Supplementary Information

Mechanosynthesis of pharmaceutically relevant sulfonyl-(thio)ureas

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1. Experimental Section

Mechanosynthesis of sulfonyl-(thio)ureas was carried out in a Retsch MM400 mill at a frequency of 30 Hz using a 10 mL stainless steel milling jar and a single ball made of the same material (10 mm diameter). Gram-scale synthesis reactions were carried out in a 25 mL stainless steel milling jar. ^{1}H and ^{13}C NMR spectra were recorded on a Varian MERCURY plus-300 or plus-400 spectrometer (300 or 400 MHz) with chemical shifts (δ) given in parts per million (ppm). The molecular weights of the pure products were determined using high-resolution mass spectra (HRMS). FT-IR spectra were collected using a Fourier Transform-Infrared Attenuated Total Reflection PerkinElmer UATR Two spectrometer in the range 400 cm^{-1} to 4000 cm^{-1}.

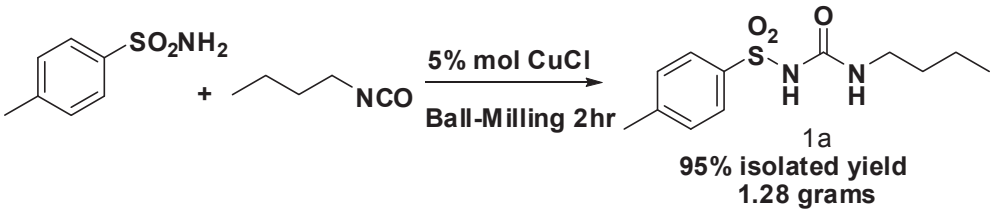
1.1 Mechanosynthesis by copper-catalysed coupling

A mixture of 0.50 mmol of sulfonamide, 0.50 mmol isocyanate (1 equiv), 0.025 mmol (5% mol) of CuCl and nitromethane as the grinding liquid (η= 0.25 mL mg^{-1}) was milled at a frequency of 30 Hz for 2 hrs. After the reaction, 3 mL of deionized water and 20 mg of $Na_2H_2EDTA{\cdot}2H_2O$ were added to the green coloured crude mixture which was then milled for further 10 minutes at a frequency of 25 Hz. The resulting white product was purified by vacuum filtration and dried in air in all cases, except for glibenclamide **3b** where the formation of the sideproduct dicyclohexylurea requires chromatography.

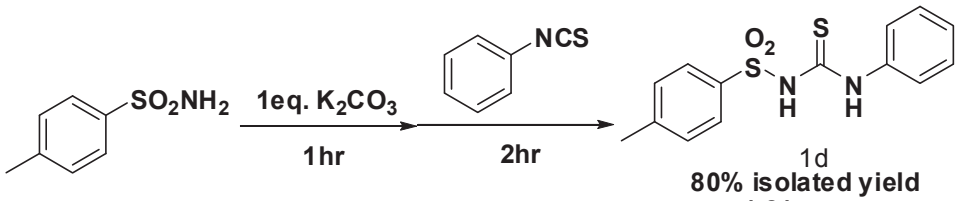
1.2 Base-assisted mechanosynthesis using K_2CO_3

A mixture of 0.50 mmol of sulfonamide and 0.50 mmol of K_2CO_3 (1 equiv) was milled at a frequency of 30 Hz for 1hr. Then, 0.50 mmol isocyanate or isothiocyanate (1 equiv) was added and subsequently milled for another 2 hrs at 30 Hz. 20 mL of deionized water and dilute HCl was added to the crude mixture. The pH of the resultant suspension was set to pH=3 using pH paper and left to stir for 15 mins. The product was isolated via vacuum filtration and dried in air in all cases, except for the sulfonyl-urea **1d** where the formation of the sideproduct diphenylurea requires chromatography.

1.3 Gram-scale synthesis



1a
95% isolated yield
1.28 grams



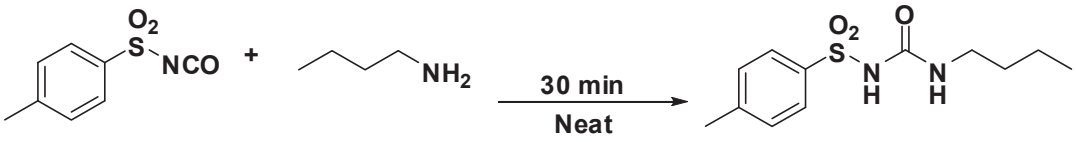
1d
80% isolated yield
1.21 grams

For gram-scale synthesis of tolbutamide (**1a**) 5.0 mmol of sulfonamide, 5.0 mmol isocyanate (1 equiv), 0.25 mmol (5% mol) of CuCl and nitromethane as the grinding liquid (η= 0.25 mL mg^{-1}) was milled at a frequency of 30 Hz for 2 hrs. The reaction was carried out using two 10 mm diameter stainless steel balls in a 25 mL stainless steel jar. After the reaction, 15 mL of deionised water and 200 mg of $Na_2H_2EDTA.2H_2O$ were added to the green coloured crude mixture which was then milled for 10 minutes more at a frequency of 25 Hz. The white product was purified via vacuum filtration and dried in air.

For the gram-scale synthesis of **1b**, a mixture of 5.0 mmol of sulfonamide and 5.0 mmol of K_2CO_3 (1 equiv) was milled at a frequency of 30 Hz for 1 hour. Then, 5.0 mmol isothiocyanate (1 equiv) was added and subsequently milled for another 2 hrs at 30 Hz. 20

mL of deionized water and dilute HCl were added to the crude mixture. The pH of the resultant suspension was set to pH=3 using pH paper and left to stir for 15 mins. The product was purified via vacuum filtration and dried in air.

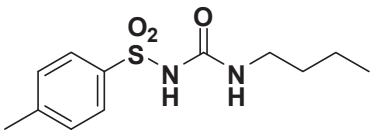
1.4 Pathway B for the synthesis of tolbutamide (1a)



The mechanosynthesis of tolbutamide **1a** (93% yield) was also explored by milling *p*-toluenesulfonyl-isocyanate and *n*-butyl-amine (retrosynthetic pathway B in the main paper). The high reactivity and moisture sensitive nature of *p*-toluenesulfonyl-isocyanate meant that reaction mixture preparation had to be done in a glovebox. Sulfonyl-isocyanates (mostly liquids) in general are less ideal, in terms of ease of handling and toxicity, as compared to sulfonamides (mostly solids).

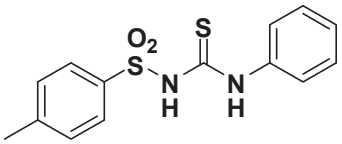
2. Summary of ^{1}H and ^{13}C NMR and HR-MS data

N-(butylcarbamoyl)-4-methylbenzenesulfonamide 1a



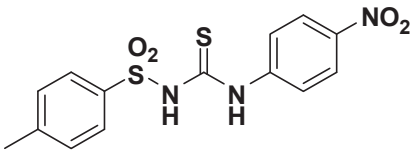
White powder (92% yield); **^{1}H-NMR** (400 MHz, DMSO-*d6*) δ 0.79 (t, *J* = 7.20Hz, 3H), δ 1.11-1.18 (m, 2H), δ 1.23-1.30 (m, 2H), δ 2.37 (s, 3H), δ 2.88-2.93 (m, 2H), δ 6.41 (t, *J* = 5.80Hz, 1H), δ 7.38 (d, *J* = 8.00Hz, 2H), 7.75 (d, *J* = 7.6Hz, 2H), δ 10.45 (s, 1H); **^{13}C-NMR** (300 MHz, DMSO-*d6*) δ 14.0, 19.7, 21.5, 31.7, 39.2, 127.6, 129.8, 137.9, 143.9, 151.7. **HRMS**: Calculated for $C_{12}H_{18}N_2NaO_3S$ [M+Na]: 293.0930; measured: 293.0925.

4-methyl-*N*-(phenylcarbamothioyl)benzenesulfonamide 1b



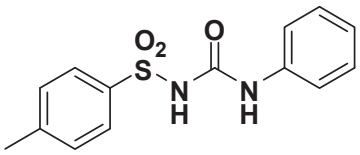
White powder (91% yield); **^{1}H-NMR** (400 MHz, DMSO-*d6*) δ 2.38 (s, 3H), δ 7.16 (t, *J* = 7.26Hz, 1H), δ 7.39-7.43 (m, 4H), δ 7.28-7.36 (m, 2H), δ 7.81 (d, *J* = 8.37Hz, 2H), δ 10.14 (s, 1H); **^{13}C-NMR** (300 MHz, DMSO-*d6*) δ 21.5, 119.4, 124.5, 126.2, 128.2, 129.0, 129.9, 138.5, 144.3, 178.0; **HRMS**: Calculated for $C_{14}H_{14}N_2NaO_2S_2$ [M+Na]: 329.0389; measured: 329.0390.

4-methyl-*N*-(4-nitrophenylcarbamothioyl)benzenesulfonamide 1c



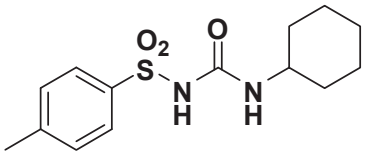
Yellow powder (80% yield); **^{1}H-NMR** (400 MHz, DMSO-*d6*) δ 2.31 (s, 3H), δ 7.18 (d, *J* = 8.12Hz, 2H), δ 7.63 (d, *J* = 8.40Hz, 2H),7.95-8.04 (m, 4H), δ 9.66 (s, 1H); **^{13}C-NMR** (300 MHz, DMSO-*d6*) δ 21.1, 118.6, 124.9, 127.9, 128.3, 140.0, 142.1, 147.8, 183.0; **HRMS**: Calculated for $C_{14}H_{12}N_3O_4S_2$ [M+Na]: 350.0275; measured: 350.0272.

4-methyl-*N*-(phenylcarbamoyl)benzenesulfonamide 1d



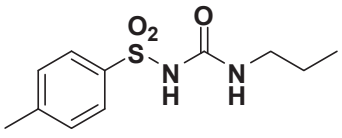
^{1}H-NMR (400 MHz, DMSO-*d6*) δ 2.37, δ 6.99 (t, *J* = 4.00 Hz, 1H), δ 2.37 δ 2.37 δ 7.37-7.41 (m, 4H), δ 7.20-7.33 (m, 2H), δ 7.82 (d, *J* = 7.84Hz, 2H), δ 8.78 (s, 1H), δ 10.63 (s, 1H); **^{13}C-NMR** (300 MHz, DMSO-*d6*) δ 21.5, 119.3, 123.5, 126.1, 127.9, 129.9, 137.7, 138.6, 144.1, 150.0 ppm. HRMS: Calculated for $C_{14}H_{14}N_2NaO_3S$ [M+Na]: 313.0617; measured: 313.0614.

***N*-(cyclohexylcarbamoyl)-4-methylbenzenesulfonamide 1e**



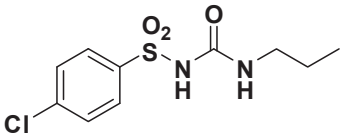
White powder (88% yield); **^{1}H-NMR** (400 MHz, DMSO-*d6*) δ 1.02-1.25 (m, 5H), δ 1.22-1.66 (m, 5H), δ 2.37 (s, 3H), δ 3.25 (d, *J* = 7.28Hz, 1H), δ 6.30 (d, *J* = 8.40Hz, 1H) δ 7.38 (d, *J* = 8.00Hz, 2H), 7.75 (d, *J* = 7.60Hz, 2H), δ 10.26 (s, 1H); **^{13}C-NMR** (300 MHz, DMSO-*d6*) δ 21.5, 24.6, 25.4, 32.7, 48.5, 127.6, 129.9, 137.9, 144.0, 150.9. **HRMS**: Calculated for $C_{14}H_{20}N_2NaO_3S$ [M+Na]: 319.1087; measured: 319.1082.

