Supplementary Information for

Taming Diamines and Acyl Chlorides by Carbon Dioxide in Selective Mono-Acylation Reactions

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1. General methods

All the commercially available chemicals have been used directly from commercial suppliers and used without purification unless otherwise indicated. Active esters and active amides were synthesized using known procedure.[1, 2] Acyl chlorides were prepared by using thionyl chloride and the corresponding carboxylic acids. All used solvents were at HPLC grade. Solvents such as toluene, acetonitrile, DCM, heptane, THF were dried and purified through PURESOLV Solvent Purification Systems before used for the reaction. CO_2 of 99.7 % purity (Air Liquide Danmark A/S) was directly used from a cylinder. Analytical thin layer chromatography has been conducted with Merck DC-Alufolien SiO_2 60 F254 0.2 mm thick pre-coated TLC plates. Nuclear Magnetic Resonance (NMR) spectra of ^{1}H and ^{13}C were recorded with a 500 MHz Ultrashield Plus 500 spectrometer and 125 MHz on a Bruker. Chemical shifts (δ) are expressed in ppm while (*J*) are expressed in Hertz (Hz). The following abbreviations are used for multiplicity for NMR resonances: s = singlet, br = broad, bs = broad singlet, d = doublet, t = triplet, q = quartet, p = pentet, and m = multiplet. HRMS analyses were carried out on Bruker MicrOTOF-QII system equipped with an ESI source with nebulizer gas at 1.2 bars, dry gas at 10 L/min, dry temperature at 200 °C, capillary at 4500 V and end plate offset at –500 V. The ion transfer was conducted with funnel 1 and funnel RF's at 200.0 Vpp and hexapole RF at 100.0 Vpp while the quadrupole ion energy was set at 5.0 eV with a low mass cut-off at 100.00 m/z. In the collision cell, collision energy was set at 8.0 eV, collision RF at 100.0 Vpp, and a transfer time of 80.0 µs and pre-pulse storage of 1.0 µs were used.

2. Analysis of crude reaction mixtures

General Procedure for analysis of crude reaction mixture: crude ^{1}H-NMR yields were determined after quenching the reaction with H_2O (5 mL) by integration of α-methylene protons for reactions with phenylacetyl chloride (**2a**), α-vinylic protons for reactions with cinnamoyl chloride (**2b**), or N-H amide protons for benzoyl derivatives as shown below (Figure **S1**-**S3**).

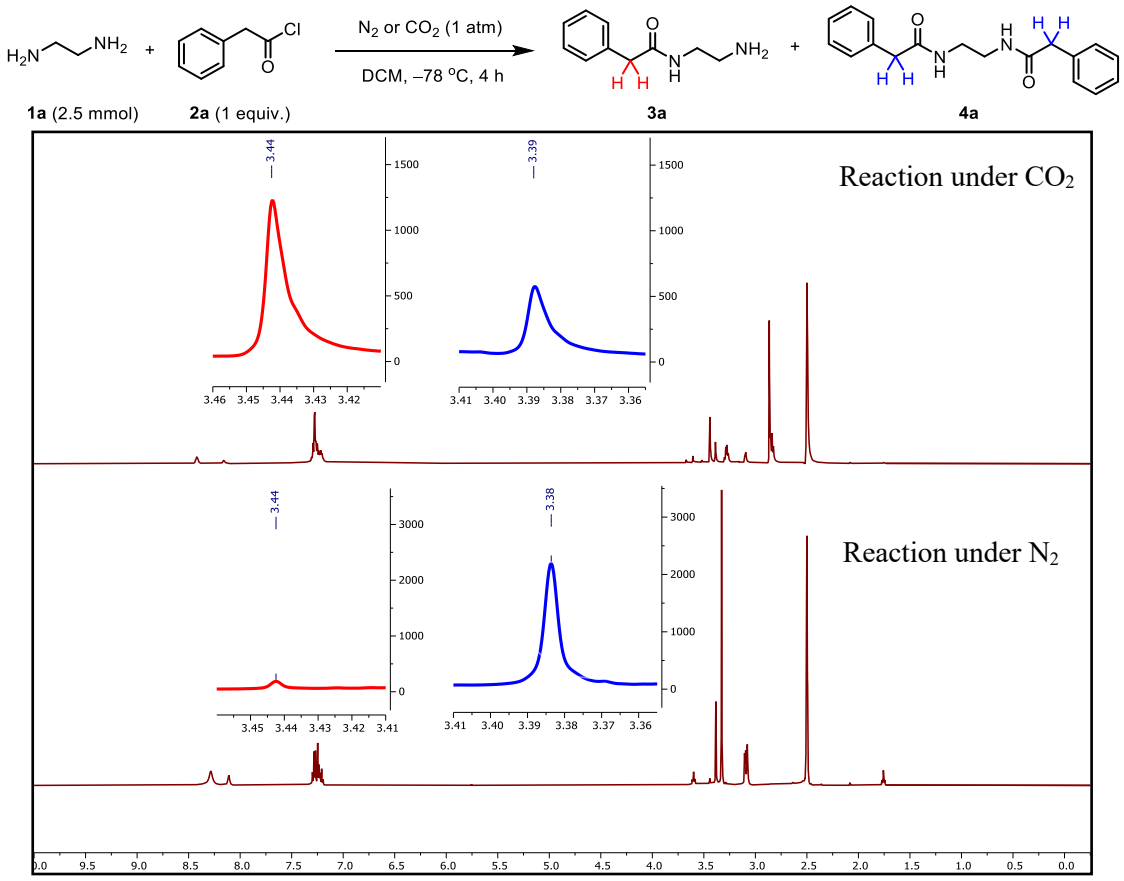


Fig. S1. ^{1}H NMR spectra in DMSO-d_6 of reaction crude mixtures under CO_2 (top) and under N_2 (bottom), ^{1}H NMR signals were highlighted in red for **3a** (mono acylated) and cyan for **4a** (diacylated product).

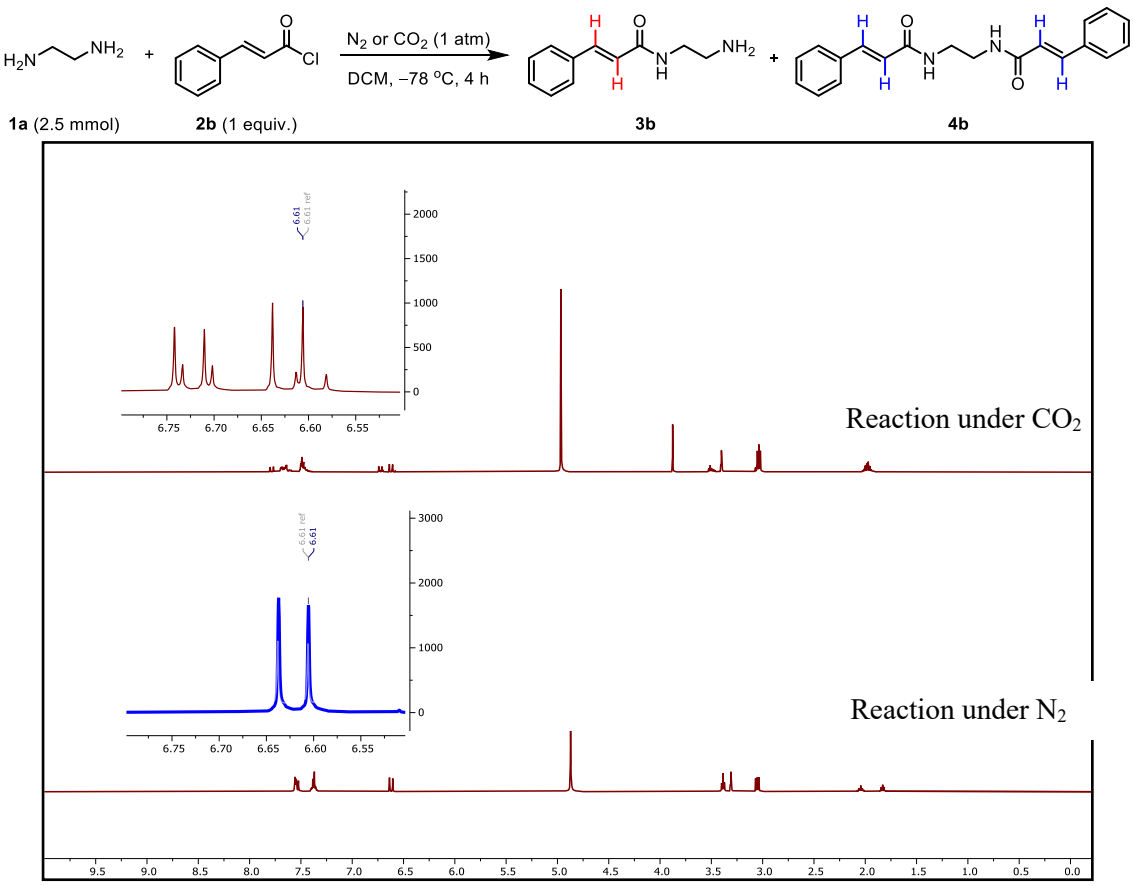


Fig. S2. ^{1}H NMR spectra in DMSO-d_6 of reaction crude mixtures under CO_2 (top) and under N_2 (bottom). ^{1}H NMR signals were highlighted in red for **3b** (mono acylated) and cyan for **4b** (diacylated product).

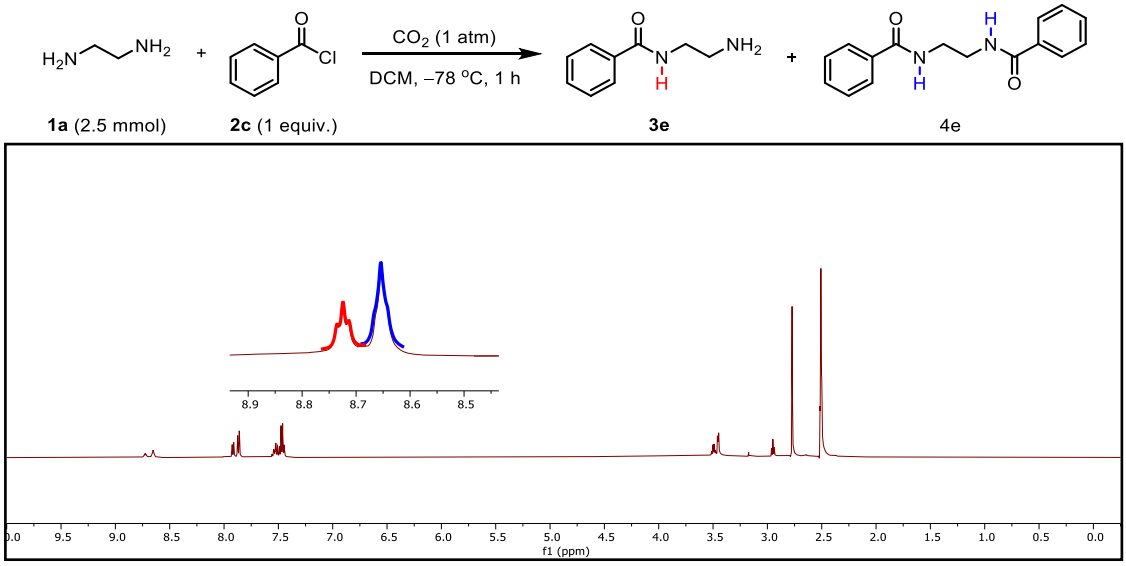
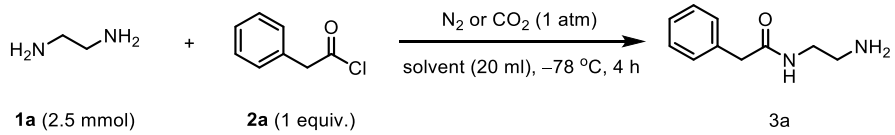


Fig. S3. ^{1}H NMR spectra in DMSO-d_6 of reaction crude mixtures under CO_2 (top). ^{1}H NMR signals were highlighted in red for **3e** (mono acylated) and cyan for **4e** (diacylated product).

3. Solvent Screening

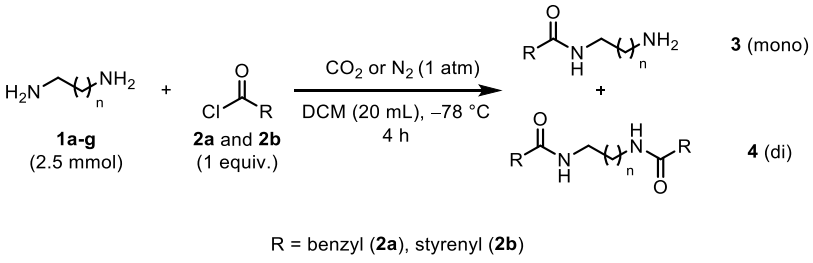
General Procedure for solvent screening of acylation of ethylene diamine



To an oven-dried 25 mL round bottom flask, ethylene diamine (**1a**, 2.5 mmol, 1 equiv.) and selected solvent (10 mL) were charged under N_2 or CO_2 atmosphere and stirred for 15 min at –78 °C. A solution of phenylacetyl chloride (**2a**, 2.5 mmol, 1 equiv.) was prepared under N_2 in selected solvent (10 mL), cooled to –78 °C, and transferred to the reaction flask containing the diamine. The reaction mixture was allowed to stir at –78 °C for 4 hours then quenched with water (5 mL) and left to stir to room temperature. The crude reaction mixture was dissolved in MeOH and MeCN (1:1, v:v, 50-100 mL until the mixture becomes homogeneous). An aliquot was analysed by ^{1}H-NMR spectroscopy in DMSO-d_6, and crude yield was determined by integration of α-methylene protons as shown in Figure S1.

4. Screening of diamines for chain length

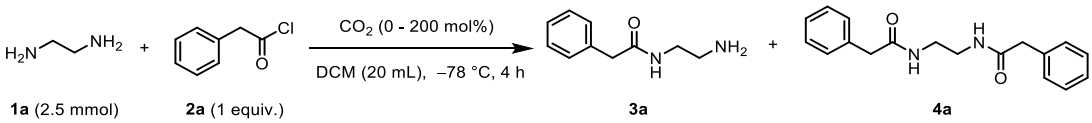
General Procedure for acylation of symmetrical diamines



To an oven-dried 25 mL round bottom flask, diamine (**1a-g,** 2.5 mmol, 1 equiv.) and DCM (10 mL) were charged under N_2 or CO_2 atmosphere and stirred for 15 min at –78 °C. A solution of acyl chloride (**2a** or **2b**, 2.5 mmol) was prepared under N_2 in DCM (10 mL), cooled to –78 °C, and transferred to the reaction flask containing the diamine. The reaction mixture was allowed to stir at –78 °C for 4 hours then quenched with water (5 mL) and left to stir to room temperature. The crude reaction mixture was dissolved in MeOH and MeCN (1:1, v/v, total 50-100 mL until the mixture becomes homogeneous). An aliquot was analysed by ^{1}H-NMR spectroscopy in DMSO-d_6, and crude yield was determined by integration of α-methylene or α-ethylene protons as shown in Figure S1 or S2.

5. CO_2 Concentration Screening

General Procedure for CO_2 concentration screen of acylation of ethylene diamine



To an oven-dried 25 mL round bottom flask, ethylene diamine (**1a**, 2.5 mmol, 1 equiv.) and DCM (10 mL) were charged under N_2 atmosphere. From a flask purged and refilled with CO_2, a 60 mL syringe was filled fully up with CO_2 and transferred over to the reaction flask by gently applying pressure to limited inflow of atmospheric air. Shortly before the addition of CO_2 into the reaction mixture, excess CO_2 from the syringe is expelled until the right CO_2 concentration is achieved, and the needle is injected into the reaction flask. The flask is allowed to stir for 15 min at –78 °C. A solution of phenylacetyl chloride (**2a**, 2.5 mmol, 1 equiv.) was prepared under N_2 in DCM (10 mL), cooled to –78 °C, and transferred to the reaction flask containing the diamine. The reaction mixture was allowed to stir at –78 °C for 4 hours then quenched with water (5 mL) and left to stir to room temperature. The crude reaction mixture was dissolved in MeOH and MeCN (1:1, v:v, 50-100 mL until the mixture becomes homogeneous). An aliquot was analyzed by ^{1}H-NMR spectroscopy in DMSO-d_6, and crude yield was determined by integration of α-methylene protons as shown in Figure S4.

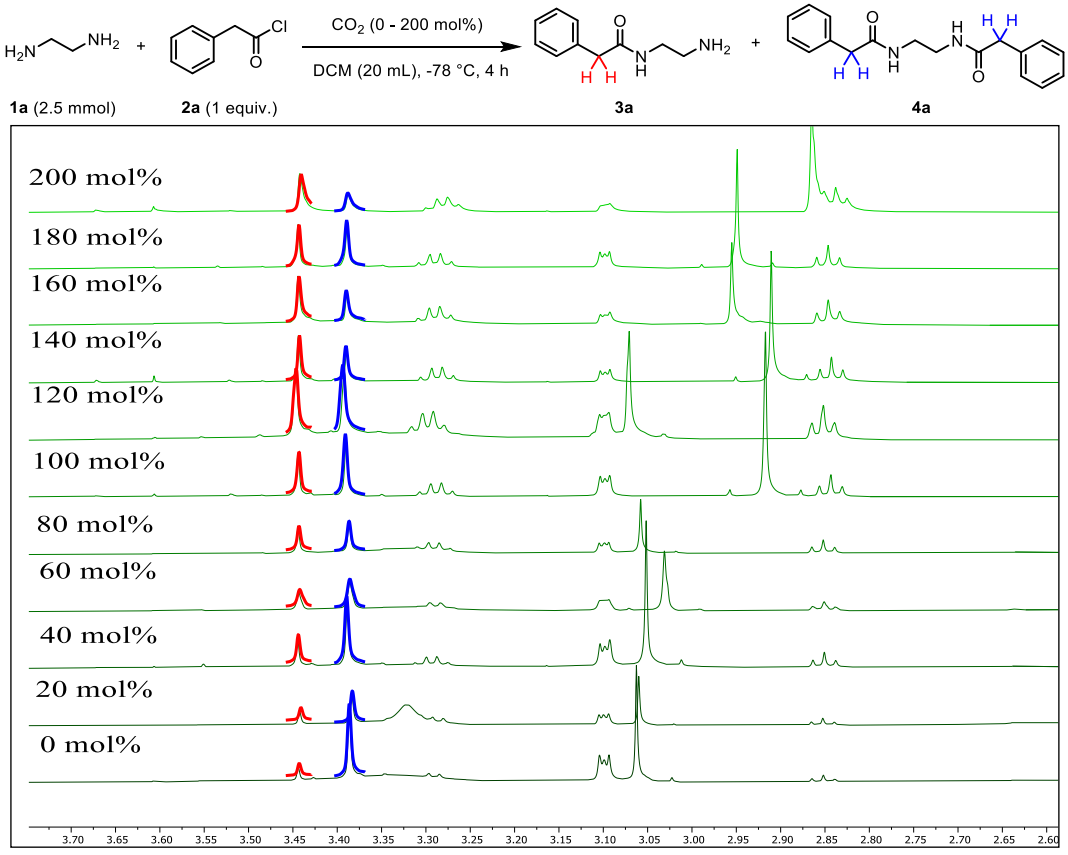
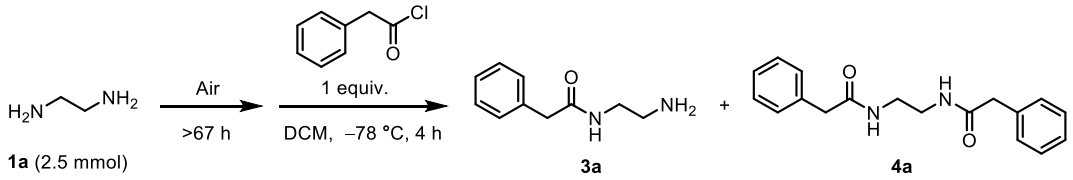


Fig. S4. H-NMR spectra in DMSO-d_6 of crude reaction mixtured between ethylene diamine (**1a**) and phenylacetyl chloride (**2a**) with different CO_2 loadings.

6. Direct air capture reaction for monoacylation reaction

General Procedure for reactions with CO_2 by direct air capture



To an oven-dried reaction vessel, ethylene diamine (**1a**, 2.5 mmol, 1 equiv.) was charged under ambient atmosphere. The diamine was spread around the reaction vessel by twisting the vessel around the left open to react with the ambient CO_2 (Figure S5). After the allotted time, 10 mL of DCM was added and sealed. The flask is allowed to stir for 15 min at –78 °C. A solution of phenylacetyl chloride (**2a**, 2.5 mmol, 1 equiv.) was prepared under N_2 in DCM (10 mL), cooled to –78 °C, and transferred to the reaction flask containing the diamine. The reaction mixture was allowed to stir at –78 °C for 4 hours then quenched with water (5 mL) and left to stir to room temperature. The crude reaction mixture was dissolved in MeOH and MeCN (1:1, v/v, 50-100 mL until the mixture becomes homogeneous). An aliquot was analyzed by ^{1}H-NMR spectroscopy in DMSO-d_6, and crude yield was determined by integration of α-methylene protons as shown in Figure S1.

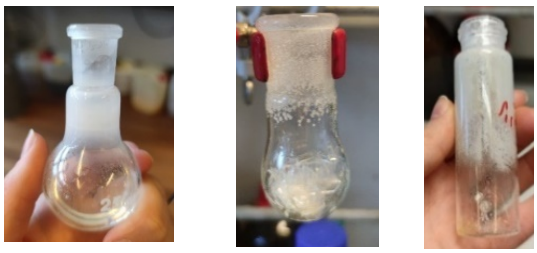


Fig. S5. Ethylene diamine exposure to air: Left) placed on the bottom of round bottom flask and left under air for 67 h; middle) placed on the bottom of round bottom flask with glass particles for better aeration in the flask to increase the surface area and left for 67 h; Right) placed in a vial and left under air for 90 h.

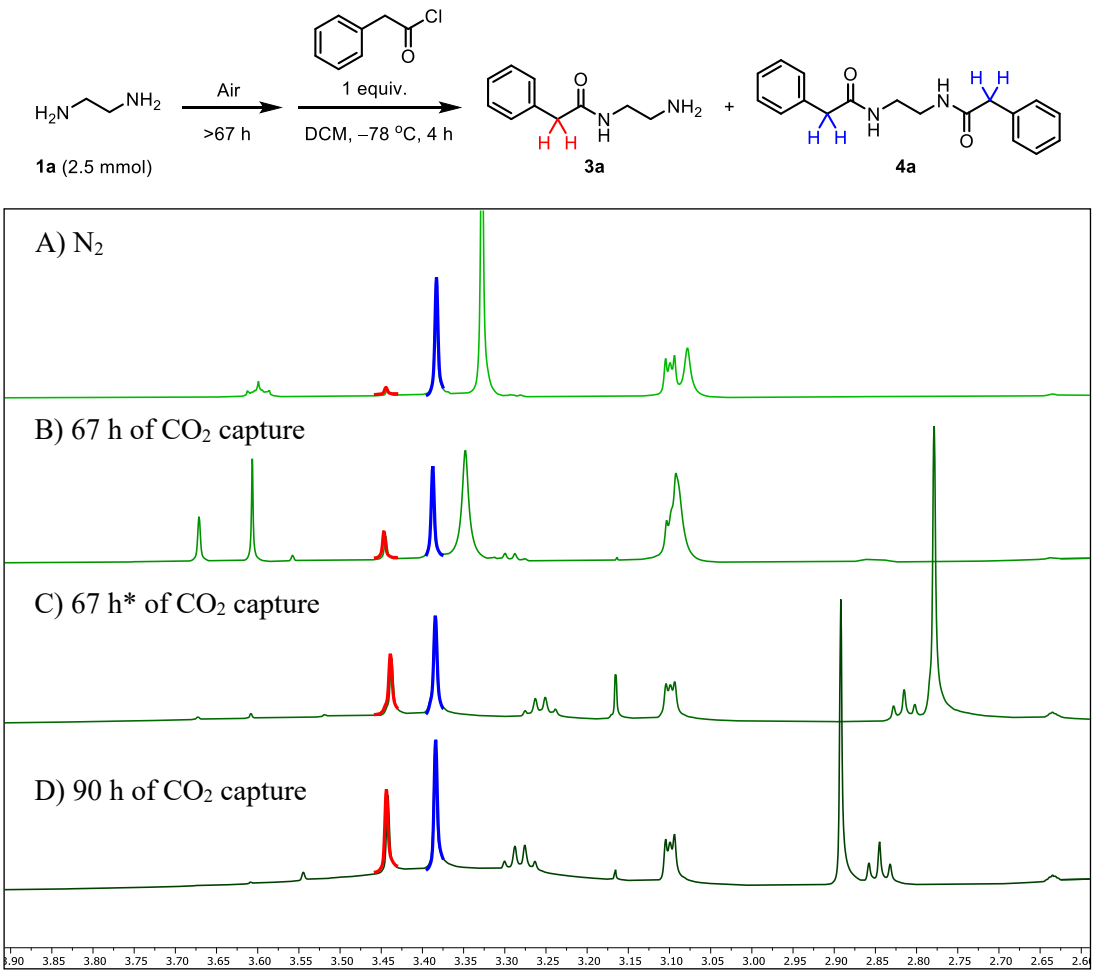
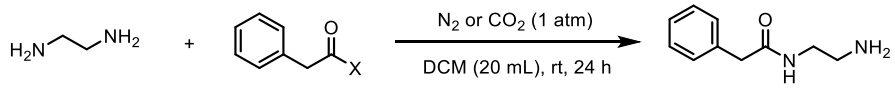


Fig. S6. ^{1}H-NMR spectra in DMSO-d_6 of crude reaction mixtured between ethylene diamine (**1a**) and phenylacetyl chloride (**2a**) after diamine CO_2 capture in different conditions: A) N_2, B) after exposing the diamine to air for 67 h, C) after exposing the diamine to air for 67 h with glass particles (broken glass) for better aeration and D) after exposing the diamine to air for 90 h

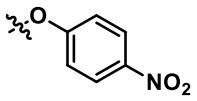
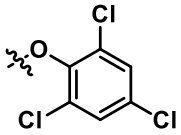
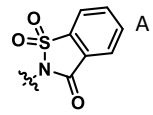
7. Active esters and amides for monoacylation

General Procedure for monoacylation with active esters or amides



1a (2.5 mmol) **2** (1 equiv.) **3a**

To an oven-dried 25 mL round bottom flask, ethylene diamine (**1a**, 2.5 mmol, 1 equiv.) and DCM (10 mL) were charged under N_2 or CO_2 atmosphere and stirred for 15 min at room temperature. A solution of phenylacetyl derivative (**2**, 2.5 mmol, 1 equiv.) was prepared under N_2 in DCM (15 mL) and transferred to the reaction flask containing the diamine. The reaction mixture was allowed to stir at room temperature for 24 hours then quenched with water (5 mL) and left to stir to room temperature. The crude reaction mixture was dissolved in MeOH and MeCN (1:1, v/v, 50-100 mL until the mixture becomes homogeneous). An aliquot was analyzed by ^{1}H-NMR spectroscopy in DMSO-d_6, and crude yield was determined by integration of α-methylene protons as shown above (Figure S1).

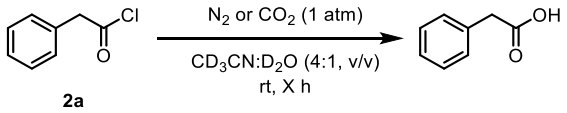
X (leaving group)	atmosphere (1 atm)	yield mono (%)	di (%)
	N_2	55	45
	CO_2	49	51
	N_2	86	14
	CO_2	57	43
 A	N_2	25	75
	CO_2	13	87

[A]25 mL of DCM was used instead of 20 mL.

Table S1. The compiled selectivity of monoacylation of ethylene diamine (**1a**) with shown active esters/amide under CO_2 and N_2 at room temperature. Under CO_2, there is a clear decrease in the selectivity compared to under N_2 with less reactive acyl donors than acyl chloride.

8. Hydrolysis of acyl chloride

The NMR solvent for the reaction was prepared by mixing CD_3CN (1.6 mL) and D_2O (0.4 mL) together, which was divided equally (1 mL) and placed in NMR tubes flushed with N_2 or CO_2. Phenylacetyl acid chloride (**2a**) (15 μL) was then added to both tubes, shaken and ^{1}H-NMR spectra was recorded in different intervals of time. Selectivity of hydrolyzed acid chloride was calculated by integrating aromatic peaks to a total of five and α-methylene peaks as presented below in Fig. S7. The remaining acyl chloride was then determined by subtracting hydrolyzed α-methylene integration from two.



time (X)	atmosphere (1 atm)	^{1}H-NMR integration ratio (total 100) acyl chloride (**2a**)	hydrolyzed acyl chloride
10 min	N_2	5.0	95.0
	CO_2	31.5	68.5
1 h	N_2	1.5	98.5
	CO_2	11.5	88.5
24 h	N_2	0.1	99.9
	CO_2	0.1	99.9

Table S2. Selectivity difference of phenylacetyl chloride (**2a**) hydrolysis under CO_2 or N_2 in different intervals of time.

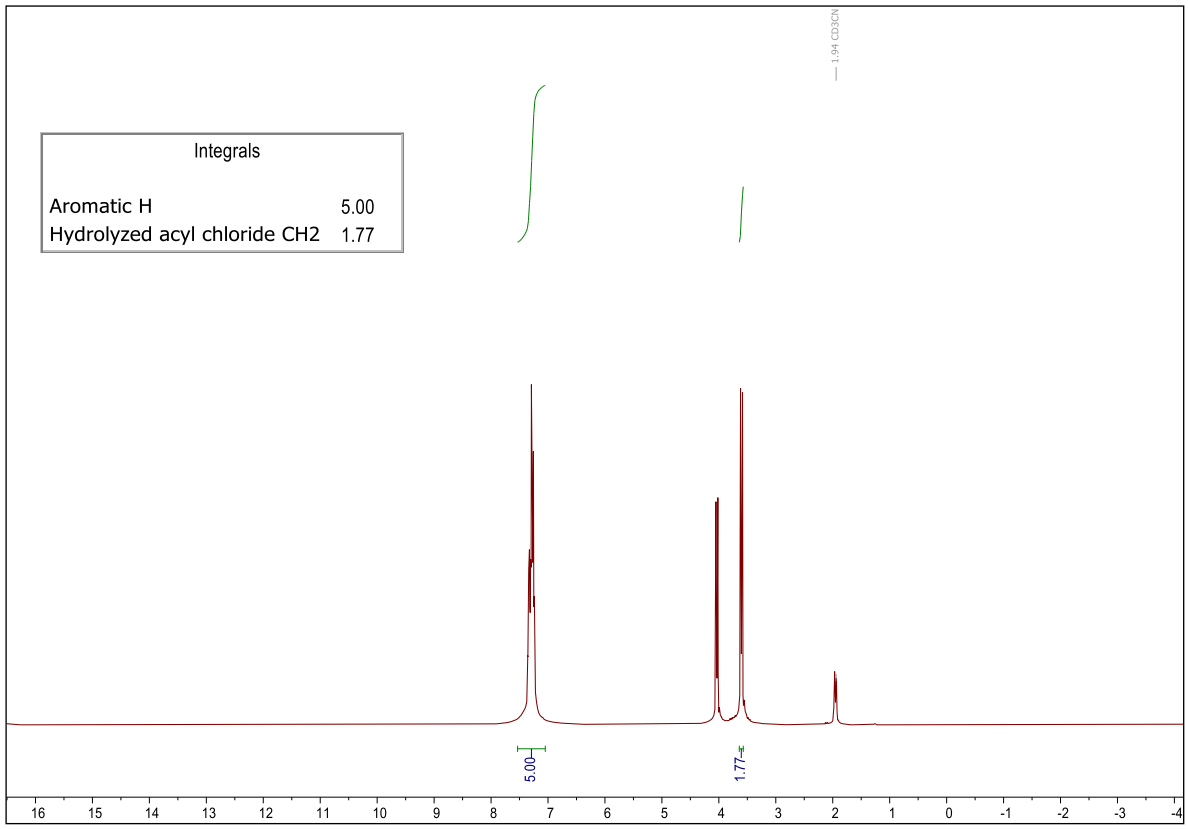


Fig S7. ^{1}H-NMR spectrum of phenyl acetyl acid chloride (**2a**) hydrolysis under CO_2 after 1 h (table S2).

9. Mechanistic studies

The following computational calculations for reaction energy diagram were carried out with Gaussian 1, Revision A.03. When necessary, the geometry was first optimized by varying the dihedral angle 1,2-diamines and carbamates and carbamic acids. Geometry optimization was conducted with the b3lyp/6-31+g(d,p) basis set for all atoms. Vibrational frequencies were calculated at the same level of theory to confirm each structure is whether an energy minimum or a transitions state. The single point energies were calculated with the 6-311++g(d,p) for all atoms.

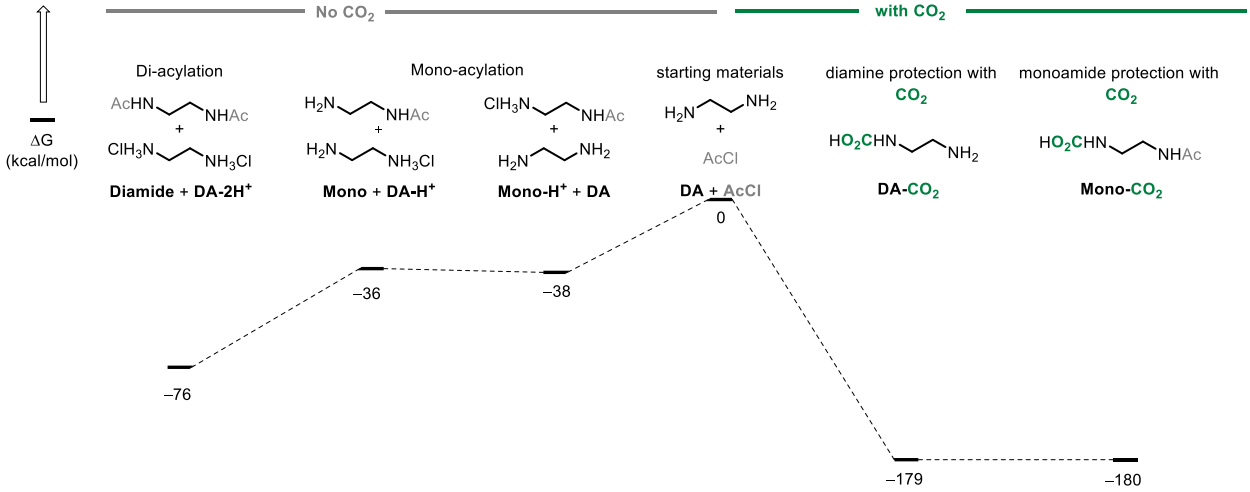


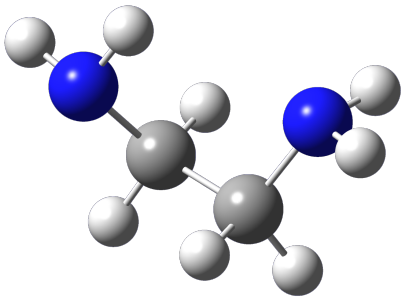
Fig. S8. Calculated energy diagram of diamine (DA) acylation with acetyl chloride in the presence and the absence of CO_2 which can form carbamic acid.

The calculated energy diagram in Figure S8 shows the thermodynamic sinks of plausible intermediates in the reaction medium. After monoacylation, both protonated diamine and monoamide are high-energy reactive intermediates when compared to the diamine and monoamides coordinated with CO_2. This is due to the larger driving force of CO_2 complexation compared to protonation, and as seen from the rapid precipitation upon exposure to CO_2, these intermediates with CO_2 are most likely presented. From these intermediates, the low barrier expected for reactions with acyl chlorides are likely higher or would require decarboxylation of the monoamide, which could thereby account for the difference in selectivity. This hypothesis was further supported by analyzing NMR spectra of the CO_2 adduct of **3b**, suggesting the carbamate formation of monoamide products (desired products) under CO_2 environment.

Table S3. Energy values for Figure S8 (Hartree)

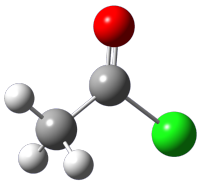
entry	ZPE	tcH	tcG	E	H	G	spEdichloromethane
DA	0.110537	0.116853	0.083057	-190.472031	-190.471087	-190.504883	-190.59382072
AcCl	0.047085	0.052677	0.019230	-613.473671	-613.472727	-613.506175	-613.53025884
CO_2	0.011688	0.015254	-0.009005	-188.632606	-188.631661	-188.655920	-188.36493349
DA-CO_2	0.126893	0.135182	0.094920	-379.093189	-379.092245	-379.132508	-379.24403369
Mono-CO_2	0.163339	0.175480	0.124638	-531.766309	-531.765364	-531.816207	-531.95836964
Mono-H^+	0.161195	0.172359	0.124028	-803.984579	-803.983634	-804.031965	-804.18568159
Mono	0.148207	0.157722	0.114559	-343.138232	-343.137288	-343.180450	-343.30630457
DA-H^+	0.122583	0.130561	0.090656	-651.315007	-651.314063	-651.353969	-651.46932667
Diamide	0.185063	0.198469	0.142622	-495.809014	-495.808070	-495.863916	-496.02409656
DA-$2H^+$	0.138609	0.147893	0.104779	-1112.162238	-1112.161294	-1112.204408	-1112.34501892

ZPE (zero-point point energy correction), tcH (thermal correction to enthalpy), tcG (thermal correction to Gibbschem free energy), E (energy), H (enthalpies), G (Gibbs free energy), spEtoluene (single point energy in dichloromethane). All structures showed zero imaginary frequency, thus confirming that they are not at transition states.



