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# Monoterpene amino alcohols in multicomponent synthesis of chiral hetero- and carbocycles

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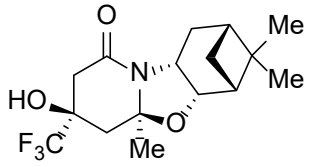
**Experimental**

**General remarks:** Melting points were measured in the open capillaries with a Stuart SMP3 melting-point apparatus. The IR spectra were recorded on Perkin-Elmer Spectrum Two FT-IR spectrometer with diamond ATR accessory in the range 400–4000 cm$^{-1}$. The $^{1}$H, $^{19}$F and $^{13}$C NMR spectra were registered on a Bruker AVANCE 500 and DRX-400 spectrometers using $Me_4Si$ ($^{1}$H) and $C_6F_6$ ($^{19}$F) as internal standards. The $^{13}$C chemical shift was calibrated using the solvent signal DMSO-$d_6$ ($\delta_C$ 39.5 ppm). For compounds *cis*-**5**, *trans*-**5**, **6, 6′** the signals in the $^{1}$H and $^{13}$C spectra were assigned based on 2D $^{1}$H-$^{1}$H-COSY, $^{1}$H-$^{1}$H-NOESY, $^{1}$H-$^{13}$C HSQC and HMBC experiments. Elemental CHN analysis of the synthesized compounds was carried out on CHN PE-2400 Series II (Perkin Elmer Instruments, USA). 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 Azura P 6.1 L instrument (for compounds *cis/trans*-**5**). Ethyl 4,4,4-trifluoro-3-oxobutanoate (**3**), acetone (**4**) and 1,4-dioxane are commercially available (purchased from P&M Invest and Macklin), (1*R*,2*S*,3*R*,5*R*)-3-amino-6,6-dimethylbicyclo[3.1.1]heptan-2-ol (**1**) (mp 78 °C, $[\alpha]^{21}_D$ = −13.9º (c 2.40, $CHCl_3$))[S1] and (1*S*,3*S*,4*S*,6*R*)-4-amino-3,7,7-trimethylbicyclo[4.1.0]heptan-3-ol (**2**) (mp 61 °C, $[\alpha]^{26}_D$ = –34.3° (c 1.0, $CHCl_3$))[S2] were obtained according to the literature procedures.

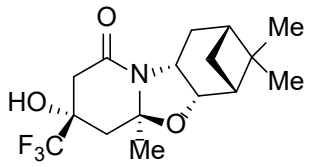
**General procedure for the synthesis of** *cis/trans*-**5**: A mixture of (1*R*,2*S*,3*R*,5*R*)-3-amino-6,6-dimethylbicyclo[3.1.1]heptan-2-ol **1** (0.169 g, 1 mmol), ethyl 4,4,4-trifluoro-3-oxobutanoate **3** (0.2 g, 1 mmol) and acetone **4** (0.063 g, 1 mmol) in 1,4-dioxane (5 mL) was placed in a 30 mL glass bottle with a hermetic screw cap. The reaction mixture was stirred for 2 days at room temperature (25 °C) and for 3 days at 80 °C. The progress of the reaction was monitored by TLC and NMR spectroscopy. Then the reaction mixture was concentrated, the formed precipitate was filtered off, washed with $Et_2O$, and crystallized from MeCN, and product *cis*-**5** was obtained. The filtrates were combined and concentrated. The solid residue was washed with $Et_2O$ and filtered off, and product *trans*-**5** was obtained.

**General procedure for the synthesis of 6 and 6'**: To a solution of ethyl 4,4,4-trifluoro-3-oxobutanoate **3** (0.38 g, 2 mmol) and acetone **4** (0.12 g, 2 mmol) in anhydrous ethanol (5 mL) was added the zeolite catalyst (molecular sieves 3Å, 400 mg). Then (1*S*,3*S*,4*S*,6*R*)-4-amino-3,7,7-trimethylbicyclo[4.1.0]heptan-3-ol **2** (0.35 g, 2 mmol) was added, and the reaction mixture was stirred for 10 days at room temperature (25 °C). Then the reaction mixture was filtered to separate zeolite catalyst. The solution was concentrated, the formed precipitate was filtered off, washed with $Et_2O$, crystallized from MeCN, washed with EtOH to afford product **6**. The filtrates were combined and concentrated. The solid residue was washed with $Et_2O$, filtered off, and **6'** product was thus obtained.

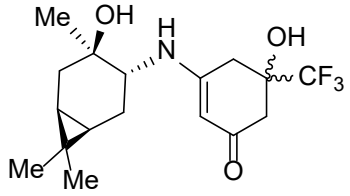



*(3R,4aS,6R,8R)-3-Hydroxy-4a,7,7-trimethyl-3-(trifluoromethyl)decahydro-1H-6,8-methanobenz[4,5]oxazolo[3,2-a]pyridin-1-one* (*cis*-**5**): colorless solid, sublimation point 220 °C. $[\alpha]^{20}_D$ = -66.5 (*c* 0.25, MeOH). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$: 1.05 (s, 3H, Me'-C$^7$), 1.20 (s, 3H, Me"-C$^7$), 1.26 (d, 1H, *J* 9.8 Hz, H-11B), 1.58 (s, 3H, Me-C$^{4a}$), 1.81 (dd, 1H, *J* 13.8, 7.0 Hz, H-9B), 1.89 (d, 1H, *J* 14.9 Hz, H-4B), 1.96 (q, 1H, *J* 5.4 Hz, H-8), 2.20–2.26 (m, 2H, H-6, H-11A), 2.33–2.40 (m, 3H, H-2B, H-4A, H-9A), 2.93 (d, 1H, *J* 14.8 Hz, H-2A), 4.25 (dt, 1H, *J* 9.8, 7.4 Hz, H-9a), 4.51 (dd, 1H, *J* 7.7, 4.5 Hz, H-5a), 6.36 (s, 1H, OH). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$: 22.2 (Me'-C$^7$), 25.8 (C-11), 27.4 (Me"-C$^7$), 27.6 (Me-C$^{4a}$), 31.8 (C-9), 38.0 (br.s, C-2), 38.2 (C-7), 40.2 (C-8), 42.3 (C-6), 42.5 (br.s, C-4), 51.7 (C-9a), 71.2 (q, $^2J_{CF}$ 29.4 Hz, C-3), 78.9 (C-5a), 93.5 (C-4a), 125.8 (q, $^1J_{CF}$ 284.7 Hz, $CF_3$), 167.8 (C-1). $^{19}$F NMR (471 MHz, DMSO-$d_6$) $\delta$: 81.16 (s, $CF_3$). IR (ATR, $\nu$/cm$^{-1}$): 3425 (O–H), 2984–2879 (C–H), 1646 (C=O), 1197–1092 (C–F). Found (%): C, 57.48; H, 6.63; N, 4.19. Calc. for $C_{16}H_{22}F_3NO_3$ (%): C, 57.65; H, 6.65; N, 4.20.

HPLC: 85.7% *ee*, Chiralpak AS-H, hexane : Pr$^{i}$OH = 10:1, flow rate = 1.0 mL/min, T = 25 °C, UV = 210 nm, $t_R$ = 11.02 min (minor), $t_R$ = 22.22 min (major).

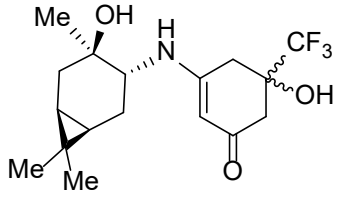



*(3S,4aS,6R,8R)-3-Hydroxy-4a,7,7-trimethyl-3-(trifluoromethyl)decahydro-1H-6,8-methanobenz[4,5]oxazolo[3,2-a]pyridin-1-one* (*trans*-**5**): colorless solid, mp 196–198 °C. $[\alpha]^{20}_D$ = -86.9 (*c* 0.425, MeOH). $^1$H NMR (500 MHz, DMSO-*d*$_6$) *δ*: 1.06 (s, 3H, Me'- C$^7$), 1.20 (s, 3H, Me"- C$^7$), 1.22 (br. d, 1H, *J* 10.0 Hz, H-11B), 1.69 (s, 3H, Me-C$^{4a}$), 1.79 (dd, 1H, *J* 13.8, 7.0 Hz, H-9B), 1.91–1.96 (m, 2H, H-4B and H-8), 2.03 (d, 1H, *J* 13.8 Hz, H-4A), 2.17–2.25 (m, 2H, H-11A and H-6), 2.34 (ddd, 1H, *J* 13.8, 9.9, 5.1 Hz, H-9A), 2.61 (d, 1H, *J* 16.4 Hz, H-2B), 2.79 (br. d, 1H, *J* 16.4 Hz, H-2A), 4.23 (ddd, 1H, *J* 9.9, 7.8, 7.0 Hz, H-9a), 4.58 (dd, 1H, *J* 7.8, 4.7 Hz, H-5a), 6.64 (s, 1H, OH). $^{13}$C NMR (126 MHz, DMSO-*d*$_6$) *δ*: 22.2 (Me'-C$^7$), 25.80 (C-11), 25.84 (Me-C$^{4a}$), 27.3 (Me"-C$^7$), 31.9 (C-9), 37.9 (C-7), 38.9 (C-2), 40.1 (C-8), 41.5 (C-4), 42.4 (C-6), 51.1 (C-9a), 70.3 (q, $^2J_{CF}$ 28.8 Hz, C-3), 78.9 (C-5a), 94.4 (C-4a), 126.2 (q, $^1J_{CF}$ 285.6 Hz, $CF_3$), 168.2 (C-1). $^{19}$F NMR (376 MHz, DMSO-*d*$_6$) *δ*: 79.86 (s, $CF_3$) . IR (ATR, *ν*/cm$^{-1}$): 3227 (O–H), 3000–2861 (C–H), 1653 (C=O), 1192–1110 (C–F). Found (%): C, 57.66; H, 6.64; N, 4.19. Calc. for $C_{16}H_{22}F_3NO_3$ (%): C, 57.65; H, 6.65; N, 4.20. HPLC: 98.3% ee, Chiralpak AS-H, hexane : iPrOH = 10:1, flow rate = 1.0 mL/min, T = 25 °C, UV = 210 nm, $t_R$ = 10.30 min (minor), $t_R$ = 19.77 min (major).




*5-Hydroxy-3-(((1R,3R,4R,6S)-4-hydroxy-4,7,7-trimethylbicyclo[4.1.0]hept-3-yl)amino)-5-(trifluoromethyl)cyclohex-2-en-1-one*, diastereomer **6**: colorless solid, point of decomposition 260 °C. $[\alpha]^{20}_D$ = +28.9 (*c* 0.5, DMSO). $^1$H NMR (500 MHz, DMSO-*d*$_6$) *δ*: 0.62 (br.t, 1H, *J* 8.5 Hz, H-1'), 0.70 (td, 1H, *J* 9.8, 4.7 Hz, H-6'), 0.96 (s, 3H, Me'-C$^{7'}$), 1.01 (s, 3H, Me"-C$^{7'}$), 1.13 (s, 3H, Me-C$^{4'}$), 1.29 (dd, 1H, *J* 14.4, 4.7 Hz, H-5'B), 1.57–1.64 (m, 1H, H-2'B), 1.88 (dd, 1H, *J* 14.4, 9.8 Hz, H-5'A), 1.91 (dd, 1H, *J* 14.7, 6.6 Hz, H-2'A), 2.22 (d, 1H, *J* 16.1 Hz, H-6B), 2.44 (d, 1H, *J* 16.1, Hz H-6A), 2.63 (d, 1H, *J* 16.6 Hz, H-4B), 2.69 (d, 1H, *J* 16.6 Hz, H-4A), 2.99–3.04 (m, 1H, H-3'), 4.14 (s, 1H, OH-C$^{4'}$), 4.99 (s, 1H, H-2), 6.14 (s, 1H, OH-C$^5$), 6.65 (d, 1H, *J* 8.6 Hz, NH). $^{13}$C NMR (126 MHz, DMSO-*d*$_6$) *δ*: 15.2 (Me"-C$^{7'}$), 17.1 (C-7'), 19.1 (br.s, C-1'), 19.6 (C-6'), 20.6 (br.s,

Me-C$^{4'}$), 25.4 (br.s, C-2'), 28.4 (Me'-C$^{7'}$), 33.8 (br.s, C-4), 34.6 (C-5'), 41.0 (br.s, C-6), 56.7 (C-3'), 70.4 (C-4'), 72.1 (q, $^{2}J_{CF}$ 28.0 Hz, C-5), 94.0 (C-2), 125.8 (q, $^{1}J_{CF}$ 285.6 Hz, $CF_3$), 159.8 (C-3), 189.2 (C-1). $^{19}$F NMR (376 MHz, DMSO-$d_6$) $\delta$: 80.39 (s, $CF_3$). IR (ATR, $\nu$/cm$^{-1}$): 3394–3365 (N–H, O–H), 2947–2868 (C–H), 1587 (C=O), 1524 (C=C), 1177–1100 (C–F). Found (%): C, 58.72; H, 6.95; N, 4.03. Calc. for $C_{17}H_{24}F_3NO_3$ (%): C, 58.78; H, 6.96; N, 4.03.




