

Isoxazole mediated synthesis of 4-(1*H*)Pyridones: improved preparation of antimalarial candidate GSK932121

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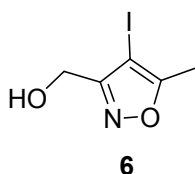
Supporting Information

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Materials and methods. Commercial grade reagents were used without further purification unless stated otherwise. Solvents were dried using a commercial solvent purification system and stored under nitrogen. ¹H-NMR were recorded on a Bruker 400 (400 MHz) spectrometer and ¹³C NMR spectra were recorded on a Bruker 400 (100 MHz) spectrometer, MS were recorded on a Waters ZQ2000 spectrometer and HRMS were recorded by using QSTAR Elite System spectrometer. Melting points are uncorrected.

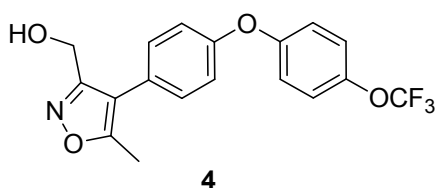
Preparation of compound 6



To a suspension of ICl (6.3g) in water (75 ml) was added the hydroxymethylmethylisoxazole **7** (3.4g), followed by TFA (11.1 ml). The mixture was heated at 65°C under nitrogen. After 2h of heating, additional ICl (1g) was added and the mixture heated for 2.5h. The mixture was allowed to cool to room temperature, then diluted with H₂O (150 ml) and treated with 10% Na₂S₂O₅ (25ml). The mixture was made basic

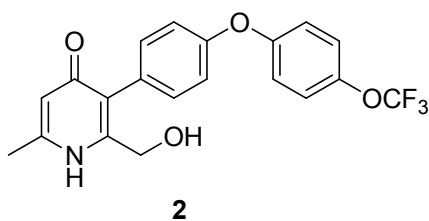
by addition of solid Na₂CO₃ (15g) portionwise (pH=7.5-8.0), then extracted with DCM (1x100 ml + 2x75ml). The combined organic layers were washed with H₂O (50ml) and brine (50ml), dried over Na₂SO₄, filtered and concentrated to dryness to afford 6.58g of compound **6** as a whitish solid (91% yield). **mp** 74-76 °C; **¹H-NMR** (300 MHz, CDCl₃) δ(ppm) 4.70 (d, *J* = 6.4 Hz, 2H), 2.48 (s, 3H), 2.15 (t, *J* = 6.5 Hz, 1H); **¹³C-NMR** (100 MHz, CDCl₃) δ(ppm) 171.0, 163.4, 57.4, 56.7, 12.3; **HRMS** calculated for C₅H₆INO₂Na [M+H]: 261.9336, found: 261.9339.

Preparation of compound 4



A mixture of isoxazole **6** (6g), boronic acid **5** (8g) and 10% palladium on activated charcoal (1.25g) in ethanol (150 ml) was desoxygenated by bubbling nitrogen for 30 min, then 10% NaHCO₃ solution (75 ml) was added dropwise onto it. The mixture was heated to 85°C for 5h under nitrogen atmosphere, then allowed to cool to room temperature and stirred overnight. The mixture was filtered through a nylon membrane (0.45 μm) and the filter cake washed with DCM/MeOH 2:1 (3x75 ml). 1N NaOH (15 ml) was added and the organic solvents removed under reduced pressure. A black solid appeared, which was eliminated by filtration. The filter cake was washed with some DCM/MeOH 2:1 mixture. H₂O (60 ml) was added and elimination of organic solvents continued to afford an aqueous suspension containing a solid precipitated. The solid was filtered, then washed with 1N NaOH (3x50 ml) and water (4x50 ml). Once it was dried under vacuum the solid was washed with heptane (3x50 ml) and finally dried. 8.82g of compound **4** were obtained as a white solid. **mp** 164-166 °C; **¹H-NMR** (400 MHz, DMSO-d₆) δ(ppm) 7.55 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.17 (d, *J* = 9.1 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 2H), 5.48 (t, *J* = 5.6 Hz, 1H), 4.48 (d, *J* = 5.6 Hz, 2H), 2.44 (s, 3H); **¹³C-NMR** (100 MHz, DMSO-d₆) δ(ppm) 165.5, 161.4, 155.6, 155.4, 143.8 (q, *J* = 2.2 Hz), 130.7, 125.4, 123.0, 120.1 (q, *J* = 256.1 Hz), 120.1, 119.0, 114.9, 53.9, 11.4; **MS** (ES) *m/z* 366 [M+H]⁺.

