Supporting Information

Synthesis of polysubstituted pyridazines via Cu-mediated C(sp^3)-C(sp^3) coupling/annulation of saturated ketones with acylhydrazones

Honggui Zhou,[‖,a] Zhefeng Li,[‖,a] Juehong Chen,[a] Si Zhou,[a] Xinyu Wang,[a] Linwei Zhang,[a] Jiuxi Chen[a] and Ningning Lv[*,a,b]

[a]College of Chemistry & Materials Engineering, Wenzhou University, Wenzhou 325035, China.
[b]Key Lab of Biohealth Materials and Chemistry of Wenzhou, Wenzhou 325035, China.
E-mail: ningninglv@wzu.edu.cn;
Supporting Information Placeholder

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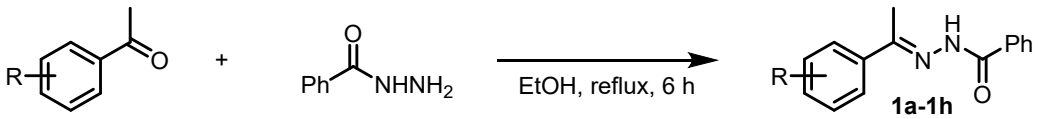
1. General Information.

Unless otherwise noted, all chemicals, containing 2-phenylacetophenones, ligands, propiophenones, *tert*-butylhydrazinecarboxylate, (1-phenylethylidene)benzohydrazide, Cu-catalysts, acid additives, base additives, oxidants, and all solvents, were obtained from commercial source and used as received without any further purification. (*E*)-*N*′-(1-phenylethylidene)Benzohydrazide substrates (**1**) were synthesized according to the relevant reference,[1] 2-phenylacetophenone substrates (**2**) were synthesized according to the relevant reference,[2] *tert*-butyl(*E*)-2-(Phenylethylidene)hydrazine-1-carboxylate substrates (**4**) were synthesized according to the relevant references.[3-6] 1-Phenylprop-2-en-1-one (**5h**) and (1-phenylethylidene)hydrazine (**1i**) were synthesized according to the relevant references.[7-8] ^{1}H NMR and ^{13}C NMR spectra were measured on a 500 MHz and 400 MHz Bruker spectrometer, using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as the internal standard at room temperature. Chemical shifts are given δ relative to tetramethylsilane, and the coupling constants J are given in hertz. The multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quarter (q) and multiplet (m). High-resolution mass spectra (HRMS) were recorded on an electrospray ionization (ESI-TOF) quadrupole time-of-flight mass spectrometer. Melting points were measured with WRR digital point apparatus. Analytical thin-layer chromatography (TLC) was performed on pre-coated, glass-backed silica gel plates. Flash column chromatography was performed over silica gel (300-400 mesh) using ethyl acetate (EA)/petroleum ether (PE) as eluent. X-ray crystallographic analysis was done at the X-ray crystallography facility, Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences (CAS).

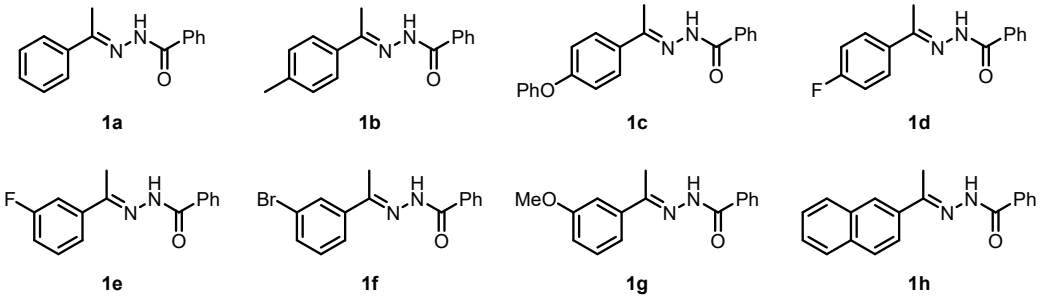
2. Experimental Section for the Synthesis of Substrates.

2.1. General procedure for the synthesis of acylhydrazones (1a-1h)[1]

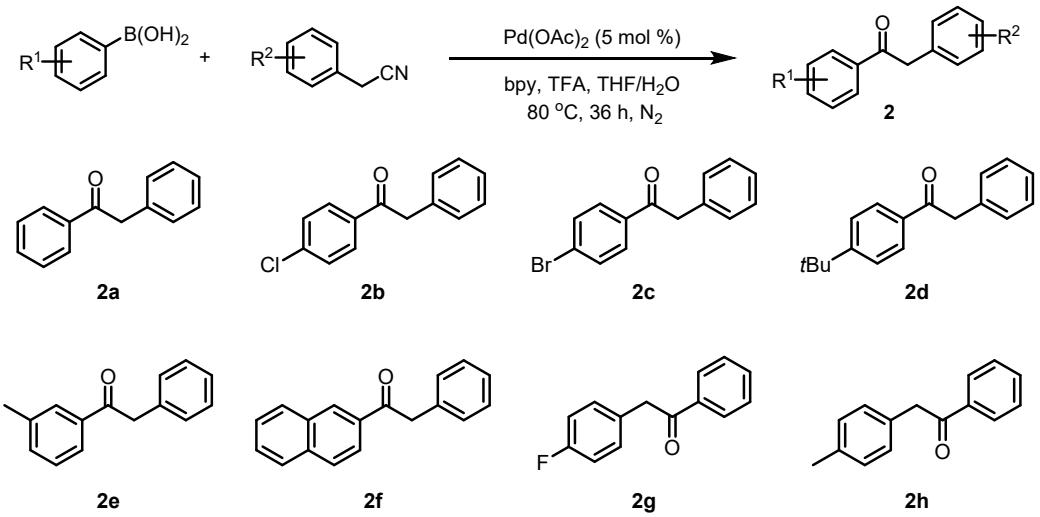


Standard procedure for the preparation of substituted acylhydrazones (**1a-1h**) were according to the reported procedure:[1] to a stirred solution of benzoyl hydrazine (10

mmol) in EtOH was added aryl ketones (10 mmol). The reaction mixture was heated under reflux for 6 hours, the precipitates were collected on a Büchner funnel. The acylhydrazones (**1a-1h**) were obtained in a quantitative yield and were purified by recrystallization from ethanol and washed with diethyl ether. In all cases, the obtained acylhydrazone was ***E*** configuration.



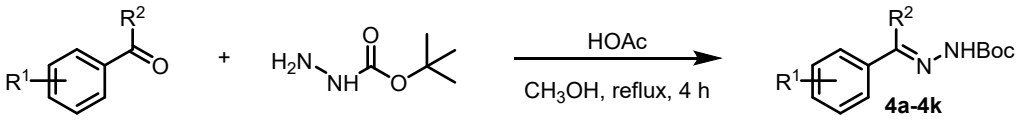
2.2. General procedure for the synthesis of 2-phenylacetophenones (2a-2h)[2]



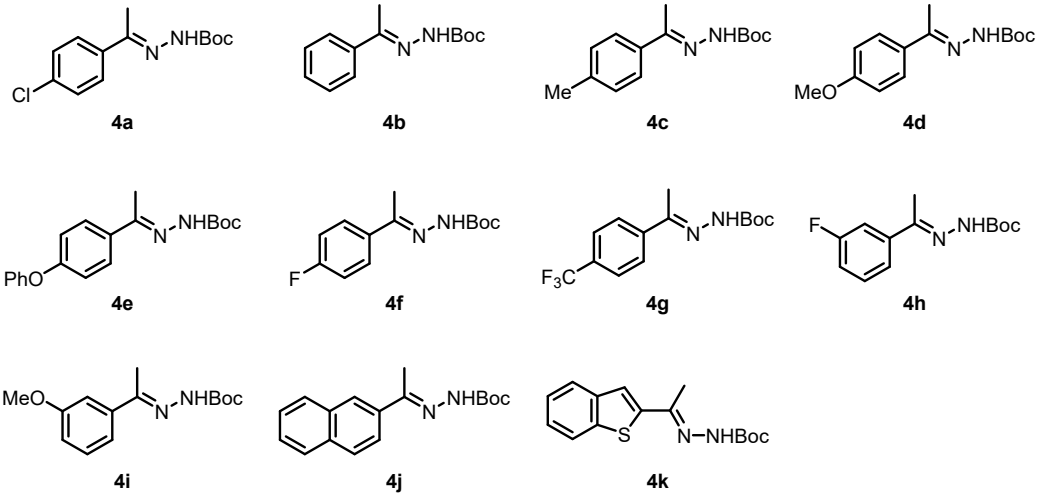
Standard procedure for the preparation of substituted 2-phenylacetophenones (**2a-2h**) were according to the reported procedure:[2] to a Schlenk tube with a magnetic stirring bar were charged the substituted 2-phenylacetonitriles (2 mmol), substituted arylboronic acids (4.0 mmol), $Pd(OAc)_2$ (5 mol %), 2,2'-bipyridine (10 mol %), TFA (10 equiv), THF (10 mL), and H_2O (4 mL) under a N_2 atmosphere. The reaction mixture was stirred at 80 °C for 36 h. After cooling to room temperature, the mixture was poured into EtOAc (25 mL), which was washed with saturated $NaHCO_3$ solution (2 × 10 mL) and then brine (1 × 10 mL). After extracting the aqueous layer with EtOAc (3 × 10 mL), the combined organic layers were dried (Na_2SO_4), and evaporated under vacuum. The residue was purified by flash column chromatography (PE/EtOAc) to afford the

substituted 2-phenylacetophenones (**2a-2h**).

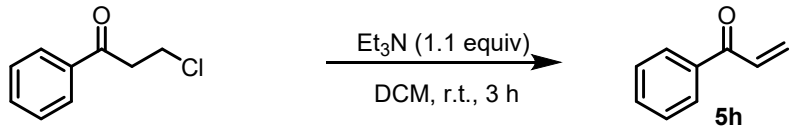
2.3. General procedure for the synthesis of acylhydrazones (4a-4k)[3-6]



Standard procedure for the preparation of substituted acylhydrazones (**4a-4k**) were according to the reported procedures:[3-6] to a stirred solution of tertiary butyl carbazate (10 mmol, 1.32 g) and HOAc (2 mmol, 0.12 g) in CH_3OH (5 mL) was added corresponding substituted acetophenones (10 mmol) and allowed to stir the reaction mixture at reflux for about 4 h. The completion of the reaction was monitored by TLC chromatography. After completion of the reaction, the reaction mixture was cooled and filtered to remove the solvent. The filtered solid was recrystallized with petroleum ether to get the pure corresponding acylhydrazones (**4a-4k**). In all cases, the obtained acylhydrazone was ***E*** configuration.



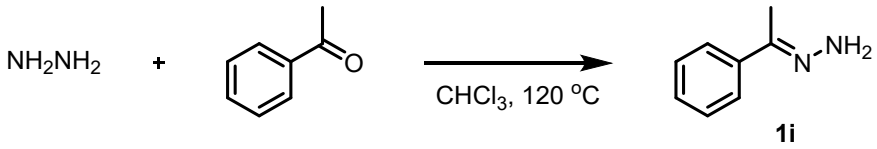
2.4. General procedure for the synthesis of 1-phenylprop-2-en-1-one (5h)[7]



Standard procedure for the preparation of 1-phenylprop-2-en-1-one (**5h**) was according to the reported procedure:[7] to a 50 mL round bottom flask equipped with magnetic stir bar was added 3-chloro-1-phenylpropan-1-one (10 mmol) in DCM (20 mL), then Et_3N (11 mmol) was added dropwise for about 10 min, afterwards, the reaction was stirred

at room temperature for the appropriate time (monitored by TLC). After completion of the reaction, the mixture was poured into DCM (15 mL) and washed with water (3 x 20 mL), then dried with anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography (hexane-EtOAc) to afford the targeted 1-phenylprop-2-en-1-one (**5h**).

2.5. General procedure for the synthesis of (1-phenylethylidene)hydrazine (1i)[8]

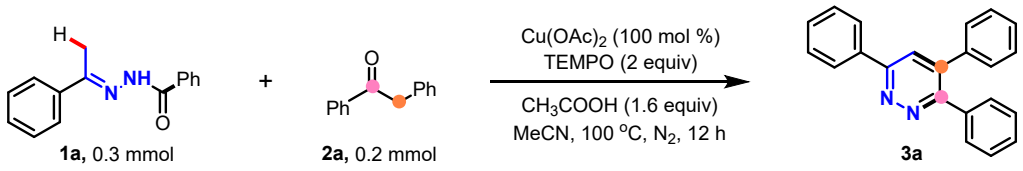


1i

Standard procedure for the preparation of (1-phenylethylidene)hydrazine (**1i**) was according to the reported procedure:[8] to a 100 mL round bottom flask equipped with magnetic stir bar was added hydrazine hydrate (1.2 mol) and acetophenone (40.0 mmol) in $CHCl_3$ (30 mL), then stirred the reaction mixture at 120 °C for 4 hours. After cooling to room temperature, the mixture was extracted with DCM. The combined organic layer was washed with brine, then dried with Na_2SO_4 and evaporated under vacuum to afford the targeted product **1i**. The obtained hydrazine was ***E*** configuration.

3. Optimization of Reaction Conditions.

Table S1. Optimization of reaction conditions for the synthesis of 3,4,6-trisubstituted pyridazine.[a,b]



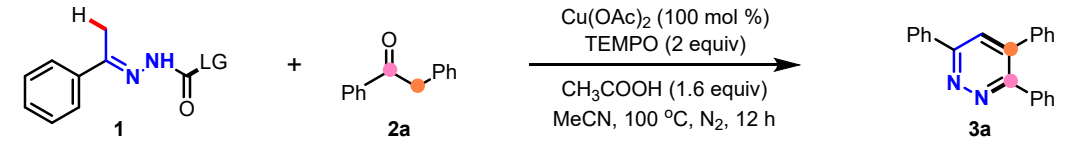
1a, 0.3 mmol **2a,** 0.2 mmol **3a**

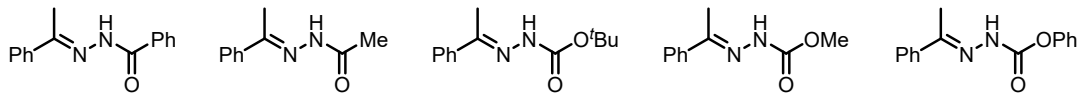
entry	Deviation from the standard conditions	yield(%)[b]
1	**none**	**90**
2	without Cu-salt	trace
3	without TEMPO	33
4	without acid additive	55
5	$CuBr_2$ instead of $Cu(OAc)_2$	15
6	$Cu(OTf)_2$ instead of $Cu(OAc)_2$	17
7	$Cu(acac)_2$ instead of $Cu(OAc)_2$	48
8	CuI instead of $Cu(OAc)_2$	46

9	DMF instead of MeCN	trace
10	THF instead of MeCN	15
11	DMSO instead of MeCN	35
12	EtOH instead of MeCN	45
13	$PhCH_3$ instead of MeCN	15
14	$^nC_4H_9COOH$ instead of HOAc	79
15	PivOH instead of HOAc	75
16	0.5 equiv. $Cu(OAc)_2$ was used	74
17	1.5 equiv. $Cu(OAc)_2$ was used	75
18	120 °C instead of 100 °C	80
19	80 °C instead of 100 °C	48
20	air instead of N_2	58
21	O_2 instead of N_2	19

[a]Reaction Conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), $Cu(OAc)_2$ (100 mol%), TEMPO (2 equiv), HOAc (1.6 equiv), MeCN (2 mL), 100 °C, N_2, 12 h. [b]Isolated yields.

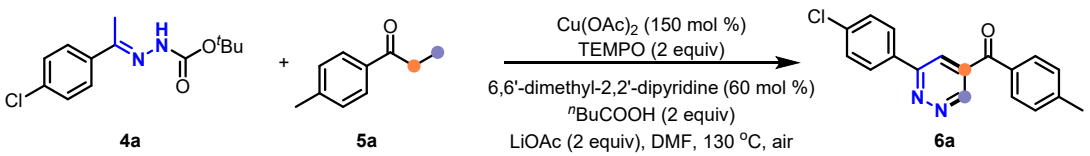
Table S2. Screening of the leaving group on the acylhydrazone for the synthesis of 3,4,6-trisubstituted pyridazine.[a,b]





[a]Reaction Conditions: **1** (0.3 mmol), **2a** (0.2 mmol), $Cu(OAc)_2$ (100 mol%), TEMPO (2 equiv), HOAc (1.6 equiv), MeCN (2 mL), 100 °C, N_2, 12 h. [b]Isolated yields.

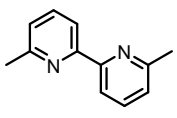
Table S3. Optimization of reaction conditions for the synthesis of 3,5-disubstituted pyridazine.[a,b]



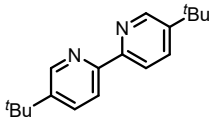
entry	deviation from the standard conditions	yield(%)[b]
1	**none**	**76**
2	without Cu-salt	trace
3	without TEMPO	trace
4	without ligand	50

5	without base additive	57
6	without acid additive	56
7	$Cu(acac)_2$ instead of $Cu(OAc)_2$	<10
8	$Cu(OTf)_2$ instead of $Cu(OAc)_2$	<10
9	$CuSO_4$ instead of $Cu(OAc)_2$	24
10	$CuCl_2$ instead of $Cu(OAc)_2$	trace
11	CuI instead of $Cu(OAc)_2$	<10
12	MeCN instead of DMF	15
13	DCE instead of DMF	<10
14	THF instead of DMF	20
15	DMSO instead of DMF	57
16	NMP instead of DMF	60
17	HOAc instead of $^{n}C_4H_9COOH$	66
18	PivOH instead of $^{n}C_4H_9COOH$	69
19	Li_2CO_3 instead of LiOAc	50
20	LiOH instead of LiOAc	58
21	LiOMe instead of LiOAc	60
22	L2 instead of L1	55
23	L3 instead of L1	40
24	L4 instead of L1	65
25	L5 instead of L1	65
26	N_2 instead of air	62
27	O_2 instead of air	38
28	140 ℃ instead of 130 ℃	74
29	120 ℃ instead of 130 ℃	68

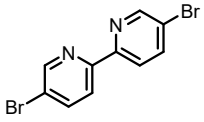
[a]Reaction Conditions: **4a** (0.25 mmol), **5a** (0.2 mmol), $Cu(OAc)_2$ (150 mol%), TEMPO (2 equiv), 6,6'-dimethyl-2,2'-bipyridine (60 mol%), $^{n}C_4H_9COOH$ (2 equiv), LiOAc (2 equiv), DMF (2 mL), 130 °C, air, 12 h. [b]Isolated yields.



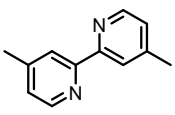
L1



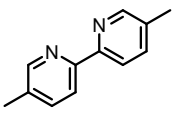
L2



L3

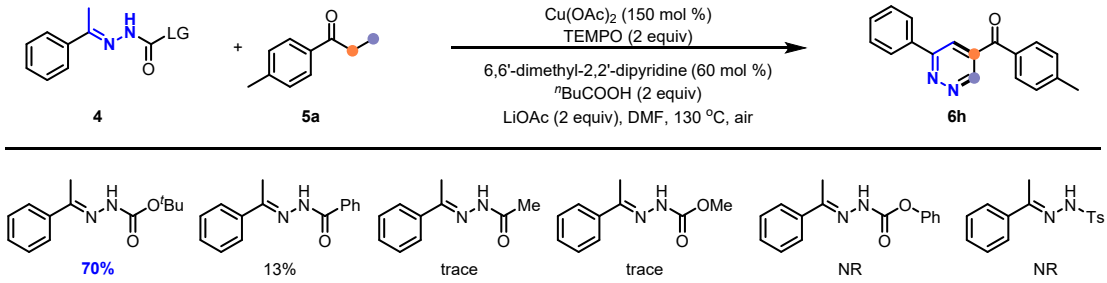


L4



L5

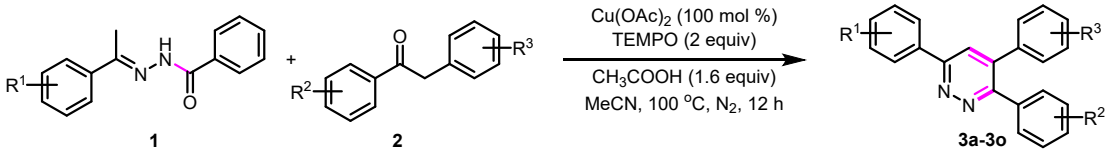
Table S4. Screening of the leaving groups on the acylhydrazone for the synthesis of 3,5-disubstituted pyridazine.[a,b]



[a]Reaction Conditions: **4** (0.25 mmol), **5a** (0.2 mmol), $Cu(OAc)_2$ (150 mol%), TEMPO (2 equiv), 6,6'-dimethyl-2,2'-bipyridine (60 mol%), $^nC_4H_9COOH$ (2 equiv), LiOAc (2 equiv), DMF (2 mL), 130 °C, air, 12 h. [b]Isolated yields.

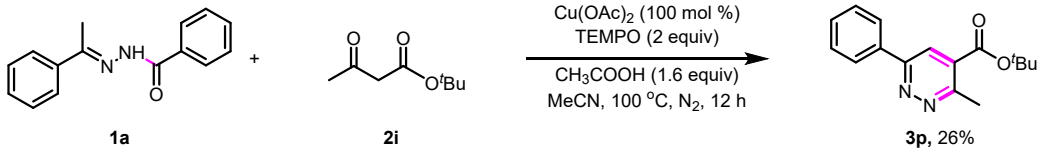
4. General Procedure for Accessing Polysubstituted Pyridazines.

4.1. General procedure for the synthesis of 3,4,6-triaryl pyridazines (3a-3o).



In a 25 mL Schlenk reaction tube with a stir bar, *N*-benzoylhydrazones (**1**) (0.3 mmol), substituted 2-phenylacetophenone (**2**) (0.2 mmol), $Cu(OAc)_2$ (0.2 mmol, 36.2 mg), TEMPO (0.4 mmol, 62.4 mg), HOAc (0.32 mmol) were dissolved in MeCN (2.0 mL) under a nitrogen atmosphere. The reaction mixture was then heated at 100 °C (oil bath) with vigorous stirring for 12 hours. After the reaction completion, the mixture was poured into ethyl acetate, and washed with saturated brine (1 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by a silica gel packed flash chromatography column with petroleum ether/ethyl acetate (15:1) as the eluent to afford the desired 3,4,6-triarylpyridazines (**3a-3o**).

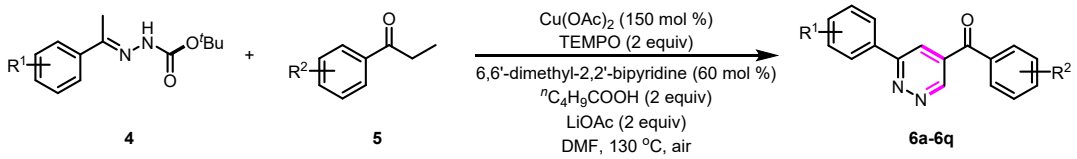
4.2. General procedure for the synthesis of *tert*-butyl 3-methyl-6-phenylpyridazine-4-carboxylate (3p).



In a 25 mL Schlenk reaction tube with a stir bar, substituted acylhydrazones (**1a**) (0.3 mmol), *tert*-butyl 3-oxobutanoate (**2i**) (0.2 mmol), $Cu(OAc)_2$ (0.2 mmol, 36.2 mg),

TEMPO (0.4 mmol, 62.4 mg), HOAc (0.32 mmol) were dissolved in MeCN (2.0 mL) under a nitrogen atmosphere. The reaction mixture was then heated at 100 °C (oil bath) with vigorous stirring for 12 hours. After the reaction completion, the mixture was poured into ethyl acetate, and washed with saturated brine (1 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by a silica gel packed flash chromatography column with petroleum ether/ethyl acetate (15:1) as the eluent to afford the desired tert-butyl 3-methyl-6-phenylpyridazine-4-carboxylate (**3p**) in a yield of 26%.

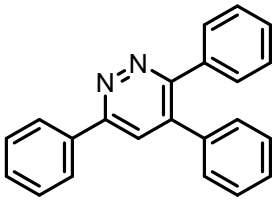
4.3. General procedure for the synthesis of 3,5-disubstituted pyridazines (6a-6q).



In a 25 mL Schlenk reaction tube with a stir bar, substituted acylhydrazone (**4**) (0.25 mmol), substituted propiophenone (**5**) (0.2 mmol), $Cu(OAc)_2$ (0.3 mmol, 54.3 mg), 6,6'-dimethyl-2,2'-bipyridine (0.12 mmol, 22.1 mg), TEMPO (0.4 mmol, 62.4 mg), LiOAc (0.4 mmol, 25.6 mg), $^nC_4H_9COOH$ (0.4 mmol, 40.8 mg) were dissolved in DMF (2 mL) under air atmosphere. The reaction mixture was then heated at 130 °C (oil bath) with vigorous stirring for 12 hours. After the reaction equilibrium, the mixture was poured into ethyl acetate and washed with saturated brine (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by a silica gel packed flash chromatography column with petroleum ether/ethyl acetate (12:1) as the eluent to afford the desired 3-aryl-5-benzoylpyridazines products (**6a-6q**).

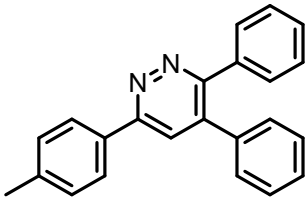
5. Analytical Data for All Products.

3,4,6-triphenylpyridazine (**3a**):



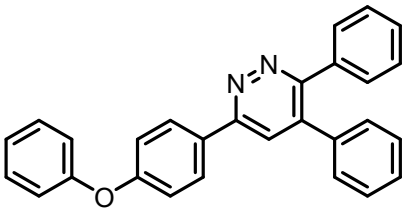
Yellow solid (55.4 mg, 90%). mp: 165-166 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 15/1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.5 Hz, 2H), 7.86 (s, 1H), 7.57-7.50 (m, 5H), 7.37-7.30 (m, 6H), 7.28-7.26 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.2, 157.8, 139.5, 137.2, 136.7, 136.2, 130.1, 129.1, 129.1, 128.8, 128.7, 128.1, 127.1, 124.8. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{22}H_{17}N_2$ 309.1386, Found 309.1374.

3,4-diphenyl-6-(*p*-tolyl)pyridazine (**3b**):



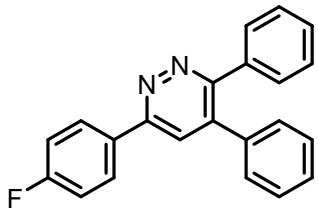
Yellow solid (53.5 mg, 83%). mp: 196-197 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 15/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.5 Hz, 2H), 7.87 (s, 1H), 7.55 (d, *J* = 7.5 Hz, 2H), 7.42-7.30 (m, 10H), 2.49 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.3, 157.7, 139.5, 138.8, 136.9, 136.2, 134.2, 130.0, 130.0, 129.5, 129.0, 129.0, 128.7, 128.1, 127.1, 124.8, 21.3. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{23}H_{19}N_2$ 323.1543, Found 323.1545.

6-(4-phenoxyphenyl)-3,4-diphenylpyridazine (**3c**):



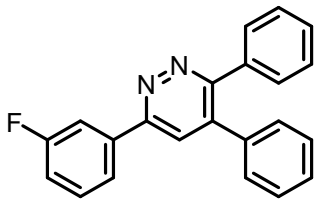
Yellow solid (66.4 mg, 83%). mp: 165-166 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 15/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.4 Hz, 2H), 7.88 (s, 1H), 7.57 (d, *J* = 7.2 Hz, 2H), 7.48-7.33 (m, 10H), 7.24-7.17 (m, 5H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.5, 156.5, 137.3, 136.8, 130.9, 130.1, 130.0, 129.2, 128.8, 128.8, 128.7, 128.2, 124.4, 124.0, 119.6, 118.8. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{28}H_{21}N_2O$ 423.1468, Found 423.1451.

6-(4-fluorophenyl)-3,4-diphenylpyridazine (**3d**):



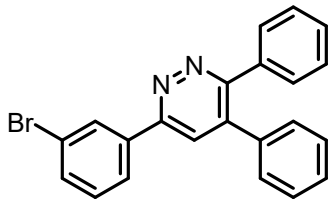
Yellow solid (54.1 mg, 83%). mp: 174-175 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 15/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10-8.06 (m, 2H), 7.70 (s, 1H), 7.39 (d, J = 7.2 Hz, 2H), 7.26-7.19 (m, 6H), 7.16-7.13 (m, 3H), 7.11-7.09 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.2 (d, $J_{C\text{-}F}$ = 248.8 Hz), 158.2, 156.8, 139.6, 137.1, 136.6, 132.3 (d, $J_{C\text{-}F}$ = 3.8 Hz), 130.0, 129.1, 129.0, 129.0, 128.8, 128.8, 128.2, 124.5, 116.1 (d, $J_{C\text{-}F}$ = 22.5 Hz). **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{22}H_{16}FN_2$ 327.1292, Found 327.1321.

6-(3-fluorophenyl)-3,4-diphenylpyridazine (**3e**):



Yellow solid (51.5 mg, 79%). mp: 202-203 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 15/1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.87-7.84 (m, 2H), 7.73 (s, 1H), 7.41-7.38 (m, 3H), 7.27-7.24 (m, 4H), 7.23-7.21 (m, 2H), 7.17 (d, J = 7.0 Hz, 2H), 7.10 (t, J = 9.0 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.4 (d, $J_{C\text{-}F}$ = 243.8 Hz), 158.7, 156.5, 139.6, 138.4 (d, $J_{C\text{-}F}$ = 7.5 Hz), 137.0, 136.6, 130.6 (d, $J_{C\text{-}F}$ = 7.5 Hz), 130.1, 129.1, 128.9, 128.9, 128.8, 128.2, 124.9, 122.6 (d, $J_{C\text{-}F}$ = 2.5 Hz), 117.0 (d, $J_{C\text{-}F}$ = 21.3 Hz), 114.1 (d, $J_{C\text{-}F}$ = 23.8 Hz). **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{22}H_{16}FN_2$ 327.1292, Found 327.1313.

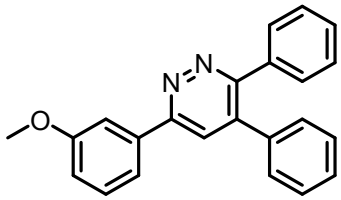
6-(3-bromophenyl)-3,4-diphenylpyridazine (**3f**):



Yellow solid (57.3 mg, 74%). mp: 140-141 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 15/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 (s,

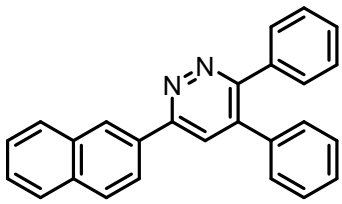
1H), 8.04 (d, *J* = 7.6 Hz, 1H), 7.73 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.34-7.30 (m, 1H), 7.30-7.22 (m, 6H), 7.17 (d, *J* = 3.6 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.2, 133.0, 130.6, 130.1, 130.0, 129.1, 128.9, 128.9, 128.8, 128.2, 125.6, 123.3. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{22}H_{16}BrN_2$ 387.0491, Found 387.0475.

6-(3-methoxyphenyl)-3,4-diphenylpyridazine (**3g**):



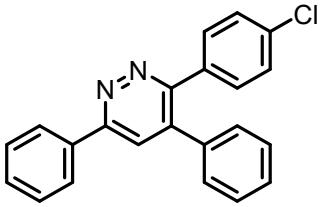
Yellow solid (54.8 mg, 81%). mp: 107-108 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 15/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 12.0 Hz, 2H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.28-7.17 (m, 8H), 6.97 (d, *J* = 8.4 Hz, 1H), 3.82 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.3, 139.5, 137.5, 137.2, 136.8, 130.1, 130.1, 129.1, 128.8, 128.2, 125.0, 119.4, 116.5, 112.0, 55.5. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{23}H_{19}N_2O$ 339.1492, Found 339.1509.

6-(naphthalen-2-yl)-3,4-diphenylpyridazine (**3h**):



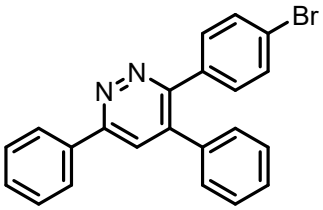
Yellow solid (59.4 mg, 83%). mp: 173-174 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 15/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.37 (d, *J* = 8.4 Hz, 1H), 8.03-7.97 (m, 3H), 7.91 (d, *J* = 4.4 Hz, 1H), 7.56-7.53 (m, 4H), 7.40-7.29 (m, 8H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.2, 157.6, 139.5, 137.3, 136.8, 134.2, 133.4, 130.1, 129.1, 128.9, 128.9, 128.8, 128.8, 128.8, 128.2, 127.8, 127.1, 126.9, 126.6, 125.0, 124.3. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{26}H_{19}N_2$ 359.1543, Found 359.1532.

3-(4-chlorophenyl)-4,6-diphenylpyridazine (**3i**):



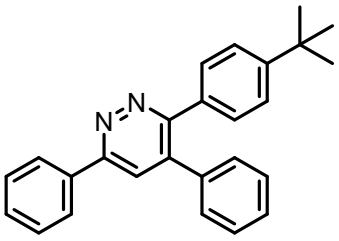
Yellow solid (50.7 mg, 74%). mp: 138-139 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 15/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.2 Hz, 2H), 7.74 (s, 1H), 7.46-7.37 (m, 5H), 7.31-7.26 (m, 3H), 7.18-7.15 (m, 2H), 6.92-6.88 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.2, 162.2, 137.1, 136.0, 132.8, 132.0, 131.9, 130.1, 129.1, 129.0, 128.9, 128.9, 127.1, 124.9, 115.4, 115.2. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{22}H_{16}ClN_2$ 343.0997, Found 343.0997.

3-(4-fluorophenyl)-4,6-diphenylpyridazine (**3j**):



Yellow solid (55.7 mg, 72%). mp: 160-161 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 15/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 7.2 Hz, 2H), 7.93 (s, 1H), 7.65-7.59 (m, 3H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.48-7.46 (m, 3H), 7.38-7.34 (m, 4H). **^{13}C NMR** (125 MHz, CDCl3) δ 157.9, 157.1, 139.4, 136.9, 136.0, 135.2, 135.1, 131.4, 130.2, 129.1, 129.0, 129.0, 129.0, 128.4, 127.1, 124.9. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{22}H_{16}BrN_2$ 387.0491, Found 387.0493.

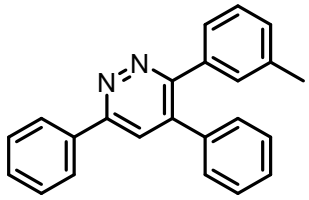
3-(4-(*tert*-butyl)phenyl)-4,6-diphenylpyridazine (**3k**):



Yellow solid (42.2 mg, 58%). mp: 122-123 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 15/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 6.8 Hz, 2H), 7.72 (s, 1H), 7.45-7.39 (m, 3H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.28-7.18 (m, 7H), 1.21 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.1, 157.5, 152.0, 139.3, 137.5,

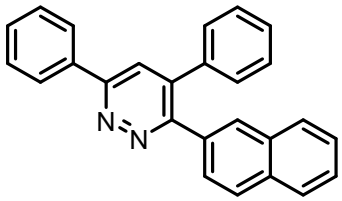
136.3, 133.7, 130.0, 129.8, 129.1, 129.1, 128.8, 128.7, 127.1, 125.1, 124.9, 34.7, 31.3. **HRMS (ESI-TOF)** m/z: $[M + Na]^+$ Calcd for $C_{26}H_{24}N_2Na$ 387.1832, Found 387.1858.

4,6-diphenyl-3-(*m*-tolyl)pyridazine (**3l**):



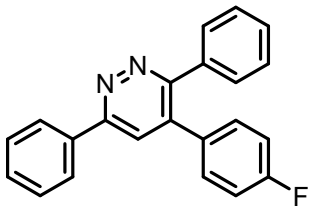
Yellow solid (39.3 mg, 61%). mp: 117-118 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 15/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 6.0 Hz, 2H), 7.75 (s, 1H), 7.48-7.41 (m, 3H), 7.36 (s, 1H), 7.28-7.26 (m, 3H), 7.19-7.17 (m, 2H), 7.09-7.05 (m, 3H), 2.22 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 137.9, 137.3, 136.6, 136.2, 130.7, 130.0, 129.5, 129.1, 129.1, 128.7, 128.7, 127.8, 127.2, 127.1, 124.8, 21.4. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{23}H_{19}N_2$ 323.1543, Found 323.1511.

3-(naphthalen-2-yl)-4,6-diphenylpyridazine (**3m**):



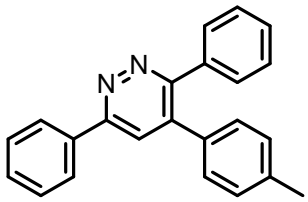
Yellow solid (59.4 mg, 83%). mp: 153-154 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 15/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 6.8 Hz, 2H), 8.05 (s, 1H), 7.76 (s, 1H), 7.69-7.64 (m, 2H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.45-7.33 (m, 6H), 7.24-7.18 (m, 5H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.1, 157.8, 139.7, 137.3, 136.2, 134.3, 133.3, 133.2, 130.1, 129.2, 129.1, 128.9, 128.8, 128.7, 127.7, 127.6, 127.3, 127.2, 126.8, 126.2, 124.9. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{26}H_{19}N_2$ 359.1543, Found 359.1532.

4-(4-fluorophenyl)-3,6-diphenylpyridazine (3n):



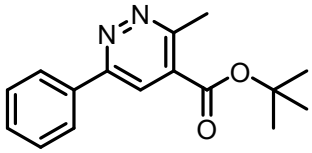
Yellow solid (29.3 mg, 45%). mp: 175-176 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 15/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.0 Hz, 2H), 7.80 (s, 1H), 7.55-7.46 (m, 5H), 7.35-7.29 (m, 3H), 7.25-7.21 (m, 2H), 7.01-7.05 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.0 (d, J_{C-F} = 248.8 Hz), 158.2, 157.8, 138.5, 136.6, 136.0, 133.2 (d, J_{C-F} = 2.5 Hz), 131.0 (d, J_{C-F} = 7.5 Hz), 130.2, 130.0, 129.1, 128.9, 128.3, 127.1, 124.7, 116.0 (d, J_{C-F} = 21.3 Hz). **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{22}H_{16}FN_2$ 327.1292, Found 327.1313.

3,6-diphenyl-4-(*p*-tolyl)pyridazine (**3o**):



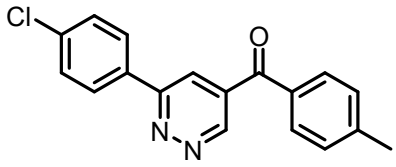
Yellow solid (47.0 mg, 73%). mp: 128-129 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 15/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.0 Hz, 2H), 7.83 (s, 1H), 7.56-7.49 (m, 5H), 7.35-7.29 (m, 3H), 7.18-7.12 (m, 4H), 2.36 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 160.3, 158.3, 157.5, 139.5, 137.5, 137.2, 136.7, 130.1, 130.0, 129.1, 128.8, 128.1, 125.0, 119.3, 116.5, 111.9, 55.5. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{23}H_{19}N_2$ 323.1543, Found 323.1555.

