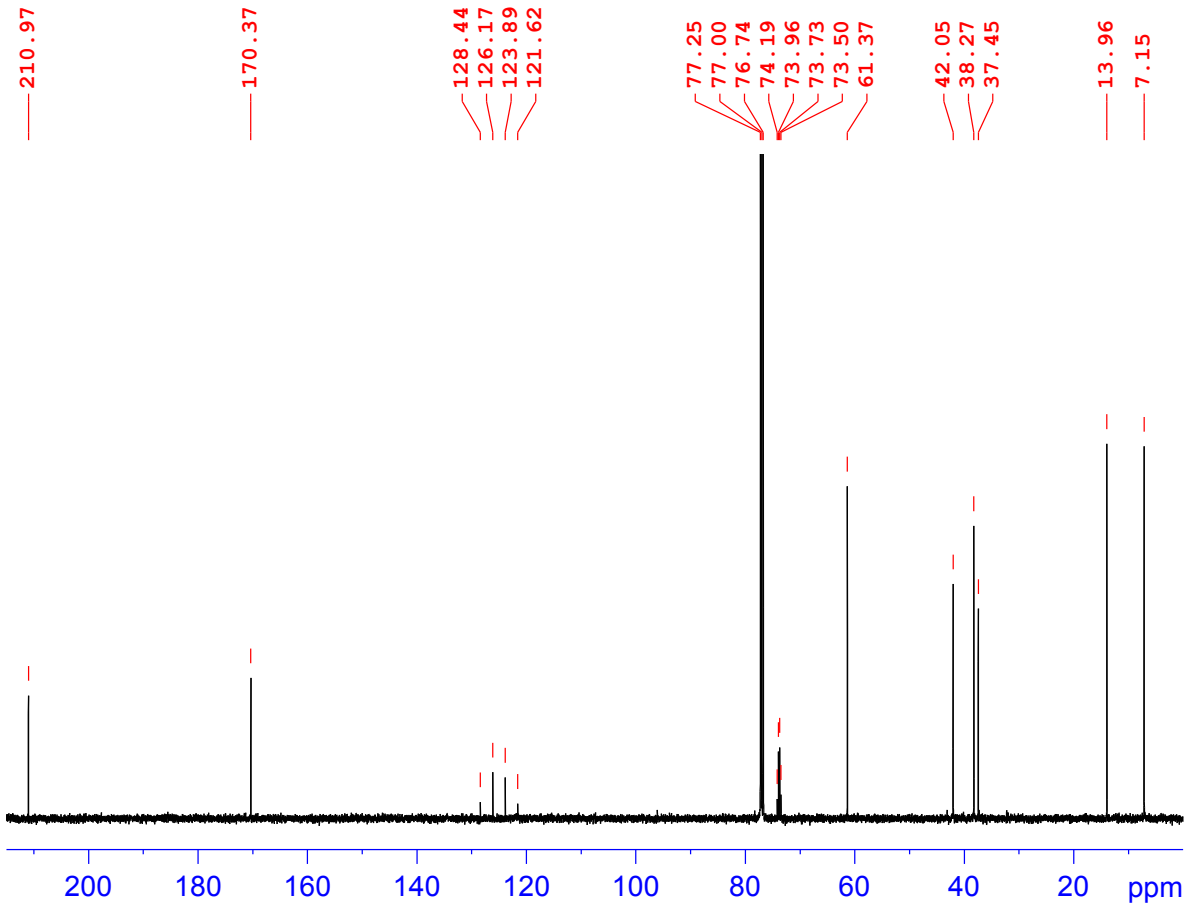

Fig. S106 ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of **6d**.

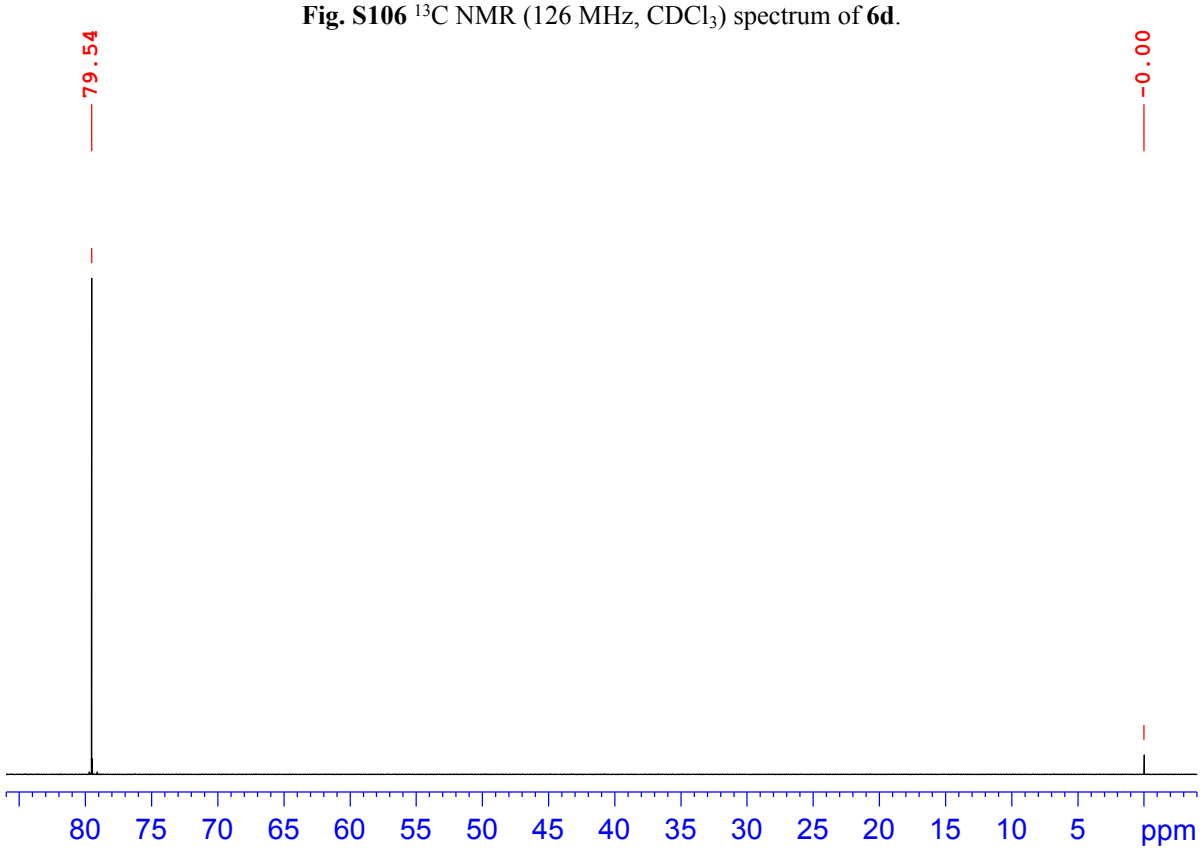

Fig. S1073 ^{19}F NMR (470 MHz, $CDCl_3$) spectrum of **6d**.

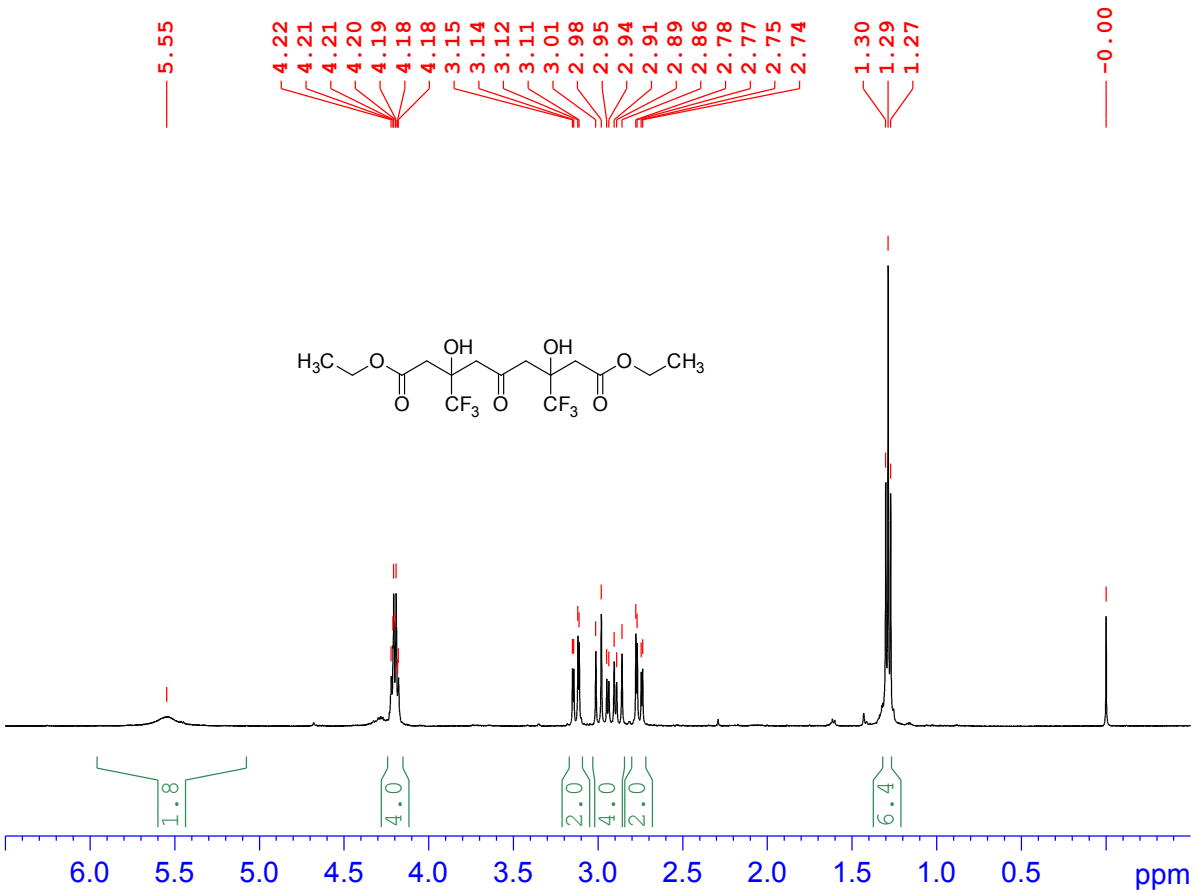

Fig. S108 ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **7**.

