Supporting information

Palladium-Catalyzed C−H/C−H Cross Coupling by Mechanochemistry: Direct Alkenylation and Heteroarylation of *N*1-Protected 1*H*-Indazoles

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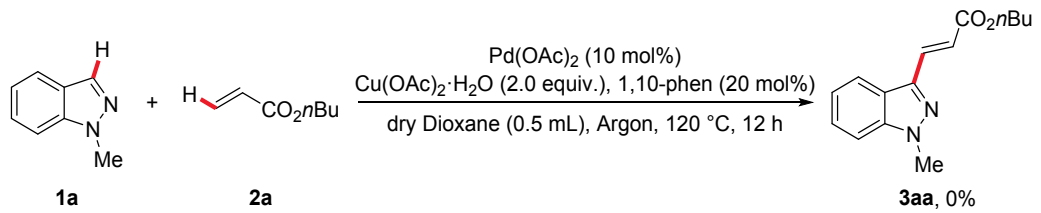
1. Chemical Conditions Optimization



Scheme S1: Model reaction of 1a and 2a under solvent-heating condition. Reaction condition: To **1a** (1.0 mmol), **2a** (2.0 mmol), $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2{\cdot}H_2O$ (2.0 equiv.) and 1,10-phen (20 mol%) were added in dry dioxane (0.5 mL) at room temperature, and then the mixture was stirred at 120 °C under argon for 12 hours.

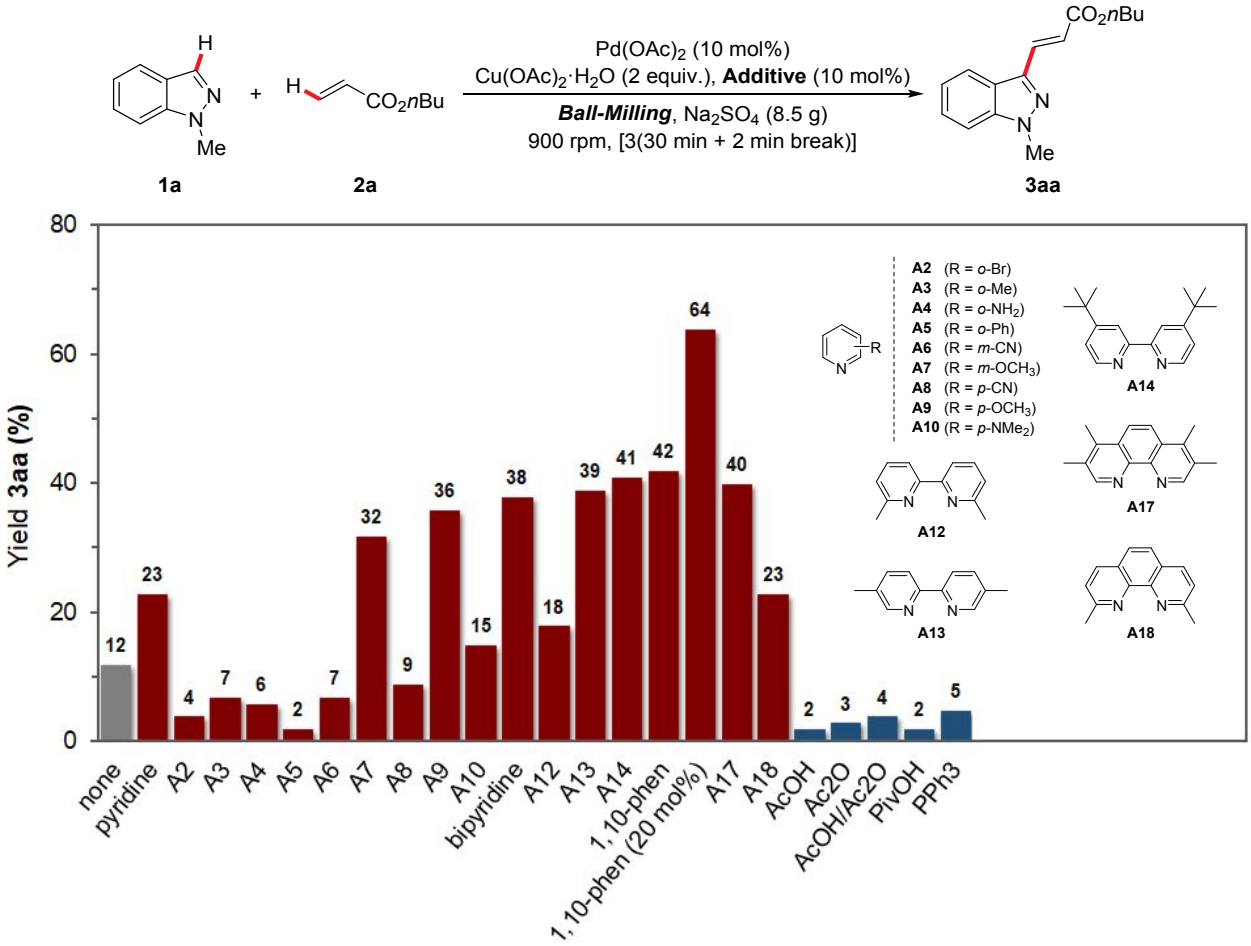
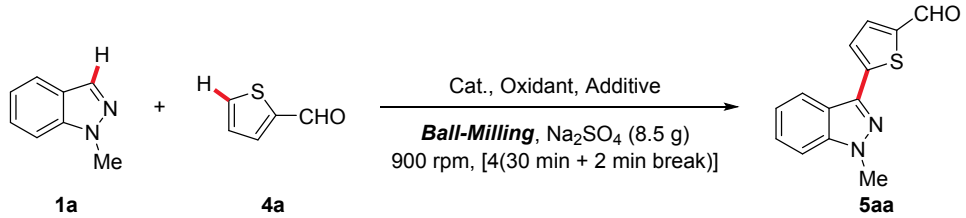


Figure S1. The influences of the additives on the C−H/C−H alkenylation reaction. Reaction conditions: **1a** (1.0 mmol), **2a** (2.0 mmol), $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2{\cdot}H_2O$ (2.0 equiv.), additive (10 mol%) and Na_2SO_4 (8.5 g) at 900 rpm in a planetary mill [3(30 min + 2 min break)], using 138 stainless-steel balls (d_{MB} = 6 mm, Φ_{MB} = 0.228) in a 80 mL stainless steel vial.

Table S1. Optimization of the C−H/C−H heteroarylation reaction[a]



Entry	Catalyst	Oxidant	Additive	Yield (%)
1	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	1,10-phen	9
2	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	–	8
3	$PdCl_2$	$Cu(OAc)_2{\cdot}H_2O$	–	6
4	$Pd(OPiv)_2$	$Cu(OAc)_2{\cdot}H_2O$	–	4
5	$PdCl_2(PPh_3)_2$	$Cu(OAc)_2{\cdot}H_2O$	–	10
6	$Pd(PPh_3)_4$	$Cu(OAc)_2{\cdot}H_2O$	–	9
7	$Pd_2(dba)_3$	$Cu(OAc)_2{\cdot}H_2O$	–	21
8[b]	$Pd_2(dba)_3$	$Cu(OAc)_2{\cdot}H_2O$	–	42
9[b,c]	**$Pd_2(dba)_3$**	**$Cu(OAc)_2{\cdot}H_2O$**	**–**	**45**, 32[d], 25[e]
10	$Pd_2(dba)_3$	Ag_2CO_3	–	10
11	$Pd_2(dba)_3$	AgOAc	–	11
12	$Pd_2(dba)_3$	Ag_2O	–	10
13	$Pd_2(dba)_3$	MnO_2	–	n.d.
14	$Pd_2(dba)_3$	BQ	–	n.d.
15	$Pd_2(dba)_3$	–	–	n.d.
16	–	$Cu(OAc)_2{\cdot}H_2O$	–	n.d.
17	$Pd_2(dba)_3$	$Cu(OAc)_2{\cdot}H_2O$	PPh_3	12
18	$Pd_2(dba)_3$	$Cu(OAc)_2{\cdot}H_2O$	Xphos	10
19	$Pd_2(dba)_3$	$Cu(OAc)_2{\cdot}H_2O$	Sphos	16
20	$Pd_2(dba)_3$	$Cu(OAc)_2{\cdot}H_2O$	pyridine	7
21	$Pd_2(dba)_3$	$Cu(OAc)_2{\cdot}H_2O$	1,10-phen	14
22	$Pd_2(dba)_3$	$Cu(OAc)_2{\cdot}H_2O$	K_2CO_3	11

[a] Reaction conditions: **1a** (1.0 mmol), **4a** (2.0 mmol), catalyst (10 mol%), oxidant (2.0 equiv.), additive (20 mol%) and Na_2SO_4 (8.5 g) at 900 rpm in a planetary mill [4(30 min + 2 min break)], using 448 stainless-steel balls (d_{MB} = 4 mm, Φ_{MB} = 0.228) in a 80 mL stainless steel vial. [b] $Pd_2(dba)_3$ (20 mol%). [c] $Cu(OAc)_2{\cdot}H_2O$ (1.5 equiv.). [d] **4a** (1.5 equiv.). [e] **4a** (1.0 equiv.).

2. Mechanical Parameters Screening

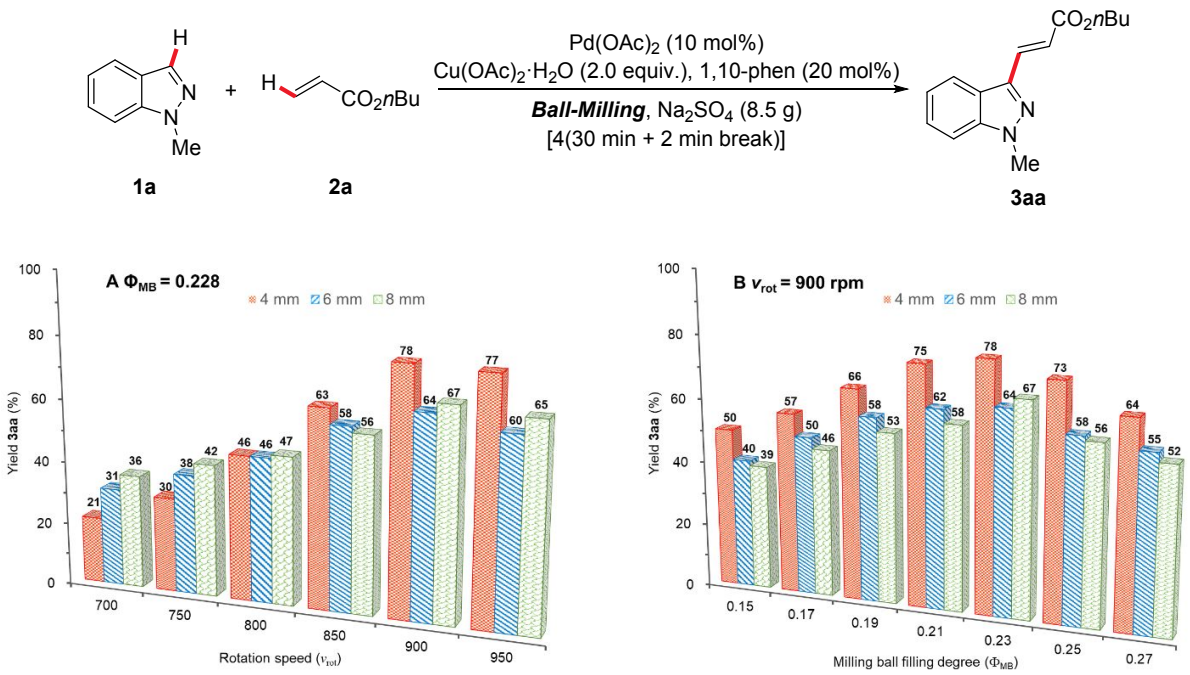
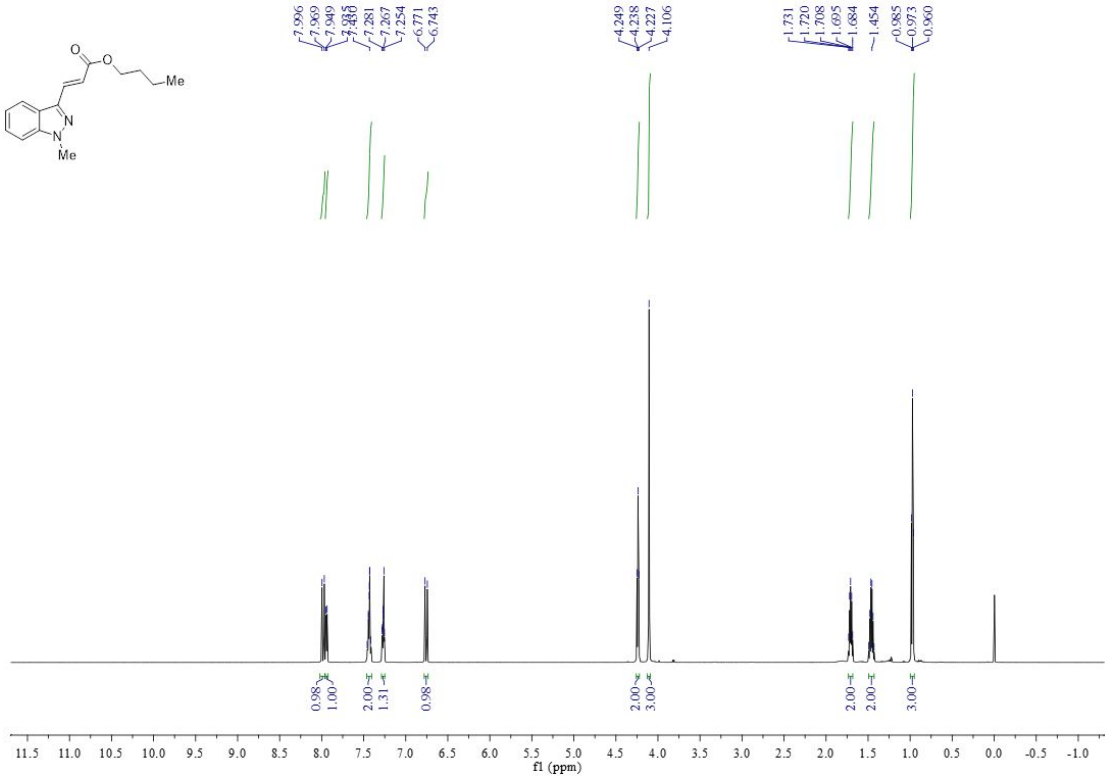
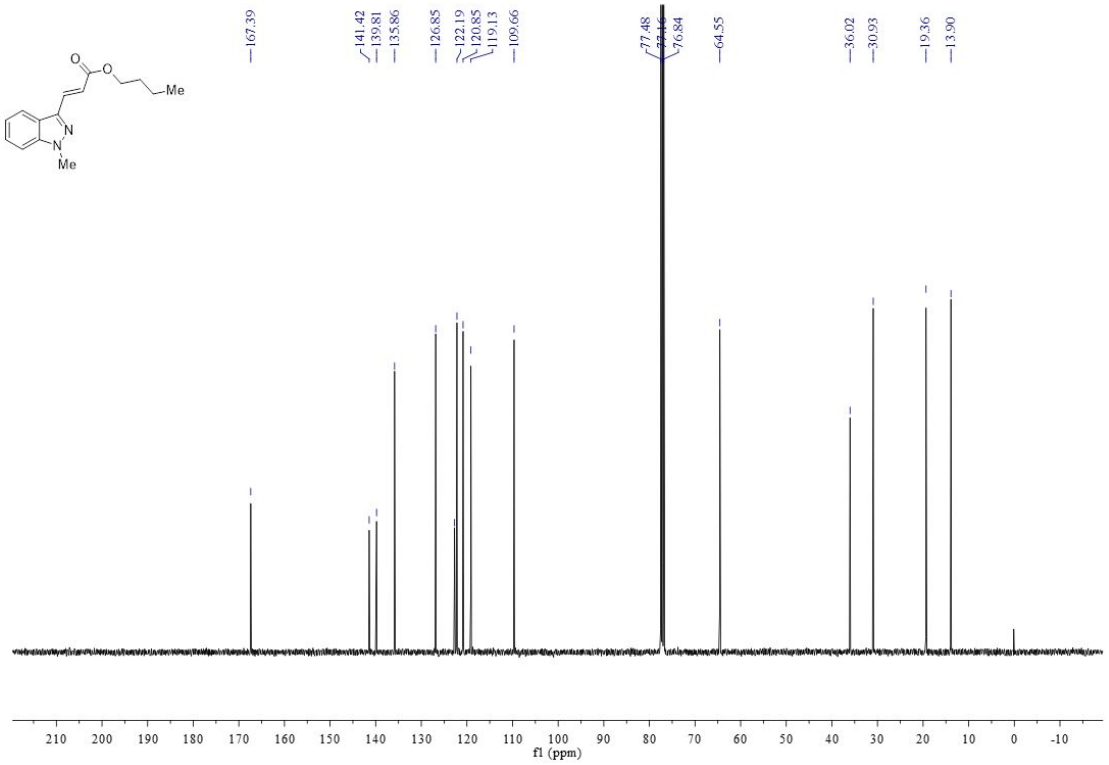


Figure S2. The influences of milling ball filling degree (Φ_{MB}), rotation speed (v_{rot}), and milling-ball size (d_{MB}) on the C−H/C−H alkenylation reaction. Reaction conditions: **1a** (1.0 mmol), **2a** (2.0 mmol), $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2{\cdot}H_2O$ (2.0 equiv.), 1,10-phen (20 mol%) and Na_2SO_4 (8.5 g), at specific rotation speed in a planetary mill [4(30 min + 2 min break)], using specific size stainless-steel balls in a 80 mL stainless steel vial.

3. NMR Spectra

***Butyl (E)-3-(1-methyl-1H-indazol-3-yl)acrylate* (3aa)**





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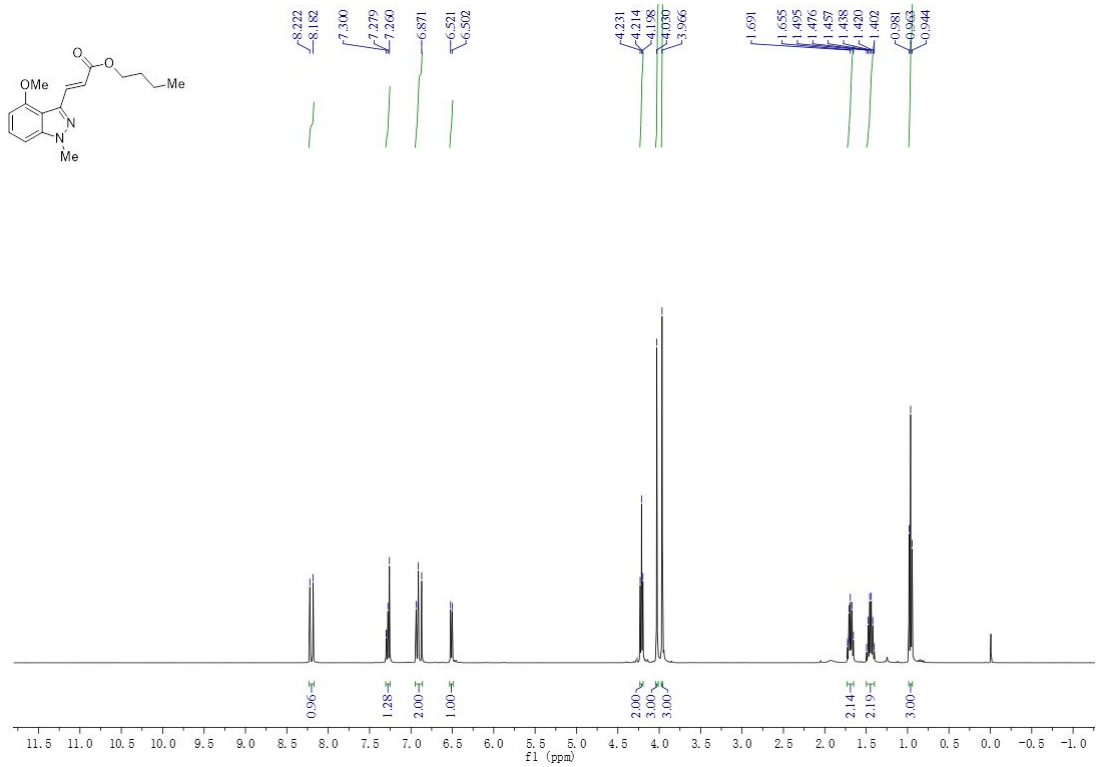

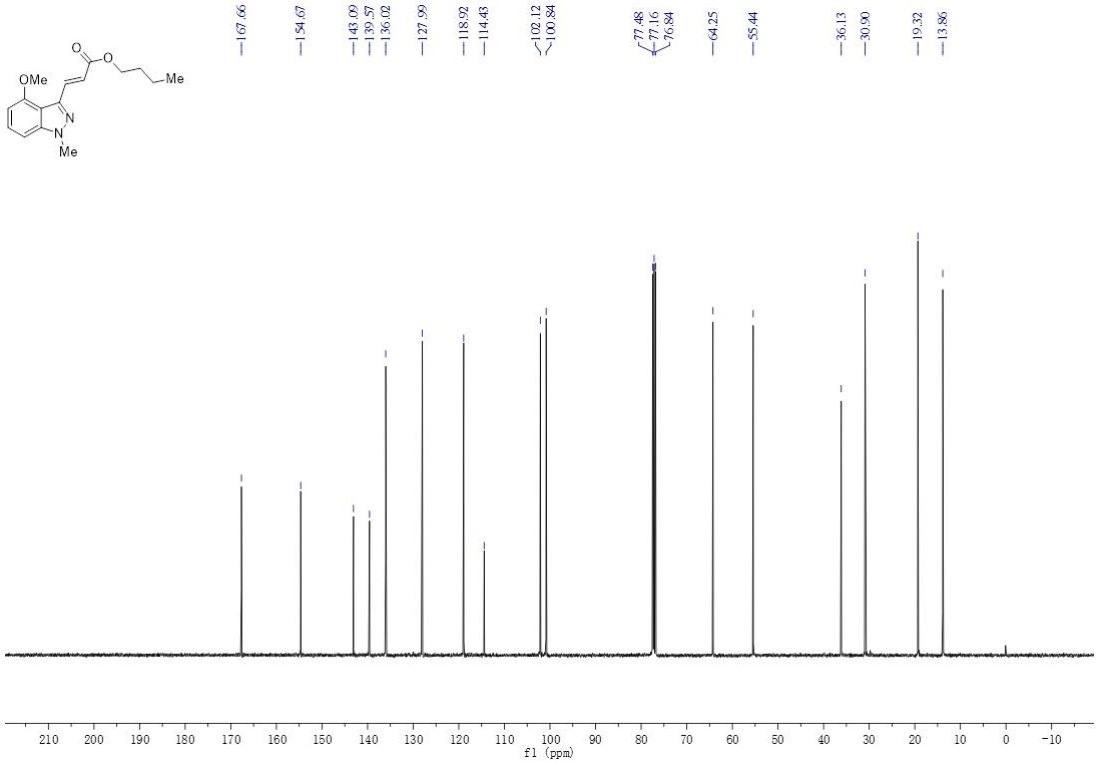

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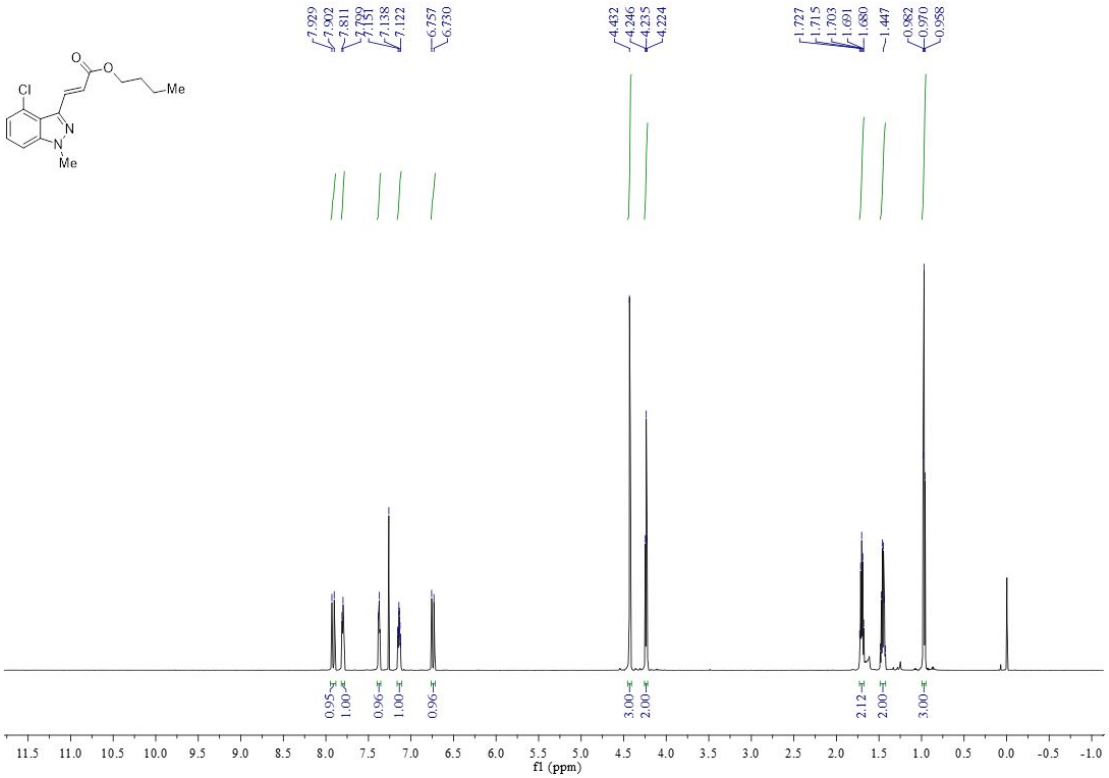

