Design and organocatalytic synthesis of spirooxindole-cyclopentene-isoxazole hybrids as novel MDM2-p53 inhibitors

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Supporting information

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1. General methods

- Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with Bruker AV 400 MHz or 600 MHz spectrometers. Proton chemical shifts are reported in parts per million (δ scale), and are referenced using residual protium in the NMR solvent ($CDCl_3$: δ 7.26 ($CHCl_3$)). Data are reported as follows: chemical shift [multip licity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet), coupling constant(s) (Hz), integration].

- Carbon-13 nuclear magnetic resonance (13C NMR) spectra were recorded with Bruker AV 100 MHz or 150 MHz spectrometers. Carbon chemical shifts are reported in parts per million (δ scale), and are referenced using the carbon resonances of the solvent (CDCl3: δ 77.0 (CHCl3)). Data are reported as follows: chemical shift [multiplicity (if not singlet), assignment (Cq = fully substituted carbon)].

- High resolution mass spectra (HRMS) were recorded on a Waters SYNAPT G2 using an electrospray (ESI) ionization source.

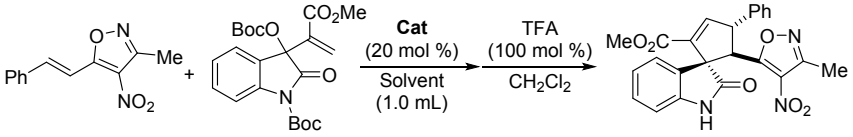
- Column chromatography was performed on silica gel (400-500 mesh) eluting with ethyl acetate and petroleum ether. TLC was performed on glass-backed silica plates. UV light and I2 were used to visualize products.

- Melting points were determined on a Mel-Temp apparatus and are uncorrected.

- The MBH carbonates1 and 4-nitro-5-alkenylisoxazoles2 were prepared according to the literature procedures.

2. Reaction conditions screening for the [3+2] annulation

Table S1 Reaction conditions screening for the [3+2] annulation. [a]



1a **2a** **4a**

Entry	**Cat**	Solvent	*T* (°C)	t (h)	Yield [b] (%)	d.r. [c] (%)
1	DABCO	Tol	RT	12	-	-
2	PPh_3	Tol	RT	12	-	-
3	DMAP	Tol	RT	6	82	11:1
4	DMAP	DCM	RT	6	91	15:1
5	DMAP	DCE	RT	6	88	14:1
6	DMAP	EtOAc	RT	6	77	10:1
7	DMAP	MeCN	RT	6	70	8:1
8	DMAP	DCM	0	6	91	15:1
9	**DMAP**	**DCM**	**-10**	**8**	**90**	**>19:1**
10	DMAP	DCM	-20	10	84	>19:1
11 [d]	DMAP	DCM	-10	8	88	>19:1
12 [e]	DMAP	DCM	-10	8	90	18:1

[a] MBH carbonate **1a** (0.1 mmol) with 4-nitro-5-alkenylisoxazole **2a** (0.11 mmol, 1.1 equiv) were employed as model substrates.

[b] Yield was calculated from the isolated pure diastereomer.

[c] d.r. value was determined by 1H NMR analysis of the crude reaction mixture.

[d] MBH carbonate **1a** (0.1 mmol) with 4-nitro-5-alkenylisoxazole **2a** (0.2 mmol, 2.0 equiv) were employed.

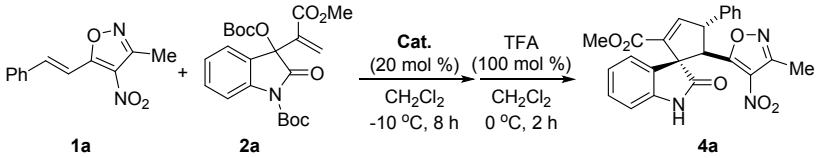
[e] MBH carbonate **1a** (0.1 mmol) with 4-nitro-5-alkenylisoxazole **2a** (0.05 mmol, 1.0 equiv) were employed.

To test the feasibility of our proposal, the initial reaction of 4-nitro-5-styrylisoxazole **1a** and MBH carbonate **2a** was carried out in the presence of common used Lewis bases (DBACO, PPh_3, and DMAP) in toluene (1.0 mL) at ambient temperature. To our delight, the expected deprotected [3+2] annulation product **4a** was cleanly obtained in remarkable yield and diastereoselectivity when using DMAP as catalyst after 6 hours (Table 1, entry 3). The reaction exhibited exclusive α-regioselectivity, and no desired product was observed with the catalysis of PPh_3 and DBACO (entries 1-2). This result encouraged us to explore other conditions to get more desirable results in terms of reaction efficiency and diastereoselectivity (entries 4-7). Impressively, using dichloromethane as solvent afforded **4a** in 88% yield with diastereoselectivity of up to 15:1 (entry 4). Next, we investigated the influence of other

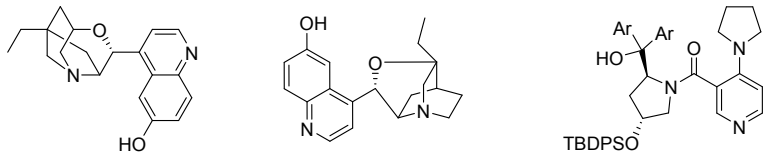
reaction parameters, including temperature and ratio of reagents. Lowering reaction temperature in overall led to excellent d.r. value regardless of longer reaction time (entries 8-10). Notably, the optimal temperature of -10 ^{o}C furnished target desirable product with impressive >20:1 diastereoselectivity, albeit with a negligible loss in yield (entry 9). Moreover, changing the ratio of reagents led to inferior results either in yield or diastereoselective performance (entries 11-12).

3. Chiral catalysts screening for the [3+2] annulation

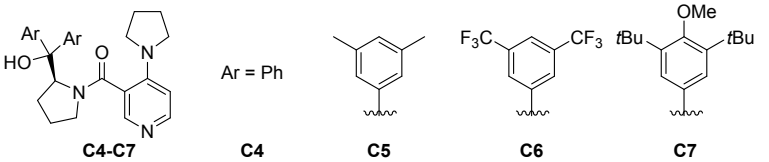
Table S2 Attempt to asymmetric catalytic synthesis of chiral product. [a]



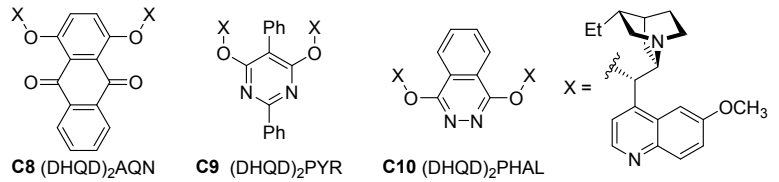
1a **2a** **4a**



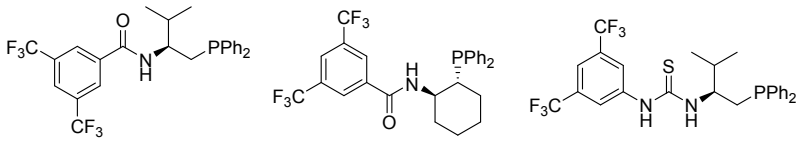
C1 α-IC **C2** β-ICD **C3** Ar = 3,5-$Me_2C_6H_3$



C4-C7 **C4** **C5** **C6** **C7**



C8 $(DHQD)_2$AQN **C9** $(DHQD)_2$PYR **C10** $(DHQD)_2$PHAL



C11 **C12** **C13**

Entry	**Cat**	Yield [b] (%)	d.r. [c] (%)	e.e. [d] (%)
1	DMAP	90	>19:1	-
2	**C1**	37	8:1	<10
3	**C2**	30	8:1	<-10
4	**C3**	72	15:1	12
5	**C4**	64	17:1	10
6	**C5**	58	17:1	16
7	**C6**	50	16:1	14
8	**C7**	48	17:1	16
9	**C8**	32	12:1	<10
10	**C9**	41	7:1	<10
11	**C10**	34	9:1	11
12	**C11**	<10	-	-
13	**C12**	<10	-	-
14	**C13**	<10	-	-

[a] A mixture of **1** (0.1 mmol), **2** (0.11 mmol, 1.1 equiv) and catalyst (20 mol%) in DCM (1.0 mL) was stirred at -10 °C for about 8 h. After the consumption of 1, the mixture was stirred at -10 °C followed by addition of TFA (100 mol% in 0.5 mL DCM) and then moved to room temperature for 2 h.

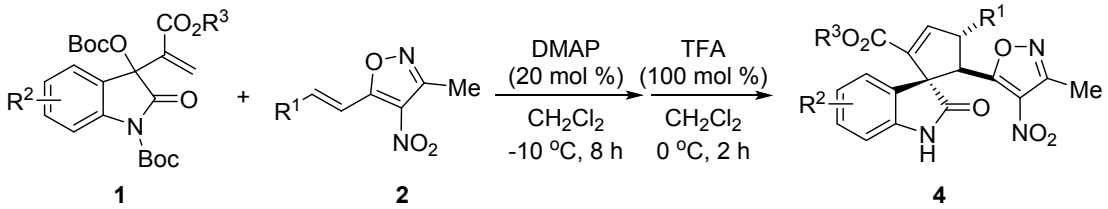
[b] Yield was calculated from the isolated pure diastereomer.

[c] d.r. value was determined by ^{1}H NMR analysis of the crude reaction mixture.

[d] e.e. values were calculated from chiral HPLC analysis of major isomer **4a**.

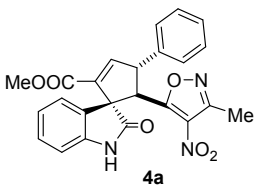
With the optimal conditions in hand, then we attempted to develop an asymmetric catalytic version of this [3+2] annulation using a series of classic catalysts such as chiral phosphines catalysts and chiral amine catalysts. We screened a variety of chiral quinine catalysts, tertiary phosphines catalyst, chiral DMAP-type catalysts for their ability to generate the chiral product **4a**. α-Isocupreine **C1** (α-IC) and β-isocupreidine **C2** (β-ICD) were found to be efficient in the reaction, affording the desired [3+2] product **4a** in poor yield, with accepted diastereoselectivity but no enantiomerical purity (entry 2-3). Inspired by the high efficiency of DMAP, a series of chiral DMAP-type catalysts were utilized and found moderate efficiency, giving product **4a** with high diastereoselectivity but poor enantiomerical purity (entry 4-8). Chiral quinine catalyst provided low reaction efficiency, accepted diastereoselectivity but poor enantiomerical purity. Similar as PPh_3, chiral tertiary phosphines catalyst failed to catalyze this reaction smoothly (entry 12-14).

4. General procedures for the synthesis of products 4



A mixture of MBH carbonate **1** (0.1 mmol) with 4-nitro-5-alkenylisoxazole **2** (0.11 mmol, 1.1 equiv) was added dimethylaminopyridine (DMAP, 20 mol%) in dichloromethane (1.0 mL) at -10 °C. The reaction mixture was stirred at -10 °C for about 8 hours. After the consumption of MBH carbonate **1**, the mixture was stirred at -10 °C followed by addition of trifluoroacetic acid (TFA, 100 mol% in 0.5 mL DCM) and then moved to room temperature for about 2 hours. The mixture was stirred until the reaction had stopped progressing as observed by TLC analysis, then diluted with EtOAc and washed with saturated aqueous $NaHCO_3$, and brine. Then the solution was concentrated and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:1 to 3:1) to afford product **4**, which was dried under vacuum and further analyzed by ^1H NMR, ^{13}C NMR and high-resolution mass spectrometry.

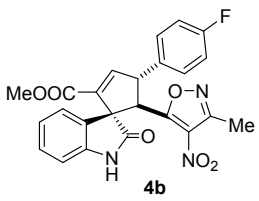
Methyl-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxo-4-phenylspiro[cyclopentane-1,3'-indolin]-2-ene-2-carboxylate 4a:



4a

white solid, 40.1 mg, 90% yield, dr >19:1, m.p. >210 °C; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.32 (s, 1H), 7.40 (d, J = 7.2 Hz, 2H), 7.36 (t, J = 7.8 Hz, 2H), 7.30 (t, J = 7.2 Hz, 1H), 7.19 (d, J = 1.8 Hz, 1H), 7.15 – 7.11 (m, 1H), 7.05 (d, J = 7.8 Hz, 1H), 6.88 (t, J = 7.8 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 5.24 (dd, J = 8.4, 1.8 Hz, 1H), 4.99 (d, J = 8.4 Hz, 1H), 3.63 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 178.6, 170.2, 162.5, 155.9, 148.1, 141.3, 139.8, 136.4, 130.8, 129.5, 129.3, 128.2, 128.0, 127.2, 124.4, 122.3, 110.2, 64.3, 55.4, 52.9, 52.2, 11.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{24}H_{19}N_3O_6Na$ 468.1172, found 468.1170.

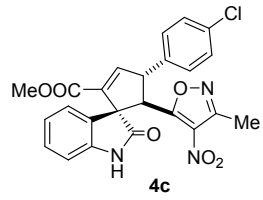
Methyl-4-(4-fluorophenyl)-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxospiro[cyclo-pentane-1,3'-indolin]-2-ene-2-carboxylate 4b:



4b

white solid, 38.3 mg, 86% yield, dr >19:1, m.p. >210 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.20 (s, 1H), 7.40 – 7.38 (m, 2H), 7.16 (d, *J* = 1.8 Hz, 1H), 7.13 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.05 (t, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.88 (t, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 5.24 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.93 (d, *J* = 9.0 Hz, 1H), 3.64 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 178.6, 170.1, 162.6 (d, J_{CF} = 246.0 Hz), 162.4, 156.0, 147.7, 141.2, 136.5, 135.6 (d, J_{CF} = 2.4 Hz), 130.8, 129.7, 129.6 (d, J_{CF} = 8.7 Hz), 127.1, 124.3, 122.4, 116.3 (d, J_{CF} = 21.0 Hz), 110.2, 64.2, 55.5, 52.2, 52.2, 11.5; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{24}H_{18}FN_3O_6Na$ 486.1077, found 486.1079.

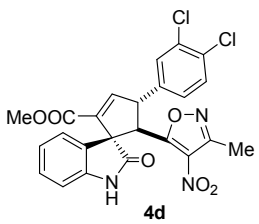
methyl-4-(4-chlorophenyl)-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxospiro[cyclo-pentane-1,3'-indolin]-2-ene-2-carboxylate 4c:



4c

white solid, 41.4 mg, 93% yield, dr >19:1, m.p. >210 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.12 (s, 1H), 7.35 – 7.32 (m, 4H), 7.15 – 7.13 (m, 2H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.88 (t, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 5.22 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.92 (d, *J* = 8.4 Hz, 1H), 3.63 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 178.4, 169.9, 162.4, 156.0, 147.3, 141.2, 138.3, 136.7, 134.2, 130.8, 129.6, 129.5, 129.4, 127.0, 124.3, 122.4, 110.2, 64.2, 55.3, 52.3, 52.2, 11.5; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{24}H_{18}ClN_3O_6Na$ 502.0782, found 502.0781.

Methy-4-(3,4-dichlorophenyl)-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxospiro[cyclo pentane-1,3'-indolin]-2-ene-2-carboxylate 4d:

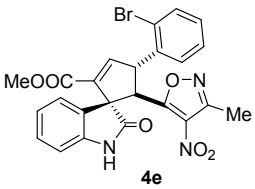


4d

white solid, 34.3 mg, 77% yield, dr 15:1, m.p. >210 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) ^{1}H NMR (600 MHz,) δ 8.24 (s, 1H), 7.50 (d, *J* = 1.8 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.29 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.14 (t, *J* = 7.8 Hz, 1H), 7.12 (d, *J* = 2.4 Hz,

1H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.87 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 5.19 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.91 (d, *J* = 8.4 Hz, 1H), 3.64 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) ^{13}C NMR (150 MHz,) δ 178.4, 169.7, 162.3, 156.1, 146.5, 141.3, 140.0, 137.2, 133.4, 132.6, 131.4, 130.8, 130.0, 129.7, 127.4, 126.8, 124.2, 122.4, 110.3, 64.3, 55.1, 52.3, 52.0, 11.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{24}H_{17}Cl_2N_3O_6Na$ 536.0392, found 536.0389.

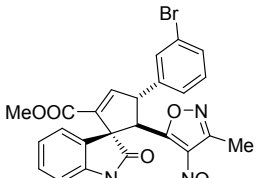
Methyl-4-(2-bromophenyl)-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxospiro[cyclo pentane-1,3'-indolin]-2-ene-2-carboxylate 4e:



4e

white solid, 40.5 mg, 91% yield, dr >19:1, m.p. >210 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.08 (s, 1H), 7.71 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.53 (d, *J* = 7.8, 0.6 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.17 (td, *J* = 7.8, 1.2 Hz, 1H), 7.14 – 7.13 (m, 2H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.87 (t, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.73 (dd, *J* = 7.2, 2.4 Hz, 1H), 4.99 (d, *J* = 7.2 Hz, 1H), 3.62 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 178.6, 170.5, 162.5, 155.7, 147.7, 141.3, 139.7, 136.5, 133.1, 130.5, 130.1, 129.7, 129.6, 128.7, 127.2, 124.5, 124.0, 122.4, 110.9, 64.5, 53.8, 52.2, 52.1, 11.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{24}H_{18}BrN_3O_6Na$ 546.0277, found 546.0276.

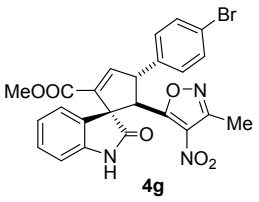
Methyl-4-(3-bromophenyl)-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxospiro[cyclo pentane-1,3'-indolin]-2-ene-2-carboxylate 4f:



4f

white solid, 37.9 mg, 85% yield, dr 15:1, m.p. >210 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.19 (s, 1H), 7.53 (t, *J* = 1.8 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.25 (t, *J* = 7.8 Hz, 1H), 7.15 – 7.14 (m, 2H), 7.00 (d, *J* = 7.8 Hz, 1H), 6.87 (t, *J* = 7.2 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 5.20 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.94 (d, *J* = 8.4 Hz, 1H), 3.64 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 178.4, 169.9, 162.4, 156.0, 147.1, 142.2, 141.2, 136.9, 131.5, 131.1, 131.0, 130.7, 129.7, 127.0, 126.7, 124.3, 123.3, 122.4, 110.2, 64.3, 55.2, 52.4, 52.3, 11.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{24}H_{18}BrN_3O_6Na$ 546.0277, found 546.0279.

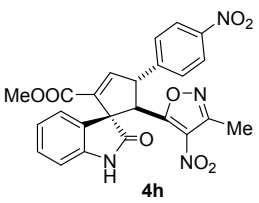
Methyl-4-(4-bromophenyl)-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxospiro[cyclo pentane-1,3'-indolin]-2-ene-2-carboxylate 4g:



4g

white solid, 41.0 mg, 92% yield, dr >19:1, m.p. >210 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.98 (s, 1H), 7.49 (d, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.15 – 7.13 (m, 2H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.88 (t, *J* = 7.2 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.21 (dd, *J* = 8.4, 1.8 Hz, 1H), 4.91 (d, *J* = 8.4 Hz, 1H), 3.63 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 178.4, 169.9, 162.4, 156.0, 147.2, 141.1, 138.8, 136.7, 132.5, 130.7, 129.7, 129.7, 127.0, 124.3, 122.4, 122.3, 110.2, 64.2, 55.3, 52.3, 52.2, 11.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{24}H_{18}BrN_3O_6Na$ 546.0277, found 546.0280.

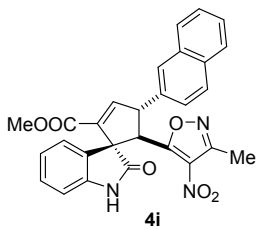
Methyl-5-(3-methyl-4-nitroisoxazol-5-yl)-4-(4-nitrophenyl)-2'-oxospiro[cyclo pentane-1,3'-indolin]-2-ene-2-carboxylate 4h:



4h

white solid, 37.2 mg, 84% yield, dr 10:1, m.p. >210 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) δ 8.23 (d, *J* = 9.0 Hz, 2H), 8.13 (s, 1H), 7.62 (d, *J* = 9.0 Hz, 2H), 7.17 – 7.14 (m, 2H), 6.99 (d, *J* = 7.2 Hz, 1H), 6.89 (t, *J* = 7.2 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 5.36 (dd, *J* = 8.4, 1.8 Hz, 1H), 4.95 (d, *J* = 8.4 Hz, 1H), 3.65 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) δ 178.1, 169.4, 162.1, 156.0, 147.8, 147.1, 145.9, 141.1, 137.5, 130.6, 129.7, 129.0, 126.6, 124.5, 124.2, 122.4, 110.2, 64.3, 54.9, 52.3, 52.2, 11.4; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{24}H_{18}N_4O_8Na$ 531.1022, found 531.1020.