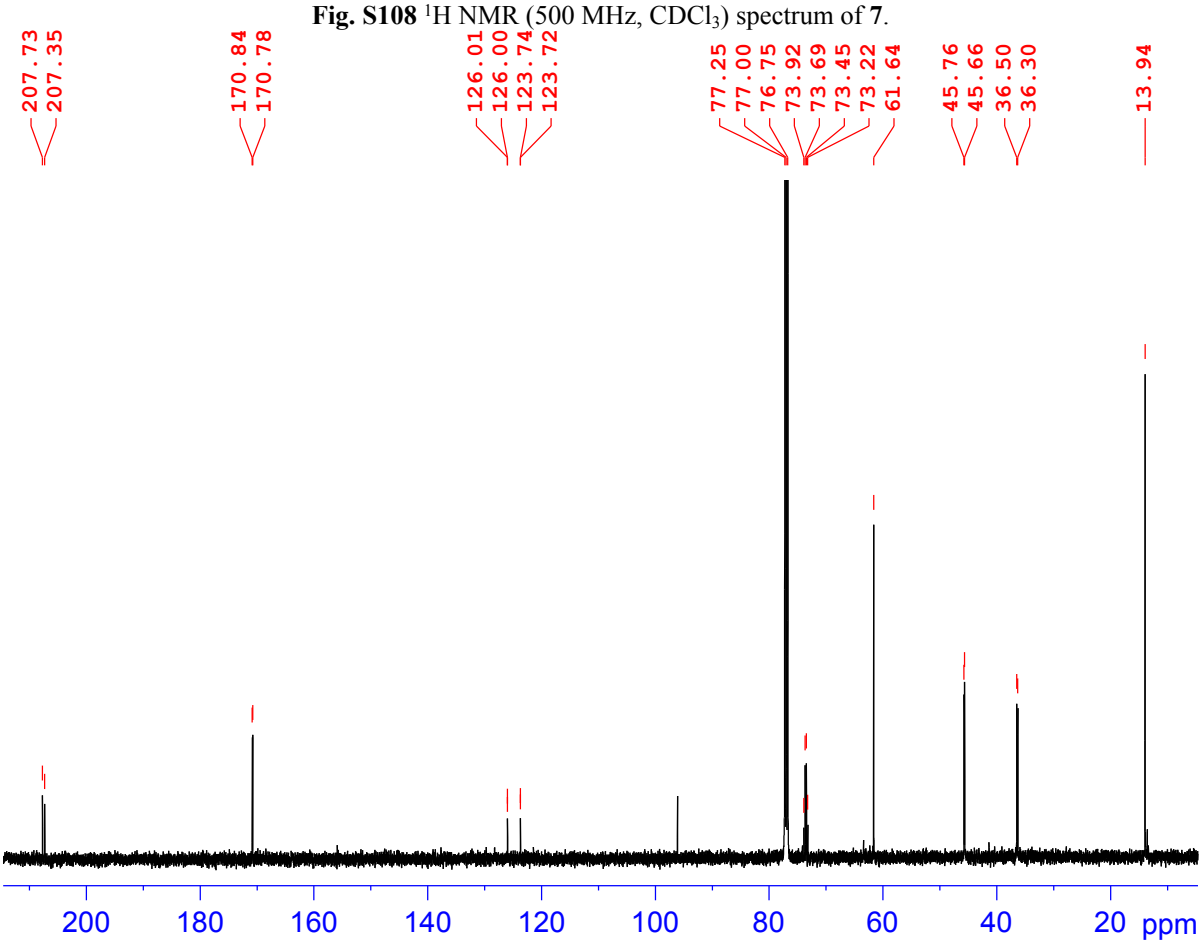

Fig. S109 ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of **7**.

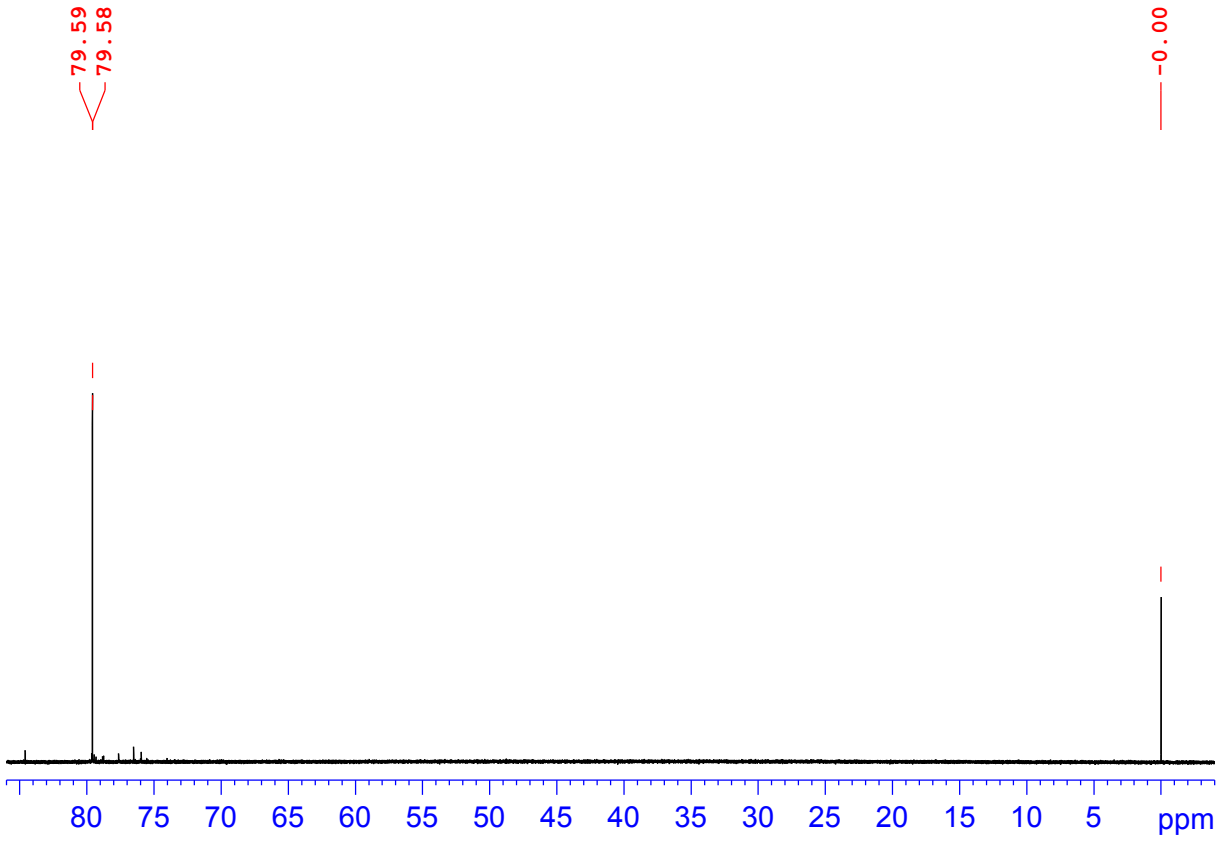

Fig. S110 ^{19}F NMR (470 MHz, $CDCl_3$) spectrum of **7**.

