

Supplementary Information

5-Hydroxy-7-azaindolin-2-one, a novel hybrid of pyridinol and sunitinib: design, synthesis and cytotoxicity against cancer cells

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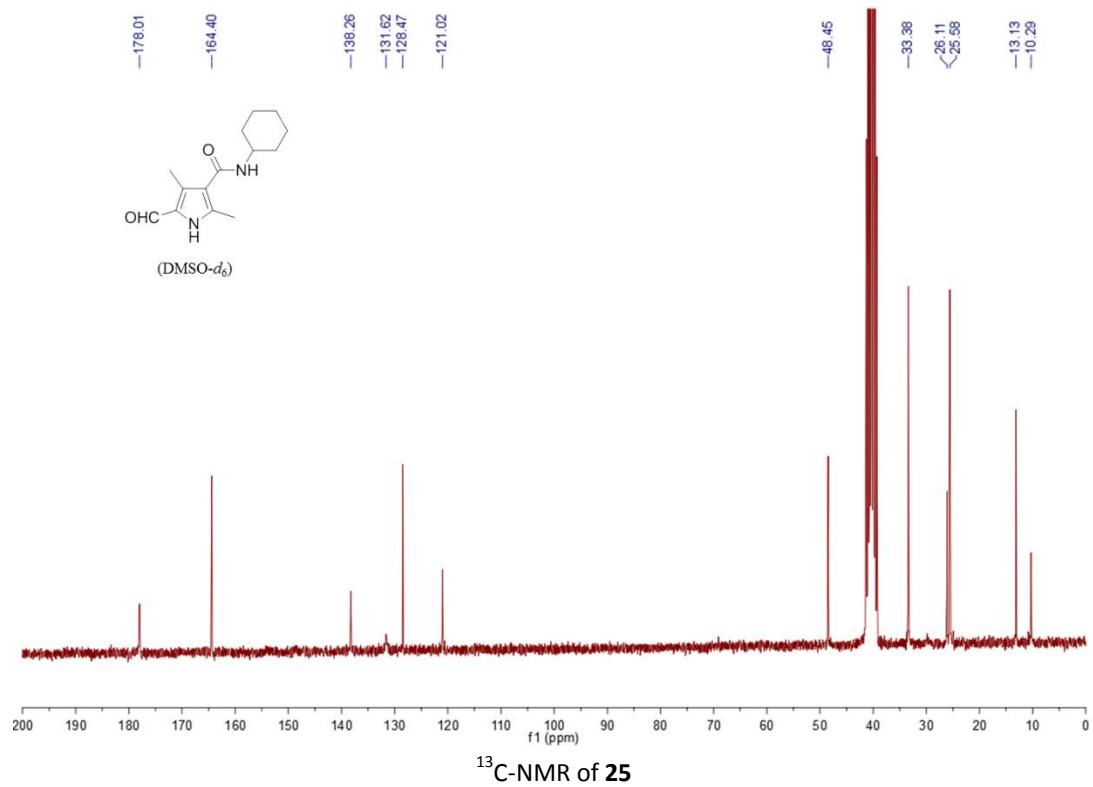
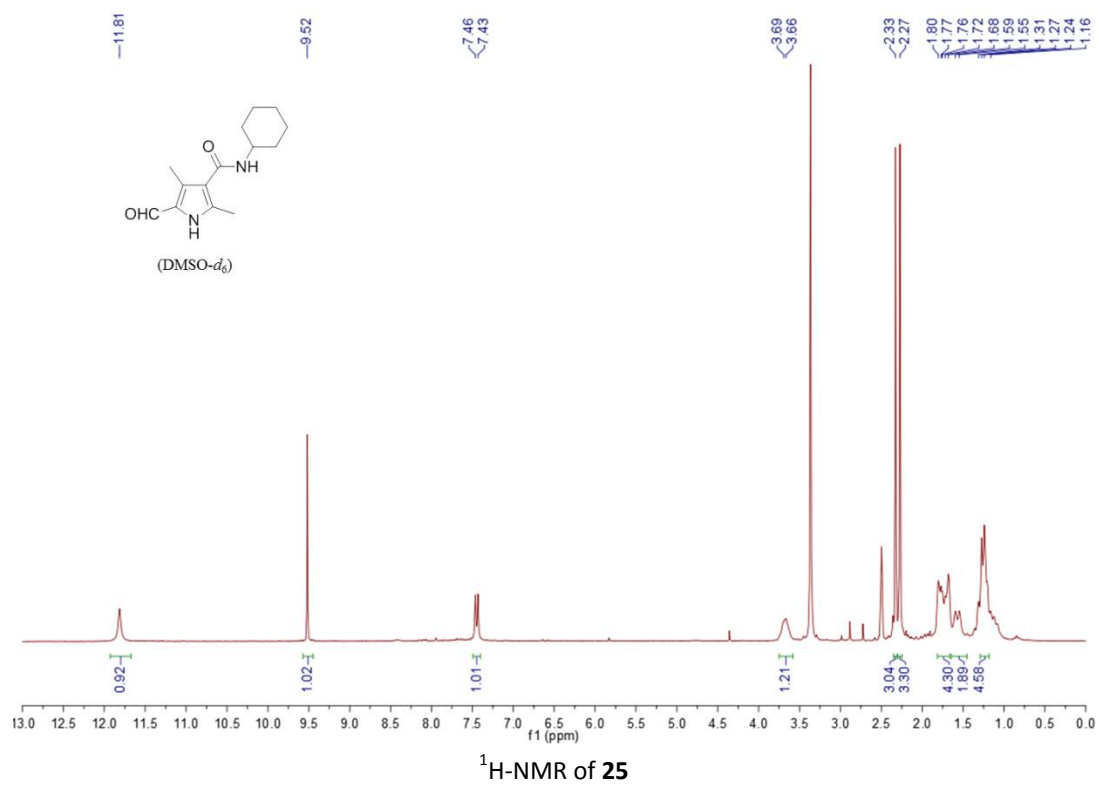
[†]These authors contributed equally to this work.

