Pd-Catalyzed Tandem Cyclization of Ethyl Glyoxalate and Amines: Rapid Assembly of Highly Substituted Cyclic Dehydro-α-Amino Acid Derivatives

Yueting Luo,[†] Xiaoxia Lu,[‡] Yong Ye,[*†] Ya Guo[†], Huanfeng Jiang,[†]and Wei Zeng[*†]

[†]*School of Chemistry and Chemical Engineering, South China University of Technology 381 Wushan Road, Tianhe District, Guangzhou 510640, China, and* [‡]*Chengdu Institute of Biology, Academy of Sciences, Chengdu 610041,China*

zengwei@scut.edu.cn; yeyong@scut.edu.cn

Supporting Information

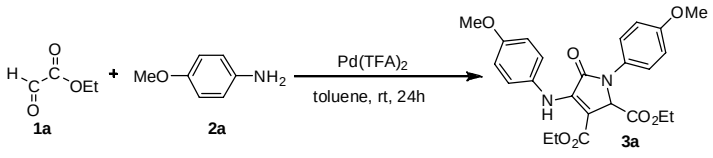
Content

1. General experimental information

1.1. General methods

All reactions were carried out in flame-dried sealed tubes with magnetic stirring. Unless otherwise noted, all other commercially available reagents and solvents were used without further purification. Flash chromatography was performed on Qingdao Haiyang Chemical Co. Ltd silica gel (40~63 mm) by standard technique. ^{1}H and ^{13}C NMR spectra were recorded with tetramethylsilane (TMS) as internal standard at ambient temperature unless otherwise indicated on a Bruker Avance DPX 600 fourier Transform spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. Chemical shifts are reported in parts per million (ppm) and coupling constants are reported as Hertz (Hz). Splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m). High resolution exact mass measurements (HRMS) were performed on an IF-TOF spectrometer (Micromass). Gas chromatograph mass spectra were obtained with a SHIMADZU model GCMS-QP5000 spectrometer. Infrared spectra (IR) were obtained by a Bruker TENSOR 27 FTIR spectrophotometer and are reported as wavelength numbers (cm^{-1}). Infrared spectra were recorded by preparing a KBr pellet containing the title compound. Crystal data were collected on a Bruker D8 Advance employing graphite monochromated Mo-Kα radiation (λ=0.71073 Å) at 293(2) K and operating in the φ-ωscan mode. The structure was solved by direct methods SHELXS-97.

1.2. [a]Effect of the ratio of ethyl glyoxalate/amine (1a/2) on tandem cyclization of *p*-anisidine (2a)

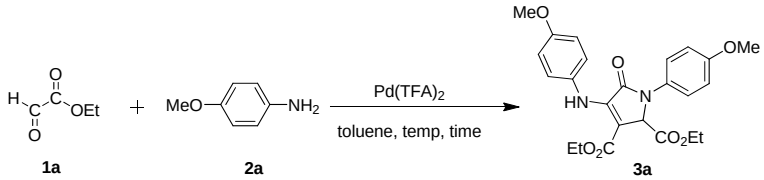


entry	**1a** (mmol)	yield (%)[b]
1	0.1	trace
2	0.15	trace
3	0.3	37
4	0.6	61
5	0.9	57

[a]Reaction conditions: *p*-anisidine (0.3 mmol), $Pd(TFA)_2$ (0.015 mmol, 5.0 mol %), toluene (2.0 mL), all

reactions were carried out under Ar at room temperature for 24 h in sealed tube. [b]Isolated yield after purification.

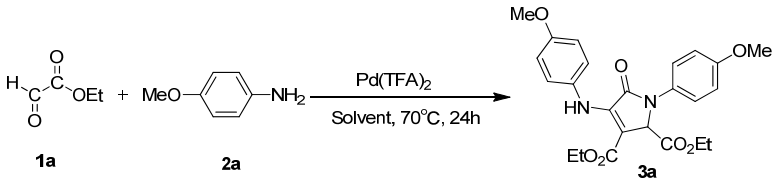
1.3. [a]Effect of the reaction time and temperature on tandem cyclization of ethyl glyoxalate with *p*-anisidine



entry	temp (℃)	time (h)	yield (%)[b]
1	r.t.	24	61
2	50	24	50[c]
3	70	24	63
4	90	24	42[c]
5	110	24	44
6	70	48	66
7	70	72	62

[a]Reaction conditions: ethyl glyoxalate (0.6 mmol), *p*-anisidine (0.3 mmol), $Pd(TFA)_2$ (0.015 mmol, 5.0 mol %), toluene (2.0 mL), all reactions were carried out under Ar at the given temperature for the given time in sealed tube. [b]Isolated yield after purification. [c]^{1}H-NMR yield.

1.4. [a]Effect of the solvent on tandem cyclization of ethyl glyoxalate with *p*-anisidine

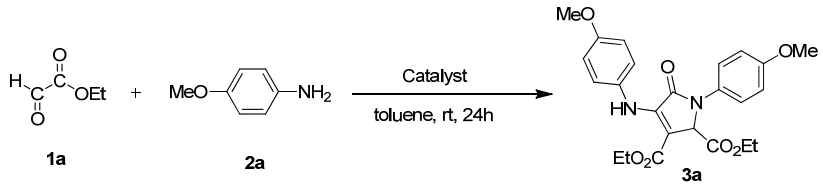


entry	solvent	yield (%)[b]
1	toluene	63
2	CH_2Cl_2	42[c]
3	EtOAc	43[c]
4	CH_3CN	11[c]
5	$ClCH_2CH_2Cl$	55
6	1,4-Dioxane	0
7	CH_3NO_2	0

8	CH_3COCH_3	0
9	DMF	0

[a]Reaction conditions: ethyl glyoxalate (0.6 mmol), *p*-anisidine (0.3 mmol), $Pd(TFA)_2$ (0.015 mmol, 5.0 mol %), solvent (2.0 mL), all reactions were carried out under Ar at 70℃ for 24 h in sealed tube. [b]Isolated yield after purification. [c]^{1}H-NMR yield without purification.

1.5. [a]Catalyst screening for tandem cyclization from ethyl glyoxalate with *p*-anisidine

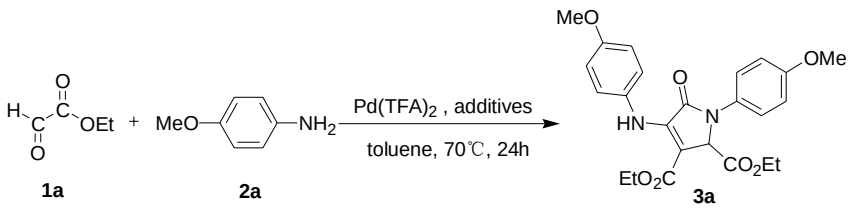


1a 2a 3a

entry	catalyst (equiv)	yield (%)[b]
1	$TiCl_4$ (1)	0
2	$FeCl_3$ (1)	0
3	$ZrCl_4$ (1)	0
4	$CdCl_2$•2.5 H_2O (1)	0
5	$Pd(TFA)_2$ (0.1)	55
6	$Pd(TFA)_2$ (0.05)	61
7	$PdCl_2(PPh_3)_2$ (0.05)	10[c]
8	$PdCl_2(PhCN)_2$ (0.05)	trace
9	$PdCl_2(Ph_2PCH_2)_2$ (0.05)	8[c]
10	$PdCl_2$ (0.05)	15[c]
11	$PdCl_2(CH_3CN)_2$ (0.05)	18[c]
12	$Pd(OAC)_2$ (0.05)	10[c]
13	Pd/C (0.05)	0

[a]Reaction conditions: ethyl glyoxalate (0.6 mmol), *p*-anisidine (0.3 mmol), toluene (2.0 mL), all reactions were carried out under Ar at room temperature for 24 h in sealed tube. [b]Isolated yield after purification. [c]^{1}H-NMR yield.

1.6. [a]Effect of the additives on tandem cyclization of ethyl glyoxalate with *p*-anisidine

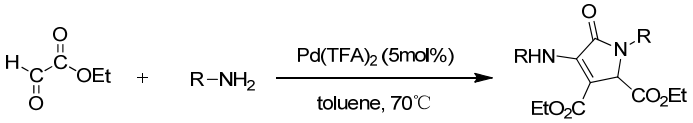


1a 2a 3a

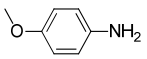
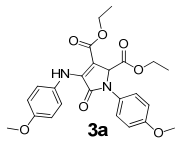
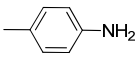
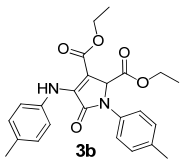
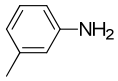
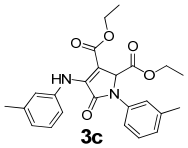
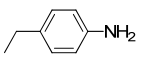
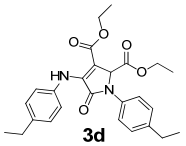
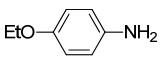
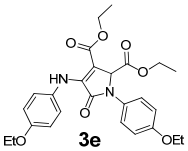
entry	additive (equiv)	yield (%)[b]
1	AcOH (0.5)	60
2	AcOH (1)	62
3	i-PrOH (0.1)	51
4	Na_2CO_3 (1)	0
5	Et_3N (1)	0
6	$Na_2S_2O_8$(1)	21
7	--	66

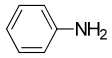
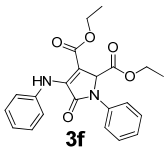
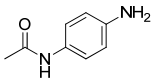
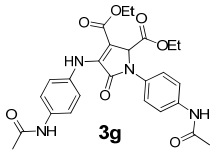
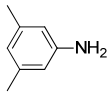
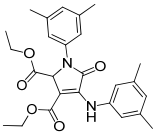
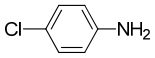
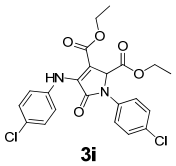
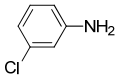
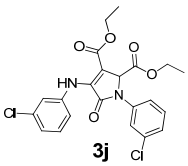
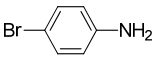
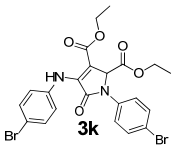
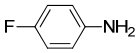
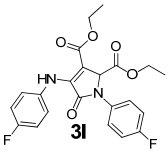
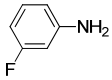
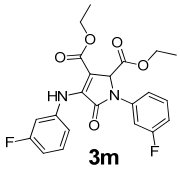
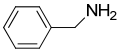
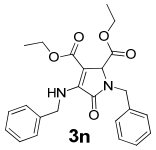
[a]Reaction conditions: ethyl glyoxalate (0.6 mmol), *p*-anisidine (0.3 mmol), toluene (2.0 mL), all reactions were carried out under Ar at 70℃ for 48 h in sealed tube. [b]Isolated yield after purification.

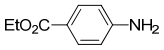
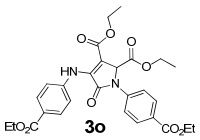
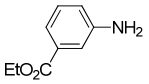
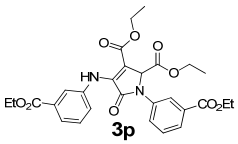
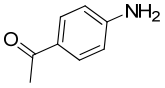
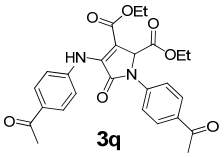
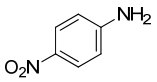
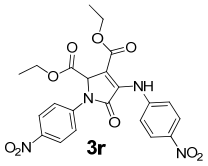
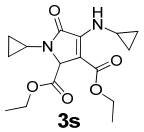
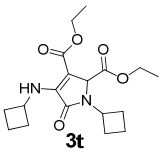
1.7. [a]Pd-catalyzed tandem cyclization of ethyl glyoxalate with amines



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

entry	amines (**2**)	time (h)	product	yield (%)[b]
1		48	 **3a**	68
2		24	 **3b**	62
3		24	 **3c**	36
4		12	 **3d**	71
5		24	 **3e**	63

6		24	 **3f**	56
7		24	 **3g**	38[c]
8		24	 **3h**	35
9		40	 **3i**	76
10		12	 **3j**	65
11		40	 **3k**	74
12		12	 **3l**	71
13		16	 **3m**	37
14		48	 **3n**	40

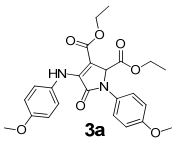
15		36	 **3o**	57
16		24	 **3p**	69
17		24	 **3q**	52
18		49	 **3r**	0
19		56	 **3s**	56
20		48	 **3t**	34

[a]Reaction were run with ethyl glyoxalate **1a** (0.6 mmol), amines **2** (0.3 mmol), $Pd(TFA)_2$ (0.015 mmol, 5.0 mol %), toluene (2.0 mL) under Ar in sealed pressure tube at 70 ℃ for the given time unless otherwise noted. [b]Isolated yield after purification. [c]Using ethyl acetate as solvent.

1.8. General procedure for the synthesis of compound 3a-3v

To a solution of amine (0.3 mmol, 1.0 equiv) and ethyl glyoxalate (0.6 mmol, 2.0 equiv) in toluene (2.0 mL) was added $Pd(TFA)_2$ (0.015 mmol, 5.0 mol %), anhydrous sodium sulfate (1.5 mmol, 5.0 equiv) in a sealed tube. The mixture was stirred at 70℃ under Ar atmosphere. Upon completion as monitored by TLC, the crude material was then filtered and the filtrate was concentrated under vacuum, which was purified by flash column chromatography on silica gel to furnish the target product.

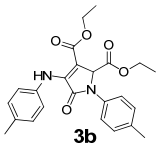
1.8.1. Diethyl 1- (4- methoxyphenyl)- 4- ((4- methoxyphenyl) amino)- 5- oxo- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (3a)



3a

White solid, m.p.= 137.5-137.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (s, 1 H), 7.44 (d, *J* = 8.9 Hz, 2 H), 7.13 (d, *J* = 8.7 Hz, 2 H), 7.16 – 7.05 (m, 4 H), 5.33 (s, 1 H), 4.26 – 4.14 (m, 2 H), 4.10 (q, *J* = 14.1, 7.1 Hz, 2 H), 3.79 (d, *J* = 2.2 Hz, 6 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 1.12 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.67, 164.42, 163.66, 157.91, 157.46, 144.99, 130.89, 129.40, 125.45, 124.21, 114.28, 113.67, 100.98, 62.20, 61.85, 60.32, 55.45, 14.22, 14.03; HRMS (EI) calcd for $C_{24}H_{26}N_2O_7Na$ $[M + Na]^+$: 477.1632, found 477.1624; IR (KBr): 3297, 2929, 2049, 1714, 1635, 1513, 1368, 1244, 1032, 757, 662, 525 cm^{-1}.

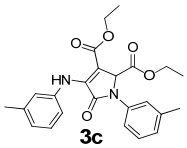
1.8.2. Diethyl 5- oxo- 1- (*p*- tolyl)- 4- (*p*- tolylamino)- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (3b)



3b

Yellow solid, m.p.= 152.3-153.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1 H), 7.47 (d, *J* = 8.5 Hz, 2 H), 7.16 (d, *J* = 8.3 Hz, 2 H), 7.09 (q, *J* = 8.4 Hz, 4 H), 5.39 (s, 1 H), 4.25 –4.14 (m, 2 H), 4.11 (q, *J* = 7.1 Hz, 2 H), 2.33 (s, 3 H), 2.32 (s, 3 H), 1.21 (t, *J* = 7.1 Hz, 3 H), 1.12 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.62, 164.28, 163.68, 144.51, 136.04, 135.40, 135.04, 134.06, 129.65, 129.02, 123.56, 121.92, 101.78, 61.88, 60.38, 21.00, 20.96, 14.15, 14.01; HRMS (EI) calcd for $C_{24}H_{26}N_2O_5Na$ $[M + Na]^+$: 445.1734, found 445.1726; IR (KBr): 3286, 2922, 1908, 1744, 1715, 1665, 1247, 1181, 1155, 944, 804, 757, 520 cm^{-1}.

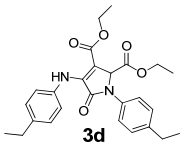
1.8.3. Diethyl 5- oxo- 1- (m- tolyl)- 4- (m- tolylamino)- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (3c)



3c

Yellow solid, m.p.= 113.5-113.6°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (s, 1 H), 7.46 (s, 1 H), 7.36 (d, *J* = 8.1 Hz, 1 H), 7.27 – 7.17 (m, 2 H), 7.05 –6.92 (m, 4 H), 5.41 (s, 1 H), 4.27 – 4.04 (m, 4 H), 2.34 (s, 6 H), 1.20 (t, *J* = 7.1 Hz, 3 H), 1.12 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.55, 164.17, 163.80, 144.16, 139.09, 138.32, 137.99, 136.56, 128.92, 128.23, 127.07, 126.07, 123.99, 122.68, 120.57, 118.92, 102.52, 61.94, 61.90, 60.45, 21.48, 21.38, 14.12, 13.99; HRMS (EI) calcd for $C_{24}H_{26}N_2O_5Na$ $[M + Na]^+$: 445.1734, found 445.1728; IR (KBr): 3292, 2919, 1909, 1754, 1712, 1660, 1244, 1183, 1156, 940, 806, 755, 524 cm^{-1}.

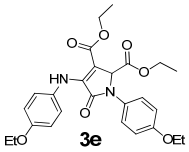
1.8.4. Diethyl 1- (4- ethylphenyl)- 4- ((4- ethylphenyl) amino)- 5- oxo- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (3d)



3d

Yellow solid, m.p.= 121.5-121.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1 H), 7.48 (d, *J* = 8.1 Hz, 2 H), 7.19 (d, *J* = 7.9 Hz, 2 H), 7.16 – 7.05 (m, 4 H), 5.39 (s, 1 H), 4.27 – 4.04 (m, 4 H), 2.68 – 2.57 (m, 4 H), 1.25 – 1.17 (m, 9 H), 1.12 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.61, 164.29, 163.76, 142.43, 141.32, 135.64, 134.20, 128.48, 127.82, 123.50, 122.10, 101.92, 61.97, 61.86, 60.37, 28.37, 15.51, 15.46, 14.12, 13.97; HRMS (EI) calcd for $C_{26}H_{30}N_2O_5Na$ [M + Na]$^{+}$: 473.2047, found 473.2056; IR (KBr): 3290, 3965, 1747, 1718, 1635, 1513, 1458, 1365, 1289, 1242, 1178, 1030, 835, 759, 655, 531 cm^{-1}.

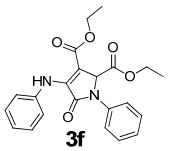
1.8.5. Diethyl 1- (4- ethoxyphenyl)- 4- ((4- ethoxyphenyl) amino)- 5- oxo- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (3e)



3e

Yellow solid, m.p.= 144.6-145.3°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1 H), 7.42 (d, *J* = 9.0 Hz, 2 H), 7.11 (d, *J* = 8.8 Hz, 2 H), 6.84 (dd, *J* = 15.1, 8.9 Hz, 4 H), 5.32 (s, 1 H), 4.24 –4.13 (m, 2 H), 4.13 – 4.05 (m, 2 H), 4.04 – 3.95 (m, 4 H), 1.44 – 1.34 (m, 6 H), 1.21 (t, *J* = 7.1 Hz, 3 H), 1.11 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.70, 164.38, 163.68, 157.28, 156.83, 144.92, 130.81, 129.27, 125.36, 124.17, 114.82, 114.21, 100.91, 63.65, 63.62, 62.23, 61.81, 60.27, 14.85, 14.75, 14.19, 14.02; HRMS (EI) calcd for $C_{26}H_{30}N_2O_7Na$ [M + Na]$^{+}$: 505.1945, found 505.1939; IR (KBr): 3291, 2980, 2928, 1744, 1710, 1633, 1512, 1475, 1393, 1371, 1294, 1241, 1191, 1113, 1042, 923, 827, 762, 526 cm^{-1}.

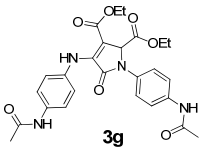
1.8.6. Diethyl 5- oxo- 1- phenyl- 4- (phenylamino)- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (3f)



3f

Yellow solid, m.p.= 113.4-113.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1 H), 7.61 (d, *J* = 8.2 Hz, 2 H), 7.40 – 7.29 (m, 4 H), 7.24 – 7.13 (m, 4 H), 5.44 (s, 1 H), 4.27 – 4.08 (m, 4 H), 1.20 (t, *J* = 7.1 Hz, 3 H), 1.11 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.43, 164.13, 163.84, 143.96, 138.08, 136.61, 129.15, 128.46, 126.25, 125.22, 123.33, 121.92, 102.81, 61.97, 61.88, 60.51, 14.11, 13.98; HRMS (EI) calcd for $C_{22}H_{22}N_2O_5Na$ [M + Na]$^{+}$: 417.1421, found 417.1414; IR (KBr): 3290, 2927, 1746, 1639,1593,1496, 1366, 1291, 1249, 1116, 1027, 760, 691, 519 cm^{-1}.

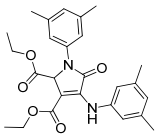
1.8.7. Diethyl 1- (4- acetylphenyl)- 4- ((4- acetylphenyl) amino)- 5- oxo- 2, 5- dihydro- 1H- pyrrole- 2, 3-dicarboxylate (3g)



3g

Yellow solid, m.p.= 166.7-168.8°C; ^{1}H NMR (400 MHz, DMSO) δ 10.06 (s, 1 H), 9.92 (s, 1 H), 8.97 (s, 1 H), 7.62 (d, *J* = 8.8 Hz, 2 H), 7.49 (dd, *J* = 16.3, 8.7 Hz, 4 H), 7.00 (d, *J* = 8.5 Hz, 2 H), 5.61 (s, 1 H), 4.15 – 3.84 (m, 4 H), 2.05 (s, 3 H), 2.03 (s, 3 H), 1.02 (t, *J* = 6.5 Hz, 3 H), 0.99 (t, *J* = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO) δ 168.65, 168.35, 167.98, 164.22, 162.40, 141.35, 137.39, 135.36, 134.69, 131.17, 122.96, 122.16, 119.26, 118.66, 102.47, 61.94, 61.30, 59.74, 23.91, 23.86, 13.80, 13.72; HRMS (EI) calcd for $C_{26}H_{28}N_4O_7Na$ $[M + Na]^+$: 531.1858, found 531.1854; IR (KBr): 3726, 3667, 3642, 2923,2853, 1675, 1513, 1371, 1262, 1021, 745cm^{-1}.

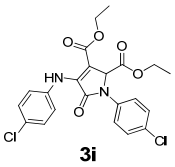
1.8.8. Diethyl 1- (3, 5- dimethylphenyl)- 4- ((3, 5- dimethylphenyl) amino)- 5- oxo- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (3h)



3h

Yellow solid, m.p.=153.5-154.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1 H), 7.23 (s, 2 H), 6.82 (d, *J* = 17.4 Hz, 4 H), 5.39 (s, 1 H), 4.27 – 4.03 (m, 4 H), 2.30 (s, 12 H), 1.20 (t, *J* = 7.1 Hz, 3 H), 1.13 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.67, 164.19, 163.76, 144.33, 138.79, 138.03, 137.93, 136.52, 127.99, 127.09, 121.27, 119.73, 102.23, 61.99, 61.81, 60.38, 29.72, 21.38, 21.29, 14.15, 14.02; HRMS (EI) calcd for $C_{26}H_{30}N_2O_5Na$ $[M + Na]^+$: 473.2047, found 473.2041; IR (KBr): 3462, 2922, 1746, 1712, 1639, 1600, 1467, 1368, 1313, 1261, 1187, 1026, 841, 753 cm^{-1}.

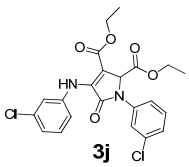
1.8.9. Diethyl 1- (4- chlorophenyl)- 4- ((4- chlorophenyl) amino)- 5- oxo- 2, 5- dihydro -1 H- pyrrole- 2, 3- dicarboxylate (3i)



3i

Yellow solid, m.p.= 149.0-149.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1 H), 7.56 (d, *J* = 8.9 Hz, 2 H), 7.31 (dd, *J* = 25.7, 8.9 Hz, 4 H), 7.10 (d, *J* = 8.7 Hz, 2 H), 5.39 (s, 1 H), 4.29 – 4.16 (m, 2 H), 4.13 (q, *J* = 7.1 Hz, 2 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 1.14 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.08, 164.03, 163.53, 143.88, 136.43, 135.11, 131.63, 130.72, 129.28, 128.57, 124.73, 122.84, 103.44, 62.24, 61.57, 60.75, 14.16, 14.03; HRMS (EI) calcd for $C_{22}H_{20}N_2O_5Cl_2Na$ $[M + Na]^+$: 485.0641, found 485.0650; IR (KBr): 3524, 3179, 3121, 1896, 1744, 1696, 1542, 1419, 1371, 1299, 1218, 1037, 820, 569 cm^{-1}.