*5-Hydroxy-3-(((1R,3R,4R,6S)-4-hydroxy-4,7,7-trimethylbicyclo[4.1.0]heptan-3-yl)amino)-5-(trifluoromethyl)cyclohex-2-en-1-one*, diastereomer **6′**: colorless solid, mp 253–256 °C. $[\alpha]^{20}_{D}$ = -5.9 (*c* 0.425, DMSO). $^{1}$H NMR (500 MHz, DMSO-$d_6$) $\delta$: 0.63 (br.t, 1H, *J* 8.5 Hz, H-1'), 0.70 (td, 1H, *J* 9.5, 4.6 Hz, H-6'), 0.97 (s, 3H, Me'-C$^{7'}$), 1.02 (s, 3H, Me''-C$^{7'}$), 1.10 (s, 3H, Me-C$^{4'}$), 1.28 (dd, 1H, *J* 14.4, 4.6 Hz, H-5'B), 1.66 (ddd, 1H, *J* 14.7, 10.8, 8.0 Hz, H-2'B), 1.85 (dd, 1H, *J* 14.4, 9.5 Hz, H-5'A), 1.90 (br. dd, 1H, *J* 14.7, 7.0 Hz, H-2'A), 2.23 (dd, *J* 16.2, 1.8 Hz, H-6B), 2.41 (d, 1H, *J* 16.2 Hz, H-6A), 2.60 (br. d, 1H, *J* 16.3 Hz, H-4B), 2.71 (d, 1H, *J* 16.3 Hz, H-4A), 3.00–3.06 (m, 1H, H-3'), 4.17 (s, 1H, OH-C$^{4'}$), 4.98 (s, 1H, H-2), 6.19 (s, 1H, OH-C$^{5}$), 6.67 (d, 1H, *J* 8.5 Hz, NH). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$: 15.2 (Me''-C$^{7'}$), 17.1 (C-7'), 19.2 (C-1'), 19.5 (C-6'), 20.4 (Me-C$^{4'}$), 25.7 (C-2'), 28.4 (Me'-C$^{7'}$), 33.7 (C-4), 34.6 (C-5'), 40.8 (C-6), 56.5 (C-3'), 70.7 (C-4'), 72.2 (q, $^{2}J_{CF}$ 27.8 Hz, C-5), 93.9 (C-2), 125.8 (q, $^{1}J_{CF}$ 285.8 Hz, $CF_3$), 160.1 (C-3), 188.9 (C-1). $^{19}$F NMR (376 MHz, DMSO-$d_6$) $\delta$: 80.25 (s, $CF_3$). IR (ATR, $\nu$/cm$^{-1}$): 3457, 3344, 3235 (N–H, O–H), 2992–2870 (C–H), 1587 (C=O), 1539 (C=C), 1176–1100 (C–F). Found (%): C, 58.66; H, 6.94; N, 4.03. Calc. for $C_{17}H_{24}F_3NO_3$ (%): C, 58.78; H, 6.96; N, 4.03.

**X-ray Analysis:**

Data for compound *trans*-**5** was collected with an Xcalibur 3 CCD diffractometer at 295(2) K (MoKα irradiation, graphite monochromator, CCD detector, ω/2θ scanning) by using graphite-monochromated Mo-Kα (λ = 0.71073 Å) radiation. Empirical absorption correction was applied. Using Olex2,[S3] the structure was solved with the ShelXS structure solution program using Direct Methods and refined with the ShelXL[S4,S5] in anisotropic approximation for non-hydrogen atoms. The H-atoms of the C-H bonds were added in the calculated positions; the H-atoms of the OH-group were refined independently in the isotropic approximation. Deposition Number 2406848 contain the supplementary crystallographic data for this paper. These data are provided free of

charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

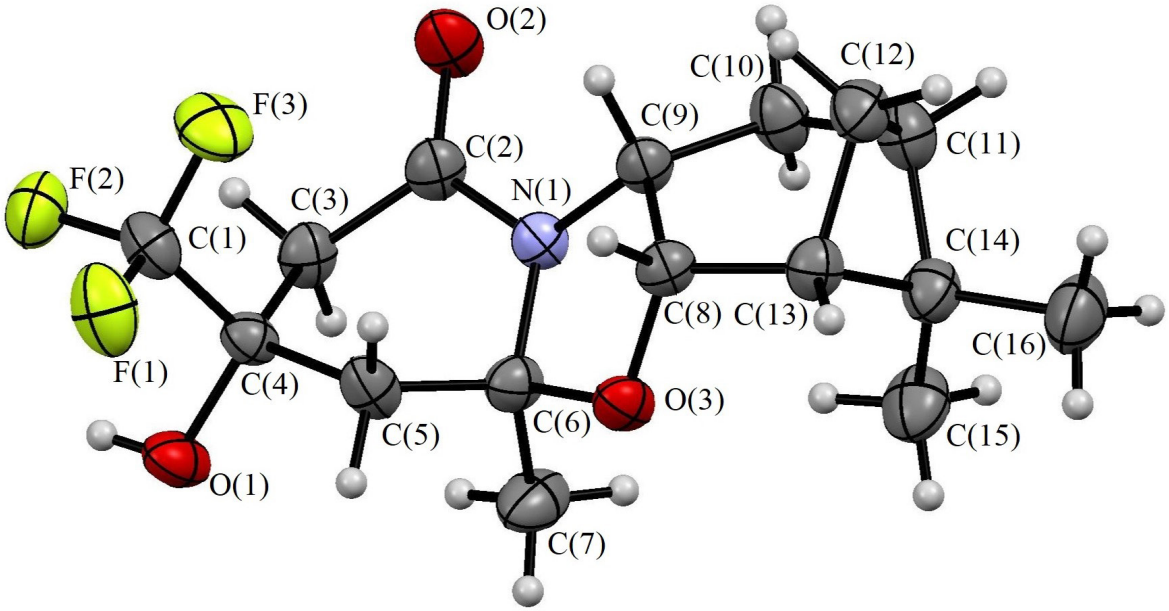



**Figure S1**. ORTEP view of molecule *trans*-**5** according to XRD (CCDC 2406848).

**Table S1.** Crystal data and structure refinement for *trans*-**5**

| | |
|---|---|
| Empirical formula | $C_{16}H_{22}F_3NO_3$ |
| Formula weight | 333.35 |
| Temperature/K | 295(2) |
| Crystal system | monoclinic |
| Space group | $P2_1$ |
| a/Å | 12.6750(9) |
| b/Å | 10.1414(6) |
| c/Å | 13.6473(11) |
| α/° | 90.00 |
| β/° | 107.810(8) |
| γ/° | 90.00 |
| Volume/Å$^3$ | 1670.2(2) |
| Z | 4 |
| $\rho_{calc}$mg/mm$^3$ | 1.326 |
| m/mm$^{-1}$ | 0.112 |
| F(000) | 704.0 |

| | |
|---|---|
| Crystal size/$mm^3$ | 0.47 × 0.34 × 0.18 |
| 2Θ range for data collection | 5.1 to 60.98° |
| Index ranges | $-16 \leq h \leq 17$, $-14 \leq k \leq 14$, $-12 \leq l \leq 18$ |
| Reflections collected | 8155 |
| Independent reflections | 6366[R(int) = 0.0450] |
| Data/restraints/parameters | 6366/1/423 |
| Goodness-of-fit on $F^2$ | 1.006 |
| Final R indexes [I>=2σ (I)] | $R_1 = 0.0686$, $wR_2 = 0.1573$ |
| Final R indexes [all data] | $R_1 = 0.1414$, $wR_2 = 0.2183$ |
| Largest diff. peak/hole / e $Å^{-3}$ | 0.51/-0.47 |
| Flack parameter | 0.3(12) |

**References**


S1. C. M. Binder, A. Bautista, M. Zaidlewicz, M. P. Krzemiński, A. Oliver and B. Singaram, *J. Org. Chem.*, 2009, **74**, 2337; https://doi.org/10.1021/jo802371z.

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S4. G. M. Sheldrick, *Acta Crystallogr., Sect. C: Struct. Chem.*, 2015, **71**, 3; https://doi.org/10.1107/S2053229614024218.

S5. G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr*., 2015, **71**, 3; https://doi.org/10.1107/S2053273314026370.

**Copies of $^{1}H$, $^{19}F$, $^{13}C$ NMR spectra and 2D $^{1}H$-$^{1}H$ COSY, $^{1}H$-$^{13}C$ HSQC, $^{1}H$-$^{13}C$ HMBC, $^{1}H$-$^{1}H$ NOESY experiments**

