# Re-discovery of an old Named Reaction: from micellar catalysis to unusual Schotten–Baumann conditions

## Supporting Information

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## Materials and Methods

**General.** All chemicals, reagents, and solvents were purchased from commercial sources and were used without further purification unless otherwise noted. $^{1}$H NMR data are reported relative to residual solvent signals, and are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. The multiplicities are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. All $^{1}$H NMR and $^{13}$C NMR spectra were recorded on Varian 300 MHz spectrometer equipped with a Mercury console, at frequency of 300 and 80 MHz respectively, using DMSO-$d_6$ or $CDCl_3$. The HPLC analysis were performed on an Agilent Technologies instruments 1260 infinity II with quaternary pump and a Diode-Array Detector (DAD).

**HPLC method**

**Apparatus and conditions**

| | |
|---|---|
| Instrument | HPLC Agilent 1260, binary pump |
| Column | X-Bridge C18, 150 x 4.6 mm; 3.5 µm (P/N:186003034) |
| Column Temperature | 25 °C |
| Autosampler Temperature | 25 °C |
| Flow | 1.0 ml/min |
| Mobile phases | A: $KH_2PO_4$ 10mM in $H_2O$ - pH 3.0 |
| | B: $CH_3CN$ |

Gradient:

| Time | A | B |
|---|---|---|
| 0 | 90 | 10 |
| 5.0 | 90 | 10 |
| 15.0 | 35 | 65 |
| 20.0 | 35 | 65 |
| 20.1 | 10 | 90 |
| 25.1 | 10 | 90 |

| | |
|---|---|
| Wavelength | 220 nm |
| Injection volume | 3 µL |
| Sample concentration | ~1.0 mg/mL |
| Diluent | $CH_3CN/H_2O$ – (50/50) |

**Sample Preparations**

Blank: use diluent as blank

Reference Solution: into a 50 ml volumetric flask accurately weight 50 mg of reference compound. Dissolve and dilute to volume with diluent.

Sample Solution: Into a 50 ml volumetric flask accurately weight 50 mg of sample. Dissolve and dilute to volume with diluent.

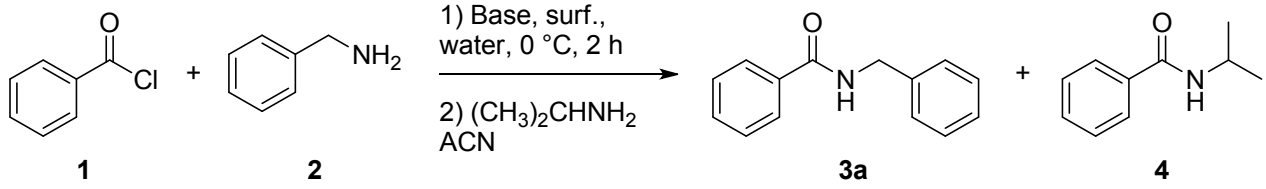
The HPLC method was developed using standards of the following compound, since negligible amount of the corresponding benzoic acid was detected:

(1) The amine used;

(2) The carboxylic acid formed by hydrolysis of the corresponding acyl chloride

(3) The product of the quenching of the residual acyl chloride with isopropylamine

(4) The product of the reaction




**1** **2** **3a** **4**

Once the chromatograms were acquired, we calculated the response factors (RF) from the HPLC area and the known concentration of the standard solutions.

$$\boldsymbol{Response\ Factor\ (RF)} = \frac{peak\ area}{concentration\ (\frac{mg}{ml})}$$

The RF are then used to determine the relative response factors (RRF) respect to the product (**3a**).

$$\boldsymbol{RRF} = \frac{RF\ compound\ x}{RF\ product\ (\boldsymbol{3a})}$$

In this way it was possible to correct the areas of the compounds for their respective RRF.

$$\boldsymbol{Corrected\ RRF\ area} = \frac{Peak\ area\ compund\ x}{RRF\ compound\ x}$$

Since the RRF corrected areas are proportional to the weight/weight ratio % of the compounds in solution, it was possible to derive the latter with the following equation:

$$\boldsymbol{Ratio}\ \frac{\boldsymbol{weight}}{\boldsymbol{weight}} = \frac{corr.\ RRF\ area\ x}{\Sigma\ corr.\ RRF\ area}$$

Then, if we consider the product **3a** weight as 1, we could divide the ratio by the compound's molecular weight, to obtain it moles in solution.

$$\boldsymbol{Moles} = \frac{ratio\ \frac{weight}{weight}\ (x)}{molecular\ weight\ (x)}$$

The moles have been used to derive the "in solution" molar yields. We decided to calculate the molar yields of the product (**3**) in two ways: from the moles of residual amine (**2**) and from the moles of unreacted acyl chloride, quantified by the sum of the moles of (**1**) and (**3a**).

$$\boldsymbol{Molar\ yield}\ (\%)\boldsymbol{calculated\ on\ 2} = \frac{moles\ \boldsymbol{3a}}{moles\ \boldsymbol{3a}+moles\ \boldsymbol{2}} \cdot 100$$

$$\boldsymbol{Molar\ yield}\ \%\ \boldsymbol{calculated\ on\ Acyl\ Cl} = \frac{moli\ \boldsymbol{3a}}{moles\ \boldsymbol{1}\ +\ moels\ \boldsymbol{3a}\ +\ moles\ \boldsymbol{4}} \cdot 100$$

The average of the molar yields allows to obtain the best estimation of the average molar yield (%) in solution.

### qNMR assay

qNMR assay for the isolated dry solid were obtained using an internal calibrant, following the ACS guidelines.[1]

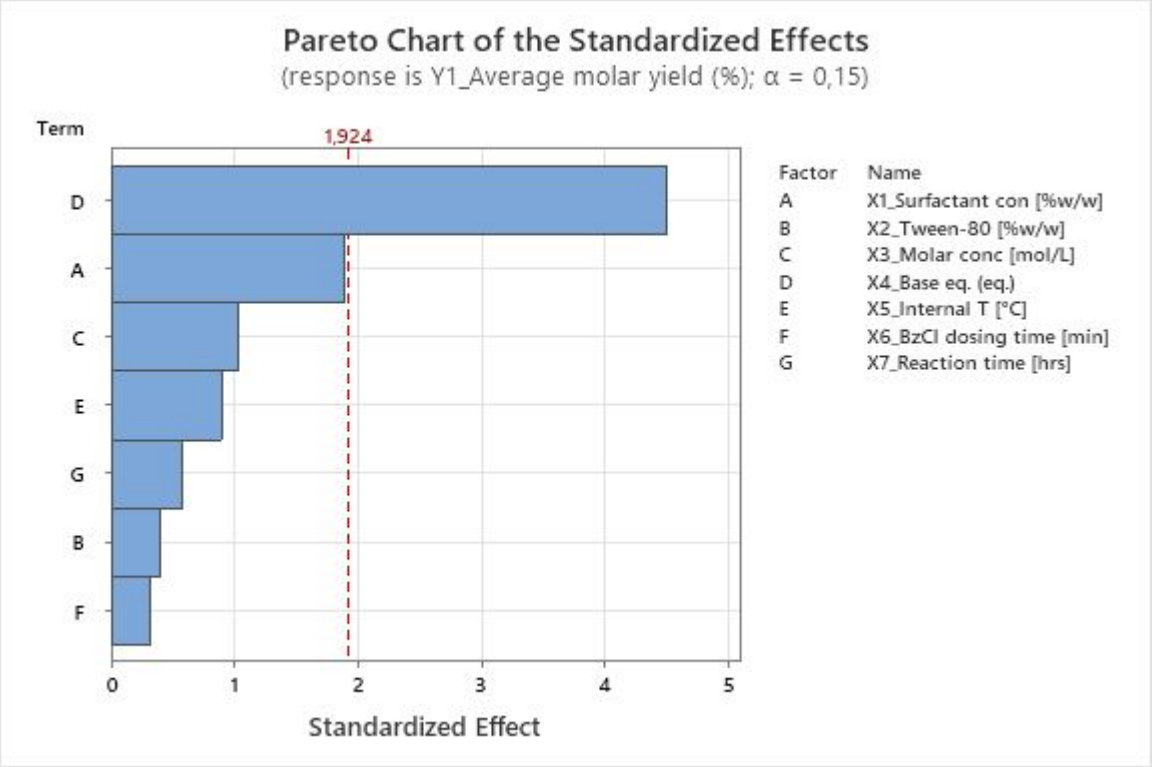
## Screening DoE

The screening Design of Experiments results were analyzed using Minitab® 21.3.1 software. In particular, the linear regression was performed with $\alpha = 0.15$ and the Analysis of Variance is reported below.

