Direct amide formation in a continuous-flow system mediated by carbon disulfide

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Table of Content

1. General

All solvents and reagents were of analytical grade and used directly without further purification. Fe, Cu, Fe_2O_3, NiO, CuO, Boric acid, $AlCl_3$, Al_2O_3 (for chromatography, activated, neutral, Brockmann I, 50-200 μm, 60 A) catalysts, carbon disulfide (anhydrous, ≥99%) reagent and organic bases (trimethylamine, pyridine, 4-(dimethylamino)pyridine) used in this study were purchased from Sigma-Aldrich (Budapest, Hungary), while Acetonitrile (100,0%) was HPLC LC MS-grade solvents from VWR International (Debrecen, Hungary).

2. General aspects of the Continuous-Flow (CF) amidation

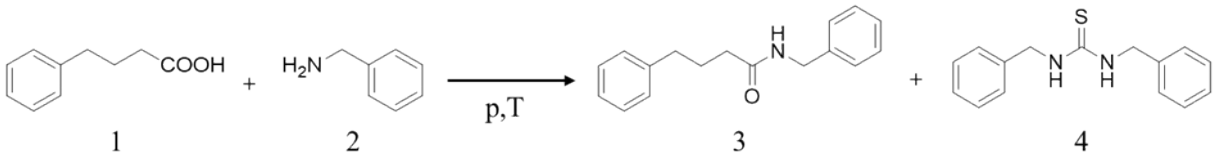
The CF amidation reactions were carried out in a home-made flow reactor consisting of an HPLC pump (Jasco PU-987 Intelligent Prep. Pump), a stainless steel HPLC column as catalyst bed (internal dimensions 250mm L × 4.6 ID × ¼ in OD), a stainless steel preheating coil (internal diameter 1 mm and length 30 cm) and a commercially available backpressure regulator (Thalesnano back pressure module 300™, Budapest, Hungary, to a maximum of 300 bar). Parts of the system were connected with stainless steel tubing (internal diameter 1 mm). The HPLC column was charged with 4 g of the alumina catalyst. It was then placed into a GC oven unit (Carlo Erba HR 5300 up to maximum a 350 °C). For the CF reactions, 100 mM solution of the appropriate starting material was prepared in solvent. The solution was homogenized by sonication for 5 min and then pumped through the CF reactor under the set conditions. After the completion of the reaction, the reaction mixture was collected, and the rest solvent was evaporated by a vacuum rotary evaporator.

3. Product analysis

The products obtained were characterized by ^{1}H NMR spectroscopy. ^{1}H-NMR and APT-^{13}C-NMR spectra were recorded on a Bruker AV NEO Ascend 500 spectrometer and Varian , in DMSO-d_6 as applied solvent, at 500.2 MHz. Chemical shifts (δ) are expressed in ppm and are internally referenced (^{1}H NMR: 2.50 ppm in DMSO-d_6).

4. Tables and Figures

Table S1. The model reaction and optimization of amide formation in flow reactor

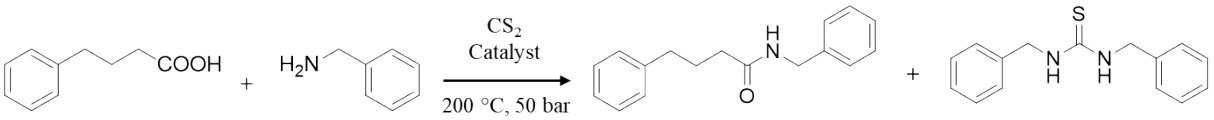


1 2 3 4

Entry	*Substrate A*	*Substrate B*	*Lewis acid*	*Reagent*	*Solvent*	*Condition*	*Conversion*
1	4-PBA	BA	-	-	ACN	200°C 0.1 ml/min 50 bar	0%
2	4-PBA	BA	Alumina	-	ACN	200°C 0.1 ml/min 50 bar	0%[a]
3	4-PBA	BA	-	CS_2	ACN	200 °C 0.1 ml/min 50 bar	22%
4	4-PBA	BA	Alumina	CS_2	ACN	200 °C 0.1 ml/min 50 bar	53%[b]
5	4-PBA	BA	Alumina	CS_2 Triethylamine	ACN	200 °C 0.1 ml/min 50 bar	62%
6	4-PBA	BA	Alumina	CS_2 Pyridine	ACN	200 °C 0.1 ml/min 50 bar	58%
7	4-PBA	BA	Alumina	CS_2 DMAP	ACN	200 °C 0.1 ml/min 50 bar	>99%

4-PBA: 4-phenylbutyric acid, BA: benzylamine, DMAP: 4-(dimethylamino)pyridine, ACN: acetonitrile, CS_2: carbon disulfide, a: Acetylation side reaction was only observed; b: 31% thiourea formation was observed.

Table S2. Screen of alternative catalysts

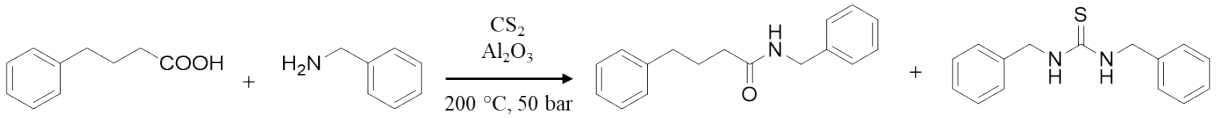


1 2 3 4

Entry	*Lewis acid*	*Reagent*	*Solvent*	*Conversion into **3** (%)*
1	boric acid	CS_2	acetonitrile	2%
2	Fe	CS_2	acetonitrile	3%
3	Cu	CS_2	acetonitrile	17%
4	Fe_2O_3	CS_2	acetonitrile	10%
5	NiO	CS_2	acetonitrile	4%
6	CuO	CS_2	acetonitrile	40%
7	Al_2O_3	CS_2	acetonitrile	53%

1 equiv. 4-phenylbutyric acid (100 mM), 1 equiv. benzyl amine (100 mM), *Reagent*: 1.5 equiv. CS_2 *Condition:* 200 ^{0}C, 50 bar, 0.1 mL min^{-1}, 27 min residence time

Table S3. Direct amide bond formation in a range of solvents



1 2 3 4

Entry	*Solvent*	*Conversion into **3** (%)*
1	Water	0%
2	Methanol	31%
3	Isopropanol	10%
4	Toluene	43%
5	Acetonitrile	53%
6	Dichloromethane	0%
7	Dimethylsulfoxide	4%

1 equiv. 4-phenylbutyric acid (100 mM), 1 equiv. benzyl amine (100 mM), *Lewis acid*: alumina, *Reagent*: 1.5 equiv. CS_2 *Condition:* 200 ^{o}C, 50 bar, 0.1 mL min^{-1}, 27 min residence time

Table S4. Effect of the different amount of carbon disulfide

Entry	*Lewis acid*	*Reagent*	*Solvent*	*Conversion into **3** (%)*
1	Al_2O_3	0.5 equiv CS_2	acetonitrile	26%
2	Al_2O_3	1 equiv CS_2	acetonitrile	43%
3	Al_2O_3	1.5 equiv CS_2	acetonitrile	53%
4	Al_2O_3	2 equiv CS_2	acetonitrile	49%
5	Al_2O_3	3 equiv CS_2	acetonitrile	45%

1 equiv. 4-phenylbutyric acid (100 mM), 1 equiv. benzyl amine (100 mM), Lewis acid: alumina, Reagent: CS_2 Condition: 200 ^{o}C, 50 bar, 0.1 mL min^{-1}, 27 min residence time

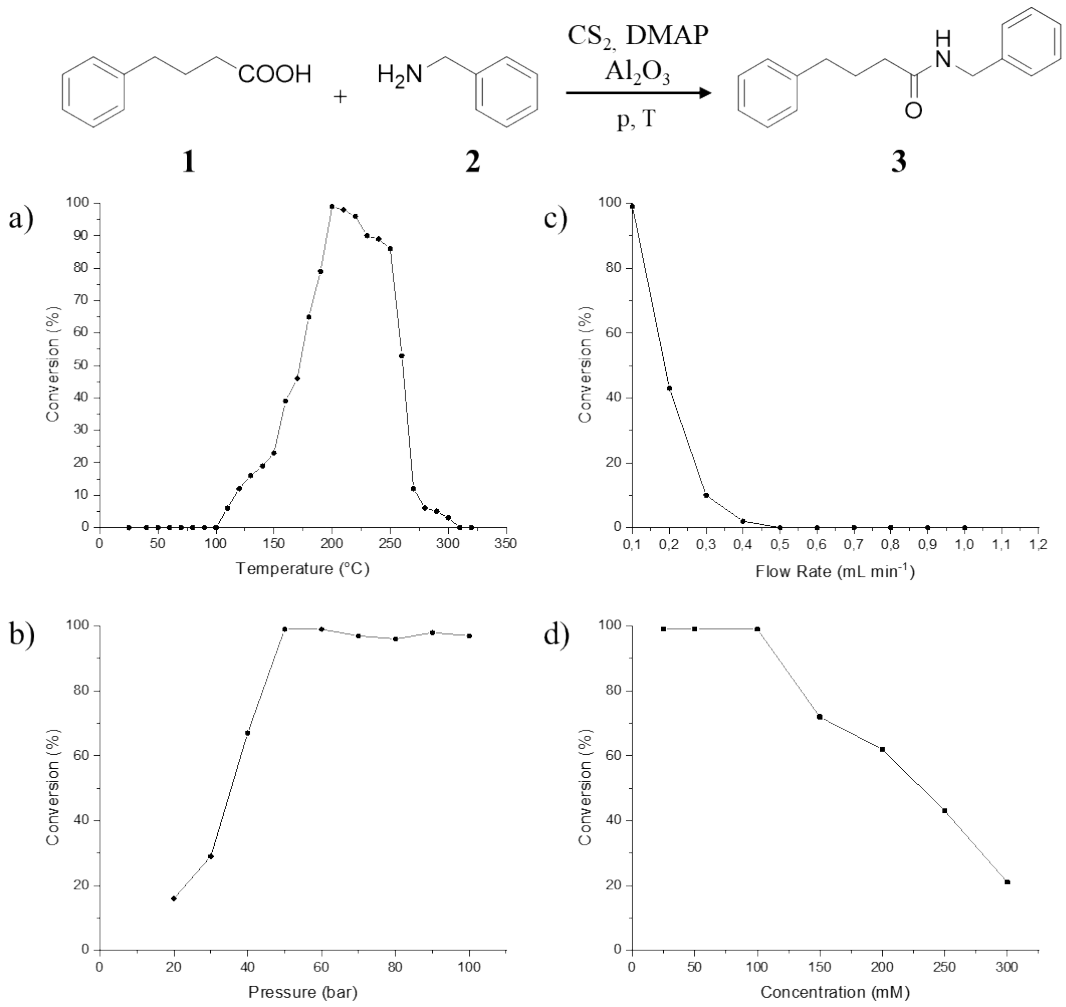
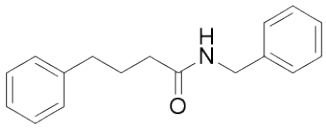


Fig. S1 The effect of temperature (a), pressure (b), flow rate (c), and concentration of the starting materials (d) on the reaction conversion catalyzed by Al_2O_3. The effect of the pressure was measured at room temperature, the influence of temperature was determined at 50 bar, while the effect of the flow rate and concentration was analyzed under the optimized conditions.

