

Exploring the Synthetic Potential of γ -Lactam Derivatives Obtained from a Multicomponent Reaction. Applications as Antiproliferative Agents.

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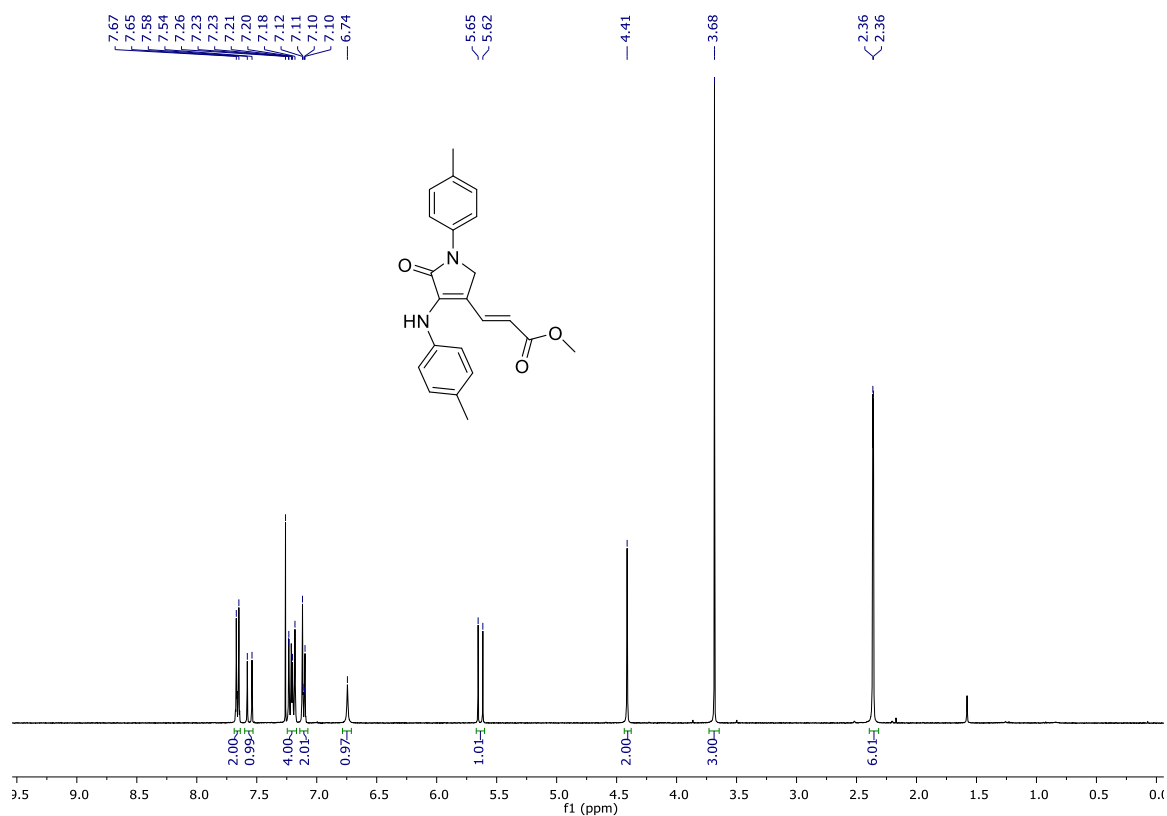
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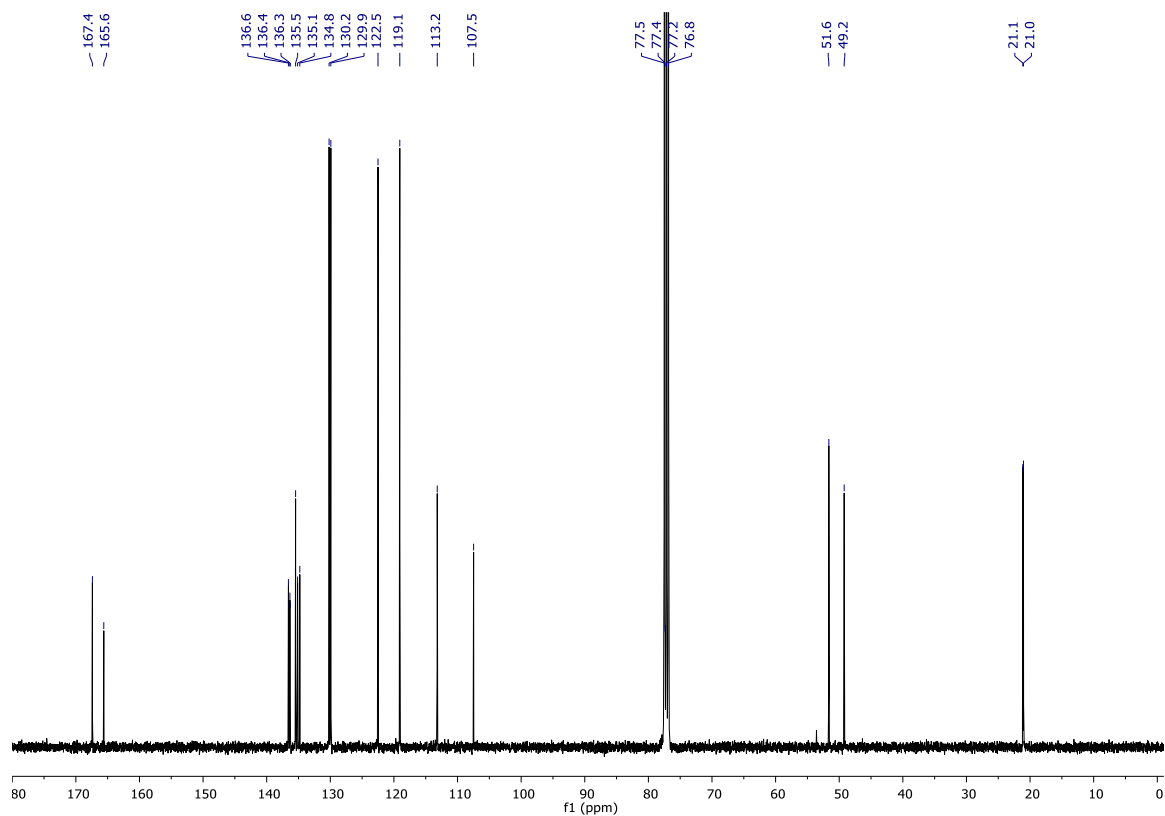
1. Characterization by NMR Spectroscopy of products 7-10.

Methyl (E)-3-(5-oxo-1-(p-tolyl)-4-(p-tolylamino)-2,5-dihydro-1H-pyrrol-3-yl)acrylate (7a).

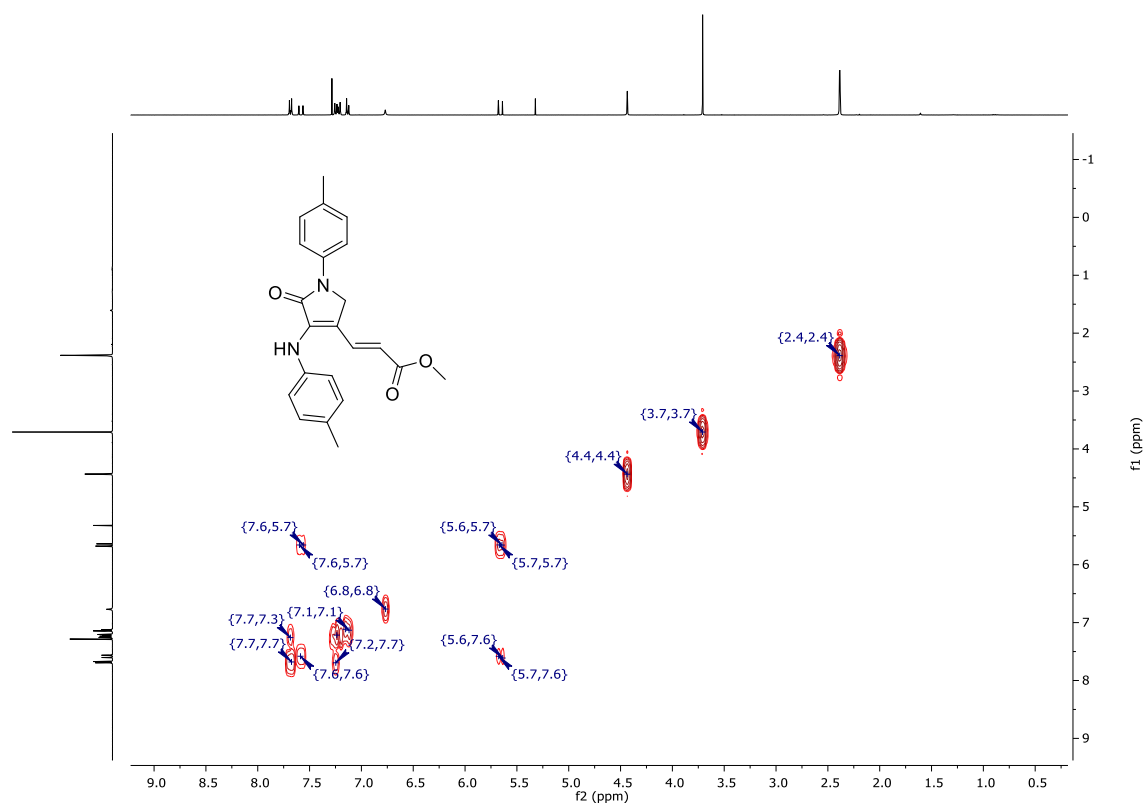
^1H NMR (400 MHz, CDCl_3)



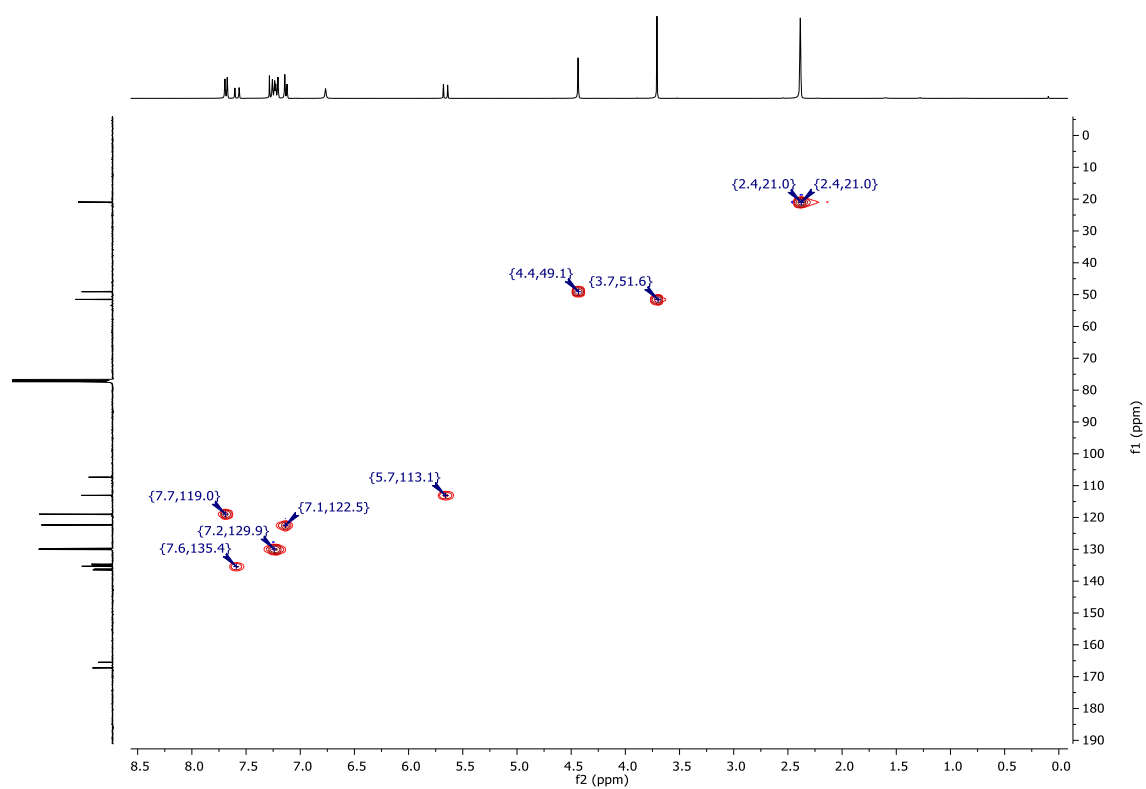
^{13}C NMR { ^1H } (101 MHz, CDCl_3)



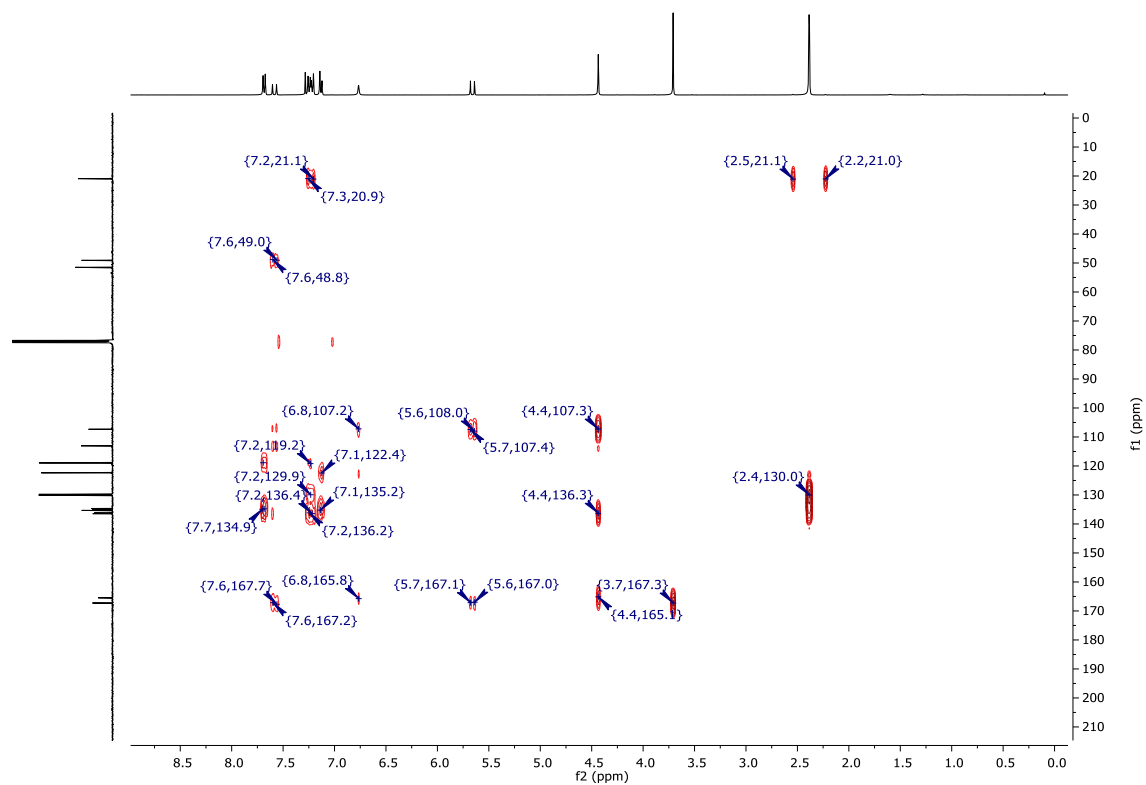
2D-COSY NMR {¹H – ¹H} (400 MHz, CDCl₃)



2D-HSQC NMR {¹H – ¹³C} (¹H: 400 MHz, ¹³C: 101 MHz, CDCl₃)

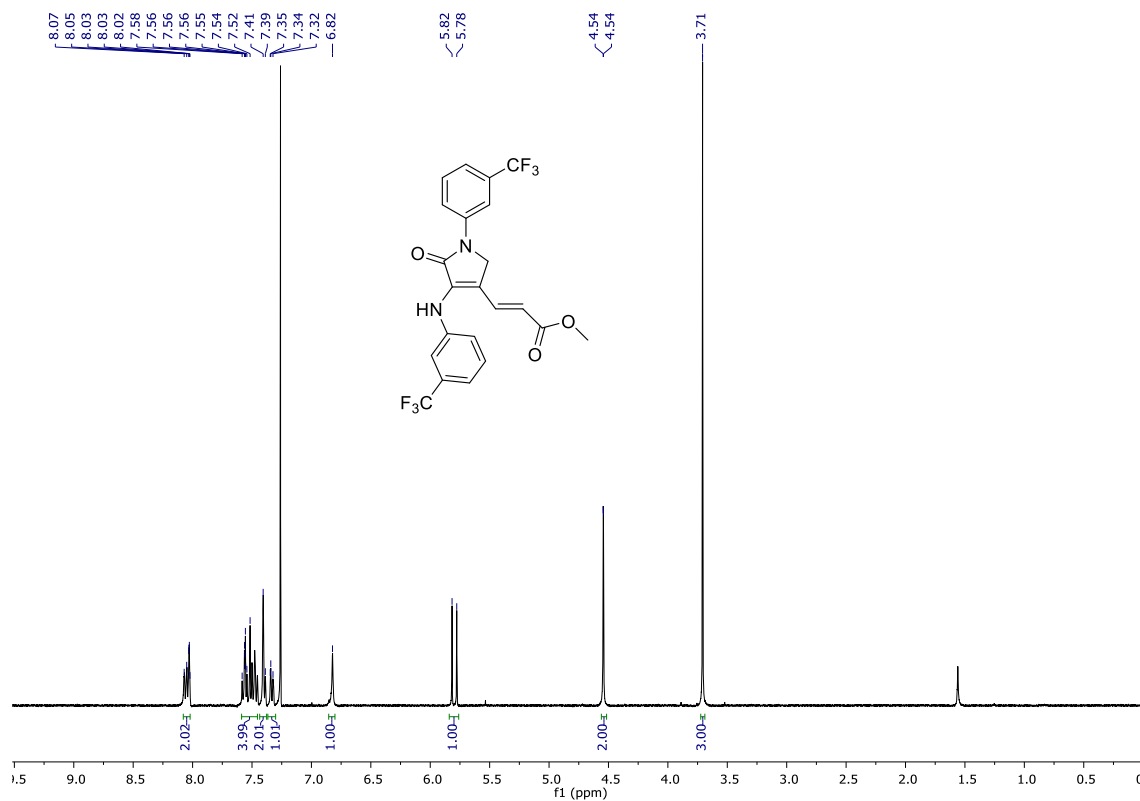


2D-HMBC NMR ($^1\text{H} - ^{13}\text{C}$) (^1H : 400 MHz, ^{13}C : 101 MHz, CDCl_3)

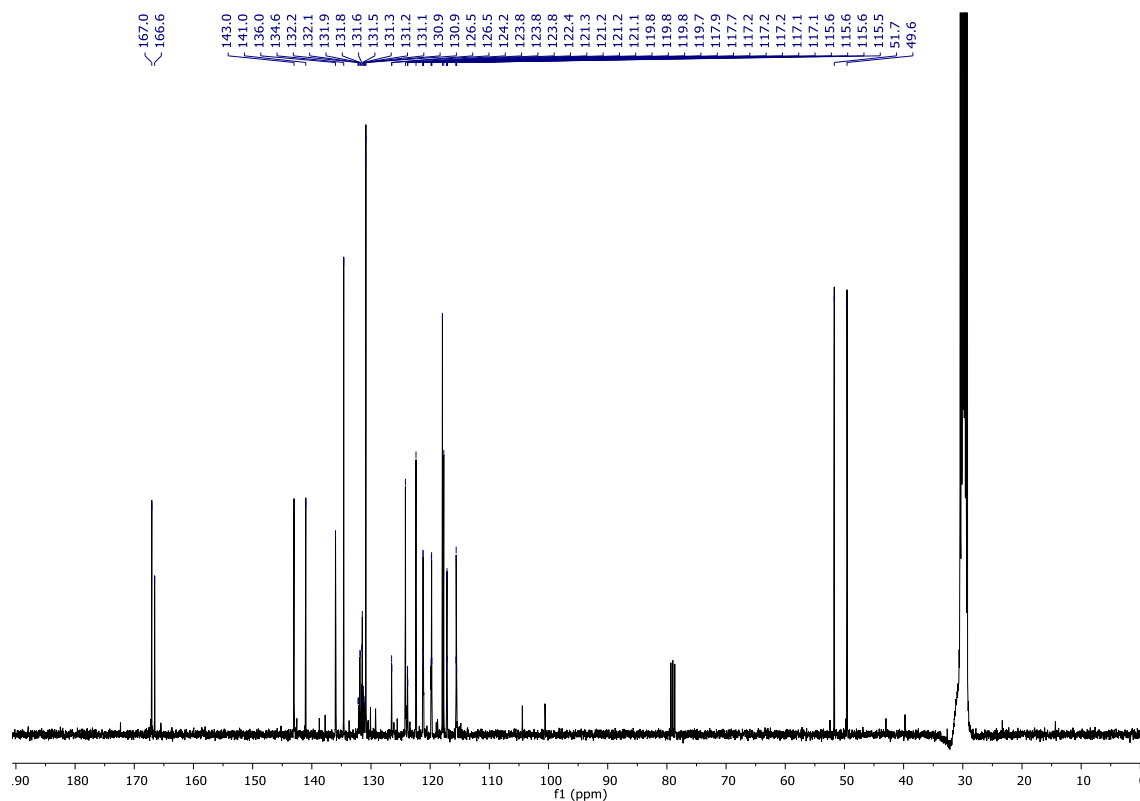


Methyl (E)-3-(5-oxo-1-(3-(trifluoromethyl)phenyl)-4-((3-(trifluoromethyl)phenyl)amino)-2,5-dihydro-1H-pyrrol-3-yl)acrylate (7b).

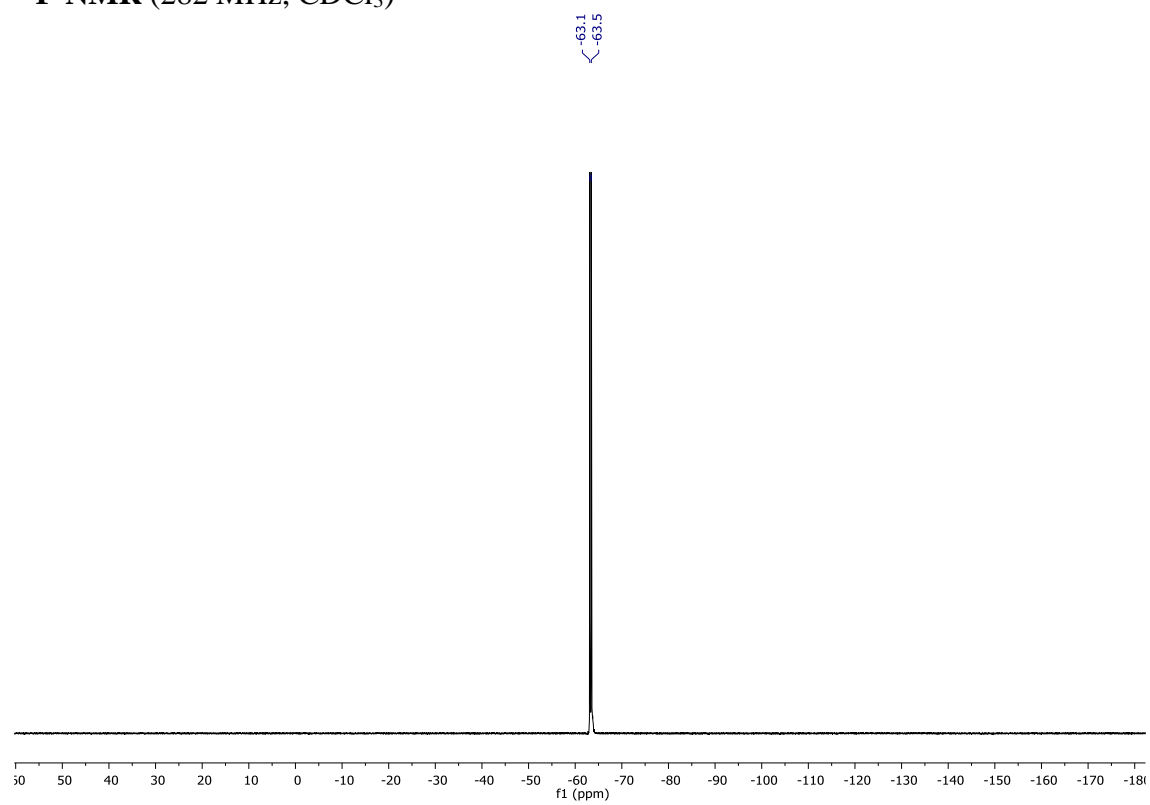
¹H NMR (400 MHz, CDCl₃)



¹³C NMR {¹H} (101 MHz, Acetone d₆)

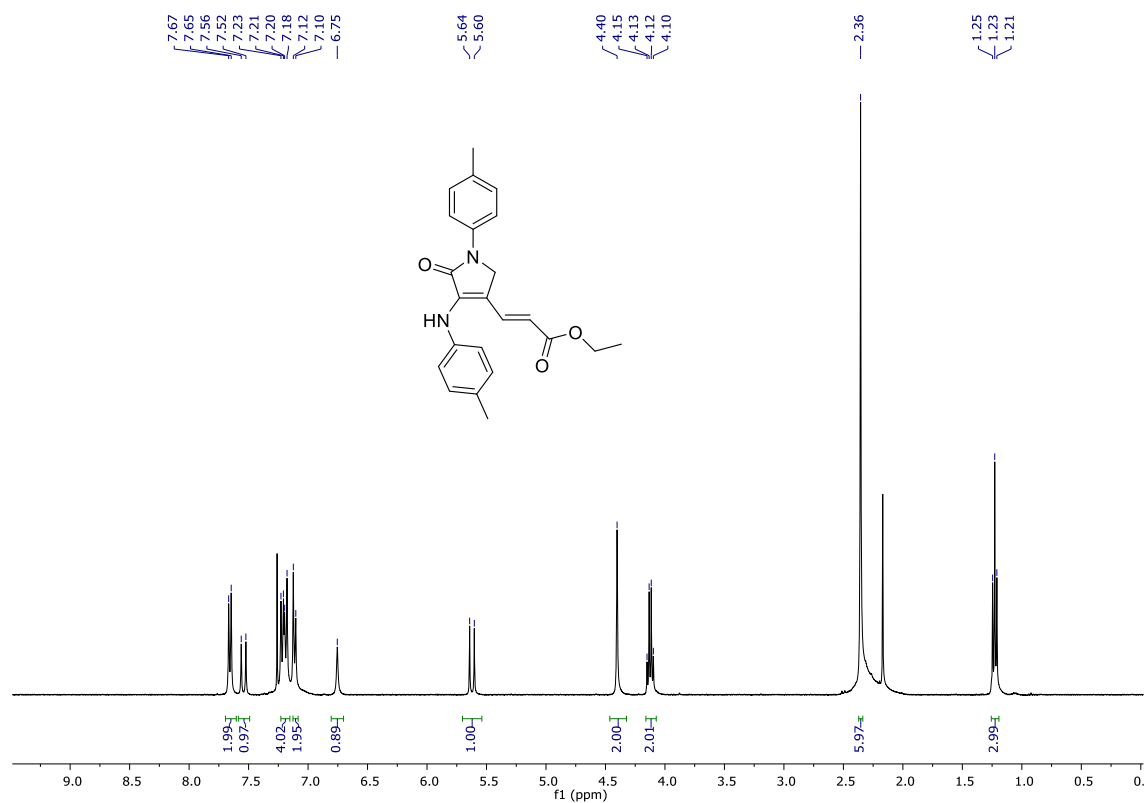


^{19}F -NMR (282 MHz, CDCl_3)

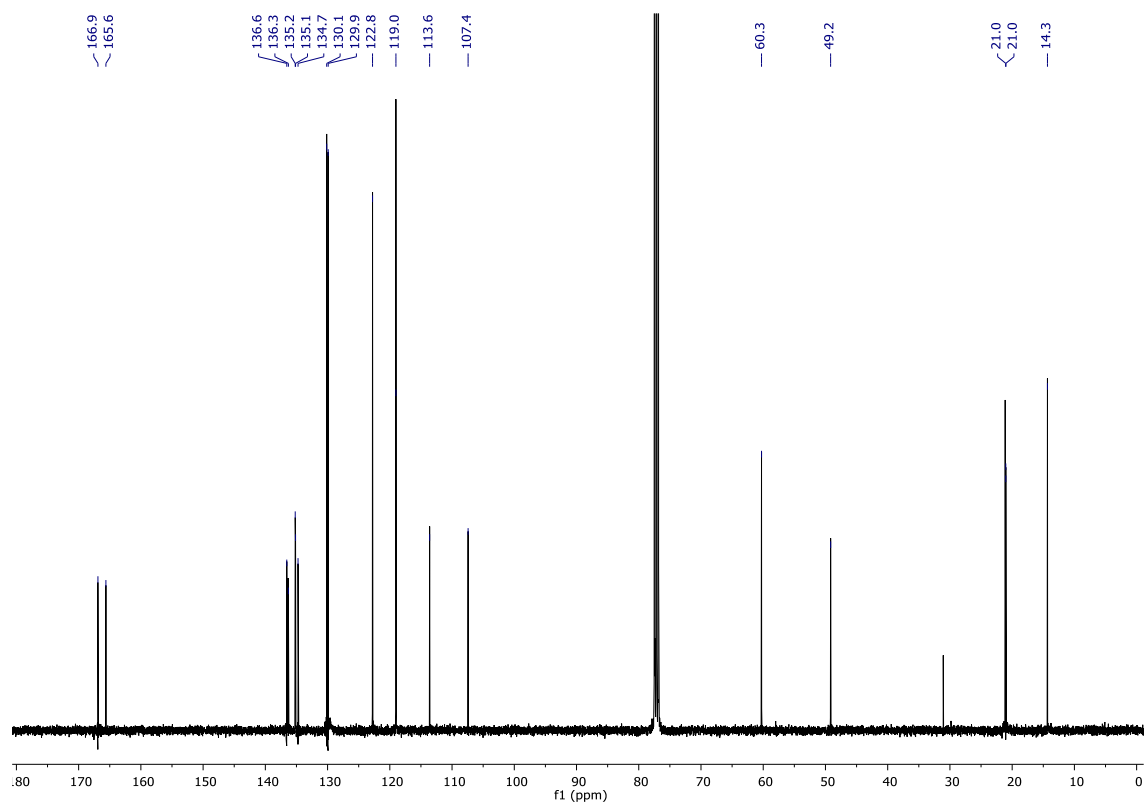


Ethyl (*E*)-3-(5-oxo-1-(*p*-tolyl)-4-(*p*-tolylamino)-2,5-dihydro-1*H*-pyrrol-3-yl)acrylate
(7c).

