Supplementary Information

HSD1787, a tetrahydro-3*H*-pyrazolo[4,3-*f*]quinoline compound synthesized via Povarov reaction, potently inhibits proliferation of cancer cell lines at nanomolar concentrations

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Contents of Supporting Information

Figure S42: ^{13}C NMR of compound 19

Single crystal X-ray diffraction data

Single crystals of compound 1 were coated with trace of fomblin oil and quickly transferred to the goniometer head of a Bruker Quest diffractometer with a fixed chi angle, a sealed tube fine focus X-ray tube, single crystal curved graphite incident beam monochromator, a Photon100 CMOS area detector and an Oxford Cryosystems low temperature device. Examination and data collection were performed with Mo Kα radiation (λ = 0.71073 Å) at 150 K. Data were collected, reflections were indexed and processed, and the files scaled and corrected for absorption using APEX3 [1]. The space group was assigned and the structure was solved by direct methods using XPREP within the SHELXTL suite of programs [2] and refined by full matrix least squares against F^2 with all reflections using Shelxl2018 [3] using the graphical interface Shelxle [4]. H atoms attached to carbon and oxygen atoms were positioned geometrically and constrained to ride on their parent atoms, with carbon hydrogen bond distances of 0.95 Å for and aromatic C-H, 0.99 Å for aliphatic CH_2 moieties, and 0.84 for hydroxyl OH atoms, respectively. Hydroxyl H atoms were allowed to rotate but not to tip to best fit the experimental electron density. U_{iso}(H) values were set to a multiple of U_{eq}(C/O) with 1.5 for OH, and 1.2 for C-H and CH_2 units, respectively. Complete crystallographic data, in CIF format, have been deposited with the Cambridge Crystallographic Data Centre. CCDC 2017003 contains 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.

[1] Bruker (2016). Apex3 v2016.9-0, Saint V8.34A, SAINT V8.37A, Bruker AXS Inc.: Madison (WI), USA, 2013/2014.

[2] a) SHELXTL suite of programs, Version 6.14, 2000-2003, Bruker Advanced X-ray Solutions, Bruker AXS Inc., Madison, Wisconsin: USA) b) Sheldrick GM. A short history of SHELX. *Acta Crystallogr A.* **2008**, *64(1)*, 112–122.

[3] a) Sheldrick GM. University of Göttingen, Germany, **2018**. b) Sheldrick GM. Crystal structure refinement with SHELXL. *Acta Crystallogr Sect C Struct Chem.* **2015**, *71(1)*, 3–8.

[4] Hübschle CB, Sheldrick GM, Dittrich B. ShelXle: a Qt graphical user interface for SHELXL. *J. Appl. Crystallogr.* **2011**, *44(6)*, 1281–1284.

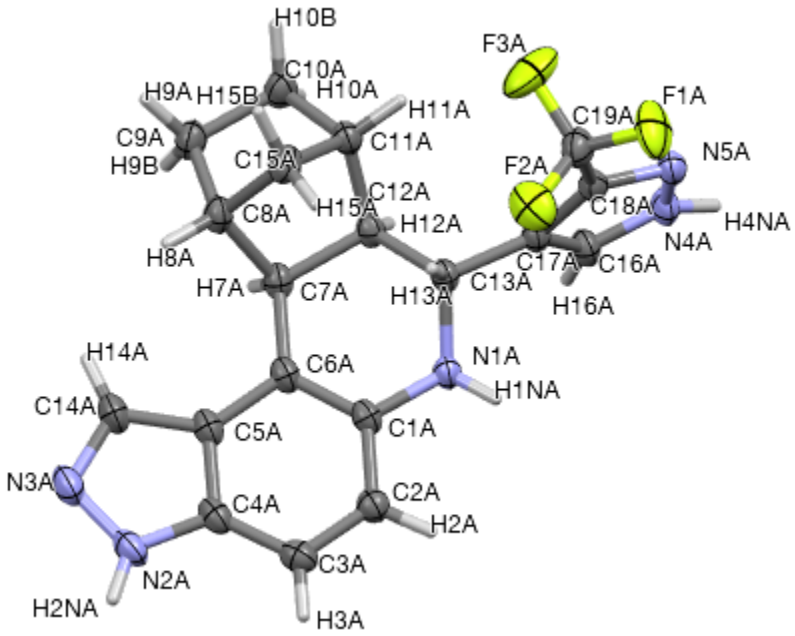

Table S1. Experimental details for single crystal X-ray diffraction of compound 1

	Compound 1
Crystal data CCDC 2017003	
Chemical formula	$C_{19}H_{18}F_3N_5 \cdot 2(C_2H_6O)$
M_r	465.52
Crystal system, space group	Triclinic, *P*1
Temperature (K)	150
a, *b*, *c* (Å)	9.8976 (5), 15.4264 (8), 16.4770 (9)
α, β, γ (°)	105.039 (2), 105.423 (2), 93.516 (2)
V (Å^3)	2319.1 (2)
Z	4
F(000)	984
D_x (Mg m^{-3})	1.333

Radiation type	Cu *K*α
No. of reflections for cell measurement	9714
θ range (°) for cell measurement	2.9–79.6
μ (mm^{-1})	0.87
Crystal shape	Plate
Colour	Colourless
Crystal size (mm)	0.31 × 0.20 × 0.04
Data collection	
Diffractometer	Bruker AXS D8 Quest CMOS diffractometer with PhotonII charge-integrating pixel array detector (CPAD)
Radiation source	I-mu-S microsource X-ray tube
Monochromator	Laterally graded multilayer (Goebel) mirror
Detector resolution (pixels mm^{-1})	7.4074
Scan method	ω and phi scans
Absorption correction	Multi-scan *SADABS* 2016/2: Krause, L., Herbst-Irmer, R., Sheldrick G.M. & Stalke D., J. Appl. Cryst. 48 (2015) 3-10
T_{min}, T_{max}	0.588, 0.754
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	60418, 10031, 8494
R_{int}	0.058
θ values (°)	θ_{max} = 80.9, θ_{min} = 2.9
$(\sin \theta/\lambda)_{max}$ ($Å^{-1}$)	0.640

Range of *h*, *k*, *l*	*h* = −12→10, *k* = −19→19, *l* = −21→21
Refinement	
Refinement on	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.047, 0.134, 1.11
No. of reflections	10031
No. of parameters	740
No. of restraints	390
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0646P)^2 + 0.5949P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	0.001
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.29, −0.26
Extinction method	*SHELXL2018*/3 (Sheldrick 2018), $Fc^*=kFc[1+0.001xFc^2\lambda^3/\sin(2\theta)]^{-1/4}$
Extinction coefficient	0.0021 (3)

Computer programs: Apex3 v2017.3-0 (Bruker, 2017), *SAINT* V8.38A (Bruker, 2016), *SHELXS97* (Sheldrick, 2008), *SHELXL2018*/3 (Sheldrick, 2015, 2018), SHELXLE Rev946 (Hübschle *et al.*, 2011).

The structure is a racemic mixture, space group P-1. There are two crystallographically independent molecules in the cell. They are chemically identical (same conformation and configuration). There are also four ethanol molecules. A bit disordered, but well resolved. Amine H atoms are located (i.e., the H atom positions are verified by the data. Description of the minor disorder :The fluorine atoms of the two trifluoromethyl groups were refined as disordered by slight rotation. The major and minor disordered moieties were each restrained to have similar geometries. Uij components of ADPs for disordered atoms closer to each other than 2.0 Angstrom were restrained to be similar. Subject to these conditions the occupancy ratios refined to 0.807(18) to 0.193(18) (molecule A) and to 0.56(4) to 0.44(4)

(molecule B). Two of the four solvate ethanol molecules were refined as disordered by inversion at the methylene carbon atom. The two disordered moieties were restrained to have similar geometries as another not disordered ethanol molecule. Uij components of ADPs for disordered atoms closer to each other than 2.0 Angstrom were restrained to be similar. Subject to these conditions the occupancy ratio refined to 0.759(7) to 0.241(7) (disorder of O4 / O5) and to 0.619(6) to 0.381(6) (disorder of O3 / O6).

