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Straightforward Synthesis of Molsidomine and Mesocarb Analogue via Mechanochemical Desymmetrization of CDI

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b) Institut Universitaire de France (IUF)

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Supporting information

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I. General information

All reagents were purchased from Sigma Aldrich, Fluorochem and Alfa Aesar and used without further purification. The mechanochemical reactions were carried out either in a vibrating Retsch Mixer Mill 400 (vbm) or in a Fritsch Pulverisette 7 Planetary Mill (pbm). In the case of liquid assisted grinding (LAG), η is defined as the ratio of added liquid volume to the total mass of reagents. It is expressed in mL/mg.

HPLC conversion was measured on an Agilent technologies 1220 Infinity LC using a Chromolith® high resolution RP-18^e 50-4.6 mm column and a linear gradient of 0 to 100% CH₃CN/0.1% TFA in H₂O/0.1% TFA over 3 min, detection at 214 nm. Flow rate : 3 mL/min.

NMR spectra were recorded on a Bruker AVANCE 400 MHz spectrometer, operating at 400.17 MHz (¹H), 376.53 MHz (¹⁹F), 161.99 (³¹P) and 100.62 MHz (¹³C). Chemical shifts are reported in parts per million (ppm) using residual solvents peaks as internal standards (CDCl₃ at 7.26 ppm for ¹H and 77.16 for ¹³C, DMSO-*d*₆ at 2.50 ppm for ¹H and 39.52 for ¹³C). Splitting patterns are reported as singlet (s), doublet (d), triplet (t), quadruplet (q), heptuplet (hept), multiplet (m) and overlap of non-equivalent resonances (m). Coupling constants are reported in Hertz (Hz).

Mass spectra were obtained by LC-MS with ESI using a Water Alliance 2695 as LC, coupled to a Waters ZQ spectrometer with electrospray source, a simple quadrupole analyzer and a UV Waters 2489 detector. High resolution MS analyses were performed on UPLC Acquity H-Class from Waters hyphenated to a Q-ToF mass spectrometer (Synapt G2-S from Waters) with a dual ESI source.

Flash chromatography was performed by using prepacked silica columns on a Biotage® Isolera™ Four system.

CDI stands for 1,1'-carbonyldiimidazole.

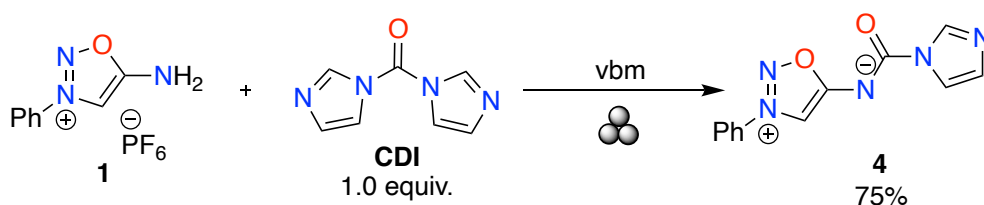
II. Optimization of mechanosynthesis of iminosydnone carbamoylimidazole **4**

The carbamoylimidazole compound **4** was prepared mechanochemically with optimization of the milling conditions. Reactions were performed in vibratory ball-mill (vbm) with 1.0 equivalent of CDI. A preliminary trial showed that grinding an equimolar mixture of ImSyd **1** and CDI in neat conditions led to the formation of the expected ImSyd-carbonylimidazole, but a significant amount of nitroso-compound coming from the ring opening of **1** was detected (**Table S1**, entry 1). Liquid Assisted Grinding (LAG) was attempted using EtOAc or MeCN, without bringing any significant improvement (**Table S1**, entry 2 and 3). Nevertheless, DMF showed a dramatic effect, allowing to reach full conversion in 30 min and minimal ring-opening at a milling frequency of 25 Hz (**Table S1** entry 4). Switching from pure DMF to a mixture DMF/MeCN (3/1) did not make any change (**Table S1**, entry 5). A milling time of only 10 min proved to be sufficient to lead the reaction to completion (**Table S1**, entry 6). However, lowering the milling frequency to 20 Hz was detrimental, as full conversion was obtained albeit with 22% of ring opening (**Table S1**, entry 7).

It is well known that CDI is prone to hydrolysis by atmospheric moisture and that commercial batches of CDI often contain a variable proportion of imidazole.¹ The presence of this basic molecule in the highly concentrated medium of the milling jar might explain the undesired ring opening. Indeed, when carried out in solution in our hands, the reaction did not yield any ring opening product. This could be explained by the fact that in diluted dry solvent, a low amount of imidazole does not react with the starting material and that the nucleophilic attack of ImSyd **1** on CDI can occur smoothly. Our hypothesis was confirmed when we reproduced the experiment in tuned conditions with a brand-new batch of CDI. In this case, no nitroso by-product was detected by HPLC and the ImSyd-carbonylimidazole **4** was obtained after only 10 min of milling, with a similar yield as in solution (**Table S1**, entry 8).

¹ Engstrom, K. M.; Sheikh, A.; Ho, R.; Miller, R. W. *Org. Process Res. Dev.* **2014**, *18*, 488-494.

Table S1 Preparation of ImSyd carbonylimidazole via ball milling



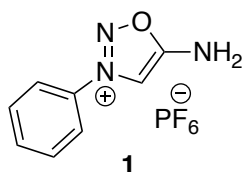
Entry	Liquid Additive ^a	Milling frequency (Hz)	Milling time (min)	Conversion (%) ^b	Ring opening (%) ^b	Yield (%)
1	–	30	60	80	20	n.d. ^c
2	EtOAc	30	3x30	96	35	n.d. ^c
3	MeCN	30	60	85	20	n.d. ^c
4	DMF	25	30	100	2	70
5	DMF/MeCN (3/1)	25	30	100	2	70
6	DMF/MeCN (3/1)	25	10	100	2	70
7	DMF	20	60	100	22	n.d. ^c
8 ^c	DMF	25	10	100	0	75

^a Ratio η=0,5 μL/mg of reagents. ^bdetermined by HPLC. ^c n.d.: not determined. ^dNew batch of CDI.

Note : reaction in solution in DMF/MeCN (3/1), 1.1 equiv. of CDI, r.t., 90 min : 100% conversion, no ring opening, 74% yield.

III. Synthetic procedures and analytical data

5-amino-3-phenyl-1,2,3-oxadiazolium hexafluorophosphate (1)



Chemical Formula: C₈H₈N₃OPF₆
Molecular weight: 307.14
CAS number: 4340-63-0 (neutral)

In a 10 mL stainless steel grinding jar with 1 ball of the same material (10 mm diameter) were introduced 2-(phenylethylamino)acetonitrile (133 mg, 1.0 mmol, 1 equiv.), sodium hydrogenosulfate (720 mg, 6 mmol, 6 equiv.) and sodium nitrite (70 mg, 1.0 mmol, 1 equiv.). The jar was closed and submitted to vibratory milling at 30 Hz for 60 min. Potassium hexafluorophosphate (190 mg, 1.0 mmol, 1.0 equiv.) was added to the reaction mixture which was ground again at 30 Hz for 60 min. The resulting powder was suspended in EtOAc and filtered over a pad of Celite. The filtrate was concentrated *under vacuum* to yield the expected iminosydnone hexafluorophosphate salt **1** as a beige powder (287 mg, 0.93 mmol, 93%).

¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 7.76-7.86 (m, 3H), 8.02-8.04 (m, 2H), 8.60 (s, 1H), 9.69 (s, 2H).

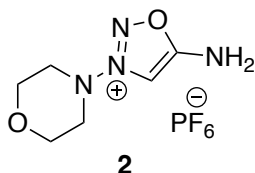
¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): 102.5, 122.8 (2C), 130.4 (2C), 132.8, 133.7, 169.5.

¹⁹F NMR (376 MHz, DMSO-d₆) δ (ppm): -70.2, (d, J = 711 Hz).

³¹P NMR (162 MHz, DMSO-d₆) δ (ppm): -144.0 (hept, J = 711 Hz).

LCMS (ESI) *m/z*: 162 [M-PF₆]⁺.

5-amino-3-(4-morpholinyl)-1,2,3-oxadiazolium hexafluorophosphate (2)



Chemical Formula: C₆H₁₁N₄O₂PF₆
Molecular Weight: 316.14
CAS number: 33876-97-0 (neutral)

Method A: in a 10 mL zirconium oxide grinding jar with 2 balls of the same material (10 mm diameter) were introduced 2-(4-morpholinylamino)acetonitrile (199 mg, 1.4 mmol, 1 equiv.), sodium hydrogenosulfate (1010 mg, 8.4 mmol, 6 equiv.) and sodium nitrite (109 mg, 1.54 mmol, 1.1 equiv.). The jar was closed and submitted to vibratory milling at 30 Hz for 60 min. Potassium hexafluorophosphate (260 mg, 1.4 mmol, 1 equiv.) was added to the reaction mixture which was ground again at 30 Hz for 60 min. The resulting solid was suspended in EtOAc and filtered over a pad of Celite. The filtrate was concentrated *under vacuum* to yield the expected iminosydnone hexafluorophosphate salt **2** as a yellow solid (399 mg, 1.26 mmol, 90%).

¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 3.60 (t, J = 4.7 Hz, 4H), 3.87 (t, J = 4.7 Hz, 4H), 8.19 (s, 1H), 9.35 (s, 2H).

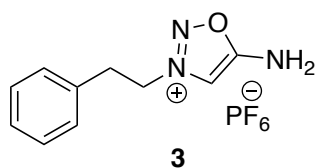
¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): 53.4 (2C), 64.6 (2C), 96.5, 168.5.

¹⁹F NMR (376 MHz, DMSO-d₆) δ (ppm): -70.2, (d, J = 711 Hz).

³¹P NMR (162 MHz, DMSO-d₆) δ (ppm): -144.0 (hept, J = 711 Hz).

LCMS (ESI) *m/z*: 171 [M-PF₆]⁺.