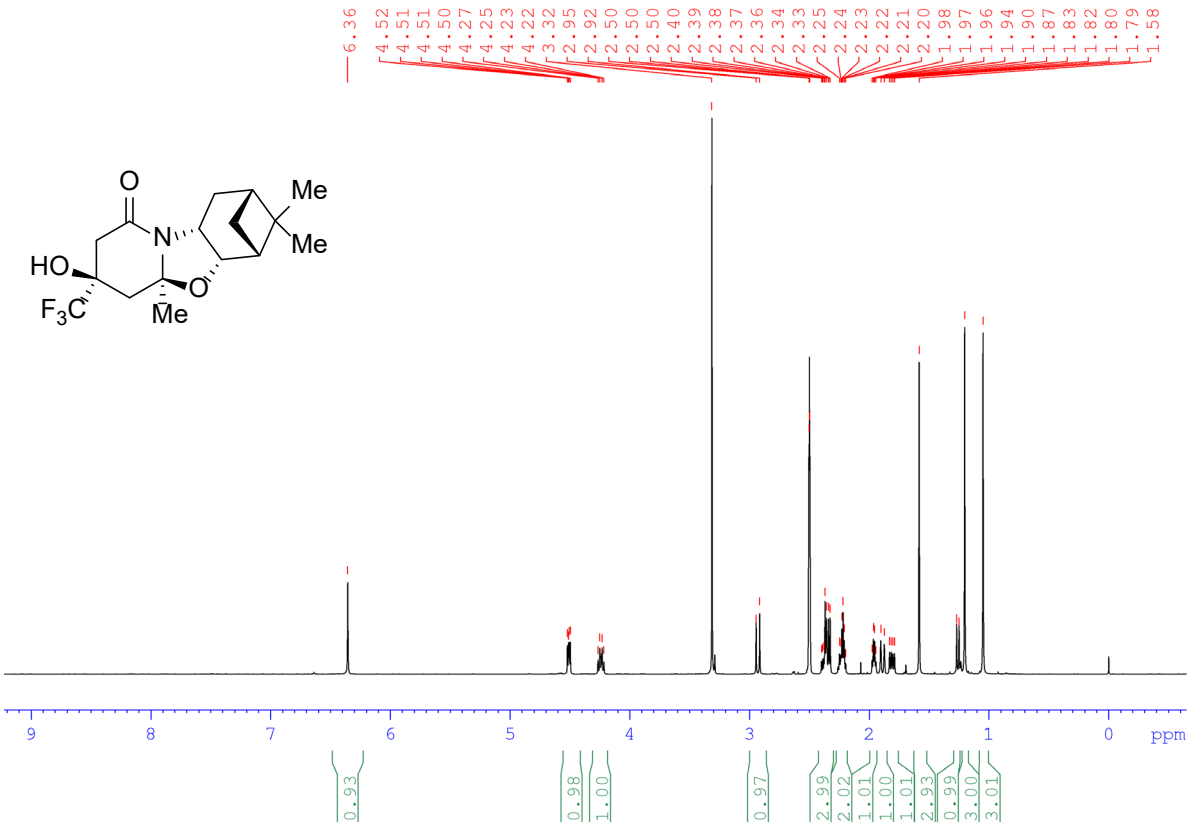


**Figure S2**. $^{1}H$ NMR (500 MHz, DMSO-$d_6$) spectrum of *cis*-**5**

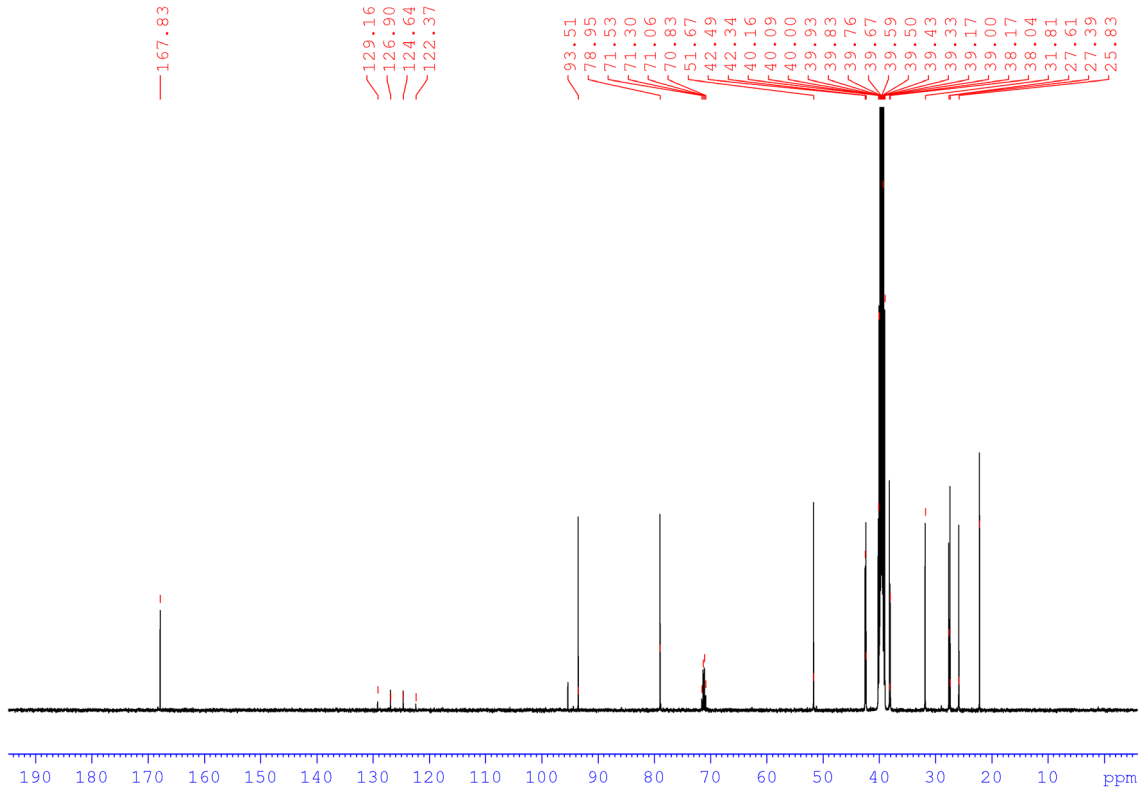


**Figure S3**. $^{13}C$ NMR (126 MHz, DMSO-$d_6$) spectrum of *cis*-**5**

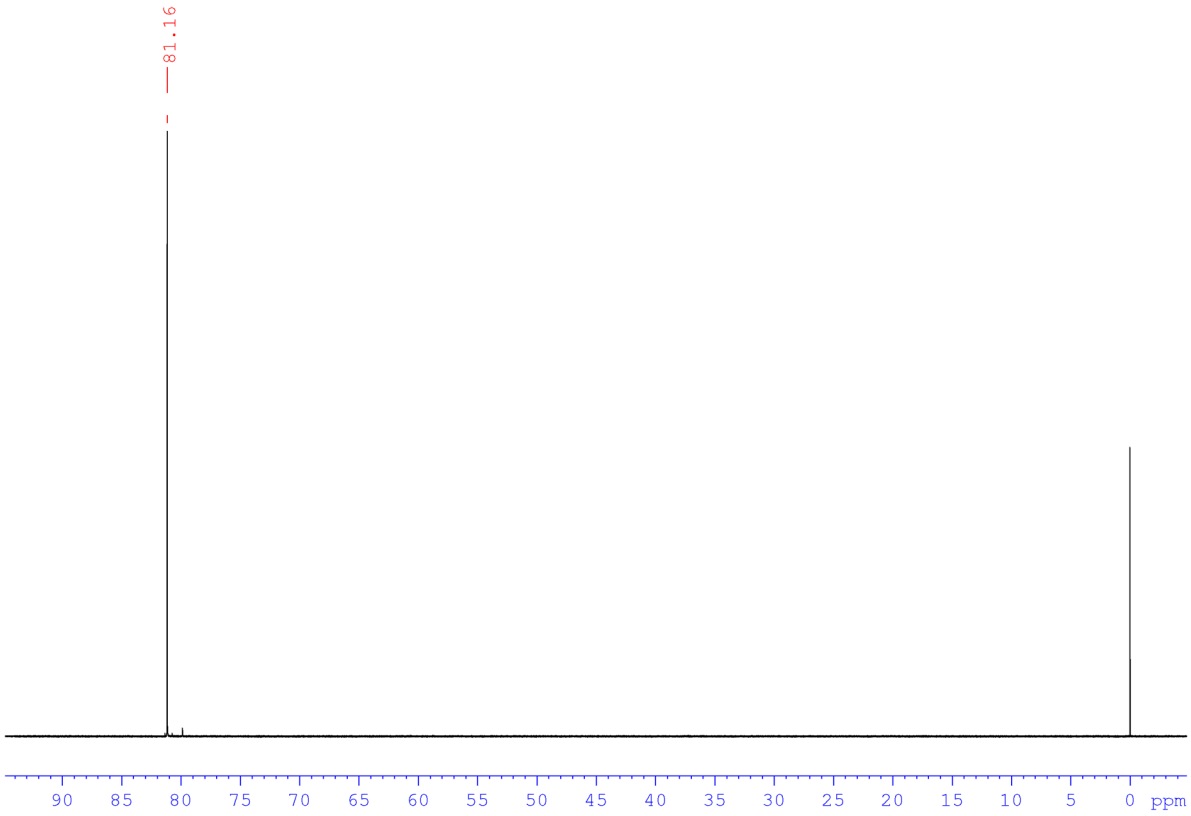


**Figure S4**. $^{19}F$ NMR (470 MHz, DMSO-$d_6$) spectrum of *cis*-**5**

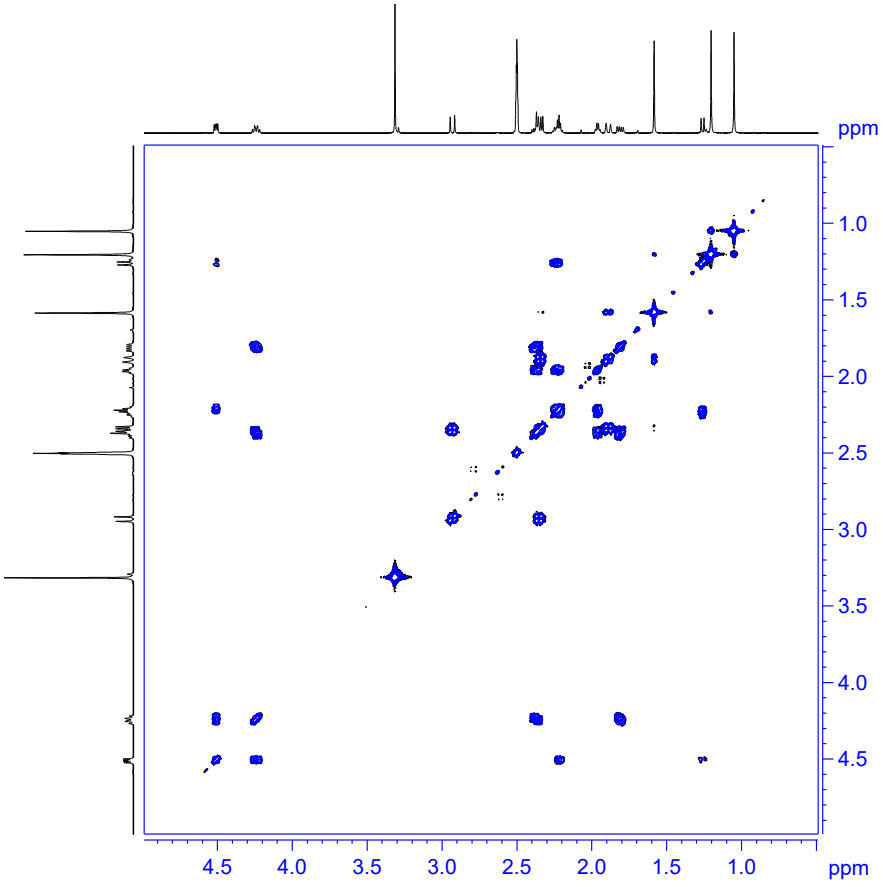


