Electronic Supplementary Material (ESI) for Faraday Discussions.

A mechanochemical approach to the synthesis of sydnones and derivatives

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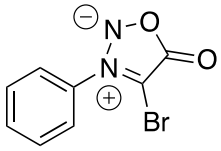
Supplementary information

I. Synthetic procedures and analytical data

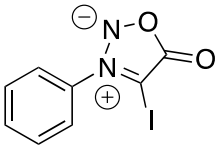
4-Bromo-3-phenylsydnone (3)



Chemical Formula: $C_8H_5BrN_2O_2$
Molecular weight: 241.04 g/mol

Procedure: Sydnone **1** (50.1 mg, 1 eq., 0.309 mmol) was put in a ZrO_2 milling jar along with NBS (65.9 mg, 1.2 eq., 0.370 mmol). A ZrO_2 ball (10 mm diameter) was added in the reactor, which was then closed and parafilmed. The reactor was milled for 1.5 h at 30 Hz. The reaction mixture was taken up with EtOAc and H_2O, extracted with EtOAc (3 times). The organic phase was washed with NaOH (1 M, 3 times) and brine, dried over $MgSO_4$ and evaporated. The mixture was taken up with CH_2Cl_2 and precipitated in pentane, filtered and the filtrate was recrystallized again in CH_2Cl_2/pentane yielding the title compound in 38 %.
^{1}H NMR (400MHz, $CDCl_3$) δ (ppm): 7.60-7.76 (m, 5H).
^{13}C NMR (125 MHz, CD_3CN) δ (ppm): 86.4, 126.1, 131.1, 133.7, 135.1, 166.9.
LCMS (ESI) m/z: 241.1 + 243.1 $[M+H]^+$.
HRMS ESI-(+) calcd. For $C_8H_5BrN_2O_2$ $[M+H]^+$ 240.9613, found 240.9604.

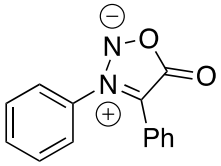
4-iodo-3-phenylsydnone (4)



Chemical Formula: $C_8H_5IN_2O_2$
Molecular weight: 288.04 g/mol

Procedure: 1 (207.1 mg, 1 eq., 1.277 mmol) was added in a screw-top ZrO_2 milling jar along with NIS (316.2 mg, 1.1 eq., 1.405 mmol) and AcOH (73 µL, 1 eq., 1.277 mmol). A ZrO_2 ball (10 mm diameter) was added in the reactor, which was then closed and parafilmed. The reactor was milled for 1.5 h at 30 Hz. The reaction mixture was taken up with EtOAc and H_2O, extracted with EtOAc (3 times). The organic phase was washed with NaOH (1 M, 3 times) and brine, dried over $MgSO_4$ and evaporated, yielding the title compound in 74 %.
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.59-7.74 (m, 5H).
^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 50.7, 125.2, 130.2, 132.8, 135.3, 169.0.
LCMS (ESI) *m/z*: 289.1 $[M+H]^+$.

3,4-diphenylsydnone (5)



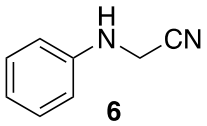
Chemical Formula: $C_{14}H_{10}N_2O_2$
Molecular weight : 238.24 g/mol

Procedure A: Suzuki-Miyaura coupling. Compound **4** (1 eq., 0.044 mmol) was added in a screw-top SS milling jar (1.5 mL) along with the boron species (1.1 eq., 0.052 mmol), $Pd(OAc)_2$ (5 mol%, 0.002 mmol), the ligand (10 mol%, 0.004 mmol) and the base (2 eq., 0.087 mmol) . A SS ball (7 mm diameter) was added in the reactor, which was then closed. The reactor was milled for 0.5 h at 30 Hz with the heatgun set *ca.* 1 cm above. The reaction mixture was taken up with EtOAc and H_2O, extracted with EtOAc (3 times). The organic phase was washed with NaOH (1 M, 3 times) and brine, dried over $MgSO_4$ and evaporated. The reaction mixture was then passed through a short pad of silica with cyclohexane:EtOAc (70:30) as eluent.

Procedure B: C-H activation. 4 (15.8 mg, 1 eq., 0.098 mmol) was added in a screw-top SS milling jar (1.5 mL) along with iodobenzene (12 µL, 1.1 eq., 0.107 mmol), $Pd(OAc)_2$ (1.1 mg, 5 mol%, 0.005 mmol), XPhos (4.6 mg, 10 mol%, 0.01 mmol) and Cs_2CO_3 (63.6 mg, 2 eq., 0.195 mmol). A SS ball (7 mm diameter) was added in the reactor, which was then closed. The reactor was milled for 0.5 h at 30 Hz with the heatgun set *ca.* 1 cm above. The reaction mixture was taken up with EtOAc and H_2O, extracted with EtOAc (3 times). The organic phase was washed with NaOH (1 M, 3 times) and brine, dried over $MgSO_4$ and evaporated. The reaction mixture was then passed through a short pad of silica with cyclohexane:EtOAc (70:30) as eluent.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.27-7.30 (m, 5H), 7.47-7.50 (m, 2H), 7.56-7.60 (m, 2H), 7.65-7.69 (m, 1H).
^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 124.5, 125.0, 127.5, 128.8, 128.9, 130.3, 132.3, 134.8, 167.3.
LCMS (ESI) *m/z*: 239.2 $[M+H]^+$

2-(Phenylamino)acetonitrile (6)



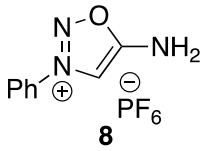
6

Chemical Formula: $C_8H_8N_2$
Molecular Weight: 132.17

Procedure: in a 15 mL PTFE jar with 1 stainless steel ball (10 mm diameter) were introduced aniline (275 µL, 3.0 mmol, 1 eq.), bromoacetonitrile (215 µL, 3.0 mmol, 1 eq) and potassium carbonate (414 mg, 3.0 mmol, 1 eq.). The jar was closed and submitted to vibratory milling at 30 Hz for 90 min. The reaction mixture was recovered and diluted with EtOAc and filtered. The filtrate was washed with 10% aqueous $KHSO_4$ solution, saturated $NaHCO_3$ solution and brine. After drying over $MgSO_4$ and filtration the solvent was removed *under vacuum* to furnish the desired aminonitrile as an orange oil (344 mg, 2.6 mmol, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.10 (s, 2H), 6.73 (d, *J* = 7.8 Hz, 2H), 6.90 (t, *J* = 7.4 Hz, 1H), 7.26-7.31 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 32.8, 113.7 (2C), 117.1, 120.2, 129.7 (2C), 145.1.
LCMS (ESI) *m/z*: 133 $[M+H]^+$.

5-Amino-3-phenyl-1,2,3-oxadiazolium hexafluorophosphate (8)

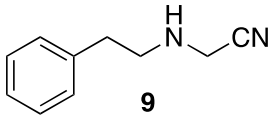


8

Chemical Formula: $C_8H_8N_3OPF_6$
Molecular Weight: 307.14

Procedure: 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 eq.), sodium hydrogenosulfate (720 mg, 6 mmol, 6 eq.) and sodium nitrite (70 mg, 1.0 mmol, 1 eq.). The jar was closed and submitted to vibratory milling at 30 Hz for 60 min. Potassium hexafluorophosphate (190 mg, 1.0 mmol, 1 eq) 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 as a beige powder (287 mg, 0.93 mmol, 93%).
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.76-7.86 (m, 3H), 8.02-8.04 (m, 2H), 8.60 (s, 1H), 9.69 (s, 2H).
^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 102.5, 122.8 (2C), 130.4 (2C), 132.8, 133.7, 169.5.
LCMS (ESI) *m/z*: 162 $[M-PF_6^-]^+$.

2-[(2-Phenylethyl)amino]acetonitrile (9)



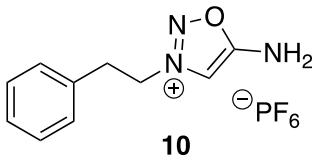
9

Chemical Formula: $C_{10}H_{12}N_2$
Molecular Weight: 160.22

Procedure: Potassium carbonate (415 mg, 3.0 mmol, 3 eq), phenethylamine (126 μL, 1.0 mmol, 1 eq.) and bromoacetonitrile (72 μL, 1.0 mmol, 1 eq) were introduced in a 10 mL zirconium oxide grinding jar with 2 balls of the same material (10 mm diameter). The jar was closed and submitted to vibratory milling at 25 Hz for 60 min. The white solid was recovered with EtOAc and the suspension was filtered. The filtrate was washed with water and brine, dried over $MgSO_4$ and the solvent was evaporated *under vacuum* to give the desired aminonitrile as a translucid oil (150 mg, 0.93 mmol, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.84 (t, *J* = 6.9 Hz, 2H), 3.02 (t, *J* = 6.9 Hz, 2H), 3.59 (s, 2H), 7.21-7.25 (m, 3H), 7.30-7.34 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 35.9, 37.5, 49.9, 117.8, 126.7, 128.8, 139.0.
HRMS ESI-(+) calcd. for $C_{10}H_{13}N_2$ $[M+H]^+$ 161.1073, found 161.1075.