4-methyl-*N*-(propylcarbamoyl)benzenesulfonamide 1f



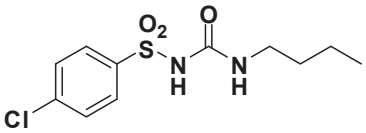
White powder (86% yield) **^{1}H-NMR** (400 MHz, DMSO-*d6*) δ 0.73 (t, *J* = 7.00Hz, 3H), δ 1.28-1.32 (m, 2H), δ 2.37 (s, 3H), δ 2.84-2.91 (m, 2H), δ 6.42 (t, *J* = 5.80Hz, 1H), δ 7.38 (d, *J* = 8.00Hz, 2H), 7.75 (d, *J* = 7.6Hz, 2H), δ 10.46 (s, 1H); **^{13}C-NMR** (300 MHz, DMSO-*d6*) δ 11.4, 21.4, 23.0, 41.2, 127.6, 129.7, 137.7, 143.7, 151.7; **HRMS**: Calculated for $C_{11}H_{16}N_2NaO_3S$ [M+Na]: 279.0774; measured: 279.0764.

4-chloro-*N*-(propylcarbamoyl)benzenesulfonamide 2a



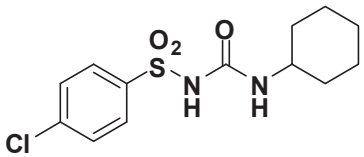
White powder (92% yield); **^{1}H-NMR** (400 MHz, DMSO-*d6*) δ 0.73 (t, *J* = 7.48Hz, 3H), δ 1.26-1.35 (m, 2H) δ 2.85-2.89 (m, 3H), δ 6.51 (t, *J* = 5.80Hz, 1H), δ 7.67 (d, *J* = 8.36Hz, 2H), δ 7.88 (d, *J* = 7.96Hz, 2H), δ 10.66 (s, 1H); **^{13}C-NMR** (300 MHz, DMSO-*d6*) δ 11.5, 22.9, 41.4, 129.6, 129.7, 138.5; **HRMS**: Calculated for $C_{10}H_{13}ClN_2NaO_3S$ [M+Na]: 299.0228; measured: 299.0229.

***N*-(butylcarbamoyl)-4-chlorobenzenesulfonamide 2b**



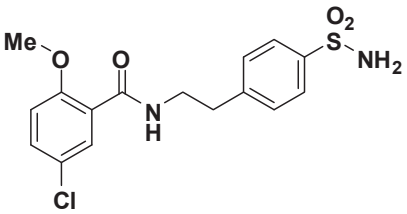
Off-white powder (92% yield); **^{1}H-NMR** (400 MHz, DMSO-*d6*) δ 0.79 (t, *J* = 7.20Hz, 3H), δ 1.10-1.18 (m, 2H), δ 1.22-1.30 (m, 2H), δ 2.88-2.93 (m, 2H), δ 6.50 (t, *J* = 5.80Hz, 1H), δ 7.67 (d, *J* = 8.00Hz, 2H), 7.88 (d, *J* = 7.6Hz, 2H), δ 10.64 (s, 1H); **^{13}C-NMR** (300 MHz, DMSO-*d6*) δ 13.9, 19.7, 31.1, 31.7, 129.6, 129.7, 138.4, 139.6, 151.7; **HRMS**: Calculated for $C_{11}H_{15}ClN_2NaO_3S$ [M+Na]: 313.0384; measured: 313.0376.

4-chloro-*N*-(cyclohexylcarbamoyl)benzenesulfonamide 2c



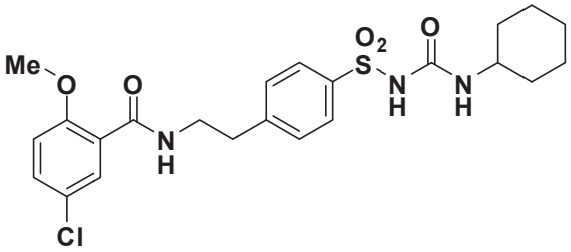
White powder (91% yield); **^{1}H-NMR** (400 MHz, DMSO-*d6*) δ 1.03-1.22 (m, 5H), δ 1.46-1.66 (m, 5H), δ 3.26 (d, *J* = 7.28Hz, 1H), δ 6.39 (d, *J* = 8.40Hz, 1H) δ 7.66 (d, *J* = 8.28Hz, 2H), 7.88 (d, *J* = 8.64Hz, 2H), δ 10.44 (s, 1H)**^{13}C-NMR** (300 MHz, DMSO-*d6*) δ 24.6, 25.4, 32.7, 48.6, 129.6, 129.7, 138.4; **HRMS**: Calculated for $C_{13}H_{17}ClN_2NaO_3S$ [M+Na]: 339.0541; measured: 339.0541.

5-chloro-2-methoxy-*N*-(4-sulfamoylphenethyl)benzamide 3a



White powder (74% yield); **^{1}H-NMR** (400 MHz, DMSO-*d6*) δ 2.89 (t, *J* = 7.04Hz, 2H), δ 3.48-3.53 (m, 2H), δ 3.79 (s, 3H) δ 7.14 (d, *J* = 8.96Hz, 2H), δ 7.29 (s, 2H), δ 7.43 (d, *J* = 8.24Hz, 2H), δ 7.47-7.50 (m, 1H), δ 7.62 (d, *J* = 2.84Hz, 1H), δ 7.74 (d, *J* = 8.12Hz, 2H), δ 8.25 (t, *J* = 5.52Hz, 1H); **^{13}C-NMR** (300 MHz, DMSO-*d6*) δ 35.1, 56.7, 114.6, 124.8, 125.3, 126.1, 129.6, 130.0, 131.2, 142.5, 144.1, 156.1, 164.0. **HRMS**: Calculated for $C_{16}H_{17}ClN_2NaO_4S$ [M+Na]: 391.0490; measured: 391.0478.

5-chloro-*N*-(4-(*N*-(cyclohexylcarbamoyl)sulfamoyl)phenethyl)-2-methoxybenzamide 3b



White powder; **^{1}H-NMR** (400 MHz, DMSO-*d6*) δ 1.03-1.22 (m, 5H), δ 1.46-1.66 (m, 5H), 2.89 (t, *J* = 7.04Hz, 2H),), δ 3.26 (d, *J* = 7.28Hz, 1H), δ 3.48-3.53 (m, 2H), δ 3.79 (s, 3H) δ 7.14 (d, *J* = 8.96Hz, 2H), δ 7.43 (d, *J* = 8.24Hz, 2H), δ 7.47-7.50 (m, 1H), δ 7.62 (d, *J* = 2.84Hz, 1H), δ 7.74 (d, *J* = 8.12Hz, 2H), δ 8.25 (t, *J* = 5.52Hz, 1H); **^{13}C-NMR** (300 MHz, DMSO-*d6*) δ 24.6, 25.4, 31.2, 32.7, 35.1, 48.5, 56.7, 114.6, 124.7, 125.3, 127.7, 129.8, 129.9, 131.9, 138.6, 145.7, 150.8, 156.1, 164.0; **HRMS**: Calculated for $C_{23}H_{28}ClN_3NaO_5S$ [M+Na]: 516.1330; measured: 516.1331.

3. Selected Fourier-transform attenuated total reflectance (FTIR-ATR) spectra

According to powder X-ray diffraction the crude reaction mixtures were amorphous and we were not able to detect product formation by solid-state diffraction methods. However, comparisons of FTIR-ATR spectra of crude reaction mixtures from both base-assisted and copper-catalysed reactions showed that all of the iso(thio)cyanate had been consumed by the disappearance of the characteristic absorption band around 2200 cm^{-1}.

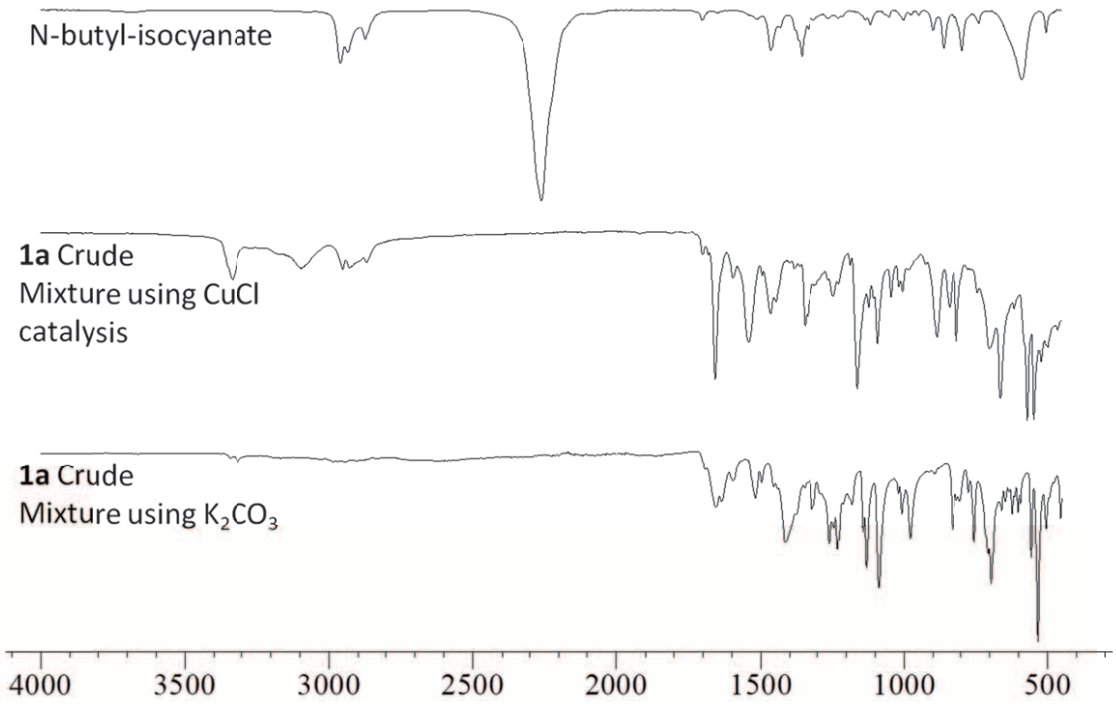


Figure S1. FTIR-ATR spectra for *n*-butylisocyanate reactant and the freshly prepared crude reaction mixture from the synthesis of tolbutamide (**1a**) via base-assisted and copper-catalysed routes. The disappearance of the isocyanate stretching band at 2200 cm^{-1} is evident in both cases.

