Supporting Information

Palladium-Catalyzed Site-Selective Direct Olefination of 6- Electron-Withdrawing Group Substitued 3-Arylbenzo[*d*]isoxazoles

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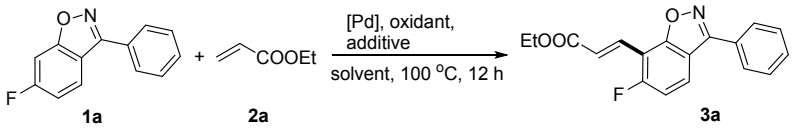
1. General Information

Unless otherwise indicated, all reagents were obtained from commercial sources and used as received without further purification. All solvents were only dried over 4 Å molecular sieves. Reaction products were purified *via* column chromatography on silica gel (300–400 mesh). Melting points were determined using an open capillaries and uncorrected. NMR spectra were determined on Bruker AV400 in $CDCl_3$ with TMS as internal standard for ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz), respectively. HRMS were measured on a QSTAR Pulsar I LC/TOF MS mass spectrometer or Micromass GCTTM gas chromatograph-mass spectrometer.

2. General Procedures and Characterization Data of the Products

2.1 Table 1 Optimization of the reaction conditions[a]



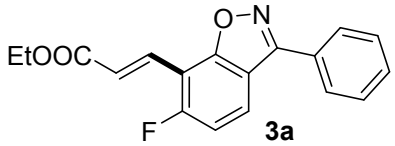
1a **2a** **3a**

Entry	Catalyst	Oxidant	Solvent	Additive	Yield[b]
1	$Pd(OAc)_2$	AgOAc	dioxane	–	42%
2	$Pd(OAc)_2$	AgOAc	DCE	–	23%
3	$Pd(OAc)_2$	AgOAc	*t*-AmyOH	–	16%
4	$Pd(OAc)_2$	AgOAc	TFA	–	0
5	$Pd(OAc)_2$	AgOAc	DMF	–	40%
6	$Pd(OAc)_2$	AgOAc	DMF/DMSO (9:1)	–	51%
7	$Pd(OAc)_2$	AgOAc	DMF/DMSO (9:1)	AcOH	32%
8	$Pd(OAc)_2$	AgOAc	DMF/DMSO (9:1)	PivOH	59%
9	$Pd(OAc)_2$	AgOAc	DMF/DMSO (9:1)	2-PBA	62%
10	$Pd(OAc)_2$	AgOAc	DMF/DMSO (9:1)	MesCOOH	65%
11	$Pd(OAc)_2$	AgOAc	DMF/DMSO (9:1)	EudCOOH	68%
12	$Pd(OAc)_2$	Ag_2CO_3	DMF/DMSO (9:1)	EudCOOH	61%
13	$Pd(OAc)_2$	Ag_3PO_4	DMF/DMSO (9:1)	EudCOOH	10%
14	**$Pd(OAc)_2$**	**Ag_2O**	**DMF/DMSO (9:1)**	**EudCOOH**	**74%**
15	$Pd(OAc)_2$	$Cu(OAc)_2$	DMF/DMSO (9:1)	EudCOOH	12%
16	$Pd(OAc)_2$	BQ	DMF/DMSO (9:1)	EudCOOH	8%
17	$PdCl_2$	Ag_2O	DMF/DMSO (9:1)	EudCOOH	42%
18	$Pd(PPh_3)_4$	Ag_2O	DMF/DMSO (9:1)	EudCOOH	57%
19	–	Ag_2O	DMF/DMSO (9:1)	EudCOOH	0
20	$Pd(OAc)_2$	–	DMF/DMSO (9:1)	EudCOOH	7%

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (10 mol%), oxidant (2.0 equiv), additive (3.0 equiv), solvent (2 mL), 100 ℃, 12 h. [b] Isolated yield of **3aa**. DCE = 1,2-dichloroethane; *t*-AmylOH = 2-methyl-2-butanol; PivOH = pivalic acid; 2-PBA = 2-phenylbenzoic acid; BQ = 1,4-benzoquinone; MesCOOH = 2,4,6-trimethylbenzoic acid; EudCOOH = 3,4,5-trimethoxybenzoic acid.

General procedure: A mixture of substrate **1a** (43 mg, 0.2 mmol), **2a** (43 μL, 0.94 g/mL, 0.4 mmol), Pd catalyst (10 mol %), oxidant (2.0 equiv) and additive (3.0 equiv) in solvent (2 mL) was stirred, and then the mixture was heated to 100 °C for 12 h. Upon completion of the reaction, to

the mixture were added saturated brine (20 mL) and dichloromethane (20 mL), then the aqueous layer was extracted with dichloromethane (20 mL × 2). The combined organic layer was dried over anhydrous $MgSO_4$. Finally, the solution was concentrated *in vacuo* to provide a crude product, which was further purified *via* a column chromatography on silica gel (eluents: petroleum ether/ethyl acetate = 20:1) to supply the product **3a**.

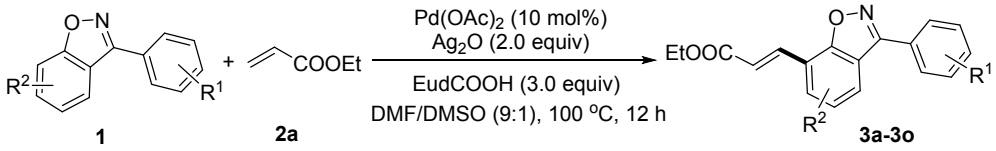


3a

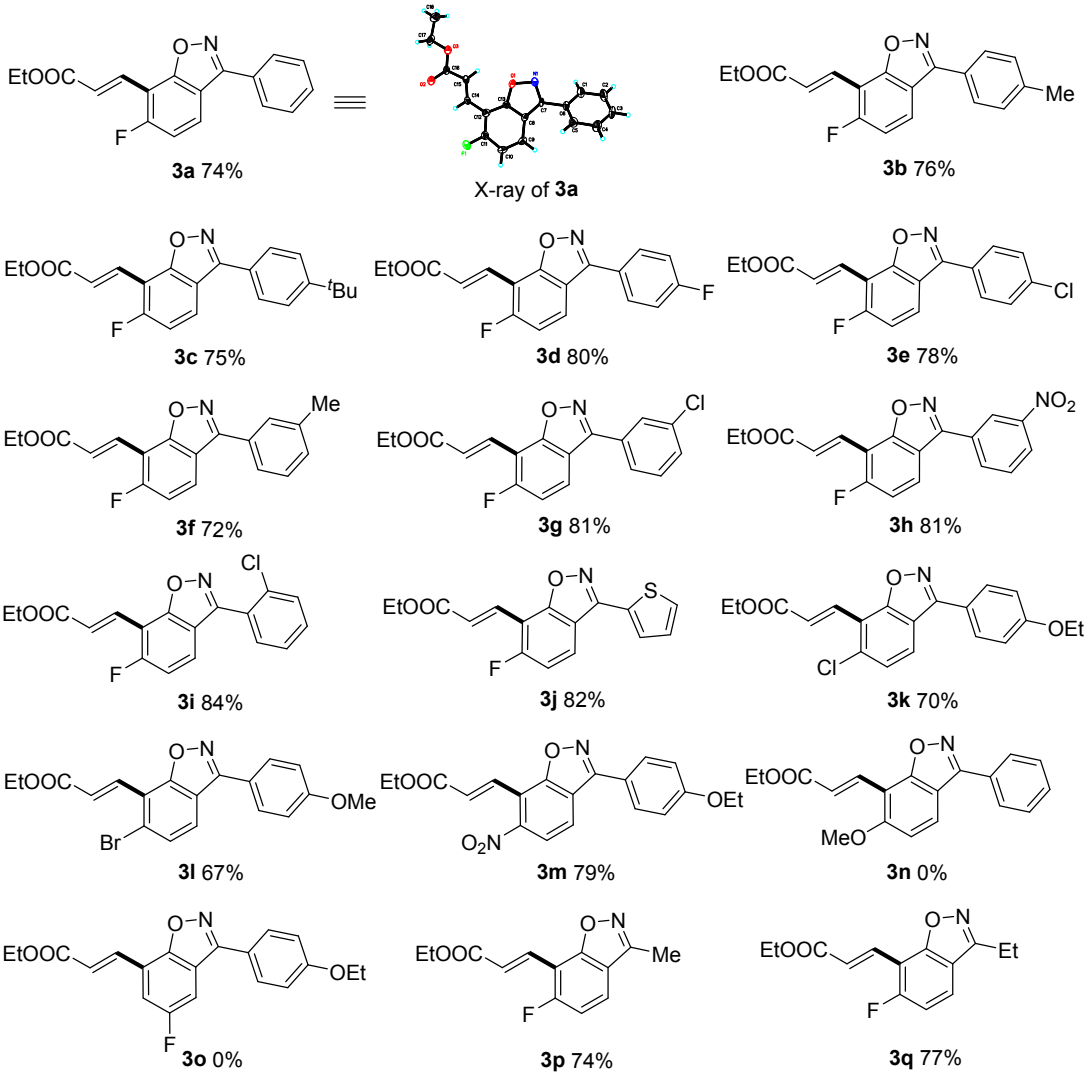
Ethyl (*E*)-3-(6-fluoro-3-phenylbenzo[*d*]isoxazol-7-yl)acrylate (3a): white solid, the best result: 46 mg (74% yield), m.p. 108–109 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.02 (d, J = 16.4 Hz, 1H), 7.92−7.90 (m, 2H), 7.84 (dd, J_1 = 8.8 Hz, J_2 = 4.8 Hz, 1H), 7.59−7.56 (m, 3H), 7.23 (d, J = 16.4 Hz, 1H), 7.20 (t, J = 8.8 Hz, 1H), 4.32 (q, J = 7.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.8, 162.7 (d, $^3J_{CF}$ = 8.0 Hz), 162.3 (d, $^1J_{CF}$ = 256.8 Hz), 157.4, 130.7, 130.4 (d, $^3J_{CF}$ = 4.5 Hz), 129.3 (2C), 128.2 (2C), 127.9, 125.1, 124.0 (d, $^3J_{CF}$ = 11.7 Hz), 117.8, 113.6 (d, $^2J_{CF}$ = 25.8 Hz), 107.9 (d, $^2J_{CF}$ = 16.5 Hz), 60.8, 14.3; HRMS (EI): *m/z* [M^+] calcd. for $C_{18}H_{14}FNO_3$: 311.0958; found: 311.0956.