Methyl-5-(3-methyl-4-nitroisoxazol-5-yl)-4-(naphthalen-2-yl)-2'-oxospiro[cyclo pentane-1,3'-indolin]-2-ene-2-carboxylate 4i:

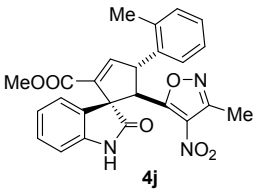


4i

white solid, 41.4 mg, 93% yield, dr >19:1, m.p. >210 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) ^{1}H NMR (600 MHz,) δ 8.44 (s, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 6.6 Hz, 1H), 7.55 – 7.50 (m, 3H),

7.30 (d, J = 2.4 Hz, 1H), 7.16 – 7.12 (m, 2H), 6.92 (t, J = 7.2 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 6.00 (dd, J = 8.4, 1.2 Hz, 1H), 5.24 (d, J = 9.0 Hz, 1H), 3.64 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 178.9, 170.3, 162.6, 155.9, 149.0, 141.4, 136.1, 134.1, 131.3, 130.7, 129.6, 129.3, 128.8, 127.4, 126.9, 126.9, 126.1, 124.5, 122.7, 122.3, 110.3, 64.5, 54.8, 52.2, 11.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{28}H_{21}N_3O_6Na$ 518.1328, found 518.1330.

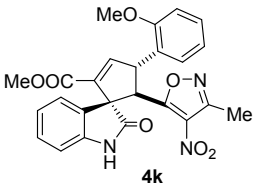
Methyl-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxo-4-(o-tolyl)spiro[cyclopentane-1,3'-indolin]-2-ene-2-carboxylate 4j:



4j

white solid, 39.2 mg, 88% yield, dr >19:1, m.p. >210 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.06 (s, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.29 (t, J = 7.2 Hz, 1H), 7.21 – 7.18 (m, 1H), 7.15 – 7.13 (m, 3H), 7.04 (d, J = 7.2 Hz, 1H), 6.88 (t, J = 7.6 Hz, 1H), 6.79 (d, J = 7.8 Hz, 1H), 5.48 (dd, J = 8.4, 2.4 Hz, 1H), 5.07 (d, J = 8.4 Hz, 1H), 3.62 (s, 3H), 2.35 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 178.7, 170.5, 162.5, 155.9, 148.9, 141.2, 138.1, 135.8, 135.7, 130.9, 130.6, 129.5, 128.7, 128.0, 127.4, 124.4, 122.3, 110.1, 64.3, 54.8, 52.1, 49.0, 19.9, 11.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{21}N_3O_6Na$ 482.1328, found 482.1325.

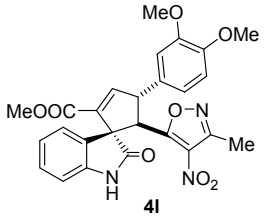
Methyl-4-(2-methoxyphenyl)-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxospiro[cyclopentane-1,3'-indolin]-2-ene-2-carboxylate 4k:



4k

white solid, 38.3 mg, 86% yield, dr >19:1, m.p. >210 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.38 (s, 1H), 7.43 (dd, J = 7.5, 1.4 Hz, 1H), 7.28 – 7.27(m, 1H), 7.25 (t, J = 1.8 Hz, 1H), 7.11 (td, J = 7.8, 1.2 Hz, 1H), 7.07 (d, J = 7.8 Hz, 1H), 7.0 – 6.9 (m, 1H), 6.87 (t, J = 7.2 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 7.8 Hz, 1H), 5.57 (dd, J = 8.4, 2.4 Hz, 1H), 5.03 (d, J = 8.4 Hz, 1H), 3.69 (s, 3H), 3.61 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 178.8, 171.7, 162.7, 156.9, 155.4, 148.9, 141.3, 135.6, 130.3, 129.4, 129.2, 128.7, 128.1, 127.6, 124.7, 122.1, 121.3, 110.7, 110.0, 64.3, 55.4, 53.2, 52.1, 47.1, 11.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{21}N_3O_7Na$ 498.1277, found 498.1279.

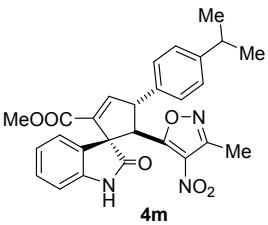
Methyl-4-(3,4-dimethoxyphenyl)-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxospiro [cyclopentane-1,3'-indolin]-2-ene-2-carboxylate 4l:



4l

white solid, 35.6 mg, 80% yield, dr 13:1, m.p. 190–191 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.15 (s, 1H), 7.16 (d, *J* = 2.4 Hz, 1H), 7.13 (dt, *J* = 7.8, 0.6 Hz, 1H), 7.01 – 6.99 (m, 2H), 6.92 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.87 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.18 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.98 (d, *J* = 8.4 Hz, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 3.63 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 178.6, 170.4, 162.5, 155.8, 149.6, 148.8, 148.3, 141.1, 135.8, 132.2, 130.6, 129.4, 127.2, 124.2, 122.2, 120.2, 111.4, 110.7, 110.0, 64.1, 56.1, 55.9, 55.3, 52.7, 52.1, 11.4; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{26}H_{23}N_3O_8Na$ 528.1383, found 528.1381.

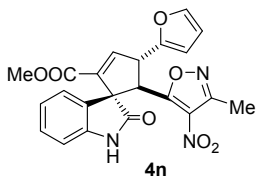
Methyl-4-(4-isopropylphenyl)-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxospiro[cyclo pentane-1,3'-indolin]-2-ene-2-carboxylate 4m:



4m

white solid, 37.9 mg, 85% yield, dr >19:1, m.p. 188–189 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.36 (s, 1H), 7.31 (d, *J* = 7.8 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 2.4 Hz, 1H), 7.14 – 7.11 (m, 1H), 7.05 (d, *J* = 7.2 Hz, 1H), 6.88 (t, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 5.22 (dd, *J* = 8.4, 1.8 Hz, 1H), 4.97 (d, *J* = 8.4 Hz, 1H), 3.62 (s, 3H), 2.89 (dt, *J* = 13.8, 7.2 Hz, 1H), 2.31 (s, 3H), 1.24 (d, *J* = 1.2 Hz, 3H), 1.22 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 178.9, 170.3, 162.6, 155.9, 149.0, 148.4, 141.2, 137.1, 136.1, 130.8, 129.5, 127.9, 127.4, 127.3, 124.4, 122.3, 110.2, 64.3, 55.4, 52.6, 52.2, 33.9, 24.1, 24.0, 11.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{27}H_{25}N_3O_6Na$ 510.1641, found 510.1644.

Methyl-4-(furan-2-yl)-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxospiro[cyclo pentane-1,3'-indolin]-2-ene-2-carboxylate 4n:

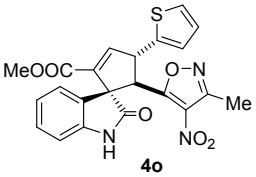


4n

white solid, 37.0 mg, 83% yield, dr >19:1, m.p. 205–206 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.47 (s, 1H), 7.36 (s, 1H), 7.22

(d, *J* = 1.8 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 6.88 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.33 (dd, *J* = 3.0, 1.8 Hz, 1H), 6.30 (d, *J* = 3.6 Hz, 1H), 5.33 (dd, *J* = 9.0, 2.4 Hz, 1H), 5.15 (d, *J* = 9.0 Hz, 1H), 3.62 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 178.2, 169.7, 162.4, 155.8, 151.6, 145.1, 142.9, 141.3, 136.4, 130.8, 129.7, 126.8, 124.5, 122.3, 110.7, 110.3, 107.3, 63.9, 52.2, 51.7, 46.5, 11.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{17}N_3O_7Na$ 458.0964, found 458.0966.

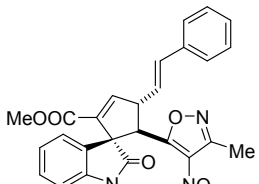
Methyl-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxo-4-(thiophen-2-yl)spiro[cyclo pentane-1,3'-indolin]-2-ene-2-carboxylate 4o:



4o

white solid, 35.6 mg, 80% yield, dr >19:1, m.p. >210 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.61 (s, 1H), 7.24 – 7.23 (m, 2H), 7.13 (t, *J* = 7.8 Hz, 1H), 7.05 (d, *J* = 6.6 Hz, 2H), 6.98 (dd, *J* = 4.8, 3.6 Hz, 1H), 6.88 (t, *J* = 7.2 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 5.53 (dd, *J* = 9.0, 3.6 Hz, 1H), 5.05 (d, *J* = 8.4 Hz, 1H), 3.63 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 178.3, 169.6, 162.4, 155.9, 146.9, 141.9, 141.4, 136.2, 131.1, 129.7, 127.6, 126.8, 125.8, 125.5, 124.4, 122.3, 110.4, 64.1, 55.4, 52.3, 47.9, 11.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{17}N_3O_6SNa$ 474.0736, found 474.0733.

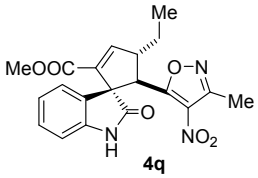
Methyl-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxo-4-((*E*)-styryl)spiro[cyclopentane-1,3'-indolin]-2-ene-2-carboxylate 4p:



4p

white solid, 32.5 mg, 73% yield, dr >15:1, m.p. 156–157 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) δ 7.63 (s, 1H), 7.37 – 7.36 (m, 2H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.14 – 7.12 (m, 2H), 6.93 (d, *J* = 7.2 Hz, 1H), 6.86 (td, *J* = 7.8, 0.6 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.60 (d, *J* = 16.2 Hz, 1H), 6.28 (dd, *J* = 15.6, 8.4 Hz, 1H), 4.87 (d, *J* = 7.8 Hz, 1H), 4.83 – 4.79 (m, 1H), 3.62 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 178.1, 170.4, 162.5, 155.8, 147.9, 141.0, 135.9, 133.9, 129.6, 128.8, 128.3, 127.2, 126.6, 124.4, 122.4, 109.9, 64.2, 52.5, 52.1, 51.4, 11.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{26}H_{21}N_3O_6Na$ 494.1328, found 494.1325.

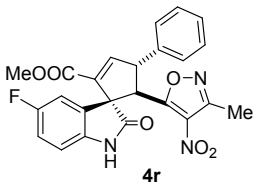
Methyl-4-ethyl-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxospiro[cyclopentane-1,3'-indolin]-2-ene-2-carboxylate 4q:



4q

white solid, 32.2 mg, 84% yield, dr 15:1, m.p. 160–161 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.53 (s, 1H), 7.21 (d, *J* = 2.1 Hz, 1H), 7.10 (td, *J* = 7.8, 1.2 Hz, 1H), 6.90 (d, *J* = 7.2 Hz, 1H), 6.83 (t, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 4.67 (d, *J* = 7.8 Hz, 1H), 3.93 (qd, *J* = 7.2, 1.8 Hz, 1H), 3.58 (s, 3H), 2.35 (s, 3H), 1.87 – 1.80 (m, 1H), 1.75 – 1.68 (m, 1H), 1.00 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 179.1, 171.2, 162.7, 155.8, 149.2, 141.3, 134.9, 130.6, 129.4, 127.4 124.3, 122.1 110.1, 64.3, 52.0, 51.6, 49.7, 27.6, 12.2, 11.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{20}H_{19}N_3O_6Na$ 420.1172, found 420.1171.

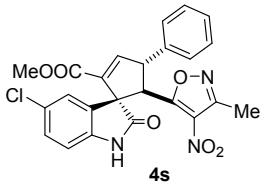
Methyl-5'-fluoro-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxo-4-phenylspiro[cyclo pentane-1,3'-indolin]-2-ene-2-carboxylate 4r:



4r

white solid, 30.7 mg, 80% yield, dr >19:1, m.p. >210 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.54 (s, 1H), 7.37 – 7.35 (m, 4H), 7.32 – 7.30 (m, 1H), 7.21 (d, *J* = 1.8 Hz, 1H), 6.86 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.84 – 6.83 (m, 1H), 6.77 (dd, *J* = 8.4, 4.2 Hz, 1H), 5.21 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.99 (d, *J* = 9.0 Hz, 1H), 3.65 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 178.7, 169.7, 162.4, 158.6 (d, J_{CF} = 240.0 Hz), 155.9, 148.4, 139.4, 137.4, 136.1, 130.9, 129.4, 128.7 (d, J_{CF} = 7.5 Hz), 128.3, 127.9, 116.1 (d, J_{CF} = 23.3 Hz), 112.3 (d, J_{CF} = 24.9 Hz), 110.9 (d, J_{CF} = 8.1 Hz), 64.6, 55.2, 53.0, 52.3, 11.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{24}H_{18}FN_3O_6Na$ 486.1077, found 486.1080.

Methyl-5'-chloro-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxo-4-phenylspiro[cyclo pentane-1,3'-indolin]-2-ene-2-carboxylate 4s:

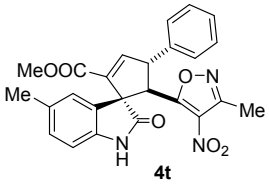


4s

white solid, 31.4 mg, 82% yield, dr >19:1, m.p. >210 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.47 (s, 1H), 7.38 – 7.36 (m, 4H), 7.33 – 7.30 (m, 1H), 7.21 (d, *J* = 2.4 Hz, 1H), 7.12 (dd, *J* =

8.4, 2.4 Hz, 1H), 7.05 (d, *J* = 1.8 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 5.22 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.97 (d, *J* = 9.0 Hz, 1H), 3.66 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 178.3, 169.6, 162.4, 155.9, 148.5, 139.9, 139.4, 136.0, 130.9, 129.6, 129.4, 128.9, 128.4, 127.9, 127.6, 124.8, 111.3, 64.3, 55.2, 53.0, 52.3, 11.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{24}H_{18}ClN_3O_6Na$ 502.0782, found 502.0780.

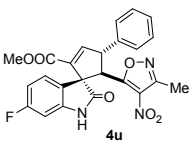
Methyl-5'-methyl-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxo-4-phenylspiro[cyclo pentane-1,3'-indolin]-2-ene-2-carboxylate 4t:



4t

white solid, 30.7 mg, 80% yield, dr >19:1, m.p. 160–161 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.97 (s, 1H), 7.41 – 7.39 (m, 2H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.84 (s, 1H), 6.69 – 6.67 (m, 1H), 5.23 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.98 (d, *J* = 9.0 Hz, 1H), 3.64 (s, 3H), 2.32 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 178.5, 170.2, 162.6, 155.9, 147.9, 139.8, 138.7, 136.4, 131.8, 130.8, 129.8, 129.3, 128.2, 128.0, 127.2, 125.1, 109.7, 64.3, 55.4, 52.9, 52.2, 21.1, 11.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{21}N_3O_6Na$ 482.1328, found 482.1330.

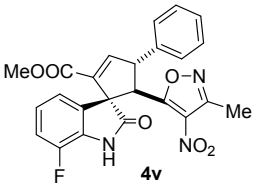
Methyl-6'-fluoro-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxo-4-phenylspiro[cyclo pentane-1,3'-indolin]-2-ene-2-carboxylate 4u:



4u

white solid, 29.9 mg, 78% yield, dr >19:1, m.p. 209–210 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.48 (s, 1H), 7.38 – 7.35 (m, 4H), 7.33 – 7.30 (m, 1H), 7.19 (d, *J* = 1.8 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.87 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.84 (d, *J* = 1.8 Hz, 1H), 5.22 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.96 (d, *J* = 9.0 Hz, 1H), 3.65 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 178.6, 169.8, 162.4, 156.0, 148.3, 142.5, 139.5, 136.1, 135.2, 130.9, 129.4, 128.3, 127.9, 125.6, 125.3, 122.4, 111.0, 63.8, 55.2, 53.1, 52.3, 11.6; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{24}H_{18}ClN_3O_6Na$ 502.0782, found 502.0785.

Methyl-7'-fluoro-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxo-4-phenylspiro[cyclo pentane-1,3'-indolin]-2-ene-2-carboxylate 4v:

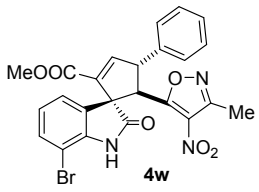


4v

white solid, 28.8 mg, 75% yield, dr >19:1, m.p. >210 °C; ^{1}H

NMR (600 MHz, $CDCl_3$) δ (ppm) 8.10 (s, 1H), 7.39 – 7.34 (m, 4H), 7.32 – 7.29 (m, 1H), 7.19 (d, *J* = 1.8 Hz, 1H), 6.94 – 6.91 (m, 1H), 6.87 – 6.84 (m, 2H), 5.23 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.98 (d, *J* = 9.0 Hz, 1H), 3.64 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 177.5, 169.9, 162.4, 156.0, 148.4, 146.8 (d, J_{CF} = 243.5 Hz), 139.5, 136.0, 130.9, 129.9 (d, J_{CF} = 2.3 Hz), 129.4, 128.7 (d, J_{CF} = 12.6 Hz), 128.3, 128.0, 122.9 (d, J_{CF} = 5.6 Hz), 120.1 (d, J_{CF} = 2.4 Hz), 116.72 (d, J_{CF} = 17.1 Hz), 64.4, 55.3, 53.1, 52.3, 11.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{24}H_{18}FN_3O_6Na$ 486.1077, found 486.1079.

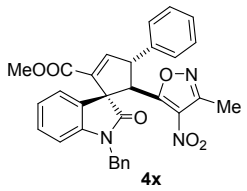
Methyl-7'-bromo-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxo-4-phenylspiro[cyclo pentane-1,3'-indolin]-2-ene-2-carboxylate 4w:



4w

white solid, 27.6 mg, 72% yield, dr >19:1, m.p. >210 °C; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.71 (s, 1H), 7.36 – 7.34 (m, 4H), 7.32 – 7.29 (m, 1H), 7.26 (bro, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 6.79 (t, *J* = 7.8 Hz, 1H), 5.21 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.97 (d, *J* = 8.4 Hz, 1H), 3.64 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 177.0, 169.7, 162.3, 156.0, 148.3, 140.7, 139.4, 136.1, 132.3, 130.9, 129.4, 128.4, 128.4, 128.0, 123.5, 123.3, 103.0, 65.4, 55.3, 53.2, 52.3, 11.6; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{24}H_{18}N_3BrO_6Na$ 546.0277, found 546.0280.

Methyl-1'-benzyl-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxo-4-phenylspiro[cyclo pentane-1,3'-indolin]-2-ene-2-carboxylate 4x:

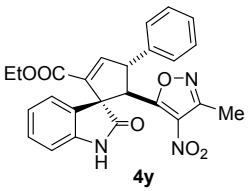


4x

white solid, 34.5 mg, 90% yield, dr >19:1, m.p. 174–175 °C; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) δ 7.45 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.41 (d, *J* = 7.2 Hz, 2H), 7.38 – 7.36 (m, 2H), 7.34 – 7.32 (m, 2H), 7.31 – 7.29 (m, 1H), 7.28 – 7.25 (m, 1H), 7.21 (d, *J* = 1.8 Hz, 1H), 7.06 (td, *J* = 7.8, 1.2 Hz, 1H), 7.01 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.84 (td, *J* = 7.8, 1.2 Hz, 1H), 6.60 (d, *J* = 7.8 Hz, 1H), 5.26 – 5.23 (m, 2H), 5.01 (d, *J* = 7.8 Hz, 1H), 4.60 (d, *J* = 15.6 Hz, 1H), 3.53 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 177.1, 170.3, 162.3, 155.8, 148.3, 130.7, 129.3, 129.3, 128.7, 128.1, 128.0,

127.6, 127.5, 126.8, 123.9, 122.3, 109.3, 64.0, 55.6, 52.8, 51.9, 44.8, 11.4; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{31}H_{25}N_3O_6Na$ 558.1641, found 558.1644.