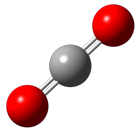
C -0.72656000 0.58763400 0.28517900
H -1.24122300 1.50786500 -0.01043200
H -0.64926100 0.60402600 1.38707900
C 0.68370400 0.60191300 -0.29892800
H 1.17745800 1.54687000 -0.02715600
H 0.60569500 0.56895500 -1.38902900
N -1.47092400 -0.55982800 -0.23453400
H -0.93871600 -1.40748300 -0.06122400
H -2.37291800 -0.65482200 0.21857700
N 1.42630400 -0.59142800 0.13545000
H 2.24743900 -0.74735000 -0.43770700
H 1.74100500 -0.49654700 1.09597300

AcCl



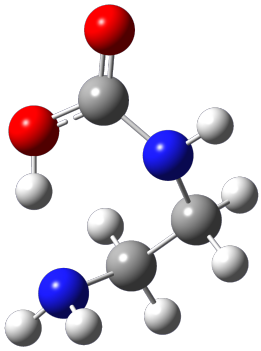
C -0.48771100 0.24242300 0.00005000
O -0.84524900 1.36763500 -0.00000200
C -1.32685900 -1.00095600 0.00004100
H -2.38022400 -0.72261300 -0.00057500
H -1.08955700 -1.60082000 -0.88080600
H -1.09035300 -1.60088100 0.88091700
Cl 1.30644400 -0.14503400 -0.00000400

CO_2



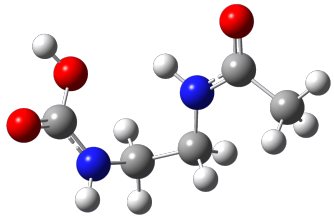
O 0.00000000 0.00000000 1.16074500
C 0.00000000 0.00000000 0.00000000
O 0.00000000 0.00000000 -1.16074500

DA-CO_2



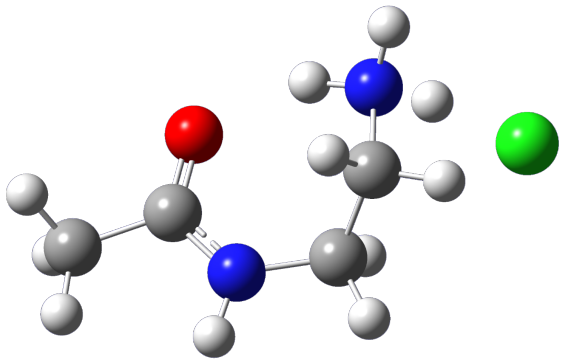
C -1.75338400 0.16882100 0.53447000
H -2.72508800 0.63078700 0.75127900
H -1.39350200 -0.27885100 1.46392500
C -0.81793200 1.29366900 0.09455200
H -0.71871300 1.97612900 0.94948600
H -1.30621600 1.86081100 -0.70636700
N -1.83020800 -0.90538000 -0.46951700
H -0.15776600 -1.33418200 -0.15351200
H -2.51434400 -1.60838500 -0.20976300
N 0.50763500 0.90776500 -0.41543200
H 1.07891100 1.71412200 -0.62951700
C 1.34742700 -0.13405300 -0.00624300
O 2.54600000 0.01311400 0.06186800
O 0.75664900 -1.31305100 0.23545400
H -2.08312400 -0.54825600 -1.38613900

Mono-CO_2



C 0.86001700 1.55632000 -0.56032900
H 1.09733700 2.62294700 -0.54336000
H 1.06517200 1.19933900 -1.57059500
C -0.62826500 1.38837000 -0.23573400
H -1.18962000 2.04656200 -0.91358400
H -0.81492300 1.73953400 0.78466100
N 1.76592900 0.88083800 0.36060200
H 2.02467200 1.33989800 1.22005100
N -1.04719800 0.00239900 -0.37532800
H -0.42218400 -0.63766700 -0.84907300
C -2.24333300 -0.54558600 0.00672900
O -2.49938100 -1.71932800 -0.21261200
C -3.21799200 0.37582900 0.71910200
H -2.80969700 0.70965900 1.67781600
H -3.43951600 1.26660500 0.12448300
H -4.13804700 -0.17585700 0.89902300
C 2.27741800 -0.37266400 0.23659000
O 3.02077800 -0.90708300 1.02851200
O 1.85836800 -0.98017000 -0.91614400
H 2.27049200 -1.85464500 -0.92252800

Mono-H^+



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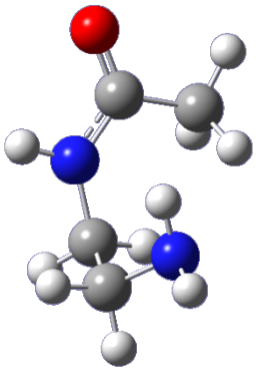
Monoamide



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O 2.31926900 -0.46666000 -0.84538400
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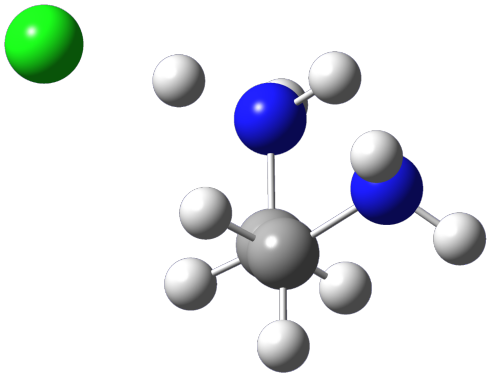
DA-H^+



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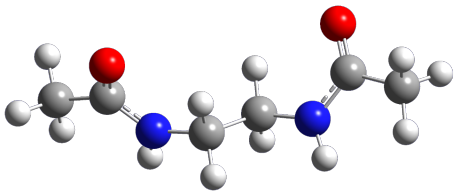
Diamide



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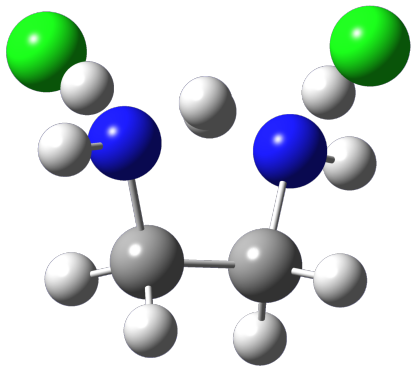
DA-2H^{+}



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H 1.32943300 1.71845700 0.75596900
N -0.02139600 0.23633900 -1.42023500
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N 0.02139000 0.23499900 1.41997800
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Cl -2.40332500 -0.86304400 0.04869600
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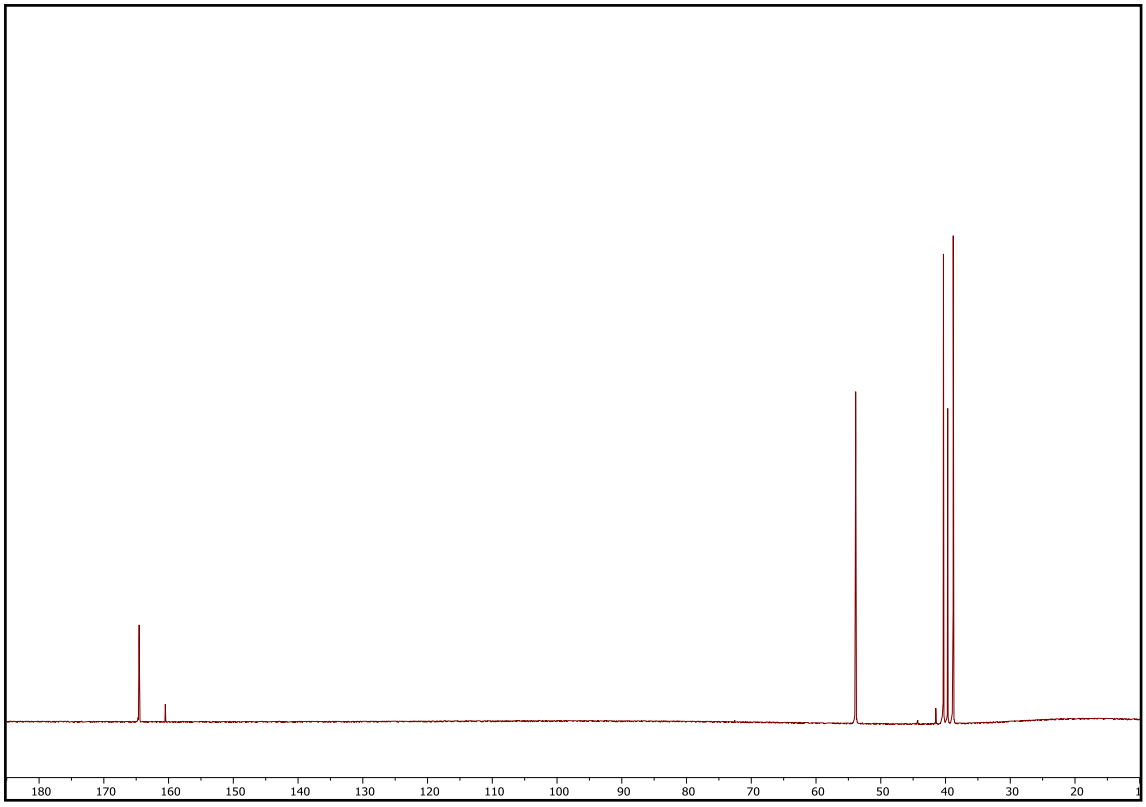
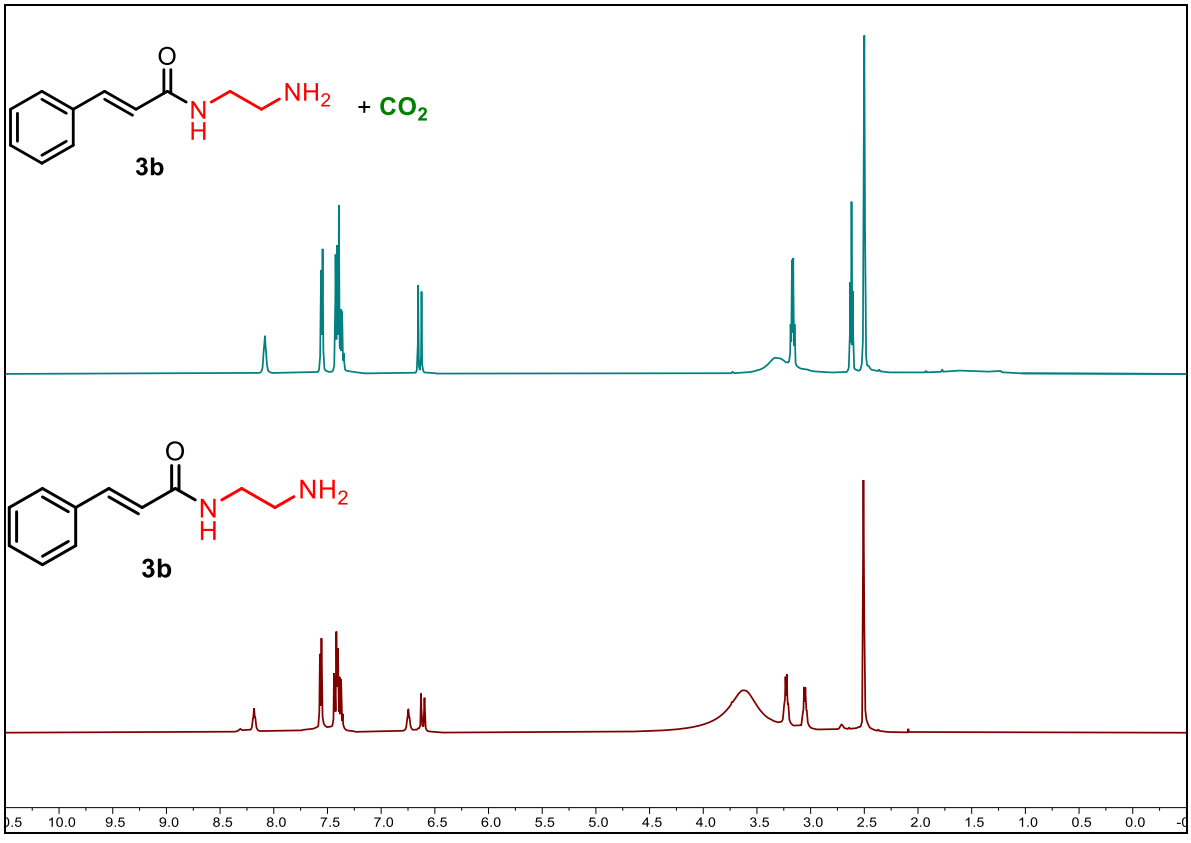


Fig S9. ^{13}C-NMR in methanol-d_4 spectrum of CO_2 adduct of 1,2-diamine (**1a**) precipitated from DCM.



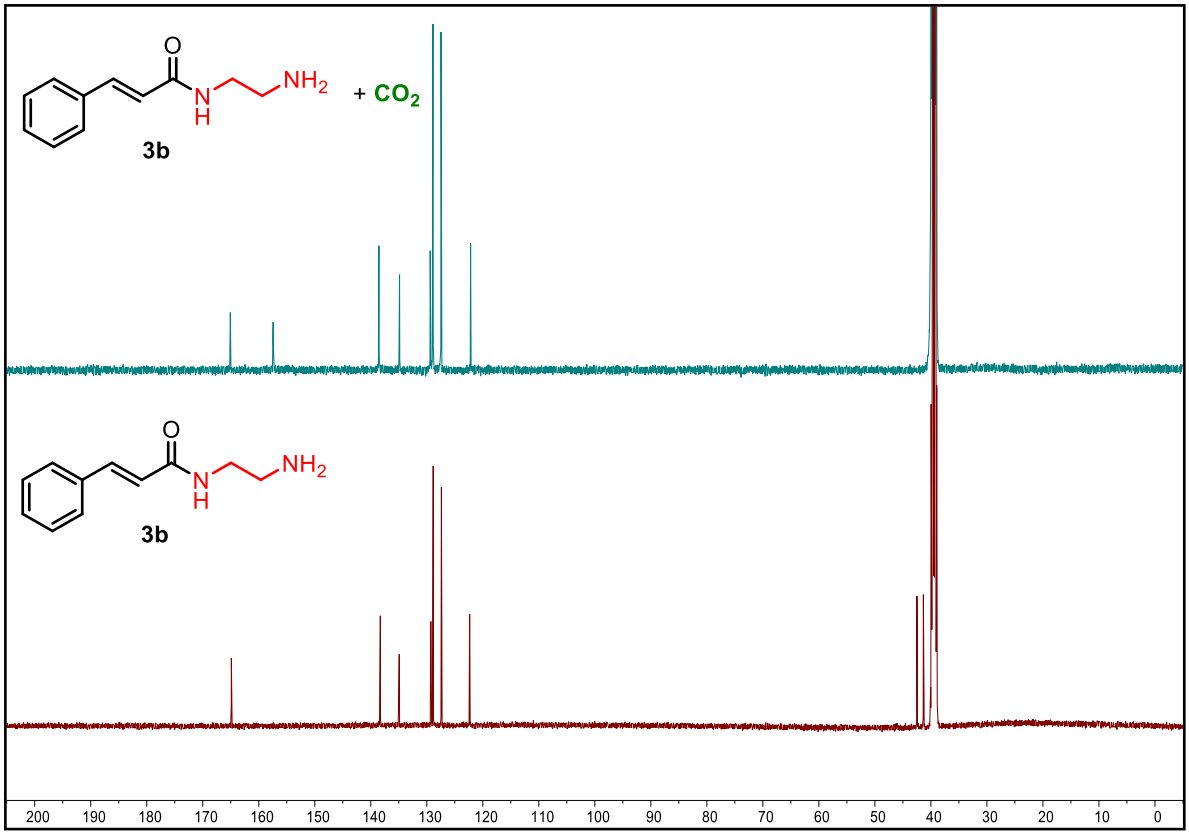


Fig S10. ^{1}H and ^{13}C-NMR spectra of CO_2 treated sample of *N*-(2-aminoethyl)cinnamamide (**3b**) (top), and of isolated *N*-(2-aminoethyl)cinnamamide (**3b**) (bottom) in DMSO-d_6. Note: significant shifts of ^{1}H NMR CH2 signals were observed including a potential carbamate carbon on 13C NMR spectrum of **3b**+CO_2 (157 ppm)

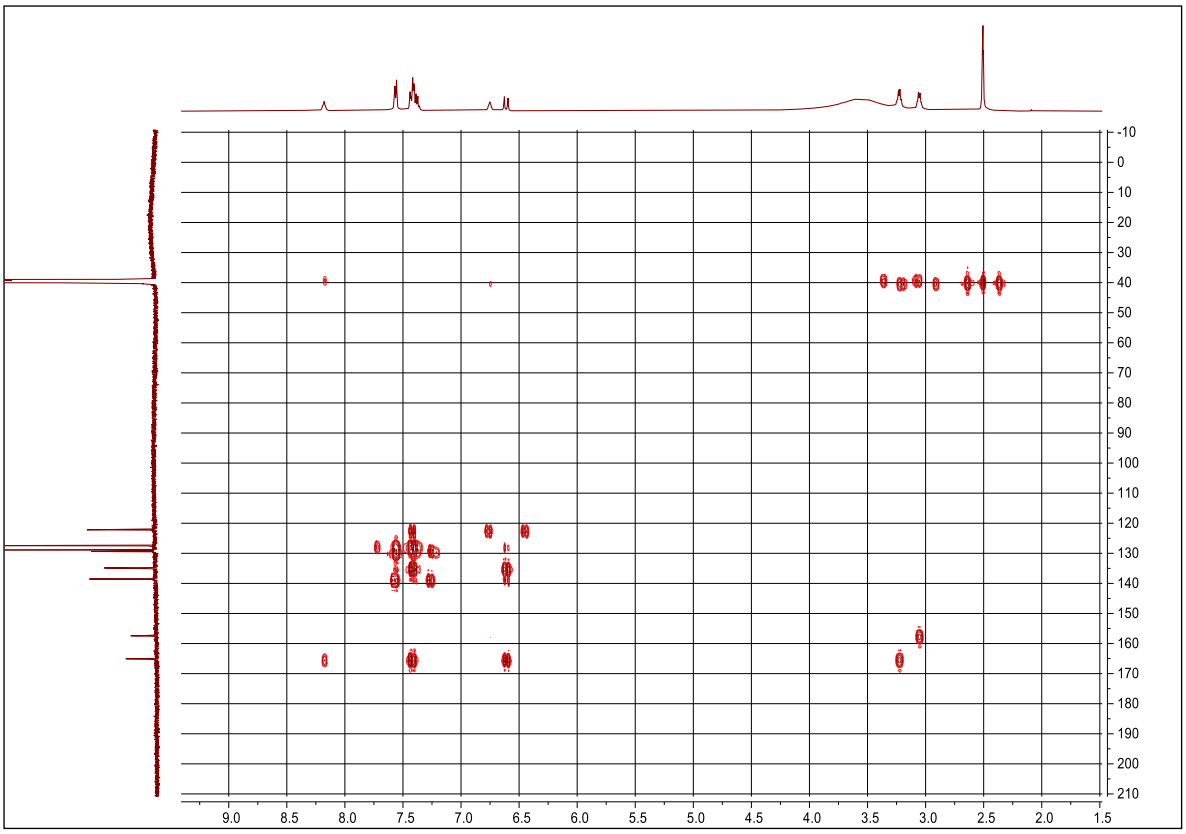
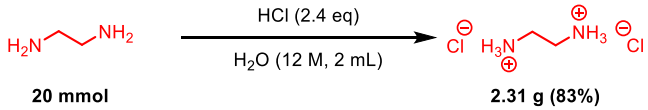


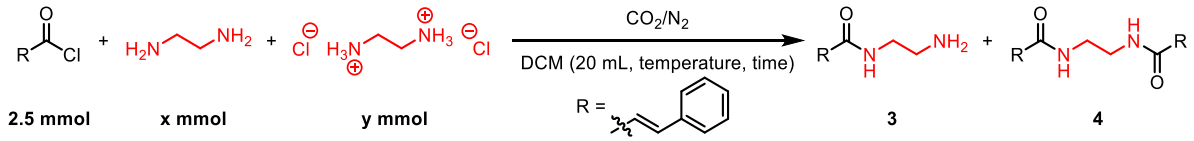
Fig S11. [^{13}C,^{1}H]-HMBC spectrum of CO_2 treated sample of *N*-(2-aminoethyl)cinnamamide (**3b**) in DMSO-d_6.

Protonation of ethylene diamine



Ethylene diamine (1.4 mL, 20 mmol) was dropwise added to cooled concentrated HCl (5 mL). The protonated diamine solution was added dropwise into acetone (50 mL). The precipitate was filtered off and washed with acetone to give a white powder of ethane-1,2-diaminium chloride (2.31 g, 83%) and used as it in following screenings

General Procedure for control experiments with protonated diamine



To an oven-dried 25 mL round bottom flask, ethane-1,2-diaminium (x mmol), ethylene diamine (y mmol) and DCM (10 mL) were charged under N_2 or CO_2 atmosphere and stirred for 15 min at given temperatures. A solution of cinnamoyl chloride (2.5 mmol) was prepared under N_2 in DCM (10 mL), cooled to given temperature, and transferred to the reaction flask containing the diamine. The reaction mixture was allowed to stir at given temperature for allotted time then quenched with water (5 mL) and left to stir to room temperature. The crude reaction mixture was dissolved in MeOH and MeCN (1:1, v/v, total 50-100 mL until the mixture becomes homogeneous). An aliquot was analysed by ^{1}H-NMR spectroscopy in DMSO-d_6, and crude yield was determined by integration of α-ethylene protons as shown in Figure S2.

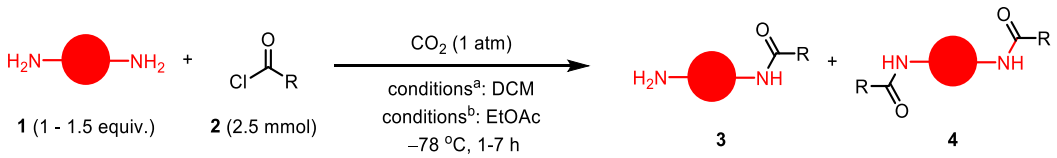
Entry	x mmol	y mmol	Atmosphere (1 atm)	Temperature (°C)	Time (h)	Yield	
						Mono (%)	Di (%)
1	0	2.5	CO_2	rt	9	0	0
2	0	2.5	N_2	rt	9	0	0
3	1.25	1.25	CO_2	rt	24	13	53
4	1.25	1.25	N_2	rt	24	27	43
5	1.25	1.25	CO_2	0	24	trace	40
6	1.25	1.25	N_2	0	24	trace	35
7	1.25	1.25	CO_2	-78	24	trace	11
8	1.25	1.25	N_2	-78	24	trace	28

Table S4. Control experiments of cinnamoyl chloride (**2b**) under different varying amounts of protonated diamine and temperature.

While the fully protonated diamine is inert even at room temperature, we see half-protonation only slightly helps under nitrogen atmosphere. The increased selectivity towards monoamide can therefore not simply be due to protonation protecting the second amine. Since the protonation lowered the selectivity towards monoamide, these experiments indicate that both amines in the diamine is relevant for the selectivity in conjunction with CO_2 as would be expected by the formation of carbamic acid/carbamate intermediate.

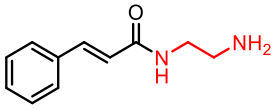
10. Substrate scope

General Procedure for synthesis of monoamides in Figure 4A



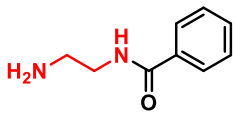
To an oven-dried 50 mL round bottom flask, diamine (1, 2.5 – 3.75 mmol, 1 – 1.5 eq) and a solvent a) or b) (10 mL) is charged and allowed to stir under CO_2 atmosphere for 15 min at –78 °C. A solution of acyl chloride (**2**, 2.5 mmol) was prepared under N_2 in a solvent a) or b) (10 mL), cooled to –78 °C, and transferred to the reaction flask containing the diamine. The reaction mixture was allowed to stir at –78 °C for the allotted time then quenched with methanol (10 mL) and left to stir to room temperature. If needed, a small amount of methanol was added until the mixture became homogeneous. An aliquot was taken and concentrated to record ^{1}H-NMR spectra. Selectivity and conversion with **conditions a**) of **all** monoamides (except **3n**) were calculated according ^{1}H-NMR spectra of crude mixtures as shown in section S12, following the same procedure as per Figs. S1-3. Of the monoamides that were isolated (**3b**, **3e-h**, **3k**, **3n**, **3p-s**), the isolation procedure is described separately for each compound. NMR spectra are presented in section S13. Selectivity and conversion with **conditions b**) of monoamides (**3b**, **3c**, **3d,3e, 3f, 3g, 3j, 3k**, **3l**, **3m, 3r**) were calculated according to ^{1}H-NMR spectra of crude mixtures while using 1,2,3-trimethoxybenzene (0.025 mol/L) as internal standard. The example of crude NMR is presented in section S12.

N-(2-aminoethyl)cinnamamide (**3b**)[3]



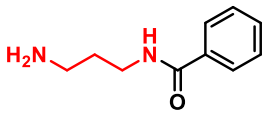
Compound isolation: After synthesis according to general procedure, 10 mL of 1 M HCl water solution was added and washed with chloroform 3 x 25 mL. 6 M NaOH solution is added to basify until the NaCl salt crashed out (around 10 mL). Compound **3b** was then extracted with mixture of chloroform and DCM (1:1) 5 x 10 mL. Organic phase was concentrated under vacuum to give pure **3b** (198 mg, 42%) as a yellow oil. ^{1}H-NMR (500 MHz, DMSO-d_6) δ = 8.09 (t, J = 5.6 Hz, 1H), 7.59 – 7.54 (m, 2H), 7.45 – 7.38 (m, 3H), 7.41 – 7.34 (m, 1H), 6.65 (d, J = 15.9 Hz, 1H), 3.18 (q, J = 6.2 Hz, 2H), 2.63 (t, J = 6.4 Hz, 2H), 1.57 (s, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ = 164.93, 138.33, 134.95, 129.32, 128.89, 127.43, 122.38, 42.53, 41.38. HRMS m/z: $[M + H]^+$ Calculated for $C_{11}H_{15}N_2O$ 191.1184; Found 191.1181.

N-(2-aminoethyl)benzamide (**3e**)



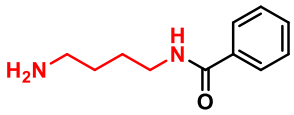
Compound isolation: After synthesis according to general procedure, the reaction mixture is concentrated and dissolved in H_2O (10 mL). The aqueous phase is washed with ethyl acetate (2 x 25 mL). The combined organic phase is back-extracted with H_2O (10 mL), and combined aqueous phase is concentrated to a residue. Diethyl ether (40 mL) is added and allowed to stir (< 500 RPM). Anhydrous ethanol is added dropwise until the solution is homogenous and precipitation is induced. The solution is filtered and concentrated to yield **3e** (166 mg, 41%) as a pale yellow oil that solidifies upon standing; ^{1}H-NMR (500 MHz, DMSO-d_6) δ = 8.51 (br t, 1Hf), 7.88 (dd, J = 7.0, 1.5 Hz, 2H), 7.52 (tt, J = 7.4, 2.1 Hz, 1H), 7.46 (t, J = 7,0 Hz, 2H), 3.34 (q, J = 6.0 Hz, 2H), 2.77 (t, J = 6.4 Hz, 2H) ^{13}C-NMR (126 MHz, DMSO-d_6) δ = 166.39, 134.47, 131.06, 128.17, 127.20, 41.46, 40.56. HRMS (ESI) m/z: $[M + H]^+$ Calculated for $C_9H_{13}N_2O$; 165.10224, Found: 165.10224.

N-(3-aminopropyl)benzamide (**3f**)



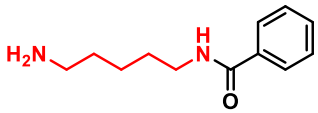
Compound isolation: Compound was isolated with same procedure as with **3e** to afford **3f** (186 mg, 44%) as a colorless oil; ^{1}H-NMR (500 MHz, DMSO-d_6) δ = 8.53 (br t, 1H), 7.83 (dt, *J* = 6.9, 1.6 Hz, 2H), 7.52 (tt, 7.2, 2.1 Hz, 1H), 7.46 (t, *J* =7.8, 2H), 3.32 (q, *J* = 5.7 Hz, 2H), 2.62 (t, J =6.7 Hz, 2H), 1.61 (p, J =6.8 Hz, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ = 166.10, 134.62, 130.97, 128.21, 127.05, 39.09, 36.99, 32.31. HRMS (ESI) m/z: $[M + H]^+$ Calculated for $C_{10}H_{15}N_2O$; 179.11789, Found: 179.11788.

N-(4-aminobutyl)benzamide (**3g**)



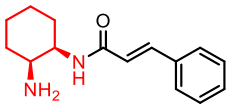
Compound isolation: Compound was isolated with same procedure as with **3e** to afford **3g** (366 mg, 76%) as a colorless oil that solidifies upon standing; ^{1}H-NMR (500 MHz, DMSO-d_6) δ = 8.52 (br t, 1H), 7.84 (dt, *J* = 7.1, 1.2 Hz, 2H), 7.51 (tt, *J* =7.3, 2.2 Hz, 1H), 7.45 (tt, *J* =7.1, 1.6 Hz, 2H), 3.25 (q, *J* =6.2 Hz, 2H), 2.63 (t, *J* =7.0 Hz, 2H), 1.54 (p, *J* =6.7 Hz, 2H), 1.45 (p, *J* =6.8 Hz, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ = 166.06, 134.69, 130.98, 128.21, 127.13, 40.52, 38.93, 28.90, 26.53. HRMS (ESI) m/z: $[M + H]^+$ Calculated for $C_{11}H_{17}N_2O$; 193.13354, Found: 193.13352.

N-(5-aminopentyl)benzamide (**3h**)



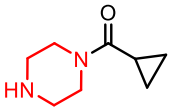
Compound isolation: Compound was isolated with same procedure as with **3e** to afford **3h** (307 mg, 60%) as a pale yellow oil that solidifies upon standing; ^{1}H-NMR (500 MHz, DMSO-d_6) δ = 8.46 (br t, 1H), 7.84 (d, *J* =7.5 Hz, 2H), 7.51 (t, *J* =7.2 Hz, 1H), 7.45 (t, *J* =7.7 Hz, 2H), 3.25 (q, *J* =6.5 Hz, 2H), 2.64 (t, 7.2 Hz), 1.56-1.42 (m, 4H), 1.37-1.31 (m, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ = 166.08, 134.70, 128.20, 127.12, 30.13, 30.07, 28.82, 23.62, 23.28i HRMS (ESI) m/z: $[M + H]^+$ Calculated for $C_{12}H_{19}N_2O$; 207.14919, Found: 207.14916.

N-((1R,2S)-2-aminocyclohexyl)cinnamamide (**3k**)



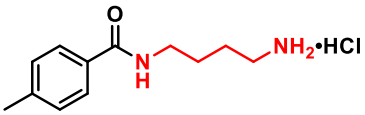
Compound isolation: Compound was isolated with same procedure as with **3b** to afford **3k** (431 mg, 70%) as a yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 15.6 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.42 – 7.30 (m, 3H), 6.56 – 6.45 (m, 1H), 4.10 (tt, *J* =8.3, 4.0 Hz, 1H), 3.15 (dt, *J* = 5.8, 3.7 Hz, 1H), 2.27 (s, 2H), 1.79 – 1.39 (m, 8H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ = 129.53, 128.78, 127.79, 121.31, 50.01, 49.80, 31.96, 27.53, 23.14, 20.35. HRMS m/z: $[M + H]^+$ Calculated for $C_{15}H_{20}N_2OH$ 245.1653; Found 245.1652.

Cyclopropyl(piperazin-1-yl)methanone (**3n**)[4]



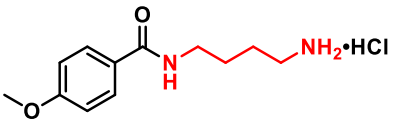
Compound isolation: Compound was isolated with same procedure as with **3e** to afford **3n** (182 mg, 47%) as a colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 3.75 – 3.37 (m, 4H), 2.99 – 2.60 (m, 4H), 1.66 (tt, *J* = 8.0, 4.7 Hz, 1H), 1.19 (s, 1H), 0.99 – 0.86 (m, 2H), 0.75 – 0.59 (m, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ = 172.02, 77.29, 77.04, 76.78, 46.72, 46.47, 45.86, 43.25, 31.93, 29.70, 22.69, 14.12, 10.93, 7.33. HRMS m/z: $[M + H]^+$ Calculated for $C_8H_{14}N_2OH$ 155.1184.; Found 155.1181.

N-(4-aminobutyl)-4-methylbenzamide (**3p**) hydrochloride (**3p·HCl**)



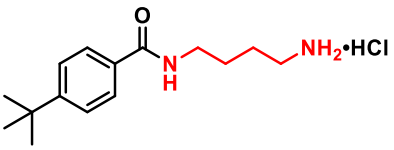
Compound isolation: Compound was isolated with same procedure as with **3e** to afford **3p** (275 mg, 45%) as white crystals; ^{1}H-NMR (500 MHz, DMSO-d_6) δ = 8.46 (t, J = 5.8 Hz, 1H), 7.86 (br s, 3H), 7.76 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 7.9 Hz, 2H), 3.26 (q, J = 5.9, 2H), 2.79 (q, J = 6.4 Hz, 2H), 1.62-1.53 (m, 4H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ = 166.04, 140.88, 131.75, 128.74, 127.15, 38.56, 38.36, 26.18, 24.53, 20.92. HRMS (ESI) m/z: $[M + H]^+$ Calculated for $C_{12}H_{19}N_2O$; 207.14919, Found: 207.14917.

N-(4-aminobutyl)-4-methoxybenzamide (**3r**) hydrochloride (**3r·HCl**)



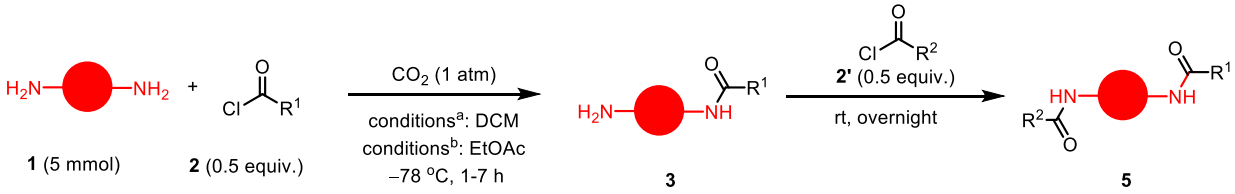
Compound isolation: Compound was isolated with same procedure as with **3e** to afford **3r** (341 mg, 53%) as white crystals; ^{1}H-NMR (500 MHz, DMSO-d_6) δ = 8.41 (t, J = 5.1 Hz, 1H), 7.92 (br s, 3H), 7.84 (d, J = 8.6 Hz, 2H), 6.98 (d, J = 8.7 Hz, 2H), 3.80 (s, 3H), 3.25 (q, J = 6.1 Hz, 2H), 2.79 (t, J = 6.9 Hz, 2H), 1.61-1.52 (m, 4H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ = 165.67, 161.45, 128.96, 126.77, 113.42, 55.34, 38.57, 38.35, 26.24, 24.54 HRMS (ESI) m/z: $[M + H]^+$ Calculated for $C_{12}H_{19}N_2O_2H$; 223.14410, Found: 223.14409.

N-(4-aminobutyl)-4-(*tert*-butyl)benzamide (**3s**) hydrochloride (**3s·HCl**)



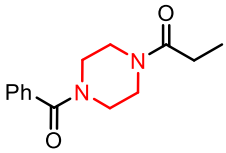
Compound isolation: Compound was isolated with same procedure as with **3e** to afford **3s** (262 mg, 37%) as colorless oil that crystalizes upon standing; ^{1}H-NMR (500 MHz, DMSO-d_6) δ = 8.48 (t, J = 5.2 Hz, 1H), 7.90 (br s, 3H), 7.79 (d, J =8.6 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 3.27 (q, J = 5.9 Hz, 2H), 2.79 (q, J = 6.4 Hz, 2H), 1.61-1.54 (m, 4H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ = 166.07, 153.82, 131.81, 127.01, 134.96, 38.55, 38.33, 34.58, 30.95, 26.17, 24.50. HRMS (ESI) m/z: $[M + H]^+$ Calculated for $C_{15}H_{25}N_2O$; 249.19614, Found: 249.19611.