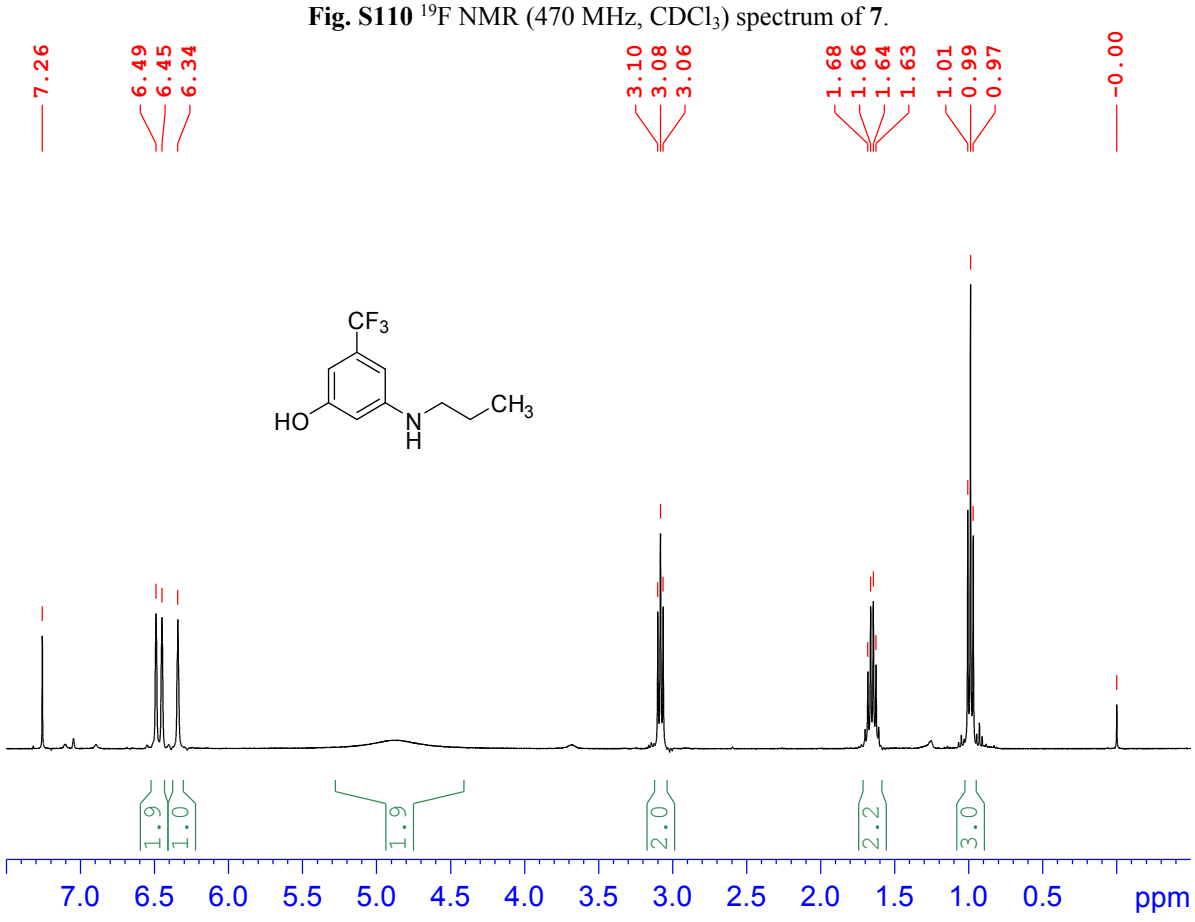

Fig. S111 ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **10a**.

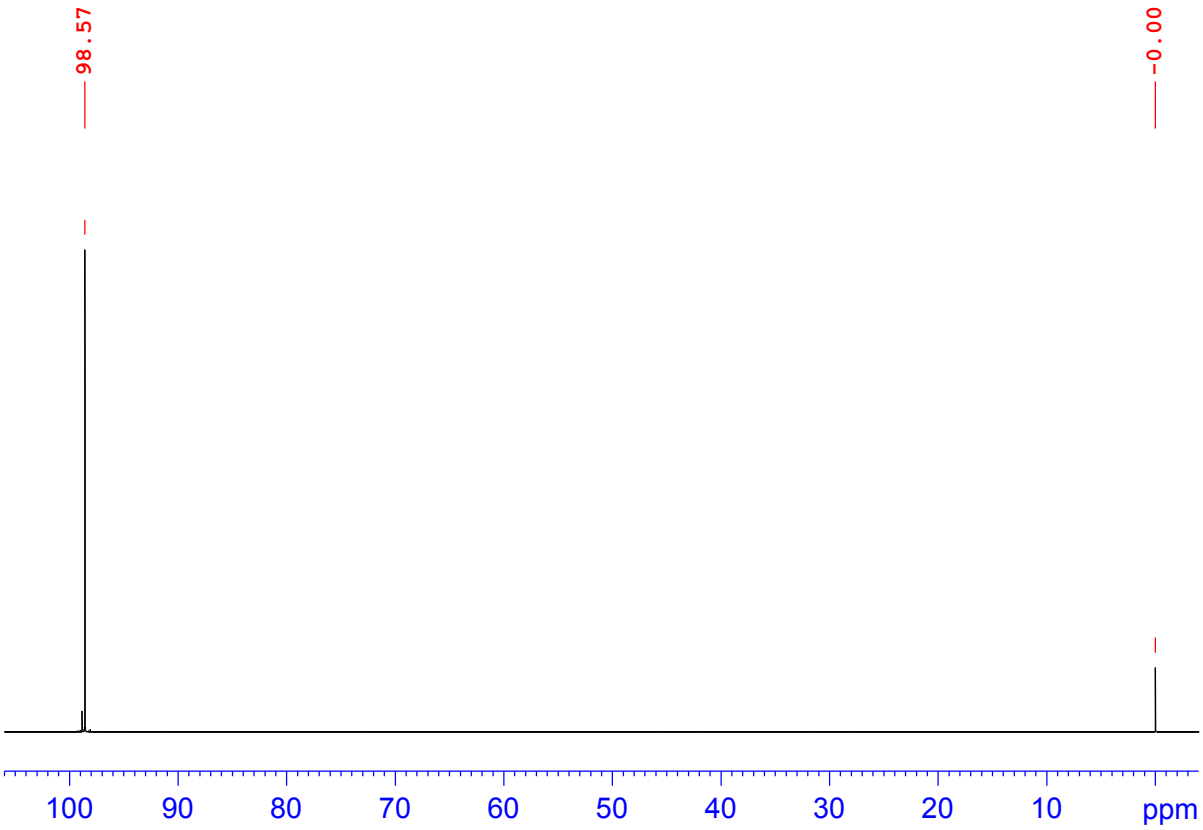

Fig. S112 ^{19}F NMR (470 MHz, $CDCl_3$) spectrum of **10a**.

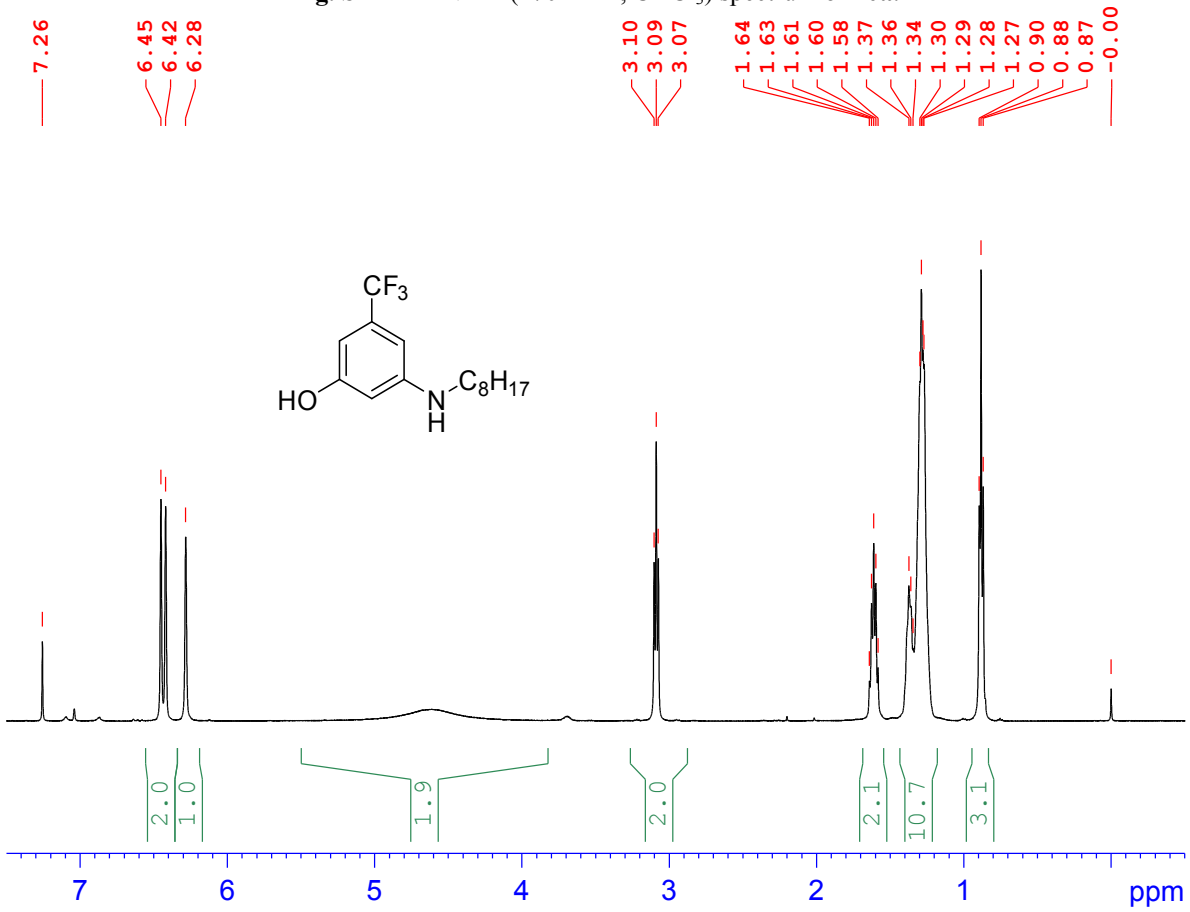

Fig. S113 ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **10b**.