Preparation of compound 2

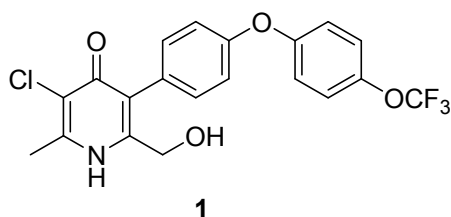


To a mixture of isoxazole **4** (0.548g) and anhydrous lithium chloride (0.572g) in dry tetrahydrofuran (15ml) was added redistilled diisopropylamine (0.63ml) and the mixture cooled to -75°C under argon atmosphere. A solution of *n*-BuLi (2 ml, 1.7M in hexanes) was added and the mixture was stirred under argon atmosphere for 1 hour, then *N*-methoxy-*N*-methylacetamide (0.223ml) was added dropwise and the mixture stirred at -75°C for 4h. 2N HCl (10 ml) was added and the mixture stirred at room temperature for 0.5h, then 1N HCl (75 ml) and *t*-BuOMe (75 ml) were added and the mixture partitioned. The organic layer was washed with 1N HCl (2x75 ml), 10% NaHCO₃ (75 ml), H₂O (75 ml) and brine (75 ml). It was dried over Na₂SO₄, filtered and evaporated to dryness to afford 0.62g of a pale brown oil which was used for the next step without further purification.

The crude above described (0.62g) was dissolved in EtOH (25 ml) and 10% palladium on activated charcoal (60 mg) was added under nitrogen atmosphere onto the solution. The mixture thus obtained was hydrogenated for 8h (2 bar H₂ pressure) in a Parr reactor. Additional 10% palladium on activated charcoal (60 mg) was added and the mixture hydrogenated under the same conditions for 14h.

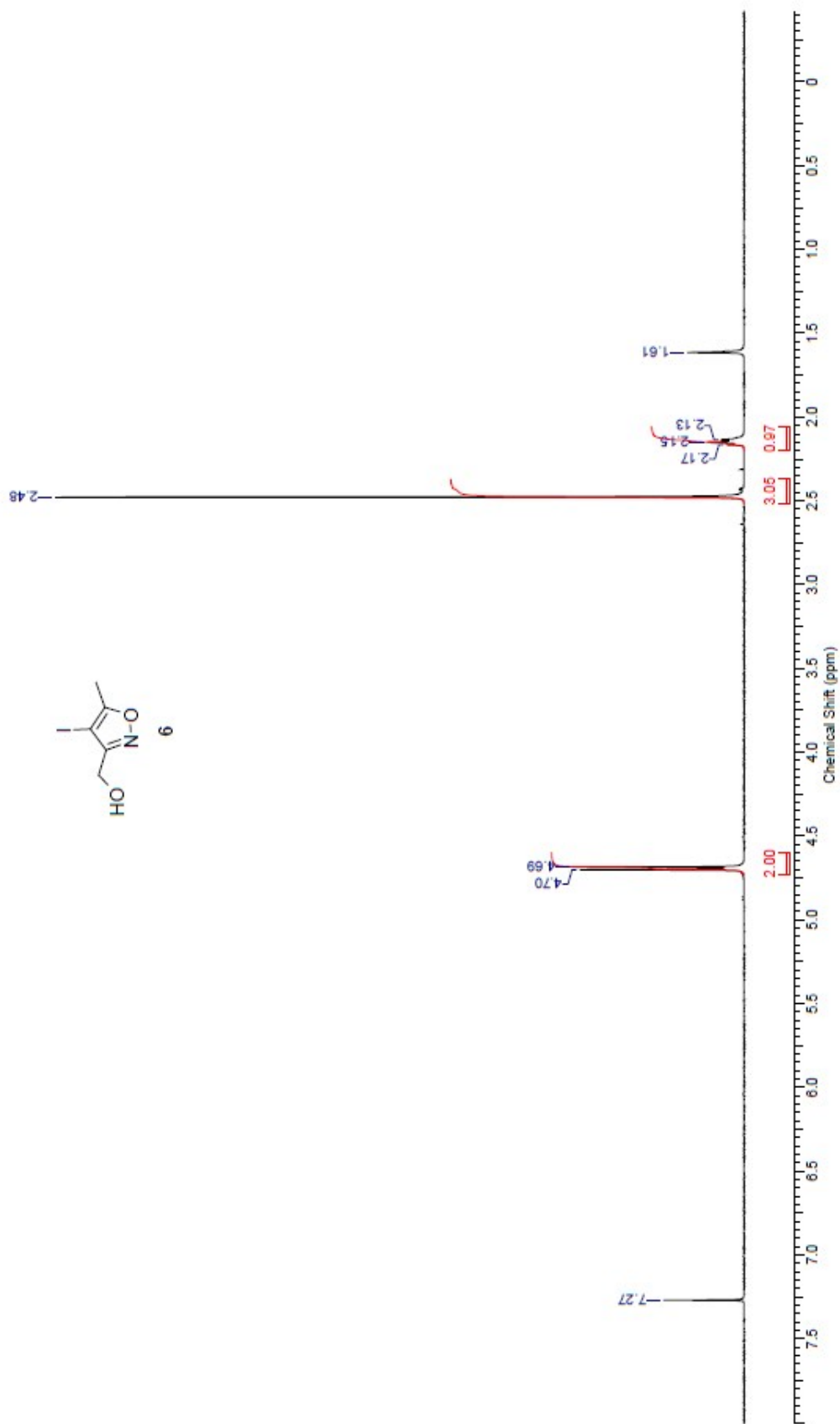
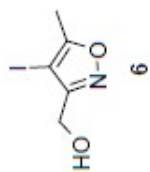
The mixture was filtered through a Nylon 0.45 μm membrane and washed with 2:1 DCM/MeOH (3x5ml). Elimination of the solvents to dryness gave 0.61g of crude which were dissolved in EtOAc (5 ml). To this solution was added 1ml of hexane and then allowed to crystallize in the fridge. The solid obtained was filtered off, washed with 3:2 hexane/ethyl acetate mixture (2x4ml) and dried under vacuum to give 0.42 g of compound **2** as a white solid. **mp** 156-158 $^{\circ}\text{C}$; **¹H-NMR** (400 MHz, DMSO-*d*₆) δ (ppm) 10.95 (bd, 1H), 7.40 (d, $J = 8.5$ Hz, 2H), 7.21 (d, $J = 8.6$ Hz, 2H), 7.14 (d, $J = 9.1$ Hz, 2H), 7.03 (d, $J = 8.5$ Hz, 2H), 5.97 (s, 1H), 5.49 (bd, 1H), 4.23 (s, 2H), 2.25 (s, 3H); **¹³C-NMR** (100 MHz, DMSO-*d*₆) δ (ppm) 176.6, 155.8, 154.8, 146.4, 146.0, 143.6 (q, $J = 1.5$ Hz), 132.3, 130.4, 124.2, 123.0, 120.1 (q, $J = 256.1$ Hz), 119.7, 118.1, 114.8, 58.5, 18.6; **HRMS** calculated for C₂₀H₁₆F₃NO₄ [M+H]: 392.1104; found: 392.1109.

