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Manuscript title: CisPro stabilizing tetrel bonding interactions in prolyl carbamates

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Contents

List of Abbreviations:

1. Structure

Me	:	Methyl
Et	:	Ethyl
^{i}Pr	:	isopropyl
^{t}Bu	:	tert-butyl

2. Synthesis

anhyd.	:	anhydrous
aq.	:	aqueous
MCF	:	methylchloroformate
ECF	:	ethylchloroformate
NMM	:	4-Methylmorpholine
TEA	:	triethylamine
THF	:	Tetrahydrofuran
DCM	:	Dichloromethane
eq. or equiv.	:	equivalent
EtOAc	:	ethyl acetate
MeOH	:	methyl alcohol
mg	:	milligram(s)
ml	:	milliliter
mM	:	millimolal (concentration)
mmol	:	millimole(s)
Moc	:	methyloxycarbonyl
Boc	:	tert-butyloxycarbonyl
$(Boc)_2O$	:	Di-tert-butyl dicarbonate
Na_2SO_4	:	sodium sulphate
$NaHCO_3$	:	sodium bicarbonate
qu.	:	quantitative
R_f	:	retardation factor (in TLC)
TLC	:	thin layer chromatography

3. Characterization

2°	:	secondary
3°	:	tertiary

Å	:	angstrom
Calcd.	:	calculated
$CDCl_3$	:	deuterated chloroform
DMSO-d_6	:	deuterated dimethyl sulfoxide
D_2O	:	deuterated water
cm	:	centimeter
nm	:	nanometer
NMR	:	nuclear magnetic resonance
Hz	:	Hertz
MHz	:	mega hertz
ppm	:	parts per million
quin	:	quintet
d	:	doublet
dd	:	doublet of a doublet
dt	:	doublet of a triplet
q	:	quartet
s	:	singlet
t	:	triplet
td	:	triplet of doublet
g	:	gram(s)
h	:	hour(s)
HRMS	:	High resolution mass spectrum
K	:	Kelvin (temperature)
m	:	multiplet
M	:	Molar
mM	:	millimolar
µM	:	micromolar
min	:	minute(s)
nm	:	nanometers (wavelength)
KJ	:	kilojoules
mol	:	mole
RT or rt	:	room temperature
sec	:	seconds

Supporting Information:

S1-Forward and Reverse inter-carbonyl interactions:

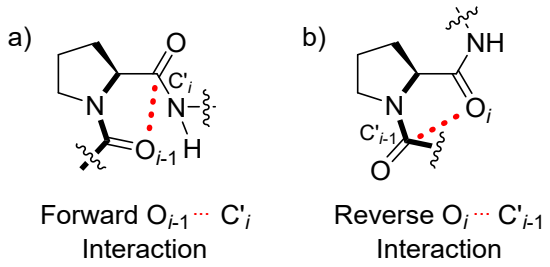


Figure S1: O···C′ interactions, in both forward (O_{i-1}···C'_i) and reverse (O_i···C'_{i-1}) directions (indicated by red dots) on the cis/trans isomerism at Xaa-Pro peptide bond.

S2-*cis/trans* Isomerisation:

Natural steric and electronic interactions stabilizing *trans*Pro & *cis*Pro rotamers:

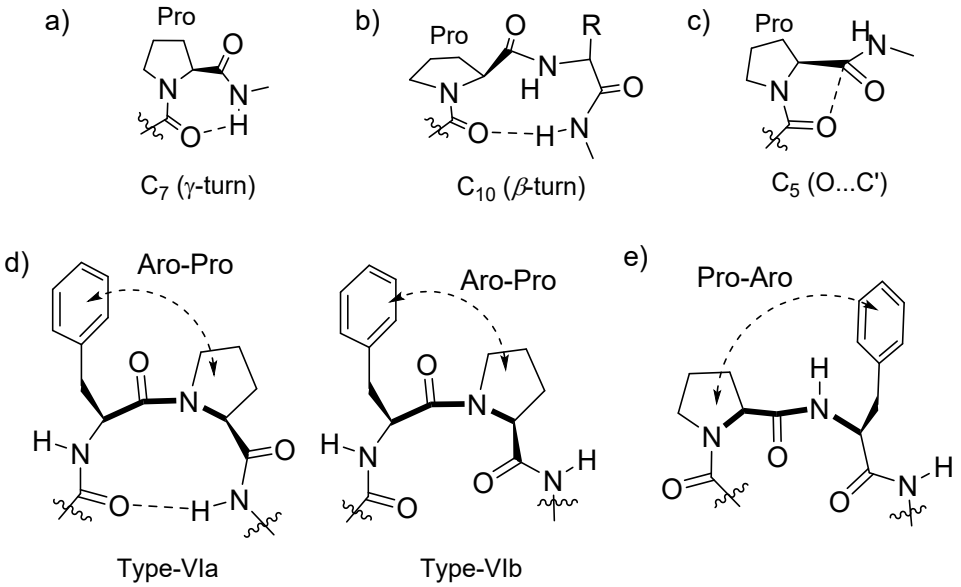


Figure S2: Local electronic interactions favour *trans*Pro conformers at Pro, (a) C_7 H-bond interaction, (b) C_{10} H-bond interaction and (c) C_5 O···C′ interaction; Electronic interactions favouring the *cis*Pro conformers, (d) Aro-Pro & (e) Pro-Aro (C-H/π) side chain side chain interactions.

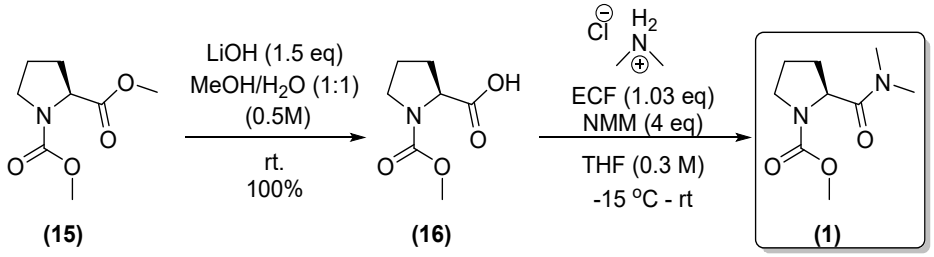
S3-Experimental Section:

Materials and Methods.

All the reactions were performed in oven dried apparatus and were stirred using magnetic stir bars. Column chromatography was performed on silica gel (100-200µm). TLC was carried out on Kieselgel coated on aluminium sheets. Compounds were visualized by one of the (or all of the) following methods: (1) fluorescence quenching, (2) spray with a 0.2% (w/v) ninhydrin solution in absolute ethanol, (3) spray with 1% H_2SO_4 solution in EtOH/H_2O (1:5 v/v), (4) charring on hot plate. Ethylacetate and hexanes (or petroleum ether) were obtained from Sd-fine chemicals and were fractionally distilled at their respective boiling points, before use. Dichloromethane was dried by distillation over P_2O_5. NMM was distilled over CaH_2. NMR spectra were recorded on 400 MHz spectrometers in $CDCl_3$. Chemical shifts are expressed in parts per million (ppm) from the residual non-deuterated chloroform in $CDCl_3$ (δ_H = 7.26, δ_C = 77.00). *J* values are in Hz. Multiplicities are indicated using the following abbreviations: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), quin (quintet), hept (heptet), m (multiplet), bs (broad singlet). Infrared (IR) spectra were recorded in a FT/IR spectrometer, for thin-films (0.1 mmol) made from solutions in $CHCl_3$ (10 mmol) on sodium chloride plates or in neat (KBr pellets), with frequencies given in reciprocal centimetres (cm^{-1}). High resolution mass spectra were obtained by the ESI technique.

S4-Synthesis:

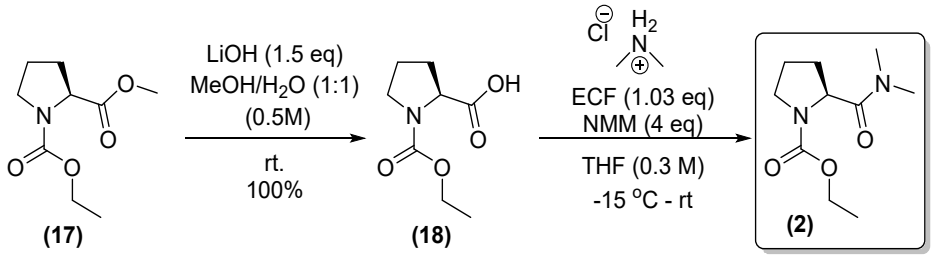
S4.1. Methyl (*S*)-2-(dimethylcarbamoyl)pyrrolidine-1-carboxylate (1):



Compound **10** (Moc-Pro-OH) (400mg, 2.14 mmol) was dissolved in methanol (3 mL) added lithium hydroxide (LiOH) (135 mg, 3.2 mmol) dissolved in water (1.5 mL) at rt. The reaction mixture was stirred at rt for 1.5 h. Methanol was removed using rotary evaporator and the aqueous part was acidified with 1N HCl at 0 °C until pH became 1-2. The product was extracted with EtOAc (2 X 10 mL) and the organic layer was concentrated to get **16** (370 mg, 2.14 mmol, 100%) which was used in the further reaction without further purification.

Compound **1** was synthesized by following the general procedure for the synthesis of amides by treating **16** (370 mg, 2.14 mmol) with ethyl chloroformate (ECF) (210 µL, 2.2 mmol), N-Methyl morpholine (NMM) (940 µL, 8.5 mmol) and **N,N-Dimethylamine hydrochloride** (209 mg, 2.6 mmol) in THF:DMF (5:1) (7 mL, 0.3M) at -15 °C. The reaction mixture was allowed to stir at -15 °C for 30 min and then allowed to stir at rt for 6 h. Removal of solvent resulted in a residue which was dissolved in ethyl acetate (EtOAc) (10 mL), washed with 10 mL water (2 X 5 mL) and 1N HCl solution (2 X 5 mL) and saturated $NaHCO_3$ solution (2 X 5 mL) and the organic layer was concentrated to get a residue which was subjected to purification by silica gel flash column chromatography (EtOAc -100%) yielded the desired product as a viscous oil (89 mg, 0.45 mmol, 21% yield); (TLC- EtOAc:MeOH (9:1) – R_f = 0.41); IR (NaCl, 10 mM in $CHCl_3$): 3024, 3008, 2958, 2888, 1693, 1652, 1456, 1392, 1232, 1142, 905, 809, 724 cm^{-1}. ***trans* isomer:** ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 4.68 (dd, J = 8.1 Hz, 3.4 Hz, 1H), 3.69 (s, 3H), 3.64-3.43 (m, 2H), 3.10 (s, 3H), 2.96 (s, 3H), 2.19-2.04 (m, 2H), 1.91-1.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 171.9, 155.3, 56.5, 52.2, 46.3, 36.8, 35.7, 29.3, 24.1; ***cis* isomer:** ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 4.60 (dd, J = 8.4 Hz, 3.2 Hz, 1H), 3.64 (s, 3H), 3.66-3.53 (m, 2H), 3.1 (s, 3H), 2.96 (s, 3H), 2.22-2.14 (m, 1H), 2.05-1.98 (m, 1H), 1.91-1.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 171.9, 154.8, 56.3, 52.3, 46.9, 36.7, 35.7, 30.3, 23.1; HRMS *m/z* Calcd for $C_9H_{16}N_2O_3Na$ 223.1059, Found 223.1059.

S4.2. Ethyl (*S*)-2-(dimethylcarbamoyl)pyrrolidine-1-carboxylate (2):

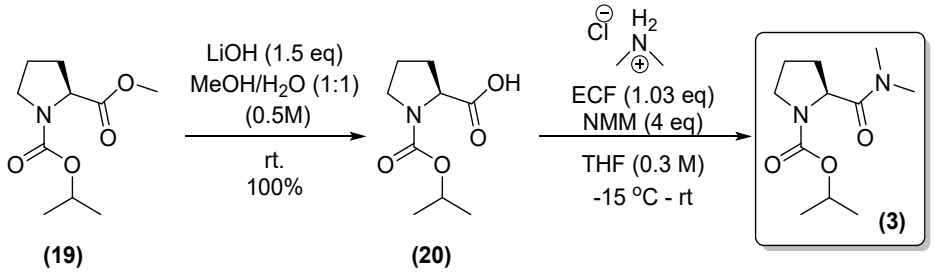


Compound **17** (500mg, 2.5 mmol) was dissolved in methanol (3.8 mL) added lithium hydroxide (LiOH) (156 mg, 3.73 mmol) dissolved in water (1.2 mL) at rt. The reaction mixture was stirred at rt for 2 h. Methanol was removed using rotary evaporator and the aqueous part was acidified with 1N HCl at 0 °C until pH became 1-2. The product was extracted with EtOAc (2 X 10 mL) and the organic layer was concentrated to get **18** (465 mg, 2.5 mmol, 100%) which was used in the further reaction without further purification.

Compound **2** was synthesized by following the general procedure for the synthesis of amides by treating **18** (465 mg, 2.48 mmol) with ethyl chloroformate (ECF) (245 µL, 2.56

mmol), N-Methyl morpholine (NMM) (1093 µL, 8.5 mmol) and **N,N-Dimethylamine hydrochloride** (243 mg, 3 mmol) in THF:DMF (5:1) (8.3 mL, 0.3M) at -15 °C. The reaction mixture was allowed to stir at -15 °C for 30 min and then allowed to stir at rt for 4 h. Removal of solvent resulted in a residue which was dissolved in ethyl acetate (EtOAc) (10 mL), washed with 10 mL water (2 X 5 mL) and 1N HCl solution (2 X 5 mL) and saturated $NaHCO_3$ solution (2 X 5 mL) and the organic layer was concentrated to get a residue which was subjected to purification by silica gel flash column chromatography (EtOAc:Hexane -98:2) yielded the desired product as a viscous oil (140 mg, 0.79 mmol, 32% yield); (TLC- EtOAc:MeOH (9:1) – R_f = 0.63); IR (NaCl, 10 mM in $CHCl_3$): 3024, 3007, 2935, 2879, 1687, 1656, 1431, 1338, 1247, 1142, 912, 839, 777, 658 cm^{-1}; ***trans* isomer:** ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 4.69 (dd, *J* = 8.1 Hz, 3.6 Hz, 1H), 4.19-4.07 (m, 2H), 3.65-3.45 (m, 2H), 3.10 (s, 3H), 3.0 (s, 3H), 2.19-2.04 (m, 2H), 1.94-1.84 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 172.2, 155.1, 61.0, 56.5, 46.4, 36.9, 35.8, 29.4, 24.1, 14.6; ***cis* isomer:** ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 4.61 (dd, *J* = 8.3 Hz, 3.9 Hz, 1H), 4.15-4.04 (m, 2H), 3.67-3.54 (m, 2H), 3.08 (s, 3H), 3.0 (s, 3H), 2.22-2.05 (m, 2H), 1.94-1.84 (m, 2H), 1.18 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 172.4, 154.4, 60.9, 56.1, 46.8, 36.8, 35.8, 30.3, 23.4, 14.5; HRMS *m/z* Calcd for $C_{10}H_{18}N_2O_3Na$ 237.1215, Found 237.1216.

S4.3. Isopropyl (*S*)-2-(dimethylcarbamoyl)pyrrolidine-1-carboxylate (3):

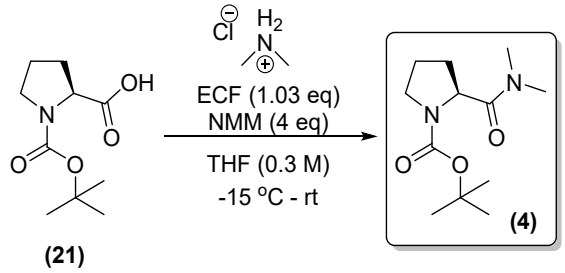


Compound **19** (500mg, 2.32 mmol) was dissolved in methanol (6 mL) added lithium hydroxide (LiOH) (146 mg, 3.5 mmol) dissolved in water (2 mL) at rt. The reaction mixture was stirred at rt for 1.5 h. Methanol was removed using rotary evaporator and the aqueous part was acidified with 1N HCl at 0 °C until pH became 1-2. The product was extracted with EtOAc (2 X 10 mL) and the organic layer was concentrated to get **20** (467 mg, 2.32 mmol, 100%) which was used in the further reaction without further purification.