***tert*-butyl 3-methyl-6-phenylpyridazine-4-carboxylate** (**3p**):



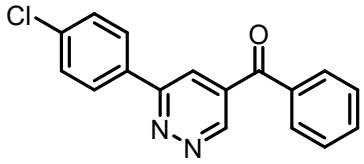
Yellow solid (14.0 mg, 26%). mp: 112-123 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 15/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12-8.09 (m, 3H), 7.55-7.48 (m, 3H), 2.98 (s, 3H), 1.64 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.7, 158.4, 156.7, 135.8, 130.4, 130.1, 129.1, 127.0, 123.5, 83.8, 28.2, 22.0. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{16}H_{19}N_2O_2$ 271.1441, Found 271.1443.

(6-(4-chlorophenyl)pyridazin-4-yl)(*p*-tolyl)methanone (**6a**):



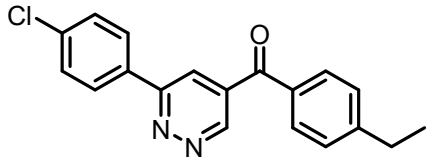
Yellow solid (46.9 mg, 76%). mp: 178-179 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 12/1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.09-8.06 (m, 3H), 7.75 (d, *J* = 7.6 Hz, 2H), 7.51 (d, *J* = 9.2 Hz, 2H), 7.35 (d, *J* = 7.6 Hz, 2H), 2.47 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 192.8, 158.8, 148.2, 145.7, 137.1, 135.6, 134.0, 132.7, 130.3, 129.8, 129.5, 128.5, 122.5, 21.9. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{18}H_{14}ClN_2O$ 309.0789, Found 309.0760.

(6-(4-chlorophenyl)pyridazin-4-yl)(phenyl)methanone (**6b**):



Yellow solid (35.3 mg, 60%). mp: 146-147 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 12/1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.14-8.08 (m, 3H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.71 (t, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 2H), 7.52 (d, *J* = 9.0 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 193.2, 158.9, 148.1, 137.1, 135.2, 135.2, 134.4, 134.0, 130.1, 129.5, 129.1, 128.5, 122.5. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{17}H_{12}ClN_2O$ 295.0633, Found 295.0613.

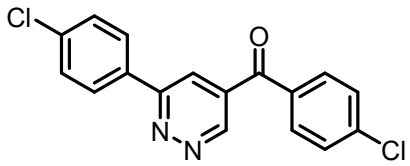
(6-(4-chlorophenyl)pyridazin-4-yl)(4-ethylphenyl)methanone (**6c**):



Yellow solid (35.4 mg, 55%). mp: 156-157 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 12/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.09-8.06 (m, 3H), 7.78 (d, *J* = 6.0 Hz, 2H), 7.51 (d, *J* = 6.0 Hz, 2H), 7.38 (d, *J* = 6.4 Hz, 2H), 2.76 (q, *J* = 6.0 Hz, 2H), 1.30 (t, *J* = 6.0 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 192.8, 158.8, 151.8, 148.2, 137.1, 135.6, 134.1, 132.9, 130.4, 129.5, 128.6, 128.5, 122.5, 29.1, 15.1. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{19}H_{16}ClN_2O$

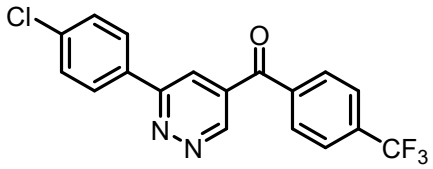
323.0946; Found 323.0938.

(4-chlorophenyl)(6-(4-chlorophenyl)pyridazin-4-yl)methanone (6d):



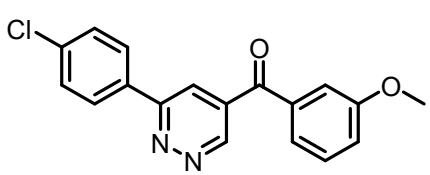
Yellow solid (41.4 mg, 63%). mp: 194-195 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 12/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.09-8.05 (m, 3H), 7.81 (d, *J* = 8.8 Hz, 2H), 7.56-7.52 (m, 4H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 192.0, 159.0, 147.8, 141.2, 137.2, 134.9, 133.9, 133.5, 131.4, 129.5, 128.5, 122.3. **HRMS (ESI-TOF)** m/z:$[M + H]^+$ Calcd for $C_{17}H_{11}Cl_2N_2O$ 329.0243; Found 329.0238.

(6-(4-chlorophenyl)pyridazin-4-yl)(4-(trifluoromethyl)phenyl)methanone (6e):



Yellow solid (34.8 mg, 48%). mp: 180-181 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 12/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.09-8.08 (m, 3H), 7.97 (d, *J* = 8.0 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 192.4, 159.1, 147.7, 138.0, 137.3, 135.5 (q, $J_{C\text{-}F}$ = 32.5 Hz), 134.2, 133.7, 130.3, 129.6, 128.5, 126.2 (q, $J_{C\text{-}F}$ = 2.5 Hz), 123.3 (q, $J_{C\text{-}F}$ = 271.2 Hz), 122.2. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{18}H_{11}ClF_3N_2O$ 363.0507, Found 363.0532.

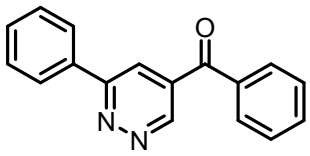
(6-(4-chlorophenyl)pyridazin-4-yl)(3-methoxyphenyl)methanone (**6f**):



Yellow solid (31.8 mg, 49%). mp: 156-157 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 12/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.12-8.09 (m, 3H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.47-7.43 (m, 2H), 7.34 (d, *J* = 7.2

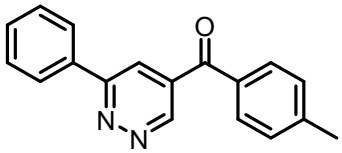
Hz, 1H), 7.28-7.24 (m, 1H), 3.89 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 193.0, 160.2, 158.9, 148.1, 137.1, 136.5, 135.3, 134.0, 130.0, 129.5, 128.5, 123.0, 122.5, 120.9, 114.0, 55.6. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{18}H_{14}ClN_2O_2$ 325.0738, Found 325.0714.

phenyl(6-phenylpyridazin-4-yl)methanone (**6g**):



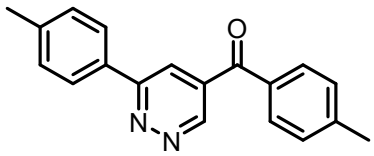
Yellow solid (33.3 mg, 64%). mp: 130-131 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 12/1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.14-8.12 (m, 2H), 8.10 (s, 1H), 7.86 (d, J = 7.5 Hz, 2H), 7.71 (t, J = 7.0 Hz, 1H), 7.58-7.53 (m, 5H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 193.4, 160.0, 148.0, 135.6, 135.3, 135.1, 134.3, 130.7, 130.1, 129.2, 129.1, 127.3, 122.8. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{17}H_{13}N_2O$ 261.1022, Found 261.1033.

(6-phenylpyridazin-4-yl)(*p*-tolyl)methanone (6h):



Yellow solid (38.4 mg, 70%). mp: 170-171 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 12/1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.14 (d, J = 8.0 Hz, 2H), 8.08 (s, 1H), 7.77 (d, J = 8.0 Hz, 2H), 7.57-7.54 (m, 3H), 7.36 (d, J = 8.0 Hz, 2H), 2.48 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 193.0, 159.9, 148.0, 145.6, 135.7, 135.5, 132.8, 130.6, 130.3, 129.8, 129.2, 127.3, 122.8, 21.9. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{18}H_{15}N_2O$ 275.1179, Found 275.1186.

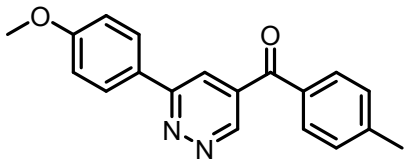
***p*-tolyl(6-(*p*-tolyl)pyridazin-4-yl)methanone** (**6i**):



Yellow solid (30.0 mg, 52%). mp: 164-165 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 12/1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.05-8.02 (m, 3H), 7.76 (d, J = 8.5 Hz, 2H), 7.36-7.34 (m, 4H), 2.47 (s, 3H), 2.44

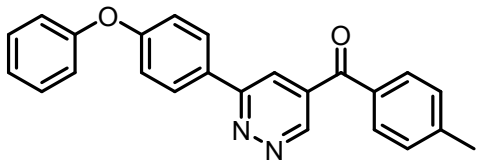
(s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 193.0, 159.8, 147.7, 145.5, 141.0, 135.4, 132.9, 132.8, 130.3, 129.9, 129.7, 127.2, 122.4, 21.8, 21.4. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{19}H_{17}N_2O$ 289.1335, Found 289.1358.

(6-(4-methoxyphenyl)pyridazin-4-yl)(*p*-tolyl)methanone (**6j**):



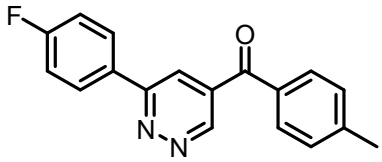
Yellow solid (45.6 mg, 75%). mp: 153-154 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 12/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.10 (d, J = 8.8 Hz, 2H), 8.02 (s, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 7.6 Hz, 2H), 7.04 (d, J = 8.8 Hz, 2H), 3.88 (s, 3H), 2.47 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 193.1, 161.8, 159.4, 147.4, 145.5, 135.4, 132.8, 130.3, 129.7, 128.7, 128.0, 122.0, 114.6, 55.5, 21.9. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{19}H_{17}N_2O_2$ 305.1285, Found 305.1297.

(6-(4-phenoxyphenyl)pyridazin-4-yl)(*p*-tolyl)methanone (**6k**):



Yellow solid (40.3 mg, 55%). mp: 130-131 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 12/1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.19 (d, J = 7.5 Hz, 2H), 7.84 (s, 1H), 7.55-7.51 (m, 5H), 7.35-7.30 (m, 3H), 7.16-7.15 (m, 4H), 2.37 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 196.2, 158.3, 157.7, 139.5, 138.8, 137.0, 136.2, 134.2, 130.0, 130.0, 129.5, 129.0, 129.0, 128.7, 128.1, 127.1, 124.8, 21.3. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{24}H_{19}N_2O_2$ 367.1441, Found 367.1479.

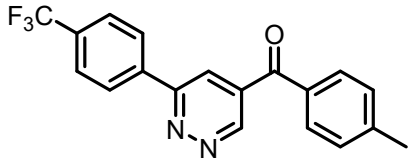
(6-(4-fluorophenyl)pyridazin-4-yl)(*p*-tolyl)methanone (**6l**):



Yellow solid (34.5 mg, 59%). mp: 146-147 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 12/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.43 (s,

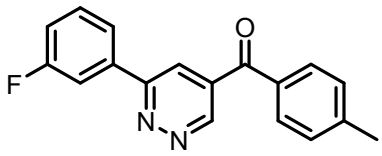
1H), 8.22-8.17 (m, 2H), 8.12 (s, 1H), 7.82 (d, J = 6.4 Hz, 2H), 7.42 (d, J = 6.8 Hz, 2H), 7.32-7.27 (m, 2H), 2.54 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 192.9, 164.5 (d, J_{C-F} = 250.0 Hz), 148.0, 145.7, 135.7, 132.7, 131.8 (d, J_{C-F} = 3.8 Hz), 130.3, 129.8, 129.3 (d, J_{C-F} = 8.8 Hz), 122.4, 116.3 (d, J_{C-F} = 21.3 Hz), 21.9. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{18}H_{14}FN_2O$ 293.1085, Found 293.1064.

***p*-tolyl(6-(4-(trifluoromethyl)phenyl)pyridazin-4-yl)methanone (6m)**:



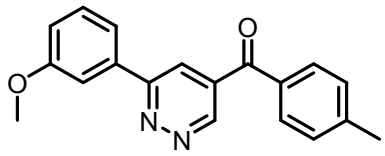
Yellow solid (41.0 mg, 60%). mp: 196-197 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 12/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.27 (d, J = 8.0 Hz, 2H), 8.13 (s, 1H), 7.79 (q, J = 8.8 Hz, 4H), 7.37 (d, J = 8.0 Hz, 2H), 2.49 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 192.6, 158.6, 148.6, 145.8, 139.0, 135.7, 132.6, 132.4 (q, J_{C-F} = 32.5 Hz), 130.3, 129.8, 127.6, 126.1 (q, J_{C-F} = 3.8 Hz), 123.9 (q, J_{C-F} = 270.0 Hz), 123.0, 21.9. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{19}H_{14}F_3N_2O$ 343.1053, Found 343.1066.

(6-(3-fluorophenyl)pyridazin-4-yl)(*p*-tolyl)methanone (6n):



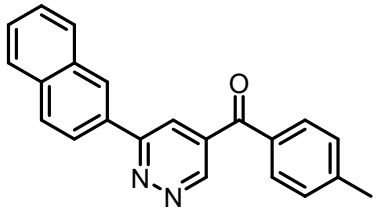
Yellow solid (25.1 mg, 43%). mp: 124-125 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 12/1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.09 (s, 1H), 7.95-7.90 (m, 2H), 7.80-7.77 (m, 2H), 7.53 (s, 1H), 7.42-7.36 (m, 2H), 7.29-7.23 (m, 1H), 2.50 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 192.7, 163.4 (d, J_{C-F} = 245.0 Hz), 158.7, 148.4, 145.7, 137.9, 135.6, 132.7, 130.8 (d, J_{C-F} = 7.5 Hz), 130.3, 129.8, 122.8 (d, J_{C-F} = 32.5 Hz), 117.6 (d, J_{C-F} = 20.0 Hz), 114.3 (d, J_{C-F} = 25.0 Hz), 21.8. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{18}H_{14}FN_2O$ 293.1085, Found 293.1081.

(6-(3-methoxyphenyl)pyridazin-4-yl)(*p*-tolyl)methanone (6o):



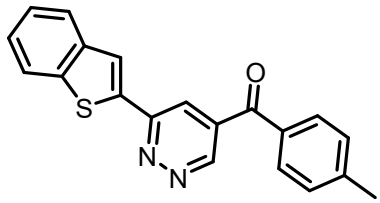
Yellow solid (25.5 mg, 42%). mp: 144-145°C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 12/1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.06 (s, 1H), 7.78-7.75 (m, 3H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 1H), 3.91 (s, 3H), 2.47 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 192.9, 160.4, 159.6, 148.1, 145.6, 137.0, 135.5, 132.8, 130.3, 130.2, 129.8, 122.8, 119.5, 116.9, 112.3, 55.5, 21.8. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{19}H_{17}N_2O_2$ 305.1285, Found 305.1294.

(6-(naphthalen-2-yl)pyridazin-4-yl)(*p*-tolyl)methanone (**6p**):



Yellow solid (31.8 mg, 49%). mp: 189-190 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 12/1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.61 (s, 1H), 8.29 (d, *J* = 8.5 Hz, 1H), 8.23 (s, 1H), 8.01 (d, *J* = 9.0 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 7.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.57- 7.55 (m, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 2.49 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 193.0, 159.9, 148.0, 145.6, 135.6, 134.4, 133.4, 132.9, 132.8, 130.3, 129.8, 129.1, 128.9, 127.8, 127.5, 127.4, 126.8, 124.1, 122.9, 21.8. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{22}H_{17}N_2O$ 325.1335, Found 325.1302.

(6-(benzo[*b*]thiophen-2-yl)pyridazin-4-yl)(*p*-tolyl)methanone (**6q**):

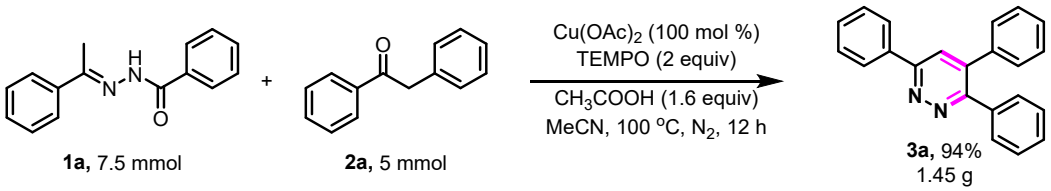


Yellow solid (13.9 mg, 21%). mp: 178-179 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 12/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.14 (s, 1H), 7.99 (s, 1H), 7.93-7.90 (m, 1H), 7.86-7.83 (m, 1H), 7.79-7.77 (d, *J* =

8.0 Hz, 2H), 7.42-7.37 (m, 4H), 2.49 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 192.6, 148.2, 145.7, 141.5, 140.0, 139.8, 135.3, 132.7, 130.3, 129.8, 126.2, 124.9, 124.6, 124.0, 122.8, 121.7, 21.9. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{20}H_{15}N_2OS$ 331.0900, Found 331.0929.

6. Synthetic Applications.

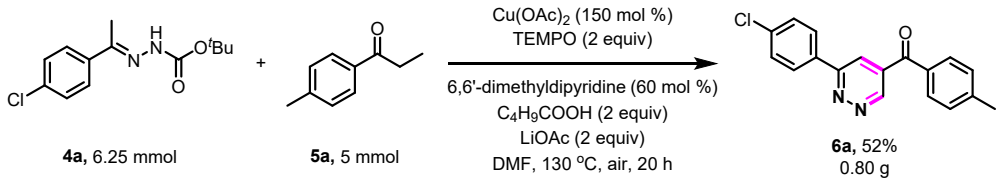
6.1. Gram-scale reaction for the synthesis of triphenyl pyridazine (3a).



In a 100 mL Schlenk reaction tube with a stir bar, benzoylhydrazone (**1a**) (7.5 mmol, 1.79 g), 2-phenylacetophenone (**2a**) (5 mmol, 0.98 g), $Cu(OAc)_2$ (5 mmol, 0.905 g), TEMPO (10 mmol, 1.56 g), HOAc (8 mmol, 1 mL) were dissolved in MeCN (50 mL) under a nitrogen atmosphere. The reaction mixture was then heated at 100 °C (oil bath) with vigorous stirring for 12 hours. After the reaction equilibrium, the mixture was poured into ethyl acetate, and was washed with saturated brine (1 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by a silica gel packed flash chromatography column with petroleum ether/ethyl acetate (15:1) as the eluent to afford the desired product **3a** within a 94% yield.

6.2. Gram-scale reaction for the synthesis of disubstituted pyridazine (6a)

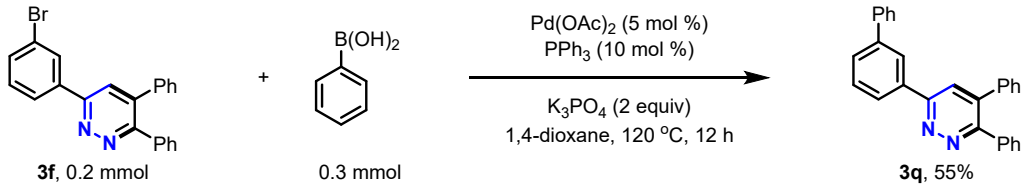
Gram-scale reactions:



In a 100 mL Schlenk reaction tube with a stir bar, acylhydrazone (**4a**) (6.25 mmol, 1.68 g), 4'-methylpropiophenone (**5a**) (5 mmol, 0.67 g), $Cu(OAc)_2$ (7.5 mmol, 1.36 g), 6,6'-dimethyldipyridine (3 mmol, 0.55 g), TEMPO (10 mmol, 1.56g), LiOAc (10 mmol, 0.65 g), $^{n}C_4H_9COOH$ (10 mmol, 1.02 g) were dissolved in DMF (50 mL) under air atmosphere. The reaction mixture was then heated at 130 °C (oil bath) with vigorous stirring for 20 hours. After the reaction equilibrium, the mixture was poured into ethyl

acetate and was washed with saturated brine (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by a silica gel packed flash chromatography column with petroleum ether/ethyl acetate (12:1) as the eluent to afford the desired products **6a** within 52% yield.

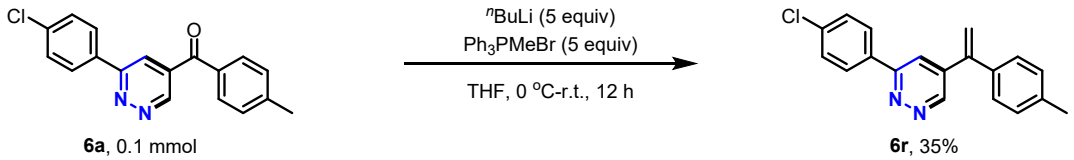
6.3. Cross-coupling of the resulting pyridazines 3f with phenyl boronic acid.[9]



According to the reported reference:[9] in a 10 mL Schlenk reaction tube with a stir bar, the as-prepared pyridazine **3f** (0.2 mmol, 77.2 mg), phenyl boronic acid (36.6 mg, 0.3 mmol), $Pd(OAc)_2$ (2.24 mg, 0.01 mmol), PPh_3 (5.24 mg, 0.02 mmol) and K_3PO_4 (84.9 mg, 0.4 mmol) were dissolved in 1,4-dioxane (2 mL). The reaction mixture was then heated at 120 °C (oil bath) with vigorous stirring for 12 hours under air atmosphere. After the reaction equilibrium, the mixture was poured into ethyl acetate and then brine (2 × 10 mL). After the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The filtrate was concentrated in vacuo and purified by a silica gel packed flash chromatography column with petroleum ether/ethyl acetate (10:1) as the eluent to afford the desired product 6-([1,1'-biphenyl]-3-yl)-3,4-diphenylpyridazine **3q**.

White solid (42.3 mg, 55%). mp: 141.9-143.2 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 10/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.90 (s, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 2H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.39-7.27 (m, 8H), 7.24 (s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.1, 140.7, 137.2, 136.8, 136.7, 130.1, 129.6, 129.2, 129.0, 128.9, 128.8, 128.8, 128.2, 127.4, 127.2, 126.0, 125.0. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{28}H_{21}N_2$ 385.1705, Found 385.1710.

6.4. Wittig reaction of the pyridazine product 6a.[10]



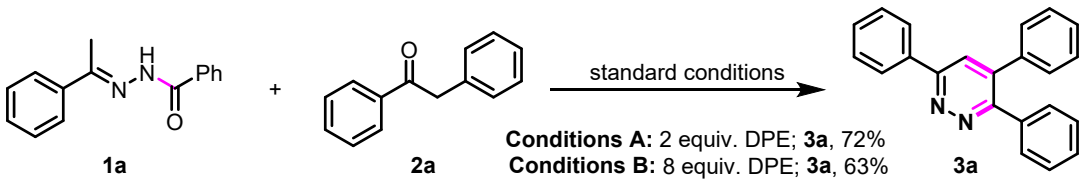
According to the reported reference:[10] under nitrogen atmosphere, a suspension of Ph_3PMeBr (357 mg, 1 mmol, 5.0 equiv) in THF (2.0 mL) was added ^{n}BuLi (2.4 M in hexane, 0.42 mL, 1 mmol, 5.0 equiv) at 0 °C (ice bath), and the mixture was stirred at 0 °C for 30 min to yield a yellow mixture. A solution of the targeted pyridazine **6a** (62.2 mg, 0.20 mmol, 1.0 equiv) in THF (2.0 mL) was added at 0 °C. The reaction mixture was stirred at room temperature for 12 h. The resulting solution was quenched with saturated NH_4Cl solution and extracted with ethyl acetate (3×10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtrated and concentrated in vacuo, and the residue was purified by column chromatography on silica gel (PE/EtOAc = 5:1) to give the corresponding product **6r**.

White solid (21.4 mg, 35%). mp: 149.6-151.0 °C. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 5/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.16 (d, *J* = 2.0 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 2 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.21 (s, 4H), 5.76 (s, 1H), 5.72 (s, 1H), 2.40 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.2, 149.5, 145.0, 140.2, 139.0, 136.5, 135.6, 134.8, 129.6, 129.3, 128.5, 127.9, 122.1, 118.4, 21.3. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{19}H_{16}ClN_2$ 307.0997, Found 307.1003.

7. Mechanistic Investigations.

7.1. Mechanistic studies for the synthesis of 3,4,6-triaryl pyridazines.

7.1.1. Radical-trapping experiments.

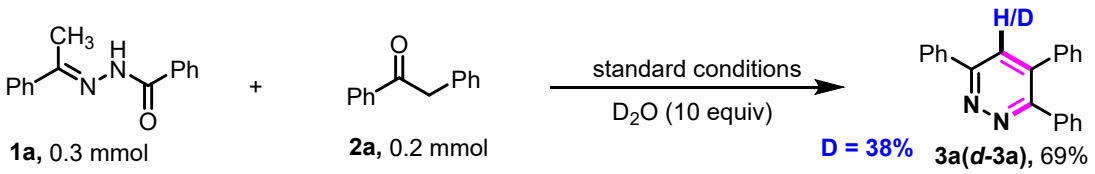


Conditions A: In a 25 mL Schlenk reaction tube with a stir bar, acylhydrazone (**1a**) (0.3 mmol, 71.4 mg), 2-phenylacetophenone (**2a**) (0.2 mmol, 39.2 mg), $Cu(OAc)_2$ (0.2 mmol, 36.2 mg), TEMPO (0.4 mmol, 62.4 mg), HOAc (0.32 mmol), and radical-

scavenger DPE (0.4 mmol, 72.1 mg) were dissolved in MeCN (2 mL) under a nitrogen atmosphere. The reaction mixture was then heated at 100 °C (oil bath) with vigorous stirring for 12 hours. After the reaction equilibrium, the mixture was poured into ethyl acetate and washed with saturated brine (1 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo and purified by a silica gel packed flash chromatography column with petroleum ether/ethyl acetate (15:1) as the eluent to afford the desired products **3a** in a 72% yield.

Conditions B: In a 25 mL Schlenk reaction tube with a stir bar, acylhydrazone (**1a**) (0.3 mmol, 71.4 mg), 2-phenylacetophenone (**2a**) (0.2 mmol, 39.2 mg), $Cu(OAc)_2$ (0.2 mmol, 36.2 mg), TEMPO (0.4 mmol, 62.4 mg), HOAc (0.32 mmol), and radical-scavenger DPE (1.6 mmol, 288.4 mg) were dissolved in MeCN (2 mL) under a nitrogen atmosphere. The reaction mixture was then heated at 100 °C (oil bath) with vigorous stirring for 12 hours. After the reaction equilibrium, the mixture was poured into ethyl acetate and washed with saturated brine (1 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo and purified by a silica gel packed flash chromatography column with petroleum ether/ethyl acetate (15:1) as the eluent to afford the desired products **3a** in a 63% yield. These results revealed that radical process might not be involved in this cascade annulation.

7.1.2. Deuterium-labeling experiments.



In a 25 mL Schlenk reaction tube with a stir bar, acylhydrazone (**1a**) (0.3 mmol, 71.4 mg), 2-phenylacetophenone (**2a**) (0.2 mmol, 39.2 mg), $Cu(OAc)_2$ (0.2 mmol, 36.2 mg), TEMPO (0.4 mmol, 62.4 mg), HOAc (0.32 mmol) and D_2O (2 mmol, 40 mg) were dissolved in MeCN (2 mL) under a nitrogen atmosphere. The reaction mixture was then heated at 100 °C (oil bath) with vigorous stirring for 12 hours. After the reaction equilibrium, the mixture was poured into ethyl acetate and washed with saturated brine (1 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The

filtrate was concentrated in vacuo and purified by a silica gel packed flash chromatography column with petroleum ether/ethyl acetate (15:1) as the eluent to afford the desired pyridazine product **3a(*d*-3a)** in a 69% yield. It was found that a 38% deuteration was detected on the C-H bond of pyridazine aromatic ring, revealing that the C(sp^3)-H bond cleavage of acylhydrazone was reversible.

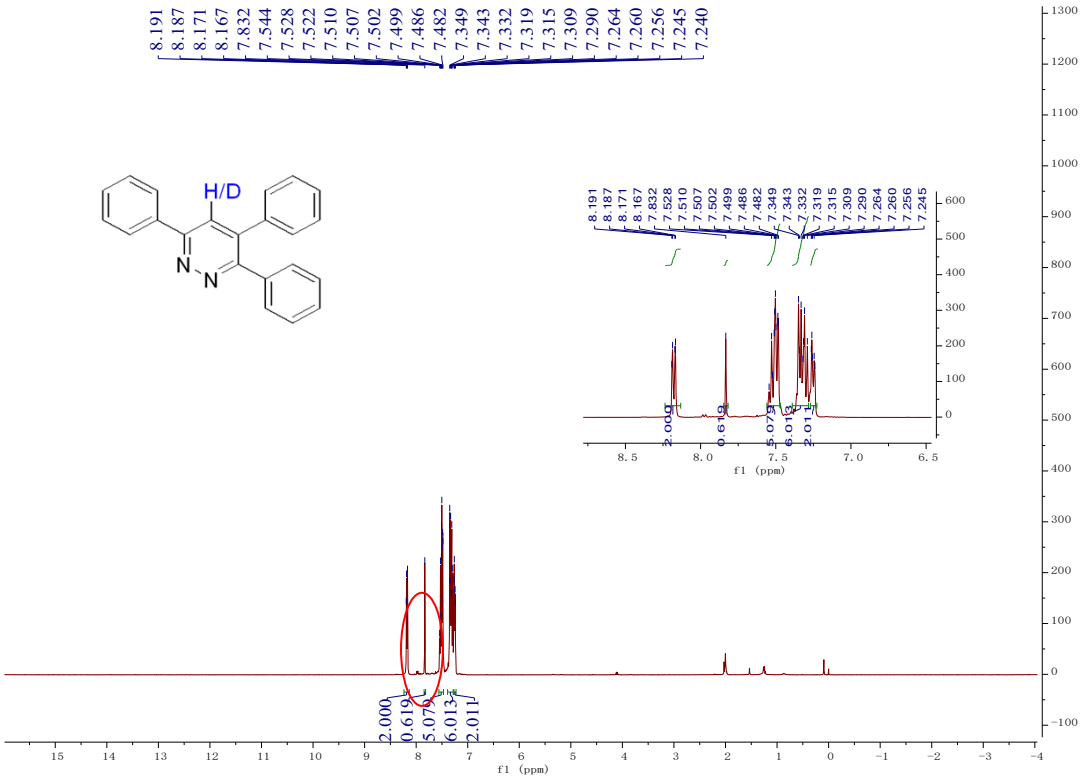
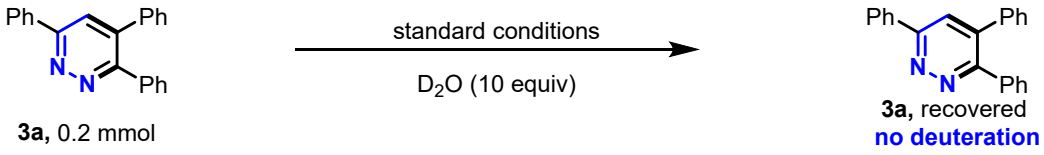


Figure S1. The ^{1}H NMR spectrum of pyridazine product **3a(*d*-3a)** from the model reaction in the presence of D_2O



3a, 0.2 mmol

3a, recovered

no deuteration

In a 25 mL Schlenk reaction tube with a stir bar, pyridazine product (**3a**) (0.2 mmol, 71.4 mg), $Cu(OAc)_2$ (0.2 mmol, 36.2 mg), TEMPO (0.4 mmol, 62.4 mg), HOAc (0.32 mmol) and D_2O (2 mmol, 40 mg) were dissolved in MeCN (2 mL) under a nitrogen atmosphere. The reaction mixture was then heated at 100 °C (oil bath) with vigorous stirring for 12 hours. After the reaction equilibrium, the mixture was poured into ethyl acetate and washed with saturated brine (1 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo and purified by a silica gel packed flash chromatography column with petroleum ether/ethyl acetate

(15:1) as the eluent to afford the pyridazine product **3a**. It was found that no deuteration was detected on the C(sp^2)-H bond of pyridazine aromatic ring.

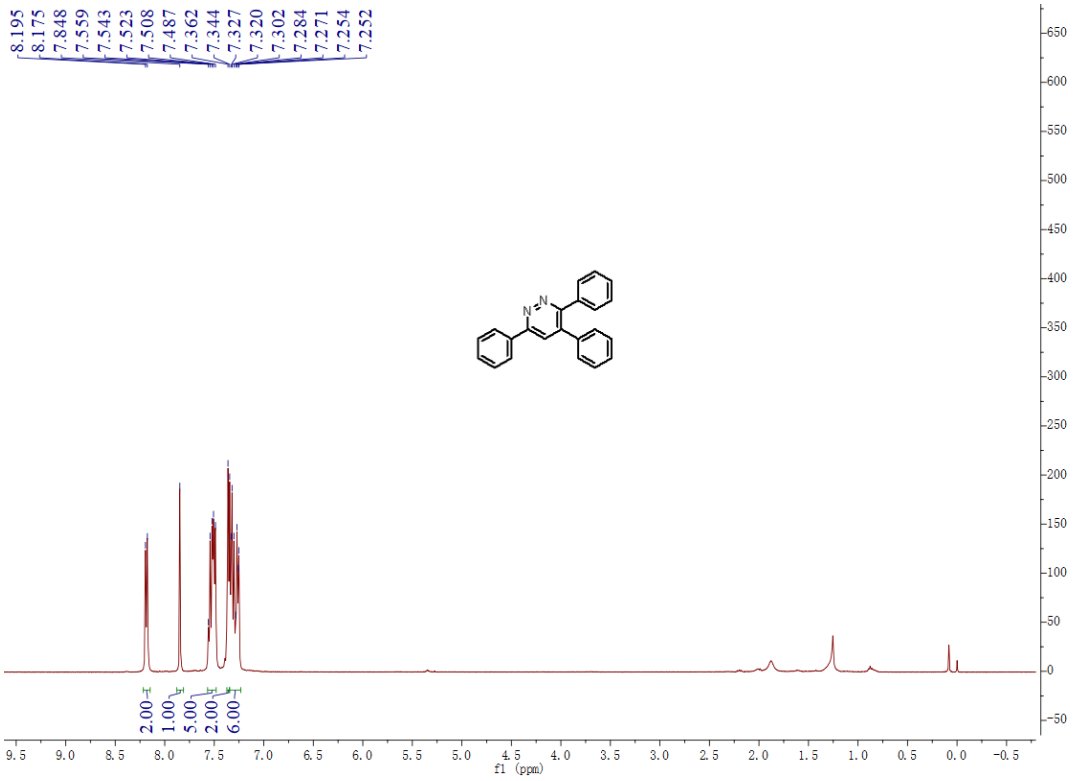
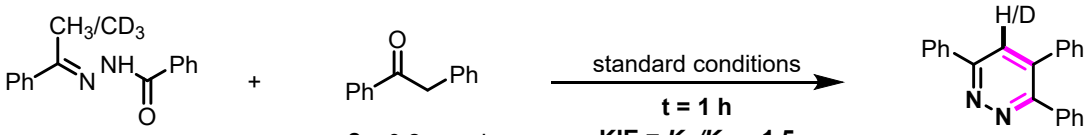


Figure S2: ^{1}H NMR spectrum of product **3a** with the treatment of D_2O under standard conditions



1a, 0.15 mmol
***d*$_3$-1a**, 0.15 mmol

2a, 0.2 mmol

3a(*d*-3a), 15%
D = 40%

In a 25 mL Schlenk reaction tube with a stir bar, acylhydrazone (**1a**) (0.15 mmol, 35.7 mg), deuterated acylhydrazone (***d*$_3$-1a**)[11] (0.15 mmol, 36.2 mg), 2-phenylacetophenone (**2a**) (0.2 mmol, 39.2 mg), $Cu(OAc)_2$ (0.2 mmol, 36.2 mg), TEMPO (0.4 mmol, 62.4 mg), HOAc (0.32 mmol) were dissolved in MeCN (2 mL) under a nitrogen atmosphere. The reaction mixture was then heated at 100 °C (oil bath) with vigorous stirring for 1 hour. After the reaction equilibrium, the mixture was poured into ethyl acetate and washed with saturated brine (1 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo and purified by a silica gel packed flash chromatography column with petroleum ether/ethyl acetate (15:1) as the eluent to afford the desired pyridazine product **3a(*d*-3a)** in a 15% yield. It was found that the value of competitive kinetic isotope effect of acylhydrazone equals 1.5,

suggesting the cleavage of C(sp^3)-H bond on the acylhydrazone might not be the rate-determining step for the synthesis of 3,4,6-trisubstituted pyridazine.

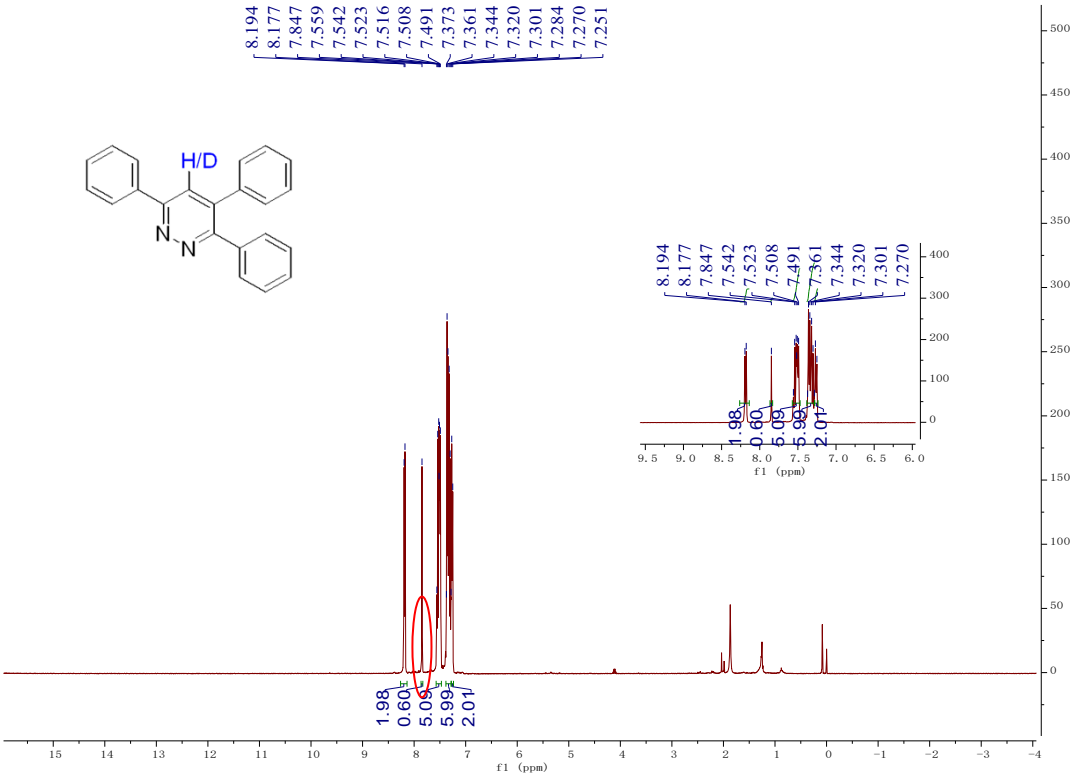
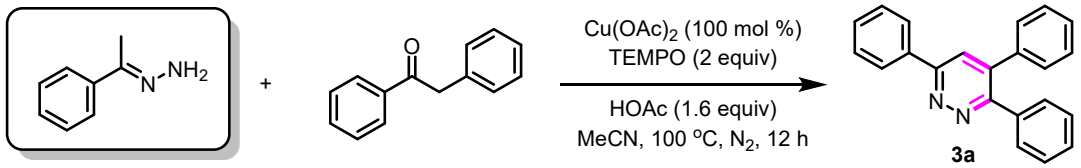


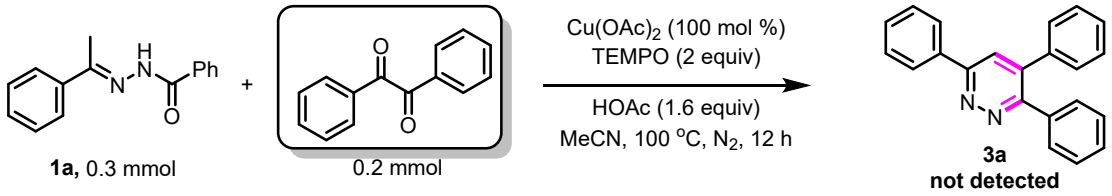
Figure S3. The ^{1}H NMR spectrum of pyridazine **3a**(***d*-3a**) from the competitive kinetic isotope effect experiment

7.1.3. Control experiments.

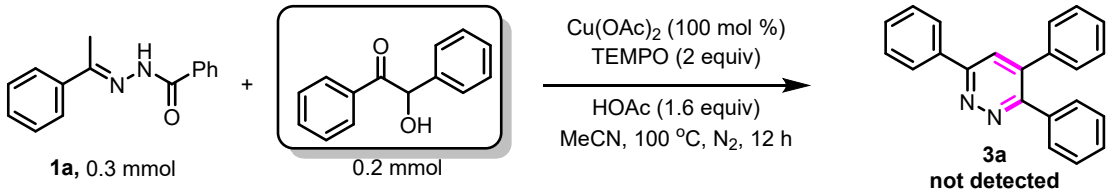


1i, 0.3 mmol **2a,** 0.2 mmol **3a not detected**

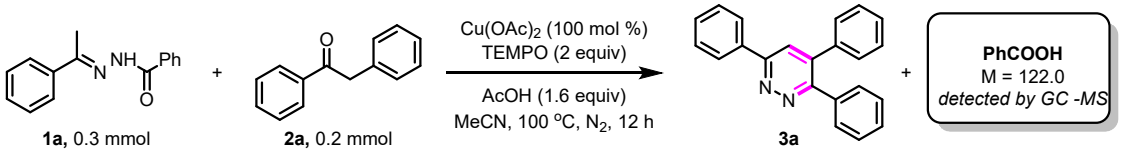
In a 25 mL Schlenk reaction tube with a stir bar, (*E*)-(1-phenylethylidene)hydrazine (**1i**) (0.3 mmol, 40.2 mg), 2-phenylacetophenone (**2a**) (0.2 mmol, 39.2 mg), $Cu(OAc)_2$ (0.2 mmol, 36.2 mg), TEMPO (0.4 mmol, 62.4 mg), HOAc (0.32 mmol, 1.6 equiv) were dissolved in MeCN (2 mL) under a nitrogen atmosphere. The reaction mixture was then heated at 100 °C (oil bath) with vigorous stirring for 12 hours. After the reaction completion, the mixture was monitored by TLC, and it was found that no desired pyridazine product **3a** was formed during the reaction course, revealing that (*E*)-(1-phenylethylidene)hydrazine was not the possible intermediate and benzoyl substituent was crucial for this [4+2] annulation reaction.