Synthesis of unsymmetric diamides in Fig. 4B



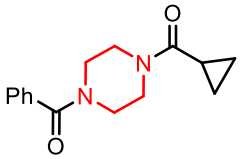
General procedure of monoacylation reaction under CO_2 was followed until quenching the reaction with water. Instead of that, 2.5 mmol of second acylating agent was added to the reaction and left stirring overnight in room temperature. Selectivity and conversion of compounds (conditions[a]) **5c**, **5d**, **5e**, **5g**, **5h**, **5j**, **5k**, and **5l** were calculated according ^{1}H-NMR spectra of crude mixtures, following the same procedure as per Figs. S1-2. The side product was assigned as a symmetrical diamide from 1st acylation reaction. Crude ^{1}H-NMR spectra are presented in section S12. Compounds **5c**, **5d**, **5e**, **5g**, **5h**, **5j**, **5l** were also synthesized with the conditions[b]. Selectivity and conversion were calculated according to ^{1}H-NMR spectra of crude mixtures while using 1,2,3-trimethoxybenzene (0.025 mol/L) as internal standard.

1-(4-benzoylpiperazin-1-yl)propan-1-one (*Sunifiram*) (**5a**)[5]



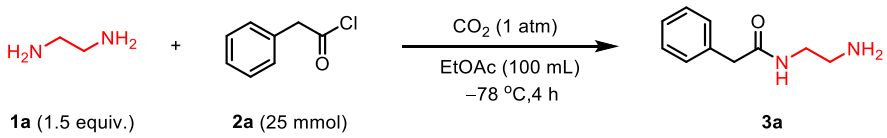
Compound isolation: The crude reaction mixture was filtered to remove diamine-CO_2 adducts. The filtrate was subjected to acid-base work up to remove hydrolyzed acyl chloride and monoamides. The symmetric diacylated products were crystalized out in DCM and *n*-heptane mixture to yield **5a** (345 mg, 56%) after solvent evaporation as a colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.41 (q, *J* = 6.8 Hz, 5H), 3.75 (s, 4H), 3.59 – 3.54 (m, 4H), 2.36 (q, *J* = 7.2 Hz, 2H), 1.16 (t, *J* = 7.3 Hz, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ = 172.59, 170.69, 135.18, 133.09, 130.11, 129.99, 128.66, 128.34, 127.09, 77.30, 77.05, 76.79, 29.70, 26.52, 9.38. HRMS m/z: $[M + H]^+$ Calculated for $C_{14}H_{18}N_2O_2H$ 247.1446; Found 247.1440.

(4-benzoylpiperazin-1-yl)(cyclopropyl)methanone (**5b**)[6]



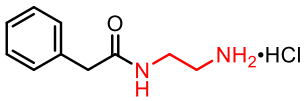
Compound isolation: Compound was isolated with same procedure as with 5**a** to afford **5b** (521 mg, 80%) as a colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.43 (qdd, *J* = 6.5, 4.2, 2.2 Hz, 5H), 3.70 (s, 8H), 1.73 (tt, *J* = 7.9, 4.7 Hz, 1H), 1.01 (tt, *J* = 4.8, 3.2 Hz, 2H), 0.83 – 0.77 (m, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ = 172.35, 170.67, 135.26, 130.08, 128.65, 127.10, 127.08, 11.05, 7.70, 7.68. HRMS m/z: $[M + H]^+$ Calculated for $C_{15}H_{18}N_2O_2H$ 259.1446; Found 259.1442.

11. A specific procedure for a large scale reaction



To a 250 mL round bottom 3-neck flask, diamine (**1a**, 37.5 mmol) and ethyl acetate (50 mL) were added under CO_2 atmosphere and stirred for 20 min at –78 °C. A solution of acyl chloride was prepared under N_2 by mixing an acyl chloride (**2a**, 25 mmol) in ethyl acetate (50 mL) at –78 °C and then transferred in (dropwise using cannula and N_2 flow to control the flow) to the reaction flask containing the diamine. The reaction mixture was stirred at the same temperature until quenched with methanol (100 mL) and then the mixture was warmed to room temperature. An aliquot was taken to record crude ^{1}H-NMR spectra (presented in section S11) and calculate the conversion and selectivity as per Fig. S1.

N-(2-aminoethyl)-2-phenylacetamide (**3a**) hydrochloride (**3a**·**HCl**)[7]



Compound isolation: The crude reaction mixture was concentrated and redissolved in H_2O (100 mL). The aqueous phase was washed with chloroform (3x50 mL) and back-extracted with H_2O (50 mL). The combined water phases were evaporated, and diethyl ether (50 mL) and absolute ethanol (100 mL) was added and left to stir for 30 min. After stirring the mixture was filtered, and filtrate was concentrated under vacuum to give protonated **3a** monoamide (2.62 g, 49%) as a off-white solid. ^{1}H-NMR (500 MHz, DMSO-d_6) δ = 8.45 (t, J = 5.7 Hz, 1H), 8.16 (s, 6H), 7.47 (s, 1H), 7.34 – 7.19 (m, 3H), 3.45 (s, 1H), 3.30 (q, J = 6.2 Hz, 1H), 3.07 (s, 2H), 2.86 (t, J = 6.4 Hz, 1H), 2.60 (s, 1H), 2.48 (s, 1H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ = 170.79, 136.06, 129.10, 128.15, 126.35, 42.26, 38.48, 36.78, 36.55. HRMS m/z: $[M + H]^+$ Calculated for $C_{10}H_{15}N_2O$ 179.1184; Found 179.1179.

12. Crude ^{1}H-NMR Spectra

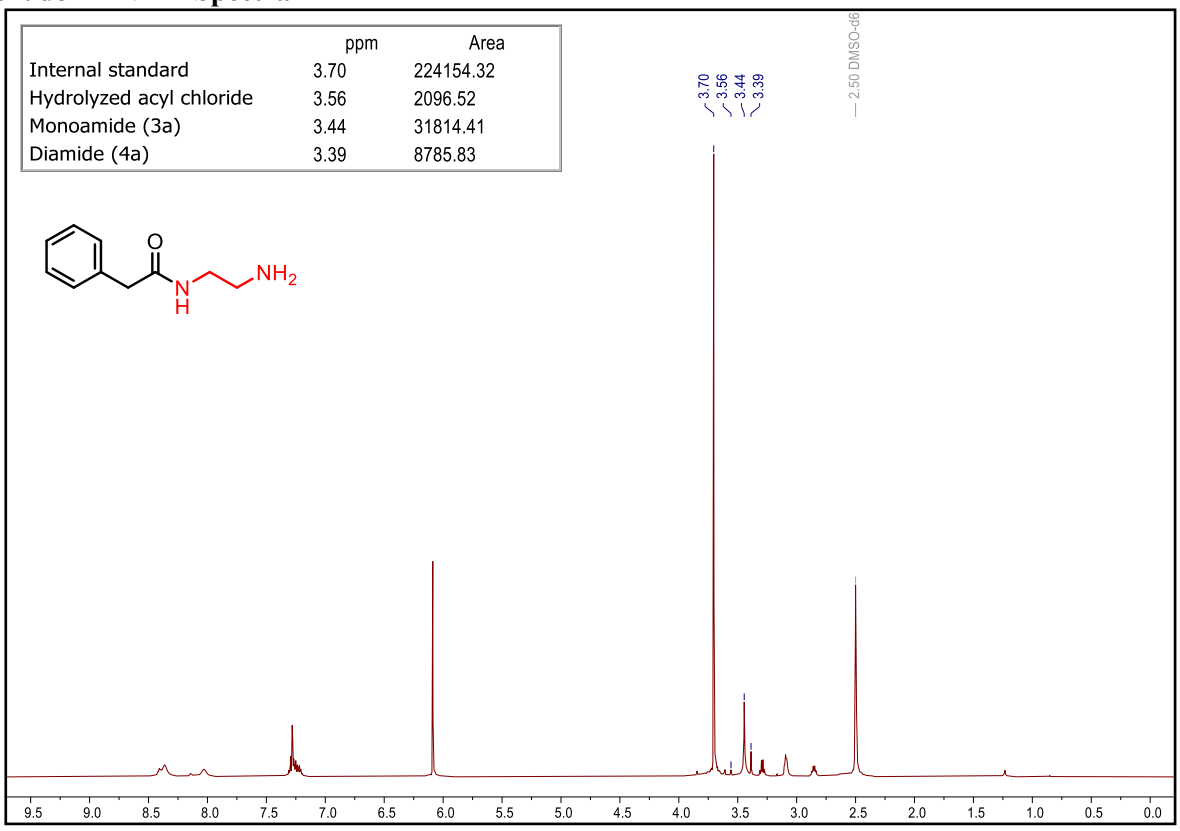


Fig S12. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3a** (conditions[a]: DCM).

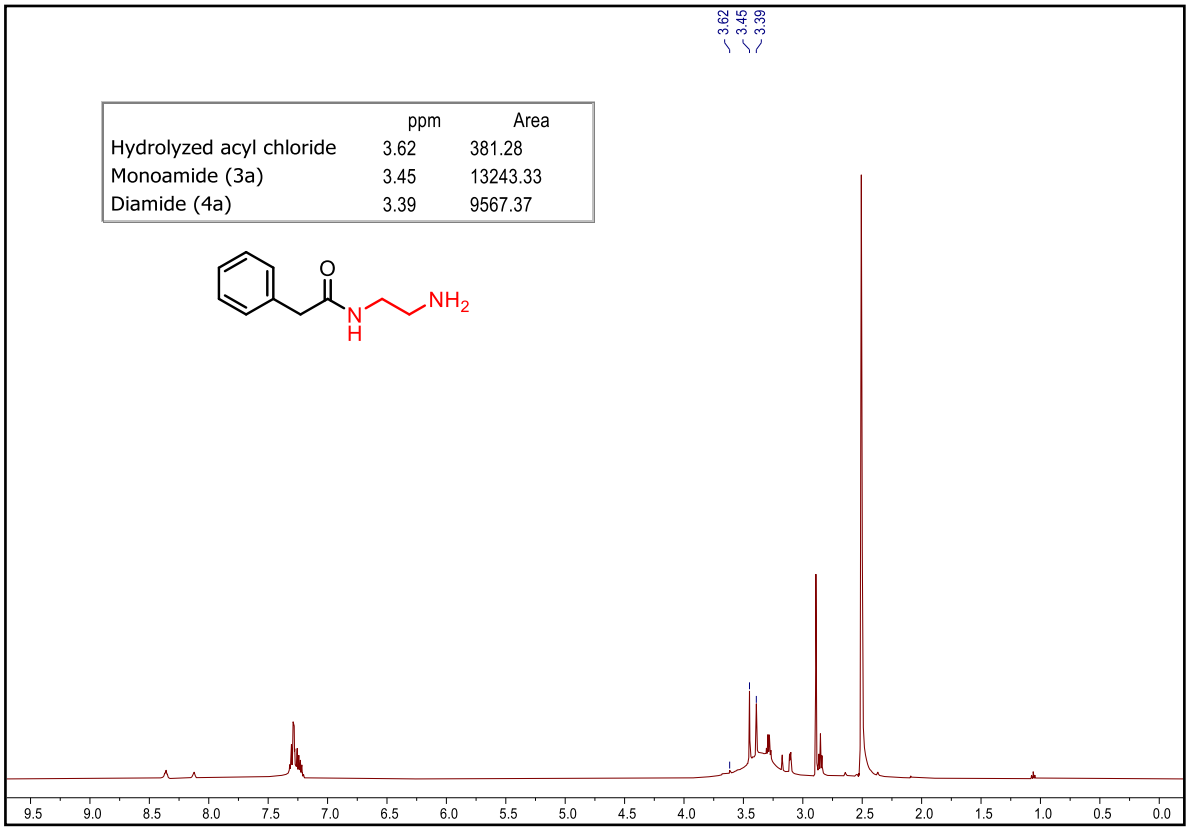


Fig S13. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3a** (conditions[b]: EtOAc).

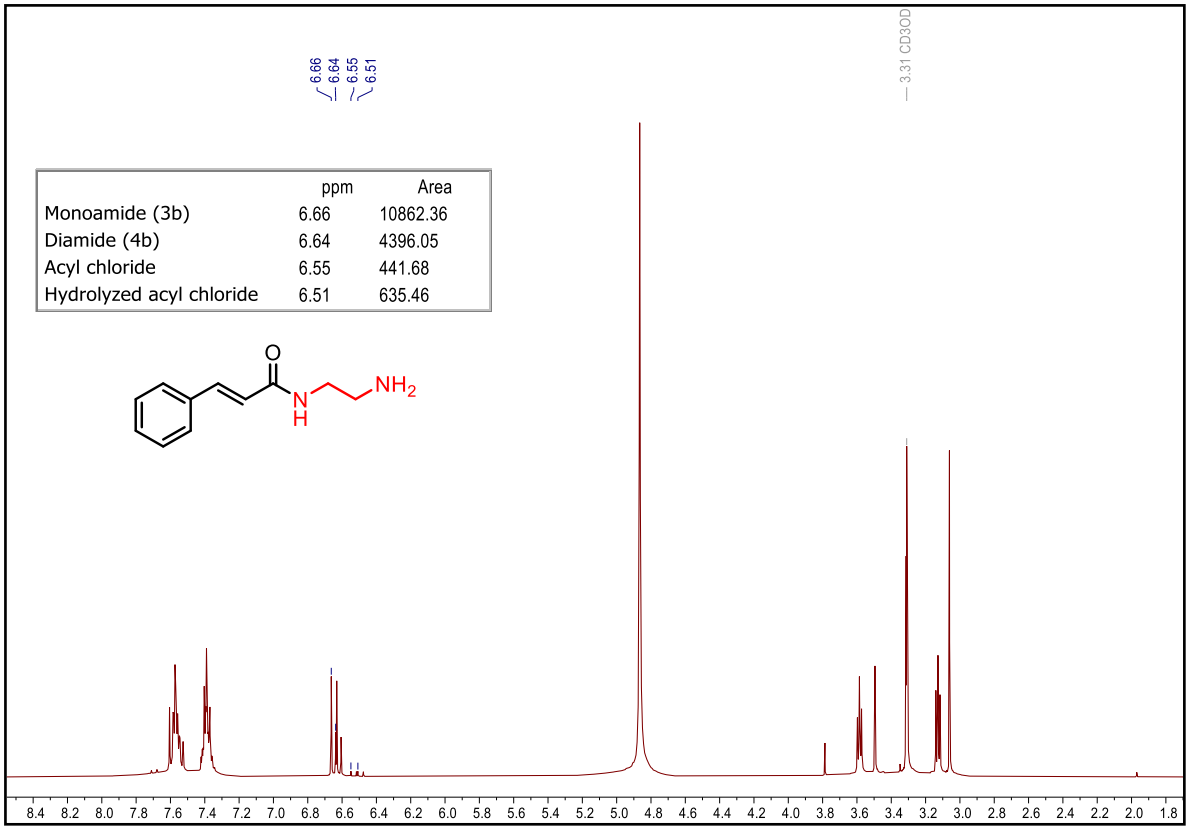


Fig S14. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3b** (conditions[a]: DCM).

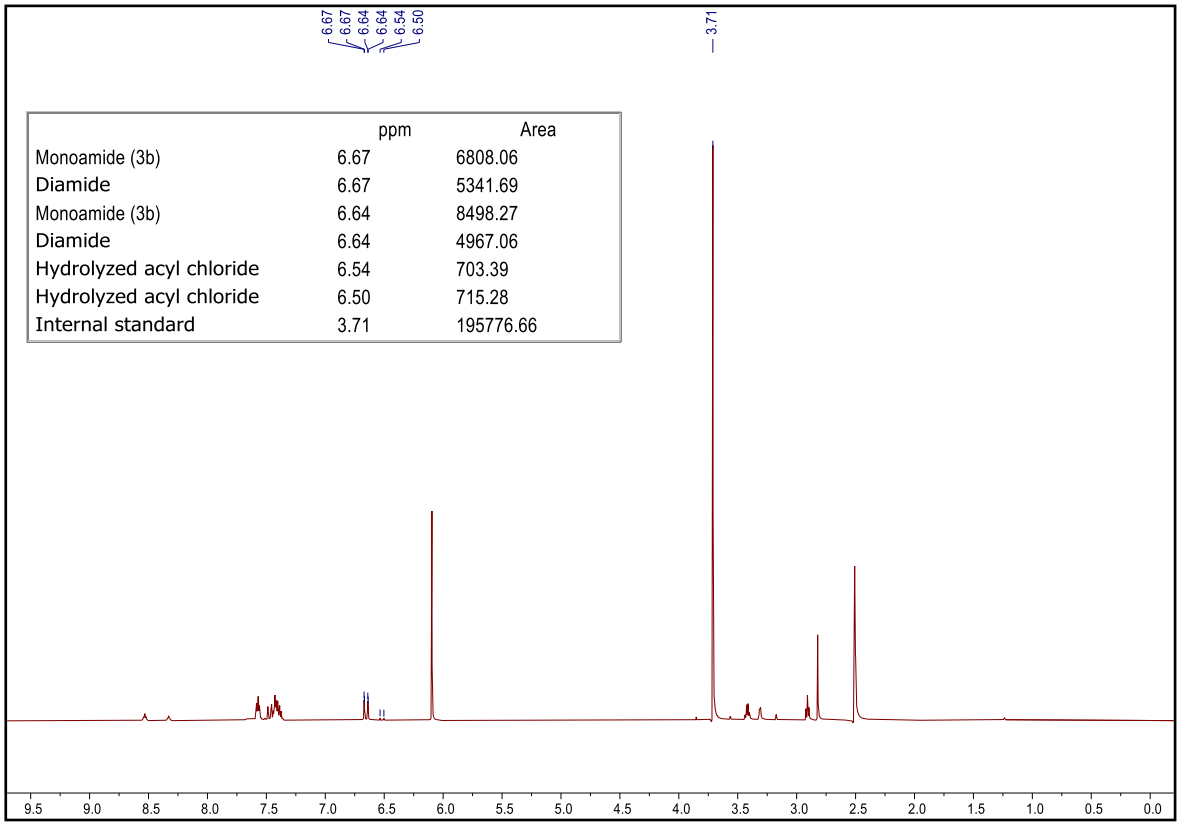


Fig S15. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3b** (conditions[b]: EtOAc).

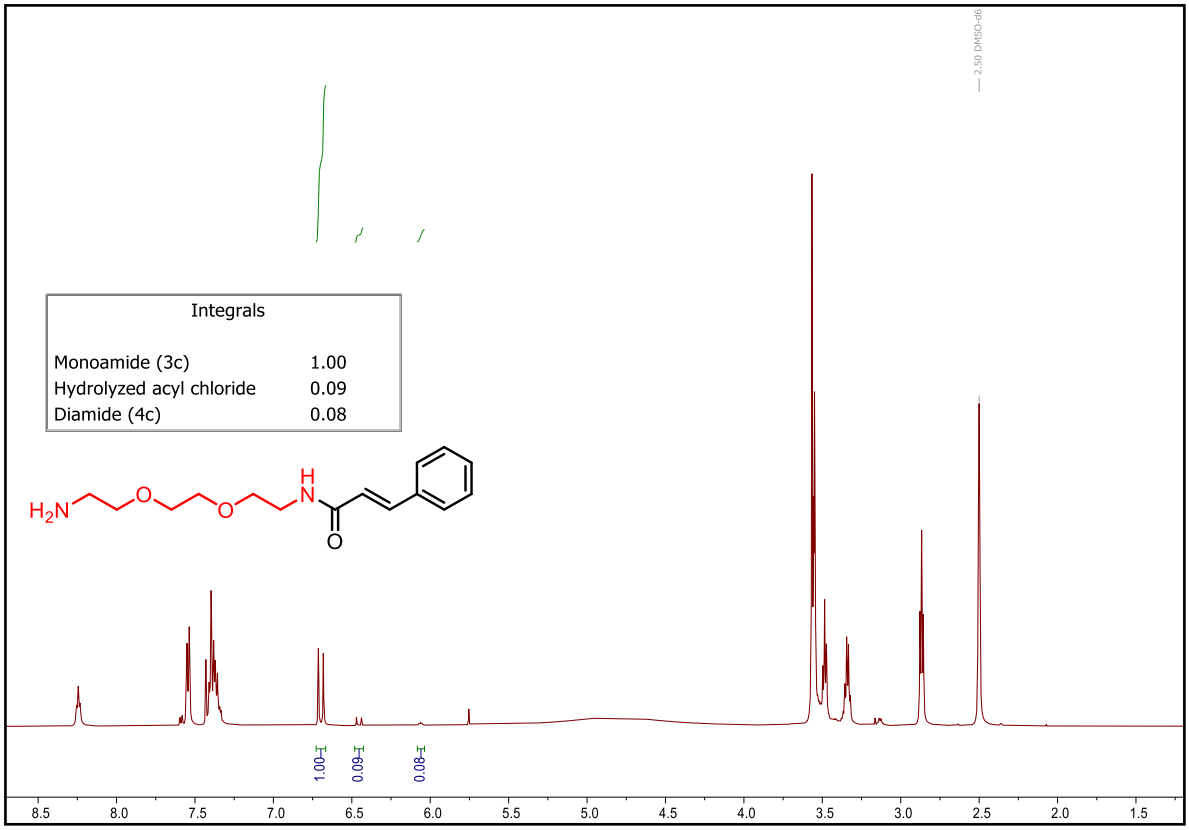


Fig S16. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3c** (conditions[a]: DCM).

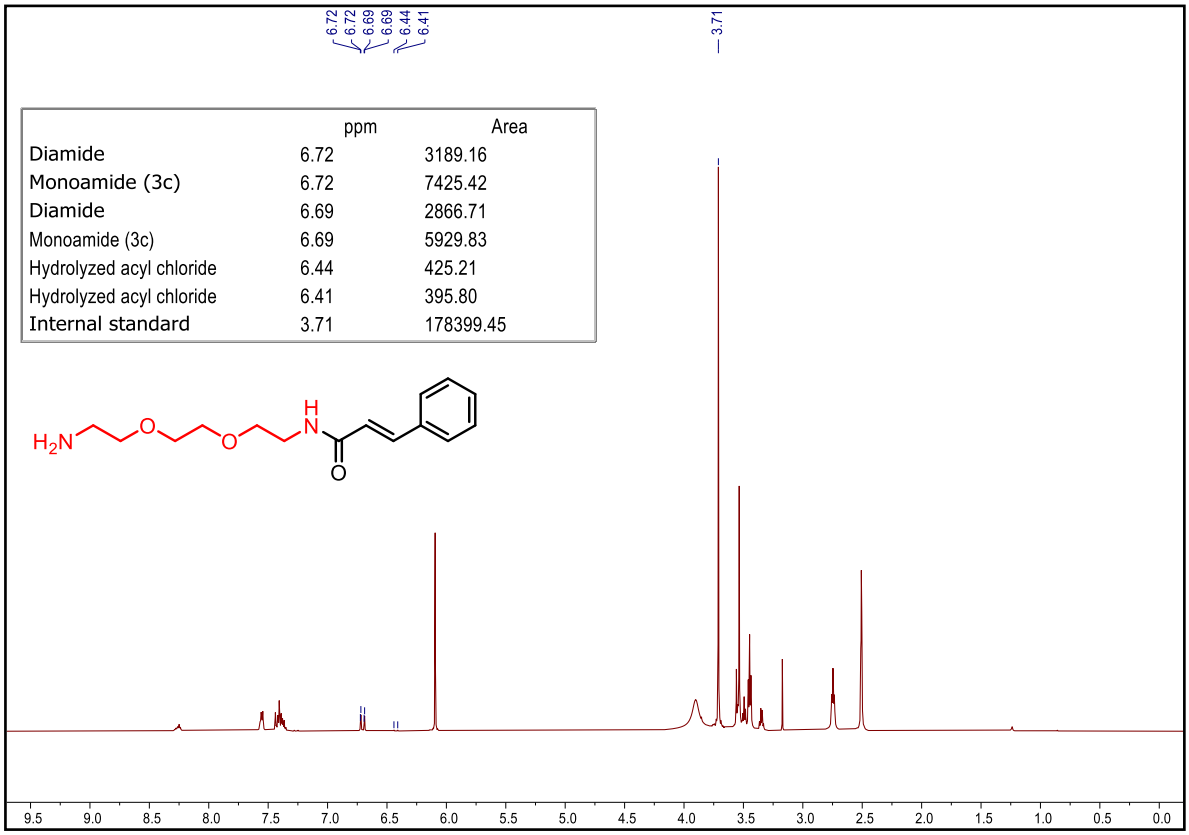


Fig S17. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3c** (conditions[b]: EtOAc).

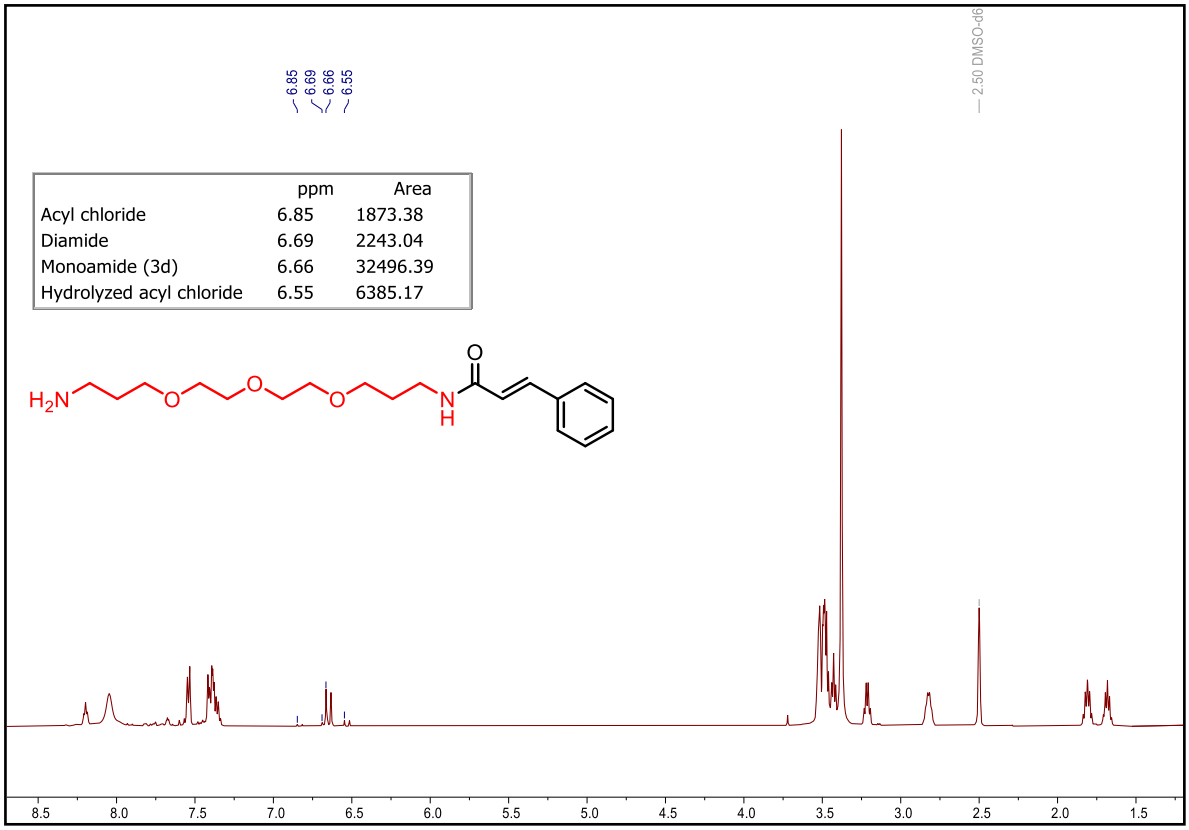


Fig S18. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3d** (conditions[a]: DCM).

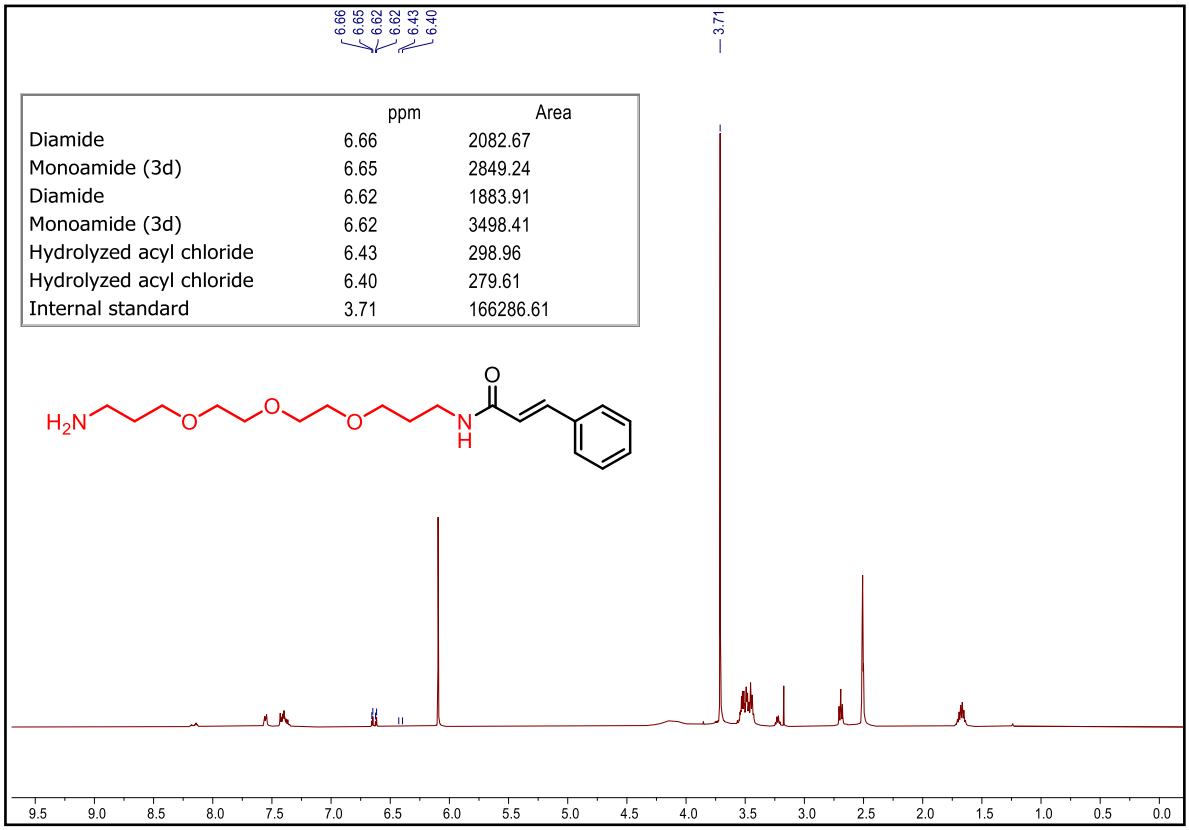


Fig S19. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3d** (conditions[b]: EtOAc).

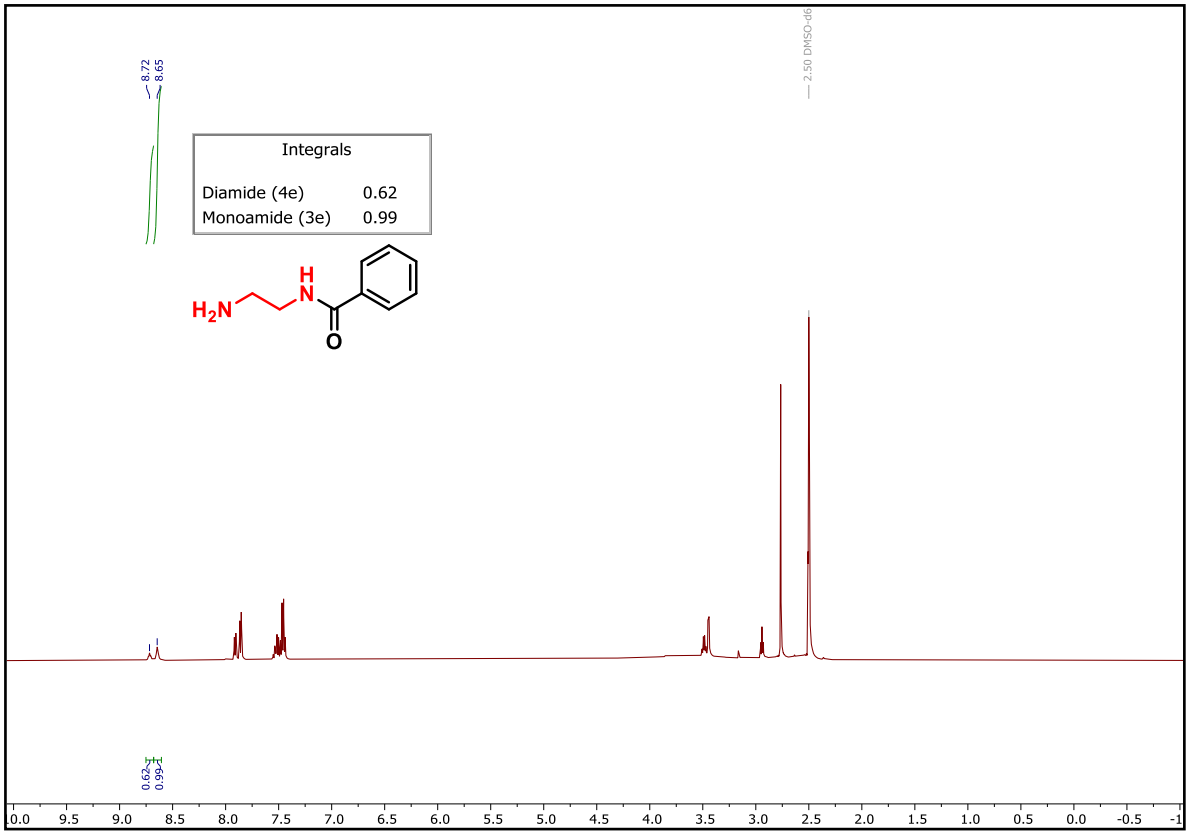


Fig S20. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3e** (conditions[a]: DCM).

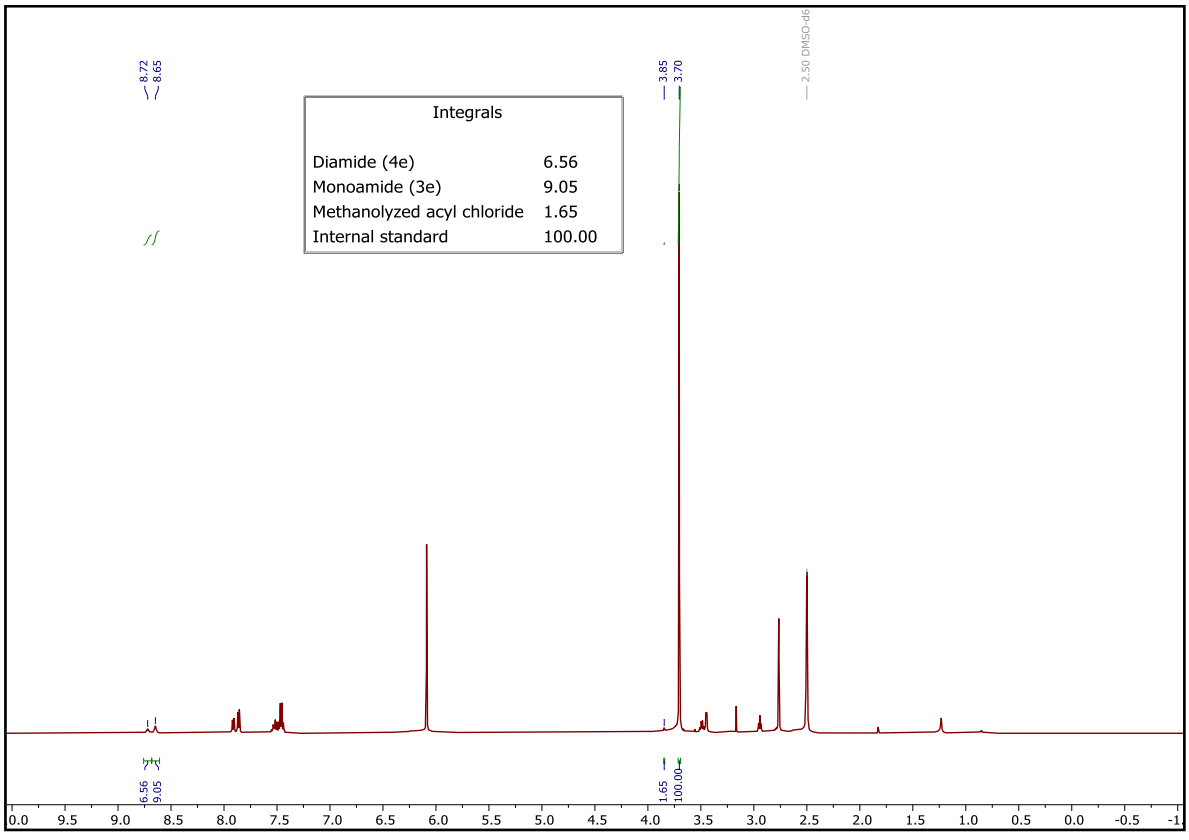


Fig S21. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3e** (conditions[b]: EtOAc).