Figure S1: ^{1}H spectra of compound 1 in DMSO-d_6

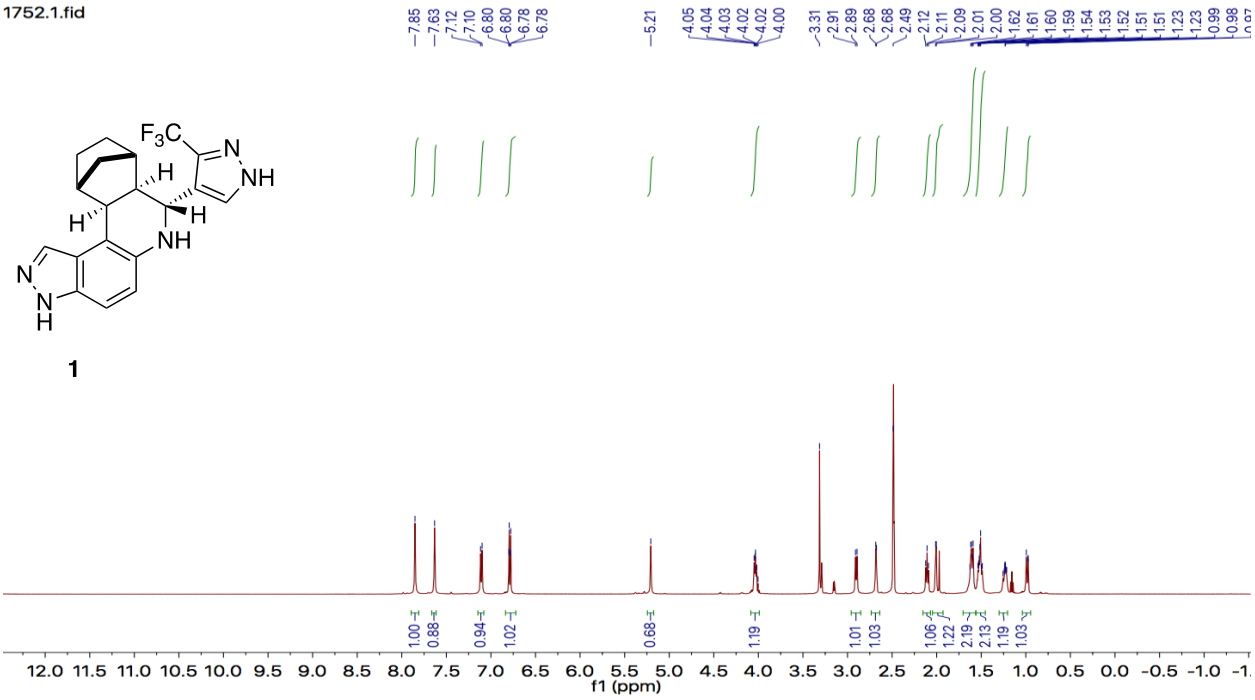

Figure S2: ^{13}C spectra of compound 1 in DMSO-d_6

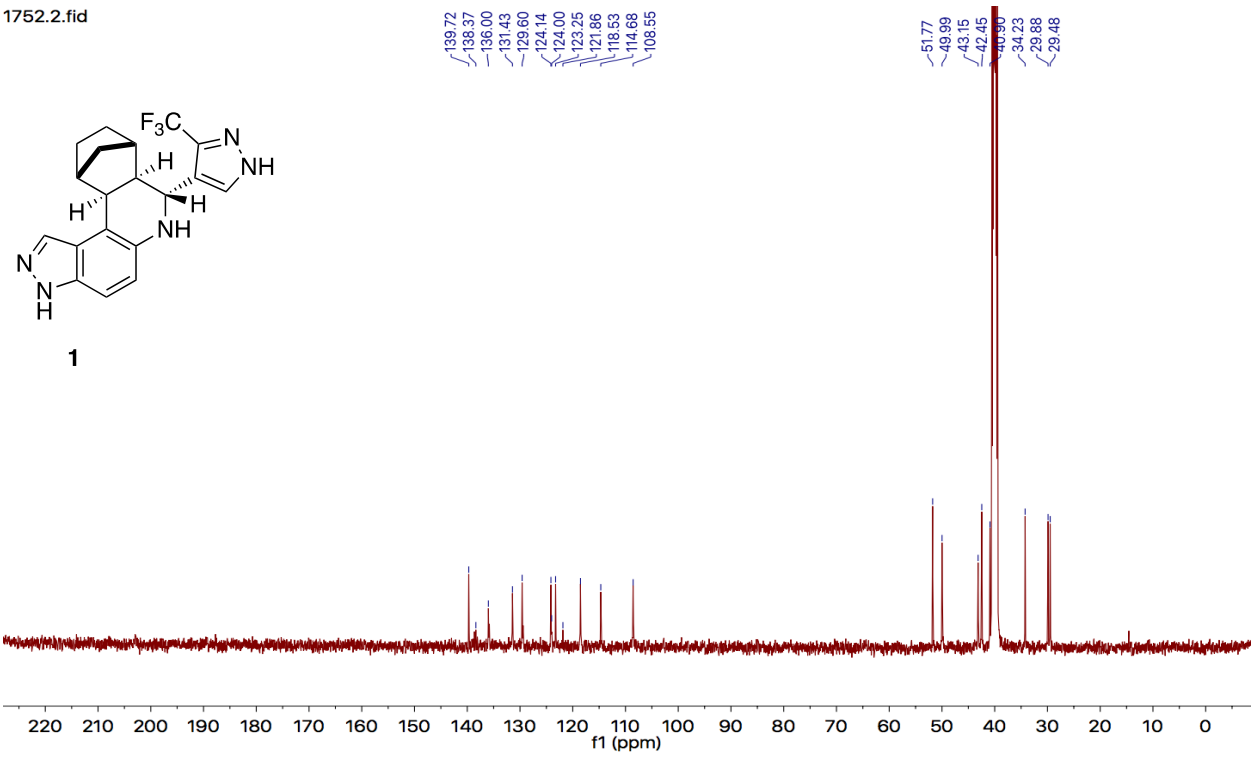

Figure S3: ^{1}H spectra of compound 2 in DMSO-d_6

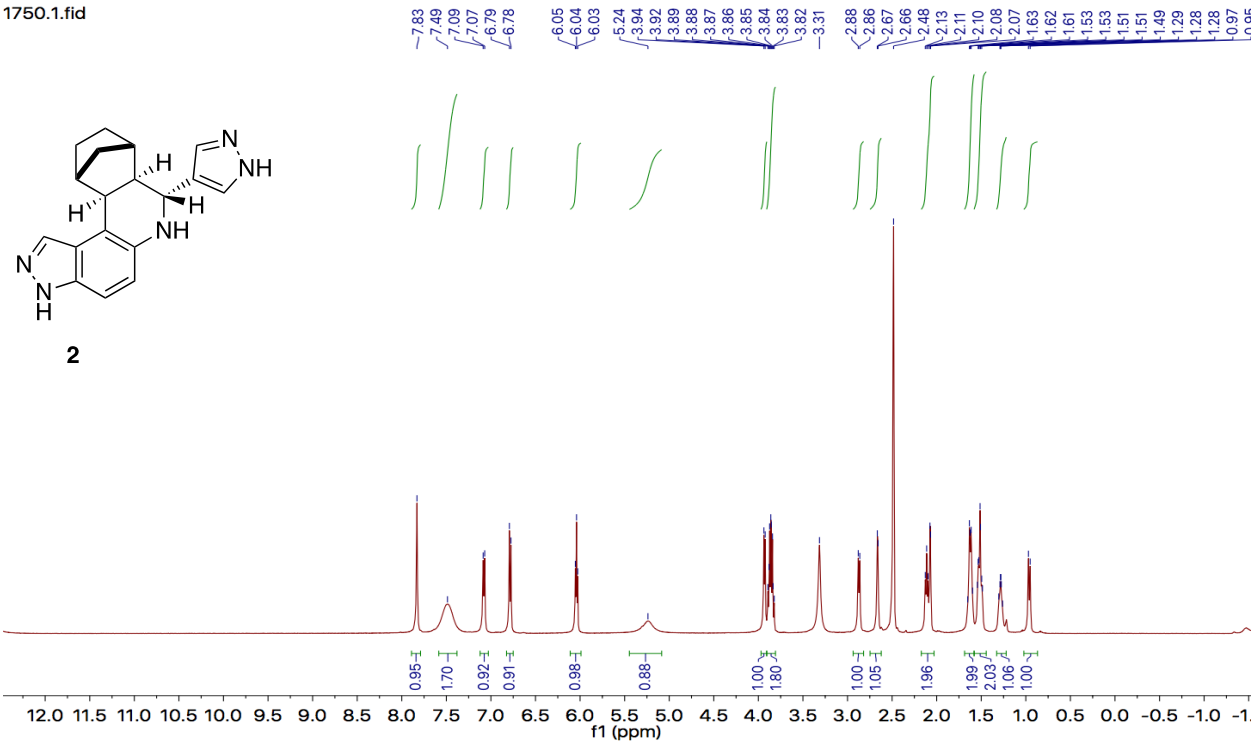

Figure S4: ^{13}C spectra of compound 2 in DMSO-d_6

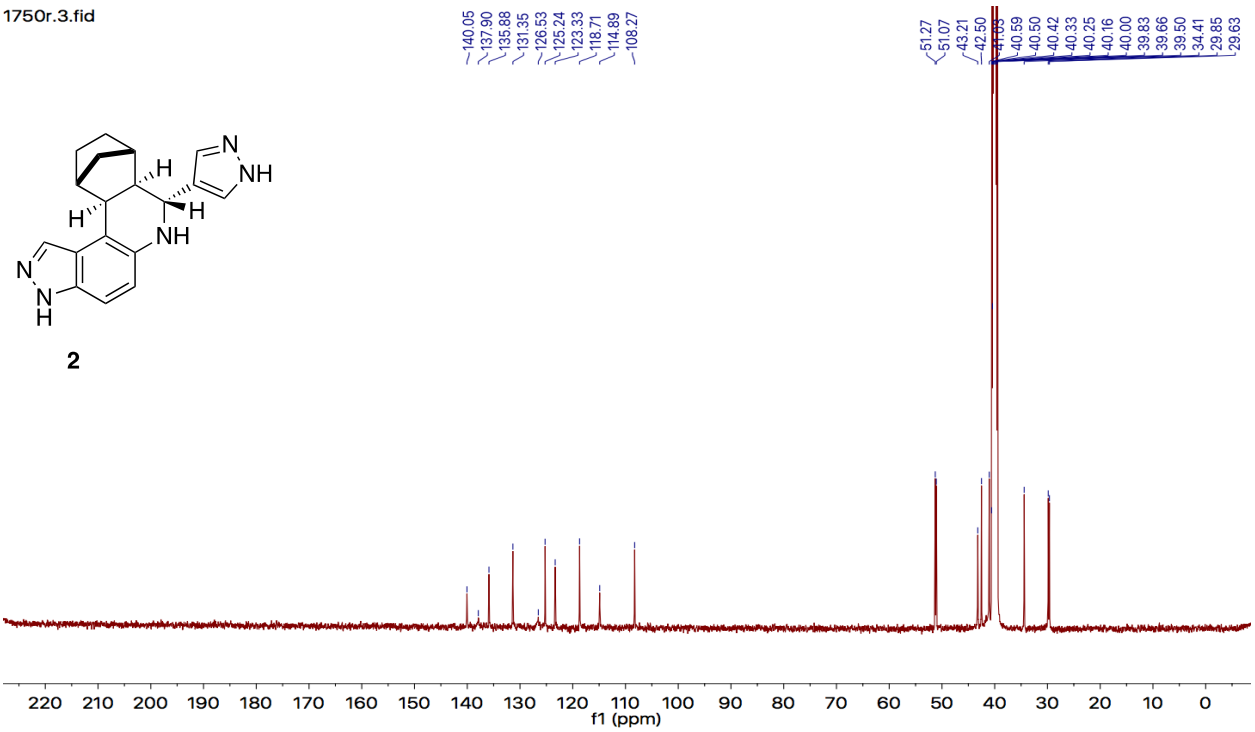

Figure S5: ^{1}H spectra of compound 3 in methanol-d_4

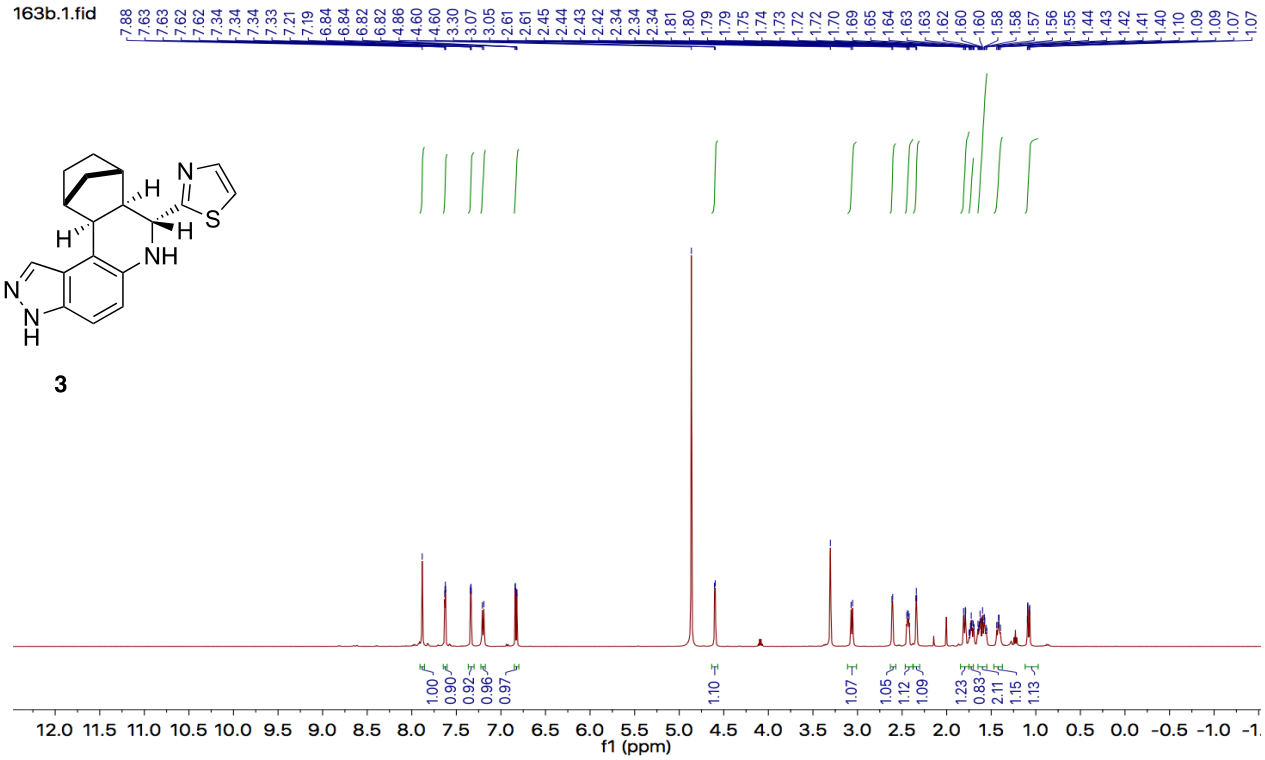

Figure S6: ^{13}C spectra of compound 3 in methanol-d_4

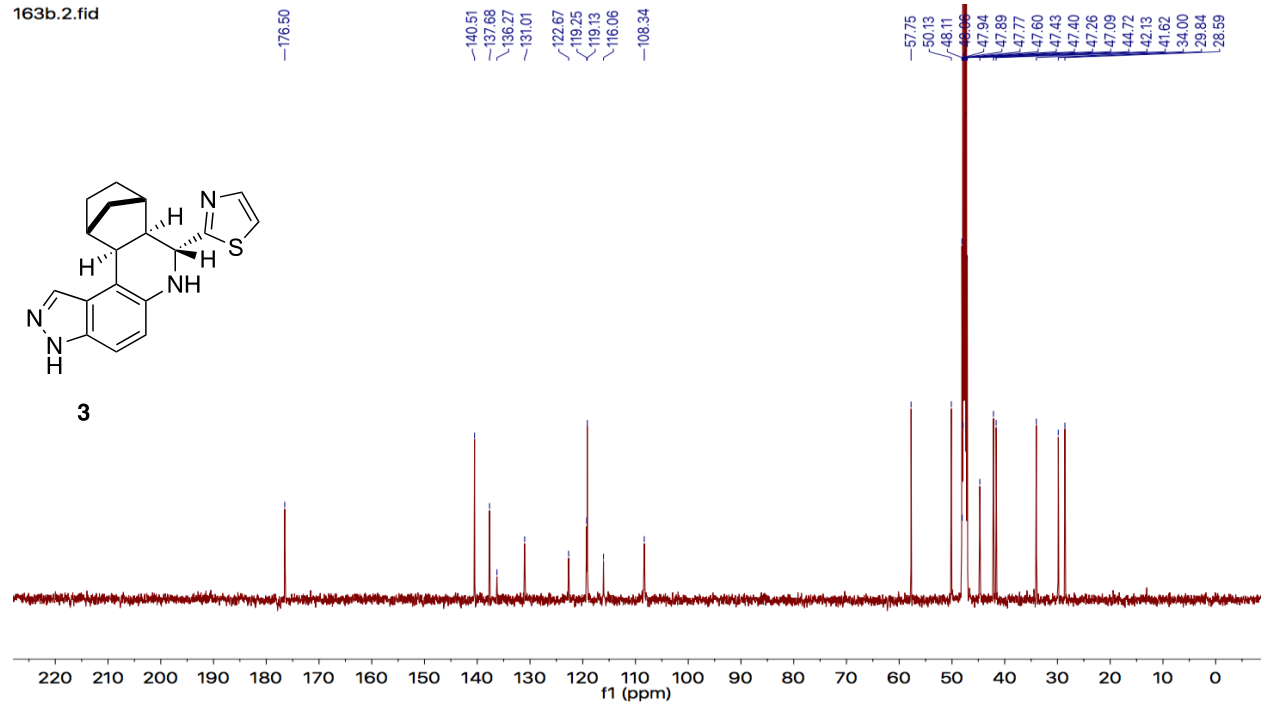