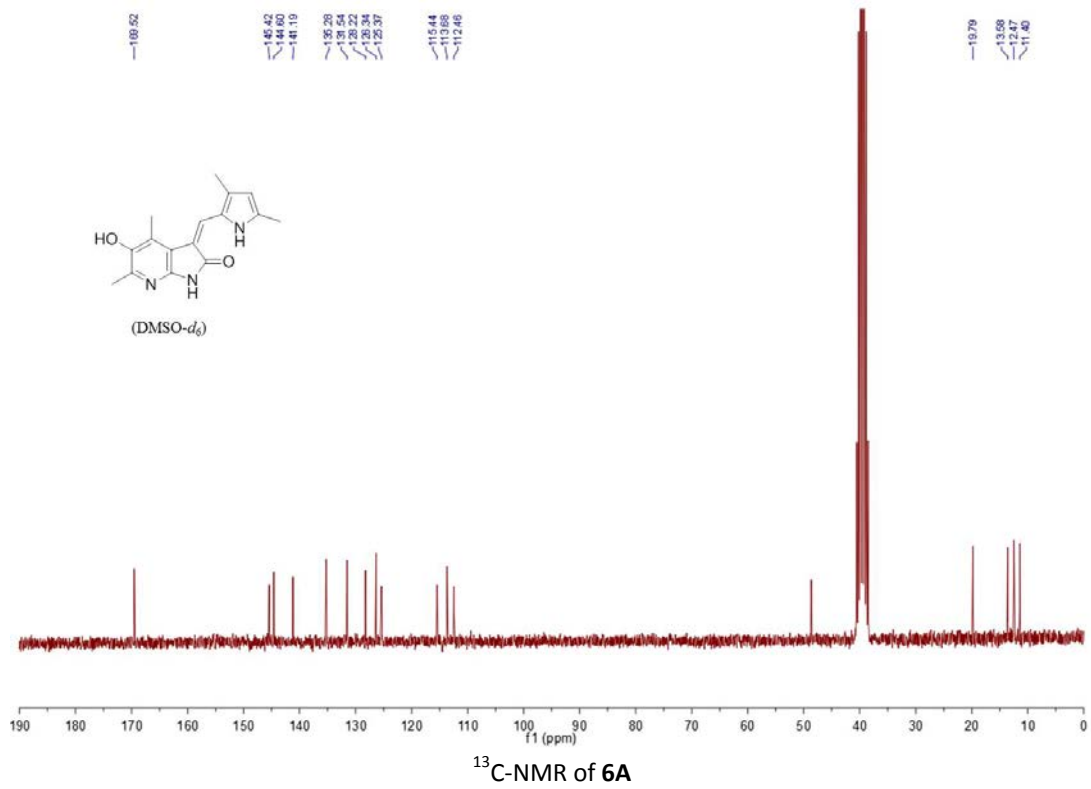
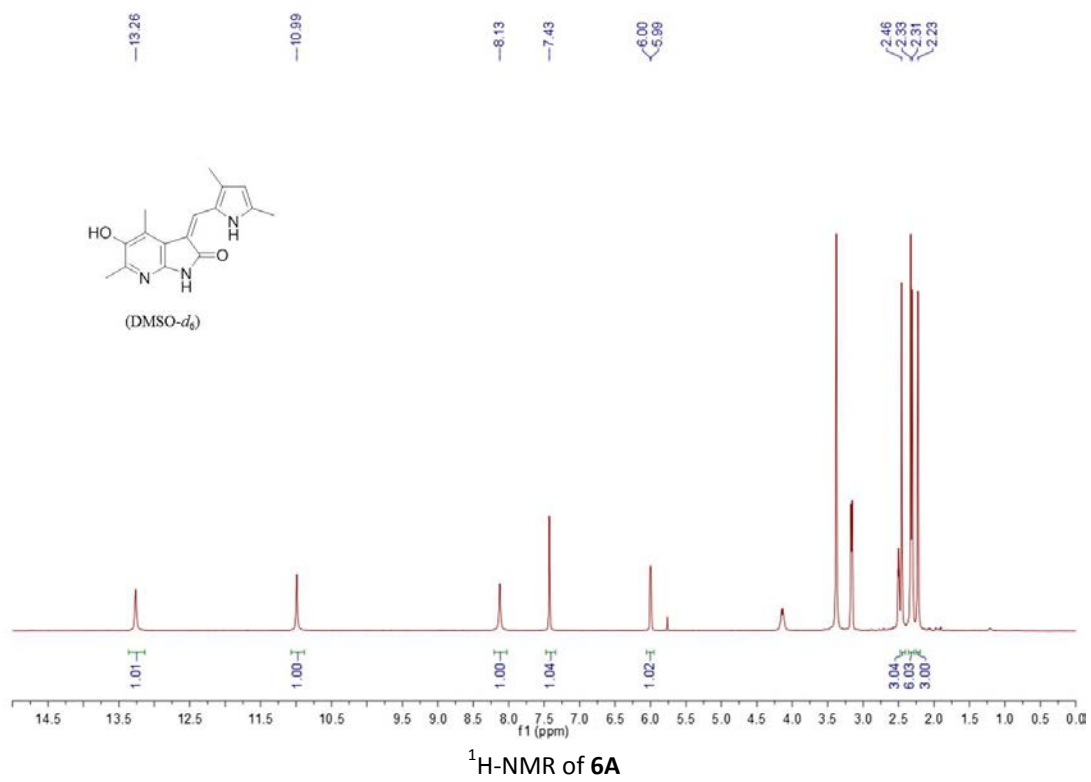
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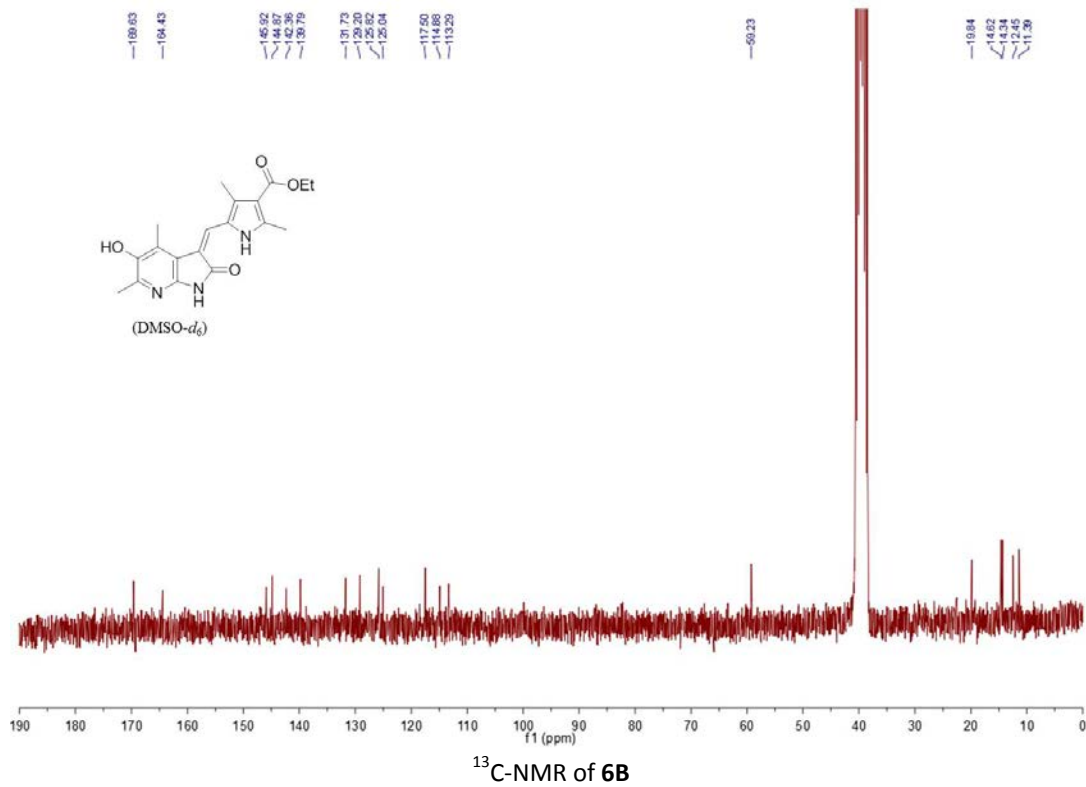
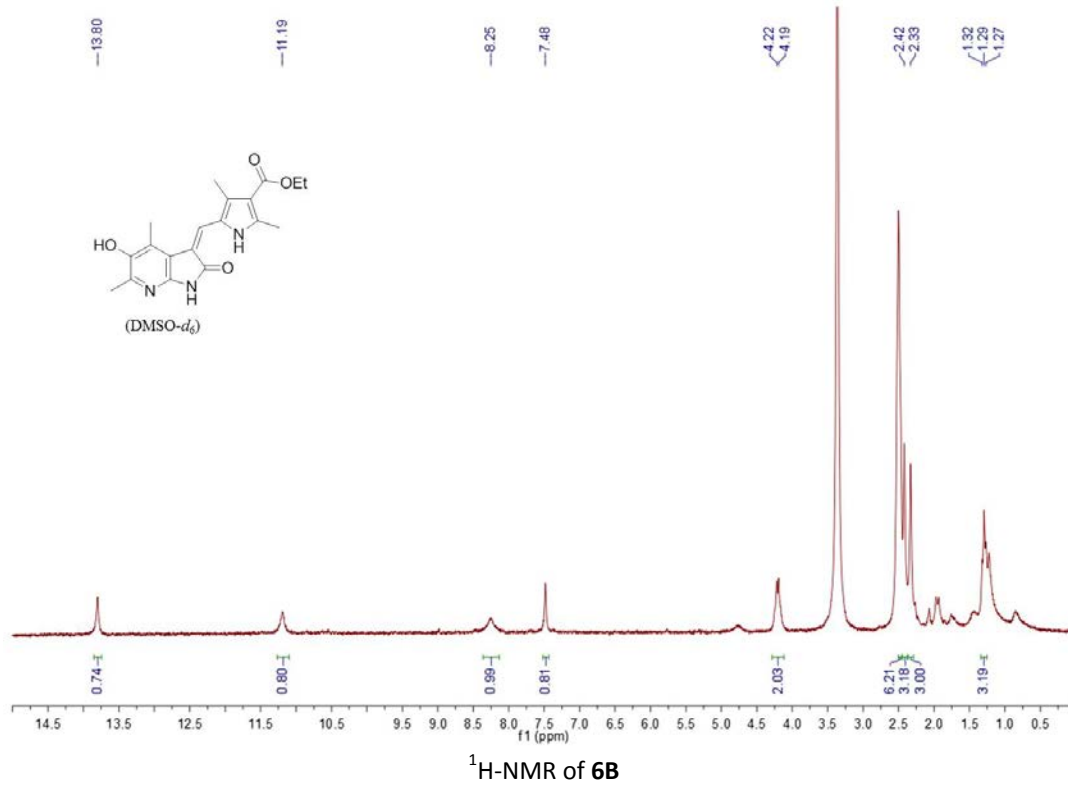
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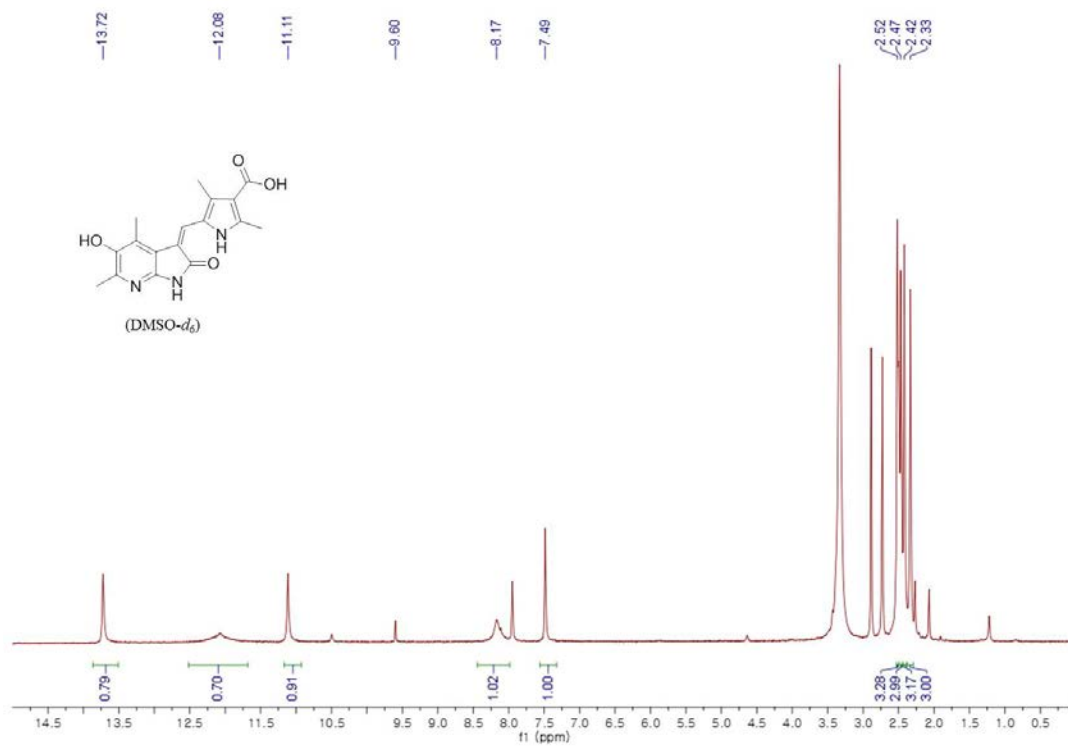
Synthesis of *N*-cyclohexyl-5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxamide (**25**)

