One-pot mechanosynthesis of aromatic amides and dipeptides from carboxylic acids and amines

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Supplementary Material

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1. Experimental

1.1 List of abbreviations

DCC – *N*,*N′*-dicyclohexylcarbodiimide
DIC – *N*,*N′*-diisopropylcarbodiimide
CDI – carbonyl diimidazole
EDC·HCl – *N*-ethyl-*N′*-(3-dimethylaminopropyl)carbodiimide hydrochloride
Boc-Gly-OH – *N*-(*tert*-butoxycarbonyl)glycine
Boc-L-Ala-OH – *N*-(*tert*-butoxycarbonyl)-L-alanine
Boc-D-Ala-OH – *N*-(*tert*-butoxycarbonyl)-D-alanine
Gly-OBn·TsOH – glycine benzyl ester tosylate
L-Ala-OBn·TsOH – L-alanine benzyl ester tosylate
DMAP – 4-(dimethylamino)pyridine
Boc-Gly-Gly-OBn – *N*-(*tert*-butoxycarbonyl)glycylglycine benzyl ester
Boc-L-Ala-L-Ala-OBn – *N*-(*tert*-butoxycarbonyl)-L-alanyl-L-alanine benzyl ester
Boc-L-Ala-Gly-OBn – *N*-(*tert*-butoxycarbonyl)-L-alanylglycine benzyl ester
Boc-D-Ala-Gly-OBn – *N*-(*tert*-butoxycarbonyl)-D-alanylglycine benzyl ester
Boc-D-Ala-L-Ala-OBn – *N*-(*tert*-butoxycarbonyl)-D-alanyl-L-alanine benzyl ester

1.2 General comments

All chemicals were purchased from commercial sources (Sigma Aldrich or Alfa Aesar) and were used as received. The experiments were carried out in a Retsch MM400 mill at a frequency of 30 Hz using a 10 mL stainless steel grinding jar and a single stainless steel ball of 12 mm diameter (unless otherwise stated). Dry nitromethane was used as the liquid phase throughout all liquid-assisted grinding (LAG) experiments.

^{1}H and ^{13}C NMR spectra were recorded on a Brucker Avance (300 and 600 MHz) spectrometers with tetramethylsilane as an internal standard, while FTIR-ATR spectra were obtained on an ABB Bomem MB102 spectrophotometer.

Single crystals of all compounds were obtained from the mother liquid at room temperature. The single crystal diffraction data were collected at 153 (**2d** and **2e**) and 293 K (**4**). Diffraction intensity data were collected by ω-scans on an Oxford Diffraction Xcalibur 3 using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) and reduced using the CrysAlis^{PRO} program package.[1] The data for compound **4** was reduced using an automatic twin lattice finding and data reduction of twinned data set routines in CrysAlis^{PRO}. A summary of general and crystal data, intensity data collection and final refinement parameters are presented in Table S2. The structures were solved by direct methods using SHELXS.[2] The structure of compound **4** was determined from a twinned crystal, but only the data from the main twin component was used (farction of the component was 0.68:0.32). The twin matrix corresponds to twofold rotation about the *c* axis (−100/0−10/001). The refinement procedure by full-matrix least squares methods based on F^2 values against all reflections included anisotropic displacement parameters for all non-H atoms. The positions of H-atoms were determined on stereochemical grounds. Refinements were performed using SHELXL-97.[2] The SHELX programs operated within the WinGX[3] program package. Geometrical calculations and molecular graphics were done with PLATON,[4] MERCURY[5] and PyMOL.[6] Supplementary crystallographic data sets for the structures are available through the Cambridge Structural Data base with deposition numbers 900474-900476. Copy of this information may be obtained free of charge from the director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

Crystal structures of *N*-(4-chlorophenyl)benzamide (**1e**) and *N*-benzoylmorpholine (**6a**) have been solved by simulated annealing from powder diffraction data and refined using the Rietveld method with geometrical restraints set to expected values for bond distances and angles as well as planarity restraints. Preferred orientation in the patterns, arising from data being collected in Bragg-Brentano geometry, was modelled using spherical harmonics of the 6th order. All calculations including indexing, structure solution and Rietveld refinement have been carried out using the program Topas (Topas version 4.2, Bruker-AXS, Karlsruhe, Germany).

1.3 Optimisation of the reaction conditions in the mechanosynthesis of benzamide 1a

Table S1. Optimisation of the reaction parameters for the synthesis of *N*-(4-methoxyphenyl) benzamide (**1a**).

Entry	Coupling reagent	Milling time, balls^a	Conversion^b / %
1	DCC	30 min, 2 × 8 mm	87
2	DCC	30 min, 12 mm	88
3	DIC	30 min, 2 × 8 mm	88
4	DIC	30 min, 12 mm	88
5	CDI	30 min, 2 × 8 mm	-
6	CDI	30 min, 12 mm	-
7	EDC·HCl	30 min, 2 × 8 mm	83
8	EDC·HCl	30 min, 12 mm	97
9	EDC·HCl	10 min, 12 mm	97
10	EDC·HCl	5 min, 12 mm	95

^{a}Neat grinding at 30 Hz; ^{b}Determined by integration of the corresponding signals in the ^{1}H NMR spectra of the reaction mixtures.

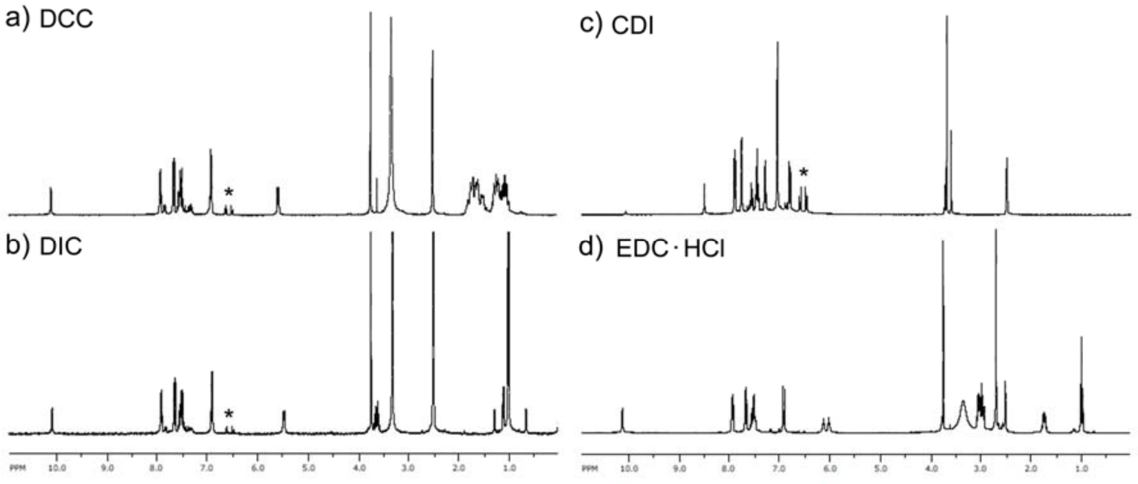


Figure S1. ^{1}H NMR spectra of the reaction mixtures after 30 minutes of neat grinding of benzoic acid with *p*-anisidine and different coupling reagents using a single 12 mm ball. Unreacted *p*-anisidine is labelled with „*“. It is notable that the reaction does not proceed with CDI as the coupling reagent, whereas EDC·HCl provides quantitative conversion to amide **1a**.

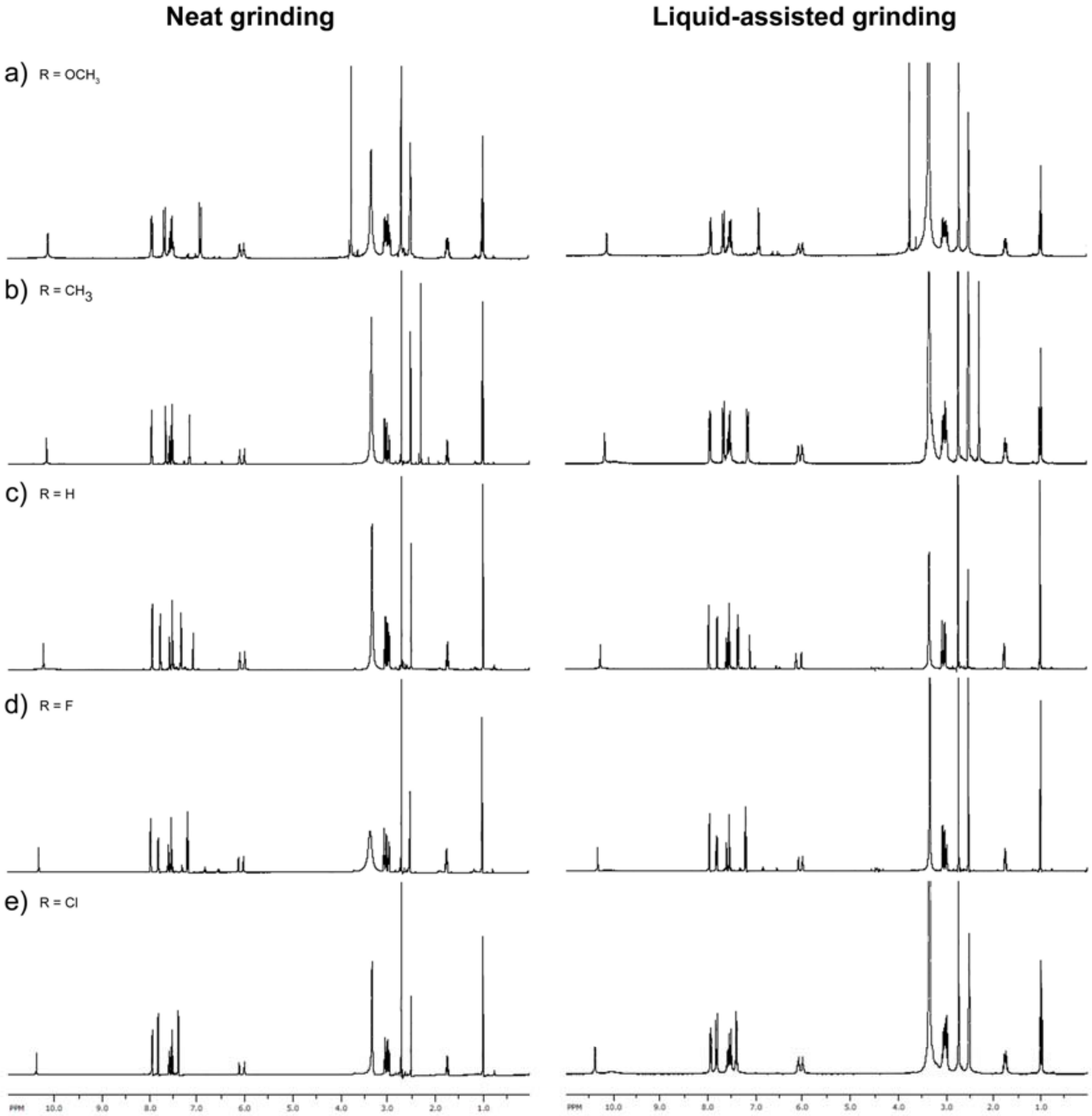


Figure S2. ^{1}H NMR spectra of reaction mixtures after 10 minutes of neat and liquid-assisted grinding of benzoic acid with *p*-substituted anilines.

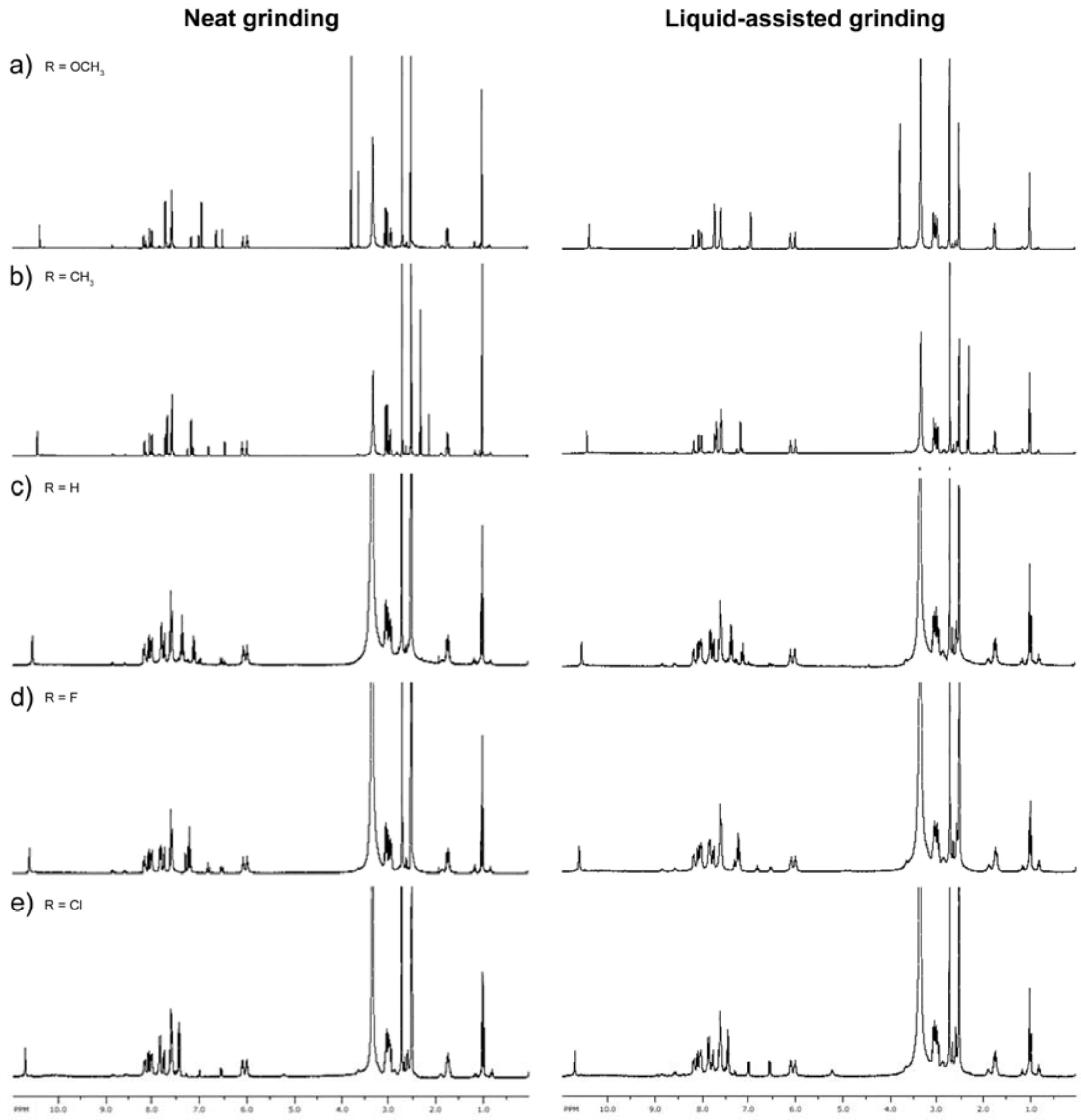


Figure S3. ^{1}H NMR spectra of reaction mixtures after 30 minutes of neat and liquid-assisted grinding of 1-naphthoic acid with *p*-substituted anilines.

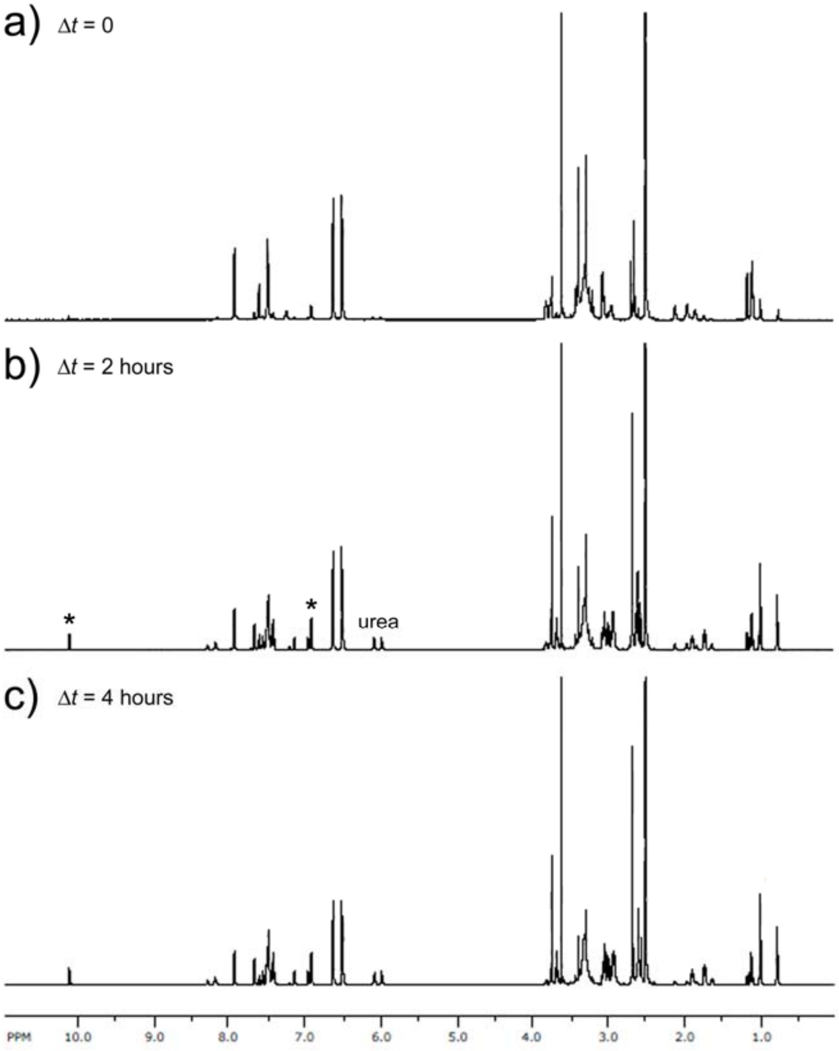
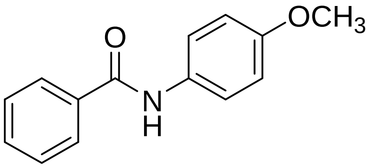


Figure S4. ^{1}H NMR spectra of an equimolar mixture of benzoic acid, *p*-anisidine and EDC·HCl recorded in d_6-DMSO at room temperature. a) Immediately after dissolving the sample in d_6-DMSO, b) after 2 hours and c) 4 hours. This shows that the conversion precentages determined from ^{1}H NMR spectra are not an artifact of sample preparation as the spectra of crude reaction mixtures were recorded immediately after dissolving the samples.

1.4 Synthesis of *N*-arylbenzamides 1a-e

N-(4-methoxyphenyl)benzamide (1a)

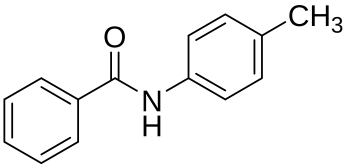
An equimolar mixture of *p*-anisidine (0.572 mmol, 70.5 mg), benzoic acid (0.572 mmol, 69.9 mg) and EDC·HCl (0.572 mmol, 109.7 mg) was ground in the presence of 62.5 μL of dry nitromethane (LAG experiment, η = 0.25 μL mg^{-1}) for 10 minutes. After allowing nitromethane to evaporate in a well-ventilated fume hood, the resulting crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford amide **1a** in 95% yield.



δ_H(300 MHz; d_6-DMSO; Me_4Si) 3.75 (3 H, s, OCH_3), 6.92 (2 H, d, *J* 9.0, Ar), 7.46-7.62 (3 H, m, Ar), 7.67 (2 H, d, *J* 9.0, Ar), 7.94 (2 H, d, *J* 6.8, Ar), 10.12 (1 H, s, NH). δ_C(150 MHz, d_6-DMSO; Me_4Si) 55.2, 113.7, 122.0, 127.5, 128.3, 131.4, 132.2, 135.0, 155.5, 165.1. HRMS-MALDI found: 228.1013; calc. for $C_{14}H_{14}NO_2$ (M+H$^+$): 228.1019.

N-(4-methylphenyl)benzamide (1b)

An equimolar mixture of *p*-toluidine (0.594 mmol, 63.6 mg), benzoic acid (0.594 mmol, 72.5 mg) and EDC·HCl (0.594 mmol, 113.8 mg) was ground in the presence of 62.5 μL of dry nitromethane (LAG experiment, η = 0.25 μL mg^{-1}) for 10 minutes. After allowing nitromethane to evaporate in a well-ventilated fume hood, the resulting crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford amide **1b** in 97% yield.

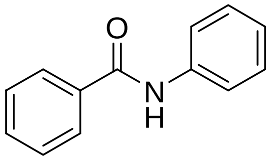


δ_H(300 MHz; d_6-DMSO; Me_4Si) 2.28 (3 H, s, CH_3), 7.15 (2 H, d, *J* 8.2, Ar), 7.47-7.62 (3 H, m, Ar), 7.65 (2 H, d, *J* 8.3, Ar), 7.94 (2 H, d, *J* 6.9, Ar), 10.15 (1 H, s, NH). δ_C(75 MHz, d_6-DMSO; Me_4Si) 20.5, 120.4, 127.6, 128.3, 129.0, 131.4, 132.6, 135.0, 136.6, 165.3. HRMS-MALDI found: 212.1073; calc. for $C_{14}H_{14}NO$ (M+H$^+$): 212.1070.

***N*-phenylbenzamide (1c)**

An equimolar mixture of aniline (0.614 mmol, 57.2 mg, 56.0 μL), benzoic acid (0.614 mmol, 75.0 mg) and EDC·HCl (0.614 mmol, 117.8 mg) was ground in the presence of 62.5 μL of dry nitromethane (LAG experiment, η = 0.25 μL mg^{-1}) for 10 minutes. After allowing nitromethane to evaporate in a well-ventilated fume hood, the resulting crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford amide **1c** in 92% yield.

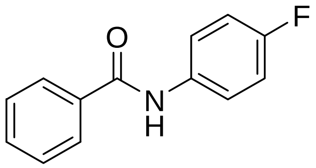
δ_H(300 MHz; d_6-DMSO; Me_4Si) 7.10 (1 H, t, *J* 7.4, Ar), 7.35 (2 H, t, *J* 7.9, Ar), 7.46-7.65 (3 H, m, Ar), 7.77 (2 H, d, *J* 7.7, Ar), 7.95 (2 H, d, *J* 6.7, Ar), 10.23 (1 H, s, NH). δ_C(75 MHz, d_6-DMSO; Me_4Si) 120.4, 123.6, 127.6, 128.4, 128.6, 131.5, 135.0, 139.2, 165.6. HRMS-MALDI found: 198.0907; calc. for $C_{13}H_{12}NO$ (M+H$^+$): 198.0913.



***N*-(4-fluorophenyl)benzamide (1d)**

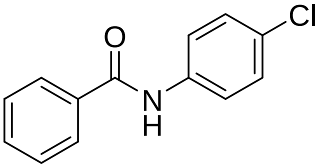
An equimolar mixture of 4-fluoroaniline (0.588 mmol, 65.4 mg, 56.5 μL), benzoic acid (0.588 mmol, 71.8 mg) and EDC·HCl (0.588 mmol, 112.8 mg) was ground in the presence of 62.5 μL of dry nitromethane (LAG experiment, η = 0.25 μL mg^{-1}) for 10 minutes. After allowing nitromethane to evaporate in a well-ventilated fume hood, the resulting crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford amide **1d** in 95% yield.

δ_H(300 MHz; d_6-DMSO; Me_4Si) 7.09-7.30 (2 H, m, Ar), 7.44-7.65 (3 H, m, Ar), 7.70-7.86 (2 H, m, Ar), 7.95 (2 H, d, *J* 6.6, Ar), 10.29 (1 H, s, NH). δ_C(150 MHz, d_6-DMSO; Me_4Si) 115.08; 115.23 (d, *J* 22.3, Ar^F), 122.14;122.19 (d, *J* 7.6, Ar^F), 127.6, 128.4, 131.6, 134.8, 135.5, 157.5;159.1 (d, *J* 240.2, Ar^F), 165.5. HRMS-MALDI found: 216.0822; calc. for $C_{13}H_{11}FNO$ (M+H$^+$): 216.0819.



***N*-(4-chlorophenyl)benzamide (1e)**

An equimolar mixture of 4-chloroaniline (0.567 mmol, 72.3 mg), benzoic acid (0.567 mmol, 69.2 mg) and EDC·HCl (0.567 mmol, 108.6 mg) was ground in the presence of 62.5 μL of dry nitromethane (LAG experiment, η = 0.25 μL mg^{-1}) for 10 minutes. After allowing nitromethane to evaporate in a well-ventilated fume hood, the resulting crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford amide **1e** in 99% yield.

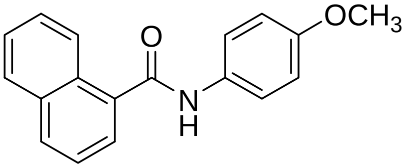


δ_H(300 MHz; d_6-DMSO; Me_4Si) 7.41 (2 H, d, *J* 8.8, Ar), 7.47-7.66 (3 H, m, Ar), 7.82 (2 H, d, *J* 8.8, Ar), 7.95 (2 H, d, *J* 7.0, Ar), 10.36 (1 H, s, NH). δ_C(75 MHz, d_6-DMSO; Me_4Si) 121.8, 127.2, 127.6, 128.4, 128.5, 131.7, 134.7, 138.1, 165.6. HRMS-MALDI found: 332.0524; calc. for $C_{13}H_{11}ClNO$ (M+H$^+$): 332.0524.

1.5 Synthesis of *N*-aryl-1-naphthamides 2a-e

N-(4-methoxyphenyl)-1-naphthamide (2a)

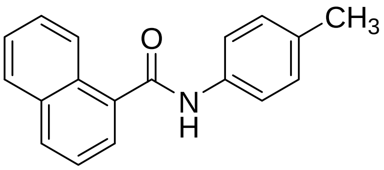
An equimolar mixture of *p*-anisidine (0.513 mmol, 63.2 mg), 1-naphthoic acid (0.513 mmol, 88.4 mg) and EDC·HCl (0.513 mmol, 98.4 mg) was ground in the presence of 62.5 μL of dry nitromethane (LAG experiment, η = 0.25 μL mg^{-1}) for 30 minutes. After allowing nitromethane to evaporate in a well-ventilated fume hood, the resulting crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford amide **2a** in 88% yield.



δ_H(300 MHz; d_6-DMSO; Me_4Si) 3.76 (3 H, s, OCH_3), 6.95 (2 H, d, *J* 7.8, Ar), 7.51-7.81 (6 H, m, overlapped Ar), 7.96-8.11 (2 H, m, Ar), 8.13-8.26 (1 H, m, Ar), 10.42 (1 H, s, NH). δ_C(75 MHz, d_6-DMSO; Me_4Si) 55.2, 113.8, 121.3, 125.0, 125.2, 125.3, 126.3, 126.9, 128.3, 129.7, 129.9, 132.5, 133.1, 134.9, 155.5, 166.8. HRMS-MALDI found: 278.1172; calc. for $C_{18}H_{16}NO_2$ (M+H$^+$): 278.1176.

N-(4-methylphenyl)-1-naphthamide (2b)

An equimolar mixture of *p*-toluidine (0.531 mmol, 56.9 mg), 1-naphthoic acid (0.531 mmol, 91.4 mg) and EDC·HCl (0.531 mmol, 101.7 mg) was ground in the presence of 62.5 μL of dry nitromethane (LAG experiment, η = 0.25 μL mg^{-1}) for 30 minutes. After allowing nitromethane to evaporate in a well-ventilated fume hood, the resulting crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford amide **2b** in 87% yield.

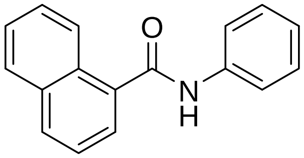


δ_H(300 MHz; d_6-DMSO; Me_4Si) 2.30 (3 H, s, CH_3), 7.18 (2 H, m, Ar), 7.40-7.85 (6 H, m, overlapped Ar), 7.92-8.29 (3 H, m, overlapped Ar), 10.47 (1 H, s, NH). δ_C(75 MHz, d_6-DMSO; Me_4Si) 20.5, 119.8, 125.0, 125.1, 125.3, 126.3, 126.9, 128.3, 129.1, 129.7, 130.0, 132.6, 133.1, 134.9, 136.8, 167.1. HRMS-MALDI found: 284.1039; calc. for $C_{18}H_{15}NONa$ (M+Na$^+$): 284.1046.

N-phenyl-1-naphthamide (2c)

An equimolar mixture of aniline (0.547 mmol, 50.9 mg, 49.8 μL), 1-naphthoic acid (0.547 mmol, 94.2 mg) and EDC·HCl (0.547 mmol, 104.9 mg) was ground in the presence of 62.5

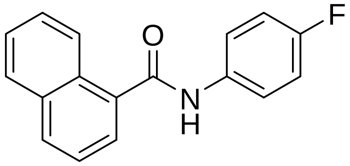
μL of dry nitromethane (LAG experiment, $\eta = 0.25$ μL mg^{-1}) for 30 minutes. After allowing nitromethane to evaporate in a well-ventilated fume hood, the resulting crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford amide **2c** in 85% yield.



δ_H(300 MHz; d_6-DMSO; Me_4Si) 7.12 (1 H, t, *J* 6.9, Ar), 7.38 (2 H, t, *J* 7.3, Ar), 7.54-7.66 (3 H, m, overlapped Ar), 7.71-7.87 (3 H, m, overlapped Ar), 7.98-8.12 (2 H, m, overlapped Ar), 8.13-8.26 (1 H, m, Ar), 10.57 (1 H, s, NH). δ_C(75 MHz, d_6-DMSO; Me_4Si) 119.8, 123.7, 125.0, 125.1, 125.4, 126.3, 127.0, 128.3, 128.7, 129.6, 130.0, 133.1, 134.8, 139.3, 167.3. HRMS-MALDI found: 270.0887; calc. for $C_{17}H_{13}NONa$ (M+Na$^+$): 270.0889.

N-(4-fluorophenyl)-1-naphthamide (2d)

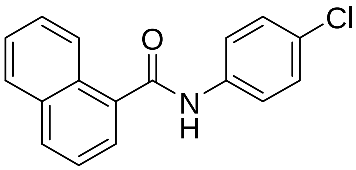
An equimolar mixture of 4-fluoroaniline (0.526 mmol, 58.5 mg, 50.5 μL), 1-naphthoic acid (0.526 mmol, 90.6 mg) and EDC·HCl (0.526 mmol, 100.9 mg) was ground in the presence of 62.5 μL of dry nitromethane (LAG experiment, $\eta = 0.25$ μL mg^{-1}) for 30 minutes. After allowing nitromethane to evaporate in a well-ventilated fume hood, the resulting crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford amide **2d** in 80% yield.



