Supporting Information

Title: Building a Sulfonamide Library by Eco-friendly Flow Synthesis

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Compounds Characterization Checklists

Compound			Identity and Purity						
Entry (from Table 2)	New	Known (Ref.)	m.p.	^{1}H-NMR	^{13}C-NMR	^{1}H-NMR Copies	^{13}C-NMR Copies	IR	HRMS
1		X (1)	X	X	X				
2		X (2)	X	X	X				
3		X (3)	X	X	X				
4		X (4)	X	X	X				
5		X (5)	X	X	X				
6		X (6)	X	X	X			X	
7		X (7)	X	X	X				
8		X (8)	X	X	X				
9		X (9)		X	X				
10		X (10)		X	X				
11		X (11)	X	X	X				
12		X (12)	X	X	X				
13	X		X	X	X	X	X		X
14		X (13)		X	X				
15		X (14)		X	X				
16		X (15)	X	X	X				
17		X (16)	X	X	X				
18	X		X	X	X	X	X		X
19		X (17)	X	X	X				
20		X (18)	X	X	X				
21		X (19)	X	X	X				
22	X		X	X	X	X	X		X
23		X (20)		X	X	X	X		X

24	X			X	X				
25		X (21)	X	X	X				
26		X (22)	X	X	X				
27		X (23)	X	X	X				
28	X		X	X	X	X	X		X
29	X			X	X	X	X		X
30	X		X	X	X	X	X		X
31	X		X	X	X	X	X		X
32	X			X	X	X	X		
33		(24)		X	X				
34		(25)	X	X	X				
35		(26)	X	X	X				
36	X			X	X	X	X		
37	X			X	X	X	X		
38		(27)		X	X				
39	X			X	X	X	X		

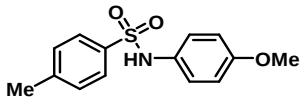
General Methods

Melting points were determined with a Buchi 535 electrothermal apparatus and are uncorrected. NMR spectra were obtained with a Bruker AC 200 MHz or 400 MHZ spectrometer and the chemical shifts are reported in parts per million (ppm). The abbreviations used are as follows: s, singlet; bs, broad singlet; d, doublet; dd, double doublet; m, multiplet. TLC were carried out on pre-coated TLC plates with silica gel 60 F-254 (Merck). Spots were visualized by UV lamp. All experiments were performed using a commercially available Vapourtec R2+/R4 module. Purity of the new compounds was >95% according to the mass and GC analysis. GC/MS analyses were carried out with an Agilent 6850 gas chromatograph equipped with an Agilent 5975B Mass Selective Detector.

General method for the preparation of sulfonamides under eco-flow conditions

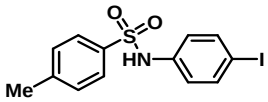
Sulfonyl chloride (0.20 mmol) was dissolved in acetone (2 mL) and the resulting solution was injected in the reagent loop A. An aqueous $NaHCO_3$ 0.4 M (1 mL) was added to a solution of the amine (0.22 mmol) dissolved in PEG-400 (1 mL). The H_2O/PEG400 solution (2 mL, 1:1, v/v) was then injected in the reagent loop B. A degassed solution of acetone and water were connected with pump A and B, respectively and the flow rate was fixed at 0.5 $ml \cdot min^{-1}$ (0.25 $mL \cdot min^{-1}$ + 0.25 $mL \cdot min^{-1}$). After switching the sample loops, the mixtures exited were joined in a T-piece, entered in a 10 ml PTFE coil reactor warmed at 25 °C fitted with the back pressure regulator (100 psi), directed in UV detector and the output was recovered in a fraction collector. The reaction mixture was drooped in a tube containing Et_2O/HCl 3N (5 mL, 4:1, v/v). The two phases were separated, and the organic one was washed with H_2O (2 x 1 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give the desired pure compound. All the solvents were recovered by distillation.

N-(4-Methoxy-phenyl)-4-methyl-benzenesulfonamide (Table 2, entry 1)



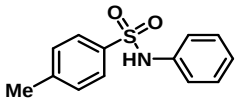
Whitish powder. mp: 95-97 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.39 (3H, s, C*H3*Ph), 3.76 (3H, s, OC*H3*), 6.76 (2H, d, *J* = 8.9 Hz, 3'-C*H* + 5'-C*H*), 6.90 (1H, s, N*H*), 7.01 (2H, d, *J* = 8.9 Hz, 2'-C*H* + 6'-C*H*), 7.22 (2H, d, *J* = 8.3 Hz, 3-C*H* + 5-C*H*), 7.63 (2H, d, *J* = 8.3 Hz, 2-C*H* + 6-C*H*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 21.4, 55.3, 114.3 (x2), 125.2 (x2), 127.3 (x2), 128.9, 129.5 (x2), 135.9, 143.6, 157.8.

N-(4-Iodo-phenyl)-4-methyl-benzenesulfonamide (Table 2, entry 2)



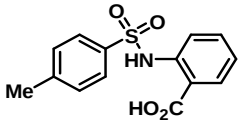
Pale yellow powder. mp: 96-97 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.40 (3H, s, CH_3Ph), 6.87 (2H, d, *J* = 8.8 Hz, 2'-C*H* + 6'-C*H*), 7.26 (2H, d, *J* = 8.0 Hz, 3-C*H* + 5-C*H*), 7.53 (2H, d, *J* = 8.8 Hz, 3'-C*H* + 5'-C*H*), 7.70 (2H, d, *J* = 8.0 Hz, 2-C*H* + 6-C*H*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 21.5, 89.0, 122.9 (x2), 127.2 (x2), 129.7 (x2), 135.6, 136.4, 138.2 (x2), 144.2.

4-Methyl-N-phenyl-benzenesulfonamide (Table 2, entry 3)



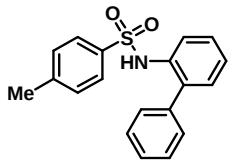
White powder. mp: 102-103 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.39 (3H, s, CH_3Ph), 7.24 (2H, d, *J* = 8.0 Hz, 3-C*H* + 5-C*H*), 7.11-7.30 (5H, m, 2'-C*H* + 3'-C*H* +4'-C*H* + 5'-C*H* + 6'-C*H*), 7.72 (2H, d, *J* = 8.0 Hz, 2-C*H* + 6-C*H*). ^{13}C-NMR ($CDCl_3$, 400 MHz) δ: 21.4, 121.3 (x2), 125.1, 127.2 (x2), 129.2 (x2), 129.6 (x2), 136.0, 136.5, 143.8.

2-(Toluene-4-sulfonylamido)-benzoic acid (Table 2, entry 4)



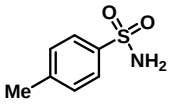
White powder. mp: 96-97 °C. ^{1}H-NMR ($CDCl_3$ + CD_3OD, 400 MHz) δ: 2.40 (3H, s, CH_3Ph), 6.87 (2H, d, J = 8.8 Hz, 2'-CH + 6'-CH), 7.26 (2H, d, J = 8.0 Hz, 3-CH + 5-CH), 7.53 (2H, d, J = 8.8 Hz, 3'-CH + 5'-CH), 7.70 (2H, d, J = 8.0 Hz, 2-CH + 6-CH). ^{13}C-NMR ($CDCl_3$ + CD_3OD, 100.6 MHz) δ: 21.5, 89.0, 122.9 (x2), 127.2 (x2), 129.7 (x2), 135.6, 136.4, 138.2 (x2), 144.2.

N-(Biphenyl-2-yl)-4-methyl-benzenesulfonamide (Table 2, entry 5)



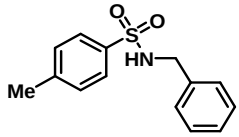
Whitish powder. mp: 99-100 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.42 (3H, s, CH_3Ph), 6.60 (1H, s, NH), 6.87-6.90 (2H, m, Ar), 7.11-7.17 (2H, m, Ar), 7.20-7.22 (2H, d, J = 8.0 Hz, Ar), 7.33-7.39 (4H, m, Ar), 7.49-7.51 (2H, d, J = 8.3 Hz, Ar), 7.73-7.75 (2H, d, J = 8.3 Hz, Ar). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 21.5, 121.2, 124.8, 127.1 (x2), 128.0, 128.6, 128.8 (x2), 129.0 (x2), 129.5 (x2), 130.2, 133.6, 133.8, 136.1, 137.1, 143.8.

4-methylbenzenesulfonamide (Table 2, entry 6)



White powder. mp: 136-138 °C. ^{1}H-NMR ($CDCl_3$ + CD_3OD, 400 MHz) δ: 2.31 (3H, s, CH_3Ph), 3.85 (2H, s, NH_2), 7.19 (2H, d, J = 8.0 Hz, 3-CH + 5-CH), 7.67 (2H, d, J = 8.0 Hz, 2-CH + 6-CH). ^{13}C-NMR ($CDCl_3$ + CD_3OD, 100.6 MHz) δ: 21.1, 125.8 (x2), 129.3 (x2), 139.6, 142.9. IR (KBr, cm^{-1}): ν 3358, 3260, 1918, 1526, 1300, 1157, 903, 817, 704, 523.

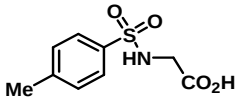
N-Benzyl-4-methyl-benzenesulfonamide (Table 2, entry 7)



Whitish powder. mp: 118-120 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.38 (3H, s, CH_3Ph), 4.05 (2H, s, CH_2NH), 7.13-7.26 (7H, m, Ar), 7.70 (2H, d, J = 8.0 Hz, 2-CH + 6-CH). ^{13}C-NMR

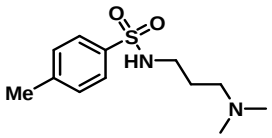
($CDCl_3$, 100.6 MHz) δ: 21., 47.2, 127.1 (x2), 127.8 (x3), 128.6 (x2), 129.7 (x2), 136.2, 136.8, 143.4.

2-(4-methylphenylsulfonamido)acetic acid (Table 2, entry 8)



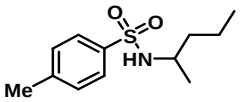
White powder. mp: 146-147 °C. ^{1}H-NMR ($CDCl_3$ + CD_3OD, 400 MHz) δ: 2.35 (3H, s, C*H*$_3$Ph), 3.65 (2H, s, NHC*H*$_2$), 3.82 (2H, s, N*H* + CO_2*H*), 7.24 (2H, d, *J* = 8.3 Hz, 3'-C*H* + 5'-C*H*), 7.68 (2H, d, *J* = 8.3 Hz, 2'-C*H* + 6'-C*H*). ^{13}C-NMR ($CDCl_3$ + CD_3OD, 100.6 MHz) δ: 21.2, 43.6, 126.9 (x2), 129.5 (x2), 136.0, 143.6, 170.6.

N-(3-Dimethylamino-propyl)-4-methyl-benzenesulfonamide (Table 2, entry 9)



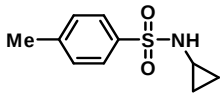
Pale yellow oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.59-1.63 (2H, m, CH_2C*H*$_2$$CH_2$), 2.19 (6H, s, N(C*H*$_3$)$_2$), 2.31 (2H, t, *J* = 6.0 Hz, NHCH_2CH_2C*H*$_2$N), 2.44 (3H, s, C*H*$_3$Ph), 3.06 (2H, t, *J* = 6.1 Hz, NHC*H*$_2$$CH_2CH_2$N), 7.32 (2H, d, *J* = 8.2 Hz, 3-C*H* + 5-C*H*), 7.76 (2H, d, *J* = 8.2 Hz, 2-C*H* + 6-C*H*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 21.4, 24.8, 44.2, 45.2 (x2), 59.4, 127.0 (x2), 129.5 (x2), 137.1, 142.9.

4-Methyl-N-(pentan-2-yl)-benzenesulfonamide (Table 2, entry 10)



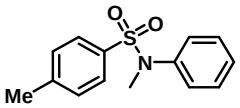
Pale yellow oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 0.80 (3H, t, *J* = 7.2 Hz, CH_2C*H*$_3$), 1.03 (3H, d, *J* = 6.8 Hz, CHC*H*$_3$), 1.28-1.39 (4H, m, C*H*$_2$C*H*$_2$), 2.44 (3H, s, C*H*$_3$Ph), 3.29-3.33 (1H, m, C*H*CH_3), 7.30 (2H, d, *J* = 8.0 Hz, 3-C*H* + 5-C*H*), 7.79 (2H, d, *J* = 8.0 Hz, 2-C*H* + 6-C*H*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 13.6, 18.6, 21.4, 21.5, 39.5, 49.7, 126.9 (x2), 129.5 (x2), 138.2, 143.0.