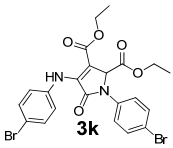
1.8.10. Diethyl 1- (3- chlorophenyl)- 4- ((3- chlorophenyl) amino)- 5- oxo- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (3j)



3j

Yellow solid, m.p.= 104.0-108.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (s, 1 H), 7.72 (s, 1 H), 7.51 (d, *J* = 8.2 Hz, 1 H), 7.38 – 7.11 (m, 5 H), 7.06 (d, *J* = 7.9 Hz, 1 H), 5.40 (s, 1 H), 4.30 – 4.07 (m, 4 H), 1.23 (t, *J* = 7.2 Hz, 3 H), 1.16 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 167.98, 163.82, 163.61, 143.34, 139.20, 137.74, 134.94, 134.08, 130.18, 129.40, 126.24, 125.28, 123.36, 121.60, 121.48, 119.27, 104.33, 62.29, 61.60, 60.85, 14.11, 14.00; HRMS (EI) calcd for $C_{22}H_{20}N_2O_5Cl_2Na$ $[M + Na]^+$: 485.0641, found 485.0648; IR (KBr): 3472, 2923, 1743, 1697,1632, 1591, 1473, 1401, 1333, 1267, 1214, 1034, 860, 775, 687, 501, 441 cm^{-1}.

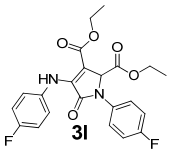
1.8.11. Diethyl 1- (4- bromophenyl)- 4- ((4- bromophenyl) amino)- 5- oxo- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (3k)



3k

Yellow solid, m.p.= 150.9-151.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (s, 1 H), 7.55 – 7.45 (m, 4 H), 7.41 (d, *J* = 8.7 Hz, 2 H), 7.04 (d, *J* = 8.6 Hz, 2 H), 5.38 (s, 1 H), 4.27 – 4.16 (m, 2 H), 4.13 (q, *J* = 7.1 Hz, 2 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 1.14 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.04, 163.99, 163.51, 143.75, 136.96, 135.65, 132.24, 131.51, 124.99, 123.01, 119.42, 118.42, 103.63, 62.27, 61.49, 60.78, 14.16, 14.05; HRMS (EI) calcd for $C_{22}H_{19}N_2O_5Br_2$ $[M - H]^-$: 548.9666, found 548.9611; IR (KBr): 3247, 3117, 2983, 1897, 1745, 1696, 1539, 1488, 1371, 1216, 1037, 888, 816, 661, 518 cm^{-1}.

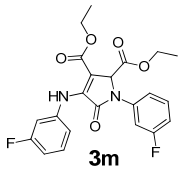
1.8.12. Diethyl 1- (4- fluorophenyl)- 4- ((4- fluorophenyl) amino)- 5- oxo- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (3l)



3l

Yellow solid, m.p.= 141.3-142.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (s, 1 H), 7.61 – 7.42 (m, 2 H), 7.11 – 7.18 (m, 2 H), 7.10 – 6.95 (m, 4 H), 5.35 (s, 1 H), 4.28 – 4.15 (m, 2 H), 4.11 (q, *J* = 7.1 Hz, 2 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 1.12 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.27, 164.15, 163.65, 161.90, 161.67, 159.45, 159.24, 144.36, 133.88 (d, *J* = 3.0 Hz), 132.44 (d, *J* = 3.0 Hz), 125.58 (d, *J* = 8.4 Hz), 124.22 (d, *J* = 8.3 Hz), 116.11, 115.89, 115.34, 115.11, 102.43, 62.0 (d, *J* = 9.2 Hz), 60.57, 29.69, 14.16, 13.99; HRMS (EI) calcd for $C_{22}H_{20}N_2O_5F_2Na$ $[M + Na]^+$: 453.1232, found 453.1214; IR (KBr): 3227, 2924, 1739, 1696, 1634, 1550, 1509, 1371, 1332, 1291, 1214, 1035, 826, 860, 660, 523, 476 cm^{-1}.

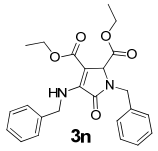
1.8.13. Diethyl 1- (3- fluorophenyl)- 4- ((3- fluorophenyl) amino)- 5- oxo- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (3m)



3m

Yellow solid, m.p.= 109.4-109.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1 H), 7.54 (d, *J* = 10.8 Hz, 1 H), 7.40 – 7.21 (m, 3 H), 7.02 – 6.83 (m, 4 H), 5.40 (s, 1 H), 4.29 – 4.11 (m, 4 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 1.15 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.01, 164.13, 163.82, 163.66, 161.69, 161.39, 143.41, 139.67 (d, *J* = 10.4 Hz), 138.13 (d, *J* = 10.4 Hz), 130.35 (d, *J* = 9.2 Hz), 129.54(d, *J* = 9.3 Hz), 118.76 (d, *J* = 2.9 Hz), 116.36 (d, *J* = 3.1 Hz), 112.95 (d, *J* = 21.2 Hz), 111.98 (d, *J* = 21.2 Hz), 110.51 (d, *J* = 24.3 Hz), 108.90 (d, *J* = 26.1 Hz), 104.39, 62.26, 61.67, 60.82, 14.02 (d, *J* = 12.5 Hz); HRMS (EI) calcd for $C_{22}H_{20}N_2O_5F_2Na$ $[M + Na]^+$: 453.1232, found 453.1229; IR (KBr): 3295, 2925, 1715, 1645, 1610, 1540, 1492, 1370, 1193, 1028, 925, 862, 770, 682, 520, 453 cm^{-1}.

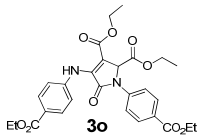
1.8.14. Diethyl 1- benzyl- 4- (benzylamino)- 5- oxo- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (3n)



3n

White solid, m.p.= 108.9-109.9°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 – 7.09 (m, 11 H), 5.25 – 5.07(m, 2 H), 5.02 (d, *J* = 14.9 Hz, 1 H), 4.60 (s, 1 H), 4.26 – 4.01 (m, 5 H), 1.29 – 1.15 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.02, 165.63, 139.04, 135.70, 128.75, 128.73, 128.59, 127.96, 127.56, 127.46, 61.70, 59.78, 45.61, 14.30, 14.09; HRMS (EI) calcd for $C_{24}H_{26}N_2O_5Na$ $[M + Na]^+$: 445.1734, found 445.1728; IR (KBr): 3334, 2981, 1742, 1704, 1631, 1450, 1366, 1212, 1089, 1028, 764, 699 cm^{-1}.

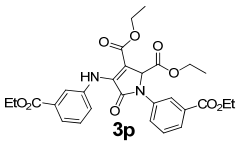
1.8.15. Diethyl 1- (4- (ethoxycarbonyl)phenyl)- 4- ((4- (ethoxycarbonyl) phenyl) amino)- 5- oxo- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (3o)



3o

Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1 H), 8.04 (d, *J* = 8.8 Hz, 2 H), 7.98 (d, *J* = 8.5 Hz, 2 H), 7.75 (d, *J* = 8.9 Hz, 2 H), 7.16 (d, *J* = 8.6 Hz, 2 H), 5.48 (s, 1 H), 4.39 – 4.30 (m, 4 H), 4.26 – 4.17 (m, 2 H), 4.12 (q, *J* = 7.0 Hz, 2 H), 1.42 – 1.31 (m, 6 H), 1.20 (t, *J* = 7.1 Hz, 3 H), 1.13 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 167.83, 166.03, 165.77, 163.78, 163.61, 142.88, 142.20, 140.58, 130.69, 130.12, 127.61, 126.51, 121.73, 120.04, 105.89, 62.35, 61.44, 61.06, 60.95, 60.83, 14.33, 14.30, 14.07, 13.99; HRMS (EI) calcd for $C_{28}H_{30}N_2O_9Na$ $[M + Na]^+$: 561.1844, found 561.1853; IR (KBr): 3465, 2982, 1714, 1644, 1603, 1513, 1470, 1367, 1275, 1179,1104, 1023, 855, 768, 698 cm^{-1}.

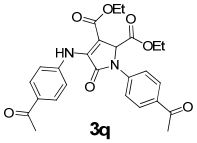
1.8.16. Diethyl 1- (3- (ethoxycarbonyl) phenyl)- 4- ((3- (ethoxycarbonyl)phenyl)amino)- 5- oxo- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (3p)



3p

Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1 H), 8.17 (s, 1 H), 7.98 – 7.81 (m, 4 H), 7.49 – 7.43 (m, 1 H), 7.39 (d, *J* = 4.3 Hz, 2 H), 5.50 (s, 1 H), 4.42 – 4.33 (m, 4 H), 4.28 – 4.08 (m, 4 H), 1.44 – 1.33 (m, 6 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 1.15 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.10, 166.01, 165.76, 163.96, 163.72, 143.65, 138.11, 136.76, 131.61, 131.00, 129.29, 128.41, 127.75, 127.30, 126.44, 126.30, 124.20, 122.43, 103.91, 62.17, 61.69, 61.28, 61.10, 60.73, 14.33, 14.31, 14.16, 13.97; HRMS (EI) calcd for $C_{28}H_{30}N_2O_9Na$ $[M + Na]^+$: 561.1844, found 561.1824; IR (KBr): 3296, 2982, 1718, 1641, 1588, 1450, 1369, 1291, 1241, 1104, 1025, 755, 684 cm^{-1}.

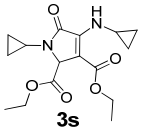
1.8.17. Diethyl 1- (4- acetylphenyl)- 4- ((4- acetylphenyl) amino)- 5- oxo- 2, 5- dihydro- 1H- pyrrole- 2, 3-dicarboxylate (3q)



3q

Yellow solid, m.p.= 127.9-128.6°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1 H), 7.99 (d, *J* = 8.7 Hz, 2 H), 7.94 (d, *J* = 8.4 Hz, 2 H), 7.81 (d, *J* = 8.7 Hz, 2 H), 7.21 (d, *J* = 8.4 Hz, 2 H), 5.52 (s, 1 H), 4.31 – 4.09 (m, 4 H), 2.59 (s, 3 H), 2.59 (s, 3 H), 1.26 (t, *J* = 6.9 Hz, 3 H), 1.16 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.80, 167.76, 163.68, 143.07, 142.31, 140.75, 134.26, 133.39, 129.61, 129.11, 121.88, 120.18, 106.31, 62.46, 61.37, 61.07, 29.69, 26.50, 26.46, 14.12, 14.01; HRMS (EI) calcd for $C_{26}H_{26}N_2O_7Na$ $[M + Na]^+$: 501.1638, found 501.1633 ; IR (KBr): 3386, 2977, 2856, 1794, 1788, 1665, 1540, 1328, 1229, 1218, 887, 743cm^{-1}.

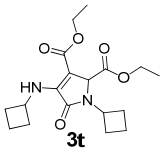
1.8.18. Diethyl 1- cyclopropyl- 4- (cyclopropylamino)- 5- oxo- 2, 5- dihydro- 1 H- pyrrole- 2, 3-dicarboxylate (3s)



3s

Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.59 (s, 1 H), 4.57 (s, 1 H), 4.24 – 4.04 (m, 4 H), 3.42 – 3.31(m, 1 H), 2.65 – 2.46 (m, 1 H), 1.28 – 1.15 (m, 6 H), 0.93 – 0.64 (m, 6 H), 0.58 – 0.45 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.49, 166.58, 164.65, 99.99, 98.09, 61.64, 59.74, 24.38, 14.31, 14.15, 8.43, 8.40, 6.32, 4.36; HRMS (EI) calcd for $C_{16}H_{22}N_2O_5Na$ $[M + Na]^+$: 345.1421, found 345.1434; IR (KBr): 3309, 2983, 1712, 1630, 1530, 1370, 1193, 1112, 1027, 767, 627 cm^{-1}.

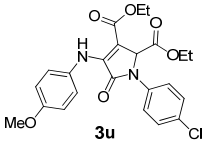
1.8.19. Diethyl 1- cyclobutyl- 4- (cyclobutylamino)- 5- oxo- 2, 5- dihydro- 1 H- pyrrole- 2, 3-dicarboxylate (3t)



3t

Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (s, 1 H), 5.16 (s, 1 H), 4.74 (s, 1 H), 4.44 – 4.32 (m, 1 H), 4.25 – 4.07 (m, 4 H), 2.45 – 2.06 (m, 6 H), 1.92 – 1.80 (m, 2 H), 1.74 – 1.62 (m, 4 H), 1.29 – 1.21 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 170.21, 167.34, 165.24, 98.47, 96.81, 61.65, 59.62, 48.03, 32.86, 30.39, 28.65, 27.91, 15.44, 14.39, 14.35, 14.02; HRMS (EI) calcd for $C_{18}H_{26}N_2O_5Na$ $[M + Na]^+$: 373.1734, found 373.1738; IR (KBr): 3331, 2980, 1783,1744, 1704, 1627, 1469, 1366, 1187, 1115, 1029, 767 cm^{-1}.

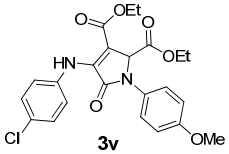
1.8.20. Diethyl 1- (4- chlorophenyl)- 4- ((4- methoxyphenyl) amino)- 5- oxo- 2, 5- dihydro- 1H- pyrrole- 2, 3- dicarboxylate (3u)



3u

Yellow solid, m.p.= 145.7-146.2°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1 H), 7.36 (d, *J* = 9.0 Hz, 2 H), 7.18 (d, *J* = 8.8 Hz, 2 H), 7.03 (d, *J* = 8.6 Hz, 2 H), 6.82 (d, *J* = 9.0 Hz, 2 H), 5.27 (s, 1 H), 4.18 – 4.00 (m, 4 H), 3.71 (s, 3 H), 1.15 (t, *J* = 7.1 Hz, 3 H), 1.05 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.33, 164.05, 163.62, 158.07, 144.03, 136.66, 130.38, 129.20, 128.45, 124.53, 124.28, 114.37, 103.30, 62.41, 61.97, 60.57, 55.46, 14.14, 14.01; HRMS (EI) calcd for $C_{23}H_{23}ClN_2O_6Na$ $[M + Na]^+$: 481.1147, found 481.1150; IR (KBr): 3287, 2927, 2876, 1766, 1727, 1689, 1643, 1516, 1489, 1362, 1277, 998, 832, 764cm^{-1}.

1.8.21. Diethyl 4- ((4- chlorophenyl)amino)- 1- (4- methoxyphenyl)- 5- oxo- 2, 5- dihydro- 1H- pyrrole- 2, 3- dicarboxylate (3v)

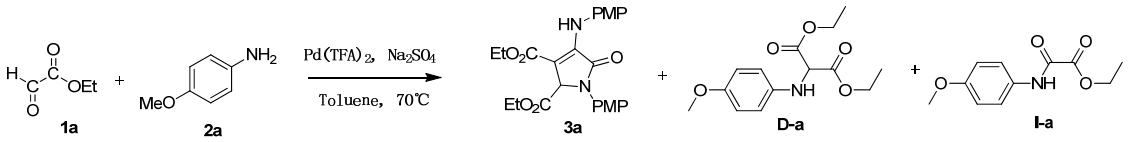


3v

Yellow solid, m.p.=142.3-143.7°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1 H), 7.57 (d, *J* = 8.9 Hz, 2 H), 7.32 (d, *J* = 8.9 Hz, 2 H), 7.12 (d, *J* = 8.8 Hz, 2 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 5.37 (s, 1 H), 4.29 – 4.06 (m, 4 H), 3.80 (s, 3 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 1.14 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.39, 164.35, 163.61, 157.63, 135.32, 131.39, 130.71, 129.18, 125.61, 122.78, 113.74, 101.21, 62.07, 61.40, 60.45, 55.43, 29.70, 14.22, 14.02; HRMS (EI) calcd for $C_{23}H_{23}ClN_2O_6Na$ $[M + Na]^+$: 481.1147, found 481.1144; IR (KBr): 3295, 2925, 2853, 1744, 1714, 1680, 1634, 1512, 1495, 1464, 1277, 1194, 1032, 750, 517cm^{-1}.

1.9. The mechanism exploration of Pd-catalyzed tandem cyclization of ethyl glyoxalate with amines

1.9.1. The GC-MS spectra about the reaction progress of 1a with 2a



To a solution of ethyl glyoxalate (**1a**) (0.6 mmol, 2.0 equiv) in toluene was added *p*-anisidine (**2a**) (0.3 mmol, 1.0 equiv), $Pd(TFA)_2$ (0.015 mmol, 5.0 mol %) and anhydrous sodium sulfate (1.5 mmol, 5.0 equiv) in a sealed tube. The mixture was stirred at 70℃ for the indicated time. The reaction progress was monitored by GC-MS, and the corresponding GC-MS traces were shown as follows.

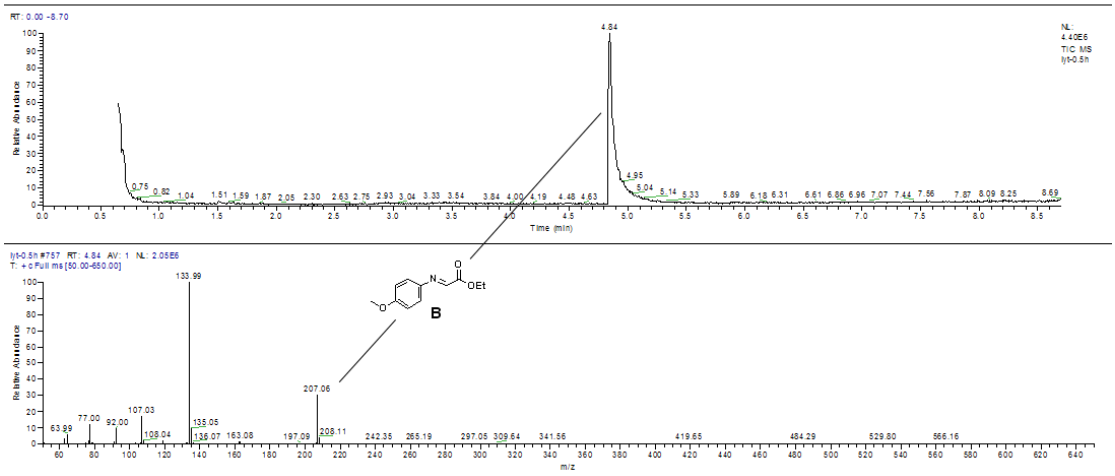
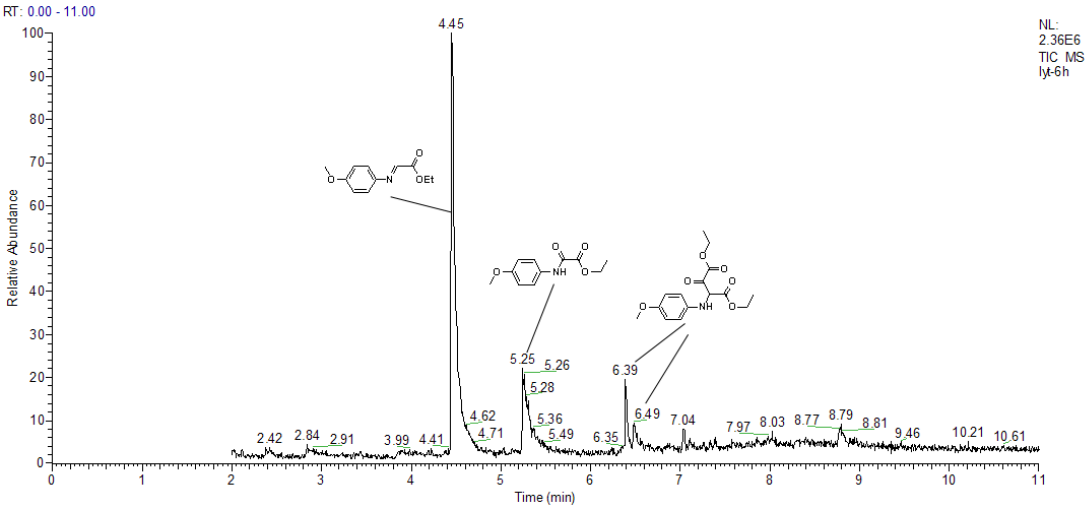


Figure 1. GC-MS spectra of the reaction mixture stirred for 0.5 h. We could find that an intermediate of *C*-acylimine ethyl 2- (4- methoxyphenylimino) acetate (**B**) [1] formed with complete conversion. FW of **B** is 207.06.



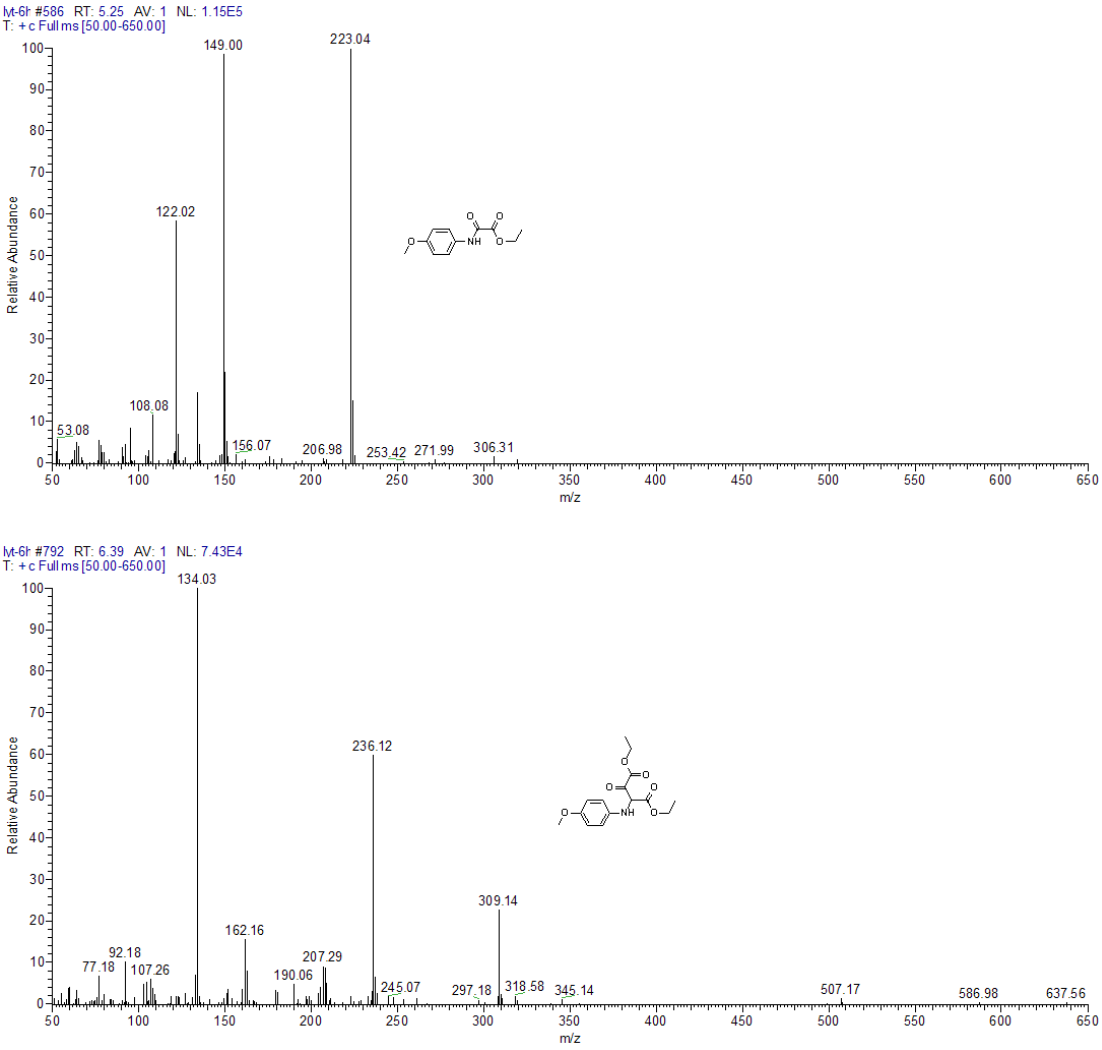
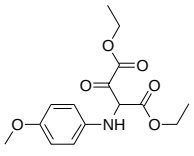


Figure 2. GC-MS spectra of the reaction mixture stirred for 6 h. An intermediate **D-a** (FW=309.14) and a byproduct **I-a** (FW=223.04) could be detected, which were isolated and identified by NMR and IR as follows.

