Coupling of acceptor-substituted diazo compounds and tertiary thioamides: synthesis of enamino carbonyl compounds and their pharmacological evaluation

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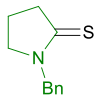
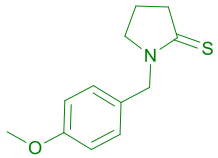
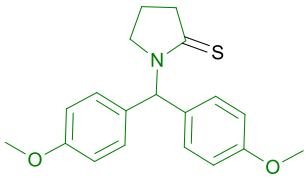
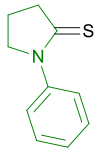
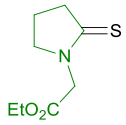
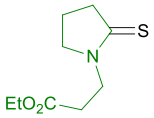
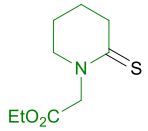
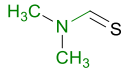
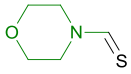
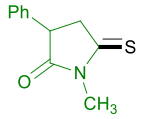
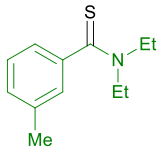
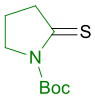
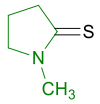
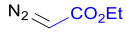
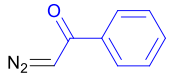
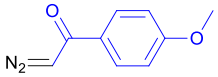
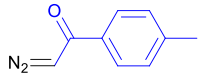
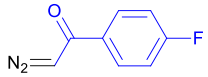
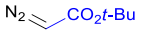
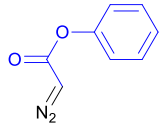
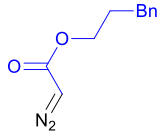
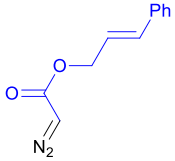
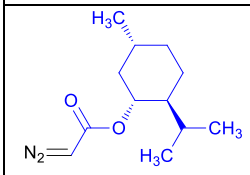
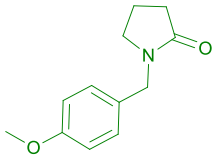
 **3a**[1]	 **3b**	 **3c**
 **3d**	 **3e**	 **3f**
 **3g**	 **3h** (commercially available)	 **3i**[2]
 **3j**	 **3k**	 **3l**
 **3m**[3]		

Structures and labels of thioamides used in the preparation of coupled products

 **4a** (commercial source)	 **4b**[4]	 **4c**[5]
 **4d**	 **4e**[5]	 **4f** (commercial source)
 **4g**[6]	 **4h**[6]	 **4i**[6]
 **4j**[6]		

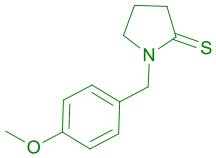
Synthesis of 1-(4-methoxybenzyl)pyrrolidin-2-one[7]



NaH (60% dispersion in paraffin liquid, 2.19 mmol) was washed three times with petroleum ether. The flask was purged with nitrogen, and dried THF was added (3.40 mL). The suspension was cooled to 0 °C, and 2-pyrrolidine (2.00 mmol) and 4-methoxybenzyl chloride (2.19 mmol) were added dropwise to the stirred mixture. After 1 h, the temperature was increased to 60 °C and stirred for another 17 h. The reaction was cooled to 0 °C and quenched with ether. The mixture was washed with water, dried with $MgSO_4$, and evaporated to give the product in crude form. Further purification with 80% EtOAc in hexanes gave the pure product (249 mg, 1.21 mmol, 61%). ^1H and ^{13}C spectra of the product matches the literature values.[7]

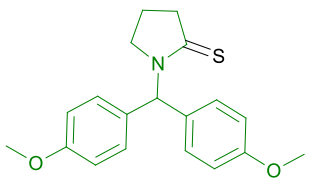
Synthesis of thioamides

1-(4-Methoxybenzyl)pyrrolidine-2-thione (**3b**)



This procedure is based on a published method for preparing other thioamides.[1] 1-(4-methoxybenzyl)pyrrolidin-2-one (0.431 mmol, preparation shown above) was dissolved in CH_2Cl_2 (1.74 mL) and added to a solution of Lawesson reagent (0.216 mmol) in CH_2Cl_2 (1.74 mL). The reaction was stirred for two hours at room temperature, concentrated, and purified by flash column chromatography. Column chromatography was performed by eluting with 30% ethyl acetate in petroleum ether that gave the product (81.0 mg, 0.366 mmol, 85%). R_f = 0.43 (40% ethyl acetate in petroleum ether); m.p. 92–94 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 4.90 (s, 2H), 3.78 (s, 3H), 3.55 (t, J = 7.6 Hz, 2H), 3.06 (t, J = 7.6 Hz, 2H), 1.98 (tt, J = 7.6, 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.3, 159.4, 129.8, 127.3, 114.2, 55.4, 53.9, 51.1, 45.0, 19.4; HRMS (ESI^+) *m/z*: $(M + H)^+$ calcd for $C_{12}H_{16}NOS$, 222.0953; measured, 222.0967.

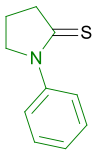
1-(bis(4-methoxyphenyl)methyl)pyrrolidine-2-thione (**3c**)



This procedure is based on a published method for preparing other thioamides.[3] Precursor amide (0.642 mmol) was dissolved in CH_2Cl_2 (2.00 mL) and added to a solution of Lawesson reagent (0.335 mmol) in CH_2Cl_2 (2.00 mL). The reaction was stirred for two hours at room temperature, concentrated, and purified by flash column chromatography. Column chromatography was performed by eluting with CH_2Cl_2 until

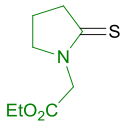
the impurity was no longer visible, followed by 50% ethyl acetate in petroleum ether that gave the product as a white solid (182 mg, 0.555 mmol, 86%). R_f = 0.46 (dichloromethane); m.p. 119–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.39 (s, 1H), 7.13 (d, J = 8.8 Hz, 4H), 6.88 (d, J = 8.8 Hz, 4H), 3.81 (s, 6H), 3.48 (t, J = 7.2 Hz, 2H), 3.11 (t, J = 7.6 Hz, 2H), 2.03 (tt, J = 7.2, 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.8, 159.2, 129.8, 129.5, 114.1, 62.3, 55.4, 51.2, 45.0, 20.0; HRMS (ESI$^+$) m/z: $(M + H)^+$ calcd for $C_{19}H_{22}NO_2S$, 328.13126; measured, 328.13754.

1-Phenylpyrrolidine-2-thione (**3d**)[8]



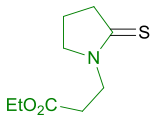
This procedure is based on a published method for preparing other thioamides.[1] Precursor amide (2.00 mmol) was dissolved in CH_2Cl_2 (2.50 mL) and added to a solution of Lawesson reagent (1.00 mmol) in CH_2Cl_2 (2.50 mL). The reaction was stirred for two hours at room temperature, concentrated, and purified by flash column chromatography. Column chromatography was performed by eluting with 40% ethyl acetate in petroleum ether that gave the product (345 mg, 1.95 mmol, 98%) as a white solid. ^{1}H and ^{13}C spectra of the product match the literature values.[8]

Ethyl 2-(2-thioxopyrrolidin-1-yl)acetate (**3e**)[9]



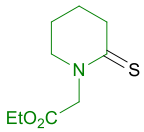
This procedure is based on a published method for preparing other thioamides.[4] Precursor amide[9] (2.50 mmol) was dissolved in CH_2Cl_2 (3.00 mL) and added to a solution of Lawesson reagent (1.25 mmol) in CH_2Cl_2 (3.00 mL). The reaction was stirred for two hours at room temperature, concentrated, and purified by flash column chromatography. Column chromatography was performed by eluting with 30% ethyl acetate in petroleum ether that gave the product (445 mg, 2.38 mmol, 95%) as a colorless oil. ^{1}H and ^{13}C spectra of the product match the literature values.[9]

Ethyl 3-(2-thioxopyrrolidin-1-yl)propanoate (**3f**)[10]



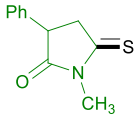
This procedure is based on a published method for preparing other thioamides.[4] Precursor amide[11] (2.50 mmol) was dissolved in CH_2Cl_2 (3.00 mL) and added to a solution of Lawesson reagent (1.25 mmol) in CH_2Cl_2 (3.00 mL). The reaction was stirred for two hours at room temperature, concentrated, and purified by flash column chromatography. Column chromatography was performed by eluting with 30% ethyl acetate in petroleum ether that gave the product (470 mg, 2.33 mmol, 93%) as a colorless liquid. ^{1}H and ^{13}C spectra of the product match the literature values.[10]

Ethyl 2-(2-thioxopiperidin-1-yl)acetate (**3g**)[9]



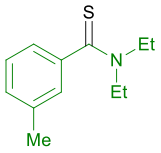
This procedure is based on a published method for preparing other thioamides.[4] Precursor amide[9] (0.75 mmol) was dissolved in CH_2Cl_2 (1.00 mL) and added to a solution of Lawesson reagent (0.375 mmol) in CH_2Cl_2 (1.00 mL). The reaction was stirred for two hours at room temperature, concentrated, and purified by flash column chromatography. Column chromatography was performed by eluting with 5% ethyl acetate in CH_2Cl_2 that gave the product (139 mg, 0.691 mmol, 92%) as a colorless oil. ^{1}H and ^{13}C spectra of the product match the literature values.[9]

1-Methyl-3-phenyl-5-thioxopyrrolidin-2-one (**3j**)



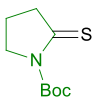
This procedure is based on the reported experimental for preparing similar monothioimides.[12] Imide **3j** (0.780 mmol) was dissolved in toluene (7.00 mL) and added to the suspension of Lawesson reagent (3.88 mmol) in toluene (7.00 mL). The reaction was refluxed for 30.0 minutes. The solvent was evaporated, and the crude was purified by flash chromatography (100% CH_2Cl_2), affording pre **3j** (130 mg, 0.634 mmol, 81%) as a light-yellow solid. R_f = 0.51 (100% dichloromethane). The structure was confirmed using the HSQC experiment and comparing the ^{1}H and ^{13}C chemical shift values with the starting imide.[13] ^{1}H NMR (400 MHz, $CDCl_3$): δ:7.39–7.20 (m, 5H), 4.03 (dd, J = 4.4, 9.2 Hz, 1H), 3.64 (dd, J = 9.2, 19.6 Hz, 1H), 3.36 (s, 3H), 3.27 (dd, J = 4.4, 19.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 209.7, 179.1, 136.9, 129.4, 128.2, 127.6, 47.6, 46.7, 29.6. HRMS (ESI$^+$) m/z: $(M + H)^+$ calcd for $C_{11}H_{12}SNO$, 206.0561; measured, 206.0568.

N,*N*-Diethyl-3-methylbenzothioamide (**3k**)[14]



This procedure is based on a published method for preparing other thioamides.[4] *N*,*N*-Diethyl-*m*-toluamide (2.00 mmol) was dissolved in CH_2Cl_2 (2.50 mL) and added to a solution of Lawesson reagent (1.00 mmol) in CH_2Cl_2 (2.50 mL). The reaction was stirred for two hours at room temperature, concentrated, and purified by flash column chromatography. Column chromatography was performed by eluting with 15% ethyl acetate in petroleum that gave the product (139 mg, 0.691 mmol, 92%) as a yellow solid. ^{1}H and ^{13}C spectra of the product match the literature values.[14]

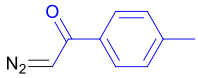
tert-Butyl 2-thioxopyrrolidine-1-carboxylate (**3l**)



Pyrrolidine-2-thione[3] (1.00 mmol), 4-DMAP (1.00 mmol), and Et_3N (1.00 mmol) were dissolved in anhydrous dichloromethane. The solution was cooled to 0 ˚C with continuous stirring. A solution of di-

tert-butyl dicarbonate [$(Boc)_2O$] (1.00 mmol) in anhydrous dichloromethane was added to the reaction mixture dropwise. The reaction was allowed to come to room temperature, and it was stirred for another 24 h. The solvent was evaporated, and the crude reaction mixture was charged onto a silica gel column. Flash column chromatography (20% ethyl acetate in petroleum ether) gave pure **3l** (149 mg, 0.74 mmol, 74%) as a yellow solid. R_f = 0.20 (10% ethyl acetate in petroleum ether); m.p. 85–87 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.98 (t, J = 7.6 Hz, 2H), 2.97 (t, J = 8.0 Hz, 2H), 1.97 (tt, J = 8.0, 7.6 Hz, 2H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 207.7, 150.2, 83.8, 53.7, 48.9, 27.8, 20.0; HRMS (ESI$^+$) *m/z*: (M + H)$^+$ calcd for $C_9H_{16}NO_2S$, 202.0902; measured, 202.0892.

Synthesis of 2-Diazo-1(p-tolyl)ethanone (**4d**)[15]

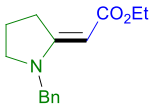


This procedure is based on a published method for the preparation of other diazo compounds.[5] 3-(chlorosulfonyl)benzoic acid (10.0 mmol) was added to a solution of sodium azide (15.0 mmol) and potassium carbonate (11.0 mmol). The mixture was stirred at rt for 10 min. to afford a solution called SAFE COCKTAIL.

Potassium *tert*-butoxide (1.50 mmol) was added to an ice-cold solution of 4-methylacetophenone (0.750 mmol), and ethyl formate (2.25 mmol) in THF (1.00 mL), and the mixture was stirred for 1 h. The ice bath was removed, and the reaction was stirred for another 15 h at rt. SAFE COCKTAIL prepared above was slowly added to the reaction at 0 °C and stirred for another 1 h. Potassium hydroxide (1.75 mmol) and acetonitrile (1.00 mL) were added, and the reaction was stirred at rt for 1 h. The mixture was extracted with $CHCl_3$ (3 mL X 2), dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography using 20% EtOAc in petroleum ether to afford **4d** (107 mg, 0.668 mmol, 89%) as a yellow solid. ^{1}H and ^{13}C spectra of the product match the literature values.[15]

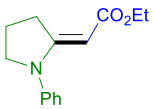
Synthesis of enamino previously reported carbonyl compounds

(*E*)-Ethyl 2-(1-benzylpyrrolidin-2-ylidene)acetate (**5a**)[8, 16]



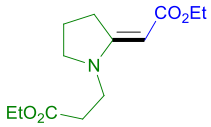
Using general procedure A, 0.200 mmol of **3a** was converted into crude **5a**. Flash column chromatography (100% dichloromethane then 50% EtOAc in petroleum ether) gave pure **5a** (42.0 mg, 0.171 mmol, 86%). The ^{1}H and ^{13}C NMR values matched the reported values.[8, 16] 1D-NOESY further confirmed the stereochemistry.

(*E*)-Ethyl 2-(1-phenylpyrrolidin-2-ylidene)acetate (**5d**)[8, 17]



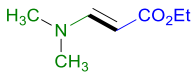
Using general procedure B, 0.200 mmol of **3d** was converted into crude **5d**. Flash column chromatography (5% EtOAc in petroleum ether) gave pure **5d** (31.0 mg, 0.134 mmol, 67%) as a yellow solid. The stereochemistry was assigned using 1D-NOESY. ^{1}H and ^{13}C NMR spectra match the reported values.[8, 17]

(*E*)-Ethyl 3-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)propanoate (**5f**)[10]



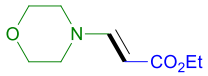
Using general procedure B, 0.200 mmol of **3f** was converted into crude **5f**. Flash column chromatography (30% EtOAc in hexane) gave pure **5f** (41.0 mg, 0.161 mmol, 81%) as a yellow solid. ^{1}H and ^{13}C NMR spectra match the reported values.[10]

(*E*)-Ethyl 3-(dimethylamino)acrylate (**5h**)[18]



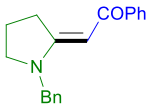
Using general procedure B, 0.200 mmol of **3h** was converted into crude **5h**. Flash column chromatography (15% EtOAc in dichloromethane) gave **5h**. The yield (91%) was determined by ^{1}H-NMR using benzaldehyde (0.200 mmol, 20.8 μL) as an internal standard. R_f = 0.48 (20% ethyl acetate in dichloromethane). ^{1}H spectrum of the major (*E*)-isomer match the reported value, and ^{13}C NMR only shows signals for the major isomer, which matches the reported values.[18] The ratio of rotational isomers was 1:7.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.90 (m, 1H, minor), 7.49 (d, J = 7.2 Hz, 1H), 4.52 (d, J = 7.2 Hz, 1H), 4.25–4.18 (m, 2H, minor), 4.13 (q, J = 7.2 Hz, 2H, major), 3.28 (br m, 6H, minor), 2.86 (br s, 4H, major), 1.26 (t, J = 7.2, 7.2 Hz, 3H).

(*E*)-Ethyl 3-mopholinoacrylate (**5i**)[19]



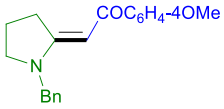
Using general procedure B, 0.200 mmol of **3i** was converted into crude **5i**. Flash column chromatography (10% EtOAc in petroleum ether) gave pure **5i** (29.0 mg, 0.157 mmol, 78%) as a light yellow oil. ^{1}H and ^{13}C NMR spectra match the reported values.[19] R_f = 0.23 (10% ethyl acetate in dichloromethane).

(*E*)-2-(1-Benzylpyrrolidin-2-ylidene)-1-phenylethanone (**5m**)[4]



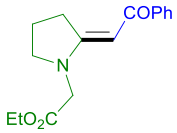
Using general procedure B, 0.200 mmol of **3a** was converted into crude **5m**. Flash column chromatography (50% EtOAc in petroleum ether) gave pure **5i** (50.0 mg, 0.180 mmol, 90%) as a yellow solid. ^{1}H and ^{13}C NMR spectra match the reported values.[4]

(*E*)-2-(1-Benzylpyrrolidin-2-ylidene)-1-(4-methoxyphenyl)ethanone (**5n**)[20]



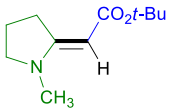
Using general procedure B, 0.200 mmol of **3a** was converted into crude **5n**. Flash column chromatography (35% EtOAc in dichloromethane) gave pure **5n** (55.0 mg, 0.179 mmol, 90%) as a yellow viscous oil. ^{1}H and ^{13}C NMR spectra match the reported values.[20] The stereochemistry was determined by a 1D-NOESY experiment.

(*E*)-Ethyl 2-(2-(2-oxo-2-phenylethylidene)pyrrolidin-1-yl)acetate (**5q**)[9]



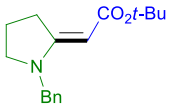
Using general procedure B, 0.200 mmol of **3e** was converted into crude **5q**. Flash column chromatography (50% EtOAc in petroleum ether) gave pure **5q** (35.0 mg, 0.128 mmol, 64%) as a dark yellow viscous oil. ^{1}H and ^{13}C NMR spectra match the reported values.[9] The stereochemistry was assigned using 1D-NOESY. R_f = 0.22 (50% ethyl acetate in petroleum ether).

(*E*)-*tert*-Butyl 2-(1-methylpyrrolidin-2-ylidene)acetate (**5u**)[21]



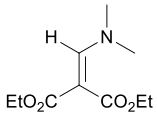
Using general procedure A, 0.200 mmol of **3m** was converted into crude **5v**. Flash column chromatography (100% CH_2Cl_2) gave **5v** (26.0 mg, 0.131 mmol, 82%).^{1}H and ^{13}C NMR spectra match the reported values.[21]

(*E*)-*tert*-Butyl 2-(1-benzylpyrrolidin-2-ylidene)acetate (**5v**)[22]



Using general procedure B, 0.200 mmol of **3a** was converted into crude **5v**. Three equivalents of diazo compound were used in this experiment. Flash column chromatography (15% EtOAc in petroleum ether) gave **5v** (50.0 mg, 0.183 mmol, 92%) as a yellow solid. The compound was obtained as a mixture of rotamers. The stereochemistry of the major rotamer was determined by the 2D-NOESY experiment. R_f = 0.48 (20% ethyl acetate in petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.35–7.25 (m, 3H), 7.18–7.17 (m, 2H), 4.63 (br s, 1H (major)), 4.15 (br s, 1H (minor)), 3.51–3.39 (m, 4H (minor)), 3.30 (t, J = 7.2 Hz, 2H (major)), 3.20 (t, J = 7.8 Hz, 2H (major)), 2.47–2.43 (m, 2H (minor)), 1.95 (tt, J = 7.2, 7.6 Hz, 2H (major)), 1.46 (s 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.6, 164.6, 136.4, 128.8, 127.5, 127.3, 80.3, 77.6, 52.3, 50.1, 32.6, 28.8, 21.3.

Diethyl 2-((dimethylamino)methylene)malonate (**BZW-I-44**)[23]



1,2-Dichloroethane (0.74 mL) was added to a vial containing *N*,*N*-dimethylthioformamide (168 μmol). The resulting mixture was added to a vial containing diethyl diazomalonate (218 μmol), and the well-mixed solution was transferred to a pressure vessel containing 5 mol% Cu(I)Br. The two vials were washed with DCE (0.36 mL X 2) to ensure complete transfer, and the contents were transferred to the reaction vessel. The vessel was placed in an oil bath, and the oil bath was heated to 90 °C for 18.5 h. The crude product was purified by flash column chromatography (40% EtOAc in petroleum ether) to give

pure BZW-I-44 (31.0 mg, 144 µmol, 86%) as a yellow oil. ^{1}H and ^{13}C spectra of the product match the literature values.[23]

Rapid Assessment of Reaction

Calibration for Determining Reaction Yield

The calibration line was determined using five different concentrations of **5a** that were lower than the maximum concentration used in the screening process (graph below). Mesitylene was used as the internal standard. The GC peak area of standard (kept constant at 100%) vs. the GC peak area for each concentration of **5a** gave each point of the line. The following GCMS parameters were used for this process:

Instrument: Shimadzu GCMS QP5000

Column: DB-WAX 60m 0.25mm i.d. df = 0.25 µm

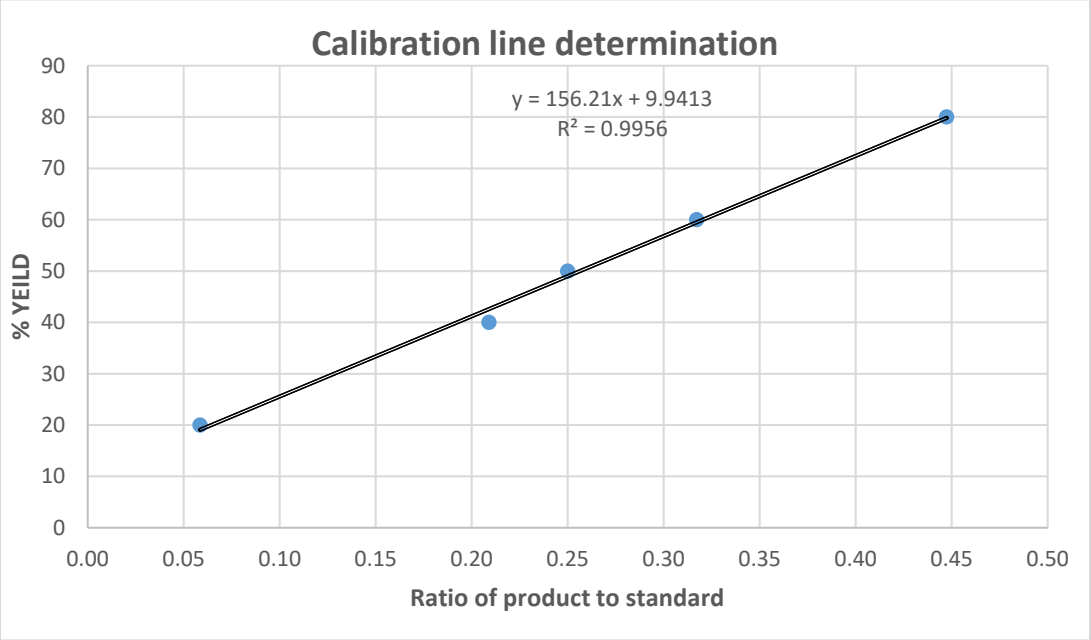
Carrier Gas: He 180 kpa, split ratio: 70:1

Method: Initial temp 50 ºC, hold 3 min, rate of increment 40 ºC/min, final temp 280 ºC, hold 3 min.

Detector: Flame Ionization Detector (FID)

Retention Time of **5a** = 9.38 min.

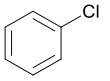
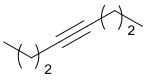
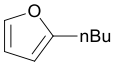
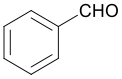
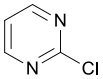
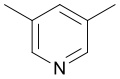
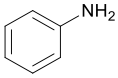
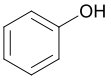
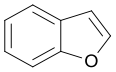
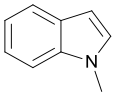
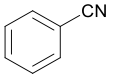
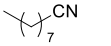
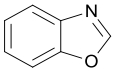
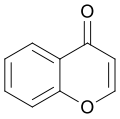
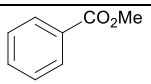
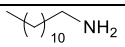
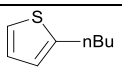
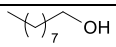
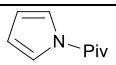
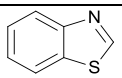
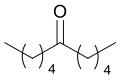
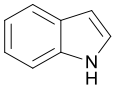
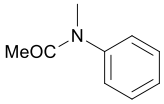
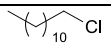
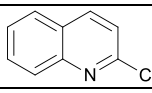
Retention Time of mesitylene = 5.31 min.



Calibration for Additives

We individually analyzed each of the additives, starting material, and product by GC-MS to determine their retention times (t_R) (Table S1). Retention time of **3a** = 8.80 min. Retention time of standard (mesitylene) = 5.33 in. Additives are classified into functional groups and heterocycles categories.[24]

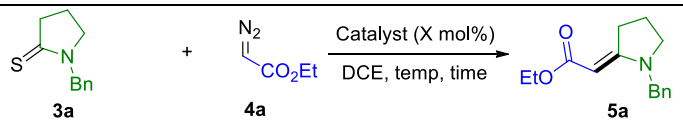
Table S1

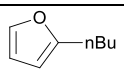
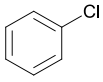
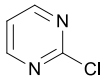
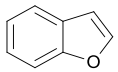
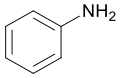
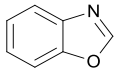
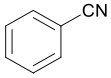
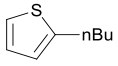
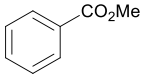
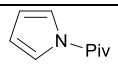
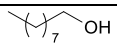
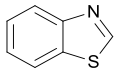
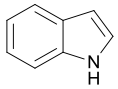
Functional Group Additives				Heterocyclic Additives			
Additive (Group A)	t_R (min)	Additive (Group B)	t_R (min)	Additive (Group C)	t_R (min)	Additive (Group D)	t_R (min)
	4.34		4.35		4.72		4.02
	4.94		5.29		5.41		5.38
	5.39		5.41		5.52		6.87
	5.44		6.42		5.64		7.34
	6.06		7.39		5.86		
	6.34				6.20		
	6.43				6.69		
	6.76				6.93		
	6.95				7.14		
	7.47				7.47		

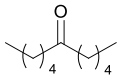
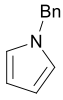
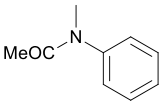
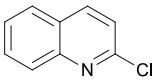
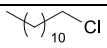
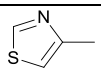
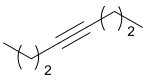
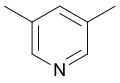
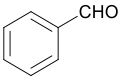
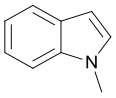
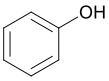
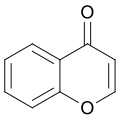
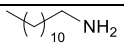
Procedure: A solution of **3a** (1.25 mmol) in DCE (12.5 mL) was distributed equally to 10 flamed dried screw-capped reaction vials, each containing copper (I) bromide (0.013 mmol, 10 mol%) and a stirring bar. One additive (0.125 mmol) was added to each vial, and all vials were stirred. Ethyl diazoacetate **4a** (in ≥13% CH_2Cl_2, 0.250 mmol, 2 eq, 31.0 µL) was added to each vial in three equal portions. The first portion was transferred to each vial at 0 h, and the reaction was heated at 40 °C. The second portion of **4a** was added after 8 h of stirring, and the third portion after another 8 h (16 h). After 24 h the reaction was allowed to come rt. The solvent was evaporated, an internal standard mesitylene (17.5 µL, 0.125 mmol) was added and the mixture analyzed by GCMS.

We conducted the screening in three batches. Batch one group A, batch two group B and D, and batch three group C. Each batch had a control reaction with no additives. The information obtained from these experiments is tabulated below.

Table S2



Functional Group Additives					Heterocyclic Additives				
Entry	Additive	Yield of **5a** (%)*	Additive remaining (%)*	**3a** remaining (%)*	Entry	Additive	Yield of **5a** (%)*	Additive remaining (%)*	**3a** remaining (%)*
1.	none	99	-	0	17.		97	99	0
2.		98	97	93	18.		29	8	22
3.		18	100	93	19.		90	98	2
4.		58	72	33	20.		99	49	4
5.		50	100	72	21.		76	93	0
6.		18	100	61	22.		40	94	27
7.		96	98	5	23.		63	96	5
8.		24	83	54	24.		97	8	0

9.		43	100	50	25.		76	82	9
10.		68	83	44	26.		72	76	4
11.		30	7	89	27.		48	58	43
12.		100	71	2.5	28.		49	81	46
13.		0	99	81	29.		0	56	76
14.		0	44	63	30.		99	72	0
15.		91	96	6					
16.		0	0	67					

Green (above 66%), Yellow (34–66%), red (below 34%). *GC yield.