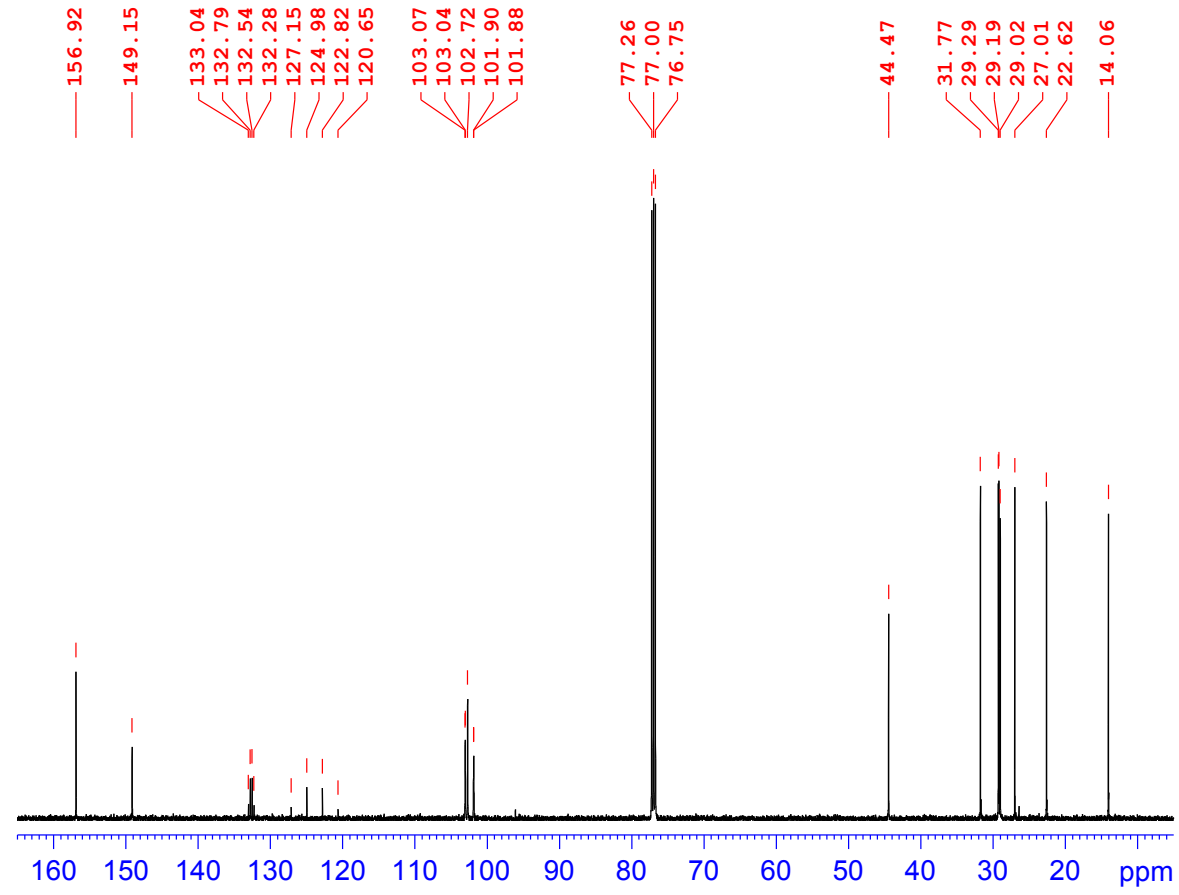

Fig. S114 ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of **10b**.

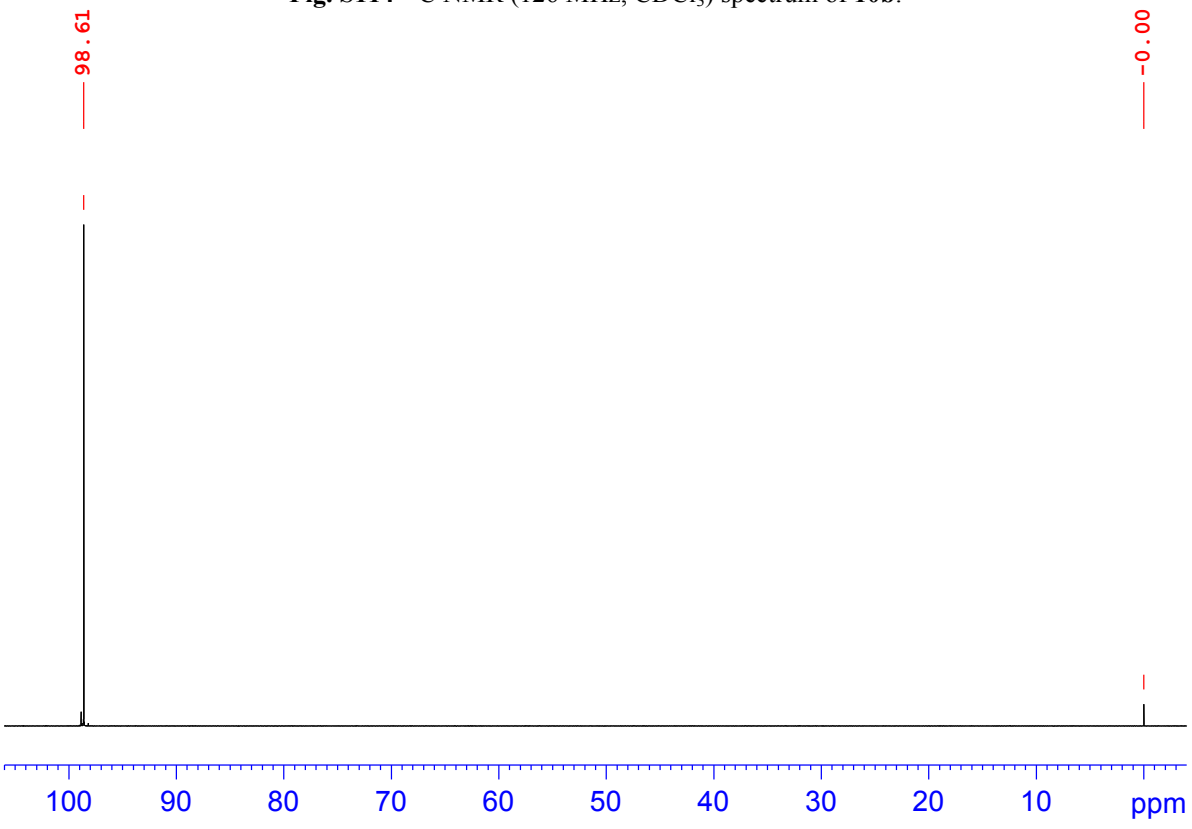

Fig. S115 ^{19}F NMR (470 MHz, $CDCl_3$) spectrum of **10b**.

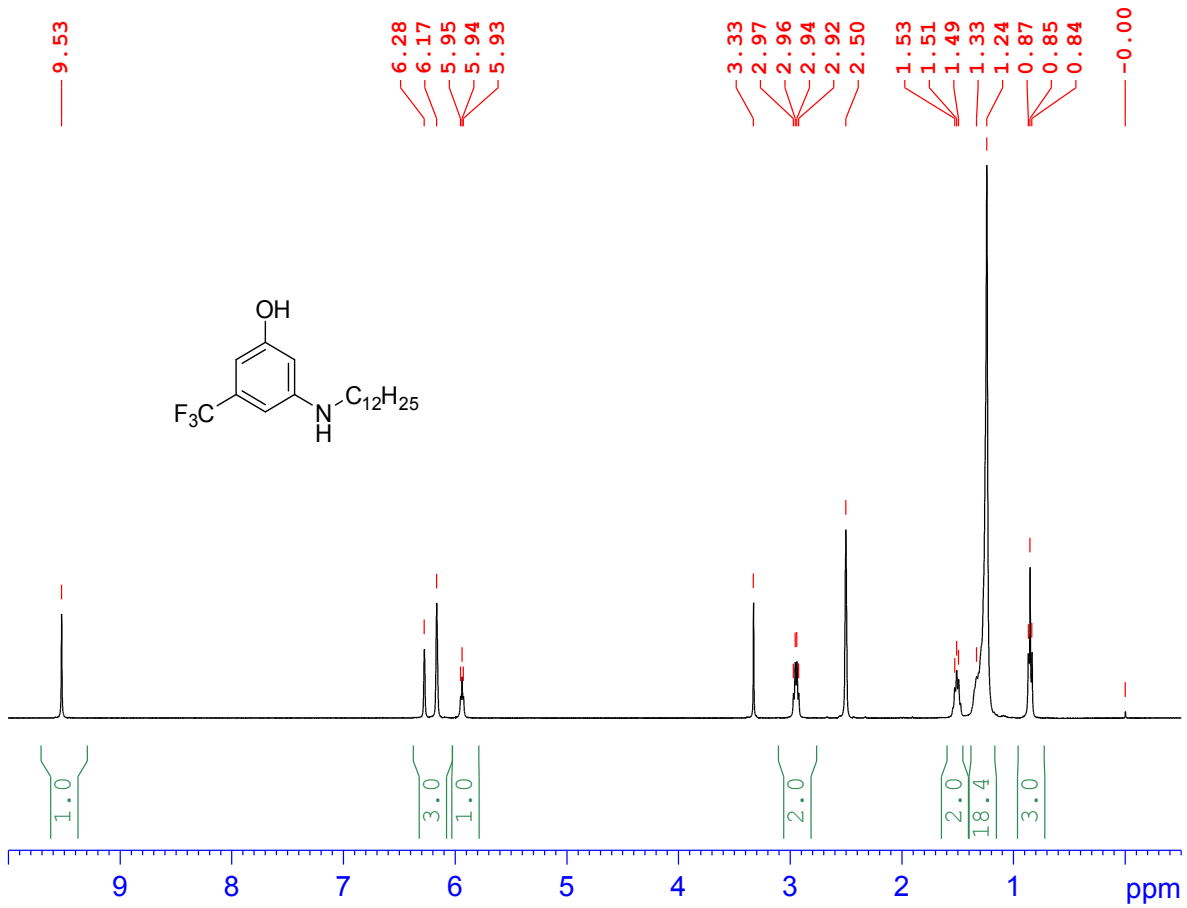

Fig. S116 ^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **10c**.