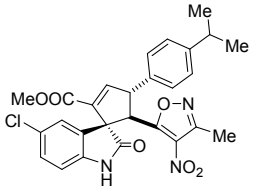
Ethyl-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxo-4-phenylspiro[cyclopentane-1,3'-indolin]-2-ene-2-carboxylate 4y:



4y

white solid, 33.3 mg, 87% yield, dr >19:1, m.p. >210 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.19 (s, 1H), 7.41 (d, *J* = 7.2 Hz, 2H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.20 (d, *J* = 1.8 Hz, 1H), 7.12 (t, *J* = 7.2 Hz, 1H), 7.04 (d, *J* = 7.2 Hz, 1H), 6.88 (t, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.23 (dd, *J* = 9.0, 2.4 Hz, 1H), 5.00 (d, *J* = 8.4 Hz, 1H), 4.10 – 4.01 (m, 2H), 2.31 (s, 3H), 1.10 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 178.6, 170.2, 162.0, 155.8, 147.8, 141.2, 139.8, 136.5, 130.7, 129.4, 129.2, 128.1, 127.9, 127.3, 124.3, 122.2, 109.9, 64.2, 61.1, 55.3, 52.8, 13.8, 11.4; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{21}N_3O_6Na$ 482.1328, found 482.1330.

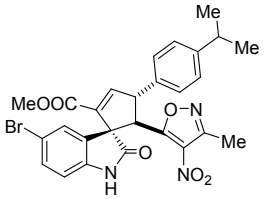
Methyl-5'-chloro-4-(4-isopropylphenyl)-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxo-spiro[cyclopentane-1,3'-indolin]-2-ene-2-carboxylate 4z:



4z

white solid, 31.44 mg, 82% yield, dr 18:1, m.p. 200–201 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.42 (s, 1H), 7.29 – 7.26 (m, 2H), 7.21 (d, *J* = 7.8 Hz, 2H), 7.19 (d, *J* = 1.8 Hz, 1H), 7.11 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.04 (d, *J* = 1.8 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 5.20 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.95 (d, *J* = 9.0 Hz, 1H), 3.65 (s, 3H), 2.89 (dt, *J* = 13.8, 7.2 Hz, 1H), 2.35 (s, 3H), 1.24 (d, *J* = 1.2 Hz, 3H), 1.23 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 178.2, 169.7, 162.3, 155.8, 149.0, 148.7, 139.8, 136.6, 135.7, 130.9, 129.4, 128.9, 127.8, 127.4, 127.3, 124.7, 111.1, 64.2, 55.1, 52.6, 52.2, 33.8, 23.9, 11.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{27}H_{24}ClN_3O_6Na$ 544.1251, found 544.1248.

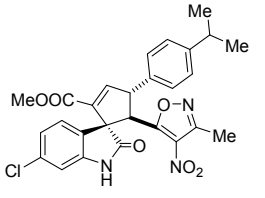
Methyl-5'-bromo-4-(4-isopropylphenyl)-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxo-spiro[cyclopentane-1,3'-indolin]-2-ene-2-carboxylate 4aa:



4aa

white solid, 30.7 mg, 80% yield, dr >19:1, m.p. >210 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.54 (s, 1H), 7.29 (d, *J* = 7.8 Hz, 2H), 7.26 – 7.24 (m, 1H), 7.21 (d, *J* = 7.8 Hz, 2H), 7.19 (d, *J* = 2.4 Hz, 1H), 7.18 (d, *J* = 1.8 Hz, 1H), 6.72 (d, *J* = 8.3 Hz, 1H), 5.20 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.95 (d, *J* = 9.0 Hz, 1H), 3.65 (s, 3H), 2.89 (dt, *J* = 13.8, 7.2 Hz, 1H), 2.35 (s, 3H), 1.24 (d, *J* = 1.8 Hz, 3H), 1.23 (d, *J* = 1.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 178.3, 169.8, 162.4, 155.9, 149.1, 148.8, 140.4, 136.7, 135.7, 132.4, 131.0, 129.4, 127.9, 127.5, 127.4, 114.7, 111.7, 64.3, 55.2, 52.7, 52.3, 33.9, 24.0, 24.0, 11.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{27}H_{24}BrN_3O_6Na$ 588.0746, found 588.0745.

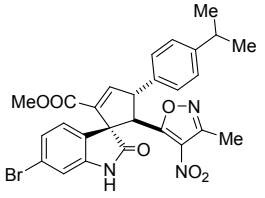
Methyl-6'-chloro-4-(4-isopropylphenyl)-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxo-spiro[cyclopentane-1,3'-indolin]-2-ene-2-carboxylate 4ab:



4ab

white solid, 29.1 mg, 76% yield, dr 15:1, m.p. 203–204 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.63 (s, 1H), 7.29 (d, *J* = 7.8 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 1.8 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.86 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.85 (d, *J* = 1.2 Hz, 1H), 5.20 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.95 (d, *J* = 9.0 Hz, 1H), 3.64 (s, 3H), 2.89 (dt, *J* = 13.8, 7.2 Hz, 1H), 2.35 (s, 3H), 1.24 (d, *J* = 1.2 Hz, 3H), 1.23 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 178.7, 169.9, 162.4, 155.9, 149.0, 148.6, 142.5, 136.7, 135.7, 135.0, 130.9, 127.7, 127.4, 125.6, 125.2, 122.2, 110.9, 63.7, 55.1, 52.6, 52.2, 33.8, 23.9, 23.9, 11.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{27}H_{24}ClN_3O_6Na$ 544.1251, found 544.1254.

Methyl-6'-bromo-4-(4-isopropylphenyl)-5-(3-methyl-4-nitroisoxazol-5-yl)-2'-oxo-spiro[cyclopentane-1,3'-indolin]-2-ene-2-carboxylate 4ac:

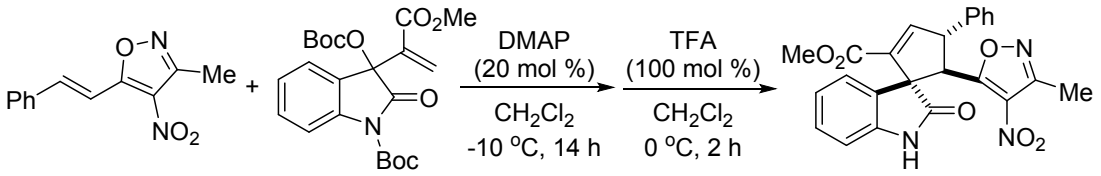


4ac

white solid, 29.9 mg, 78% yield, dr 15:1, m.p. >210 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.52 (s, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 2.4 Hz, 1H), 7.02 (dd, *J* =

7.8, 1.8 Hz, 1H), 6.99 (d, *J* = 1.8 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 5.20 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.94 (d, *J* = 9.0 Hz, 1H), 3.64 (s, 3H), 2.89 (dt, *J* = 13.8, 7.2 Hz, 1H), 2.36 (s, 3H), 1.24 (d, *J* = 1.8 Hz, 3H), 1.22 (d, *J* = 1.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 178.6, 170.0, 162.5, 156.0, 149.1, 148.7, 142.6, 136.8, 135.8, 131.0, 127.9, 127.5, 126.3, 125.6, 125.2, 123.1, 113.8, 63.9, 55.1, 52.7, 52.3, 33.9, 24.0, 24.0, 11.6; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{27}H_{24}BrN_3O_6Na$ 588.0746, found 588.0743.

5. Gram-scale synthesis of products 4a



1a, 1.13 g **2a** **4a**, 1.02 g, 88% yield,16:1 dr

Scheme S1 Gram-scale synthesis of isoxazole-containing spirooxindole cyclopentene derivatives.

A gram-scale mixture of MBH carbonate **1a** (4.9 mmol, 1.13 g) with 4-nitro-5-alkenylisoxazole **2a** (5.4 mmol, 2.34 g) was added dimethylaminopyridine (DMAP, 20 mol%) in dichloromethane (3.0 mL) at -10 °C. The reaction mixture was stirred at -10 °C for about 8 hours. After the consumption of MBH carbonate **1a**, the mixture was stirred at -10 °C followed by addition of trifluoroacetic acid (TFA, 100 mol% in 1.0 mL DCM) and then moved to room temperature for about 2 hours. The mixture was stirred until the reaction had stopped progressing as observed by TLC analysis, then diluted with EtOAc and washed with saturated aqueous $NaHCO_3$, and brine. Then the solution was concentrated and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:1 to 3:1) to afford 1.02 g of the diastereochemical outcome **4a**.

6. Crystal data of 4g

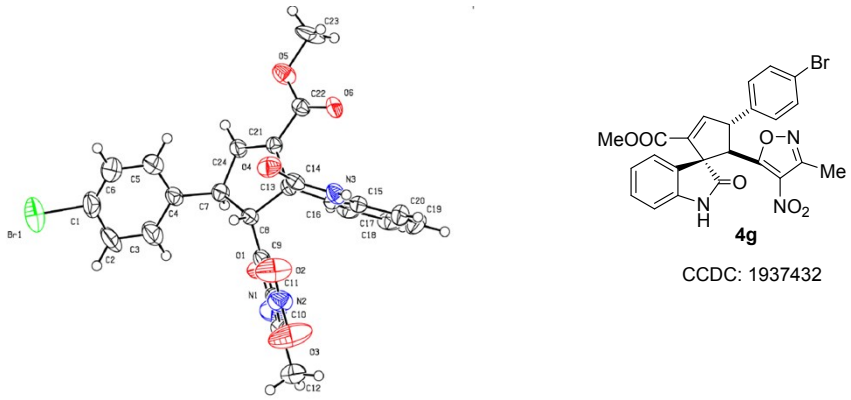


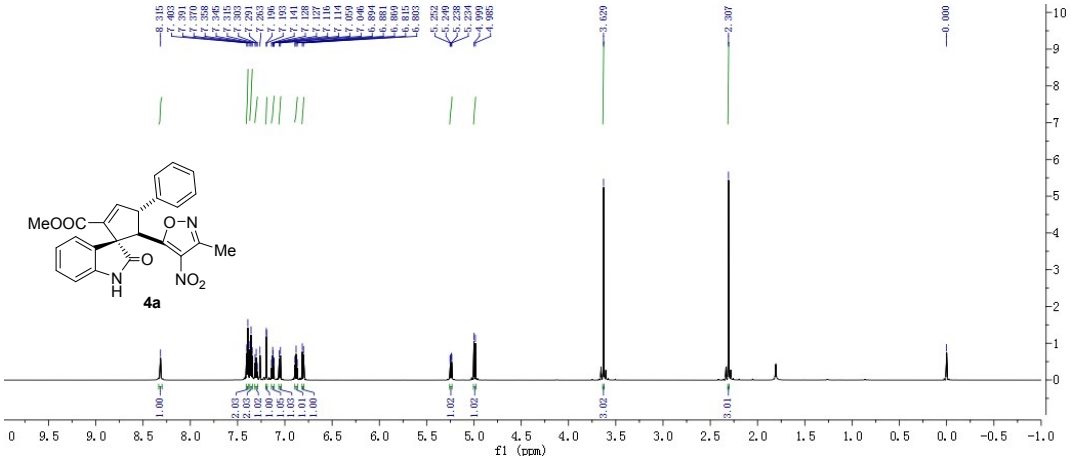
Figure S1 X-ray crystal structure of **4g**. The thermal ellipsoids are drawn at a 50% probability level.

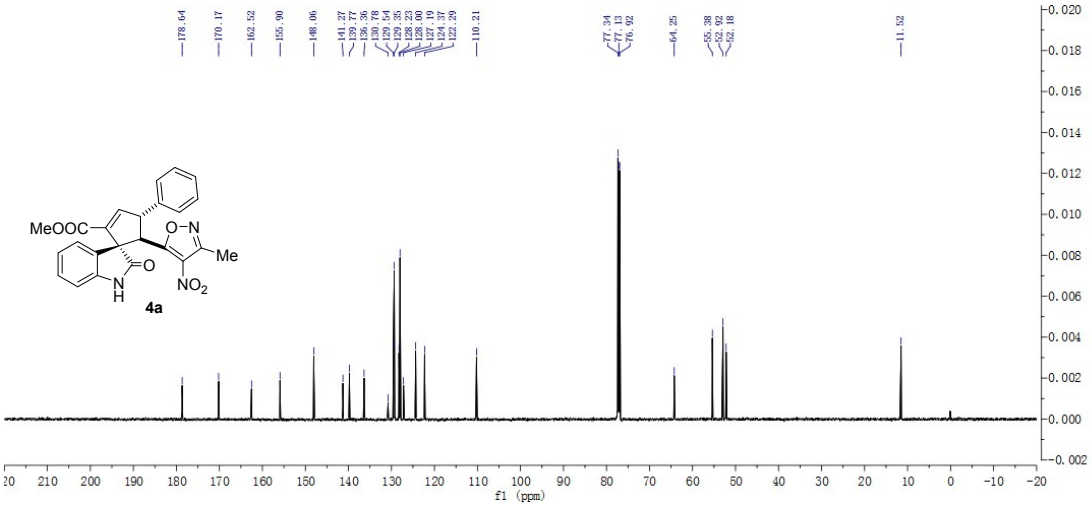
Single crystals suitable for XRD were obtained by vapor diffusion experiment: compound **4g** was dissolved in 0.5 mL dichloromethane and 1.0 mL methanol in a glass vial, which was then placed in sealed glass container. Crystals were obtained in about 4-5 days.

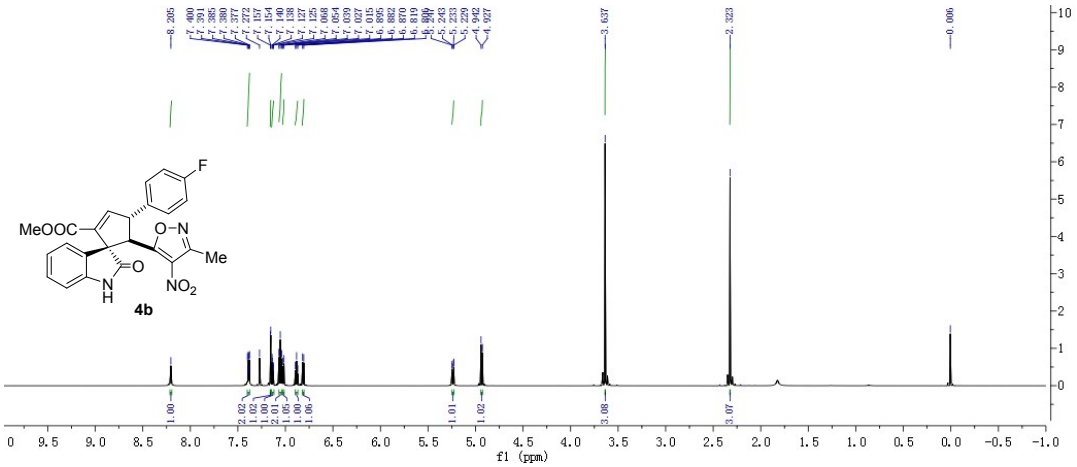
Identification code	XX
Empirical formula	$C_{24}H_{18}BrN_3O_6$
Formula weight	524.31
Temperature/K	150
Crystal system	orthorhombic
Space group	Cmce
a/Å	8.7145(16)
b/Å	15.395(3)
c/Å	34.142(6)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	4580.5(15)
Z	8
ρ_{calc}g/cm^3	1.521
μ/mm^{-1}	1.841
F(000)	2128.0
Crystal size/mm^3	? × ? × ?
Radiation	MoKα (λ = 0.71073)

2Θ range for data collection/°	5.502 to 55.04
Index ranges	$-9 \leq h \leq 11$, $-19 \leq k \leq 20$, $-43 \leq l \leq 42$
Reflections collected	17773
Independent reflections	2743 [R_{int} = 0.0562, R_{sigma} = 0.0460]
Data/restraints/parameters	2743/0/292
Goodness-of-fit on F^2	1.032
Final R indexes [I>=2σ (I)]	R_1 = 0.0509, wR_2 = 0.0965
Final R indexes [all data]	R_1 = 0.1073, wR_2 = 0.1162
Largest diff. peak/hole / e $Å^{-3}$	0.35/-0.39

7. NMR spectra



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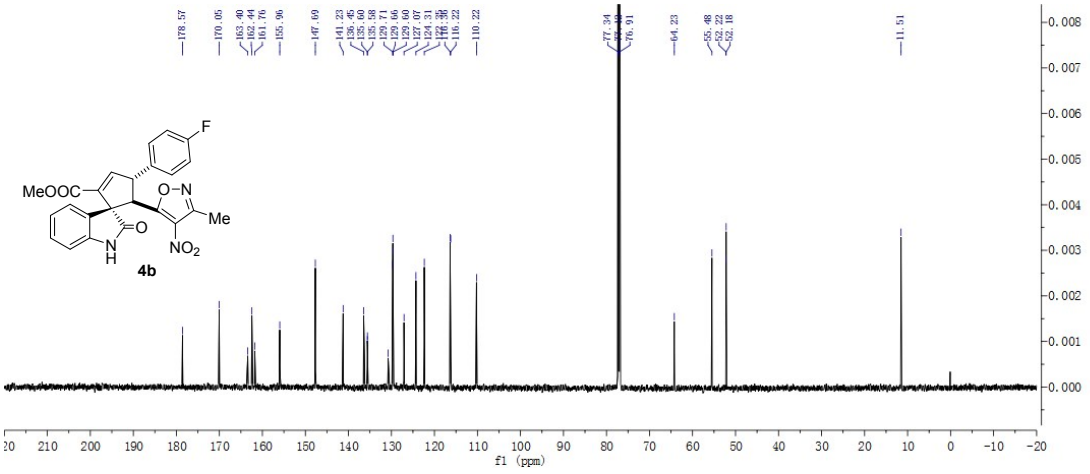
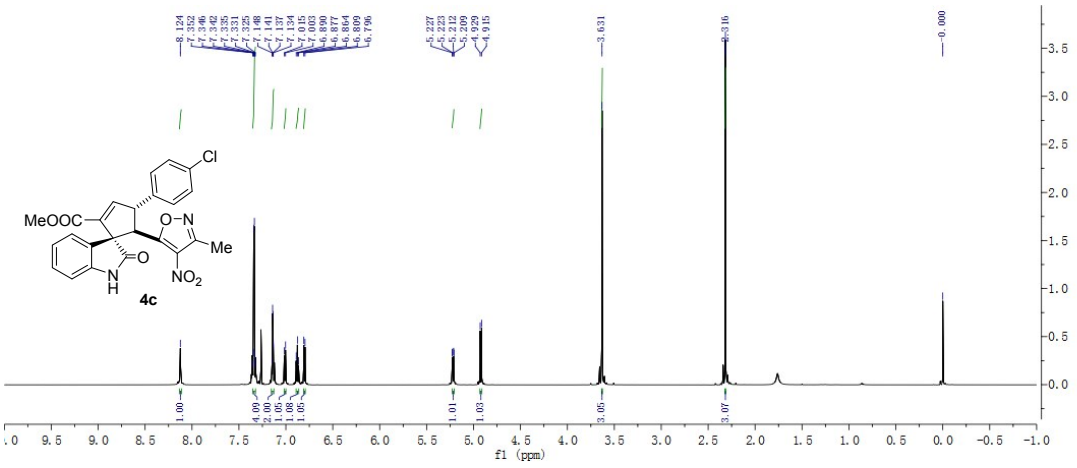
MeOOC
O–N
Me
O
N
H
NO2
4b
f1 (ppm)