5. ^{1}H and ^{13}C NMR spectra



N-benzyl-4-phenylbutanamide

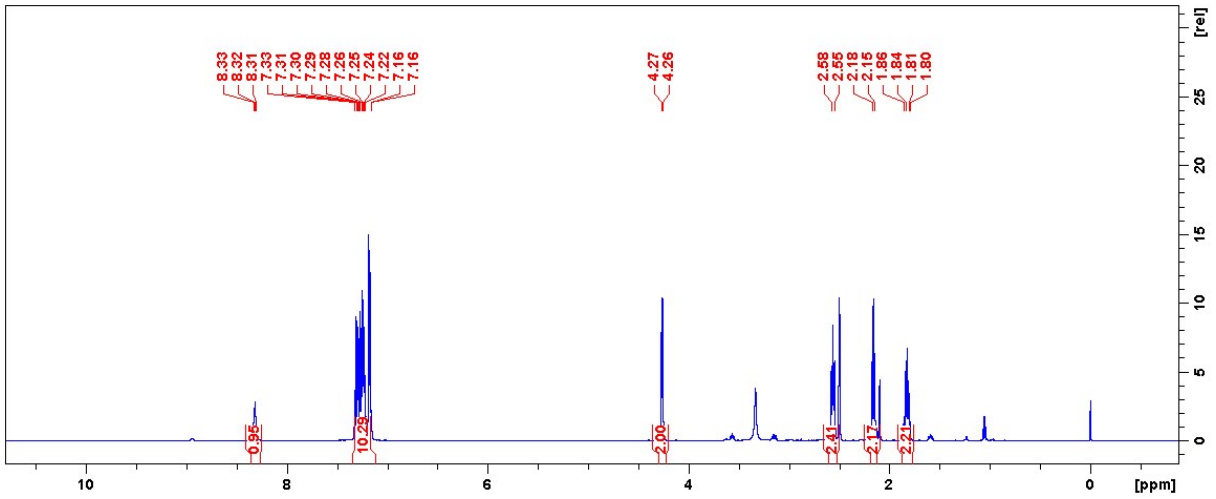


Figure S2. ^{1}H NMR spectrum of N-benzyl-4-phenylbutanamide measured in DMSO-d6 at 296 K.

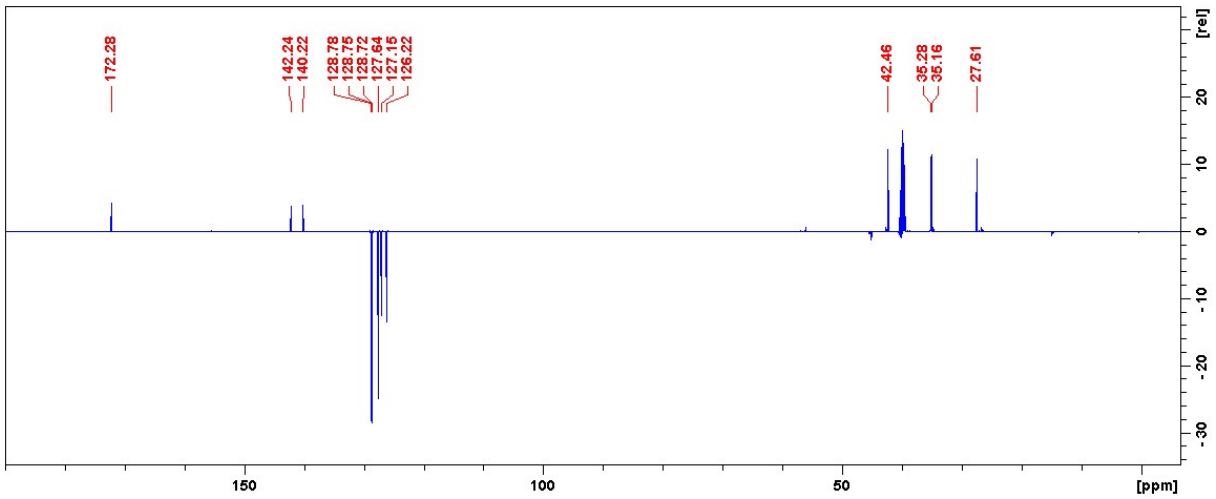
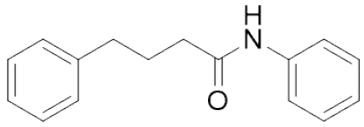


Figure S3. APT NMR spectrum of N-benzyl-4-phenylbutanamide measured in DMSO-d6 at 296 K.



N,4-diphenylbutanamide

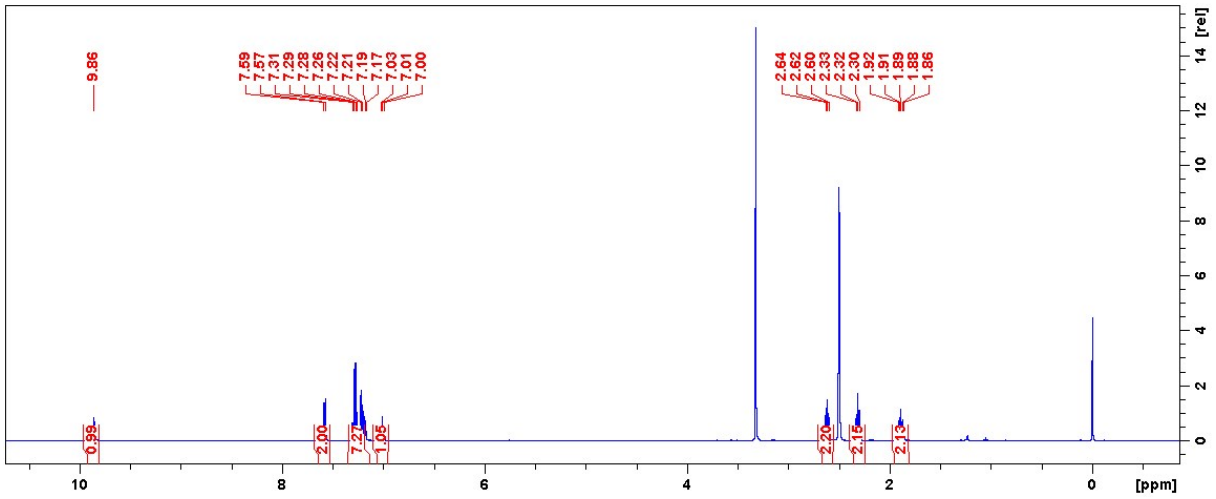


Figure S4. ^{1}H NMR spectrum of N,4-diphenylbutanamide measured in DMSO-d6 at 296 K.

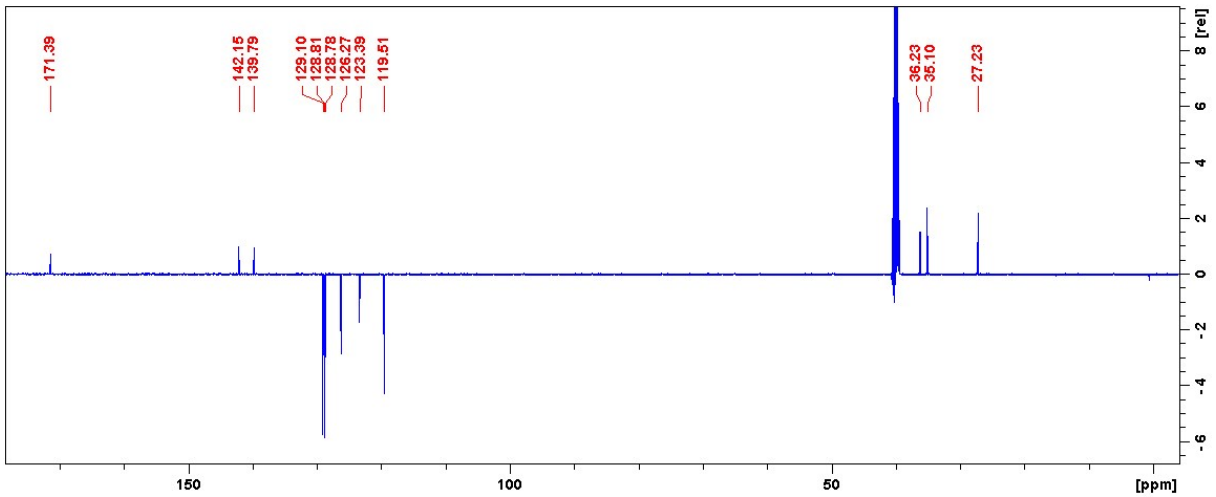
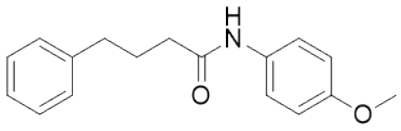


Figure S5. APT NMR spectrum of N,4-diphenylbutanamide measured in DMSO-d6 at 296 K.