Characterization of Compounds

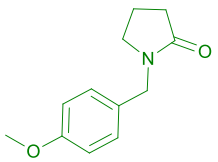


Fig. **S1**. ^{1}H NMR of 1-(4-methoxybenzyl)pyrrolidin-2-one

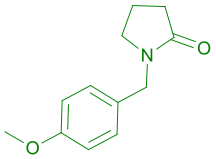


Fig. **S2**. ^{13}C NMR of 1-(4-methoxybenzyl)pyrrolidin-2-one

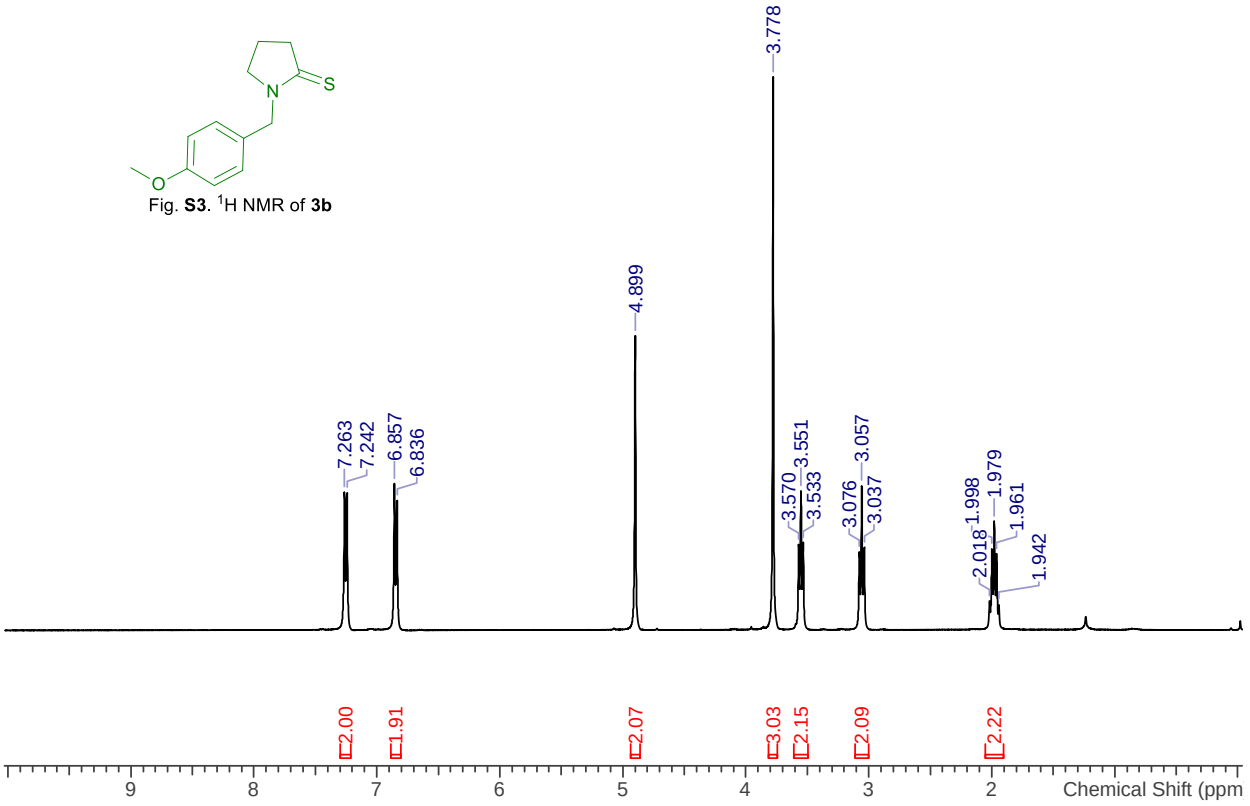


Fig. **S3**. ^{1}H NMR of **3b**

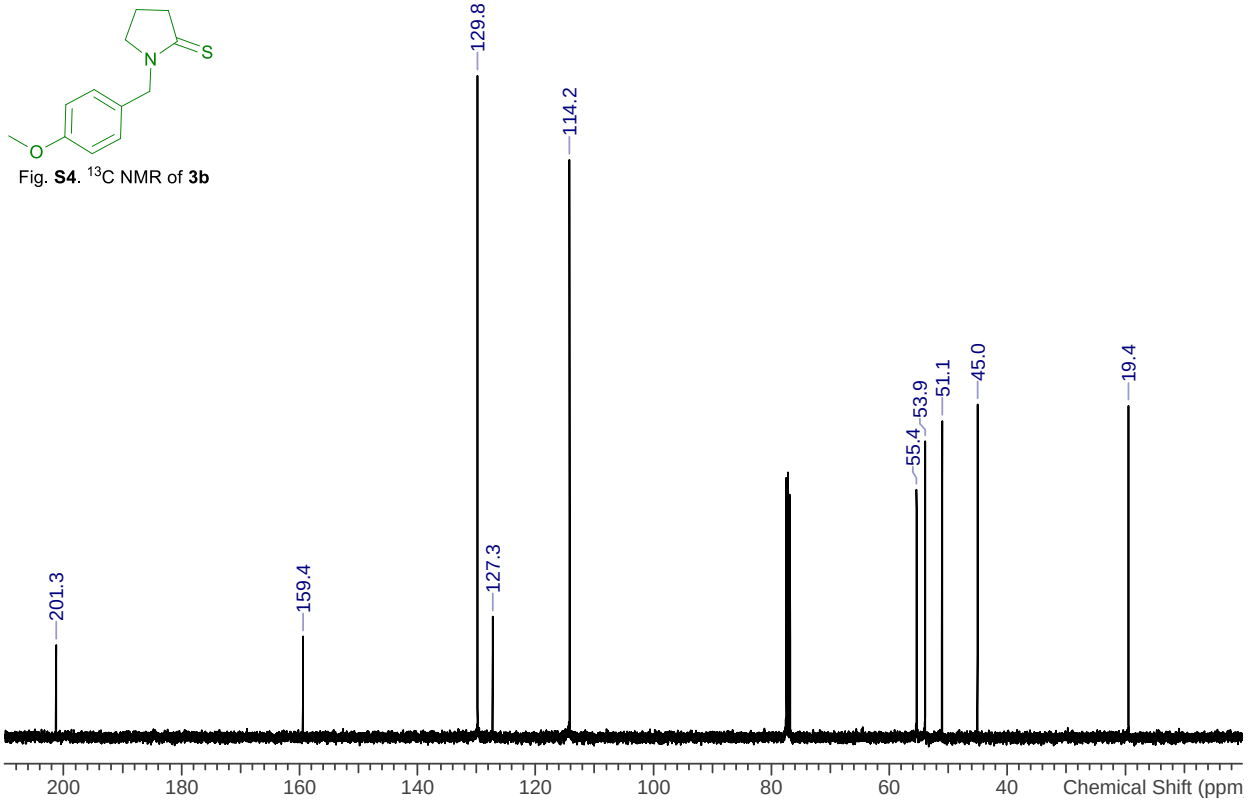


Fig. **S4**. ^{13}C NMR of **3b**

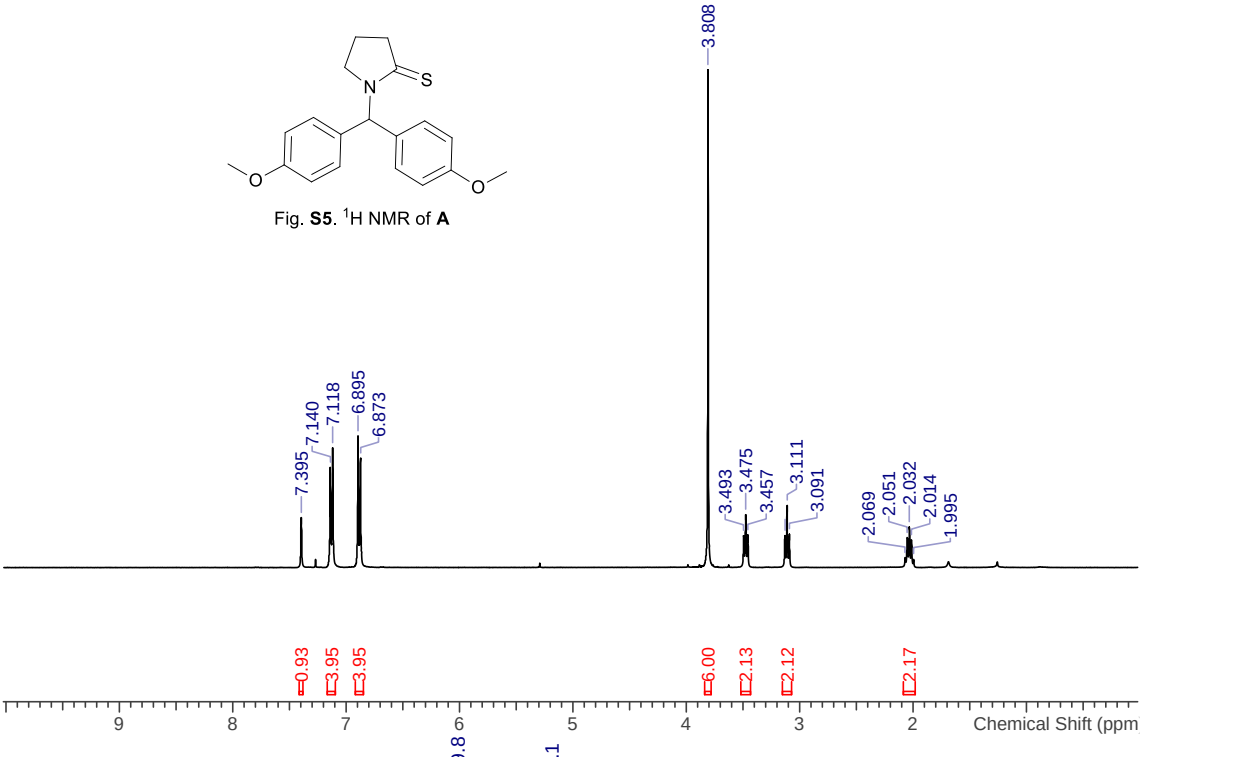


Fig. **S5**. ^{1}H NMR of **A**

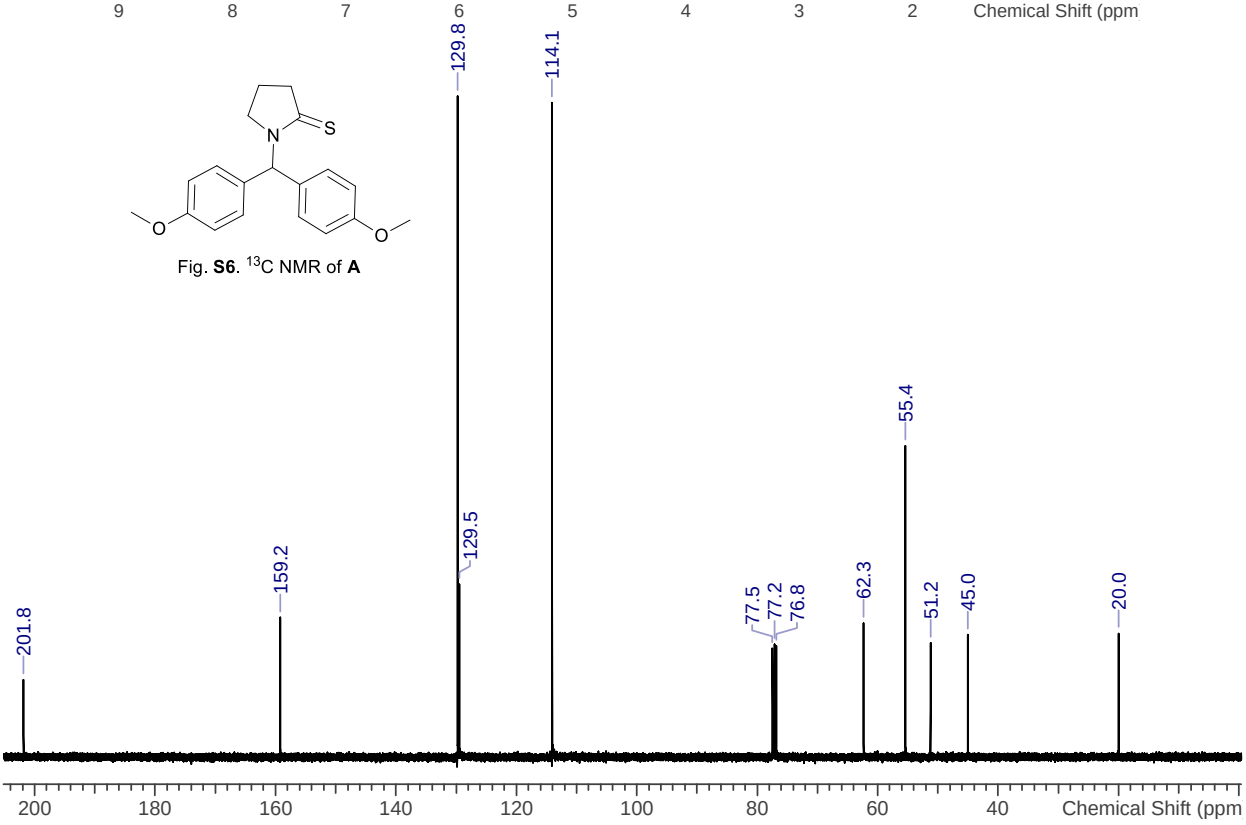


Fig. **S6**. ^{13}C NMR of **A**

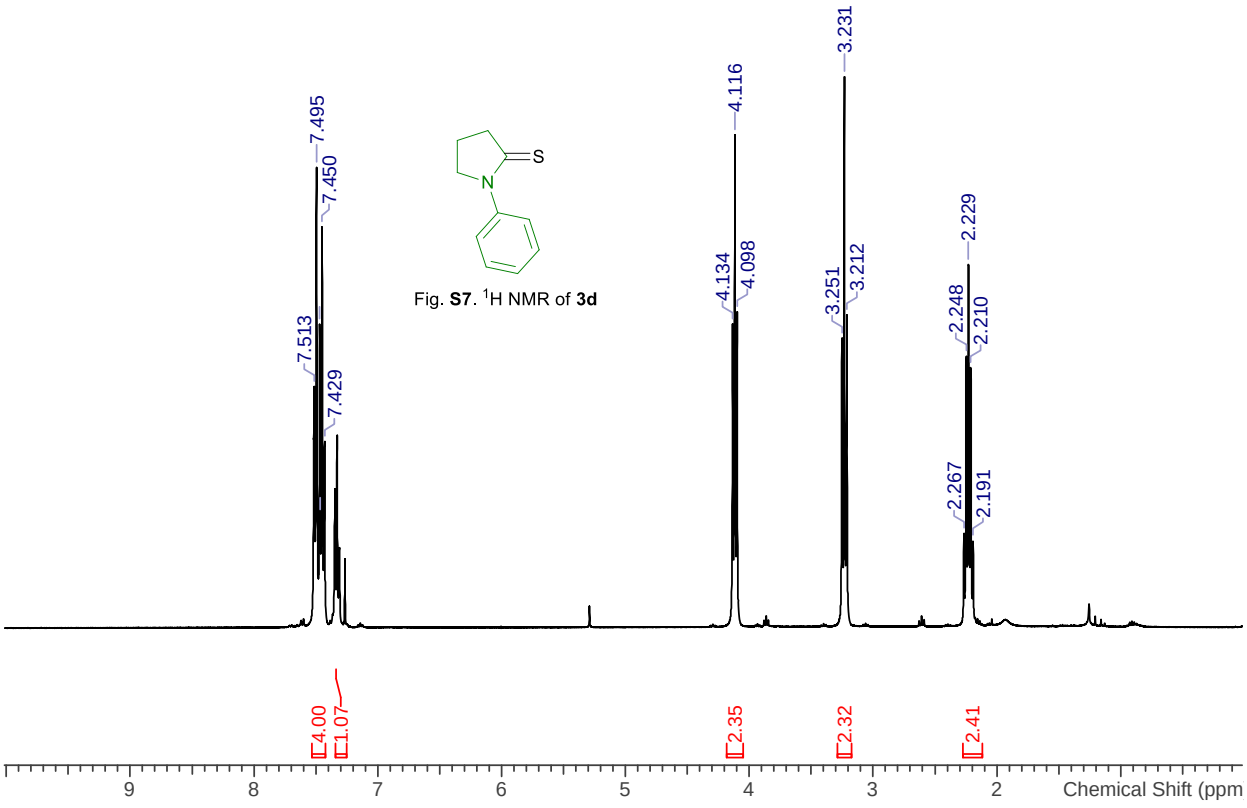


Fig. **S7**. ^{1}H NMR of **3d**

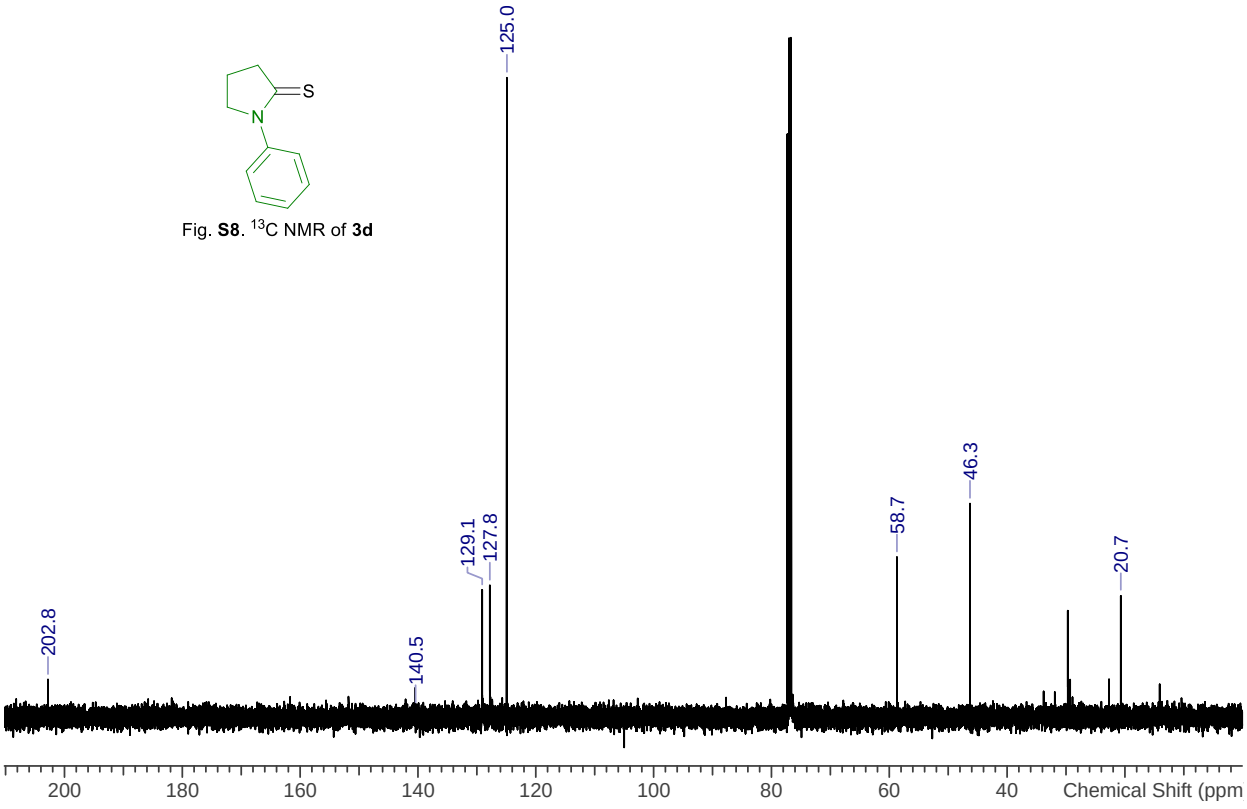


Fig. **S8**. ^{13}C NMR of **3d**

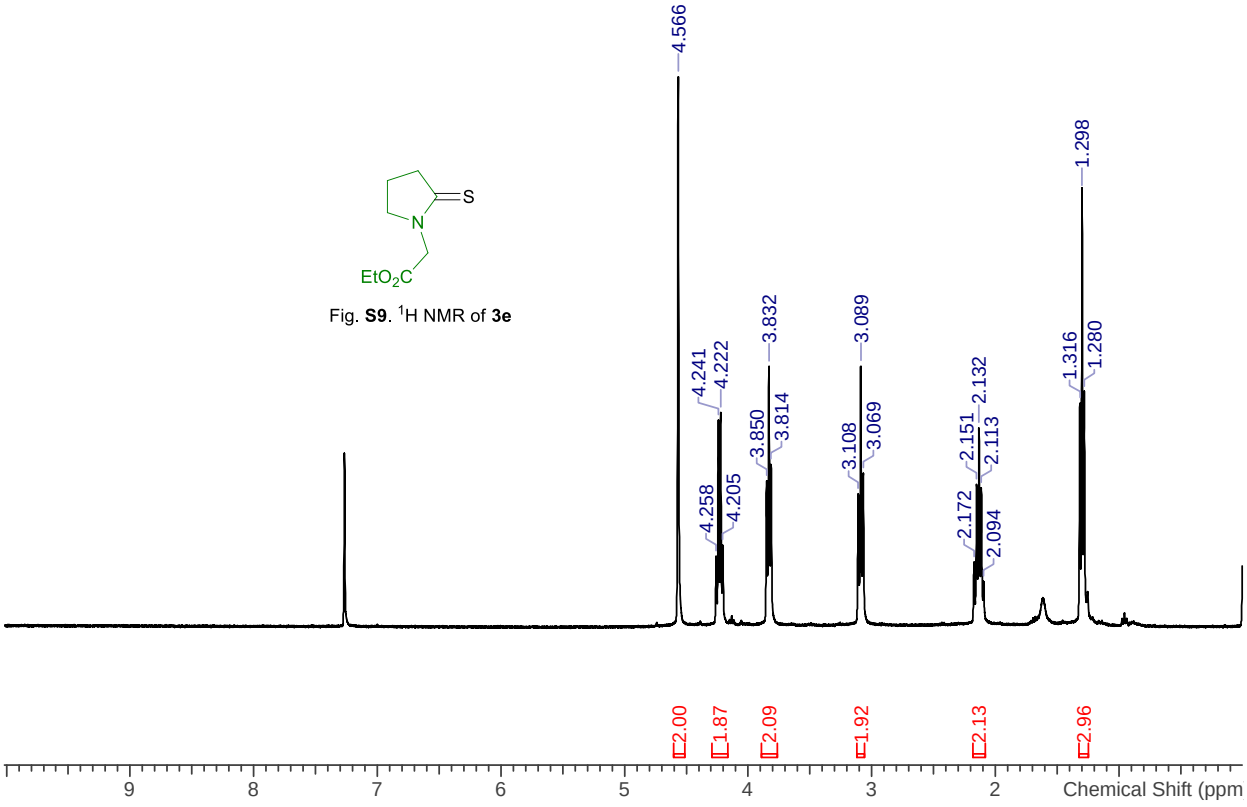


Fig. **S9**. ^{1}H NMR of **3e**

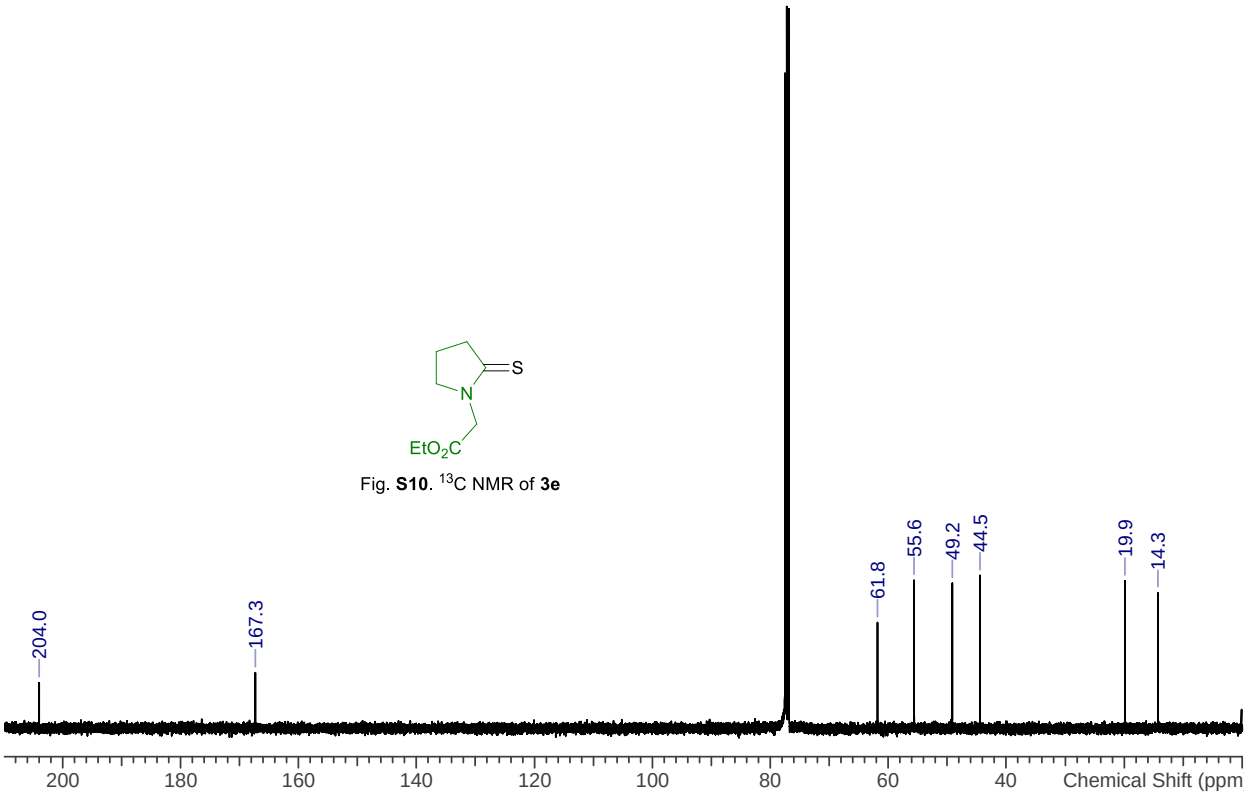


Fig. **S10**. ^{13}C NMR of **3e**

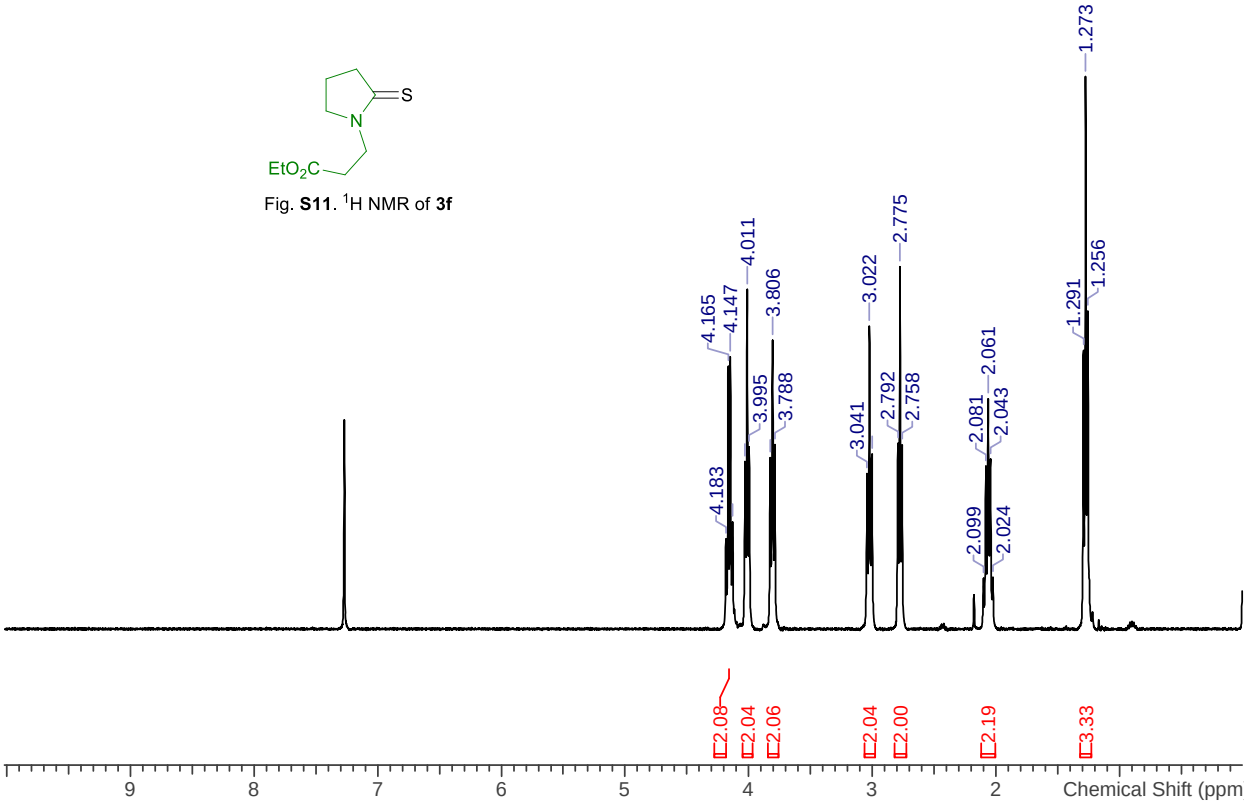


Fig. **S11**. ^{1}H NMR of **3f**

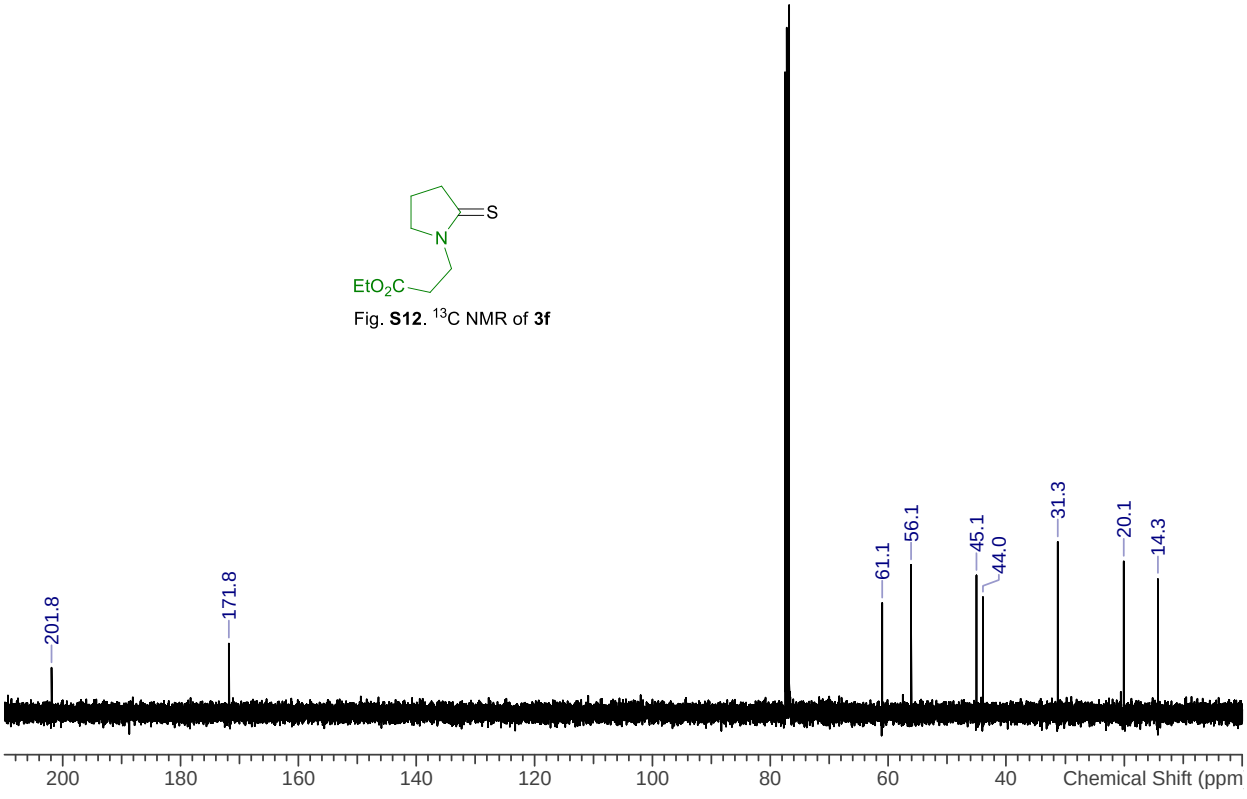


Fig. **S12**. ^{13}C NMR of **3f**

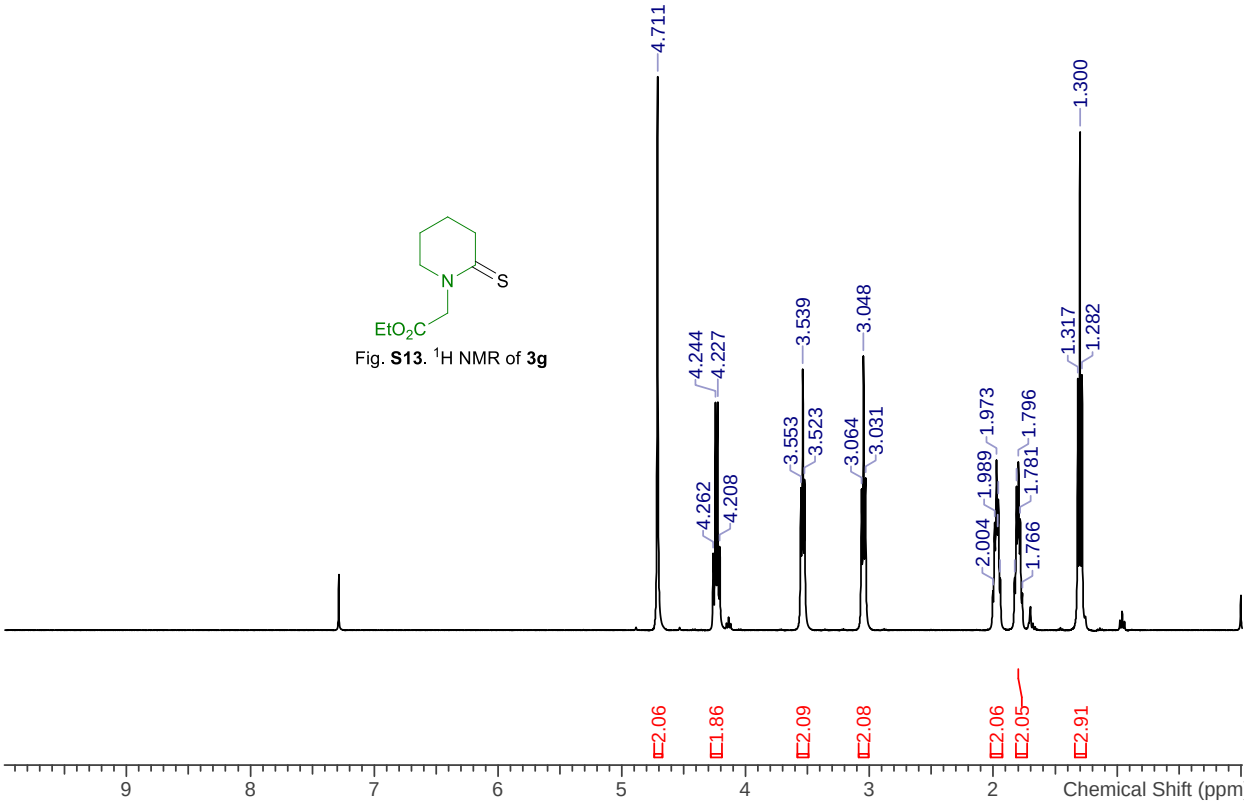


Fig. **S13**. ^{1}H NMR of **3g**

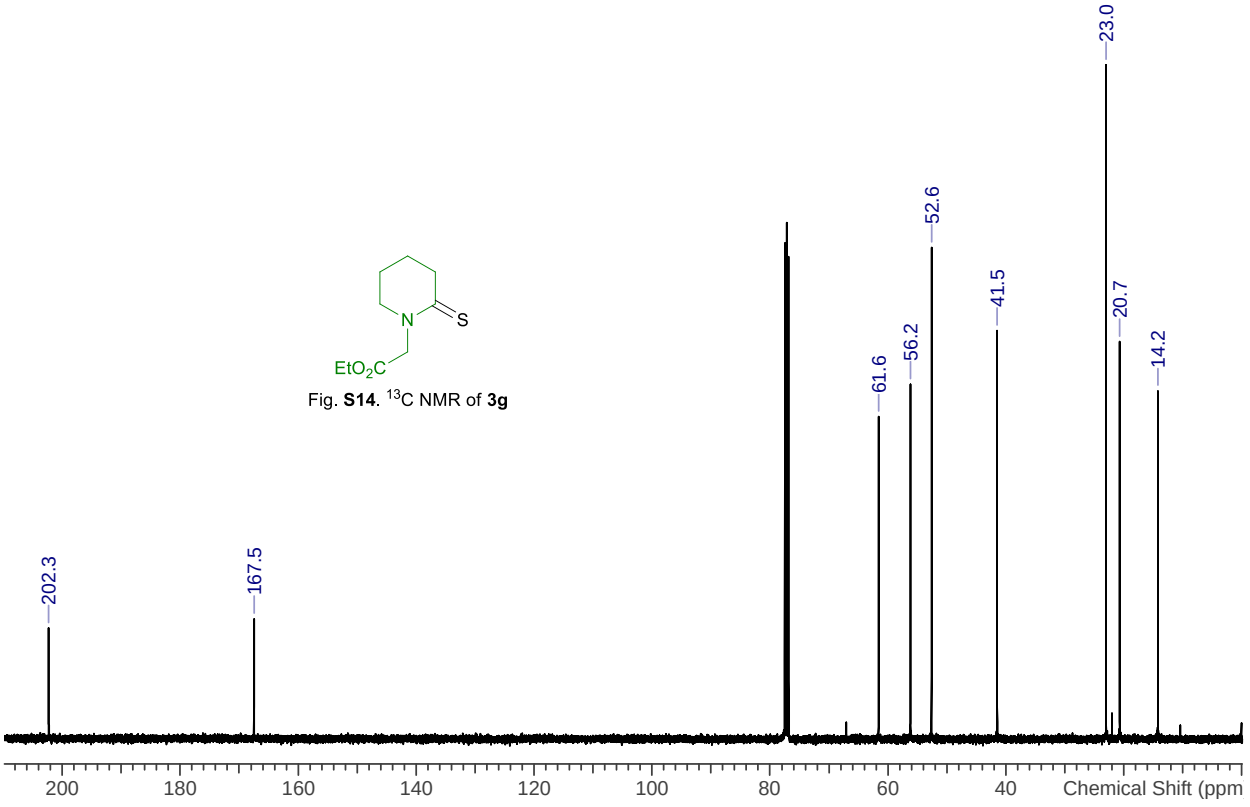


Fig. **S14**. ^{13}C NMR of **3g**

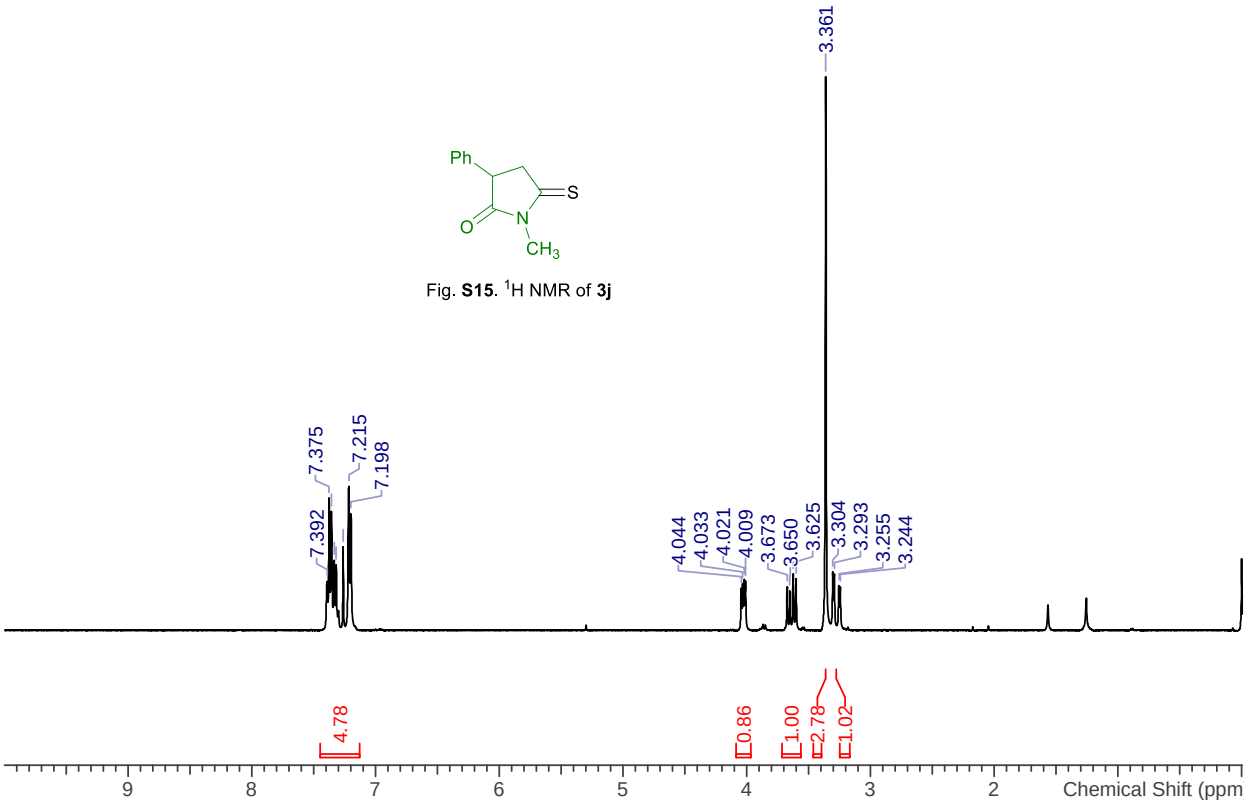


Fig. **S15**. ^{1}H NMR of **3j**

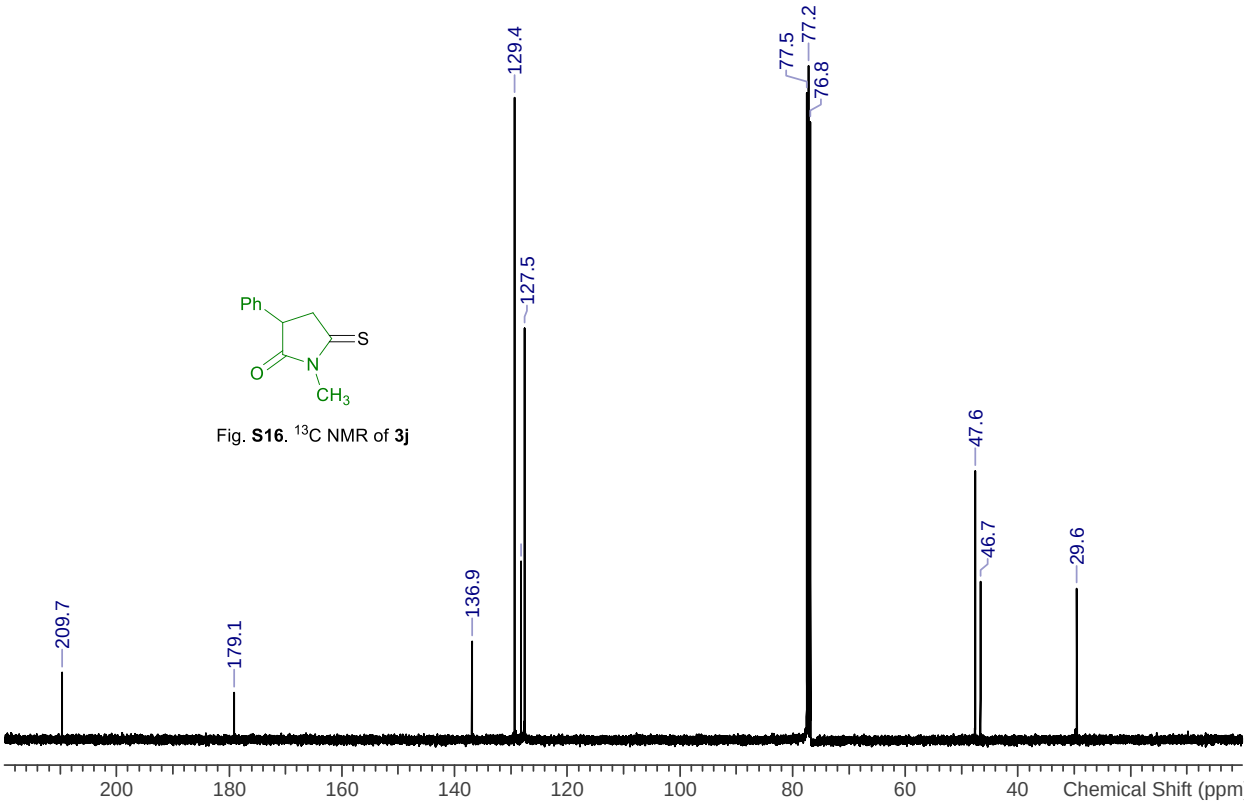


Fig. **S16**. ^{13}C NMR of **3j**

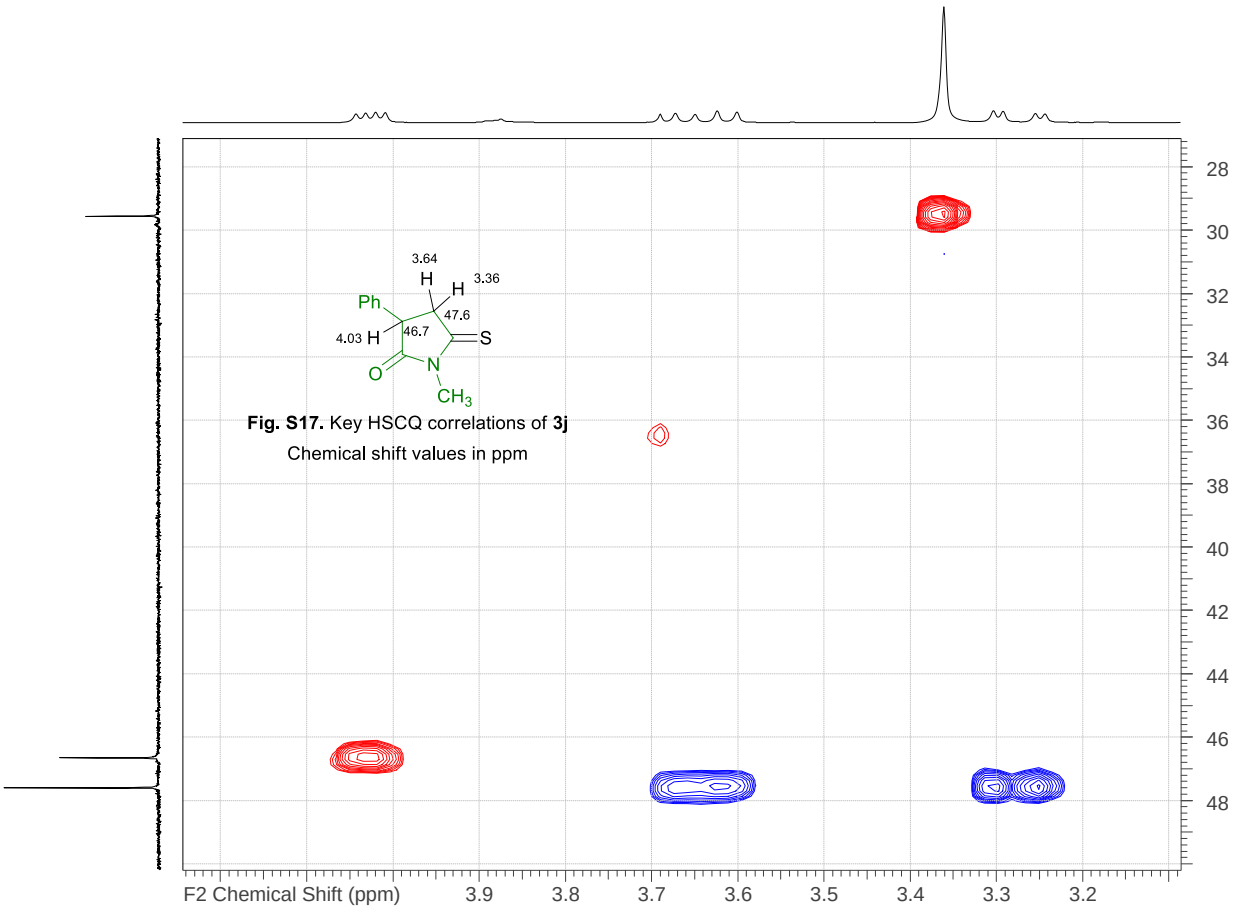


Fig. S17. Key HSCQ correlations of **3j**
Chemical shift values in ppm

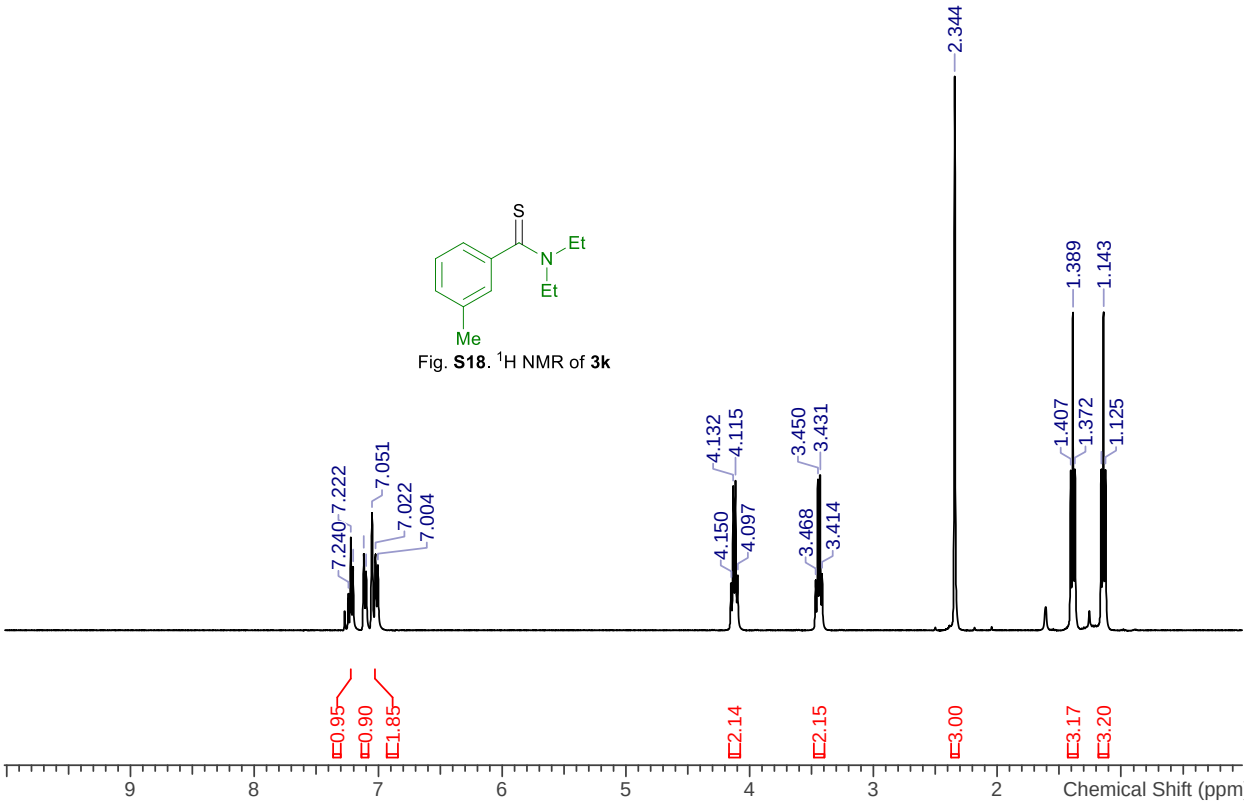


Fig. **S18**. ^{1}H NMR of **3k**

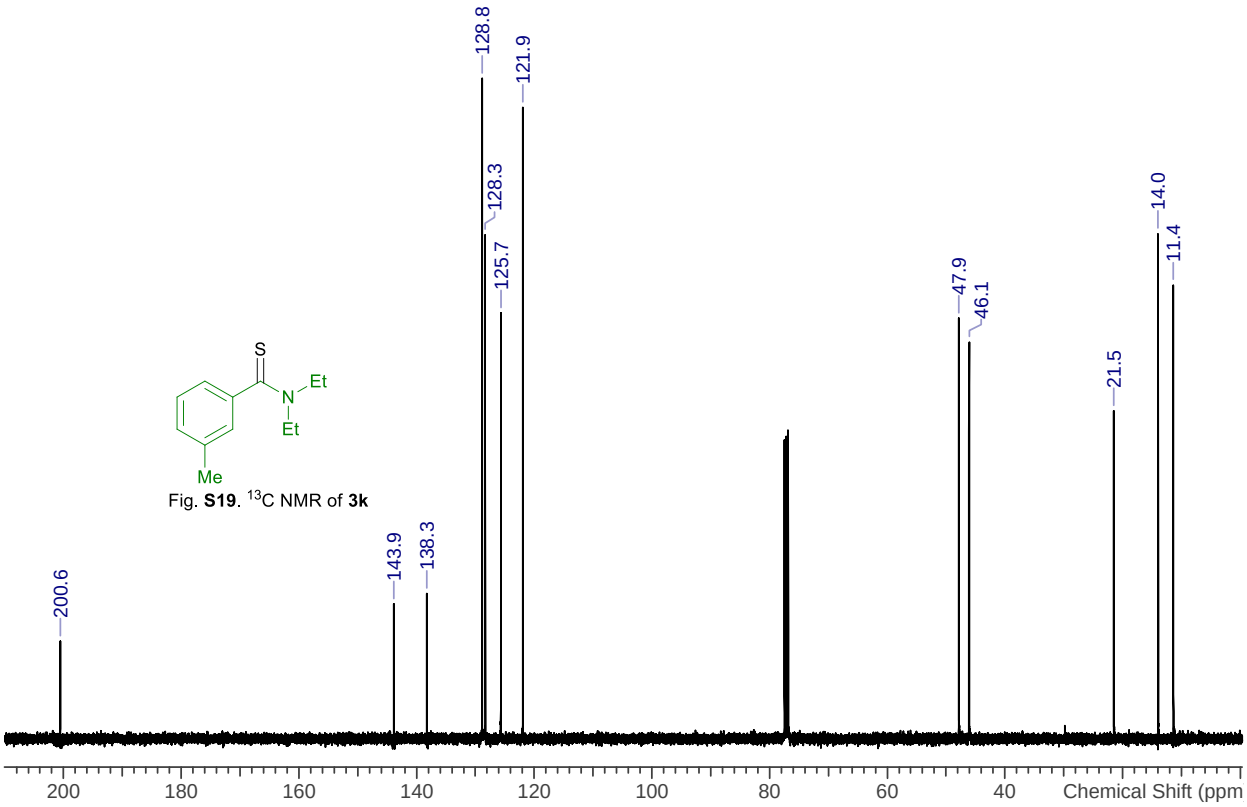


Fig. **S19**. ^{13}C NMR of **3k**

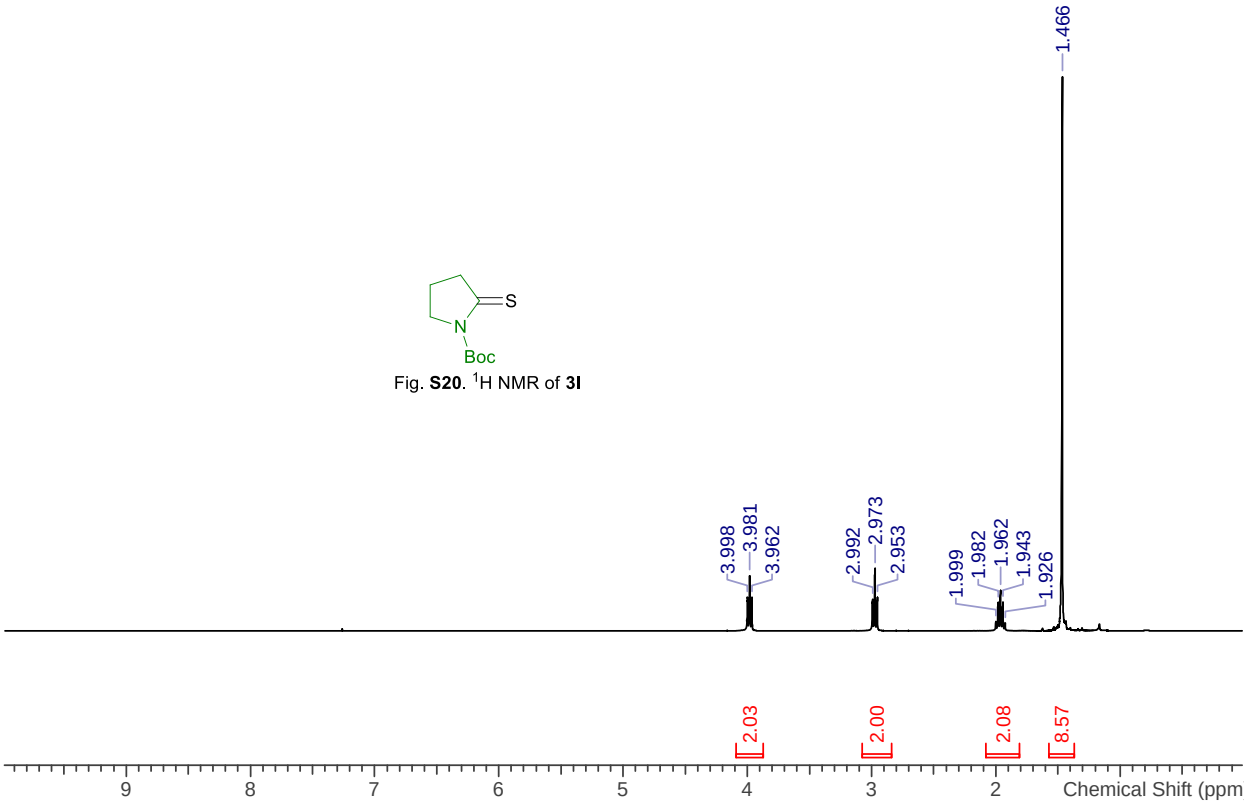


Fig. **S20**. ^{1}H NMR of **3l**

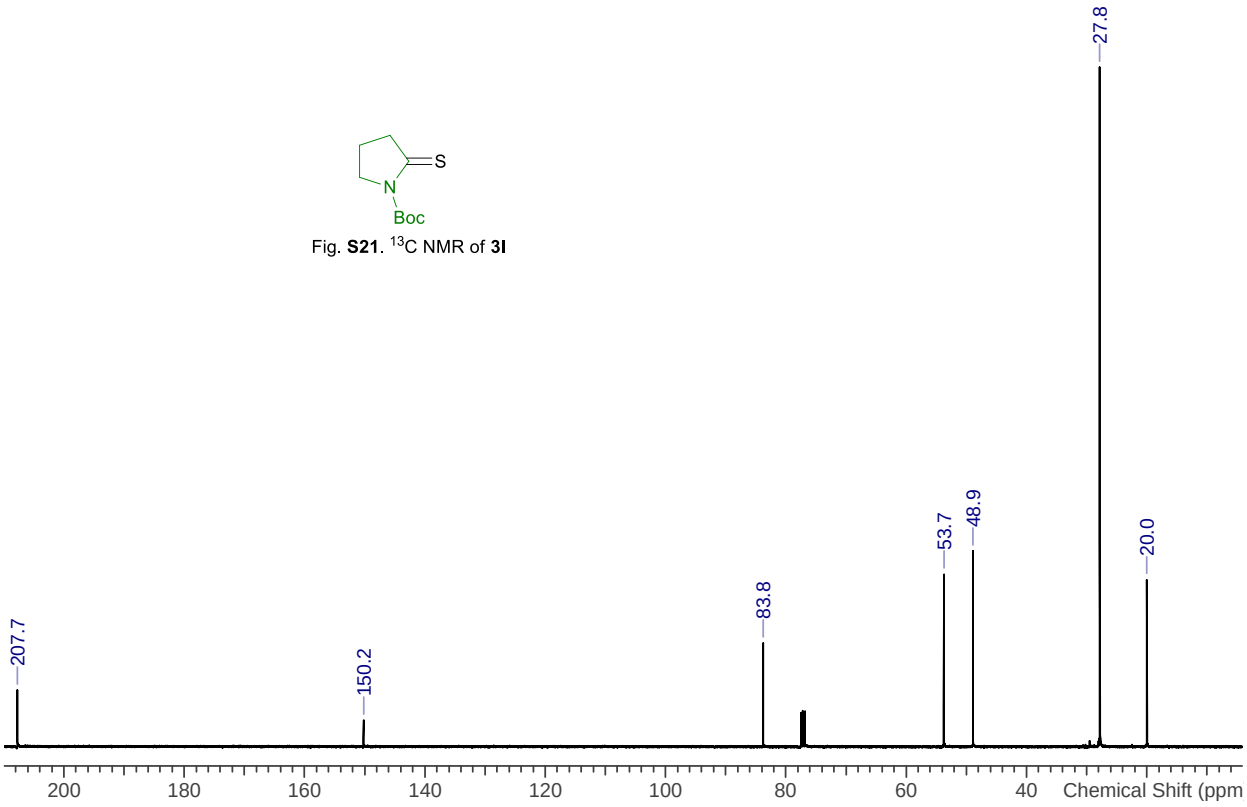


Fig. **S21**. ^{13}C NMR of **3l**

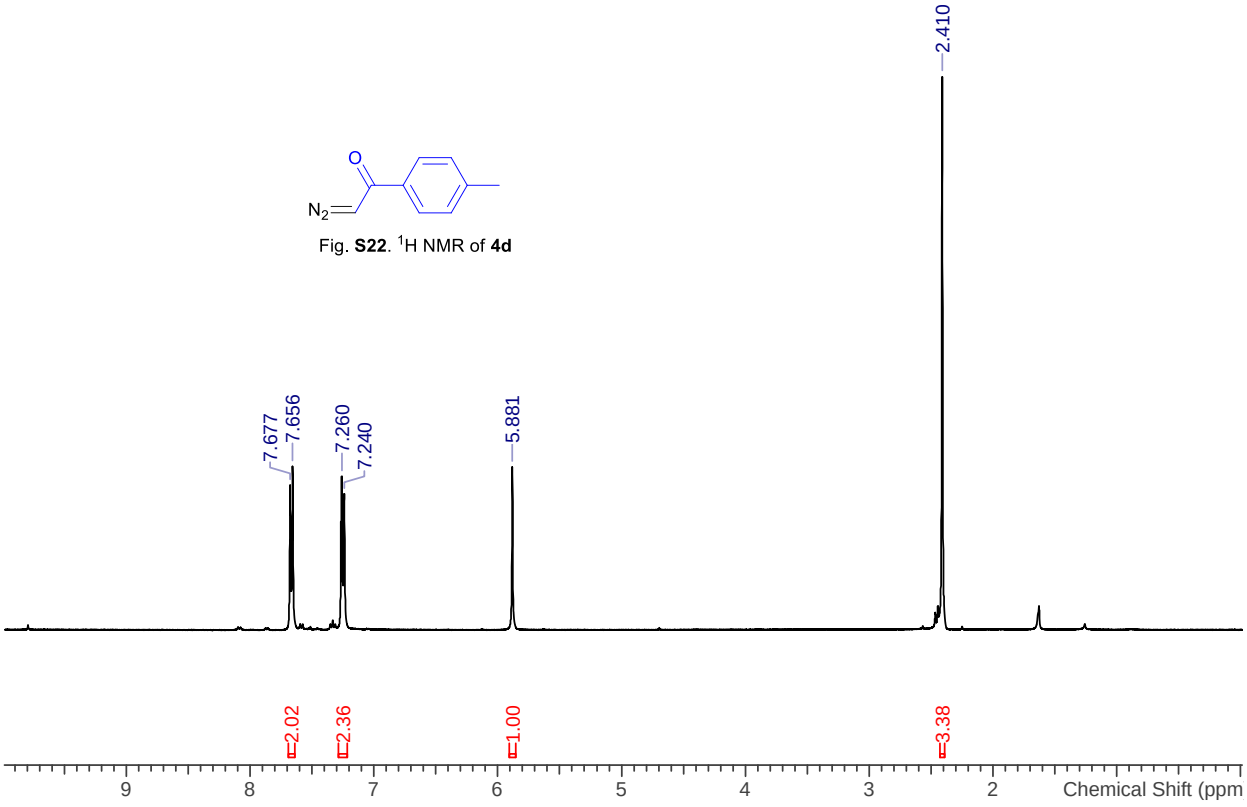


Fig. **S22**. ^{1}H NMR of **4d**

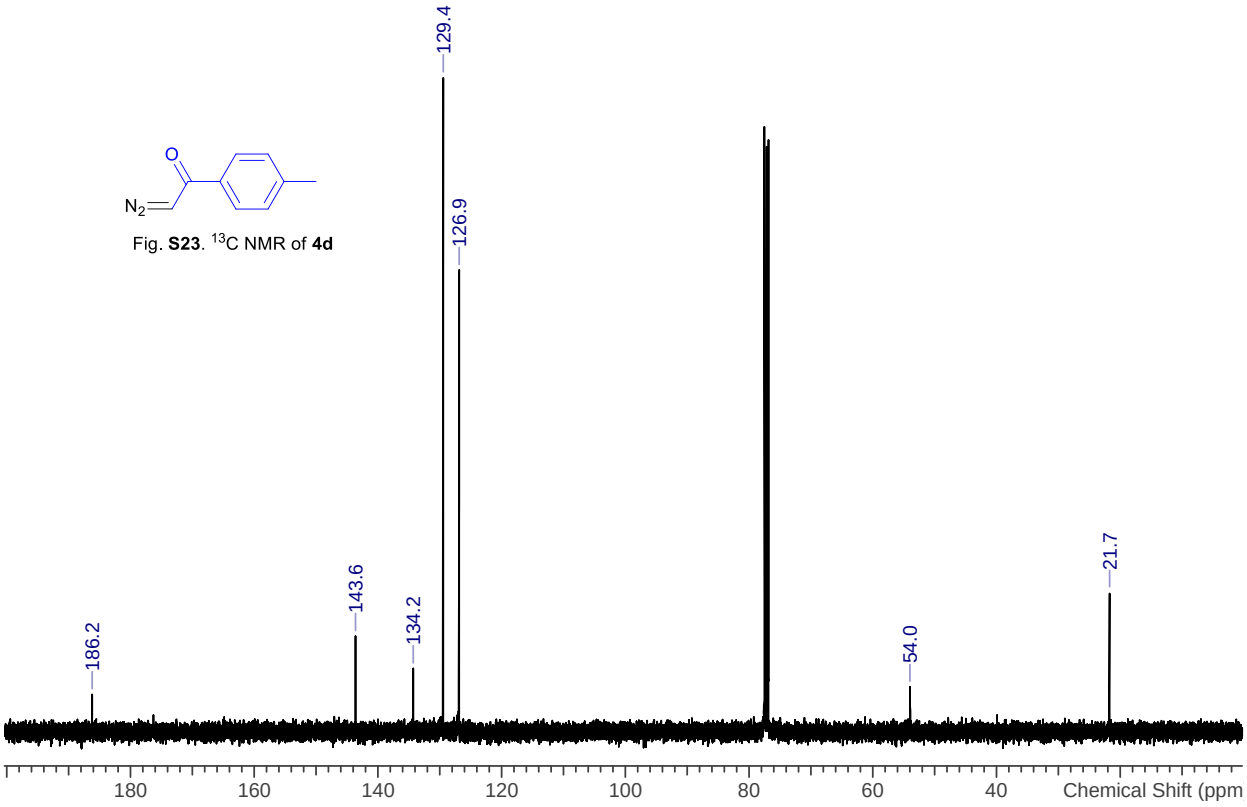


Fig. **S23**. ^{13}C NMR of **4d**

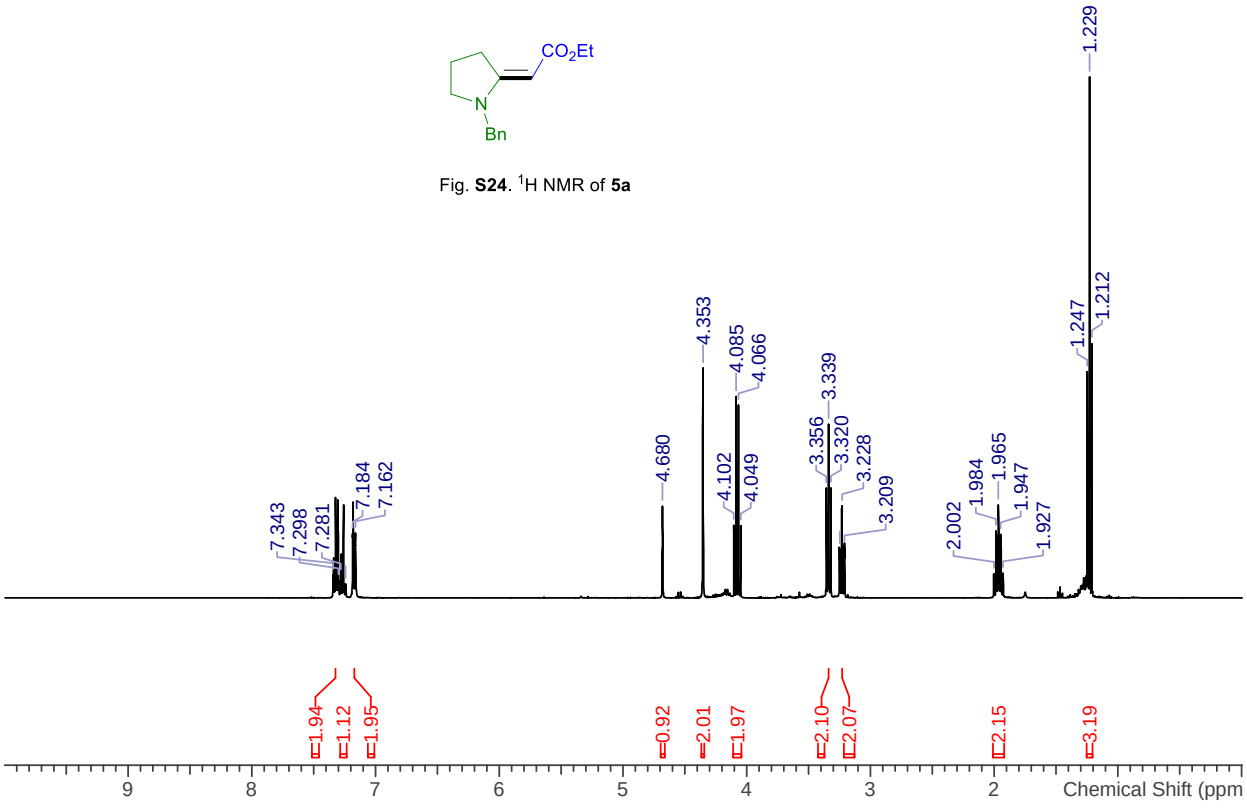


Fig. **S24**. ^{1}H NMR of **5a**