In a 25 mL Schlenk reaction tube with a stir bar, acylhydrazone (**1a**) (0.3 mmol, 71.4 mg), benzil (0.2 mmol, 39.2 mg), $Cu(OAc)_2$ (0.2 mmol, 36.2 mg), TEMPO (0.4 mmol, 62.4 mg), HOAc (0.32 mmol) were dissolved in MeCN (2 mL) under a nitrogen atmosphere. The reaction mixture was then heated at 100 °C (oil bath) with vigorous stirring for 12 hours. After the reaction completion, the mixture was monitored by TLC, and it was found that no desired pyridazine product **3a** was detected. These results indicated that benzil was not the key intermediate for the synthesis of pyridazine.



In a 25 mL Schlenk reaction tube with a stir bar, acylhydrazone (**1a**) (0.3 mmol, 71.4 mg), benzoin (0.2 mmol, 42.4 mg), $Cu(OAc)_2$ (0.2 mmol, 36.2 mg), TEMPO (0.4 mmol, 62.4 mg), HOAc (0.32 mmol) were dissolved in MeCN (2 mL) under a nitrogen atmosphere. The reaction mixture was then heated at 100 °C (oil bath) with vigorous stirring for 12 hours. After the reaction completion, the mixture was monitored by TLC, and it was found that no desired pyridazine product **3a** was detected. These results indicated that benzoin was not the key intermediate for the synthesis of pyridazine.



In a 25 mL Schlenk reaction tube with a stir bar, acylhydrazone (**1a**) (0.3 mmol, 71.4 mg), 2-phenylacetophenone (**2a**) (0.2 mmol, 39.2 mg), $Cu(OAc)_2$ (0.2 mmol, 36.2 mg), TEMPO (0.4 mmol, 62.4 mg), HOAc (0.32 mmol, 1.6 equiv) were dissolved in MeCN (2 mL) under a nitrogen atmosphere. The reaction mixture was then heated at 100 °C (oil bath) with vigorous stirring for 12 hours. After the reaction completion, the mixture was detected by GC-MS, and it was found that benzoic acid was formed during the

reaction course.

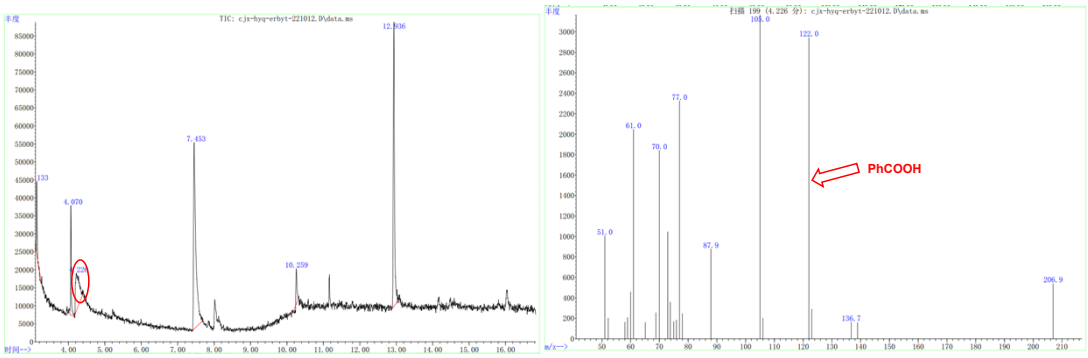
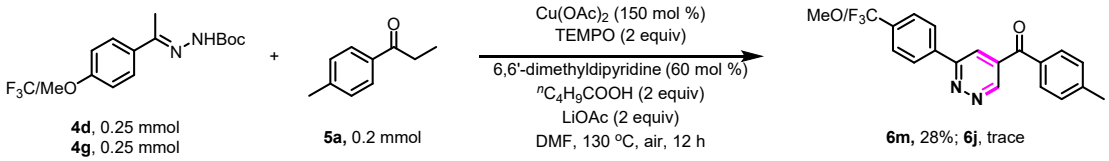


Figure S4. The detection of benzoic acid by GC-MS from the crude model reaction mixture

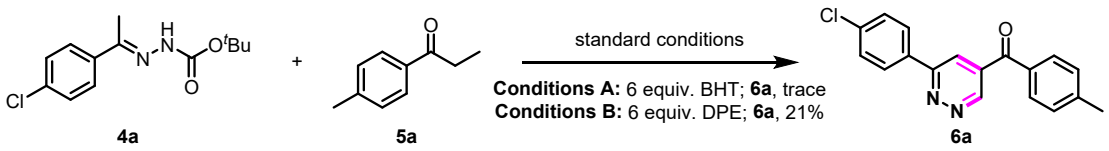
7.2. Mechanistic studies for the synthesis of 3,5-disubstituted pyridazines.

7.2.1. Competitive experiment.



In a 25 mL Schlenk reaction tube with a stir bar, acylhyrazones (**4d**) (0.25 mmol, 66.0 mg) and (**4g**) (0.25 mmol, 75.5 mg), 4'-methylpropiophenone (**5a**) (0.2 mmol, 26.8 mg), $Cu(OAc)_2$ (0.3 mmol, 54.3 mg), 6,6'-dimethylpyridine (0.12 mmol, 22.0 mg), TEMPO (0.4 mmol, 62.4 mg), LiOAc (0.4 mmol, 25.6 mg), $^nC_4H_9COOH$ (0.4 mmol, 40.8 mg) were dissolved in DMF (2 mL) under air atmosphere. The reaction mixture was then heated at 130 °C (oil bath) with vigorous stirring for 12 hours. After the reaction equilibrium, the mixture was poured into ethyl acetate and was washed with saturated brine (3 × 10 mL). After the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by a silica gel packed flash chromatography column with petroleum ether/ethyl acetate (12:1) as the eluent to afford the desired pyridazine products. The results revealed that pyridazine **6m** was isolated in a 28% yield, in contrast, only a trace amount of pyridazine **6j** was detected, which underlined that electron-deficient acylhydrazone facilitated this tandem annulation reaction better.

7.2.2. Radical-trapping experiment.

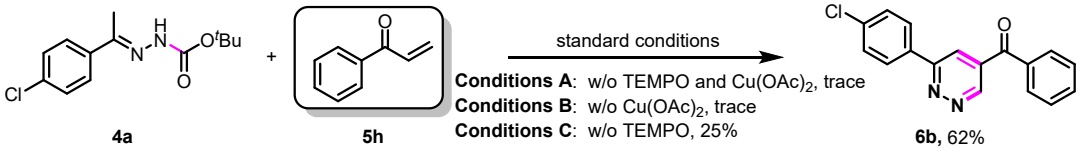


4a 5a 6a

Conditions A: In a 25 mL Schlenk reaction tube with a stir bar, acylhydrazone (**4a**) (0.25 mmol, 67.0 mg), 4'-methylpropiophenone (**5a**) (0.2 mmol, 26.8 mg), $Cu(OAc)_2$ (0.3 mmol, 54.3 mg), TEMPO (0.4 mmol, 62.4 mg), 6,6-dimethylpyridine (0.12 mmol, 22.1 mg), LiOAc (0.4 mmol, 25.6 mg), $^{n}C_4H_9COOH$ (0.4 mmol, 40.8 mg), and radical-scavenger BHT (1.2 mmol, 264.3 mg) were dissolved in DMF (2 mL) under air atmosphere. The reaction mixture was then heated at 130 °C (oil bath) with vigorous stirring for 12 hours. After the reaction completion, the mixture was detected by TLC, and it was found that the desired pyridazine product **6a** was not detected, revealing that this transformation might involve radical process.

Conditions B: In a 25 mL Schlenk reaction tube with a stir bar, acylhydrazone (**4a**) (0.25 mmol, 67.0 mg), 4'-methylpropiophenone (**5a**) (0.2 mmol, 26.8 mg), $Cu(OAc)_2$ (0.3 mmol, 54.3 mg), TEMPO (0.4 mmol, 62.4 mg), 6,6-dimethylpyridine (0.12 mmol, 22.1 mg), LiOAc (0.4 mmol, 25.6 mg), $^{n}C_4H_9COOH$ (0.4 mmol, 40.8 mg) and radical-scavenger DPE (1.2 mmol, 216.3 mg) were dissolved in DMF (2 mL) under air atmosphere. The reaction mixture was then heated at 130 °C (oil bath) with vigorous stirring for 12 hours. After the reaction completion, the mixture was poured into ethyl acetate and washed with saturated brine (1 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo and purified by a silica gel packed flash chromatography column with petroleum ether/ethyl acetate (12:1) as the eluent to afford the desired 3,5-disubstituted pyridazine product **6a**. The results indicated that the yield of targeted products **6a** was drastically decreased to 21%, revealing that radical process might be involved in this cascade annulation.

7.2.3. Control experiments.



4a 5h 6b, 62%

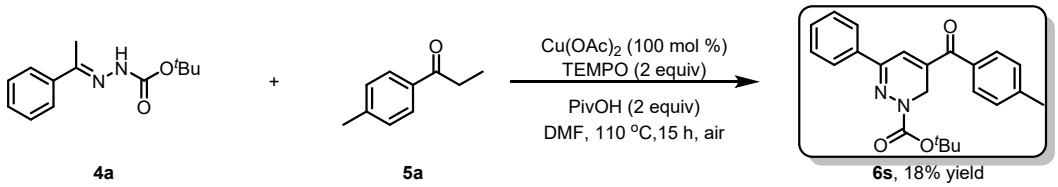
Conditions A: In a 25 mL Schlenk reaction tube with a stir bar, acyldrazone (**4a**) (0.25

mmol, 67.0 mg), 1-phenyl-2-propen-1-one (**5h**) (0.2 mmol, 26.4 mg), 6,6-dimethylpyridine (0.12 mmol, 22.1 mg), LiOAc (0.4 mmol, 25.6 mg) and $^{n}C_4H_9COOH$ (0.4 mmol, 40.8 mg) were dissolved in DMF (2 mL) under air atmosphere. The reaction mixture was then heated at 130 °C (oil bath) with vigorous stirring for 12 hours. After the reaction completion, the mixture was monitored by TLC, and it was found that only trace of desired product **6b** was detected.

Conditions B: In a 25 mL Schlenk reaction tube with a stir bar, acyldrazone (**4a**) (0.25 mmol, 67.0 mg), 1-phenyl-2-propen-1-one (**5h**) (0.2 mmol, 26.4 mg), TEMPO (0.4 mmol, 62.4 mg), 6,6-dimethylpyridine (0.12 mmol, 22.1 mg), LiOAc (0.4 mmol, 25.6 mg) and $^{n}C_4H_9COOH$ (0.4 mmol, 40.8 mg) were dissolved in DMF (2 mL) under air atmosphere. The reaction mixture was then heated at 130 °C (oil bath) with vigorous stirring for 12 hours. After the reaction completion, the mixture was monitored by TLC, and it was found that only trace of the desired product **6b** was detected.

Conditions C: In a 25 mL Schlenk reaction tube with a stir bar, acyldrazone (**4a**) (0.25 mmol, 67.0 mg), 1-phenyl-2-propen-1-one (**5h**) (0.2 mmol, 26.4 mg), $Cu(OAc)_2$ (0.3 mmol, 54.3 mg), 6,6-dimethylpyridine (0.12 mmol, 22.1 mg), LiOAc (0.4 mmol, 25.6 mg) and $^{n}C_4H_9COOH$(0.4 mmol, 40.8 mg) were dissolved in DMF (2 mL) under air atmosphere. The reaction mixture was then heated at 130 °C (oil bath) with vigorous stirring for 12 hours. After the reaction completion, the mixture was poured into ethyl acetate and was washed with saturated brine (3 × 10 mL). After the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo and purified by a silica gel packed flash chromatography column with petroleum ether/ethyl acetate (12:1) as the eluent to afford the desired pyridazine product **6b** within a 25% yield.

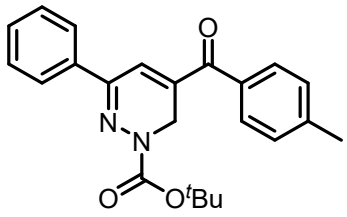
The aforementioned results indicated that 1-phenyl-2-propen-1-one (**5h**) was the indeed intermediate formed from propiophenone, and the subsequent annulation of 1-phenyl-2-propen-1-one with acylhydrazone was promoted by $Cu(OAc)_2$ and TEMPO.



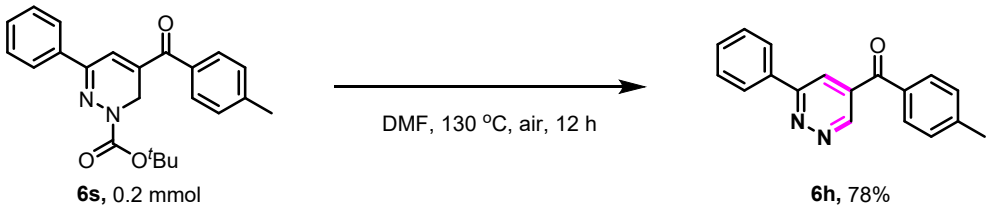
4a **5a** **6s**, 18% yield

In a 25 mL Schlenk reaction tube with a stir bar, acylhydrazone (**4a**) (0.25 mmol), 1-(*p*-tolyl)propan-1-one (**5a**) (0.2 mmol), $Cu(OAc)_2$ (0.2 mmol, 36.2 mg), Tempo (0.4 mmol, 62.4 mg), PivOH (0.4 mmol, 40.8 mg) were dissolved in DMF (2 mL) under air atmosphere. The reaction mixture was then heated at 110 °C (oil bath) with vigorous stirring for 15 hours. After the reaction equilibrium, the mixture was poured into ethyl acetate, which was washed with saturated brine (3 × 10 mL). After the reaction equilibrium, the mixture was poured into ethyl acetate and washed with saturated brine (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by a silica gel packed flash chromatography column with petroleum ether/ethyl acetate (12:1) as the eluent to afford the desired 1,6-dihydropyridazine motif (**6s**) in a 18% yield.

***tert*-butyl 5-(4-methylbenzoyl)-3-phenylpyridazine-1(6*H*)-carboxylate (6s):**



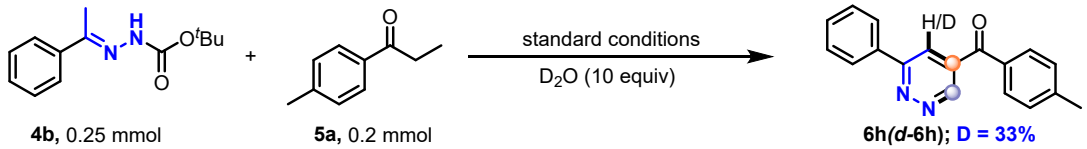
Yellow liquid. Column chromatography on silica gel (Eluent: petroleum ether/ethyl acetate, 12/1). **^{1}H NMR** (500 MHz, $CDCl_3$) 7.74-7.73 (m, 2H), 7.68 (d, J = 7.0 Hz, 2H), 7.37-7.36 (m, 3H), 7.30 (d, J = 7.5 Hz, 2H), 6.94 (s, 1H), 4.66 (s, 2H), 2.43 (s, 3H), 1.60 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 193.6, 135.0, 134.9, 133.9, 130.0, 129.4, 129.3, 128.9, 128.1, 126.2, 126.0, 125.0, 82.7, 40.9, 38.5, 21.7. **HRMS (ESI-TOF)** m/z: $[M + H]^+$ Calcd for $C_{23}H_{25}N_2O_3$ 377.1860, Found 377.1871.



6s, 0.2 mmol **6h,** 78%

In a 25 mL Schlenk reaction tube with a stir bar, 1,6-dihydropyridazine (**6s**) (0.2 mmol, 75.2 mg) were dissolved in DMF (2 mL) under air atmosphere. The reaction mixture was then heated at 130 °C (oil bath) with vigorous stirring for 12 hours. After the reaction equilibrium, the mixture was poured into ethyl acetate and was washed with saturated brine (3 × 10 mL). After the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo and purified by a silica gel packed flash chromatography column with petroleum ether/ethyl acetate (12:1) as the eluent to afford the desired pyridazine product **6h** smoothly within a 78% yield. These results streamlined that 1,6-dihydropyridazine was the key intermediate of this reaction, and it could be transformed into the targeted pyridazine **6h** just in DMF solution without any $Cu(OAc)_2$ and TEMPO.

7.2.4. Deuterium labeling experiments.



4b, 0.25 mmol + **5a,** 0.2 mmol → **6h(*d*-6h); D = 33%**

In a 25 mL Schlenk reaction tube with a stir bar, acylhydrazone (**4b**) (0.25 mmol, 58.5 mg), 4'-methylpropiophenone (**5a**) (0.2 mmol, 26.8 mg), $Cu(OAc)_2$ (0.3 mmol, 54.3 mg), TEMPO (0.4 mmol, 62.4 mg), 6,6-dimethyl-2,2'-dipyridine (0.12 mmol, 22.1 mg), LiOAc (0.4 mmol, 25.6 mg), $^nC_4H_9COOH$ (0.4 mmol, 40.8 mg) and D_2O (2 mmol, 40 mg) were dissolved in DMF (2 mL) under air atmosphere. The reaction mixture was then heated at 130 °C (oil bath) with vigorous stirring for 12 hours. After the reaction completion, the mixture was poured into ethyl acetate and washed with saturated brine (1 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo and purified by a silica gel packed flash chromatography column with petroleum ether/ethyl acetate (12:1) as the eluent to afford the desired 3,5-disubstituted pyridazine product **6h**(***d*-6h**). It was found that a 33% deuteration was detected on the C-H bond of pyridazine skeleton, revealing that the C-H bond cleavage of the methyl group on the acylhydrazone might be the reversible process.

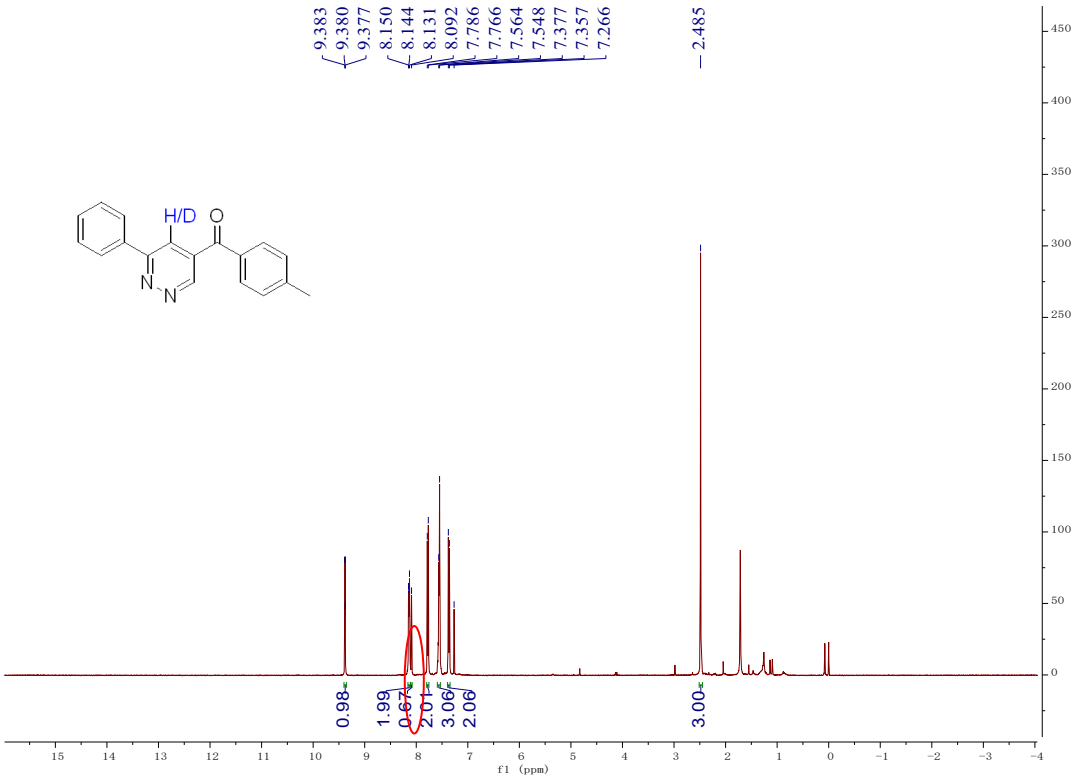
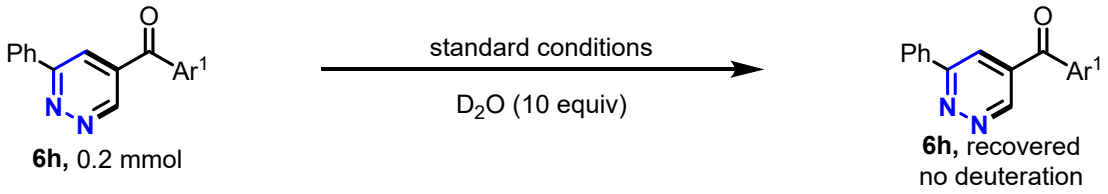


Figure S5. The ^{1}H NMR spectrum of 3,5-disubstituted pyridazine **6h**(***d*-6h**) from the model reaction treated by D_2O



In a 25 mL Schlenk reaction tube with a stir bar, pyridazine product (**6h**) (0.2 mmol, 26.8 mg), $Cu(OAc)_2$ (0.3 mmol, 54.3 mg), TEMPO (0.4 mmol, 62.4 mg), 6,6-dimethyl-2,2'-dipyridine (0.12 mmol, 22.1 mg), LiOAc (0.4 mmol, 25.6 mg), $^{n}C_4H_9COOH$ (0.4 mmol, 40.8 mg) and D_2O (2 mmol, 40 mg) were dissolved in DMF (2 mL) under air atmosphere. The reaction mixture was then heated at 130 °C (oil bath) with vigorous stirring for 12 hours. After the reaction completion, the mixture was poured into ethyl acetate and washed with saturated brine (1 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo and purified by a silica gel packed flash chromatography column with petroleum ether/ethyl acetate (12:1) as the eluent to afford the desired 3,5-disubstituted pyridazine product **6h**. It was found that no deuteration was detected on the C-H bond of pyridazine skeleton.

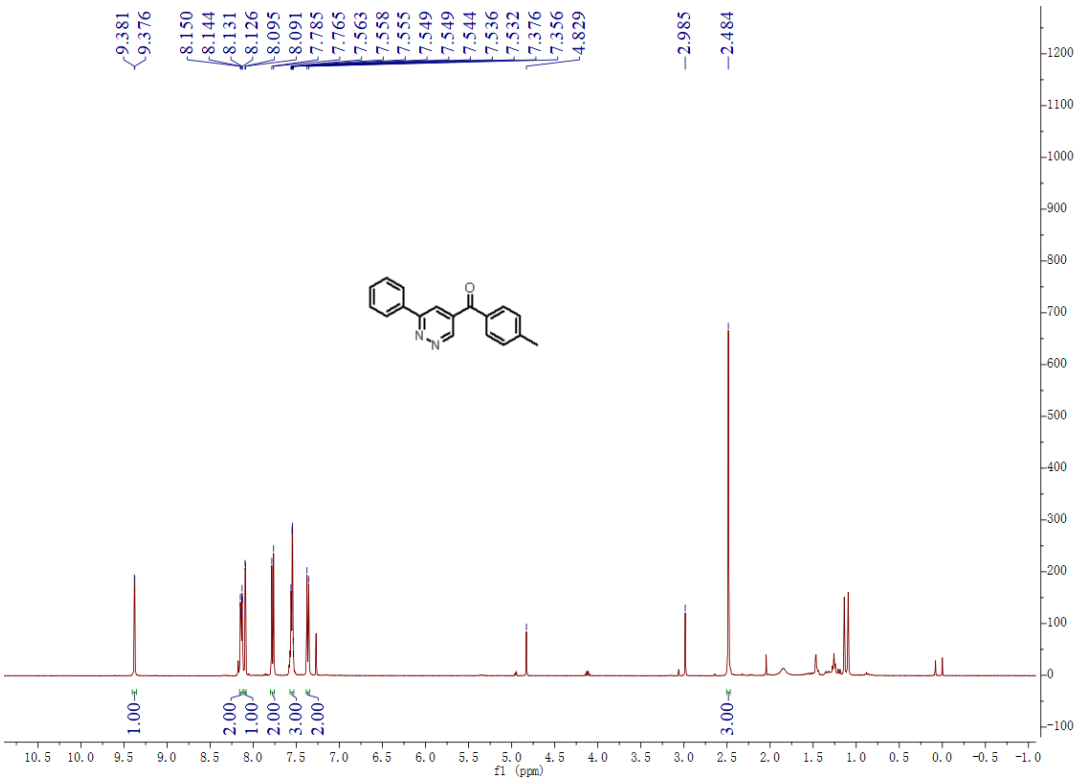
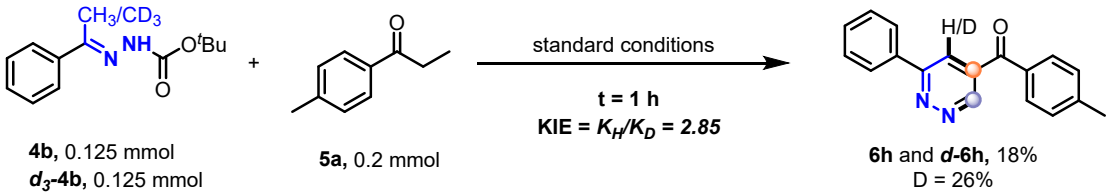


Figure S6: ^{1}H NMR spectrum of product 6h with the treatment of D_2O under standard conditions



In a 25 mL Schlenk reaction tube with a stir bar, acylhydrazone (**4b**) (0.125 mmol, 29.25 mg), deuterated acylhydrazone (***d*$_3$-4b**)[11] (0.125 mmol, 29.63 mg), 4'-methylpropiophenone (**5a**) (0.2 mmol, 26.8 mg), $Cu(OAc)_2$ (0.3 mmol, 54.3 mg), TEMPO (0.4 mmol, 62.4 mg), 6,6-dimethyl-2,2'-dipyridine (0.12 mmol, 22.1 mg), LiOAc (0.4 mmol, 25.6 mg), and $^{n}C_4H_9COOH$ (0.4 mmol, 40.8 mg) were dissolved in DMF (2 mL) under air atmosphere. The reaction mixture was then heated at 130 °C (oil bath) with vigorous stirring for 1 hour. After the reaction completion, the mixture was poured into ethyl acetate and washed with saturated brine (1 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo and purified by a silica gel packed flash chromatography column with petroleum ether/ethyl acetate (12:1) as the eluent to afford the desired 3,5-disubstituted pyridazine product **6h** and ***d*-6h**. It was found that the value of competitive kinetic isotope effect

equals **2.85**, which suggesting the aliphatic C-H bond cleavage of methyl on the acylhydrazone might be the rate-determining step for the synthesis of 3,5-disubstituted pyridazine.

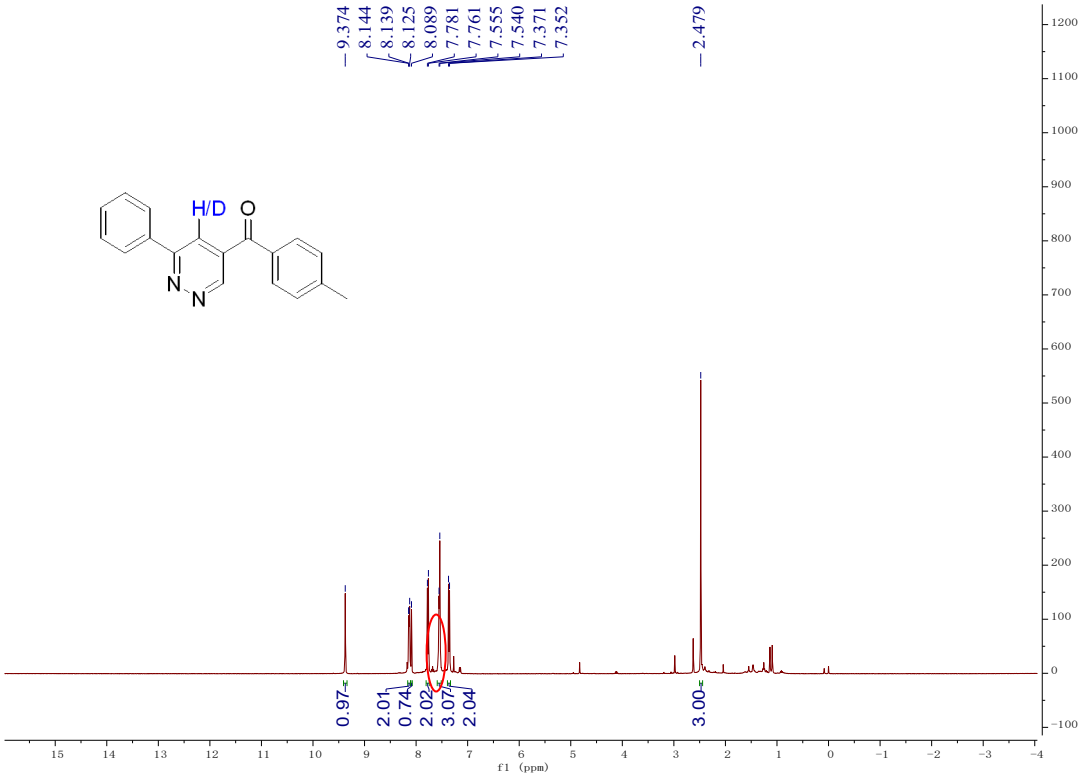
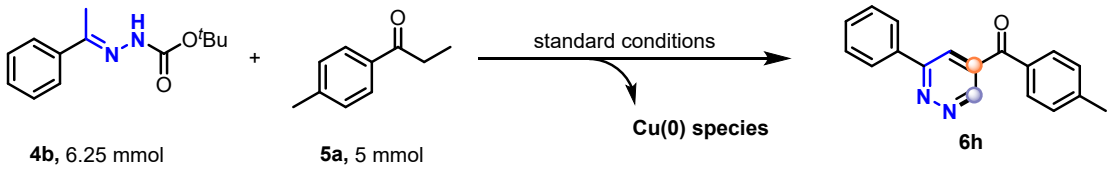


Figure S7. The ^{1}H NMR spectrum of **6h(*d*-6h)** from the competitive kinetic isotope experiment

7.2.5. XRD Detection of Cu(0) species from the crude model reaction to 3,5-disubstituted pyridazine.



In a 100 mL round-bottom flask with a stir bar, acylhydrazone (**4b**) (6.25 mmol, 1.462 g), 4'-methylpropiophenone (**5a**) (5 mmol, 670 mg), $Cu(OAc)_2$ (7.5 mmol, 1.357 g), TEMPO (10 mmol, 1.56 g), 6,6-dimethyl-2,2'-dipyridine (3 mmol, 552.5 mg), LiOAc (10 mmol, 640 mg), and $^{n}C_4H_9COOH$ (10 mmol, 1020 mg) were dissolved in DMF (50 mL) under air atmosphere. The reaction mixture was then heated at 130 °C (oil bath) with vigorous stirring for 12 hours. After the reaction completion, the mixture was filtered directly, and residue was detected by XRD. It was found that Cu(0) species was

generated during the reaction course.

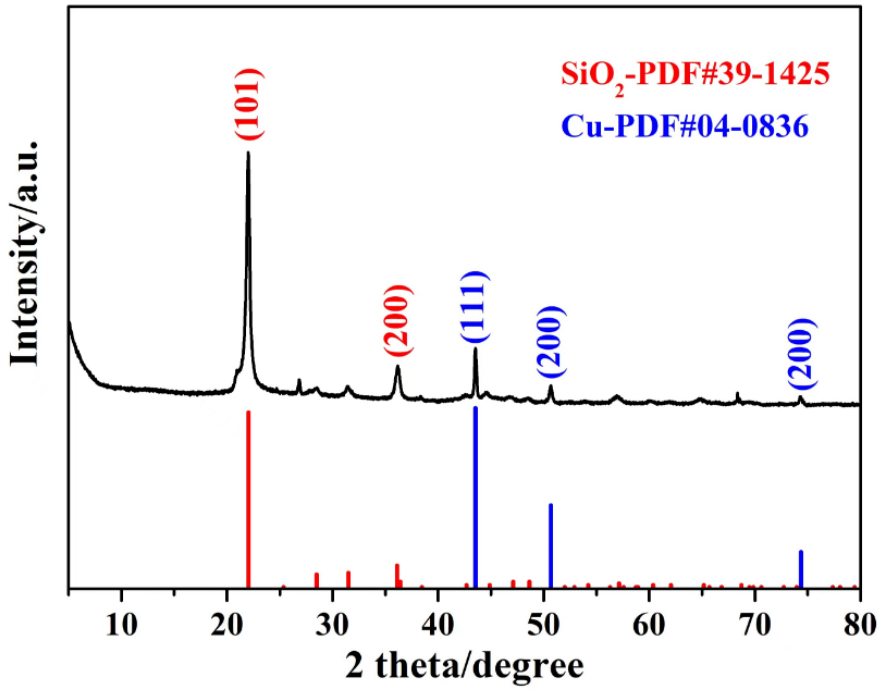
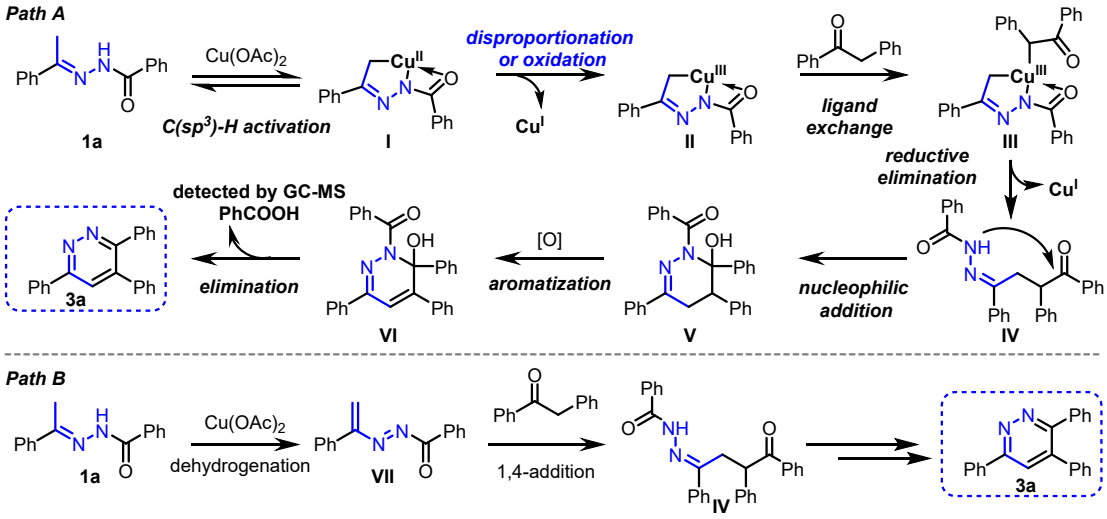


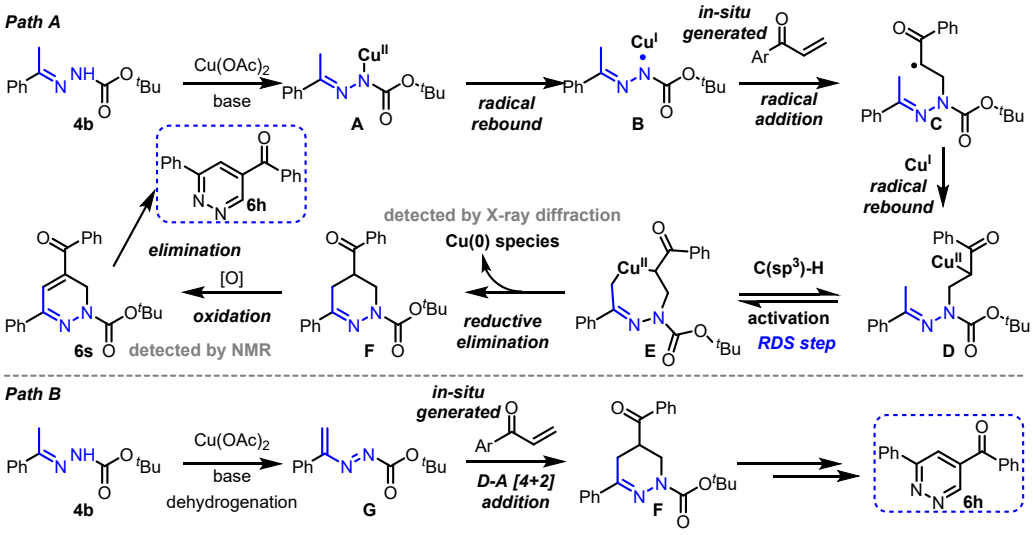
Figure S8. PXRD pattern of the scaled-up model reaction mixture for the synthesis of 3,5-disubstituted pyridazine

7.3. Probable mechanisms for the synthesis of polysubstituted pyridazines.

7.3.1 The possible pathways for the synthesis of 3,4,6-trisubstituted pyridazines.



7.3.2 The possible pathways for the synthesis of 3,5-disubstituted pyridazines.



8. References.

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[11] S. Kopf, F. Ye, H. Neumann and M. Beller, *Chem. Eur. J.,* 2021, **27**, 9768−9773.