5-Amino-3-(2-phenylethyl)-1,2,3-oxadiazolium hexafluorophosphate (10)

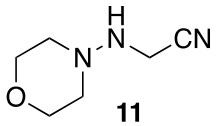


10

Chemical Formula: $C_{10}H_{12}N_3OPF_6$
Molecular Weight: 335.19

Procedure: 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 eq.), sodium hydrogenosulfate (600 mg, 5.0 mmol, 6 eq) and sodium nitrite (70 mg, 1.0 mmol, 1.2 eq.). The jar was closed and submitted to vibratory milling at 30 Hz for 90 min. Potassium hexafluorophosphate (156 mg, 0.83 mmol, 1 eq.) 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 as an off-white powder (260 mg, 0.77 mmol, 93%).
^{1}H NMR (400 MHz, DMSO-d_6) 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).
^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 33.8, 54.4, 102.8, 127.2, 128.7 (2C), 128.8 (2C), 135.8, 169.0.
LCMS (ESI) *m/z*: 190 $[M\text{-}PF_6^-]^+$.

2-(4-Morpholinylamino)acetonitrile (11)

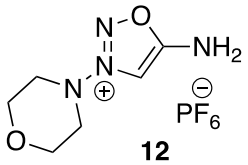


11

Chemical Formula: $C_6H_{11}N_3O$
Molecular Weight: 141.17

Procedure: Silica (400 mg, 6.6 mmol, 6 eq.), paraformaldehyde (35 mg, 1.1 mmol, 1 eq) and 4-aminomorpholine (110 µL, 1.1 mmol, 1 eq.) were introduced in a 10 mL stainless steel grinding jar with 5 stainless steel balls (7 mm diameter). The jar was closed and submitted to vibratory milling at 25 Hz for 30 min. Potassium cyanide (80 mg, 1.21 mmol, 1.1 eq.) was added to the reaction mixture and the jar subjected to milling for a new period of 90 min at 25 Hz.
The white powder was recovered with EtOAc and the suspension was filtered over a pad of Celite. The filtrate was concentrated under *vacuum* to furnish the expected aminonitrile as a yellow oil (195 mg, 1.02 mmol, 93%).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.59 (m, 1H), 2.76 (m, 4H), 3.69 (d, *J* = 5.8 Hz, 2H), 3.73 (t, *J* = 4.6 Hz, 4H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 37.8, 56.8 (2C), 67.0 (2C), 118.4.
LCMS (ESI) *m/z*: 142 $[M+H]^+$.

5-Amino-3-(4-morpholinyl)-1,2,3-oxadiazolium hexafluorophosphate (12)



12

Chemical Formula: $C_6H_{11}N_4O_2PF_6$
Molecular Weight: 316.14

Procedure:
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 eq), sodium hydrogenosulfate (1.010 mg, 8.4 mmol, 6 eq) and sodium nitrite (109 mg, 1.54 mmol, 1.1 eq). The jar was closed and submitted to vibratory milling at 30 Hz for 60 min. Potassium hexafluorophosphate (260 mg, 1.4 mmol, 1 eq) 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 as a yellow solid (399 mg, 1.26 mmol, 90%).

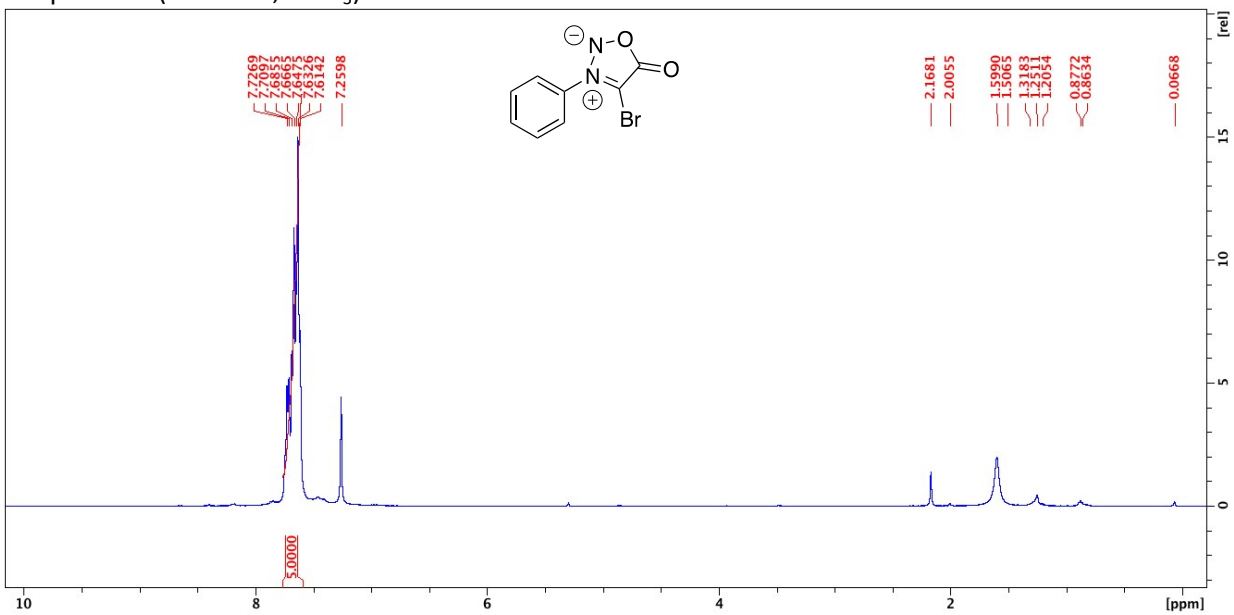
Method B: in a 10 mL zirconium oxide grinding jar with 1 ball of the same material (12 mm diameter) were introduced 2-(4-morpholinylamino)acetonitrile (154 mg, 1.08 mmol, 1 eq.), sodium hydrogenosulfate (720 mg, 6 mmol, 5.5 eq.) and sodium nitrite (75 mg, 1.08 mmol, 1 eq.). The jar was closed and submitted to vibratory milling at 30 Hz for 60 min. Potassium hexafluorophosphate (180 mg, 0.95 mmol, 1 eq.) was added to the reaction mixture which was ground again at 30 Hz for 60 min. The resulting solid was suspended in a minimal amount of water (1.5 mL) and filtered over sintered glass, rinsing with 0.5 mL of water. The solid was dried under *vacuum* over P_2O_5 to yield the expected iminosydnone hexafluorophosphate salt as a beige solid (163 mg, 0.51 mmol, 47%).

^{1}H NMR (400 MHz, DMSO-d_6) 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).
^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 53.4 (2C), 64.6 (2C), 96.5, 168.5.
LCMS (ESI) *m/z*: 171 $[M\text{-}PF_6^-]^+$.

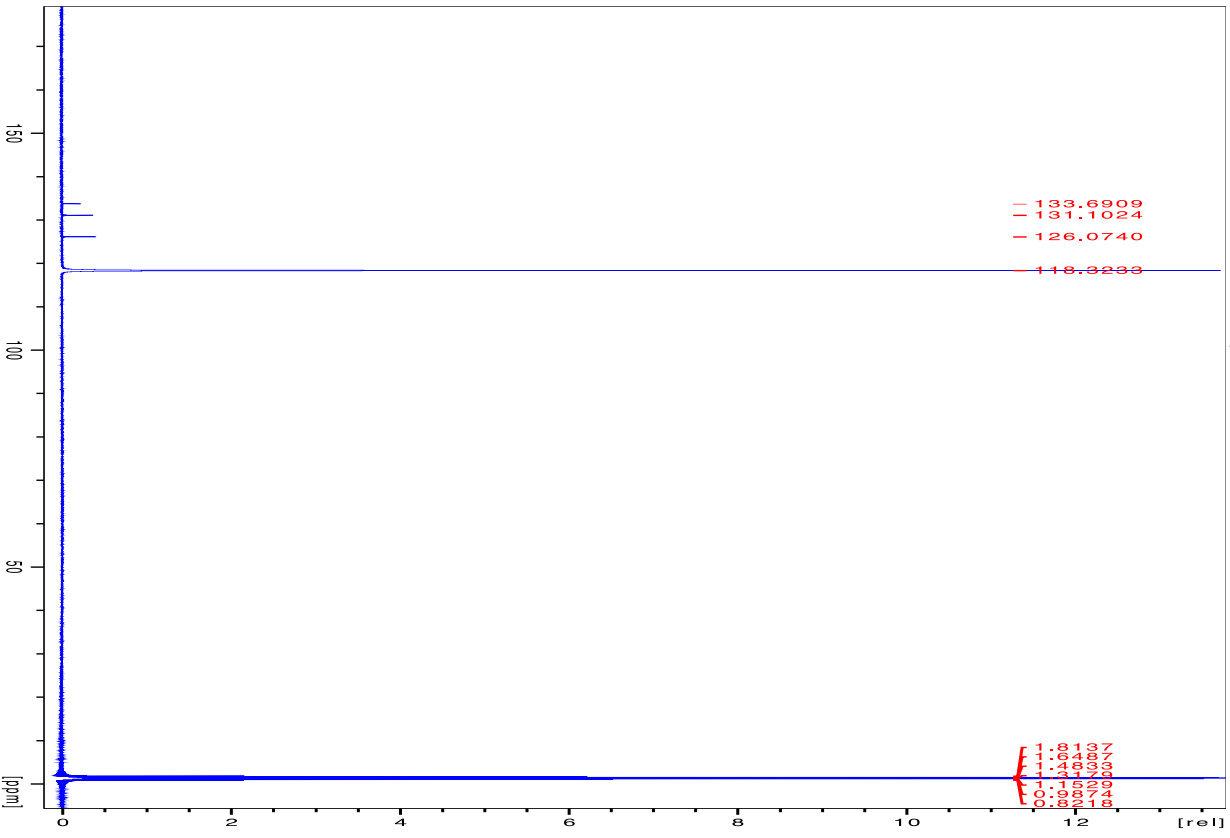
II. ^{1}H and ^{13}C NMR spectra

4-bromo-3-phenylsydnone (3)