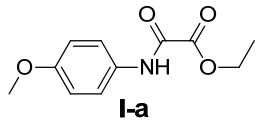
Diethyl 2- ((4- methoxyphenyl) amino)- 3- oxosuccinate (D-a)



D-a

Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 9.0 Hz, 1 H), 6.91 (d, J = 9.0 Hz, 1 H), 5.85 (d, J = 1.5 Hz, 1 H), 5.56 (d, J = 1.5 Hz, 1 H), 4.19 (q, J = 7.1 Hz, 1 H), 3.79 (s, 2 H), 1.31 (t, J = 7.1 Hz, 2 H), 1.19 (t, J = 7.1 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.43, 165.22, 158.50, 126.86, 124.14, 114.68, 99.14, 86.98, 65.34, 62.48, 55.47, 15.11, 13.93; HRMS (EI) calcd for $C_{15}H_{19}NO_6Na$ $[M + Na]^+$: 332.1104, found 332.1112; IR (KBr): 2926, 1737, 1611, 1514, 1443, 1400, 1374, 1252, 1209, 1110, 1028, 972, 895, 833, 518 cm^{-1}.

Ethyl 2- ((4- methoxyphenyl) amino)- 2- oxoacetate[2] (I-a)



I-a

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1 H), 7.54 (d, J = 9.0 Hz, 2 H), 6.86 (d, J = 9.0 Hz, 2 H), 4.35 (q, J = 7.1 Hz, 2 H), 3.76 (s, 3 H), 1.37 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.14, 157.14, 153.79, 129.61, 121.47, 114.29, 63.54, 55.44, 13.96; IR (KBr): 3353, 3119, 3088, 2982, 2903, 2850, 1884, 1723, 1704, 1544, 1513, 1299, 1244, 1175, 1020, 837, 702, 539 cm^{-1}.

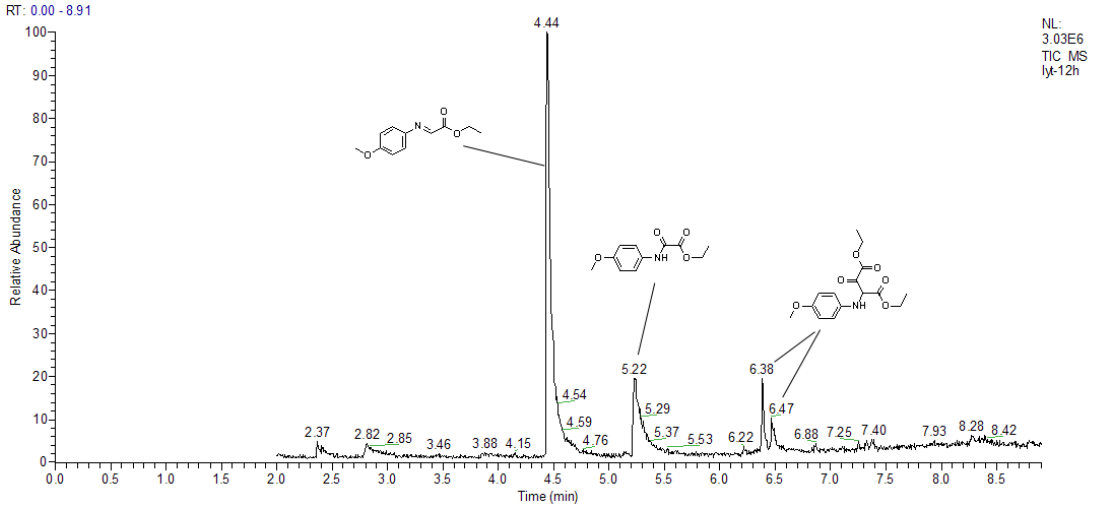


Figure 3. GC spectra of the reaction mixture stirred for 12 h.

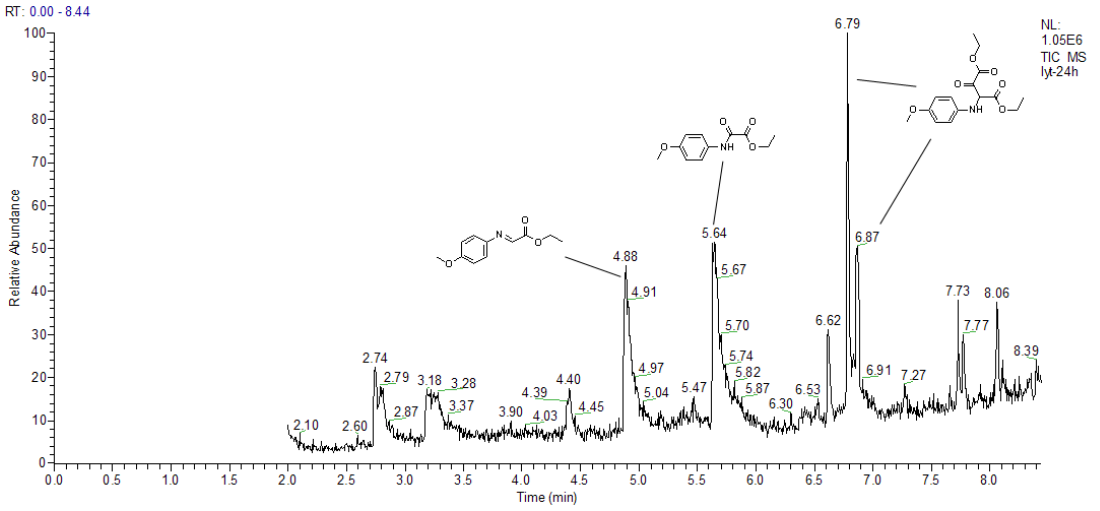


Figure 4. GC spectra of the reaction mixture stirred for 24 h.

1.10. X-Ray crystallographic data of 3a

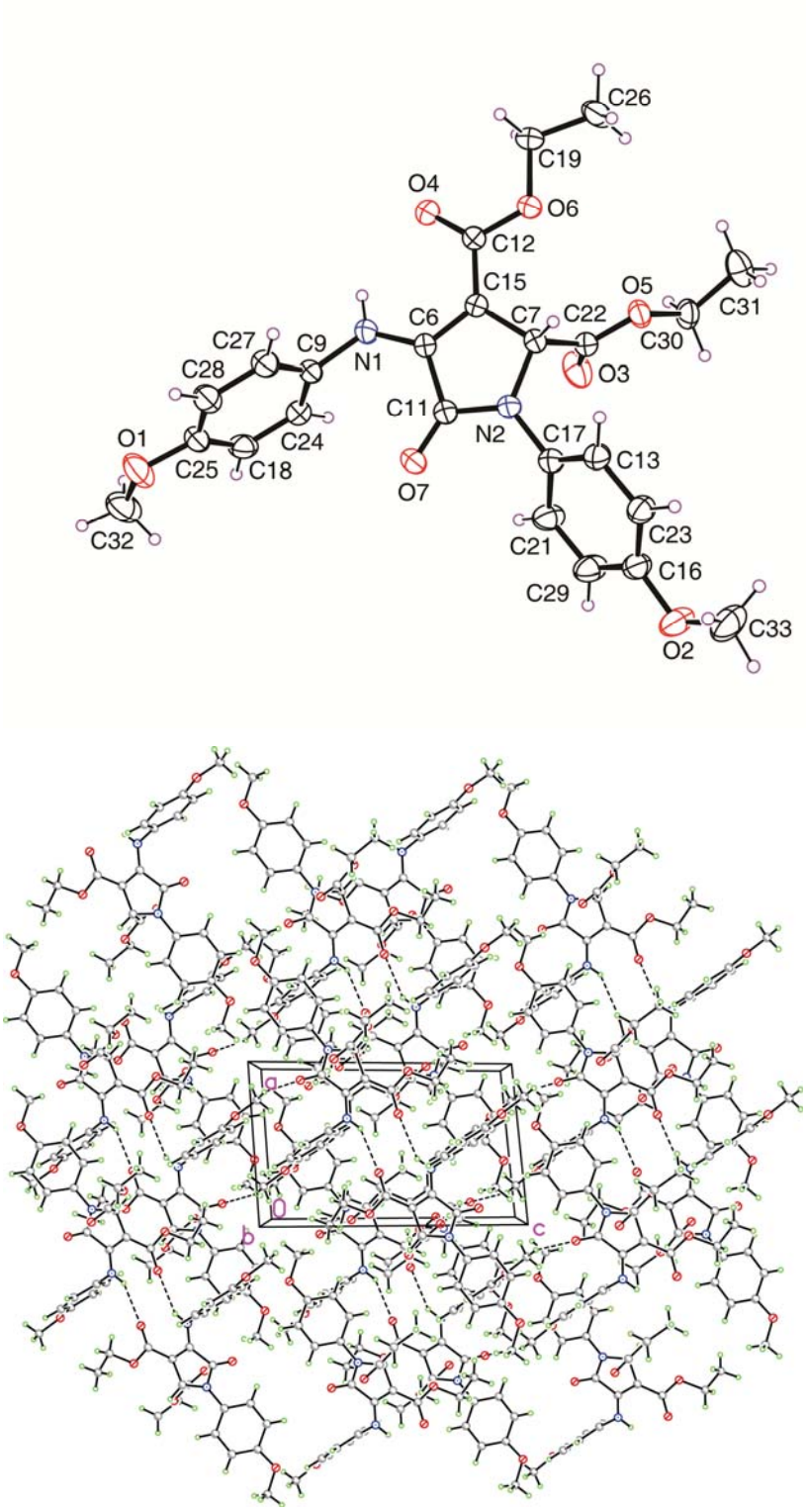


Figure 5. The Single crystal structure of compound **3a**

Table 1. Crystal data and structure refinement for **3a**.

Identification code	**3a**
Empirical formula	$C_{24}H_{26}N_2O_7$
Formula weight	454.47
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P-1
Unit cell dimensions	a = 8.2709(17) Å alpha = 103.20(3)°. b = 10.867(2) Å beta = 91.14(3) °. c = 13.310(3) Å gamma = 105.39(3) °.
Volume	1118.8(4) $Å^3$
Z	2
Calculated density	1.349 Mg/m^3
Absorption coefficient	0.100 mm^{-1}
F(000)	480
Crystal size	0.30 x 0.20 x 0.15 mm^3
Theta range for data collection	3.06 to 27.48°.
Limiting indices	-10<=h<=10, -14<=k<=14, -17<=l<=17
Reflections collected / unique	10974 / 5057 [R(int) = 0.0457]
Completeness to theta = 27.48°	98.3 %
Max. and min. transmission	0.9852 and 0.9706
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5057 / 0 / 298
Goodness-of-fit on F^2	1.036
Final R indices [I>2sigma(I)]	R1 = 0.0591, wR2 = 0.1540
R indices (all data)	R1 = 0.1212, wR2 = 0.2161
Largest diff. peak and hole	0.341 and -0.288 e. $Å^{-3}$

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **3a**.

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(5)	2009(2)	3729(2)	4591(2)	53(1)
O(6)	-634(2)	2272(2)	5952(1)	52(1)
O(4)	-3187(2)	828(2)	5457(2)	61(1)
O(7)	-1077(2)	-1151(2)	1856(2)	64(1)
N(2)	735(3)	580(2)	3027(2)	48(1)
C(6)	-1888(3)	-188(2)	3542(2)	44(1)
C(7)	679(3)	1450(2)	4032(2)	45(1)
N(1)	-3459(3)	-955(2)	3504(2)	58(1)
C(9)	-4237(3)	-2163(3)	2761(2)	48(1)
O(2)	6092(3)	1737(2)	606(2)	74(1)
C(11)	-761(3)	-354(3)	2683(2)	48(1)
C(12)	-1746(3)	1289(2)	5271(2)	45(1)
C(13)	3740(3)	1145(3)	2844(2)	53(1)
O(3)	56(3)	3075(2)	3264(2)	78(1)
C(15)	-1046(3)	851(2)	4318(2)	45(1)
C(16)	4853(4)	1460(3)	1249(2)	55(1)
C(17)	2133(3)	857(3)	2412(2)	48(1)
C(18)	-5916(4)	-3368(3)	1185(2)	61(1)
C(19)	-1249(4)	2749(3)	6940(2)	53(1)
O(1)	-6737(4)	-5759(2)	849(2)	91(1)
C(21)	1873(4)	875(3)	1380(2)	65(1)
C(22)	872(3)	2836(2)	3899(2)	47(1)
C(23)	5105(4)	1457(3)	2269(2)	56(1)
C(24)	-5070(4)	-2184(3)	1857(2)	56(1)
C(25)	-5938(4)	-4530(3)	1439(2)	59(1)
C(26)	100(4)	3917(3)	7538(2)	70(1)
C(27)	-4240(4)	-3334(3)	3001(2)	57(1)
C(28)	-5087(4)	-4515(3)	2335(3)	63(1)
C(29)	3229(4)	1175(4)	811(2)	68(1)
C(30)	2231(4)	5084(2)	4530(3)	60(1)
C(31)	3314(5)	5974(3)	5463(3)	80(1)
C(32)	-7750(5)	-5856(4)	-36(3)	95(1)
C(33)	7775(4)	2039(5)	1018(3)	93(1)

Table 3. Bond lengths [Å] and angles [°] for **3a**.

O(5)-C(22)	1.322(3)
O(5)-C(30)	1.456(3)
O(6)-C(12)	1.346(3)
O(6)-C(19)	1.453 (3)
O(4)-C(12)	1.218(3)
O(7)-C(11)	1.210(3)
N(2)-C(11)	1.367(3)
N(2)-C(17)	1.437(3)
N(2)-C(7)	1.461(3)
C(6)-N(1)	1.337(3)
C(6)-C(15)	1.360(4)
C(6)-C(11)	1.498(3)
C(7)-C(15)	1.499(3)
C(7)-C(22)	1.523(4)
N(1)-C(9)	1.431(3)
C(9)-C(24)	1.368(4)
C(9)-C(27)	1.380(4)
O(2)-C(16)	1.364(3)
O(2)-C(33)	1.412(4)
C(12)-C(15)	1.439(3)
C(13)-C(17)	1.365(4)
C(13)-C(23)	1.387(4)
O(3)-C(22)	1.186(3)
C(16)-C(23)	1.371(4)
C(16)-C(29)	1.380(4)
C(17)-C(21)	1.390(4)
C(18)-C(25)	1.375(4)
C(18)-C(24)	1.384(4)
C(19)-C(26)	1.497(4)
O(1)-C(25)	1.367(4)
O(1)-C(32)	1.399(5)
C(21)-C(29)	1.375(4)
C(25)-C(28)	1.368(5)
C(27)-C(28)	1.380(4)
C(30)-C(31)	1.493(5)
C(22)-O(5)-C(30)	115.2(2)
C(12)-O(6)-C(19)	115.9(2)
C(11)-N(2)-C(17)	124.7(2)
C(11)-N(2)-C(7)	112.8(2)
C(17)-N(2)-C(7)	121.5(2)
N(1)-C(6)-C(15)	127.9(2)
N(1)-C(6)-C(11)	123.5(2)
C(15)-C(6)-C(11)	108.5(2)

N(2)-C(7)-C(15)	102.3(2)
N(2)-C(7)-C(22)	109.2(2)
C(15)-C(7)-C(22)	111.6(2)
C(6)-N(1)-C(9)	127.1(2)
C(24)-C(9)-C(27)	119.5(3)
C(24)-C(9)-N(1)	121.6(3)
C(27)-C(9)-N(1)	118.8(3)
C(16)-O(2)-C(33)	117.7(3)
O(7)-C(11)-N(2)	126.2(2)
O(7)-C(11)-C(6)	128.0(2)
N(2)-C(11)-C(6)	105.8(2)
O(4)-C(12)-O(6)	122.7(2)
O(4)-C(12)-C(15)	124.4(2)
O(6)-C(12)-C(15)	112.9(2)
C(17)-C(13)-C(23)	120.9(3)
C(6)-C(15)-C(12)	123.7(2)
C(6)-C(15)-C(7)	110.3(2)
C(12)-C(15)-C(7)	126.0(2)
O(2)-C(16)-C(23)	125.4(3)
O(2)-C(16)-C(29)	115.5(3)
C(23)-C(16)-C(29)	119.1(3)
C(13)-C(17)-C(21)	119. 1(3)
C(13)-C(17)-N(2)	120.2(3)
C(21)-C(17)-N(2)	120.6(3)
C(25)-C(18)-C(24)	119.6(3)
O(6)-C(19)-C(26)	107.6(2)
C(25)-O(1)-C(32)	117.9(3)
C(29)-C(21)-C(17)	119.9(3)
O(3)-C(22)-O(5)	124.6(3)
O(3)-C(22)-C(7)	123.3(3)
O(5)-C(22)-C(7)	112.0(2)
C(16)-C(23)-C(13)	120.1(3)
C(9)-C(24)-C(18)	120.5(3)
O(1)-C(25)-C(28)	114.5(3)
O(1)-C(25)-C(18)	125.3(3)
C(28)-C(25)-C(18)	120.1(3)
C(9)-C(27)-C(28)	120.1(3)
C(25)-C(28)-C(27)	120.1(3)
C(21)-C(29)-C(16)	120.9(3)
O(5)-C(30)-C(31)	108.5(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for **3a**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\ hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(5)	54(1)	41(1)	53(1)	7(1)	-5(1)	1(1)
O(6)	47(1)	54(1)	42(1)	0(1)	8(1)	4(1)
O(4)	49(1)	65(1)	53(1)	3(1)	13(1)	-3(1)
O(7)	58(1)	61(1)	52(1)	-10(1)	10(1)	-1(1)
N(2)	43(1)	48(1)	44(1)	2(1)	10(1)	6(1)
C(6)	43(1)	40(1)	43(2)	6(1)	4(1)	3(1)
C(7)	44(1)	40(1)	42(2)	4(1)	5(1)	4(1)
N(1)	46(1)	55(1)	53(2)	-5(1)	13(1)	-3(1)
C(9)	44(1)	48(1)	41(2)	-1(1)	6(1)	2(1)
O(2)	56(1)	113(2)	60(2)	33(1)	19(1)	21(1)
C(11)	45(1)	46(1)	46(2)	5(1)	7(1)	6(1)
C(12)	45(2)	46(1)	40(2)	8(1)	2(1)	6(1)
C(13)	51(2)	60(2)	43(2)	14(1)	3(1)	7(1)
O(3)	92(2)	58(1)	77(2)	18(1)	-28(1)	11(1)
C(15)	42(1)	45(1)	41(2)	7(1)	6(1)	5(1)
C(16)	51(2)	66(2)	48(2)	14(1)	12(1)	16(1)
C(17)	46(1)	49(1)	44(2)	6(1)	8(1)	11(1)
C(18)	64(2)	75(2)	41(2)	10(2)	4(1)	16(2)
C(19)	60(2)	58(2)	40 (2)	5(1)	11(1)	18(1)
O(1)	108(2)	67(1)	70(2)	-13(1)	-16(2)	2(1)
C(21)	50(2)	96(2)	48(2)	15(2)	3(1)	21(2)
C(22)	45(1)	47(1)	43(2)	9(1)	4(1)	6(1)
C(23)	49(2)	63(2)	56(2)	18(1)	6(1)	12(1)
C(24)	62(2)	52(2)	49(2)	13(1)	9(2)	7(1)
C(25)	56(2)	53(2)	53(2)	-5(1)	7(1)	3(1)
C(26)	68(2)	76(2)	50(2)	-11(2)	-2(2)	18(2)
C(27)	55(2)	59(2)	52(2)	6(1)	4(1)	11(1)
C(28)	72(2)	54(2)	55(2)	6(1)	1(2)	13(2)
C(29)	58(2)	104(3)	45(2)	23(2)	6(2)	22(2)
C(30)	60(2)	39(1)	73(2)	12(1)	5(2)	2(1)
C(31)	81(2)	47(2)	95(3)	-3(2)	-9(2)	10(2)
C(32)	68(2)	109(3)	76(3)	-21(2)	-3(2)	10(2)
C(33)	50(2)	142(4)	88(3)	45(3)	16(2)	13(2)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for **3a**.

	x	y	z	U(eq)
H(7A)	1550	1440	4538	53
H(1 A)	-4069	-693	3977	69
H(13A)	3923	1133	3533	64
H(18A)	-6468	-3377	567	74
H(19A)	-1500	2067	7319	64
H(19B)	-2269	2998	6830	64
H(21A)	785	685	1077	78
H(23A)	6194	1664	2577	67
H(24A)	-5068	-1397	1692	67
H(26A)	-269	4251	8198	104
H(26B)	331	4589	7159	104
H(26C)	1104	3661	7640	104
H(27A)	-3671	-3326	3613	69
H(28A)	-5078	-5303	2495	75
H(29A)	3050	1185	121	82
H(30A)	1146	5266	4506	72
H(30B)	2759	5227	3907	72
H(31A)	3478	6873	5432	119
H(31B)	4384	5788	5482	119
H(31C)	2775	5835	6076	119
H(32A)	-8238	-6766	-374	142
H(32B)	-7078	-5421	-500	142
H(32C)	-8630	-5447	160	142
H(33A)	8518	2209	490	139
H(33B)	7941	1309	1258	139
H(33C)	8012	2803	1586	139

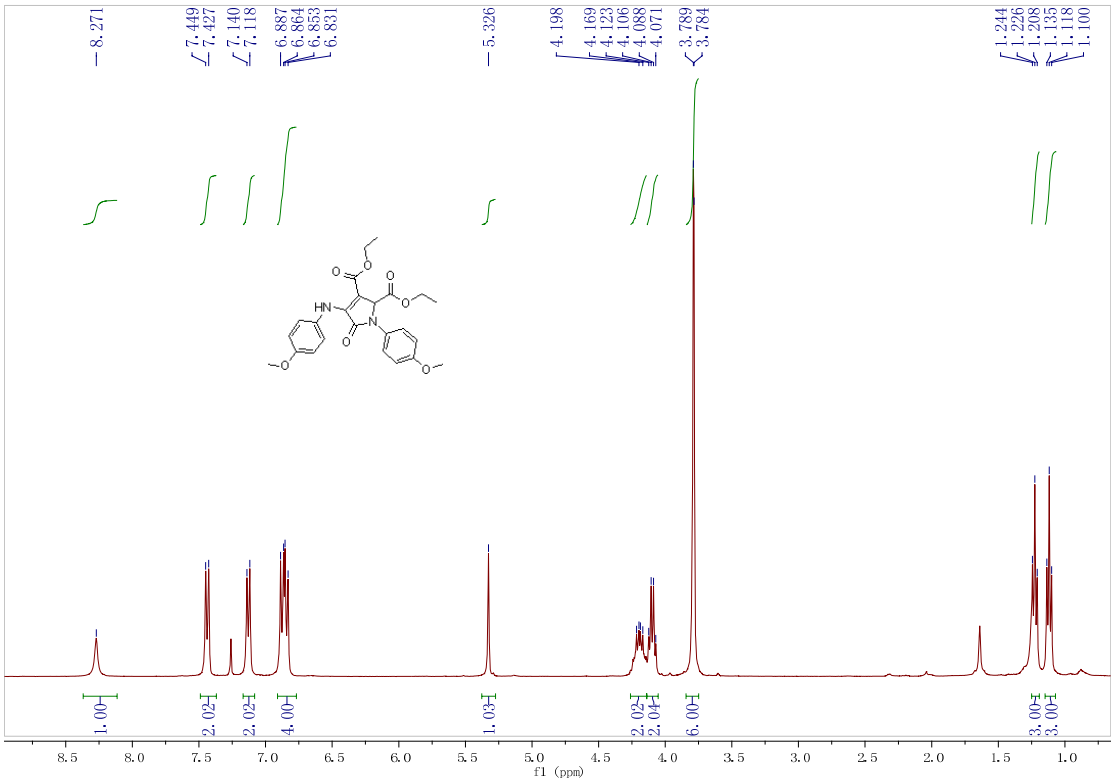
2. Reference

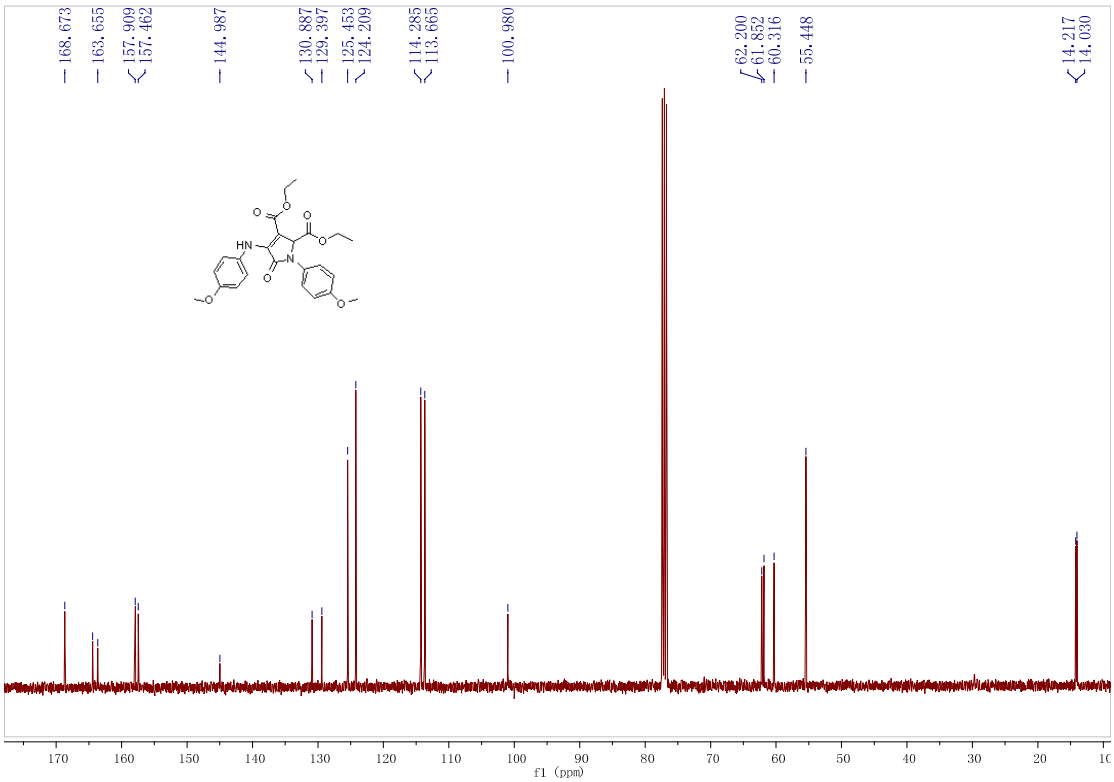
(1) Zhu, S. J.; Dong, J.; Fu, S. M.; Jiang, H. F.; Zeng, W. *Org. Lett*. **2011**, *13*, 4914.