5-amino-3-(2-phenylethyl)-1,2,3-oxadiazolium hexafluorophosphate (**3**)



Chemical Formula: C₁₀H₁₂N₃OPF₆
Molecular Weight: 335.19
CAS number: 22293-46-5 (neutral)

In a 10 mL zirconium oxide grinding jar with 1 ball of the same material (12 mm diameter) were introduced 2-[(2-phenylethyl)amino]acetonitrile (133 mg, 0.83 mmol, 1 equiv.), sodium hydrogenosulfate (600 mg, 5.0 mmol, 6 equiv.) and sodium nitrite (70 mg, 1.0 mmol, 1.2 equiv.). The jar was closed and submitted to vibratory milling at 30 Hz for 90 min. Potassium hexafluorophosphate (156 mg, 0.83 mmol, 1 equiv.) was added to the reaction mixture which was ground again at 30 Hz for 90 min. The resulting powder was suspended in EtOAc and filtered over a pad of Celite. The filtrate was concentrated *under vacuum* to yield the expected iminosydnone hexafluorophosphate salt **3** as an off-white powder (260 mg, 0.77 mmol, 93%).

¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 3.30 (t, *J* = 7.2 Hz, 2H), 4.91 (t, *J* = 7.2 Hz, 2H), 7.25-7.36 (m, 5H), 7.97 (s, 1H), 9.43 (s, 2H).

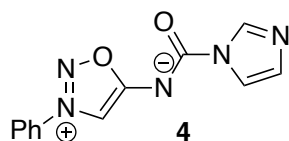
¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): 33.8, 54.4, 102.8, 127.2, 128.7 (2C), 128.8 (2C), 135.8, 169.0.

¹⁹F NMR (376 MHz, DMSO-d₆) δ (ppm): -70.2, (d, *J* = 711 Hz).

³¹P NMR (162 MHz, DMSO-d₆) δ (ppm): -144.0 (hept, *J* = 711 Hz).

LCMS (ESI) *m/z*: 190 [M-PF₆]⁺.

5-[(1*H*-imidazol-1-ylcarbonyl)amino]-3-phenyl-1,2,3-oxadiazolium (**4**)



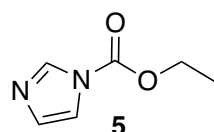
Chemical Formula: C₁₂H₉N₅O₂
Molecular Weight: 255.24
CAS number: 2413631-96-4

In a 10 mL stainless steel grinding jar with 1 ball of the same material (10 mm diameter) were introduced N-phenyliminosydnone **1** (109 mg, 0.35 mmol), CDI (58 mg, 0.35 mmol, 1 equiv.) and DMF as a liquid additive (67 mL, *h* = 0.4 mL/mg of solid reagent). The jar was closed and submitted to vibratory milling at 25 Hz for 10 min. The reaction mixture was recovered with MeCN, filtered over cotton and the solvent was evaporated *under vacuum*. The crude product was purified by flash chromatography on silica (eluent DCM/MeOH 100/0 to 97/3) to afford the expected compound **4** as an off-white solid (67 mg, 0.26 mmol, 75%).

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.06 (s, 1H), 7.65 (br s, 1H), 7.68-7.73 (m, 2H), 7.77 (m, 1H), 7.86-7.88 (m, 2H), 8.44 (s, 1H), 8.46 (s, 1H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 104.6, 117.5, 121.7 (2C), 129.3, 130.9 (2C), 133.6, 133.8, 137.5, 154.6, 175.1.

1-(Ethoxycarbonyl)imidazole (**5**)



Chemical Formula: C₆H₈N₂O₂
Molecular Weight: 140.14
CAS number: 19213-72-0

In a 10 mL zirconium oxide grinding jar with 1 ball of the same material (12 mm diameter) were introduced CDI (414 mg, 2.55 mmol, 1.2 equiv.) and ethanol (98 mg, 2.13 mmol, 1.0 equiv.). The jar

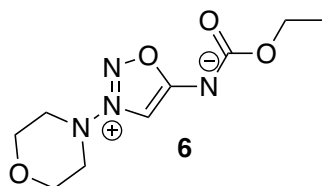
was closed and submitted to vibratory milling at 25 Hz for 30 min. The reaction mixture was recovered and diluted with EtOAc, washed with 0.5 M aqueous HCl, water and brine. After drying over MgSO₄, filtration and evaporation of the solvent under *vacuum*, the expected carbamate was obtained as a colourless oil (240 mg, 1.71 mmol, 80%) without need of further purification.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 1.43 (t, *J* = 7.1 Hz, 3H), 4.47 (q, *J* = 7.1 Hz, 2H), 7.06 (s, 1H), 7.42 (s, 1H), 8.13 (s, 1H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 14.2, 64.5, 117.2, 130.6, 137.2, 148.8.

LCMS (ESI) *m/z*: 141 [M+H]⁺.

5-[(Ethoxycarbonyl)amino]-3-(4-morpholinyl)-1,2,3-oxadiazolium (Molsidomine 6)



Chemical Formula: C₉H₁₄N₄O₄

Molecular Weight: 242.23

CAS number: 25717-80-0

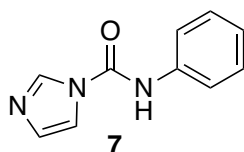
In a 20 mL zirconium oxide grinding jar with 80 balls of the same material (5 mm diameter) were introduced iminosynone salt **2** (400 mg, 1.26 mmol, 1 equiv.) and 1-(ethoxycarbonyl)imidazole **5** (213 mg, 1.52 mmol, 1.2 equiv.). EtOAc (200 mL, *h* = 0.5 mL/mg of solid reagent) was added in the jar as a liquid additive. The jar was closed and submitted to planetary milling at 600 rpm for 12x45 min with 30 min pause between each cycle. The reaction mixture (yellow oil) was recovered and diluted with EtOAc, then the solvent was removed under *vacuum*. The residue was purified by flash chromatography on silica (cyclohexane/EtOAc 90/10 to 0/100) to yield molsidomine **6** as a white solid (198 mg, 0.82 mmol, 65%).

¹H NMR (400 MHz, CDCl₃) δ (ppm): 1.30 (t, *J* = 7.1 Hz, 3H), 3.51 (t, *J* = 4.7 Hz, 4H), 3.96 (t, *J* = 4.7 Hz, 4H), 4.16 (q, *J* = 7.1 Hz, 2H), 7.70 (s, 1H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 14.6, 54.8 (2C), 61.5, 65.6 (2C), 99.2, 161.7, 174.3.

LCMS (ESI) *m/z*: 243 [M+H]⁺.

1-(Phenylcarbamoyl)imidazole (7)



Chemical Formula: C₁₀H₉N₃O

Molecular Weight: 187.20

CAS number: 33876-94-7

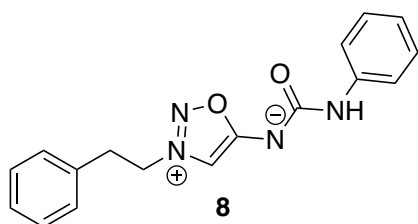
In a 10 mL zirconium oxide grinding jar with 1 ball of the same material (12 mm diameter) were introduced aniline (140 mg, 1.5 mmol, 1 equiv.), sodium chloride (870 mg, 15 mmol, 10 equiv.) and CDI (292 mg, 1.80 mmol, 1.2 equiv.). The jar was closed and submitted to vibratory milling at 30 Hz for 30 min. The reaction mixture was recovered with cold water and the suspension was filtered on sintered glass. The solid was dried over P₂O₅ under *vacuum* to yield a white powder (290 mg), containing 92% mass. of **7**. The product was used as it is for the next step.

¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 7.09 (s, 1H), 7.17 (m, 1H), 7.40 (m, 2H), 7.65 (d, 2H), 7.87 (s, 1H), 8.44 (s, 1H), 10.39 (s, 1H).

¹³C NMR (100 MHz, DMSO-*d*₆) δ (ppm): 117.2, 121.1, 124.6, 128.8, 129.6, 136.5, 137.5, 147.0.

LCMS (ESI) *m/z*: not stable in the conditions of ionization.

5-[[[(Phenylamino)carbonyl]amino]-3-(2-phenylethyl)-1,2,3-oxadiazolium (Sydnocarb analog **8**)



Chemical Formula: C₁₇H₁₆N₄O₄

Molecular Weight: 308.34

CAS number: 17589-96-7

In a 10 mL zirconium oxide grinding jar with 1 balls of the same material (12 mm diameter) were introduced iminosydnone salt **3** (225 mg, 0.67 mmol, 1 equiv.) and 1-phenylcarbamoyleimidazole **7** (170 mg, 1.84 mmol, 1.25 equiv.). EtOAc (120 mL, h = 0.3 mL/mg of solid reagent) was added in the jar as a liquid additive. The jar was closed and submitted to vibratory milling at 30 Hz for 60 min. The reaction mixture (yellow oil) was recovered and diluted with EtOAc and the solution was washed with water and brine. After drying over MgSO₄ and filtration, the solvent was removed under *vacuum* and the residue purified by flash chromatography on silica (cyclohexane/EtOAc 100/0 to 30/70) to yield the expected compound **8** as an off-white solid (156 mg, 0.50 mmol, 75%).