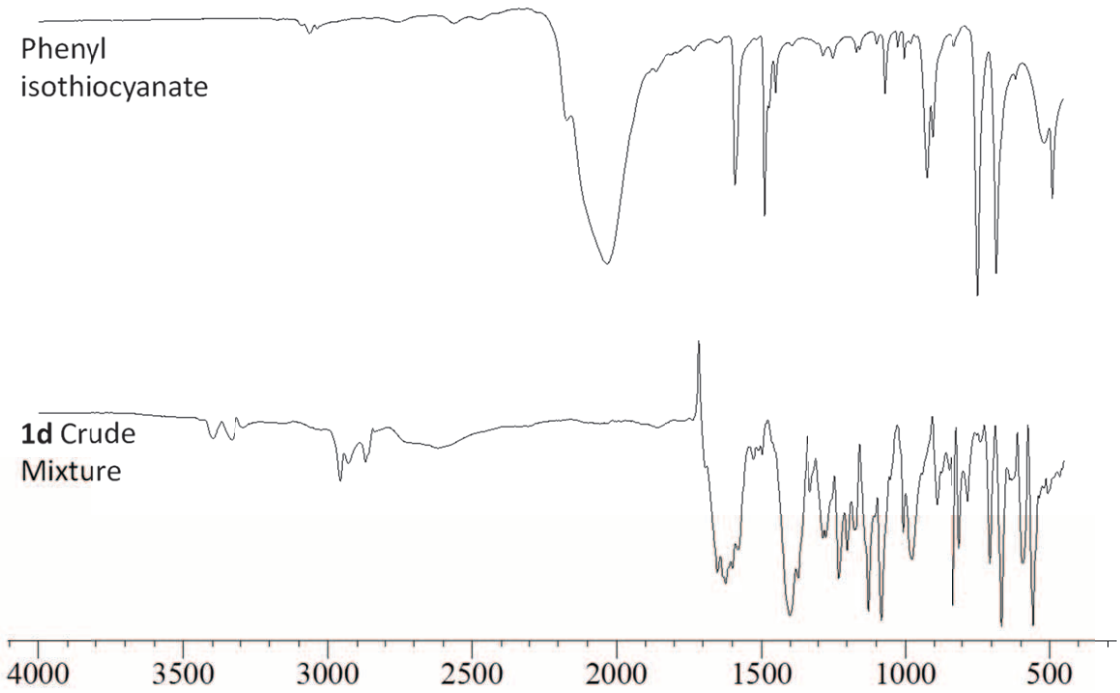


Figure S2. FTIR-ATR spectra for phenyl-isothiocyanate reactant and the freshly prepared crude reaction mixture from the synthesis of the sulfonyl-thiourea **1d** via base-assisted mechanochemical route. The disappearance of the thioisocyanate stretching band at ca. 2000 cm^{-1} is evident.

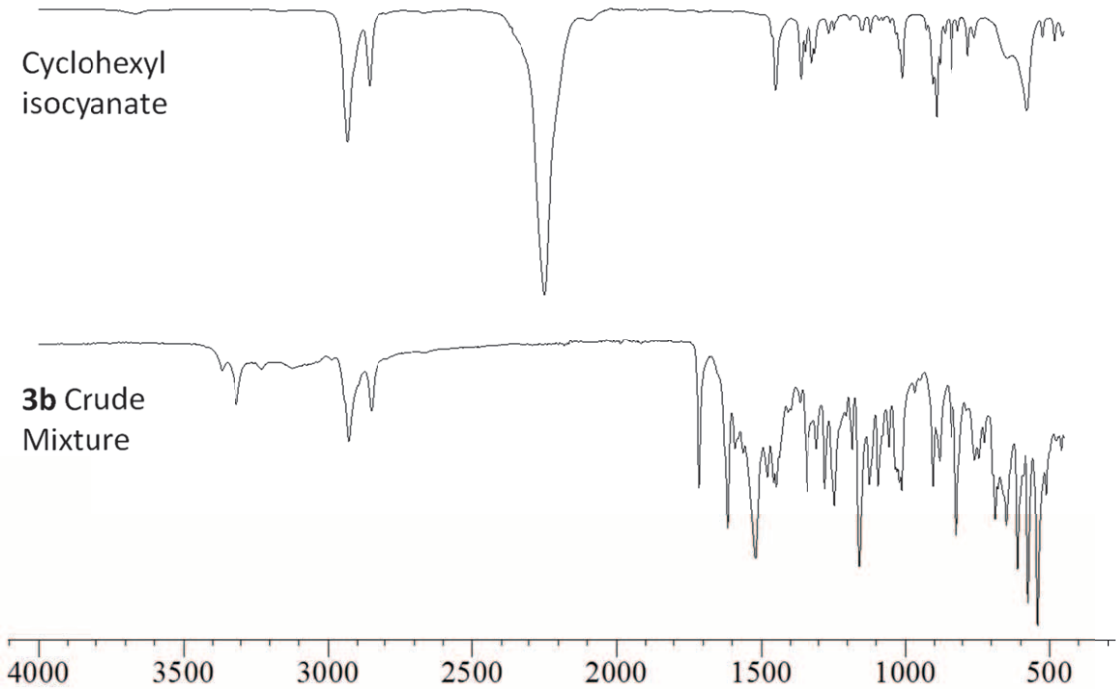
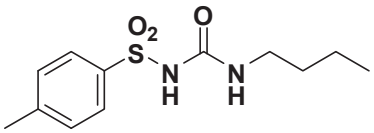
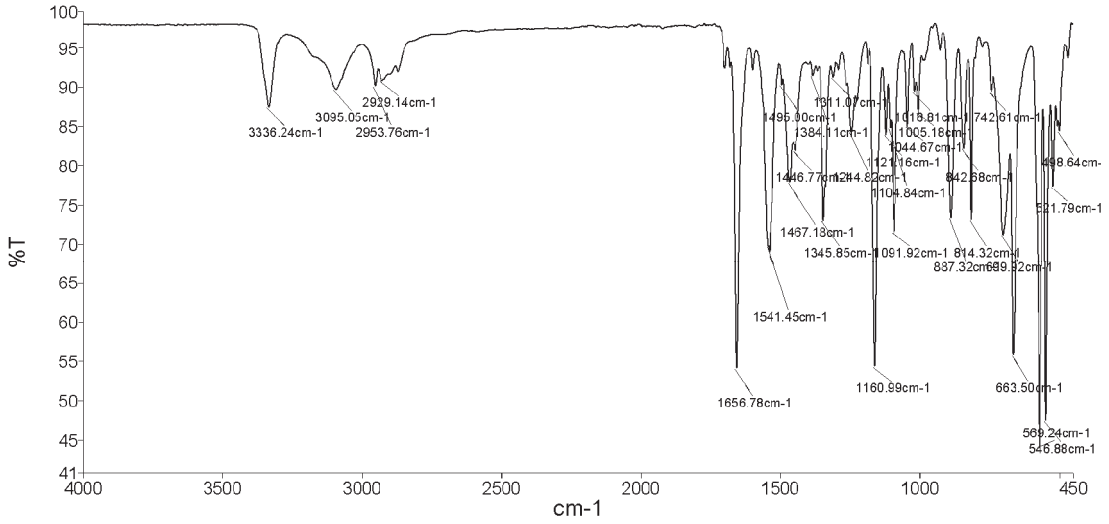


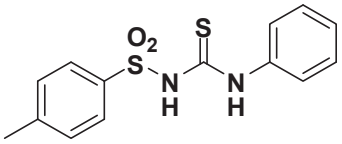
Figure S3. FTIR-ATR spectra for cyclohexyl-isocyanate reactant and the freshly prepared crude reaction mixture from the synthesis of glibenclamide (**3b**) via copper-catalysed mechanochemical route. The disappearance of the isocyanate stretching band at ca. 2000 cm^{-1} is evident.

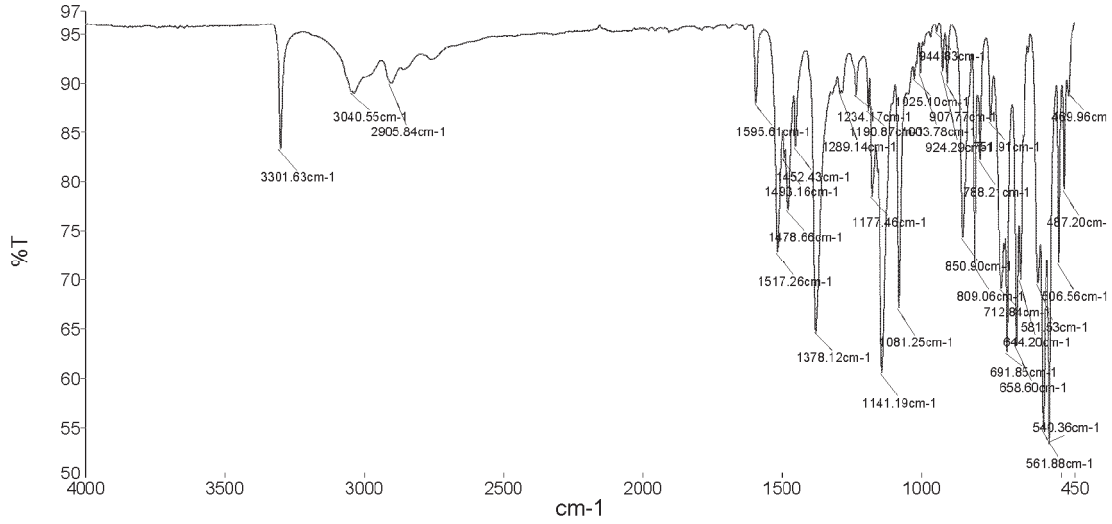
FTIR-ATR spectrum of *N*-(butylcarbamoyl)-4-methylbenzenesulfonamide 1a