(2) Langer, P.; Schroeder, R. *Eur. J. Org. Chem.* **2004**, 1025.

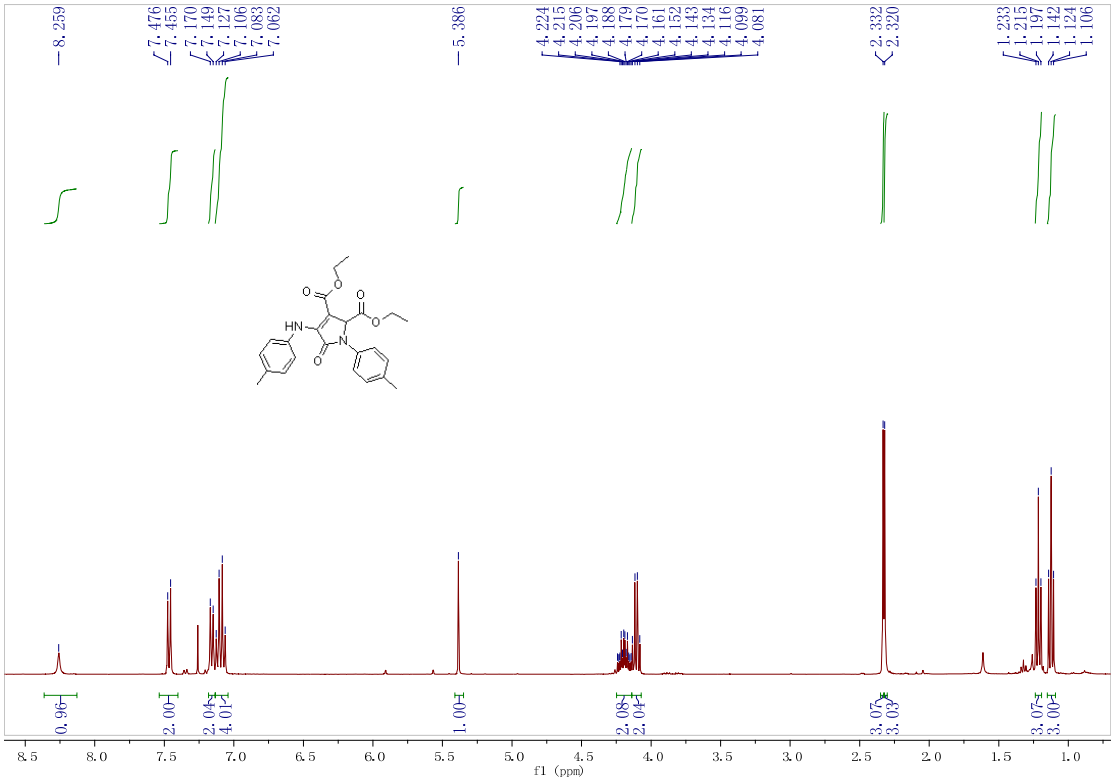
3. ^{1}H NMR and ^{13}C NMR spectrum for 3a-3v, D-a and I-a.

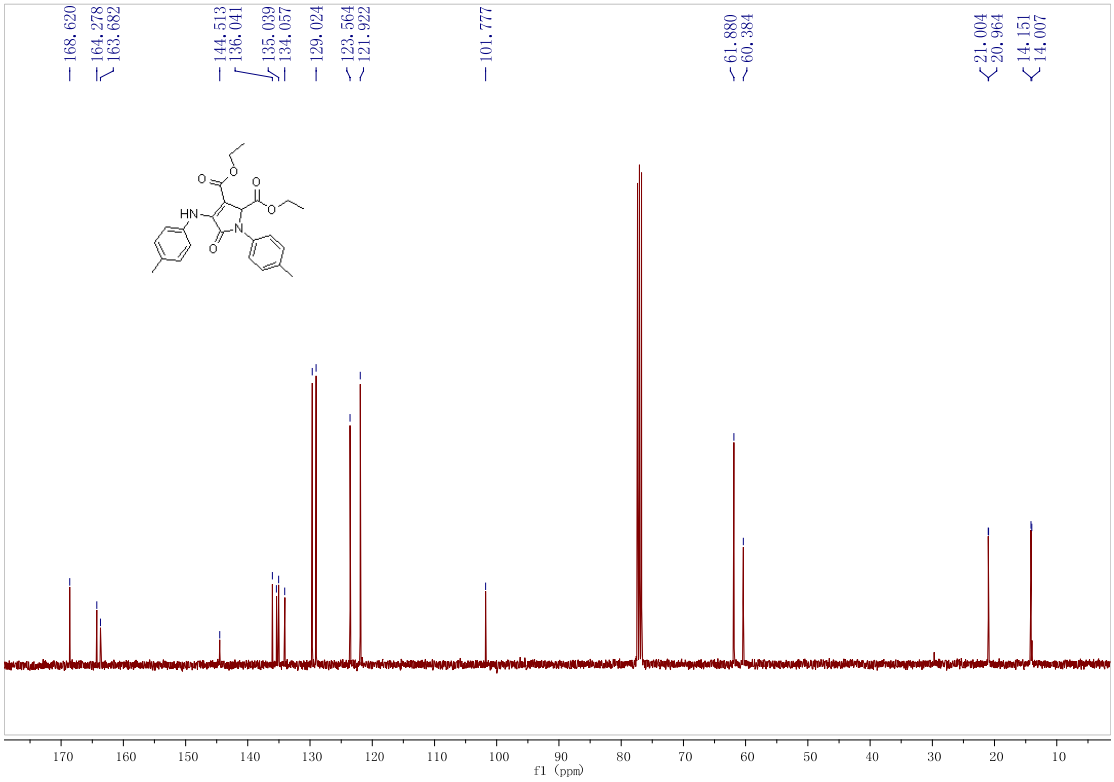
^{1}H NMR and ^{13}C NMR spectrum for diethyl 1- (4- methoxyphenyl)- 4- ((4- methoxyphenyl) amino)- 5- oxo- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (**3a**) ($CDCl_3$ as solvent)



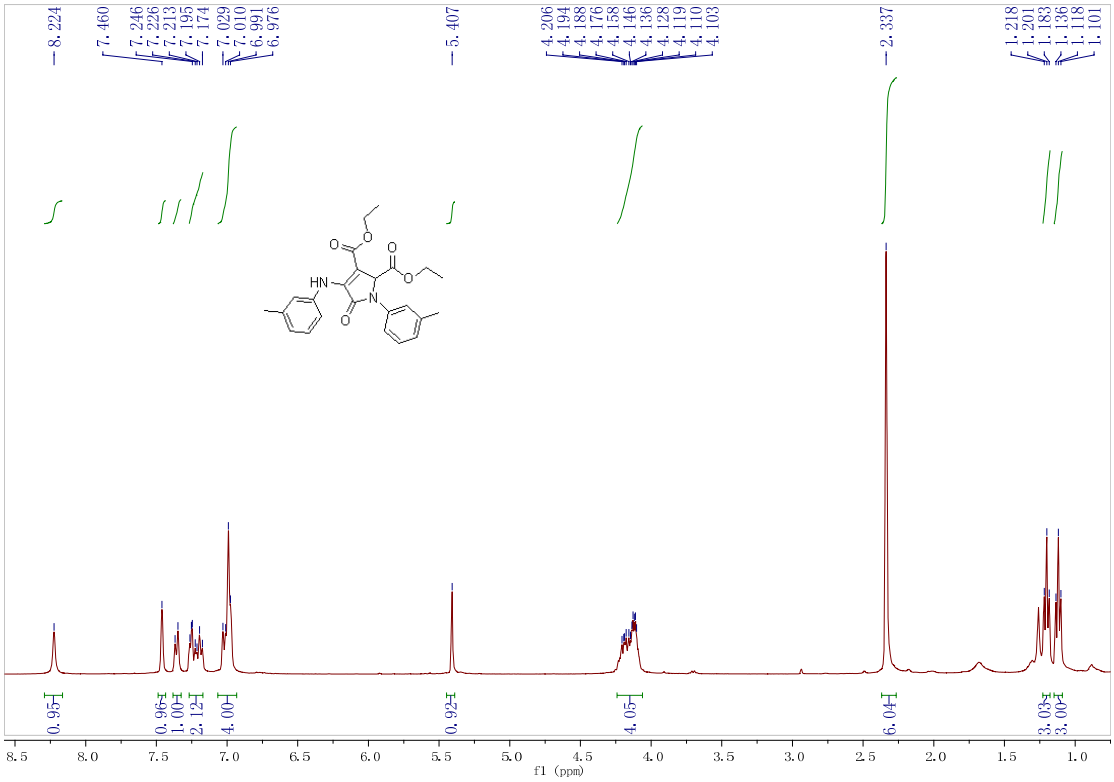


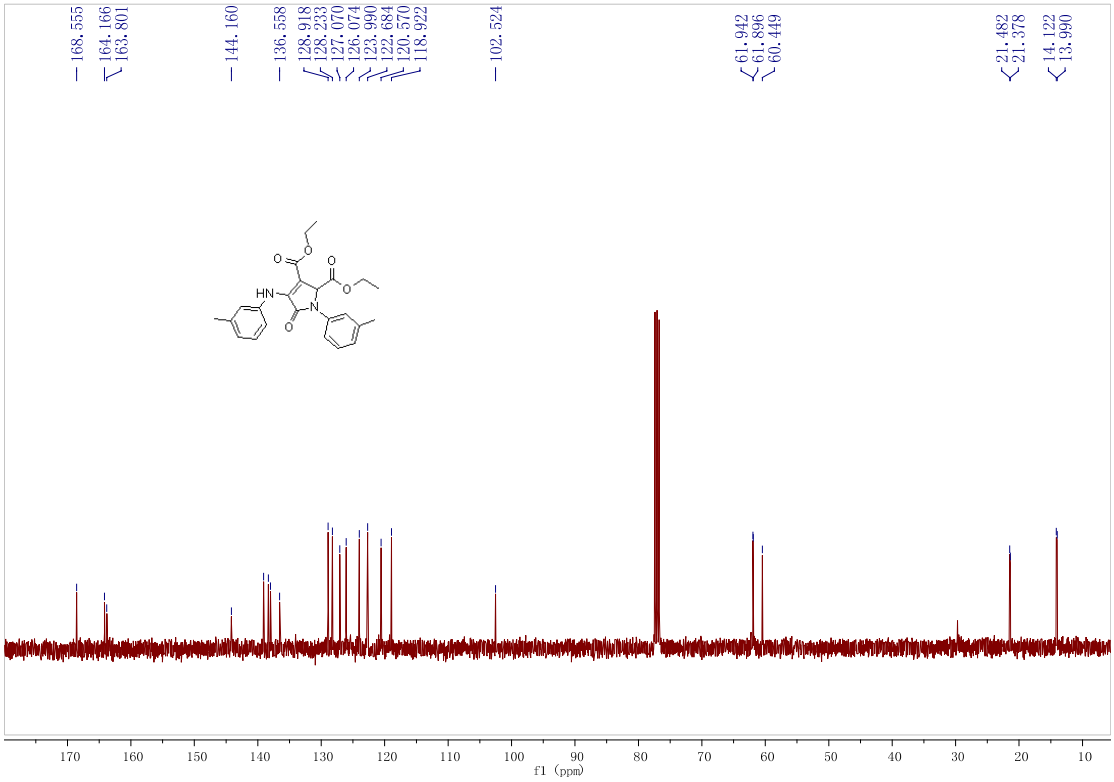
^{1}H NMR and ^{13}C NMR spectrum for diethyl 5- oxo- 1- (*p*- tolyl)- 4- (*p*- tolylamino)-2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (**3b**) ($CDCl_3$ as solvent)



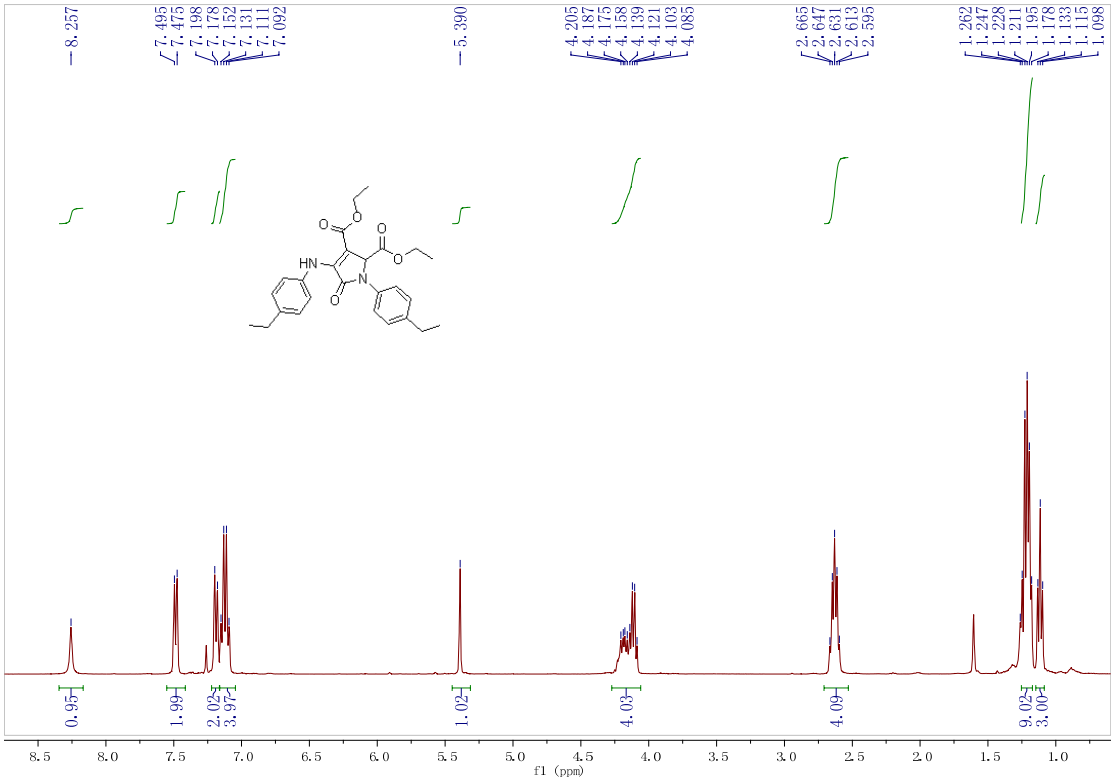


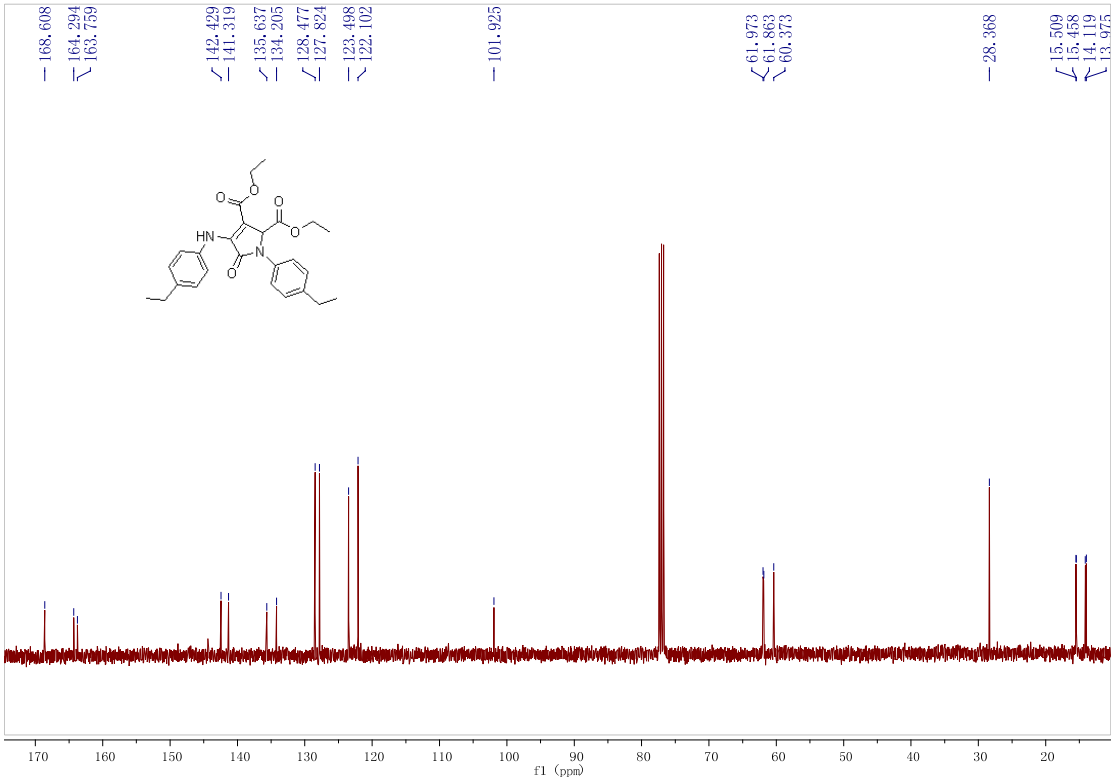
^{1}H NMR and ^{13}C NMR spectrum for diethy 5- oxo- 1- (m- tolyl)- 4- (m- tolylamino)-2, 5- dihydro- 1 H –pyrrole -2, 3- dicarboxylate (**3c**) ($CDCl_3$ as solvent)



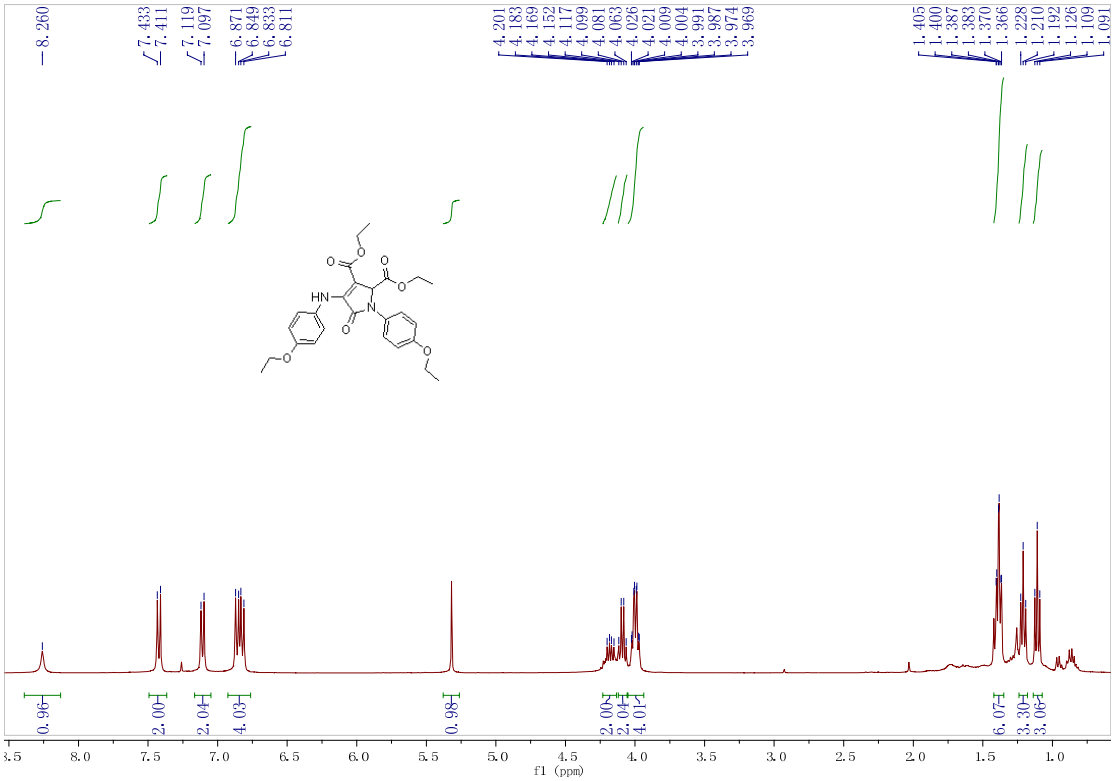


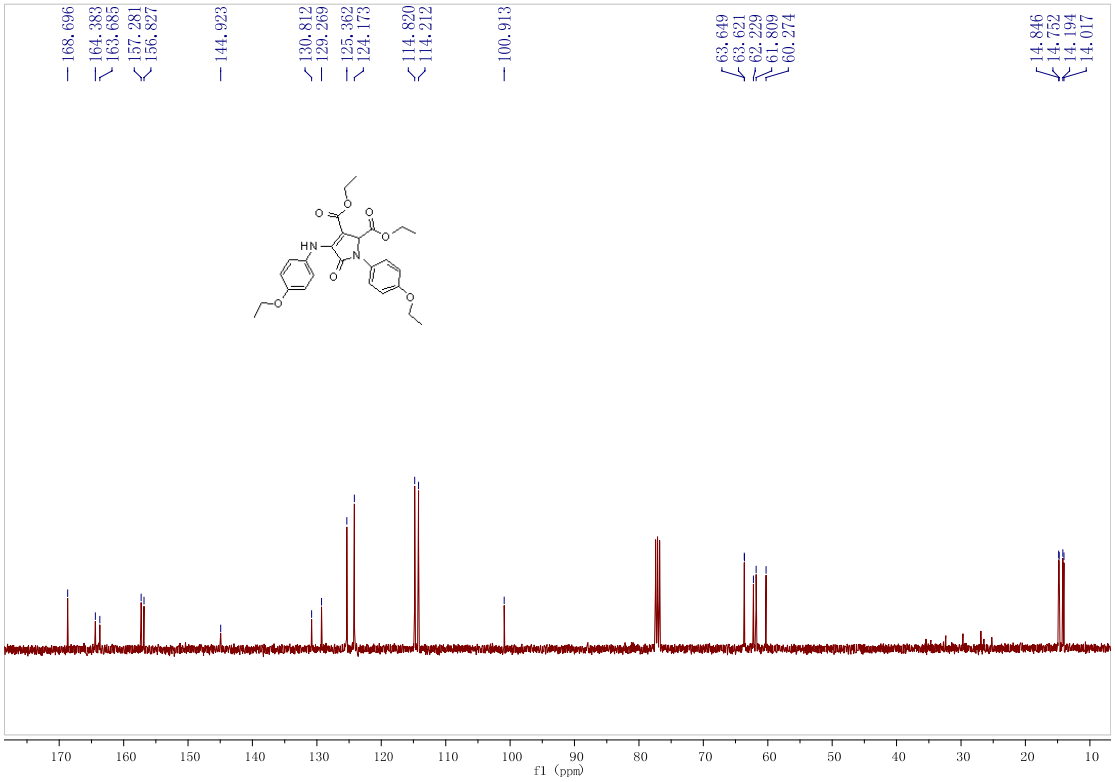
^{1}H NMR and ^{13}C NMR spectrum for diethy 1- (4- ethylphenyl)- 4- ((4- ethylphenyl) amino)- 5- oxo- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (**3d**) ($CDCl_3$ as solvent)