### Analysis of Variance

| Source | DF | Adj SS | Adj MS | F-Value | P-Value |
|---|---|---|---|---|---|
| Model | 7 | 151,674 | 21,668 | 3,75 | 0,152 |
| Linear | 7 | 151,674 | 21,668 | 3,75 | 0,152 |
| X1_Surfactant conc. [%w/w] | 1 | 20,544 | 20,544 | 3,56 | 0,156 |
| X2_Tween-80 [%w/w] | 1 | 0,898 | 0,898 | 0,16 | 0,720 |
| X3_Molar conc [mol/L] | 1 | 6,195 | 6,195 | 1,07 | 0,376 |
| X4_Base eq. (eq.) | 1 | 116,892 | 116,892 | 20,24 | 0,020 |
| X5_Internal T [°C] | 1 | 4,590 | 4,590 | 0,79 | 0,438 |
| X6_BzCl dosing time [min] | 1 | 0,594 | 0,594 | 0,10 | 0,769 |
| X7_Reaction time [hrs] | 1 | 1,960 | 1,960 | 0,34 | 0,601 |
| Error | 3 | 17,323 | 5,774 | | |
| Curvature | 1 | 17,044 | 17,044 | 122,36 | 0,008 |
| Pure Error | 2 | 0,279 | 0,139 | | |
| Total | 10 | 168,997 | | | |

The Pareto Chart of the Standardized Effect is reported below.




## Refining DoE

The refining Design of Experiments results were analyzed using Minitab® 21.3.1 software. In particular, the linear regression was performed with $\alpha = 0.05$ and the results are reported below.

### Coded Coefficients

| Term | Coef | SE Coef | T-Value | P-Value | VIF |
|---|---|---|---|---|---|
| Constant | 95,4597 | 0,0992 | 962,11 | 0,000 | |
| X1_Surfactant con [%w/w] | -0,0300 | 0,0976 | -0,31 | 0,767 | 1,00 |
| X2_Base eq. (eq.) | -0,7717 | 0,0976 | -7,91 | 0,000 | 1,00 |
| X1_Surfactant con [%w/w]*X1_Surfactant con [%w/w] | -0,254 | 0,144 | -1,77 | 0,121 | 1,17 |
| X2_Base eq. (eq.)*X2_Base eq. (eq.) | 0,501 | 0,144 | 3,49 | 0,010 | 1,17 |
| X1_Surfactant con [%w/w]*X2_Base eq. (eq.) | 0,352 | 0,119 | 2,95 | 0,021 | 1,00 |

### Model Summary

| S | R-sq | R-sq(adj) | R-sq(pred) |
|---|---|---|---|
| 0,238952 | 92,29% | 86,78% | 63,06% |

### Analysis of Variance

| Source | DF | Adj SS | Adj MS | F-Value | P-Value |
|---|---|---|---|---|---|
| Model | 5 | 4,78182 | 0,95636 | 16,75 | 0,001 |
| Linear | 2 | 3,57822 | 1,78911 | 31,33 | 0,000 |
| X1_Surfactant con [%w/w] | 1 | 0,00540 | 0,00540 | 0,09 | 0,767 |
| X2_Base eq. (eq.) | 1 | 3,57282 | 3,57282 | 62,57 | 0,000 |
| Square | 2 | 0,70658 | 0,35329 | 6,19 | 0,028 |

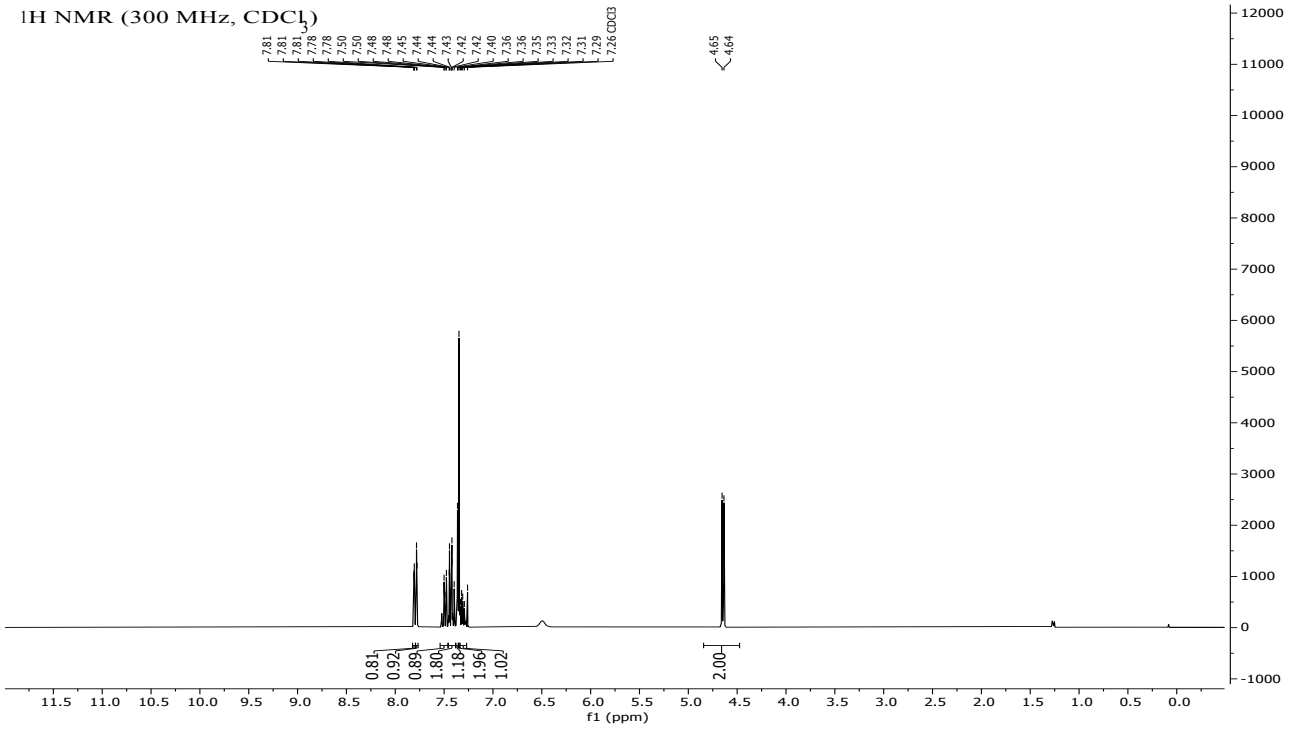
| | | | | | |
|---|---|---|---|---|---|
| X1_Surfactant con [%w/w]*X1_Surfactant con [%w/w] | 1 | 0,17790 | 0,17790 | 3,12 | 0,121 |
| X2_Base eq. (eq.)*X2_Base eq. (eq.) | 1 | 0,69381 | 0,69381 | 12,15 | 0,010 |
| 2-Way Interaction | 1 | 0,49702 | 0,49702 | 8,70 | 0,021 |
| X1_Surfactant con [%w/w]*X2_Base eq. (eq.) | 1 | 0,49702 | 0,49702 | 8,70 | 0,021 |
| Error | 7 | 0,39969 | 0,05710 | | |
| Lack-of-Fit | 3 | 0,16037 | 0,05346 | 0,89 | 0,518 |
| Pure Error | 4 | 0,23932 | 0,05983 | | |
| Total | 12 | 5,18151 | | | |

