Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Construction of Pyrazolone Analogues via Rhodium-Catalyzed C-H Activation from Pyrazolones and Non-activated Free Allyl Alcohols

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Contents of Supporting Information

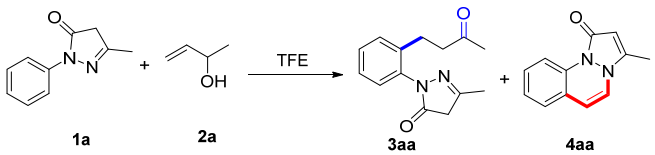
1. General Methods

NMR data were obtained for ^{1}H at 400 MHz or 600 MHz, and for ^{13}C at 100 MHz or 151 MHz. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard in $CDCl_3$ solution. ESI HRMS was recorded on a Waters SYNAPT G2 and Water XEVO G2 Q-ToF. UV detection was monitored at 220 nm. TLC was performed on glass-backed silica plates. Column chromatography was performed on silica gel (200-300 mesh), eluting with ethyl acetate and petroleum ether.

2. Optimization of the Reaction Conditions

We initiated our investigation by examining the reaction parameters for the coupling of 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one **1a** and but-3-en-2-ol **2a**, the results are summarized in the Table S1. No product could be formed in the absence of transition metal catalysts and silver salt as additive (entry 1). To our delight, the C-C bond cleavage pyrazolo [1,2-α] cinnoline derivative **4aa** was obtained in 27% yield along with slight alkylated γ-ketones substituted Edaravone **3aa** on the attendance of $[Cp^*RhCl_2]_2$ and silver salt in TFE for a very short reaction time (entry 2). After screening copious silver and copper salts, the yields were not enhanced evidently (entries 3-6). The addition of oxidative would cause decompose of substrates. After that, we endeavored to add some acid or base in the basic of $AgNTf_2$, and the 1-AdCOOH gave the product **4aa** with the highest yield compared with other acids and generated product **3aa** with a little amount (entries 7-9). The low yields were acquired by employing $[RuCl_2(p\text{-cymene})]_2$ as catalyst (entry 10). The other frequently used catalysts for this coupling reaction, such as $[Cp^*IrCl_2]_2$ and $[Cp^*CoCl_2]_2$, could not provide the desired products **3aa** and **4aa** (entries 11 and 12). In addition, changing reaction temperature gave rise to poor results under the $Cp^*Rh(CH_3CN)_3(SbF_6)_2$ catalyst system (entries 13 and 14). The selectivity of two products was not improved when we increased the acid (1-AdCOOH or TsOH) to 5.0 equiv (entries 15 and 16). Moreover, AcOH served as solvent gave 82% total yield while 5.0 equiv of phenoxyacetic acid was added. Meanwhile, the products were obtained with a little decreased yield without phenoxyacetic acid (entries 17 and 18). In addition, there were no products formed when TFA was used as solvent whether the phenoxyacetic acid was existed (entries 19 and 20). Moreover, the oxygen gas did not provide advantage to the product selectivity, the ratio of **3aa** to **4aa** was 1.2:1 (entry 21). Finally, the large-scale reaction was performed with slightly reduce total yield (entry 22).

Table S1. Optimization of the Reaction Conditions[a]



1a **2a** **3aa** **4aa**

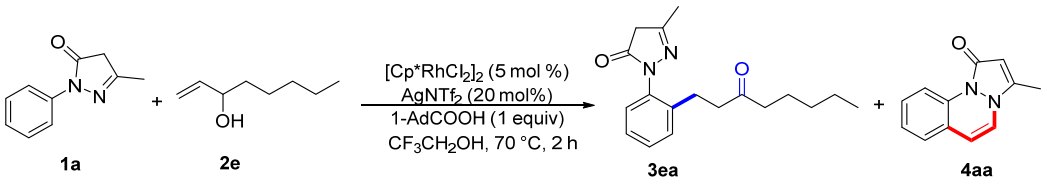
Entry	Catalyst	Additive/[equiv.]	Temp./ °C	Time/ h	Yield of **3aa**[b]	Yield of **4aa**[b]
1	--	--	80	12	0	0
2	$[Cp^*RhCl_2]_2$	$AgNTf_2$ /0.2	80	4	5%	27%
3	$[Cp^*RhCl_2]_2$	$AgSbF_6$ /0.2	80	4	7%	21%
4	$[Cp^*RhCl_2]_2$	AgOTf/0.2	80	4	7%	23%
5	$[Cp^*RhCl_2]_2$	AgOAc /0.2	80	4	decompose	N.D

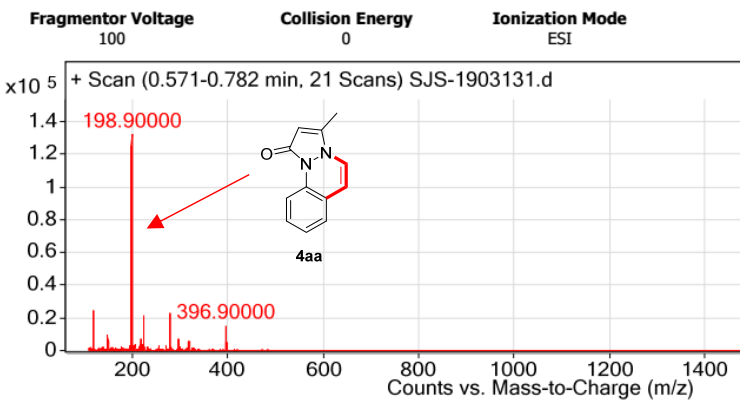
6	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2·H_2O$ /0.3	80	4	decompose	decompose
7	**$[Cp^*RhCl_2]_2$**	**$AgNTf_2$ /0.2, 1-AdCOOH/1**	80	**4**	**6%**	**47%**
8	$[Cp^*RhCl_2]_2$	$AgNTf_2$ /0.2, PivOH/1	80	4	7%	36%
9	$[Cp^*RhCl_2]_2$	$AgNTf_2$ /0.2, NaOAc/1	80	4	18%	N.D
10	$[RuCl_2(p\text{-cymene})]_2$	$AgNTf_2$ /0.2, 1-AdCOOH/1	80	4	7%	45%
11	$[Cp^*IrCl_2]_2$	$AgNTf_2$ /0.2, 1-AdCOOH/1	80	4	0%	0%
12	$[Cp^*CoCl_2]_2$	$AgNTf_2$ /0.2, 1-AdCOOH/1	80	4	0%	0%
13	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$	Phenoxyacetic acid /5	60	12	23%	12%
14	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$	Phenoxyacetic acid /5	100	12	38%	19%
15	$[Cp^*RhCl_2]_2$	$AgNTf_2$ /0.2, 1-AdCOOH/5	80	12	38%	46%
16	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$	TsOH /5	70	12	N. D	N. D
17[c]	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$	Phenoxyacetic acid /5	70	12	32%	50%
18[c]	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$	--	70	12	33%	34%
19[d]	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$	Phenoxyacetic acid /5	70	12	N. D	N. D
20[d]	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$	--	70	12	N. D	N. D
21[e]	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$	Phenoxyacetic acid /5	70	12	39%	32%
22[f]	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$	Phenoxyacetic acid /5	70	12	44%	39%

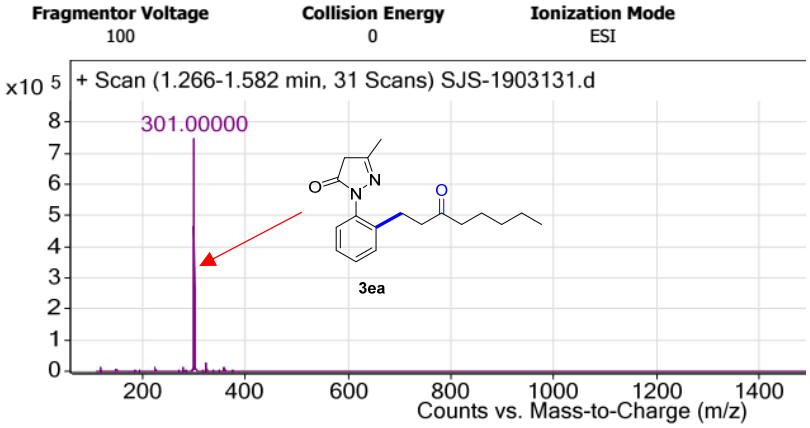
[a] Reaction conditions unless otherwise specified: **1a** (0.05 mmol), **2a** (5 equiv), catalyst (5 mol %), CF_3CH_2OH (0.5 mL), under air. [b] Isolated yield. [c] AcOH as solvent. [d] TFA as solvent. [e] under 1.0 atm of O_2. [f] 2.0 mmol of **1a**.

3. Mechanism Study

5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **1a** (34.8 mg, 0.2 mmol), oct-1-en-3-ol **2e** (154 uL, 5.0 equiv.), $[Cp^*RhCl_2]_2$ (6.0 mg, 5 mol %), $AgNTf_2$ (15.5 mg, 0.2 equiv.), 1-AdCOOH (36.0 mg, 1 equiv.) were stirred in CF_3CH_2OH (2.0 mL) at 70 °C for 2 h. After completion, the reaction mixture was detected by LCMS, the product **3ea** and **4aa** were exist.

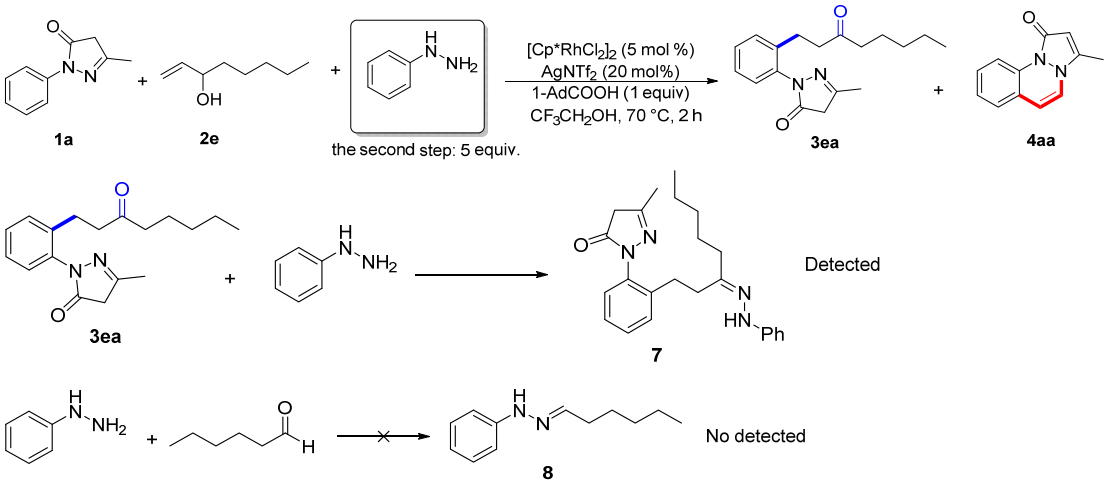


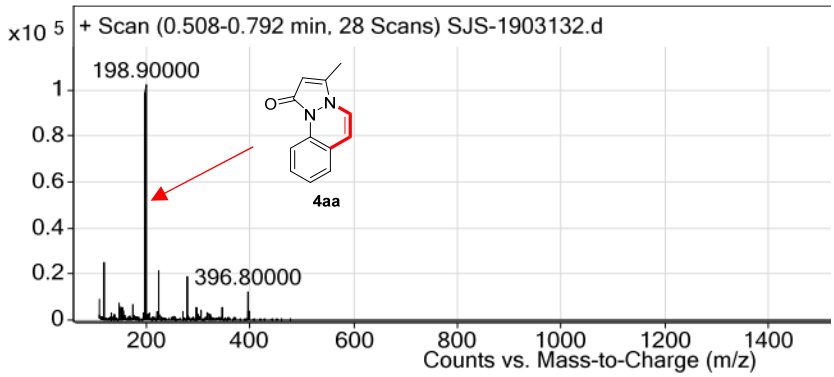


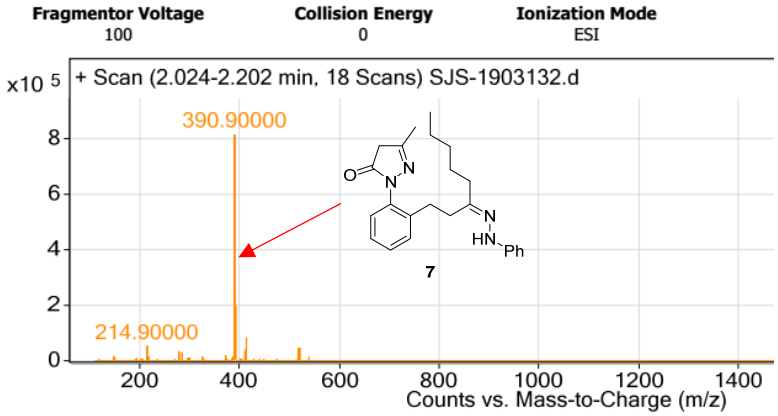


Scheme S1

5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **1a** (34.8 mg, 0.2 mmol), oct-1-en-3-ol **2e** (154 μL, 5.0 equiv.), $[Cp^*RhCl_2]_2$ (6.0 mg, 5 mol %), $AgNTf_2$ (15.5 mg, 0.2 equiv.), 1-AdCOOH (36.0 mg, 1 equiv.) were stirred in CF_3CH_2OH (2.0 mL) at 70 °C. After 2 hours, phenylhydrazine (98 μL, 5.0 equiv) was added in the mixture to stir for another 30 min. As a result, the released acetone was trapped by 2,4-dinitrophenylhydrazine. The corresponding product **4aa** and compound **7** was detected by LCMS meanwhile the compound **8** was not detected.



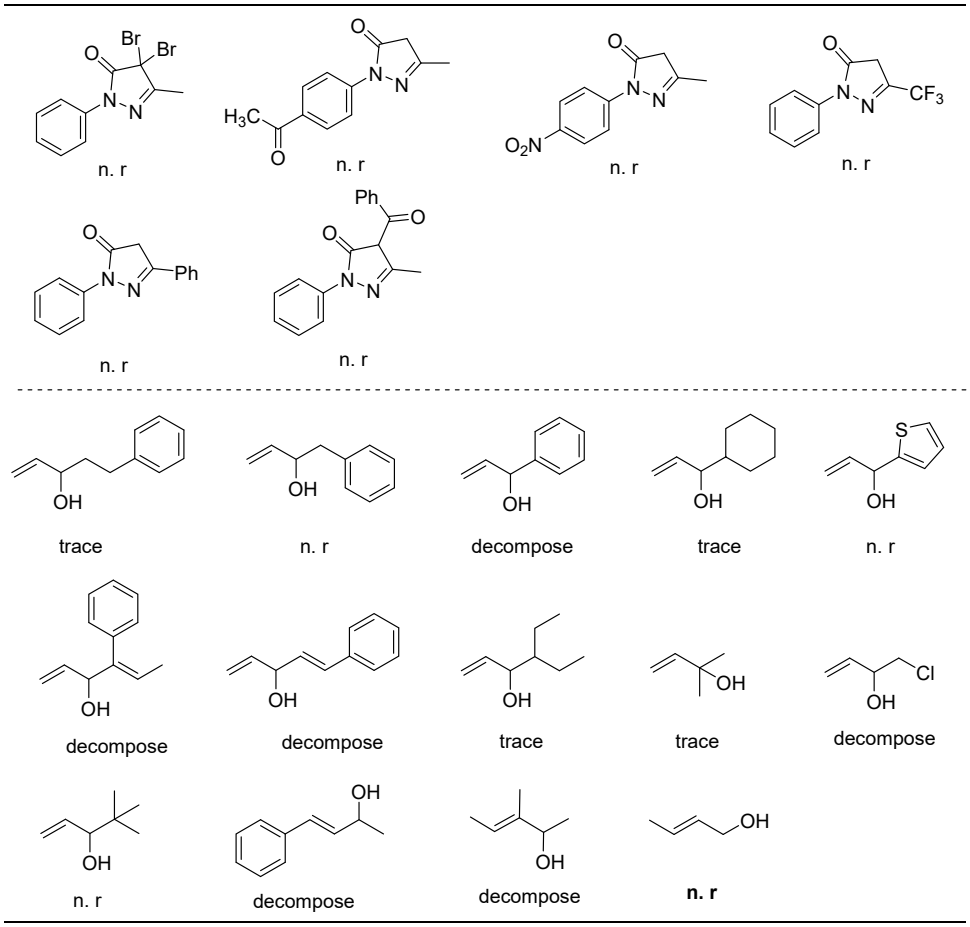




Scheme S2

4. Invalid Examples

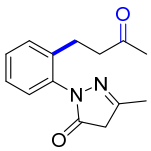
However, some other substrates such as acetyl and nitro group substituted pyrazols, trifluoromethyl or phenyl group at C-3 position could not be tolerated under the optimized reaction conditions. In addition, the allyl alcohol bearing other substituents were not tolerated, probably due to the steric hindrance influence the coordination of transition metal catalysts with pyrazolones (Scheme S3).

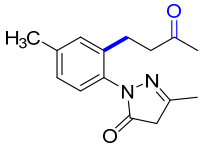


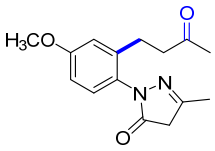
Scheme S3

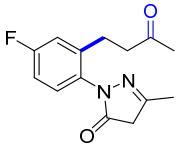
5. General Procedure for Synthesis of γ-Ketones Substituted Edaravone and Pyrazolo [1,2-α] Cinnoline Derivatives and Characterization Data

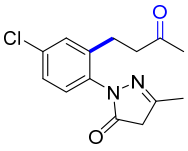
5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **1a** (34.8 mg, 0.2 mmol), but-3-en-2-ol **2a** (87 uL, 5.0 equiv), Cp*Rh$(CH_3CN)_3(SbF_6)_2$ (8.4 mg, 5 mol %), phenoxyacetic acid (152.2 mg, 5.0 equiv.) were stirred at seal tube with CF_3CH_2OH (2.0 mL) at 70 °C for 12 h. After completion, the reaction mixture was purified by flash chromatography eluting with ethyl acetate and petroleum ether (3:1) to give the products **3aa** as a light brown oil (24.9 mg, 51%) and **4aa** as a light yellow oil (18.2 mg, 46%).

5-methyl-2-(2-(3-oxobutyl)phenyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3aa**). 12 h, light brown oil, 51% yield.  ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (tt, *J* = 4.3, 2.3 Hz, 4H), 3.40 (s, 2H), 2.88~2.82 (m, 2H), 2.79 ~2.73 (m, 2H), 2.17 (s, 3H), 2.11 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 171.8, 156.4, 138.5, 135.3, 130.1, 128.9, 127.4, 127.2, 44.3, 41.6, 30.0, 25.4, 17.1 ppm. ESI HRMS: calcd. for $C_{14}H_{16}N_2O_2$+H 245.1290, found 245.1289.

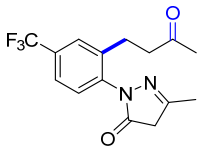
5-methyl-2-(4-methyl-2-(3-oxobutyl)phenyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3ba**). 12 h, light brown oil, 42% yield.  ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.5 Hz, 1H), 7.07 (d, *J* = 7.1 Hz, 2H), 3.38 (s, 2H), 2.82~2.78 (m, 2H), 2.77~2.71 (m, 2H), 2.33 (s, 3H), 2.15 (s, 3H), 2.11 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.0, 171.9, 156.2, 138.9, 138.2, 132.7, 130.7, 127.9, 127.3, 44.4, 41.6, 30.0, 25.4, 21.2, 17.1 ppm. ESI HRMS: calcd. for $C_{15}H_{18}N_2O_2$+H 259.1447, found 259.1443.