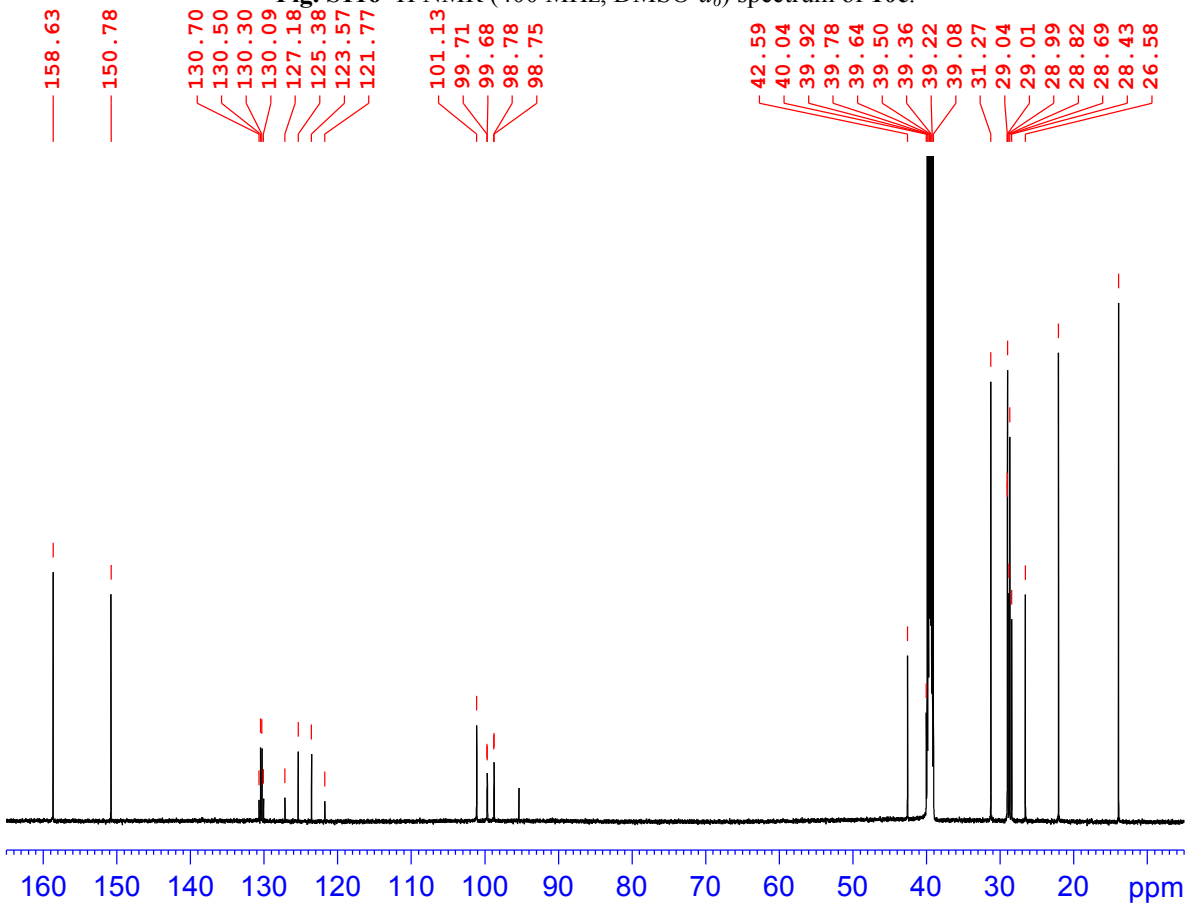

Fig. S117 ^{13}C NMR (151 MHz, DMSO-d_6) spectrum of **10c**.

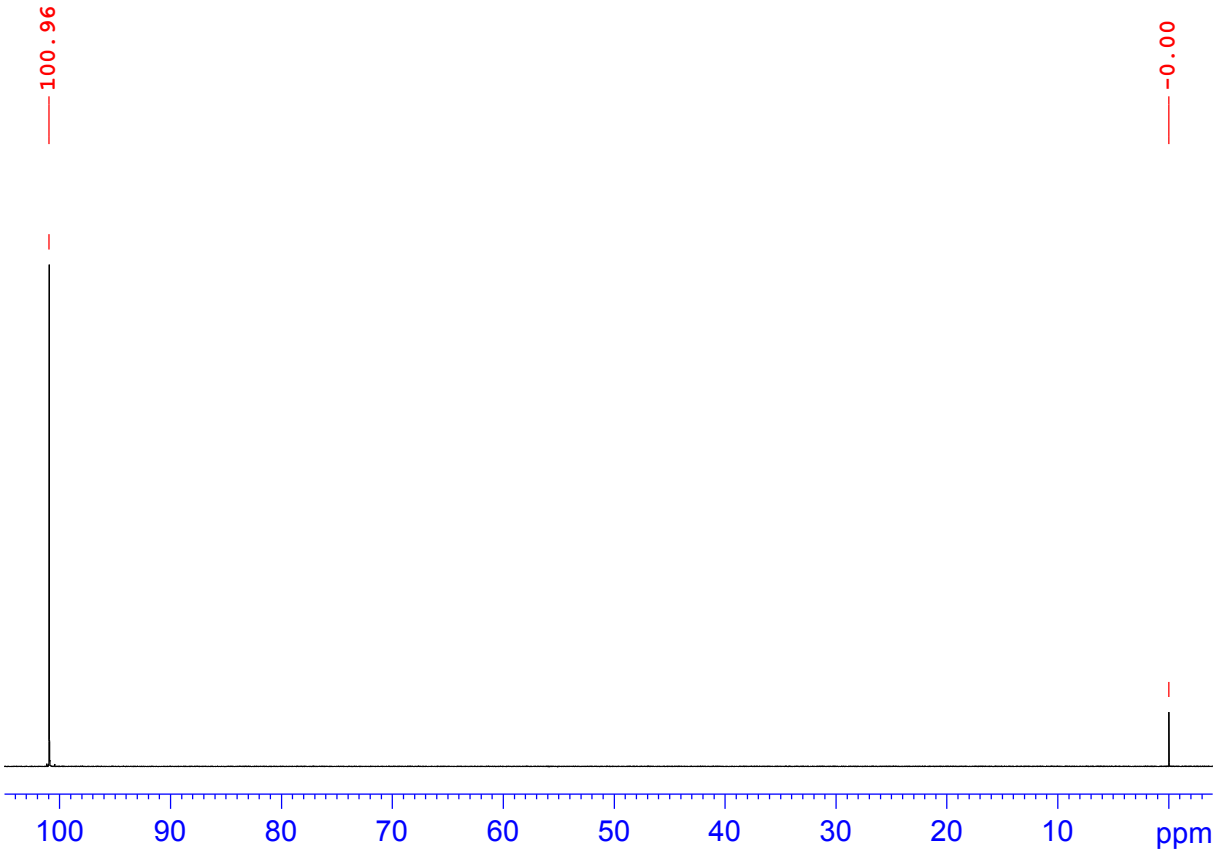

Fig. S118 ^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **10c**.

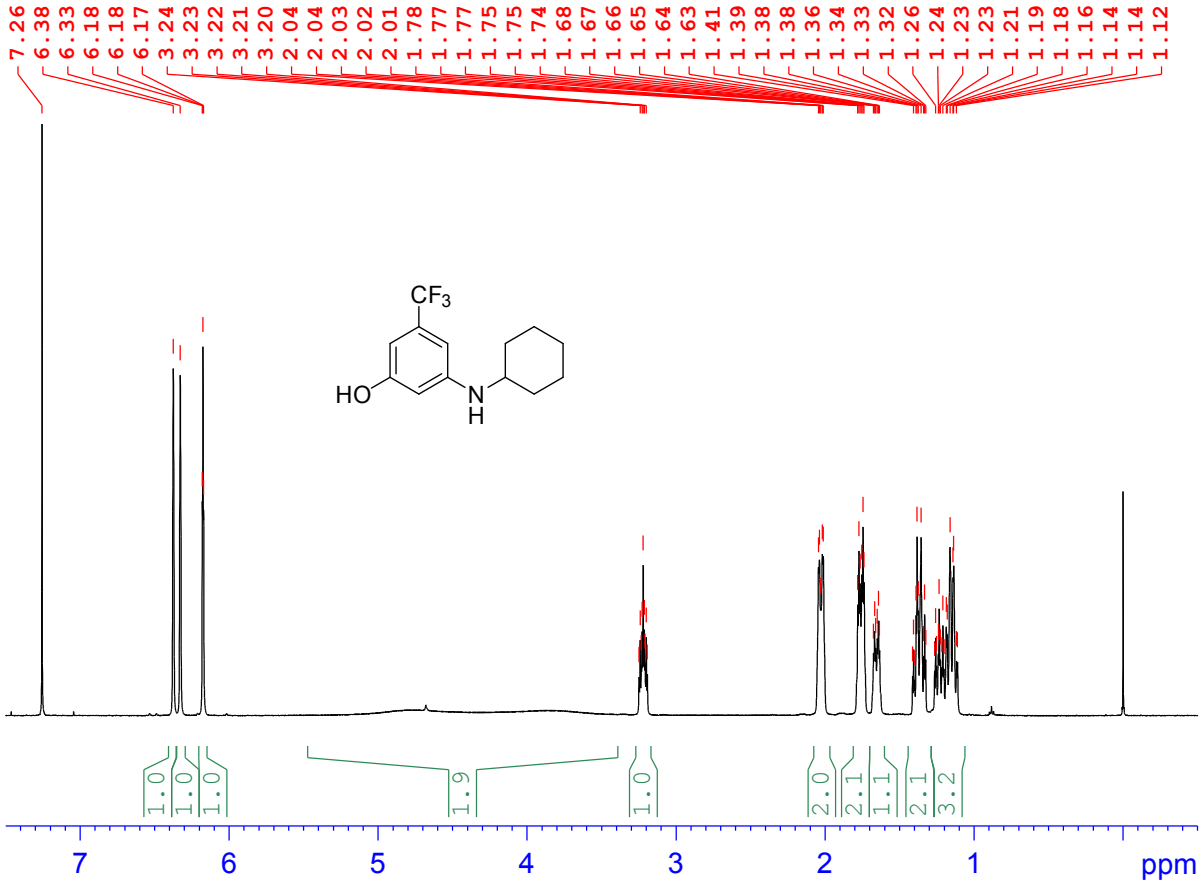

Fig. S119 ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **10d**.