δ_H(300 MHz; d_6-DMSO; Me_4Si) 7.09-7.35 (2 H, m, Ar), 7.48-7.92 (6 H, m, overlapped Ar), 7.96-8.25 (3 H, m, overlapped Ar), 10.62 (1 H, s, NH). δ_C(150 MHz, d_6-DMSO; Me_4Si) 115.23;115.38 (d, *J* 22.2, Ar^F), 121.56;121.61 (d, *J* 7.8, Ar^F), 125.0, 125.1, 125.5, 126.4, 127.0, 128.3, 129.6, 130.1, 133.1, 134.6, 135.69;135.71 (d, *J* 2.3, Ar^F), 157.5;159.1 (d, *J* 240.3, Ar^F), 167.2. HRMS-MALDI found: 266.0966; calc. for $C_{17}H_{13}FNO$ (M+H$^+$): 266.0976.

N-(4-chlorophenyl)-1-naphthamide (2e)

An equimolar mixture of 4-chloroaniline (0.509 mmol, 64.9 mg), 1-naphthoic acid (0.509 mmol, 87.6 mg) and EDC·HCl (0.509 mmol, 97.5 mg) was ground in the presence of 62.5 μL of dry nitromethane (LAG experiment, $\eta = 0.25$ μL mg^{-1}) for 30 minutes. After allowing nitromethane to evaporate in a well-ventilated fume hood, the resulting crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford amide **2e** in 80% yield.

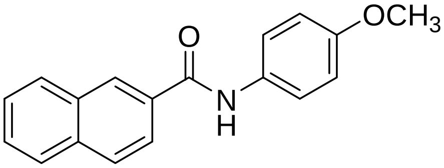


δ_H(600 MHz; d_6-DMSO; Me_4Si) 7.44 (2 H, d, *J* 8.8, Ar), 7.58-7.64 (3 H, m, overlapped Ar), 7.76 (1 H, d, *J* 7.0, Ar), 7.85 (2 H, d, *J* 8.7, Ar), 8.00-8.04 (1 H, m, Ar), 8.09 (1 H, d, *J* 8.3, Ar), 8.15-8.21 (1 H, m, Ar), 10.68 (1 H, s, NH). δ_C(150 MHz, d_6-DMSO; Me_4Si) 121.3, 125.0, 125.1, 125.5, 126.4, 127.1, 127.3, 128.3, 128.6, 129.6, 130.3, 133.1, 134.4, 138.3, 167.3. HRMS-MALDI found: 282.0687; calc. for $C_{17}H_{13}ClNO$ ($M+H^+$): 282.0680.

1.6 Synthesis of *N*-aryl-2-naphthamides 3a-e

N-(4-methoxyphenyl)-2-naphthamide (3a)

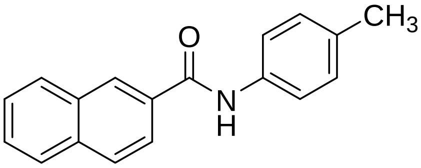
An equimolar mixture of *p*-anisidine (0.513 mmol, 63.2 mg), 2-naphthoic acid (0.513 mmol, 88.4 mg) and EDC·HCl (0.513 mmol, 98.4 mg) was ground in the presence of 62.5 µL of dry nitromethane (LAG experiment, η = 0.25 µL mg^{-1}) for 30 minutes. After allowing nitromethane to evaporate in a well-ventilated fume hood, the resulting crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford amide **3a** in 96% yield.



δ_H(300 MHz; d_6-DMSO; Me_4Si) 3.76 (3 H, s, OCH_3), 6.95 (2 H, d, *J* 8.9, Ar), 7.56-7.67 (2 H, m, Ar), 7.73 (2 H, d, *J* 8.9, Ar), 7.93-8.13 (4 H, m, overlapped Ar), 8.56 (1 H, s, Ar), 10.31 (1 H, s, NH). δ_C(150 MHz, d_6-DMSO; Me_4Si) 55.1, 113.7, 121.9, 124.4, 126.7, 127.6, 127.65, 127.72, 127.9, 128.8, 132.1, 132.26, 132.33, 134.1, 155.5, 165.1. HRMS-MALDI found: 278.1183; calc. for $C_{18}H_{16}NO_2$ (M+H$^+$): 278.1176.

N-(4-methylphenyl)-2-naphthamide (3b)

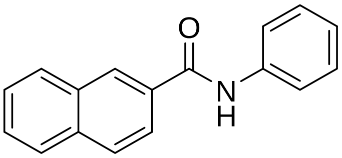
An equimolar mixture of *p*-toluidine (0.531 mmol, 56.9 mg), 2-naphthoic acid (0.531 mmol, 91.4 mg) and EDC·HCl (0.531 mmol, 101.7 mg) was ground in the presence of 62.5 µL of dry nitromethane (LAG experiment, η = 0.25 µL mg^{-1}) for 30 minutes. After allowing nitromethane to evaporate in a well-ventilated fume hood, the resulting crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford amide **3b** in 96% yield.



δ_H(600 MHz; d_6-DMSO; Me_4Si) 2.30 (3 H, s, CH_3), 7.18 (2 H, d, *J* 8.2, Ar), 7.59-7.67 (2 H, m, Ar), 7.71 (2 H, d, *J* 8.2, Ar), 7.98-8.06 (3 H, m, overlapped Ar), 8.08 (1 H, d, *J* 7.6, Ar), 8.57 (1 H, s, Ar), 10.33 (1 H, s, NH). δ_C(150 MHz, d_6-DMSO; Me_4Si) 20.4, 120.3, 124.4, 126.8, 127.6, 127.7, 127.8, 127.9, 128.9, 129.0, 132.0, 132.3, 132.6, 134.2, 136.7, 165.3. HRMS-MALDI found: 262.1233; calc. for $C_{18}H_{16}NO$ (M+H$^+$): 262.1227.

***N*-phenyl-2-naphthamide (3c)**

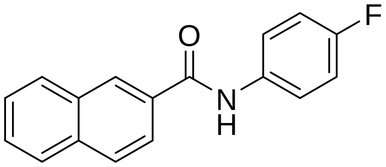
An equimolar mixture of aniline (0.547 mmol, 50.9 mg, 49.8 μL), 2-naphthoic acid (0.547 mmol, 94.2 mg) and EDC·HCl (0.547 mmol, 104.9 mg) was ground in the presence of 62.5 μL of dry nitromethane (LAG experiment, η = 0.25 μL mg^{-1}) for 30 minutes. After allowing nitromethane to evaporate in a well-ventilated fume hood, the resulting crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford amide **3c** in 96% yield.



δ_H(600 MHz; d_6-DMSO; Me_4Si) 7.12 (1 H, t, *J* 7.4, Ar), 7.38 (2 H, t, *J* 7.8, Ar), 7.60-7.68 (2 H, m, Ar), 7.83 (2 H, d, *J* 7.7, Ar), 7.99-8.07 (3 H, m, overlapped Ar), 8.09 (1 H, d, *J* 7.6, Ar), 8.58 (1 H, s, Ar), 10.41 (1 H, s, NH). δ_C(150 MHz, d_6-DMSO; Me_4Si) 120.3, 123.6, 124.4, 126.8, 127.6, 127.7, 127.89, 127.94, 128.6, 128.9, 132.0, 132.2, 134.2, 139.2, 165.5. HRMS-MALDI found: 248.1073; calc. for $C_{17}H_{14}NO$ (M+H$^+$): 248.1070.

***N*-(4-fluorophenyl)-2-naphthamide (3d)**

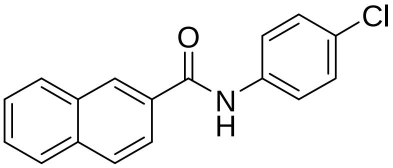
An equimolar mixture of 4-fluoroaniline (0.526 mmol, 58.5 mg, 50.5 μL), 2-naphthoic acid (0.526 mmol, 90.6 mg) and EDC·HCl (0.526 mmol, 100.9 mg) was ground in the presence of 62.5 μL of dry nitromethane (LAG experiment, η = 0.25 μL mg^{-1}) for 30 minutes. After allowing nitromethane to evaporate in a well-ventilated fume hood, the resulting crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford amide **3d** in 94% yield.



δ_H(300 MHz; d_6-DMSO; Me_4Si) 7.22 (2 H, t, *J* 8.9, Ar), 7.57-7.71 (2 H, m, Ar), 7.78-7.92 (2 H, m, Ar), 7.95-8.16 (4 H, m, overlapped Ar), 8.58 (1 H, s, Ar), 10.47 (1 H, s, NH). δ_C(75 MHz, d_6-DMSO; Me_4Si) 114.99;115.28 (d, *J* 22.1, Ar^F), 122.08;122.19 (d, *J* 7.8, Ar^F), 124.3, 126.8, 127.6, 127.8, 127.9, 128.0, 128.9, 132.0, 132.1, 134.2, 135.52;135.55 (d, *J* 2.6, Ar^F), 156.7;159.8 (d, *J* 240.3, Ar^F), 165.4. HRMS-MALDI found: 266.0985; calc. for $C_{17}H_{13}FNO$ (M+H$^+$): 266.0976.

***N*-(4-chlorophenyl)-2-naphthamide (3e)**

An equimolar mixture of 4-chloroaniline (0.509 mmol, 64.9 mg), 2-naphthoic acid (0.509 mmol, 87.6 mg) and EDC·HCl (0.509 mmol, 97.5 mg) was ground in the presence of 62.5 μL of dry nitromethane (LAG experiment, η = 0.25 μL mg^{-1}) for 30 minutes. After allowing nitromethane to evaporate in a well-ventilated fume hood, the resulting crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford amide **3e** in 95% yield.



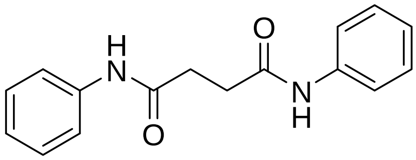
δ_H(300 MHz; d_6-DMSO; Me_4Si) 7.44 (2 H, d, *J* 8.9, Ar), 7.58-7.70 (2 H, m, Ar), 7.87 (2 H, d, *J* 8.9, Ar), 7.97-8.14 (4 H, m, overlapped Ar), 8.58 (1 H, s, Ar), 10.53 (1 H, s, NH). δ_C(75 MHz, d_6-DMSO; Me_4Si) 121.8, 124.3, 126.8, 127.2, 127.6, 127.8, 128.0 (2 C overlapped), 128.5, 128.9, 131.95, 131.99, 134.3, 138.2, 165.6. HRMS-MALDI found: 282.0677; calc. for $C_{17}H_{13}ClNO$ (M+H$^+$): 282.0680.

1.7 Synthesis of aliphatic and aromatic amides 4-9

N,N'-diphenylsuccinamide (4)

A mixture of aniline (0.727 mmol, 67.7 mg, 66.2 μL), succinic acid (0.363 mmol, 42.9 mg) and EDC·HCl (0.727 mmol, 139.4 mg) was ground neat for 10 minutes. The crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford diamide **4** in 77% yield.

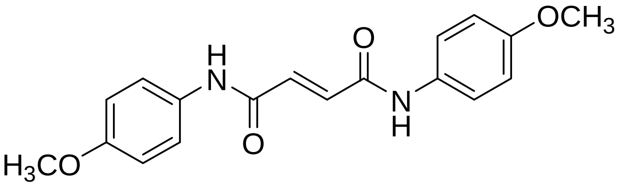
δ_H(300 MHz; d_6-DMSO; Me_4Si) 2.54-2.84 (4 H, m, CH_2), 6.85-7.13 (2 H, m, Ar), 7.15-7.43 (4 H, m, Ar), 7.46-7.78 (4 H, m, Ar), 9.99 (2 H, s, NH). δ_C(75 MHz, d_6-DMSO; Me_4Si) 31.2, 118.9, 122.9, 128.6, 139.3, 170.4. HRMS-MALDI found: 269.1291; calc. for $C_{16}H_{17}N_2O_2$ $(M+H^+)$: 269.1284.



N,N'-bis(4-methoxyphenyl)fumaramide (5)

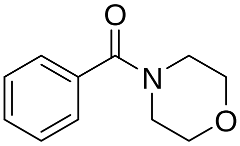
A mixture of *p*-anisidine (0.670 mmol, 82.6 mg), fumaric acid (0.335 mmol, 38.9 mg) and EDC·HCl (0.670 mmol, 128.5 mg) was ground in the presence of 62.5 μL of dry nitromethane (LAG experiment, η = 0.25 μL mg^{-1}) for 30 minutes. After allowing nitromethane to evaporate in a well-ventilated fume hood, the resulting crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford diamide **5** in 79% yield.

δ_H(600 MHz; d_6-DMSO; Me_4Si) 3.74 (6 H, s, OCH_3), 6.92 (4 H, d, J 8.9, Ar), 7.14 (2 H, s, CH), 7.62 (4 H, d, J 8.9, Ar), 10.36 (2 H, s, NH). δ_C(150 MHz, d_6-DMSO; Me_4Si) 55.1, 113.9, 120.8, 131.9, 133.7, 155.6, 161.6. HRMS-MALDI found: 327.1335; calc. for $C_{18}H_{19}N_2O_4$ $(M+H^+)$: 327.1339.



N-benzoylmorpholine (6a)

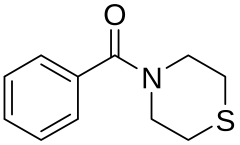
A mixture of morpholine (0.623 mmol, 54.3 mg, 53.9 μL), benzoic acid (0.623 mmol, 76.1 mg) and EDC·HCl (0.623 mmol, 119.5 mg) was ground in the presence of 62.5 μL of dry nitromethane (LAG experiment, η = 0.25 μL mg^{-1}) for 10 minutes. The grinding jar was washed with methanol and the crude reaction mixture was purified by column chromatography affording amide **6a** in 93% yield.



δ_H(300 MHz; d_6-DMSO; Me_4Si, 25 °C) 3.30-3.86 (8 H, unresolved overlapping multiplets, CH_2), 7.32-7.56 (5 H, m, Ar). δ_C(75 MHz, d_6-DMSO; Me_4Si, 25 °C) 42.0, 47.2, 66.0, 126.9, 128.3, 129.5, 135.5, 169.0. HRMS-MALDI found: 192.1010; calc. for $C_{11}H_{14}NO_2$ $(M+H^+)$: 192.1019.

***N*-benzoylthiomorpholine (6b)**

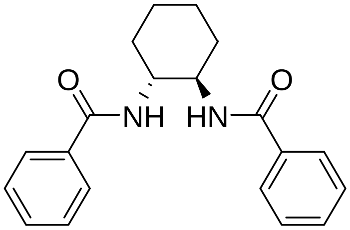
A mixture of thiomorpholine (0.600 mmol, 61.9 mg, 57.0 µL), benzoic acid (0.600 mmol, 73.2 mg) and EDC·HCl (0.600 mmol, 115.0 mg) was ground in the presence of 62.5 µL of dry nitromethane (LAG experiment, η = 0.25 µL mg^{-1}) for 10 minutes. The grinding jar was washed with methanol and the crude reaction mixture was purified by column chromatography affording amide **6b** in 92% yield.



δ_H(600 MHz; d_6-DMSO; Me_4Si, 25 °C) 2.53-2.76 (4 H, unresolved multiplet, CH_2), 3.41-3.97 (4 H, unresolved overlapping multiplets, CH_2), 7.32-7.56 (5 H, m, Ar). δ_H(600 MHz; d_6-DMSO; Me_4Si, 105 °C) 2.61-2.67 (4 H, m, CH_2), 3.70-3.78 (4 H, m, CH_2), 7.35-7.46 (5 H, m, Ar). δ_C(150 MHz, d_6-DMSO; Me_4Si, 25 °C) 26.7, 43.8, 49.5, 126.5, 128.4, 129.3, 136.0, 169.3. HRMS-MALDI found: 208.0791; calc. for $C_{11}H_{14}NOS$ $(M+H^+)$: 208.0791.

(1*R*,2*R*)-*N*^{1},*N*^{2}-dibenzoyl-1,2-diaminocyclohexane ((1*R*,2*R*)-7)

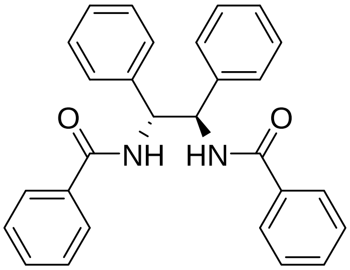
A mixture of (1*R*,2*R*)-(–)-1,2-diaminocyclohexane (0.337 mmol, 38.5 mg), benzoic acid (0.674 mmol, 82.3 mg) and EDC·HCl (0.674 mmol, 129.2 mg) was ground in the presence of 62.5 µL of dry nitromethane (LAG experiment, η = 0.25 µL mg^{-1}) for 30 minutes. After allowing nitromethane to evaporate in a well-ventilated fume hood, the resulting crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford diamide **(1*R*,2*R*)-7** in 98% yield.



$[\alpha]_D^{20}$ = –63° (c = 0.55 in chloroform). δ_H(300 MHz; d_6-DMSO; Me_4Si) 1.22-1.40 (2 H, m, CH_2), 1.22-1.40 (2 H, m, CH_2), 1.42-1.62 (2 H, m, CH_2), 1.67-1.82 (2 H, m, CH_2), 1.84-1.98 (2 H, m, CH_2), 3.86-4.00 (2 H, m, CH), 7.32-7.53 (6 H, m, overlapped Ar), 7.65-7.79 (4 H, m, Ar), 8.21 (2 H, d, *J* 7.5, NH). δ_C(75 MHz, d_6-DMSO; Me_4Si) 24.7, 31.6, 52.9, 127.1, 128.1, 130.9, 134.9, 166.4. HRMS-MALDI found: 323.1750; calc. for $C_{20}H_{23}N_2O_2$ ($M+H^+$): 323.1754.

(1*R*,2*R*)-*N*^{1},*N*^{2}-dibenzoyl-1,2-diphenylethylenediamine ((1*R*,2*R*)-8)

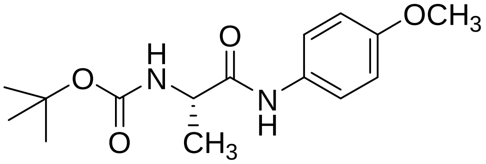
A mixture of (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine (0.298 mmol, 63.2 mg), benzoic acid (0.595 mmol, 72.7 mg) and EDC·HCl (0.595 mmol, 114.1 mg) was ground in the presence of 62.5 μL of dry nitromethane (LAG experiment, η = 0.25 μL mg^{-1}) for 30 minutes. After allowing nitromethane to evaporate in a well-ventilated fume hood, the resulting crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford diamide **(1*R*,2*R*)-8** in 88% yield.



δ_H(300 MHz; d_6-DMSO; Me_4Si) 5.68 (2 H, d, *J* 7.8, CH), 7.09-7.29 (6 H, m, overlapped Ar), 7.31-7.60 (10 H, m, overlapped Ar), 7.71 (4 H, d, *J* 6.7, Ar), 8.99 (2 H, d, *J* 7.5, NH). δ_C(75 MHz, d_6-DMSO; Me_4Si) 57.3, 126.8, 127.1, 127.2, 127.8, 128.2, 131.1, 134.7, 140.6, 166.4. HRMS-MALDI found: 421.1902; calc. for $C_{28}H_{25}N_2O_2$ ($M+H^+$): 421.1910.

N-(*N*-(*tert*-butoxycarbonyl)-L-alanyl)-4-methoxyaniline (9a)

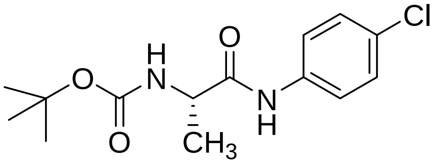
A mixture of *p*-anisidine (0.496 mmol, 61.1 mg), Boc-L-Ala-OH (0.496 mmol, 93.9 mg) and EDC·HCl (0.496 mmol, 95.1 mg) was ground in the presence of 62.5 μL of dry nitromethane (LAG experiment, η = 0.25 μL mg^{-1}) for 30 minutes. After allowing nitromethane to evaporate in a well-ventilated fume hood, the resulting crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford amide **9a** in 87% yield.



$[\alpha]_D^{20}$ = –71° (*c* = 0.63 in chloroform). δ_H(300 MHz; d_6-DMSO; Me_4Si) 1.24 (3 H, d, *J* 7.0, CH_3), 1.38 (9 H, s, CH_3^{Boc}), 3.71 (3 H, s, OCH_3), 4.00-4.15 (1 H, m, CH), 6.87 (2 H, d, *J* 8.9, Ar), 7.00 (1 H, d, *J* 7.2, Ar), 7.49 (2 H, d, *J* 8.9, Ar), 9.74 (1 H, s, NH). δ_C(150 MHz, d_6-DMSO; Me_4Si) 18.1, 28.1, 50.2, 55.1, 77.9, 113.7, 120.6, 132.1, 155.0, 155.1, 171.2. HRMS-MALDI found: 295.1645; calc. for $C_{15}H_{23}N_2O_4$ ($M+H^+$): 295.1652.

_N_-(_N_-(_tert_-butoxycarbonyl)-L-alanyl)-4-chloroaniline (9b)

A mixture of 4-chloroaniline (0.492 mmol, 62.7 mg), Boc-L-Ala-OH (0.492 mmol, 93.1 mg) and EDC·HCl (0.492 mmol, 94.3 mg) was ground in the presence of 62.5 μL of dry nitromethane (LAG experiment, η = 0.25 μL mg^{-1}) for 30 minutes. After allowing nitromethane to evaporate in a well-ventilated fume hood, the resulting crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford amide **9b** in 88% yield.

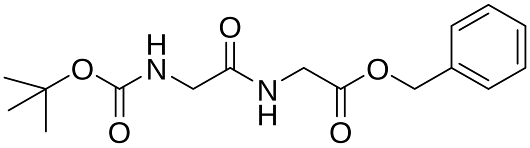


$[\alpha]_D^{20}$ = –51° (*c* = 1.25 in methanol). δ_H(300 MHz; d_6-DMSO; Me_4Si) 1.24 (3 H, d, *J* 7.1, CH_3), 1.38 (9 H, s, CH_3^{Boc}), 3.71 (3 H, s, OCH_3), 4.00-4.15 (1 H, m, CH), 7.09 (1 H, d, *J* 7.1, Ar), 7.35 (2 H, d, *J* 8.9, Ar), 7.63 (2 H, d, *J* 8.9, Ar), 10.05 (1 H, s, NH). δ_C(75 MHz, d_6-DMSO; Me_4Si) 17.8, 28.1, 50.4, 78.0, 120.6, 126.6, 128.5, 138.0, 155.1, 172.0. HRMS-MALDI found: 299.1165; calc. for $C_{14}H_{20}ClN_2O_3$ (M+H$^+$): 299.1157.

1.8 Synthesis of dipeptides 10a-e

_N_-(_tert_-butoxycarbonyl)glycylglycine benzyl ester (10a)

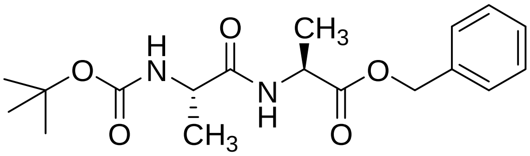
A mixture of Gly-OBn·TsOH (0.355 mmol, 119.8 mg), Boc-Gly-OH (0.355 mmol, 62.2 mg), EDC·HCl (0.355 mmol, 68.0 mg), DMAP (0.710 mmol, 86.8 mg) and sodium chloride (7.10 mmol, 415 mg) was ground in the presence of 62.5 μL of dry nitromethane (LAG experiment, η = 0.25 μL mg^{-1}) for 180 minutes. After allowing nitromethane to evaporate under reduced pressure using high-vacuum line, the resulting crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford dipeptide **10a** in 70% yield.



δ_H(300 MHz; d_6-DMSO; Me$_4$Si) 1.38 (9 H, s, CH$_3^{Boc}$), 3.57 (2 H, d, J 5.9, CH$_2$), 3.91 (2 H, d, J 5.9, CH$_2$), 5.13 (2 H, s, CH$_2$), 7.00 (1 H, t, J 5.7, NH), 7.28-7.48 (5 H, m, Ph), 8.22 (1 H, t, J 5.8, NH). δ_C(75 MHz, d_6-DMSO; Me$_4$Si) 28.1, 43.0, 65.8, 78.0, 127.8, 128.0, 128.4, 135.9, 155.7, 169.7, 169.9. HRMS-MALDI found: 345.1422; calc. for $C_{16}H_{22}N_2O_5Na$ (M+Na$^+$): 345.1421.

_N_-(_tert_-butoxycarbonyl)-L-alanyl-L-alanine benzyl ester (10b)

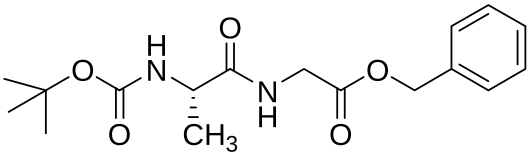
A mixture of L-Ala-OBn·TsOH (0.341 mmol, 120.0 mg), Boc-L-Ala-OH (0.341 mmol, 64.6 mg), EDC·HCl (0.341 mmol, 65.4 mg), DMAP (0.682 mmol, 83.4 mg) and sodium chloride (6.82 mmol, 400 mg) was ground in the presence of 62.5 μL of dry nitromethane (LAG experiment, η = 0.25 μL mg^{-1}) for 180 minutes. After allowing nitromethane to evaporate under reduced pressure using high-vacuum line, the resulting crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford dipeptide **10b** in 80% yield.



$[\alpha]_D^{20}$ = –54.3° (c = 0.57 in methanol). δ_H(300 MHz; d_6-DMSO; Me$_4$Si) 1.13 (3 H, d, J 7.1, CH$_3$), 1.30 (3 H, d, J 7.3, CH$_3$), 1.36 (9 H, s, CH$_3^{Boc}$), 3.92-4.04 (1 H, m, CH), 4.25-4.39 (1 H, m, CH), 5.10 (2 H, s, CH$_2$), 6.86 (1 H, d, J 7.4, NH), 7.26-7.47 (5 H, m, Ph), 8.22 (1 H, d, J 6.9, NH). δ_C(75 MHz, d_6-DMSO; Me$_4$Si) 16.8, 18.0, 28.1, 47.5, 49.2, 65.8, 77.9, 127.7, 127.9, 128.3, 135.9, 154.9, 172.3, 172.7. HRMS-MALDI found: 373.1736; calc. for $C_{18}H_{26}N_2O_5Na$ (M+Na$^+$): 373.1734.

***N*-(*tert*-butoxycarbonyl)-L-alanylglycine benzyl ester (10c)**

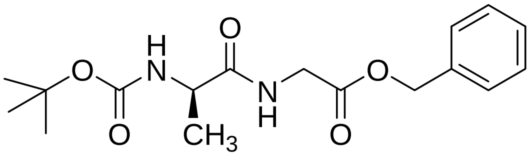
A mixture of Gly-OBn·TsOH (0.348 mmol, 117.4 mg), Boc-L-Ala-OH (0.348 mmol, 65.9 mg), EDC·HCl (0.348 mmol, 66.7 mg), DMAP (0.696 mmol, 85.0 mg) and sodium chloride (6.96 mmol, 407 mg) was ground in the presence of 62.5 μL of dry nitromethane (LAG experiment, η = 0.25 μL mg^{-1}) for 180 minutes. After allowing nitromethane to evaporate under reduced pressure using high-vacuum line, the resulting crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford dipeptide **10c** in 78% yield.



$[\alpha]_D^{20}$ = –25.4° (*c* = 1.26 in methanol). δ_H(300 MHz; d_6-DMSO; Me_4Si) 1.17 (3 H, d, *J* 7.2, CH_3), 1.37 (9 H, s, CH_3^{Boc}), 3.79-4.06 (3 H, m, overlapped CH and CH_2), 5.12 (2 H, s, CH_2), 6.92 (1 H, d, *J* 6.7, NH), 7.26-7.47 (5 H, m, Ph), 8.22 (1 H, t, *J* 5.8, NH). δ_C(75 MHz, d_6-DMSO; Me_4Si) 18.1, 28.2, 40.7, 49.4, 65.8, 77.9, 127.9, 128.0, 128.4, 135.9, 154.9, 169.7, 173.3. HRMS-MALDI found: 359.1569; calc. for $C_{17}H_{24}N_2O_5$ (M+Na$^+$): 359.1577.

***N*-(*tert*-butoxycarbonyl)-D-alanylglycine benzyl ester (10d)**

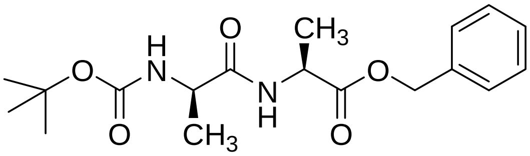
A mixture of Gly-OBn·TsOH (0.348 mmol, 117.4 mg), Boc-D-Ala-OH (0.348 mmol, 65.9 mg), EDC·HCl (0.348 mmol, 66.7 mg), DMAP (0.696 mmol, 85.0 mg) and sodium chloride (6.96 mmol, 407 mg) was ground in the presence of 62.5 μL of dry nitromethane (LAG experiment, η = 0.25 μL mg^{-1}) for 180 minutes. After allowing nitromethane to evaporate under reduced pressure using high-vacuum line, the resulting crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford dipeptide **10d** in 79% yield.



$[\alpha]_D^{20}$ = +27.6° (*c* = 0.60 in methanol). δ_H(300 MHz; d_6-DMSO; Me_4Si) 1.17 (3 H, d, *J* 7.2, CH_3), 1.37 (9 H, s, CH_3^{Boc}), 3.80-4.05 (3 H, m, overlapped CH and CH_2), 5.12 (2 H, s, CH_2), 6.89 (1 H, d, *J* 6.7, NH), 7.26-7.47 (5 H, m, Ph), 8.19 (1 H, t, *J* 5.8, NH). δ_C(150 MHz, d_6-DMSO; Me_4Si) 18.1, 28.1, 40.6, 49.4, 65.7, 77.9, 127.8, 127.9, 128.3, 135.8, 154.8, 169.6, 173.2. HRMS-MALDI found: 359.1573; calc. for $C_{17}H_{24}N_2O_5Na$ (M+Na$^+$): 359.1577.