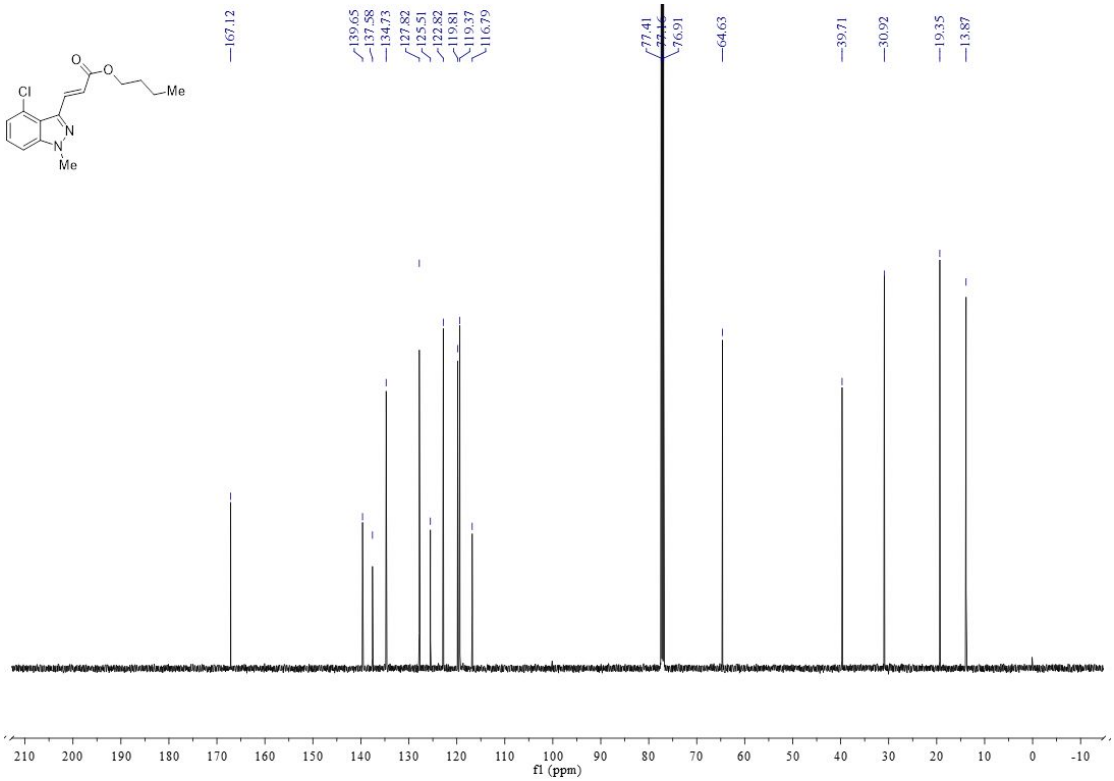

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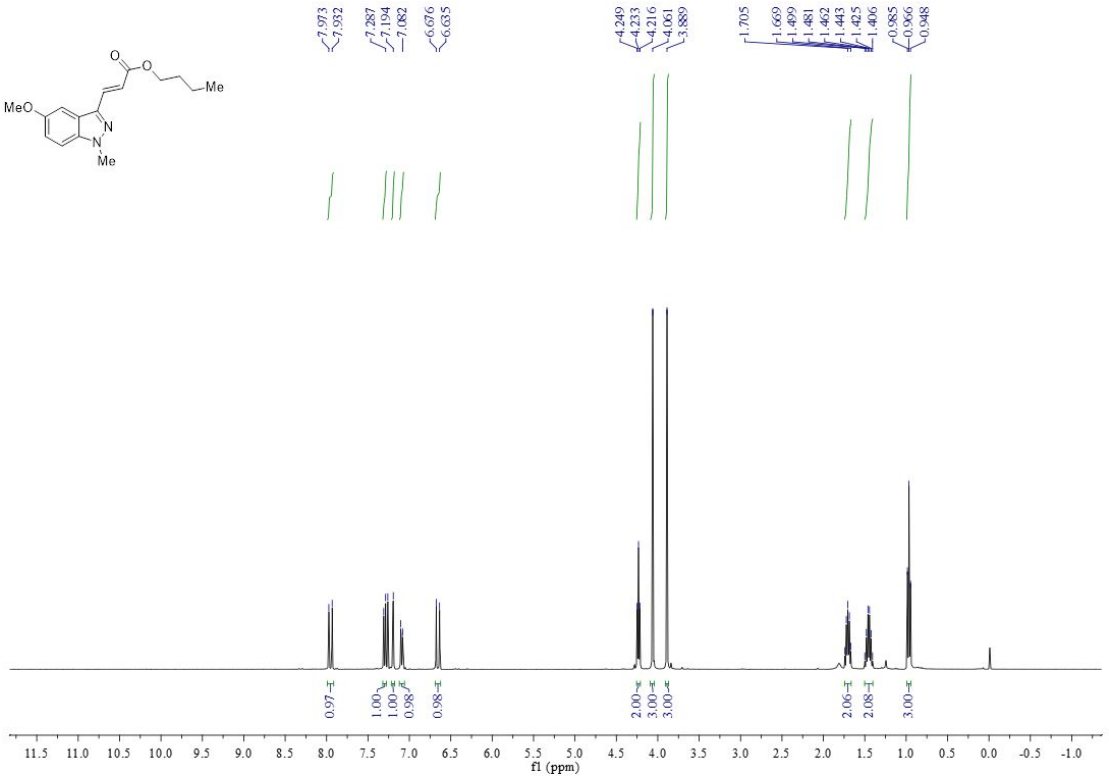
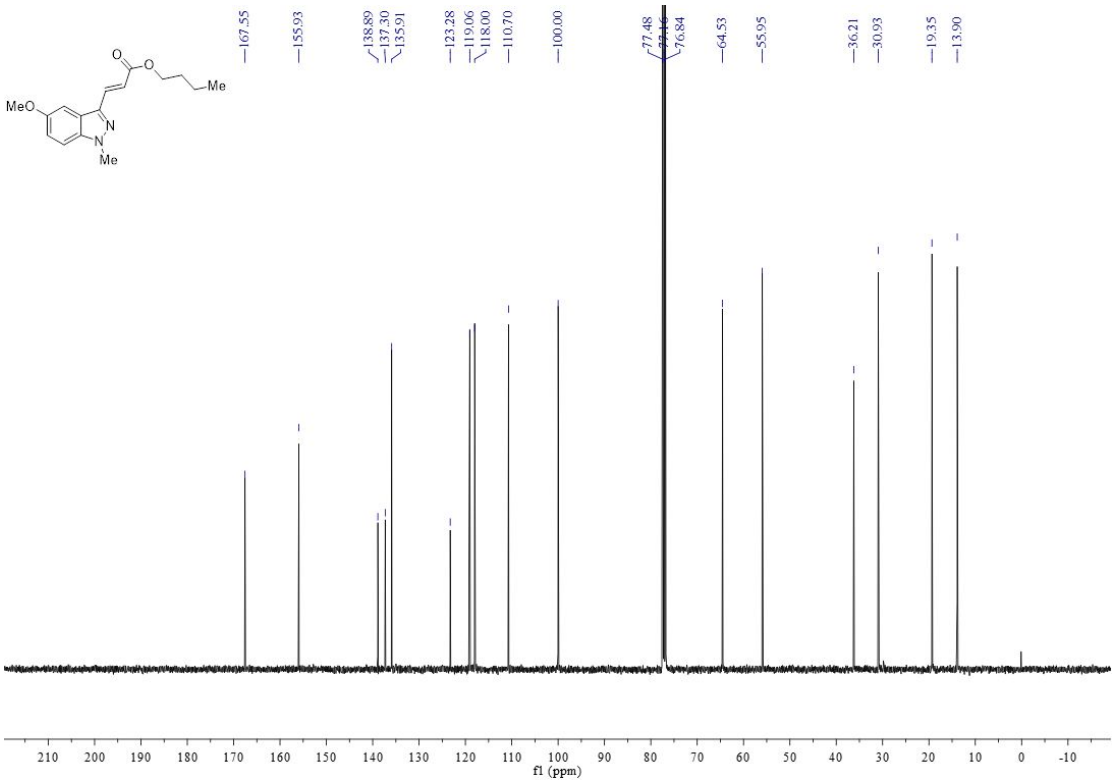
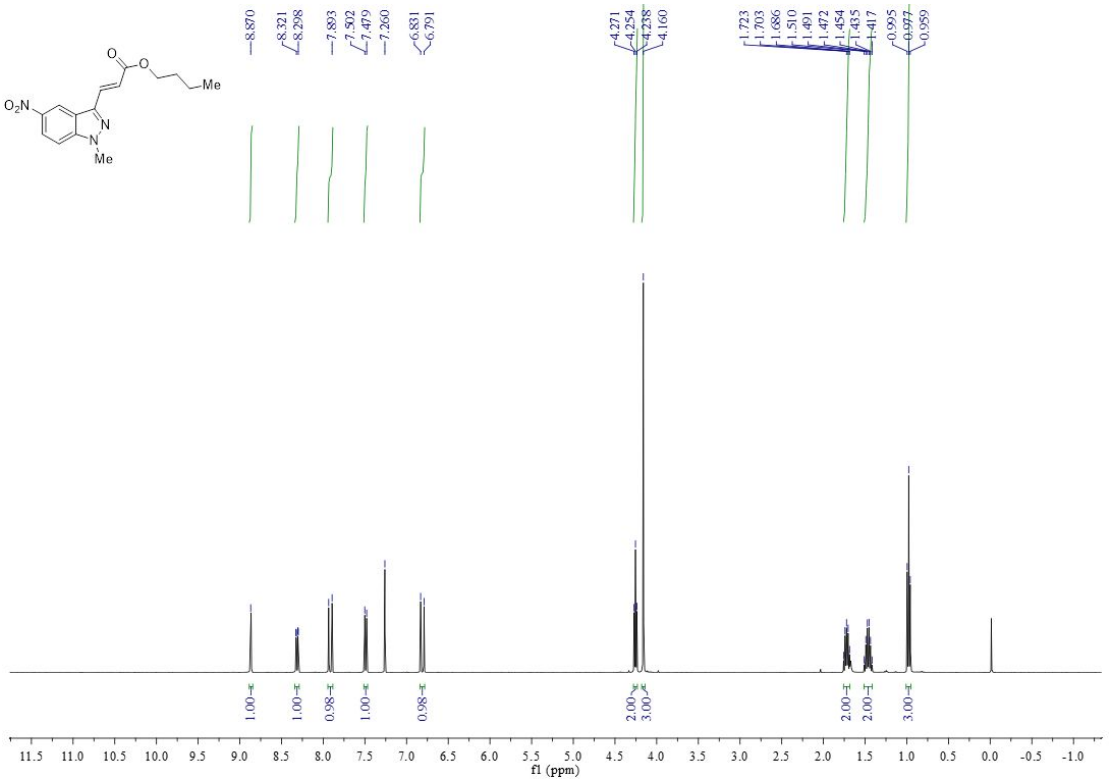
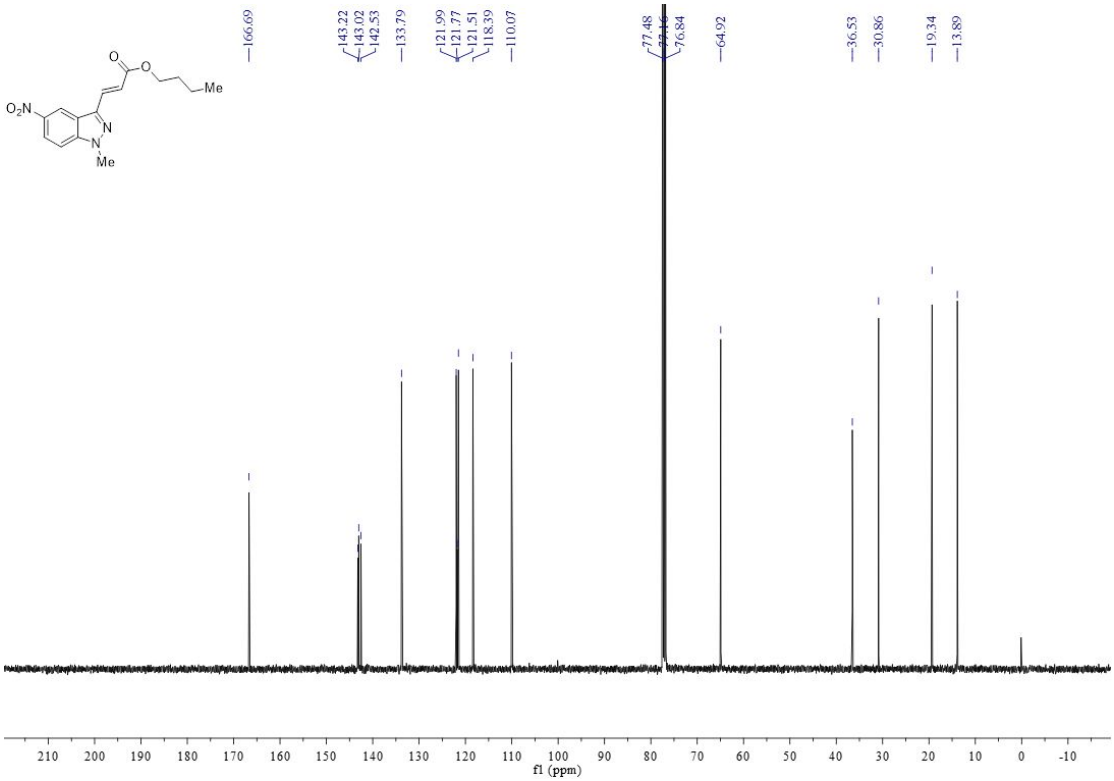




Butyl (E)-3-(1-methyl-5-nitro-1H-indazol-3-yl)acrylate **(3ea)**





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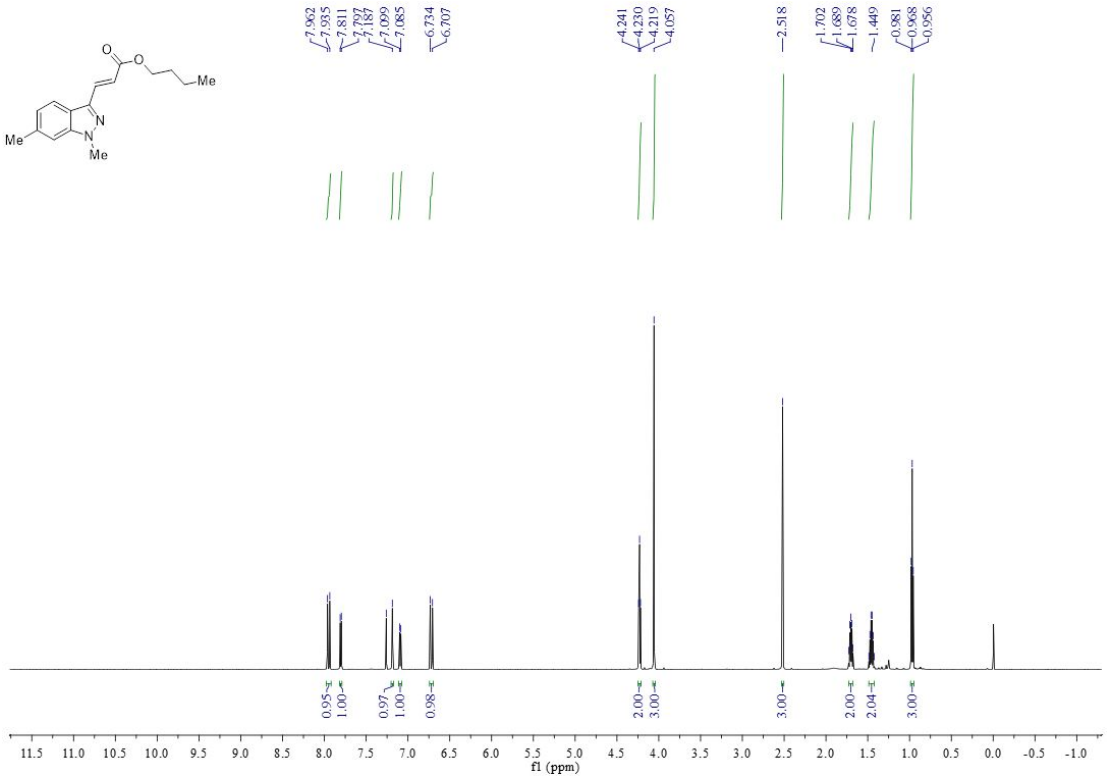

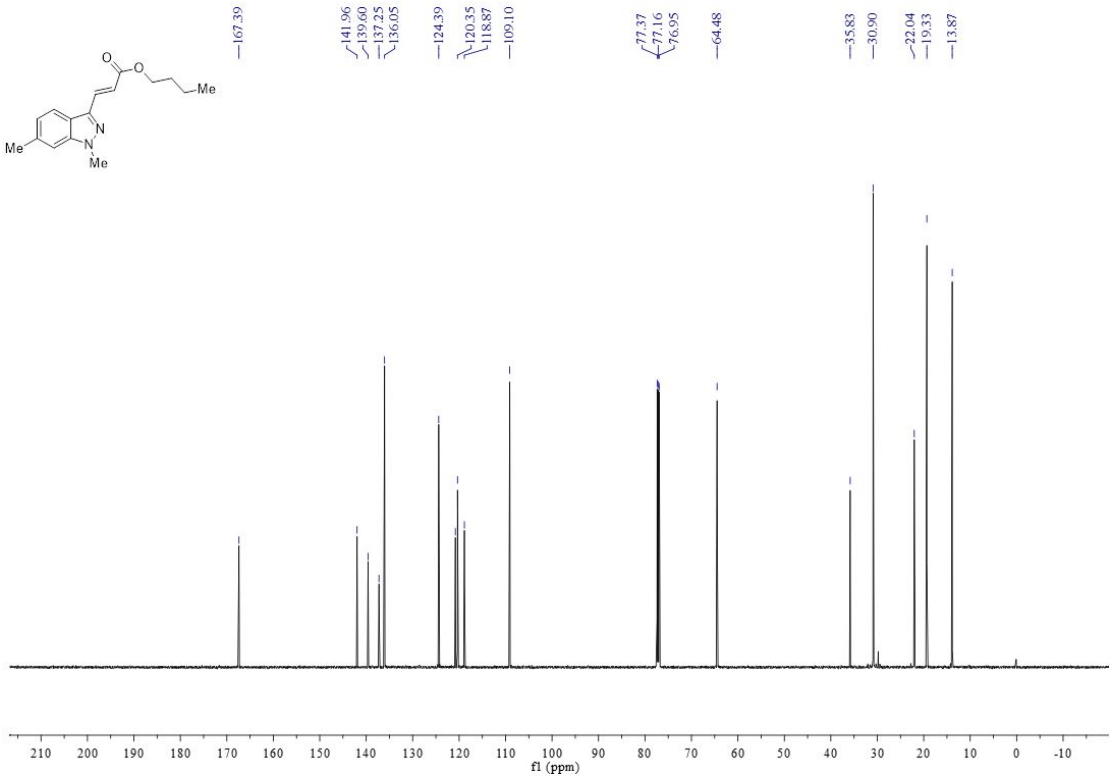

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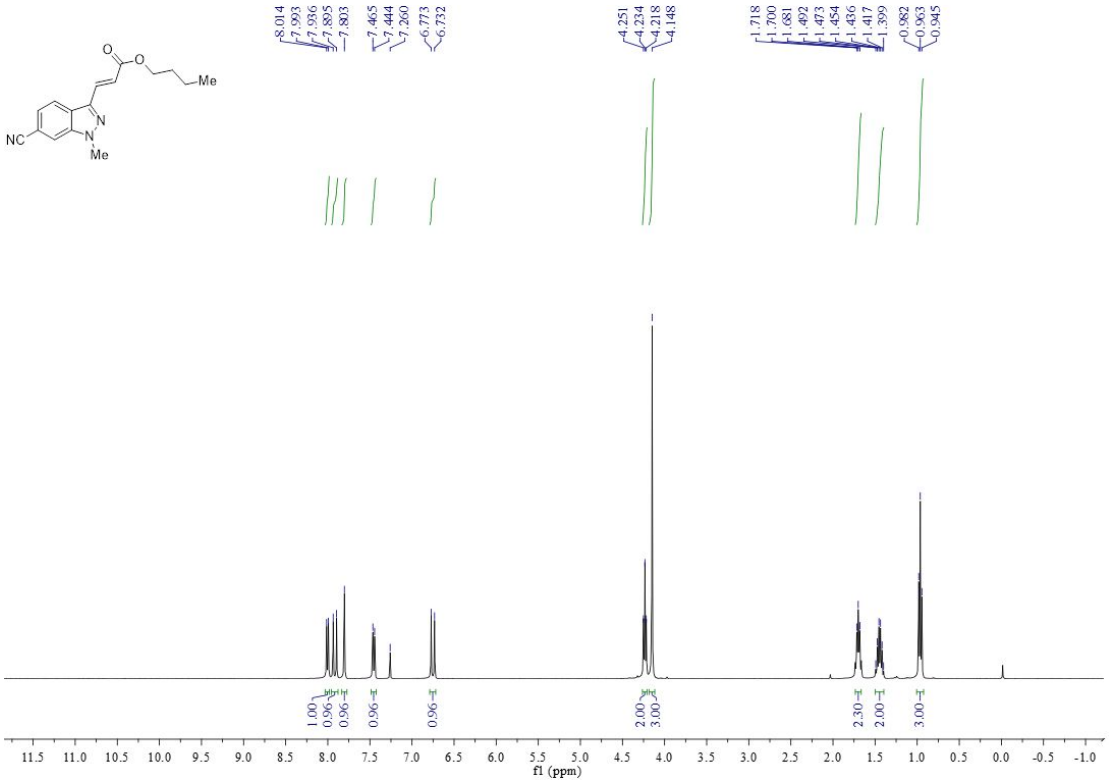
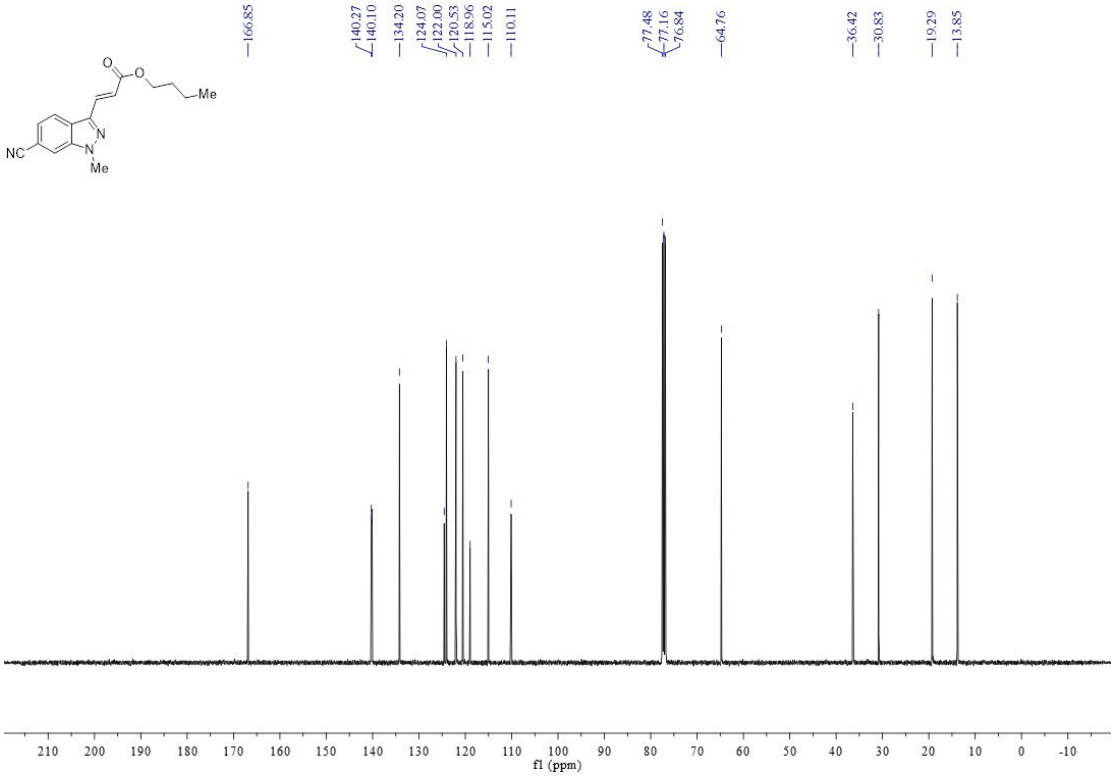
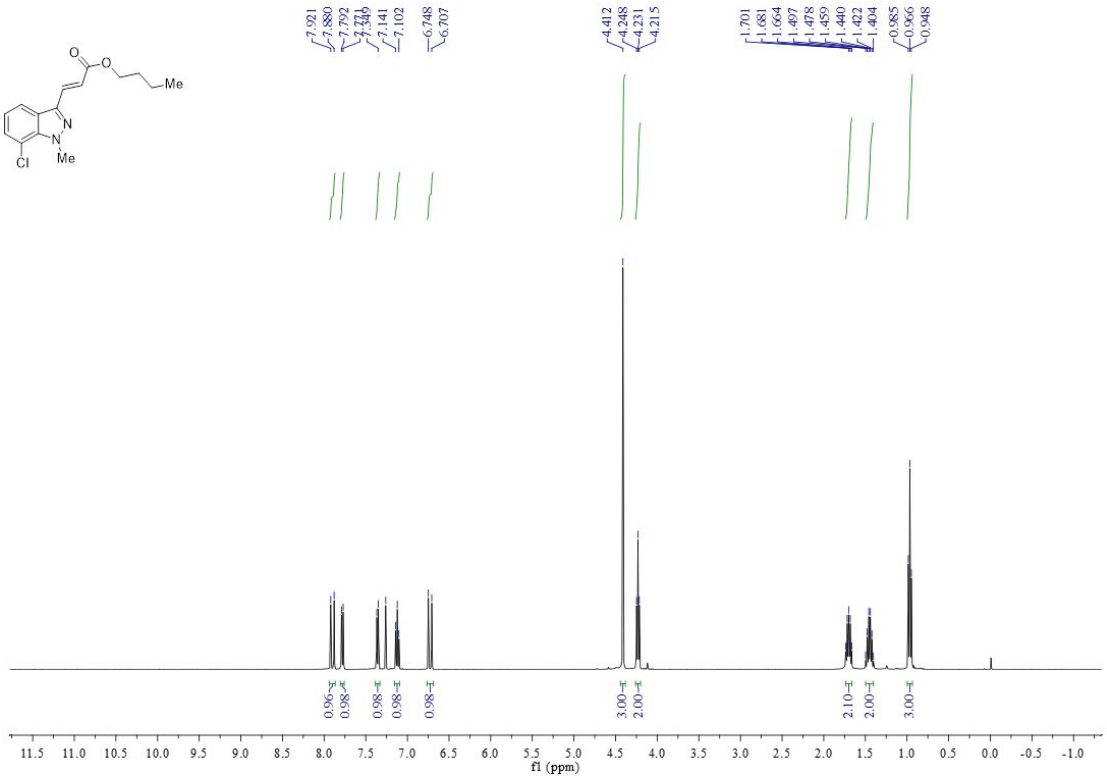
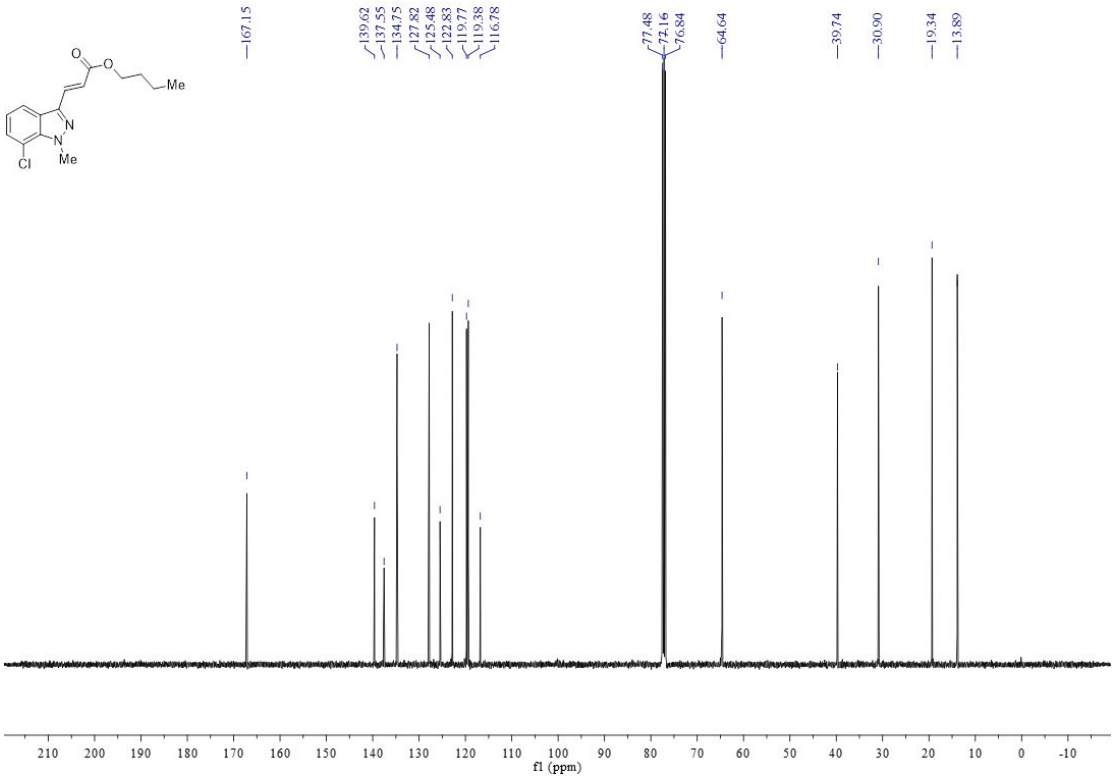


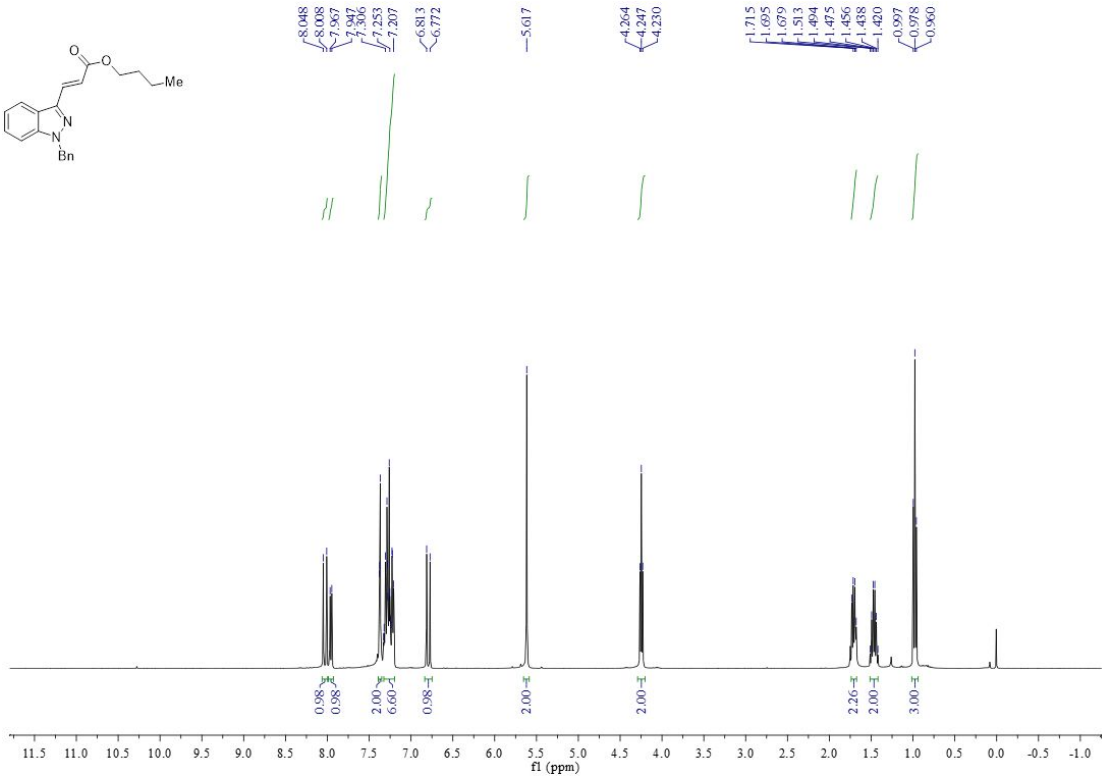


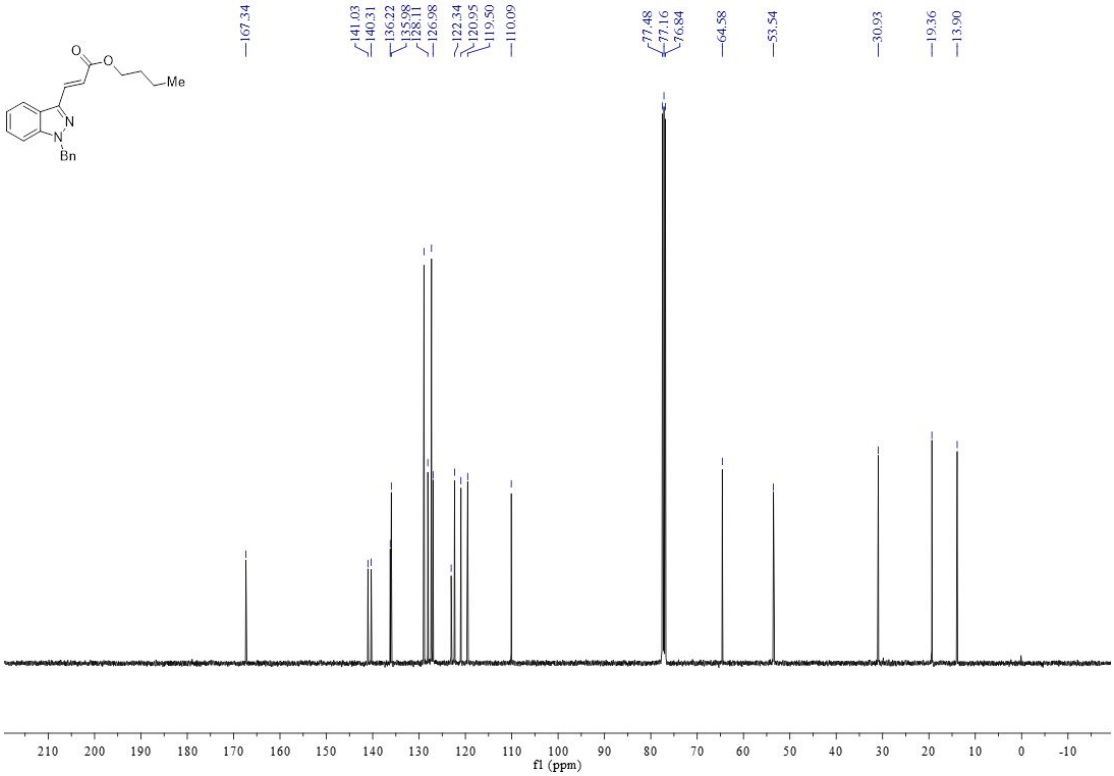
Butyl (E)-3-(7-chloro-1-methyl-1H-indazol-3-yl)acrylate **(3ha)**



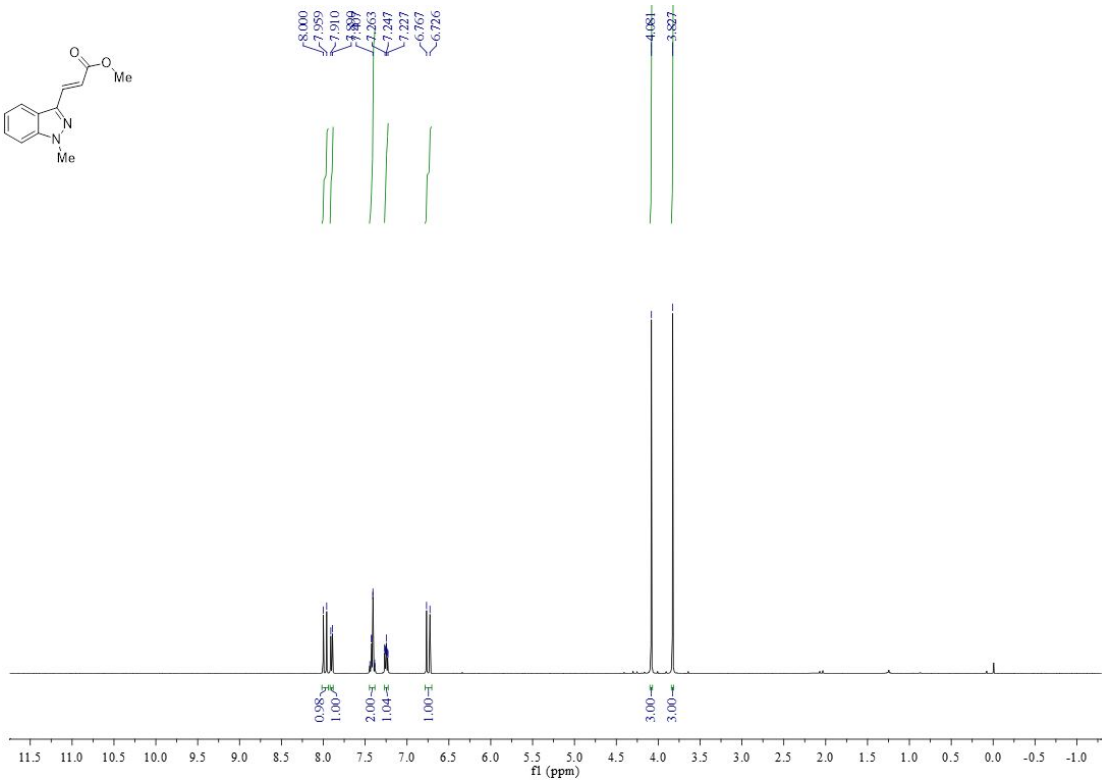


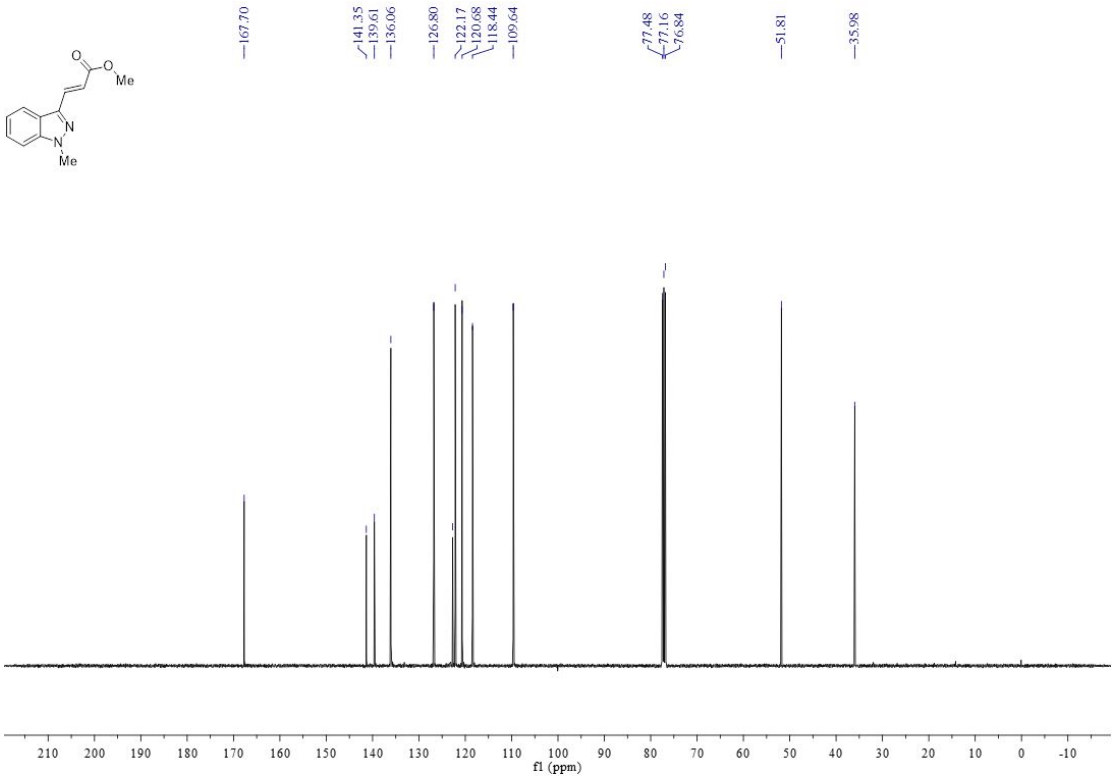
Butyl (E)-3-(1-benzyl-1H-indazol-3-yl)acrylate **(3ia)**