2.2 Substrate scope of 3-arylbenzo[*d*]isoxazoles and alkenes

(1) **Table 2** Substrate scope of 3-arylbenzo[*d*]isoxazoles[a,b]

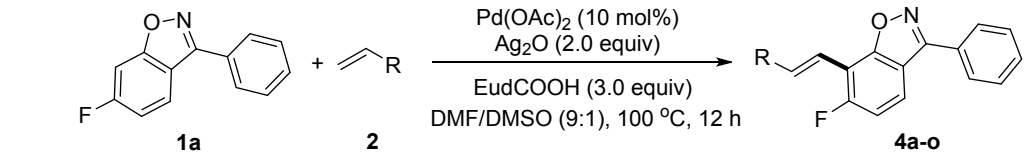


1 **2a** **3a-3o**

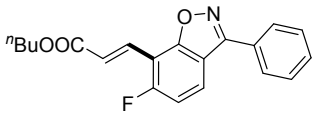


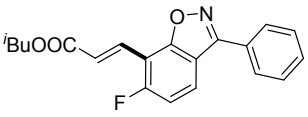
[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Pd(OAc)_2$ (10 mol%), Ag_2O (2.0 equiv), EudCOOH (3.0 equiv), DMF/DMSO (9:1, 2 mL), 100 ℃, 12 h. [b] Isolated yield.

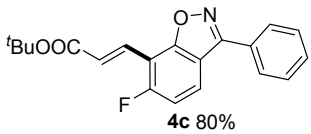
(2) **Table 3** Substrate scope of alkenes[a,b]

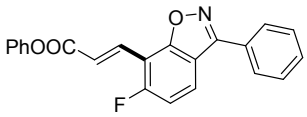


1a **2** **4a-o**

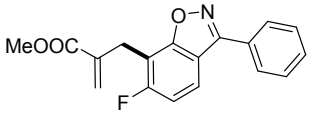

4a 78%


4b 81%


4c 80%


4d 70%


4e 76%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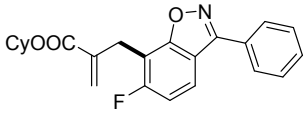
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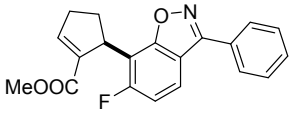
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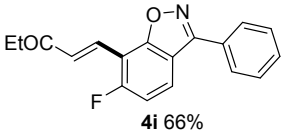
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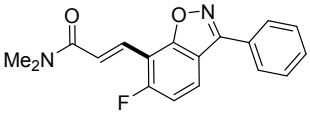
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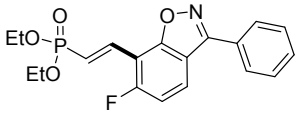
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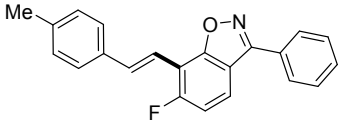
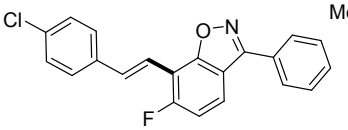
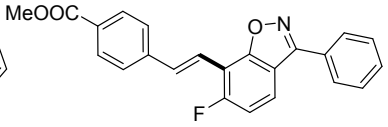
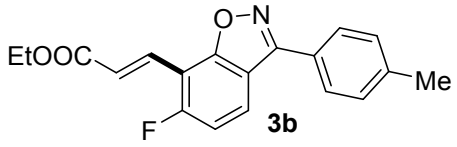

4m 66%


4n 77%


4o 83%

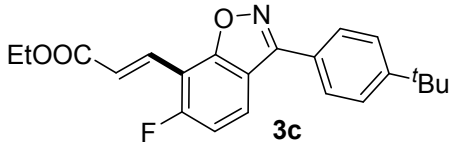
[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $Pd(OAc)_2$ (10 mol%), Ag_2O (2.0 equiv), EudCOOH (3.0 equiv), DMF/DMSO (9:1, 2 mL), 100 ℃, 12 h. [b] Isolated yield.

General procedure: A mixture of substrate **1** (0.2 mmol), **2** (0.4 mmol), $Pd(OAc)_2$ (4.5 mg, 10 mol %), Ag_2O (93 mg, 2.0 equiv) and EudCOOH (127 mg, 3.0 equiv) in DMF/DMSO (9:1, 2 mL) was stirred, and then the mixture was heated to 100 °C for 12 h. Upon completion of the reaction, to the mixture were added saturated brine (20 mL) and dichloromethane (20 mL), then the aqueous layer was extracted with dichloromethane (20 mL × 2). The combined organic layer was dried over anhydrous $MgSO_4$. Finally, the solution was concentrated *in vacuo* to provide a crude product, which was further purified *via* a column chromatography on silica gel (eluents: petroleum ether/ethyl acetate = 20:1) to supply the product **3** or **4**.


3b

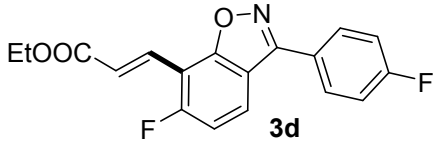
Ethyl (*E*)-3-(6-fluoro-3-(*p*-tolyl)benzo[*d*]isoxazol-7-yl)acrylate (3b): white solid, 49 mg (76% yield), m.p. 89–90 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.02 (d, J = 16.4 Hz, 1H), 7.84 (dd, J_1

= 8.4 Hz, J_2 = 4.8 Hz, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 16.4 Hz, 1H), 7.19 (t, J = 8.8 Hz, 1H), 4.32 (q, J = 7.2 Hz, 2H), 2.46 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.8, 162.6 (d, $^3J_{CF}$ = 8.1 Hz), 162.3 (d, $^1J_{CF}$ = 256.8 Hz), 157.3, 141.0, 130.4 (d, $^3J_{CF}$ = 4.5 Hz), 130.3 (2C), 128.0 (2C), 125.1, 124.9, 124.1 (d, $^3J_{CF}$ = 11.6 Hz), 117.9, 113.4 (d, $^2J_{CF}$ = 25.9 Hz), 107.9 (d, $^2J_{CF}$ = 16.4 Hz), 60.8, 21.5, 14.3; HRMS (EI): *m/z* [M^+] calcd. for $C_{19}H_{16}FNO_3$: 325.1114; found: 325.1113.



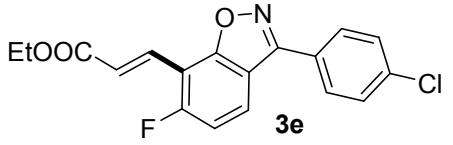
3c

Ethyl (*E*)-3-(3-(4-(*tert*-butyl)phenyl)-6-fluorobenzo[*d*]isoxazol-7-yl)acrylate (3c): white solid, 55 mg (75% yield), m.p. 91–92 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.02 (d, J = 16.4 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 16.4 Hz, 1H), 7.17 (d, J = 8.8 Hz, 1H), 4.32 (q, J = 7.2 Hz, 2H), 1.39 (s, 9H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.8, 162.6 (d, $^3J_{CF}$ = 8.1 Hz), 162.3 (d, $^1J_{CF}$ = 256.8 Hz), 157.2, 154.1, 130.4 (d, $^3J_{CF}$ = 4.5 Hz), 127.9 (2C), 126.3 (2C), 125.0, 124.9, 124.2 (d, $^3J_{CF}$ = 11.6 Hz), 117.9, 113.4 (d, $^2J_{CF}$ = 25.8 Hz), 107.8 (d, $^2J_{CF}$ = 16.6 Hz), 60.8, 35.0, 31.2 (3C), 14.3; HRMS (EI): *m/z* [M^+] calcd. for $C_{22}H_{22}FNO_3$: 367.1584; found: 367.1582.