***N*-(*tert*-butoxycarbonyl)-D-alanyl-L-alanine benzyl ester (10e)**

A mixture of L-Ala-OBn·TsOH (0.341 mmol, 120.0 mg), Boc-D-Ala-OH (0.341 mmol, 64.6 mg), EDC·HCl (0.341 mmol, 65.4 mg), DMAP (0.682 mmol, 83.4 mg) and sodium chloride (6.82 mmol, 400 mg) was ground in the presence of 62.5 μL of dry nitromethane (LAG experiment, η = 0.25 μL mg^{-1}) for 180 minutes. After allowing nitromethane to evaporate under reduced pressure using high-vacuum line, the resulting crude reaction mixture was suspended in 15 mL of distilled water and stirred at room temperature for 15 minutes. The precipitated product was filtered off and dried in air to afford dipeptide **10e** in 81% yield.



$[\alpha]_D^{20}$ = –3.5° (c = 1.13 in methanol). δ_H(300 MHz; d_6-DMSO; Me$_4$Si) 1.16 (3 H, d, J 7.1, CH$_3$), 1.29 (3 H, d, J 7.2, CH$_3$), 1.37 (9 H, s, CH$_3^{Boc}$), 3.94-4.08 (1 H, m, CH), 4.24-4.38 (1 H, m, CH), 5.11 (2 H, s, CH$_2$), 6.77 (1 H, d, J 6.9, NH), 7.27-7.47 (5 H, m, Ph), 8.17 (1 H, d, J 7.4, NH). δ_C(150 MHz, d_6-DMSO; Me$_4$Si) 17.0, 18.3, 28.1, 47.6, 49.4, 65.8, 78.0, 127.6, 127.9, 128.3, 135.9, 154.8, 172.1, 172.5. HRMS-MALDI found: 373.1730; calc. for $C_{18}H_{26}N_2O_5Na$ (M+Na$^+$): 373.1734.

1.9 Solution synthesis of dipeptides 10c-e (a typical peptide coupling procedure)[7]

N-(*tert*-butoxycarbonyl)-L-alanylglycine benzyl ester (10c)

Method a: To a stirred solution of Boc-L-Ala-OH (2.00 mmol, 378 mg) and Gly-OBn·TsOH (2.00 mmol, 675 mg) in 10 mL of dichloromethane cooled to 0 °C, triethylamine (2.00 mmol, 202 mg, 297 μL), DCC (2.00 mmol, 413 mg) and catalytic quantity of DMAP were added, and the reaction mixture was stirred overnight under dry conditions. The solid precipitate was separated by filtration and the filtrate was washed with 1 M HCl(aq), water, $NaHCO_3$(aq) (5 wt%), water, and dryed over Na_2SO_4. The dry solution was allowed to stay at −10 °C overnight. The dicyclohexylurea precipitate was removed by cold filtration and the filtrate was evaporated to yield dipeptide **10c** in 82% yield as clear colourless oil which solidifies on standing. $[\alpha]_D^{20}$ = –23.8° (*c* = 1.26 in methanol). δ_H(300 MHz; d_6-DMSO; Me_4Si) 1.17 (3 H, d, *J* 7.2, CH_3), 1.37 (9 H, s, CH_3^{Boc}), 3.74-4.07 (3 H, m, overlapped CH and CH_2), 5.12 (2 H, s, CH_2), 6.89 (1 H, d, *J* 7.2, NH), 7.36 (5 H, m, Ph), 8.19 (1 H, t, *J* 5.9, NH). δ_C(150 MHz, d_6-DMSO; Me_4Si) 18.1, 28.1, 40.6, 49.4, 65.7, 77.9, 127.8, 127.9, 128.3, 135.8, 154.8, 169.6, 173.2.

Method b: To a stirred solution of Boc-Ala-OH (0.70 mmol, 132 mg) and Gly-OBn· TsOH (0.70 mmol, 236 mg) in 5 mL of dichloromethane cooled to 0 °C, triethylamine (0.70 mmol, 71 mg, 98 μL), EDC·HCl (0.70 mmol, 134 mg) and catalytic quantity of DMAP were added, and the reaction mixture was stirred overnight under dry conditions. After evaporation of the reaction mixture, the dry residue was washed two times with 8 mL of water with sonification, and dried to yield 187 mg of dipeptide **10c** (79%). Additional 16 mg of the product precipitated from the combined water extracts upon standing, yielding 203 mg (86%) of **10c** in total. The ^{1}H NMR and ^{13}C NMR were the same as in *method a*. $[\alpha]_D^{20}$ = −24.6° (*c* = 1.26 in methanol).

N-(*tert*-butoxycarbonyl)-D-alanylglycine benzyl ester (10d)

The conditions were identical as in preparation of **10c** by *method a* yielding 603 mg (90%) of dipeptide **10d**. $[\alpha]_D^{20}$ = +25.2° (*c* = 1.27 in methanol).

N-(*tert*-butoxycarbonyl)-D-alanyl-L-alanine benzyl ester (10e)

The conditions were identical as in preparation of **10c** by *method a* yielding 653 mg (93%) of dipeptide **10e** in the form of clear colourless viscous oil which solidifies on standing. $[\alpha]_D^{20}$ = −5.1° (*c* = 1.48 in methanol).

2. FTIR-ATR spectra

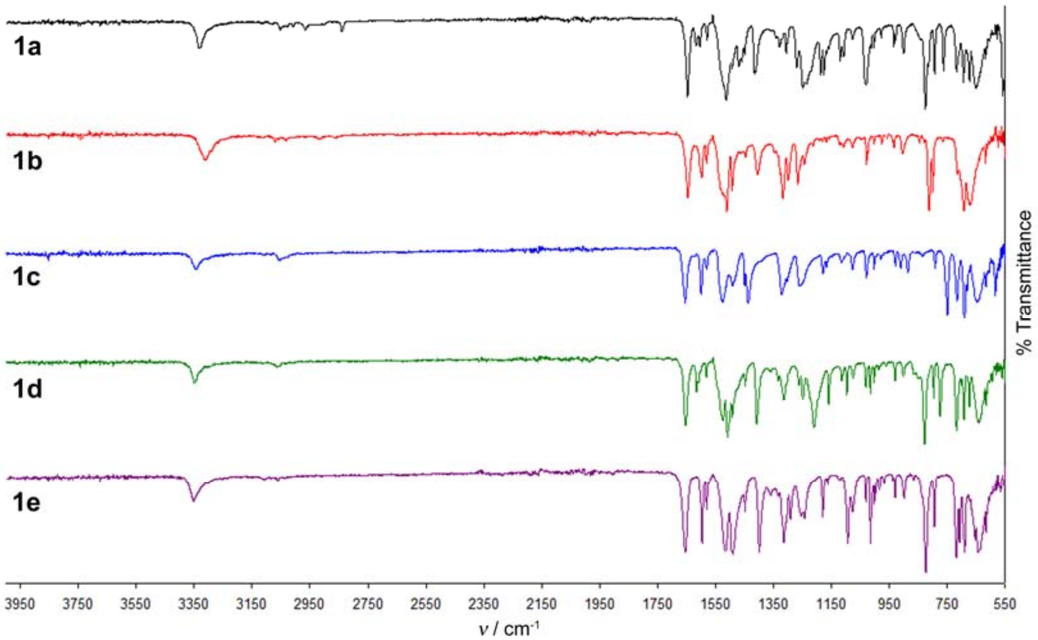


Figure S5. FTIR-ATR spectra of *N*-arylbenzamides **1a-e**.

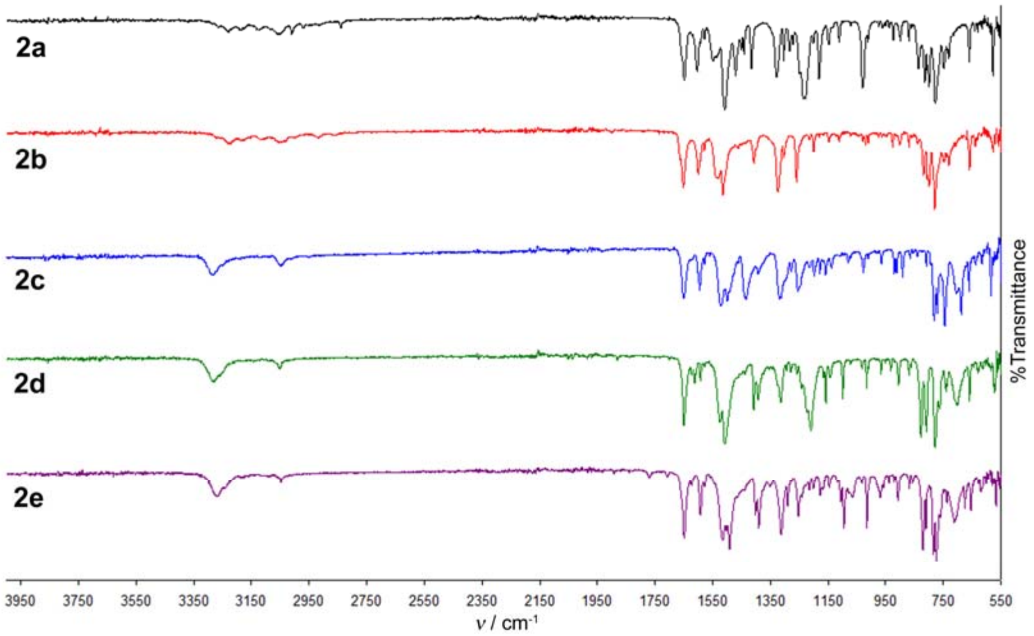


Figure S6. FTIR-ATR spectra of *N*-aryl-1-naphthamides **2a-e**.

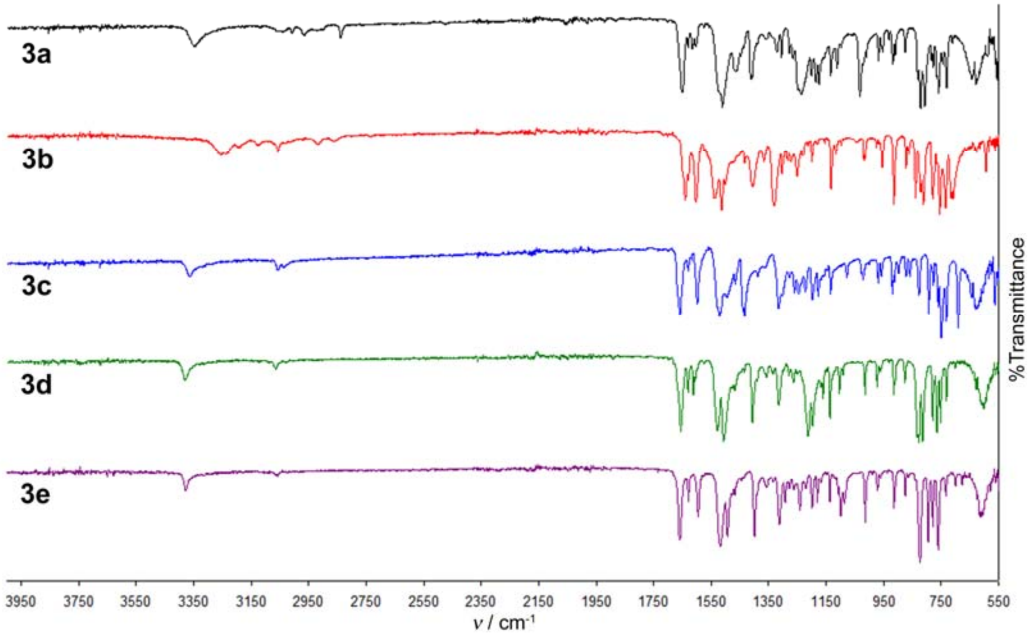


Figure S7. FTIR-ATR spectra of *N*-aryl-2-naphthamides **3a-e**.

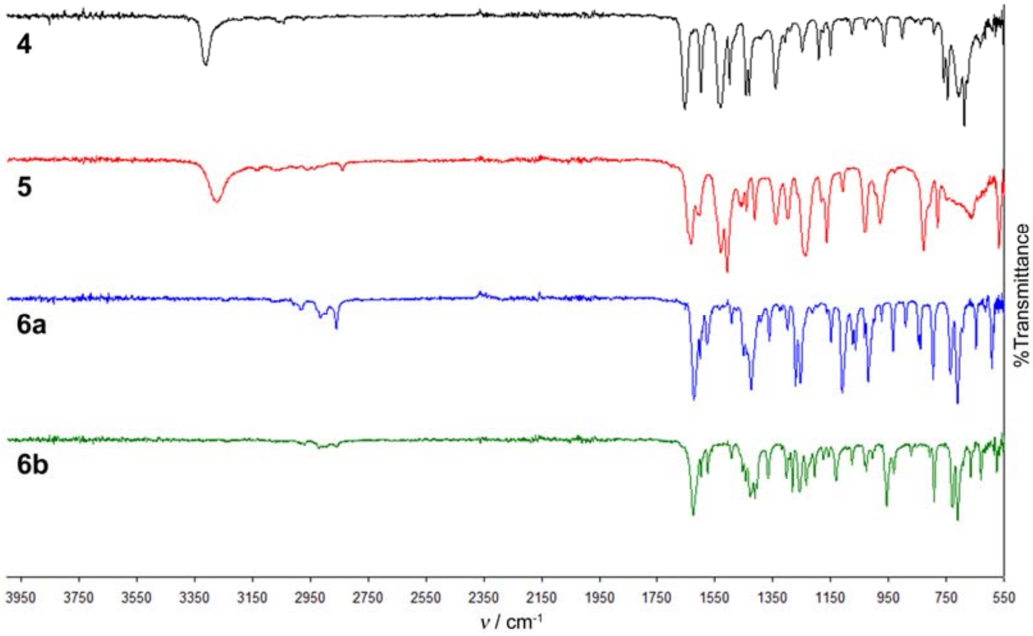


Figure S8. FTIR-ATR spectra of *N*,*N′*-diphenylsuccinamide (**4**), *N*,*N′*-(4-methoxy-phenyl)fumaramide (**5**), *N*-benzoylmorpholine (**6a**) and *N*-benzoylthiomorpholine (**6b**).

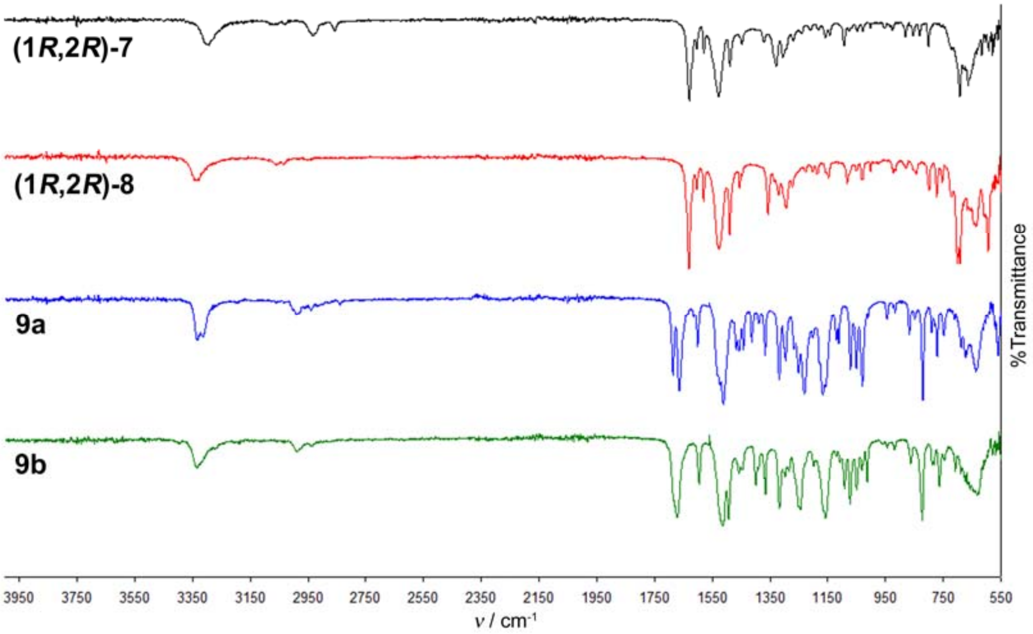


Figure S9. FTIR-ATR spectra of (1*R*,2*R*)-N^1,N^2-dibenzoyl-1,2-diaminocyclohexane (**(1*R*,2*R*)-7**), (1*R*,2*R*)-N^1,N^2-dibenzoyl-1,2-diphenylethylenediamine (**(1*R*,2*R*)-8**), *N*-(*N*-(*tert*-butoxycarbonyl)-L-alanyl)-4-methoxyaniline (**9a**) and *N*-(*N*-(*tert*-butoxycarbonyl)-L-alanyl)-4-chloroaniline (**9b**).

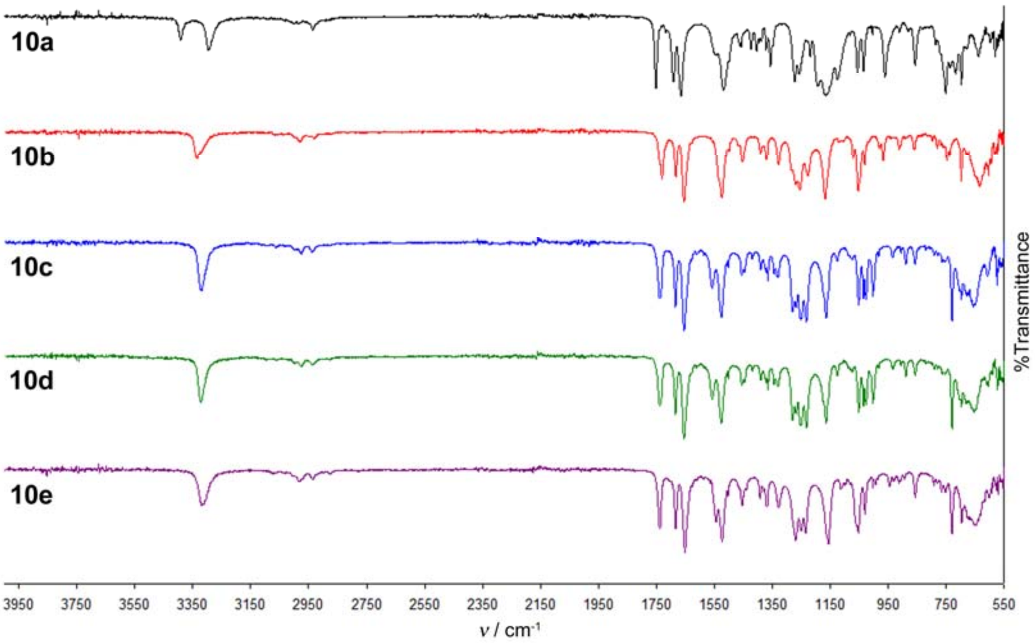


Figure S10. FTIR-ATR spectra of Boc-Gly-Gly-OBn (**10a**), Boc-L-Ala-L-Ala-OBn (**10b**), Boc-L-Ala-Gly-OBn (**10c**), Boc-D-Ala-Gly-OBn (**10d**) and Boc-D-Ala-L-Ala-OBn (**10e**).

3. ^{1}H and ^{13}C NMR spectra

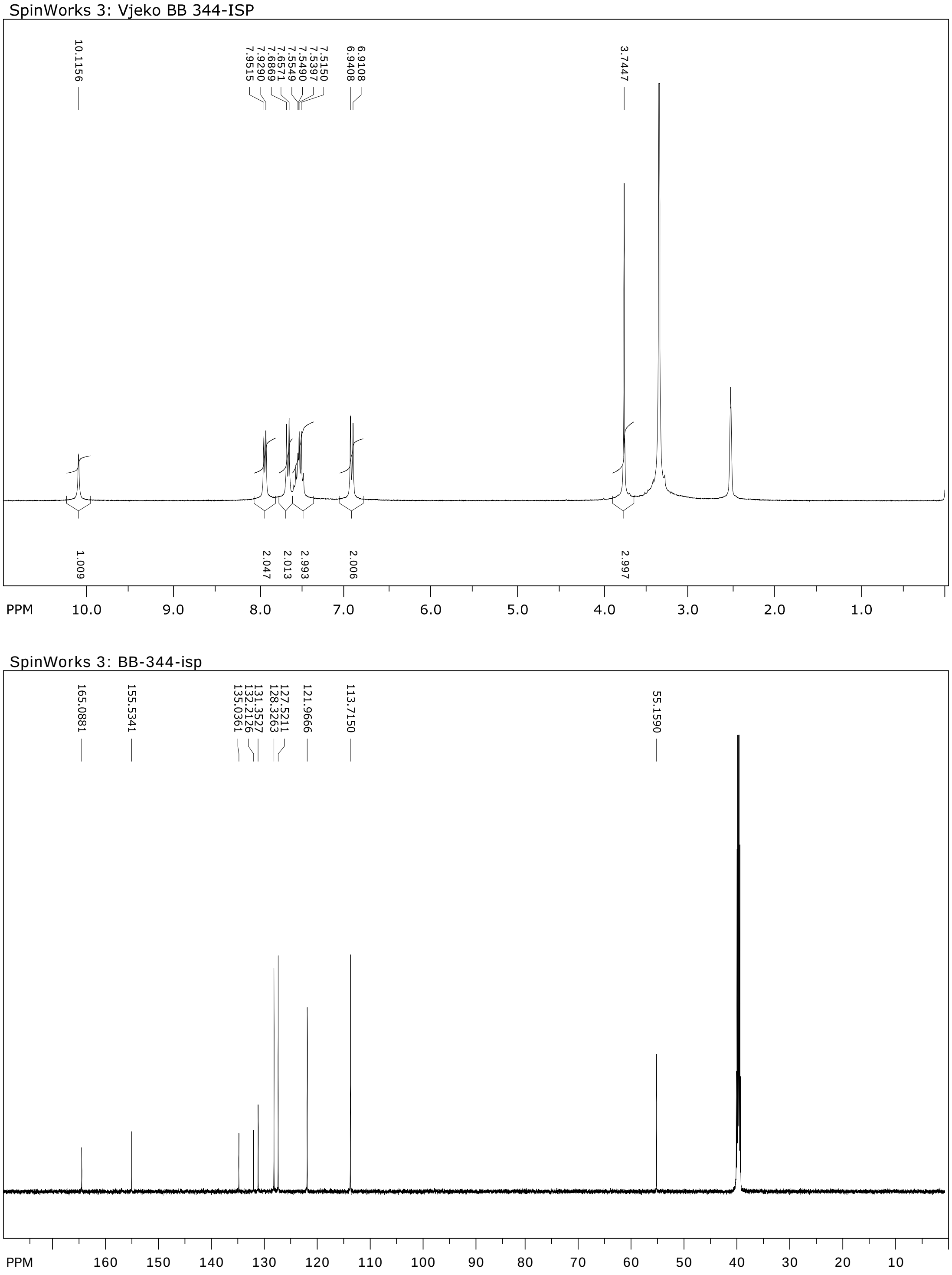


Figure S11. ^{1}H and ^{13}C NMR spectra of *N*-(4-methoxyphenyl)benzamide (**1a**).

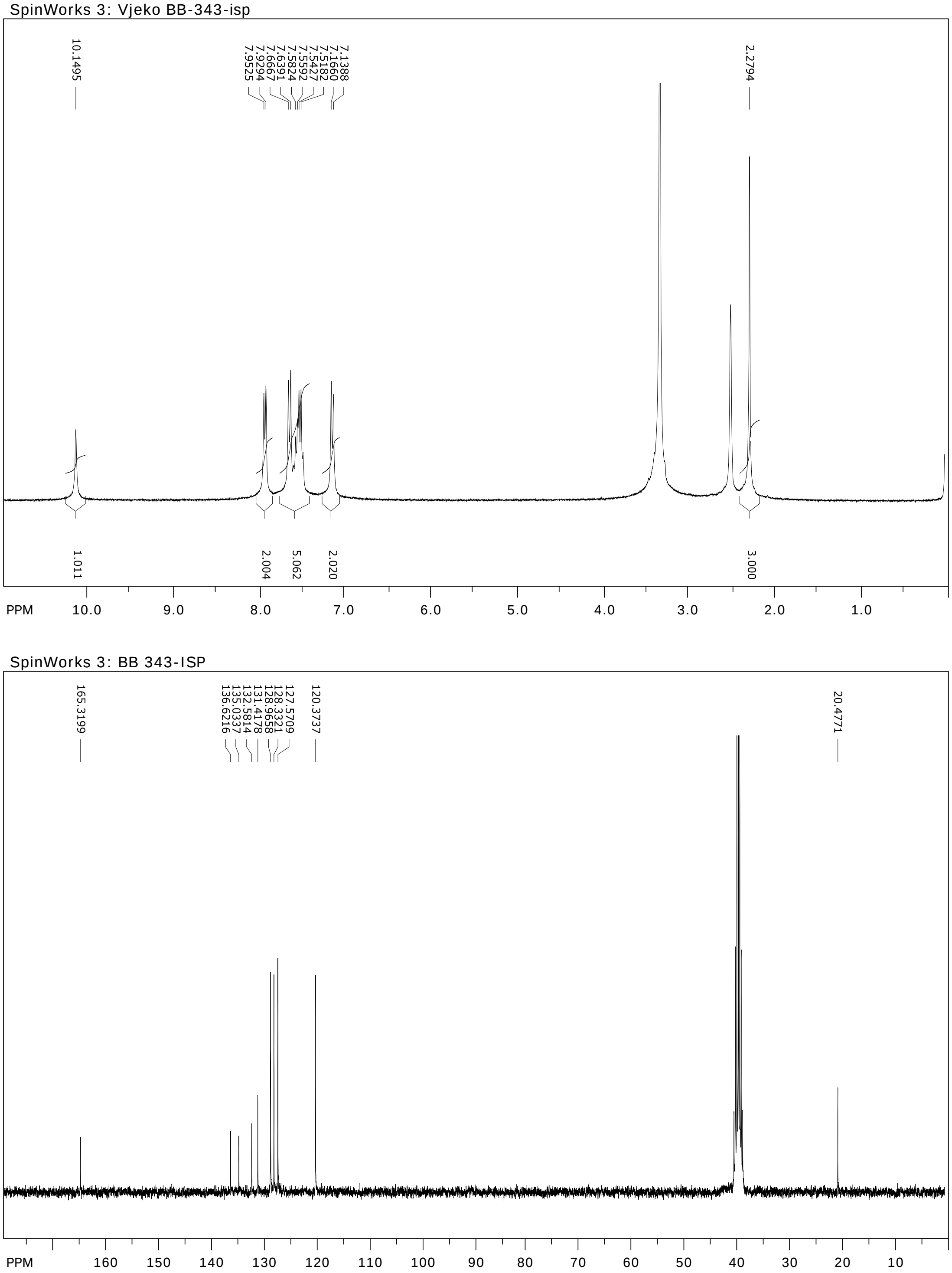


Figure S12. ^{1}H and ^{13}C NMR spectra of *N*-(4-methylphenyl)benzamide (**1b**).

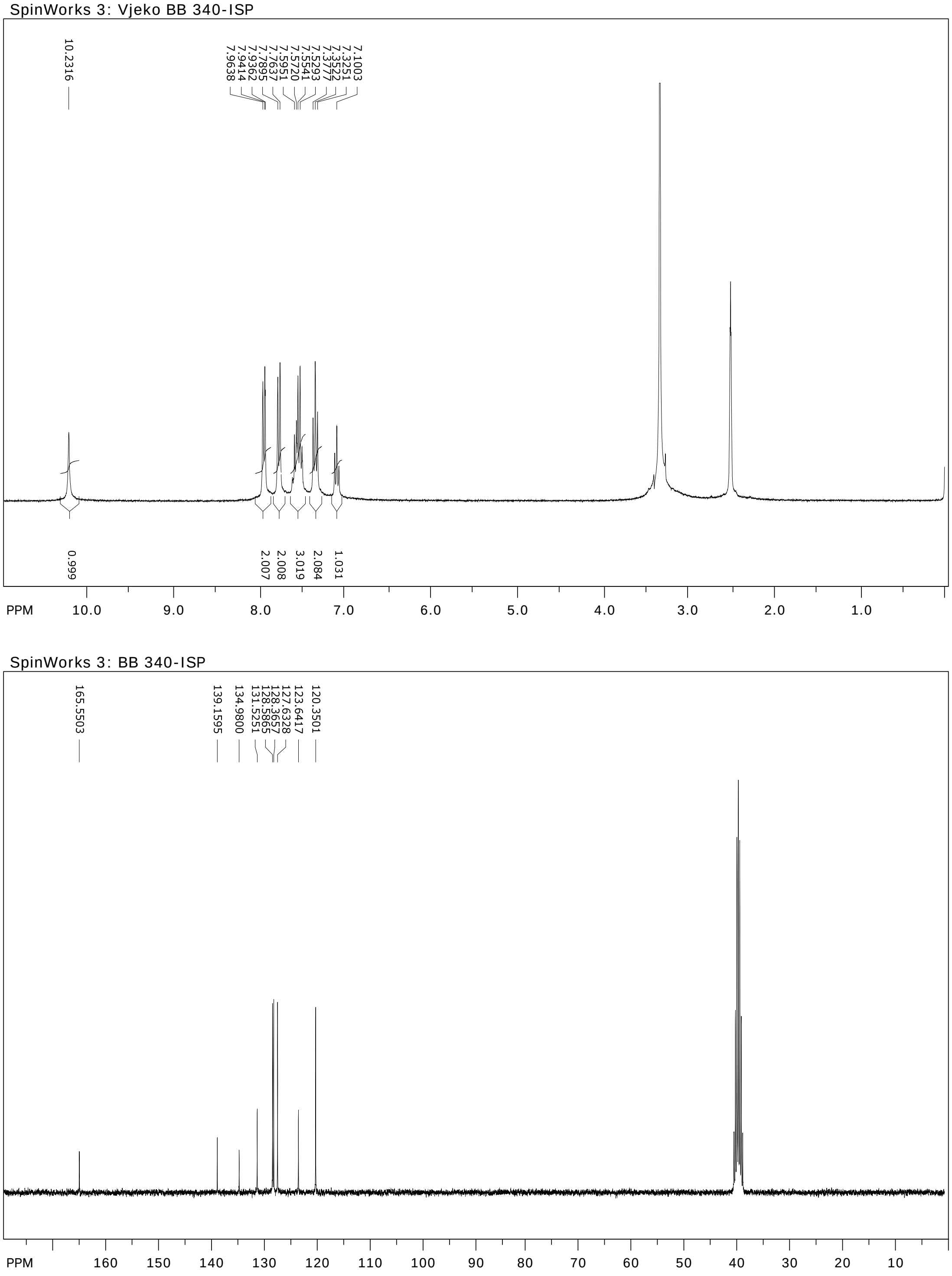


Figure S13. ^{1}H and ^{13}C NMR spectra of *N*-phenylbenzamide (**1c**).

