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Base-catalyzed one-pot tandem reaction: an effective strategy for the synthesis of pyrazolo[3,4-*d*]pyrimidinone derivatives

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ABSTRACT

An effective one-pot multicomponent synthesis of pyrazolo[3,4-*d*]pyrimidinone derivatives through the tandem heterocyclization of hydrazine, methylenemalononitrile and aldehyde has been developed. This highly effective method includes nucleophilic addition, heterocyclization, substitution, intramolecular Pinner, Dimroth rearrangement and dehydroaromatization.

1. Introduction

Pyrazolopyrimidine compounds are exist widely in nature and biologically active compounds.[1] Pyrazolopyrimidinones, as a subtype, possess a series of biological activities such as anti-cancer,[2] anti-schistosomal,[3] anti-inflammatory,[4] anti-obesity,[5] adenosine receptors (A_3) antagonists,[6] herbicide,[7] PDE inhibitor.[8] Ibrutinib and sildenafil, recently received extensive attention, are the most representative pyrazolopyrimidine drugs (Figure 1).

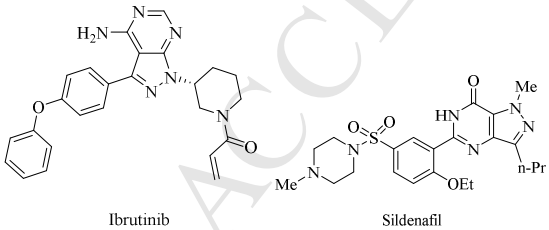
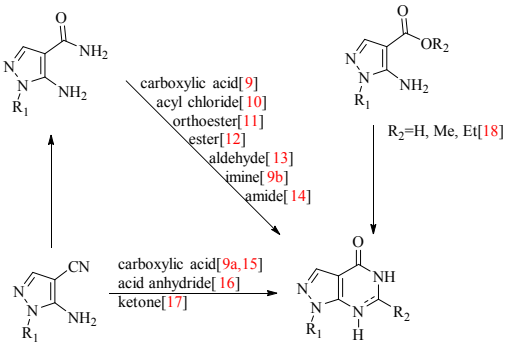


Figure 1. Representative pyrazolopyrimidine drugs

The traditional methods (Scheme 1) for the synthesis of pyrazolo[3,4-*d*]pyrimidinones need multiple steps, including the reaction of 5-aminopyrazole-4-carboxamide hydrolyzed from *o*-aminonitrile and carboxylic acid,[9] acyl chloride,[10] orthoester,[11] ester,[12] aldehyde,[13] imine,[9b] amide[14], and the cyclization of 5-aminopyrazole-4-carbonitrile with carboxylic acid,[9a, 15] acid anhydride,[16] ketone.[17] Other 5-aminopyrazole carboxylic acid or ester[18] can be converted to pyrazolopyrimidinones as well. But there are some drawbacks such as the requirement of oxidant,[16] multistep sequences,[19] high reaction temperature,[16,20] complicated reagents,[21] high pressure[12b] or long reaction time.[18a]



Scheme 1. The general syntheses of pyrazolo[3,4-*d*]pyrimidinones

In our previous studies, the cyclocondensation of ketone and aromatic *o*-aminonitrile catalyzed by base afforded pyrimidinone derivatives.[17] And we thought 5-aminopyrazole-4-carbonitrile is synthesized in the condition of base. So we designed one-pot multicomponent heterocyclization of methylenemalononitriles, hydrazines and aldehydes for the synthesis of 4*H*-pyrazolo[3,4-*d*]pyrimidin-4-ones (Scheme 2).

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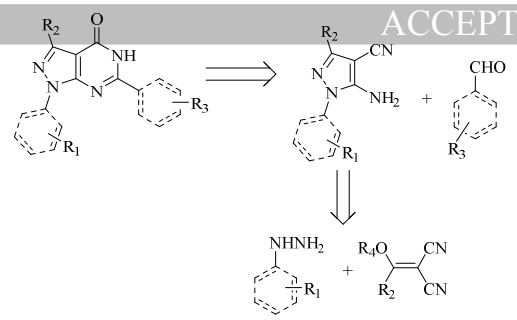
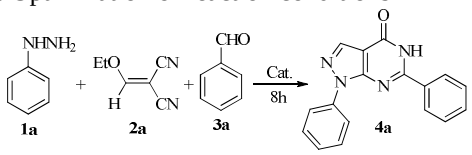


Scheme 2. The retrosynthetic design of reaction.

2. Results and Discussion

The reaction of 2-(ethoxymethylene)malononitrile phenylhydrazine, and benzaldehyde is selected as the model to optimize the reaction conditions, and the results were summarized in Table 1. No target product was obtained with acid catalyst or no catalyst (Table 1, entries 1-3), and the catalytic performance of

Table 1. Optimization of reaction conditions[a]



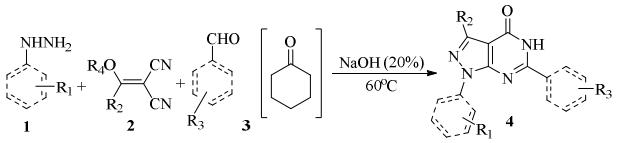
Entry	Solvent	Cat (eqiv)	Temp (^{o}C)	Yield[b] (%)
1	Toluene	-	60	0
2	Toluene	$ZnCl_2$ (1.0)	60	0
3	Toluene	TsOH (1.0)	60	0
4	Toluene	KOBu-*t* (0.2)	60	28
5	Toluene	DBU (0.2)	60	56
6	Toluene	NaOEt (0.2)	60	69
7	Toluene	KOH (0.2)	60	69
8	Toluene	NaOH (0.2)	60	83
9	DMSO	NaOH (0.2)	60	56
10	Diox[c]	NaOH (0.2)	60	14
11	Toluene	NaOH (0.2)	Reflux	73
12[d]	Toluene	NaOH (0.2)	25	63
13	Toluene	NaOH (0.1)	60	35
14	Toluene	NaOH (0.4)	60	83

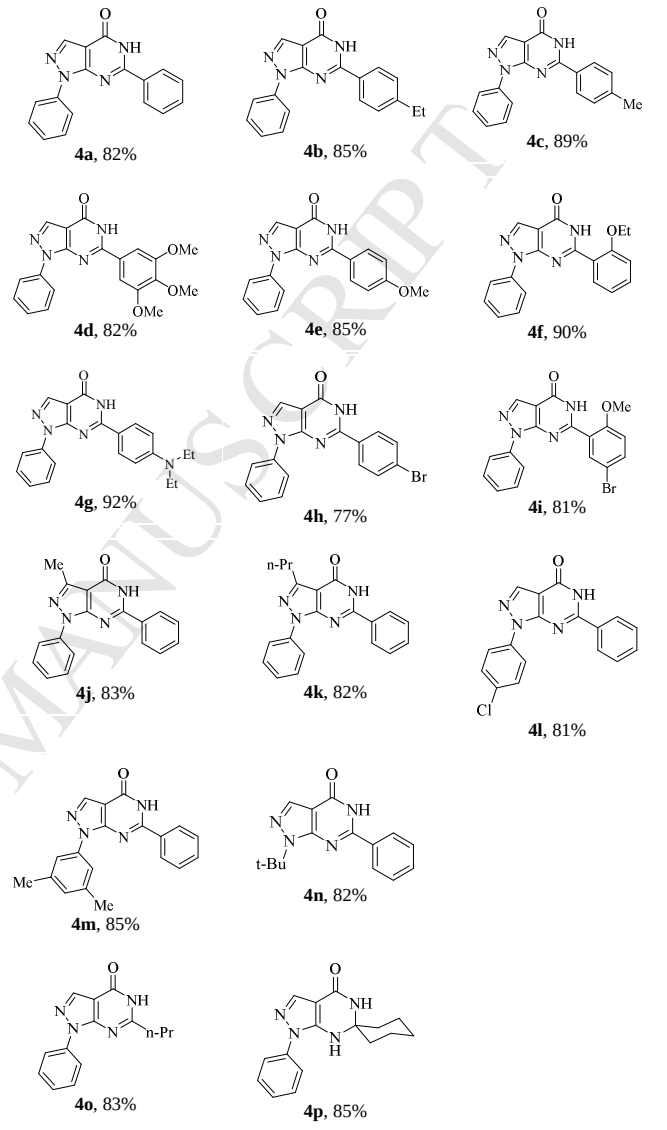
[a]Reactions conditions: **1a** (1.2 mmol), **2a** (1 mmol), **3a** (1.2 mmol) and catalyst in solvent (20 ml). [b]Isolated yields. [c]Diox = 1,4-dioxane. [d]Reaction time: 48h.

inorganic bases was higher than that of organic bases (Table 1, entries 4-8). Toluene was best solvent (Table 1, entries 8-10). The affect of temperature was also investigated (Table 1, entries 11-12). Although higher temperature facilitated the reaction, more by-products were obtained, therefore the apposite temperature was 60^{o}C. The amount of catalyst had influence on the reaction and the appropriate choice was 0.2 equivalent (Table 1, entries 8, 13, 14).

With the optimum conditions in hand, a range of 4*H*-pyrazolo[3,4-*d*]pyrimidin-4-ones were synthesized and the results

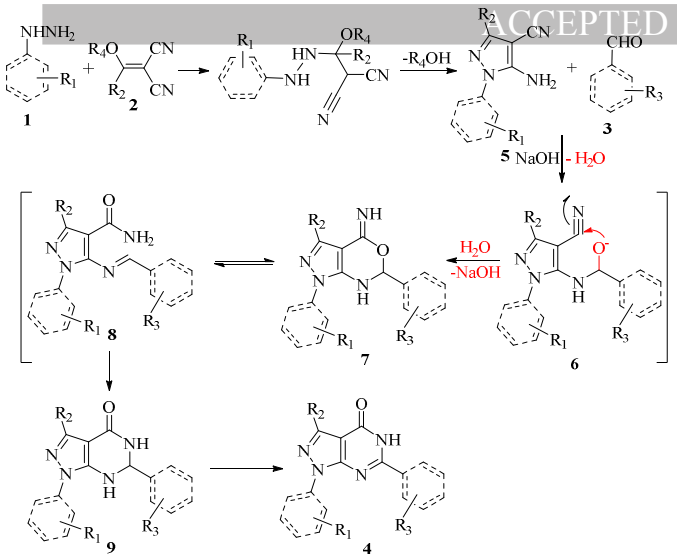
Table 2. Three-component one-pot tandem synthesis of 4*H*-pyrazolo[3,4-*d*]pyrimidin-4-ones[a]





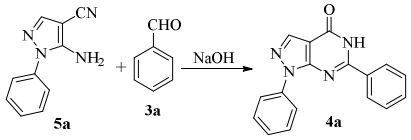
[a]Reactions conditions: **1a** (1.2 mmol), **2a** (1 mmol), **3a** (1.2 mmol) and NaOH (0.2 mmol) in toluene (20 ml); R^4=Et or Me

were listed in Table 2. Aromatic aldehydes possessing electron-donating groups (EDG) provided the corresponding target products in good to excellent yields (Table 2, **4a**-**g**). And the aromatic aldehyde with electron-withdraw groups (EWG) gave lower yields than that of aldehyde with EDG. The possible reason is that the EDG increased the nucleophilicity, which facilitated intramolecular Pinner reaction. To further expand this one-pot methodology, some 1-substituted and 3-substituted pyrazolo[3,4-*d*]pyrimidin-4-ones were synthesized in good yields (Table 2, **4j**-**m**). And the corresponding product was obtained from aliphatic hydrazine in good yields (Table 2, **4n**). Notably, reaction between ketones and chain aldehydes afforded the corresponding compounds in good yields (Table 2, **4o**-**p**). These results indicated the universality and advantages of one-pot method.



Scheme 3. Proposed mechanism of the formation of **4**.

In order to rationalize the process of reaction, a possible reaction mechanism is depicted in Scheme 3. Methylenemalononitrile **2** undergoes nucleophilic addition with hydrazine **1**, and then followed by cyclisation, aromatization to obtain the intermediate 5-aminopyrazole-4-carbonitrile **5**. The amino group of **5** attacks aldehyde to afford **6** with the catalysis of base. Then **6** undergoes intramolecular nucleophilic addition and 3,1-oxazine **7** is formed, and then rearranges to dihydro pyrazolo[3,4-*d*]pyrimidin-4-ones **9** (Dimroth rearrangement[22]). At last, **9** transforms to the target product **4** by air oxidant.[23]



Scheme 4. The synthesis of **4a** by the reaction of **5a** with **3a**.

To further demonstrate this mechanism, the key intermediates, 5-amino-1-phenyl-1*H*-pyrazole-4-carbonitrile **5a**[24], was separated and reacted with benzaldehyde **3a** in the catalyst of NaOH to give the targeted product, 1,6-diphenyl-1,5-dihydro-4*H*-pyrazolo-[3,4-*d*]pyrimidin-4-one **4a** in 85% yield (Scheme 4).

All products were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and ESI spectra. And the structure of **4n** was further confirmed by X-ray diffraction (Figure 2).[25]

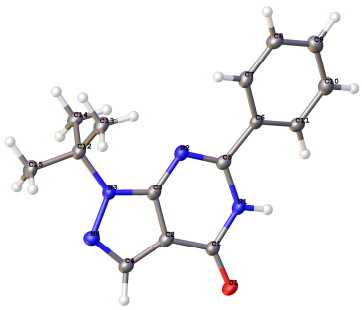


Figure 2. Molecular structure of compound **4n**.

3. Conclusions

In summary, an effective method for combining two well-known reactions into one-pot tandem reaction for synthesis of pyrazolo[3,4-*d*]pyrimidin-4-ones was developed. This is the first time to construct pyrazolo[3,4-*d*]pyrimidinones from hydrazines, methylenemalononitriles and aldehydes. This method avoids expensive catalyst, high reaction temperature and long reaction time. All products were easy to isolate and have a convenient application for the construction of pyrazolopyrimidinone skeleton.

4. Experimental section

General Methods: The raw materials including hydrazines, 2-(ethoxymethylene)malononitrile and aldehydes are commercially available. 2-(1-Ethoxyethylidene)malononitrile and 2-(1-methoxy-butylidene)malononitrile were synthesized from ortho-ester using the method reported by Markwalder.[26] Melting points were determined using XT4 microscope melting point apparatus (uncorrected). Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrophotometer with KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded at a Bruker 400 MHz spectrometer with TMS as the internal standard. Mass spectra were obtained with ESI ionization using a Bruker APEX IV and ZAB-HS mass spectrometer.

General Procedure for the Synthesis of 4: Hydrazine (**1**, 1.2 mmol) and methylenemalononitrile (**2**, 1.0 mmol) were mixed in toluene, then NaOH (0.2 mmol) and aldehyde (**3**, 1.2 mmol) was added at 60^{o}C. At the end of the reaction (TLC monitoring), the reaction mixture was extracted with EtOAc (3×20 mL). Then the organic layer was evaporated under reduced pressure. The crude product was washed by ethanol and then filtered. The filter cake was dried and purified by crystallization from ethanol to afford pure **4**.

1,6-Diphenyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (4a): White solid; m.p. > 300^{o}C; IR (KBr, *v*, cm^{-1}): 3077, 1684; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.65 (s, 1H), 8.37 (s, 1H), 8.20-8.15 (m, 4H), 7.64-7.57 (m, 5H), 7.44-7.40 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 158.7, 156.5, 152.7, 138.9, 136.5, 132.5, 132.5, 129.8, 129.2, 128.7, 127.5, 122.1, 106.5; HRMS (ESI): calcd. For $C_{17}H_{12}N_4OH$ $[M+H]^+$ 289.1084; found 289.1091.

6-(4-Ethylphenyl)-1-phenyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (4b): White solid; m.p. 253-255^{o}C; IR (KBr, *v*, cm^{-1}): 3078, 2966, 1686; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.53 (s, 1H), 8.34 (s, 1H), 8.17-8.11 (m, 4H), 7.62-7.58 (m, 2H), 7.43-7.40 (m, 3H), 2.71 (q, *J* = 8.0 Hz, 2H), 1.23 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 158.7, 156.5, 152.8, 148.8, 138.9, 136.5, 130.0, 129.8, 128.8, 127.4, 122.0, 106.3, 28.6, 15.7; HRMS (ESI): calcd. For $C_{19}H_{16}N_4OH$ $[M+H]^+$ 317.1397; found 317.1397.

1-Phenyl-6-(*p*-tolyl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (4c)[27]: White solid; m.p. 295-297^{o}C; IR (KBr, *v*, cm^{-1}): 3078, 2971, 1684; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.58 (s, 1H), 8.35 (s, 1H), 8.17-8.09 (m, 4H), 7.62-7.58 (m, 2H), 7.43-7.37 (m, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 159.0, 156.6, 152.9, 142.6, 139.0, 136.5, 129.8, 128.6, 127.4, 122.0, 106.3, 21.5; ESI-MS (*m/z*) = 303 ($[M+H]^+$).

1-Phenyl-6-(3,4,5-trimethoxyphenyl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (4d): White solid; m.p. > 300^{o}C; IR (KBr, *v*, cm^{-1}): 3103, 2939, 1685; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.65 (s, 1H), 8.36 (s, 1H), 8.19-8.17 (m, 2H), 7.63-7.59 (m, 4H), 7.43-7.39 (m, 1H), 3.90 (s, 6H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 158.8, 155.8, 153.3, 152.6, 141.1, 138.9, 136.6, 129.7, 127.4, 127.3, 121.9,

106.2 106.1, 60.7, 56.5; HRMS (ESI): calcd. For $C_{20}H_{18}N_4O_4H$ $[M+H]^+$ 379.1401; found 379.1402.