¹H NMR (400 MHz, CDCl₃)

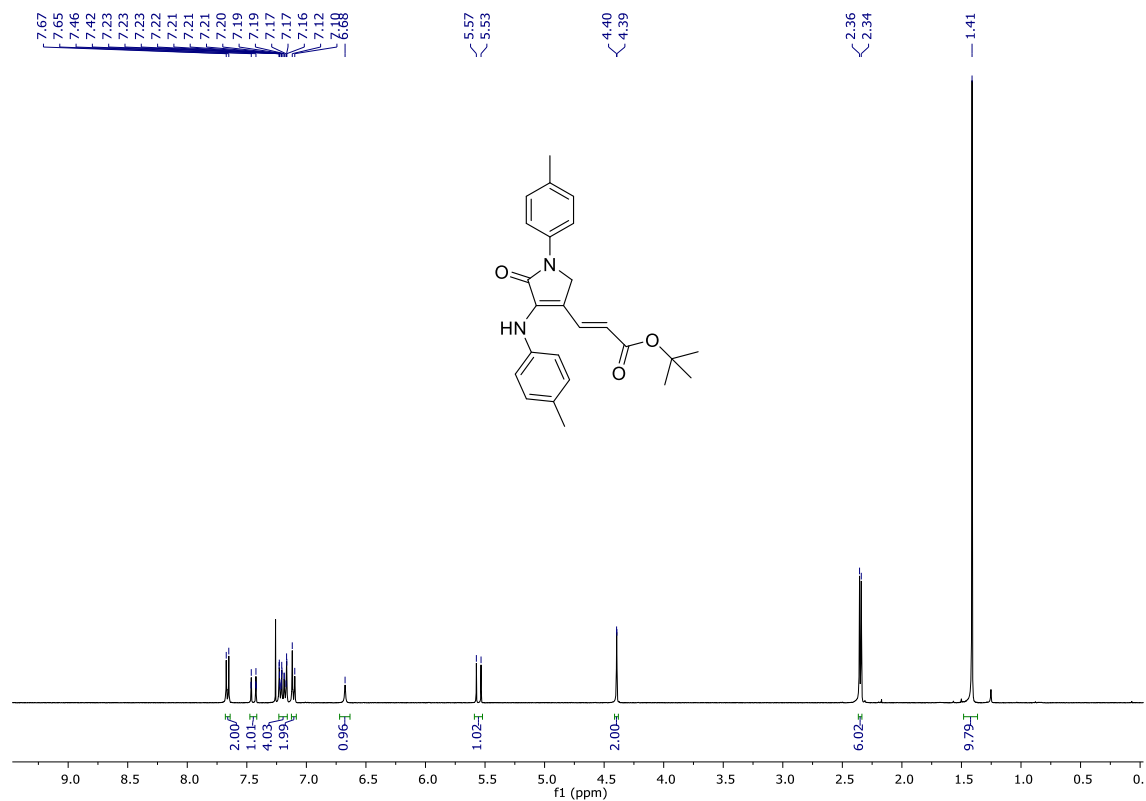


¹³C NMR {¹H} (101 MHz, CDCl₃)

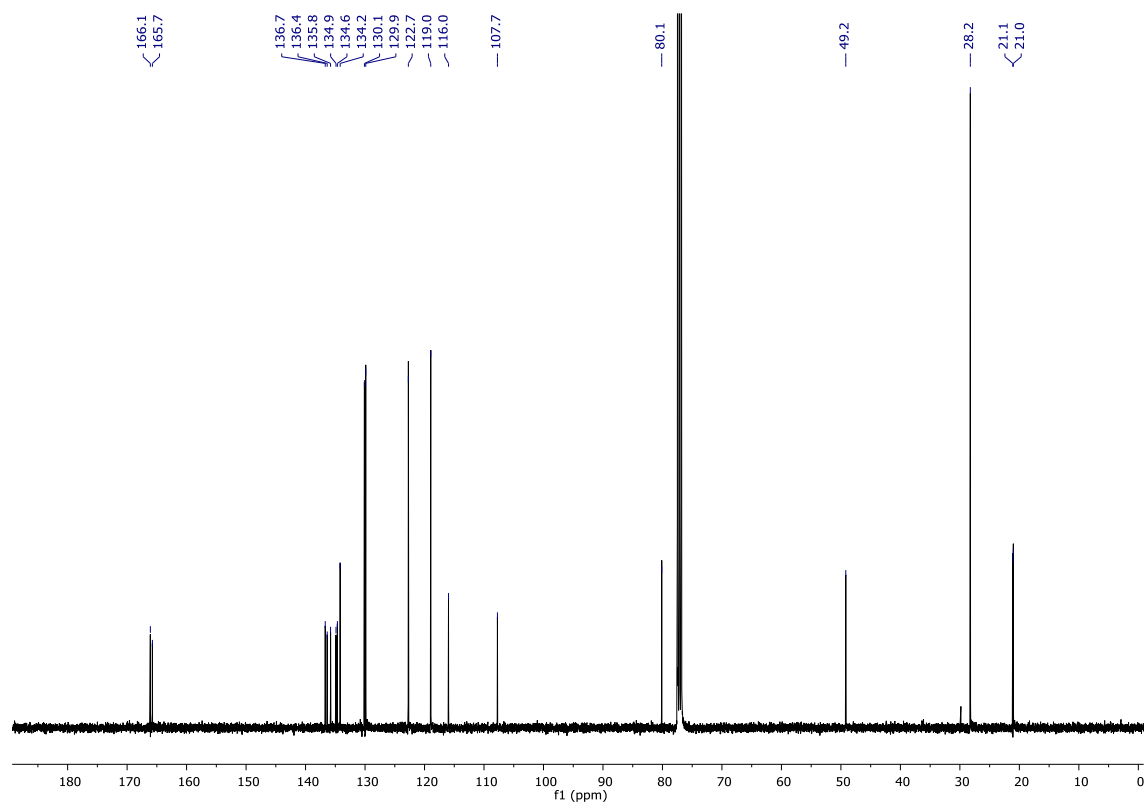


Tert-butyl (E)-3-(5-oxo-1-(p-tolyl)-4-(p-tolylamino)-2,5-dihydro-1H-pyrrol-3-yl)acrylate (7d).

^1H NMR (400 MHz, CDCl_3)



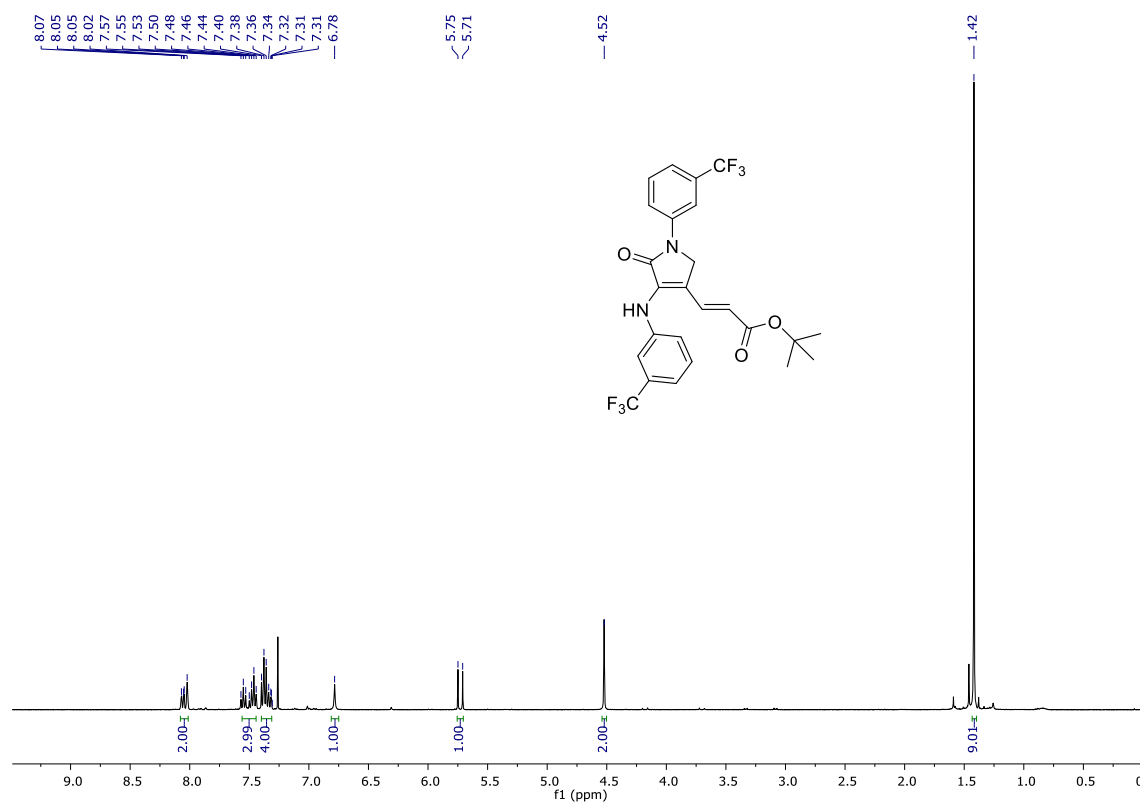
^{13}C NMR { ^1H } (101 MHz, CDCl_3)



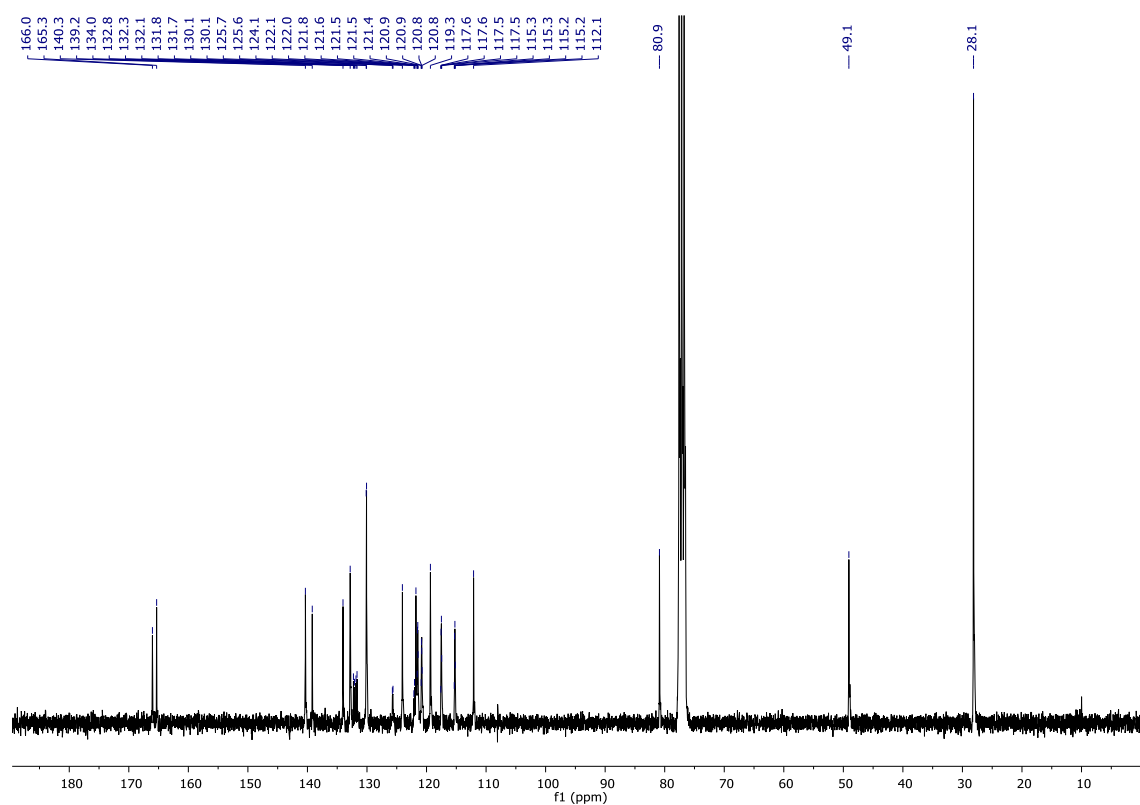
Tert-butyl

(*E*)-3-(5-oxo-1-(3-(trifluoromethyl)phenyl)-4-((3-(trifluoromethyl)phenyl)amino)-2,5-dihydro-1*H*-pyrrol-3-yl)acrylate (7e).

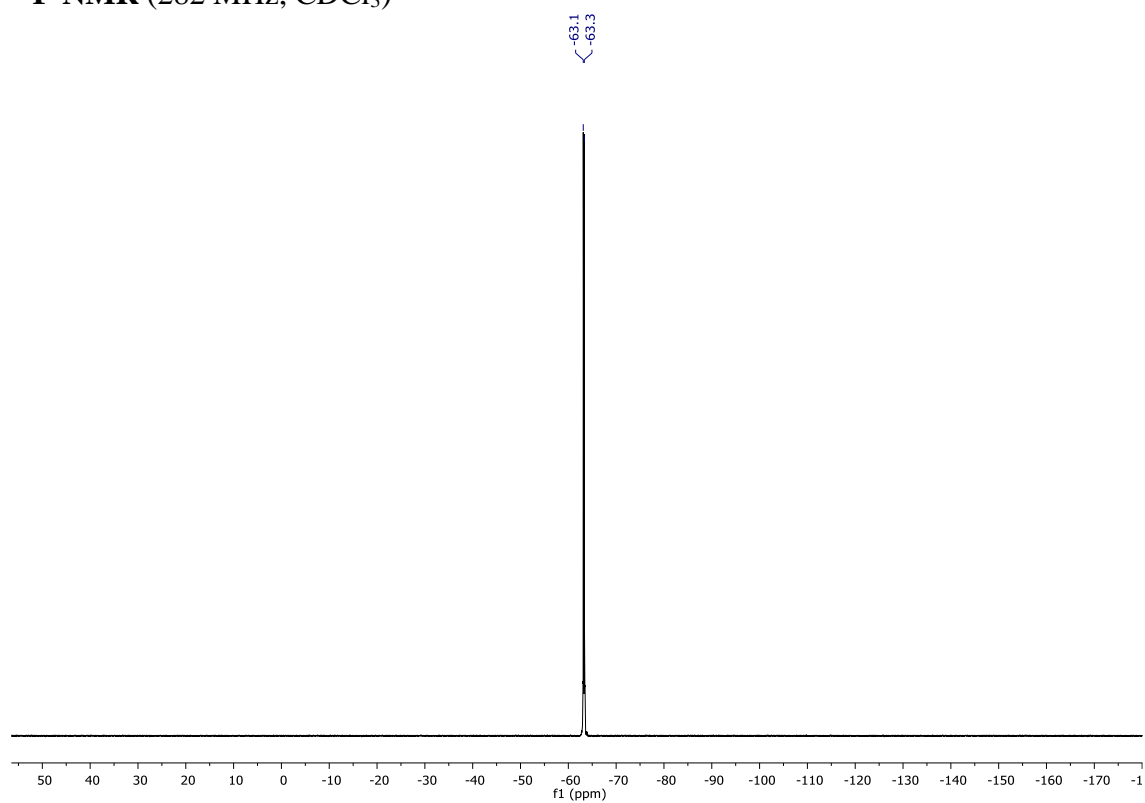
¹H NMR (400 MHz, CDCl₃)



¹³C NMR {¹H} (75 MHz, CDCl₃)

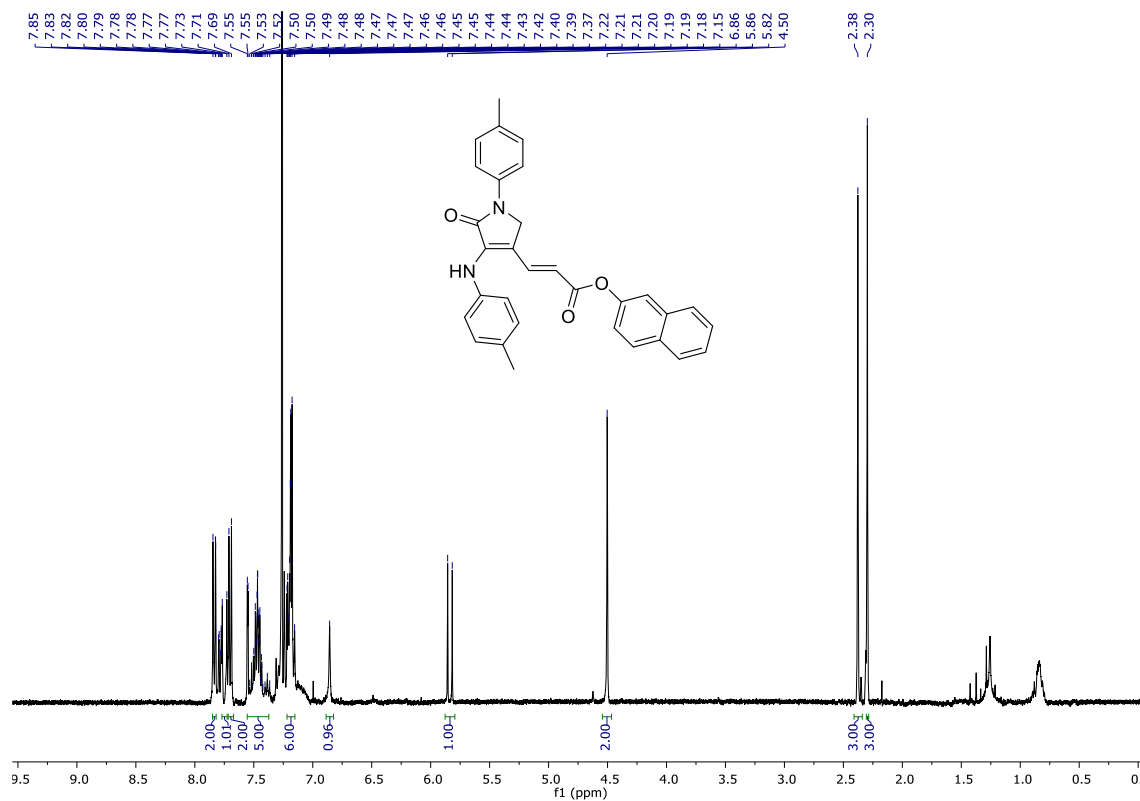


^{19}F -NMR (282 MHz, CDCl_3)

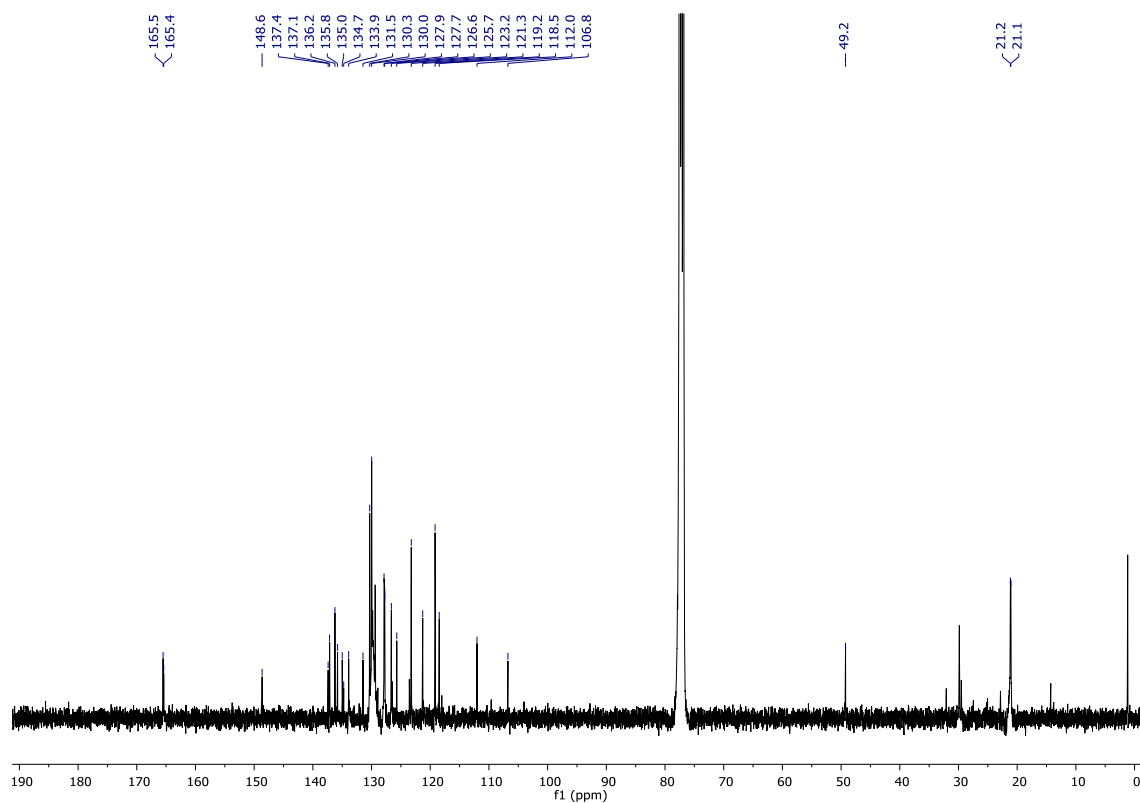


Naphthalen-2-yl (*E*)-3-(5-oxo-1-(*p*-tolyl)-4-(*p*-tolylamino)-2,5-dihydro-1*H*-pyrrol-3-yl)acrylate (7f**).**

¹H NMR (400 MHz, CDCl₃)

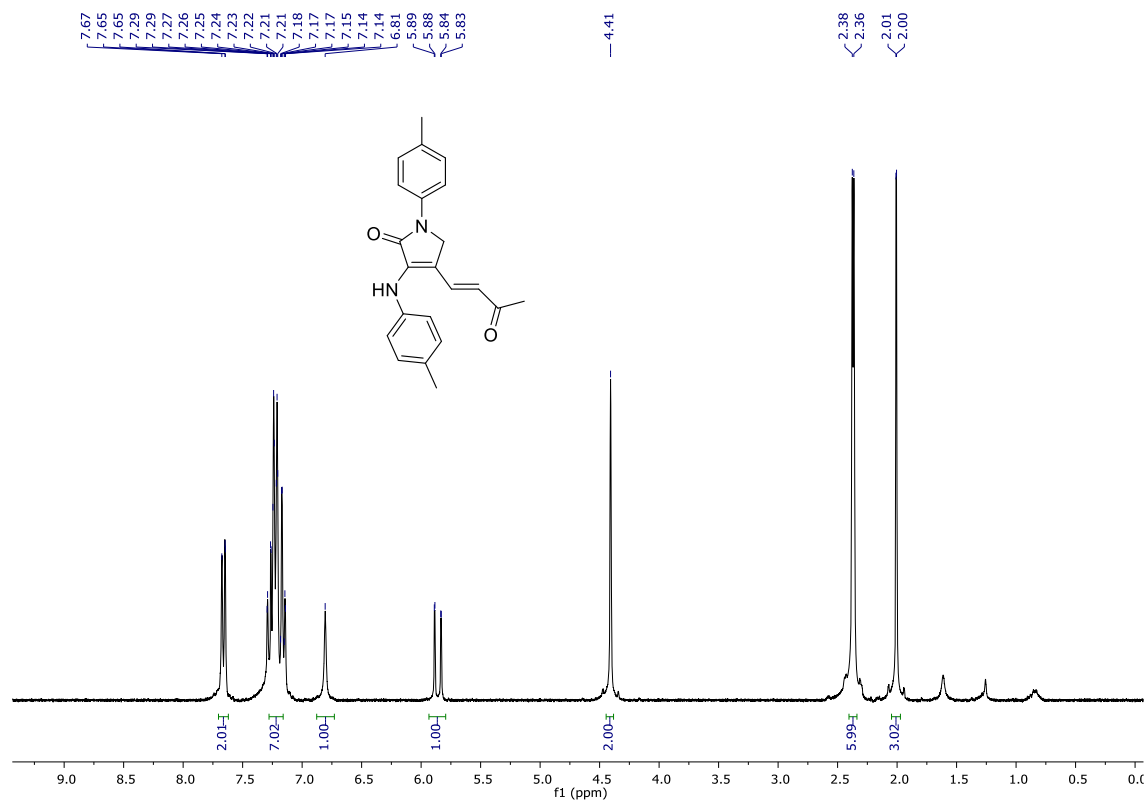


¹³C NMR {¹H} (101 MHz, CDCl₃)

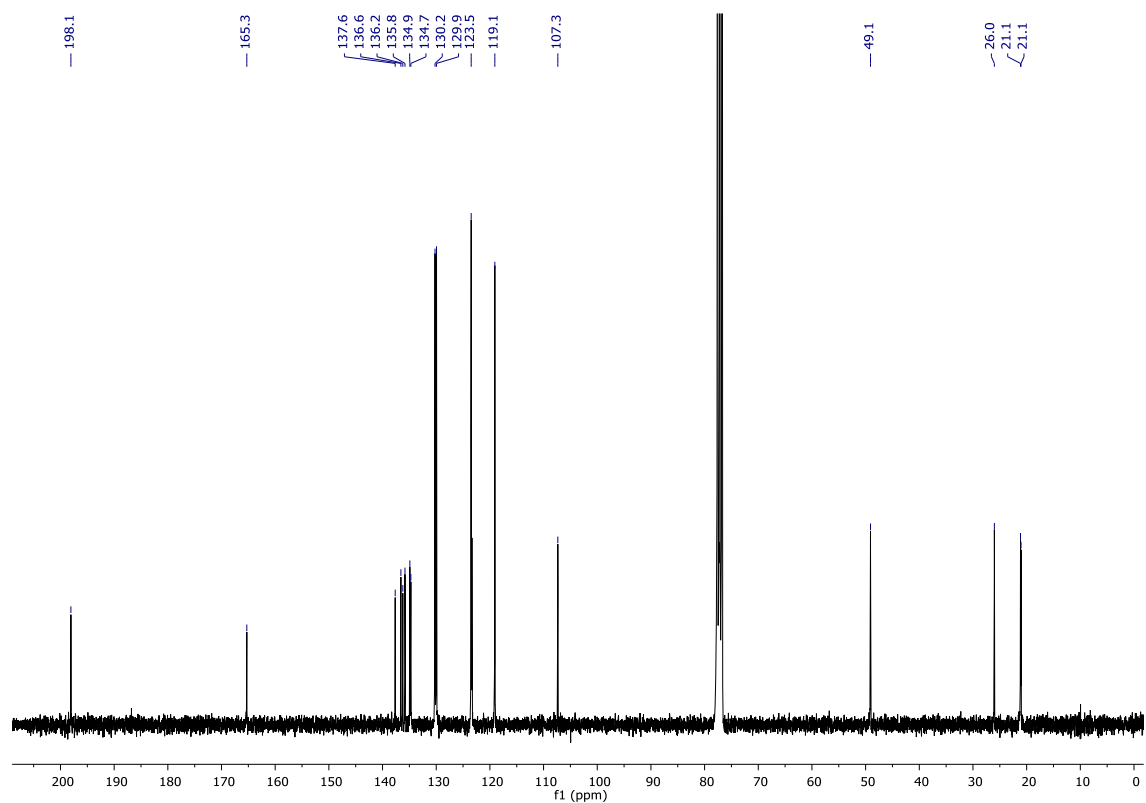


(*E*)-4-(3-oxobut-1-en-1-yl)-1-(*p*-tolyl)-3-(*p*-tolylamino)-1,5-dihydro-2*H*-pyrrol-2-one (7g).

¹H NMR (300 MHz, CDCl₃)

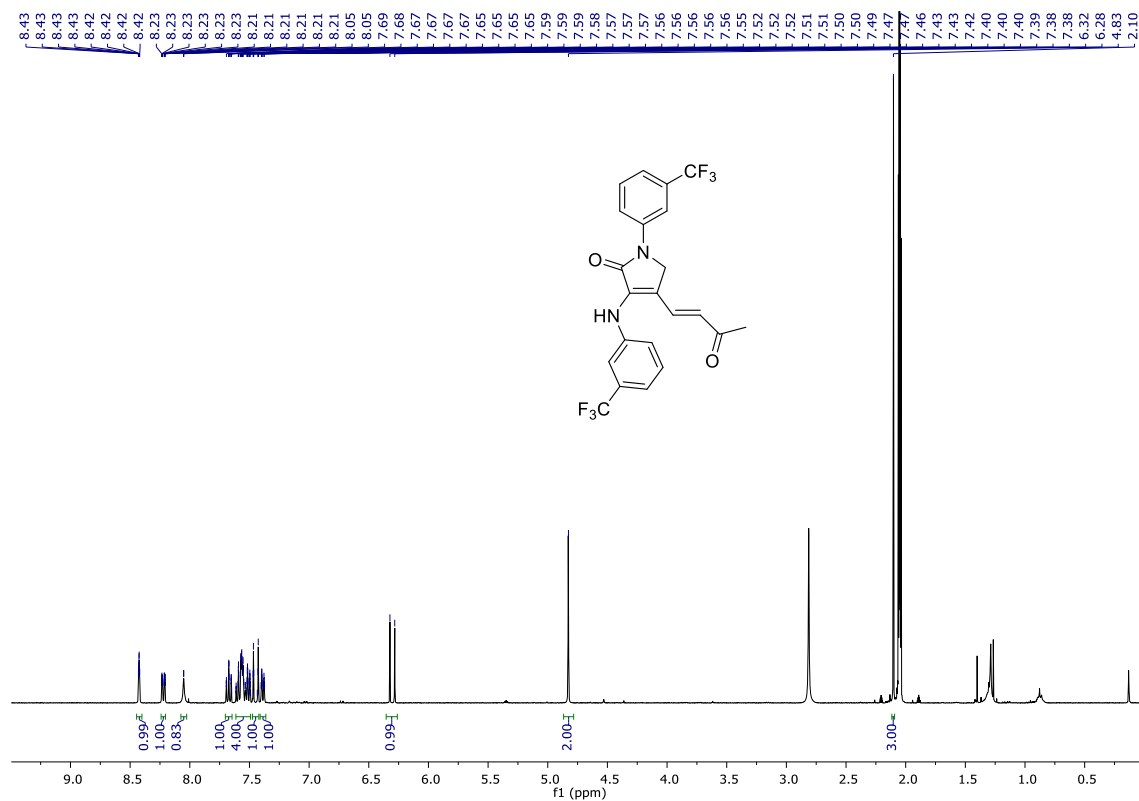


¹³C NMR {¹H} (75 MHz, CDCl₃)

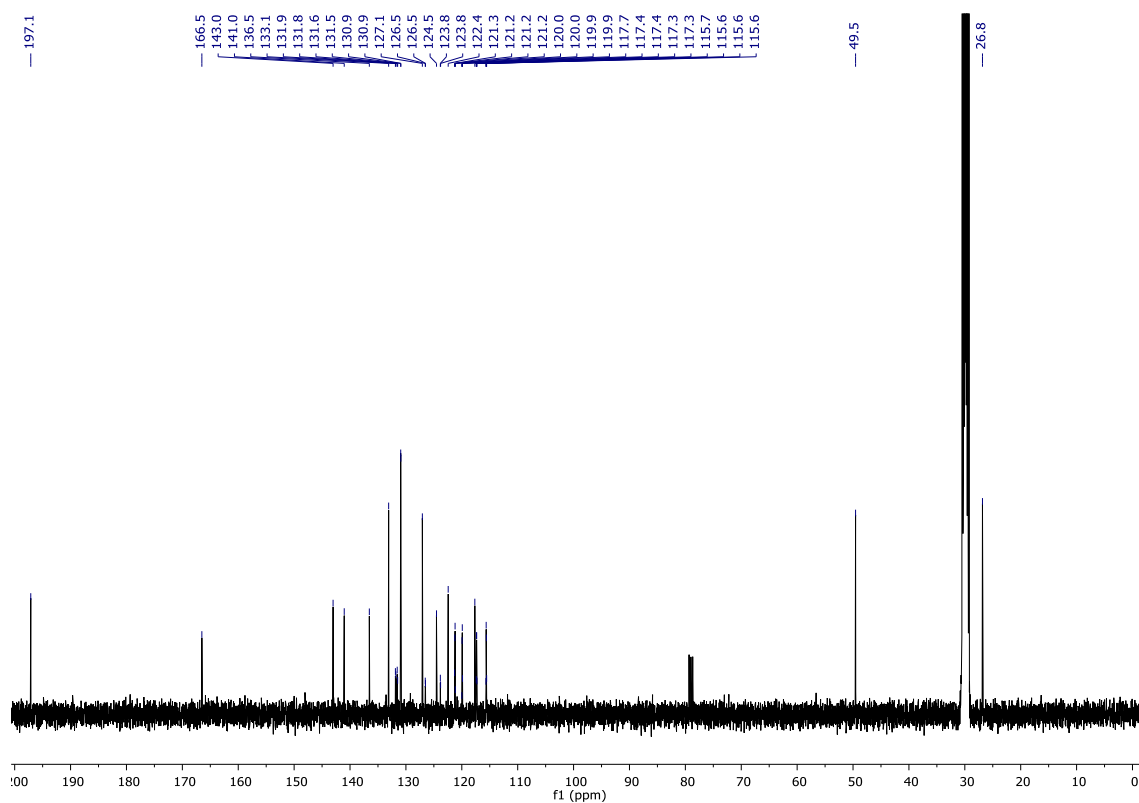


(*E*)-4-(3-oxobut-1-en-1-yl)-1-(3-(trifluoromethyl)phenyl)-3-((3-(trifluoromethyl)phenyl)amino)-1,5-dihydro-2*H*-pyrrol-2-one (6h).