N-cyclopropyl-4-methyl-benzenesulfonamide (Table 2, entry 11)



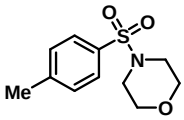
Whitish powder. mp: 52-56 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 0.57-0.61 (4H, m, C*H*$_2$C*H*$_2$), 2.70-2.91 (1H, m, C*H*), 2.44 (3H, s, C*H*$_3$-Ph), 4.98 (1H, s, N*H*), 7.32 (2H, d, *J* = 8.4 Hz, 3-C*H*$_2$ + 5-C*H*$_2$), 7.77 (2H, d, *J* = 8.4 Hz, 2-C*H*$_2$ + 6-C*H*$_2$). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 6.1 (x2), 21.5, 24.2, 127.4 (x2), 129.6 (x2), 136.6, 143.5.

4-methyl-N-methyl-N-phenyl-benzenesulfonamide (Table 2, entry 12)



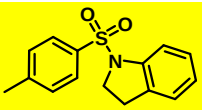
White powder. mp: 90-92 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.41 (3H, s, C*H*$_3$Ph), 3.31 (3H, s, NC*H*$_3$), 7.11 (2H, d, *J* = 8.2 Hz, 3-C*H* + 5-C*H*), 7.22-7.29 (5H, m, Ar), 7.42 (2H, d, *J* = 8.2 Hz, 2-C*H* + 6-C*H*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 21.5, 30.0, 126.6 (x2), 127.2, 127.8 (x2), 128.8 (x2), 129.3 (x2), 133.4, 141.5, 143.5.

N-(4-methylbenzenesulfonyl)morpholine (Table 2, entry 13)



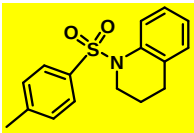
White powder. mp: 145-147 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.44 (3H, s, C*H*$_3$Ph), 2.97-2.99 (4H, m, C*H*$_2$NC*H*$_2$), 3.72-3.75 (4H, m, C*H*$_2$OC*H*$_2$), 7.34 (2H, d, *J* = 8.0 Hz, 3'-C*H* + 5'-C*H*), 7.64 (2H, d, *J* = 8.2 Hz, 2'-C*H* + 6'-C*H*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 21.5, 45.9 (x2), 66.0 (x2), 127.8 (x2), 129.7 (x2), 132.0, 143.9. HRMS: m/z calcd for $C_{11}H_{15}NO_3S$ 241.3077, found 241.3069.

N-(4-methylbenzenesulfonyl)indoline (Table 2, entry 14)



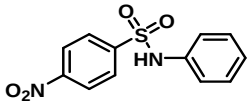
Pale yellow oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.37 (3H, s, 4C*H*$_3$), 2.89 (2H, t, *J* = 8.4 Hz, NCH$_2$C*H*$_2$), 3.91 (2H, t, *J* = 8.4 Hz, NC*H*$_2$CH$_2$), 6.97 (1H, m, Ar), 7.08 (1H, d, *J* = 7.2 Hz, Ar), 7.19 (1H, m, Ar), 7.22 (2H, d, J = 8.0 Hz, 3'-CH + 5'-CH), 7.64 (1H, d, *J* = 8.4 Hz, Ar), 7.68 (2H, d, J = 8.0 Hz, 2'-CH + 6'-CH). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 21.4, 27.8, 49.8, 114.9, 123.6, 125.0, 127.2 (x2), 127.6, 129.5 (x2), 131.7, 133.9, 141.9, 143.9.

N-(4-methylbenzenesulfonyl)1,2,3,4-tetrahydroquinoline (Table 2, entry 15)



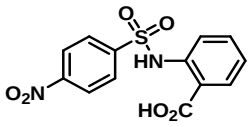
Pale yellow oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.64 (2H, m, NCH$_2$C*H*$_2$CH$_2$), 2.38 (3H, s, 4'-C*H*$_3$), 2.44 (2H, t, *J* = 6.4 Hz, NCH$_2$CH$_2$C*H*$_2$), 3.80 (2H, t, *J* = 6.4 Hz, NC*H*$_2$CH$_2$CH$_2$), 7.0 (1H, m, Ar), 7.07 (1H, m, Ar), 7.19 (1H, m, Ar), 7.19 (2H, d, J = 8.0 Hz, 3'-CH + 5'-CH), 7.49 (2H, d, *J* = 8.0 Hz, 2'-CH + 6'-CH), 7.78 (1H, d, *J* = 8.4 Hz, Ar). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 21.4, 21.5, 26.5, 46.4, 124.84, 124.87, 126.4, 127.0 (x2), 128.9, 129.4 (x2), 130.5, 136.7, 136.8, 143.4.

4-Nitro-N-phenyl-benzenesulfonamide (Table 2, entry 16)



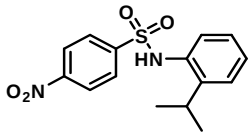
Pale yellow powder. mp: 172-173 °C. ^{1}H-NMR ($CDCl_3$+ CD_3OD, 400 MHz) δ: 7.01-7.06 (3H, m, Ar), 7.15-7.19 (2H, m, Ar), 7.85-7.87 (2H, d, *J* = 8.8 Hz, 2-C*H* + 6-C*H*), 8.18-8.20 (2H, d, *J* = 8.8 Hz, 3-C*H* + 5-C*H*). ^{13}C-NMR ($CDCl_3$+ CD_3OD, 100.6 MHz) δ: 121.6 (x2), 123.9 (x2), 125.5, 128.0 (x2), 129.2 (x2), 136.1, 145.1, 149.8.

2-(4-Nitro-benzenesulfonylamido)-benzoic acid (Table 2, entry 17)



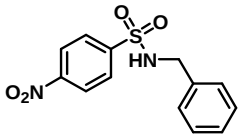
Withish powder. mp: 145-148 °C. ^{1}H-NMR ($CDCl_3$ + CD_3OD, 400 MHz) δ: 7.05 (1H, t, *J* = 7.7 Hz, 5-C*H*), 7.44 (1H, t, *J* = 8.7 Hz, 4-C*H*), 7.63 (1H, d, *J* = 8.7 Hz, 3-C*H*), 7.93 (1H, d, *J* = 7.7 Hz, 6-C*H*), 7.96 (2H, d, *J* = 8.7 Hz, 2'-C*H* + 6'-C*H*), 8.21 (2H, d, *J* = 8.7 Hz, 3'-C*H* + 5'-C*H*). ^{13}C-NMR ($CDCl_3$ CD_3OD, 100.6 MHz) δ: 116.2, 123.7, 124.1 (x2), 128.4 (x2), 131.9, 134.1, 134.4, 144.7, 150.0, 169.9.

N-(2-Isopropyl-phenyl)-4-nitro-benzenesulfonamide (Table 2, entry 18)



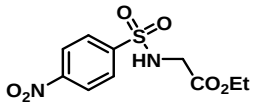
Pale yellow powder. mp: 113-116 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.01 (6H, d, *J* = 6.3 Hz, CH(C*H*$_3$)$_2$), 2.28 (1H, m, C*H*(CH$_3$)$_2$), 6.48 (1H, s, N*H*), 7.15-7.26 (4H, m, Ar), 7.90 (2H, d, *J* = 9.2 Hz, 2-C*H* + 6-C*H*), 8.29 (2H, d, *J* = 9.2Hz, 3-C*H* + 5-C*H*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 23.2, 27.6, 124.1 (x2), 126.0, 126.5, 126.7, 128.0, 128.6 (x2), 130.6, 131.5, 143.4, 145.1, 150.1. HRMS: m/z calcd for $C_{15}H_{16}N_2O_4S$ 320.3646, found 320.3637.

N-Benzyl-4-nitro-benzenesulfonamide (Table 2, entry 19)



Pale yellow powder. mp: 124-126 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 4.22 (2H, d, *J* = 6.0 Hz, NHC*H*$_2$), 5.20 (1H, t, *J*= 5.6 N*H*CH$_2$), 7.16-7.18 (2H, m, Ar), 7.25-7.27 (3H, m, Ar), 7.98 (2H, d, *J* = 8.7 Hz, 2-C*H* + 6-C*H*), 8.29 (2H, d, *J* = 8.7 Hz, 3-C*H* + 5-C*H*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 47.3, 124.2 (x2), 127.8 (x2), 128.2, 128.2 (x2), 128.7 (x2), 135.4, 146.0, 149.9.

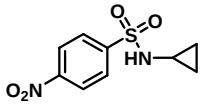
Ethyl 2-(4-Nitro-benzenesulfonylamido)acetate (Table 2, entry 20)



Whitish powder. mp: 114-115 °C. ^{1}H-NMR ($CDCl_3$+ CD_3OD, 400 MHz) δ: 1.14 (3H, t, *J* = 7.1 Hz, CH$_2$C*H*$_3$), 3.80 (2H, s, NHC*H*$_2$), 4.03 (2H, q, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 8.02 (2H, d, *J* = 8.9 Hz,

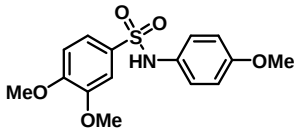
2'-C*H* + 6'-C*H*), 8.30 (2H, d, *J* = 8.9 Hz, 3'-C*H* + 5'-C*H*). ^{13}C-NMR ($CDCl_3$+ CD_3OD, 100.6 MHz) δ: 13.7, 43.9, 61.8, 124.1 (x2), 128.2 (x2), 145.8, 149.9, 168.7.

N-cyclopropyl-4-nitro-benzenesulfonamide (Table 2, entry 21)



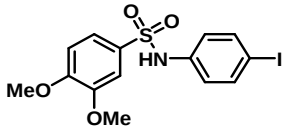
Whitish powder. mp: 150-153 °C. ^{1}H-NMR ($CDCl_3$+ CD_3OD, 400 MHz) δ: 0.52-0.56 (4H, m, CH_2CH_2), 2.18-2.20 (1H, m, NHC*H*), 8.03 (2H, d, *J* = 8.9 Hz, 2-C*H* + 6-C*H*), 8.32 (2H, d, *J* = 8.9 Hz, 3-C*H* + 5-C*H*). ^{13}C-NMR ($CDCl_3$+ CD_3OD, 400 MHz) δ: 5.7 (x2), 23.9, 124.1 (x2), 128.5 (x2), 145.8, 149.9.

3,4-Dimethoxy-N-(4-methoxy-phenyl) benzenesulfonamide (Table 2, entry 22)



White powder. mp: 33-136 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 3.75 (3H,s, 4'-OCH_3), 3.78 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 6.69 (1H, s, N*H*), 6.76 (2H, d, *J* = 8.8 Hz, 3'-C*H* + 5'-C*H*), 6.84 (1H, d, *J* = 8.4 Hz, 5-CH), 6.99 (2H, d, *J* = 8.8 Hz, 2'-C*H* + 6'-C*H*), 7.14 (1H, d, *J* = 2.0 Hz, 2-C*H*), 7.32 (1H, dd, J_1 = 2.0 Hz, J_2= 8.4 Hz, 6-C*H*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 14.2, 55.4, 56.1 (x2), 109.7, 110.3, 114.4 (x2), 121.3, 125.6 (x2), 129.0, 130.5, 148.8, 152.6, 158.0. HRMS: m/z calcd for $C_{15}H_{17}NO_5S$ 323.0827, found 323.0837.

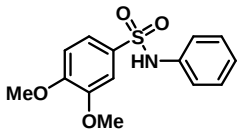
3,4-dimethoxy -N-(4-Iodo-phenyl)benzenesulfonamide (Table 2, entry 23)



Brown-yellow oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 3.79 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 6.84 (1H, d, *J* = 8.6 Hz, 5-C*H*), 6.86 (2H, d, *J* = 8.8 Hz, 1'-C*H* + 5'-C*H*), 7.23 (1H, d, *J* = 2.1 Hz, 2-C*H*), 7.39 (1H, dd, J_1 = 2.1 Hz, J_2 = 8.4 Hz, 6-C*H*), 7.52 (2H, d, *J* = 8.7 Hz, 2'-C*H* + 4'-C*H*).