6-(4-Methoxyphenyl)-1-phenyl-1,5-dihydro-4*H*-pyrazolo [3,4-*d*]pyrimidin-4-one (4e)[28]**:** Yellow solid; m.p. > 300°C; IR (KBr, *v*, cm^{-1}): 3111, 2971, 1673; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.49 (s, 1H), 8.34 (s, 1H), 8.22-8.15 (m, 4H), 7.63-7.59 (m, 2H), 7.44-7.40 (m, 1H), 7.14-7.12 (m, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 162.8, 158.8, 156.1, 152.9, 139.0, 136.5, 130.5, 130.0, 127.4, 124.5, 122.0, 114.7, 106.0, 56.0; ESI-MS (*m/z*) = 319 ($[M+H]^+$).

6-(2-Ethoxyphenyl)-1-phenyl-1,5-dihydro-4*H*-pyrazolo [3,4-*d*]pyrimidin-4-one (4f)[29]**:** Yellow solid; m.p. 210-212°C; IR (KBr, *v*, cm^{-1}): 3078, 2973, 1685; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.17 (s, 1H), 8.37 (s, 1H), 8.37-8.10 (m, 2H), 7.83-7.80 (m, 1H), 7.59-7.53 (m, 3H), 7.42-7.38 (m, 1H), 7.22-7.20 (m, 1H), 7.14-7.10 (m, 1H), 4.18 (q, *J* = 8.0 Hz, 2H), 1.36 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 157.8, 157.3, 156.0, 136.5, 133.4, 131.1, 129.7, 127.4, 122.2, 121.1, 113.5, 106.3, 64.7, 14.9; ESI-MS (*m/z*) = 333 ($[M+H]^+$).

6-(4-(Diethylamino)phenyl)-1-phenyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (4g): Yellow solid; m.p. 284-286°C; IR (KBr, *v*, cm^{-1}): 3079, 2969, 1689; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.17 (s, 1H), 8.28 (s, 1H), 8.19 (d, *J* = 8.0 Hz, 2H), 8.12 (d, *J* = 8.0 Hz, 2H), 7.62-7.58 (m, 2H), 7.42-7.38 (m, 1H), 6.78-6.76 (m, 2H), 3.43 (q, *J* = 8.0 Hz, 4H), 1.13 (t, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 158.9, 156.4, 153.4, 150.7, 139.2, 136.5, 130.2, 129.7, 127.1, 121.7, 117.2, 111.2, 105.4, 44.3, 12.9; HRMS (ESI): calcd. For $C_{21}H_{21}N_5OH$ $[M+H]^+$ 360.1819; found 360.1810.

6-(4-Bromophenyl)-1-phenyl-1,5-dihydro-4*H*-pyrazolo [3,4-*d*]pyrimidin-4-one (4h)[27]**:** White solid; m.p. > 300°C; IR (KBr, *v*, cm^{-1}): 3049, 1690; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.78 (s, 1H), 8.38 (s, 1H), 8.13-8.10 (m, 4H), 7.81-7.79 (m, 2H), 7.62-7.58 (m, 2H), 7.45-7.41 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 158.6, 155.7, 152.5, 138.8, 136.6, 132.3, 131.7, 130.7, 129.8, 127.6, 126.4, 122.2, 106.5; ESI-MS (*m/z*) = 367 ($[M+H]^+$).

6-(5-Bromo-2-methoxyphenyl)-1-phenyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (4i): Green solid; m.p. 288-290°C; IR (KBr, *v*, cm^{-1}): 3095, 2947, 1717; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.39 (s, 1H), 8.38 (s, 1H), 8.06-8.03 (m, 2H), 7.83-7.82 (m, 1H), 7.75-7.72 (m, 1H), 7.60-7.56 (m, 2H), 7.43-7.39 (m, 1H), 7.21-7.19 (m, 1H), 3.86 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 157.9, 157.0, 154.7, 152.5, 138.7, 136.5, 135.4, 133.0, 129.8, 127.6, 124.8, 122.4, 114.9, 112.1, 106.6, 56.8; HRMS (ESI): calcd. For $C_{18}H_{13}BrN_4O_2H$ $[M+H]^+$ 397.0295; found 397.0287.

3-Methyl-1,6-diphenyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*] pyrimidin-4-one (4j)[27]**:** White solid; m.p. > 300°C; IR (KBr, *v*, cm^{-1}): 3076, 2967, 1679; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.53 (s, 1H), 8.19-8.13 (m, 4H), 7.67-7.52 (m, 6H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 159.7, 157.3, 155.6, 153.7, 150.3, 139.8, 132.4, 129.7, 129.2, 128.7, 127.0, 121.8, 100.0, 31.2; ESI-MS (*m/z*) = 303 ($[M+H]^+$).

1,6-Diphenyl-3-propyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*] pyrimidin-4-one (4k): White solid; m.p. 285-287°C; IR (KBr, *v*, cm^{-1}): 3064, 2960, 1678; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.55 (s, 1H), 8.17-8.13 (m, 4H), 7.65-7.56 (m, 5H), 7.40-7.36 (m, 1H), 2.92 (t, *J* = 8.0 Hz, 2H), 1.84-1.80 (m, 2H), 0.99 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 159.2, 156.5, 153.2, 150.6, 138.9, 132.6, 132.4, 129.7, 129.2, 128.7, 127.0, 121.8, 104.1, 30.04, 21.88, 14.18; HRMS (ESI): calcd. For $C_{20}H_{18}N_4OH$ $[M+H]^+$ 331.1553; found 331.1546.

1-(4-Chlorophenyl)-6-phenyl-1,5-dihydro-4*H*-pyrazolo [3,4-*d*]pyrimidin-4-one (4l): White solid; m.p. > 300°C; IR (KBr, *v*, cm^{-1}): 3078, 1683; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.70 (s, 1H), 8.40 (s, 1H), 8.22-8.19 (m, 4H), 7.69-7.57 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 158.6, 156.8, 152.8, 137.7, 136.9, 132.6, 131.6, 129.8, 129.3, 128.8, 123.5, 106.6; HRMS (ESI): calcd. For $C_{17}H_{11}ClN_4OH$ $[M+H]^+$ 323.0694; found 323.0695.

1-(3,5-Dimethylphenyl)-6-phenyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (4m): White solid; m.p. 280-282°C; IR (KBr, *v*, cm^{-1}): 3073, 2969, 1683; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.63 (s, 1H), 8.33 (s, 1H), 8.18-8.16 (m, 2H), 7.76 (s, 2H), 7.63-7.59 (m, 3H), 7.06 (s, 1H), 2.39 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 158.7, 156.4, 152.6, 139.0, 136.3, 132.5, 132.5, 129.3, 128.9, 128.6, 119.9, 106.4, 21.6; HRMS (ESI): calcd. For $C_{19}H_{16}ClN_4OH$ $[M+H]^+$ 317.1397; found 317.1398.

1-(Tert-butyl)-6-phenyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*] pyrimidin-4-one (4n): White solid; m.p. > 300°C; IR (KBr, *v*, cm^{-1}): 3027, 2968, 1674; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.39 (s, 1H), 8.17-8.15 (m, 2H), 8.03 (s, 1H), 7.62-7.56 (m, 3H), 1.76 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 158.9, 154.0, 152.2, 133.0, 132.8, 132.2, 129.2, 128.4, 106.1, 60.6, 29.6; HRMS (ESI): calcd. For $C_{15}H_{16}N_4OH$ $[M+H]^+$ 269.1397; found 269.1400.

1-Phenyl-6-propyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (4o)[28]**:** White solid; m.p. 253-255°C; IR (KBr, *v*, cm^{-1}): 3077, 2962, 1675; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.29 (s, 1H), 8.26 (s, 1H), 8.09-8.07 (m, 2H), 7.58-7.54 (m, 2H), 7.41-7.37 (m, 1H), 2.65 (t, *J* = 8.0 Hz, 2H), 1.81-1.72 (m, 2H), 0.95 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 162.1, 158.4, 152.9, 139.0, 136.3, 129.7, 127.3, 121.9, 106.2, 36.6, 20.7, 13.9; ESI-MS (*m/z*) = 255 ($[M+H]^+$).

1'-Phenyl-1',7'-dihydrospiro[cyclohexane-1,6'-pyrazolo [3,4-*d*]pyrimidin]-4'(5'*H*)-one (4p)[30]**:** White solid; m.p. 182-184°C; IR (KBr, *v*, cm^{-1}): 3196, 2931, 1651; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.76 (s, 1H), 7.73 (s, 1H), 7.56-7.52 (m, 2H), 7.47 (s, 1H), 7.38-7.35 (m, 1H), 6.62 (s, 1H), 1.89-1.86(m, 2H), 1.68-1.62 (m, 2H) 1.56-1.51 (m, 4H), 1.46-1.42 (m, 1H), 1.31-1.26 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 161.7, 148.3, 139.0, 138.3, 129.8, 127.1, 121.9, 102.4, 71.0, 36.5, 25.2, 22.0; ESI-MS (*m/z*) = 283 ($[M+H]^+$).

Acknowledgments

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25 Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-1063677. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam. ac.Uk).
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Supporting Information

For

Base-Catalyzed One-Pot Tandem Reaction: An Effective Strategy for the Synthesis of Pyrazolo[3,4-*d*]pyrimidinone Derivatives

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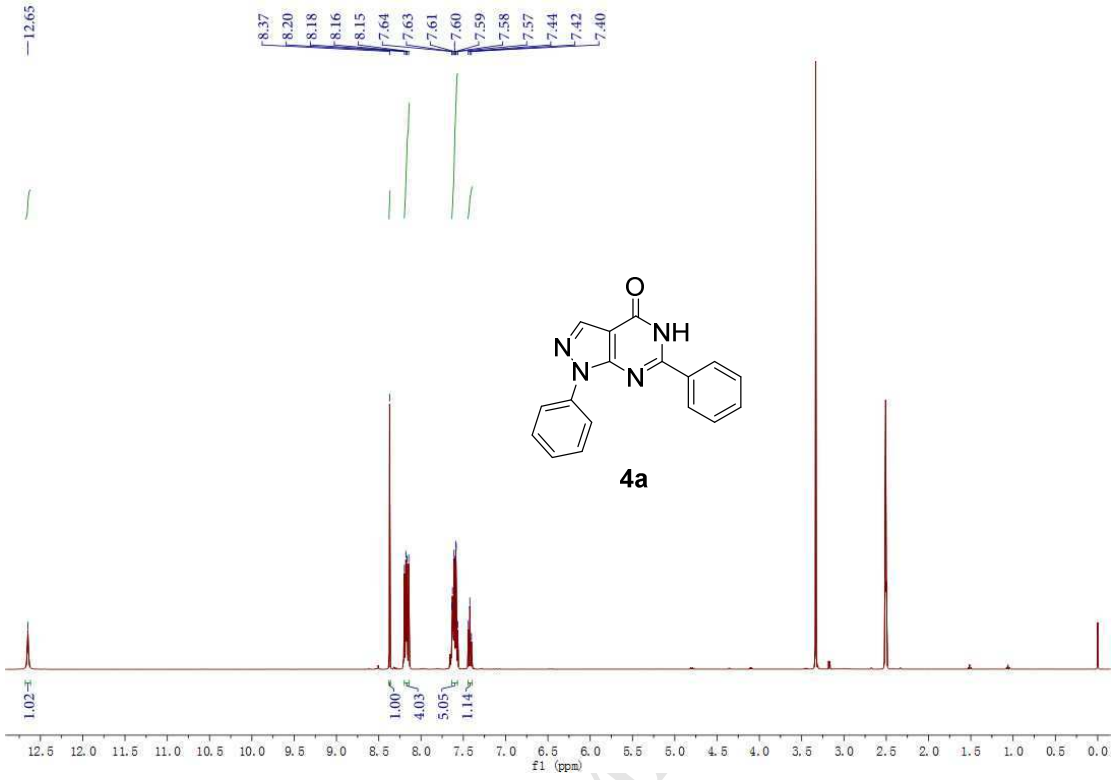
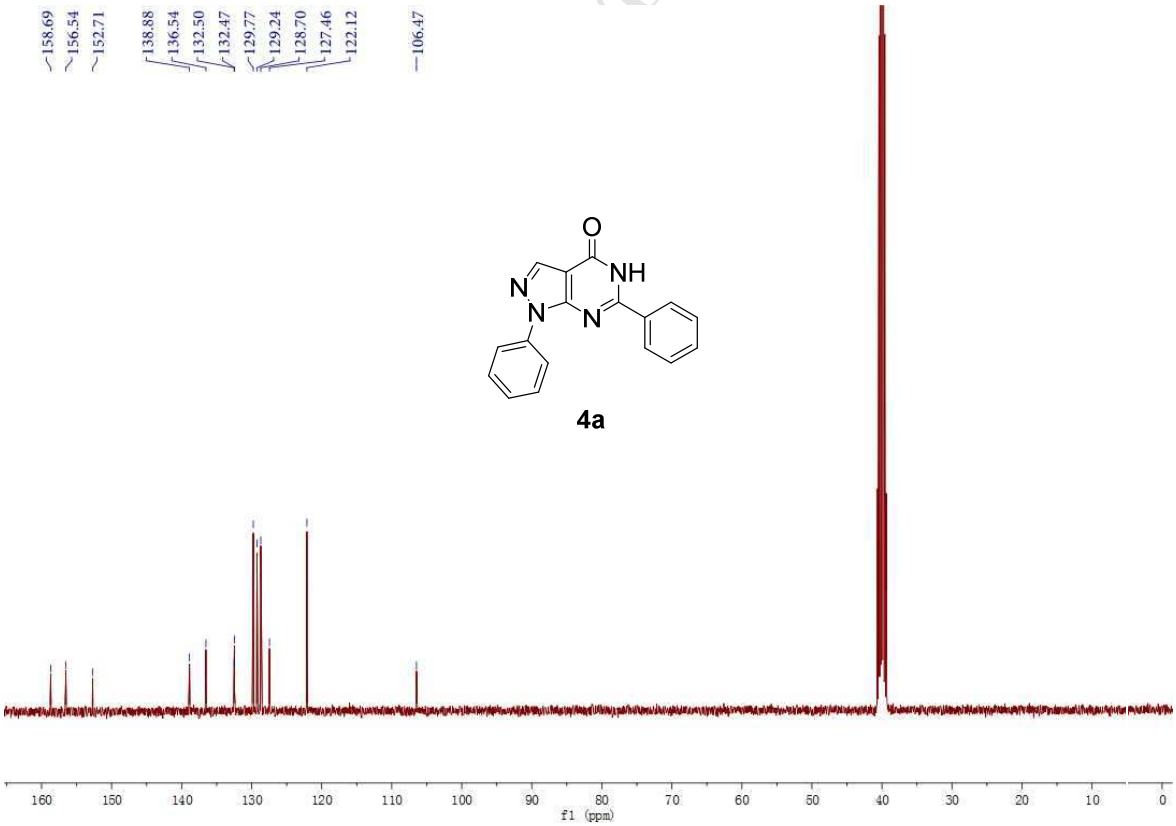
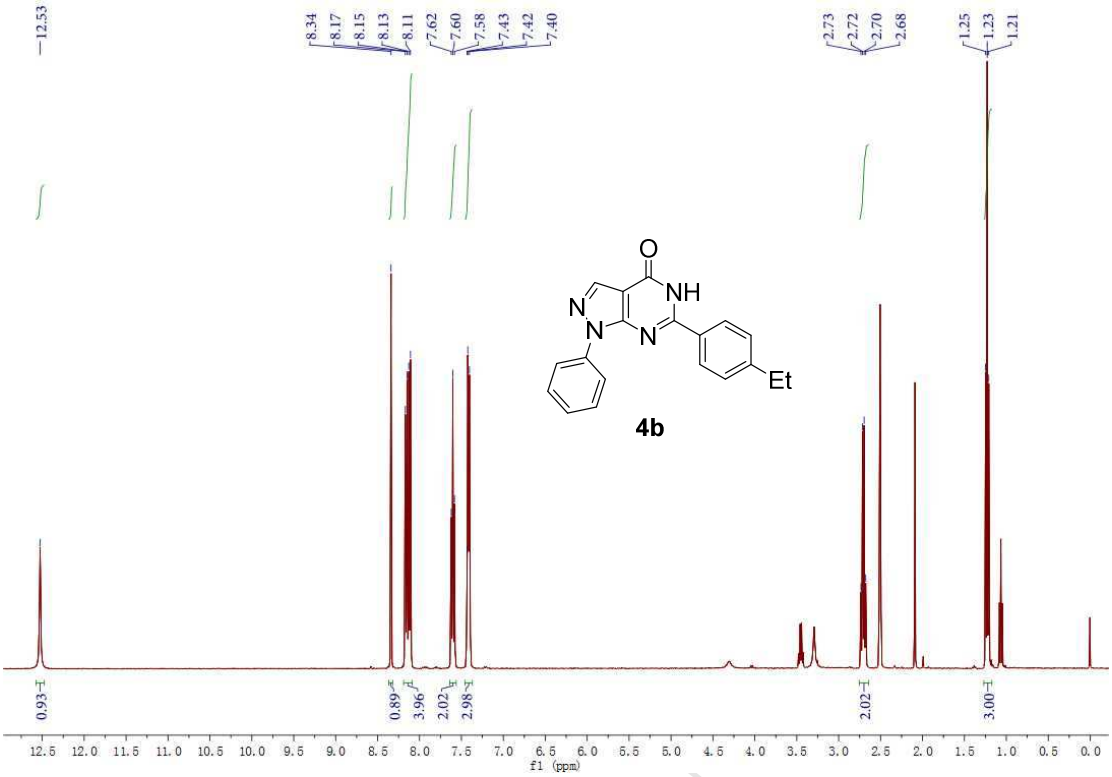
^{1}H and ^{13}C NMR spectra of 4