F
MeOOC
O–N
Me
O
N
H
NO2
4b
f1 (ppm)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6.899
6.877
6.864
6.809
6.796
5.227
5.223
5.212
5.209
4.929
4.915
3.631
3.316
0.000
Cl
MeOOC
O–N
Me
O
N
H
NO2
4c
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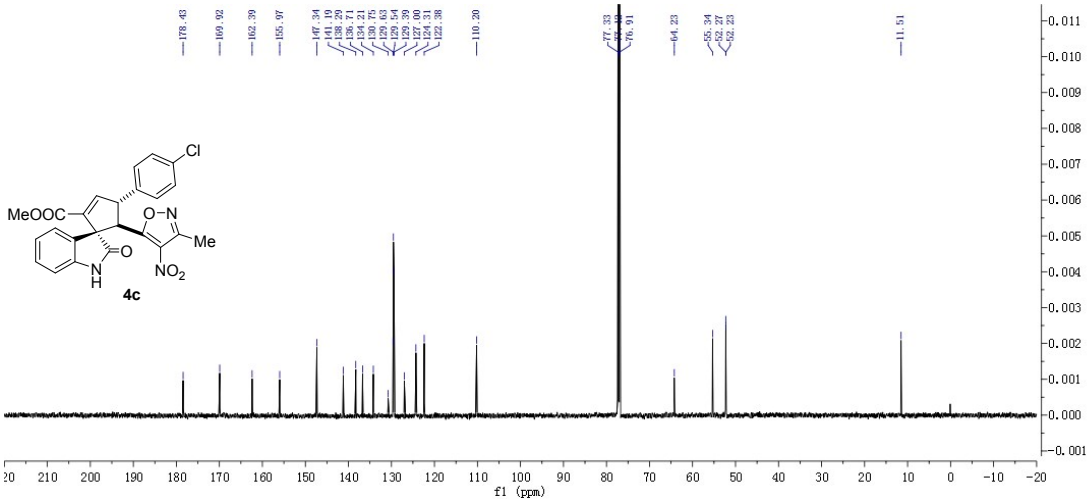
2.00
1.05
1.08
1.05
1.01
1.03
3.05
3.07
f1 (ppm)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129.63
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122.38
110.20
77.33
77.04
76.91
64.23
55.34
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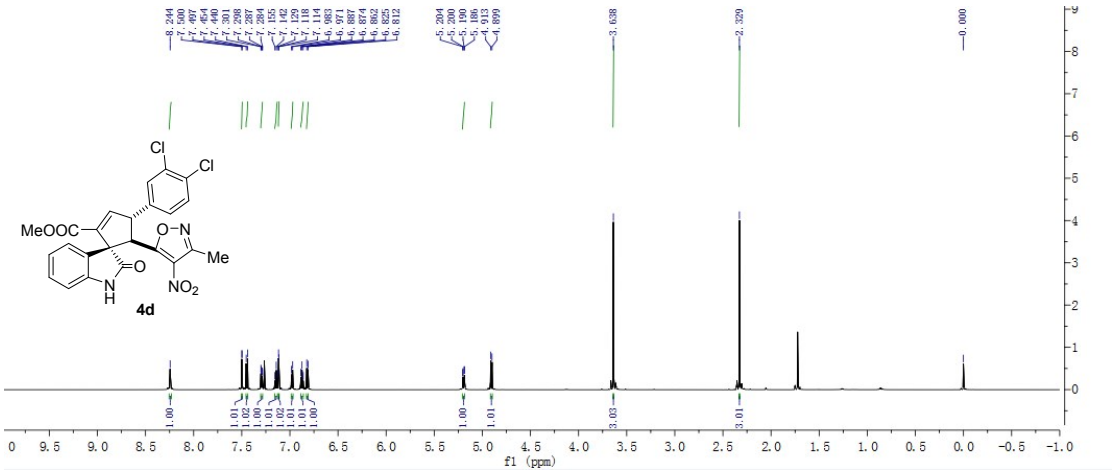
52.23
11.51
Cl
MeOOC
O–N
Me
O
N
H
NO2
4c
f1 (ppm)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7.142
7.139
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7.114
6.983
6.971
6.897
6.874
6.862
6.625
6.612
5.204
5.200
5.189
5.186
4.913
4.899
3.638
2.329
0.000
Cl
Cl
MeOOC
O–N
Me
O
N
H
NO2
4d
1.00
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1.01
1.01
1.00
1.00
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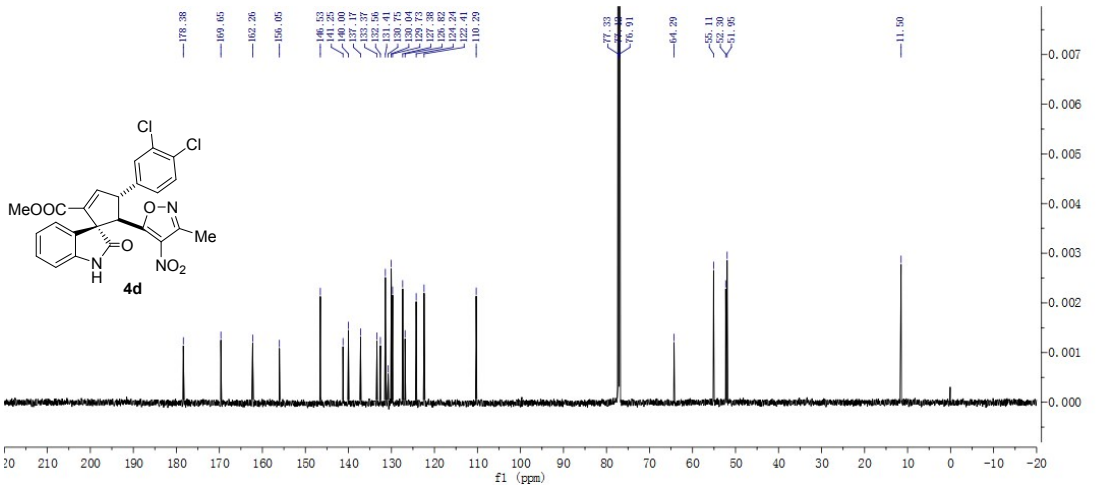
3.01
f1 (ppm)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141.25
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137.17
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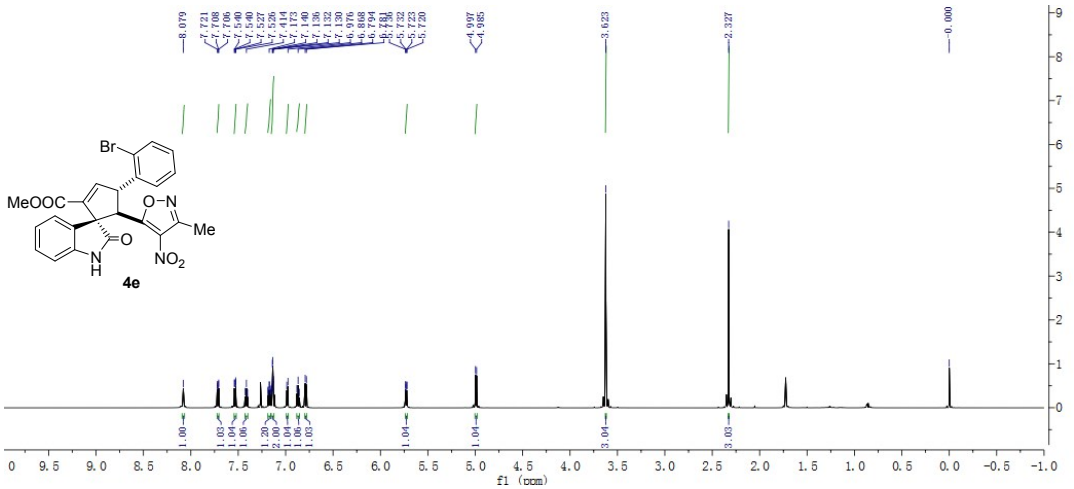
131.41
130.75
130.04
129.73
127.38
126.82
124.24
122.44
110.29
77.33
77.00
76.91
64.29
55.11
52.30
51.95
11.50
Cl
Cl
MeOOC
O–N
Me
O
N
H
NO2
4d
f1 (ppm)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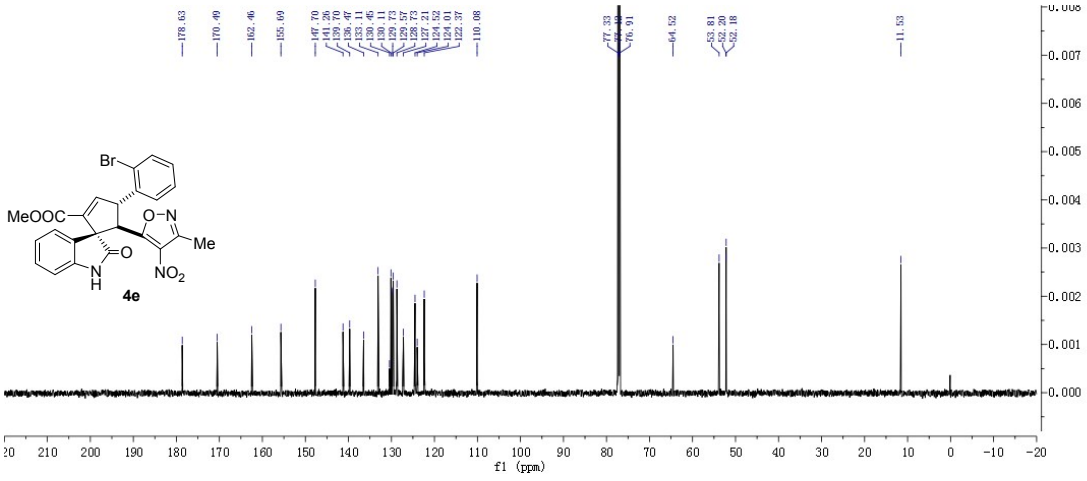
7.527
7.526
7.414
7.413
7.140
7.136
7.132
7.130
7.076
6.868
6.794
5.732
5.723
5.720
4.997
4.985
3.623
2.327
0.000
Br
MeOOC
O–N
Me
O
N
H
NO2
4e
f1 (ppm)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138.47
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130.11
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128.73
127.21
124.52
124.01
122.37
110.08
77.33
77.04
76.91
64.52
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52.18
11.53
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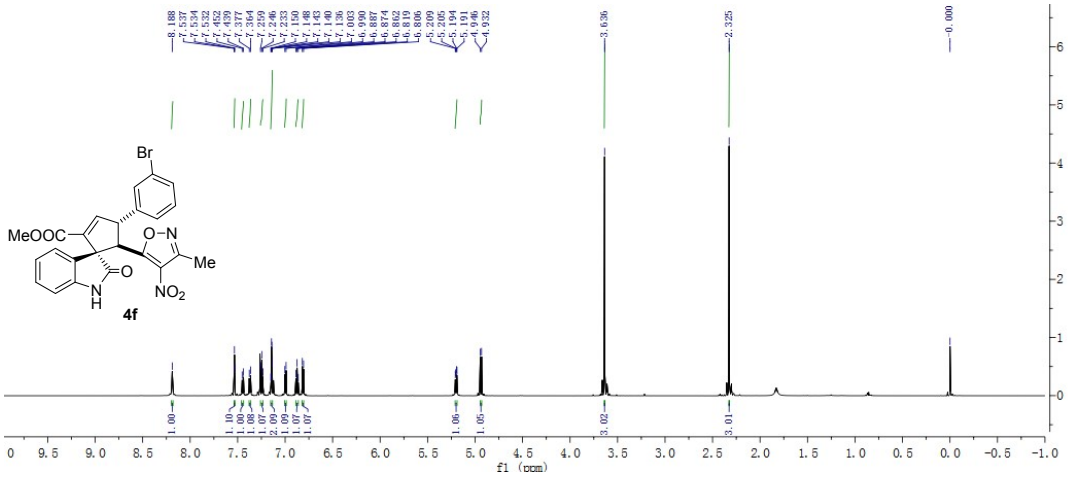
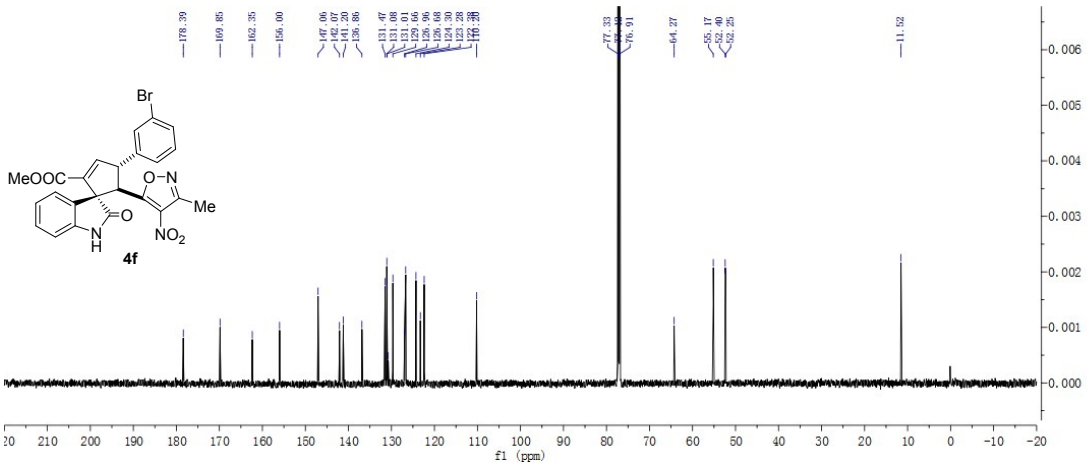
O–N
Me
O
N
H
NO2
4e
f1 (ppm)


Br
MeOOC
O–N
Me
O
N
H
NO2
4f
fl (ppm)


Br
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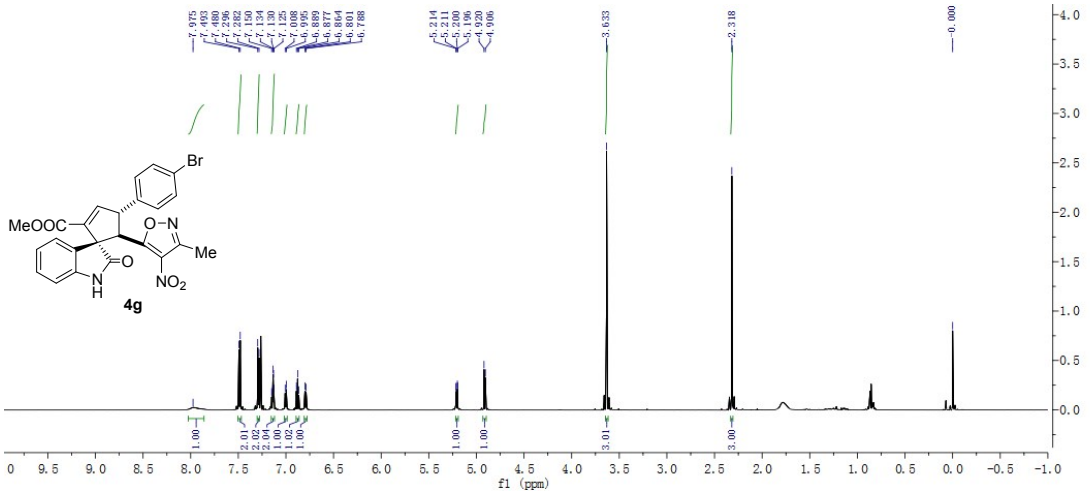
O–N
Me
O
N
H
NO2
4f
fl (ppm)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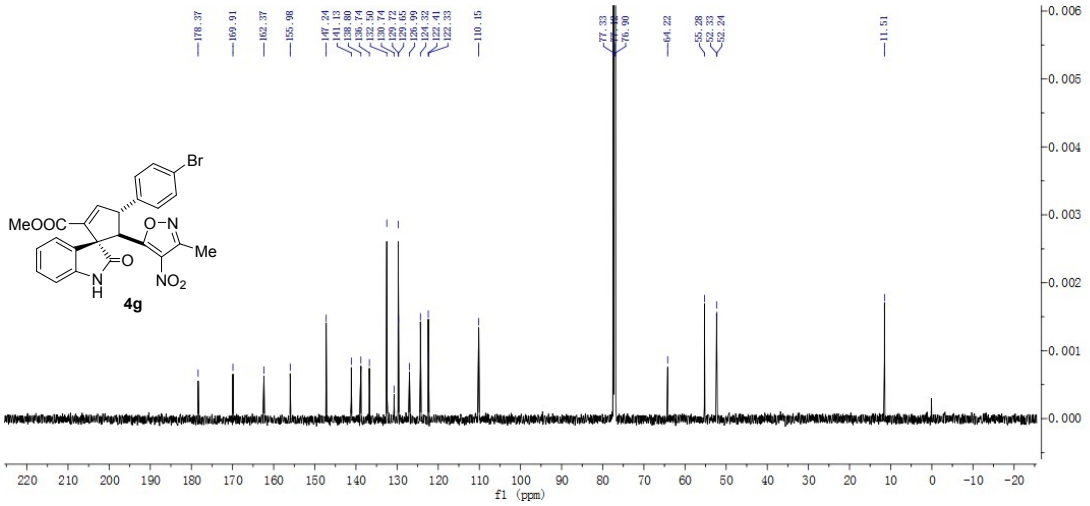
7.282
7.150
7.134
7.130
7.125
7.008
6.995
6.889
6.877
6.864
6.801
6.788
5.214
5.211
5.200
5.196
4.930
4.906
3.633
2.318
0.000
Br
MeOOC
O-N
Me
O
N
H
NO2
4g
f1 (ppm)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136.74
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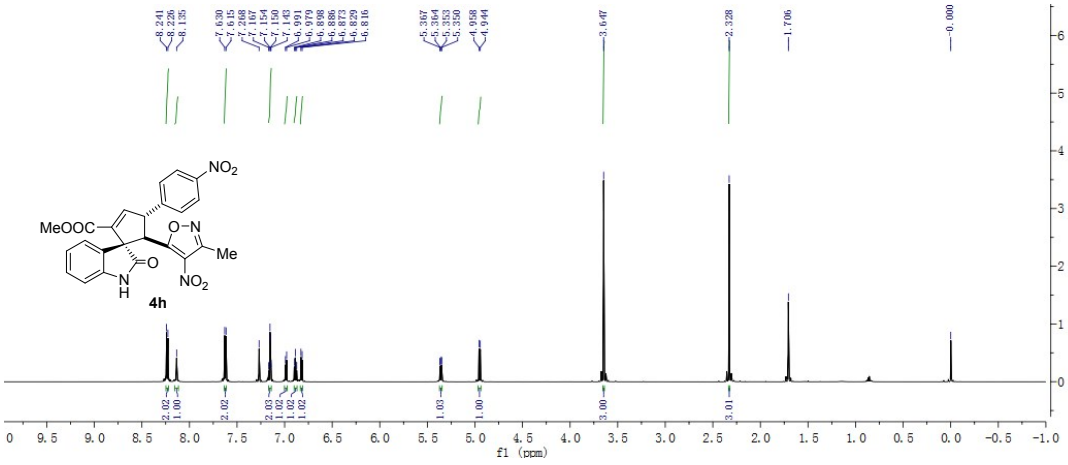
130.74
129.72
129.65
126.99
124.32
122.41
122.33
110.15
77.33
76.90
64.22
55.28
52.33
52.24
11.51
Br
MeOOC
O-N
Me
O
N
H
NO2
4g
f1 (ppm)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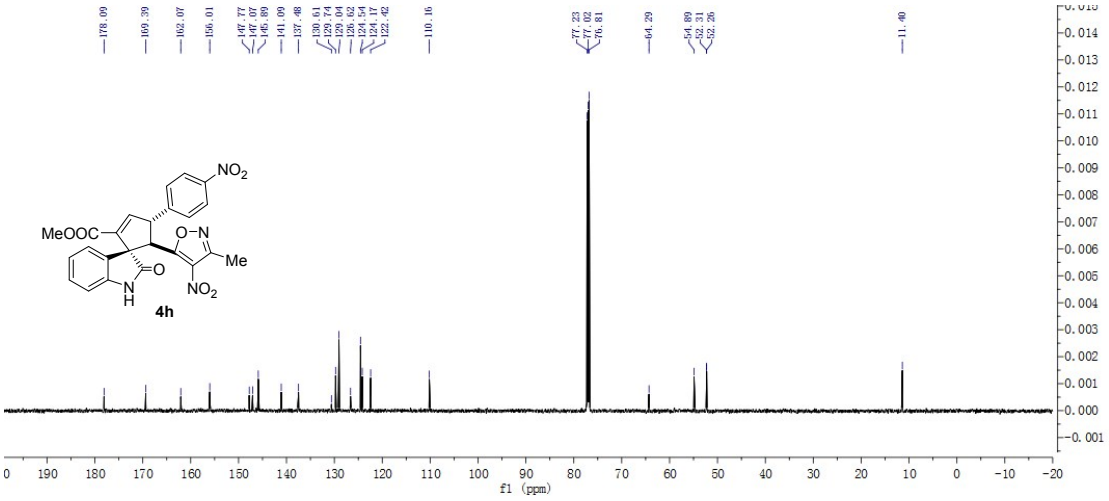
8.135
7.630
7.615
7.168
7.164
7.154
7.150
7.143
6.991
6.979
6.898
6.886
6.873
6.829
6.816
5.367
5.364
5.353
5.350
4.958
4.944
3.647
2.328
1.706
0.000
NO2
MeOOC
O-N
Me
O
N
H
NO2
4h
2.02
1.00
2.02
2.03
1.02
1.02
1.03
1.00
3.00
3.01
f1 (ppm)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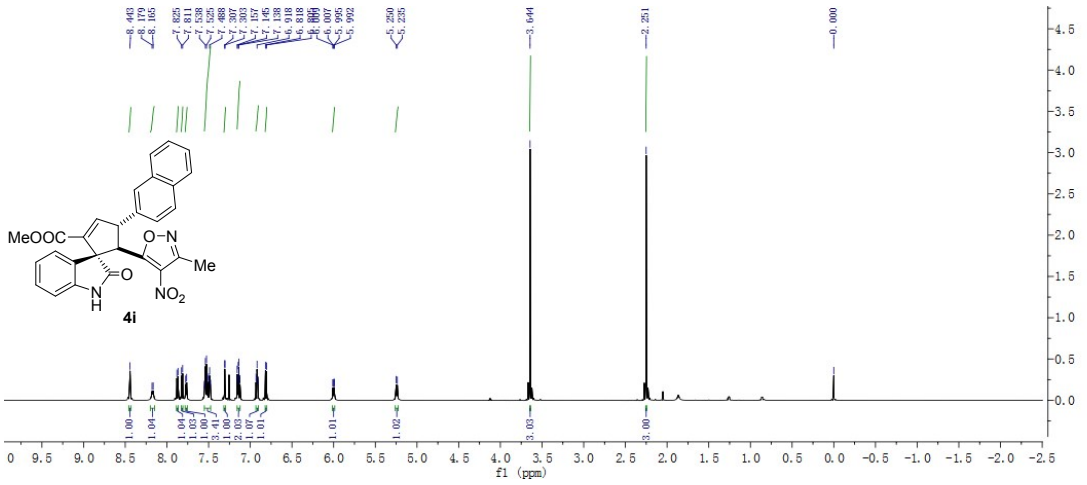
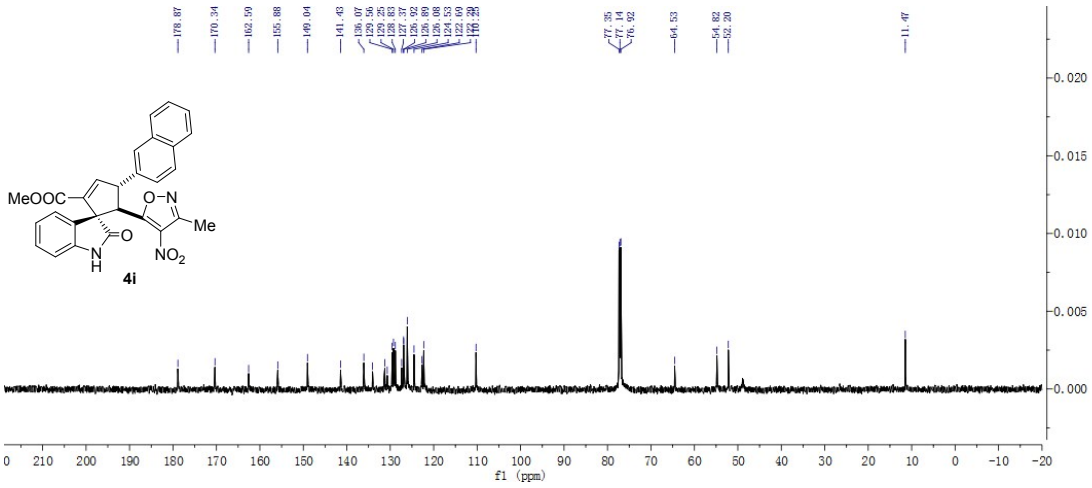
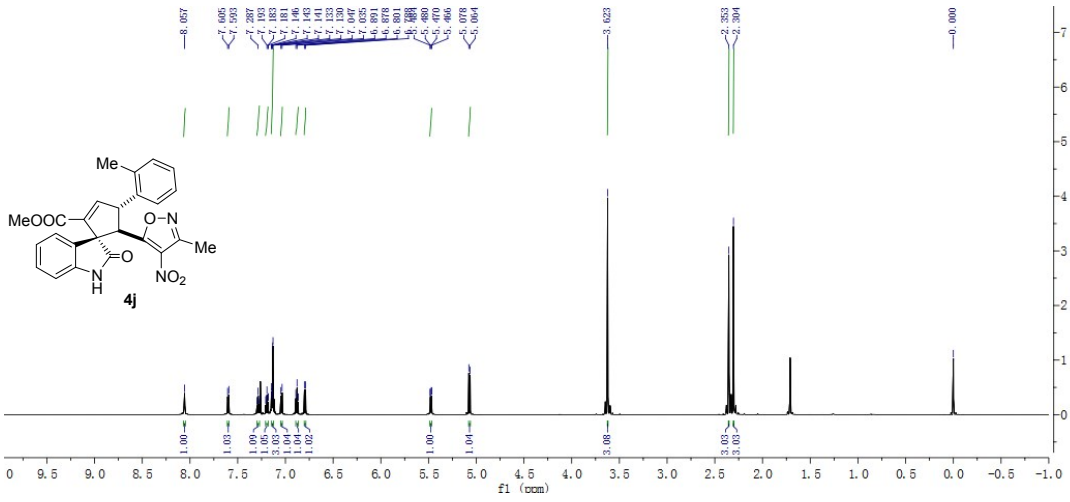
156.01
147.77
147.07
145.89
141.09
137.48
130.61
129.74
129.64
129.52
124.54
124.17
122.42
110.16
77.23
77.02
76.81
64.29
54.89
52.31
52.26
11.40
NO2
MeOOC
O-N
Me
O
N
H
NO2
4h
f1 (ppm)