Preparation of compound 1

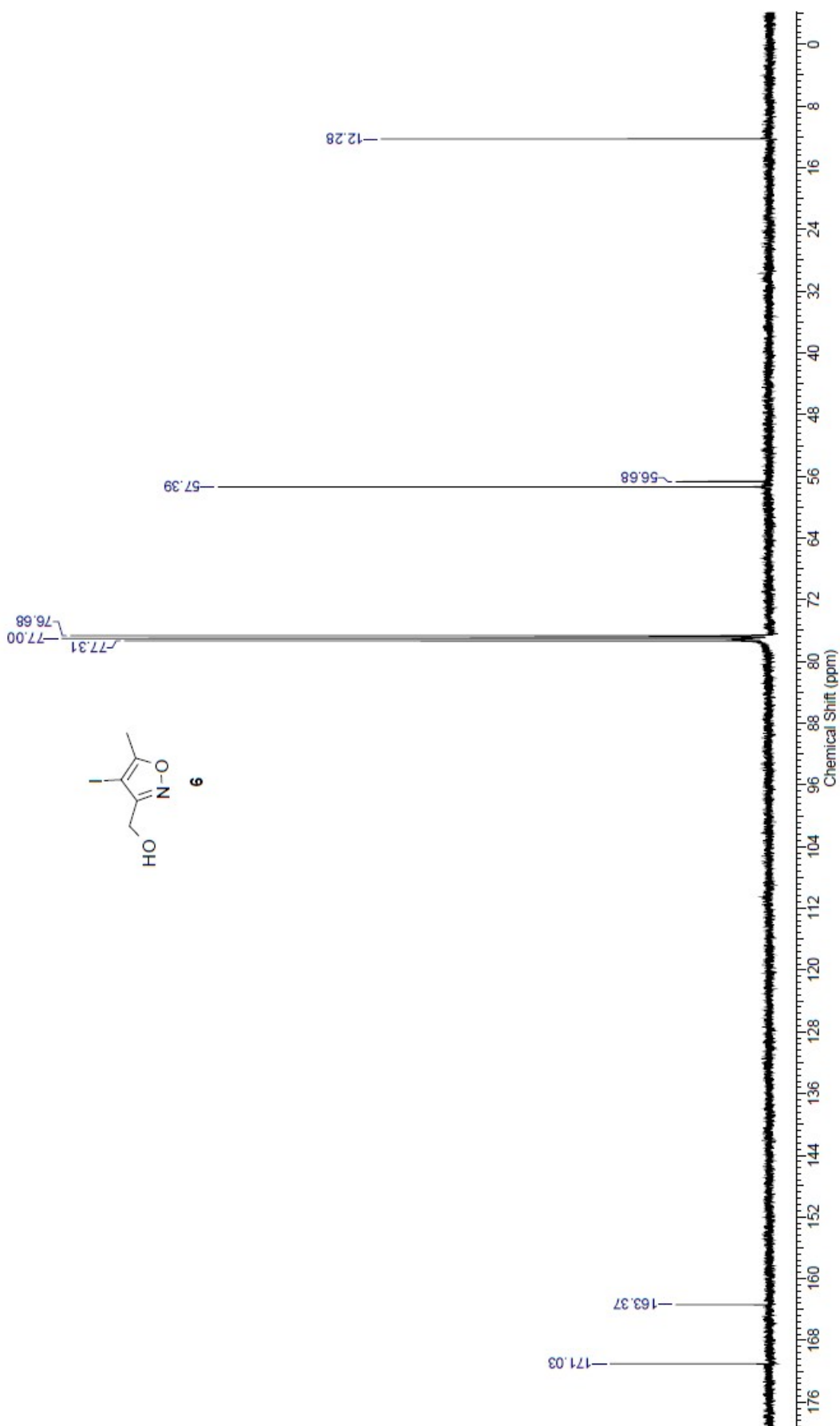
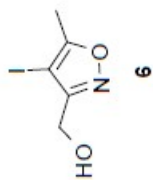