To a solution of ethyl 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (**22**) (50 mg, 0.299 mmol) in DMF (2 mL) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI, 86 mg, 0.449 mmol), hydroxybenzotriazole (61 mg, 0.449 mmol), triethylamine (83 μ L, 0.598 mmol) and cyclohexylamine (41 μ L, 0.359 mmol). The resulting mixture was stirred at room temperature for 12 h and then concentrated *in vacuo*. After dilution of the residue with water (1 mL), brine (1 mL), and sat. aq. NaHCO₃ (1 mL), pH of the resulting solution was adjusted to 10 using 6 M aq. NaOH. Extraction of the product was performed using mixed solvent (10% methanol in dichloromethane) several times, and the extract was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (CHCl₃:MeOH=15:1) to give **25** (66 mg, 89% yield) as an orange solid. ¹H-NMR (250 MHz, DMSO) δ 11.81 (s, 1H), 9.52 (s, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 3.68 (d, *J* = 7.3 Hz, 1H), 2.33 (s, 3H), 2.27 (s, 3H), 1.81–1.66 (m, 4H), 1.59–1.55 (m, 2H), 1.26 (d, *J* = 8.2 Hz, 4H). ¹³C-NMR (62.5 MHz, DMSO) δ 178.0, 164.4, 138.3, 131.6, 128.5, 121.0, 48.5, 33.4 (2C), 26.1, 25.6 (2C), 13.1, 10.3. MS (ESI) 248 [M]⁺.

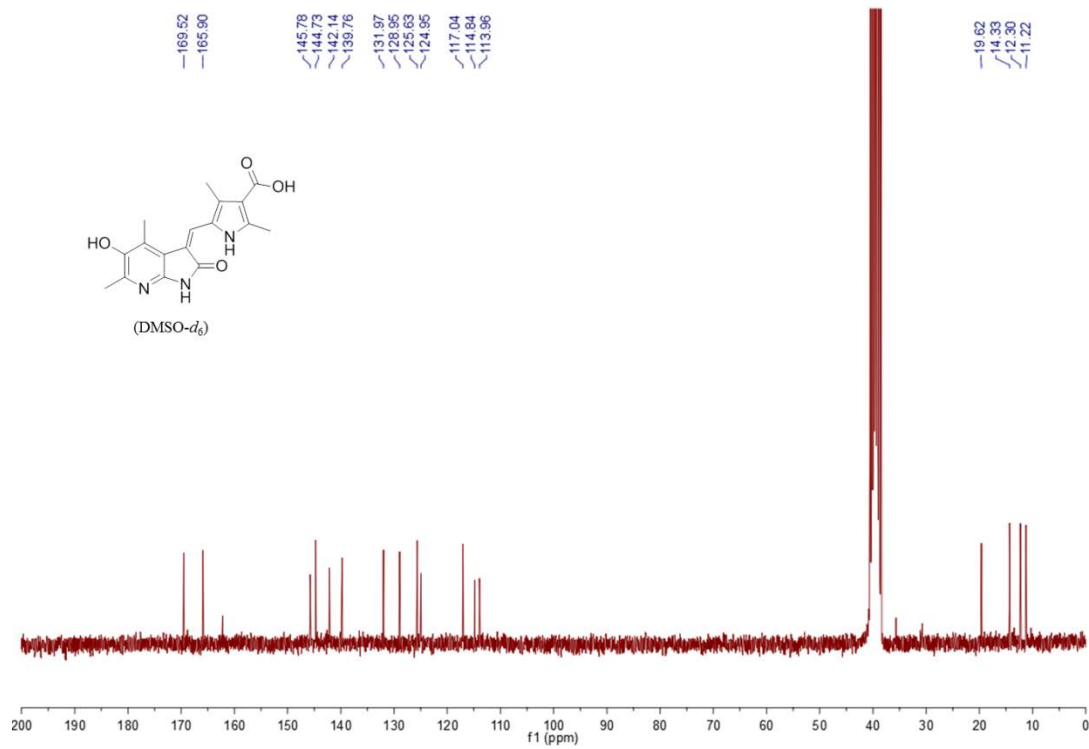




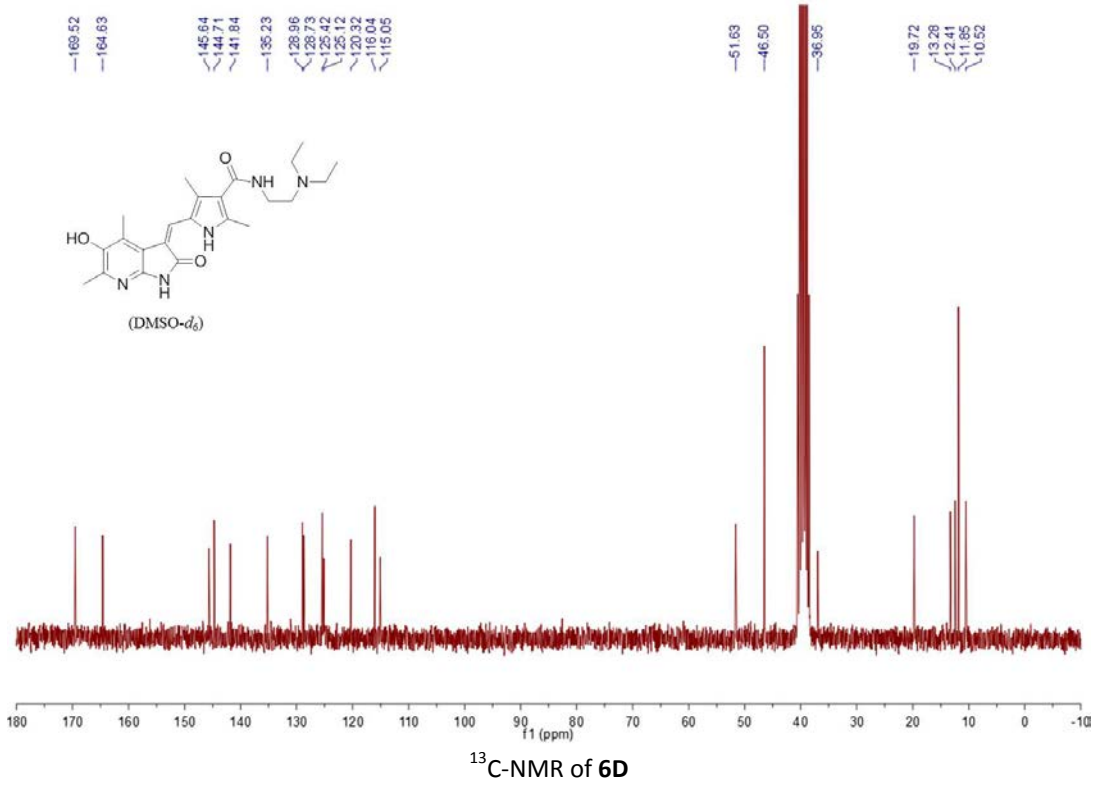
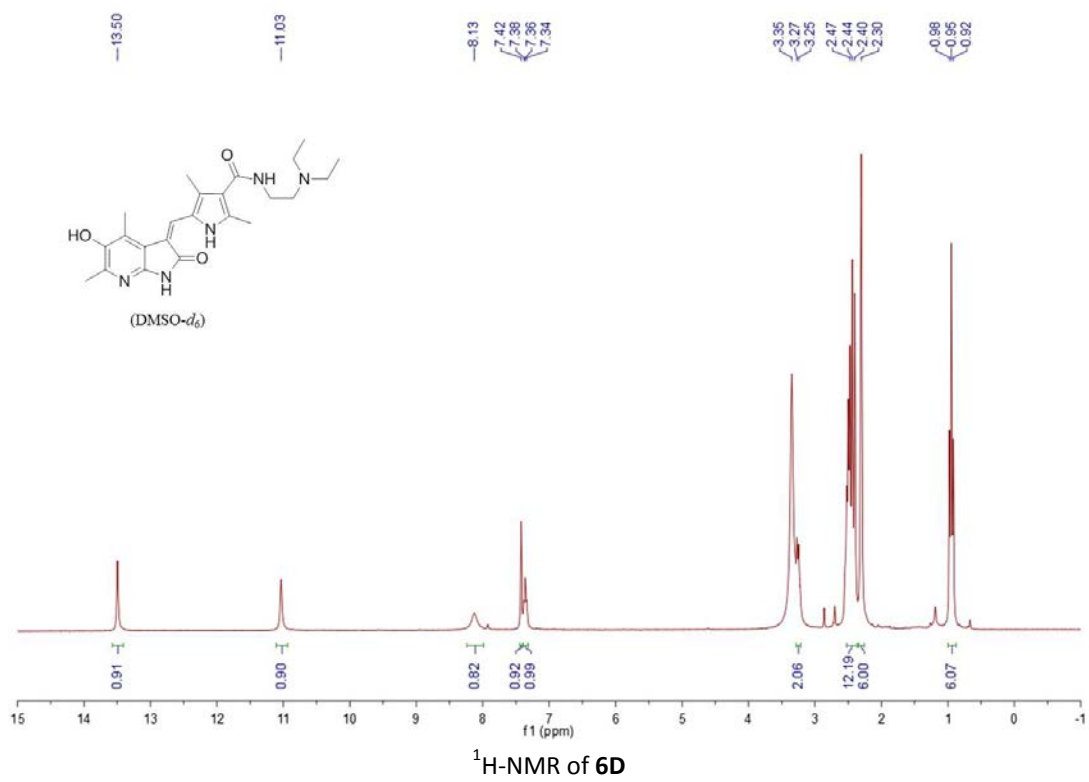