## Regression Equation in Uncoded Units

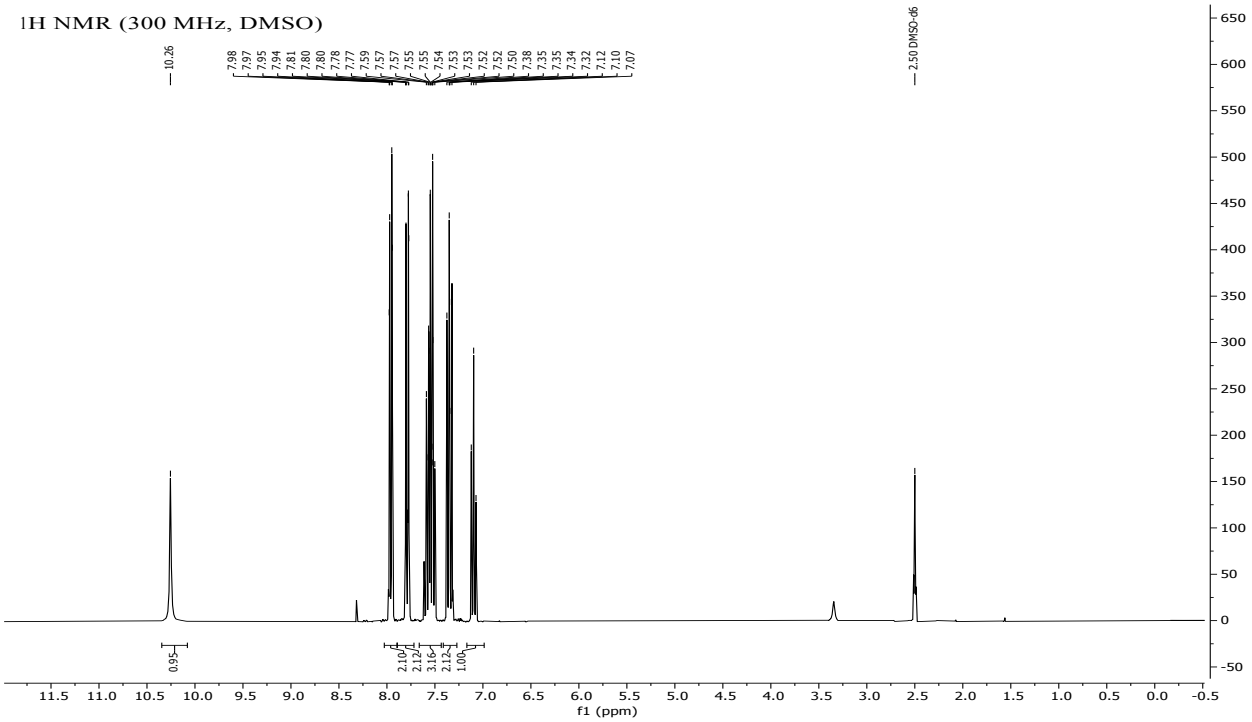
Y1_Average molar yield (%) = 103,26 + 0,87 X1_Surfactant con [%w/w]
- 9,67 X2_Base eq. (eq.)
- 1,015 X1_Surfactant con [%w/w]*X1_Surfactant con [%w/w]
+ 2,005 X2_Base eq. (eq.)*X2_Base eq. (eq.)
+ 1,410 X1_Surfactant con [%w/w]*X2_Base eq. (eq.)

## Analytical results

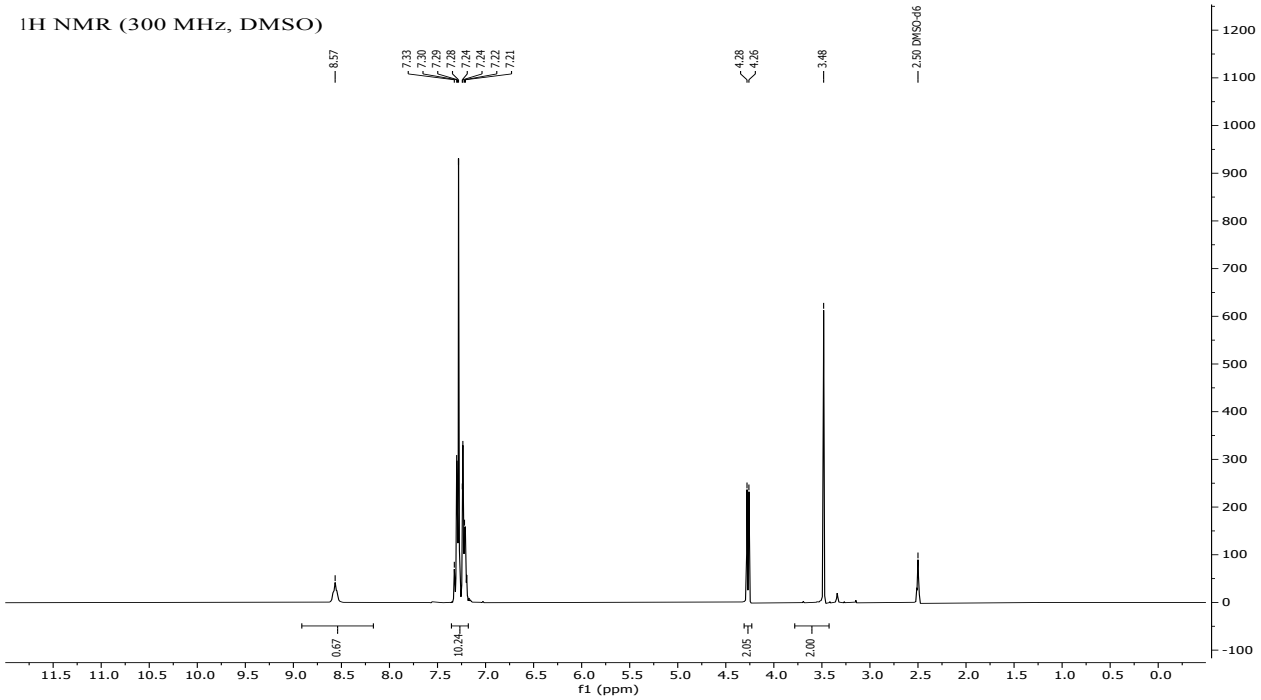
***N*-benzyl benzamide (3a):** white to off-white solid; HPLC retention time: 14.68 min.; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.83 – 7.76 (m, 2H), 7.54 – 7.46 (m, 1H), 7.46 – 7.38 (m, 2H), 7.36 (d, $J$ = 1.1 Hz, 2H), 7.35 (s, 2H), 7.34 – 7.27 (m, 1H,), 6.49 (s, 1H,), 4.64 (d, $J$ = 5.6 Hz, 2H). The $^1$H NMR spectrum shows good agreement with the literature data.[2]



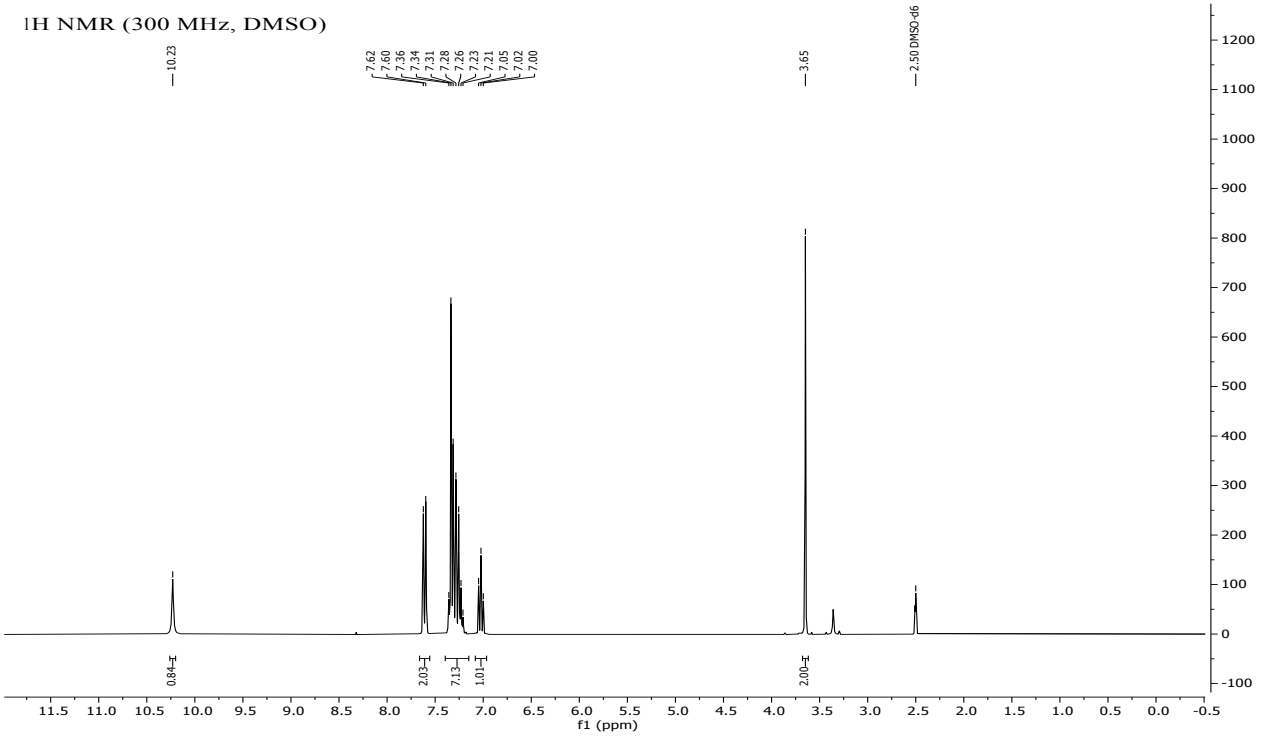
***N*-phenyl benzamide (3b):** white to off-white solid; HPLC retention time: 14.67 min.; $^1$H NMR (300 MHz, DMSO-$d^6$) δ 7.05-7.12 (t, 1H), 7.32 - 7.38 (m, 2H), 7.49 – 7.61 (m, 3H), 7.66 – 7.80 (d, J = 7.78 MHz, 2H), 7.94 – 7.98 (d, J = 7.8, 2H), 10.27 (br, 1H). The $^1$H NMR spectrum shows good agreement with the literature data.[3]