Methyl (E)-3-(1-methyl-1H-indazol-3-yl)acrylate **(3ab)**





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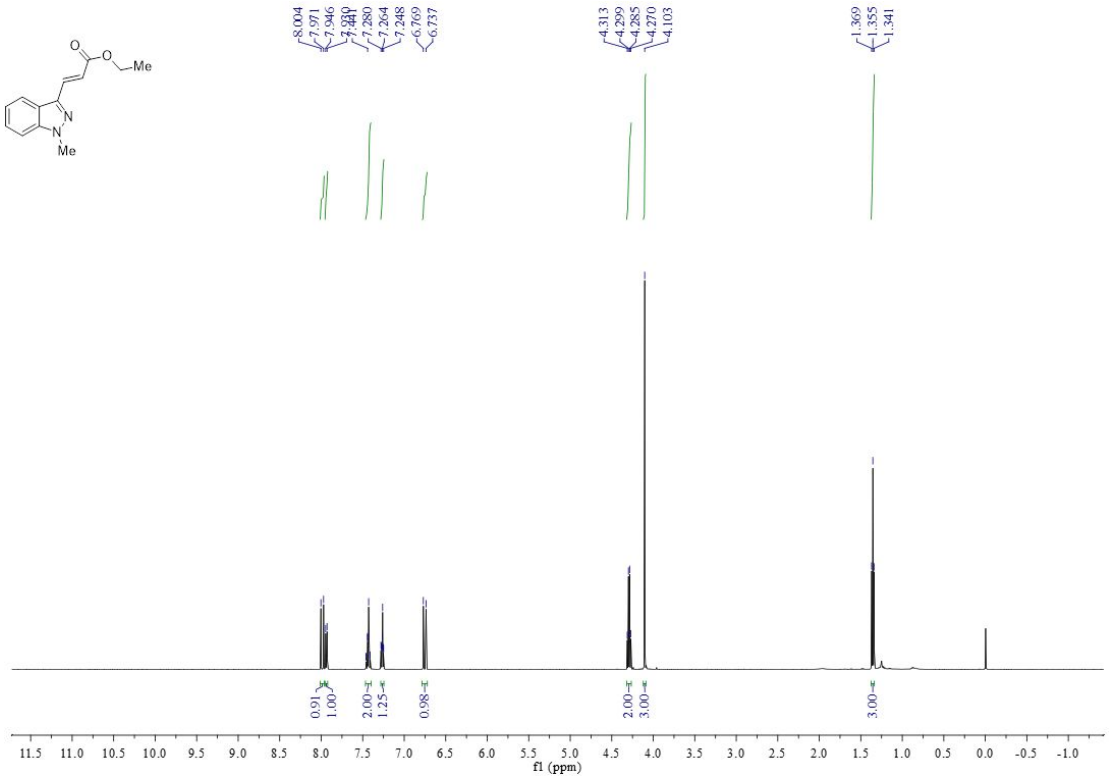
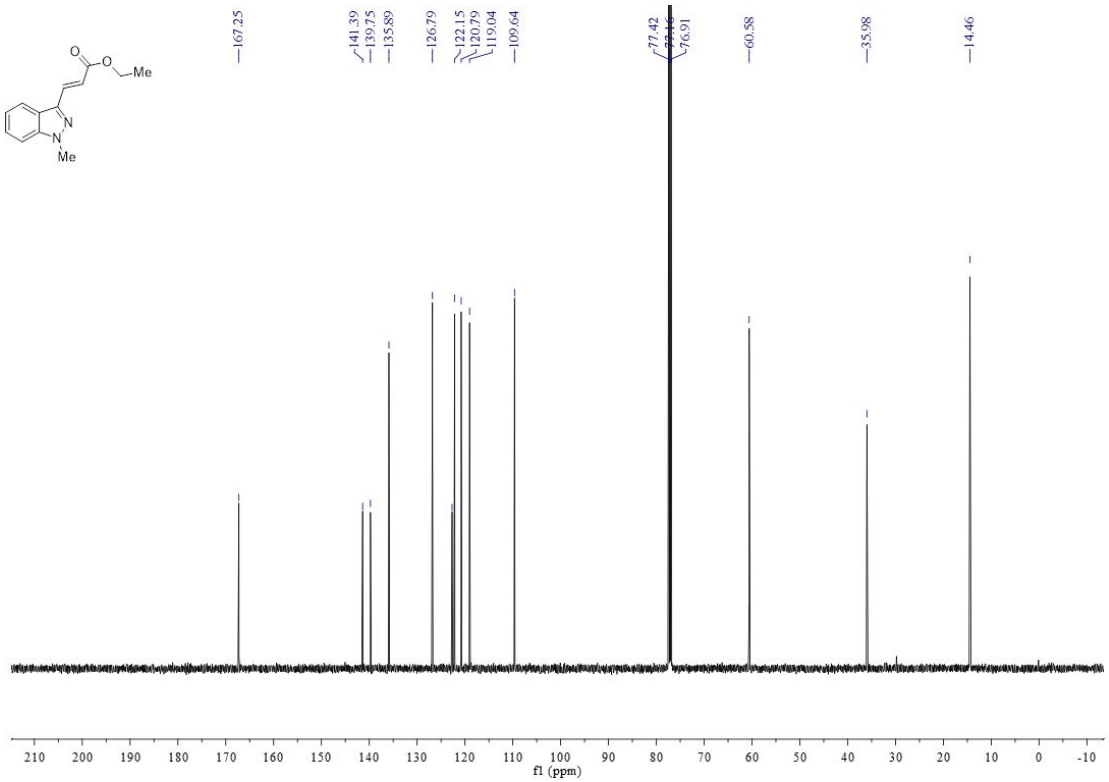
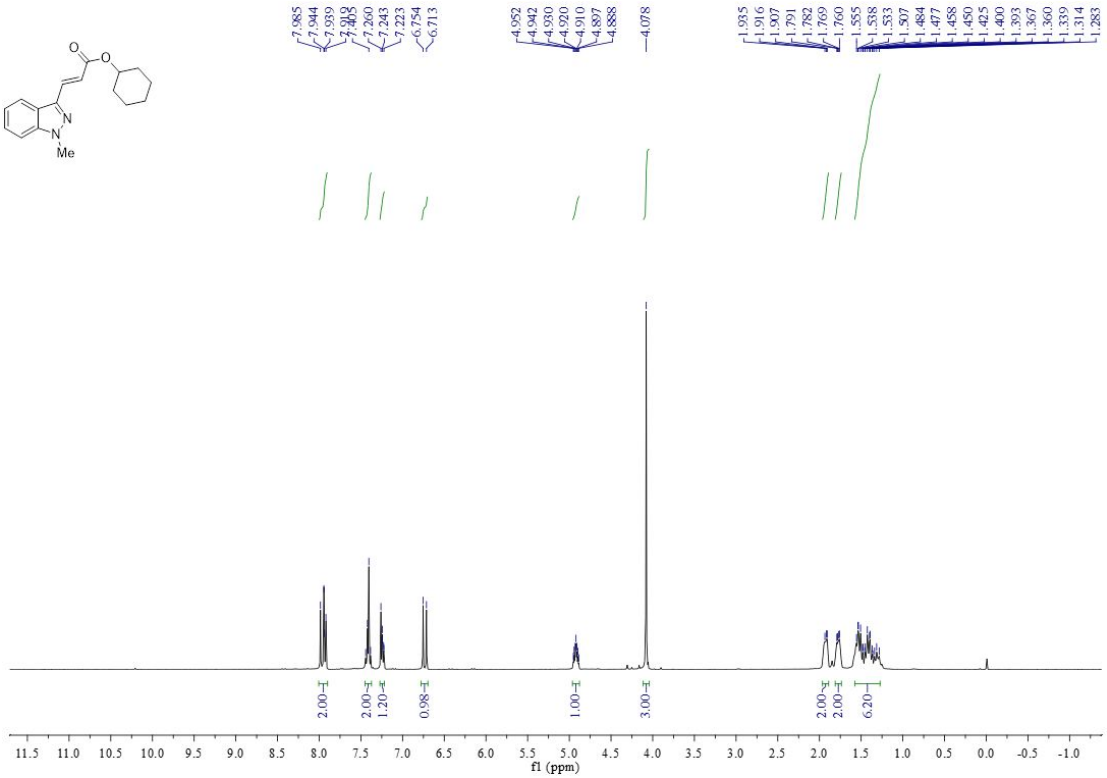
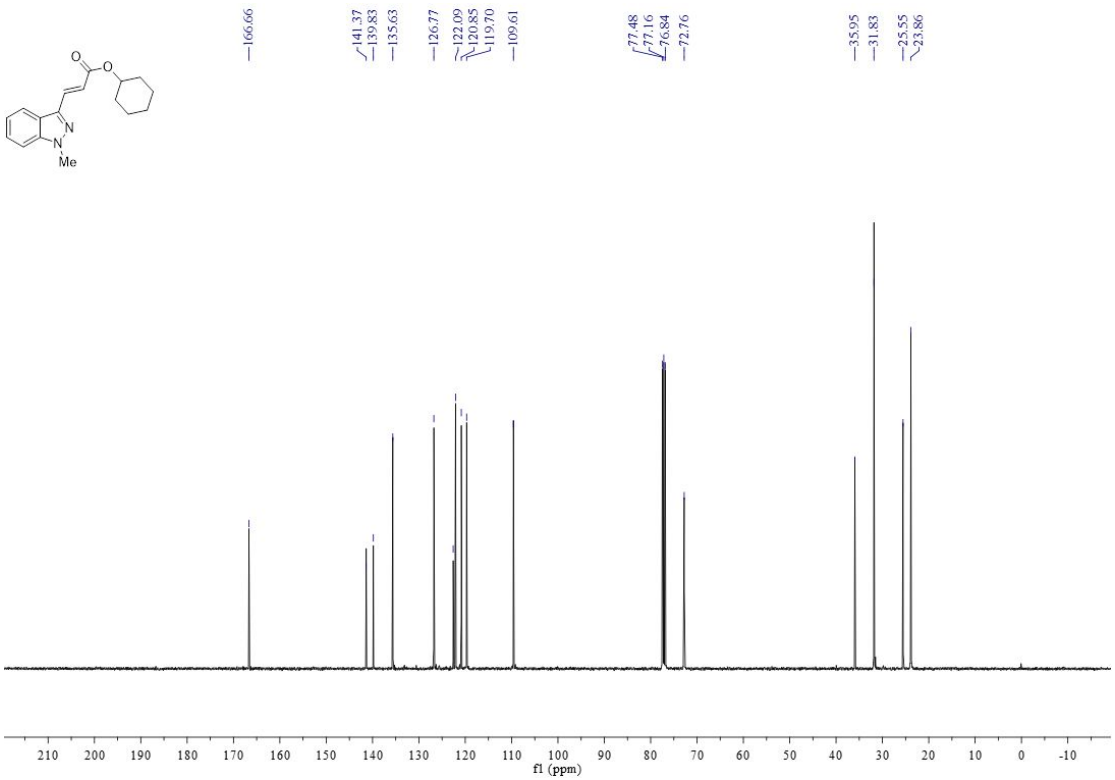


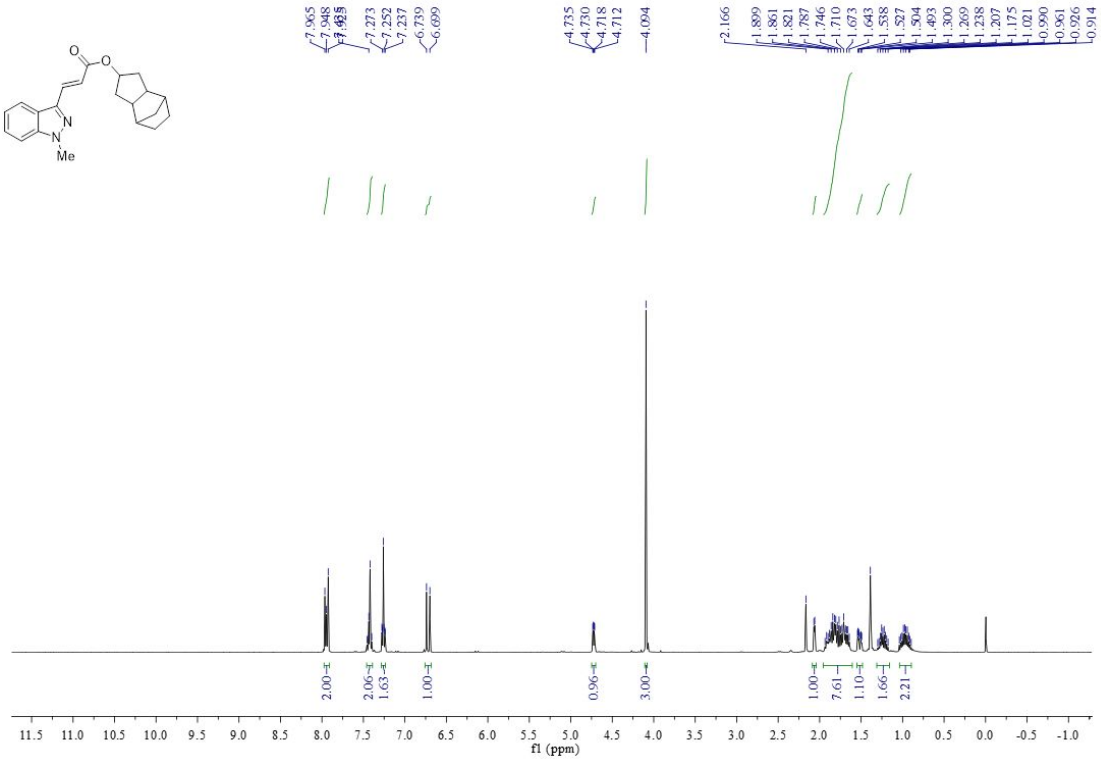


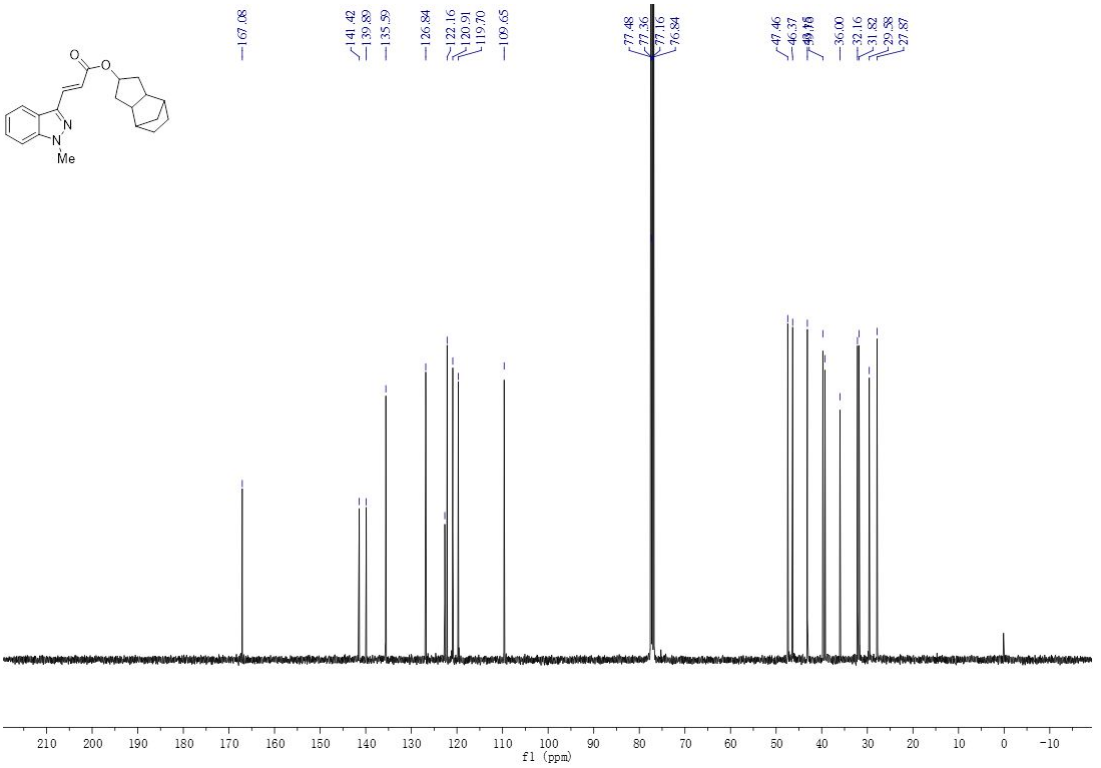
Cyclohexyl (E)-3-(1-methyl-1H-indazol-3-yl)acrylate **(3ad)**



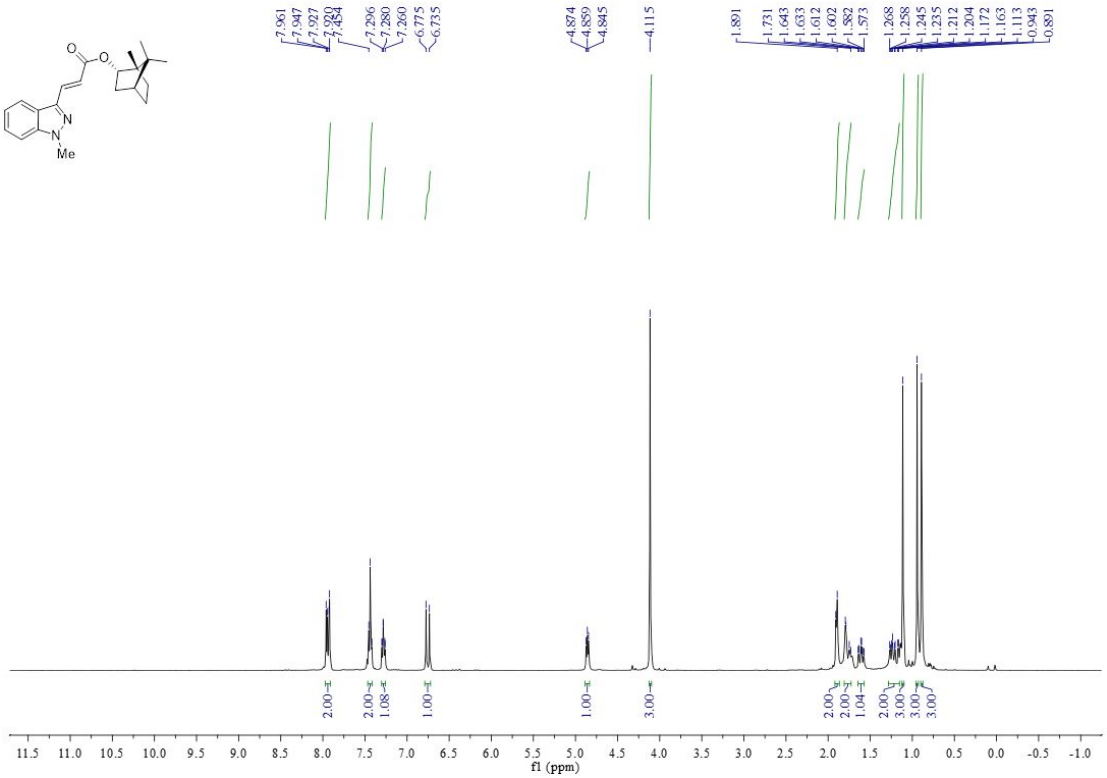


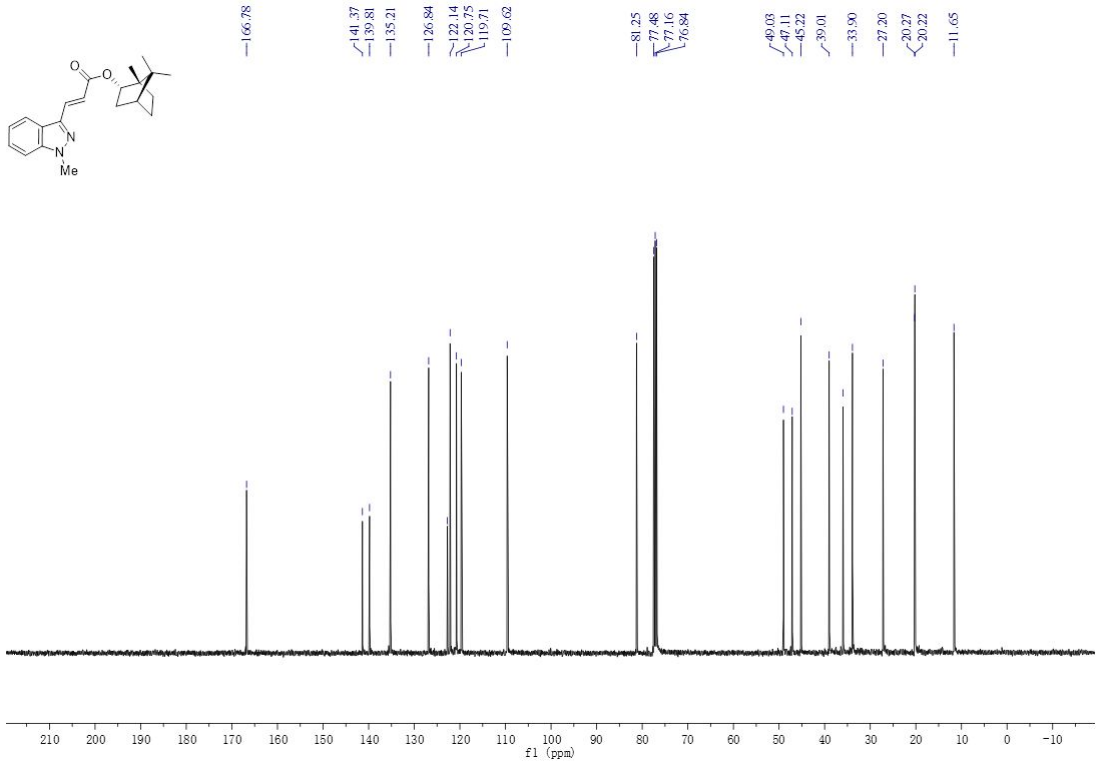
Octahydro-1H-4,7-methanoinden-2-yl (E)-3-(1-methyl-1H-indazol-3-yl)acrylate **(3ae)**



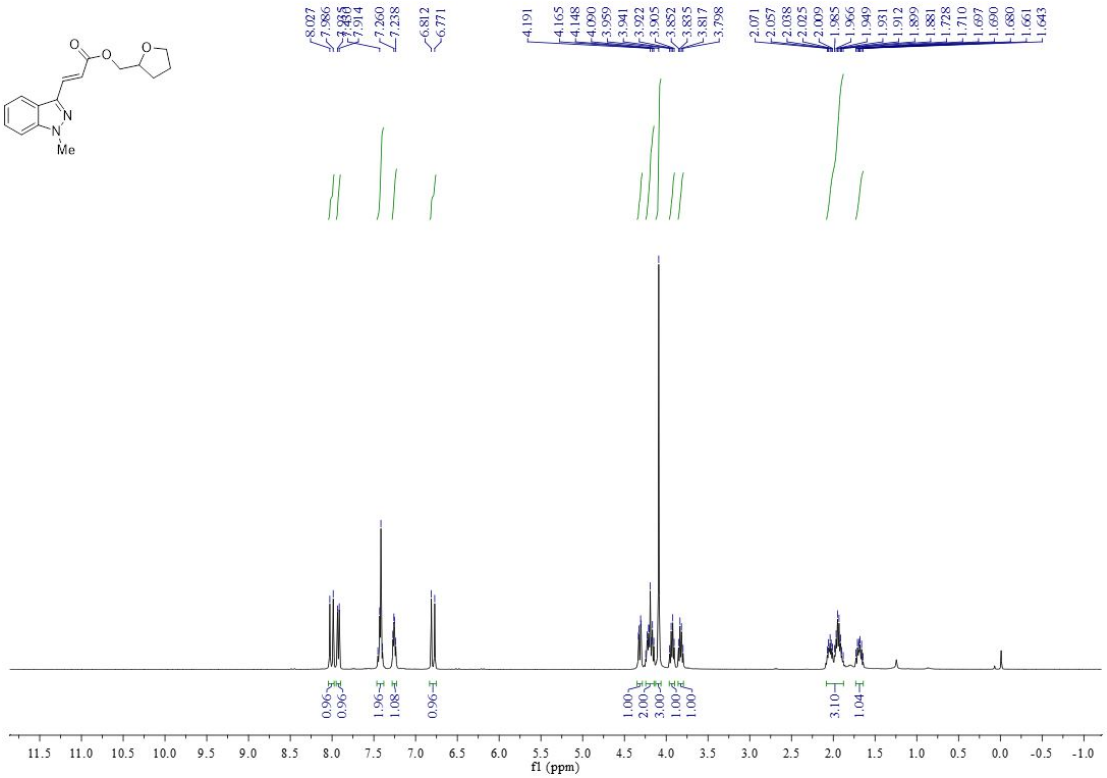


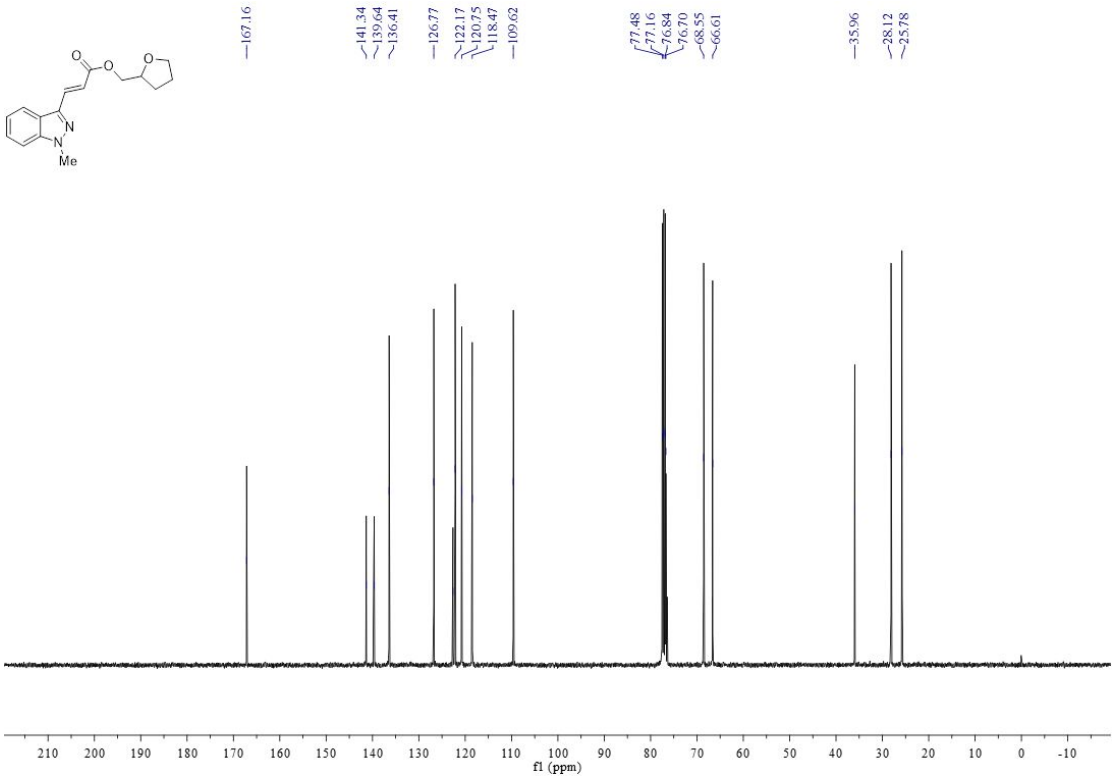
***(1S,2S,4S)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl (E)-3-(1-methyl-1H-indazol-3-yl)acrylate* (3af)**



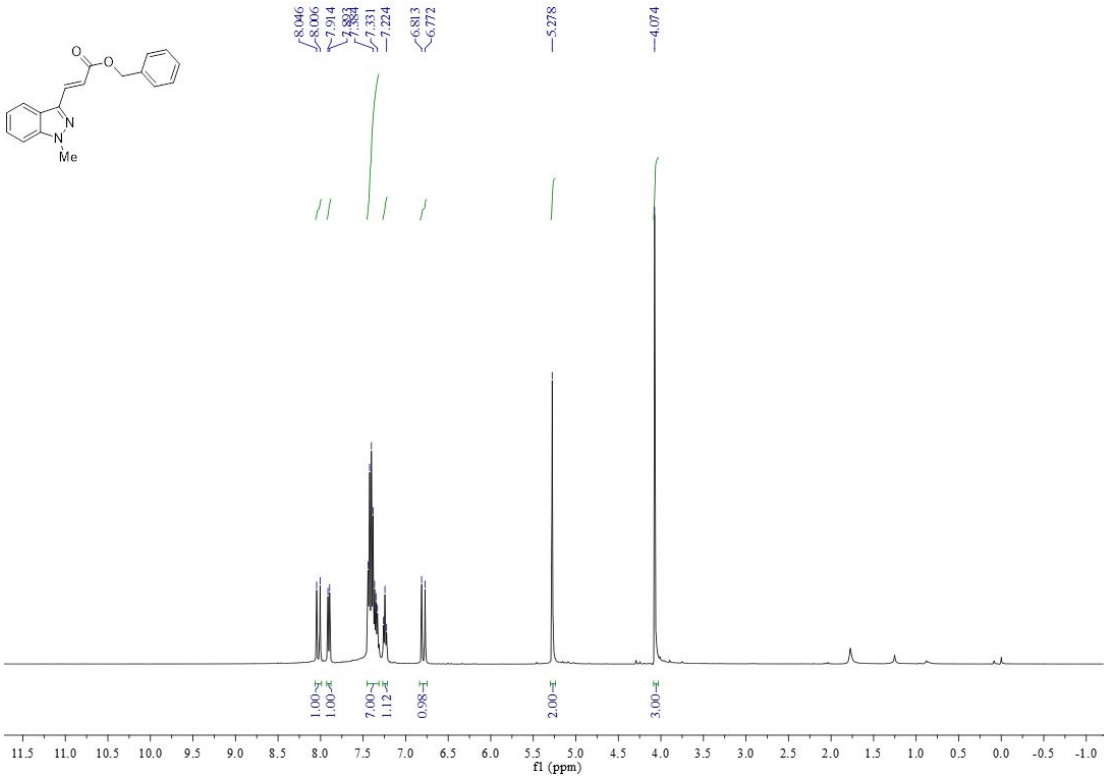


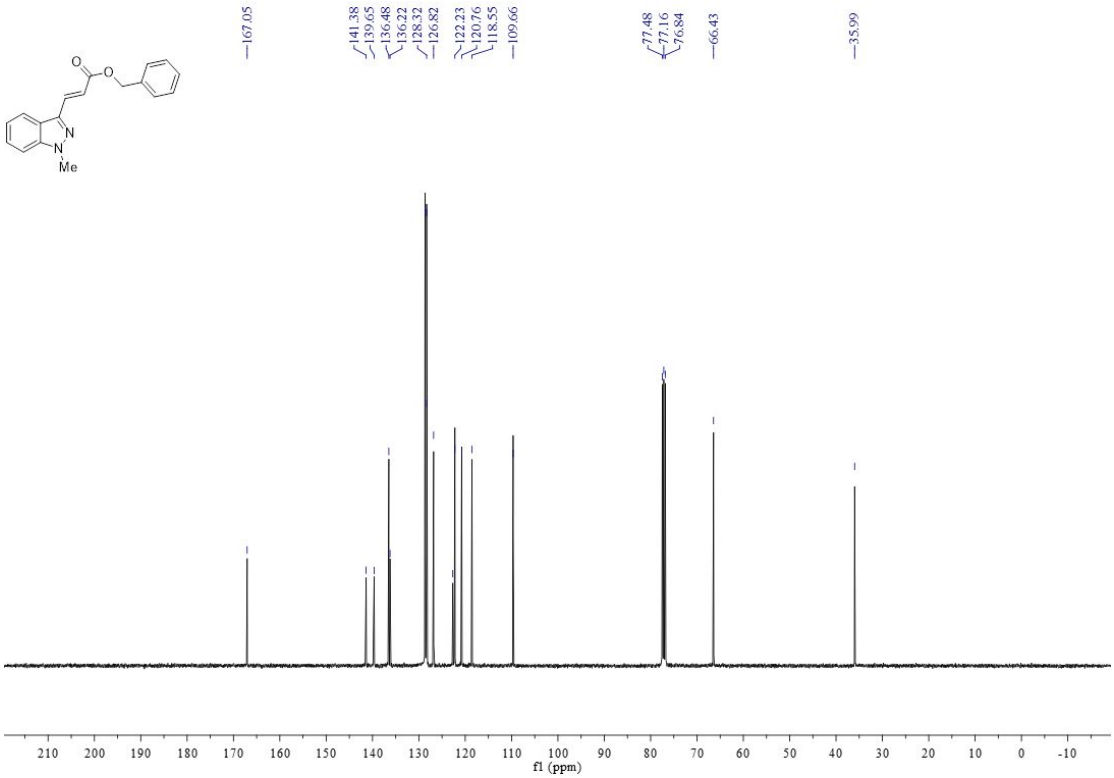
(Tetrahydrofuran-2-yl)methyl (E)-3-(1-methyl-1H-indazol-3-yl)acrylate **(3ag)**