2-(4-methoxy-2-(3-oxobutyl)phenyl)-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (**3ca**), 12 h, light brown oil, 50% yield.  ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 6.4, 1.9 Hz, 2H), 7.23 (s, 1H), 3.40 (s, 2H), 2.85~2.79 (m, 2H), 2.76~2.71 (m, 2H), 2.17 (s, 3H), 2.11 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8, 172.1, 159.8, 156.2, 140.3, 128.9, 128.1, 115.3, 112.4, 55.4, 44.3, 41.5, 30.0, 25.6, 17.1 ppm. ESI HRMS: calcd. for $C_{15}H_{18}N_2O_3$+H 275.1396, found 275.1393.

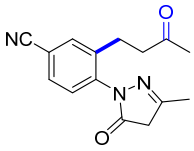
2-(4-fluoro-2-(3-oxobutyl)phenyl)-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (**3da**), 12 h, light brown oil, 57% yield.  ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26~7.22 (m, 1H), 6.98 (ddt, *J* = 11.6, 8.2, 4.0 Hz, 3H), 3.39 (s, 2H), 2.85~2.80 (m, 2H), 2.77 ~2.72 (m, 2H), 2.16 (s, 3H), 2.12 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.4, 171.9, 163.6 (d, *J* = 247.0 Hz), 156.6, 141.3 (d, *J* = 8.0 Hz), 131.3 (d, *J* = 3.0 Hz), 129.3 (d, *J* = 9.0 Hz), 116.8 (d, *J* = 23.0 Hz), 114.2 (d, *J* = 23.0 Hz), 43.8, 41.5, 30.0, 25.3, 25.3, 17.1 ppm. ESI HRMS: calcd. for $C_{14}H_{15}FN_2O_2$+H 263.1196, found 263.1198.

2-(5-chloro-2-(3-oxobutyl)phenyl)-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (**3ea**), 12 h, light brown oil, 42% yield.  ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 1H), 7.24~7.21 (m, 2H), 3.39 (s, 2H), 2.85~2.79 (m, 2H), 2.78~2.73 (m, 2H), 2.16 (s, 3H), 2.13 (s, 3H)7.27 (s, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.3, 167.7, 152.6, 136.3, 130.3, 129.8, 126.0, 124.5, 123.2, 39.9, 37.5, 25.9, 21.2, 13.0 ppm. ESI HRMS: calcd. for $C_{14}H_{15}ClN_2O_2$+H 279.0900, found 279.0900.

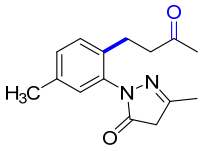
5-methyl-2-(2-(3-oxobutyl)-4-(trifluoromethyl)phenyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3fa**). 12 h, light brown oil, 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 10.1 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 1H), 3.42 (s, 2H), 2.94~2.88 (m, 2H), 2.81~2.77 (m, 2H), 2.17 (s, 3H), 2.13 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.1, 171.6, 157.0, 139.0, 138.4, 130.6 (dd, *J* = 65.0, 32.0 Hz), 127.4, 127.2 (dd, *J* = 7.0, 4.0 Hz) , 124.0 (dd, *J* = 7.0, 4.0 Hz), 123.7 (d, *J* = 270.0 Hz), 43.9, 41.6, 29.9, 25.5, 17.0 ppm. ESI HRMS: calcd. for $C_{15}H_{15}F_3N_2O_2$+H 313.1164, found 313.1162.



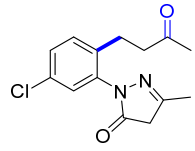
4-(3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)-3-(3-oxobutyl)benzonitrile (**3ga**), 12 h, light brown oil, 30% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61~7.54 (m, 2H), 7.44 (d, *J* = 8.2 Hz, 1H), 3.43 (s, 2H), 2.90 (t, *J* = 8.0 Hz, 2H), 2.78 (t, *J* = 8.0 Hz, 2H), 2.18 (s, 3H), 2.14 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.0, 171.8, 156.3, 137.0, 135.3, 135.0, 129.9, 129.8, 127.8, 44.4, 41.6, 29.9, 25.1, 20.7, 17.0 ppm. ESI HRMS: calcd. for $C_{15}H_{15}N_3O_2$+H 270.1243, found 270.1240.



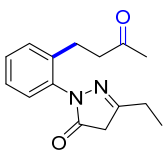
5-methyl-2-(5-methyl-2-(3-oxobutyl)phenyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3ha**), 12 h, light brown oil, 43% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 7.8 Hz, 1H), 7.13~7.08 (m, 2H), 3.39 (s, 2H), 2.80 (ddd, *J* = 8.2, 6.4, 1.8 Hz, 2H), 2.73 (ddd, *J* = 8.8, 6.4, 1.8 Hz, 2H), 2.32 (s, 3H), 2.16 (s, 3H), 2.10 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.0, 171.8, 156.3, 137.0, 135.3, 135.0, 129.9, 129.8, 127.8, 44.4, 41.6, 29.9, 25.1, 20.7, 17.0 ppm. ESI HRMS: calcd. for $C_{15}H_{18}N_2O_2$+H 259.1447, found 259.1446.



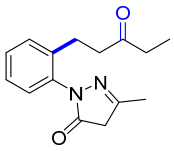
2-(5-chloro-2-(3-oxobutyl)phenyl)-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (**3ia**). 12 h, light brown oil, 55% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 6.4, 1.9 Hz, 2H), 7.23 (s, 1H), 3.40 (s, 2H), 2.85~2.79 (m, 2H), 2.76~2.71 (m, 2H), 2.17 (s, 3H), 2.11 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.5, 171.6, 156.8, 136.9, 136.3, 132.2, 131.2, 128.8, 127.3, 44.0, 41.5, 29.9, 25.0, 17.0 ppm. ESI HRMS: calcd. for $C_{14}H_{15}ClN_2O_2$+H 279.0900, found 279.0898.

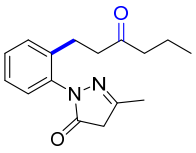


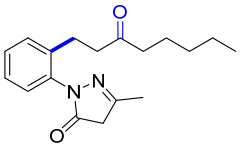
5-ethyl-2-(2-(3-oxobutyl)phenyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3ka**). 12 h, light brown oil, 51% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 9.2 Hz, 4H), 3.38 (s, 2H), 2.87~2.80 (m, 2H), 2.79~2.72 (m, 2H), 2.48 (q, *J* = 7.4 Hz, 2H), 2.10 (s, 3H), 1.23~1.13 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8, 171.7, 160.9, 138.4, 135.4, 130.2, 128.8, 127.3, 127.1, 44.4, 40.1, 29.9, 25.6, 24.6, 10.6 ppm. ESI HRMS: calcd. for $C_{15}H_{18}N_2O_2$+H 259.1447, found 259.1450.

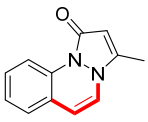


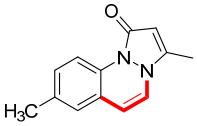
5-methyl-2-(2-(3-oxopentyl)phenyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3ac**). 12 h, light brown oil, 45% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dt, *J* = 9.7, 4.1 Hz, 4H), 3.39 (s, 2H), 2.88~2.78 (m, 2H), 2.74~2.65 (m, 3H), 2.37 (q, *J* = 7.3 Hz, 2H), 2.15 (s, 3H), 1.01 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 210.6, 171.8, 156.4, 138.6, 135.2, 130.1, 128.9, 127.3, 127.1, 42.9, 41.6, 36.0, 25.5, 17.0, 7.7 ppm. ESI HRMS: calcd. for $C_{15}H_{18}N_2O_2$+H 259.1447, found 259.1450.

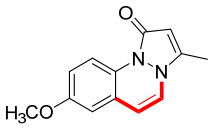


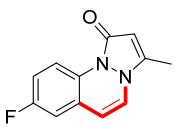
5-methyl-2-(2-(3-oxohexyl)phenyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3ad**). 12 h, light brown oil, 59% yield.  ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 4H), 3.39 (s, 2H), 2.90~2.79 (m, 2H), 2.75~2.67 (m, 2H), 2.33 (t, *J* = 6.9 Hz, 2H), 2.15 (s, 3H), 1.63~1.46 (m, 2H), 0.86 (q, *J* = 10.4, 8.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.2, 171.8, 156.3, 138.7, 135.3, 130.1, 128.9, 127.4, 127.1, 44.8, 43.4, 41.6, 25.5, 17.3, 17.0, 13.7 ppm. ESI HRMS: calcd. for $C_{16}H_{20}N_2O_2$+H 273.1603, found 273.1601.

5-methyl-2-(2-(3-oxooctyl)phenyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3ae**). 12 h, light brown oil, 46% yield.  ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 7.1 Hz, 4H), 3.39 (s, 2H), 2.87~2.81 (m, 2H), 2.74~2.68 (m, 2H), 2.34 (dd, *J* = 13.7, 6.2 Hz, 2H), 2.15 (s, 3H), 1.51 (dt, *J* = 11.2, 5.6 Hz, 2H), 1.24 (dt, *J* = 18.2, 7.5 Hz, 4H), 0.85 (q, *J* = 8.1, 7.5 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 210.4, 171.7, 156.3, 138.6, 135.2, 130.1, 128.9, 127.4, 127.1, 43.3, 42.9, 41.6, 31.3, 25.5, 23.5, 22.4, 17.1, 13.9 ppm. ESI HRMS: calcd. for $C_{18}H_{24}N_2O_2$+H 301.1916, found 301.1917.

3-methyl-1*H*-pyrazolo[1,2-*a*]cinnolin-1-one (**4aa**), 12 h, light yellow oil, 46% yield.  ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (d, *J* = 8.4 Hz, 1H), 7.45~7.41 (m, 2H), 7.26 (d, *J* = 4.4 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.15 (d, *J* = 8.0 Hz, 1H), 5.67 (s, 1H), 2.42 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 136.6, 134.6, 128.6, 125.4, 124.8, 119.6, 119.2, 115.3, 106.5, 95.7, 11.1 ppm. ESI HRMS: calcd. for $C_{12}H_{10}N_2O$+H 199.0871, found 199.0863.

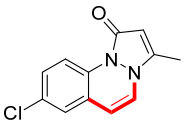
3,8-dimethyl-1*H*-pyrazolo[1,2-*a*]cinnolin-1-one (**4ba**). 12 h, light yellow oil, 39% yield.  ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, *J* = 8.4 Hz, 1H), 7.08 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.94 (s, 1H), 6.85 (d, *J* = 7.9 Hz, 1H), 5.98 (d, *J* = 7.8 Hz, 1H), 5.54 (s, 1H), 2.31 (s, 3H), 2.28 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 136.2, 134.5, 132.3, 129.1, 125.9, 119.5, 119.1, 115.3, 106.6, 95.7, 20.8, 11.0 ppm. ESI HRMS: calcd. for $C_{13}H_{12}N_2O$+H 213.1028, found 213.1029.

8-methoxy-3-methyl-1*H*-pyrazolo[1,2-*a*]cinnolin-1-one (**4ca**). 12 h, light yellow oil, 38% yield.  ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (d, *J* = 9.0 Hz, 1H), 6.90 (d, *J* = 7.9 Hz, 1H), 6.83 (dd, *J* = 9.1, 2.9 Hz, 1H), 6.66 (d, *J* = 2.9 Hz, 1H), 5.99 (d, *J* = 7.8 Hz, 1H), 5.62 (s, 1H), 3.81 (s, 3H), 2.30 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 136.0, 128.5, 121.2, 119.8, 116.9, 113.5, 110.6, 106.5, 96.1, 55.6, 11.2 ppm. ESI HRMS: calcd. for $C_{13}H_{12}N_2O_2$+H 229.0977, found 229.0975.

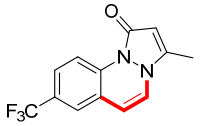


8-fluoro-3-methyl-1*H*-pyrazolo[1,2-*a*]cinnolin-1-one (**4da**). 12 h, light yellow oil, 21% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (dd, *J* = 9.2, 5.0 Hz, 1H), 7.03~6.94 (m, 2H), 6.86 (dd, *J* = 8.4, 2.9 Hz, 1H), 6.02 (d, *J* = 7.9 Hz, 1H), 5.71 (s, 1H), 2.34 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 158.4, 136.8, 130.8 (d, *J* = 3.0 Hz), 121.9 (d, *J* = 8.0 Hz), 120.4, 117.4 (d, *J* = 8.0 Hz), 115.2 (d, *J* = 23.0 Hz), 112.0 (d, *J* = 24.0 Hz), 106.0 (d, *J* = 2.0 Hz), 96.3, 11.3 ppm. ESI HRMS: calcd. for $C_{12}H_9FN_2O$+H 217.0777, found 217.0777.

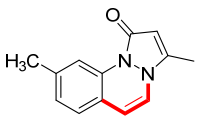
8-chloro-3-methyl-1*H*-pyrazolo[1,2-*a*]cinnolin-1-one (**4ea**). 12 h, light yellow oil, 25% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, *J* = 8.9 Hz, 1H), 7.23 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.09 (d, *J* = 2.4 Hz, 1H), 6.90 (d, *J* = 7.9 Hz, 1H), 5.94 (d, *J* = 7.9 Hz, 1H), 5.61 (s, 1H), 2.31 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 137.1, 132.9, 130.1, 128.2, 124.9, 121.4, 120.3, 116.6, 105.4, 96.0, 11.1 ppm. ESI HRMS: calcd. for $C_{12}H_9ClN_2O$+H 233.0482, found 233.0482.



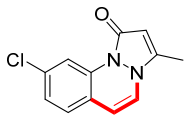
3-methyl-8-(trifluoromethyl)-1*H*-pyrazolo[1,2-*a*]cinnolin-1-one (**4fa**). 12 h, light yellow oil, 21% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (d, *J* = 8.7 Hz, 1H), 7.52 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.35 (d, *J* = 2.0 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.02 (d, *J* = 7.9 Hz, 1H), 5.64 (s, 1H), 2.34 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 138.0, 136.6, 127.0 (d, *J* = 32.0 Hz), 125.6 (dd, *J* = 8.0, 4.0 Hz), 125.0, 122.3 (dd, *J* = 8.0, 4.0 Hz), 120.5, 120.1, 115.5, 105.7, 96.0, 11.2 ppm. ESI HRMS: calcd. for $C_{21}H_{17}N_3O$+Na 350.1269, found 350.1263.



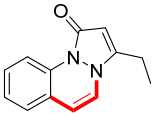
3,9-dimethyl-1*H*-pyrazolo[1,2-*a*]cinnolin-1-one (**4ha**). 12 h, light yellow oil, 31% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.07 (d, *J* = 7.6 Hz, 1H), 5.68 (s, 1H), 2.39 (s, 3H), 2.32 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 136.5, 134.4, 125.7, 125.4, 118.3, 116.9, 115.9, 106.9, 95.6, 21.9, 11.1 ppm. ESI HRMS: calcd. for $C_{13}H_{12}N_2O$+H 213.1028, found 213.1024.



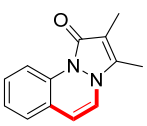
9-chloro-3-methyl-1*H*-pyrazolo[1,2-*a*]cinnolin-1-one (**4ia**). 12 h, light yellow oil, 10% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.08 (s, 1H), 7.09 (dd, *J* = 8.4, 1.8 Hz,1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 5.99 (d, *J* = 7.8 Hz, 1H), 5.59 (s, 1H), 2.31 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.0, 137.5, 134.9, 134.3, 126.5, 125.4, 119.4, 118.3, 115.7, 106.3, 95.9, 11.3 ppm. ESI HRMS: calcd. for $C_{12}H_9ClN_2O$+H 233.0482, found 233.0480.



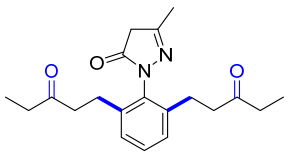
3-ethyl-1*H*-pyrazolo[1,2-*a*]cinnolin-1-one (**4ka**). 12 h, light yellow oil, 22% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (d, *J* = 8.3 Hz, 1H), 7.31 (ddd, *J* = 8.7, 5.8, 3.3 Hz, 1H), 7.15 (q, *J* = 3.6, 2.8 Hz, 2H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.06 (d, *J* = 7.9 Hz, 1H), 5.67 (s, 1H), 2.63 (q, *J* = 7.5 Hz, 2H), 1.33 (t, *J* = 7.5 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 142.5, 134.4, 128.7, 125.6, 125.1, 119.7, 119.2, 115.5, 106.8, 94.0, 18.5, 11.0 ppm. ESI HRMS: calcd. for $C_{13}H_{12}N_2O$+H 213.1028, found 213.1028.



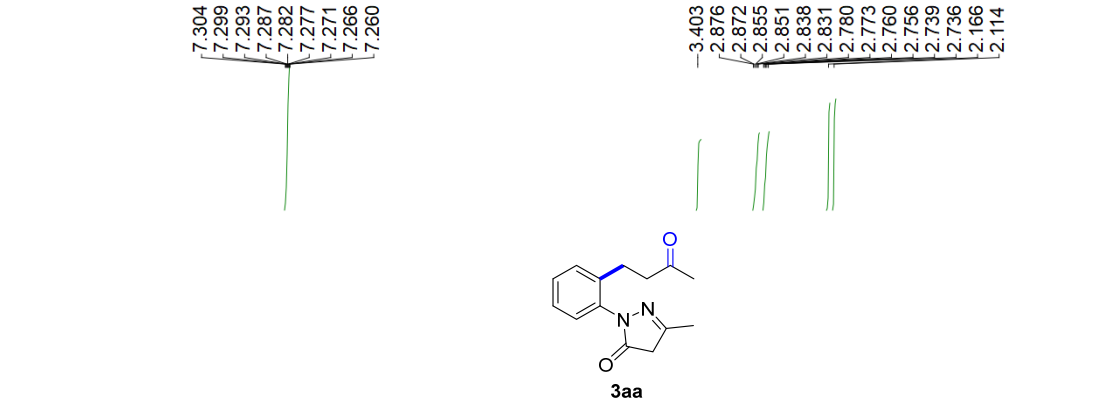
2,3-dimethyl-1*H*-pyrazolo[1,2-*a*]cinnolin-1-one (**4la**), 12 h, light yellow oil, 47% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (d, *J* = 8.3 Hz, 1H), 7.29 (dd, *J* = 8.5, 4.3 Hz, 1H), 7.10 (d, *J* = 4.3 Hz, 2H), 6.87 (d, *J* = 7.8 Hz, 1H), 5.92 (d, *J* = 7.9 Hz, 1H), 2.26 (s, 3H), 1.99 (s, 3H) ppm. 13C NMR (100 MHz, $CDCl_3$) δ 160.0, 134.3, 133.1, 128.3, 125.1, 124.7, 120.2, 119.5, 115.4, 104.8, 103.0, 9.3, 6.8 ppm. ESI HRMS: calcd. for $C_{13}H_{12}N_2O$+H 213.1028, found 213.1020.