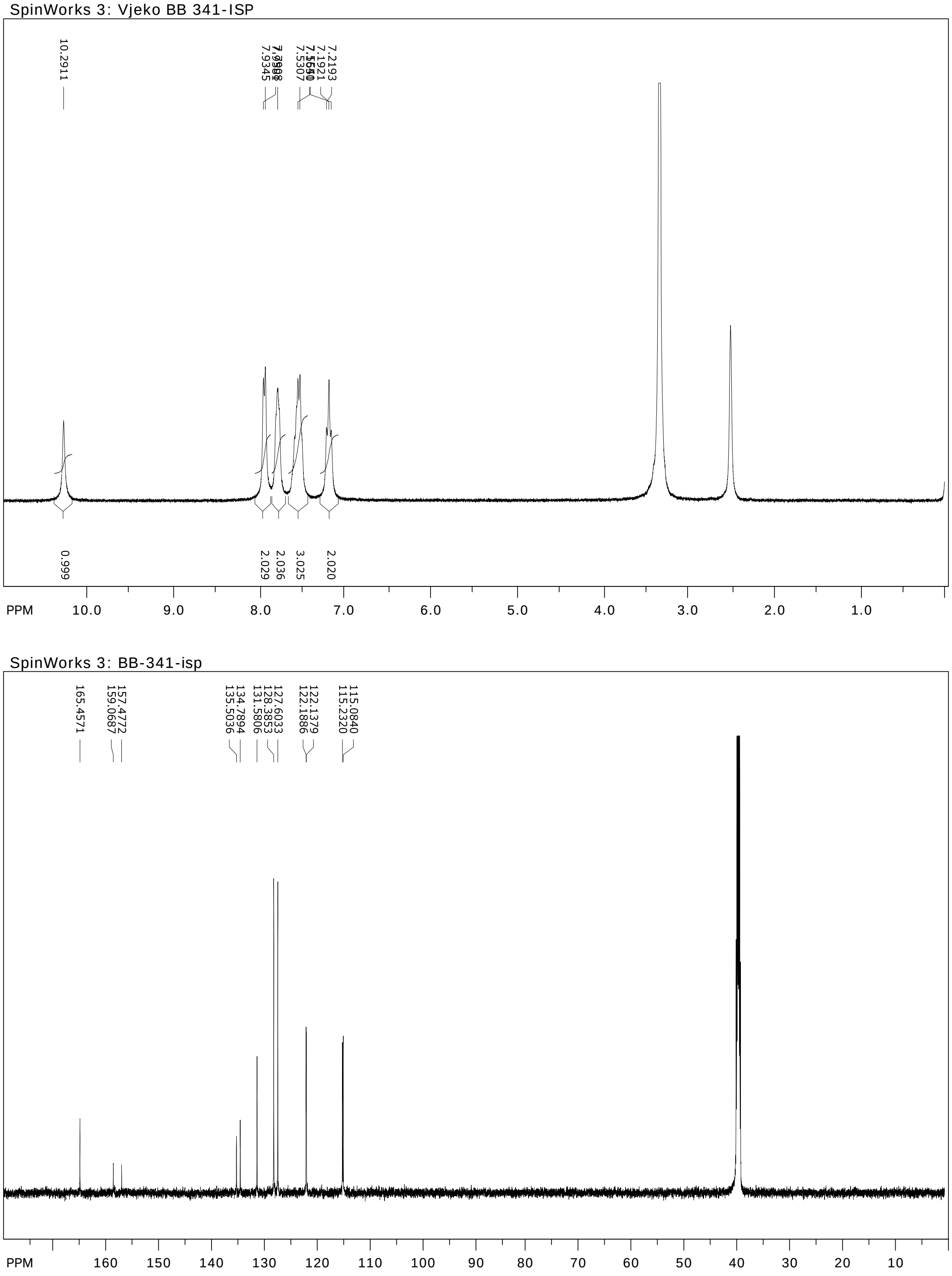
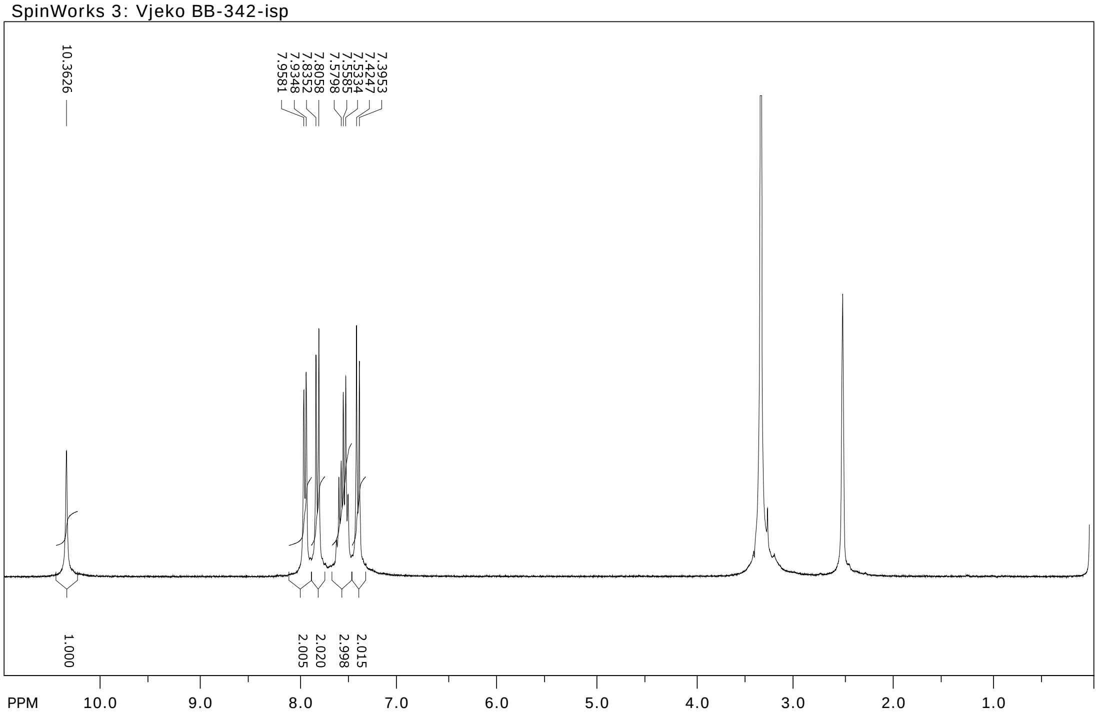


Figure S14. ^{1}H and ^{13}C NMR spectra of *N*-(4-fluorophenyl)benzamide (**1d**).



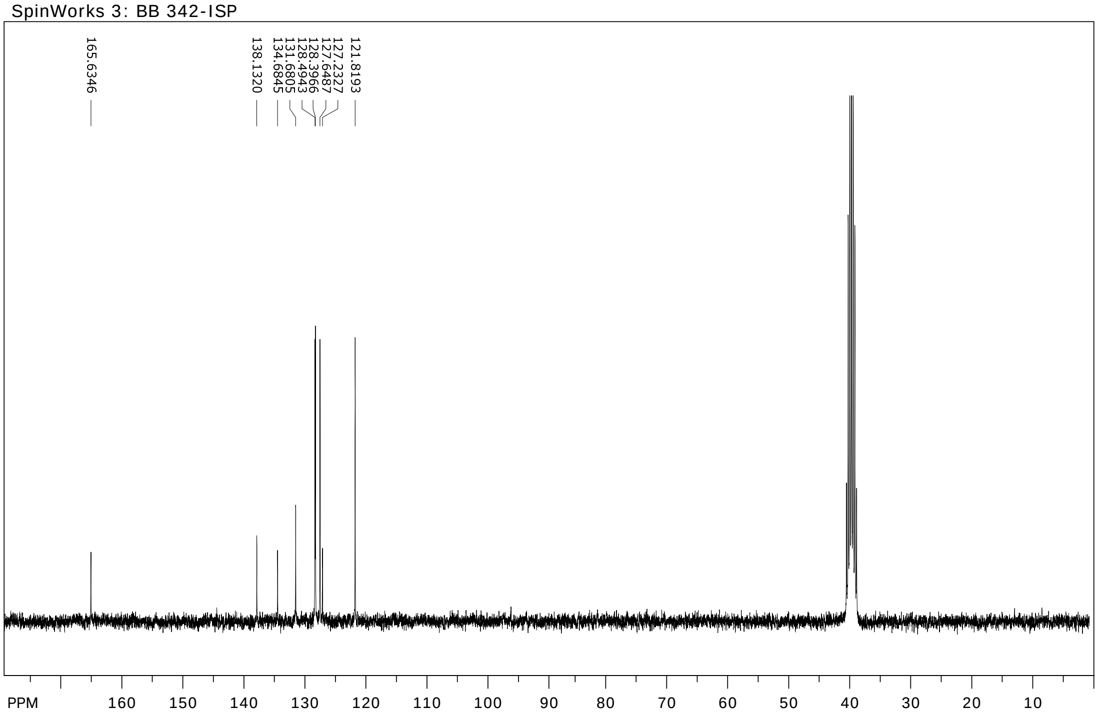


Figure S15. ^{1}H and ^{13}C NMR spectra of *N*-(4-chlorophenyl)benzamide (**1e**).

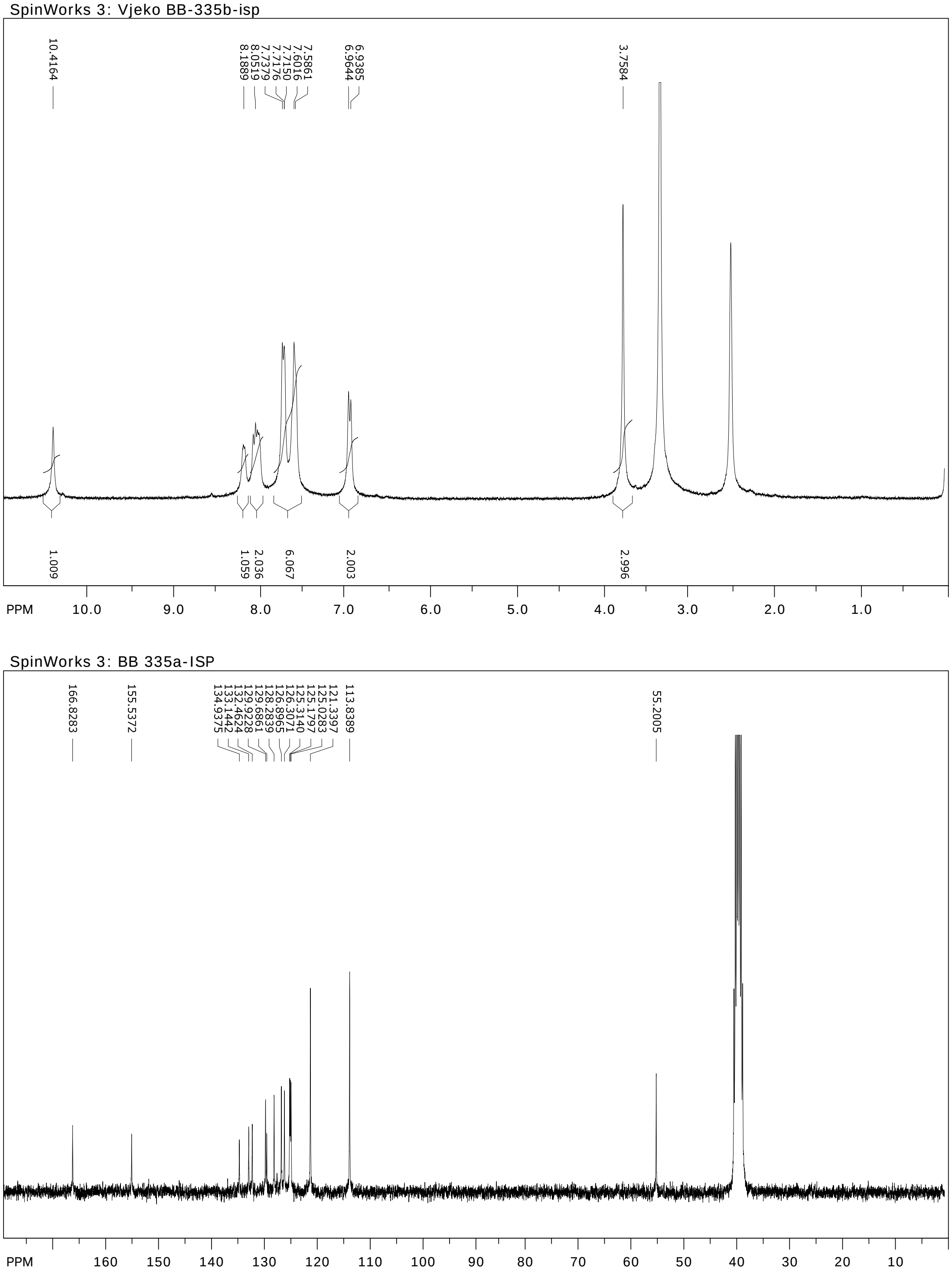


Figure S16. ^{1}H and ^{13}C NMR spectra of *N*-(4-methoxyphenyl)-1-naphthamide (**2a**).

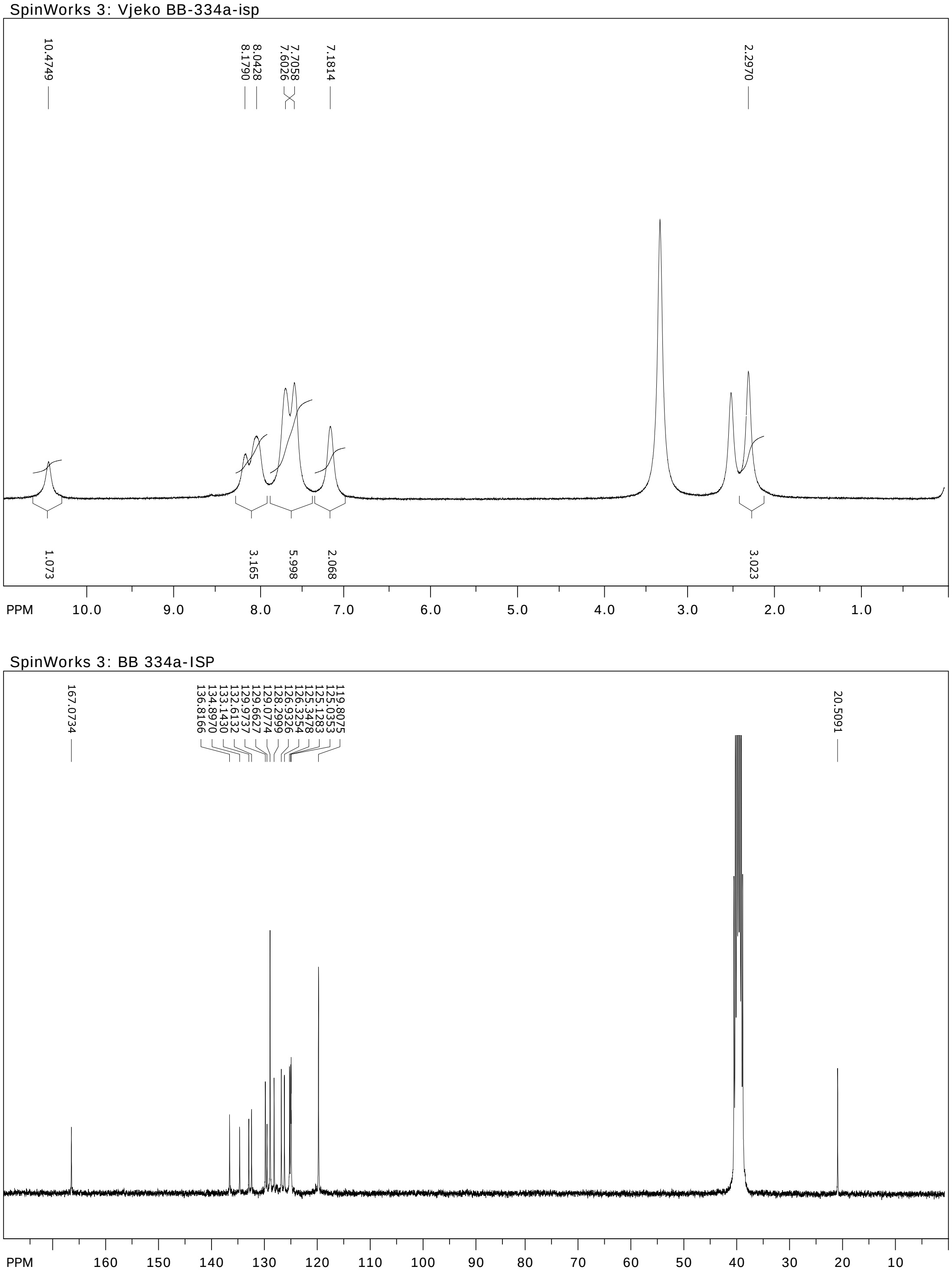


Figure S17. ^{1}H and ^{13}C NMR spectra of *N*-(4-methylphenyl)-1-naphthamide (**2b**).

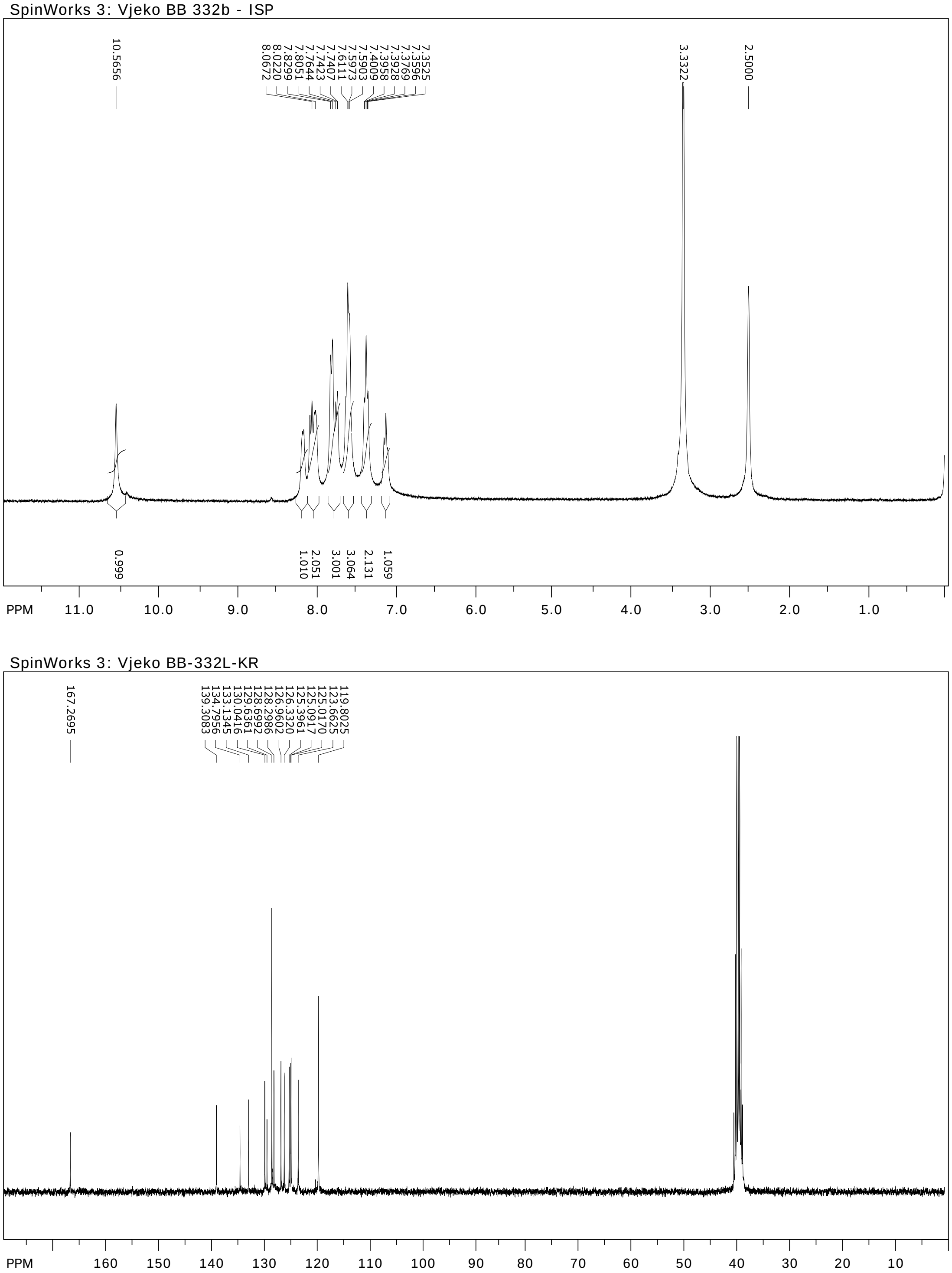


Figure S18. ^{1}H and ^{13}C NMR spectra of *N*-phenyl-1-naphthamide (**2c**).

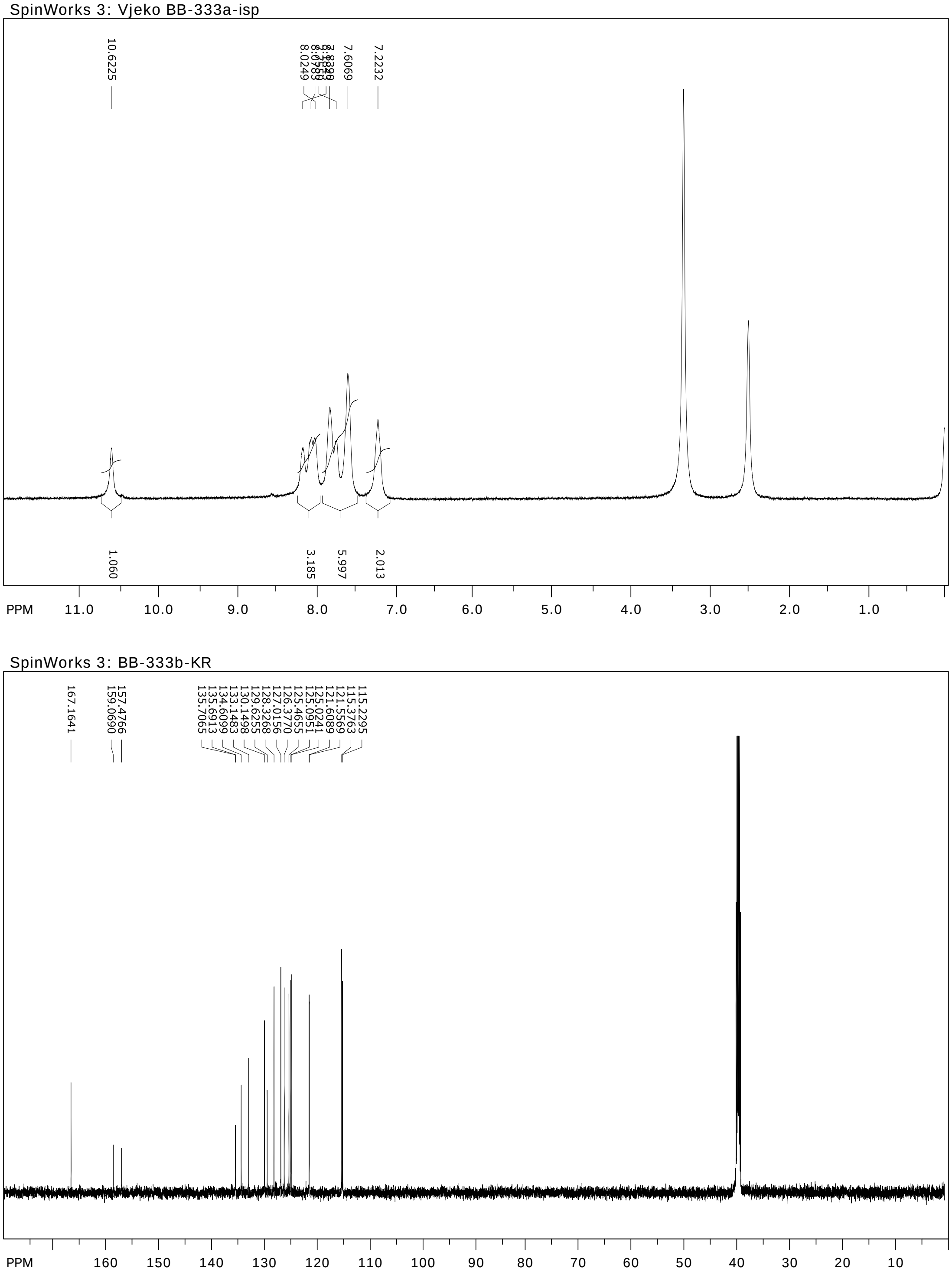


Figure S19. ^{1}H and ^{13}C NMR spectra of *N*-(4-fluorophenyl)-1-naphthamide (**2d**).

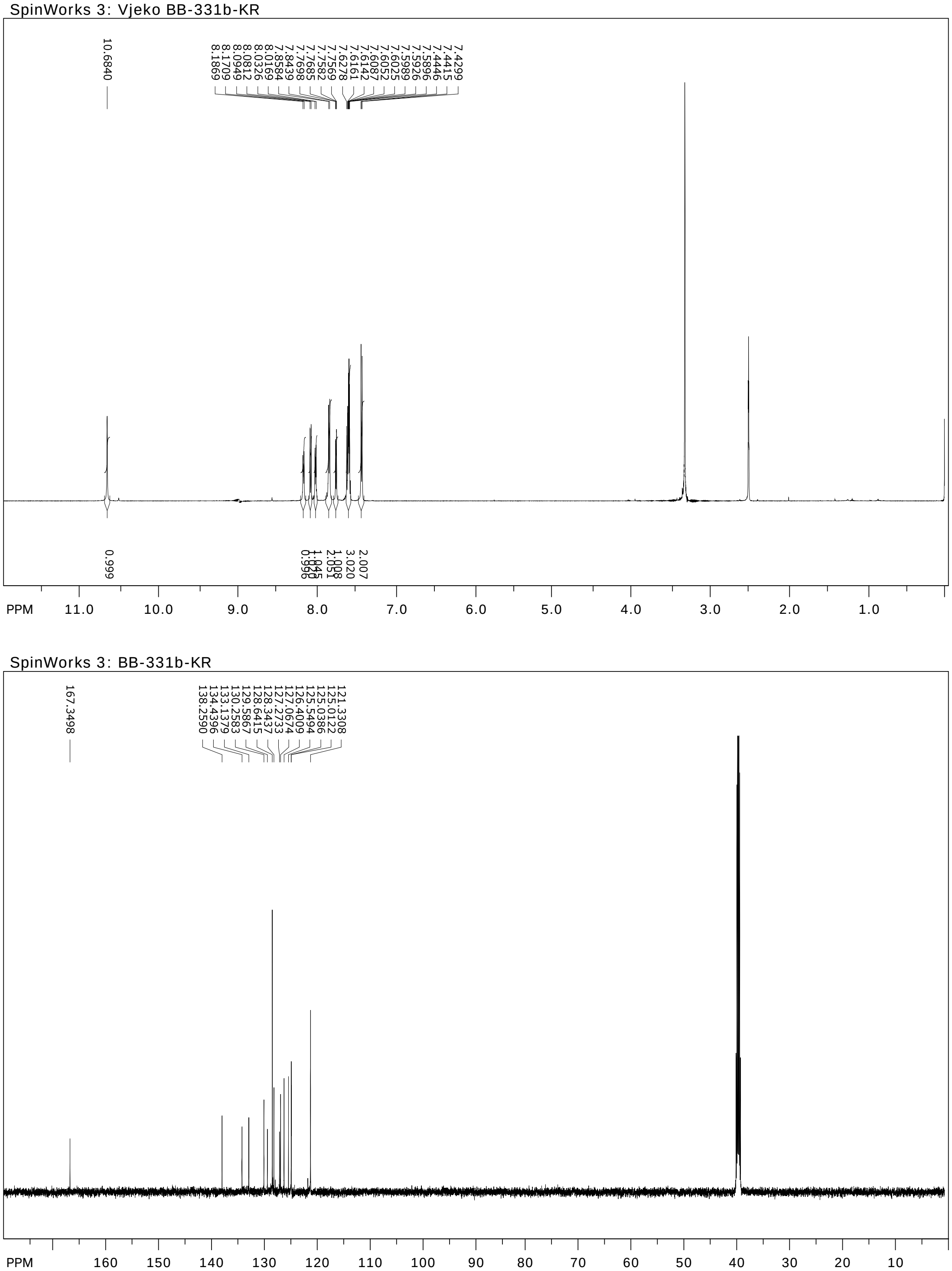


Figure S20. ^{1}H and ^{13}C NMR spectra of *N*-(4-chlorophenyl)-1-naphthamide (**2e**).

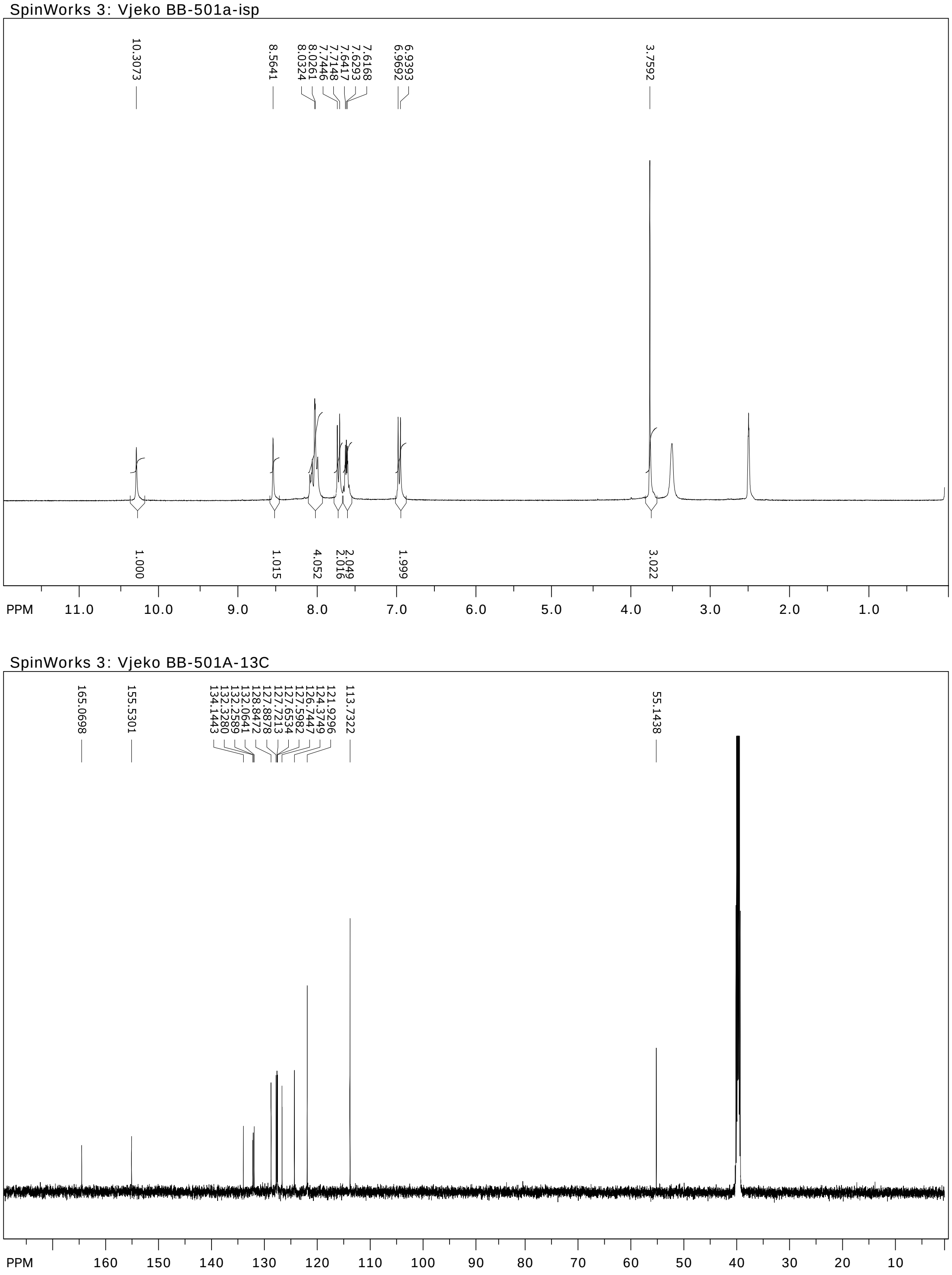


Figure S21. ^{1}H and ^{13}C NMR spectra of *N*-(4-methoxyphenyl)-2-naphthamide (**3a**).