^{1}H spectrum (400 MHz, $CDCl_3$):



^{13}C NMR spectrum (100 MHz, CD_3CN):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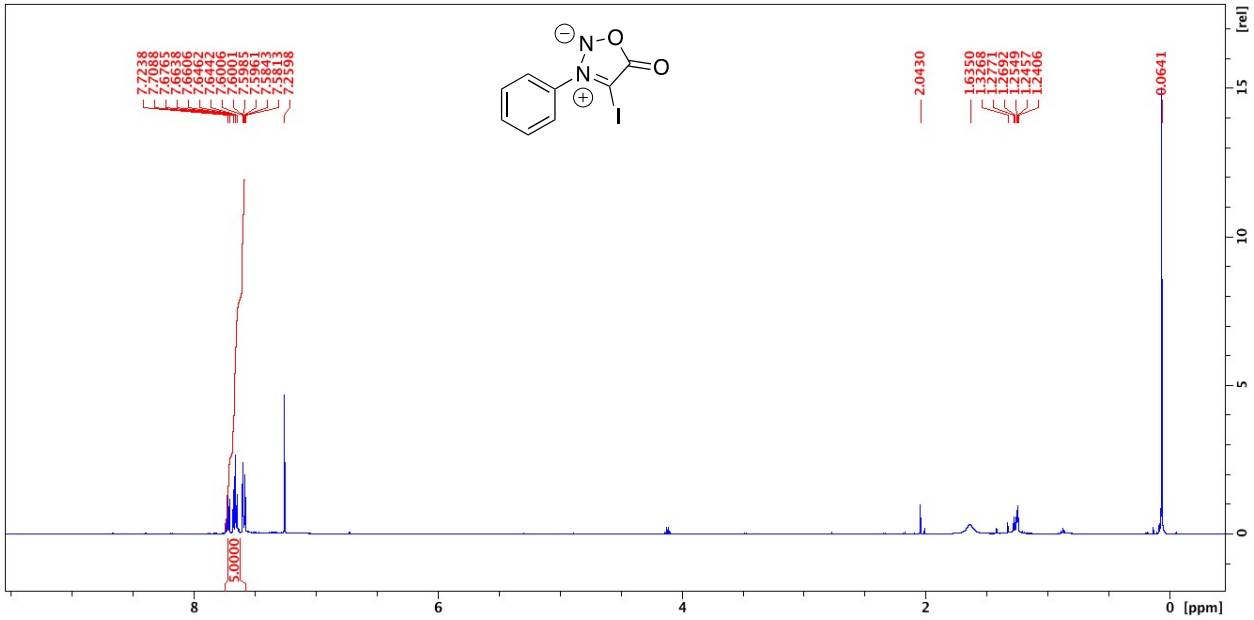
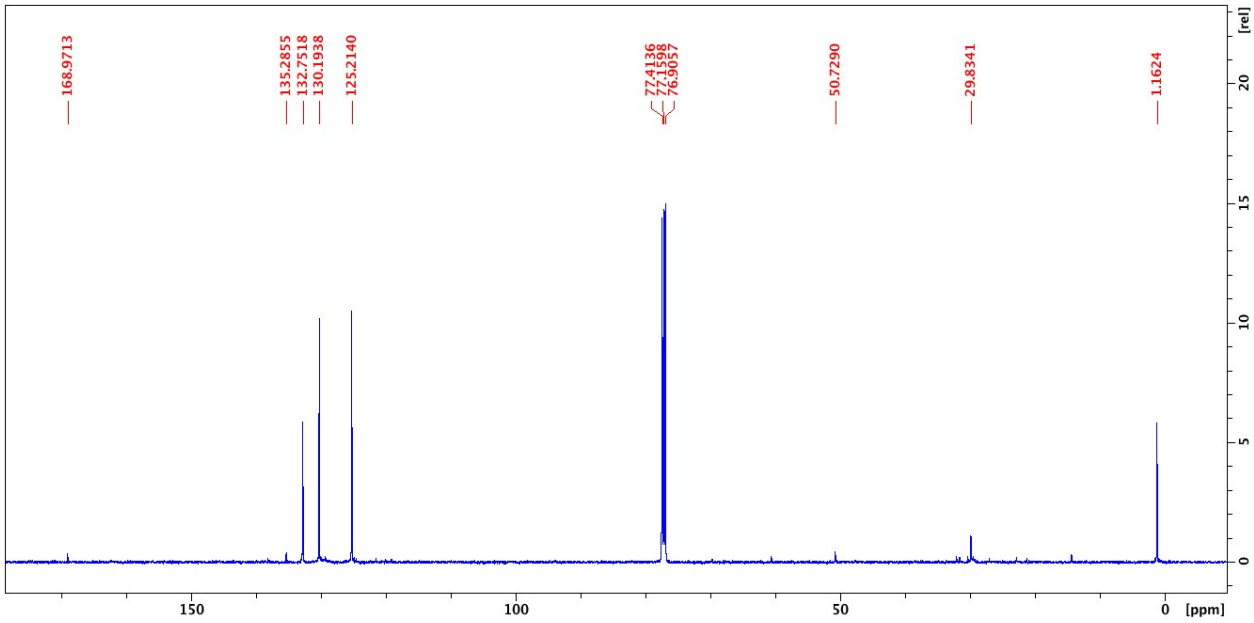
131.1024
126.0740
118.3233
1.8137
1.6487
1.4833
1.3179
1.1529
0.9874
0.8218
150
100
50
[ppm]
0
2
4
6
8
10
12
[rel]

4-iodo-3-phenylsydnone (4)

^{1}H spectrum (500 MHz, $CDCl_3$):

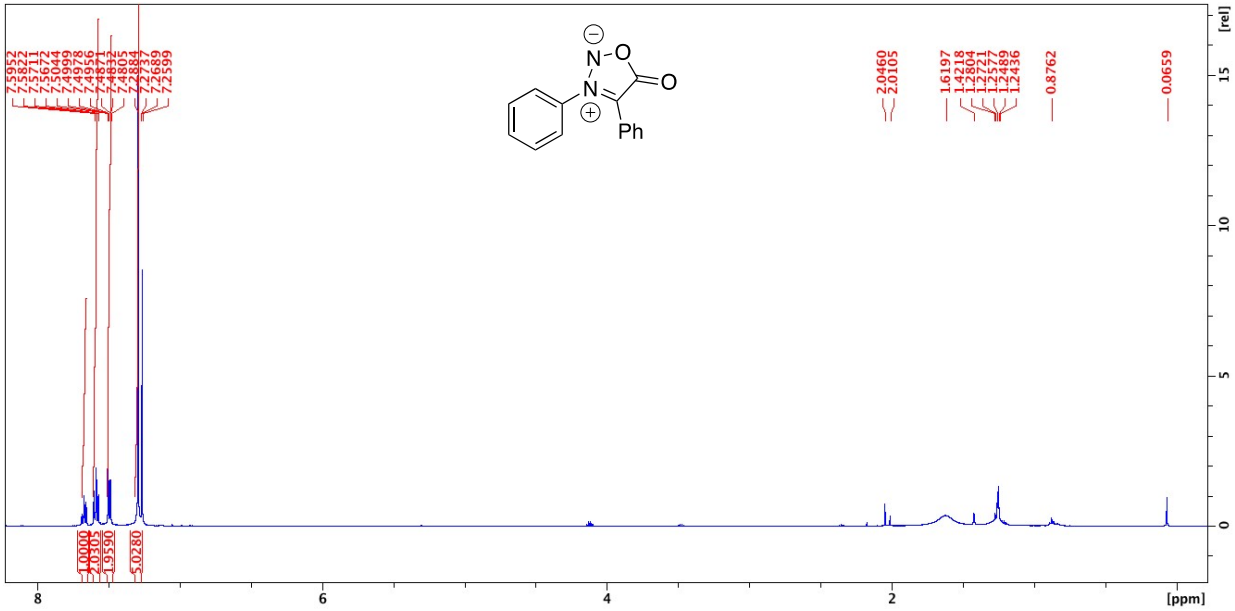


^{13}C spectrum (125 MHz, $CDCl_3$):