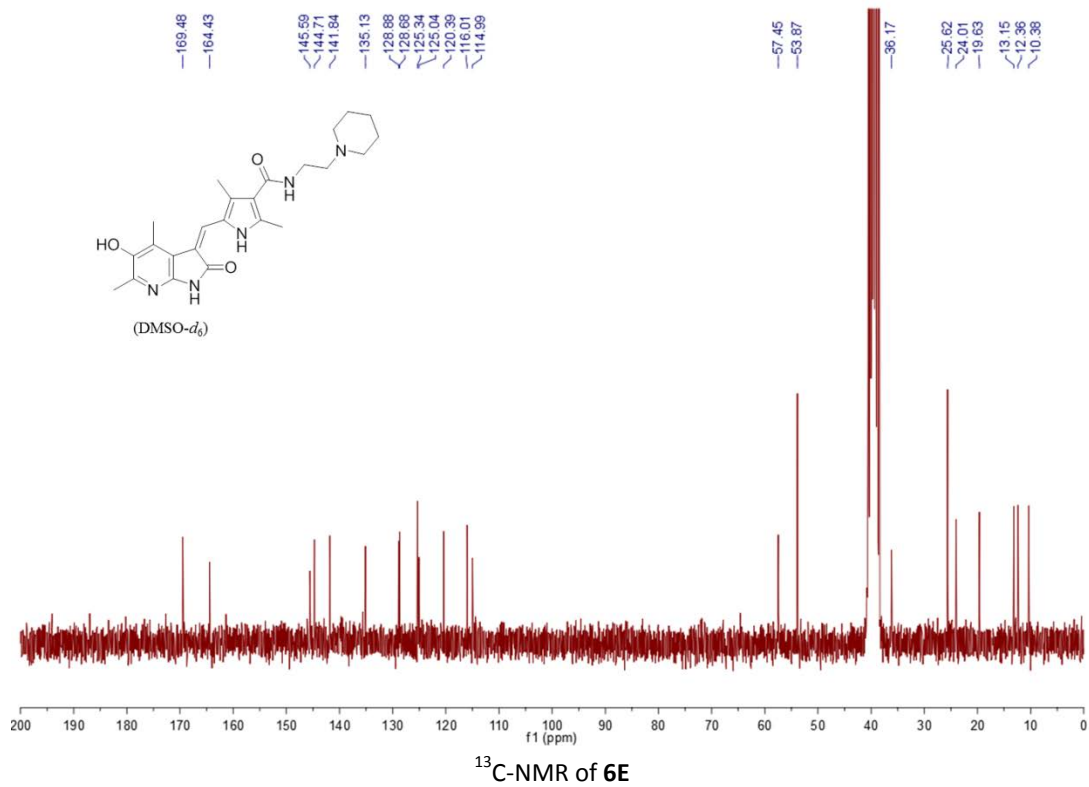
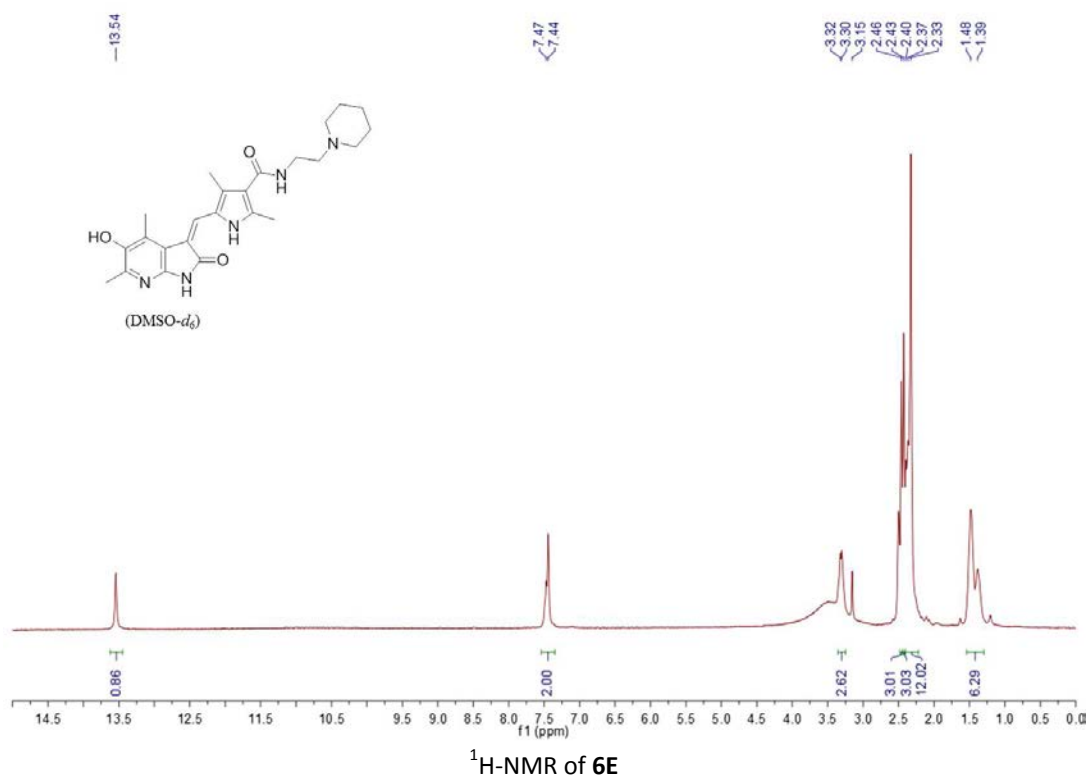