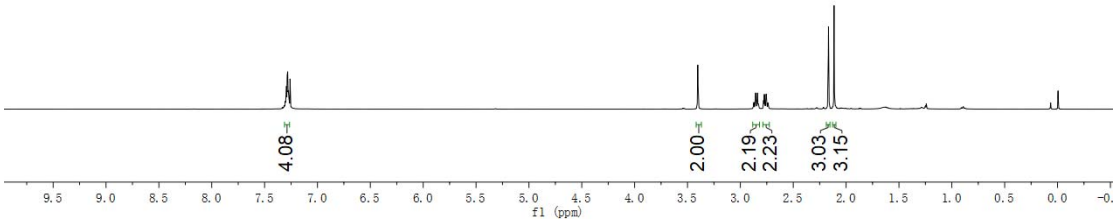


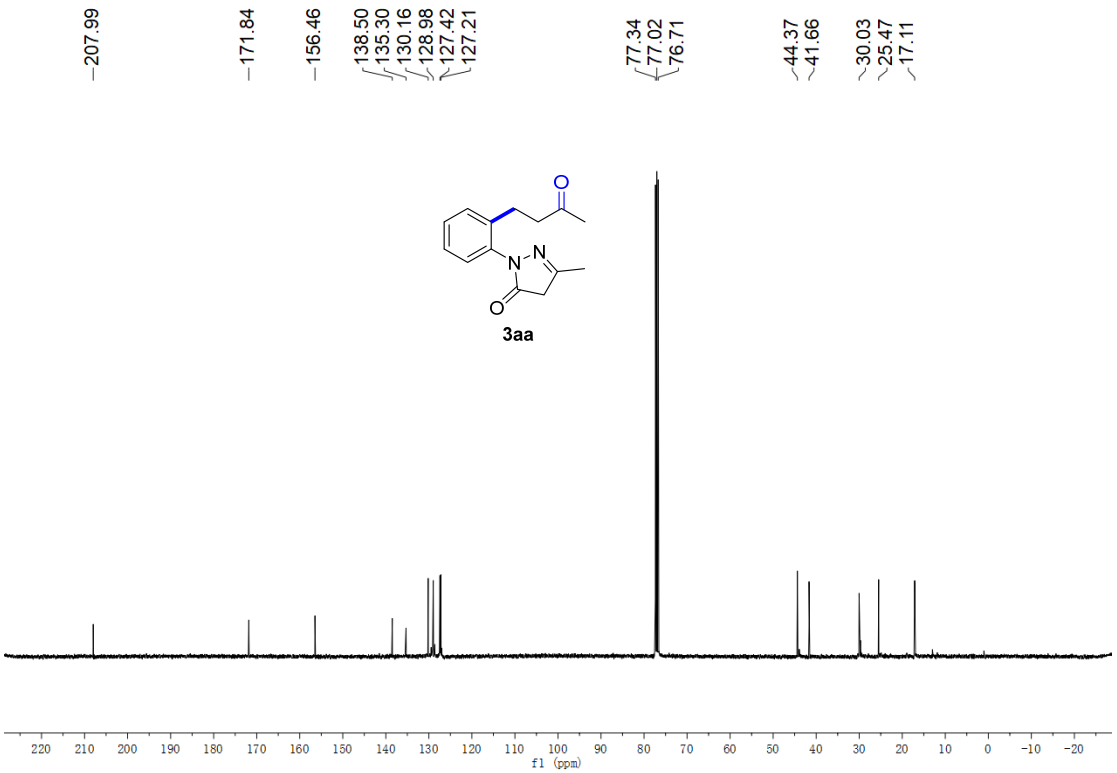
1,1'-(2-(3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)-1,3-phenylene)bis(pentan-3-one) (**6**), 12 h, light brown oil, 47% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29~7.24 (m, 1H), 7.15~7.07 (m, 2H), 3.39 (s, 2H), 2.74 (dd, *J* = 8.8, 5.1 Hz, 4H), 2.69~2.61 (m, 4H), 2.36 (q, *J* = 7.2 Hz, 4H), 2.15 (s, 3H), 0.98 (dt, *J* = 18.4, 7.2 Hz, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 210.5, 172.3, 157.2, 140.8, 133.7, 130.1, 129.7, 128.9, 128.0, 43.0, 41.2, 35.9, 25.6, 17.1, 7.7 ppm. ESI HRMS: calcd. for $C_{20}H_{26}N_2O_3$+H 343.2022, found 343.2021.

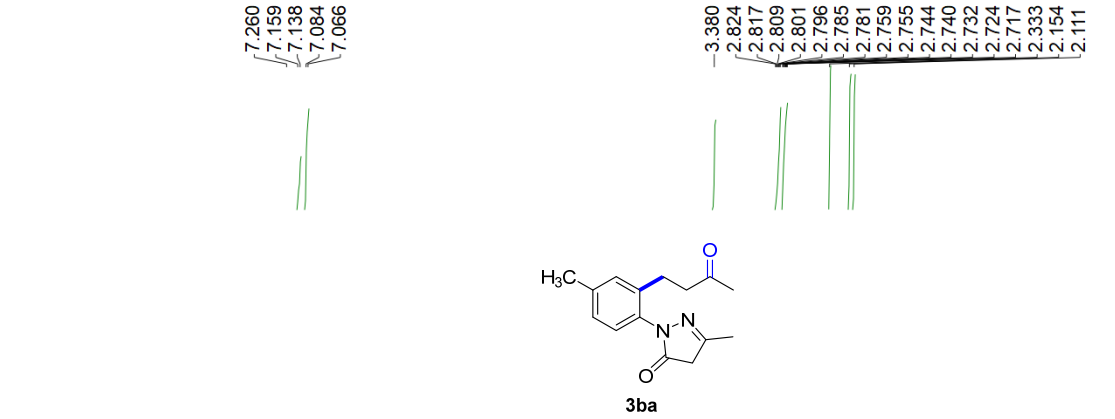


6. NMR Spectra





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7.138
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7.066
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2.801
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2.785
2.781
2.759
2.755
2.744
2.740
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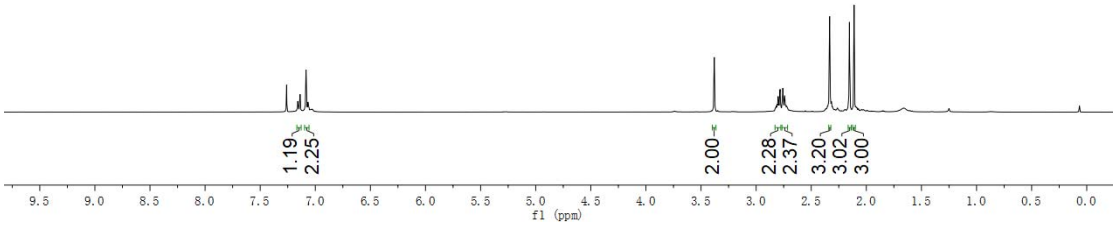
2.111
H3C
O
N
N
O
3ba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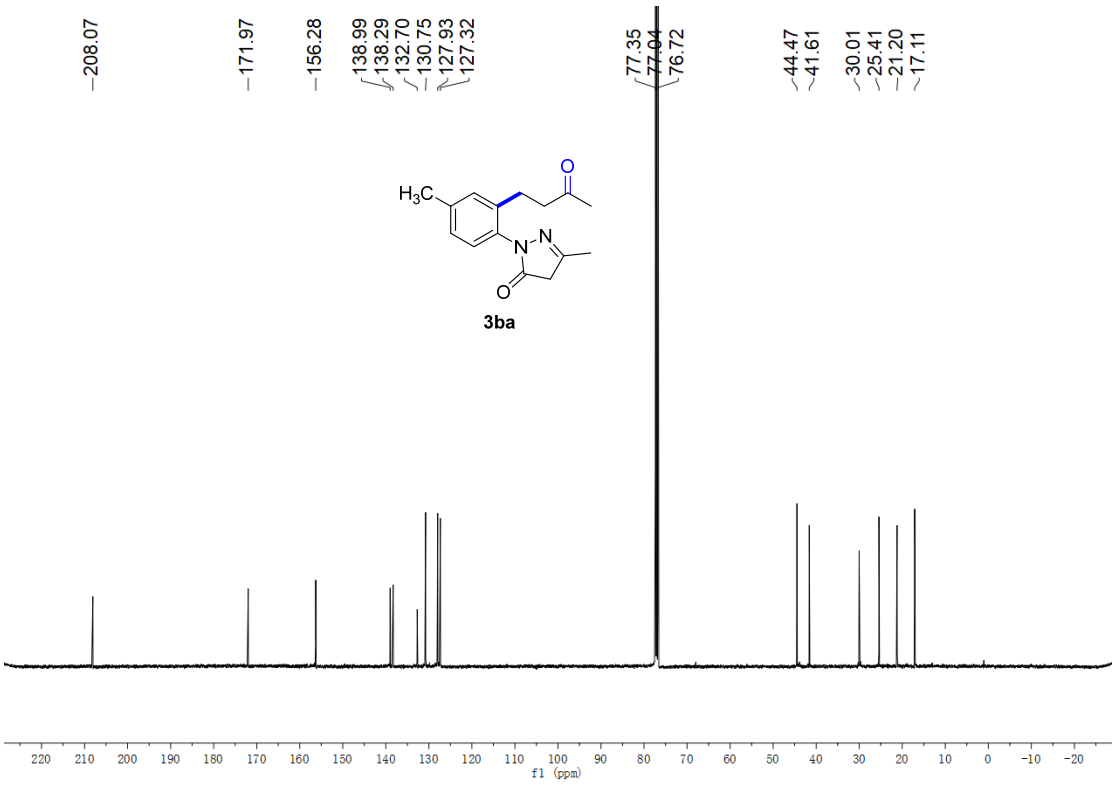
2.00
2.28
2.37
3.20
3.02
3.00
f1 (ppm)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127.93
127.32
77.35
77.04
76.72
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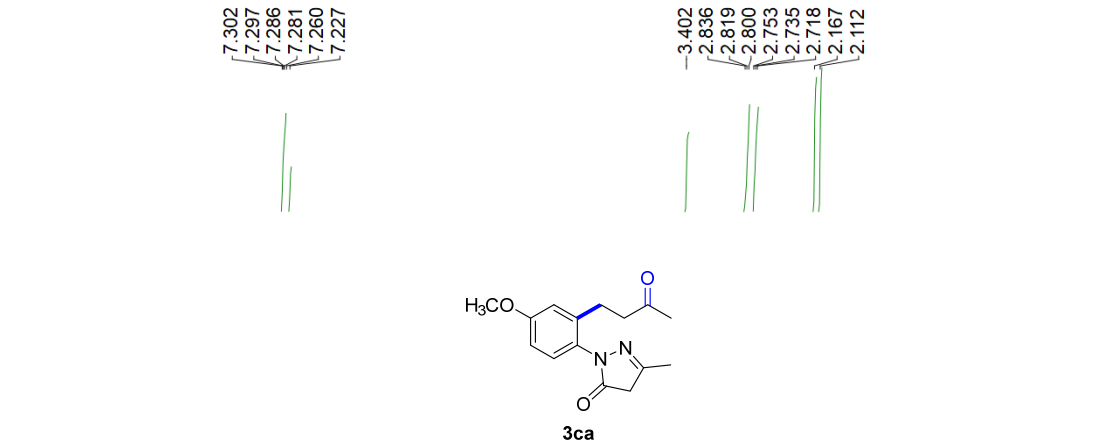
H3C
O
N
N
O
3ba
f1 (ppm)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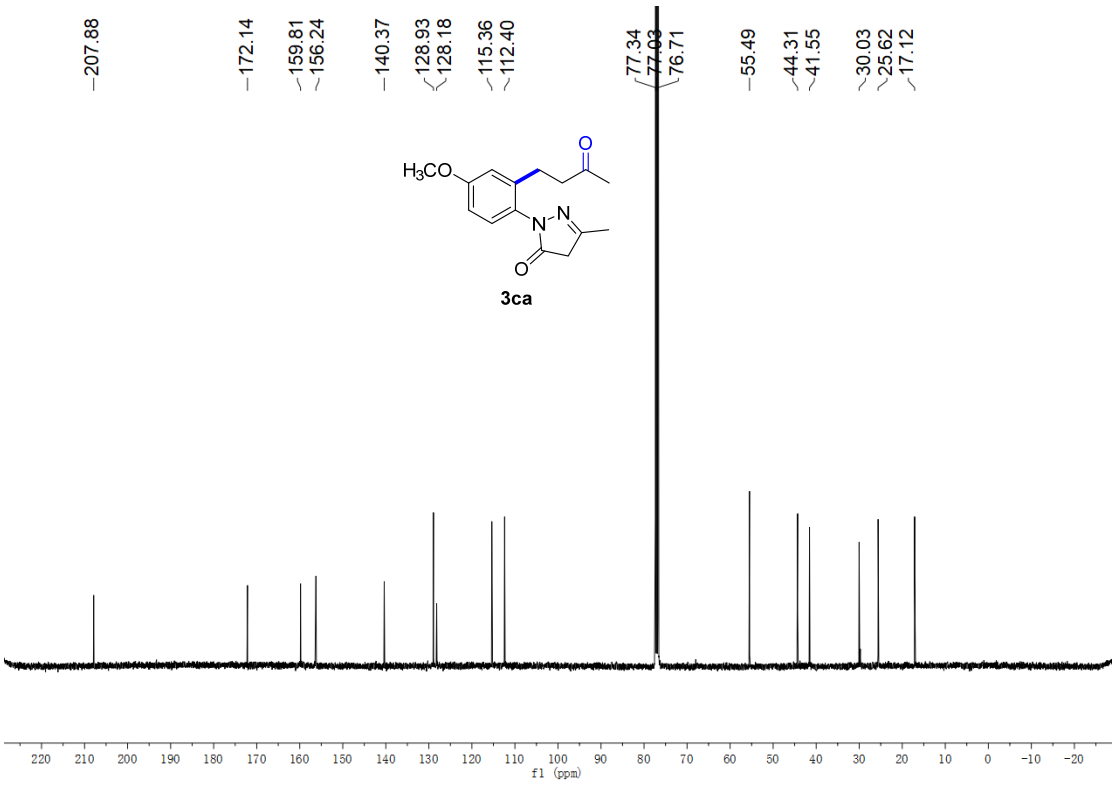
7.297
7.286
7.281
7.260
7.227
3.402
2.836
2.819
2.800
2.753
2.735
2.718
2.167
2.112
H3CO
O
N
N
O
3ca
2.16
0.99
1.74
2.35
2.29
2.94
3.15
f1 (ppm)


207.88
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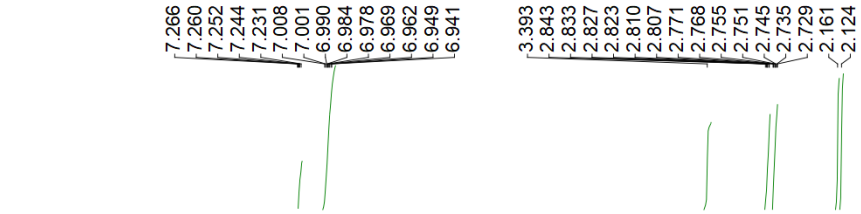
159.81
156.24
140.37
128.93
128.18
115.36
112.40
77.34
77.03
76.71
55.49
44.31
41.55
30.03
25.62
17.12
H3CO
O
N
N
O
3ca
f1 (ppm)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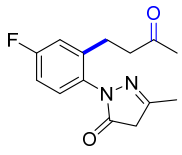
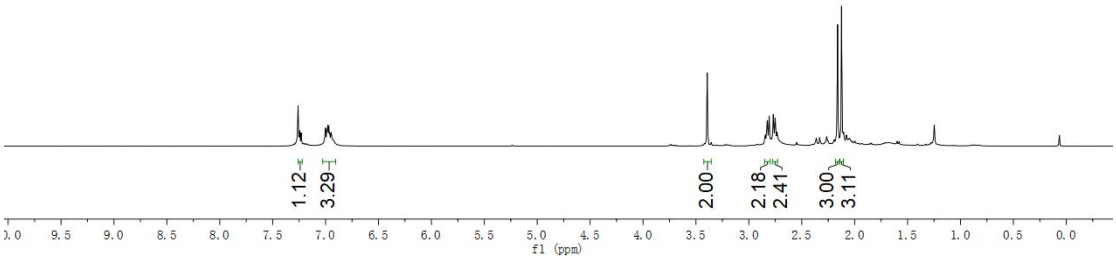
7.260
7.252
7.244
7.231
7.008
7.001
6.990
6.984
6.978
6.969
6.962
6.949
6.941
3.393
2.843
2.833
2.827
2.823
2.810
2.807
2.771
2.768
2.755
2.751
2.745
2.735
2.729
2.161
2.124


F
O
N
N
O

3da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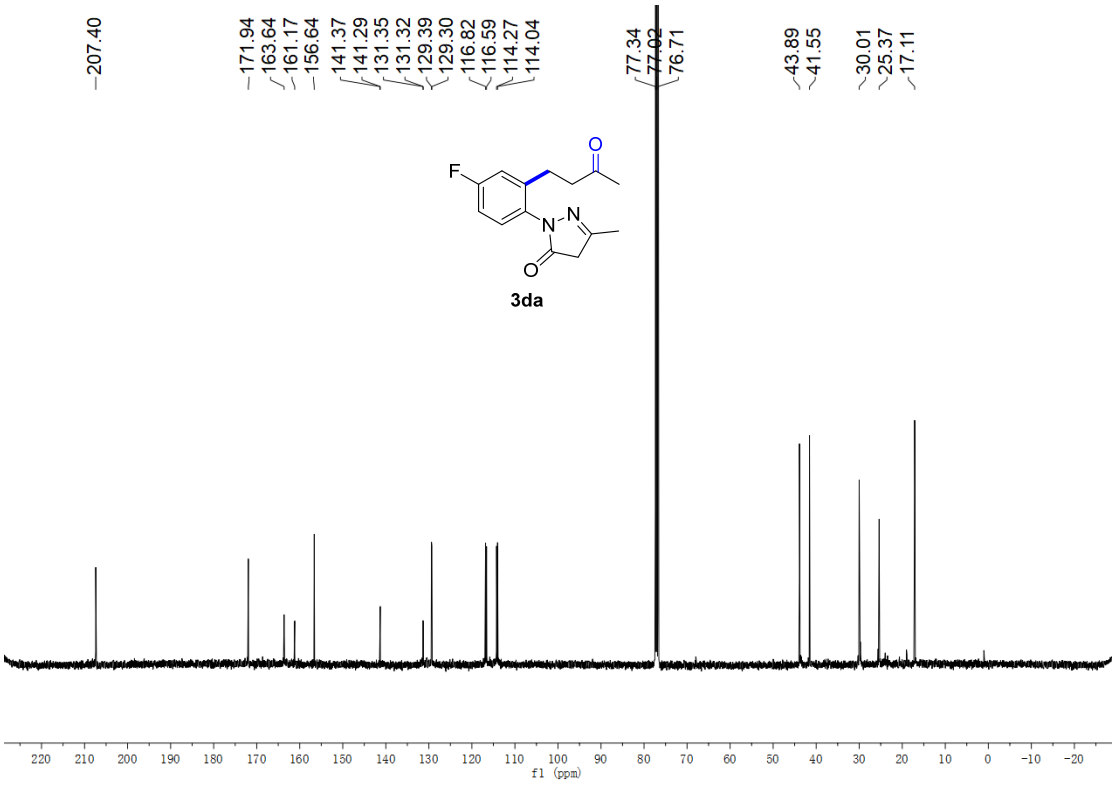
3.29
2.00
2.18
2.41
3.00
3.11
f1 (ppm)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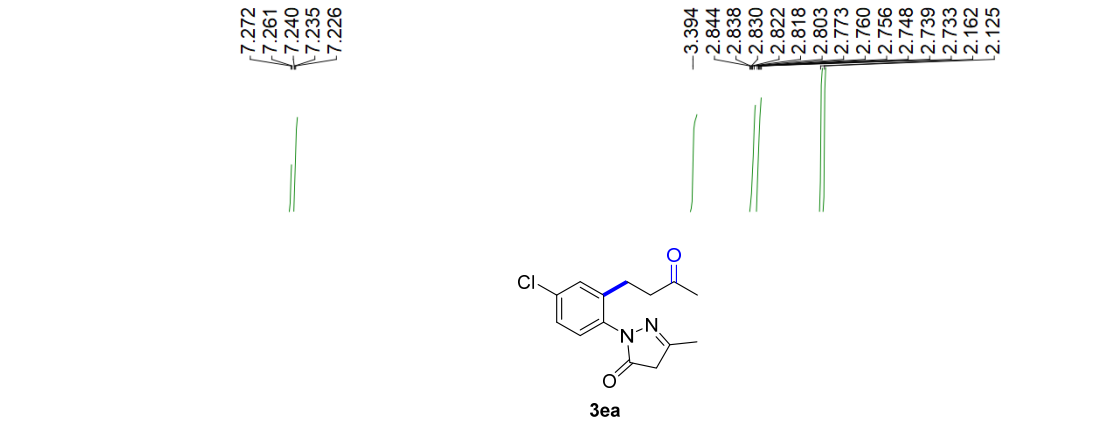
163.64
161.17
156.64
141.37
141.29
131.35
131.32
129.39
129.30
116.82
116.59
114.27
114.04
77.34
77.02
76.71
43.89
41.55
30.01
25.37
17.11
f1 (ppm)