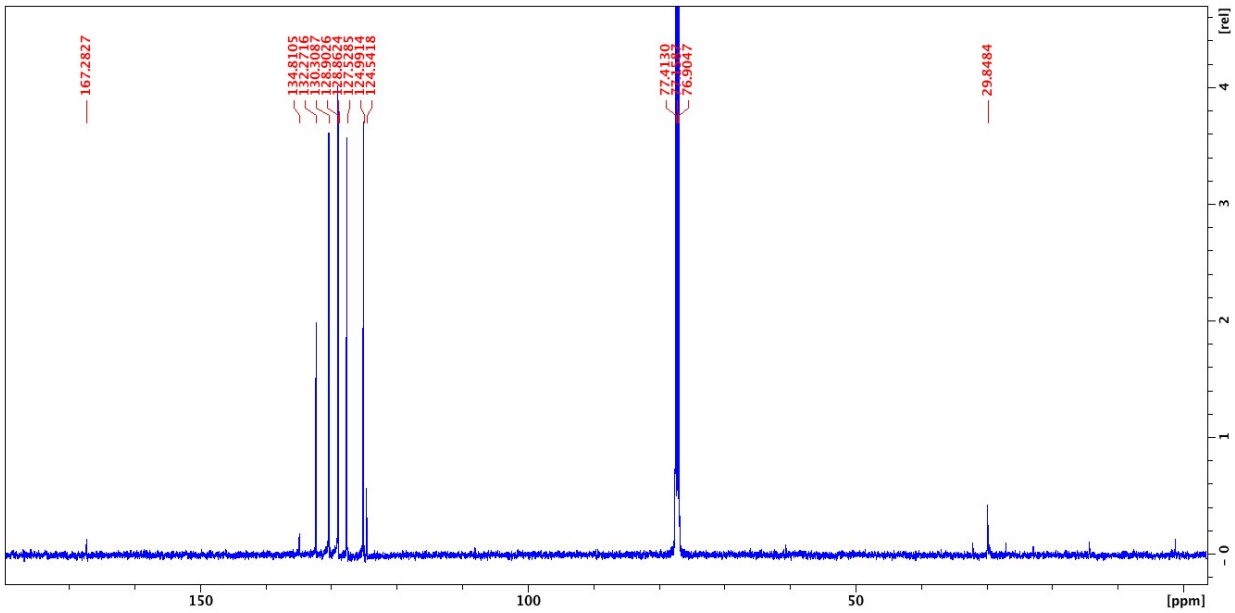


3,4-diphenylsydnone (5)

^{1}H spectrum (500 MHz, $CDCl_3$):

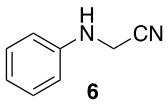


^{13}C spectrum (125 MHz, $CDCl_3$):

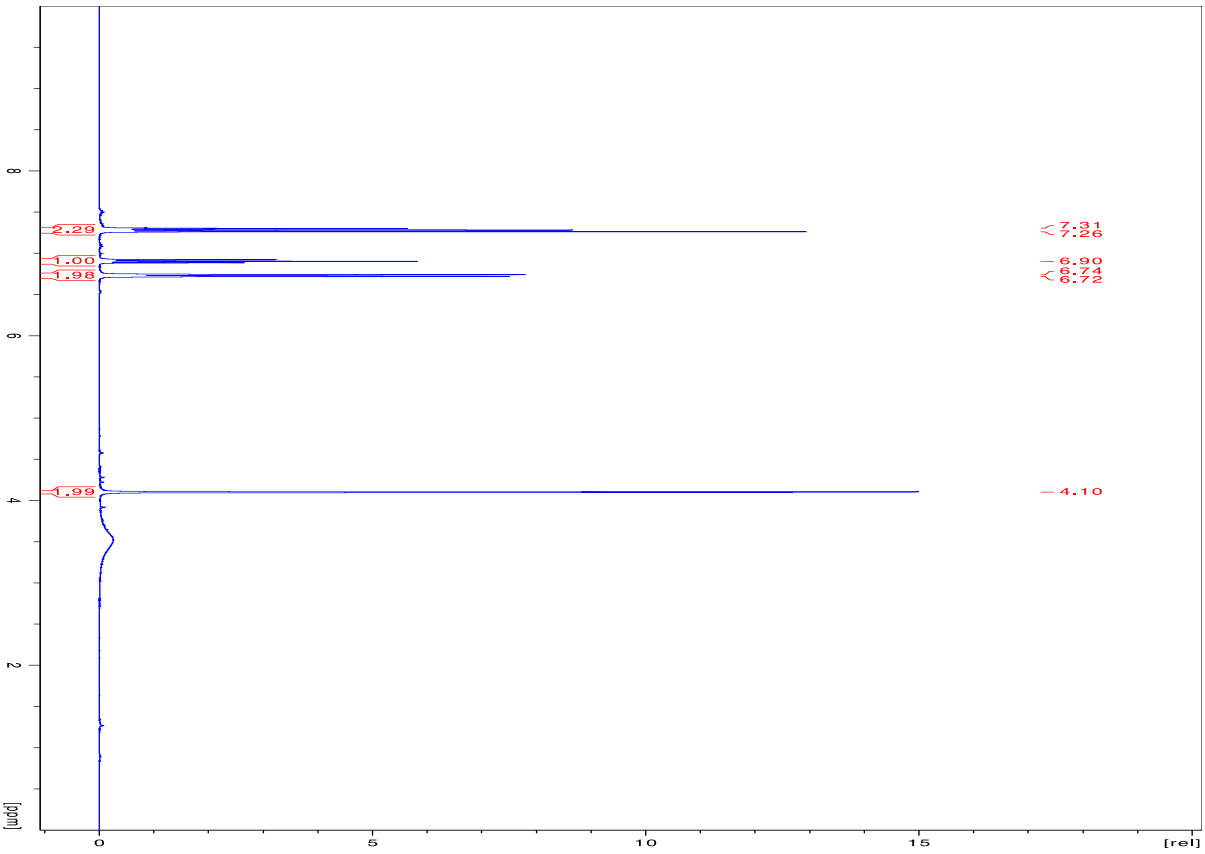


2-(Phenylamino)acetonitrile (6)

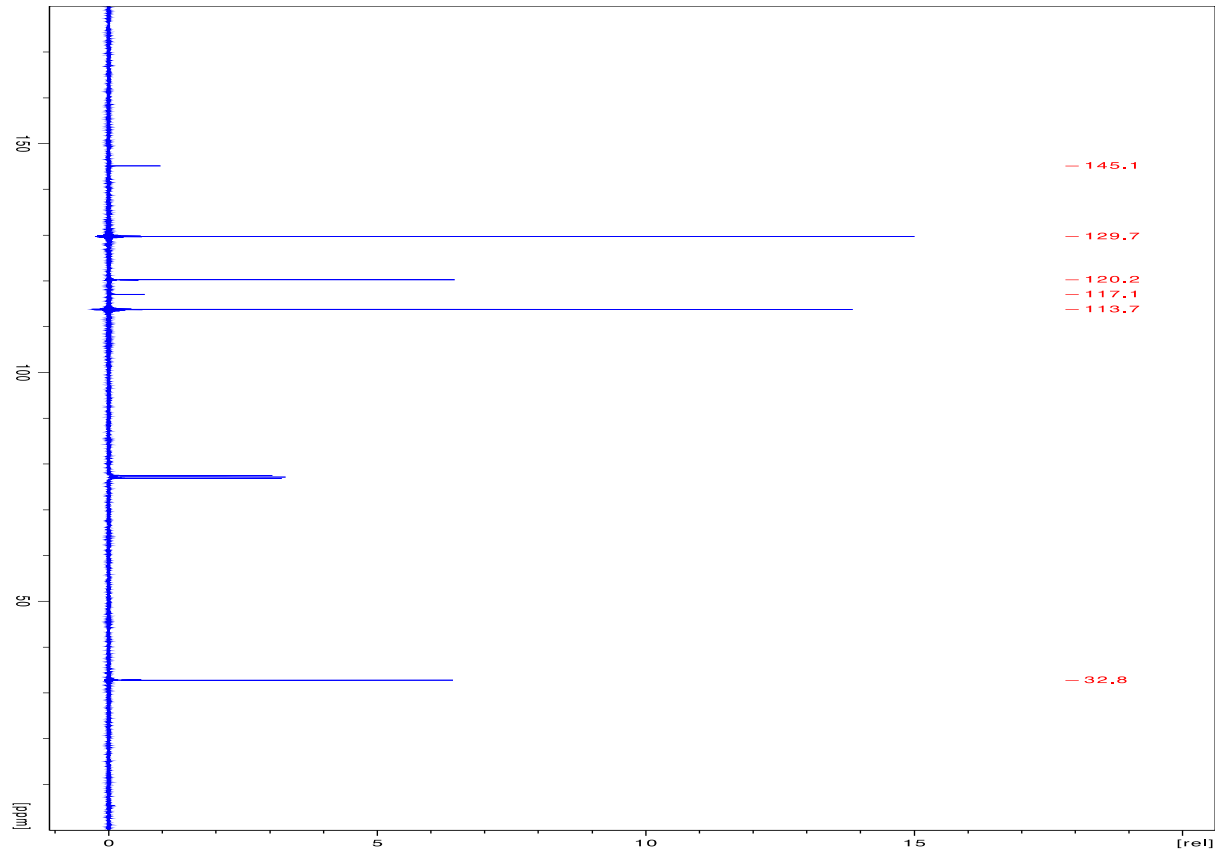
^{1}H NMR spectrum (400 MHz, $CDCl_3$):