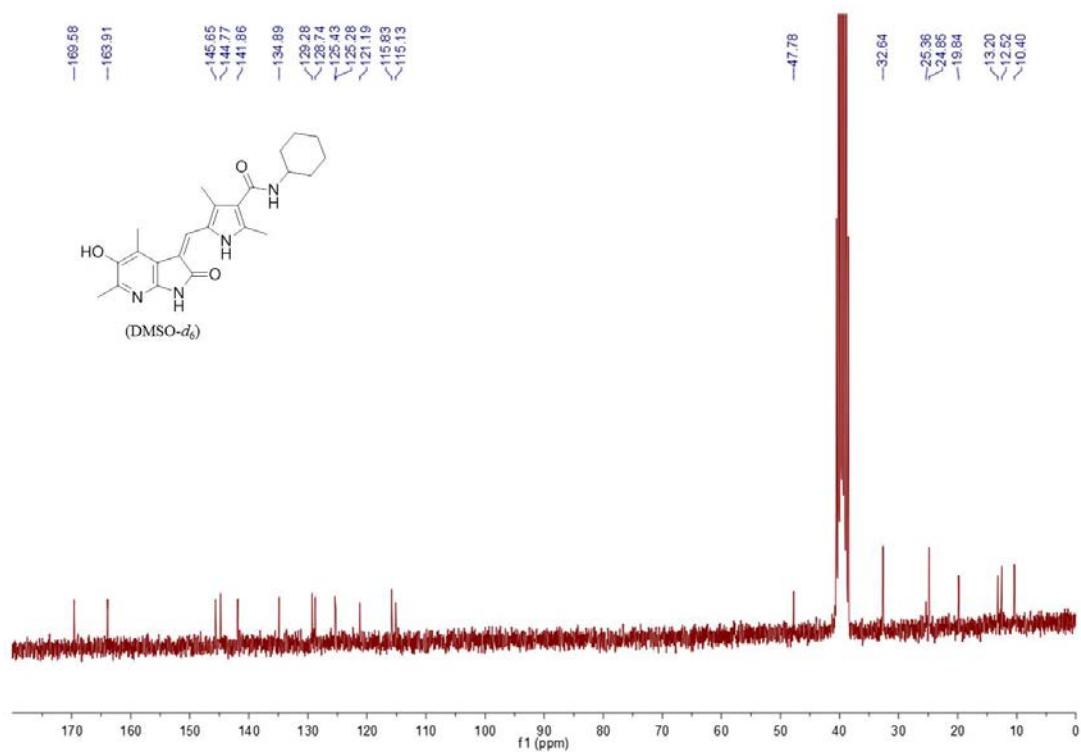
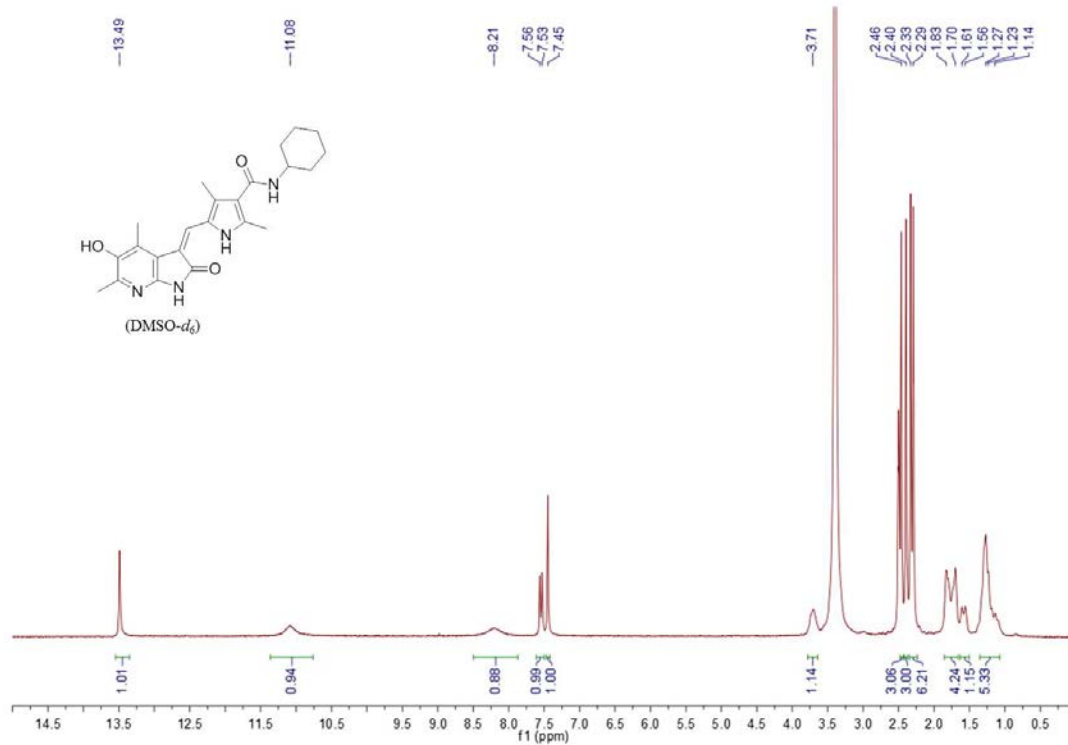
$^1\text{H-NMR}$ of 6C

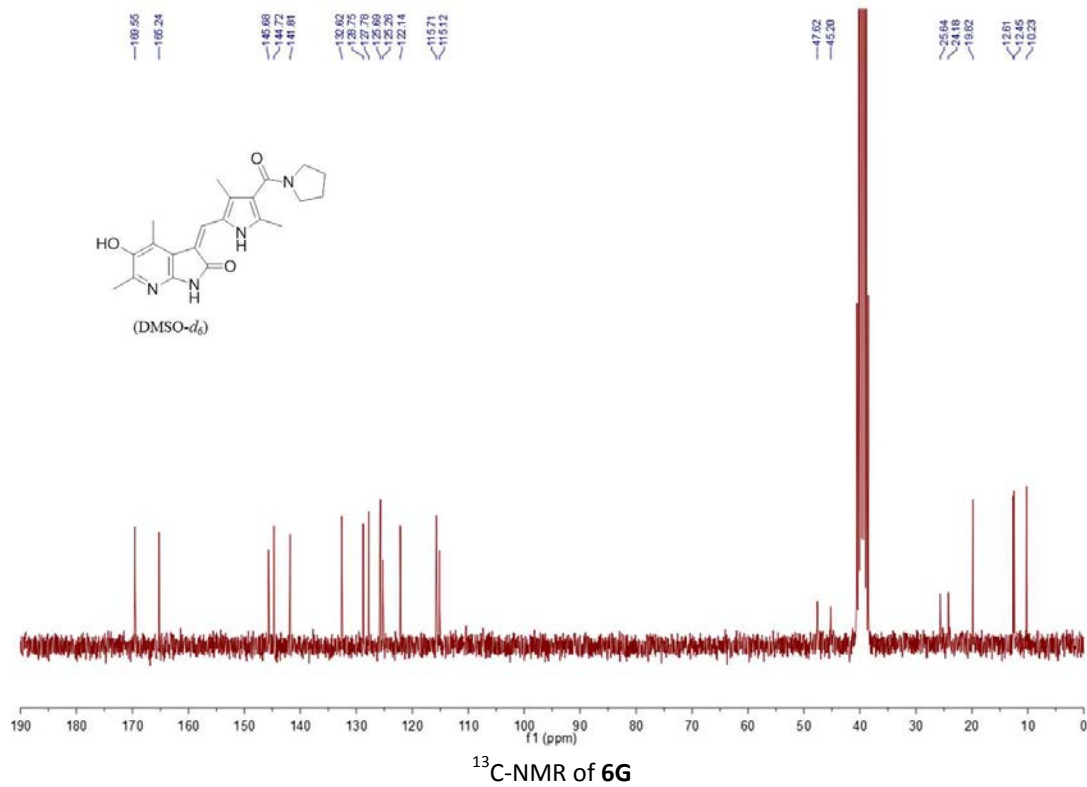
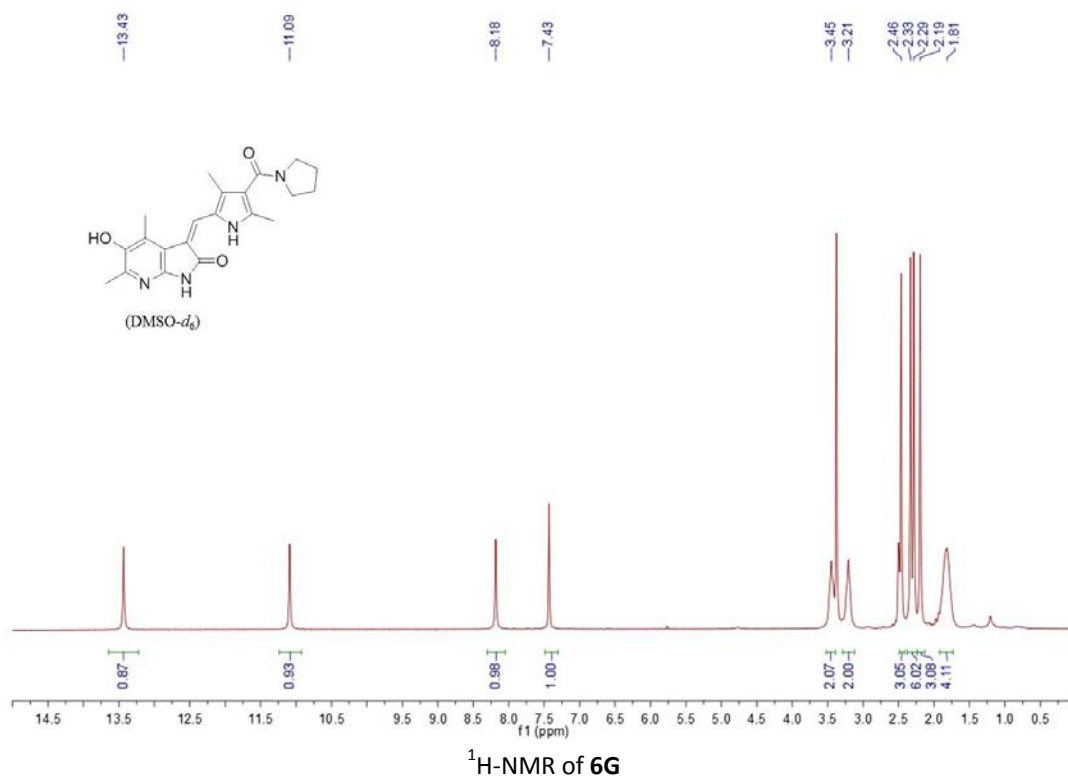