Figure S7: ^{1}H spectra of compound 4 in methanol-d_4

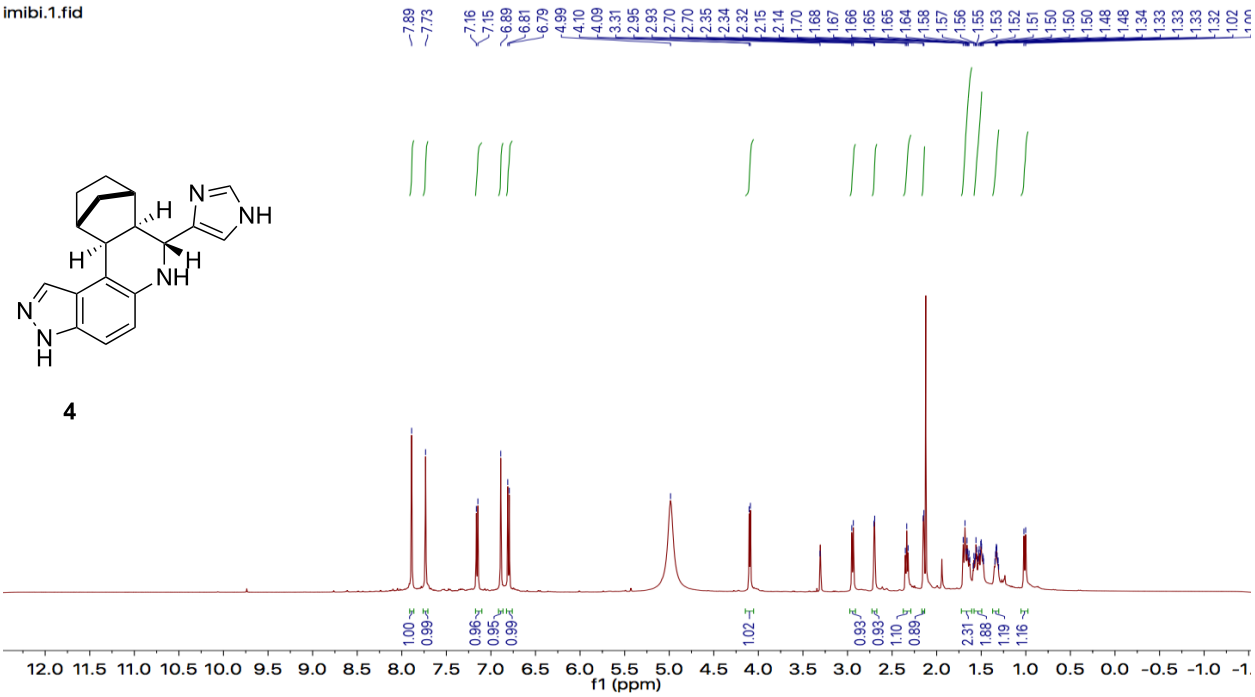

Figure S8: ^{13}C spectra of compound 4 in methanol-d_4

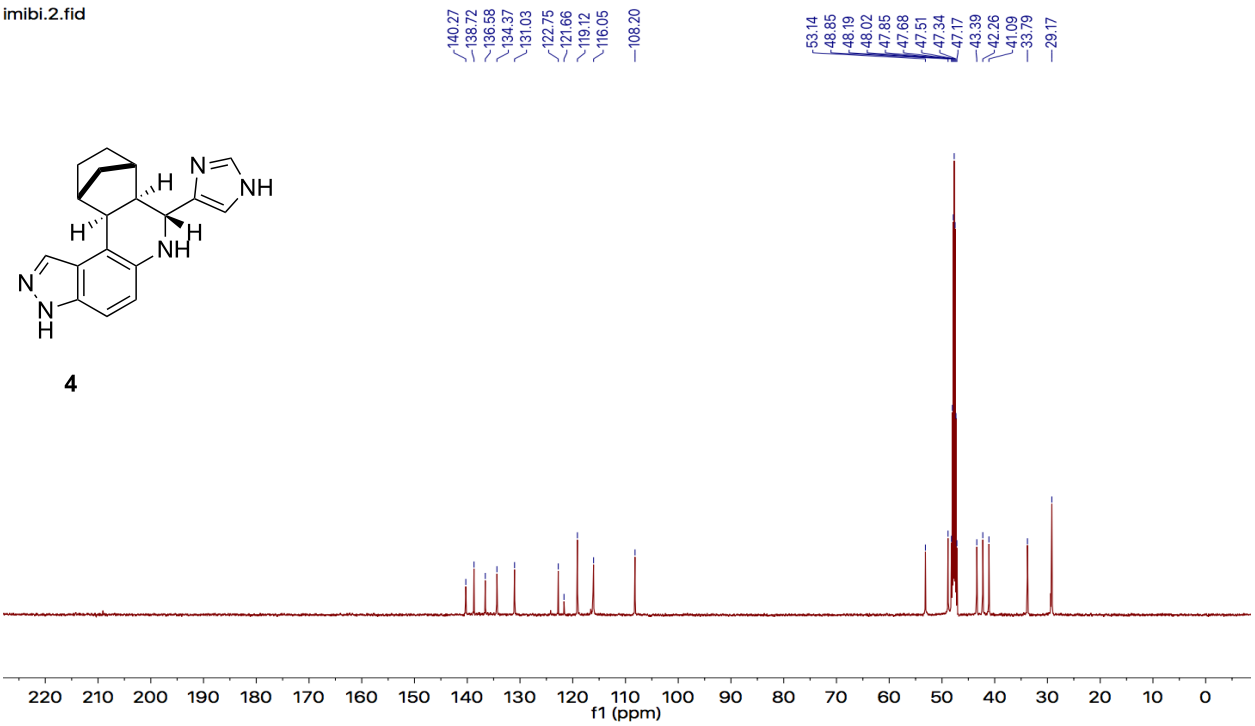

Figure S9: ^{1}H spectra of compound 5 in methanol-d_4

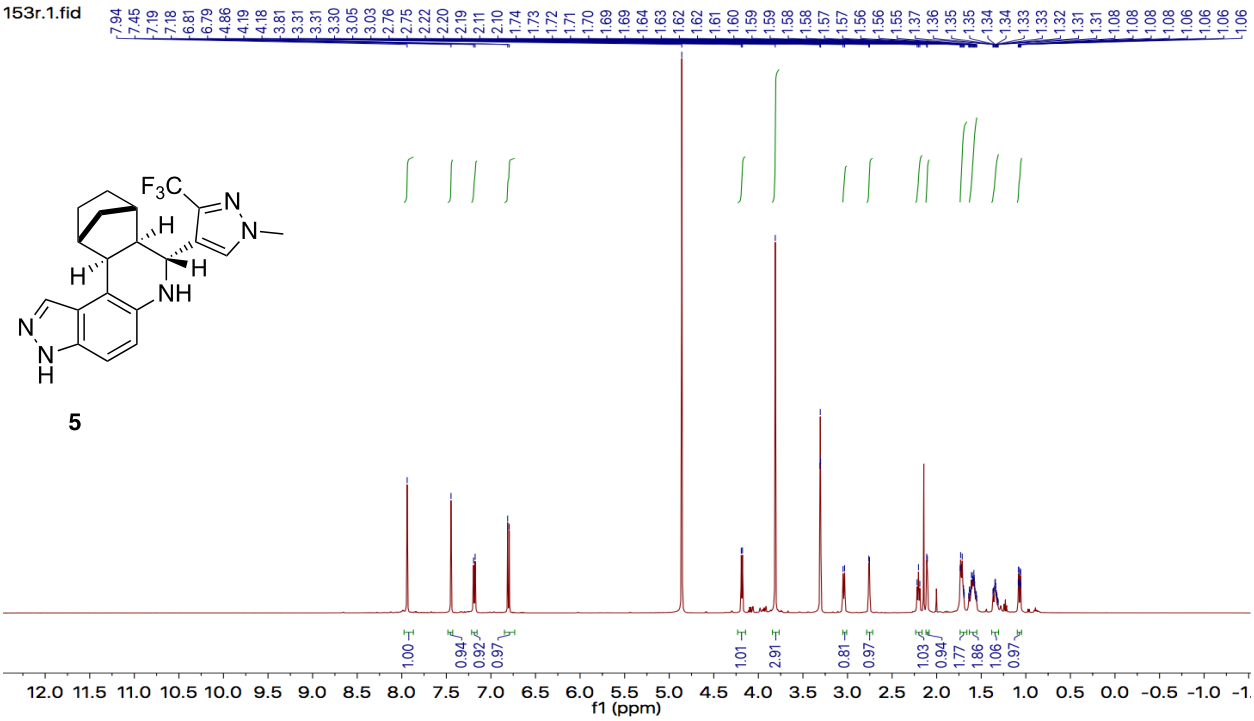

Figure S10: ^{13}C spectra of compound 5 in methanol-d_4

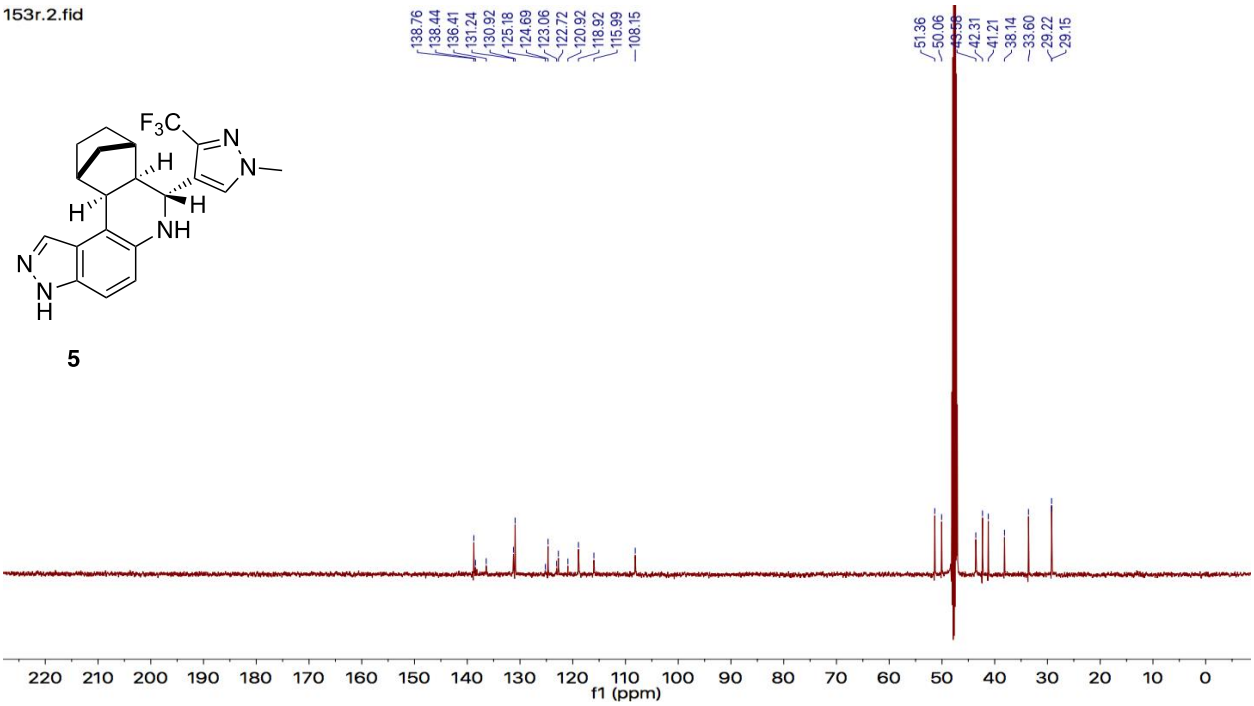

Figure S11: ^{1}H spectra of compound 6 in DMSO-d_6

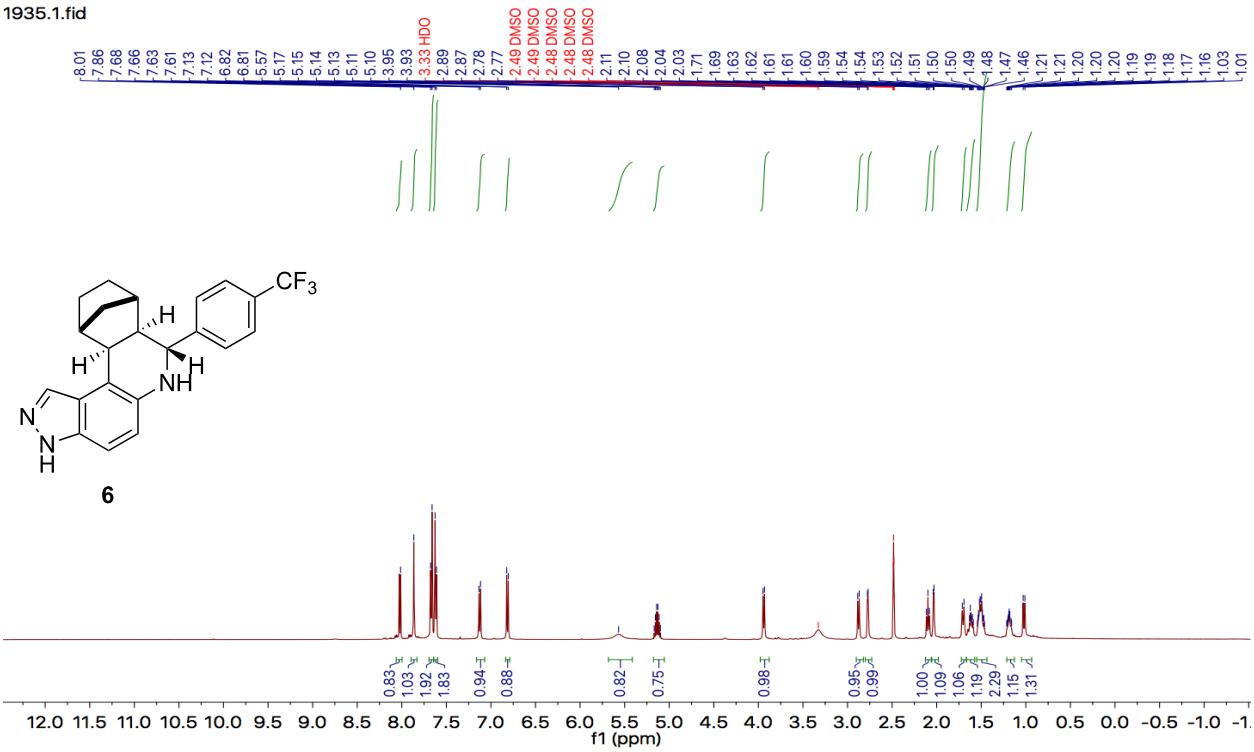

Figure S12: ^{13}C spectra of compound 6 in DMSO-d_6

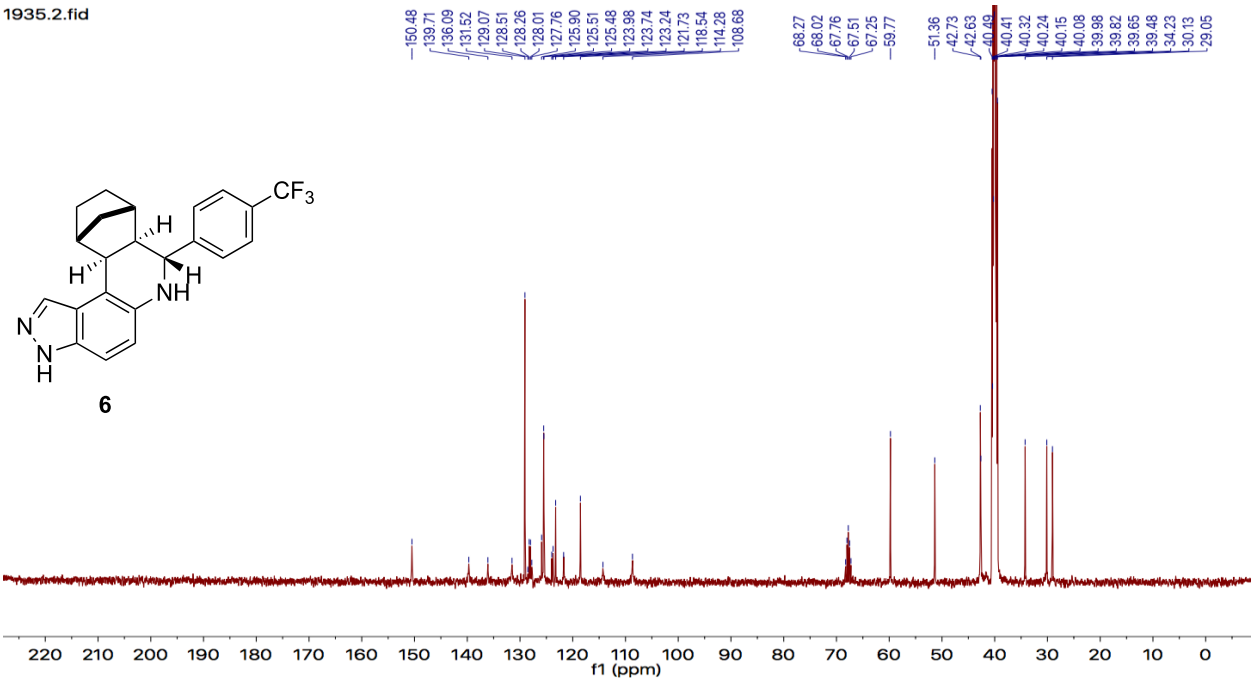