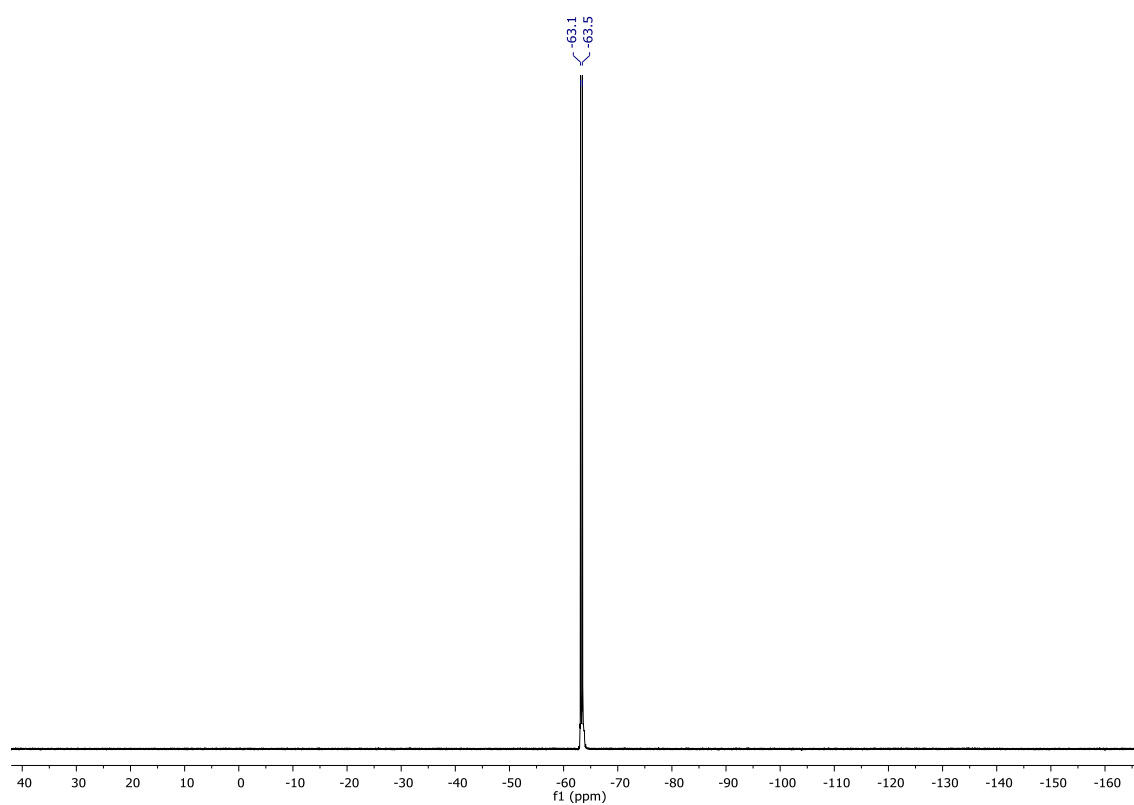
¹H NMR (400 MHz, Acetone *d*₆)



¹³C NMR {¹H} (101 MHz, Acetone *d*₆)

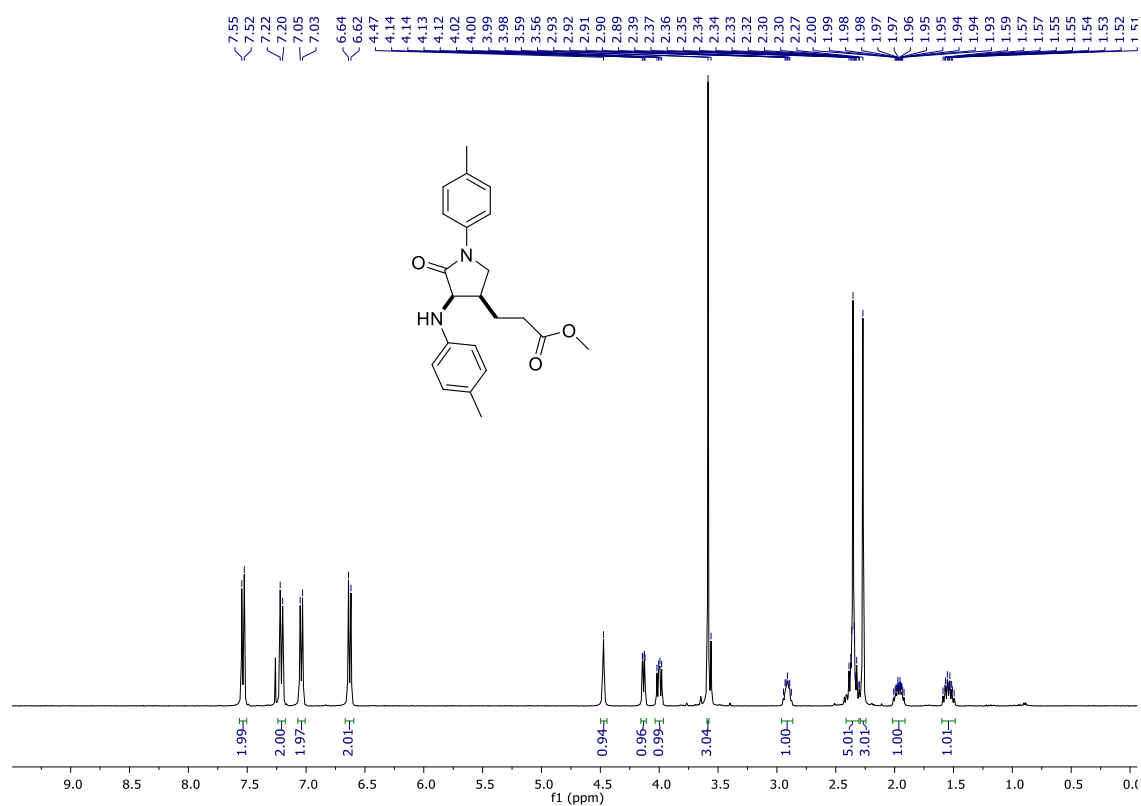


^{19}F NMR (282 MHz, CDCl_3)

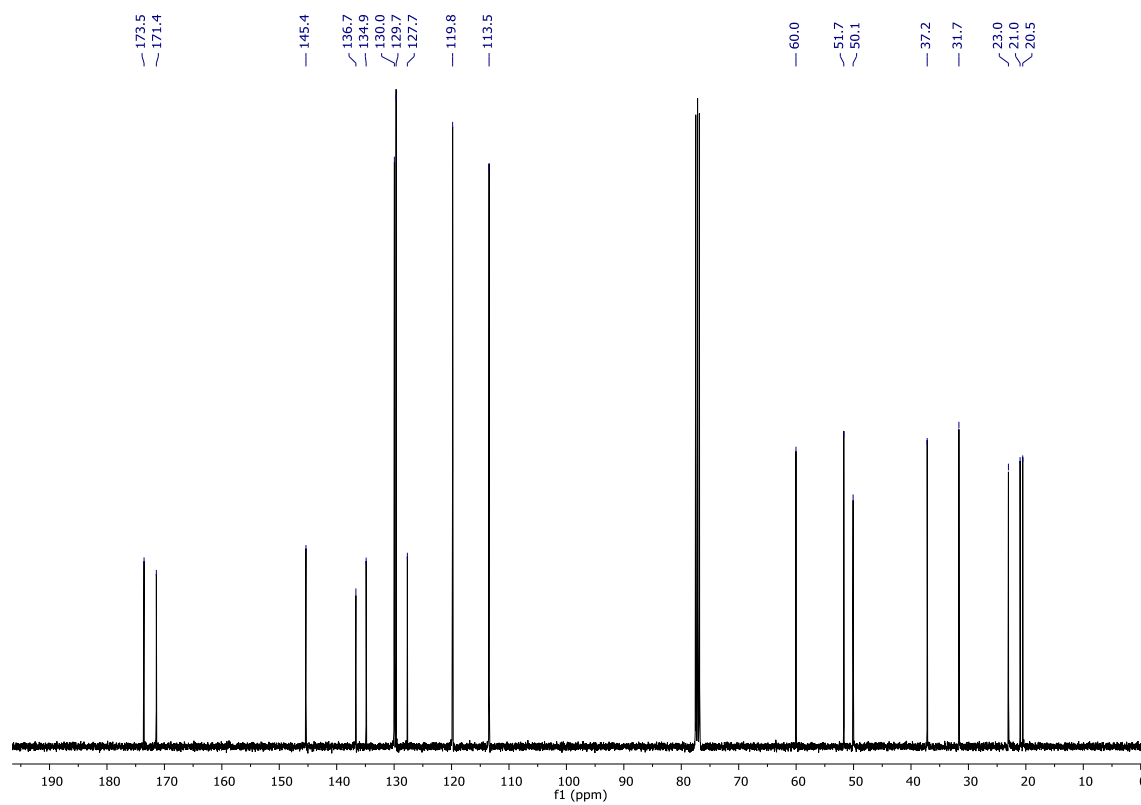


Methyl 3-((3*R,4*R**)-5-oxo-1-(*p*-tolyl)-4-(*p*-tolylamino)pyrrolidin-3-yl)propanoate**
(8).

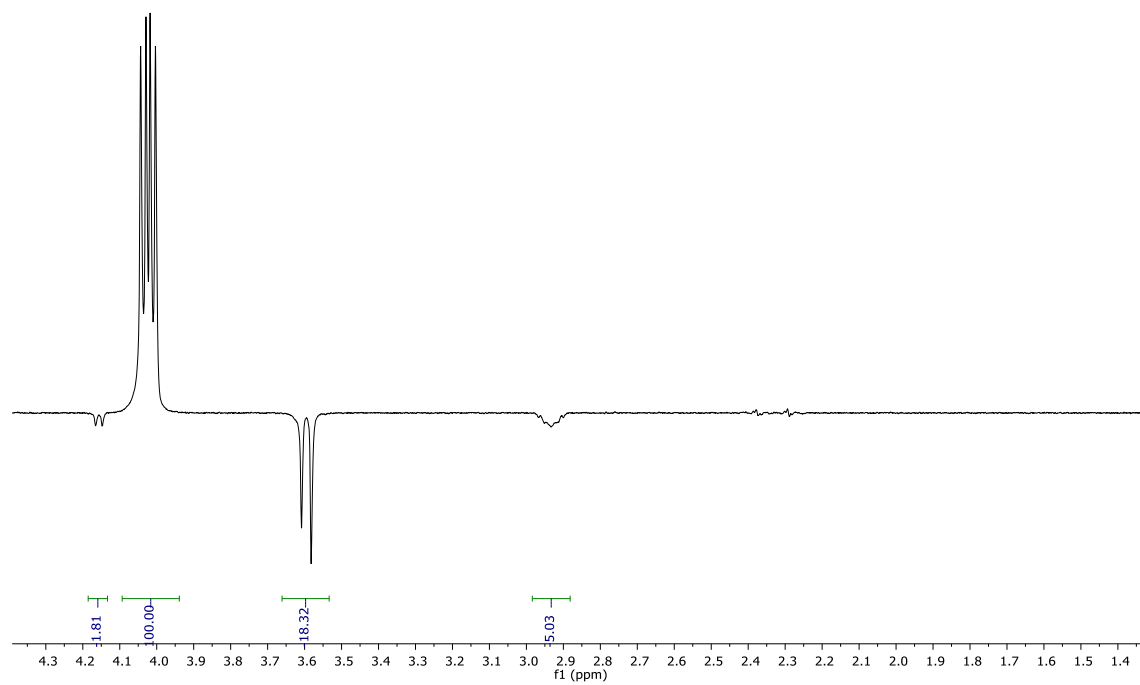
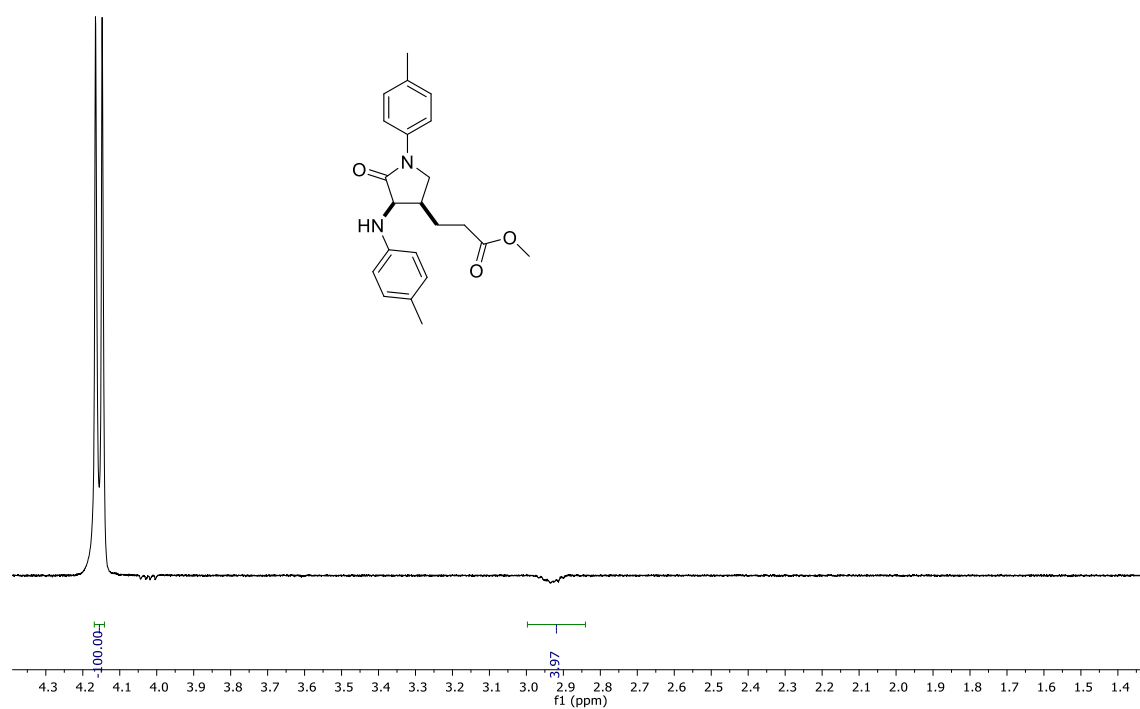
^1H NMR (400 MHz, CDCl_3)

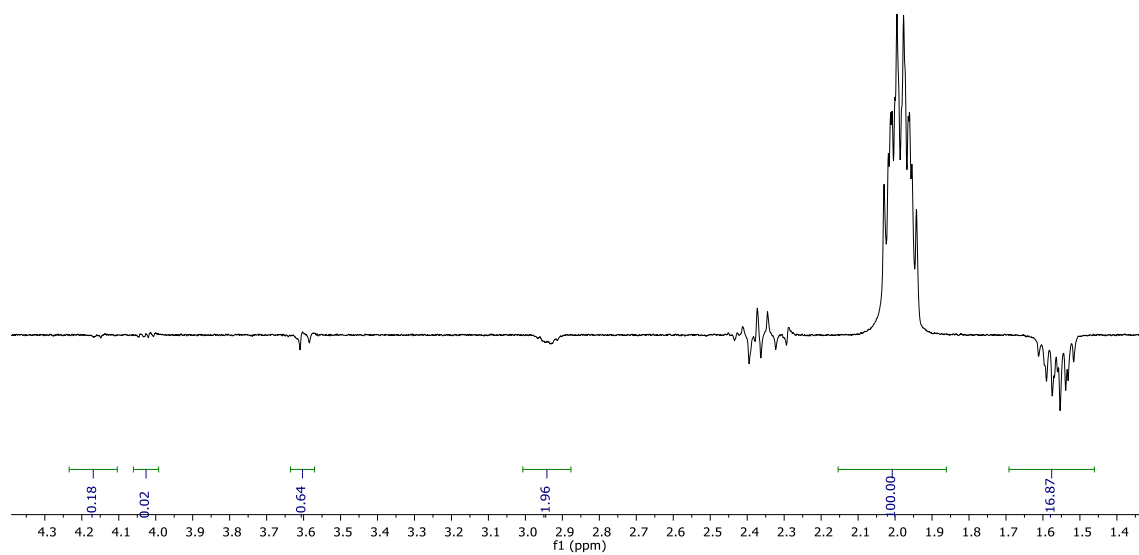
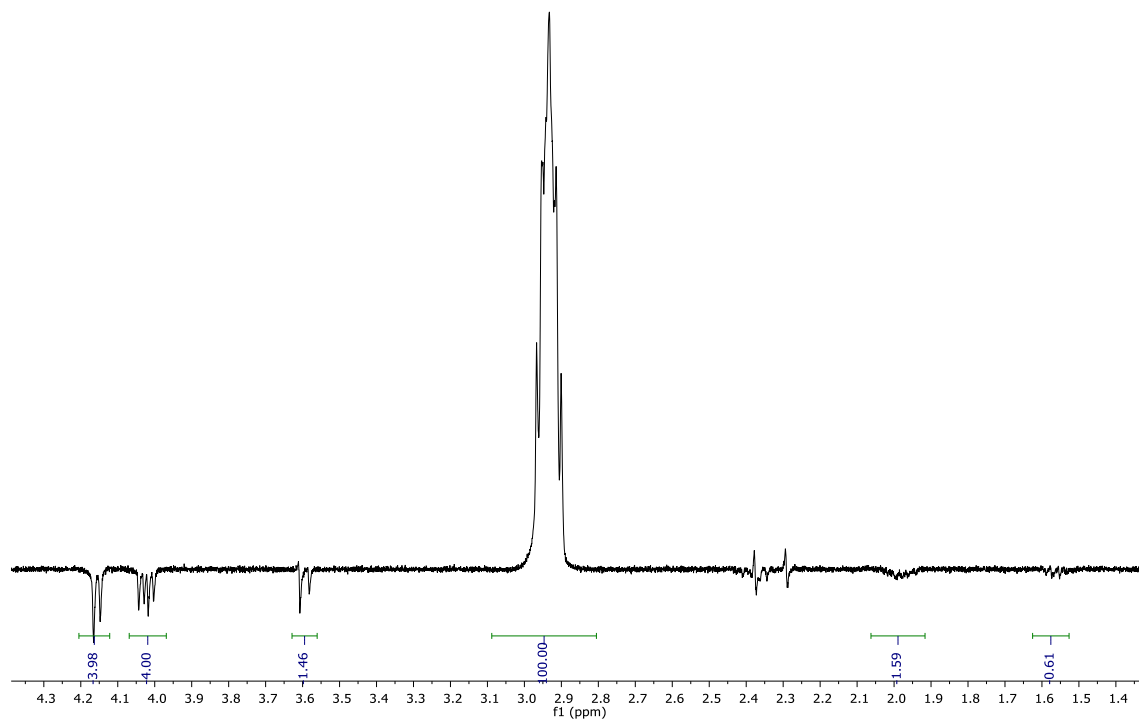


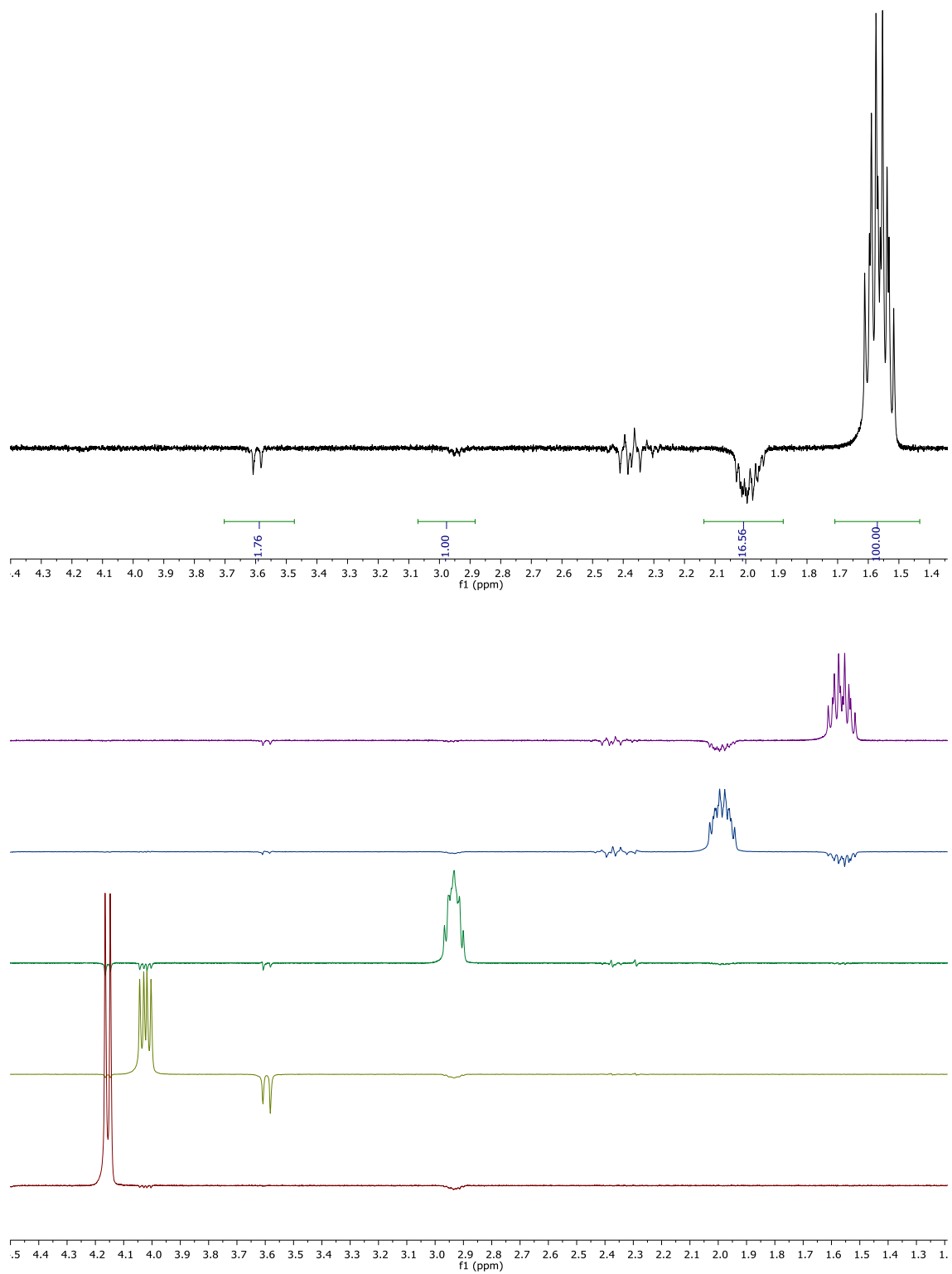
^{13}C NMR $\{^1\text{H}\}$ (101 MHz, CDCl_3)



1D-NOESY {¹H – ¹H} (400 MHz, CDCl₃)

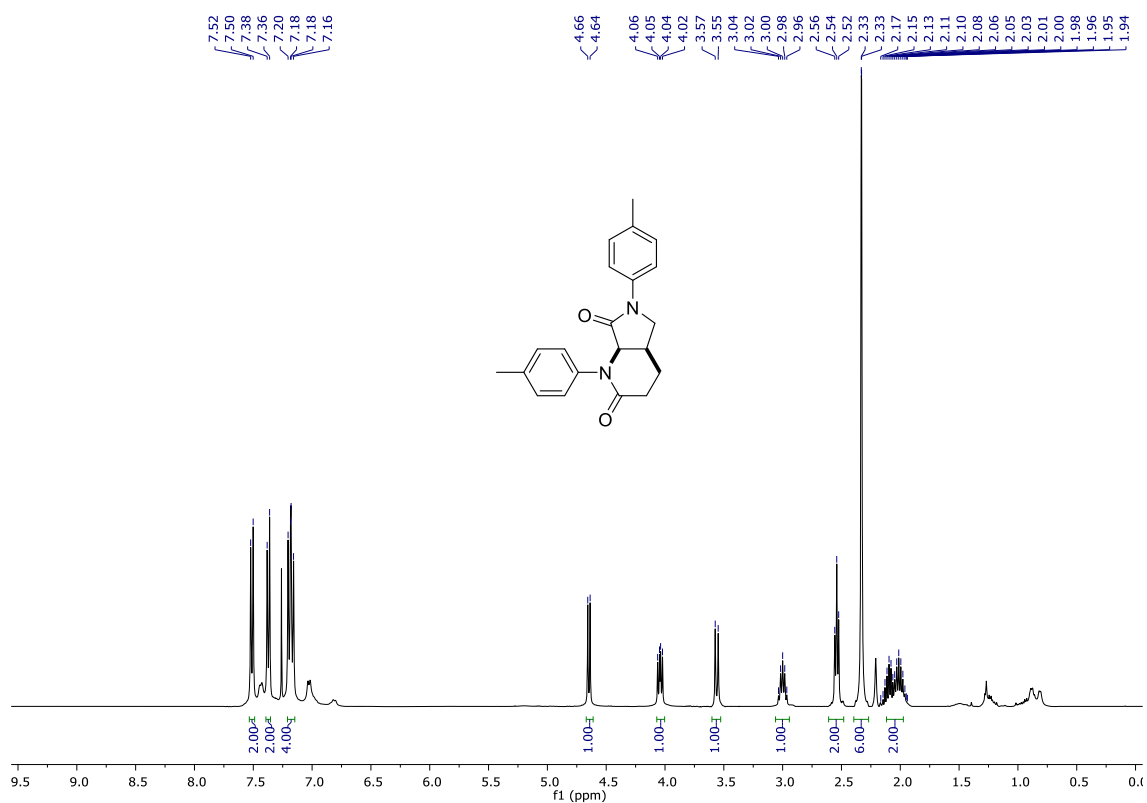




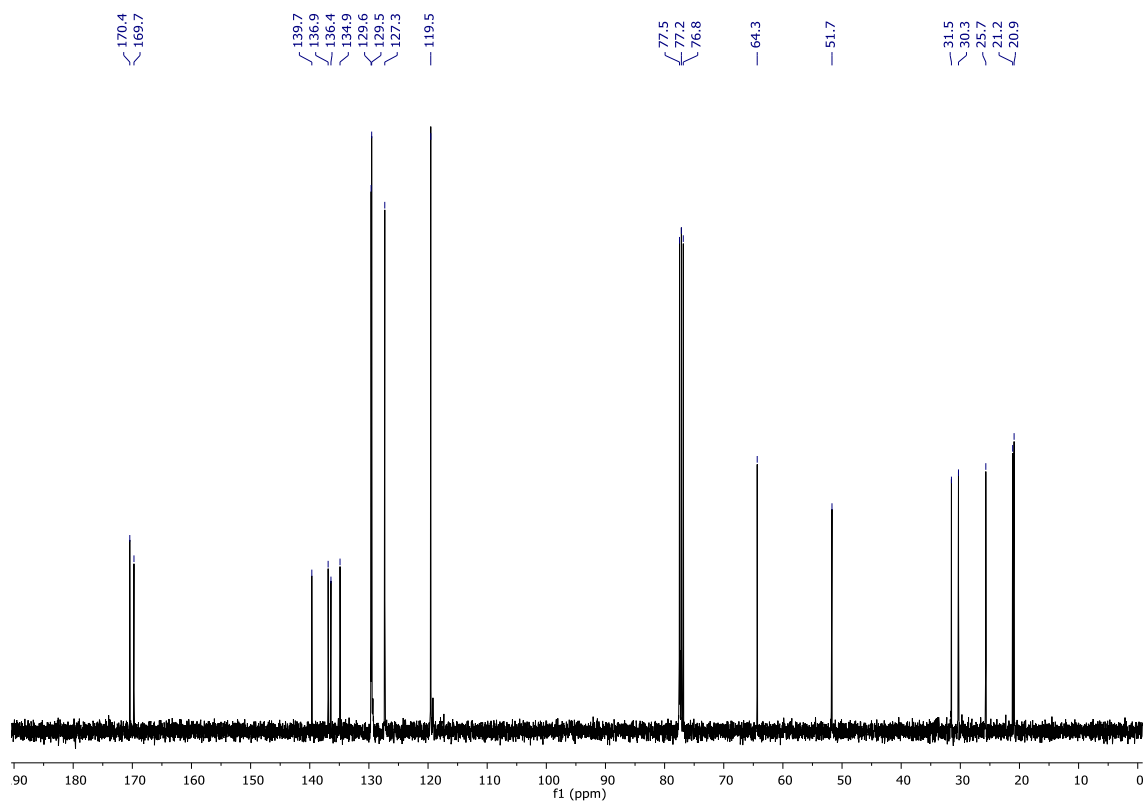


(4a*R,7a*R**)-1,6-Di-*p*-tolylhexahydro-1*H*-pyrrolo[3,4-*b*]pyridine-2,7-dione (9).**

¹H NMR (400 MHz, CDCl₃)

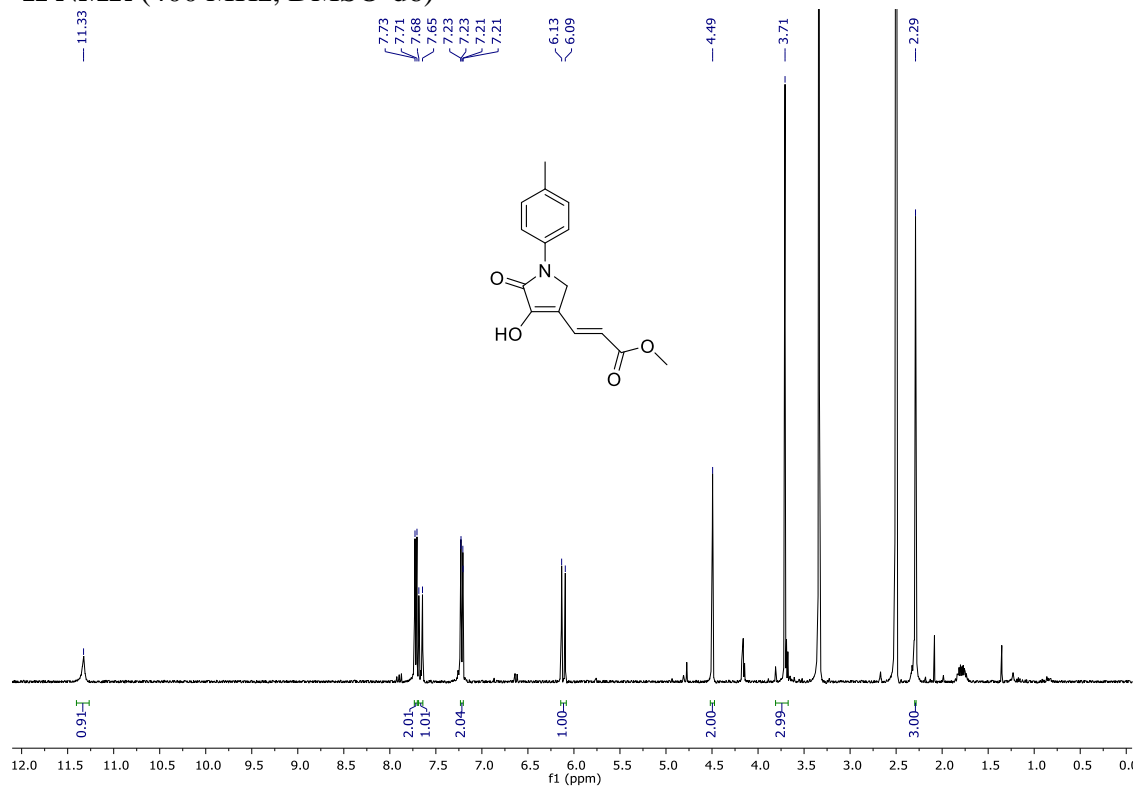


¹³C NMR {¹H} (101 MHz, CDCl₃)

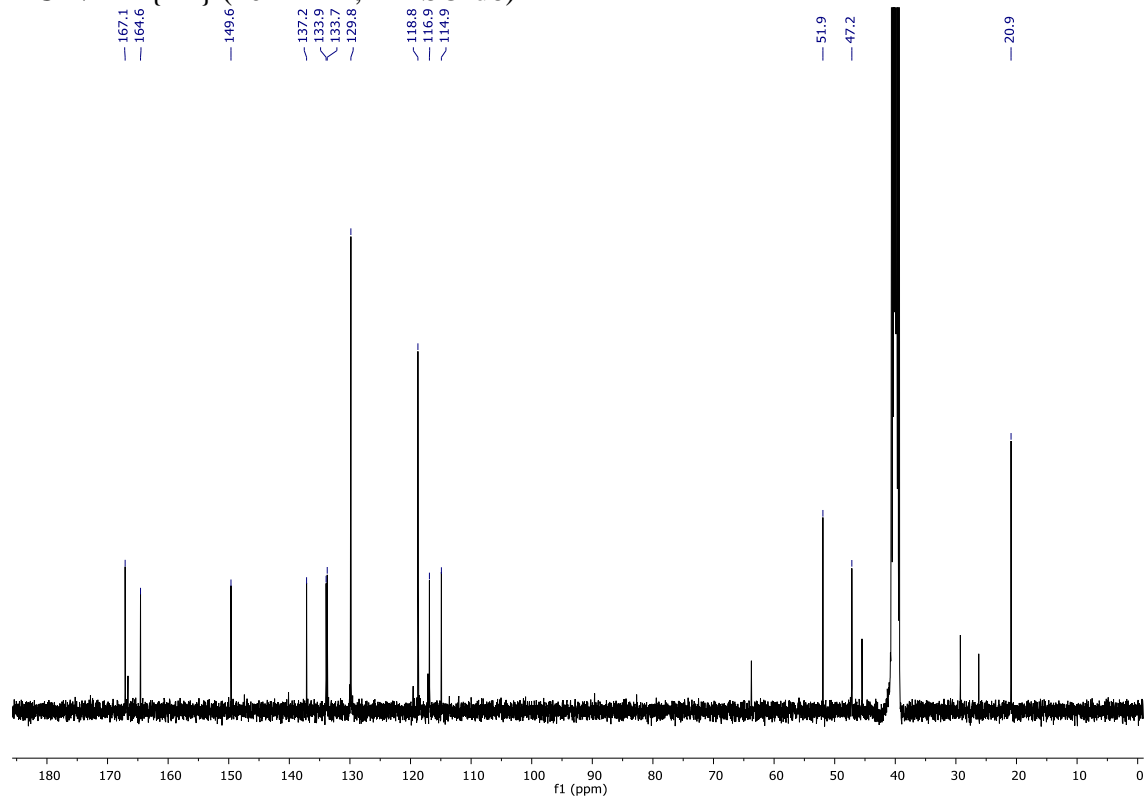


Methyl (E)-3-(4-hydroxy-5-oxo-1-(p-tolyl)-2,5-dihydro-1H-pyrrol-3-yl)acrylate (10).