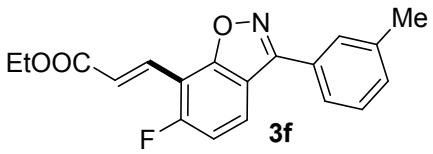
3d

Ehyl (*E*)-3-(6-fluoro-3-(4-fluorophenyl)benzo[*d*]isoxazol-7-yl)acrylate (3d): white solid, 53 mg (80% yield), m.p. 118–119 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.02 (d, J = 16.4 Hz, 1H), 7.90 (dd, J_1 = 8.8 Hz, J_2 = 5.2 Hz, 2H), 7.81 (dd, J_1 = 8.8 Hz, J_2 = 4.8 Hz, 1H), 7.28 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 16.4 Hz, 1H), 7.21 (t, J = 8.8 Hz, 1H), 4.32 (q, J = 7.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.7, 164.2 (d, $^1J_{CF}$ = 250.0 Hz), 162.7 (d, $^3J_{CF}$ = 8.0 Hz), 162.3 (d, $^1J_{CF}$ = 257.0 Hz), 156.5, 130.3 (d, $^3J_{CF}$ = 4.4 Hz), 130.1 (d, $^3J_{CF}$ = 8.1 Hz, 2C), 125.2 (d, $^3J_{CF}$ = 4.1 Hz), 124.0, 123.7 (d, $^3J_{CF}$ = 11.7 Hz), 117.6, 116.5 (d, $^2J_{CF}$ = 21.9 Hz, 2C), 113.7 (d, $^2J_{CF}$ = 25.9 Hz), 108.0 (d, $^2J_{CF}$ = 16.6 Hz), 60.9, 14.3; HRMS (EI): *m/z* [M^+] calcd. for $C_{18}H_{13}F_2NO_3$: 329.0863; found: 329.0864.



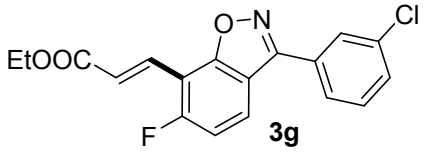
3e

Ethyl (*E*)-3-(3-(4-chlorophenyl)-6-fluorobenzo[*d*]isoxazol-7-yl)acrylate (3e): white solid, 54 mg (78% yield), m.p. 133–134 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.02 (d, J = 16.4 Hz, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.81 (dd, J_1 = 8.8 Hz, J_2 = 4.8 Hz, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 16.4 Hz, 1H), 7.21 (t, J = 8.8 Hz, 1H), 4.32 (q, J = 7.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.7, 162.8 (d, $^3J_{CF}$ = 8.0 Hz), 162.3 (d, $^1J_{CF}$ = 257.3 Hz), 156.4, 137.0, 130.2 (d, $^3J_{CF}$ = 4.4 Hz), 129.6 (2C), 129.4 (2C), 126.4, 125.3, 123.7 (d, $^3J_{CF}$ = 11.6 Hz), 117.5, 113.8 (d, $^2J_{CF}$ = 26.0 Hz), 108.0 (d, $^2J_{CF}$ = 16.7 Hz), 60.9, 14.3; HRMS (EI): *m/z* [M^+] calcd. for $C_{18}H_{13}ClFNO_3$: 345.0568; found: 345.0566.



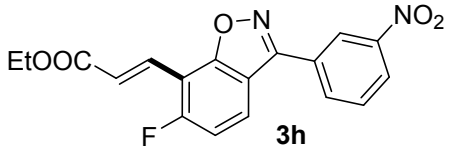
3f

Ethyl (*E*)-3-(6-fluoro-3-(*m*-tolyl)benzo[*d*]isoxazol-7-yl)acrylate (3f): white solid, 47 mg (72% yield), m.p. 85–86 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.02 (d, J = 16.4 Hz, 1H), 7.84 (dd, J_1 = 8.8 Hz, J_2 = 4.8 Hz, 1H), 7.72 (s, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.22 (d, J = 16.4 Hz, 1H), 7.19 (t, J = 8.8 Hz, 1H), 4.32 (q, J = 7.2 Hz, 2H), 2.48 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.8, 162.7 (d, $^3J_{CF}$ = 8.1 Hz), 162.3 (d, $^1J_{CF}$ = 256.8 Hz), 157.5, 139.2, 131.5, 130.4 (d, $^3J_{CF}$ = 4.6 Hz), 129.2, 128.7, 127.7, 125.3, 125.0, 124.1 (d, $^3J_{CF}$ = 11.6 Hz), 117.8, 113.5 (d, $^2J_{CF}$ = 26.0 Hz), 107.8 (d, $^2J_{CF}$ = 16.7 Hz), 6.8, 21.5, 14.7. HRMS (EI): *m/z* [M^+] calcd. for $C_{19}H_{16}FNO_3$: 325.1114; found: 325.1115.



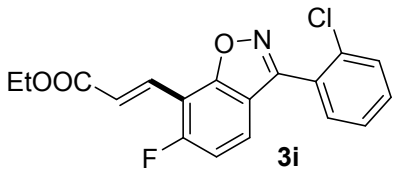
3g

Ethyl (*E*)-3-(3-(3-chlorophenyl)-6-fluorobenzo[*d*]isoxazol-7-yl)acrylate (3g): white solid, 56 mg (81% yield), m.p. 93–94 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.02 (d, J = 16.4 Hz, 1H), 7.90 (s, 1H), 7.83 (dd, J_1 = 8.8 Hz, J_2 = 4.8 Hz, 1H), 7.80 (d, J = 7.2 Hz, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.23 (t, J = 8.8 Hz, 1H), 7.22 (d, J = 16.4 Hz, 1H), 4.32 (q, J = 7.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.7, 162.8 (d, $^3J_{CF}$ = 8.1 Hz), 162.3 (d, $^1J_{CF}$ = 257.4 Hz), 156.2, 135.3, 130.8, 130.6, 130.2 (d, $^3J_{CF}$ = 4.4 Hz), 129.6, 128.1, 126.3, 125.3, 123.6 (d, $^3J_{CF}$ = 11.6 Hz), 117.4, 113.9 (d, $^2J_{CF}$ = 26.1 Hz), 108.1 (d, $^2J_{CF}$ = 16.5 Hz), 60.9, 14.3; HRMS (EI): *m/z* [M^+] calcd. for $C_{18}H_{13}ClFNO_3$: 345.0568; found: 345.0565.



3h

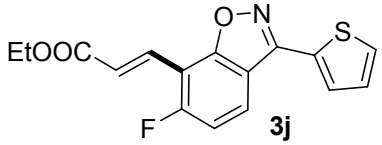
Ethyl (*E*)-3-(6-fluoro-3-(3-nitrophenyl)benzo[*d*]isoxazol-7-yl)acrylate (3h): yellow solid, 58 mg (81% yield), m.p. 143–144 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.79 (s, 1H), 8.44 (d, J = 8.0 Hz, 1H), 8.29 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 16.4 Hz, 1H), 7.87 (dd, J_1 = 8.4 Hz, J_2 = 4.8 Hz, 1H), 7.80 (t, J = 8.0 Hz, 1H), 7.29 (t, J = 8.8 Hz, 1H), 7.23 (d, J = 16.4 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 1.39 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.6, 163.0 (d, $^3J_{CF}$ = 8.0 Hz), 162.5 (d, $^1J_{CF}$ = 258.1 Hz), 155.5, 148.7, 133.9, 130.6, 130.0 (d, $^3J_{CF}$ = 4.3 Hz), 129.7, 125.6, 125.3, 123.2 (d, $^3J_{CF}$ = 11.0 Hz), 123., 117.0, 114.4 (d, $^2J_{CF}$ = 26.1 Hz), 108.3 (d, $^2J_{CF}$ = 16.8 Hz), 61.0, 14.3; HRMS (EI): *m/z* [M^+] calcd. for $C_{18}H_{13}FN_2O_5$: 356.0808; found: 356.0810.



3i

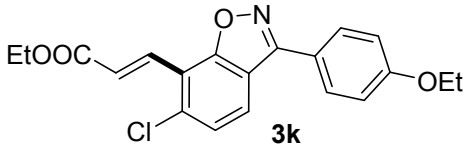
Ethyl (*E*)-3-(3-(2-chlorophenyl)-6-fluorobenzo[*d*]isoxazol-7-yl)acrylate (3i): yellow solid, 58 mg (84% yield), m.p. 125–126 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.08 (d, J = 16.0 Hz, 1H), 7.68−7.63 (m, 2H), 7.62 (dd, J_1 = 8.8 Hz, J_2 = 4.8 Hz, 1H), 7.52 (dt, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H),

7.48 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H), 7.43 (d, J = 16.0 Hz, 1H), 6.93 (t, J = 8.8 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 167.2, 164.5, 162.5 (d, $^1J_{CF}$ = 261.1 Hz), 156.1 (d, $^3J_{CF}$ = 7.8 Hz), 133.0, 132.2, 131.7, 131.1 (d, $^3J_{CF}$ = 5.2 Hz), 131.0, 127.3, 126.5, 125.2, 125.1, 117.4 (d, $^2J_{CF}$ = 31.1 Hz), 114.8, 108.0 (d, $^2J_{CF}$ = 14.6 Hz), 60.6, 14.3; HRMS (EI): *m/z* [M^+] calcd. for $C_{18}H_{13}ClFNO_3$: 345.0568; found: 345.0569.



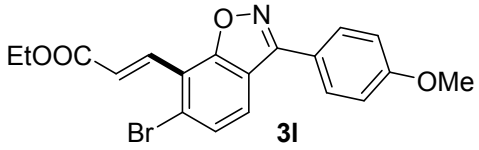
3j

Ethyl (*E*)-3-(6-fluoro-3-(thiophen-2-yl)benzo[*d*]isoxazol-7-yl)acrylate (3j): white solid, 52 mg (82% yield), m.p. 136–137 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.92 (dd, J_1 = 8.8 Hz, J_2 = 4.8 Hz, 1H), 7.78 (d, J = 15.6 Hz, 1H), 7.71 (d, J = 3.6 Hz, 1H), 7.36−7.33 (m, 2H), 7.19 (dt, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 1H), 6.36 (d, J = 15.6 Hz, 1H), 4.28 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.4, 164.5 (d, $^3J_{CF}$ = 13.4 Hz), 164.3 (d, $^1J_{CF}$ = 250.8 Hz), 151.6, 142.1, 136.1, 131.5, 131.1, 128.9, 122.7 (d, $^3J_{CF}$ = 10.9 Hz), 119.1, 116.3, 113.6 (d, $^2J_{CF}$ = 25.2 Hz), 97.7 (d, $^2J_{CF}$ = 26.6 Hz), 60.8, 14.3; HRMS (EI): *m/z* [M^+] calcd. for $C_{16}H_{12}SFNO_3$: 317.0522; found: 317.0520.