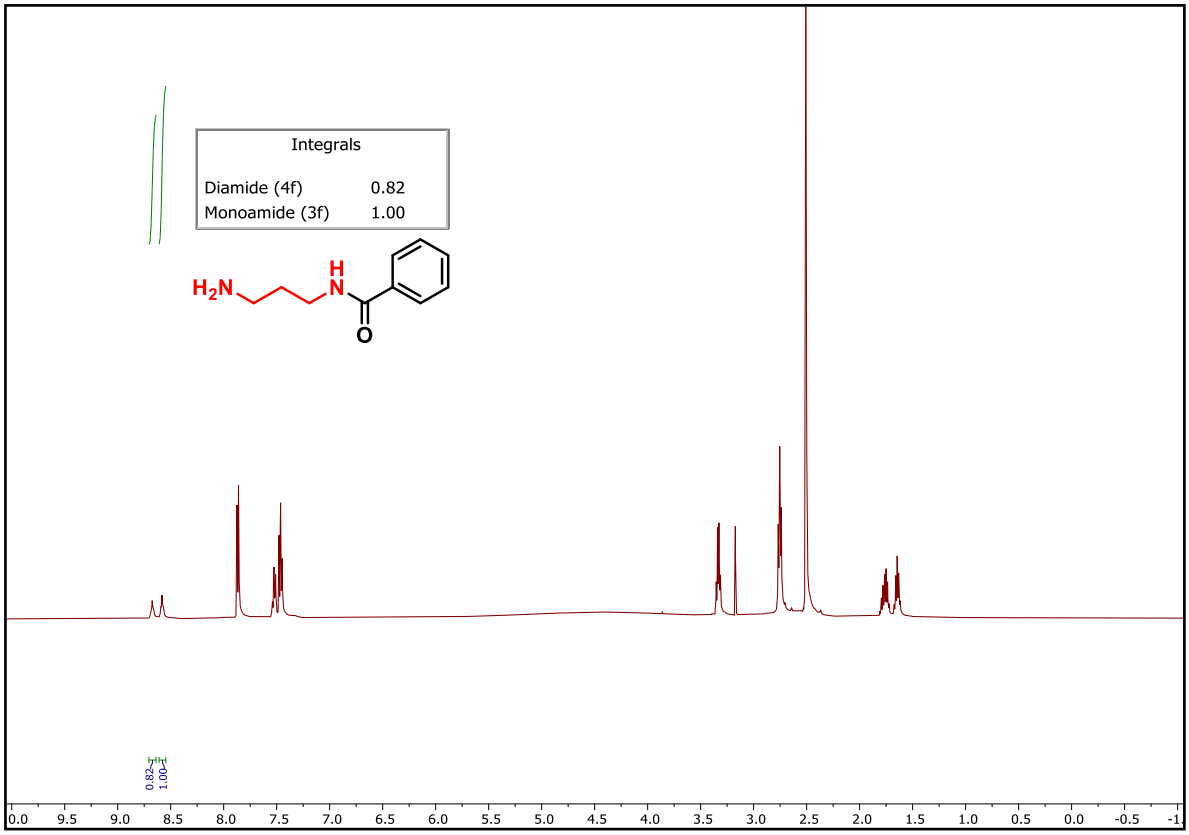


Fig S22. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3f** (conditions[a]: DCM)**.**

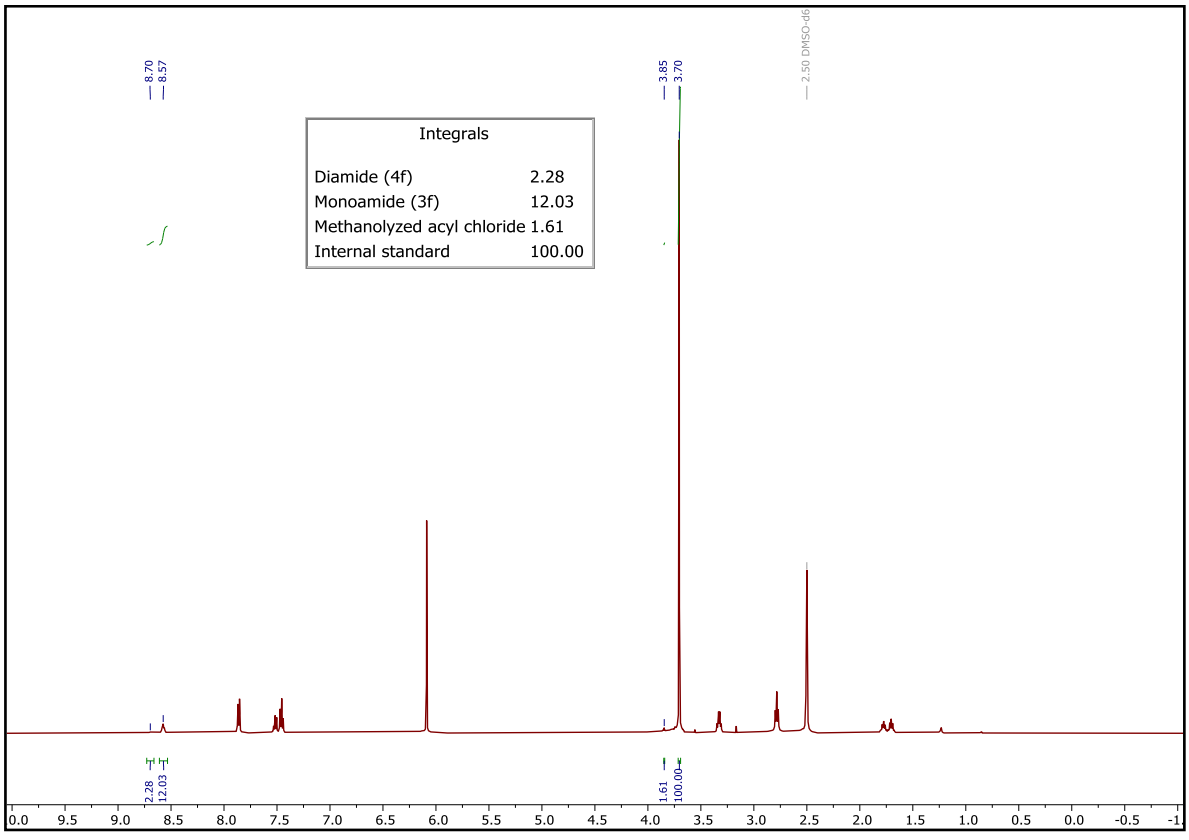


Fig S23. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3f** (conditions[b]: EtOAc)**.**

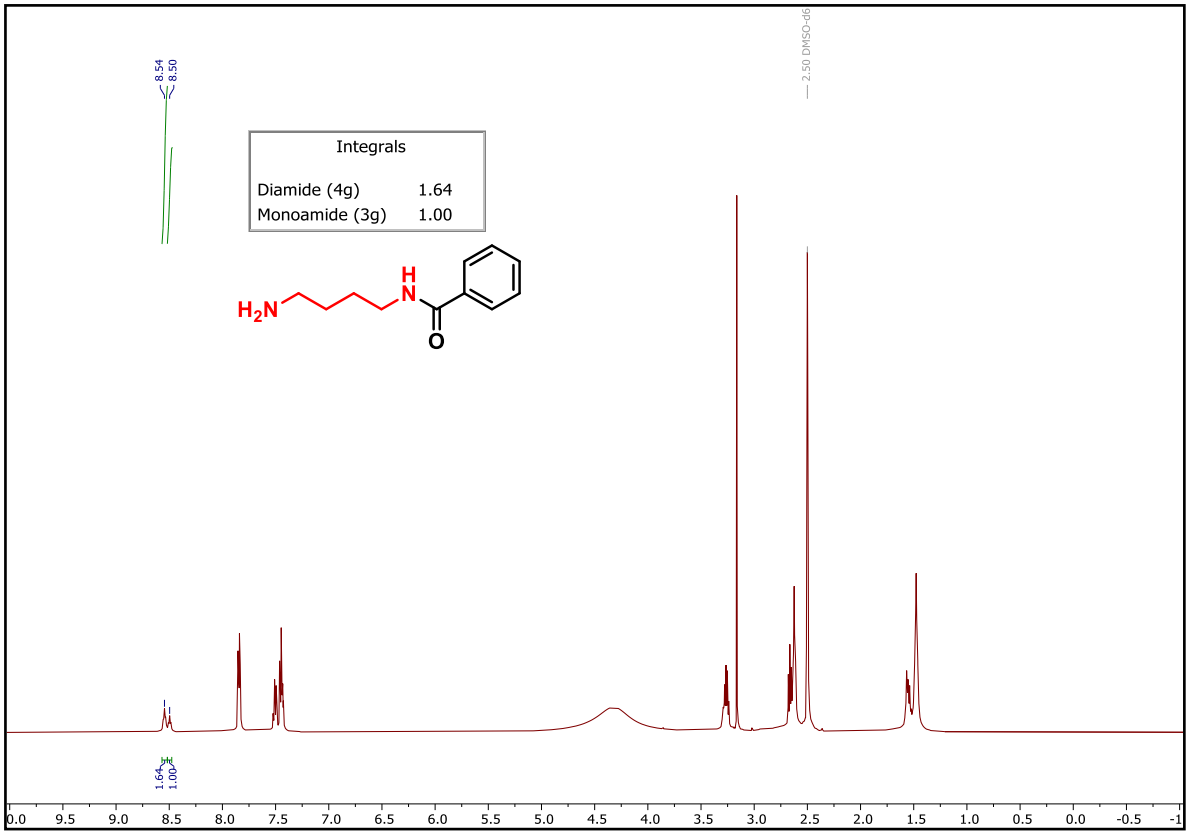


Fig S24. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3g** (conditions[a]: DCM)**.**

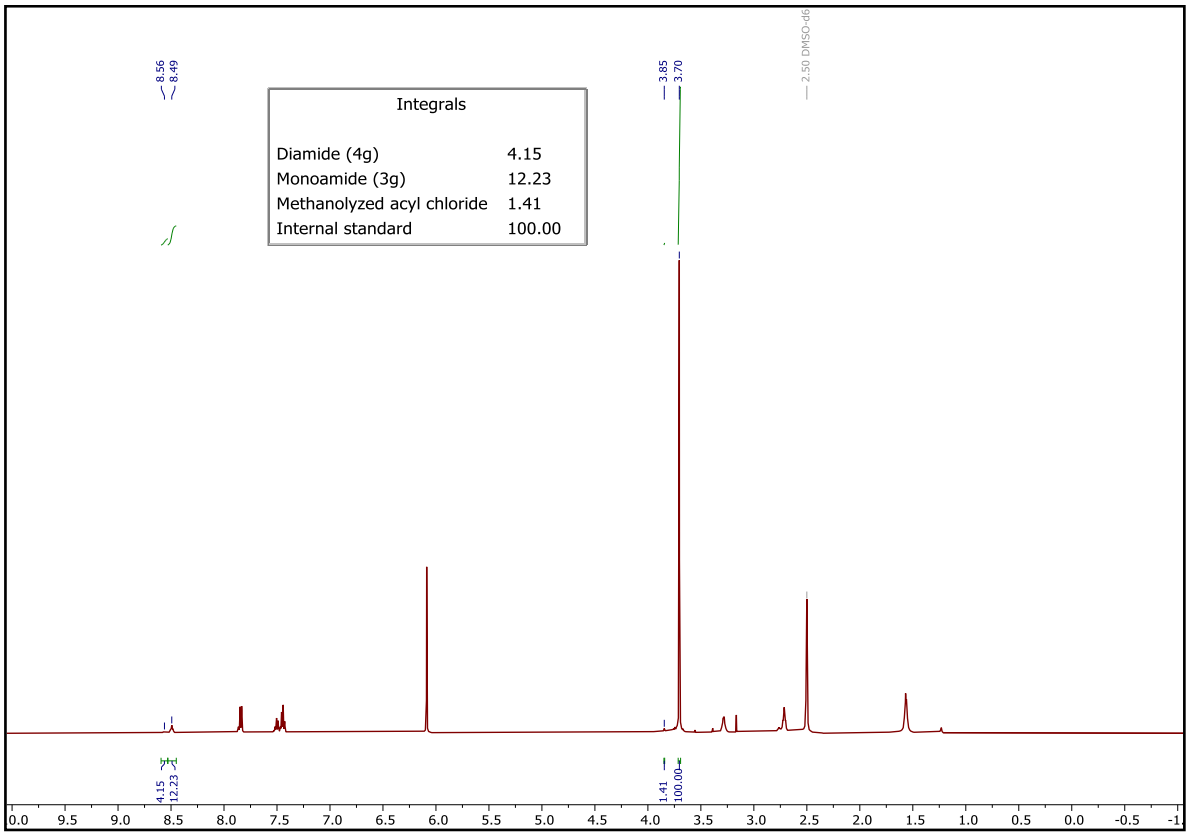


Fig S25. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3g** (conditions[b]: EtOAc)**.**

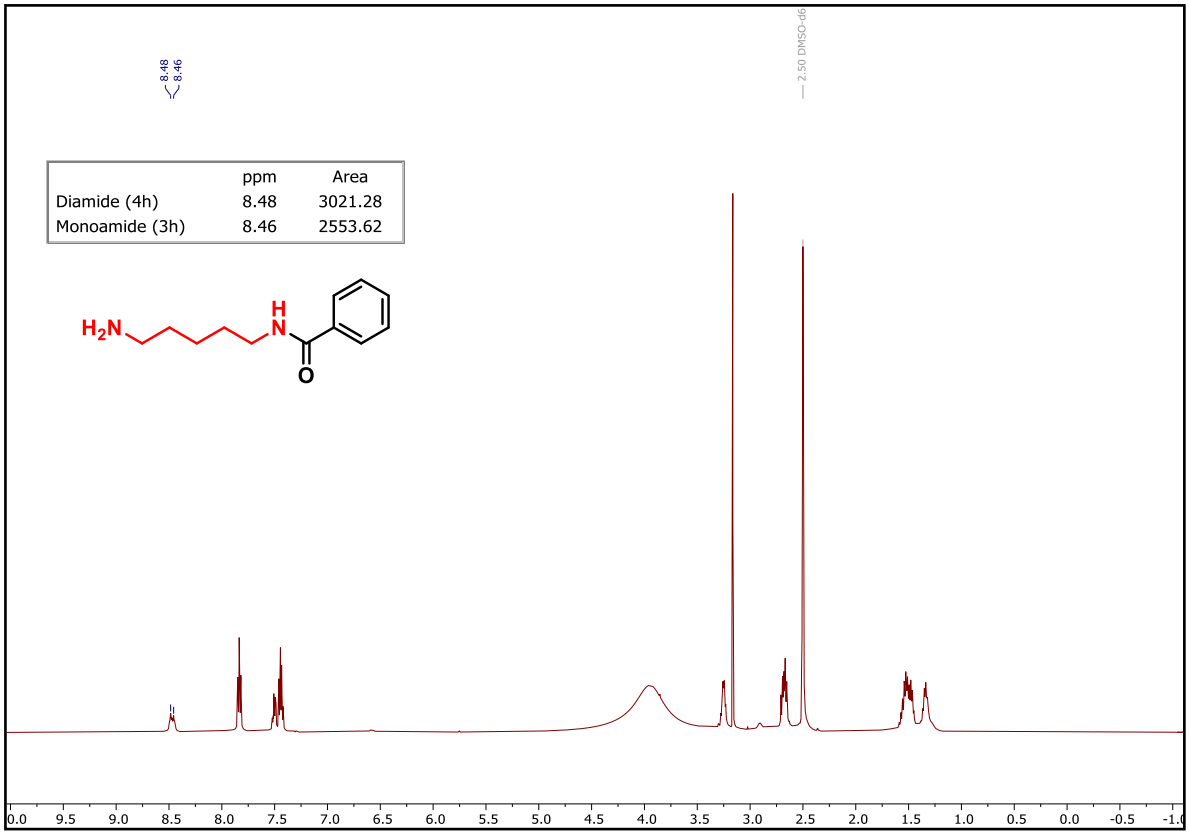


Fig S26. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3h** (conditions[a]: DCM).

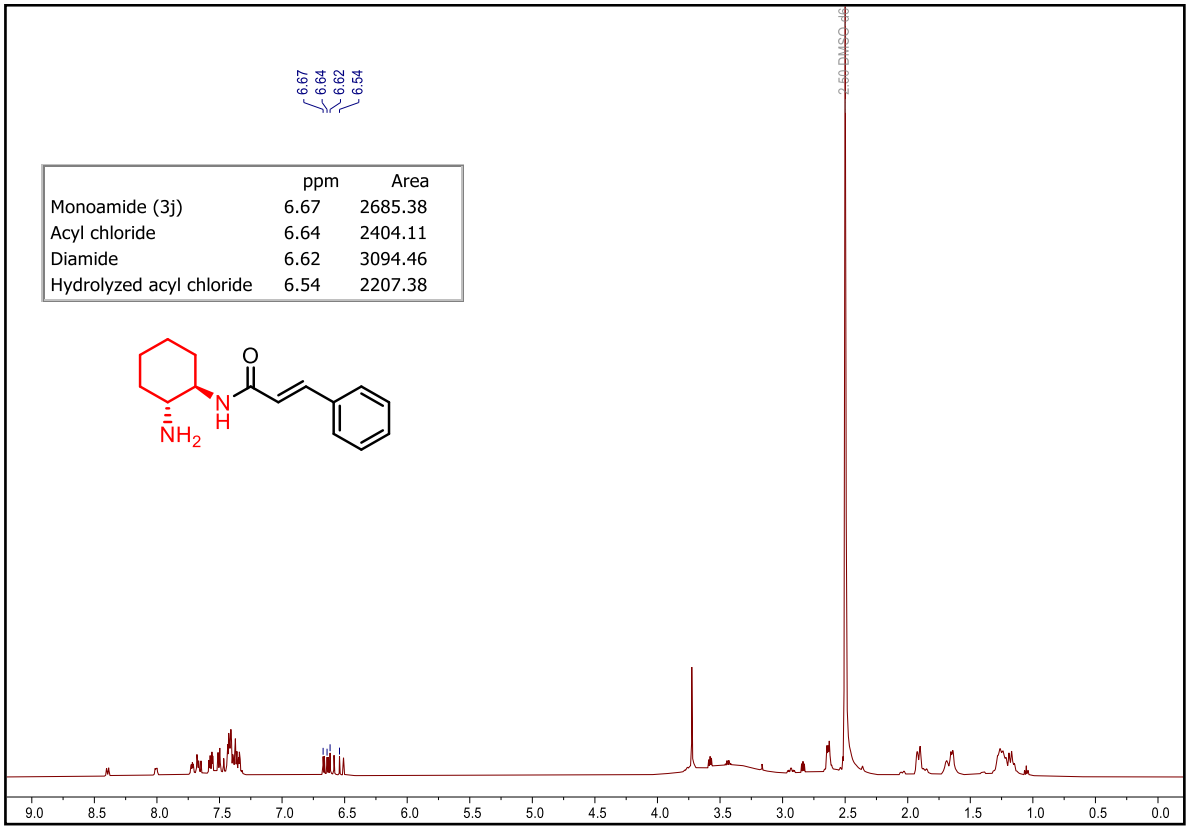


Fig S27. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3j** (conditions[a]: DCM)**.**

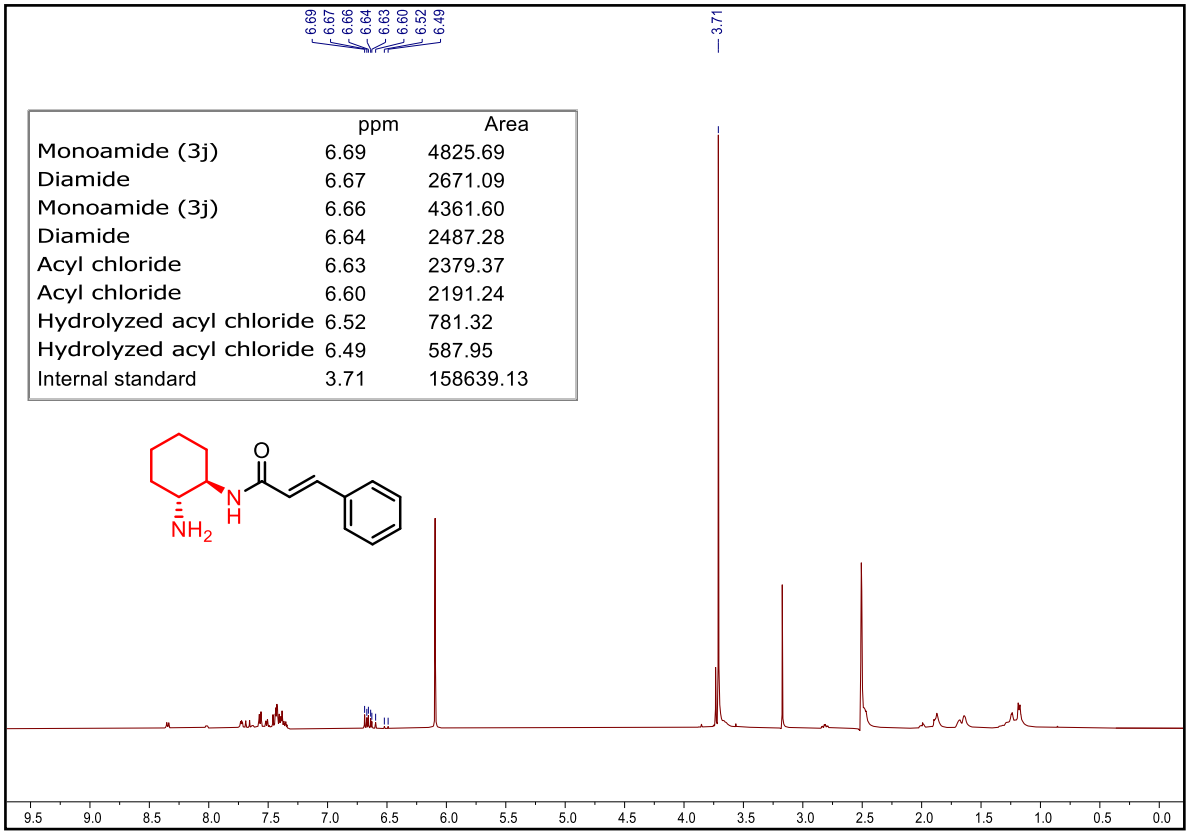


Fig S28. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3j** (conditions[b]: EtOAc)**.**

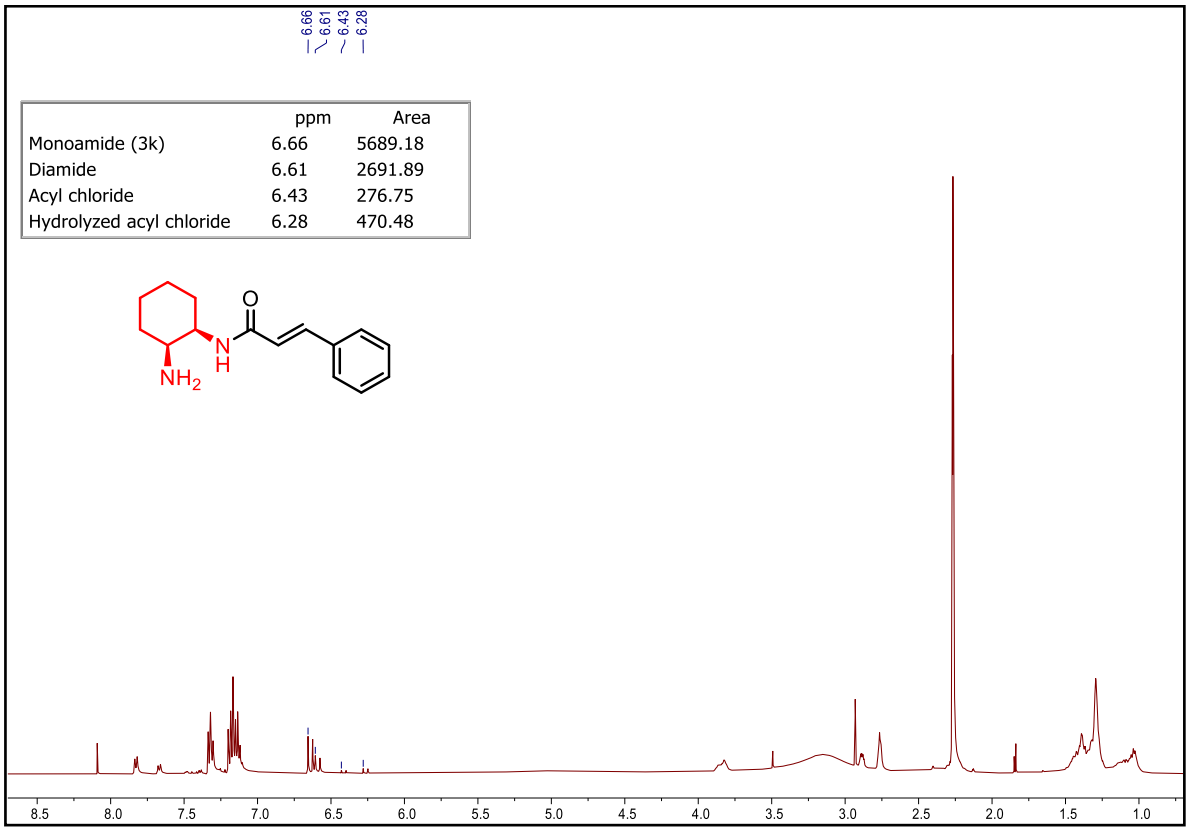


Fig S29. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3k** (conditions[a]: DCM)**.**

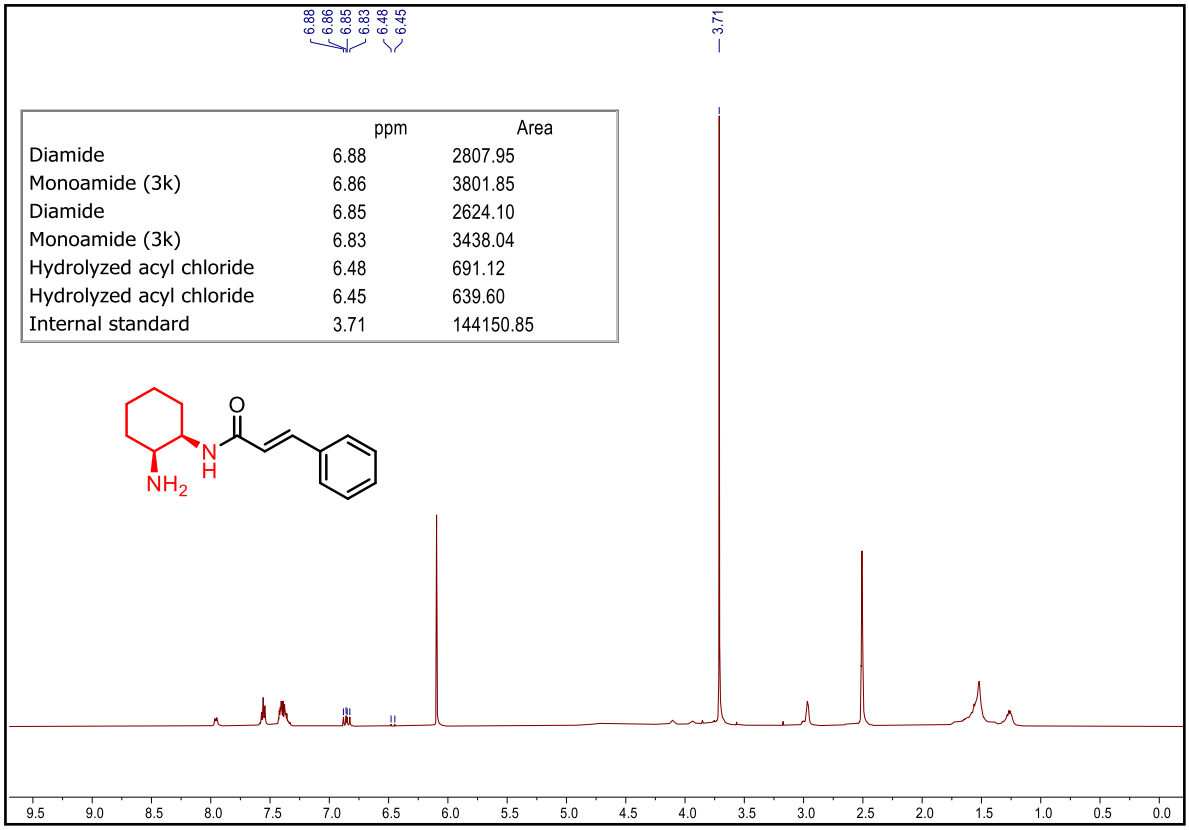


Fig S30. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3k** (conditions[b]: EtOAc)**.**

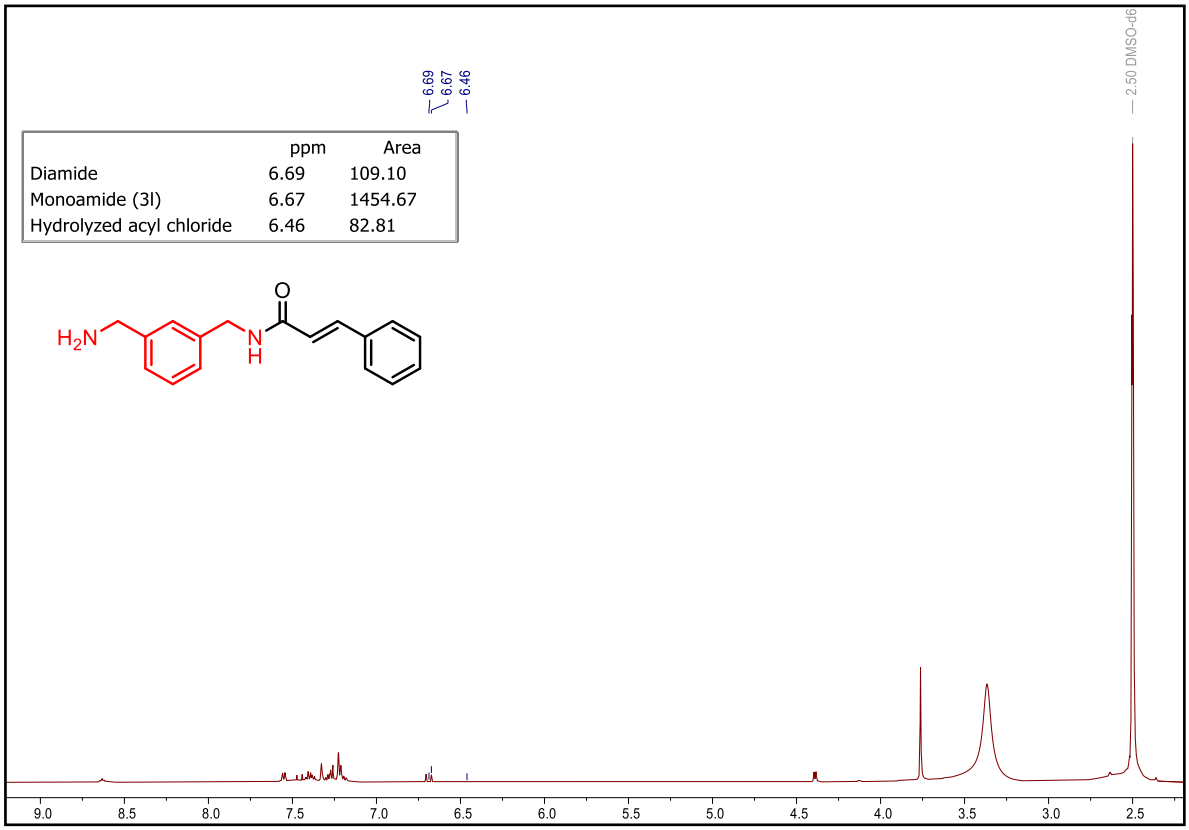


Fig S31. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3l** (conditions[a]: DCM)**.**

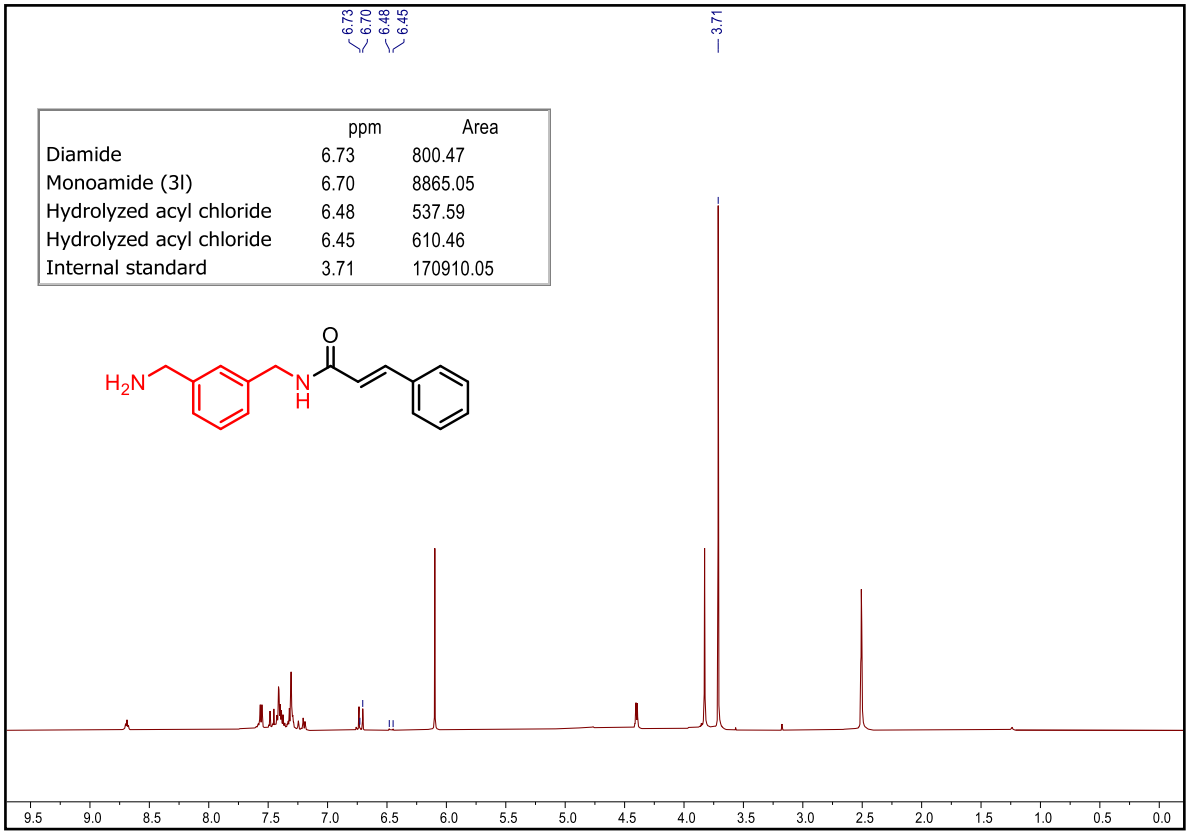


Fig S32. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3l** (conditions[b]: EtOAc)**.**

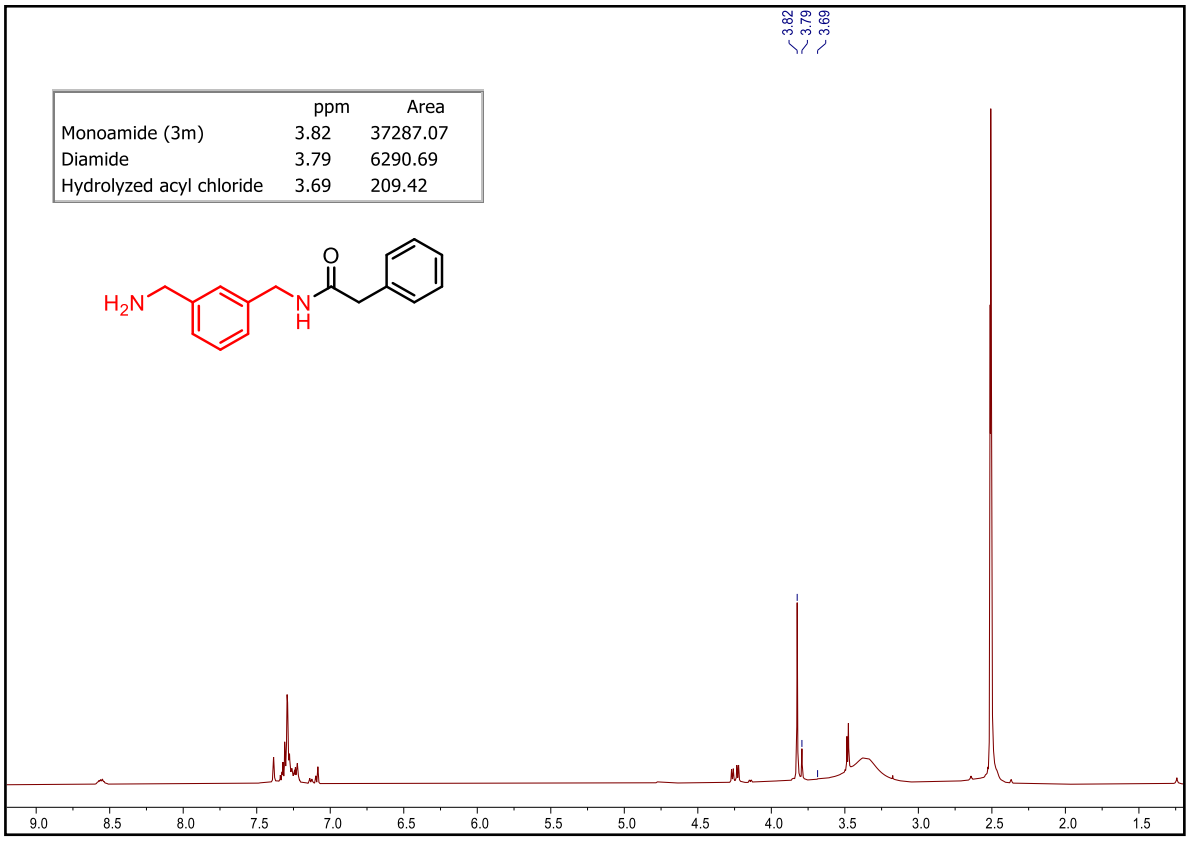


Fig S33. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3m** (conditions[a]: DCM)**.**