In a 500 mL round bottom flask was dissolved compound **2** (5.25 g) in DCM/MeOH v/v 2:1 (135 mL). The mixture was cooled at 0°C under argon atmosphere and after 30 min trichloroisocyanuric acid (1.26 g) was added. The solution was stirred under nitrogen atmosphere for 50 minutes, filtered and washed with DCM/MeOH v/v 2:1 (60 mL). The filtrate was evaporated to dryness, 10% Na₂CO₃ was added (30 mL) and the mixture was stirred. The solid was filtered and washed with H₂O (100 mL), 10% Na₂CO₃ (2x30 mL), H₂O (2x50 mL) and acetonitrile (2x15 mL and 1x20 mL), dried under vacuum to give 4.66 g of compound **1** as a off-white powder. **mp** 165-167 °C; **¹H-NMR** (400 MHz, DMSO-d₆) δ (ppm) 11.50 (bd, 1H), 7.41 (d, J = 9.2 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 9.2 Hz, 2H), 7.05 (d, J = 8.6 Hz, 2H), 5.60 (bd, 1H), 4.25 (s, 2H), 2.46 (s, 3H); **¹³C-NMR** (100 MHz, DMSO-d₆) δ (ppm) 170.4, 155.6, 155.2, 145.0, 144.1, 143.6 (q, J = 1.9 Hz), 132.3, 129.9, 123.7, 123.0, 120.9, 120.1 (q, J = 256.1 Hz), 119.9, 118.2, 58.3, 17.5; **HRMS** calculated for C₂₀H₁₅ClF₃NO₄ [M+H]: 426.0714; found: 426.0709.