¹H NMR (400 MHz, DMSO-d₆)



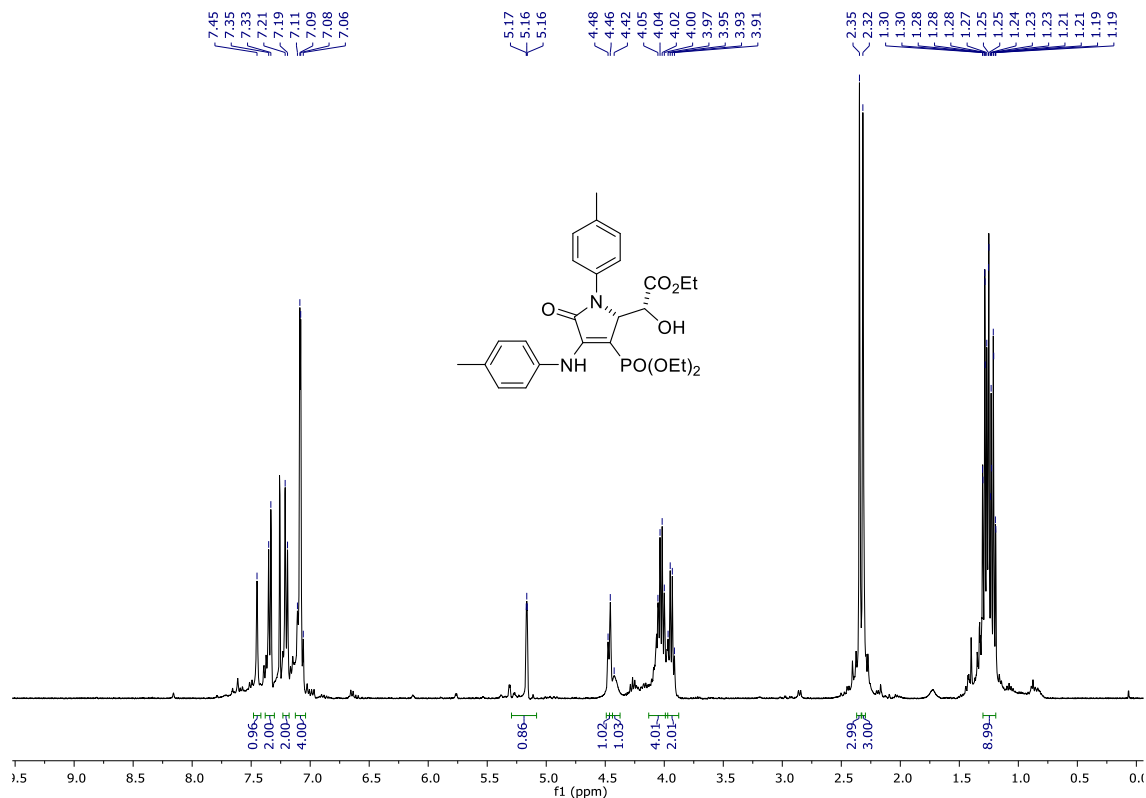
¹³C NMR {¹H} (101 MHz, DMSO-d₆)



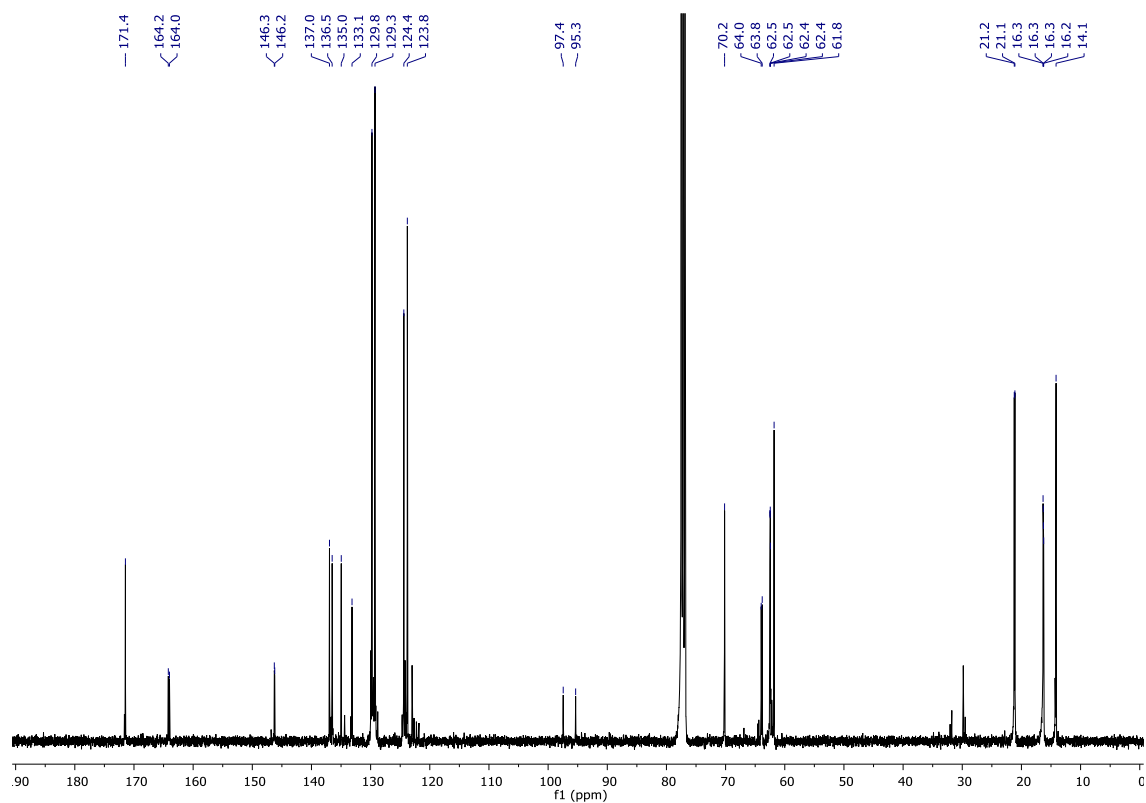
2. Characterization by NMR Spectroscopy and Crystal Structure Determination of products 12.

Ethyl (*R*^{*})-2-((*R*^{*})-3-(diethoxyphosphoryl)-5-oxo-1-(*p*-tolyl)-4-(*p*-tolylamino)-2,5-dihydro-1*H*-pyrrol-2-yl)-2-hydroxyacetate (12a).

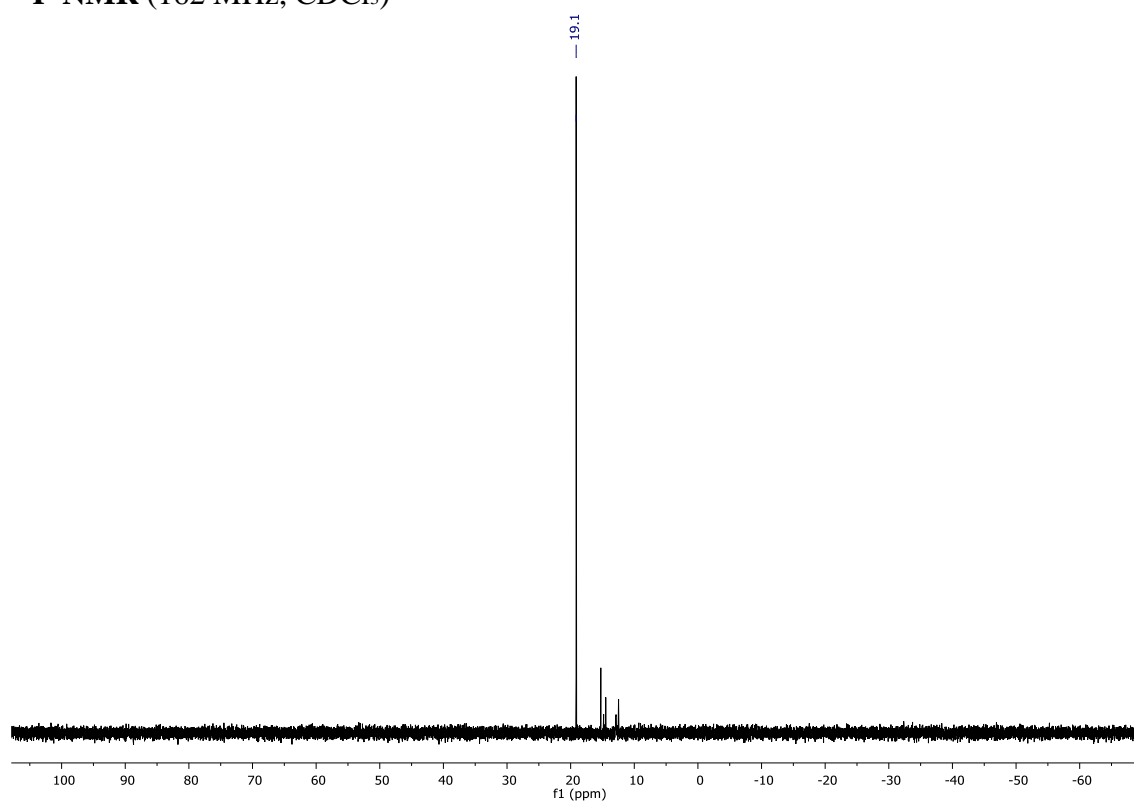
¹H NMR (400 MHz, CDCl₃)



¹³C NMR {¹H} (101 MHz, CDCl₃)

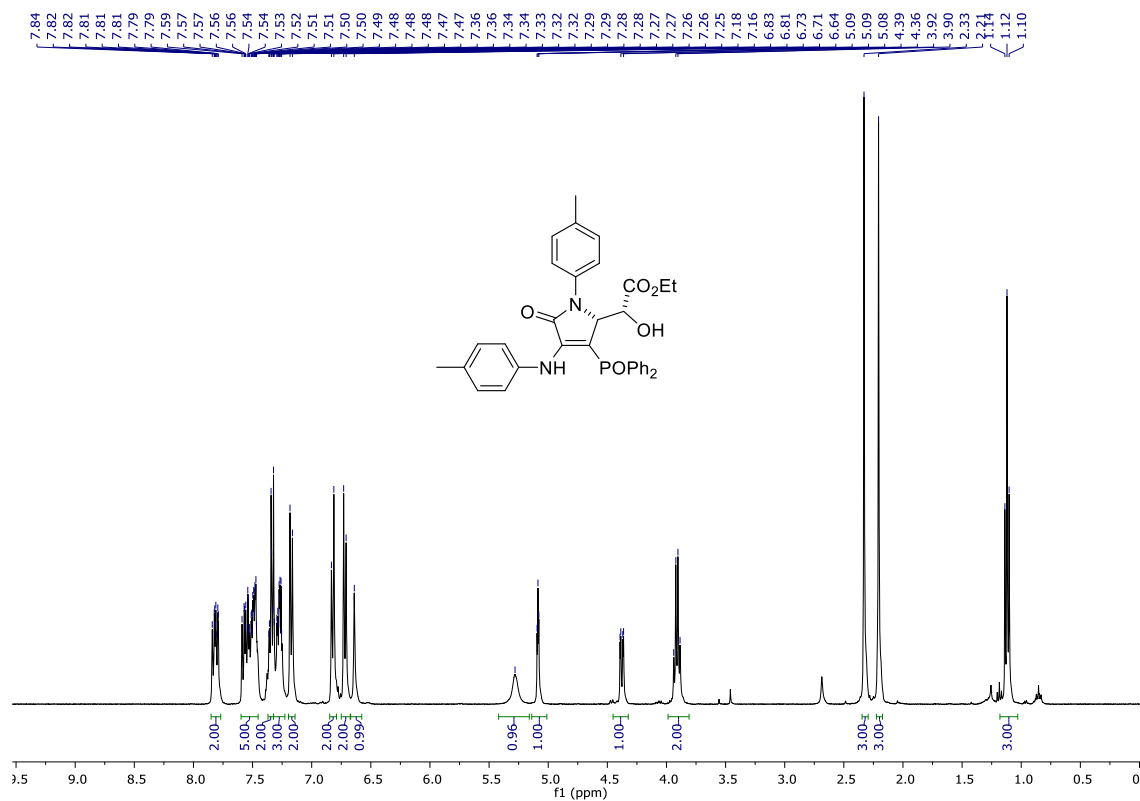


^{31}P -NMR (162 MHz, CDCl_3)

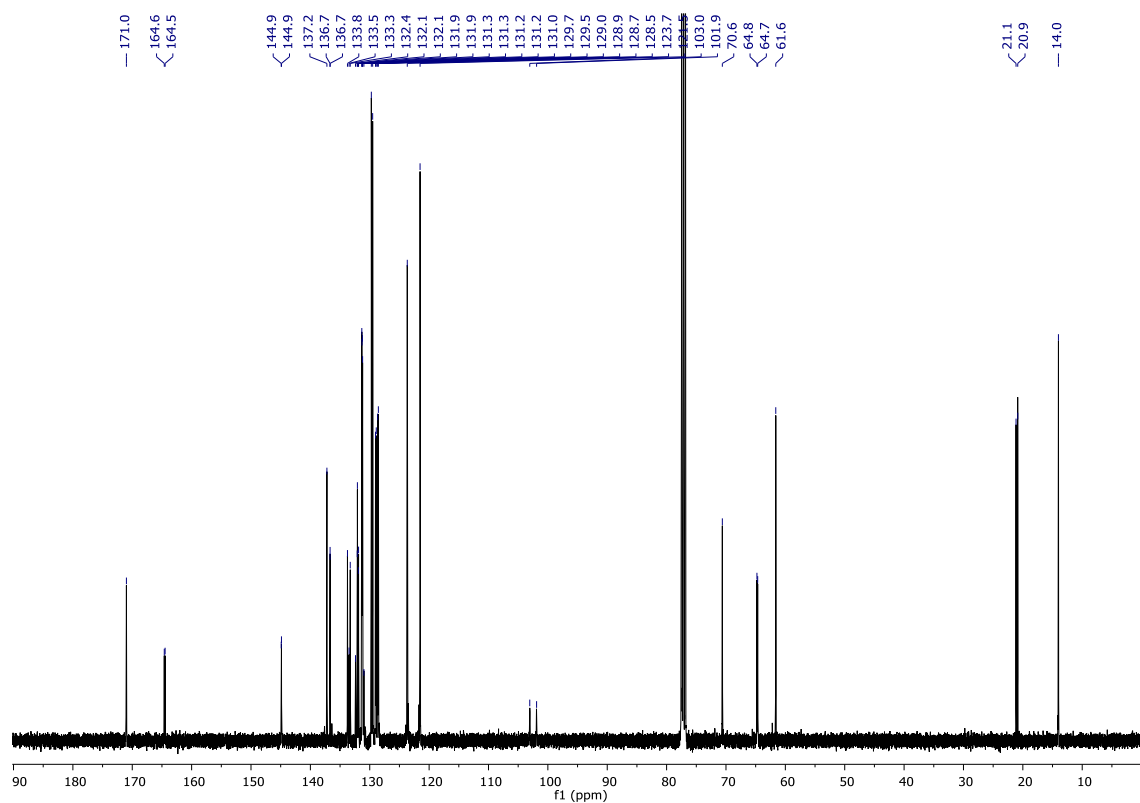


Ethyl (R*)-2-((R*)-3-(diphenylphosphoryl)-5-oxo-1-(p-tolyl)-4-(p-tolylamino)-2,5-dihydro-1H-pyrrol-2-yl)-2-hydroxyacetate (12b).

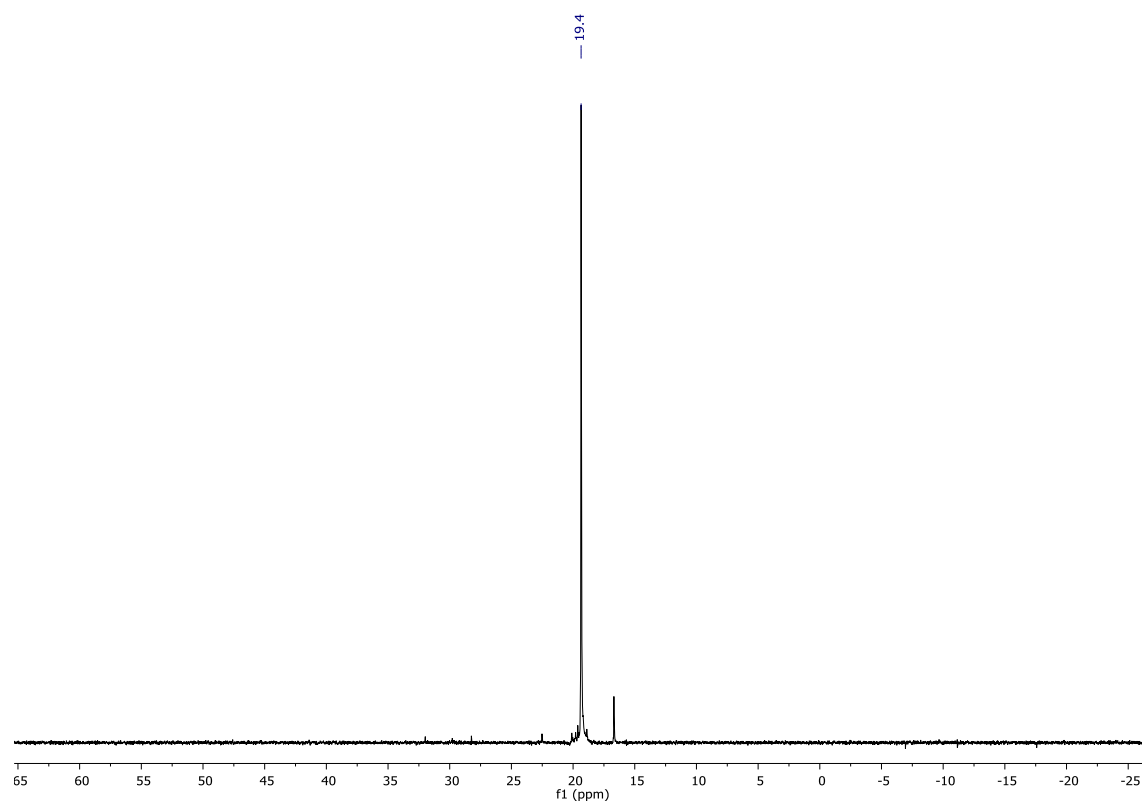
¹H NMR (400 MHz, CDCl₃)



¹³C NMR {¹H} (101 MHz, CDCl₃)



^{31}P NMR (121 MHz, CDCl_3)



Crystal structure determination of compound 12b.

The structure of compound **12b** was determined on a crystal prepared from a CH₂Cl₂/Et₂O solvent system by slow evaporation in a vial at room temperature. The X-ray data have been deposited at the Cambridge Crystallographic Data Centre (CCDC 2125880).

Intensity data were collected on an Agilent Technologies Super-Nova diffractometer, which was equipped with monochromated Mo K α radiation ($\lambda = 0.71073$ Å) and Eos CCD detector. Measurement was carried out at 151.0(10) K with the help of an Oxford Cryostream 700 PLUS temperature device. Data frames were processed (unit cell determination, analytical absorption correction with face indexing, intensity data integration and correction for Lorentz and polarization effects) using the CrysAlis software package.¹ The structure was solved using SHELXT² and refined by full-matrix least-squares with SHELXL-97.³ Final geometrical calculations were carried out with Mercury⁴ and PLATON⁵ as integrated in WinGX.⁶

Thermal ellipsoid plot/ORTEP for compound 12b. Contour probability level: 50%

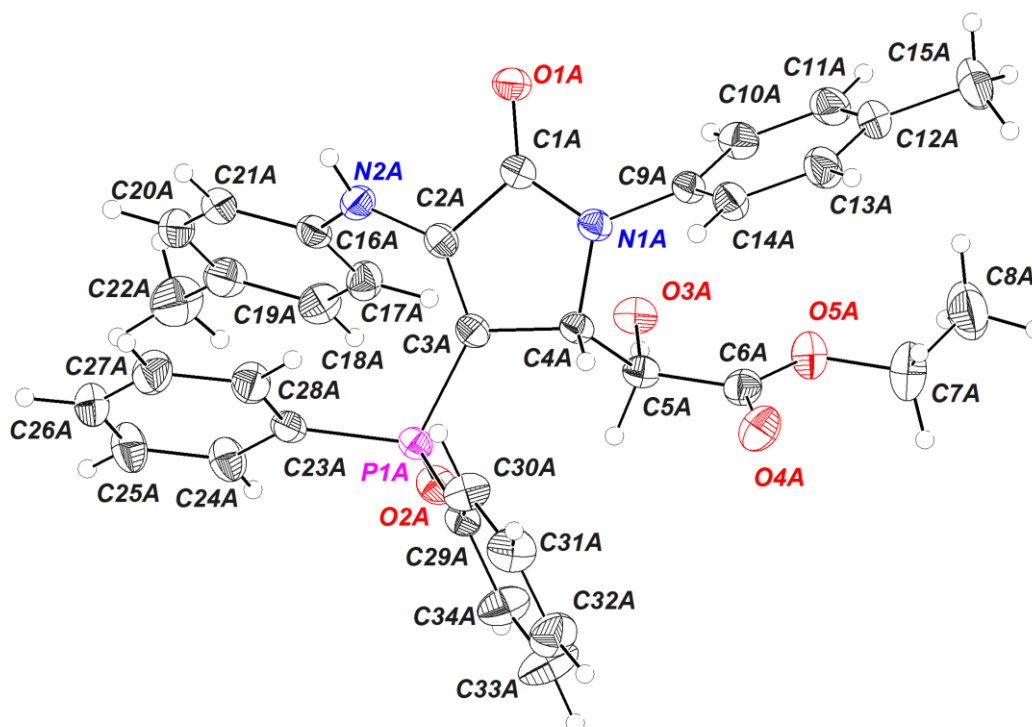


Table S1. Crystal data and structure refinement for 12b.

Identification code

a20210323_AL231

S25

Empirical formula	C ₃₄ H ₃₃ N ₂ O ₅ P
Formula weight	580.59
Temperature/K	150.0(10)
Crystal system	triclinic
Space group	P-1
a/Å	12.64056(19)
b/Å	14.4828(2)
c/Å	18.2237(3)
α/°	71.6731(14)
β/°	88.2210(13)
γ/°	78.0417(12)
Volume/Å ³	3096.20(8)
Z	4
ρ _{calc} /cm ³	1.246
μ/mm ⁻¹	1.141
F(000)	1224.0
Crystal size/mm ³	0.203 × 0.101 × 0.082
Radiation	Mo Kα (λ = 0.71073)
2θ range for data collection/°	6.574 to 137.998
Index ranges	-15 ≤ h ≤ 15, -17 ≤ k ≤ 17, -22 ≤ l ≤ 21
Reflections collected	47925
Independent reflections	11513 [R _{int} = 0.0405, R _{sigma} = 0.0308]
Data/restraints/parameters	11513/0/765
Goodness-of-fit on F ²	1.029
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0386, wR ₂ = 0.0994
Final R indexes [all data]	R ₁ = 0.0482, wR ₂ = 0.1061
Largest diff. peak/hole / e Å ⁻³	0.45/-0.34
Flack parameter	0.14(6)
Bijvoet Pairs Coverage	99%
Hooft y	0.14(4)
P2(false)	≤ 10 ⁻¹⁰⁶

¹ CrysAlisPro, Agilent Technologies, Version 1.171.37.31 (release 14-01-2014 CryAlis171.NET) (compiled Jan 14 2014, 18:38:05).

² G.M. Sheldrick, *Acta Cryst.* **2015**, A71, 3.

³ G.M. Sheldrick, *Acta Cryst.* **2008**, A64, 112; G.M. Sheldrick, *Acta Cryst.* **2015**, C71, 3.

⁴ C. F. Macrae, *J. Appl. Cryst.* **2008**, 41, 466.

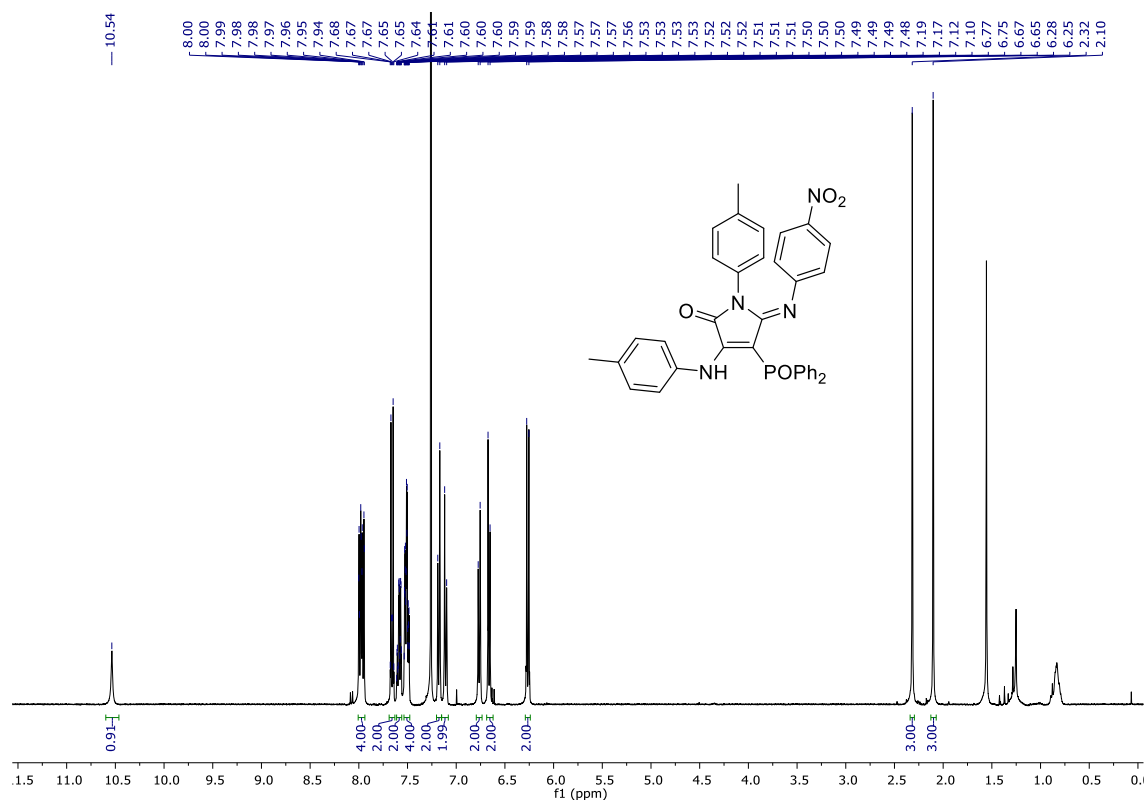
⁵ A. L. Spek (2010) PLATON, A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands; A. L. Spek, *J. Appl. Cryst.* **2003**, 36, 7.

⁶ L. J. Farrugia, *J. Appl. Cryst.* **1999**, 32, 837.

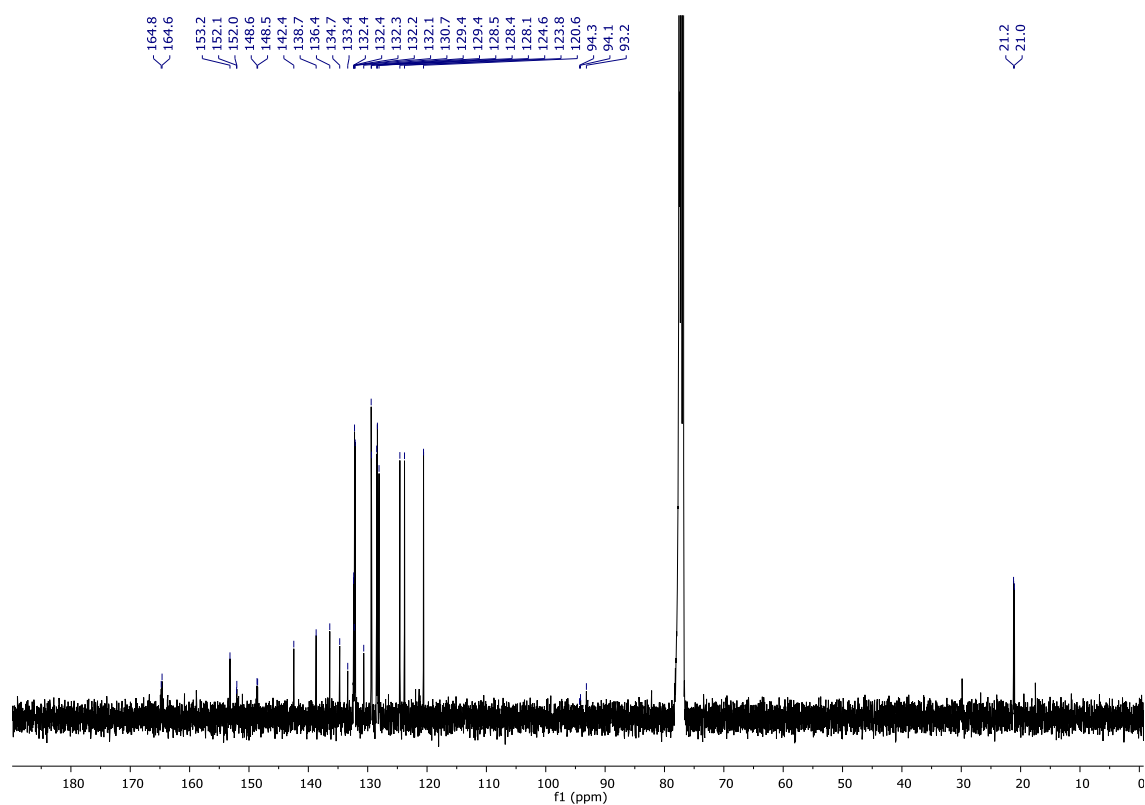
3. Characterization by NMR Spectroscopy and Crystal Structure Determination of product 13.