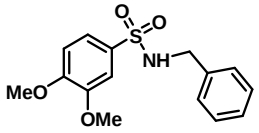
^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 56.1 (x2), 89.2, 109.4, 110.4, 121.3, 123.2 (x2), 130.0, 136.5, 138.2 (x2), 149.1, 152.9. HRMS: m/z calcd for $C_{14}H_{14}INO_4S$ 419.2358, 419.2351.

3,4-Dimethoxy-N-phenyl-benzenesulfonamide (Table 2, entry 24)



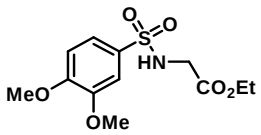
Colorless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 3.78 (3H, s, OC*H*$_3$), 3.90 (3H, s, OC*H*$_3$), 6.80 (1H, s, N*H*), 6.85 (1H, d, *J* = 8.5 Hz, 5-CH), 7.08-7.27 (6H, m, Ar), 7.40 (1H, dd, J_1 = 2.1 Hz, J_2 = 8.7 Hz, 6-C*H*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 56.1 (x2), 109.6, 110.4, 121.2, 122.0 (x2)**,** 125.5, 129.3 (x2), 130.5, 136.6, 148.9, 152.8.

N-Benzyl-3,4-dimethoxy-benzenesulfonamide (Table 2, entry 25)



Whitish powder. mp: 115-118 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 3.97 (3H, s, OC*H*$_3$), 3.94 (3H, s, OC*H*$_3$), 4.12 (2H, d, *J* = 6.0 Hz, NHC*H*$_2$), 4.97 (1H, t, *J* = 6.0 Hz, N*H*), 6.91 (1H, d, *J* = 8.8 Hz, 2-C*H*), 7.17-7.27 (5H, m, Ar), 7.30 (1H, d, *J* = 2.3 Hz, 2-C*H*), 7.49 (1H, dd, J_1 = 2.1 Hz, J_2 = 8.4 Hz, 6-C*H*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 47.2, 56.2 (x2), 109.6, 110.5, 121.1, 127.8 (x3), 128.6, 131.5, 136.3, 149.1, 152.6.

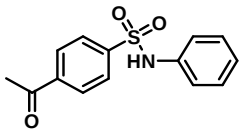
Ethyl (3,4-dimethoxy-benzenesulfonylamido)acetate (Table 2, entry 26)



White powder. mp: 89-90 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.20 (3H, t, *J* = 7.1 Hz, CH_2C*H*$_3$), 3.76 (2H, d, *J* = 5.4 Hz, NHC*H*$_2$), 3.93 (3H, s, OC*H*$_3$), 3.94 (3H, s, OC*H*$_3$), 4.09 (2H, q, *J* = 7.1 Hz, C*H*$_2$$CH_3$), 5.09 (1H, t, *J* = 5.4 Hz, N*H*), 6.93 (1H, d, *J* = 8.4 Hz, 5'-C*H*), 7.32 (1H, d, *J* = 2.0

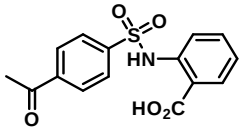
Hz, 2'-C*H*), 7.49 (1H, dd, J_1 = 2.3 Hz, J_2 = 8.4 Hz, 6'-C*H*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 13.9, 44.1, 56.1, 56.2, 61.9, 109.6, 110.4, 121.3, 130.6, 149.2, 152.7, 168.8.

4-acetyl-N-phenyl-benzensolfonamide (Table 2, entry 27)



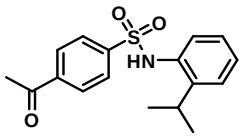
White powder. mp: 99-102 °C.^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.61 (3H, s, COCH_3), 6.97 (1H, s, N*H*), 7.08 (2H, d, *J* = 8.2 Hz, 3'-C*H* + 5'-C*H*), 7.14 (1H, t, *J* = 7.3 Hz, 4'-C*H*), 7.25 (2H, d, *J* = 7.6 Hz, 2'-C*H* + 6'-C*H*), 7.86 (2H, d, *J* = 8.7 Hz, 3-C*H* + 5-C*H*), 7.99 (2H, d, *J* = 8.7 Hz, 2-C*H* + 6-C*H*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 26.8, 122.0 (x2), 125.9, 127.5 (x2), 128.8 (x2), 129.4 (x2), 135.8, 140.2, 142.8, 196.8.

2-(4-acetylphenylsolfonamido)benzoic acid (Table 2, entry 28)



White powder. mp: 178-180 °C (dec.). ^{1}H-NMR ($CDCl_3$ + CD_3OD, 400 MHz) δ: 2.13 (3H, s, COCH_3), 6.36 (1H, t, *J* = 7.5 Hz, 4-C*H*), 7.01 (1H, t, *J* = 7.6 Hz, 5-C*H*), 7.21 (1H, d, *J* = 8.1 Hz, 3-C*H*), 7.45 (2H, d, *J* = 8.2 Hz, 3'-C*H* + 5'-C*H*), 7.49 (1H, d, *J* = 7.9 Hz, 6-C*H*), 7.57 (2H, d, *J* = 8.2 Hz, 2'-C*H* + 6'-C*H*). ^{13}C-NMR ($CDCl_3$ CD_3OD, 100.6 MHz): 25.3, 118.3, 122.7, 126.7 (x2), 128.0 (x2), 131.0, 133.4 (X2), 139.2, 139.5, 142.1, 196.9. HRMS: m/z calcd for $C_{15}H_{13}NO_5S$ 319.3335 found 319.3339.

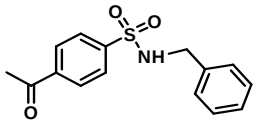
4-acetyl-N-(2-isopropylphenyl)-benzenesolfonamide (Table 2, entry 29)



Pale yellow oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 0.94 (6H, d, *J* = 6.4 Hz, C*H*$(CH_3)_2$), 2.58 (3H, s, COCH_3), 2.78-2.82 (1H, m, C*H*$(CH_3)_2$), 6.50 (1H, s, N*H*), 7.08-7.12 (1H, m, Ar), 7.16-7.17 (2H, m, Ar), 7.20-7.22 (1H, m, Ar), 7.77 (2H, d, *J* = 8.4 Hz, 3-C*H* + 5-C*H*), 7.95 (2H, d, *J* = 8.4 Hz,

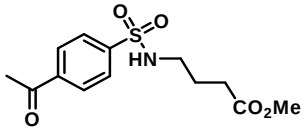
2-C*H* + 6-C*H*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 23.2 (x2), 26.8, 27.4, 125.8, 126.2, 126.6, 127.5 (x2), 128.7 (x2), 132.0 (x2), 140.1, 143.1, 143.3, 196.7. HRMS: m/z calcd for $C_{17}H_{19}NO_3S$ 317.4037, found 317.4042.

N-benzyl-4-acetylbenzensolfonamide (Table 2, entry 30)



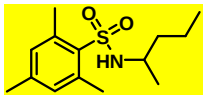
Whitish powder. mp: 169-172 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.62 (3H, s, COCH_3), 4.15 (2H, d, *J* = 6.0 Hz, NHCH_2), 4.85 (1H, t, *J* = 6.0 Hz, N*H*), 7.13-7.24 (5H, m, Ar), 7.90 (2H, d, *J* = 8.4 Hz, 3-C*H* + 5-C*H*), 8.01 (2H, d, *J* = 8.4 Hz, 2-C*H* + 6-C*H*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 26.8, 47.3, 127.3 (x2), 127.8 (x2), 128.1, 128.7 (x2), 128.9 (x2), 135.7, 139.9, 143.9, 196.7. HRMS: m/z calcd for $C_{15}H_{15}NO_3S$ 289.3505, found 289.3509.

Methyl-4-(4-acetyl-benzenesulfonylamino)-butanoate (Table 2, entry 31)



Whitish powder. mp: 169-172 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.18 (2H, m, $CH_2CH_2CH_2CO_2Me$) 2.37 (2H, t, J = 7.2 Hz, m, $CH_2CH_2CH_2CO_2Me$), 2.65 (3H, s, COCH_3), 3.06 (2H, q, *J* = 6.4, $CH_2CH_2CH_2CO_2Me$), 5.00 (1H, m, N*H*), 7.95 (2H, d, *J* = 6.0 Hz, 3-C*H* + 5-C*H*), 8.07 (2H, d, *J* = 6.0 Hz, 2-C*H* + 6-C*H*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 24.6, 26.8, 30.8, 42.6, 51.8, 127.2 (x2), 128.9 (x2), 139.9, 143.9, 173.5, 196.7. HRMS: m/z calcd for $C_{13}H_{17}NS_5S$ 299.3438, found 299.3442.

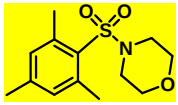
N-(pentan-2-yl)-mesitylsulfonamide (Table 2, entry 32)



Pale yellow oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 0.76-0.80 (3H, t, *J* = 7.17, CH_2CH_3), 1.01-1.02 (3H, d, *J* = 6.55, NHCHCH_3), 1.1-1.3 (4H, m, CH_2CH_2), 2.30 (3H, s, 4-CH_3), 2.65 (6H, s, 2-CH_3

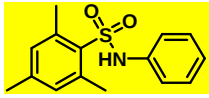
+ 6-CH_3), 3.2-3.25 (1H, m, NHC*H*), 6.95 (2H, s, 3-C*H* + 5-C*H*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ:13.6, 18.6, 20.8, 21.4, 23.0 (x2), 39.6, 49.3, 131.8 (x2), 134.8, 138.7 (x2), 141.8.

N-(mesitylsulfonyl)-morpholine (Table 2, entry 33)



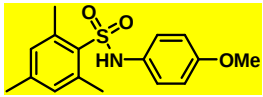
Whitish powder. mp: 65-68 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.30 (3H, s, 4'-CH_3), 2.63 (6H, s, 2'-CH_3 + 6'-CH_3), 3.13-3.16 (4H, t, *J* = 4.7 Hz, CH_2OCH_2), 3.67-3.69 (4H, t, *J* = 4.7 Hz, CH_2NCH_2), 6.96 (2H, s, 3'-C*H* + 5'-C*H*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 20.9, 22.8 (x2), 44.2 (x2), 66.1 (x2), 130.7, 131.9 (x2), 140.6 (x2), 142.8.

N-phenyl-mesitylsulfonamide (Table 2, entry 34)



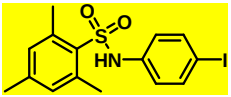
Withish powder. mp: 167-168 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.27 (3H, s, 4'-CH_3), 2.63 (6H, s, 2'-CH_3 + 6'-CH_3), 6.96 (2H, s, 3'-C*H* + 5'-C*H*), 6.98-7.22 (5H, m, Ar). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 20.9, 22.9 (x2), 121.1 (x2), 124.9, 129.2 (x2), 132.0 (x2), 133.4, 136.5, 139.3 (x2), 142.6.

N-(4-methoxyphenyl)-mesitiysulfonamide (Table 2, entry 35)



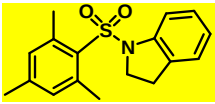
Yellow oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.27 (3H, s, 4-CH_3), 2.53 (6H, s, 2-CH_3 + 6-CH_3), 3.73 (3H, s, OCH_3), 6.89 (2H, s, 3-C*H* + 5-C*H*), 6.61-6.91 (4H, m, Ar). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 20.9, 22.9 (x2), 55.3, 114.3 (x2), 125.7 (x2), 128.6, 131.8 (x2), 133.2, 139.3 (x2), 142.4, 157.9.

N-(4-iodo-phenyl)-mesitylsulfonamide (Table 2, entry 36)



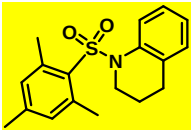
Brown oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.28 (3H, s, 4-CH_3), 2.62 (6H, s, 2-CH_3 + 6-CH_3), 6.71-6.73 (2H, m, Ar), 6.93 (2H, s, 3-C*H* + 5-C*H*), 7.49-7.51 (2H, m, Ar). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 20.9, 22.98 (x2), 88.5, 122.4 (x2), 131.9, 132.1 (x2), 132.9, 136.4, 138.2 (x2), 139.2 (x2), 142.9.