**Figure S5**. 2D $^{1}H$-$^{1}H$ COSY spectrum (500 MHz, DMSO-$d_6$) of *cis*-**5**

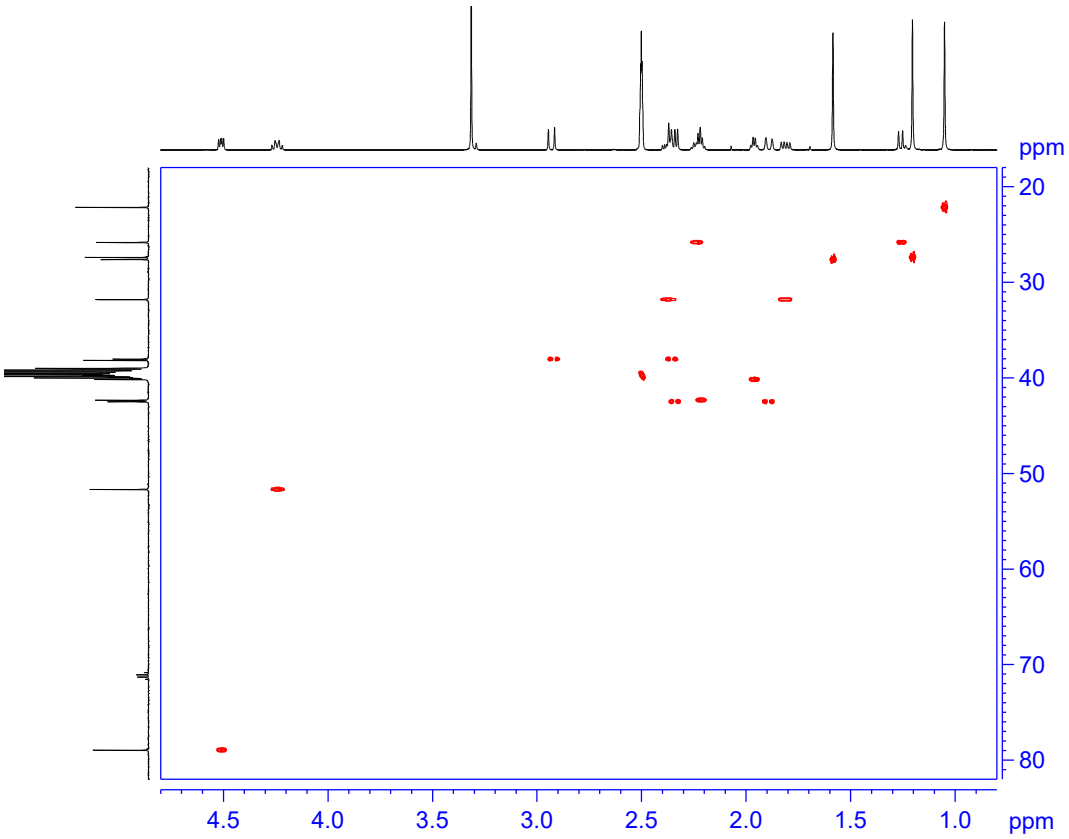


**Figure S6**. 2D $^{1}H$-$^{13}C$ HSQC spectrum (500 MHz, DMSO-$d_6$) of *cis*-**5**

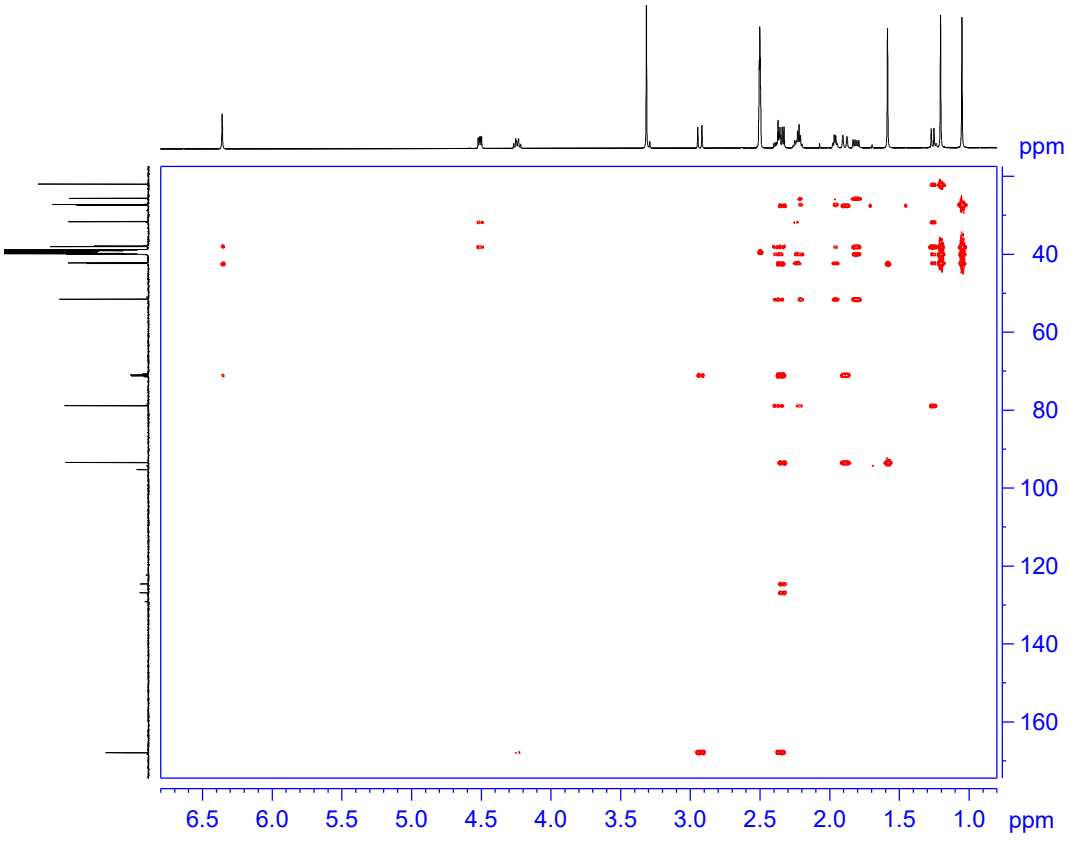


**Figure S7**. 2D $^{1}H$-$^{13}C$ HMBC spectrum (500 MHz, DMSO-$d_6$) of *cis*-**5**

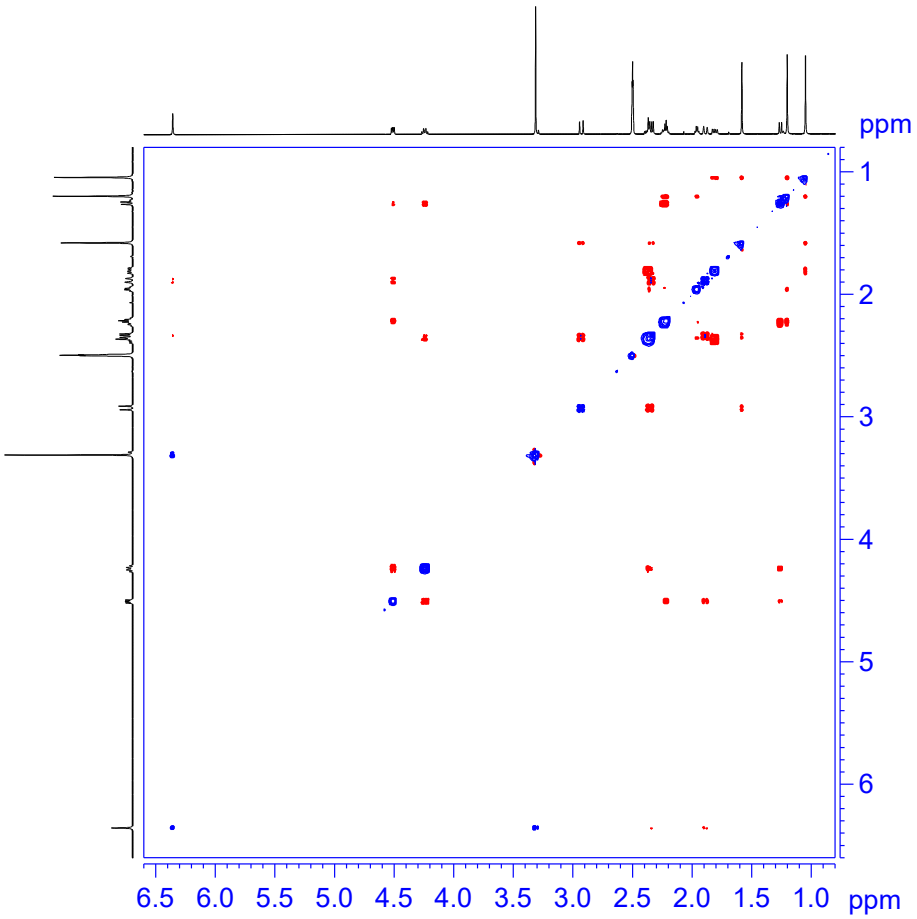


**Figure S8**. 2D $^{1}$H-$^{1}$H NOESY spectrum (500 MHz, DMSO-$d_6$) of *cis*-**5**

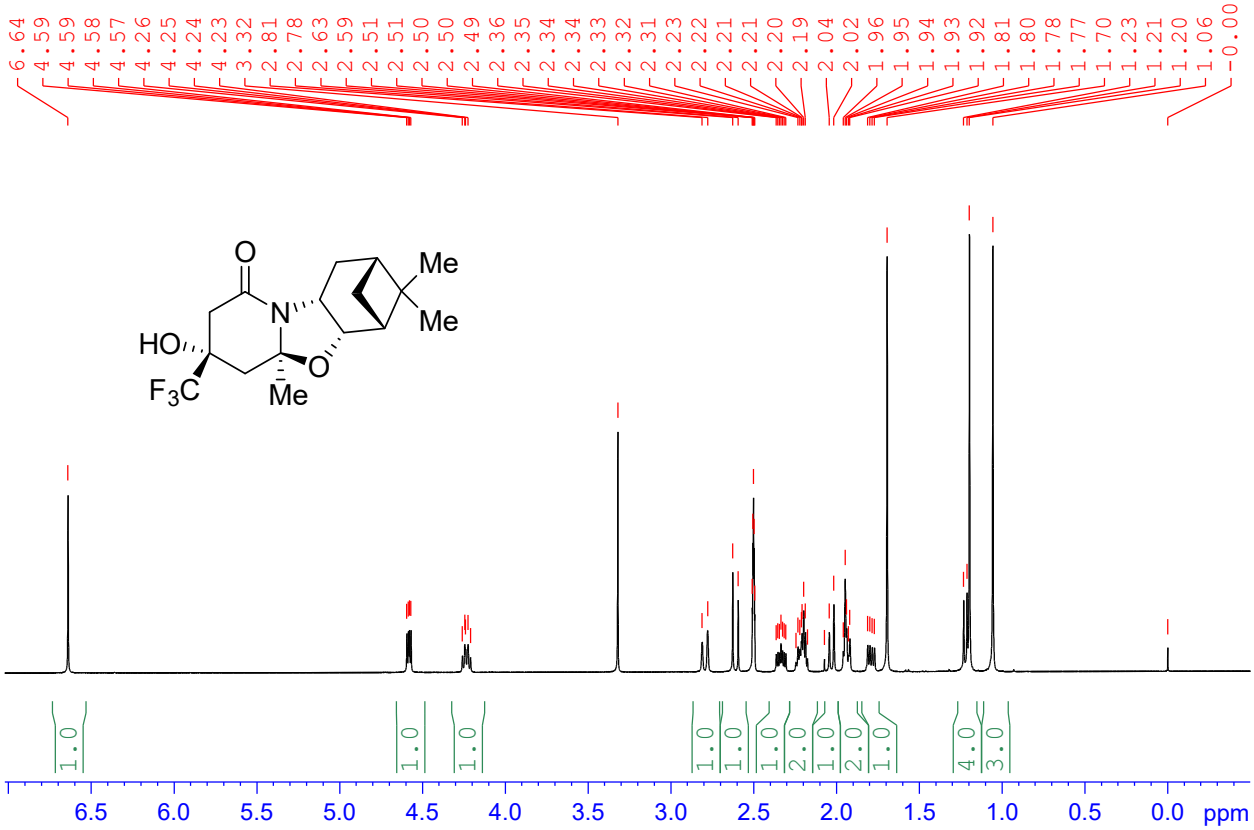