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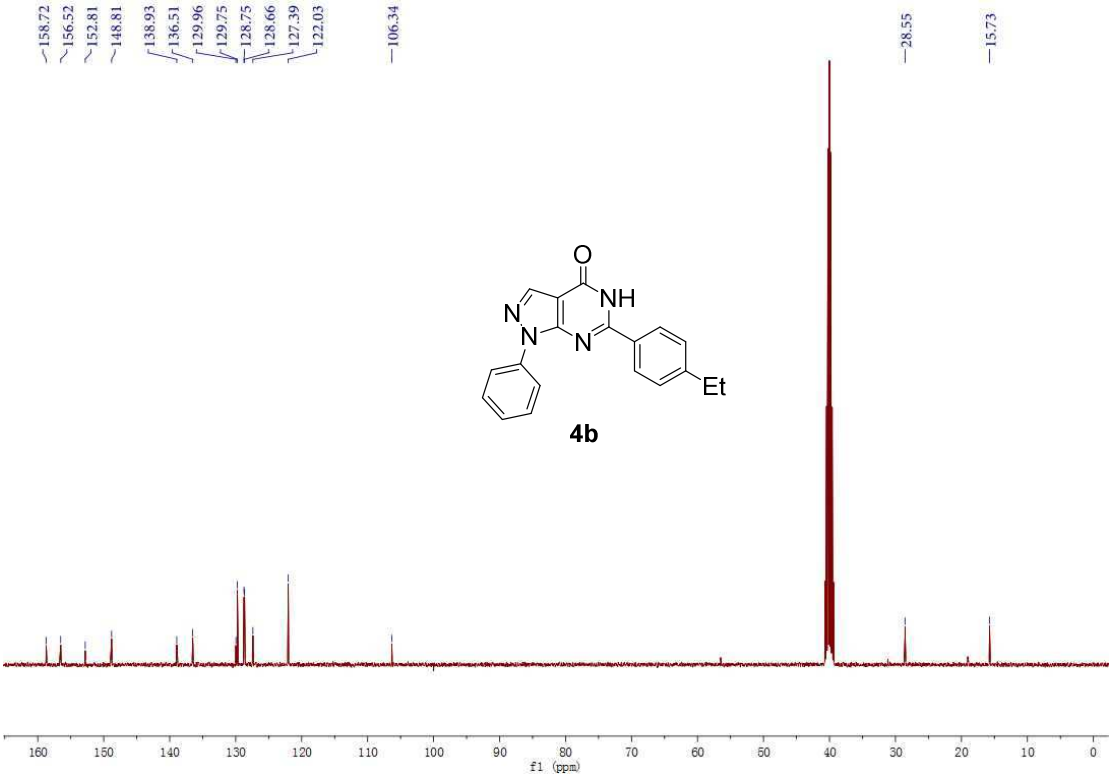
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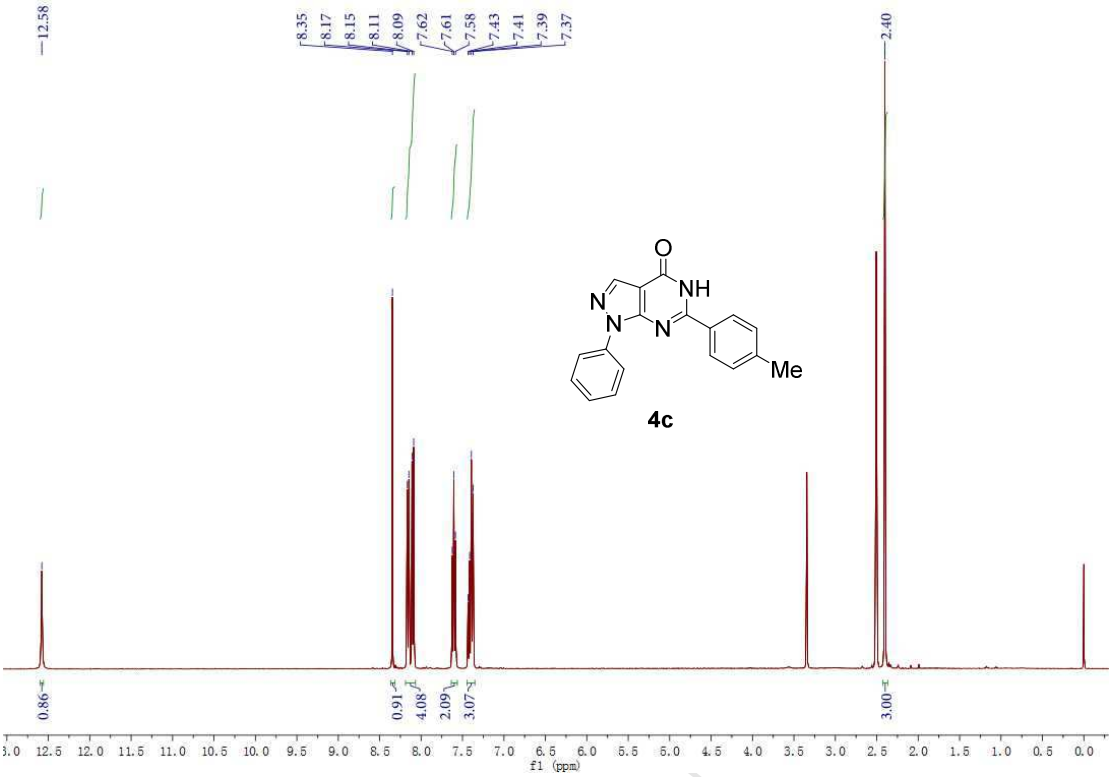
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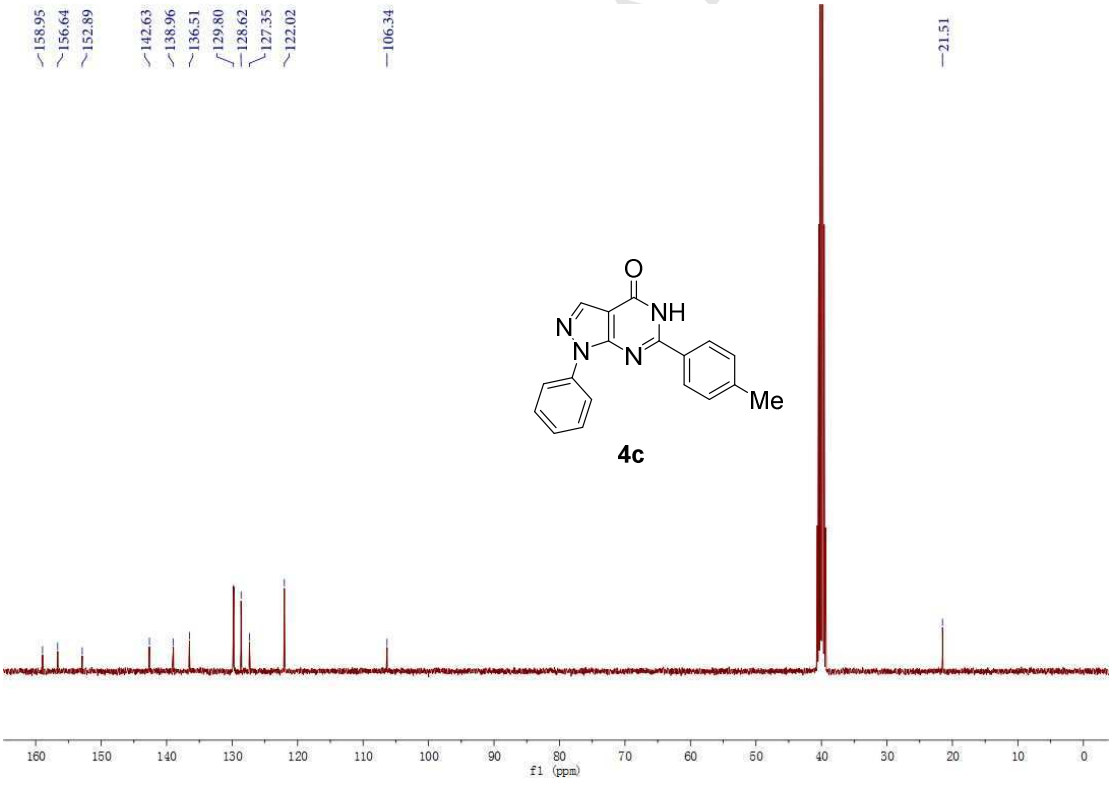
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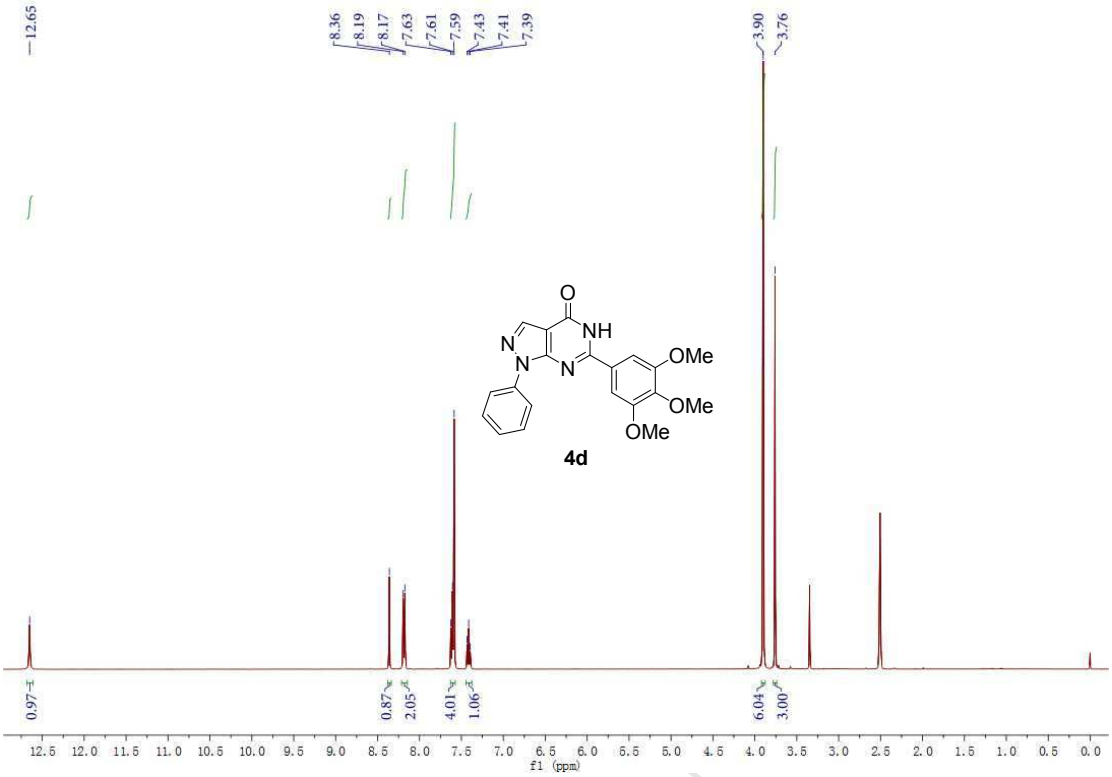
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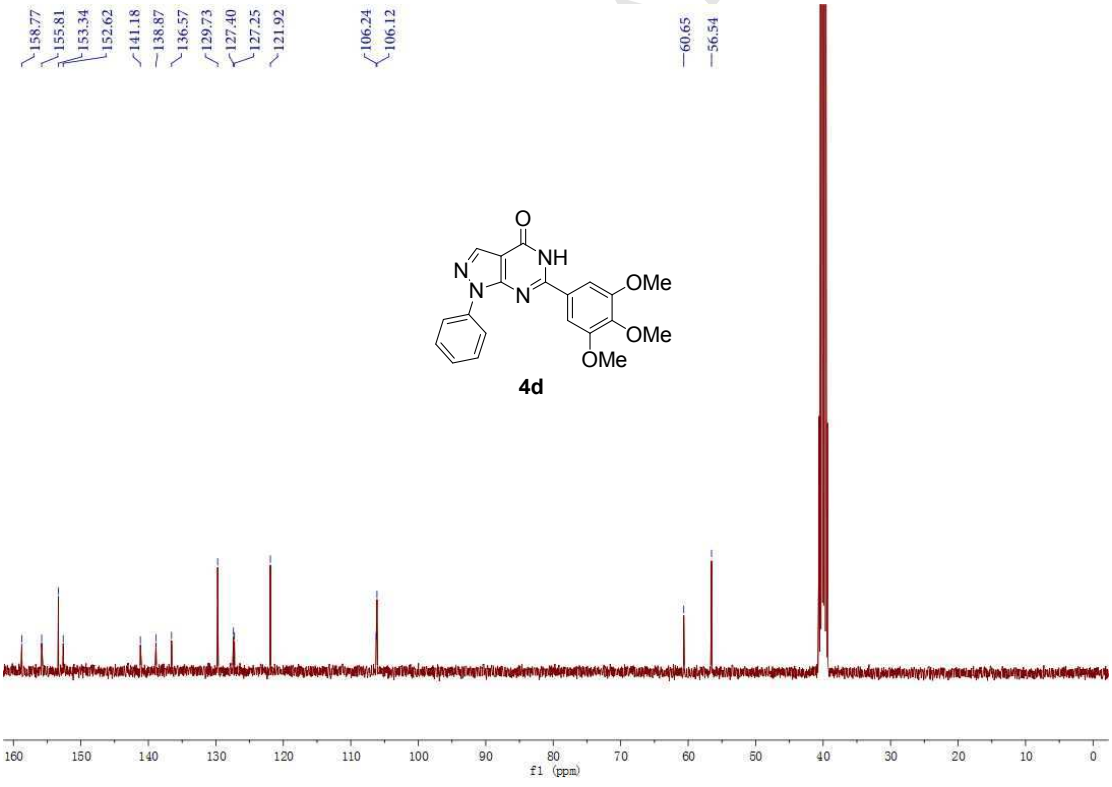
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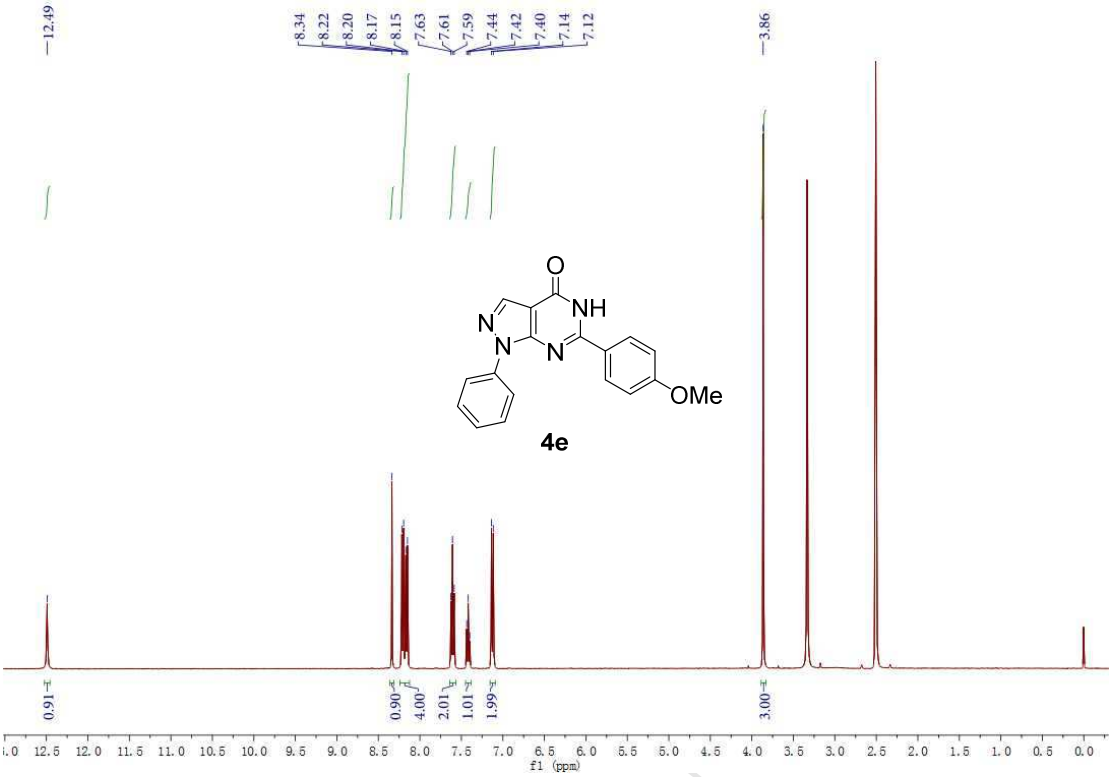
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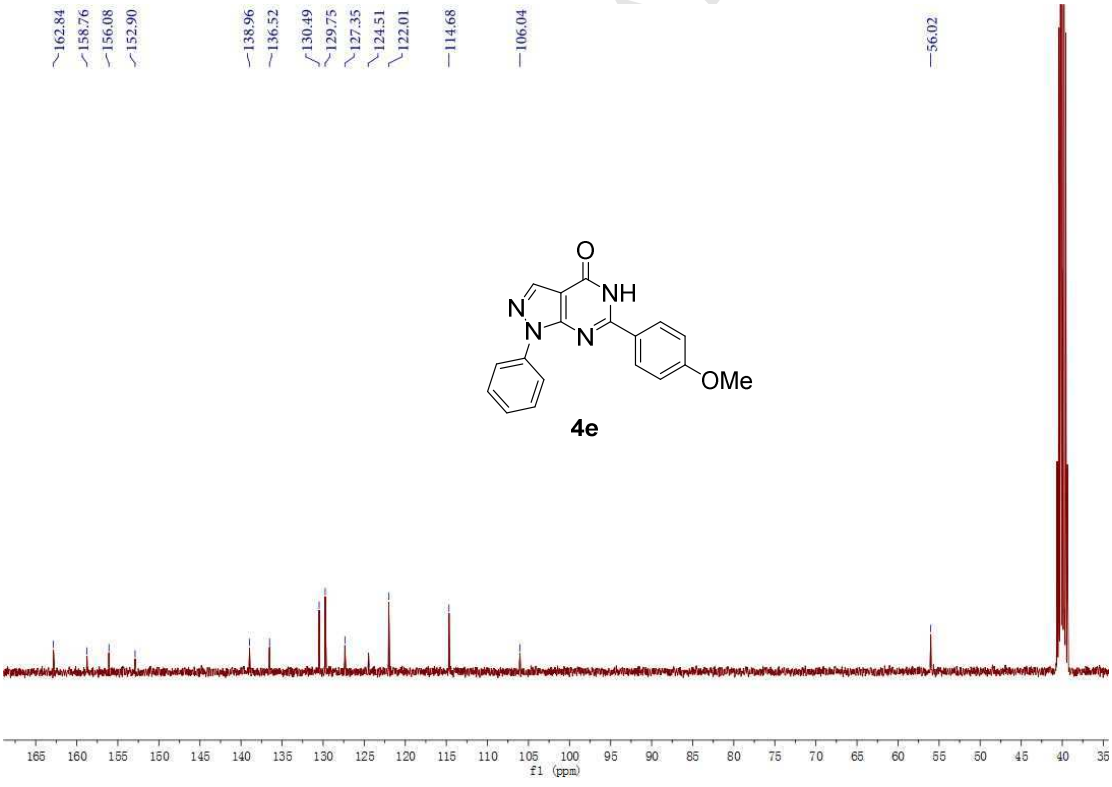
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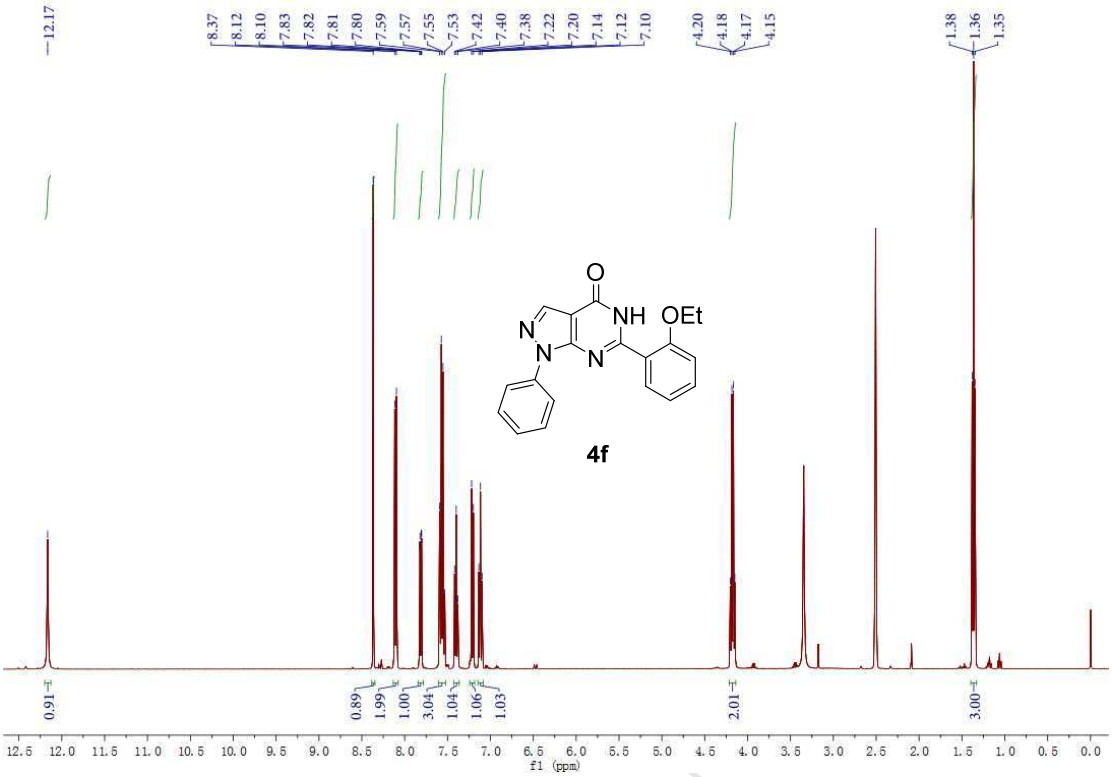
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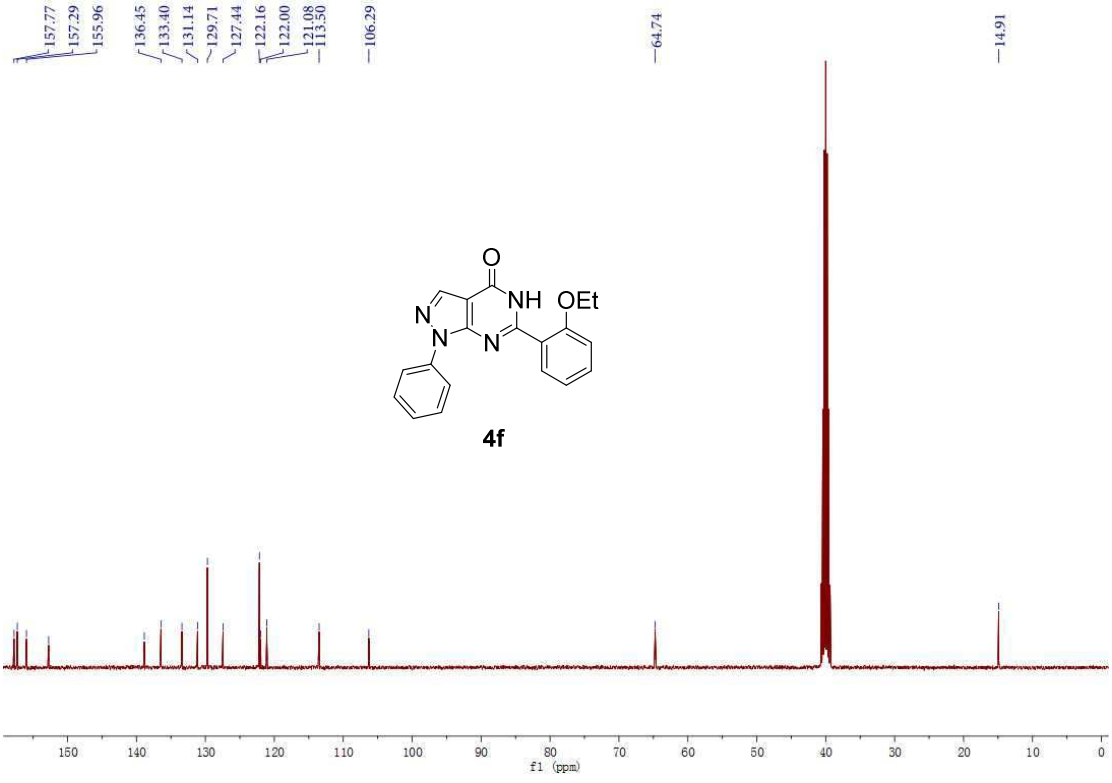
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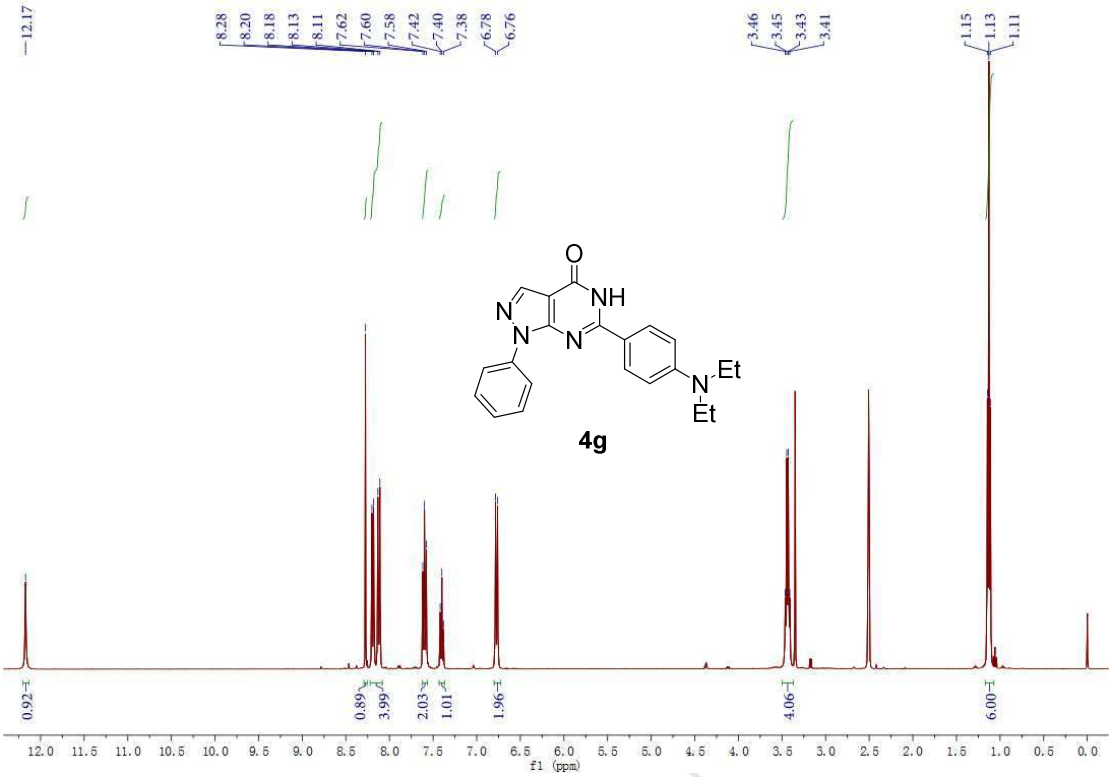
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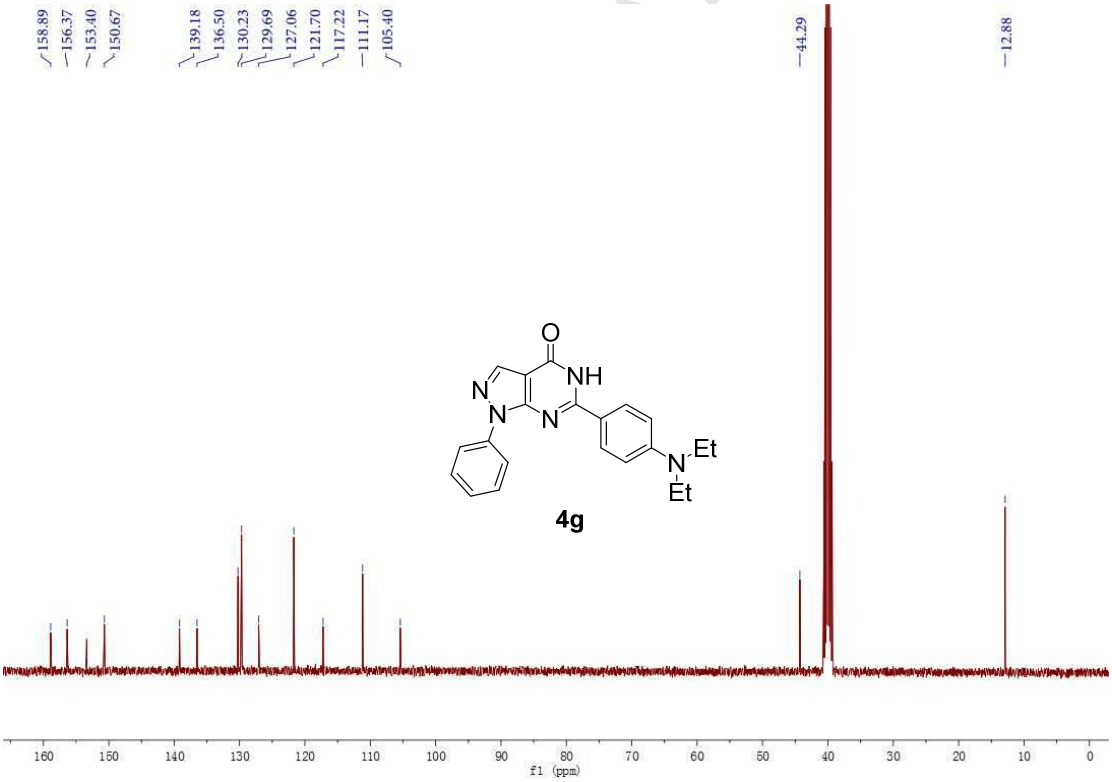
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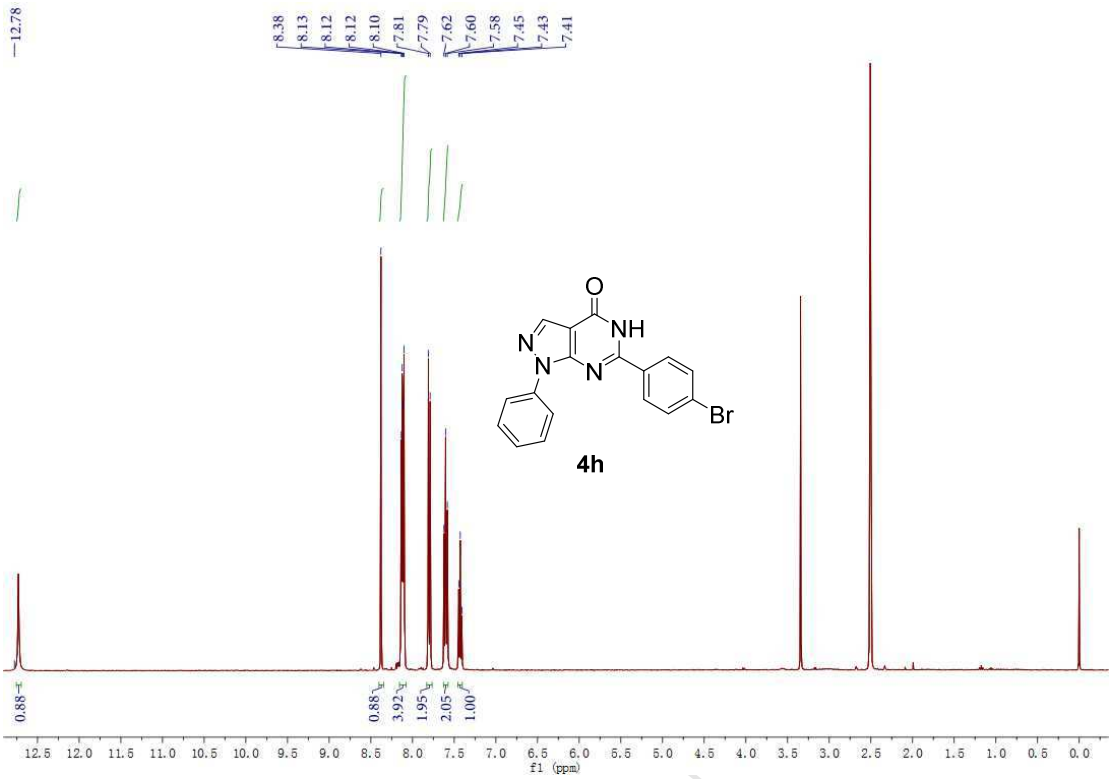
4g
f1 (ppm)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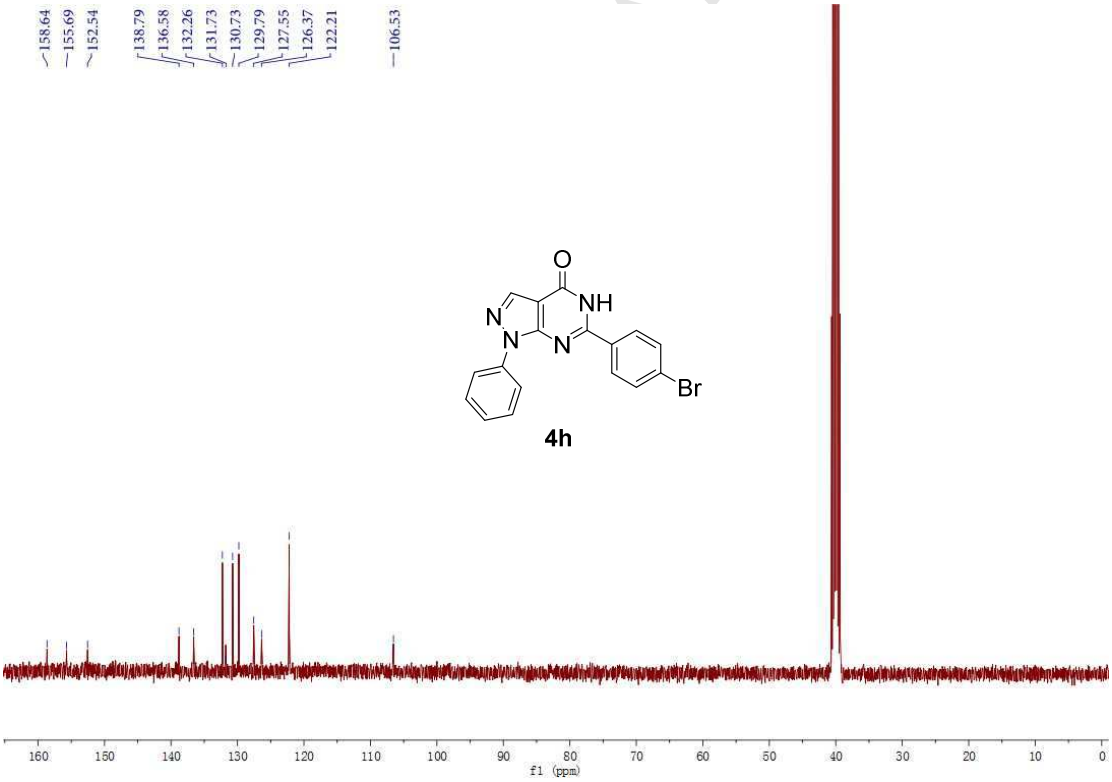
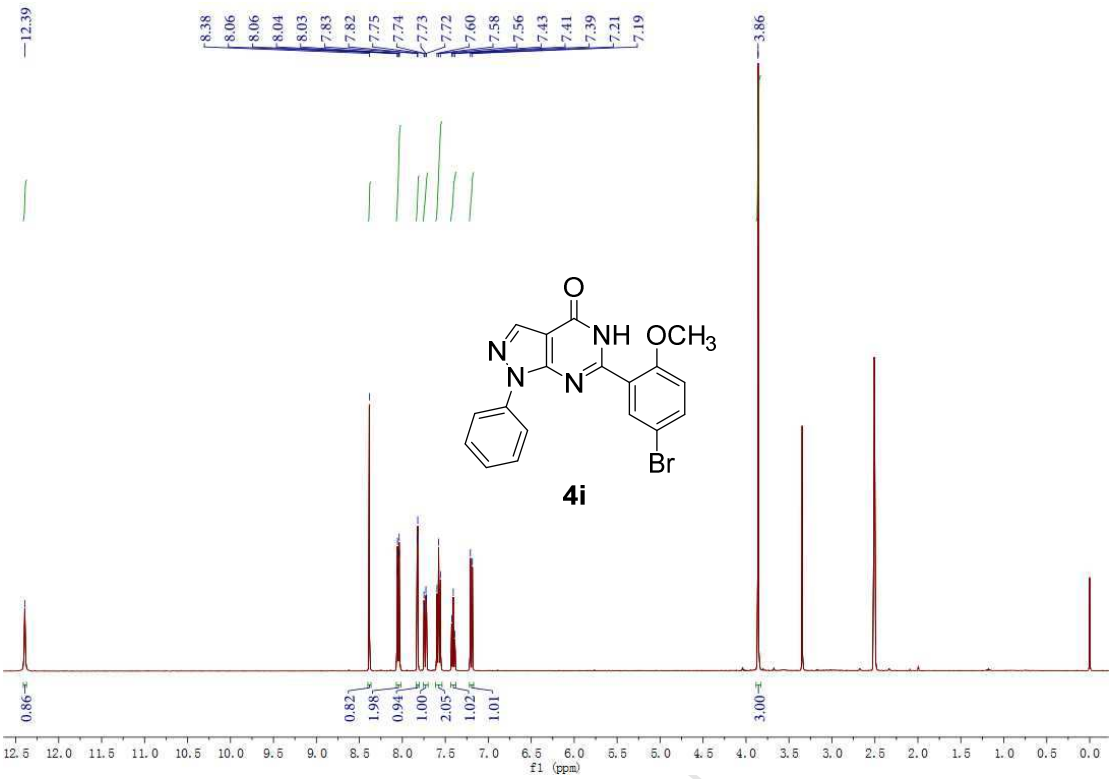
8.38
8.13
8.12
8.12
8.10
7.81
7.79
7.62
7.60
7.58
7.45
7.43
7.41
O
NH
N
N
N
Br
4h
0.88
0.88
3.92
1.95
2.05
1.00
f1 (ppm)