N-(mesitylsulfonyl)-indoline (Table 2, entry 37)



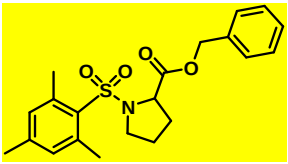
Yellow oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.31 (3H, s, 4'-CH_3), 2.66 (6H, s, 2'-CH_3 + 6'-CH_3), 3.07-3.11 (2H, t, J = 8.5 Hz, NCH_2CH_2), 3.89-3.93 (2H, t, J = 8.5 Hz, NCH_2), 6.98 (2H, s, 3'-C*H* + 5'-C*H*), 6.94-7.14 (4H, m, Ar). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 20.9, 22.8 (x2), 27.9, 48.7, 113.8, 122.7, 124.9, 127.4, 130.9, 132.1 (x2), 133.3, 140.2 (x2), 142.8, 142.9.

N-(mesitylsulfonyl)-1,2,3,4-tetraidroquinoline (Table 2, entry 38)



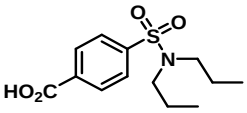
Pale yellow oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.94-1.97 (2H, m, $NCH_2CH_2CH_2$), 2.32 (3H, s, 4'-CH_3), 2.53 (6H, s, 2'-CH_3 + 6'-CH_3), 2.78-2.82 (2H, t, J = 6.8 Hz, $NCH_2CH_2CH_2$), 3.73-3.76 (2H, m, $NCH_2CH_2CH_2$), 6.96 (2H, s, 3'-C*H* + 5'-C*H*), 7.02-7.05 (4H, m, Ar). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 20.9, 22.3, 22.8 (x2), 26.6, 45.3, 123.3, 124.5, 126.1, 129.5, 130.3, 132.1 (x2), 135.0, 137.9, 139.8 (x2), 142.6.

Benzyl-N-(mesitylsulfonyl)-prolinate (Table 2, entry 39)



Colorless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.97-2.07 (4H, m, $NCH_2CH_2CH_2$), 2.27 (3H, s, 4'-CH_3), 2.61 (6H, s, 2'-CH_3 + 6'-CH_3), 3.42-3.57 (2H, m, $NCH_2CH_2CH_2$), 4.43 (1H, d.d., J_1 = 3.2 Hz, J_2 = 8.8 Hz, NC*H*), 4.88, (2H, s, CH_2-Ph), 6.89 (2H, s, 3'-C*H* + 5'-C*H*), 7.22-7.35 (5H, m, Ar). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 20.9, 22.8 (x2), 24.7, 31.4, 48.1, 59.3, 66.7, 128.0 (x2), 128.3, 128.5 (x2), 131.8 (x2), 132.5, 135.4, 140.6 (x2), 142.6, 171.8.

Scale up synthesis of Probenecib under eco-flow conditions

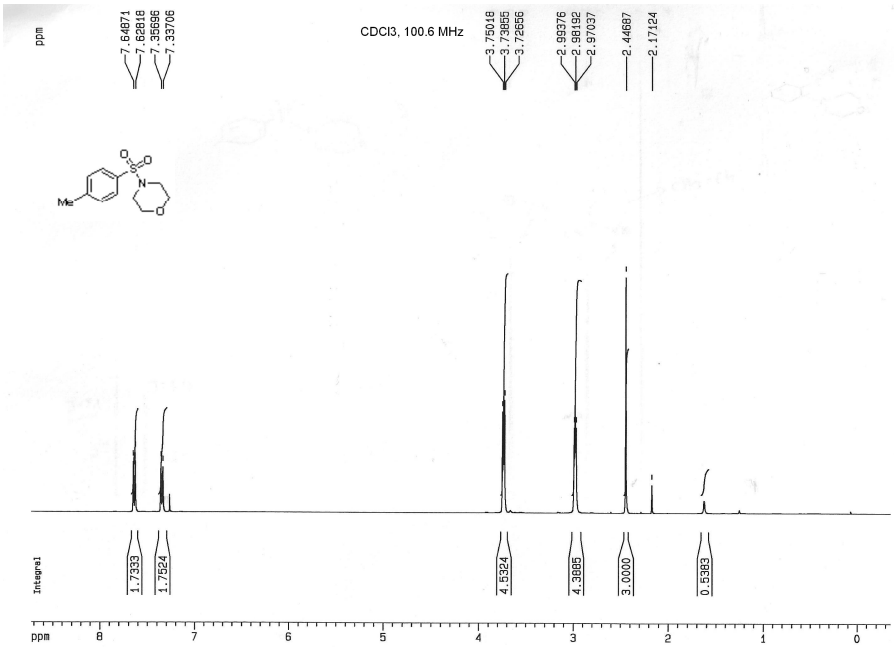


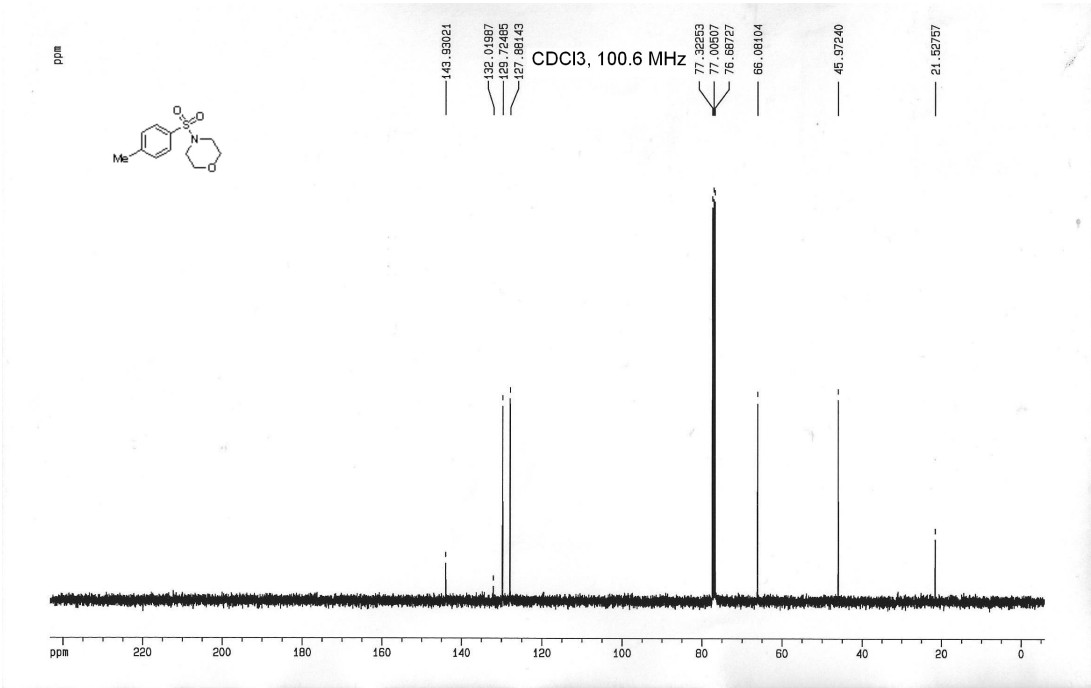
4-(chlorosulfonyl)benzoic acid (**7**) (4.41 g, 20.00 mmol) was dissolved in acetone (200 ml) and the resulting mixture was pumped at 0.25 ml·min^{-1}. An aqueous $NaHCO_3$ 0.4 M (100 ml) was added to a solution of the dipropylamine (**8**) (5.6 ml, 42.00 mmol) dissolved in PEG400 (100 ml). The H_2O/PEG400 solution pumped at 1.0 mL·min^{-1}. The two solutions were joined in a T-piece and entered in a 10 ml PTFE coil reactor warmed at 25 °C, fitted with the back pressure regulator (100 psi) and directed in UV detector. The output was acidified by adding HCl 3N up to pH = 2, and the resulted precipitate was collected by filtration, washed with H_2O and dried under vacuum at 60 °C, thus obtaining 4.56 g of pure Probenecid (**7**) (78%) as white powder.
mp: 194-196 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 0.84 (6H, t, *J* = 7.2 Hz, 2 x CH_3), 1.43-1.61 (4H, m, 2 x CH_2CH_3),3.00-3.05(4H, m, 2 x NCH_2), 7.91 (2H, d, *J* = 8.7 Hz, 3-C*H* + 5-C*H*), 8.25 (2H, d, *J* = 8.7 Hz, 2-C*H* + 6-C*H*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 11.1 (x2), 21.8 (x2), 49.8 (x2), 127.0 (x2), 130.7 (x2), 134.4, 139.1, 167.4. HRMS: m/z calcd for $C_{13}H_{17}NS_5S$ 285.1035, found 285.1043.

Recovery of the solvents: the acetone/H_2O/PEG400 media was washed with Et_2O (3 x 25 mL), and volatiles (Et_2O, acetone, water) were recovered by distillation. Aqueous NaOH 12 N

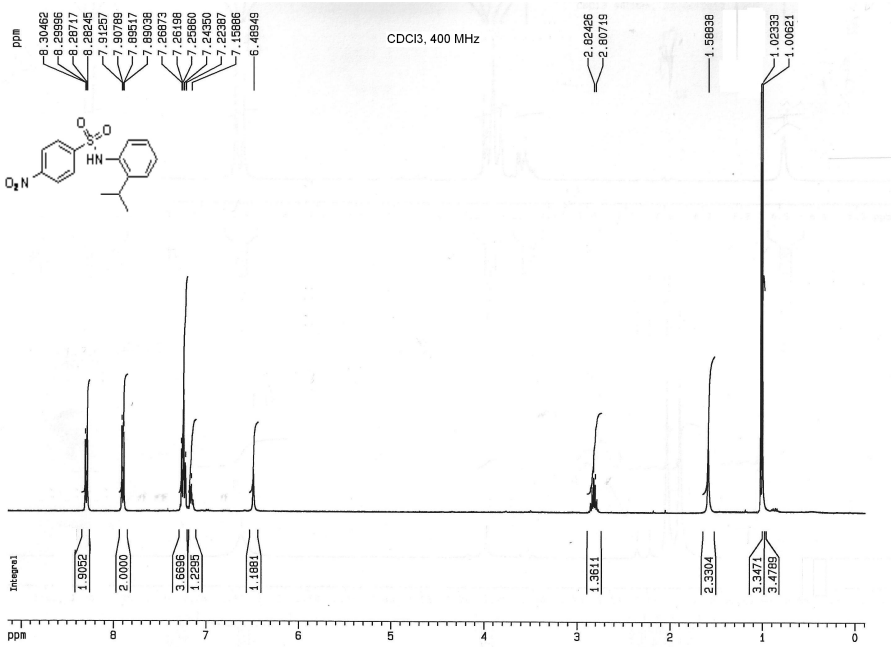
solution was added dropwise to the residual PEG400 up to pH= 14, and the thus obtained mixture was vigorously shaken with Amberlyst A15 (25 g) for 60 minutes. Removal of Amberlyst A15 by filtration and evaporation of residual water under reduced pressure, gave PEG400 (ca. 95 mL) with appreciably purity.