9. X-Ray Crystallographic Data for Product 3n.

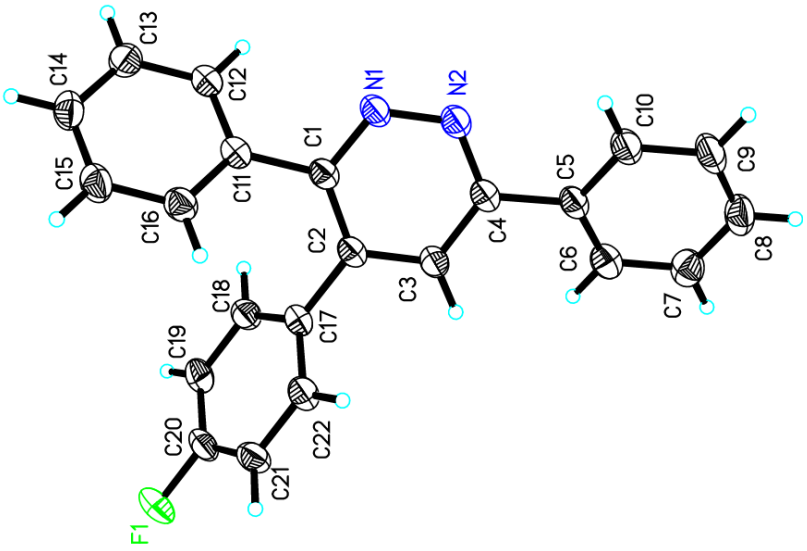

Figure S9. X-ray crystal structure of product **3n** with 30% ellipsoid probability

X-ray structure determination. Single crystals suitable for X-ray diffraction were obtained by slow evaporation of the solvent from a deuterated chloroform solution of product **3n** (**CCDC 2227388**) within several days under aerobic conditions. Crystal data collection and refinement parameters of **3n** are summarized below. X-ray diffraction data for **3n** was collected on a SMART APEX CCD diffractometer (graphite-monochromated MoKα radiation, ϕ-ω scan technique, λ = 0.71073 Å). The intensity data were integrated by means of the SAINT program. SADABS was used to perform area-detector scaling and absorption corrections. The structure was solved by direct methods and was refined against F 2 using all reflections with the aid of the SHELXTL package. All non-hydrogen atoms were found from the difference Fourier syntheses and refined anisotropically. The H atoms were included in calculated positions with isotropic thermal parameters related to those of the supporting carbon

atoms but were not included in the refinement. All calculations were performed using the Bruker Smart program.

Crystal data and structure refinement for product **3n**.

Identification code	product **3n**	
Empirical formula	C_{22} H_{15} F N_2	
Formula weight	326.36	
Temperature	213(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 8.757(4) Å	a= 103.314(11)°.
	b = 9.973(4) Å	b= 100.861(12)°.
	c = 11.506(4) Å	g = 113.664(11)°.
Volume	850.1(6) $Å^3$	
Z	2	
Density (calculated)	1.275 Mg/m^3	
Absorption coefficient	0.083 mm^{-1}	
F(000)	340	
Crystal size	0.200 x 0.150 x 0.120 mm^3	
Theta range for data collection	2.371 to 25.496°.	
Index ranges	-10<=h<=10, -12<=k<=12, -13<=l<=13	
Reflections collected	11393	
Independent reflections	3083 [R(int) = 0.0694]	
Completeness to theta = 25.242°	97.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7456 and 0.5125	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3083 / 0 / 227	
Goodness-of-fit on F^2	1.055	
Final R indices [I>2sigma(I)]	R1 = 0.0673, wR2 = 0.1716	
R indices (all data)	R1 = 0.0952, wR2 = 0.1990	
Extinction coefficient	0.062(12)	
Largest diff. peak and hole	0.282 and -0.247 $e.Å^{-3}$	