N-(4-methoxyphenyl)-4-phenylbutanamide

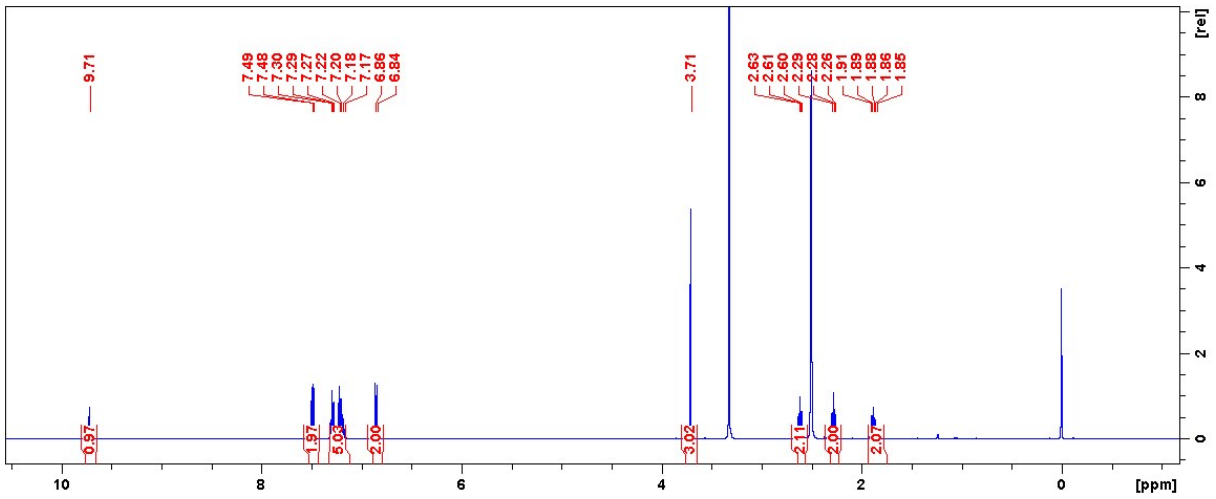


Figure S6. ^{1}H NMR spectrum of N-(4-methoxyphenyl)-4-phenylbutanamide measured in DMSO-d6 at 296 K.

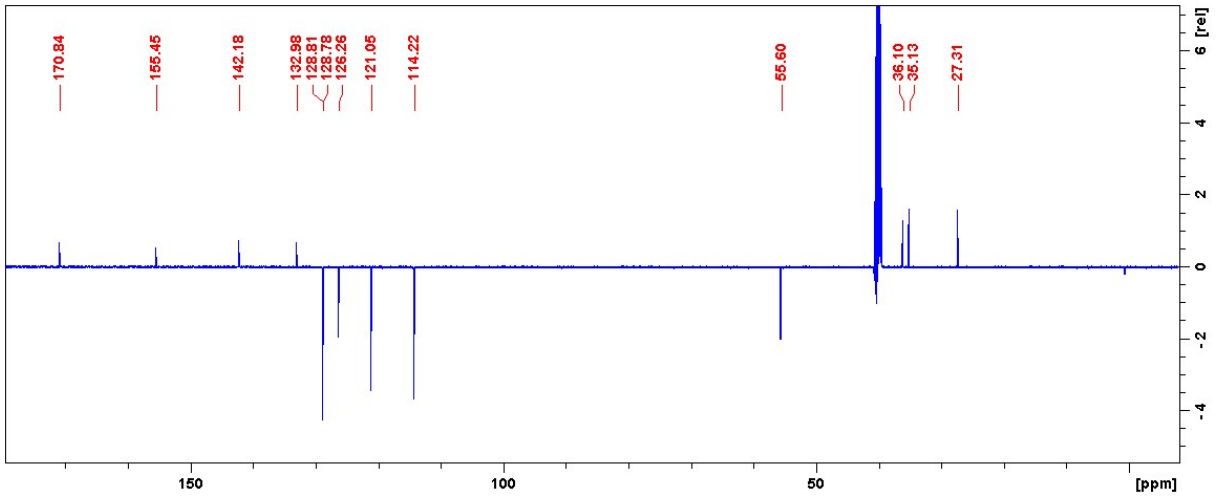
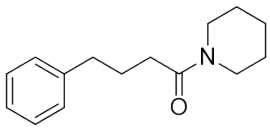


Figure S7. ATP NMR spectrum of N-(4-methoxyphenyl)-4-phenylbutanamide measured in DMSO-d6 at 296 K.



4-phenyl-1-(piperidin-1-yl)butan-1-one

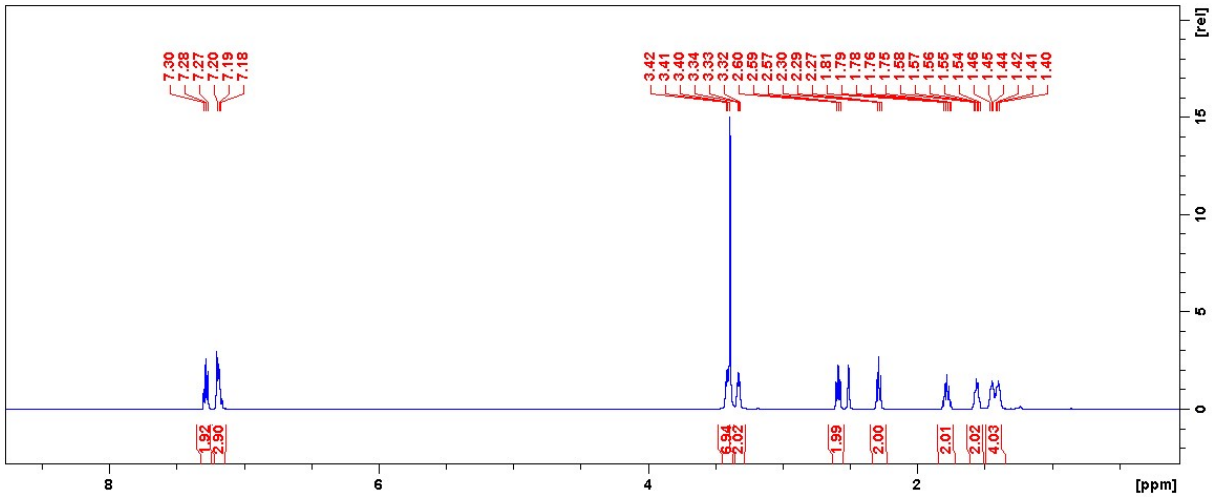


Figure S8. ^{1}H NMR spectrum of 4-phenyl-1-(piperidin-1-yl)butan-1-one measured in DMSO-d6 at 296 K.

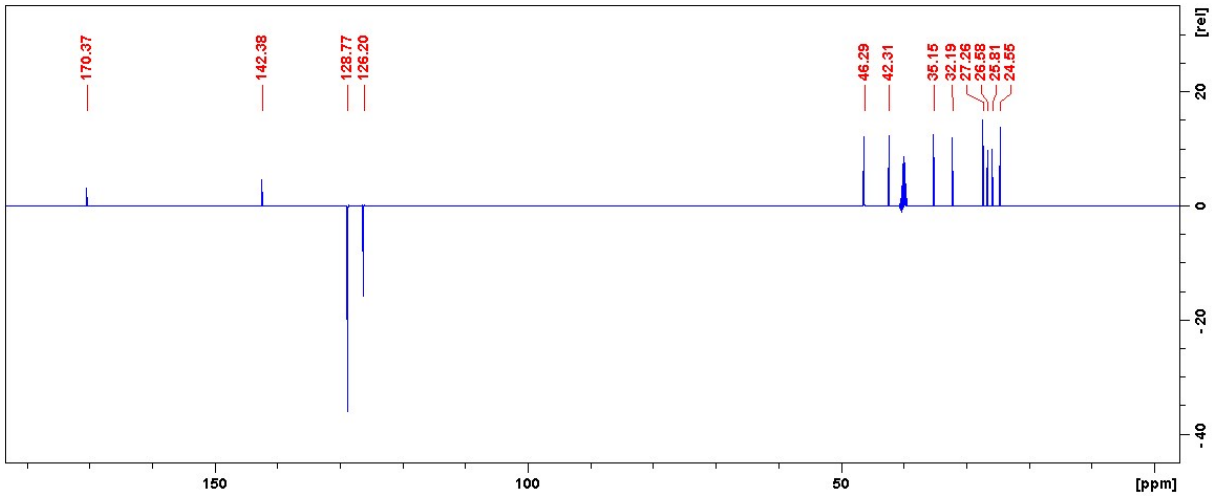
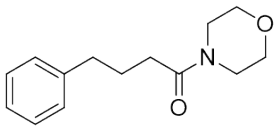


Figure S9. APT NMR spectrum of 4-phenyl-1-(piperidin-1-yl)butan-1-one measured in DMSO-d6 at 296 K.



4-phenyl-1-(piperidin-1-yl)butan-1-one

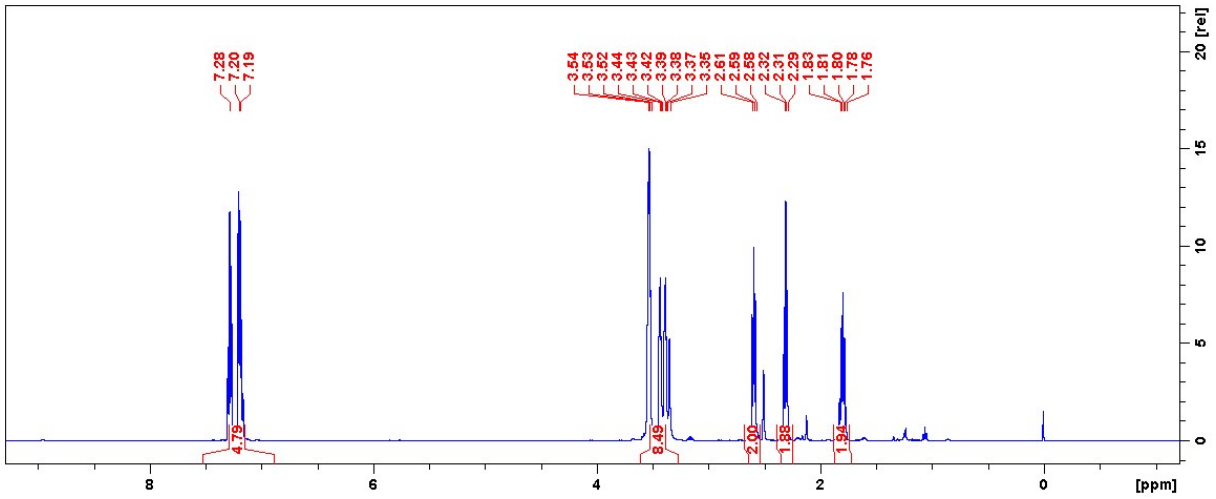


Figure S10. ^{1}H NMR spectrum of 4-phenyl-1-(piperidin-1-yl)butan-1-one measured in DMSO-d6 at 296 K.