6

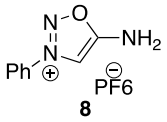


^{13}C NMR spectrum (100 MHz, $CDCl_3$):

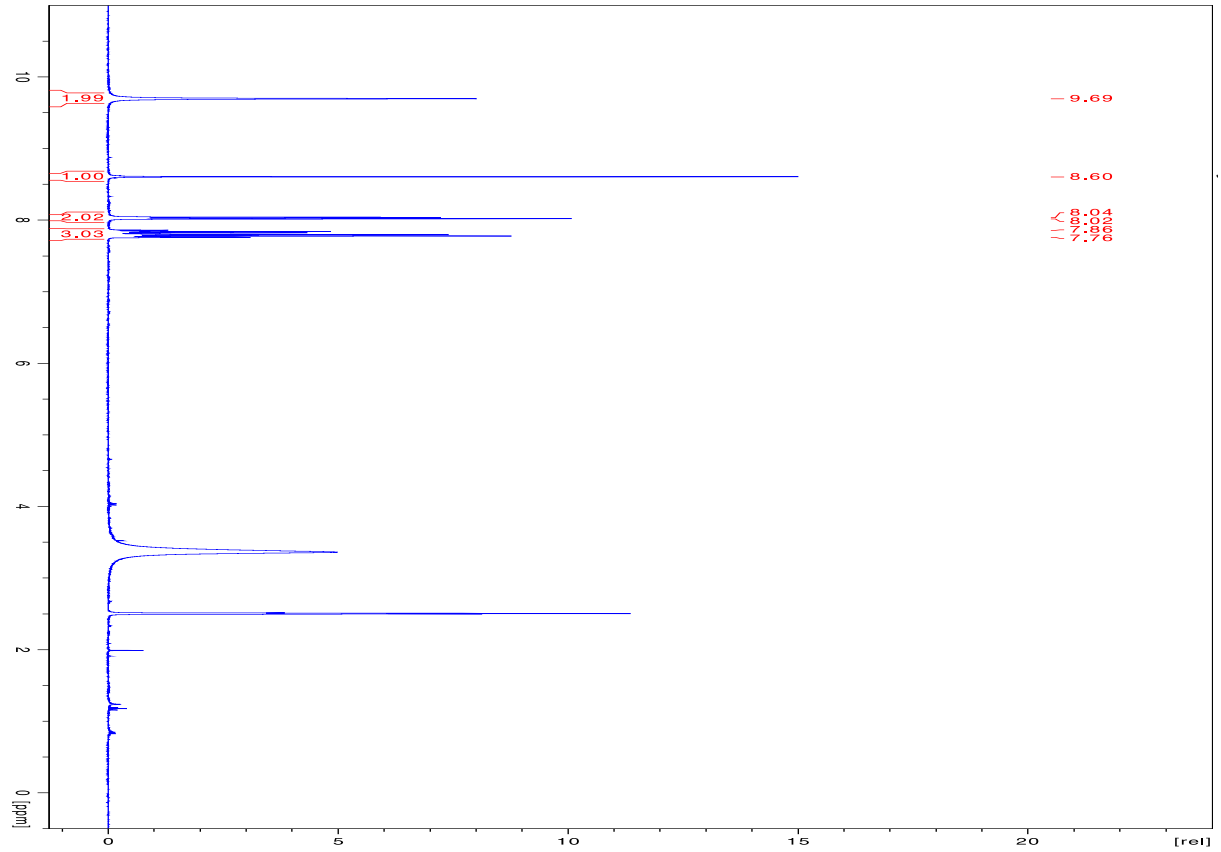

145.1
129.7
120.2
117.1
113.7
32.8
150
100
50
[ppm]
0
5
10
15
[rel]

5-Amino-3-phenyl-1,2,3-oxadiazolium hexafluorophosphate (8)

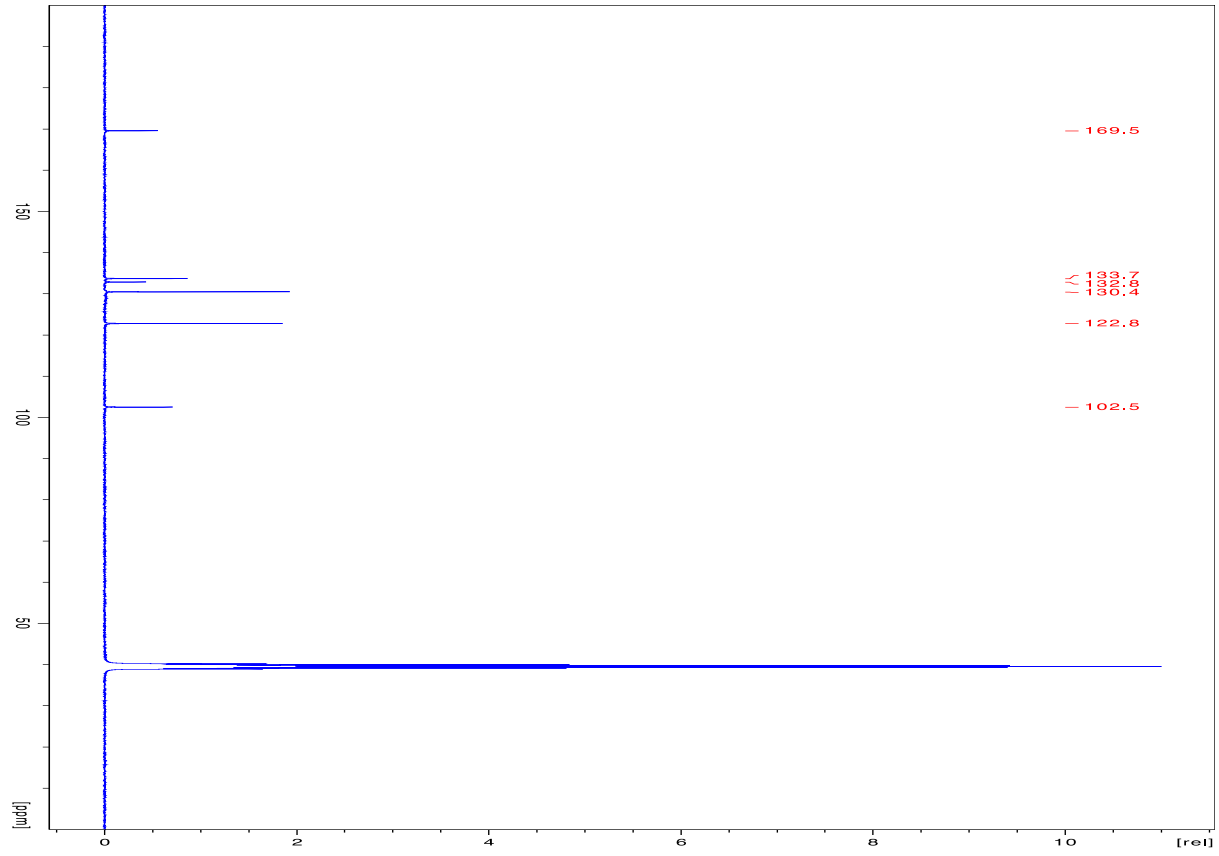
^{1}H NMR spectrum (400 MHz, DMSO-d_6):



8

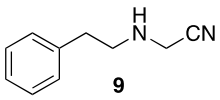


^{13}C NMR spectrum (100 MHz, DMSO-d_6):