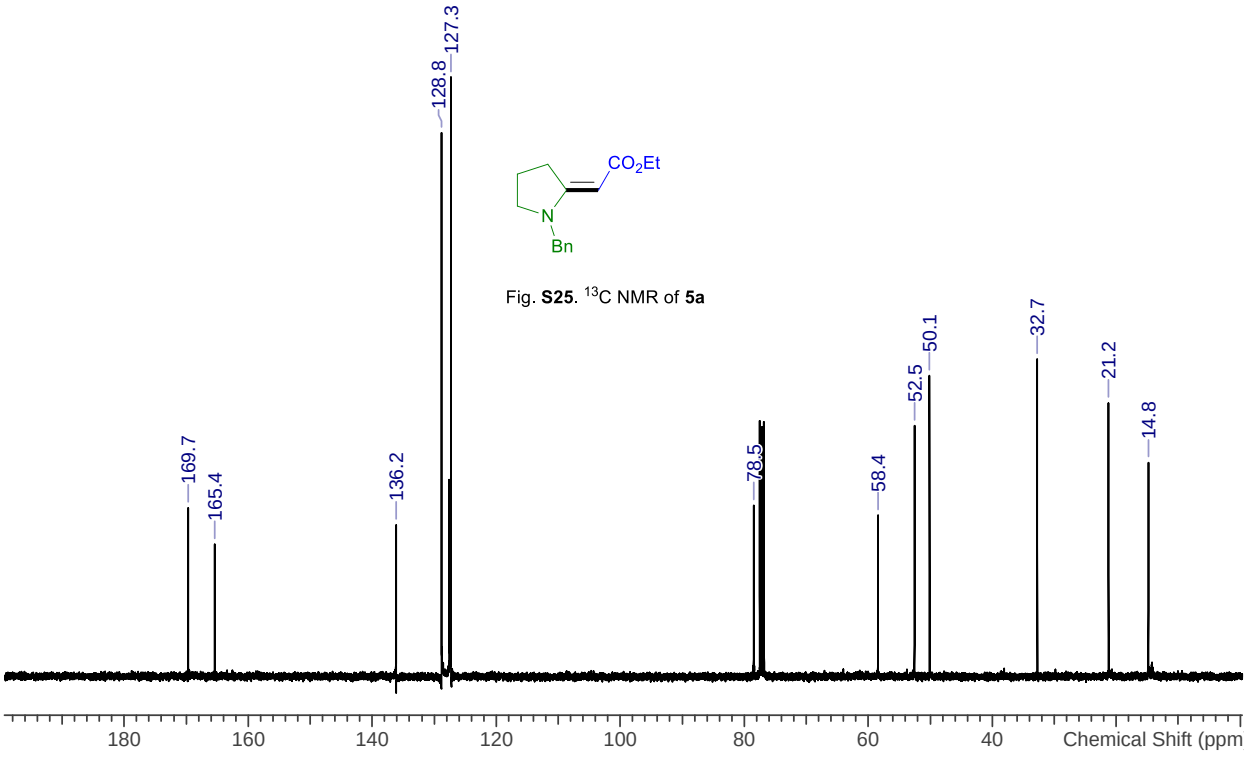


Fig. **S25**. ^{13}C NMR of **5a**

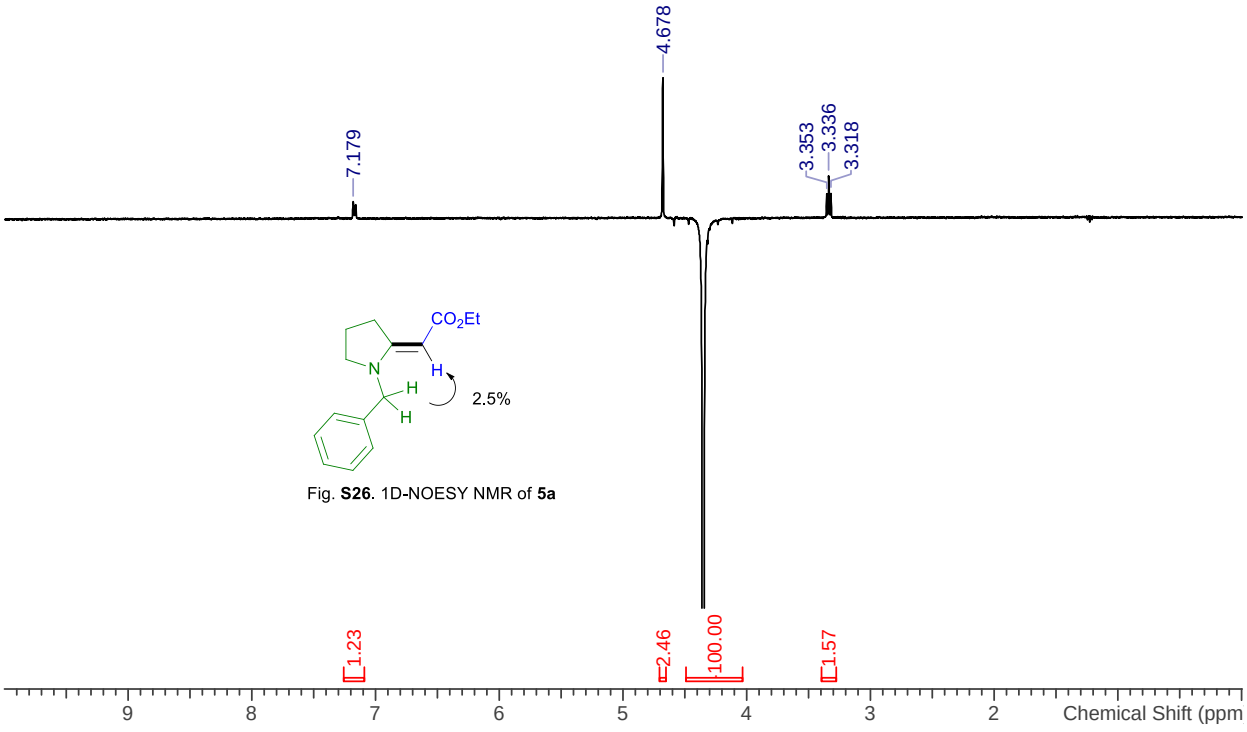


Fig. **S26**. 1D-NOESY NMR of **5a**

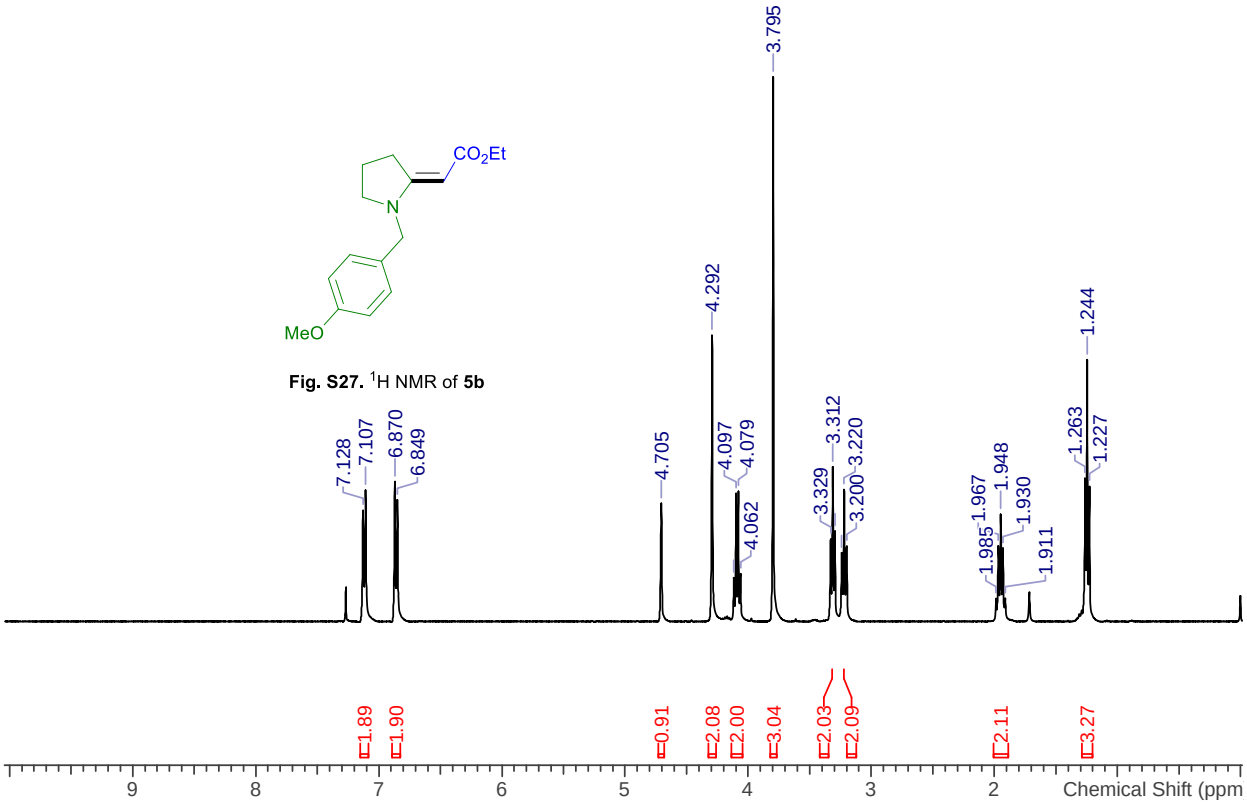


Fig. S27. ^{1}H NMR of **5b**

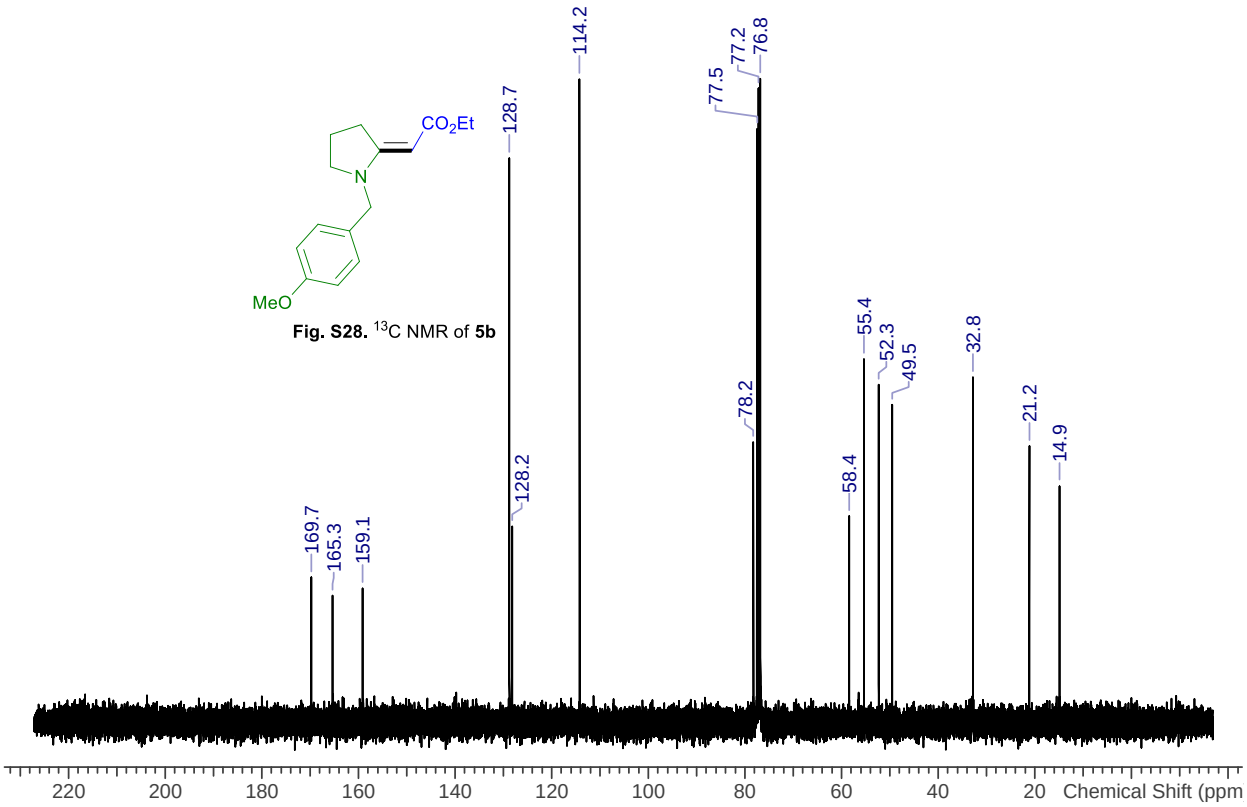


Fig. S28. ^{13}C NMR of **5b**

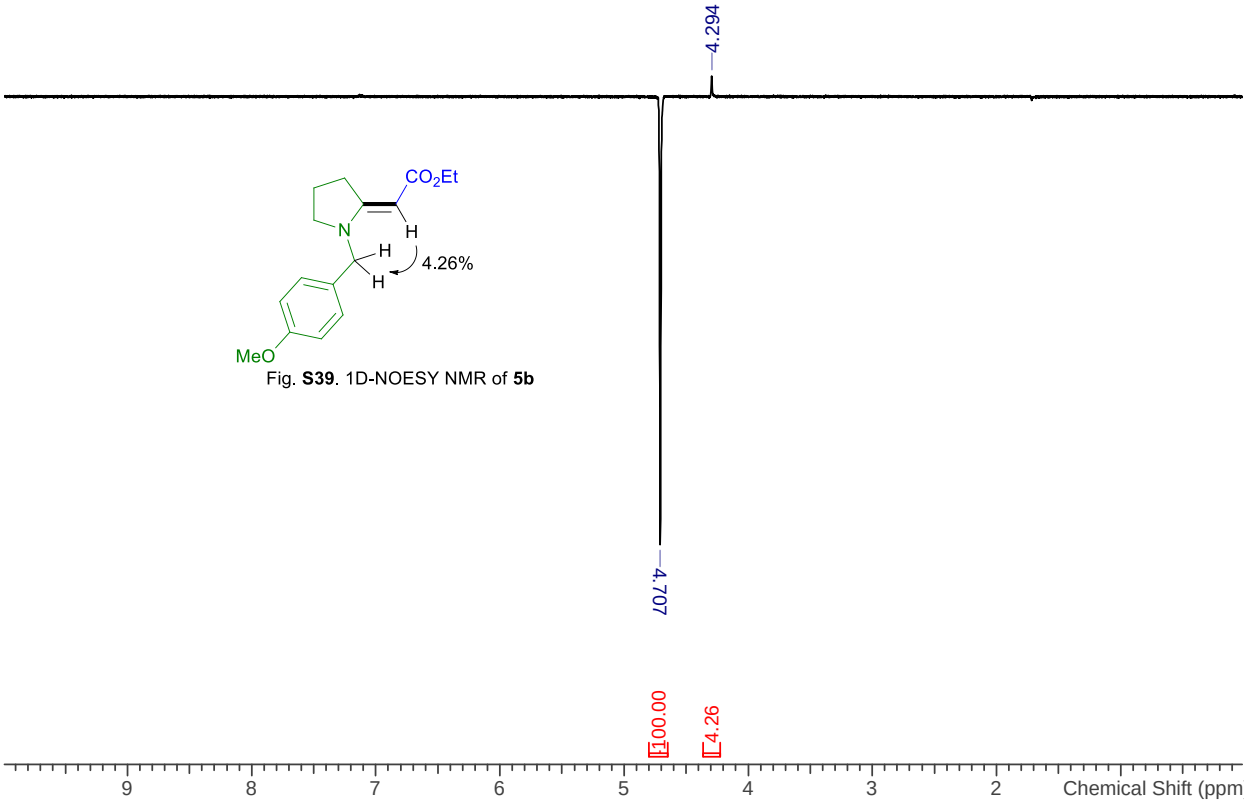


Fig. **S39**. 1D-NOESY NMR of **5b**

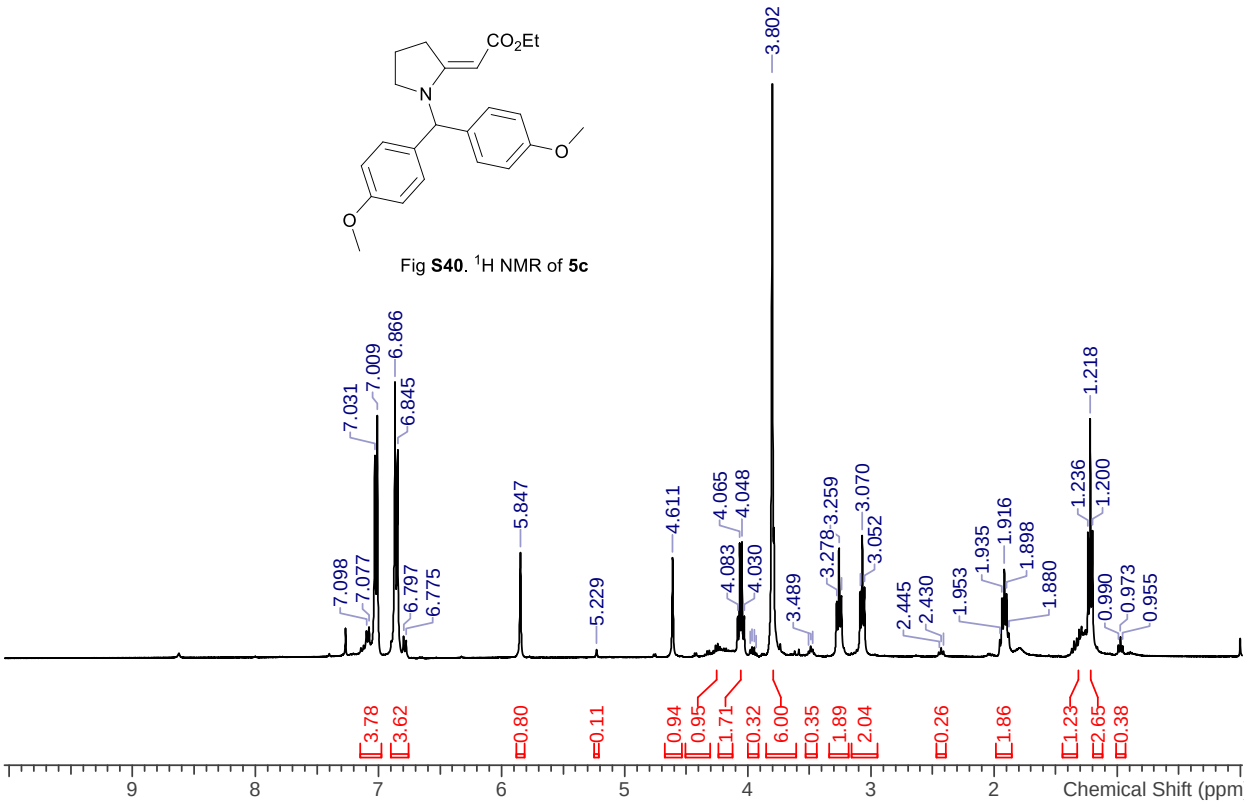


Fig **S40**. ^{1}H NMR of **5c**

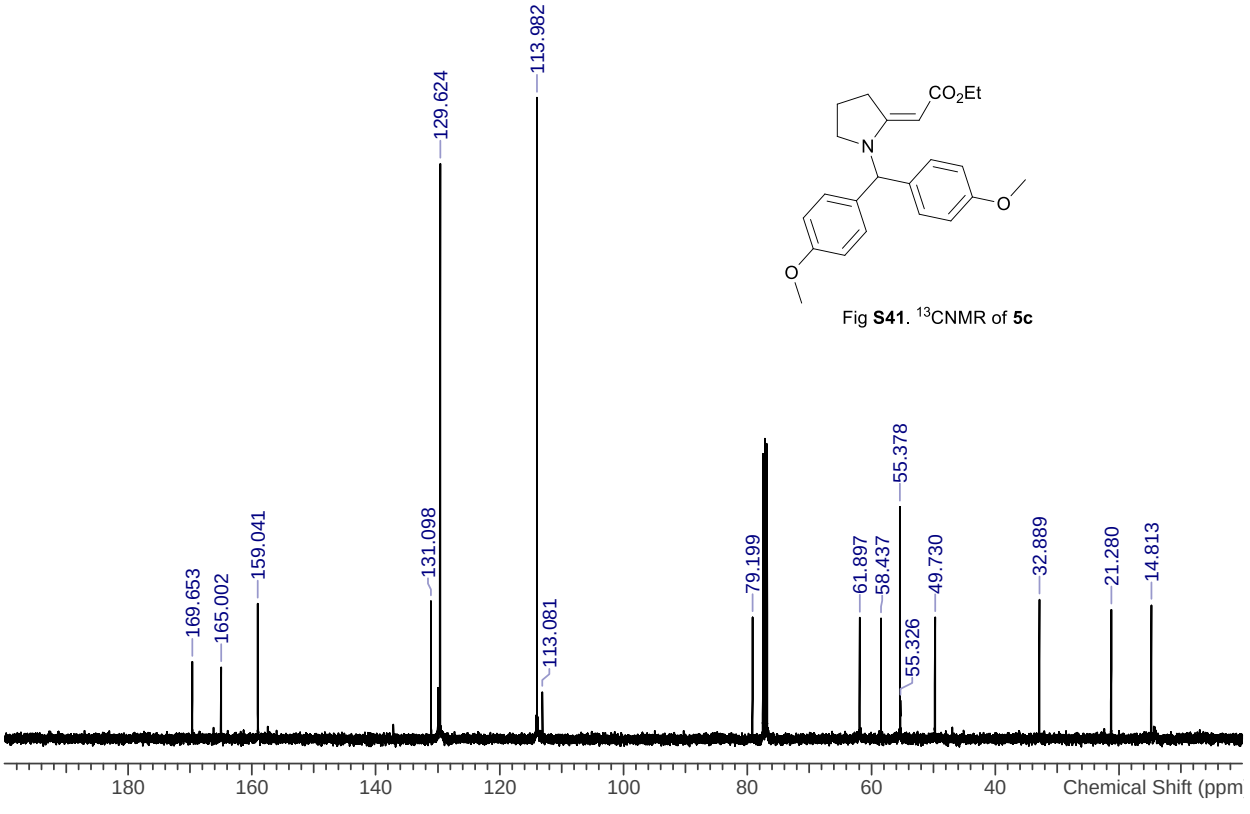


Fig **S41**. ^{13}CNMR of **5c**

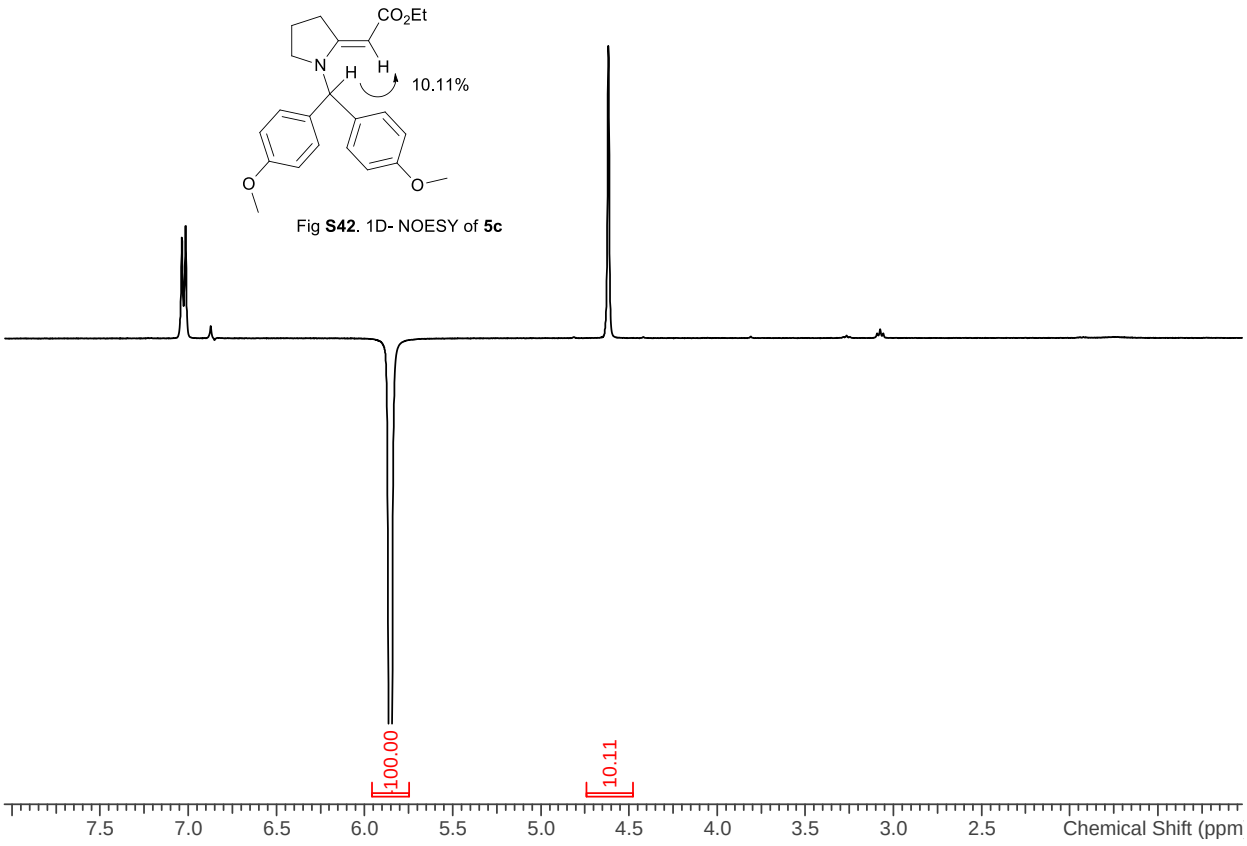


Fig **S42**. 1D- NOESY of **5c**

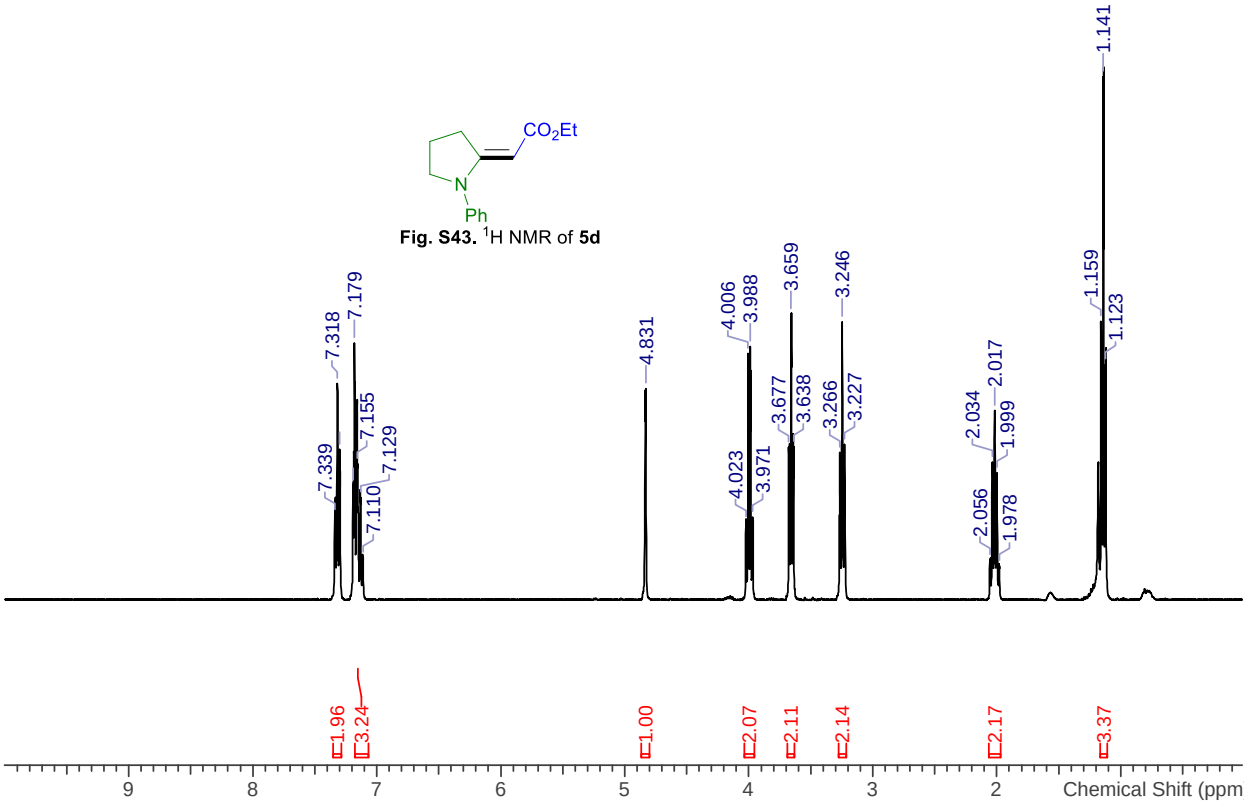


Fig. S43. ^{1}H NMR of **5d**

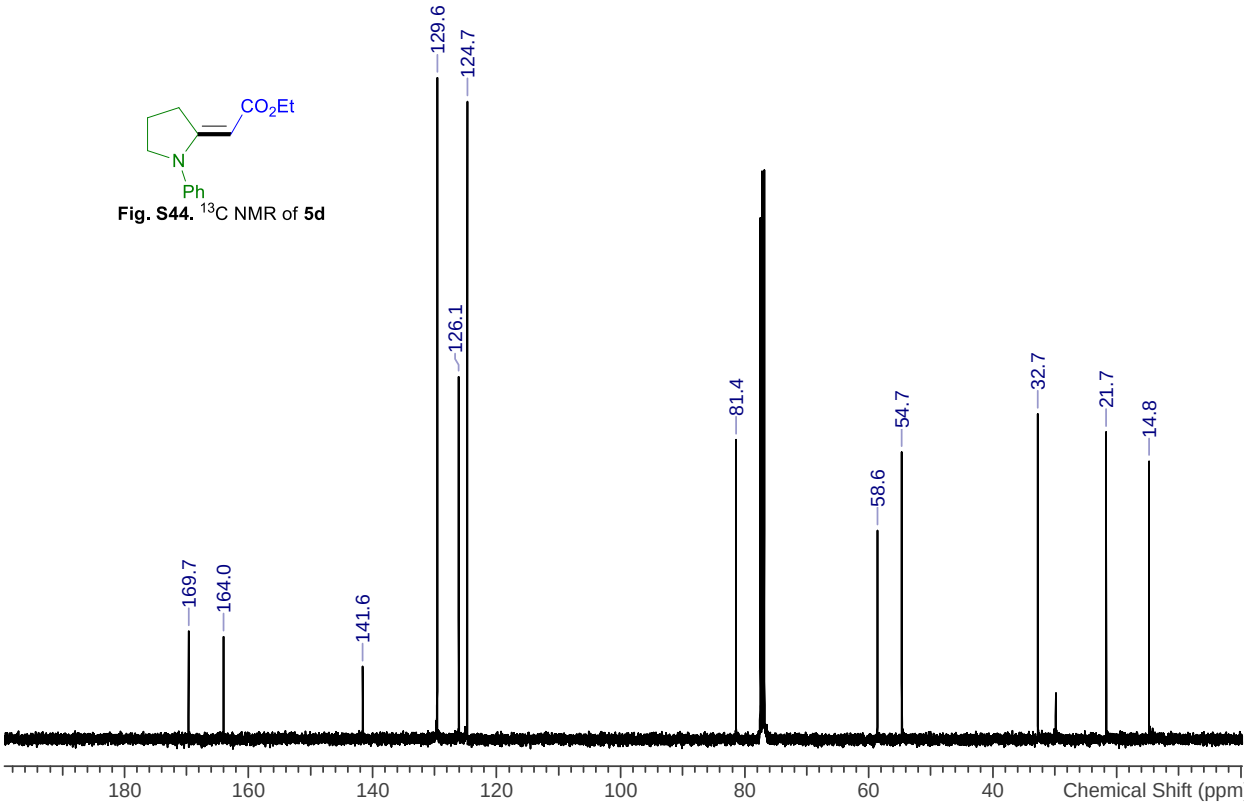


Fig. S44. ^{13}C NMR of **5d**

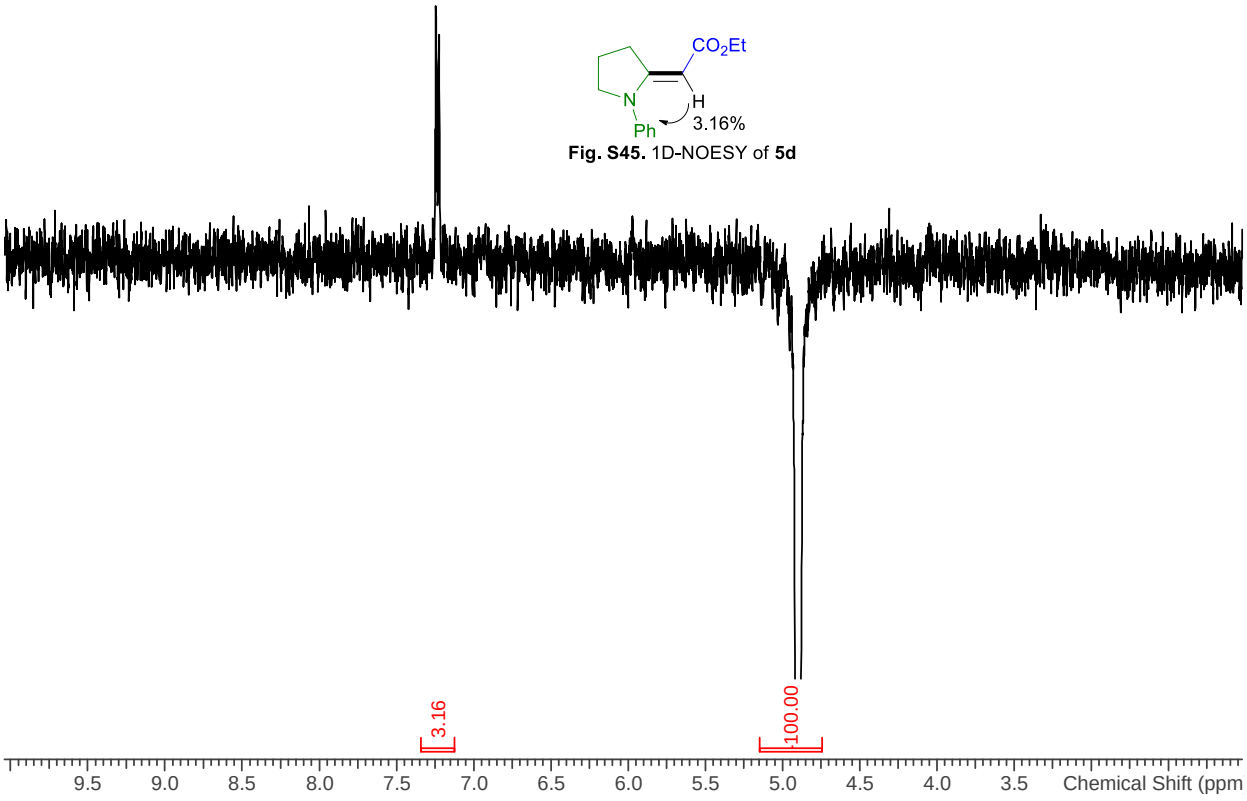


Fig. S45. 1D-NOESY of **5d**

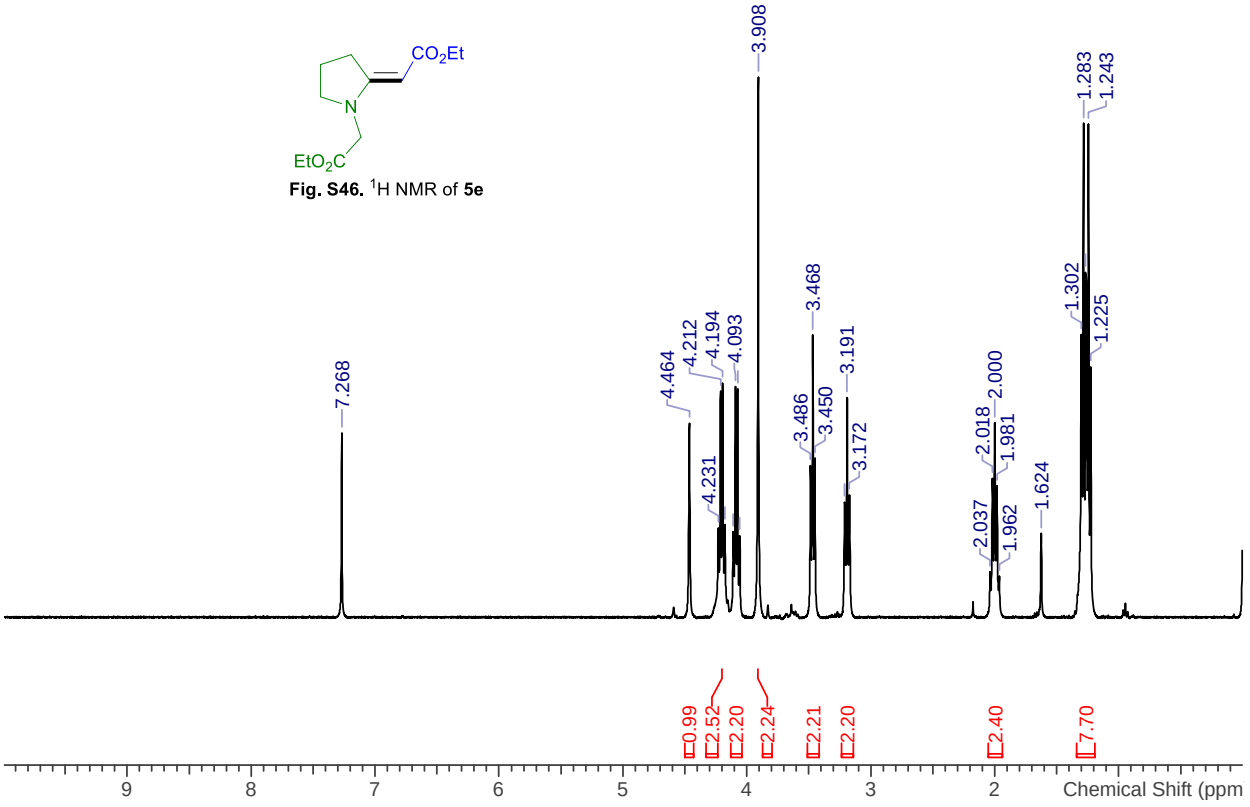


Fig. S46. ^{1}H NMR of **5e**

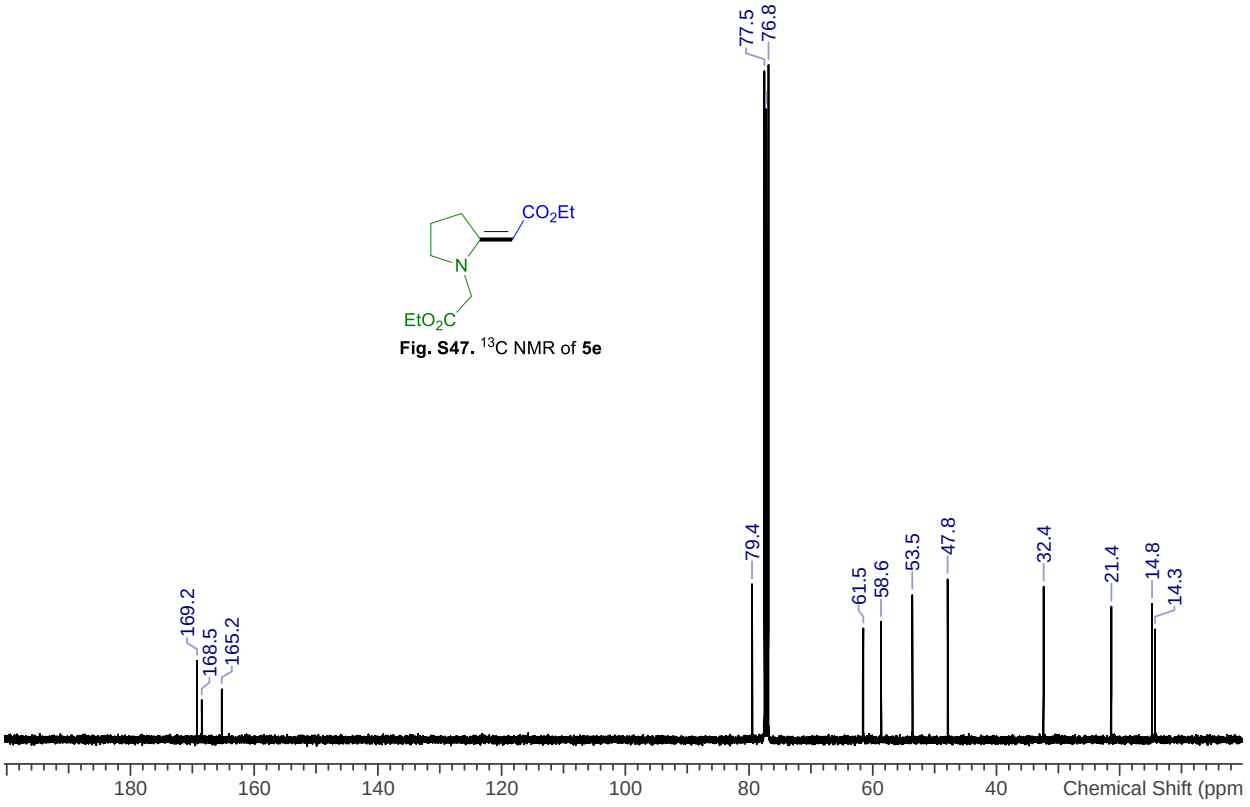


Fig. S47. ^{13}C NMR of **5e**

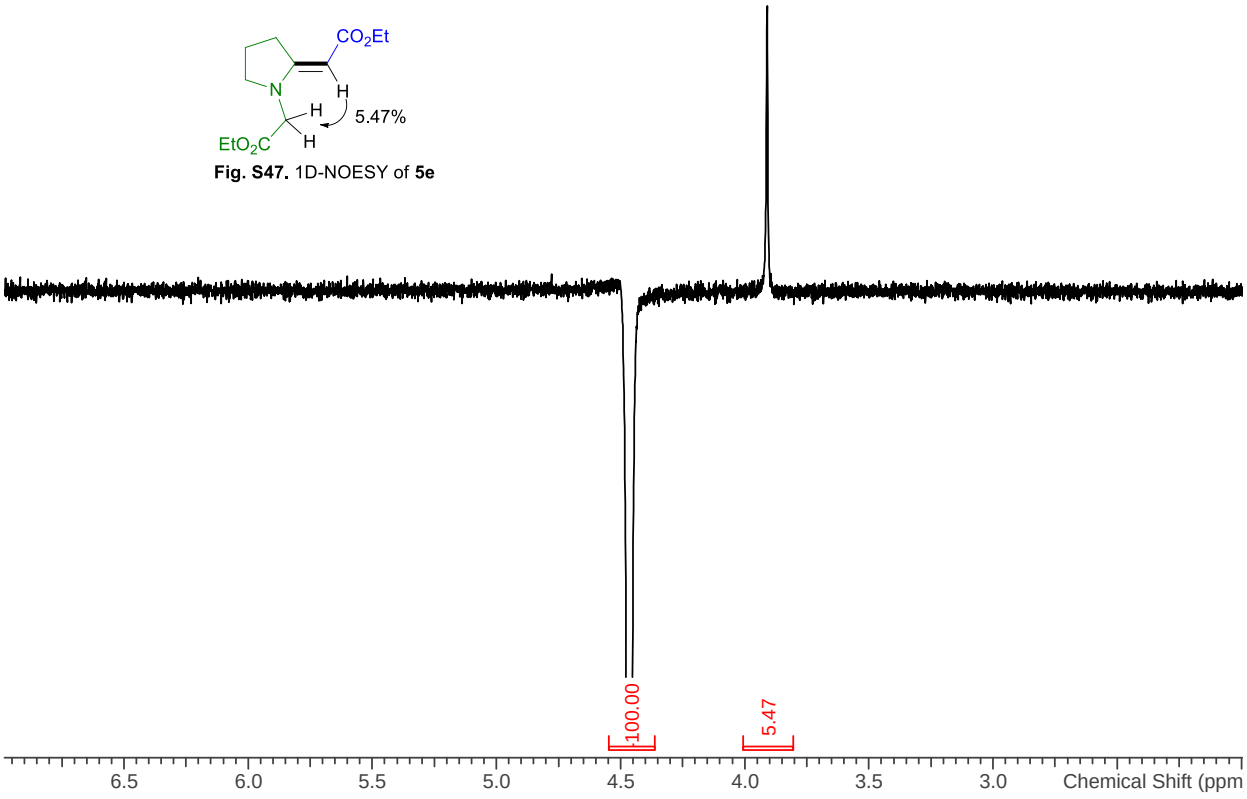


Fig. S47. 1D-NOESY of **5e**

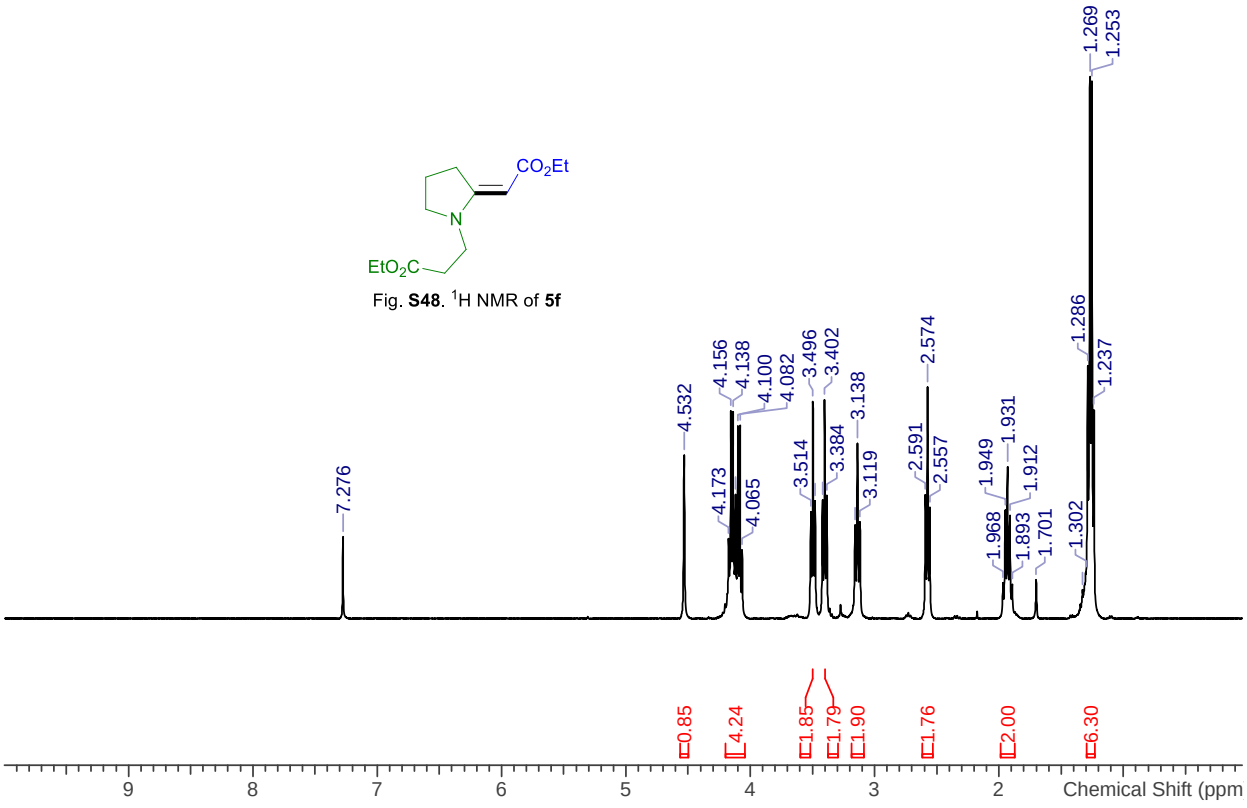


Fig. **S48**. ^{1}H NMR of **5f**

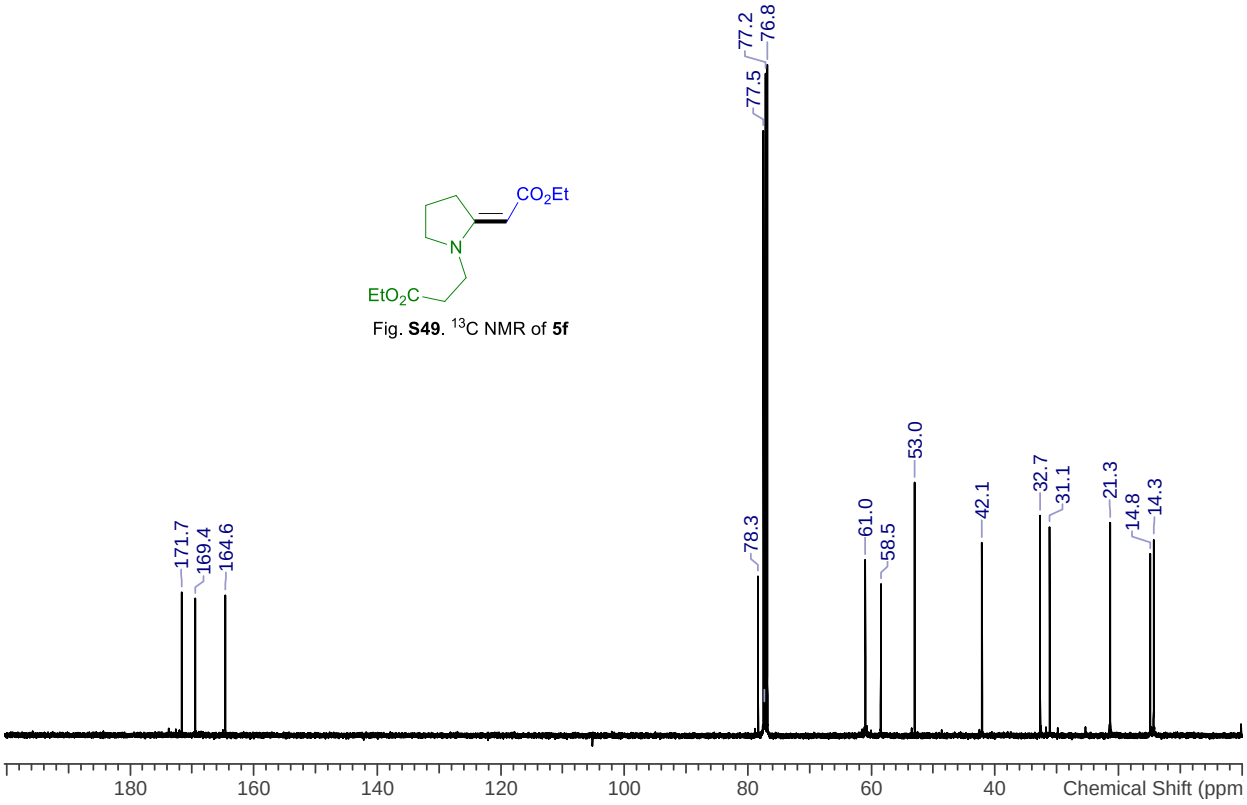


Fig. **S49**. ^{13}C NMR of **5f**

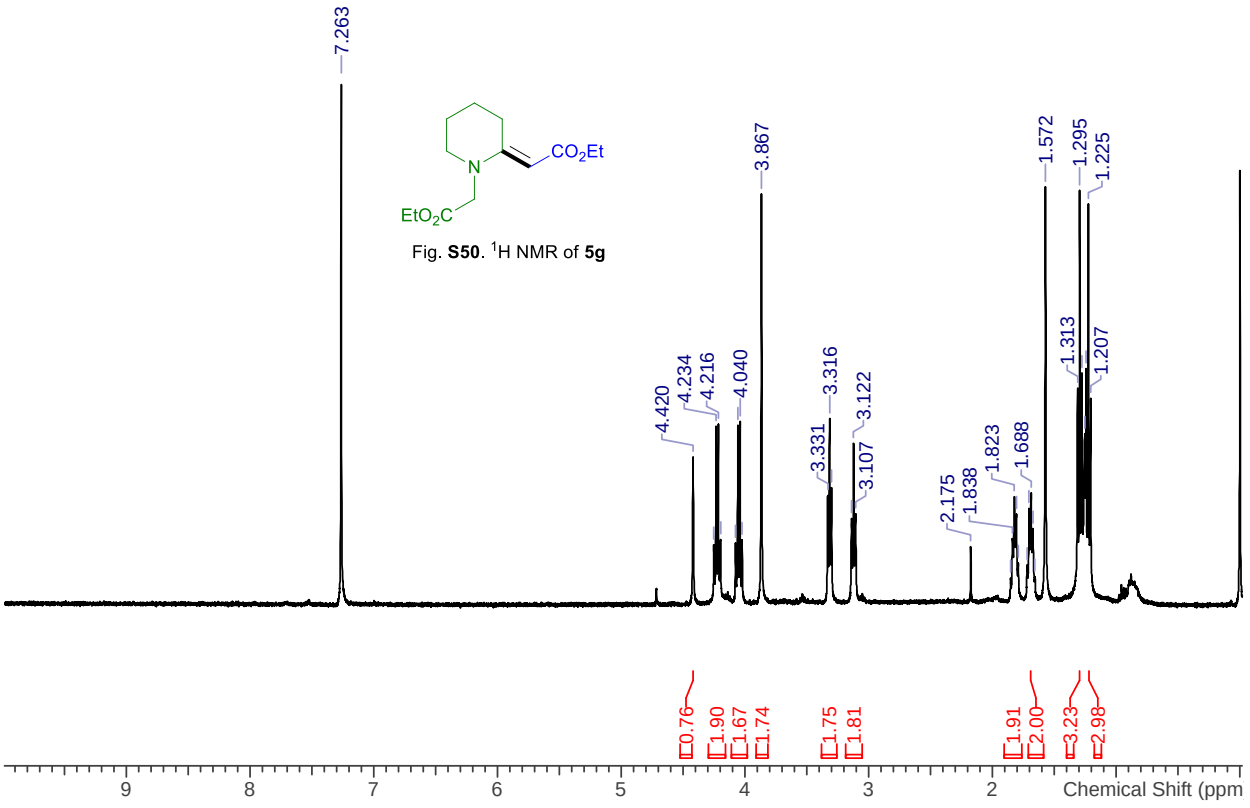


Fig. **S50**. ^{1}H NMR of **5g**

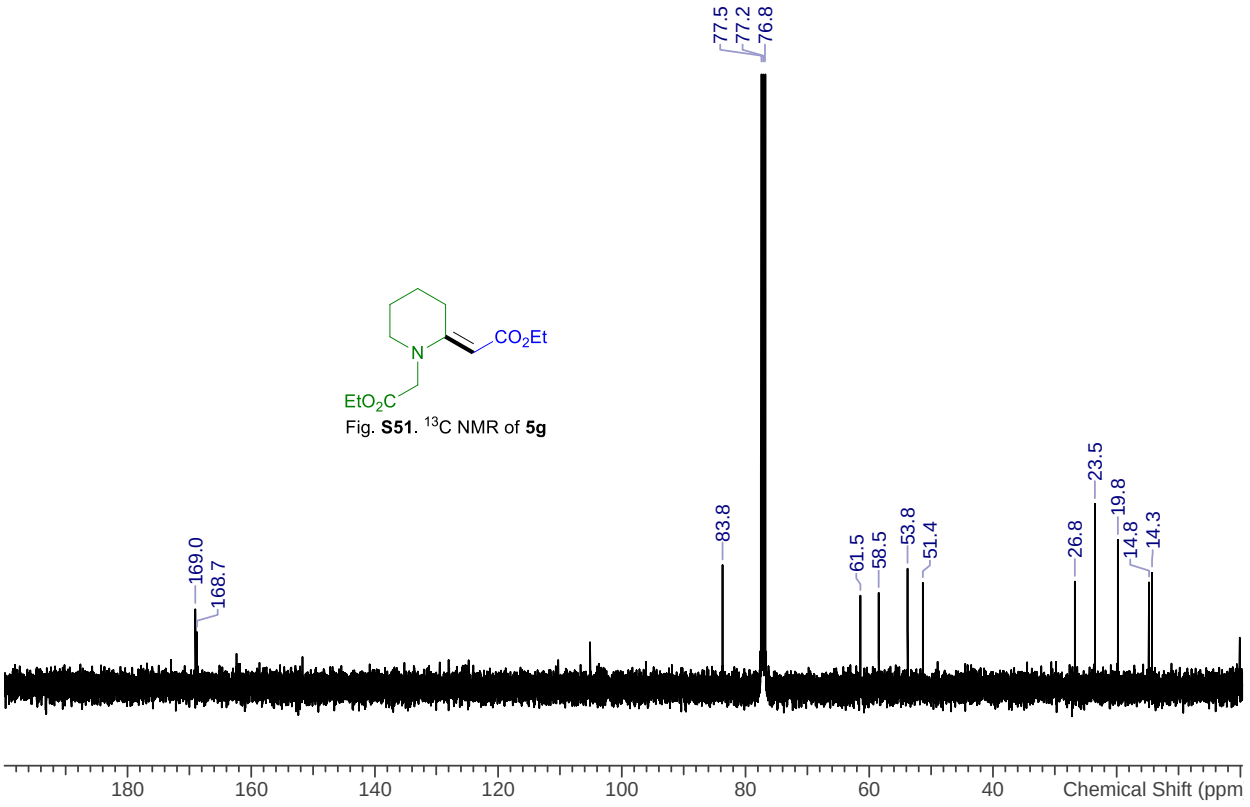


Fig. **S51**. ^{13}C NMR of **5g**

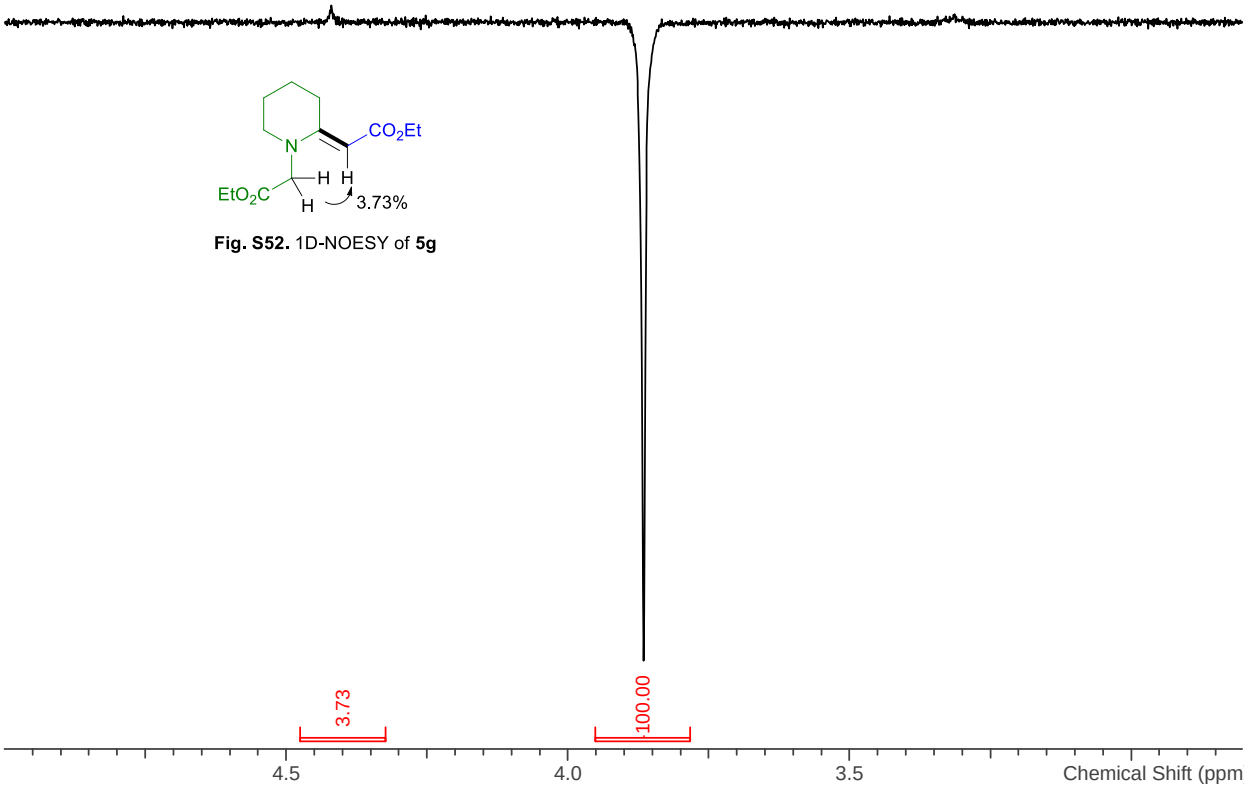


Fig. S52. 1D-NOESY of **5g**

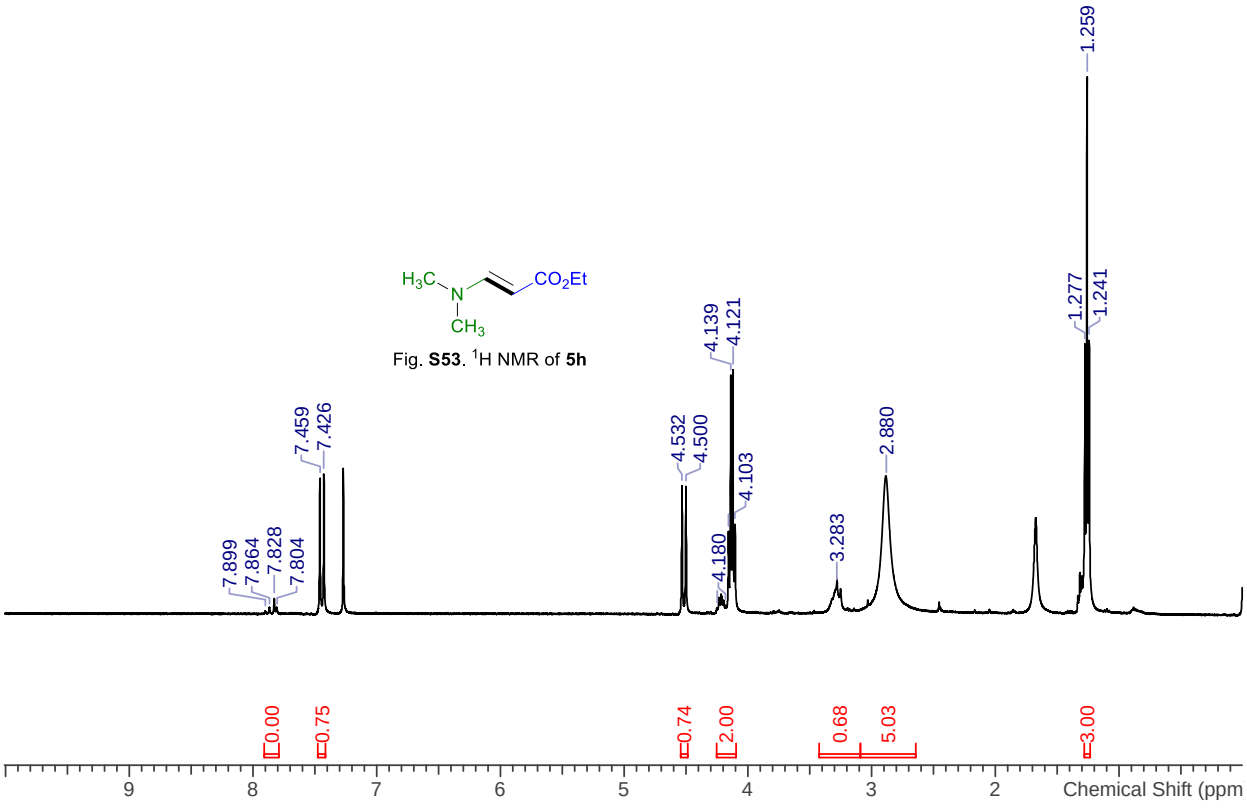


Fig. **S53**. ^{1}H NMR of **5h**

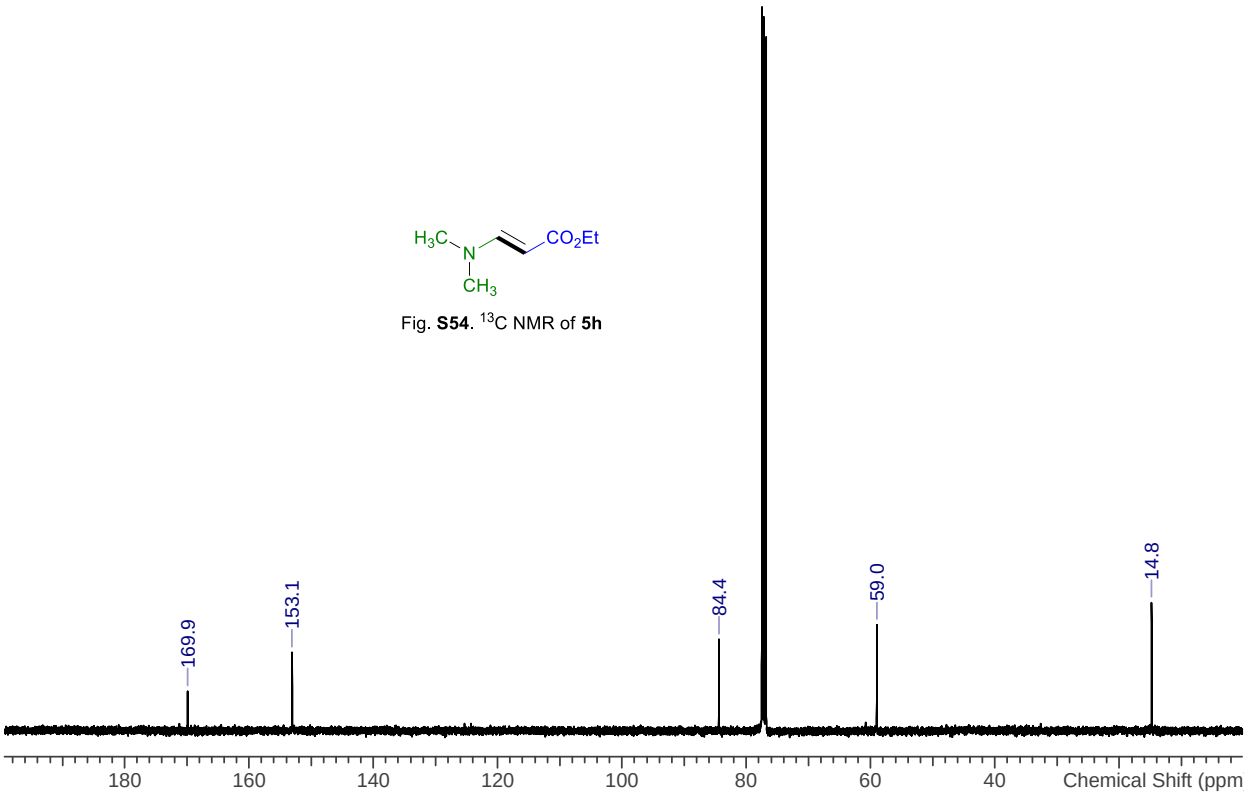


Fig. **S54**. ^{13}C NMR of **5h**

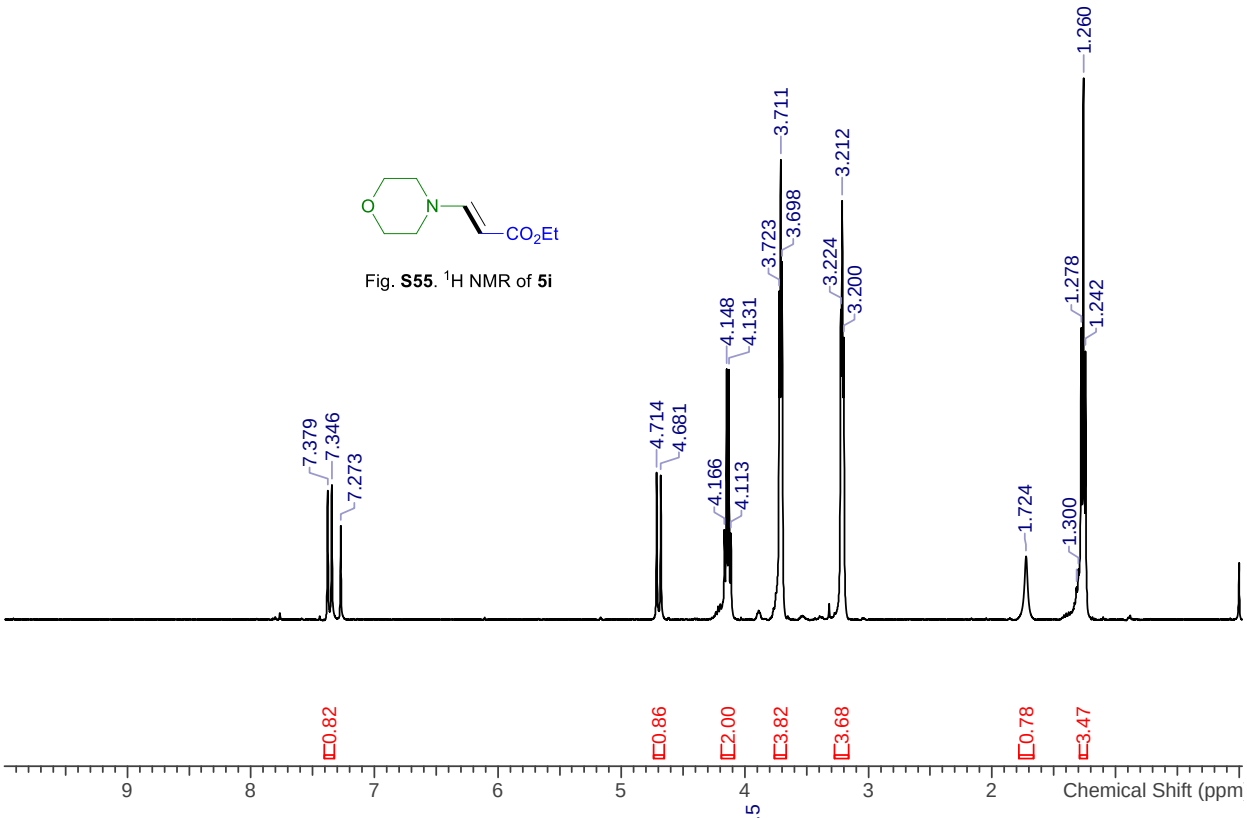


Fig. **S55**. ^{1}H NMR of **5i**

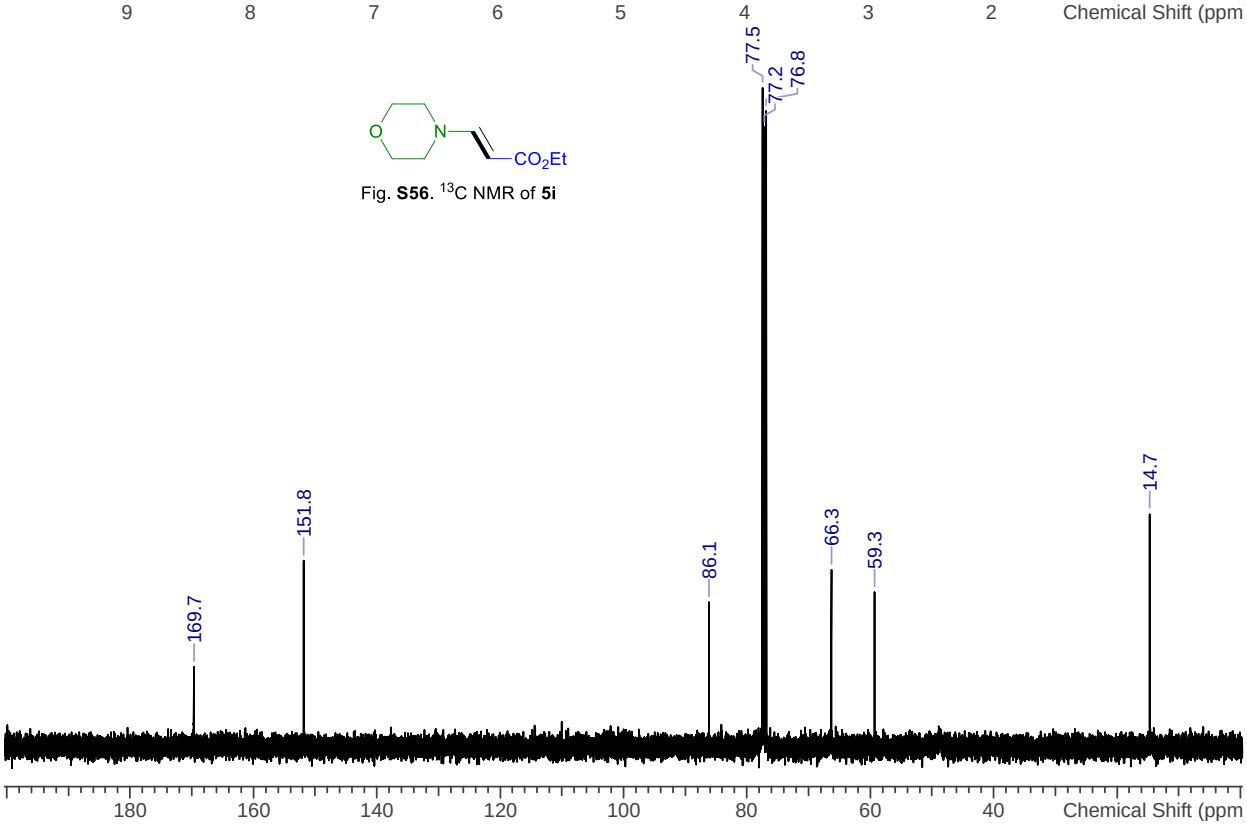


Fig. **S56**. ^{13}C NMR of **5i**

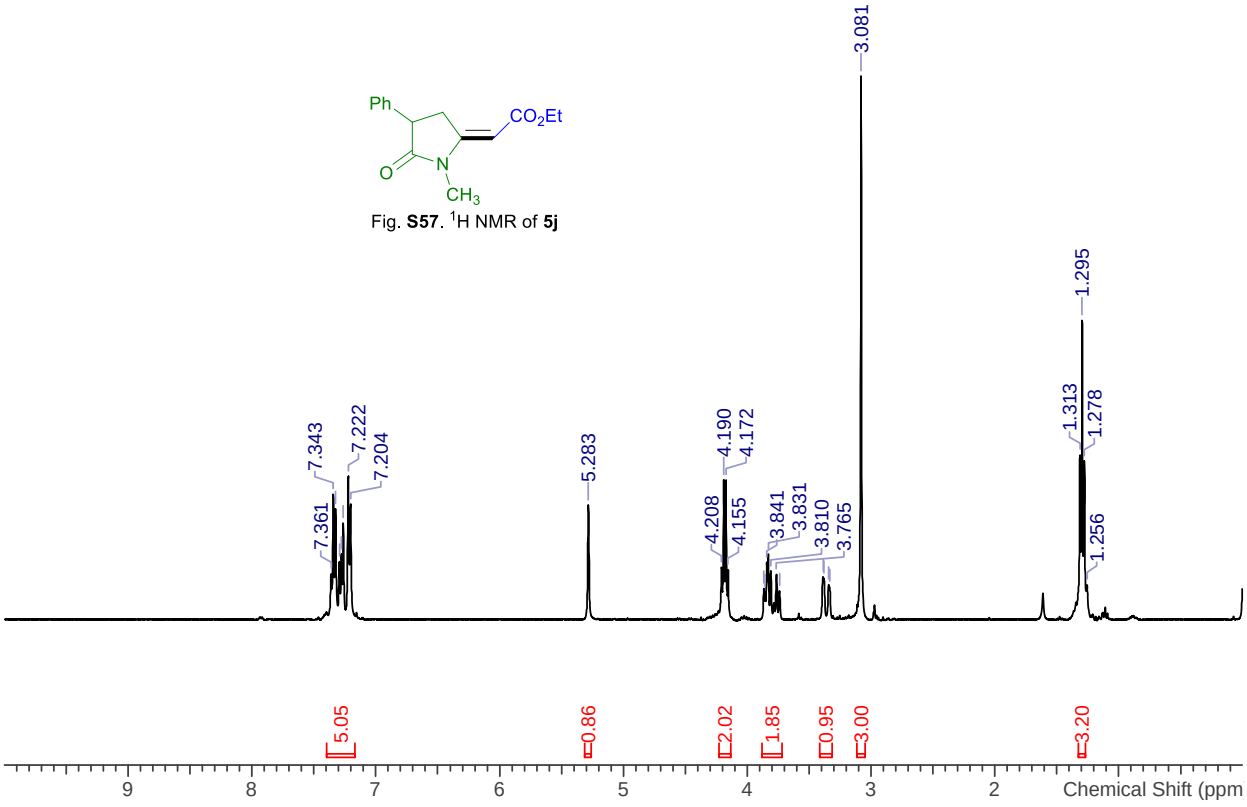


Fig. **S57**. ^{1}H NMR of **5j**

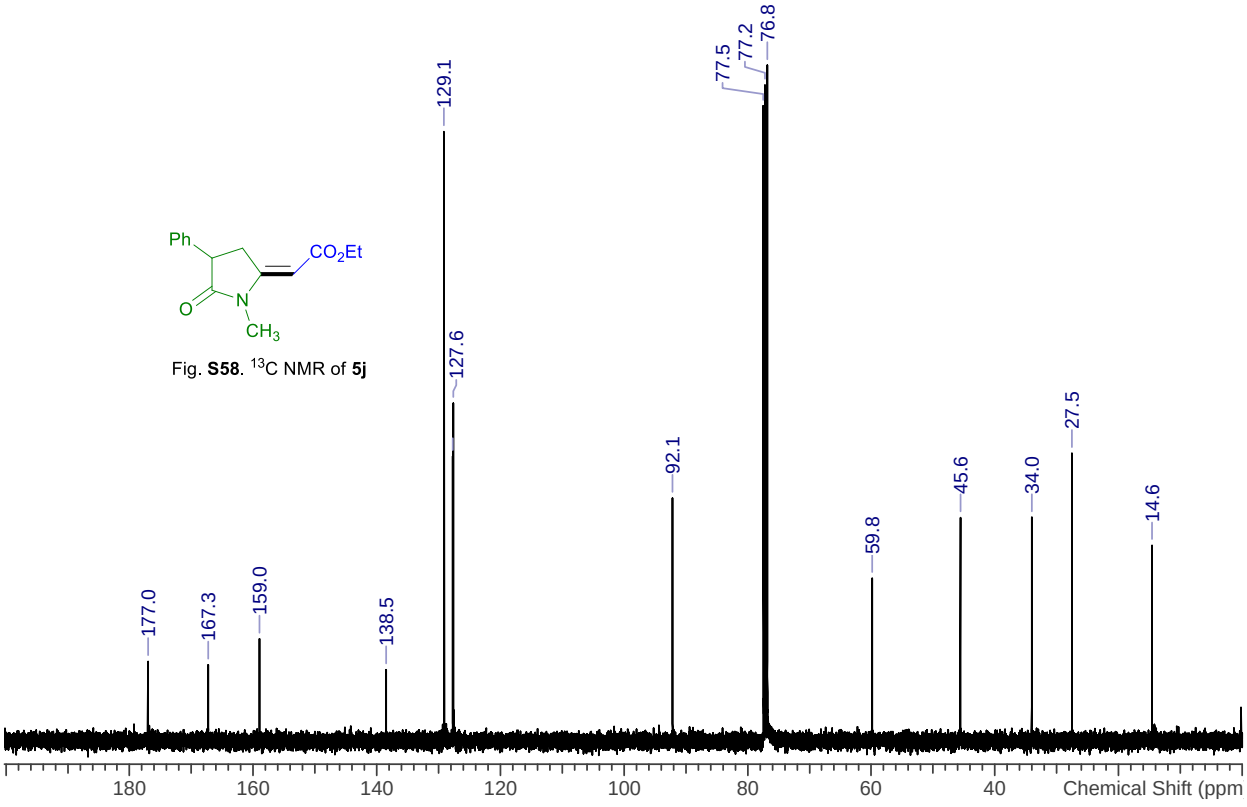


Fig. **S58**. ^{13}C NMR of **5j**

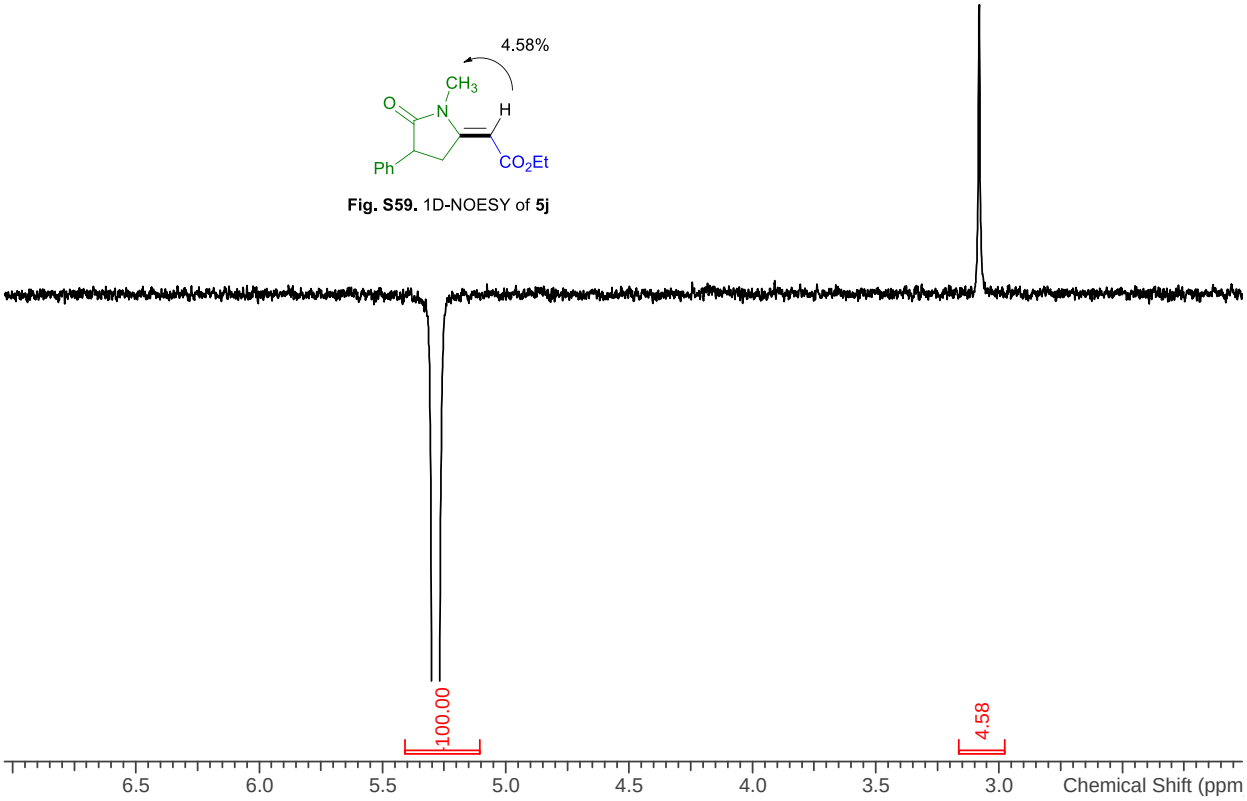


Fig. S59. 1D-NOESY of **5j**

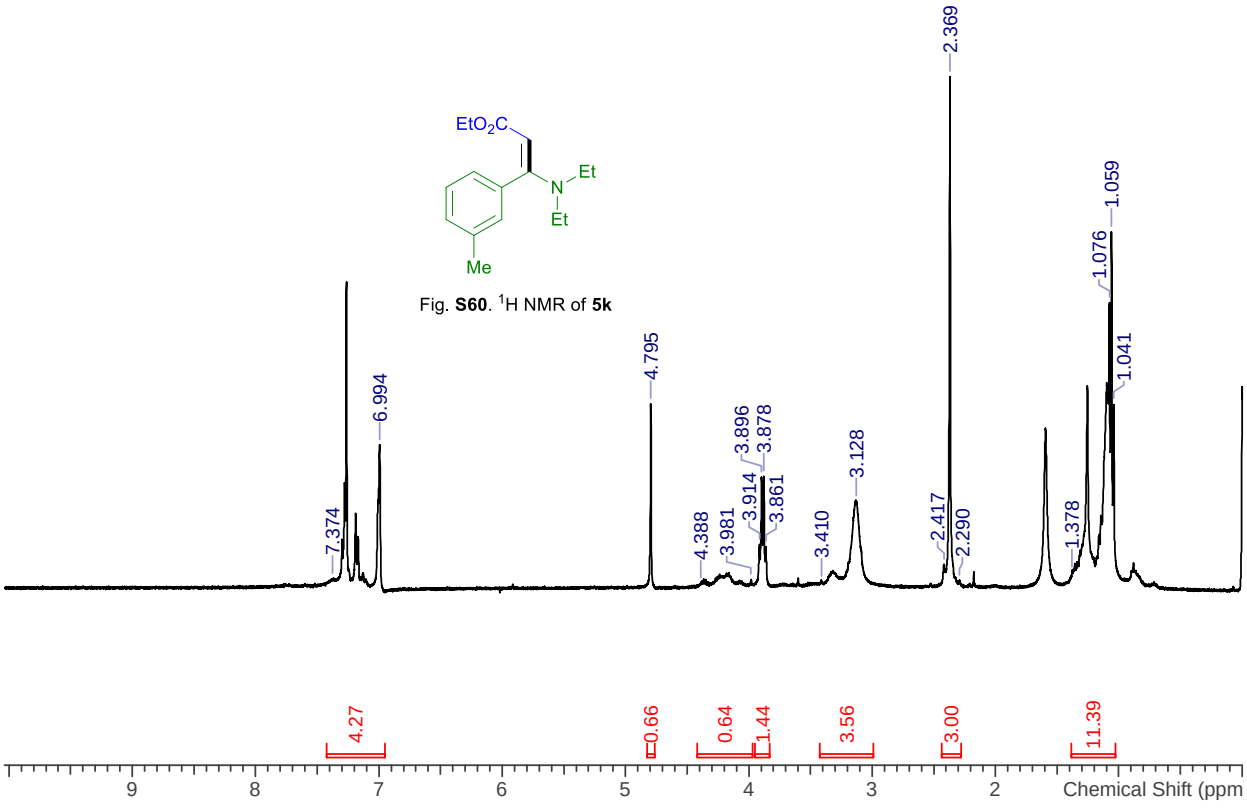