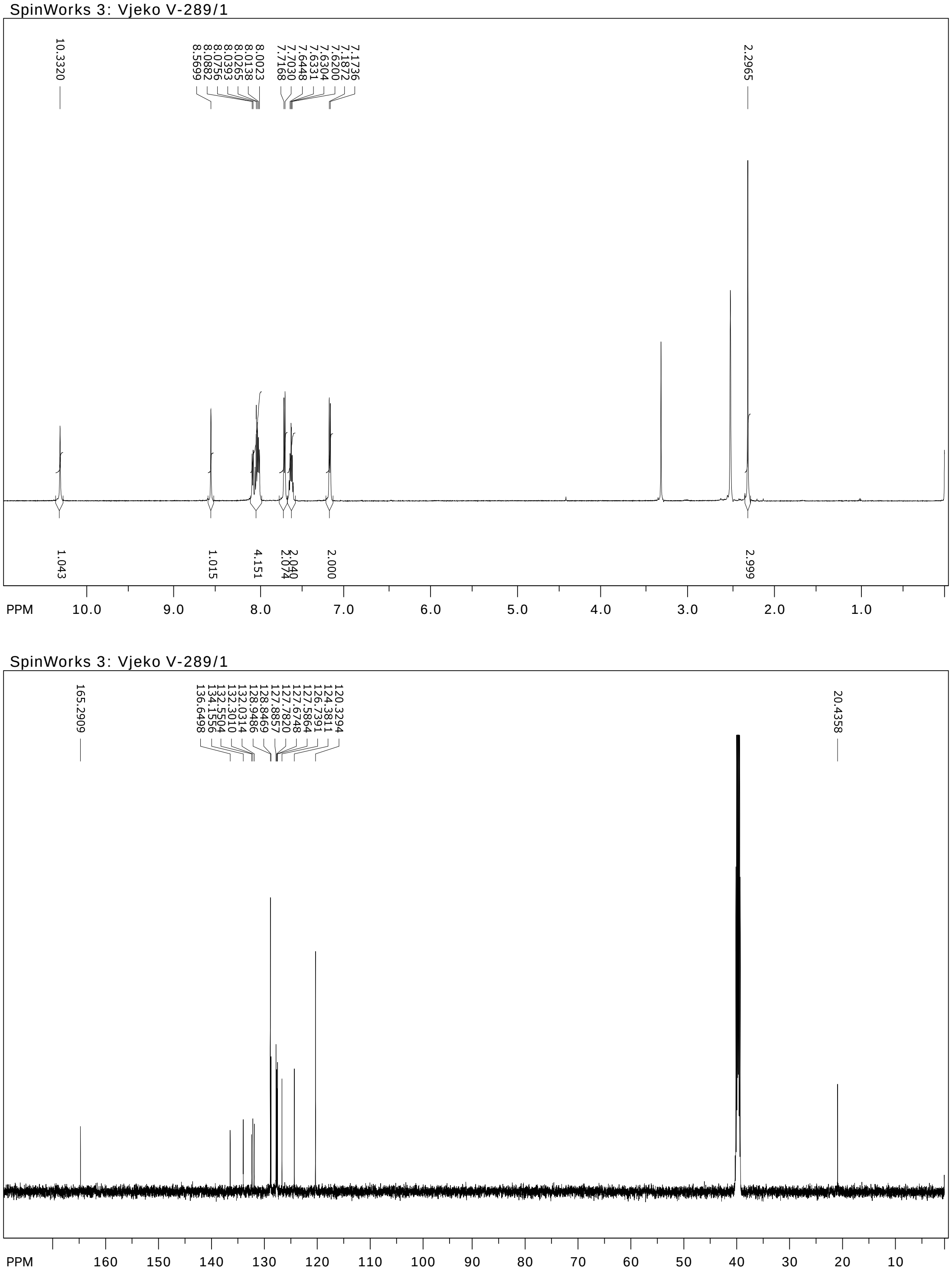


Figure S22. ^{1}H and ^{13}C NMR spectra of *N*-(4-methylphenyl)-2-naphthamide (**3b**).

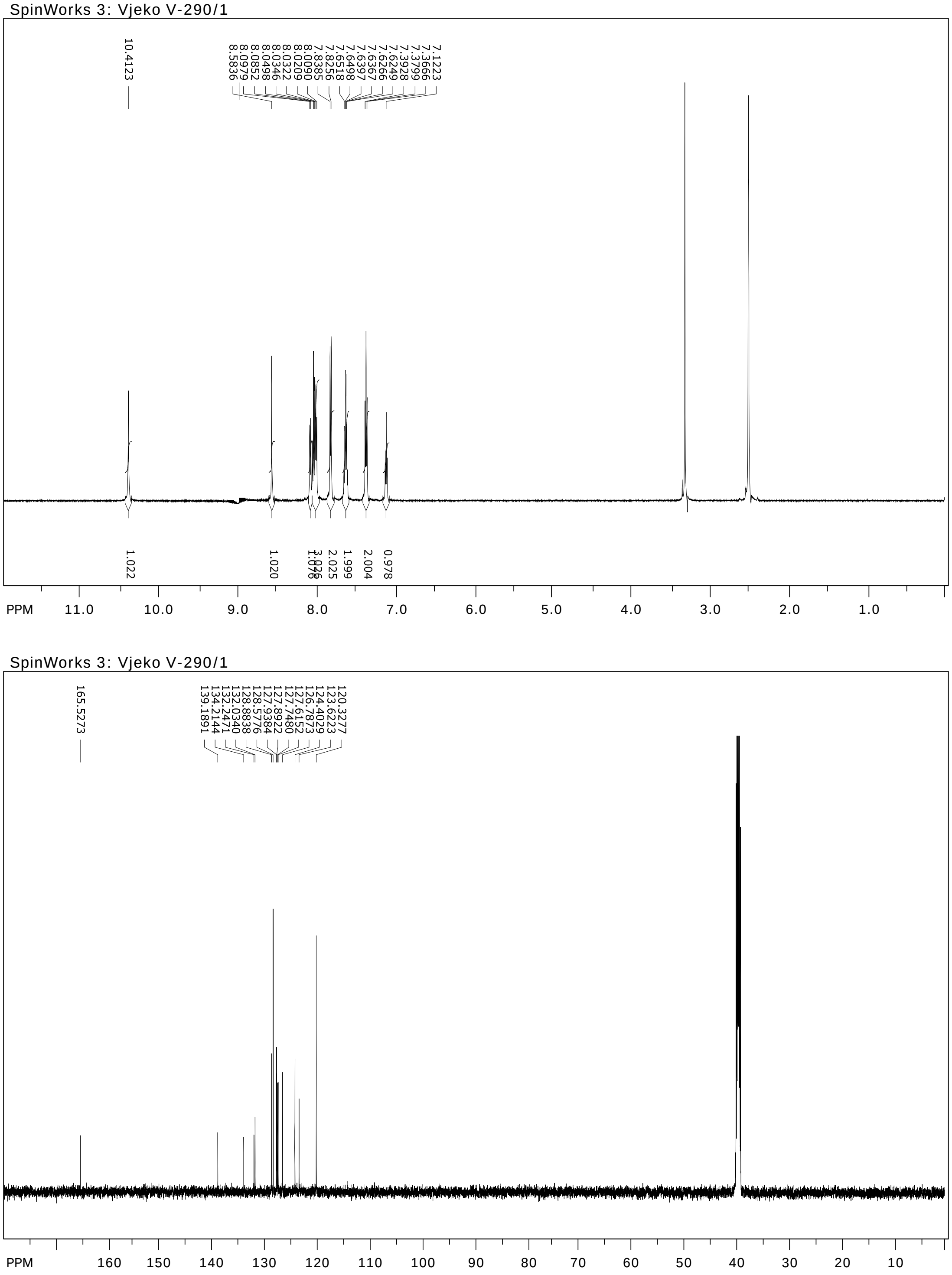


Figure S23. ^{1}H and ^{13}C NMR spectra of *N*-phenyl-2-naphthamide (**3c**).

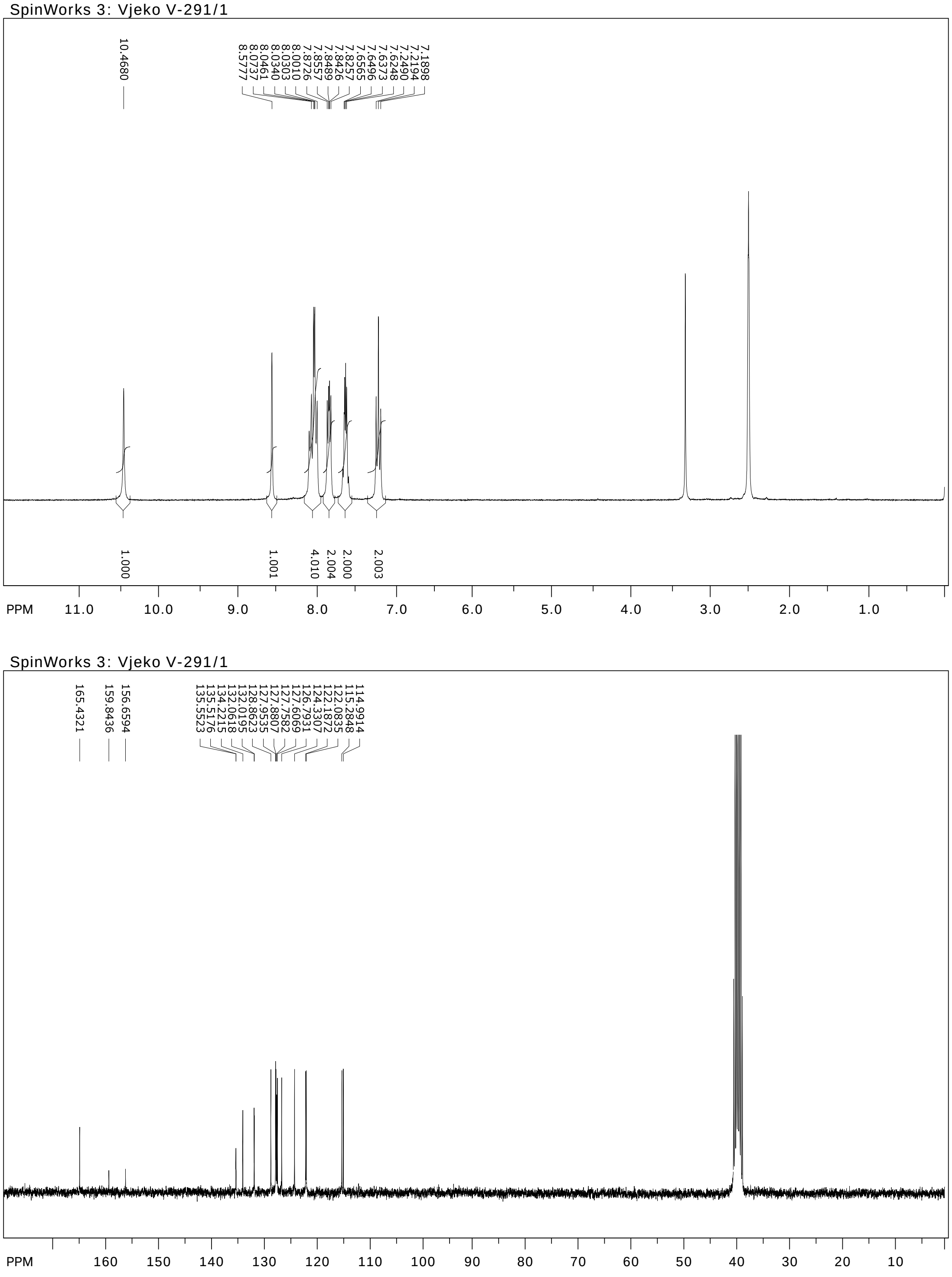


Figure S24. ^{1}H and ^{13}C NMR spectra of *N*-(4-fluorophenyl)-2-naphthamide (**3d**).

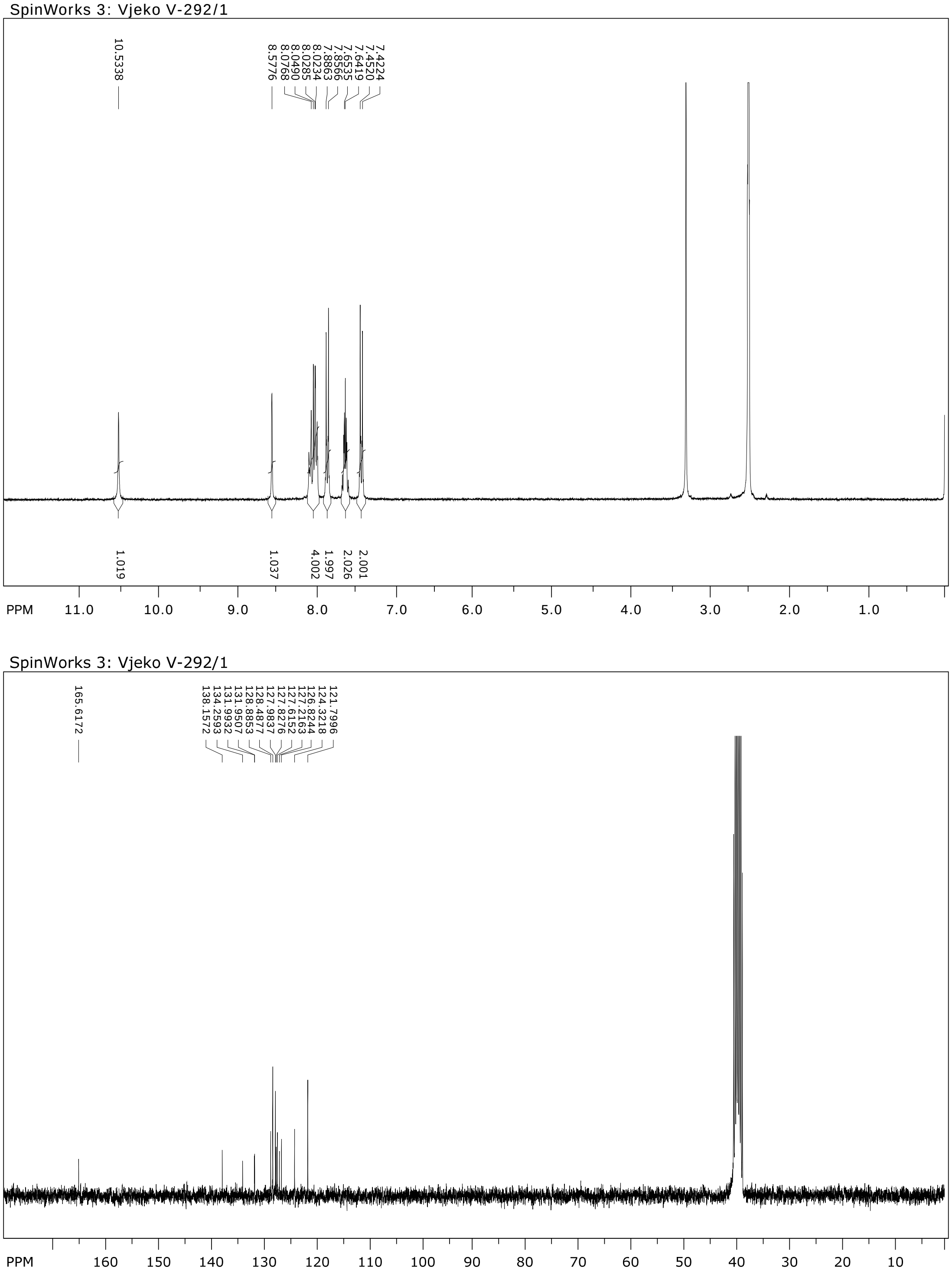
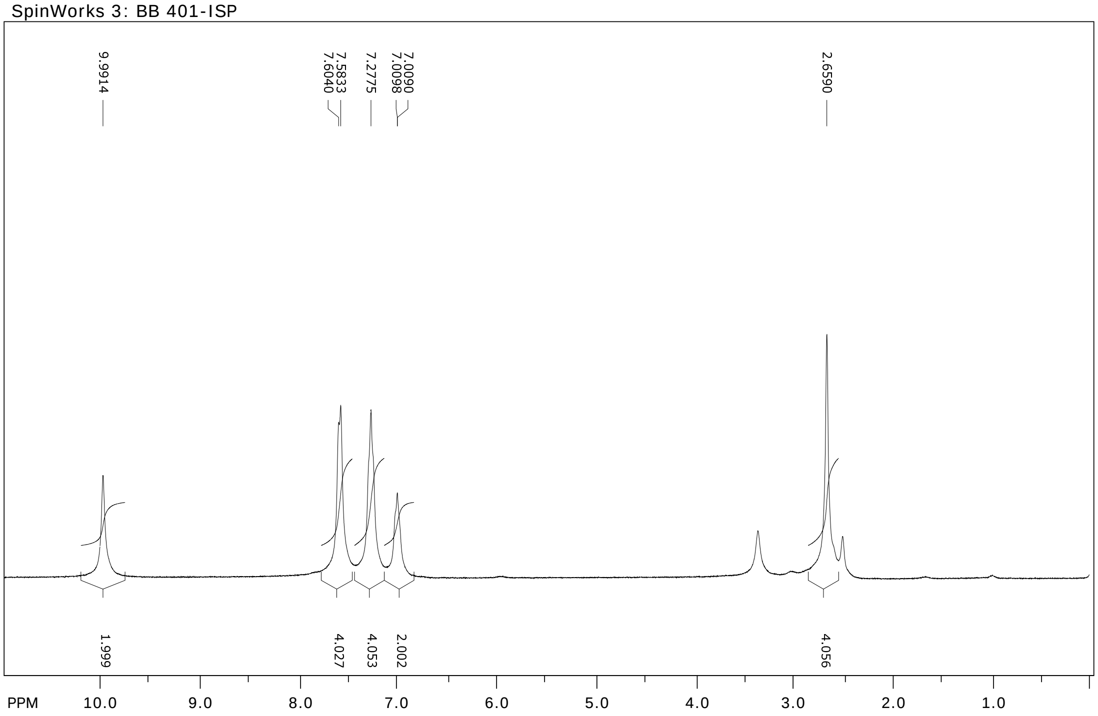


Figure S25. ^{1}H and ^{13}C NMR spectra of *N*-(4-chlorophenyl)-2-naphthamide (**3e**).



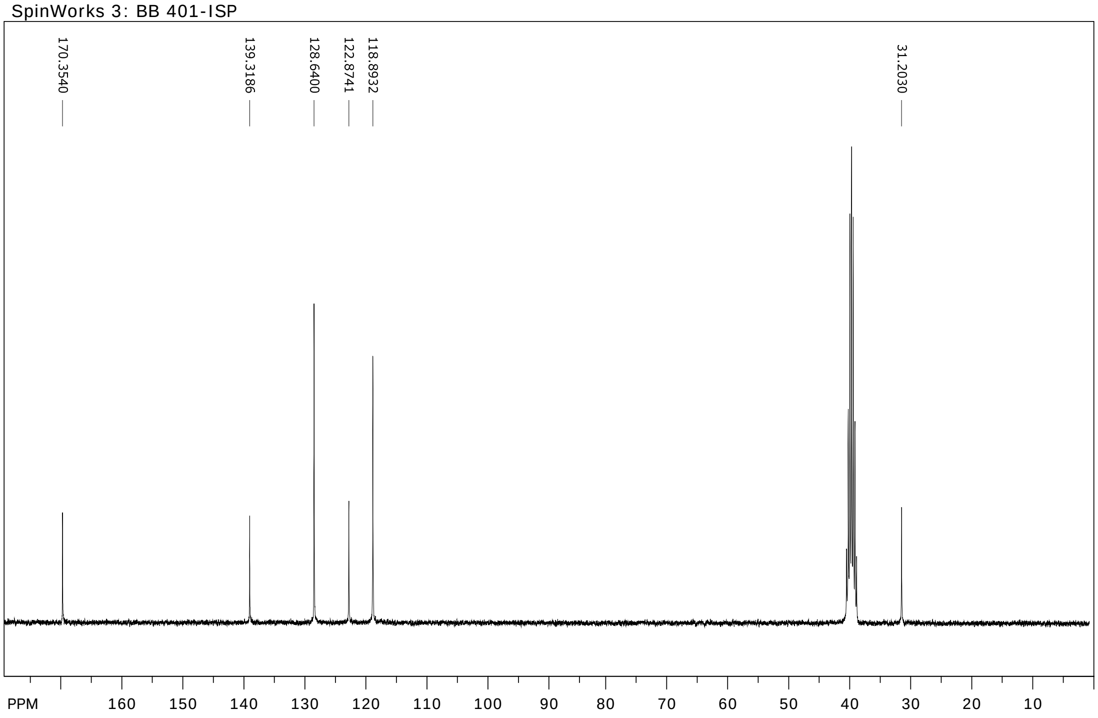


Figure S26. ^{1}H and ^{13}C NMR spectra of *N,N′*-diphenylsuccinamide (**4**).

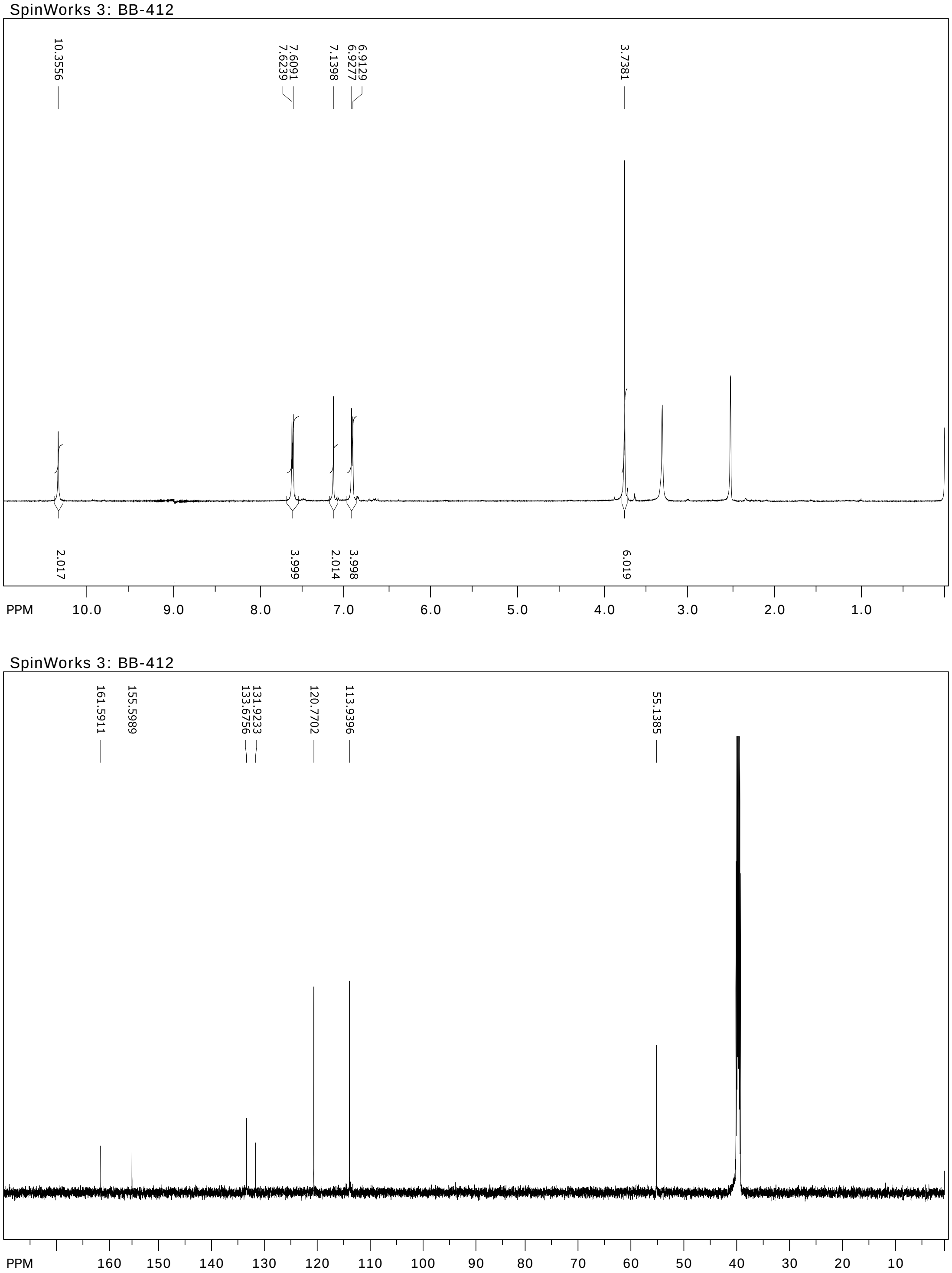
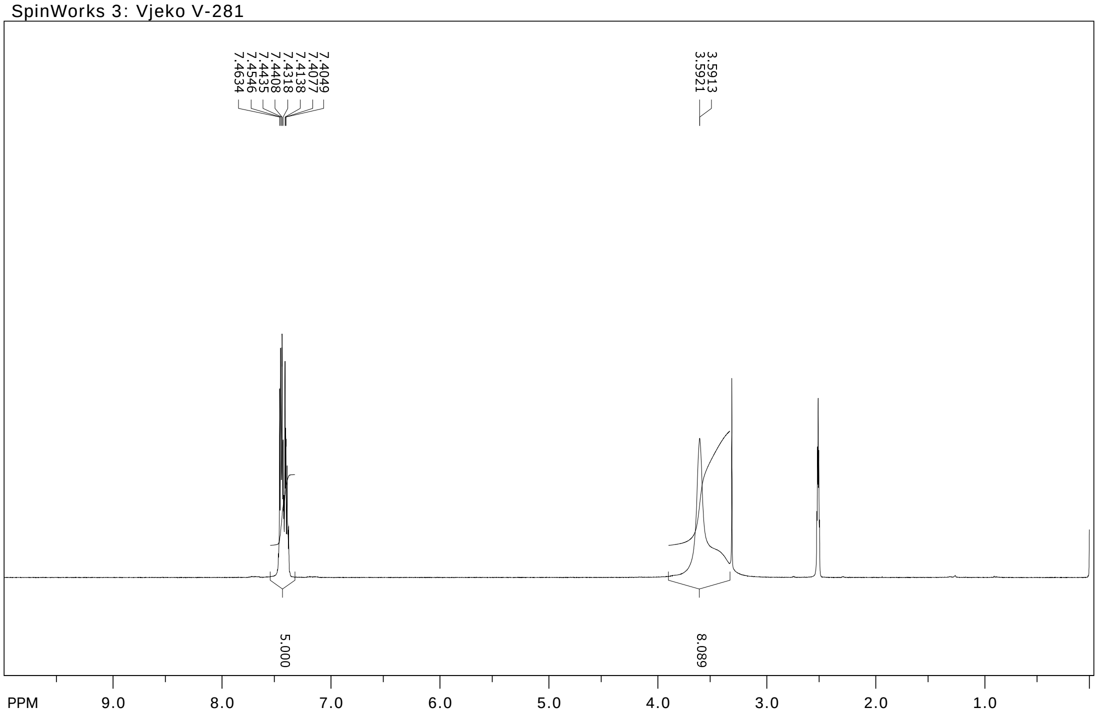


Figure S27. ^{1}H and ^{13}C NMR spectra of *N,N′*-bis(4-methoxyphenyl)fumaramide (**5**).



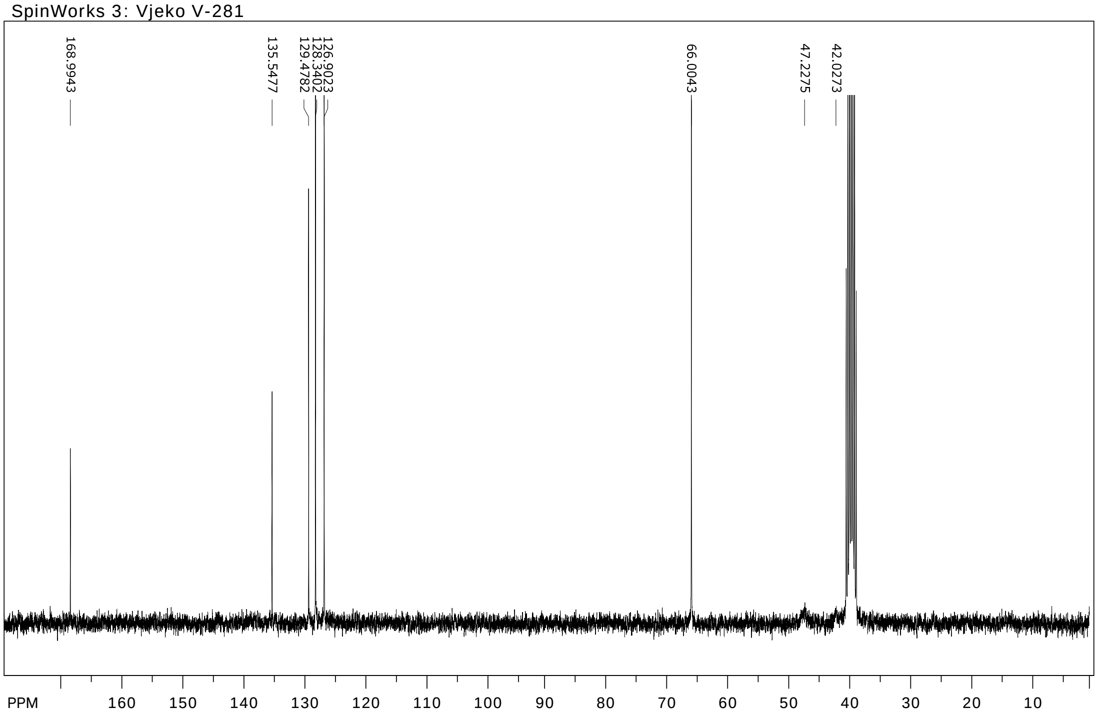


Figure S28. ^{1}H and ^{13}C NMR spectra of *N*-benzoylmorpholine (**6a**).