10. NMR Spectra for All Products.

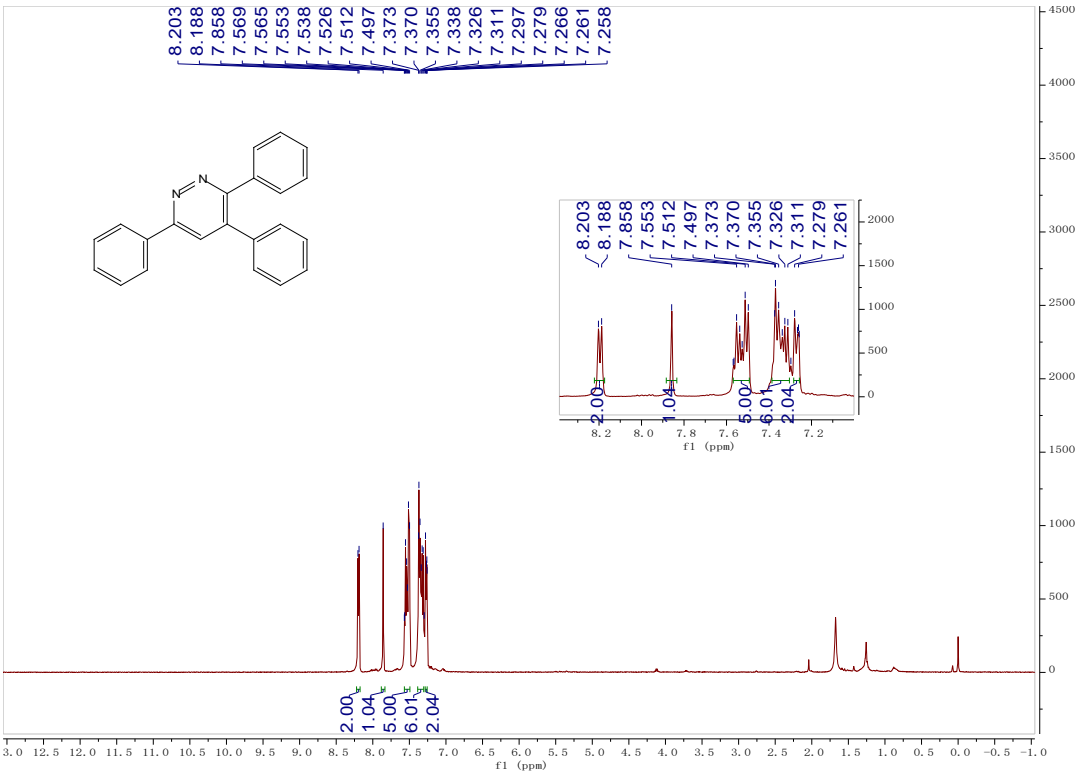

Figure S10. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3a**

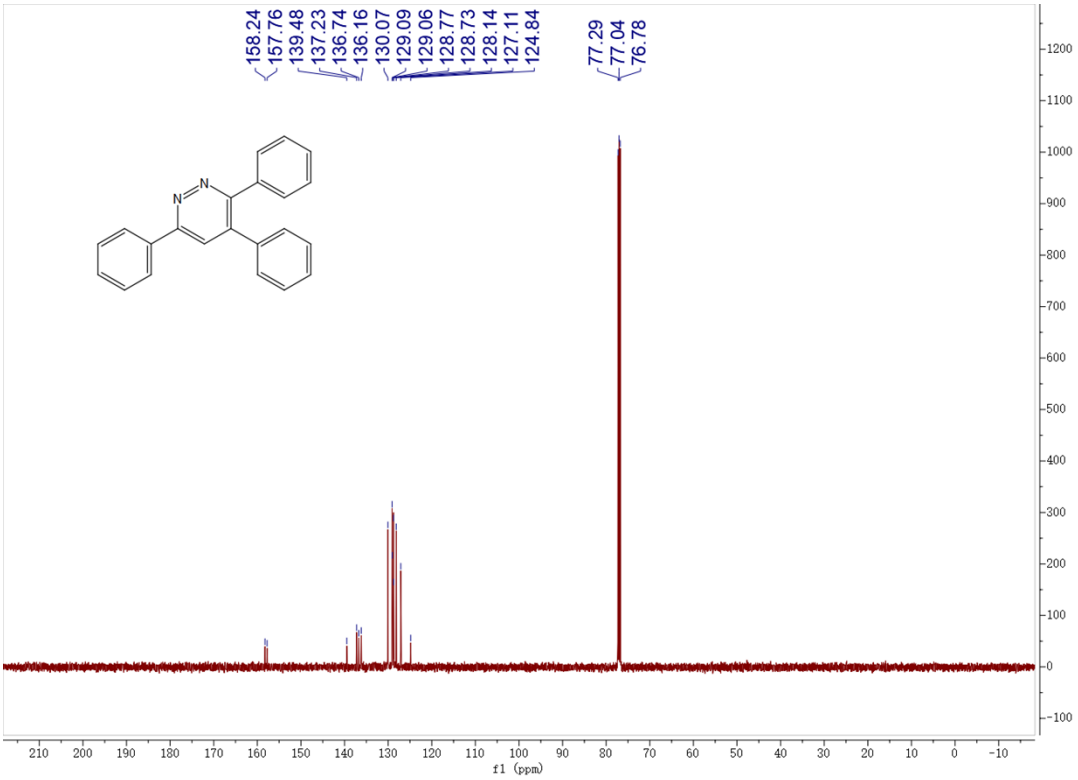

Figure S11. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3a**

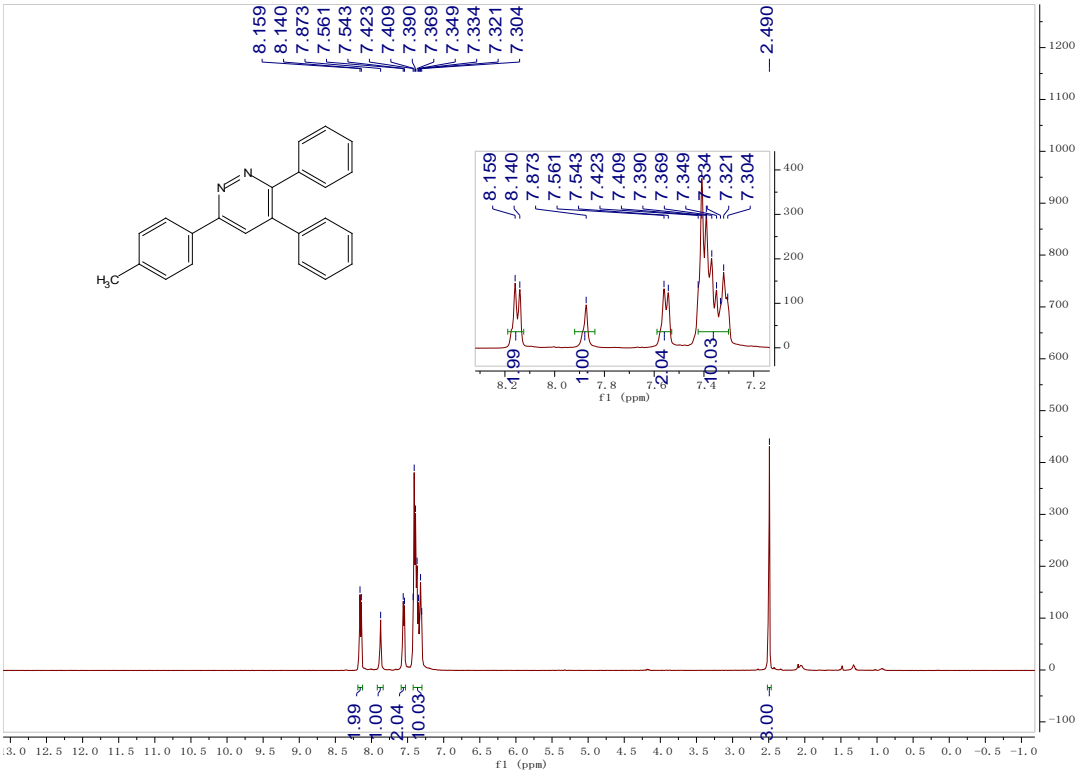

Figure S12. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **3b**

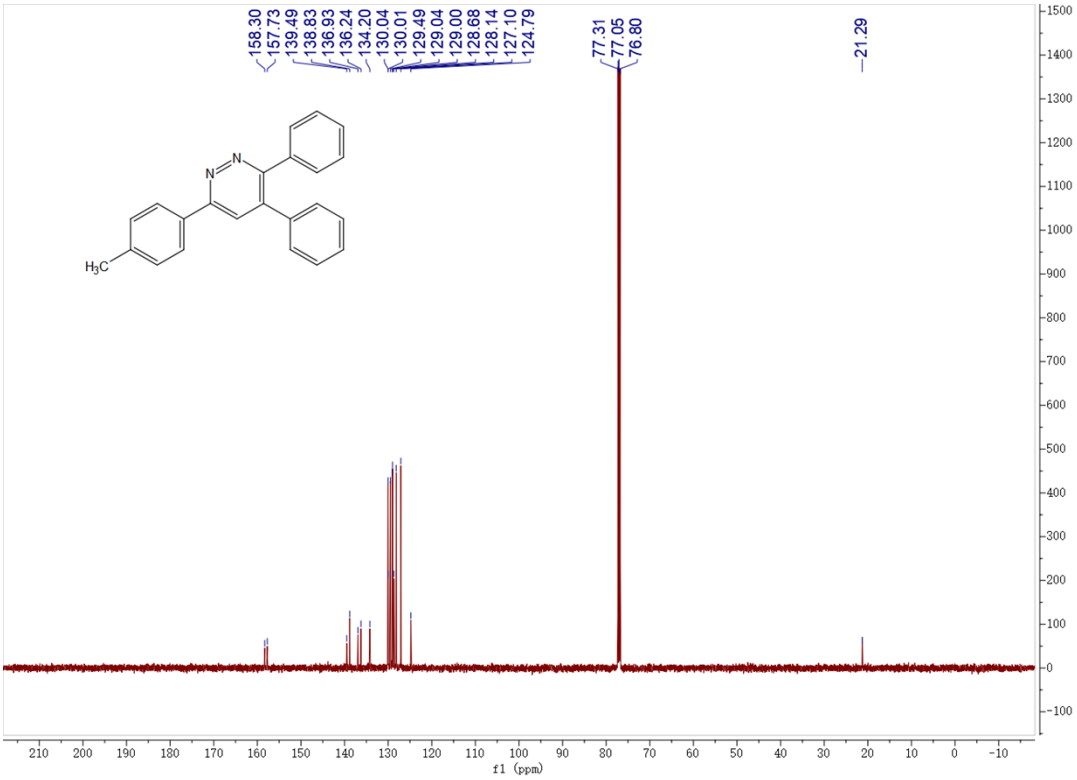

Figure S13. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3b**

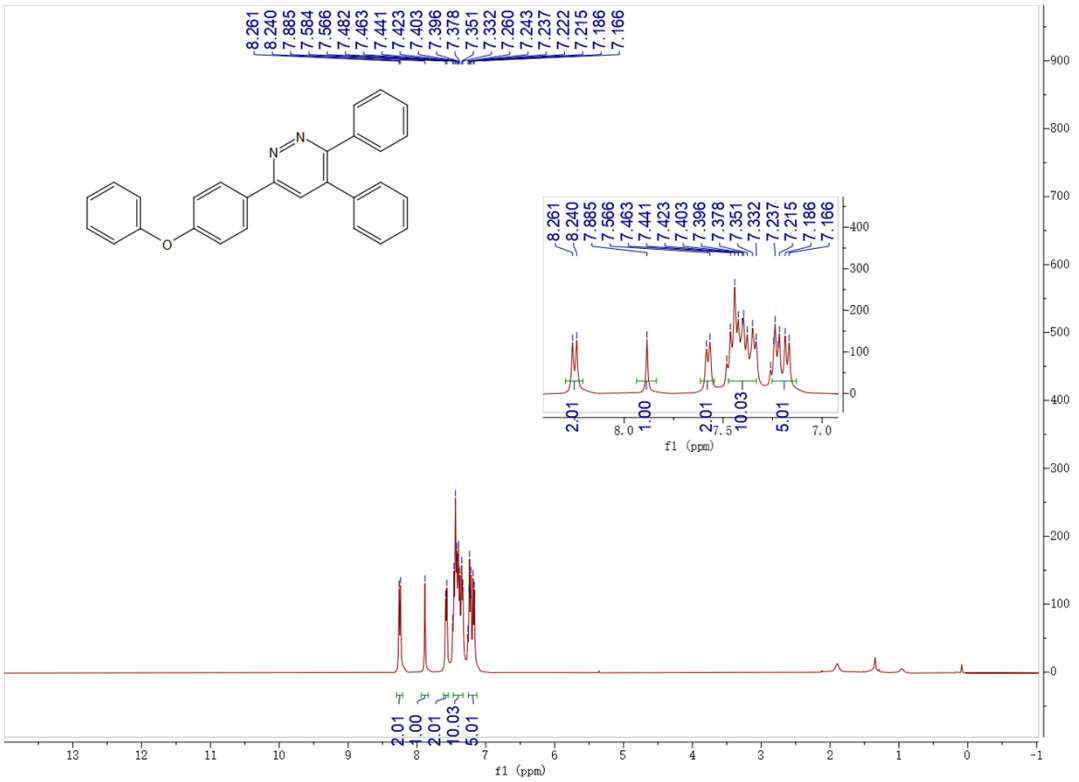

Figure S14. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **3c**

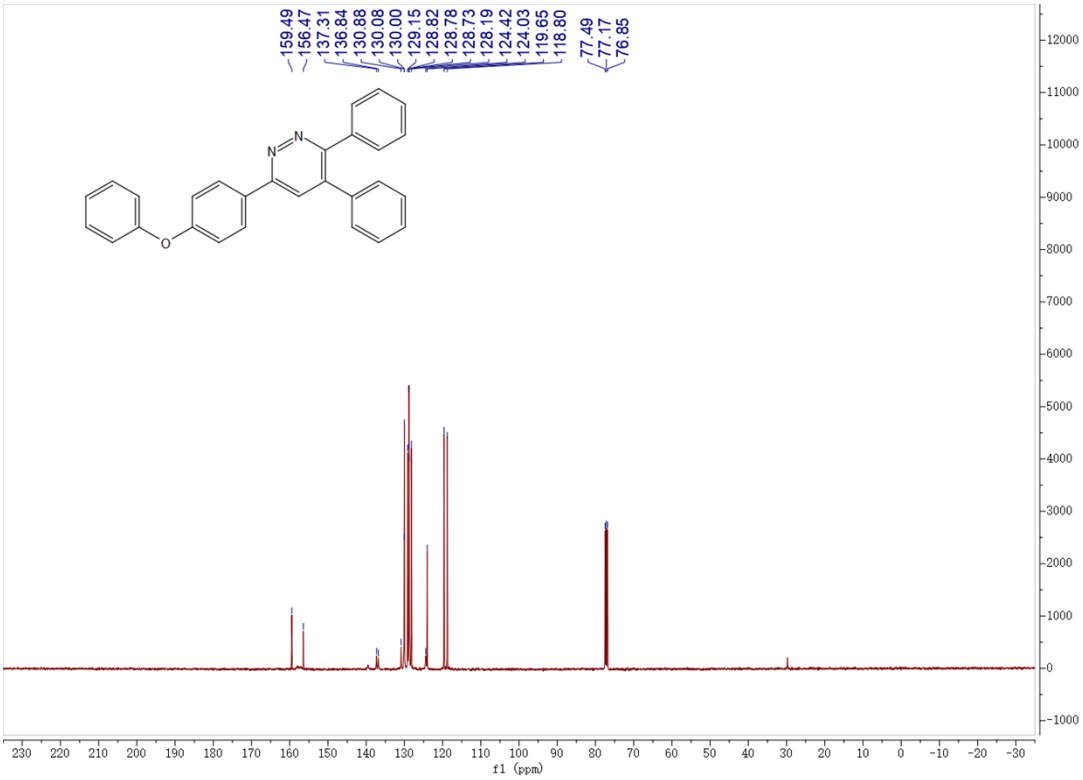

Figure S15. ^{13}C NMR (100 MHz, $CDCl_3$) of compound **3c**

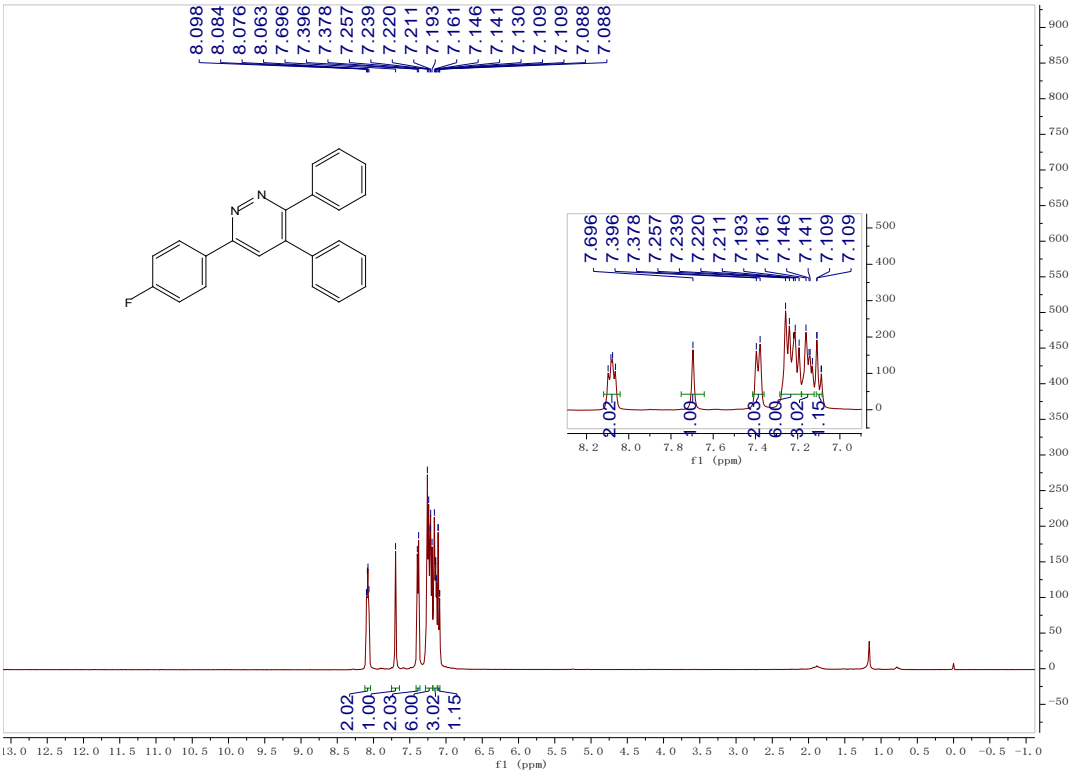

Figure S16. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **3d**

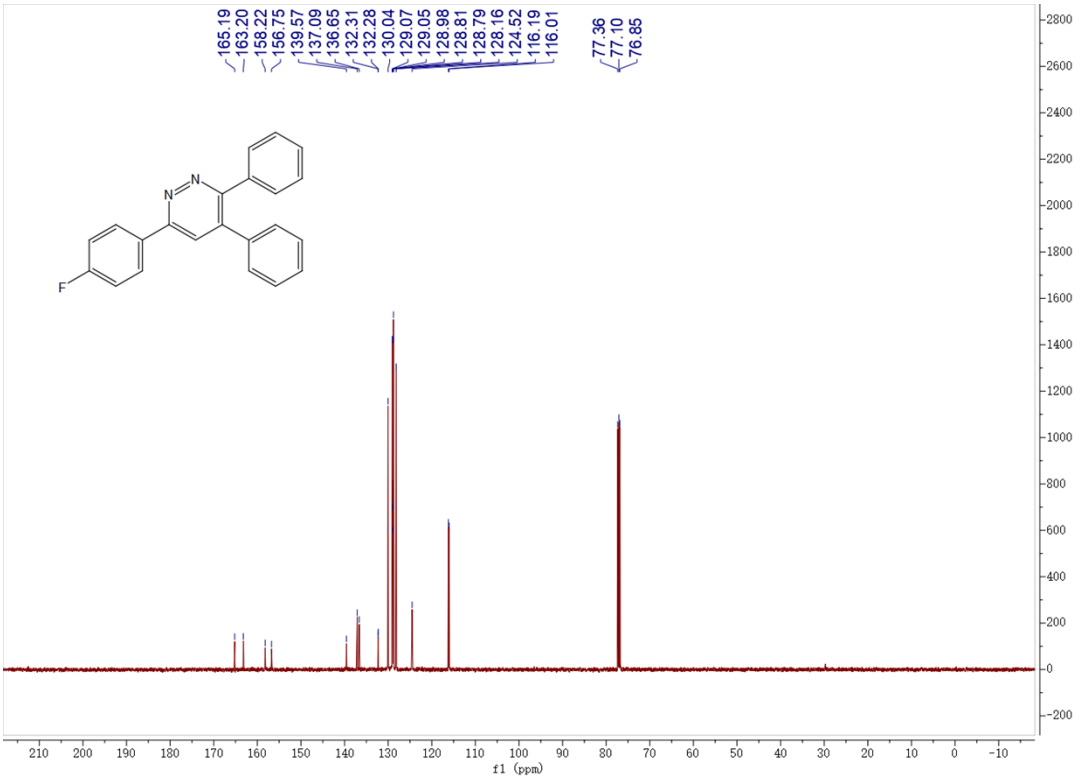

Figure S17. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3d**

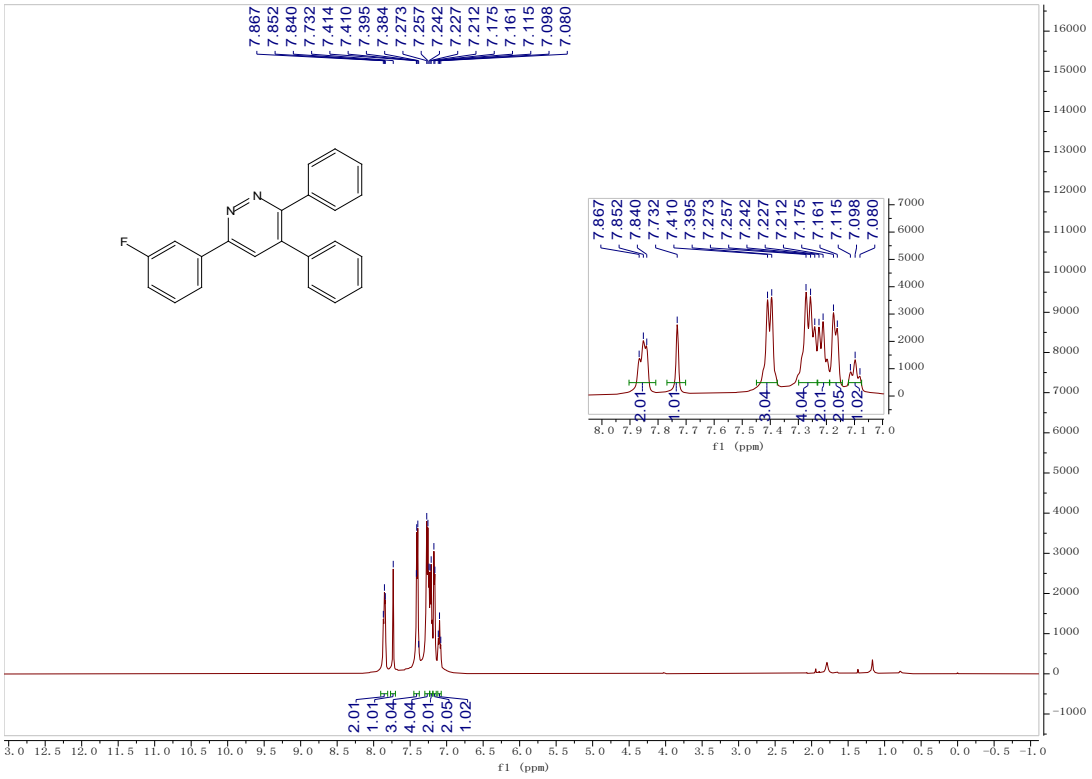

Figure S18. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3e**

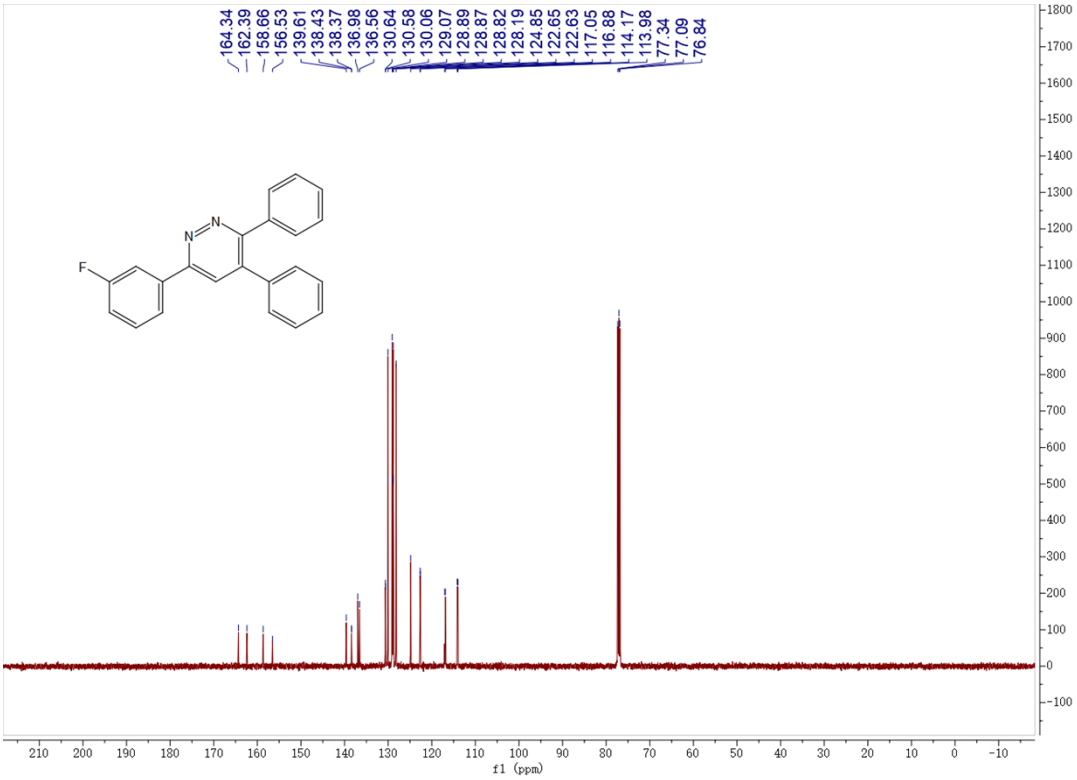

Figure S19. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3e**

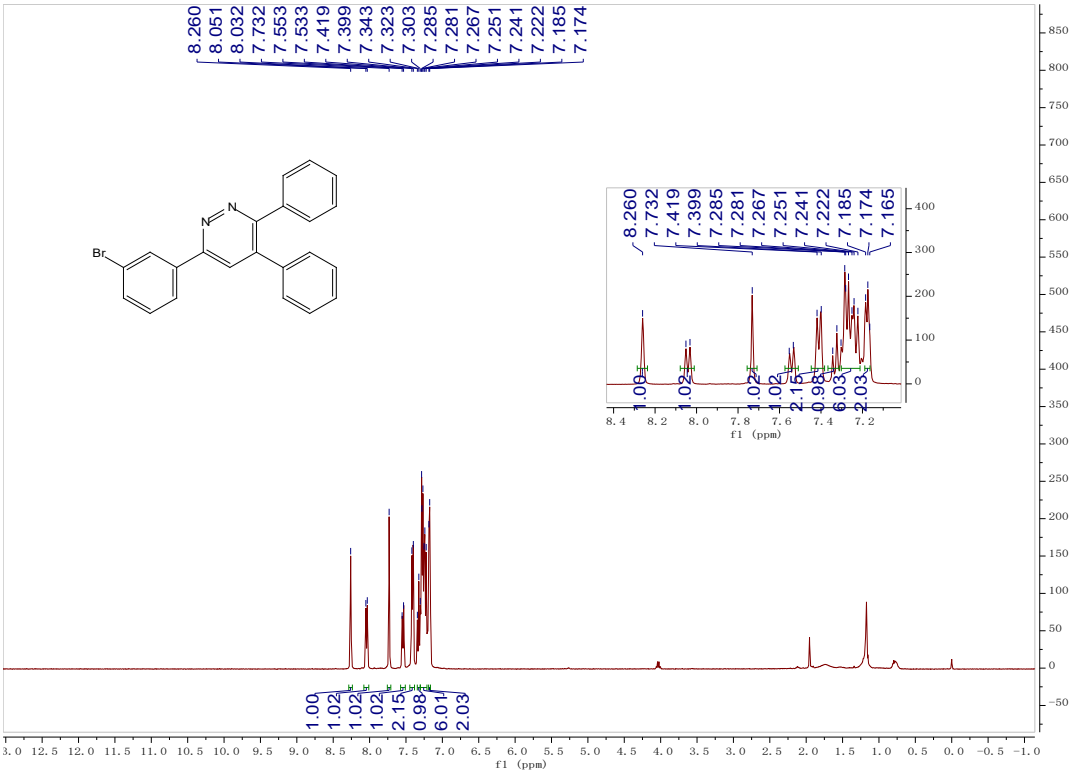

Figure S20. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **3f**

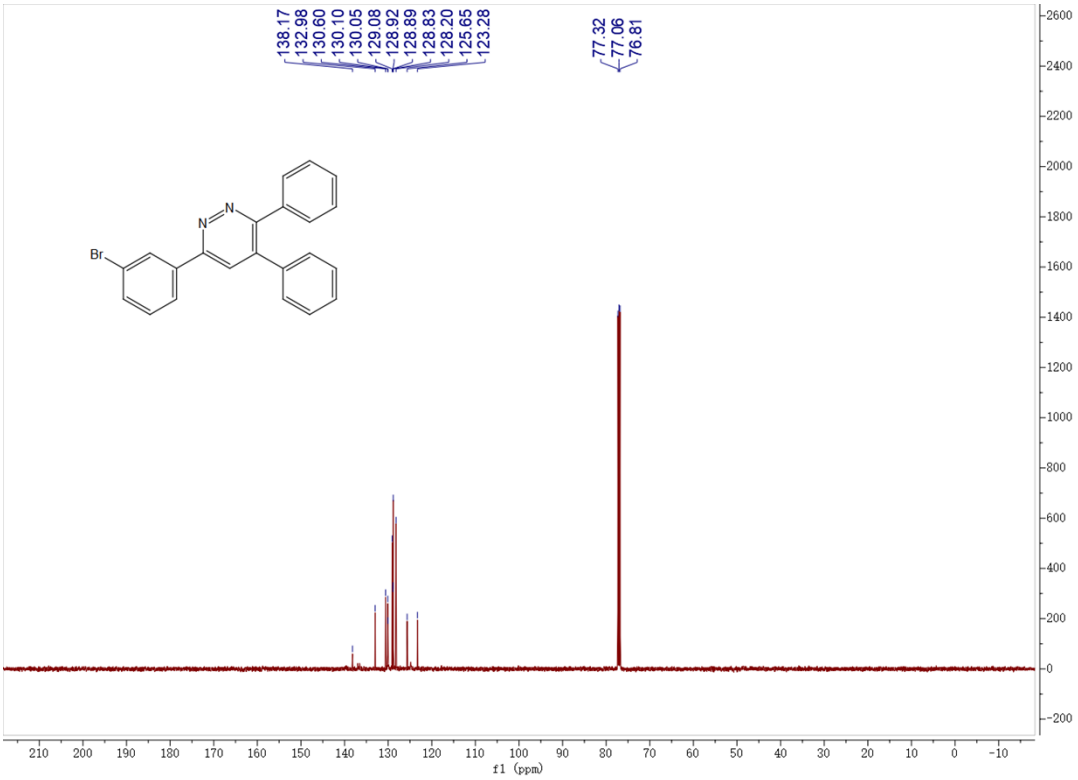

Figure S21. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3f**

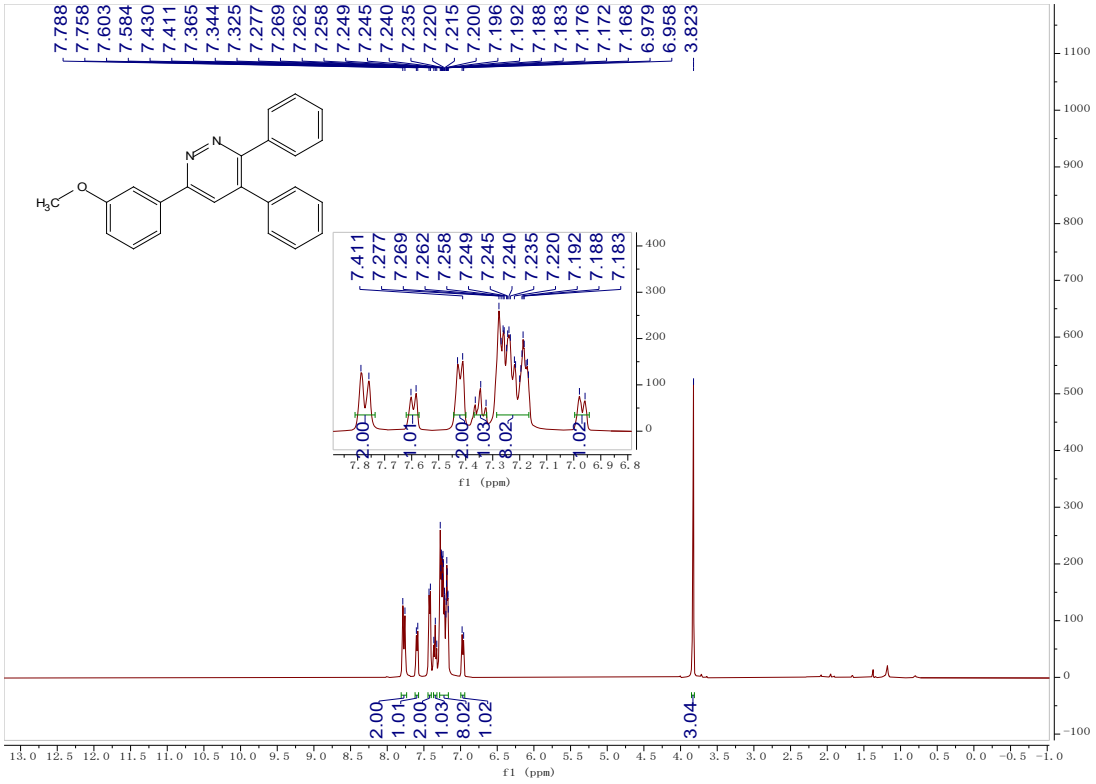

Figure S22. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **3g**

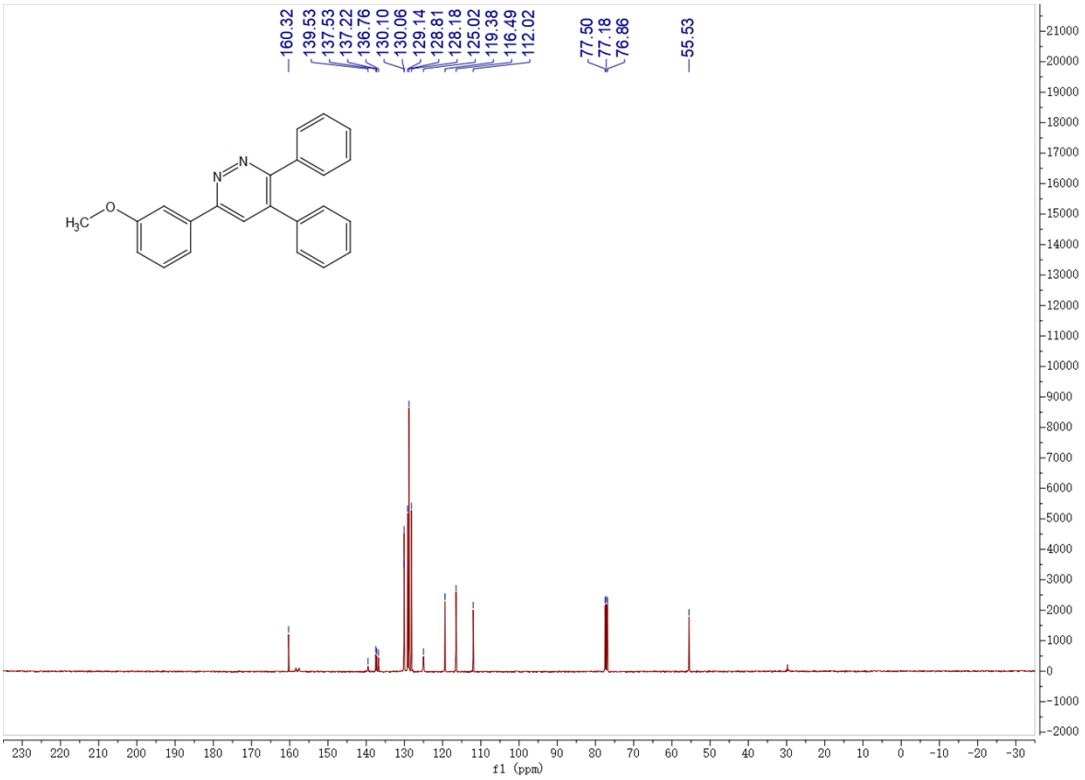

Figure S23. ^{13}C NMR (100 MHz, $CDCl_3$) of compound **3g**

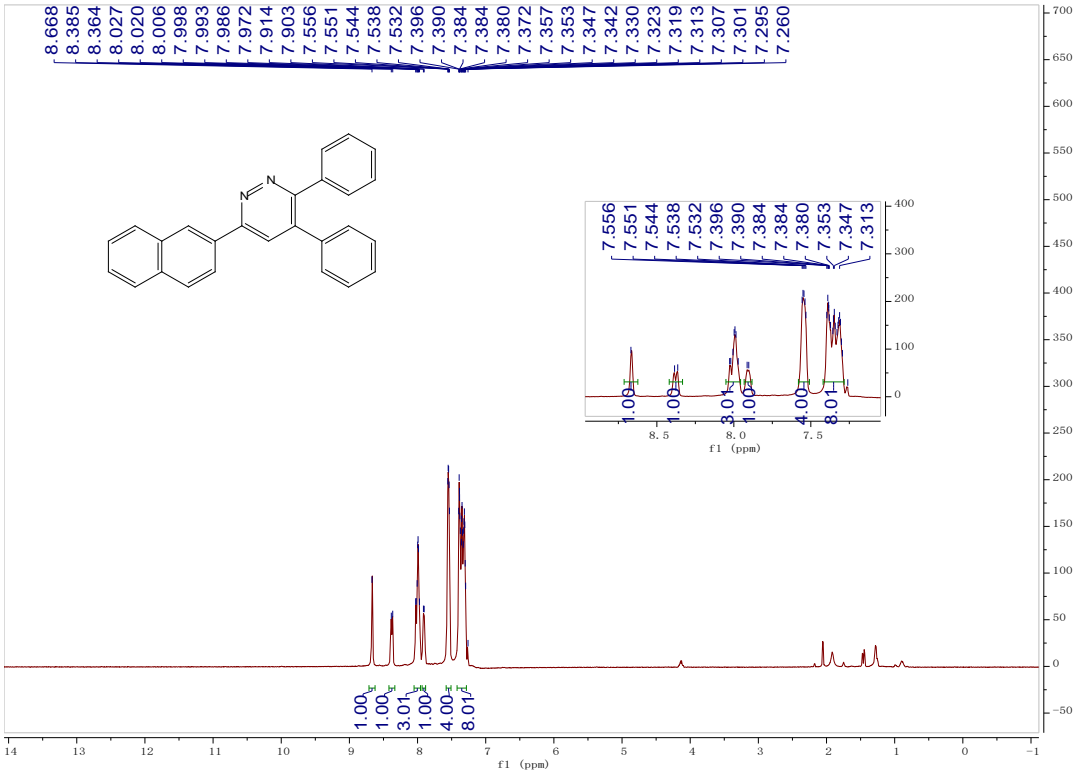

Figure S24. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **3h**

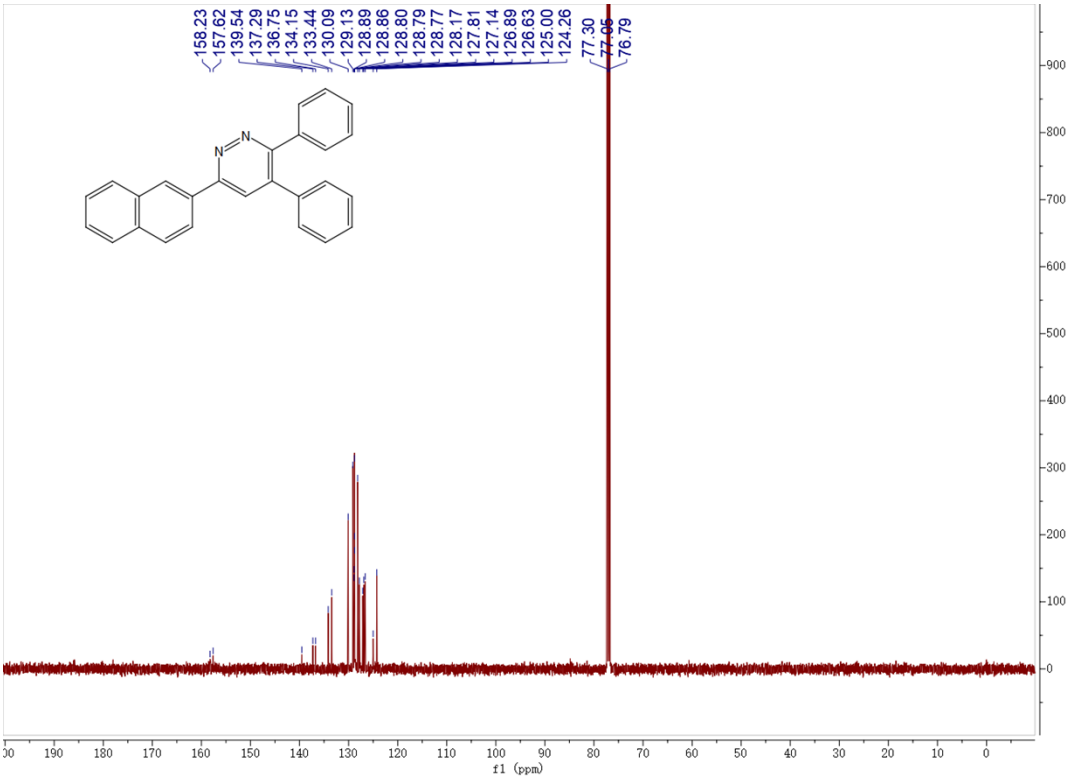

Figure S25. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3h**

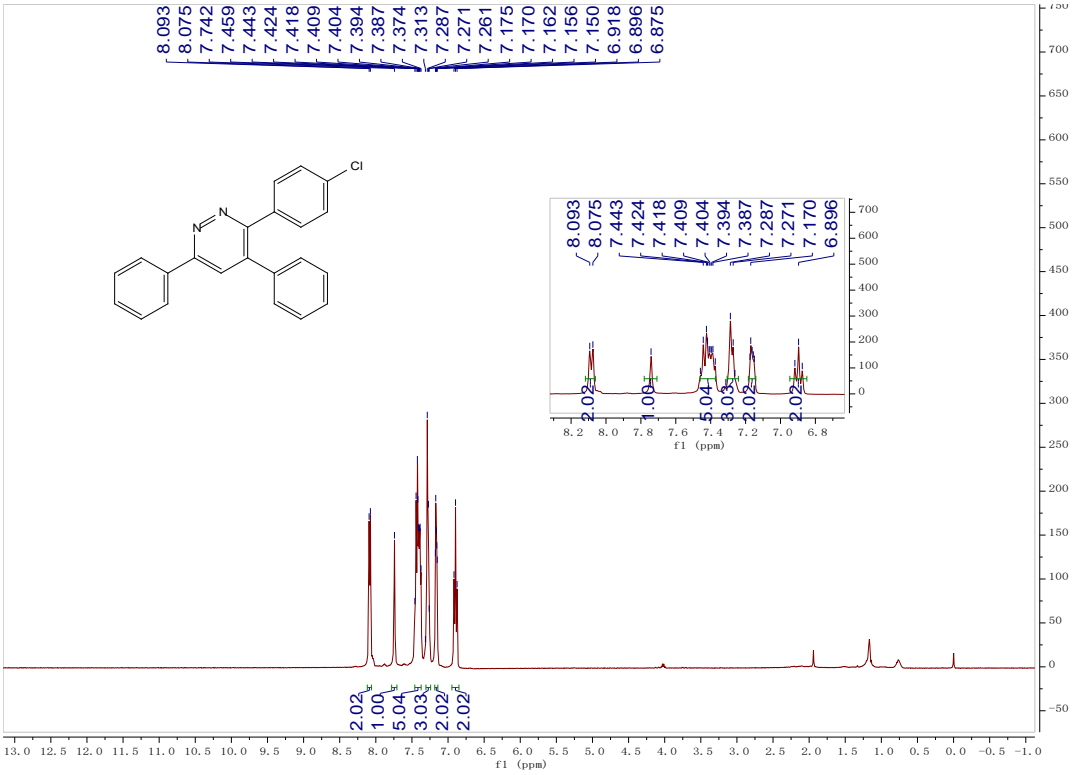

Figure S26. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **3i**

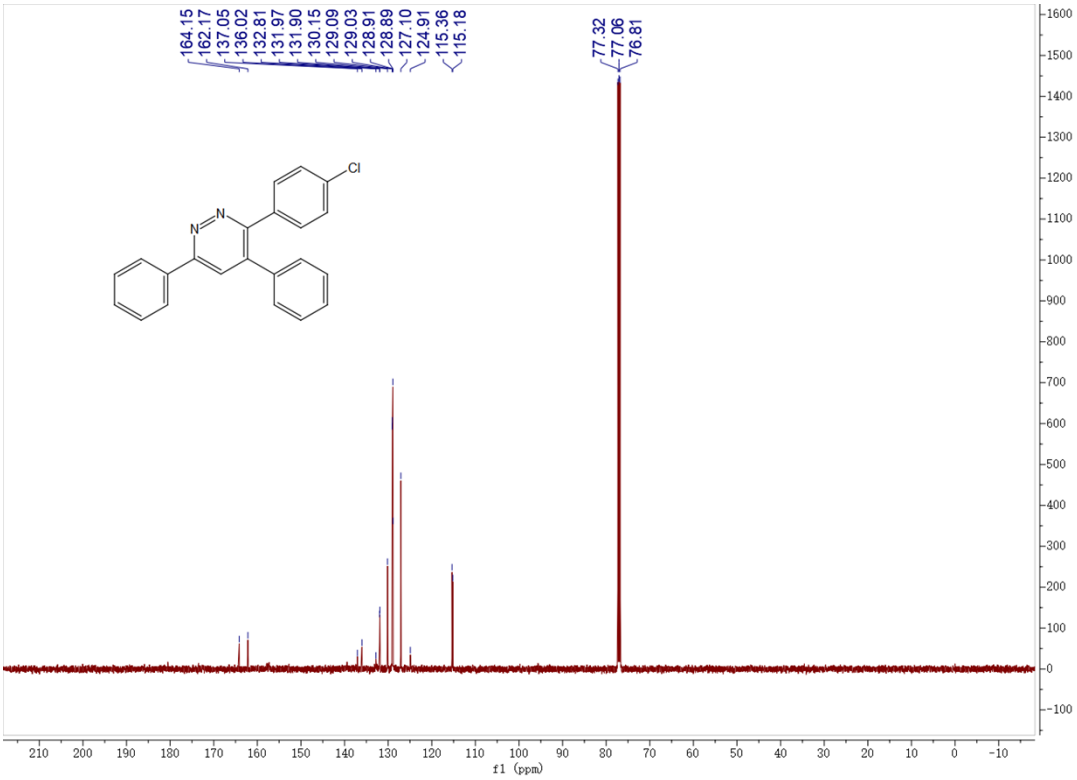

Figure S27. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3i**

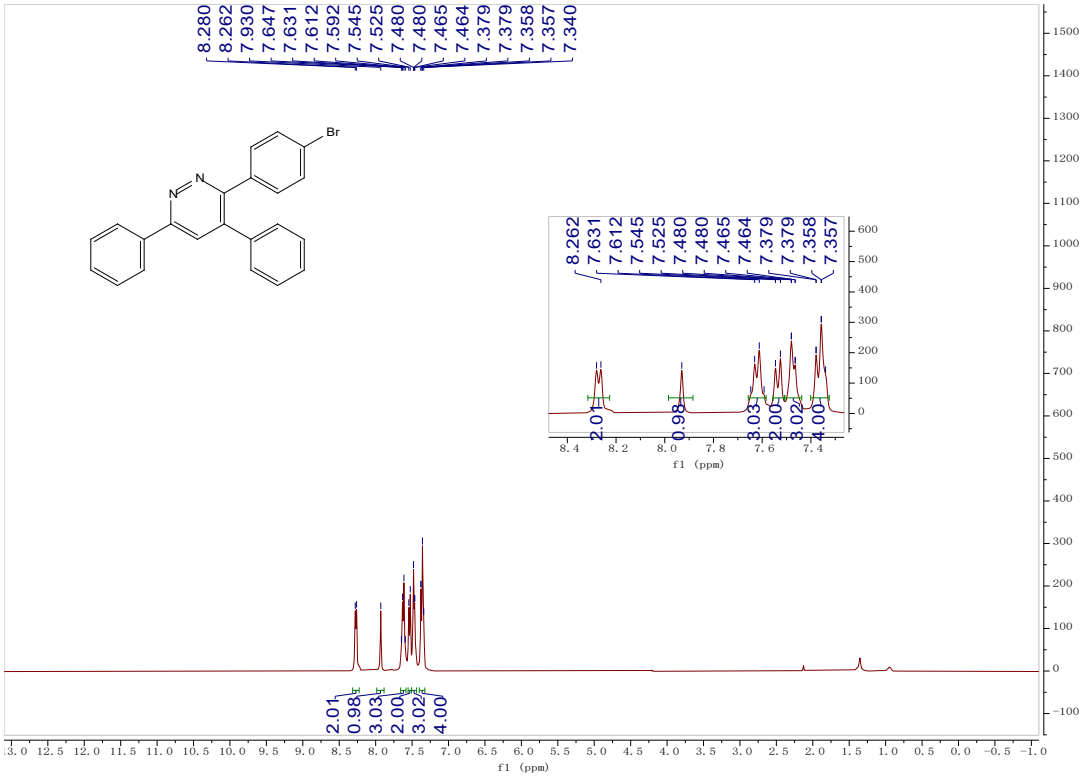

Figure S28. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **3j**

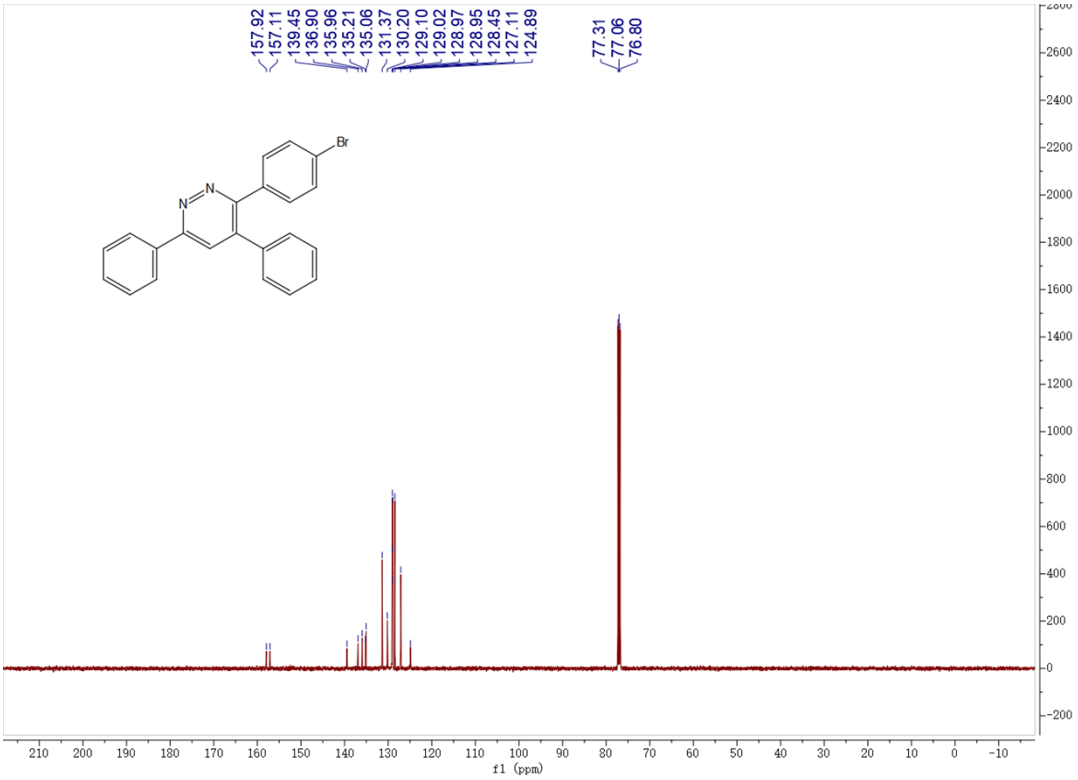

Figure S29. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3j**

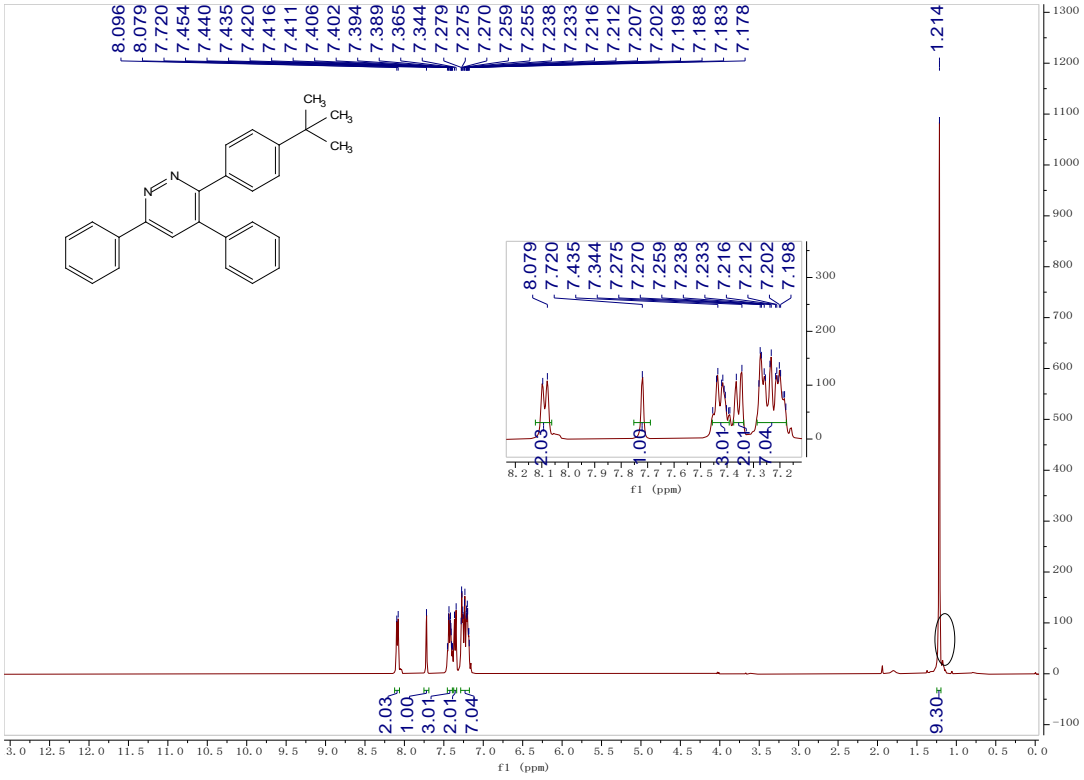

Figure S30. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **3k**

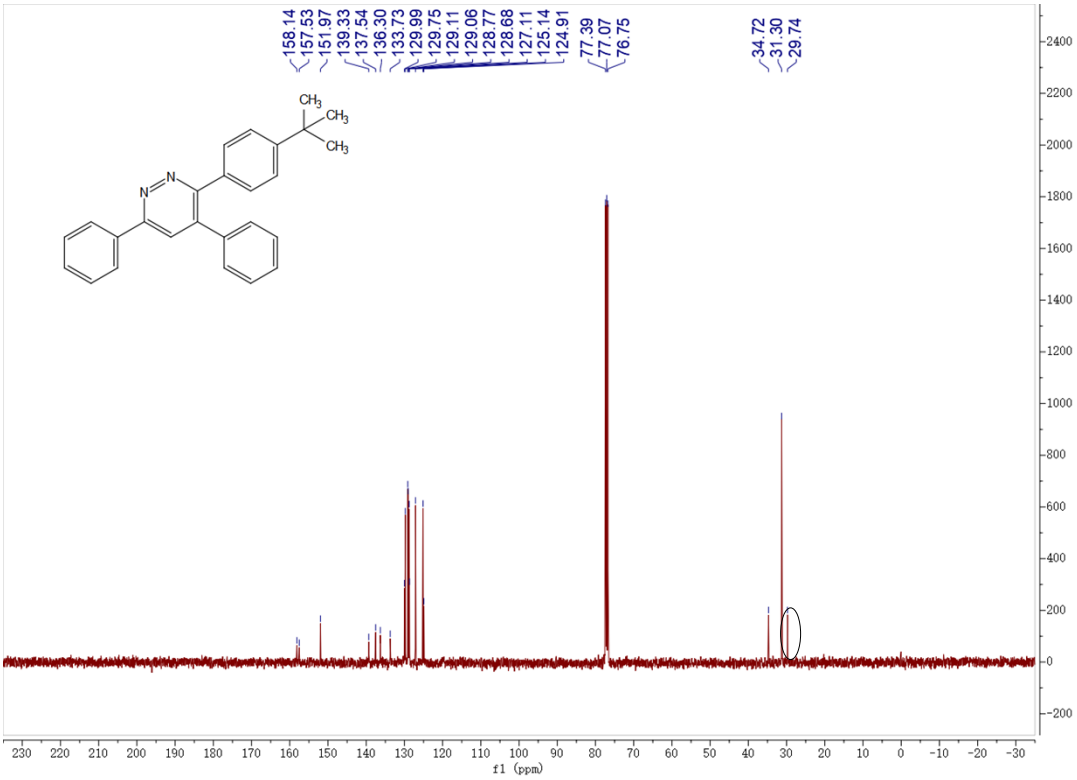

Figure S31. ^{13}C NMR (100 MHz, $CDCl_3$) of compound **3k**

The peak in black oval is the signal of Apiezon grease.