Fig. **S60**. ^{1}H NMR of **5k**

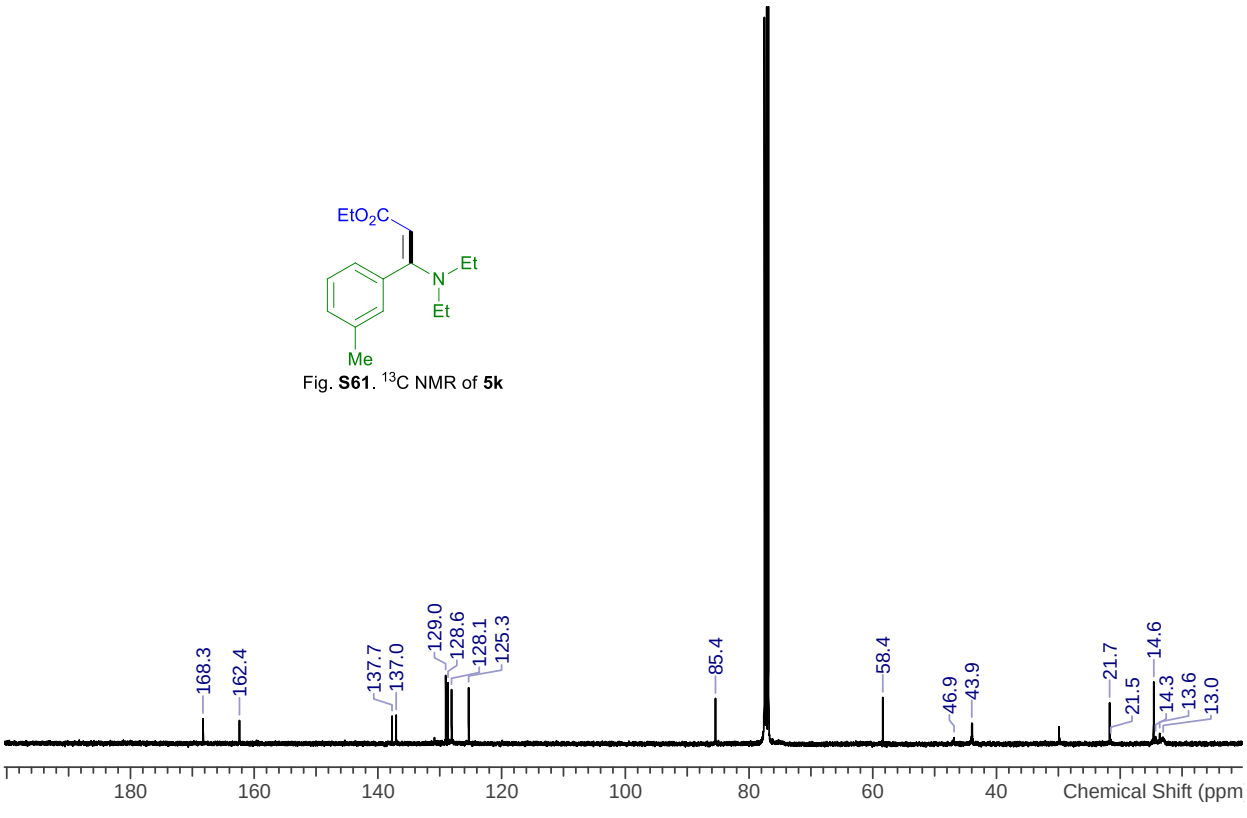


Fig. **S61**. ^{13}C NMR of **5k**

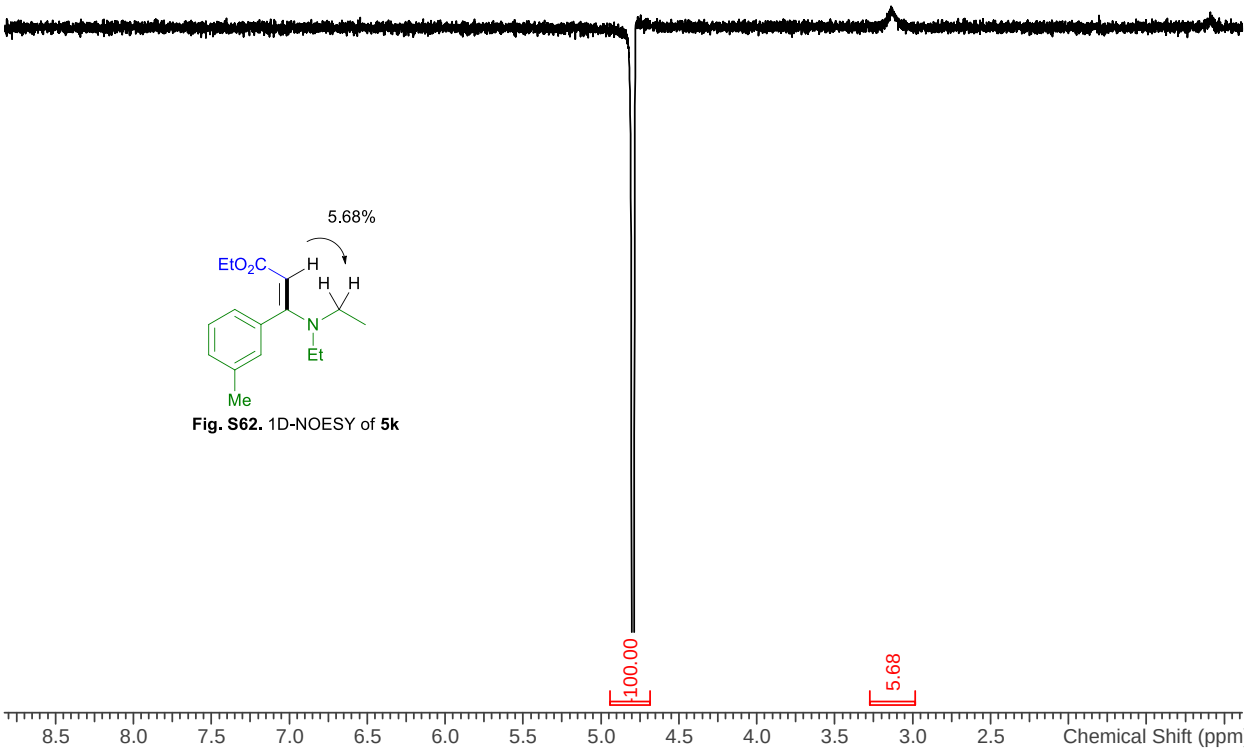


Fig. S62. 1D-NOESY of **5k**

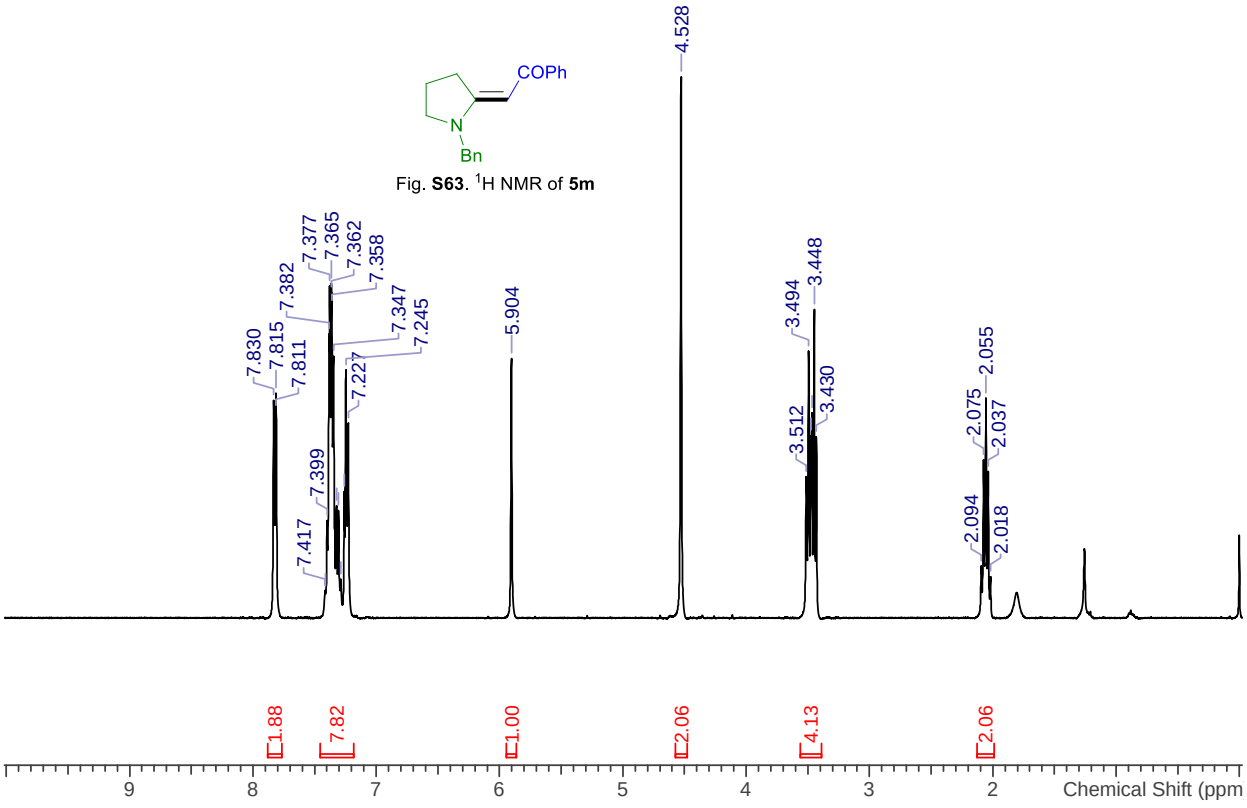


Fig. **S63**. ^{1}H NMR of **5m**

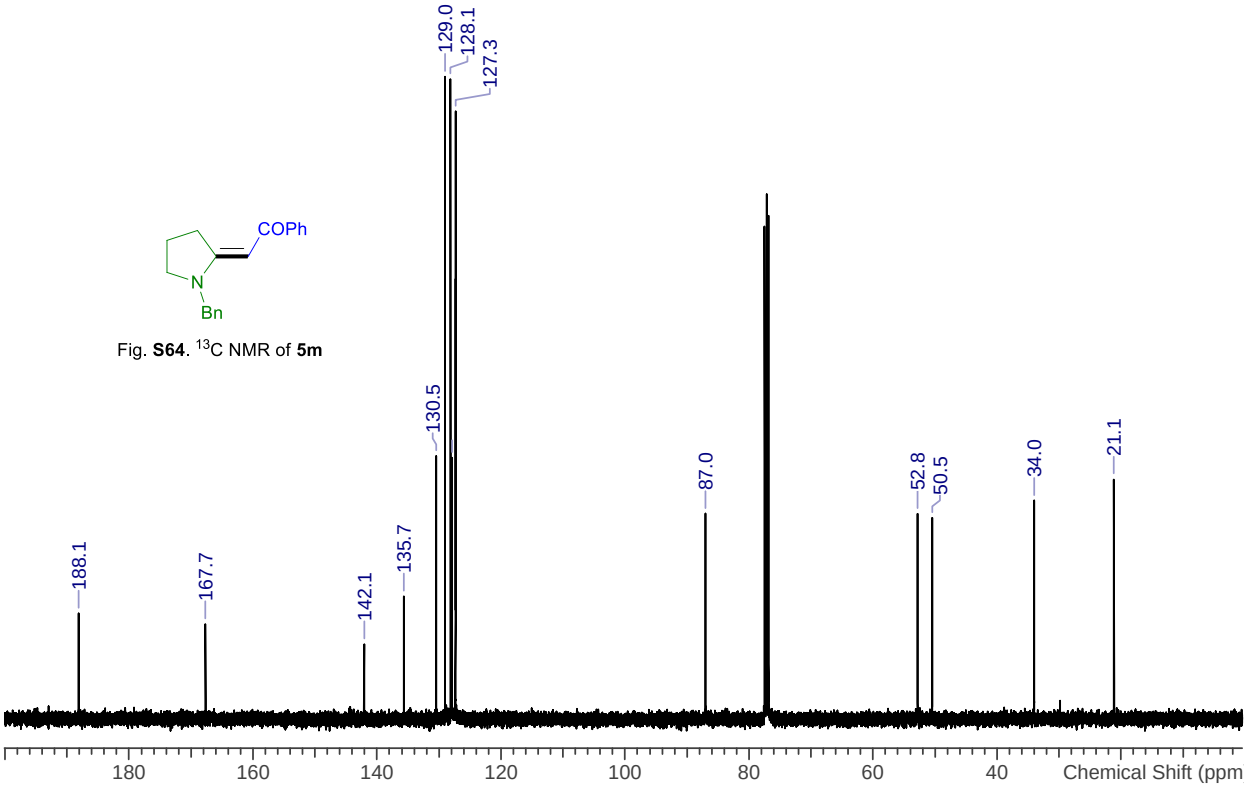


Fig. **S64**. ^{13}C NMR of **5m**

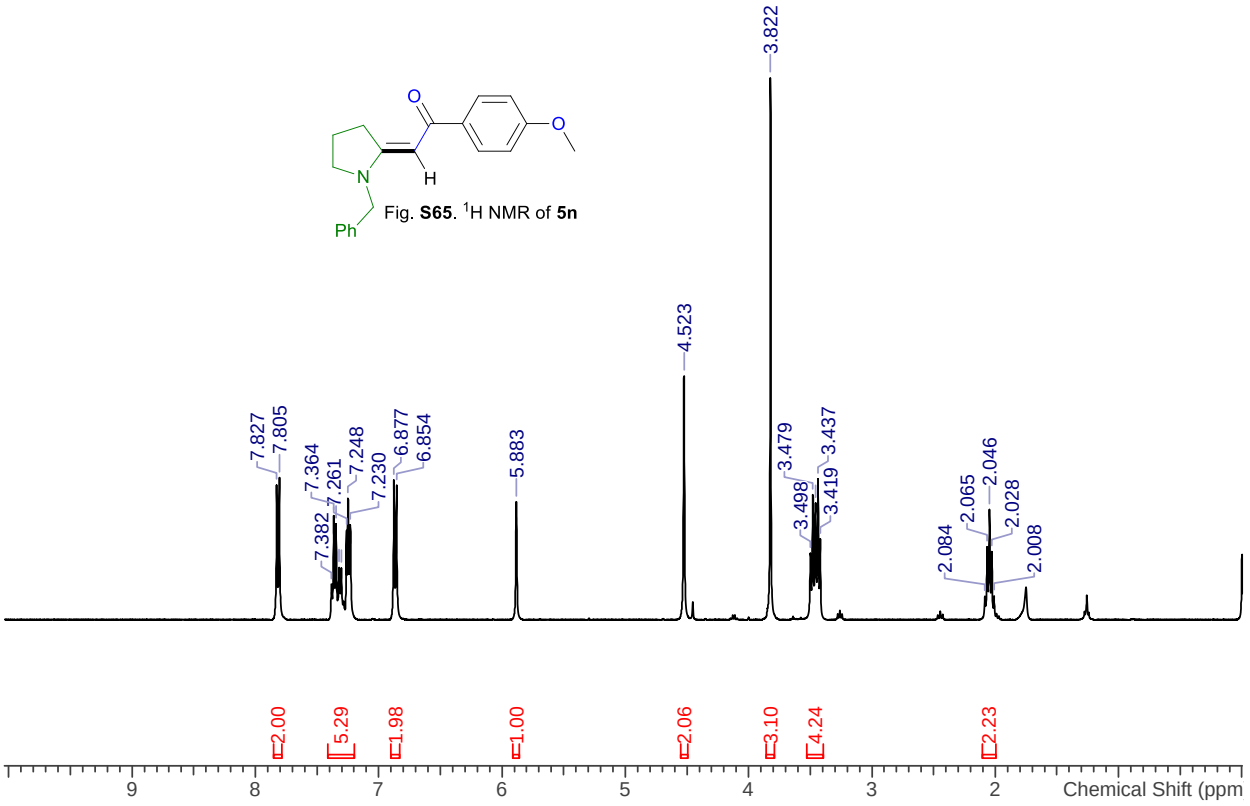


Fig. **S65**. ^{1}H NMR of **5n**

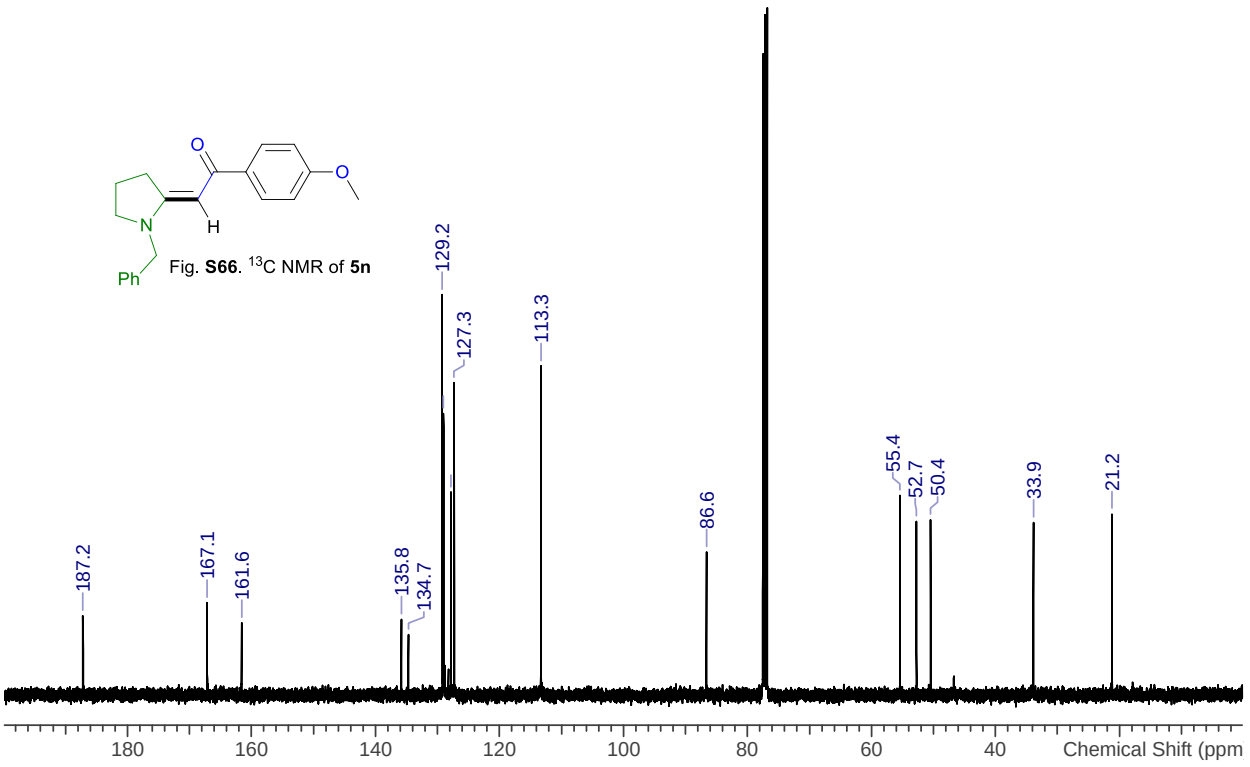


Fig. **S66**. ^{13}C NMR of **5n**

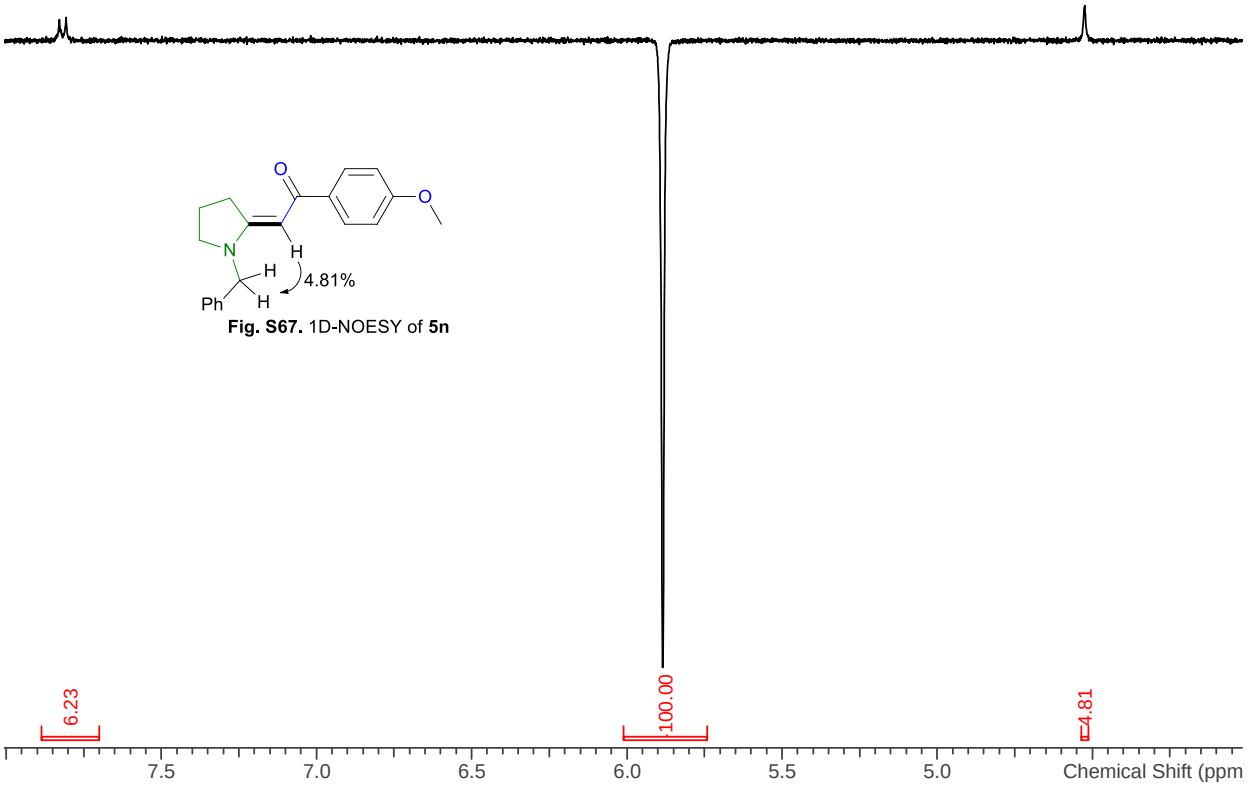


Fig. S67. 1D-NOESY of **5n**

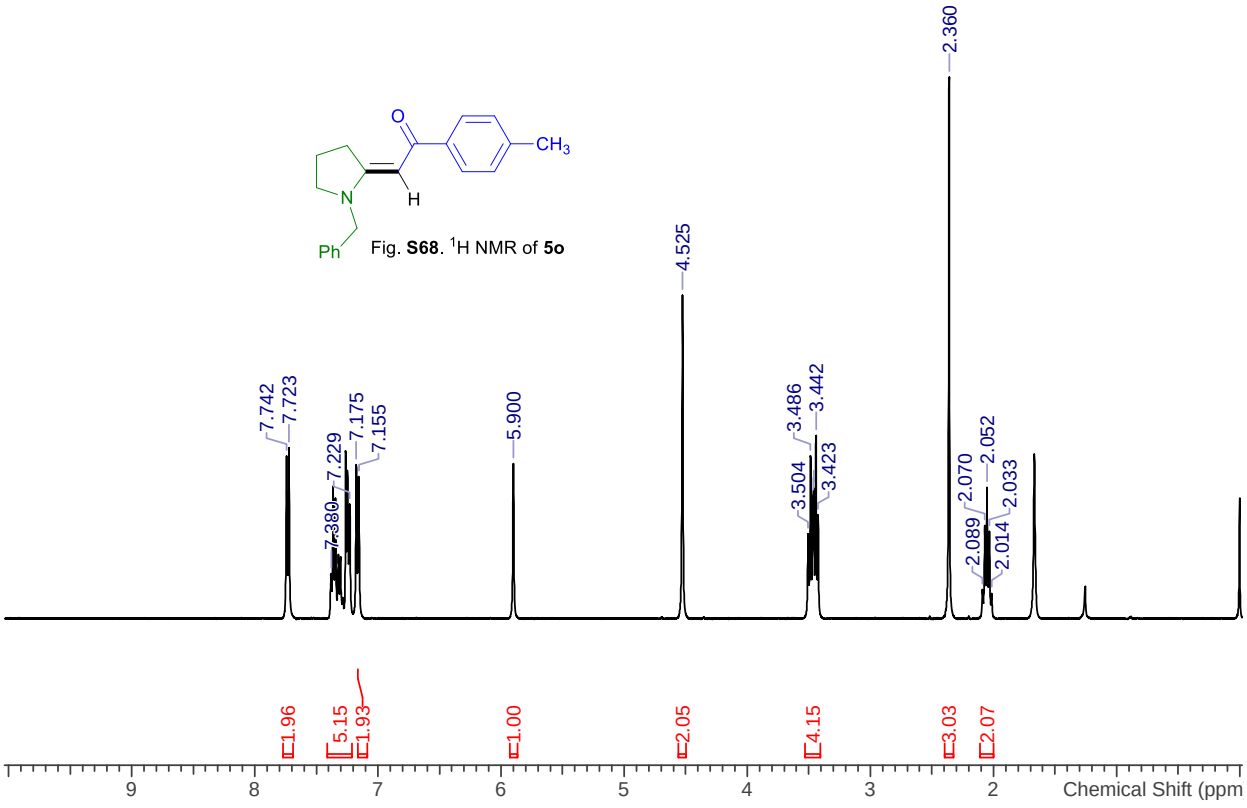


Fig. **S68**. ^{1}H NMR of **5o**

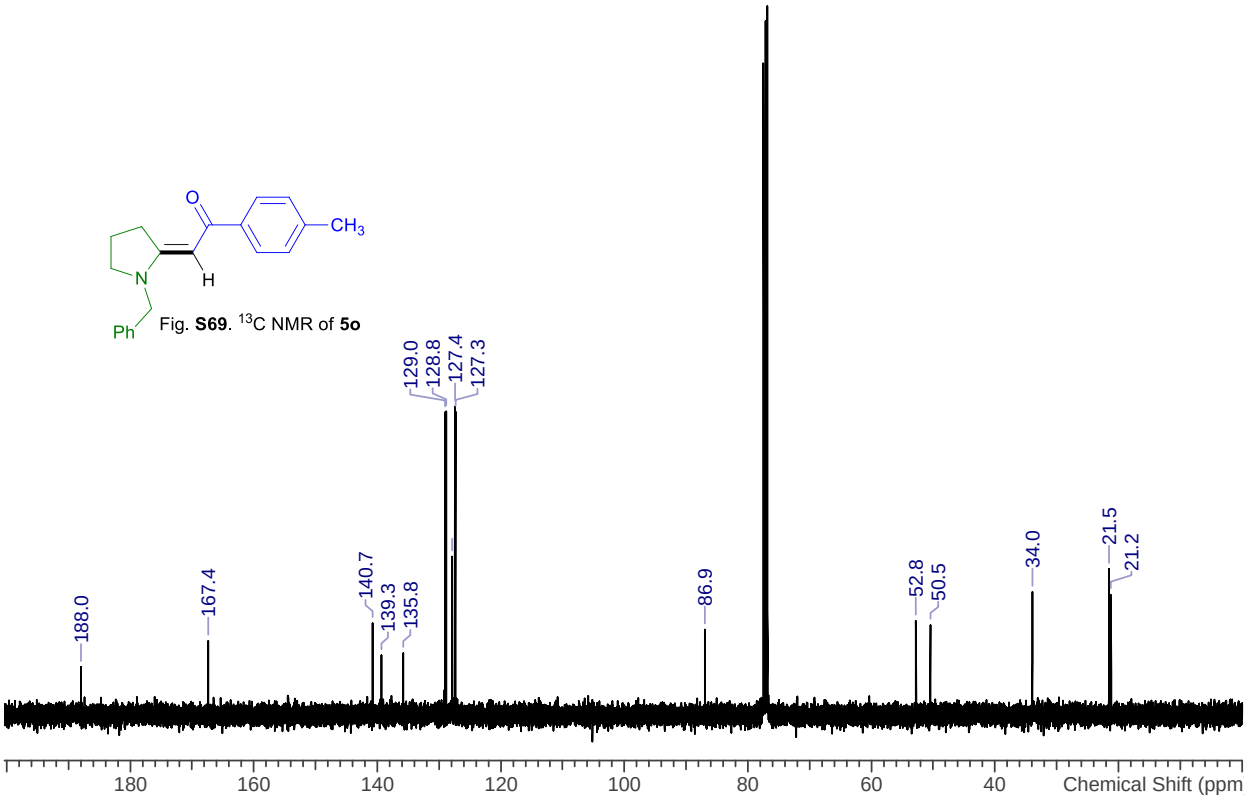


Fig. **S69**. ^{13}C NMR of **5o**

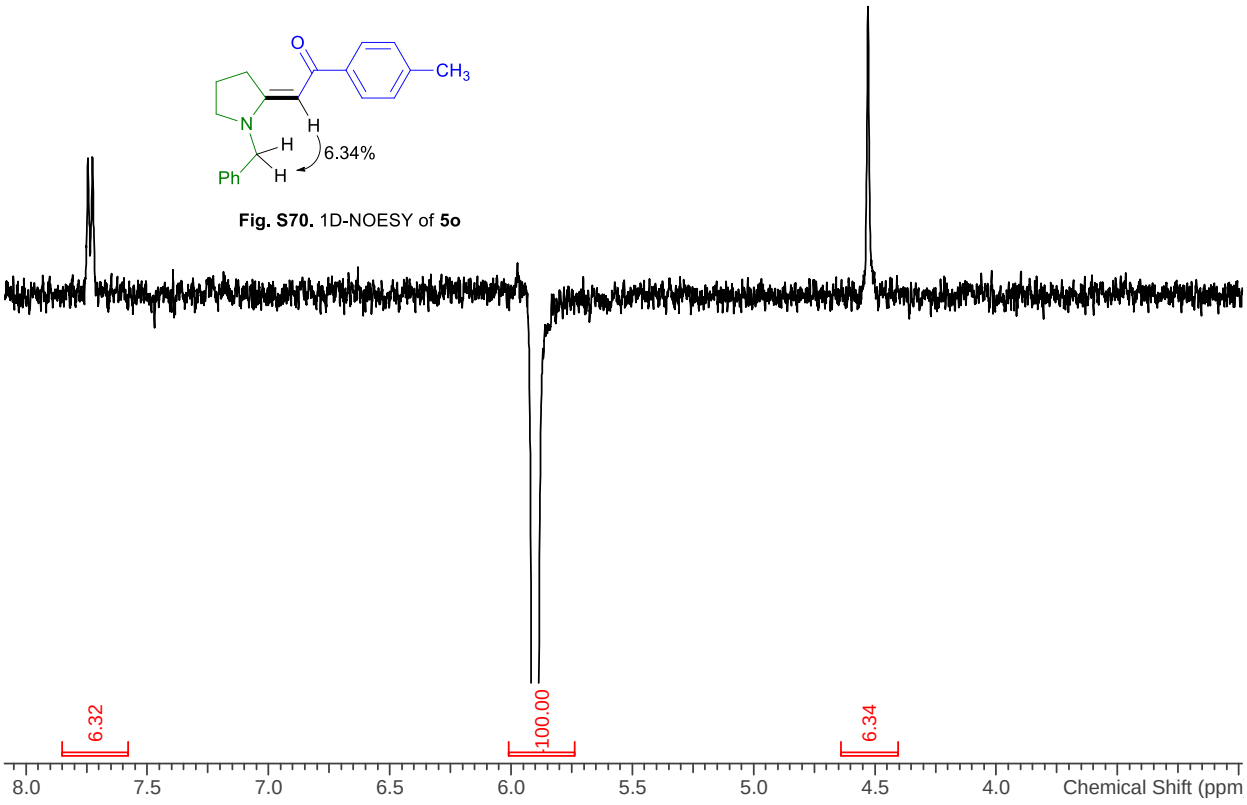


Fig. S70. 1D-NOESY of **5o**

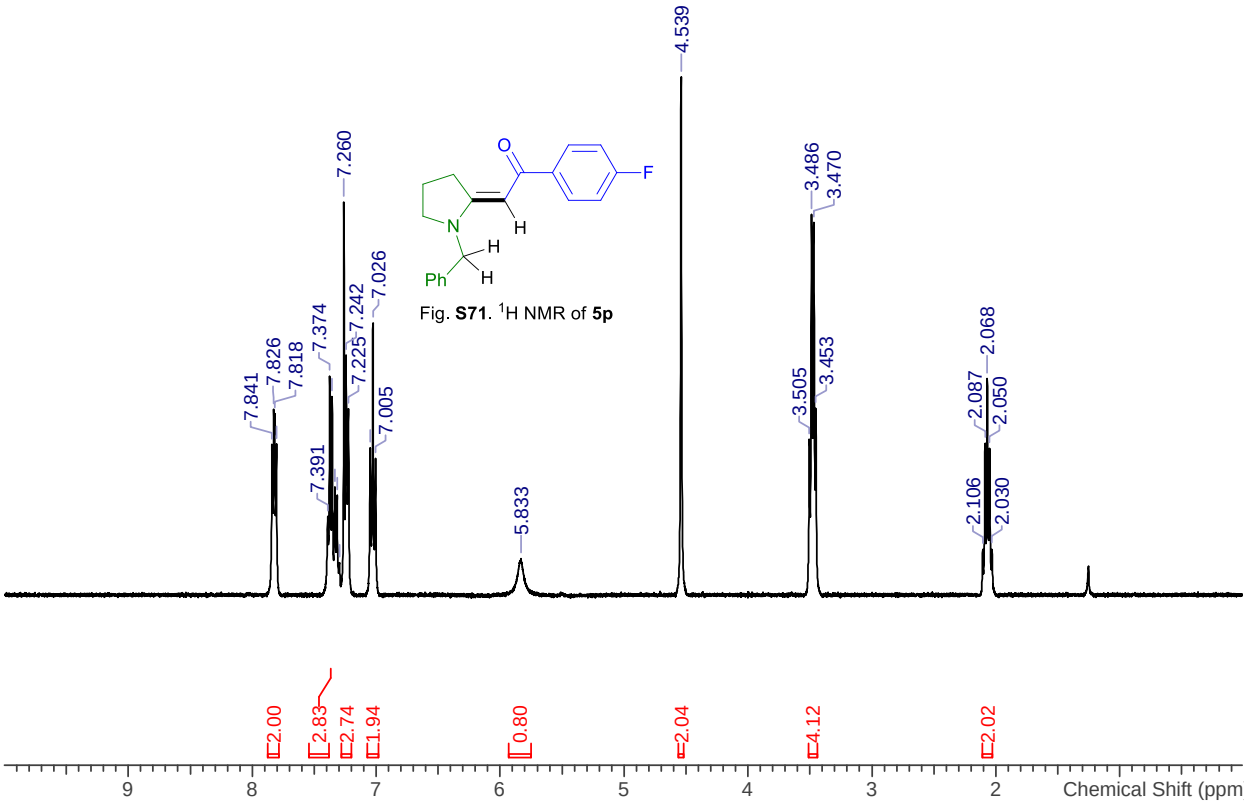


Fig. **S71**. ^{1}H NMR of **5p**

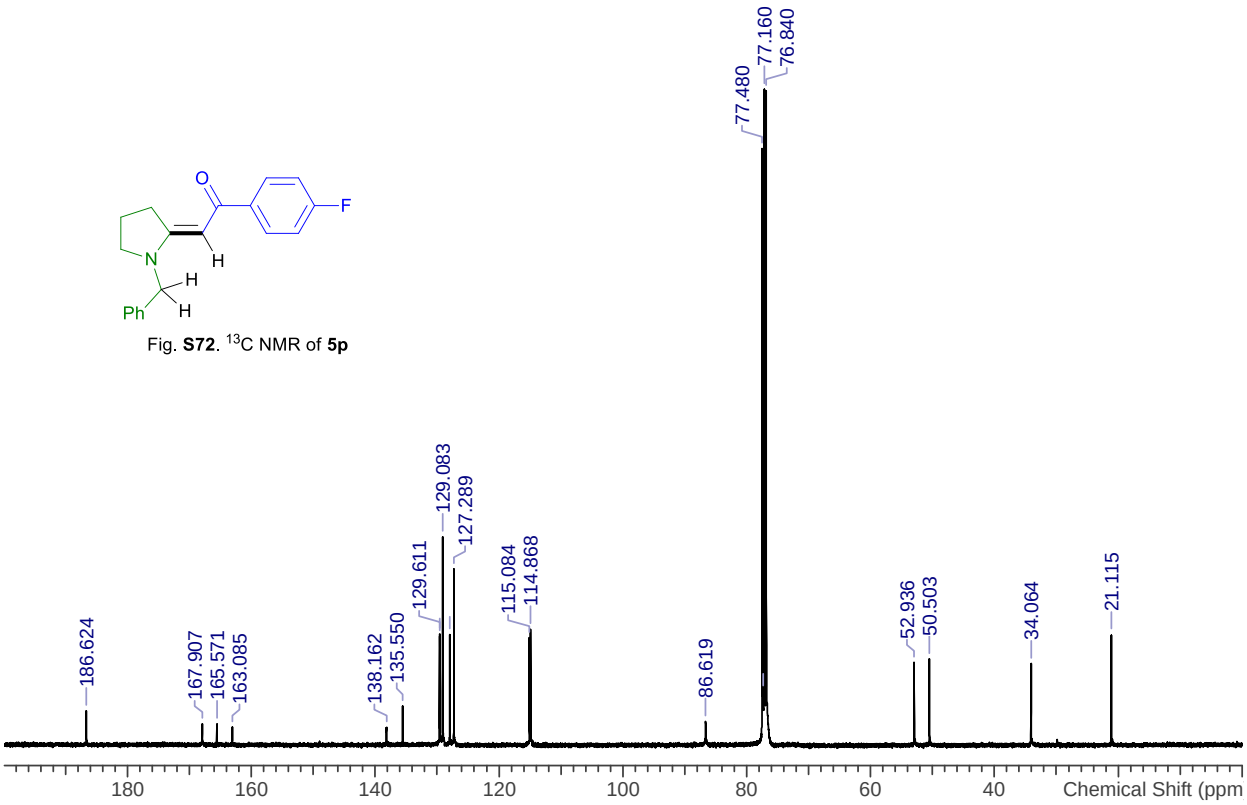


Fig. **S72**. ^{13}C NMR of **5p**

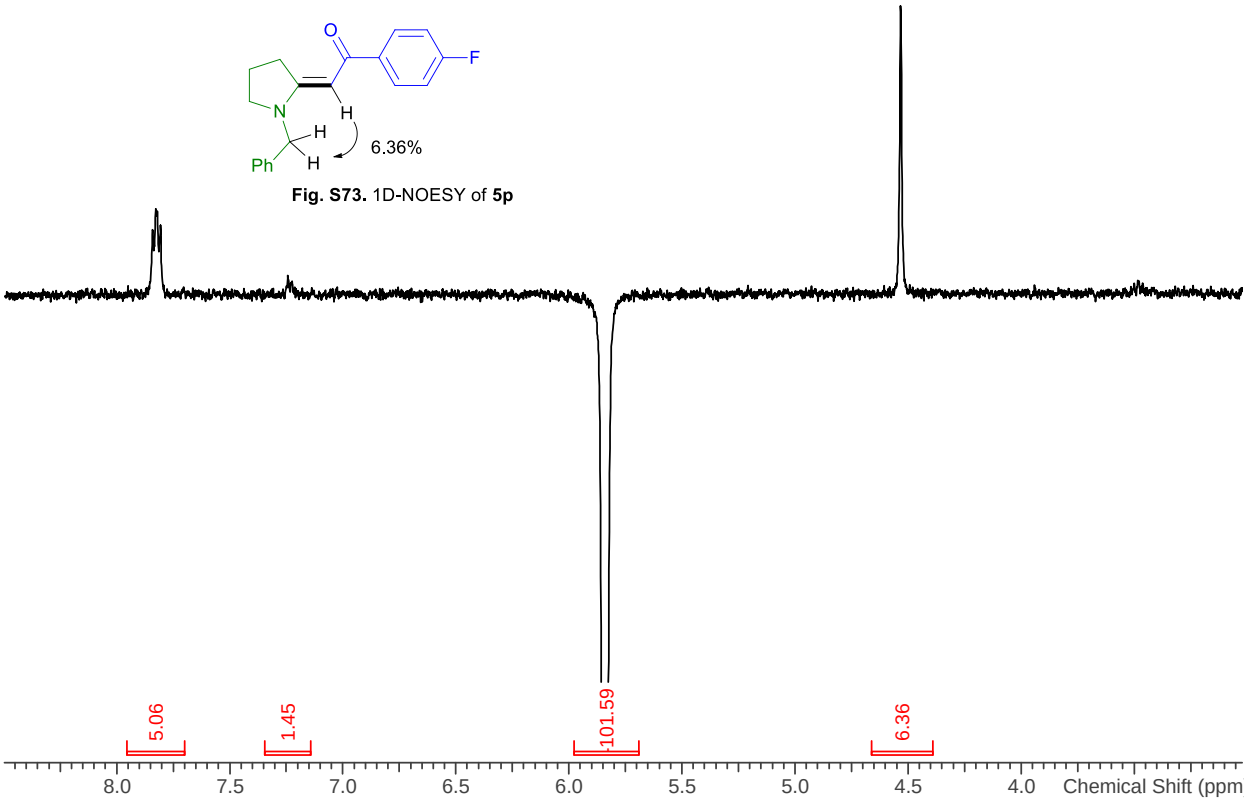


Fig. S73. 1D-NOESY of **5p**

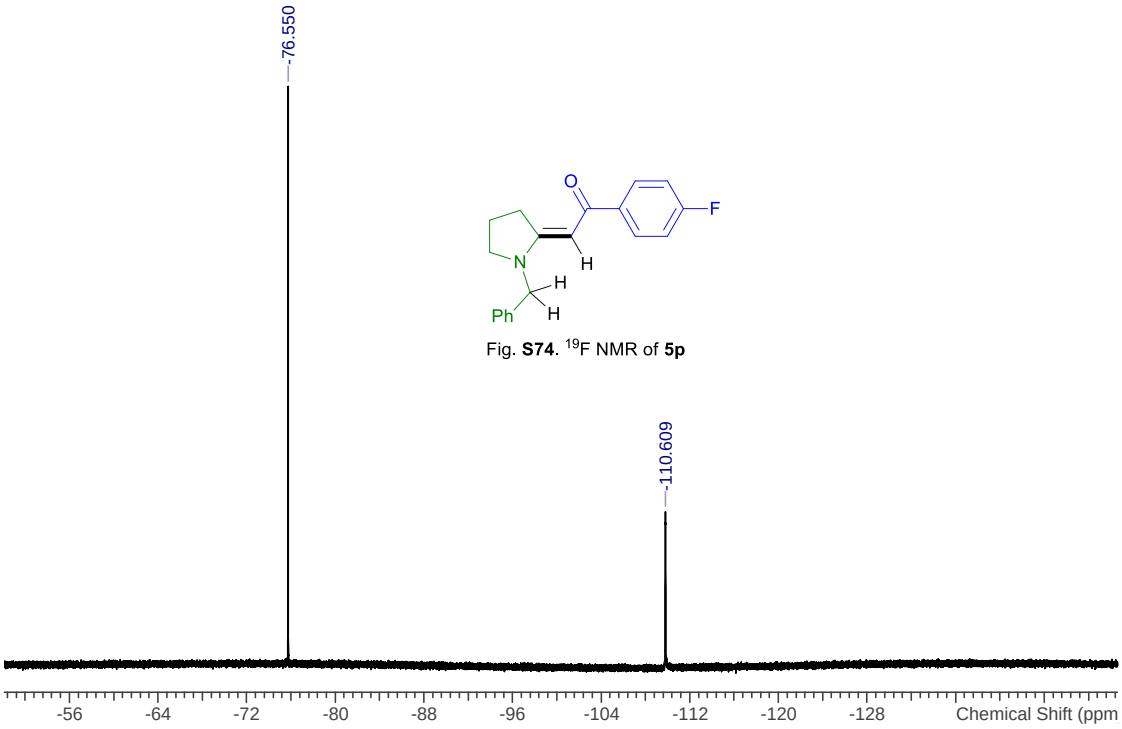


Fig. **S74**. ^{19}F NMR of **5p**

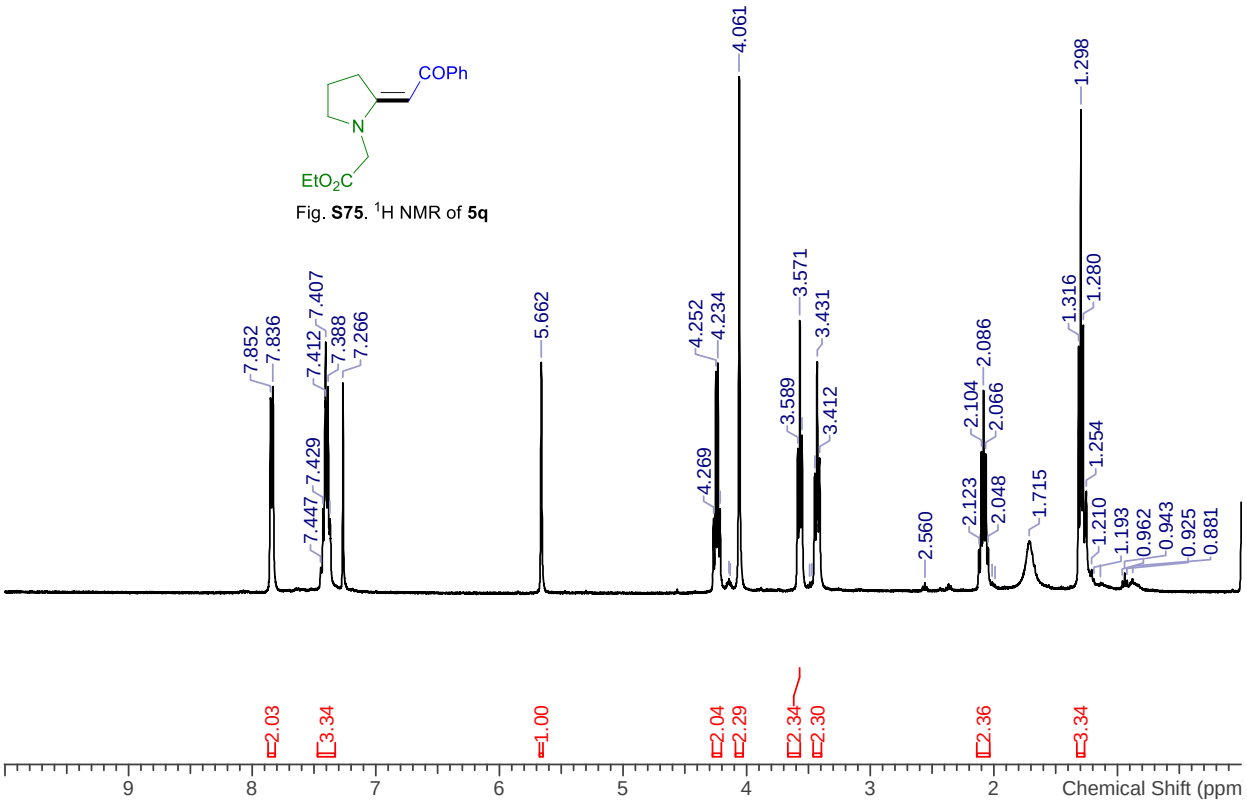


Fig. **S75**. ^{1}H NMR of **5q**

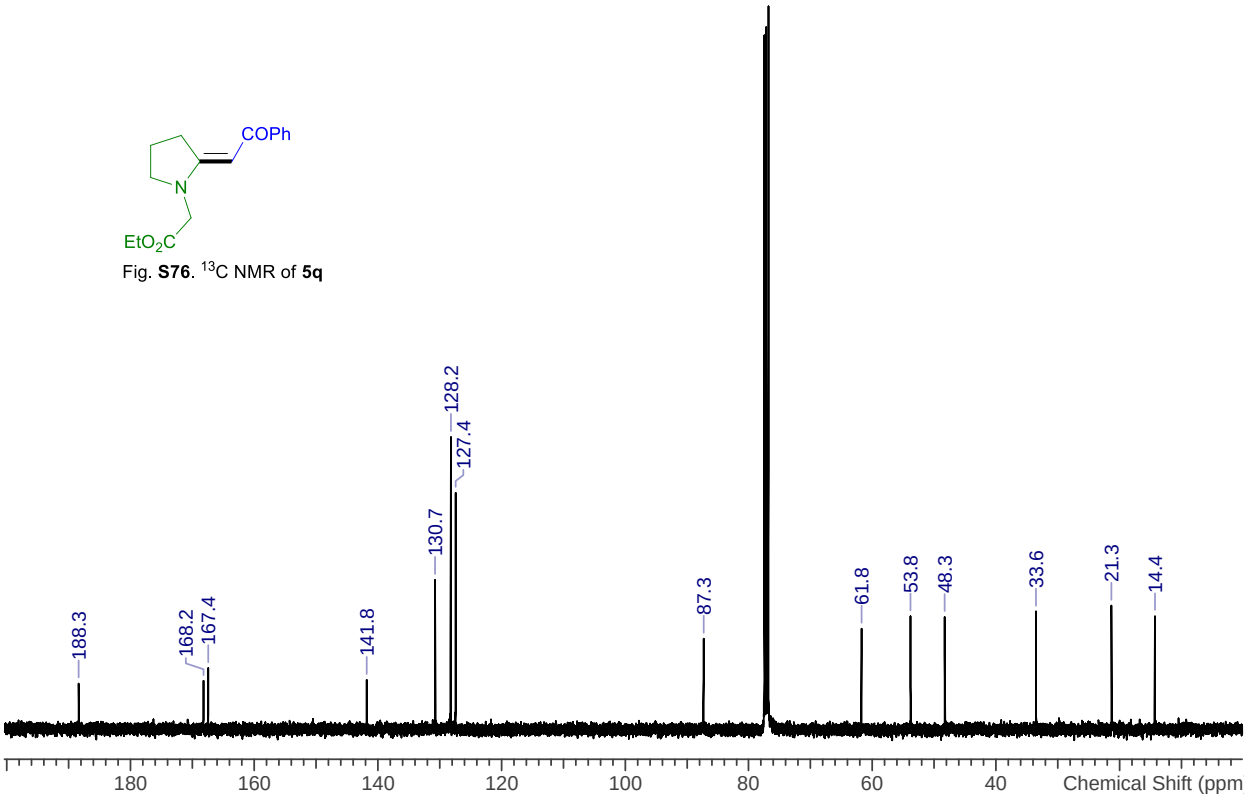


Fig. **S76**. ^{13}C NMR of **5q**

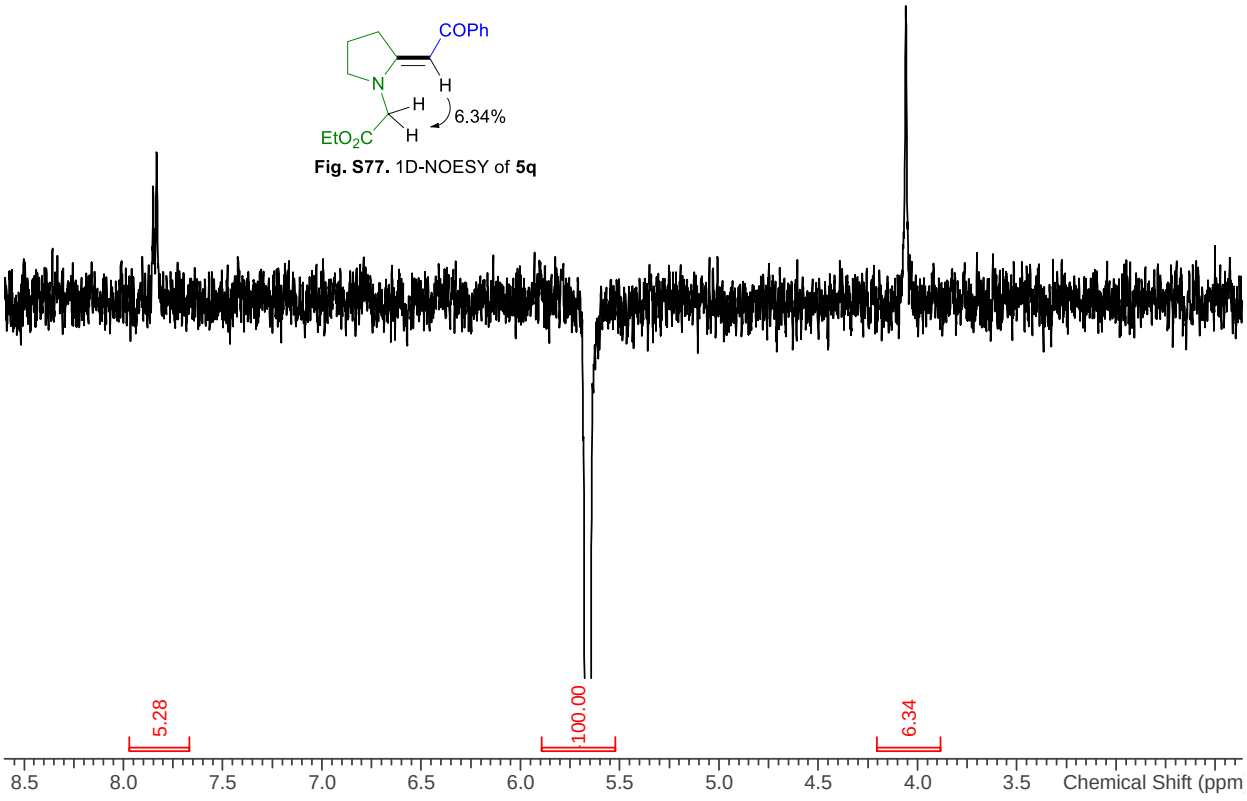


Fig. S77. 1D-NOESY of **5q**

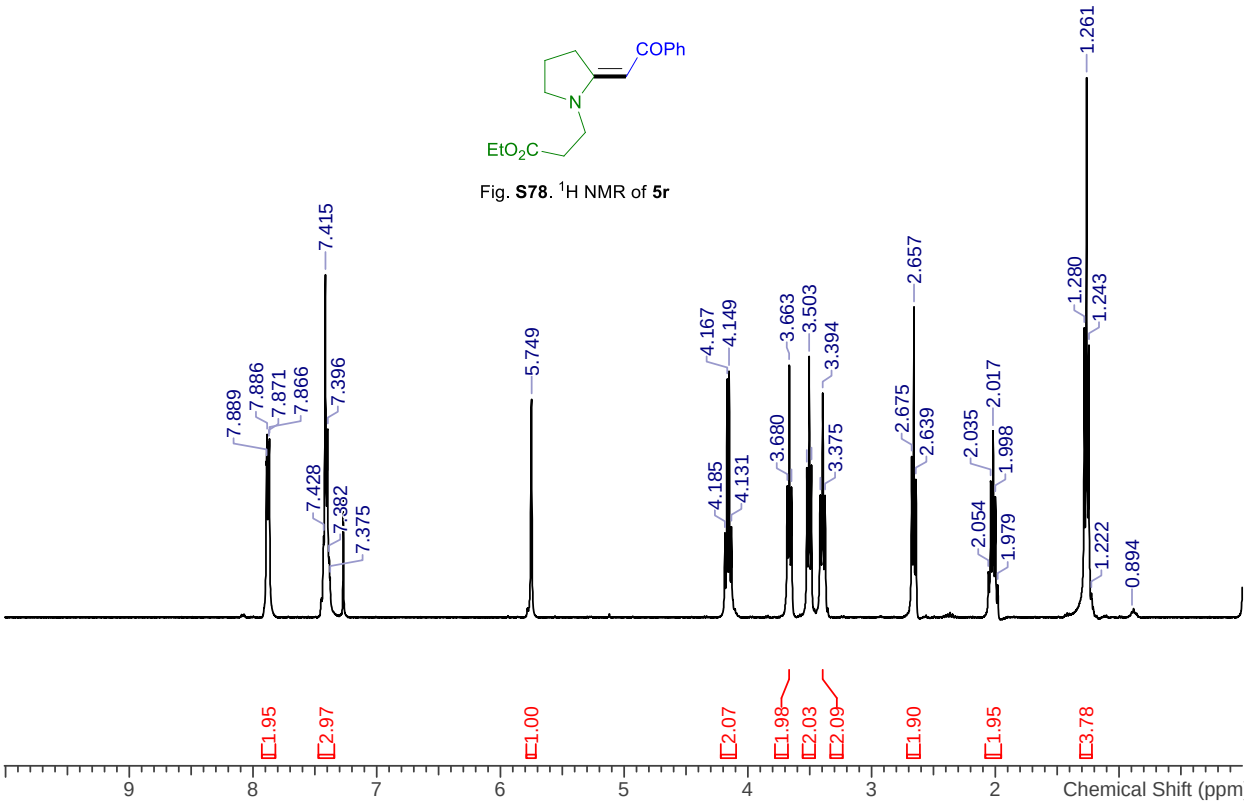


Fig. **S78**. ^{1}H NMR of **5r**

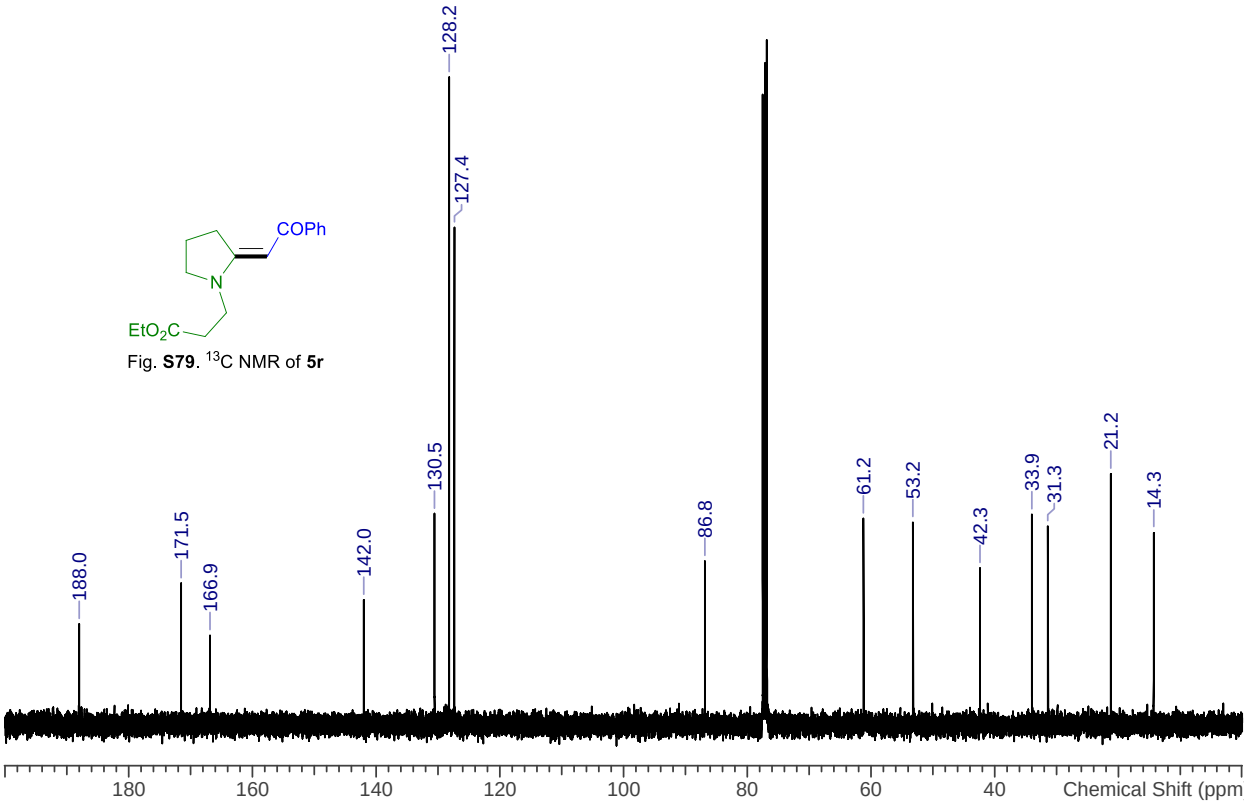


Fig. **S79**. ^{13}C NMR of **5r**

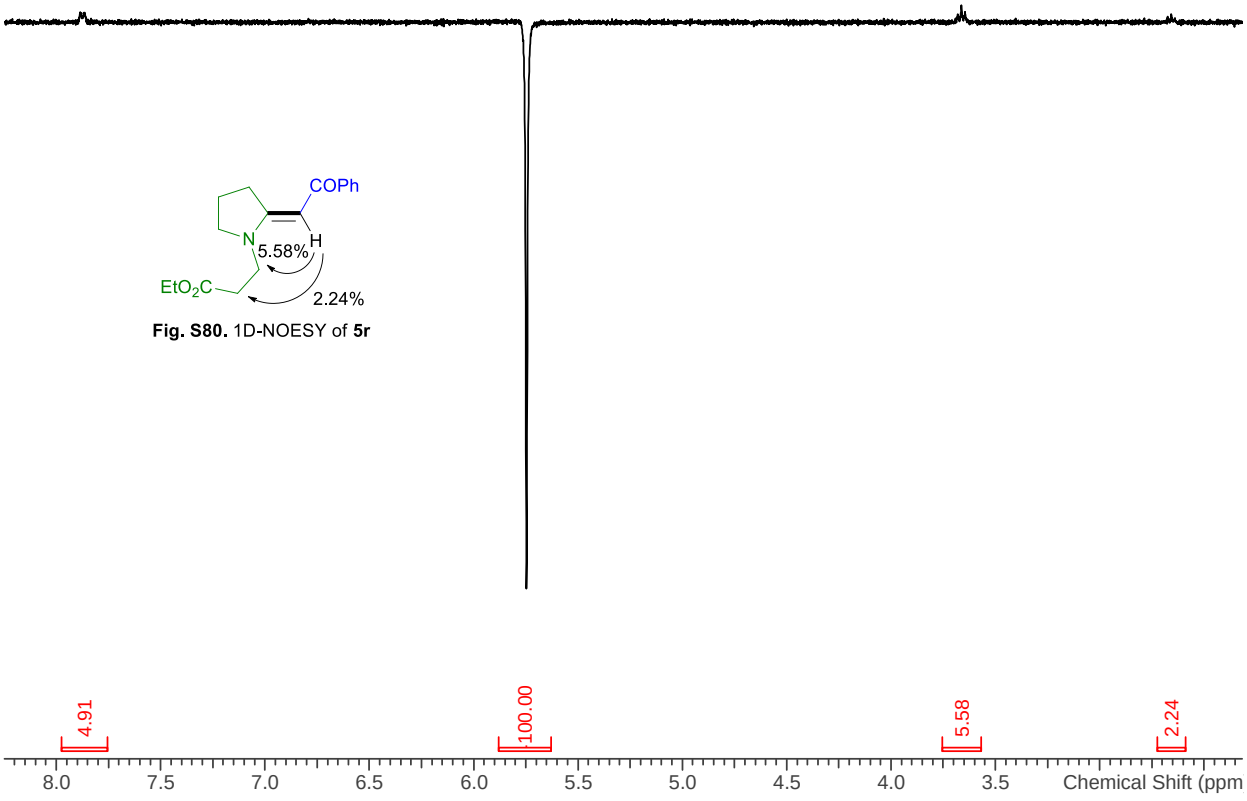


Fig. S80. 1D-NOESY of **5r**

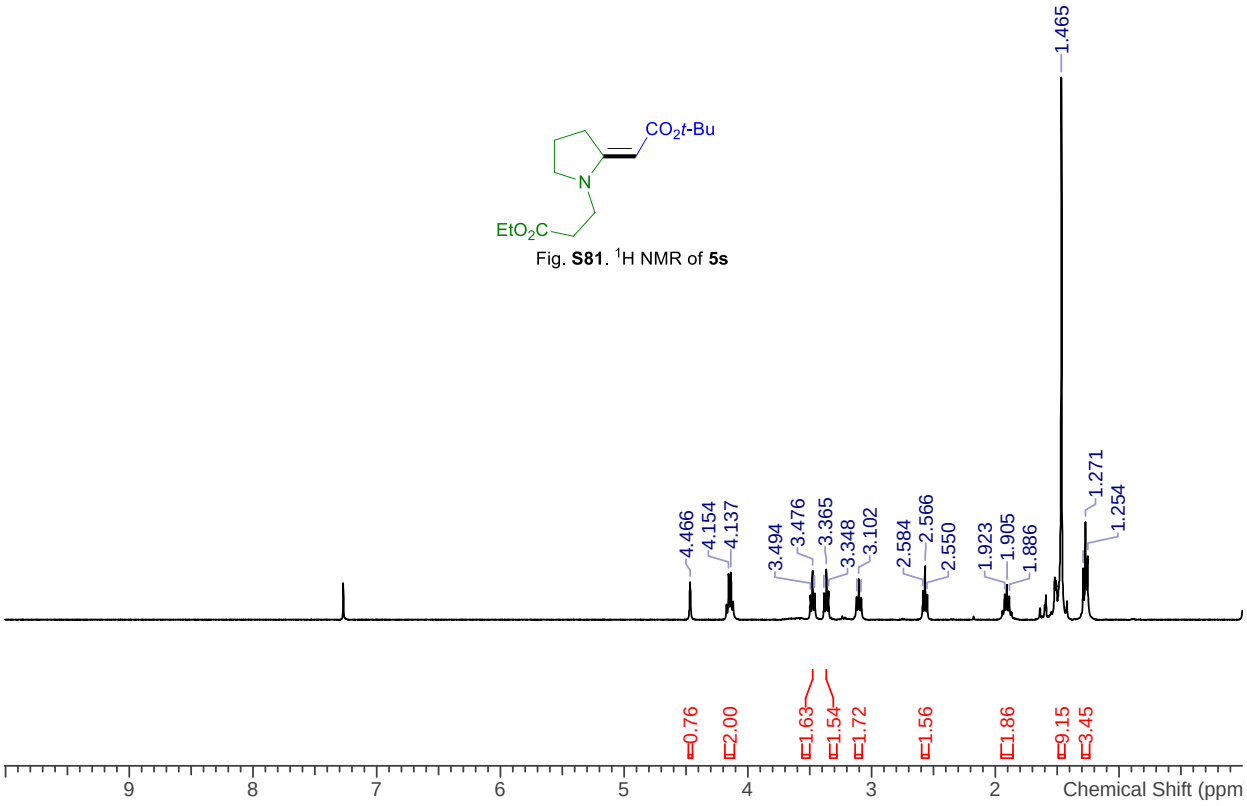


Fig. **S81**. ^{1}H NMR of **5s**

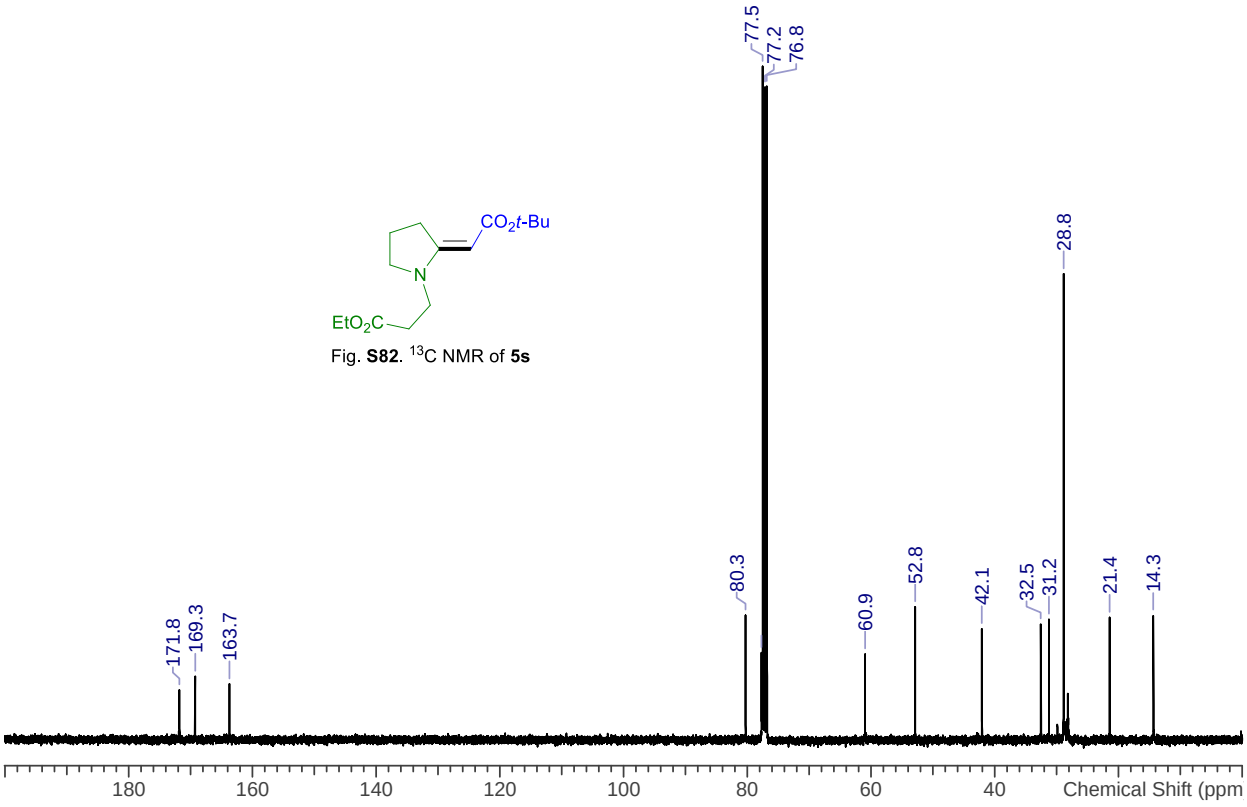


Fig. **S82**. ^{13}C NMR of **5s**

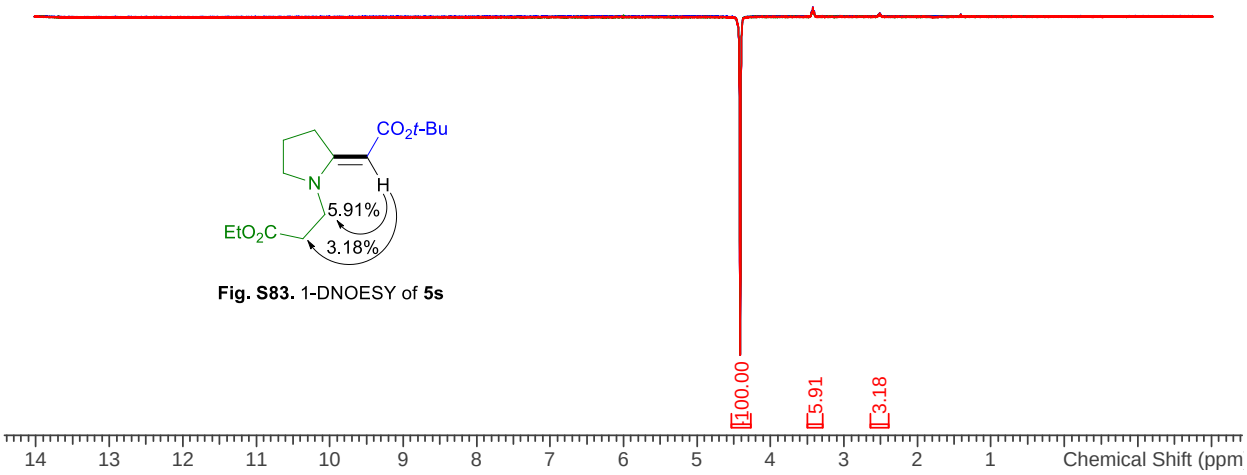


Fig. S83. 1-DNOESY of **5s**

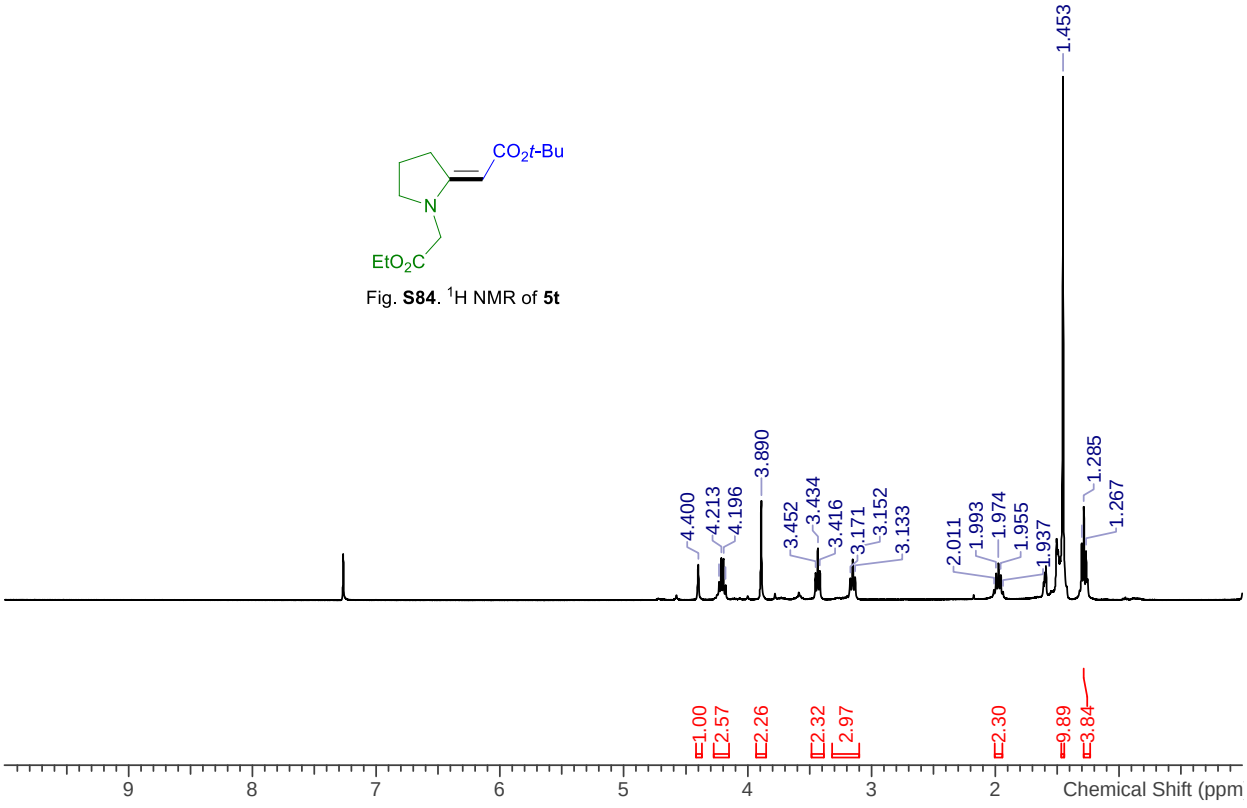


Fig. **S84**. ^{1}H NMR of **5t**

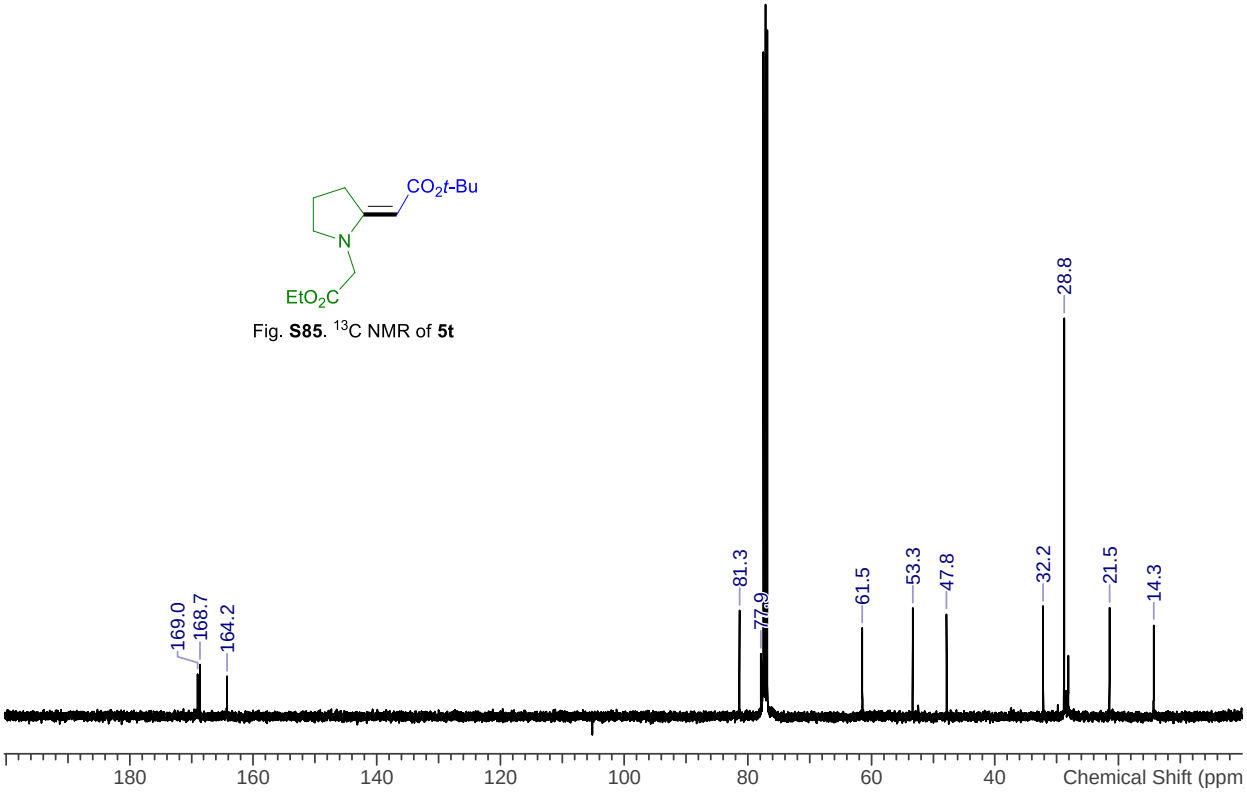


Fig. **S85**. ^{13}C NMR of **5t**

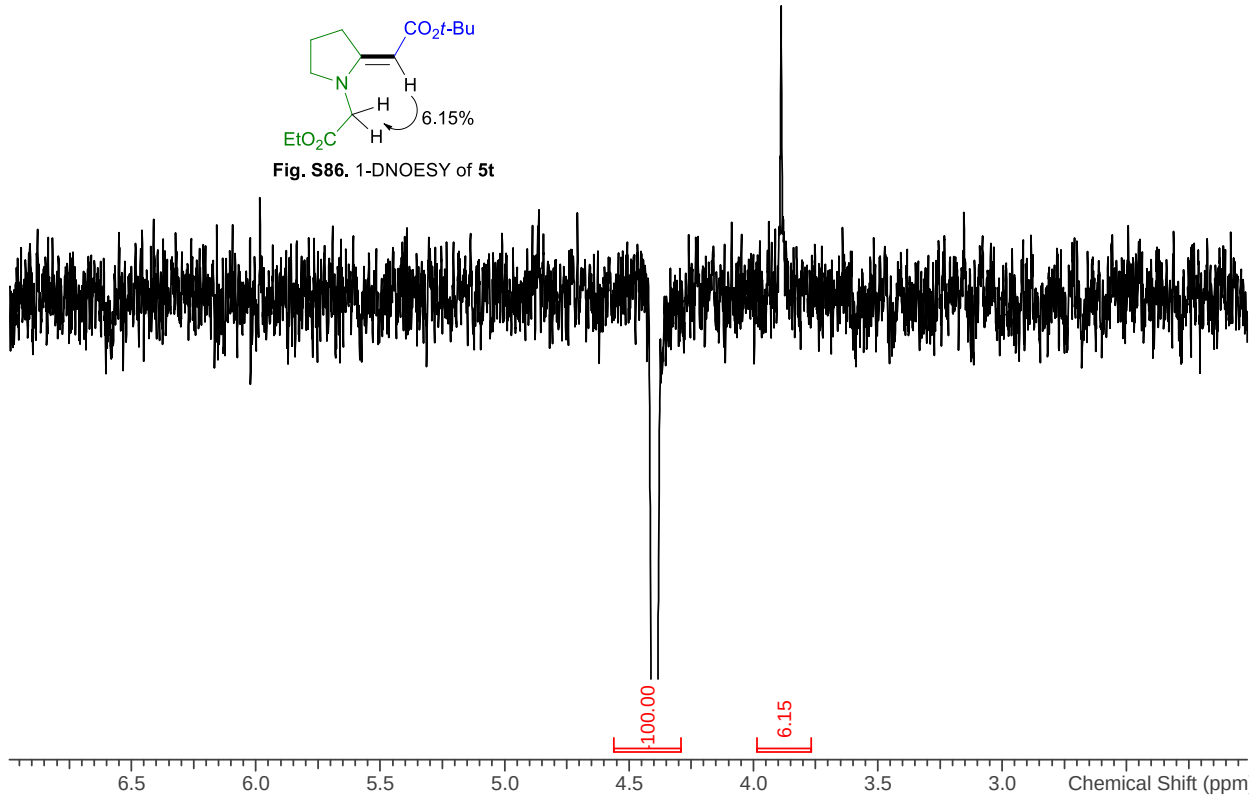