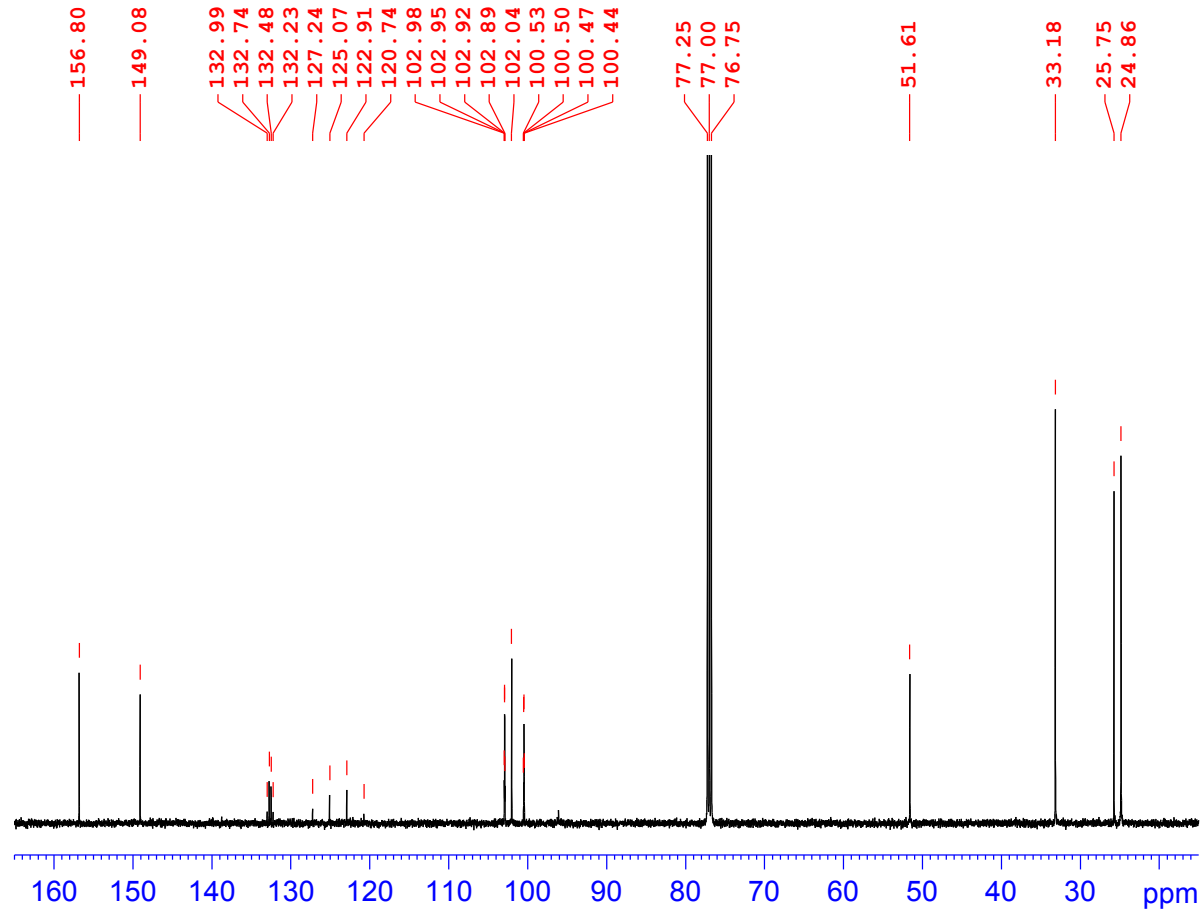

Fig. S120 ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of **10d**.

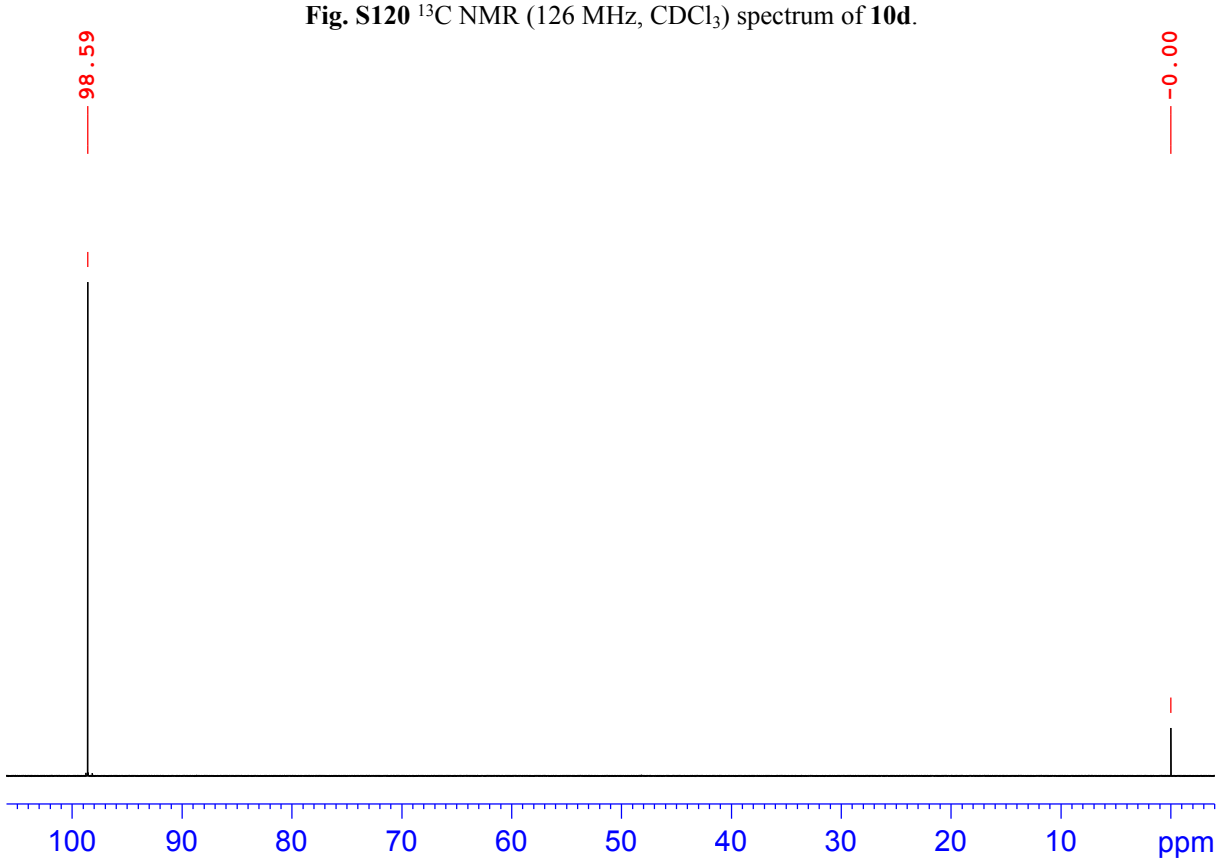

Fig. S121 ^{19}F NMR (470 MHz, $CDCl_3$) spectrum of **10d**.