Figure S13: ^{1}H spectra of compound 7 in DMSO-d_6

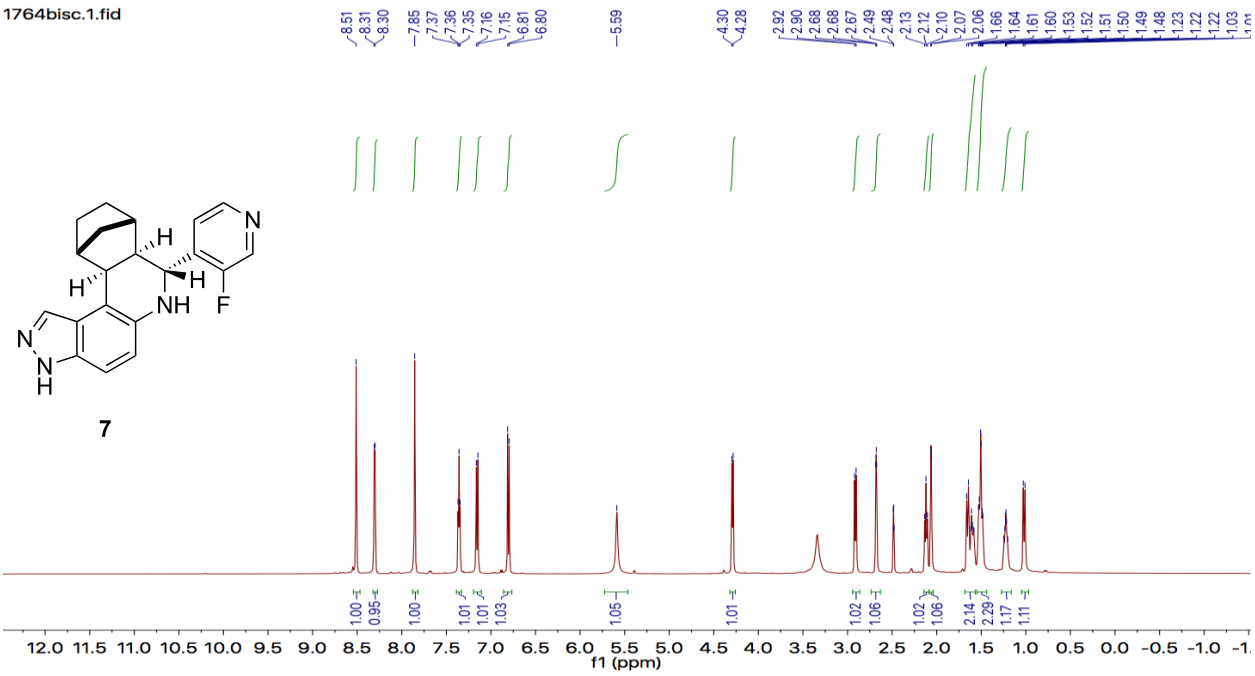

Figure S14: ^{13}C spectra of compound 7 in DMSO-d_6

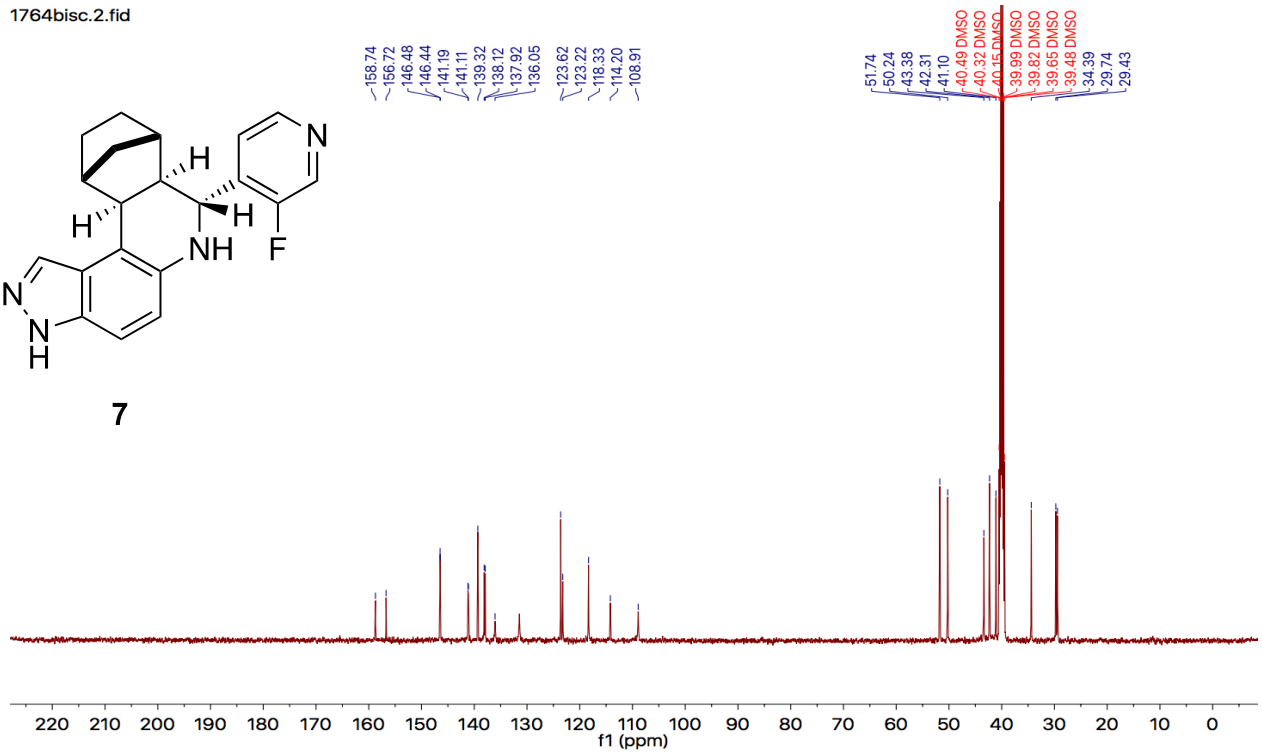

Figure S15: ^{1}H spectra of compound 8 in methanol-d_4

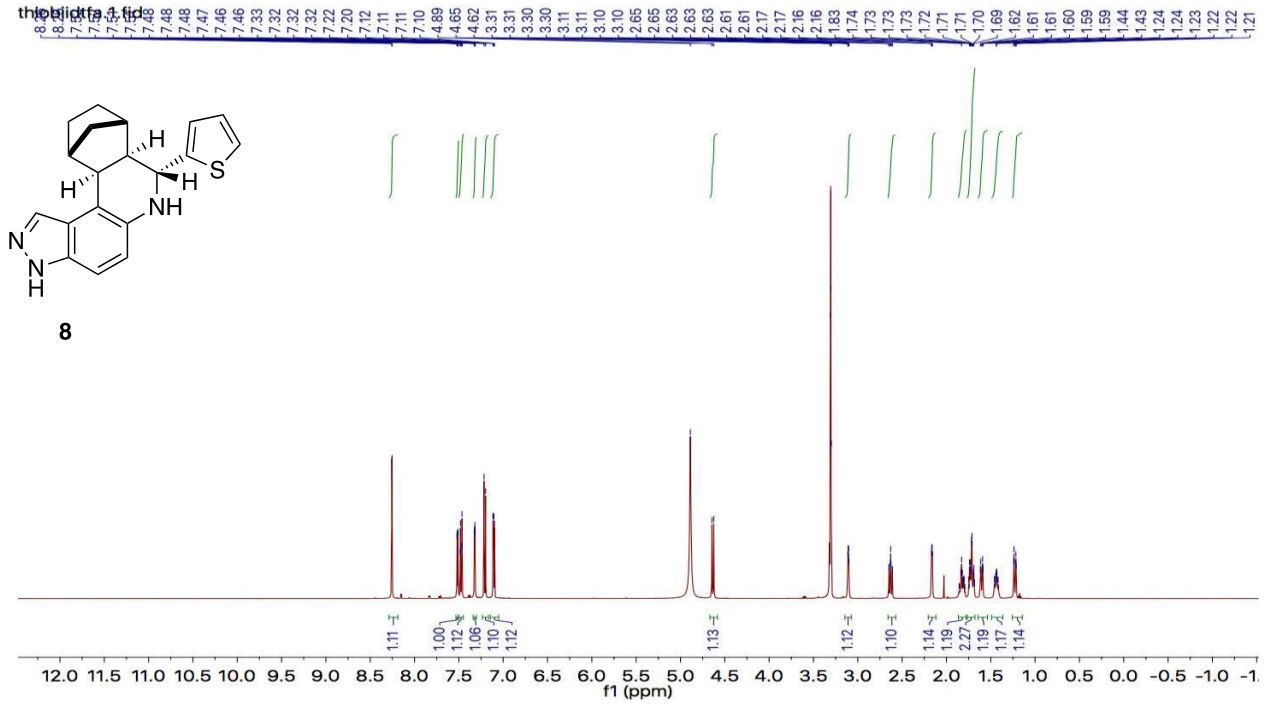

Figure S16: ^{13}C spectra of compound 8 in methanol-d_4

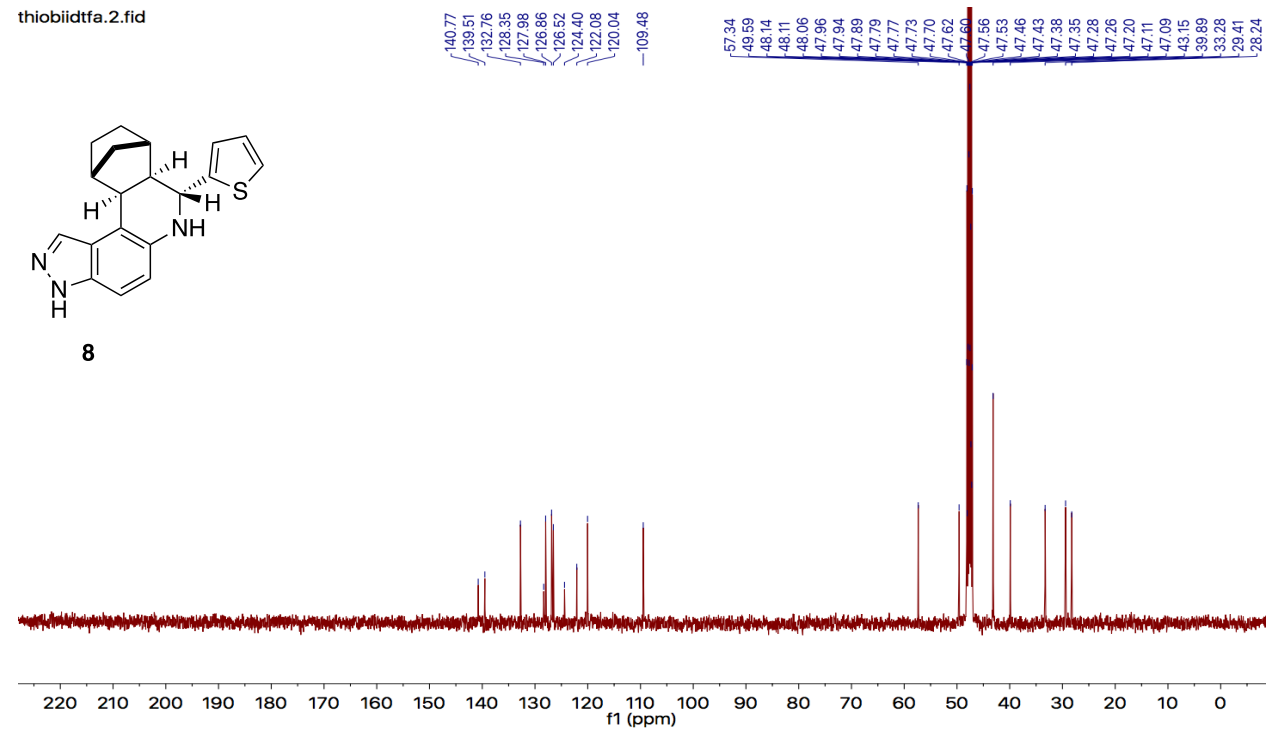

Figure S17: ^{1}H spectra of compound 9 in methanol-d_4

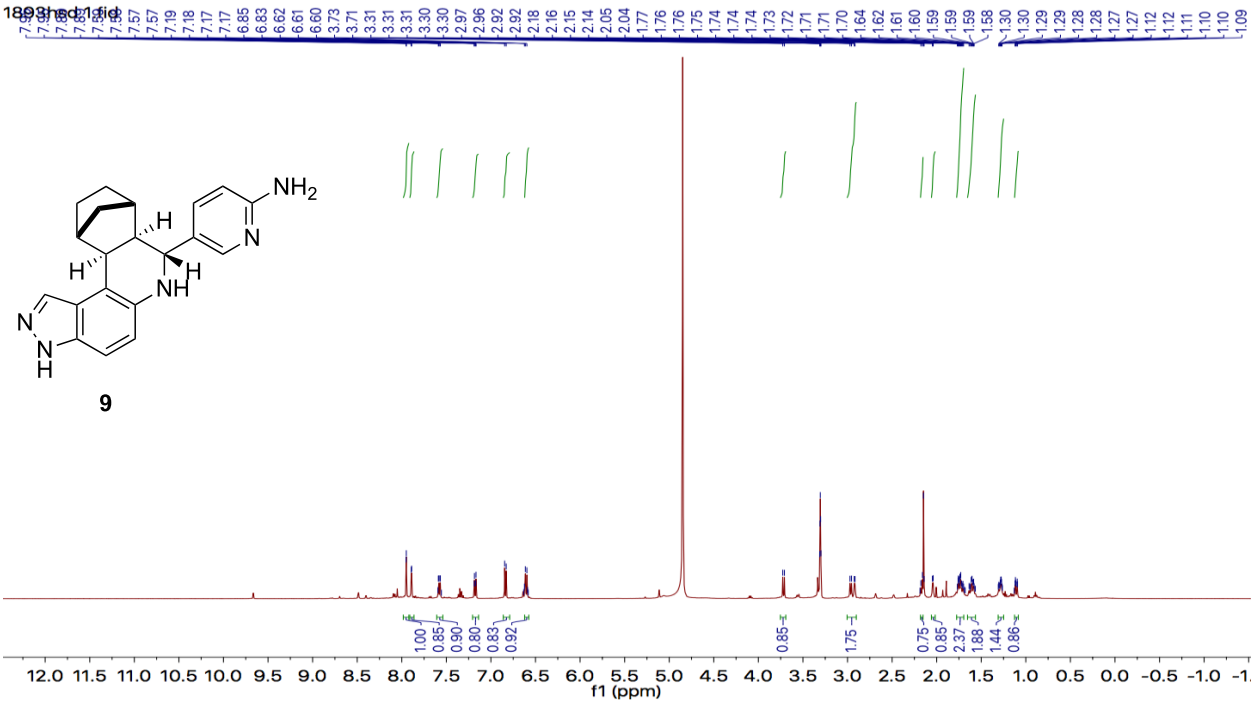

Figure S18: ^{13}C spectra of compound 9 in methanol-d_4