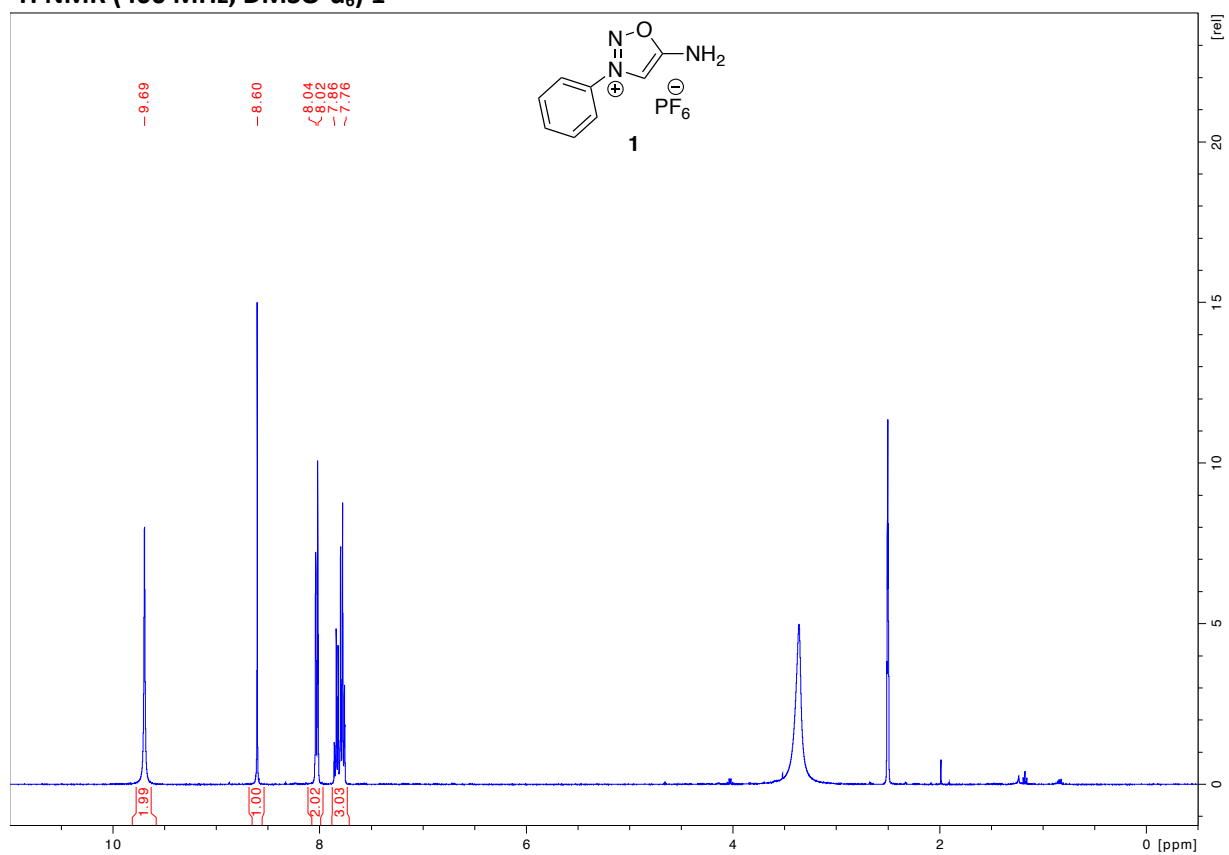
¹H NMR (400 MHz, CDCl₃) δ (ppm): 3.28 (t, *J* = 7.4 Hz, 2H), 4.56 (t, *J* = 7.4 Hz, 2H), 7.00 (t, *J* = 7.4 Hz, 1H), 7.15 (m, 2H), 7.26-7.36 (m, 6H), 7.49 (m, 2H), 7.81 (s, 1H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 35.2, 54.4, 103.9, 118.9 (2C), 122.7, 128.1, 128.6 (2C), 129.0 (2C), 129.4 (2C), 134.6, 139.6, 159.5, 173.2.

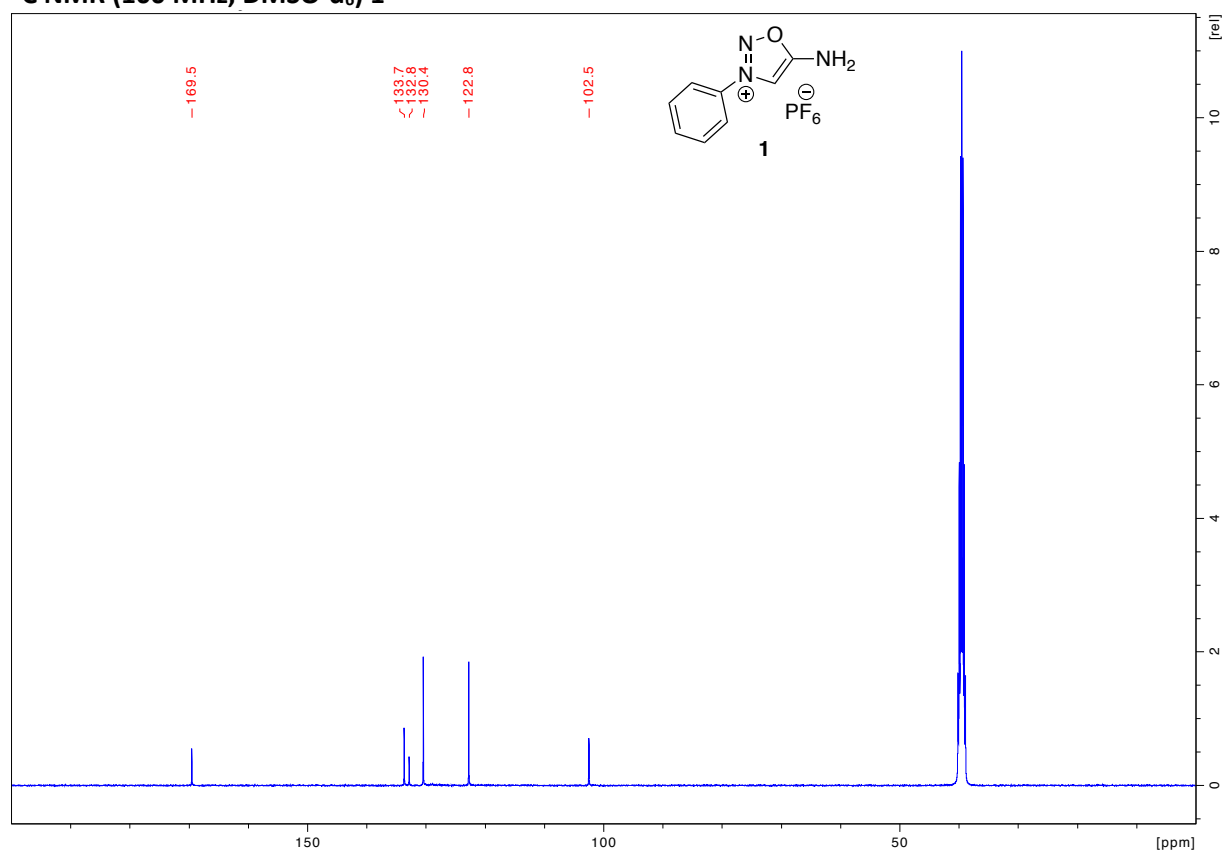
LCMS (ESI) *m/z*: 309 [M+H]⁺.