Compound **3** was synthesized by following the general procedure for the synthesis of amides by treating **20** (330 mg, 1.64 mmol) with ethyl chloroformate (ECF) (162 µL, 1.69 mmol), N-Methyl morpholine (NMM) (721 µL, 6.6 mmol) and **N,N-Dimethylamine**

hydrochloride (161 mg, 1.97 mmol) in THF:DMF (5:1) (6 mL, 0.3M) at -15 °C. The reaction mixture was allowed to stir at -15 °C for 30 min and then allowed to stir at rt for 6 h. Removal of solvent resulted in a residue which was dissolved in ethyl acetate (EtOAc) (10 mL), washed with 10 mL water (2 X 5 mL) and 1N HCl solution (2 X 5 mL) and saturated $NaHCO_3$ solution (2 X 5 mL) and the organic layer was concentrated to get a residue which was subjected to purification by silica gel flash column chromatography (EtOAc:Hexane -9:1) yielded the desired product as a viscous oil (112 mg, 0.49 mmol, 30% yield); (TLC- EtOAc:MeOH (93:7) – R_f = 0.47); IR (NaCl, 10 mM in $CHCl_3$): 3006, 2982, 2941, 2884, 1682, 1656, 1422, 1324, 1257, 1175, 1111, 908, 823, 748, 670 cm^{-1}; ***trans* isomer:** ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 4.94-4.85 (m, 1H), 4.69 (dd, *J* = 8.2 Hz, 3.5 Hz, 1H), 3.64-3.43 (m, 2H), 3.11 (s, 3H), 2.96 (s, 3H), 2.19-2.04 (m, 2H), 1.93-1.82 (m, 2H), 1.25 (d, *J* = 5.4 Hz, 3H), 1.23 (d, *J* = 5.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 172.3, 154.8, 68.3, 56.4, 46.4, 36.9, 35.8, 29.4, 24.1, 22.3, 22.2; ***cis* isomer:** ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 4.92-4.85 (m, 1H), 4.58 (dd, *J* = 8.3 Hz, 4.4 Hz, 1H), 3.66-3.52 (m, 2H), 3.08 (s, 3H), 2.96 (s, 3H), 2.19-2.06 (m, 2H), 1.93-1.84 (m, 2H), 1.20 (d, *J* = 6.2 Hz, 3H), 1.14 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 172.6, 154.1, 68.1, 55.9, 46.8, 36.9, 35.8, 30.3, 23.5, 22.3, 22.0; HRMS *m/z* Calcd for $C_{11}H_{20}N_2O_3Na$ 251.1372, Found 251.1373.

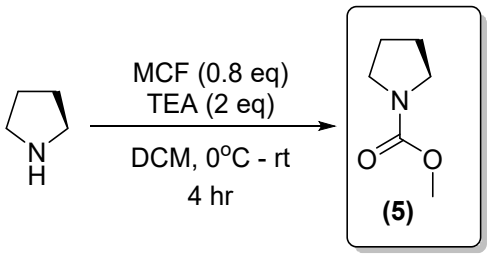
S4.4. *tert*-Butyl (*S*)-2-(dimethylcarbamoyl)pyrrolidine-1-carboxylate (4):



Compound **4** was synthesized by following the general procedure for the synthesis of amides by treating **21** (Boc-Pro-OH) (3000 mg, 13.9 mmol) with ethyl chloroformate (ECF) (1374 µL, 14.4 mmol), N-Methyl morpholine (NMM) (6.1 mL, 55.8 mmol) and **N,N-Dimethylamine hydrochloride** (1365 mg, 16.7 mmol) in THF:DMF (5:1) (28 mL, 0.5M) at -15 °C. The reaction mixture was allowed to stir at -15 °C for 30 min and then allowed to stir at rt for 6 h. Removal of solvent resulted in a residue which was dissolved in ethyl acetate (EtOAc) (10 mL), washed with 20 mL water (2 X 10 mL) and 1N HCl solution (2 X 10 mL) and saturated $NaHCO_3$ solution (2 X 10 mL) and the organic layer was concentrated to get a residue which was subjected to purification by silica gel flash column chromatography (EtOAc:Hexane -8:2)

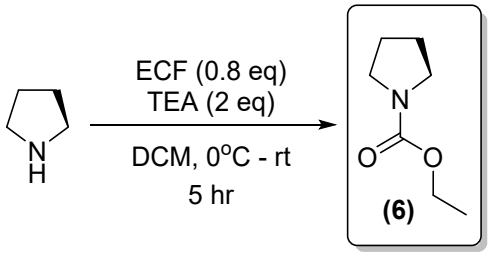
yielded the desired product as a viscous oil (979 mg, 4 mmol, 29% yield); (TLC- EtOAc:MeOH (9:1) – R_f = 0.5); IR (NaCl, 10 mM in $CHCl_3$): 3007, 2981, 2935, 2884, 1683, 1657, 1404, 1368, 1165, 1143, 908, 815, 733 cm^{-1}; ***trans* isomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 4.60 (dd, *J* = 8.4 Hz, 3.3 Hz, 1H), 3.61-3.38 (m, 2H), 3.02 (s, 3H), 2.89 (s, 3H), 2.22-1.99 (m, 2H), 1.89-1.82 (m, 2H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 172.1, 154.3, 79.2, 56.23, 46.4, 36.8, 35.74, 29.3, 28.3, 23.9; ***cis* isomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 4.48 (dd, *J* = 8.2 Hz, 4.3 Hz, 1H), 3.62-3.39 (m, 2H), 3.0 (s, 3H), 2.90 (s, 3H), 2.17-2.01 (m, 2H), 1.91-1.81 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 172.6, 153.7, 79.1, 56.2, 46.6, 36.8, 35.7, 30.2, 28.2, 23.5; HRMS *m/z* Calcd for $C_{12}H_{22}N_2O_3Na$ 265.1528, Found 265.1528.

S4.5. Methyl pyrrolidine-1-carboxylate (5):



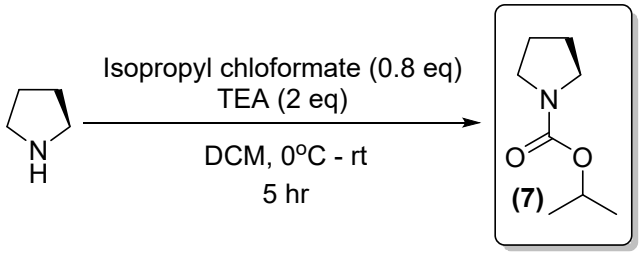
To a cold (0 °C) solution of **pyrrolidine** (500 mg, 7.03 mmol) in 14 mL Dichloromethane (DCM) added Methyl chloroformate (MCF) (435 µL, 5.62 mmol), triethylamine (Et_3N) (1.95 mL, 14.1 mmol) and the mixture was allowed to stir at 0 °C for 10 min, then allowed to stir at rt for 4 h. Removal of solvent resulted in a residue which was dissolved in ethyl acetate (EtOAc) (10 mL), washed with 10 mL water (2 X 5 mL) and 1N HCl solution (2 X 5 mL) and saturated $NaHCO_3$ solution (2 X 5 mL) and the organic layer was concentrated to get a residue which was subjected to purification by silica gel flash column chromatography (EtOAc : Hexane – 1 : 49) yielded the desired product as a colourless oil (377 mg, 3.66 mmol, 52%) (TLC: EtOAc – R_f = 0.68). IR (NaCl, 10 mM in $CHCl_3$): 3018, 2982, 2958, 2881, 1685, 1457, 1396, 1132 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.69 (s, 3H), 3.39 (t, *J* = 6.3 Hz, 2H), 3.32 (t, *J* = 6.3 Hz, 2H), 1.88-1.82 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 155.5, 52.1, 46.0, 45.6, 25.6, 24.8; HRMS *m/z* Calcd for $C_6H_{11}NO_2Na$ 152.0687, Found 152.0690.

S4.6. Ethyl pyrrolidine-1-carboxylate (6):



To a cold (0 °C) solution of **pyrrolidine** (500 mg, 7.03 mmol) in 14 mL Dichloromethane (DCM) added Ethyl chloroformate (ECF) (537 µL, 5.62 mmol), triethylamine (Et_3N) (1.95 mL, 14.1 mmol) and the mixture was allowed to stir at 0 °C for 10 min, then allowed to stir at rt for 5 h. Removal of solvent resulted in a residue which was dissolved in ethyl acetate (EtOAc) (10 mL), washed with 10 mL water (2 X 5 mL) and 1N HCl solution (2 X 5 mL) and saturated $NaHCO_3$ solution (2 X 5 mL) and the organic layer was concentrated to get a residue which was subjected to purification by silica gel flash column chromatography (EtOAc : Hexane – 2 : 48) yielded the desired product as a colourless oil (423 mg, 3.73 mmol, 53%) (TLC: EtOAc – R_f = 0.69). IR (NaCl, 10 mM in $CHCl_3$): 3016, 2982, 2880, 1679, 1436, 1384, 1130, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 4.13 (q, *J* = 7.1 Hz, 2H), 3.38 (t, *J* = 5.9 Hz, 2H), 3.33 (t, *J* = 5.9 Hz, 2H), 1.88-1.82 (m, 4H), 1.26 (t, *J* = 7Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 155.0, 60.5, 45.8, 45.4, 25.5, 24.7, 14.6; HRMS *m/z* Calcd for $C_7H_{13}NO_2Na$ 166.0844, Found 166.0841.

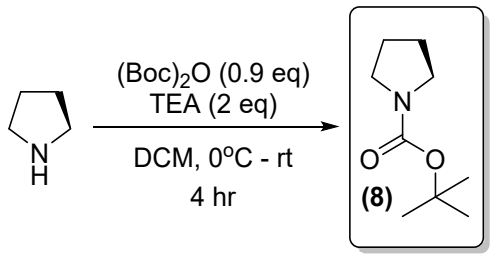
S4.7. Isopropyl pyrrolidine-1-carboxylate (7):



To a cold (0 °C) solution of **pyrrolidine** (500 mg, 7.03 mmol) in 14 mL Dichloromethane (DCM) added Isopropyl chloroformate (7 mL, 5.62 mmol) (1M in toluene), triethylamine (Et_3N) (1.95 mL, 14.1 mmol) and the mixture was allowed to stir at 0 °C for 10 min, then allowed to stir at rt for 5 h. Removal of solvent resulted in a residue which was dissolved in ethyl acetate (EtOAc) (10 mL), washed with 10 mL water (2 X 5 mL) and 1N HCl solution (2 X 5 mL) and saturated $NaHCO_3$ solution (2 X 5 mL) and the organic layer was concentrated to get a residue which was subjected to purification by silica gel flash column chromatography

(EtOAc : Hexane – 2 : 48) yielded the desired product as a colourless oil (564 mg, 3.66 mmol, 52%) (TLC: EtOAc:Hexane (1:1) – R_f = 0.58). IR (NaCl, 10 mM in $CHCl_3$): 3016, 2982, 2879, 1673.7, 1429, 1215, 1111, 908 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 4.96-4.87 (m, 1H), 3.37 (t, *J* = 6.2 Hz, 2H), 3.31 (t, *J* = 6.3 Hz, 2H), 1.87-1.82 (m, 4H), 1.23 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 154.7, 67.6, 45.7, 45.4, 25.5, 24.7, 22.1; HRMS *m/z* Calcd for $C_8H_{15}NO_2Na$ 180.1000, Found 180.1000.

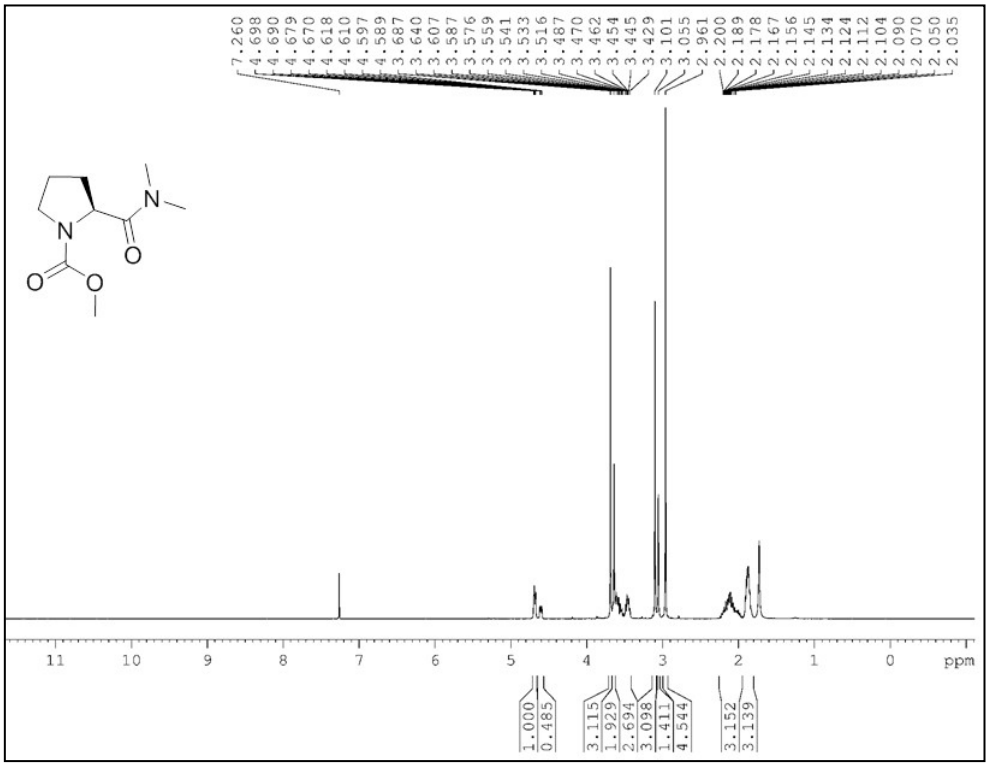
S4.8. *tert*-Butyl pyrrolidine-1-carboxylate (8):



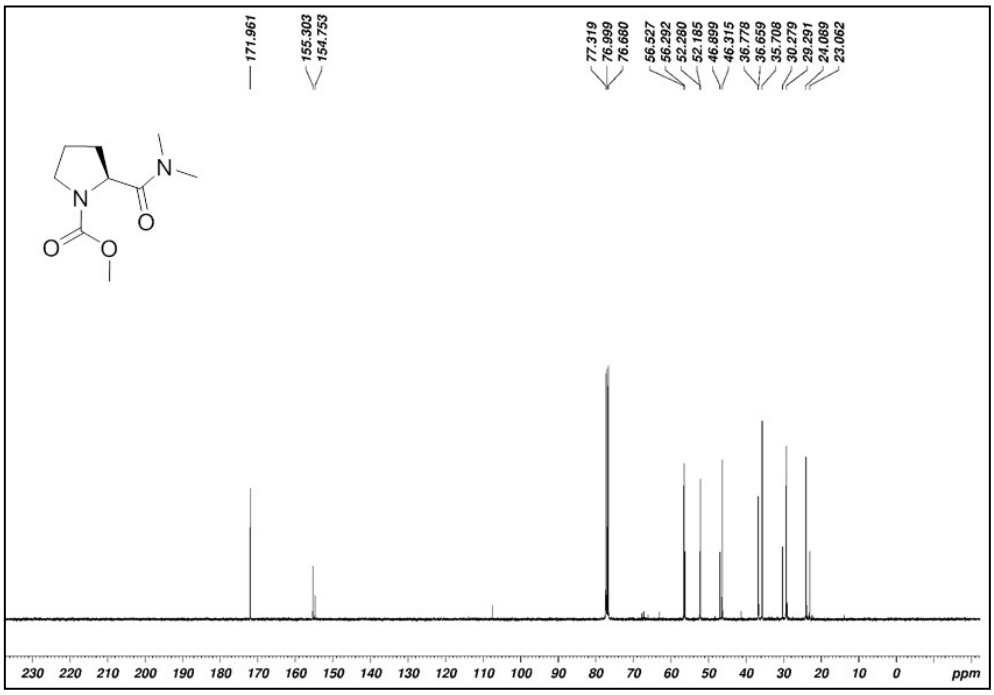
To a cold (0 °C) solution of **pyrrolidine** (500 mg, 7.03 mmol) in 14 mL Dichloromethane (DCM) added Di-tert-butyl dicarbonate ($(Boc)_2O$) (1380 mg, 6.33 mmol), triethylamine (Et_3N) (1.95 mL, 14.1 mmol) and the mixture was allowed to stir at 0 °C for 10 min, then allowed to stir at rt for 4 h. Removal of solvent resulted in a residue which was dissolved in ethyl acetate (EtOAc) (10 mL), washed with 10 mL water (2 X 5 mL) and 1N HCl solution (2 X 5 mL) and saturated $NaHCO_3$ solution (2 X 5 mL) and the organic layer was concentrated to get a residue which was subjected to purification by silica gel flash column chromatography (EtOAc : Hexane – 1 : 49) yielded the desired product as a colourless oil (650 mg, 3.8 mmol, 54%) (TLC: EtOAc:Hexane (1:1) – R_f = 0.68). IR (NaCl, 10 mM in $CHCl_3$): 3006, 2980, 2880, 1683.4, 1417, 1259, 1165, 758, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 3.35-3.31 (m, 2H), 3.29-3.26 (m, 2H), 1.85-1.81 (m, 4H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 154.5, 78.7, 45.8, 45.5, 28.4, 25.6, 24.8; HRMS *m/z* Calcd for $C_9H_{17}NO_2Na$ 194.1157, Found 194.1152.