158.64
155.69
152.54
138.79
136.58
132.26
131.73
130.73
129.79
127.55
126.37
122.21
106.53
O
NH
N
N
N
Br
4h
f1 (ppm)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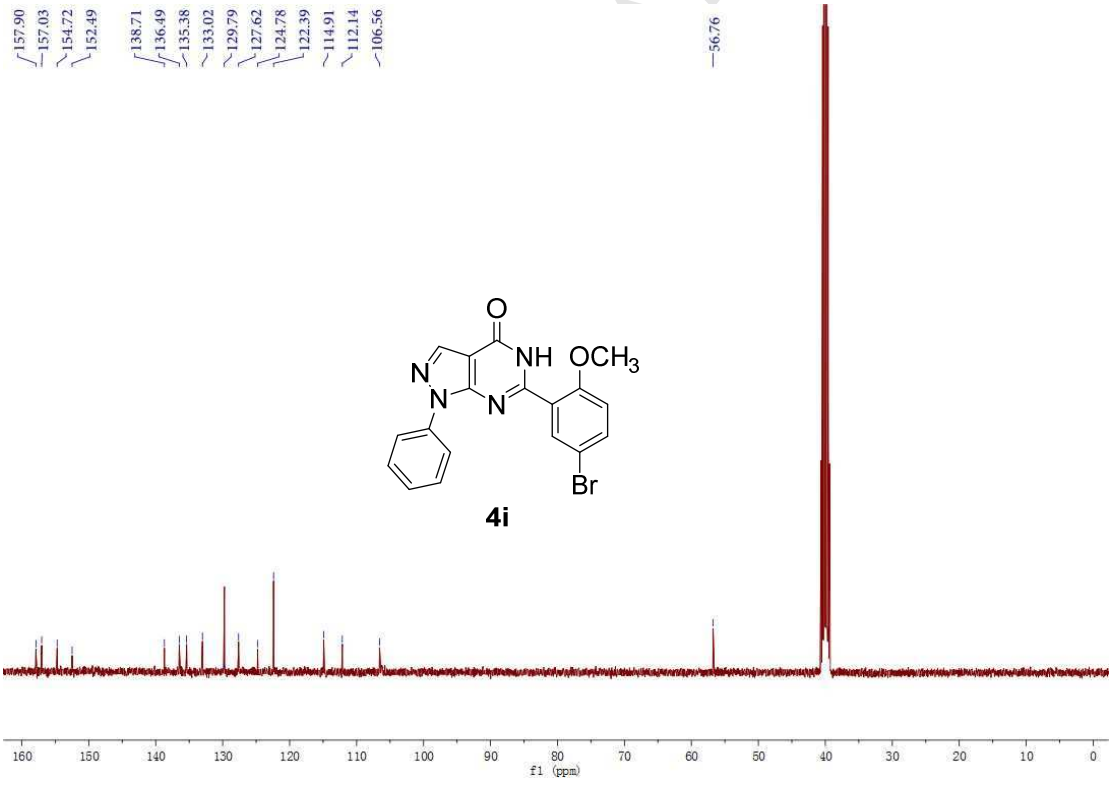
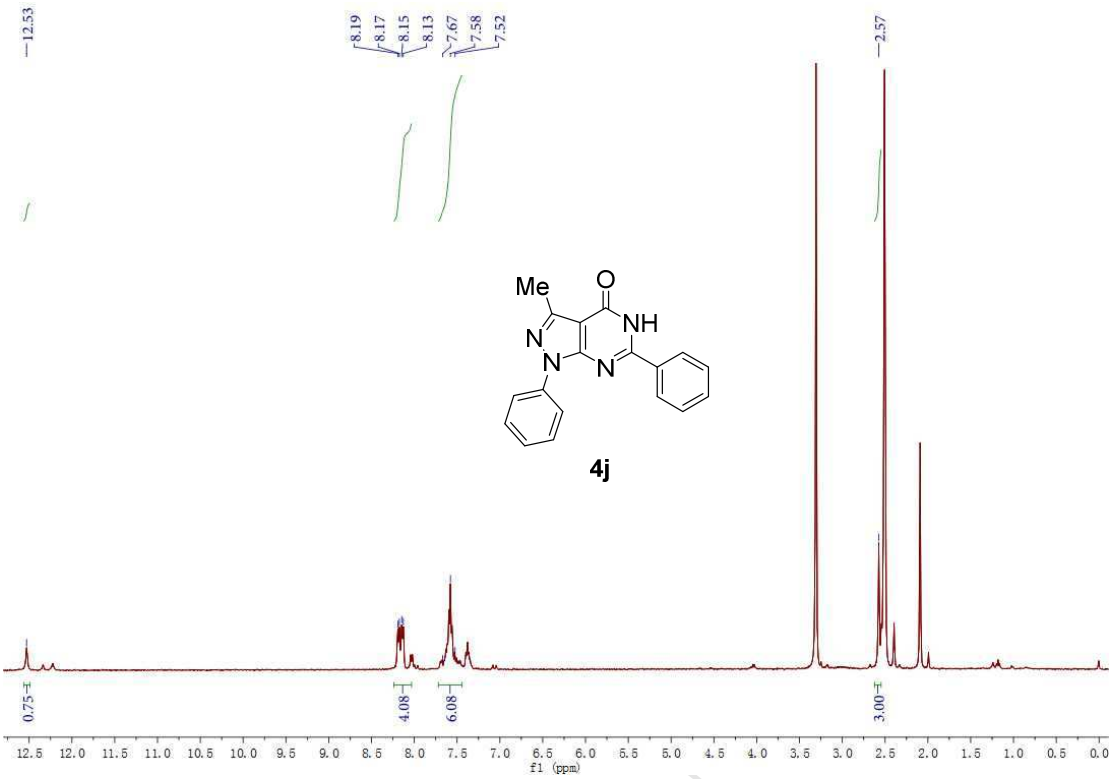
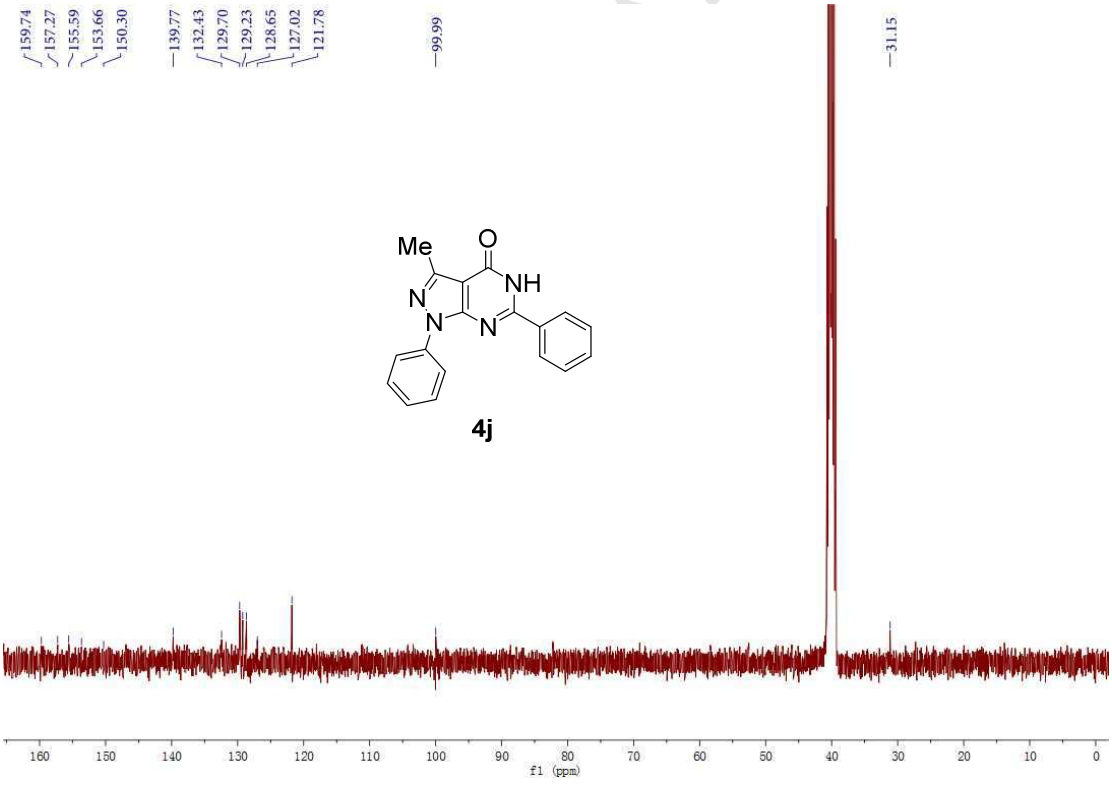
8.38
8.06
8.06
8.04
8.03
7.83
7.82
7.75
7.74
7.73
7.72
7.60
7.58
7.56
7.43
7.41
7.39
7.21
7.19
3.86
O
NH
OCH3
N
N
N
Br
4i
0.86
0.82
1.98
0.94
1.00
2.05
1.02
1.01
3.00
f1 (ppm)