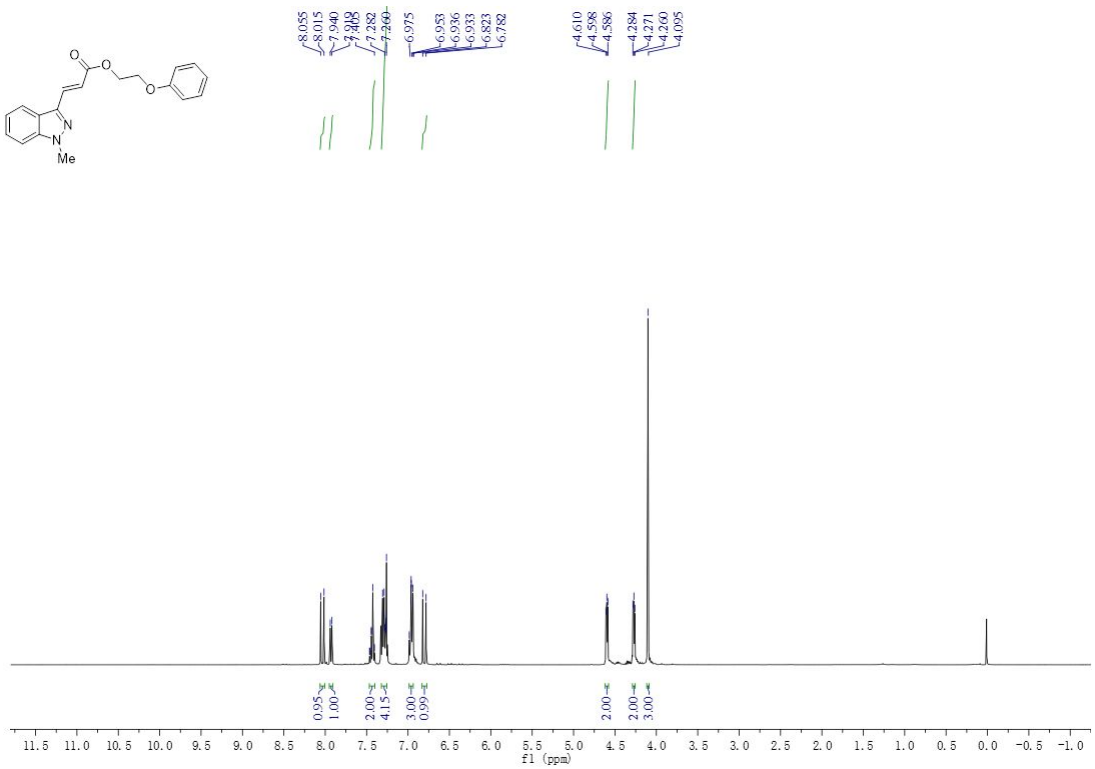


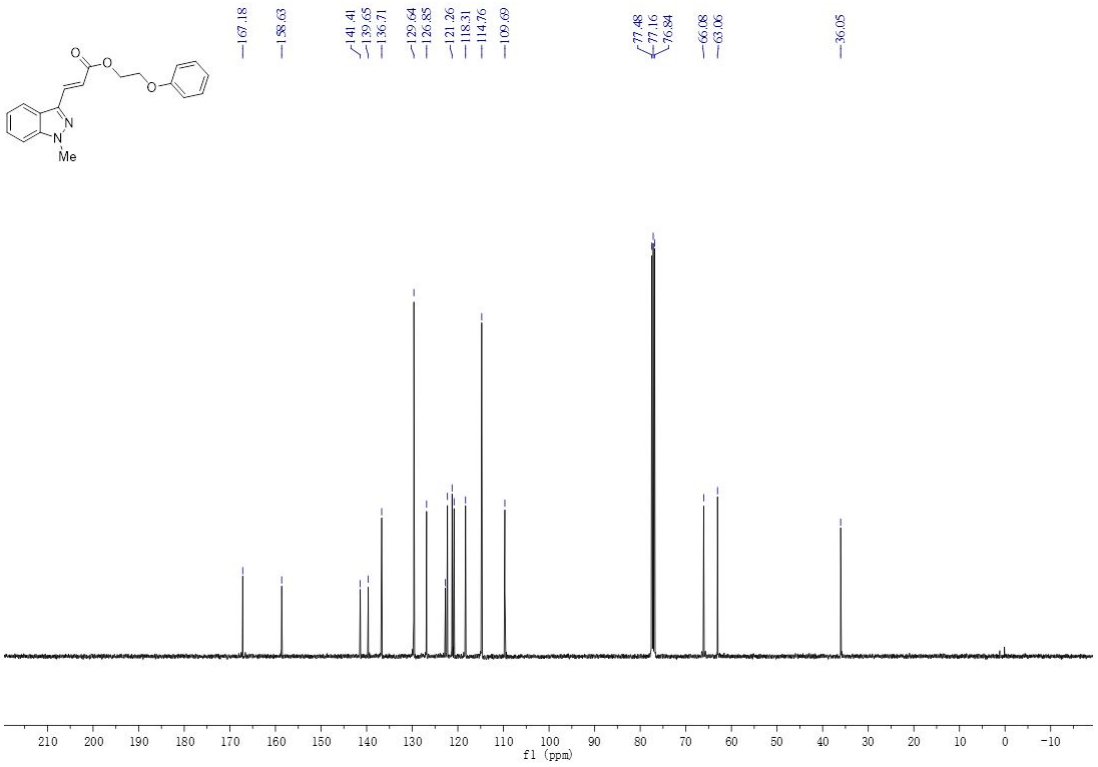
Benzyl (E)-3-(1-methyl-1H-indazol-3-yl)acrylate **(3ah)**





2-Phenoxyethyl (E)-3-(1-methyl-1H-indazol-3-yl)acrylate **(3ai)**





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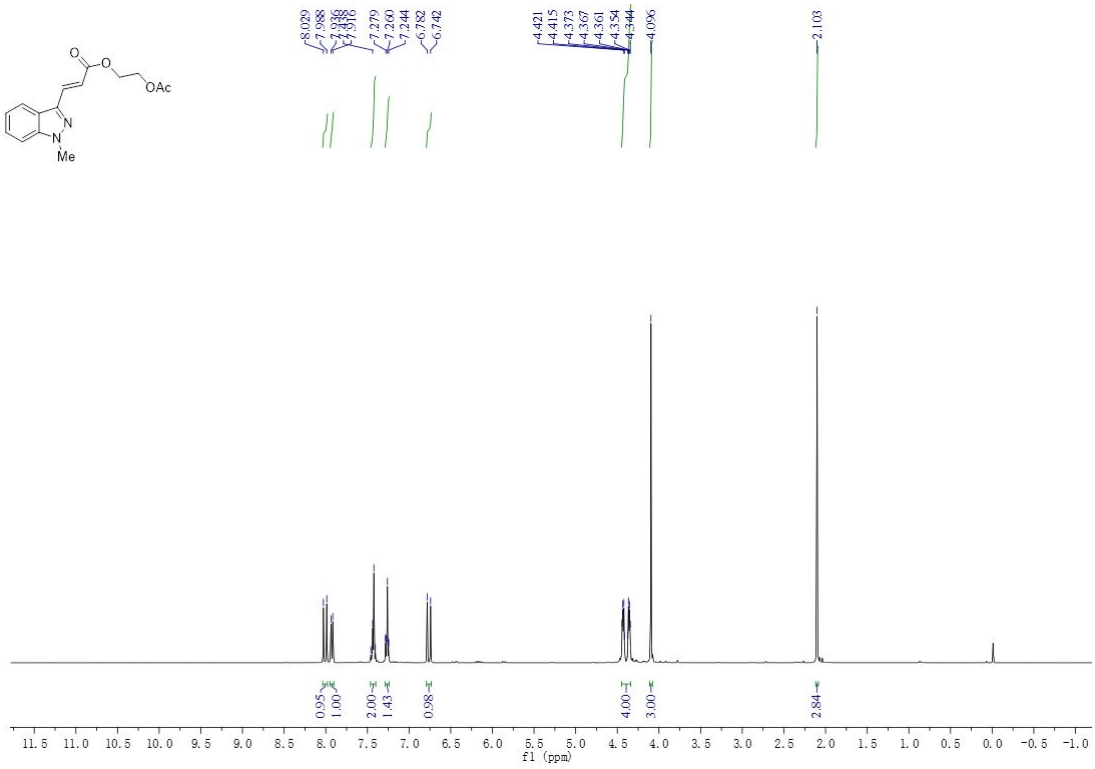
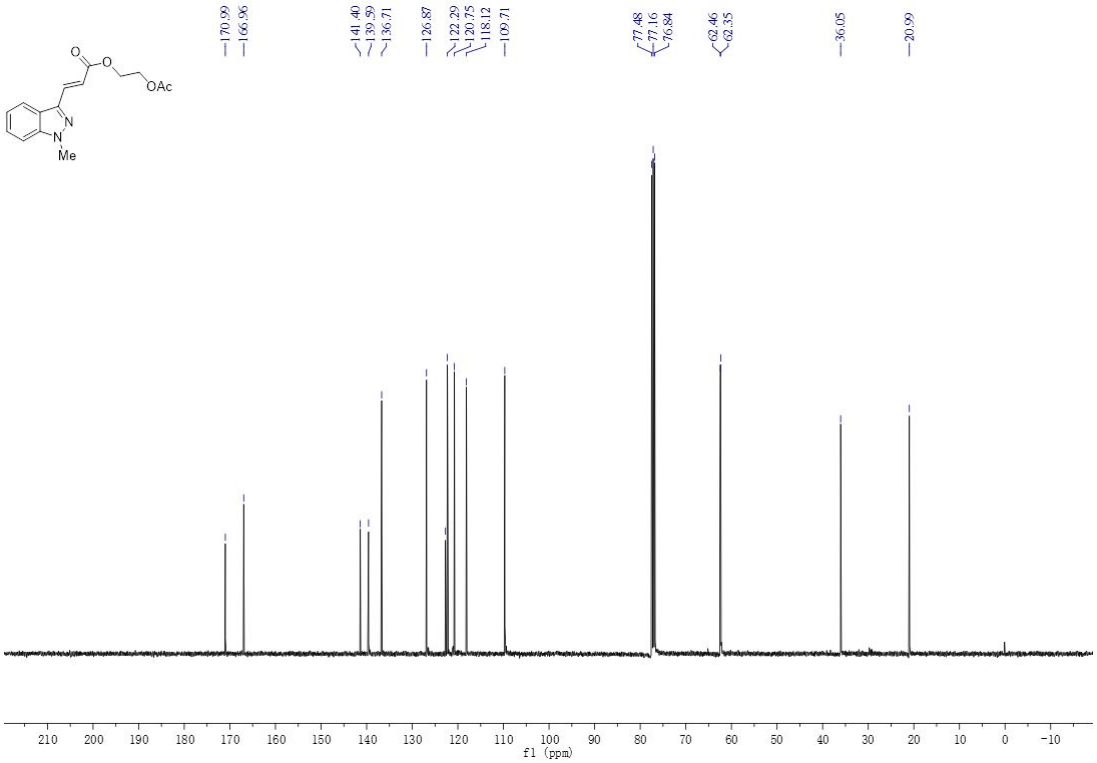
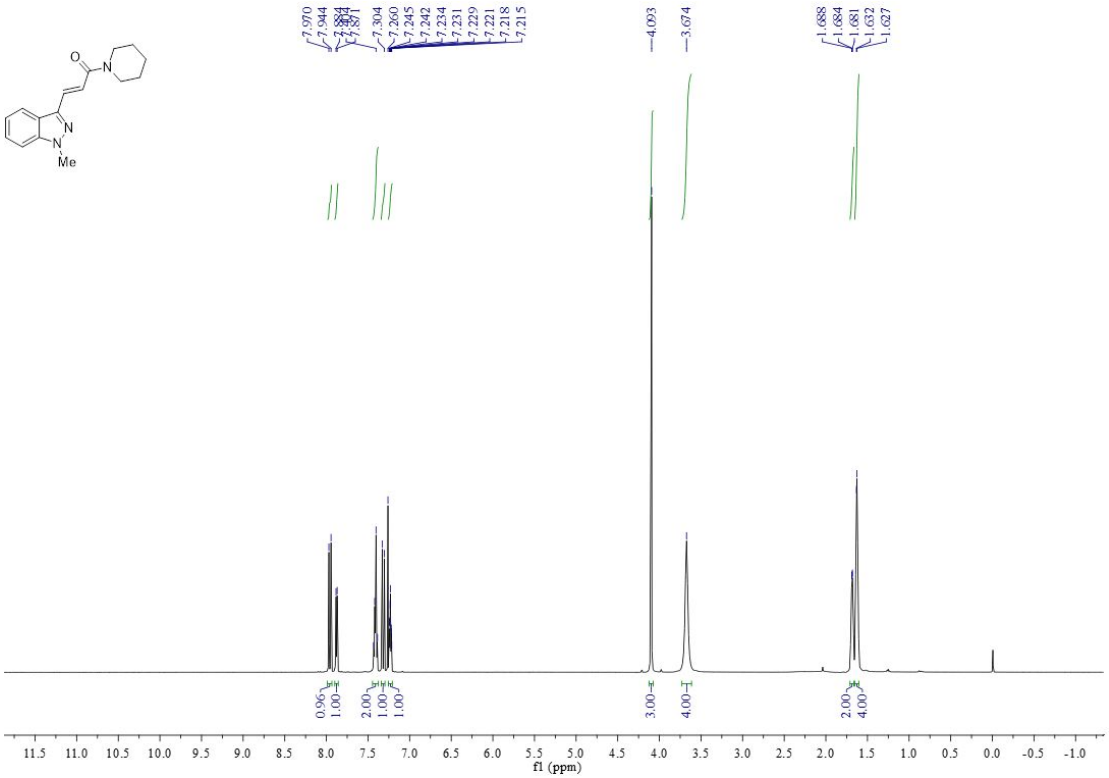
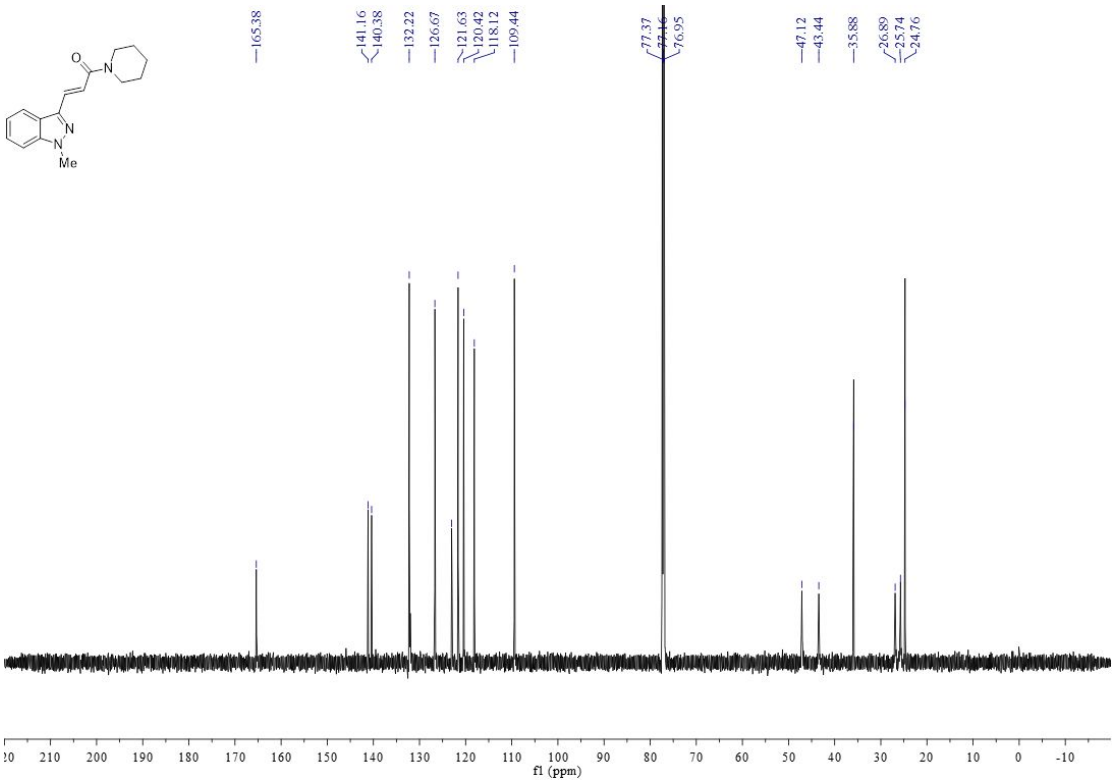


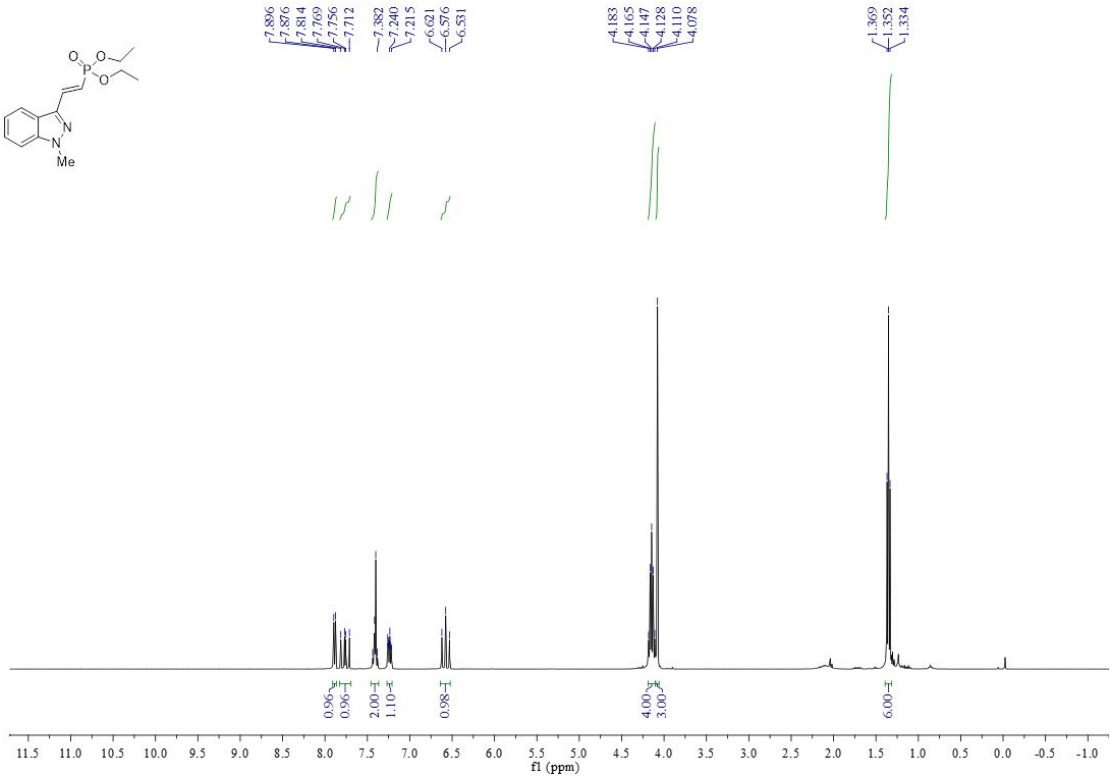


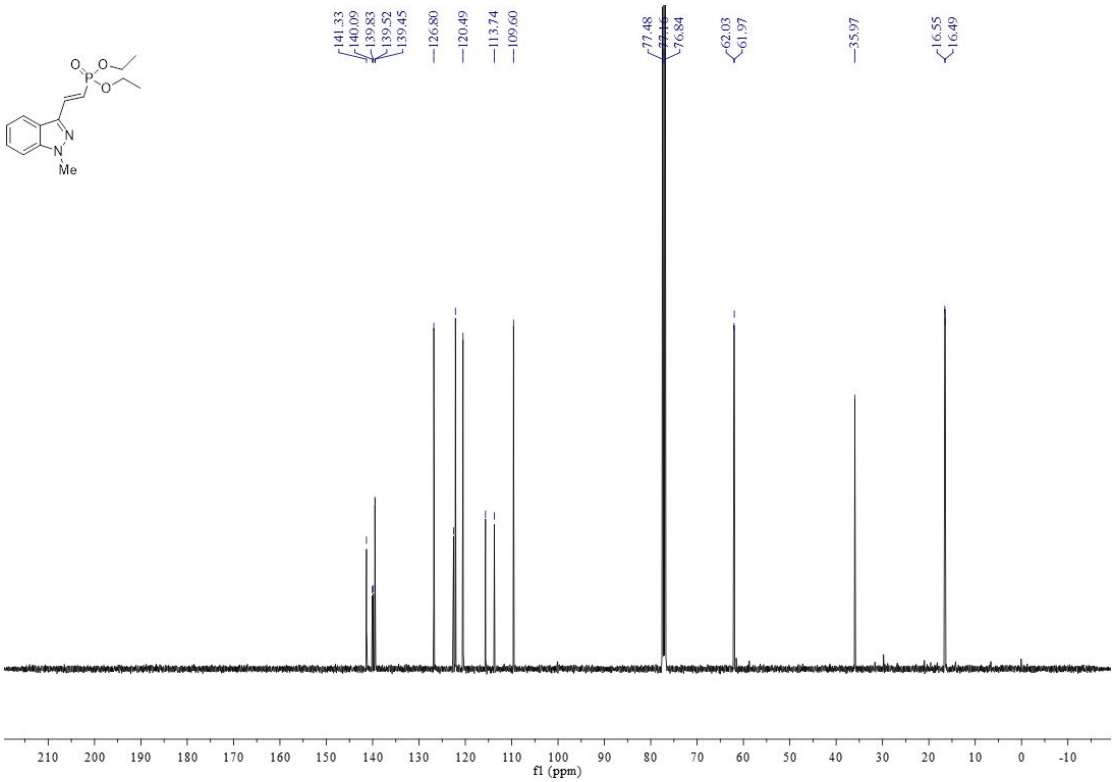
(E)-3-(1-Methyl-1H-indazol-3-yl)-1-(piperidin-1-yl)prop-2-en-1-one **(3ak)**

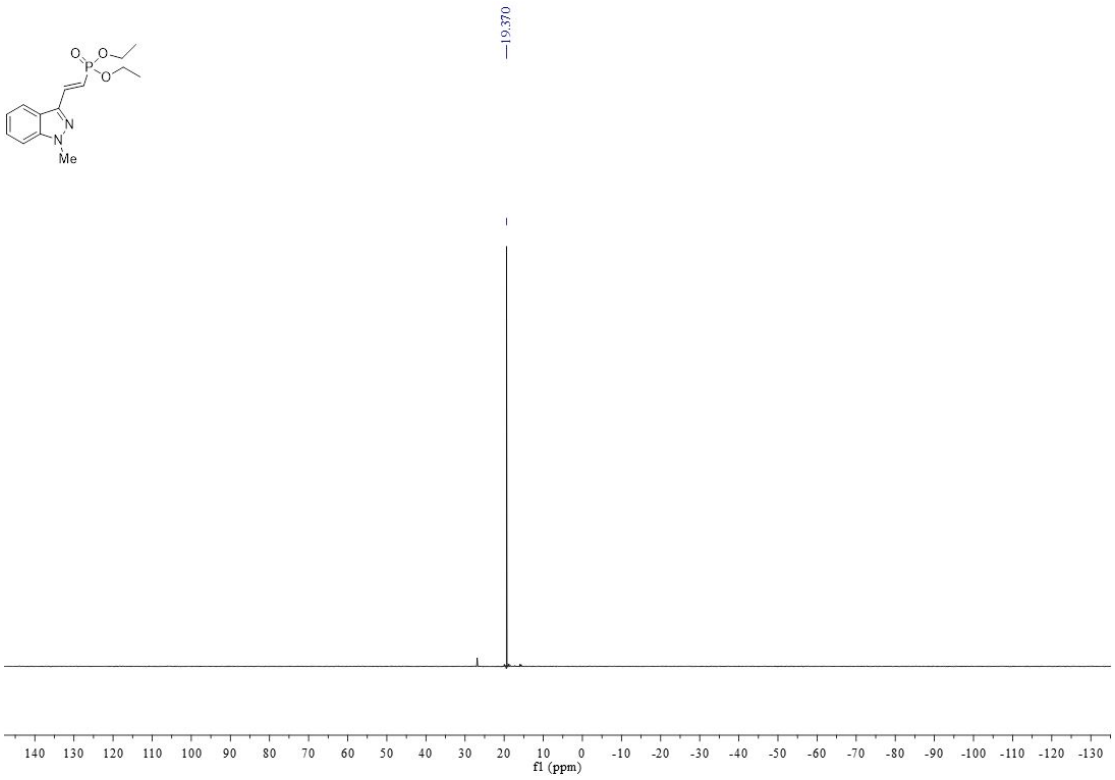




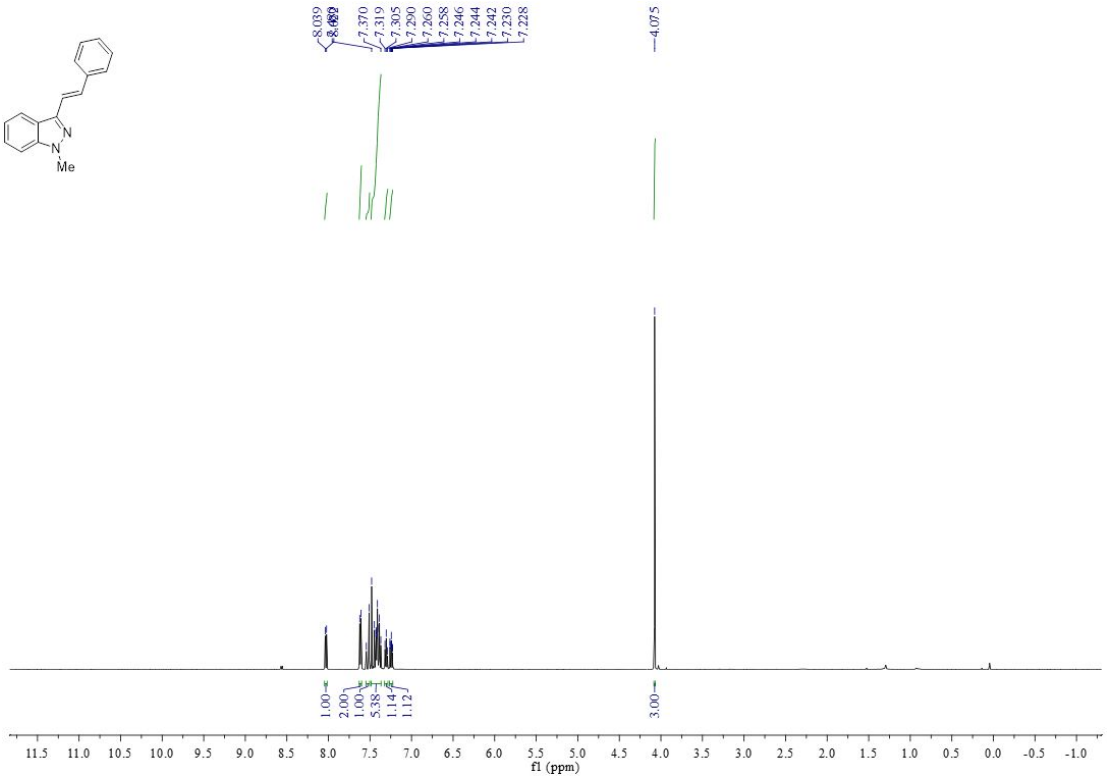
Diethyl (E)-(2-(1-methyl-1H-indazol-3-yl)vinyl)phosphonate **(3al)**

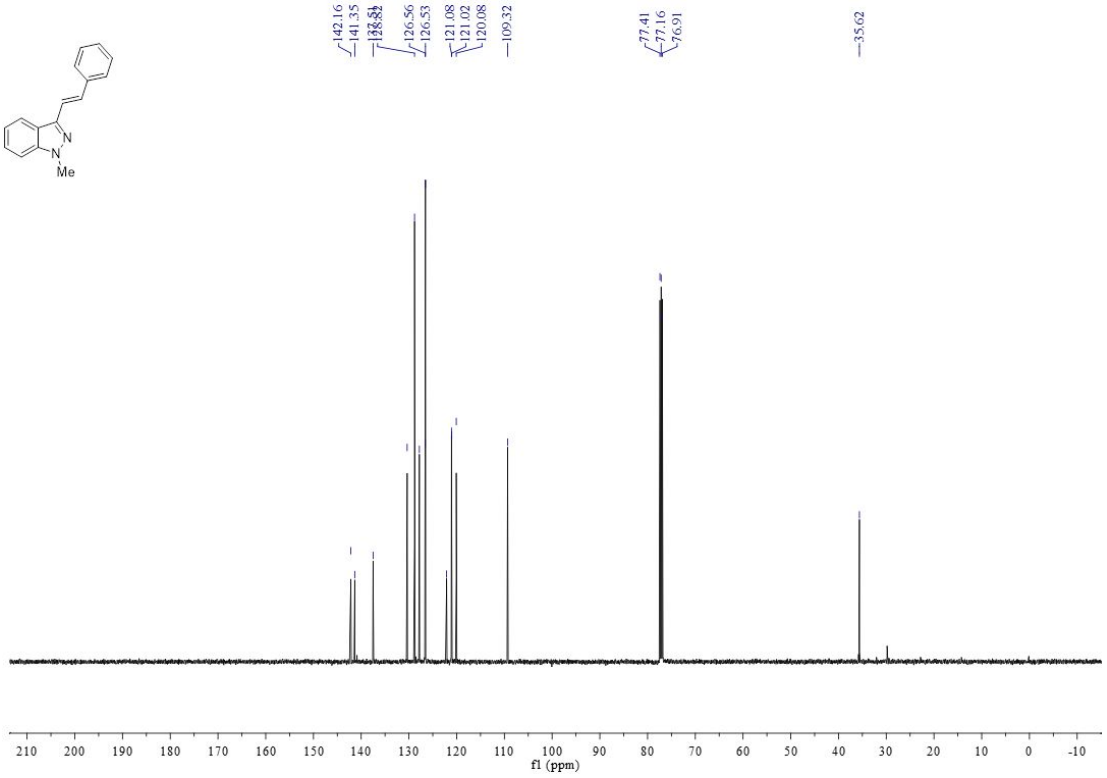




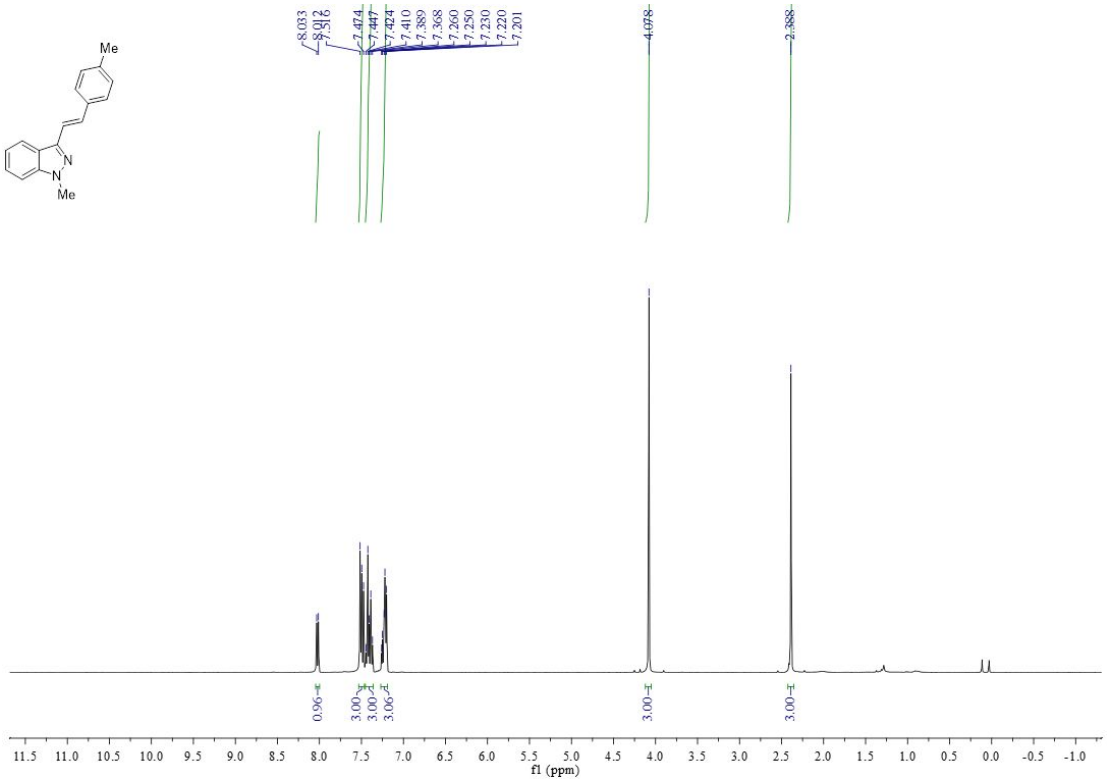

19.370
O
O
P
O
N
N
Me
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130
f1 (ppm)

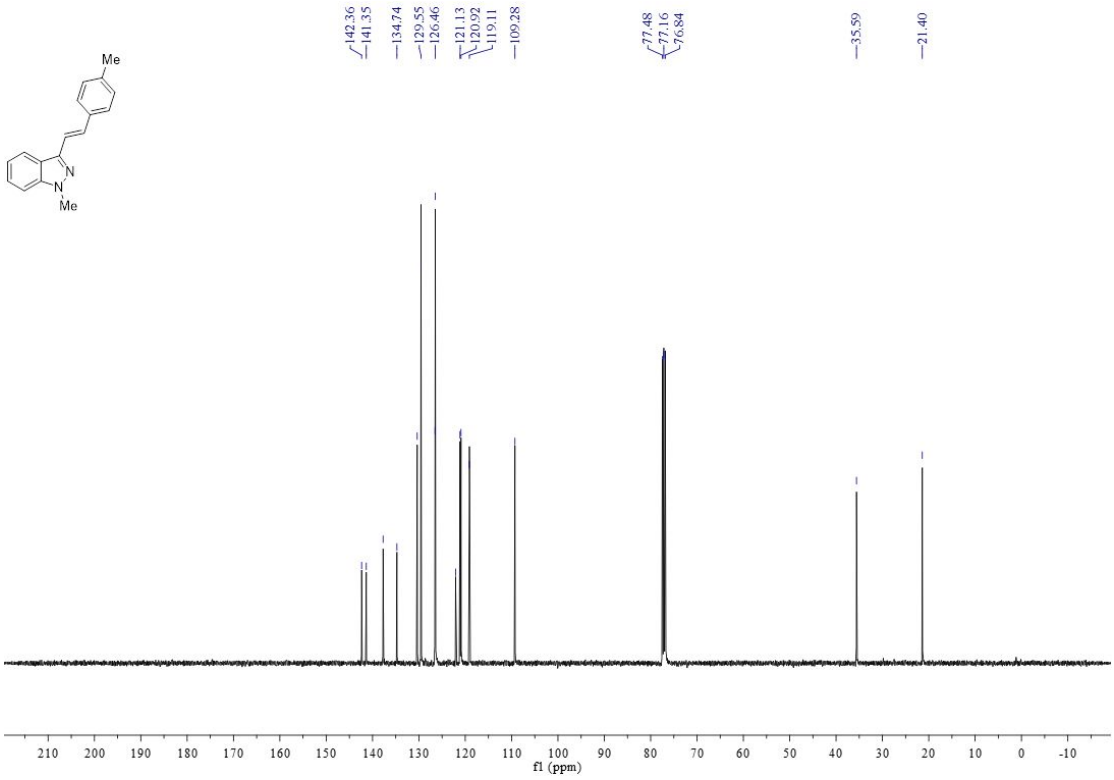
(E)-1-Methyl-3-styryl-1H-indazole **(3am)**