S5-^{1}H NMR and ^{13}C NMR Spectra:

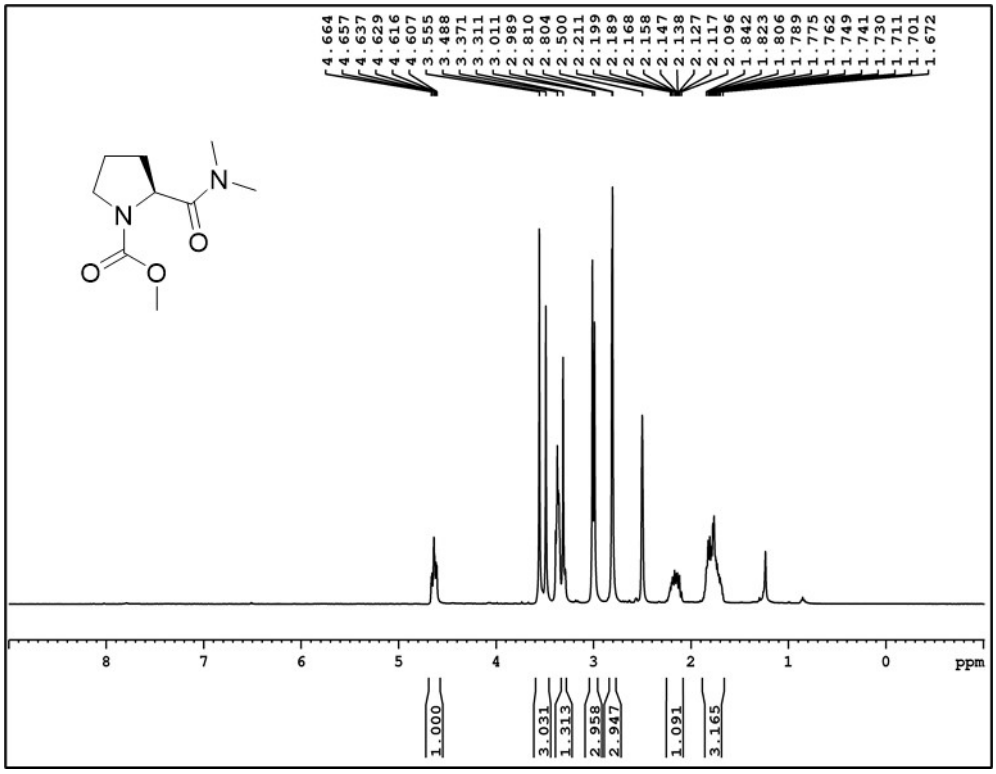
S5.1. Figure S3: ^{1}H NMR of **1** in $CDCl_3$ (400 MHz, 10 mmol).



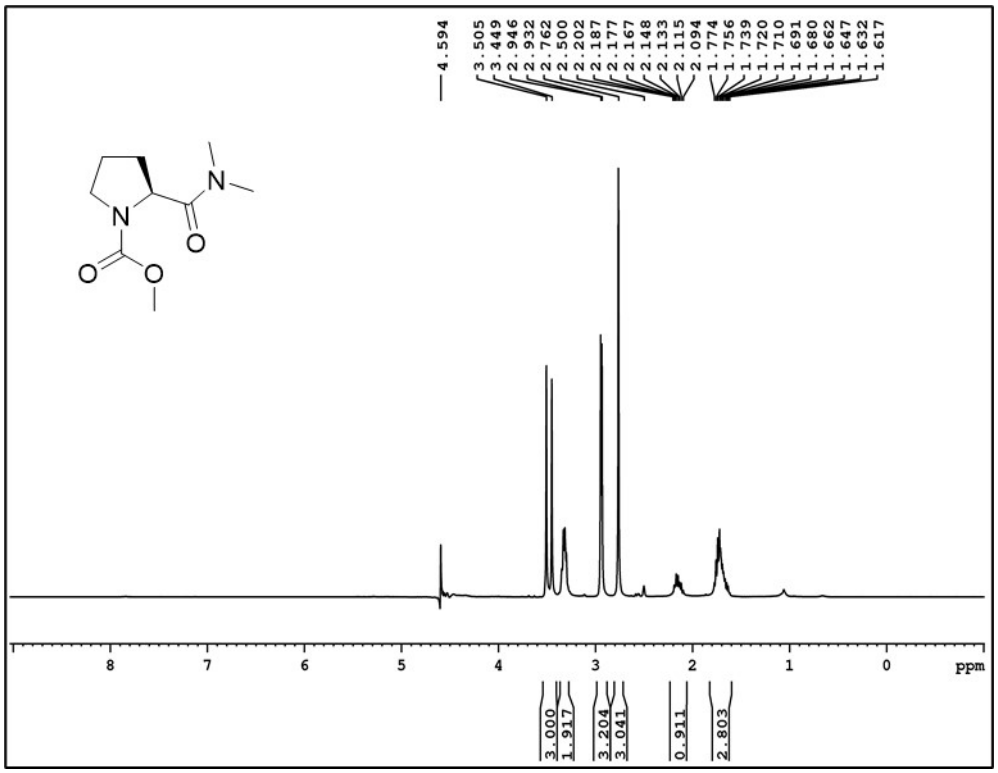
S5.2. Figure S4: ^{13}C NMR of **1** in $CDCl_3$ (100 MHz, 60 mmol).



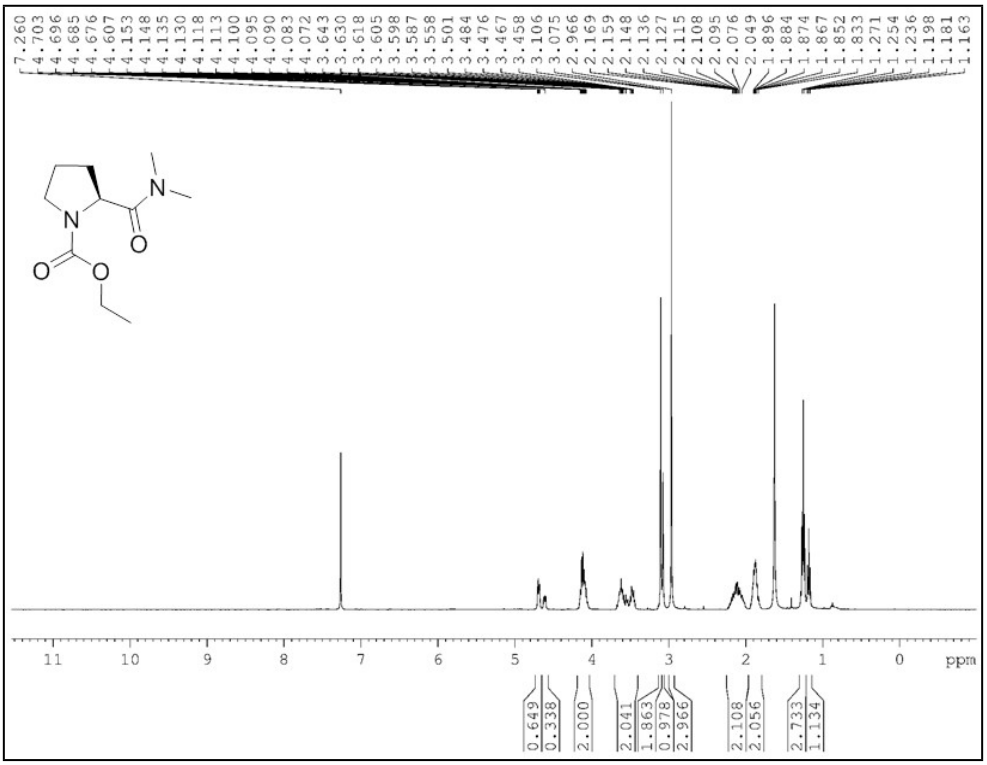
S5.3. Figure S5: ^{1}H NMR of **1** in DMSO-d_6 (400 MHz, 10 mmol).



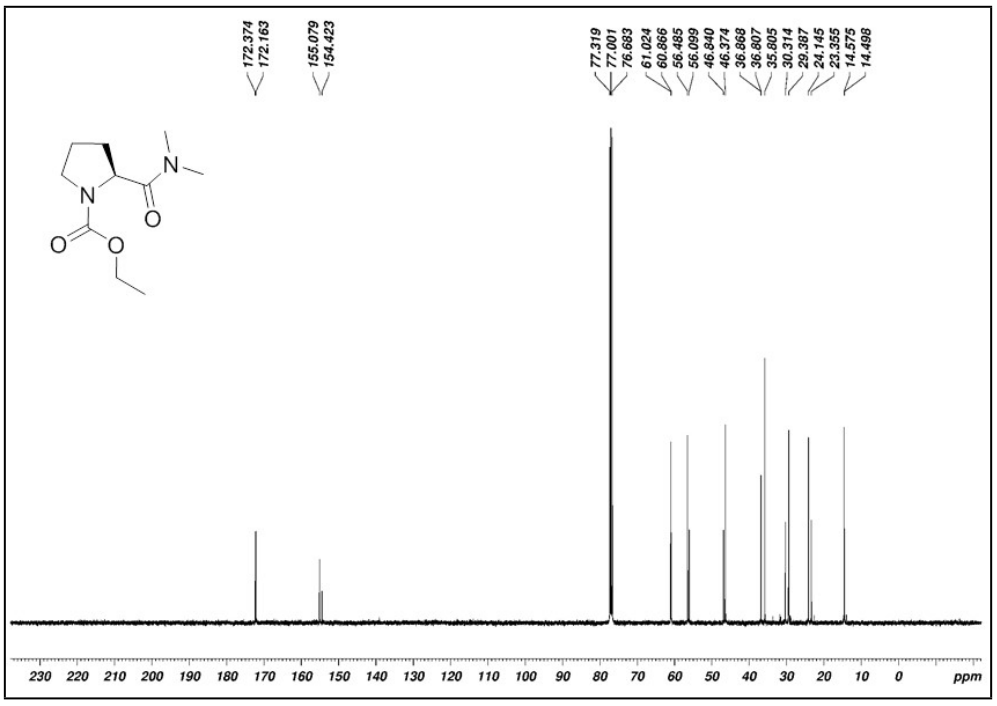
S5.4. Figure S6: ^{1}H NMR of **1** in D_2O (400 MHz, 10 mmol).



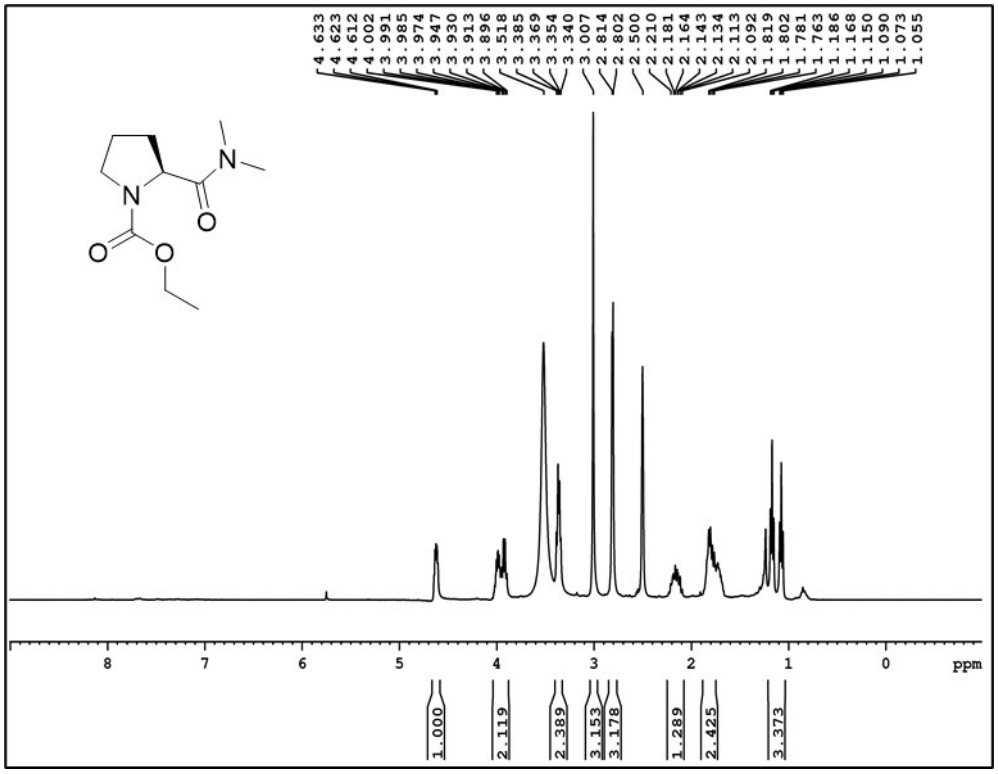
S5.5. Figure S7: ^{1}H NMR of **2** in $CDCl_3$ (400 MHz, 10 mmol).



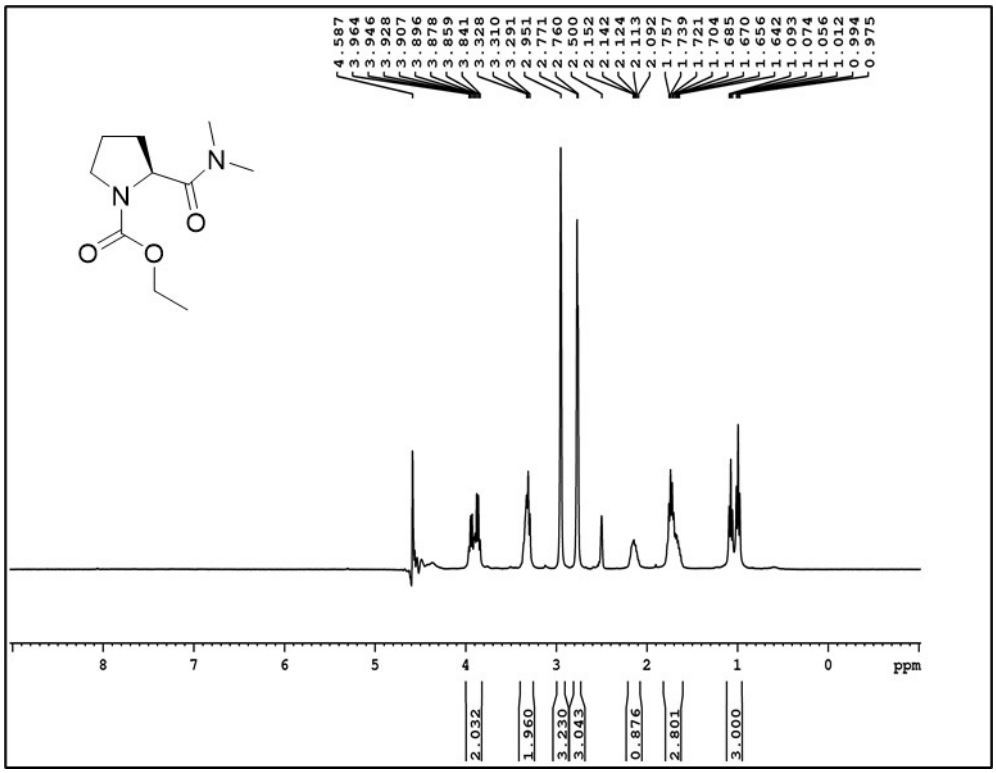
S5.6. Figure S8: ^{13}C NMR of **2** in $CDCl_3$ (100 MHz, 60 mmol).



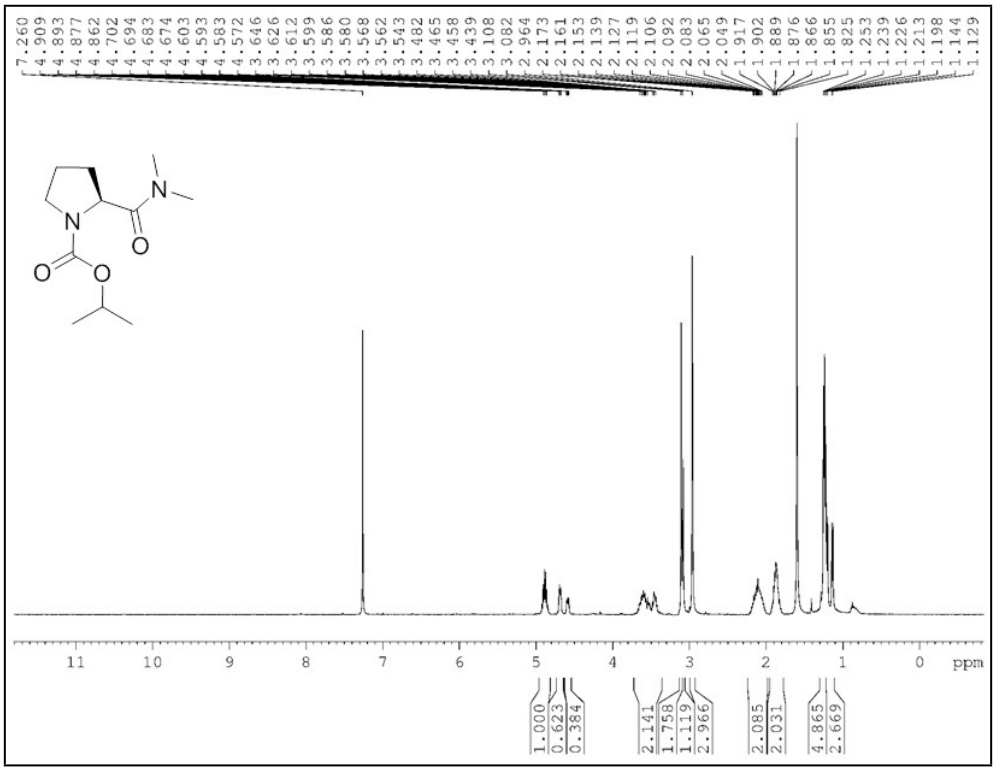
S5.7. Figure S9: ^{1}H NMR of **2** in DMSO-d_6 (400 MHz, 10 mmol).