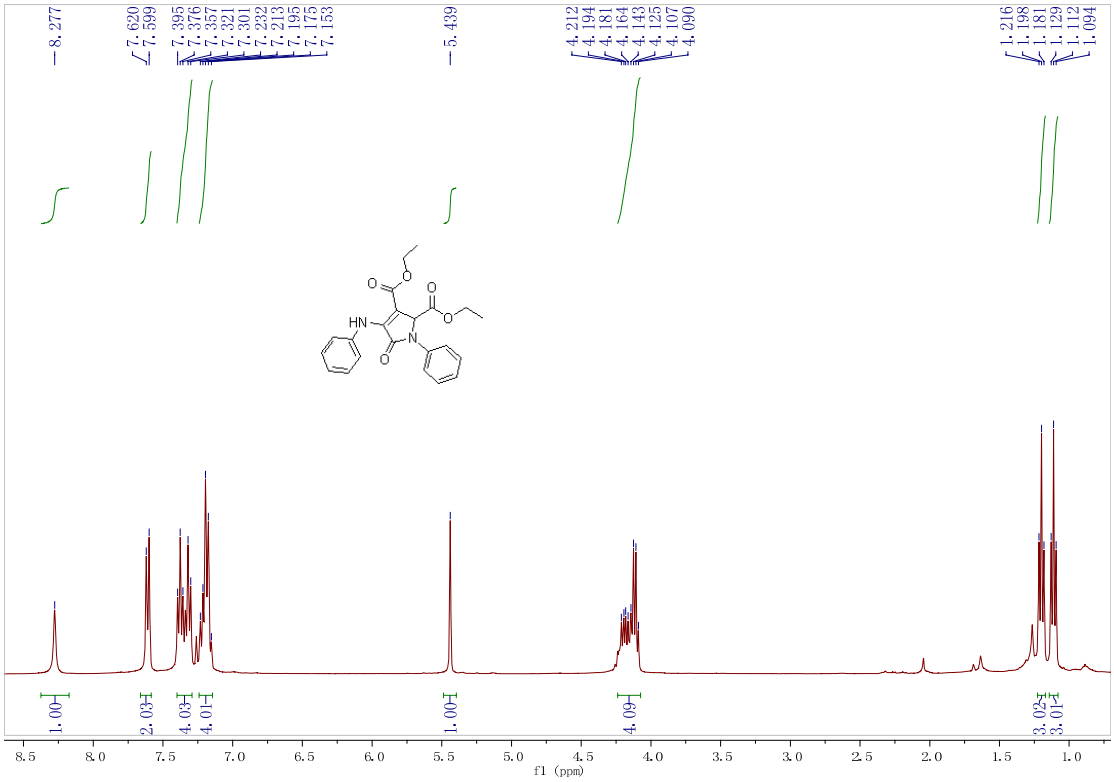


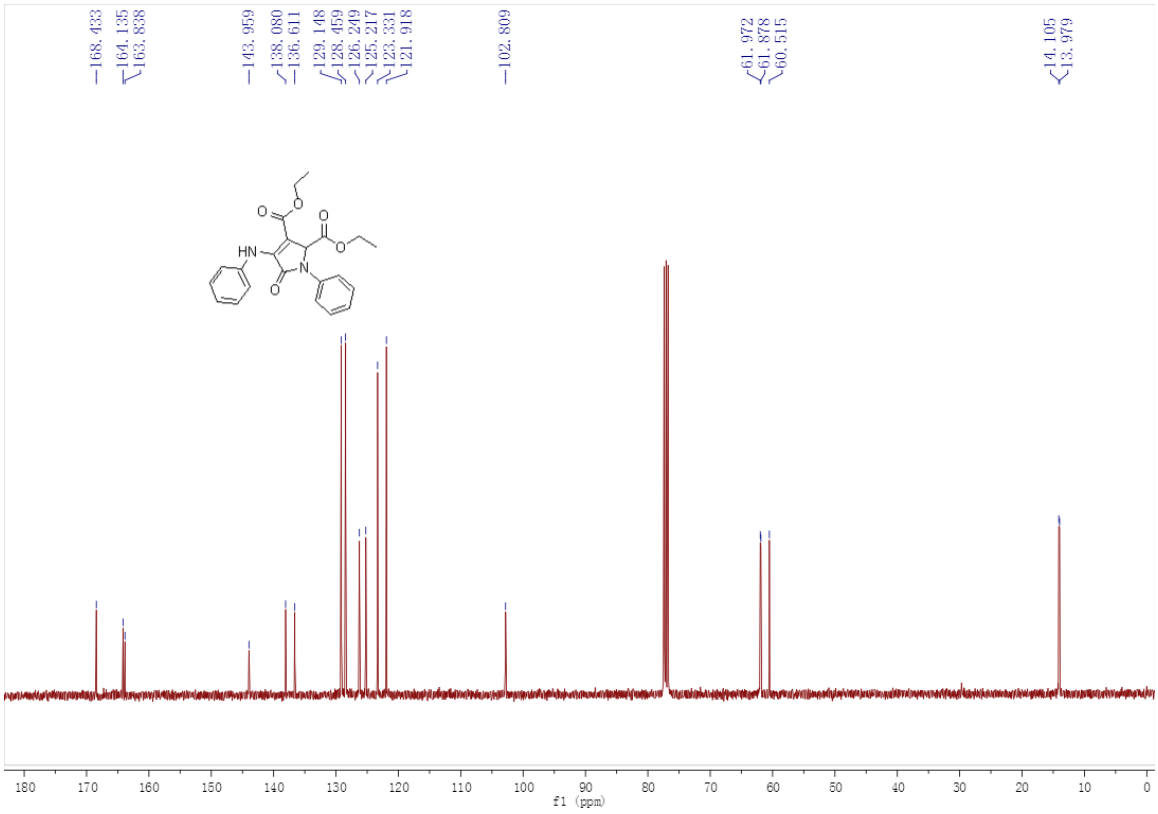
^{1}H NMR and ^{13}C NMR spectrum for diethy 1- (4- ethoxyphenyl)- 4- ((4- ethoxyphenyl) amino)- 5- oxo- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (**3e**) ($CDCl_3$ as solvent)



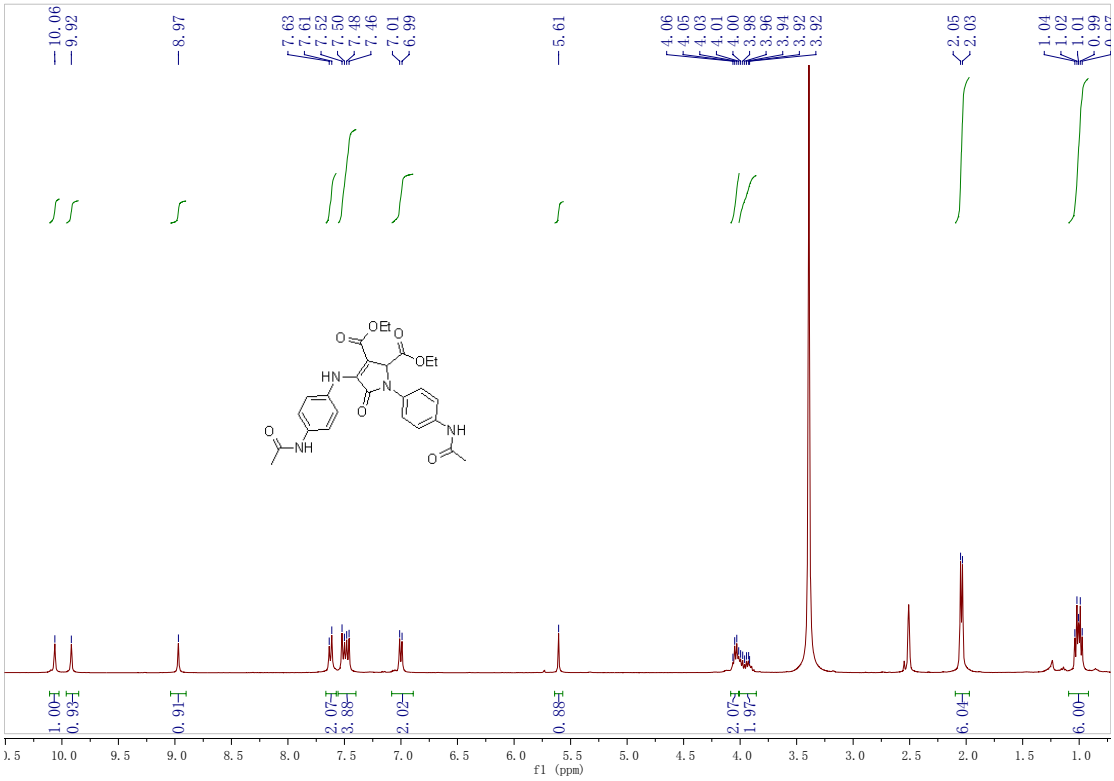


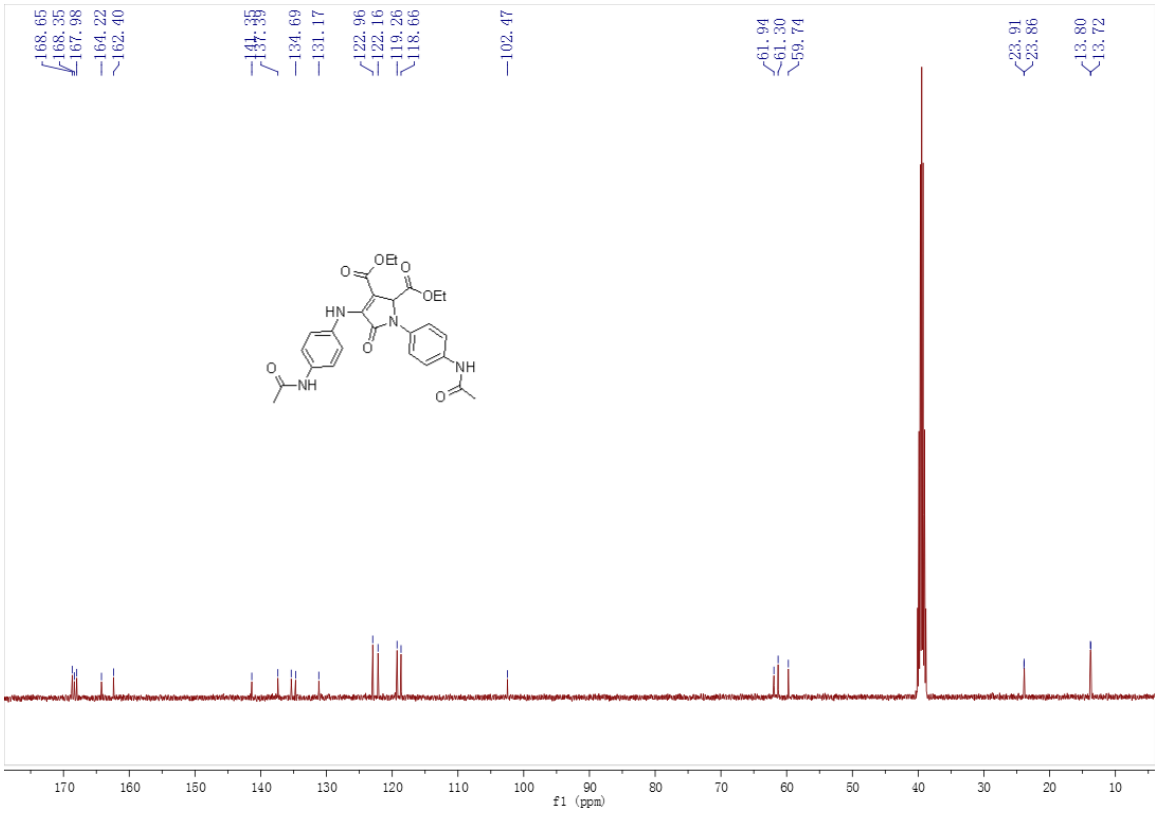
^{1}H NMR and ^{13}C NMR spectrum for diethy 5- oxo- 1- phenyl- 4- (phenylamino)- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (**3f**) ($CDCl_3$ as solvent)



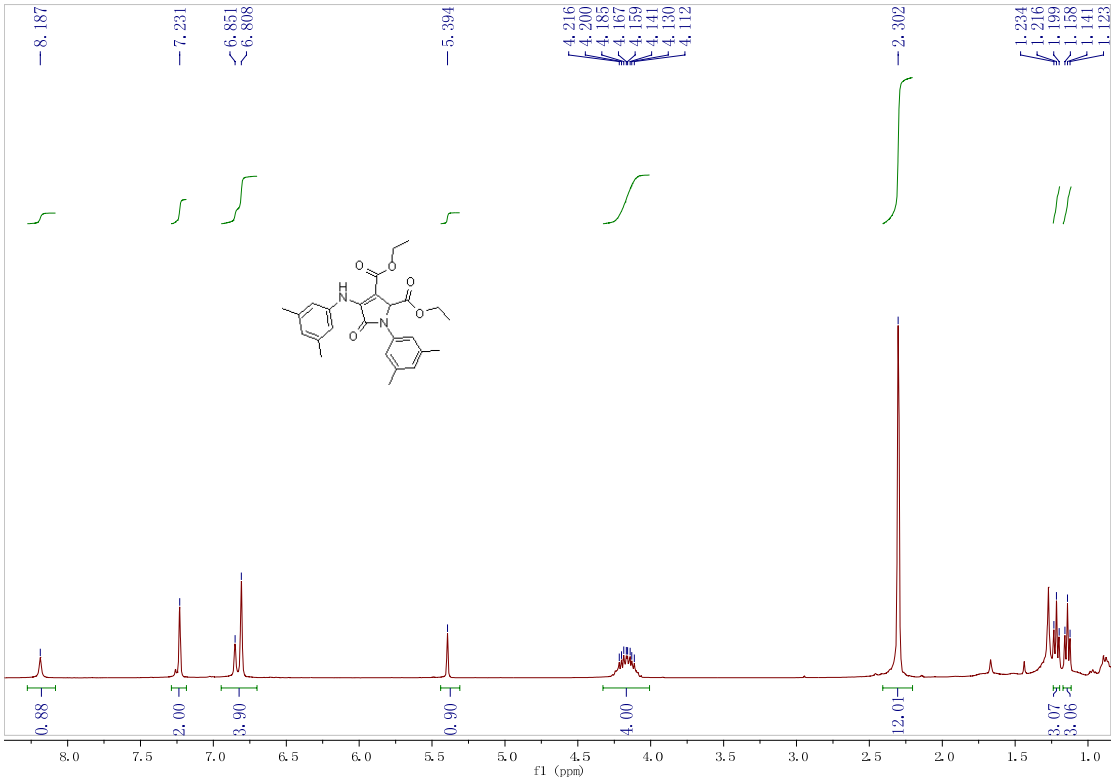


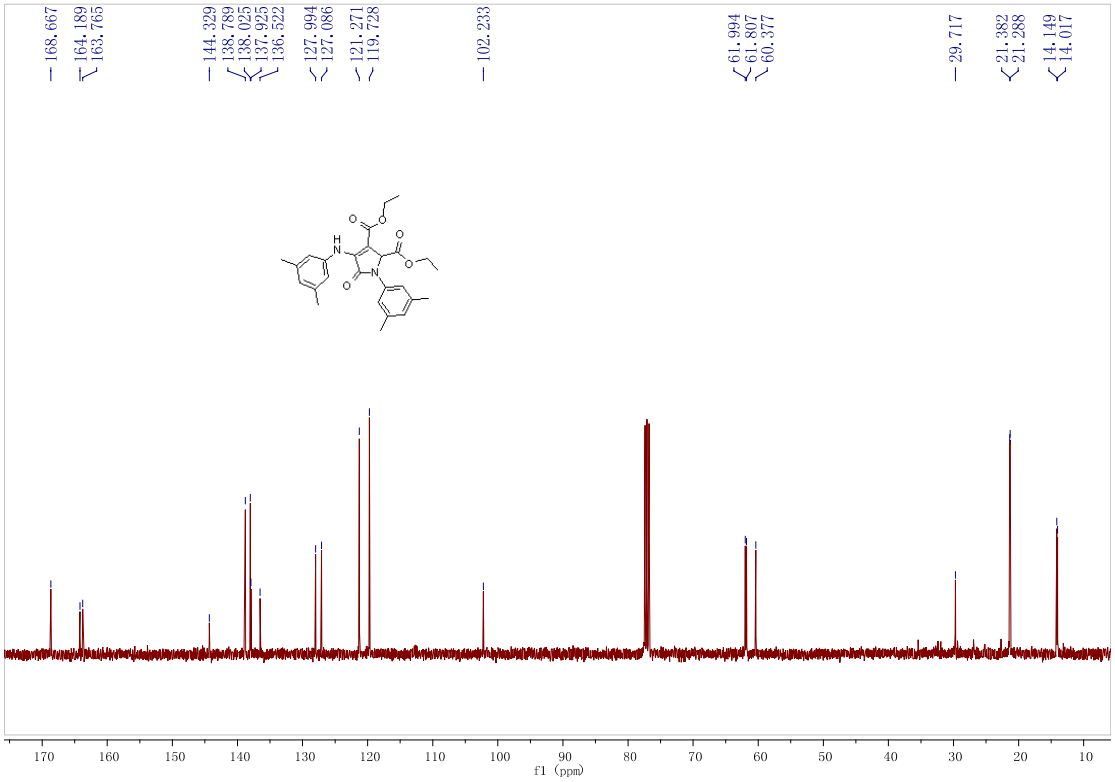
^{1}H NMR and ^{13}C NMR spectrum for diethyl 1- (4- acetamidophenyl)- 4- ((4- acetamidophenyl) amino)- 5- oxo- 2, 5- dihydro- 1H- pyrrole- 2, 3- dicarboxylate (**3g**) (*d*-DMSO as solvent)



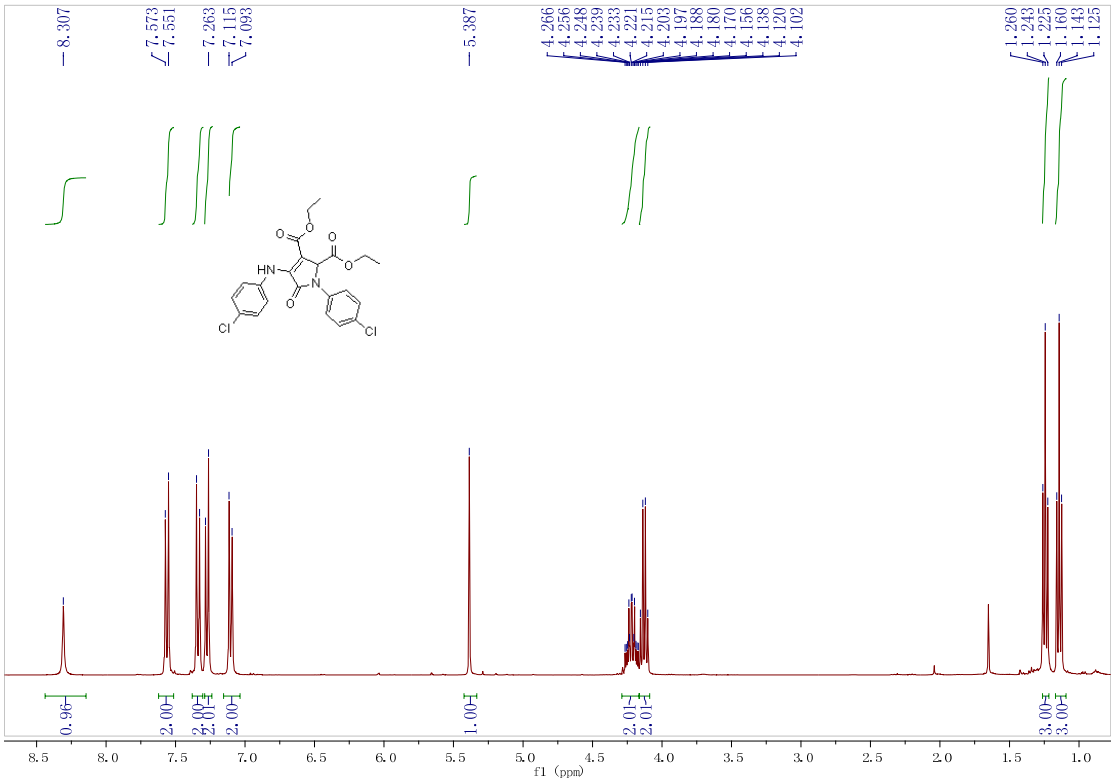


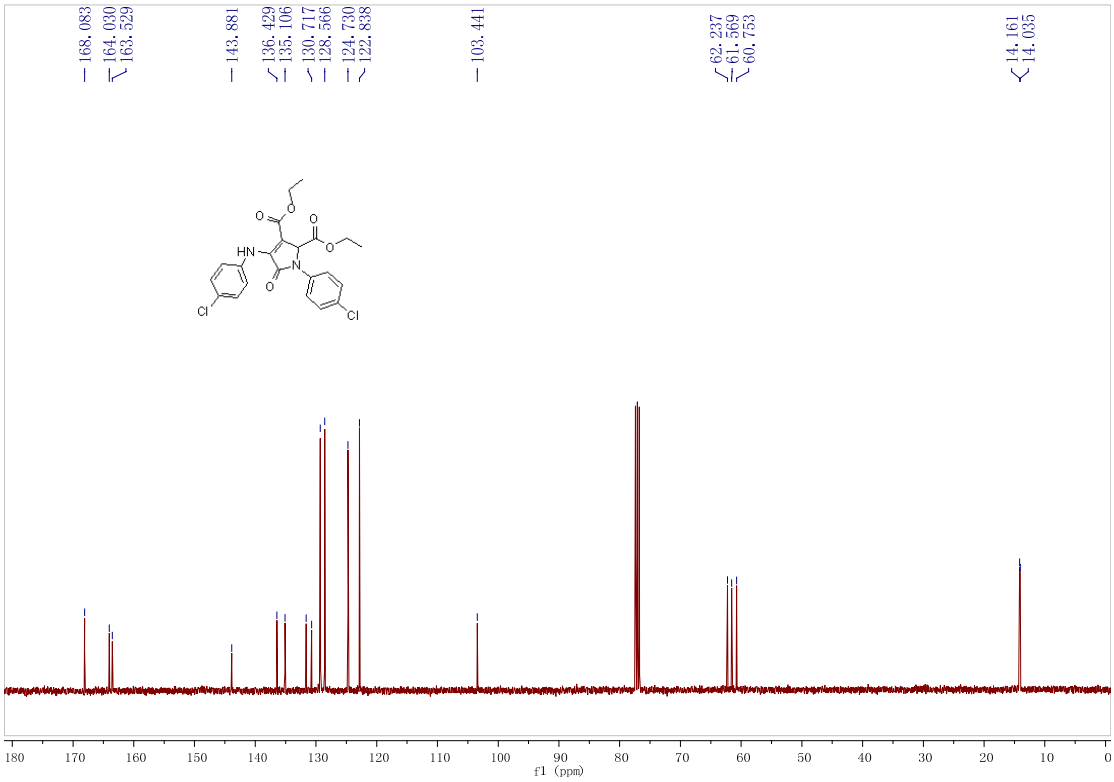
^{1}H NMR and ^{13}C NMR spectrum for diethy 1- (3, 5- dimethylphenyl)- 4- ((3, 5- dimethylphenyl) amino)- 5- oxo- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (**3h**) ($CDCl_3$ as solvent)