(Z)-4-(Diphenylphosphoryl)-5-((4-nitrophenyl)imino)-1-(p-tolyl)-3-(p-tolylamino)-1,5-dihydro-2H-pyrrol-2-one (13).

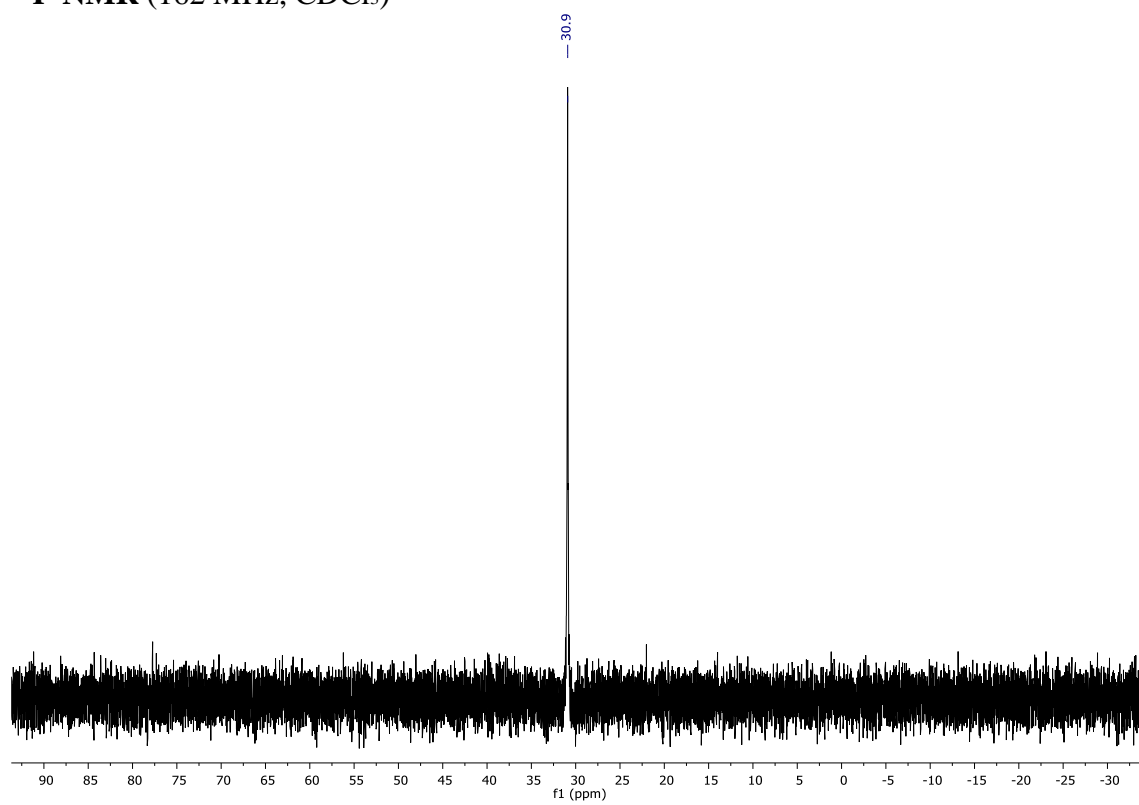
¹H NMR (400 MHz, CDCl₃)



¹³C NMR {¹H} (101 MHz, CDCl₃)



^{31}P -NMR (162 MHz, CDCl_3)



Crystal structure determination of compound 13.

The structure of compound **13** was determined on a crystal prepared from a CH₂Cl₂/hexane solvent system by slow evaporation in a vial at room temperature. The X-ray data have been deposited at the Cambridge Crystallographic Data Centre (CCDC 2125933).

Intensity data were collected on an Agilent Technologies Super-Nova diffractometer, which was equipped with monochromated Cu K α radiation (λ = 1.54184 Å) and Atlas CCD detector. Measurement was carried out at 151.0(5) K with the help of an Oxford Cryostream 700 PLUS temperature device. Data frames were processed (unit cell determination, analytical absorption correction with face indexing, intensity data integration and correction for Lorentz and polarization effects) using the CrysAlis software package.^[Error! Marcador no definido.] The structure was solved using SHELXT^[Error! Marcador no definido.] and refined by full-matrix least-squares with SHELXL-97.^[Error! Marcador no definido.] Final geometrical calculations were carried out with Mercury^[Error! Marcador no definido.] and PLATON^[Error! Marcador no definido.] as integrated in WinGX.^[Error! Marcador no definido.]

Thermal ellipsoid plot/ORTEP for compound 13. Contour probability level: 50%

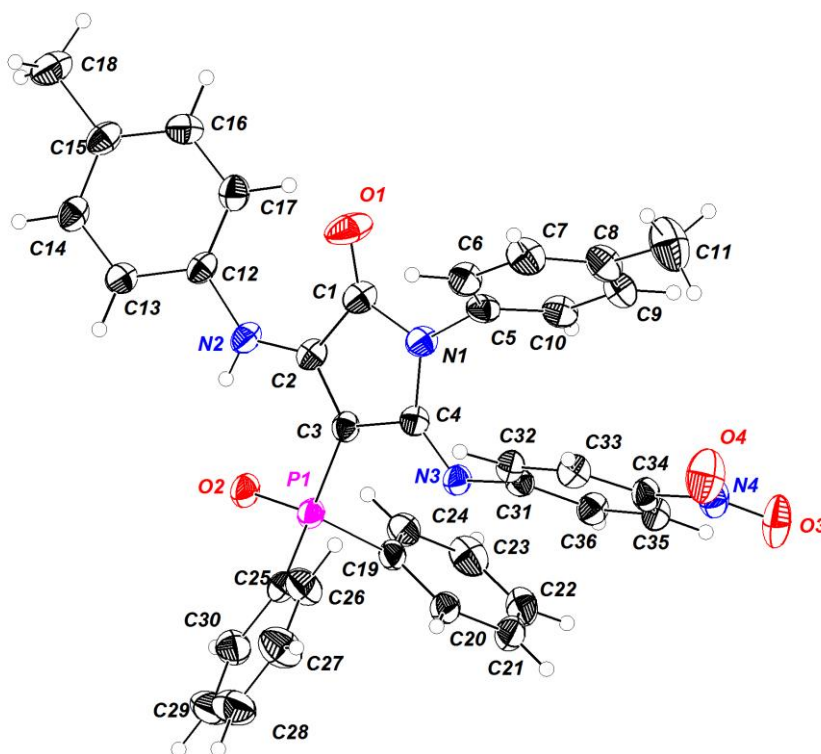


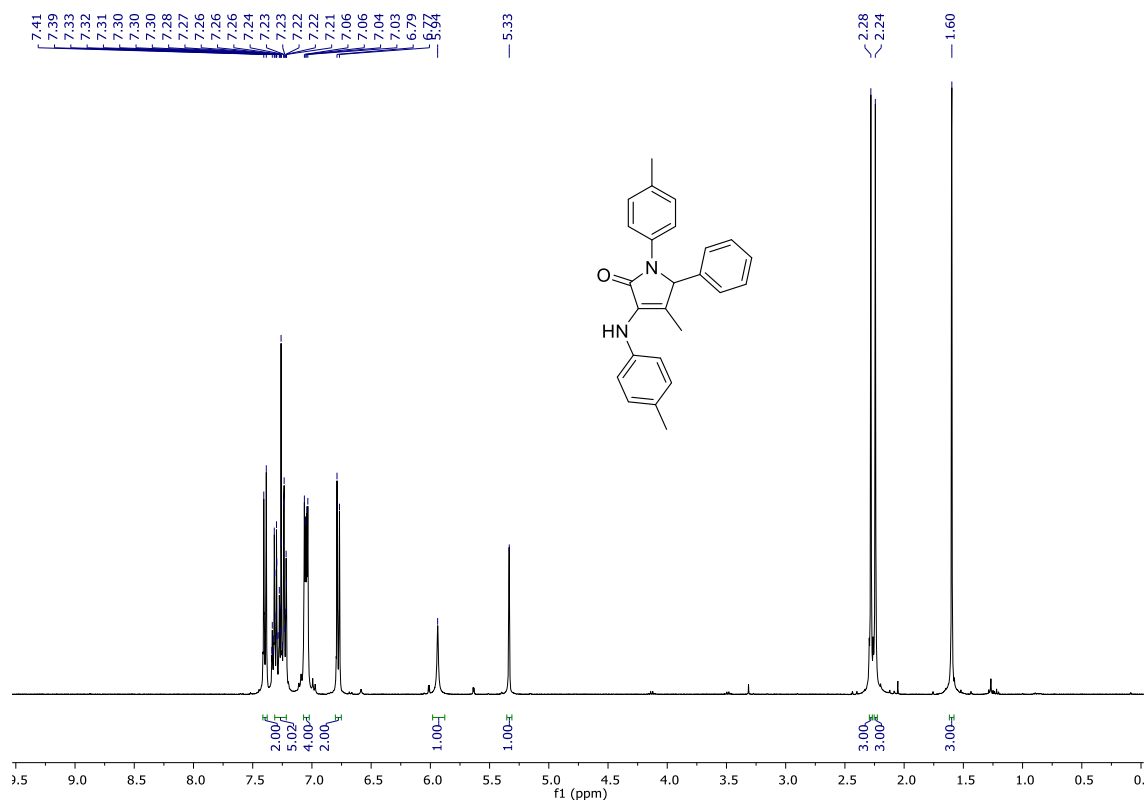
Table S2. Crystal data and structure refinement for 13.

Identification code	a20210337_AL426B
Empirical formula	C ₃₆ H ₂₉ N ₄ O ₄ P
Formula weight	612.60
Temperature/K	150.0(5)
Crystal system	triclinic
Space group	P-1
a/Å	8.0982(4)
b/Å	9.7541(5)
c/Å	19.6381(9)
α/°	84.400(4)
β/°	87.924(4)
γ/°	77.994(4)
Volume/Å ³	1509.85(13)
Z	2
ρ _{calc} /g/cm ³	1.347
μ/mm ⁻¹	1.198
F(000)	640.0
Crystal size/mm ³	0.256 × 0.095 × 0.062
Radiation	CuKα (λ = 1.54184)
2θ range for data collection/°	9.05 to 137.95
Index ranges	-9 ≤ h ≤ 9, -11 ≤ k ≤ 11, -23 ≤ l ≤ 23
Reflections collected	21424
Independent reflections	5600 [R _{int} = 0.0766, R _{sigma} = 0.0666]
Data/restraints/parameters	5600/0/408
Goodness-of-fit on F ²	1.018
Final R indexes [I >= 2σ (I)]	R1 = 0.0485, wR2 = 0.1094
Final R indexes [all data]	R1 = 0.0753, wR2 = 0.1247
Largest diff. peak/hole / e Å ⁻³	0.37/-0.35

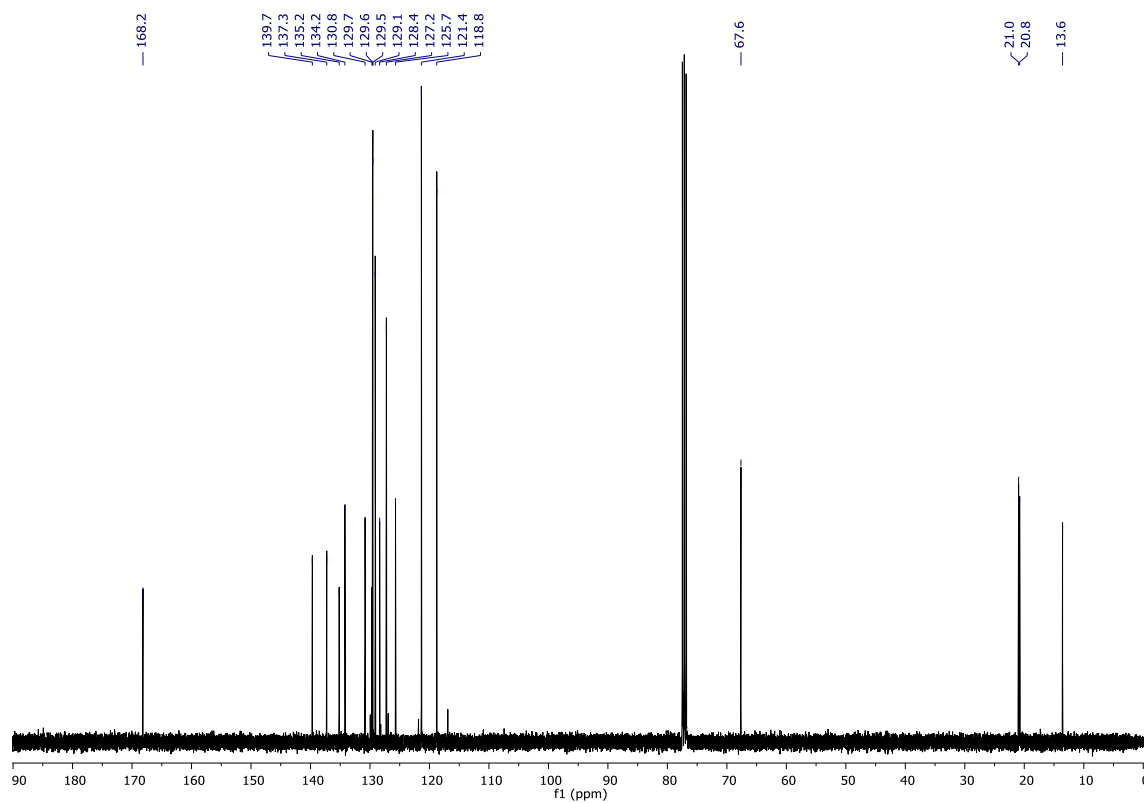
4. Characterization by NMR Spectroscopy of products 18 and 19.

4-Methyl-5-phenyl-1-(*p*-tolyl)-3-(*p*-tolylamino)-1,5-dihydro-2*H*-pyrrol-2-one (18).

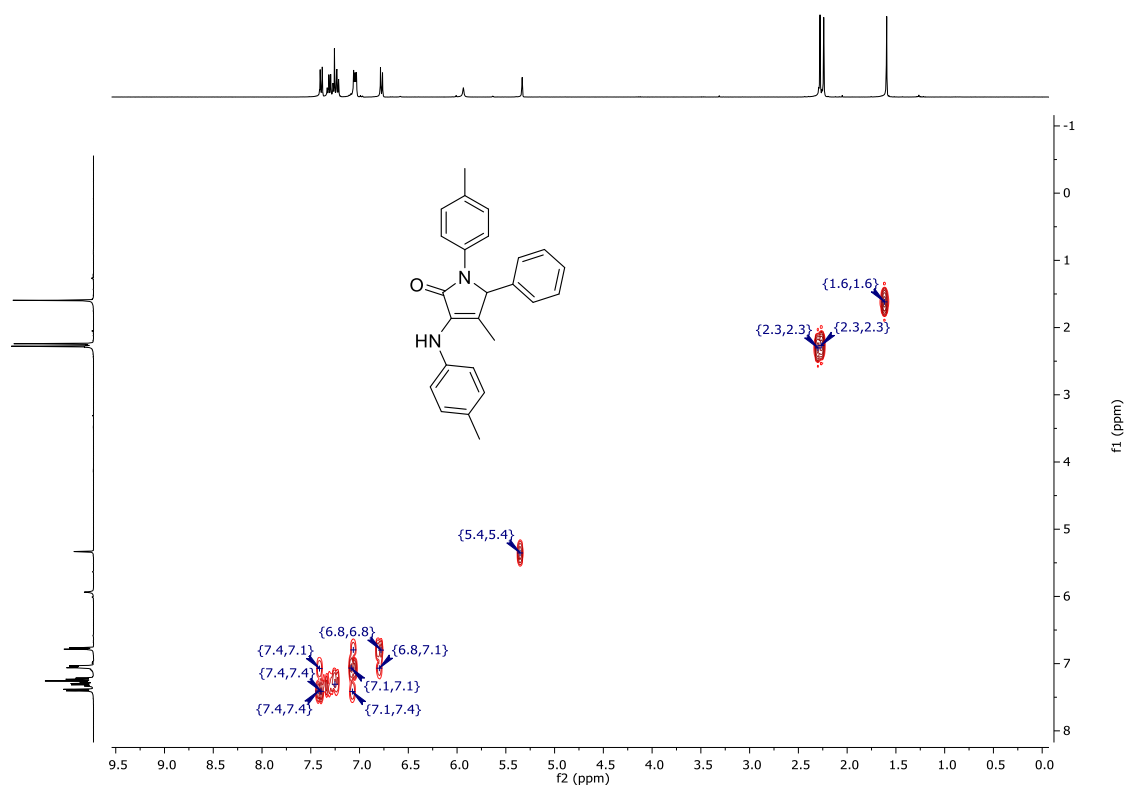
^1H NMR (400 MHz, CDCl_3)



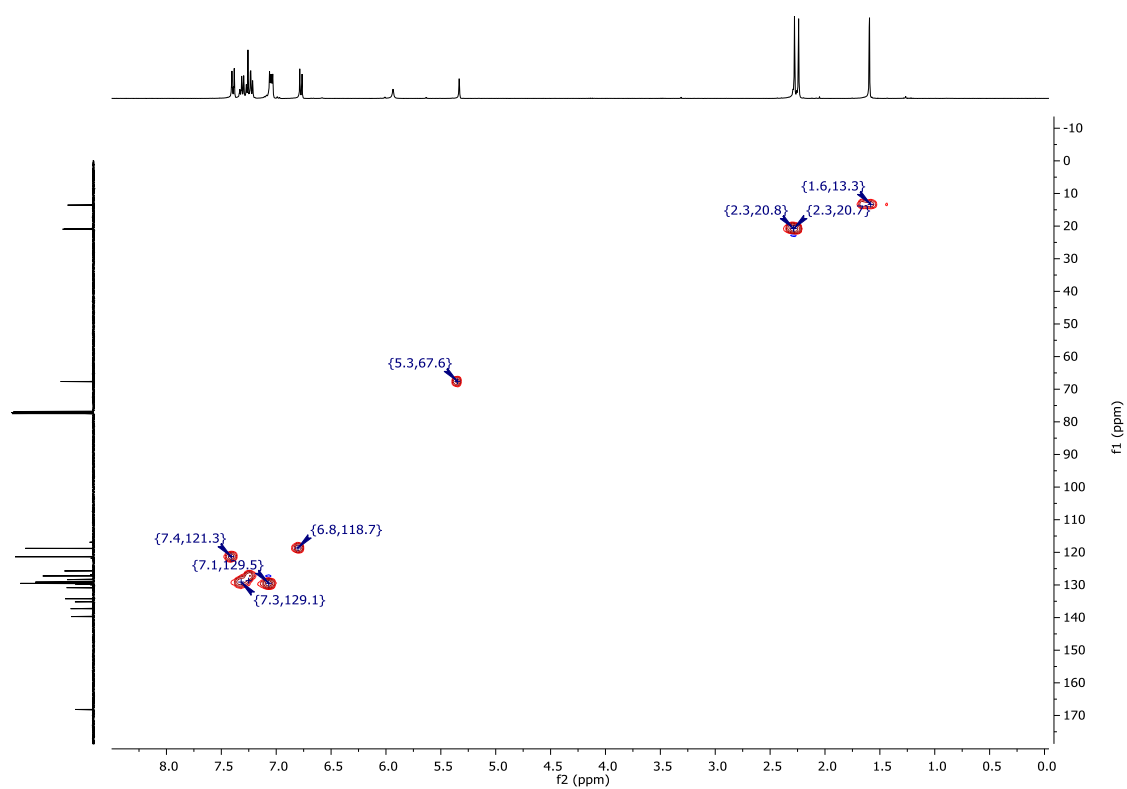
^{13}C NMR [^1H] (101 MHz, CDCl_3)



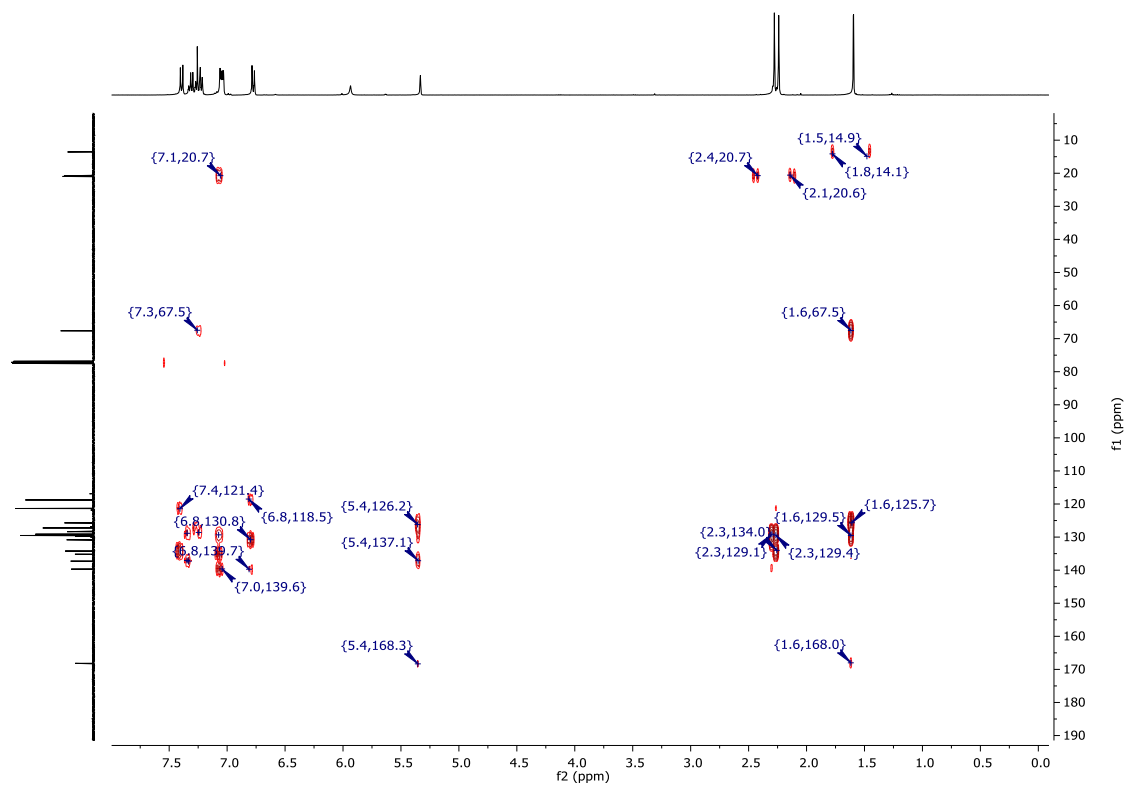
2D-COSY NMR $\{^1\text{H} - ^1\text{H}\}$ (400 MHz, CDCl_3)



2D-HSQC NMR $\{^1\text{H} - ^{13}\text{C}\}$ (^1H : 400 MHz, ^{13}C : 101 MHz, CDCl_3)

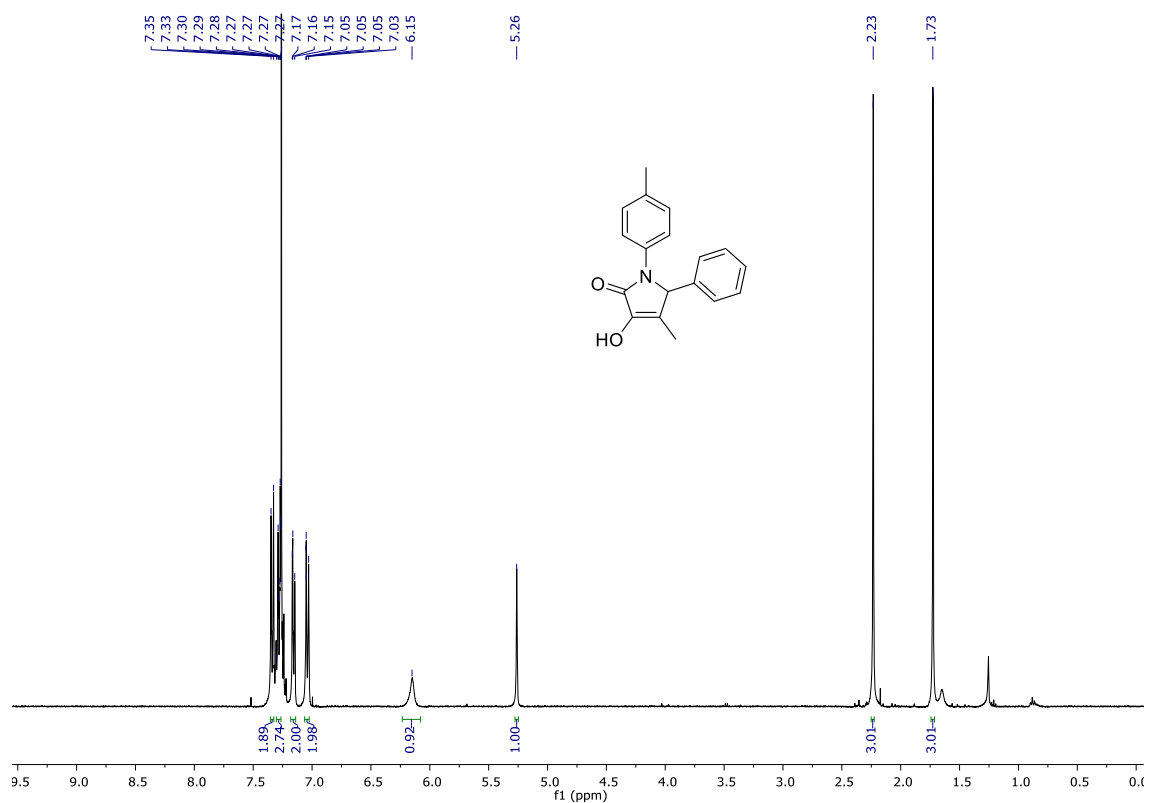


2D-HMBC NMR { $^1\text{H} - ^{13}\text{C}$ } (^1H : 400 MHz, ^{13}C : 101 MHz, CDCl_3)

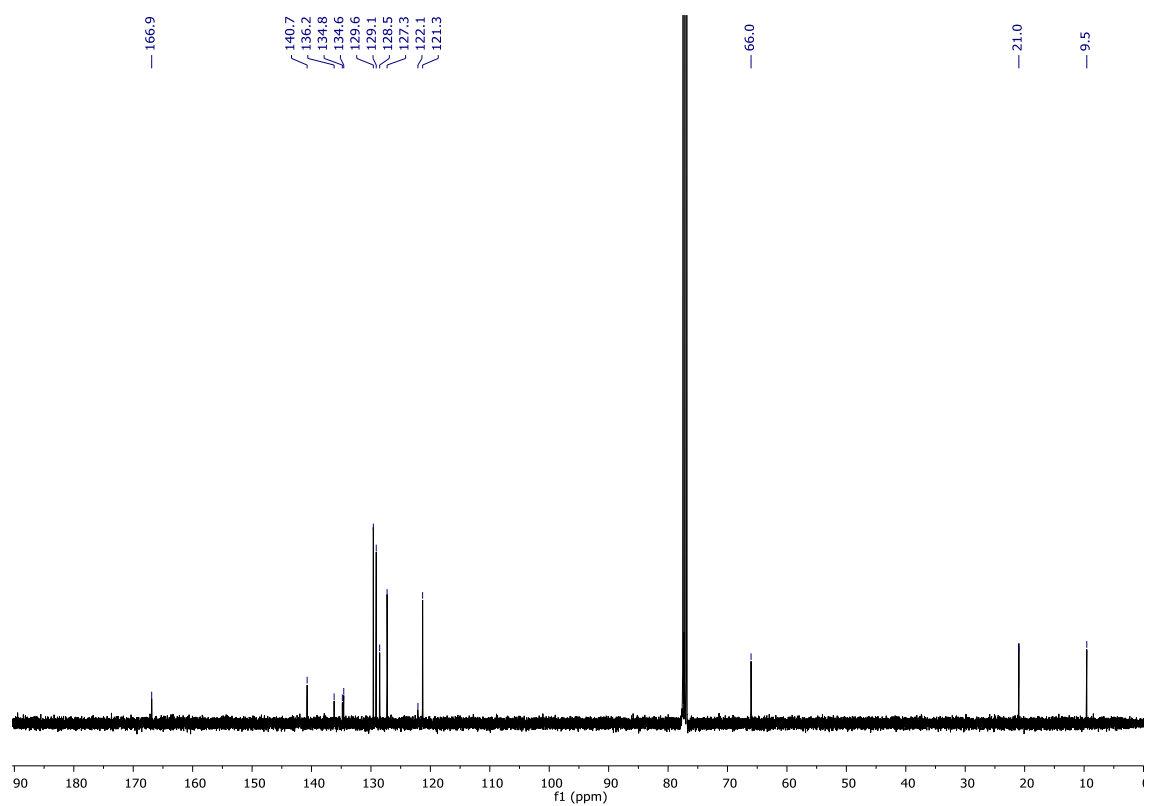


3-Hydroxy-4-methyl-5-phenyl-1-(*p*-tolyl)-1,5-dihydro-2*H*-pyrrol-2-one (19).

