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Supporting Information for

Synthesis of spiropyrazoline oxindoles by a formal [4+1] annulation reaction between 3-bromooxindoles and in situ-derived 1,2-diaza-1,3-dienes

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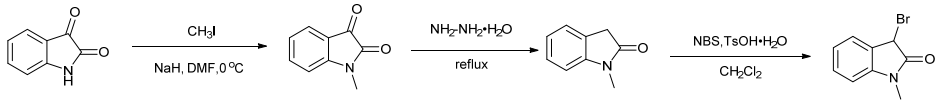
1. General information

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. All the solvents were treated according to general methods. Flash column chromatography was performed using 200-300 mesh silica gel. ^{1}H NMR spectra were recorded on 400 or 600 MHz spectrometers. Chemical shifts were reported on the delta (δ) scale in parts per million (ppm) relative to the singlet (0 ppm) for tetramethylsilane (TMS). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded at 100 MHz with complete proton decoupling. Chemical shifts are reported in ppm relative to the central line of the triplet at 77.0 ppm for $CDCl_3$. Mass spectra were measured on a MS spectrometer (EI).

2. Preparation of substrates

2.1 General procedure for the preparation of 3-bromooxindoles



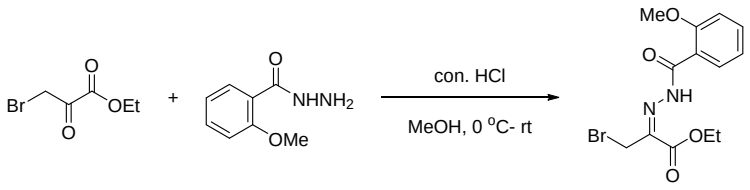
Step 1: To a 250 mL 3-necked-round bottom flask equipped with a silicone oil bubbler was added commercially available isatin (7.7 g, 50 mmol) and anhydrous DMF (80 mL). And the mixture was cooled down to 0 ^{o}C. To this solution was added NaH (1.32 g, 55 mmol), then CH_3I was added 10 min later (without gas bubbling), and stirred at 0 ^{o}C for 15 min. Upon completion of the reaction (monitored by TLC), the mixture was diluted with saturated NH_4Cl solution and extracted with ethyl acetate, the ethyl acetate layer was washed with water and brine. The combined organic layer was then dried over $MgSO_4$, filtered, and concentrated to yield the crude N-methylindoline-2, 3-dione (7.6 g, 94% yield), which was used directly in the next step. [1]

Step 2: The N-methylindoline-2, 3-dione (7.58 g, 47 mmol) was refluxed in NH_2-$NH_2 \cdot H_2O$ until the gas evolution stopped. Then the mixture was cooled to room temperature. The crude product was extracted with ethyl acetate. The combined organic layer was then dried over $MgSO_4$, purified by flash chromatography on silica gel (petroleum ether/ ethyl acetate 10:1). 1-Methylindolin-2-one was obtained as a red solid (6.78 g, 98% yield). [2]

Step 3: 1-methylindolin-2-one (6.78 g, 46 mmol) and $TsOH \cdot H_2O$ (1.75 g, 9.2 mmol) were dissolved in CH_2Cl_2 (40 mL), Then, the solution of NBS (8.2 g, 46 mmol) in CH_2Cl_2 (260 mL) was added to the mixture dropwisely and the mixture stirred at room temperature. After that, the crude product was purified by flash chromatography on silica gel (petroleum ether/ ethyl acetate 10:1). 3-bromo-1-methylindolin-2-one was obtained as a yellow solid (4.2 g, 18.4 mmol). [3]

The other 3-borooxindoles were prepared according to the above procedure.

2.2 General procedure for the preparation of *α*-halo-hydrazones



Ethyl-3-bromo-2-oxopropanoate (5.8 g, 30 mmol) and 2-methyoxybenzohydrazide (5.5 g, 33 mmol) was dissolved in MeOH (30 mL), then con. HCl (0.3 mL) was added in 0 ^{o}C. The mixture was stirred at room temperature until the large scale of white solid was formed. The crude product was filtered, washed with Et_2O. Then the crude product was recrystallized with MeOH at minus twenty degree for 2 hours. [4][5][6]

References:

[1] B. M. Trost, Y. Zhang. *J. Am. Chem. Soc.*, **2007**, *129*, 14548.

[2] Gao, J.; Chen, J.-R. ;Duan, S.-W.; Li, T.-R.; Lu, L.-Q.; Xiao, W.-J. *Asi. J. Org. Chem*. **2014**, 3, 530.

[3] Peng-Fei Zheng, Qin Ouyang, Sheng-Li Niu, Li Shuai, Yi Yuan, Kun Jiang, Tian-Yu Liu, Ying-Chun Chen. *J. Am. Chem. Soc*. **2015**, 137, 9390.

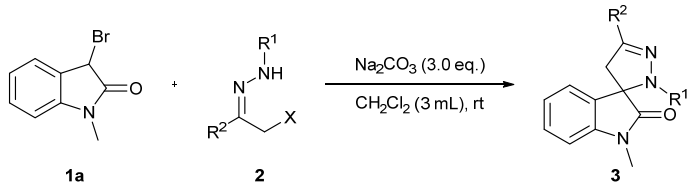
[4] Jia-Rong Chen, Wan-Rong Dong, Mathieu Candy, Fang-Fang Pan, Manuel Jorres, C. Bolm. *J. Am. Chem. Soc*. **2012**, 134, 6924.

[5] Simon J. Clarke, Thomas L. Gilchrist, Amirico Lemos, and Tony G. Roberts, *Tetrahedron*. **1991**, 47, 5615

[6] Harry C. J. Ottenheijm, Ralf Plate, Jan H. Noordik, and Jacobus D. M. Herscheid. *J. Org. Chem*., **1982**, 47, (*11*), 2147

3. Optimization studies

3.1 Screening of the N-protecting groups of hydrazones

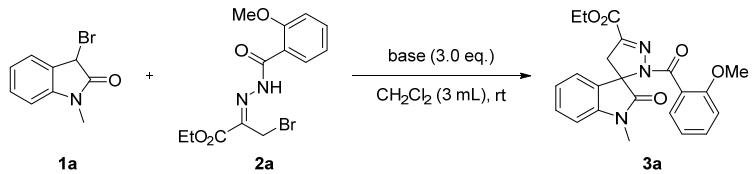


1a **2** **3**

Entry	R_1	R_2	X	Yield[b] (%)
1	C_6H_5CO	C_6H_5	Cl	ND
2	2-$MeOC_6H_4CO$	2,4-$2ClC_6H_3$	Cl	ND
3	MeCO	4-$NO_2C_6H_4$	Br	ND
4	2-$MeOC_6H_4CO$	CO_2Et	Br	19
5	Ts	C_6H_5	Br	ND
6	C_6H_5CO	C_6H_5	Br	ND
7	Boc	C_6H_5	Br	ND

The compound **2** (0.3 mmol) and Na_2CO_3 (63.59 mg, 0.6 mmol) were dissolved in CH_2Cl_2 (3 mL), the mixture was stirred for 15 min. Then, compound **1a** (45.21 mg, 0.2 mmol) was added to the mixture. Upon the completion of the reaction (monitored by TLC), the reaction was purifed by flash column chromatrography directly, eluting with petroleum ether and ethyl acetate, to afford the corresponding products.

3.2 Screening of base



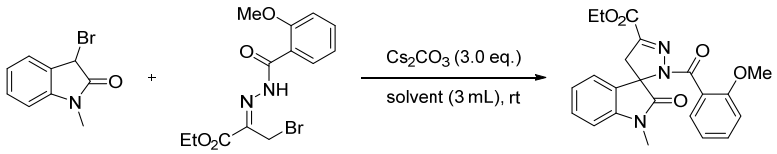
1a **2a** **3a**

Entry	Base	Time (h)	Yield[b] (%)
1	Na_2CO_3	4	19
2	K_2CO_3	4	52
3	BzOK	96	<5
4	DIPEA	96	<5

5	^{t}BuOK	4	<5
6	KOH	4	32
7	K_2HPO_4	96	<5
8	Cs_2CO_3	4	89

The compound **2a** (102.95 mg, 0.3 mmol) and base (xx mg, 0.6 mmol) were dissolved in CH_2Cl_2 (3 mL), the mixture was stirred for 15 min. Then, compound **1a** (45.21 mg, 0.2 mmol) was added to the mixture. Upon the completion of the reaction (monitored by TLC), the reaction was purifed by flash column chromatrography directly, eluting with petroleum ether and ethyl acetate, to afford the corresponding product **3a**.

3.3 Screening of the solvent

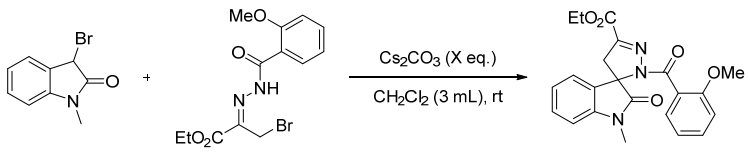


1a **2a** **3a**

Entry	Solvent	Time (h)	Yield[b] (%)
1	CH_3CN	96	<5
2	toluene	96	<5
3	THF	4	85
4	CH_2Cl_2	4	90
5	$ClCH_2CH_2Cl$	4	85
6	$CHCl_3$	4	84
7	PhCl	4	80

The compound **2a** (102.95 mg, 0.3 mmol) and Cs_2CO_3 (195.49 mg, 0.6 mmol) were dissolved in solvent (3 mL), the mixture was stirred for 15 min. Then, compound **1a** (45.21 mg, 0.2 mmol) was added to the mixture. Upon the completion of the reaction (monitored by TLC), the reaction was purifed by flash column chromatrography directly, eluting with petroleum ether and ethyl acetate, to afford the corresponding product **3a**.

3.4 Screening of the ratio of base

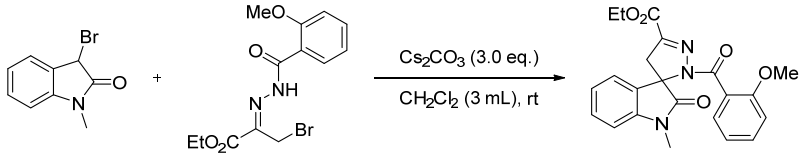


1a **2a** **3a**

Entry	Base	Time (h)	Yield[b] (%)
1	2.0	96	<5
2	2.5	4	76
3	3.0	4	89
4	5.0	4	75

The compound **2a** (102.95 mg, 0.3 mmol) and Cs_2CO_3 (2.0-5.0 equiv) were dissolved in CH_2Cl_2 (3 mL), the mixture was stirred for 15 min. Then, compound **1a** (45.21 mg, 0.2 mmol) was added to the mixture. Upon the completion of the reaction (monitored by TLC) , the reaction was purifed by flash column chromatrography directly, eluting with petroleum ether and ethyl acetate, to afford the corresponding product **3a**.

3.5 Screening of the ratio of 1a to 2a

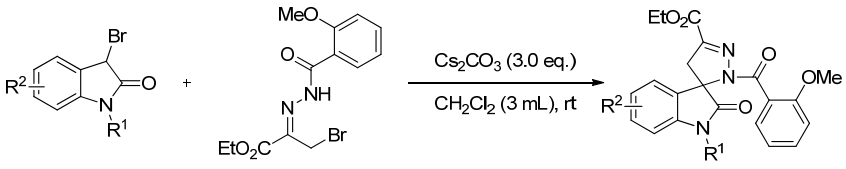


1a, X mmol **2a, Y mmol** **3a**

Entry	X/Y	Time (h)	Yield[b] (%)
1	1:1.2	4	81
2	1:1.5	4	90
3	1:2	4	75
4	1.2:1	4	72
5	1.5:1	4	71
6	2:1	4	62

The compound **2a** (Y mmol) and Cs_2CO_3 (195.49 mg, 0.6 mmol) were dissolved in CH_2Cl_2 (3 mL), the mixture was stirred for 15 min. Then, compound **1a** (X mmol) was added to the mixture. For entries 1-3, X = 0.2; for entries 4-6, Y = 0.2. Upon the completion of the reaction (monitored by TLC), the crude mixture was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 5:1) to give the desired product **3a** as a white solid.

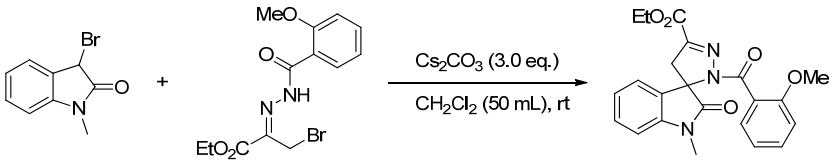
4. Representative procedure for preparation of the products 3



1 **2a** **3**

The compound **2a** (102.95 mg, 0.3 mmol) and Cs_2CO_3 (195.49 mg, 0.6 mmol) were dissolved in CH_2Cl_2 (3 mL), the mixture was stirred for 15 min. Then, compound **1** (0.2 mmol) was added to the mixture. Upon the completion of the reaction (monitored by TLC), the crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 5:1) to give the desired product **3** as a white solid.

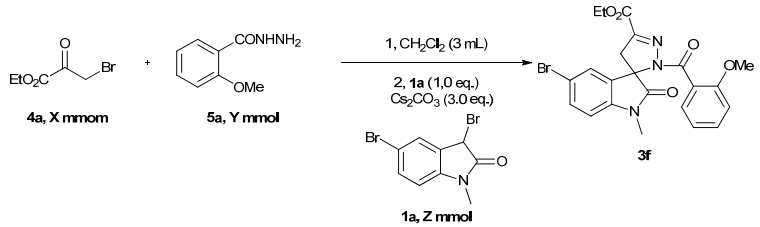
5. Gram-scale reaction



1a **2a** **3a**

The compound **2a** (2.06 g, 6.0 mmol) and Cs_2CO_3 (3.91 g, 12 mmol) were dissolved in CH_2Cl_2 (50 mL), the mixture was stirred for 15 min. Then, compound **1a** (0.9 g, 4.0 mmol) was added to the mixture. Upon the completion of the reaction (monitored by TLC), the crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 5:1) to give the desired product **3a** (3.4 mmol, 1.39 g) as a white solid in 85% yield.

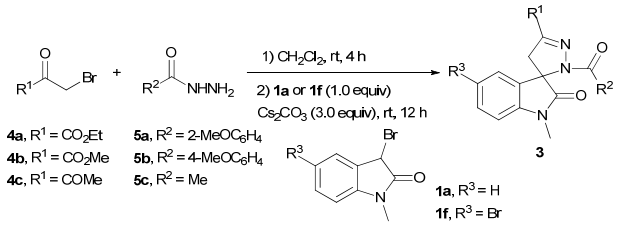
6. Optimization studies of one-pot, three-component reaction.



Entry	X/Y/Z	Time (h)	Yield[b] (%)
1	1.65:1.5:1.0	4+12	70
2	2.2:2.0:1.0	4+12	72
3	3.3:3.0:1.0	4+12	90
4	5.5:5.0:1.0	4+12	83

The compound **4a** (X mmol) and compound **5a** (Y mmol) were dissolved in CH_2Cl_2 (3 mL), the mixture was stirred for 4 hours. Then, compound **1a** (60.99 mg, 0.2 mmol) and Cs_2CO_3 (195.49 mg, 0.6 mmol) was added to the mixture. Upon the completion of the reaction (monitored by TLC), the crude mixture was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 5:1) to give the desired product **3f** as a white solid.

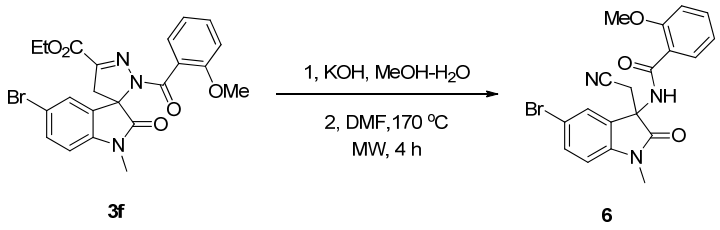
7. One-pot, two step procedure for preparation of the spirooxindoles 3.



The compound **4** (128.71 mg, 0.66 mmol) and compound **5** (99.71 mg, 0.6 mmol) were dissolved in CH_2Cl_2 (3 mL), the mixture was stirred for 4 hours. Then, compound **1** (60.99 mg, 0.2 mmol) and Cs_2CO_3

(195.49 mg, 0.6 mmol) was added to the mixture. Upon the completion of the reaction (monitored by TLC), the crude mixture was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 5:1) to give the desired product **3** as a white solid.

8. Synthetic conversion of product 3f.

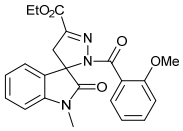


3f **6**

The compound **3g** (518.3 mg, 1.07 mmol) was dissolved in MeOH (20 mL) and a 15% KOH (aq) solution (210.43 mg, 5.26 mmol) was added. The reaction was stirred at room temperature for 2 h and concentrated to provide a residue which was reconstitutd in water and acidified using 1 N HCl until pH 1 was achived. The solid formed was filtered and washed with water to provide theacid which was dried, dissolved in DMF (10 mL) , and heated to 170 ^{o}C for 4 h in a microwae reactor. DMF was removed and the crude product was purified by column chromatograph to provide **6** as a white solid.

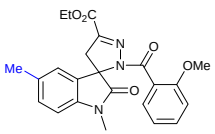
9. Spectral data of products

Ethyl 2-(2-methoxybenzoyl)-1-methyl-2-oxo-2,4-dihydrospiro[indoline-3,3-pyrazole]-5-carboxylate (3a)



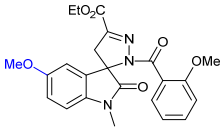
white solid; 90% yield in 4 h; 86% yield in 4+12 h. mp 188-190 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (1 H, d, *J* = 4.0 Hz), 7.34 (1 H, d, *J* = 8.0 Hz), 7.31 (1 H, s), 7.21 (1 H, d, *J* = 7.5 Hz), 7.07 (1 H, t, *J* = 7.6 Hz), 6.94 (1 H, d, *J* = 8.0 Hz), 6.90 (1 H, d, *J* = 8.0 Hz), 6.86 (1 H, s), 4.30 (2 H, q, *J* = 7.1 Hz), 3.82 (3 H, s), 3.70 (1 H, d, *J* = 20.0 Hz), 3.33 (1 H, d, *J* = 20.0 Hz), 3.31 (3 H, s), 1.31 (3 H, t, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 165.9, 160.7, 156.6, 145.1, 143.4, 132.5, 131.6, 129.8, 129.0, 125.6, 123.1, 122.2, 120.0, 111.3, 108.4, 77.3, 77.0, 76.7, 68.4, 61.9, 55.8, 44.3, 26.8, 14.1; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm^{-1}; HRMS (ESI) for $C_{22}H_{21}N_3O_5$ $[M+H]^+$: calcd 408.1554, found 408.1554.

Ethyl 2-(2-methoxybenzoyl)-1,5-dimethyl-2-oxo-2,4-dihydrospiro[indoline-3,3-pyrazole]-5-carboxylate(3b)



white solid; 67% yield in 4 h, mp 198-200 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (1 H, d, *J* = 8.0 Hz), 7.34 (1 H, dd, *J* = 7.5, 1.8 Hz), 7.26 (2 H, s), 6.94 (1 H, d, *J* = 8.0 Hz) 6.92 (1 H, s) 6.89 (1 H, d, *J* = 8.0 Hz), 4.29 (2 H, q, *J* = 6.9 Hz), 3.81 (3 H, s), 3.66 (1 H, d, *J* = 16.0 Hz), 3.64 (3 H, s), 3.29 (1 H, d, *J* = 16.0 Hz), 2.29 (3 H, s), 1.33 (3 H, t, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2, 166.2, 160.9, 156.9, 145.2, 138.5, 135.5, 134.5, 131.9, 131.8, 129.3, 123.3, 122.4, 120.3, 111.4, 102.6, 77.3, 77.0, 76.7, 68.1, 62.0, 55.8, 44.7, 30.3, 20.5, 14.0; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm^{-1}; HRMS (ESI) for $C_{23}H_{23}N_3O_5$ $[M+H]^+$: calcd 422.1710, found 422.1720.