IV. NMR spectra

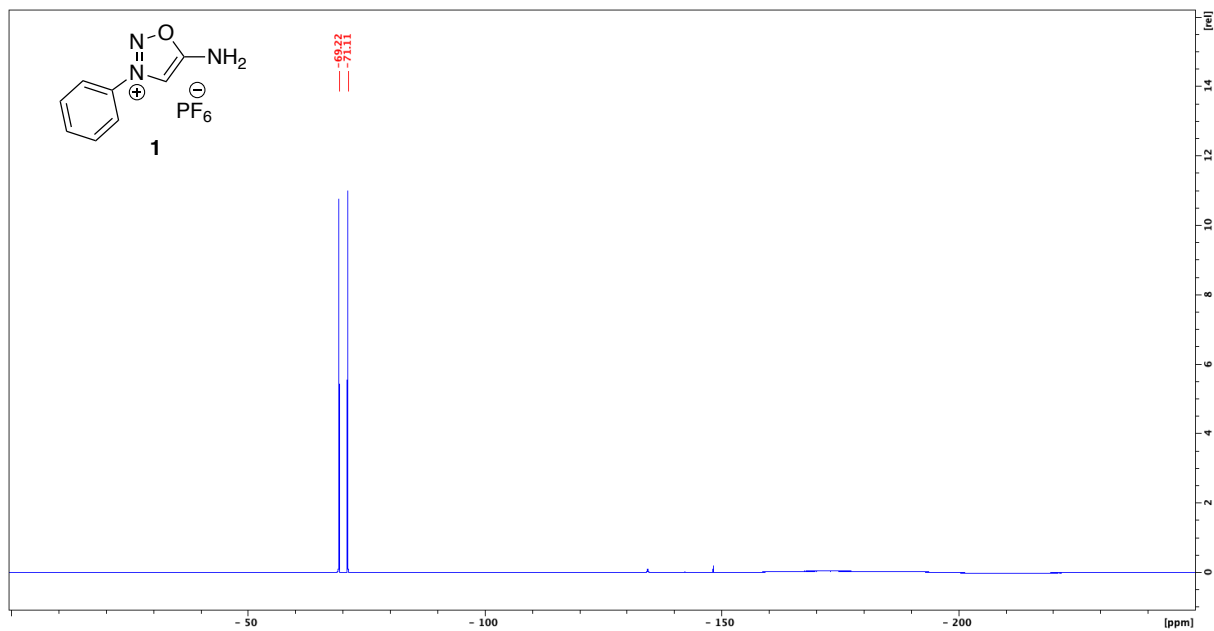
^1H NMR (400 MHz, DMSO- d_6) **1**



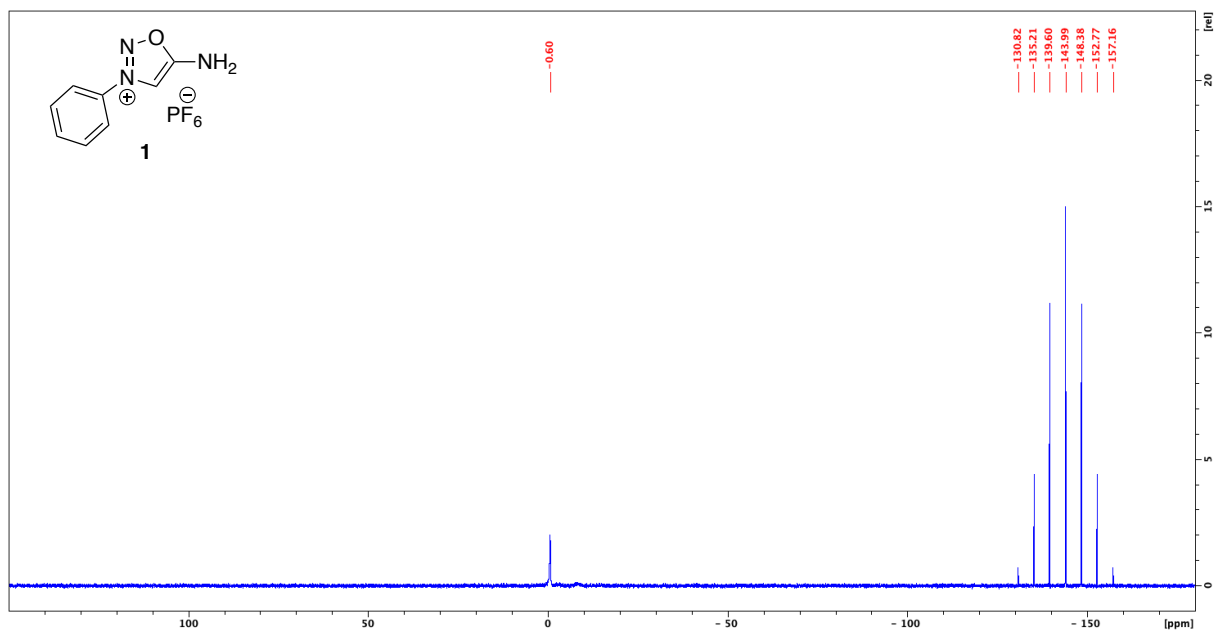
^{13}C NMR (100 MHz, DMSO- d_6) **1**



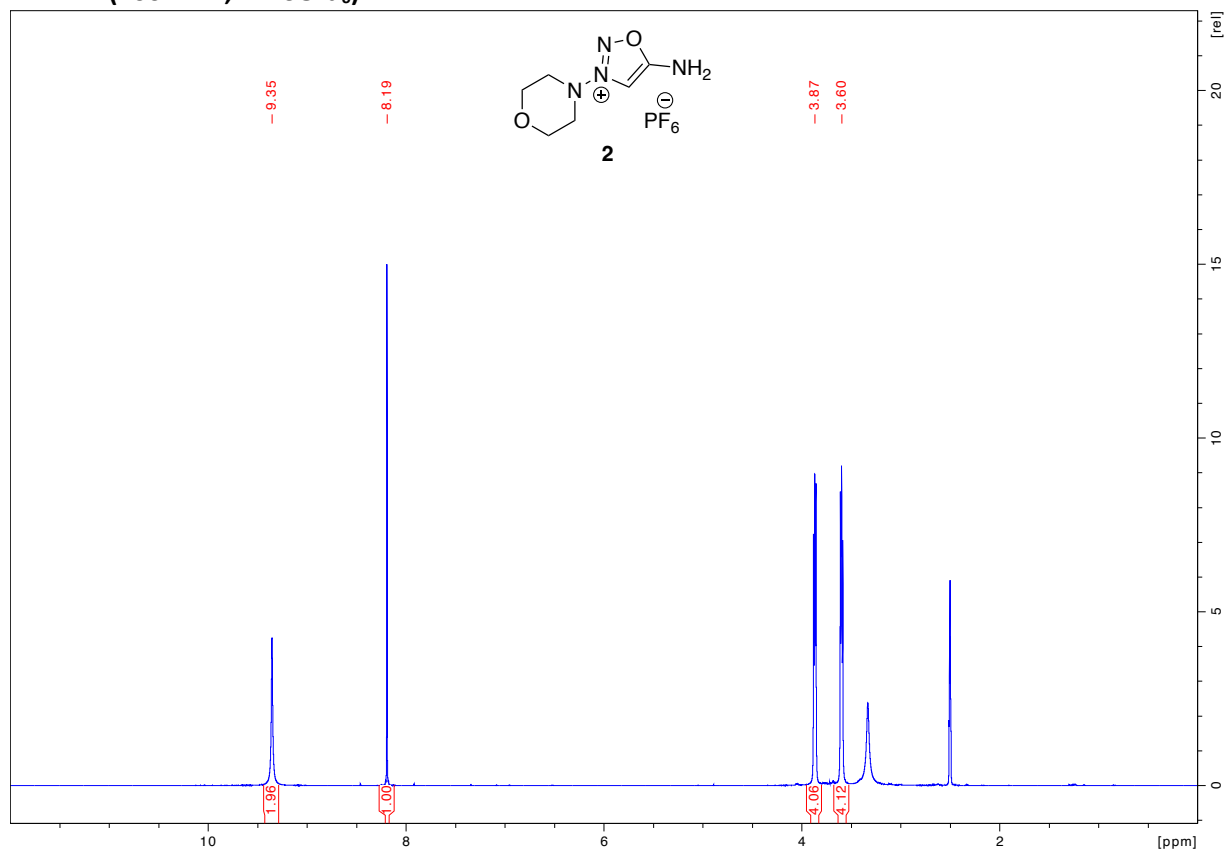
¹⁹F NMR (376 MHz, DMSO-d₆) 1



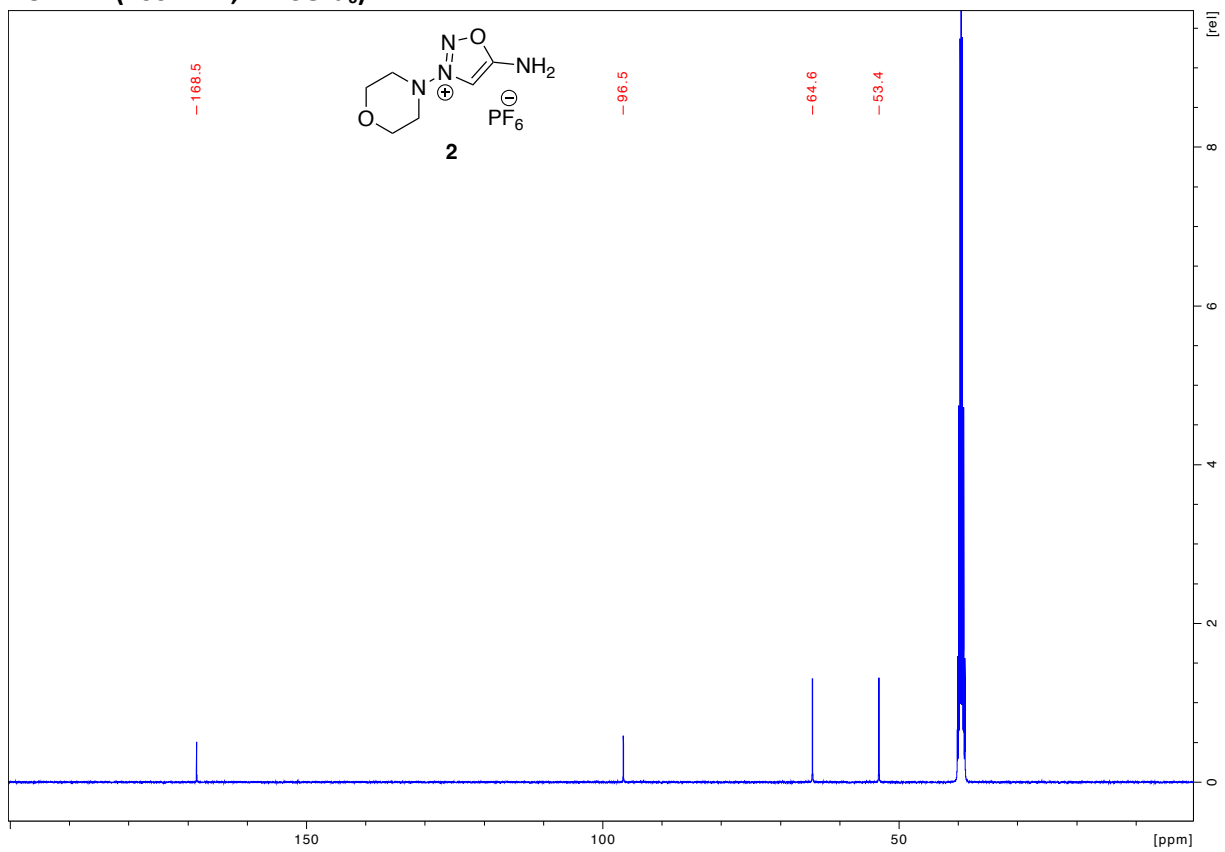