^1H NMR (400 MHz, CDCl_3)



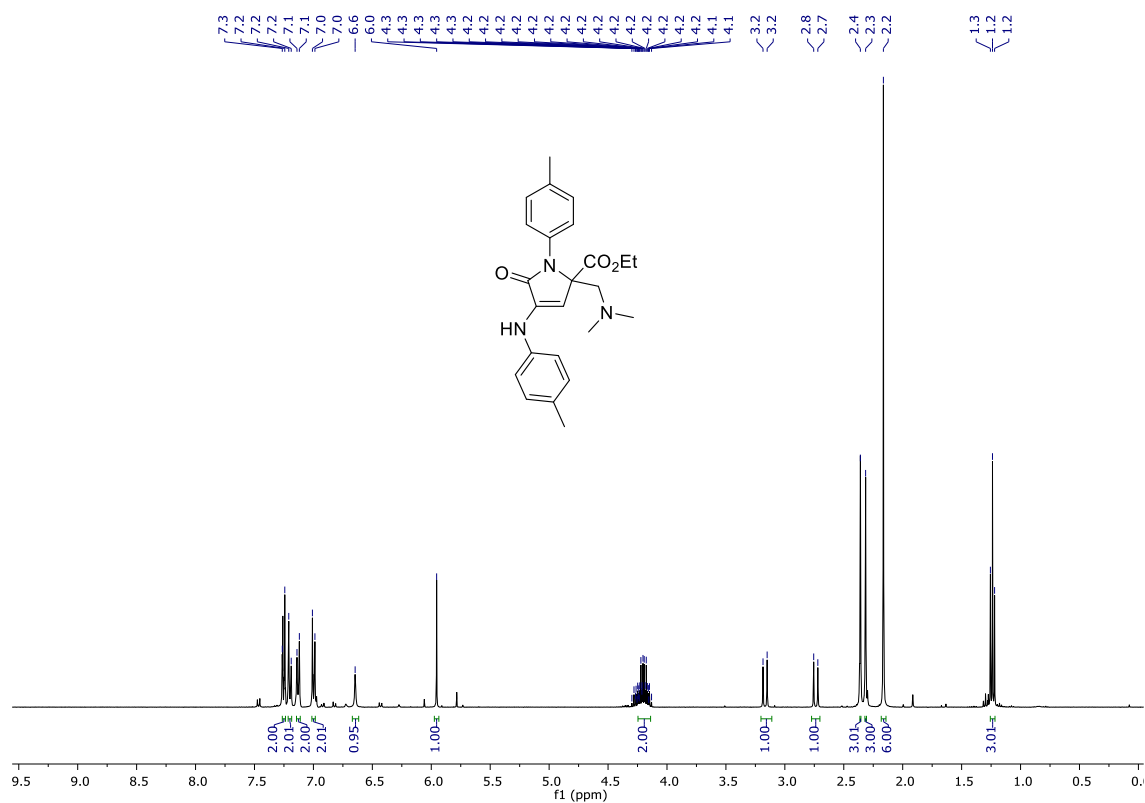
^{13}C NMR { ^1H } (101 MHz, CDCl_3)



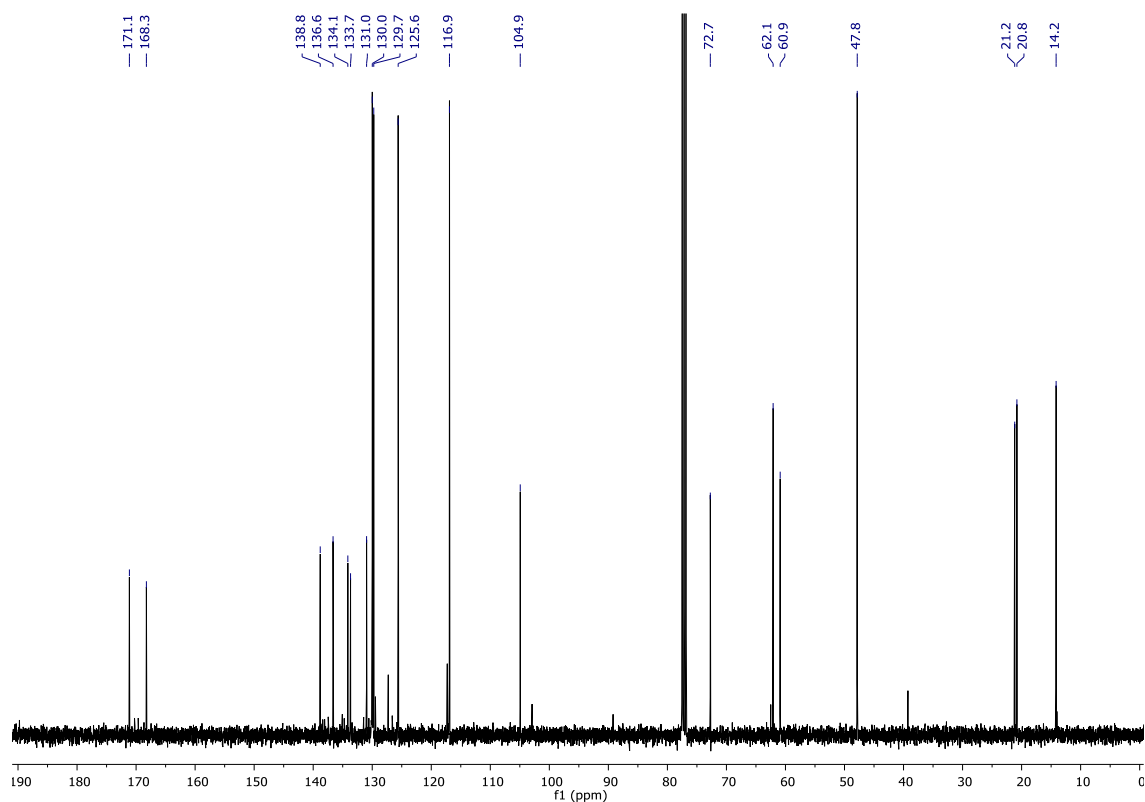
5. Characterization by NMR Spectroscopy of product 20.

Ethyl 3-((dimethylamino)methyl)-5-oxo-1-(*p*-tolyl)-4-(*p*-tolylamino)-2,5-dihydro-1*H*-pyrrole-2-carboxylate (20).

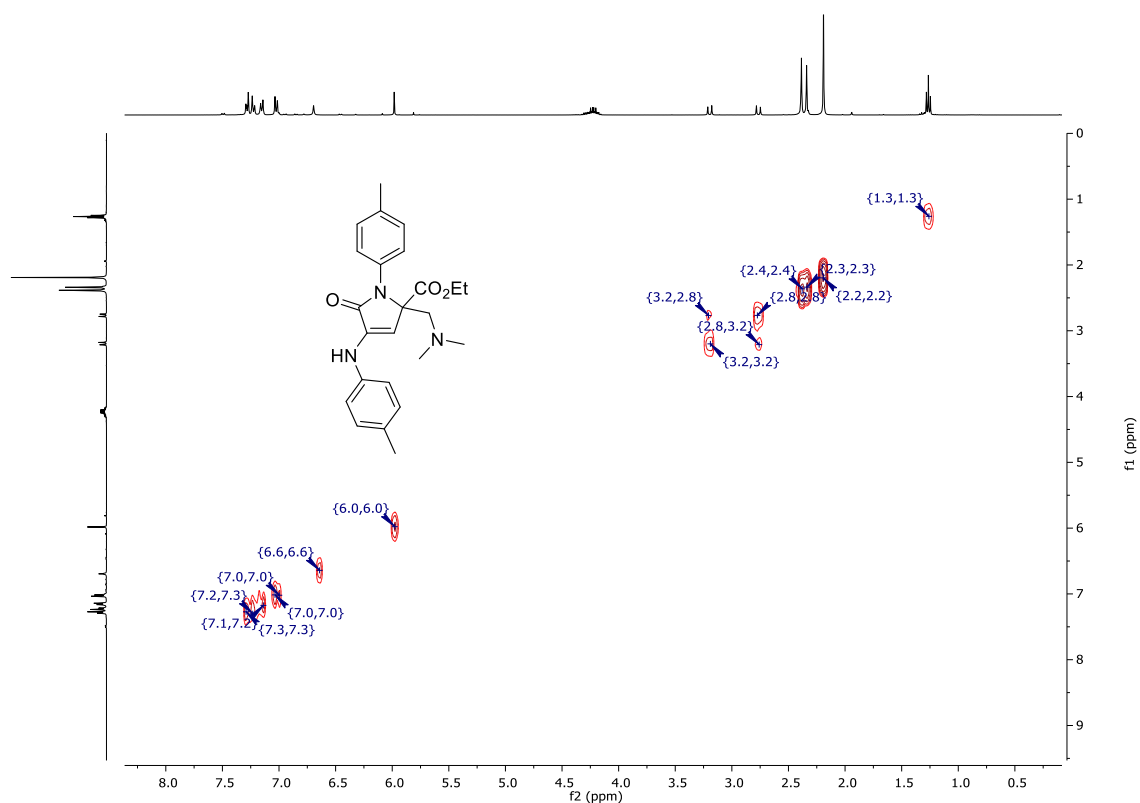
^1H NMR (400 MHz, CDCl_3)



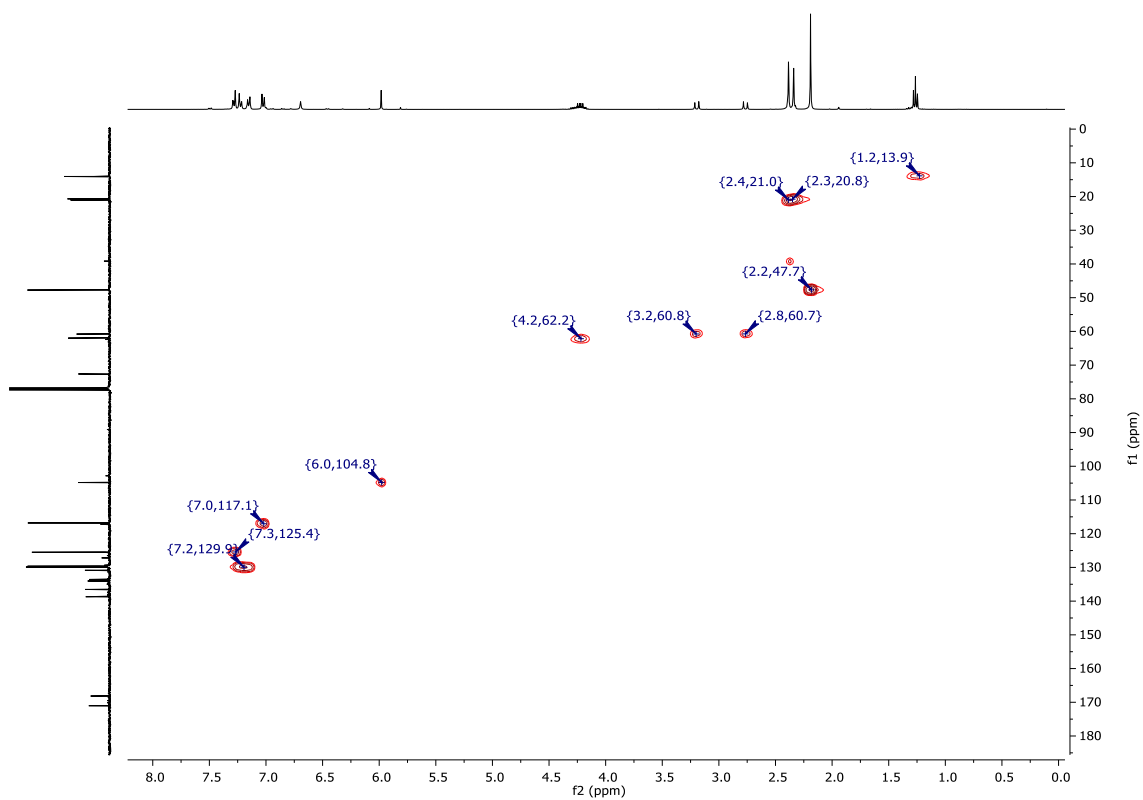
^{13}C NMR { ^1H } (101 MHz, CDCl_3)



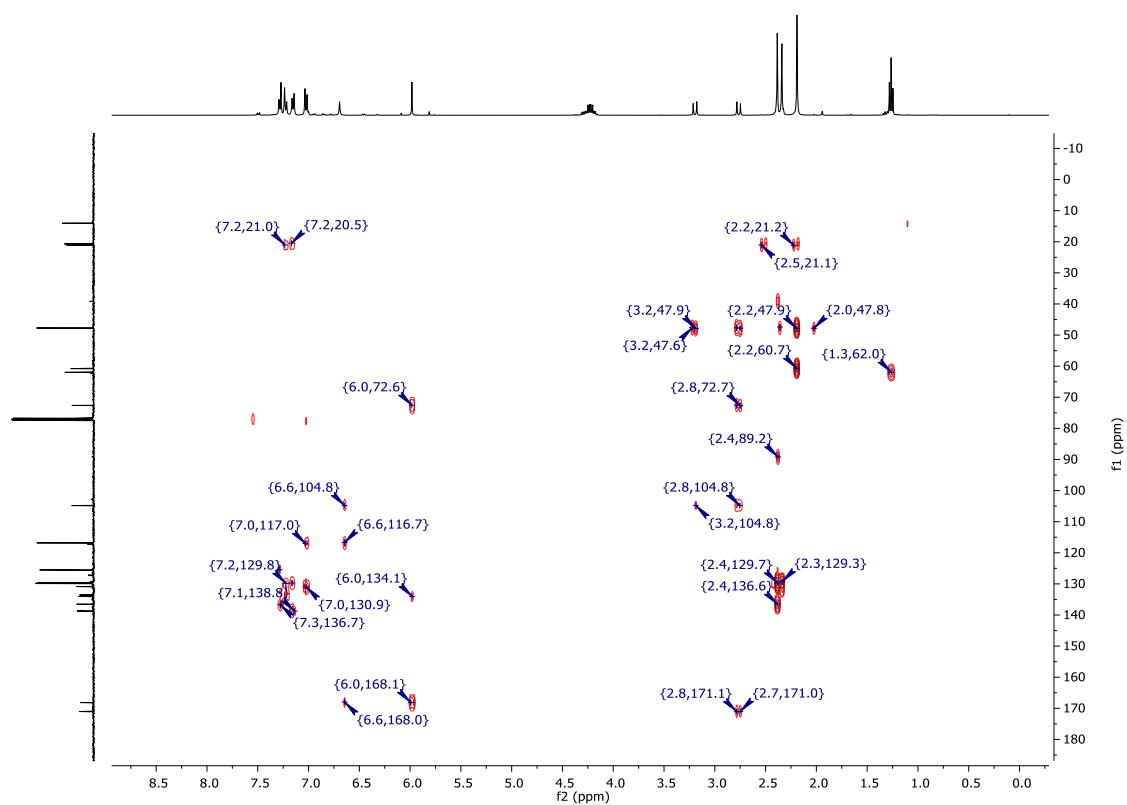
2D-COSY NMR {¹H – ¹H} (400 MHz, CDCl₃)



2D-HSQC NMR {¹H – ¹³C} (¹H: 400 MHz, ¹³C: 101 MHz, CDCl₃)



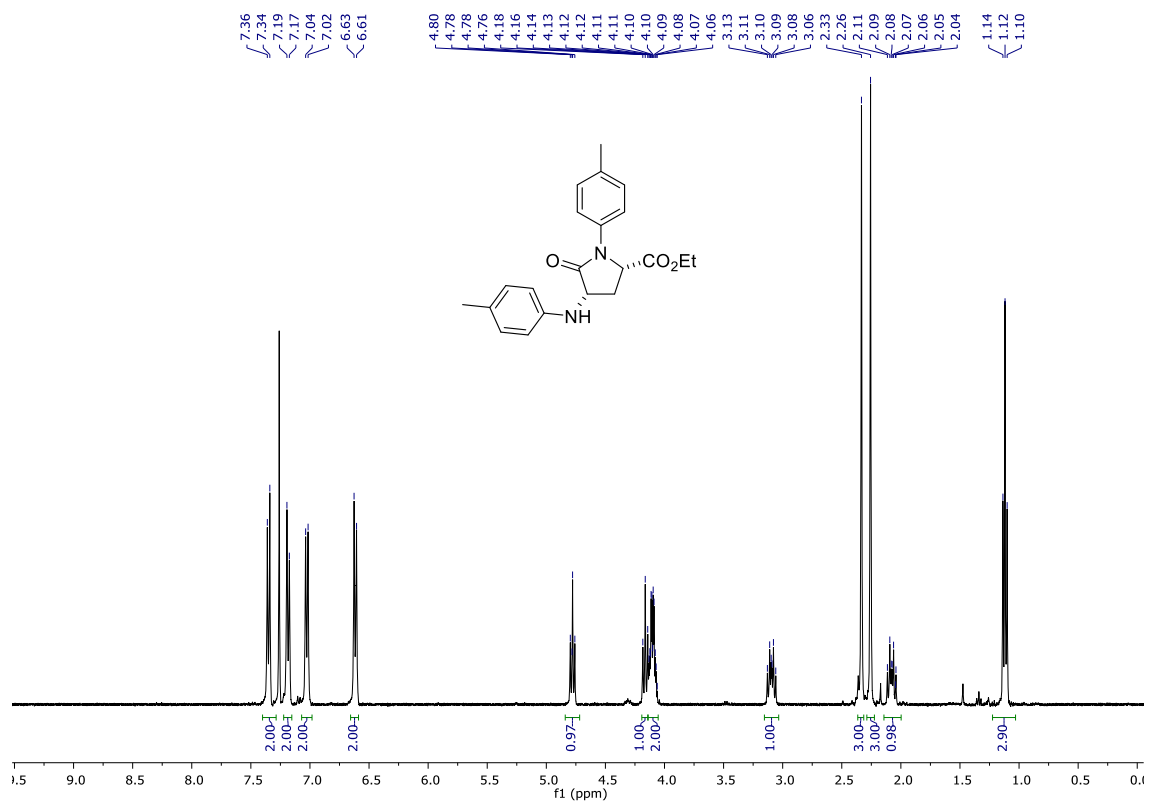
2D-HMBC NMR { $^1\text{H} - ^{13}\text{C}$ } (^1H : 400 MHz, ^{13}C : 101 MHz, CDCl_3)



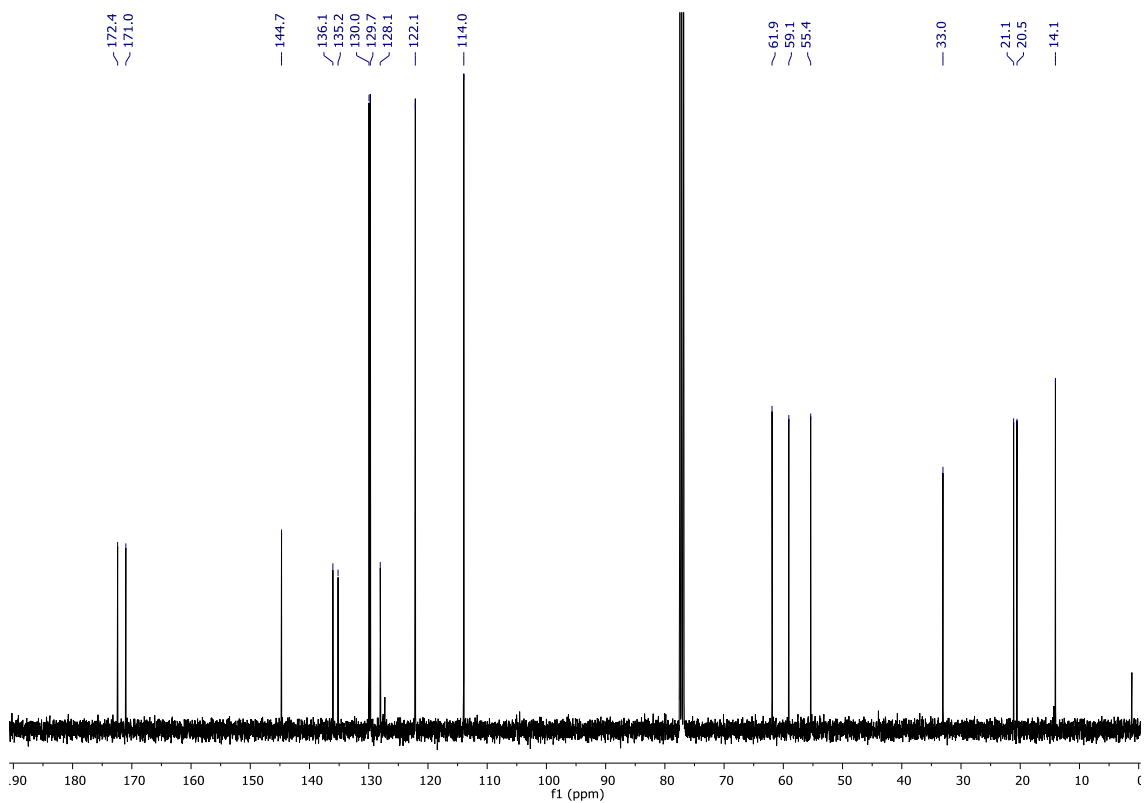
6. Characterization by NMR Spectroscopy of products 21 and 23.

Ethyl (2*S**,4*S**)-5-oxo-1-(*p*-tolyl)-4-(*p*-tolylamino)pyrrolidine-2-carboxylate (21)

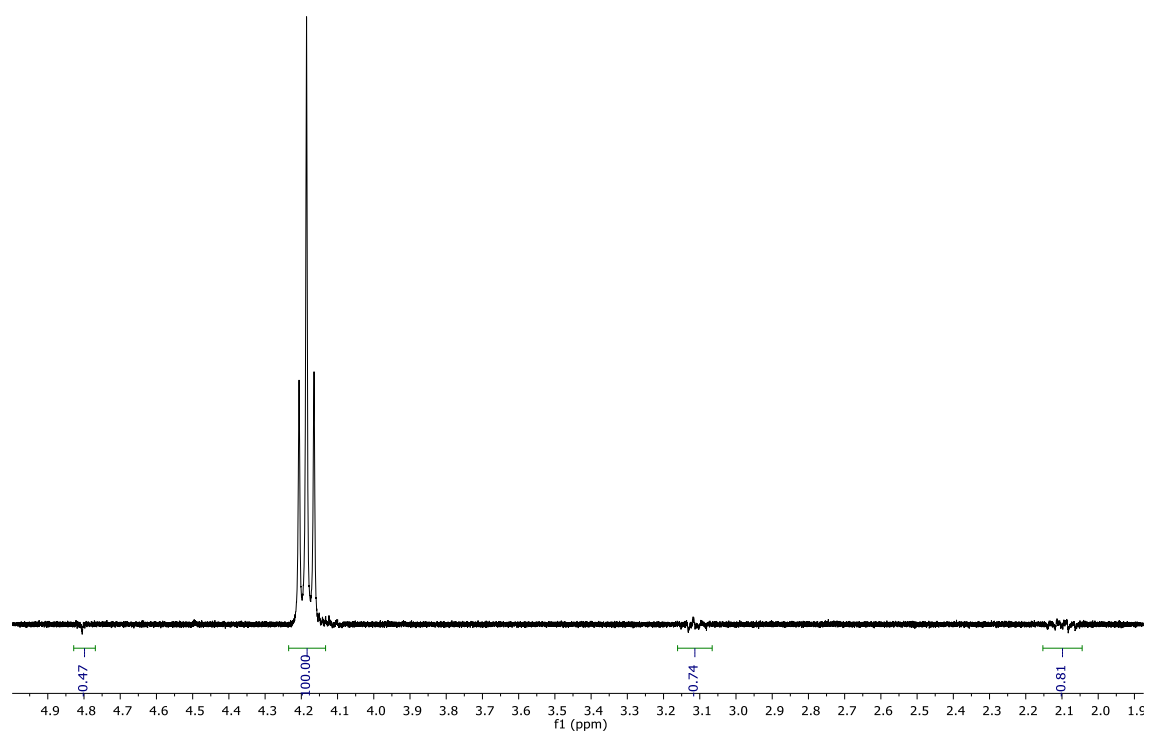
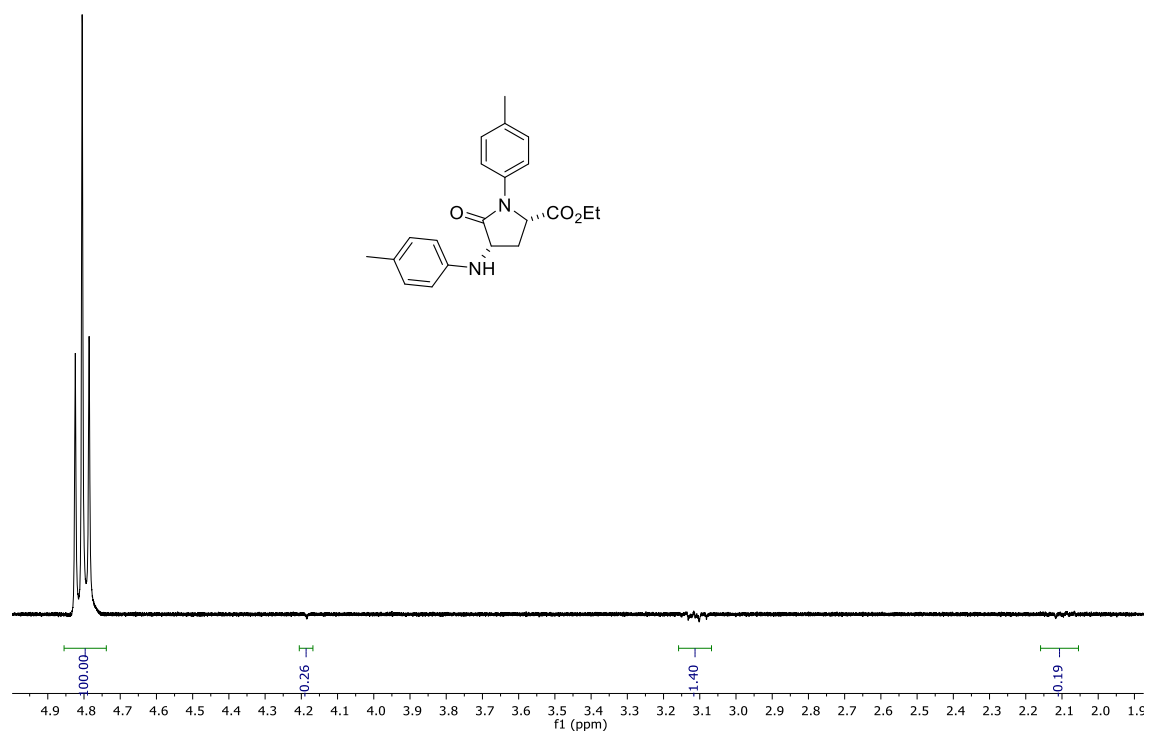
¹H NMR (400 MHz, CDCl₃)

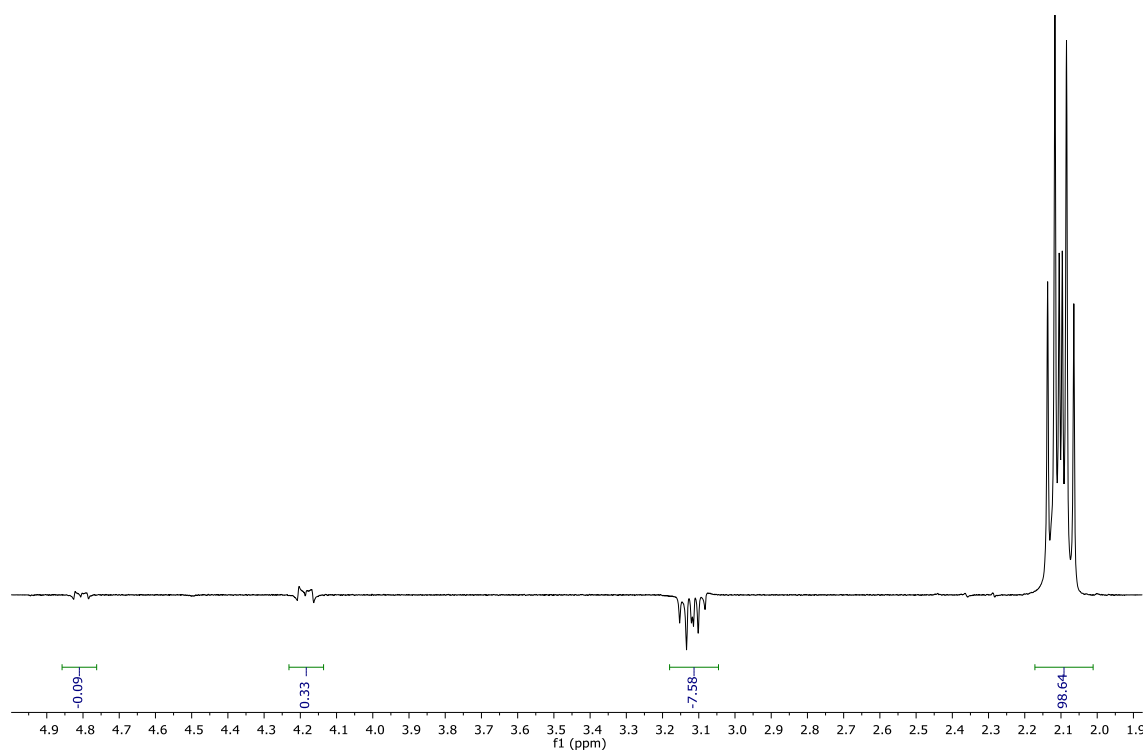
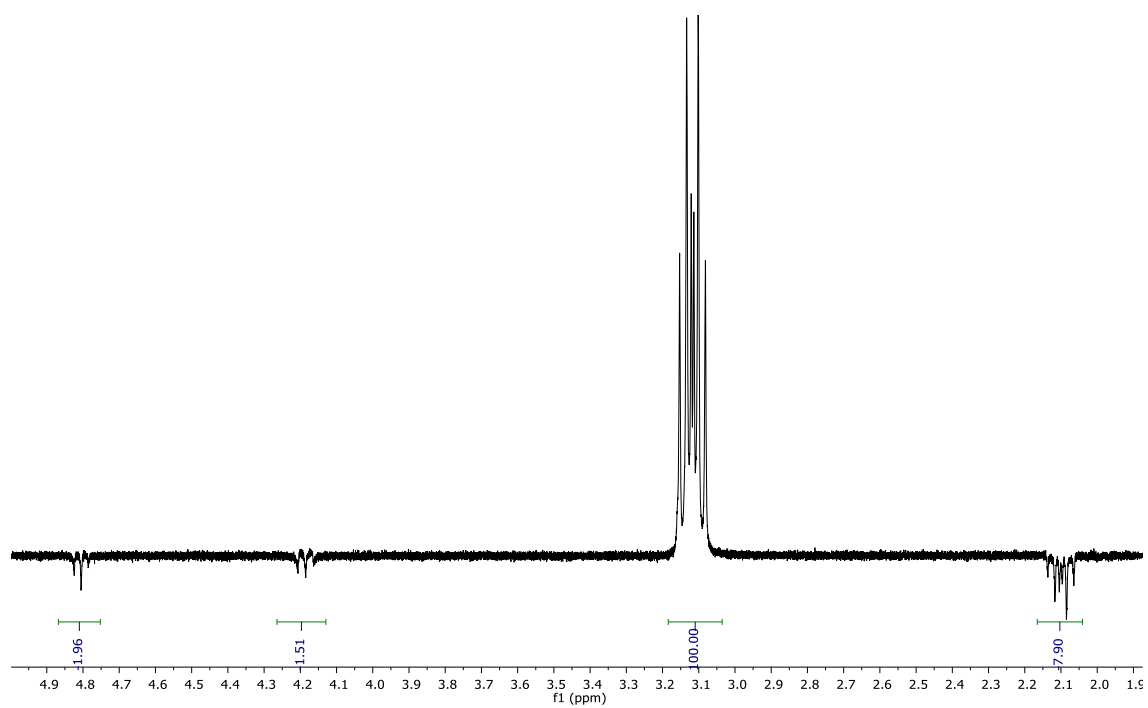


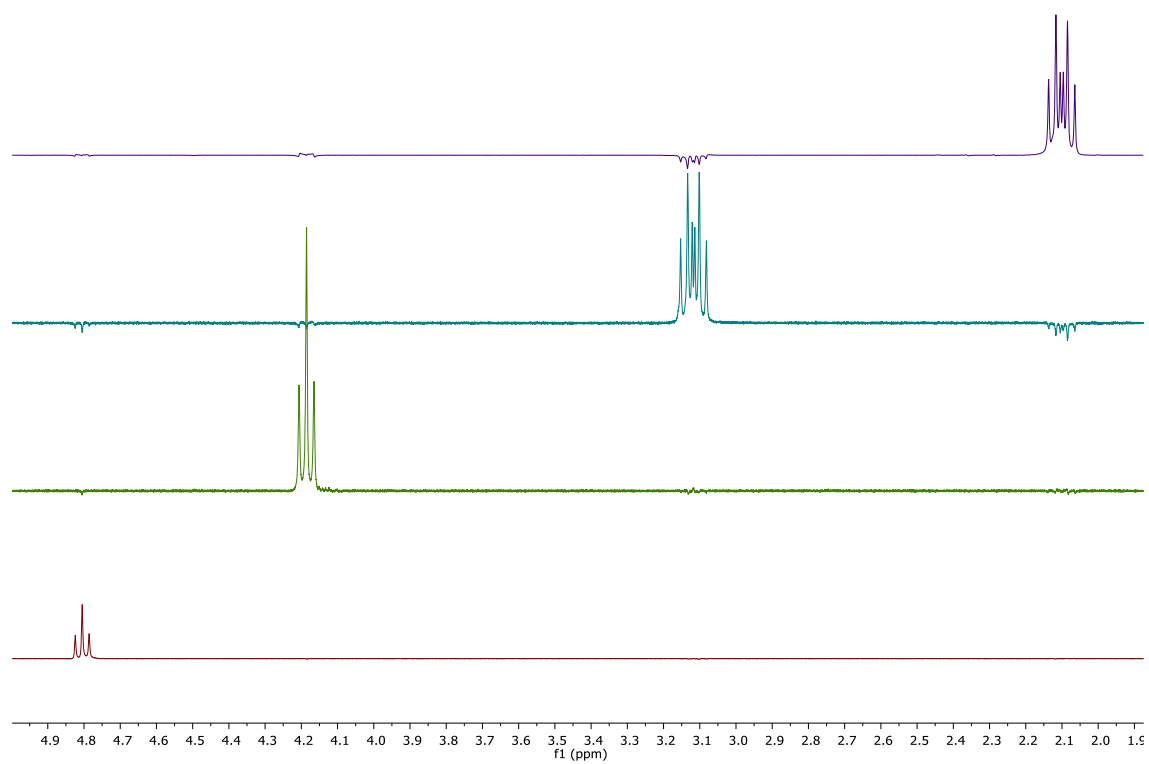
¹³C NMR {¹H} (101 MHz, CDCl₃)