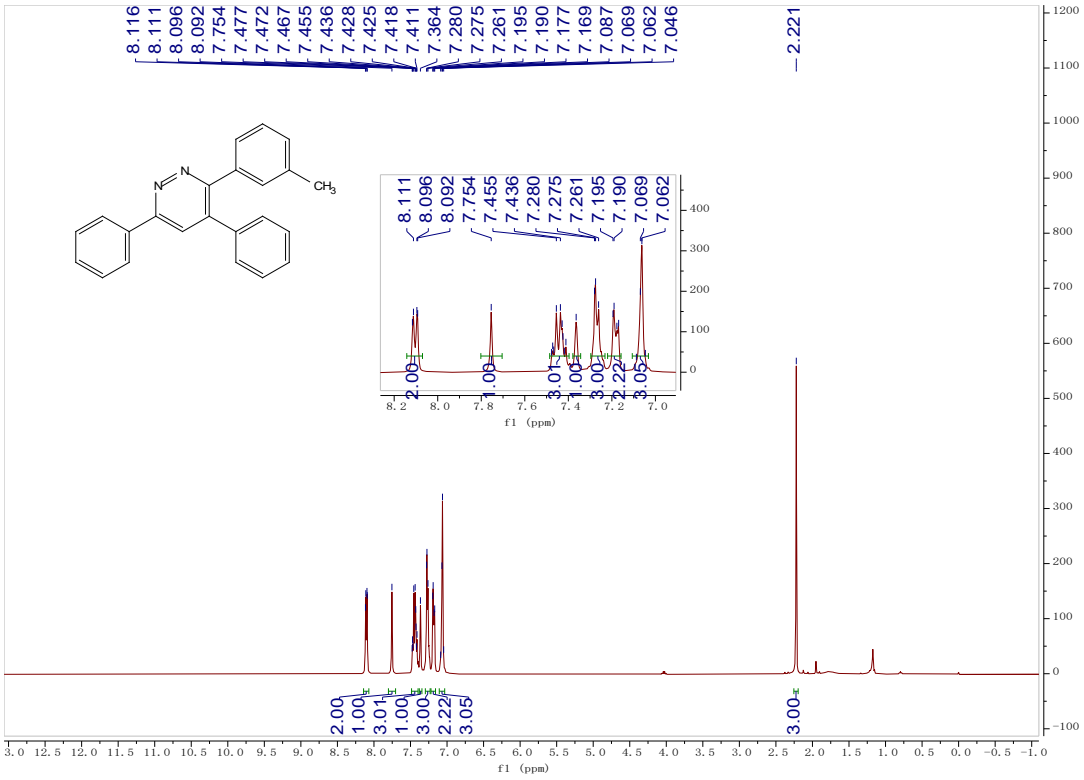

Figure S32. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **3l**

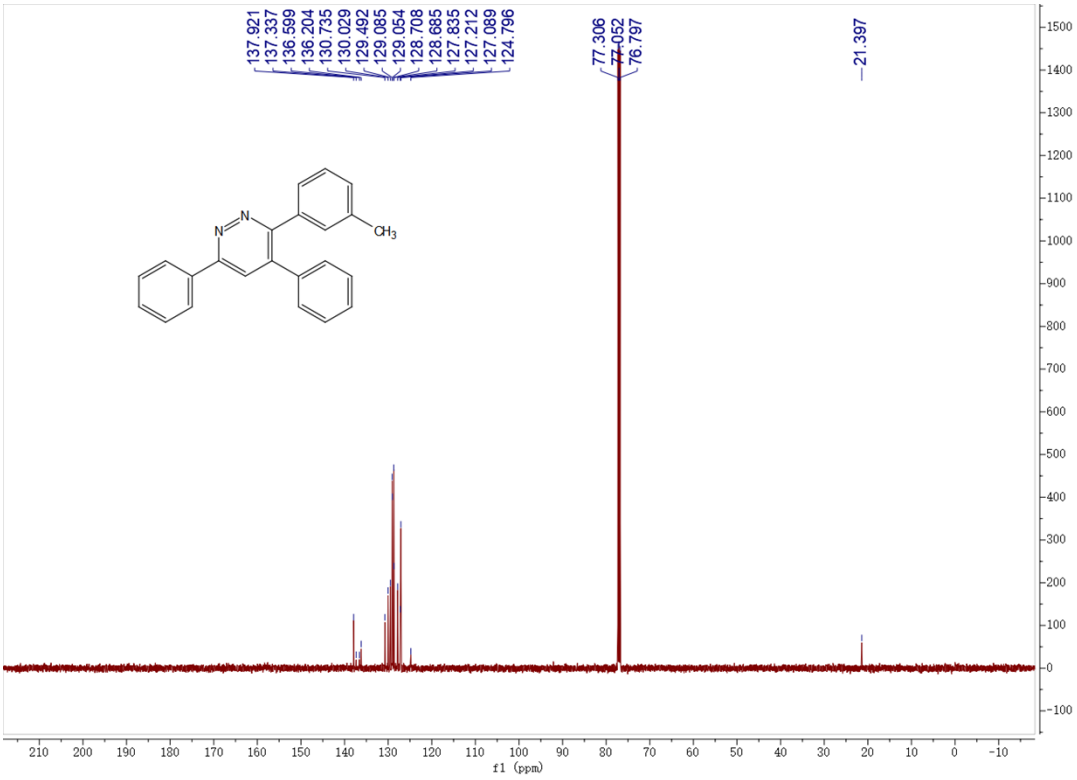

Figure S33. ^{13}**C NMR** (125 MHz, $CDCl_3$) of compound **3l**

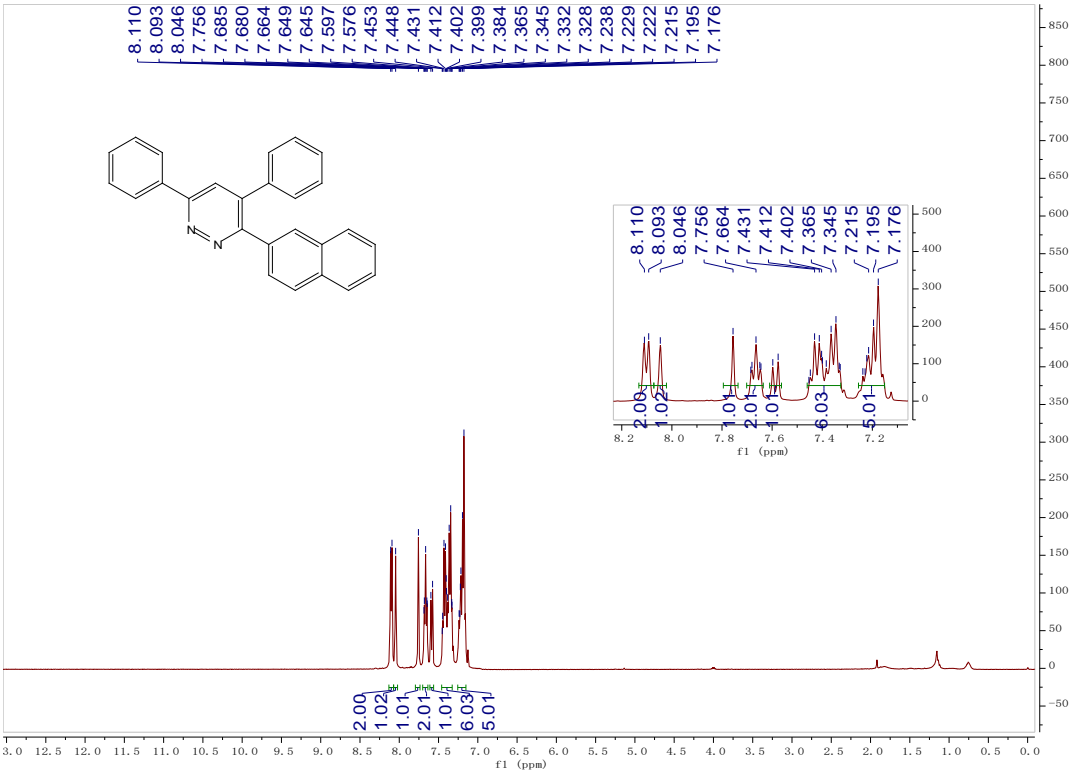

Figure S34. ^{1}**H NMR** (400 MHz, $CDCl_3$) of compound **3m**

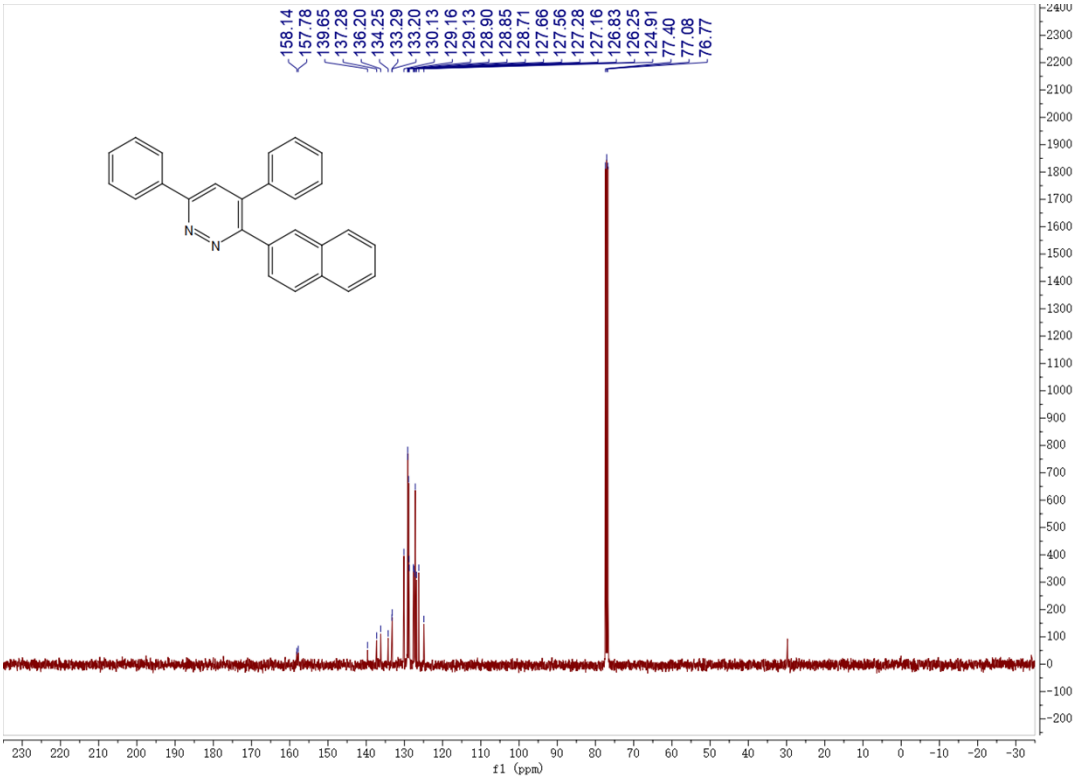

Figure S35. ^{13}C NMR (100 MHz, $CDCl_3$) of compound **3m**

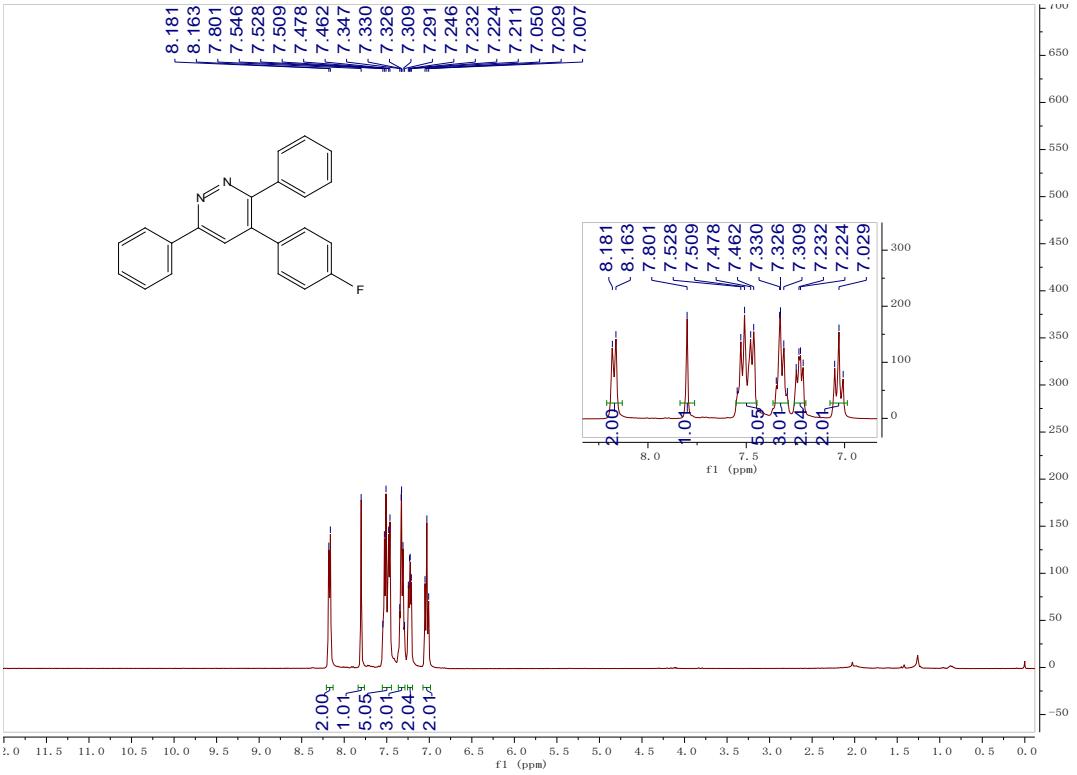

Figure S36. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **3n**

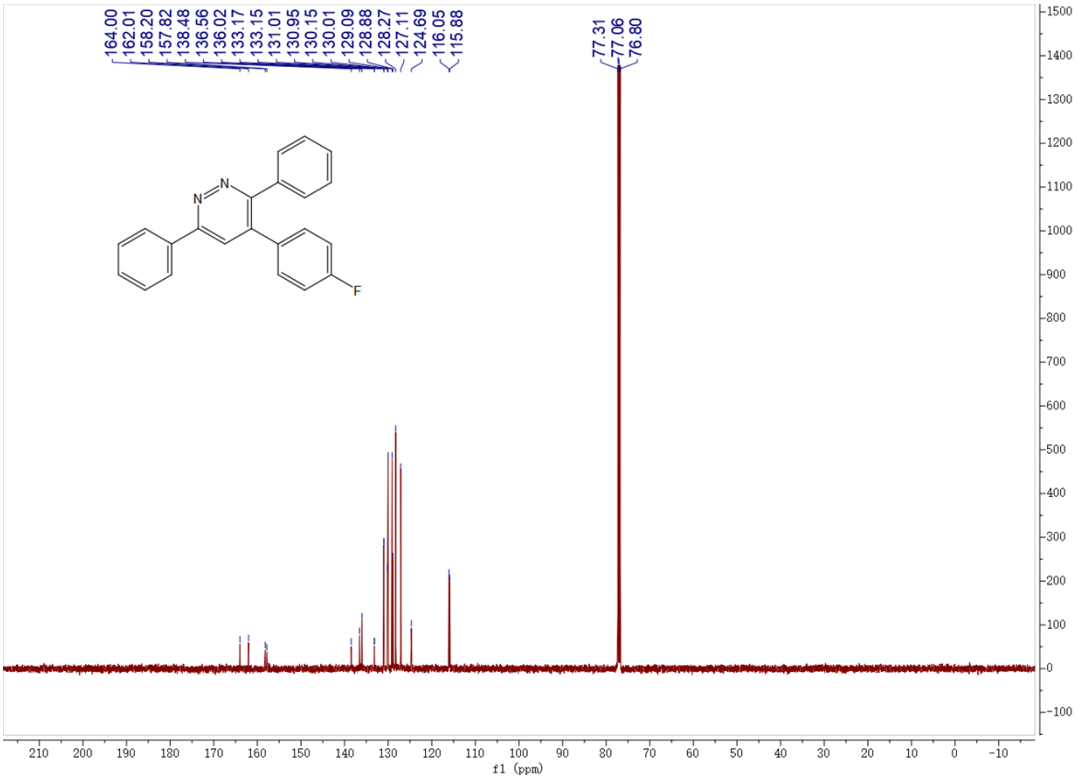

Figure S37. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 3**n**

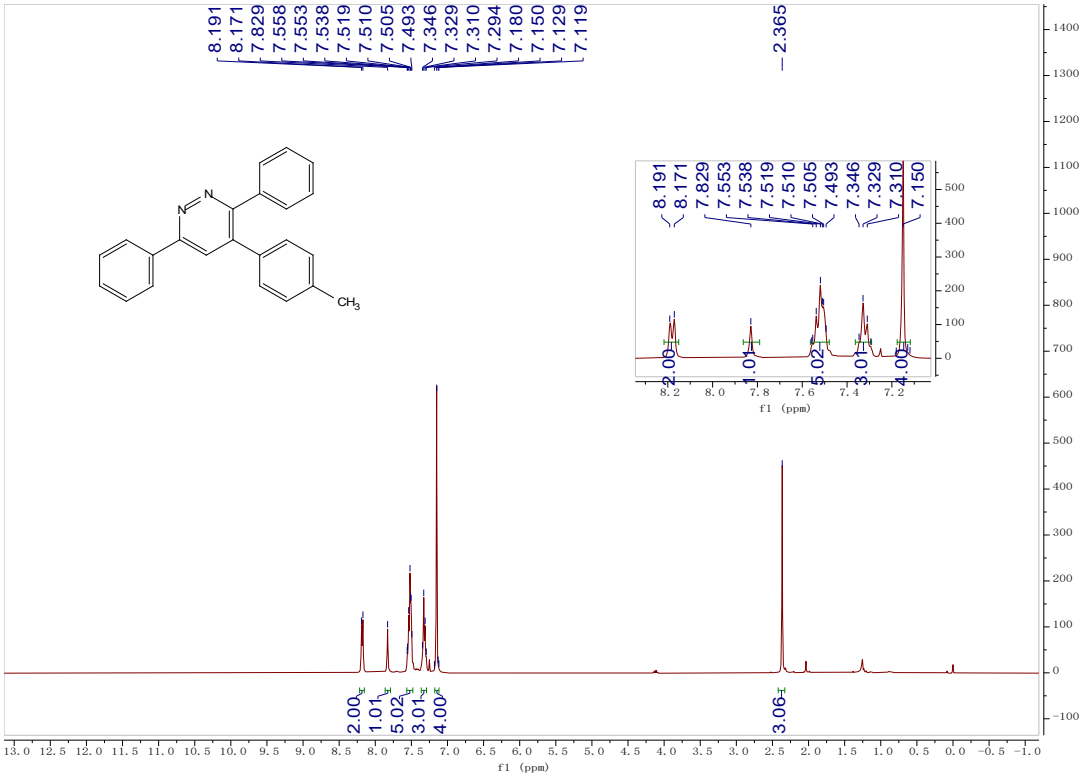

Figure S38. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **3o**

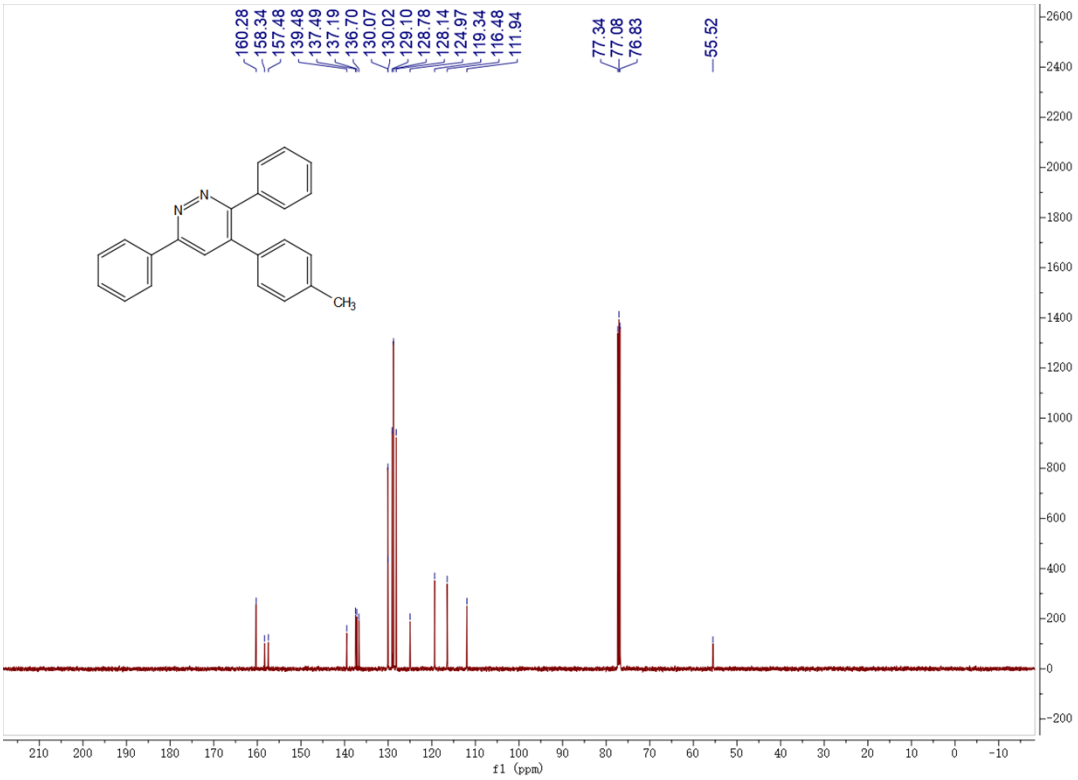

Figure S39. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3o**

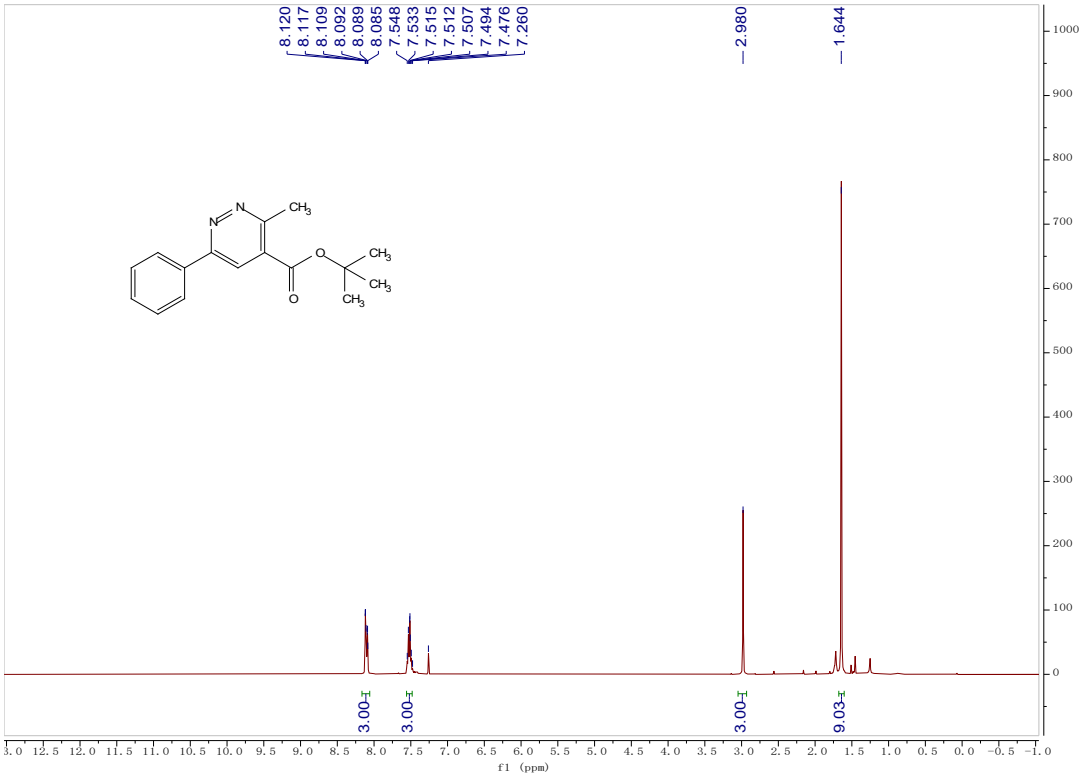

Figure S40. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **3p**

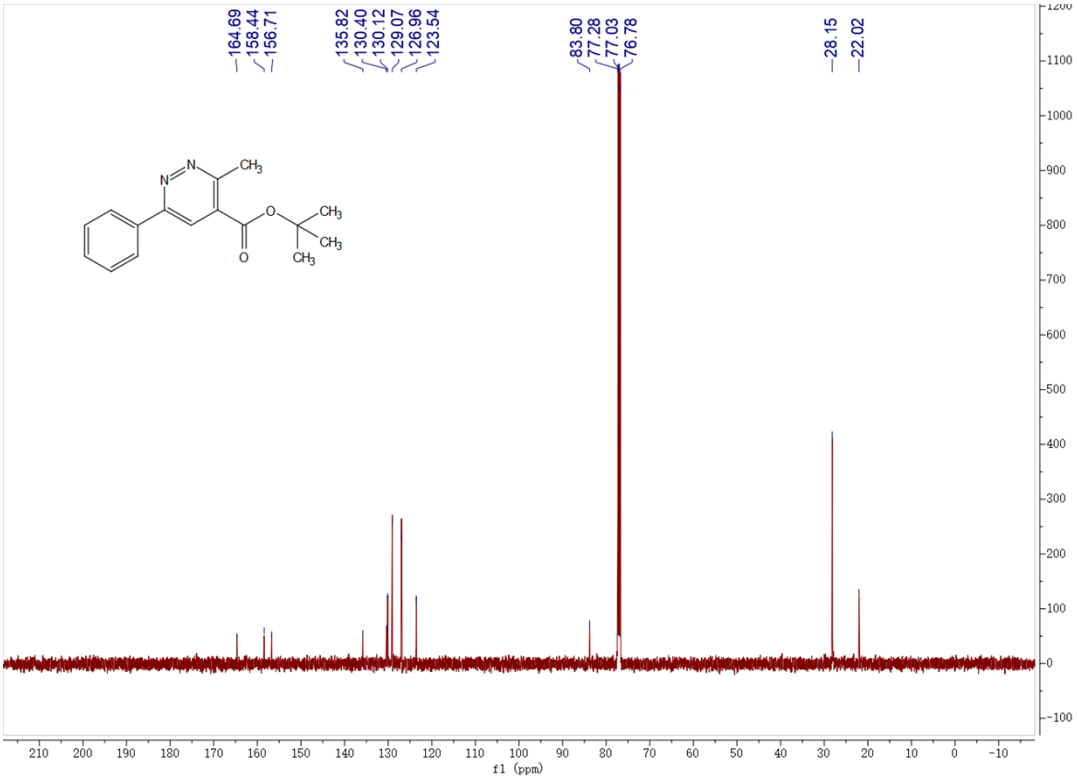

Figure S41. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3p**

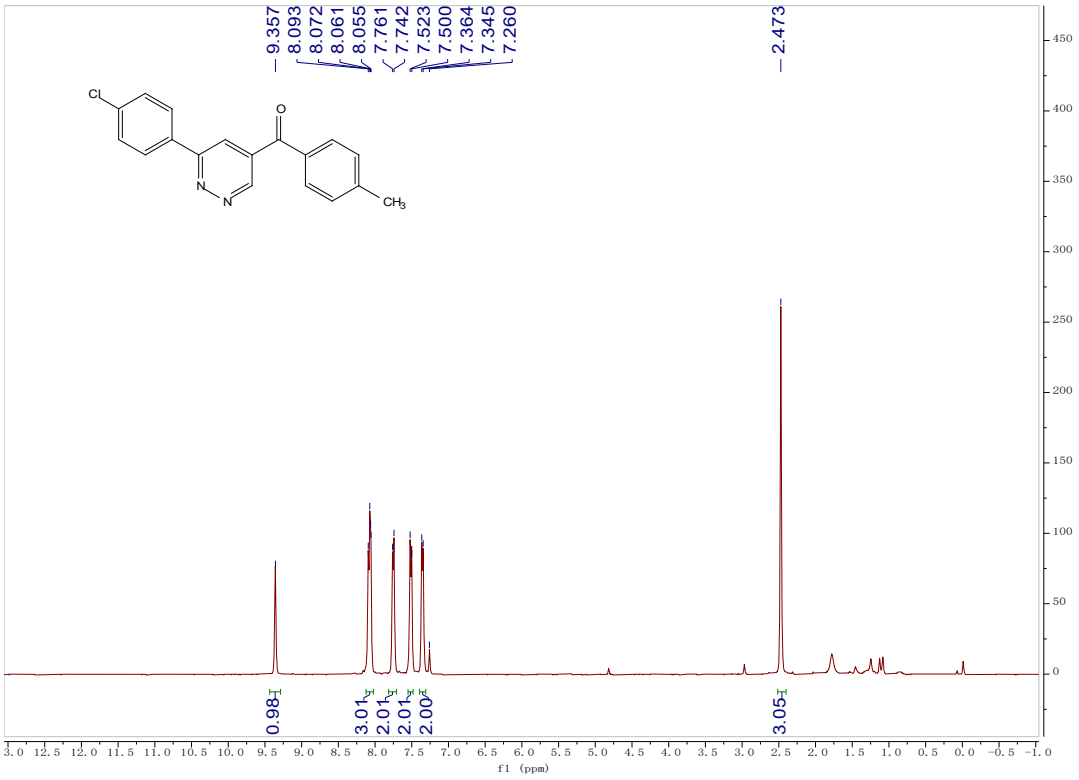

Figure S42. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **6a**

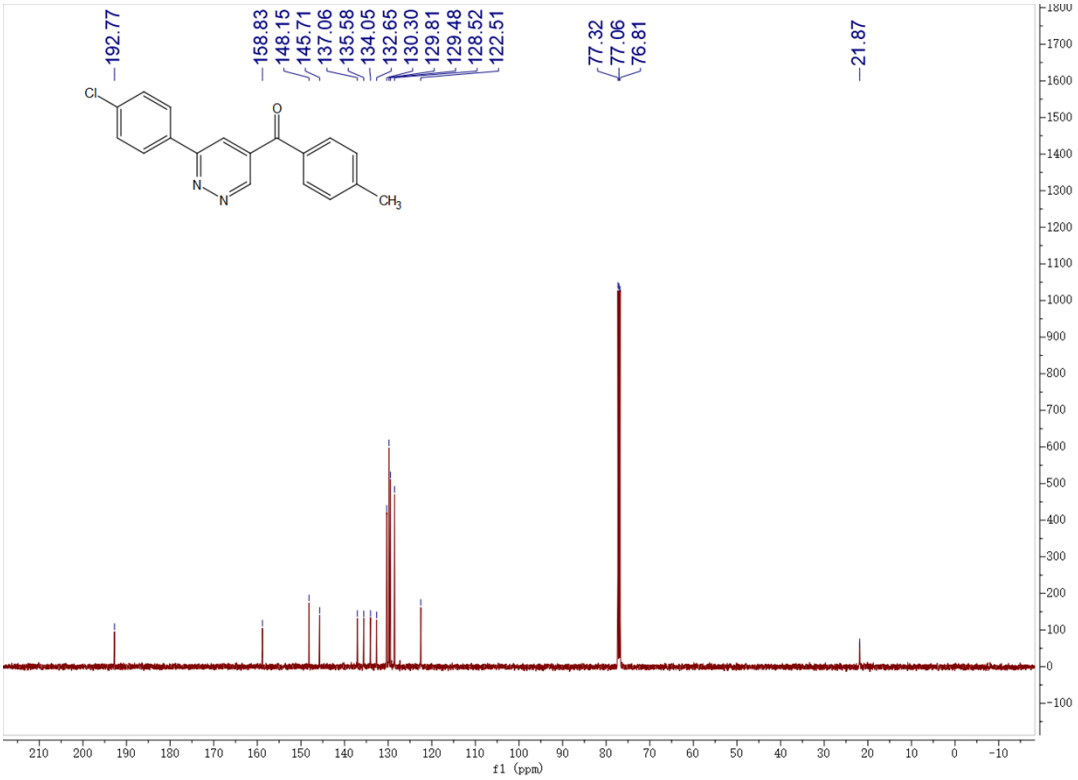

Figure S43. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **6a**

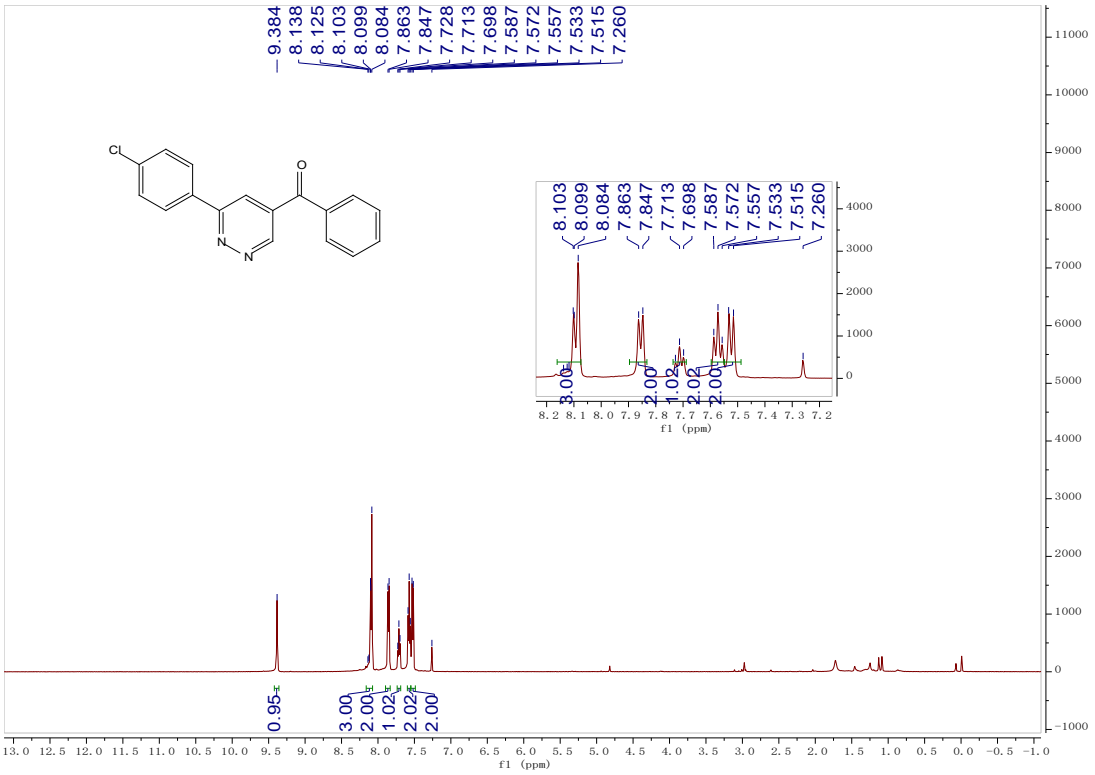

Figure S44. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **6b**

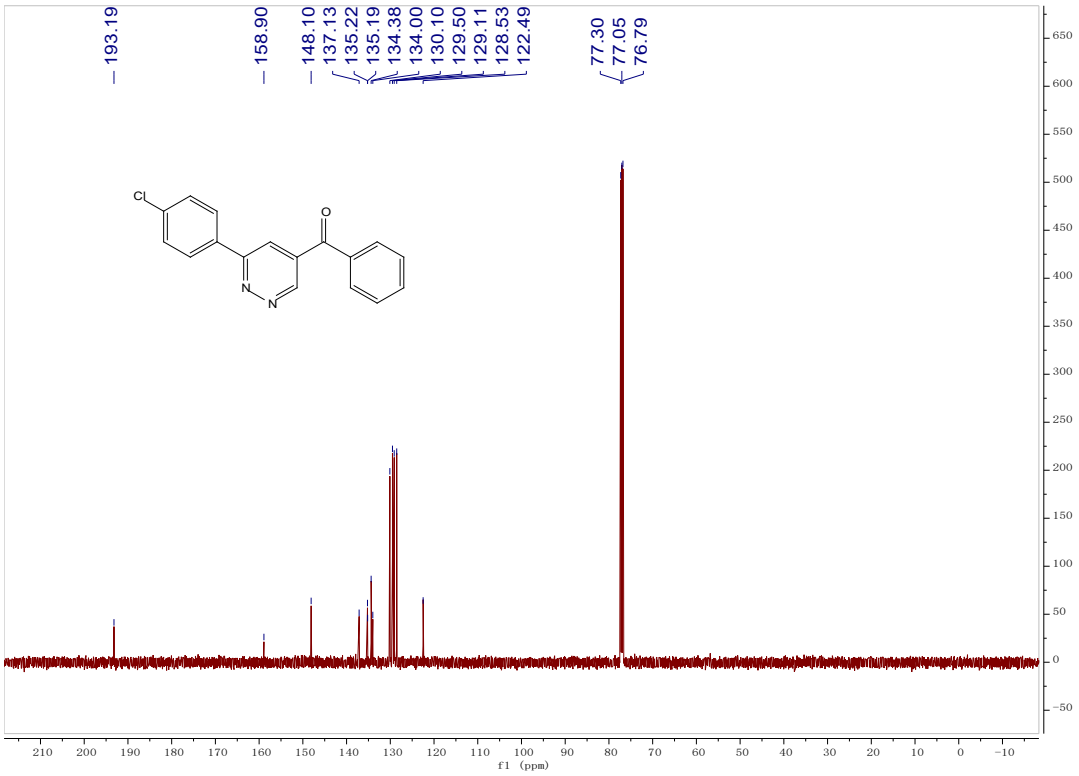

Figure S45. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **6b**

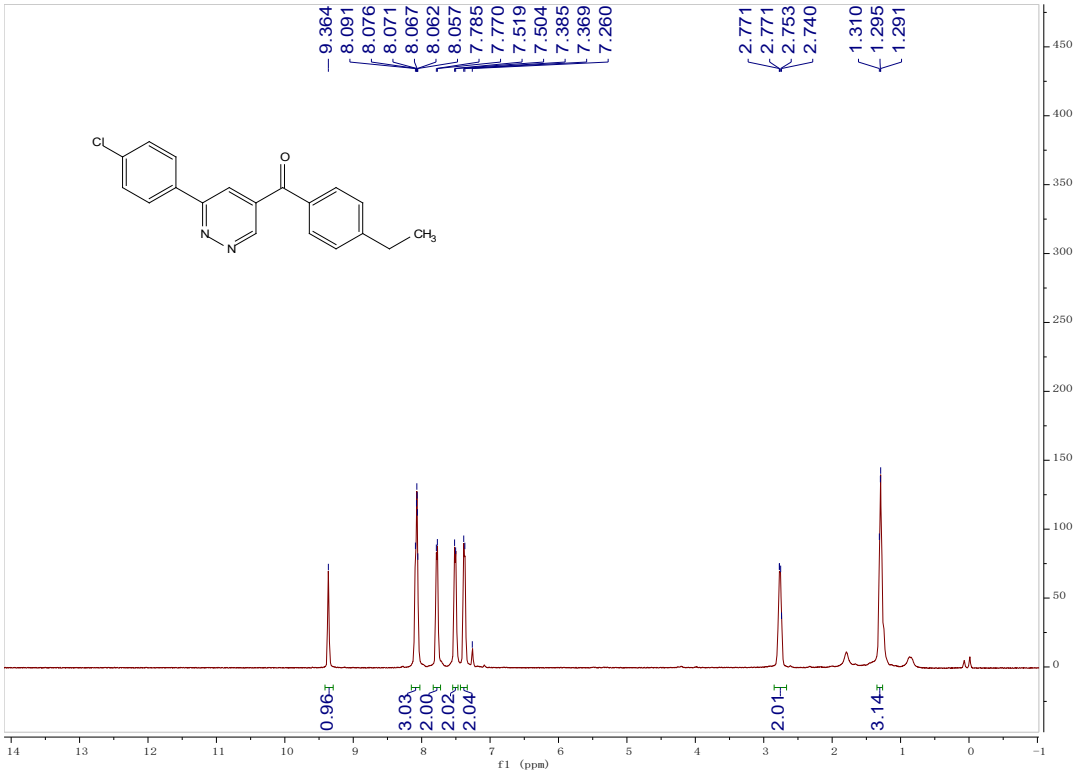

Figure S46. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6c**

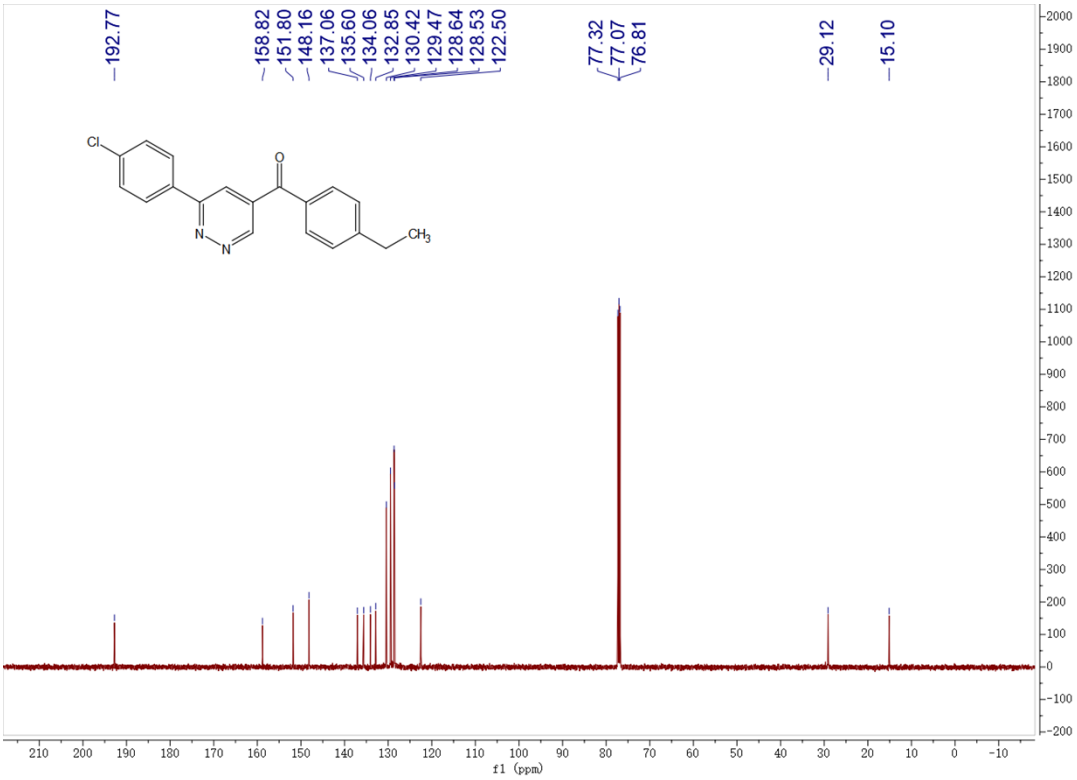

Figure S47. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **6c**

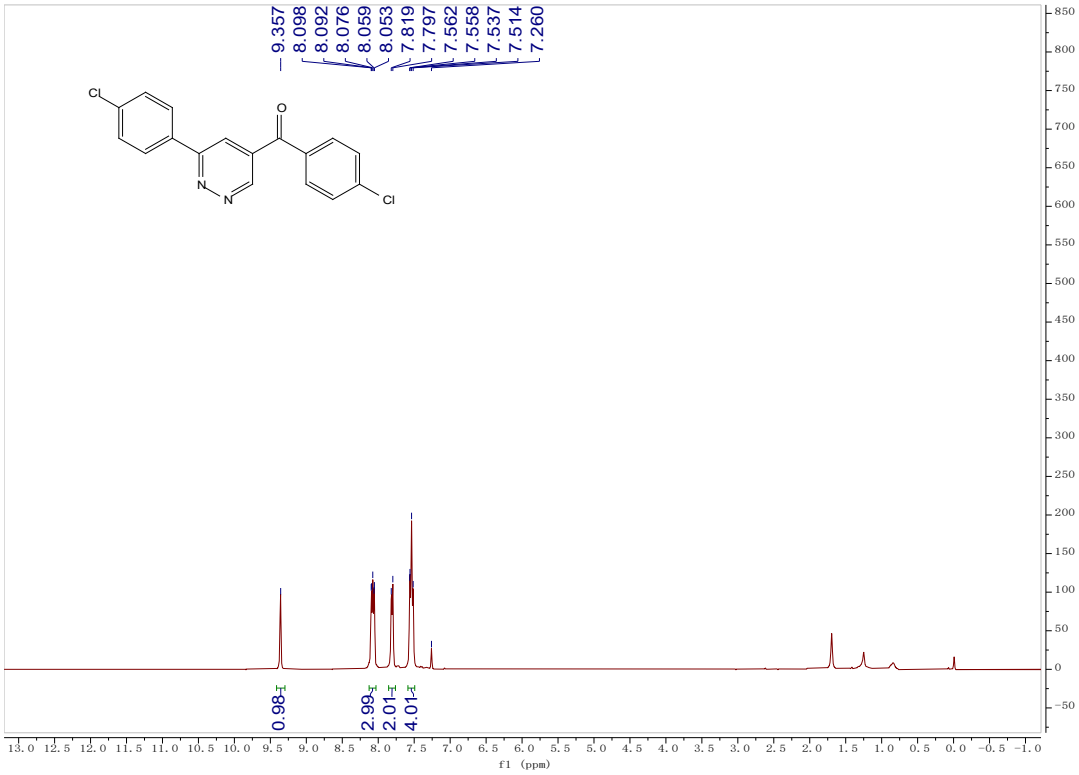

Figure S48. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6d**