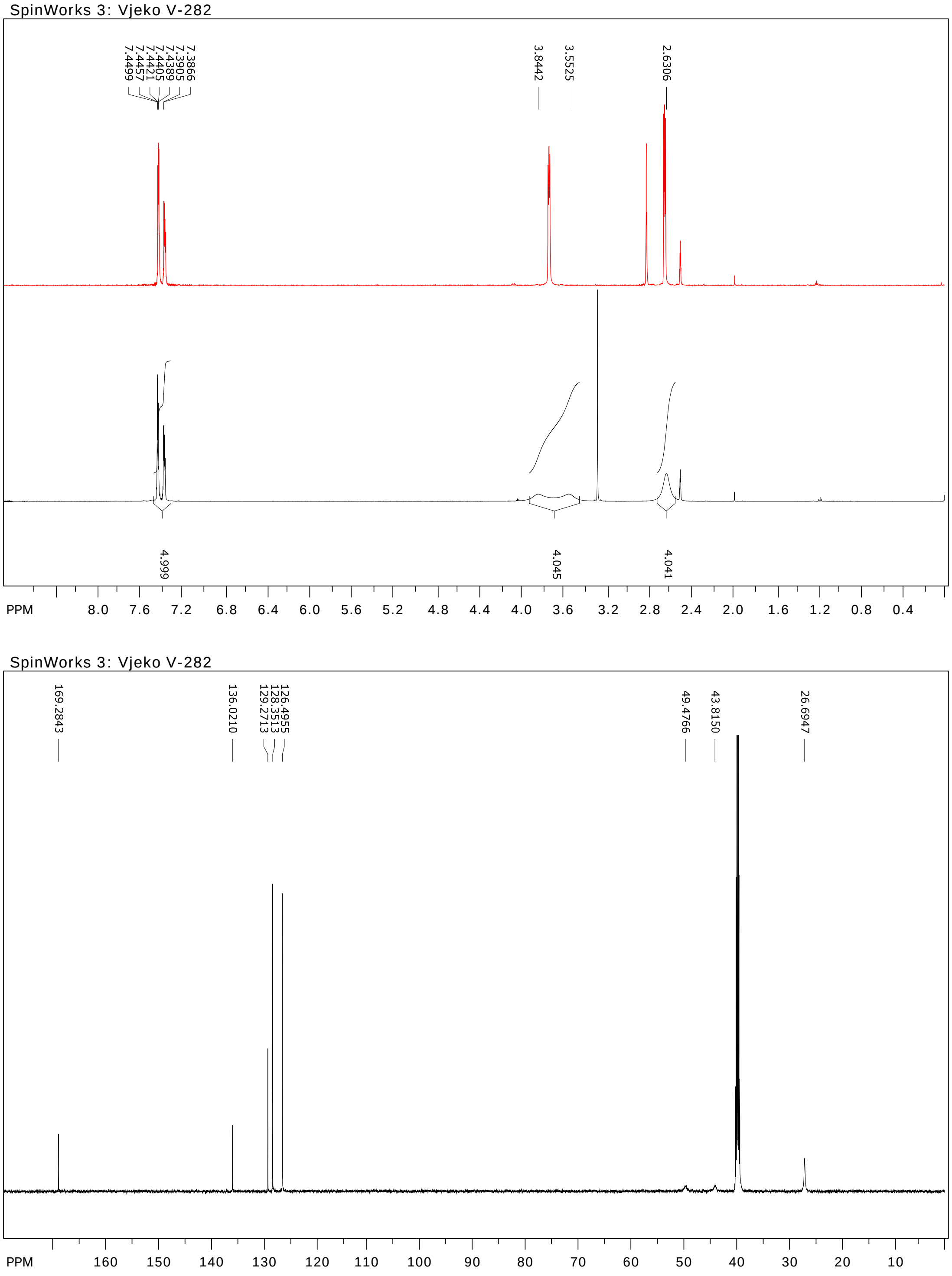
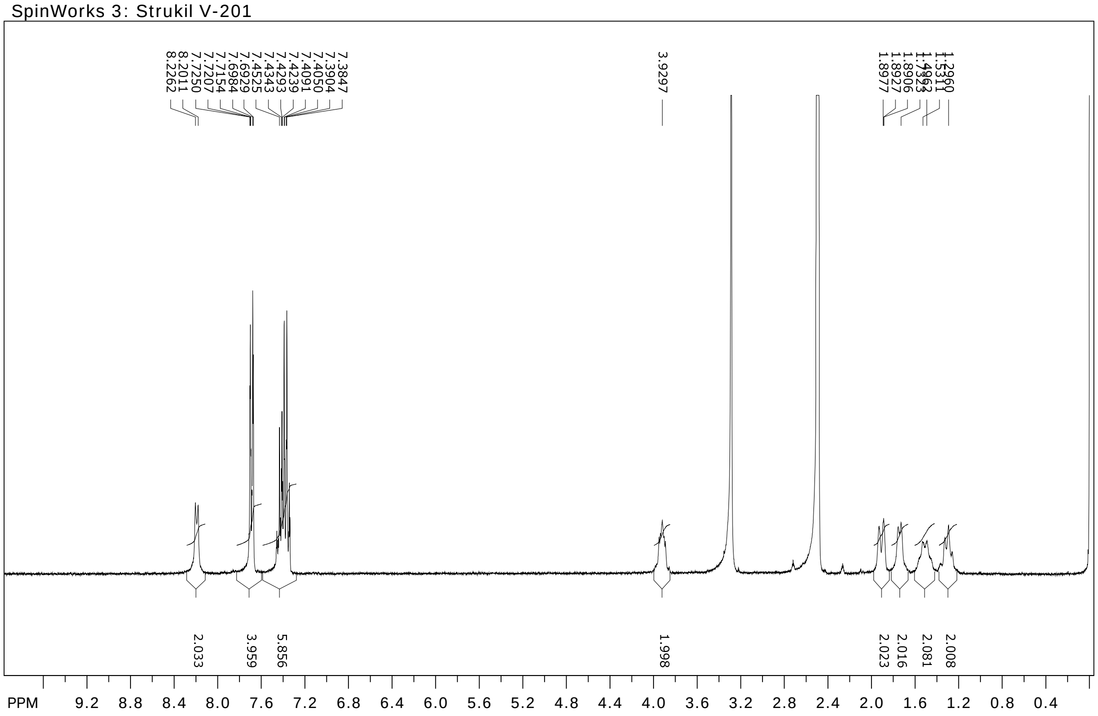


Figure S29. ^{1}H (105 °C (red) and 25 °C (black)) and ^{13}C NMR (25 °C) spectra of *N*-benzoylthiomorpholine (**6b**).



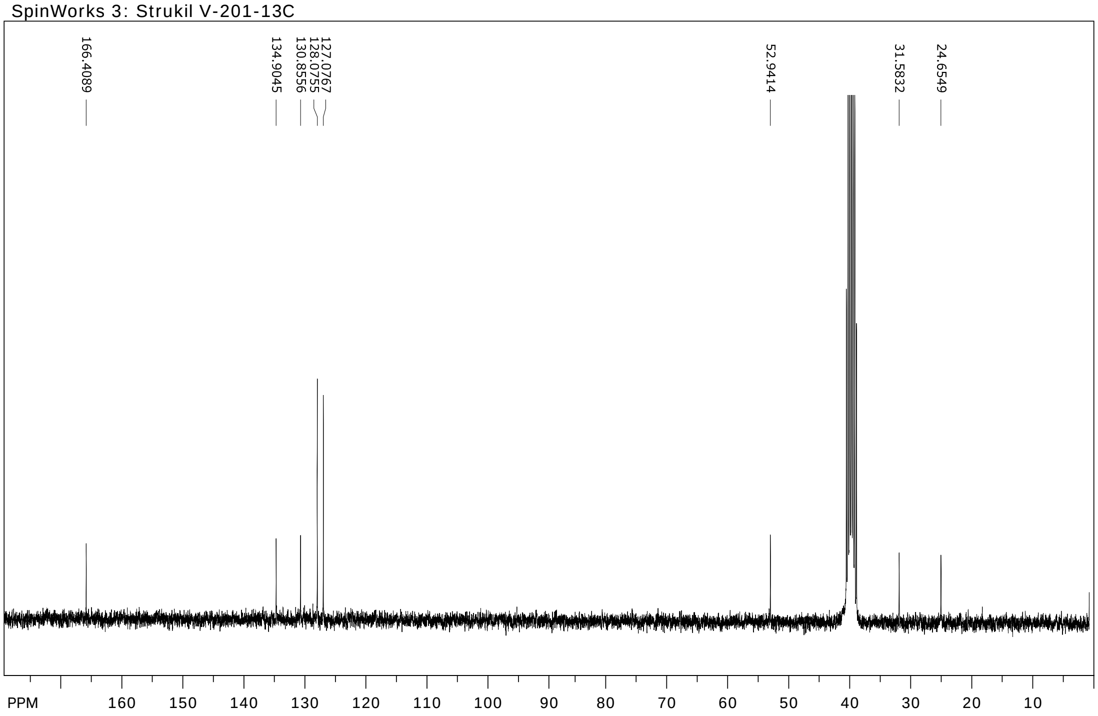


Figure S30. ^{1}H and ^{13}C NMR spectra of (1*R*,2*R*)-*N*^{1},*N*^{2}-dibenzoyl-1,2-diaminocyclohexane (**(1*R*,2*R*)-7**).

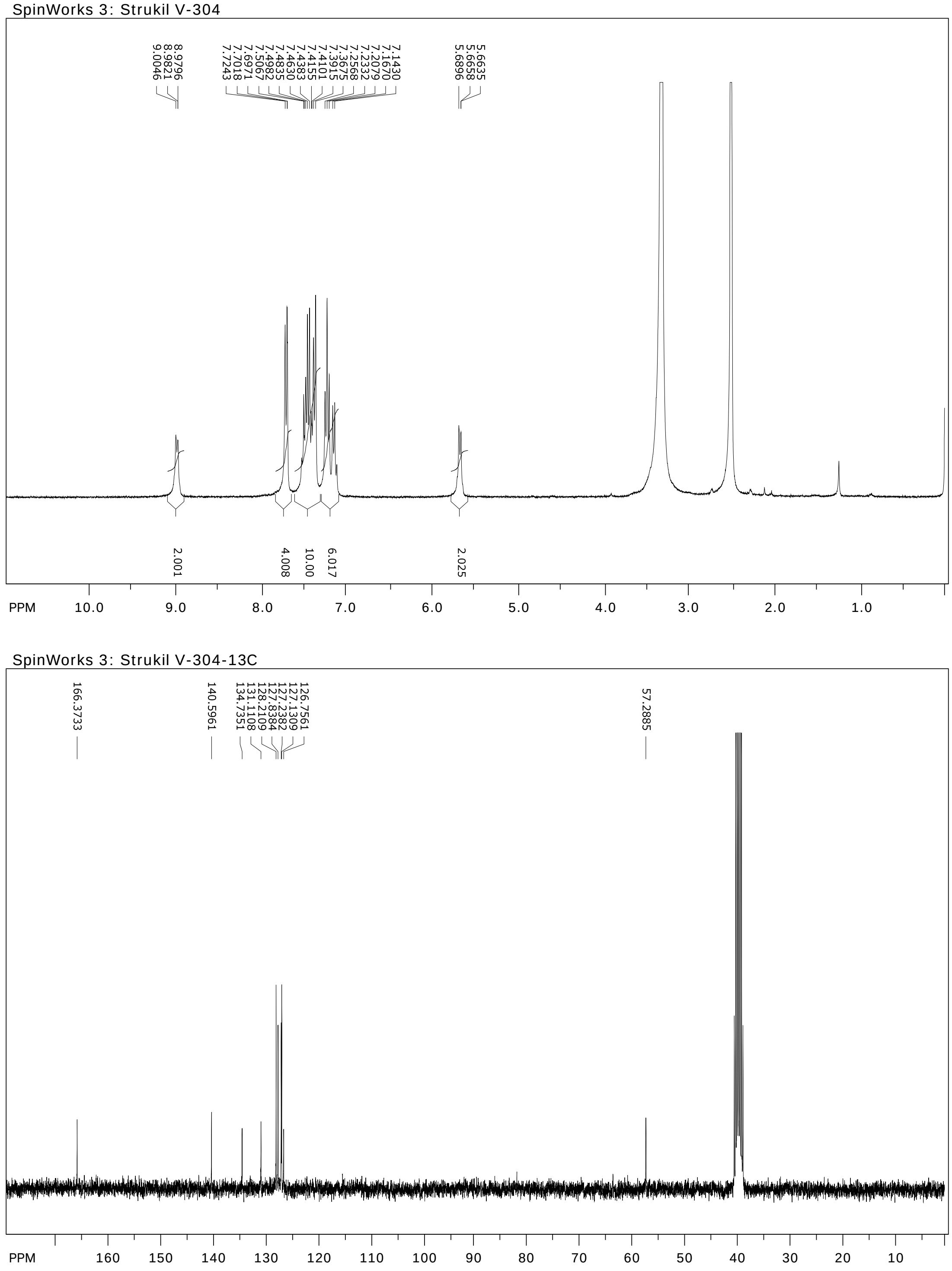


Figure S31. ^{1}H and ^{13}C NMR spectra of (1*R*,2*R*)-*N*^{1},*N*^{2}-dibenzoyl-1,2-diphenylethylenediamine (**(1*R*,2*R*)-8**).

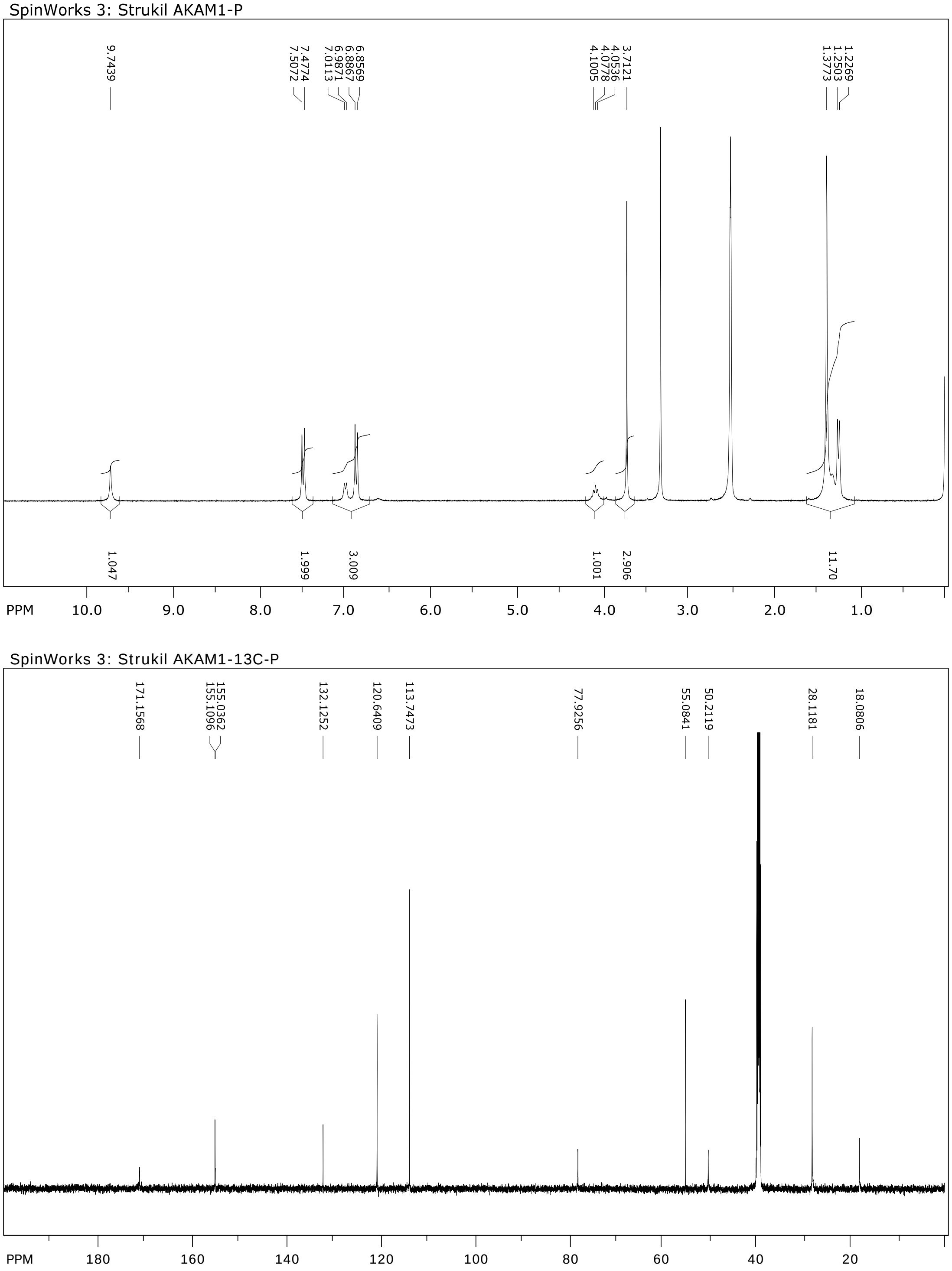


Figure S32. ^{1}H and ^{13}C NMR spectra of *N*-(*N*-(*tert*-butoxycarbonyl)-L-alanyl)-4-methoxy-aniline (**9a**).

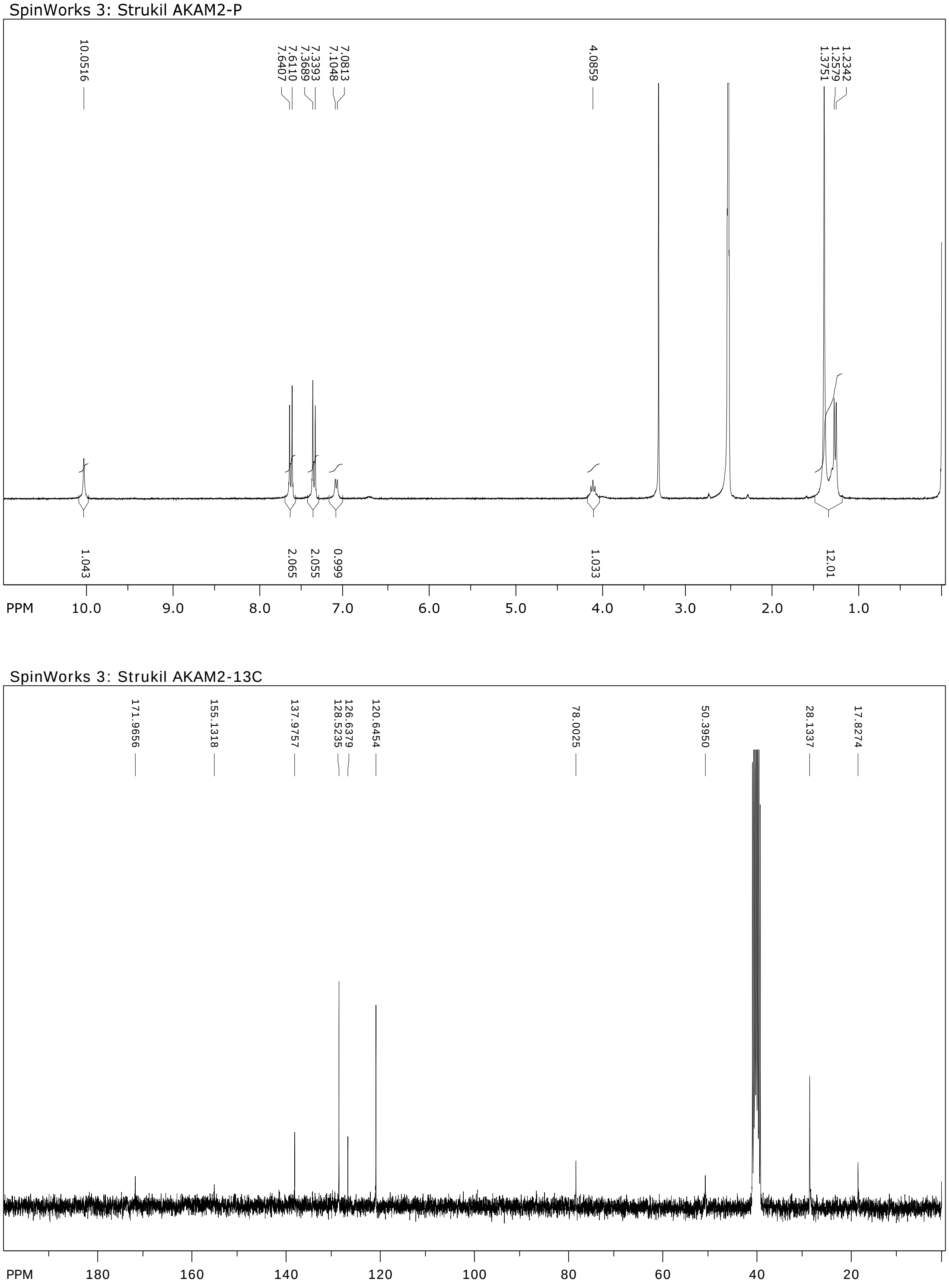
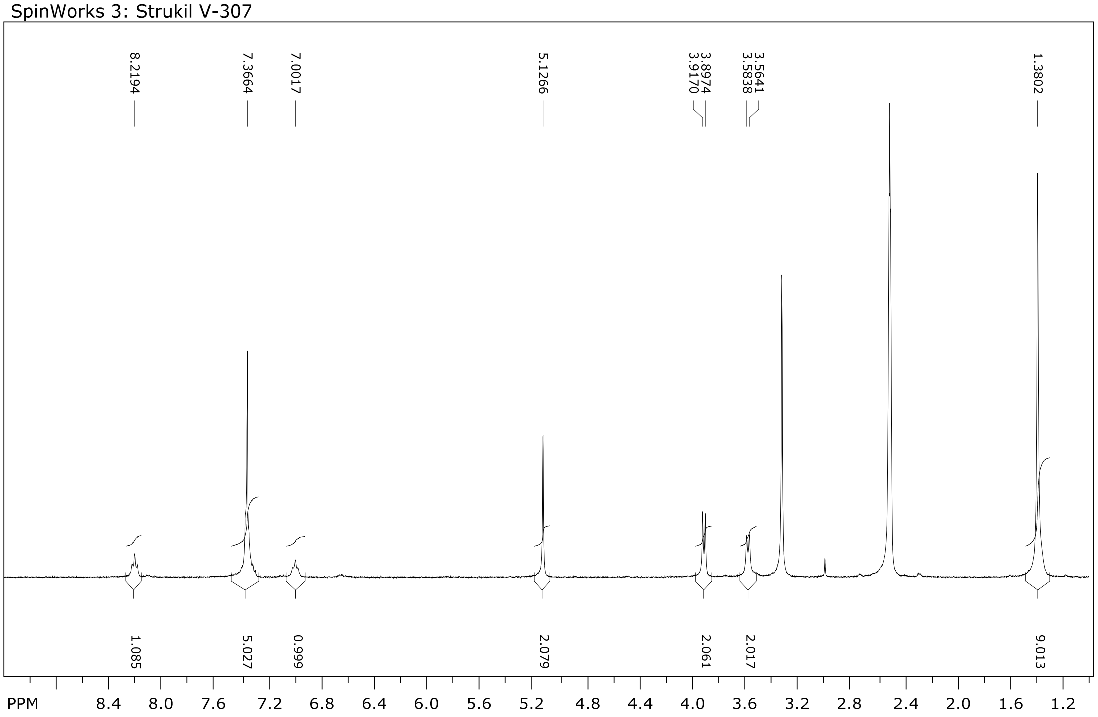


Figure S33. ^{1}H and ^{13}C NMR spectra of *N*-(*N*-(*tert*-butoxycarbonyl)-L-alanyl)-4-chloroaniline (**9b**).



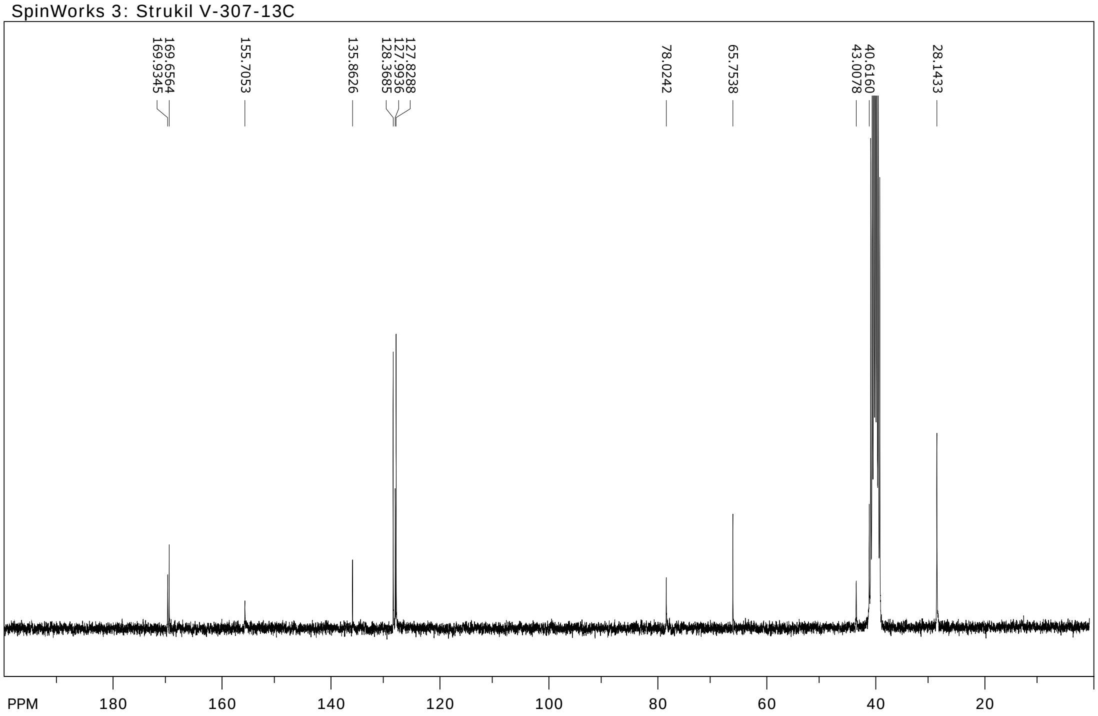
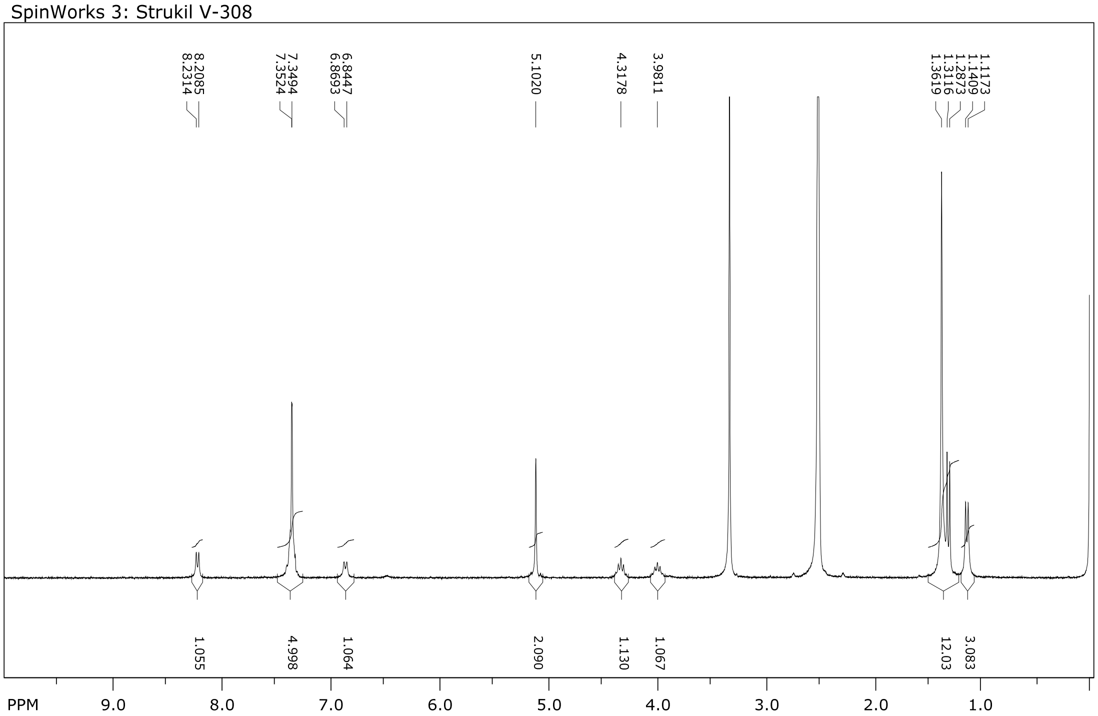


Figure S34. ^{1}H and ^{13}C NMR spectra of Boc-Gly-Gly-OBn (**10a**).