F
O
N
N
O

3da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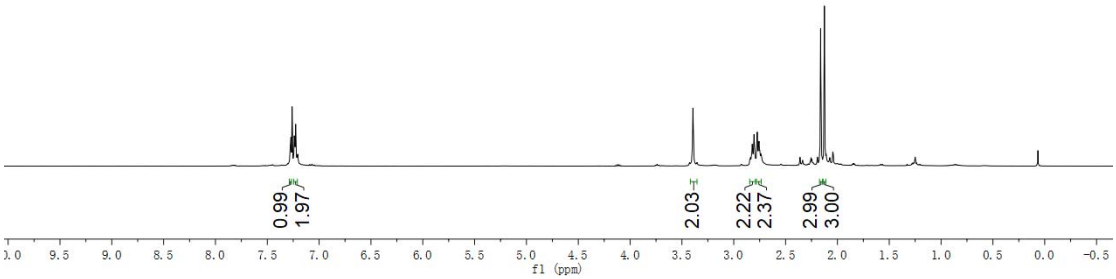
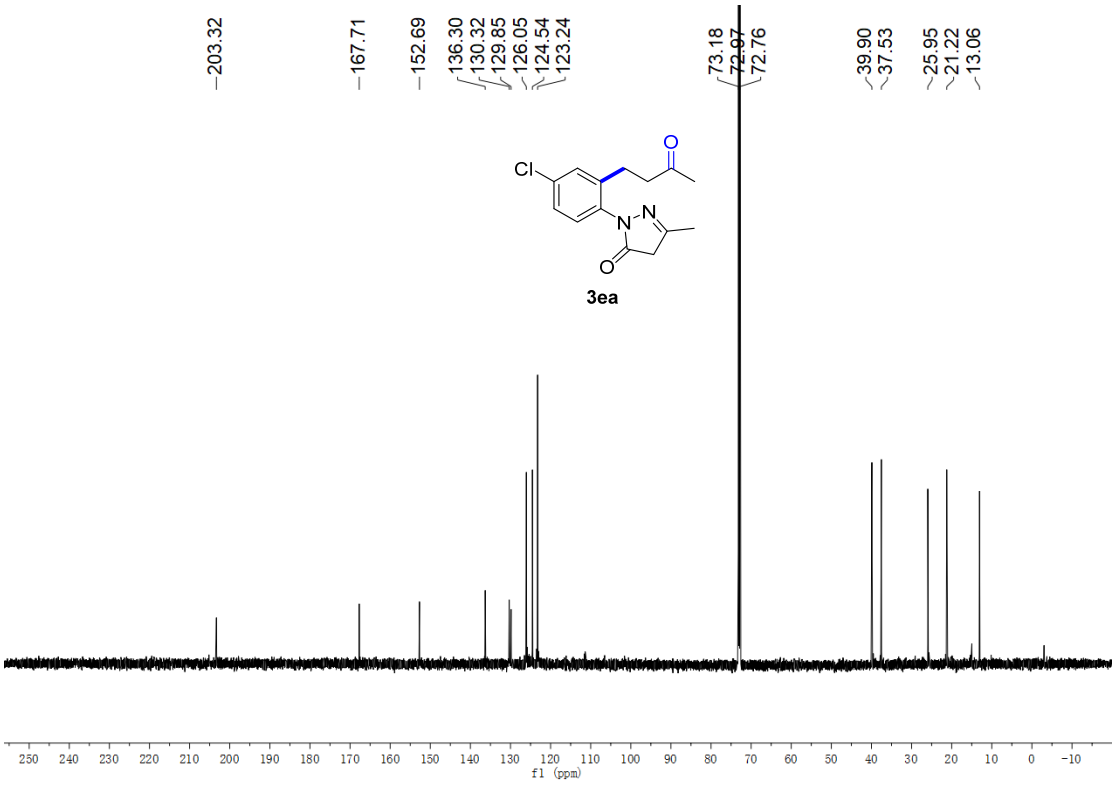
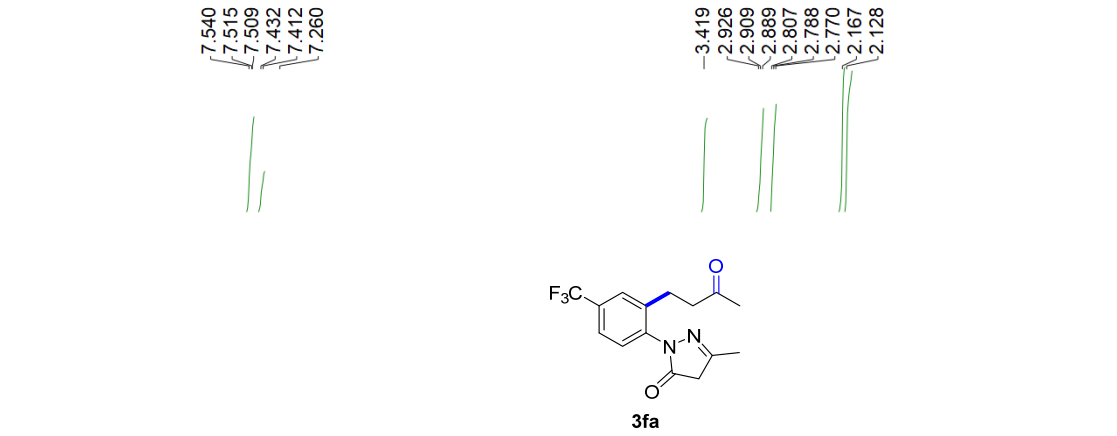
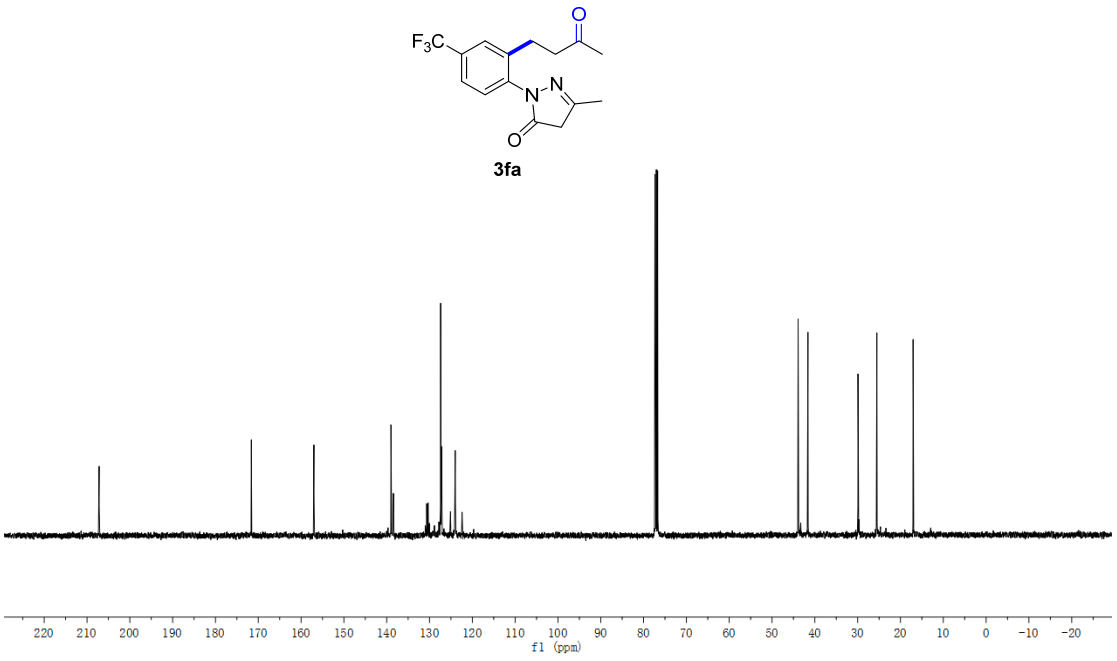
7.240
7.235
7.226
3.394
2.844
2.838
2.830
2.822
2.818
2.803
2.773
2.760
2.756
2.748
2.739
2.733
2.162
2.125
Cl
O
N
N
O
3ea


0.99
1.97
2.03
2.22
2.37
2.99
3.00
f1 (ppm)

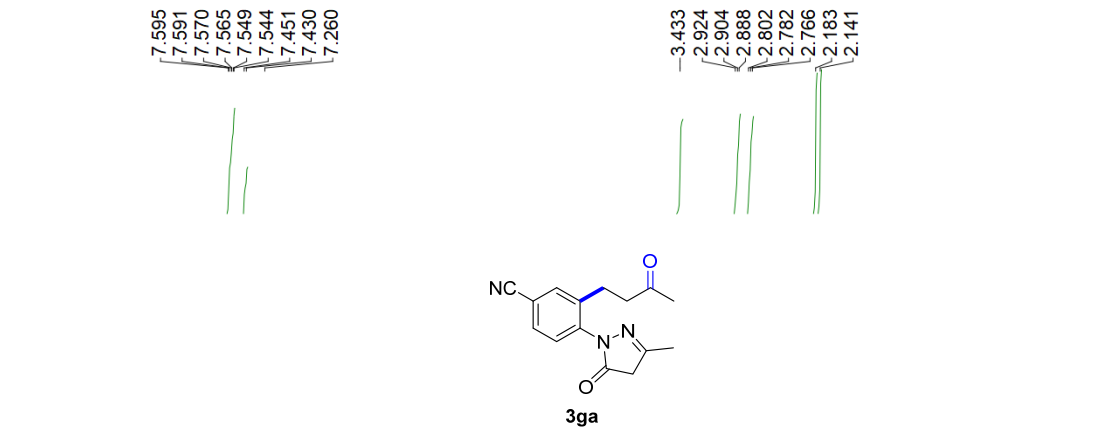

203.32
167.71
152.69
136.30
130.32
129.85
126.05
124.54
123.24
73.18
72.97
72.76
39.90
37.53
25.95
21.22
13.06
Cl
O
N
N
O
3ea
f1 (ppm)


7.540
7.515
7.509
7.432
7.412
7.260
3.419
2.926
2.909
2.889
2.807
2.788
2.770
2.167
2.128
F3C
O
N
N
O
2.03
0.87
2.00
2.21
2.30
3.08
3.00
f1 (ppm)

3fa


207.17
171.62
157.00
139.01
138.44
130.98
130.66
130.33
130.01
127.40
127.29
127.25
127.22
127.18
125.10
124.07
124.03
123.99
123.96
122.40
43.91
41.61
29.92
25.51
17.05
F3C
O
N
N
O
f1 (ppm)

3fa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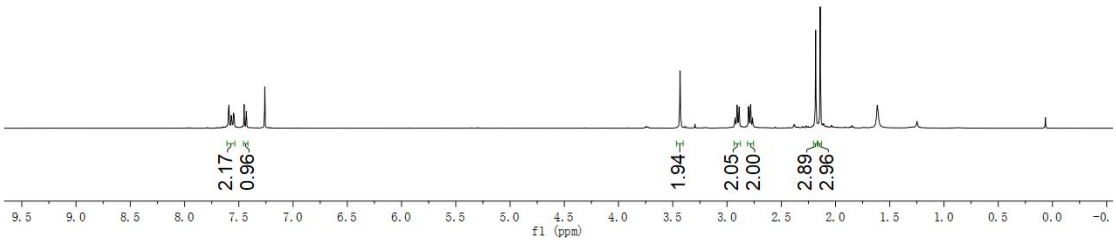
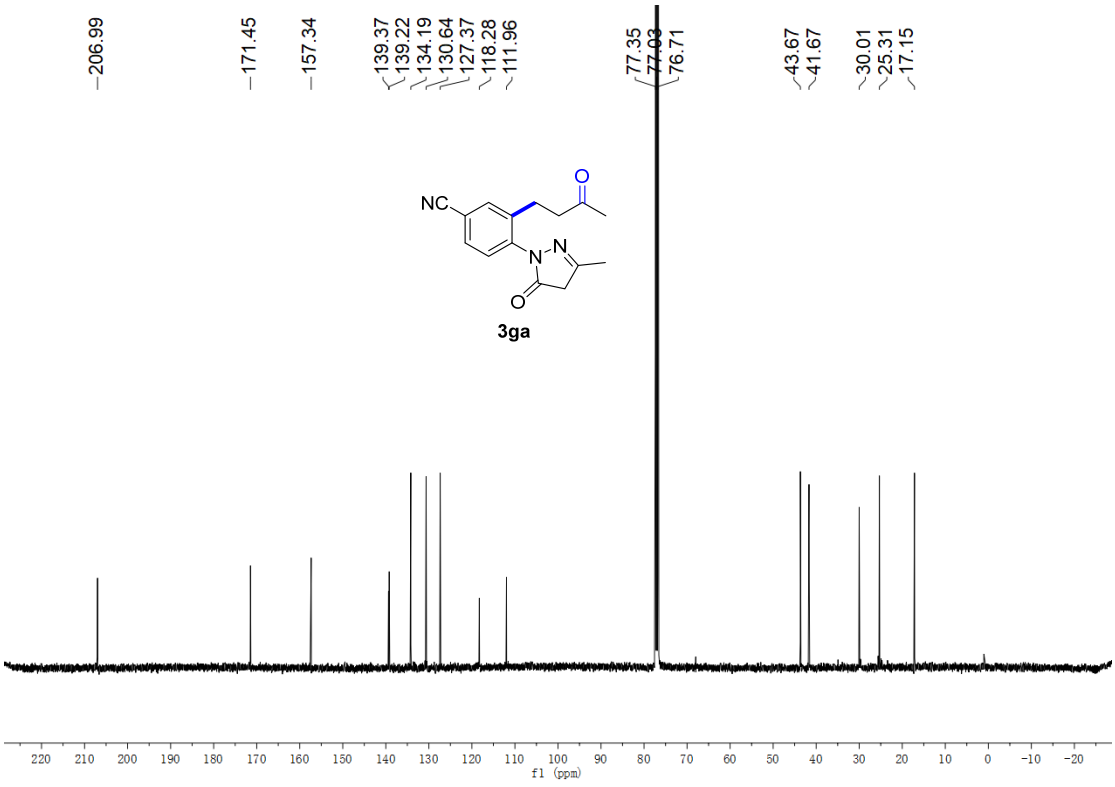
7.591
7.570
7.565
7.549
7.544
7.451
7.430
7.260
3.433
2.924
2.904
2.888
2.802
2.782
2.766
2.183
2.141
NC
O
N
N
O

3ga


2.17
0.96
1.94
2.05
2.00
2.89
2.96
f1 (ppm)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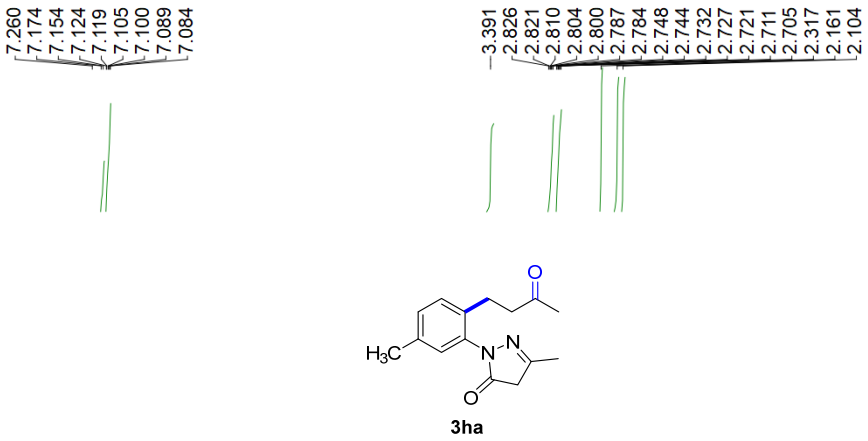
171.45
157.34
139.37
139.22
134.19
130.64
127.37
118.28
111.96
77.35
77.03
76.71
43.67
41.67
30.01
25.31
17.15
NC
O
N
N
O
f1 (ppm)

3ga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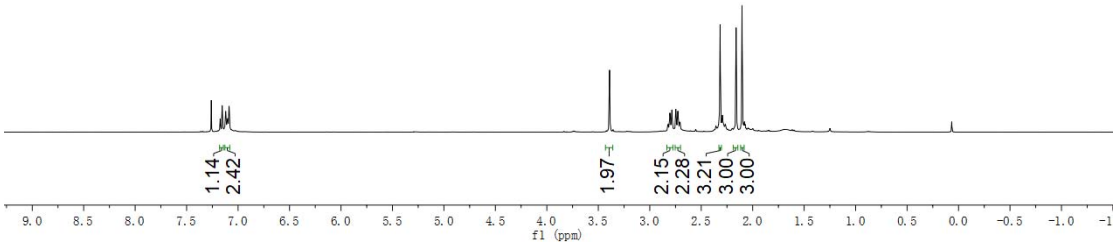
7.119
7.105
7.100
7.089
7.084
3.391
2.826
2.821
2.810
2.804
2.800
2.787
2.784
2.748
2.744
2.732
2.727
2.721
2.711
2.705
2.317
2.161
2.104
O
H3C
N
N
O