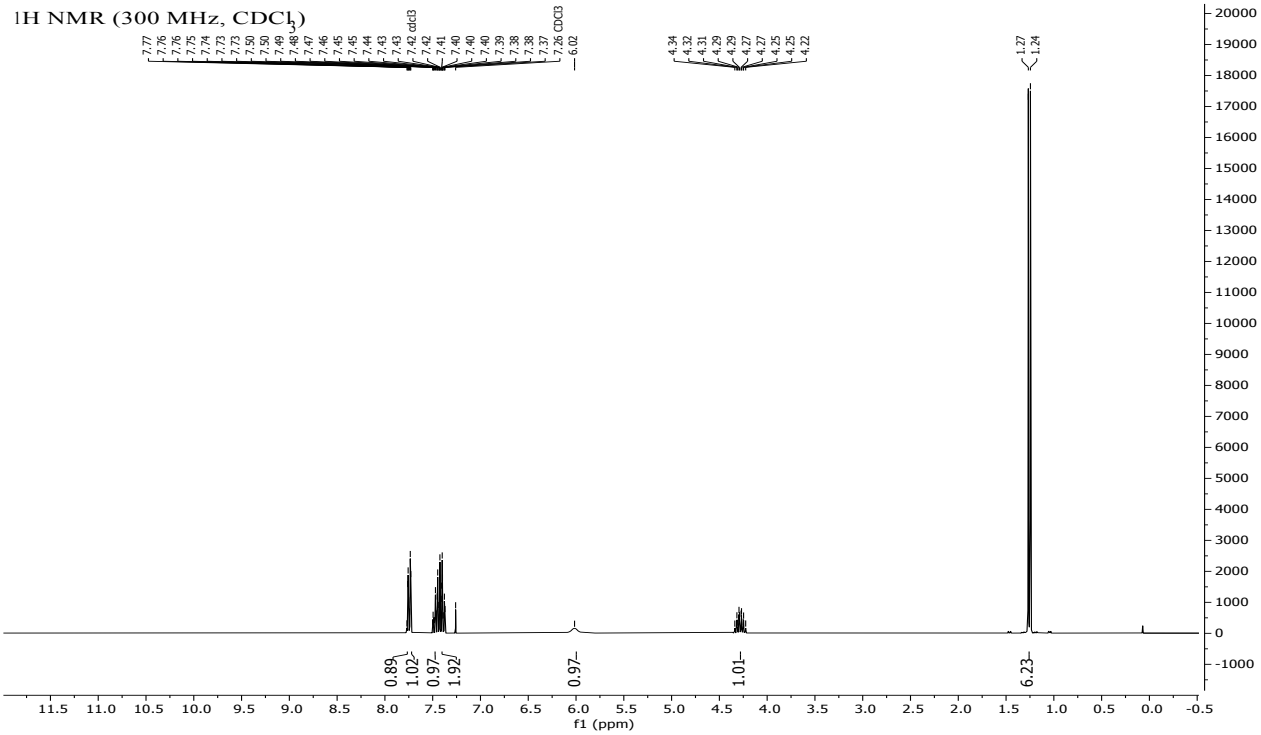
***N*-benzyl-2-phenylacetamide (3c):** white to off-white solid; HPLC retention time: 14.81 min.; $^1$H NMR (300 MHz, DMSO-$d^6$) δ 8.58 (br, 1H), 7.05 - 7.20 (m, 10H), 4.27 (d, J = 4.9 MHz, 2H), 3.48 (s, 2H). The $^1$H NMR spectrum shows good agreement with the literature data.[4]



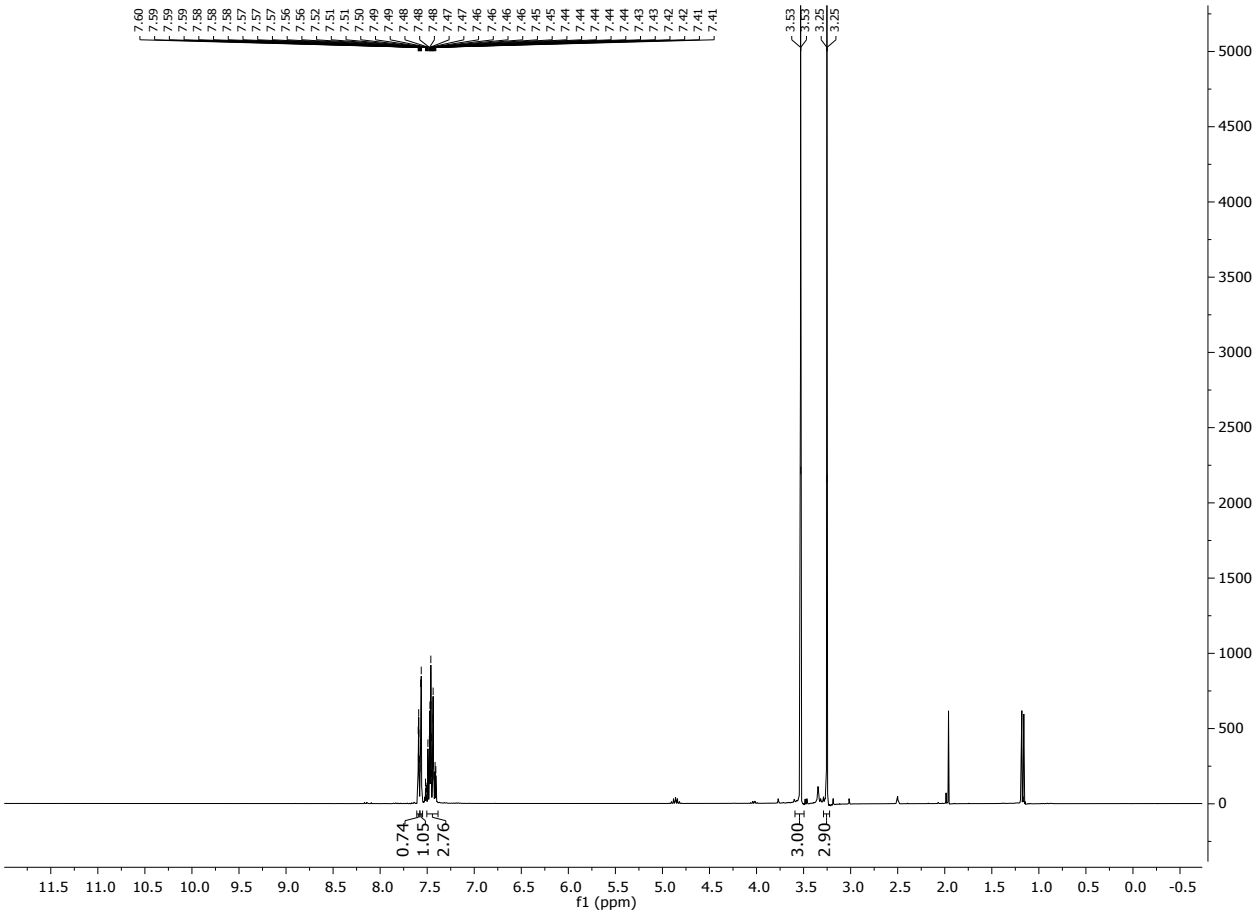
***N*,2-diphenylacetamide (3d):** white to off-white solid; HPLC retention time: 15.36 min.; $^1$H NMR (300 MHz, DMSO-$d^6$) δ 10.22 (br, 1H), 7.59 – 7.62 (d, J = 5.5, 2H), 7.20 – 7.36 (m, 7H), 7.00-7.05 (t, $J$ = 7.38 MHz,1H), 3.65 (s, 2H). The $^1$H NMR spectrum shows good agreement with the literature data.[5]