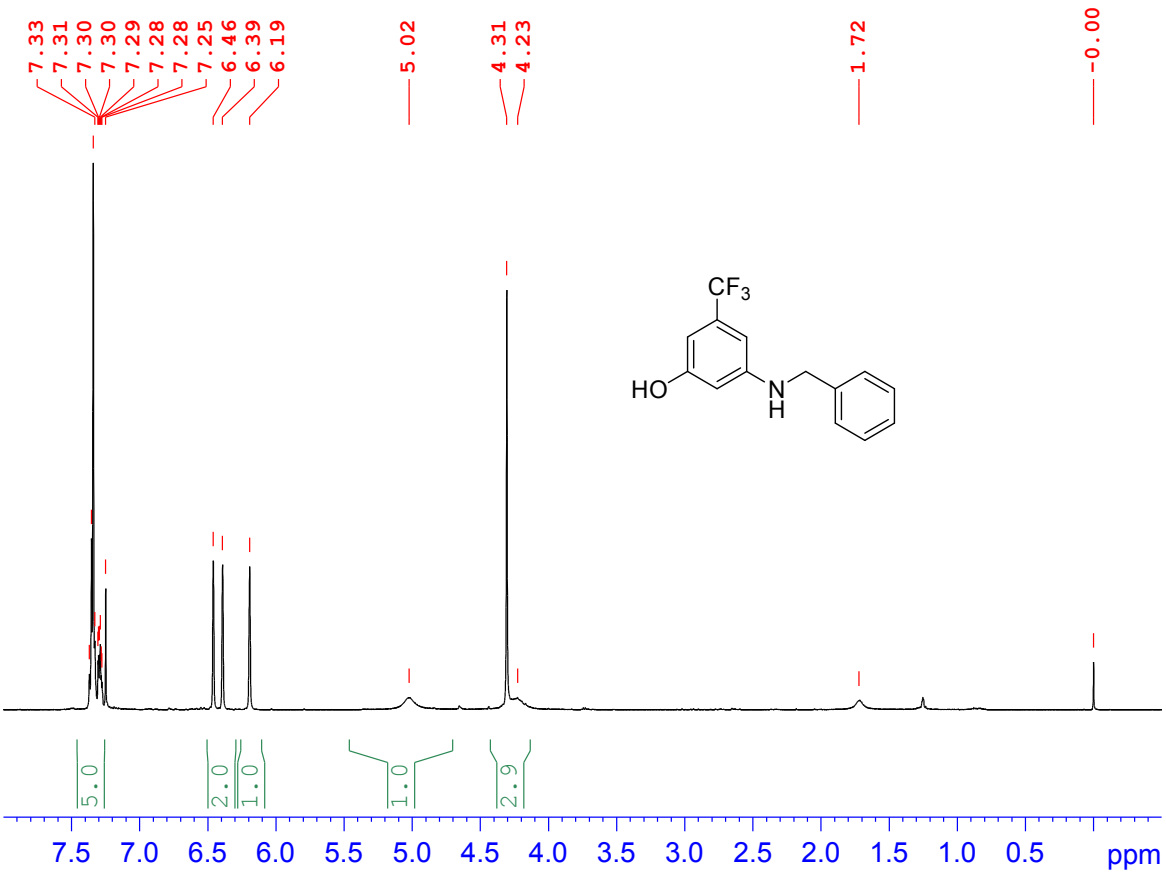

Fig. S122 ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **10e**.

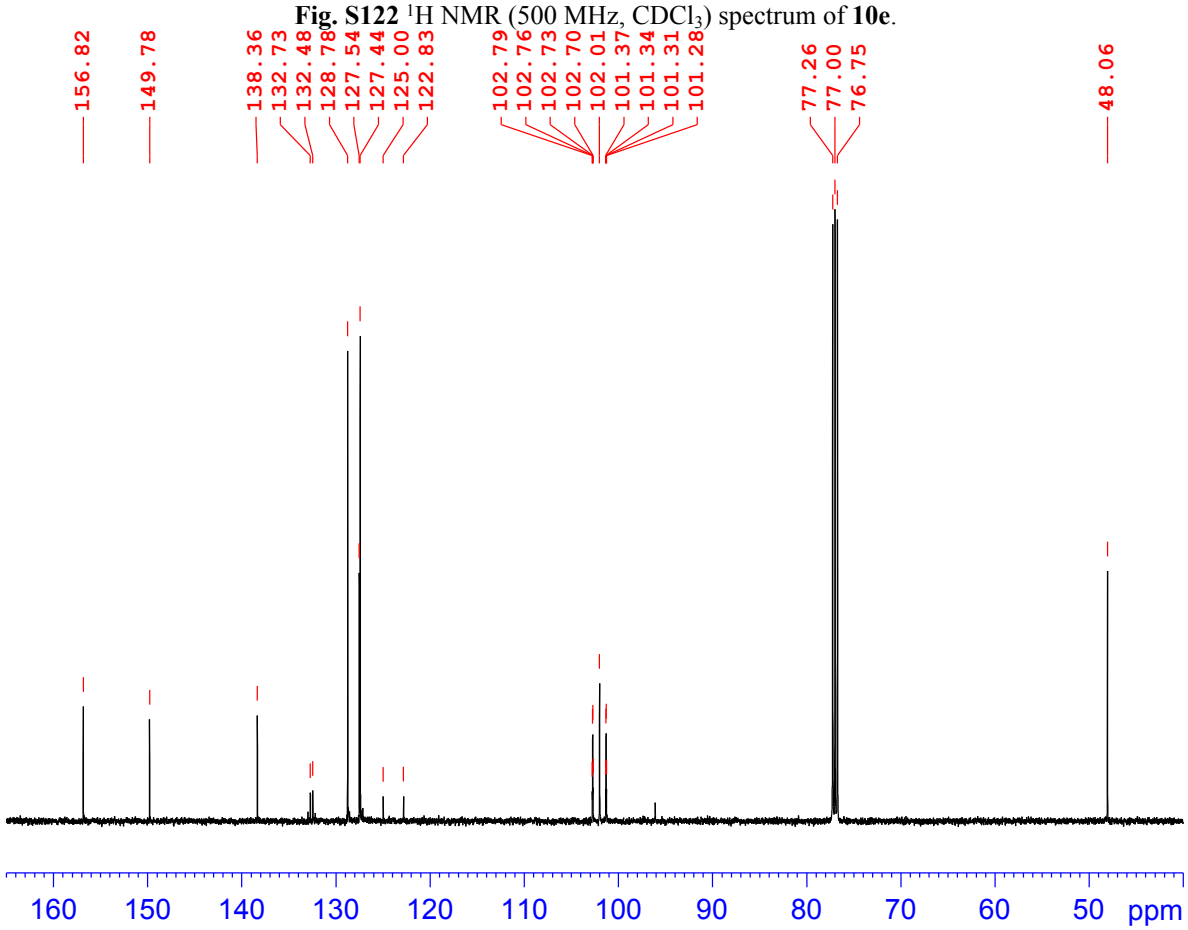

Fig. S123 ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of **10e**.

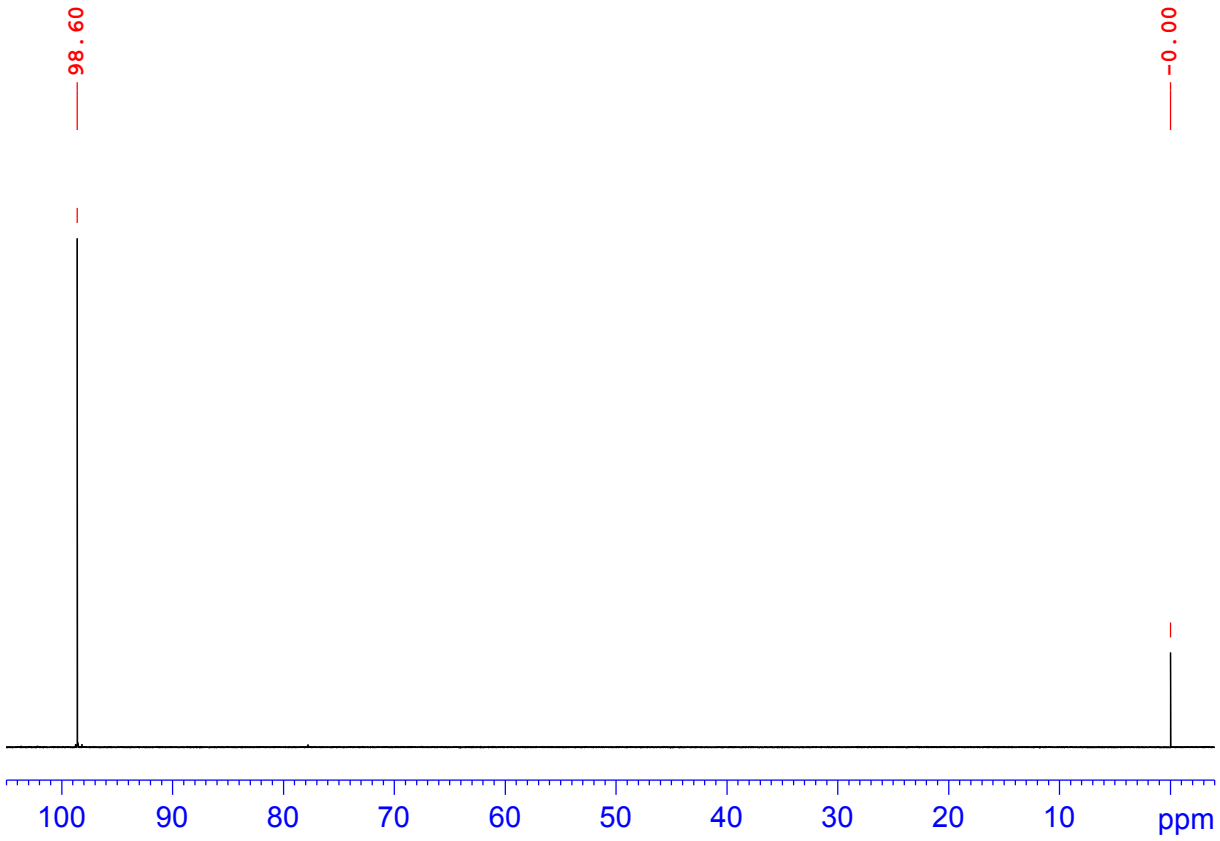

Fig. S124 ^{19}F NMR (470 MHz, $CDCl_3$) spectrum of **10e**.