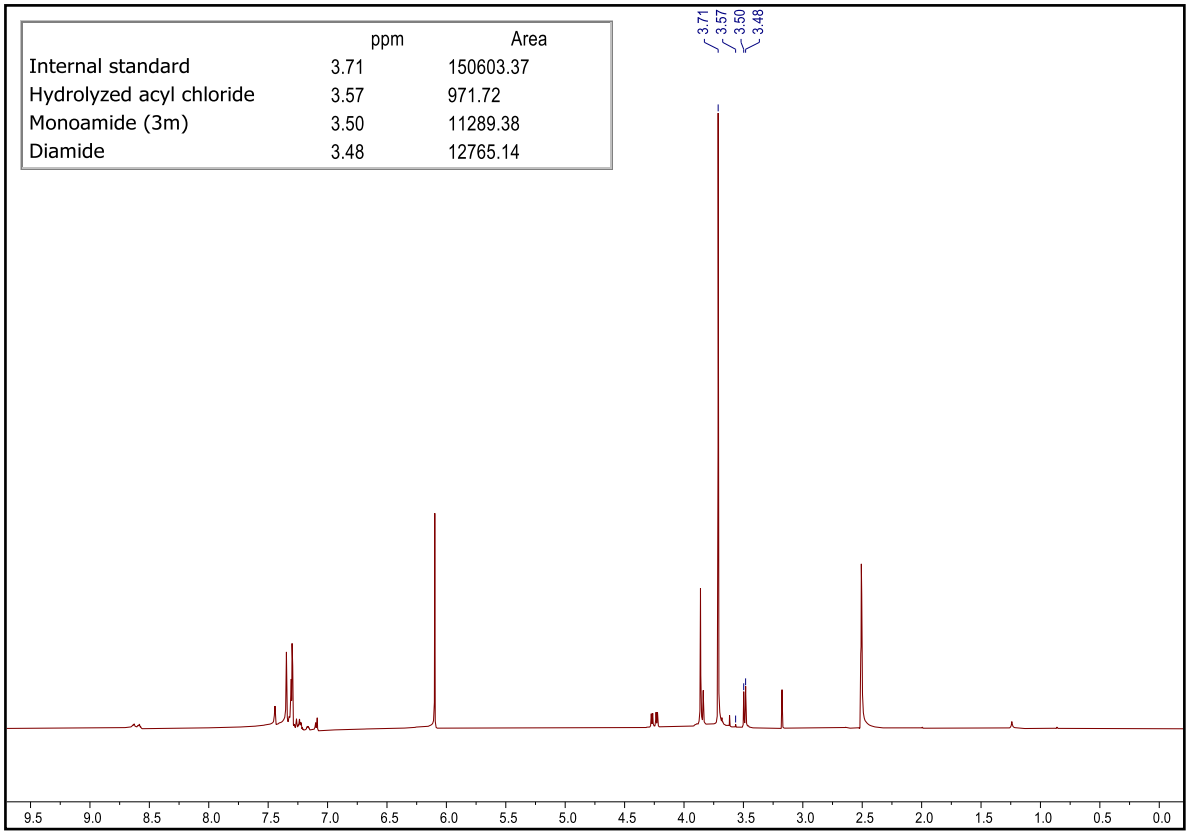


Fig S34. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3m** (conditions[b]: EtOAc)**.**

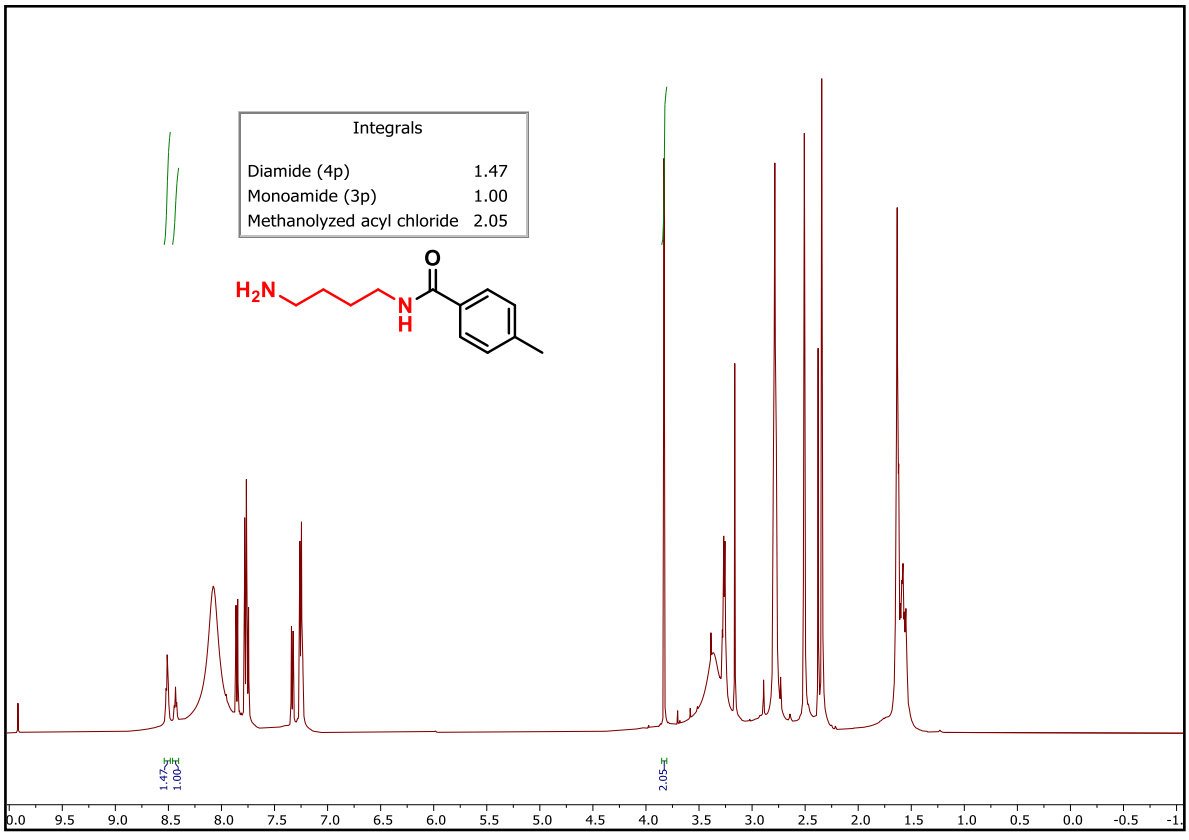


Fig S35. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3p** (conditions[a]: DCM)**.**

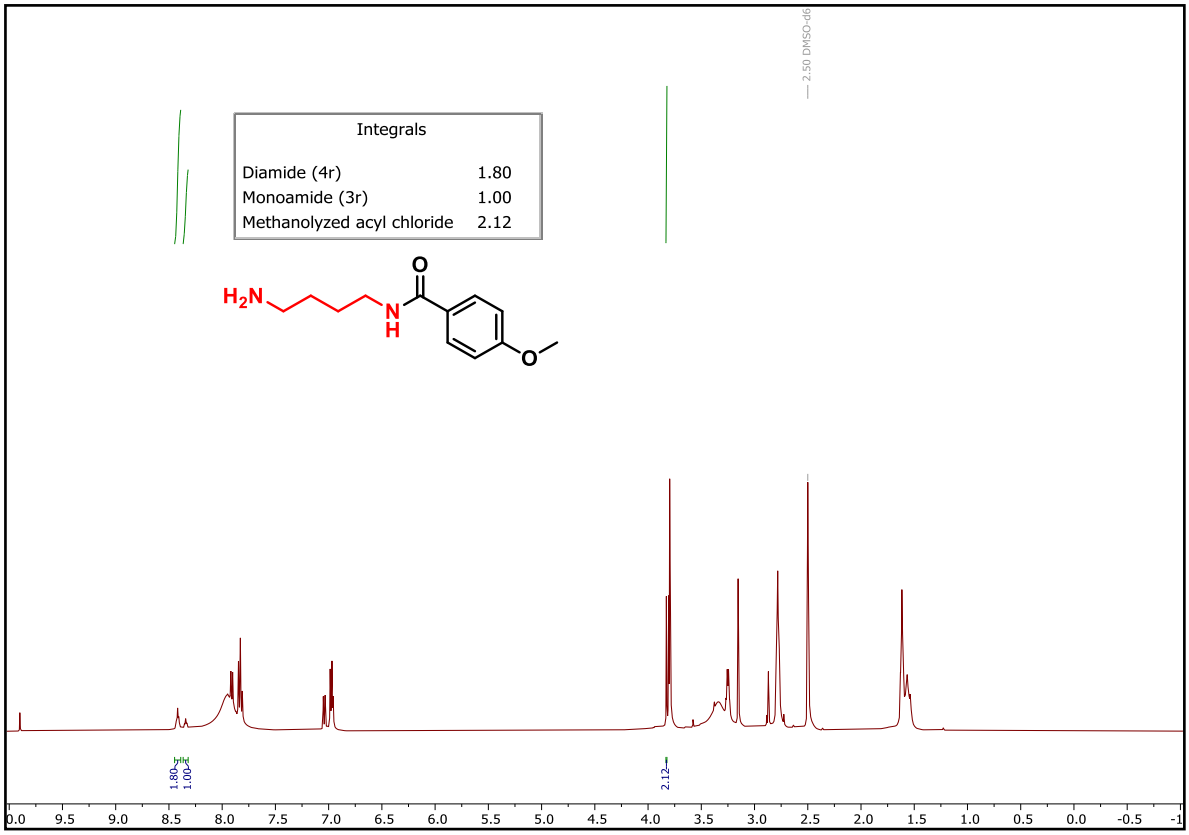


Fig S36. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3r** (conditions[a]: DCM).

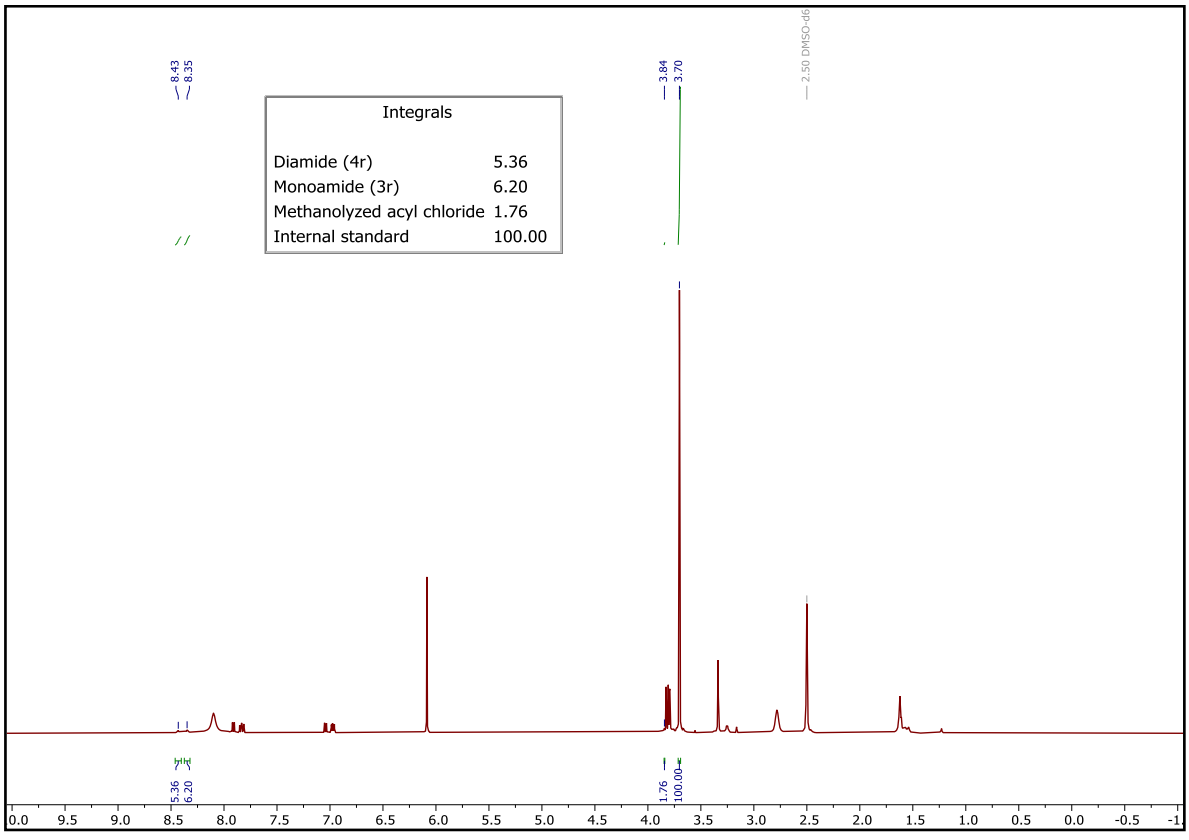


Fig S37. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3r** (conditions[b]: EtOAc).

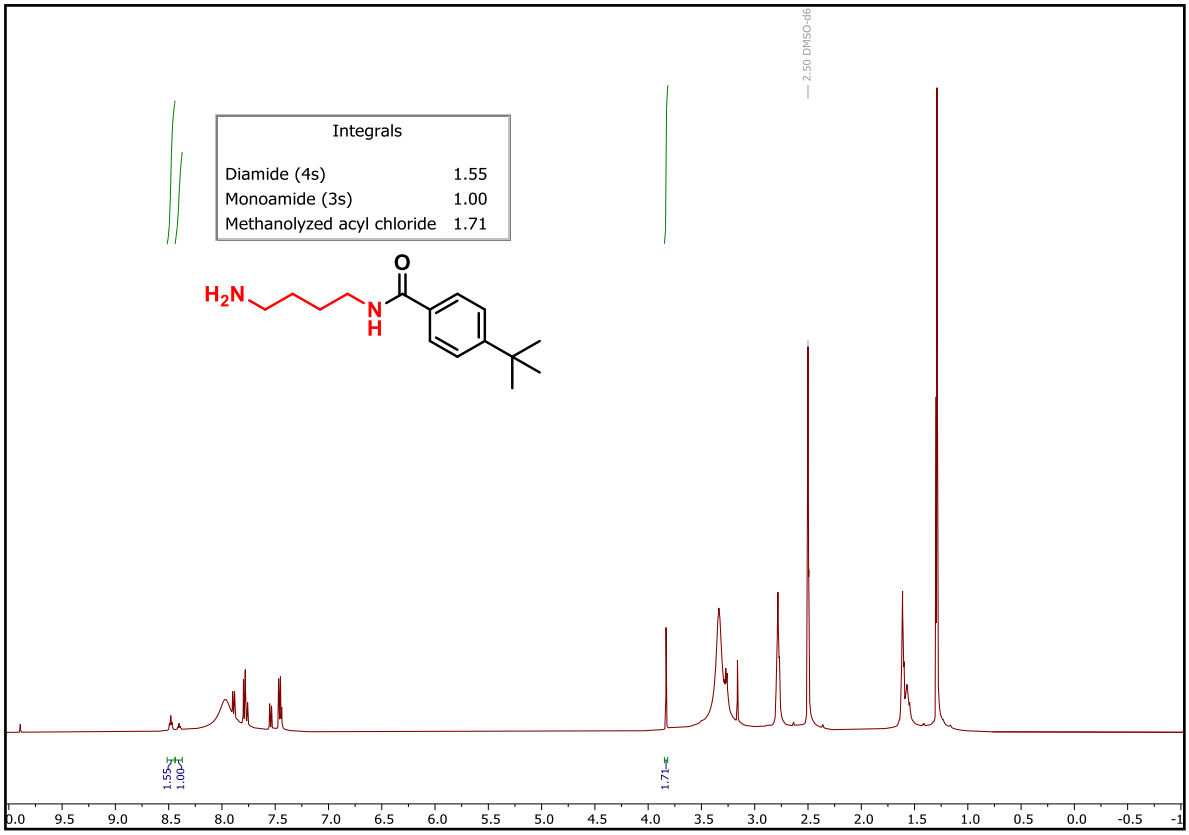


Fig S38. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **3s** (conditions[a]: DCM).

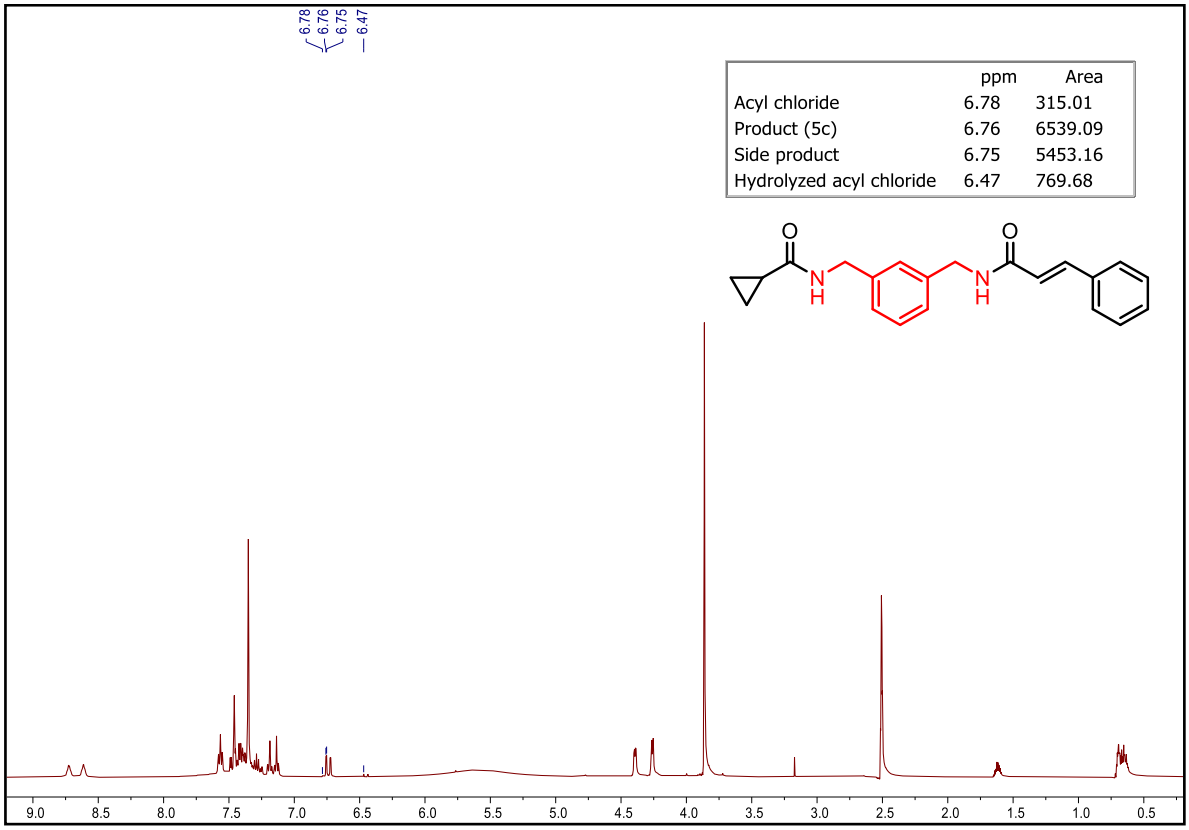


Fig S39. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **5c** (conditions[a]: DCM).

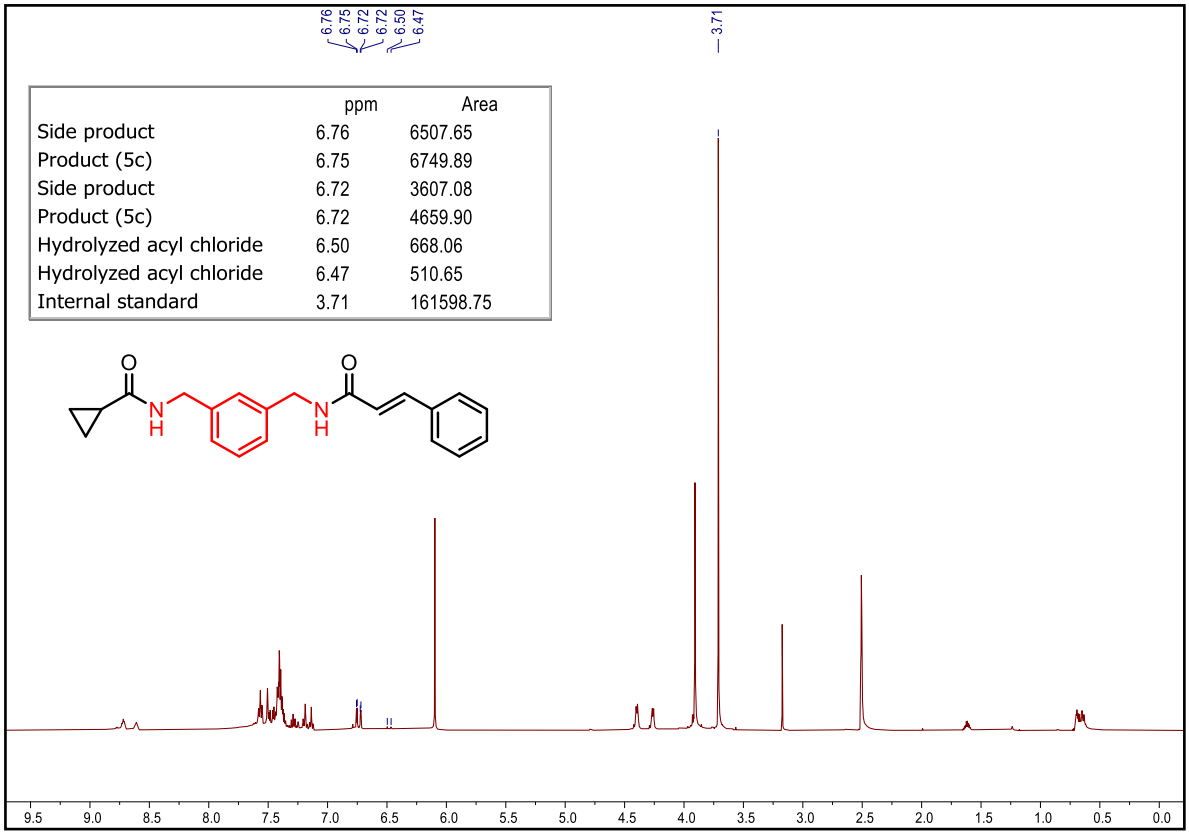


Fig S40. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **5c** (conditions[b]: EtOAc).

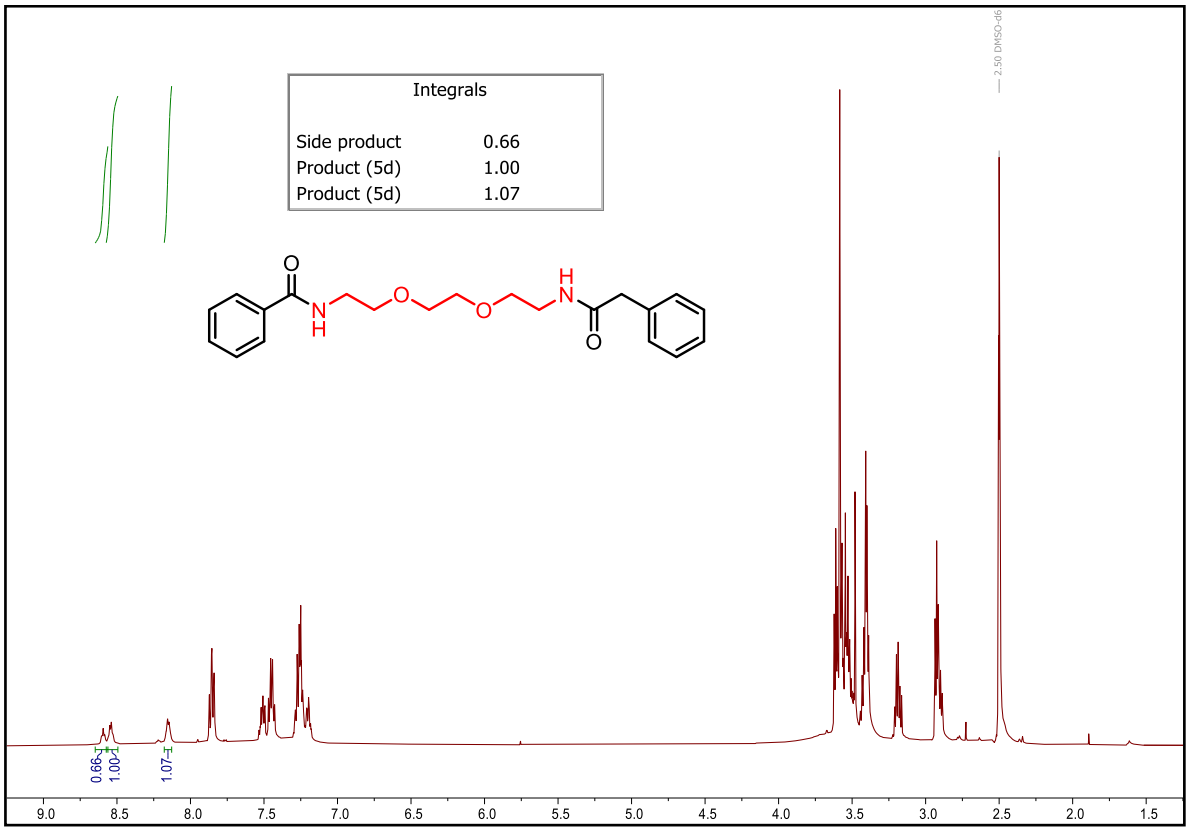


Fig S41. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **5d** (conditions[a]: DCM).

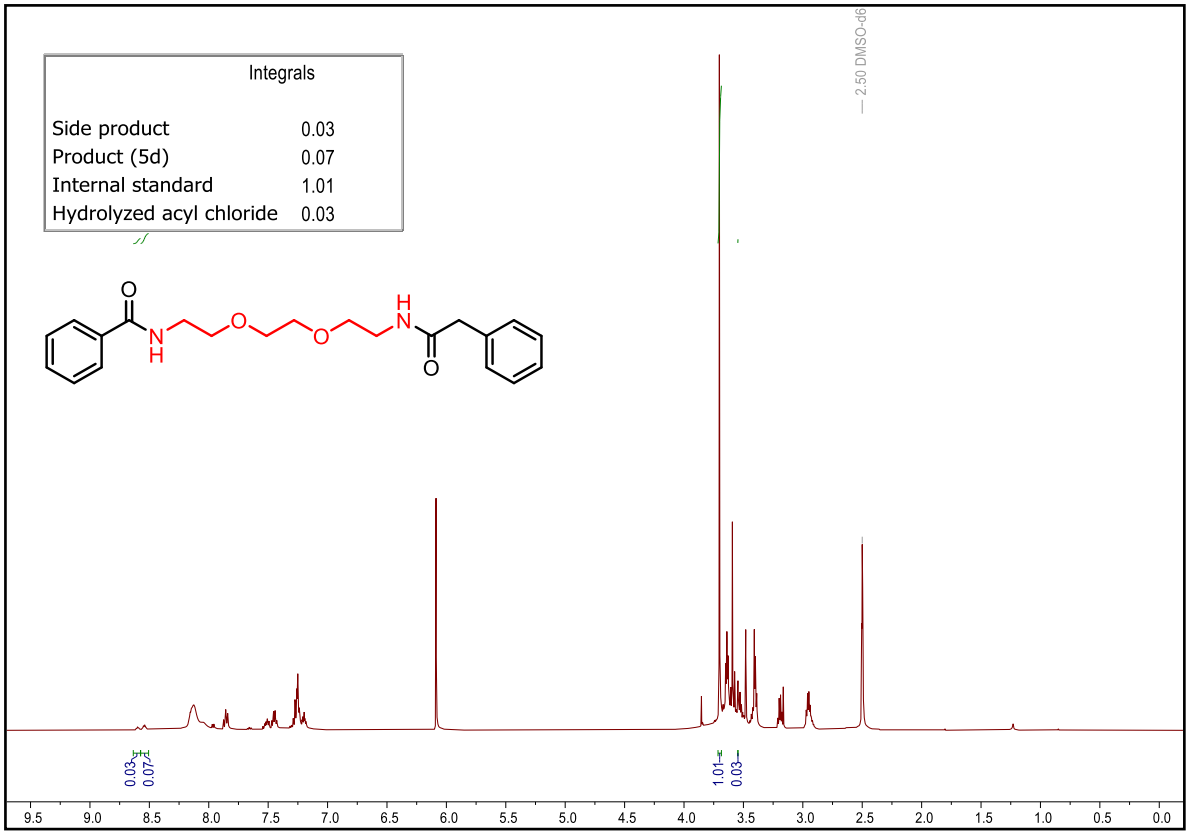


Fig S42. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **5d** (conditions[b]: EtOAc)**.**

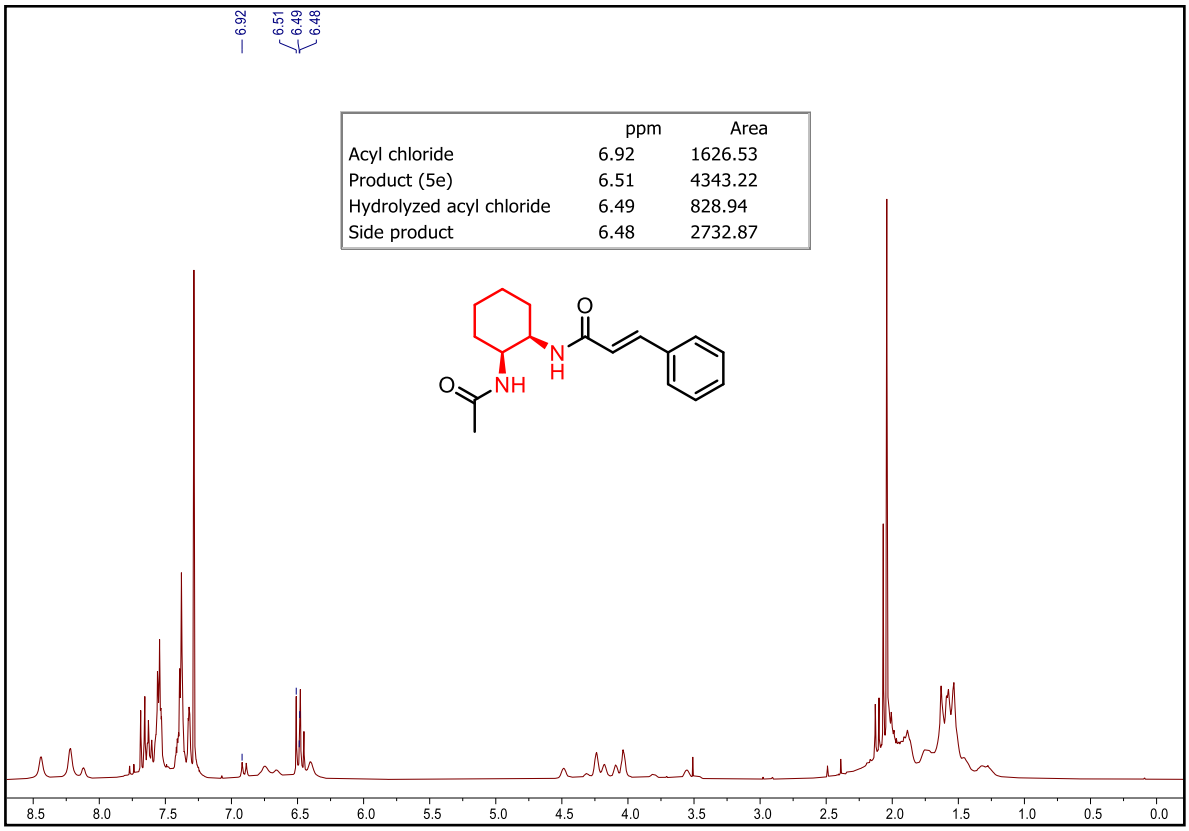


Fig S43. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **5e** (conditions[a]: DCM)**.**

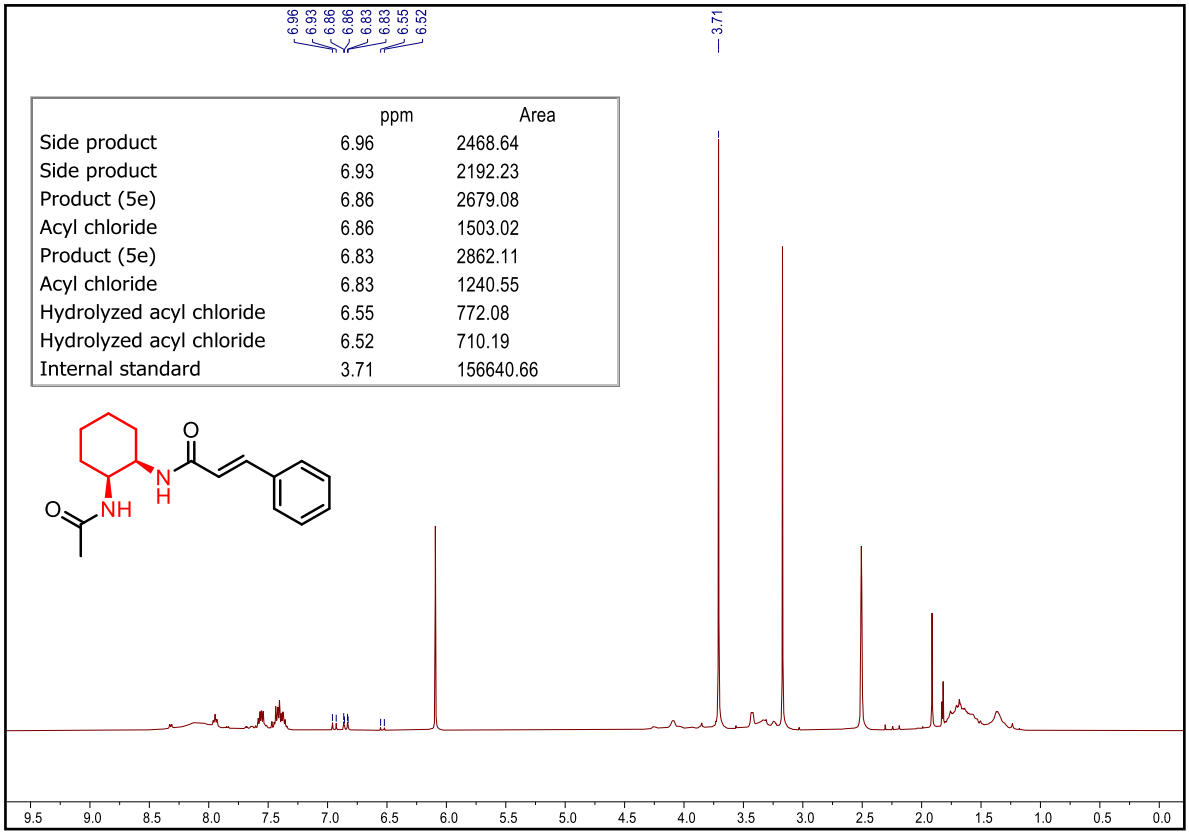


Fig S44. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **5e** (conditions[b]: EtOAc).