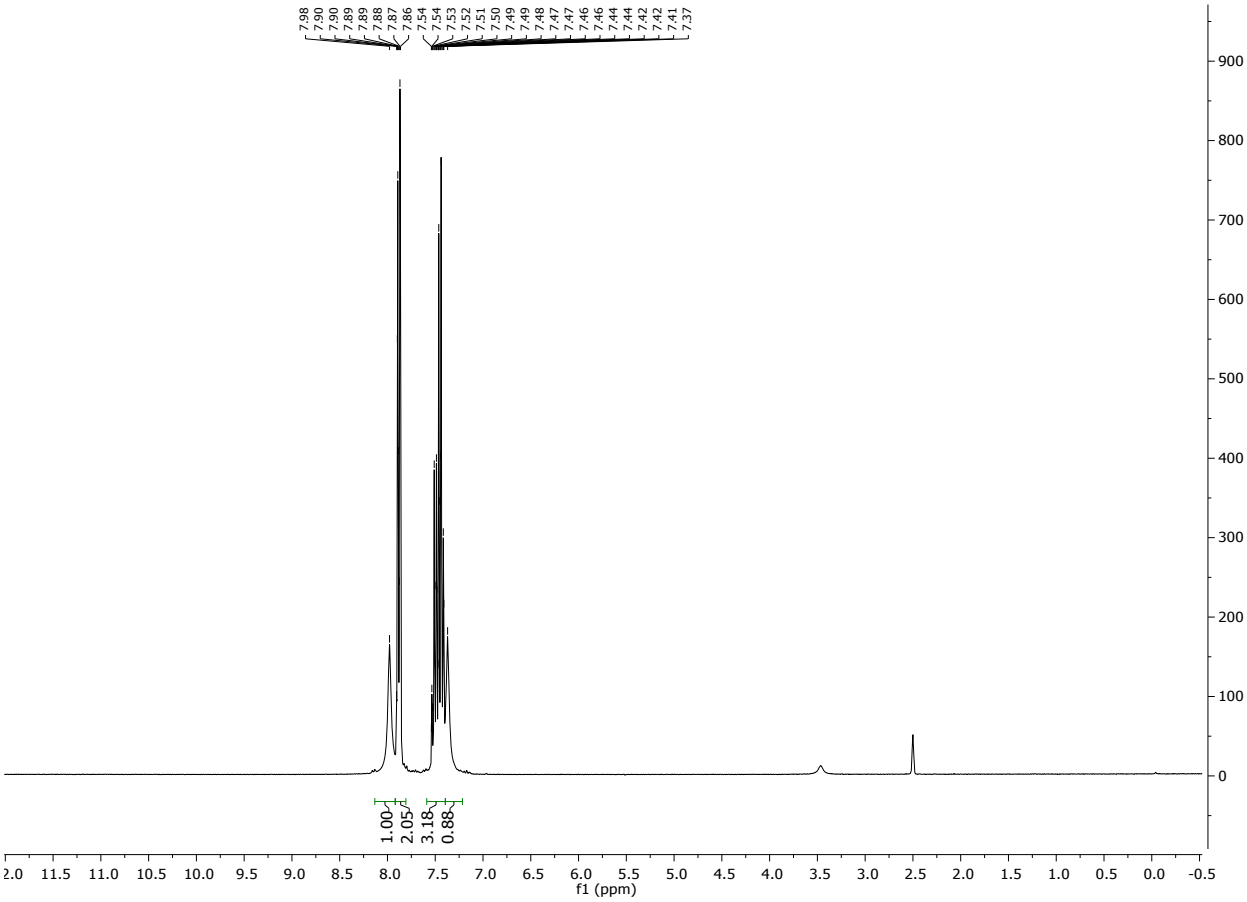
***N*-isopropyl benzamide (4):** white to off-white solid; HPLC retention time: 12.06 min.; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.83 – 7.70 (m, 2H), 7.50 – 7.37 (m, 3H), 6.02 (br, s, 1H), 4.28 (br, s, 1H), 1.26 (d, *J* = 6.5 Hz, 6H). The $^1$H NMR spectrum shows good agreement with the literature data.[6]



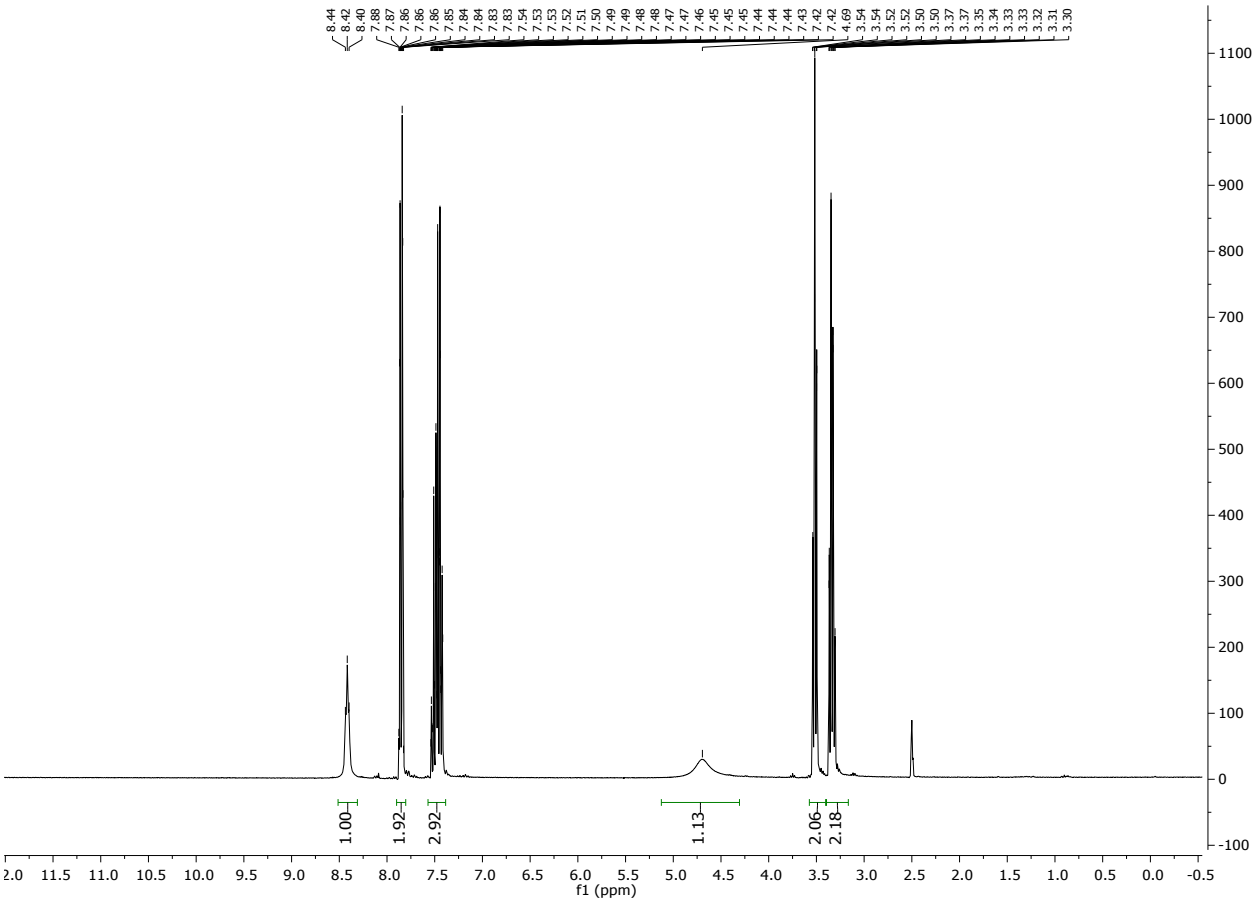
***N*-Methoxy-*N*-methylbenzamide (3e):** colorless liquid; HPLC retention time: 11.69 min.; $^1$H NMR (300 MHz, DMSO-$d^6$) δ 7.61 – 7.58 (td, J = 1.5, 0.5 Hz, 1H), 7.58 – 7.55 (m, 1H), 7.50 – 7.40 (m, 3H), 3.59 – 3.49 (d, J = 0.6 Hz, 3H), 3.28 – 3.22 (d, J = 0.6 Hz, 3H). The $^1$H NMR spectrum shows good agreement with the literature data.[7]