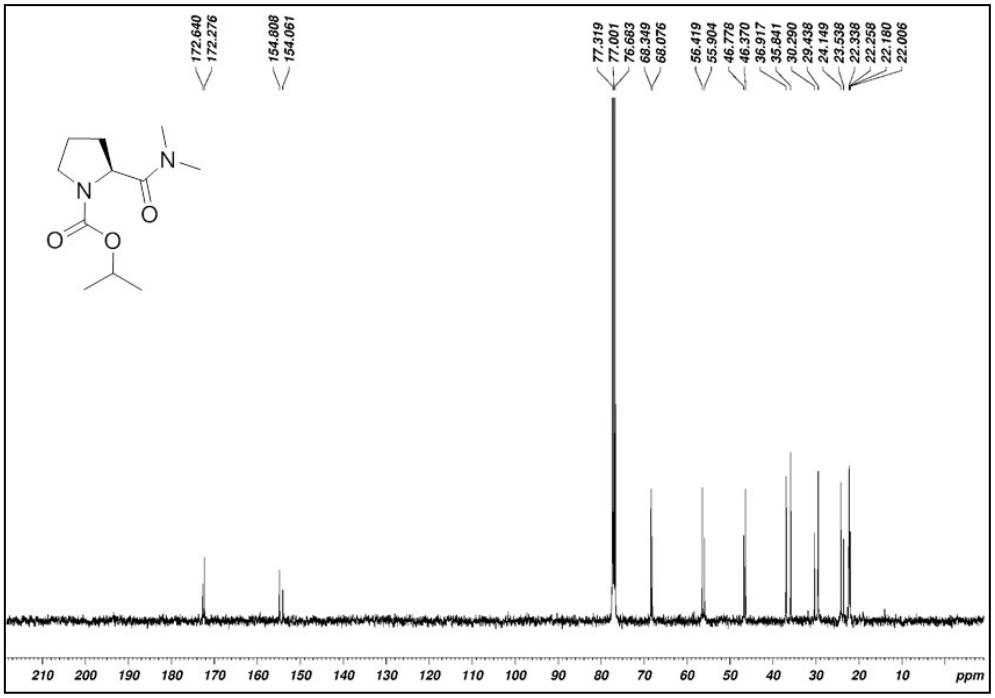
S5.8. Figure S10: ^{1}H NMR of **2** in D_2O (400 MHz, 10 mmol).



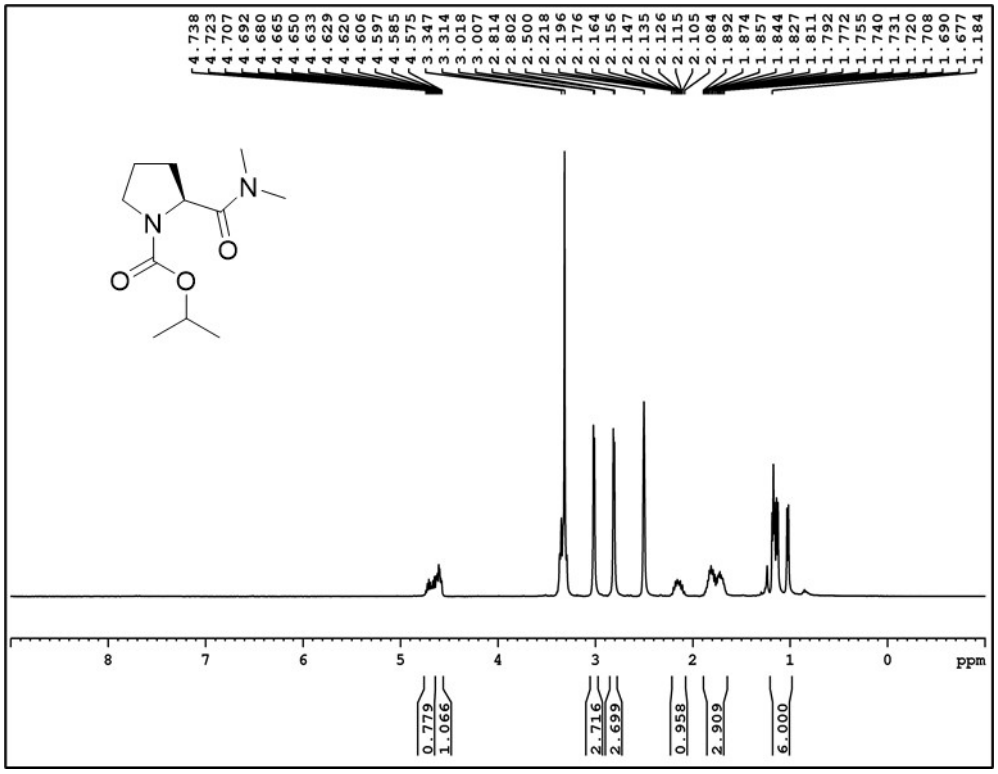
S5.9. Figure S11: ^{1}H NMR of **3** in $CDCl_3$ (400 MHz, 10 mmol).



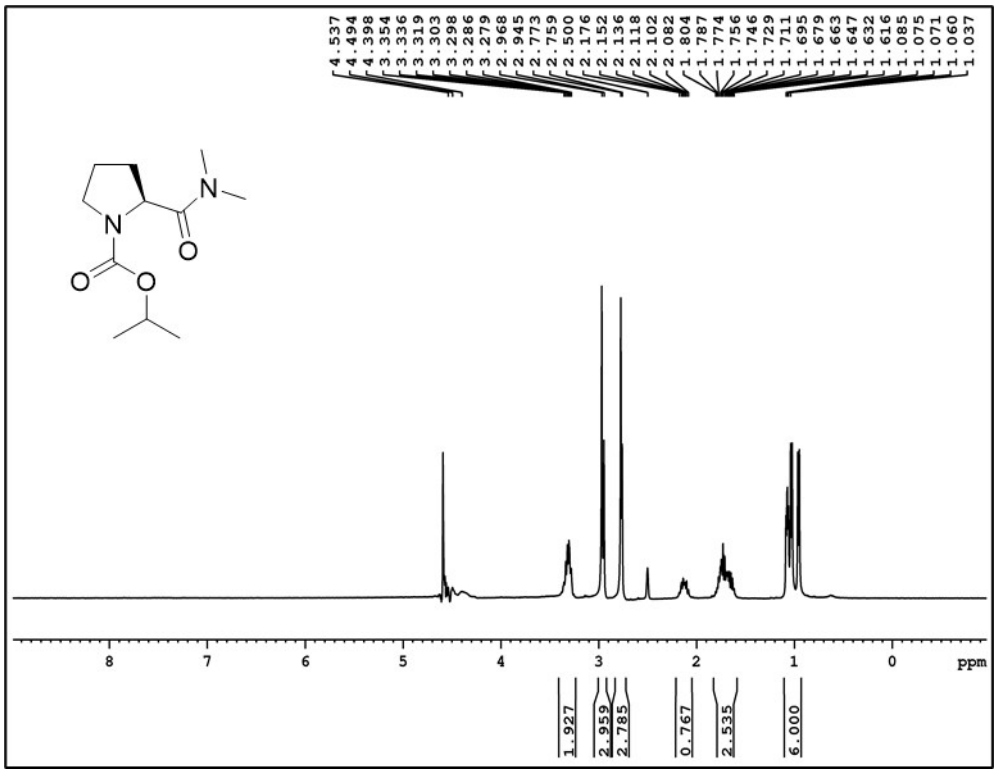
S5.10. Figure S12: ^{13}C NMR of **3** in $CDCl_3$ (100 MHz, 60 mmol).



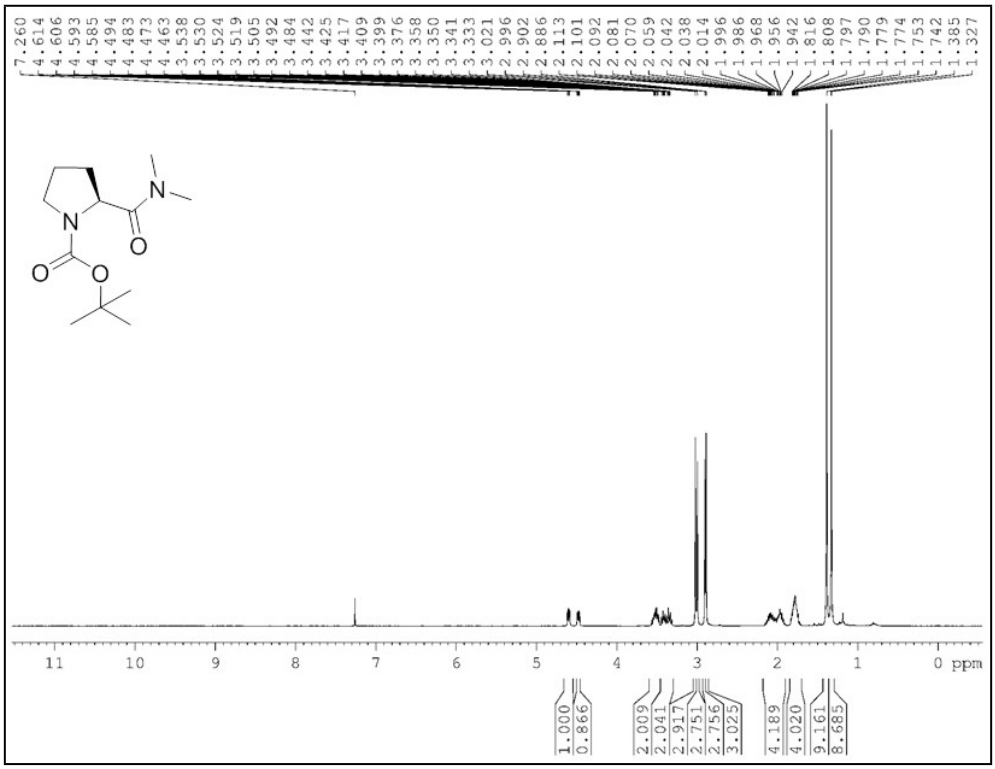
S5.11. Figure S13: ^{1}H NMR of **3** in DMSO-d_6 (400 MHz, 10 mmol).



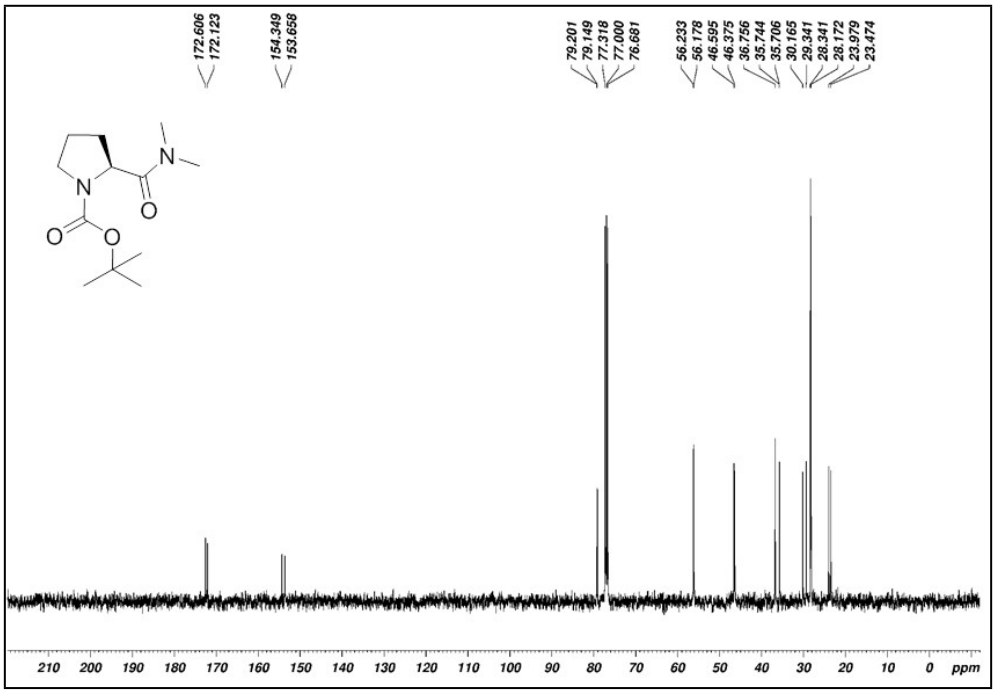
S5.12. Figure S14: ^{1}H NMR of **3** in D_2O (400 MHz, 10 mmol).



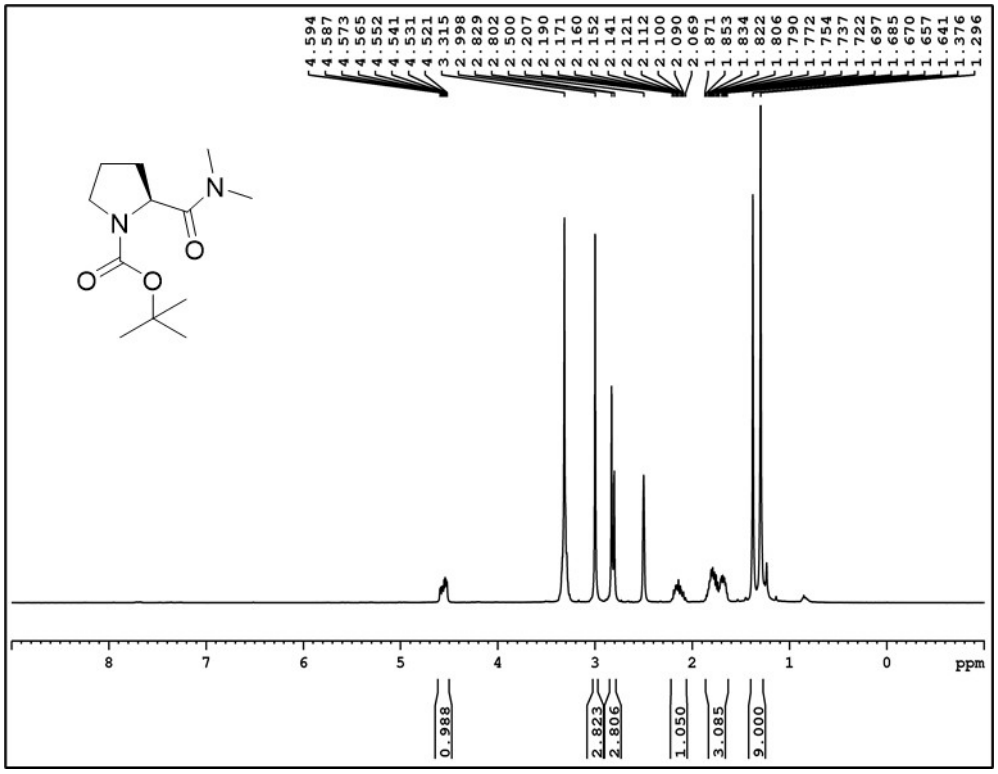
S5.13. Figure S15: ^{1}H NMR of **4** in $CDCl_3$ (400 MHz, 10 mmol).



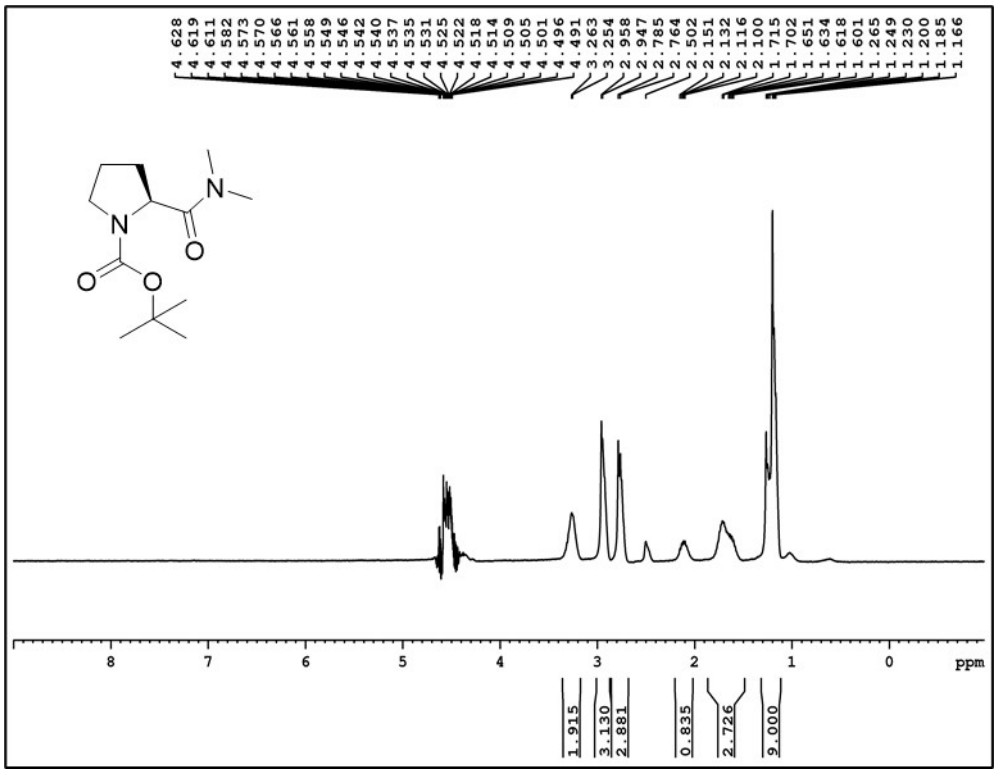
S5.14. Figure S16: ^{13}C NMR of **4** in $CDCl_3$ (100 MHz, 60 mmol).