3ha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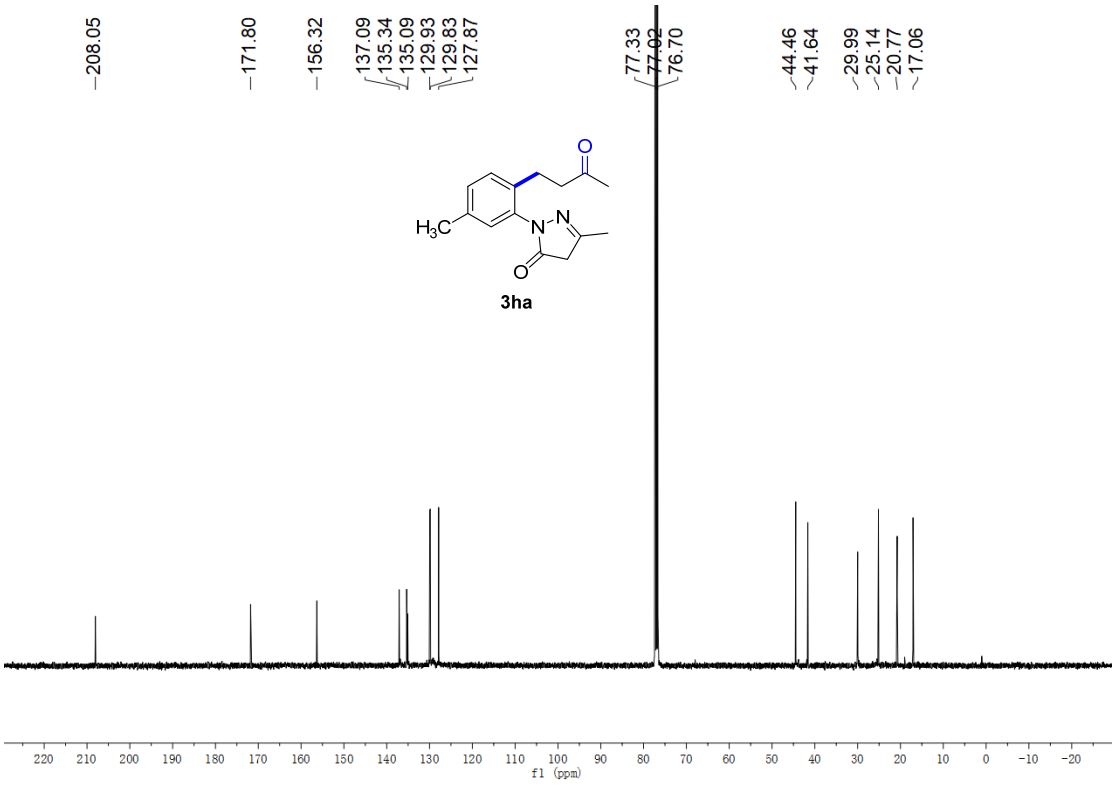
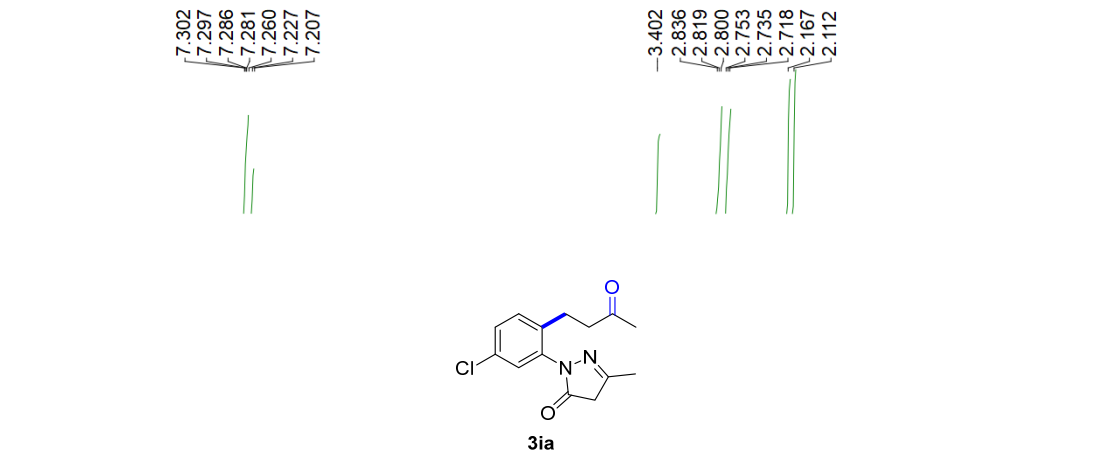
2.42
1.97
2.15
2.28
3.21
3.00
3.00
f1 (ppm)


208.05
171.80
156.32
137.09
135.34
135.09
129.93
129.83
127.87
77.33
77.02
76.70
44.46
41.64
29.99
25.14
20.77
17.06
O
H3C
N
N
O
f1 (ppm)

3ha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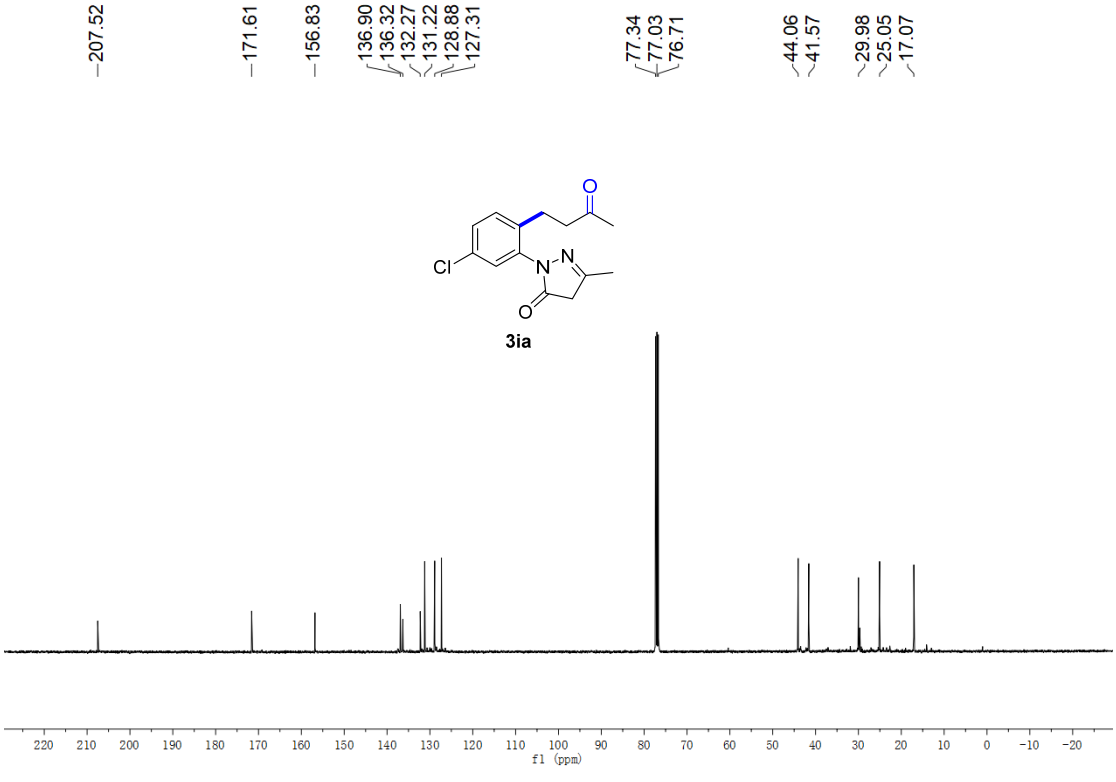
7.297
7.286
7.281
7.260
7.227
7.207
3.402
2.836
2.819
2.800
2.753
2.735
2.718
2.167
2.112
Cl
N
N
O
O
3ia
2.16
0.99
1.74
2.35
2.29
2.94
3.15
f1 (ppm)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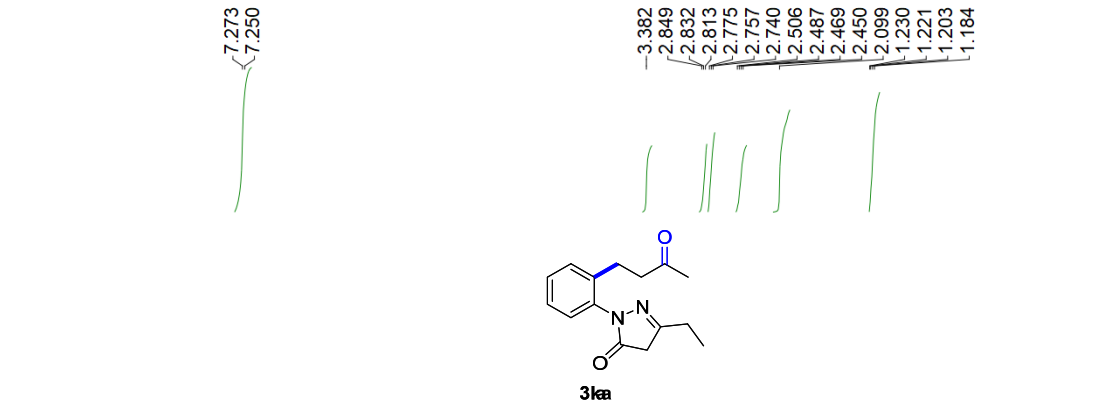
156.83
136.90
136.32
132.27
131.22
128.88
127.31
77.34
77.03
76.71
44.06
41.57
29.98
25.05
17.07
Cl
N
N
O
O
3ia
f1 (ppm)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3.382
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2.832
2.813
2.775
2.757
2.740
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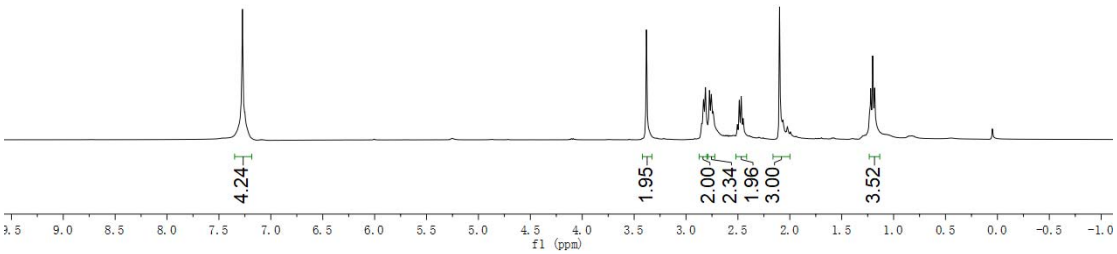
2.450
2.099
1.230
1.221
1.203
1.184
O
N
N
O

3ka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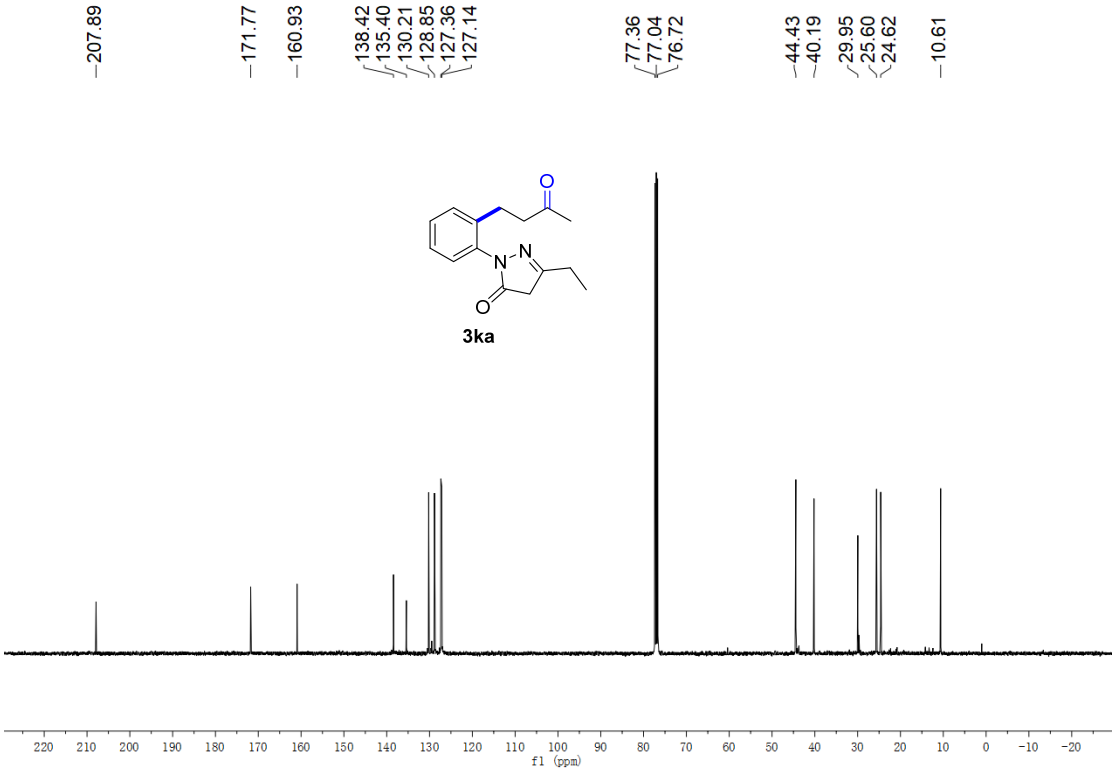
2.00
2.34
1.96
3.00
3.52
f1 (ppm)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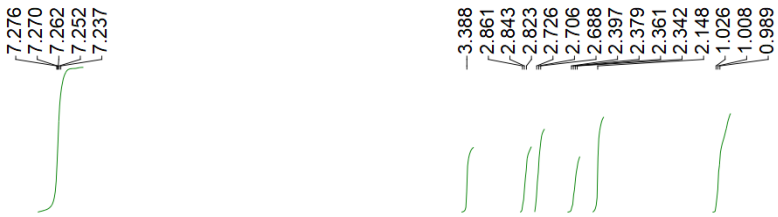
138.42
135.40
130.21
128.85
127.36
127.14
77.36
77.04
76.72
44.43
40.19
29.95
25.60
24.62
10.61
O
N
N
O
f1 (ppm)

3ka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2.843
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2.361
2.342
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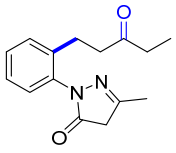
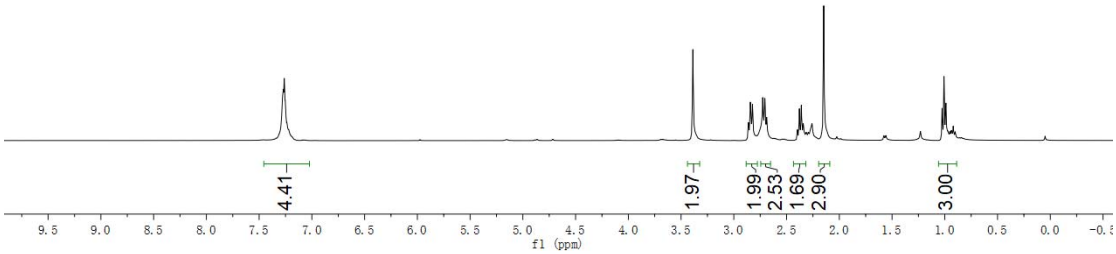
1.026
1.008
0.989


O
N
N
O

3ac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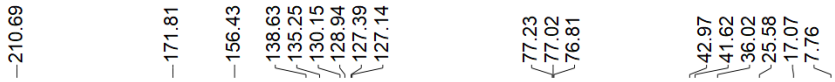
2.90
3.00
f1 (ppm)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135.25
130.15
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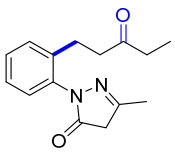
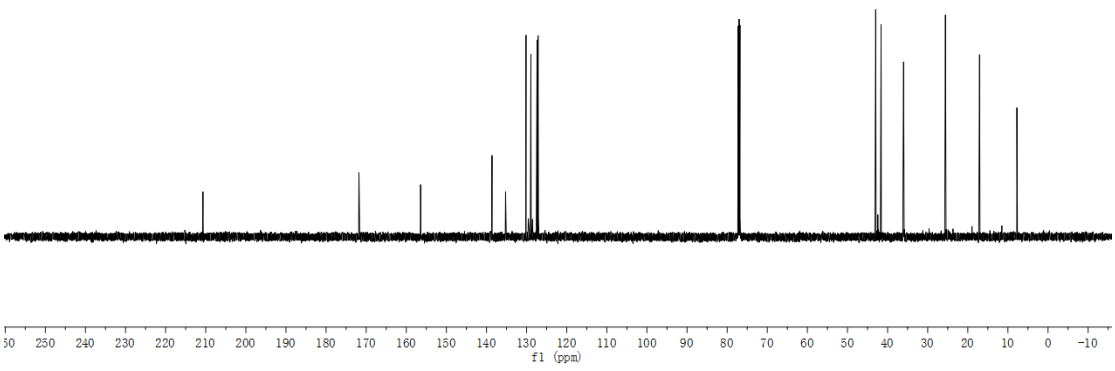
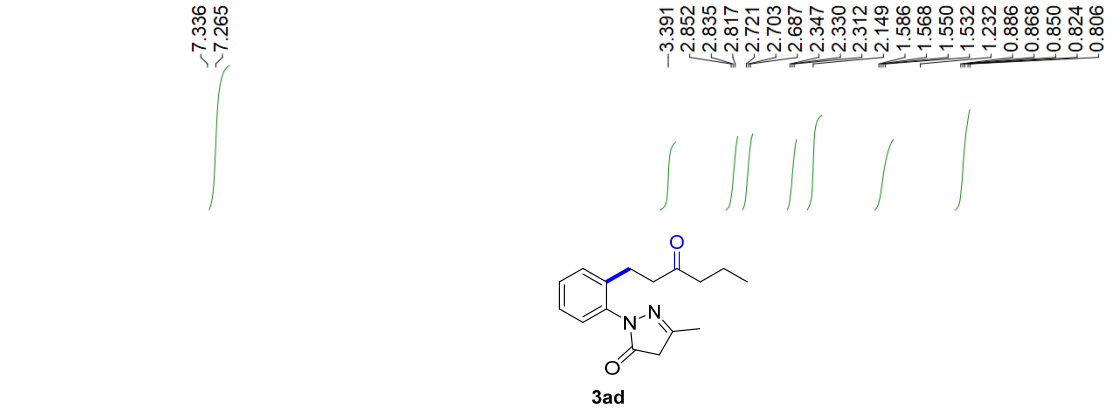
127.39
127.14
77.23
77.02
76.81
42.97
41.62
36.02
25.58
17.07
7.76


O
N
N
O

3ac


f1 (ppm)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2.703
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2.149
1.586
1.568
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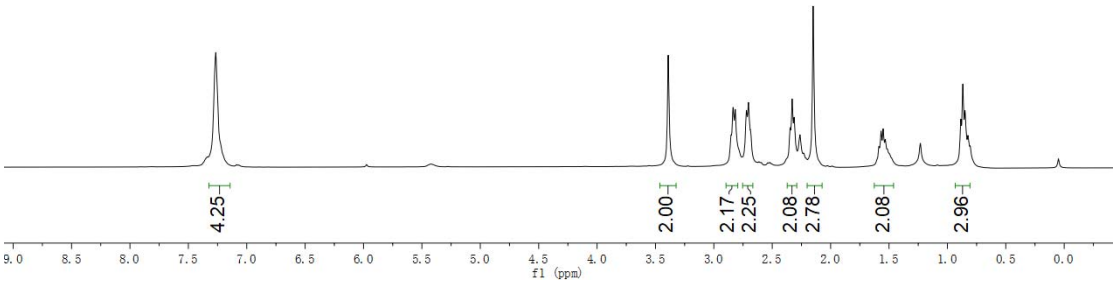
1.532
1.232
0.886
0.868
0.850
0.824
0.806
O
N
N
O