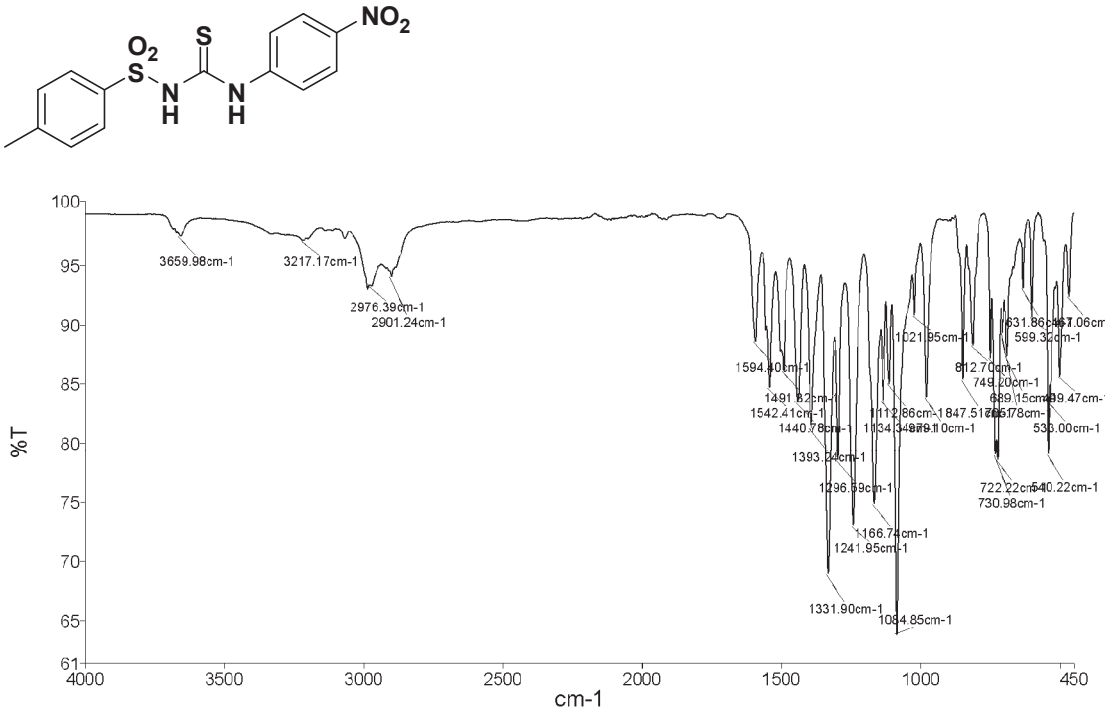


FTIR-ATR spectrum of 4-methyl-*N*-(phenylcarbamothioyl)benzenesulfonamide 1b

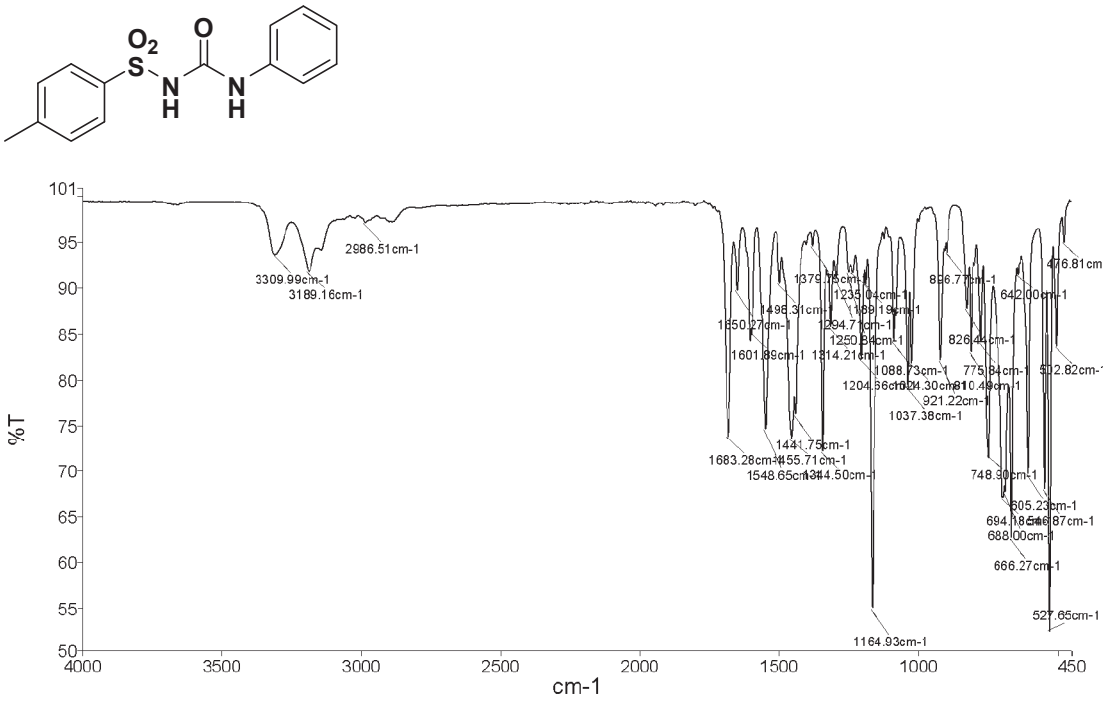




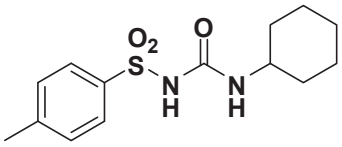
FTIR-ATR spectrum of 4-methyl-*N*-(4-nitrophenylcarbamothioyl)benzenesulfonamide 1c

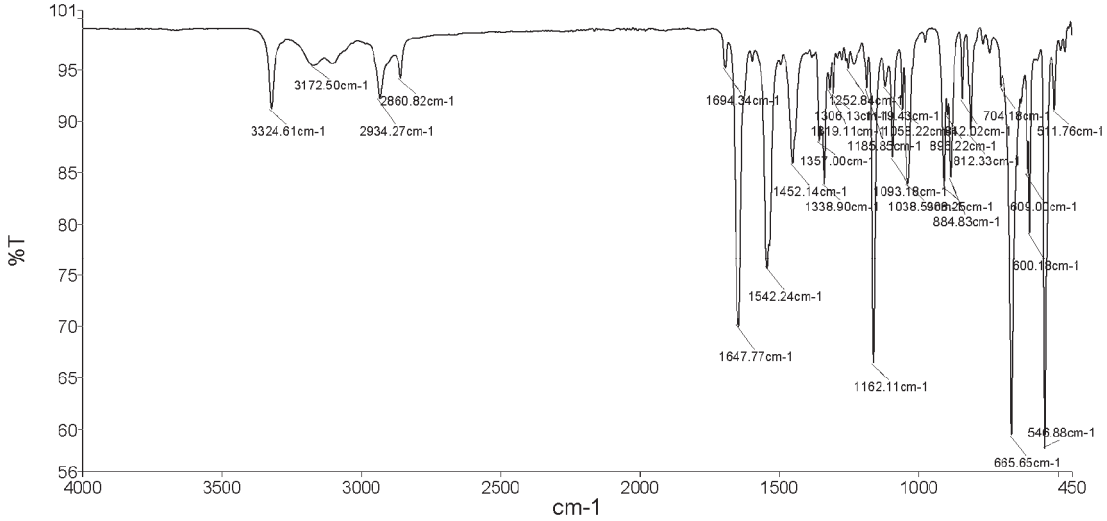


FTIR-ATR spectrum of 4-methyl-*N*-(phenylcarbamoyl)benzenesulfonamide 1d

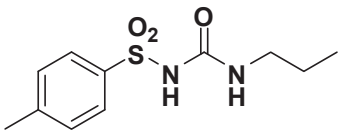


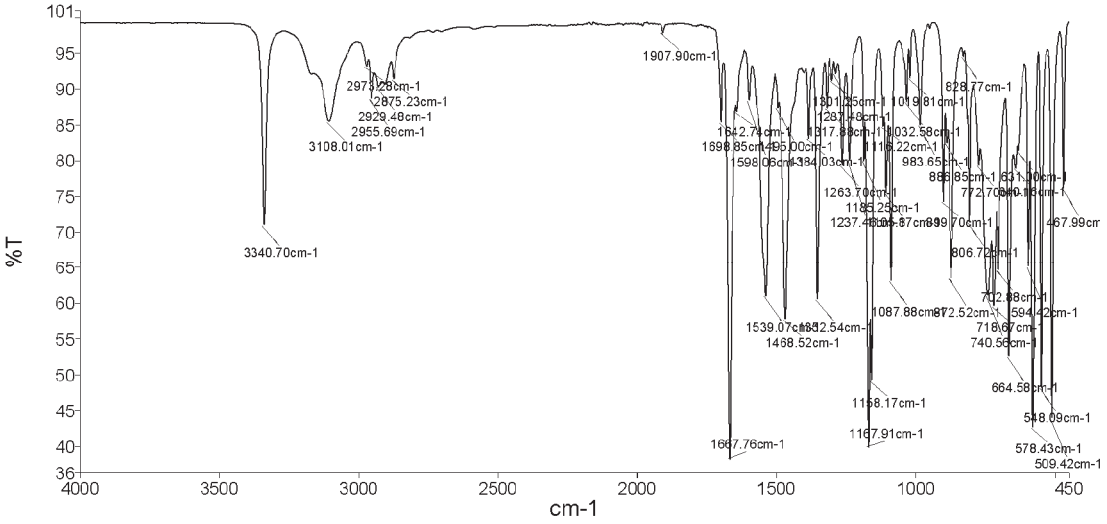
FTIR-ATR spectrum of *N*-(cyclohexylcarbamoyl)-4-methylbenzenesulfonamide 1e



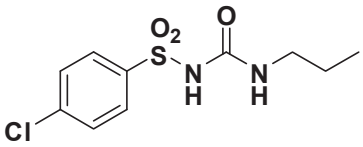


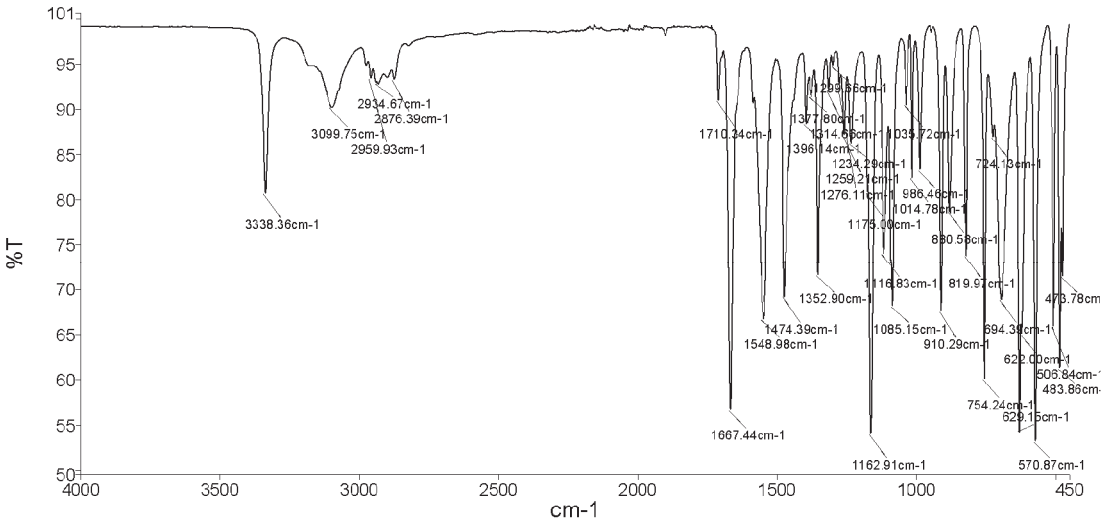
FTIR-ATR spectrum of 4-methyl-*N*-(propylcarbamoyl)benzenesulfonamide 1f



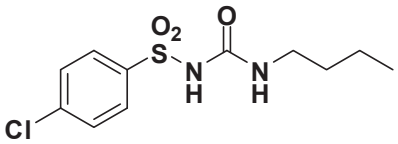


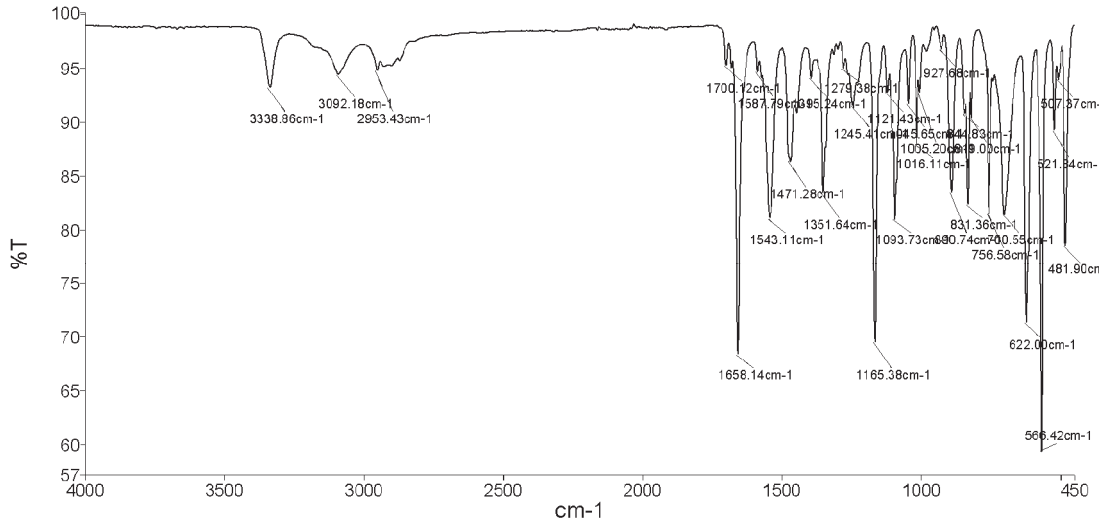
FTIR-ATR spectrum of 4-chloro-*N*-(propylcarbamoyl)benzenesulfonamide 2a