Fig. S86. 1-DNOESY of **5t**

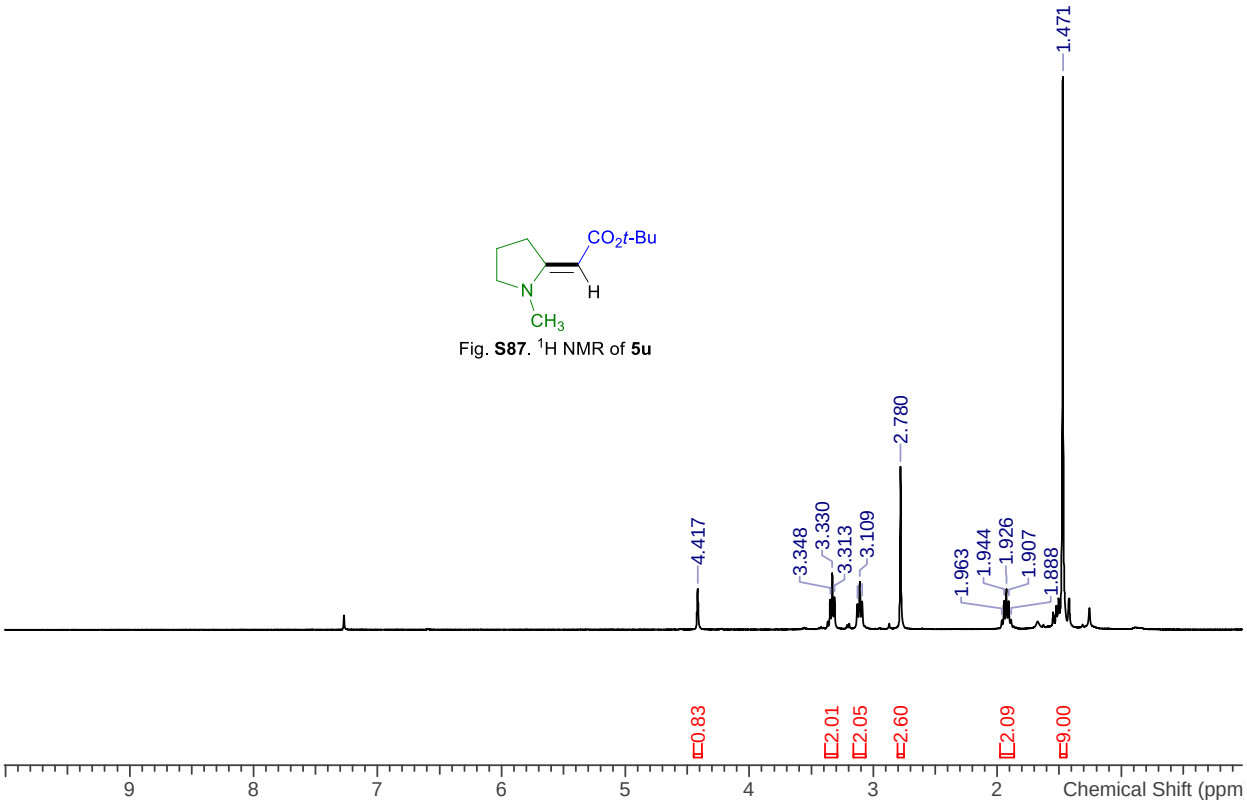


Fig. **S87**. ^{1}H NMR of **5u**

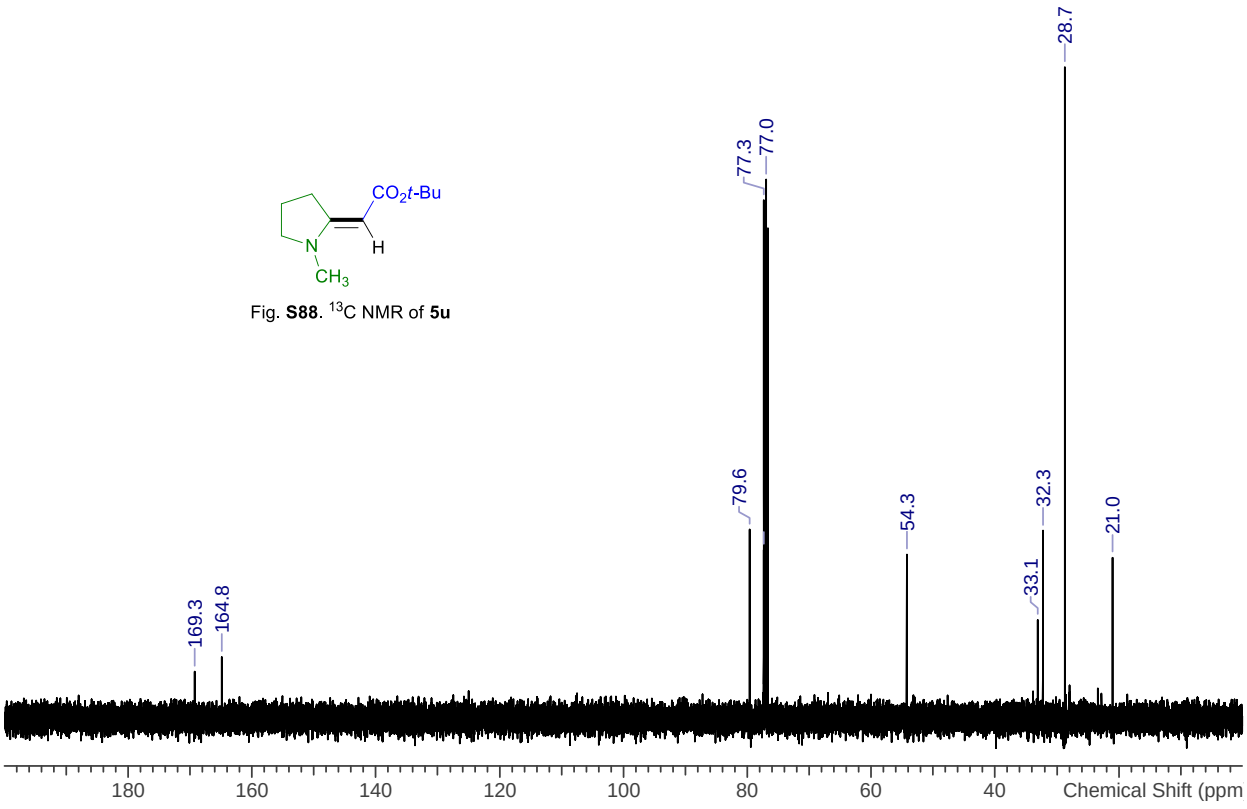


Fig. **S88**. ^{13}C NMR of **5u**

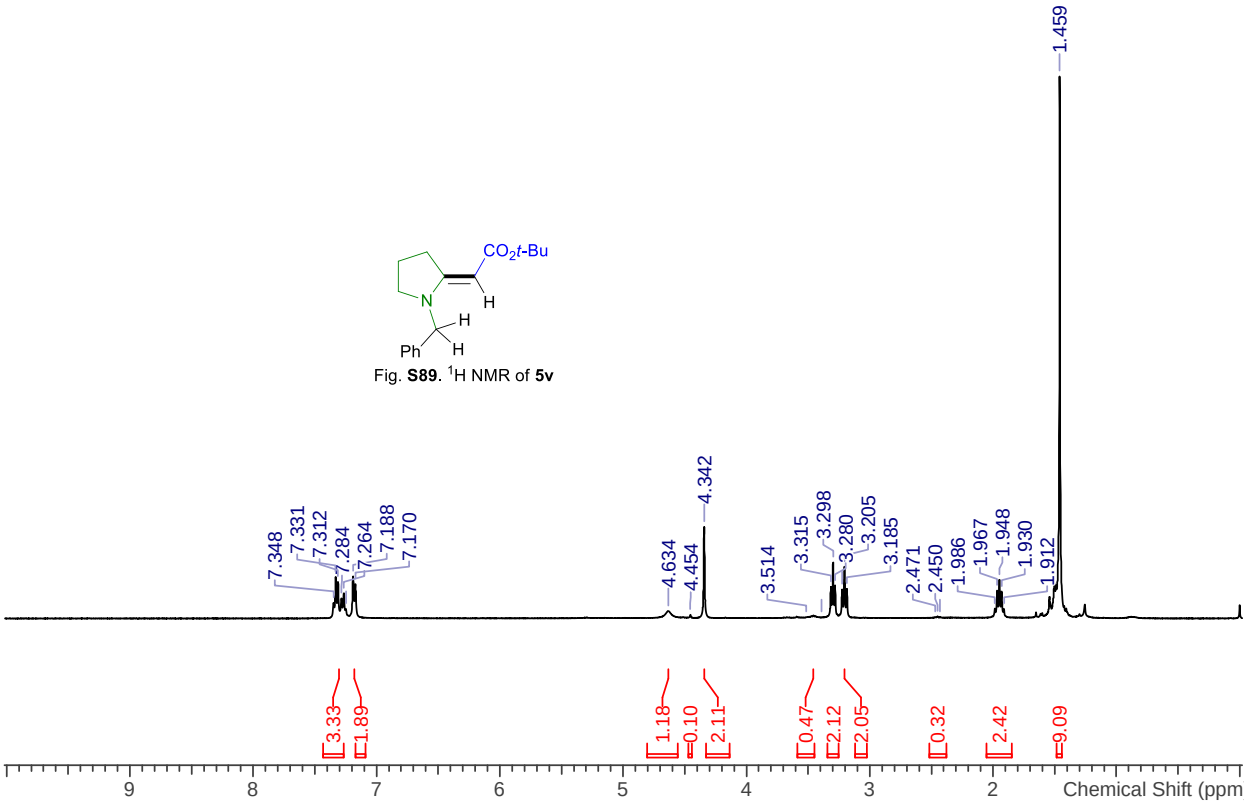


Fig. **S89**. ^{1}H NMR of **5v**

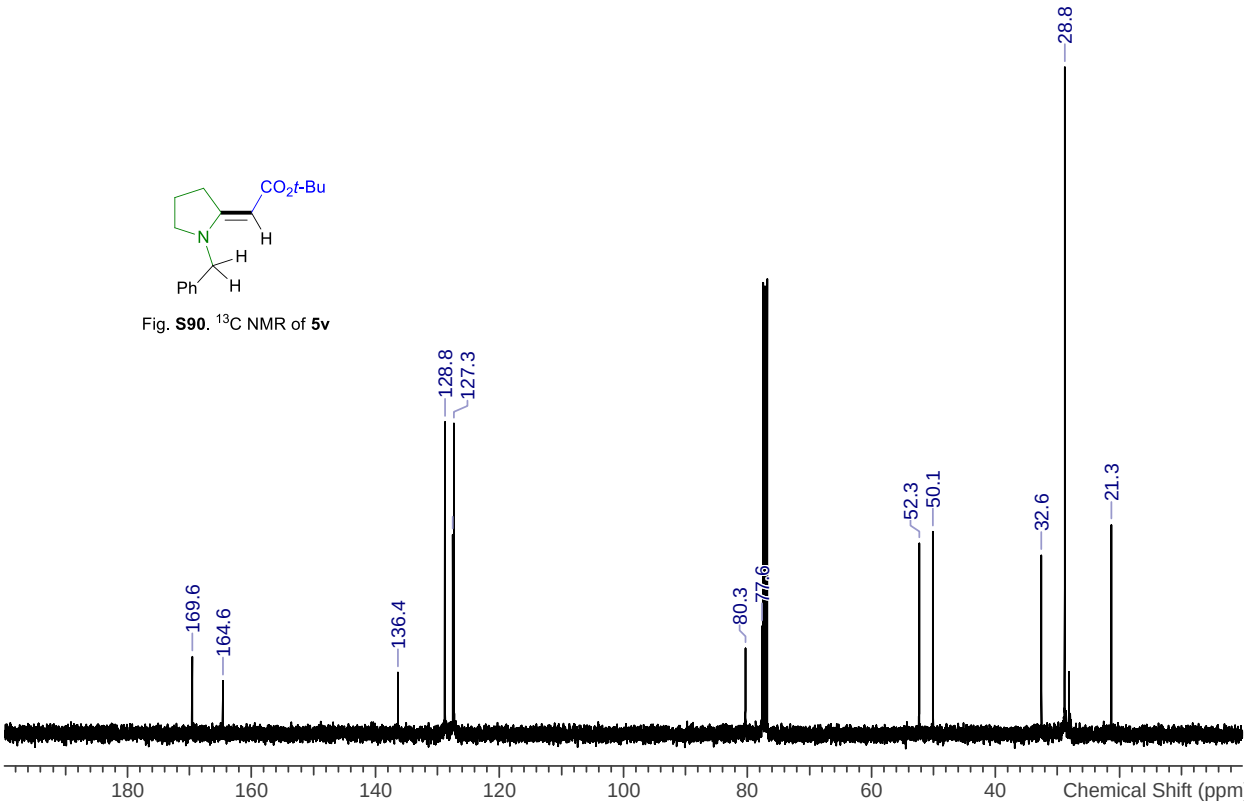


Fig. **S90**. ^{13}C NMR of **5v**

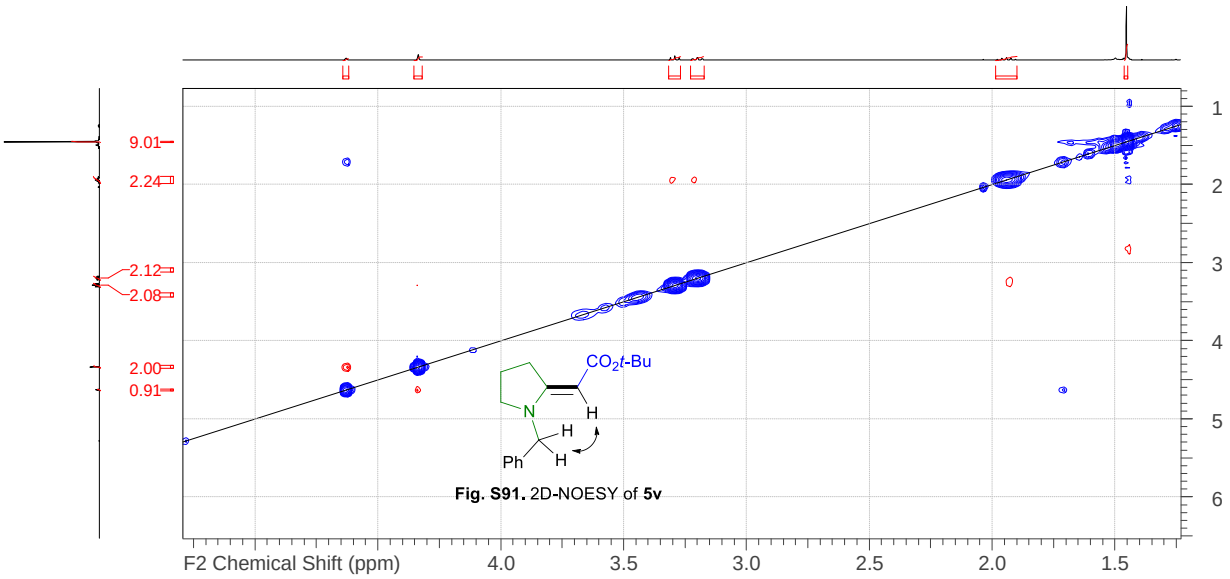


Fig. S91. 2D-NOESY of **5v**

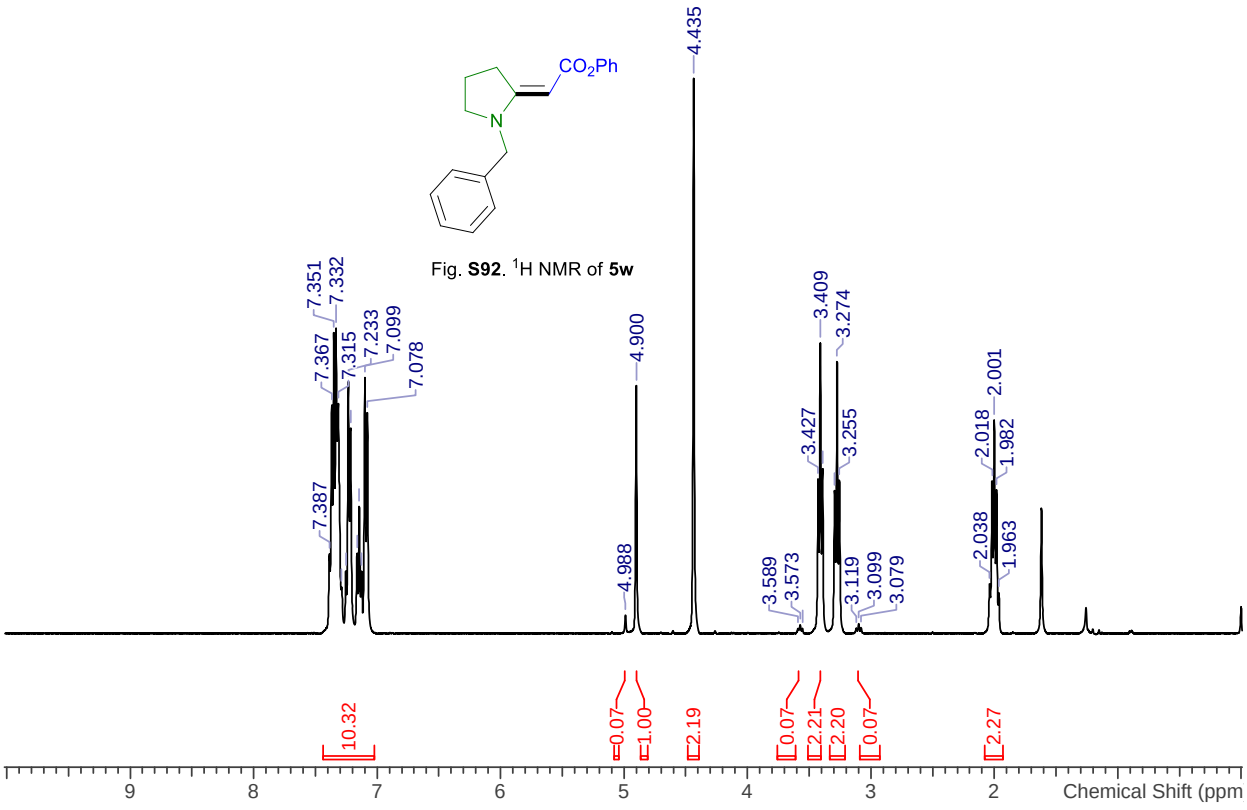


Fig. **S92**. ^{1}H NMR of **5w**

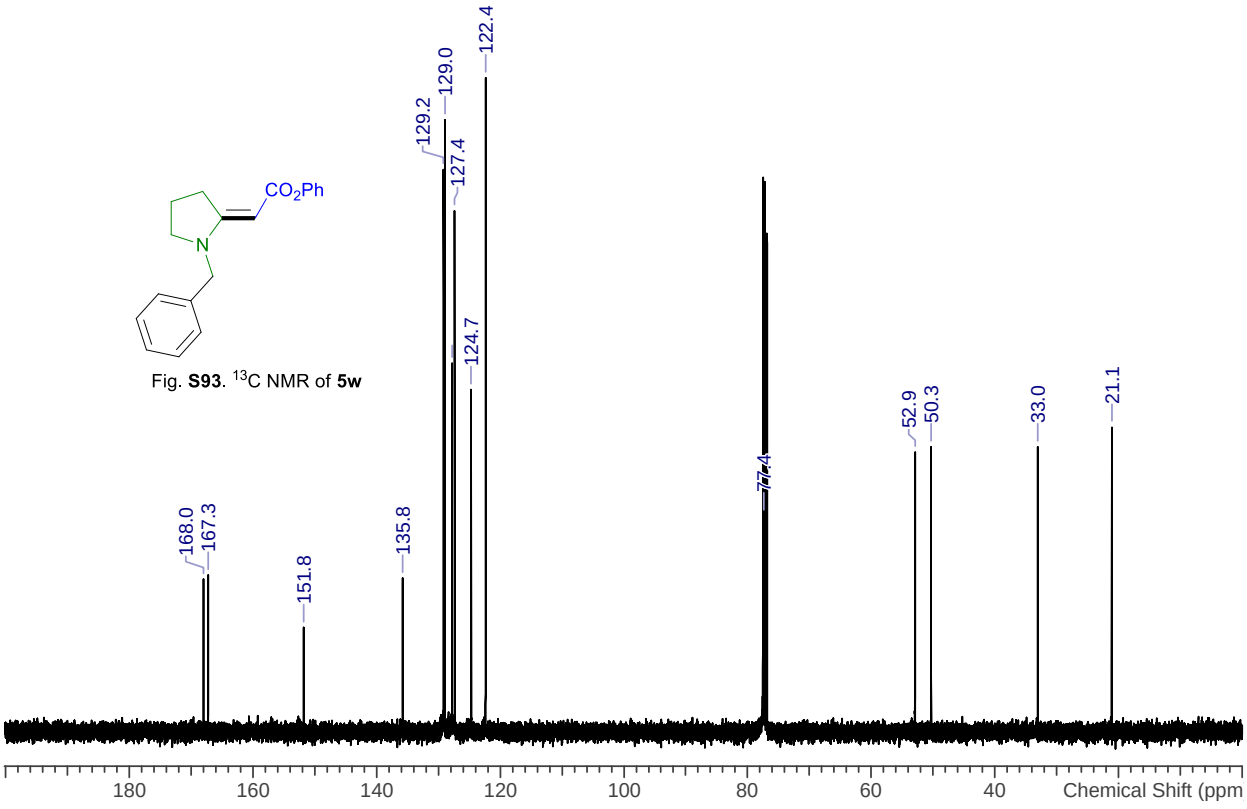


Fig. **S93**. ^{13}C NMR of **5w**

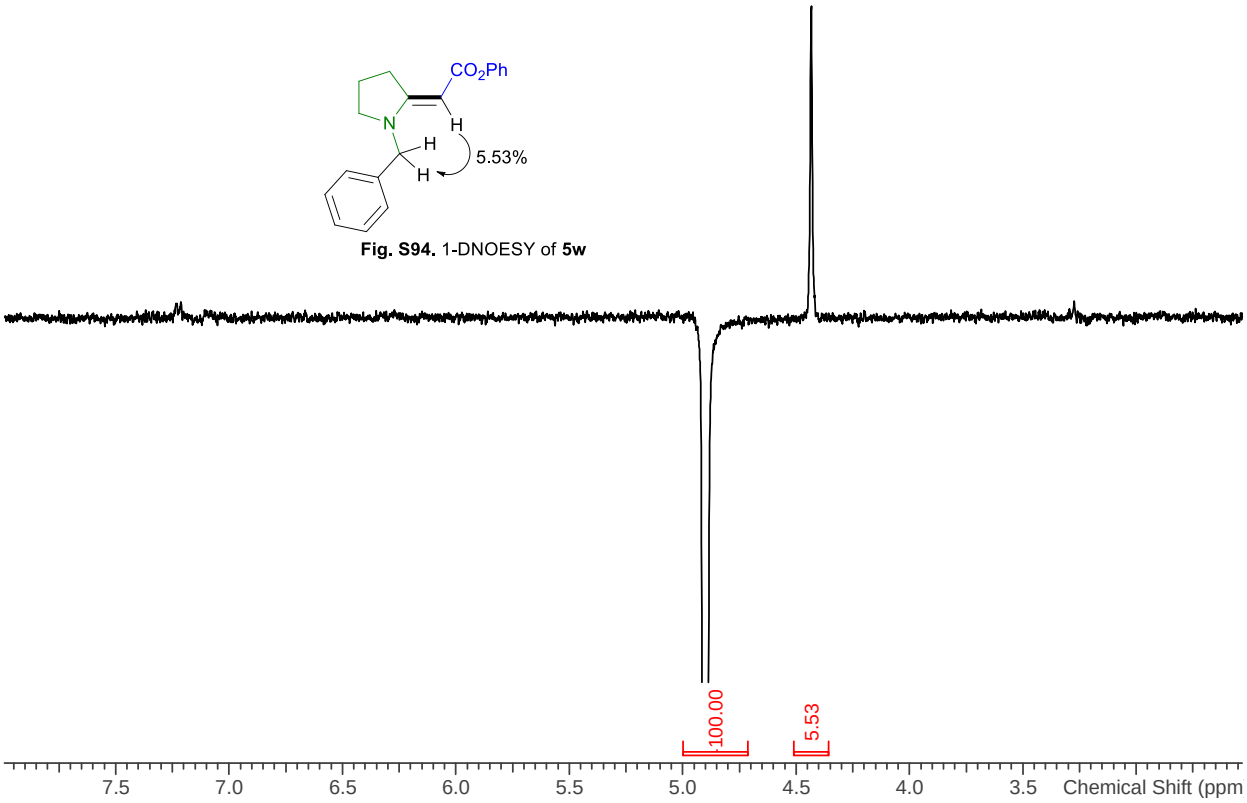


Fig. S94. 1-DNOESY of **5w**

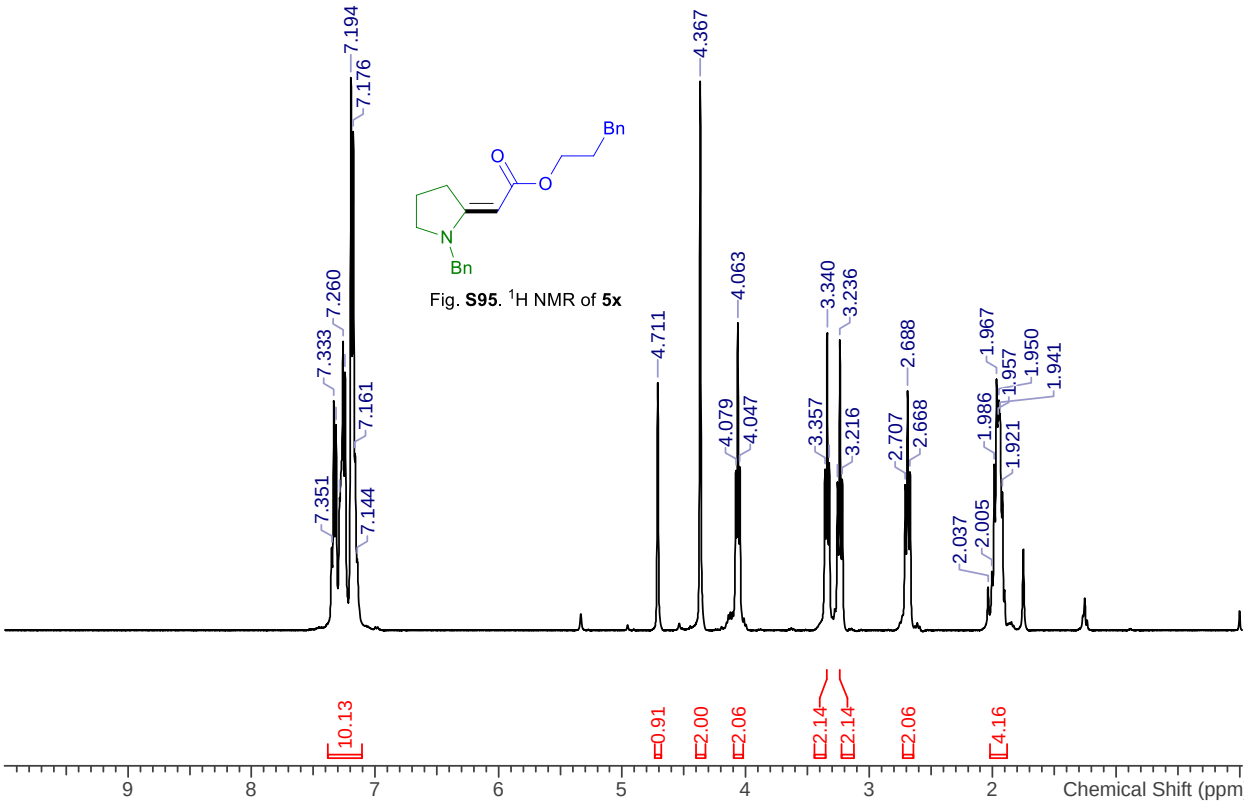


Fig. **S95**. ^{1}H NMR of **5x**

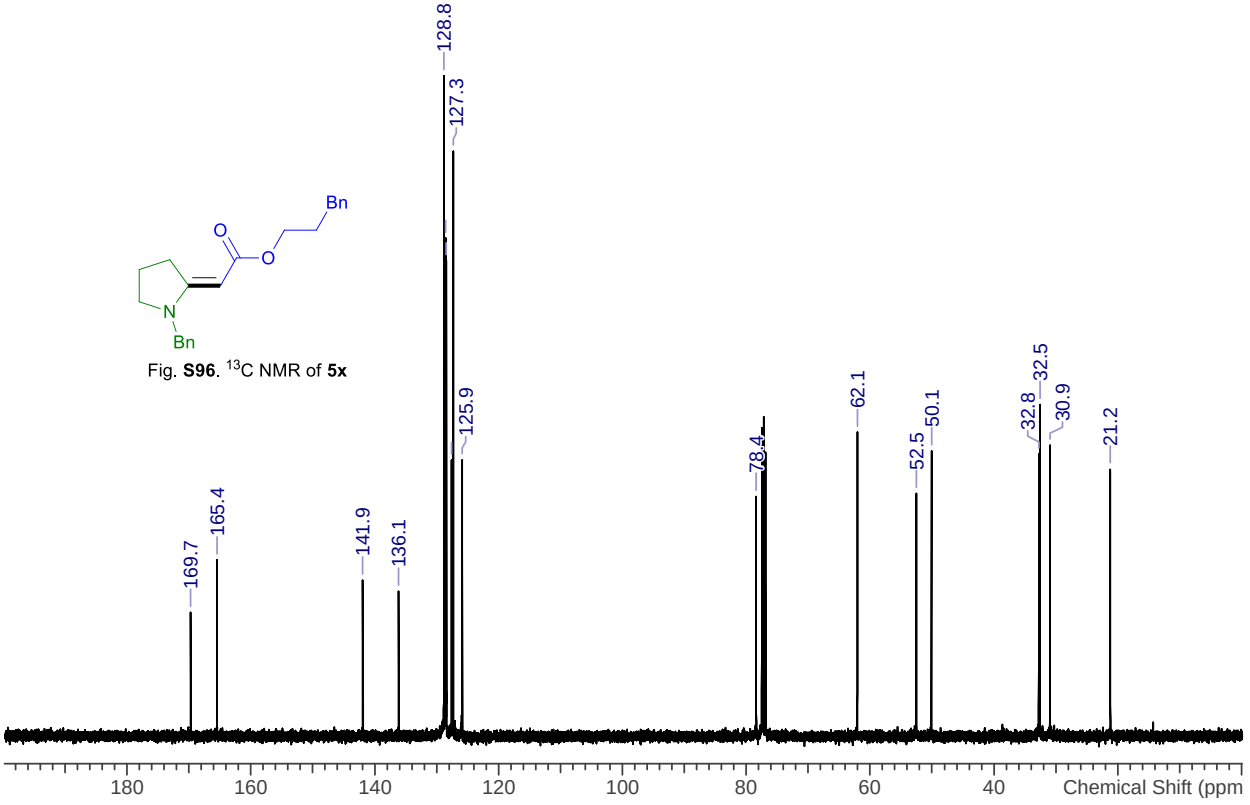


Fig. **S96**. ^{13}C NMR of **5x**

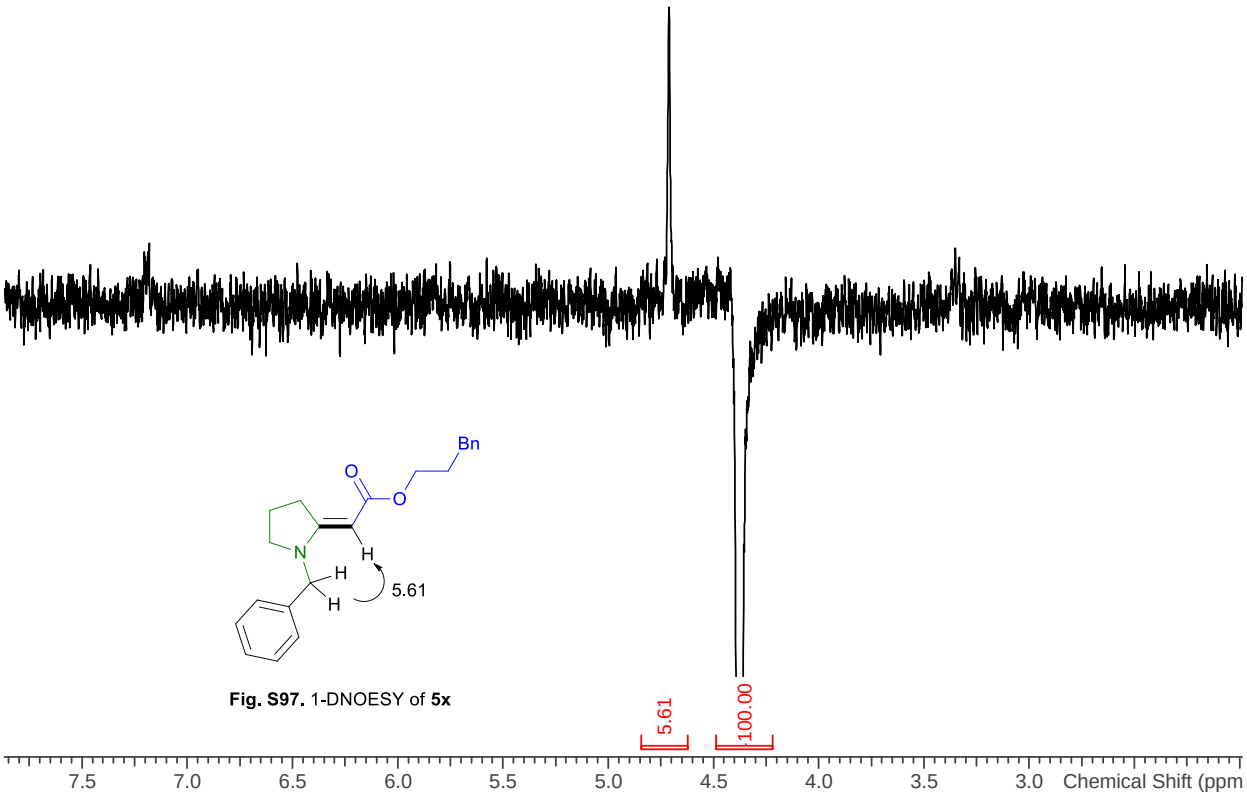


Fig. S97. 1-DNOESY of **5x**

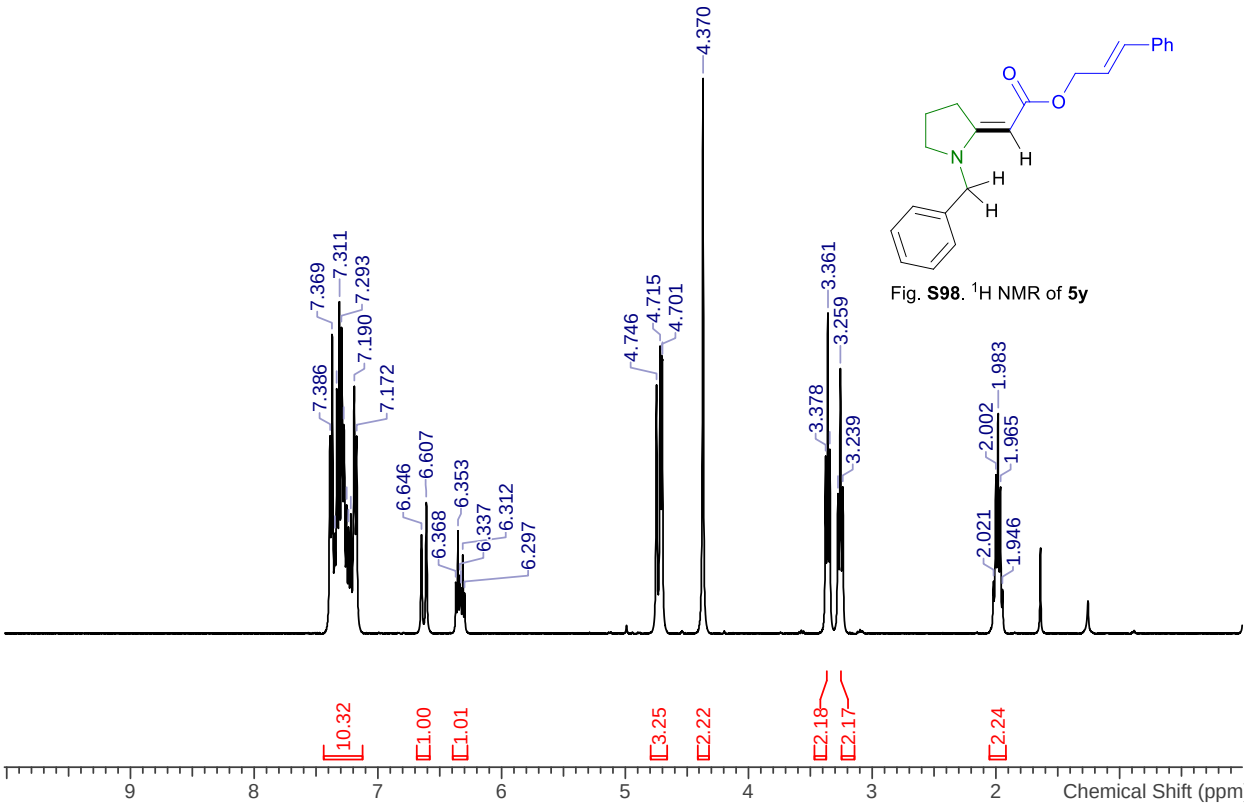


Fig. **S98**. ^{1}H NMR of **5y**

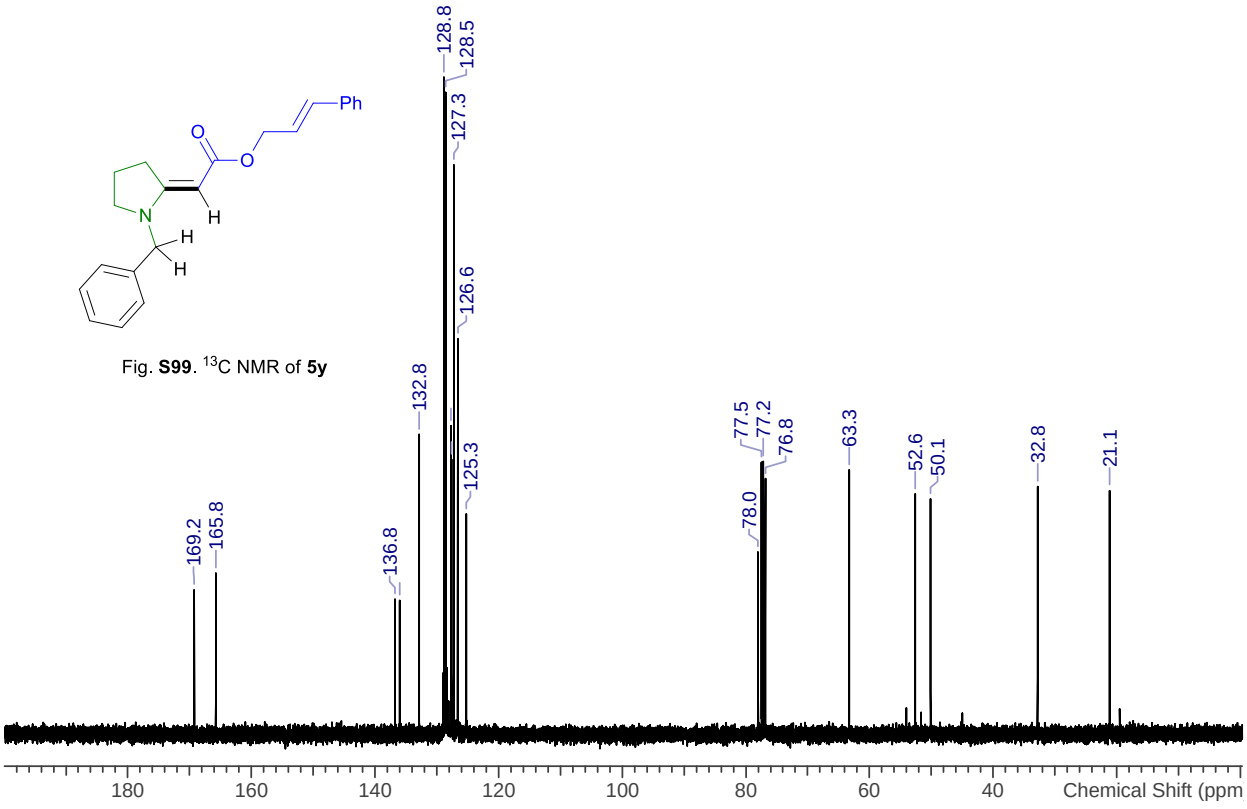


Fig. **S99**. ^{13}C NMR of **5y**

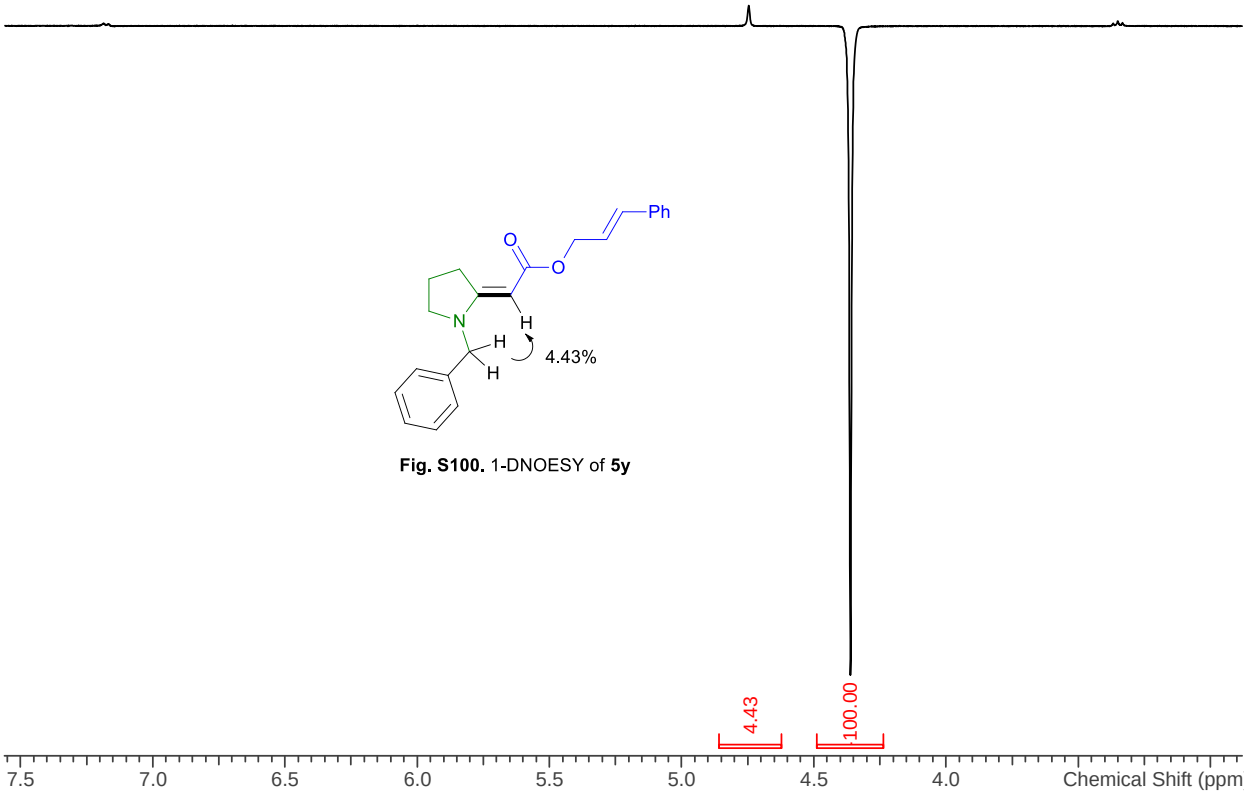


Fig. S100. 1-DNOESY of **5y**

Tabulated ^{1}H and ^{13}C chemical shift values of **5z**

Figure S101. (*E*)-(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-(1-benzylpyrrolidin-2-ylidene)acetate (**5z**)

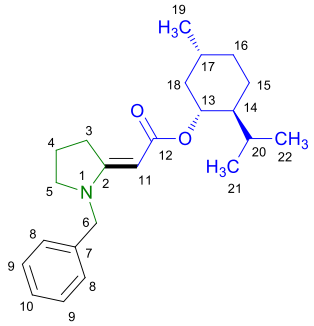


Table S3. In $CDCl_3$

Position	δC in ppm	δH in ppm (*J* in Hz)
2	165.3	
3	32.8	3.26–3.16, m
4	21.3	2.05–1.92, m
5	52.4	3.31, t (7.2)
6	50.2	4.04–4.31, m
7	136.3	
8	128.9	7.35–7.18, m
9	127.4	
10	127.6	
11	78.9	4.69–4.63, m
12	169.4	
13	71.7	4.69–4.63, m
14	47.6	1.36–1.30, m
15	23.8	1.75–1.41, m 1.09–0.84, m
16	34.7	1.75–1.41, m 1.09–0.84, m
17	31.6	1.75–1.41, m
18	41.9	2.05–1.92, m 1.09–0.84, m
19	16.7	0.78, d (6.8)
20	26.4	2.05–1.92, m
21 and 22	22.3 and 21.0	1.09–0.84, m

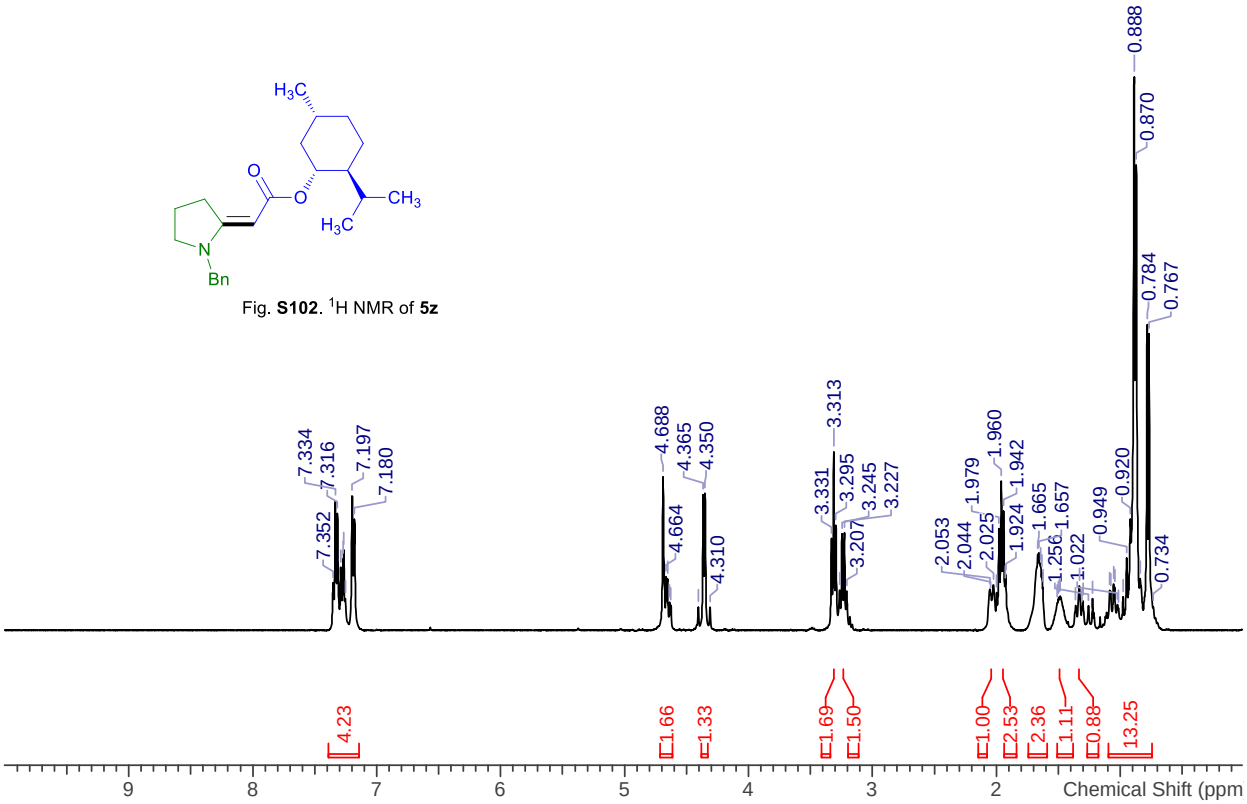


Fig. **S102**. ^{1}H NMR of **5z**

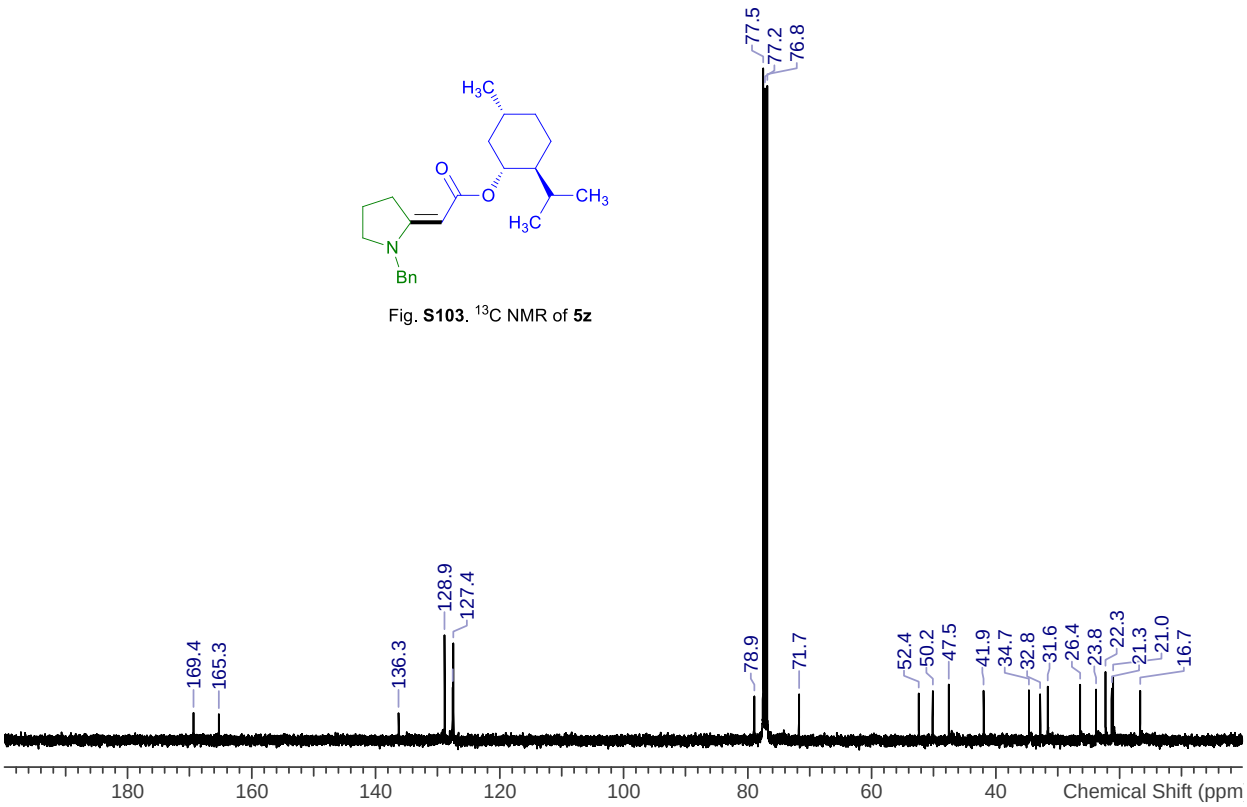


Fig. **S103**. ^{13}C NMR of **5z**

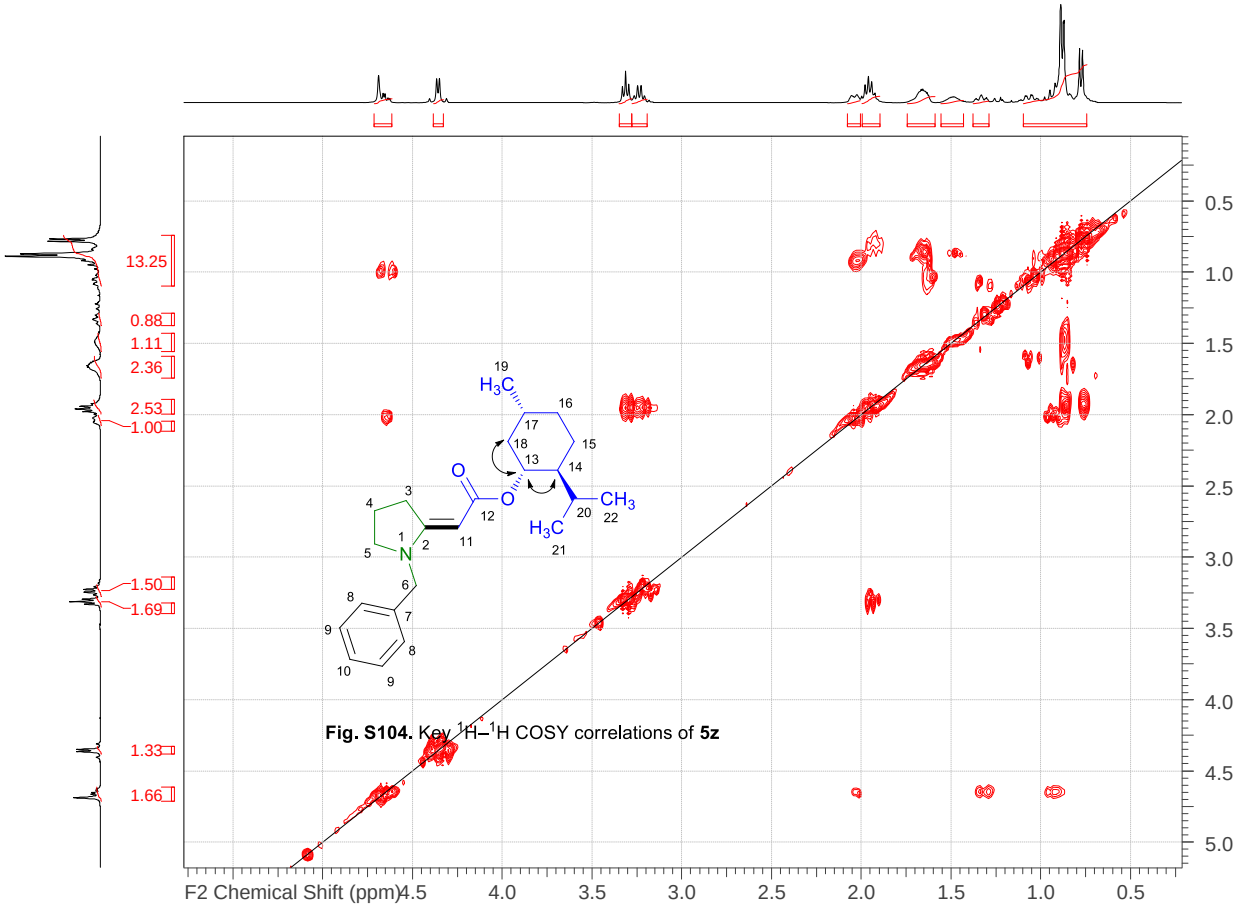