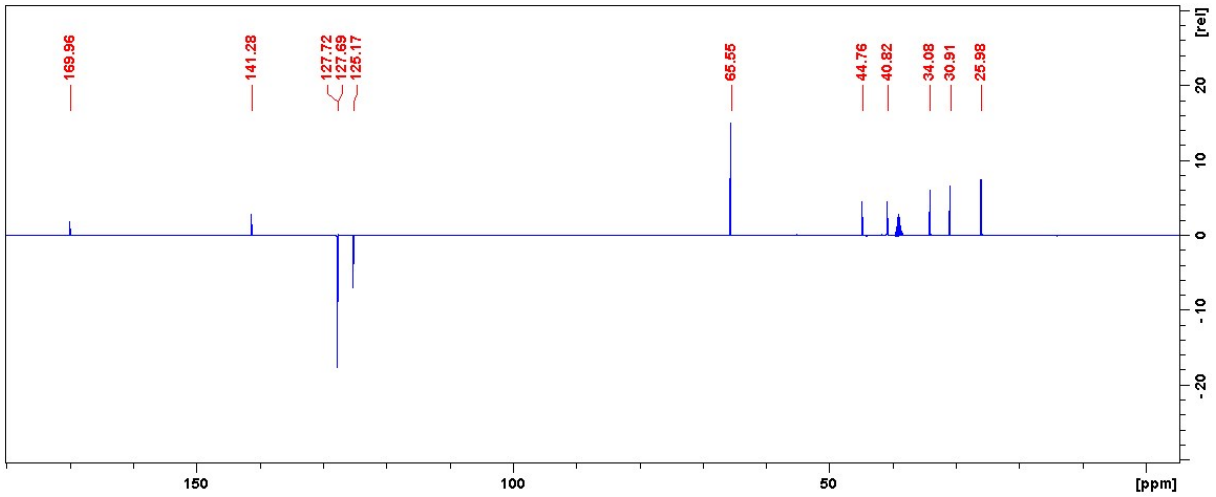
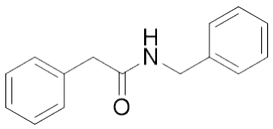


Figure S11. ATP NMR spectrum of 4-phenyl-1-(piperidin-1-yl)butan-1-one measured in DMSO-d6 at 296 K.



N-benzyl-2-phenylacetamide

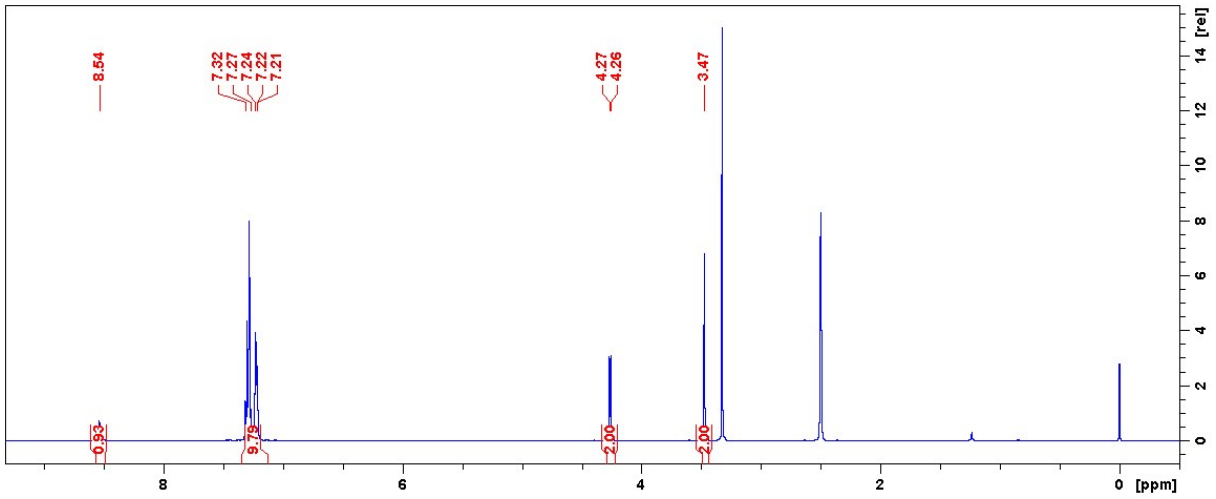


Figure S12. ^{1}H NMR spectrum of N-benzyl-2-phenylacetamide measured in DMSO-d6 at 296 K.

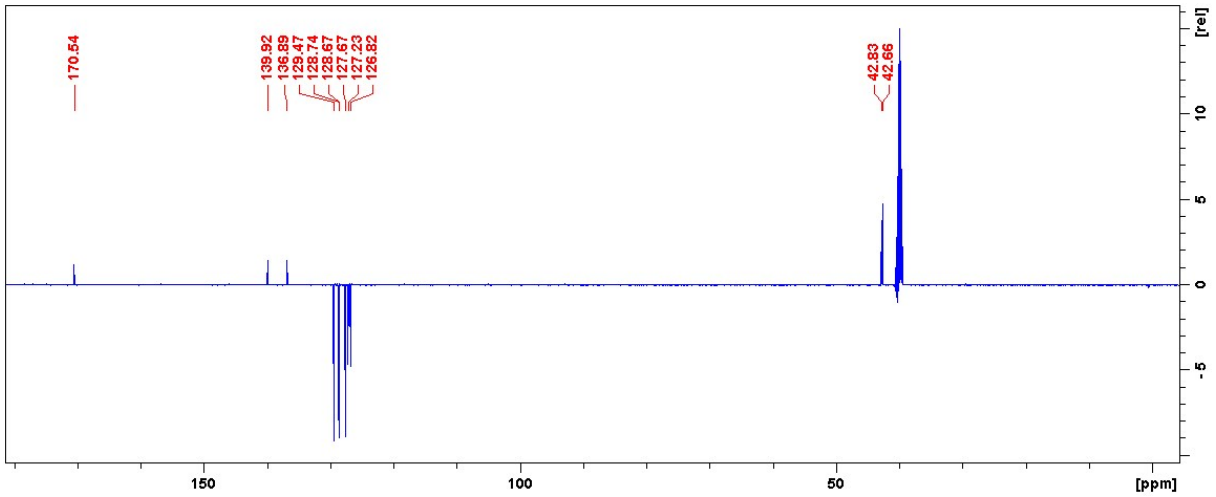
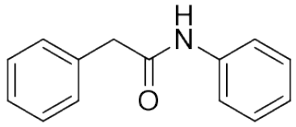


Figure S13. APT NMR spectrum of N-benzyl-2-phenylacetamide measured in DMSO-d6 at 296 K.



N,2-diphenylacetamide

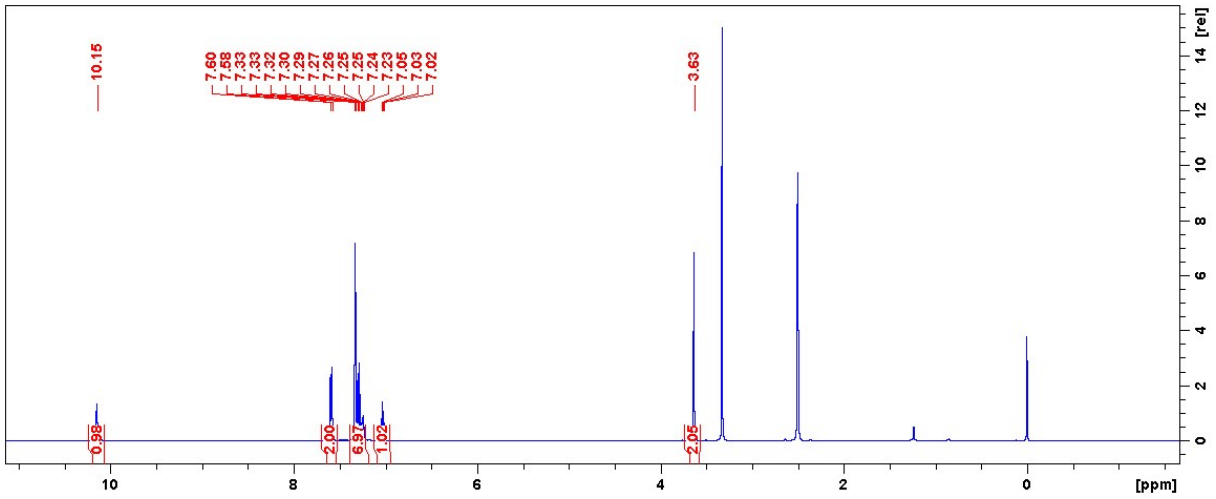


Figure S14. ^{1}H NMR spectrum of N,2-diphenylacetamide measured in DMSO-d6 at 296 K.

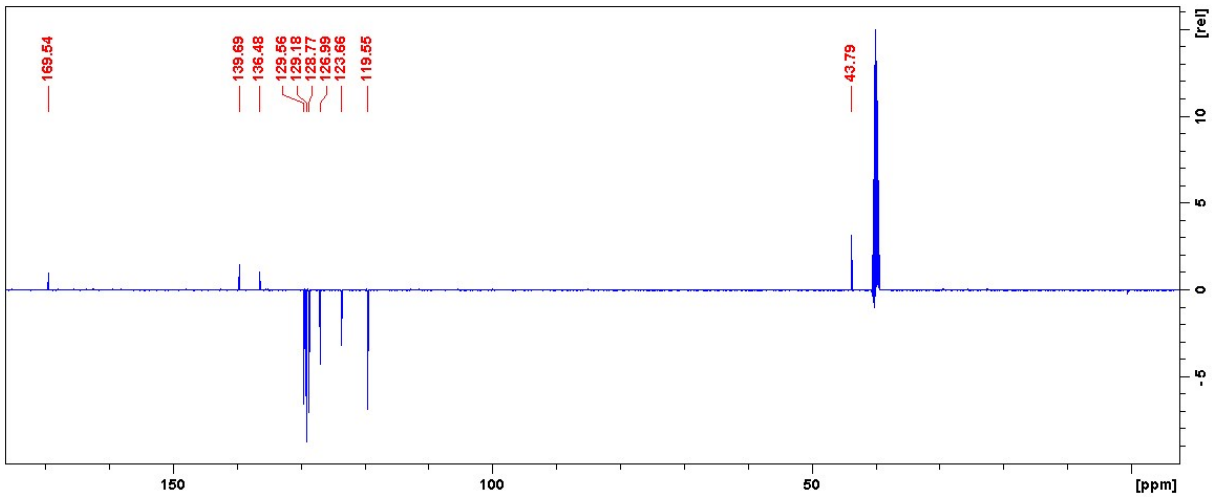
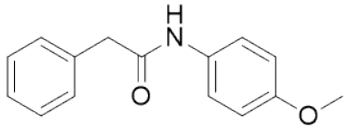


Figure S15. APT NMR spectrum of N,2-diphenylacetamide measured in DMSO-d6 at 296 K.