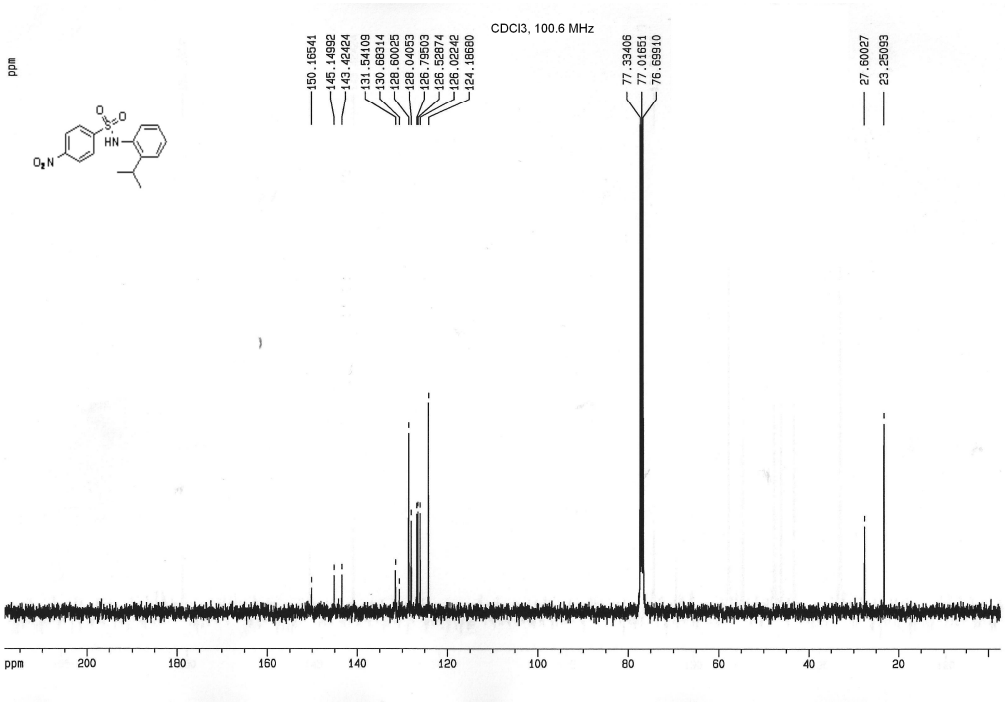
N-(4-methylbenzenesulfonyl)morpholine



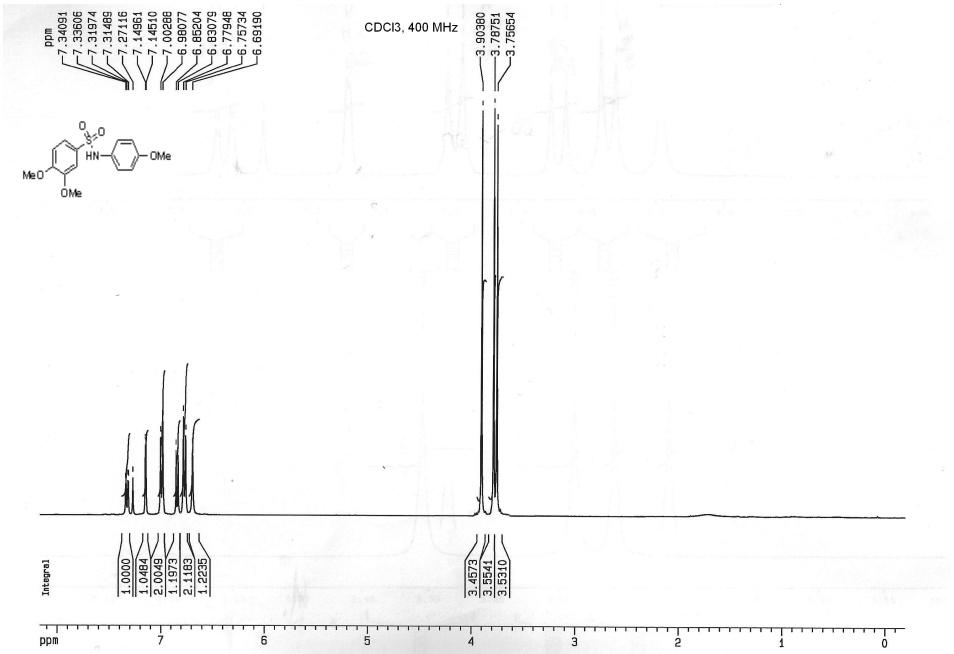


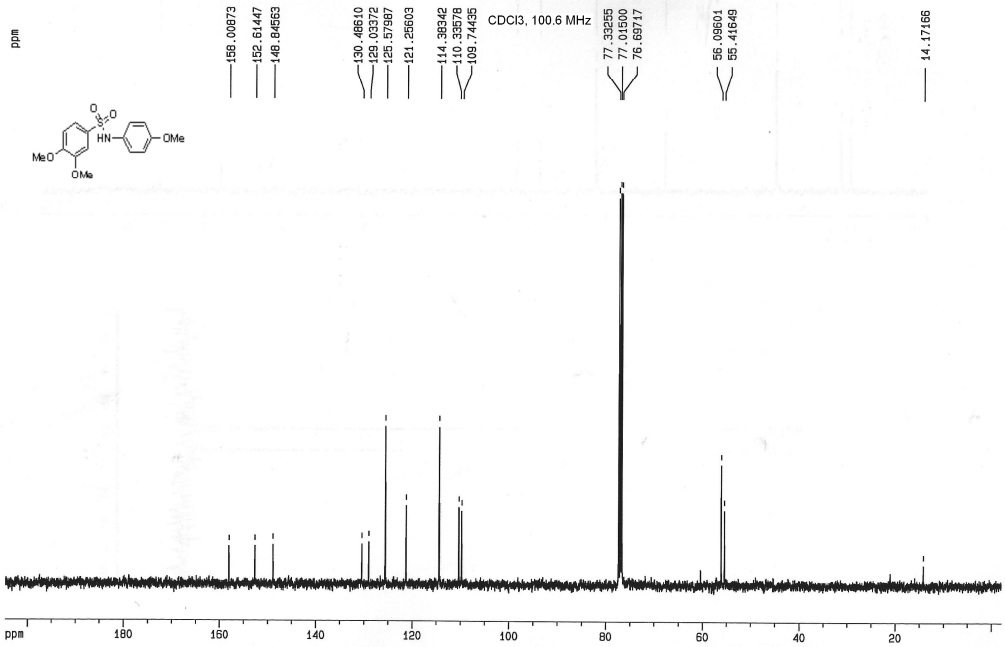
N-(2-Isopropyl-phenyl)-4-nitro-benzenesulfonamide



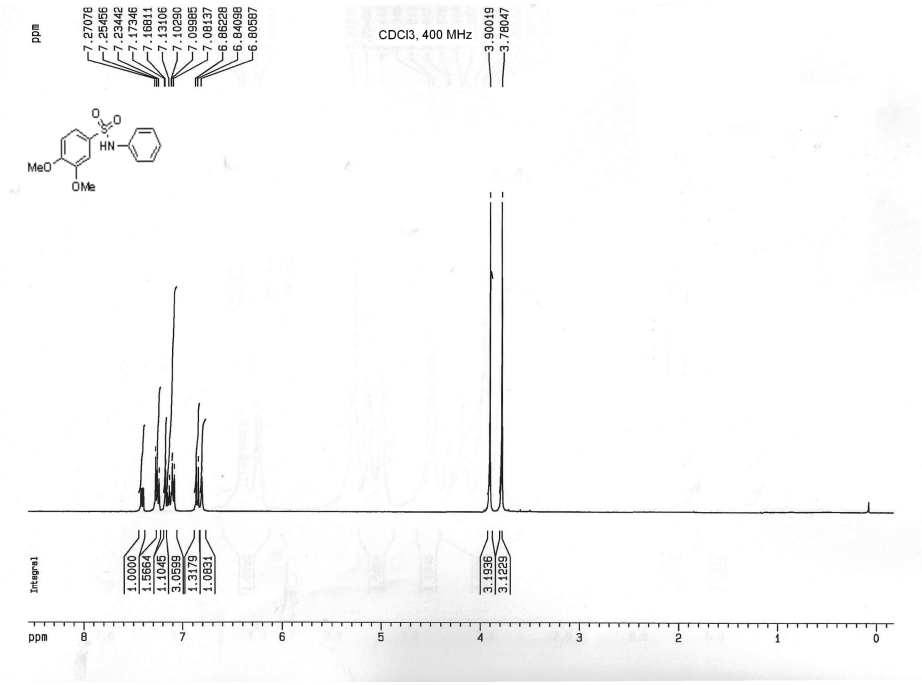


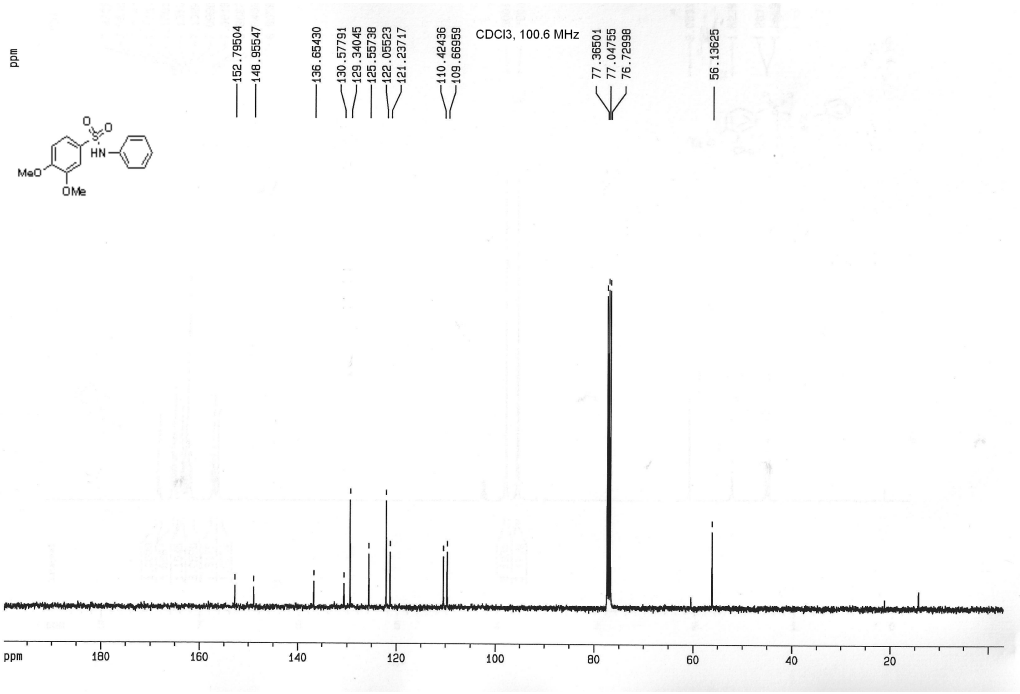
3,4-Dimethoxy-N-(4-methoxy-phenyl) benzenesulfonamide