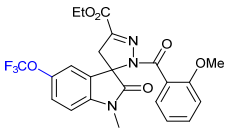
Ethyl 5-methoxy-2-(2-methoxybenzoyl)-1-methyl-2-oxo-2,4-dihydrospiro[indoline-3,3-pyrazole]-5-carboxylate(3c)



white solid; 70% yield in 4 h, mp 217-219 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 – 7.35 (1 H, m), 7.31 (1 H, dd, *J* = 7.5, 1.5 Hz), 7.23 (1 H, s), 7.06 (1 H, s), 6.93 (1 H, t, *J* = 8.0 Hz), 6.90 (1 H, d, *J* = 12.0 Hz), 6.81 (1 H, s), 4.29 (2 H, q, *J* = 7.0 Hz), 3.84 (3 H, s), 3.81 (3 H, s), 3.65 (1 H, d, *J* = 20.0 Hz), 3.33 (1 H, d, *J* = 20.0 Hz), 3.26 (3 H,

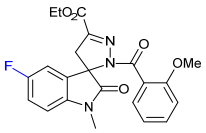
s), 1.31 (3 H, t, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 166.4, 160.8, 156.8, 145.4, 142.6, 132.7, 131.8, 130.4, 129.0, 125.7, 123.2, 120.2, 115.6, 111.3, 110.1, 77.3, 77.0, 76.7, 68.1, 62.0, 55.7, 44.1, 26.8, 20.6, 14.0; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm^{-1}; HRMS (ESI) for $C_{23}H_{23}N_3O_6$ $[M+H]^+$: calcd 438.1658, found 438.1659.

Ethyl-2-(2-methoxybenzoyl)-1-methyl-2-oxo-5-(trifluoromethoxy)-2,4-dihydrospiro[indoline-3,3-pyrazole]-5-carboxylate(3d)



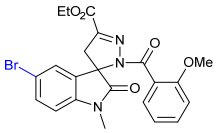
white solid; 82% yield in 4 h, mp 218-220 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.40 (1 H, t, J = 11.2 Hz), 7.33 (1 H, d, J = 7.5 Hz), 7.23 (1 H, d, J = 6.2 Hz), 7.12 (1 H, s), 6.96 (1 H, t, J = 7.5 Hz), 6.92 (1 H, d, J = 8.4 Hz), 6.88 (1 H, d, J = 8.5 Hz), 4.31 (2 H, q, J = 8.1 Hz), 3.82 (3 H, s), 3.71 (1 H, d, J = 16.0 Hz), 3.37 (1 H, d, J = 16.0 Hz), 3.32 (3 H, s), 1.32 (3 H, t, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 173.6, 166.3, 160.8, 156.8, 145.4, 142.3, 131.9, 129.8, 129.1, 120.2, 120.0 (q, $J_{C,F}$ = 222.0 Hz), 111.4, 109.2, 77.3, 77. 0, 76.7, 68.2, 62.0, 55.6, 44.2, 26.9, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -60.1; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm^{-1}; HRMS (ESI) for $C_{23}H_{20}F_3N_3O_6$ $[M+H]^+$: calcd 492.1377, found 492.1375.

Ethyl 5-fluoro-2-(2-methoxybenzoyl)-1-methyl-2-oxo-2,4-dihydrospiro[indoline-3,3-pyrazole]-5-carboxylate(3e)



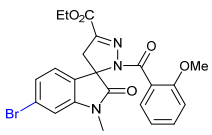
white solid; 75% yield in 4 h, mp 180-183 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (1 H, t, J = 11.6 Hz), 7.35 (1 H, d, J = 7.5 Hz), 7.06 (1 H, t, J = 8.9 Hz), 6.99 (1 H, d, J = 4 Hz), 6.96 (1 H, t, J = 4.0 Hz), 6.92 (1 H, d, J = 4.0 Hz), 6.83 – 6.81 (1 H, m), 4.31 (2 H, q, J = 7.2 Hz), 3.84 (3 H, s), 3.70 (1 H, d, J = 16.0 Hz), 3.36 (1 H, d, J = 16.0 Hz), 3.30 (3 H, s), 1.31 (3 H, t, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 173.5, 166.4, 160.9, 159.5 (d, $J_{C,F}$ = 241.0 Hz), 156.9, 145.3, 139.7(d, $J_{C,F}$ = 2.0 Hz), 131.9, 129.9 (d, $J_{C,F}$ = 8.0 Hz), 129.3, 123.3, 120.3, 116.2 (d, $J_{C,F}$ = 23.0 Hz), 111.5, 110.7 (d, $J_{C,F}$ = 25.0 Hz), 109.2 (d, $J_{C,F}$ = 8.0 Hz), 77.3, 77.0, 76.7, 68.5, 62.0, 55.8, 44.2, 26.9, 14.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -120.7; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm^{-1}; HRMS (ESI) for $C_{22}H_{20}FN_3O_5$ $[M+H]^+$: calcd 426.1460, found 426.1474.

Ethyl 5-bromo-2-(2-methoxybenzoyl)-1-methyl-2-oxo-2,4-dihydrospiro[indoline-3,3-pyrazole]-5-carboxylate(3f)



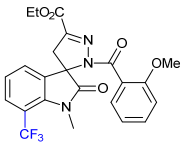
white solid; 85% yield in 4 h; 90% yield in 4+12 h, mp 199-201 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (1 H, d, J = 8.2 Hz), 7.39 (1 H, t, J = 8.1 Hz), 7.34 (2 H, d, J = 8.5 Hz), 6.95 (1 H, t, J = 8.0 Hz), 6.92 (1 H, d, J = 8.0 Hz), 6.77 (1 H, d, J = 8.3 Hz), 4.30 (2 H, q, J = 7.1 Hz), 3.84 (3 H, s), 3.68 (1 H, d, J = 12.0 Hz), 3.36 (1 H, d, J = 12.0 Hz), 3.29 (3 H, s), 1.31 (3 H, t, J = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 166.4, 160.9, 156.9, 145.4, 142.2, 131.9, 130.1, 129. 9, 129.2, 128.5, 123.3, 123.1, 120.3, 111.4, 109.6, 77.3, 77.0, 76.7, 68.3, 62.0, 55.8, 44.2, 26.9, 14.1; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm^{-1}; HRMS (ESI) for $C_{22}H_{20}BrN_3O_5$ $[M+Na]^+$: calcd 508.0479, found 508.0494.

Ethyl 6-bromo-2-(2-methoxybenzoyl)-1-methyl-2-oxo-2,4-dihydrospiro[indoline-3,3-pyrazole]-5-carboxylate(3g)



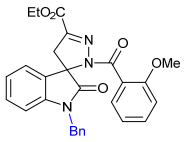
white solid; 47% yield in 4 h, mp 188-191 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (1 H, s), 7.38 (1 H, t, J = 8.0 Hz), 7.32 – 7.26 (2 H, m), 7.15 (1 H, s), 6.95 (1 H, t, J = 8.0 Hz), 6.91 (1 H, d, J = 8.0 Hz), 4.31 (2 H, q, J = 6.9 Hz), 3.84 (3 H, s), 3.69 (1 H, d, J = 20.0 Hz), 3.36 (1 H, d, J = 20.0 Hz), 3.28 (3 H, s), 1.32 (3 H, t, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 166.5, 160.7, 156.8, 145.4, 143.8, 132.0, 129.4, 129.1, 127.4, 126.0, 123.1, 120.3, 117.0, 113.8, 111.4, 77.3, 77.0, 76.7, 67.8, 62.1, 55.8, 44.0, 27.0, 14.0; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm^{-1}; HRMS (ESI) for $C_{22}H_{20}BrN_3O_5$ $[M]^+$: calcd 486.0659, found 486.0650.

Ethyl-2-(2-methoxybenzoyl)-1-methyl-2-oxo-7-(trifluoromethyl)-2,4-dihydrospiro[indoline-3,3-pyrazole]-5-carboxylate(3h)



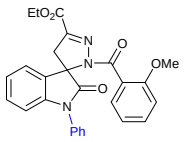
white solid; 69% yield in 4 h, mp 195-197 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (1 H, d, *J* = 8.1 Hz), 7.32 – 7.12 (3 H, m), 7.14 (1 H, t, *J* = 7.8 Hz), 6.94 – 6.89 (2 H, m), 4.30 (2 H, q, *J* = 6.7 Hz), 3.82 (3 H, s), 3.77 (1 H, d, *J* = 20.0 Hz), 3.51 (3 H, s), 3.42 (1 H, d, *J* = 20.0 Hz), 1.31 (3 H, t, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.7, 166.2, 160.9, 157.0, 145.2, 141.7, 131.4, 129.3, 127.8, 127.8, 125.8, 125.5 (q, $J_{C,F}$ = 284.0 Hz), 123.1, 122.7, 120.4, 77.3, 77.0, 76.7, 66.9, 62.0, 55.9, 44.7, 29.6, 29.5, 14.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -55.2; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm^{-1}; HRMS (ESI) for $C_{23}H_{20}F_3N_3O_5$ $[M+H]^+$: calcd 476.1428, found 476.1444.

Ethyl 1-benzyl-2-(2-methoxybenzoyl)-2-oxo-2,4-dihydrospiro[indoline-3,3-pyrazole]-5-carboxylate (3i)



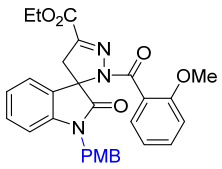
white solid; 63% yield in 4 h, mp 198-202 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 – 7.40 (3 H, m), 7.36 (3 H, d, *J* = 7.3 Hz), 7.32 – 7.26 (2 H, m), 7.23 – 7.03 (2 H, m), 6.99 (1 H, t, *J* = 8.0 Hz), 6.94 (1 H, d, *J* = 8.0 Hz), 6.61 (1 H, m), 5.11 (1 H, d, *J* = 15.9 Hz), 4.89 (1 H, d, *J* = 18.0 Hz), 4.31 (2 H, q, *J* = 7.1 Hz), 3.86 (3 H, s), 3.77 (1 H, d, *J* = 20.0 Hz), 3.42 (1 H, d, *J* = 20.0 Hz), 1.32 (3 H, t, *J* = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 166.5, 160.8, 156.8, 145.4, 141.8, 132.6, 131.8, 130.5, 130.3, 129.0, 125.9, 123.4, 120.3, 118.1, 115.7, 111.4, 111.2, 77.3, 77.0, 76.7, 68.2, 62.0, 55.8, 44.5, 42.9, 14.1; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm^{-1}; HRMS (ESI) for $C_{28}H_{25}N_3O_5$ $[M+H]^+$: calcd 484.1867, found 484.1883.

Ethyl 2-(2-methoxybenzoyl)-2-oxo-1-phenyl-2,4-dihydrospiro[indoline-3,3-pyrazole]-5-carboxylate(3j)



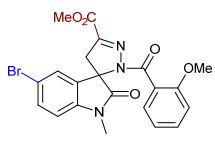
white solid; 66% yield in 4 h, mp 225-227 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (4 H, d, *J* = 4.3 Hz), 7.50 – 7.47 (1 H, m), 7.44-7.41 (2 H, t, *J* = 7.0 Hz), 7.34 (2 H, t, *J* = 7.0 Hz), 7.17 (1 H, t, *J* = 7.5 Hz), 7.01 (1 H, t, *J* = 8.0 Hz), 6.98 (1 H, d, *J* = 8.0 Hz), 6.86 (1 H, d, *J* = 7.8 Hz), 4.37 (2 H, q, *J* = 7.6 Hz), 3.89 (1 H, d, *J* = 20.0 Hz), 3.88 (3 H, s), 3.55 (1 H, d, *J* = 20.0 Hz), 1.37 (3 H, t, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 166.4, 161.1, 156.9, 145.4, 144.0, 134.3, 131.8, 129.9, 129.6, 129.3, 128.4, 126.9, 123.7, 123.5, 122.8, 120.3, 111.5, 109.8, 77.3, 77.0, 76.7, 68.7, 62.0, 55.8, 44.5, 14.0; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm^{-1}; HRMS (ESI) for $C_{27}H_{23}N_3O_5$ $[M+H]^+$: calcd 470.1710, found 470.1710.

Ethyl 2-(2-methoxybenzoyl)-1-(4-methoxybenzyl)-2-oxo-2,4-dihydrospiro[indoline-3,3-pyrazole]-5-carboxylate(3k)



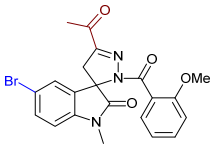
white solid; 60% yield in 4 h, mp 230-232 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 – 7.39 (1 H, m), 7.38-7.37 (1 H, m), 7.36 (1 H, s), 7.34 (2 H, t, *J* = 4.0 Hz), 7.31 (1 H, dd, *J* = 8.3, 2.0 Hz), 7.23 (1 H, s), 6.99 (1 H, t, *J* = 7.5 Hz), 6.94 (1 H, d, *J* = 8.3 Hz), 6.88 (2 H, d, *J* = 8.7 Hz), 6.56 (1 H, d, *J* = 8.3 Hz), 5.08 (1 H, m), 4.80 (1 H, d, *J* = 15.7 Hz), 4.32 (2 H, q, *J* = 7.2 Hz), 3.86 (3 H, s), 3.75 (3 H, s), 3.74 (1 H, d, *J* = 20.0 Hz), 3.40 (1 H, d, *J* = 20.0 Hz), 1.32 (3 H, t, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 166.5, 160.8, 159.1, 156.8, 145.3, 141.6, 132.5, 131.9, 130.6, 129.1, 128.5, 126.5, 125.8, 123.5, 120.4, 115.8, 114.2, 111.4, 77.3, 77.0, 76.7, 68.3, 62.0, 55.8, 55.2, 44.8, 44.0, 14.1; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm^{-1}; HRMS (ESI) for $C_{29}H_{27}N_3O_6$ $[M+H]^+$: calcd 514.1977, found 514.1979.

Methyl 5-bromo-2-(2-methoxybenzoyl)-1-methyl-2-oxo-2,4-dihydrospiro[indoline-3,3-pyrazole]-5-carboxylate(3l)



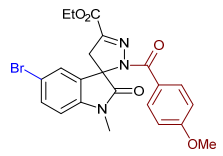
white solid; 92% yield in 4+12 h, mp 207-210 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 (1 H, d, *J* = 7.8 Hz), 7.37 (1 H, t, *J* = 8.0 Hz), 7.31 (2 H, d, *J* = 11.1 Hz), 6.94 (1 H, t, *J* = 7.5 Hz), 6.90 (1 H, d, *J* = 8.4 Hz), 6.76 (1 H, d, *J* = 8.2 Hz), 3.82 (6 H, s), 3.67 (1 H, d, *J* = 12.0 Hz), 3.36 (1 H, d, *J* = 12.0 Hz), 3.27 (3 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 166.0, 160.9, 156.3, 144.8, 142.4, 132.5, 131.5, 130.0, 128.5, 125.5, 123.0, 120.0, 115.3, 111.1, 109.9, 77.3, 77.0, 76.7, 68.0, 55.7, 52.6, 44.1, 26.8; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm^{-1}; HRMS (ESI) for $C_{21}H_{18}BrN_3O_5$ $[M+H]^+$: calcd 472.0503, found 472.0503.

5-acetyl-5-bromo-2-(2-methoxybenzoyl)-1-methyl-2,4-dihydrospiro[indoline-3,3-pyrazole]-2-one(3m)



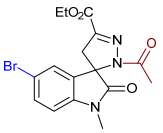
white solid; 96% yield in 4+12 h, mp 190-192 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (1 H, dd, *J* = 8.3, 2.0 Hz), 7.41 – 7.37 (1 H, m), 7.32 (1 H, dd, *J* = 7.5, 1.8 Hz), 7.27 (1 H, d, *J* = 2.0 Hz), 6.95 (1 H, t, *J* = 7.5 Hz), 6.89 (1 H, d, *J* = 8.4 Hz), 6.75 (1 H, d, *J* = 8.3 Hz), 3.84 (3 H, s), 3.56 (1 H, d, *J* = 20.0 Hz), 3.31 (1 H, d, *J* = 20.0 Hz), 3.26 (3 H, s), 2.34 (3 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.4, 172.9, 166.1, 156.4, 151.5, 142.5, 132.6, 131.7, 130.2, 128.8, 125.6, 123.2, 120.1, 115.5, 110.7, 110.0, 77.3, 77.0, 76.7, 68.5, 55.7, 42.7, 27.0, 25.9; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm^{-1}; HRMS (ESI) for $C_{21}H_{18}BrN_3O_4$ $[M+Na]^+$: calcd 478.0413, found 478.0423.

Ethyl 5-bromo-2-(4-methoxybenzoyl)-1-methyl-2-oxo-2,4-dihydrospiro[indoline-3,3-pyrazole]-5-carboxylate(3n)



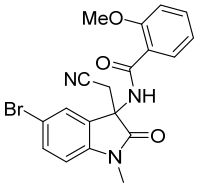
white solid; 95% yield in 16 h, mp 227-229 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (2 H, d, *J* = 8.5 Hz), 7.46 (1 H, d, *J* = 8.4 Hz), 7.31 (1 H, s), 6.90 (2 H, d, *J* = 8.6 Hz), 6.78 (1 H, d, *J* = 8.3 Hz), 4.38 (2 H, q, *J* = 6.9 Hz), 3.84 (3 H, s), 3.66 (1 H, d, *J* = 16.0 Hz), 3.32 (1 H, d, *J* = 16.0 Hz), 3.30 (3 H, s), 1.38 (3 H, t, *J* = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 164.8, 162.4, 160.6, 145.3, 142.4, 132.6, 130.7, 125.2, 123.7, 115.6, 113.1, 110.0, 77.3, 77.0, 76.7, 69.3, 62.2, 55.4, 43.4, 27.0, 14.3; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm^{-1}; HRMS (ESI) for $C_{22}H_{20}BrN_3O_5$ $[M+Na]^+$: calcd 508.0479, found 508.0479.

Ethyl 2-acetyl-5-bromo-1-methyl-2-oxo-2,4-dihydrospiro[indoline-3,3-pyrazole]-5-carboxylate(3o)



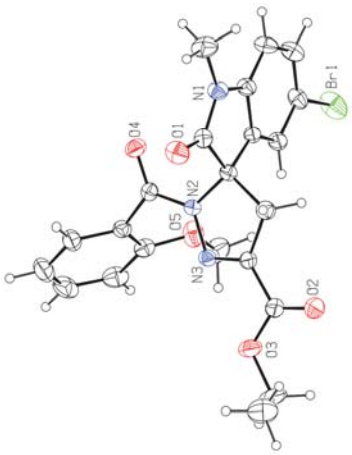
white solid; 90% yield in 4+12 h, mp 201-204 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (1 H, d, *J* = 9.6 Hz), 7.24 (1 H, s), 6.73 (1 H, d, *J* = 8.3 Hz), 4.37 (2 H, q, *J* = 7.1 Hz), 3.64 (1 H, d, *J* = 16.0 Hz), 3.31 (1 H, d, *J* = 16.0 Hz), 3.24 (3 H, s), 2.35 (3 H, s), 1.38 (3 H, t, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 168.4, 160.3, 145.0, 142.2, 132.5, 130.3, 125.2, 115.5, 109.9, 77.3, 77.0, 76.7, 67.7, 62.2, 44.3, 26.8, 21.7, 14.2; IR (in KBr): 2926, 1589, 1469, 1377, 1309, 1262, 1150, 1105 cm^{-1}; HRMS (ESI) for $C_{16}H_{16}BrN_3O_4$ $[M+H]^+$: calcd 394.0397, found 394.0401.