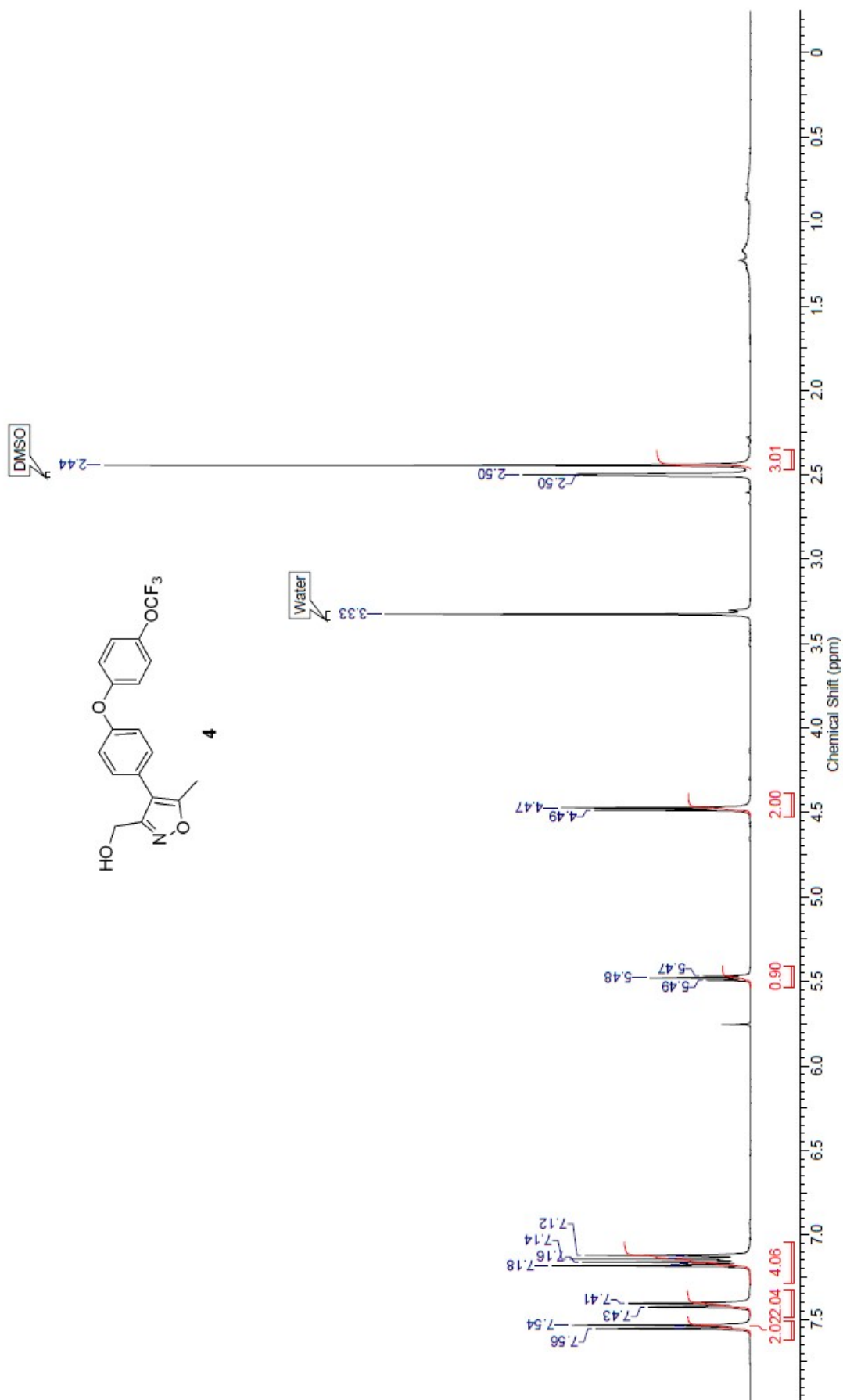
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Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	-2458.8701



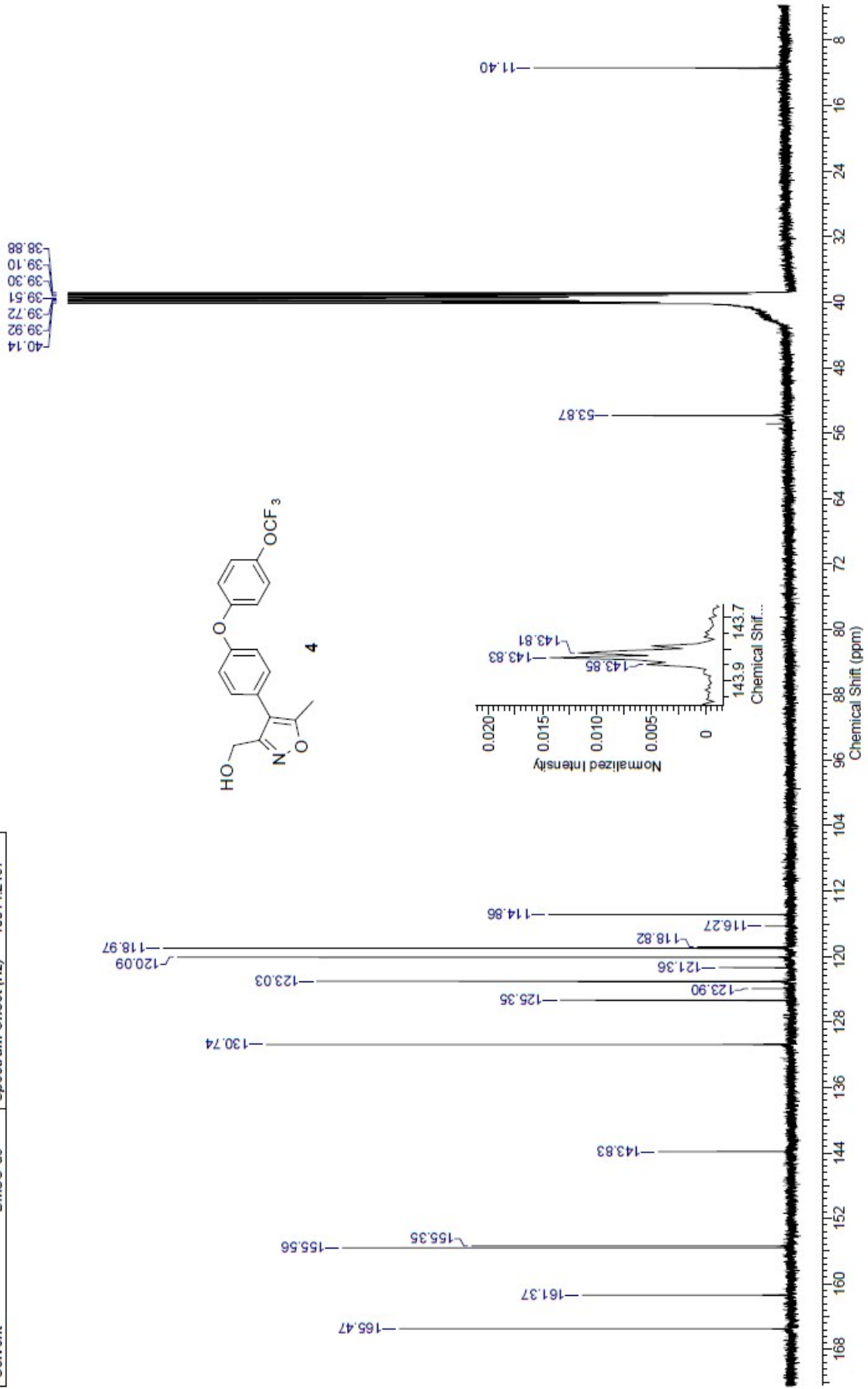
Frequency (MHz)	100.63	Nucleus	¹³ C
Solvent	CHLOROFORM-d	Sweep Width (Hz)	23980.08