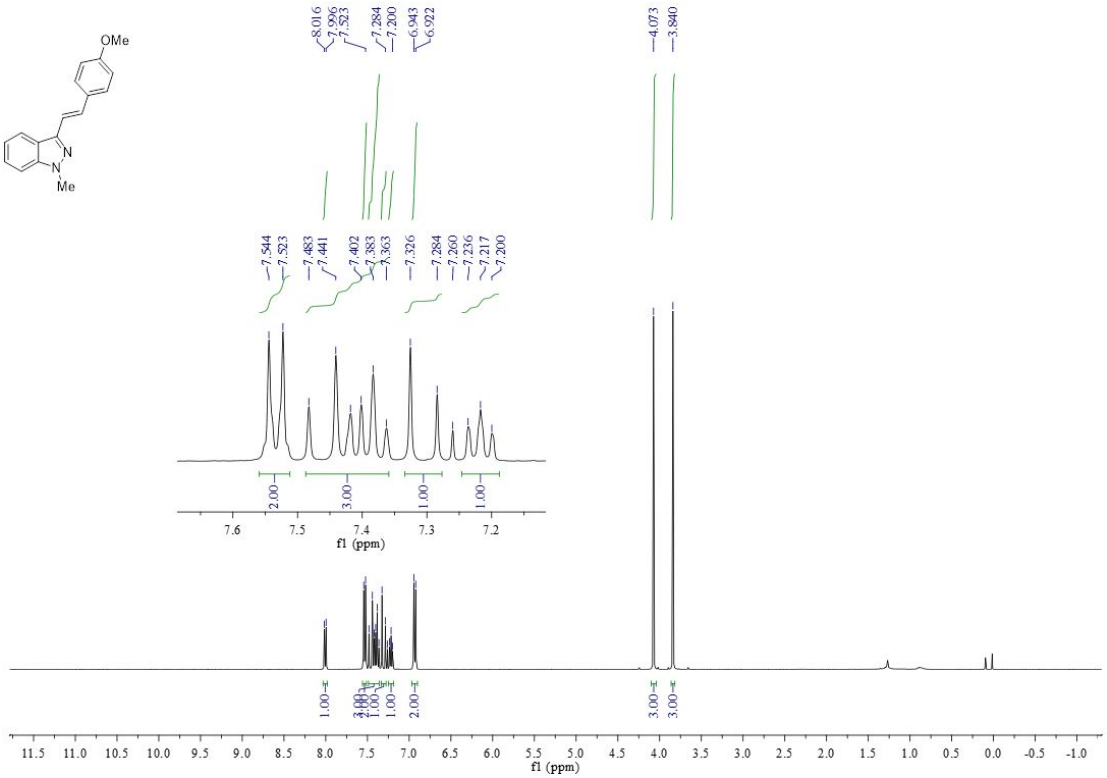


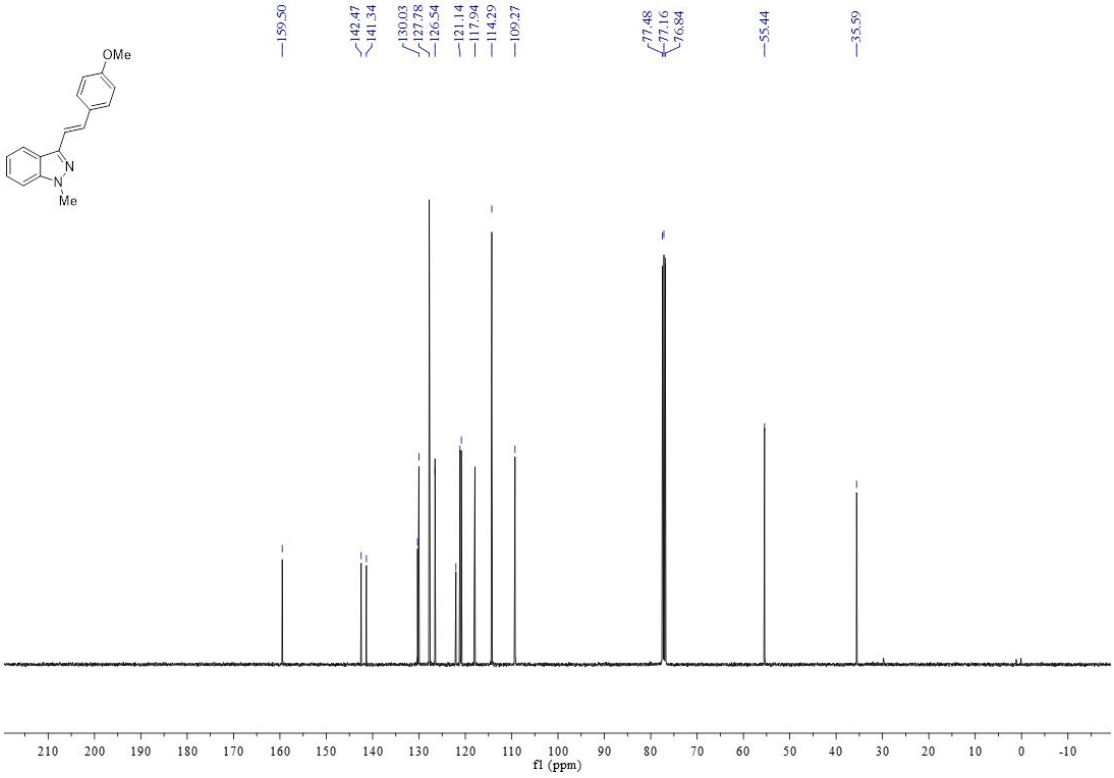
(E)-1-Methyl-3-(4-methylstyryl)-1H-indazole **(3an)**



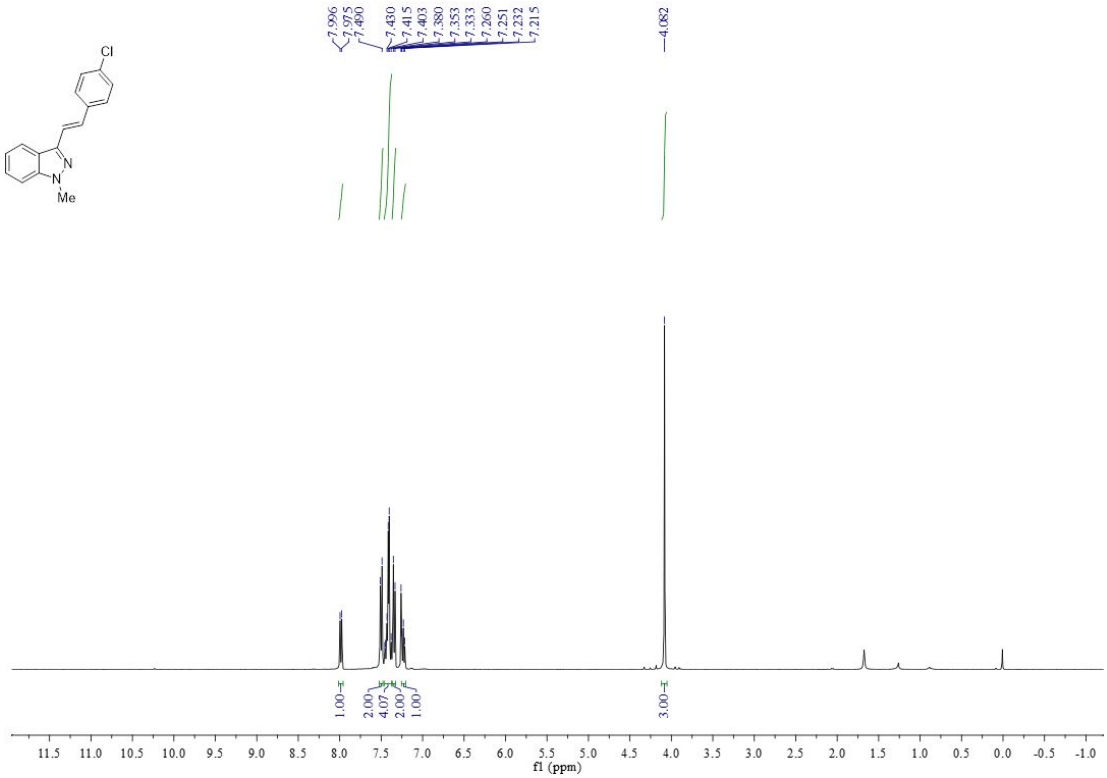


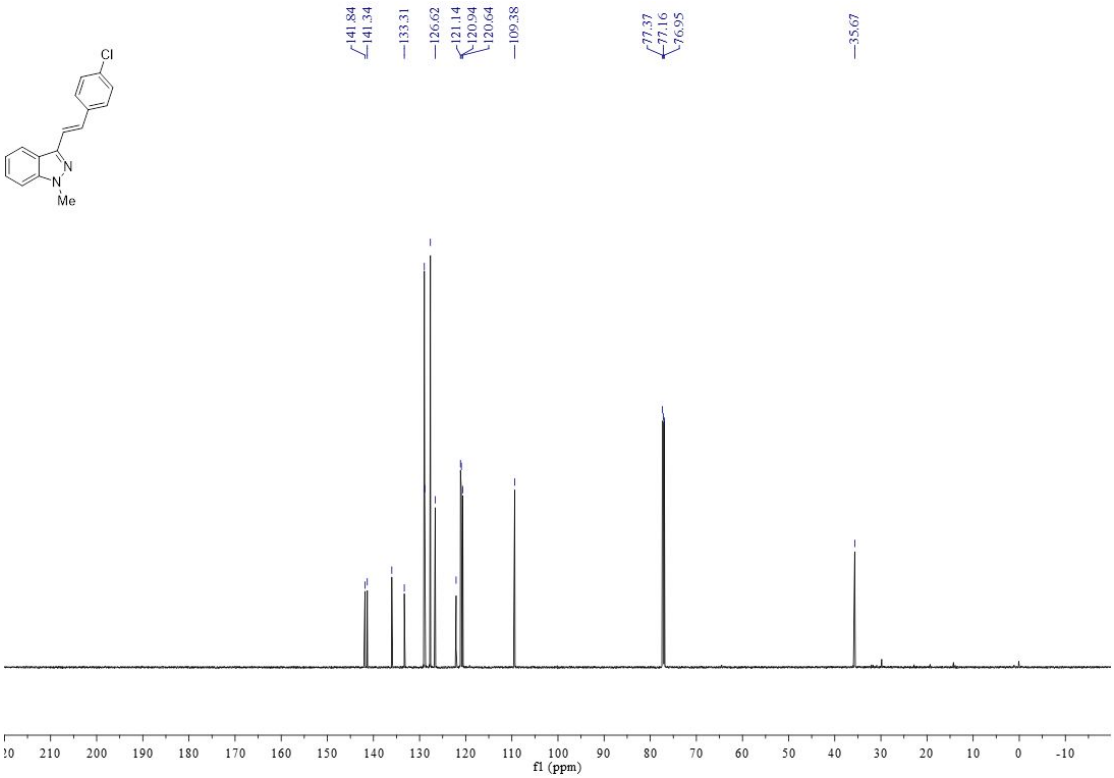
(E)-3-(4-Methoxystyryl)-1-methyl-1H-indazole **(3ao)**



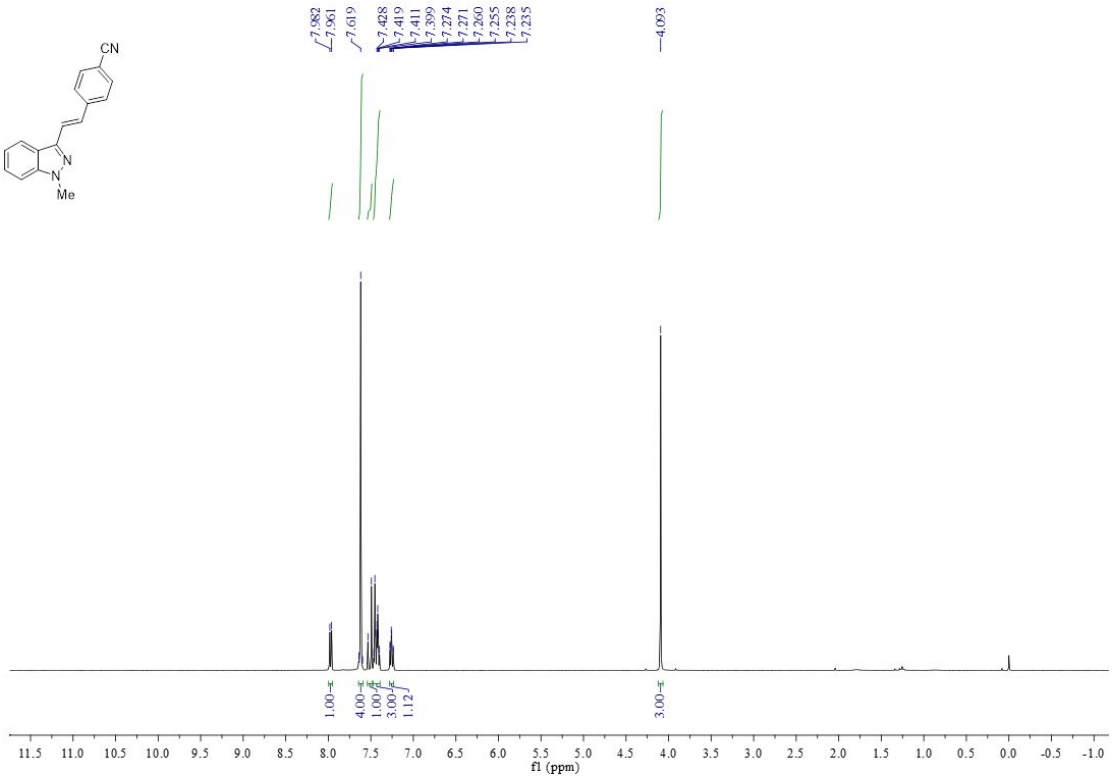


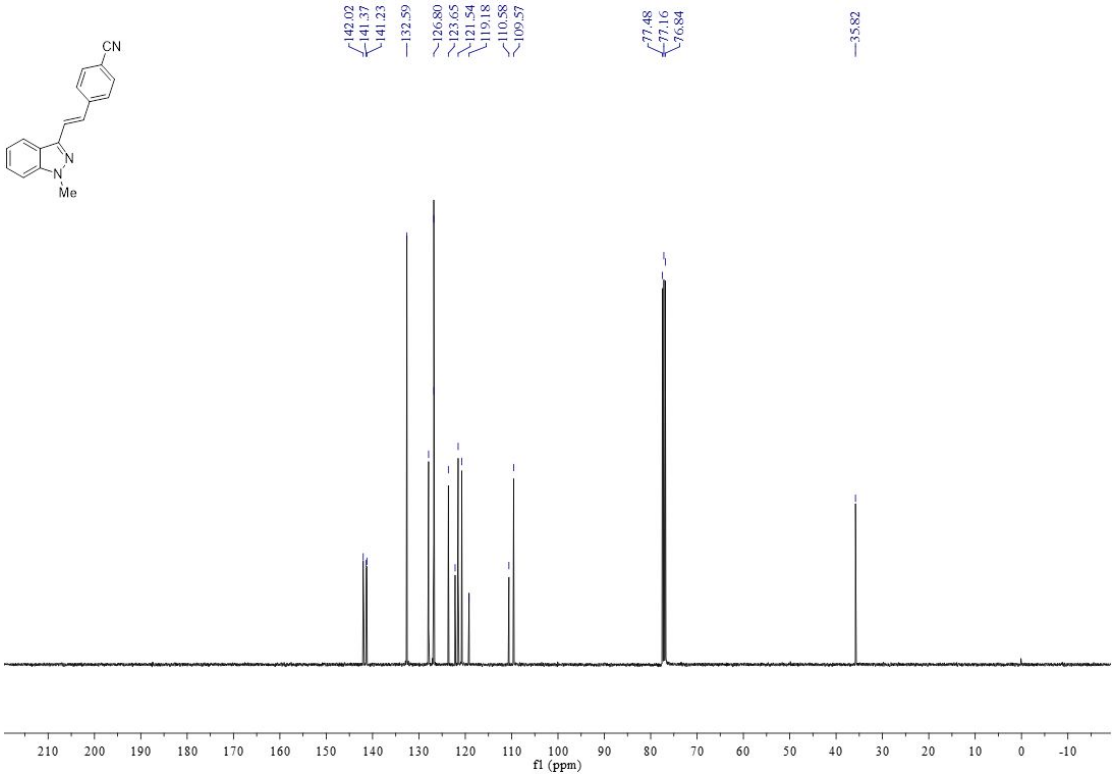
(E)-3-(4-Chlorostyryl)-1-methyl-1H-indazole **(3ap)**



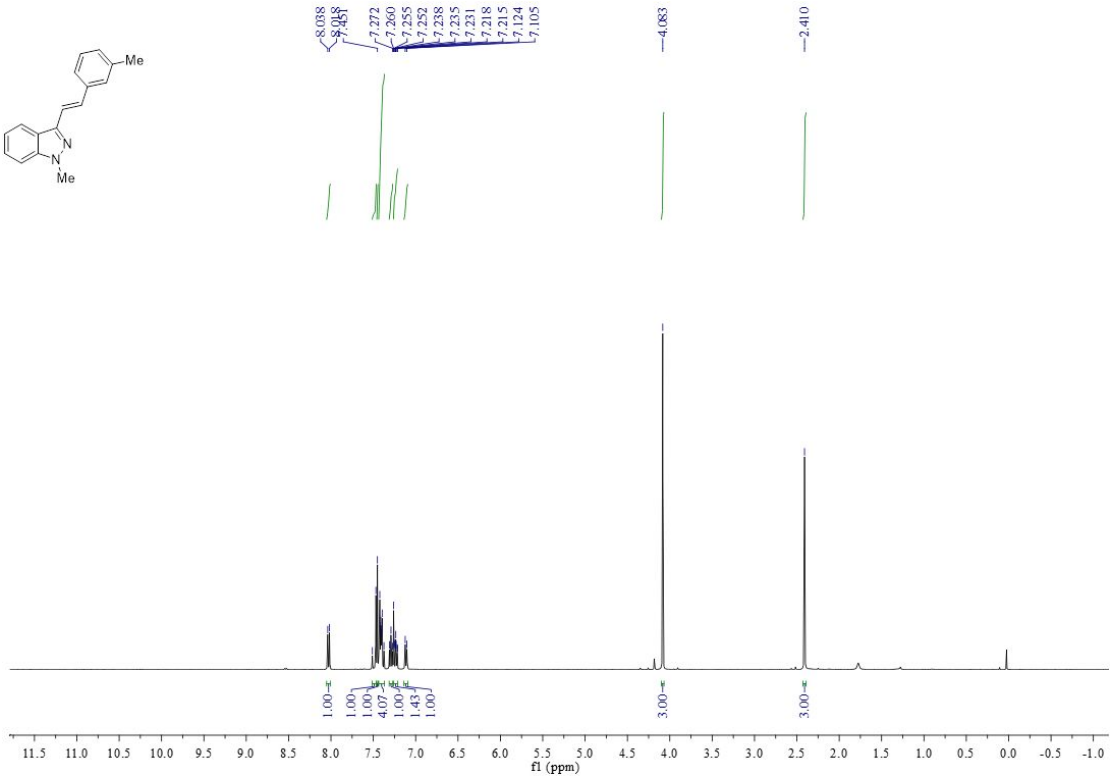


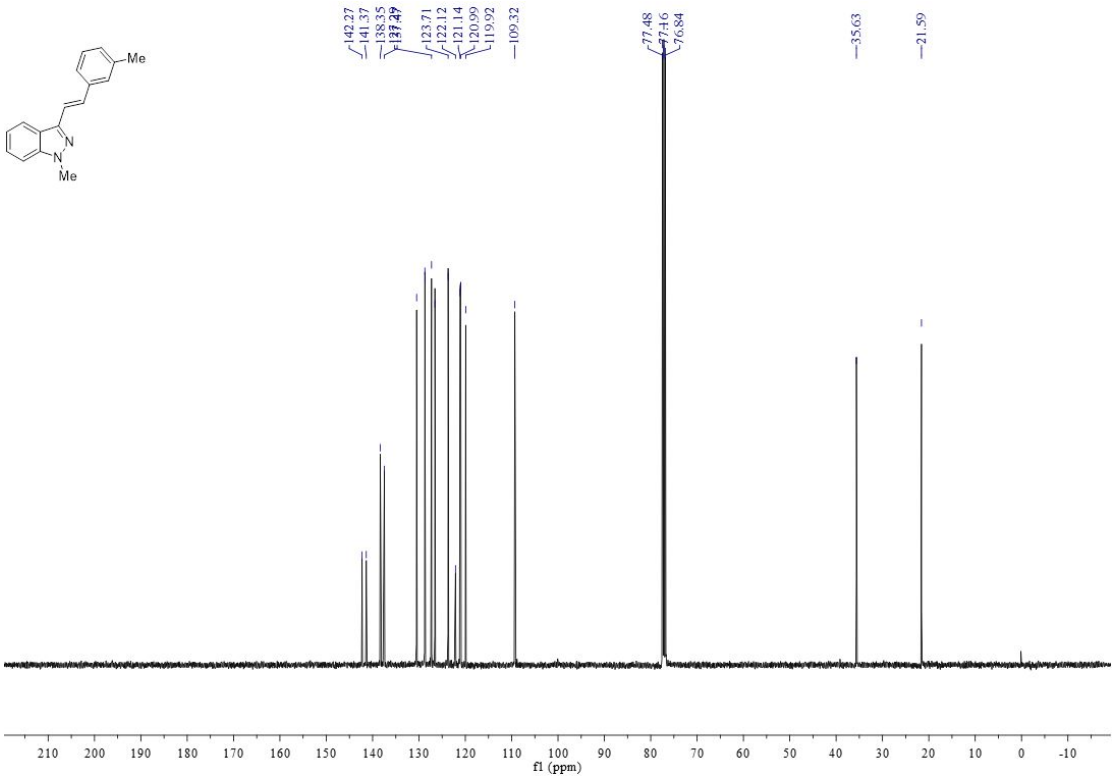
***(E)-4-(2-(1-Methyl-1H-indazol-3-yl)vinyl)benzonitrile* (3aq)**



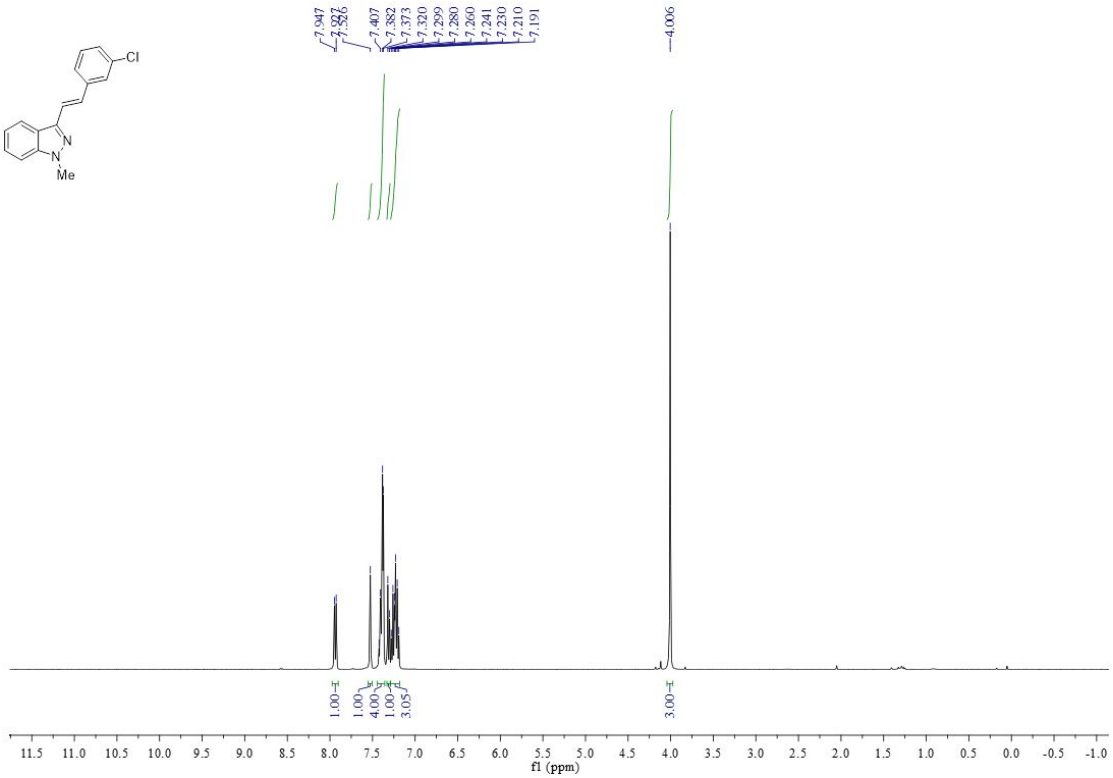


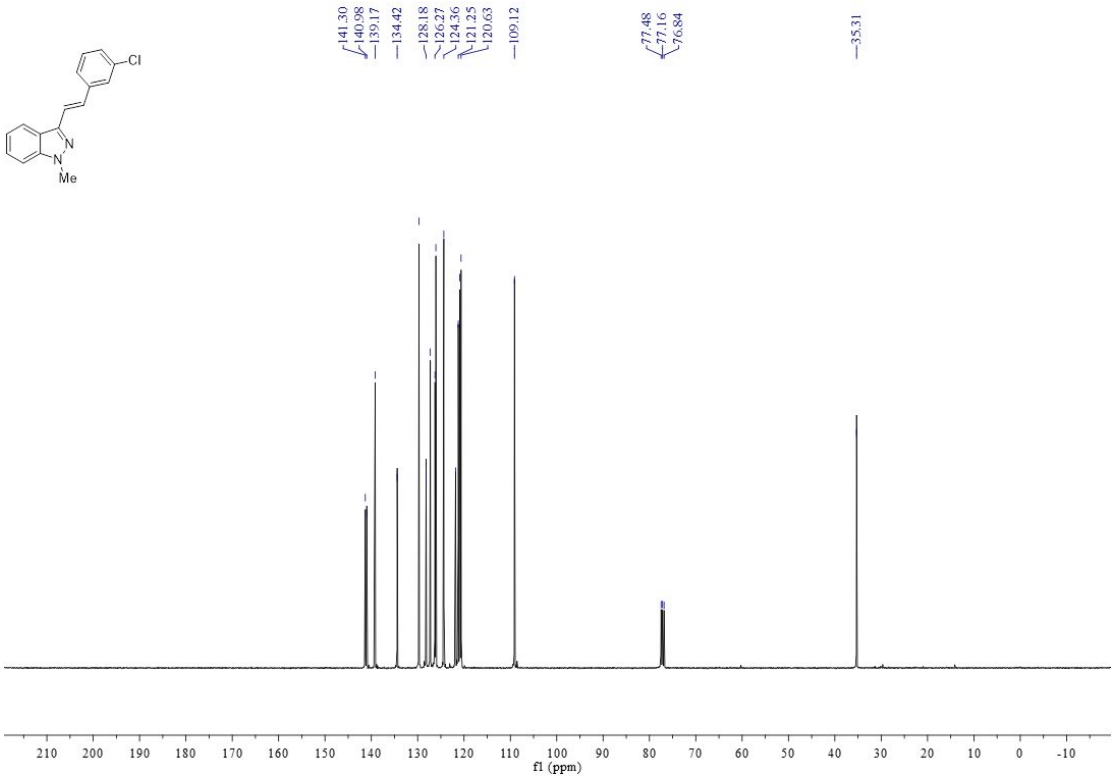
(E)-1-Methyl-3-(3-methylstyryl)-1H-indazole **(3ar)**



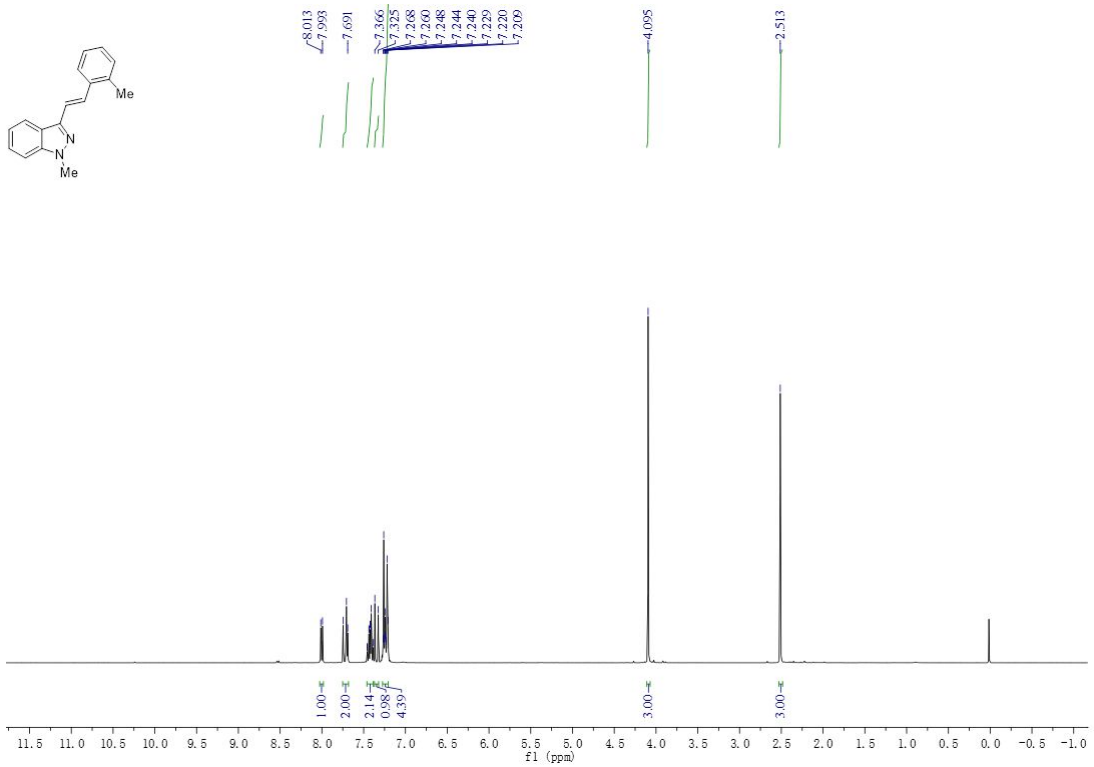


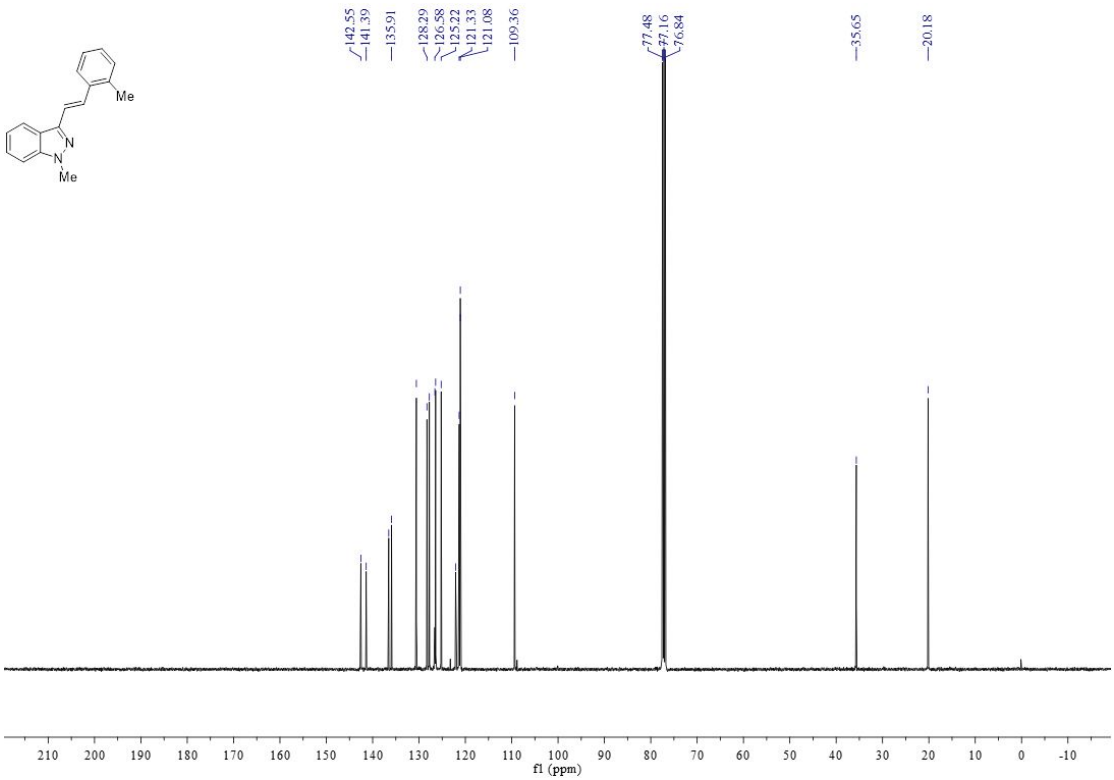
(E)-3-(3-Chlorostyryl)-1-methyl-1H-indazole **(3as)**