MeOOC
O–N
Me
O
N
H
NO2
4i
f1 (ppm)


MeOOC
O–N
Me
O
N
H
NO2
4i
f1 (ppm)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7.143
7.141
7.133
7.130
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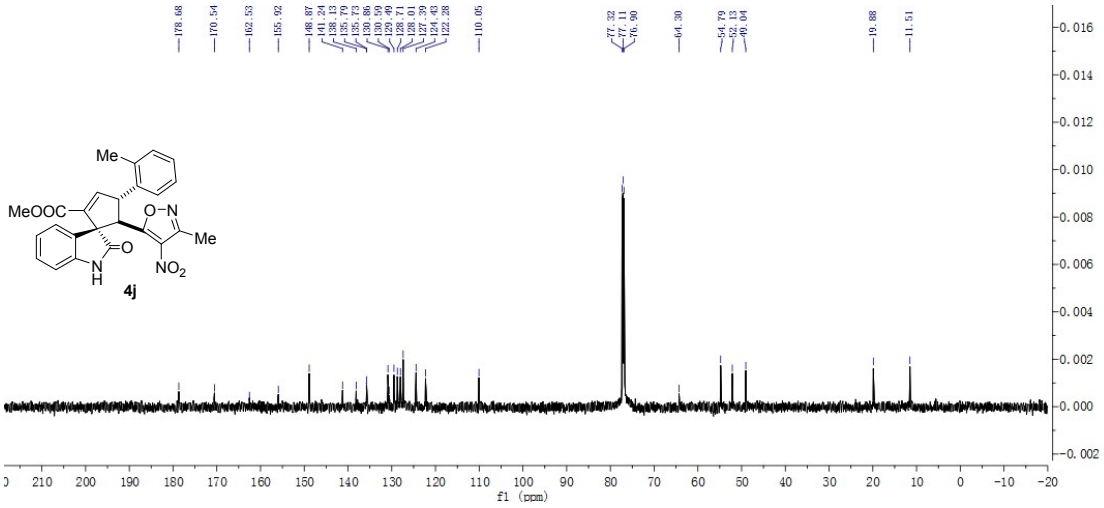
7.035
6.891
6.878
5.480
5.470
5.466
5.078
5.064
3.623
2.353
2.304
0.000
Me
MeOOC
O–N
Me
O
N
H
NO2
4j
1.00
1.03
1.09
1.05
3.03
1.04
1.04
1.02
1.00
1.04
3.08
3.03
3.03
f1 (ppm)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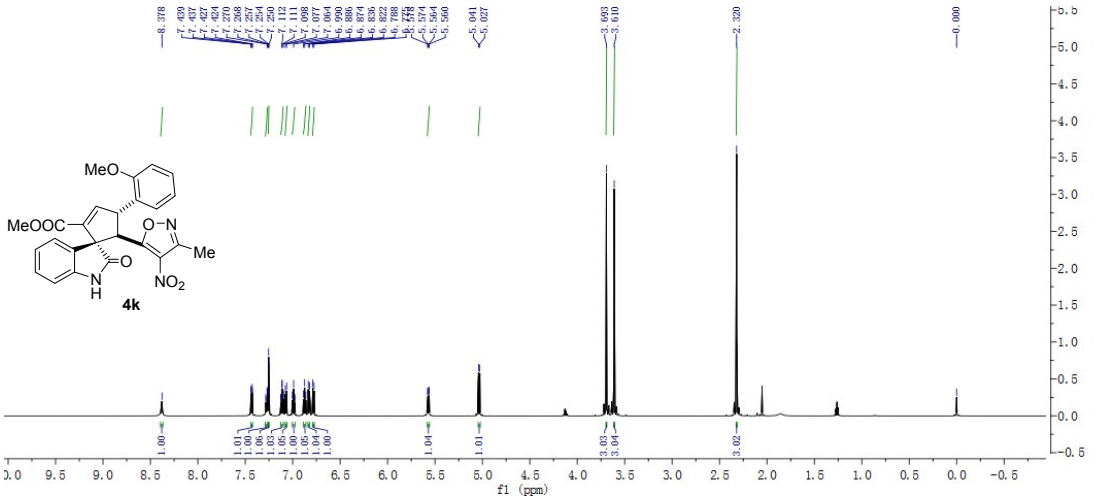
128.71
128.01
127.39
124.45
122.28
110.05
77.32
77.11
76.90
64.30
54.79
52.13
40.04
19.88
11.51
Me
MeOOC
O–N
Me
O
N
H
NO2
4j
f1 (ppm)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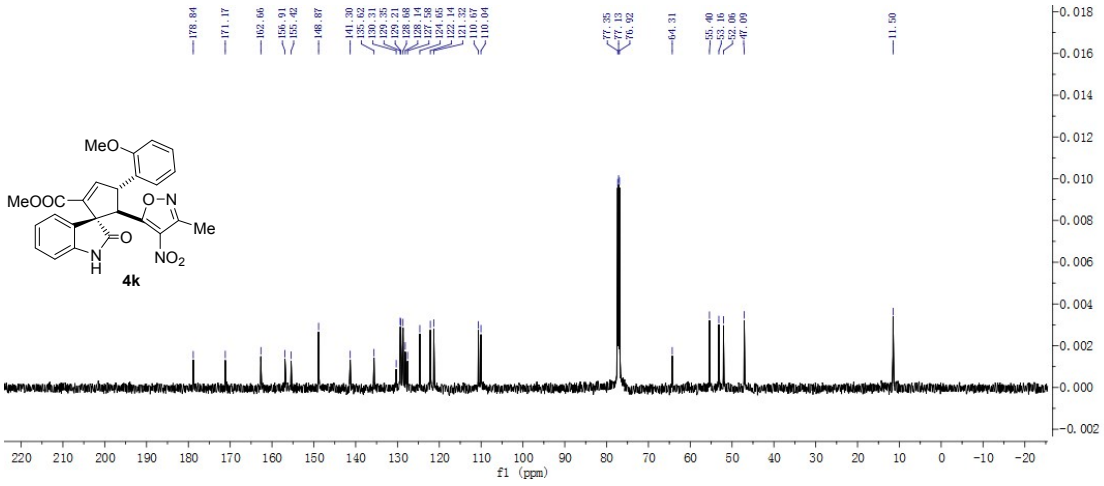
Me
O
N
H
NO2
4k
f1 (ppm)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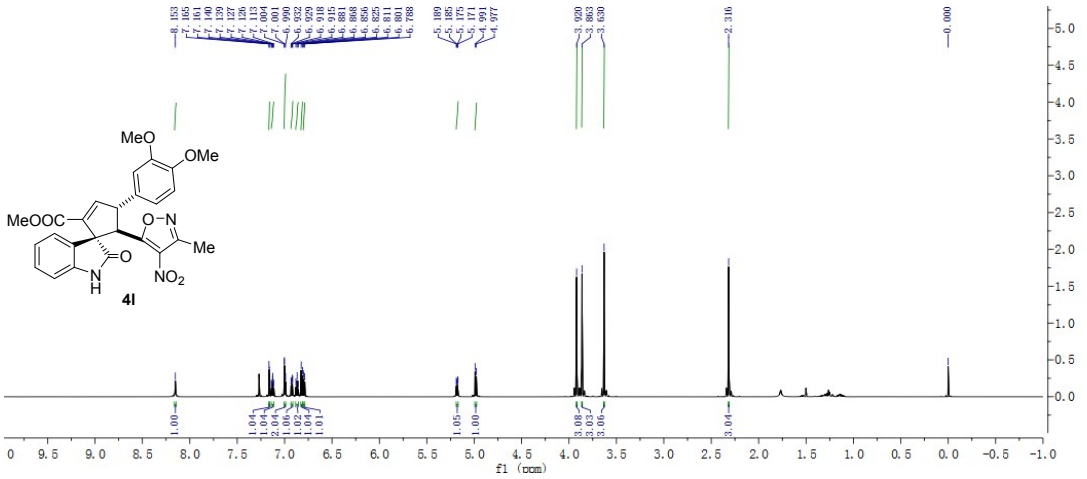
MeOOC
O–N
Me
O
N
H
NO2
4k
f1 (ppm)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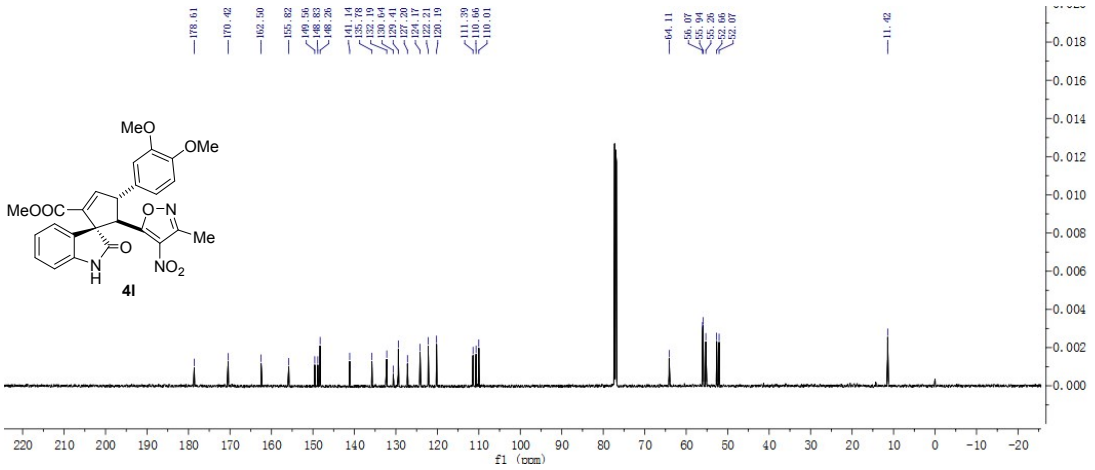
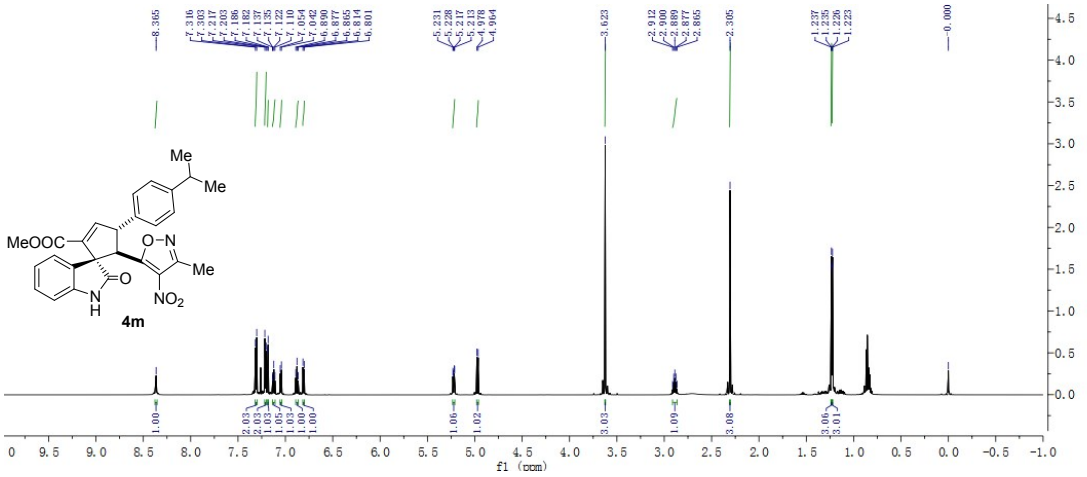
OMe
MeOOC
O–N
Me
O
N
H
NO2
4l