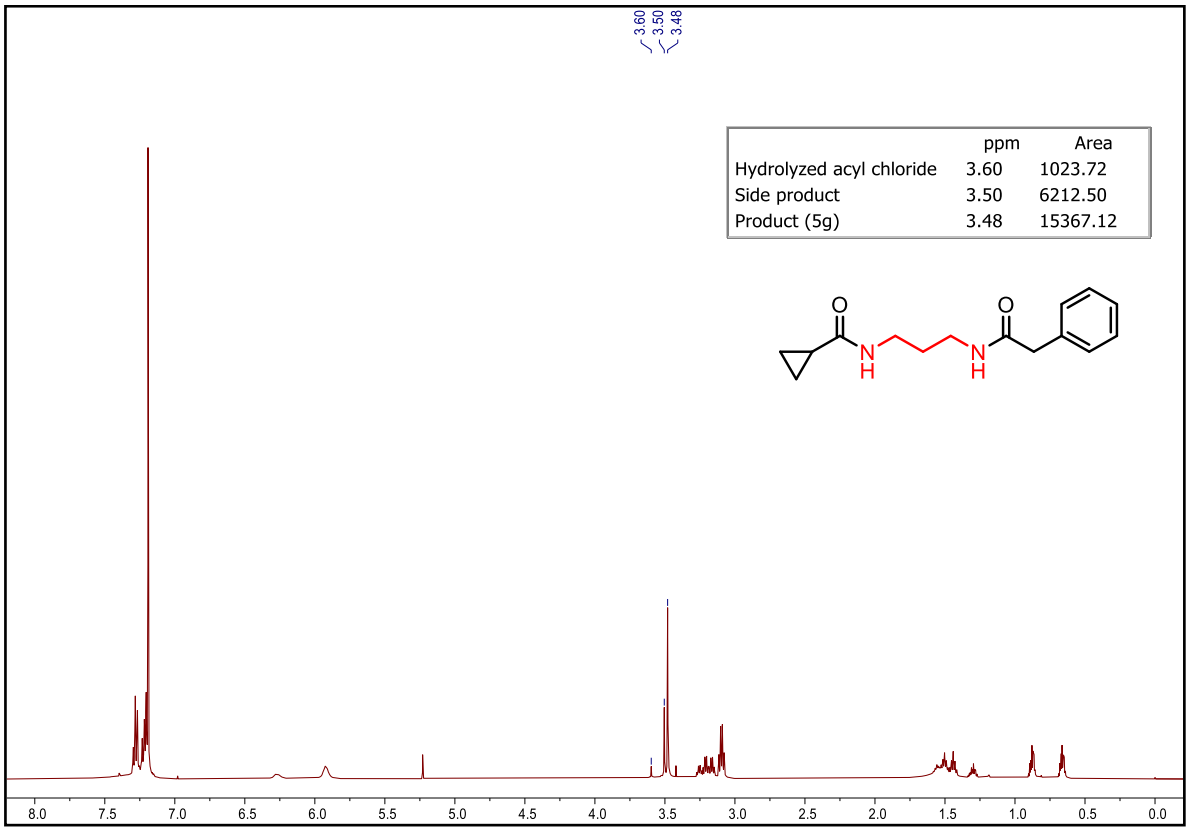


Fig S45. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **5g** (conditions[a]: DCM).

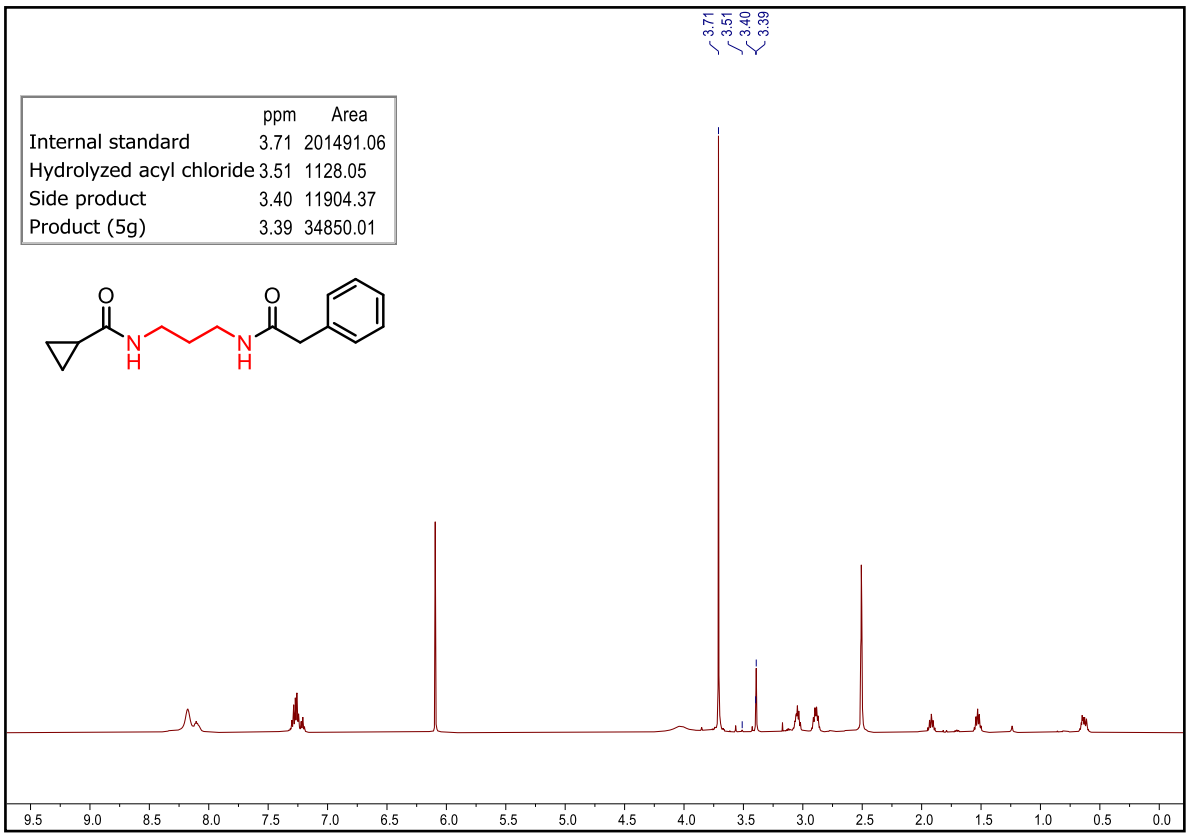


Fig S46. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **5g** (conditions[b]: EtOAc).

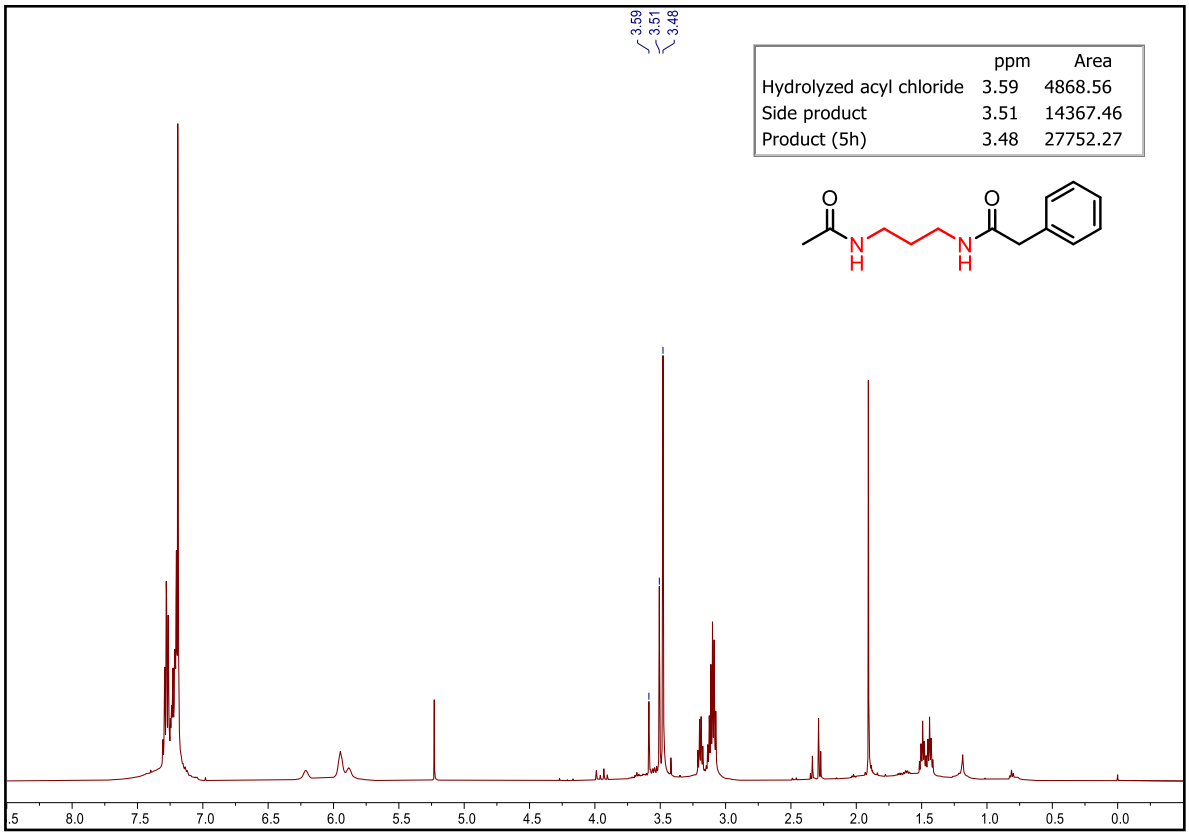


Fig S47. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **5h** (conditions[a]: DCM)**.**

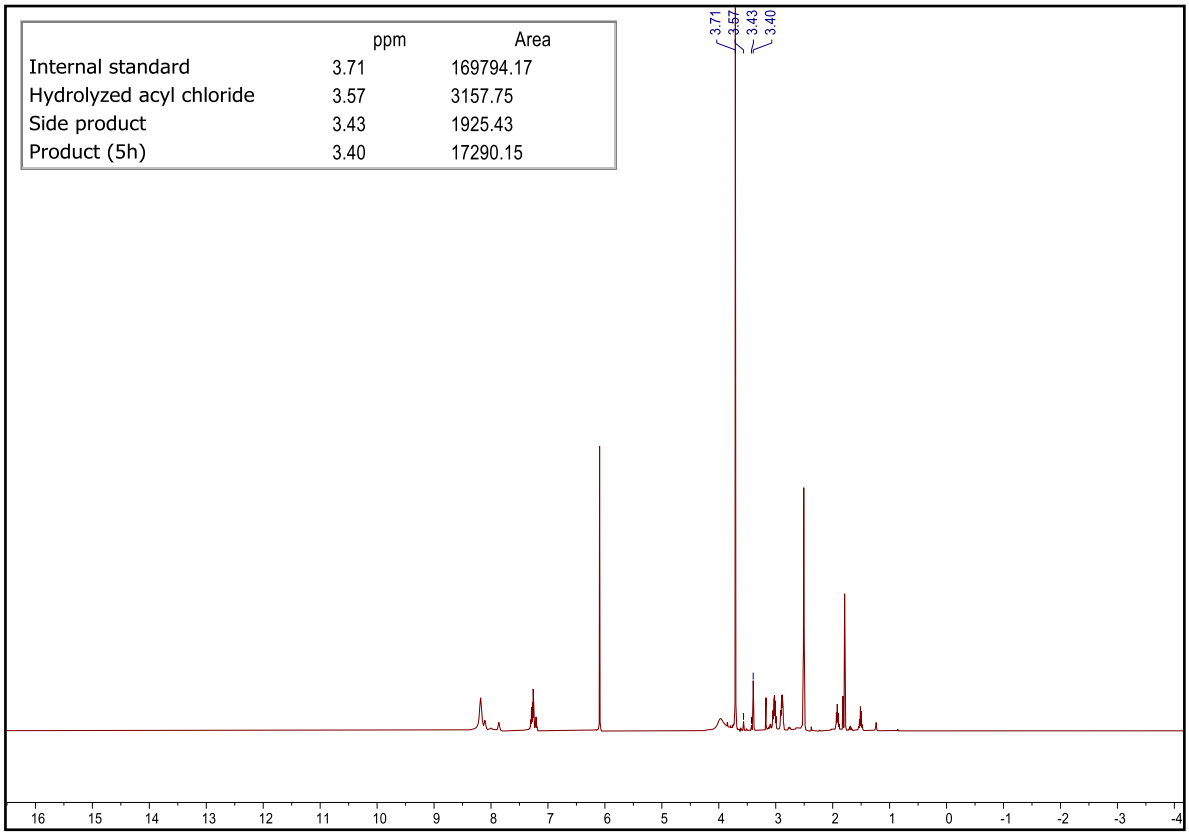


Fig S48. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **5h** (conditions[b]: EtOAc)**.**

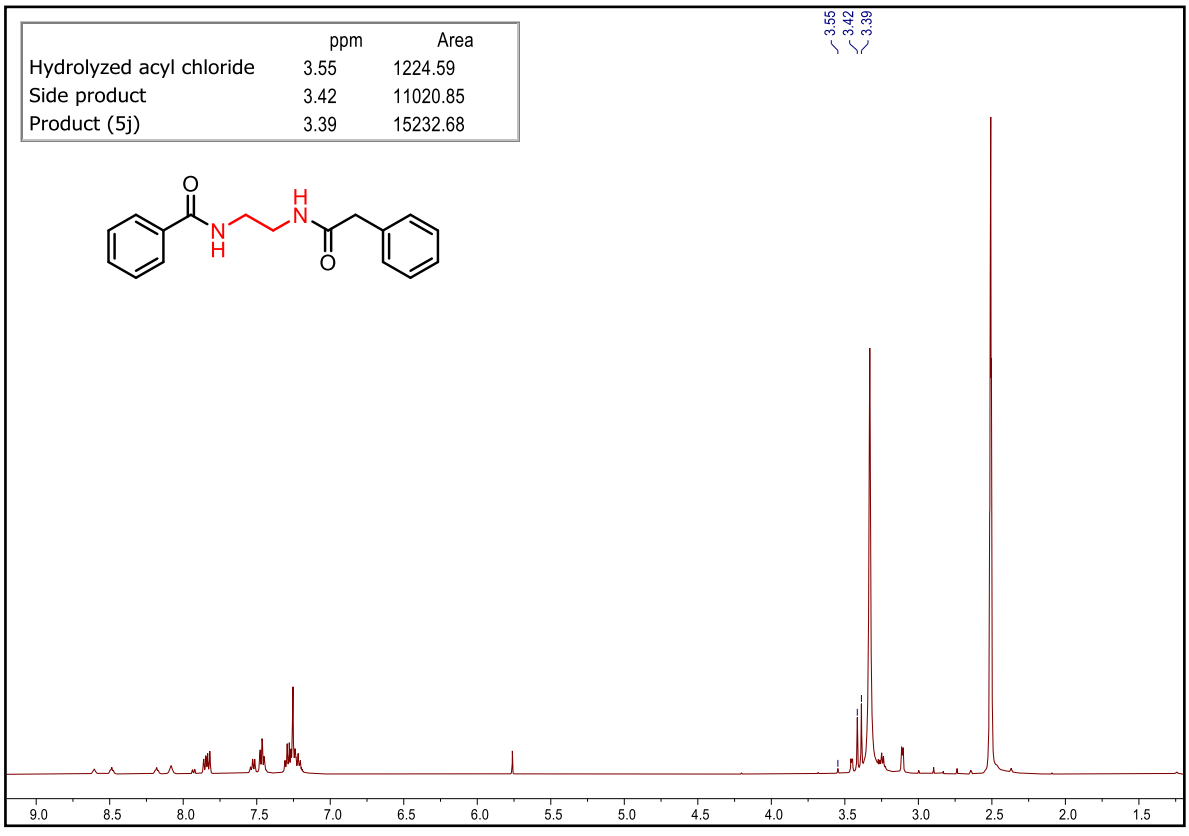


Fig S49. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **5j** (conditions[a]: DCM)**.**

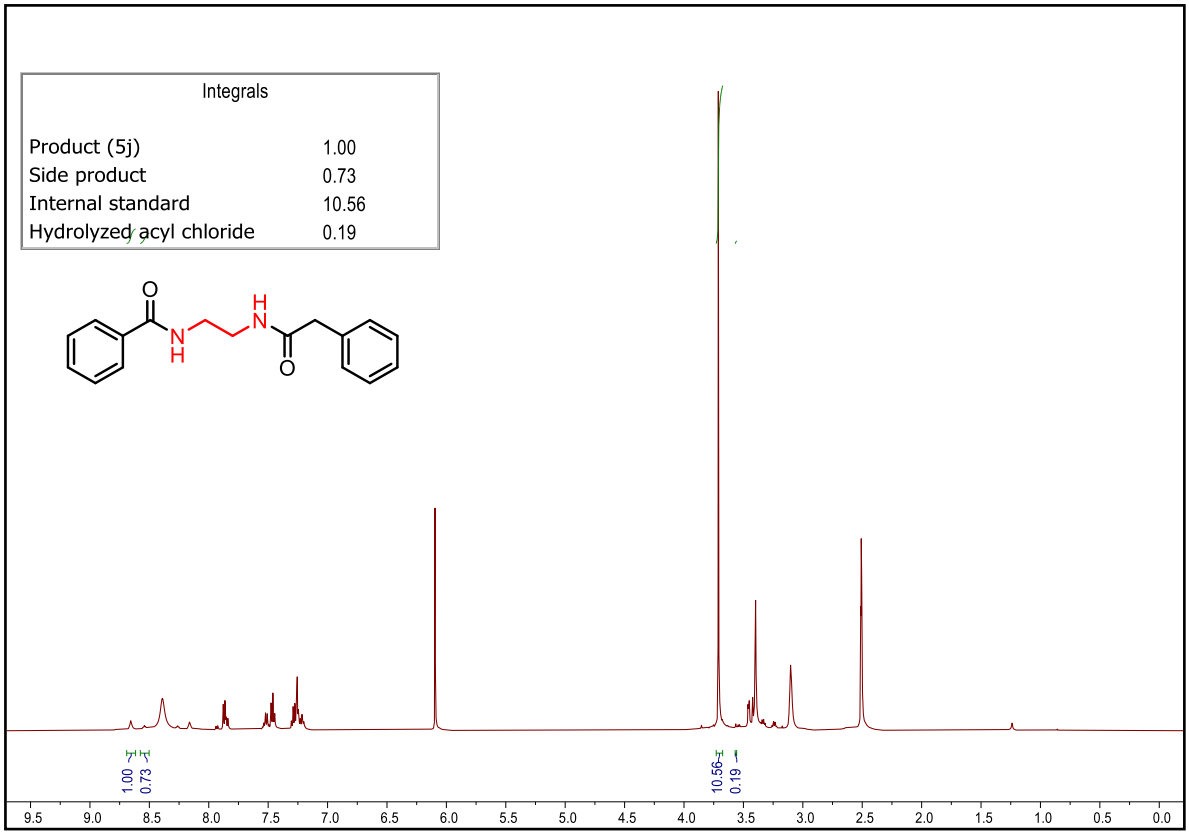


Fig S50. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **5j** (conditions[b]: EtOAc)**.**

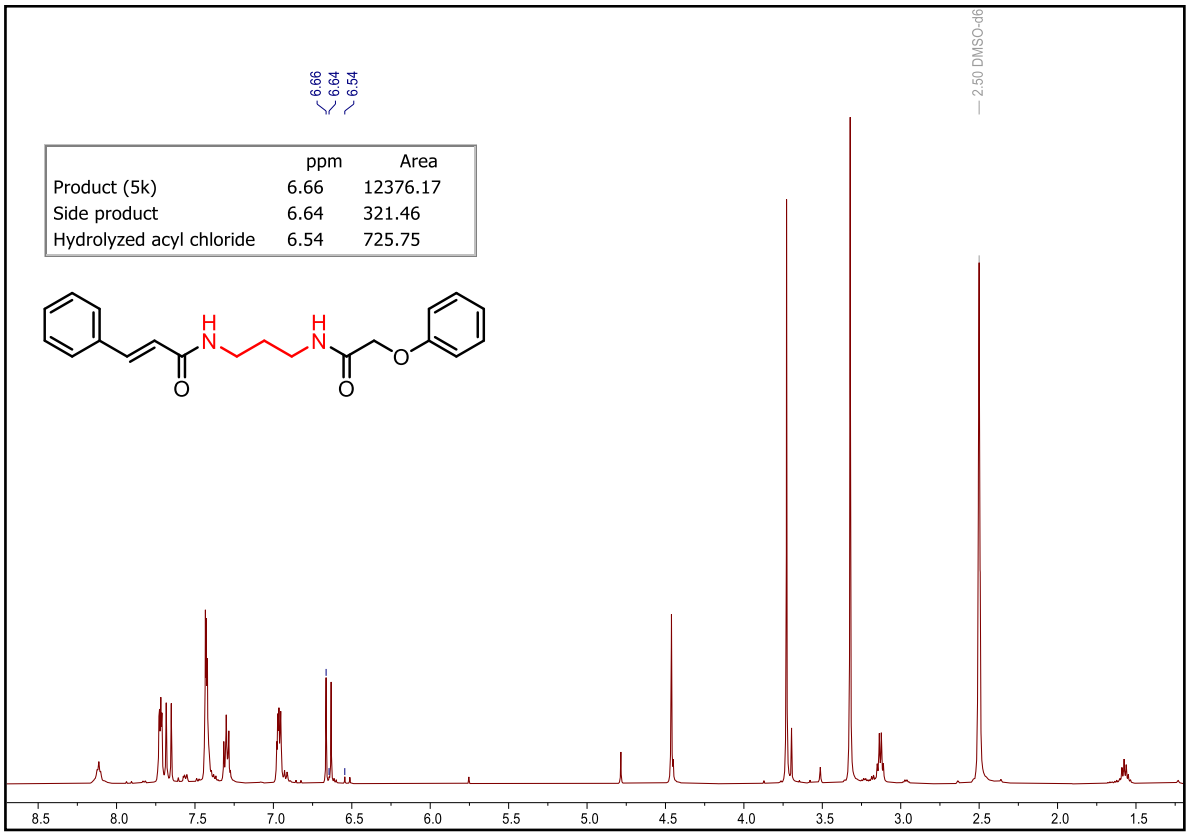


Fig S51. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **5k** (conditions[a]: DCM)**.**

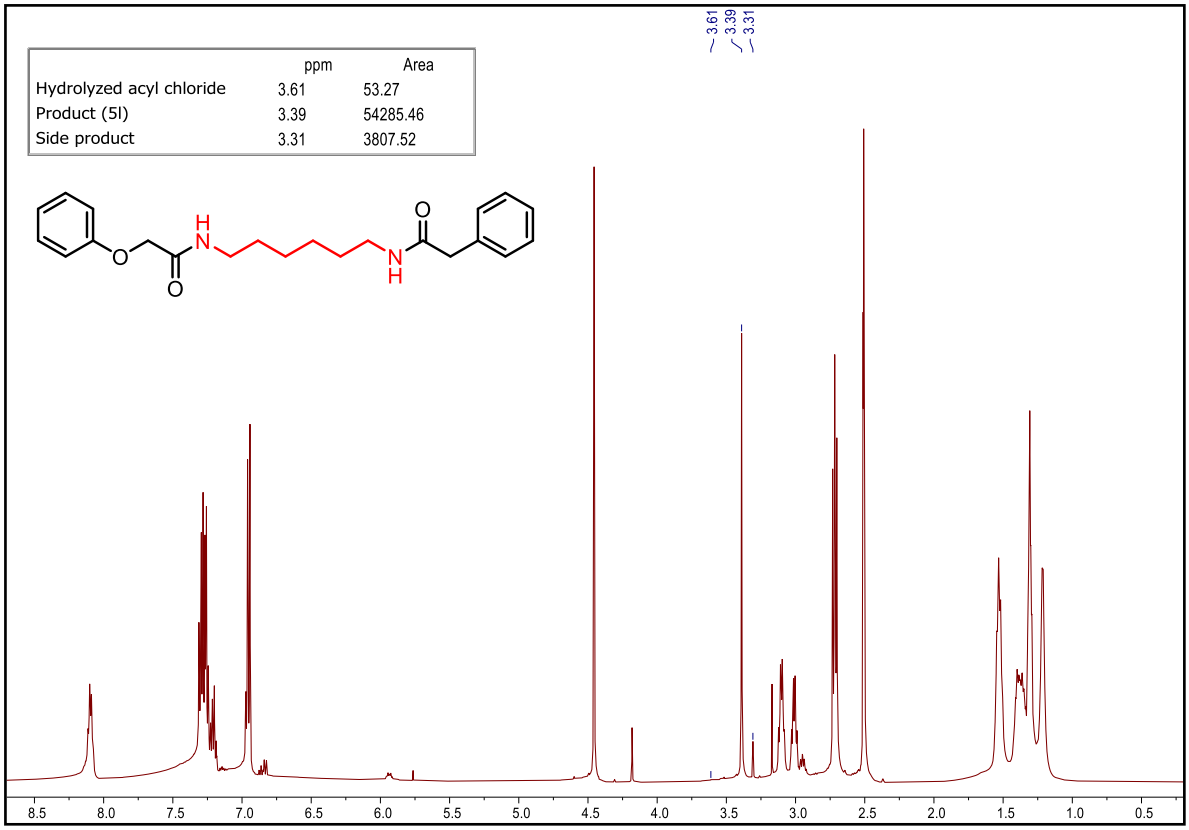


Fig S52. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **5l** (conditions[a]: DCM).

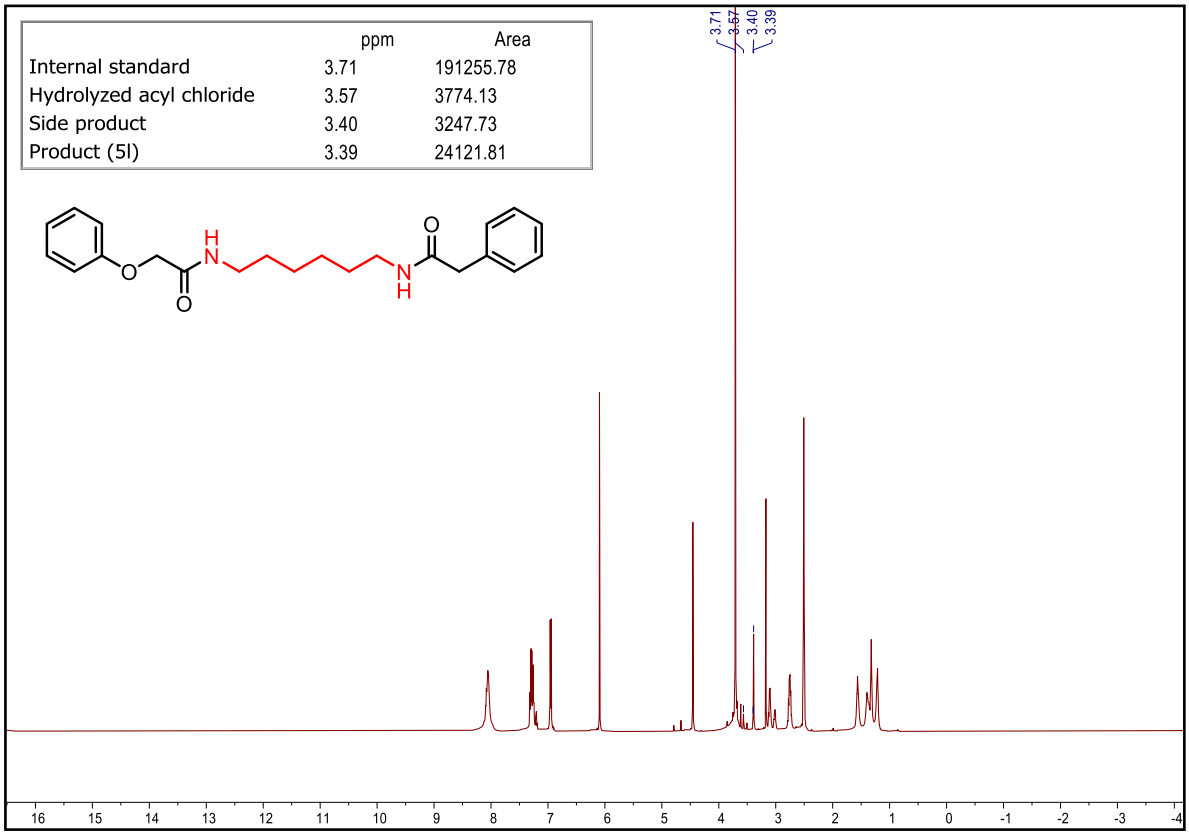
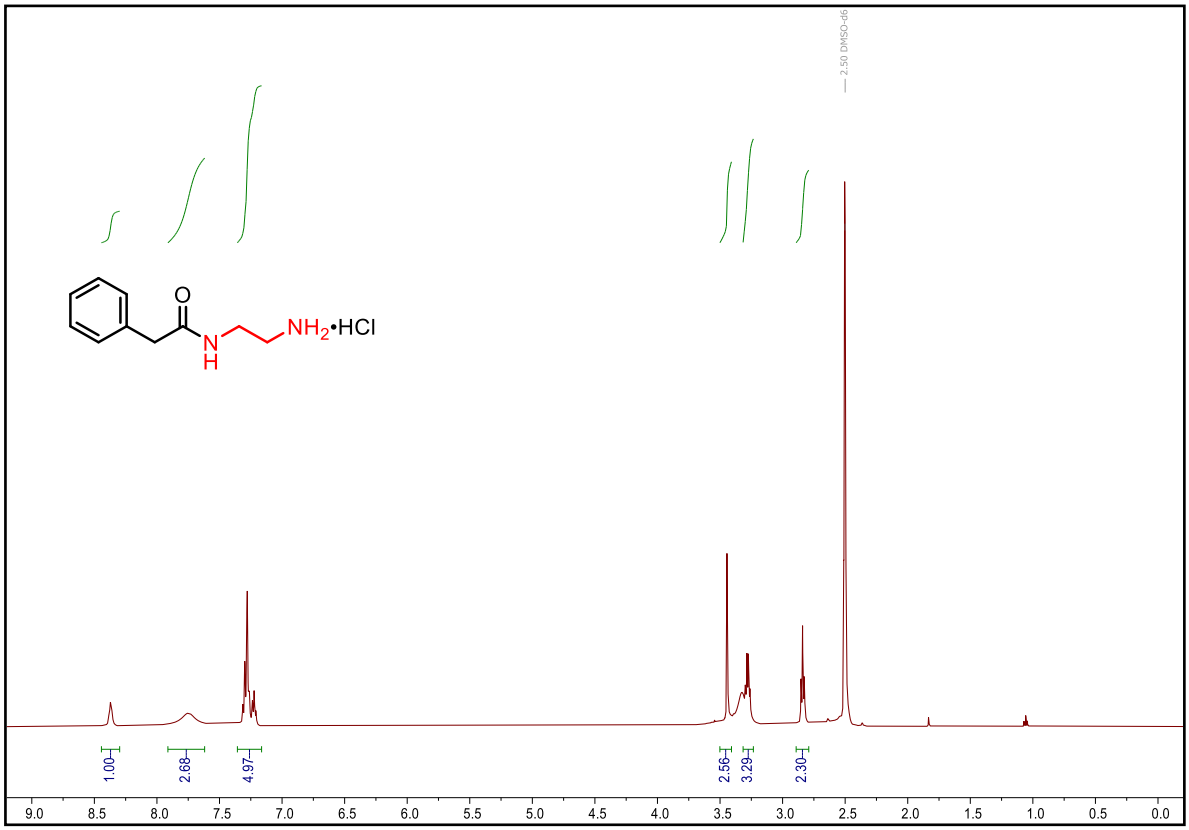


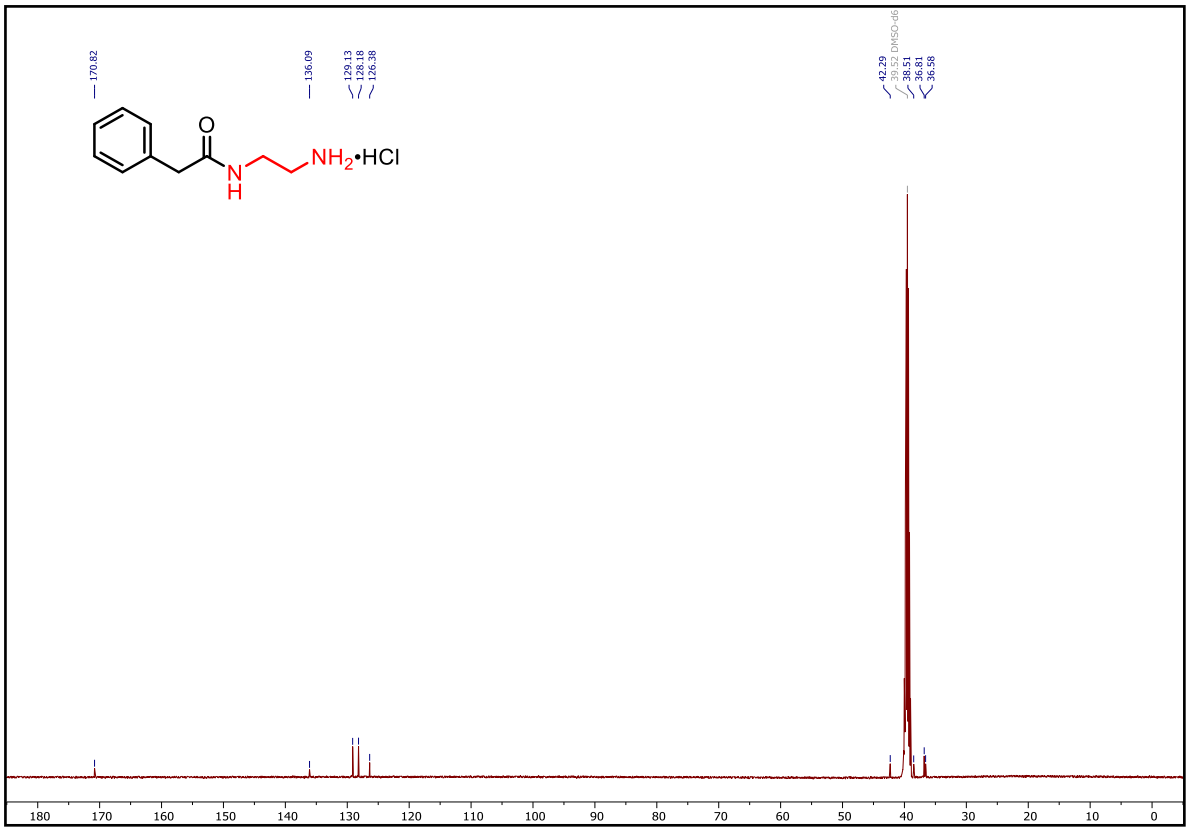
Fig S53. Crude ^{1}H-NMR in DMSO-d_6 spectrum of compound **5l** (conditions[b]: EtOAc).