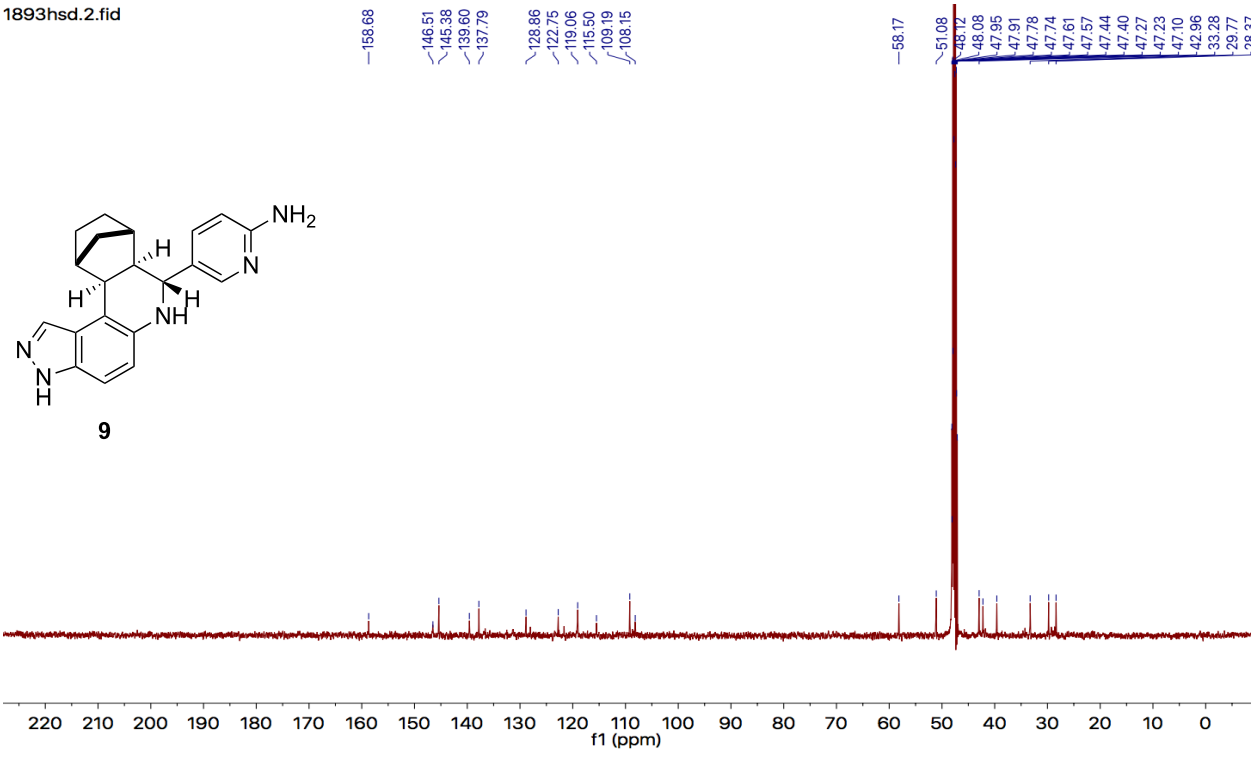

Figure S19: ^{1}H spectra of compound 10 in DMSO-d_6

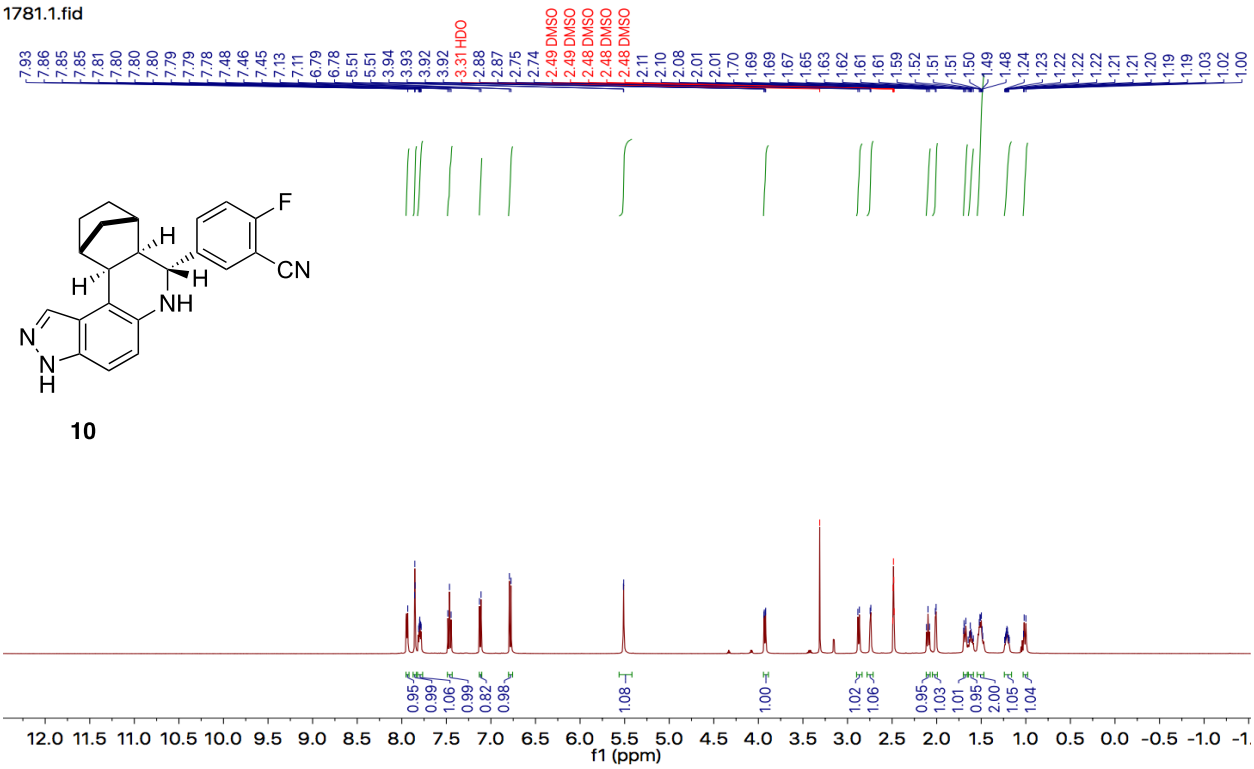

Figure S20: ^{13}C spectra of compound 10 in DMSO-d_6

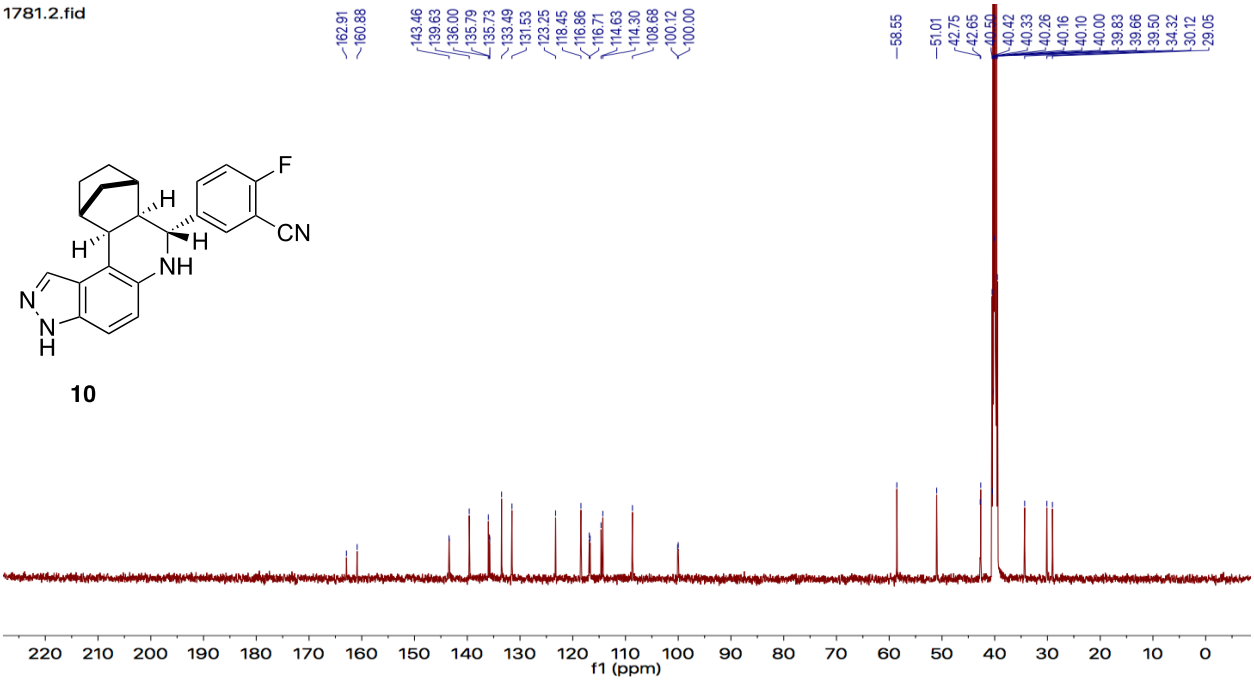

Figure S21: ^{1}H spectra of compound 11 in DMSO-d_6

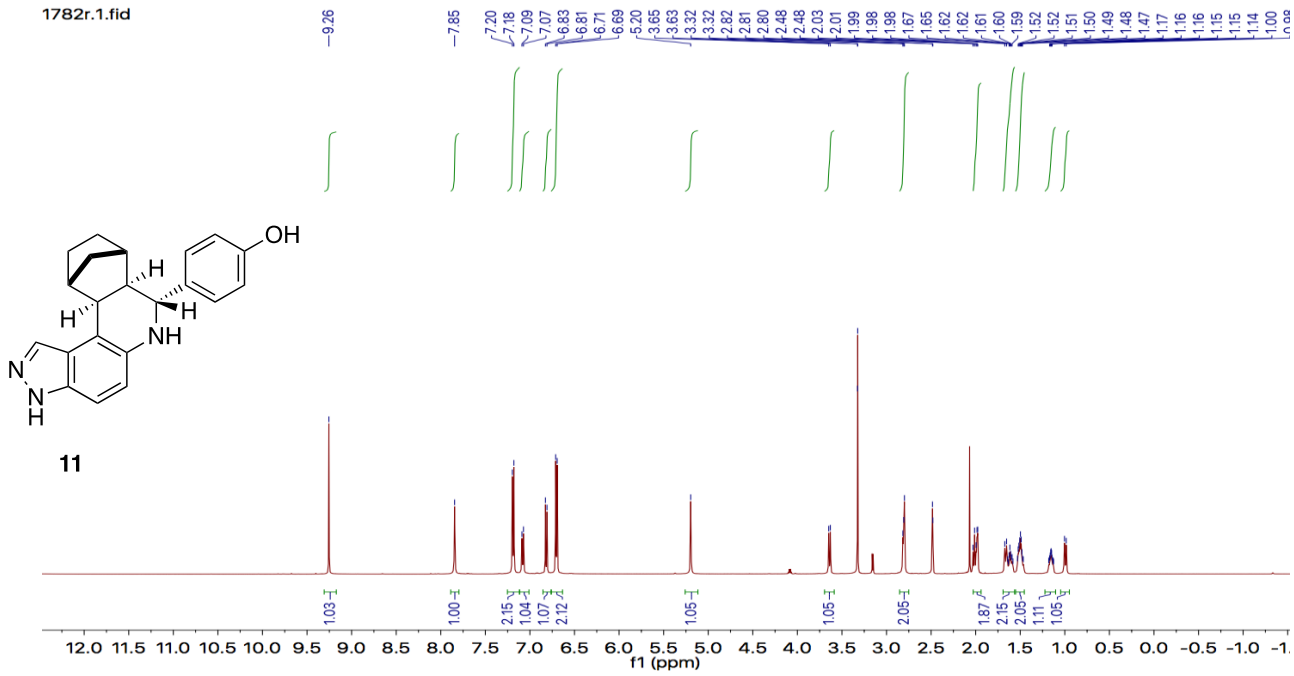

Figure S22: ^{13}C spectra of compound 11 in DMSO-d_6

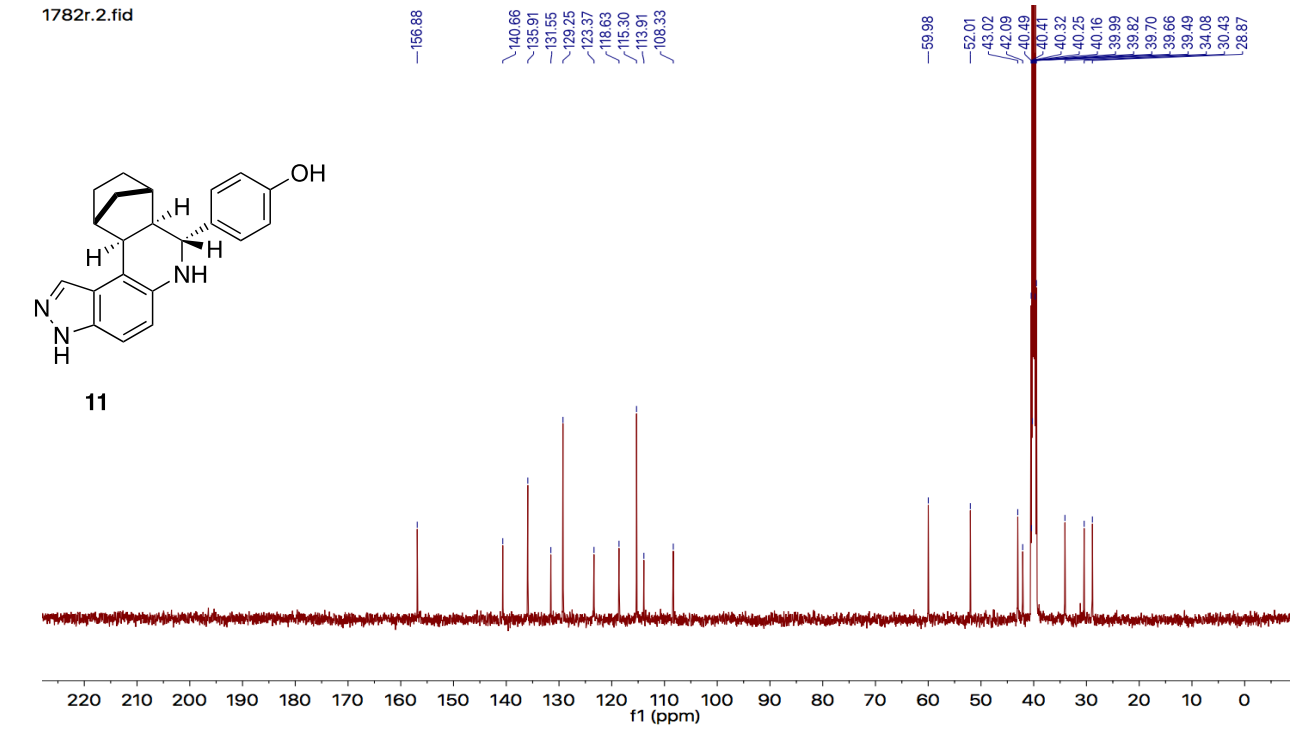

Figure S23: ^{1}H spectra of compound 12 in DMSO-d_6

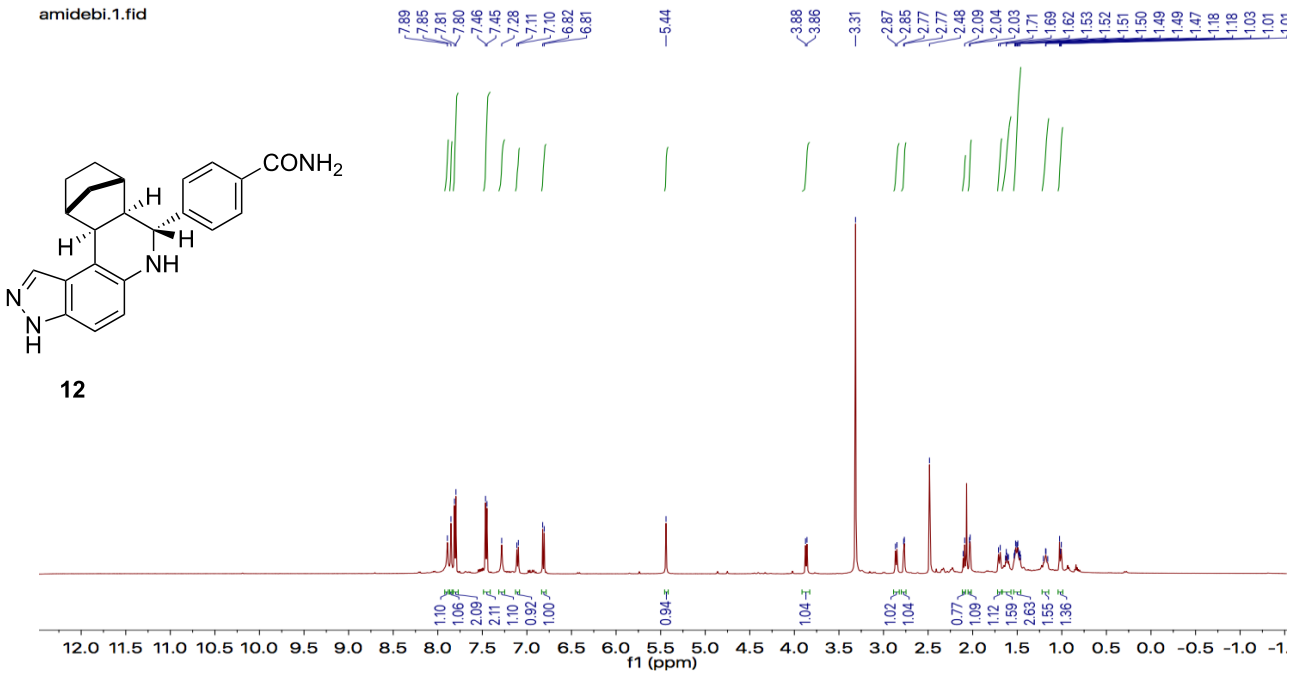

Figure S24: ^{13}C spectra of compound 12 in DMSO-d_6