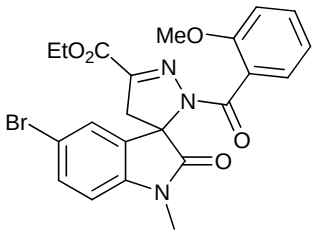
N-(5-bromo-3-(cyanomethyl)-1-methyl-2-oxindolin-3-yl)-2-methoxybenzamide (6)



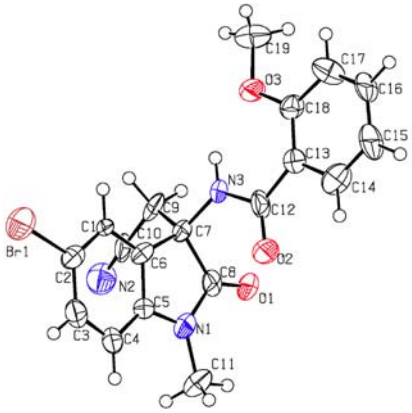
white solid, 57% yield in 4 h, mp 194-196 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.26 (1 H, s), 8.07 (1 H, d, *J* = 6.7 Hz), 7.74 (1 H, d, *J* = 2.0 Hz), 7.57 – 7.52 (2 H, m), 7.08 (2 H, t, *J* = 7.3 Hz), 6.87 (1 H, d, *J* = 8.3 Hz), 4.15 (3 H, s), 3.37 (3 H, s), 3.31 (1 H, d, *J* = 16.0 Hz), 2.72 (1 H, d, *J* = 16.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 164.4, 157.7, 142.2, 134.0, 132.9, 132.2, 129.5, 126.5, 121.3, 119.2, 116.0, 115.0, 111.4, 110.2, 77.2, 77.0, 76.8, 57.8, 56.2, 27.0, 26.2. IR (in KBr): 3437, 2960, 2926, 1732, 1464, 1304, 1252, 1162, 1057 cm^{-1}; HRMS (ESI) for $C_{19}H_{16}BrN_3O_3$ $[M+Na]^+$: calcd 436.0267, found 436.0269.

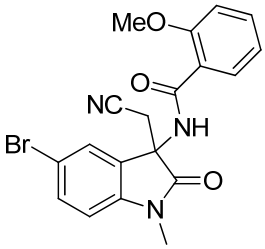
10. X-ray single crystal structures of 3f and 6





3f

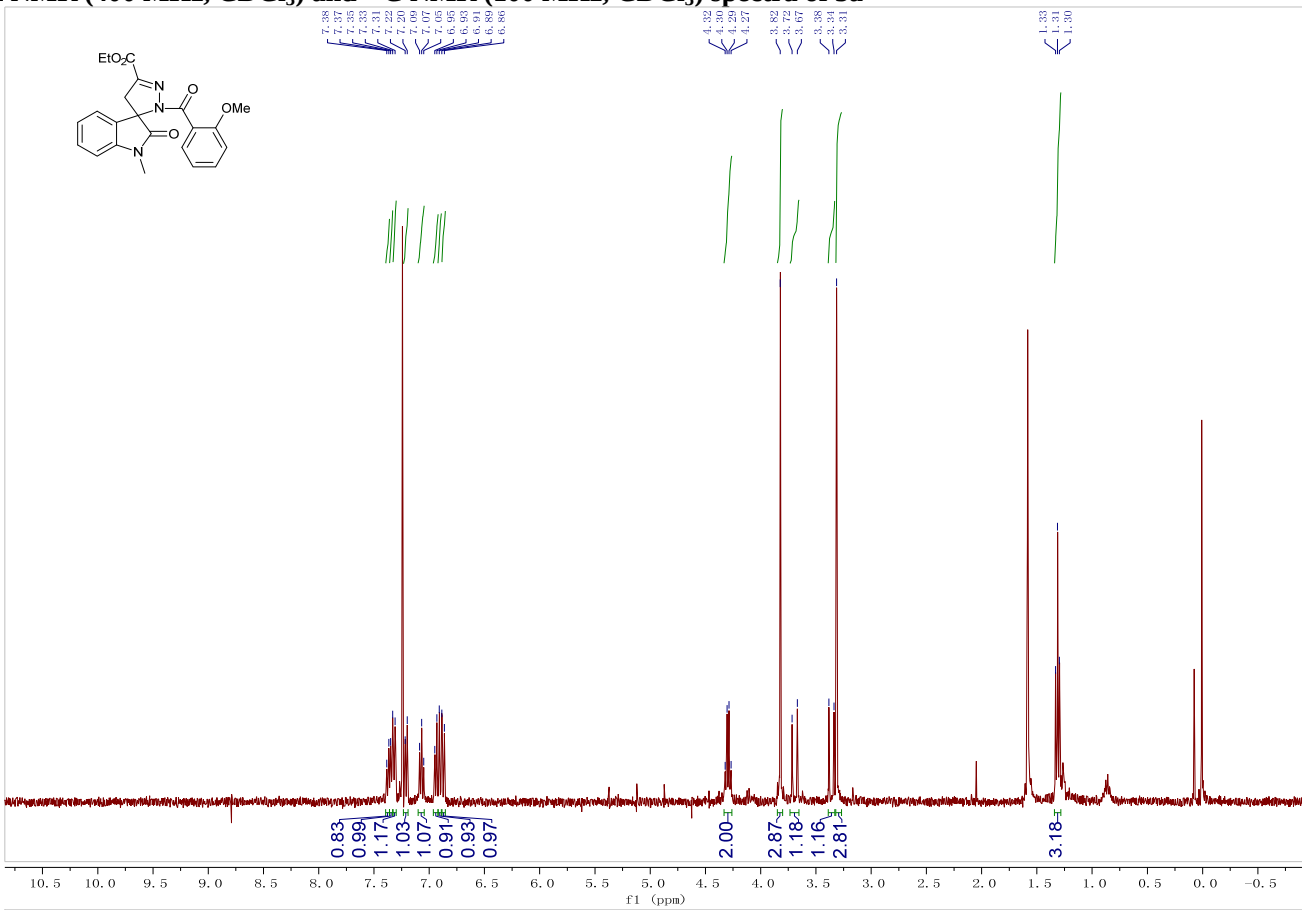


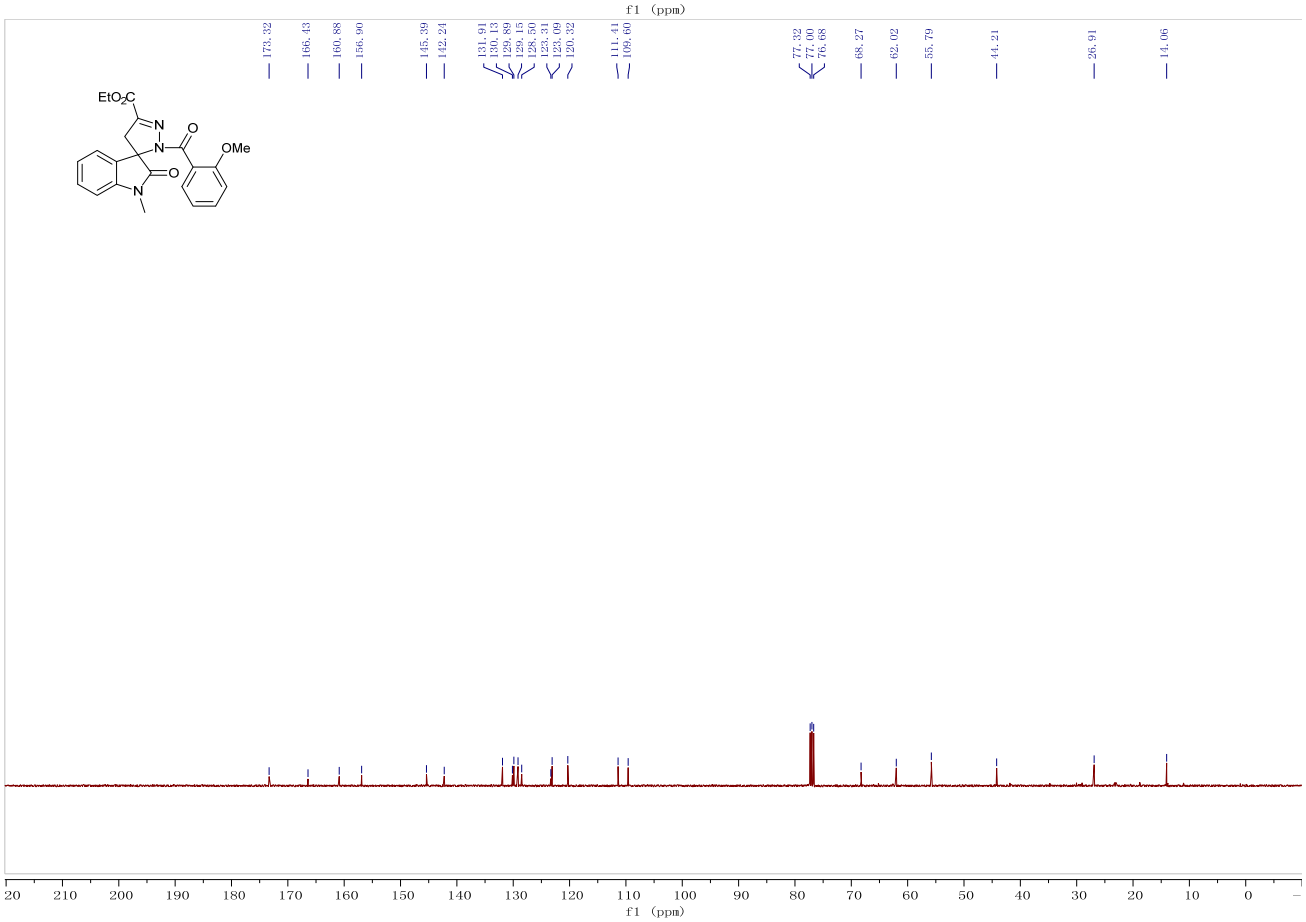


6

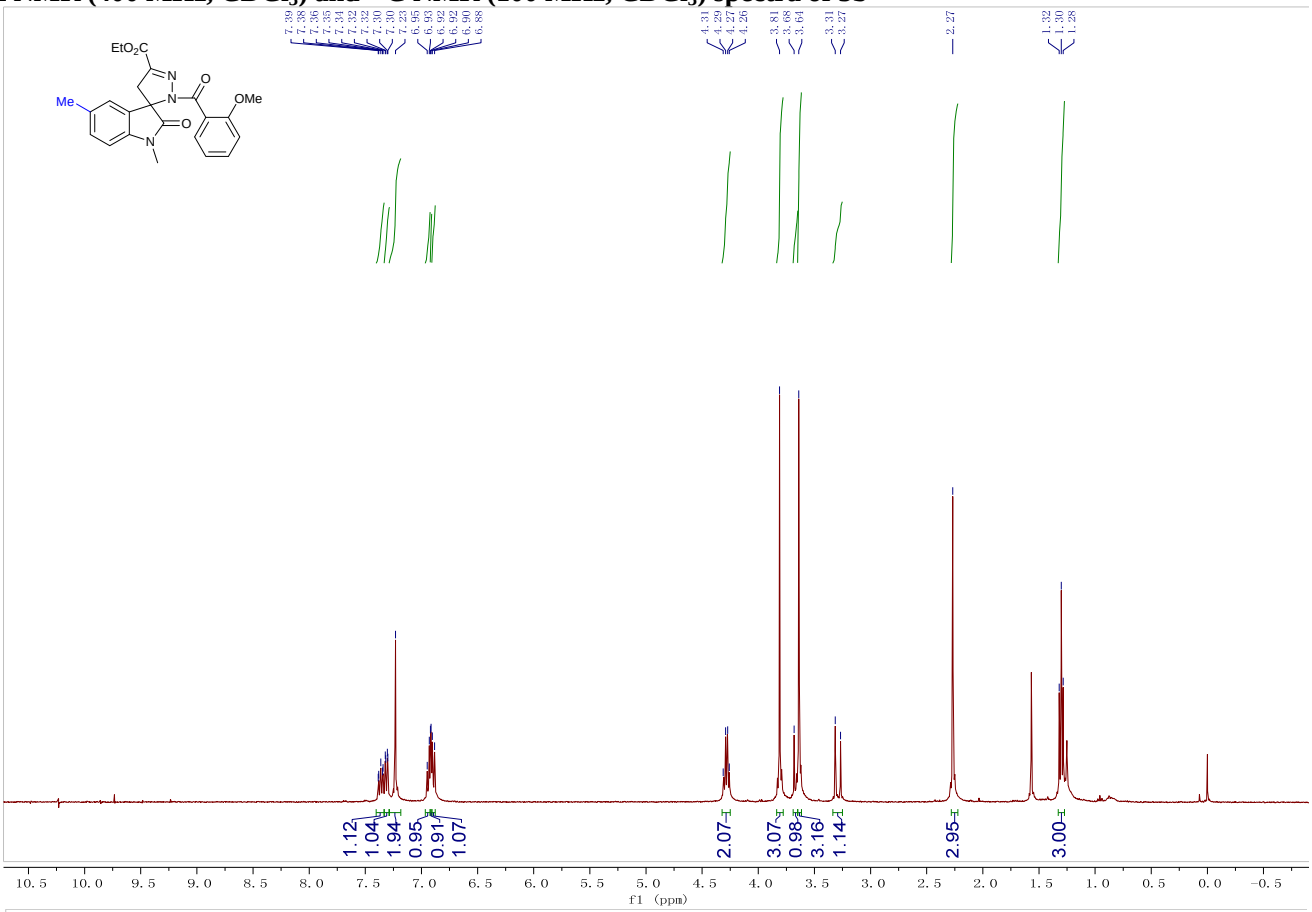
11. Copies of ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra

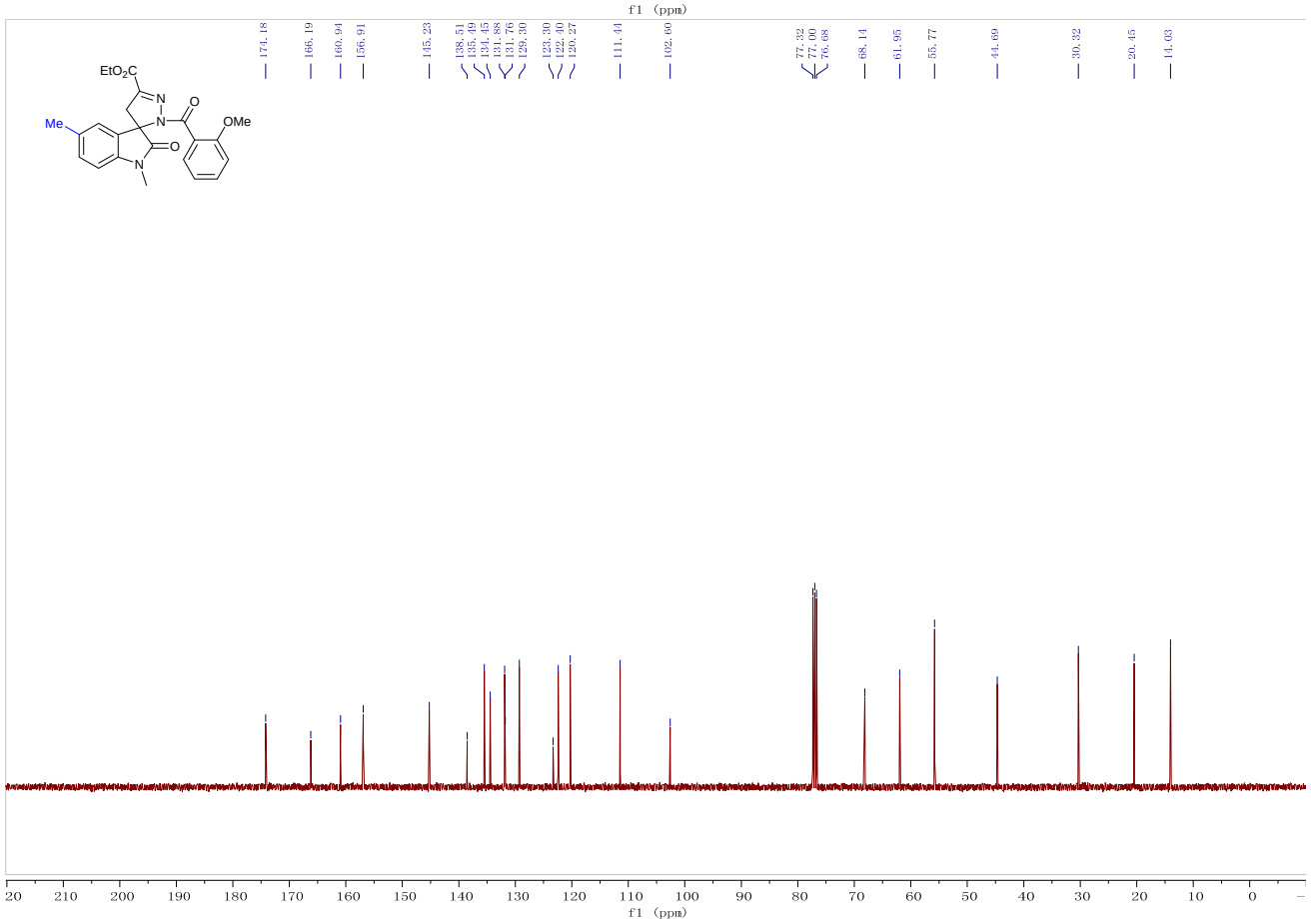
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3a