Fig. S104. Key ^{1}H–^{1}H COSY correlations of **5z**

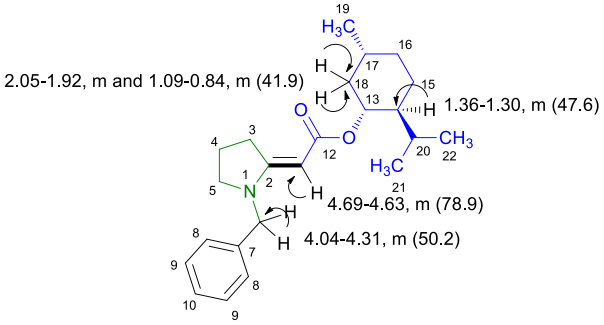
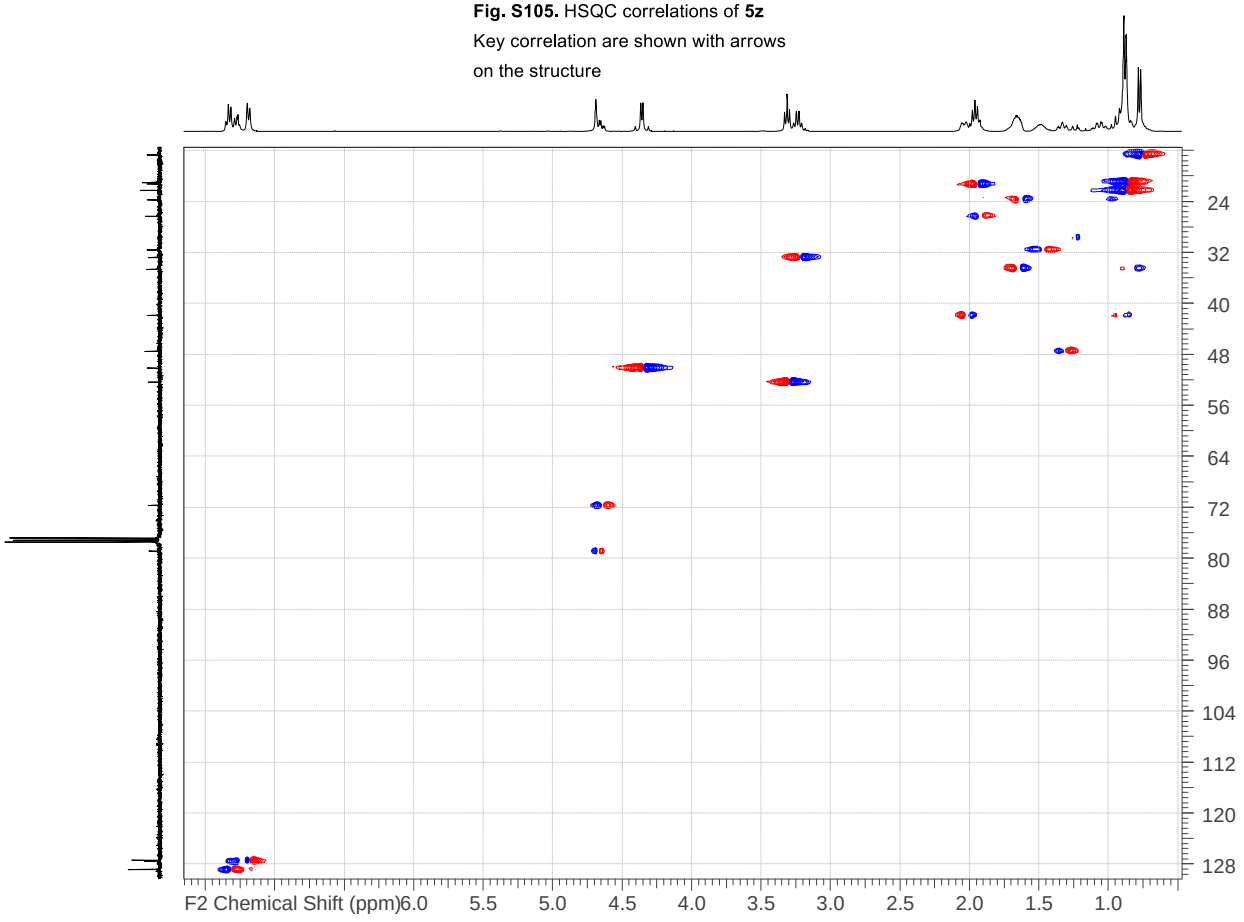


Fig. S105. HSQC correlations of **5z**
Key correlation are shown with arrows
on the structure



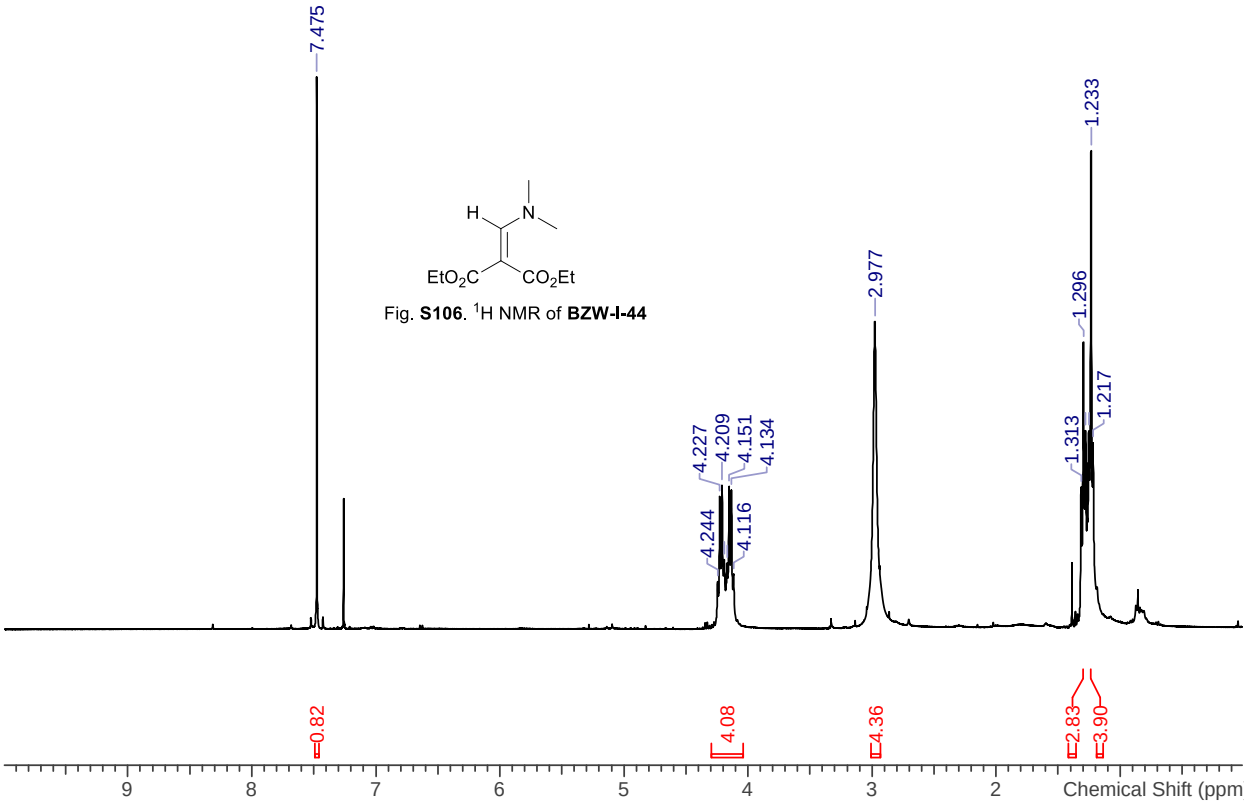


Fig. **S106**. ^{1}H NMR of **BZW-I-44**

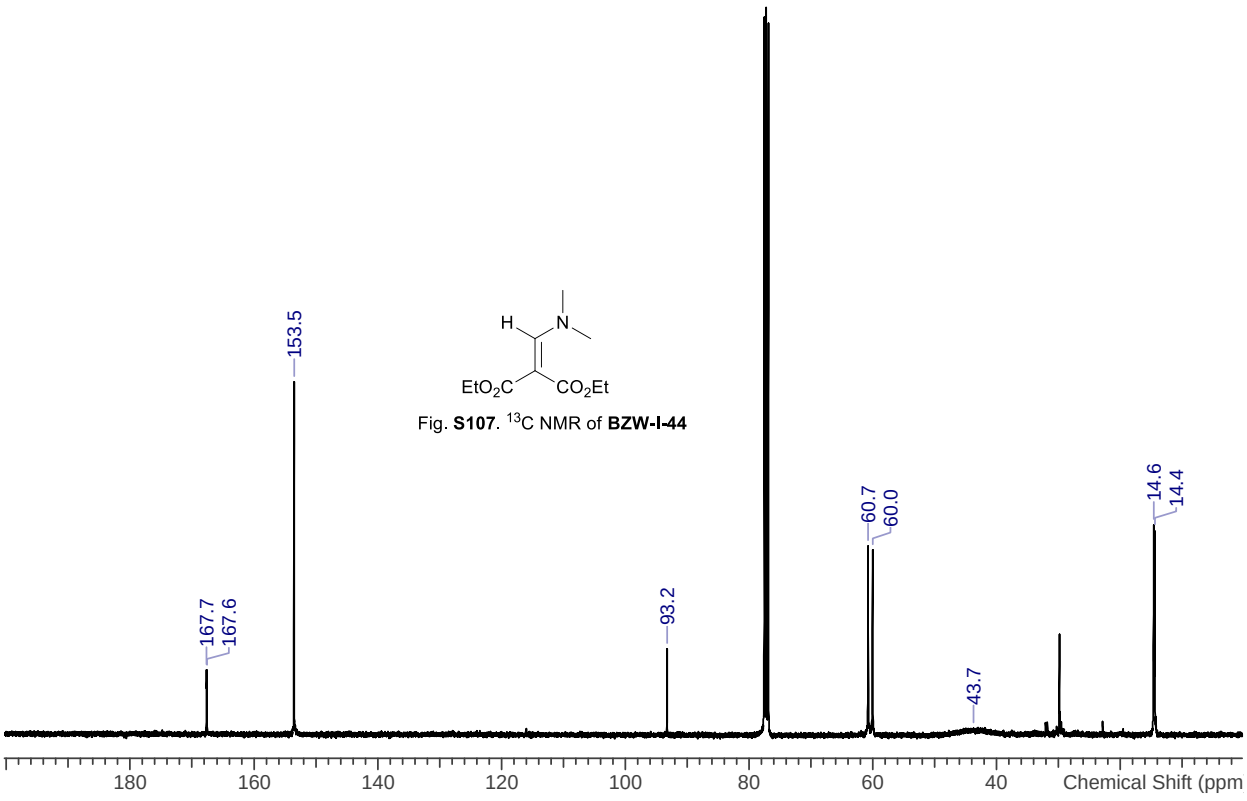


Fig. **S107**. ^{13}C NMR of **BZW-I-44**

Table S4. Docking energies of the compounds in descending order. The energies are from AutoDock Vina.

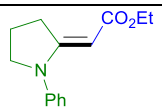
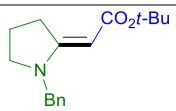
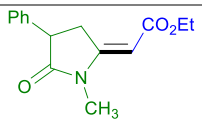
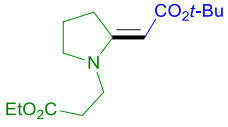
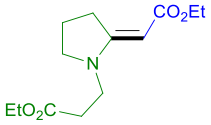
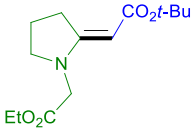
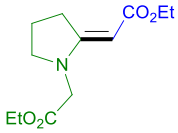
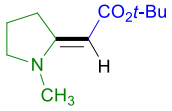
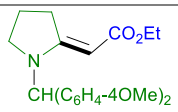
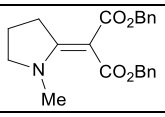
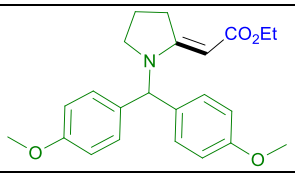
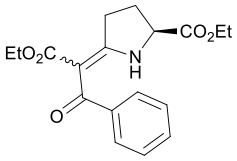
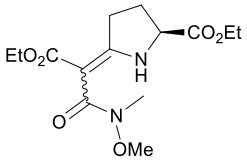
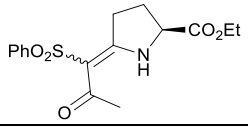
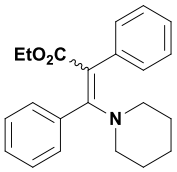
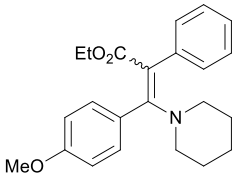
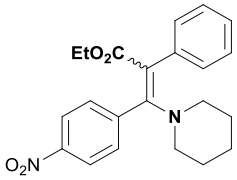
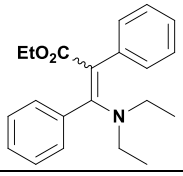
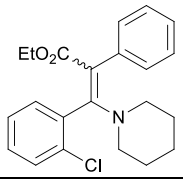
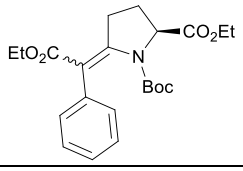
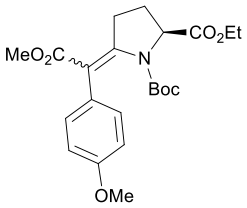
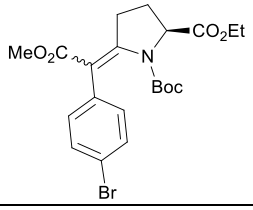
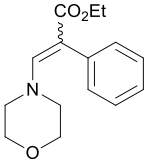
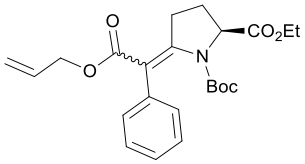
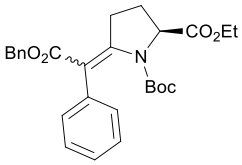
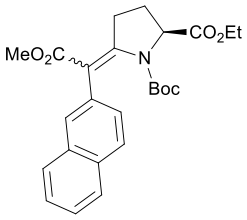
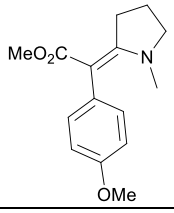
		Docking energy (kcal/mol)	
Label of sample	**Formula weight**	**Binding site 1**	**Binding site 2**
 5d	231.30	-5.3	-7.3
 5v	273.38	-4.3	-7.1
 5j	259.12	-4.4	-7
 5s	283.18	-5.6	-6.4
 5f	255.15	-5.6	-6.4
 5t	269.34	-4.1	-6.2
 **5e**	241.28	-5.8	-5.9
 5u	197.27	-4.2	-5.7
 5c	381.47	-4.7	-5.4
Indolizidine (–)-237D	237.42	-5.4	-5.9

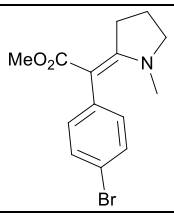
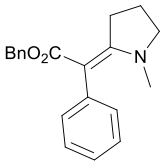