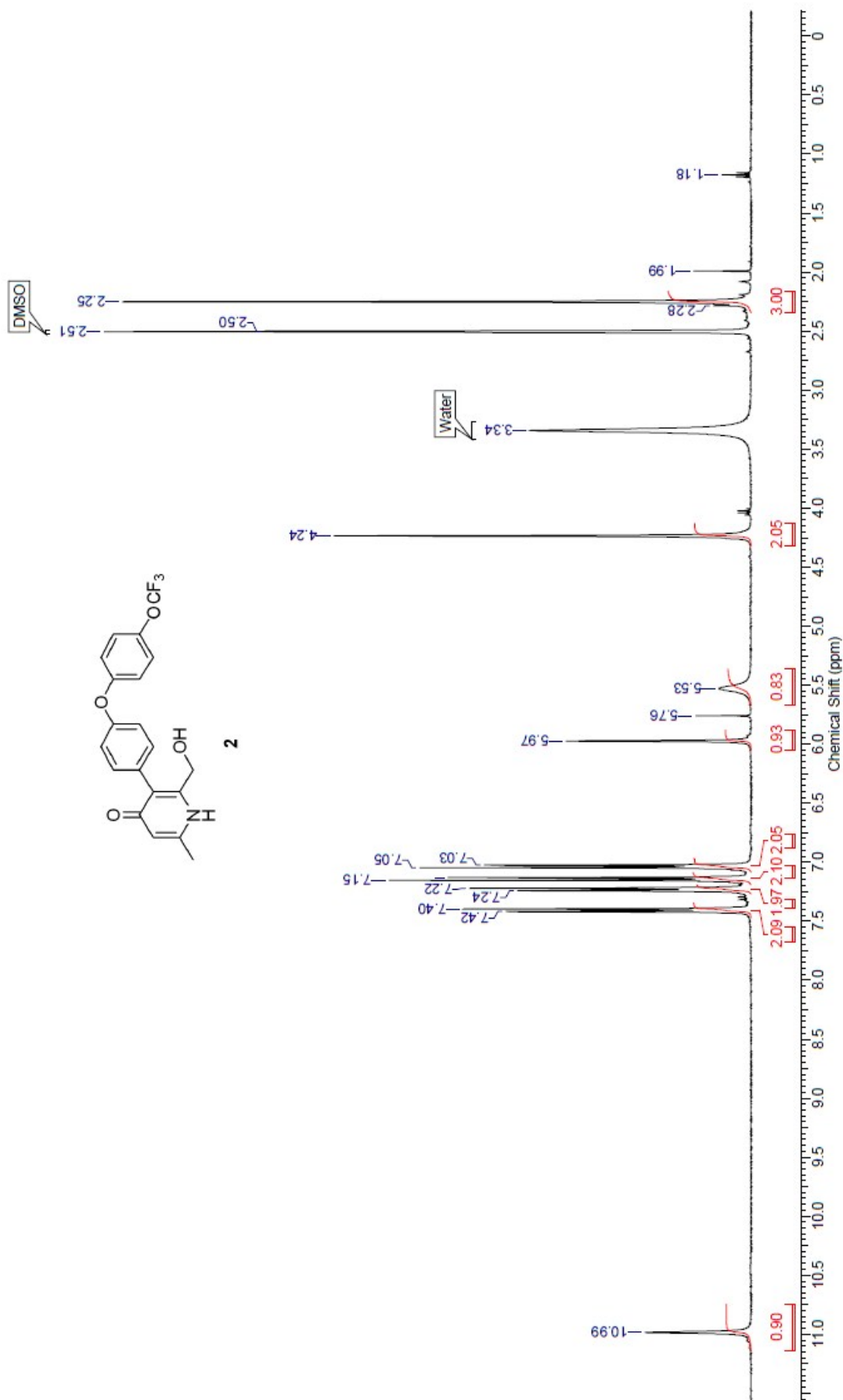
Frequency (MHz)	400.16	Nucleus	¹ H
Solvent	DMSO-d6	Spectrum Offset (Hz)	2469.0645