³¹P NMR (162 MHz, DMSO-d₆) 1



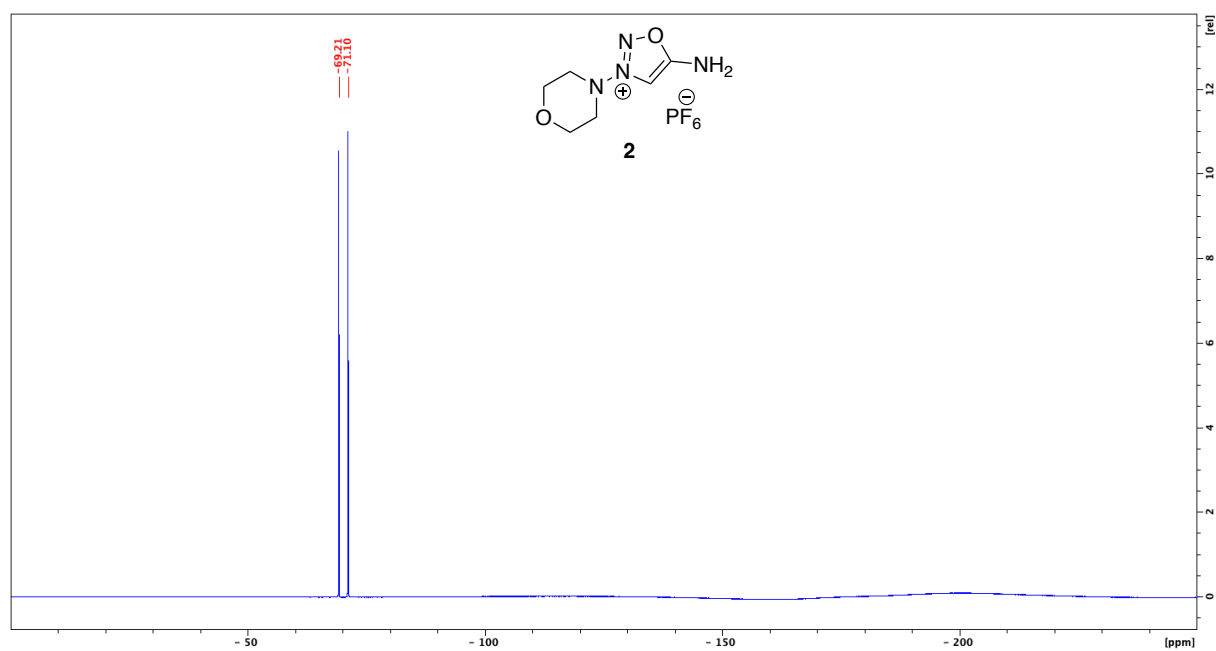
¹H NMR (400 MHz, DMSO-d₆) 2



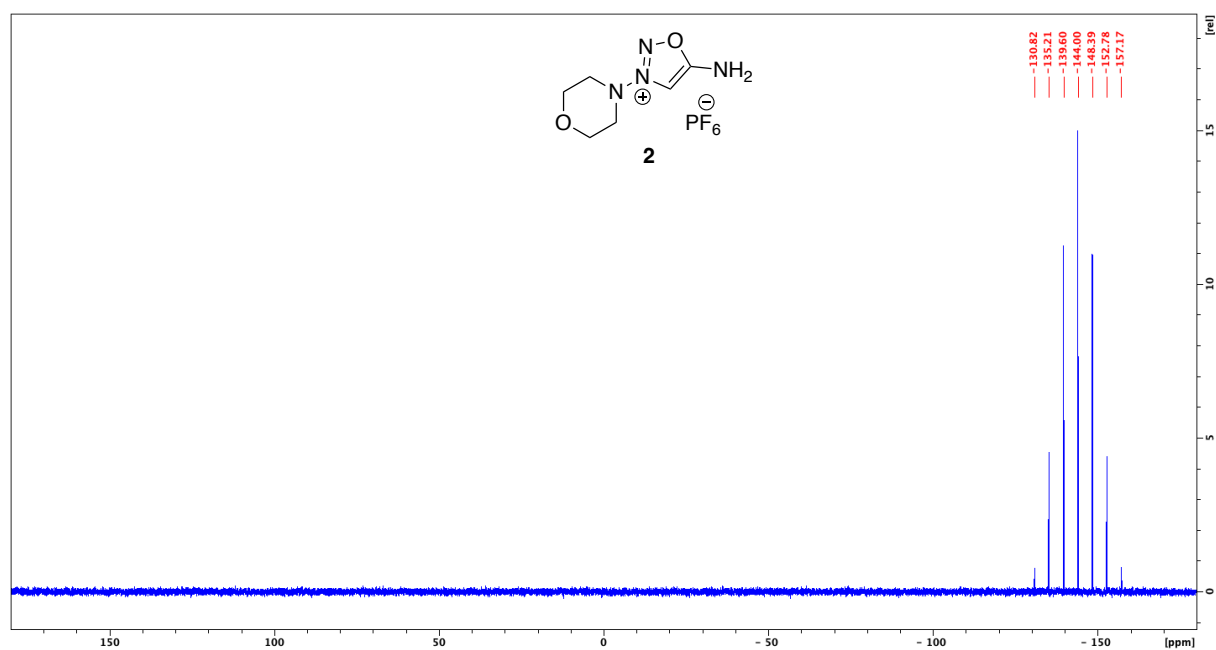
¹³C NMR (100 MHz, DMSO-d₆) 2



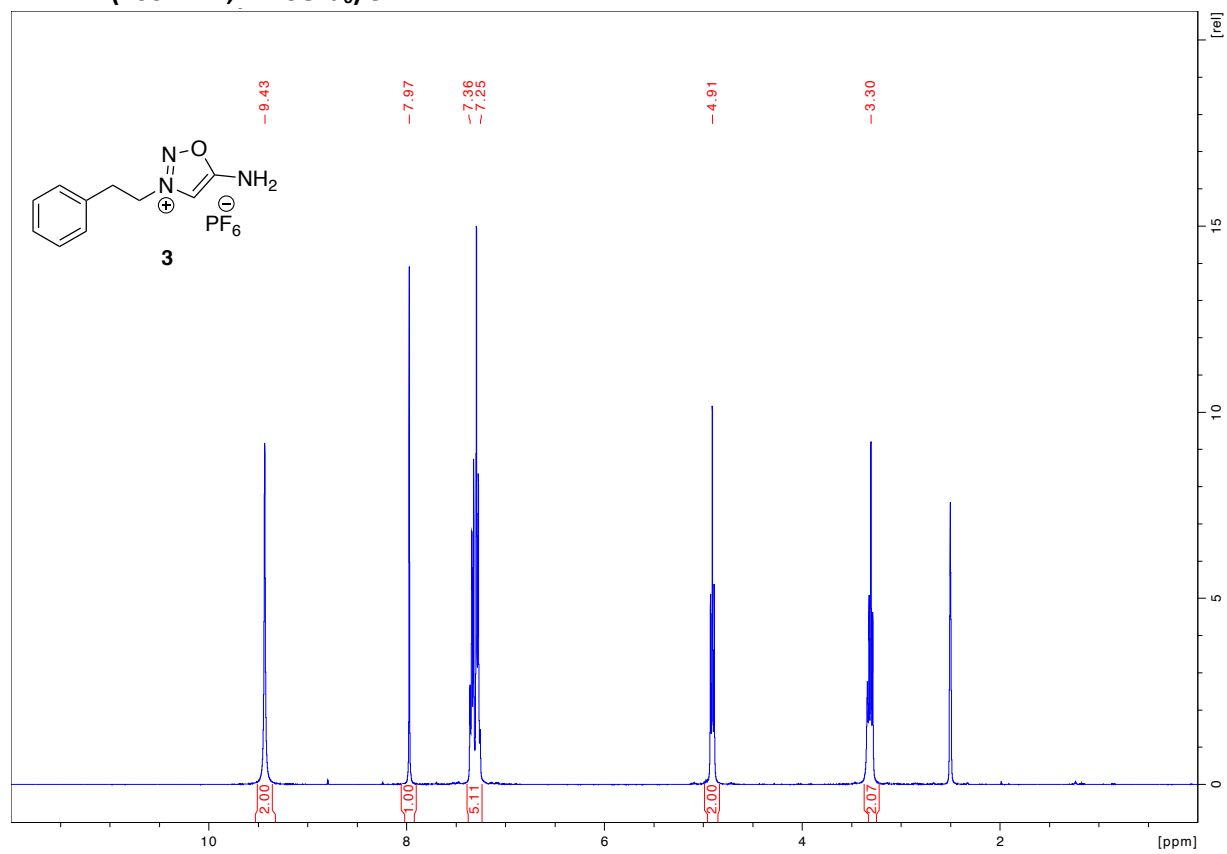
¹⁹F NMR (376 MHz, DMSO-d₆) 2



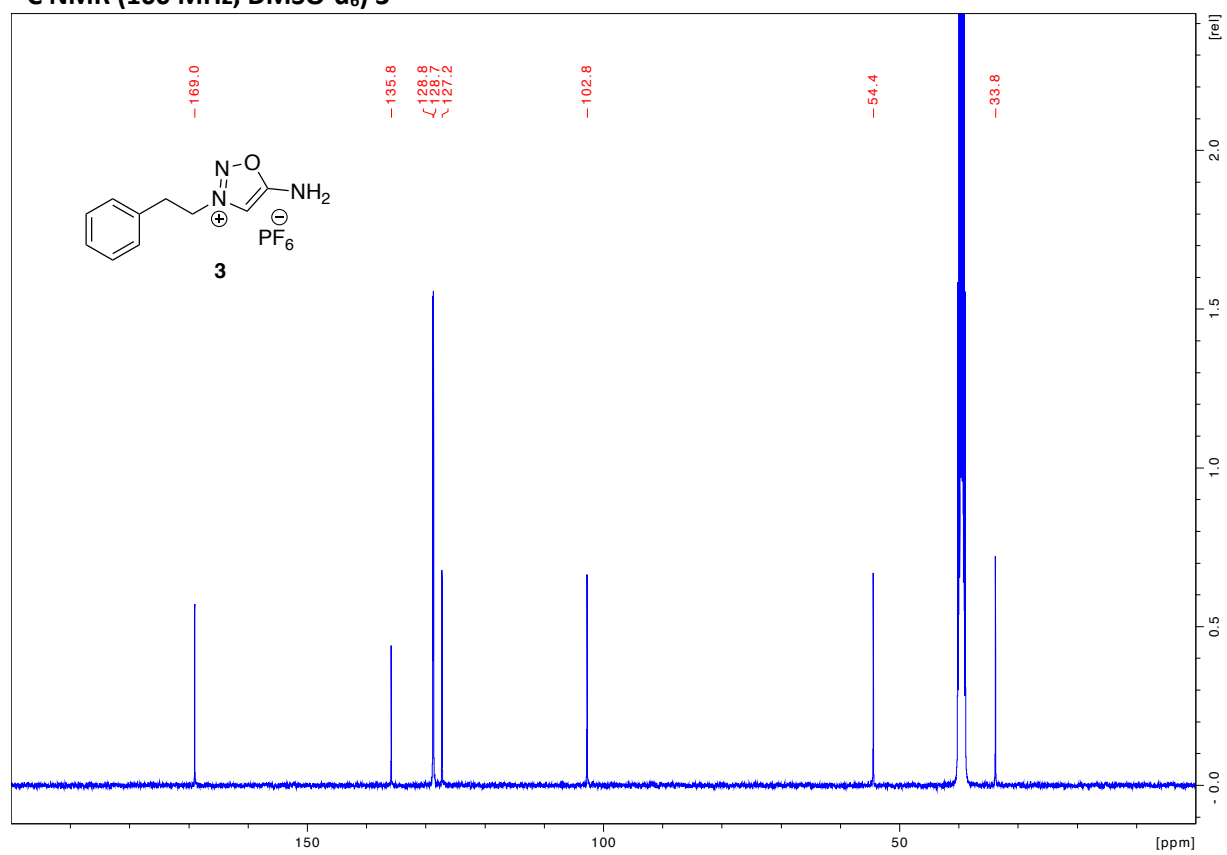