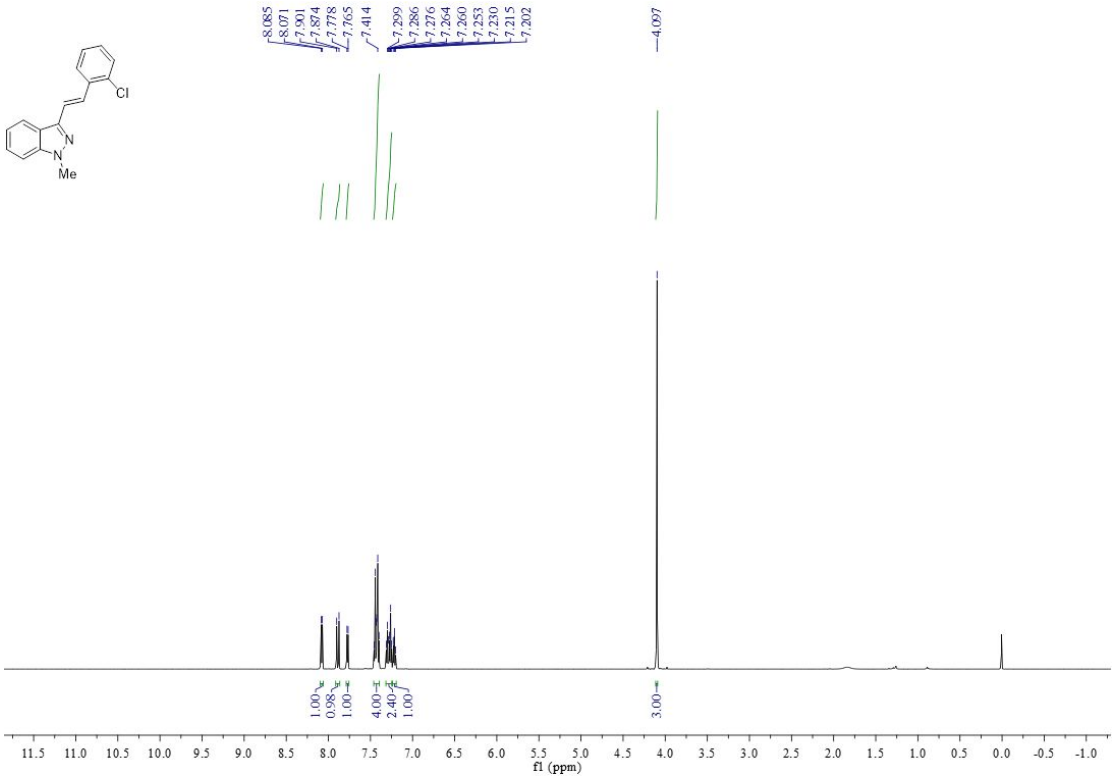


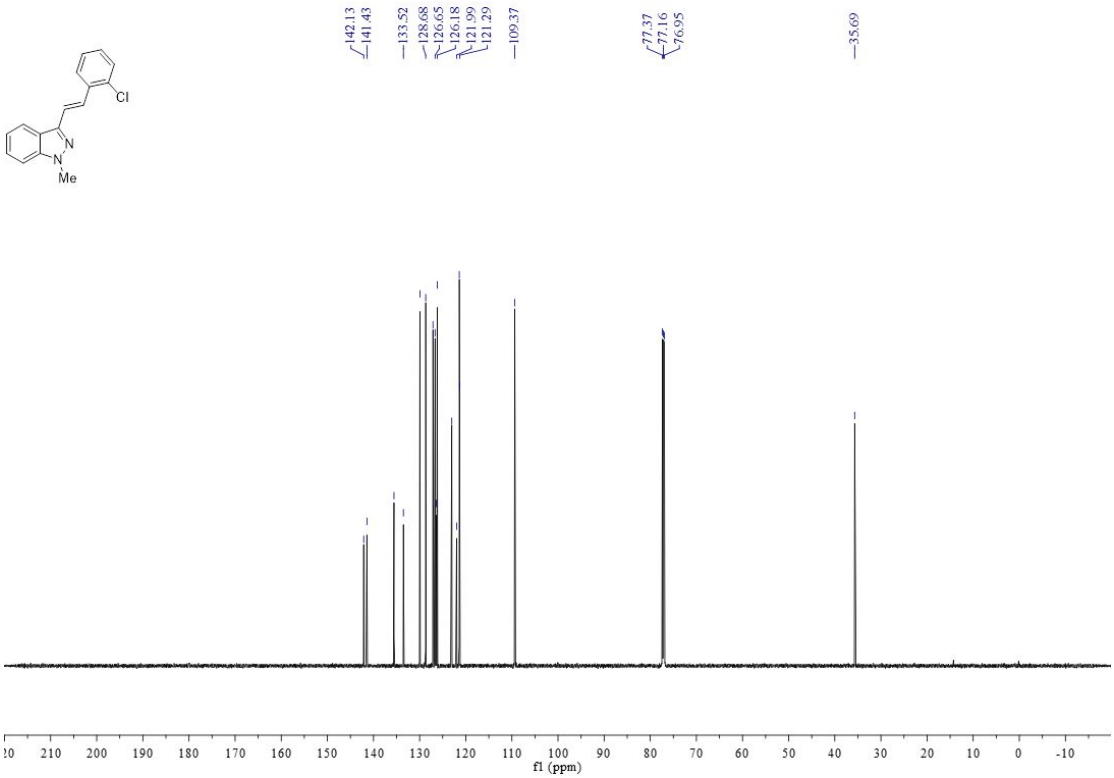
(E)-1-Methyl-3-(2-methylstyryl)-1H-indazole **(3at)**



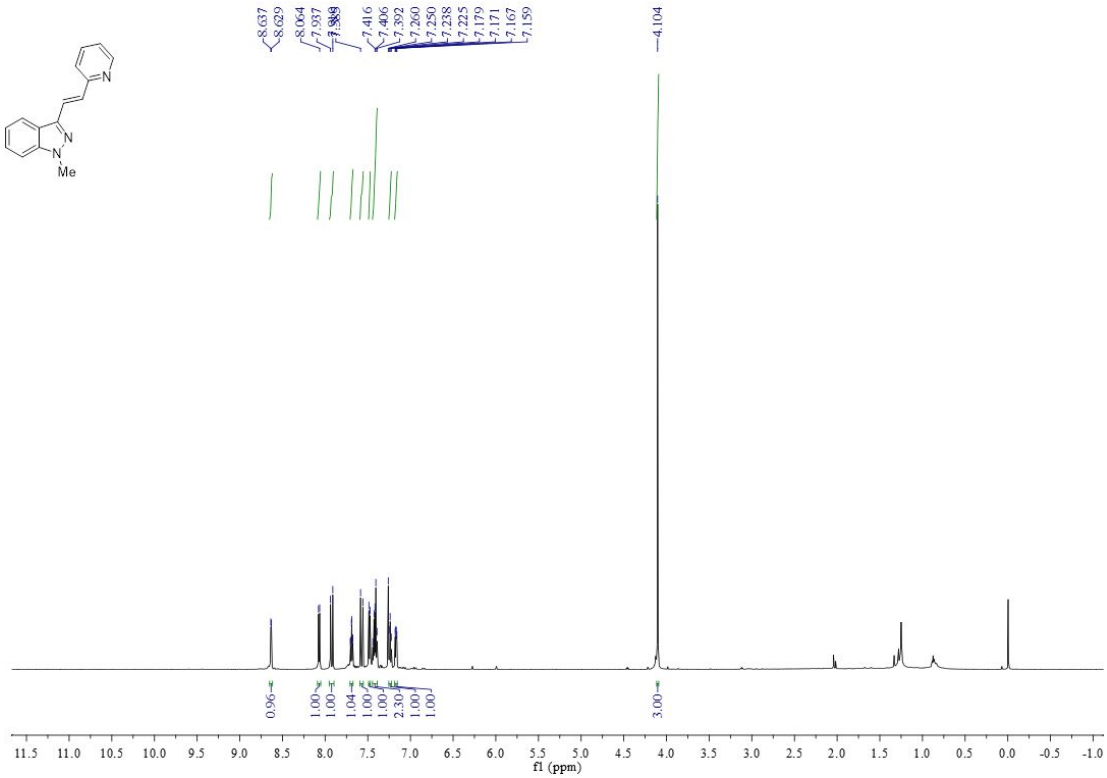


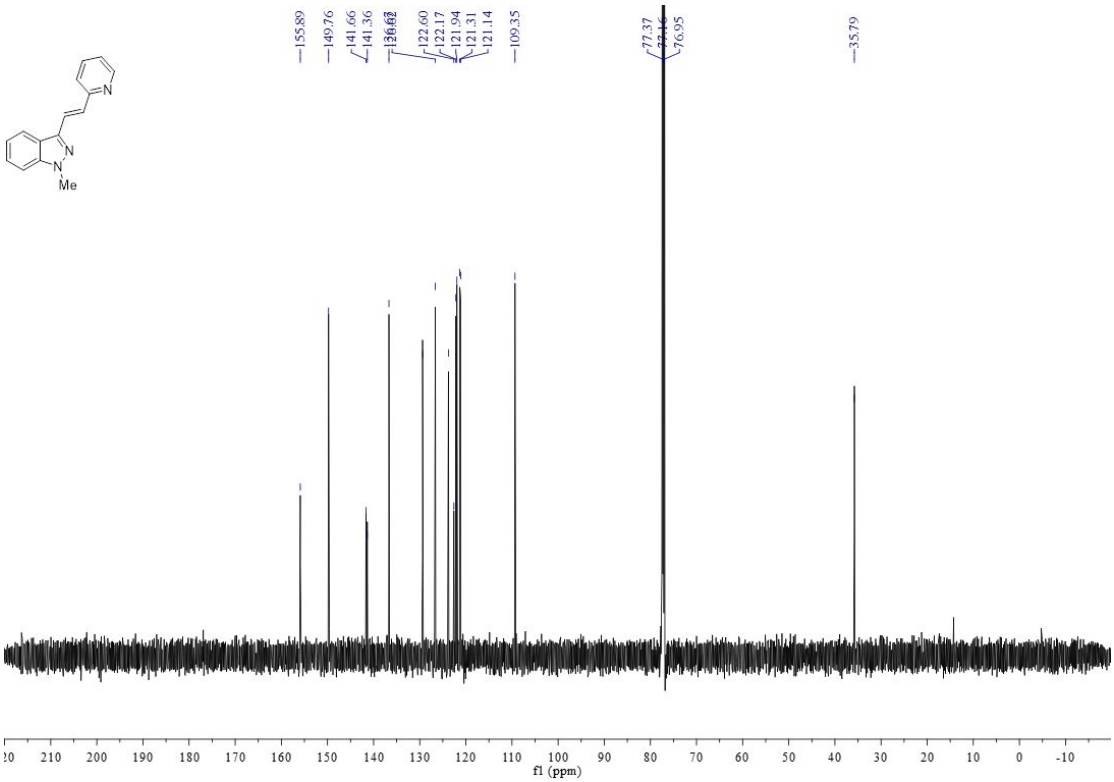
(E)-3-(2-Chlorostyryl)-1-methyl-1H-indazole **(3au)**



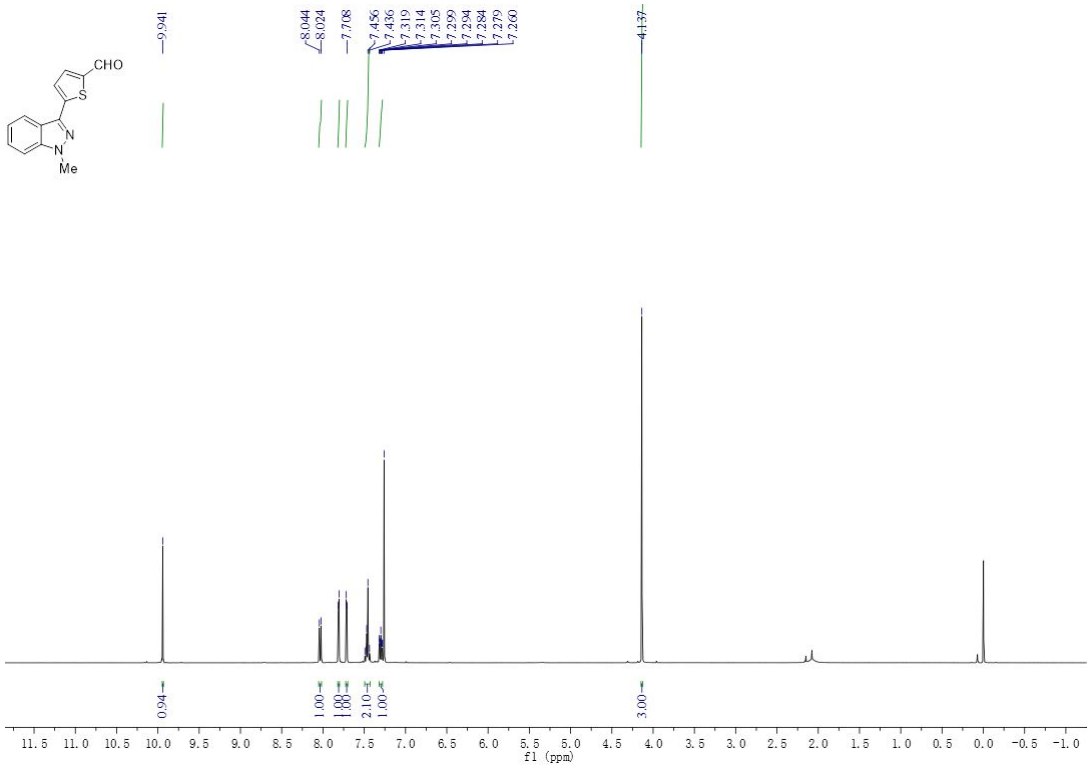


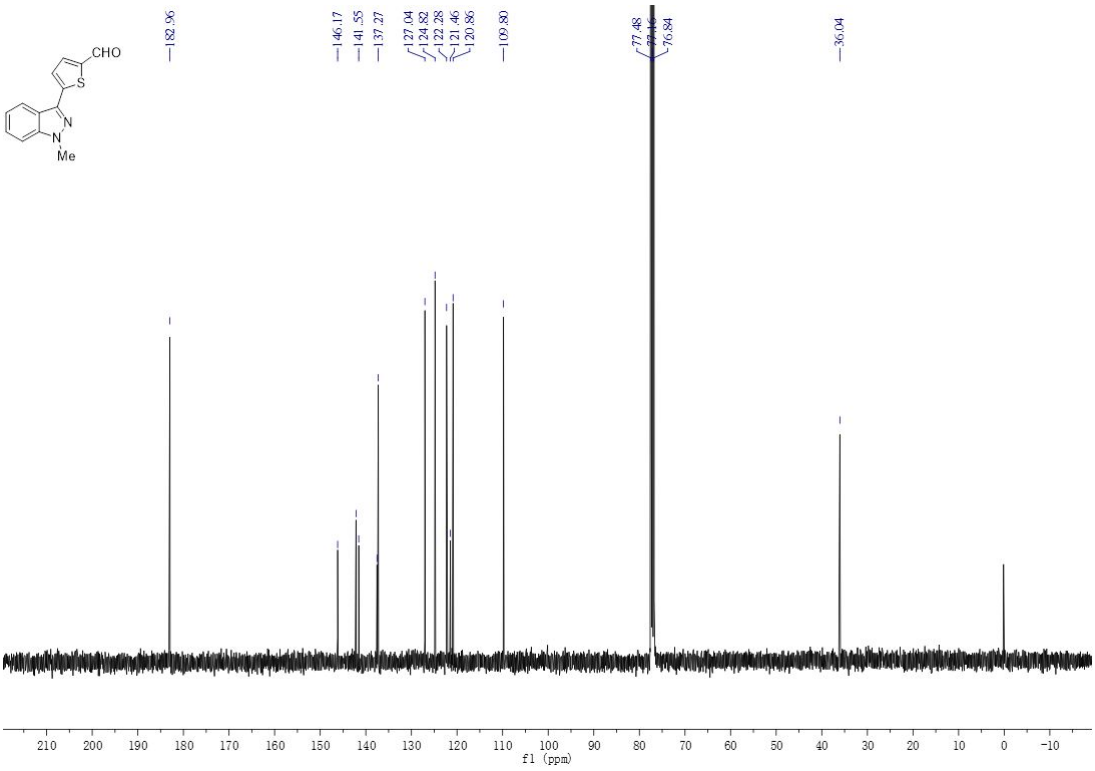
(E)-1-Methyl-3-(2-(pyridin-2-yl)vinyl)-1H-indazole **(3av)**



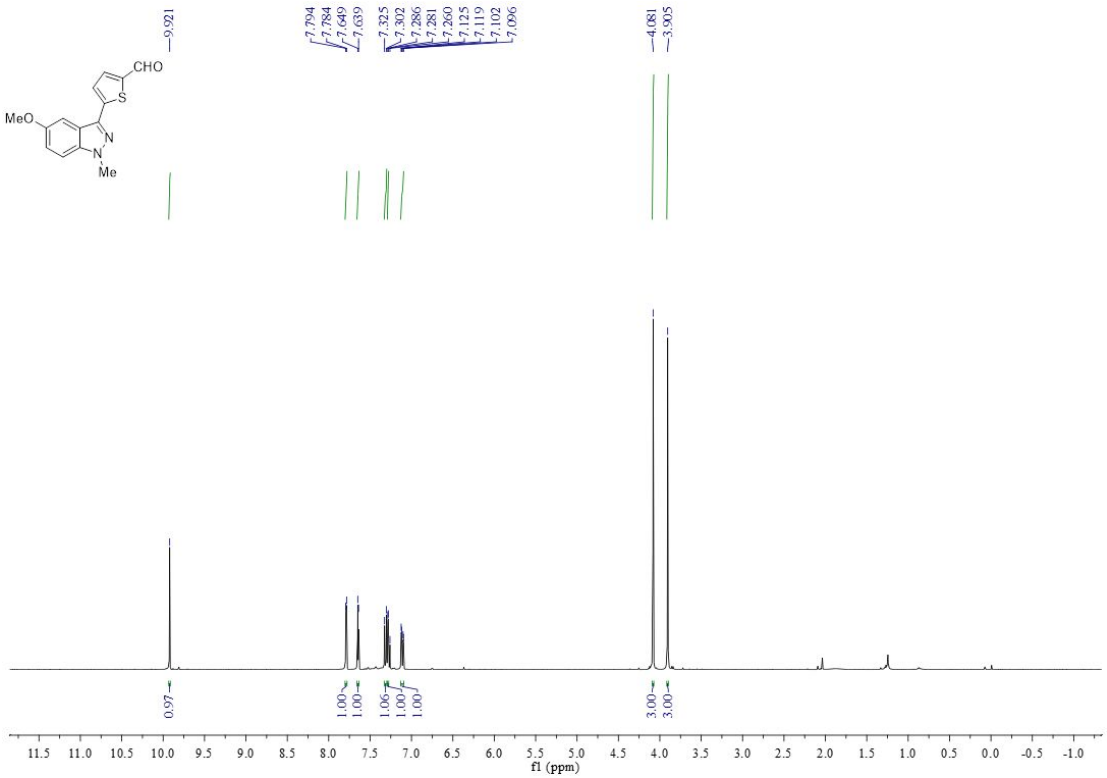


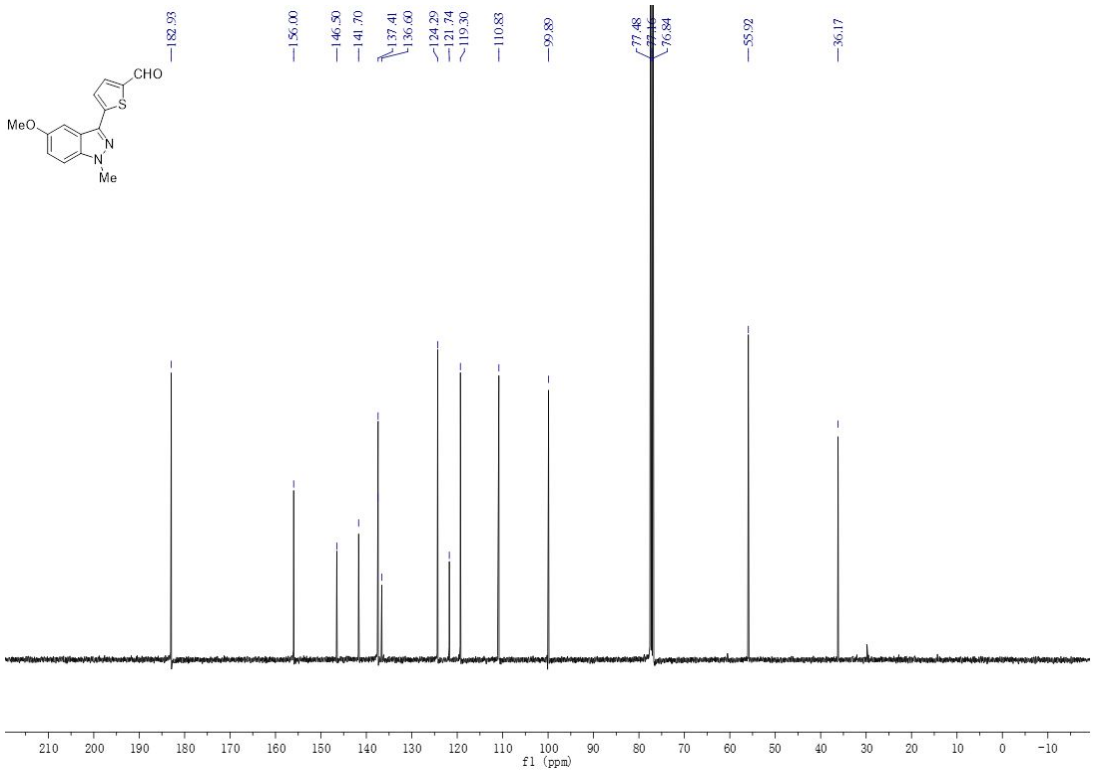
5-(1-Methyl-1H-indazol-3-yl)thiophene-2-carbaldehyde **(5aa)**



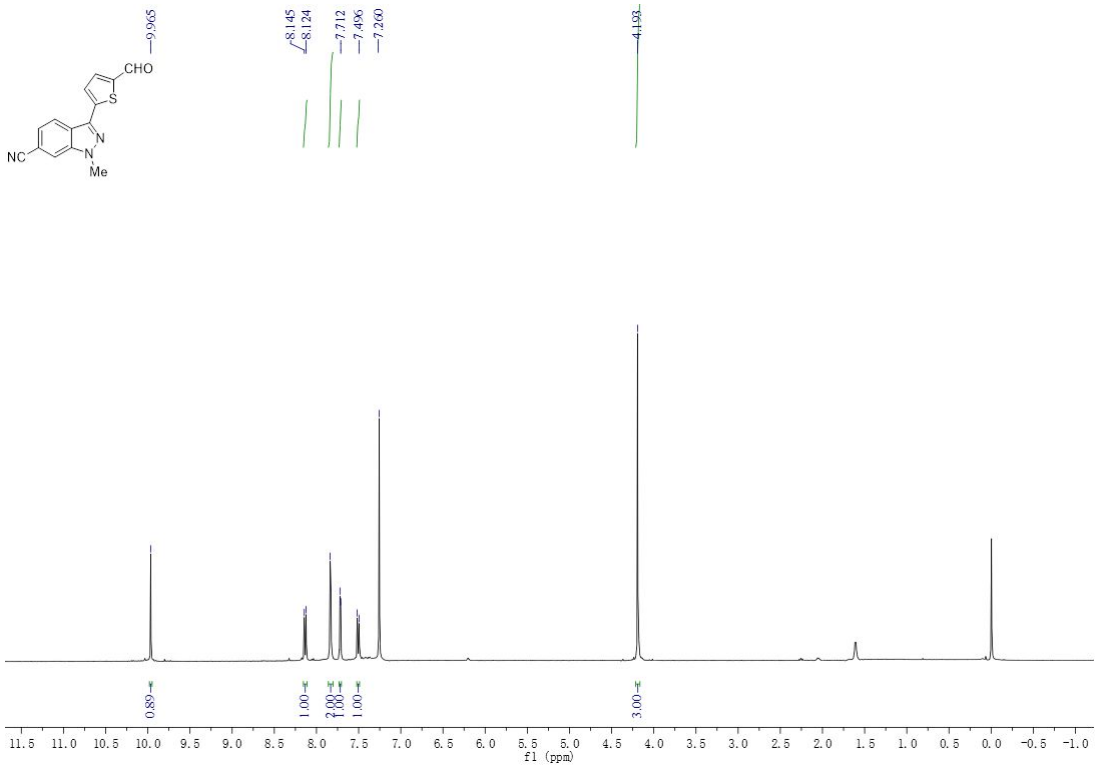


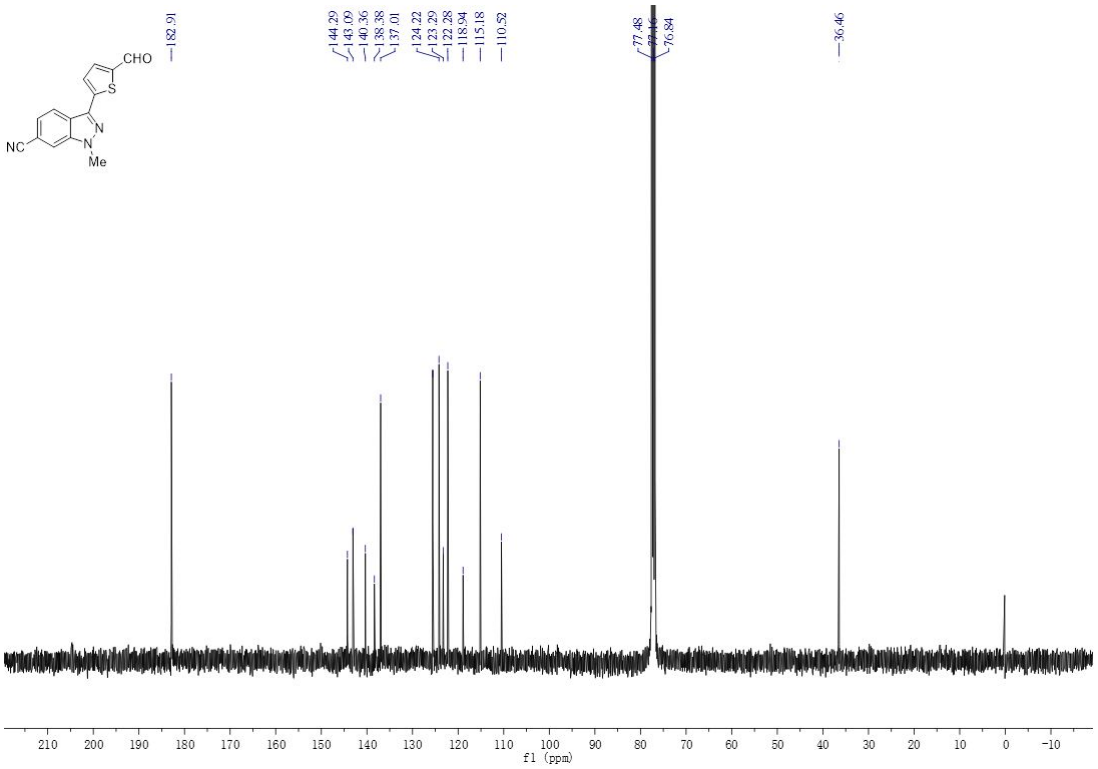
5-(5-Methoxy-1-methyl-1H-indazol-3-yl)thiophene-2-carbaldehyde **(5da)**



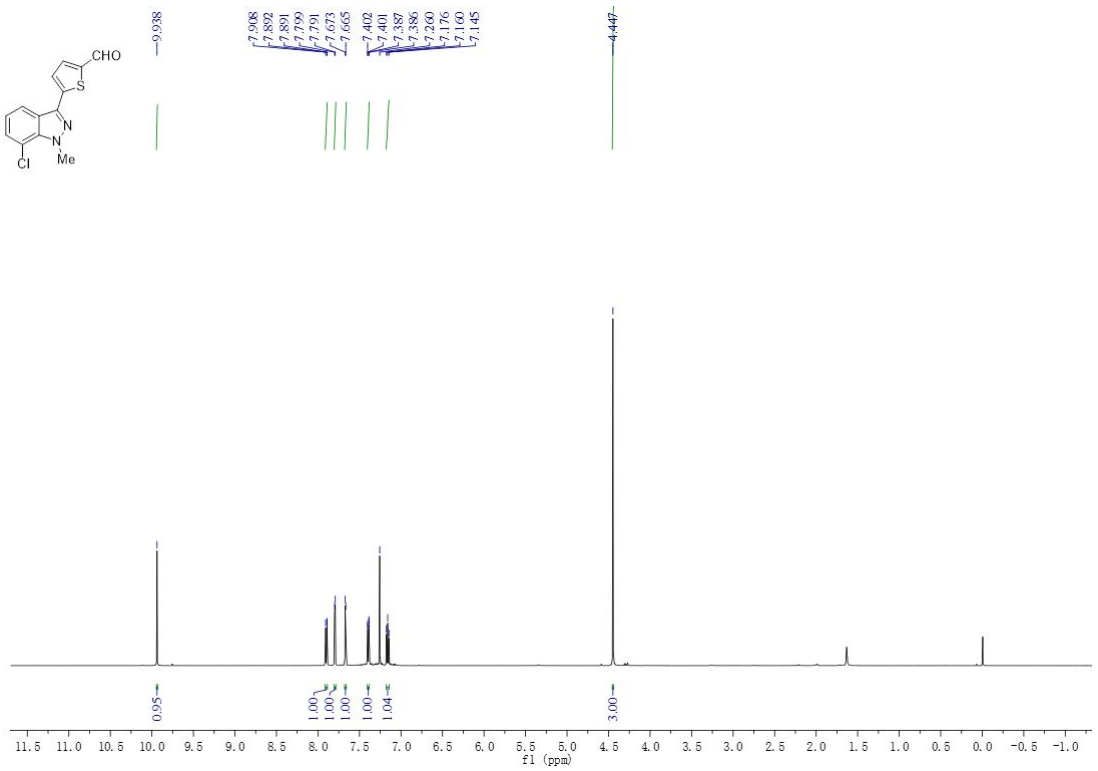


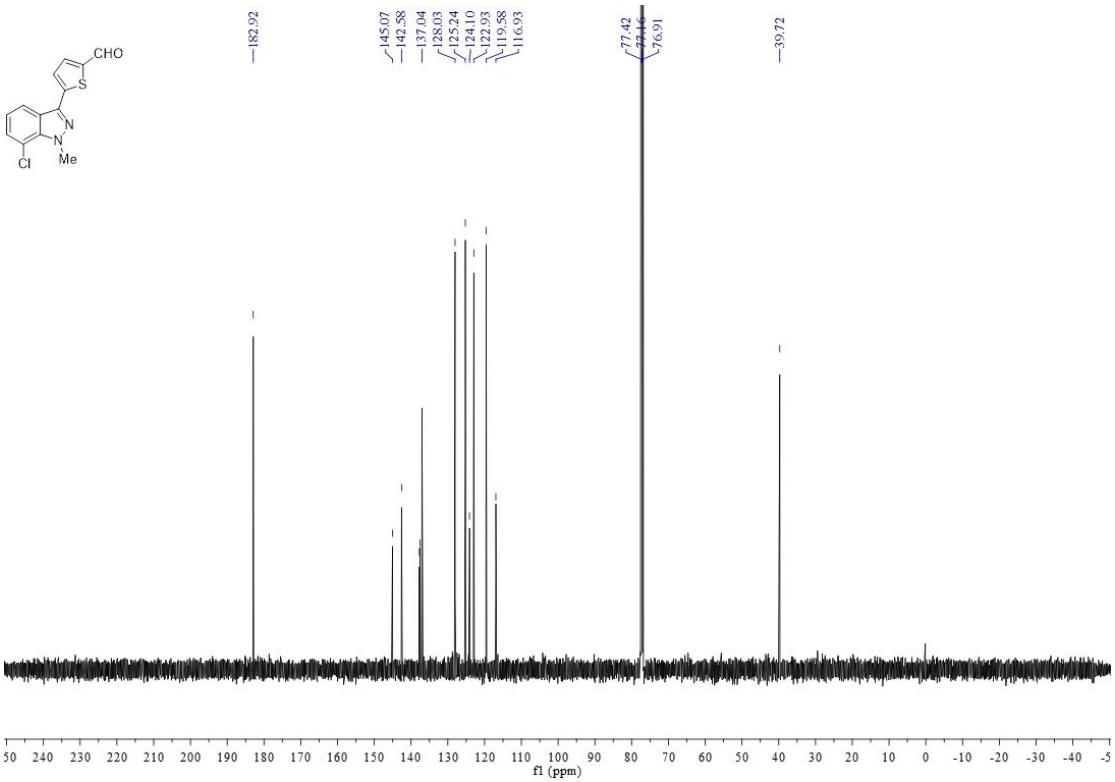
***3-(5-Formylthiophen-2-yl)-1-methyl-1H-indazole-6-carbonitrile* (5ga)**