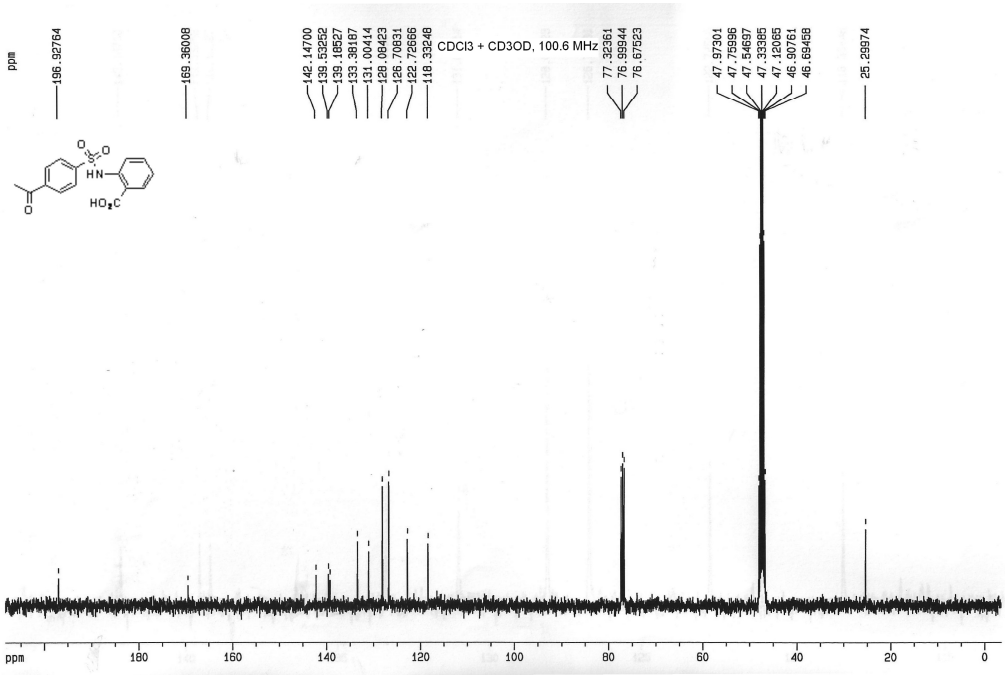


3,4-Dimethoxy-N-phenyl-benzenesulfonamide

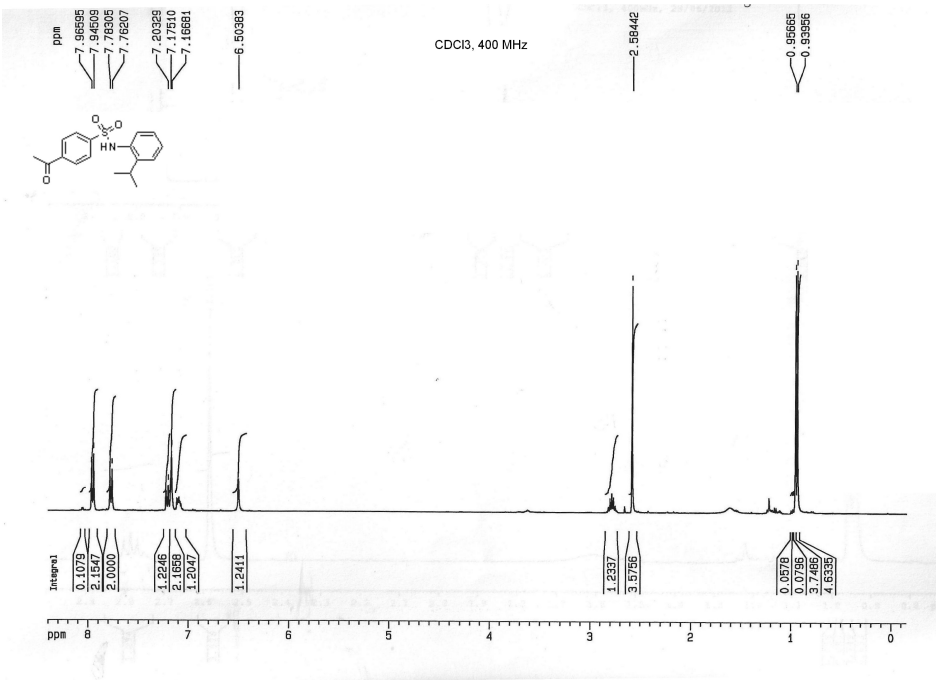


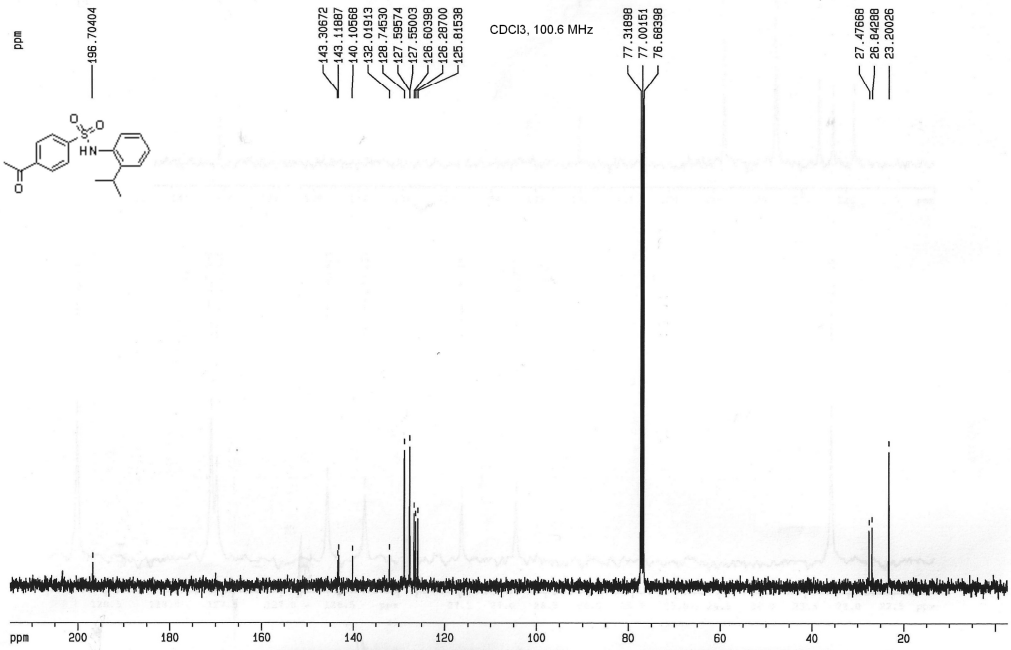


2-(4-acetylphenylsolfonamido)benzoic acid

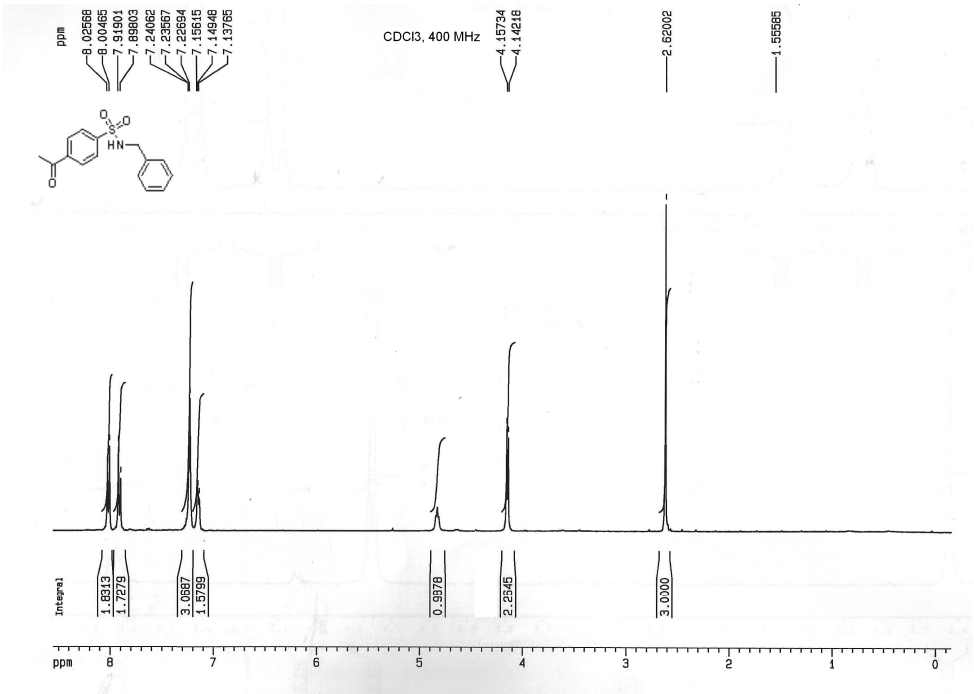


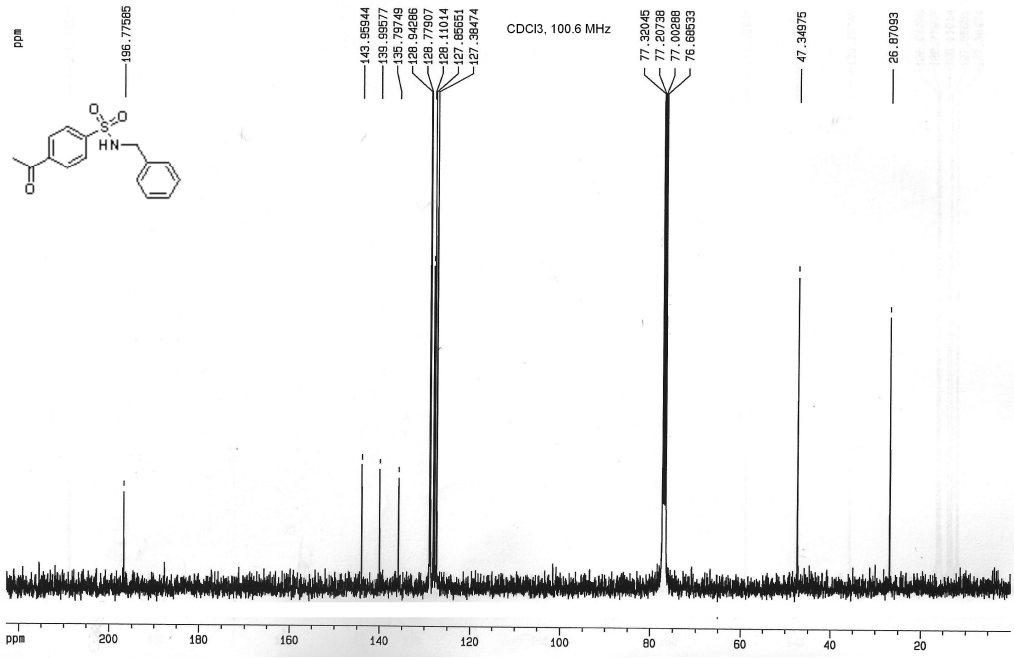
4-acetyl-N-(2-isopropylphenyl)-benzenesolfonamide