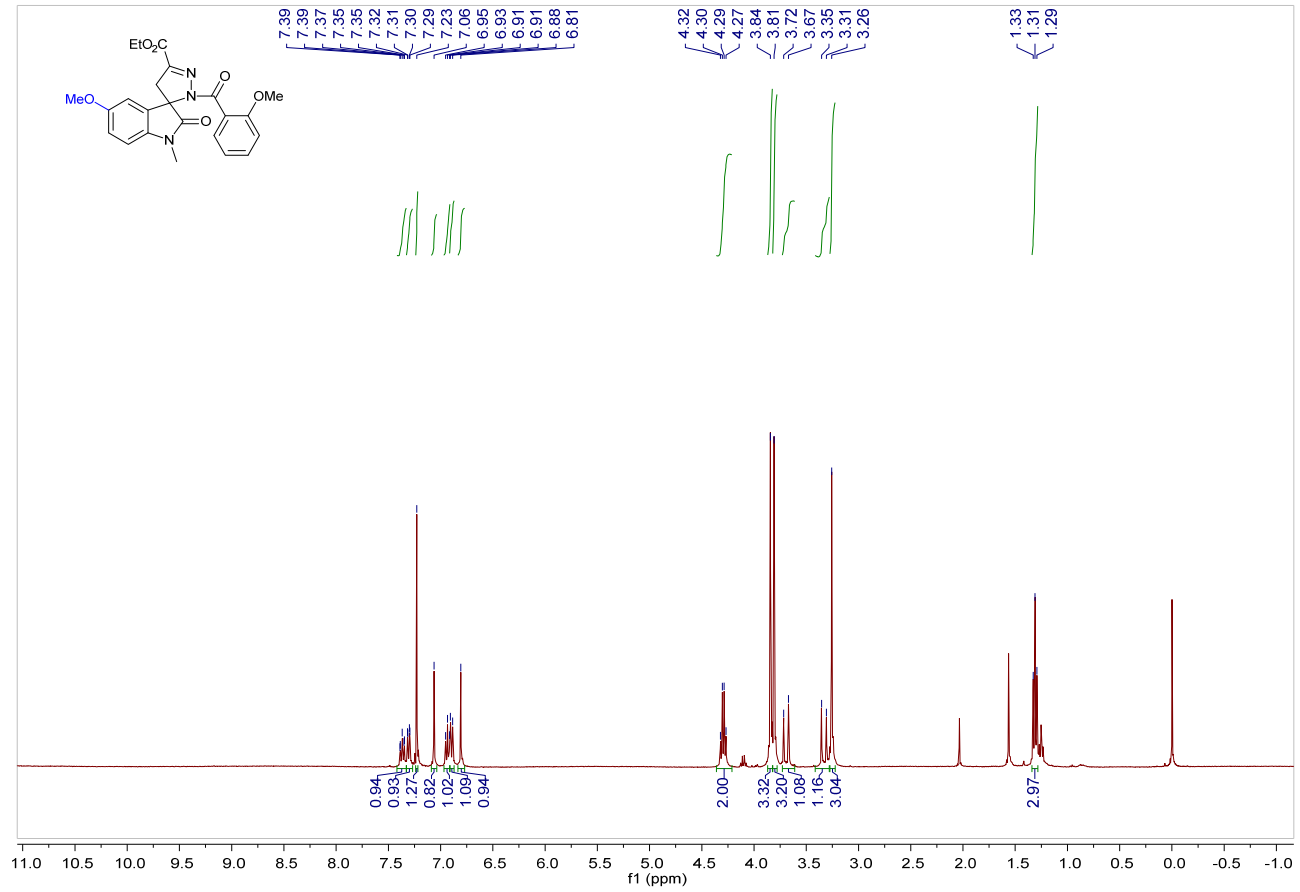


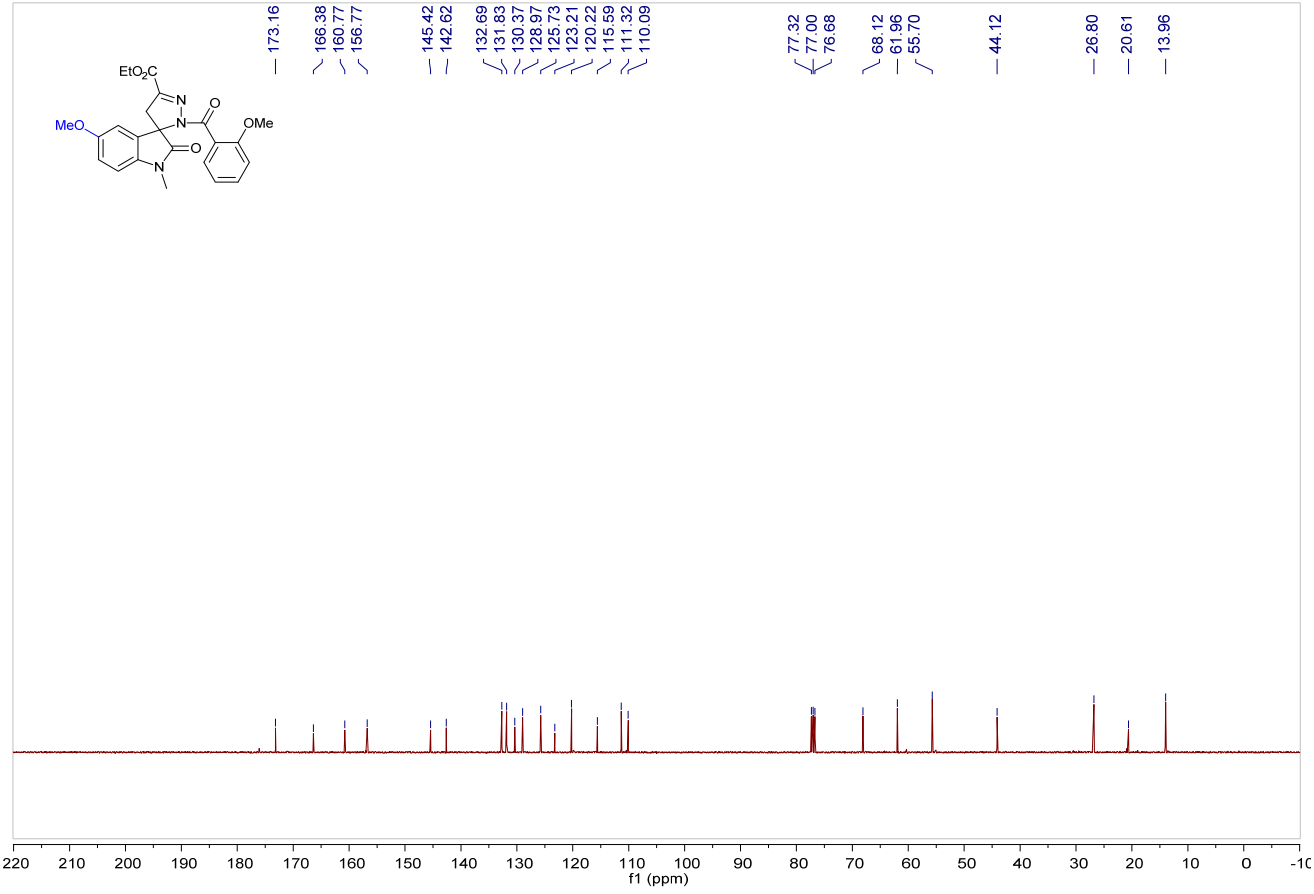
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3b



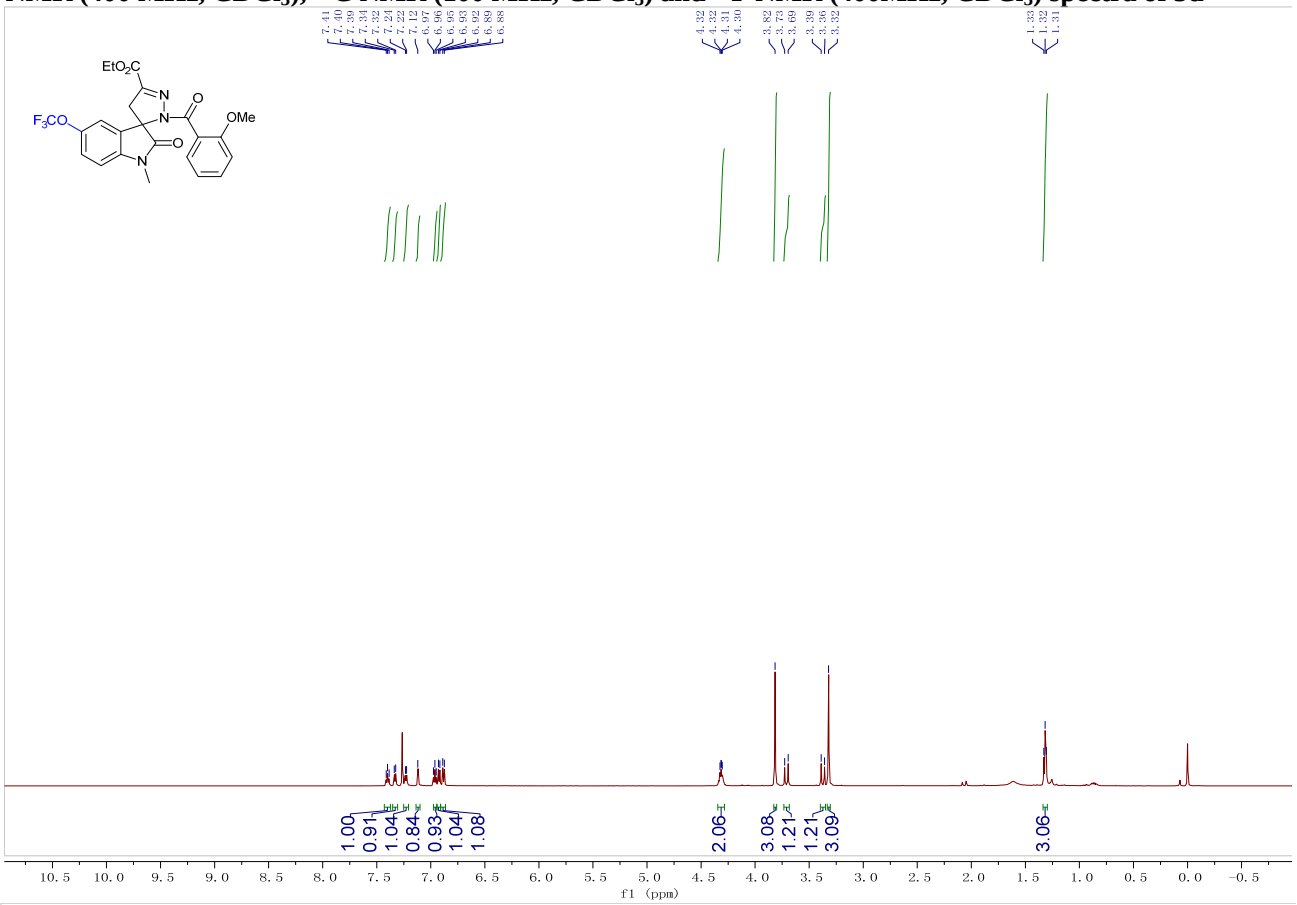


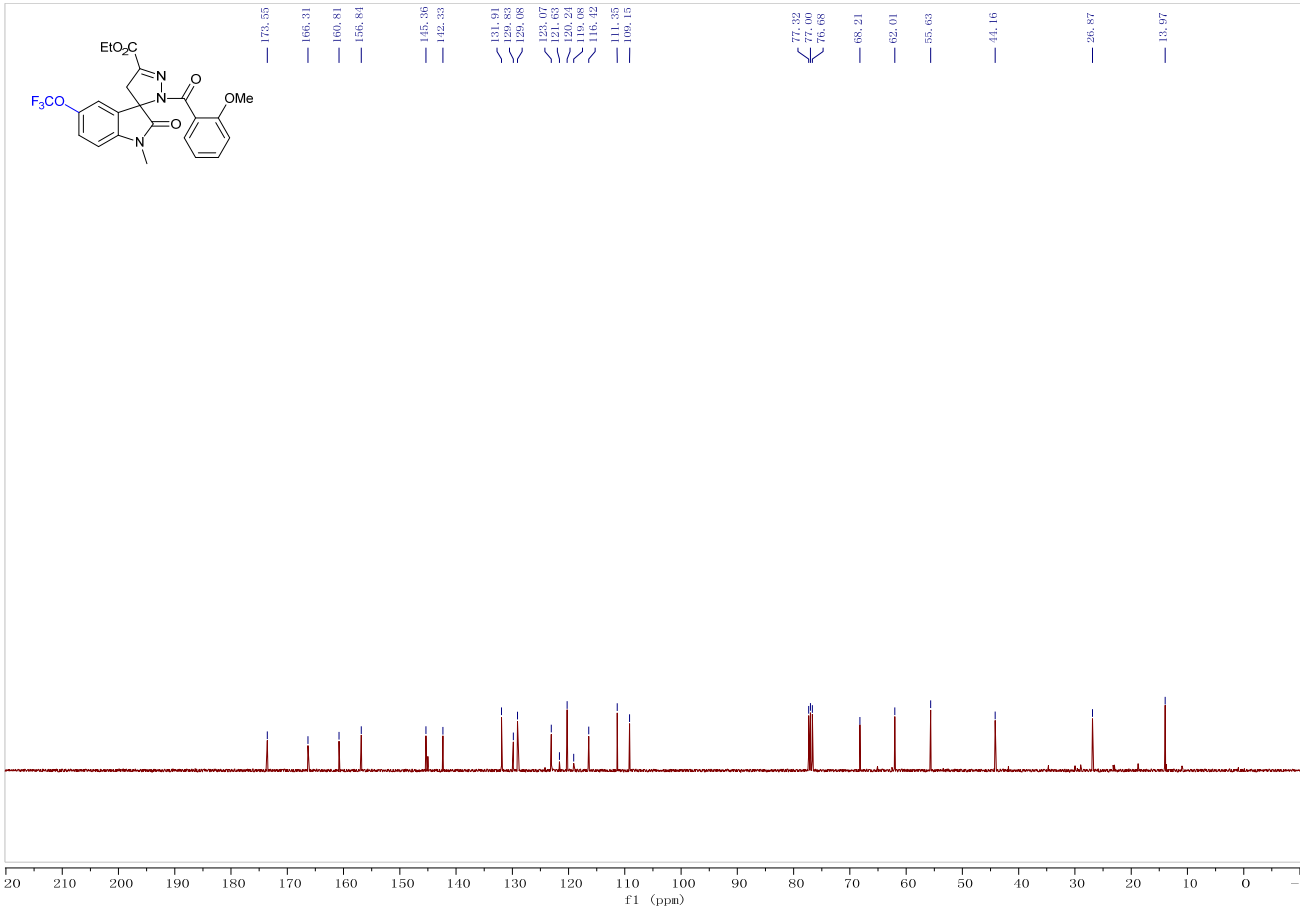
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3c

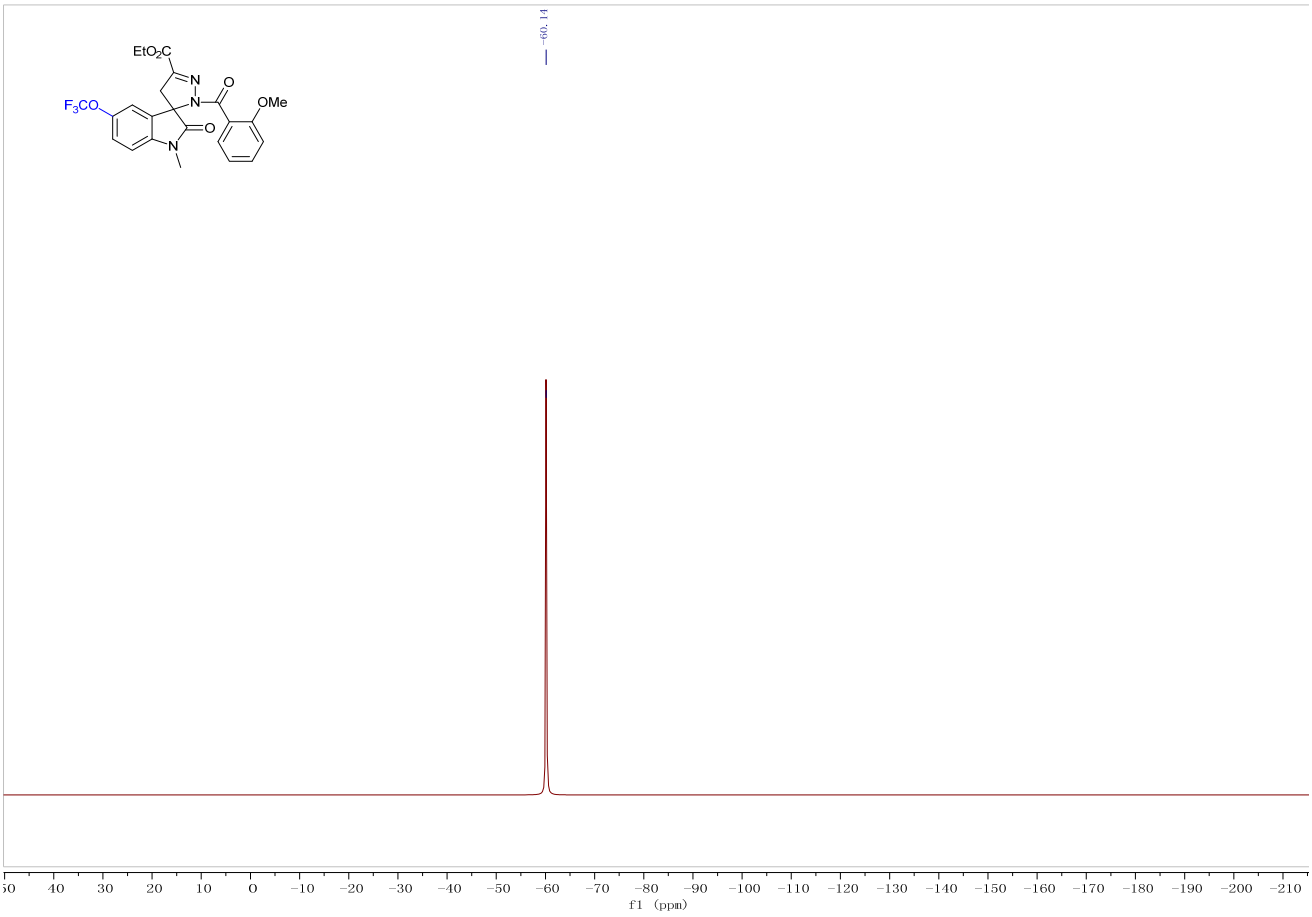




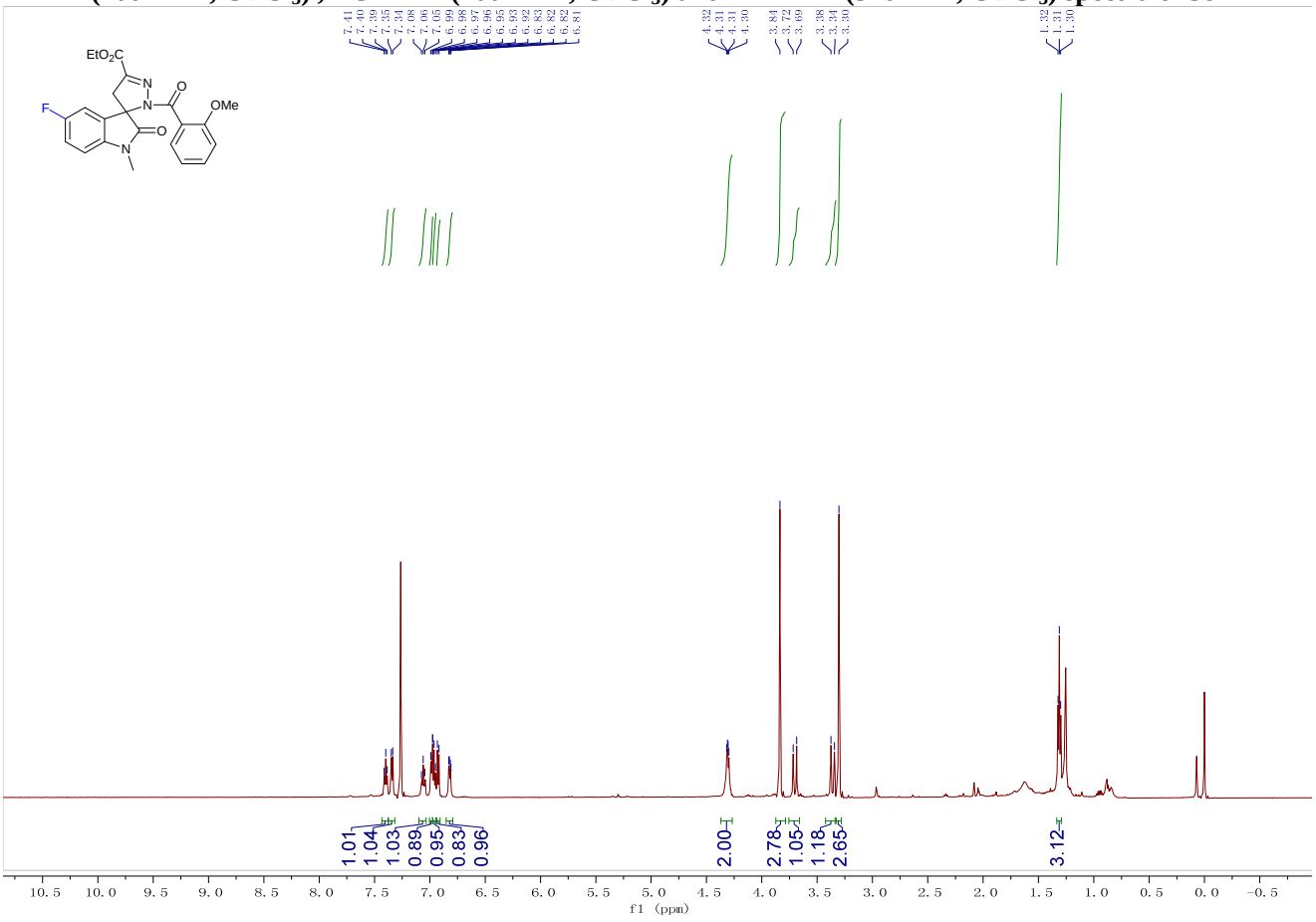
^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$) and ^{19}F NMR (400MHz, $CDCl_3$) spectra of 3d