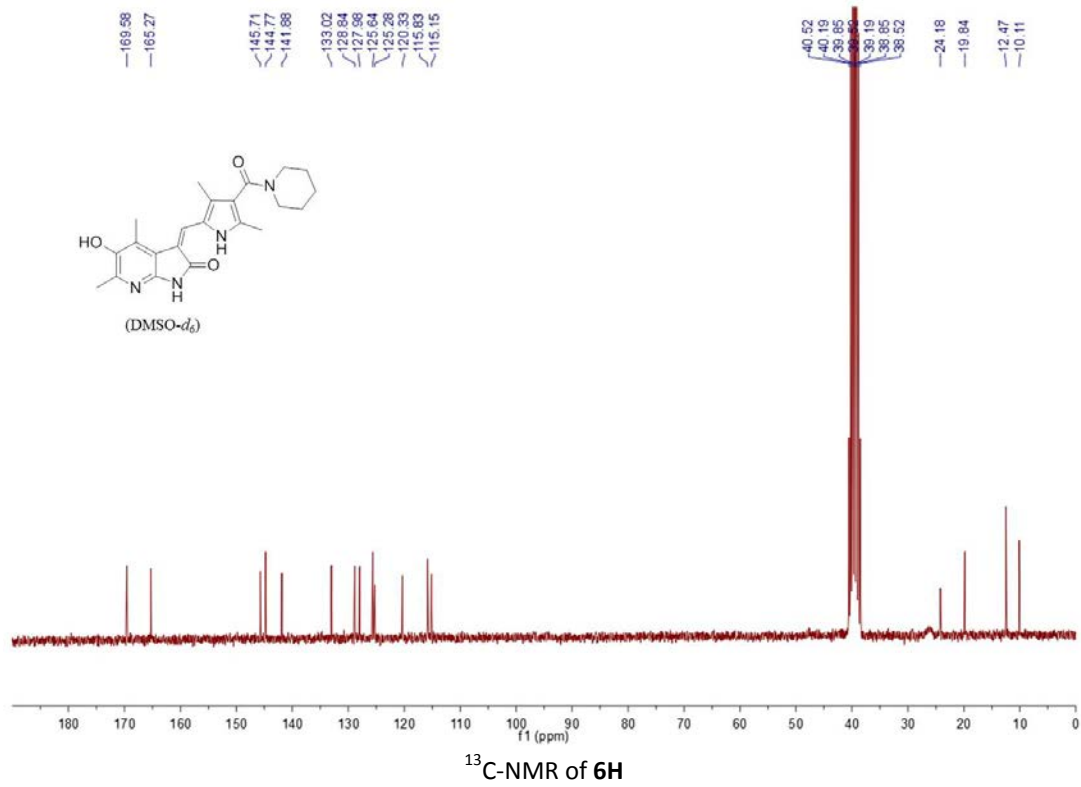
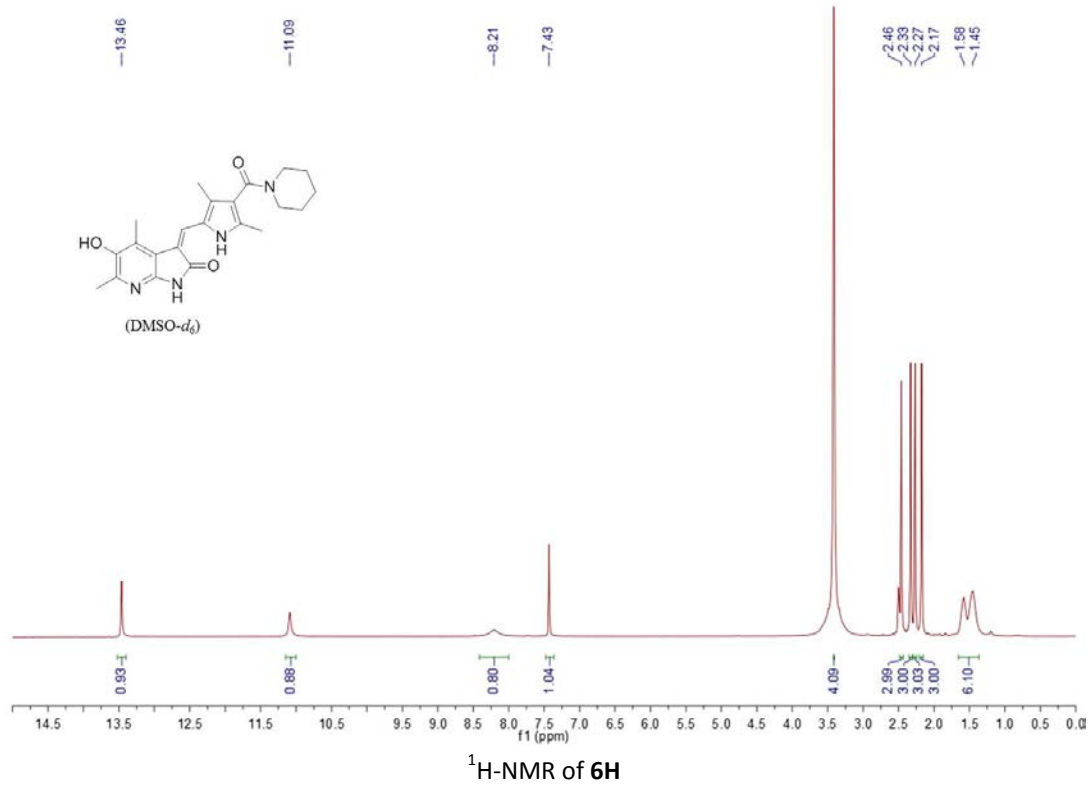
$^{13}\text{C-NMR}$ of 6C

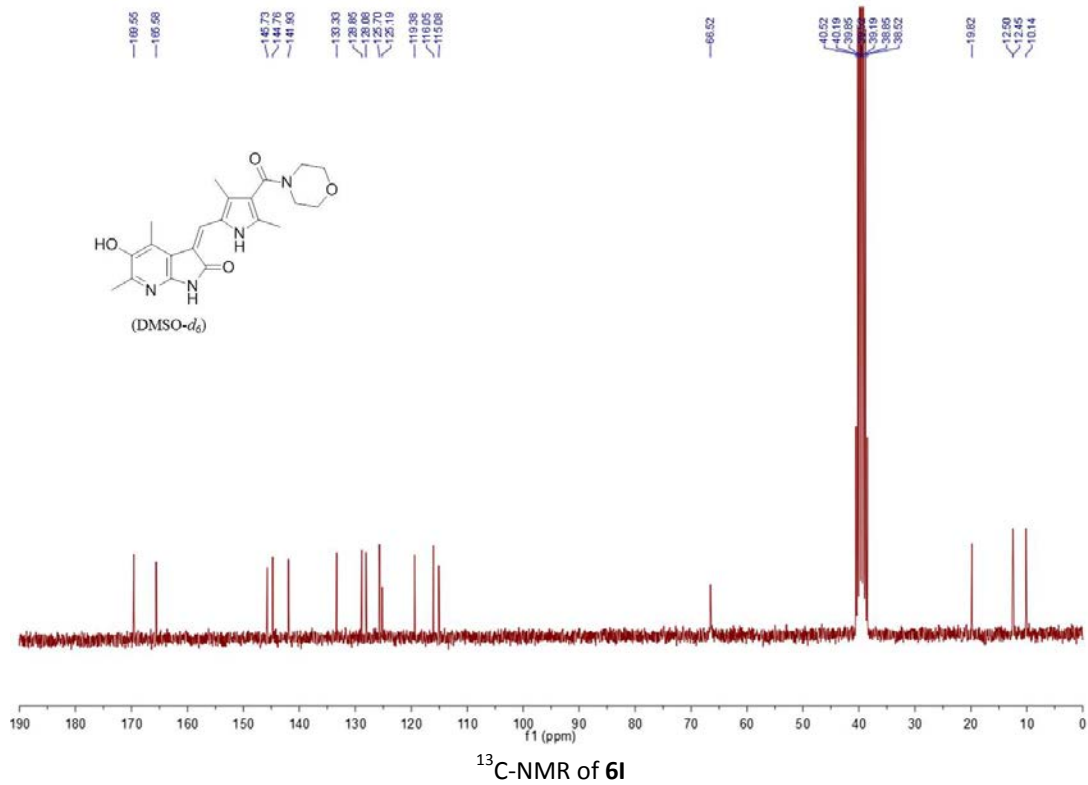
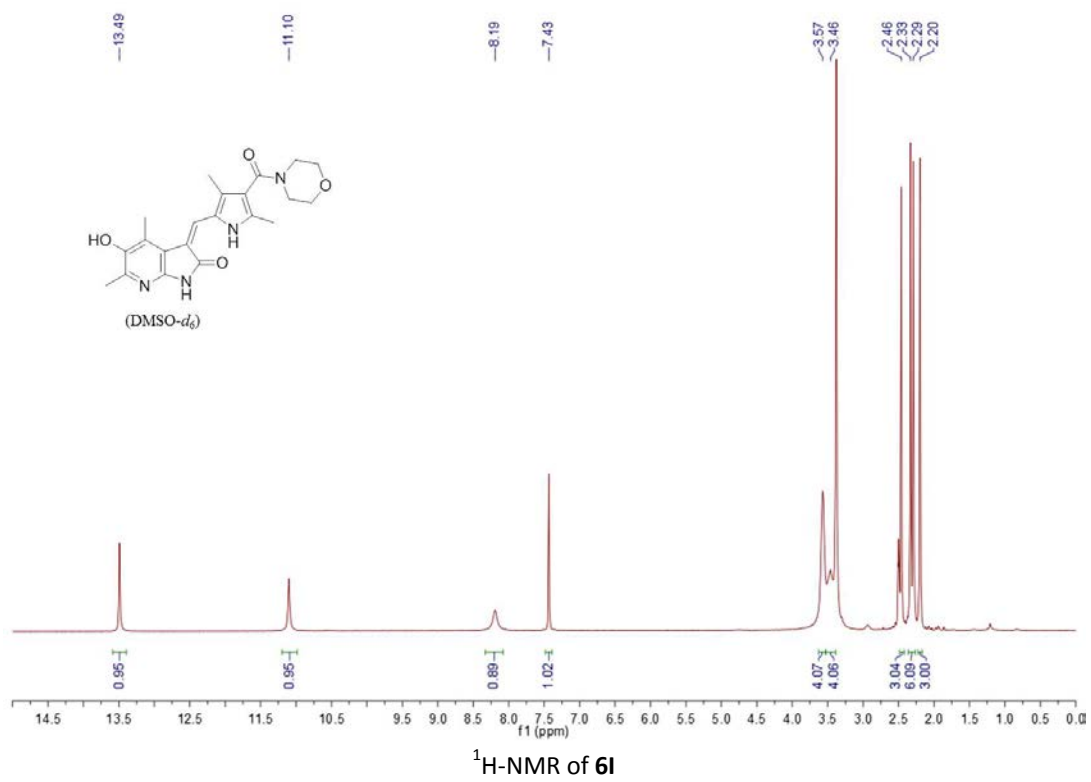