³¹P NMR (162 MHz, DMSO-d₆) 2



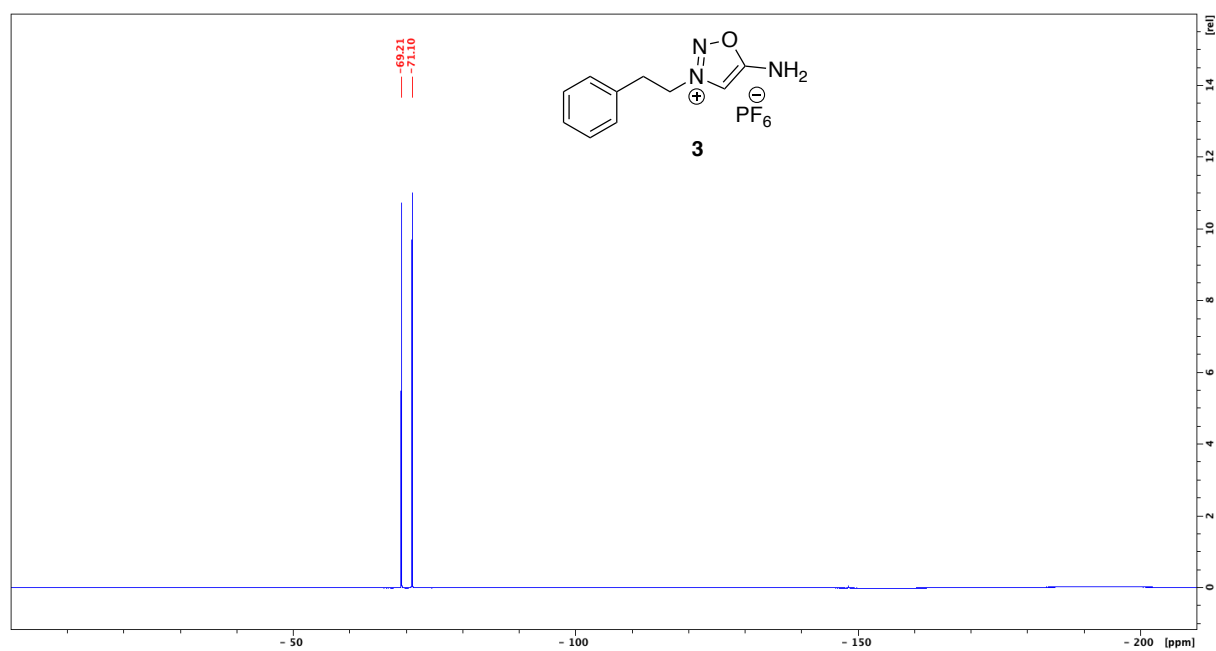
¹H NMR (400 MHz, DMSO-d₆) 3



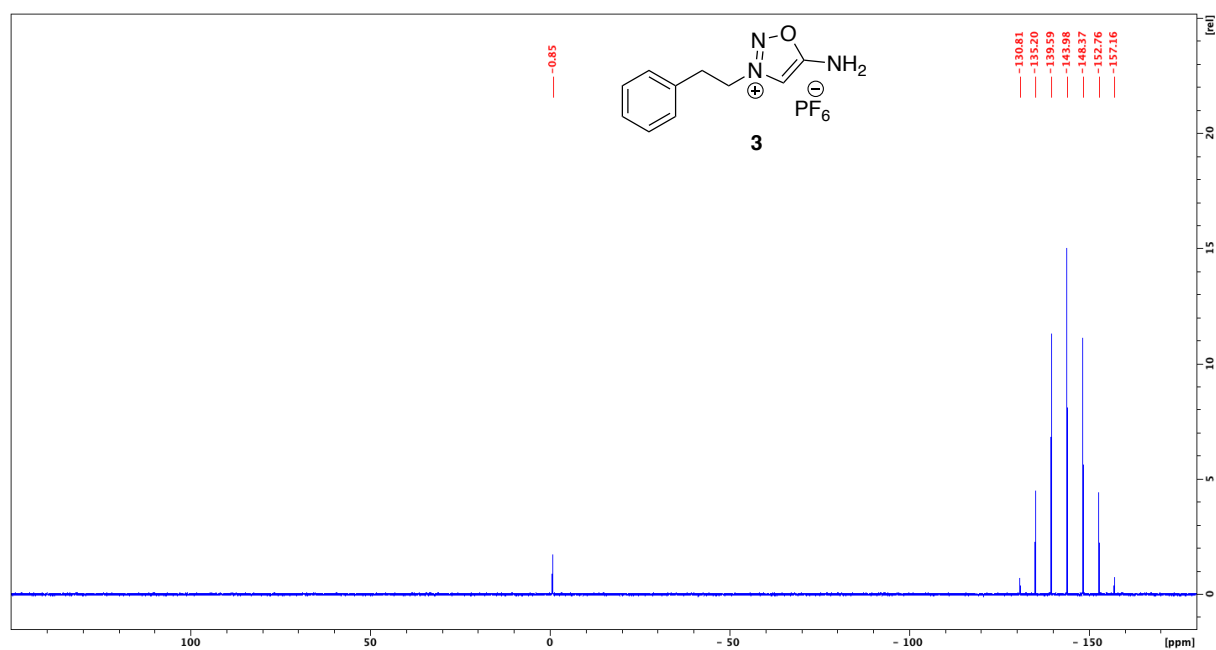
¹³C NMR (100 MHz, DMSO-d₆) 3



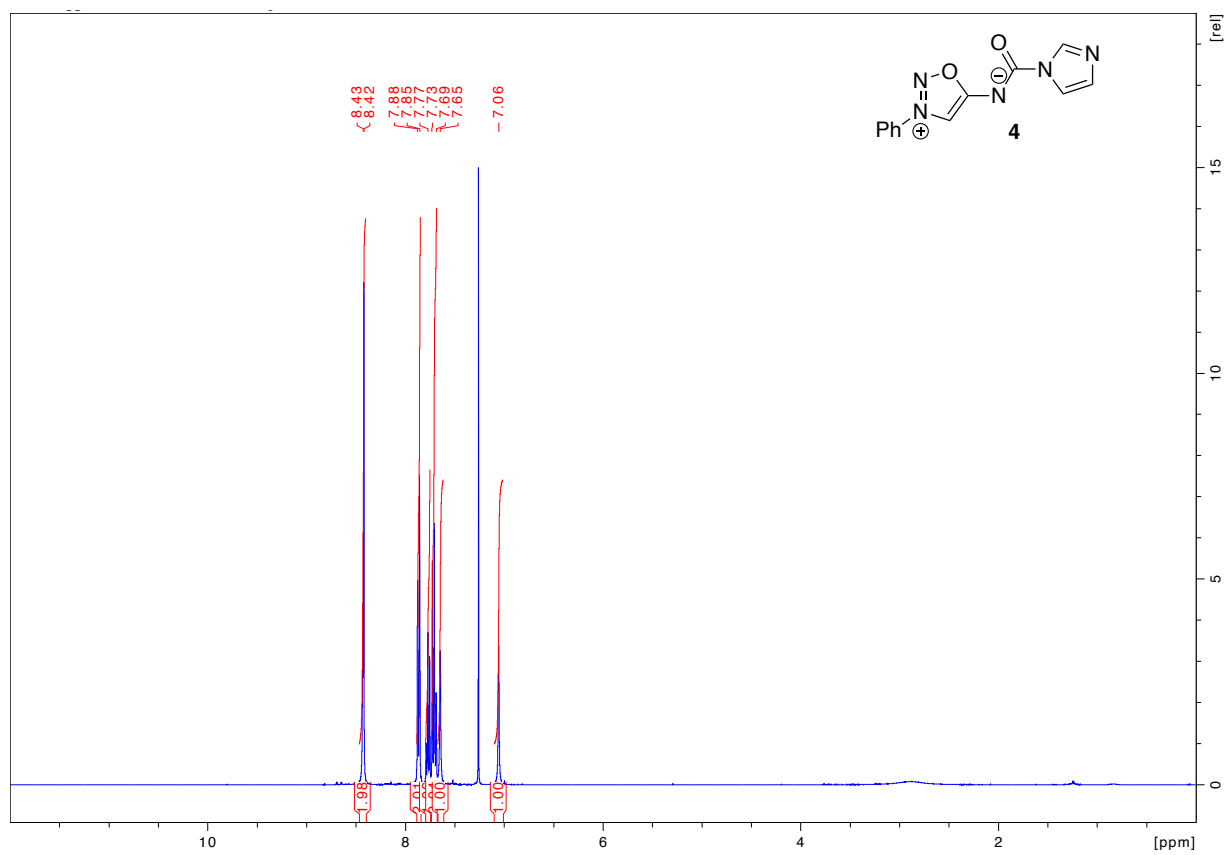
¹⁹F NMR (376 MHz, DMSO-d₆) 3



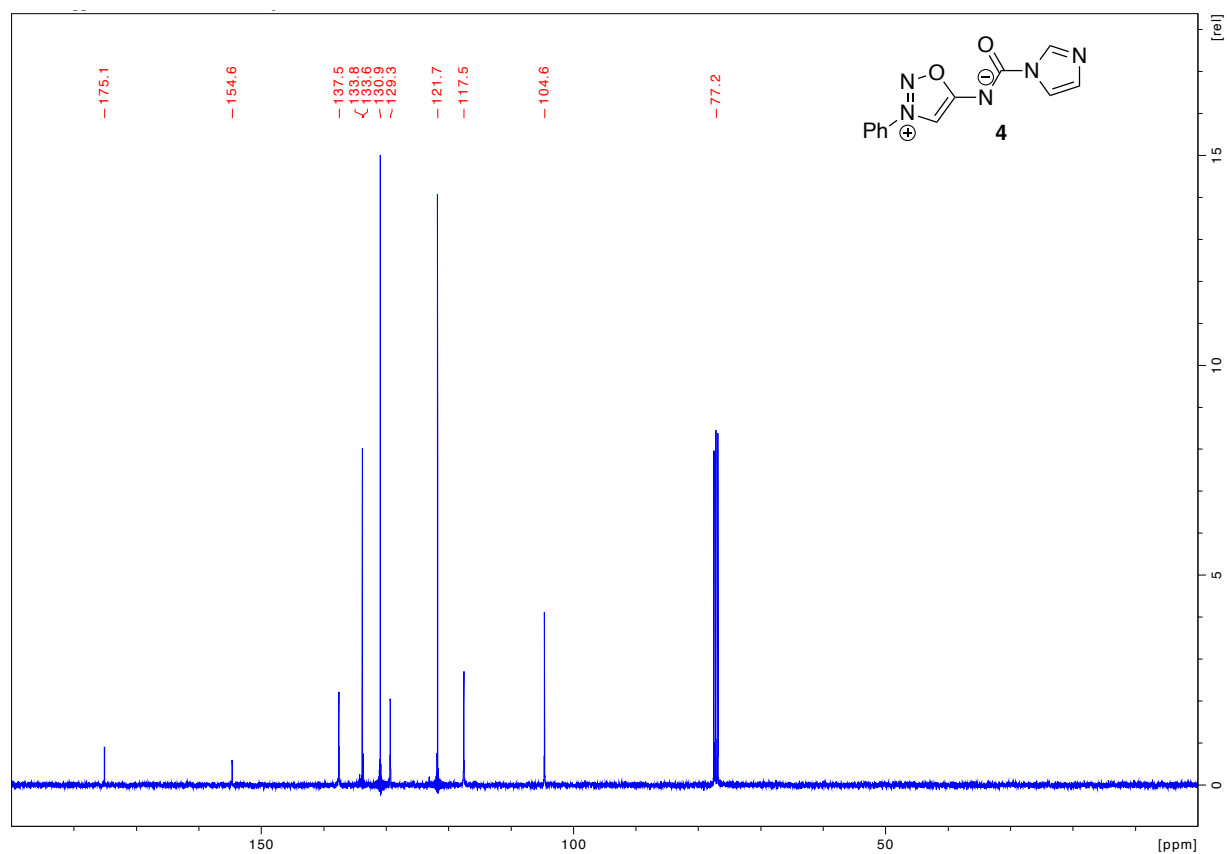
³¹P NMR (162 MHz, DMSO-d₆) 3