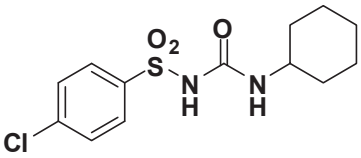


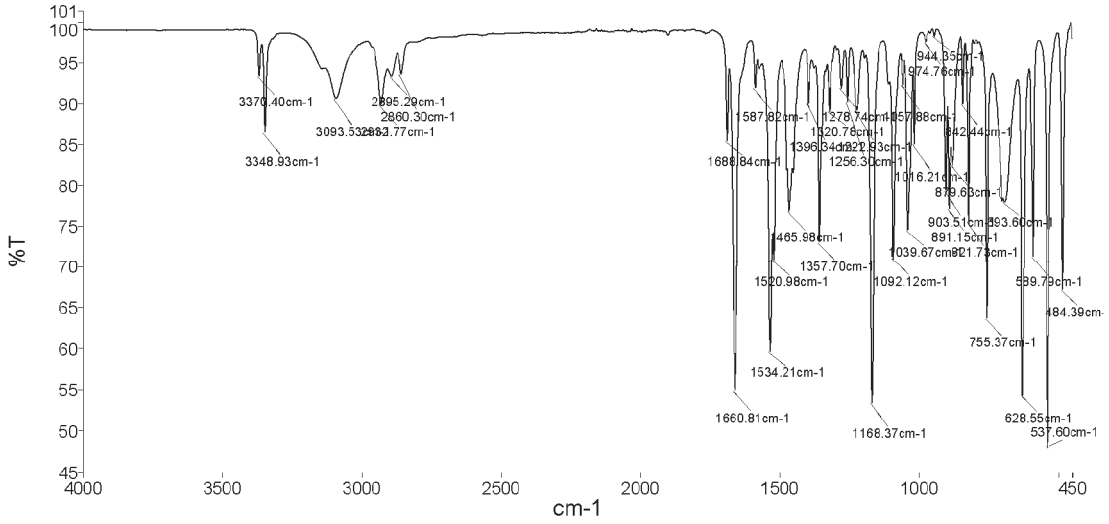
N-(butylcarbamoyl)-4-chlorobenzenesulfonamide 2b



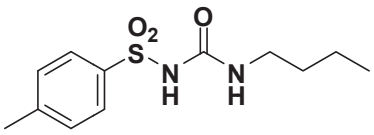


4-chloro-*N*-(cyclohexylcarbamoyl)benzenesulfonamide 2c

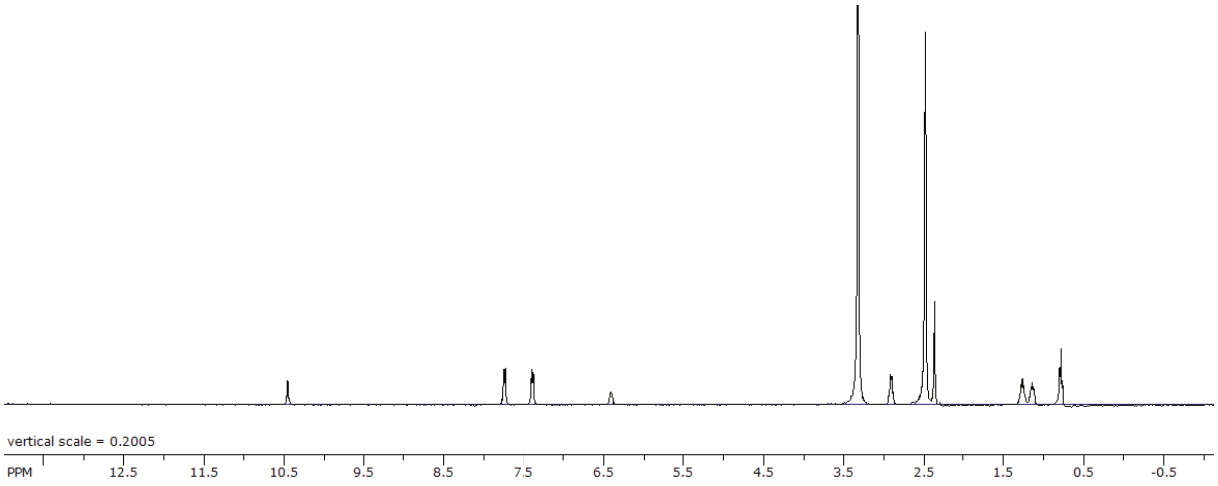




4. Selected ^{1}H and ^{13}C NMR spectra



1a



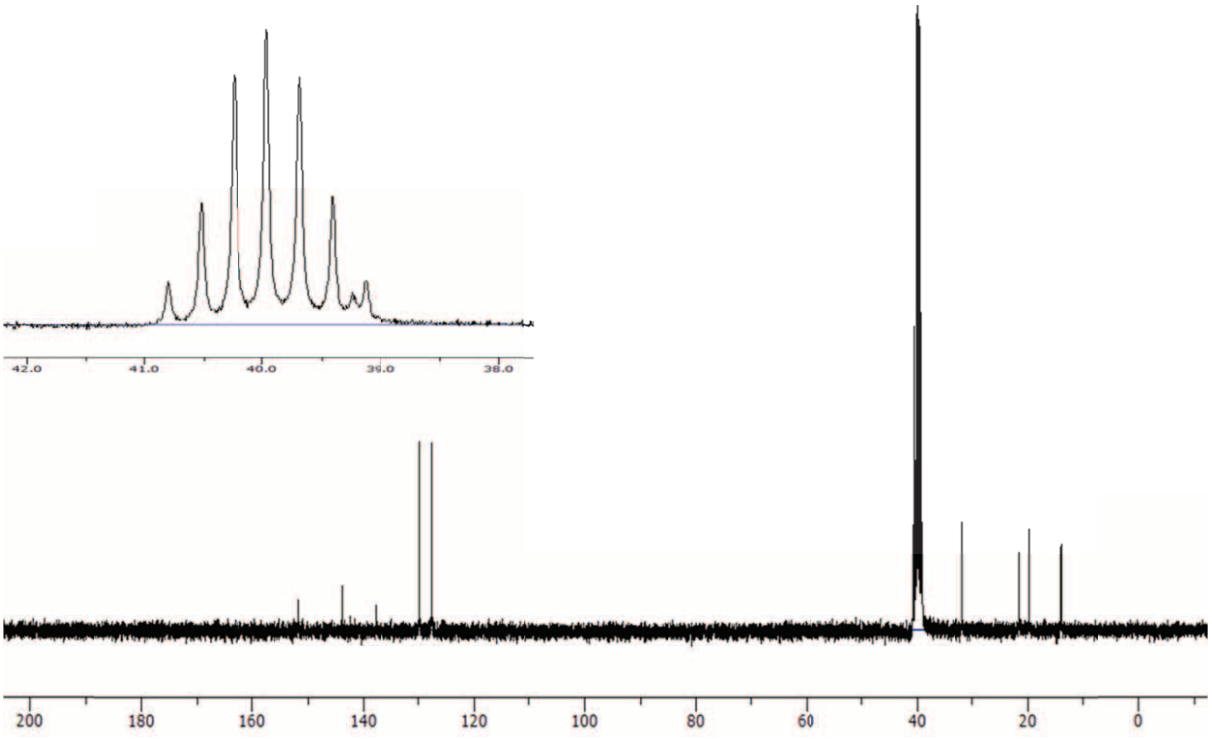


Figure S4. ^{1}H (top) and ^{13}C (bottom) NMR spectra for sulfonyl-urea **1a** (tolbutamide).

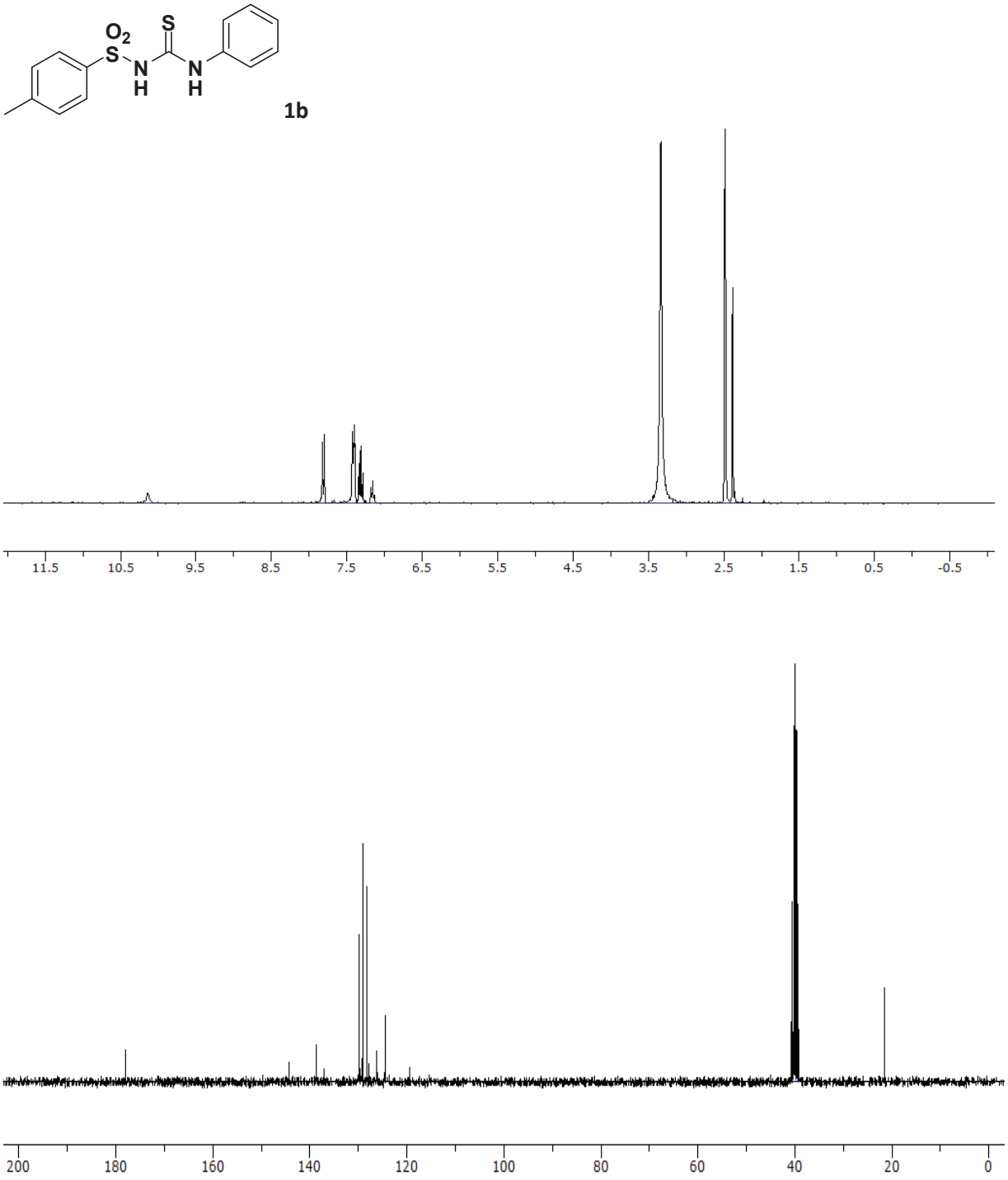


Figure S5. ^{1}H (top) and ^{13}C (bottom) NMR spectra for sulfonyl-thiourea **1b**.