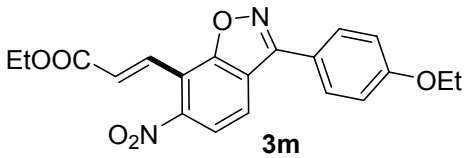
3k

Ethyl (*E*)-3-(6-chloro-3-(4-ethoxyphenyl)benzo[*d*]isoxazol-7-yl)acrylate (3k): white solid, 52 mg (70% yield), m.p. 148–149 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.16 (d, J = 16.4 Hz, 1H), 7.83 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 16.4 Hz, 1H), 7.06 (d, J = 8.8 Hz, 2H), 4.32 (q, J = 7.2 Hz, 2H), 4.11 (q, J = 6.8 Hz, 2H), 1.47 (t, J = 6.8 Hz, 3H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.9, 162.7, 161.0, 156.9, 137.4, 134.5, 129.5 (2C), 126.3, 126.1, 123.4, 120.4, 120.0, 117.7, 115.2 (2C), 63.7, 60.9, 14.8, 14.3; HRMS (EI): *m/z* [M^+] calcd. for $C_{20}H_{18}ClNO_4$: 371.0924; found: 371.0925.



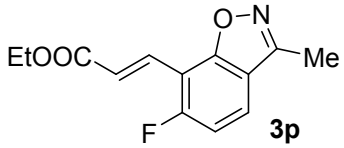
3l

Ethyl (*E*)-3-(6-bromo-3-(4-methoxyphenyl)benzo[*d*]isoxazol-7-yl)acrylate (3l): white solid, 54 mg (67% yield), m.p. 169–170℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.13 (d, J = 16.0 Hz, 1H), 7.85 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 16.0 Hz, 1H), 7.08 (d, J = 8.8 Hz, 2H), 4.32 (q, J = 7.2 Hz, 2H), 3.90 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.9, 162.6, 161.6, 157.0, 137.2, 129.6 (2C), 129.5, 128.1, 126.4, 123.6, 121.0, 120.1, 119.4, 114.8 (2C), 60.9, 55.5, 14.3; HRMS (EI): *m/z* [M^+] calcd. for $C_{19}H_{16}BrNO_4$: 401.0263; found: 401.0267.



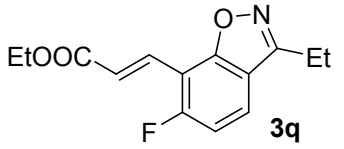
3m

Ethyl (*E*)-3-(3-(4-ethoxyphenyl)-6-nitrobenzo[*d*]isoxazol-7-yl)acrylate (3m): yellow solid, 60 mg (79% yield), m.p. 152–153 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.02 (d, J = 16.0 Hz, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.86 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 16.0 Hz, 1H), 7.10 (d, J = 8.8 Hz, 2H), 4.33 (q, J = 7.2 Hz, 2H), 4.14 (q, J = 7.2 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.0, 161.5, 161.3, 157.3, 149.5, 131.9, 129.6 (2C), 128.9, 124.3, 123.3, 120.5, 119.1, 115.4 (2C), 114.5, 63.8, 61.2, 14.7, 14.3; HRMS (EI): *m/z* [M^+] calcd. for $C_{20}H_{18}N_2O_6$: 382.165; found: 382.1166.



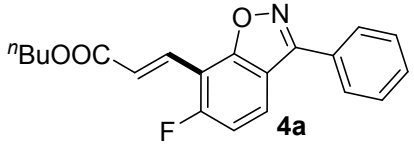
3p

Ethyl (*E*)-3-(6-fluoro-3-methylbenzo[*d*]isoxazol-7-yl)acrylate (3p): white solid, 37 mg (74% yield), m.p. 66–68 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.97 (d, J = 16.4 Hz, 1H), 7.56 (dd, J_1 = 8.8 Hz, J_2 = 4.8 Hz, 1H), 7.16 (d, J = 16.4 Hz, 1H), 7.13 (t, J = 8.8 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 2.59 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.8, 162.4 (d, $^1J_{CF}$ = 256.1 Hz), 161.8 (d, $^3J_{CF}$ = 8.2 Hz), 155.1, 130.5 (d, $^3J_{CF}$ = 4.9 Hz), 125.0, 123.0 (d, $^3J_{CF}$ = 11.7 Hz), 119.5, 112.9 (d, $^2J_{CF}$ = 26.0 Hz), 107.8 (d, $^2J_{CF}$ = 14.7 Hz), 60.8, 14.3, 9.8; HRMS (EI): *m/z* [M^+] calcd. for $C_{13}H_{12}FNO_3$: 249.0801; found: 249.0799.



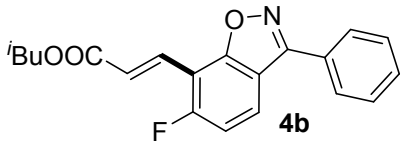
3q

Ethyl (*E*)-3-(3-ethyl-6-fluorobenzo[*d*]isoxazol-7-yl)acrylate (3q): white solid, 41 mg (77% yield), m.p. 72–74 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.97 (d, J = 16.4 Hz, 1H), 7.59 (dd, J_1 = 8.4 Hz, J_2 = 4.8 Hz, 1H), 7.16 (d, J = 16.4 Hz, 1H), 7.11 (t, J = 8.4 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 3.01 (q, J = 7.6 Hz, 2H), 1.45 (t, J = 7.6 Hz, 3H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.8, 162.3 (d, $^1J_{CF}$ = 256.1 Hz), 161.9 (d, $^3J_{CF}$ = 8.1 Hz), 159.7, 130.5 (d, $^3J_{CF}$ = 4.8 Hz), 124.9, 123.0 (d, $^3J_{CF}$ = 11.7 Hz), 118.7, 112.8 (d, $^2J_{CF}$ = 26.2 Hz), 107.8 (d, $^2J_{CF}$ = 16.6 Hz), 60.8, 18.7, 14.3, 12.1; HRMS (EI): *m/z* [M^+] calcd. for $C_{14}H_{14}FNO_3$: 263.0958; found: 263.0957.



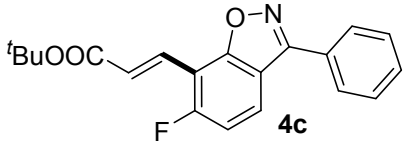
4a

Butyl (*E*)-3-(6-fluoro-3-phenylbenzo[*d*]isoxazol-7-yl)acrylate (4a): white solid, 53 mg (78% yield), m.p. 64–65 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.02 (d, J = 16.0 Hz, 1H), 7.92−7.90 (m, 2H), 7.85 (dd, J_1 = 8.4 Hz, J_2 = 4.8 Hz, 1H), 7.60−7.56 (m, 3H), 7.24 (d, J = 16.0 Hz, 1H), 7.20 (t, J = 8.8 Hz, 1H), 4.27 (t, J = 6.8 Hz, 2H), 1.73 (quint, J = 6.8 Hz, 2H), 1.47 (m, 2H), 0.99 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.9, 162.7 (d, $^3J_{CF}$ = 8.2 Hz), 162.3 (d, $^1J_{CF}$ = 257.1 Hz), 157.4, 130.7, 130.3 (d, $^3J_{CF}$ = 4.7 Hz), 129.3 (2C), 128.2 (2C), 127.9, 125.1, 124.0 (d, $^3J_{CF}$ = 11.7 Hz), 117.8, 113.6 (d, $^2J_{CF}$ = 25.9 Hz), 107.9 (d, $^2J_{CF}$ = 16.6 Hz), 64.7, 30.7, 19.2, 13.8; HRMS (EI): *m/z* [M^+] calcd. for $C_{20}H_{18}FNO_3$: 339.1271; found: 339.1270.



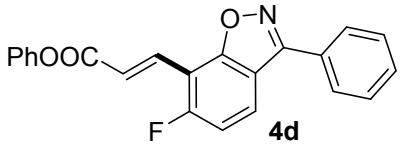
4b

Isobutyl (*E*)-3-(6-fluoro-3-phenylbenzo[*d*]isoxazol-7-yl)acrylate (4b): white solid, 55 mg (81% yield), m.p. 87–88 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.03 (d, J = 16.4 Hz, 1H), 7.92−7.90 (m, 2H), 7.85 (dd, J_1 = 8.8 Hz, J_2 = 4.8 Hz, 1H), 7.60−7.56 (m, 3H), 7.25 (d, J = 16.4 Hz, 1H), 7.20 (t, J = 8.8 Hz, 1H), 4.04 (q, J = 6.8 Hz, 2H), 2.11−2.10 (m, 1H), 1.01 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.9, 162.7 (d, $^3J_{CF}$ = 8.0 Hz), 162.3 (d, $^1J_{CF}$ = 256.9 Hz), 157.4, 130.7, 130.4 (d, $^3J_{CF}$ = 4.6 Hz), 129.3 (2C), 128.2 (2C), 127.9, 125.1, 124.0 (d, $^3J_{CF}$ = 11.6 Hz), 117.8, 113.6 (d, $^2J_{CF}$ = 25.8 Hz), 107.9 (d, $^2J_{CF}$ = 16.5 Hz), 71.0, 27.8, 19.2 (2C); HRMS (EI): *m/z* [M^+] calcd. for $C_{20}H_{18}FNO_3$: 339.1271; found: 339.1269.