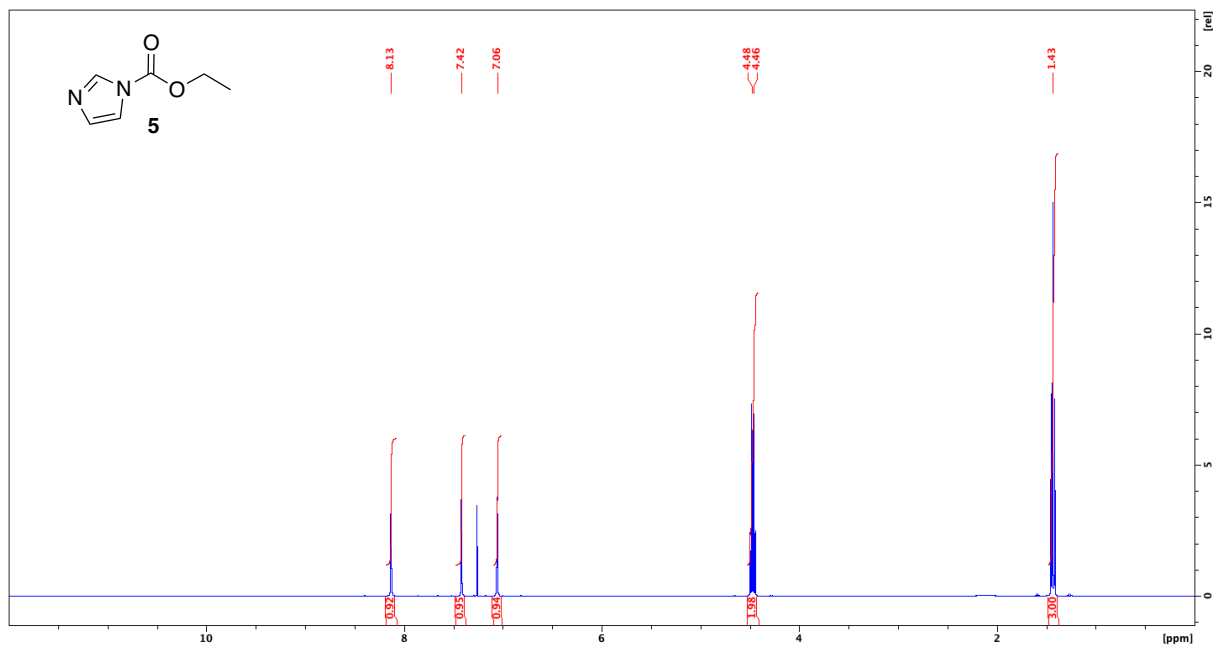
¹H NMR (400 MHz, CDCl₃) 4



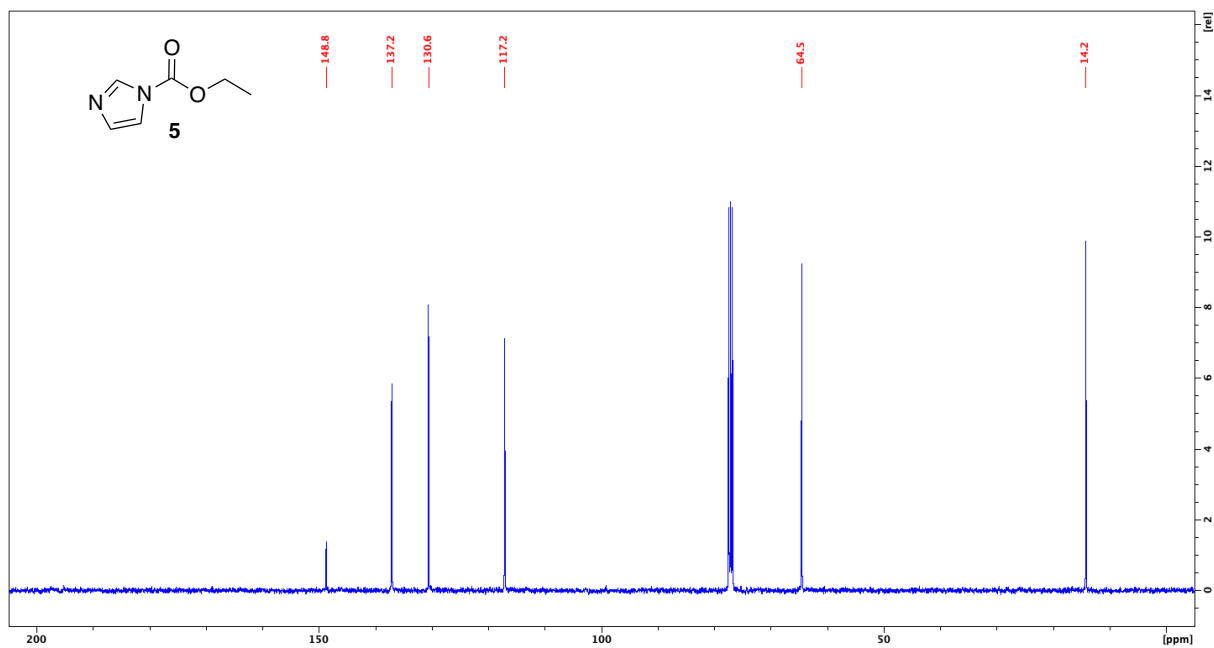
¹³C NMR (100 MHz, CDCl₃) 4



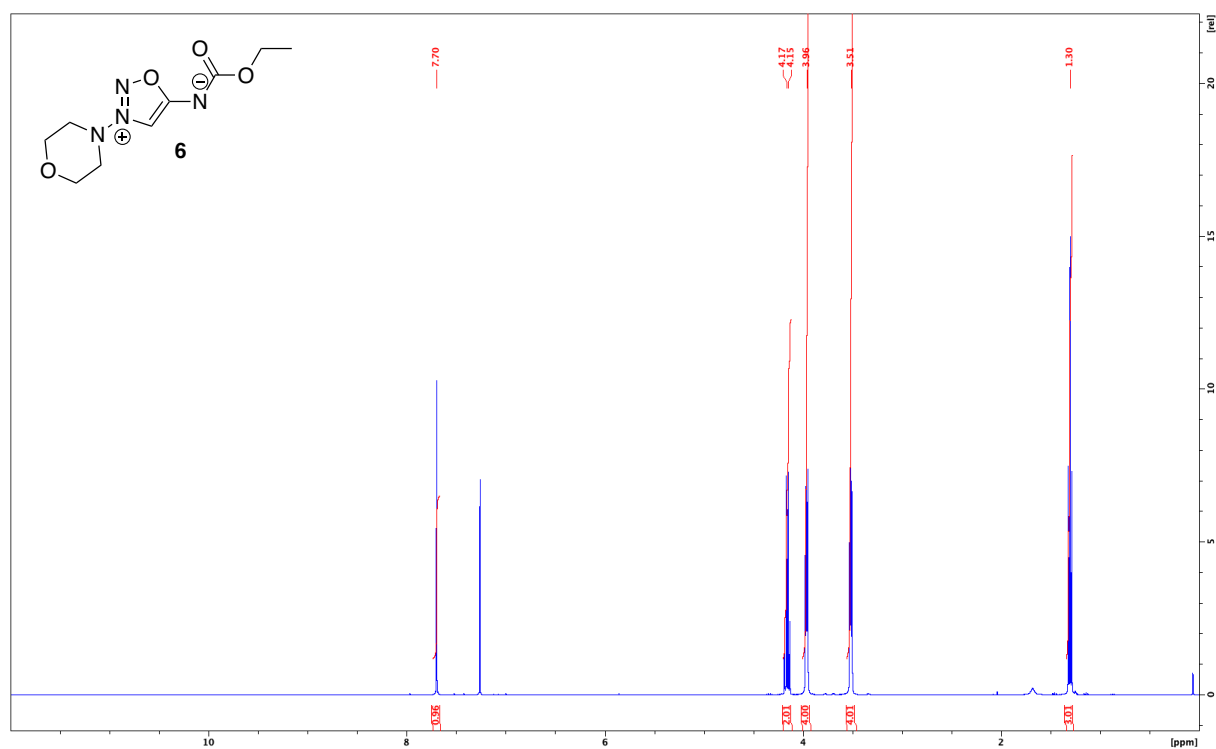
¹H NMR (400 MHz, CDCl₃) 5



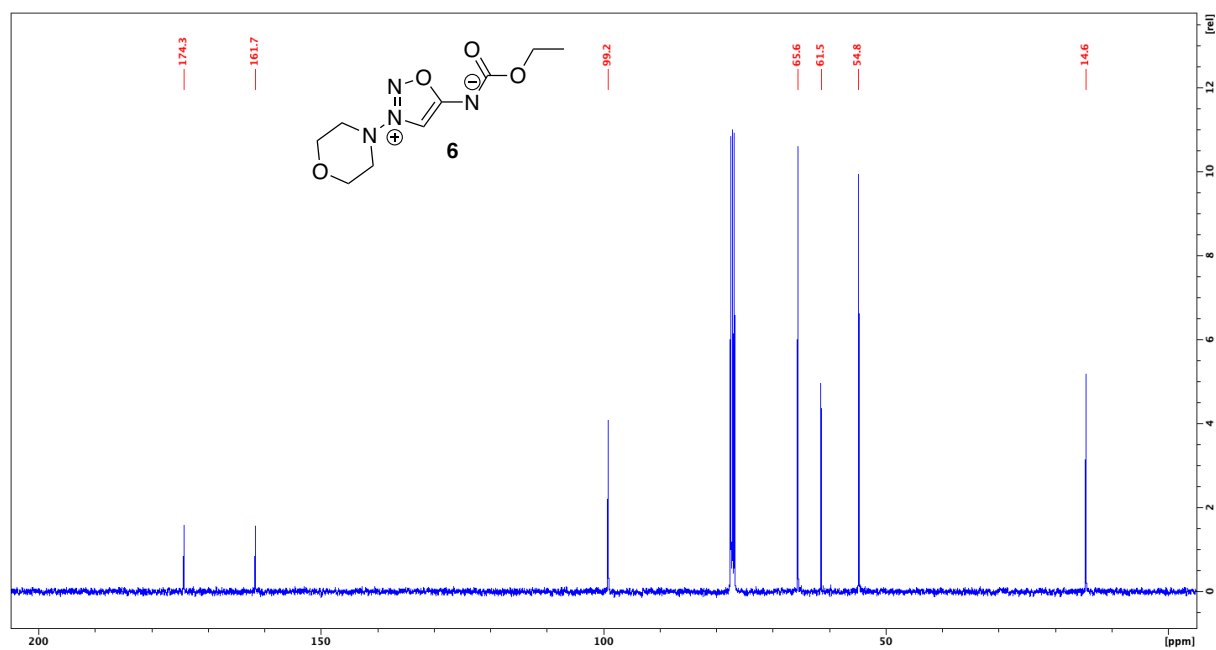
¹³C NMR (100 MHz, CDCl₃) 5