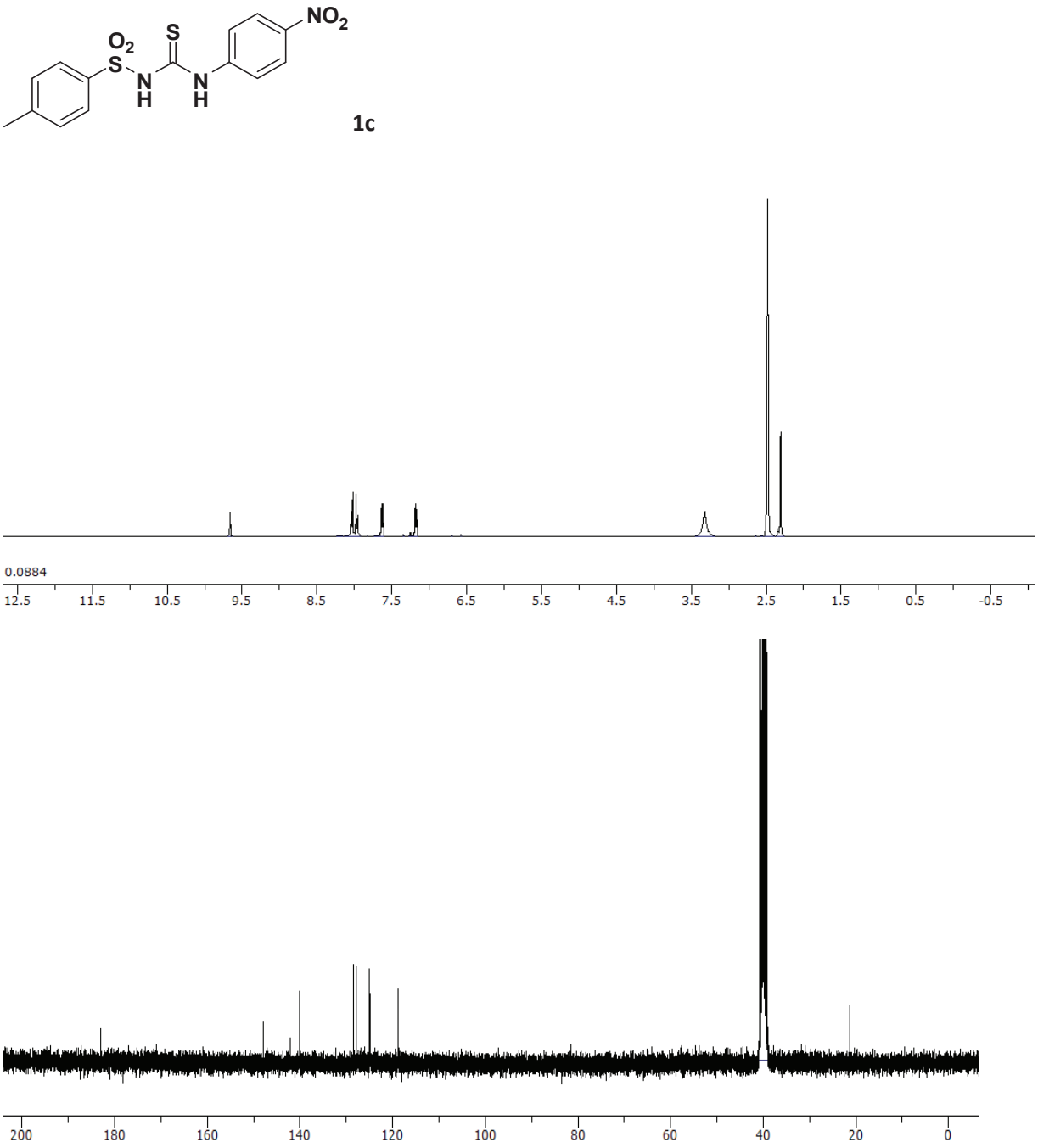


Figure S6. ^{1}H (top) and ^{13}C (bottom) NMR spectra for sulfonyl-thiourea **1c**.

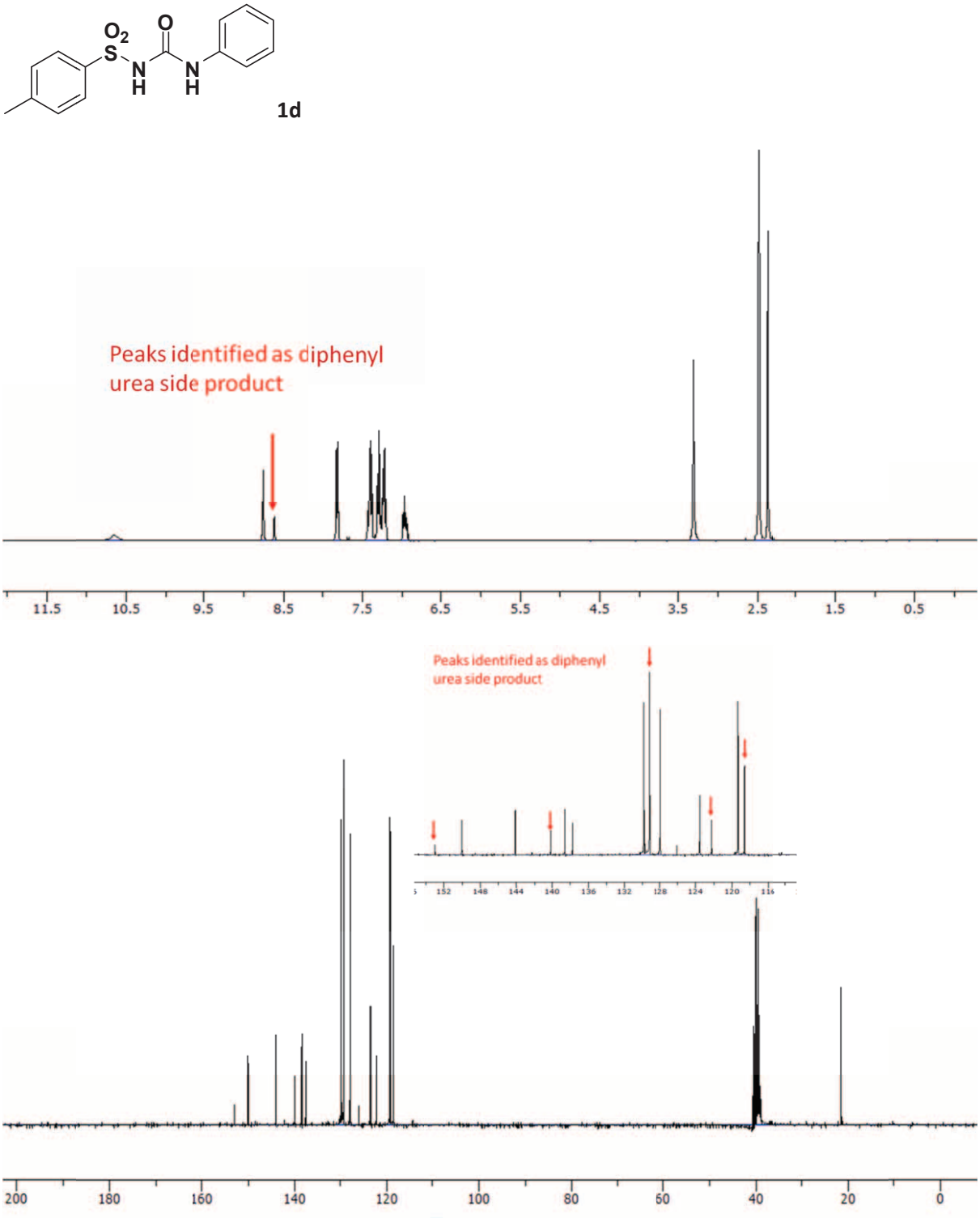


Figure S7. ^{1}H (top) and ^{13}C (bottom) NMR spectra for sulfonyl-urea **1d**. In this case the competing side-reaction of isocyanate coupling to form diphenylurea was difficult to avoid and the crude product contained 93% yield of **1d**, calculated from the ^{1}H NMR spectrum.

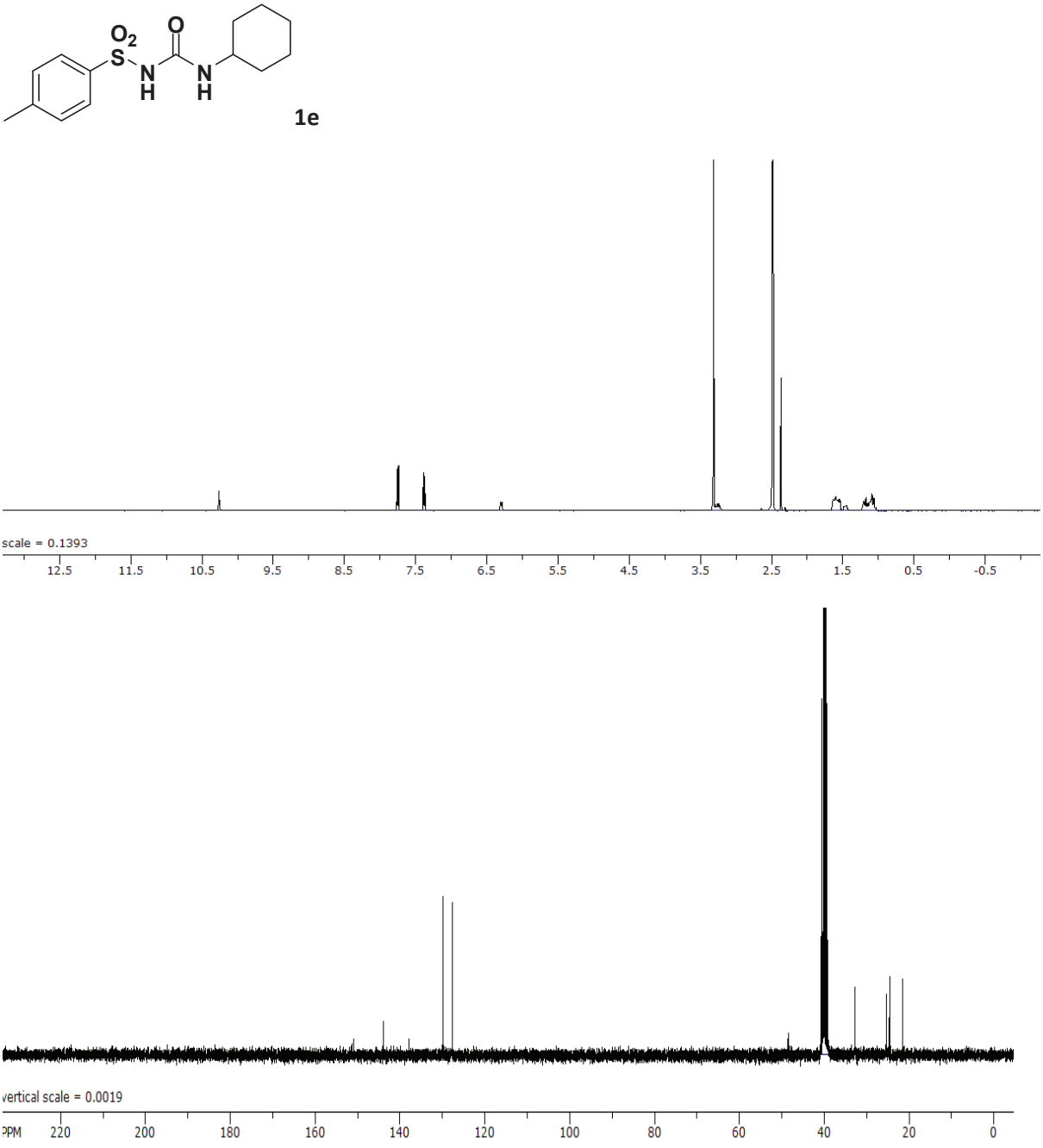


Figure S8. ^{1}H (top) and ^{13}C (bottom) NMR spectra for sulfonyl-urea **1e**.