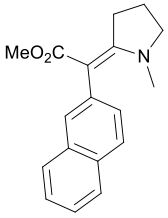
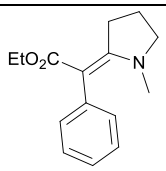
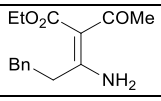
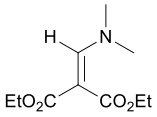
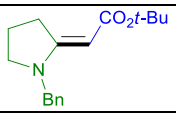
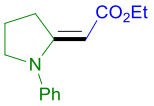
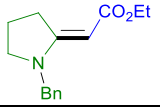
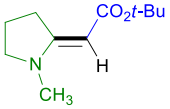
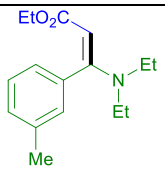
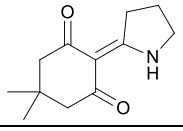
Table S5. Main protein-ligand interactions of the α6β2 nAChR-compounds complexes.

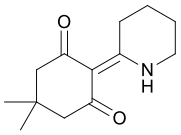
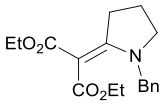
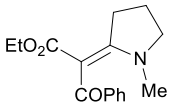
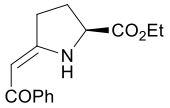
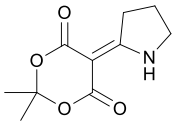
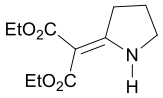
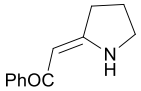
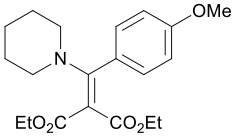
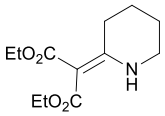
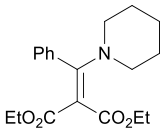
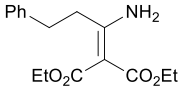
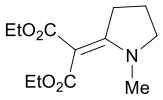
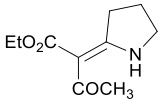
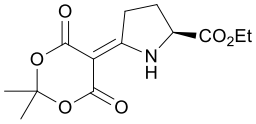
Label of sample	Hydrophobic contacts	Salt bridges	Hydrogen bonding	Pi-stacking
5v	α6 = {Tyr123, Trp179, Thr180, Tyr220, Glu224} β2 = { Trp82, Val136, Phe144, Leu146}			α6 = (Tyr227)
5d	α6 = {Tyr220, Tyr227} β2 = { Thr84, Val136, Phe144, Leu146}			
5u	α6 = {Glu224} β2 = {Val136, Leu146}	β2 = {Lys104}	α6 = {Tyr227}	
5t	α6 = {Glu224, Tyr227} β2 = {Val136, Phe144, Leu146}	β2 = {Lys188}		
5s	α6 = {Tyr220, Glu224, Tyr227} β2 = {Val136, Phe144, Leu146}	β2 = {Lys188}		
5f	α6 = {Trp179, Thr180, Tyr220, Tyr227} β2 = { Trp82, Phe144, Leu146}	β2 = {Lys104}	α6 = {Glu224, Glu225, Tyr227}	
5e	α6 = {Tyr220, Tyr227} β2 = {Thr84, Val136, Phe144}		α6 = {Glu224}	
5j	α6 = {Trp179, Tyr220, Tyr227} β2 = {Trp82, Lys104, Val136, Phe144, Leu146}			
5c	α6 = {Glu224} β2 = {Thr84, Phe144}	β2 = {Lys188}		
Indolizidine (–)-237D	α6 = {Trp179, Thr180, Tyr220, Tyr227} β2 = { Leu146}			

Table S6. Structures of enamino carbonyl compounds screened for antimicrobial activity against common pathogens.