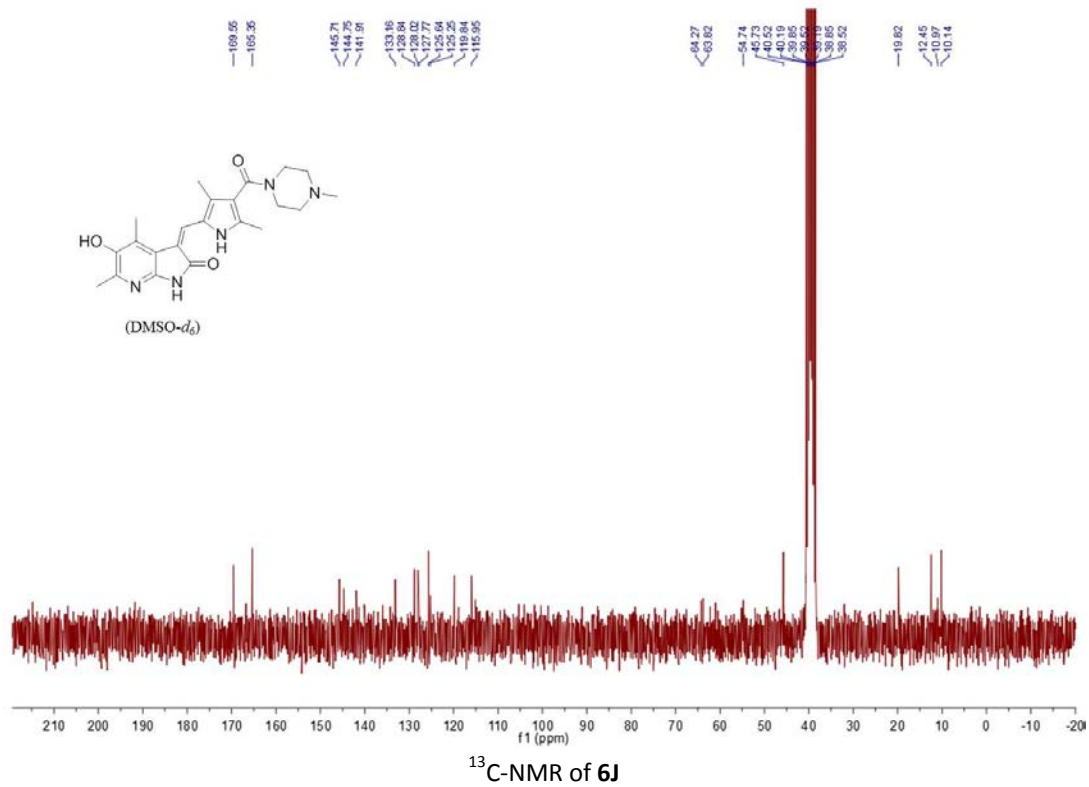
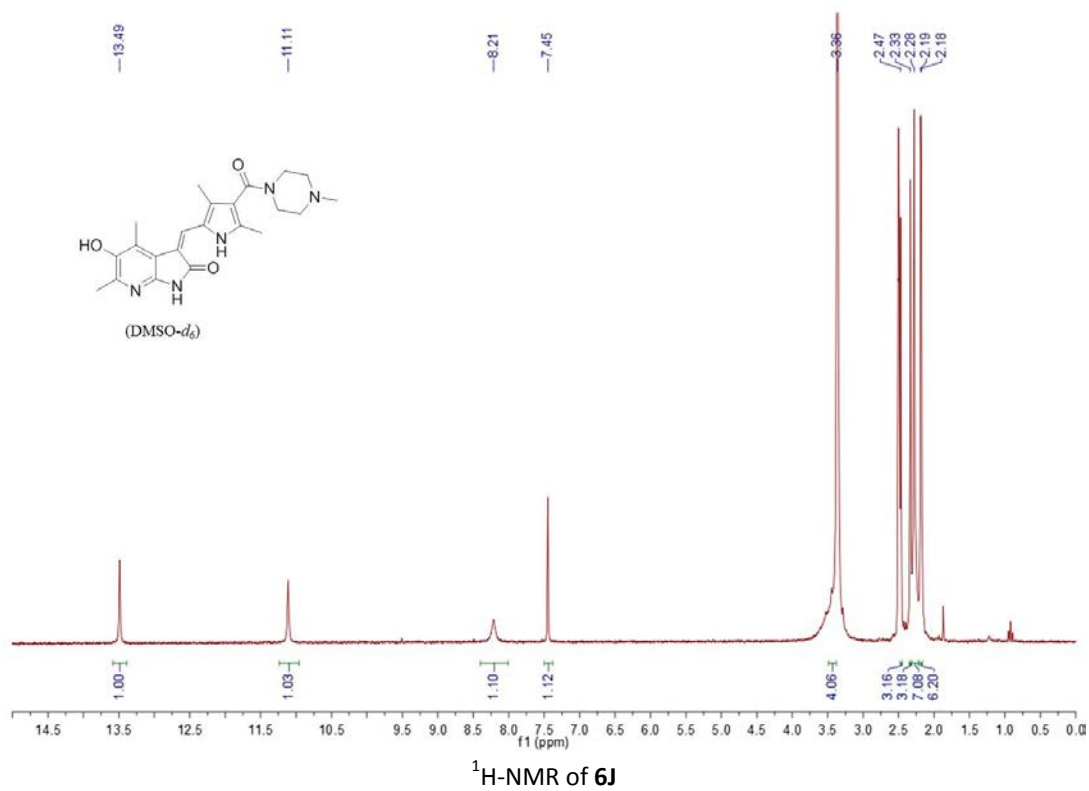