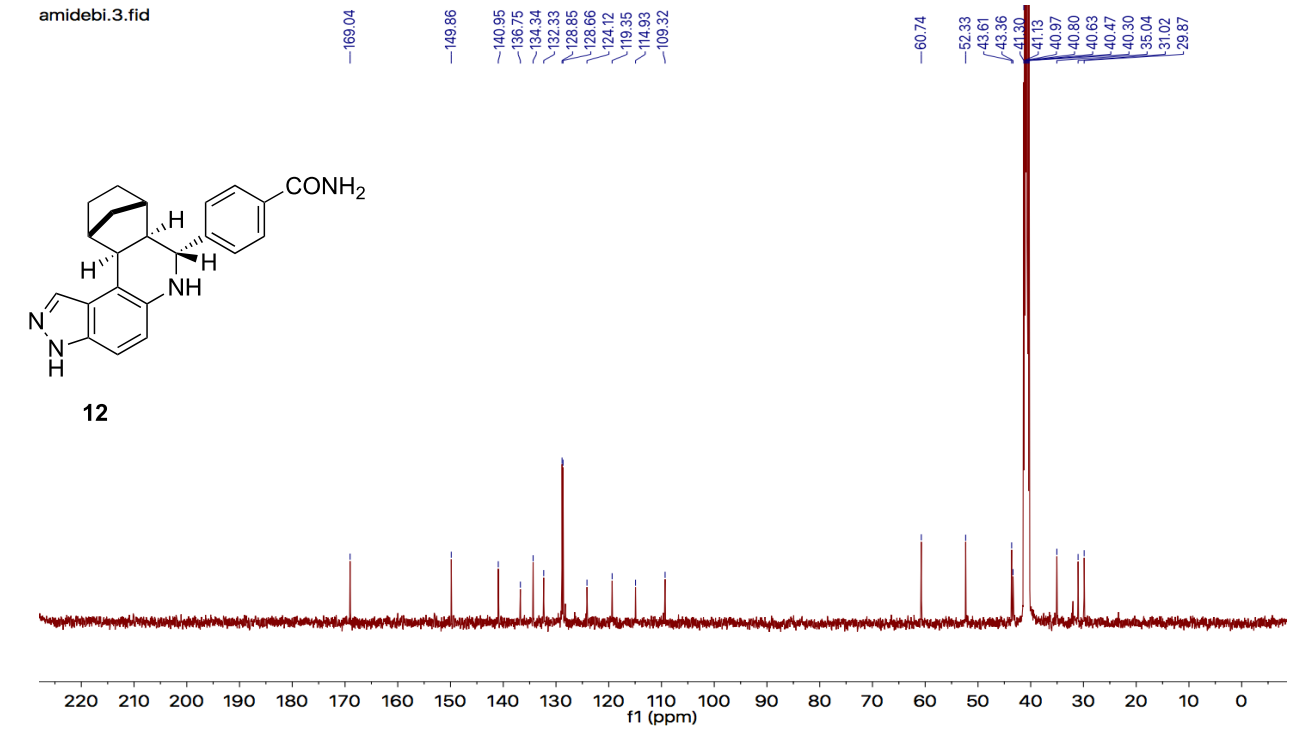

Figure S25: ^{1}H spectra of compound 13 in DMSO-d_6

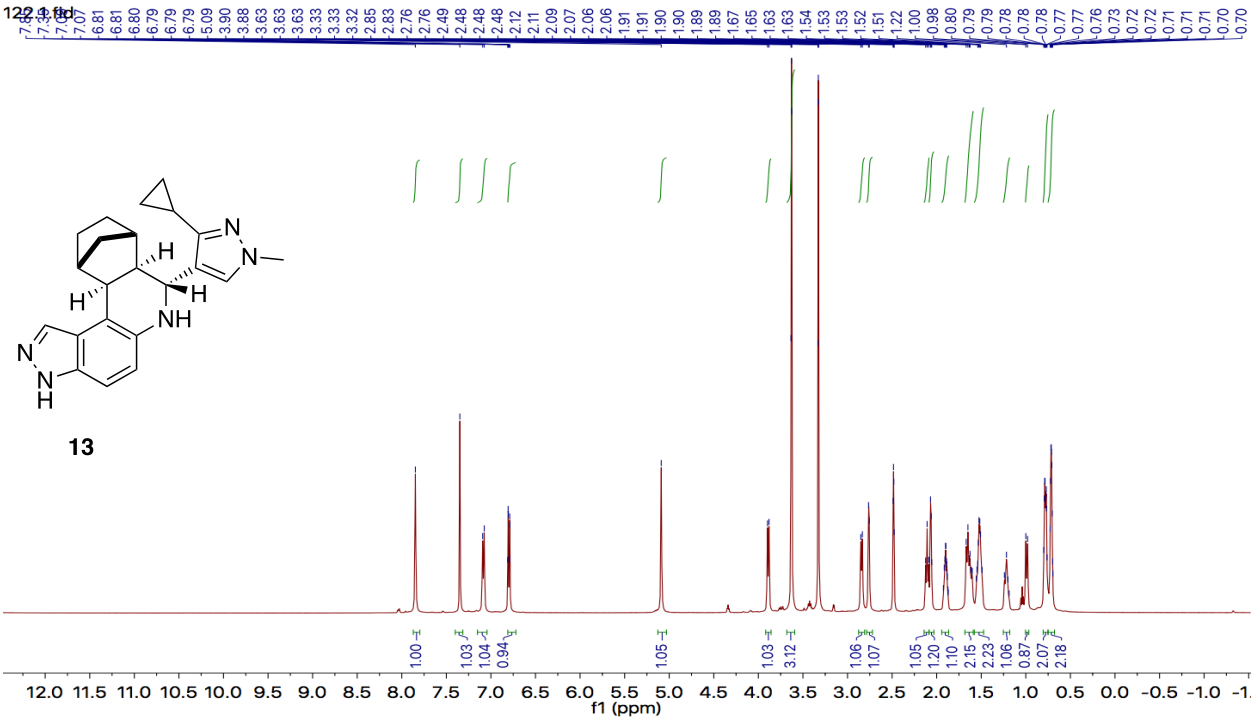

Figure S26: ^{13}C spectra of compound 13 in DMSO-d_6

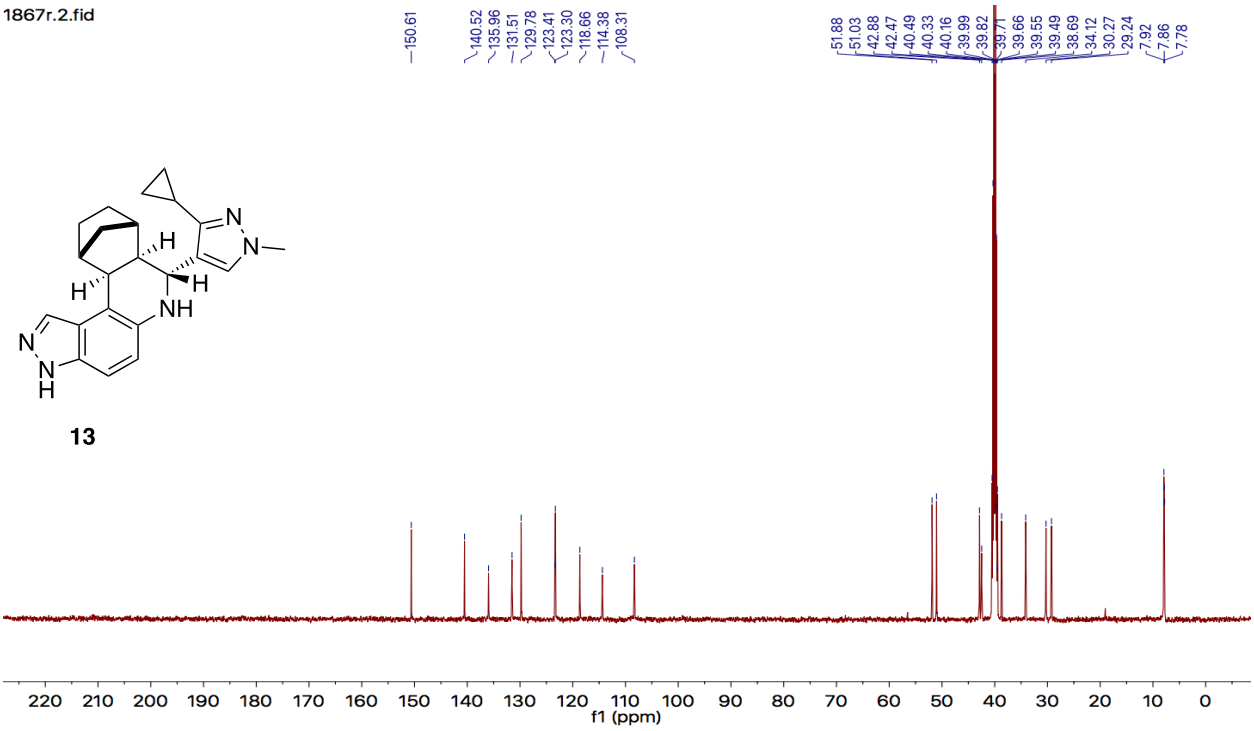

Figure S27: ^{1}H spectra of compound 14 in DMSO-d_6

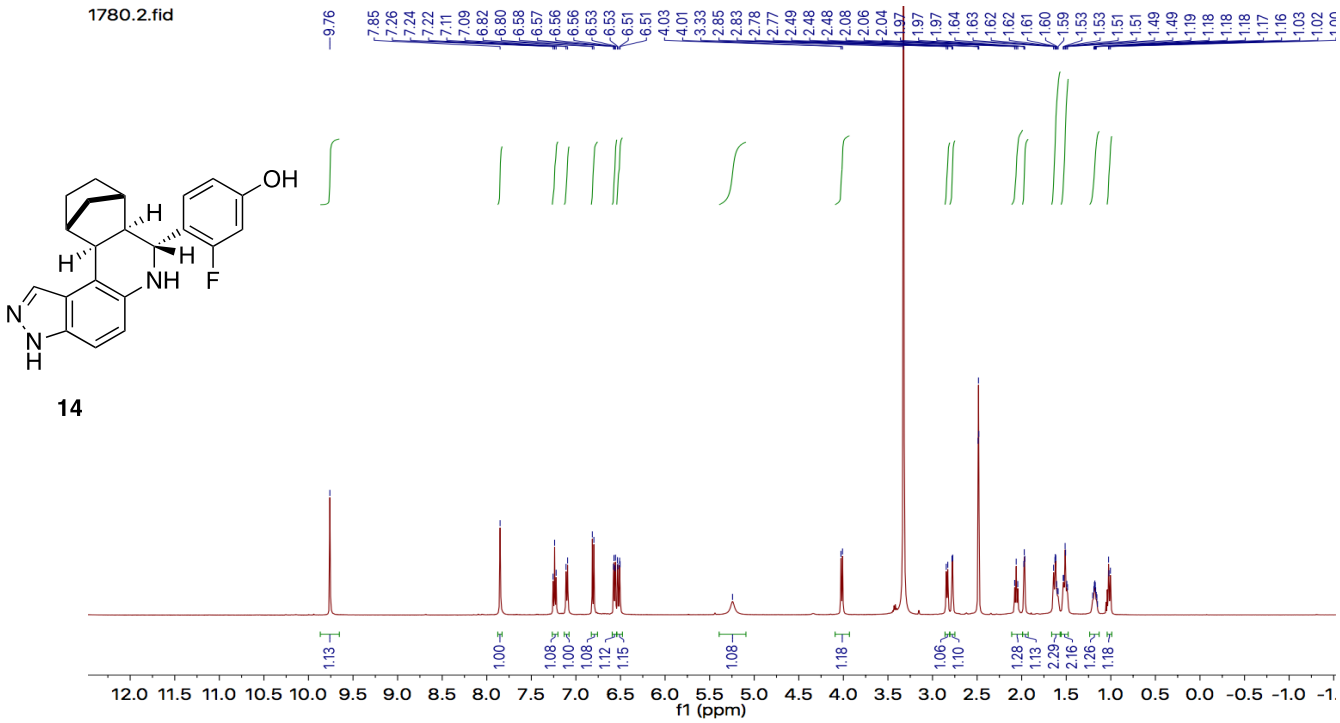

Figure S28: ^{13}C spectra of compound 14 in DMSO-d_6

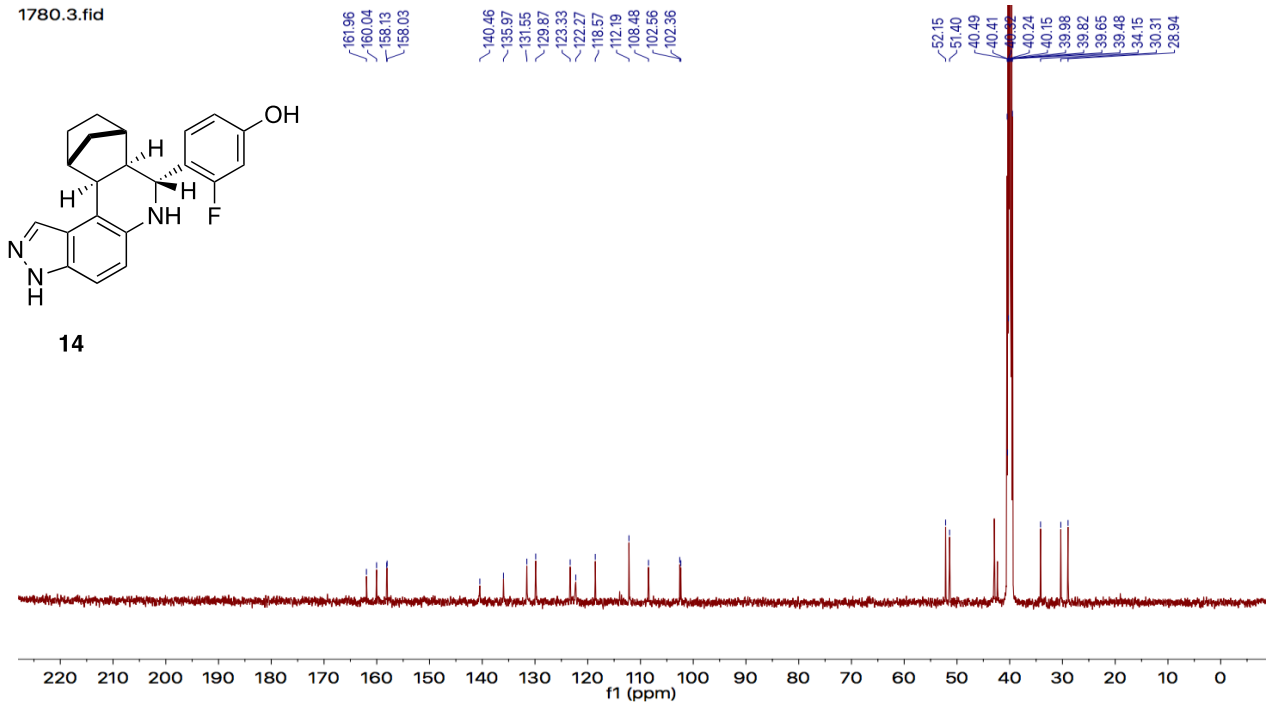

Figure S29: ^{1}H spectra of compound 15 in DMSO-d_6

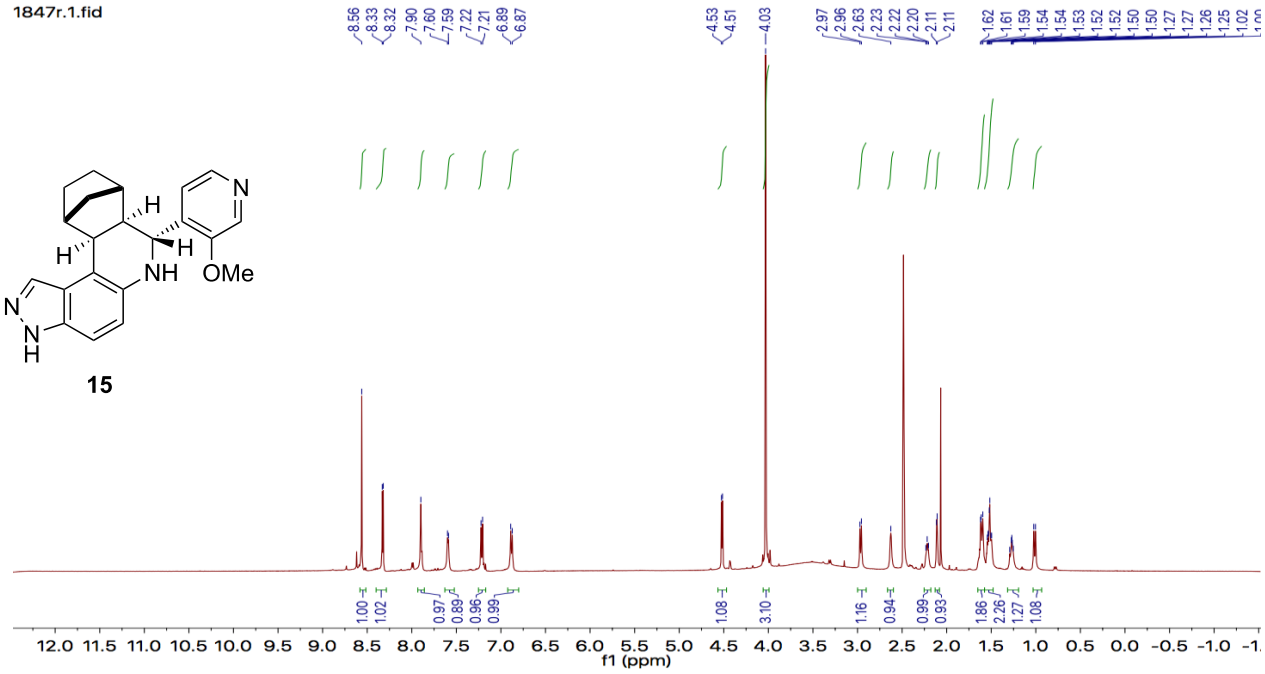

Figure S30: ^{13}C spectra of compound 15 in DMSO-d_6