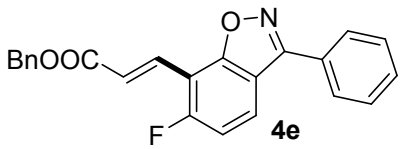
4c

***tert*-Butyl (*E*)-3-(6-fluoro-3-phenylbenzo[*d*]isoxazol-7-yl)acrylate (4c)**: white solid, 54 mg (80% yield), m.p. 148–149 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.93 (d, J = 16.4 Hz, 1H), 7.92−7.90 (m, 2H), 7.83 (dd, J_1 = 8.4 Hz, J_2 = 4.8 Hz, 1H), 7.59−7.57 (m, 3H), 7.20 (d, J = 16.4 Hz, 1H), 7.17 (t, J = 8.8 Hz, 1H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.1, 162.7 (d, $^3J_{CF}$ = 8.2 Hz), 162.2 (d, $^1J_{CF}$ = 256.6 Hz), 157.3, 130.7, 129.3, 129.2 (2C), 128.2 (2C), 127.9, 127.1, 123.7 (d, $^3J_{CF}$ = 11.6 Hz), 117.7, 113.6 (d, $^2J_{CF}$ = 26.1 Hz), 108.1 (d, $^2J_{CF}$ = 16.7 Hz), 81.0, 28.2 (3C); HRMS (EI): *m/z* [M^+] calcd. for $C_{20}H_{18}FNO_3$: 339.1271; found: 339.1270.



4d

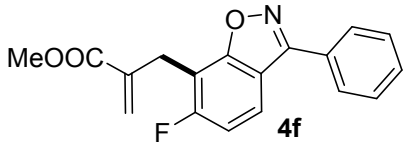
Phenyl (*E*)-3-(6-fluoro-3-phenylbenzo[*d*]isoxazol-7-yl)acrylate (4d): white solid, 50 mg (70% yield), m.p. 151–152 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.21 (d, J = 16.4 Hz, 1H), 7.94−7.91 (m, 2H), 7.90 (dd, J_1 = 8.8 Hz, J_2 = 4.8 Hz, 1H), 7.60−7.58 (m, 3H), 7.44 (d, J = 16.4 Hz, 1H), 7.43 (t, J = 8.4 Hz, 2H), 7.28 (d, J = 7.2 Hz, 1H), 7.24−7.22 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 165.2, 162.8 (d, $^3J_{CF}$ = 8.0 Hz), 162.5 (d, $^1J_{CF}$ = 257.9 Hz), 157.5, 150.8, 132.3 (d, $^3J_{CF}$ = 4.6 Hz), 130.8, 129.5 (2C), 129.3 (2C), 128.2 (2C), 127.8, 125.9, 124.6 (d, $^3J_{CF}$ = 11.7 Hz), 124.1, 121.6 (2C), 117.9, 113.6 (d, $^2J_{CF}$ = 25.9 Hz), 107.7 (d, $^2J_{CF}$ = 16.3 Hz); HRMS (EI): *m/z* [M^+] calcd. for $C_{22}H_{14}FNO_3$: 359.0958; found: 359.0961.



4e

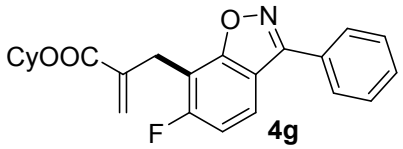
Benzyl (*E*)-3-(6-fluoro-3-phenylbenzo[*d*]isoxazol-7-yl)acrylate (4e): white solid, 57 mg (76% yield), m.p. 149–150 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.07 (d, J = 16.4 Hz, 1H), 7.92−7.89 (m, 2H), 7.85 (dd, J_1 = 8.8 Hz, J_2 = 4.8 Hz, 1H), 7.59−7.56 (m, 3H), 7.46 (d, J = 6.8 Hz, 2H), 7.41 (t, J = 6.8 Hz, 2H), 7.36 (d, J = 7.2 Hz, 1H), 7.28 (d, J = 16.4 Hz, 1H), 7.20 (t, J = 8.8 Hz, 1H), 5.32 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.6, 163.7 (d, $^3J_{CF}$ = 7.9 Hz), 162.3

(d, $^1J_{CF}$ = 263.1 Hz), 157.4, 135.9, 131.0 (d, $^3J_{CF}$ = 4.6 Hz), 130.9, 130.7, 129.2 (2C), 128.6 (2C), 128.3 (2C), 128.2 (2C), 127.9, 124.7, 124.2 (d, $^3J_{CF}$ = 11.6 Hz), 117.8, 113.6 (d, $^2J_{CF}$ = 20.8 Hz), 107.8 (d, $^2J_{CF}$ = 16.6 Hz), 66.6; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{23}H_{16}FNO_3$: 373.1114; found: 373.1113.



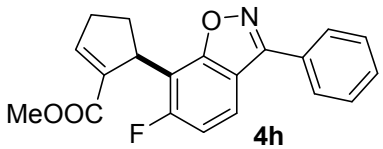
4f

Methyl 2-((6-fluoro-3-phenylbenzo[*d*]isoxazol-7-yl)methyl)acrylate (4f): white solid, 44 mg (71% yield), m.p. 39–40 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.93−7.90 (m, 2H), 7.76 (dd, J_1 = 8.8 Hz, J_2 = 4.8 Hz, 1H), 7.58−7.55 (m, 3H), 7.16 (t, J = 8.8 Hz, 1H), 6.31 (s, 1H), 5.50 (s, 1H), 4.01 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.9, 163.7 (d, $^3J_{CF}$ = 10.2 Hz), 162.0 (d, $^1J_{CF}$ = 249.5 Hz), 157.5, 136.5, 130.4, 129.2 (2C), 128.5, 128.1 (2C), 126.6, 121.1 (d, $^3J_{CF}$ = 11.2 Hz), 116.9, 113.4 (d, $^2J_{CF}$ = 26.1 Hz), 109.0 (d, $^2J_{CF}$ = 21.4 Hz), 52.1, 25.7; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{18}H_{14}FNO_3$: 311.0958; found: 311.0960.



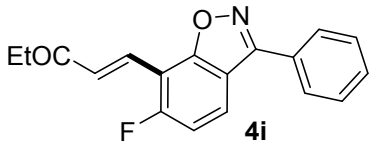
4g

Cyclohexyl 2-((6-fluoro-3-phenylbenzo[*d*]isoxazol-7-yl)methyl)acrylate (4g): yellow solid, 52 mg (69% yield), m.p. 88–89 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.93−7.90 (m, 2H), 7.75 (dd, J_1 = 8.8 Hz, J_2 = 4.8 Hz, 1H), 7.56−7.55 (m, 3H), 7.15 (t, J = 8.8 Hz, 1H), 6.31 (s, 1H), 5.49 (s, 1H), 4.88−4.82 (m, 1H), 4.00 (s, 2H), 1.87−1.70 (m, 4H), 1.54−1.25 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 165.8, 163.7 (d, $^3J_{CF}$ = 10.4 Hz), 162.0 (d, $^1J_{CF}$ = 249.4 Hz), 157.5, 137.2, 130.4, 129.2 (2C), 128.5, 128.1 (2C), 126.3, 121.0 (d, $^3J_{CF}$ = 11.1 Hz), 116.9, 113.4 (d, $^2J_{CF}$ = 26.3 Hz), 109.3 (d, $^2J_{CF}$ = 21.6 Hz), 73.3, 31.5 (2C), 25.8, 25.4, 23.7 (2C); HRMS (EI): *m/z* [M$^+$] calcd. for $C_{23}H_{22}FNO_3$: 379.1584; found: 379.1586.



4h

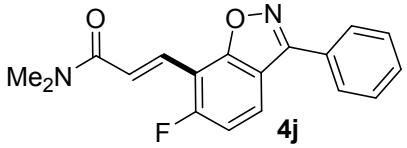
Methyl 2-(6-fluoro-3-phenylbenzo[*d*]isoxazol-7-yl)cyclopent-2-ene-1-carboxylate (4h): yellow oil, 42 mg (63% yield), ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.91−7.89 (m, 2H), 7.68 (dd, J_1 = 8.4 Hz, J_2 = 4.8 Hz, 1H), 7.56−7.54 (m, 3H), 7.12 (t, J = 8.8 Hz, 1H), 7.08−7.07 (m, 1H), 4.81 (t, J = 8.4 Hz, 1H), 3.59 (s, 3H), 3.08−3.01 (m, 1H), 2.73−2.59 (m, 2H), 2.23−2.14 (m, 1H) ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 164.8, 163.1 (d, $^3J_{CF}$ = 10.1 Hz), 161.4 (d, $^1J_{CF}$ = 248.5 Hz), 157.3, 146.0, 135.8, 130.3, 129.2 (2C), 128.6, 128.1 (2C), 120.4 (d, $^3J_{CF}$ = 11.4 Hz), 117.1, 115.3 (d, $^2J_{CF}$ = 18.9 Hz), 113.5 (d, $^2J_{CF}$ = 27.0 Hz), 51.4, 39.6, 32.9, 30.7; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{20}H_{16}FNO_3$: 337.1114; found: 337.1111.