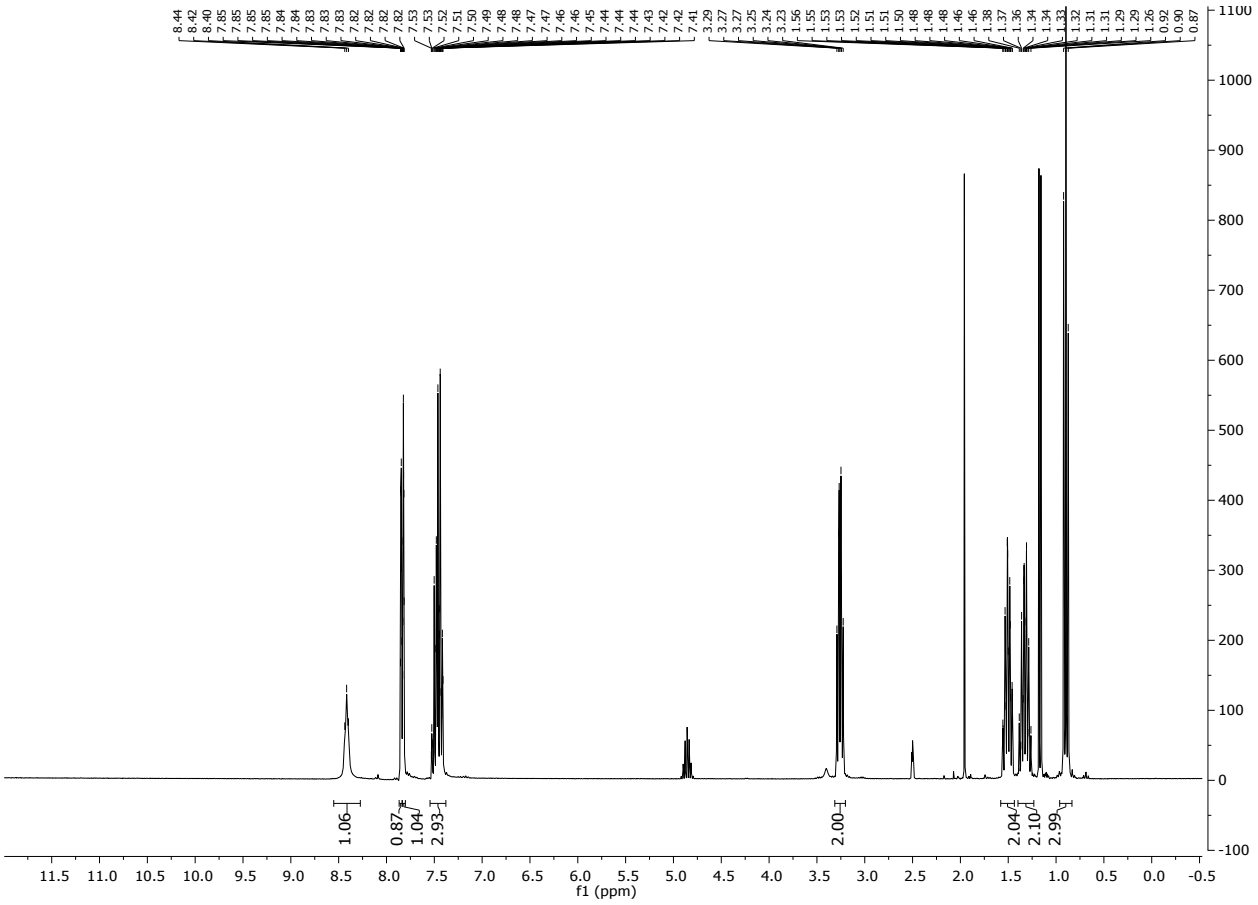
**Benzamide (3f):** white to off-white solid; HPLC retention time: 6.22 min.; $^1$H NMR (300 MHz, DMSO-$d^6$) δ 8.13 – 7.92 (br, 1H), 7.92 – 7.80 (m, 2H), 7.61 – 7.40 (m, 3H), 7.40 – 7.17 (br, 1H). The $^1$H NMR spectrum shows good agreement with the literature data.[8]



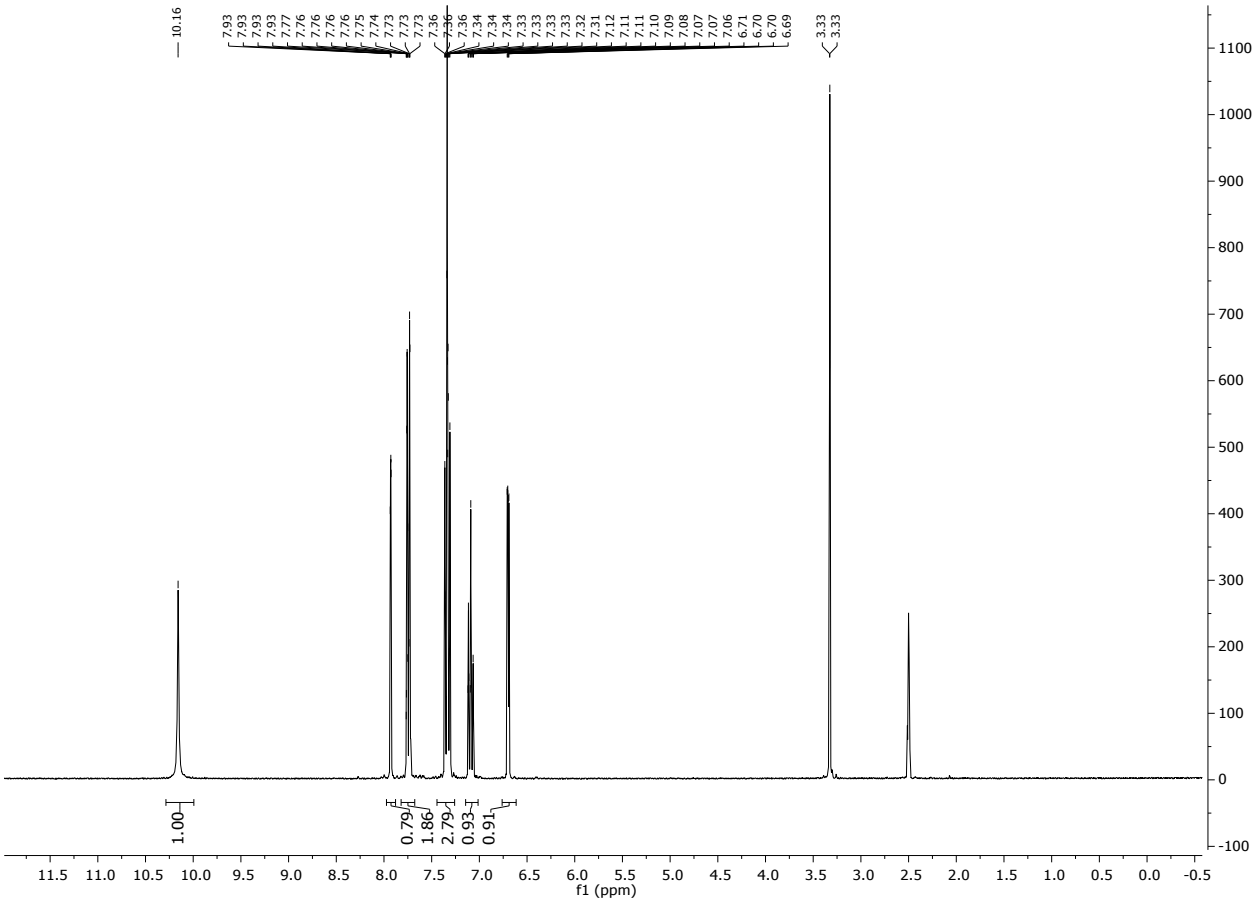
***N*-(2-Hydroxyethyl)benzamide (3g):** colorless liquid; HPLC retention time: 5.98 min.; $^1$H NMR (300 MHz, DMSO-$d^6$) δ 8.53 – 8.30 (m, 1H), 7.89 – 7.85 (dd, J = 1.9, 1.2 Hz, 1H), 7.85 – 7.81 (t, J = 1.9 Hz, 1H), 7.55 – 7.39 (m, 3H), 4.97 – 4.37 (br, 1H), 3.57 – 3.46 (td, J = 6.2, 0.7 Hz, 2H), 3.38 – 3.28 (m, 2H). The $^1$H NMR spectrum shows good agreement with the literature data.[9]