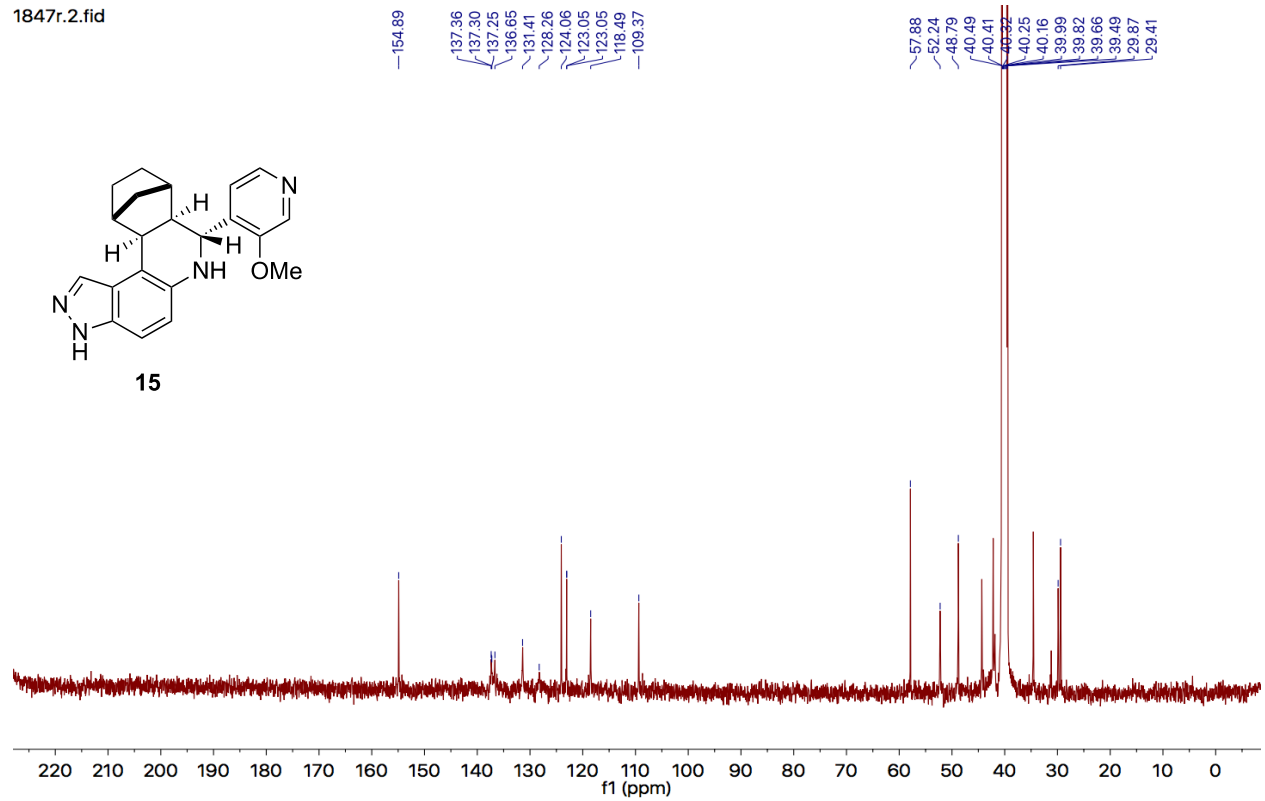

Figure S31: ^{1}H spectra of compound 16 in DMSO-d_6

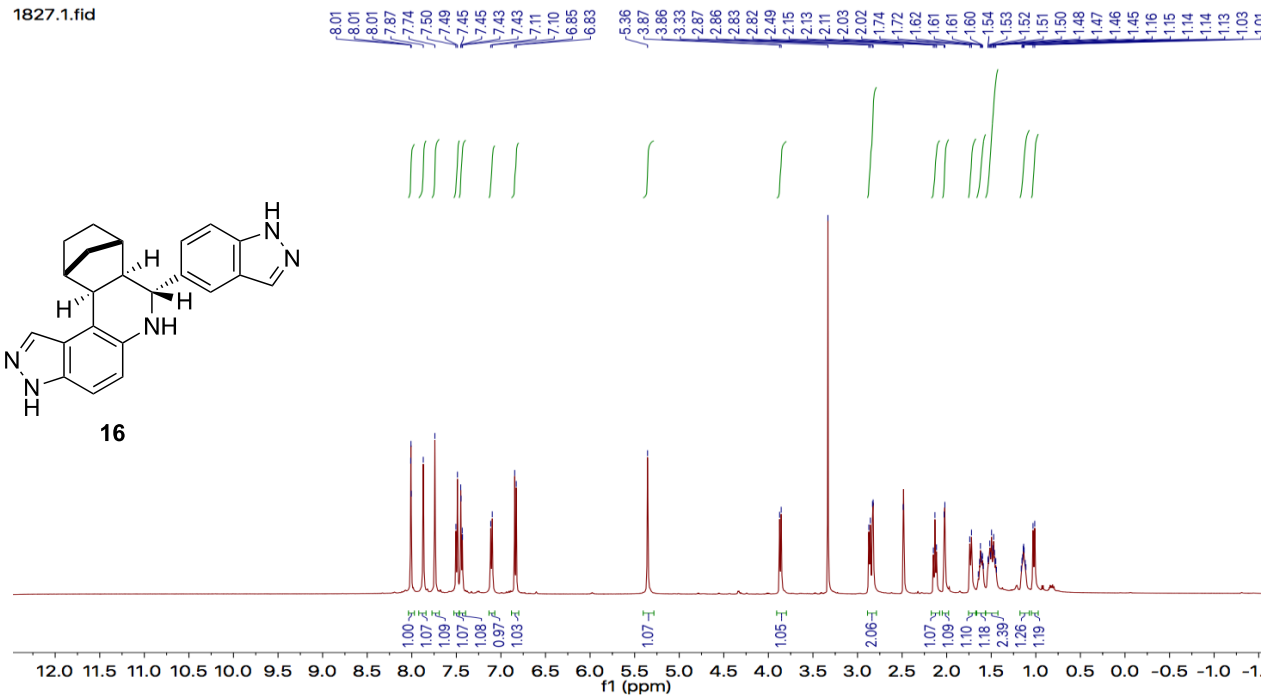

Figure S32: ^{13}C spectra of compound 16 in DMSO-d_6

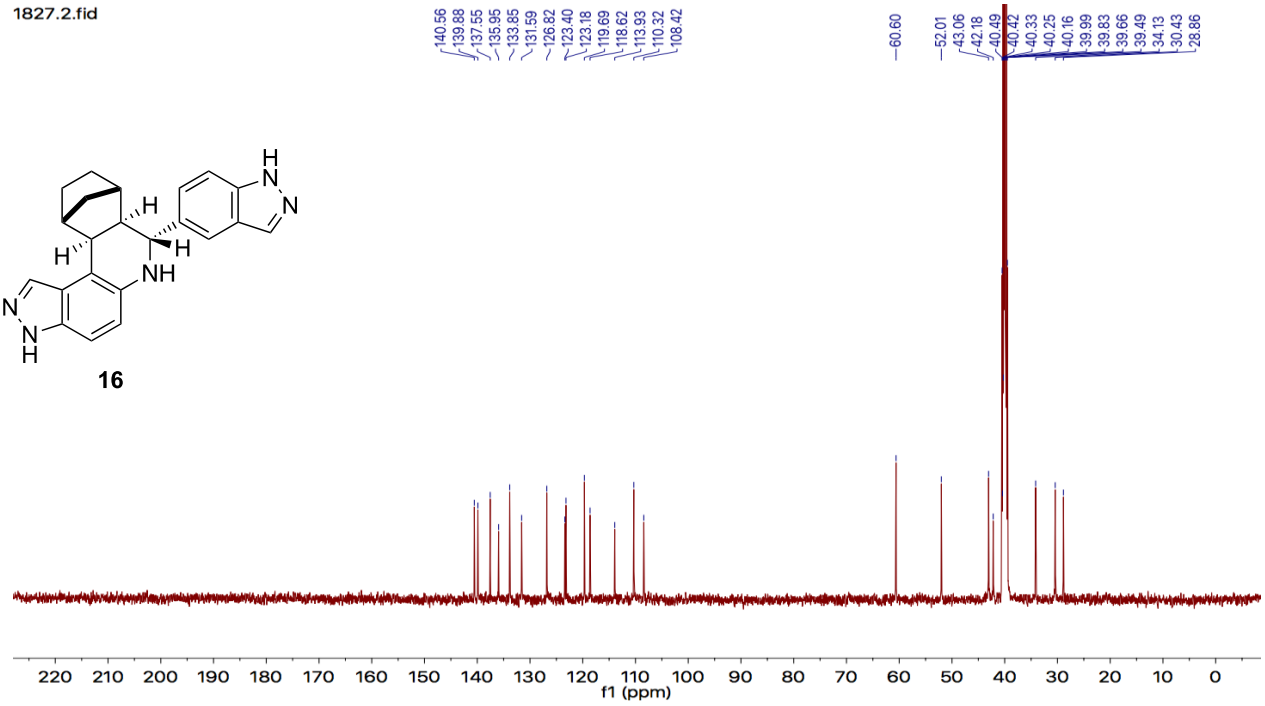

Figure S33: ^{1}H spectra of compound 17 in DMSO-d_6

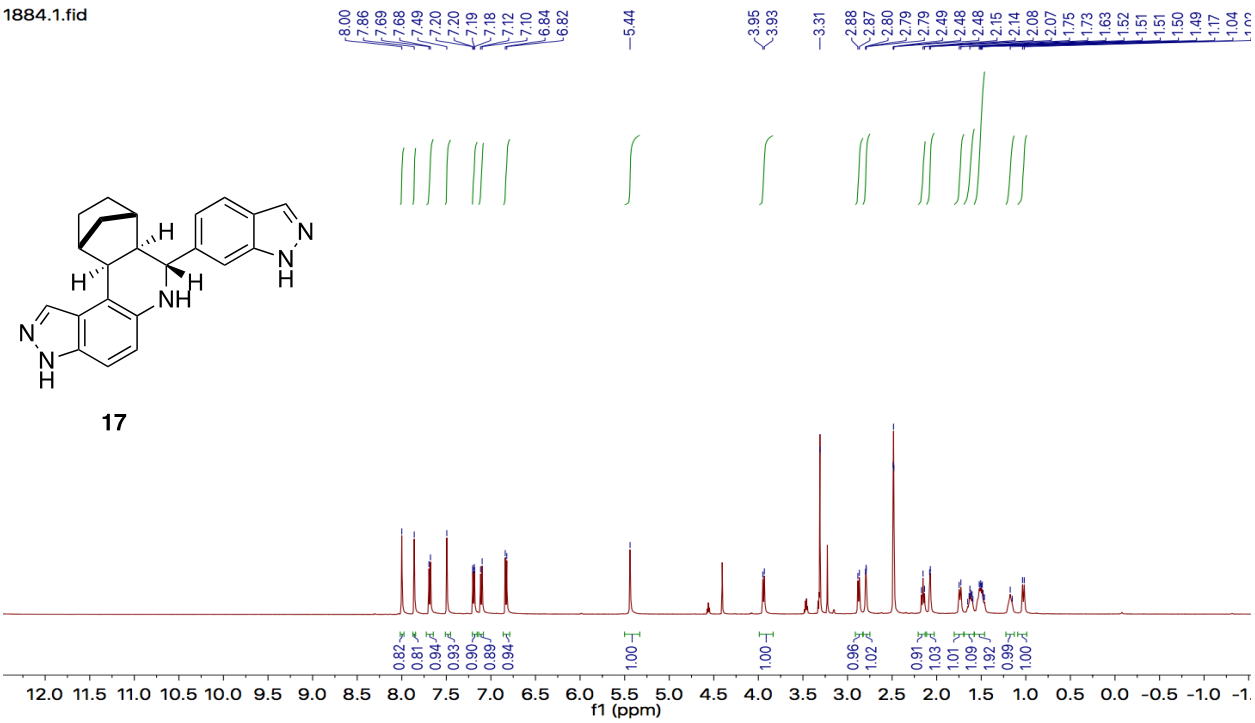

Figure S34: ^{13}C spectra of compound 17 in DMSO-d_6

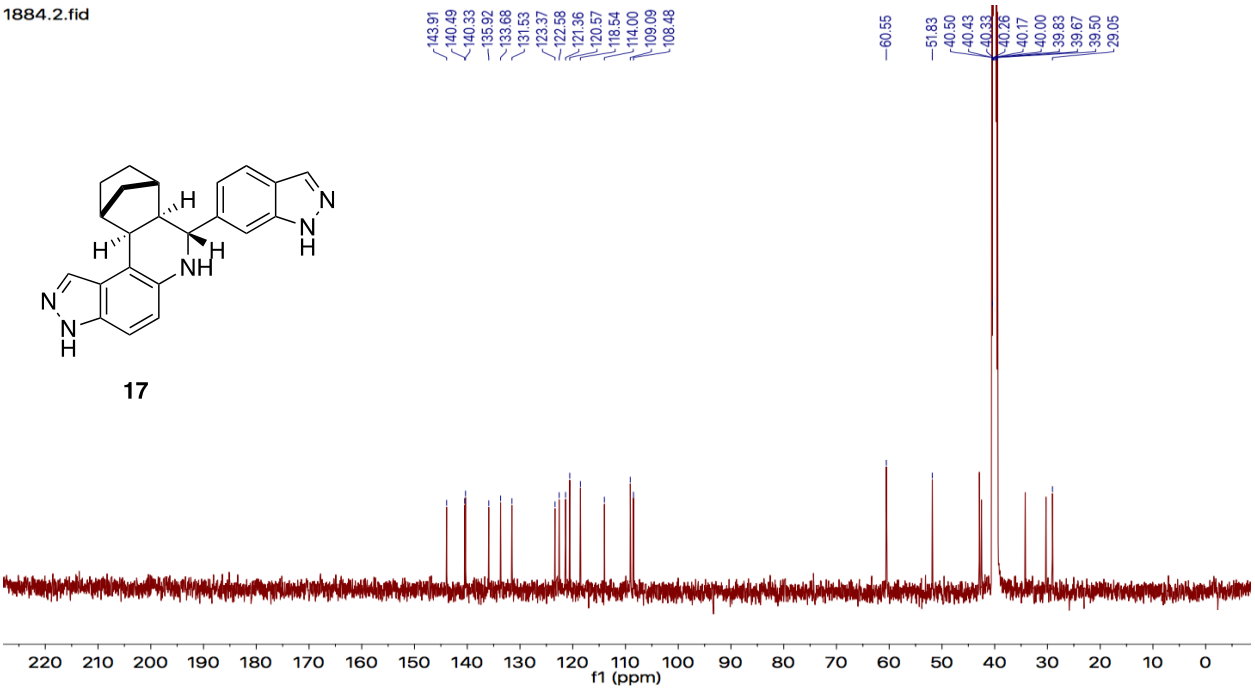

Figure S35: ^{1}H spectra of compound HSD1787 in DMSO-d_6

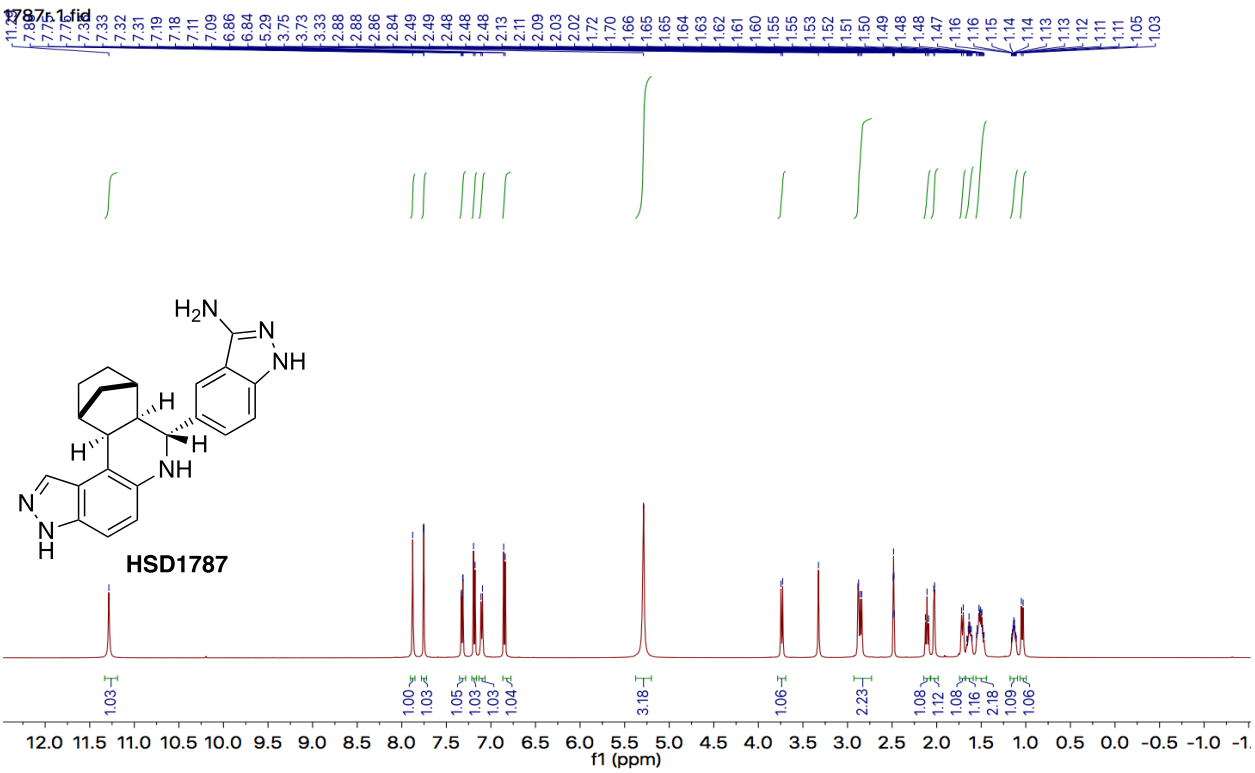

Figure S36: ^{13}C spectra of compound HSD1787 in DMSO-d_6