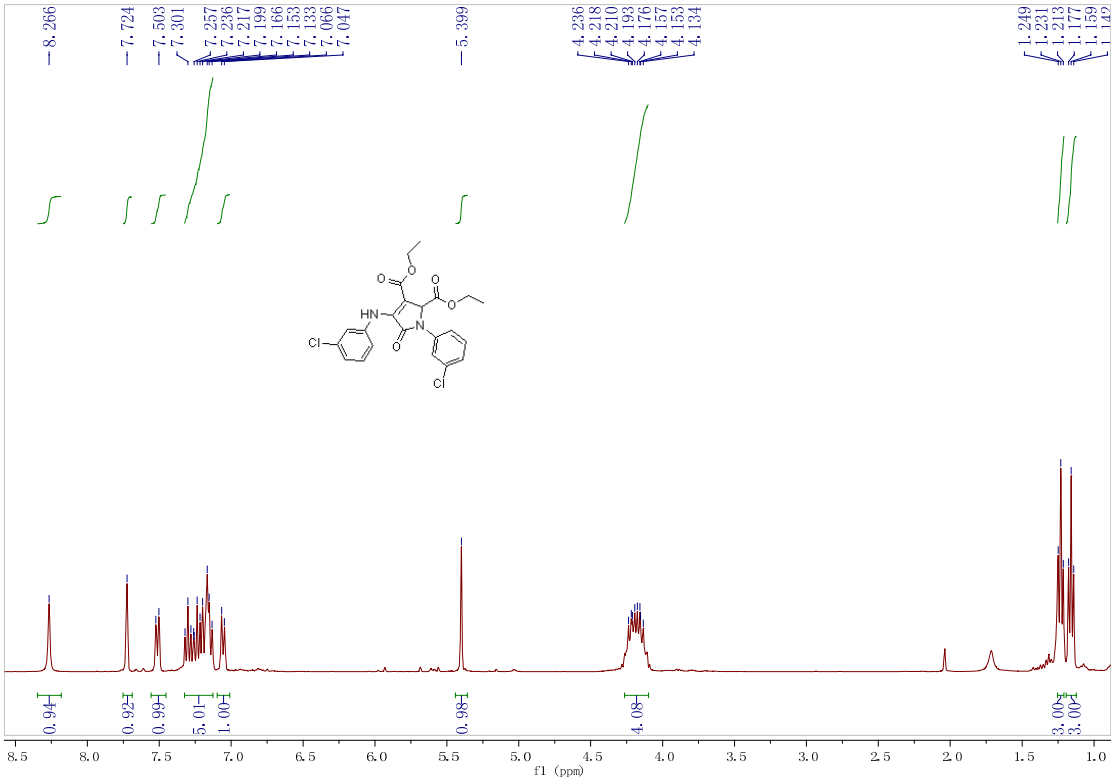


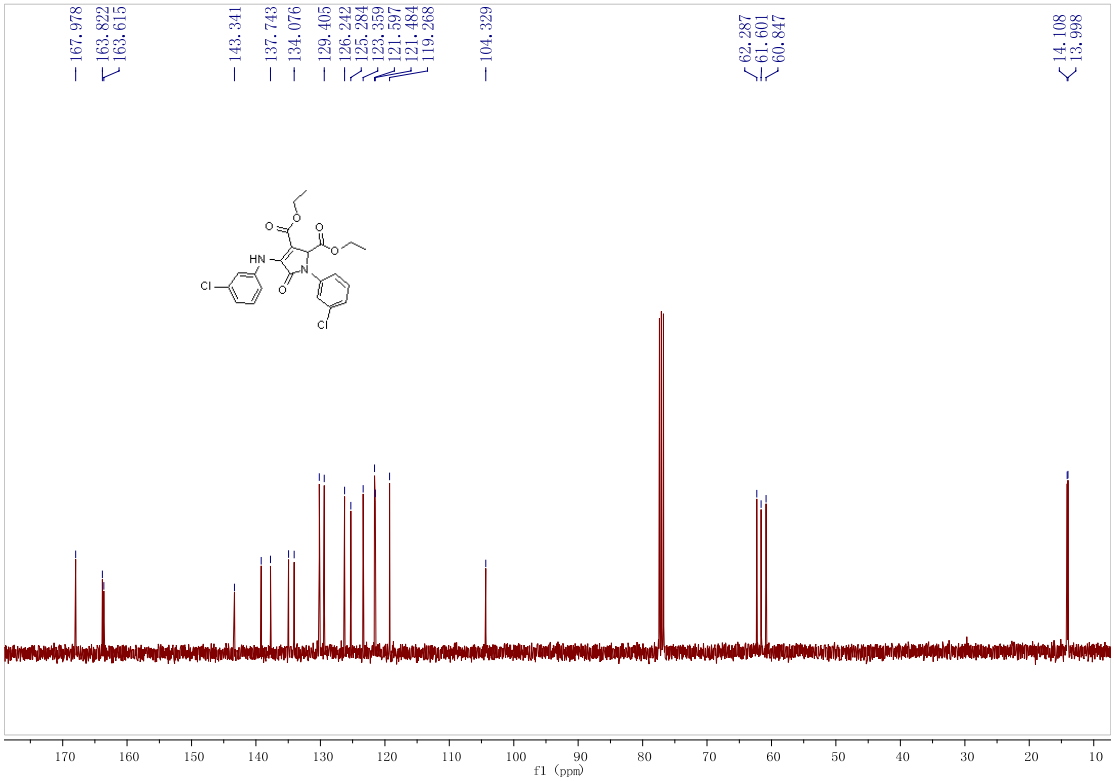
^{1}H NMR and ^{13}C NMR spectrum for diethyl 1- (4- chlorophenyl)- 4- ((4- chlorophenyl) amino)- 5- oxo- 2, 5- dihydro- 1 H- pyrrole- 2, 3-dicarboxylate (**3i**) ($CDCl_3$ as solvent)



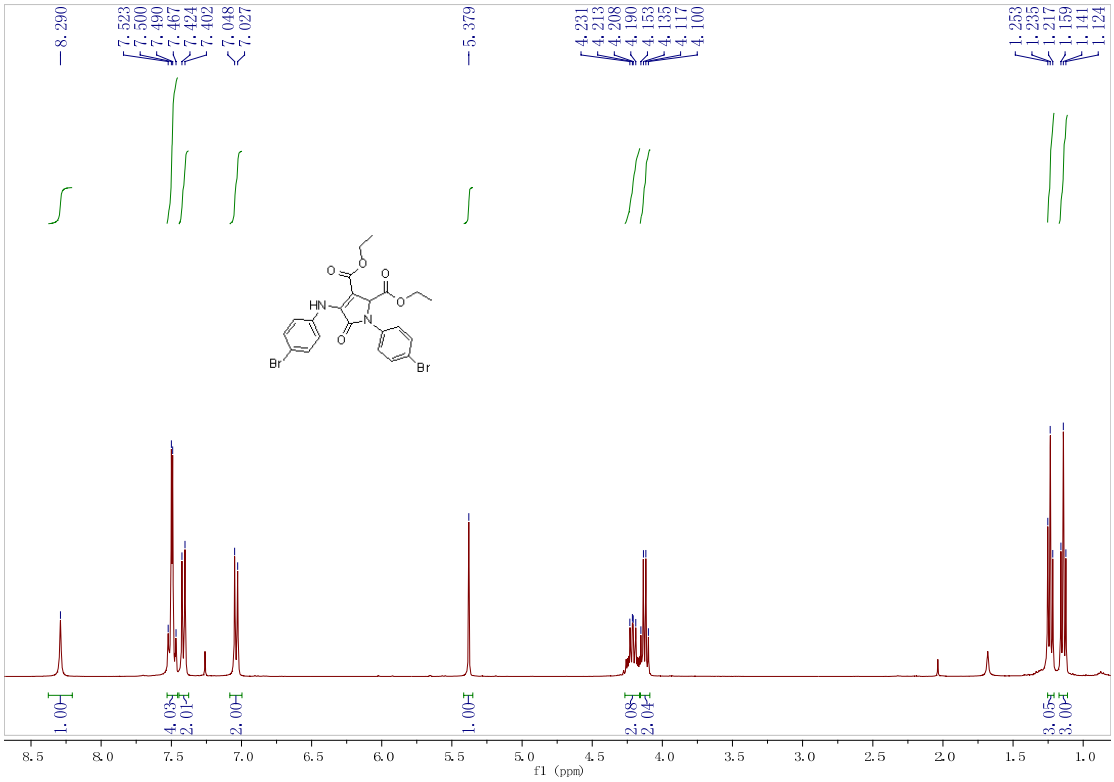


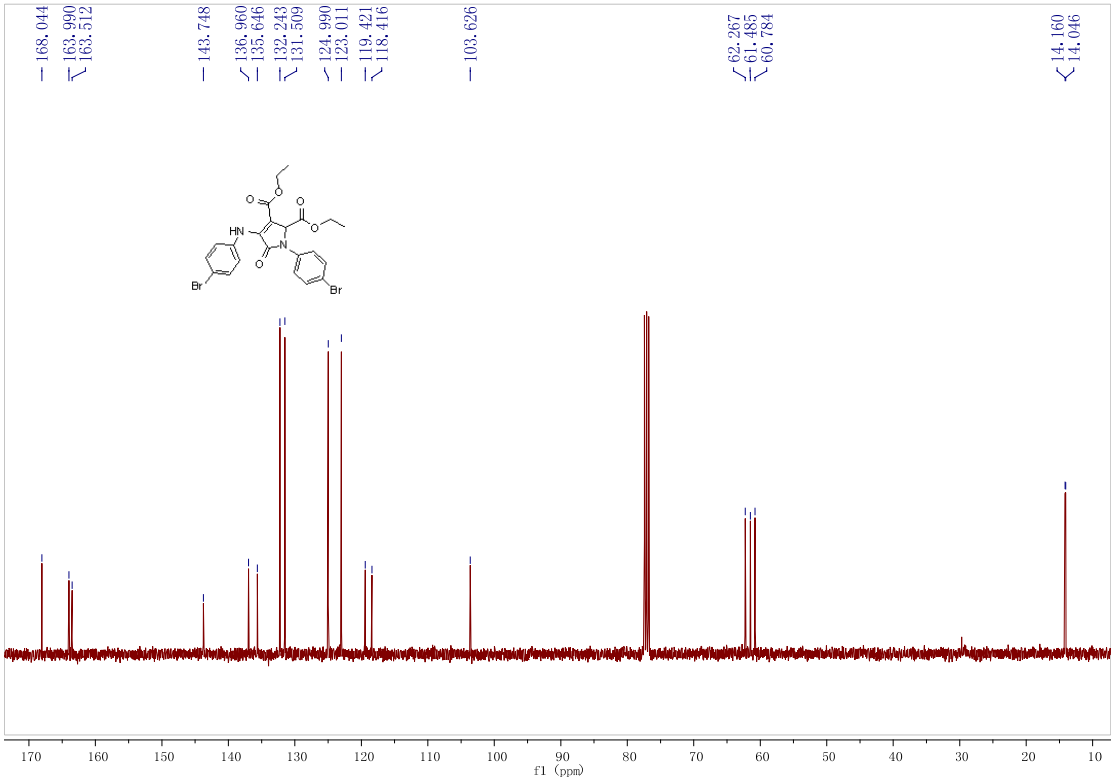
^{1}H NMR and ^{13}C NMR spectrum for diethyl 1- (3- chlorophenyl)- 4- ((3- chlorophenyl) amino)- 5- oxo- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (**3j**) ($CDCl_3$ as solvent)



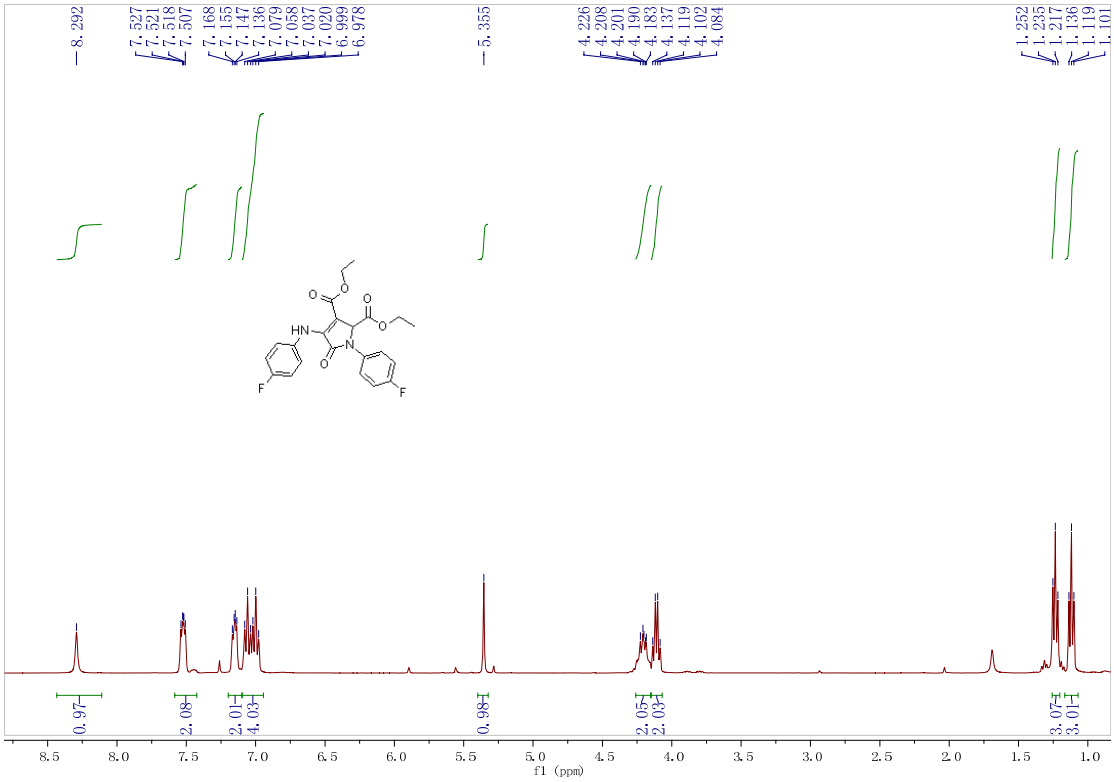


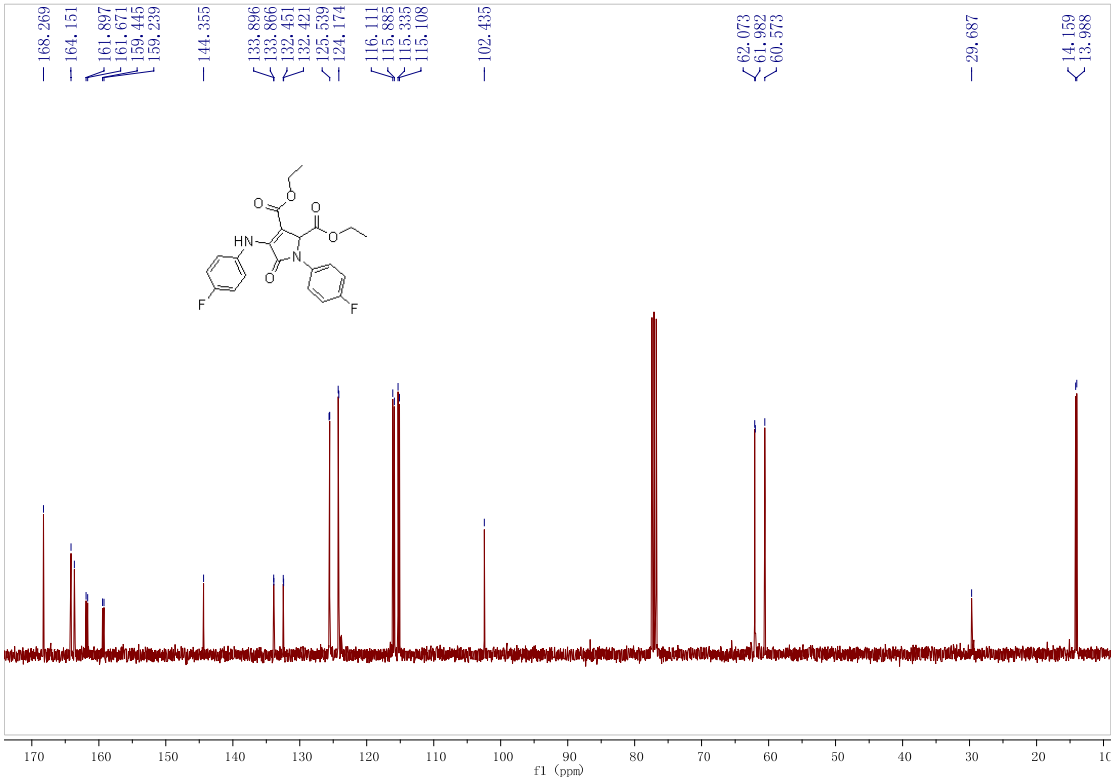
^{1}H NMR and ^{13}C NMR spectrum for Diethyl 1- (4- bromophenyl)- 4- ((4- bromophenyl) amino)- 5- oxo-2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (**3k**) ($CDCl_3$ as solvent)



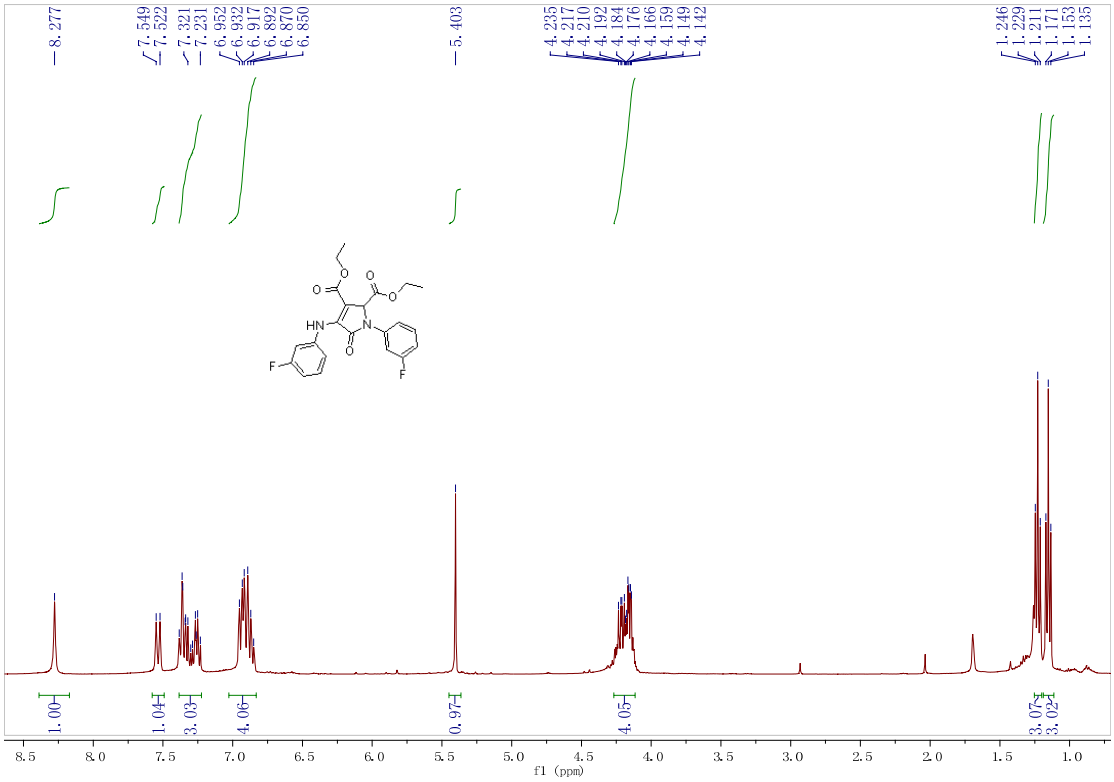


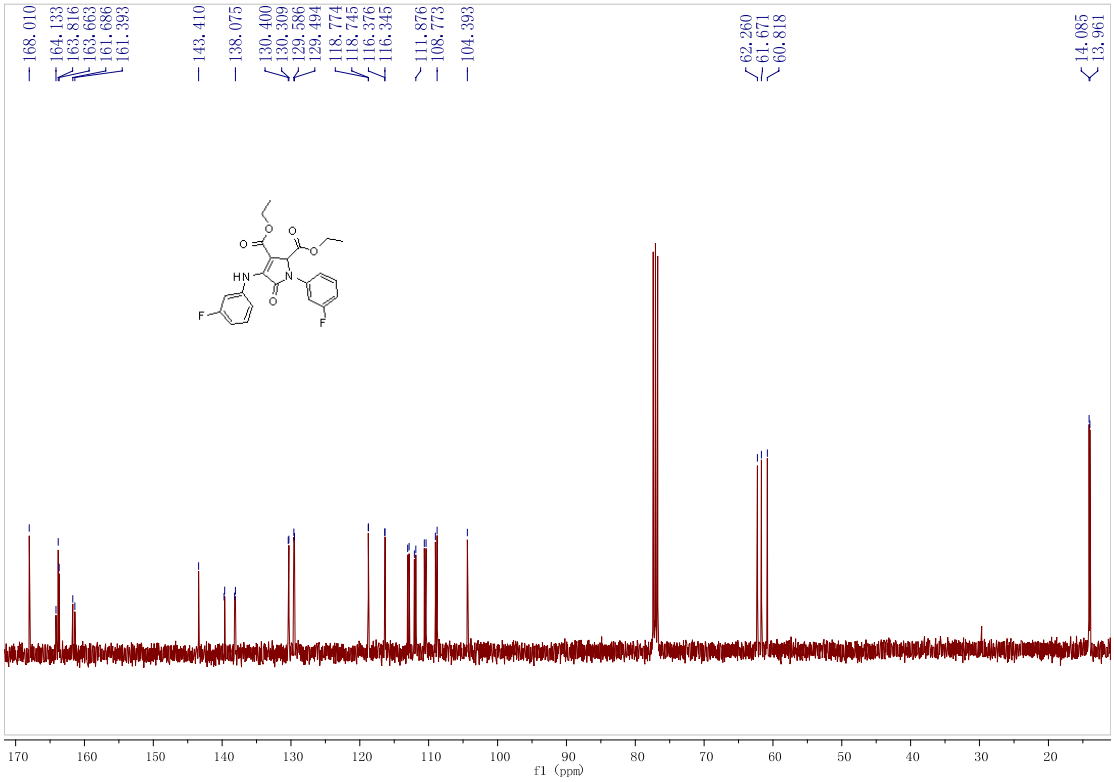
^{1}H NMR and ^{13}C NMR spectrum for diethyl 1- (4- fluorophenyl)- 4- ((4- fluorophenyl) amino)- 5- oxo- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (**3l**) ($CDCl_3$ as solvent)