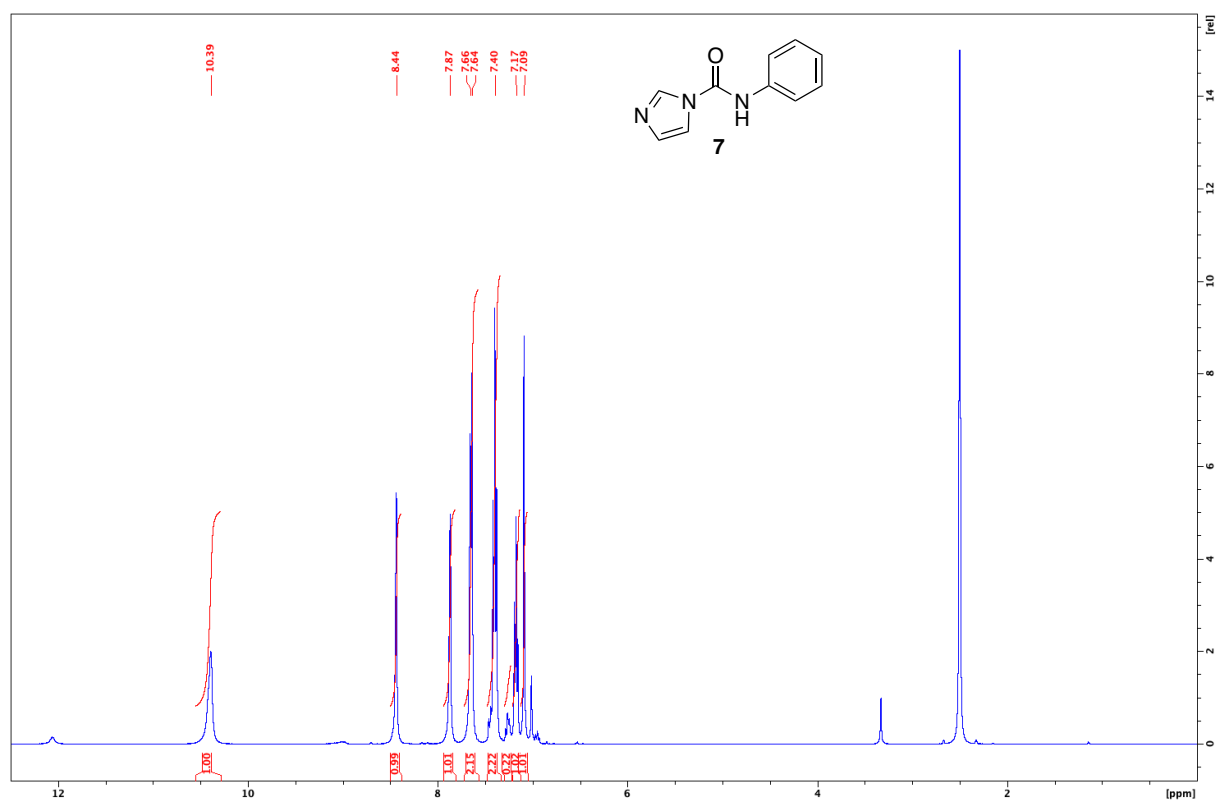
¹H NMR (400 MHz, CDCl₃) 6



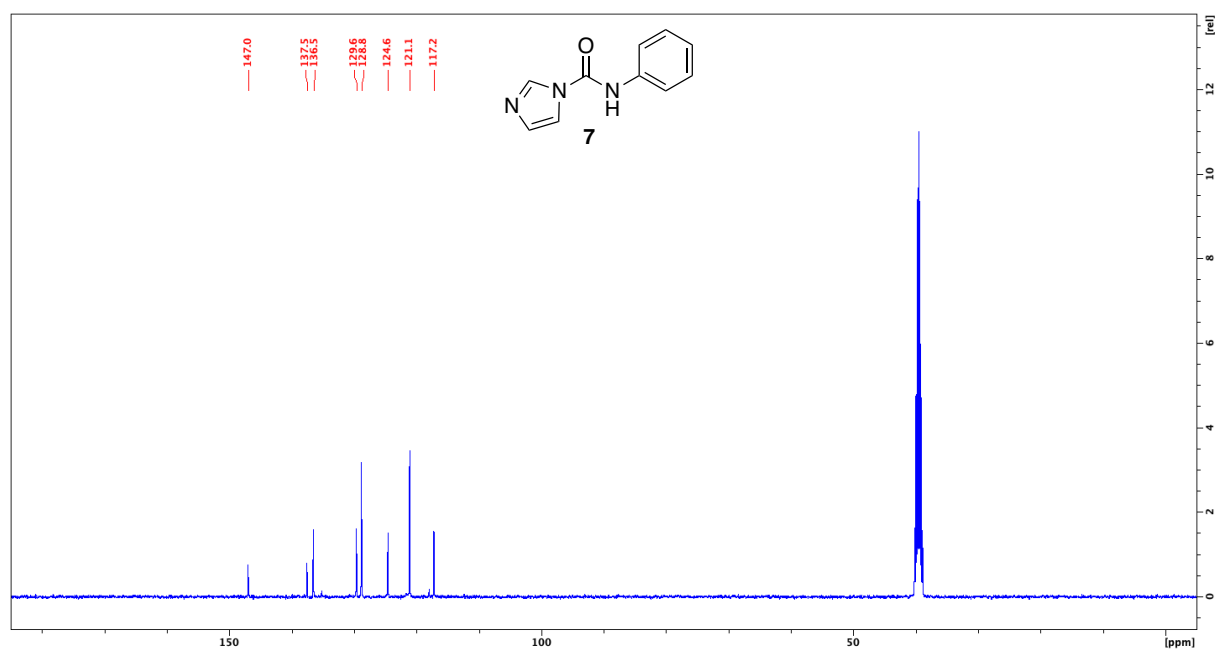
¹³C NMR (100 MHz, CDCl₃) 6



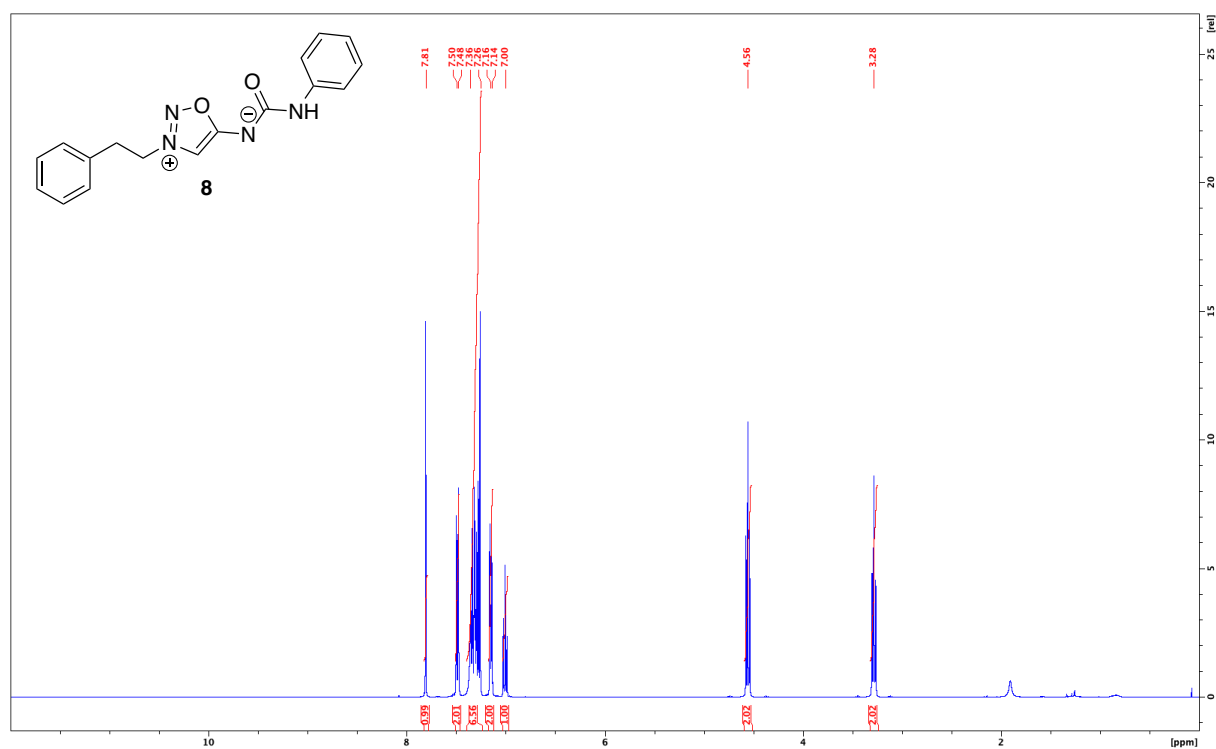
¹H NMR (400 MHz, DMSO-d₆) 7



¹³C NMR (100 MHz, DMSO-d₆) 7



¹H NMR (400 MHz, CDCl₃) 8



¹³C NMR (100 MHz, DMSO-d₆) 8