MeO
OMe
MeOOC
O–N
Me
O
N
H
NO2
4l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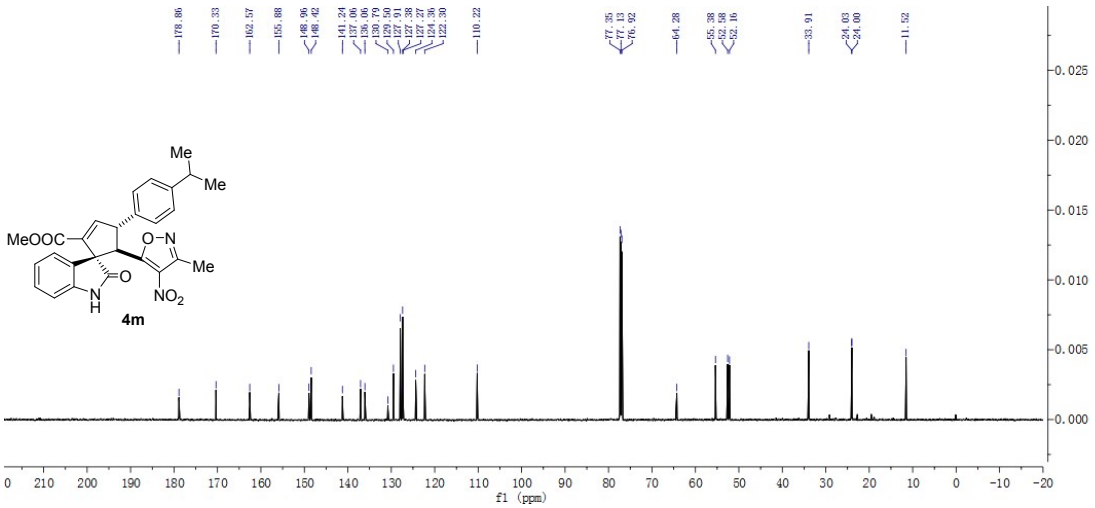
7.137
7.135
7.122
7.110
7.054
7.042
6.899
6.877
6.865
6.814
6.801
5.231
5.228
5.217
5.213
4.978
4.964
3.623
2.912
2.900
2.899
2.877
2.865
2.305
1.237
1.235
1.226
1.223
0.000
Me
Me
MeOOC
O–N
Me
O
N
H
NO2
4m
f1 (ppm)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148.42
141.24
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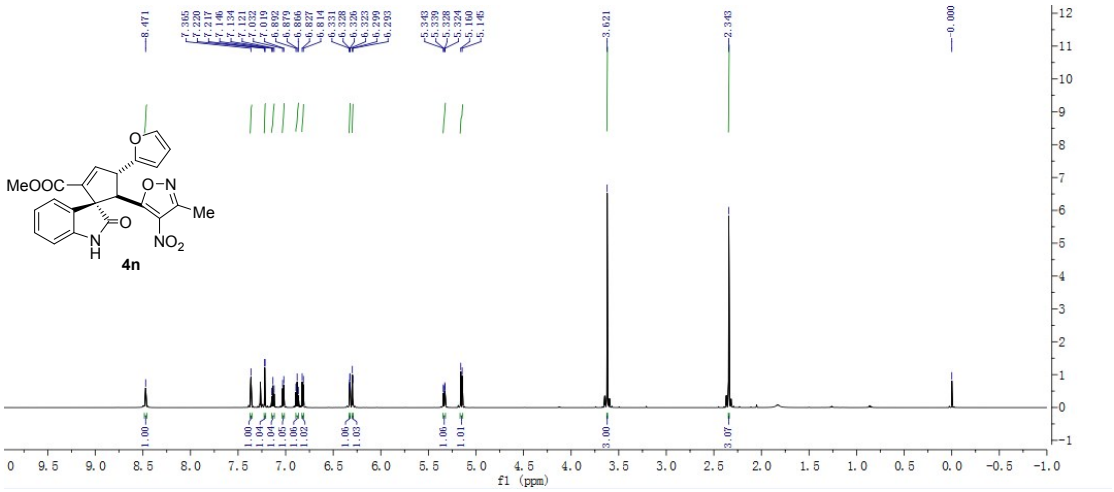
136.06
130.79
129.50
127.91
127.38
127.27
124.36
122.30
110.22
77.35
77.13
76.92
64.28
55.38
52.58
52.16
33.91
29.03
24.80
11.52
Me
Me
MeOOC
O–N
Me
O
N
H
NO2
4m
f1 (ppm)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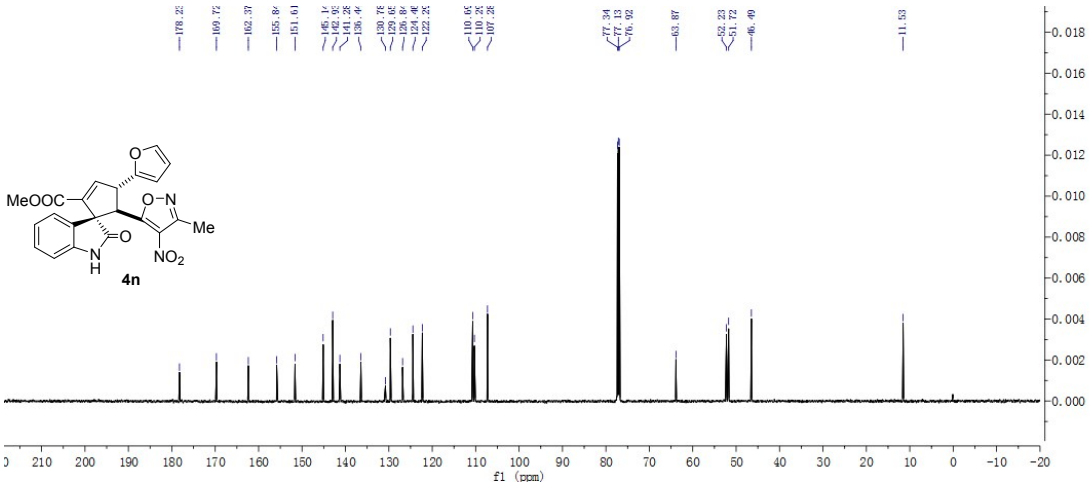
O
O–N
Me
O
N
H
NO2
4n
f1 (ppm)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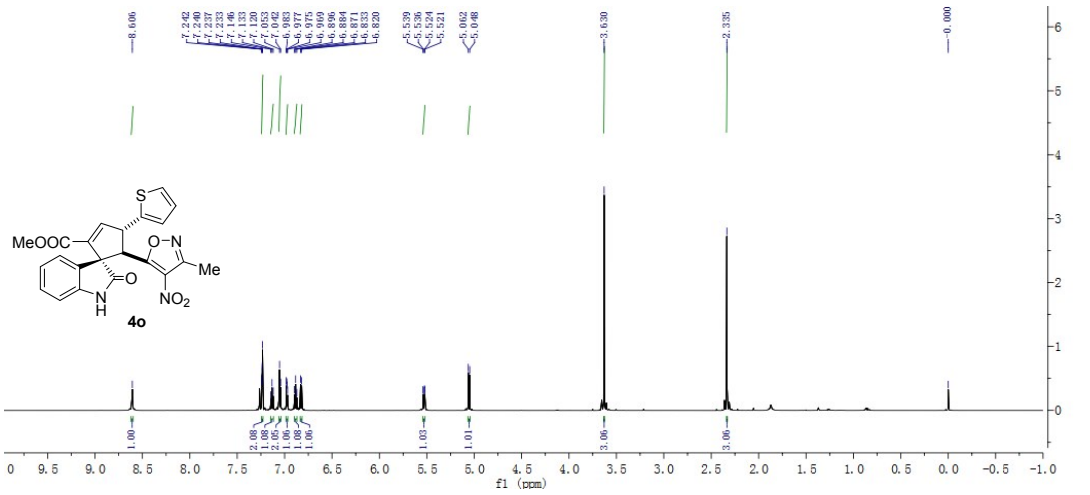
O–N
Me
O
N
H
NO2
4n
f1 (ppm)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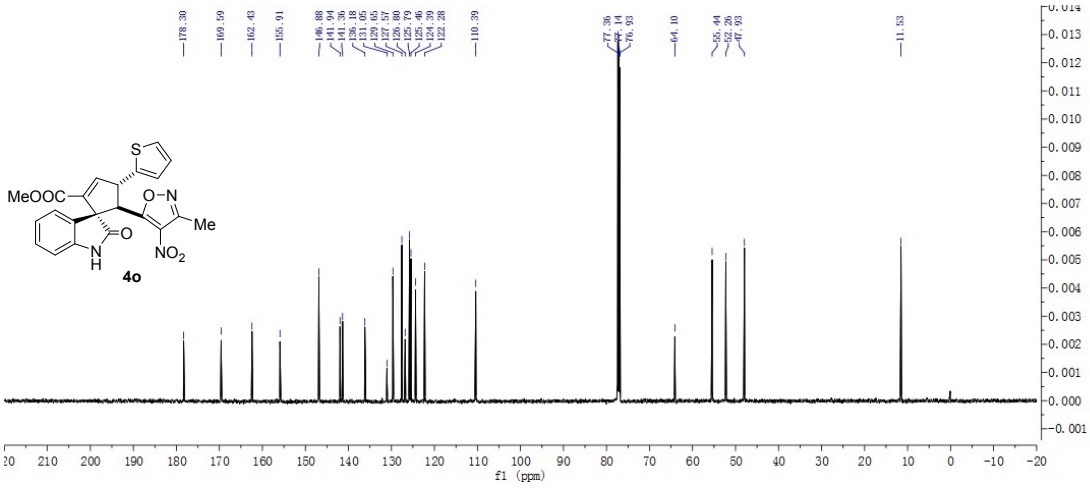
Me
O
N
H
NO2
4o
f1 (ppm)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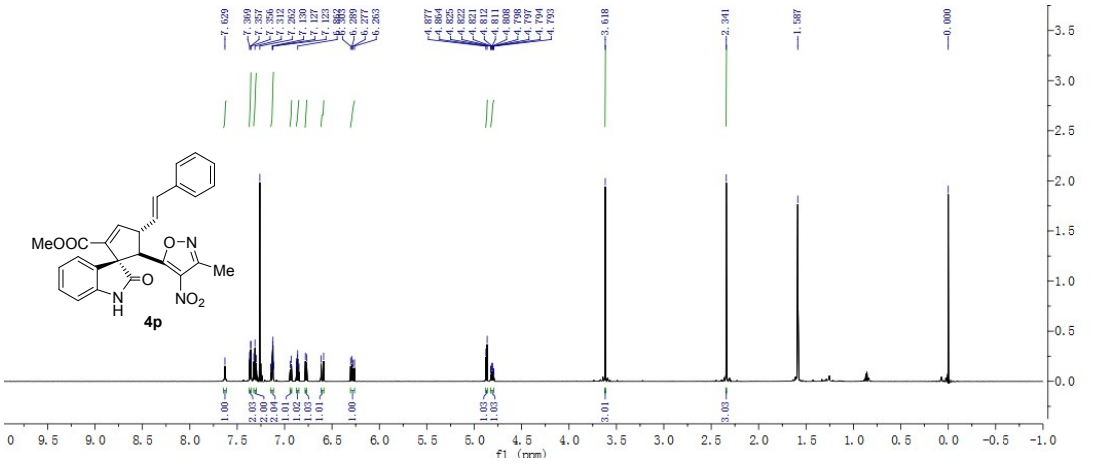
O–N
Me
O
N
H
NO2
4o
f1 (ppm)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O
N
H
NO2
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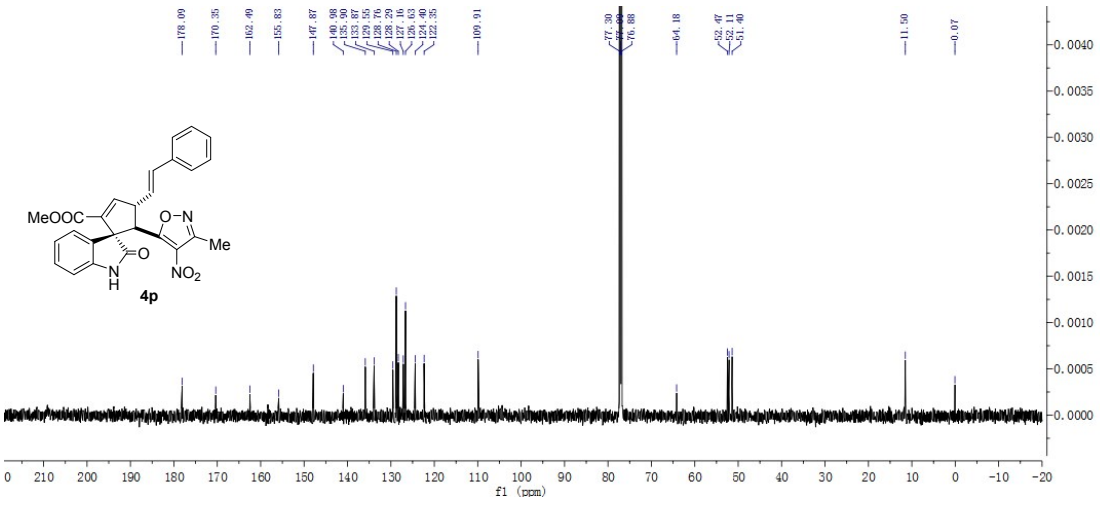
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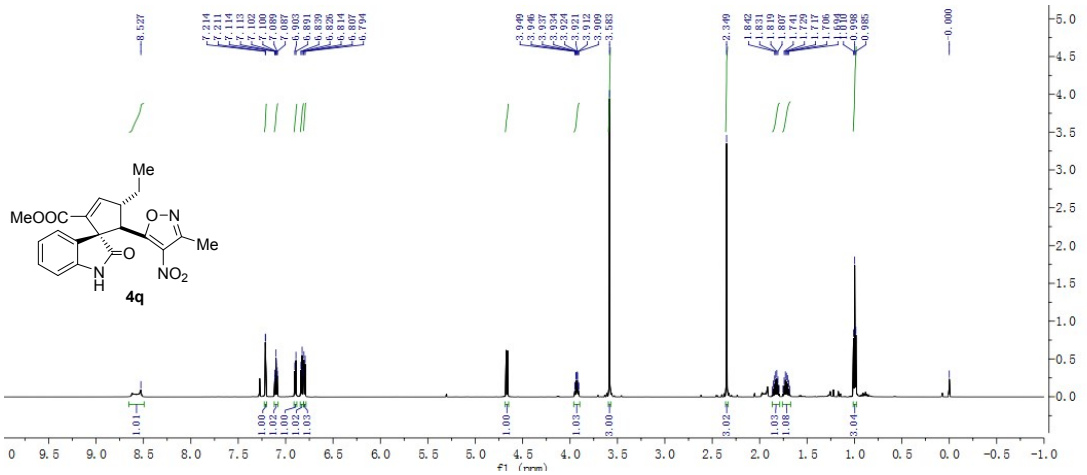
O–N
Me
O
N
H
NO2
4p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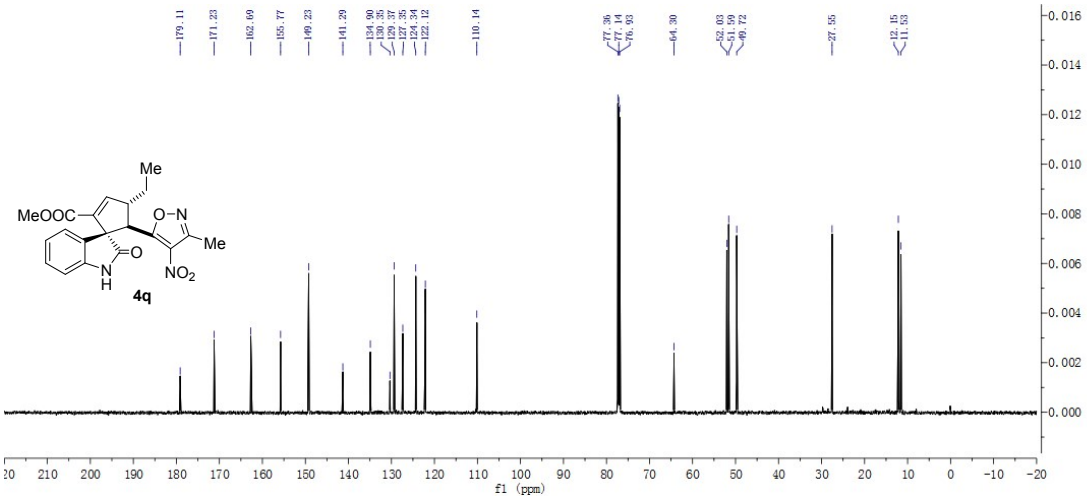
O-N
Me
O
N
H
NO2
4q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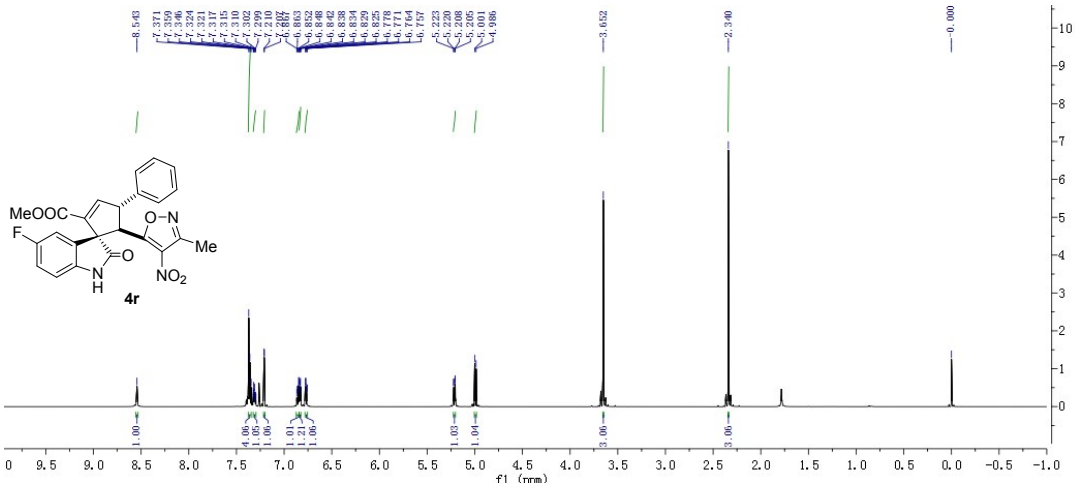
MeOOC
O-N
Me
O
N
H
NO2
4q
f1 (ppm)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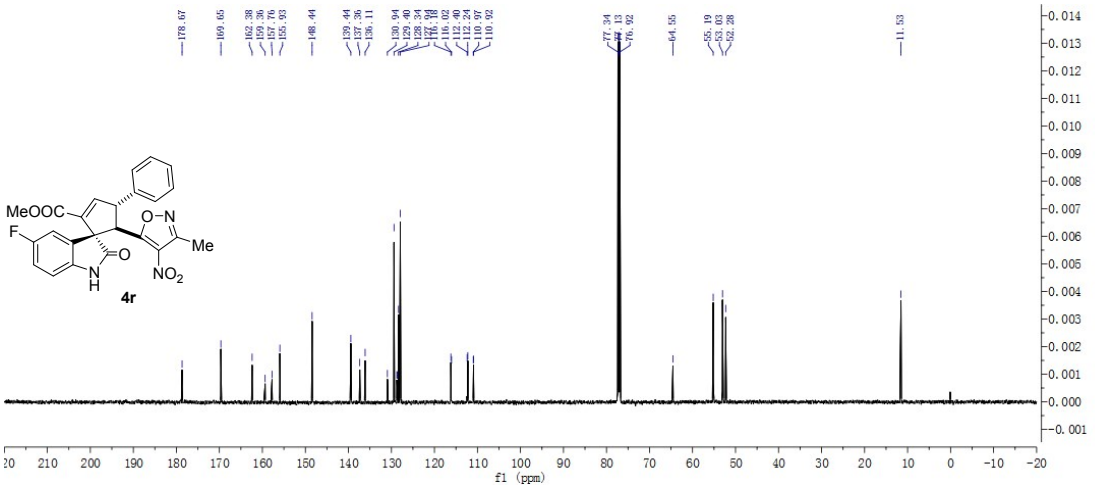
Me
O
N
H
NO2
4r
f1 (ppm)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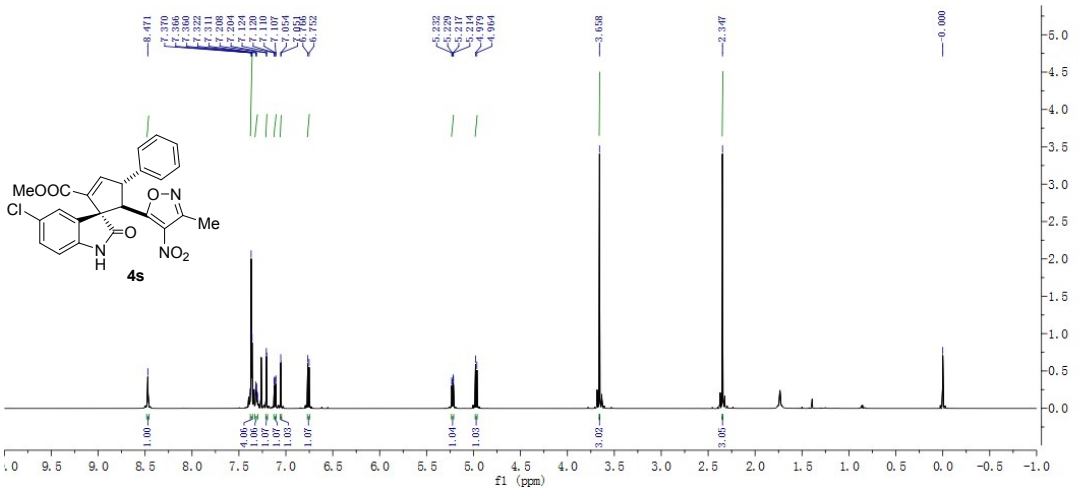
F
O–N
Me
O
N
H
NO2
4r
f1 (ppm)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7.124
7.110
7.107
7.054
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6.752
5.232
5.229
5.217
5.214
4.979
4.964
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0.000
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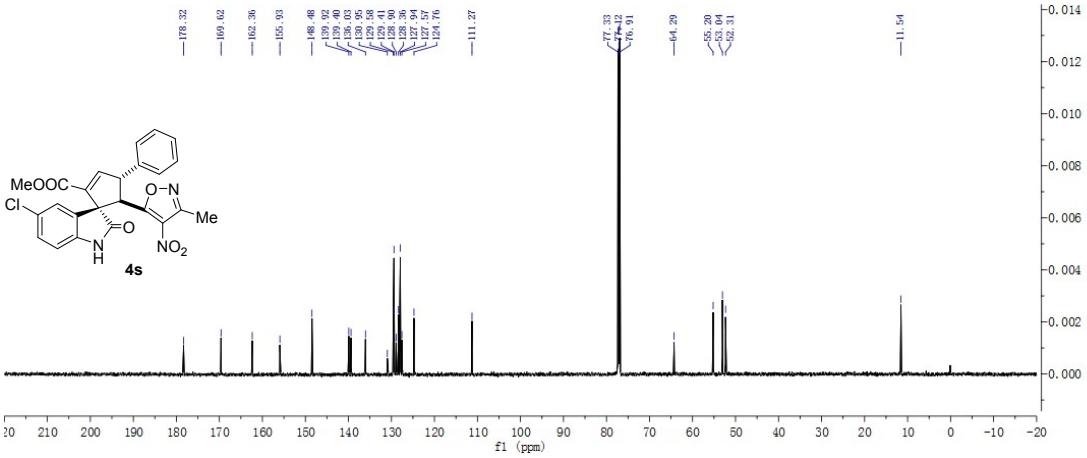
Cl
O–N
Me
NO2
O
N
H
4s
f1 (ppm)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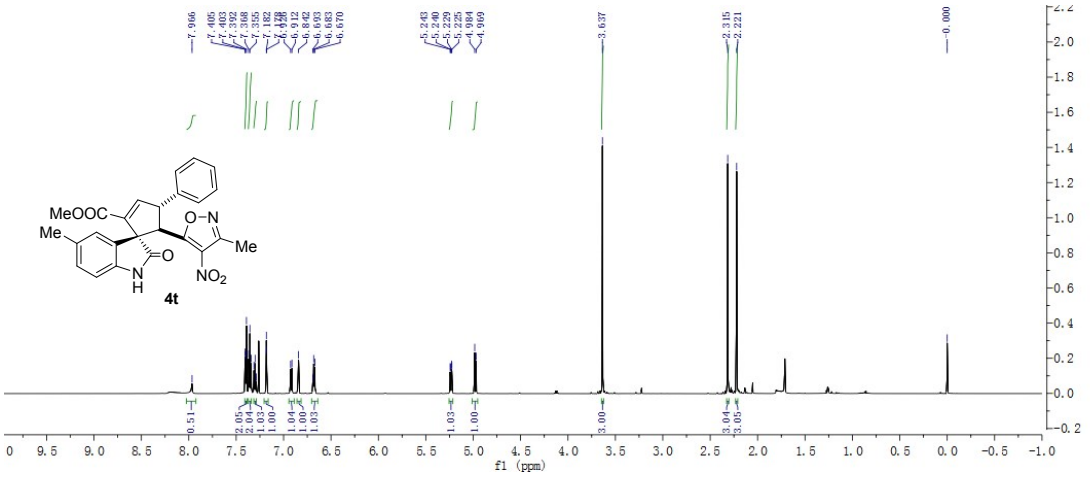
162.36
155.93
140.46
139.92
139.40
136.03
130.95
129.58
129.41
128.90
128.36
127.94
127.57
124.76
111.27
77.33
77.12
76.91
64.29
55.20
53.04
52.31
11.54
MeOOC
Cl
O–N
Me
NO2
O
N
H
4s
f1 (ppm)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Me
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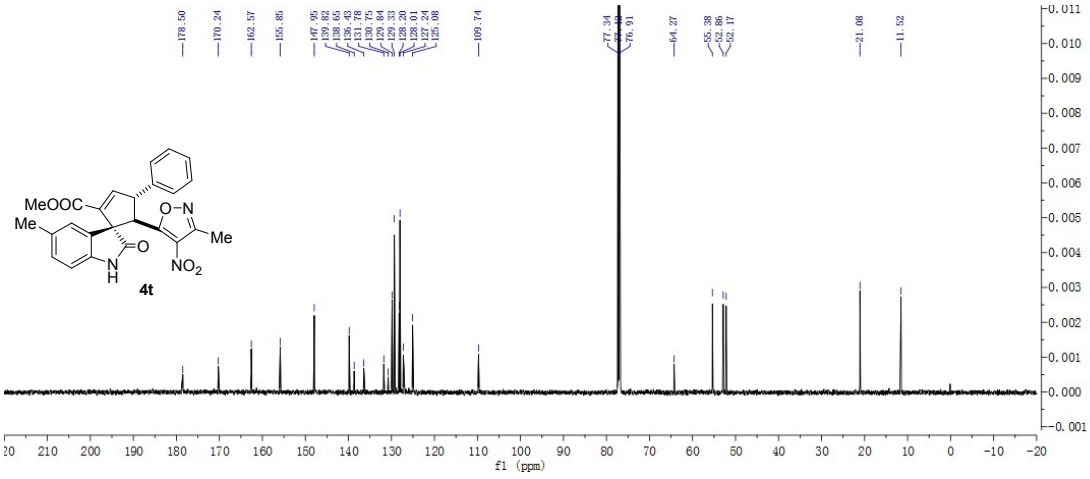
Me
O
N
H
NO2
4t
f1 (ppm)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Me
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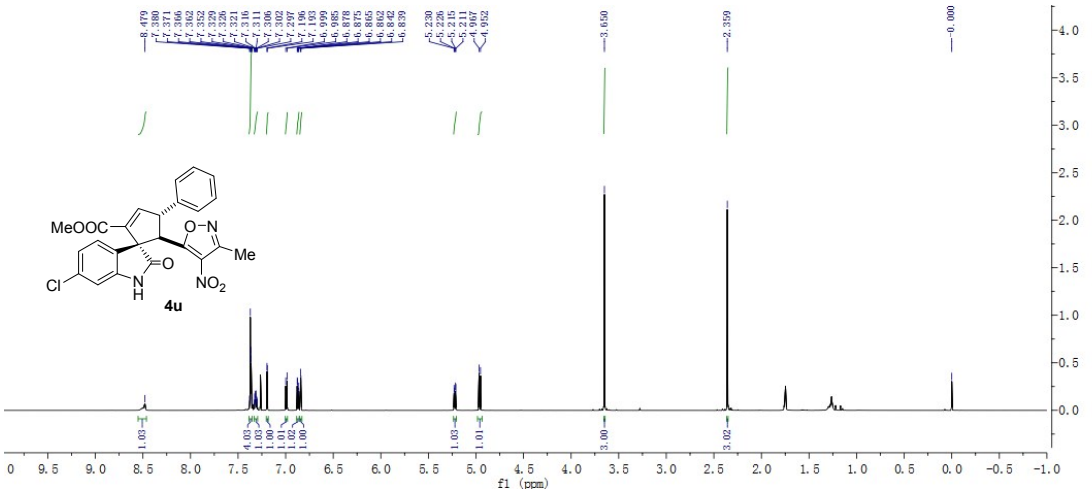
Me
O
N
H
NO2
4t
f1 (ppm)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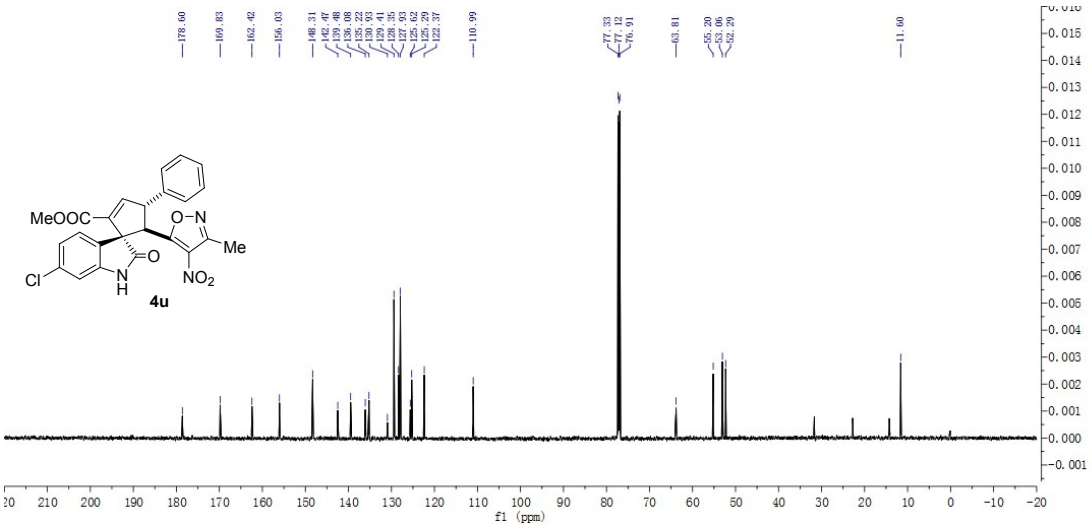
Me
O
N
H
Cl
NO2
4u
f1 (ppm)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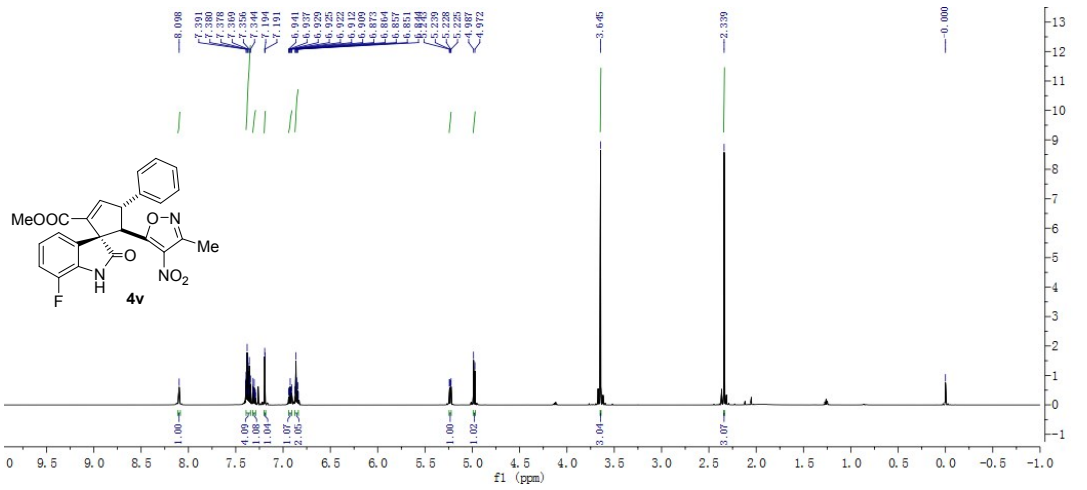
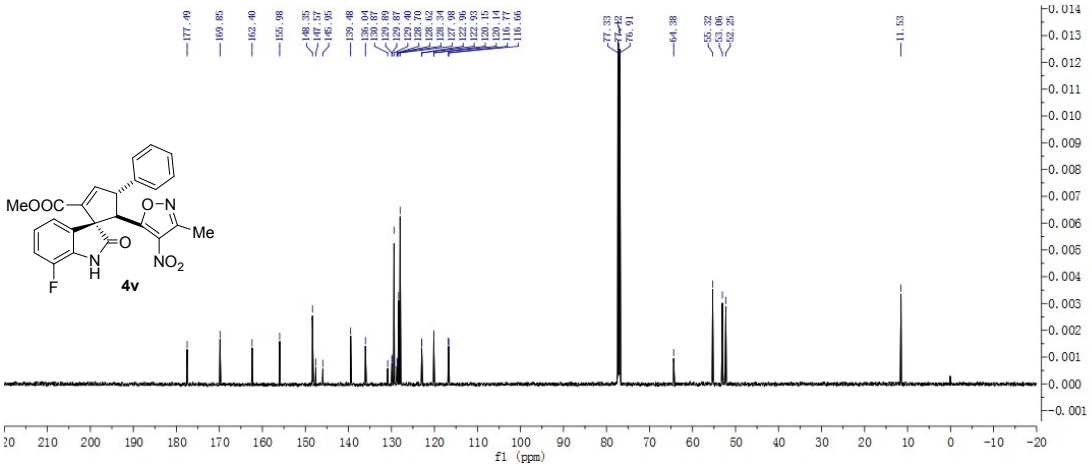
O–N
Me
O
N
H
Cl
NO2
4u
f1 (ppm)