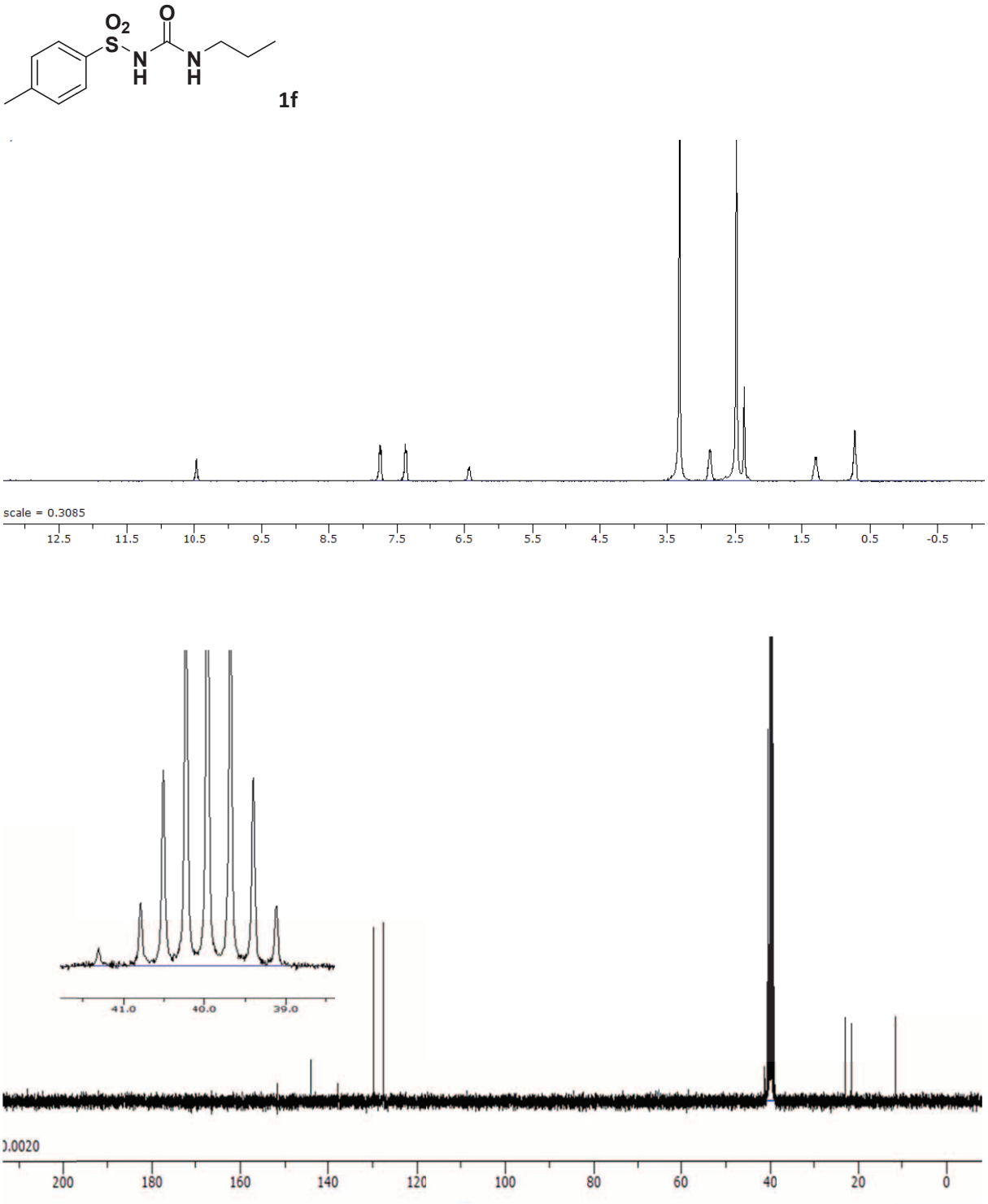


Figure S9. ^{1}H (top) and ^{13}C (bottom) NMR spectra for sulfonyl-urea **1f**.

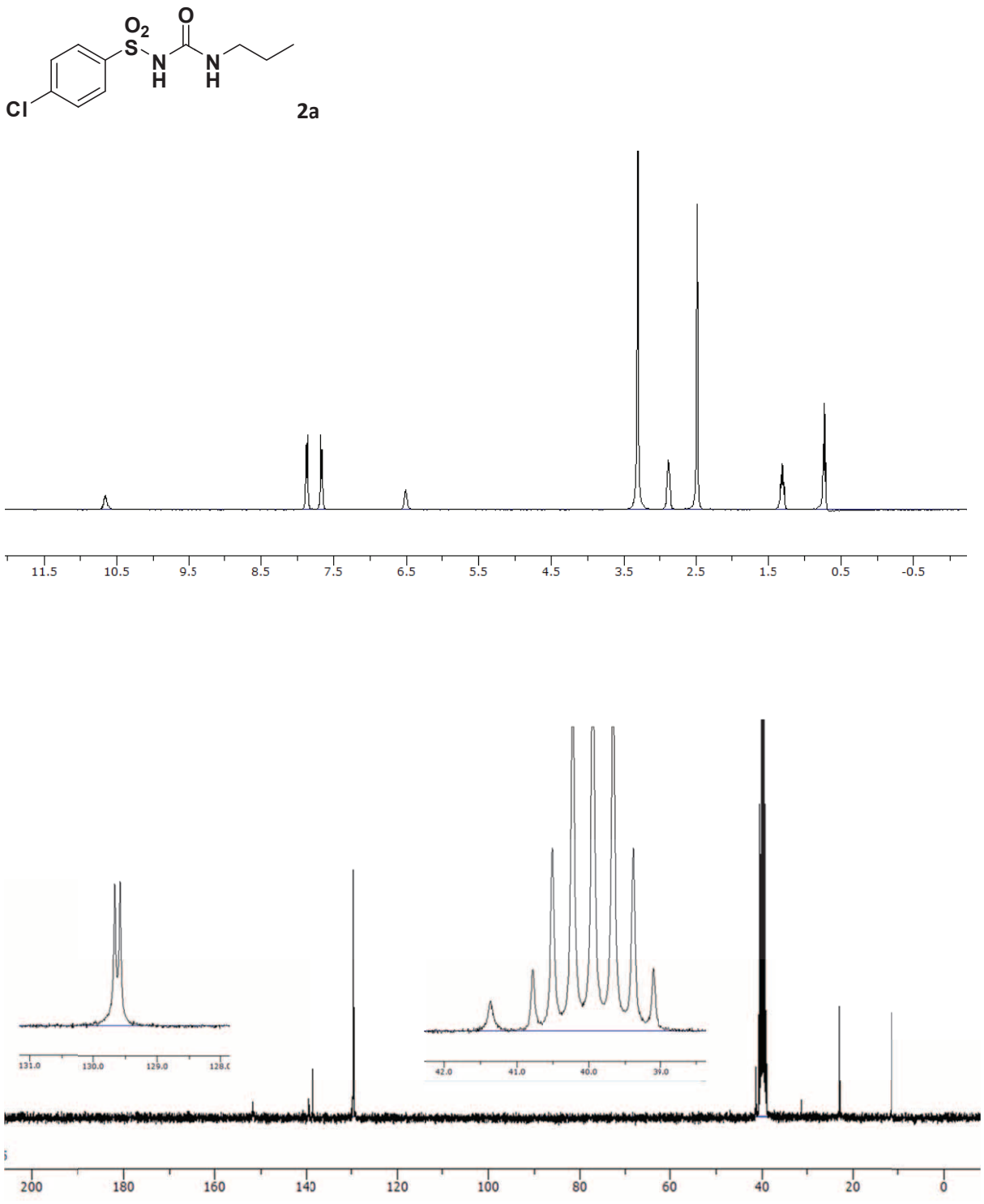


Figure S10. ^{1}H (top) and ^{13}C (bottom) NMR spectra for sulfonyl-urea **2a** (chlorpropamide).

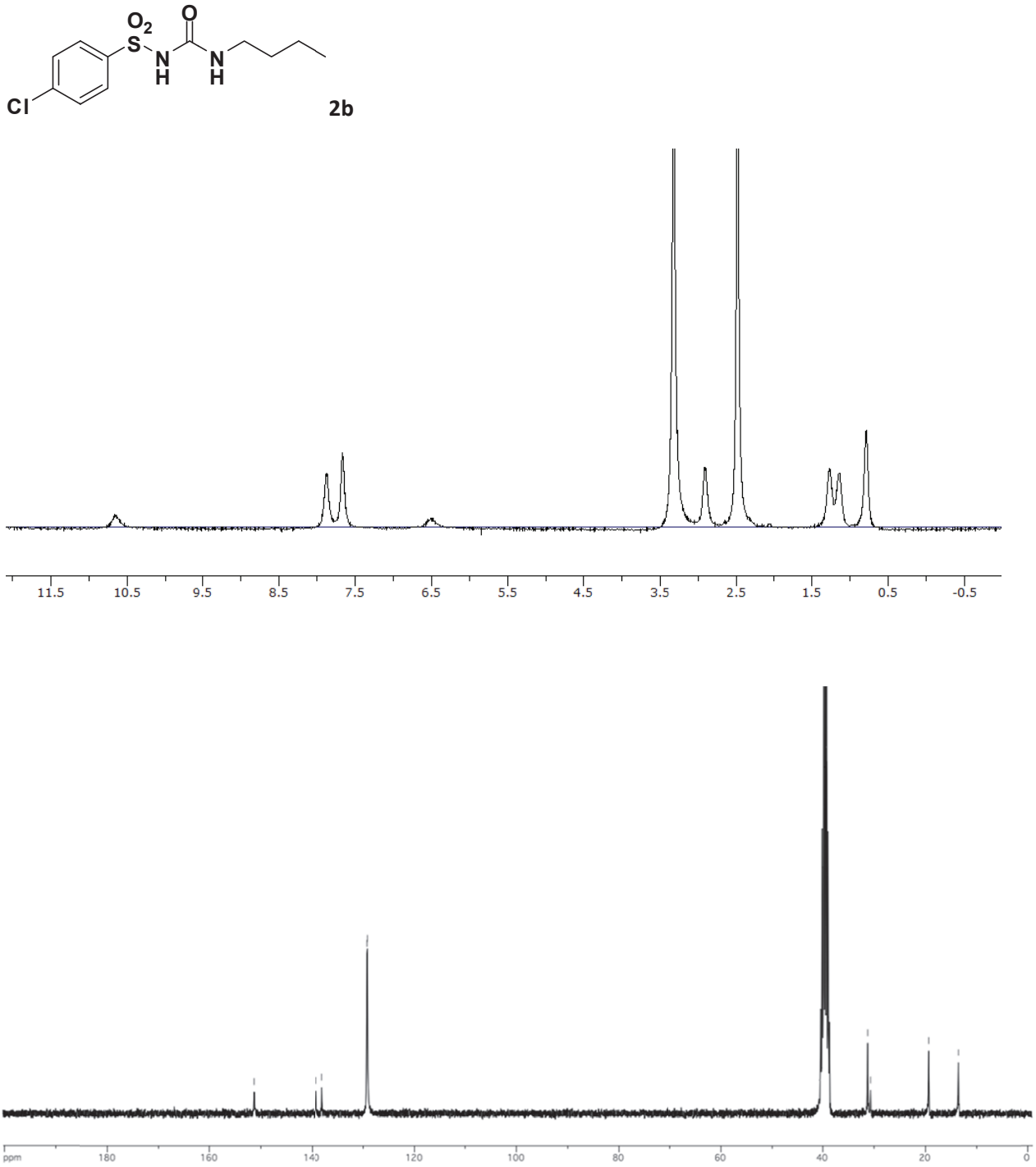


Figure S11. ^{1}H (top) and ^{13}C (bottom) NMR spectra for sulfonyl-urea **2b**.