1D-NOESY {¹H – ¹H} (400 MHz, CDCl₃)

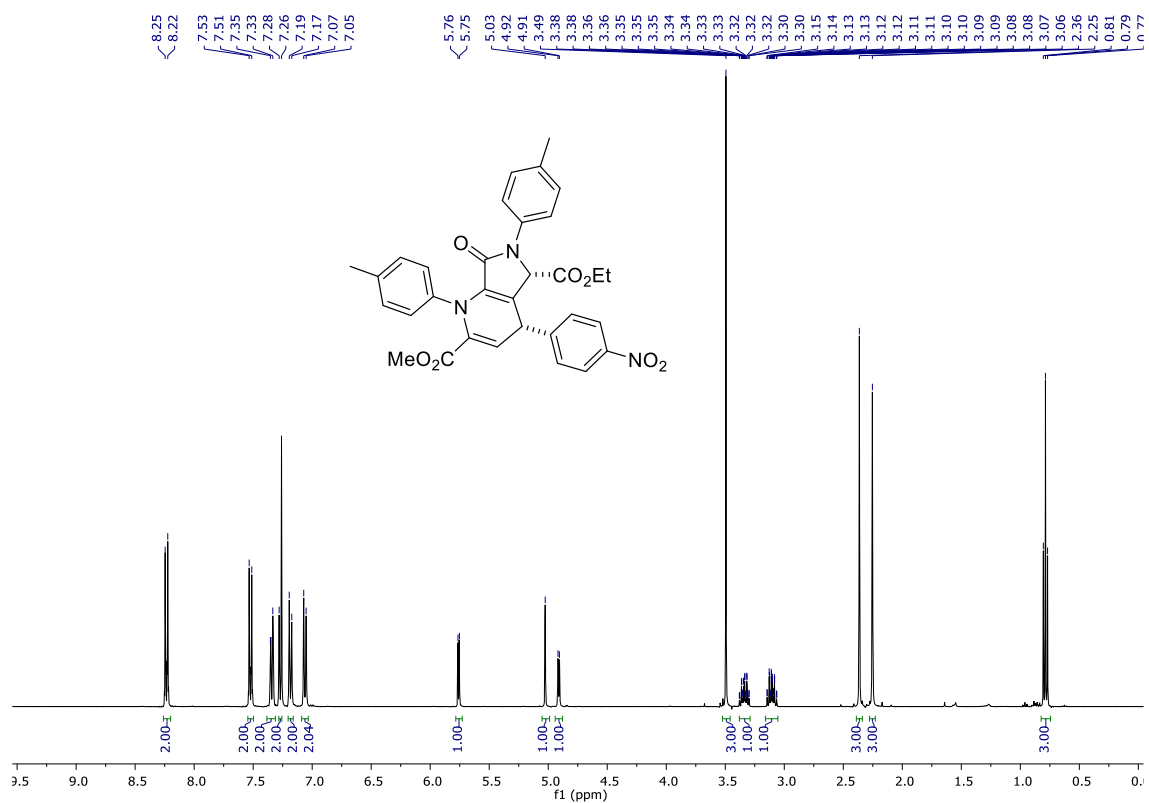




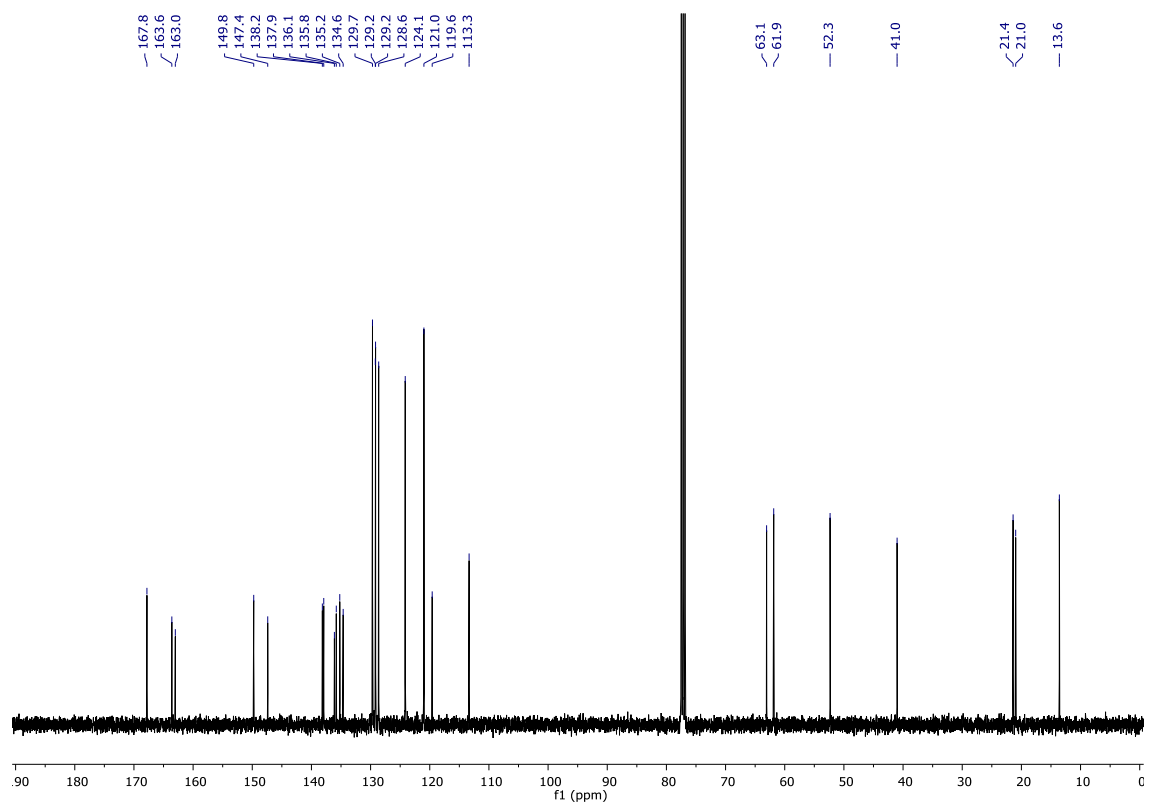


5-Ethyl 2-methyl (4*S,5*S**)-4-(4-nitrophenyl)-7-oxo-1,6-di-*p*-tolyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,4-*b*]pyridine-2,5-dicarboxylate (23)**

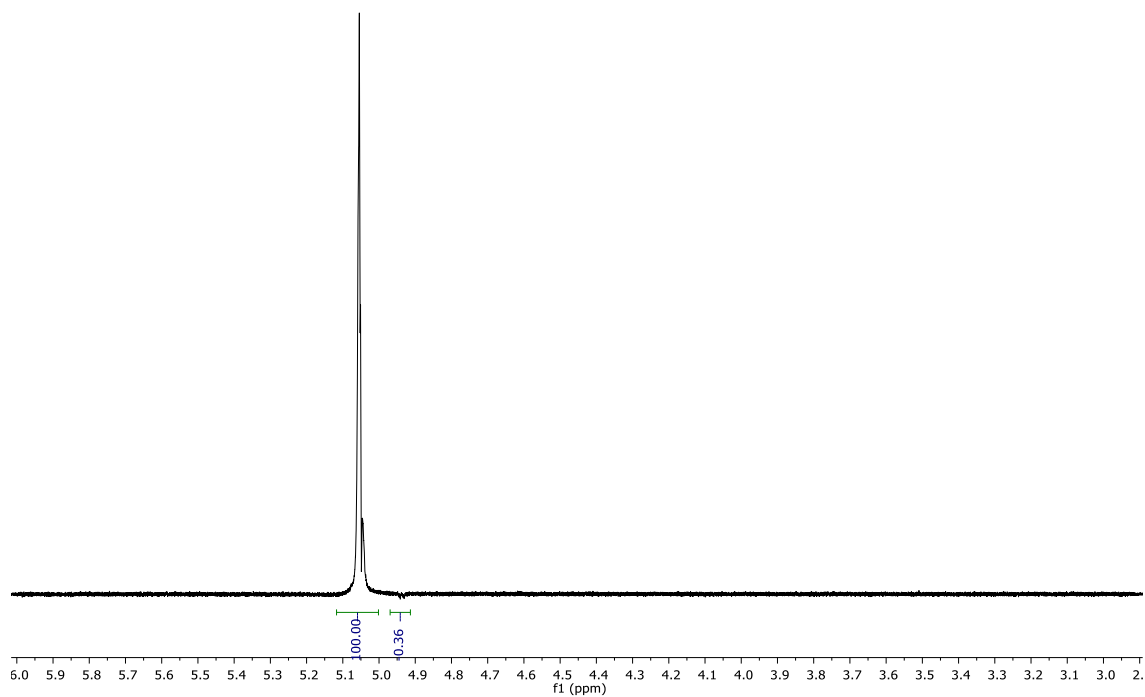
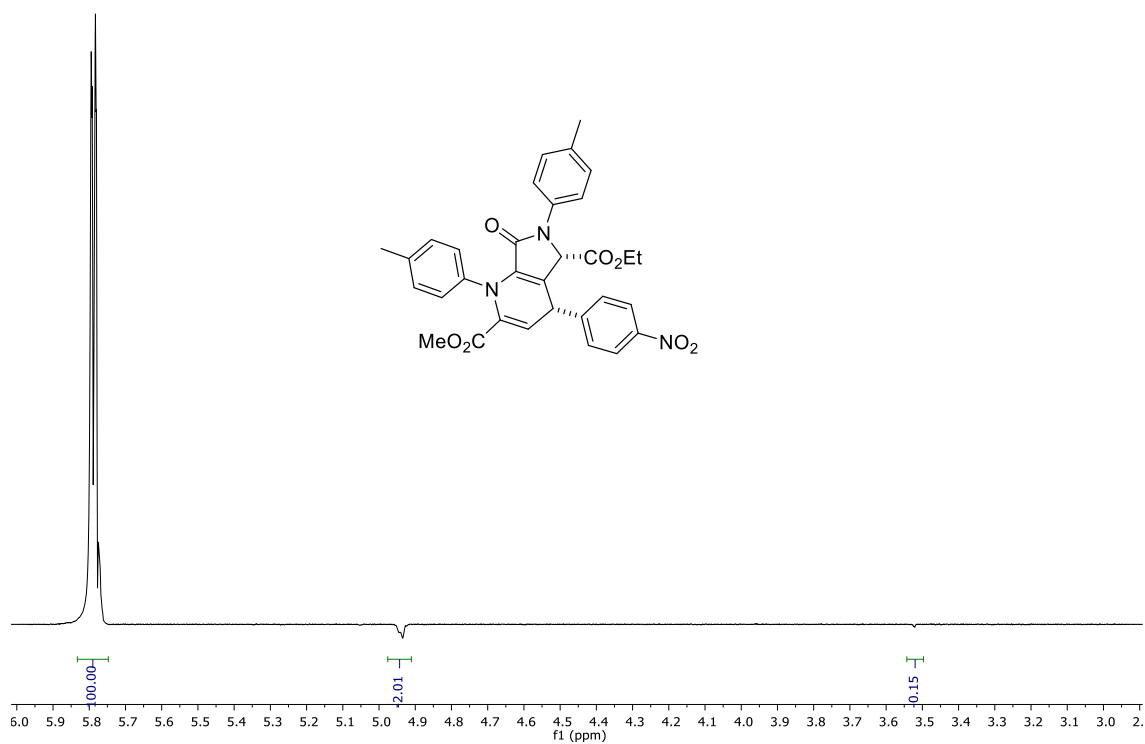
¹H NMR (400 MHz, CDCl₃)

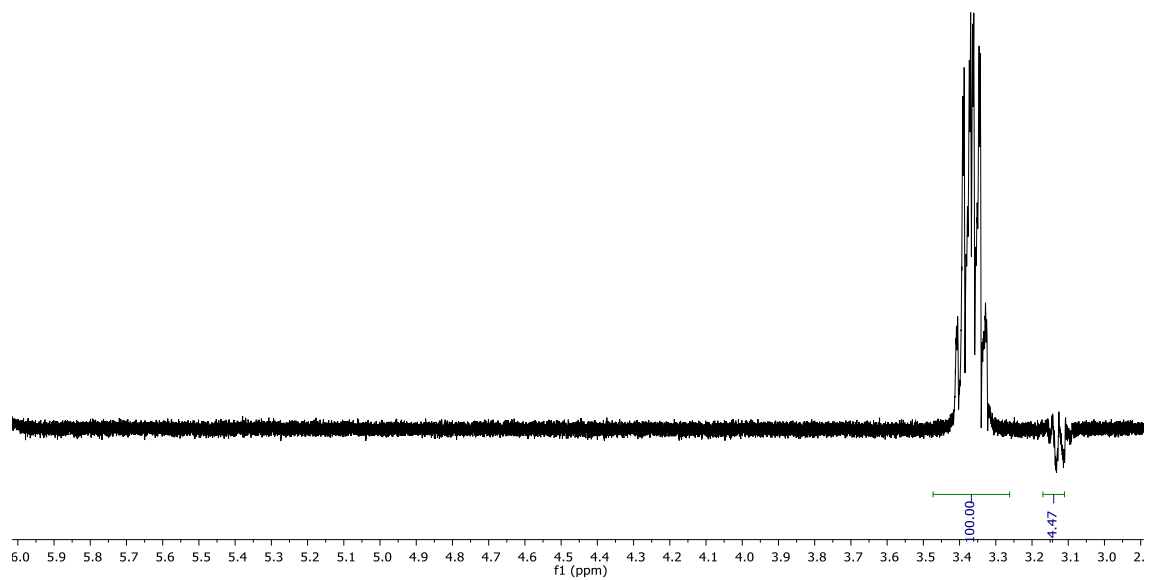
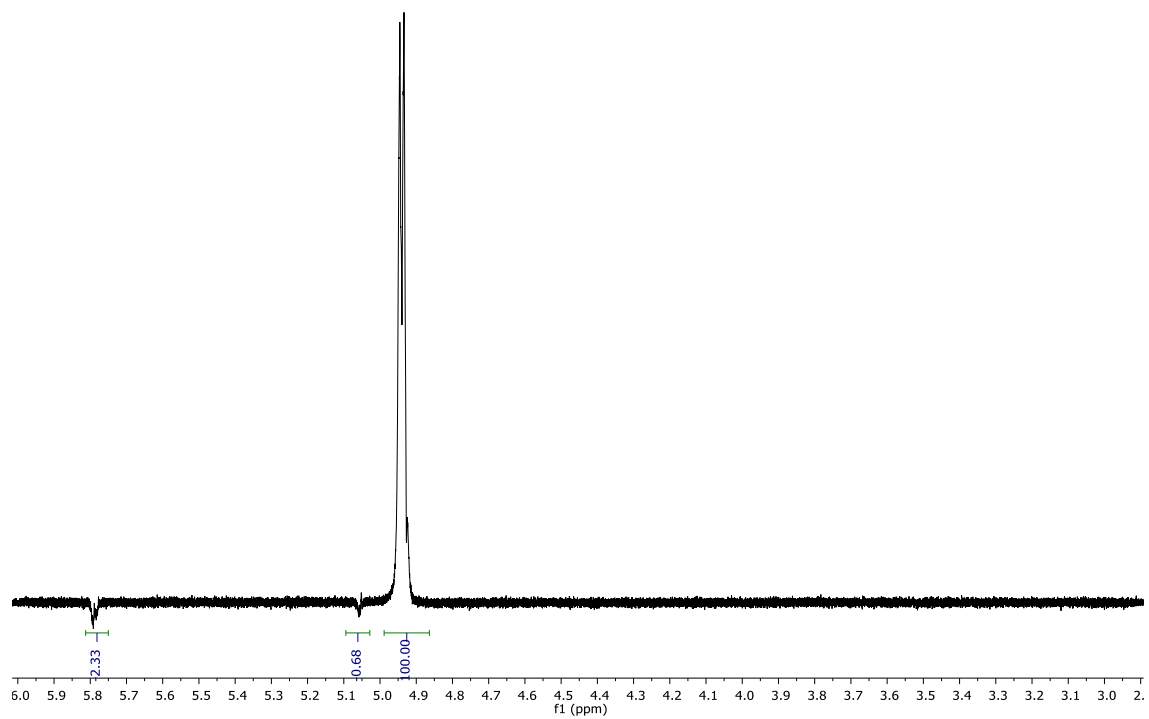


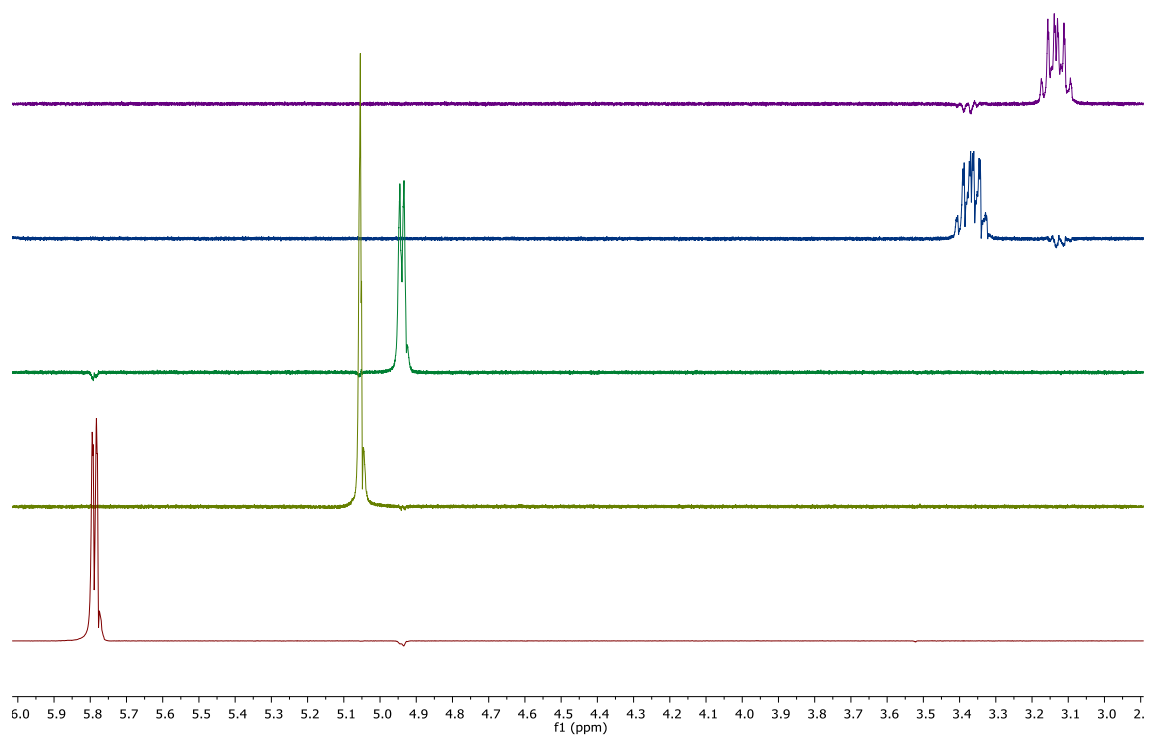
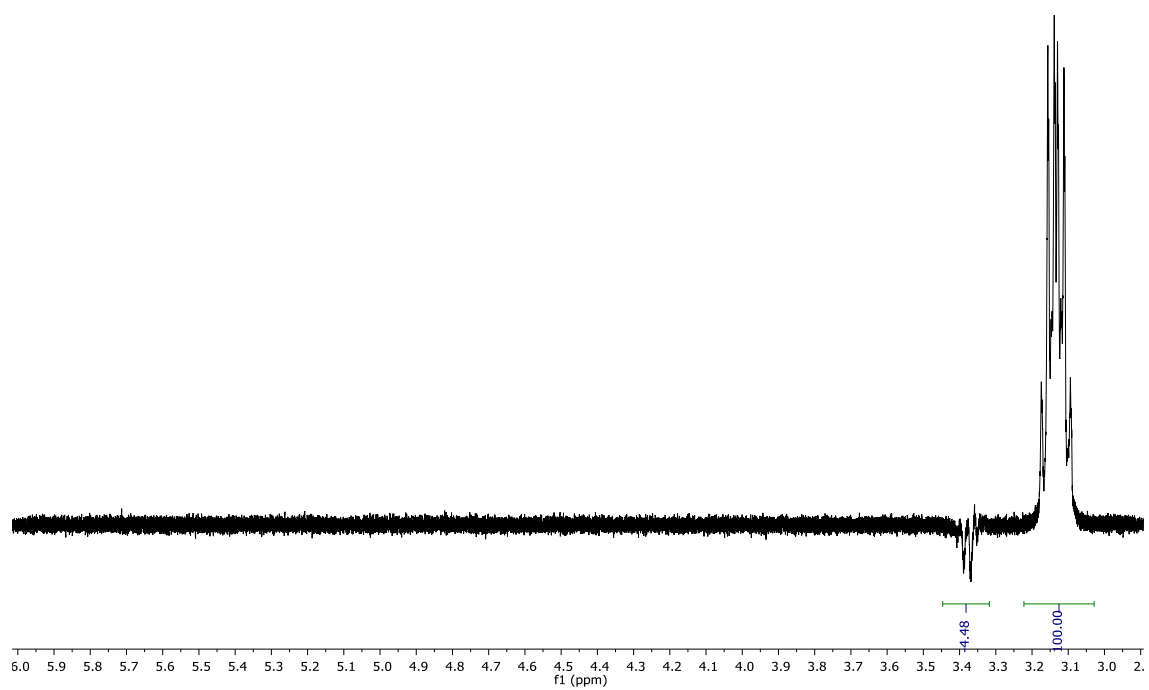
¹³C NMR {¹H} (101 MHz, CDCl₃)



1D-NOESY {¹H – ¹H} (400 MHz, CDCl₃)



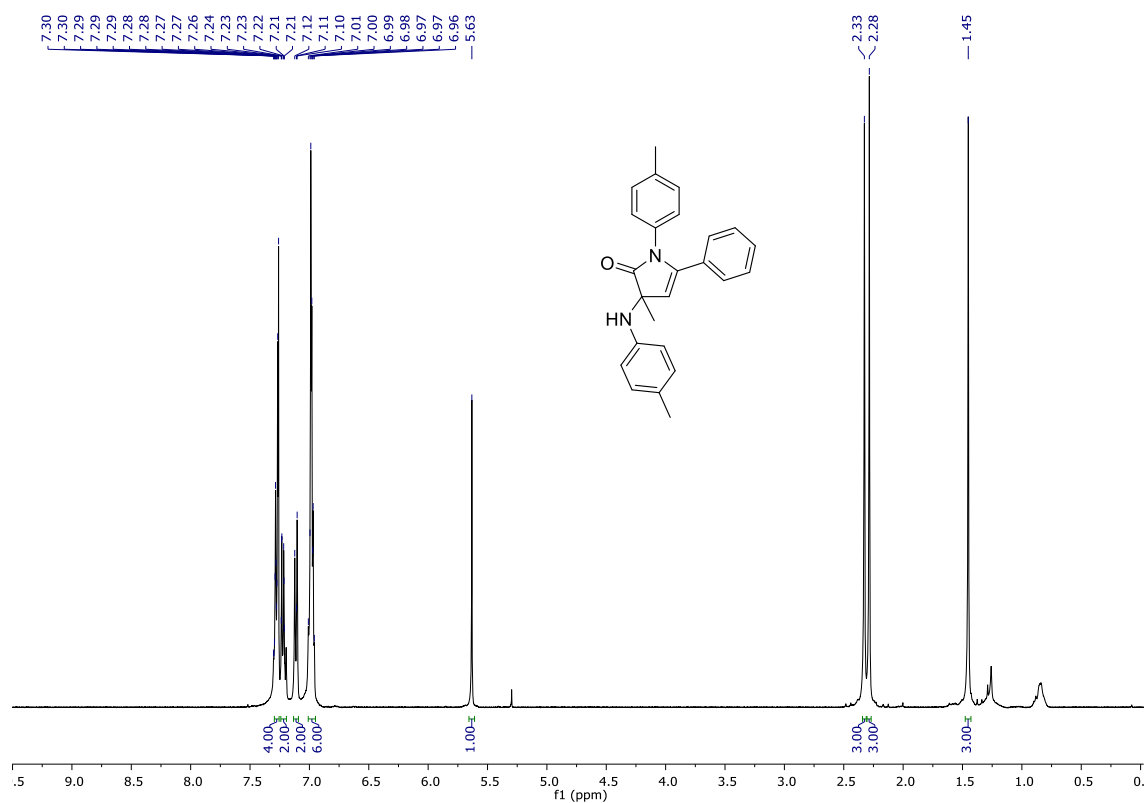




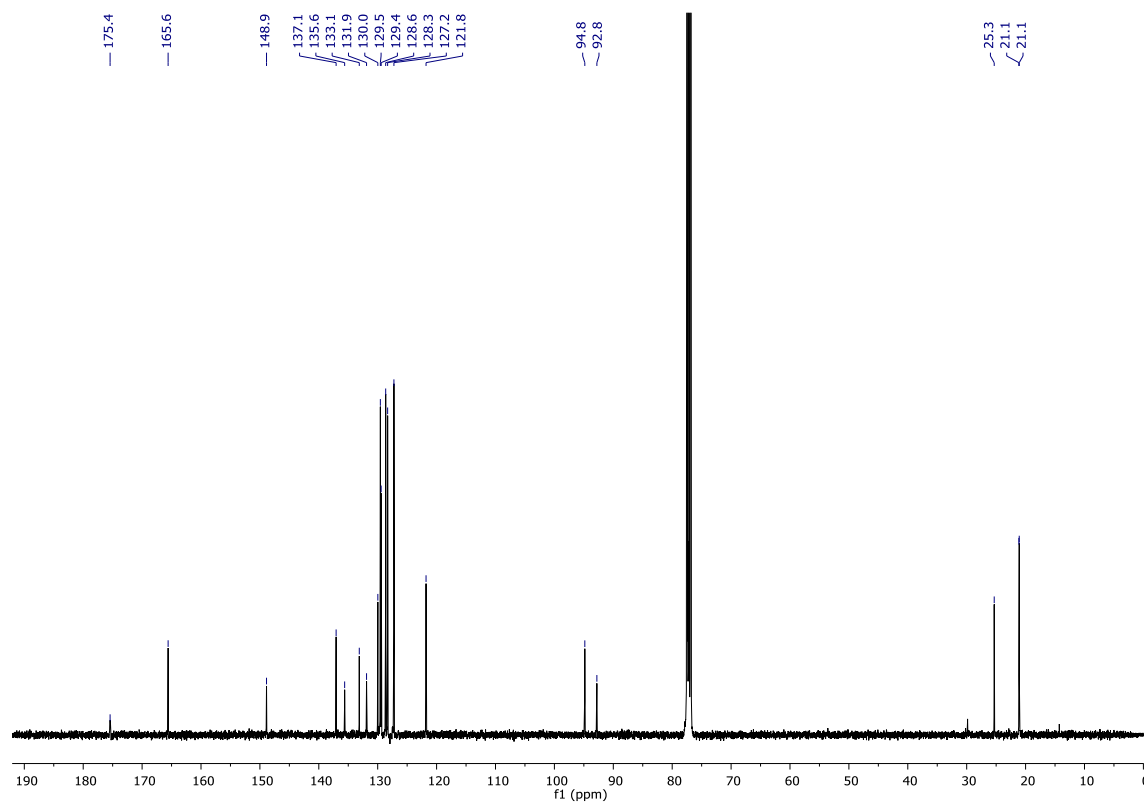
7. Characterization by NMR Spectroscopy of products 25.

3-Methyl-5-phenyl-1-(*p*-tolyl)-3-(*p*-tolylamino)-1,3-dihydro-2*H*-pyrrol-2-one (25a).