4i

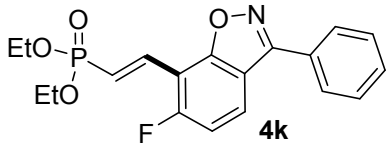
(*E*)-1-(6-Fluoro-3-phenylbenzo[*d*]isoxazol-7-yl)pent-1-en-3-one (4i): yellow solid, 39 mg (66%

yield), m.p. 136–137 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.91 (d, J = 16.4 Hz, 1H), 7.92−7.90 (m, 2H), 7.85 (dd, J_1 = 8.8 Hz, J_2 = 4.8 Hz, 1H), 7.59−7.57 (m, 3H), 7.53 (d, J = 16.4 Hz, 1H), 7.20 (t, J = 8.8 Hz, 1H), 2.77 (q, J = 7.2 Hz, 2H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 200.8, 162.7 (d, $^3J_{CF}$ = 8.0 Hz), 162.6 (d, $^1J_{CF}$ = 256.9 Hz), 157.4, 131.6 (d, $^3J_{CF}$ = 4.7 Hz), 130.7, 129.3 (2C), 128.2 (2C), 127.9, 127.7, 124.1 (d, $^3J_{CF}$ = 11.6 Hz), 117.8, 113.7 (d, $^2J_{CF}$ = 26.0 Hz), 108.2 (d, $^2J_{CF}$ = 16.5 Hz), 35.3, 8.1; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{18}H_{14}FNO_2$: 295.1009; found: 295.1008.



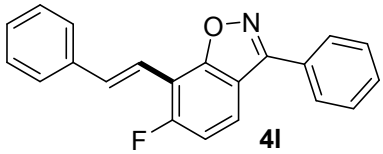
4j

(*E*)-3-(6-Fluoro-3-phenylbenzo[*d*]isoxazol-7-yl)-*N*,*N*-dimethylacrylamide (4j): white solid, 42 mg (68% yield), m.p. 195–196 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.00 (d, J = 15.6 Hz, 1H), 7.91−7.90 (m, 2H), 7.82 (dd, J_1 = 8.8 Hz, J_2 = 4.8 Hz, 1H), 7.73 (d, J = 15.6 Hz, 1H), 7.59−7.57 (m, 3H), 7.19 (t, J = 8.8 Hz, 1H), 3.27 (s, 3H), 3.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.4, 162.7 (d, $^3J_{CF}$ = 8.1 Hz), 162.2 (d, $^1J_{CF}$ = 256.5 Hz), 157.4, 130.7, 129.3 (2C), 128.2 (2C), 128.1, 127.9, 124.3, 123.2 (d, $^3J_{CF}$ = 11.5 Hz), 117.6, 113.7 (d, $^2J_{CF}$ = 26.1 Hz), 108.1 (d, $^2J_{CF}$ = 16.7 Hz), 37.5, 36.0; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{18}H_{15}FN_2O_2$: 310.1118; found: 310.1119.



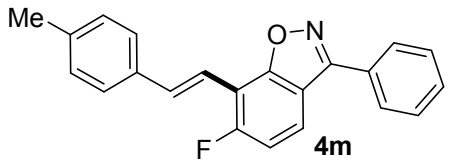
4k

Diethyl (*E*)-(2-(6-fluoro-3-phenylbenzo[*d*]isoxazol-7-yl)vinyl)phosphonate (4k): white solid, 43 mg (57% yield), m.p. 83–85 ℃; ^{1}H NMR (400 MHz, CDCl3, ppm): δ 7.91−7.89 (m, 2H), 7.85 (dd, J_1 = 8.4 Hz, J_2 = 4.8 Hz, 1H), 7.81 (d, J = 18.0 Hz, 1H), 7.59−7.56 (m, 3H), 7.20 (t, J = 8.4 Hz, 1H), 7.11 (d, J = 18.0 Hz, 1H), 4.23−4.16 (m, 4H), 1.39 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 162.6 (d, $^3J_{CF}$ = 8.0 Hz), 162.0 (d, $^1J_{CF}$ = 256.9 Hz), 157.4, 134.4 (dd, $^2J_{CP}$ = 7.4 Hz, $^3J_{CF}$ = 5.3 Hz), 130.7, 129.3 (2C), 128.2 (2C), 127.8, 124.1 (d, $^3J_{CF}$ = 11.6 Hz), 122.3 (d, $^1J_{CP}$ = 186.0 Hz), 117.9, 113.7 (d, $^2J_{CF}$ = 26.1 Hz), 108.4 (dd, $^2J_{CF}$ = 25.1 Hz, $^3J_{CP}$ = 8.9 Hz), 62.1 (d, $^2J_{CP}$ = 5.3 Hz, 2C), 16.4 (d, $^3J_{CP}$ = 6.3 Hz, 2C); HRMS (EI): *m/z* [M$^+$] calcd. for $C_{19}H_{19}NO_4PF$: 375.1036; found: 375.1031.



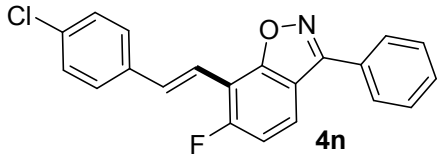
4l

(*E*)-6-fluoro-3-phenyl-7-styrylbenzo[*d*]isoxazole (4l): white solid, 43 mg (68% yield), m.p. 148−150 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.97 (d, J = 16.4 Hz, 1H), 7.95−7.93 (m, 2H), 7.71 (dd, J_1 = 8.8 Hz, J_2 = 4.8 Hz, 1H), 7.65 (d, J = 7.6 Hz, 2H), 7.60−7.58 (m, 3H), 7.44−7.40 (m, 2H), 7.43 (d, J = 16.4 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.19 (t, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 162.4 (d, $^3J_{CF}$ = 8.9 Hz), 161.0 (d, $^1J_{CF}$ = 252.0 Hz), 157.4, 137.3, 136.0, 130.5, 129.2 (2C), 128.8 (2C), 128.5, 128.4, 128.2 (2C), 126.9 (2C), 120.7, 117.5, 115.1, 113.6 (d, $^2J_{CF}$ = 26.4 Hz), 110.5 (d, $^2J_{CF}$ = 16.6 Hz); HRMS (EI): *m/z* [M$^+$] calcd. for $C_{21}H_{14}FNO$: 315.1059; found: 315.1060.



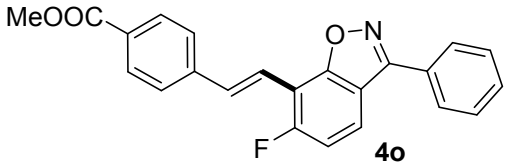
4m

(*E*)-6-fluoro-7-(4-methylstyryl)-3-phenylbenzo[d]isoxazole (4m): white solid, 43 mg (66% yield), m.p. 124−126 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.95−7.92 (m, 2H), 7.94 (d, J = 16.8 Hz, 1H), 7.68 (dd, J_1 = 8.4 Hz, J_2 = 4.8 Hz, 1H), 7.60−7.57 (m, 3H), 7.55 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 16.8 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.17 (t, J = 8.8 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 162.4 (d, $^{3}J_{CF}$ = 8.9 Hz), 160.9 (d, $^{1}J_{CF}$ = 251.7 Hz), 157.3, 138.5, 136.0, 134.5, 130.5, 129.5 (2C), 129.2 (2C), 128.4, 128.2 (2C), 126.9 (2C), 120.3 (d, $^{3}J_{CF}$ = 11.2 Hz), 117.5, 114.0, 113.6 (d, $^{2}J_{CF}$ = 26.3 Hz), 110.6 (d, $^{2}J_{CF}$ = 16.6 Hz), 21.4; HRMS (EI): *m/z* [M^+] calcd. for $C_{22}H_{16}FNO$: 329.1216; found: 329.1217.



4n

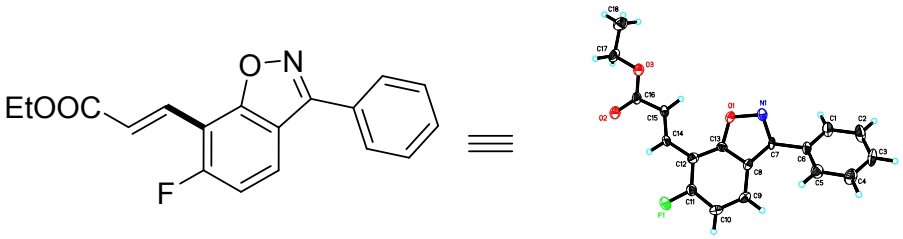
(*E*)-7-(4-chlorostyryl)-6-fluoro-3-phenylbenzo[*d*]isoxazole (4n): yellow solid, 54 mg (77% yield), m.p. 182−184 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.95−7.92 (m, 2H), 7.91 (d, J = 16.8 Hz, 1H), 7.72 (dd, J_1 = 8.8 Hz, J_2 = 4.8 Hz, 1H), 7.60−7.58 (m, 3H), 7.56 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 16.8 Hz, 1H), 7.38 (d, J = 8.4 Hz, 2H), 7.18 (t, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 162.3 (d, $^{3}J_{CF}$ = 8.8 Hz), 161.0 (d, $^{1}J_{CF}$ = 252.5 Hz), 157.4, 135.7, 134.6, 134.1, 130.6, 129.3 (2C), 129.0 (2C), 128.3, 128.2 (2C), 128.1 (2C), 121.0 (d, $^{3}J_{CF}$ = 11.3 Hz), 117.6, 115.6, 113.6 (d, $^{2}J_{CF}$ = 26.3 Hz), 110.1 (d, $^{2}J_{CF}$ = 16.5 Hz); HRMS (EI): *m/z* [M^+] calcd. for $C_{21}H_{13}FClNO$: 349.0670; found: 349.0672.