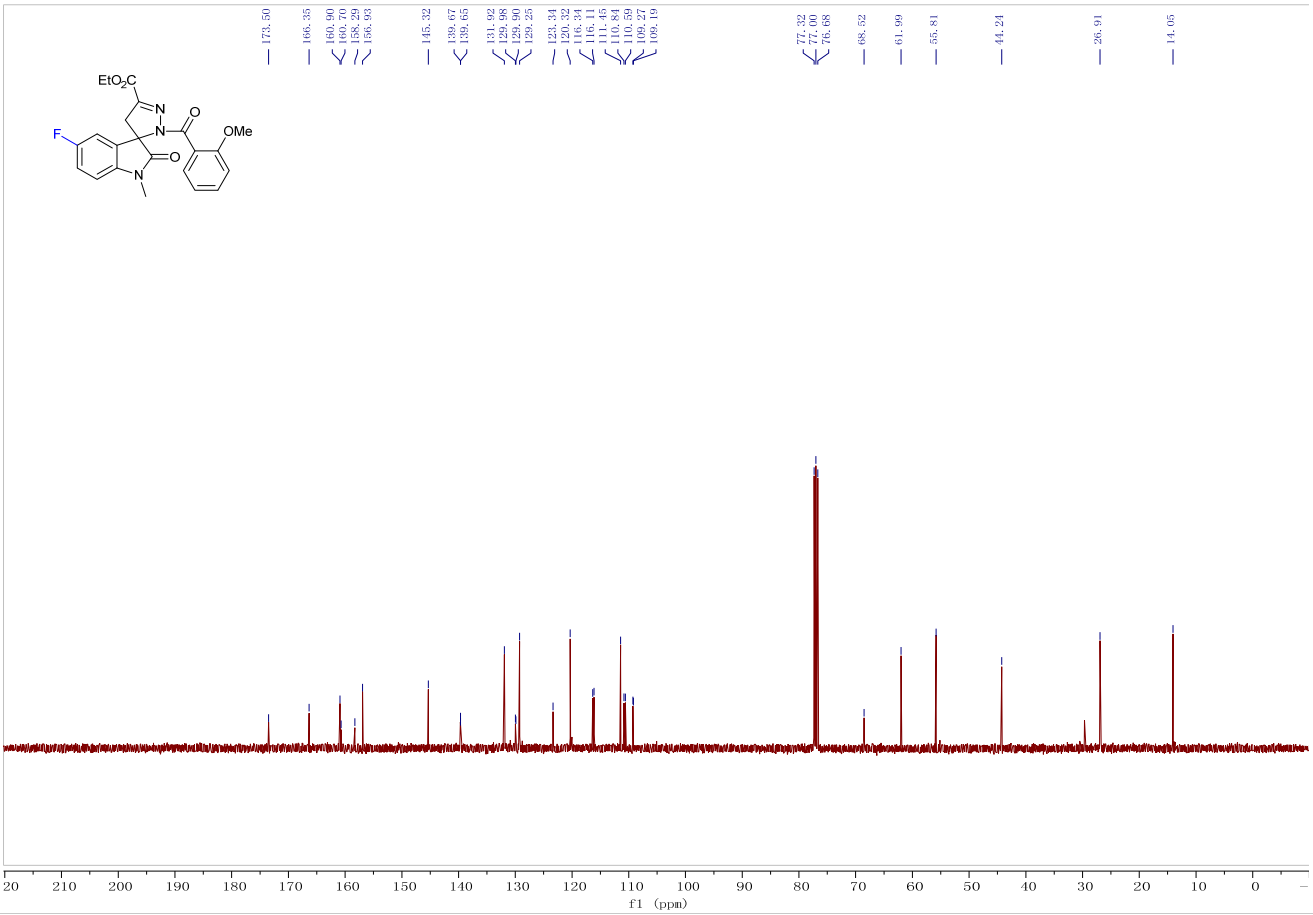


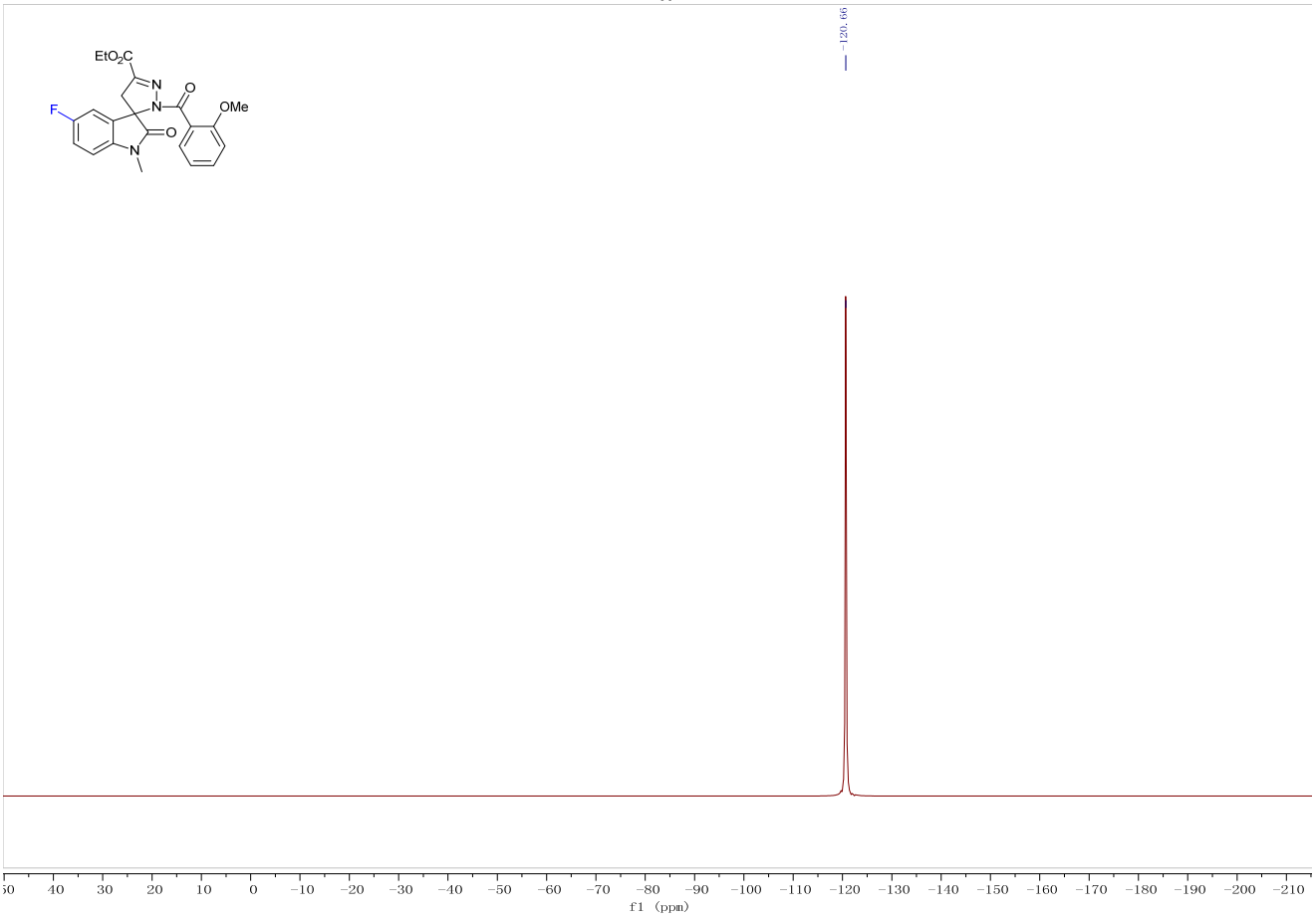




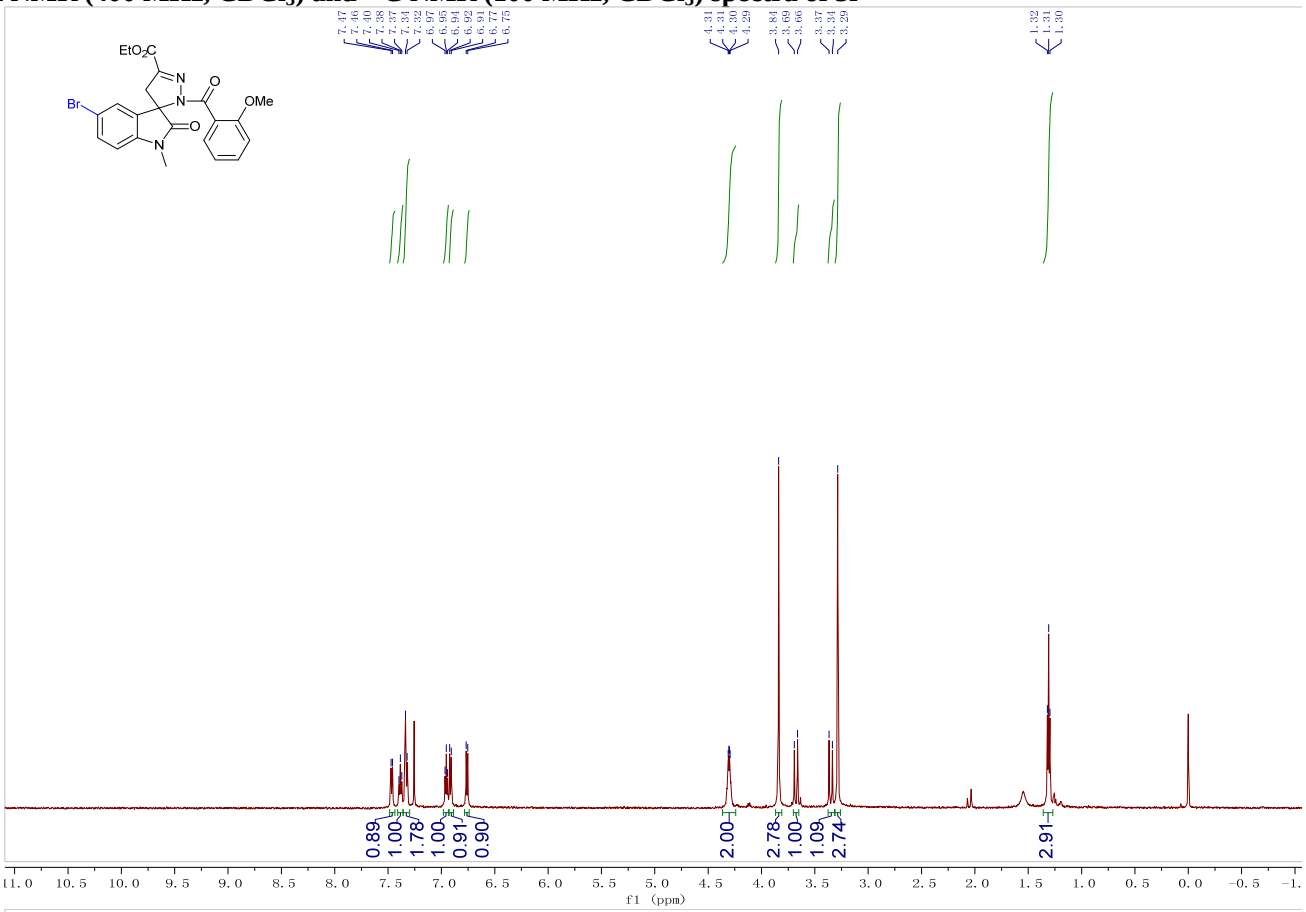
^{1}H NMR (400 MHz, $CDCl_3$) , ^{13}C NMR (100 MHz, $CDCl_3$) and ^{19}F NMR (376MHz, $CDCl_3$) spectra of 3e

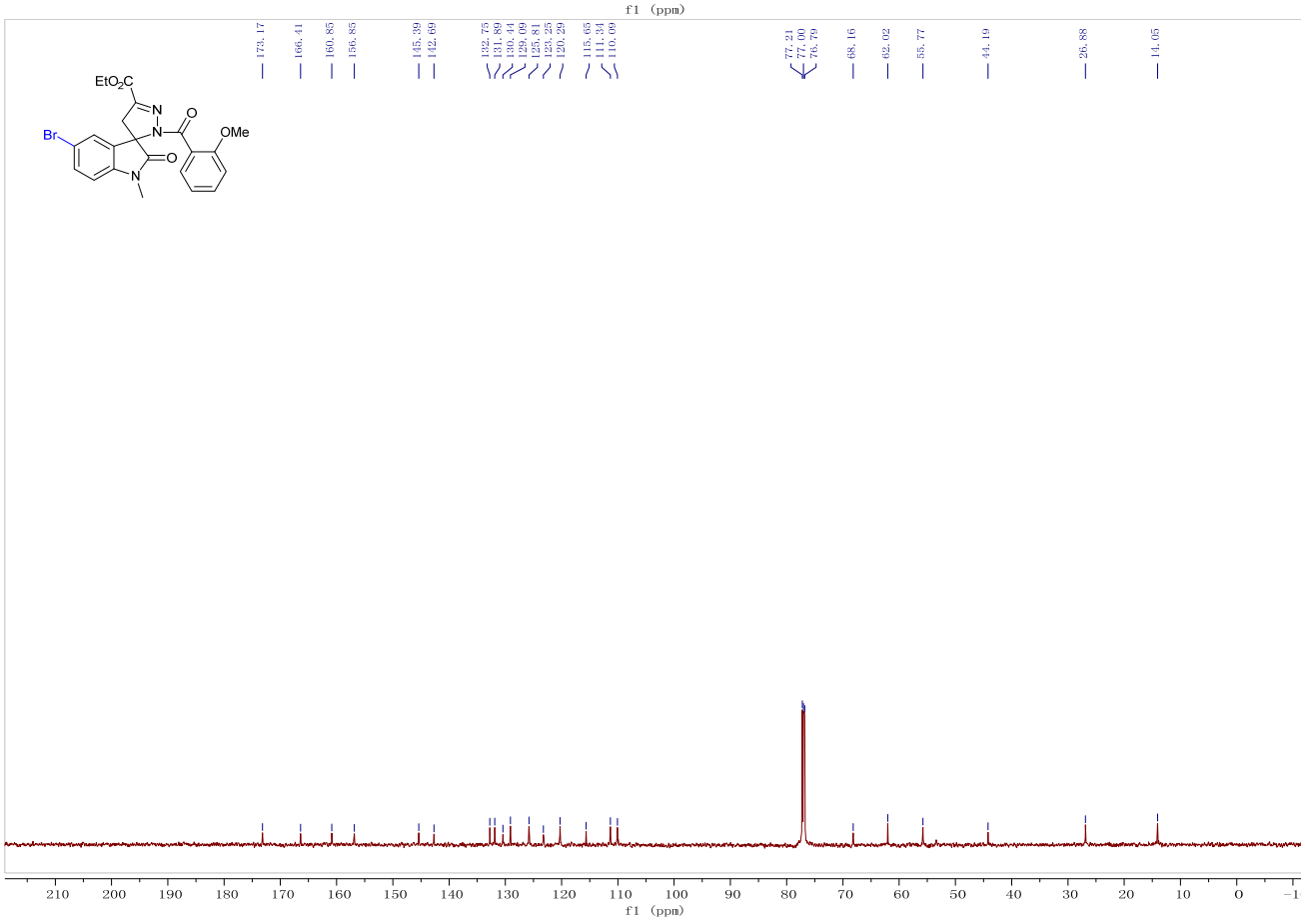



173.50
166.35
160.90
160.70
158.29
156.93
145.32
139.67
139.65
131.92
129.98
129.90
129.25
123.34
120.32
116.34
116.11
111.45
110.84
110.59
109.27
109.19
77.32
77.00
76.68
68.52
61.99
55.81
44.24
26.91
14.65
EtO2C
F
OMe
f1 (ppm)