N-(4-methoxyphenyl)-2-phenylacetamide

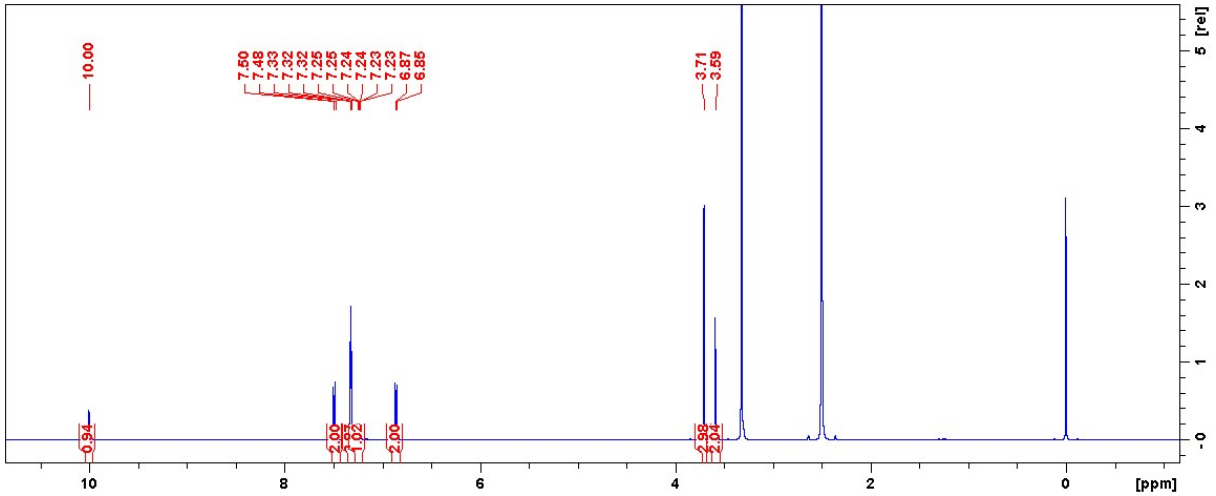


Figure S16. ^{1}H NMR spectrum of N-(4-methoxyphenyl)-2-phenylacetamide measured in DMSO-d6 at 296 K.

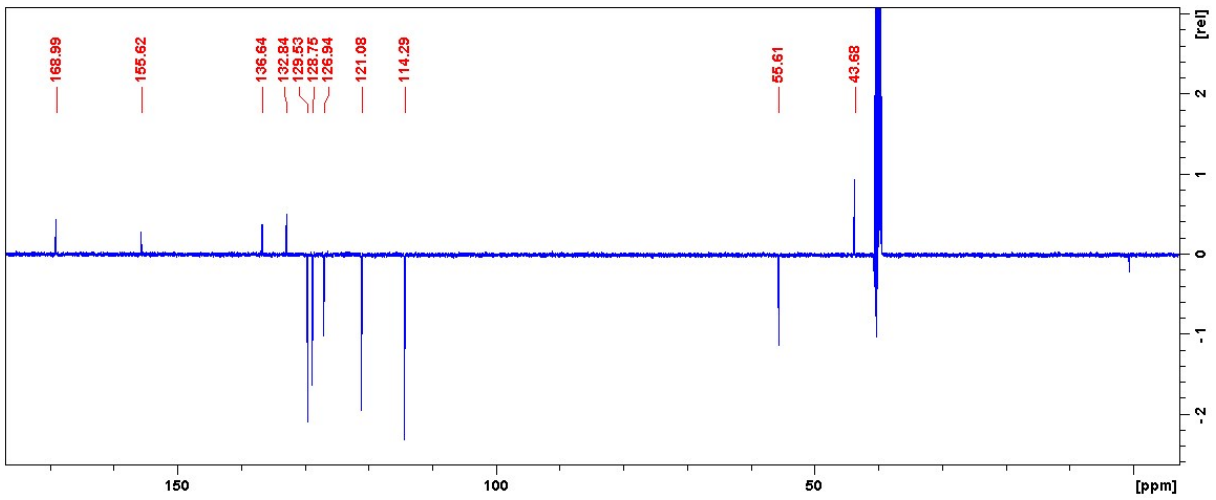
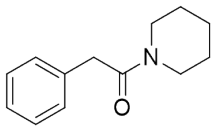


Figure S17. APT NMR spectrum of N-(4-methoxyphenyl)-2-phenylacetamide measured in DMSO-d6 at 296 K.



2-phenyl-1-(piperidin-1-yl)ethanone

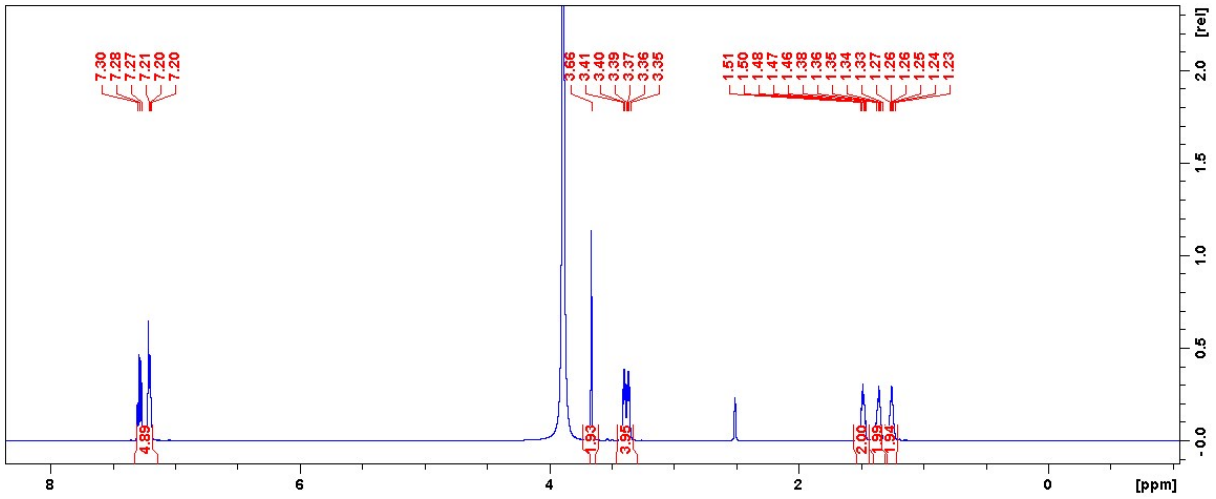


Figure S18. ^{1}H NMR spectrum of 2-phenyl-1-(piperidin-1-yl)ethanone measured in DMSO-d6 at 296 K.

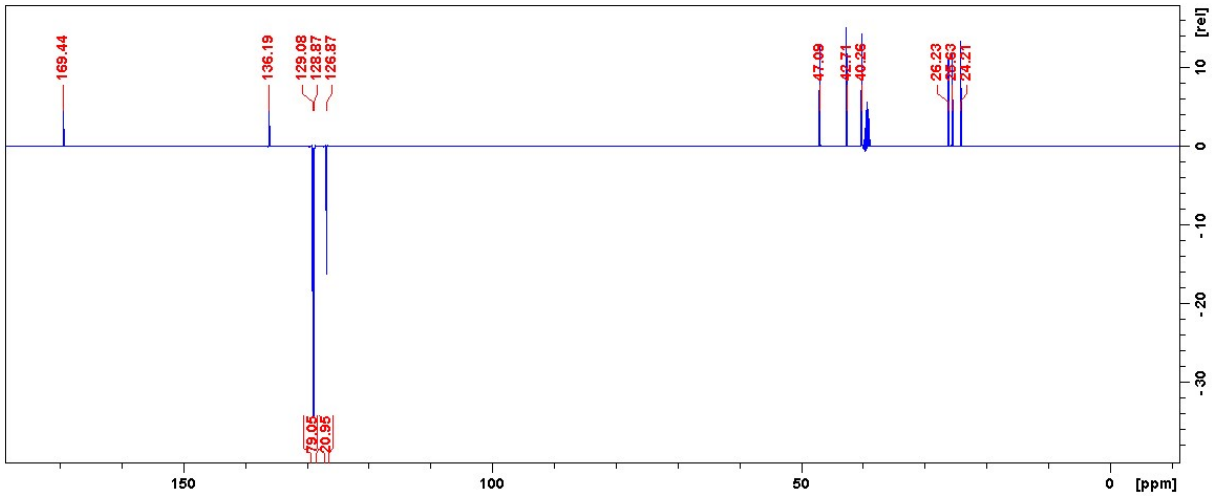
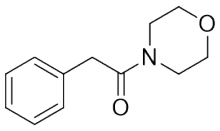


Figure S19. APT NMR spectrum of 2-phenyl-1-(piperidin-1-yl)ethanone measured in DMSO-d6 at 296 K.