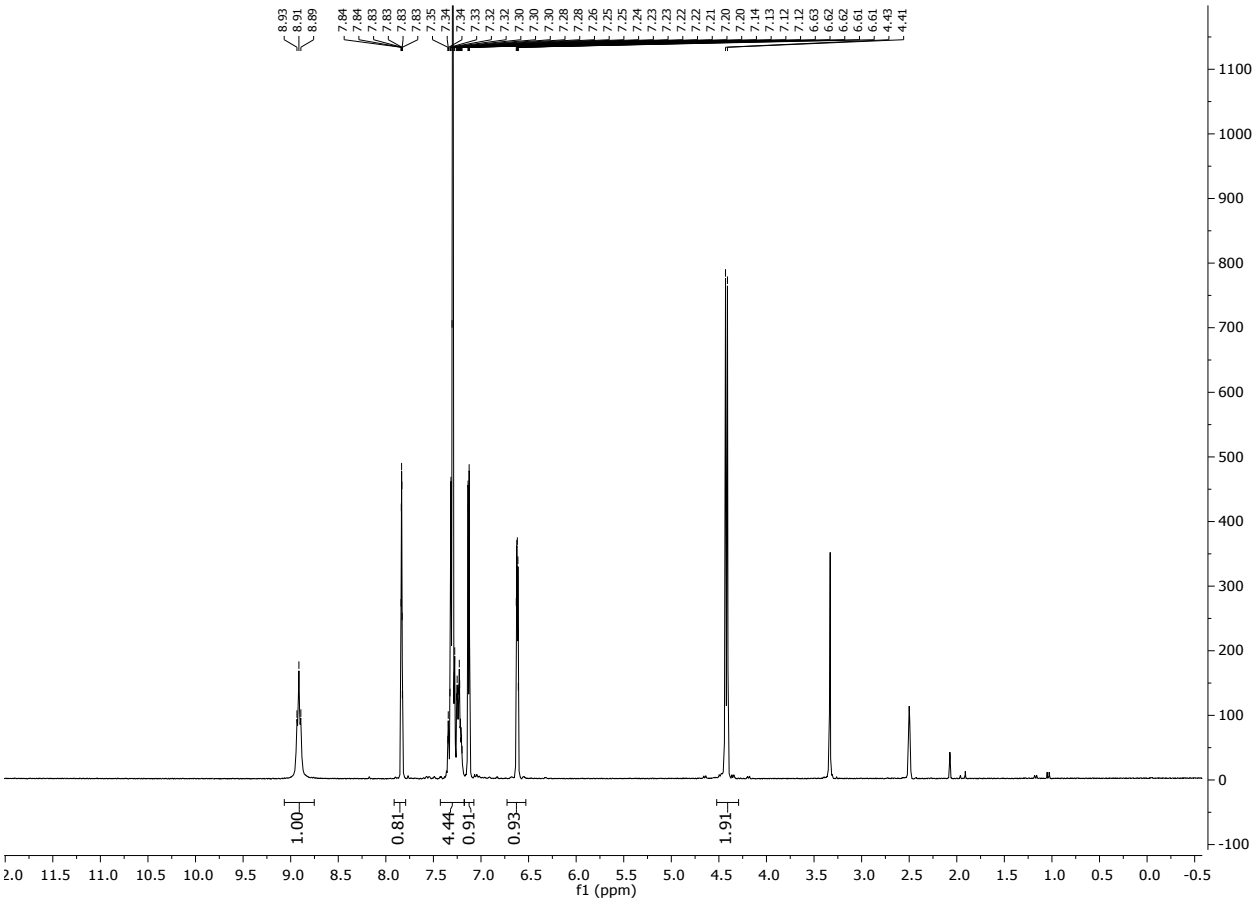
***N*-Butylbenzamide (3h):** white to off-white solid; HPLC retention time: 13.92 min.; $^1$H NMR (300 MHz, DMSO-$d^6$) δ 8.49 – 8.33 (m, 1H), 7.89 – 7.83 (dq, J = 1.7, 1.0 Hz, 1H), 7.83 – 7.79 (tt, J = 1.7, 0.6 Hz, 1H), 7.57 – 7.36 (m, 3H), 3.32 – 3.20 (td, J = 7.0, 5.7 Hz, 2H), 1.62 – 1.43 (m, 2H), 1.42 – 1.24 (m, 2H), 0.94 – 0.83 (t, J = 7.3 Hz, 3H). The $^1$H NMR spectrum shows good agreement with the literature data.[10]



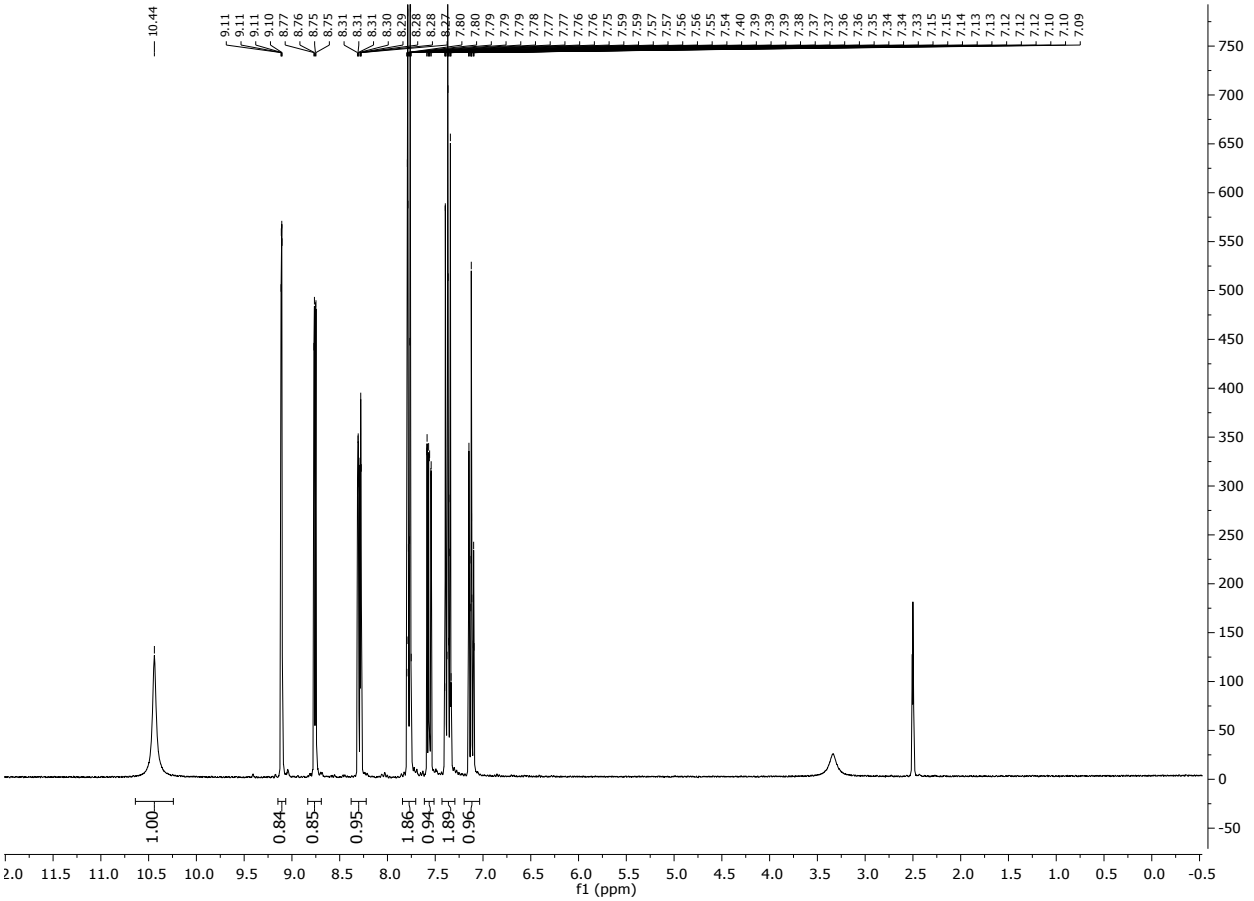
***N*-Phenyl-2-furancarboxamide (3i):** white to off-white solid; HPLC retention time: 13.55 min.; $^1$H NMR (300 MHz, DMSO-$d^6$) δ 10.32 – 10.02 (s, 1H), 7.99 – 7.87 (dd, J = 1.8, 0.8 Hz, 1H), 7.81 – 7.68 (m, 2H), 7.40 – 7.26 (m, 3H), 7.16 – 7.01 (m, 1H), 6.75 – 6.62 (dd, J = 3.5, 1.8 Hz, 1H). The $^1$H NMR spectrum shows good agreement with the literature data.[11]