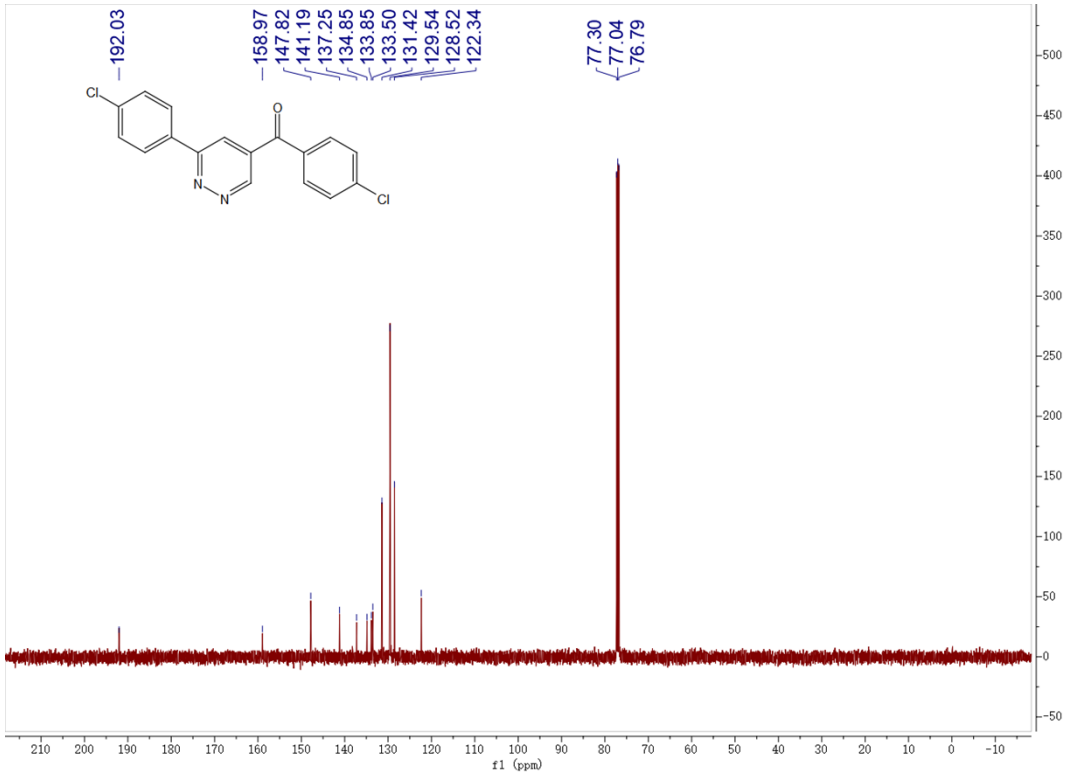

Figure S49. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **6d**

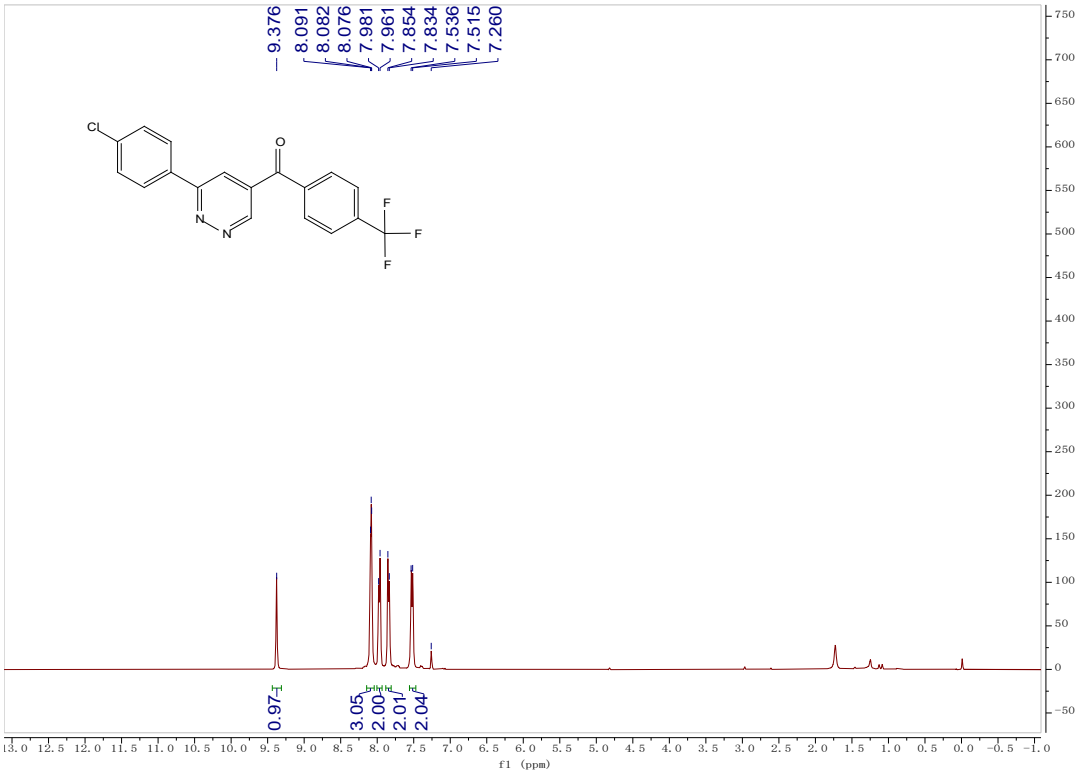

Figure S50. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6e**

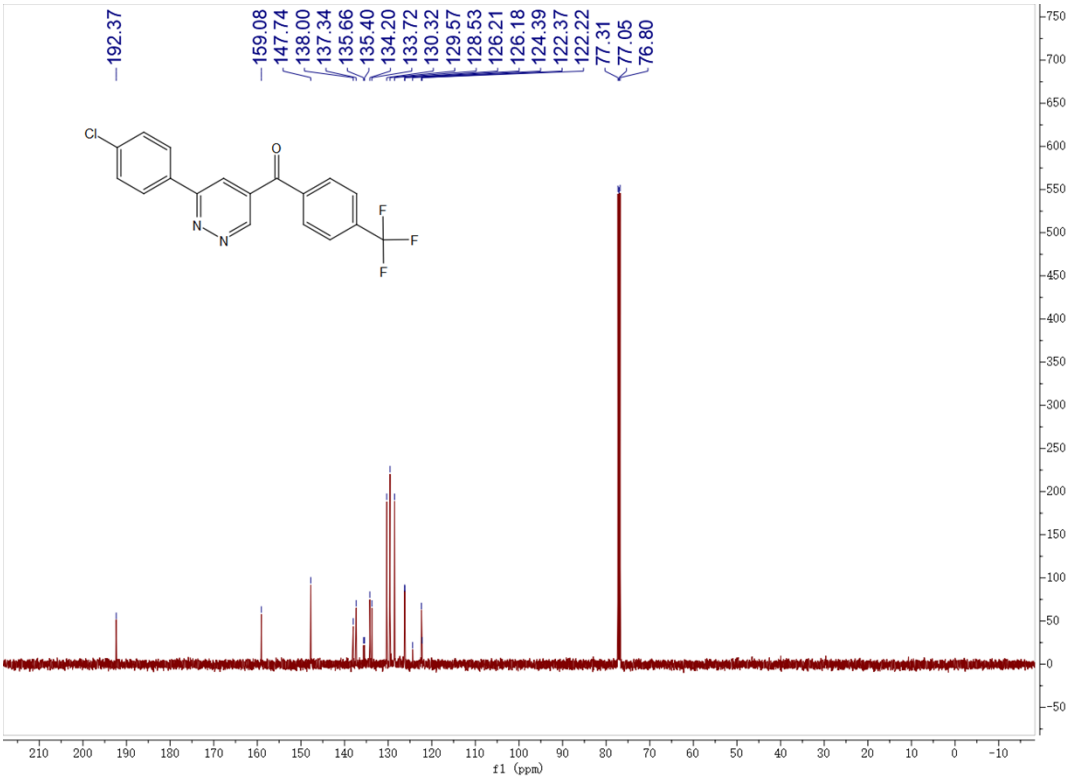

Figure S51. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **6e**

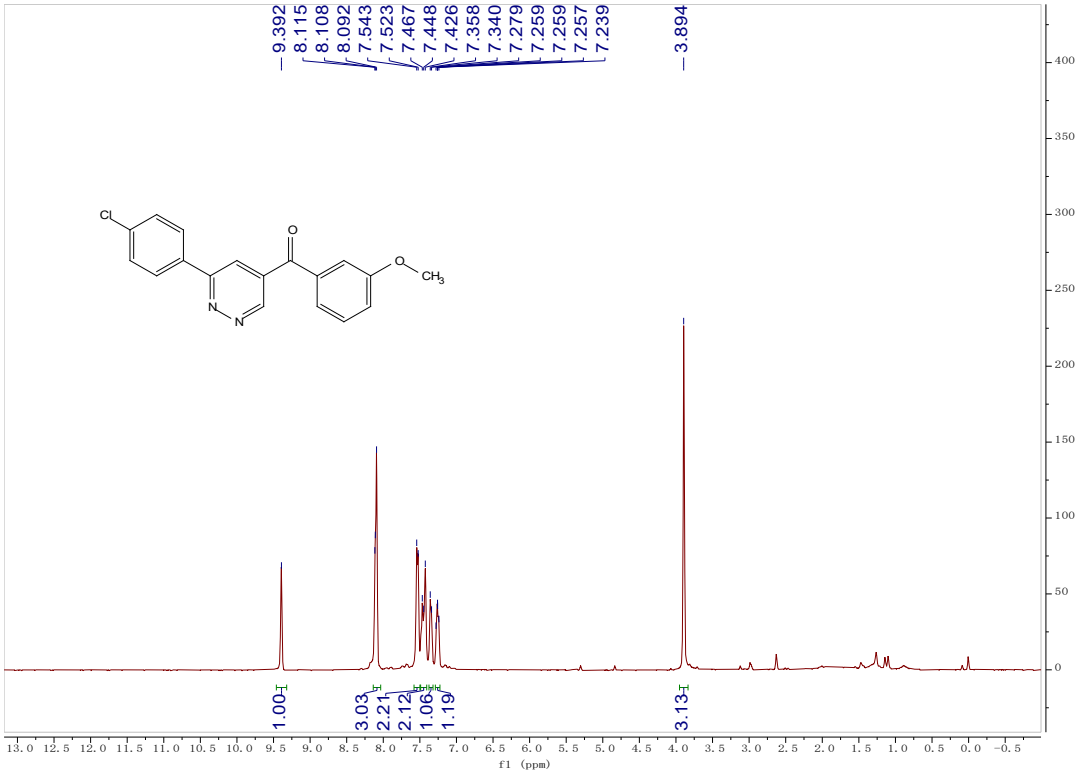

Figure S52. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6f**

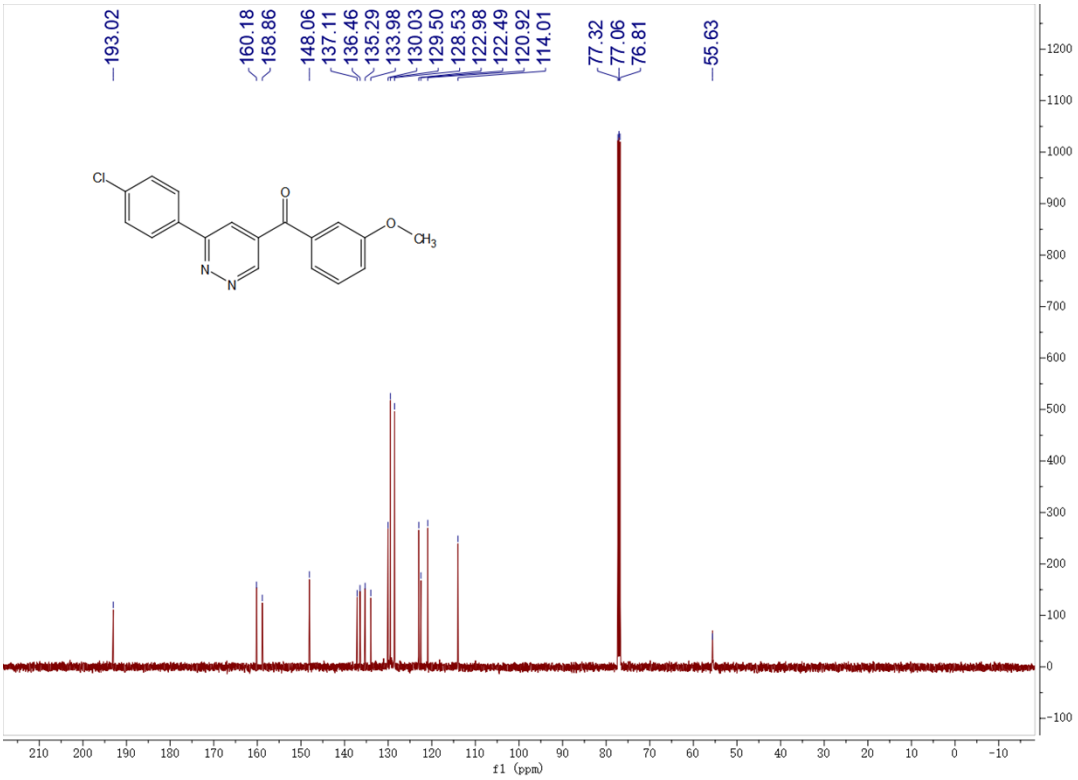

Figure S53. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **6f**

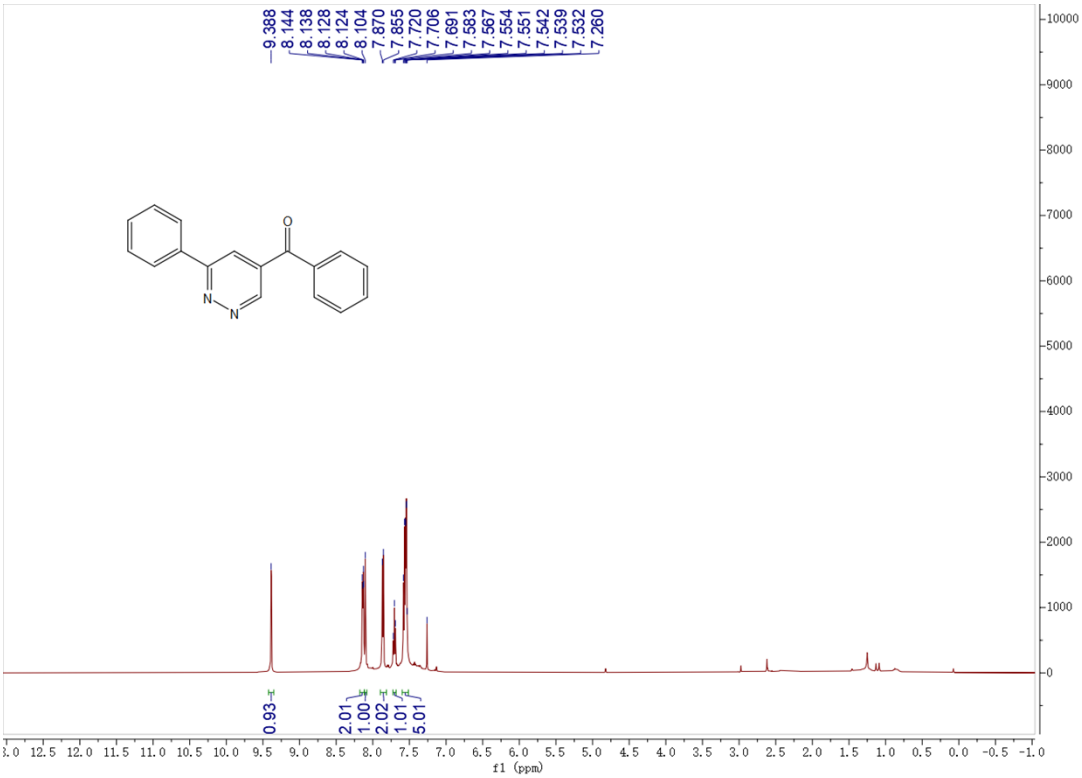

Figure S54. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **6g**

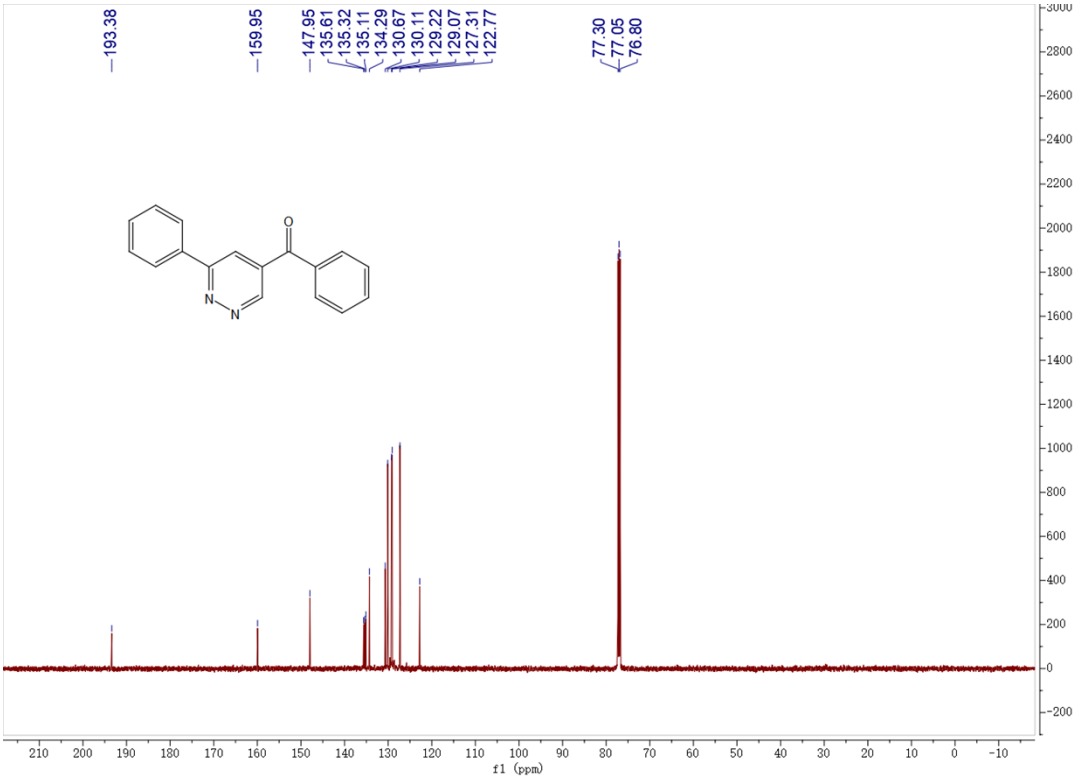

Figure S55. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **6g**

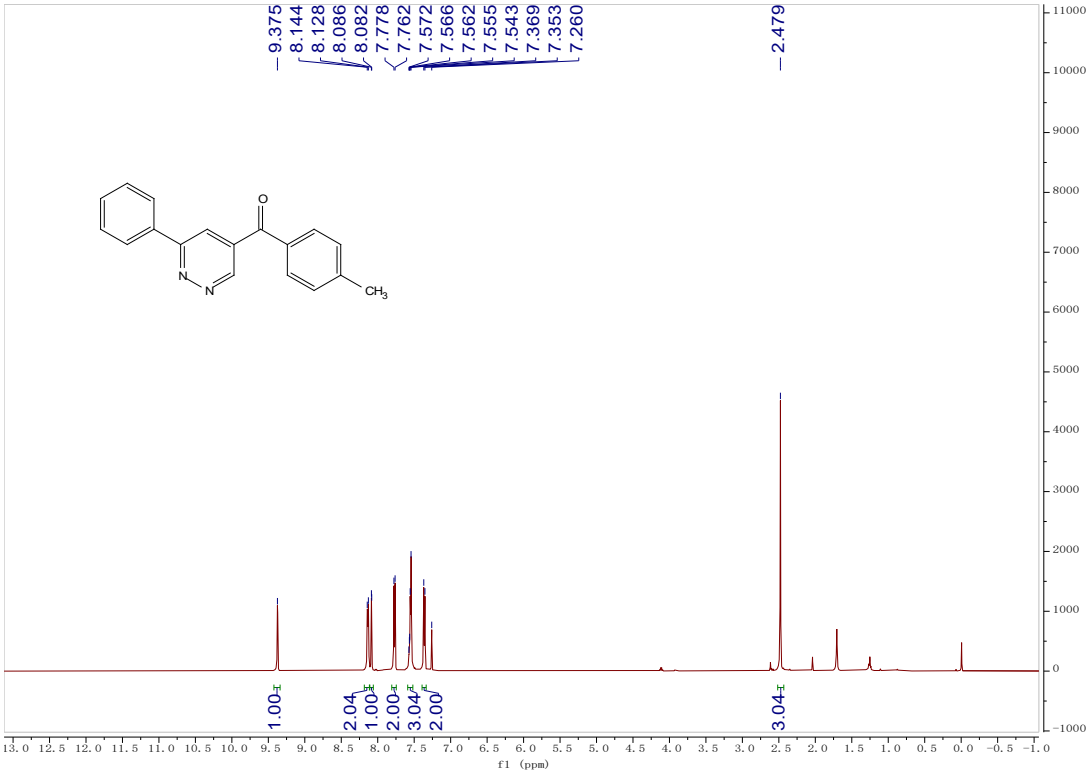

Figure S56. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **6h**

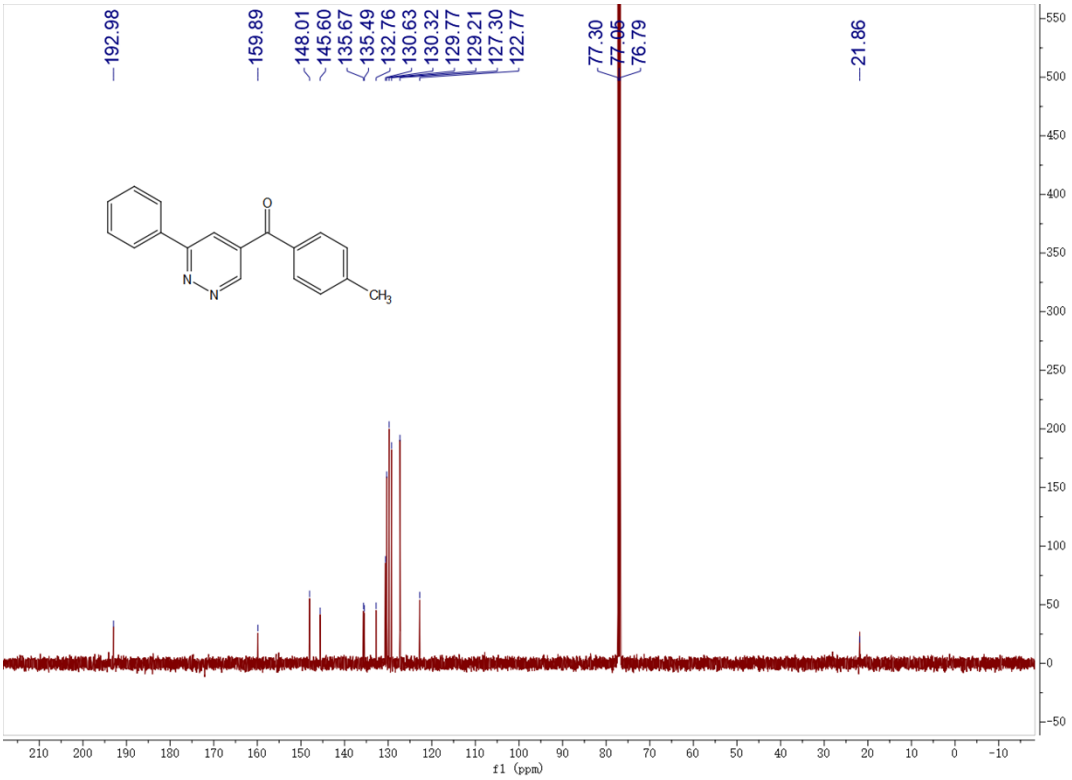

Figure S57. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **6h**

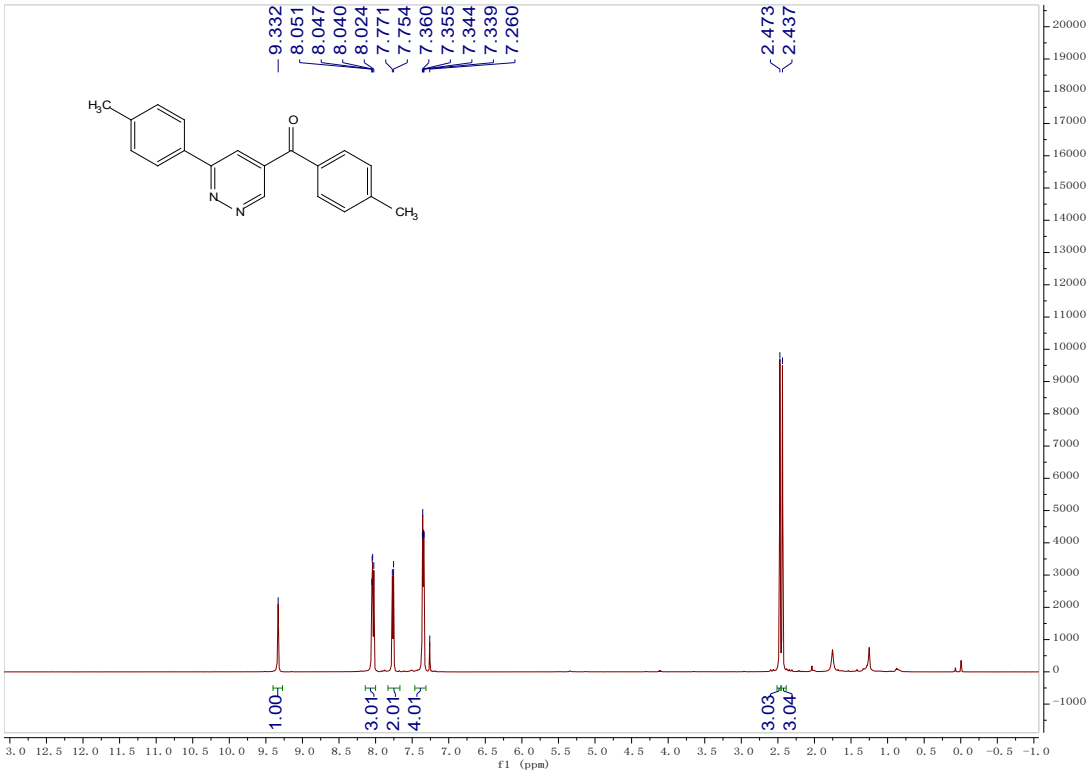

Figure S58. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **6i**

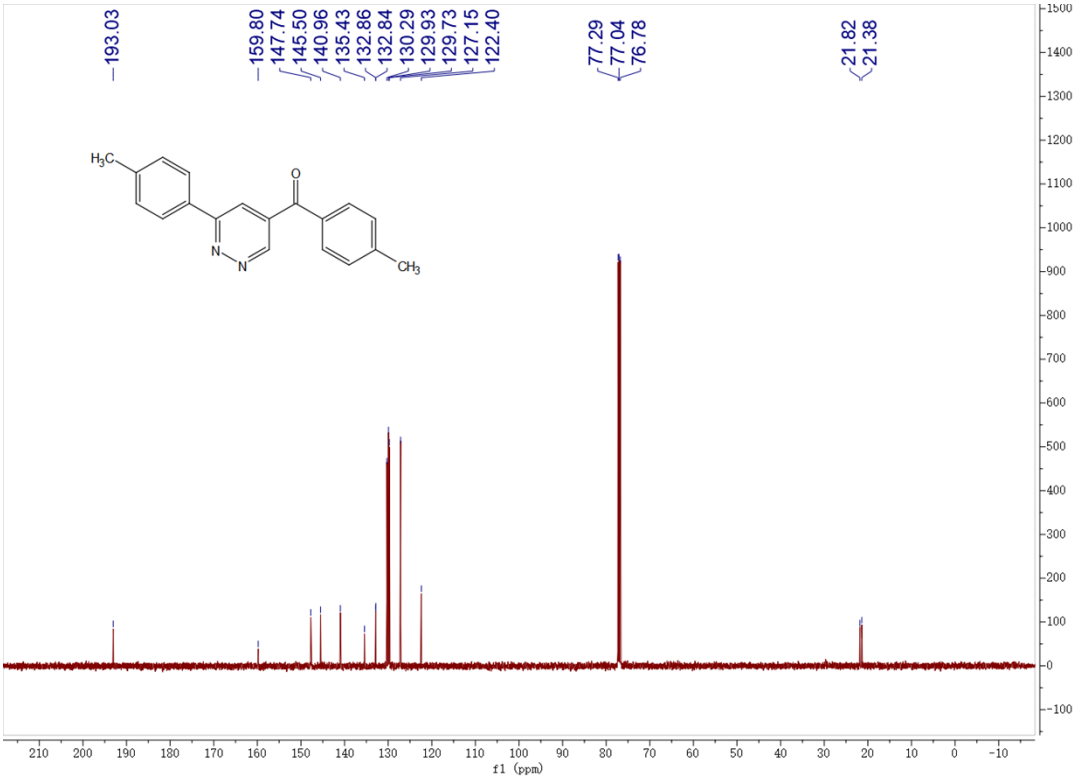

Figure S59. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **6i**

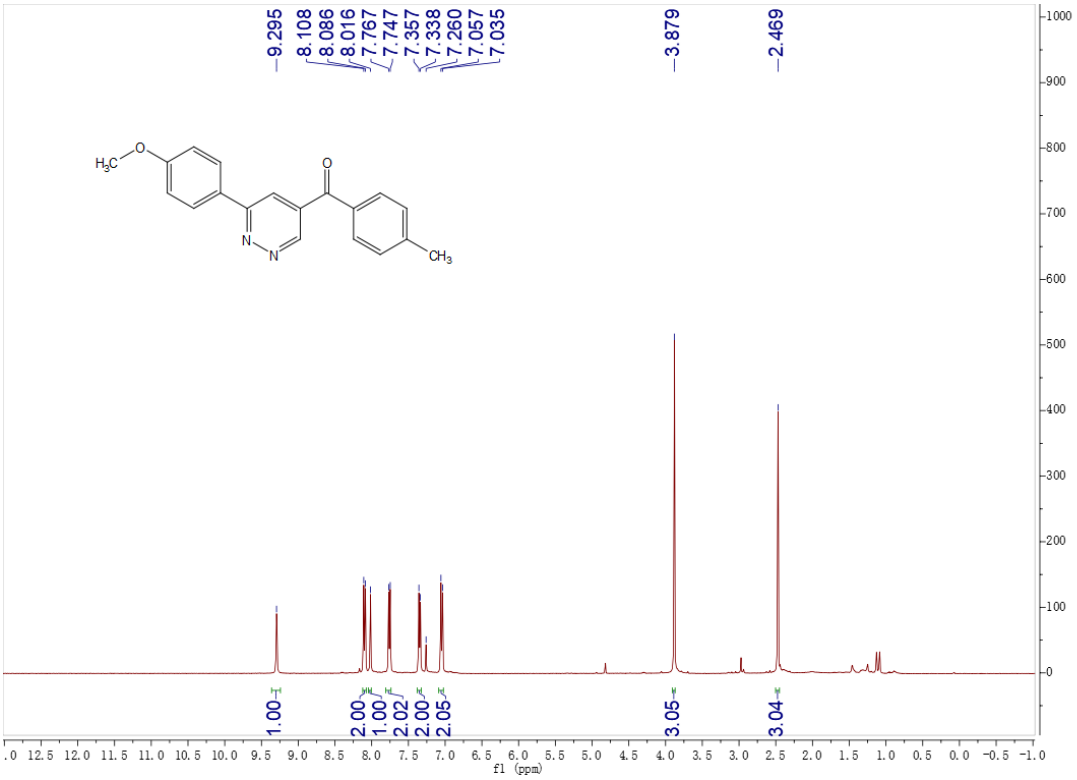

Figure S60. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6j**

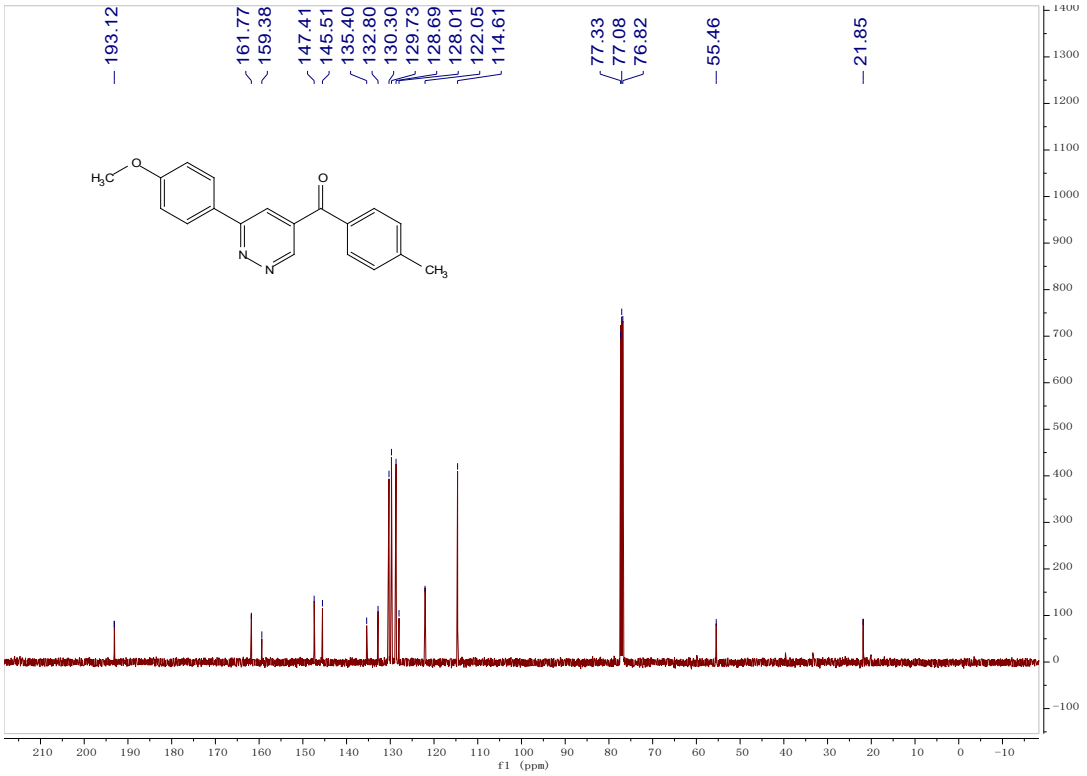

Figure S61. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **6j**

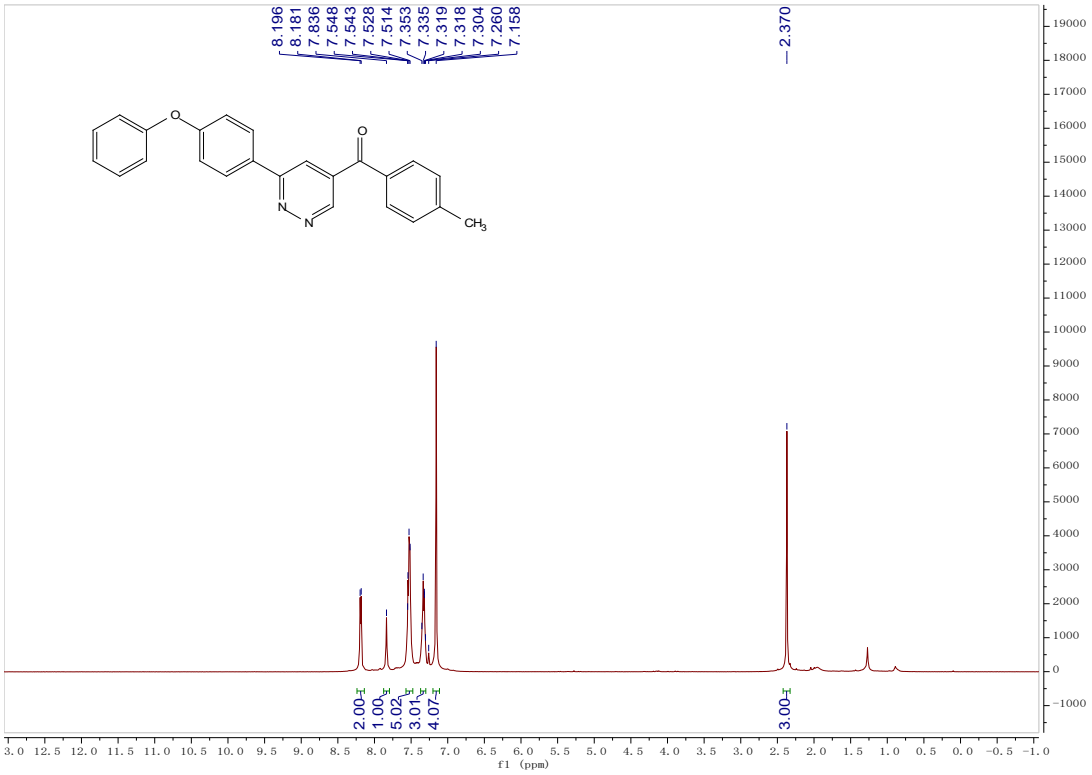

Figure S62. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **6k**

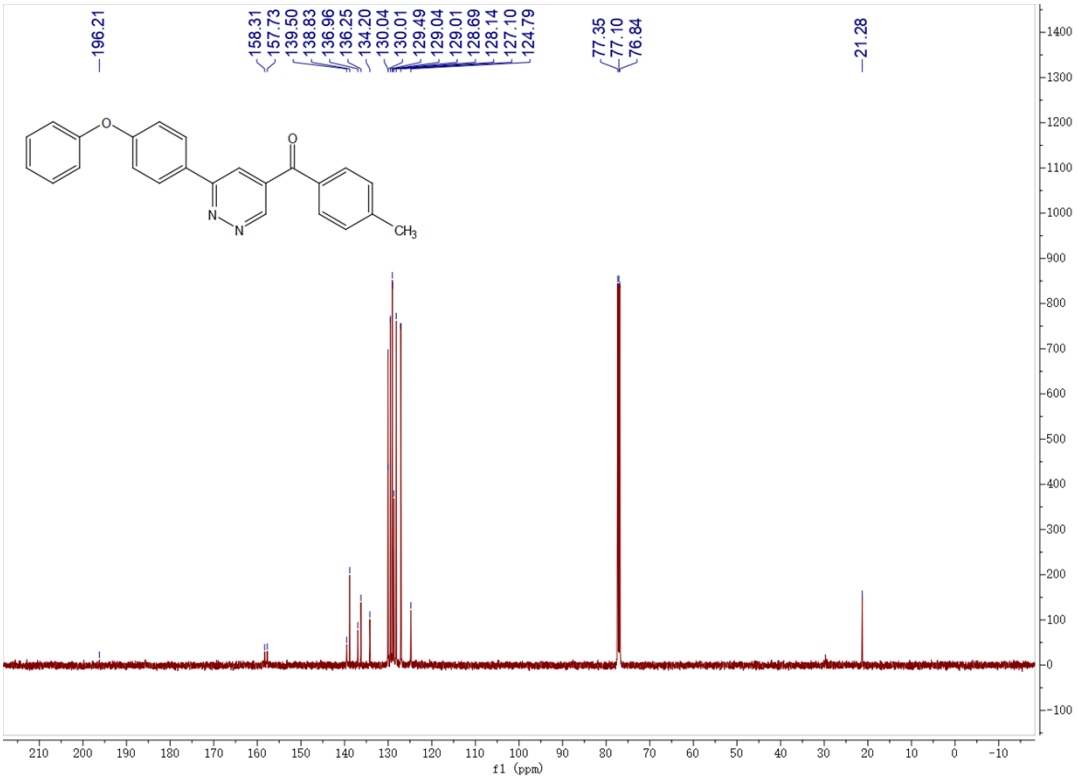

Figure S63. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **6k**

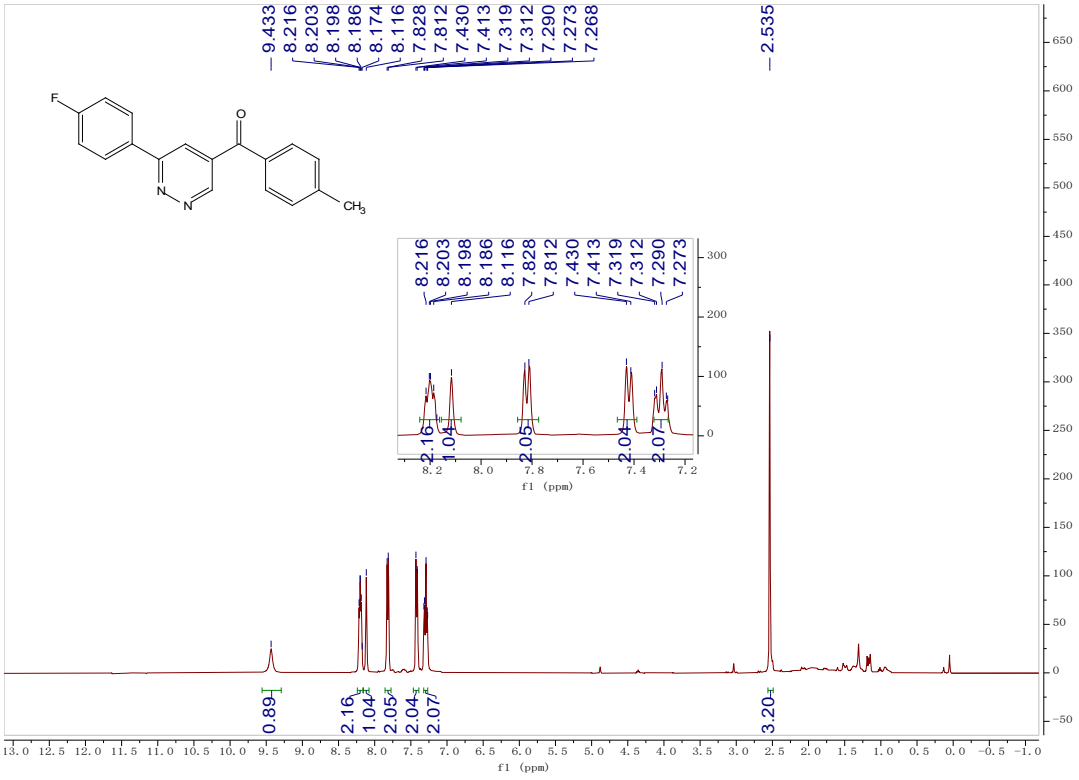

Figure S64. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6l**

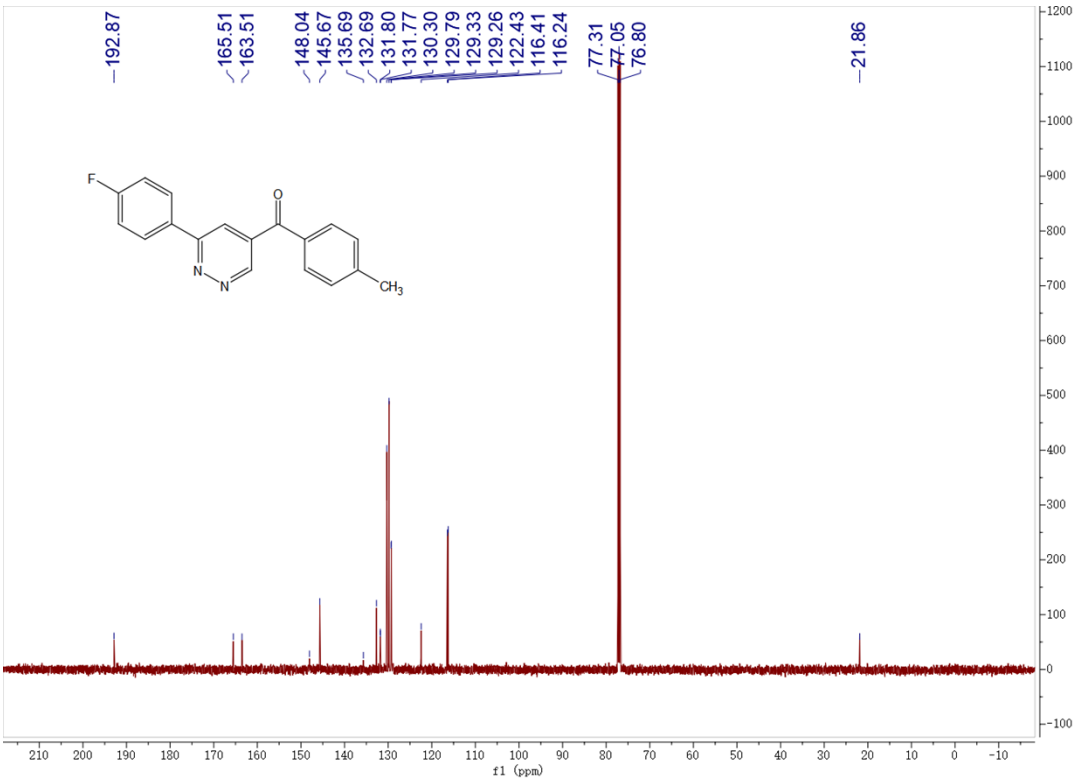