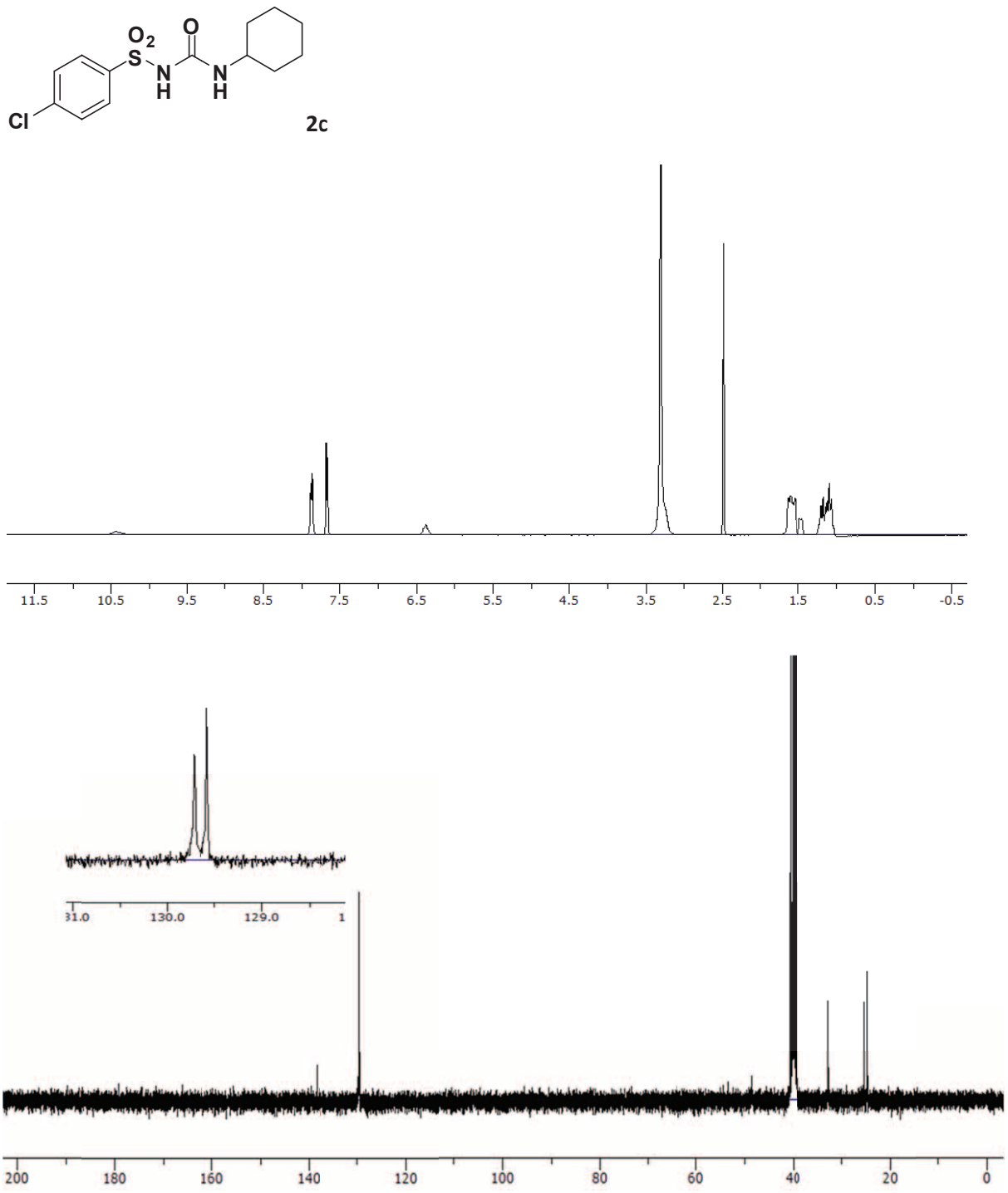


Figure S12. ^{1}H (top) and ^{13}C (bottom) NMR spectra for sulfonyl-urea **2c**.

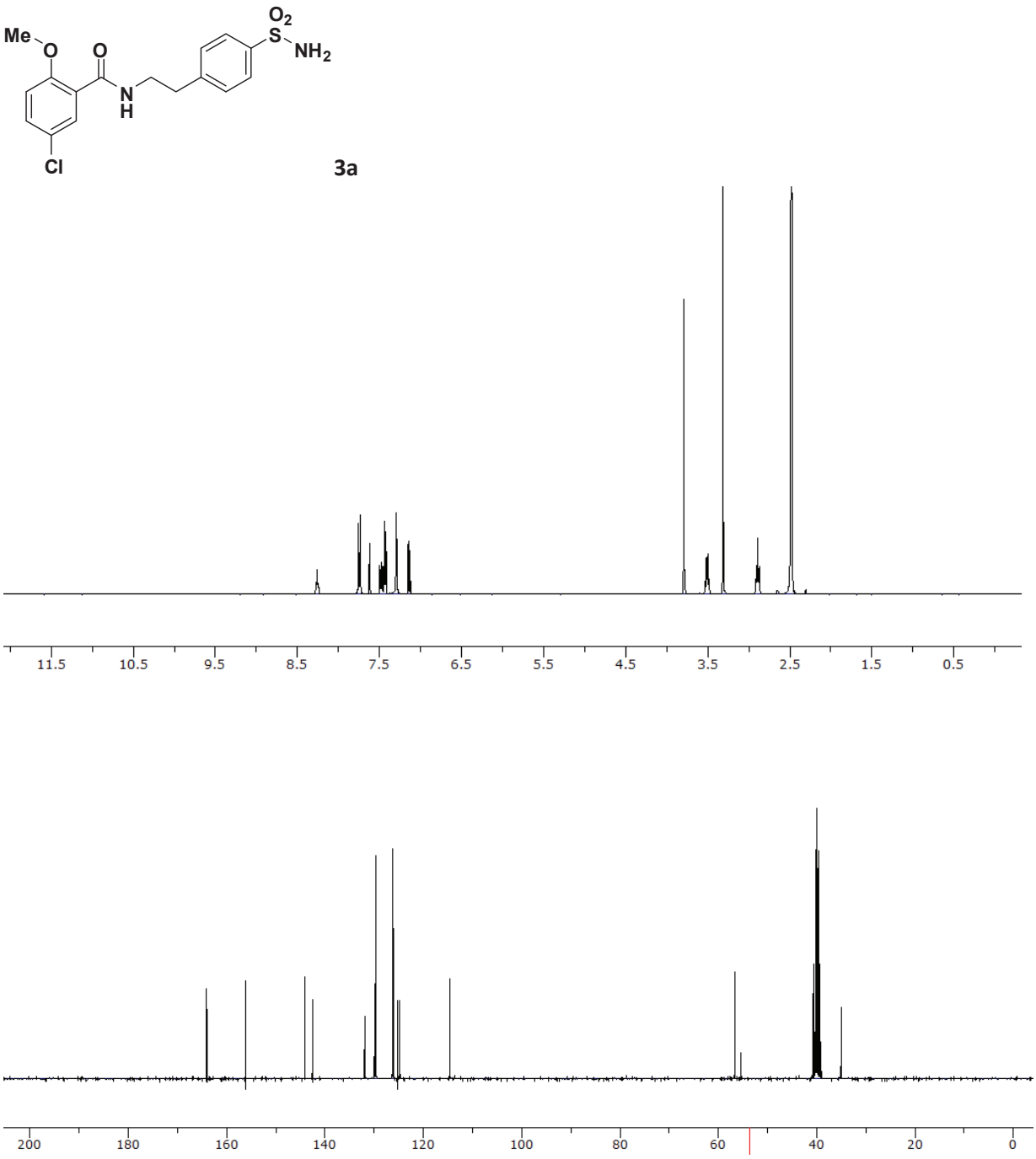


Figure S13. ^{1}H (top) and ^{13}C (bottom) NMR spectra for the glibenclamide precursor **3a**, obtained by mechanochemical amide synthesis.

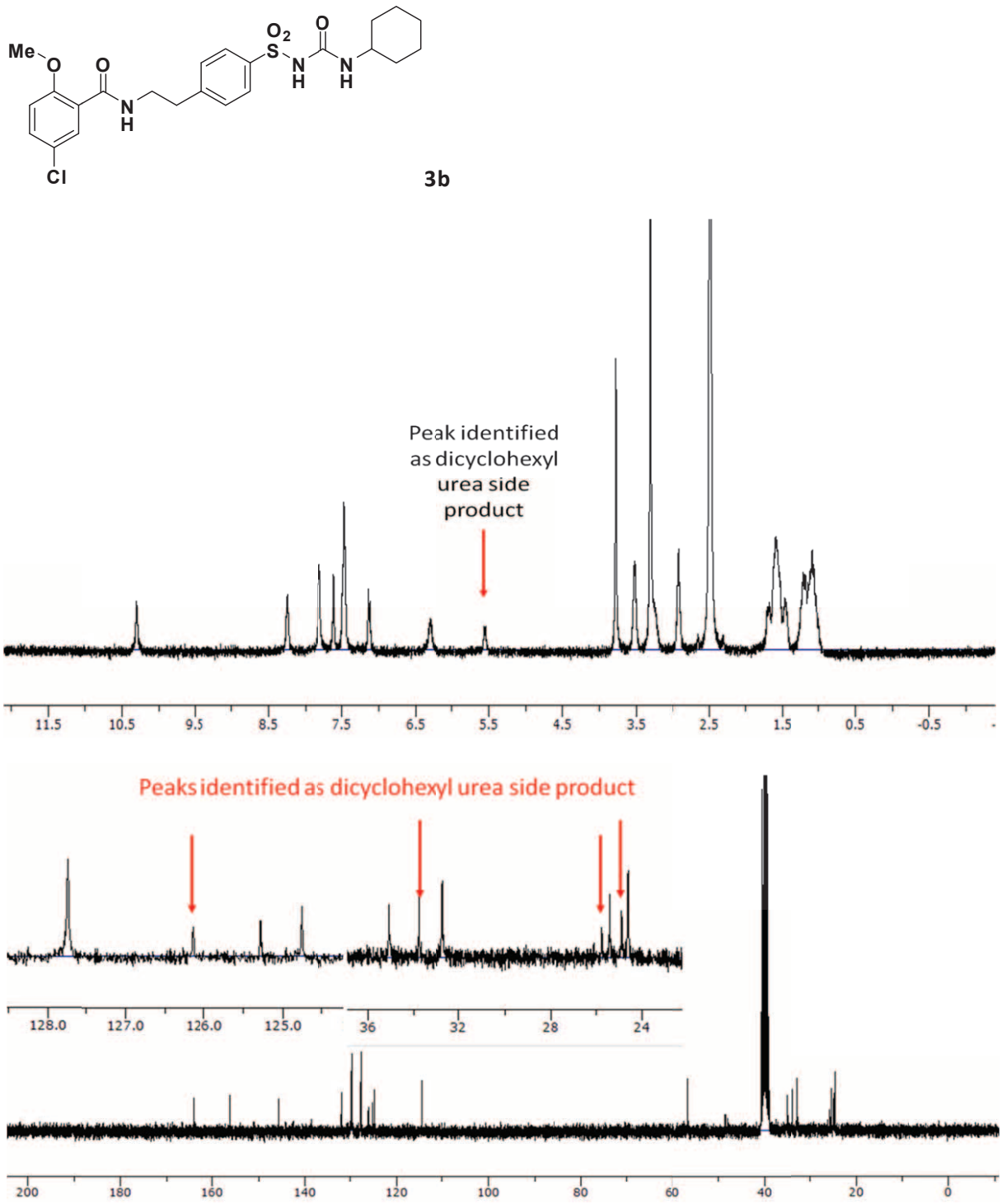


Figure S14. ^{1}H (top) and ^{13}C (bottom) NMR spectra for glibenclamide (**3b**) obtained by mechanochemical amide coupling and mechanochemical copper-catalysed coupling.