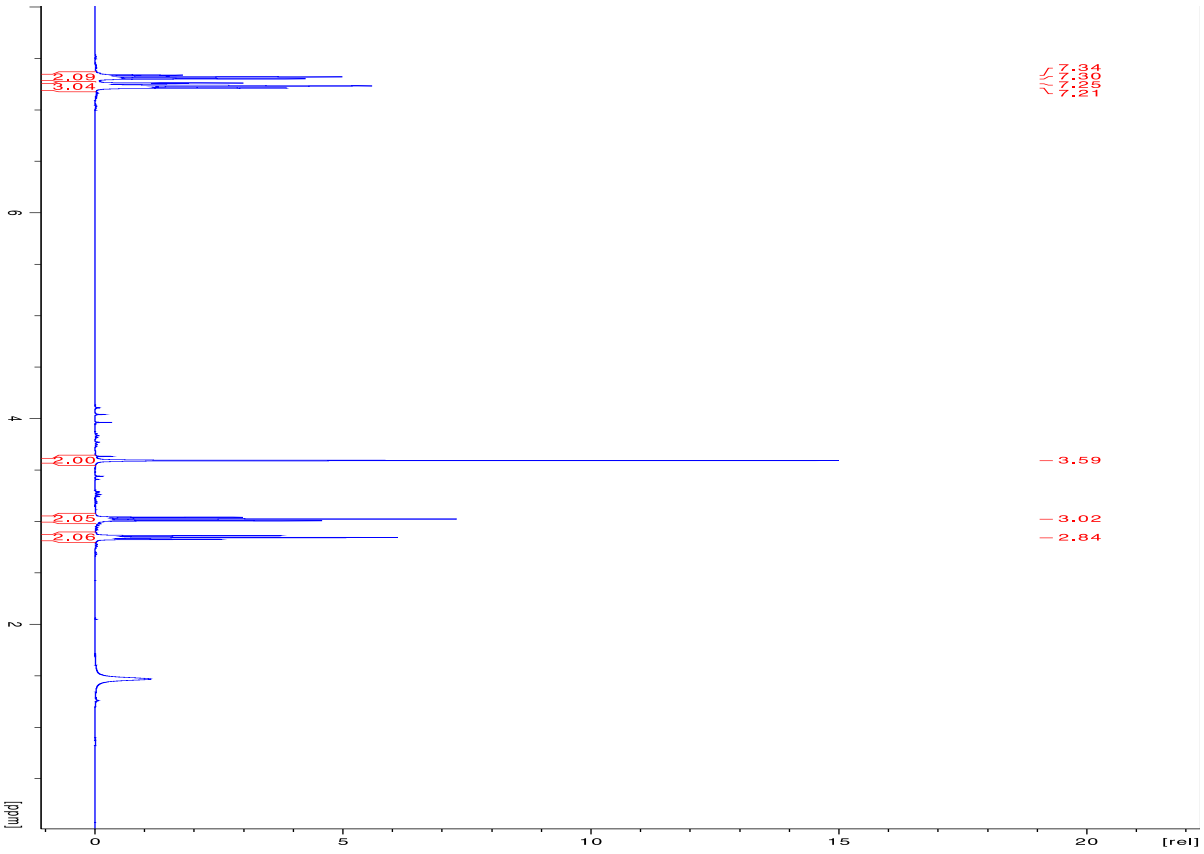

169.5
133.7
132.6
130.4
122.8
102.5
150
100
50
[ppm]
0
2
4
6
8
10
[rel]

2-[(2-Phenylethyl)amino]acetonitrile (9)

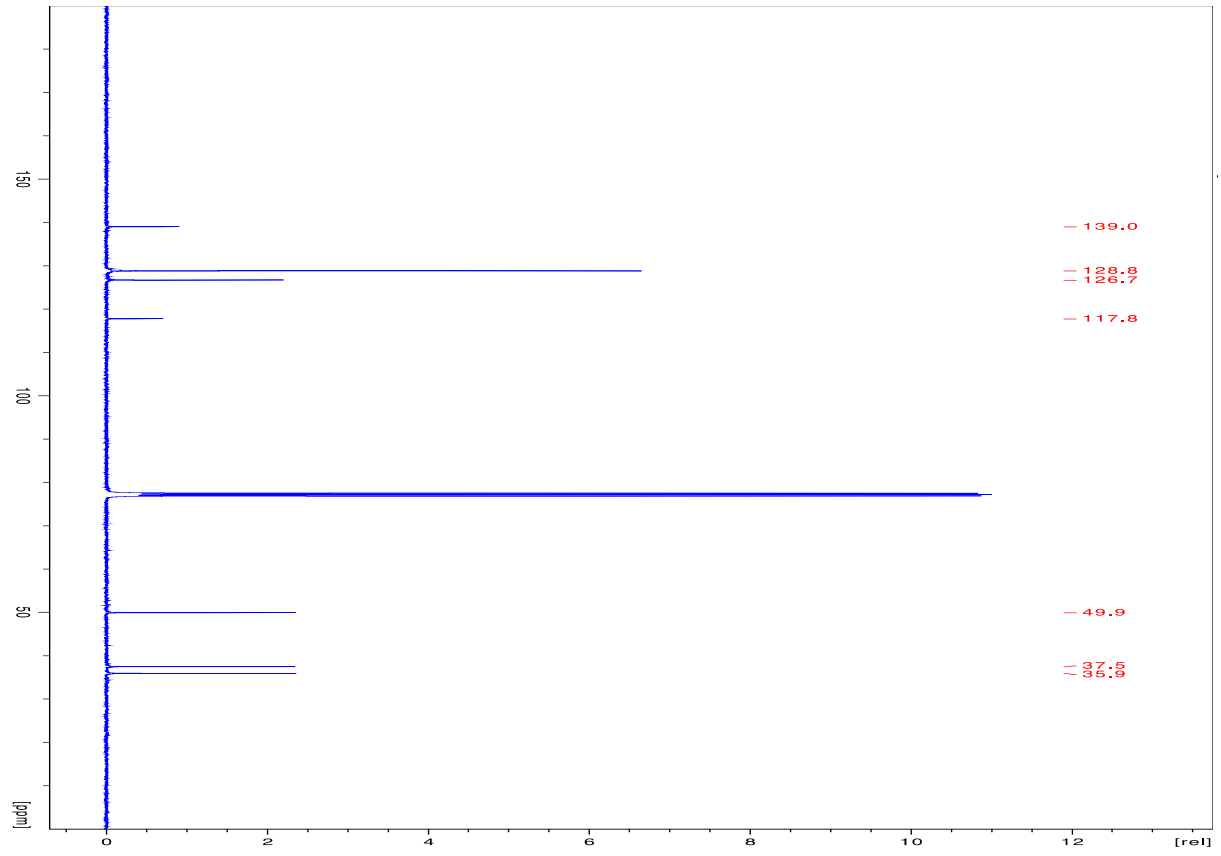
^{1}H NMR spectrum (400 MHz, $CDCl_3$):



9

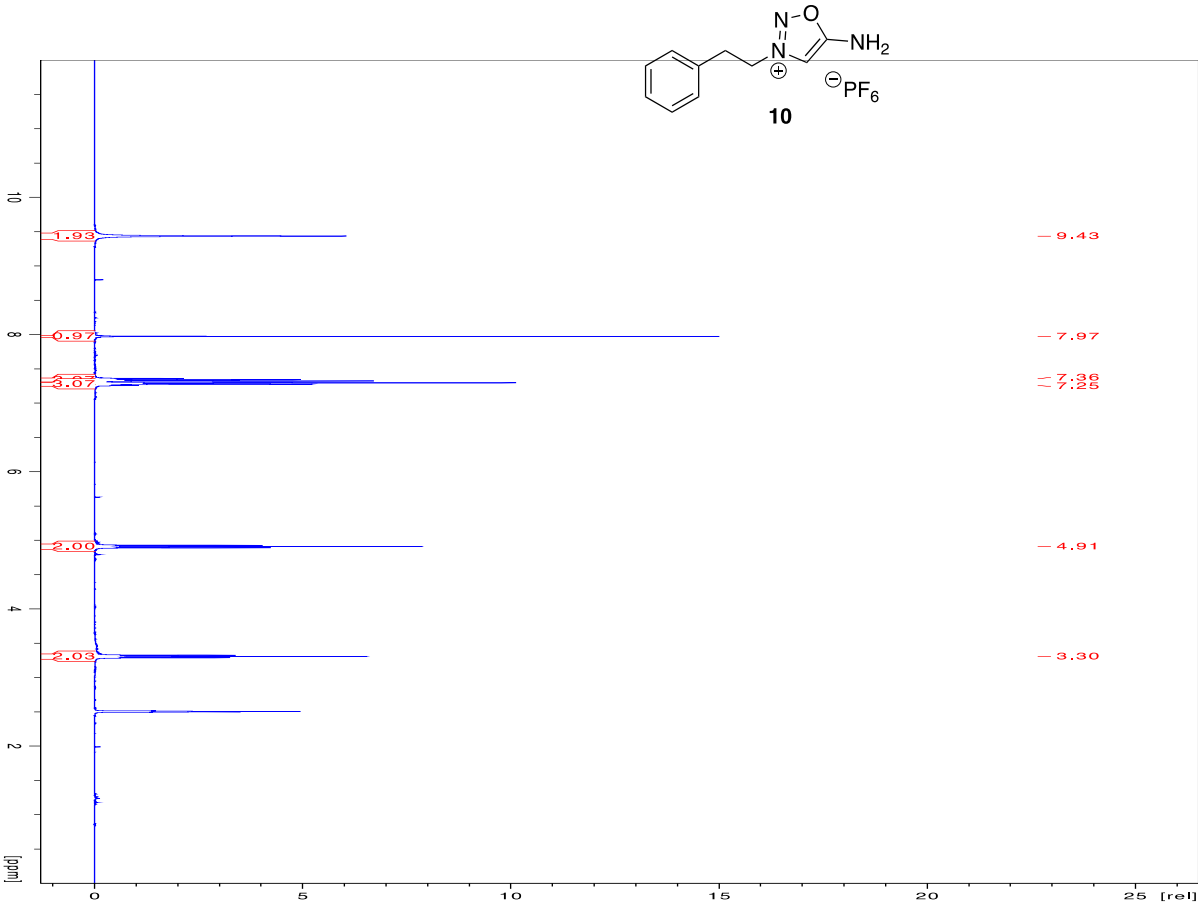


^{13}C NMR spectrum (100 MHz, $CDCl_3$):