13. NMR spectra

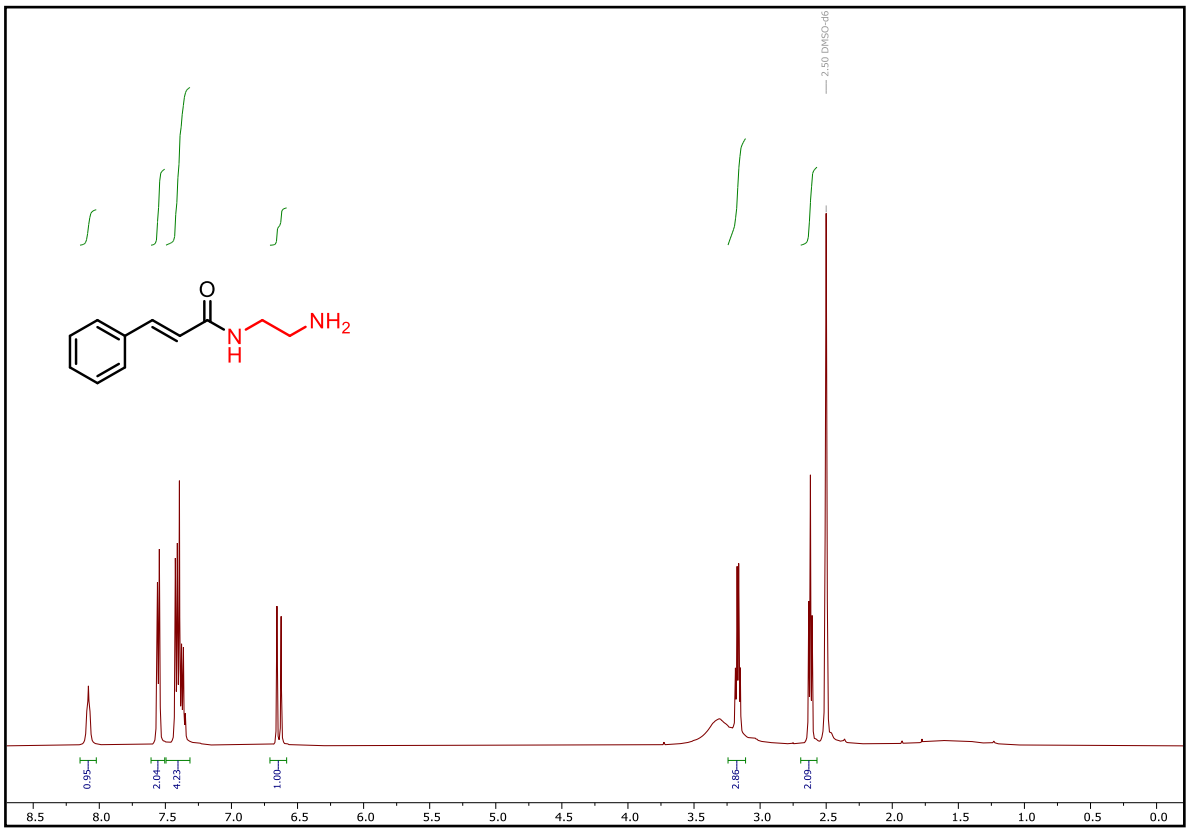
^{1}H NMR (500 MHz, DMSO-d_6) of **3a·HCl**



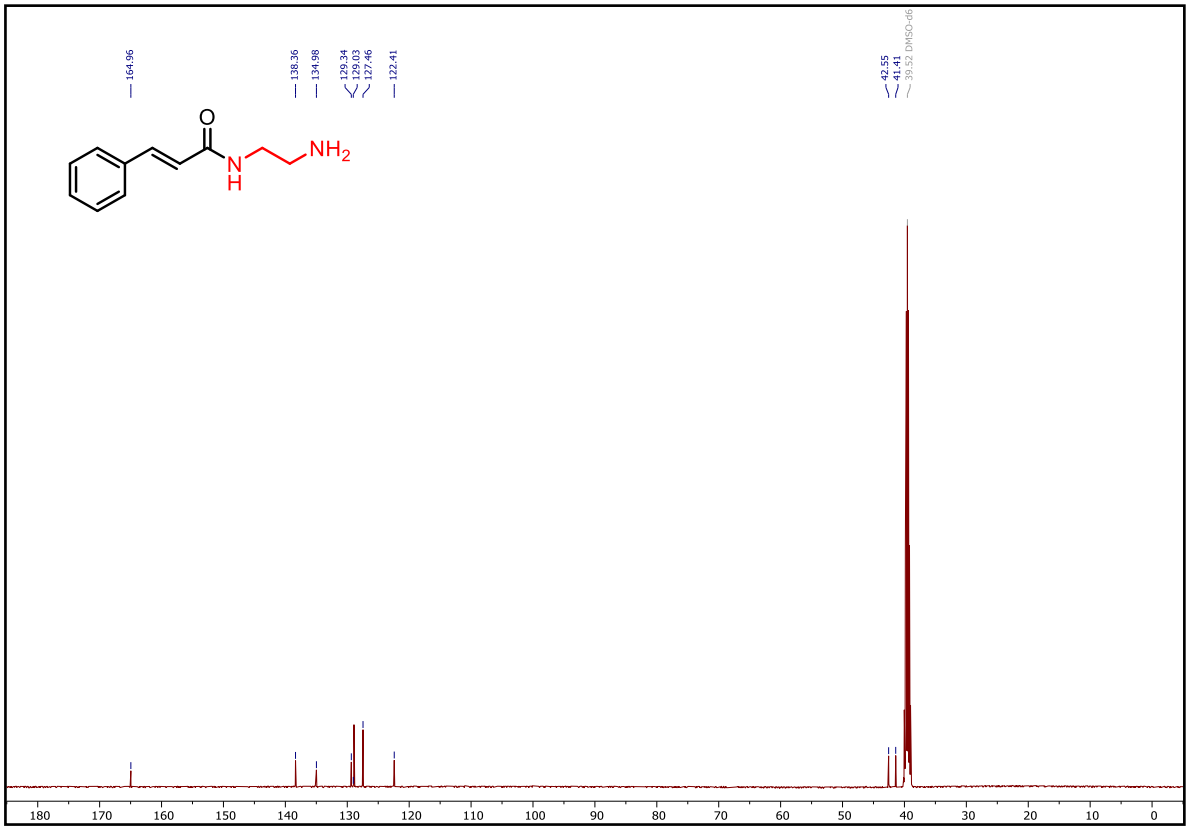
^{13}C NMR (126 MHz, DMSO-d_6) of **3a·HCl**



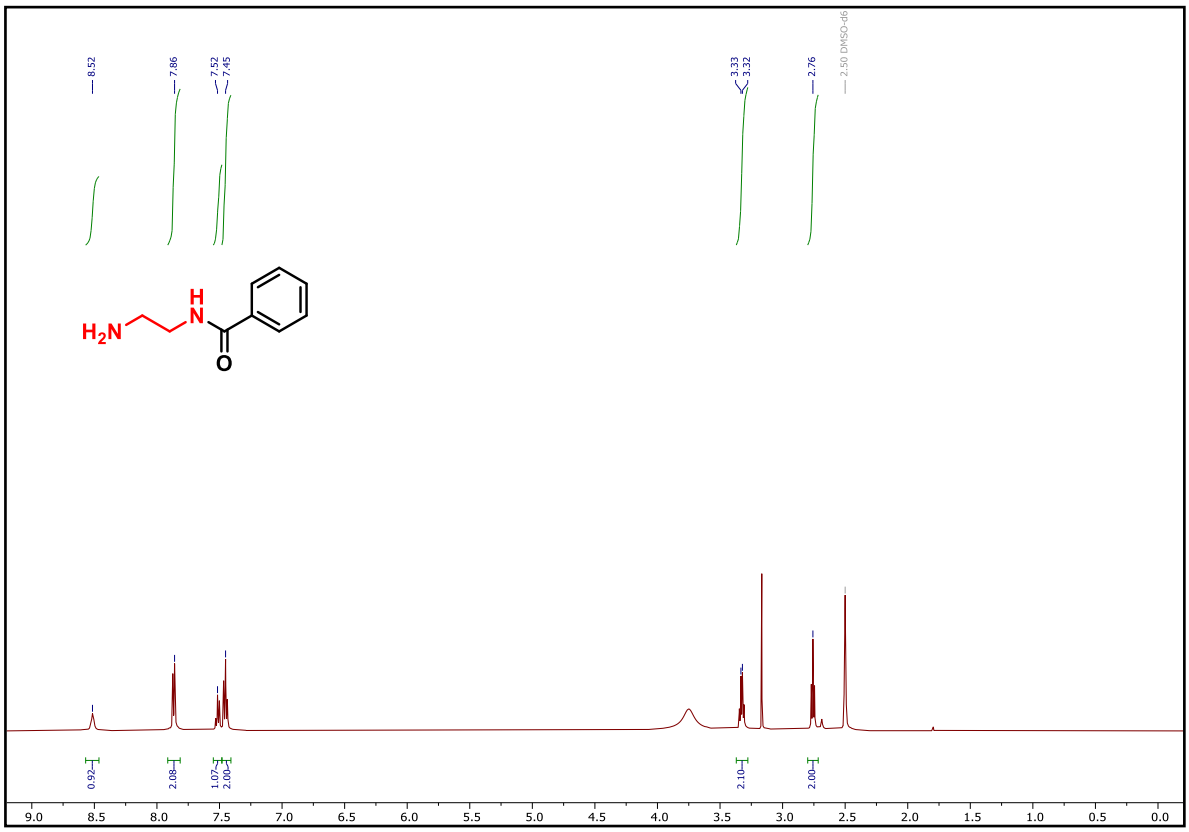
^{1}H NMR (500 MHz, DMSO-d_6) of **3b**



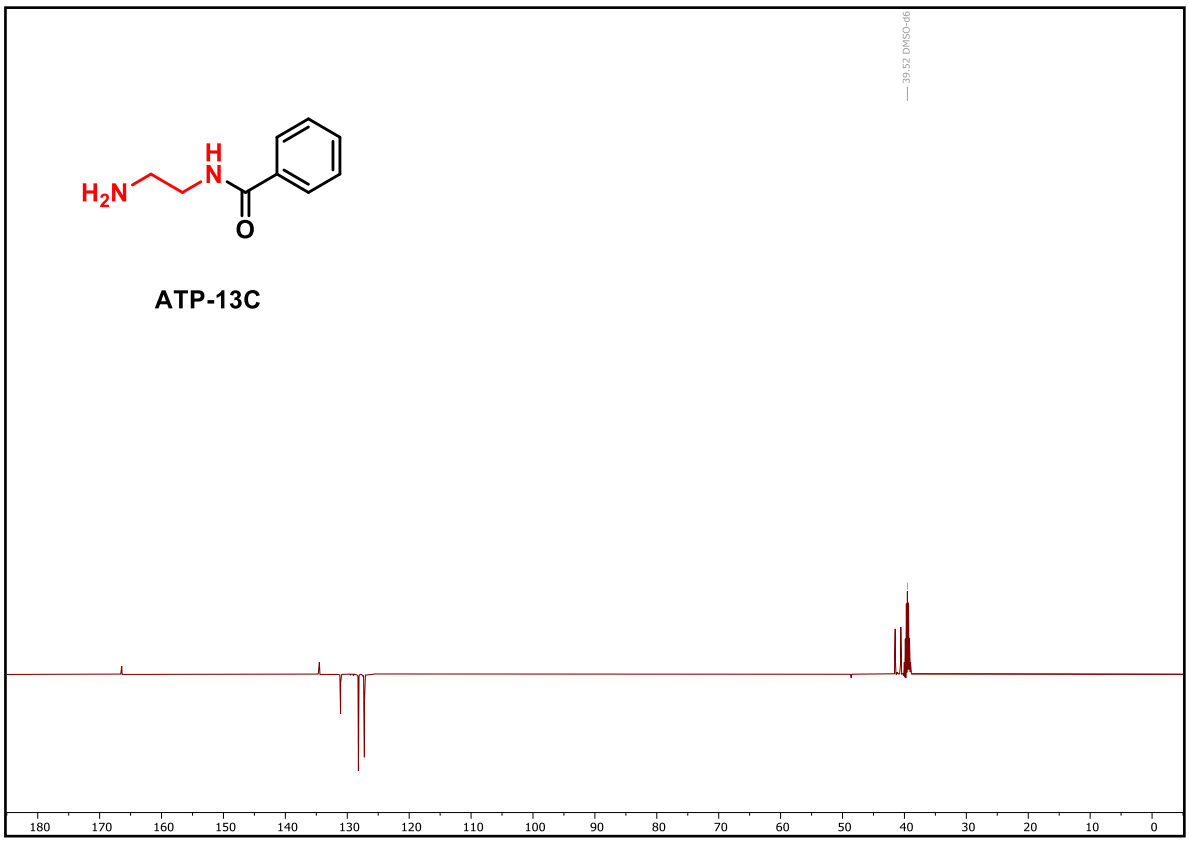
^{13}C NMR (126 MHz, DMSO-d_6) of **3b**



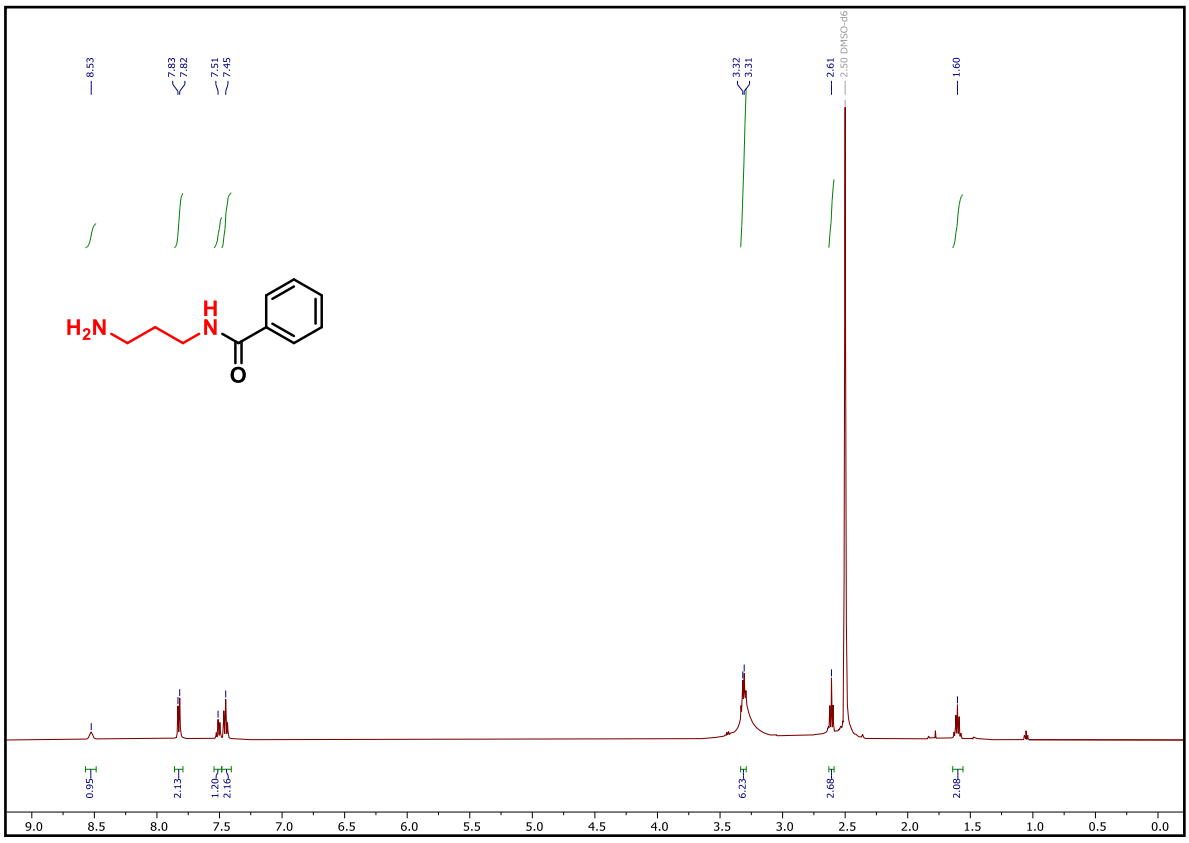
^{1}H NMR (500 MHz, DMSO-d_6) of **3e**



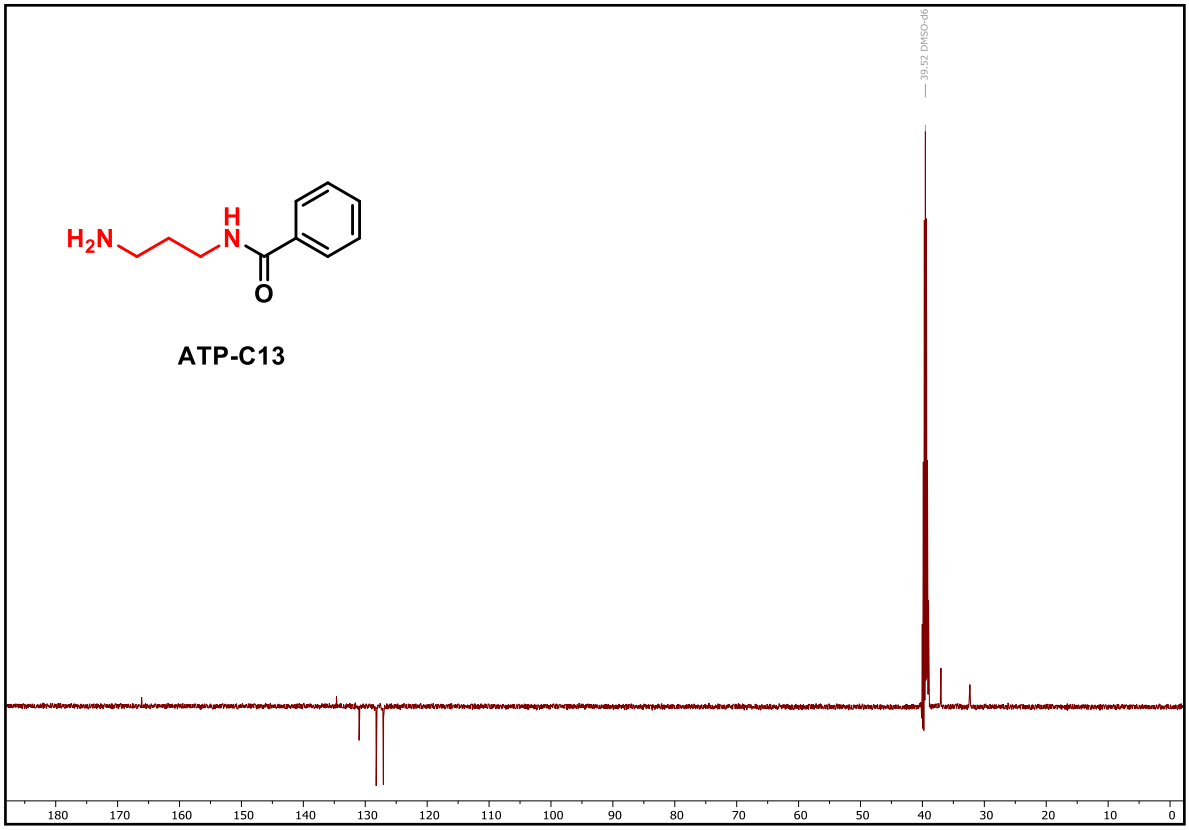
^{13}C NMR (126 MHz, DMSO-d_6) of **3e**



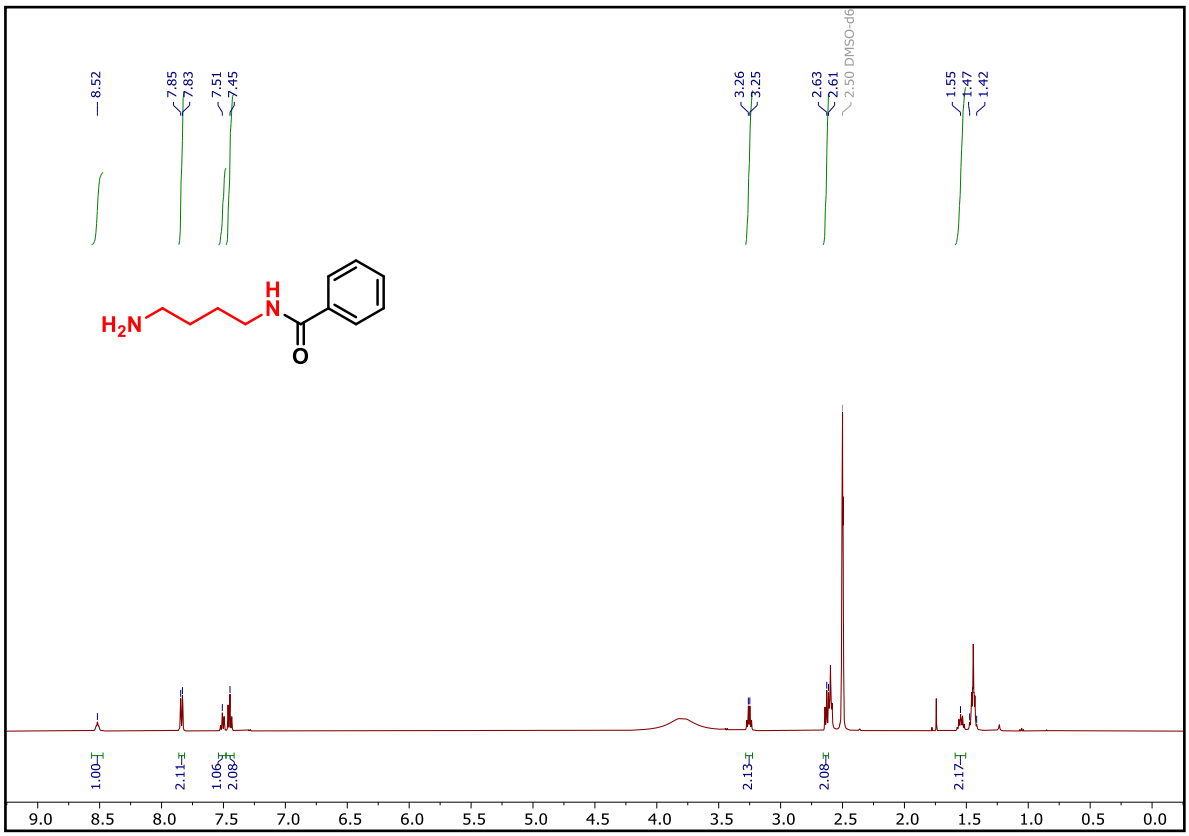
^{1}H NMR (500 MHz, DMSO-d_6) of **3f**



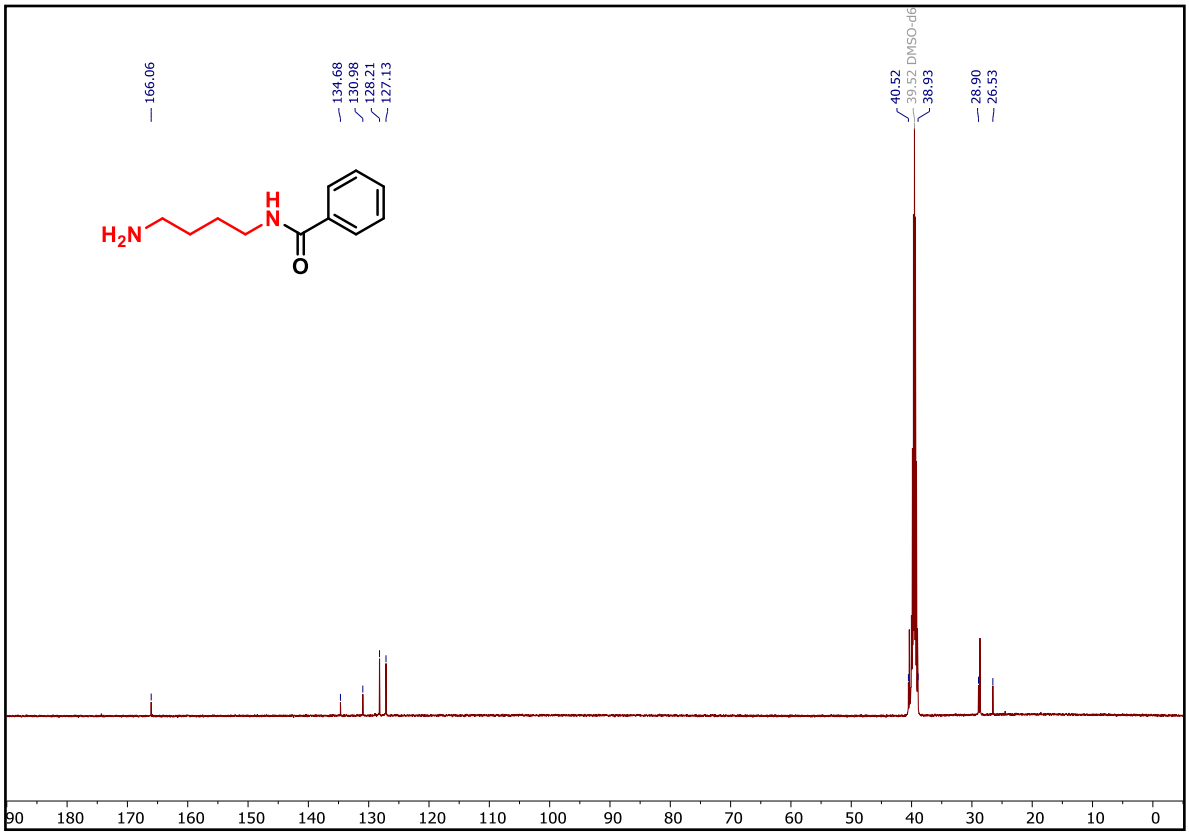
^{13}C NMR (126 MHz, DMSO-d_6) of **3f**



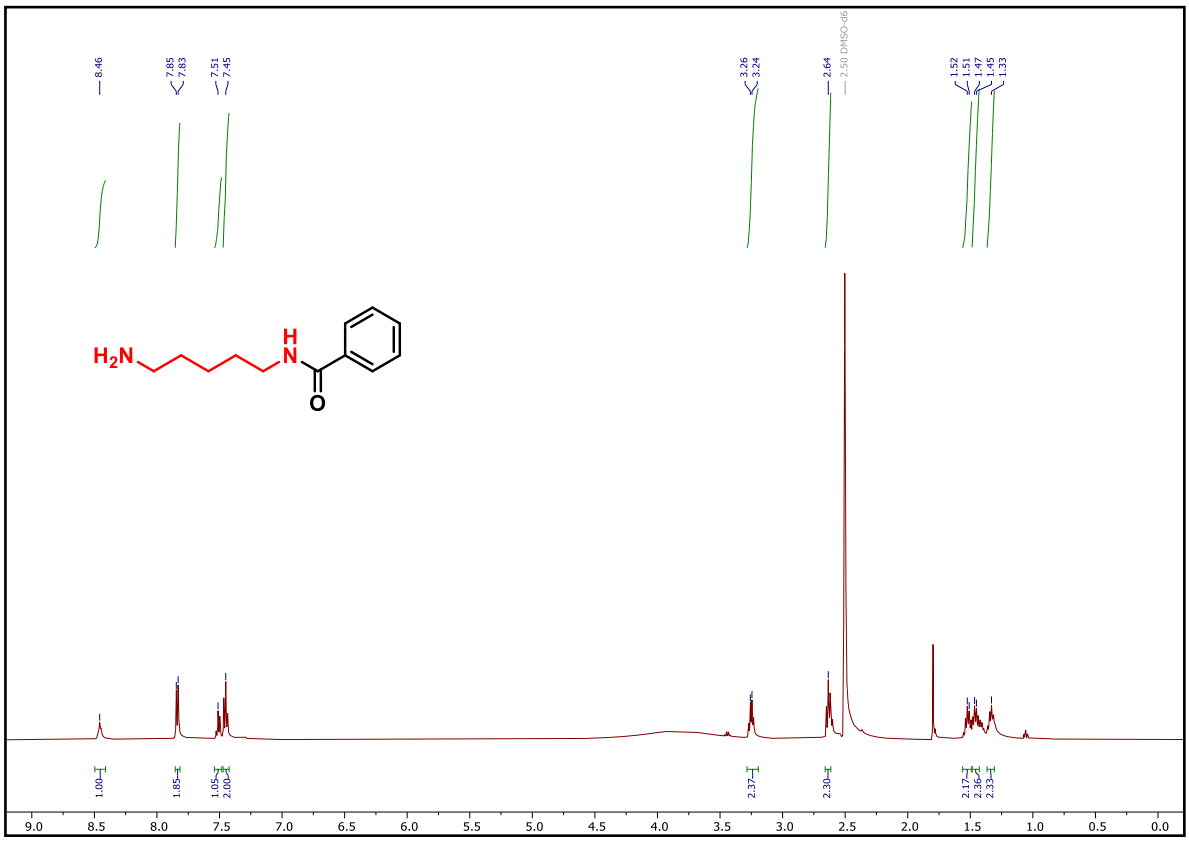
^{1}H NMR (500 MHz, DMSO-d_6) of **3g**



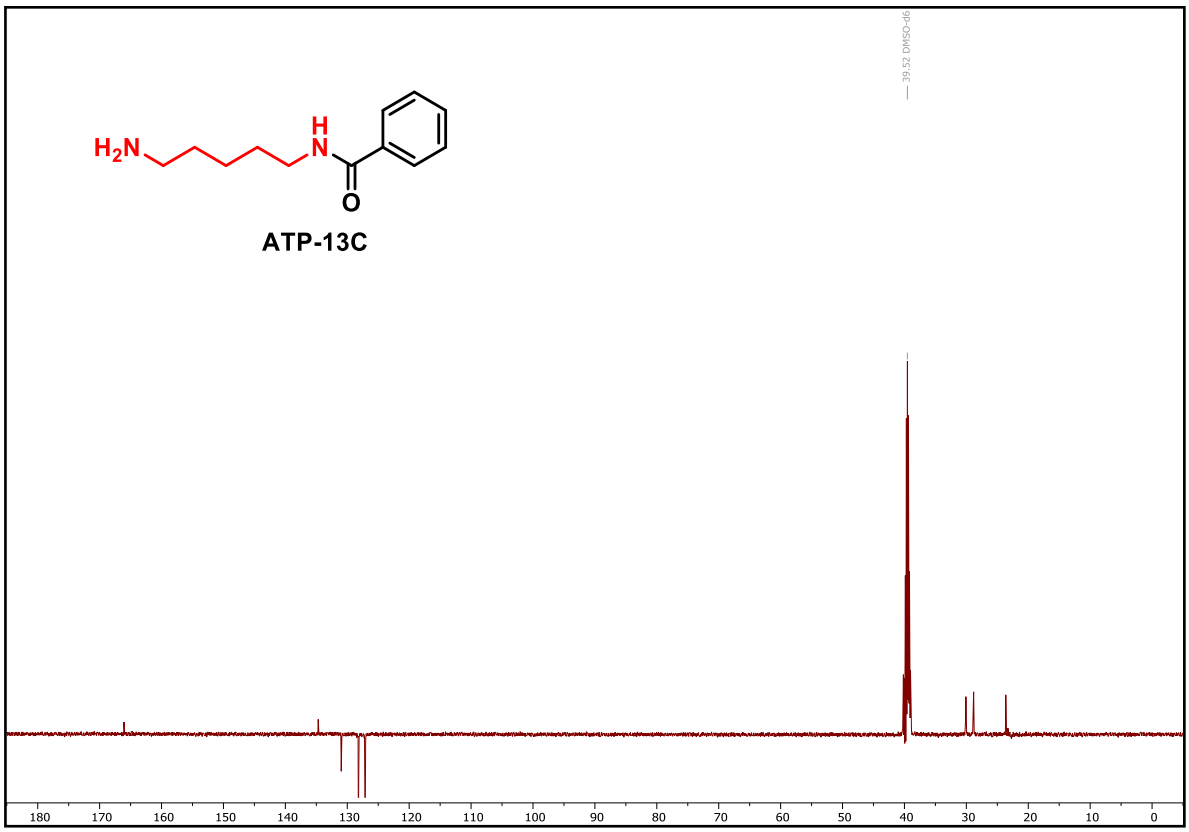
^{13}C NMR (126 MHz, DMSO-d_6) of **3g**



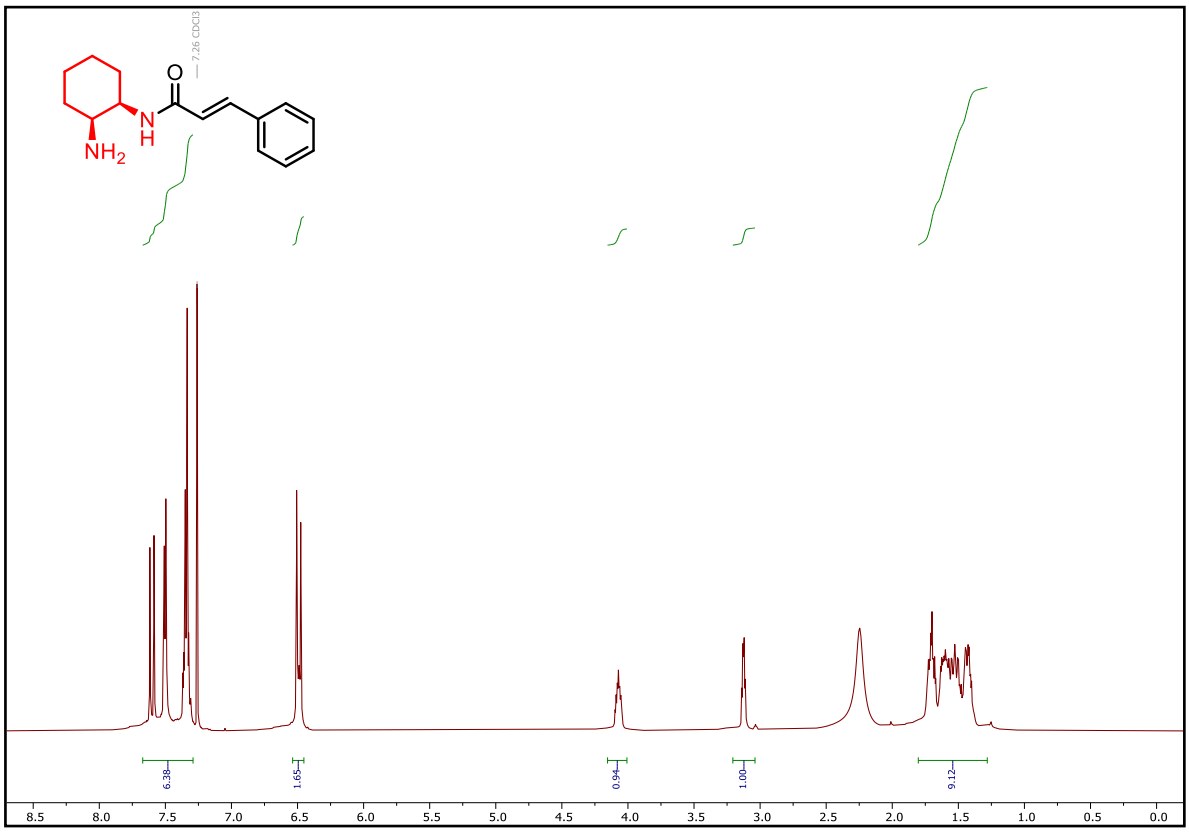
^{1}H NMR (500 MHz, DMSO-d_6) of **3h**



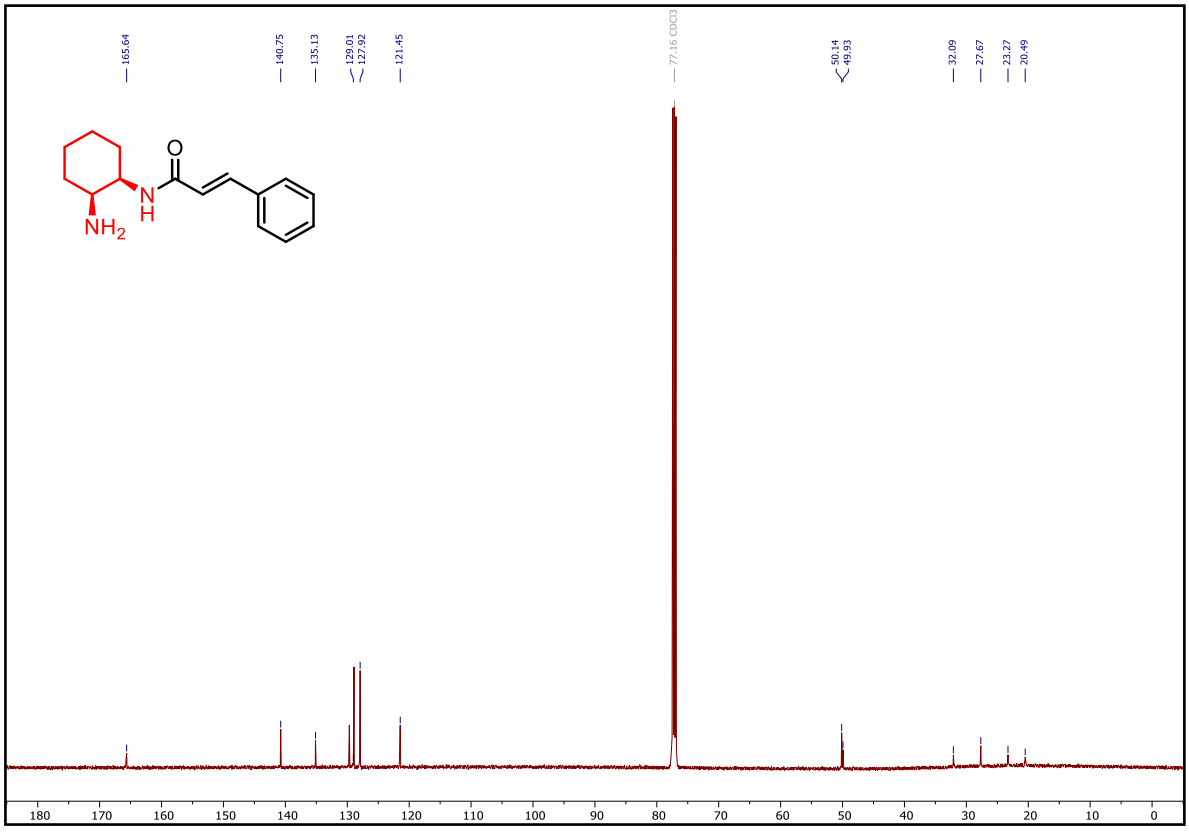
^{13}C NMR (126 MHz, DMSO-d_6) of **3h**