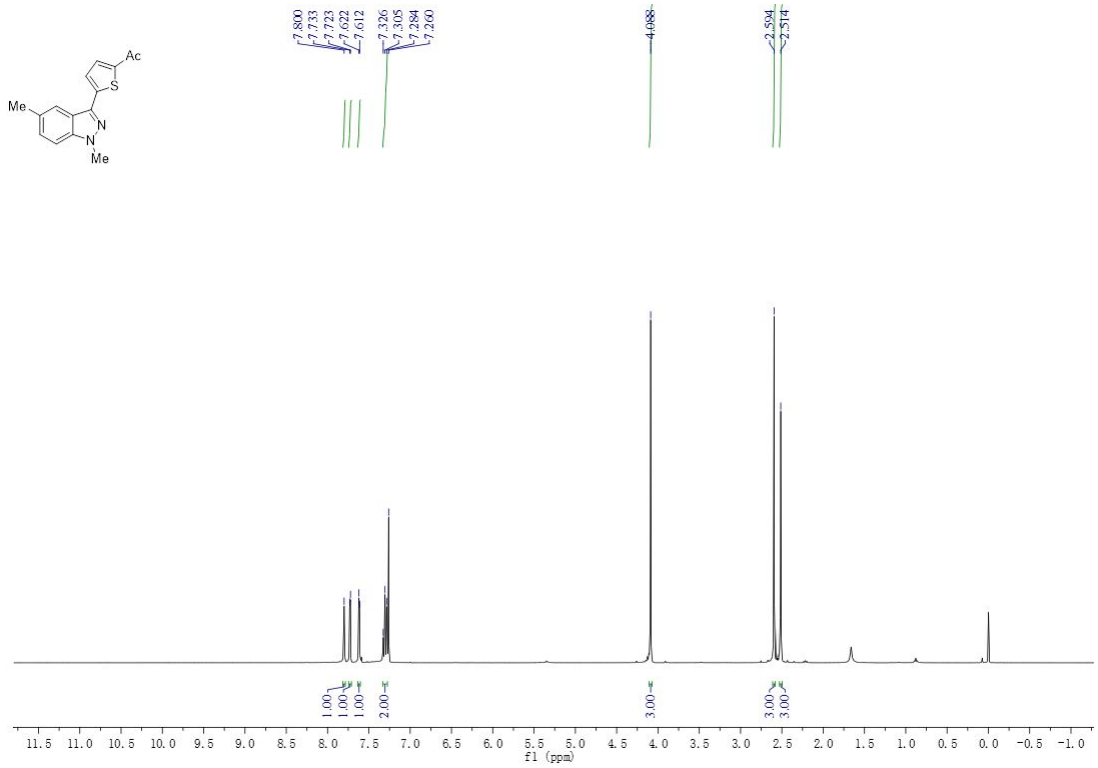


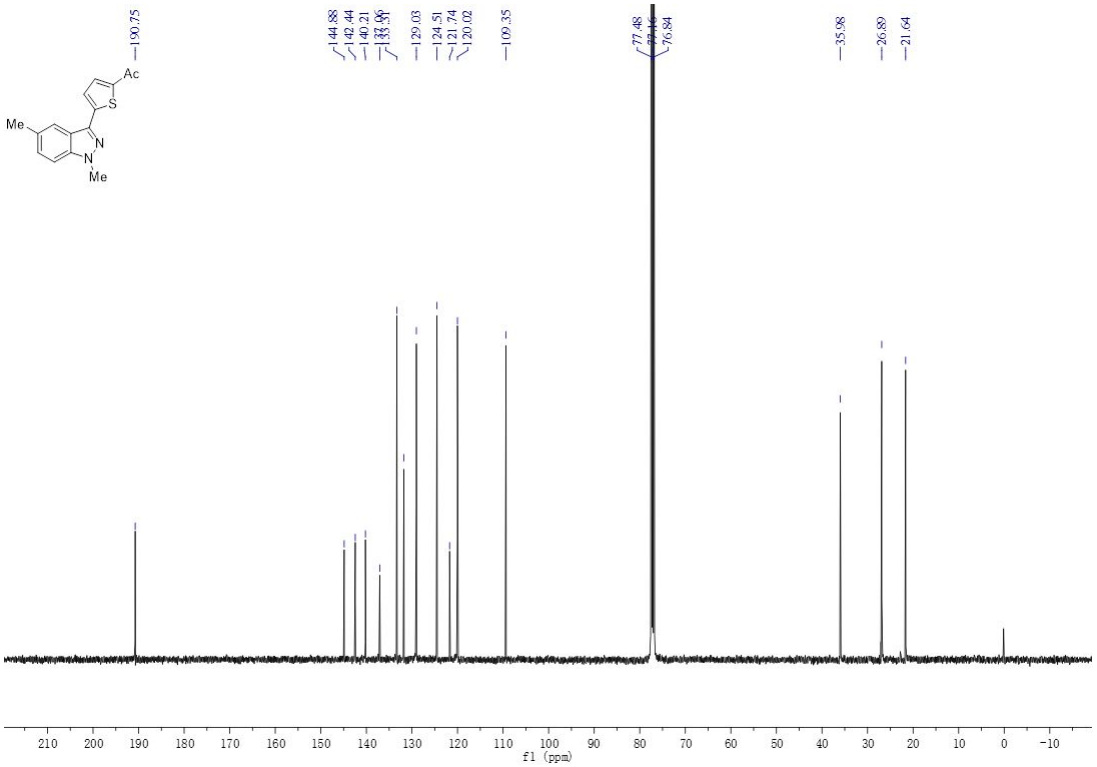
5-(7-Chloro-1-methyl-1H-indazol-3-yl)thiophene-2-carbaldehyde **(5ha)**



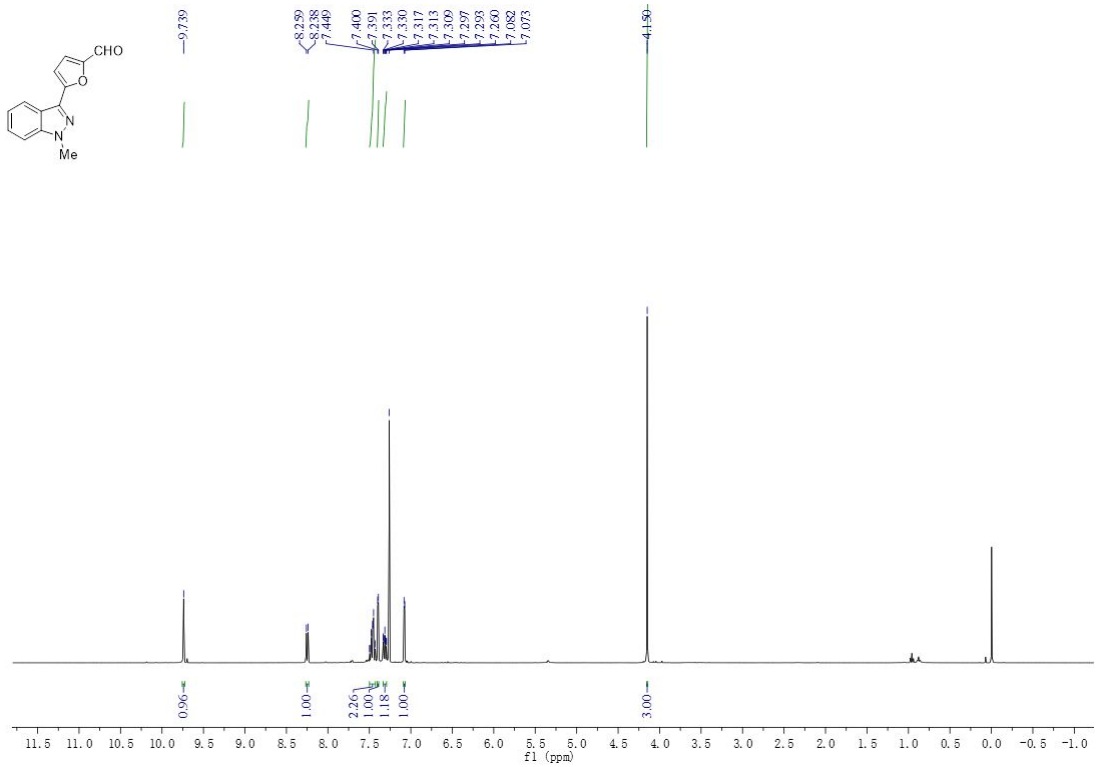


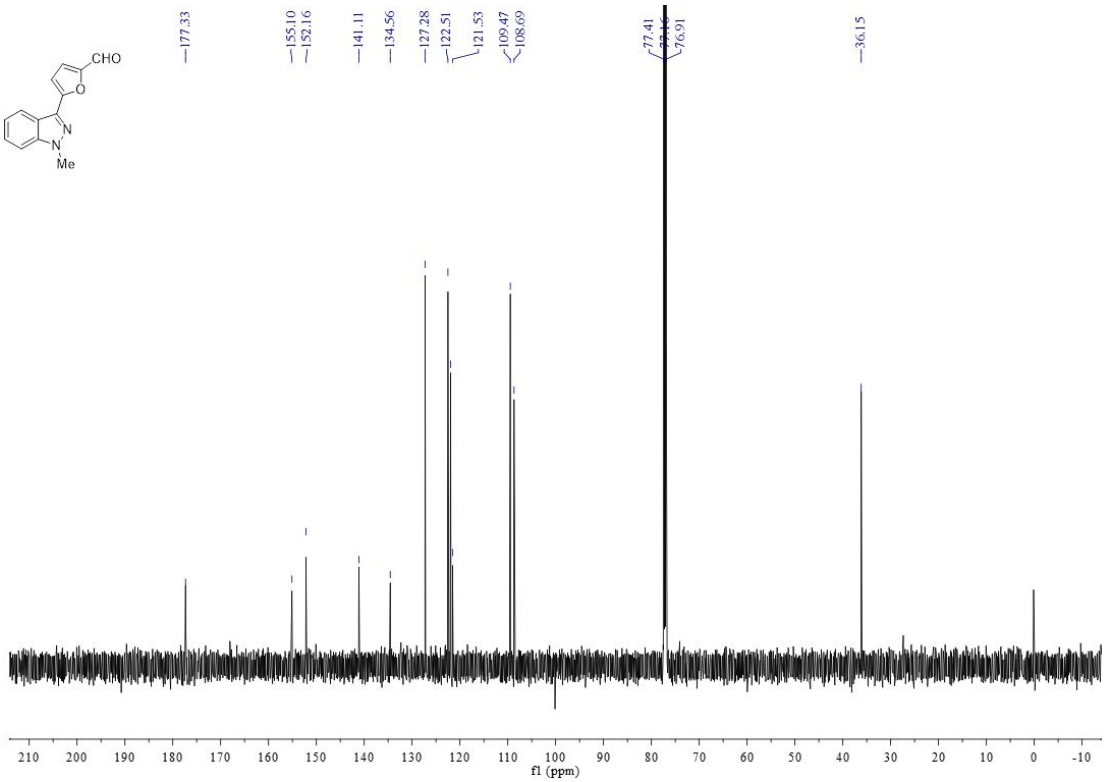
1-(5-(1,5-Dimethyl-1H-indazol-3-yl)thiophen-2-yl)ethan-1-one **(5jb)**



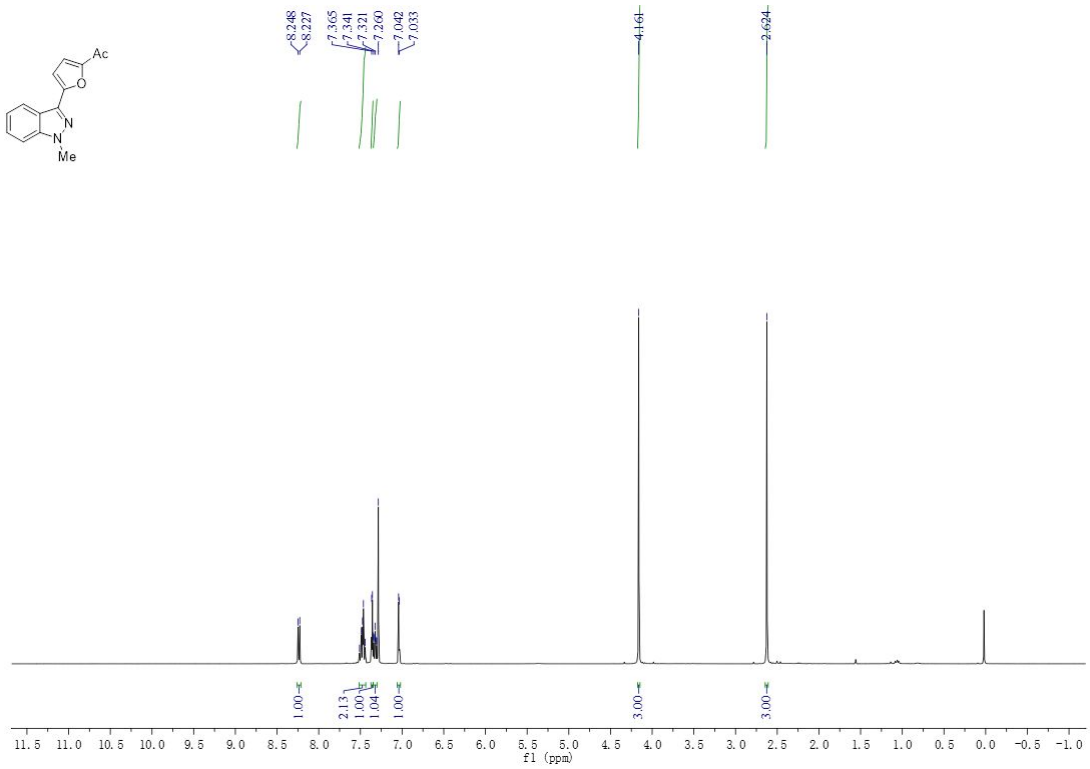


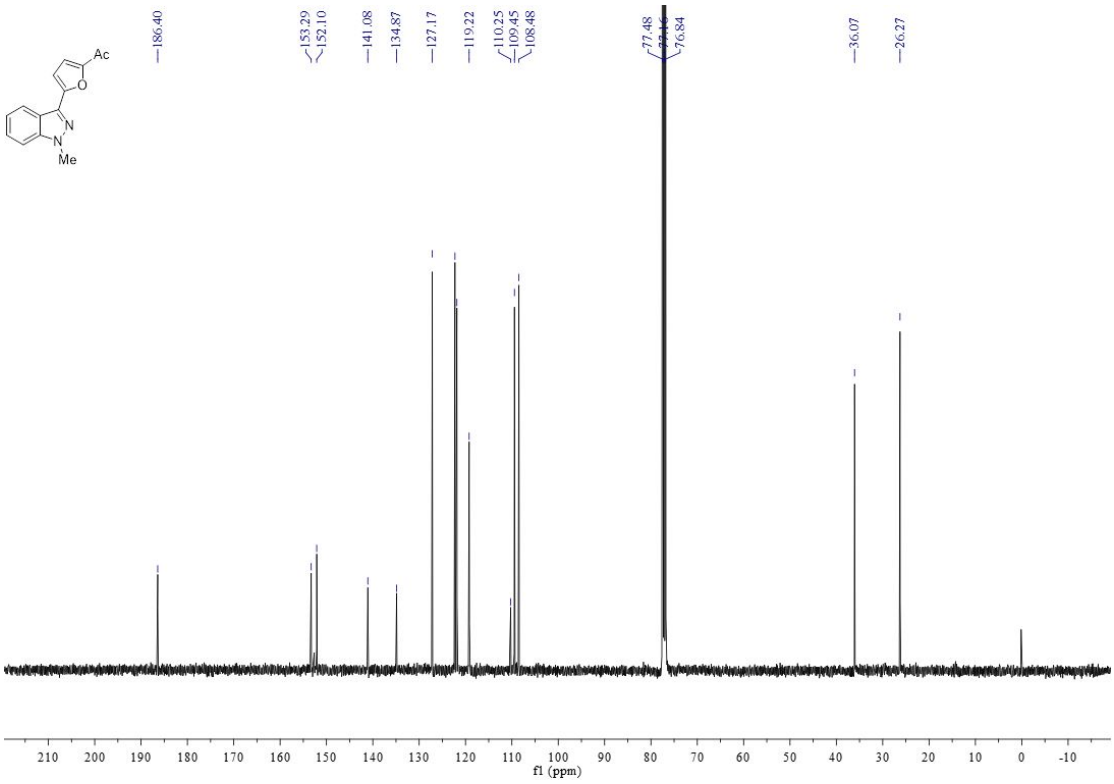
5-(1-Methyl-1H-indazol-3-yl)furan-2-carbaldehyde **(5ac)**



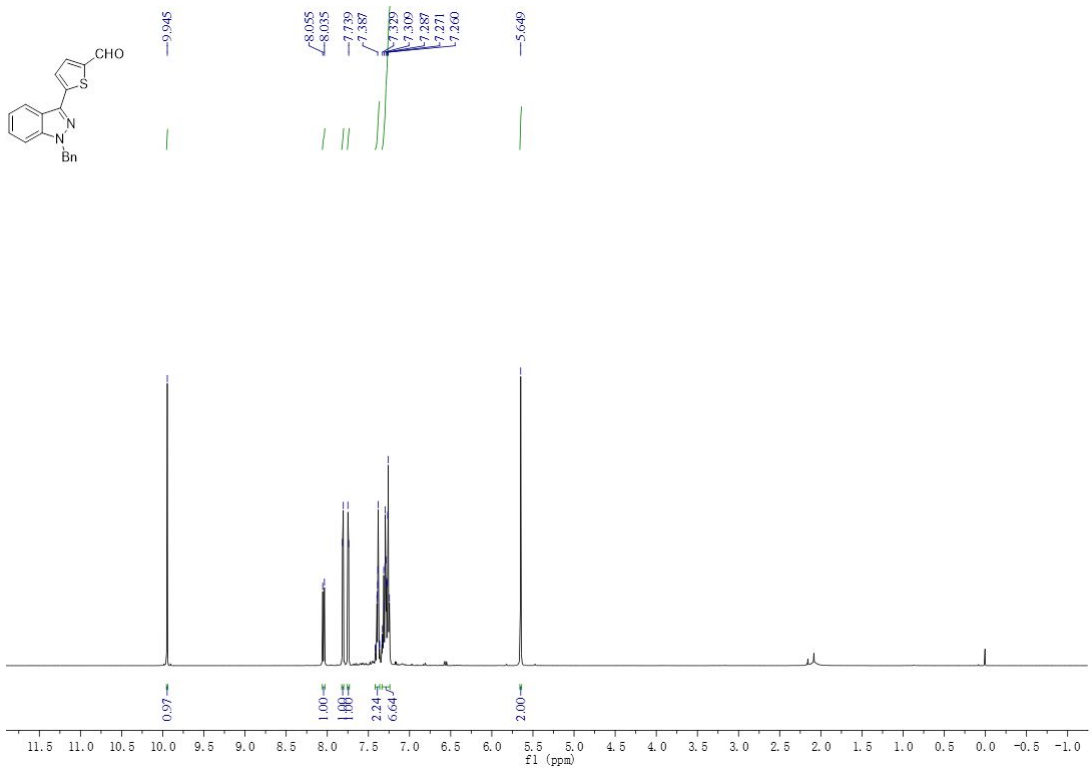


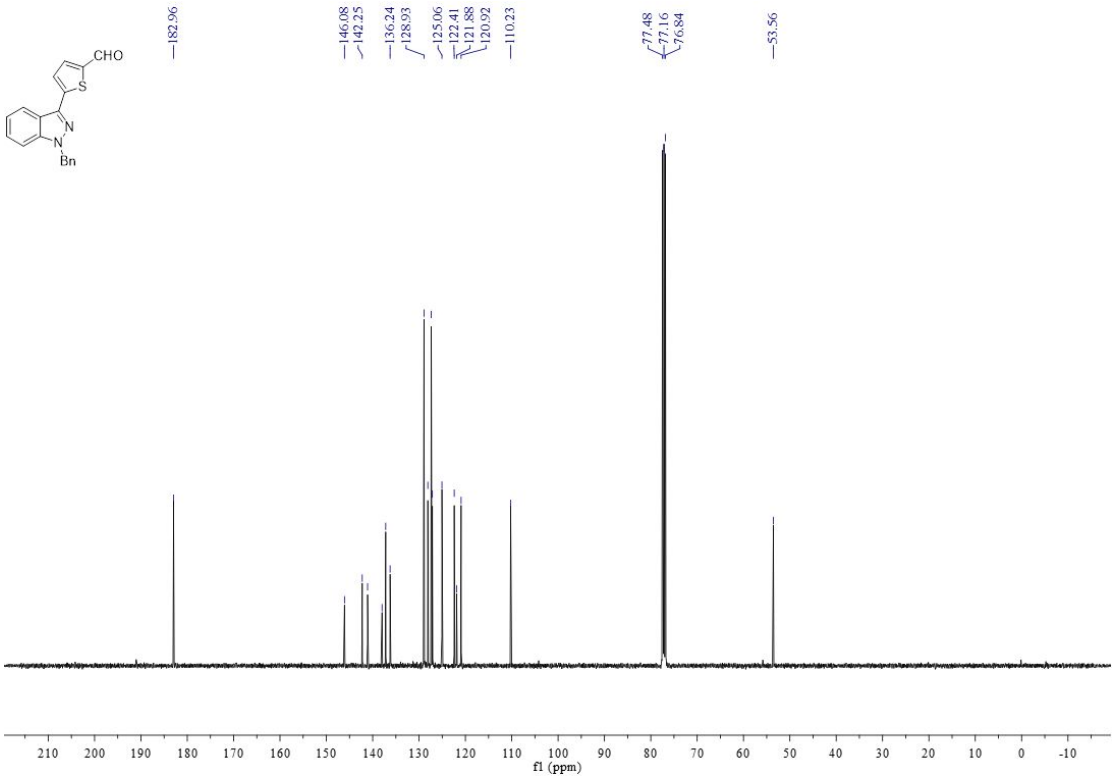
1-(5-(1-Methyl-1H-indazol-3-yl)furan-2-yl)ethan-1-one **(5ad)**



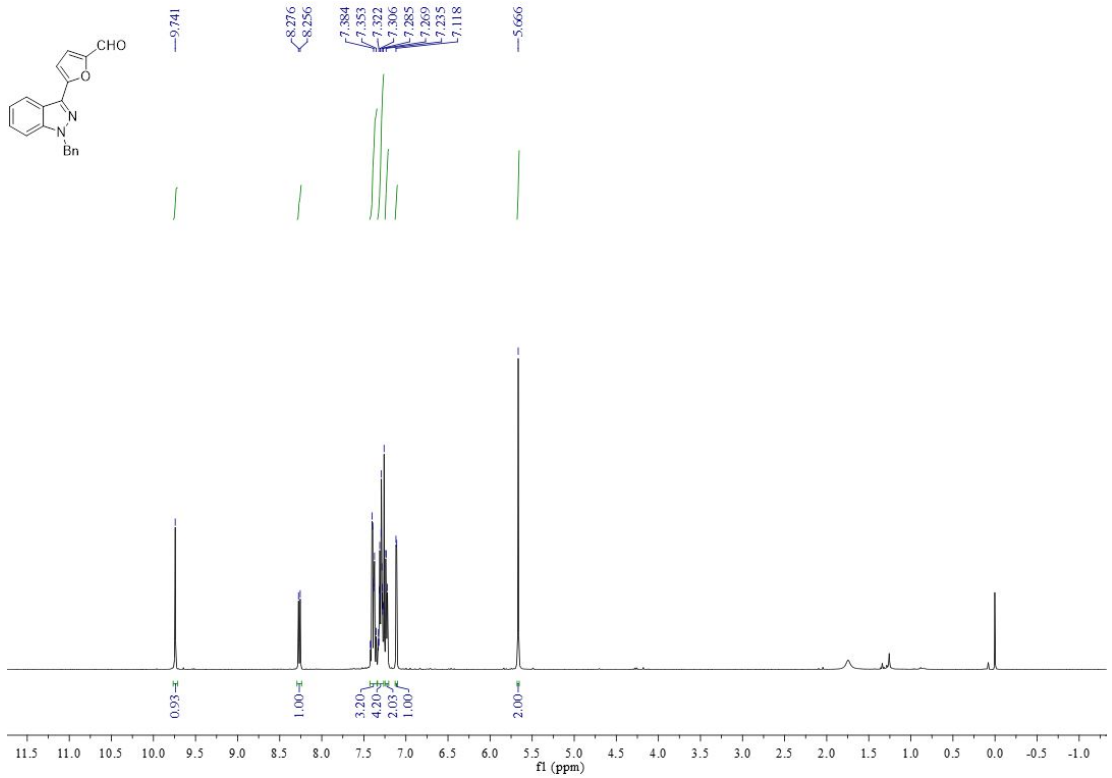


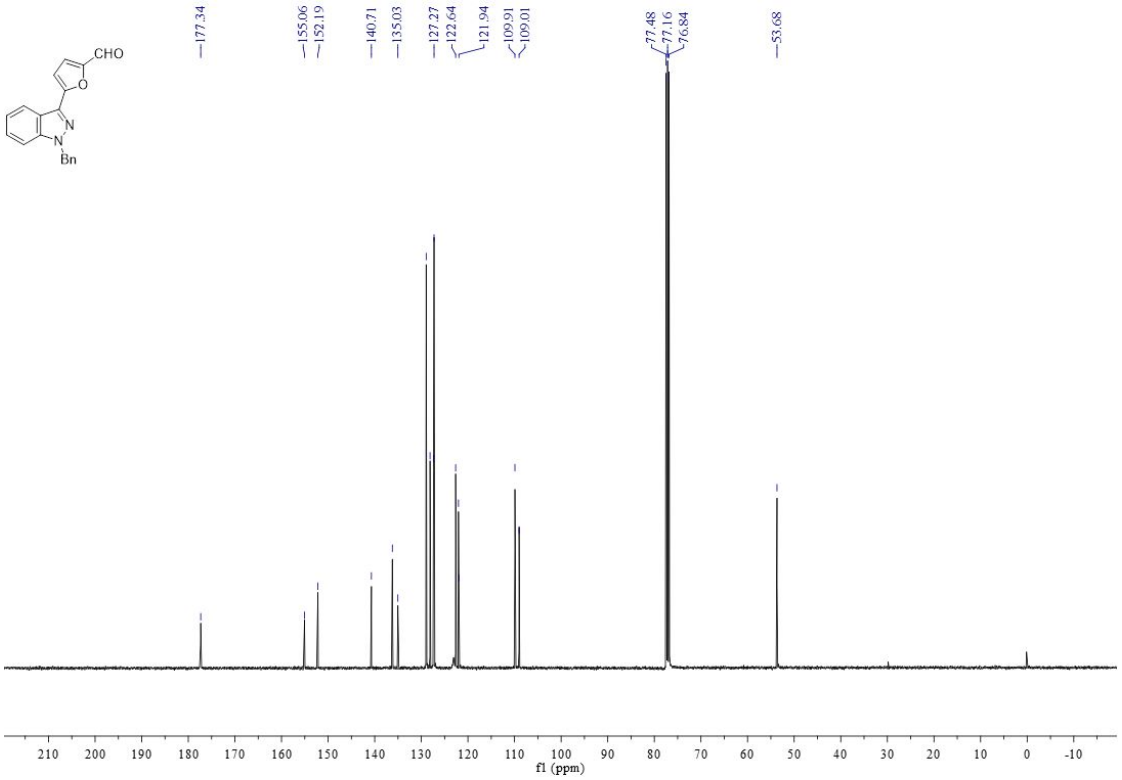
5-(1-Benzyl-1H-indazol-3-yl)thiophene-2-carbaldehyde **(5ia)**



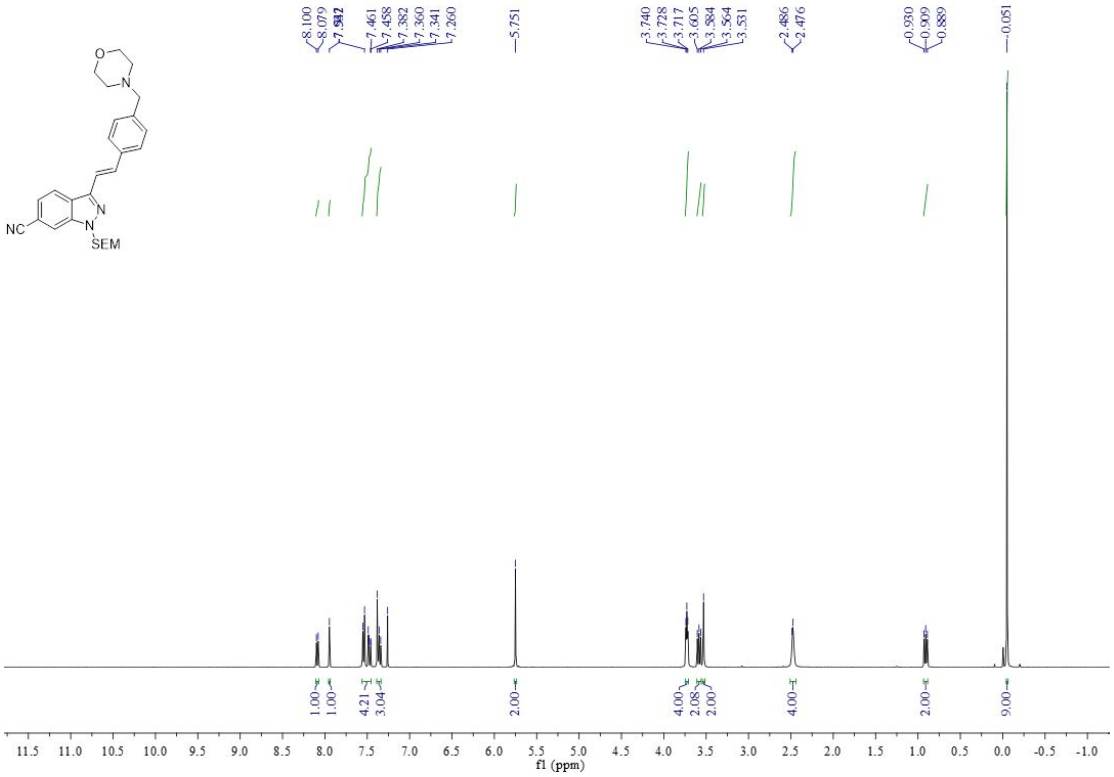


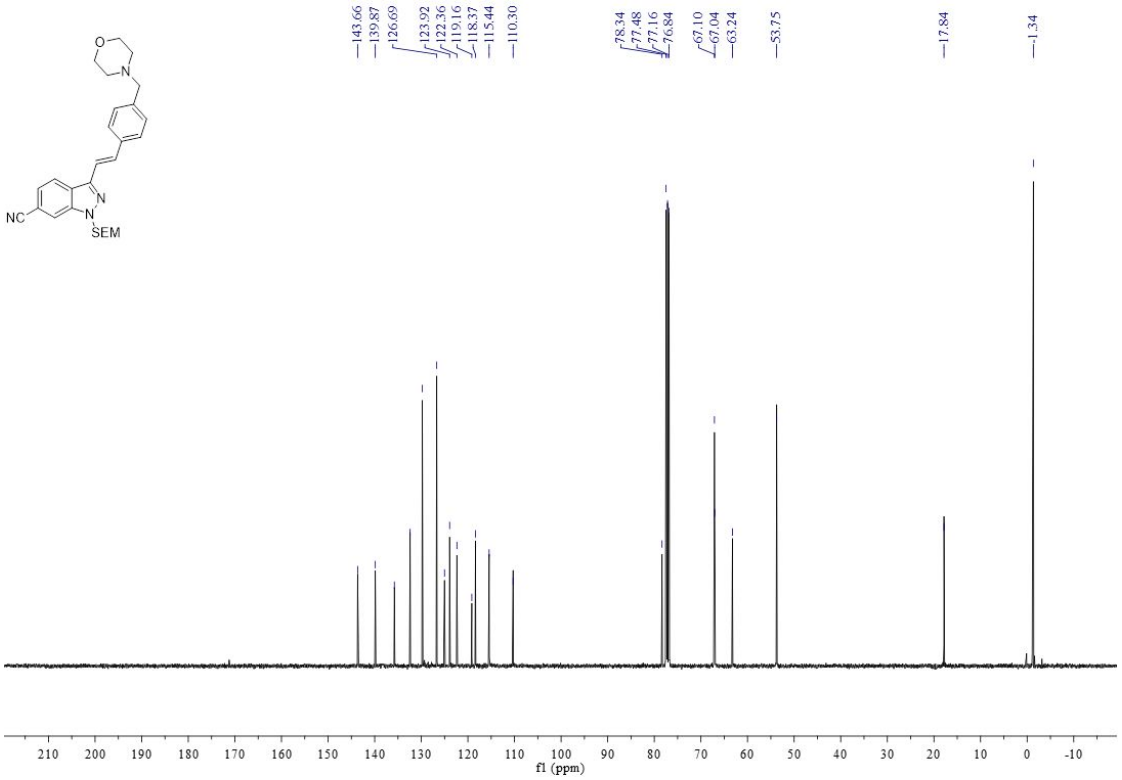
5-(1-Benzyl-1H-indazol-3-yl)furan-2-carbaldehyde **(5ic)**