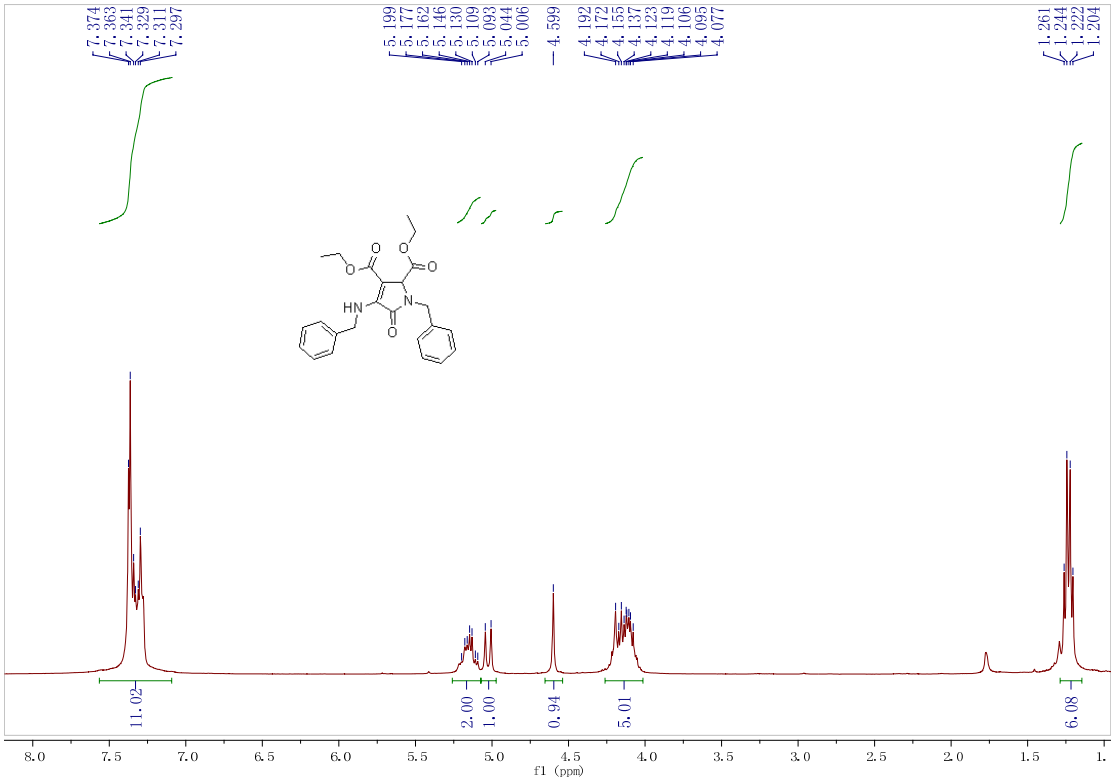


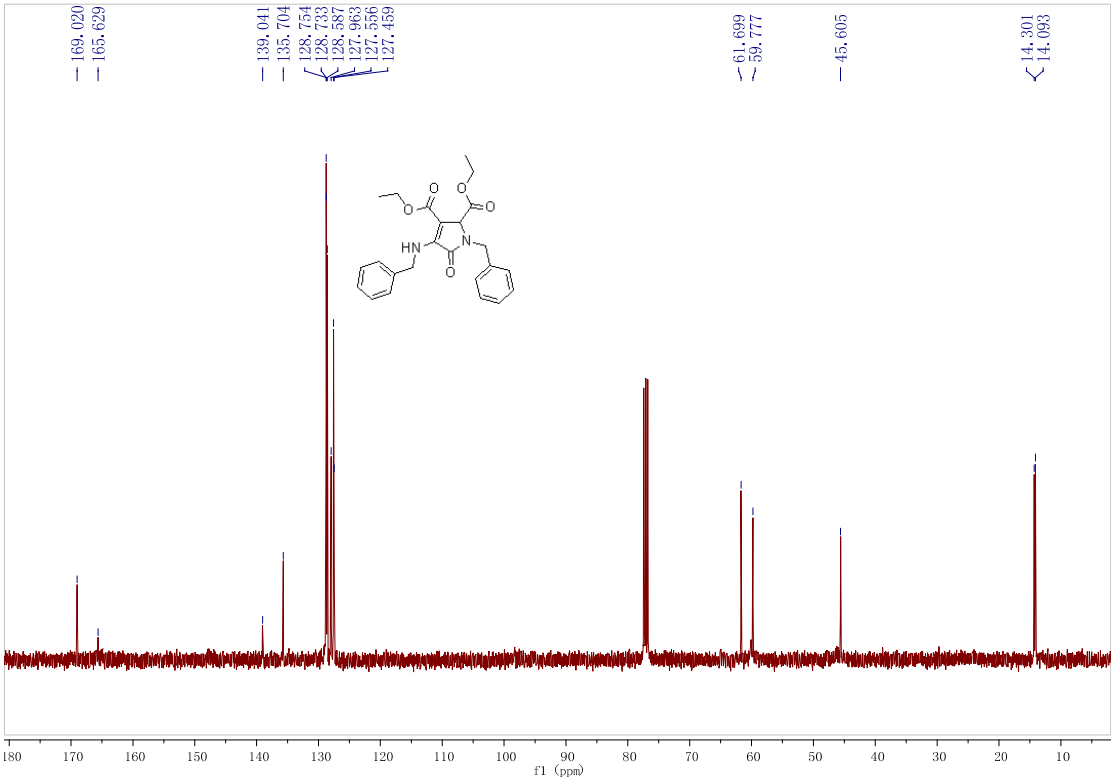
^{1}H NMR and ^{13}C NMR spectrum for diethyl 1- (3- fluorophenyl)- 4- ((3- fluorophenyl) amino)- 5- oxo- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (**3m**) ($CDCl_3$ as solvent)



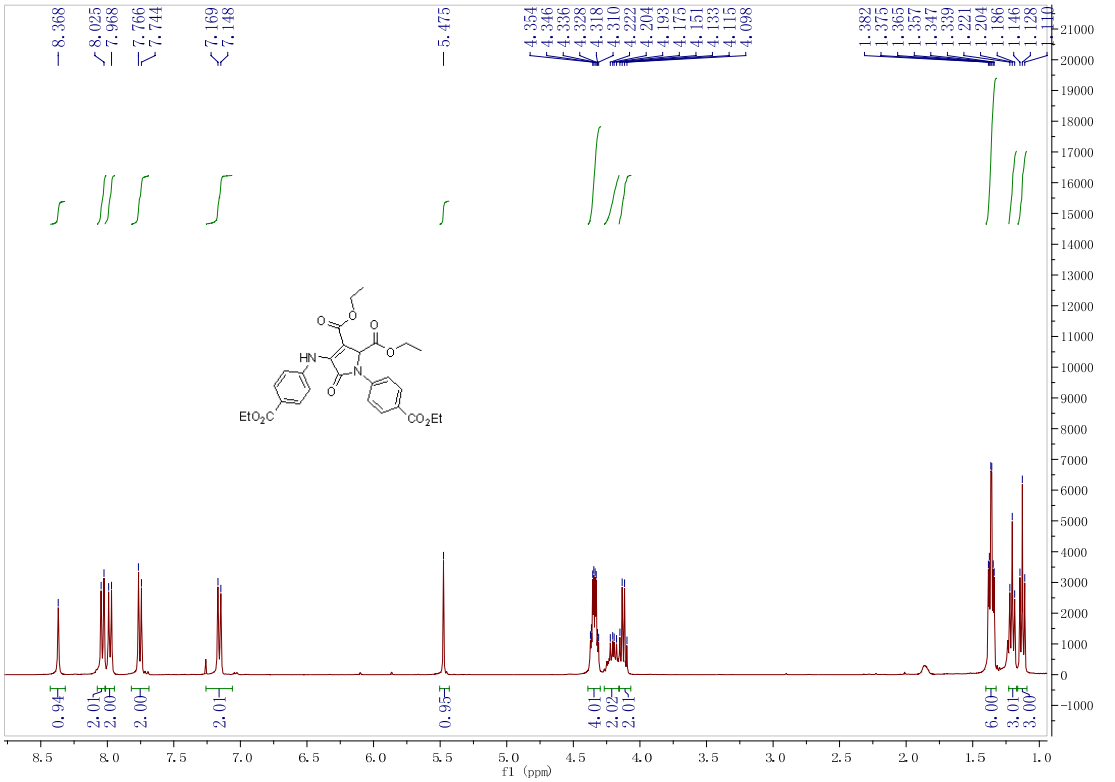


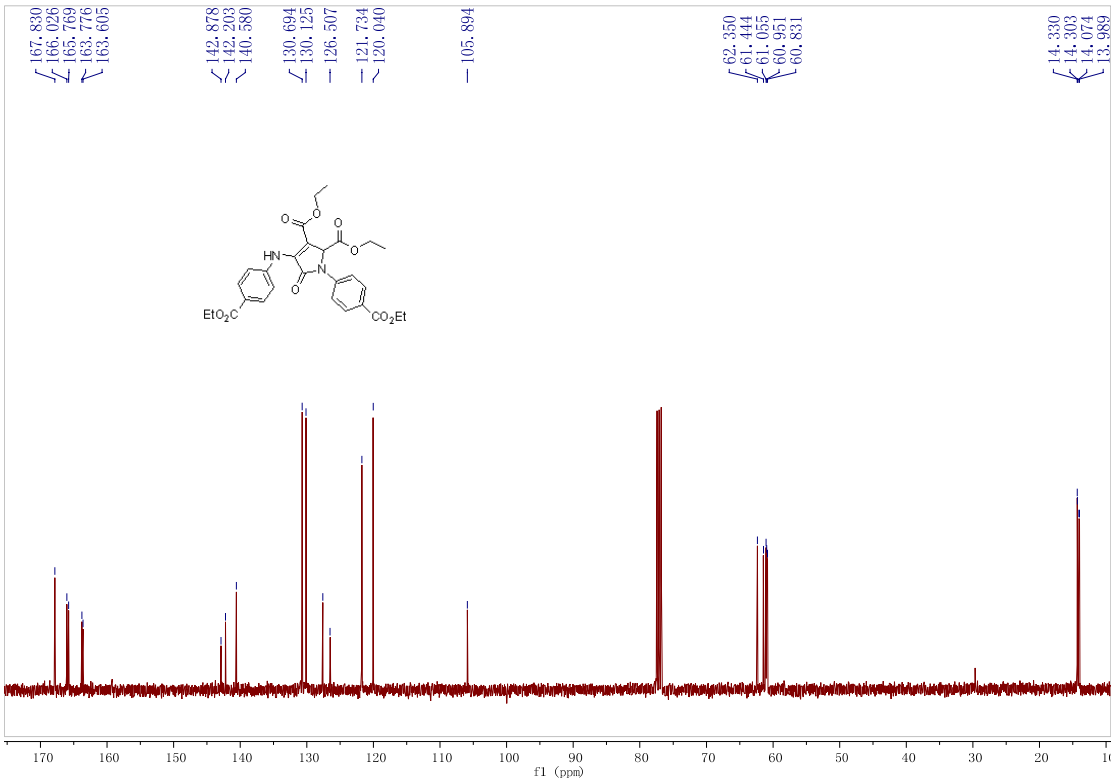
^{1}H NMR and ^{13}C NMR spectrum for diethy 1- benzyl- 4- (benzylamino)- 5- oxo-2, 5-dihydro- 1 H-pyrrole- 2, 3- dicarboxylate (**3n**) ($CDCl_3$ as solvent)



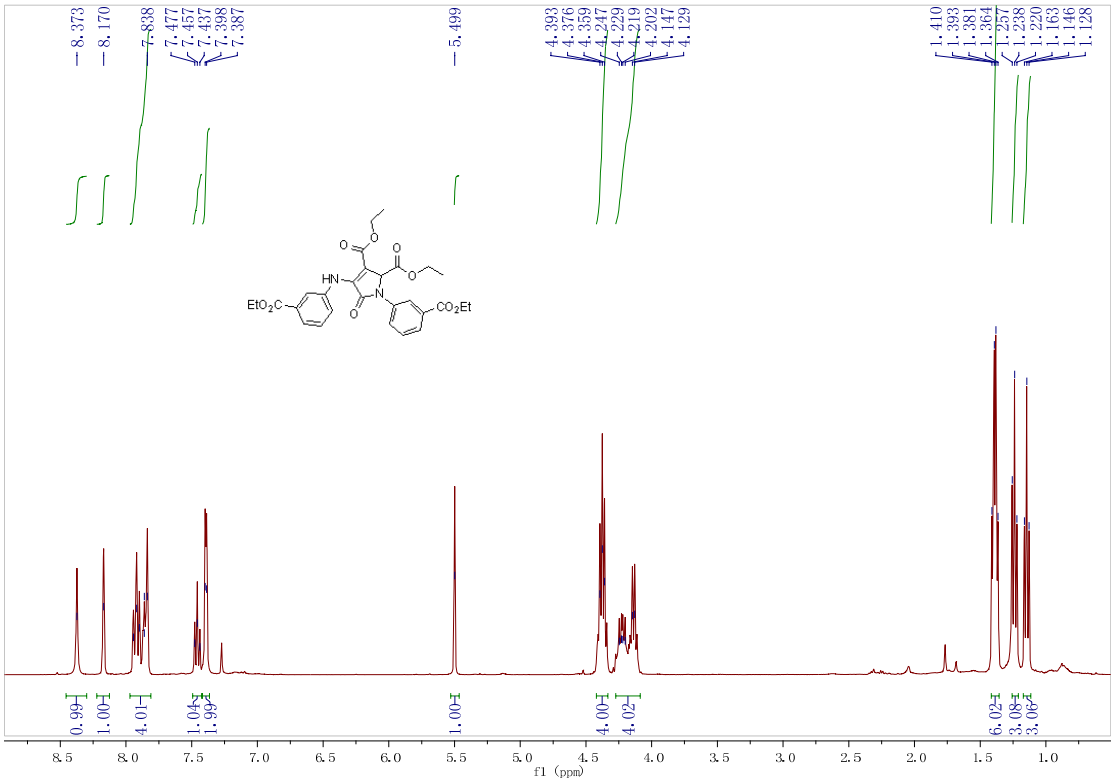


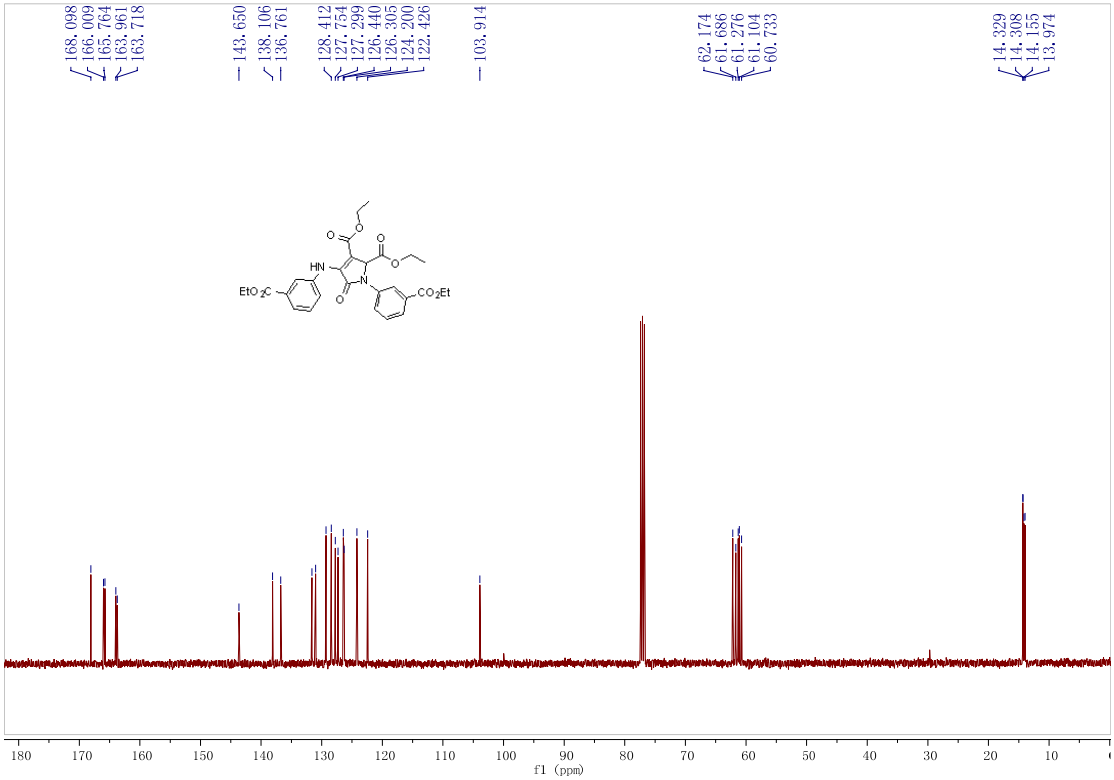
^{1}H NMR and ^{13}C NMR spectrum for diethy 1- (4- (ethoxycarbonyl) phenyl)- 4- ((4- (ethoxycarbonyl) phenyl) amino)- 5- oxo- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (**3o**) ($CDCl_3$ as solvent)



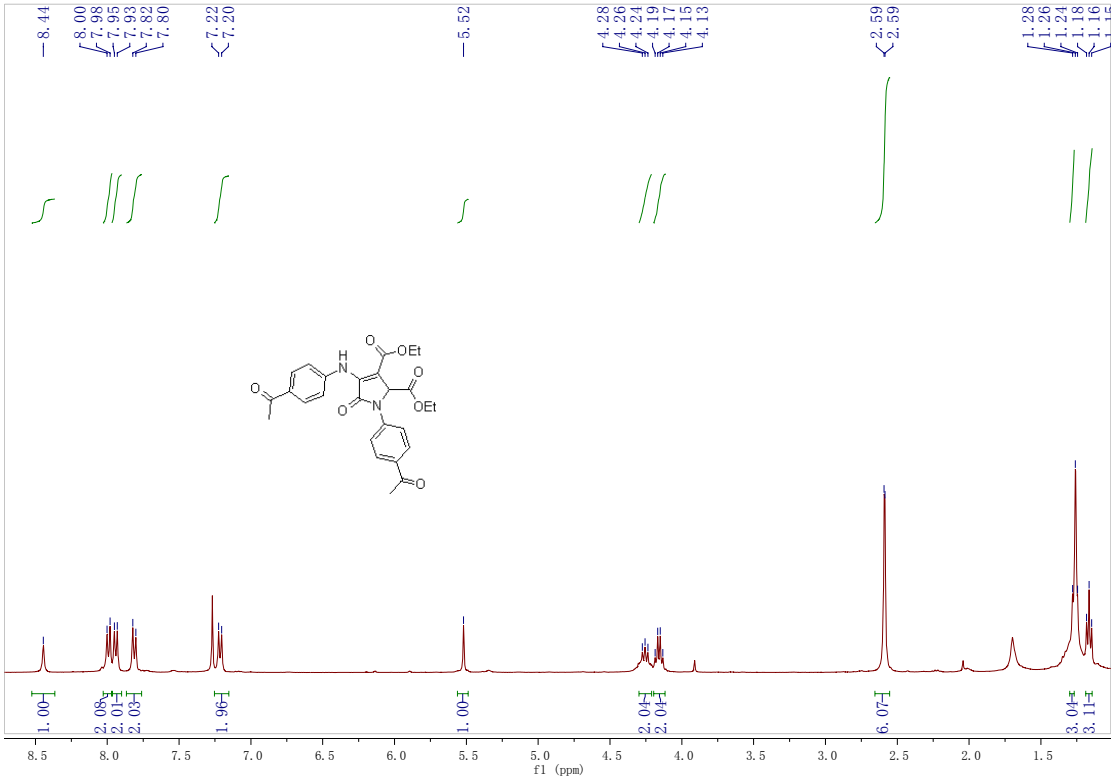


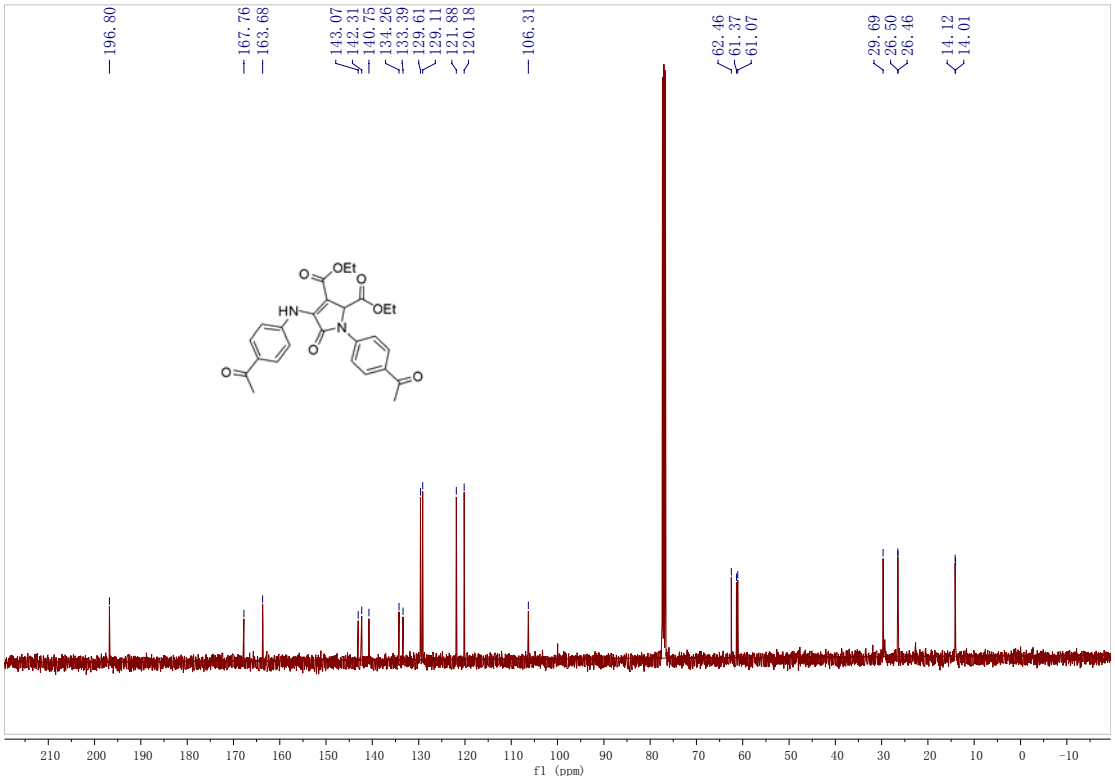
^{1}H NMR and ^{13}C NMR spectrum for diethy 1- (3- (ethoxycarbonyl) phenyl)- 4- ((3- (ethoxycarbonyl) phenyl) amino)- 5- oxo- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (**3p**) ($CDCl_3$ as solvent)



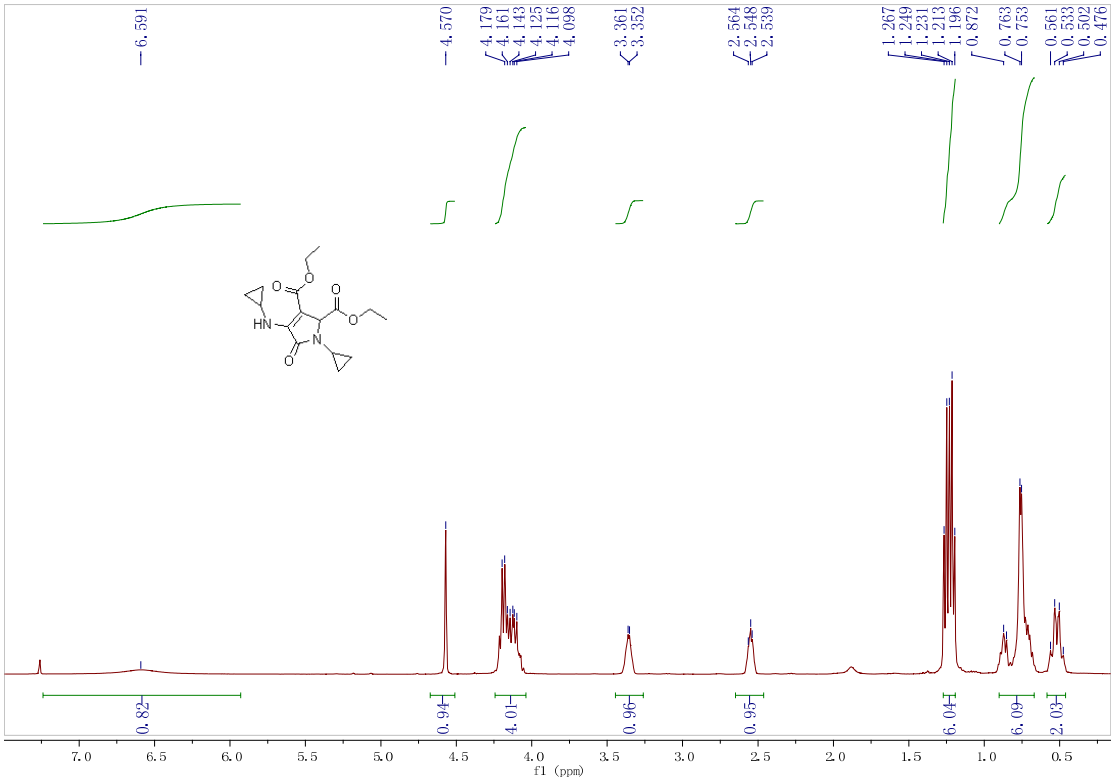


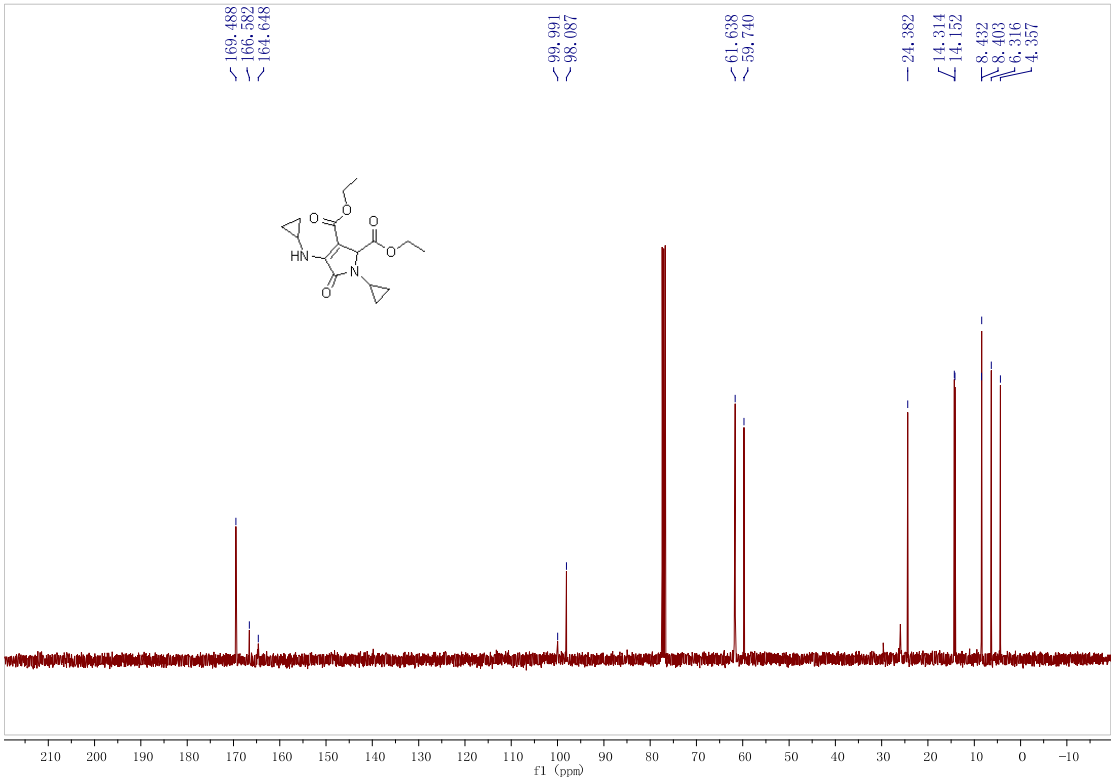
^{1}H NMR and ^{13}C NMR spectrum for diethyl 1- (4- acetylphenyl)- 4- ((4- acetylphenyl) amino)- 5- oxo- 2, 5- dihydro-1 H- pyrrole- 2, 3- dicarboxylate (**3q**) ($CDCl_3$ as solvent)