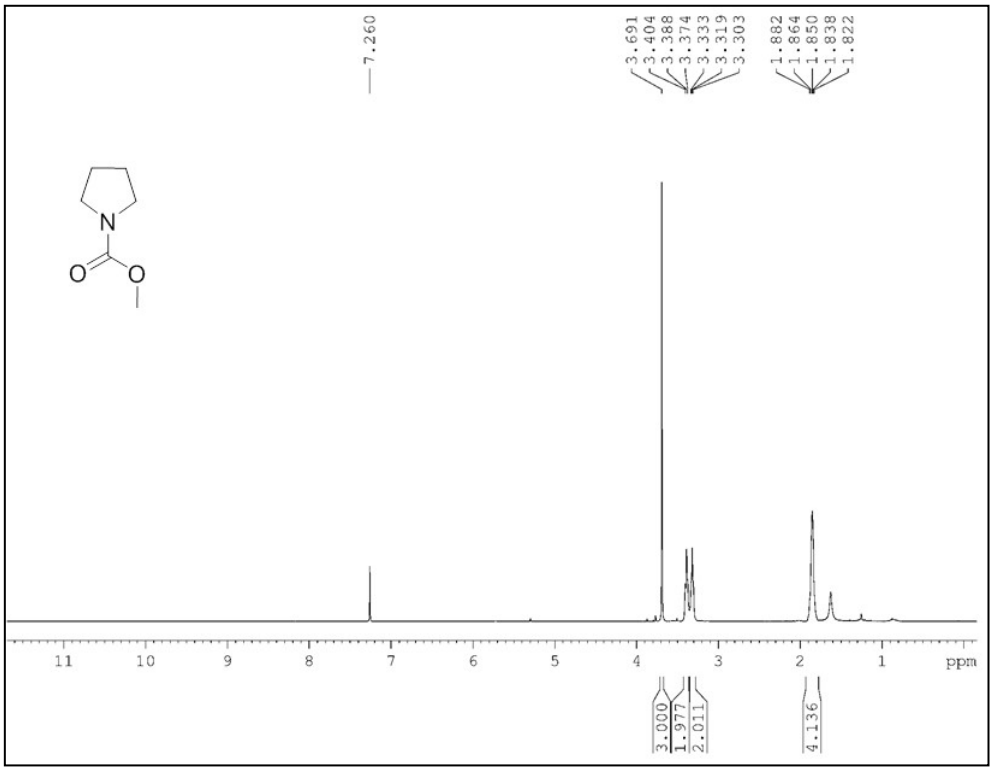
S5.15. Figure S17: ^{1}H NMR of **4** in DMSO-d_6 (400 MHz, 10 mmol).



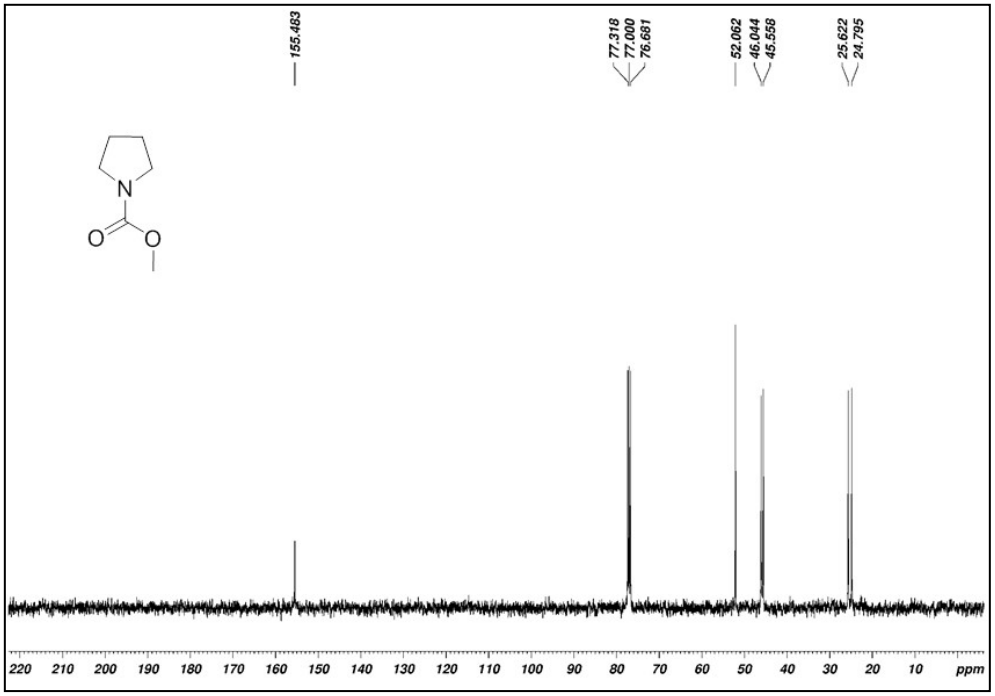
S5.16. Figure S18: ^{1}H NMR of **4** in D_2O (400 MHz, 10 mmol).



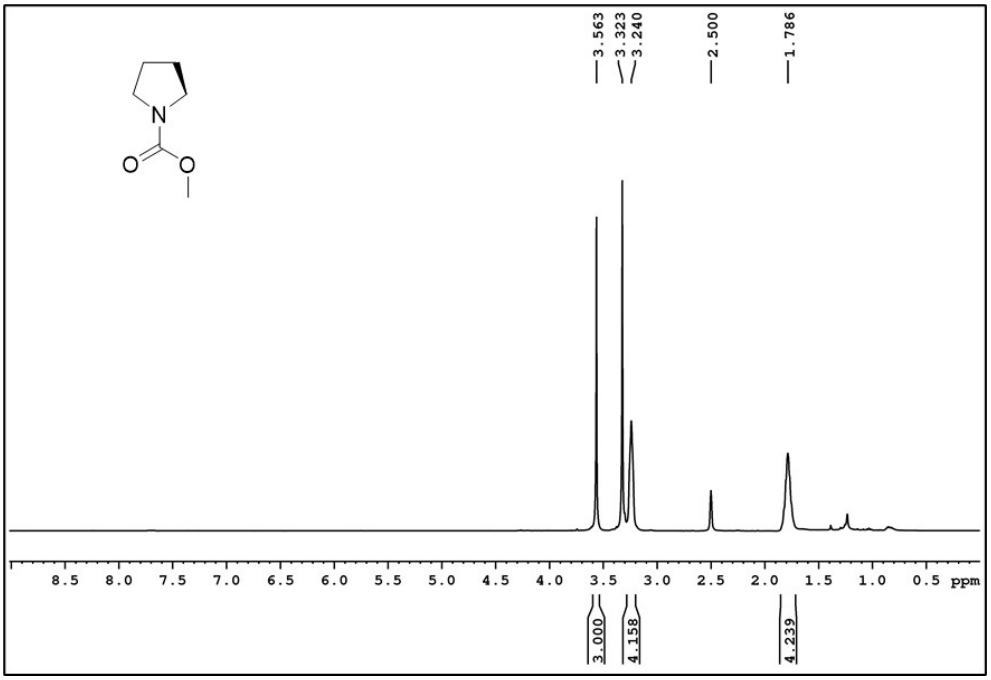
S5.17. Figure S19: ^{1}H NMR of **5** in $CDCl_3$ (400 MHz, 10 mmol).



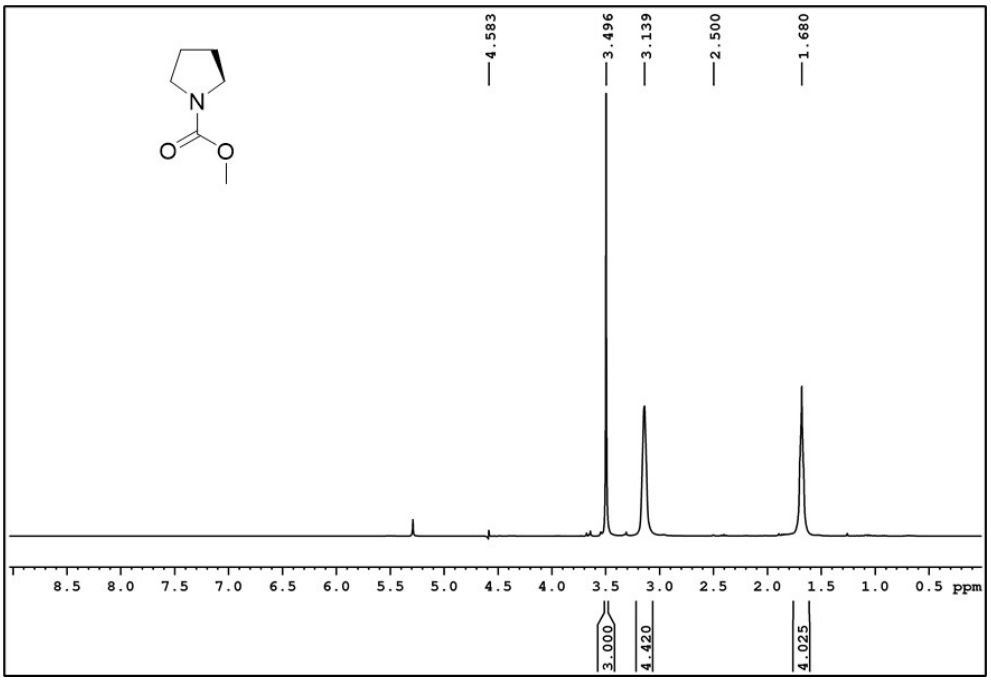
S5.18. Figure S20: ^{13}C NMR of **5** in $CDCl_3$ (100 MHz, 60 mmol).



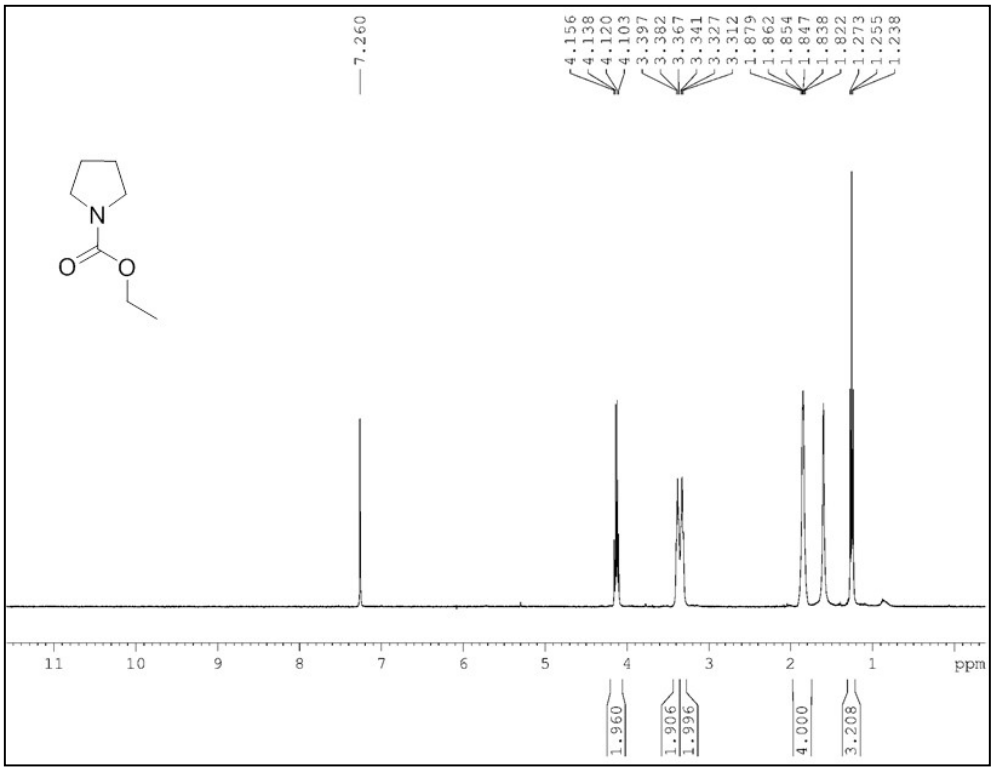
S5.19. Figure S21: ^{1}H NMR of **5** in DMSO-d_6 (400 MHz, 10 mmol).



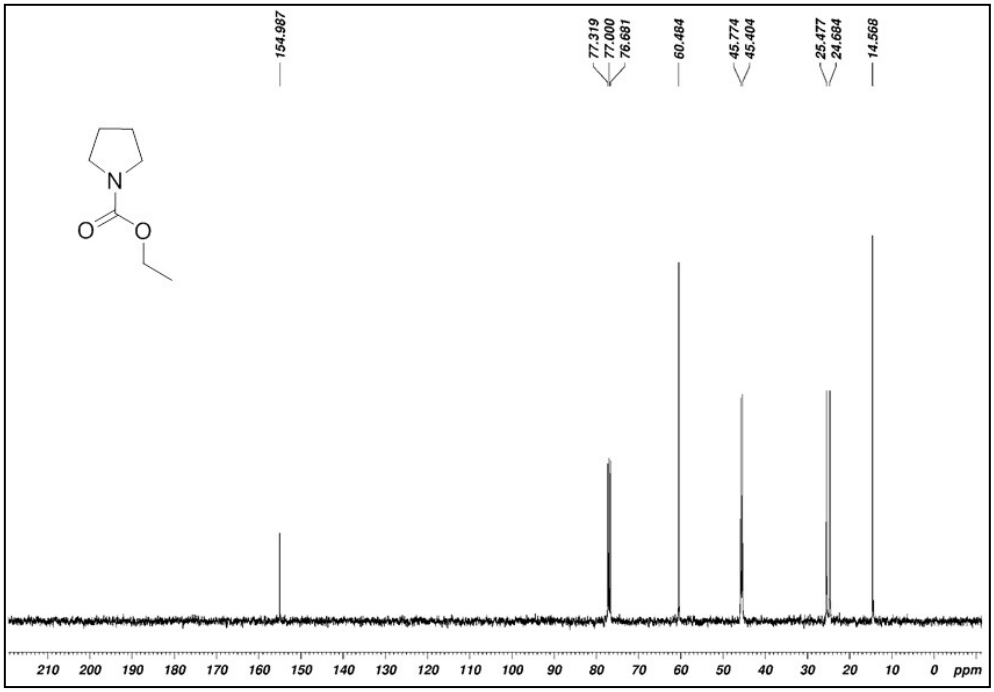
S5.20. Figure S22: ^{1}H NMR of **5** in D_2O (400 MHz, 10 mmol).



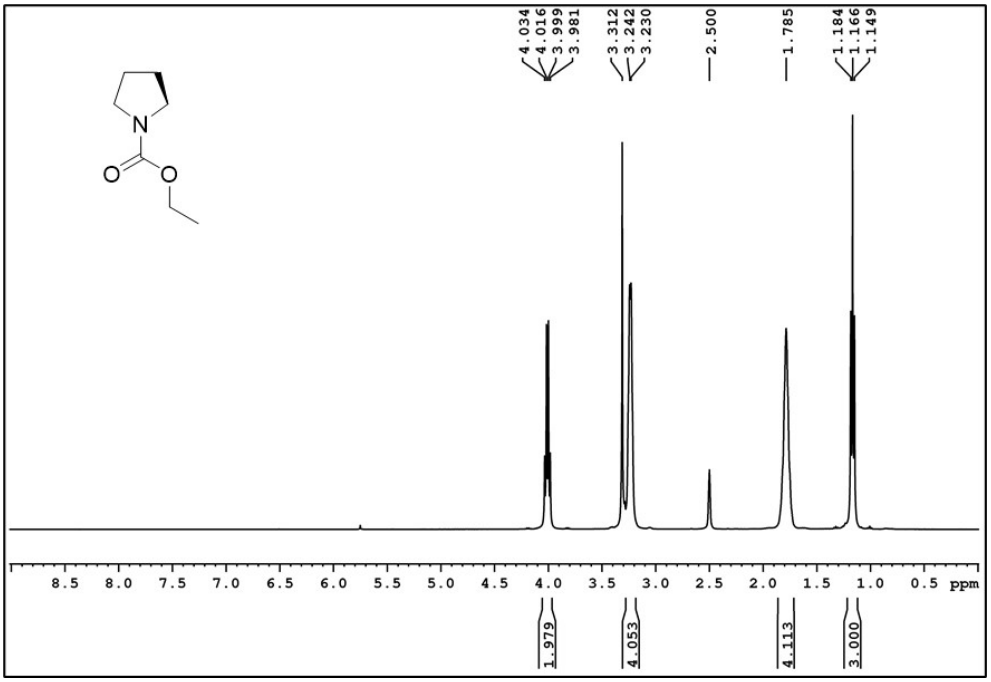
S5.21. Figure S23: ^{1}H NMR of **6** in $CDCl_3$ (400 MHz, 10 mmol).