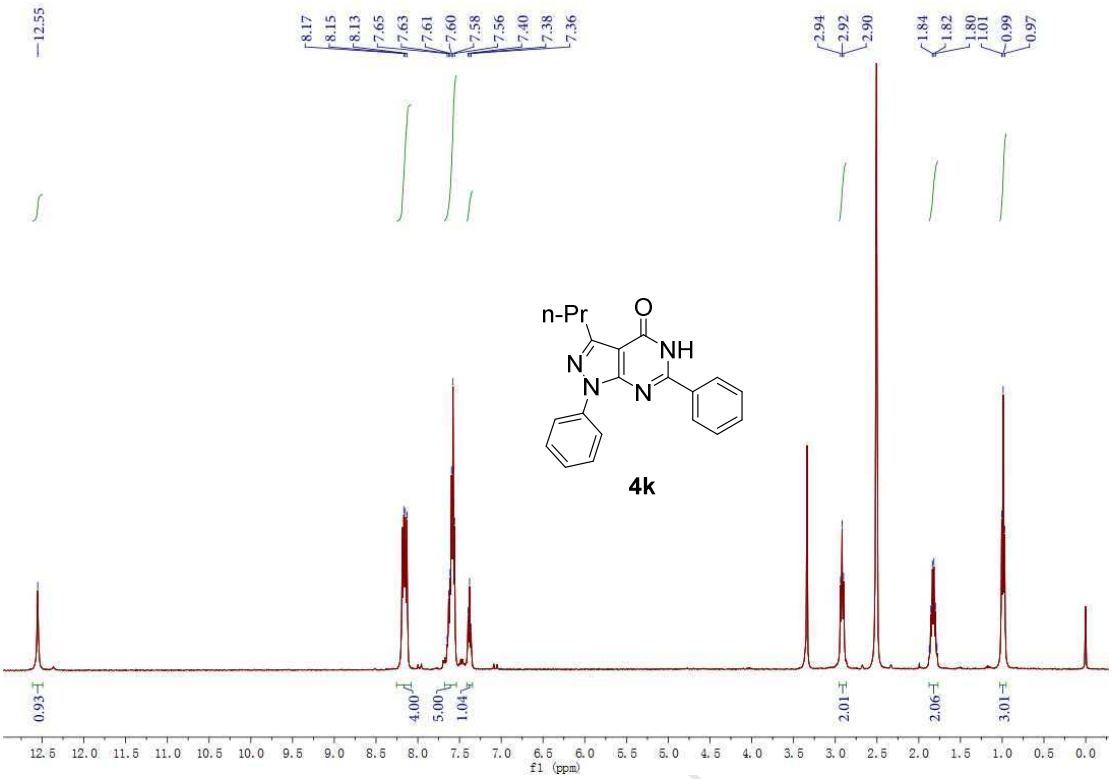

157.90
157.03
154.72
152.49
138.71
136.49
135.38
133.02
129.79
127.62
124.78
122.39
114.91
112.14
106.56
56.76
O
NH
OCH3
N
N
N
Br
4i
f1 (ppm)


12.53
8.19
8.17
8.15
8.13
7.67
7.58
7.52
2.57
Me
O
NH
N
N
N
0.75
4.08
6.08
3.00
f1 (ppm)