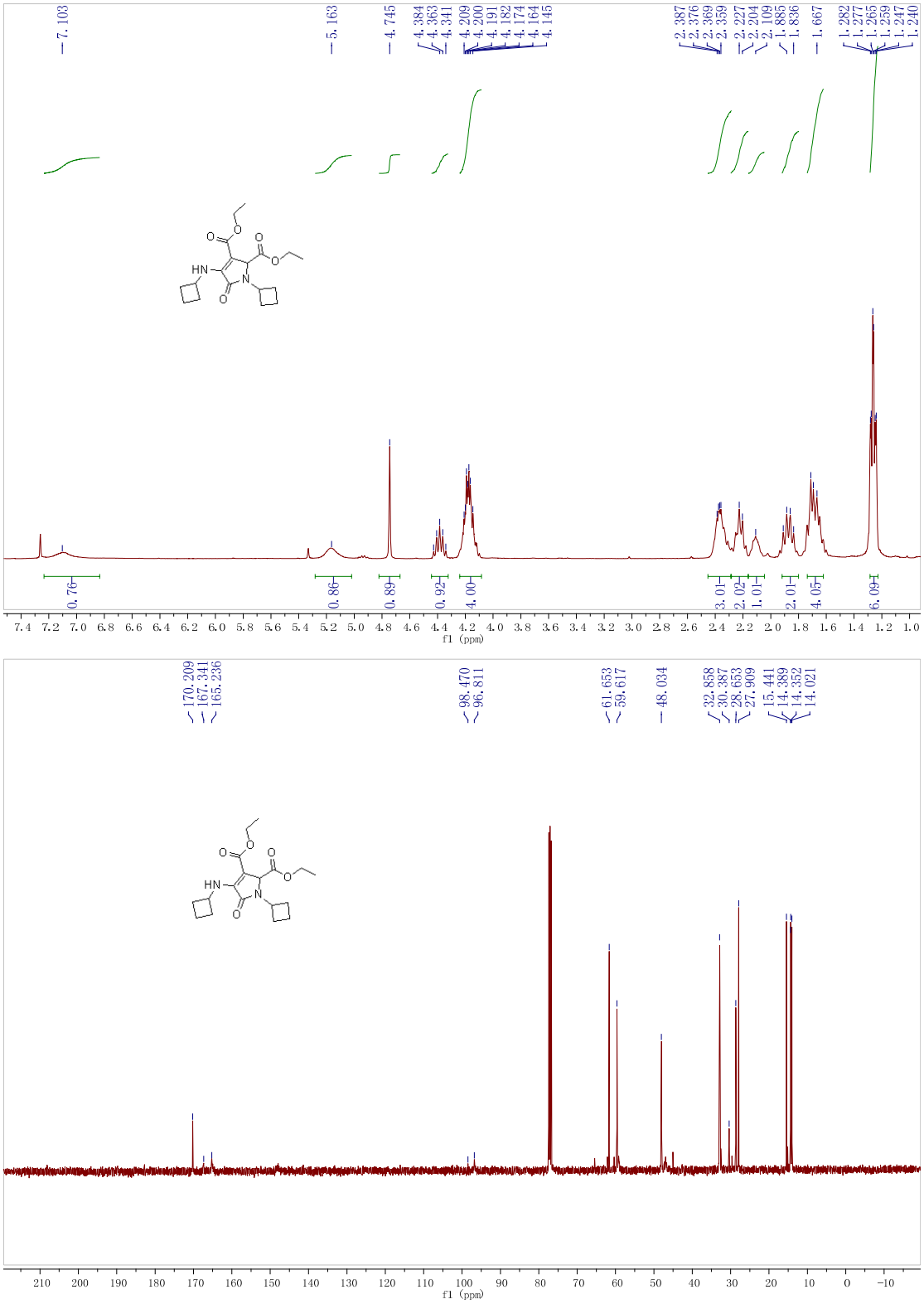


^{1}H NMR and ^{13}C NMR spectrum for diethy 1- cyclopropyl- 4- (cyclopropylamino)- 5- oxo- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (**3s**) ($CDCl_3$ as solvent)

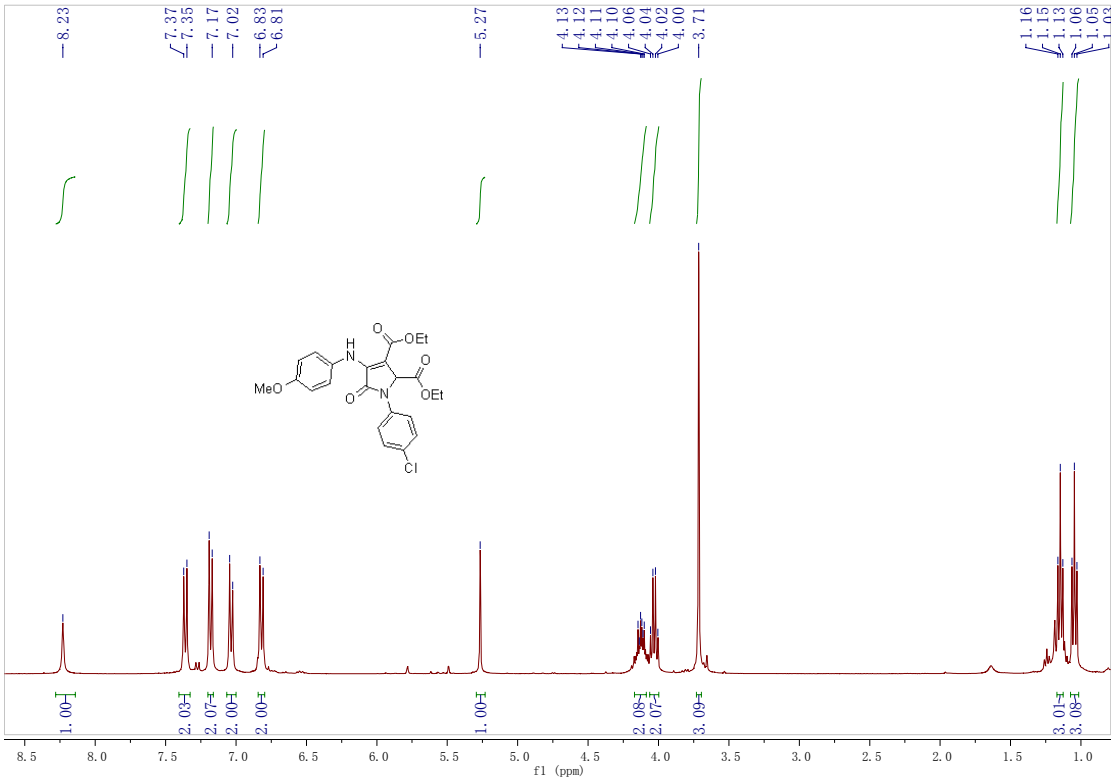


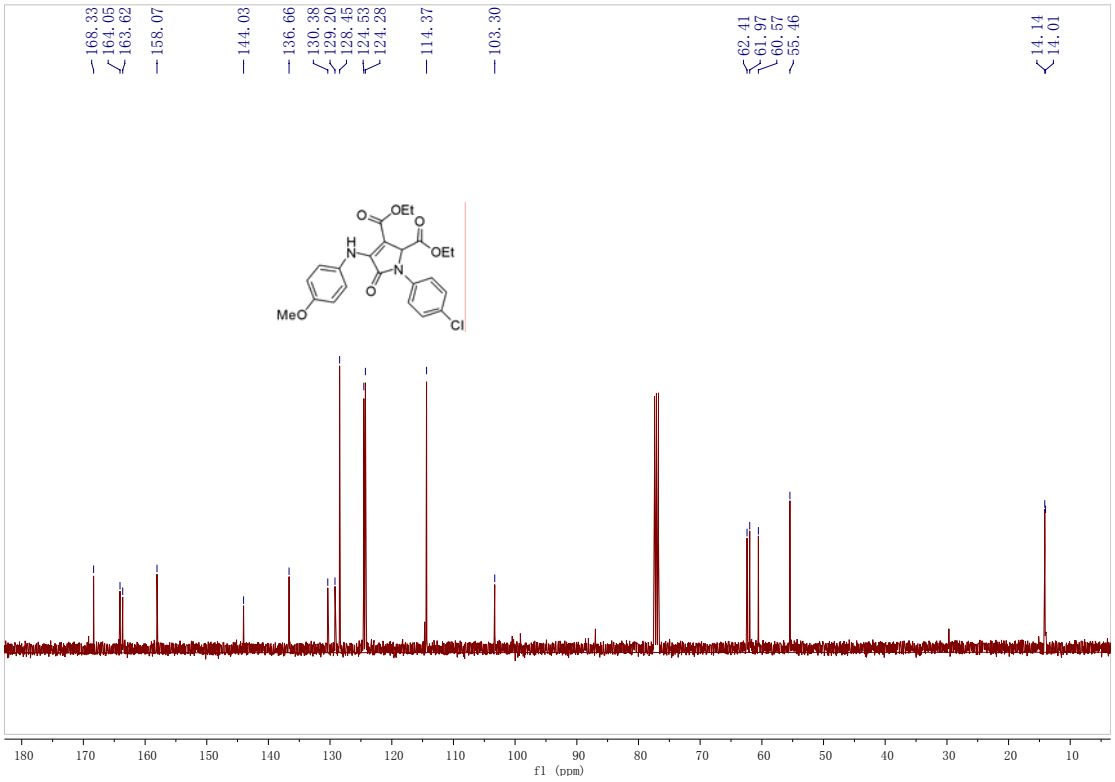


^{1}H NMR and ^{13}C NMR spectrum for diethy 1- cyclobutyl- 4- (cyclobutylamino)- 5- oxo- 2, 5- dihydro- 1 H- pyrrole- 2, 3- dicarboxylate (**3t**) ($CDCl_3$ as solvent)

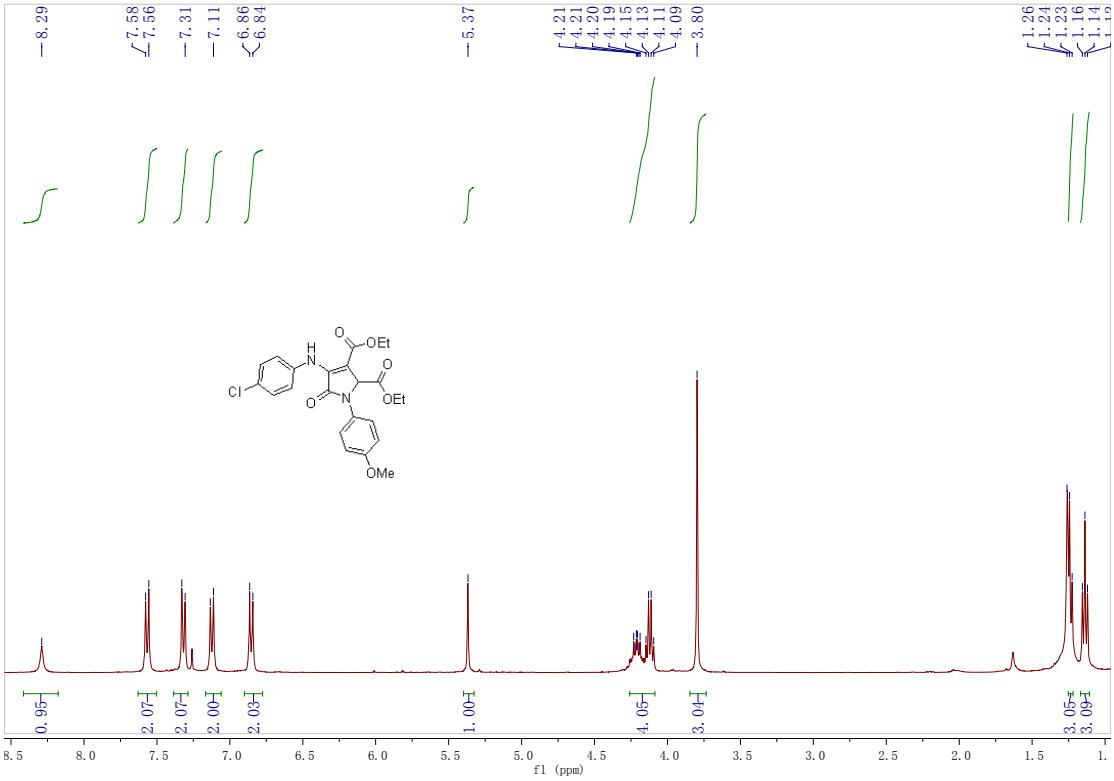


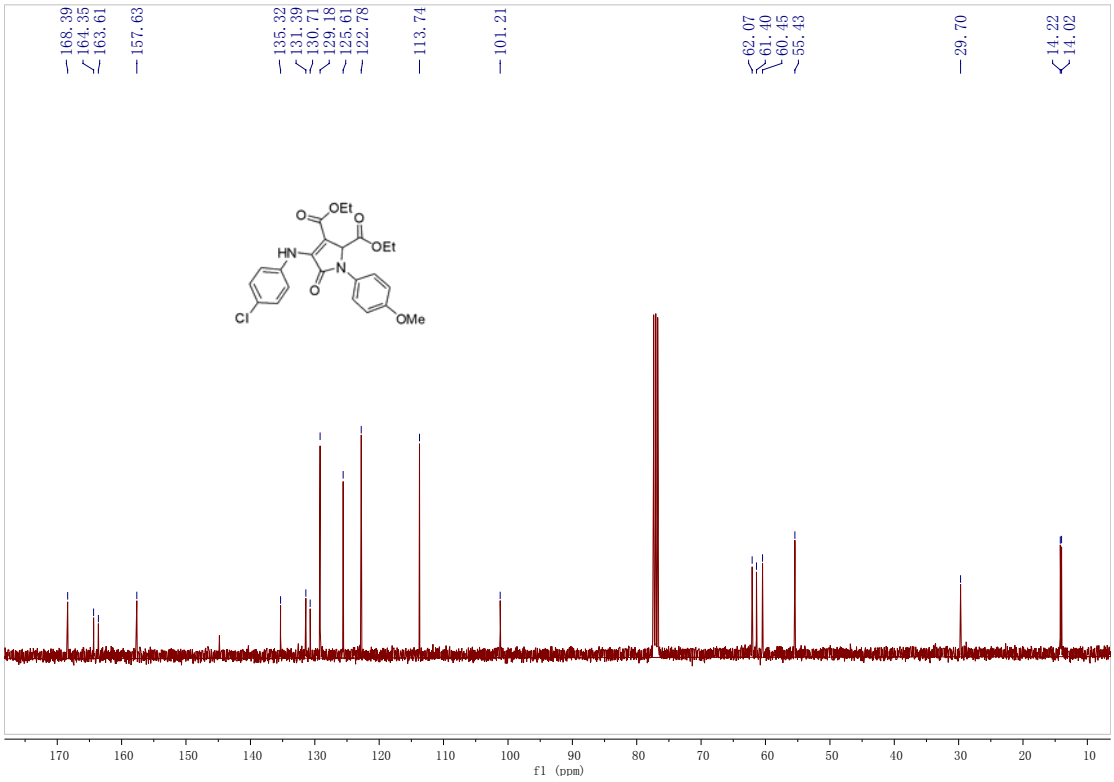
^{1}H NMR and ^{13}C NMR spectrum for diethyl 1- (4- chlorophenyl)- 4- ((4- methoxyphenyl) amino)- 5- oxo- 2, 5- dihydro- 1H- pyrrole- 2, 3- dicarboxylate (**3u**) ($CDCl_3$ as solvent)



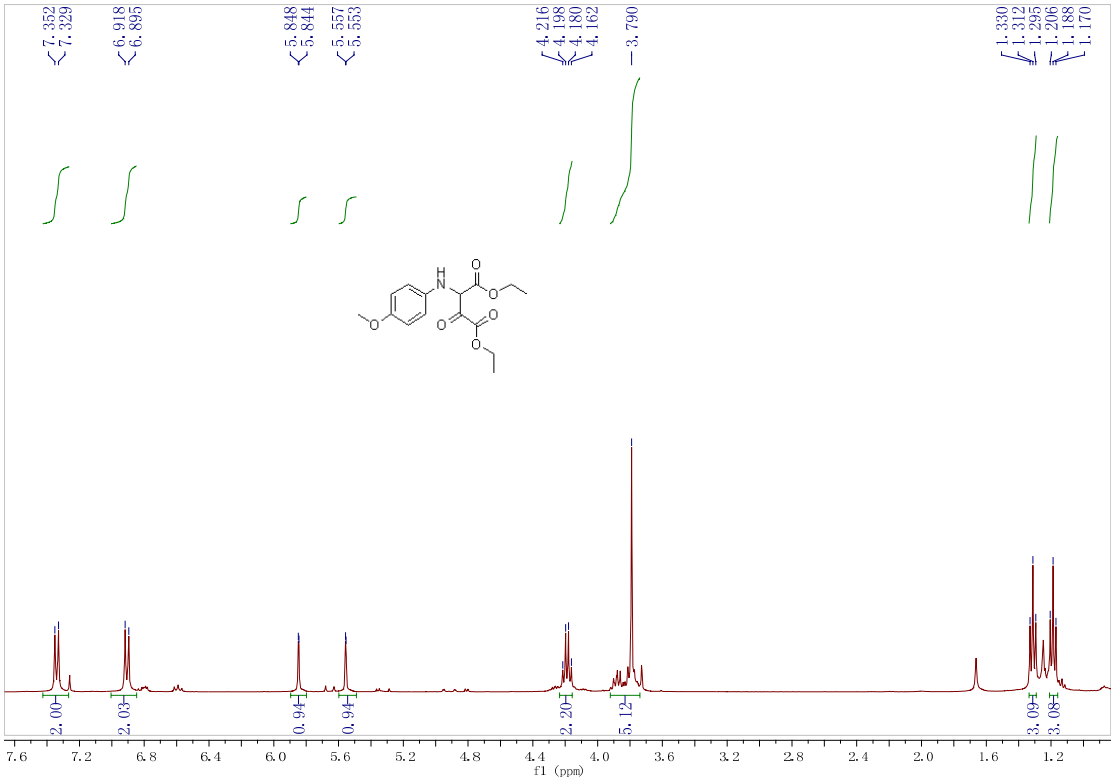


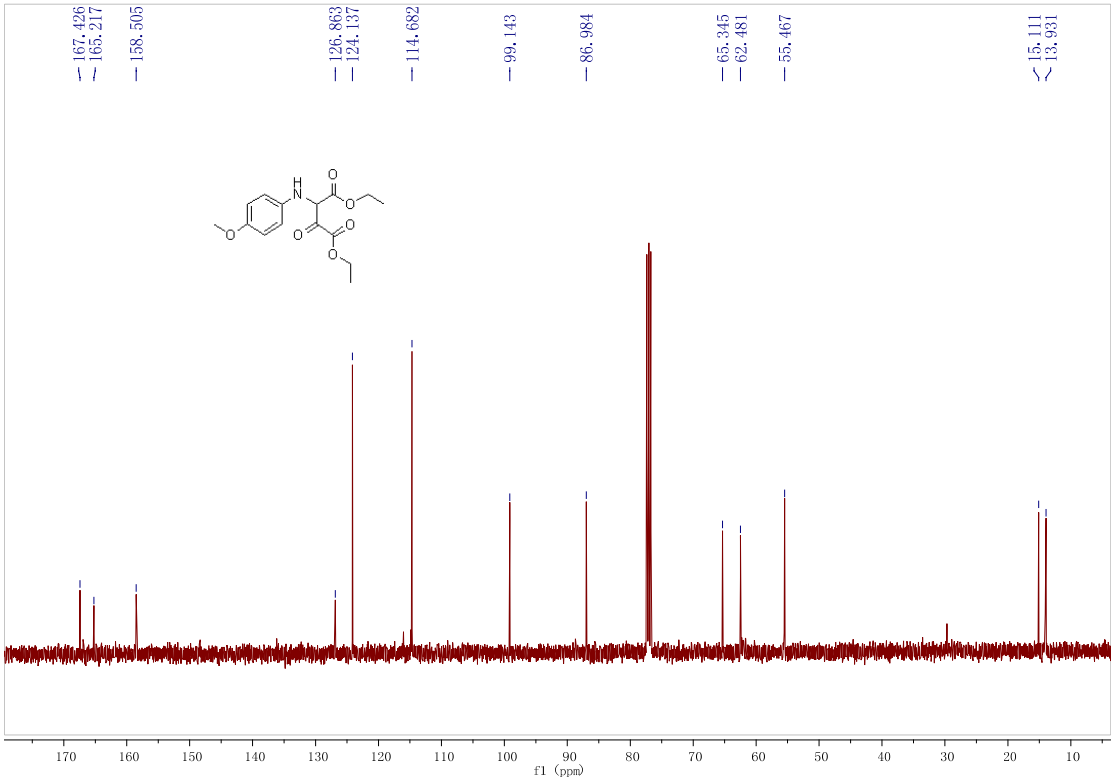
^{1}H NMR and ^{13}C NMR spectrum for diethyl 4- ((4- chlorophenyl) amino)- 1- (4- methoxyphenyl)- 5- oxo- 2, 5- dihydro- 1H- pyrrole- 2, 3- dicarboxylate (**3v**) ($CDCl_3$ as solvent)





^{1}H NMR and ^{13}C NMR spectrum for diethyl 2- ((4- methoxyphenyl) amino)- 3- oxosuccinate (**D-a**) ($CDCl_3$ as solvent)





^{1}H NMR and ^{13}C NMR spectrum for Ethyl 2- ((4- methoxyphenyl) amino)- 2- oxoacetate (**I-a**) ($CDCl_3$ as solvent)