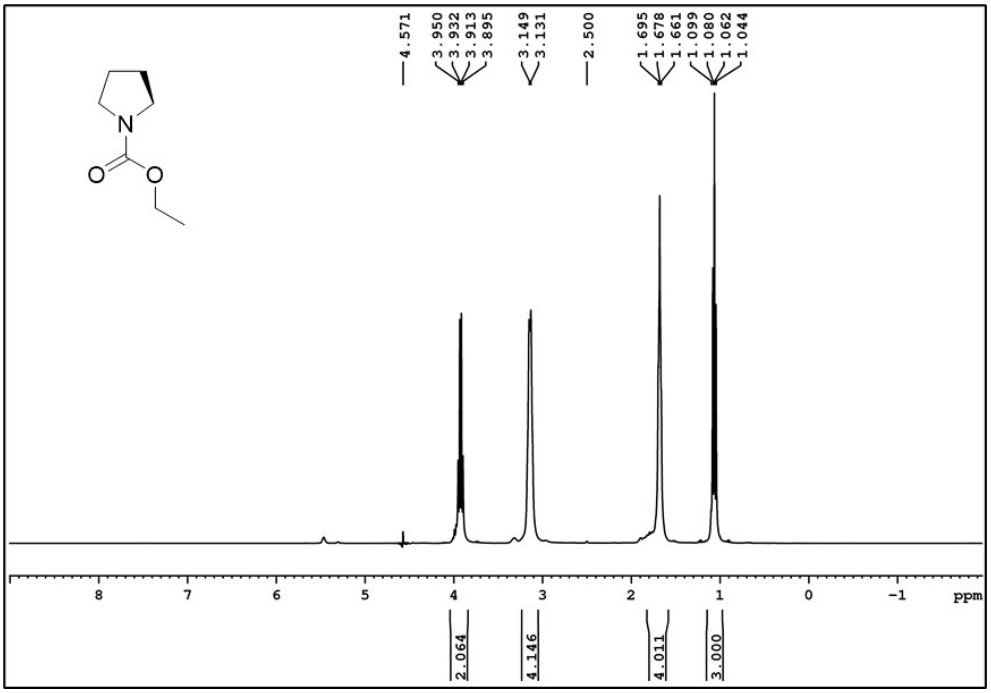
S5.22. Figure S24: ^{13}C NMR of **6** in $CDCl_3$ (100 MHz, 60 mmol).



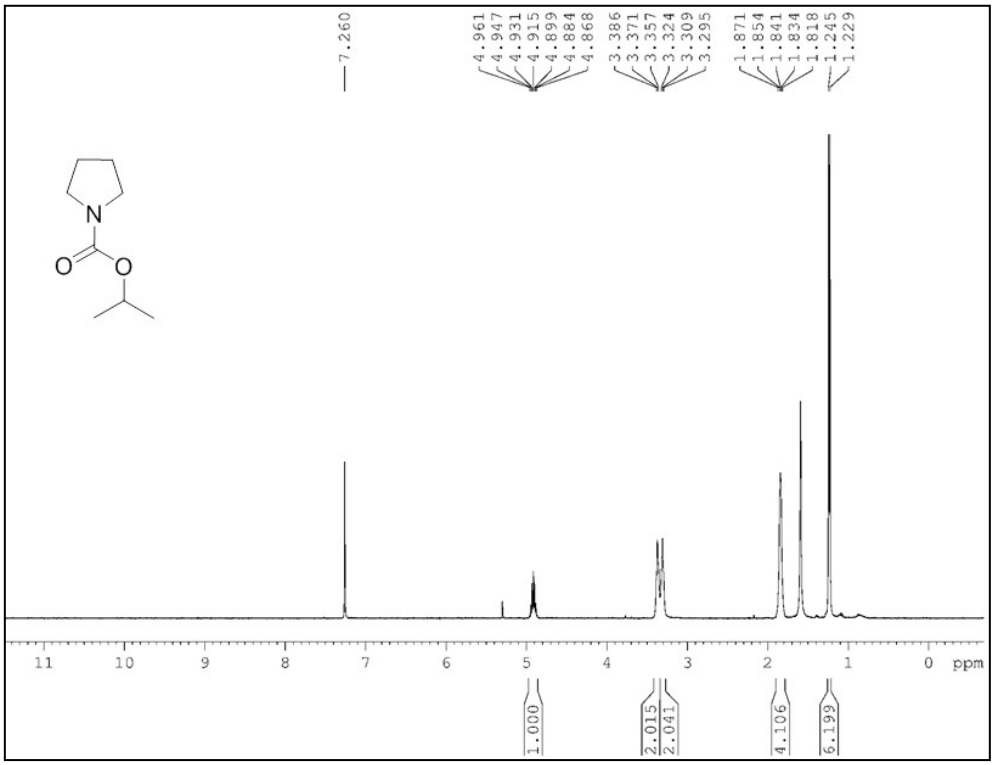
S5.23. Figure S25: ^{1}H NMR of **6** in DMSO-d_6 (400 MHz, 10 mmol).



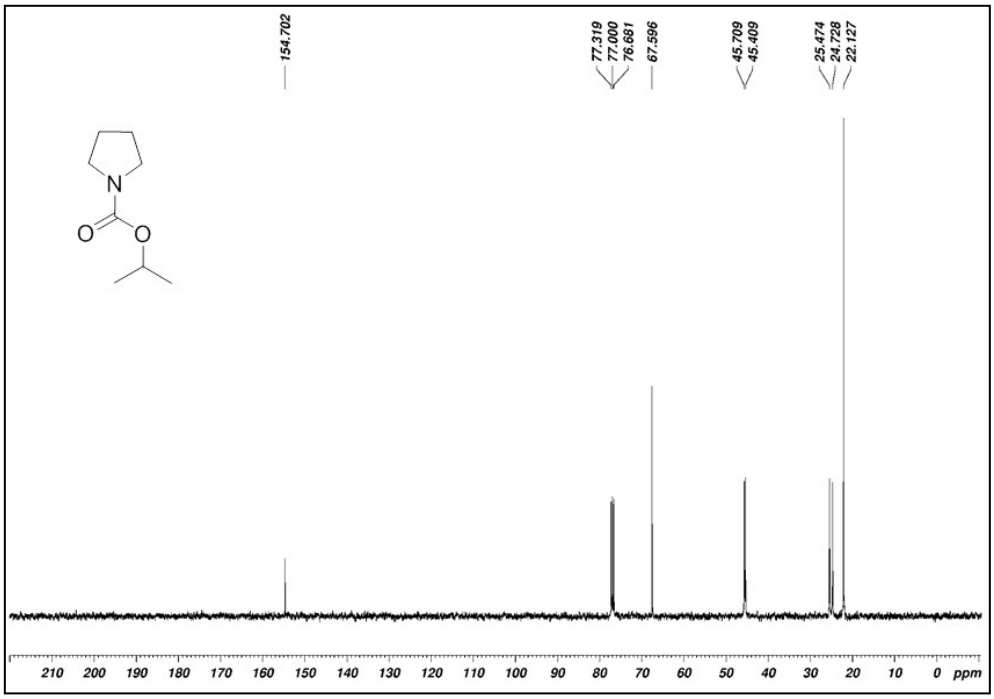
S5.24. Figure S26: ^{1}H NMR of **6** in D_2O (400 MHz, 10 mmol).



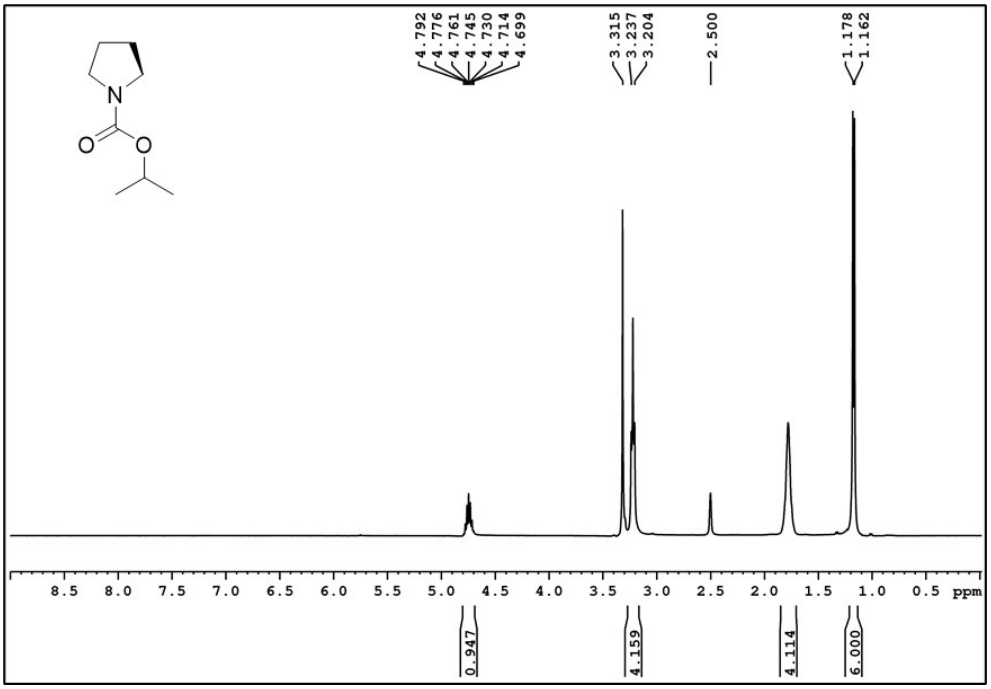
S5.25. Figure S27: ^{1}H NMR of **7** in $CDCl_3$ (400 MHz, 10 mmol).



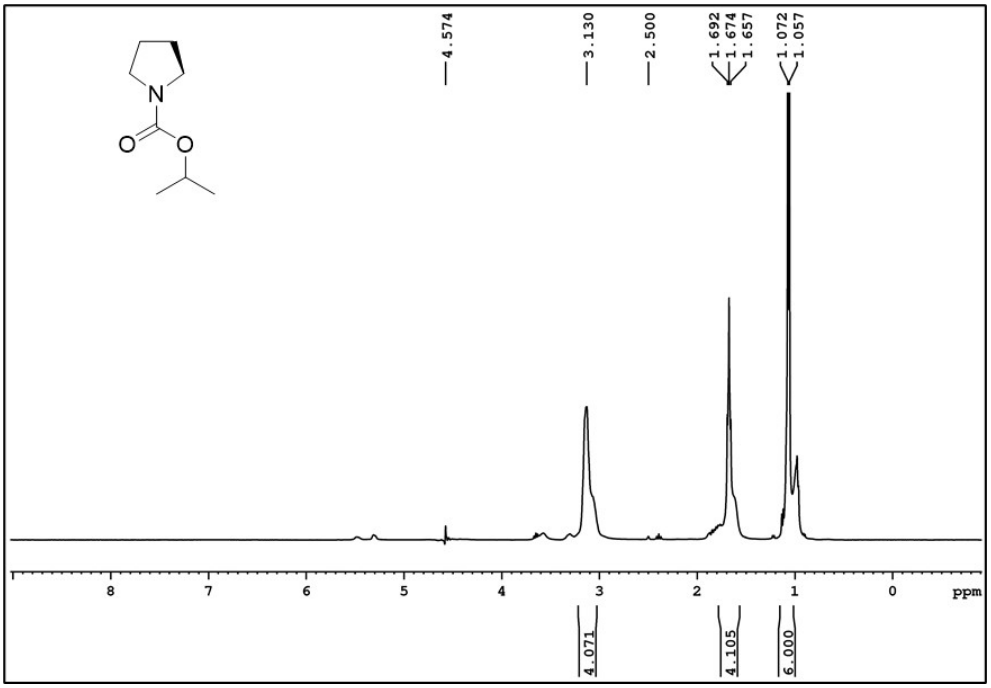
S5.26. Figure S28: ^{13}C NMR of **7** in $CDCl_3$ (100 MHz, 60 mmol).



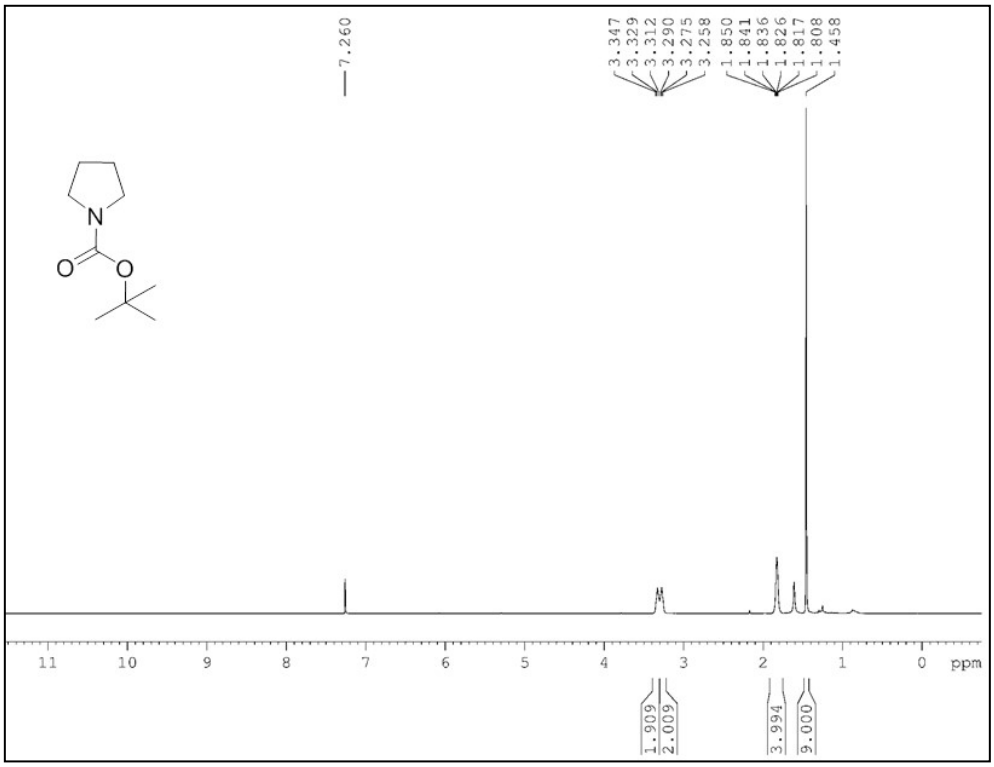
S5.27. Figure S29: ^{1}H NMR of **7** in DMSO-d_6 (400 MHz, 10 mmol).



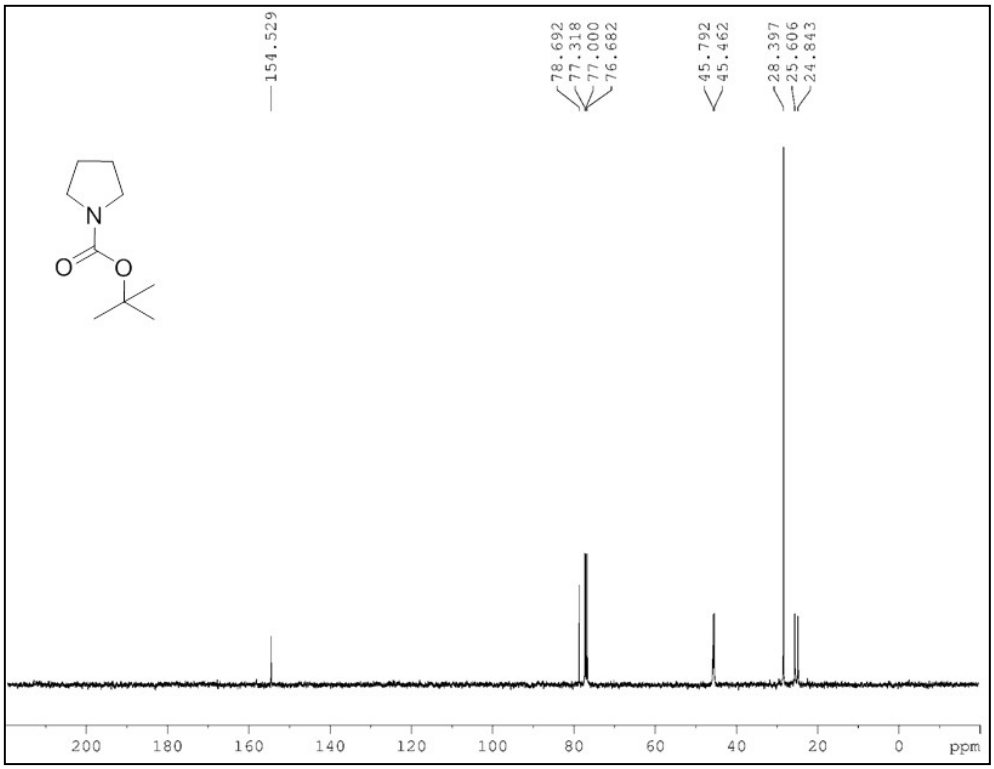
S5.28. Figure S30: ^{1}H NMR of **7** in D_2O (400 MHz, 10 mmol).



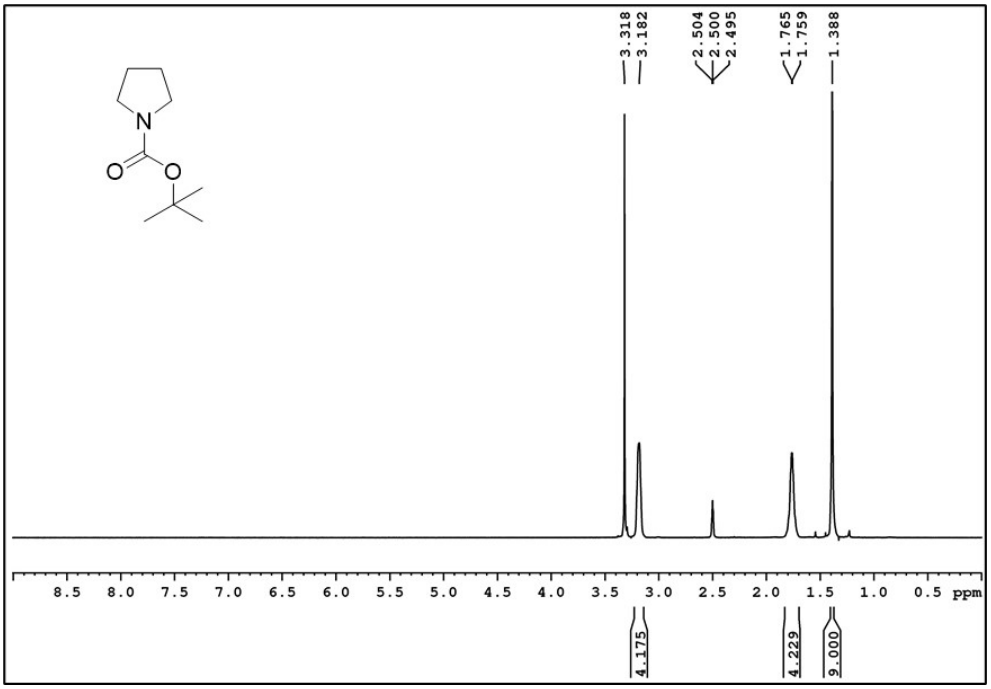
S5.29. Figure S31: ^{1}H NMR of **8** in $CDCl_3$ (400 MHz, 10 mmol).