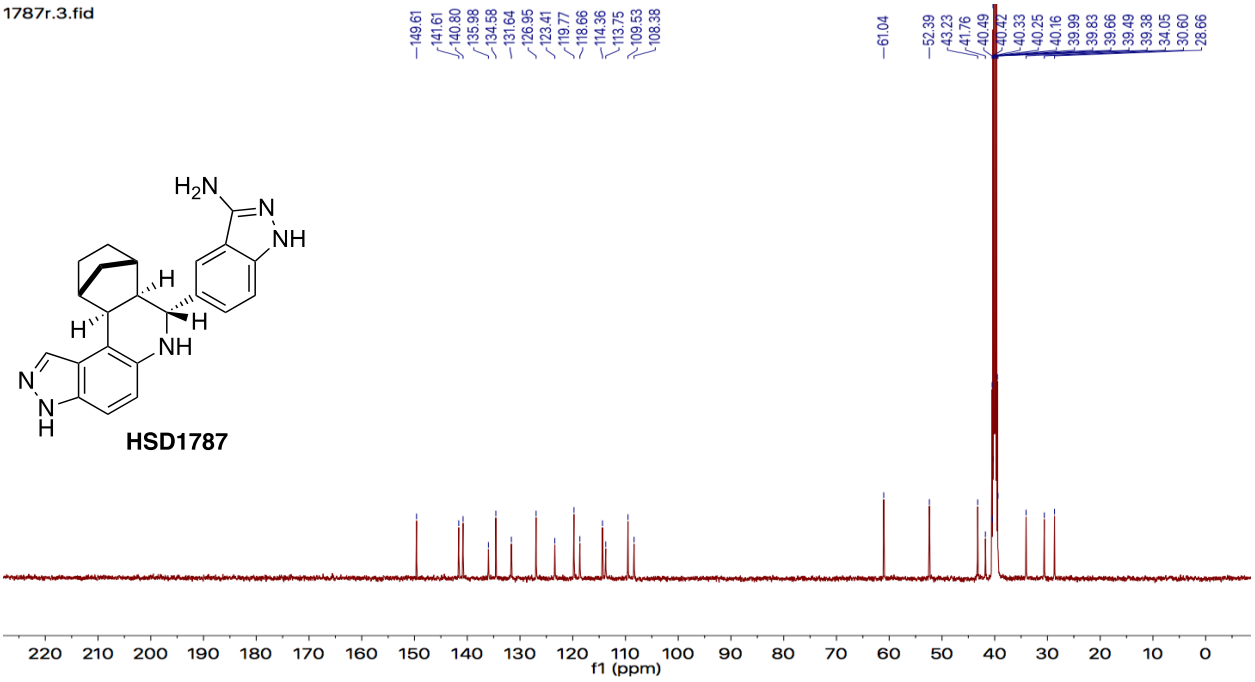

Figure S37: ^{1}H spectra of compound 18 in DMSO-d_6

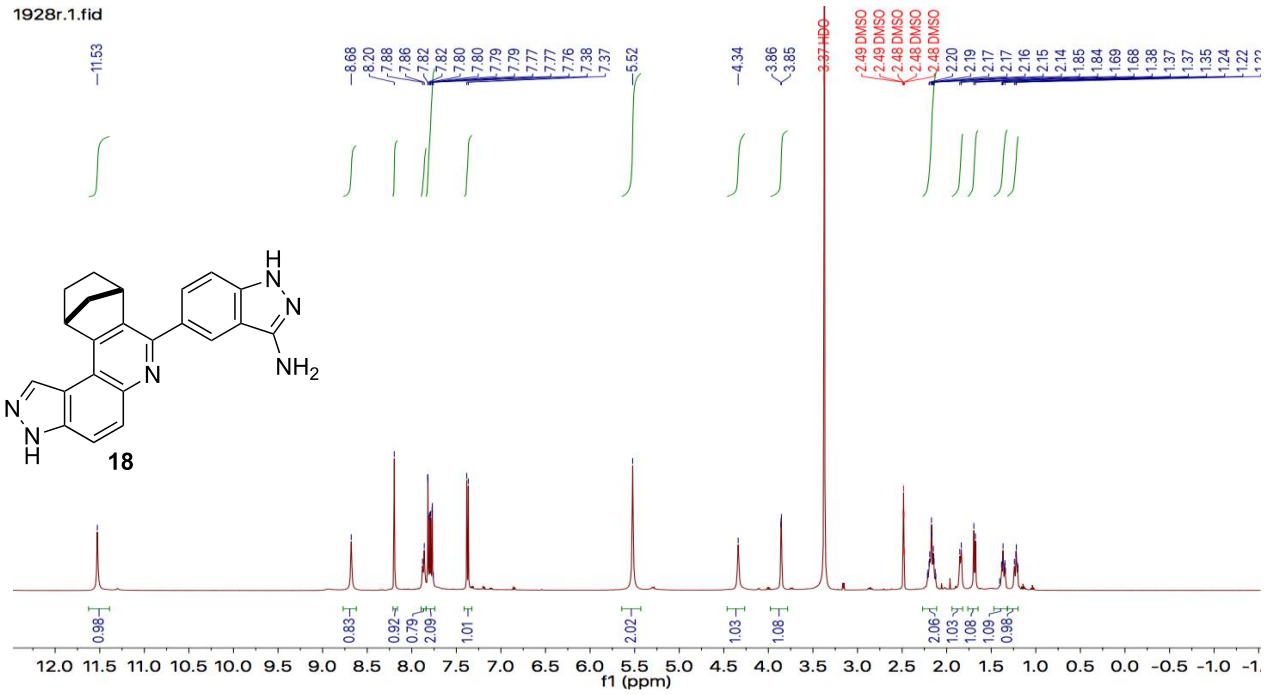

Figure S38: ^{13}C spectra of compound 18 in DMSO-d_6

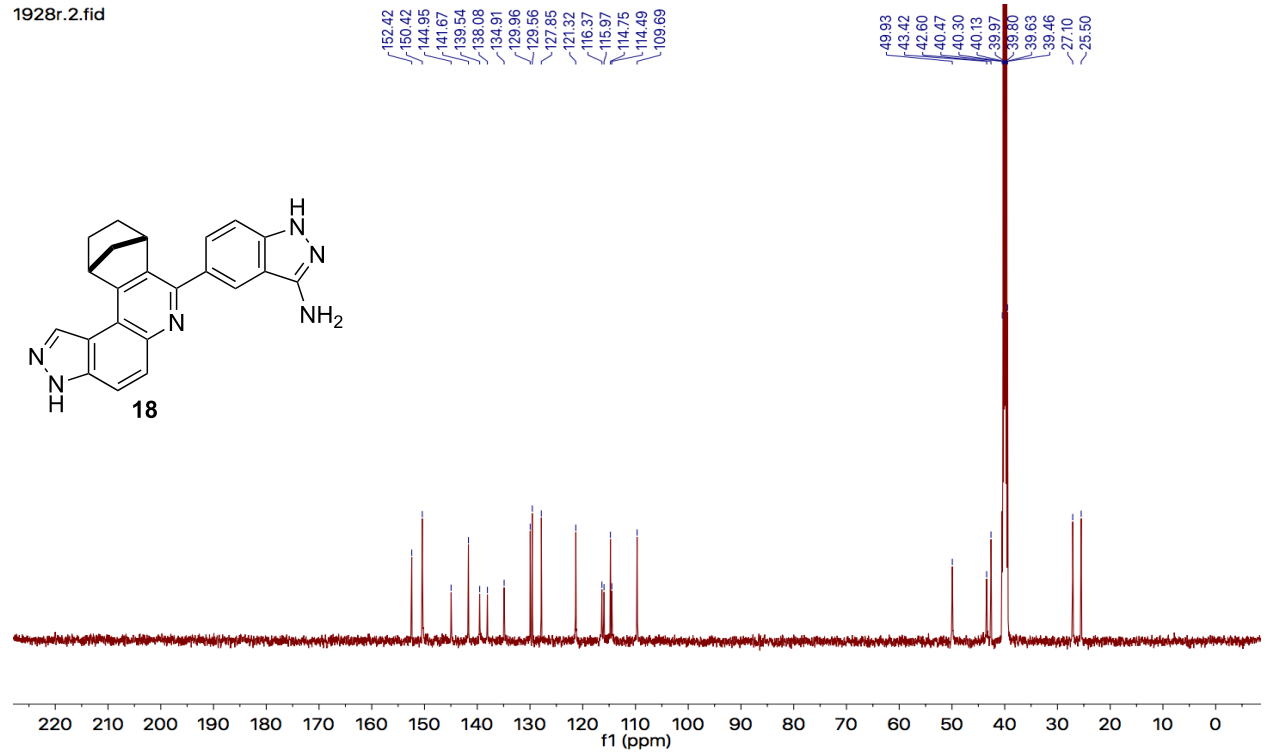

Figure S39: ^{1}H spectra of compound S-1 in DMSO-d_6

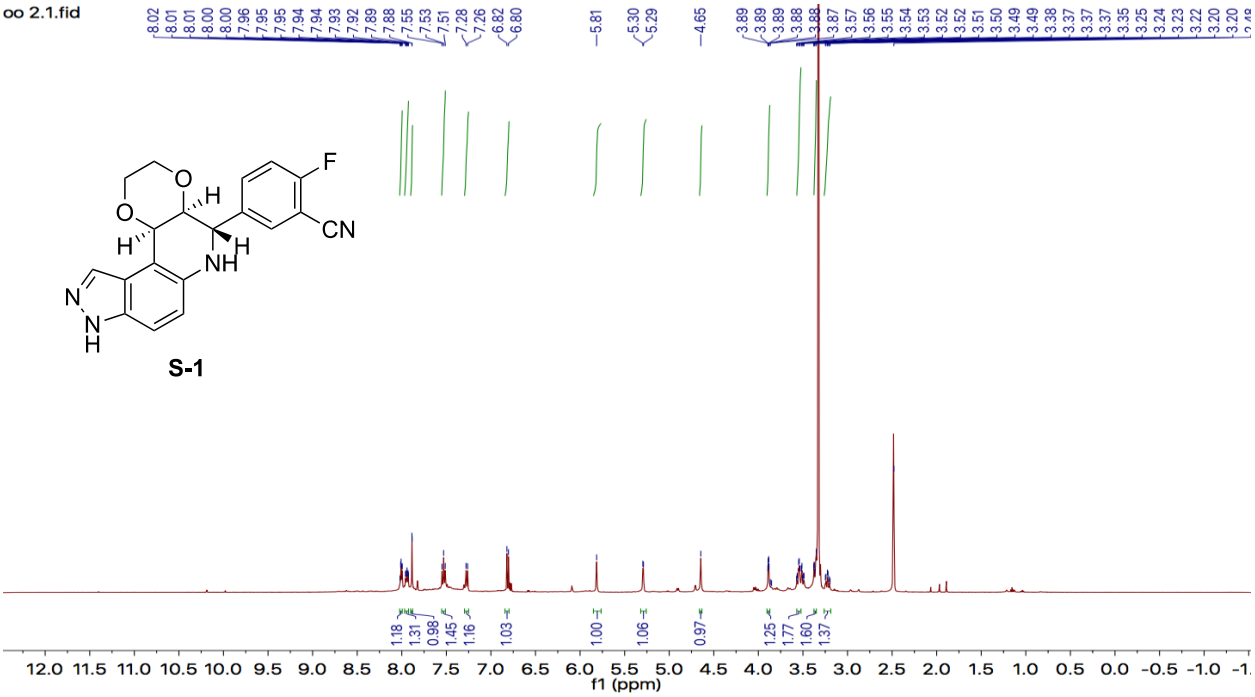

Figure S40: ^{13}C spectra of compound S-1 in DMSO-d_6

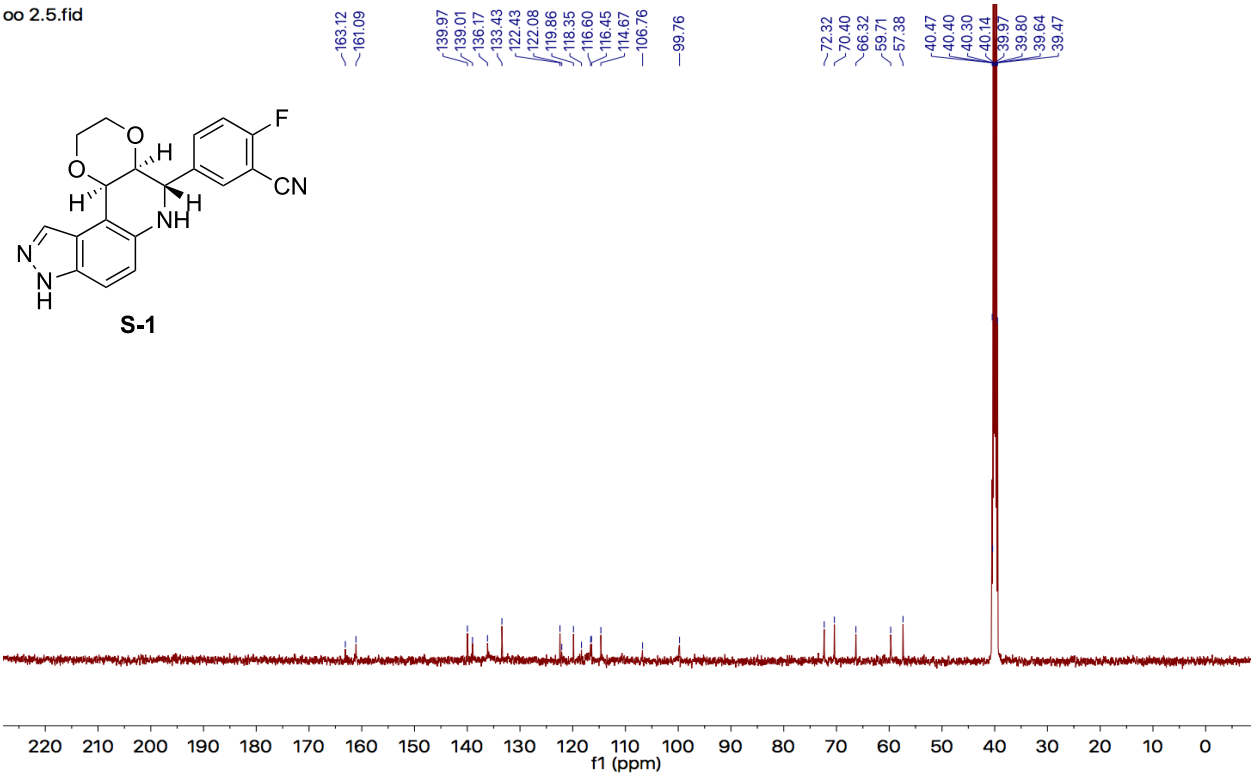

Figure S41: ^{1}H spectra of compound 19 in DMSO-d_6

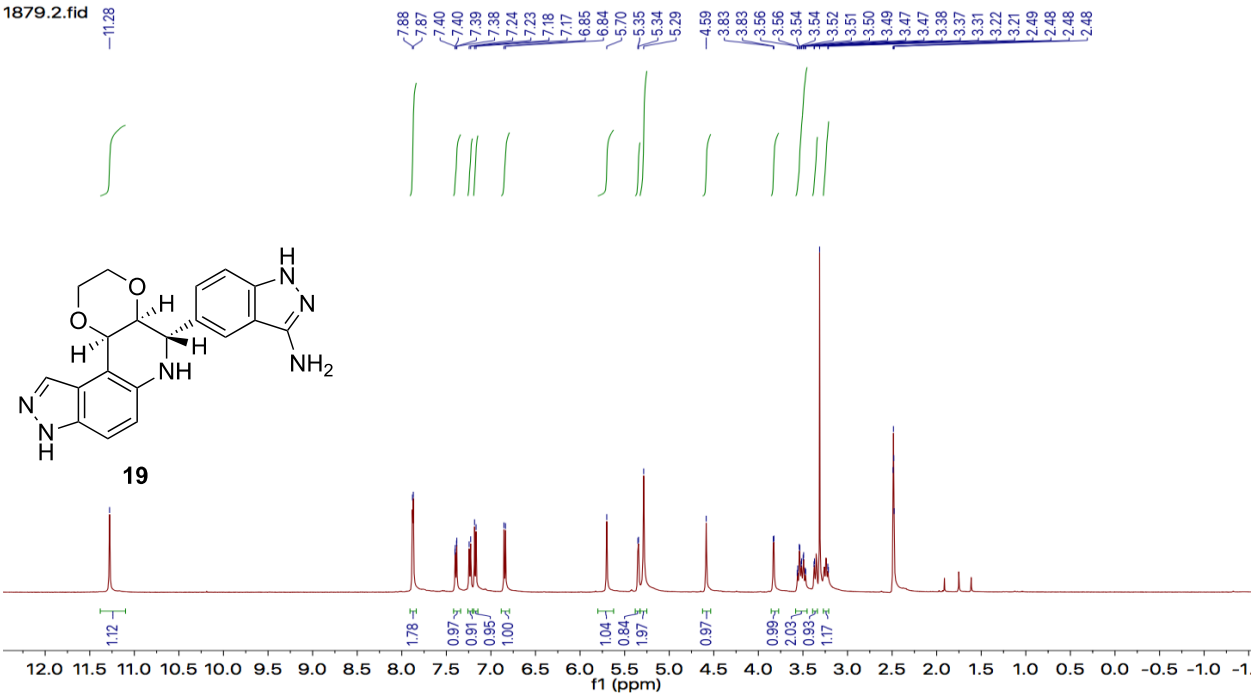

Figure S42: ^{13}C spectra of compound 19 in DMSO-d_6