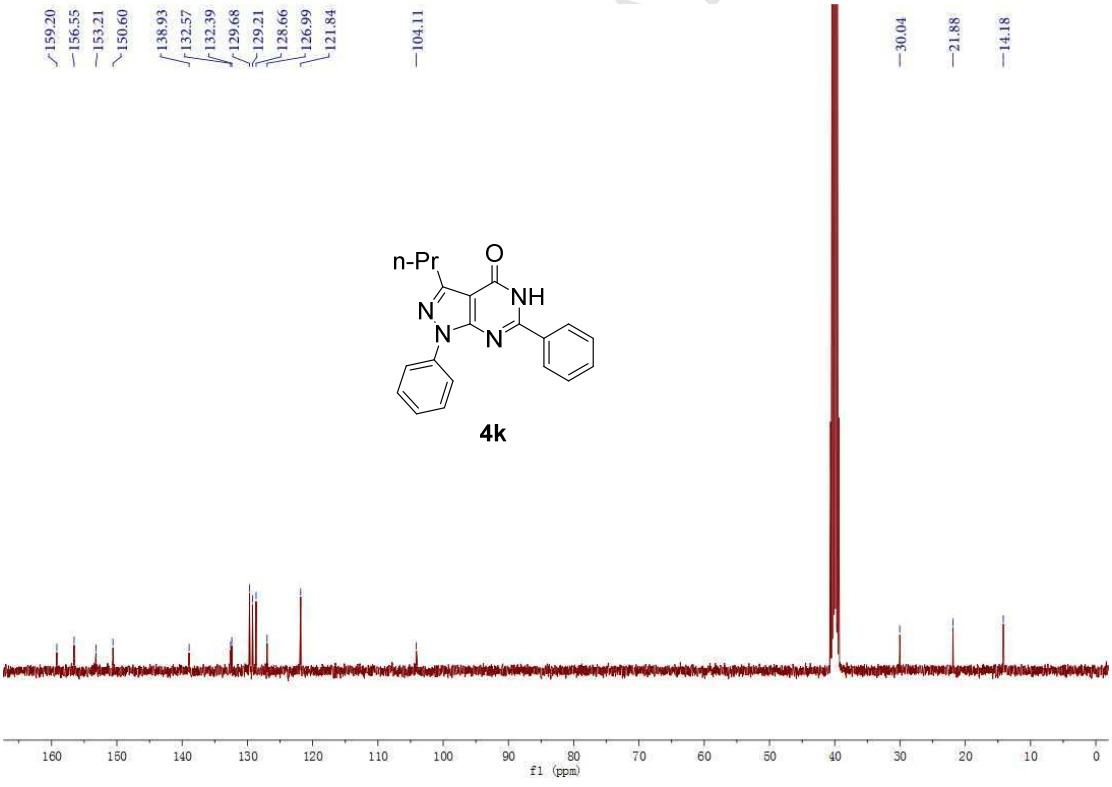
4j


159.74
157.27
155.59
153.66
150.30
139.77
132.43
129.70
129.23
128.65
127.02
121.78
99.99
31.15
Me
O
NH
N
N
N
f1 (ppm)

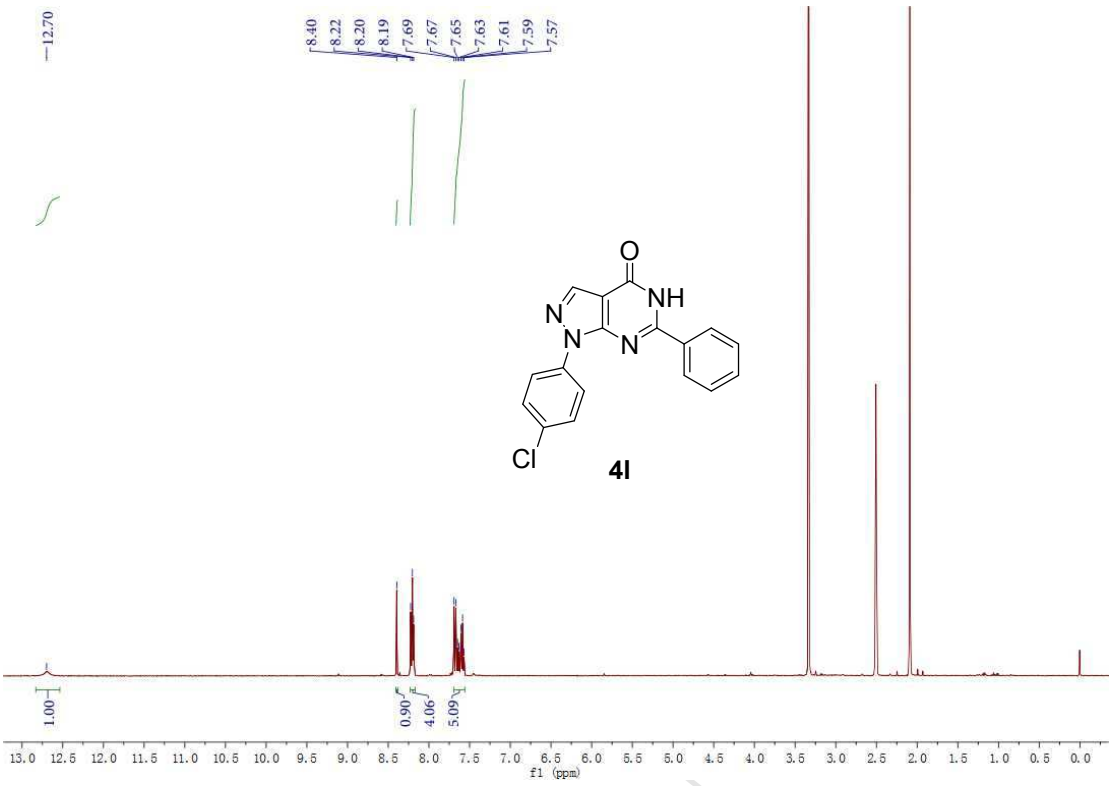
4j

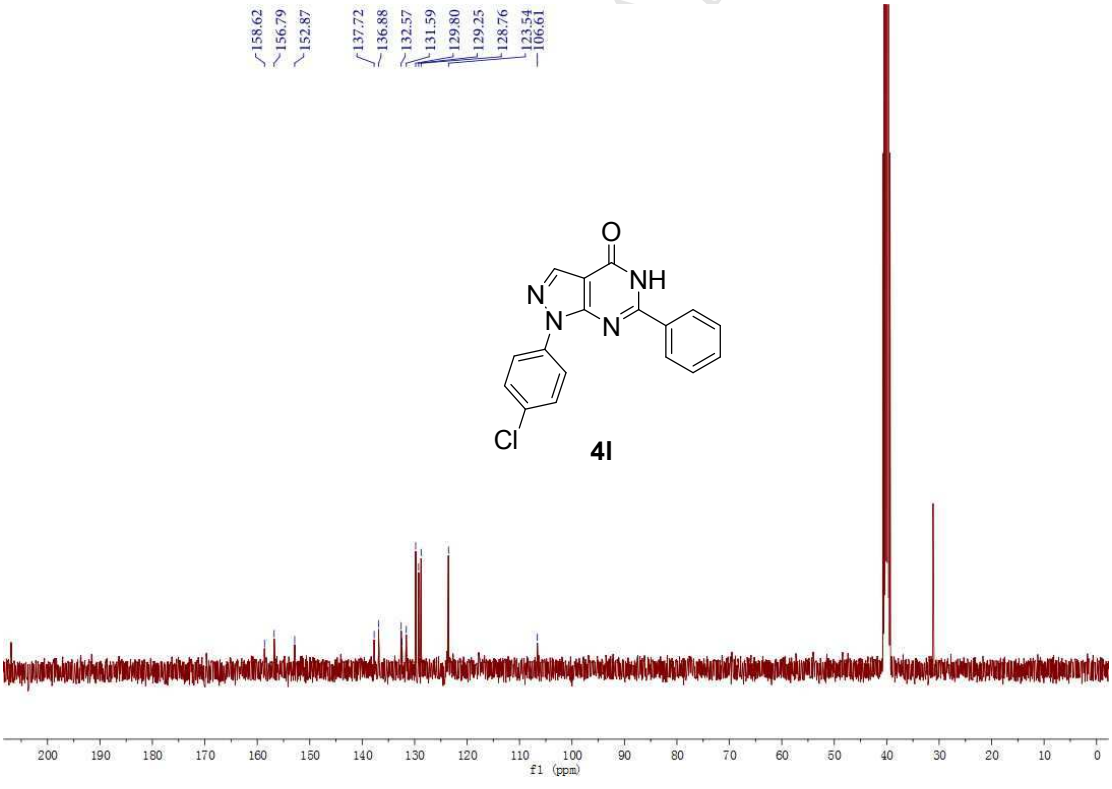

12.55
8.17
8.15
8.13
7.65
7.63
7.61
7.60
7.58
7.56
7.40
7.38
7.36
2.94
2.92
2.90
1.84
1.82
1.80
1.01
0.99
0.97
n-Pr
O
NH
N
N
N
0.93
4.00
5.00
1.04
2.01
2.06
3.01
f1 (ppm)

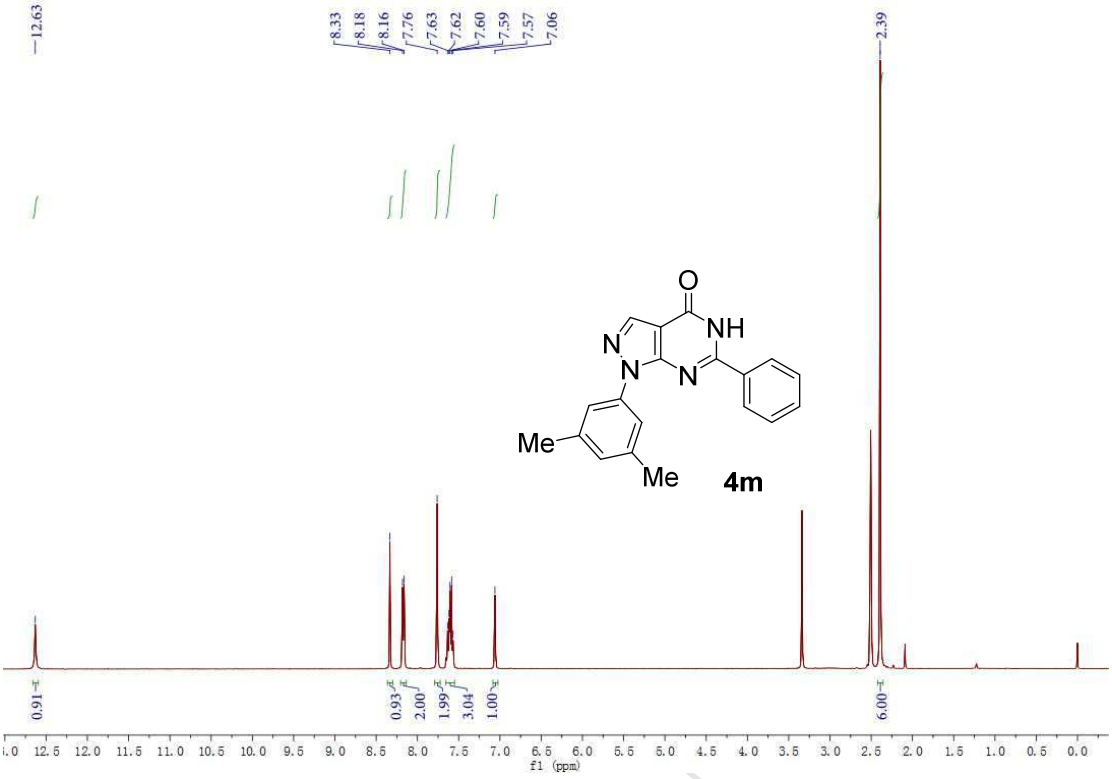
4k

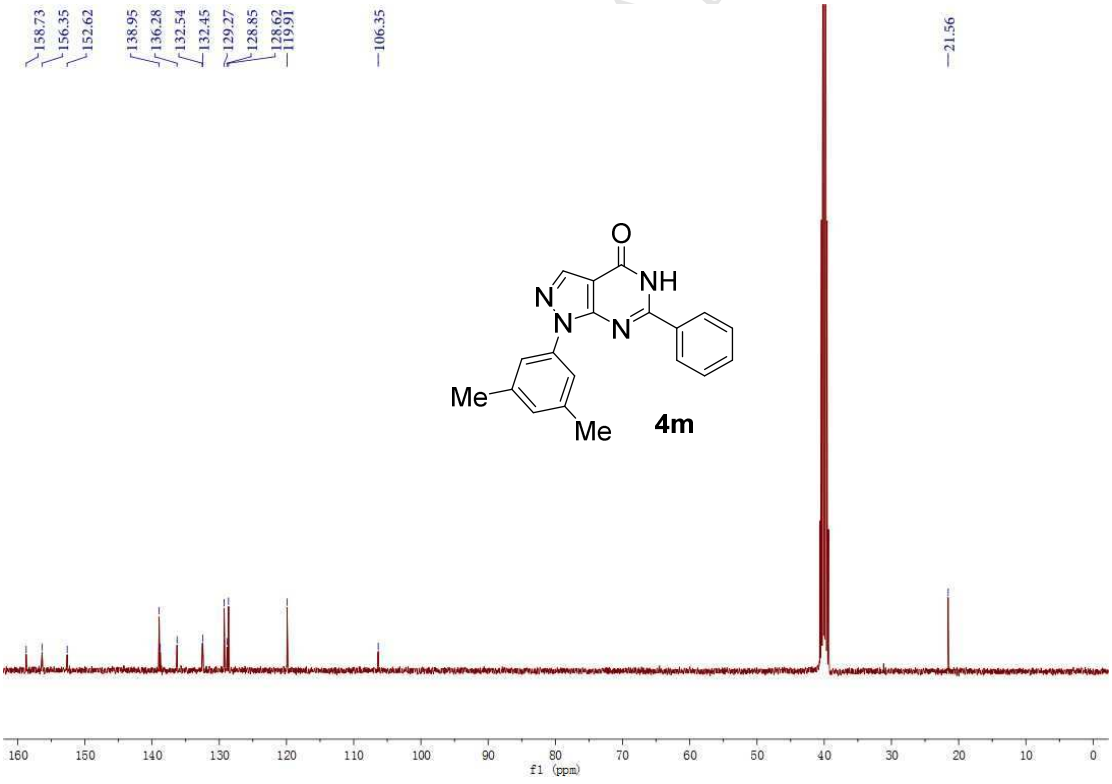

159.20
156.55
153.21
150.60
138.93
132.57
132.39
129.68
129.21
128.66
126.99
121.84
104.11
30.04
21.88
14.18
n-Pr
O
NH
N
N
N
f1 (ppm)

4k


12.70
8.40
8.22
8.20
8.19
7.69
7.67
7.65
7.63
7.61
7.59
7.57
O
NH
N
N
N
Cl
4l
1.00
0.90
4.06
5.09
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


158.62
156.79
152.87
137.72
136.88
132.57
131.59
129.80
129.25
128.76
123.54
106.61
O
NH
N
N
N
Cl
4l
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


12.63
8.33
8.18
8.16
7.76
7.63
7.62
7.60
7.59
7.57
7.06
2.39
O
NH
N
N
N
Me
Me
4m
0.91
0.93
2.00
1.99
3.04
1.00
6.00
f1 (ppm)