4o

Methyl (*E*)-4-(2-(6-fluoro-3-phenylbenzo[*d*]isoxazol-7-yl)vinyl)benzoate (4o): yellow solid, 62 mg (83% yield), m.p. 208−210 ℃; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.08 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 16.8 Hz, 1H), 7.95−7.92 (m, 2H), 7.75 (dd, J_1 = 8.8 Hz, J_2 = 4.8 Hz, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.60−7.58 (m, 3H), 7.53 (d, J = 16.8 Hz, 1H), 7.20 (t, J = 8.8 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.8, 162.4 (d, $^{3}J_{CF}$ = 8.7 Hz), 161.2 (d, $^{1}J_{CF}$ = 253.0 Hz), 157.4, 141.6, 134.75, 134.71, 130.6, 130.1 (2C), 129.6, 129.3 (2C), 128.2 (2C), 126.7 (2C), 121.4 (d, $^{3}J_{CF}$ = 11.3 Hz), 117.6, 117.4, 113.6 (d, $^{2}J_{CF}$ = 26.3 Hz), 110.0 (d, $^{2}J_{CF}$ = 16.6 Hz), 52.2; HRMS (EI): *m/z* [M^+] calcd. for $C_{23}H_{16}FNO_3$: 373.1114; found: 373.1115.

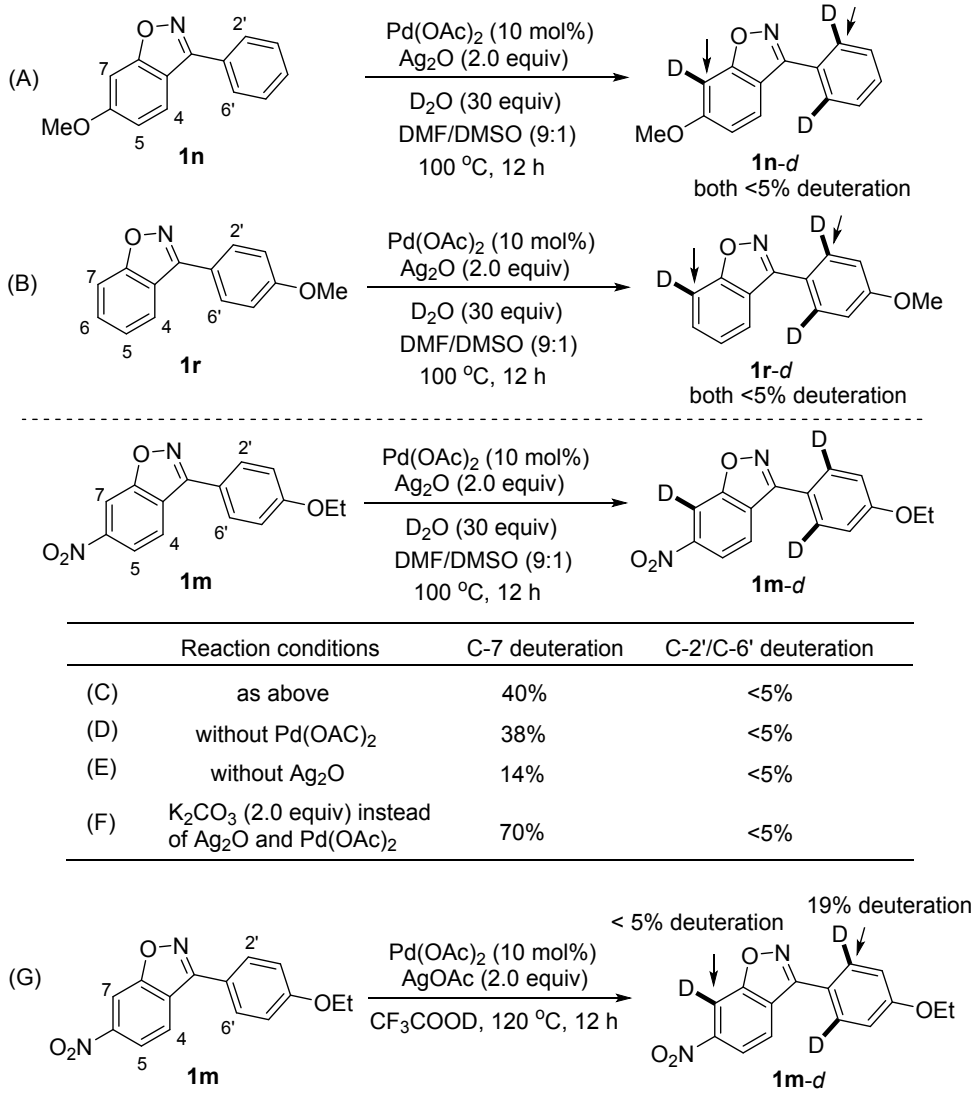
2.3 Single crystal structure of 3a



3a X-ray of **3a**

Identification code	cd17297	
Empirical formula	C18 H14 F N O3	
Formula weight	311.30	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P 1	
Unit cell dimensions	a = 7.5115(19) Å	α= 79.433(4)°.
	b = 13.839(4) Å	β= 89.551(5)°.
	c = 14.941(4) Å	γ = 89.948(5)°.
Volume	1526.7(7) $Å^3$	
Z	4	
Density (calculated)	1.354 Mg/m^3	
Absorption coefficient	0.101 mm^{-1}	
F(000)	648	
Crystal size	0.200 x 0.100 x 0.050 mm^3	
Theta range for data collection	1.497 to 25.000°.	
Index ranges	-8<=h<=8, -16<=k<=16, -14<=l<=17	
Reflections collected	8493	
Independent reflections	6735 [R(int) = 0.0300]	
Completeness to theta = 25.242°	98.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7456 and 0.5272	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6735 / 3 / 834	
Goodness-of-fit on F^2	1.036	
Final R indices [I>2sigma(I)]	R1 = 0.0659, wR2 = 0.1673	
R indices (all data)	R1 = 0.0788, wR2 = 0.1826	
Absolute structure parameter	1.6(10)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.366 and -0.476 $e.Å^{-3}$	

3. Deuterium Incorporation Studies (Scheme 2)



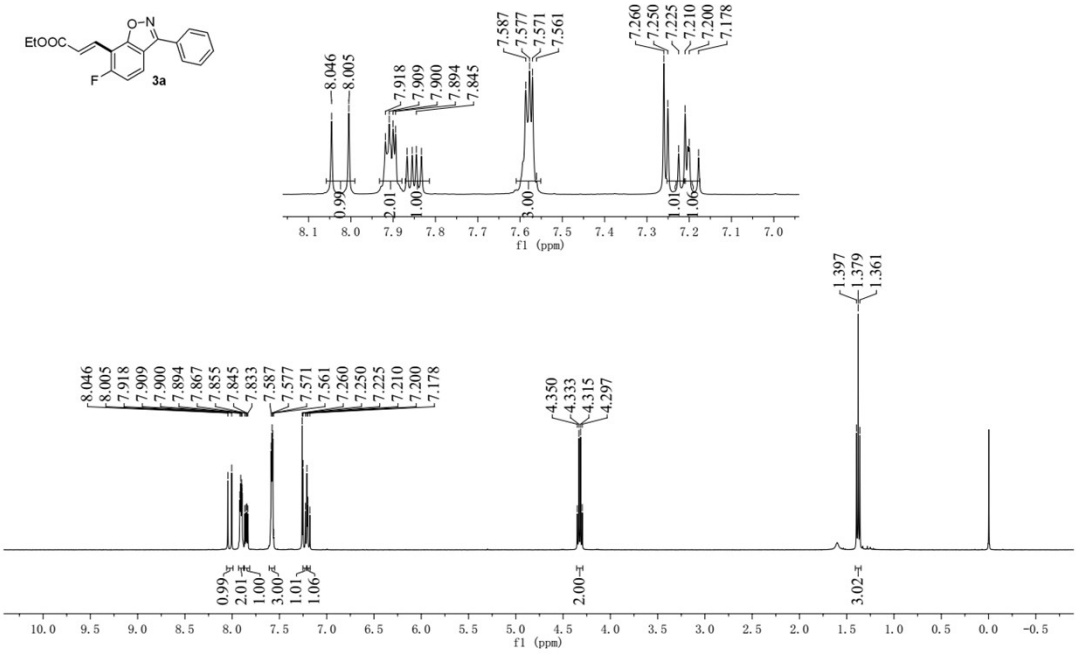
	Reaction conditions	C-7 deuteration	C-2'/C-6' deuteration
(C)	as above	40%	<5%
(D)	without $Pd(OAC)_2$	38%	<5%
(E)	without Ag_2O	14%	<5%
(F)	K_2CO_3 (2.0 equiv) instead of Ag_2O and $Pd(OAc)_2$	70%	<5%