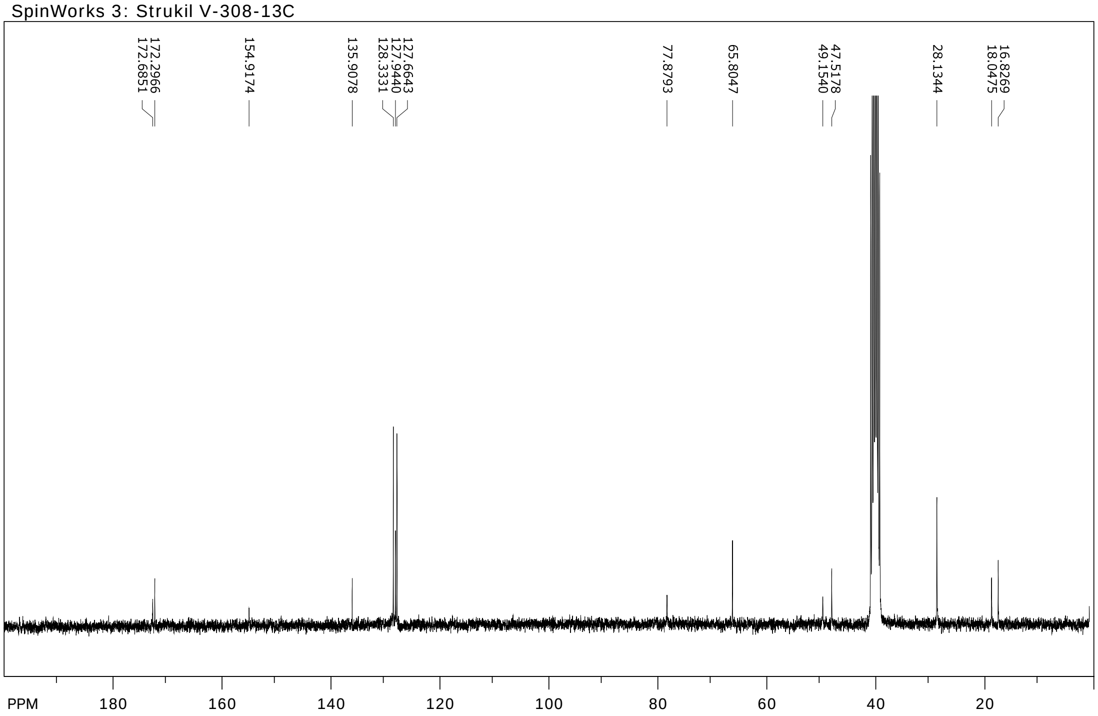
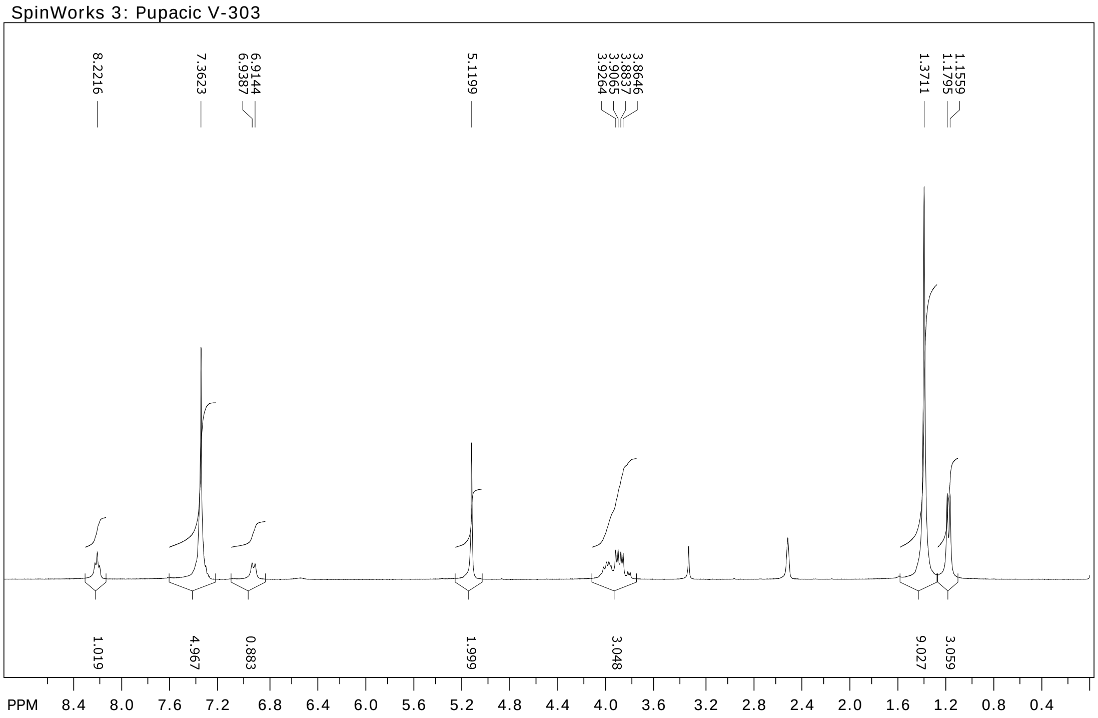


Figure S35. ^{1}H and ^{13}C NMR spectra of Boc-L-Ala-L-Ala-OBn (**10b**).



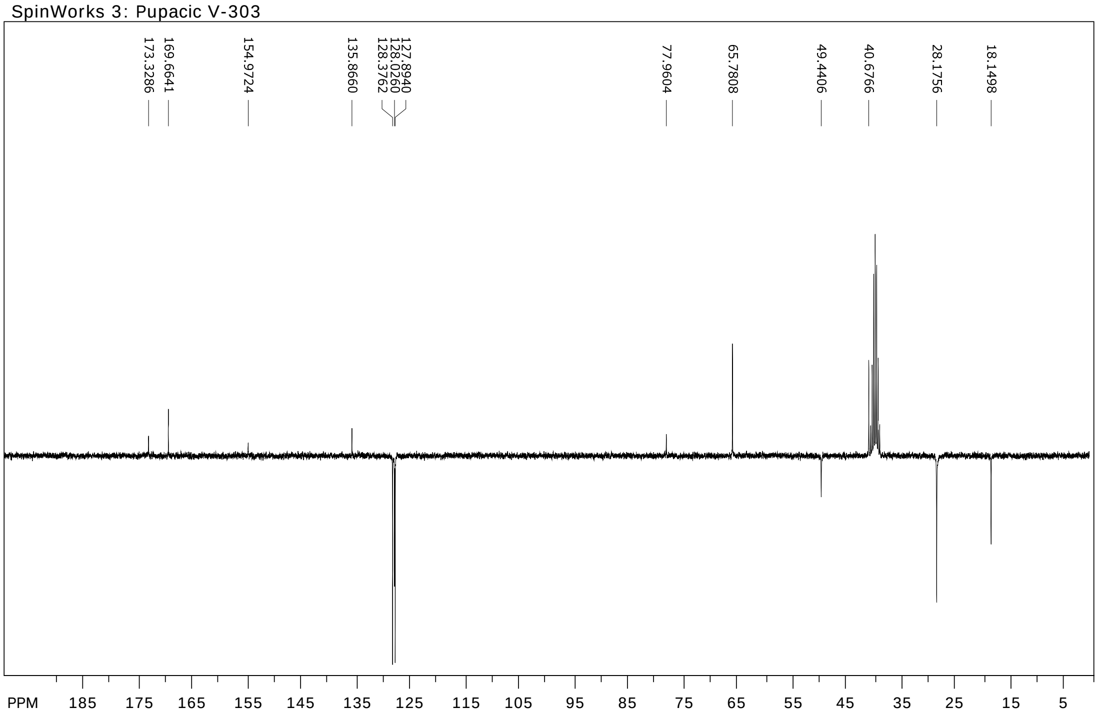


Figure S36. ^{1}H and ^{13}C NMR spectra of Boc-L-Ala-Gly-OBn (**10c**).

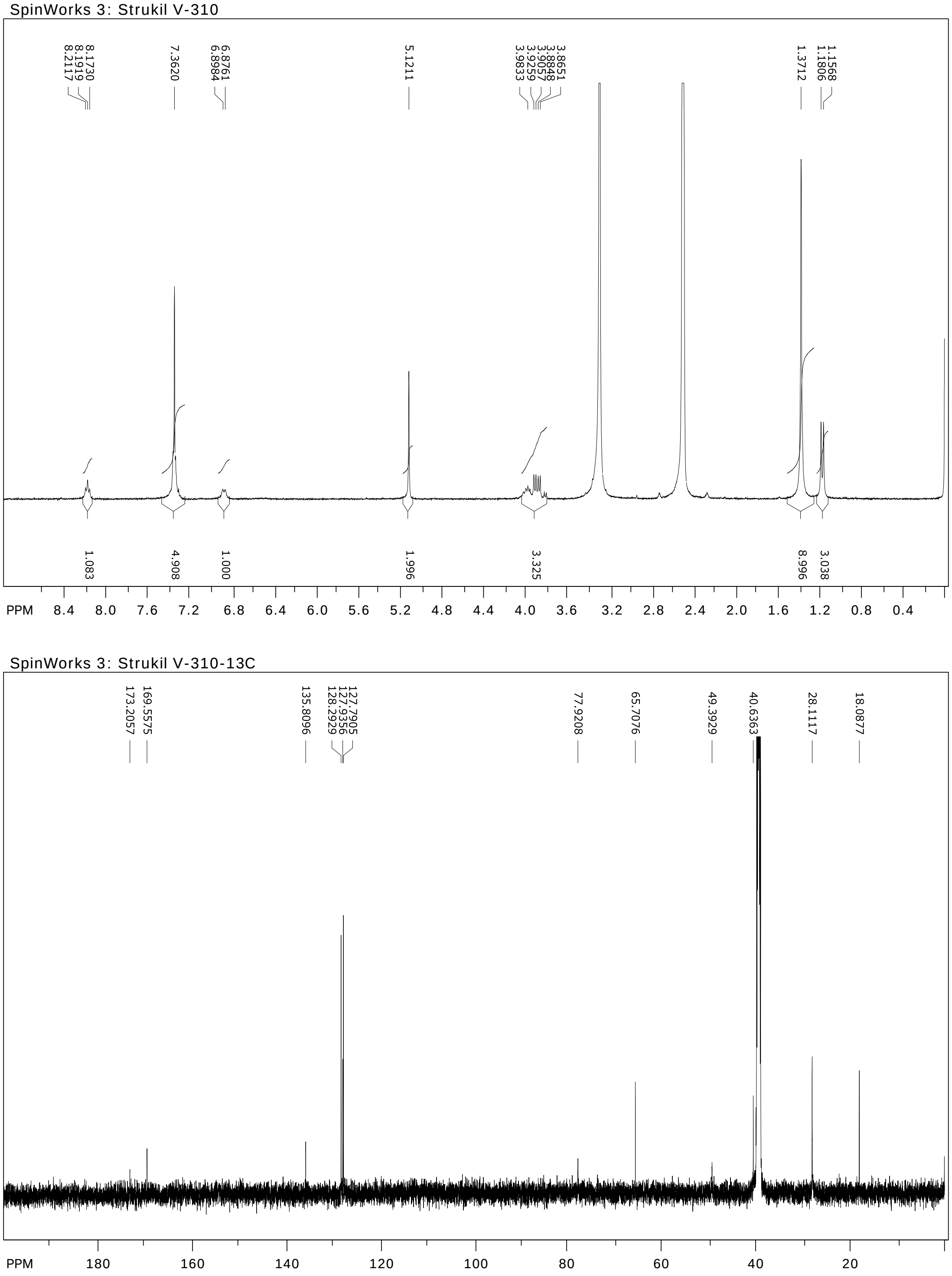


Figure S37. ^{1}H and ^{13}C NMR spectra of Boc-D-Ala-Gly-OBn (**10d**).

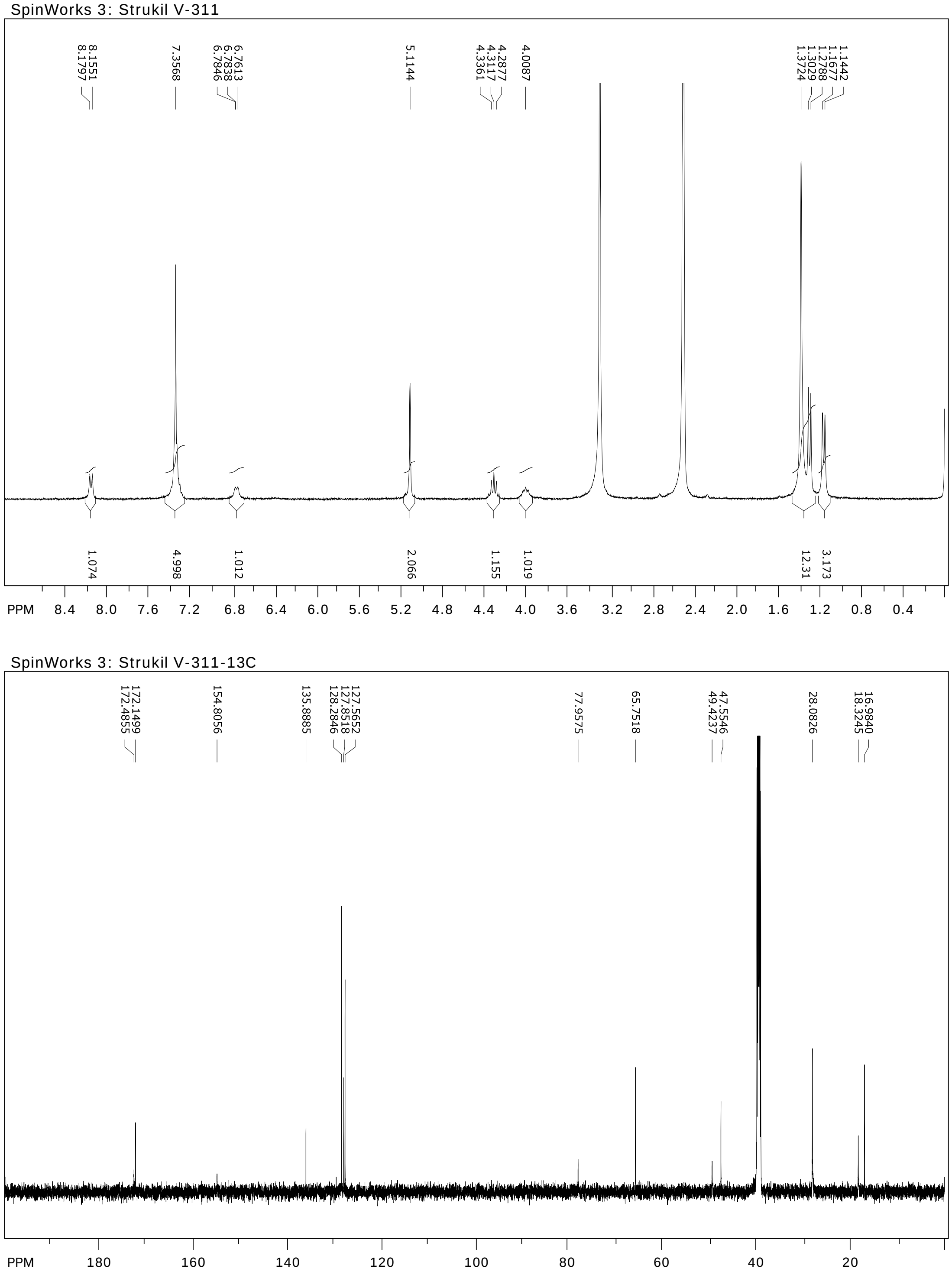


Figure S38. ^{1}H and ^{13}C NMR spectra of Boc-D-Ala-L-Ala-OBn (**10e**).

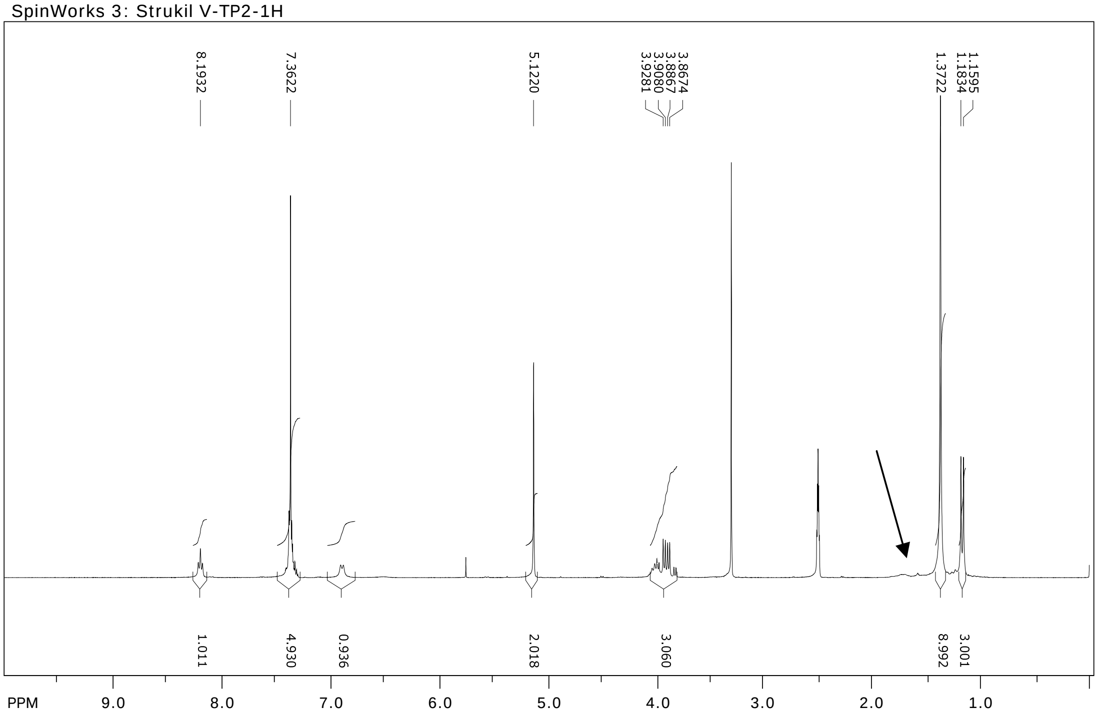


Figure S39. ^{1}H NMR spectrum of Boc-D-Ala-Gly-OBn (**10d**) obtained by solution synthesis in dichloromethane. The sample contains a small amount of *N,N'*-dicyclohexylurea as impurity (indicated by arrow).

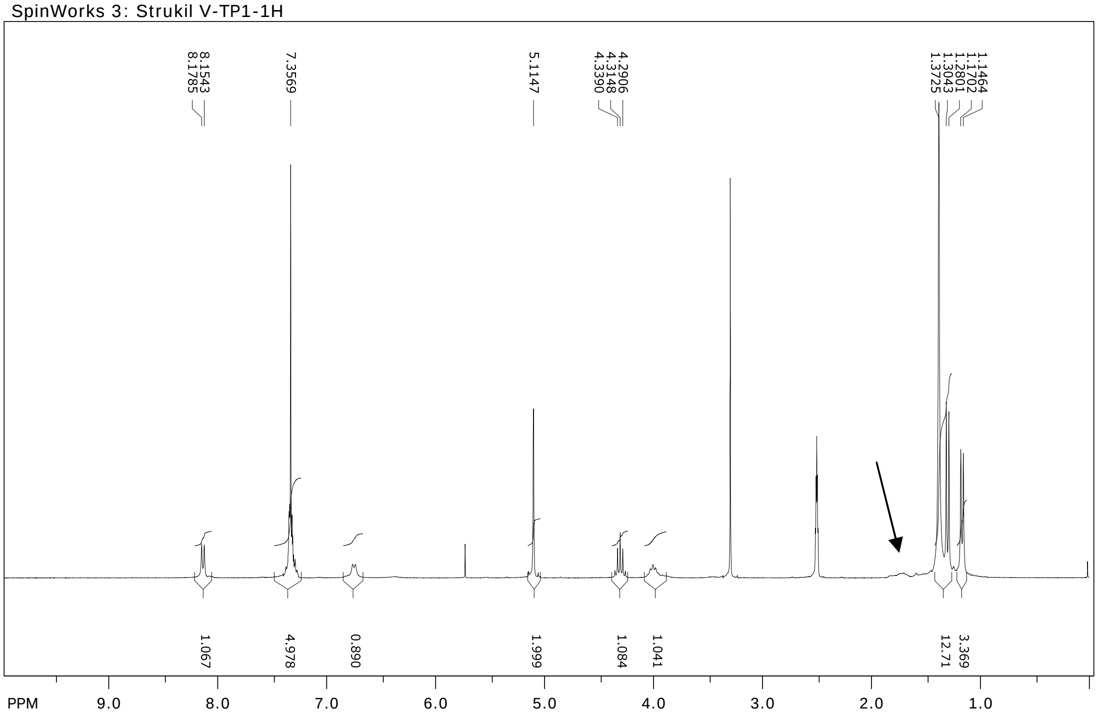


Figure S40. ^{1}H NMR spectrum of Boc-D-Ala-L-Ala-OBn (**10e**) obtained by solution synthesis in dichloromethane. The sample contains a small amount of *N,N'*-dicyclohexylurea as impurity (indicated by arrow).

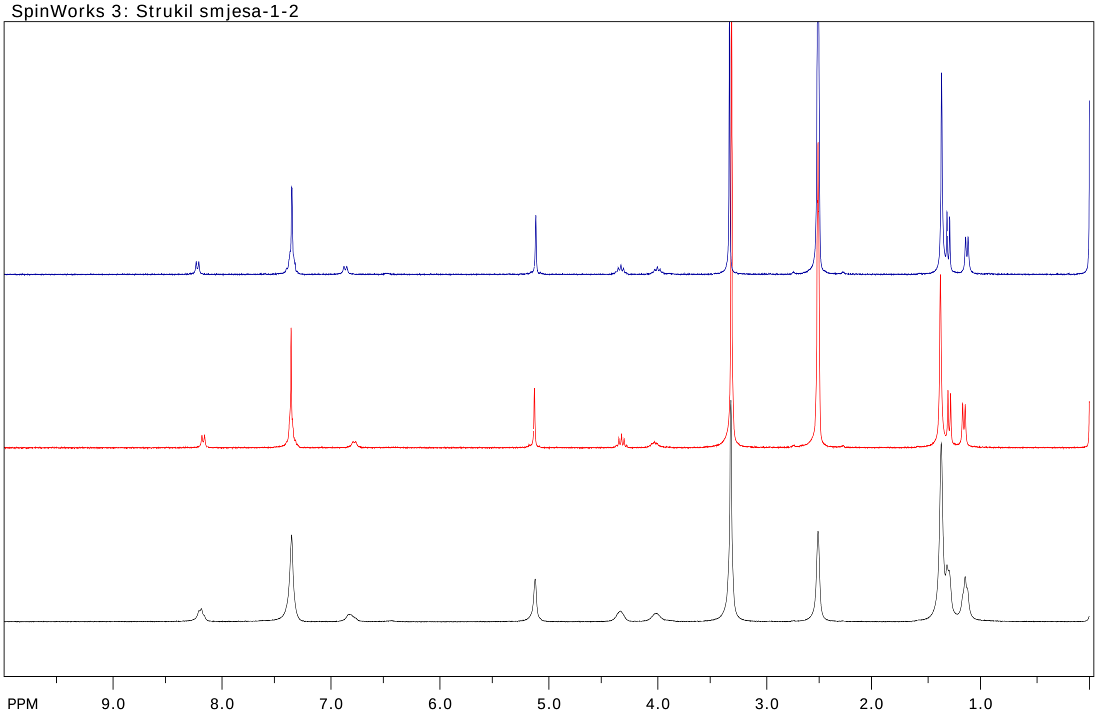


Figure S41. ^{1}H NMR spectrum of the 2:1 diastereomeric mixture of Boc-L-Ala-L-Ala-OBn (**10b**) and Boc-D-Ala-L-Ala-OBn (**10e**) (bottom). The samples of **10b** (blue) and **10e** (red) obtained by grinding are diastereomerically pure indicating that no racemisation occurs during mechanosynthesis of the corresponding dipeptides.

4. Powder and single crystal X-ray diffraction analysis of amides

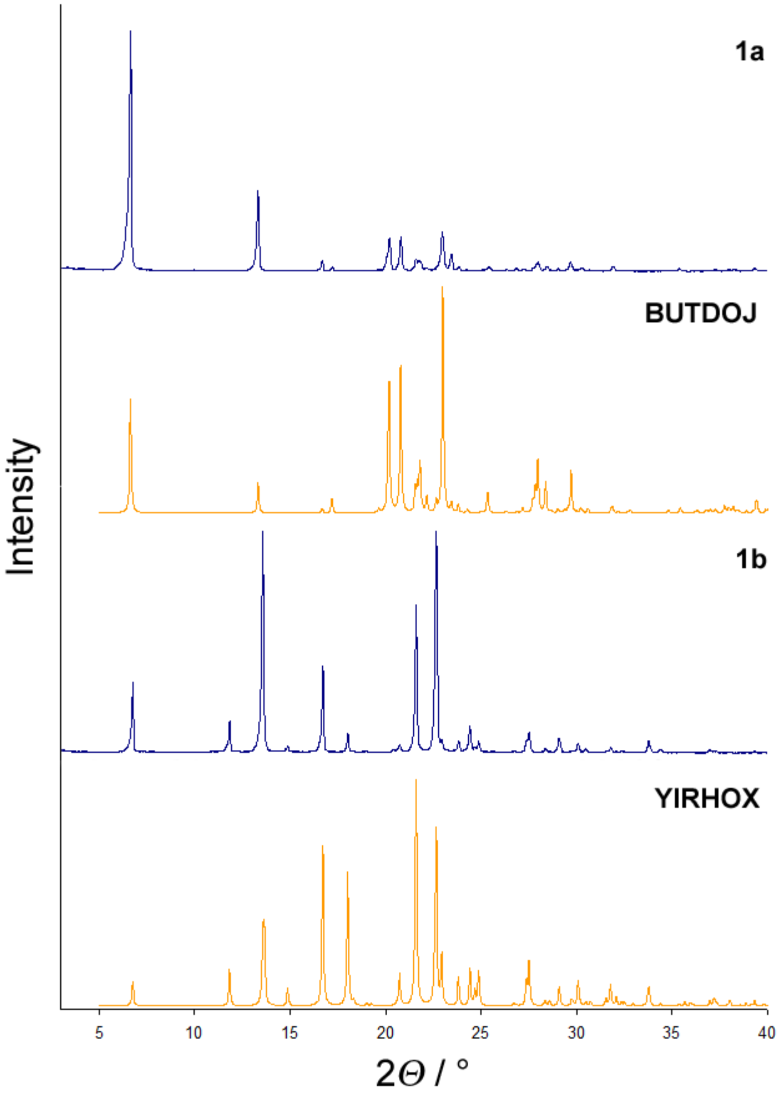


Figure S42. Comparison of measured (blue) and simulated PXRD patterns (orange) of *N*-(4-methoxyphenyl)benzamide (**1a**) and *N*-(4-methylphenyl)benzamide (**1b**).

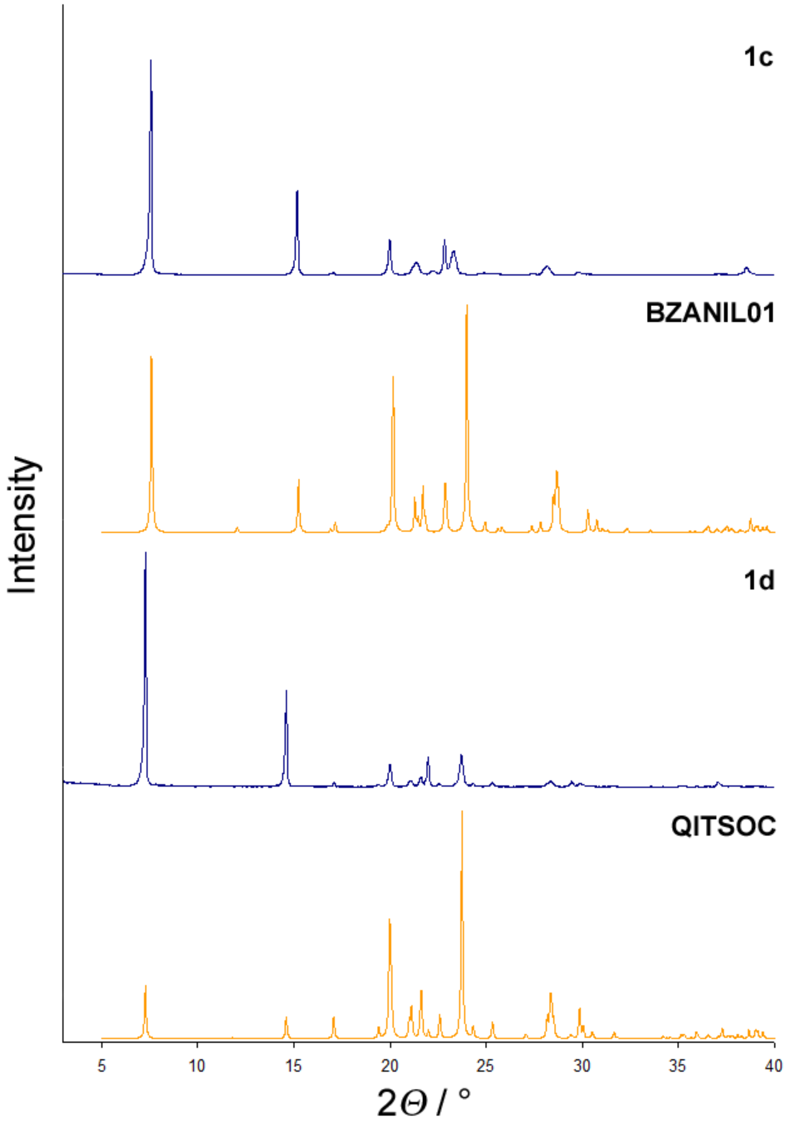


Figure S43. Comparison of measured (blue) and simulated PXRD patterns (orange) of *N*-phenylbenzamide (**1c**) and *N*-(4-fluorophenyl)benzamide (**1d**).