1-morpholino-2-phenylethanone

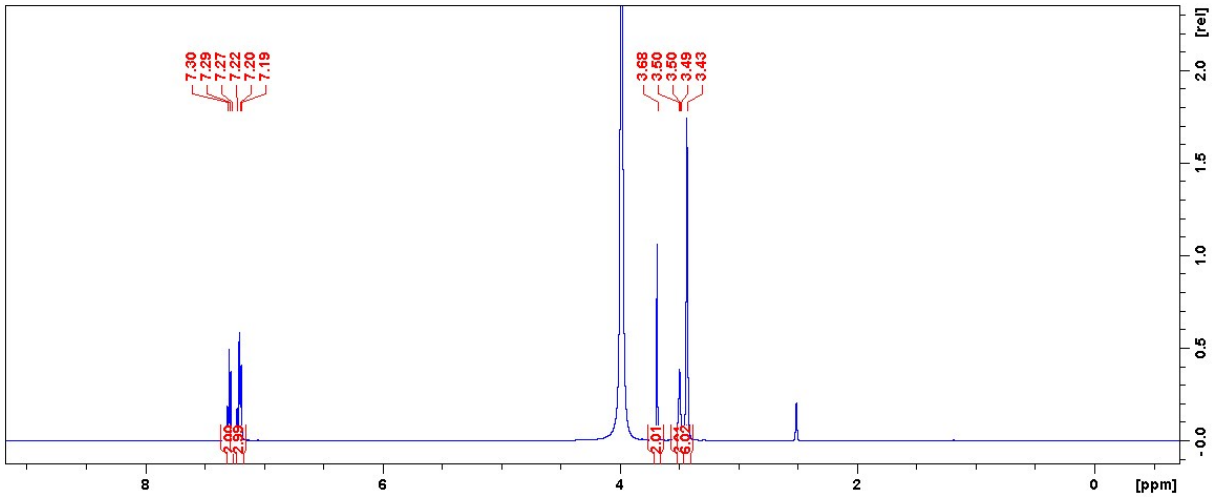


Figure S20. ^{1}H NMR spectrum of 1-morpholino-2-phenylethanone measured in DMSO-d6 at 296 K.

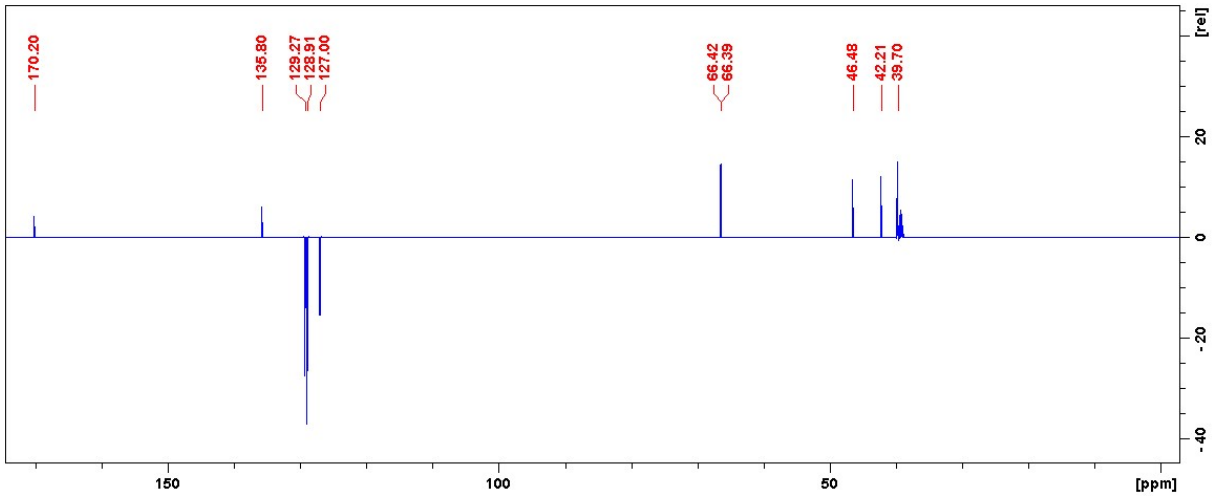
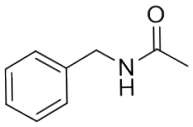


Figure S21. APT NMR spectrum of 1-morpholino-2-phenylethanone measured in DMSO-d6 at 296 K.



N-benzylacetamide

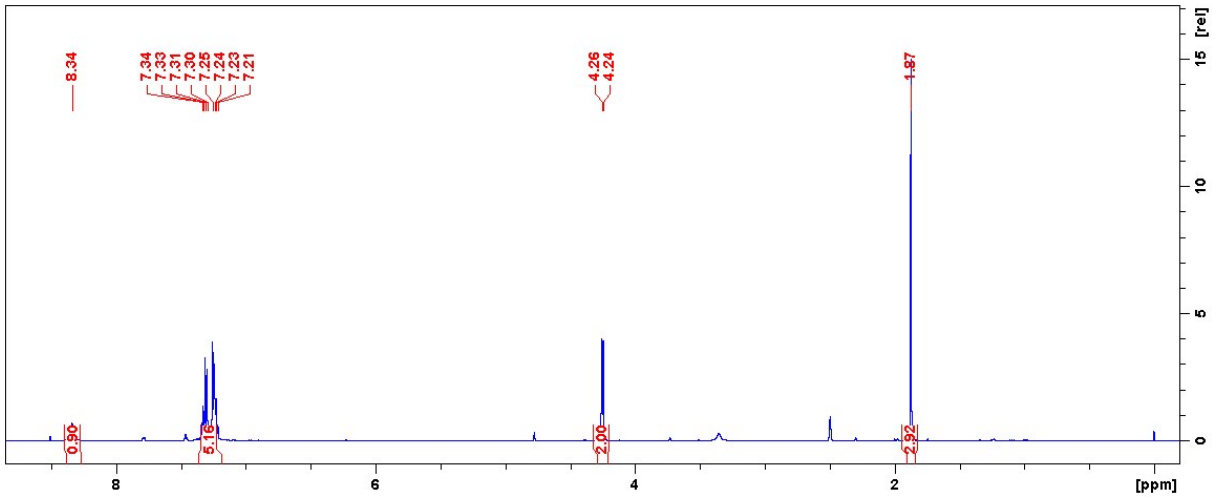


Figure S22. ^{1}H NMR spectrum of N-benzylacetamide measured in DMSO-d6 at 296 K.

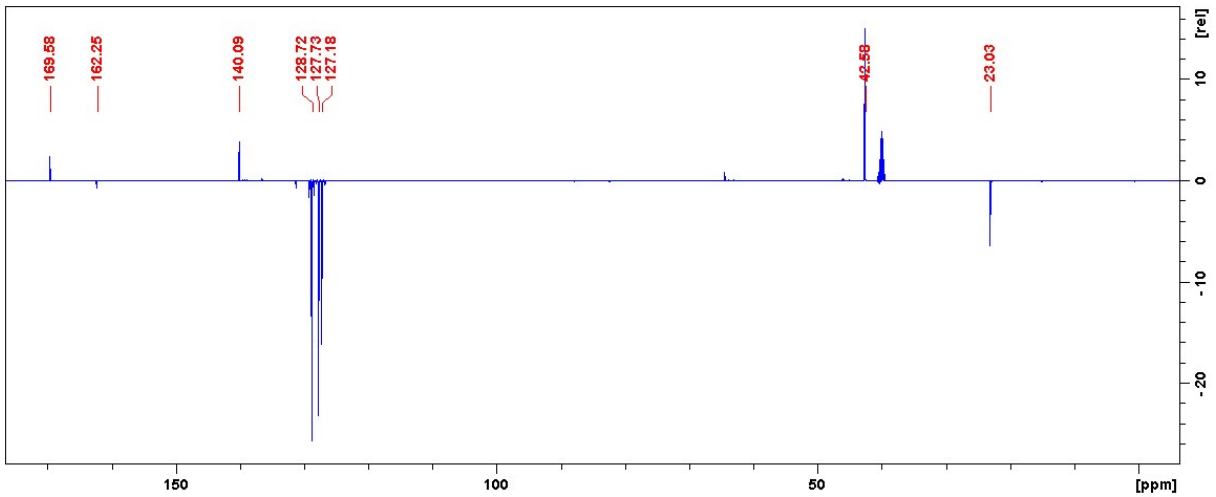
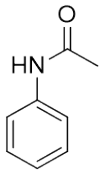


Figure S23. APT NMR spectrum of N-benzylacetamide measured in DMSO-d6 at 296 K.



N-phenylacetamide

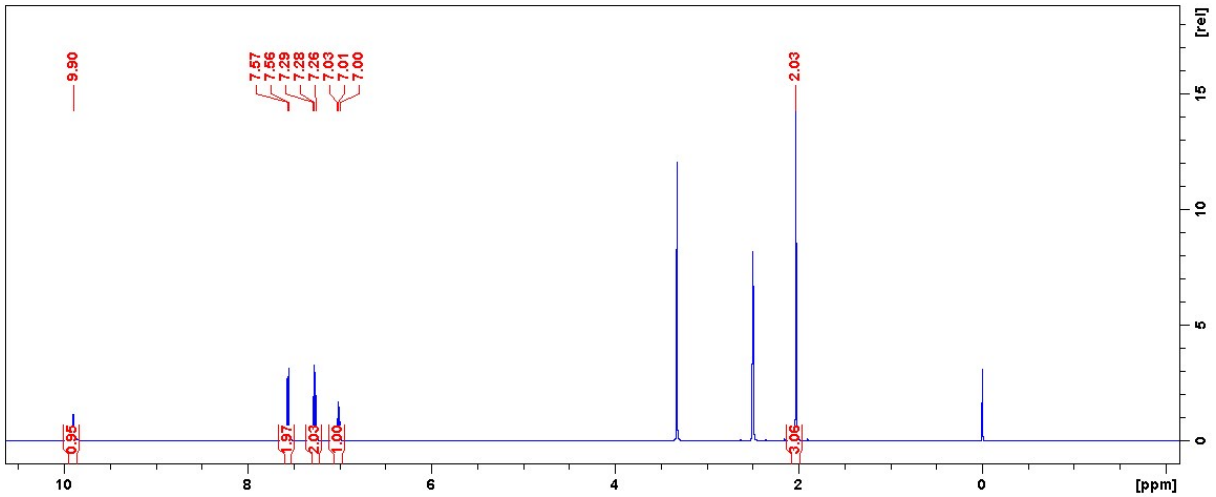


Figure S24. [1]H NMR spectrum of N-phenylacetamide measured in DMSO-d6 at 296 K.