**Figure S9**. $^{1}$H NMR (500 MHz, DMSO-$d_6$) spectrum of *trans*-**5**

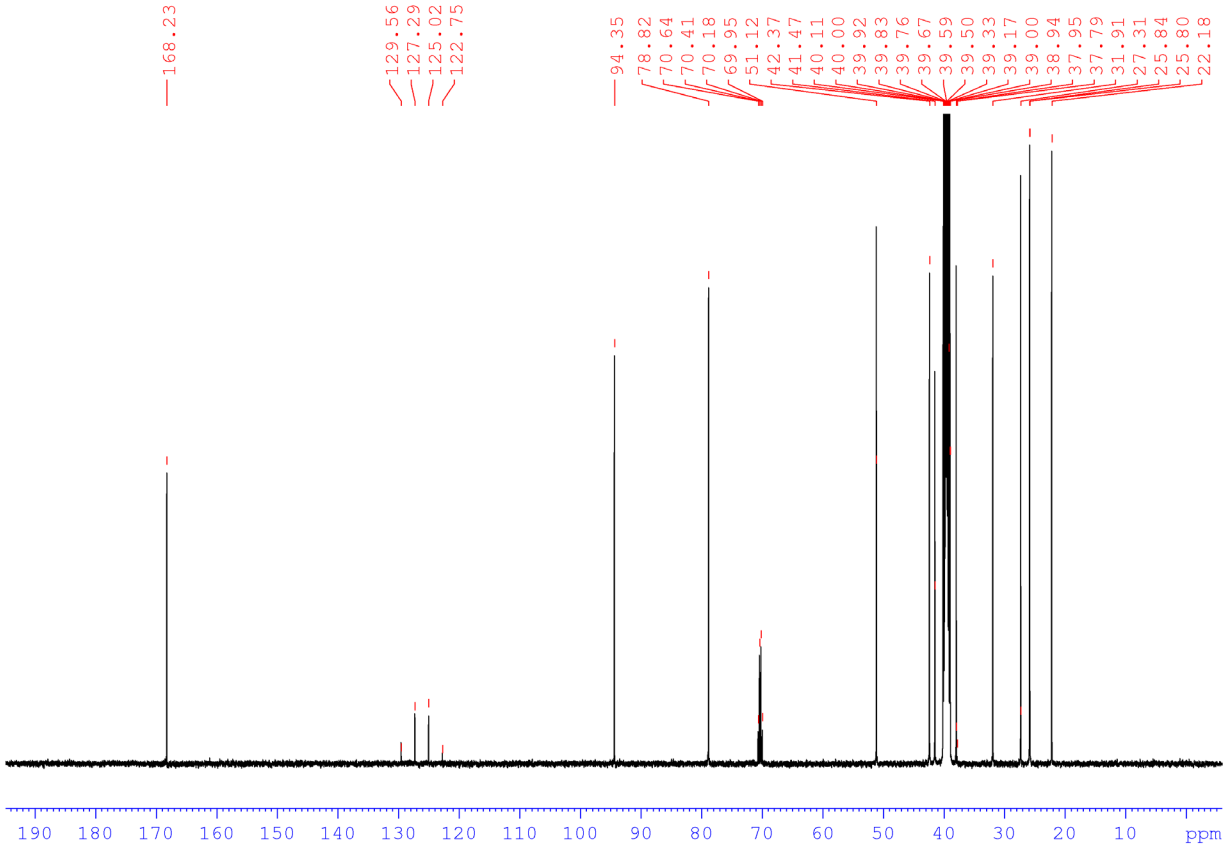


**Figure S10**. $^{13}$C NMR (126 MHz, DMSO-$d_6$) spectrum of *trans*-**5**

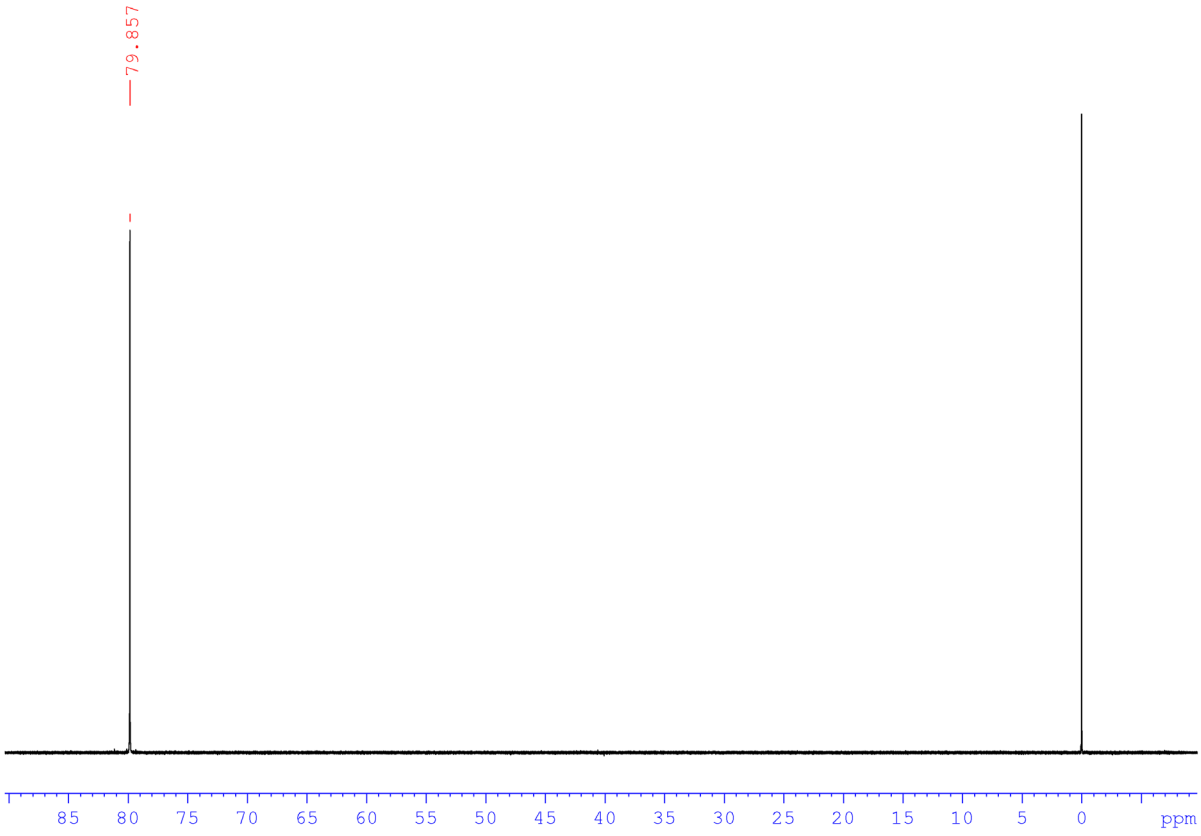


**Figure S11**. $^{19}$F NMR (376 MHz, DMSO-$d_6$) spectrum of *trans*-**5**

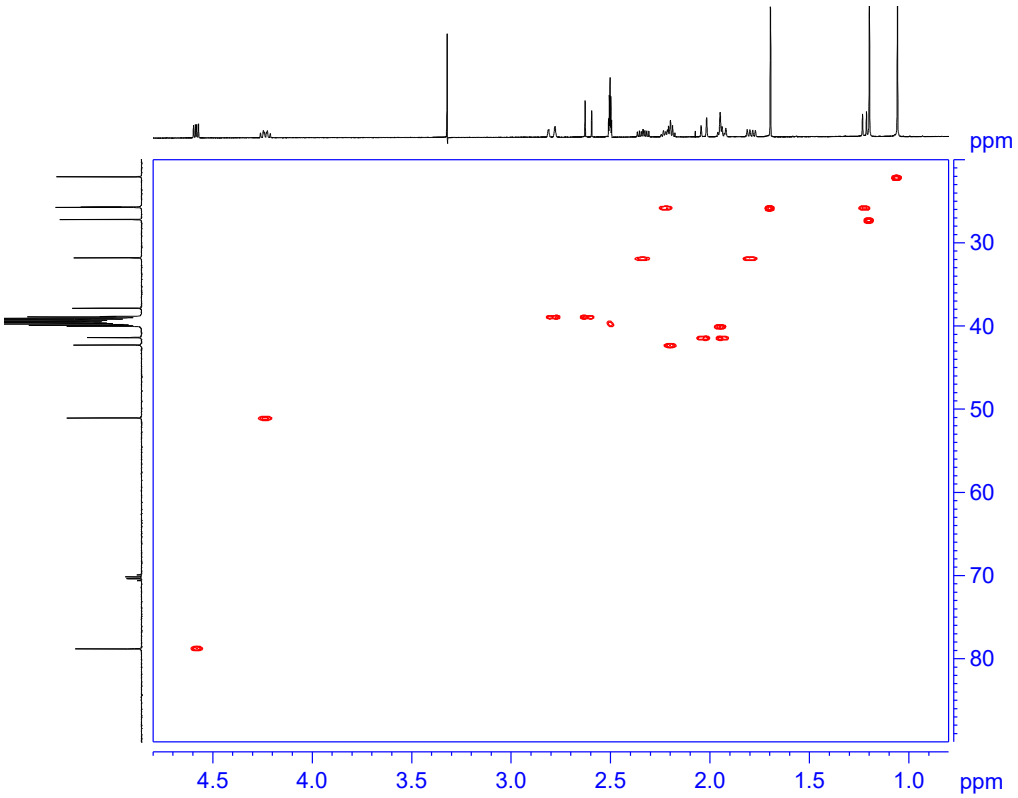