3ad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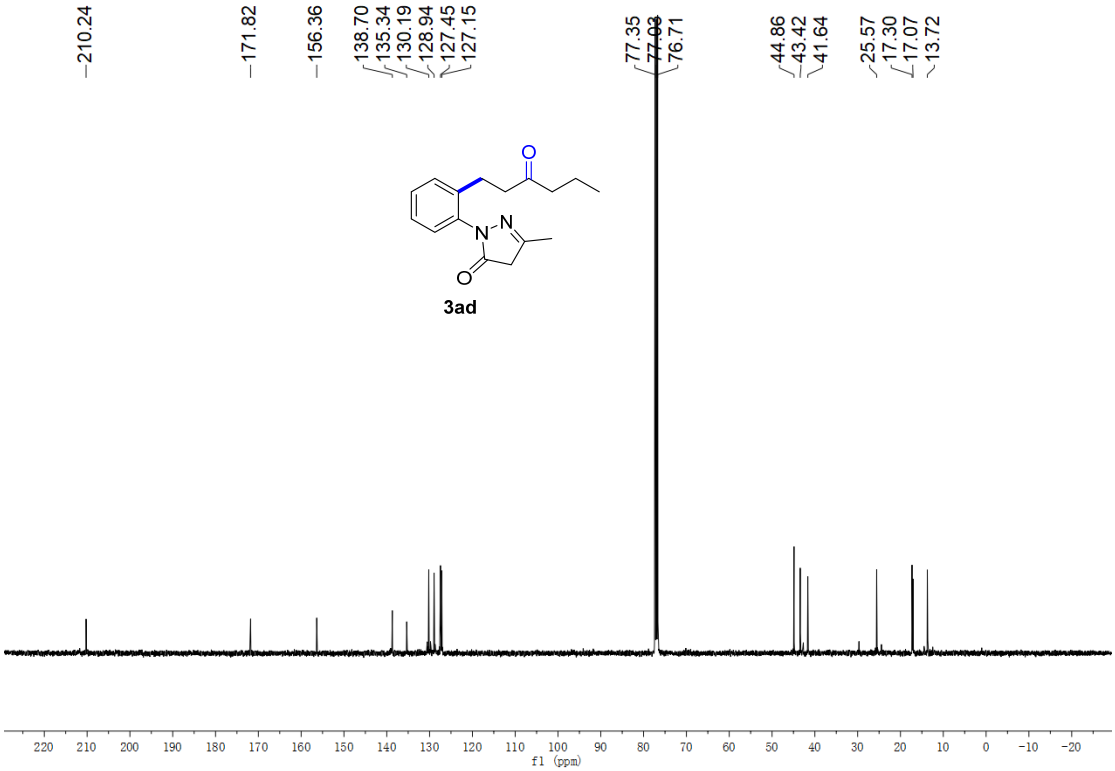
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128.94
127.45
127.15
77.35
77.03
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44.86
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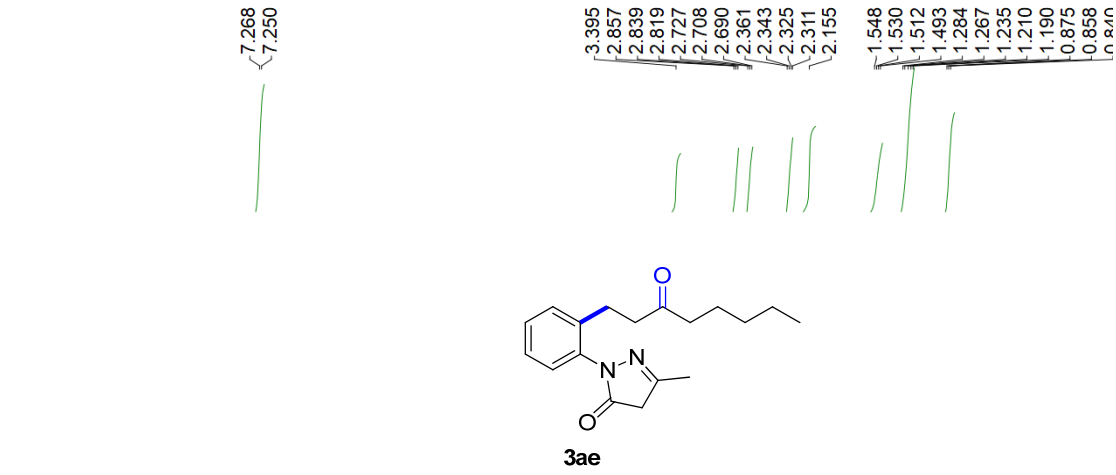
41.64
25.57
17.30
17.07
13.72
O
N
N
O
f1 (ppm)

3ad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2.857
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2.819
2.727
2.708
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2.311
2.155
1.548
1.530
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1.210
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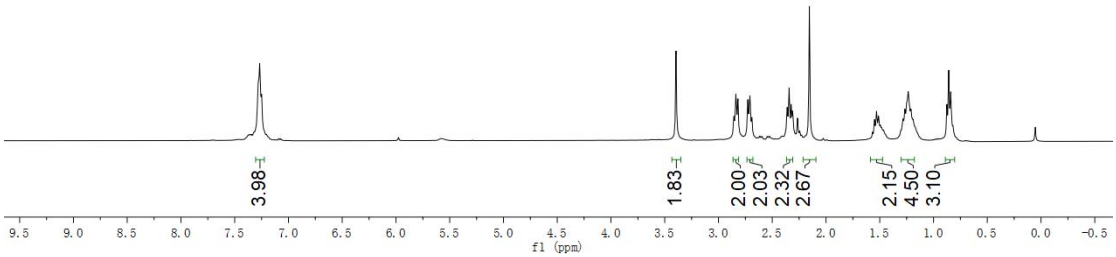
O
N
N
O

3ae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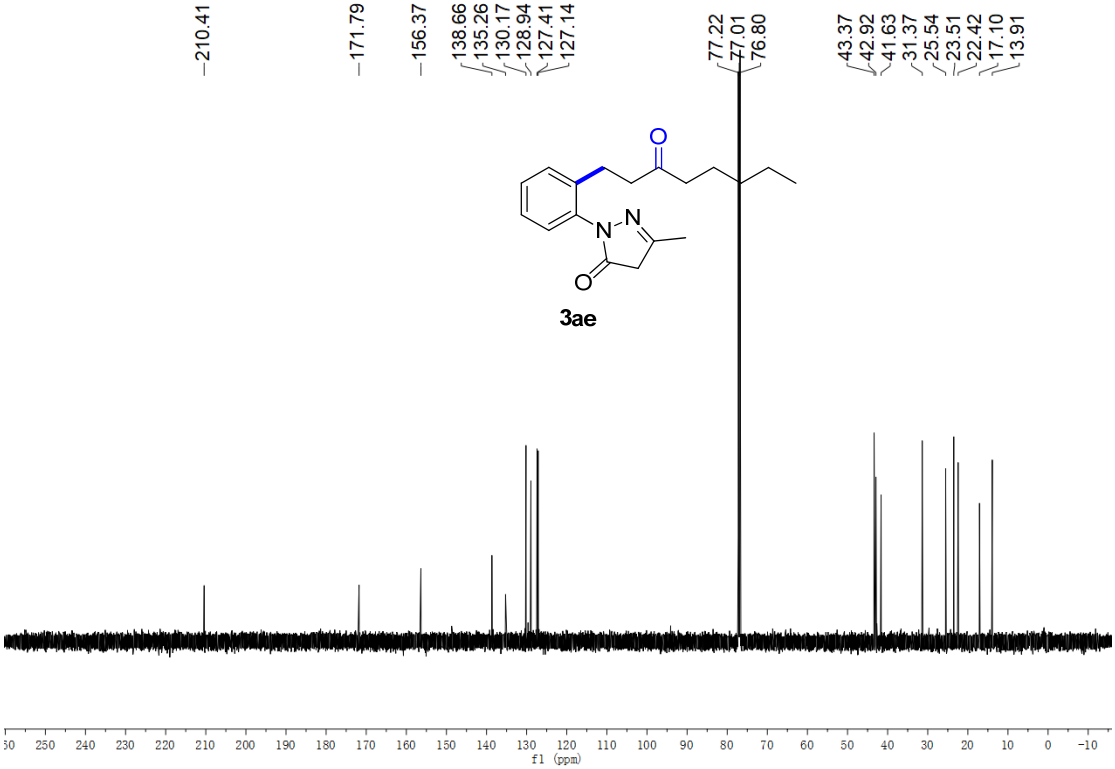
2.15
4.50
3.10
f1 (ppm)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138.66
135.26
130.17
128.94
127.41
127.14
77.22
77.01
76.80
43.37
42.92
41.63
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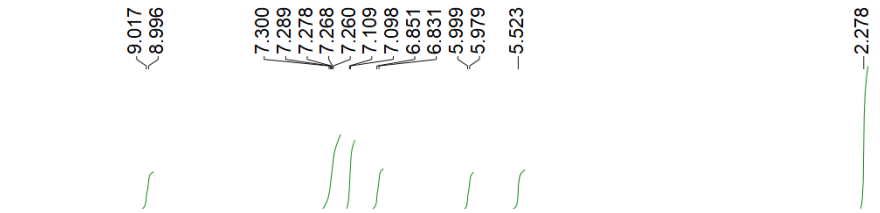
25.54
23.51
22.42
17.10
13.91
O
N
N
O
f1 (ppm)

3ae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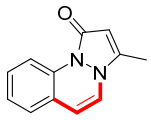
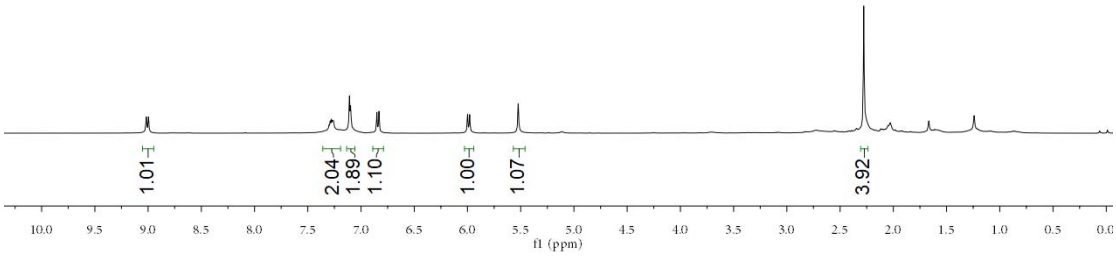
2.278



4aa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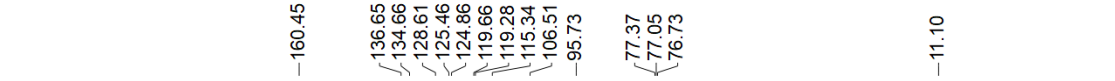
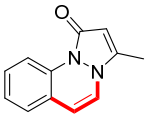
2.04
1.89
1.10
1.00
1.07
3.92
f1 (ppm)


160.45
136.65
134.66
128.61
125.46
124.86
119.66
119.28
115.34
106.51
95.73
77.37
77.05
76.73
11.10



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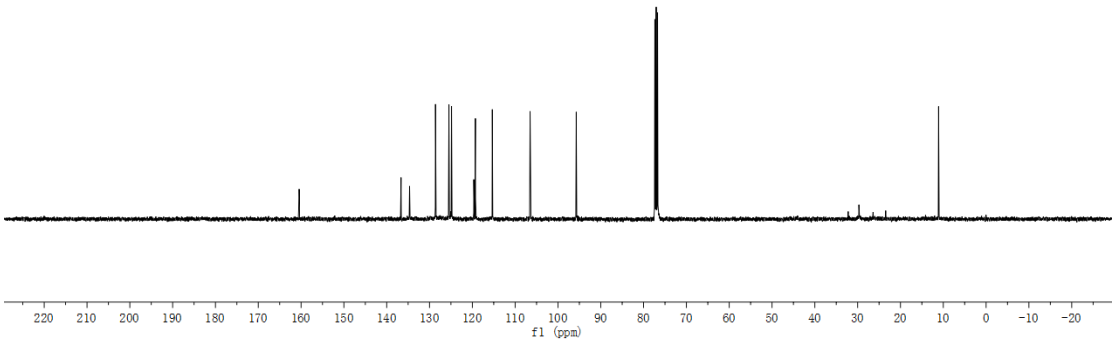
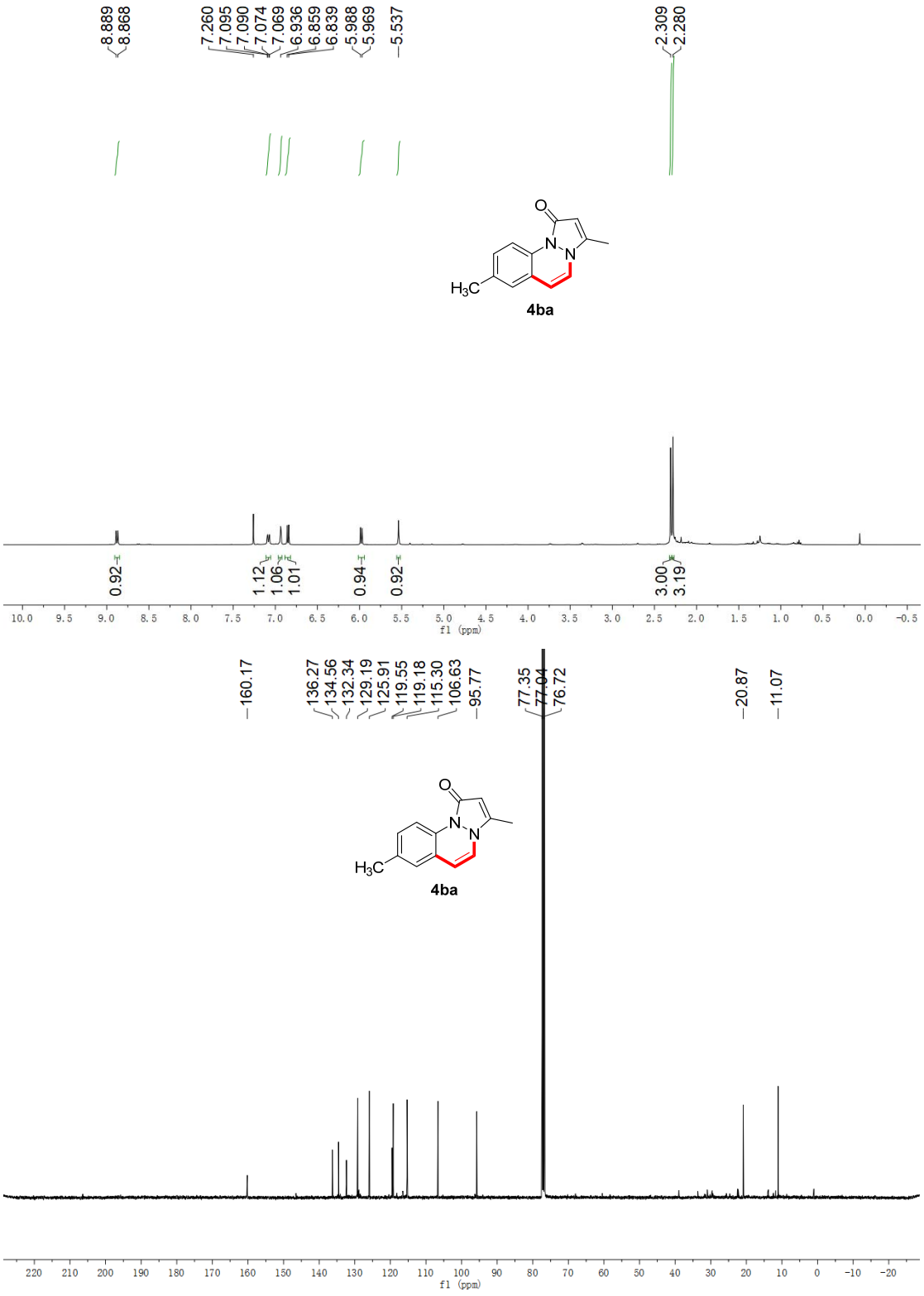
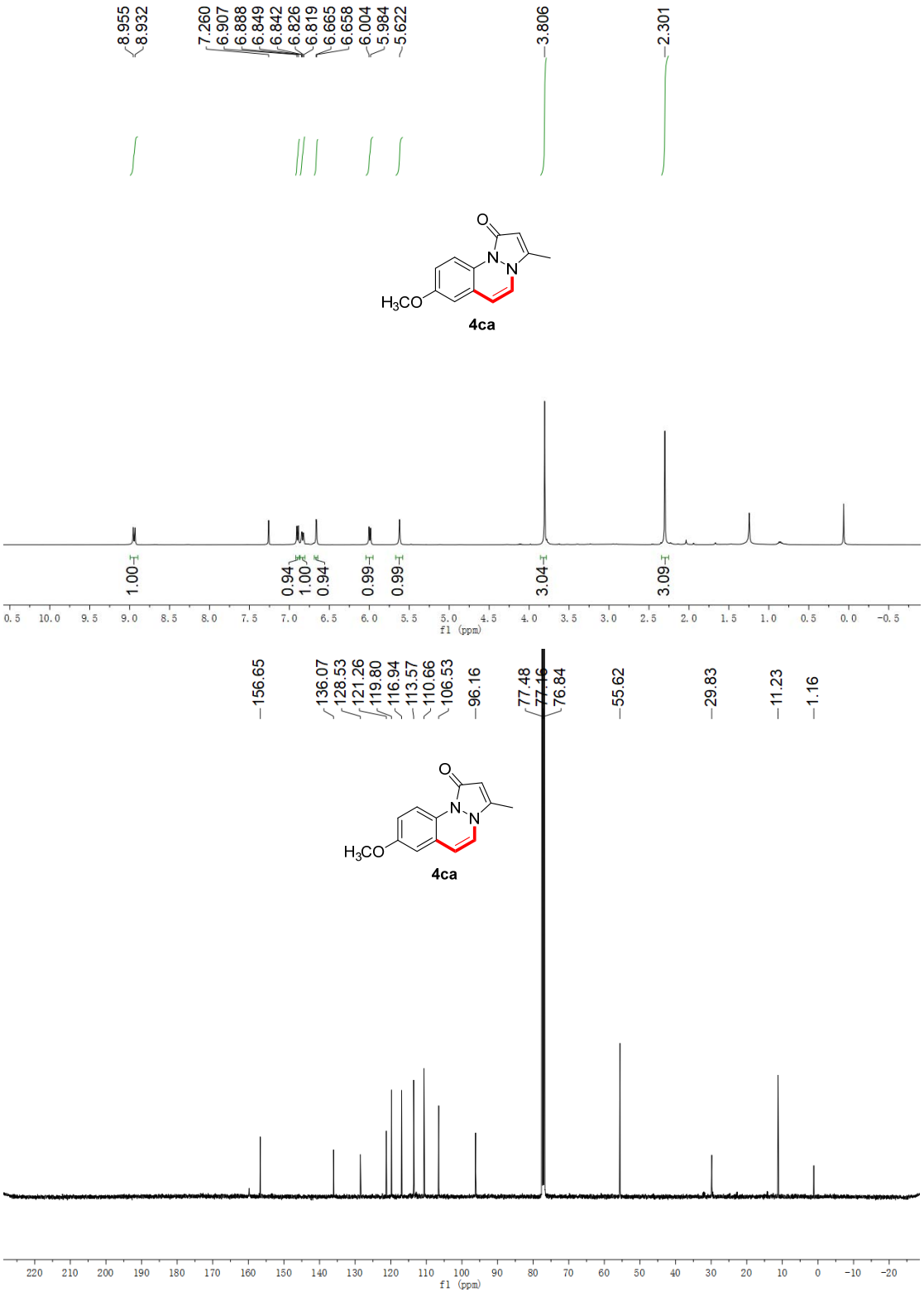
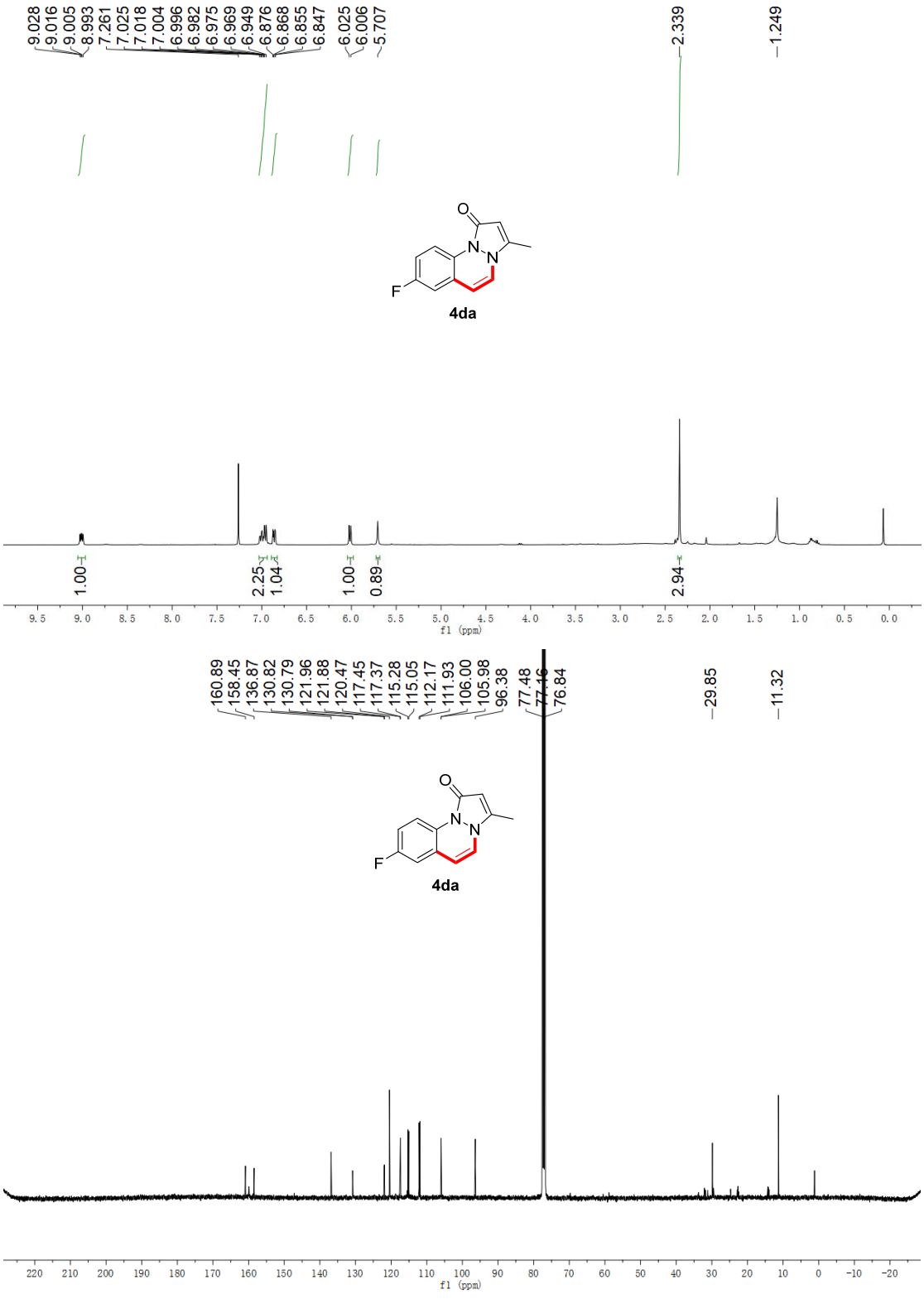
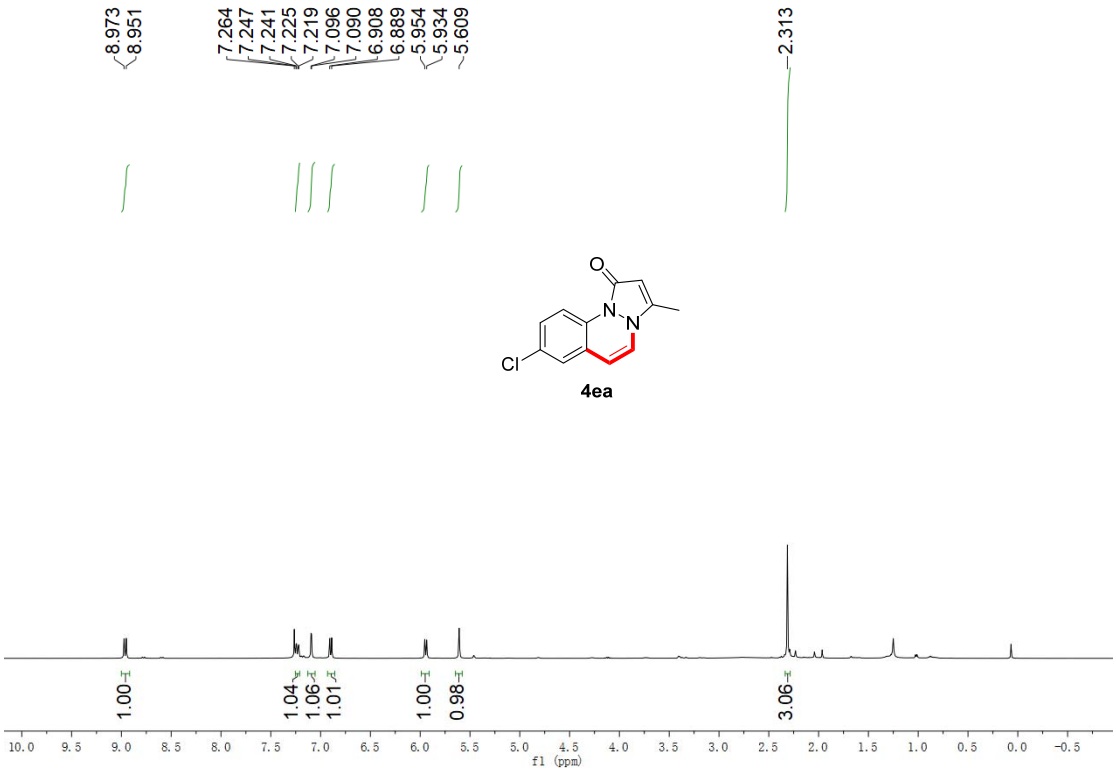
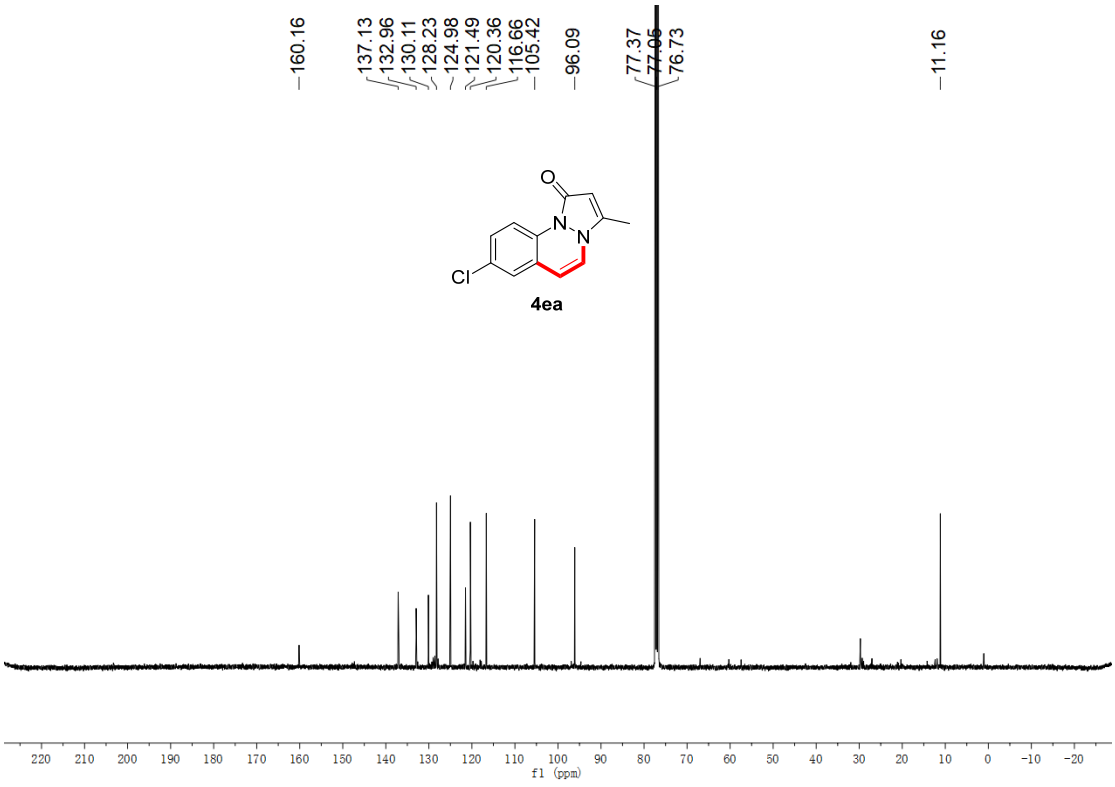