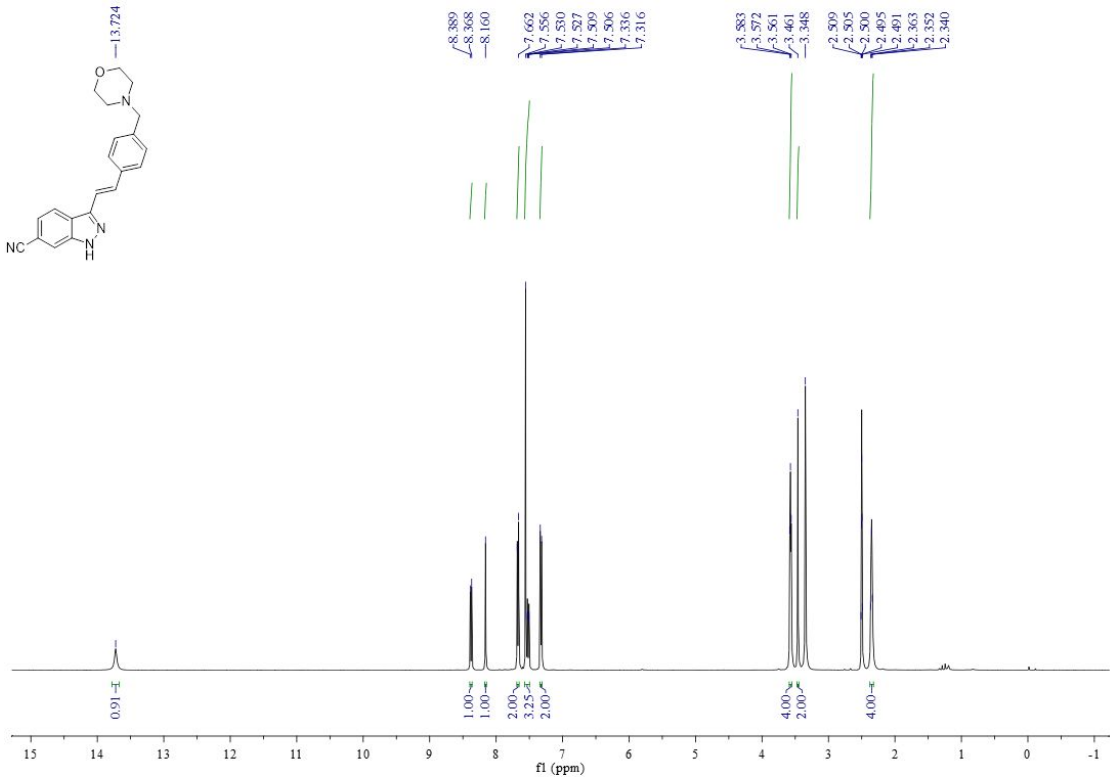


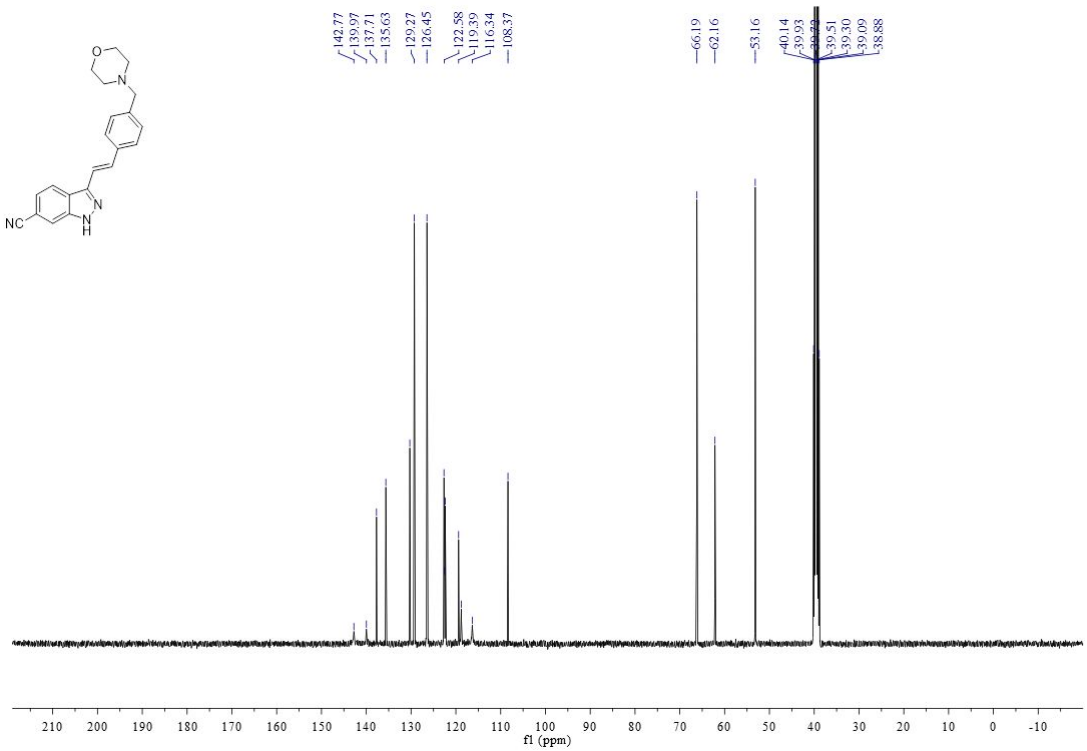
***(E)-3-(4-(Morpholinomethyl)styryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbonitrile* (3kw)**



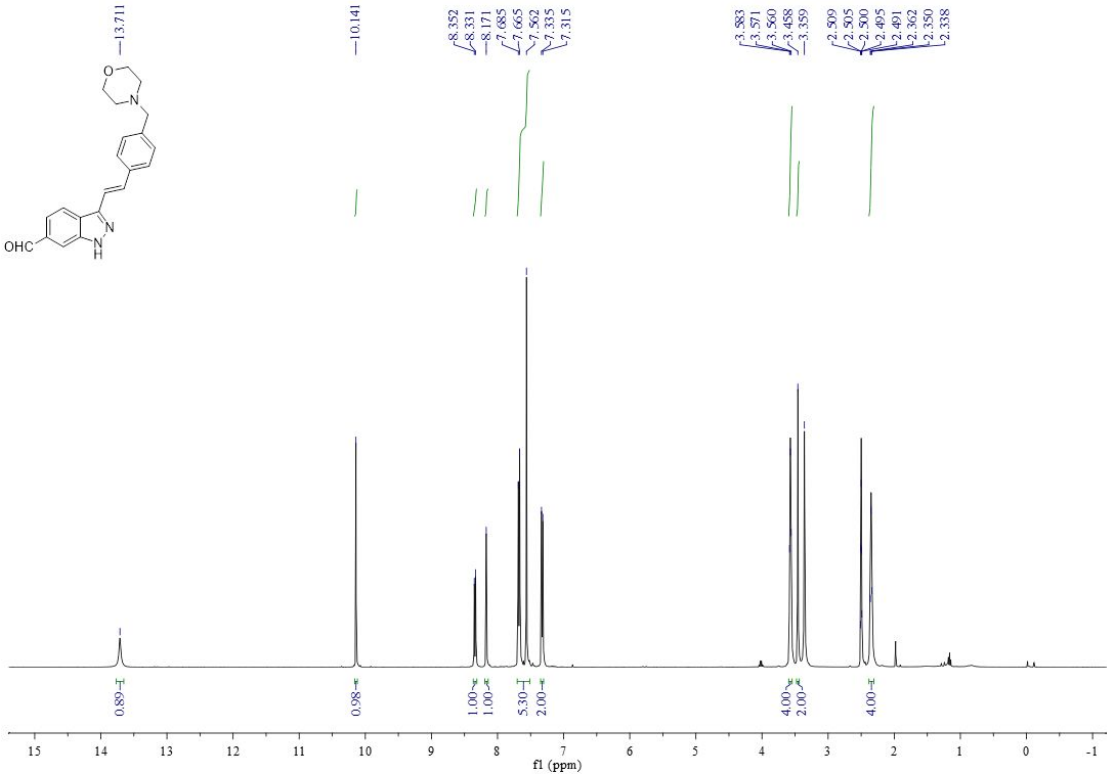


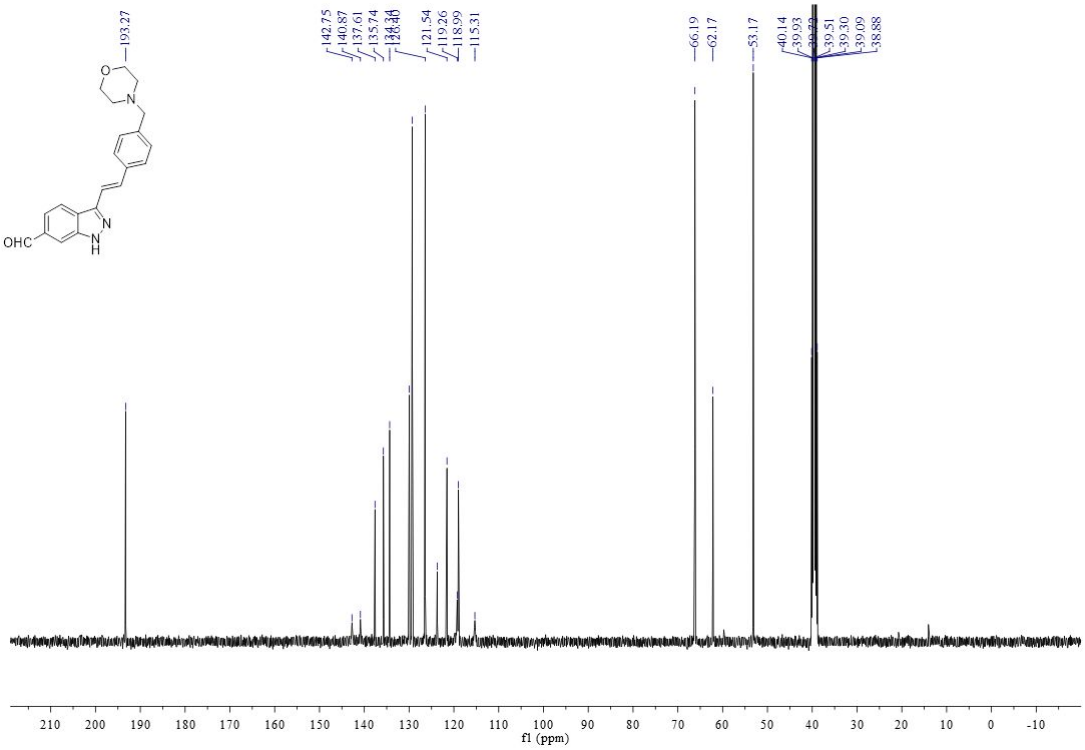
***(E)-3-(4-(Morpholinomethyl)styryl)-1H-indazole-6-carbonitrile* (3lw)**



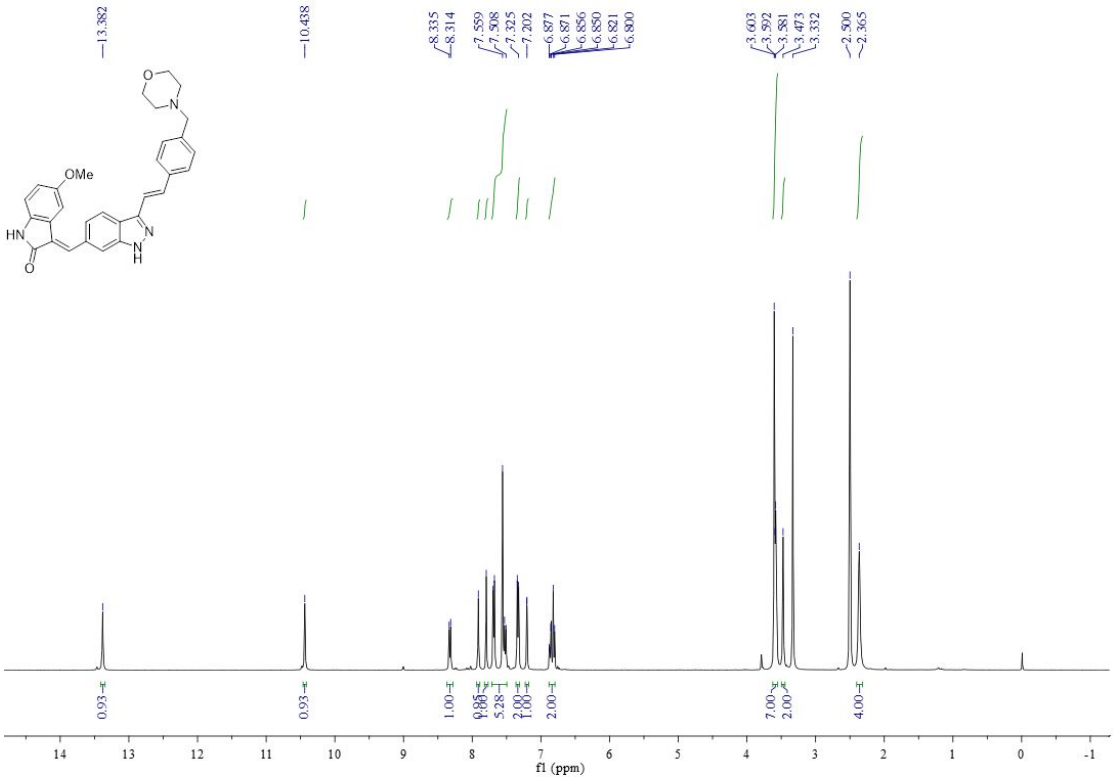


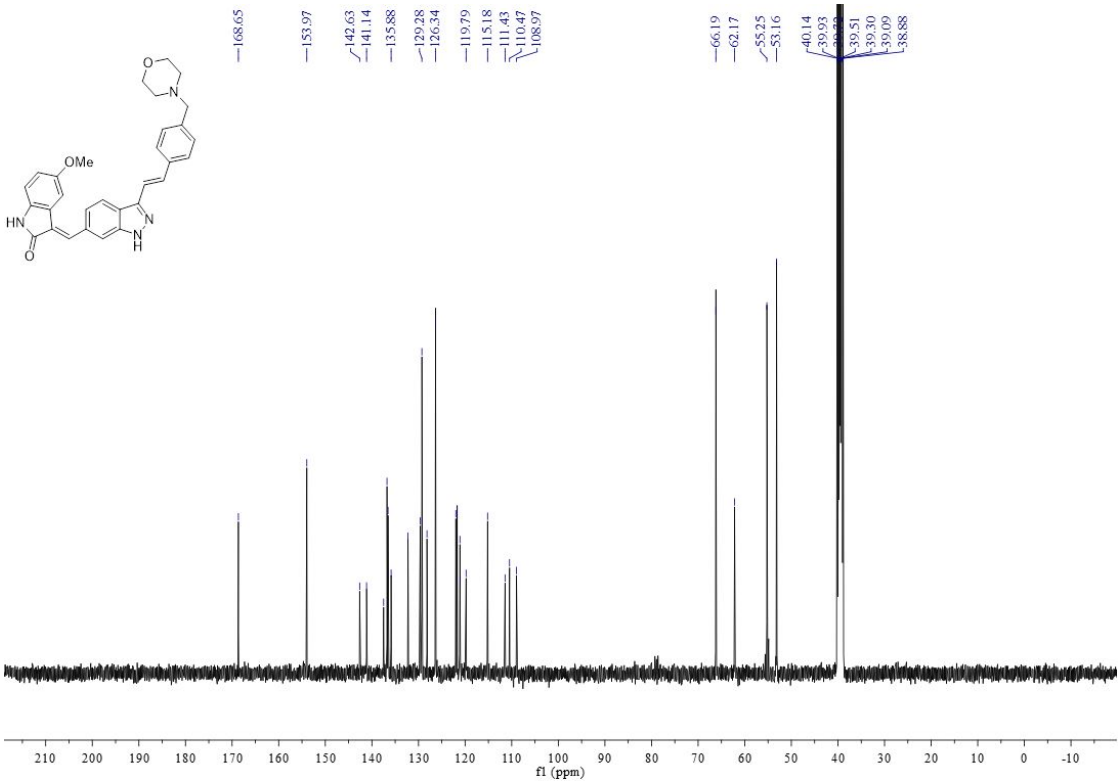
(E)-3-(4-(Morpholinomethyl)styryl)-1H-indazole-6-carbaldehyde **(3mw)**



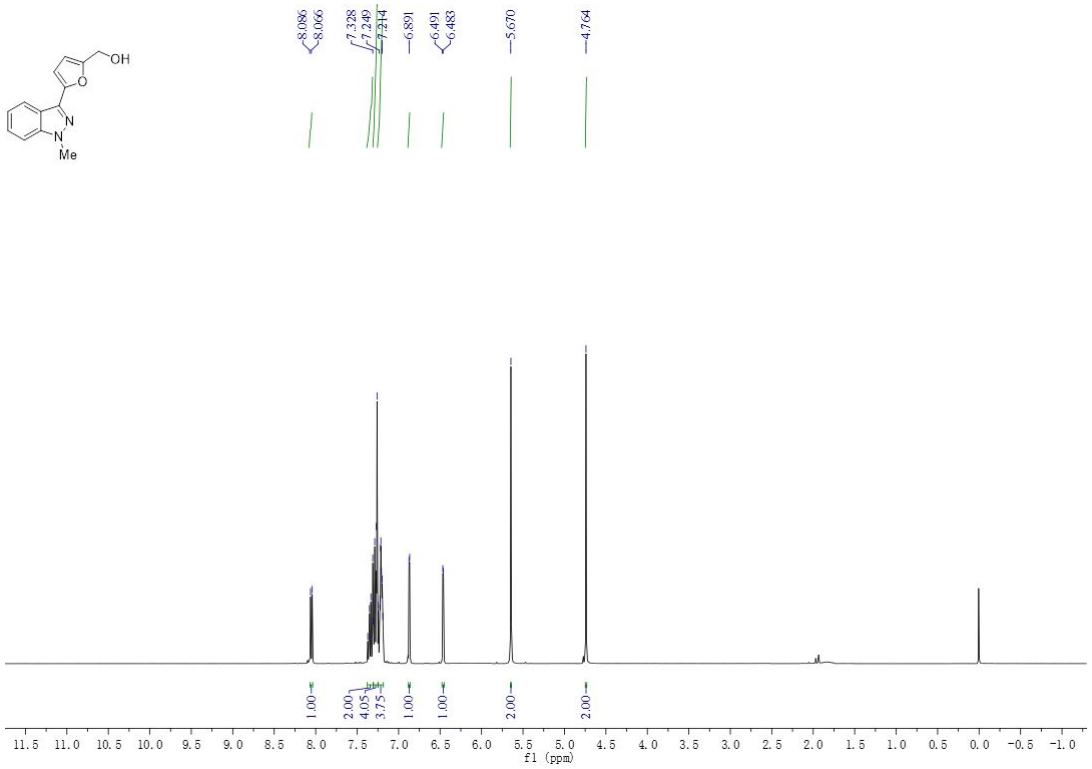


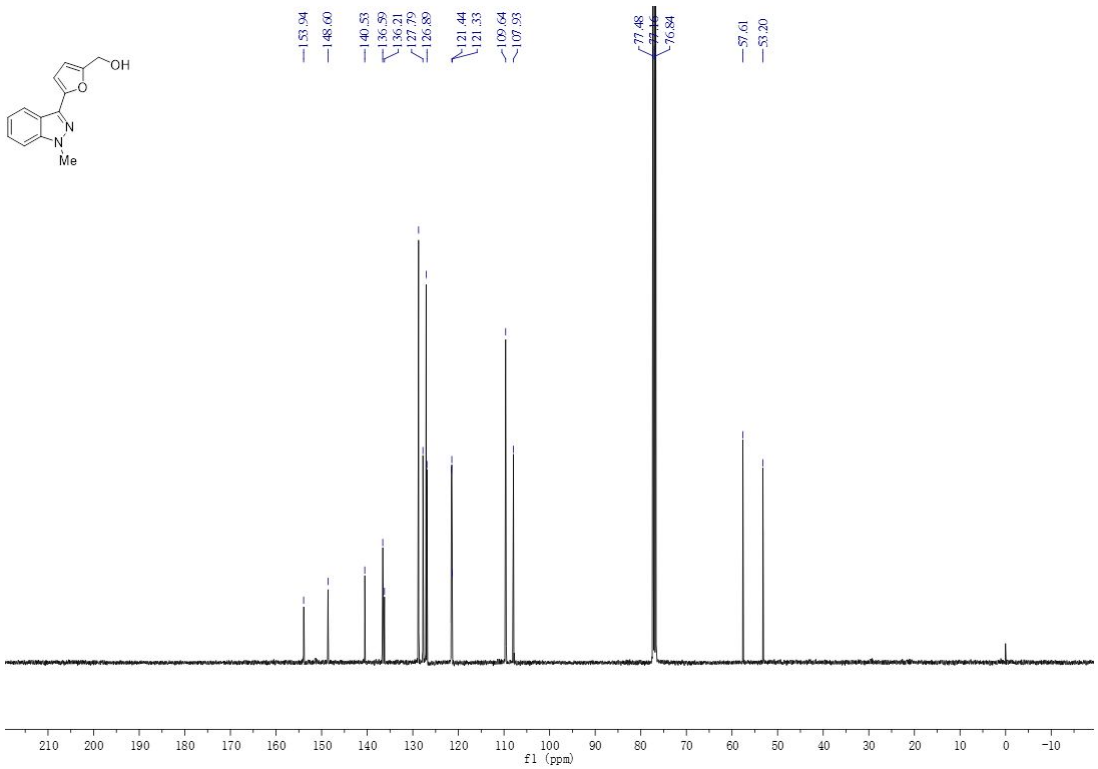
(E)-5-Methoxy-3-((3-((E)-4-(morpholinomethyl)styryl)-1H-indazol-6-yl)methylene)indolin-2-one **(3nw)**





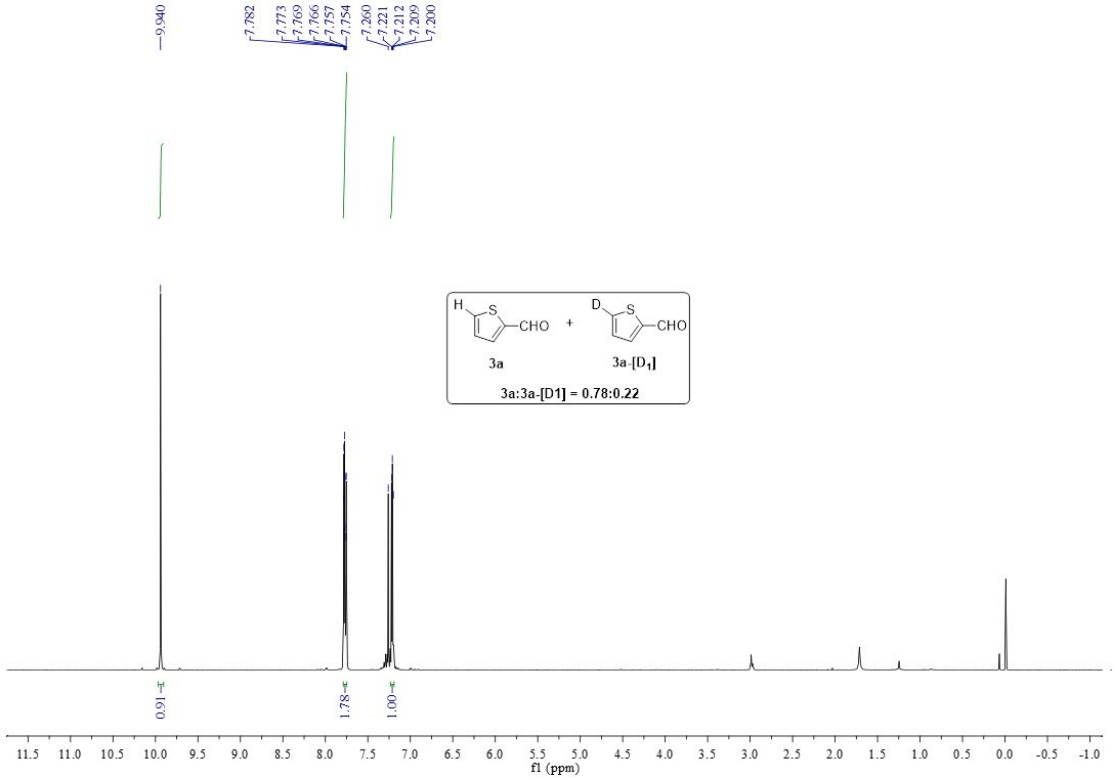
(5-(1-Benzyl-1H-indazol-3-yl)furan-2-yl)methanol **(YC-1)**



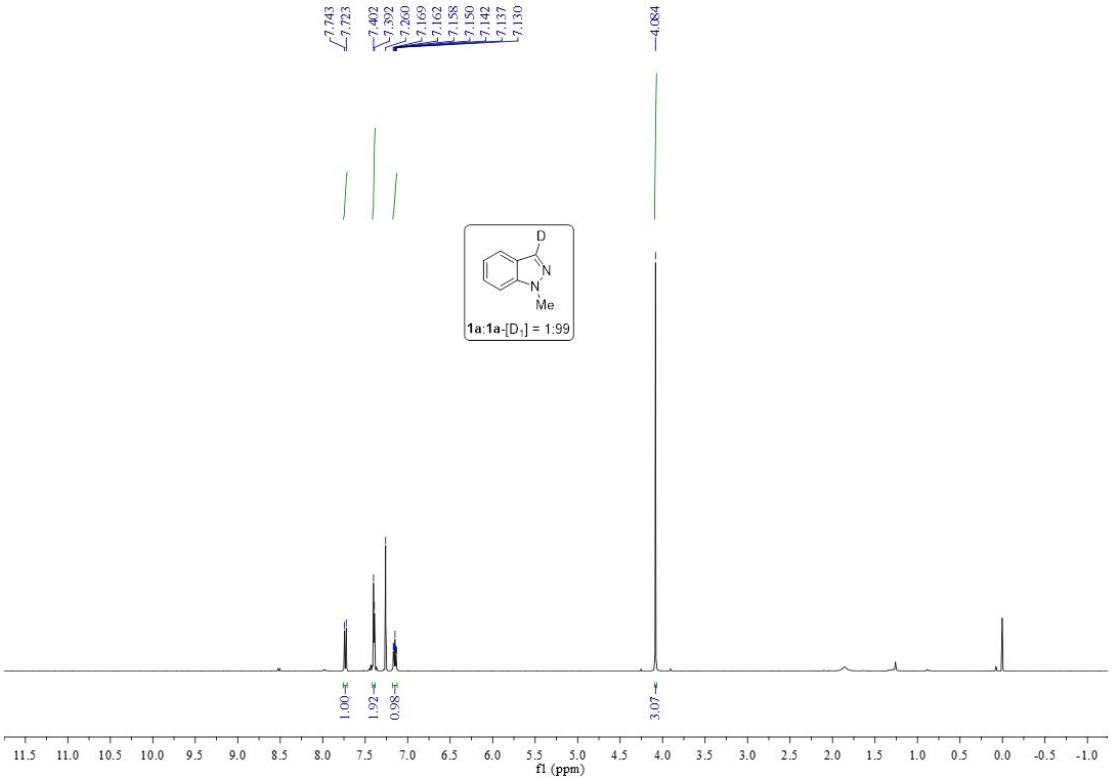


4. NMR Spectra of Mechanistic Studies

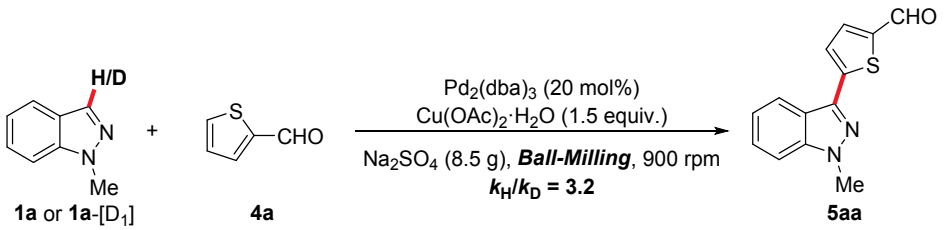
1) The experiment of H/D exchange



2) Synthesis of 1-Methyl-1*H*-indazole-3-*d* (1a-[D_1])

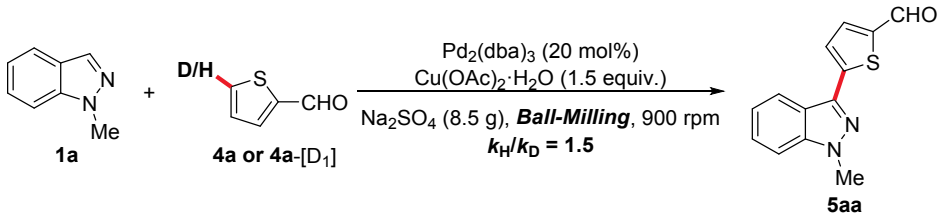


5. KIE Measurement by Independent Reaction



Scheme S2: Intermolecular KIE Experiments by Independent Reactions between 1a or 1a-[D_1] and 4a. Reaction conditions: **1a** or **1a**-[D_1] (1.0 mmol), **4a** (2.0 mmol), $Pd_2(dba)_3$ (0.2 mmol), $Cu(OAc)_2 \cdot H_2O$ (1.5 equiv.), and Na_2SO_4 (8.5 g) at 900 rpm for designated times (0.5 hour, 1 hour and 1.5 hours) in a planetary mill, using 448 stainless-steel balls (d_{MB} = 4 mm, Φ_{MB} = 0.228) in a 80 mL stainless steel vial.

Time (h)	0.5	1.0	1.5
1a/**4a** Yield of **5aa** (%)	7.9	22.5	35.6
1a-[D_1]/**4a** Yield of **5aa** (%)	2.2	7.2	10.9



Scheme S3: Intermolecular KIE Experiments by Independent Reactions between 1a and 4a or 4a-[D_1]. Reaction conditions: **1a** (1.0 mmol), **4a** or **4a**-[D_1] (2.0 mmol), $Pd_2(dba)_3$ (0.2 mmol), $Cu(OAc)_2 \cdot H_2O$ (1.5 equiv.), and Na_2SO_4 (8.5 g) at 900 rpm for designated times (0.5 hour, 1 hour and 1.5 hours) in a planetary mill, using 448 stainless-steel balls (d_{MB} = 4 mm, Φ_{MB} = 0.228) in a 80 mL stainless steel vial.

Time (h)	0.5	1.0	1.5
1a/**4a** Yield of **5aa** (%)	7.9	22.5	35.6
1a/**4a**-[D_1] Yield of **5aa** (%)	5.5	14.8	23.9

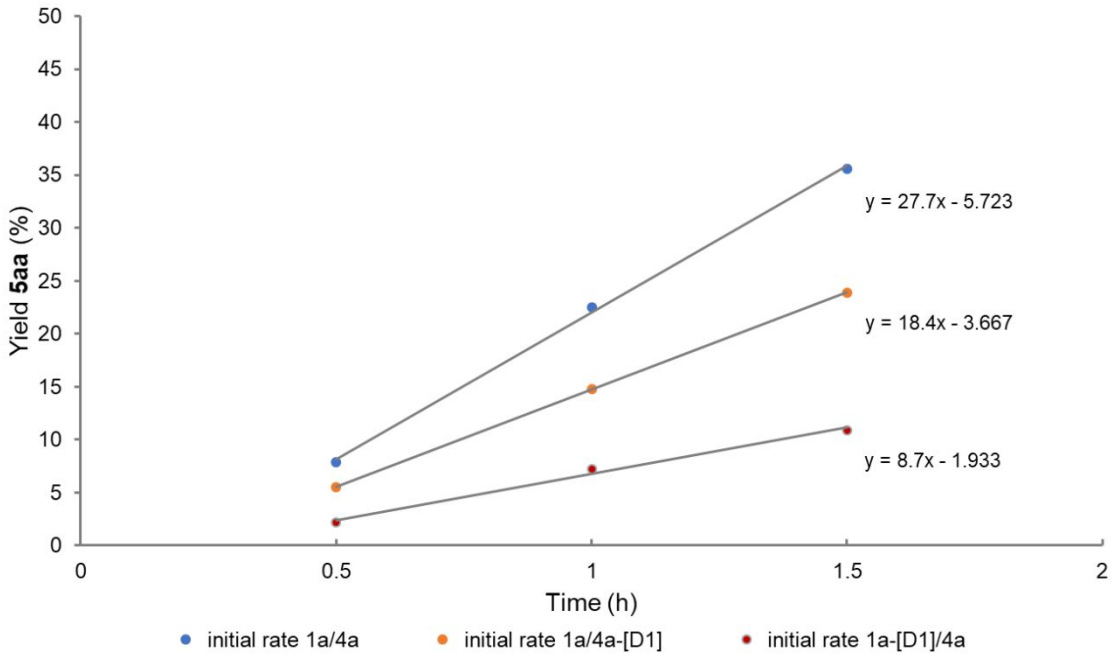


Figure S3. Initial rates of the standard reaction 1a/4a (blue), 1a/4a-[D_1] (orange), and 1a-[D_1]/4a (red).