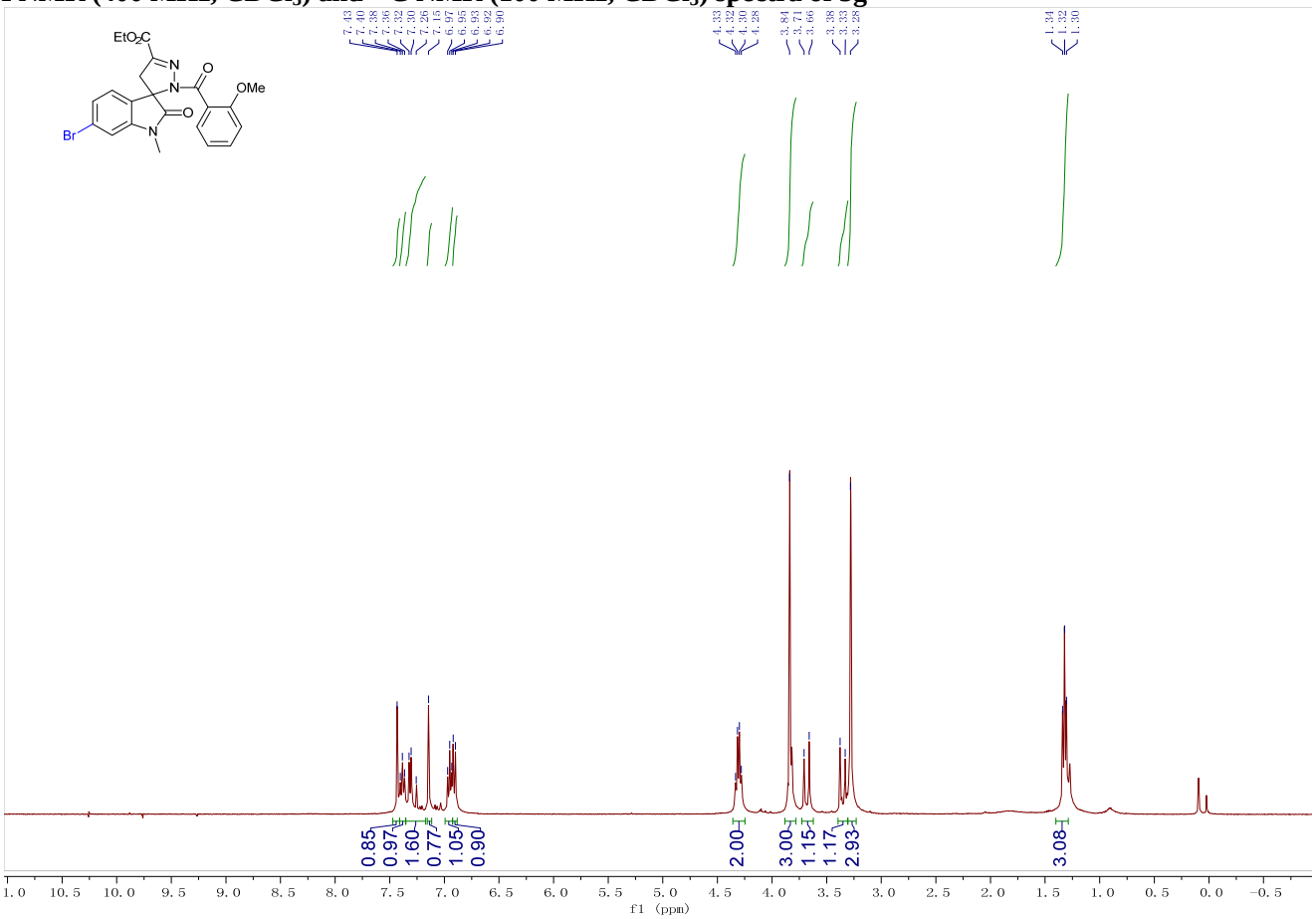

-120.66
EtO2C
F
OMe
f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3f

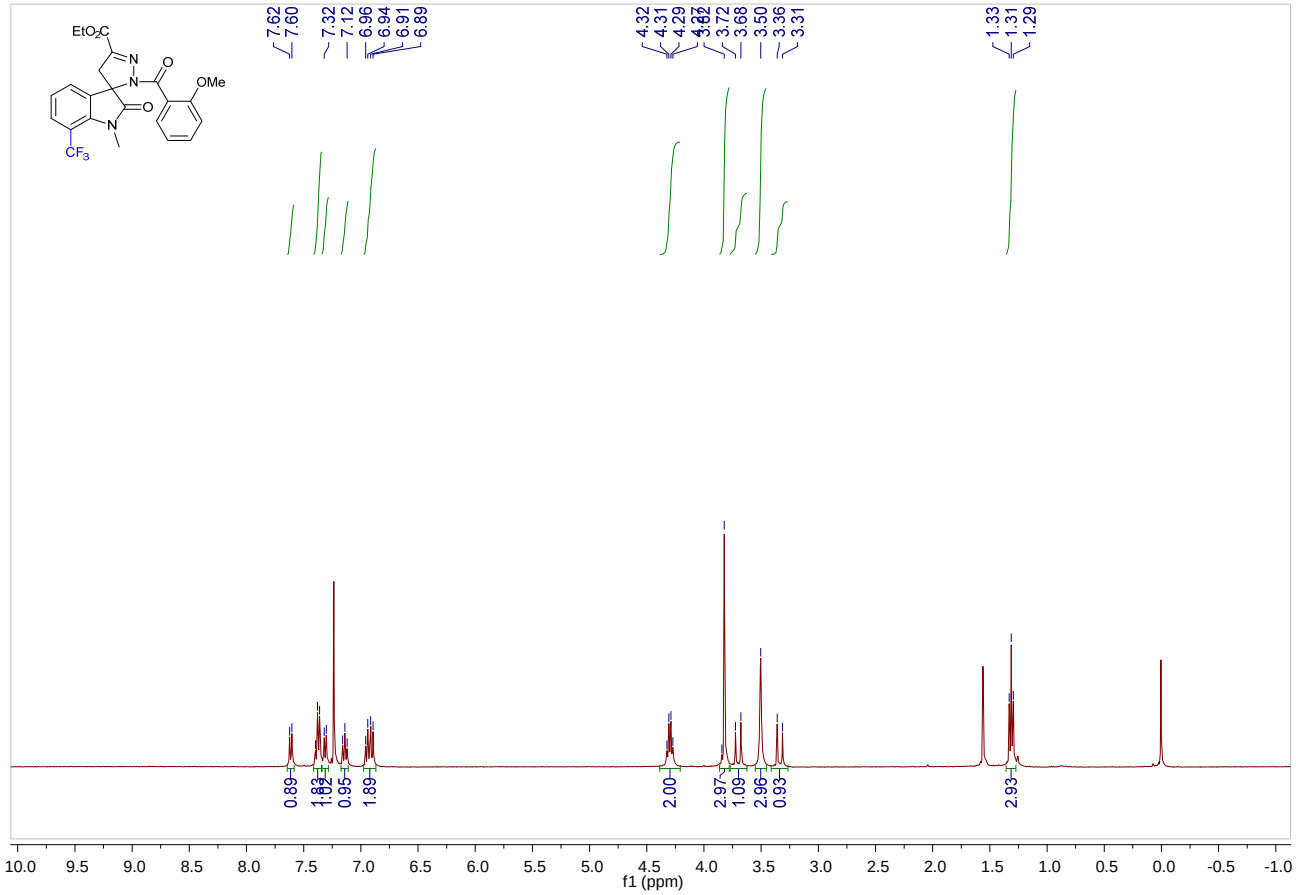


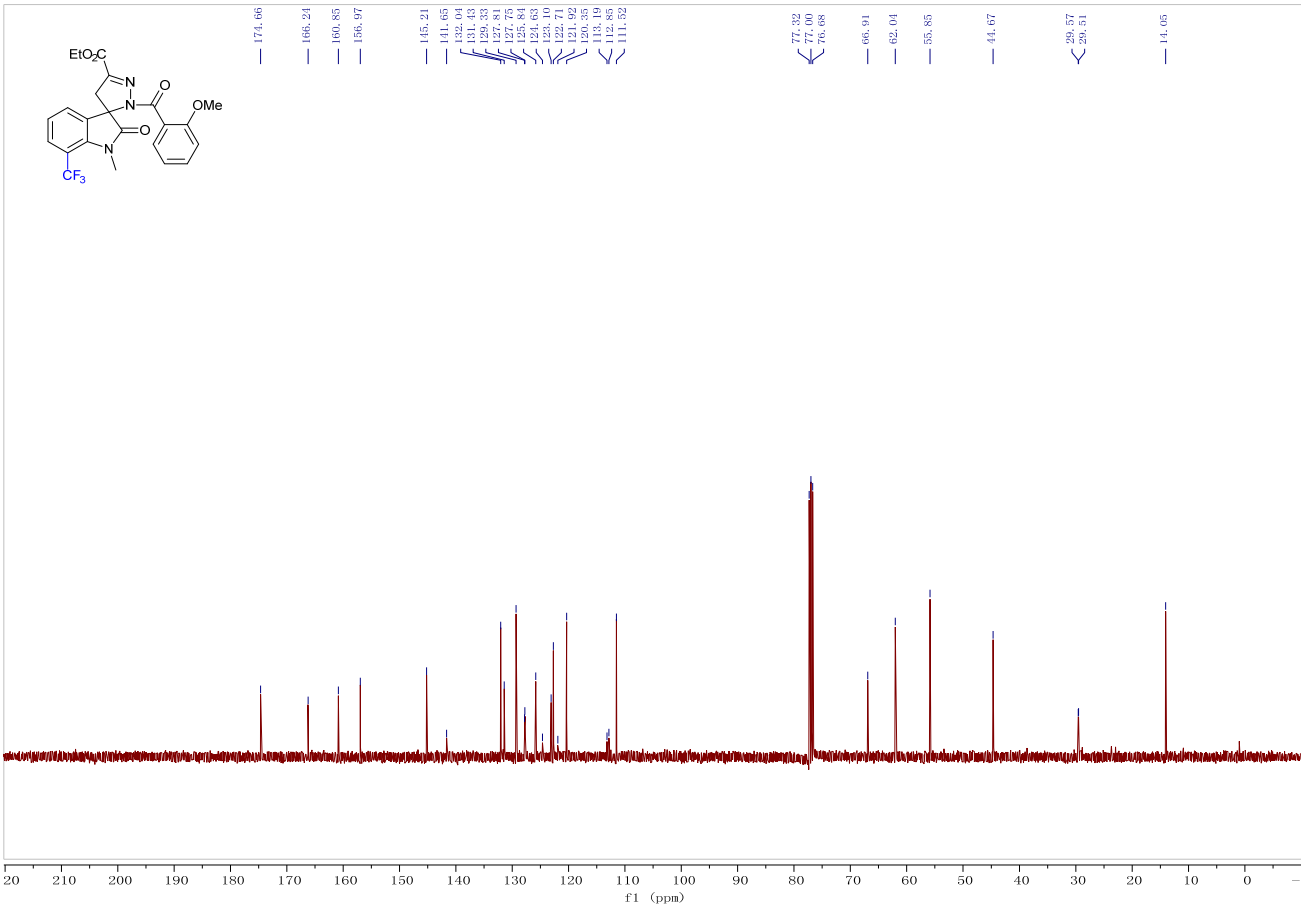


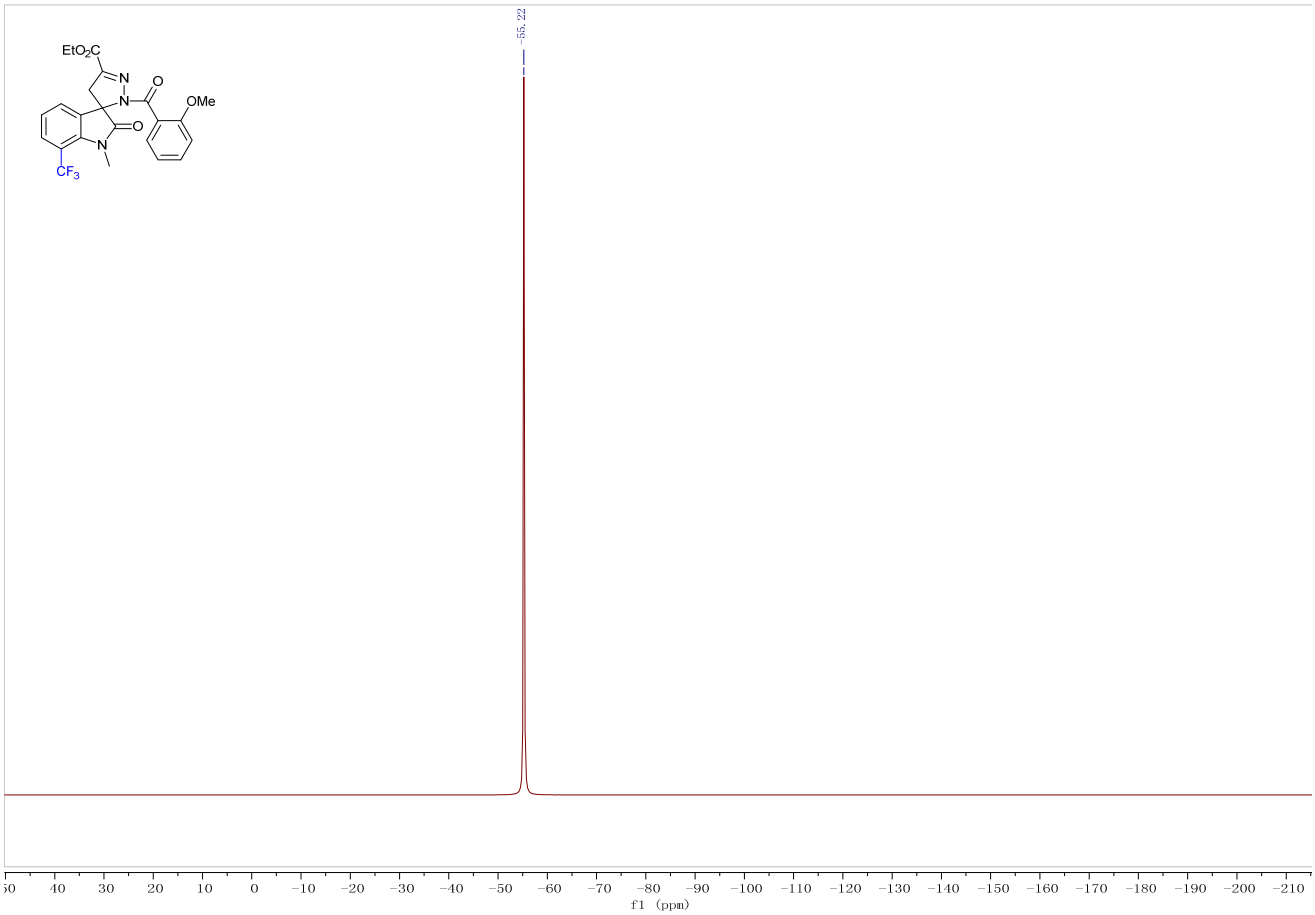
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3g



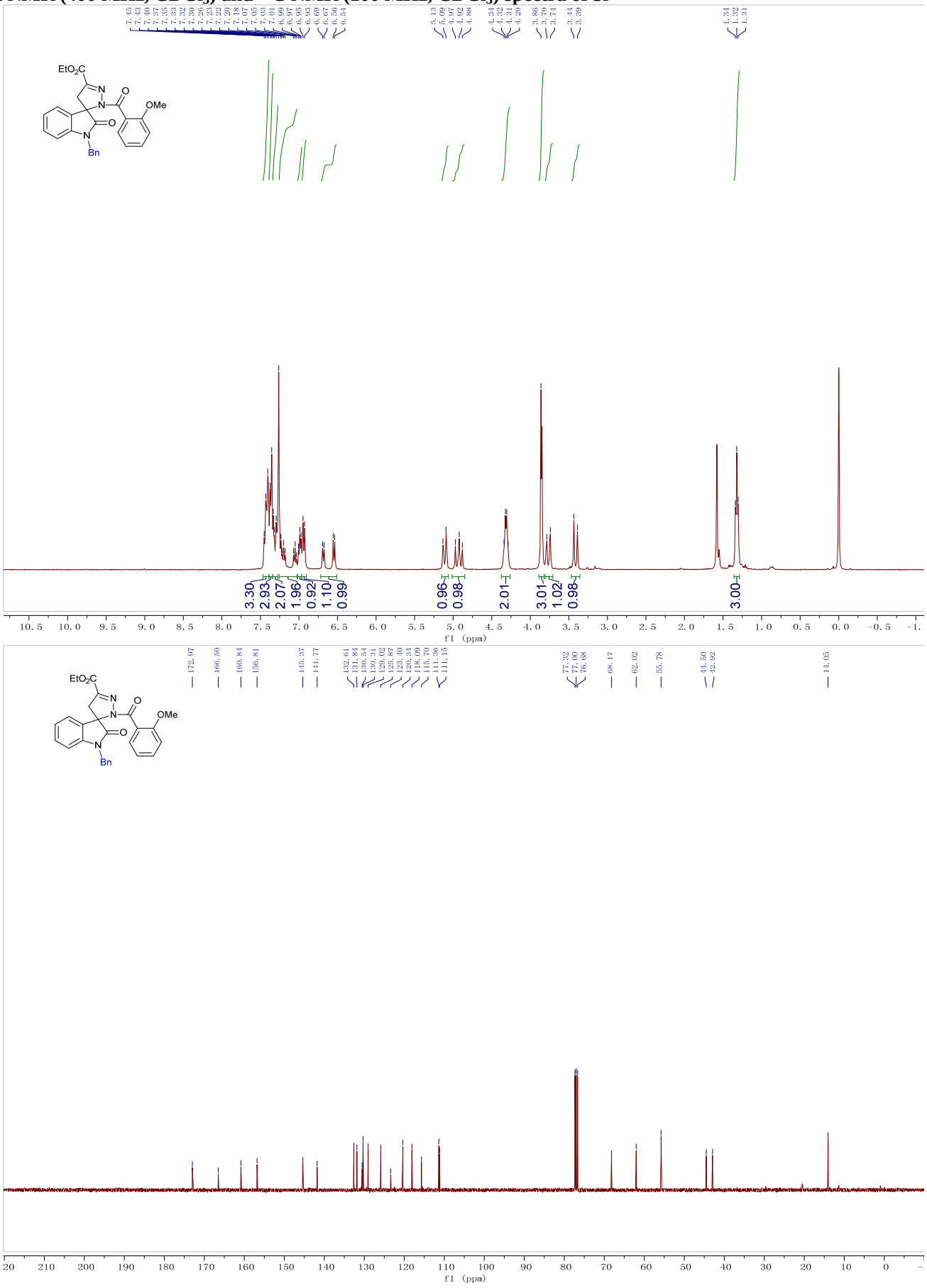
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) and ^{19}F NMR (376MHz, $CDCl_3$) spectra of 3h



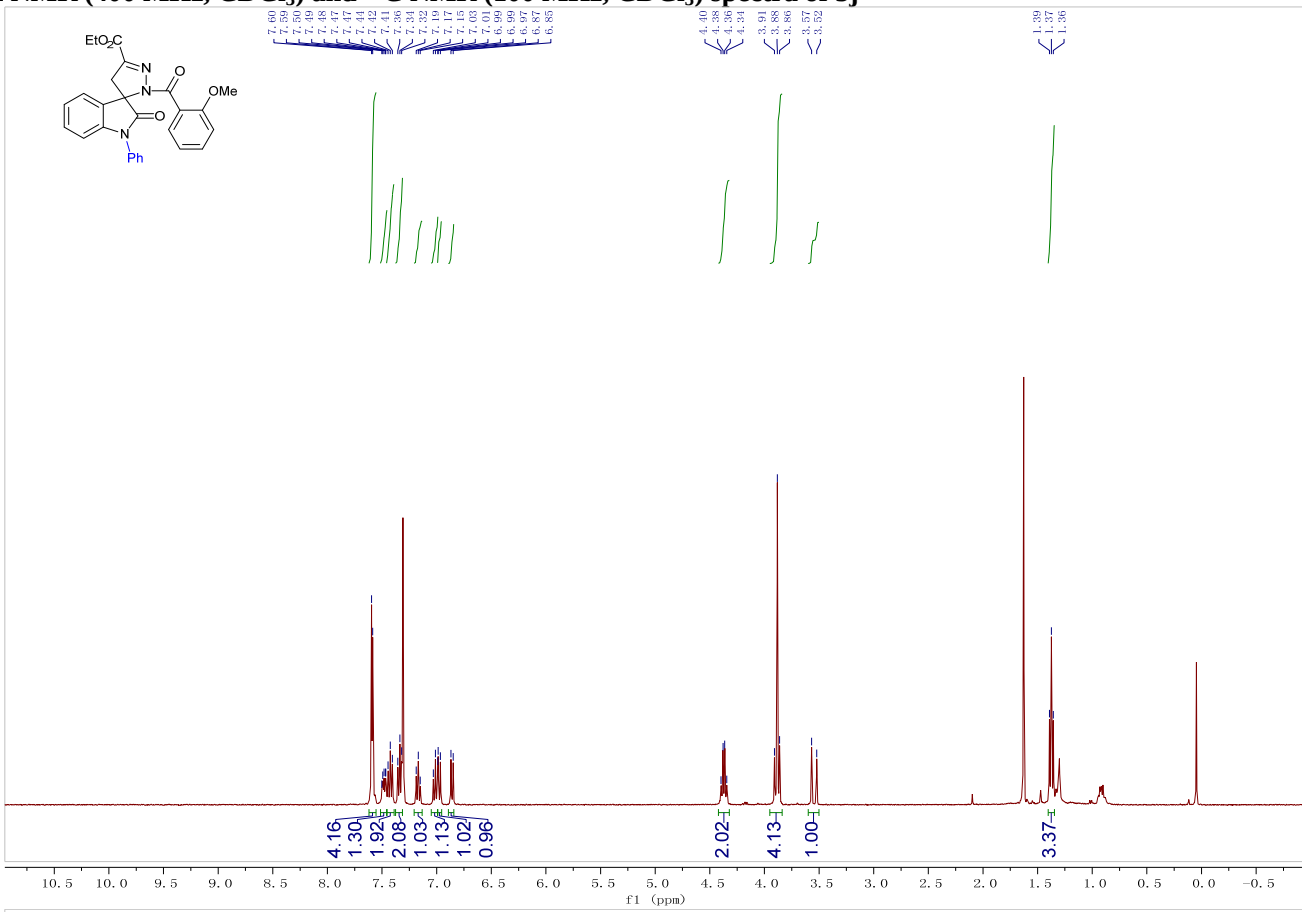


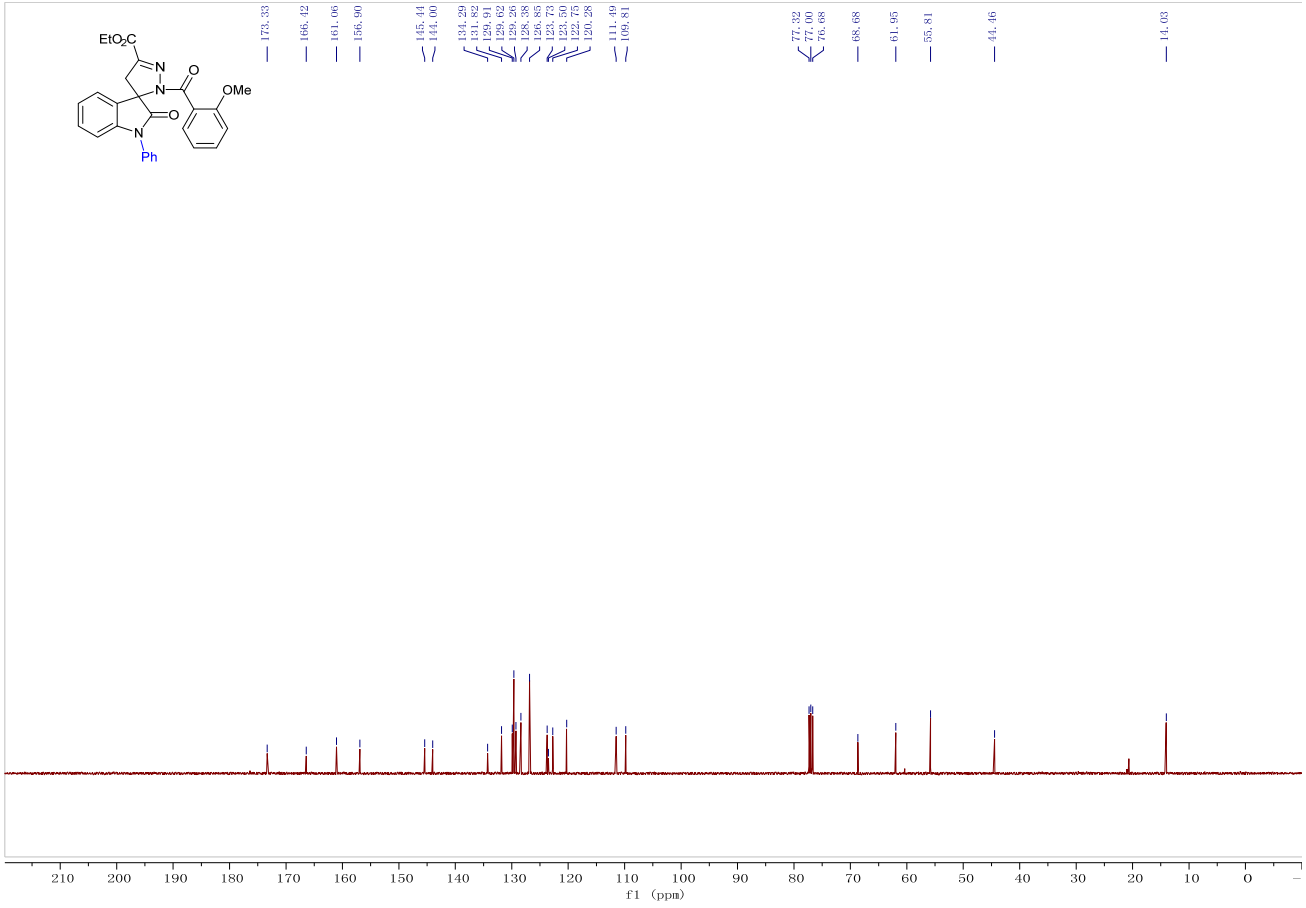

-55.22
EtO2C
N
N
O
OMe
O
N
CF3
50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3i