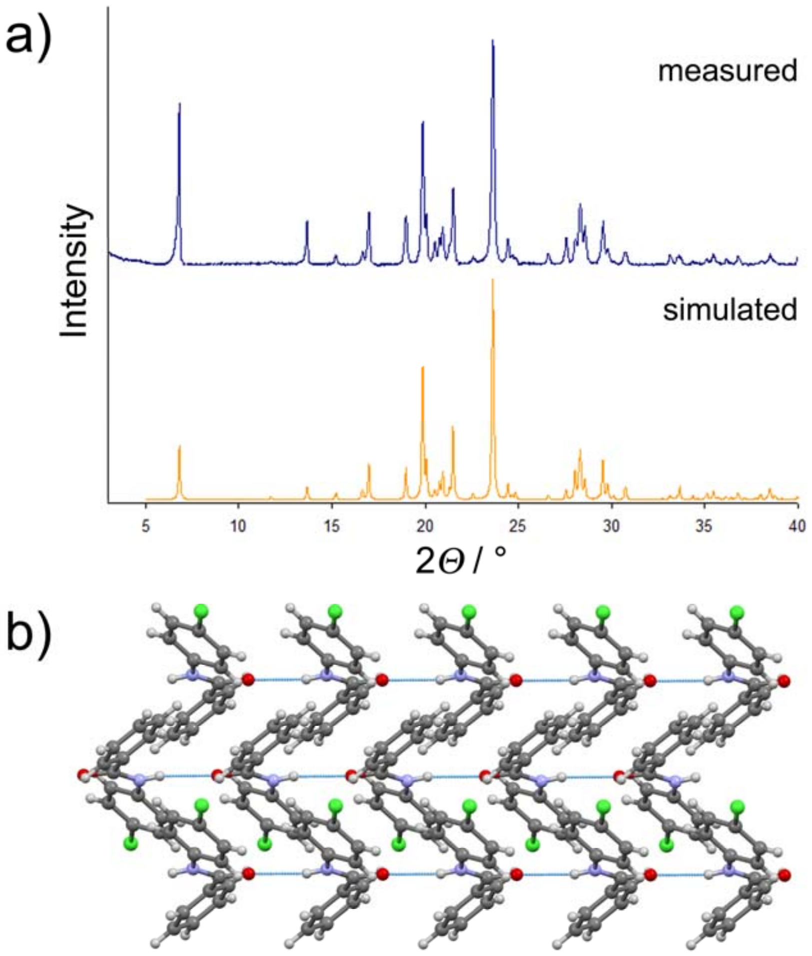


Figure S44. a) Comparison of measured (blue) and simulated PXRD patterns (orange) of *N*-(4-chlorophenyl)benzamide (**1e**). The structure of **1e** was determined from PXRD data collected on a typical laboratory diffractometer. b) Arrangement of **1e** molecules into 1-D antiparallel hydrogen-bonded arrays in the crystal structure. Hydrogen bonds are shown as light blue dashed lines.

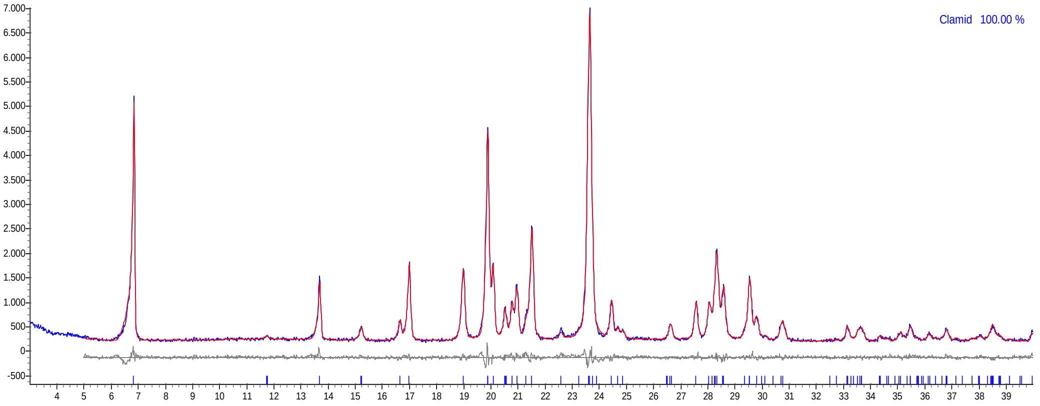


Figure S45. Rieveld plot for *N*-(4-chlorophenyl)benzamide (**1e**). Blue – measured, red – calculated, grey – difference. Calculated peak positions represented with tick marks.

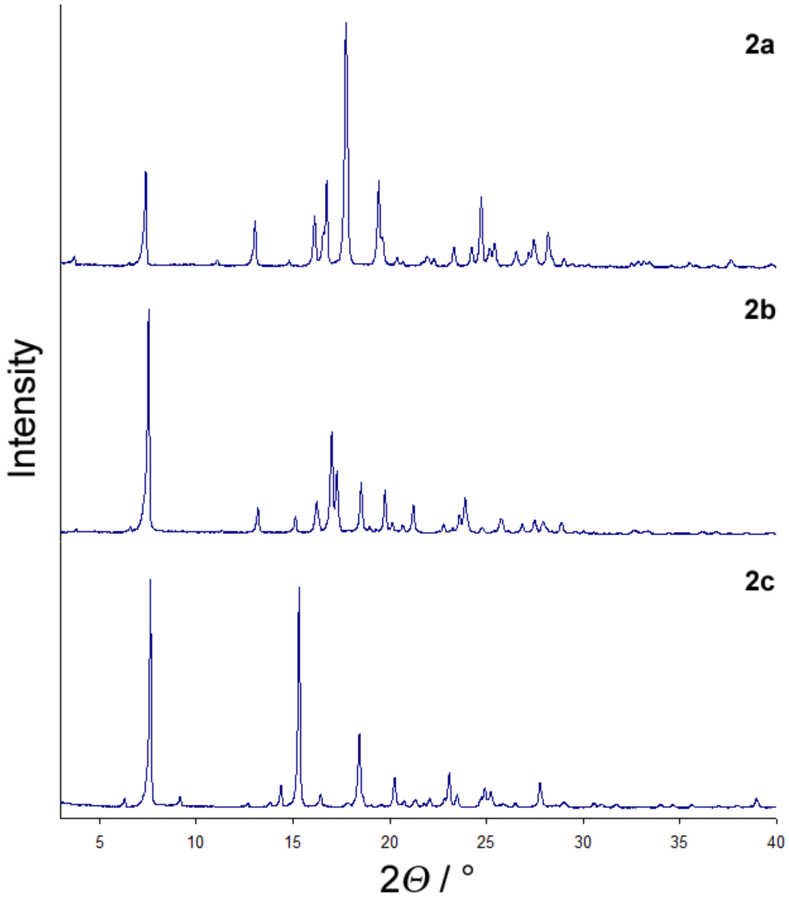


Figure S46. PXRD patterns of *N*-(4-methoxyphenyl)-1-naphthamide (**2a**), *N*-(4-methylphenyl)-1-naphthamide (**2b**) and *N*-phenyl-1-naphthamide (**2c**).

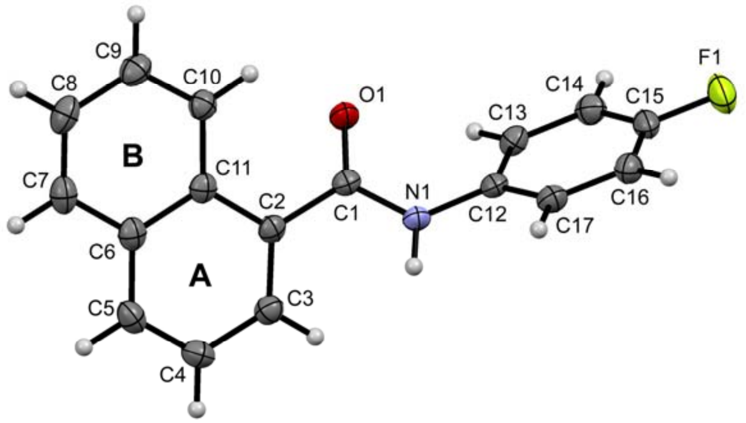


Figure S47. Molecular structure of *N*-(4-fluorophenyl)-1-naphthamide (**2d**) as determined by single-crystal X-ray diffraction (see Table S2).

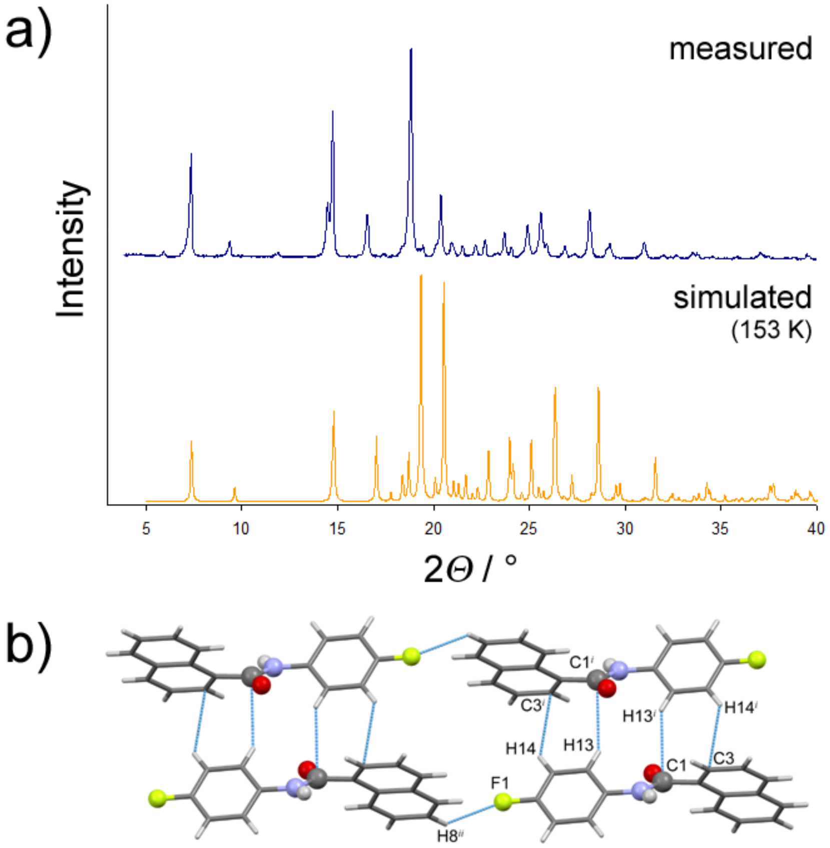


Figure S48. a) Comparison of measured (blue) and simulated PXRD patterns (orange) of *N*-(4-fluorophenyl)-1-naphthamide (**2d**). b) Interactions between **2d** molecules (shown as light blue dashed lines) involving weak C^{Ar}–H···F and C^{Ar}–H···π bonding. Symmetry codes: *i* = 1–*x*, –*y*, 1–*z*; *ii* = –1+*x*, –1+*y*, 1+*z*.

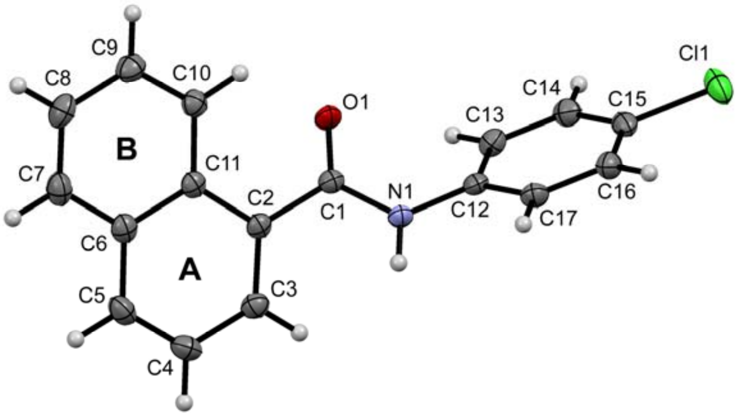


Figure S49. Molecular structure of *N*-(4-chlorophenyl)-1-naphthamide (**2e**) as determined by single-crystal X-ray diffraction (see Table S2).

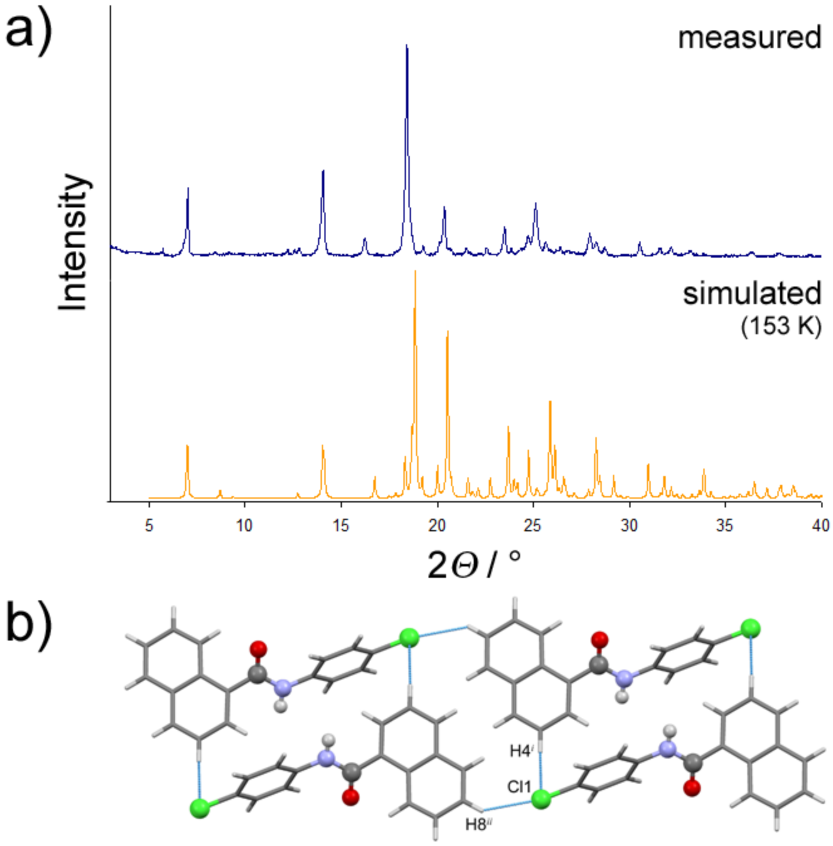


Figure S50. a) Comparison of measured (blue) and simulated PXRD patterns (orange) of *N*-(4-chlorophenyl)-1-naphthamide (**2e**). b) Interactions between **2e** molecules (shown as light blue dashed lines) involving weak C^{Ar}–H···Cl bonding. Symmetry codes: *i* = –*x*, 1–*y*, –*z*; *ii* = –1+*x*, –1+*y*, 1+*z*.

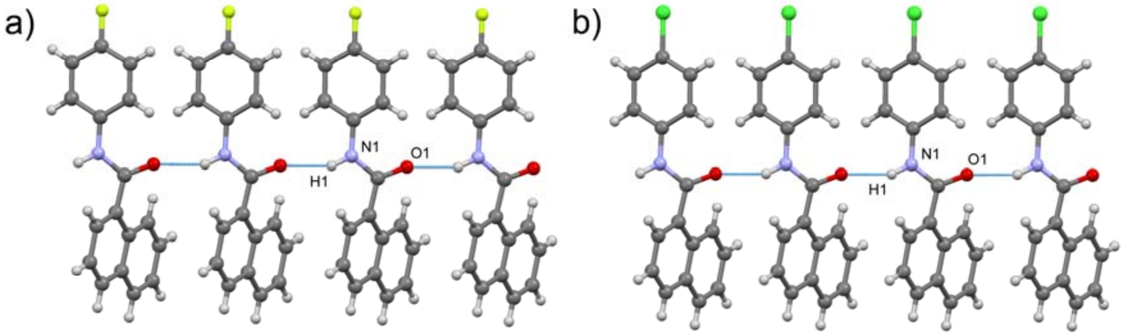


Figure S51. Characteristic C=O···H–N supramolecular C(4) synthon in crystal structures of a) *N*-(4-fluorophenyl)-1-naphthamide (**2d**) and b) *N*-(4-chlorophenyl)-1-naphthamide (**2e**). Hydrogen bonds (represented by light blue dashed lines) stretch along crystallographic *a*-axis.

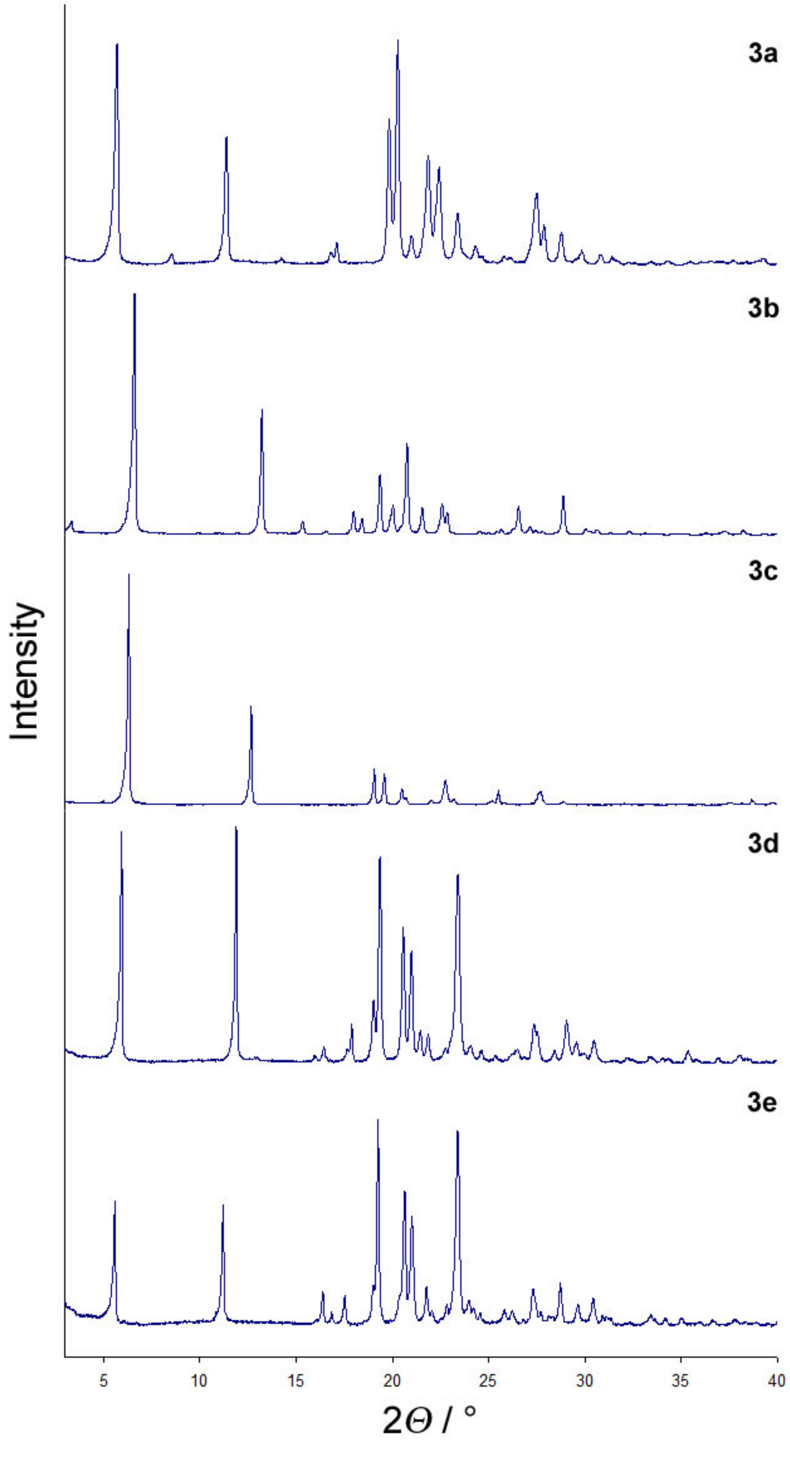


Figure S52. PXRD patterns of *N*-(4-methoxyphenyl)-2-naphthamide (**3a**), *N*-(4-methylphenyl)-2-naphthamide (**3b**), *N*-phenyl-2-naphthamide (**3c**), *N*-(4-fluorophenyl)-2-naphthamide (**3d**) and *N*-(4-chlorophenyl)-2-naphthamide (**3e**).

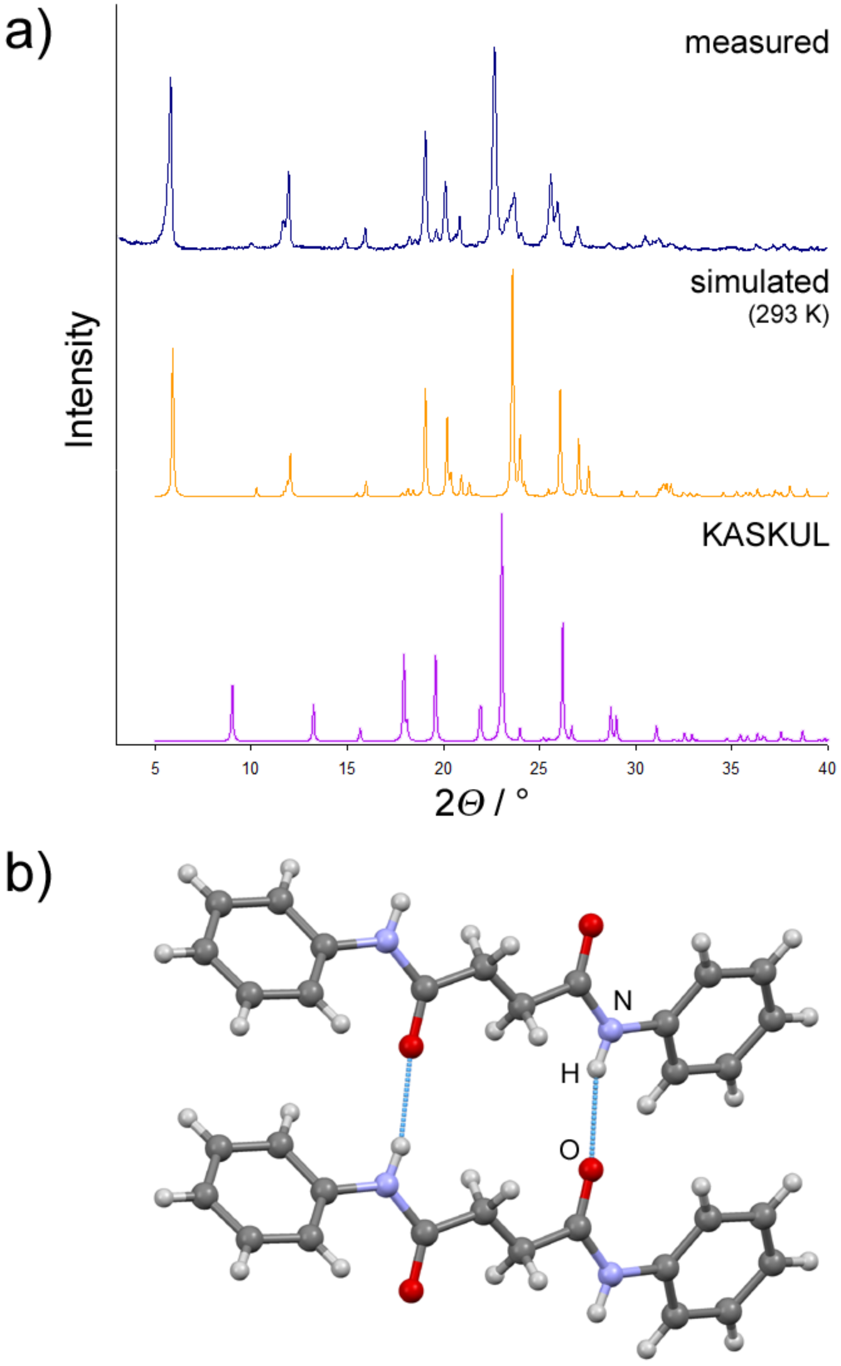


Figure S53. a) Comparison of measured and simulated PXRD patterns of *N,N'*-diphenylsuccinamide (**4**) prepared by grinding (blue) and recrystallisation of **4** from acetonitrile (orange) and known polymorph obtained by solution crystallisation from chloroform (purple, CCDC ref. code KASKUL).[8] b) Intermolecular hydrogen bonds between amide functionalities of succinamide molecules forming the characteristic $R_2^2(14)$ supramolecular synthon. Hydrogen bonds are shown as light blue dashed lines.

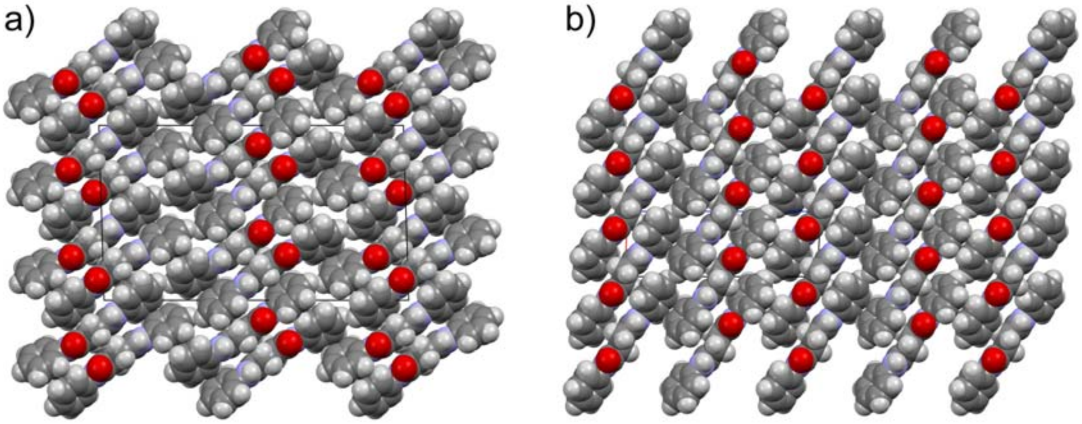


Figure S54. Crystal packing of *N,N′*-diphenylsuccinamide polymorphs. a) β-Polymorph obtained by grinding (**4**) and b) by crystallisation from chloroform solution (α-polymorph, CCDC ref. code KASKUL).[8] View down *b*-axis.

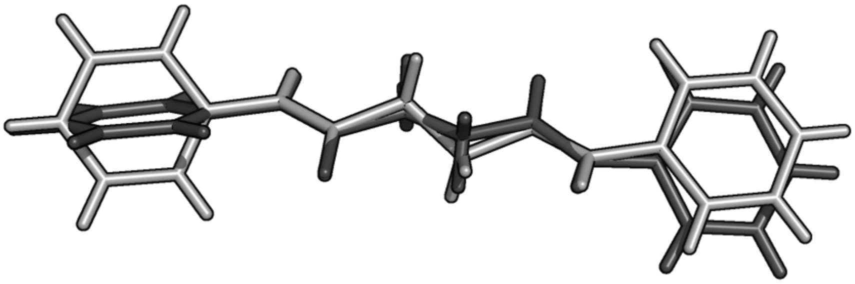


Figure S55. Differences in molecular structures of *N,N′*-diphenylsuccinamide (**4**) in the crystal structures of α-polymorph (KASKUL, light grey) and β-polymorph (this work, dark grey). are mostly reflected in the spatial arrangements of terminal phenyl rings.

Table S2. Crystallographic data for compounds **2d**, **2e** and **4**.

	2d	**2e**	**4**
Molecular formula	$C_{17}H_{12}ONF$	$C_{17}H_{12}ONCl$	$C_{16}H_{16}O_2N_2$
M_r	265.28	281.73	268.31
Crystal system	Triclinic	Triclinic	Monoclinic
Crystal size (mm^3)	0.50×0.20×0.10	0.47×0.40×0.16	0.80×0.05×0.05
Crystal habitus	Prism	Prism	Needle
Crystal colour	Colorless	Colorless	Colorless
Space group	$P\,-1$	$P\,-1$	$C\,2/c$
Temperature (K)	153	153	293
Unit cell dimensions (Å, °)			
a	5.0689(2)	5.04782(18)	17.179(4)
b	10.5607(5)	10.7197(4)	5.0906(7)
c	12.7211(6)	13.3908(6)	29.764(6)
α	71.230(5)	71.589(4)	90.00
β	80.914(4)	80.789(3)	91.721(19)
γ	82.591(4)	82.637(3)	90.00
Volume (Å^3)	634.45(5)	676.30(4)	2601.7(9)
Z	2	2	8
D_{calc} (g cm^{-3})	1.389	1.383	1.370
μ (mm^{-1})	0.097	0.276	0.092
$F(000)$	276	292	1136
Refl. collected/independent	6925/2216	7477/2358	2626/1421
No. observed refl. [$I>2\sigma(I)$]*	1921	2174	2626
No. restraints/No. parameters	0/181	0/181	0/182
R/wR [$I>2\sigma(I)$]*	0.0336/0.0876	0.0280/0.0784	0.1129/0.3349
R/wR [all data]	0.0395/0.0918	0.0307/0.0803	0.1720/0.3593
Goodness-of-fit on F^2	1.056	1.047	1.145
Largest diff. peak and hole (e Å^{-3})	0.156, −0.170	0.192, −0.258	0.379, −0.391

$^*R = \sum\|F_o|-|F_c\|/\sum F_o$, $w = 1/[\sigma^2(F_o^2)+(g_1P)^2+ g_2P]$ where $P = (F_o^2+2F_c^2)/3$, $S = \Sigma[w(F_o^2 - F_c^2)^2/(N_{obs} - N_{param})]^{1/2}$.

Table S3. Crystallographic and Rietveld refinement data for **1e** and **6a** .

	1e	**6a**
Molecular formula	$C_{13}H_{10}ONCl$	$C_{11}H_{13}O_2N$
M_r	231.68	191.23
Space group	$P\bar{1}$	*Pccn*
Temperature (K)	293	293
Unit cell dimensions (Å, °)		
a	5.3878(2)	20.1273(5)
b	7.8685(3)	10.3703(3)
c	13.6864(8)	9.4507(8)
α	73.106(5)	90
β	98.757(4)	90
γ	90.614(2)	90
Volume (Å^3)	548.36(5)	1972.6(2)
Z	1	1
D_{calc} (g cm^{-3})	1.403	1.288
Wavelength (Å)		1.54056
R-exp (%)*	4.62	3.97
R-p (%)*	4.92	9.76
R-wp (%))*	6.59	12.76
R-F^2 (%)*	1.1	5.3
GOF	1.43	3.21
Starting angle (° 2θ)	3	3
Final angle (° 2θ)	40	40
Step width (° 2θ)	0.016	0.016
No. of variables	128	111

* as defined in Topas

References

1. CrysAlis Software system, Version 1.171.33.32, Xcalibur CCD system, Oxford Diffraction Ltd. 2009, Abingdon, UK
2. G. M. Sheldrick, *Acta Cryst.*, 2008, **A64**, 112.
3. L. J. Farrugia, *J. Appl. Cryst*., 1999, **32**, 837.
4. A. L. Spek, *Acta Cryst.*, 2009, **D65**, 148.
5. C. F. Macrae, P. R. Edgington, P. McCabe, E. Pidcock, G. P. Shields, R. Taylor, M. Towler and J. van de Streek, *J. Appl. Cryst.*, 2006, **39**, 453.
6. PyMOL, The PyMOL Molecular Graphics System, Version 1.5.0.4, Schrödinger, LLC.
7. Y. S. Klausner and M. Bodansky, *Synthesis*, 1972, **4**, 453.
8. S. Anjum, M. Iqbal Choudhary, S. Ali, H. -K. Funb and A. Rahmana, *Acta Cryst.*, 2005, **E61**, o3001.