Entry	Label	Structure
1[25]	AK-I-118	
2	**5c**	
3[26]	AP-I-164	
4[26]	AP-I-165	
5[26]	AP-I-169	
6[27]	AP-II-43	
7[27]	AP-II-45	
8[27]	AP-II-47	
9[27]	AP-II-51	

10[27]	AP-II-55	
11[27]	AP-II-61	
12[27]	AP-II-100	
13[27]	AP-II-103	
14[27]	AP-II-104	
15[27]	AP-II-124	
16[27]	AP-II-129	
17[27]	AP-II-139	
18[27]	AP-II-142	

19[27]	AP-II-144	
20[27]	AP-II-153	
21[27]	AP-II-156	
22[27]	AP-II-161	
23[4]	BNH-I-49	
24	BZW-I-44	
25	**5v**	
26	**5d**	
27	**5a**	
28	**5u**	
29	**5k**	
30[3, 4]	NK-III-30	

31[3]	NK-III-49	
32[4]	NK-IV-8	
33[1]	NK-IV-49	
34[4]	NK-VII-15	
35[3]	NK-VII-18	
36[3, 4]	NK-VIII-91	
37[4, 26]	NK-VIII-169	
38[26]	NR-I-49	
39[3, 26]	SRH-II-47	
40[3, 26]	SRH-III-09	
41[3, 4]	SRH-III-27	
42[4, 26]	SRH-III-28	
43[3, 4]	SRH-III-48	
44[3]	SRH-IV-39	

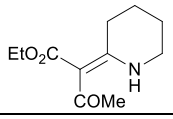
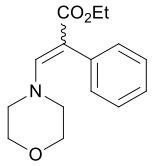
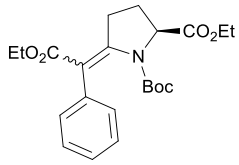
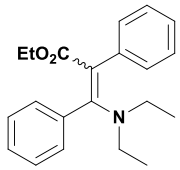
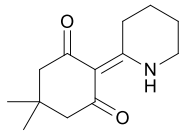
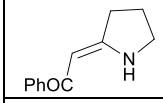
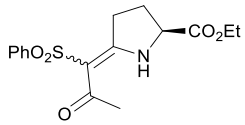
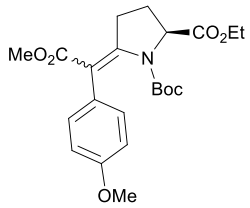
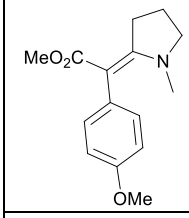
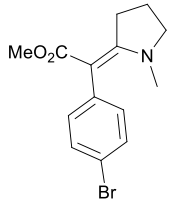
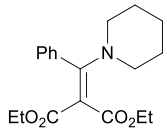
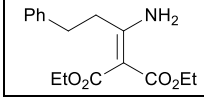
45[1]	BNH-II-01	

Table S7. Effective enamino carbonyl compounds showing antimicrobial activity against common microbial pathogens.

Sample Name	Concentration (mM) in DMSO	Zone of Inhibition (in Centimeter)			
		Community acquired MRSA (83 45-3-3)	Hospital acquired MRSA (4656)	*Campylobacter Jejuni* 0D2-67	*Candida albicans* Y-80
AP-II-104 	17.6	-	-	2	-
AP-II-61 	7.44	-	-	2.65	-
AP-II-51 	17	0.9	1.3	-	1.3
NK-III-49 	58.23	2.2	2.8	-	3.5

NK-VIII-169 	53.41	1.1	-	1.2	1.2
AP-I-169 	12.2	1.6	1.8	2	1.75
AP-II-100 	7.15	0.95	1	4.7	0.9
AP-II-142 	15.3	0.95	1.4	4.7	0.95
AP-II-144 	10.6	0.95	1	1.85	1.3
SRH-III-09 	22.07	1.3	1.4	2.1	1.7
SRH-III-27 	14.76	1.3	1.2	1.8	1.6

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