f1 (ppm)

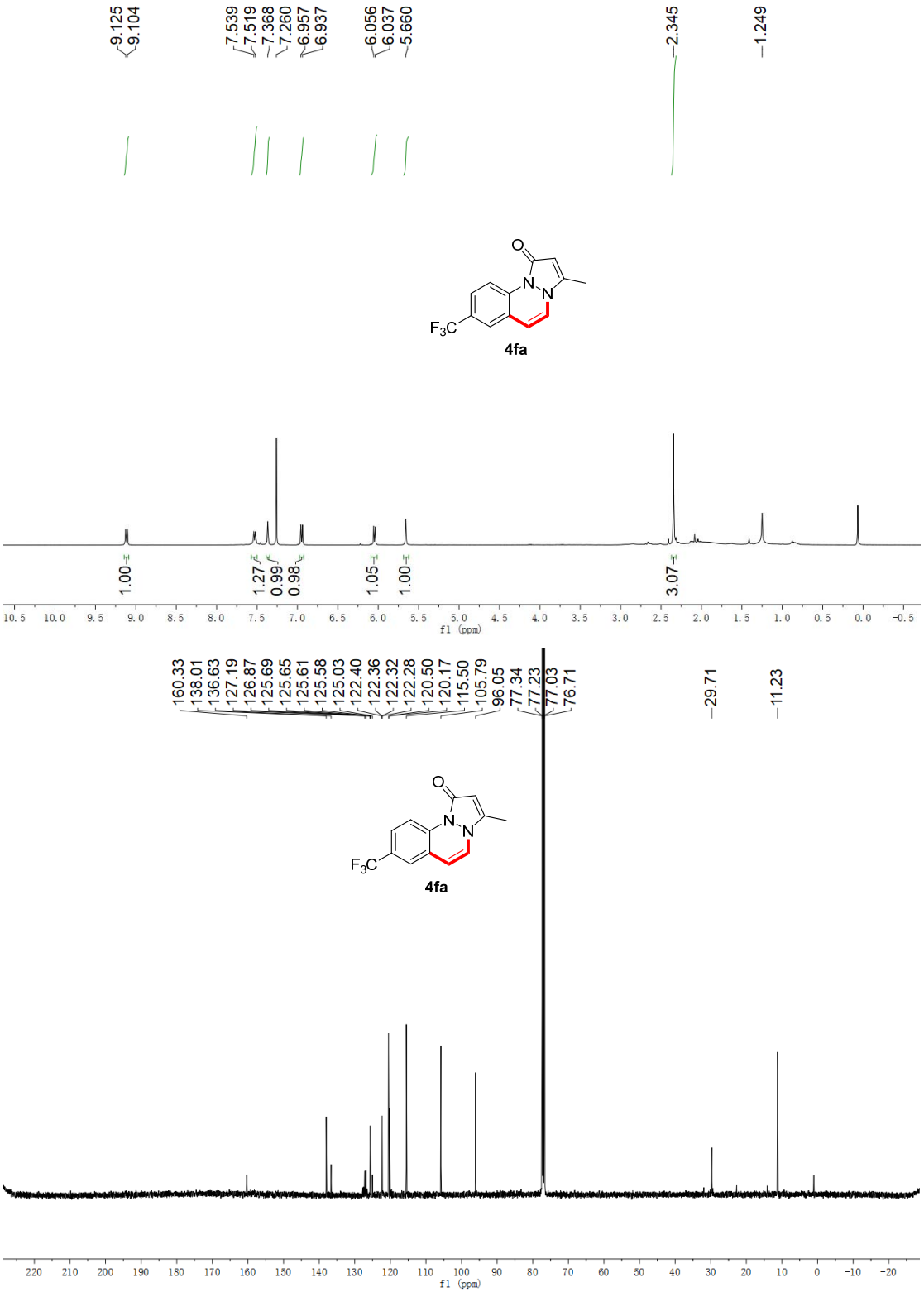

8.889
8.868
7.260
7.095
7.090
7.074
7.069
6.936
6.859
6.839
5.988
5.969
5.537
2.309
2.280
4ba
0.92
1.12
1.06
1.01
0.94
0.92
3.00
3.19
f1 (ppm)
160.17
136.27
134.56
132.34
129.19
125.91
119.55
119.18
115.30
106.63
95.77
77.35
77.04
76.72
20.87
11.07
4ba
f1 (ppm)

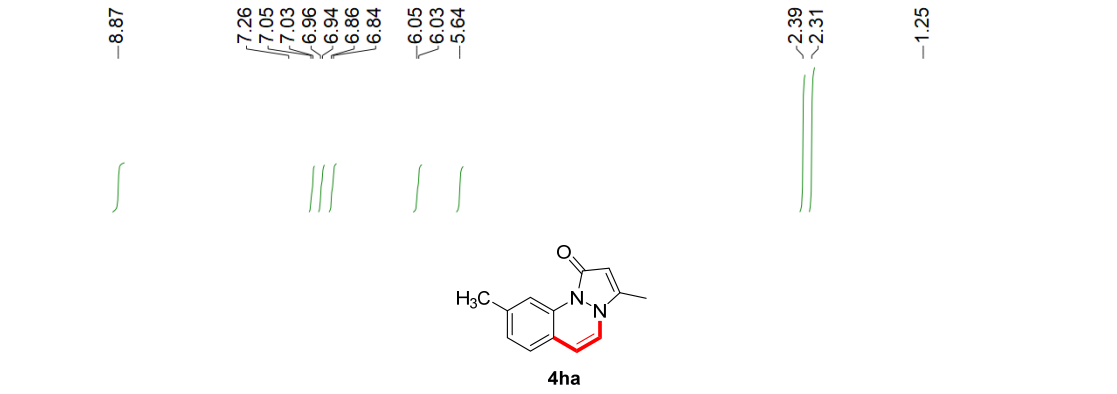

8.955
8.932
7.260
6.907
6.888
6.849
6.842
6.826
6.819
6.665
6.658
6.004
5.984
5.622
3.806
2.301
O
N
N
H3CO
4ca
1.00
0.94
1.00
0.94
0.99
0.99
3.04
3.09
f1 (ppm)
156.65
136.07
128.53
121.26
119.80
116.94
113.57
110.66
106.53
96.16
77.48
77.16
76.84
55.62
29.83
11.23
1.16
O
N
N
H3CO
4ca
f1 (ppm)


9.028
9.016
9.005
8.993
7.261
7.025
7.018
7.004
6.996
6.982
6.975
6.969
6.949
6.876
6.868
6.855
6.847
6.025
6.006
5.707
2.339
1.249
4da
1.00
2.25
1.04
1.00
0.89
2.94
f1 (ppm)
160.89
158.45
136.87
130.82
130.79
121.96
121.88
120.47
117.45
117.37
115.28
115.05
112.17
111.93
106.00
105.98
96.38
77.48
77.16
76.84
29.85
11.32
4da
f1 (ppm)

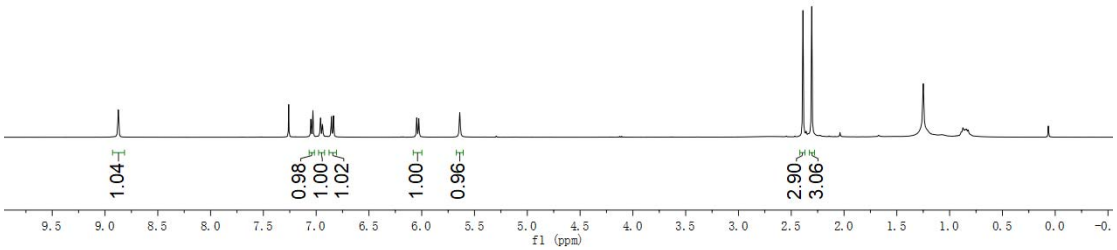

8.973
8.951
7.264
7.247
7.241
7.225
7.219
7.096
7.090
6.908
6.889
5.954
5.934
5.609
2.313
O
N
N
Cl
4ea
1.00
1.04
1.06
1.01
1.00
0.98
3.06
f1 (ppm)

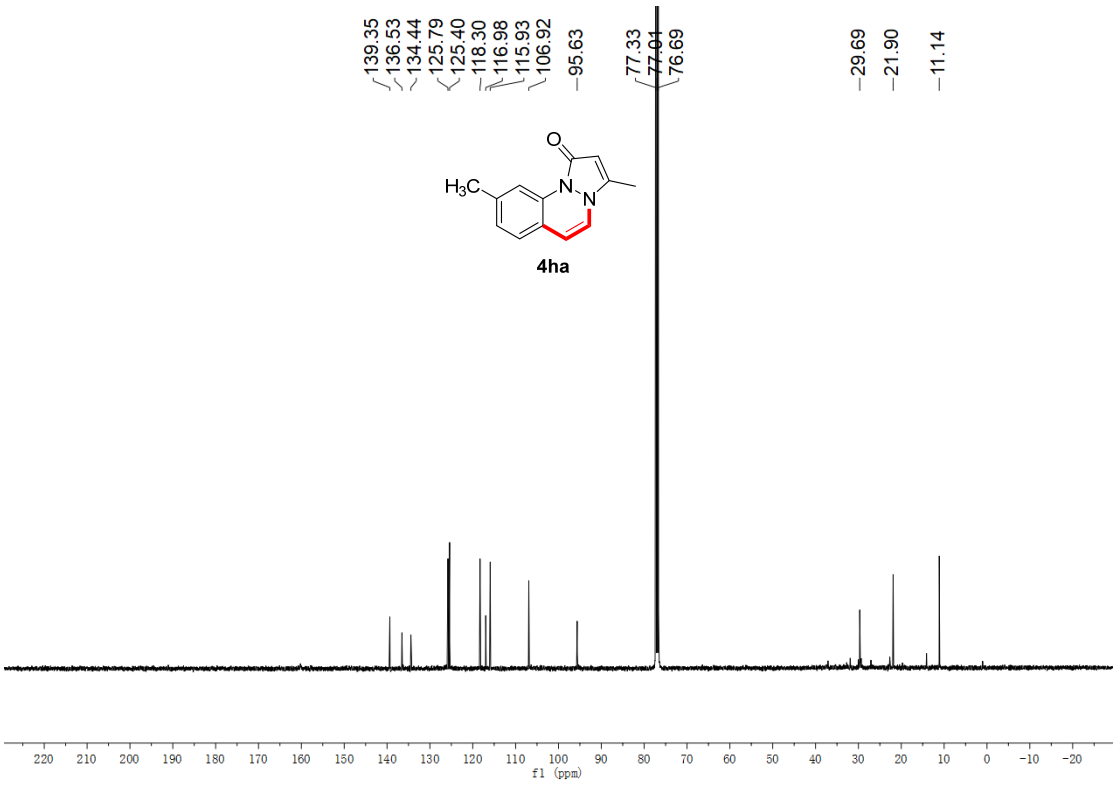

160.16
137.13
132.96
130.11
128.23
124.98
121.49
120.36
116.66
105.42
96.09
77.37
77.06
76.73
11.16
O
N
N
Cl
4ea
f1 (ppm)


9.125
9.104
7.539
7.519
7.368
7.260
6.957
6.937
6.056
6.037
5.660
2.345
1.249
4fa
1.00
1.27
0.99
0.98
1.05
1.00
3.07
f1 (ppm)
160.33
138.01
136.63
127.19
126.87
125.69
125.65
125.61
125.58
125.03
122.40
122.36
122.32
122.28
120.50
120.17
115.50
105.79
96.05
77.34
77.23
77.03
76.71
29.71
11.23
4fa
f1 (ppm)