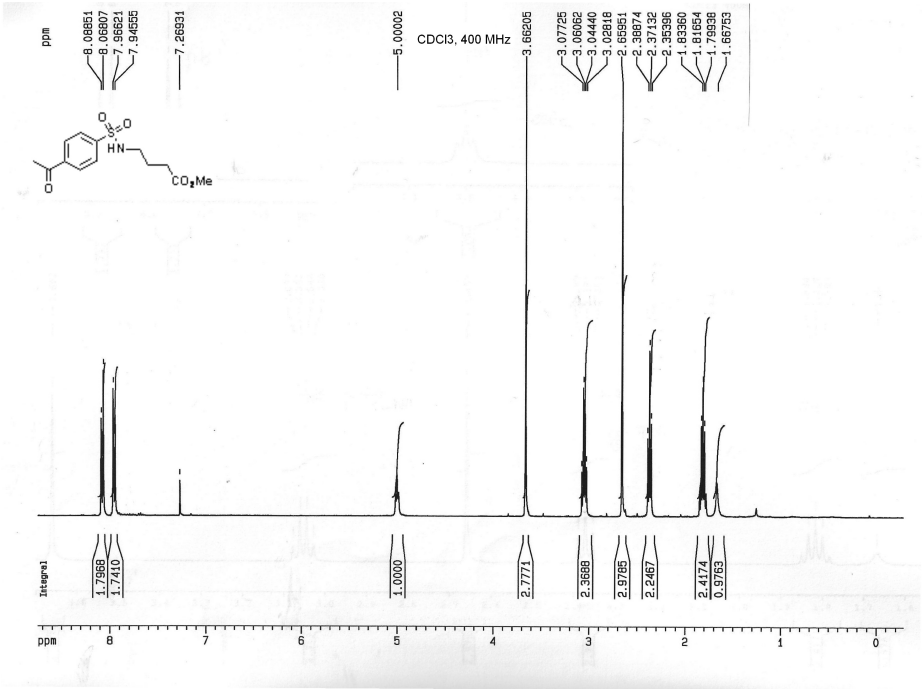


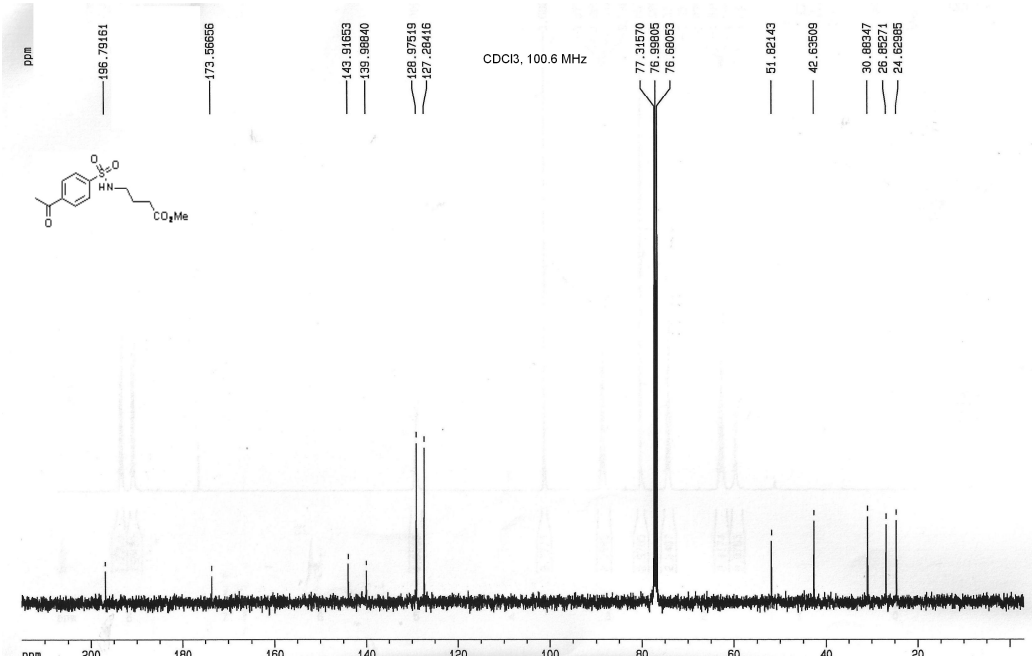
N-benzyl-4-acetylbenzensolfonamide



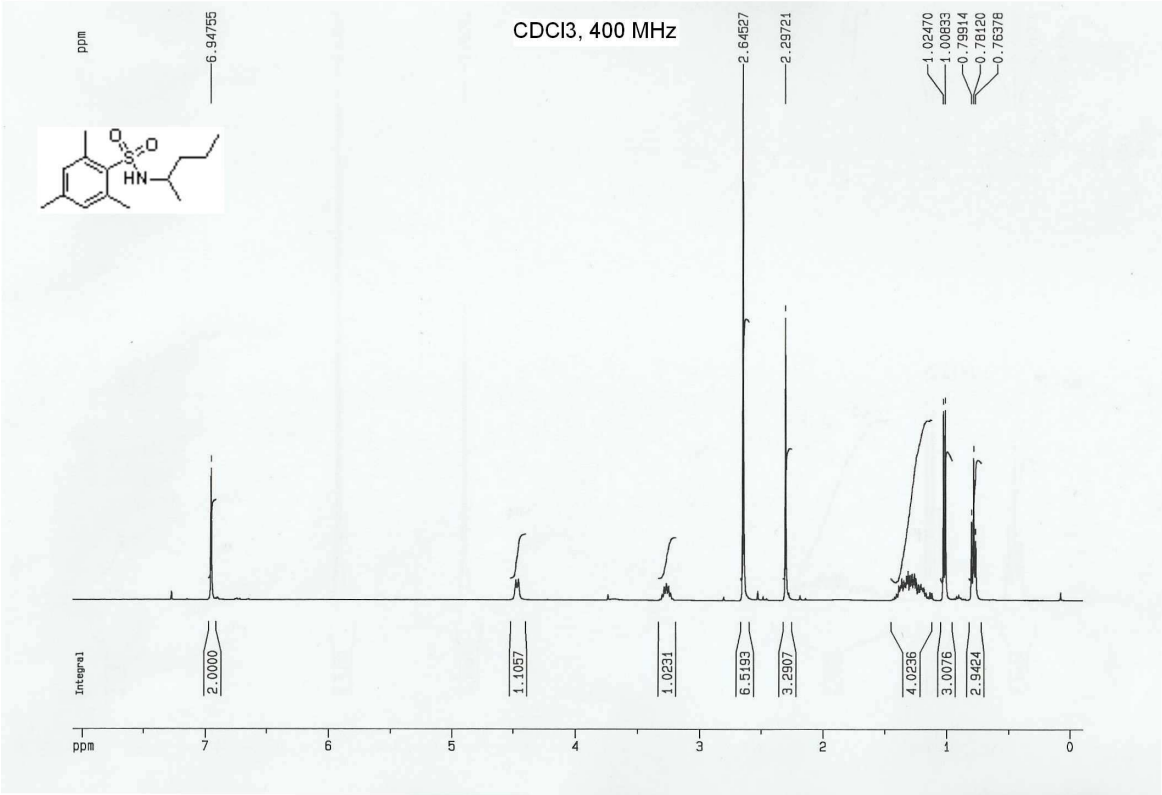


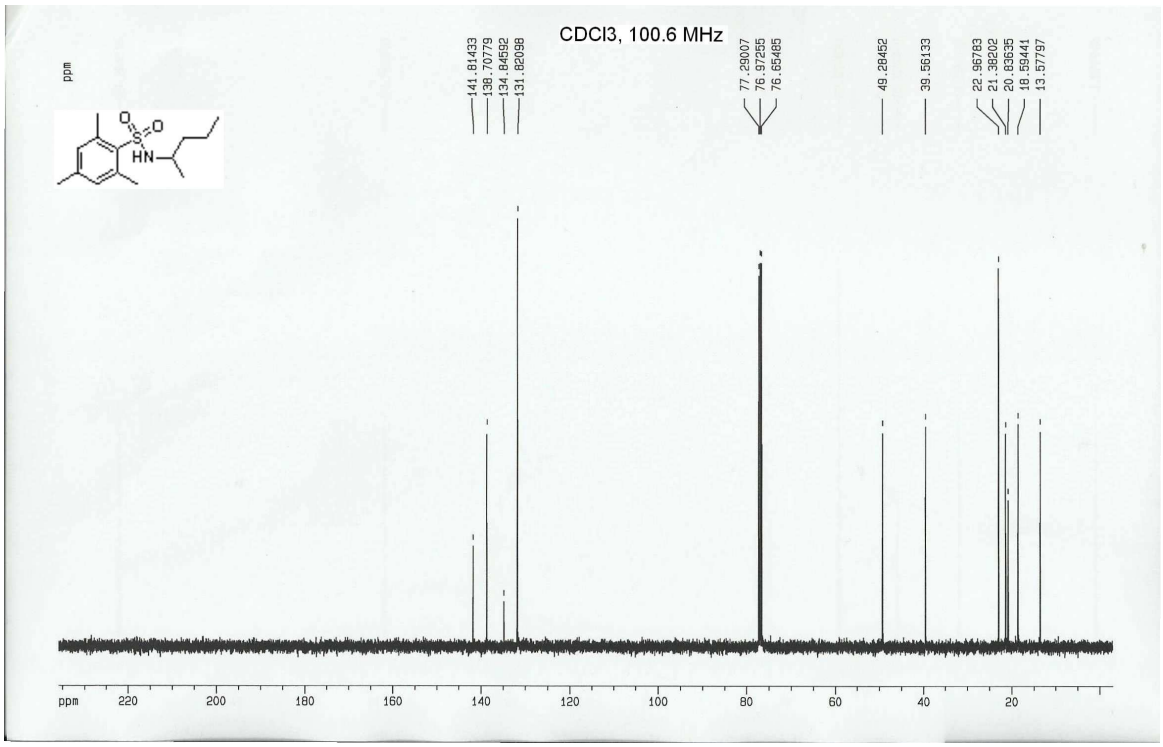
Methyl-4-(4-acetyl-benzenesulfonylamino)-butanoate