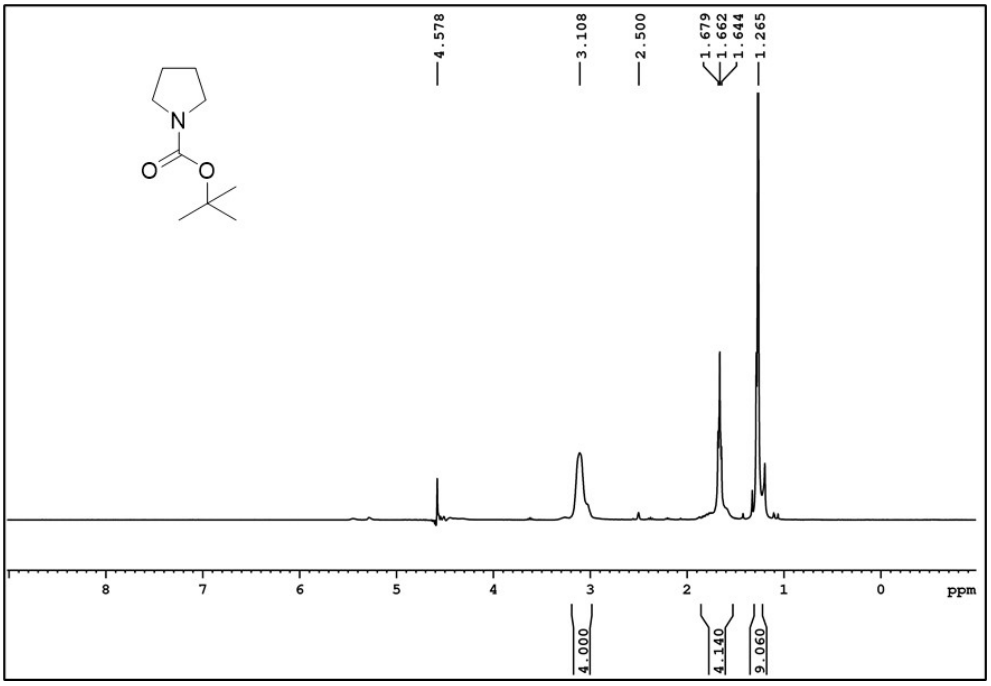
S5.30. Figure S32: ^{13}C NMR of **8** in $CDCl_3$ (100 MHz, 60 mmol).



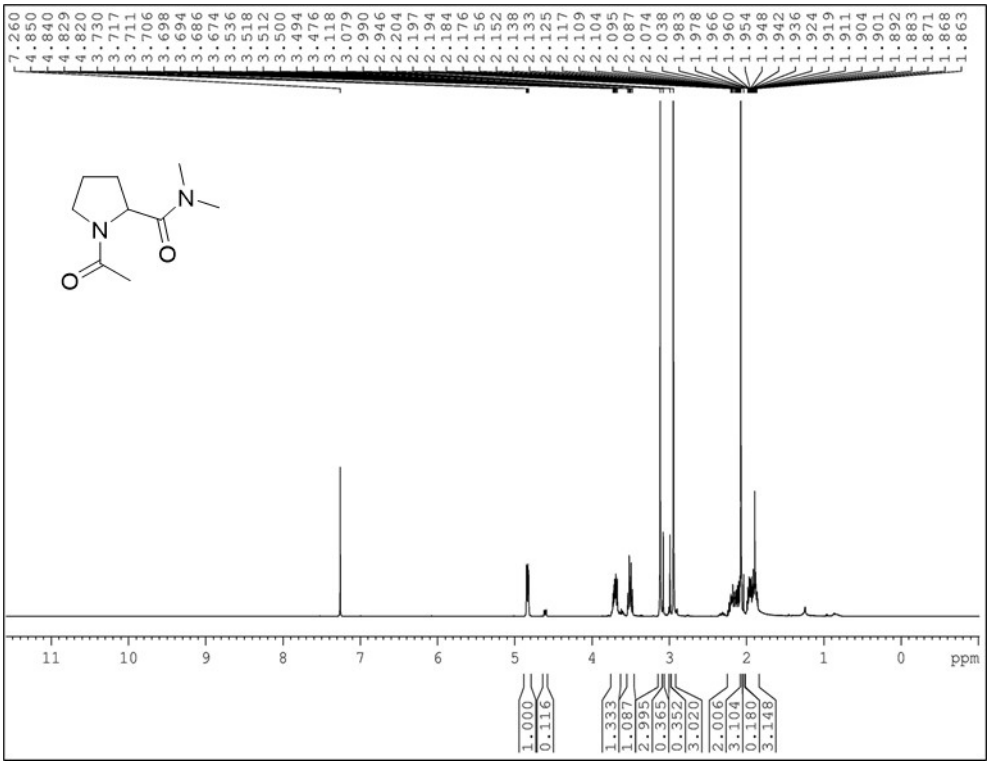
S5.31. Figure S33: ^{1}H NMR of **8** in DMSO-d_6 (400 MHz, 10 mmol).



S5.32. Figure S34: ^{1}H NMR of **8** in D_2O (400 MHz, 10 mmol).



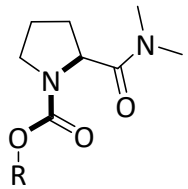
S5.33. Figure S35: ^{1}H NMR of **9** in $CDCl_3$ (400 MHz, 10 mmol).



S6-Spectral parameters at the R-O-C=O (carbamate region) and CO-N$(CH_3)_2$ (amide region) registers of Prolyl carbamates, 1-4 (both t*rans* & *cis* isomers) and pyrrolidine carbamates, 5-8:

S6.1. Comparison of relevant ^{1}H, ^{13}C NMR ($CDCl_3$) and FT-IR spectral data at the R-O-C=O register (carbamate region) of homologous *trans*Prolyl Carbamates (1-4).

*trans*Prolyl carbamate

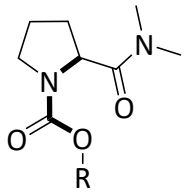


	R	^{13}C NMR C=O δ ppm	^{13}C NMR C^{α}-O δ ppm	^{13}C NMR C^{β}-C-O δ ppm	^{1}H NMR OC^{α}-H^{α} δ ppm	^{1}H NMR OCC^{β}-H^{β} δ ppm	FT-IR* C=O $\bar{\upsilon}$ cm^{-1}
1	Me	155.3	52.2	NA	3.69	NA	1693
2	Et	155.1	56.5	14.6	4.13	1.25	1687
3	^{i}Pr	154.8	68.3	22.1	4.89	1.24	1682
4	^{t}Bu	154.3	79.2	28.3	NA	1.38	1683

*weighted average FT-IR stretching frequencies for trans & cis isomer, NA=Not Applicable

S6.2. Comparison of relevant ^{1}H, ^{13}C NMR ($CDCl_3$) and FT-IR spectral data at the R-O-C=O register (carbamate region) of homologous *cis*Prolyl Carbamates (1-4).

*cis*Prolyl carbamate

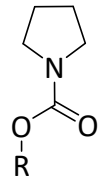


	R	^{13}C NMR C=O δ ppm	^{13}C NMR C^{α}-O δ ppm	^{13}C NMR C^{β}-C-O δ ppm	^{1}H NMR OC^{α}-H^{α} δ ppm	^{1}H NMR OCC^{β}-H^{β} δ ppm	FT-IR* C=O $\bar{\upsilon}$ cm^{-1}
1	Me	154.8	52.3	NA	3.64	NA	1693
2	Et	154.4	56.1	14.5	4.08	1.18	1687
3	^{i}Pr	154.1	68.1	22.2	4.89	1.17	1682
4	^{t}Bu	153.7	79.1	28.2	NA	1.33	1683

*weighted average FT-IR stretching frequencies for trans & cis isomer, NA=Not Applicable

S6.3. Comparison of relevant ^{1}H, ^{13}C NMR ($CDCl_3$) and FT-IR spectral data at the R-O-C=O register (carbamate region) of homologous Pyrrolidine carbamates (5-8).

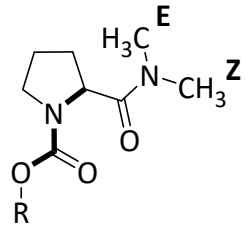
Pyrrolidine carbamate



	R	^{13}C NMR C=O δ ppm	^{13}C NMR C^{α}-O δ ppm	^{13}C NMR C^{β}-C-O δ ppm	^{1}H NMR OC^{α}-H^{α} δ ppm	^{1}H NMR OCC^{β}-H^{β} δ ppm	FT-IR C=O $\bar{\upsilon}$ cm^{-1}
5	Me	155.5	52.1	NA	3.69	NA	1685
6	Et	155.0	60.5	14.6	4.13	1.26	1679
7	^{i}Pr	154.7	67.6	22.1	4.92	1.23	1674
8	^{t}Bu	154.5	78.7	28.4	NA	1.46	1683

S6.4. Comparison of relevant ^{1}H, ^{13}C NMR ($CDCl_3$) and FT-IR spectral data at the CO-N(CH_3)$_2$ register (amide region) of homologous *trans*Prolyl Carbamates (1-4).

*trans*Prolyl carbamate

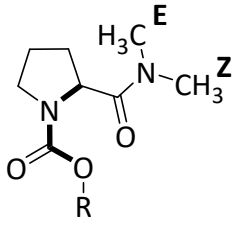


	R	^{13}C NMR C=O δ ppm	^{13}C NMR N-CH_3 δ ppm Z	E	^{1}H NMR N-CH_3 δ ppm Z	E	FT-IR C=O $\bar{\upsilon}$ cm^{-1}	FT-IR C-N $\bar{\upsilon}$ cm^{-1}
1	Me	171.9	36.8	35.7	3.10	2.96	1652	1456
2	Et	172.2	36.9	35.8	3.08	3.0	1656	1431
3	^{i}Pr	173.3	36.9	35.8	3.11	2.96	1656	1422
4	^{t}Bu	172.1	36.8	35.7	3.02	2.89	1657	1404

*weighted average FT-IR stretching frequencies between *trans* & *cis* Prolyl carbamate

S6.5. Comparison of relevant ^{1}H, ^{13}C NMR ($CDCl_3$) and FT-IR spectral data at the CO-N(CH_3)$_2$ register (amide region) of homologous *cis*Prolyl Carbamates (1-4).

*cis*Prolyl carbamate

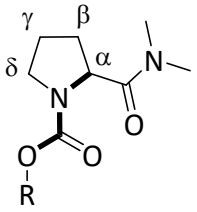


	R	^{13}C NMR C=O δ ppm	^{13}C NMR N-CH_3 δ ppm Z	E	^{1}H NMR N-CH_3 δ ppm Z	E	FT-IR* C=O $\bar{\upsilon}$ cm^{-1}	FT-IR* C-N $\bar{\upsilon}$ cm^{-1}
1	Me	171.9	36.7	35.7	3.08	2.96	1652	1456
2	Et	172.4	36.8	35.8	3.06	3.0	1656	1431
3	^{i}Pr	173.6	36.8	35.8	3.07	2.96	1656	1422
4	^{t}Bu	172.6	36.7	35.7	3.0	2.90	1657	1404

*weighted average FT-IR stretching frequencies between *trans* & *cis* Prolyl carbamate

S6.6. Comparison of relevant ^{1}H, ^{13}C NMR ($CDCl_3$) spectral data at the proline ring of homologous *trans*Prolyl Carbamates (1-4).

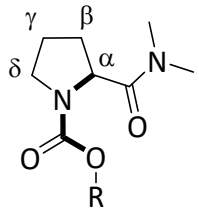
*trans*Prolyl carbamate



		^{13}C NMR δ ppm				^{1}H NMR δ ppm			
	R	C^{α}	C^{β}	C^{γ}	C^{δ}	H^{α}	H^{β}	H^{γ}	H^{δ}
1	Me	56.5	29.3	24.1	46.3	4.68	2.11	1.87	3.53
2	Et	56.5	29.4	24.1	46.4	4.69	2.11	1.89	3.55
3	^{i}Pr	56.4	29.4	24.1	46.4	4.69	2.11	1.87	3.53
4	^{t}Bu	29.3	29.3	23.9	46.4	4.60	2.11	1.85	3.49

S6.7. Comparison of relevant ^{1}H, ^{13}C NMR ($CDCl_3$) spectral data at the proline ring of homologous *cis*Prolyl Carbamates (1-4).

*cis*Prolyl carbamate



		^{13}C NMR δ ppm				^{1}H NMR δ ppm			
	R	C^{α}	C^{β}	C^{γ}	C^{δ}	H^{α}	H^{β}	H^{γ}	H^{δ}
1	Me	56.3	30.3	23.1	46.9	4.60	2.12	1.87	3.59
2	Et	56.1	30.3	23.4	46.8	4.61	2.13	1.89	3.60
3	^{i}Pr	55.9	30.3	23.5	46.8	4.58	2.12	1.88	2.59
4	^{t}Bu	56.2	30.2	23.5	46.6	4.48	2.09	1.85	3.50

S6.8. Plot of FT-IR stretching frequencies of carbamate and amide carbonyl C=O bond in prolyl carbamates (1-4).

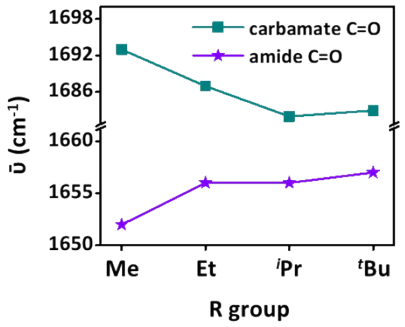
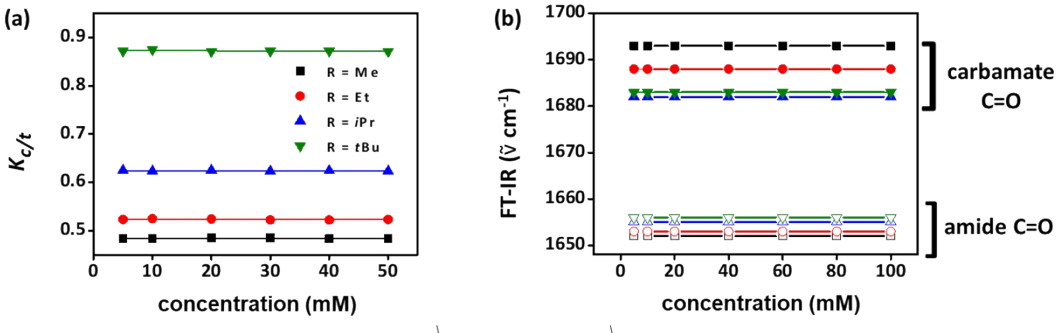


Figure S36: Plots of FT-IR stretching frequencies of carbamate C=O and amide C=O bond in prolyl carbamates (**1-4**) versus the R group of carbamates. These complex conformational and rotational equilibria cannot be deconvoluted using FT-IR spectra (10 mM, $CHCl_3$), so it is a weighted-average of FT-IR stretching frequencies between *cis*Pro and *trans*Pro rotamers of carbamates. This shows a net increase in carbamate C=O stretching frequency and a net decrease in amide C=O stretching frequency.

S7-Concentration dependent studies:



			Slope	
	R	$K_{c/t}$ (*10^{-5})	FT-IR (cm^{-1}, *10^{-15}) carbamate C=O	FT-IR (cm^{-1}, *10^{-15}) amide C=O
1	Me	-4.3 ± 3.6	6.0 ± 4.9	9.1 ± 7.3
2	Et	-2.6 ± 2.5	0.0 ± 0.0	6.0 ± 4.9
3	^{i}Pr	-3.7 ± 2.8	6.0 ± 4.9	6.0 ± 4.9
4	^{t}Bu	0.0 ± 2.5	3.0 ± 2.4	6.0 ± 4.9

Figure S37: (a) Plots of $K_{c/t}$ values against concentration (0-50 mM) of **1-4** in $CDCl_3$ solvent at 298K; (b) Plots of stretching frequencies (cm^{-1}) of carbamate C=O and amide C=O bond against concentration

(0-50 mM) of **1-4** in $CHCl_3$ solvent at 298K; (c) Value of the slopes along with standard deviation after fitting the curves in these plots.

S8-Determination of $K_{c/t}$ values:

In the process of *trans* to *cis* isomerization at Xaa-Pro bond, the ratio of the concentration of *cis* isomer to the concentration of *trans* isomer is termed as $K_{c/t}$.