**Figure S12**. 2D $^{1}$H-$^{13}$C HSQC spectrum (500 MHz, DMSO-$d_6$) of *trans*-**5**

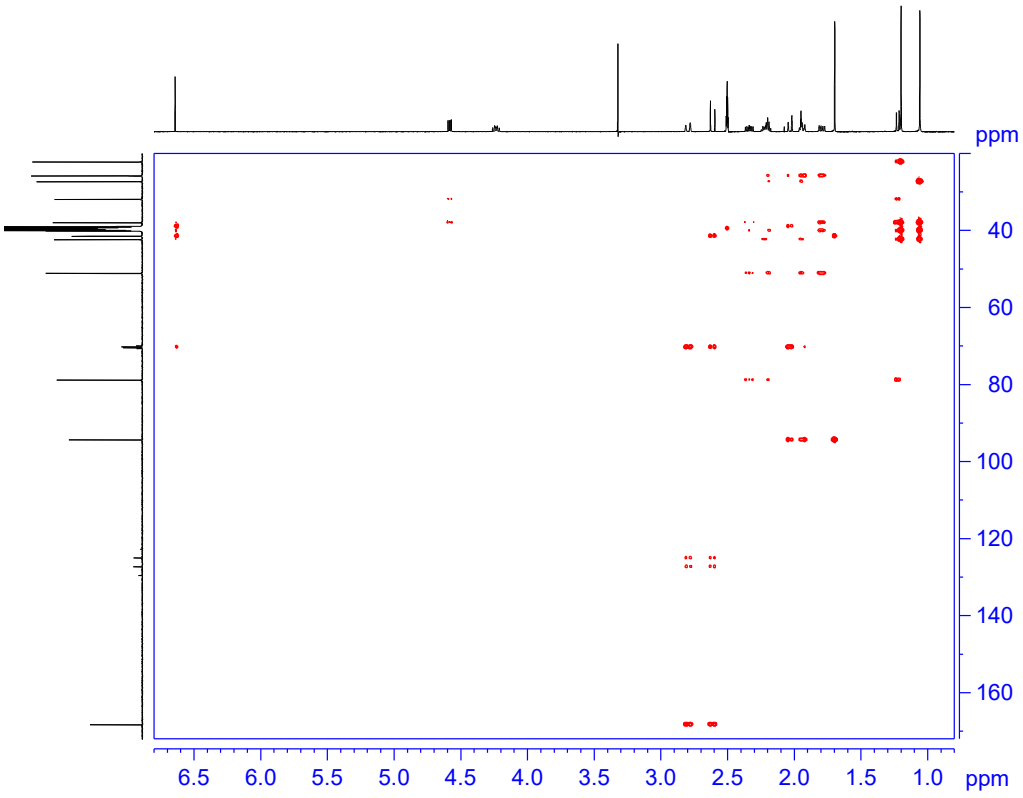


**Figure S13**. 2D $^{1}$H-$^{13}$C HMBC spectrum (500 MHz, DMSO-$d_6$) of *trans*-**5**

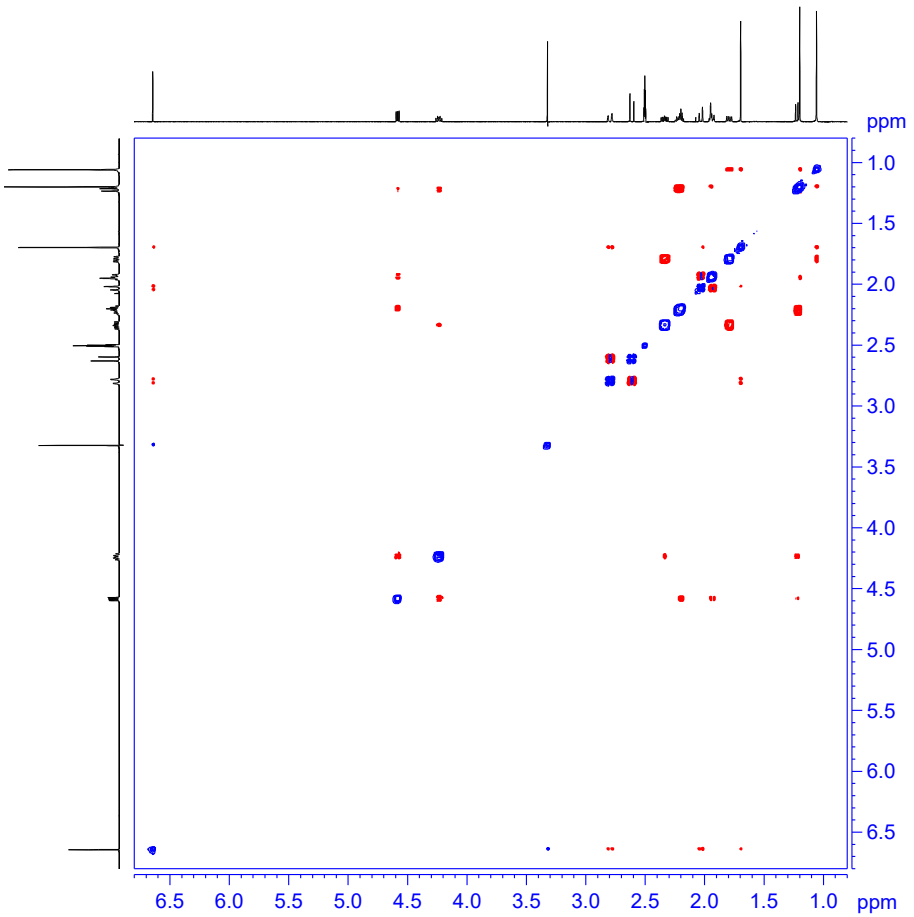


**Figure S14**. 2D $^{1}$H-$^{1}$H NOESY spectrum (500 MHz, DMSO-d$_6$) of *trans*-**5**

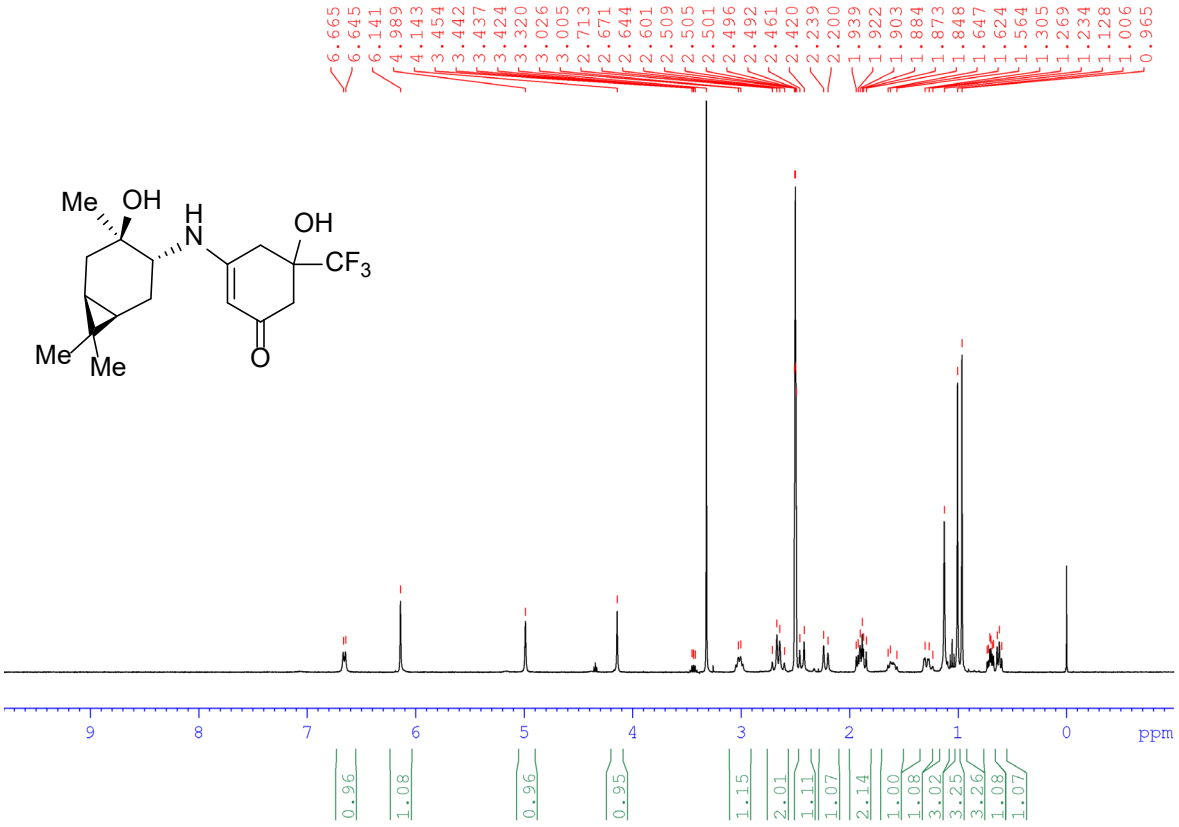


**Figure S15**. $^{1}$H NMR (500 MHz, DMSO-d$_6$) spectrum of **6**

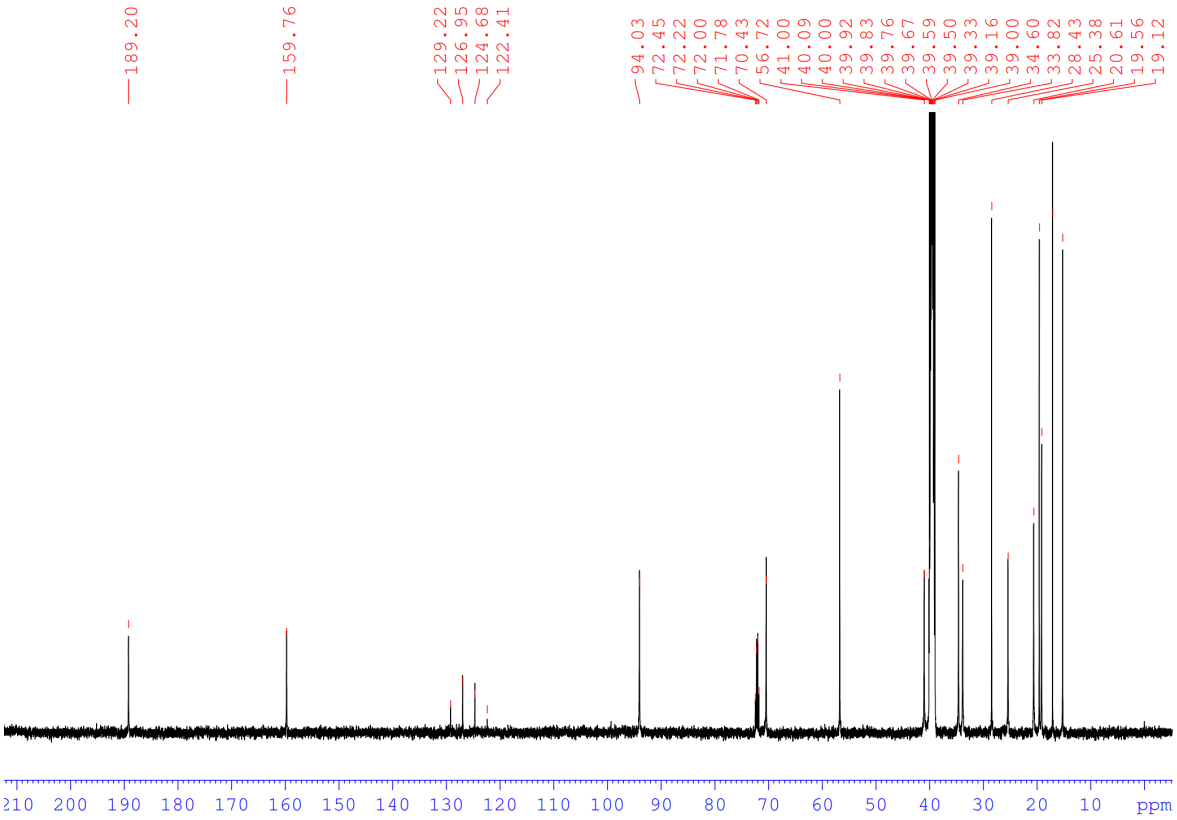