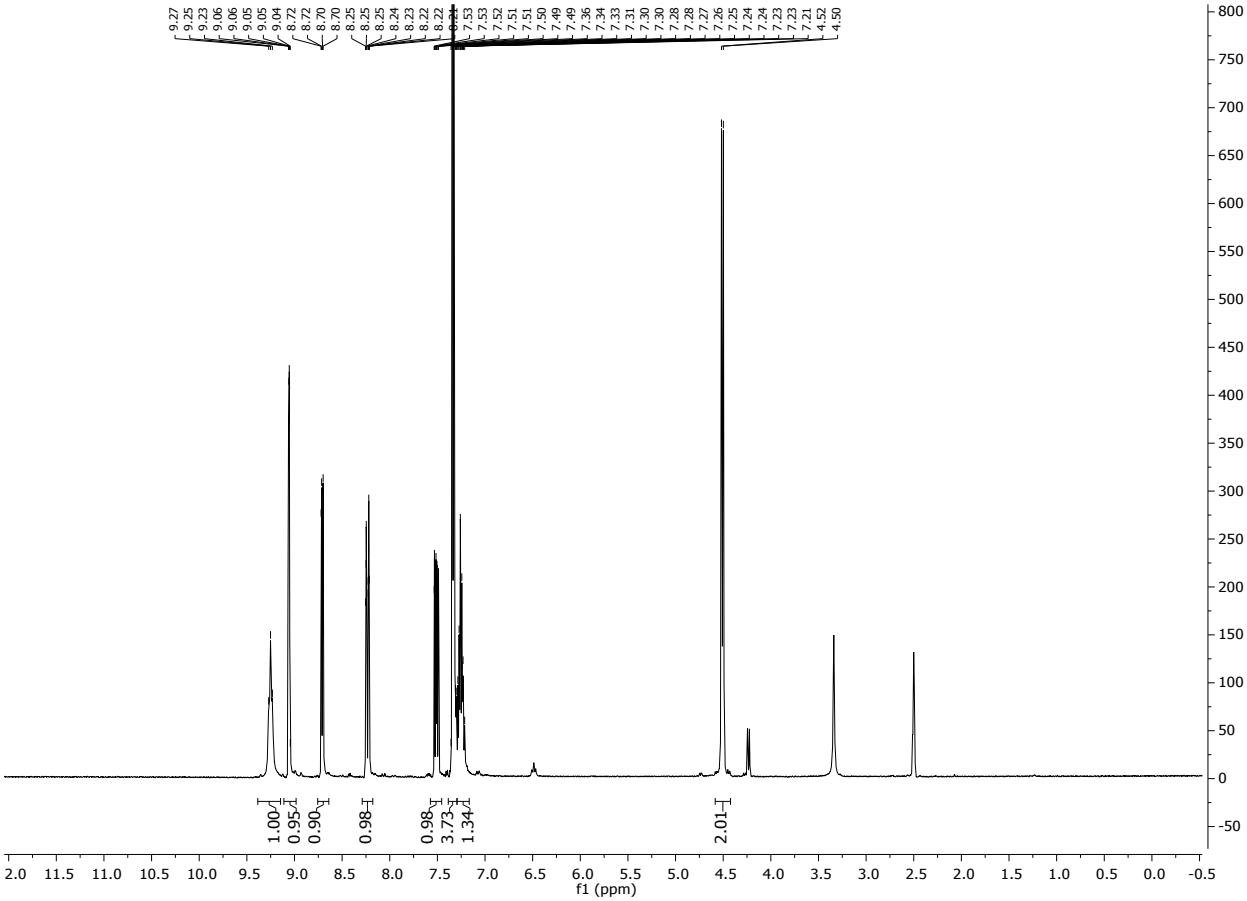
***N*-(Phenylmethyl)-2-furancarboxamide (3j):** white to off-white solid; HPLC retention time: 13.27 min.; $^1$H NMR (300 MHz, DMSO-$d^6$) δ 9.04 – 8.76 (m, 1H), 7.91 – 7.78 (dt, J = 1.8, 0.9 Hz, 1H), 7.41 – 7.17 (m, 5H), 7.16 – 7.09 (dd, J = 3.5, 0.9 Hz, 1H), 6.68 – 6.57 (dt, J = 3.2, 1.6 Hz, 1H), 4.55 – 4.27 (d, J = 6.2 Hz, 2H).The $^1$H NMR spectrum shows good agreement with the literature data.[12]



***N*-Phenylnicotinamide (3k):** white to off-white solid; HPLC retention time: 6.80 min.; $^1$H NMR (300 MHz, DMSO-$d^6$) δ 10.65 – 10.22 (br, 1H), 9.17 – 9.05 (dd, J = 2.3, 0.9 Hz, 1H), 8.82 – 8.71 (dd, J = 4.8, 1.7 Hz, 1H), 8.38 – 8.23 (ddd, J = 7.9, 2.3, 1.7 Hz, 1H), 7.85 – 7.69 (m, 2H), 7.62 – 7.52 (ddd, J = 8.0, 4.8, 0.9 Hz, 1H), 7.43 – 7.29 (m, 2H), 7.17 – 7.06 (m, 1H). The $^1$H NMR spectrum shows good agreement with the literature data.[13]



***N*-Benzylnicotinamide (3l):** white to off-white solid; HPLC retention time: 7.48 min.; $^1$H NMR (300 MHz, DMSO-$d^6$) δ 9.38 – 9.16 (m, 1H), 9.13 – 8.99 (dd, J = 2.3, 0.9 Hz, 1H), 8.75 – 8.65 (dd, J = 4.8, 1.7 Hz, 1H), 8.29 – 8.17 (ddd, J = 7.9, 2.3, 1.7 Hz, 1H), 7.56 – 7.46 (ddd, J = 8.0, 4.8, 0.9 Hz, 1H), 7.41 – 7.30 (d, J = 4.4 Hz, 4H), 7.30 – 7.18 (dtd, J = 9.0, 5.1, 4.5, 2.2 Hz, 1H), 4.57 – 4.45 (d, J = 5.8 Hz, 2H). The $^1$H NMR spectrum shows good agreement with the literature data.[14]



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