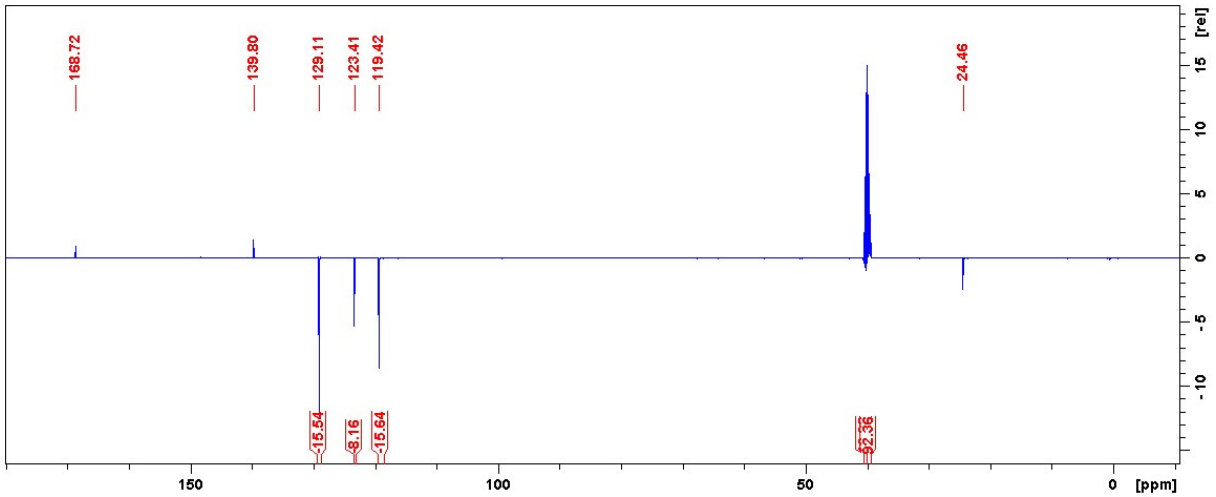
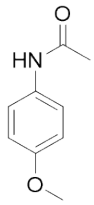


Figure S25. APT NMR spectrum of N-phenylacetamide measured in DMSO-d6 at 296 K.



N-(4-methoxyphenyl)acetamide

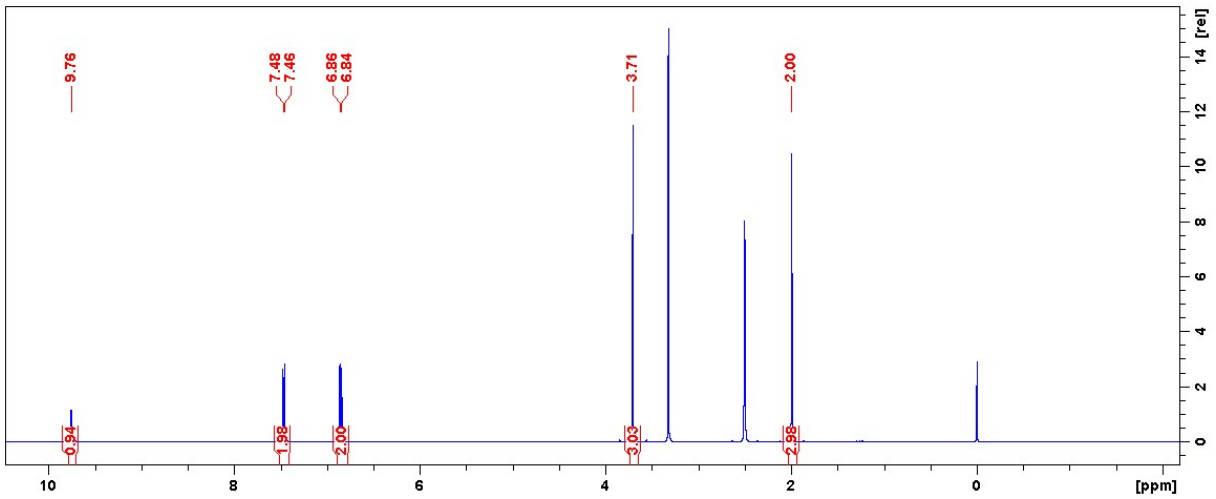


Figure S26. ^{1}H NMR spectrum of N-(4-methoxyphenyl)acetamide measured in DMSO-d6 at 296 K.

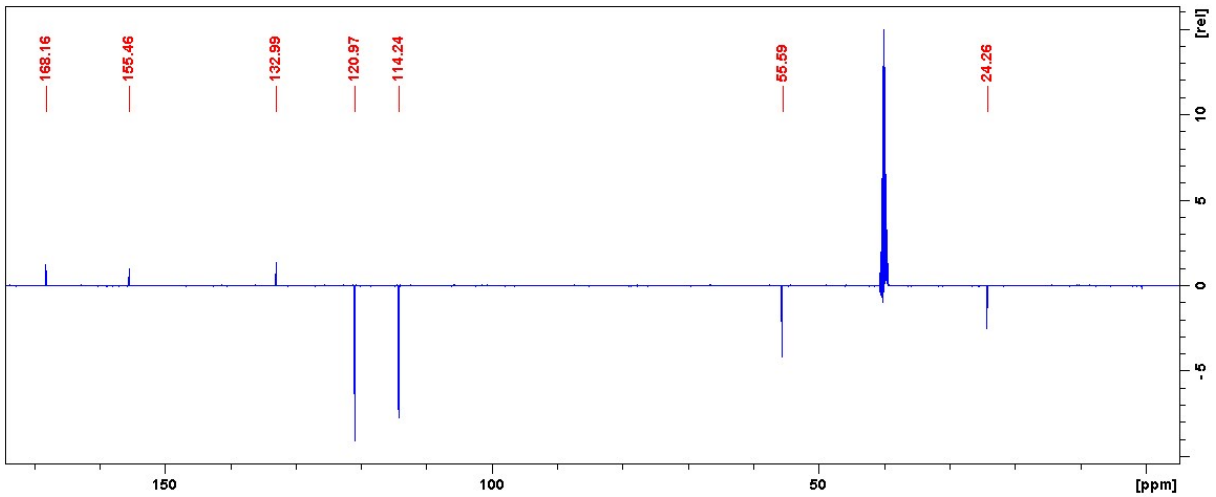
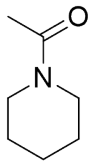


Figure S27. APT NMR spectrum of N-(4-methoxyphenyl)acetamide measured in DMSO-d6 at 296 K.



1-(piperidin-1-yl)ethanone

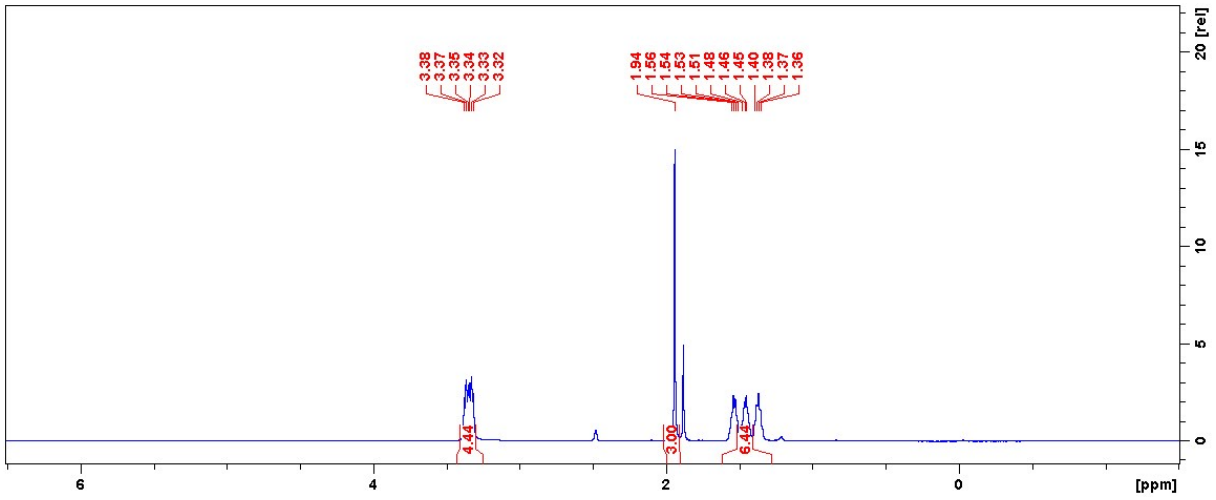


Figure S28. [1]H NMR spectrum of 1-(piperidin-1-yl)ethanone measured in DMSO-d6 at 296 K.

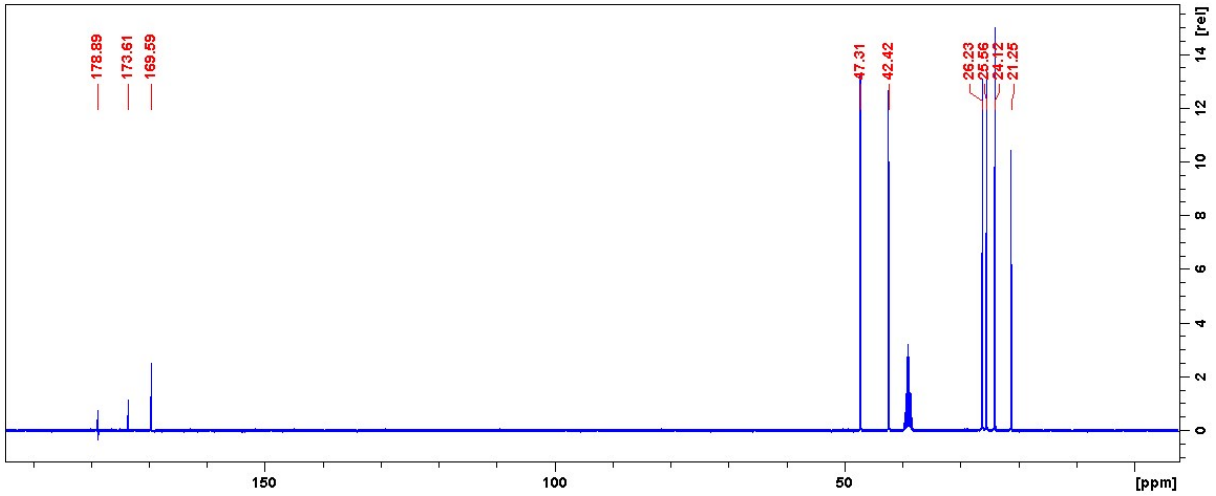
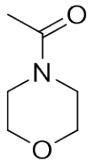


Figure S29. [13]C NMR spectrum of 1-(piperidin-1-yl)ethanone measured in DMSO-d6 at 296 K.