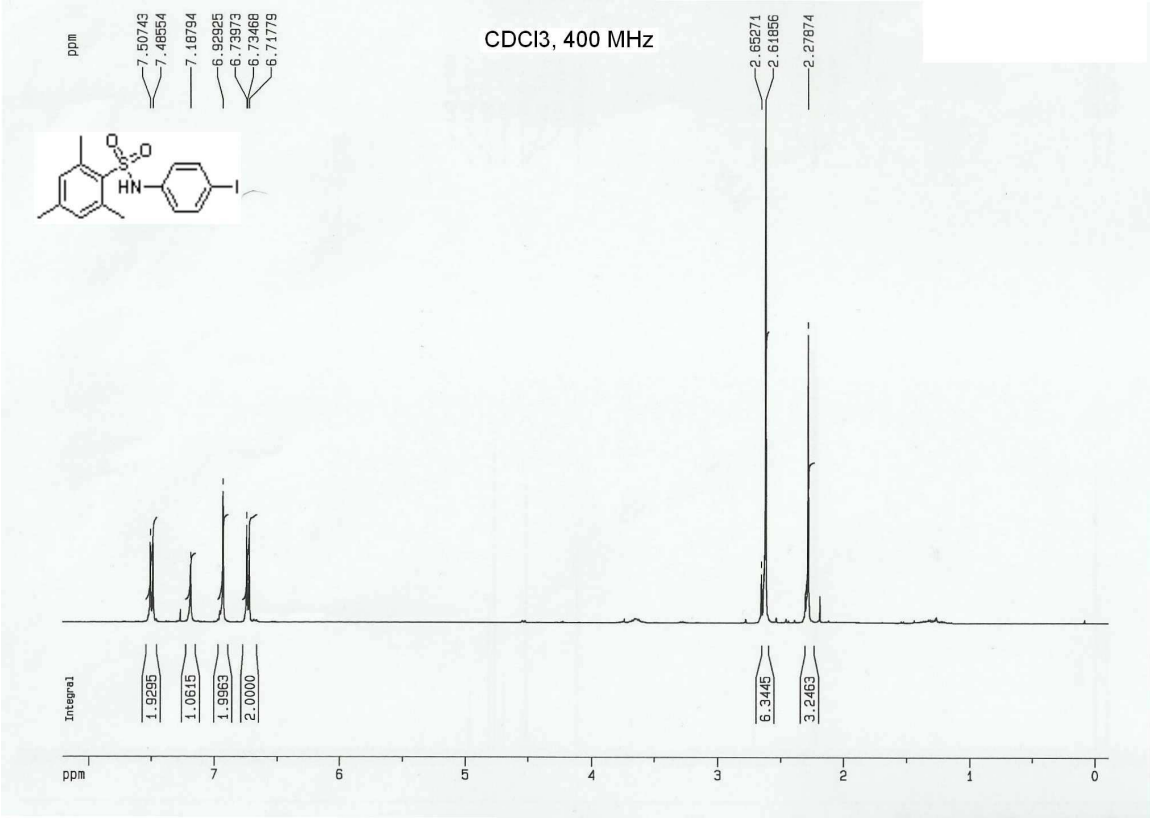


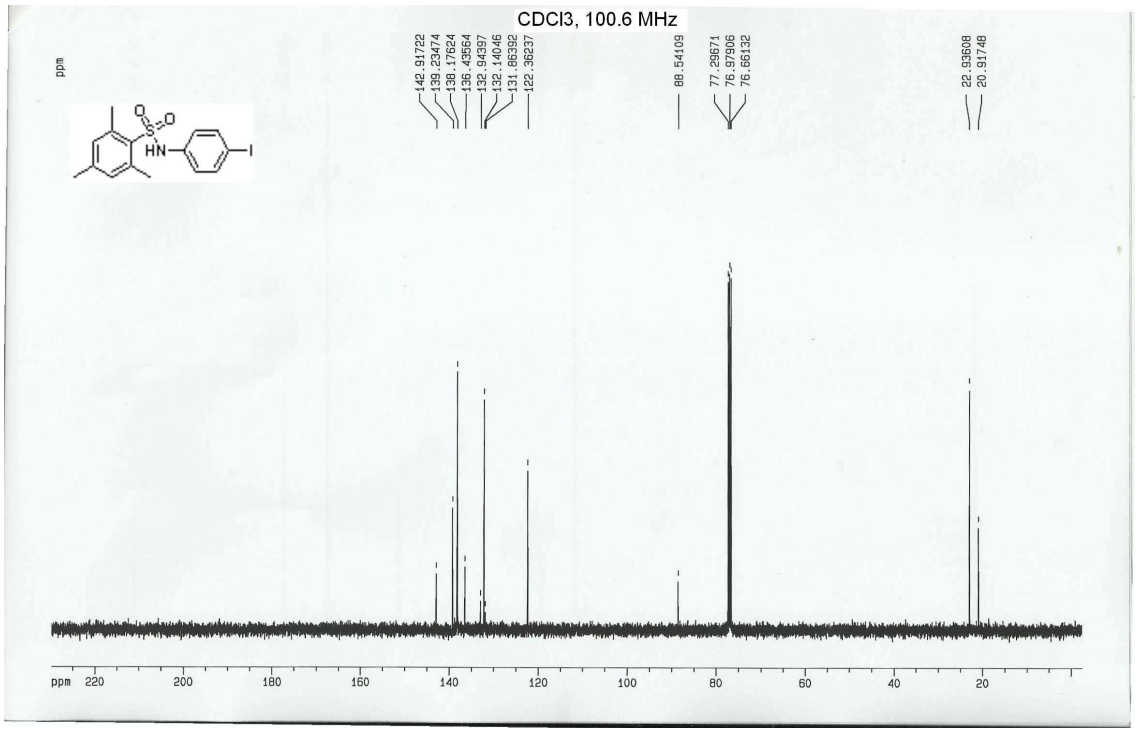
N-(pentan-2-yl)-mesitylsulfonamide



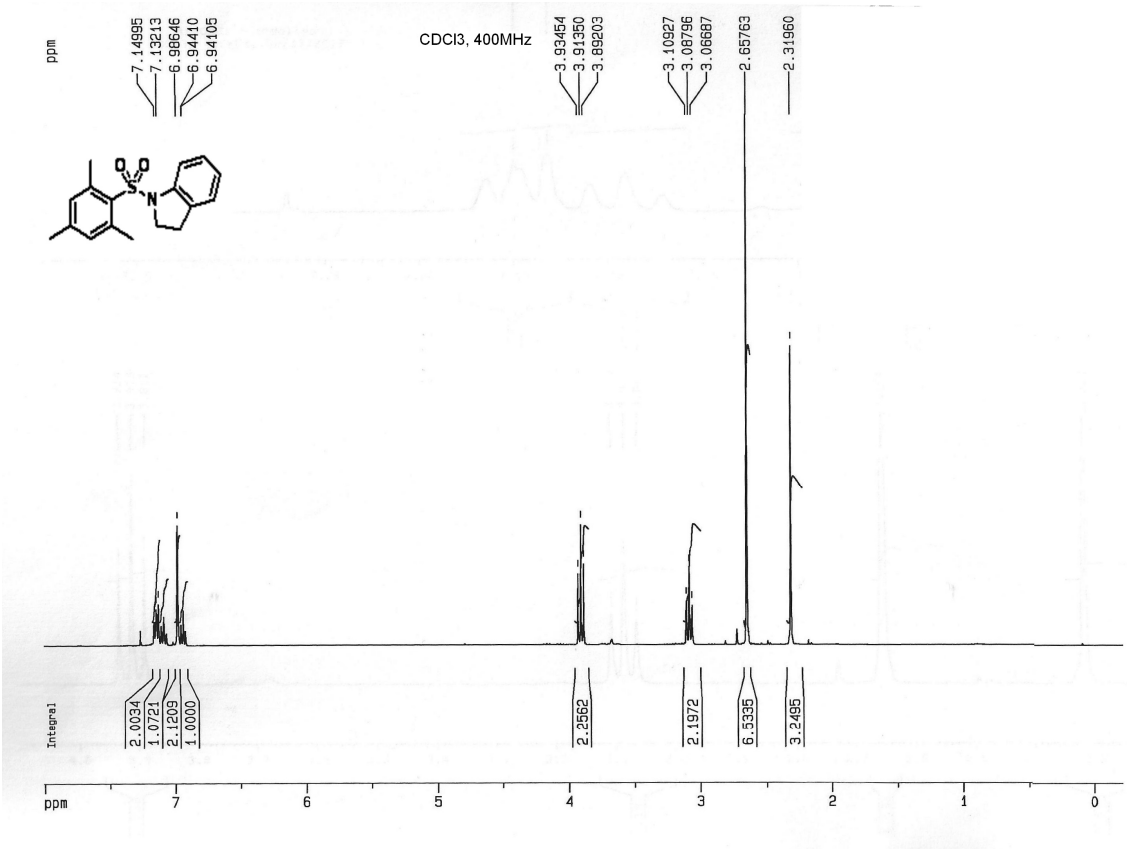


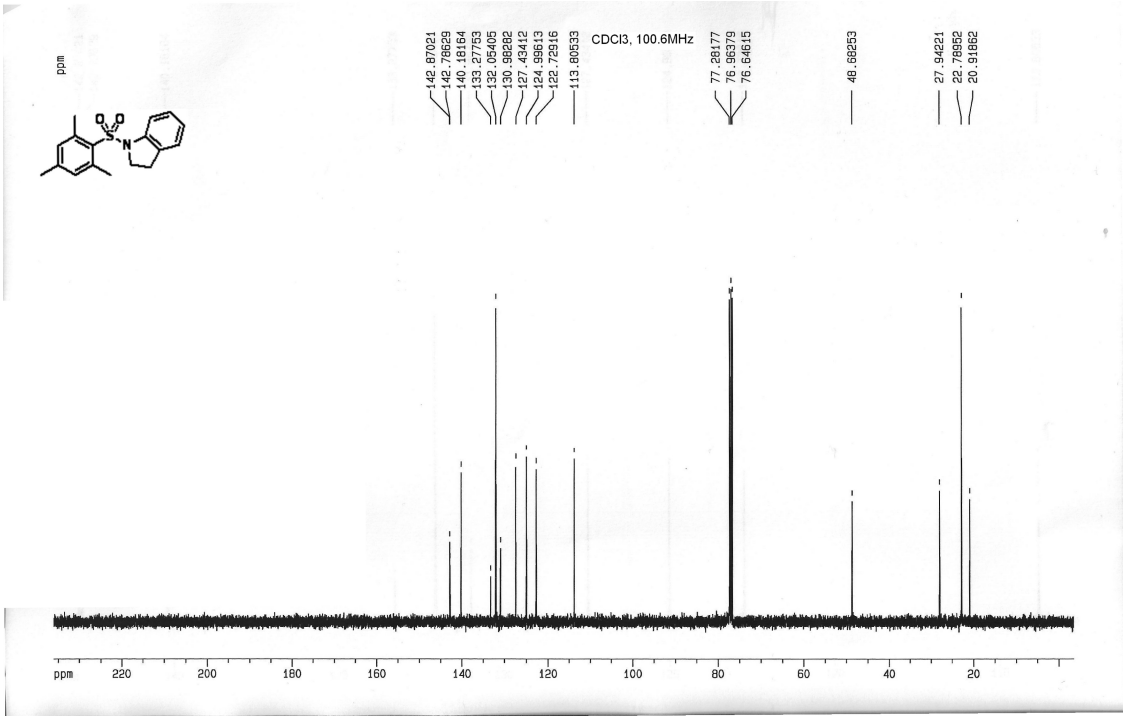
N-(4-iodo-phenyl)-mesitylsulfonamide



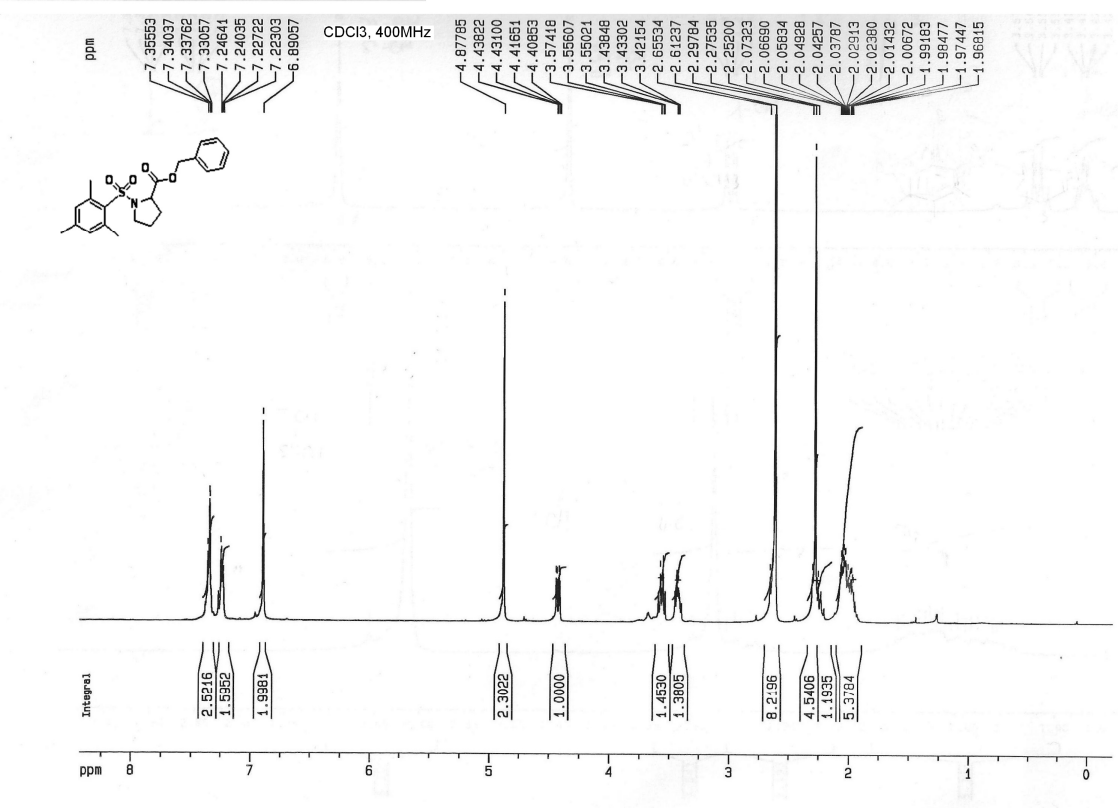


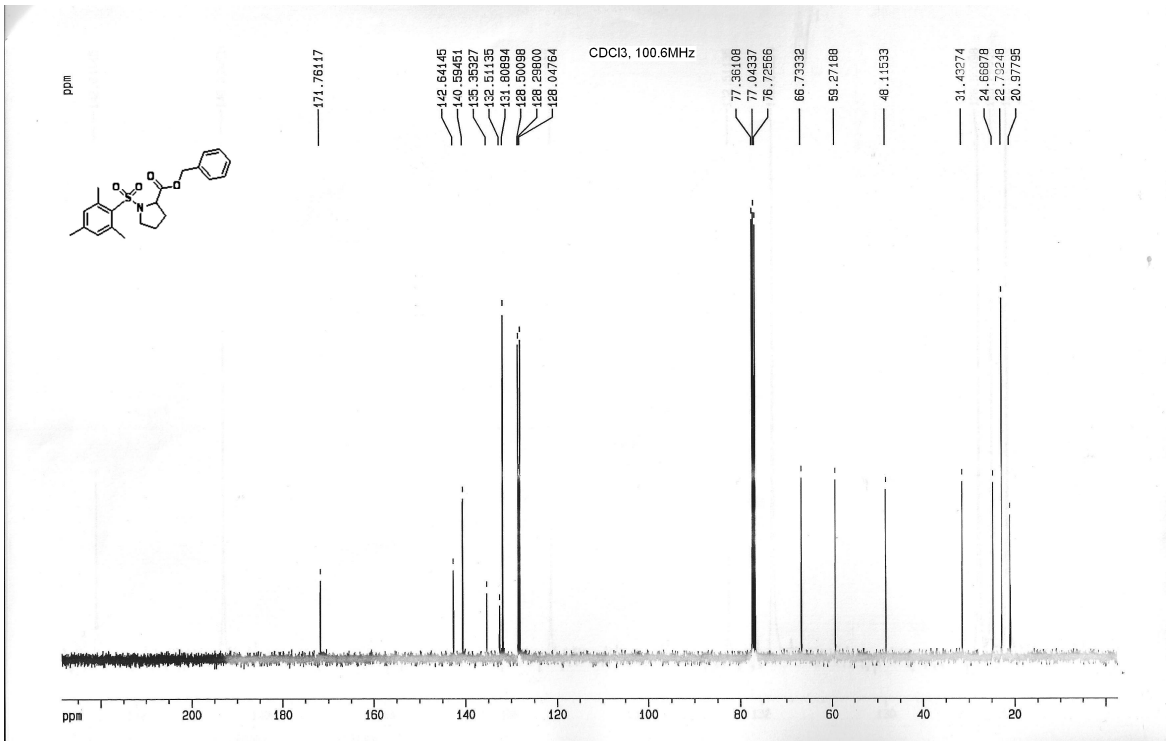
N-(mesitylsulfonyl)-indoline





Benzyl-N-(mesitylsulfonyl)-prolinate





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