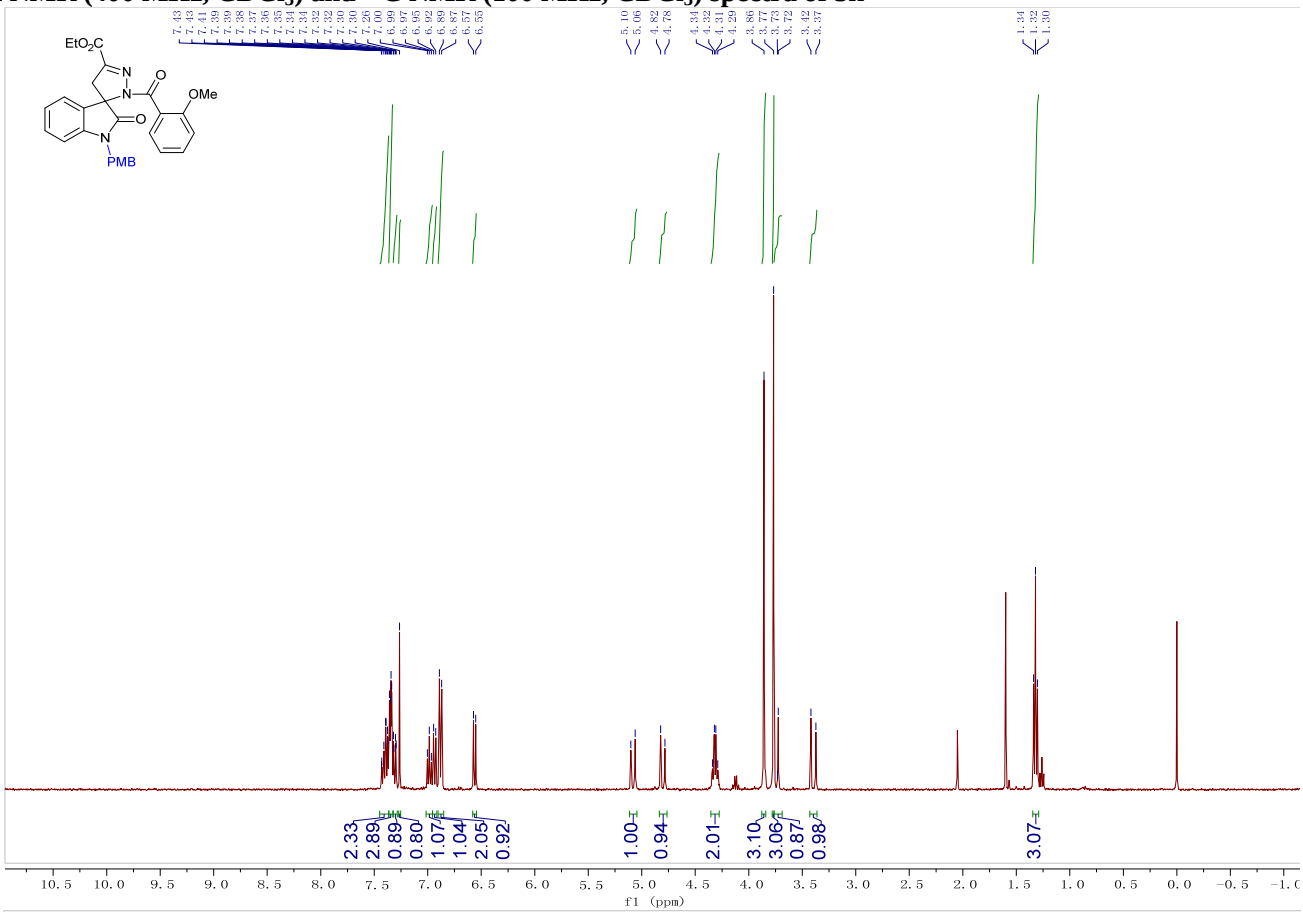


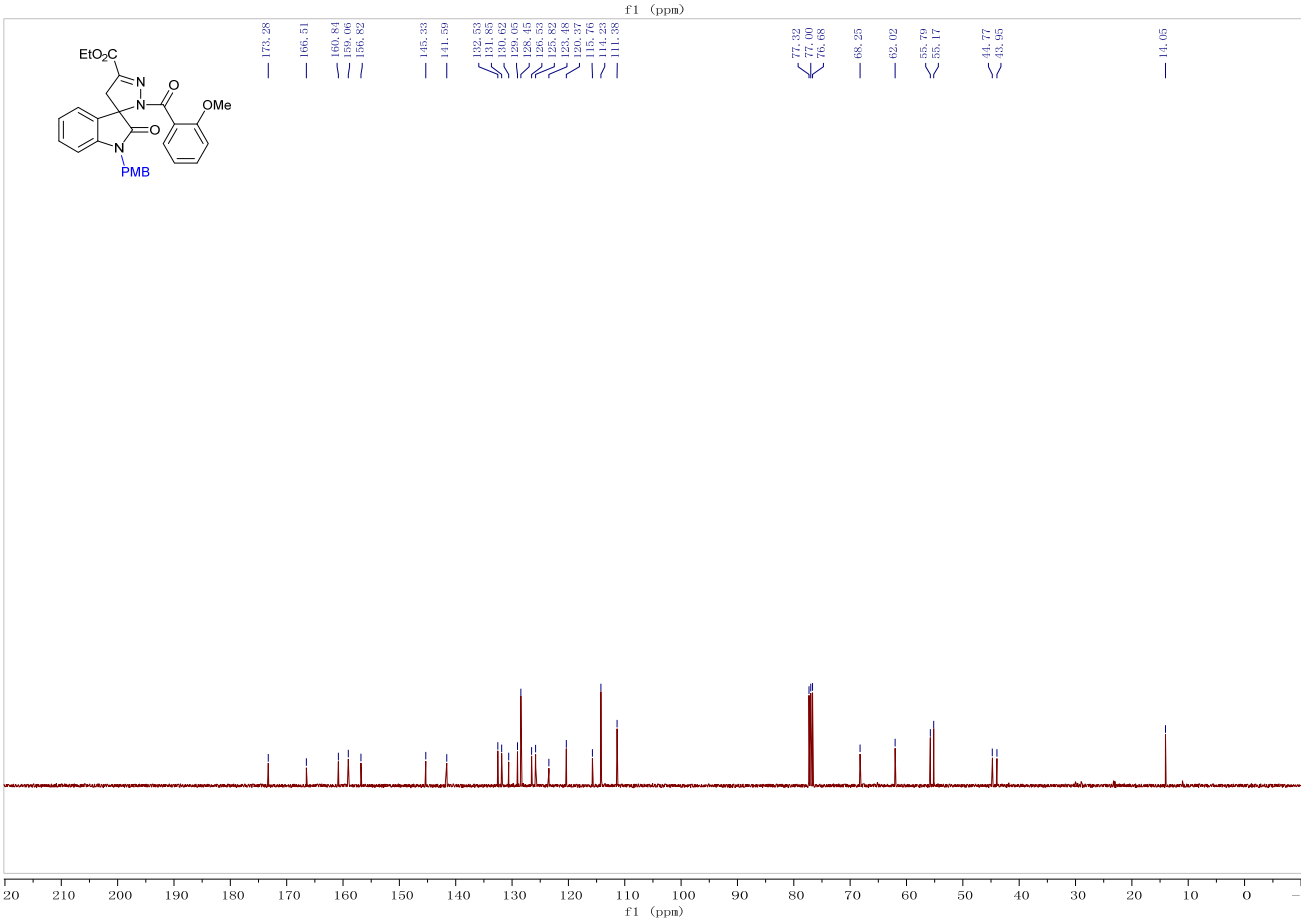
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3j



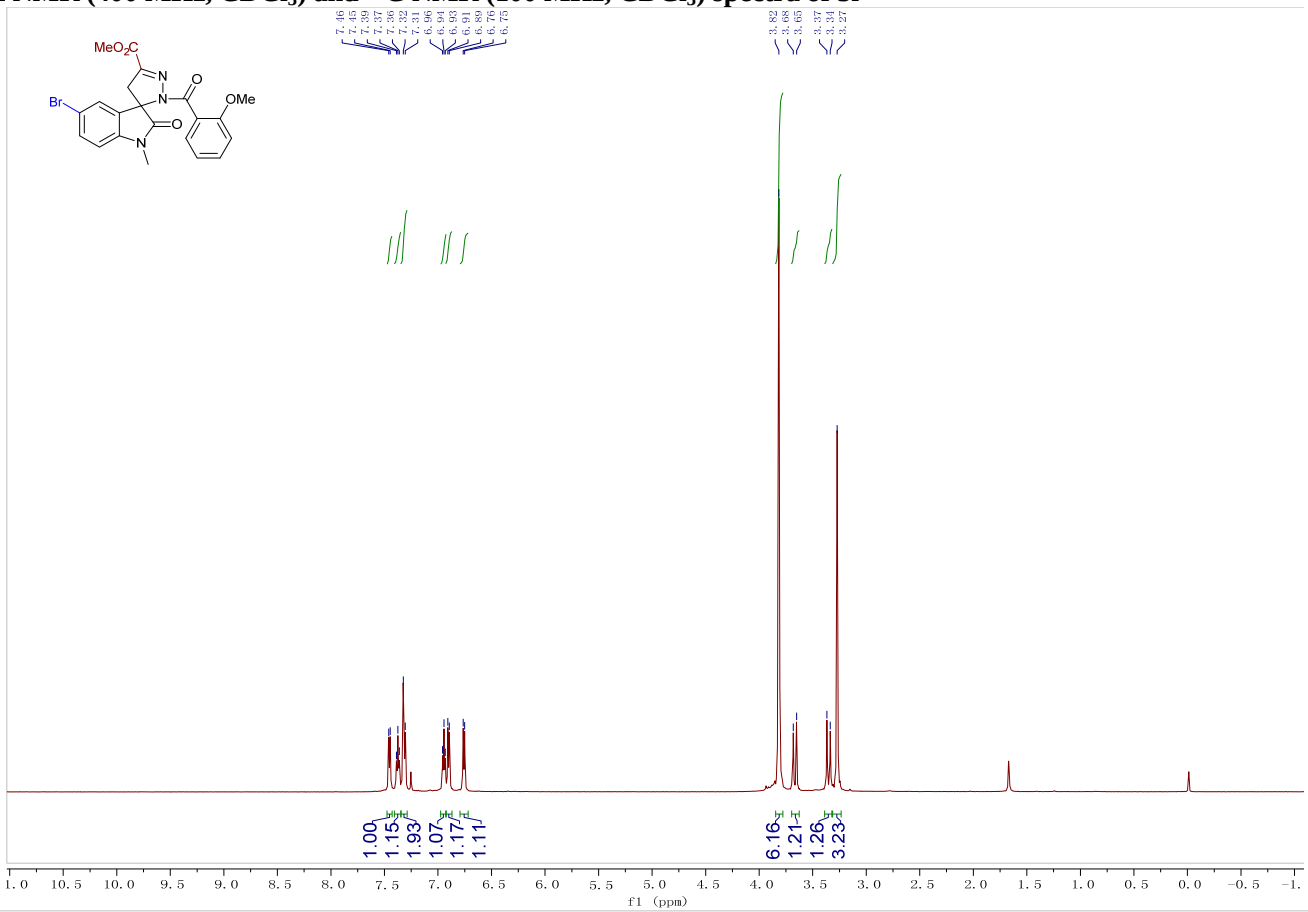


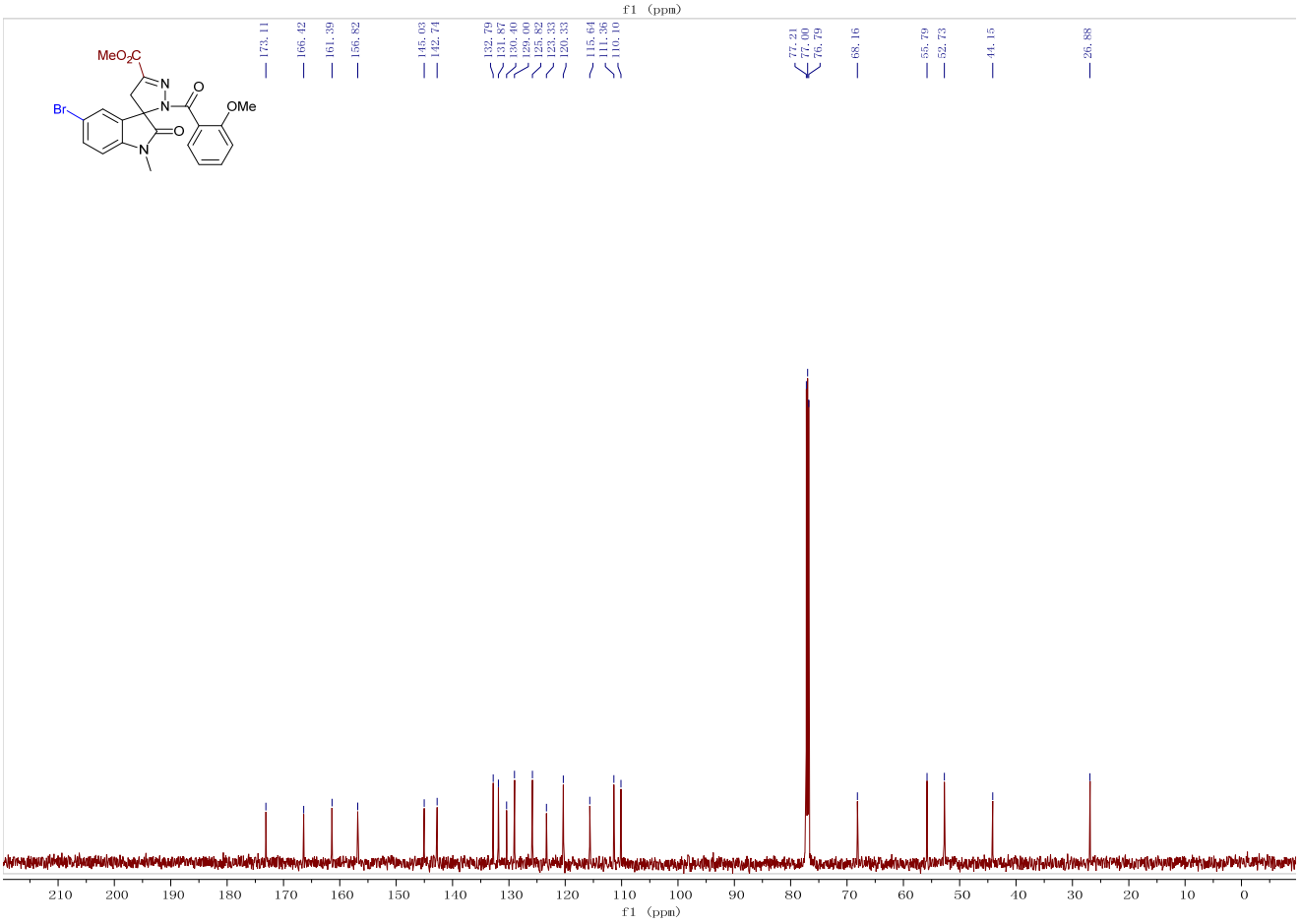
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3k