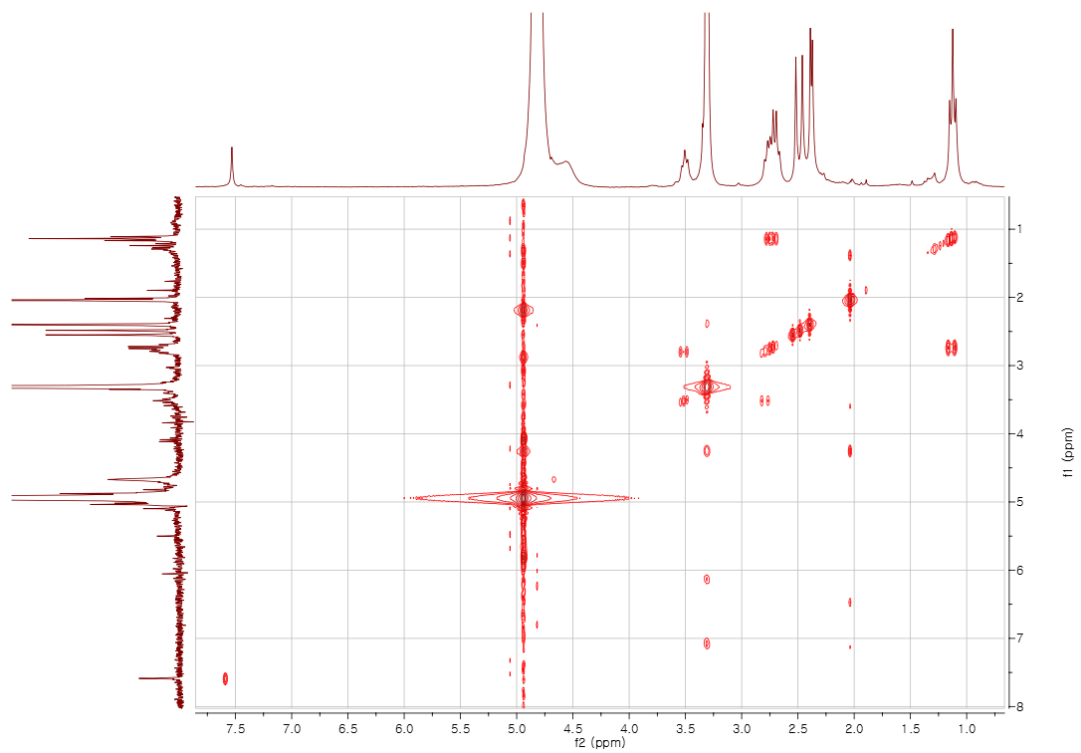




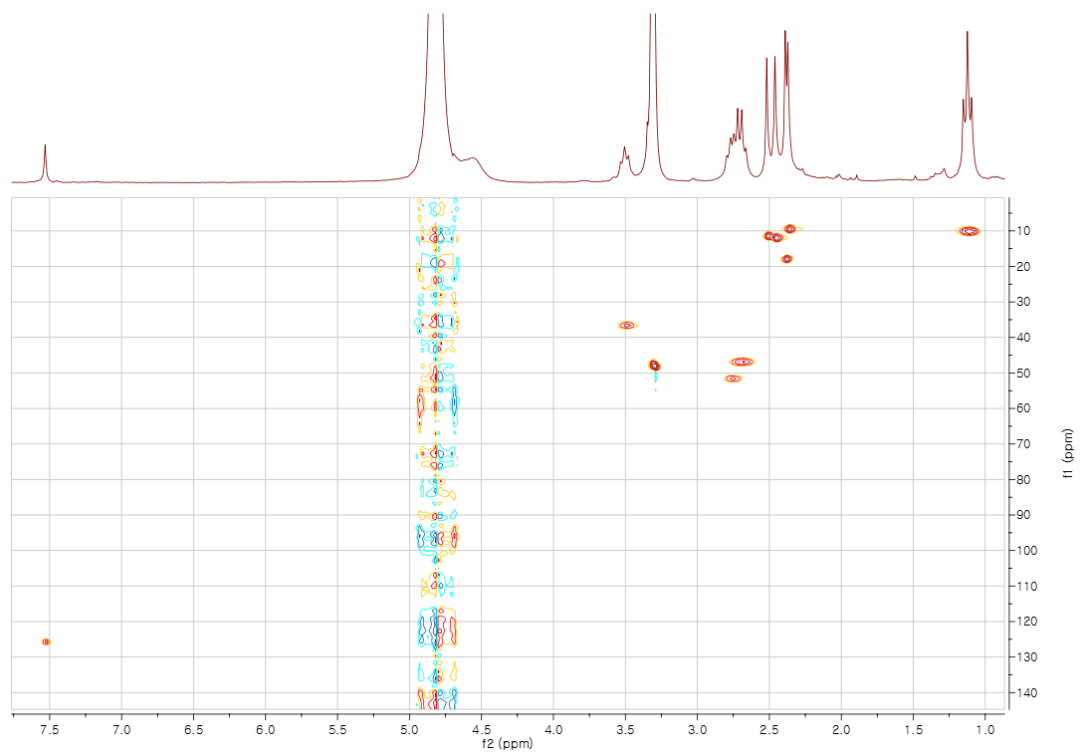




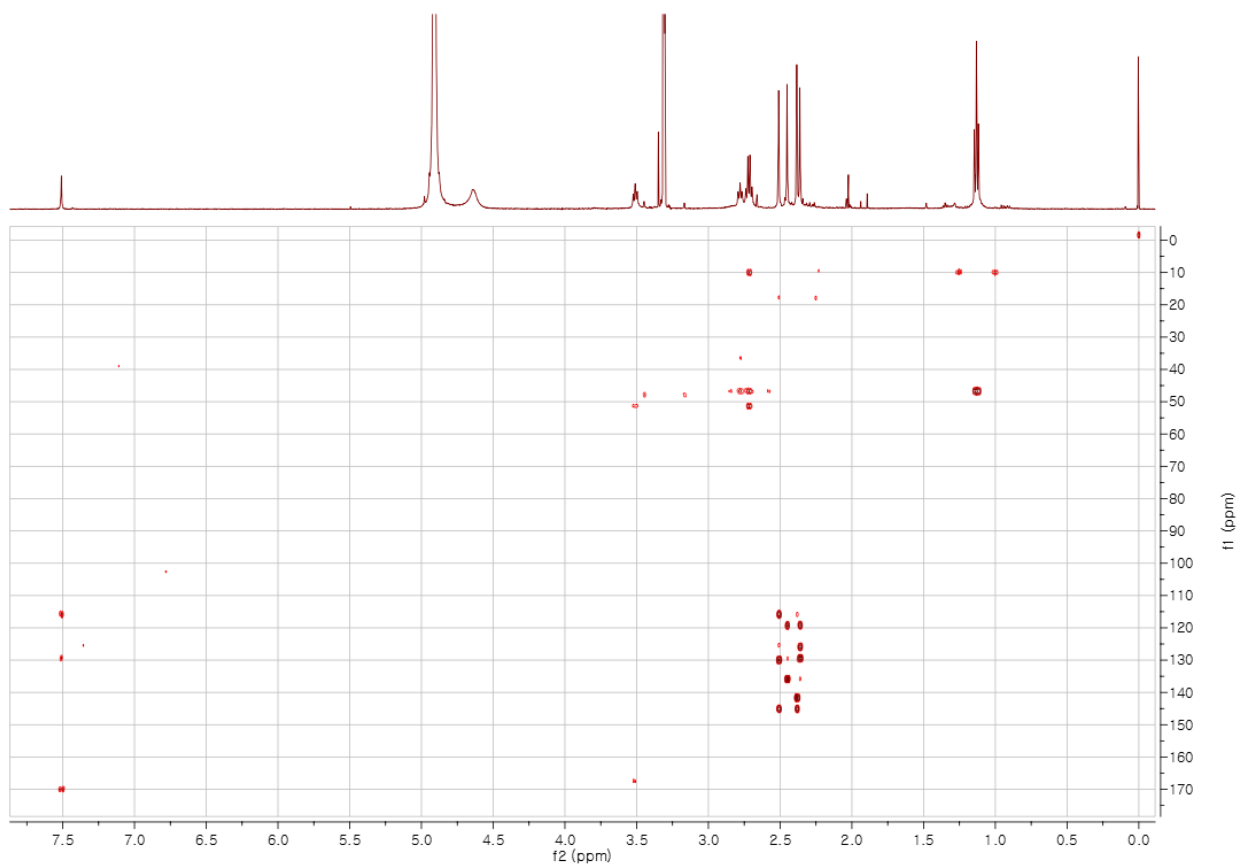




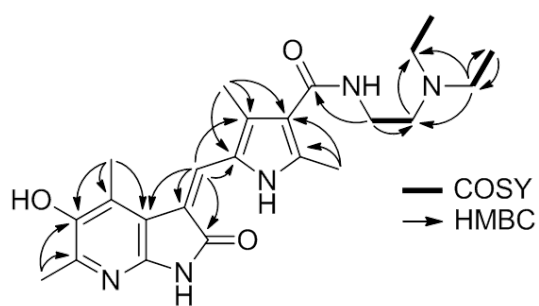
^1H - ^1H COSY spectra of **6D** (CD_3OD)



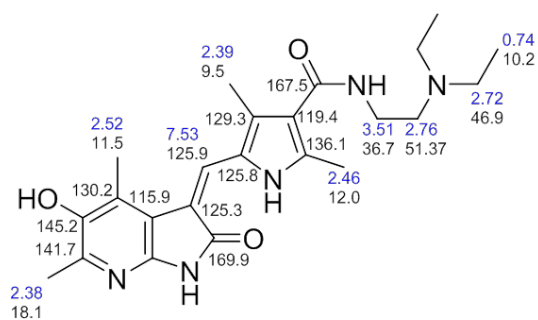
HMQC spectra of **6D** (CD_3OD)



HMBC spectra of **6D** (CD₃OD)



¹H-¹H COSY correlations and HMBC correlations of **6D**



HPLC chromatograms of 6A–6J

Column : Hydrosphere C18 250 X 4.6 mm 5 μ m
 Solvent : A- Acetonitrile (0.1% Formic acid)
 B- Water (0.1% Formic acid)

| Time | A (%) | B (%) | Flow rate (ml/min) |
|------|-------|-------|--------------------|
| 0 | 5 | 95 | 1 |
| 5 | 5 | 95 | 1 |
| 20 | 60 | 40 | 1 |
| 25 | 60 | 40 | 1 |
| 30 | 100 | 0 | 1 |
| 40 | 100 | 0 | 1 |