158.73
156.35
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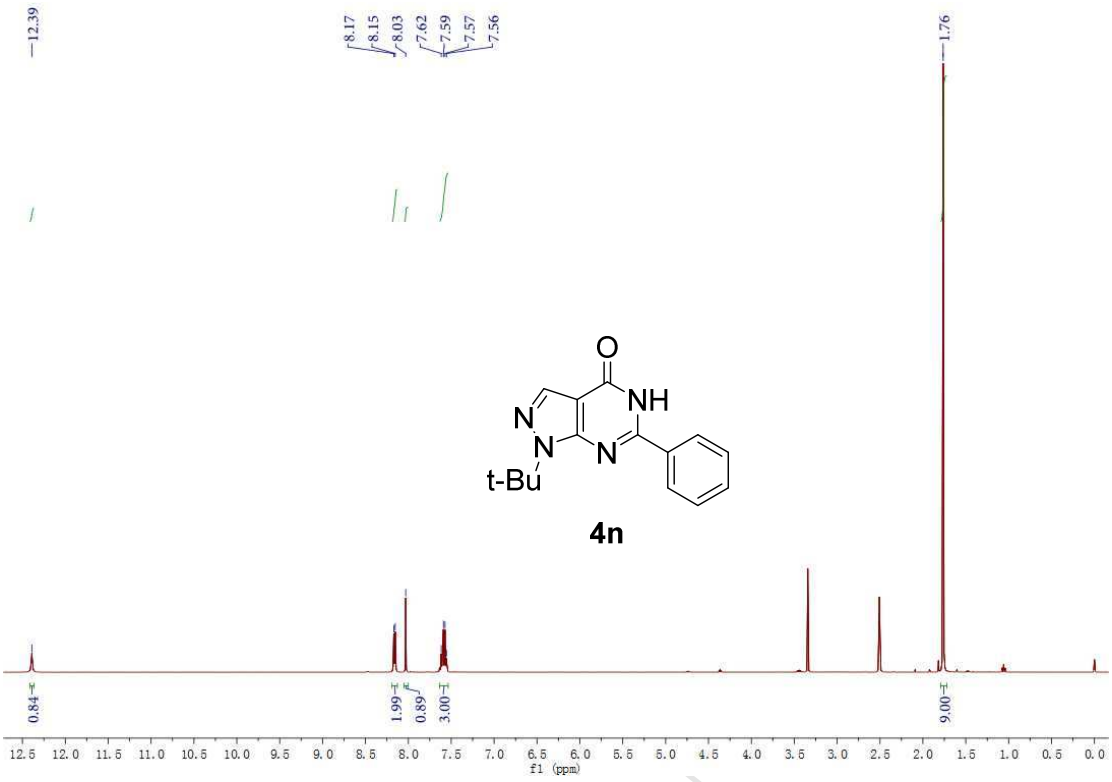
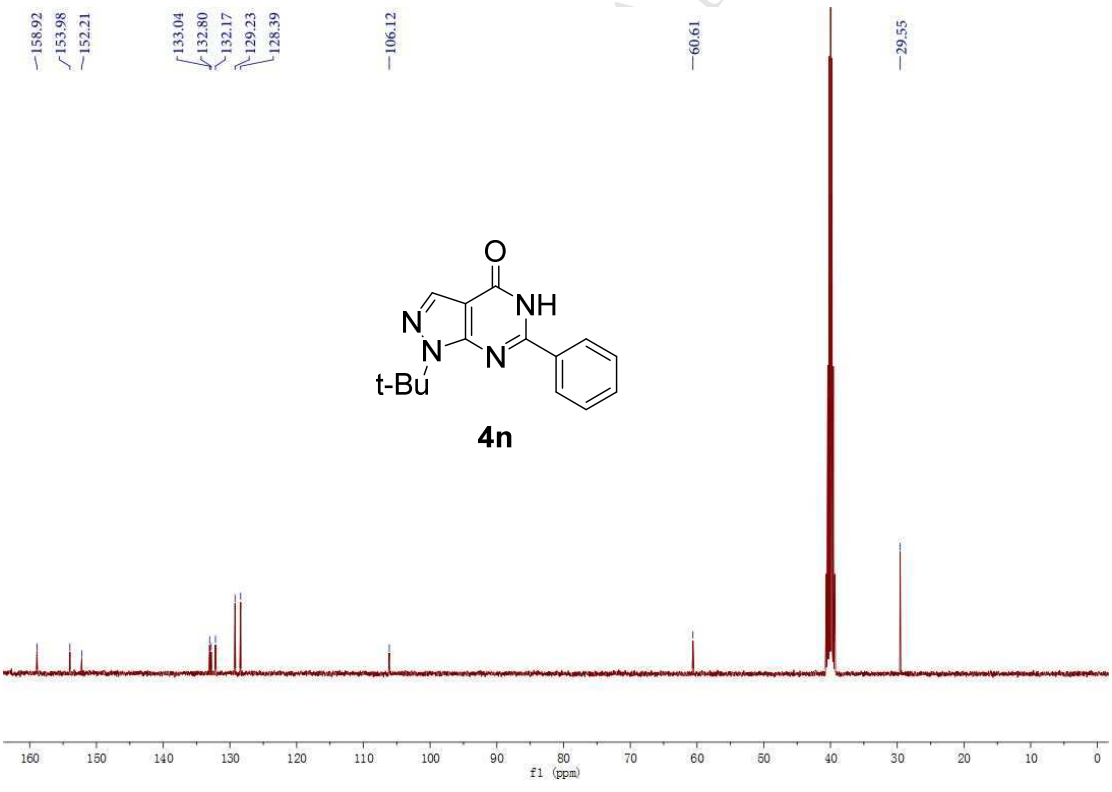
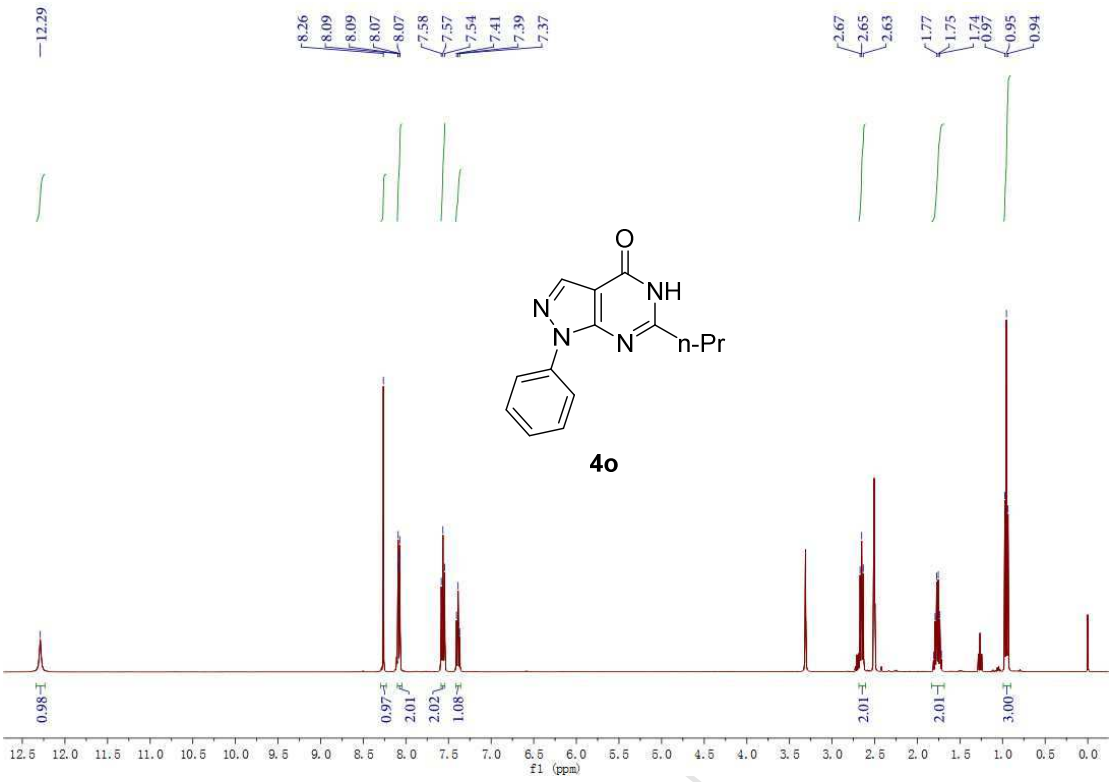
138.95
136.28
132.54
132.45
129.27
128.85
128.62
119.91
106.35
21.56
O
NH
N
N
N
Me
Me
4m
f1 (ppm)


12.39
8.17
8.15
8.03
7.62
7.59
7.57
7.56
1.76
O
NH
N
N
N
t-Bu
0.84
1.99
0.89
3.00
9.00
f1 (ppm)

4n


158.92
153.98
152.21
133.04
132.80
132.17
129.23
128.39
106.12
60.61
29.55
O
NH
N
N
N
t-Bu
f1 (ppm)

4n


12.29
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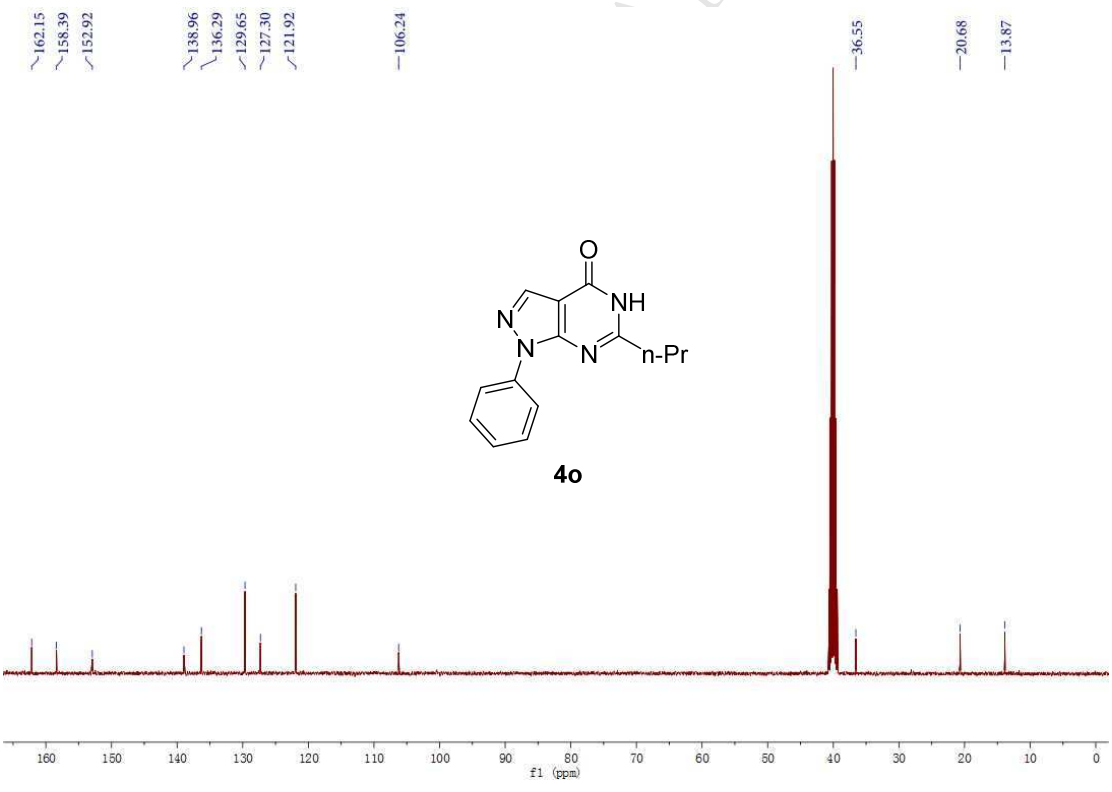
8.09
8.09
8.07
8.07
7.58
7.57
7.54
7.41
7.39
7.37
2.67
2.65
2.63
1.77
1.75
1.74
0.97
0.95
0.94
O
NH
N
N
N
n-Pr
0.98
0.97
2.01
2.02
1.08
2.01
2.01
3.00
f1 (ppm)

4o


162.15
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138.96
136.29
129.65
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121.92
106.24
36.55
20.68
13.87
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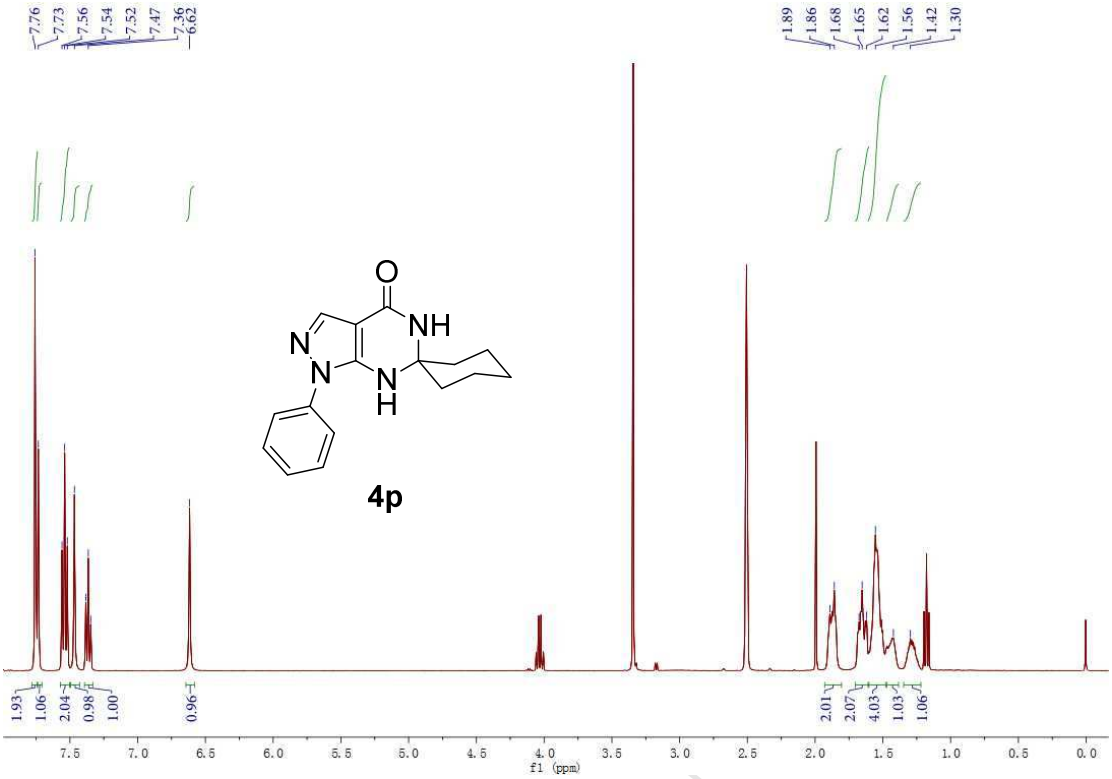
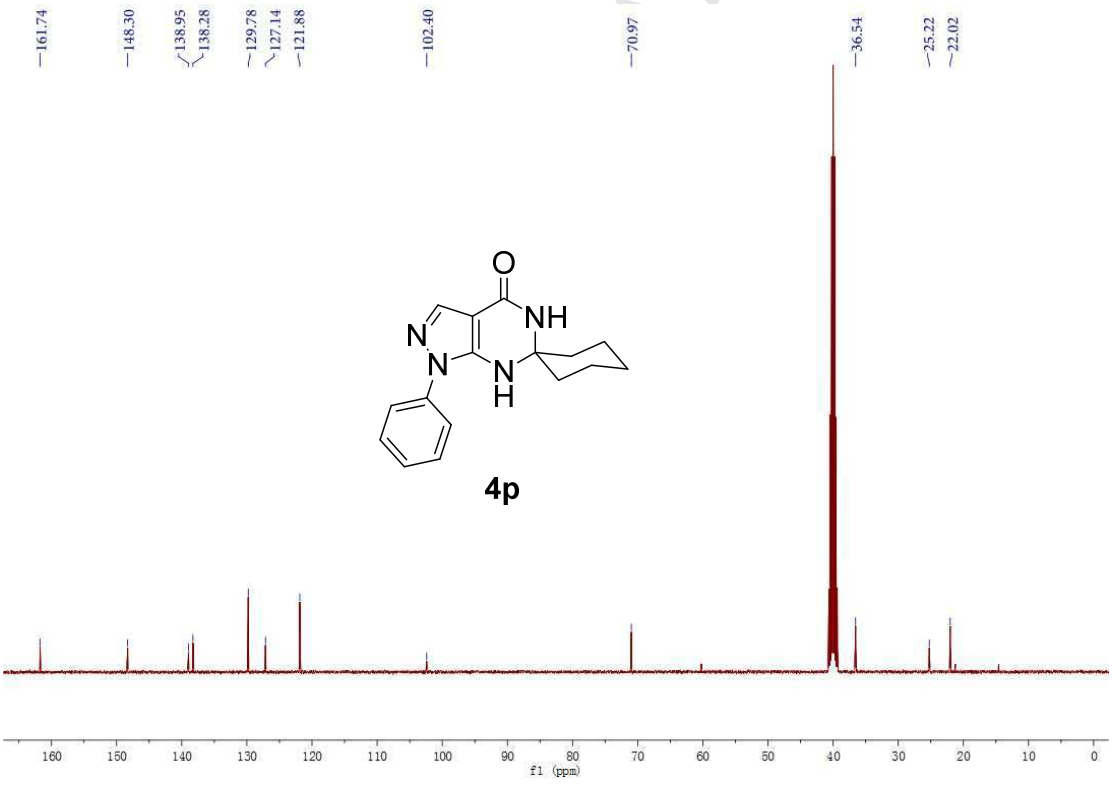
NH
N
N
N
n-Pr
f1 (ppm)

4o


7.76
7.73
7.56
7.54
7.52
7.47
7.36
6.62
1.89
1.86
1.68
1.65
1.62
1.56
1.42
1.30
O
NH
N
N
N
H
4p
1.93
1.06
2.04
0.98
1.00
0.96
2.01
2.07
4.03
1.03
1.06
f1 (ppm)

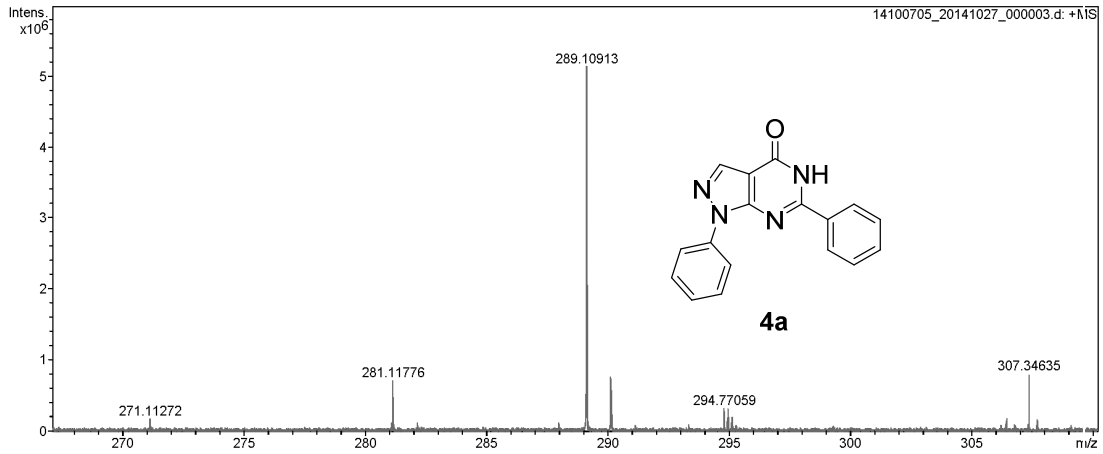

161.74
148.30
138.95
138.28
129.78
127.14
121.88
102.40
70.97
36.54
25.22
22.02
O
NH
N
N
N
H
4p
f1 (ppm)