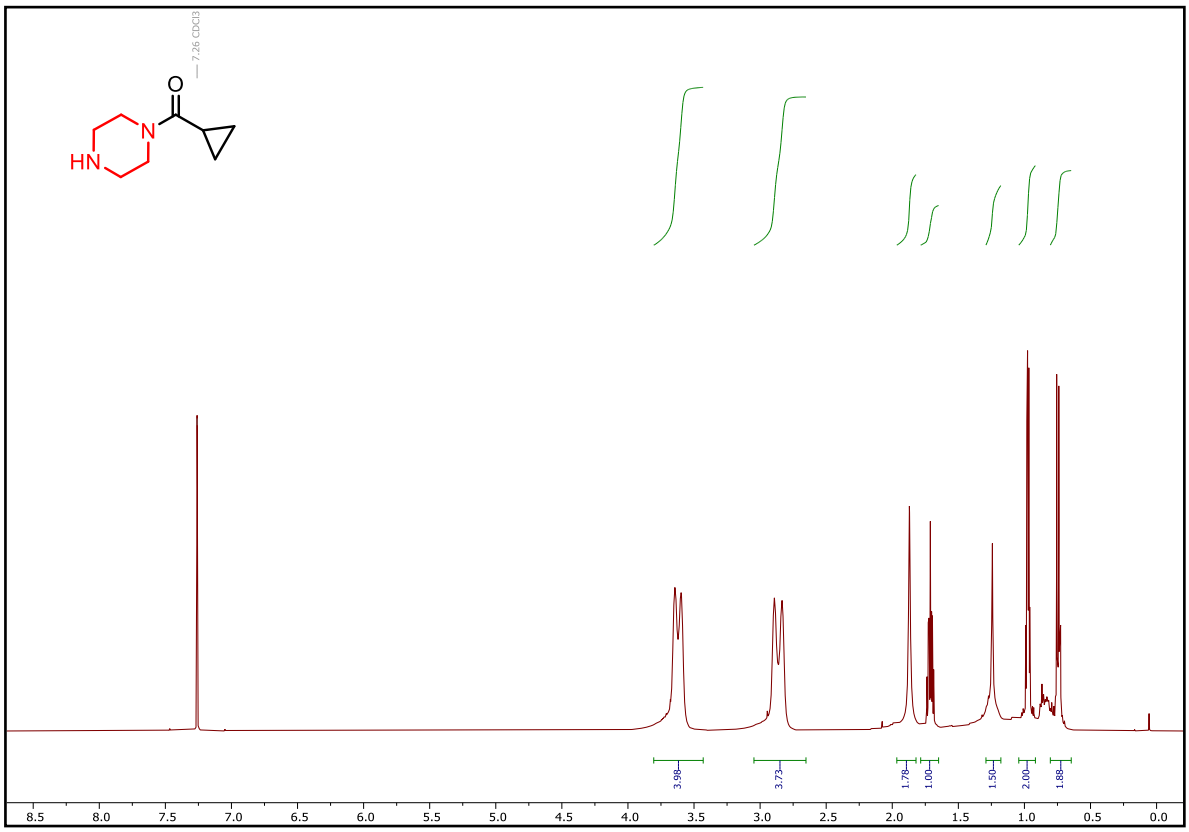
^{1}H NMR (500 MHz, $CDCl_3$) of **3k**



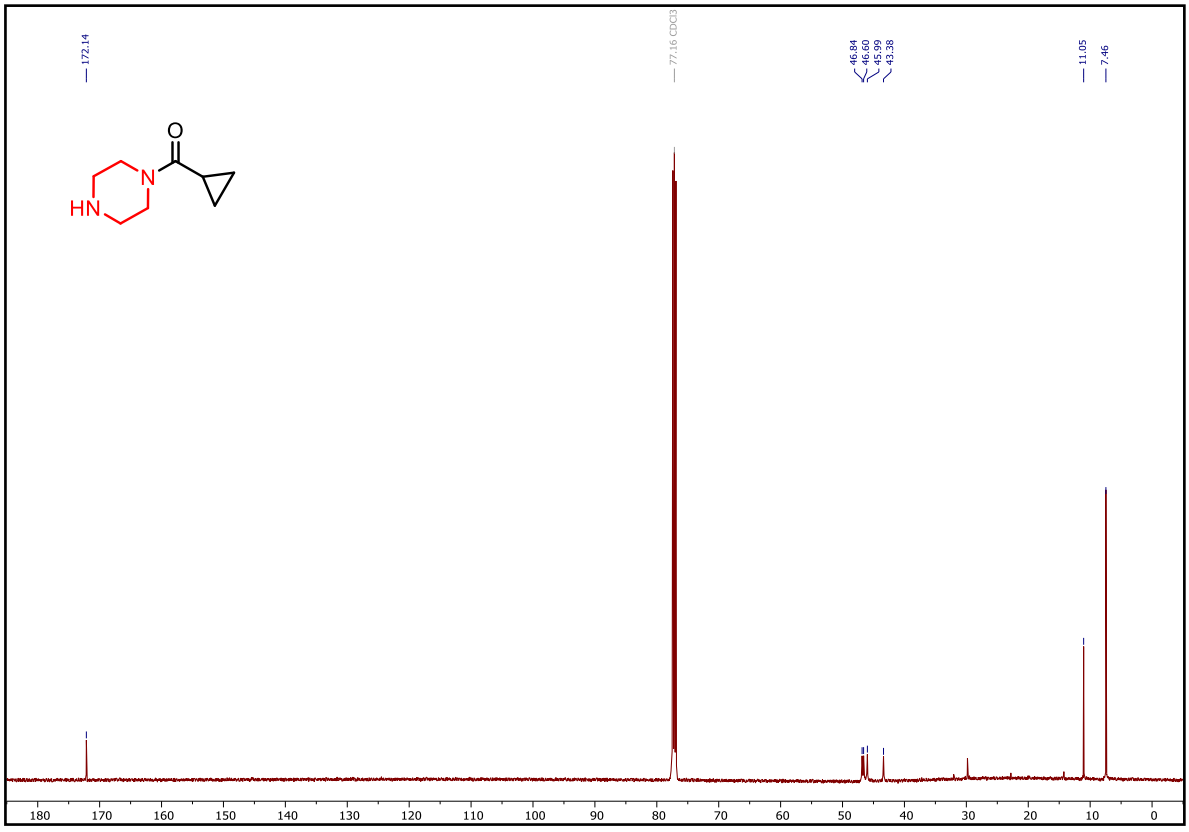
^{3}C NMR (126 MHz, $CDCl_3$) of **3k**



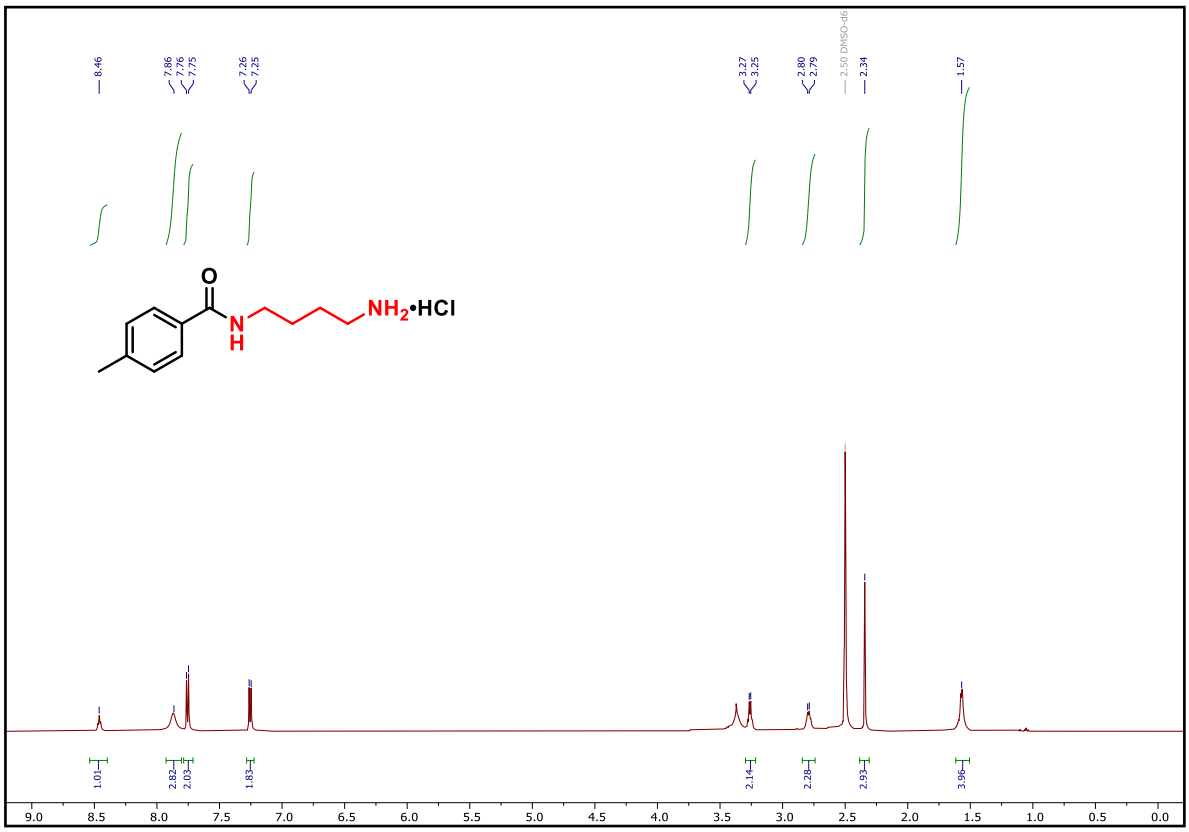
^{1}H NMR (500 MHz, $CDCl_3$) of **3n**



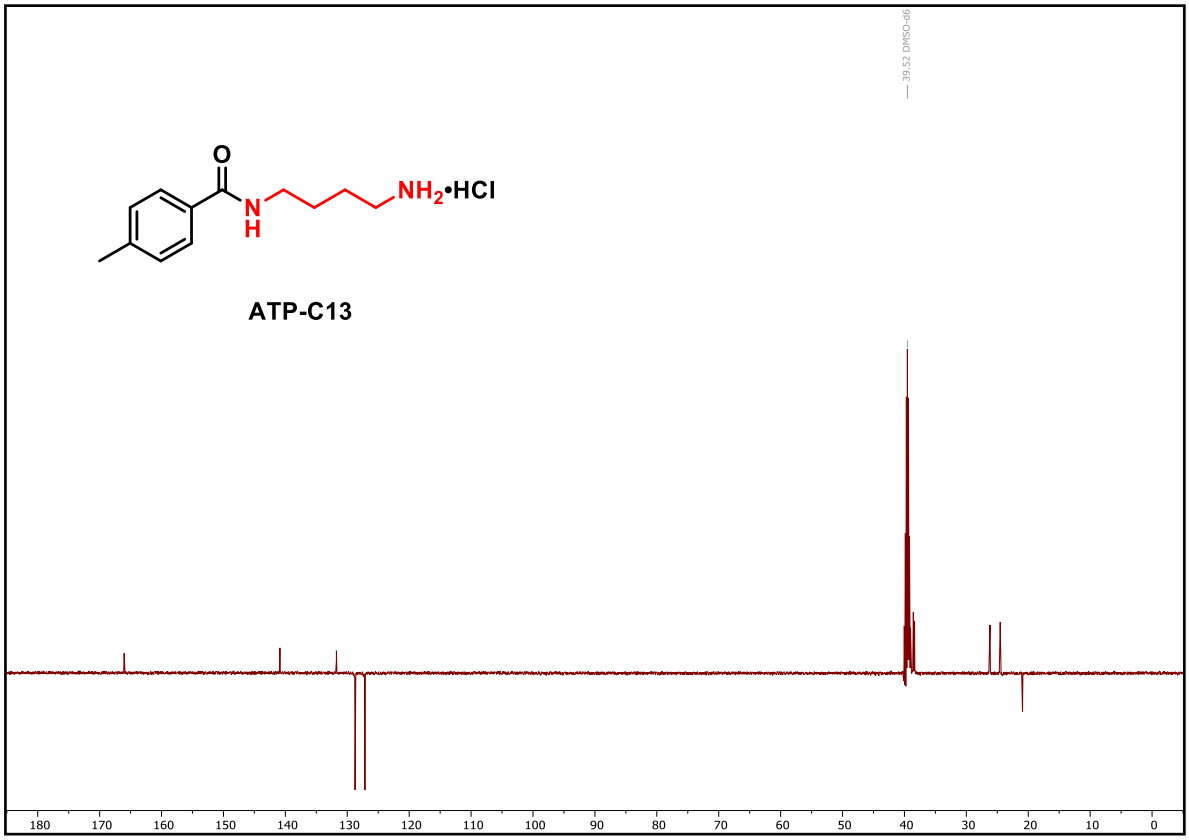
^{13}C NMR (126 MHz, $CDCl_3$) of **3n**



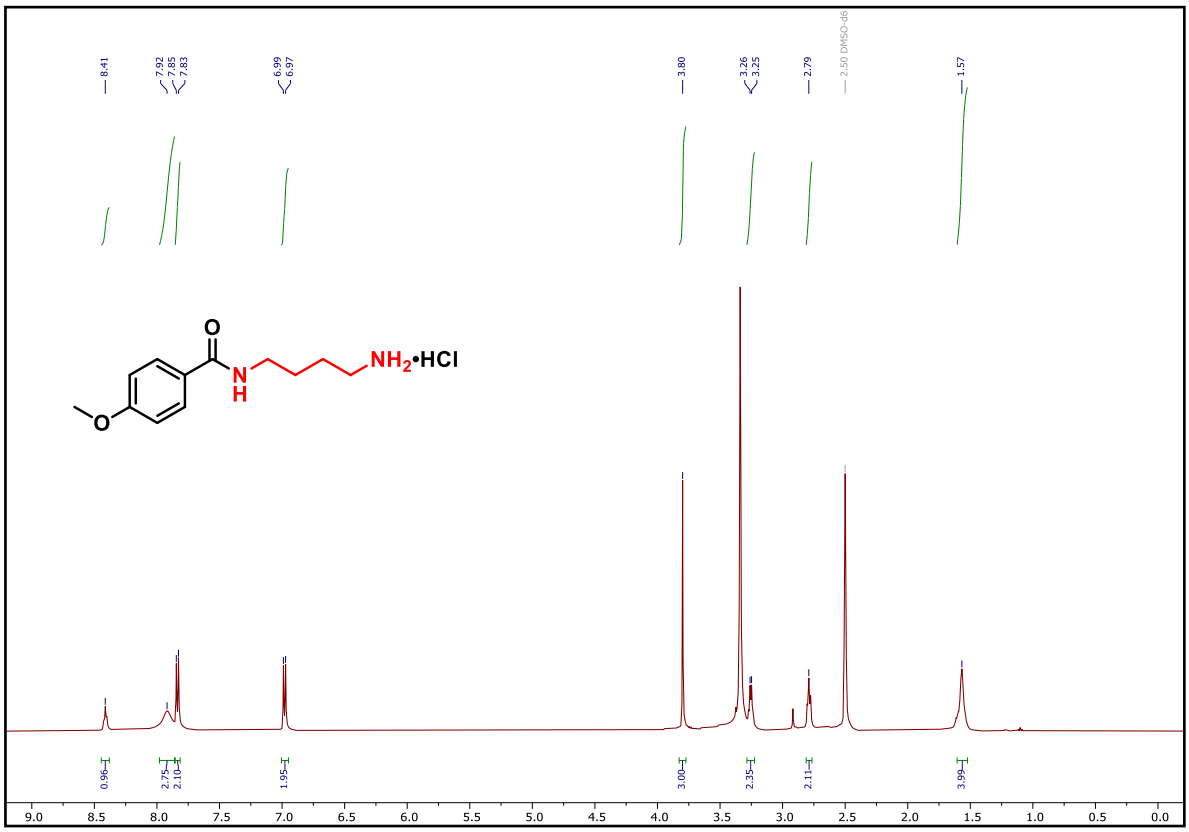
^{1}H NMR (500 MHz, DMSO-d_6) of **3p·HCl**



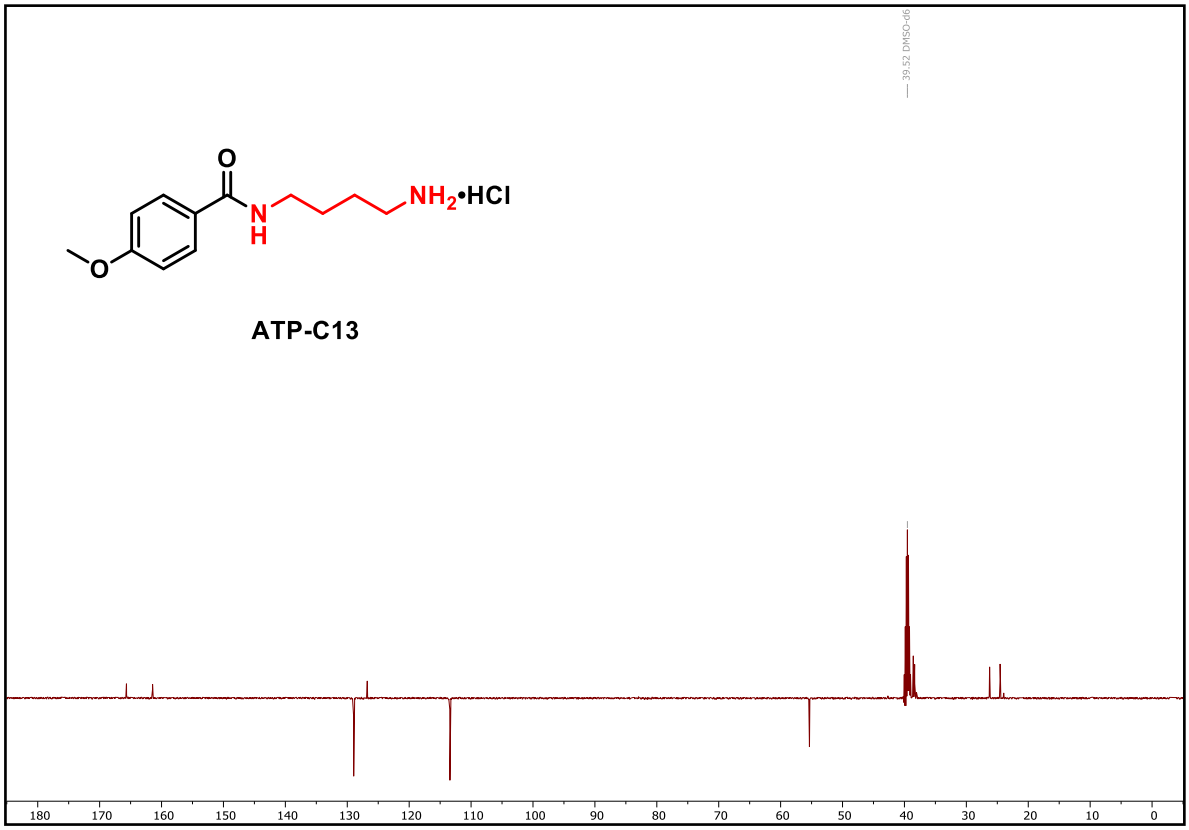
^{13}C NMR (126 MHz, DMSO-d_6) of **3p·HCl**



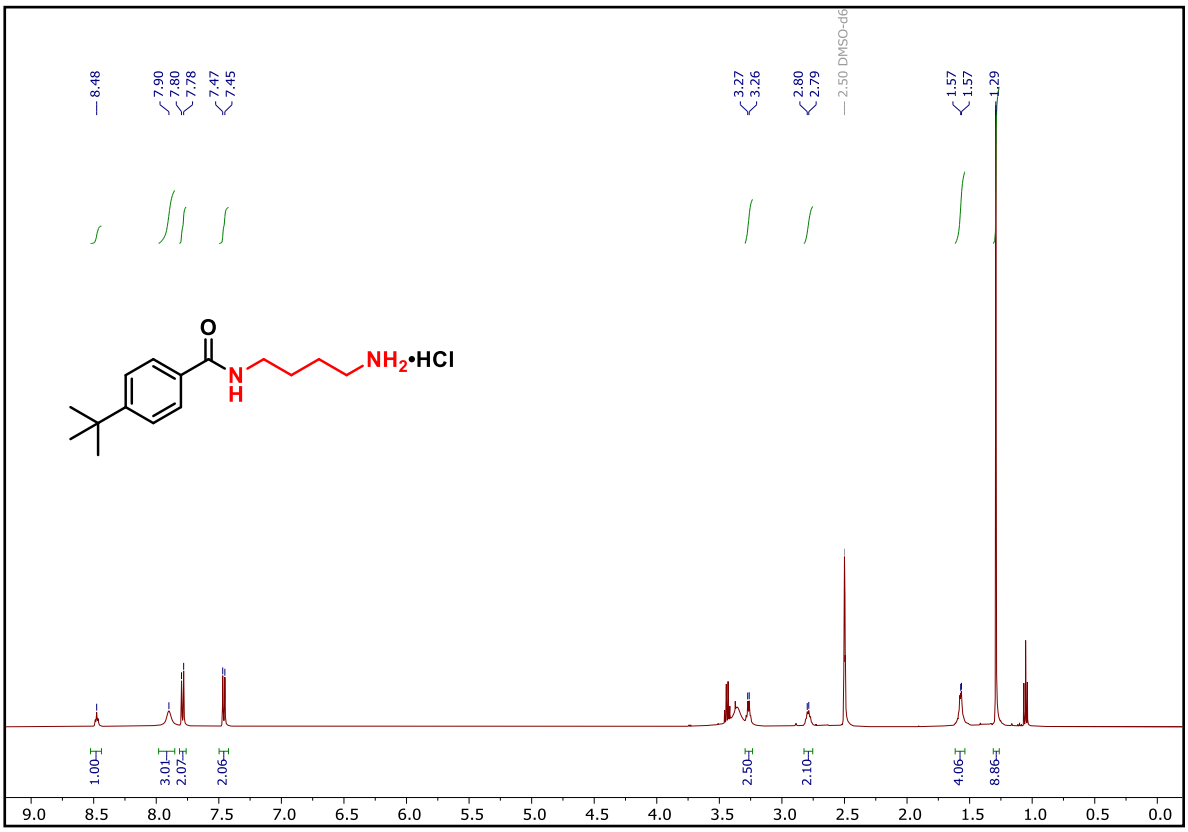
^{1}H NMR (500 MHz, DMSO-d_6) of **3r·HCl**



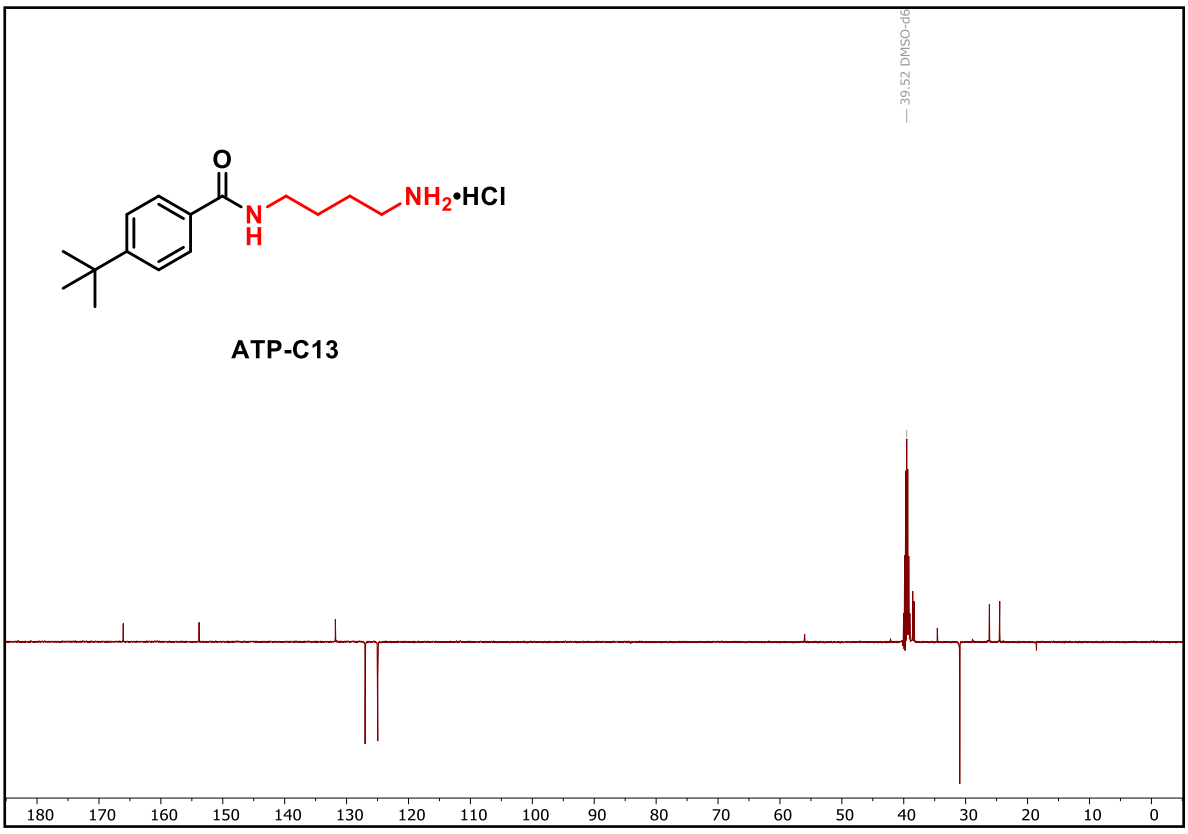
^{13}C NMR (126 MHz, DMSO-d_6) of **3r·HCl**



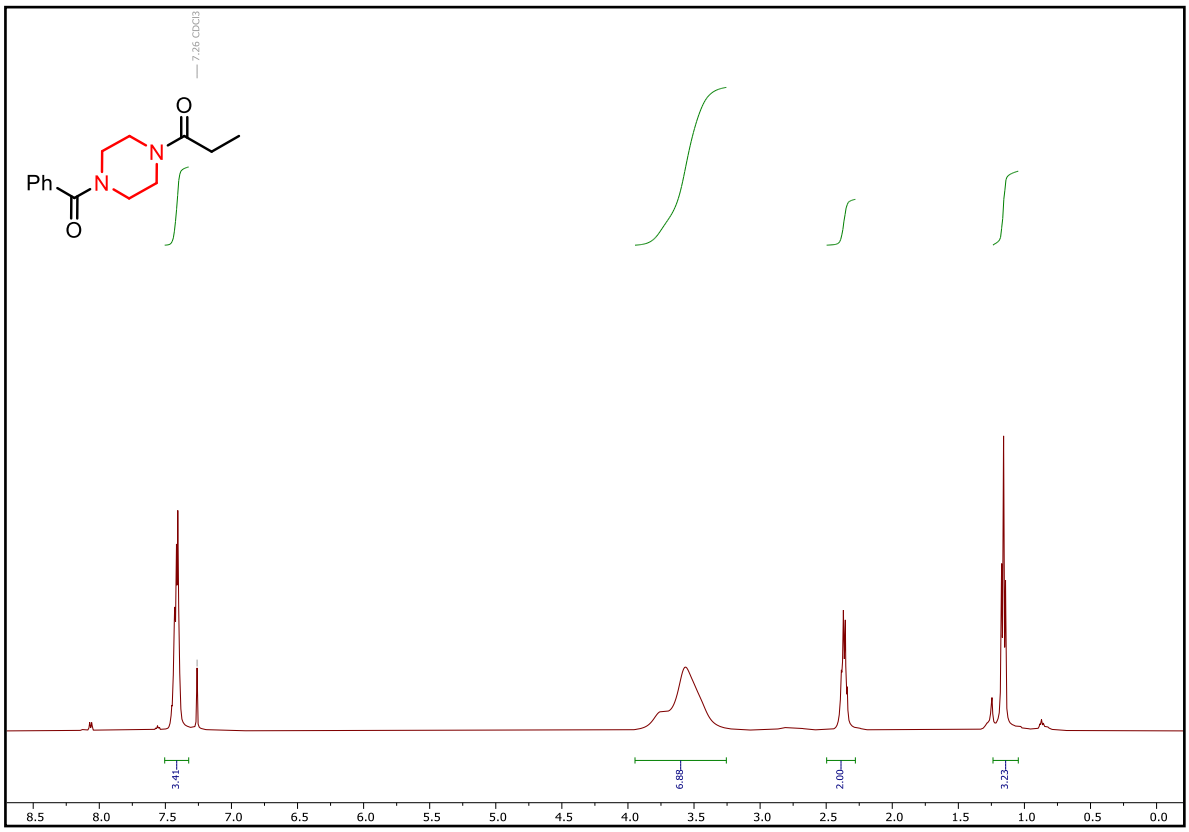
^{1}H NMR (500 MHz, DMSO-d_6) of **3s·HCl**



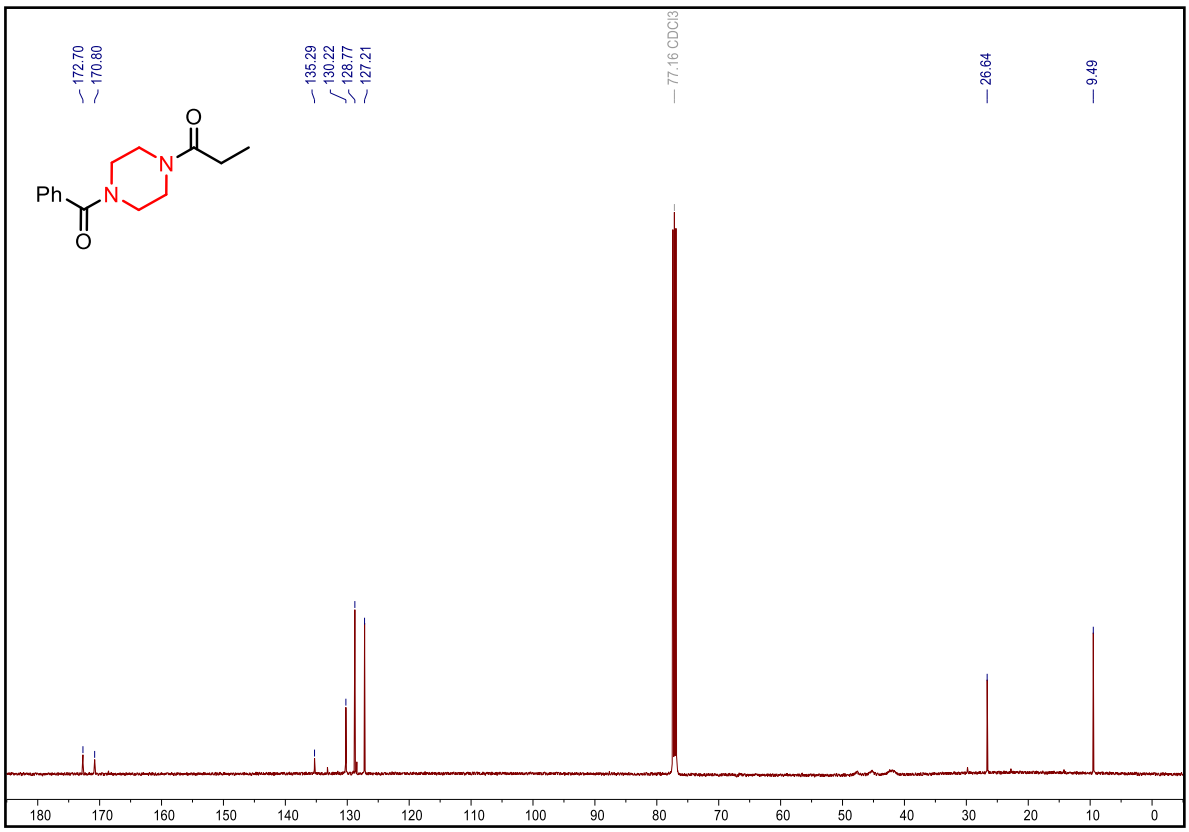
^{13}C NMR (126 MHz, DMSO-d_6) of **3s·HCl**



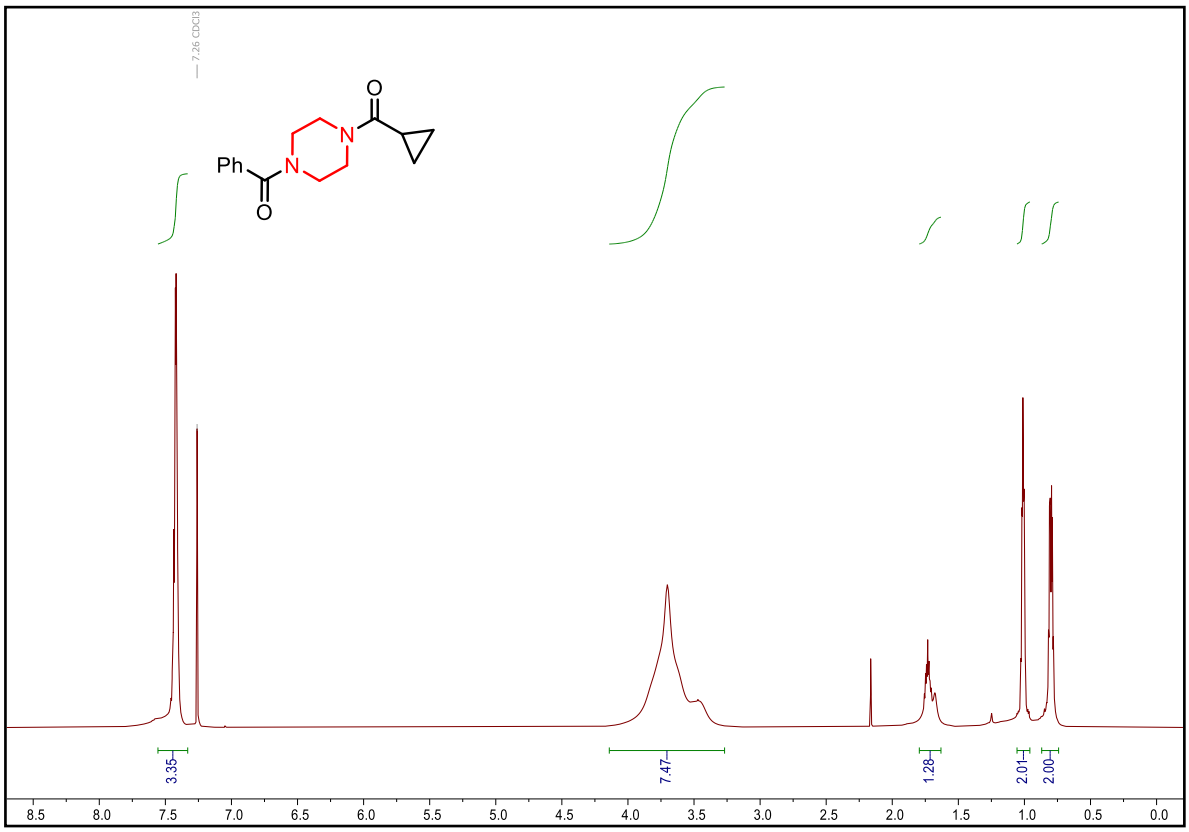
^{1}H NMR (500 MHz, $CDCl_3$) of **5a**



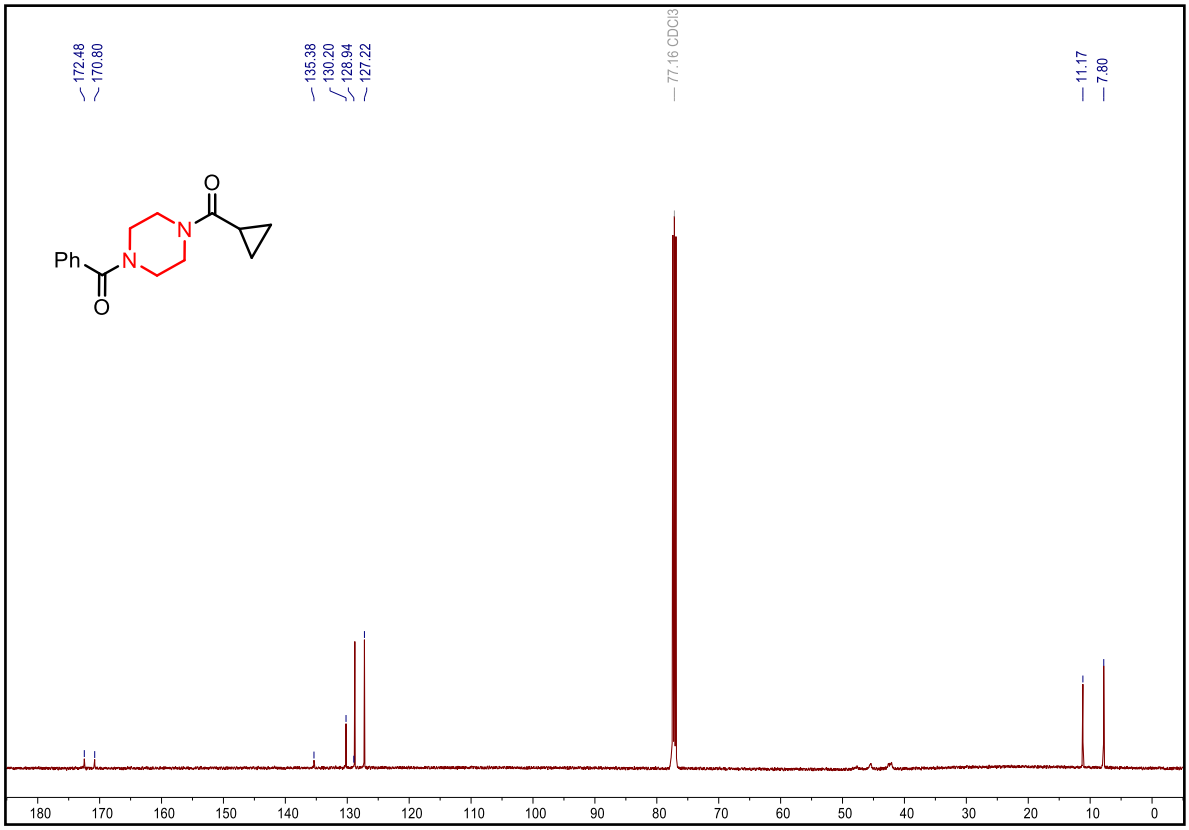
^{13}C NMR (126 MHz, $CDCl_3$) of **5a**



^{1}H NMR (500 MHz, $CDCl_3$) of **5b**



^{13}C NMR (126 MHz, $CDCl_3$) of **5b**



14. References

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