**Figure S16**. $^{13}$C NMR (126 MHz, DMSO-$d_6$) spectrum of **6**

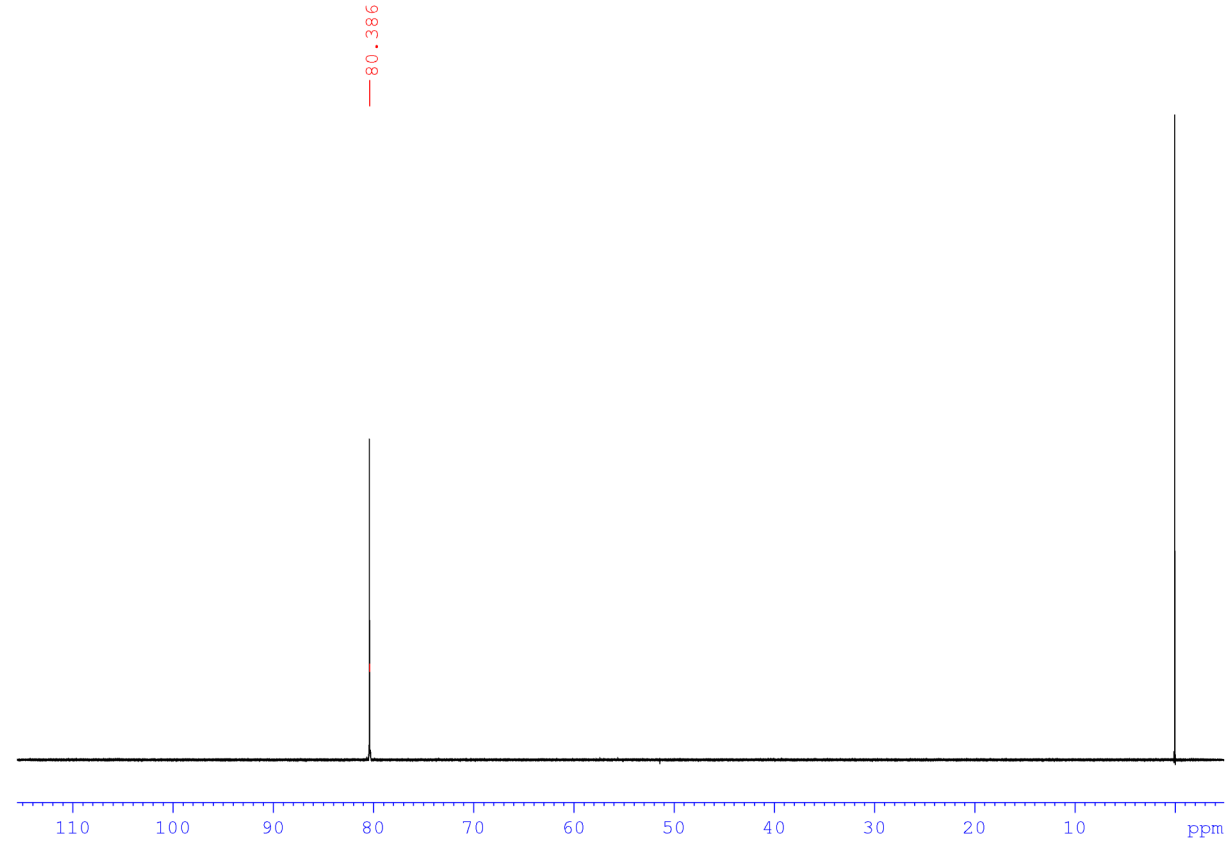


**Figure S17**. $^{19}$F NMR (376 MHz, DMSO-$d_6$) spectrum of **6**

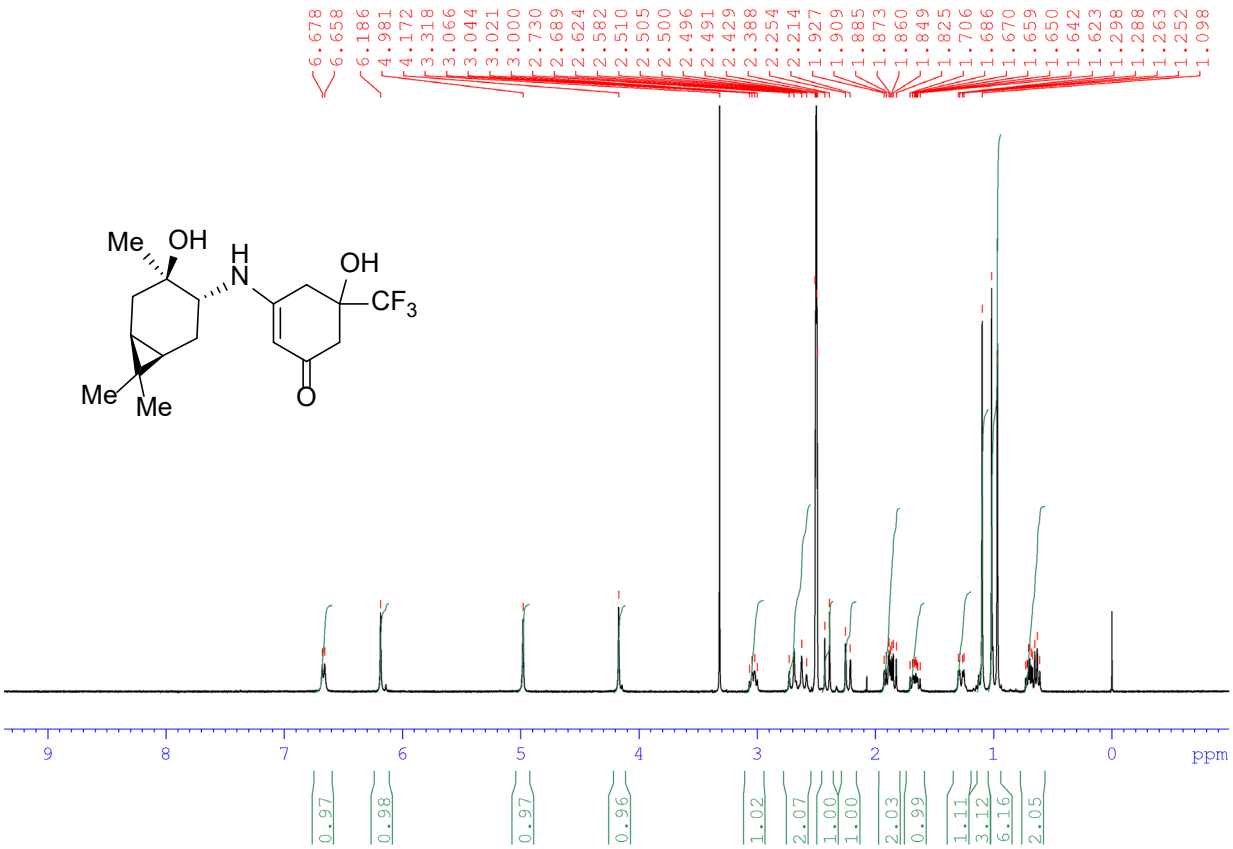


**Figure S18**. $^{1}$H NMR (500 MHz, DMSO-d$_6$) spectrum of **6′**

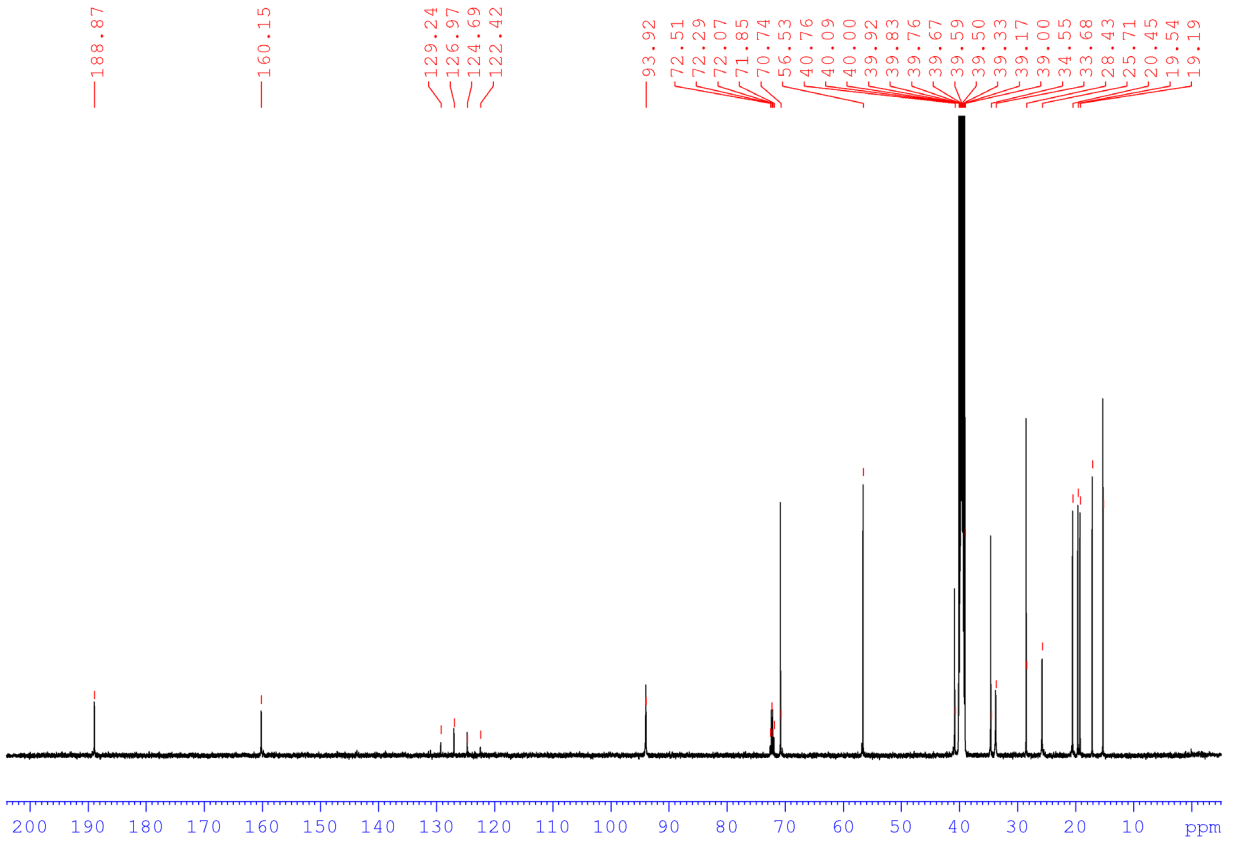


**Figure S19**. $^{13}$C NMR (126 MHz, DMSO-*d*$_6$) spectrum of **6′**

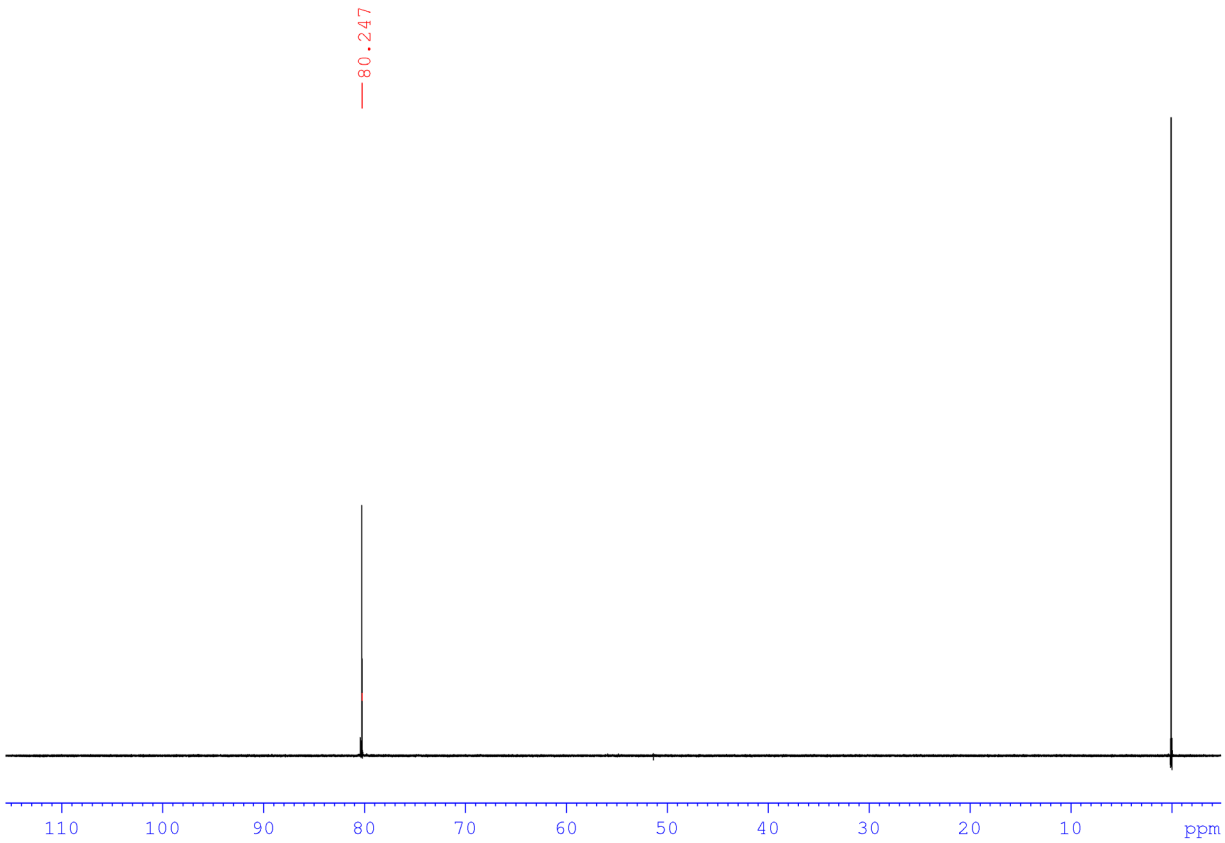