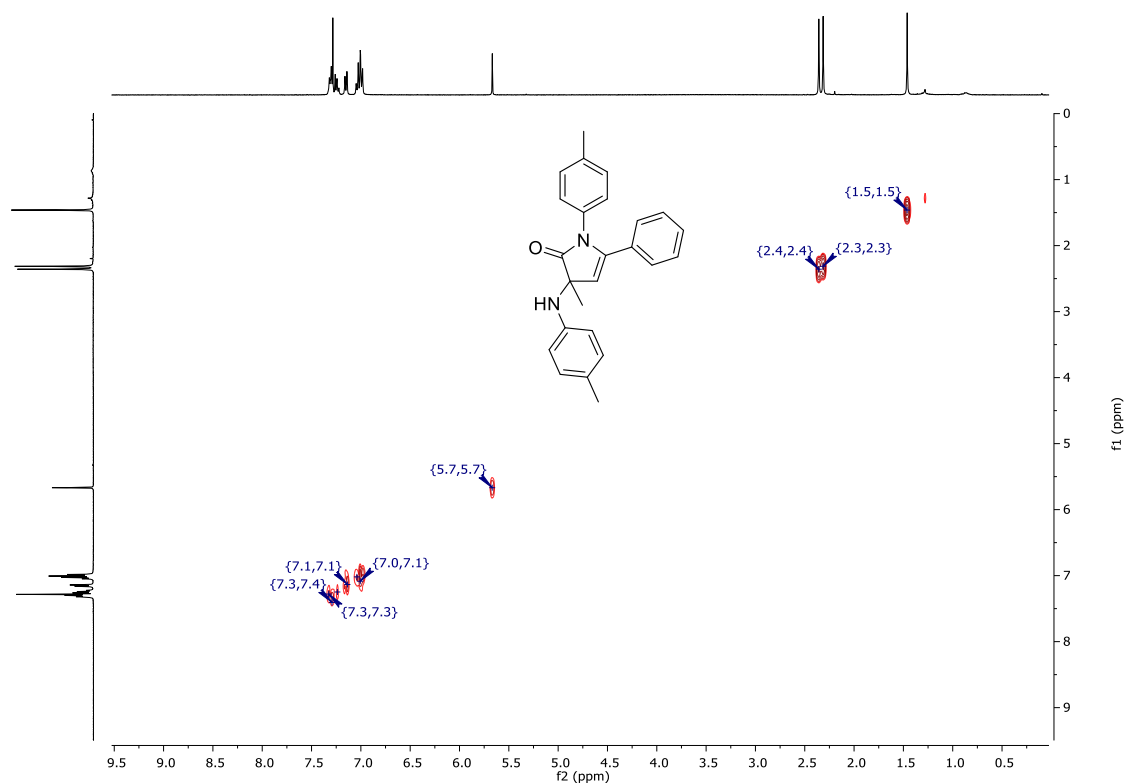
^1H NMR (400 MHz, CDCl_3)



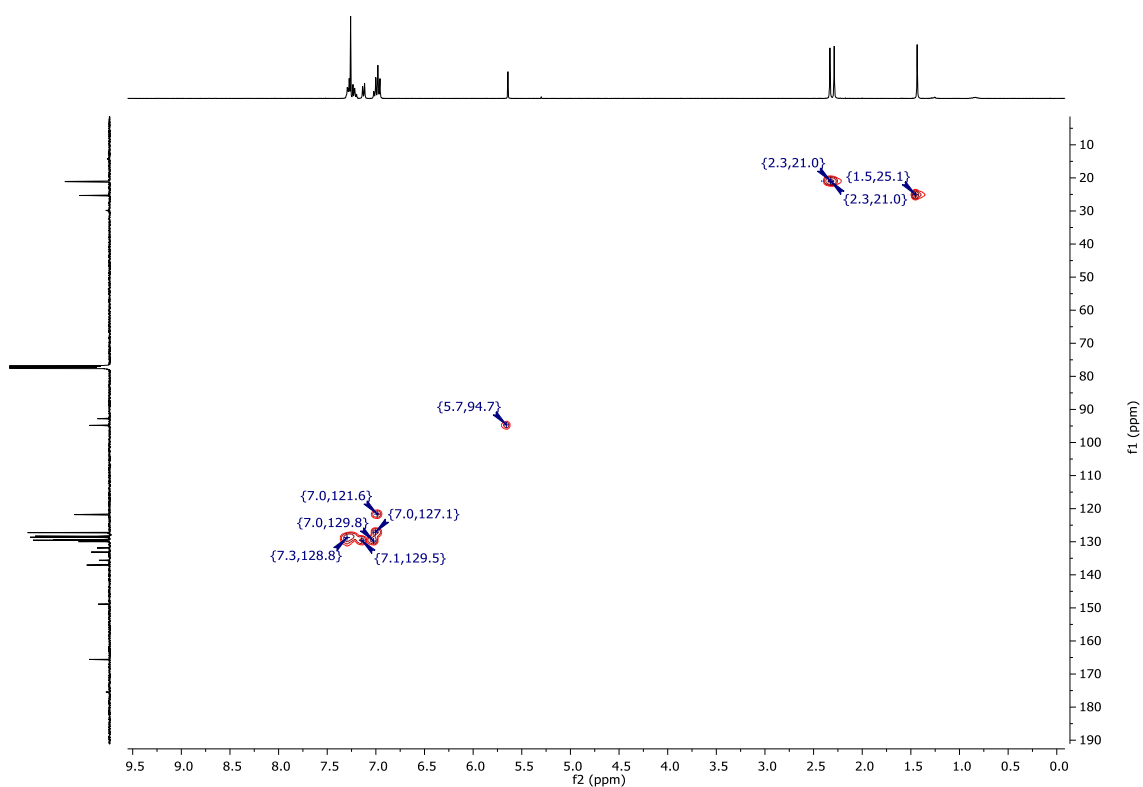
^{13}C NMR $\{^1\text{H}\}$ (101 MHz, CDCl_3)



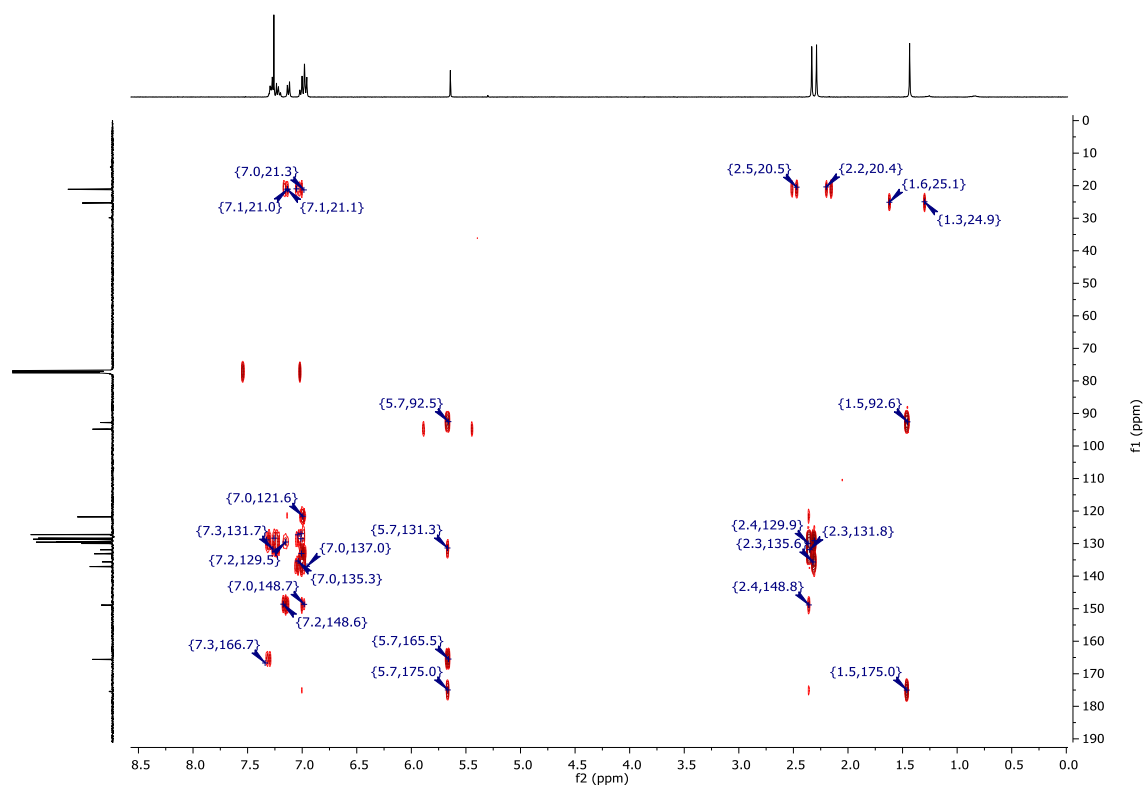
2D-COSY NMR {¹H – ¹H} (400 MHz, CDCl₃)



2D-HSQC NMR {¹H – ¹³C} (¹H: 400 MHz, ¹³C: 101 MHz, CDCl₃)

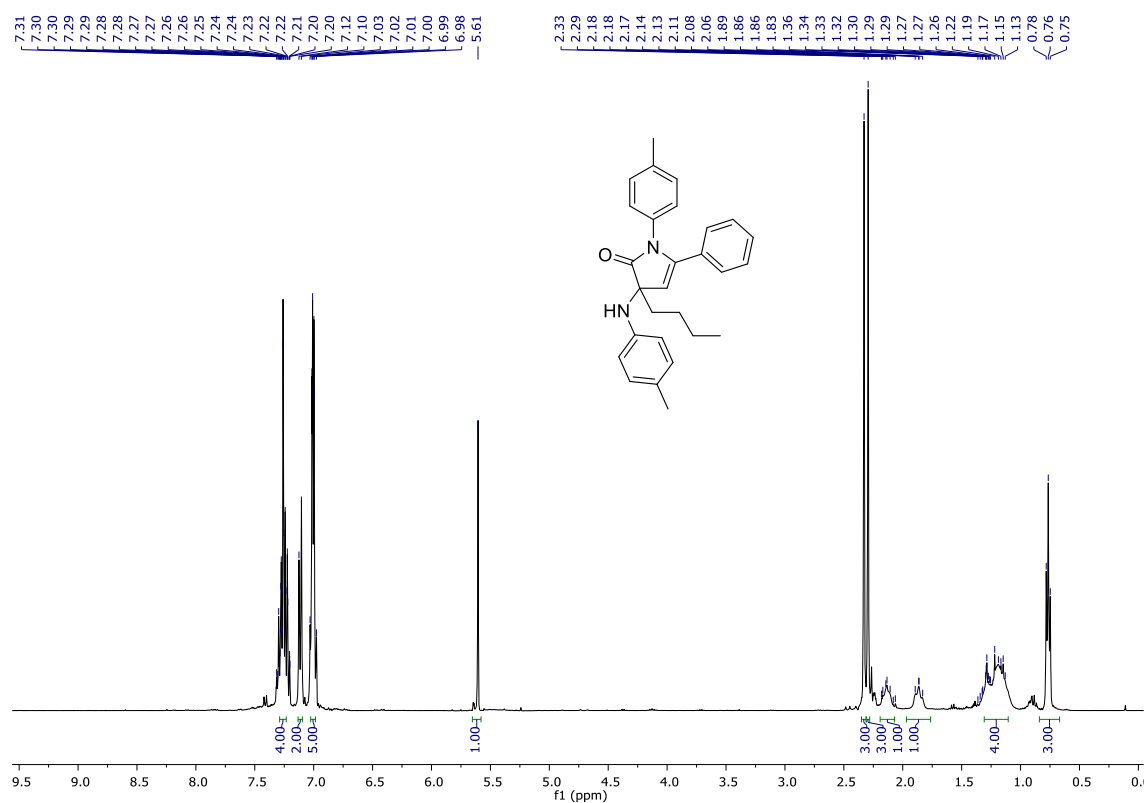


2D-HMBC NMR { $^1\text{H} - ^{13}\text{C}$ } (^1H : 400 MHz, ^{13}C : 101 MHz, CDCl_3)

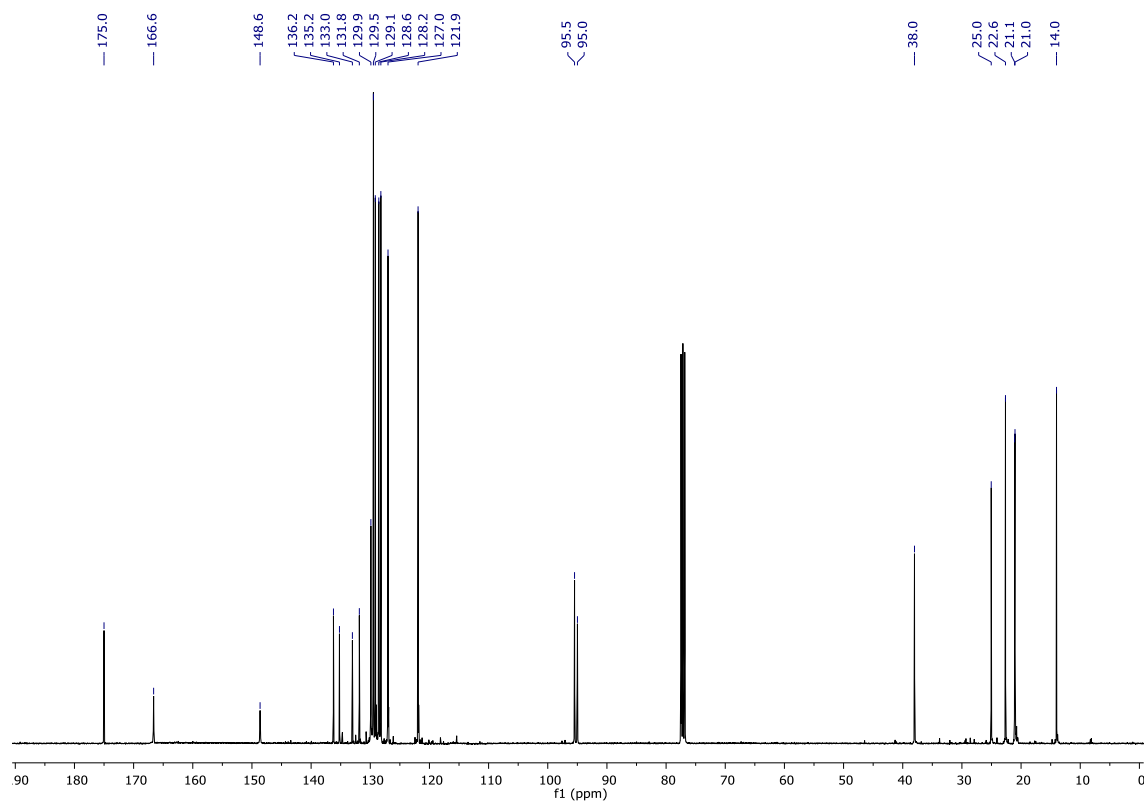


3-Butyl-5-phenyl-1-(*p*-tolyl)-3-(*p*-tolylamino)-1,3-dihydro-2*H*-pyrrol-2-one (25b).

^1H NMR (400 MHz, CDCl_3)

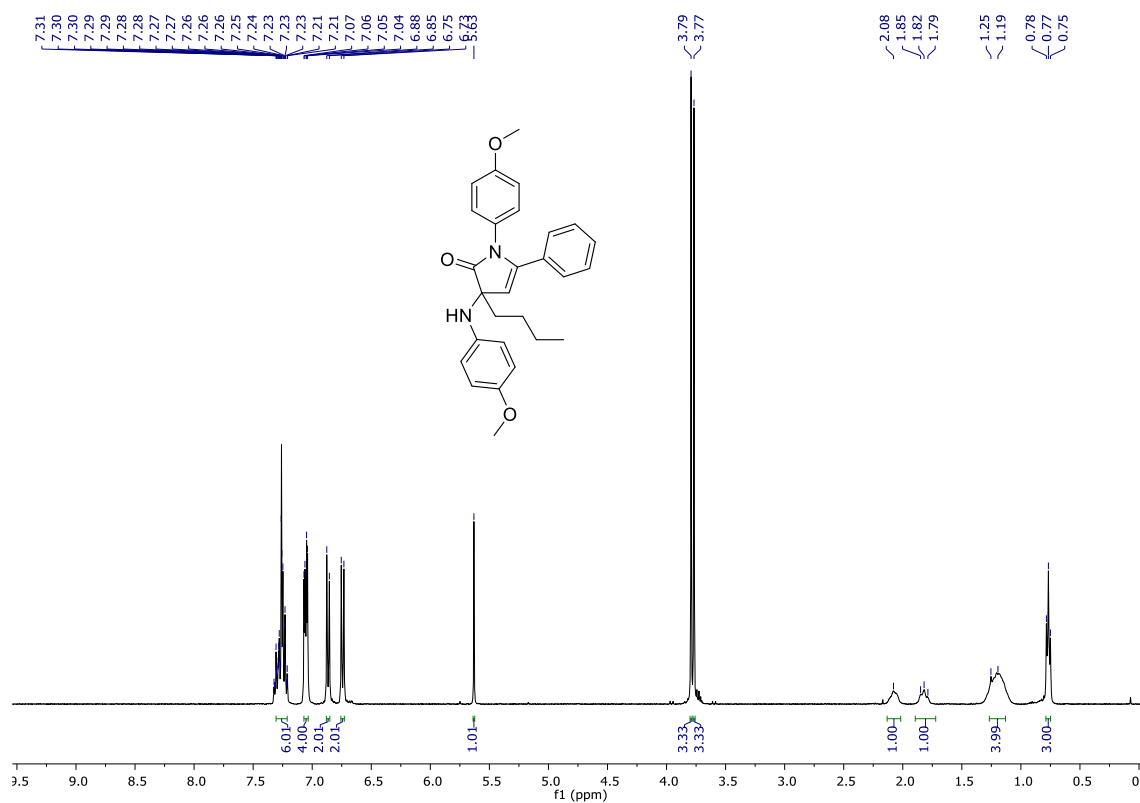


^{13}C NMR { ^1H } (101 MHz, CDCl_3)

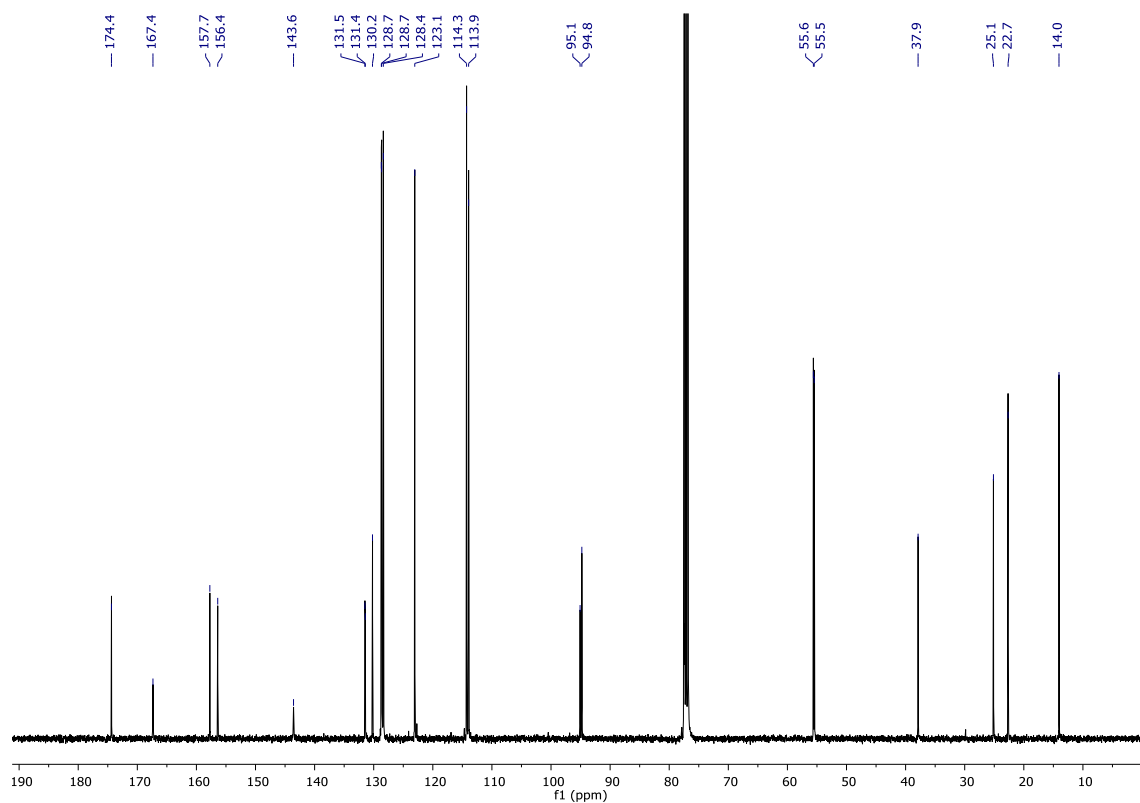


3-Butyl-1-(4-methoxyphenyl)-3-((4-methoxyphenyl)amino)-5-phenyl-1,3-dihydro-2H-pyrrol-2-one (25c).

¹H NMR (400 MHz, CDCl₃)

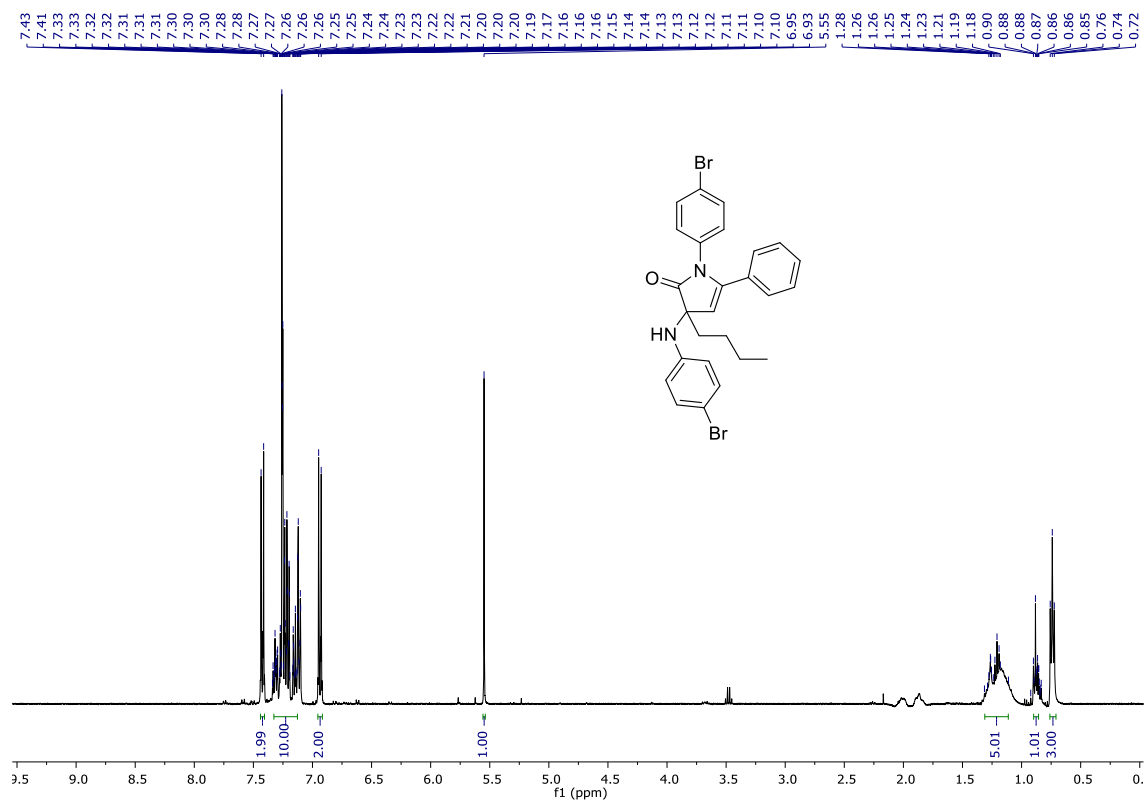


¹³C NMR {¹H} (101 MHz, CDCl₃)

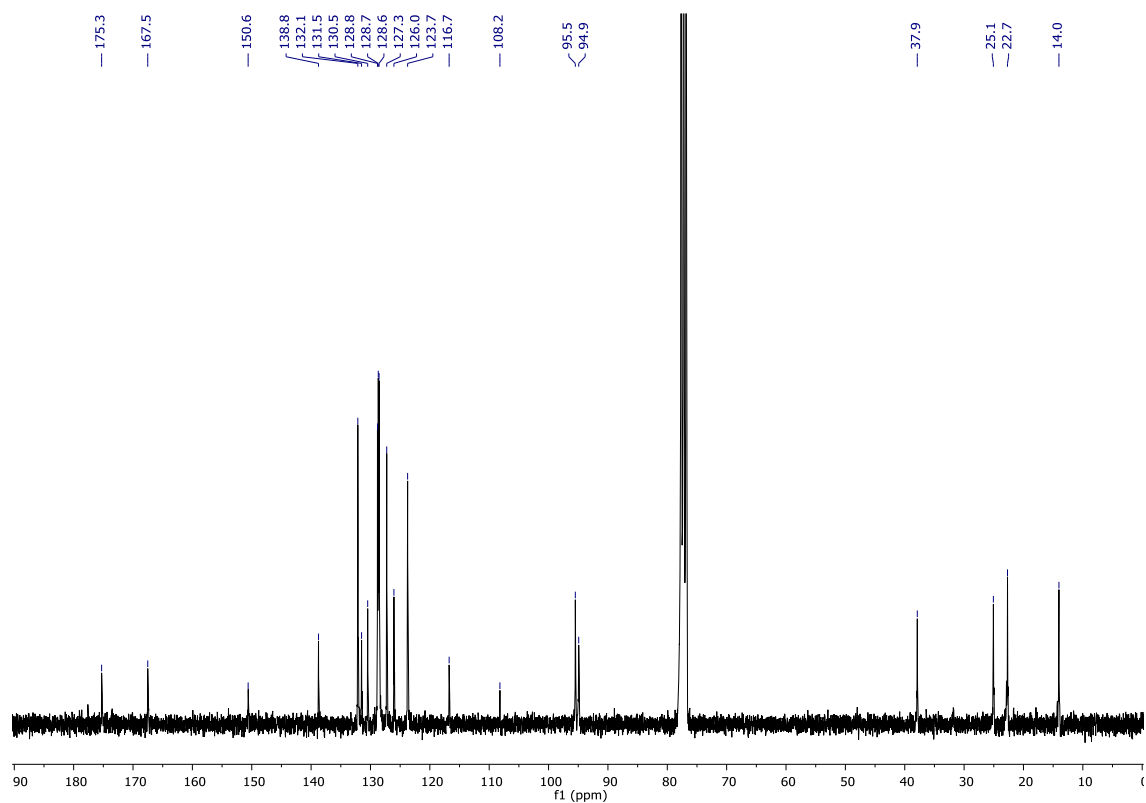


1-(4-Bromophenyl)-3-((4-bromophenyl)amino)-3-butyl-5-phenyl-1,3-dihydro-2H-pyrrol-2-one (25d).

¹H NMR (400 MHz, CDCl₃)

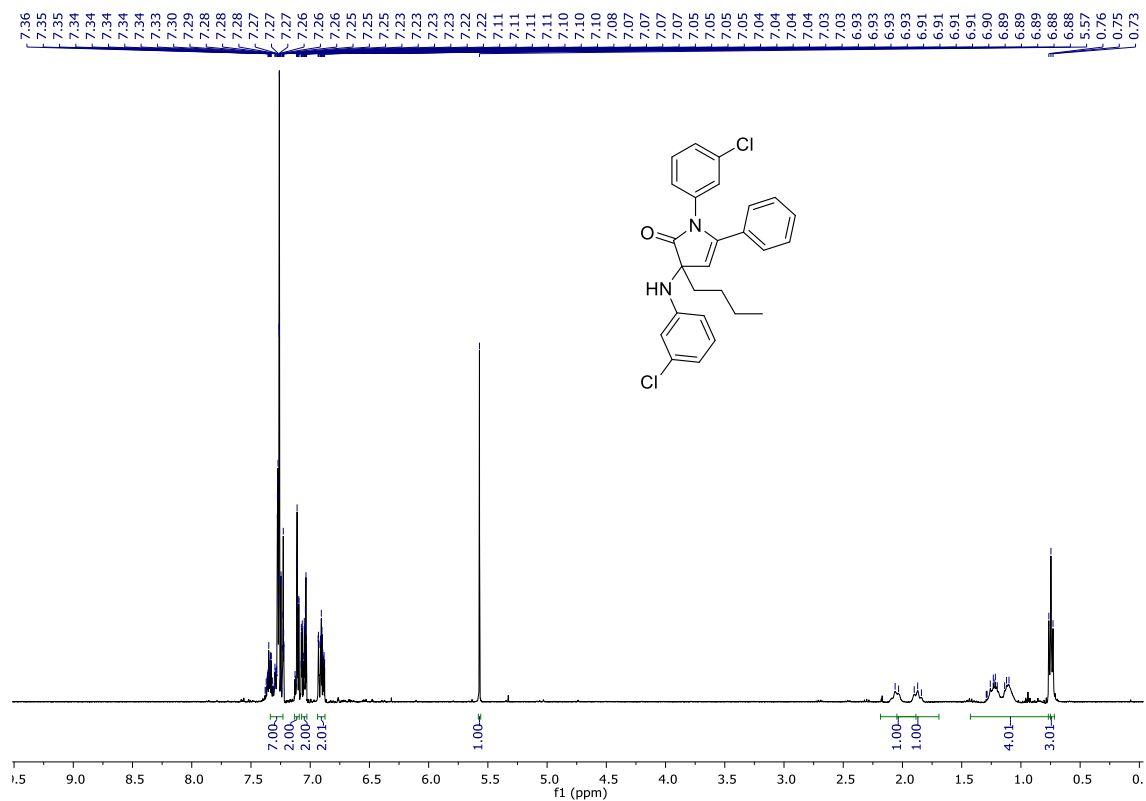


¹³C NMR {¹H} (75 MHz, CDCl₃)

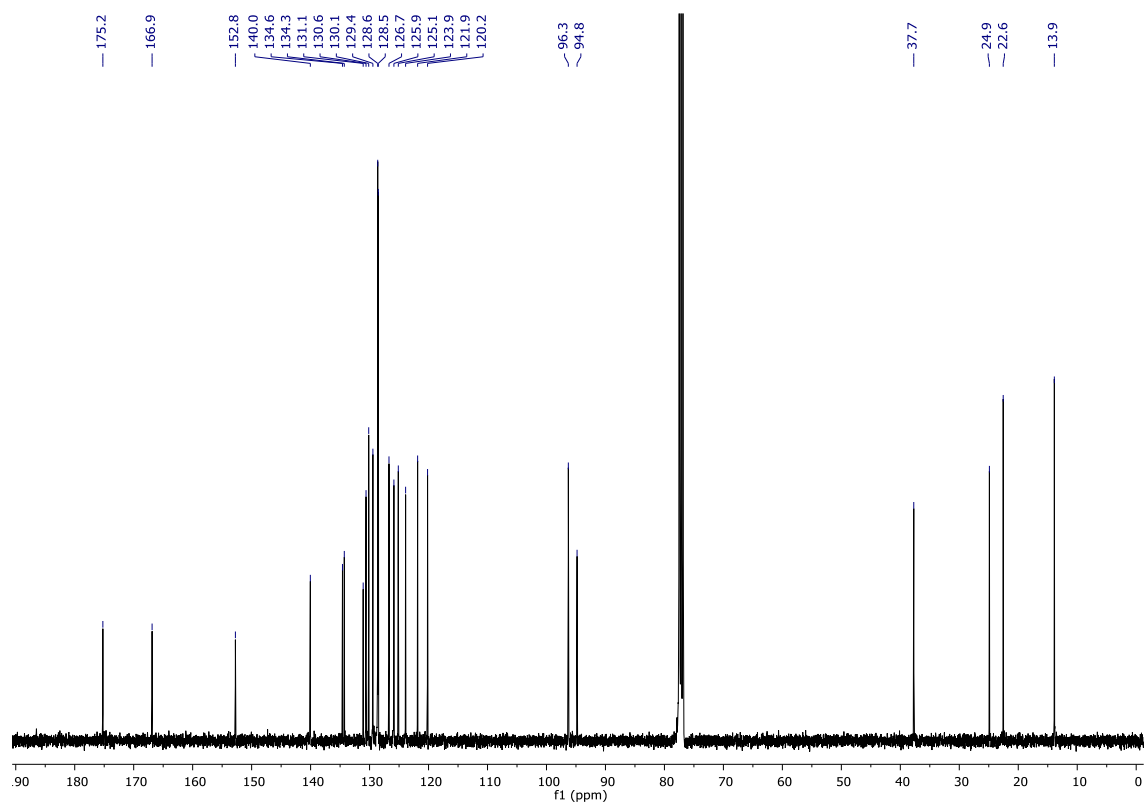


3-Butyl-1-(3-chlorophenyl)-3-((3-chlorophenyl)amino)-5-phenyl-1,3-dihydro-2H-pyrrol-2-one (25e).

¹H NMR (400 MHz, CDCl₃)



¹³C NMR {¹H} (101 MHz, CDCl₃)



8. Calculation of Lipinski's rule of five and prediction of ADME properties.

In the following table some calculations had been developed to predict ADME parameters, and determine the medicinal chemistry friendliness of our small molecules. Lipinski rules are used to evaluate if a compound is likely to be an orally active drug in humans. According to Lipinski's rule, an orally active drug has no more than one violation of the following criteria: $MW \leq 500$, $\text{LogP} \leq 4.15$, N or O atoms ≤ 10 and NH or OH atoms ≤ 5 .⁷ These calculations were performed using SwissADME program from the Swiss Institute of Bioinformatics (<http://www.swissadme.ch/>).

Comp.	MW (g/mol)	LogP	HBA	HBD	RB	TPSA (\AA^2)	Lipinski (Violations)	GI Abs.	BBB Permeation
7e	404.50	4.25	3	1	7	58.64	Yes (0)	High	Yes
12a	516.52	3.27	7	2	12	124.21	Yes (1)	High	No
12b	580.61	4.60	5	2	10	105.75	Yes (1)	High	No
25a	368.47	4.73	1	1	4	32.34	Yes (1)	High	Yes
25b	410.55	5.74	1	1	7	32.34	Yes (1)	High	No
25c	442.55	5.03	3	1	9	50.80	Yes (0)	High	Yes
25d	540.29	6.33	1	1	7	32.34	No (2)	Low	No
25e	451.39	6.15	1	1	7	32.34	Yes (1)	Low	No
26	278.35	3.26	1	1	3	32.34	Yes (0)	High	Yes

⁷ Lipinski, C.A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug. Deliv. Rev.* **2001**, *64*, 4-17.