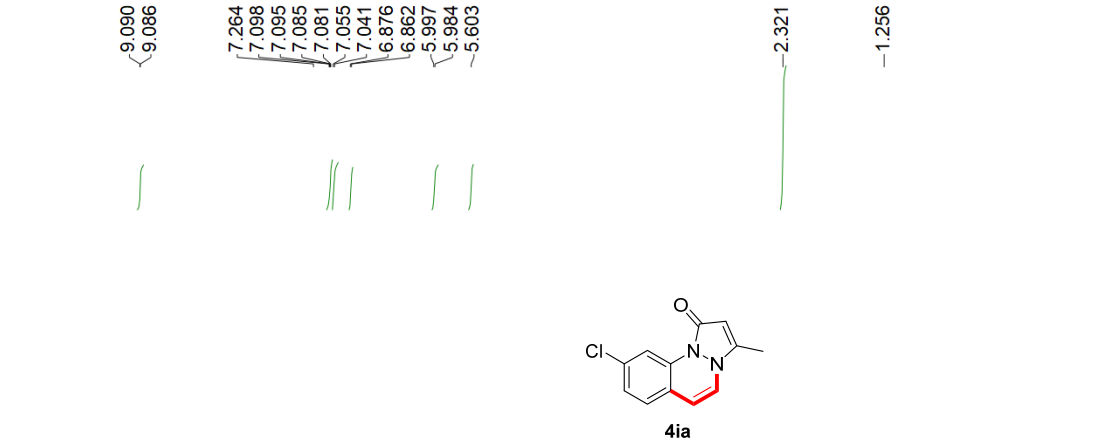

8.87
7.26
7.05
7.03
6.96
6.94
6.86
6.84
6.05
6.03
5.64
2.39
2.31
1.25
O
H3C
N
N

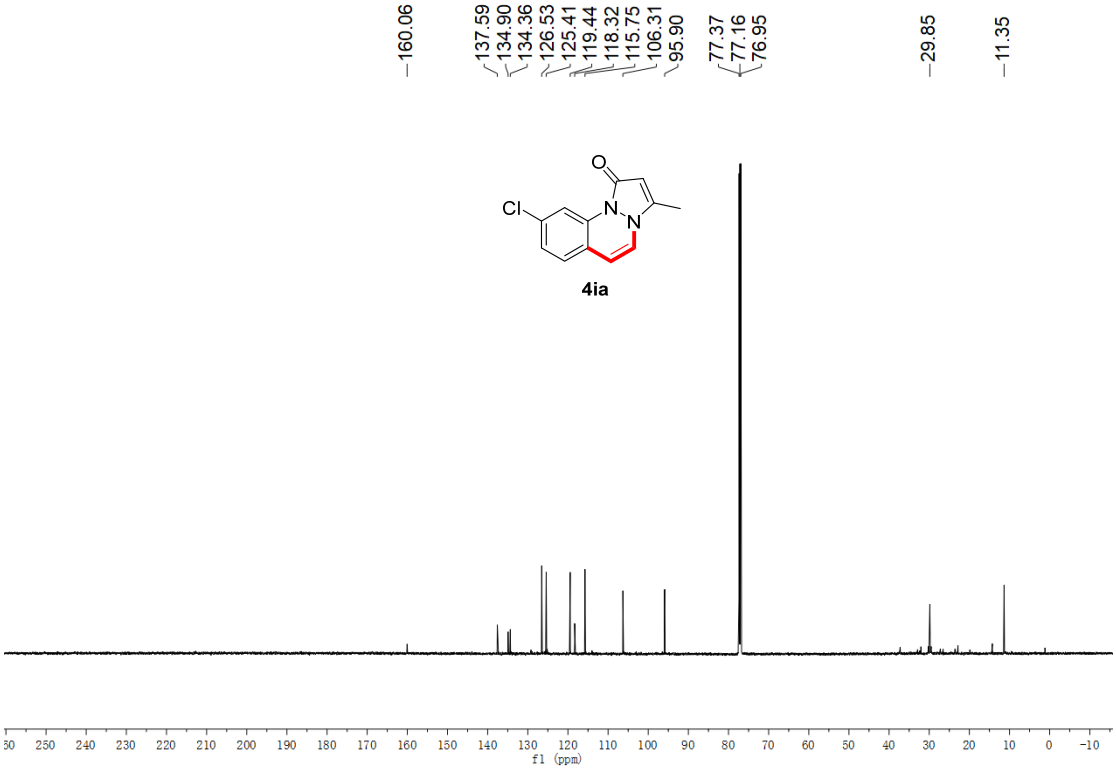
4ha


1.04
0.98
1.00
1.02
1.00
0.96
2.90
3.06
f1 (ppm)


139.35
136.53
134.44
125.79
125.40
118.30
116.98
115.93
106.92
95.63
77.33
77.01
76.69
29.69
21.90
11.14
O
H3C
N
N
f1 (ppm)

4ha


9.090
9.086
7.264
7.098
7.095
7.085
7.081
7.055
7.041
6.876
6.862
5.997
5.984
5.603
2.321
1.256
Cl
O
N
N
4ia
1.00
1.11
1.05
0.95
1.00
1.01
3.19
f1 (ppm)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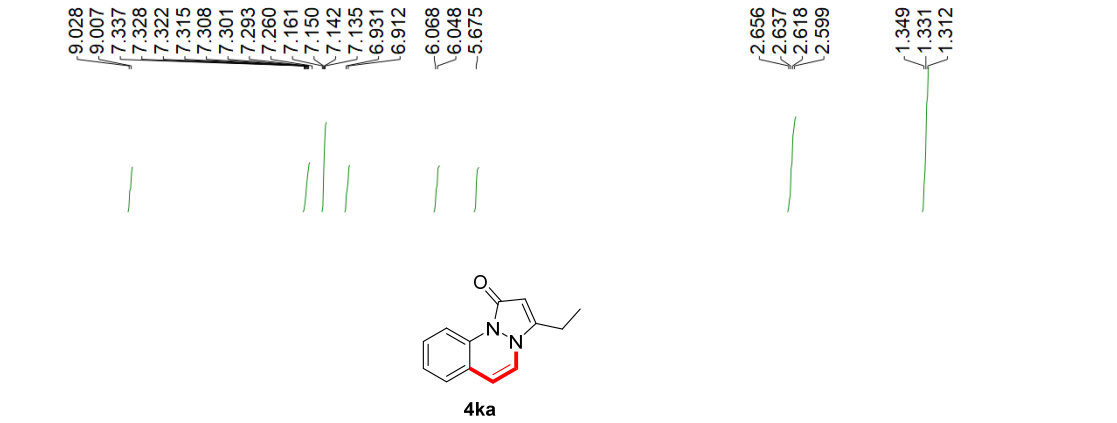
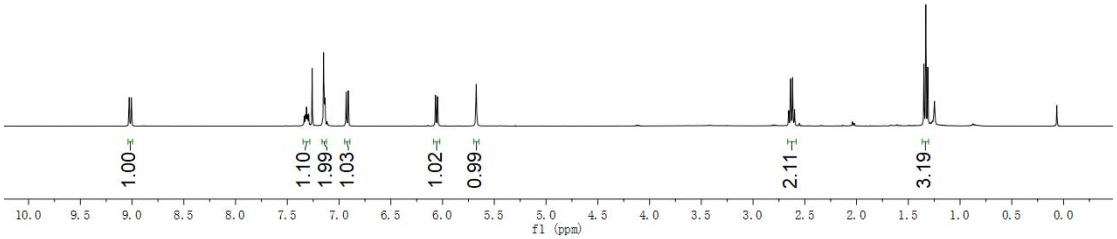
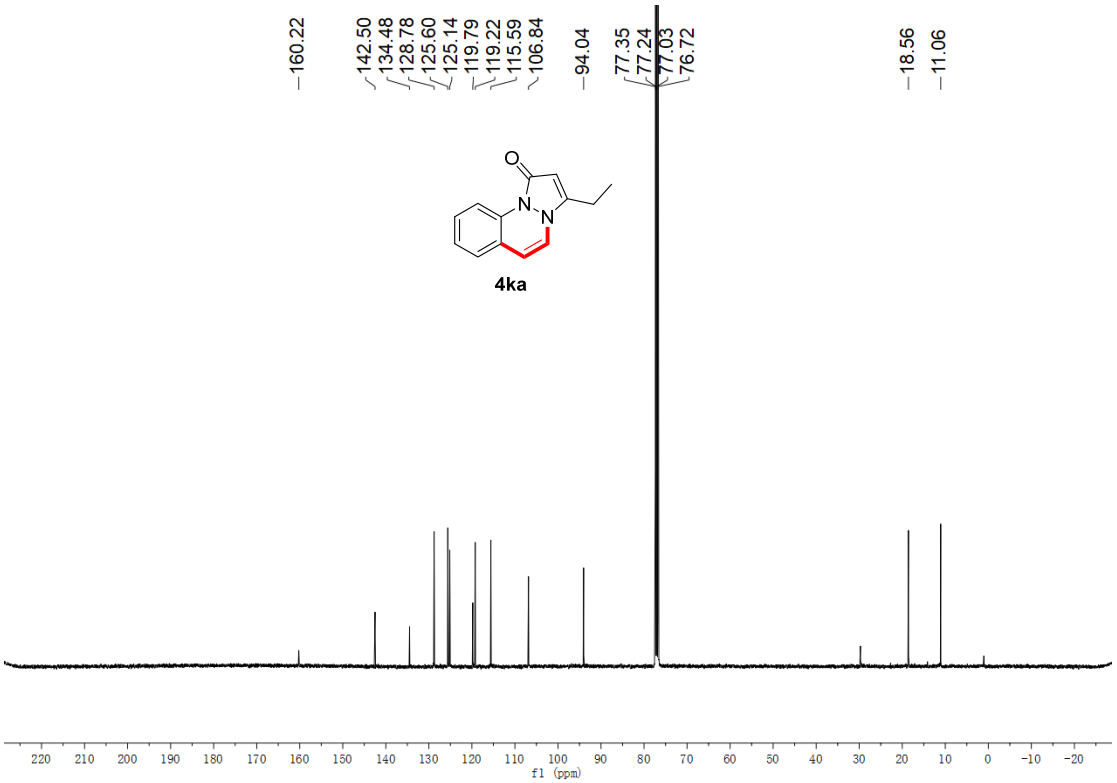
137.59
134.90
134.36
126.53
125.41
119.44
118.32
115.75
106.31
95.90
77.37
77.16
76.95
29.85
11.35
Cl
O
N
N
4ia
f1 (ppm)

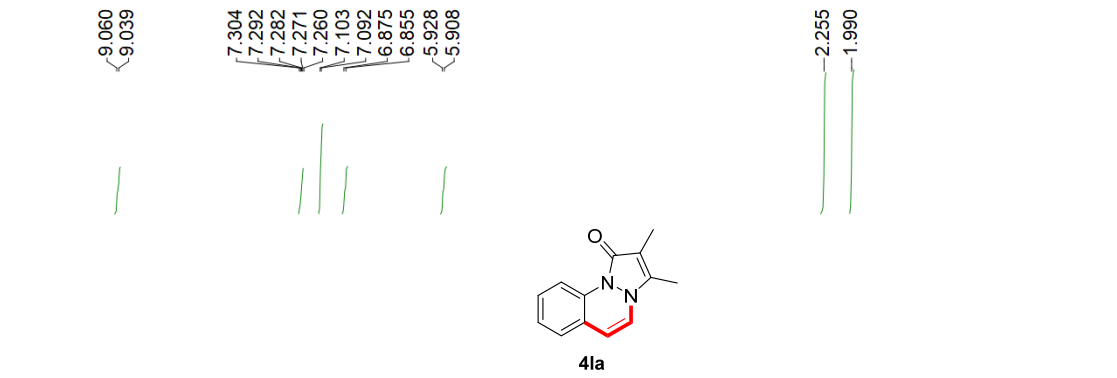

9.028
9.007
7.337
7.328
7.322
7.315
7.308
7.301
7.293
7.260
7.161
7.150
7.142
7.135
6.931
6.912
6.068
6.048
5.675
2.656
2.637
2.618
2.599
1.349
1.331
1.312

4ka


1.00
1.10
1.99
1.03
1.02
0.99
2.11
3.19
f1 (ppm)


160.22
142.50
134.48
128.78
125.60
125.14
119.79
119.22
115.59
106.84
94.04
77.35
77.24
77.03
76.72
18.56
11.06
f1 (ppm)

4ka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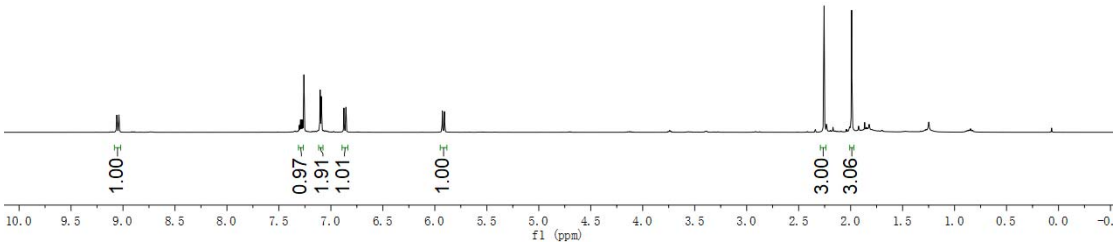
9.039
7.304
7.292
7.282
7.271
7.260
7.103
7.092
6.875
6.855
5.928
5.908
2.255
1.990
4la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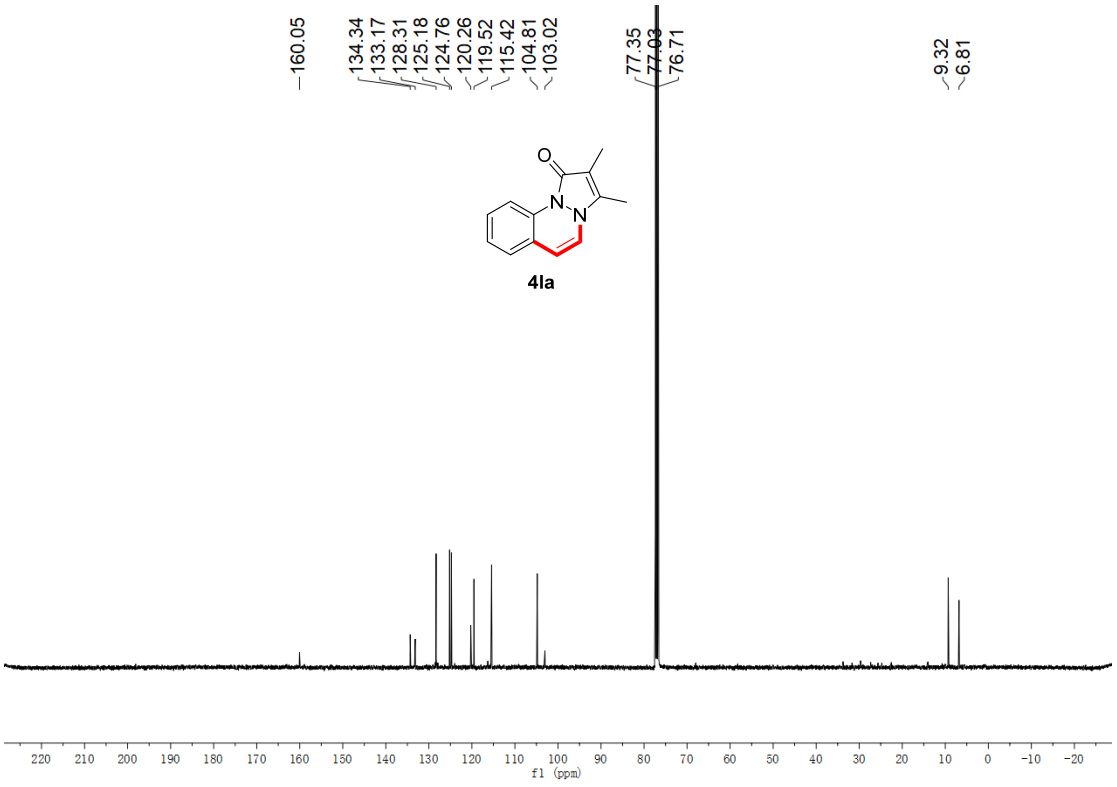
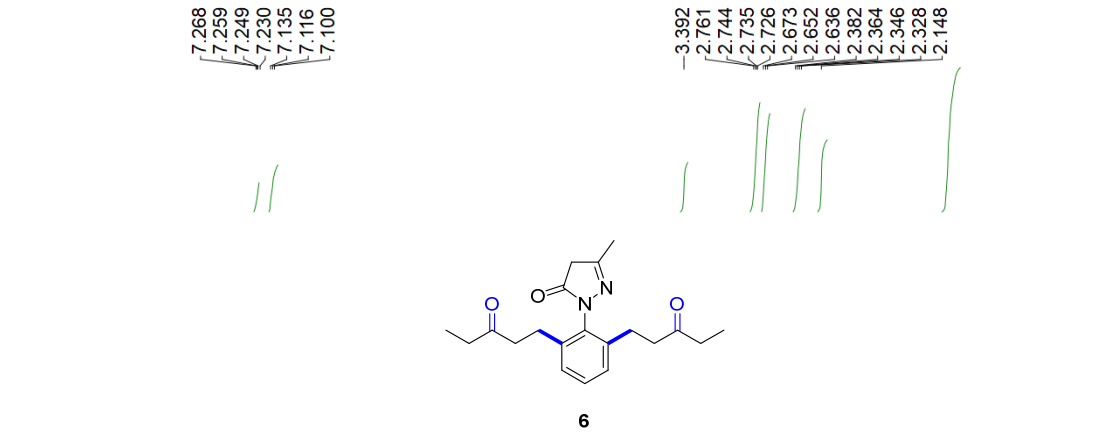
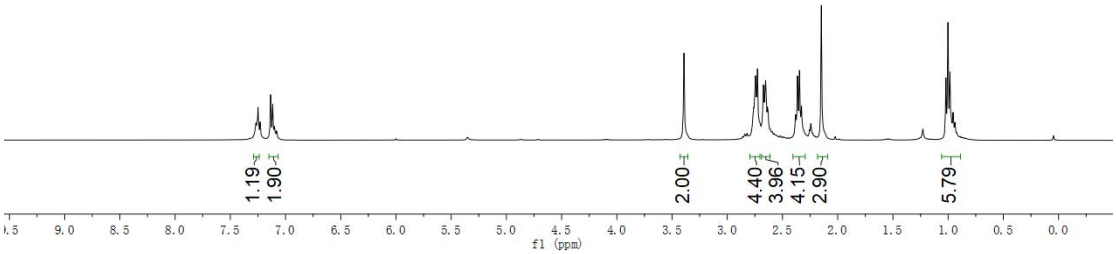
0.97
1.91
1.01
1.00
3.00
3.06
f1 (ppm)


160.05
134.34
133.17
128.31
125.18
124.76
120.26
119.52
115.42
104.81
103.02
77.35
77.03
76.71
9.32
6.81
4la
f1 (ppm)


7.268
7.259
7.249
7.230
7.135
7.116
7.100
3.392
2.761
2.744
2.735
2.726
2.673
2.652
2.636
2.382
2.364
2.346
2.328
2.148

6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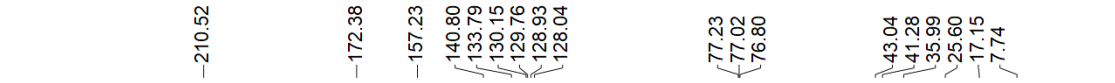
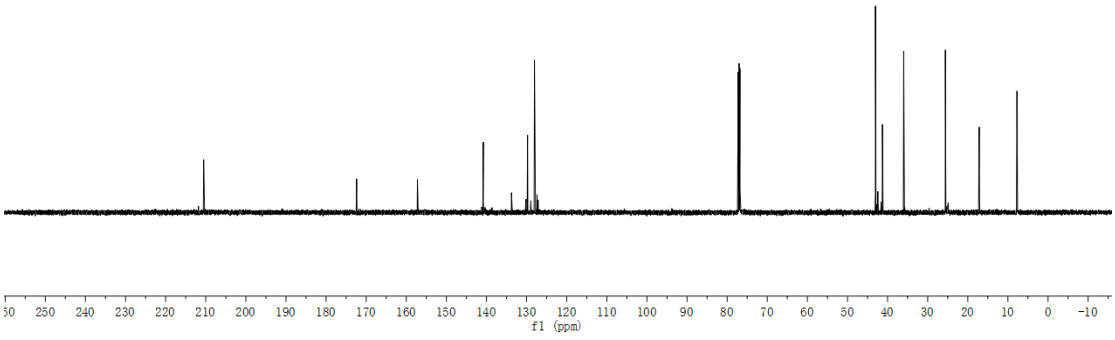
1.90
2.00
4.40
3.96
4.15
2.90
5.79
f1 (ppm)


210.52
172.38
157.23
140.80
133.79
130.15
129.76
128.93
128.04
77.23
77.02
76.80
43.04
41.28
35.99
25.60
17.15
7.74

6


f1 (ppm)