1-morpholinoethanone

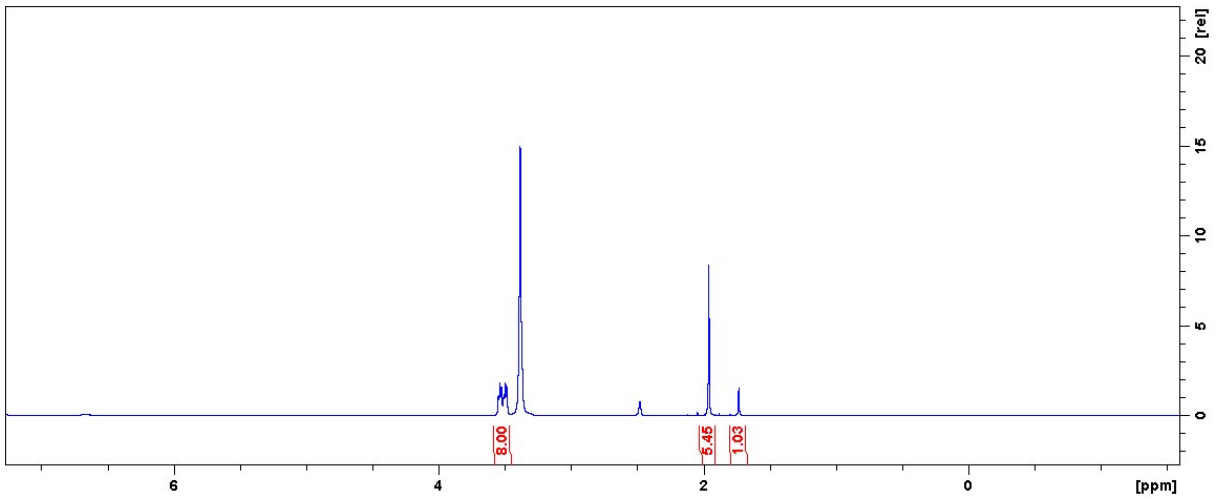


Figure S30. ^{1}H NMR spectrum of 1-morpholinoethanone measured in DMSO-d6 at 296 K.

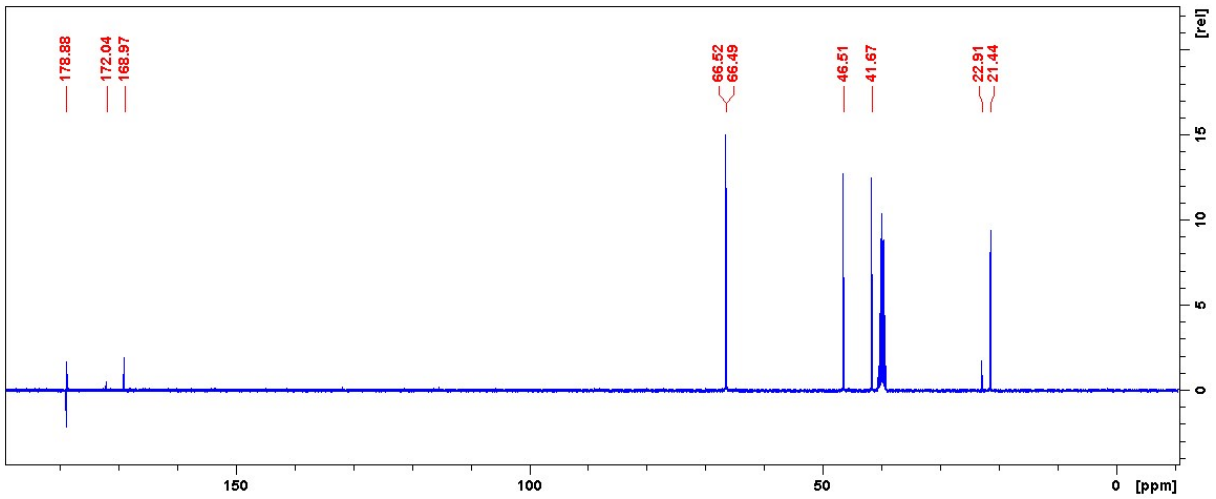


Figure S31. ^{13}C NMR spectrum of 1-morpholinoethanone measured in DMSO-d6 at 296 K.

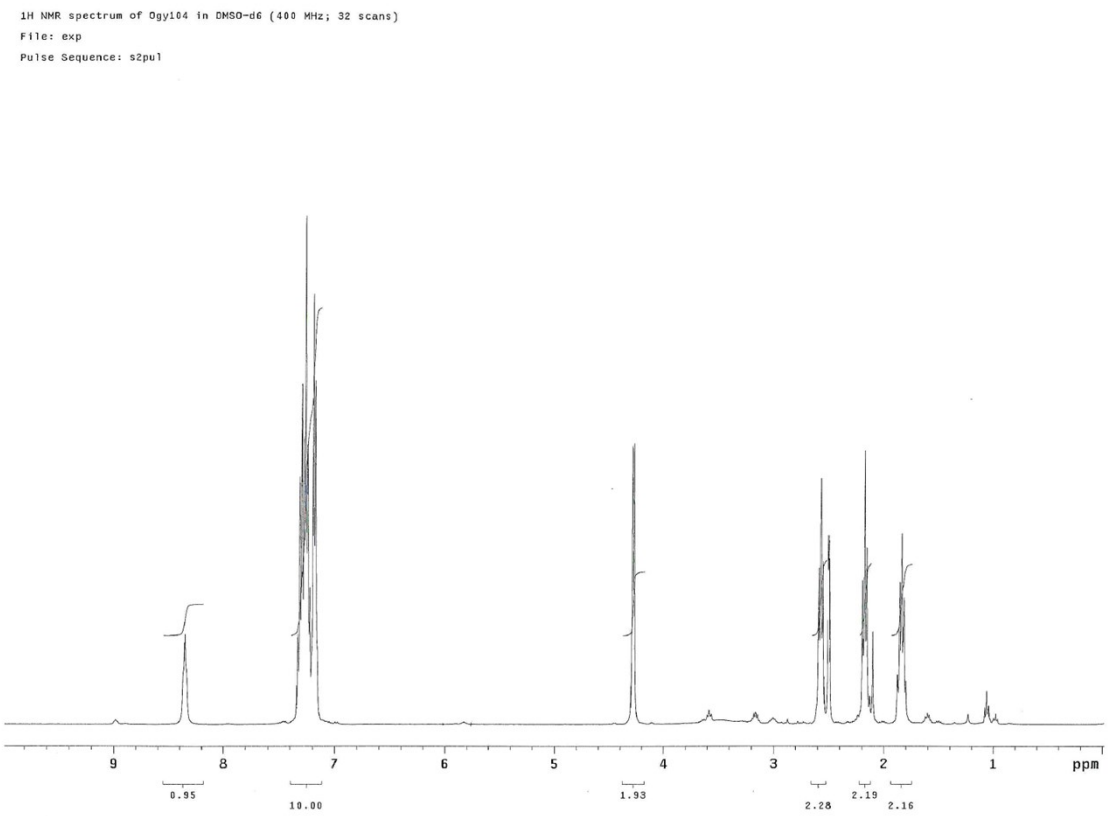


Figure S32. [1]H NMR spectrum of N-benzyl-4-phenylbutanamide measured in DMSO-d6 at 296 K gained by the scale-up reaction.

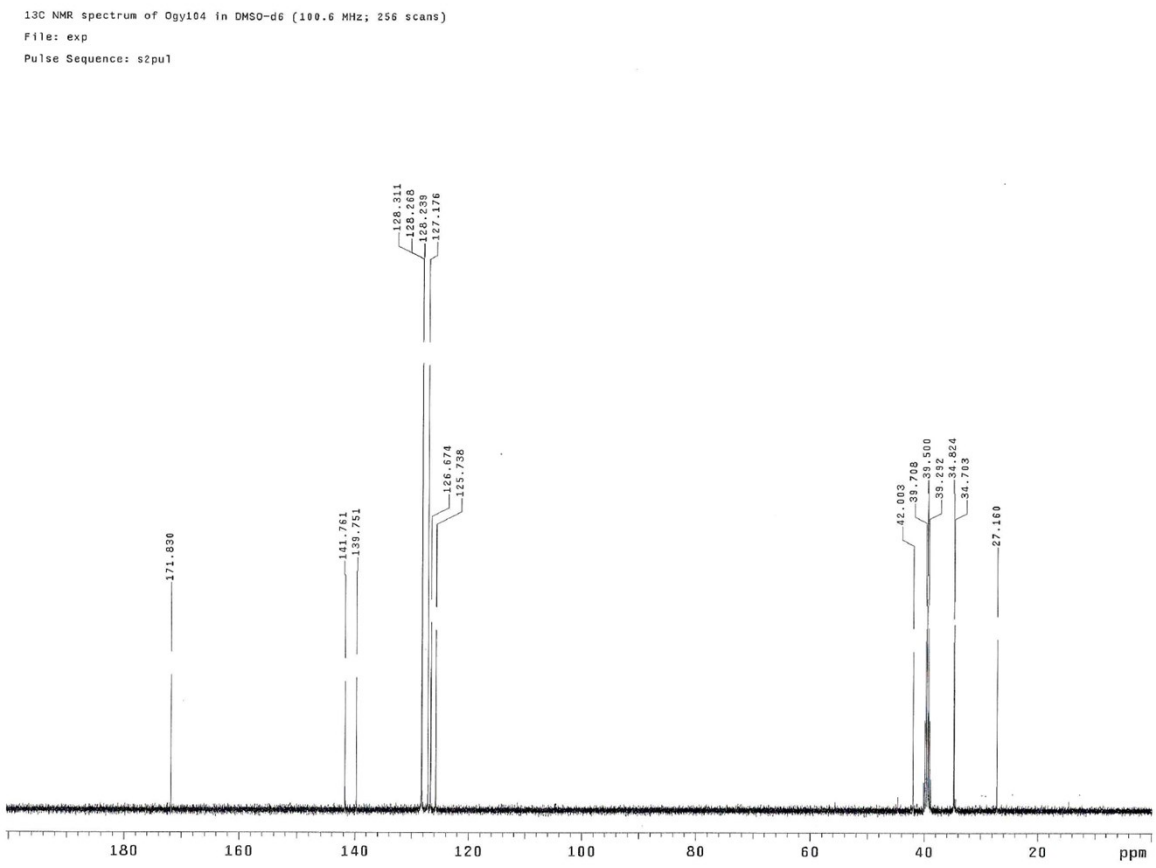


Figure S33. ^{13}C NMR spectrum of N-benzyl-4-phenylbutanamide measured in DMSO-d6 at 296 K gained by the scale-up reaction.