HRMS spectra of 4

Peking University Mass Spectrometry Sample Analysis Report

Analysis Info

Analysis Name	14100705_20141027_000003.d	Acquisition Date	10/27/2014 11:21:36 AM
Sample	Imx-032-4	Instrument	Bruker Apex IV FTMS
Comment	ESI Positive	Operator	Peking University



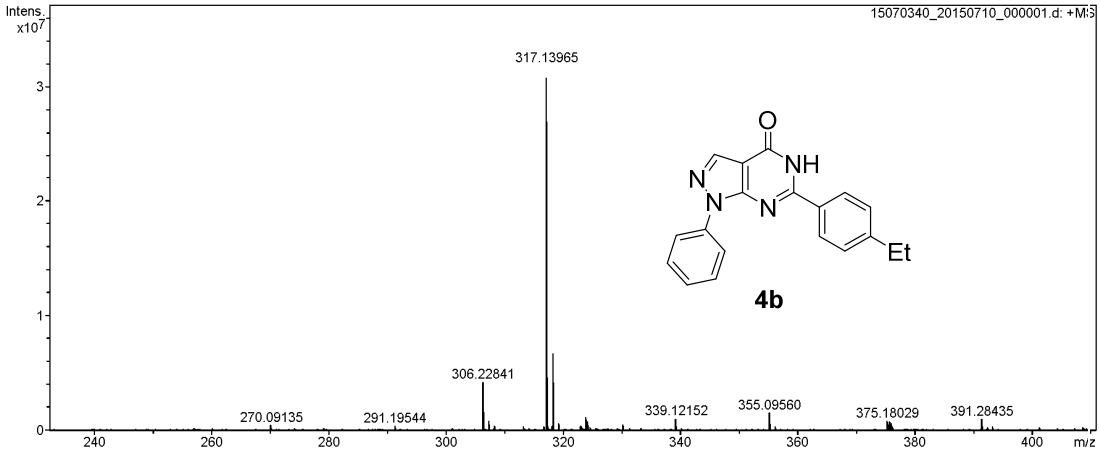
4a

Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
289.10913	1	C 17 H 13 N 4 O	100.00	289.10839	-0.74	-2.57	30.6	13.5	even	ok

Peking University Mass Spectrometry Sample Analysis Report

Analysis Info

Analysis Name	15070340_20150710_000001.d	Acquisition Date	7/10/2015 1:04:59 PM
Sample	Imx-044-2	Instrument	Bruker Apex IV FTMS
Comment	ESI Positive	Operator	Peking University



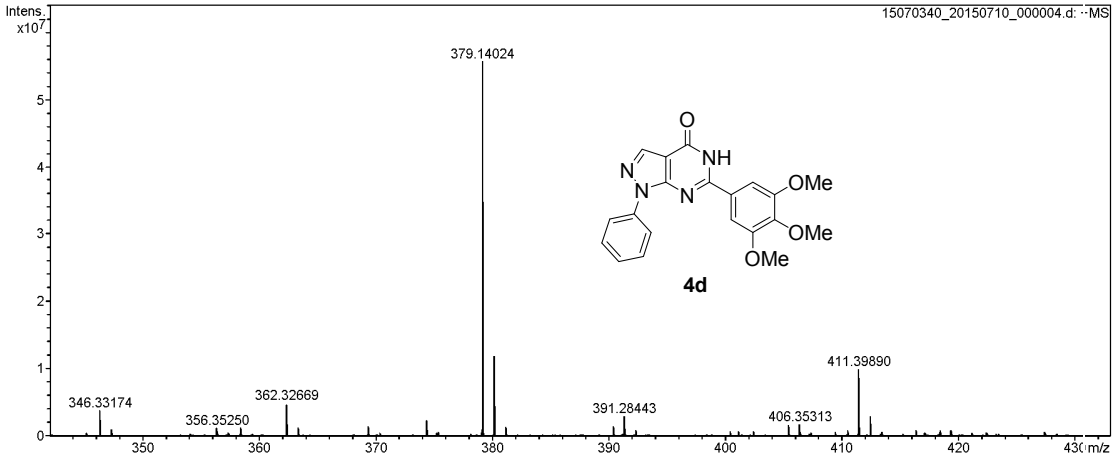
4b

Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
317.13965	31842890	C 19 H 17 N 4 O	100.00	317.13969	0.0	0.1	6.0	13.5	even	ok

Peking University Mass Spectrometry Sample Analysis Report

Analysis Info

Analysis Name	15070340_20150710_000004.d	Acquisition Date	7/10/2015 1:22:35 PM
Sample	lmx-037-5	Instrument	Bruker Apex IV FTMS
Comment	ESI Positive	Operator	Peking University

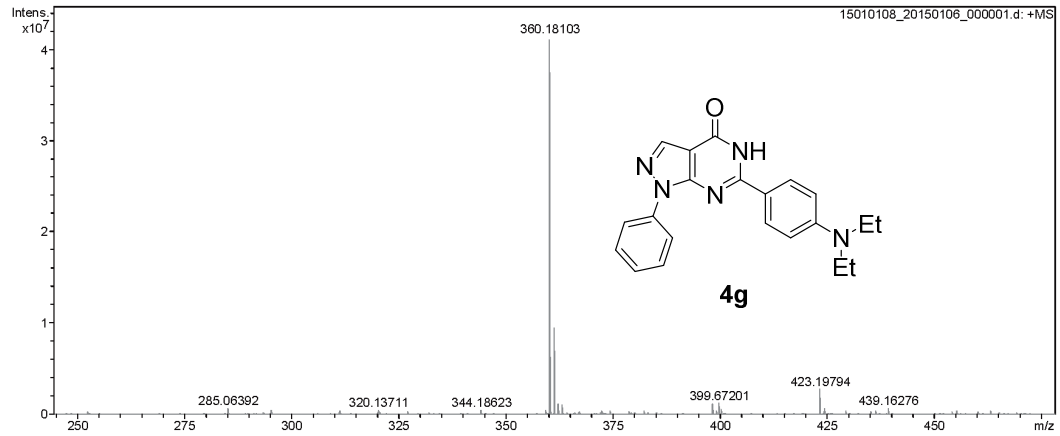


Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
379.14024	55648768	C 20 H 19 N 4 O 4	100.00	379.14008	-0.2	-0.4	10.5	13.5	even	ok

Peking University Mass Spectrometry Sample Analysis Report

Analysis Info

Analysis Name	15010108_20150106_000001.d	Acquisition Date	1/6/2015 9:46:30 AM
Sample	lmx-037-2	Instrument	Bruker Apex IV FTMS
Comment	ESI Positive	Operator	Peking University

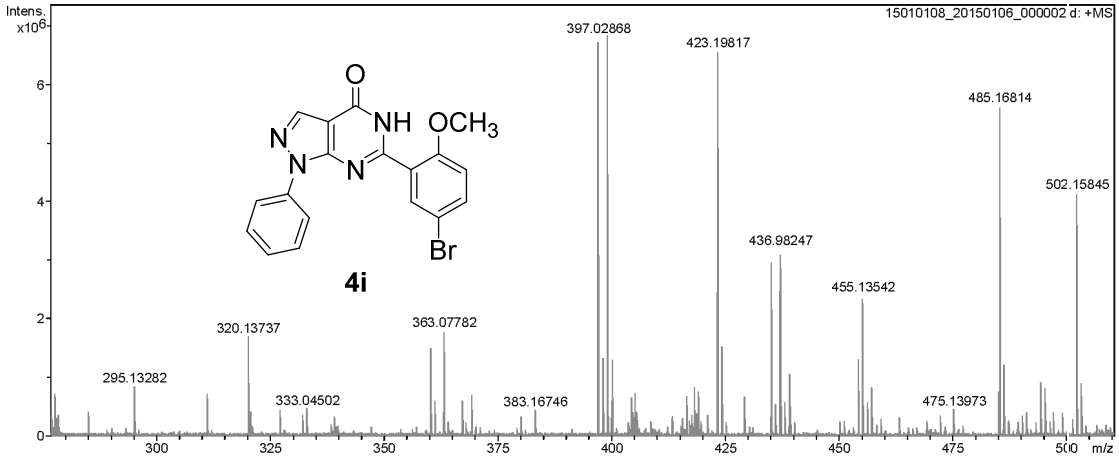


Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
360.18103	41445576	C 21 H 22 N 5 O	100.00	360.18189	0.9	2.4	6.1	13.5	even	ok

Peking University Mass Spectrometry Sample Analysis Report

Analysis Info

Analysis Name	15010108_20150106_000002.d	Acquisition Date	1/6/2015 9:48:06 AM
Sample	lmx-037-4	Instrument	Bruker Apex IV FTMS
Comment	ESI Positive	Operator	Peking University

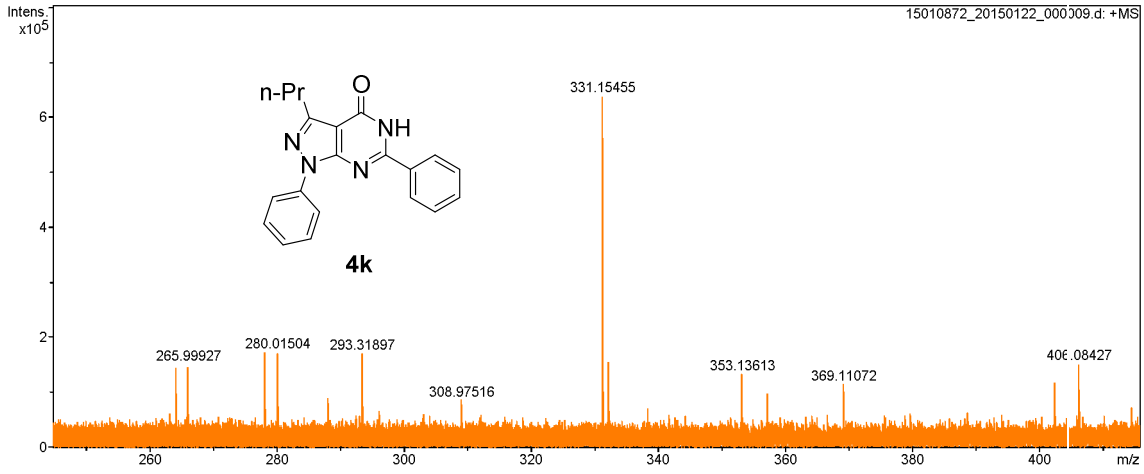


Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
397.02868	6824300	C 18 H 14 Br N 4 O 2	0.00	397.02946	0.8	2.0	446.2	13.5	even	ok

Peking University Mass Spectrometry Sample Analysis Report

Analysis Info

Analysis Name	15010872_20150122_000009.d	Acquisition Date	1/22/2015 5:23:02 PM
Sample	LMX-043-2	Instrument	Bruker Apex IV FTMS
Comment	ESI Positive	Operator	Peking University

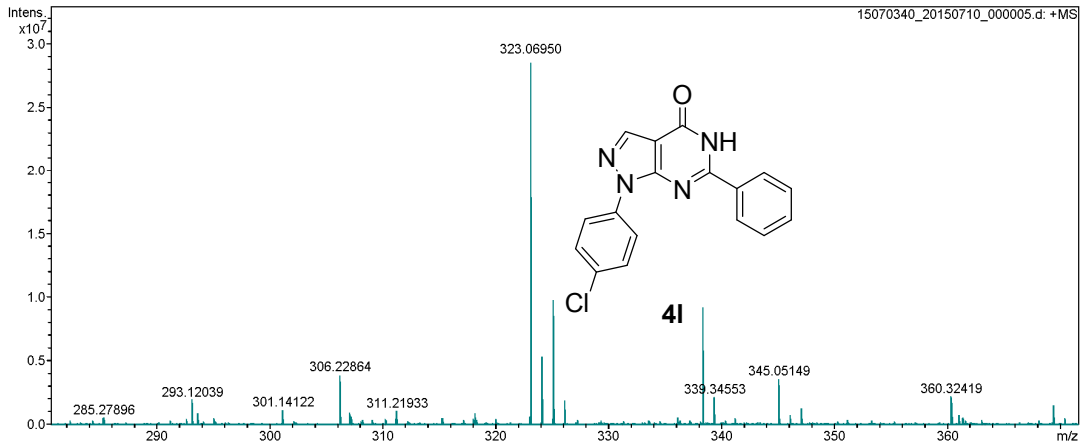


Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
331.15455	639170	C 20 H 19 N 4 O	100.00	331.15534	0.8	2.4	17.2	13.5	even	ok

Peking University Mass Spectrometry Sample Analysis Report

Analysis Info

Analysis Name	15070340_20150710_000005.d	Acquisition Date	7/10/2015 1:25:27 PM
Sample	lmx-041-1	Instrument	Bruker Apex IV FTMS
Comment	ESI Positive	Operator	Peking University

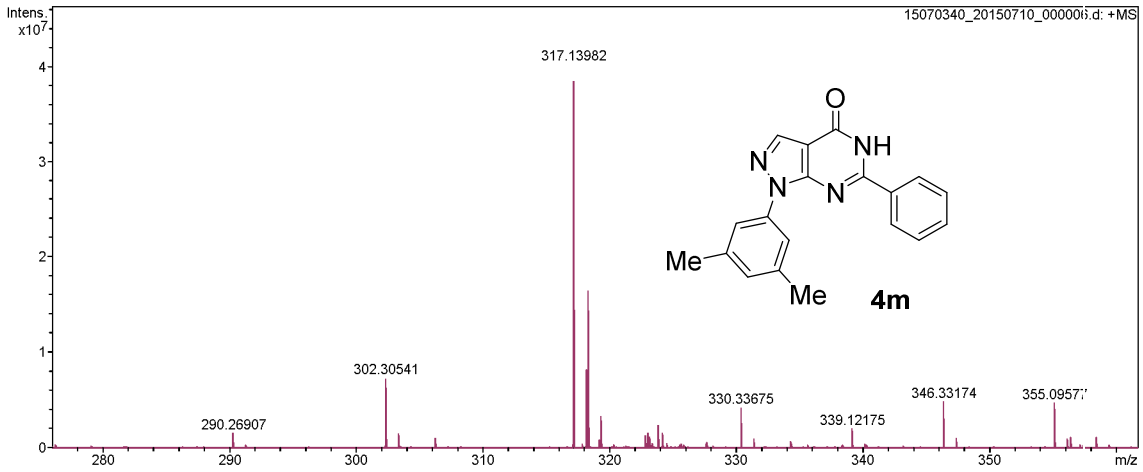


Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
323.06950	28983402	C 17 H 12 Cl N 4 O	100.00	323.06942	-0.1	-0.3	5.7	13.5	even	ok

Peking University Mass Spectrometry Sample Analysis Report

Analysis Info

Analysis Name	15070340_20150710_000006.d	Acquisition Date	7/10/2015 1:28:30 PM
Sample	lmx-039-1	Instrument	Bruker Apex IV FTMS
Comment	ESI Positive	Operator	Peking University

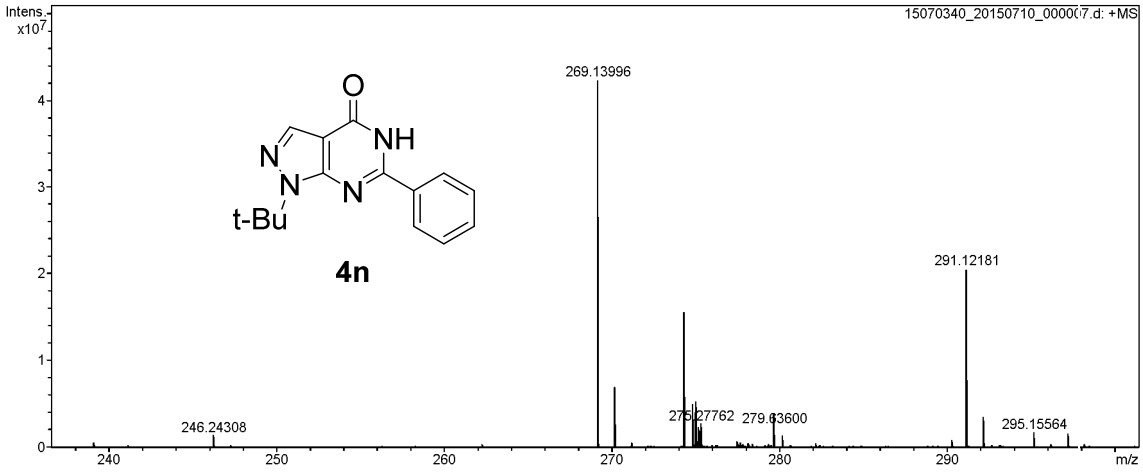


Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
317.13982	40305596	C 19 H 17 N 4 O	100.00	317.13969	-0.1	-0.4	10.1	13.5	even	ok

Peking University Mass Spectrometry Sample Analysis Report

Analysis Info

Analysis Name	15070340_20150710_000007.d	Acquisition Date	7/10/2015 1:31:23 PM
Sample	Imx-039-2	Instrument	Bruker Apex IV FTMS
Comment	ESI Positive	Operator	Peking University



Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
269.13996	42389552	C 15 H 17 N 4 O	100.00	269.13969	-0.3	-1.0	6.3	9.5	even	ok