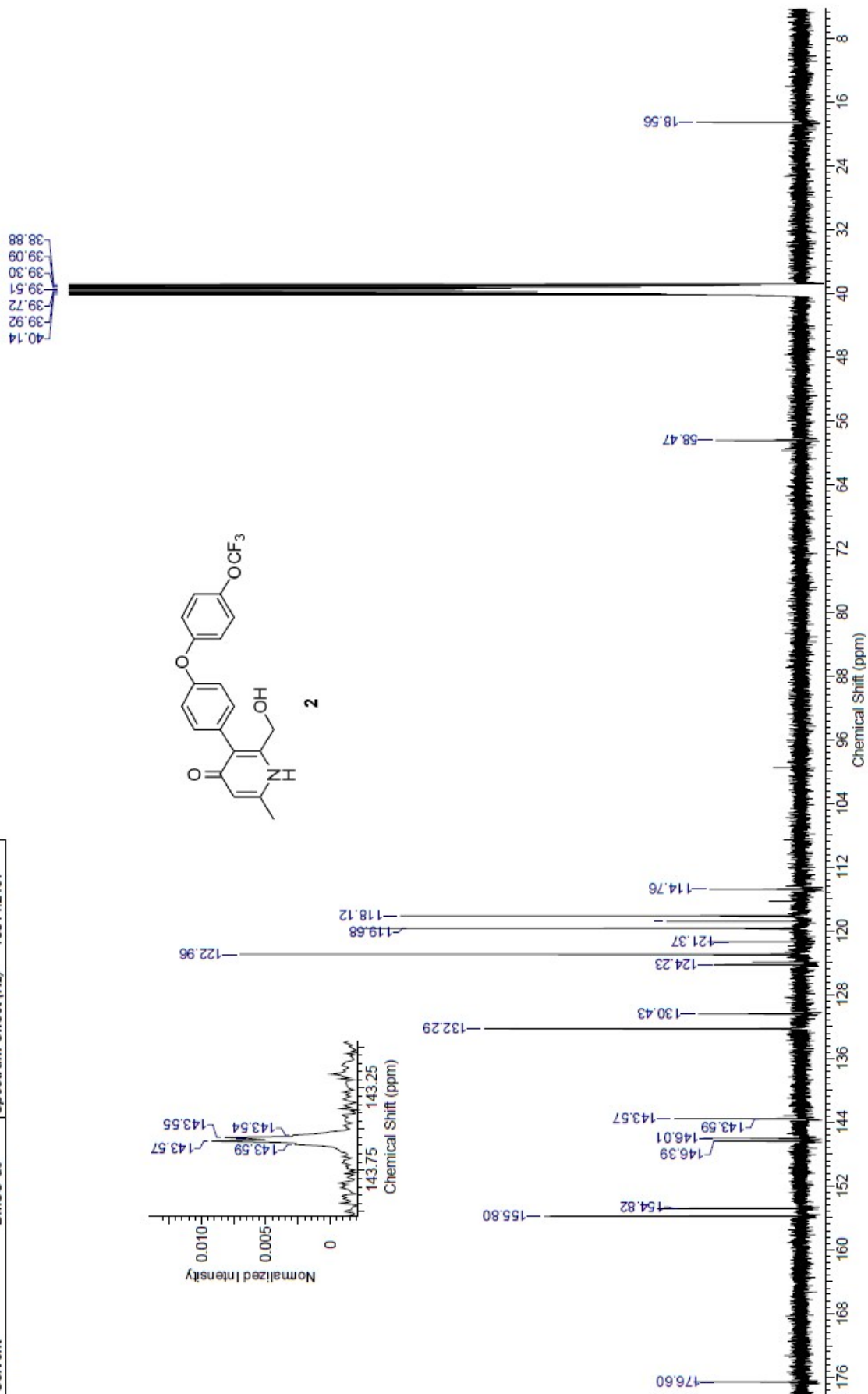
Frequency (MHz)	100.64	Nucleus	¹³ C
Solvent	DMSO-d6	Spectrum Offset (Hz)	10014.2197