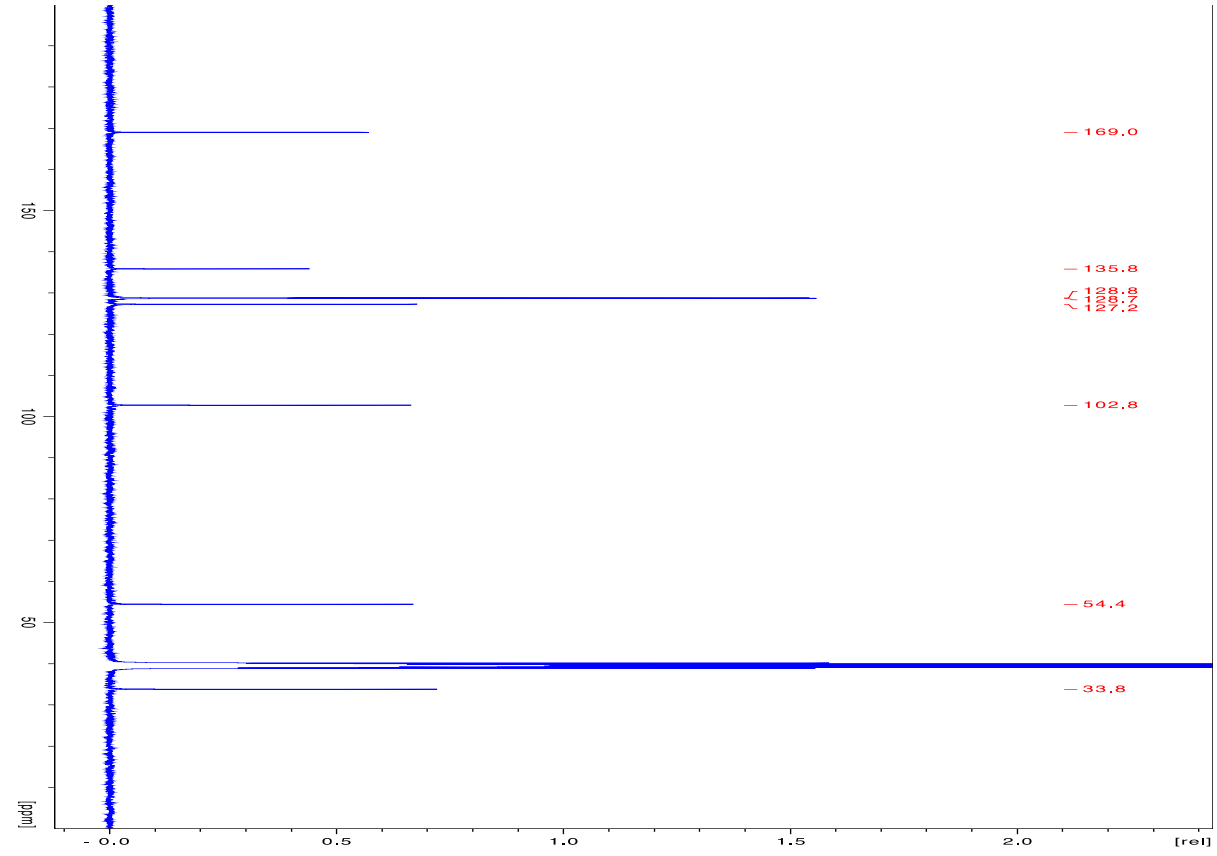

150
100
50
[ppm]
0
2
4
6
8
10
12
[rel]
139.0
128.8
126.7
117.8
49.9
37.5
35.9

5-Amino-3-(2-phenylethyl)-1,2,3-oxadiazolium hexafluorophosphate (10)

^{1}H NMR spectrum (400 MHz, DMSO-d_6):

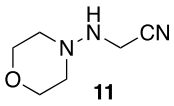


^{13}C NMR spectrum (100 MHz, DMSO-d_6):

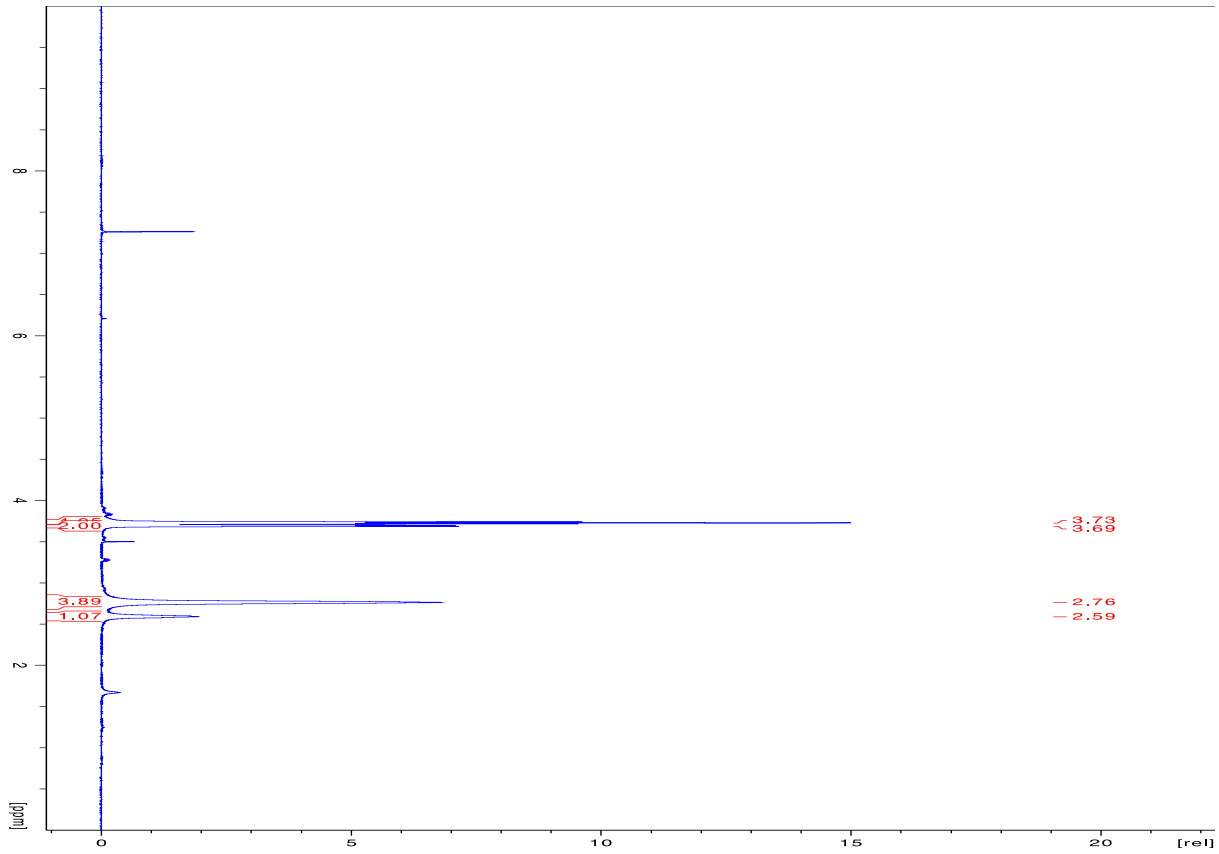

169.0
135.8
128.9
128.7
127.2
102.8
54.4
33.8
150
100
50
[ppm]
- 0.0
0.5
1.0
1.5
2.0
[rel]

2-(4-Morpholinylamino)acetonitrile (11)