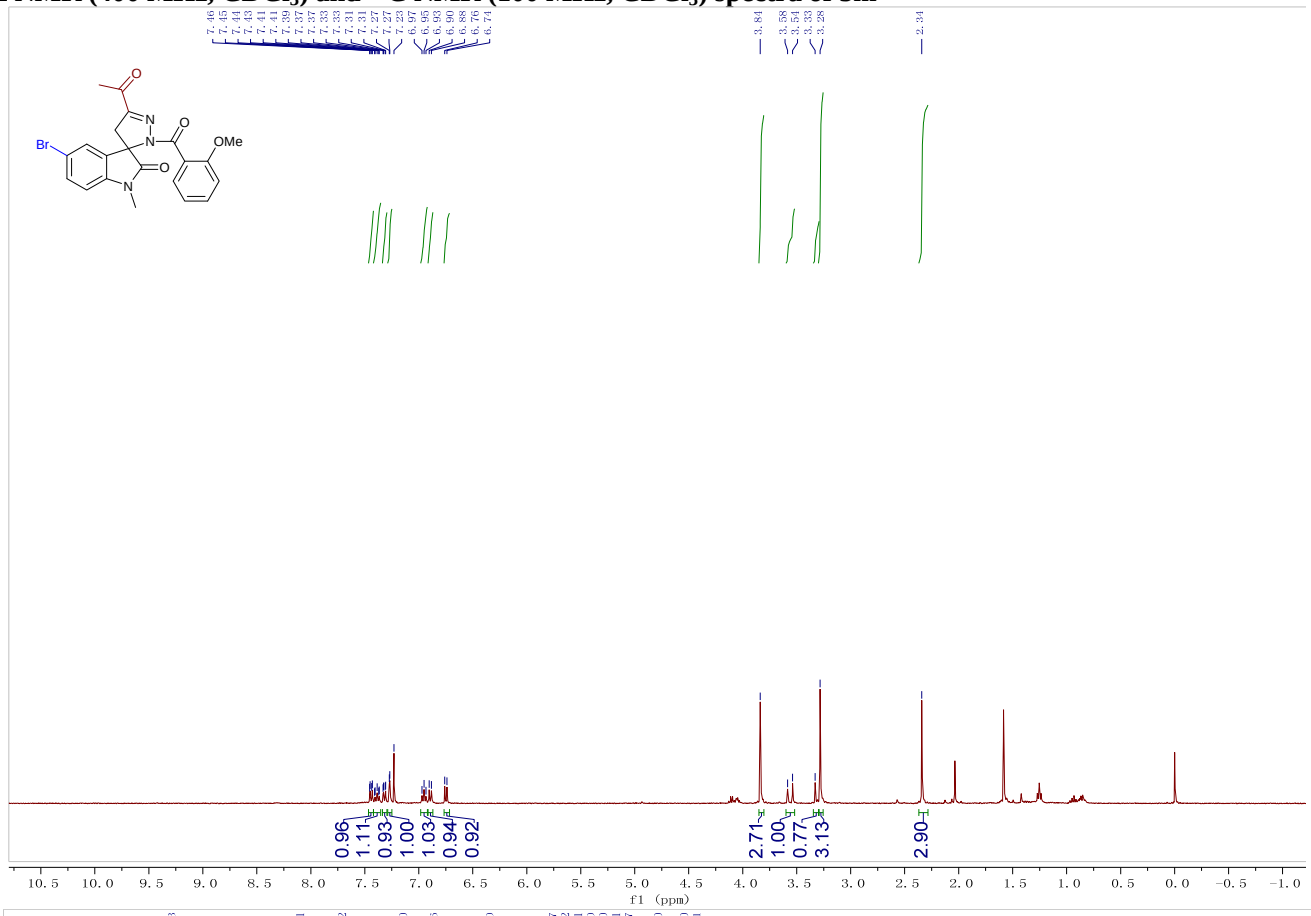


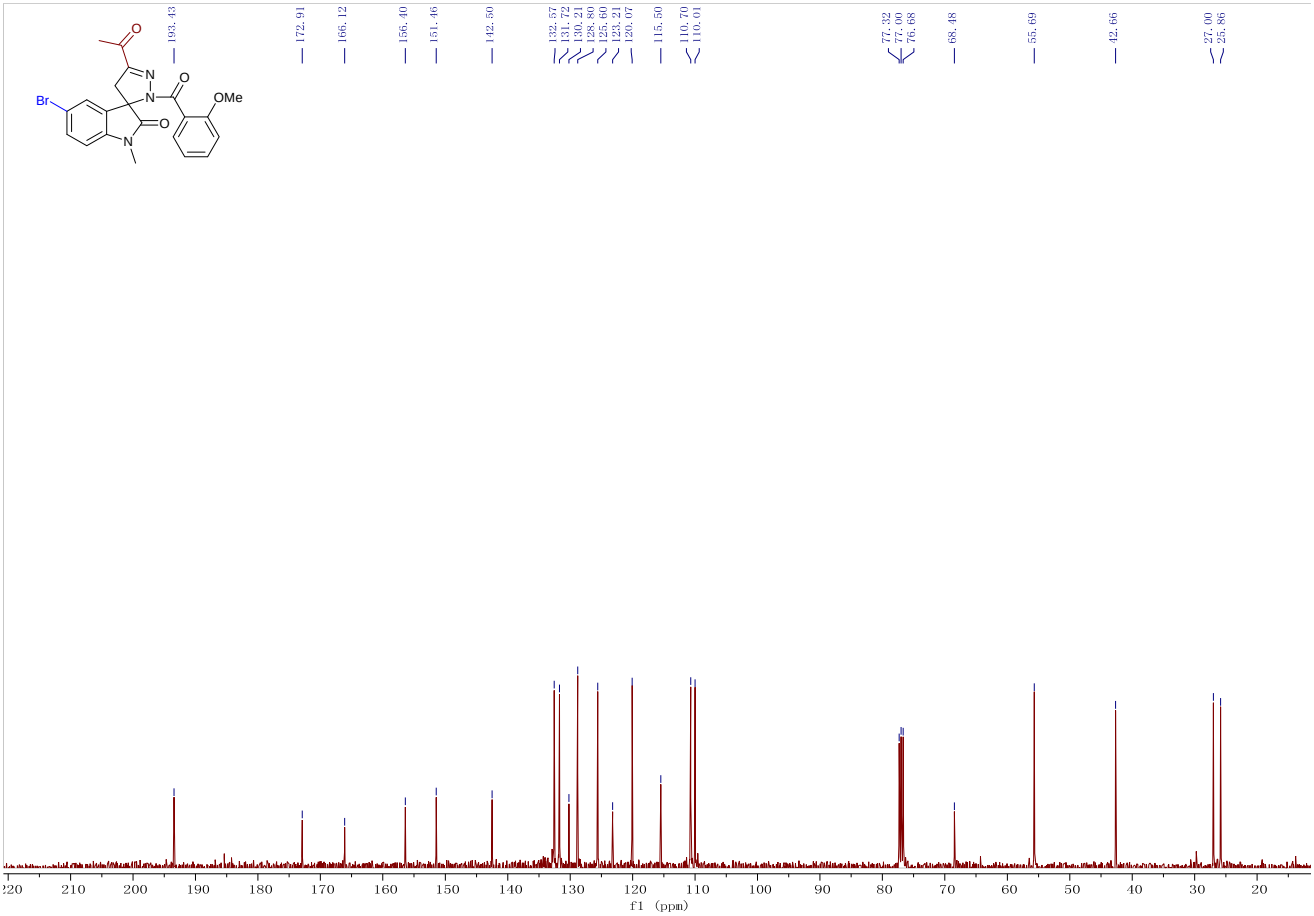
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3l



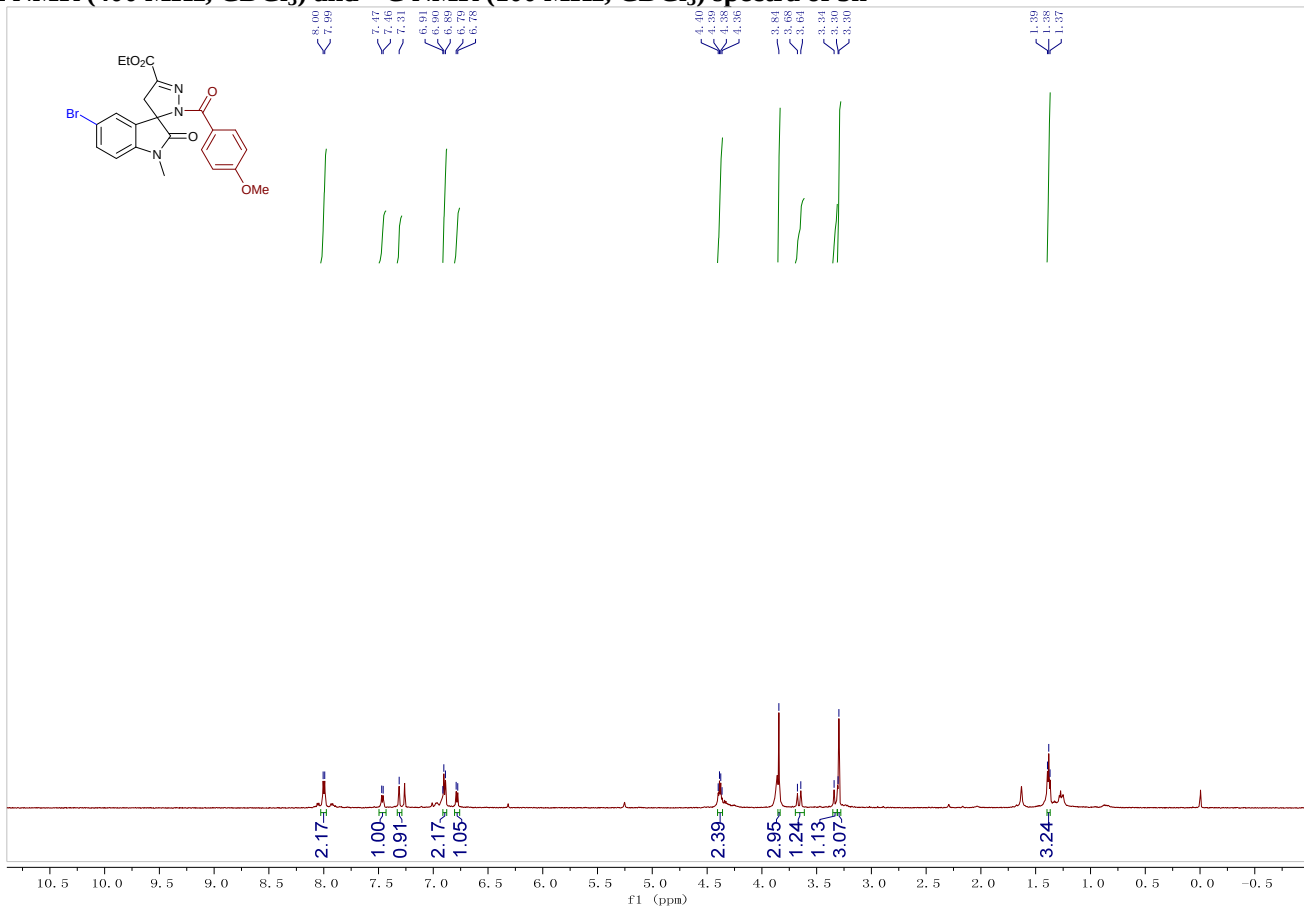


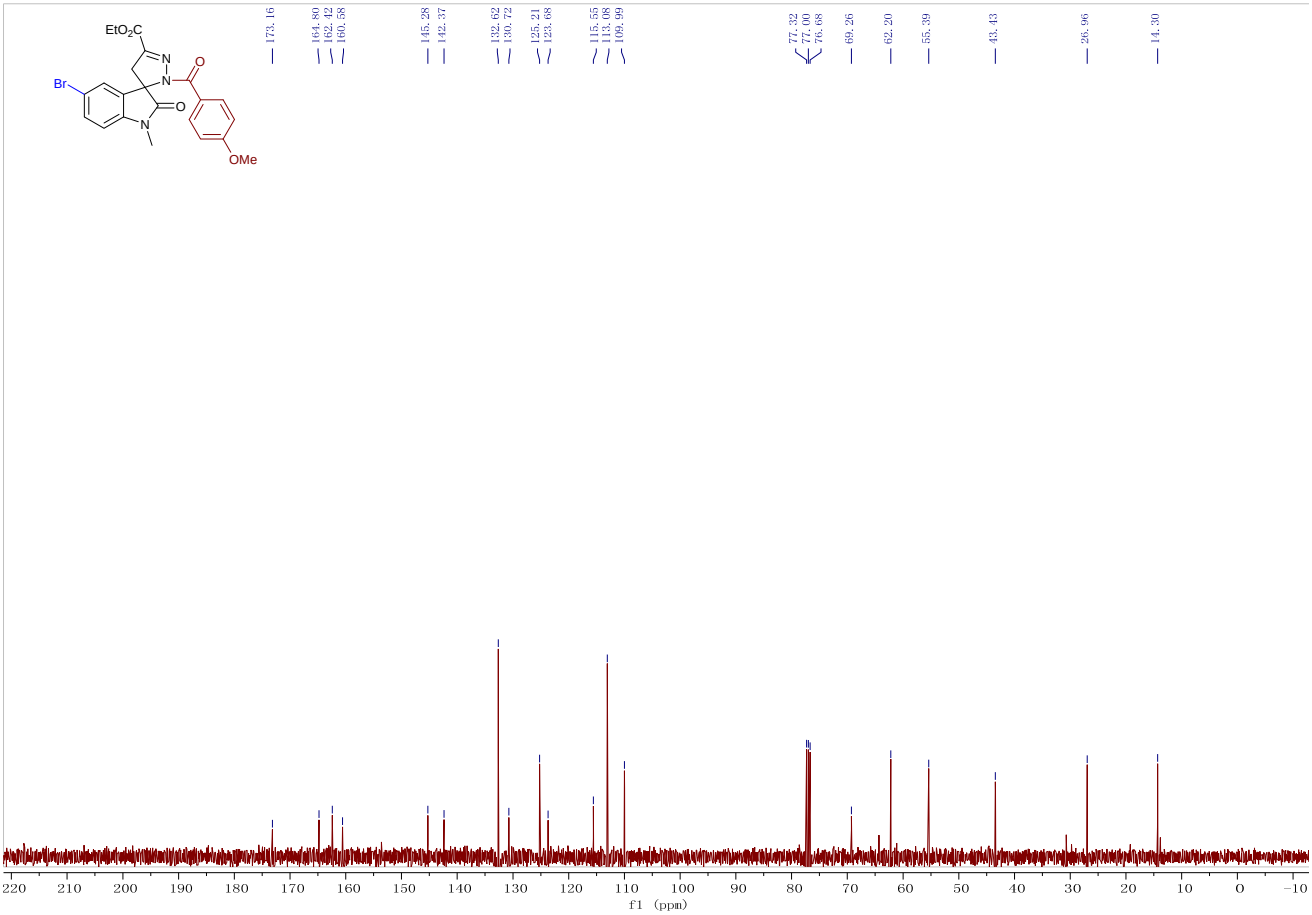
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3m



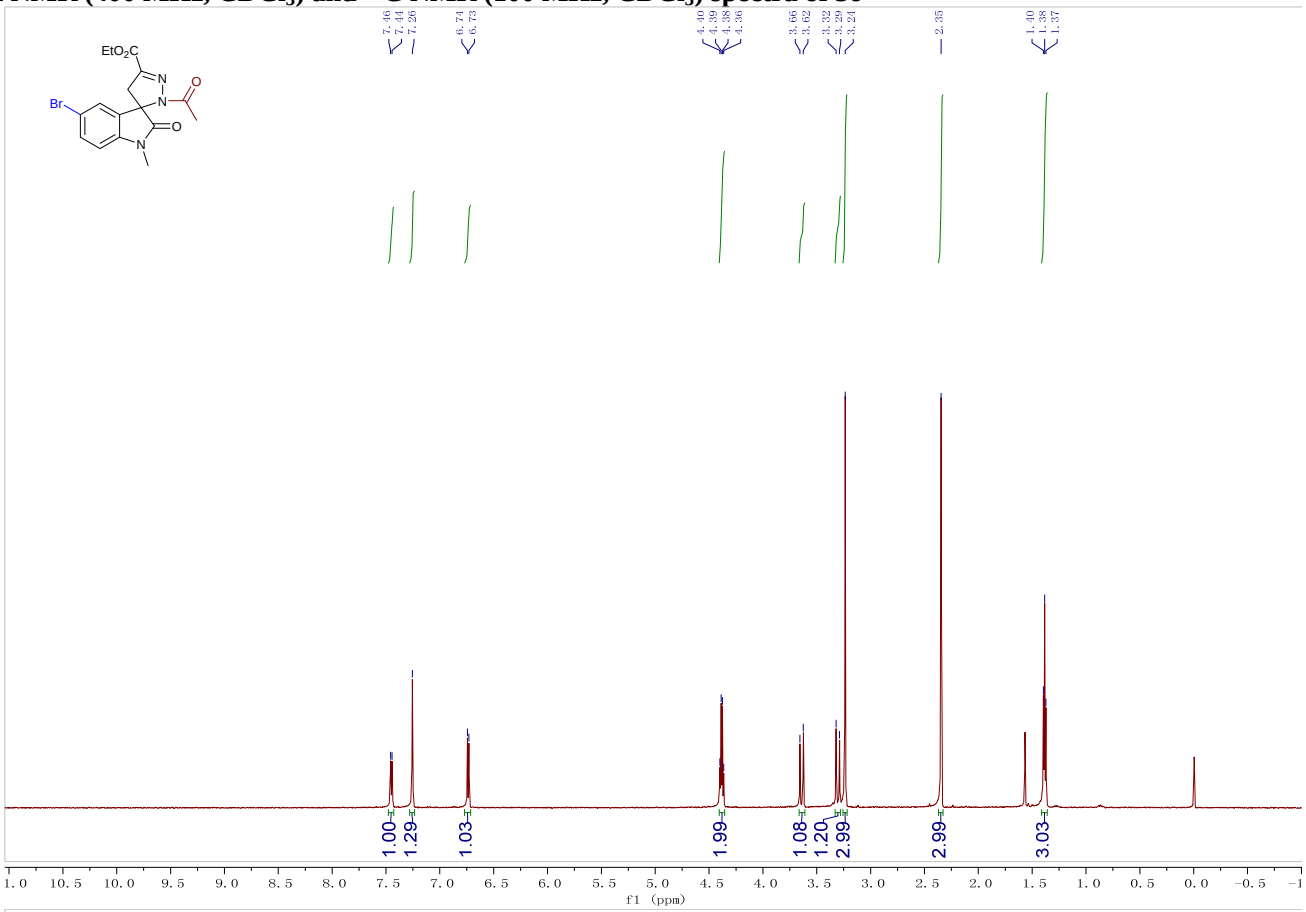


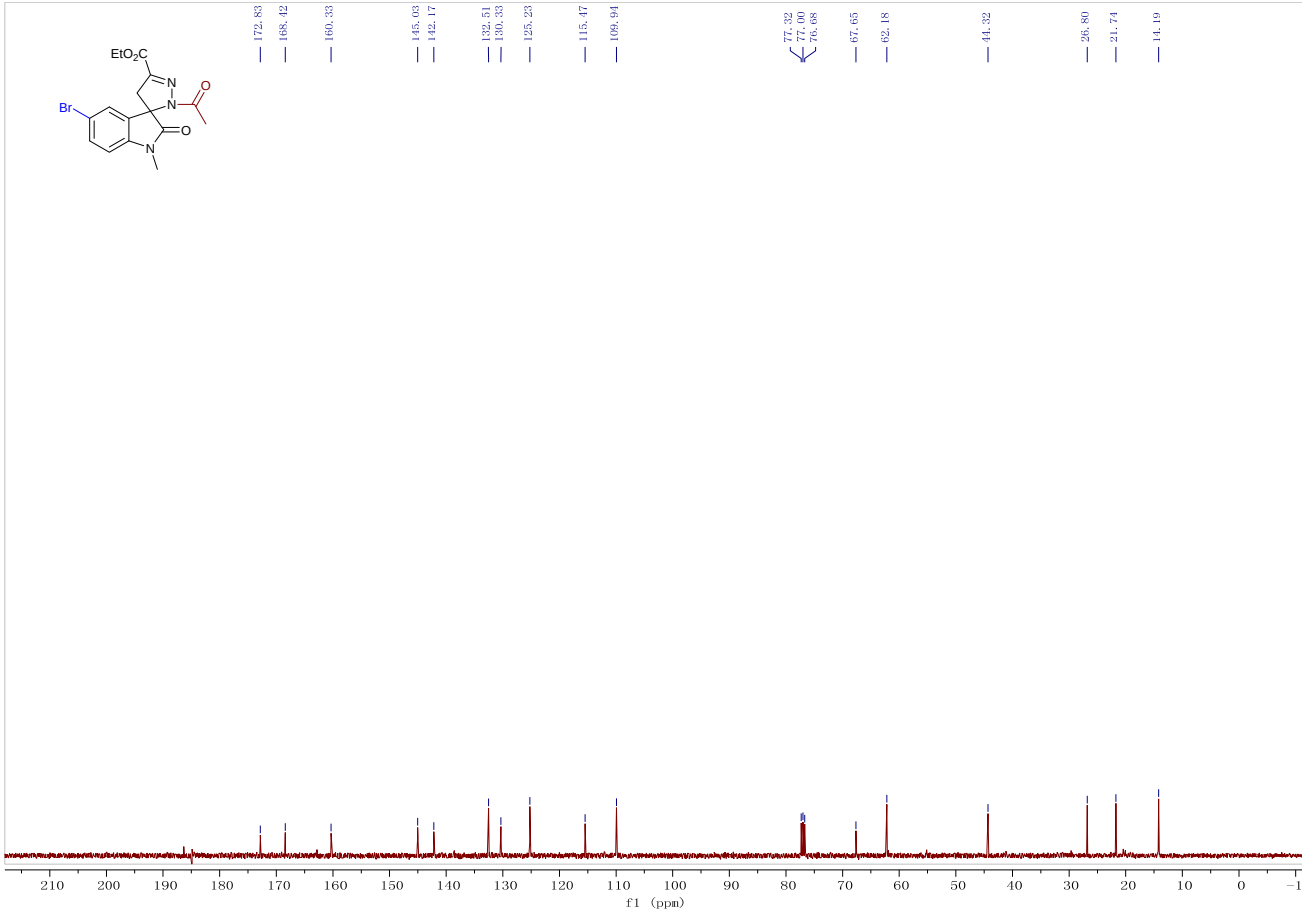
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3n





^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of 3o





^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of 6