S8.1. Problem in using ROESY for prolyl carbamate system to determine the $K_{c/t}$ values:

The value of equilibrium constant $K_{c/t}$ = [*cis*]/[*trans*] for the *trans* to *cis* isomerization of the 3^o amide bond in Acyl-Pro systems can be determined through ^{1}H NMR, TOCSY, HSQC and ROESY analyses. In the ROESY for *cis* conformer a cross peak between H^α of Pro and Acyl group, and for the *trans* conformer a cross peak between H^δ of Pro and Acyl group is observed (**Figure S38a**). And using the relative integral ratios of *cis* and *trans* (mostly H^α of Pro which corresponds to *cis* and *trans* conformers respectively) signals in ^{1}H NMR the $K_{c/t}$ is determined[1].

On the other hand, the ratio of *cis*/*trans* population cannot be determined for prolyl carbamate system in this similar way. In the prolyl carbamate system (**1**-**4**), the distance between the corresponding protons is so far away that that they do not produce good cross peaks in ROESY spectrum (**Figure S38b**).

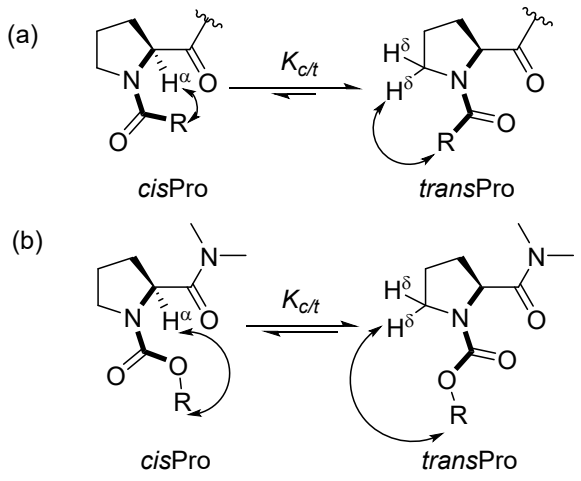


Figure S38: (a) Distinguishing the cis and trans conformers using ROESY in acyl Pro system. Cross peaks are shown by double headed arrows, (b) But for the prolyl carbamate system (**1**-**4**) it is not possible to evaluate the population of cis and trans conformers using ROESY.

S8.2. Proline Ring puckering & determination of $K_{c/t}$ values:

The proline ring puckering for both *trans*Pro and *cis*Pro rotamers are similar, it behaves as expected in the cis/trans isomerization. Both of the ^{1}H and ^{13}C NMR data show almost identical chemical shift values for the corresponding ring carbons as well as the protons in case of both of conformers. Only slight differences are observed in the trend of ^{1}H and ^{13}C NMR chemical shifts for the H^{α} proton and C^{β} carbon respectively. The behaviour of H^{α} is expected because it is the most proximal group to the charge donor, so it develops negative charge *cis*Pro isomers, which is reflected in the slight upfield shift in the ^{1}H NMR chemical shift. And, the slight difference between the ^{13}C chemical shifts of Cβ proline ring carbon atom arises from a minor effect, where the difference between the two δ values of C^{β} and C^{γ} ($\Delta\delta^{\beta\text{-}\gamma}$) for the cis conformer is greater than that of the trans conformer (**Figure S39c**), as shown in the **Figure S39d** from a Reference article[7].

It is already known that the *trans*Pro rotamer is more populated in prolyl carbamate system in compared to the *cis*Pro rotamer. From the proline ring puckering it has been confirmed that there are two sets of signals in the NMR of **1-4** in which one set of signals is significantly lower than the other, and the lower % is for *cis*Pro rotamer and higher % is *trans*Pro rotamer. Using the relative integral ratios of *cis* and *trans* signals, the $K_{c/t}$ is determined for prolyl carbamate system.

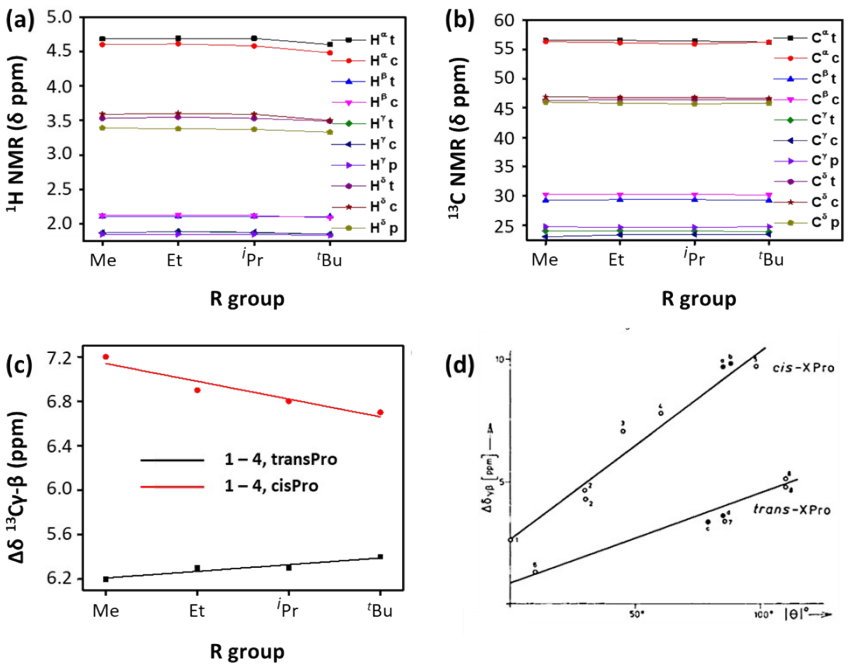


Figure S39: (a & b) ^{1}H and ^{13}C NMR chemical shifts of Proline ring for *trans*Pro (t) & *cis*Pro (c) isomers of **1-4** and pyrrolidines (p) **5-8**, with change in R group; (c & d) Δδ β-γ plot of ^{13}C NMR chemical shifts for *trans*Pro (t) & *cis*Pro (c) isomers of **1-4** with change of R group and the

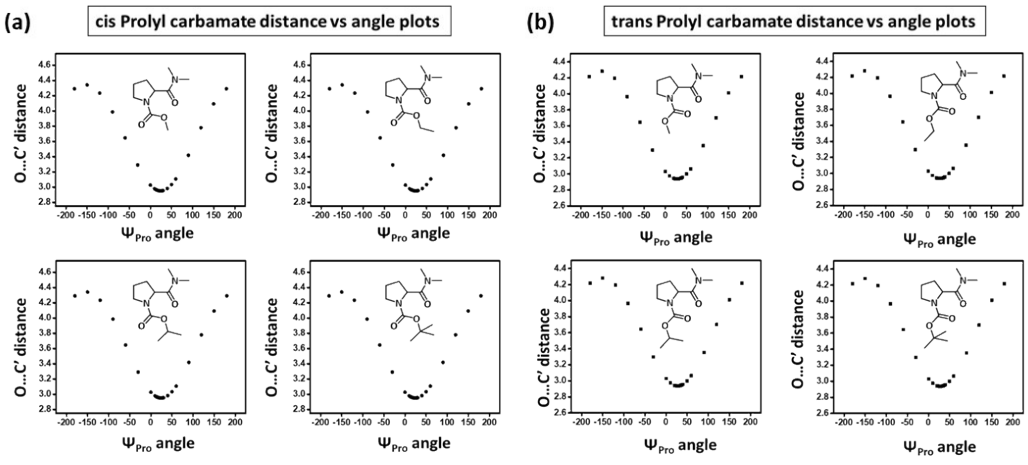
corresponding reference plot[7] showing the greater difference for *cis*Pro rotamers in comparison to the *trans*Pro rotamers, respectively.

S9-Theoretical calculations:

S9.1. Generation of initial guess structures for the rotamers of Prolyl Carbamates:

At first, the crystal structure of two molecule containing the *cis* and *trans* rotamers of tert-butyloxycarbonyl (Boc) prolyl carbamate are selected, from there the structures of the ^{t}Bu analogues of both prolyl carbamates (**4**) are accordingly formed using Gaussview 6.0.16 software. Using the analogue **4**, the other three analogues (Me (**1**), Et (**2**), ^{i}Pr (**3**)) are formed corresponding to the both rotamers using the same software.

Since, the pyrrolidine ring is constrained and the atoms in the carbamate regions are residing in one plane, there are only two single bonds in these models along which complete 360^{o} rotation is possible without direct impedance from resonance effects – they are C^{α}_{Pro}-C'_{Pro} and O-C^{α}_{R}. We ignore the rotation along the C^{α}-C^{β} bond since it is absent in Me analogue and this rotation yields symmetric rotamers. The ψ_{Pro} torsions of -30° and 120° are the two most populated energy minima for rotation along the C^{α}_{Pro}-C'_{Pro} σ-bond, with inter-carbonyl interactions between C=O donor of amide and C=O acceptor of carbamate being possible only in the vicinity of latter. Simple analysis of $O_{amide}\ldots C'_{carbamate}$ distances at varying ψ_{Pro} torsions indeed yielded least values at 24.5° in the *cis*Pro rotamer and 27.5° in the *trans*Pro (**Figure S40**) rotamer. The *cis*Pro and *trans*Pro rotamers were thus built with their ψ_{Pro} torsions restricted at 24.5° and 27.5° respectively. Each rotamers is subjected towards energy minimization using B3LYP 6-311G(**) basis set in Gaussian 09W software. The energy minimization yielded the structures of the *cis*Pro and *trans*Pro rotamers with their ψ_{Pro} torsions restricted at -31°±1° and -24.3°±1.3° respectively.



	R	Before Minimization: Min O...C' distance (Å)	Before Minimization: ΨPro N-Cα-C'-O	After Minimization: O...C' distance (Å)	After Minimization: ΨPro N-Cα-C'-O
1	Me	2.95	24.5	3.25	-31.54
2	Et	2.95	24.5	3.26	-29.99
3	^{i}Pr	2.95	24.5	3.29	-31.98
4	^{t}Bu	2.95	24.5	3.29	-31.95

	R	Before Minimization: Min O...C' distance (Å)	Before Minimization: ΨPro N-Cα-C'-O	After Minimization: O...C' distance (Å)	After Minimization: ΨPro N-Cα-C'-O
1	Me	2.94	27.5	3.30	-23.40
2	Et	2.94	27.5	3.33	-25.73
3	^{i}Pr	2.94	27.5	3.29	-23.04
4	^{t}Bu	2.94	27.5	3.31	-24.35

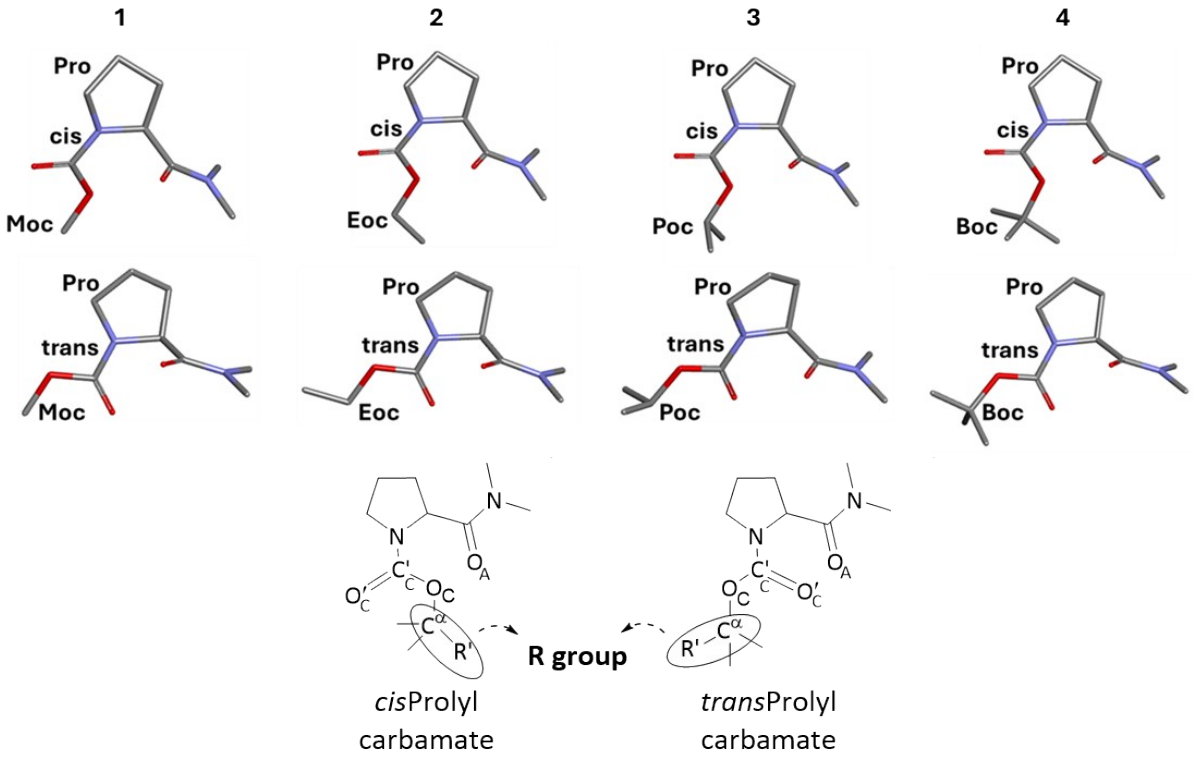
Figure S40: Rotation of of proline ring to create the minimum O…C' distance for the computational calculation and the plots of the O..C' distance vs the Ψ_{Pro} of **1-4** for (a) *cis*Prolyl and (b) *trans*Prolyl carbamates; (c) the values of minimum O…C' distance and the corresponding Ψ_{Pro} torsional angle.

S9.2. Computation of energy differences, dipole moments & electrostatic charges of prolyl carbamate rotamers:

The geometry optimization of all cisPro and transPro rotamers were carried out using the B3LYP 6-311G(**) basis set and m5 grid. The D3 corrections used the Becke-Johnson damping function[4–6].

A convergence criterion of 1.0 x10^{-3} a.u for gradients and 1.0 x10^{-7} a.u for energy was used. Solvation effects were included using the COSMO solvation model. Vibrational analysis of the optimized structures showed no imaginary frequencies which indicated that the structure was a minimum.

S9.3. Bond distance parameters from geometry optimization of prolyl carbamates:

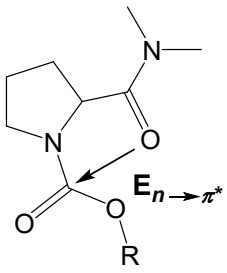


		distance (Å)			distance (Å)		
	R	$O_A...C'_C$	$O_A...C^\alpha$	$O_A...O'_C$	$O_A...C'_C$	$O_A...C^\alpha$	$O_A...O'_C$
1	Me	3.24	4.34	4.13	3.31	5.08	3.51
2	Et	3.24	4.40	4.16	3.33	5.08	3.49
3	^{i}Pr	3.29	4.26	4.19	3.29	5.12	3.50
4	^{t}Bu	3.28	4.10	4.16	3.31	5.11	3.46

Figure S41: The energy minimized structures of cisPro and transPro isomers **1-4.** Relevant interatomic distances are tabulated.

S9.4. Natural Bonding Orbital (NBO) analysis:

The wave functions for each energy minimized molecules were calculated using the B3LYP 6-311G(**) basis set in Gaussian 09W. The second-order perturbation theory has been used to estimate the energy afforded by the $n\rightarrow\pi^*$ interaction ($E_{n\rightarrow\pi^*}$) between the lone pair of amide oxygen and the π* orbital of carbamate carbonyl bond. This revealed the absence of orbital overlap interactions or any finite energies for such interactions in either (cisPro / transPro) rotamers.



	R	$E_{n\rightarrow\pi^*}$ (kcal/mol)
1	Me	0
2	Et	0
3	^{i}Pr	0
4	^{t}Bu	0

Figure S42: The energy value of the $n\rightarrow\pi^*$ interaction ($E_{n\rightarrow\pi^*}$) between the lone pair of amide oxygen and the π* orbital of carbamate carbonyl bond from the second-order perturbation theory in NBO calculation.

S9.5. Correlation of n→σ* energy with equilibrium constant of transPro→cisPro isomerism ($K_{c/t}$).

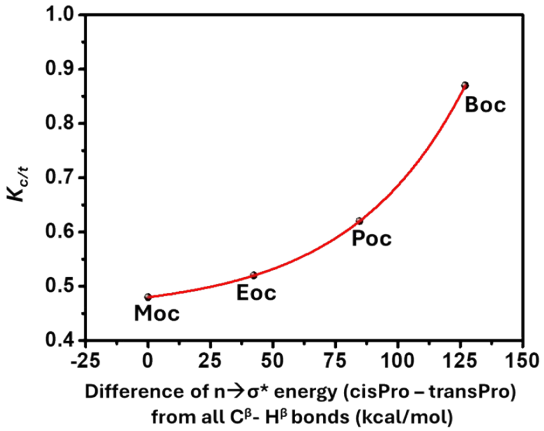


Figure S43: Correlation of the difference of n→σ* energy (cisPro-transPro) from all C^{β}- H^{β} bonds in Xaa-Pro-NMe_2 (**1-4**) (0 in Moc, 3 in Eoc, 6 in Poc and 9 in Boc) with $K_{c/t}$ of transPro→cisPro isomerism.

S10-References:

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