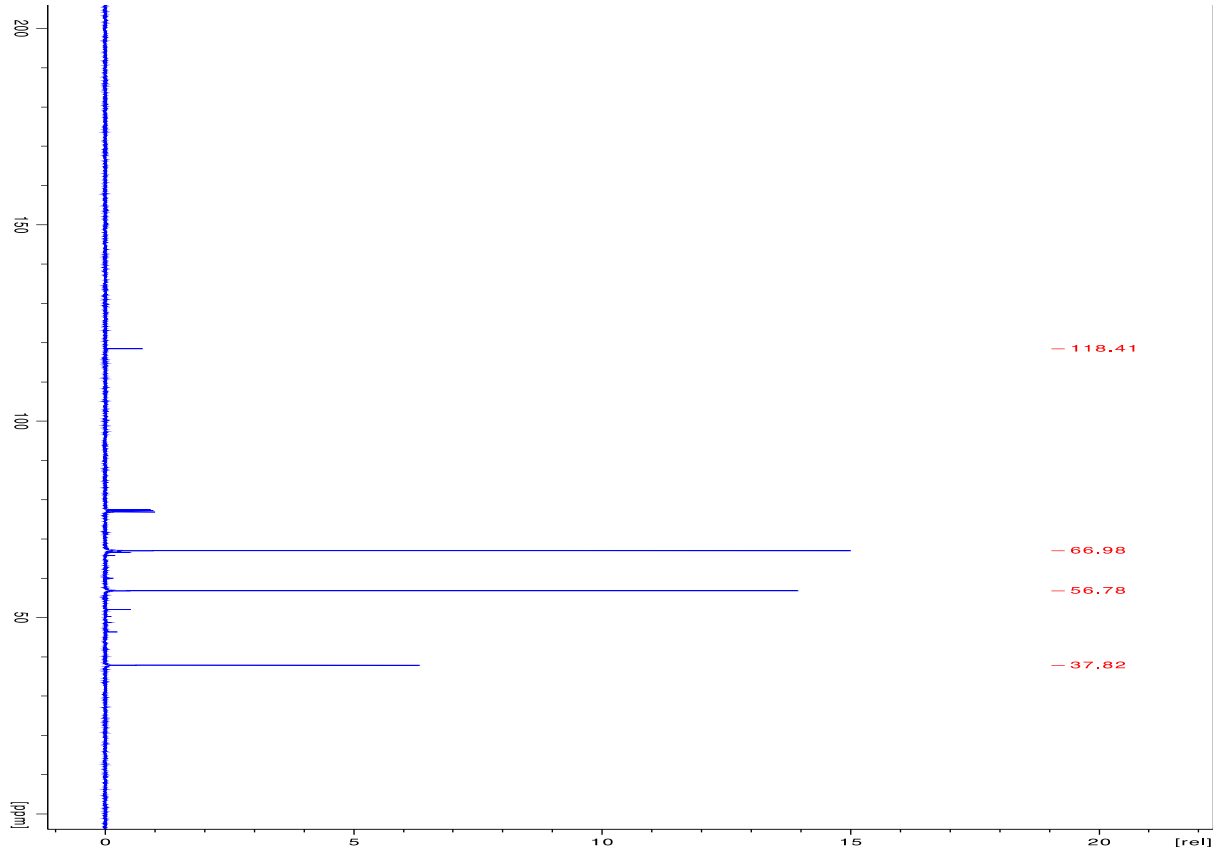
^{1}H NMR spectrum (400 MHz, $CDCl_3$):



11

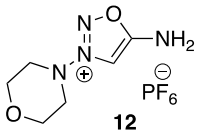


^{13}C NMR spectrum (100 MHz, $CDCl_3$):

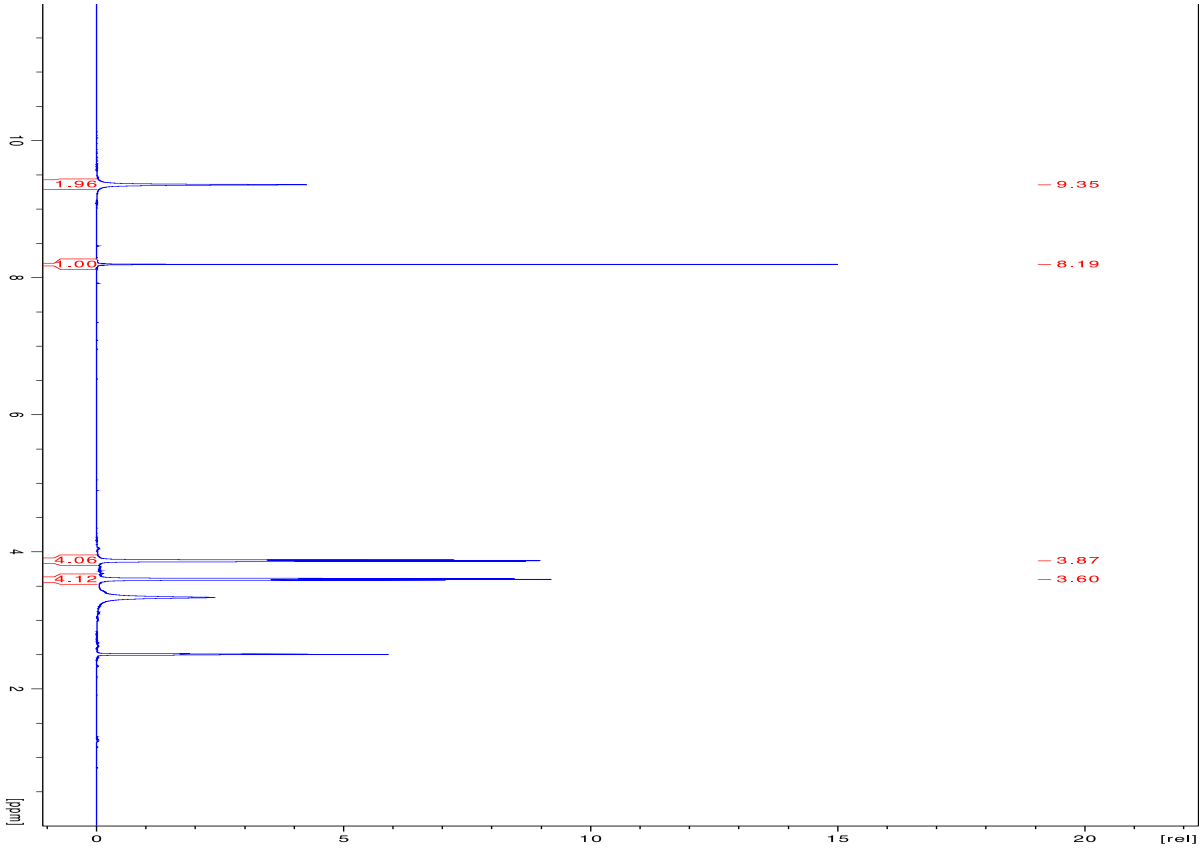

200
150
100
50
[ppm]
0
5
10
15
20
[rel]
118.41
66.98
56.78
37.82

5-Amino-3-(4-morpholinyl)-1,2,3-oxadiazolium hexafluorophosphate (12)

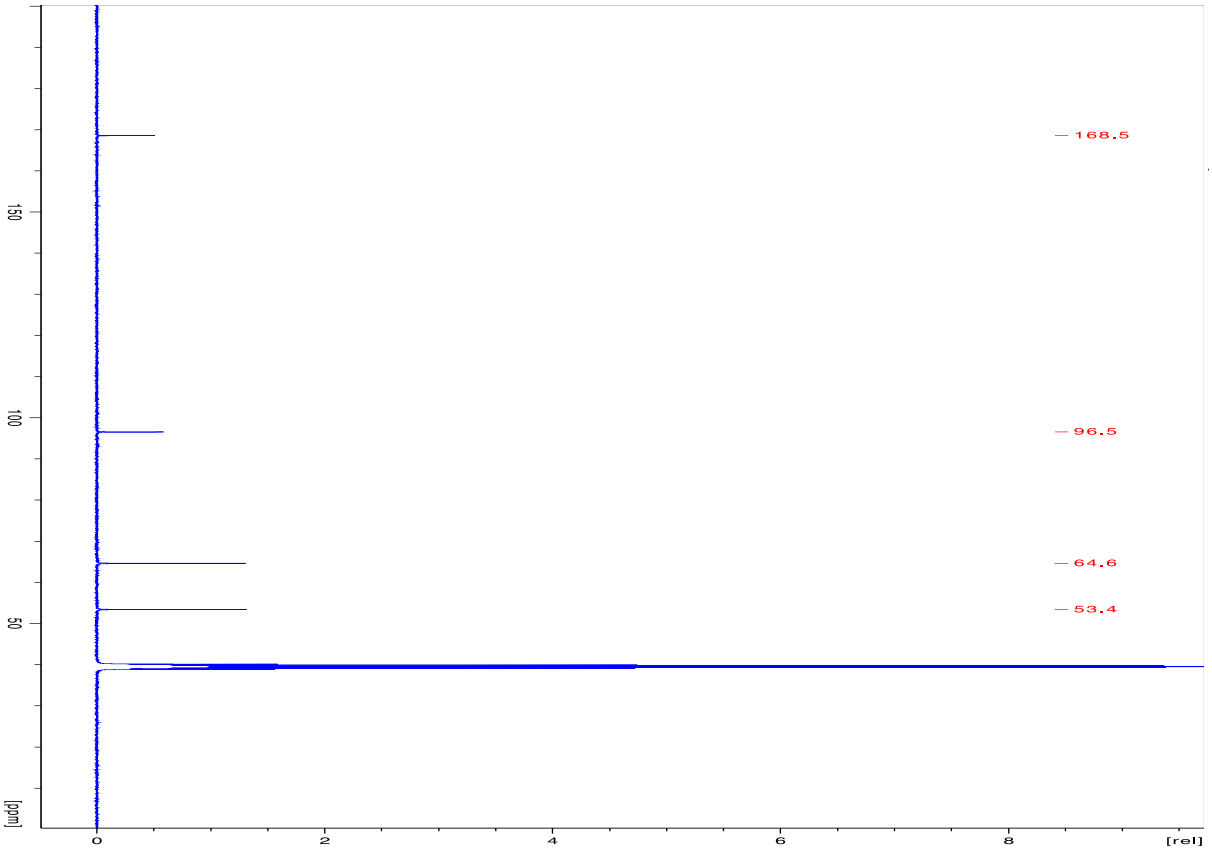
^{1}H NMR spectrum (400 MHz, DMSO-d_6):



12



^{13}C NMR spectrum (100 MHz, DMSO-d_6):


168.5
96.5
64.6
53.4
150
100
50
[ppm]
0
2
4
6
8
[rel]