MeOOC
O–N
Me
O
N
H
NO2
F
4v
f1 (ppm)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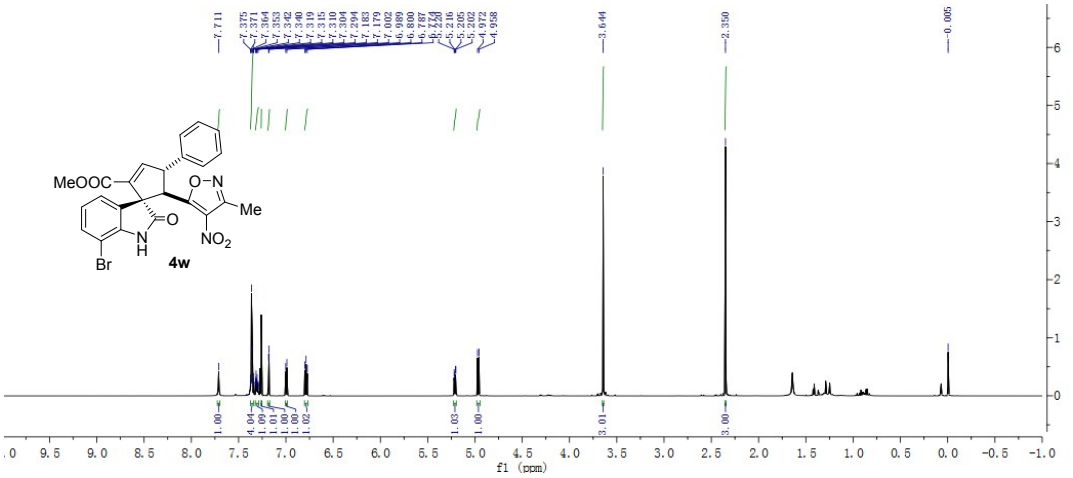
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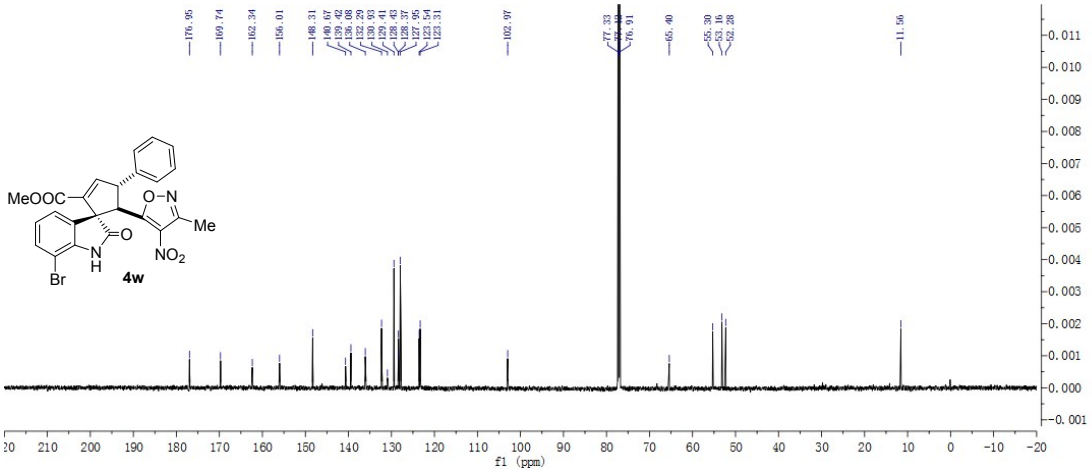
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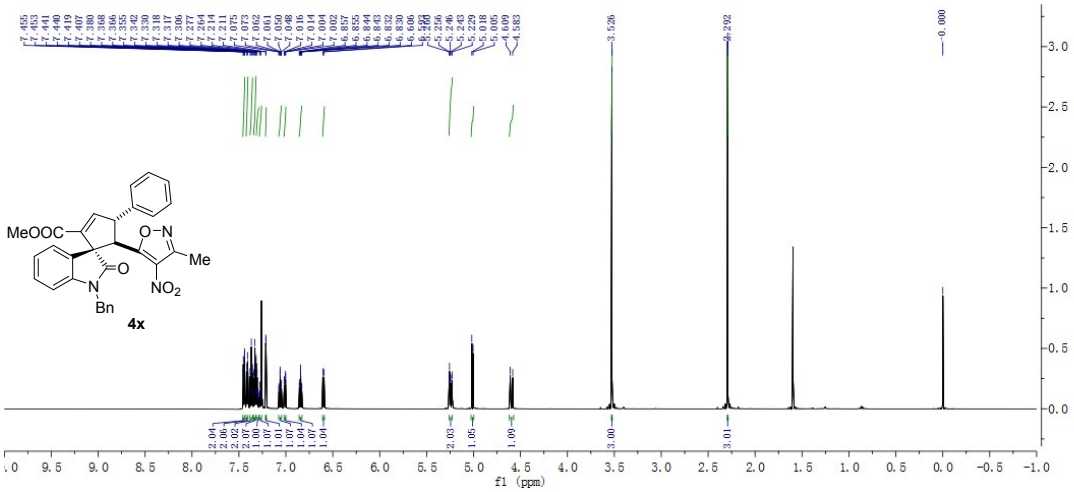
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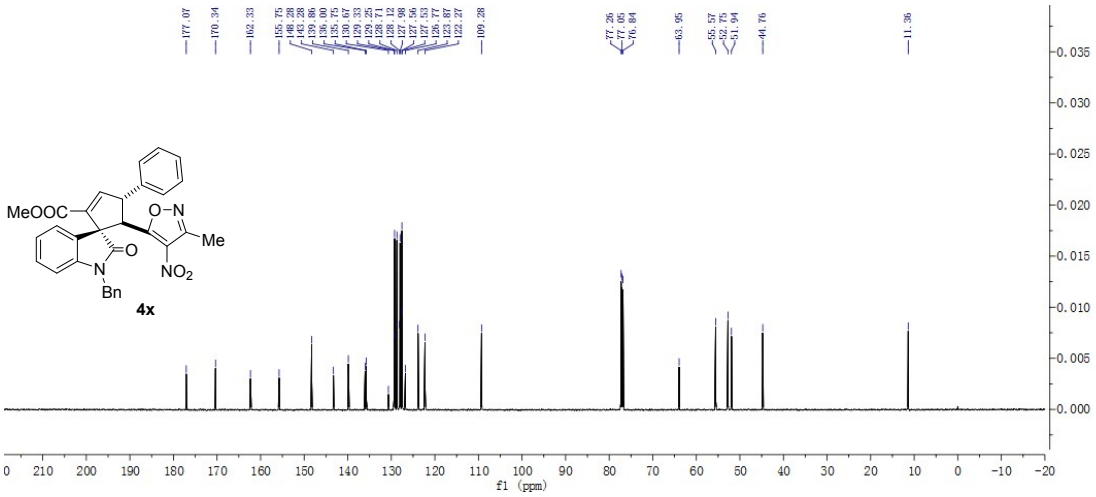
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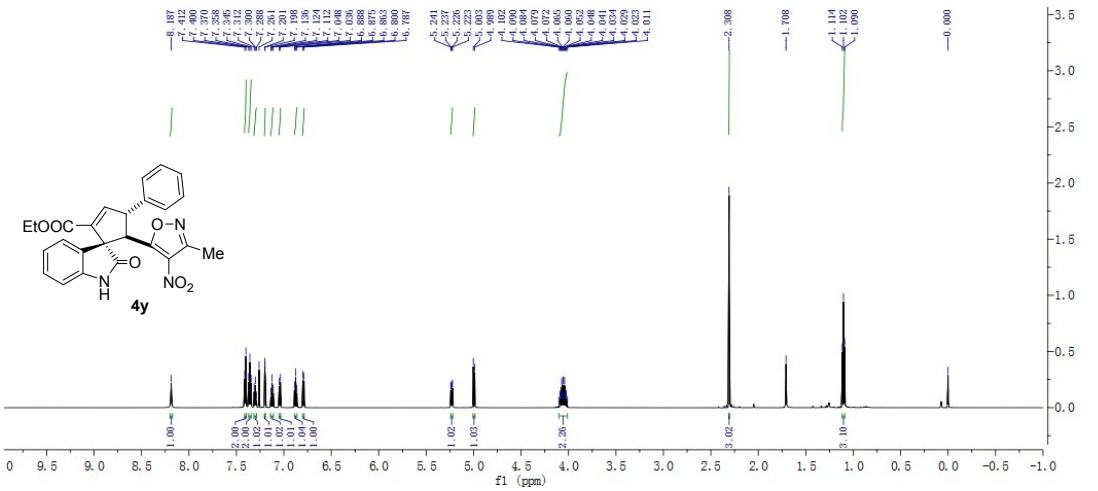
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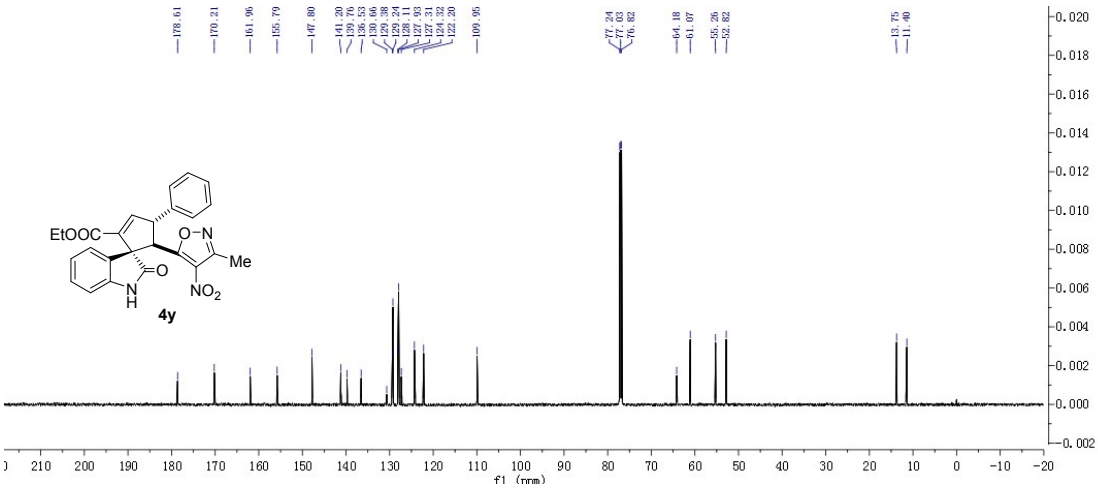
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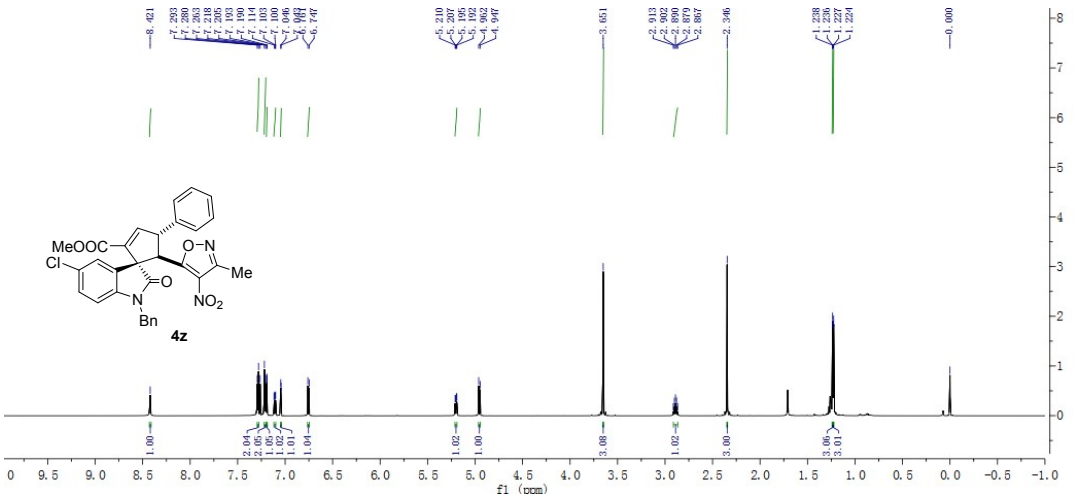
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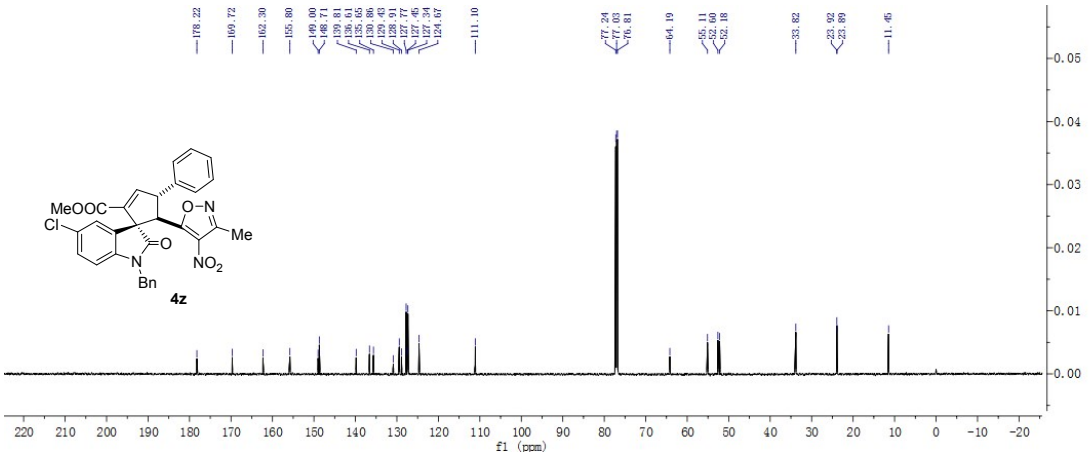
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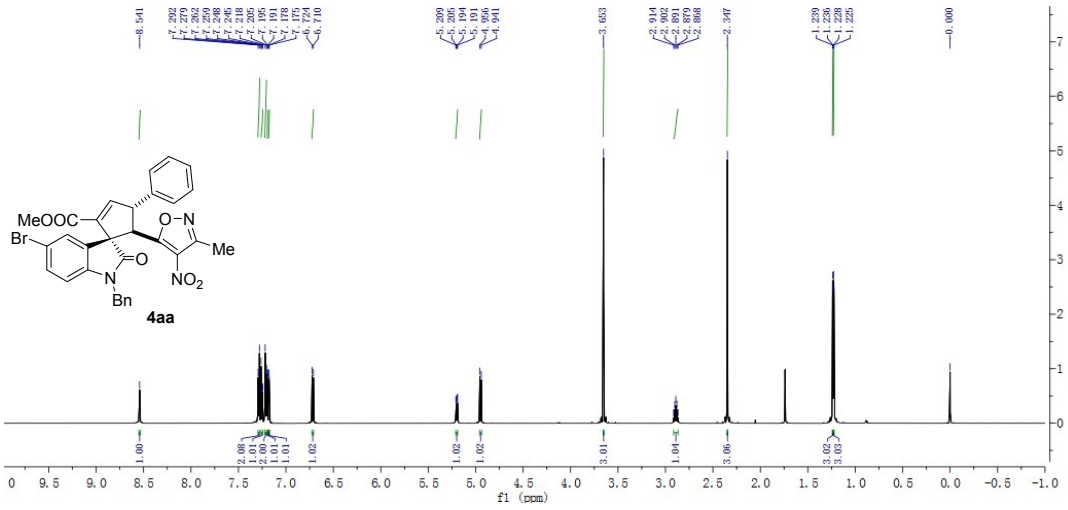
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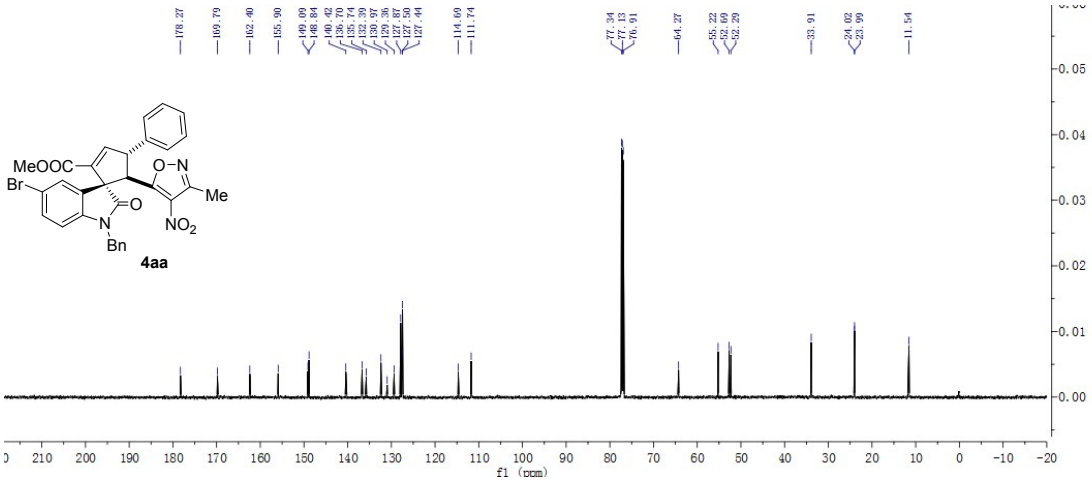
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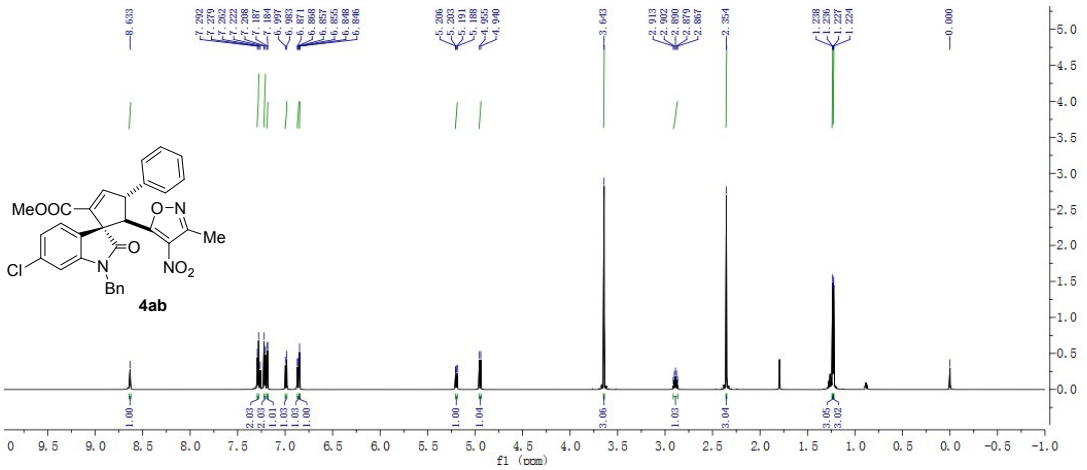
f1 (ppm)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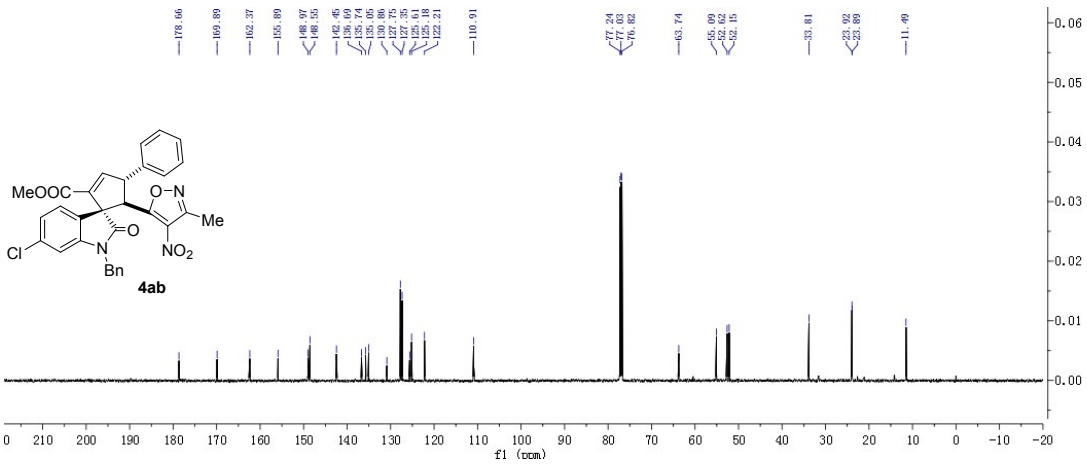
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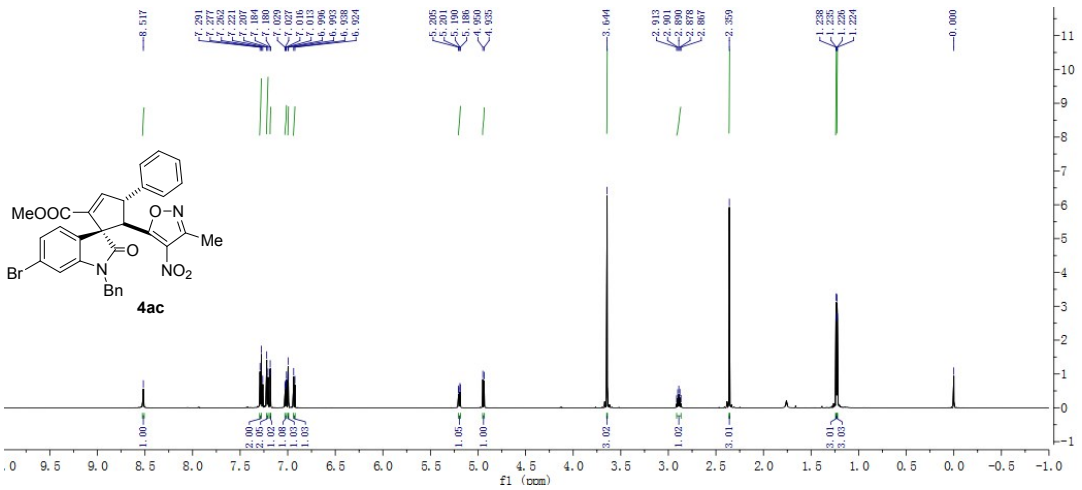
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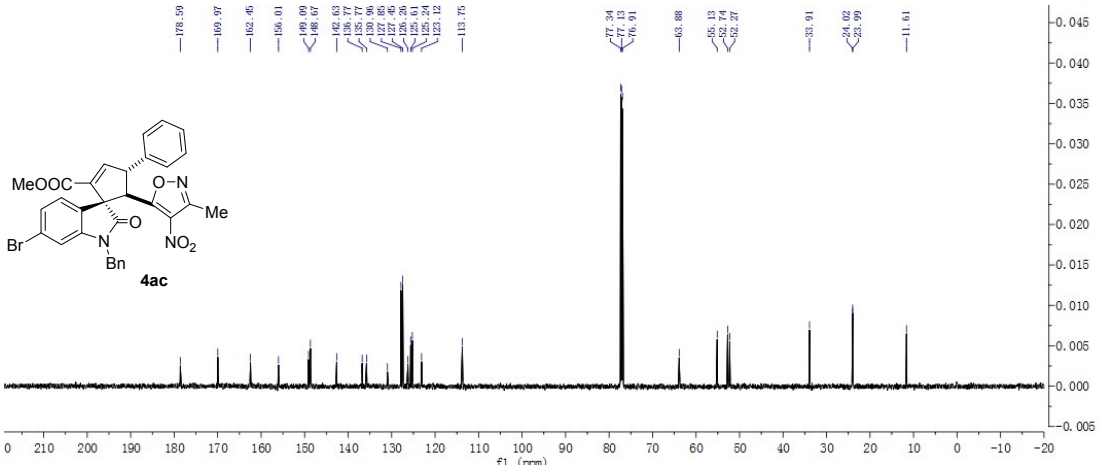
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4ac
f1 (ppm)