Figure S65. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **6l**

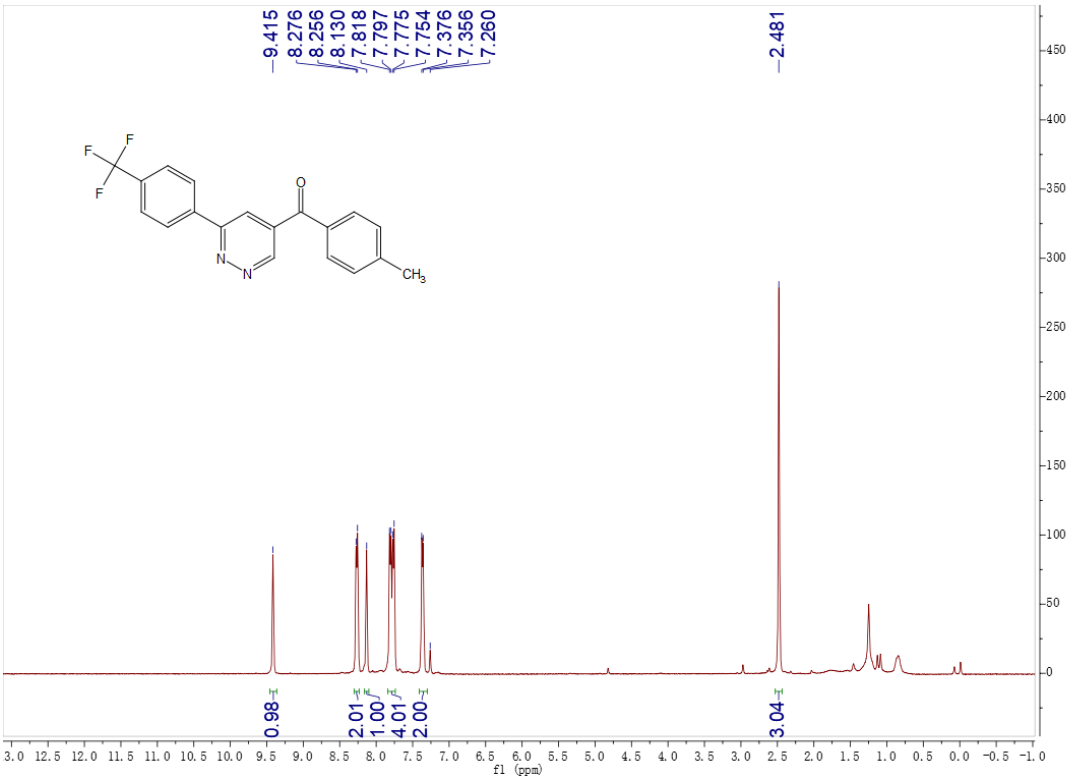

Figure S66. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6m**

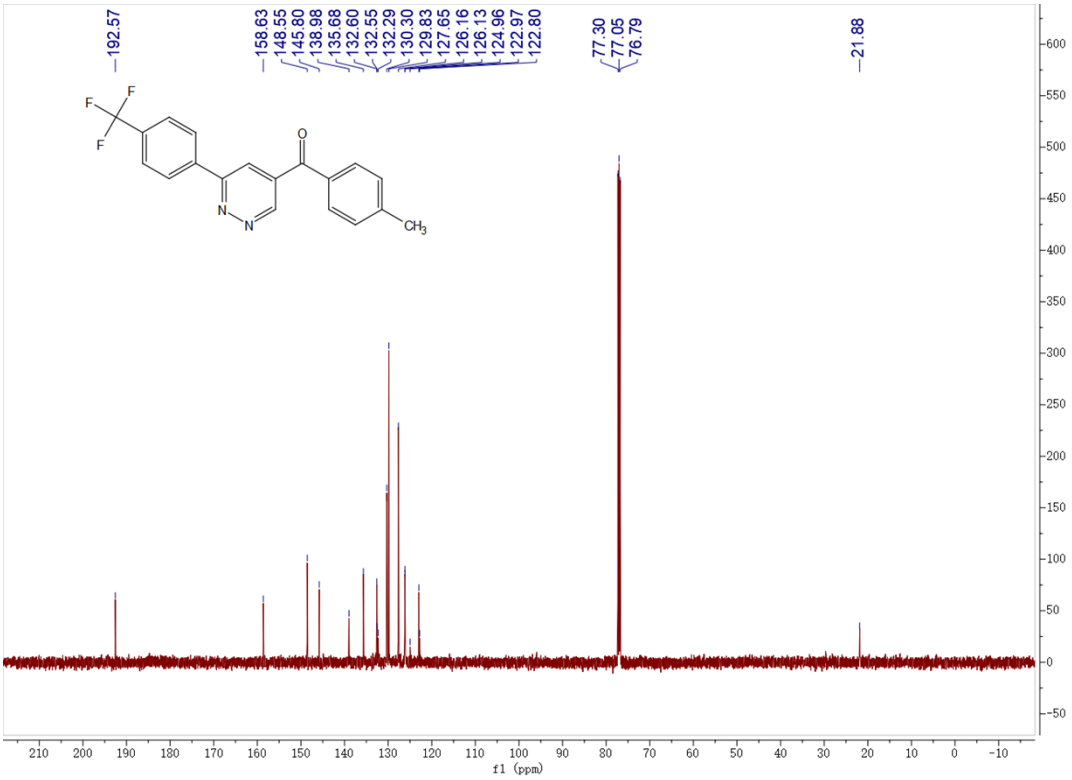

Figure S67. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **6m**

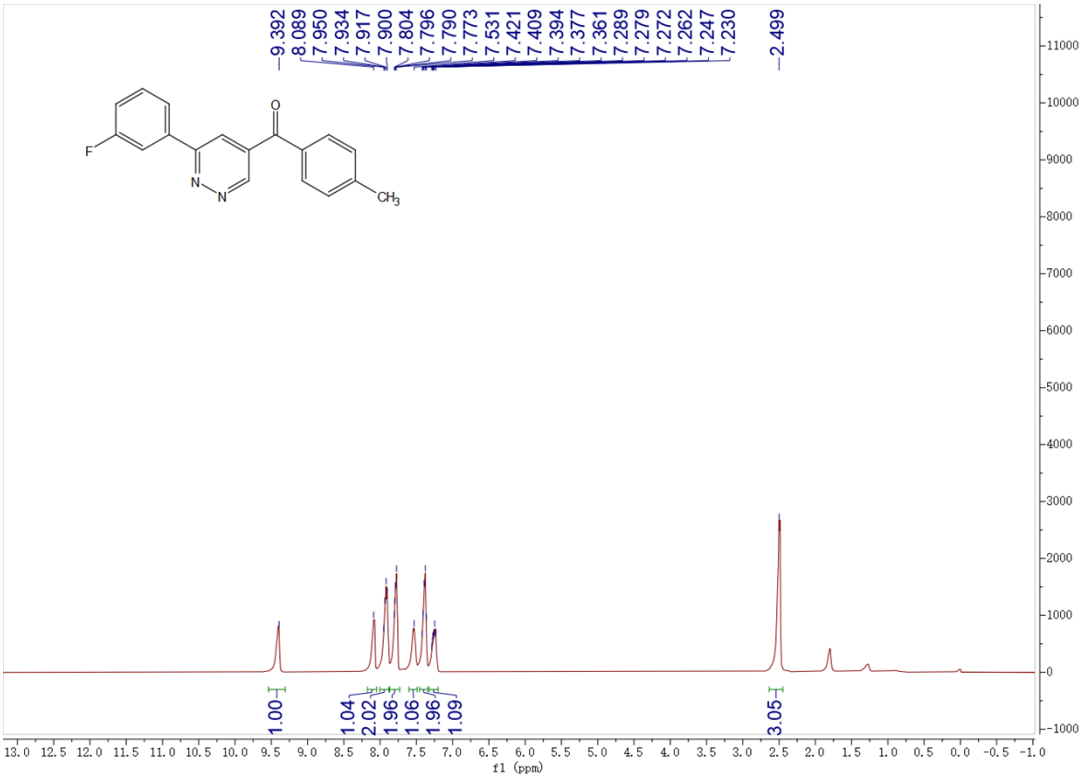

Figure S68. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **6n**

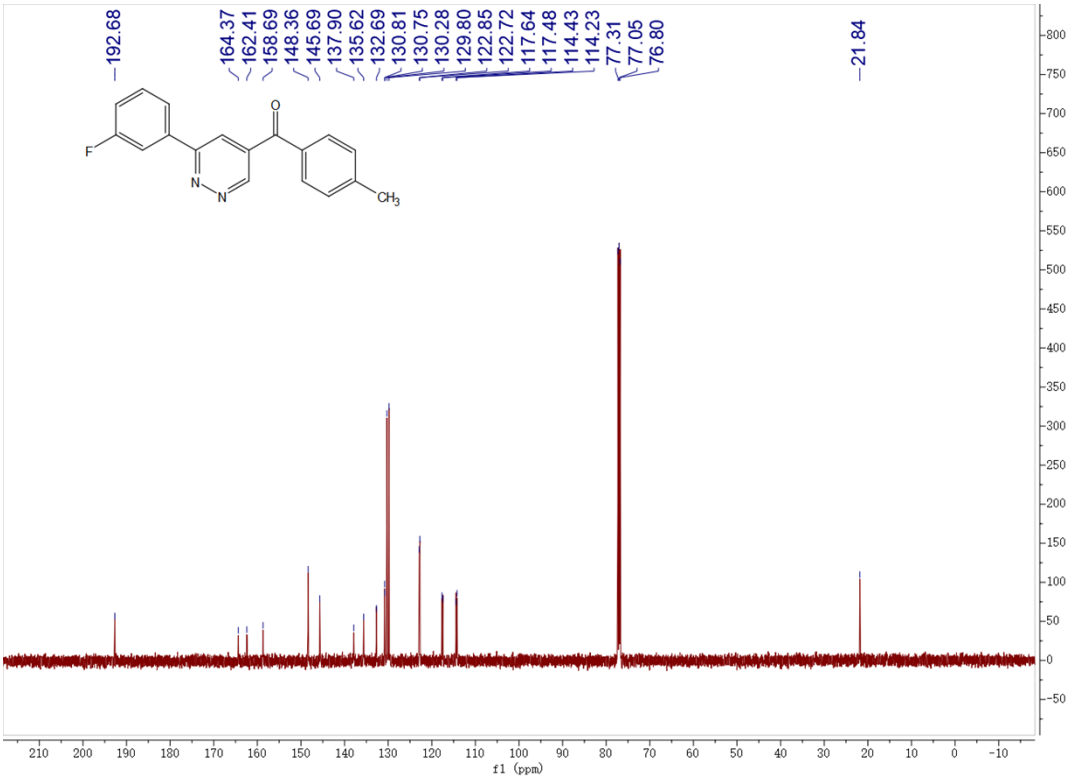

Figure S69. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **6n**

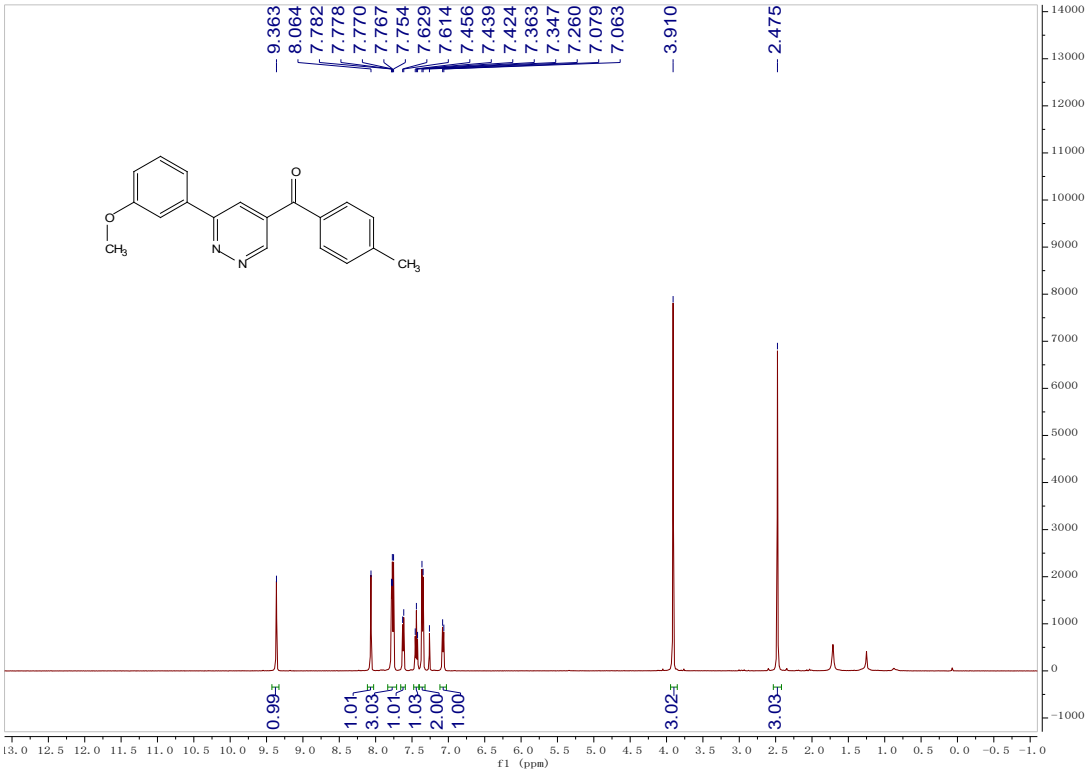

Figure S70. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **6o**

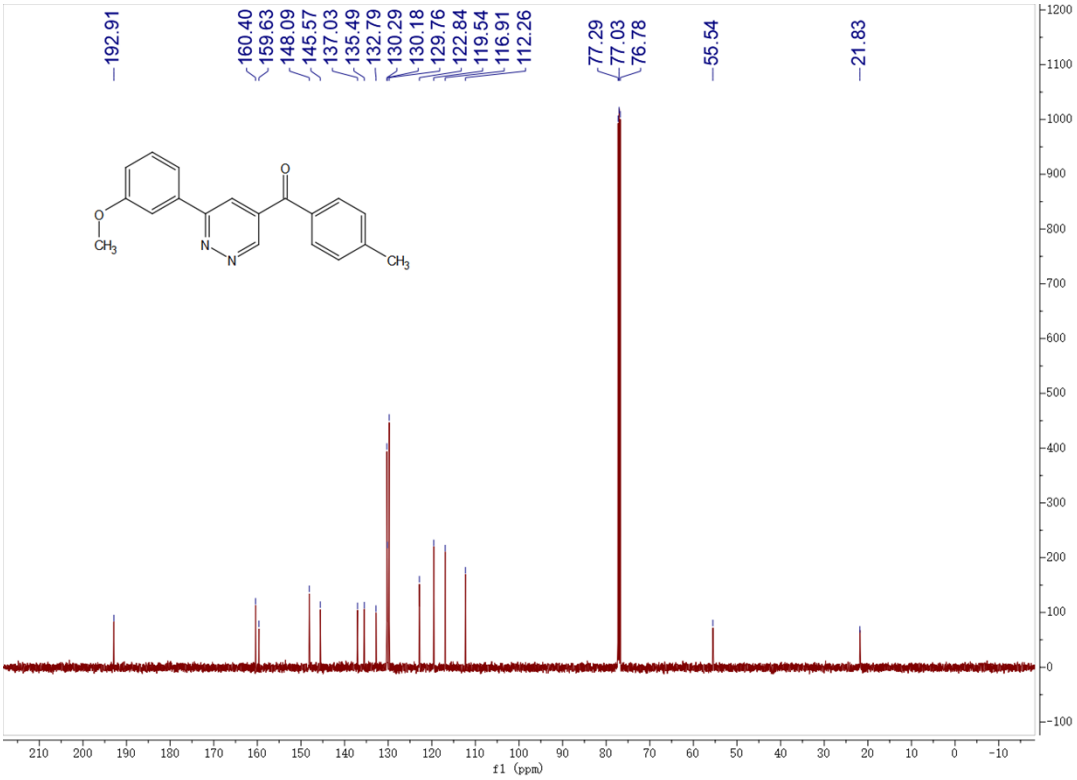

Figure S71. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **6o**

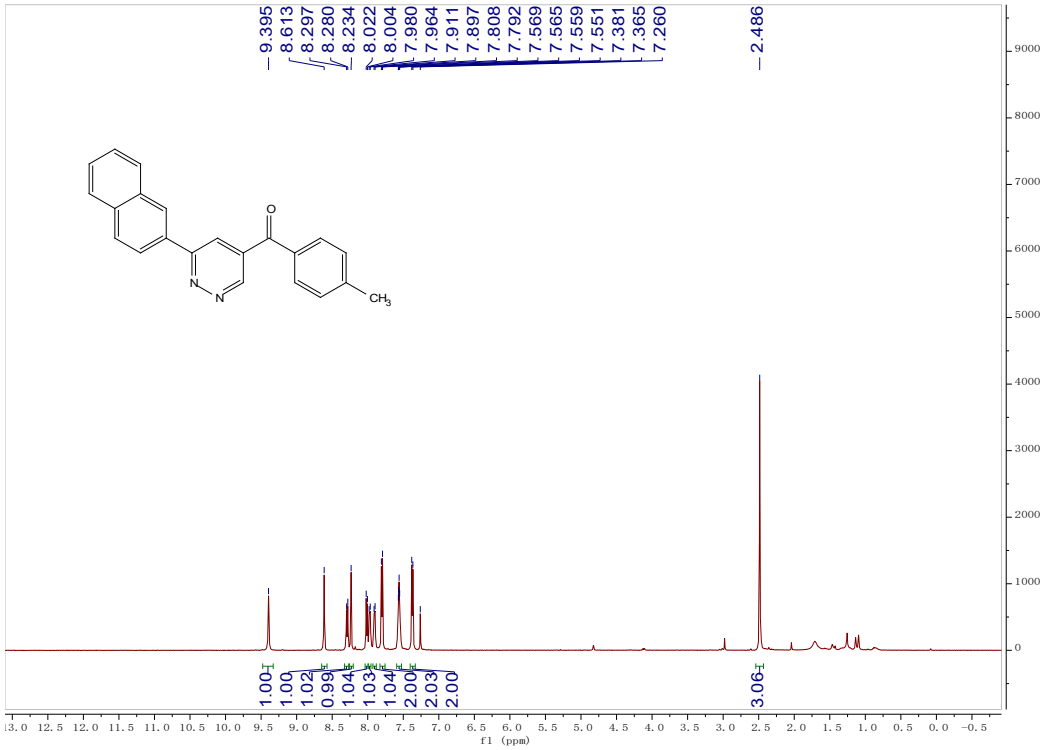

Figure S72. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **6p**

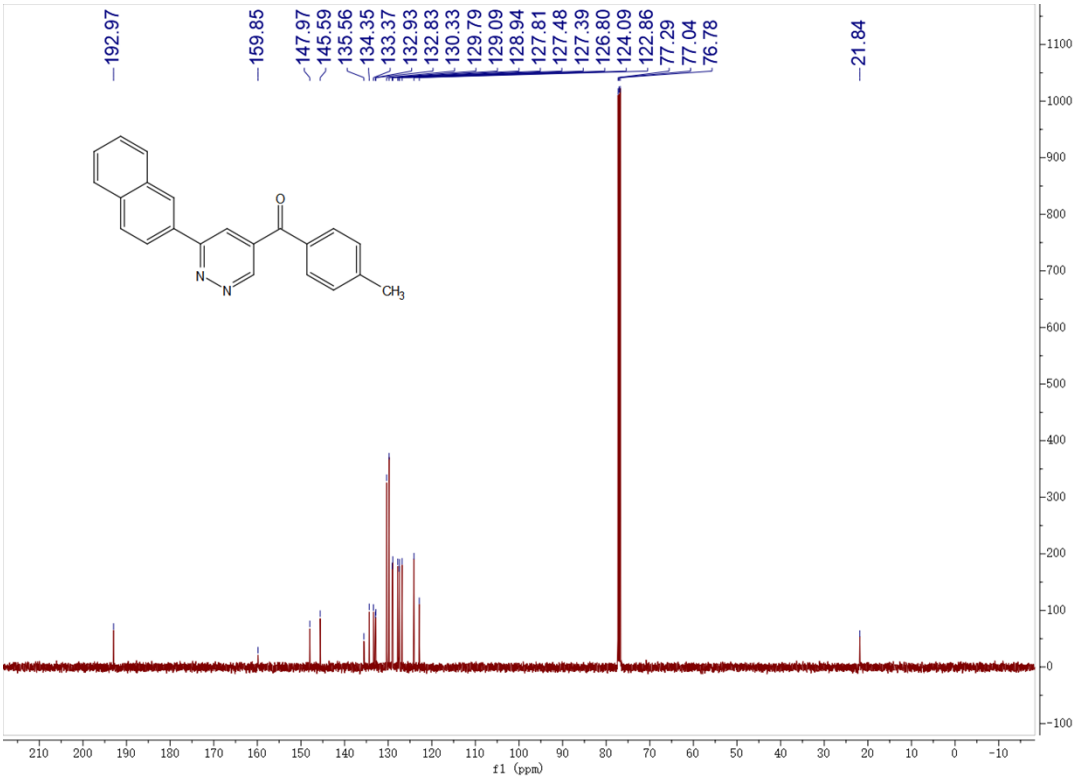

Figure S73. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **6p**

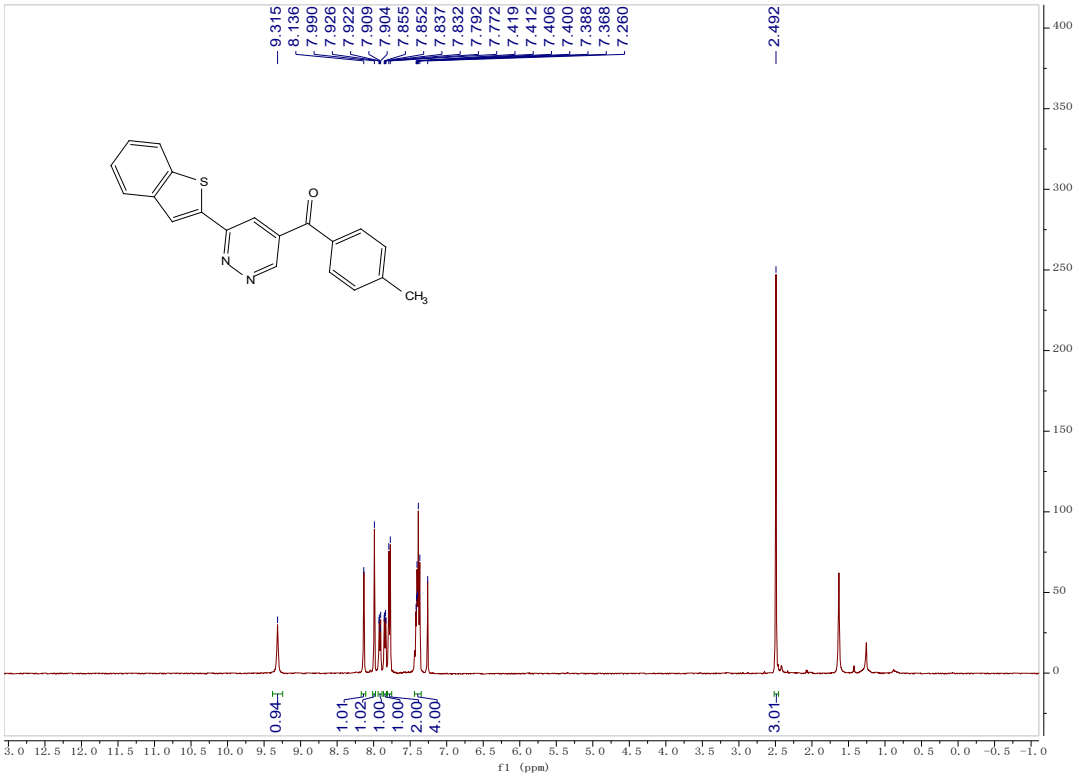

Figure S74. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6q**

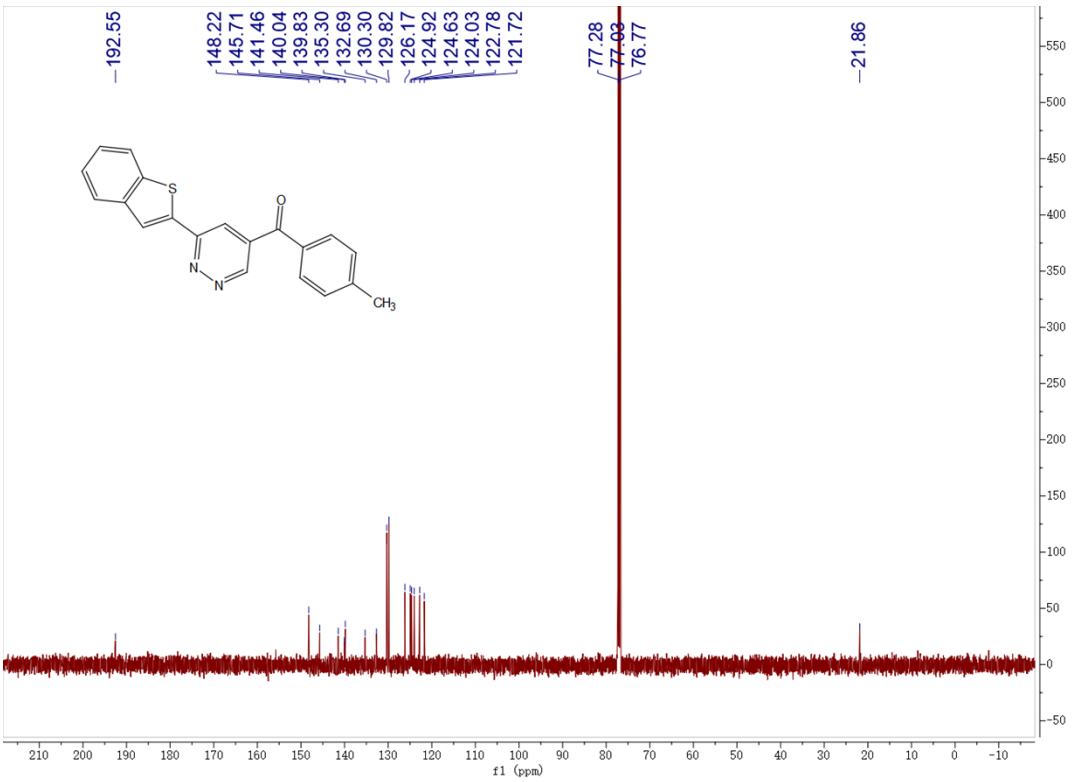

Figure S75. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **6q**

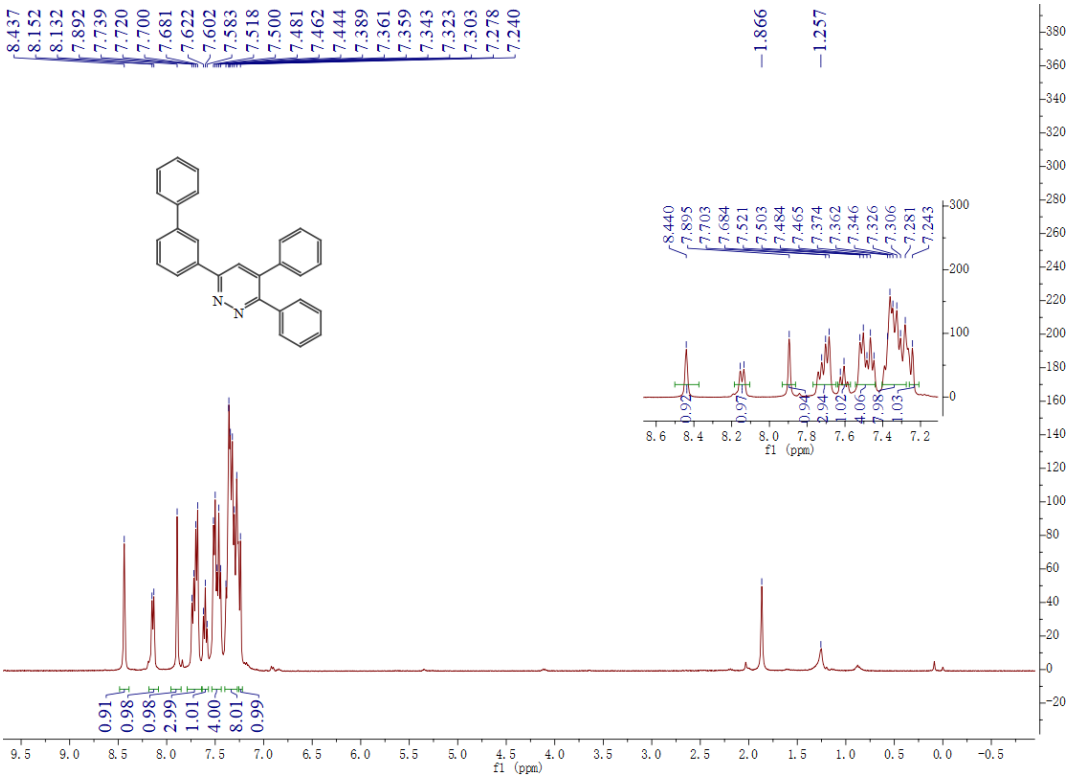

Figure S76. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **3q**

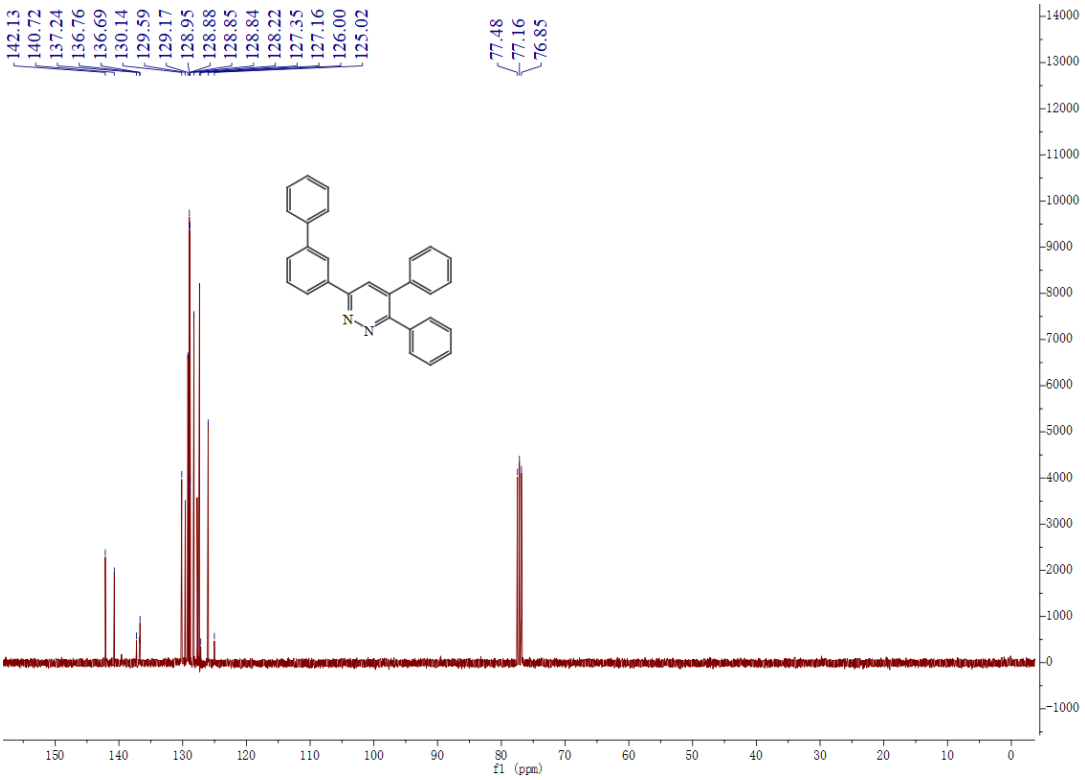

Figure S77. ^{13}C NMR (100 MHz, $CDCl_3$) of compound **3q**

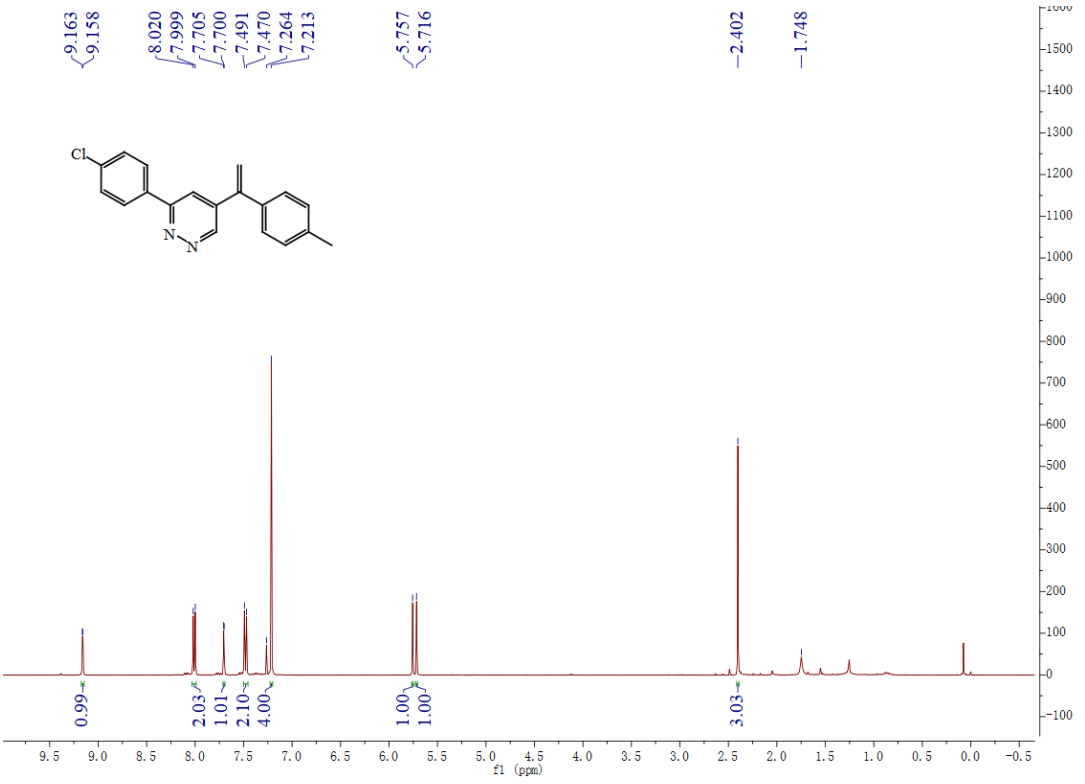

Figure S78. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6r**

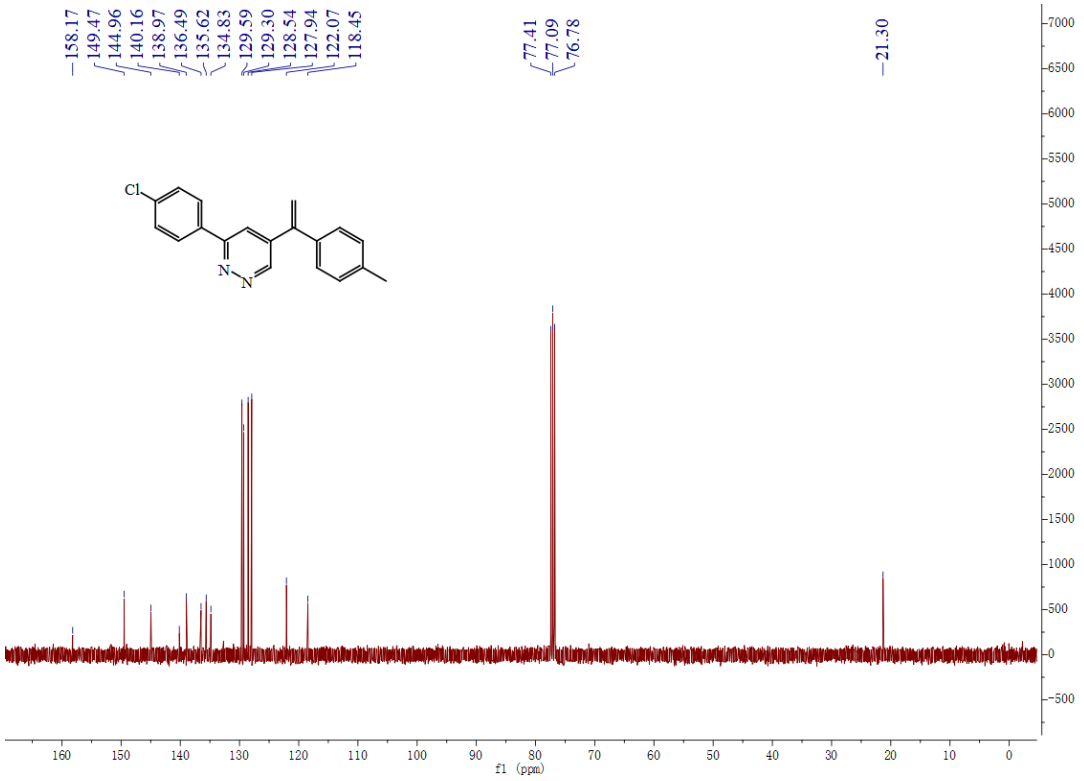

Figure S79. ^{13}C NMR (100 MHz, $CDCl_3$) of compound **6r**

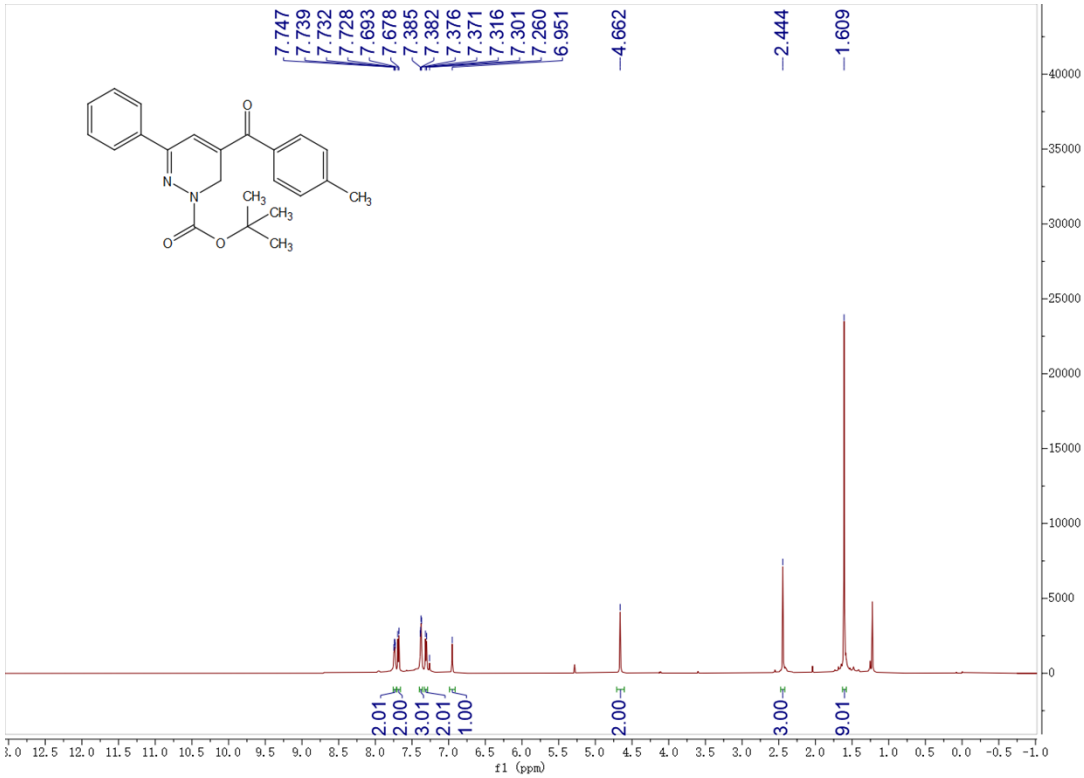

Figure S80. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **6s**

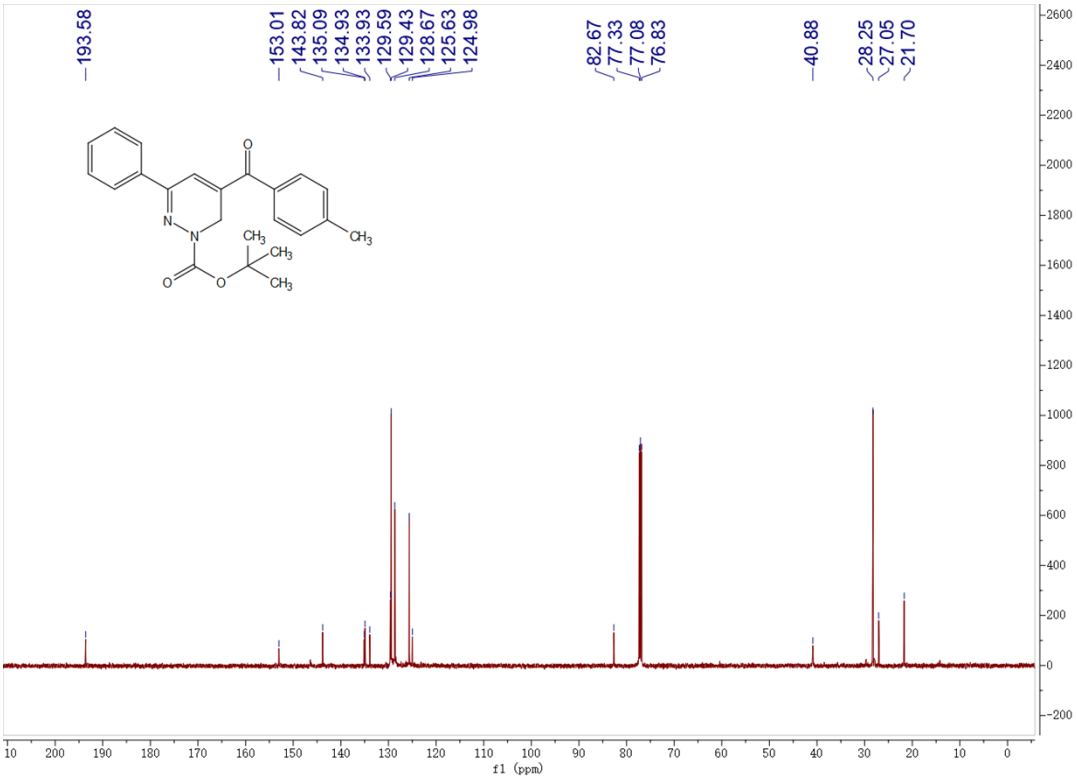

Figure S81. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **6s**