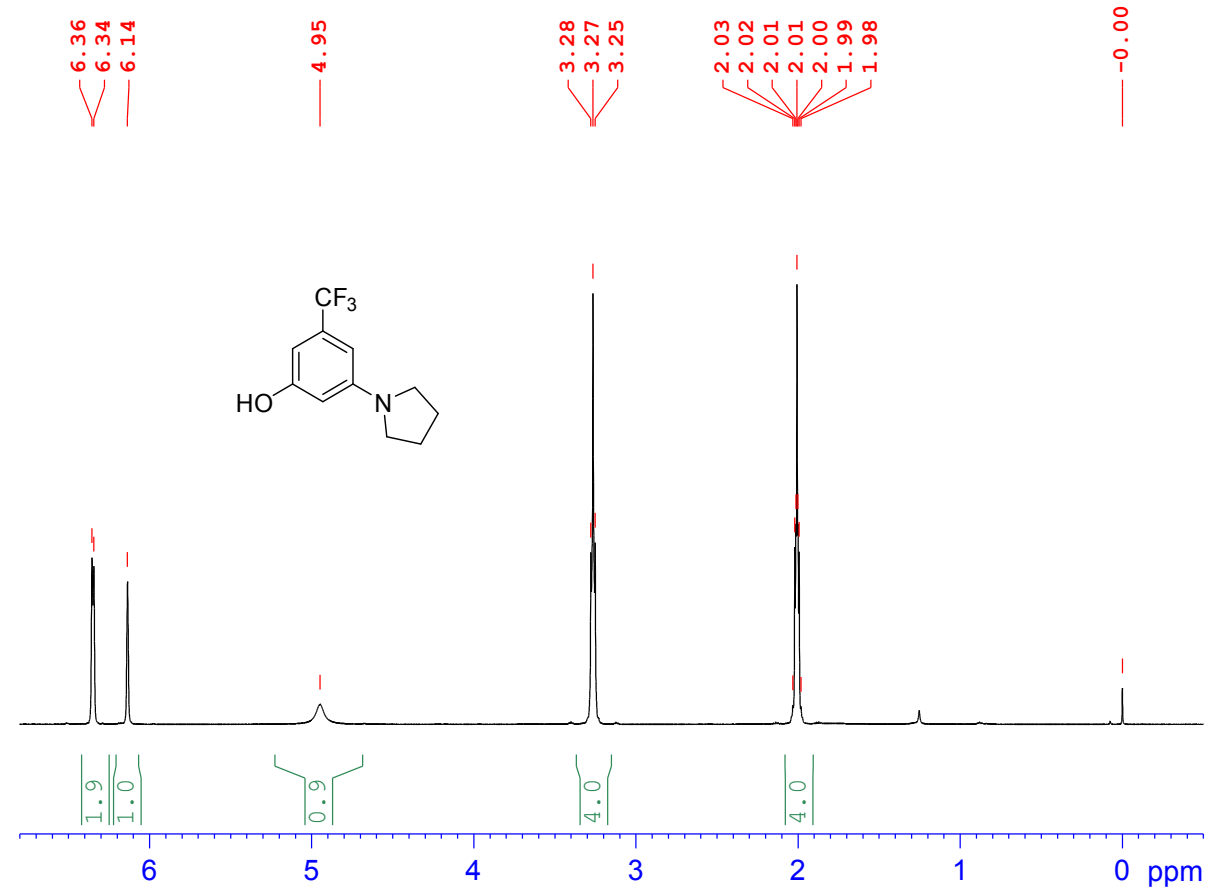

Fig. S125 ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **10f**.

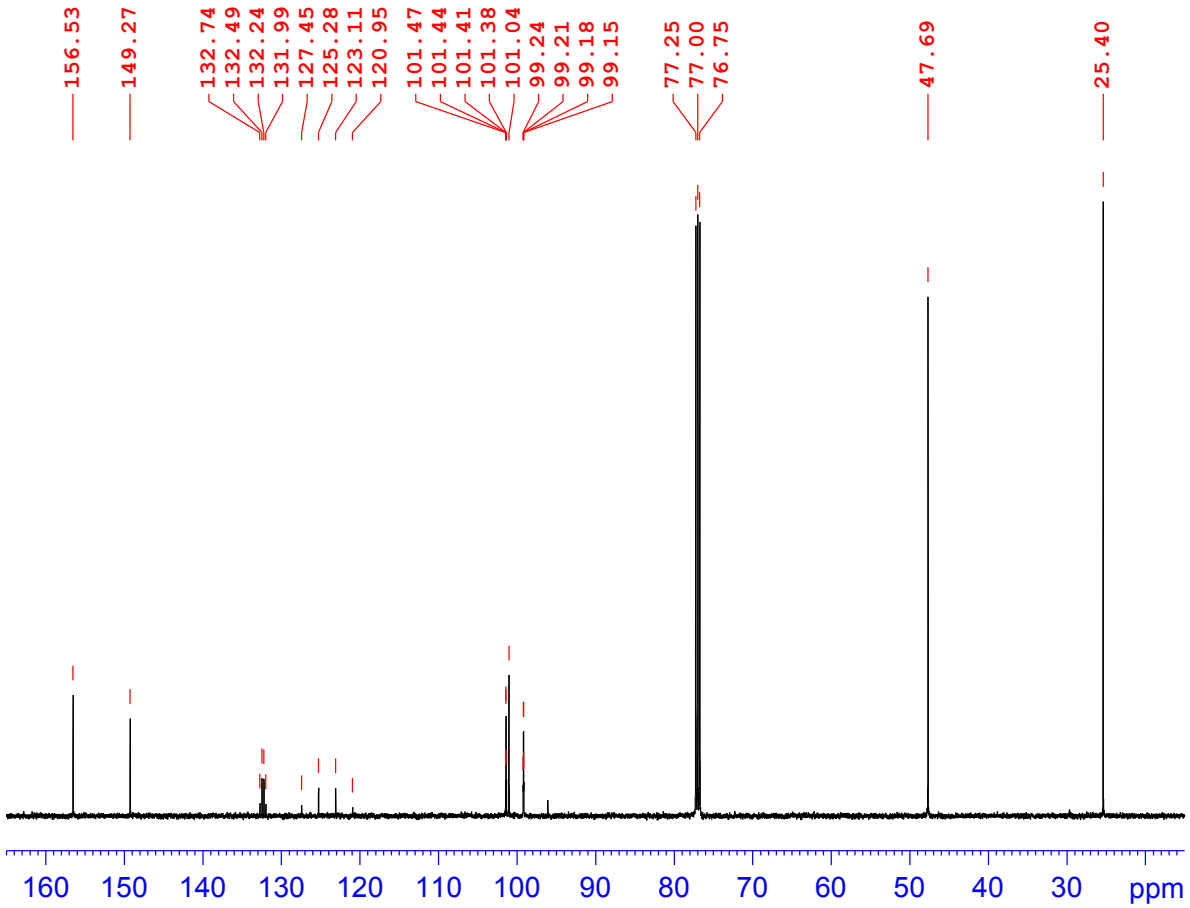

Fig. S1264 ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of **10f**.

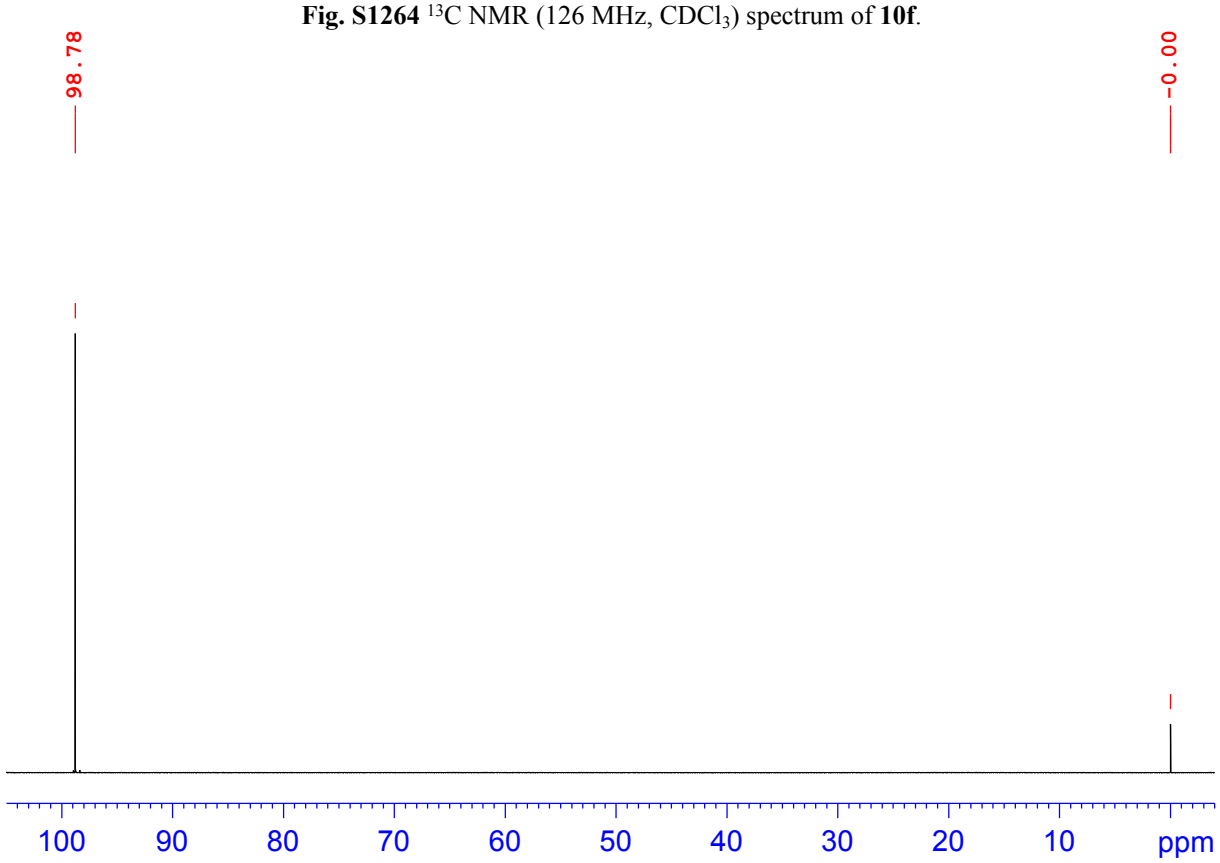

Fig. S127 ^{19}F NMR (470 MHz, $CDCl_3$) spectrum of **10f**.