**Figure S20**. $^{19}$F NMR (376 MHz, DMSO-$d_6$) spectrum of **6′**

## Copies of IR spectra

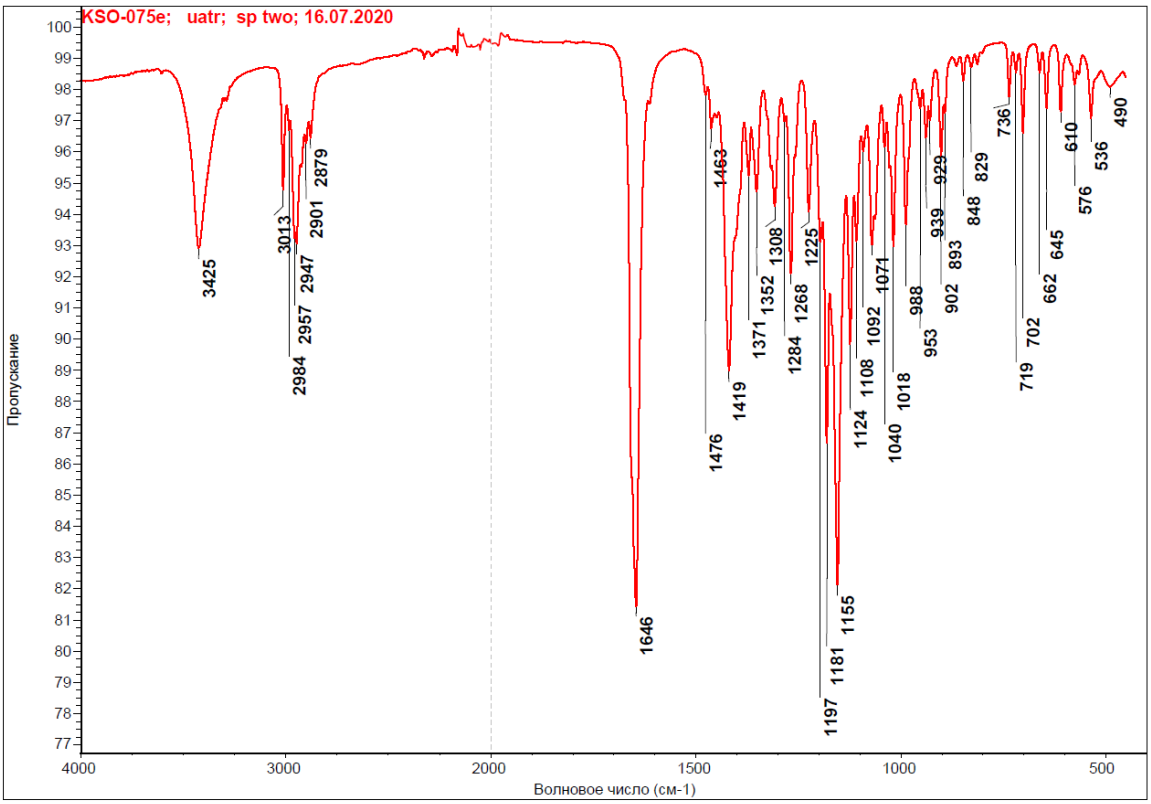


**Figure S21**. IR spectrum of *cis*-**5**.

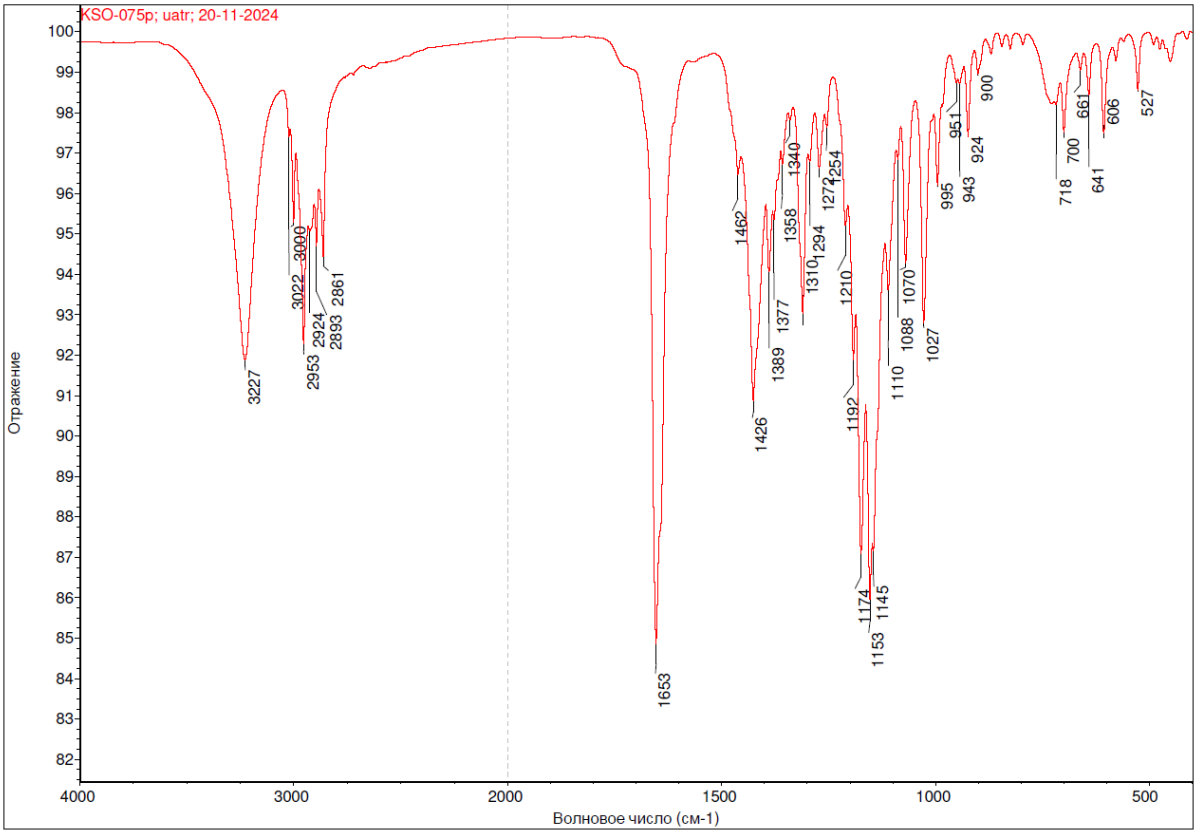


**Figure S22**. IR spectrum of *trans*-**5**.

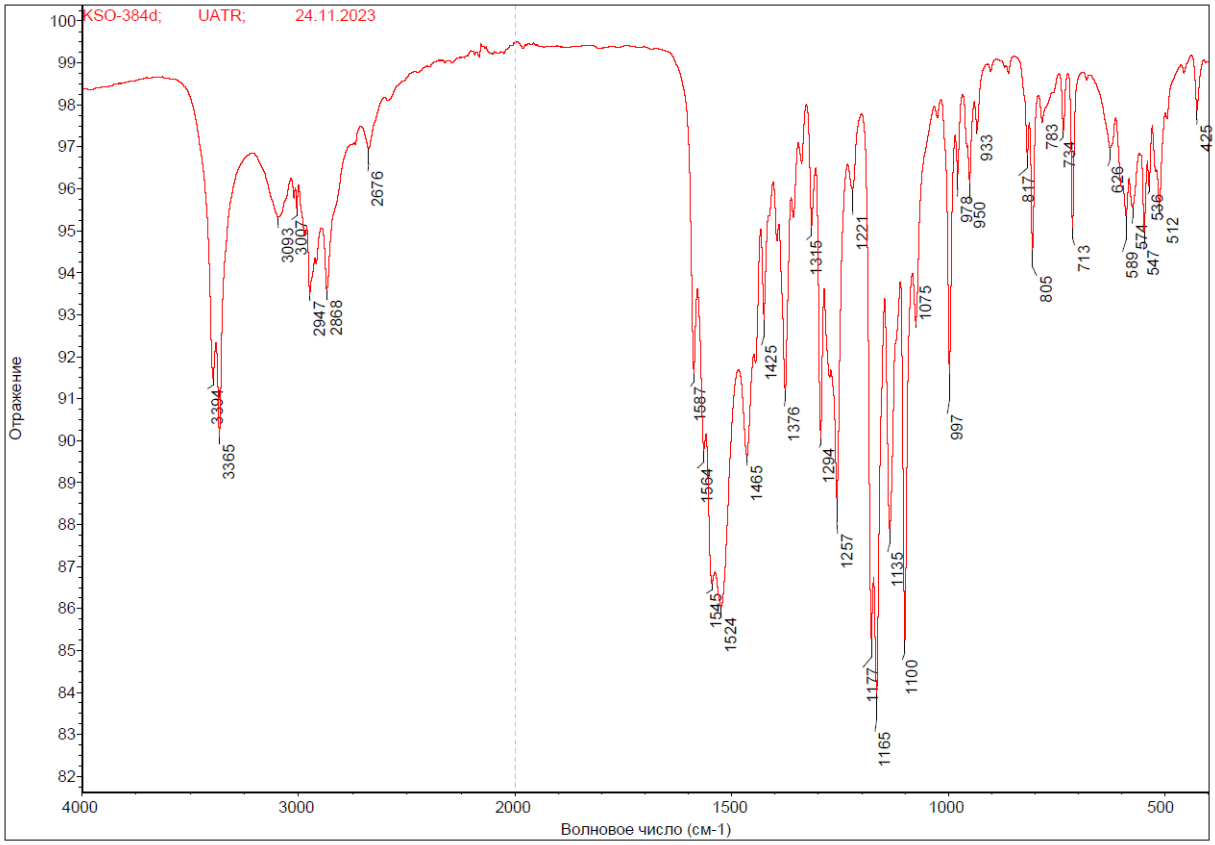


**Figure S23.** IR spectrum of **6**.

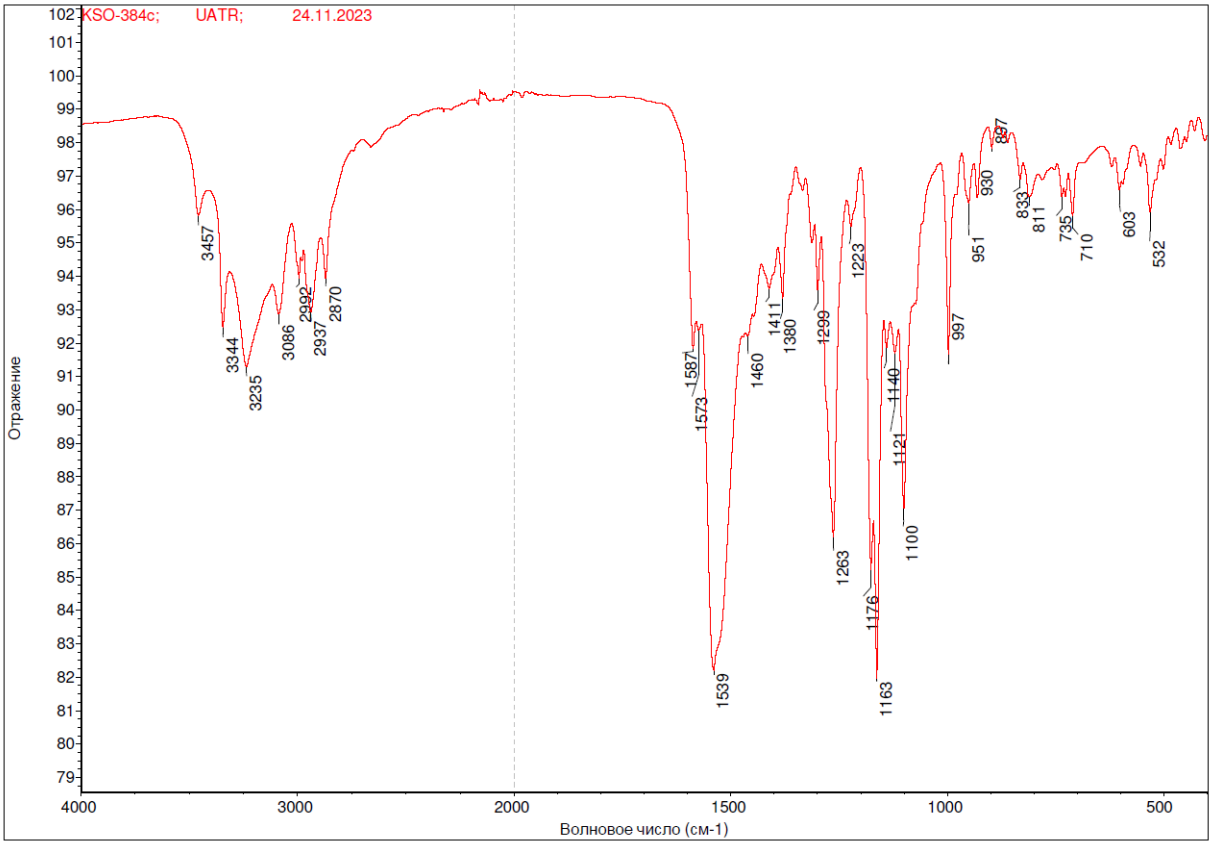


**Figure S24**. IR spectrum of **6′**.