8. Experimental procedures of bioassays

8.1 FP-based (fluorescence polarization) MDM2 binding assay

The FP-based MDM2 assay were performed according to the previous reports and manufacturer's protocol. In brief, The fluorescent background were collected and calibrated by blank buffer, and the FP-values of tested compounds were determined by using a serial stock solution of compounds in DMSO. A test sample contained the test compounds, 10 nM of MDM2 binding proteins (preincubated) and 10 nM substrate peptide in buffer sulution were added into microplates until the final volume. For each experiment, the fluorescent intensities of tested samples were read on the microplate reader after all the smaple components were voetex mixed for 30min. The inhibitory constant (*Ki*) was fitted by using the GraphPad Prism software.

8.2 Antiproliferation and selective cytotoxicity assays

The p53-wild HCT116 and LOVO colonrectal cancer cells, as well as the p53-mutated SW620, SW480, DLD-1, HT-29 and SW1116 colonrectal cancer cells were selected to perform cytotoxicity assay. In brief, The LOVO cells were seeded in 96-well plates with a density of 5×10^3 cells per well and cultured with DMEM buffer under 5% CO_2 atomsphere at 37 °C. For the antiprilferation assays, the tested compounds were added with a serial of concentrations. After 48-hours incubation, added 10 μL CCK8 (cell counting kit-8) solution into each well and then incubated 30-60 minutes. The OD values at 405nm were collected by a microplate reader. And the IC_{50} values of

each compound were calculated by the GraphPad Prism software with Logicistic regression method.

8.3 Molecular docking

The initial coordinates of MDM2 were collected from the co-crystalized structure of MDM2-inhibtor (PDB No. 4LWU) retrieved from the PDB (Protein Data Bank, http://www.pdb.org) database. Then we utilized the CDOCKER module of Accelrys Discovery Studio 3.5 Package and the CDOCKER score function to compounds 3d into the substrate pocket of MDM2 using the protocol as described in our previous reports.

8.4 Western Blotting and immunofluorescent assays

LOVO cells were seeded into six-well plates with the intensities of 3-5 × 10^5 cells per well, after 48h-incubation of compound **4z** or blank solution, the cells were collected, washed twice by cold PBS buffer, and then added the protease and phosphatase inhibitors contained lysis buffer. The total protein lysates were obtained after 15000 rpm centrifugation for 10-15 min. The protein extracts in each group were electrophoresis, transferred into PVDF membranes, incubated by corresponding primary antibodies and imaged by ECL method using the protocol as described in our previous reports. The intracellular ROS levels were detected with fluorescent probe DCF-DA (2',7'-dichlorofluorescein diacetate). In brief, LOVO cells were seeded into six-well plates, after added compound **4z** and then incubated for another two hours, the DCF-DA probe were added and then observed by a microplate reader.

8.5 Flowcytometry based apoptosis assay

LOVO cells were seeded into six-well plates with the intensities of 3-5 × 10^5 cells per well, after 48h-incubation of compound **4z** or blank solution, the cells were harvested after trypsin digestion and then washed by ice-cold PBS twice. After cold-centrifuged and resuspended, cells were stained by annexin V-FITC/PI dual staining kit at 25 °C for 30 min in dark. The stained cells were detected by a flow cytometer and analyzed by the FlowJo 7.6 software.

9. Predicted ADMET properties of 4z

The predicted ADMET properties of compound 4z, including aqueous solubility, blood-brain barrier penetration, CYP2D6 binding, hepatotoxicity, intestinal absorption, and plasma-protein binding, were calculated and predicted. The results of ADME analysis are presented in **Figure S2** of the revised manuscript. The biplot figure showed two analogous 95% and 99% confidence ellipses for the blood-brain barrier penetration and human intestinal absorption models, respectively. The detailed results of pharmacokinetic properties for derivative 4z are shown in **Table S2**.

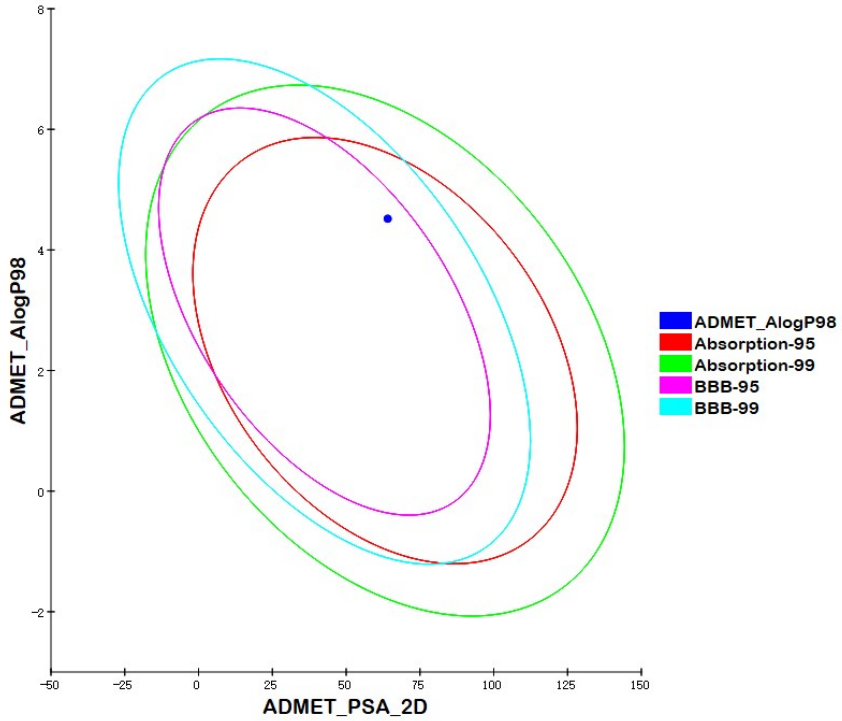

Figure S2 Plot of PSA versus AlogP for compound **4z** showing the 95% and 99% confidence limit ellipses corresponding to the blood-brain barrier and intestinal absorption models. Abbreviations: ADMET, absorption, distribution, metabolism, excretion and toxicity; AlogP, the logarithm of the partition coefficient between n-octanol and water; BBB, blood-brain barrier; PSA, polar surface area; 2D, two-dimensional.

Table S3 ADMET prediction and pharmacokinetic properties of compound 4z

Compound name	Aqueous solubility level	BBB penetration level	CYP2D6 binding prediction	Hepatotoxicity prediction	Intestinal absorption level	Plasma protein binding	PSA	AlogP98
4z	1 (Low)	3 (low)	False (non-inhibitor)	False (nontoxic)	0 (good)	True (highly bounded)	68.91	4.49

Abbreviations: AlogP, the logarithm of the partition coefficient between n-octanol and water; PSA, polar surface area; ADMET, absorption, distribution, metabolism, excretion and toxicity.

10. References

(1) Y. M. Chung, Y. J. Im and J. N. Kim, *Bull*. *Korean. Chem*. *Soc*., **2002**, *23*, 1651-1654.

(2) J. Zhang, X. Liu, X. Ma and R. Wang, *Chem*. *Commun*., **2013**, *49*, 9329-9331.