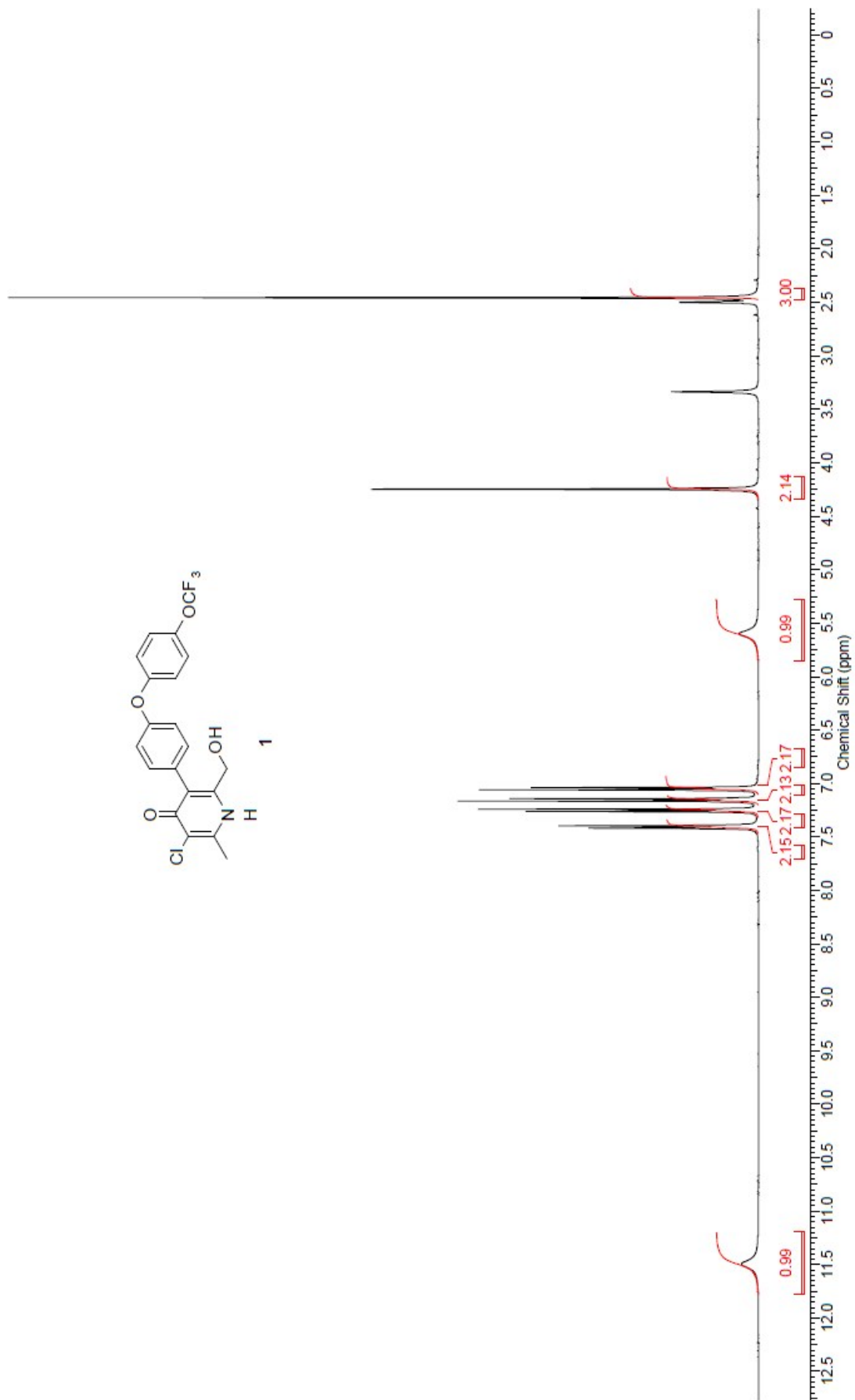
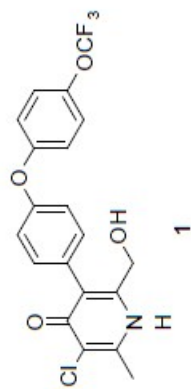
Frequency (MHz)	400.16	Nucleus	¹ H
Solvent	DMSO-d6	Spectrum Offset (Hz)	2471.1519



Frequency (MHz)	100.64	Nucleus	¹³ C
Solvent	DMSO-d6	Spectrum Offset (Hz)	10014.2197



Frequency (MHz)	400.13	Nucleus	¹ H
Solvent	DMSO-d6	Spectrum Offset (Hz)	2467.9790



Frequency (MHz)	125.77	Nucleus	13C
Solvent	DMSO-d6	Spectrum Offset (Hz)	13772.6338