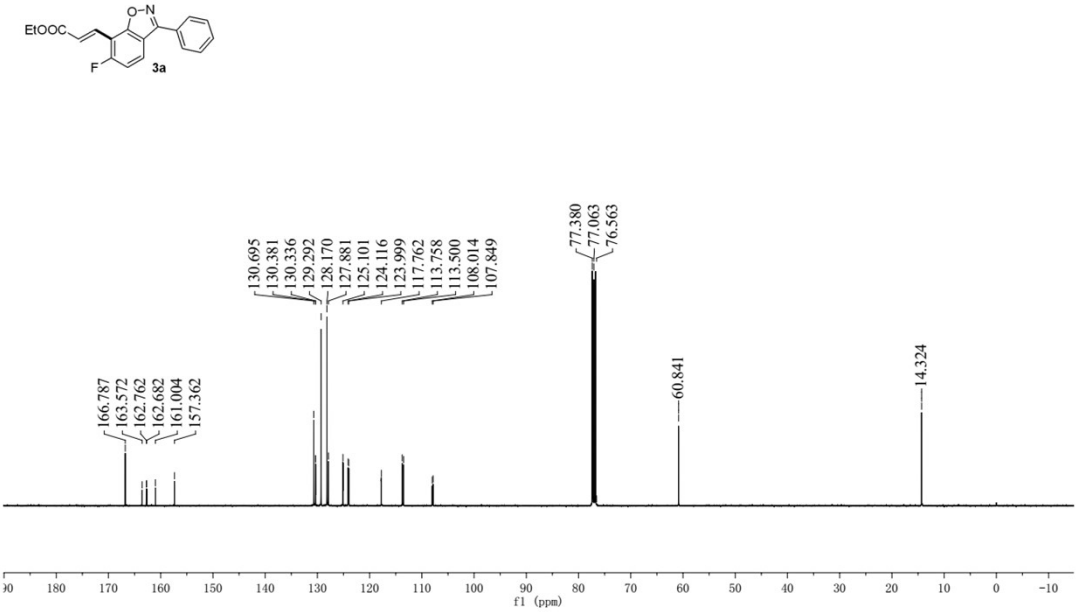
Scheme 2 Deuterium incorporation studies.

General procedure: A mixture of substrate **1** (0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 10 mol %), Ag_2O (93 mg, 2.0 equiv), K_2CO_3 (55 mg, 2.0 equiv) and D_2O (0.46 mL, 1.493 g/mL, 6.0 mmol) in DMF/DMSO (9:1, 2 mL) or CF_3COOD (2 mL) was stirred, and then the mixture was heated to 100 °C for 12 h. Upon completion of the reaction, to the mixture were added saturated brine (20 mL) and dichloromethane (20 mL), then the aqueous layer was extracted with dichloromethane (20 mL × 2). The combined organic layer was dried over anhydrous $MgSO_4$. Finally, the solution was concentrated *in vacuo* to provide a crude product, which was further purified *via* a column chromatography on silica gel (eluents: petroleum ether/ethyl acetate = 20:1) to recover the substrate **1**. The deuterations were analyzed by ^1H NMR, see: 4.2 Copies of the spectra for Scheme 2.

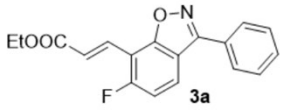
4. All Copies of Spectra

4.1 Copies of the spectra for Tables 2 and 3





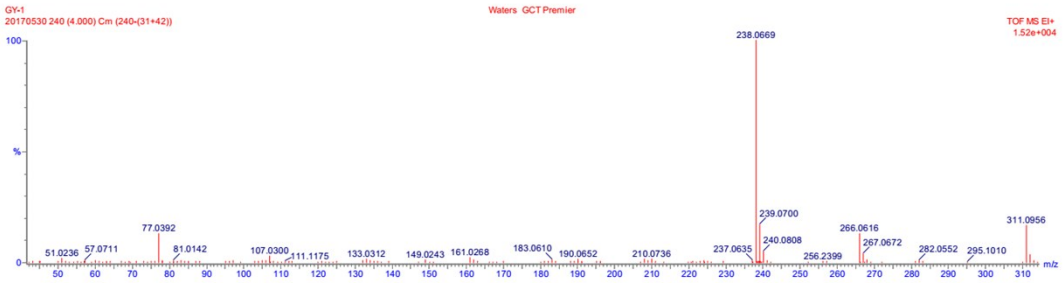
Elemental Composition Report



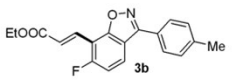
Single Mass Analysis

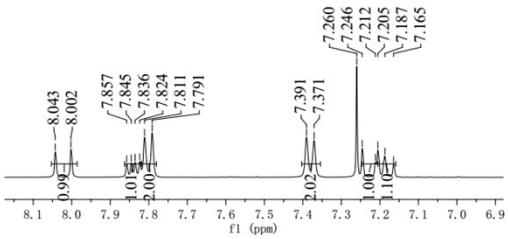
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

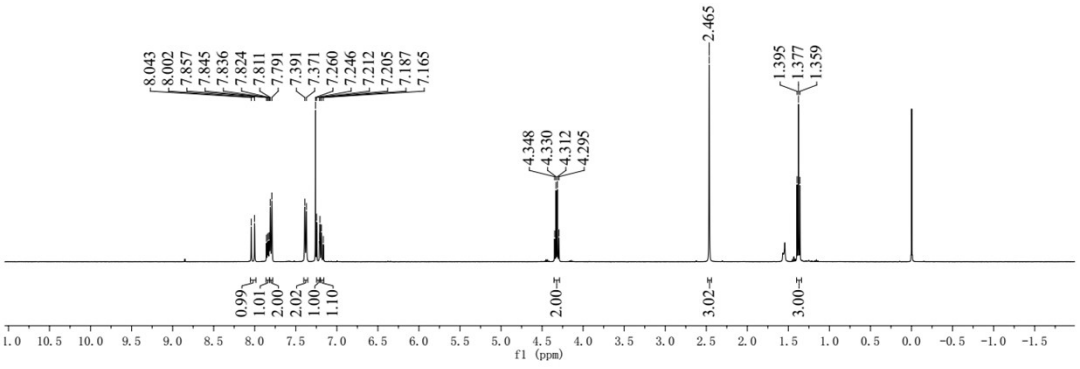
Monoisotopic Mass, Odd and Even Electron Ions
119 formula(e) evaluated with 14 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-18 H: 0-14 N: 0-1 O: 0-3 F: 0-1

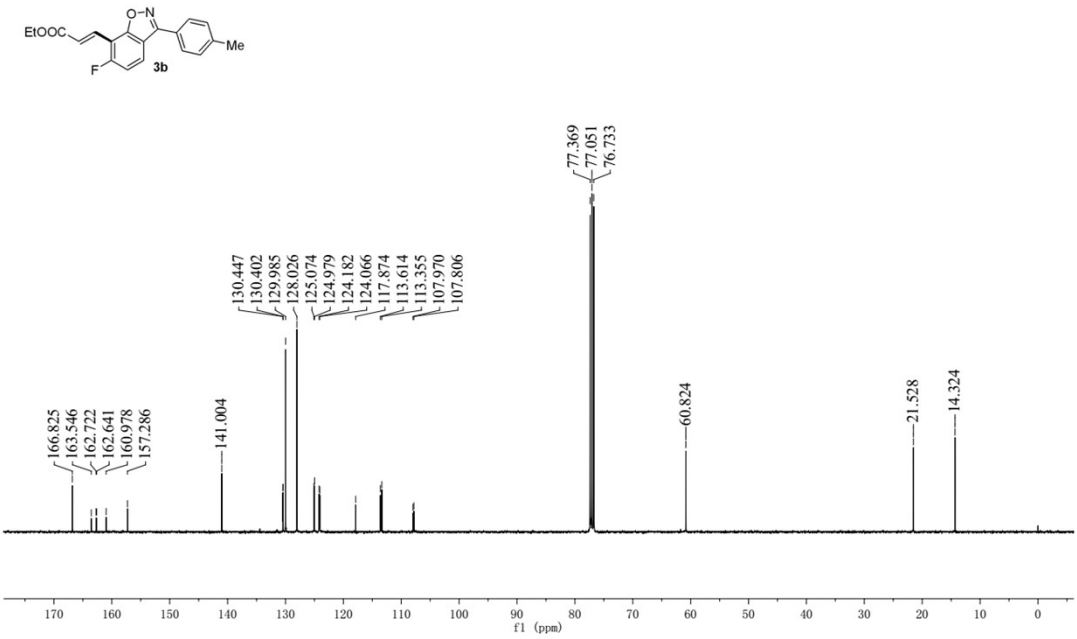


Minimum:	3.00			-1.5			
Maximum:	100.00	5.0	10.0	50.0			
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
311.0956	16.50	311.0958	-0.2	-0.6	12.0	7.5	C18 H14 N O3 F





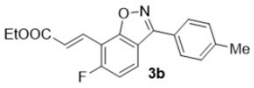




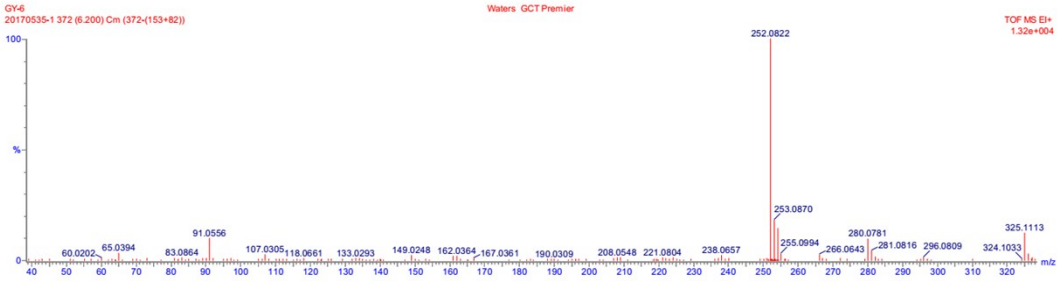
Elemental Composition Report

Single Mass Analysis

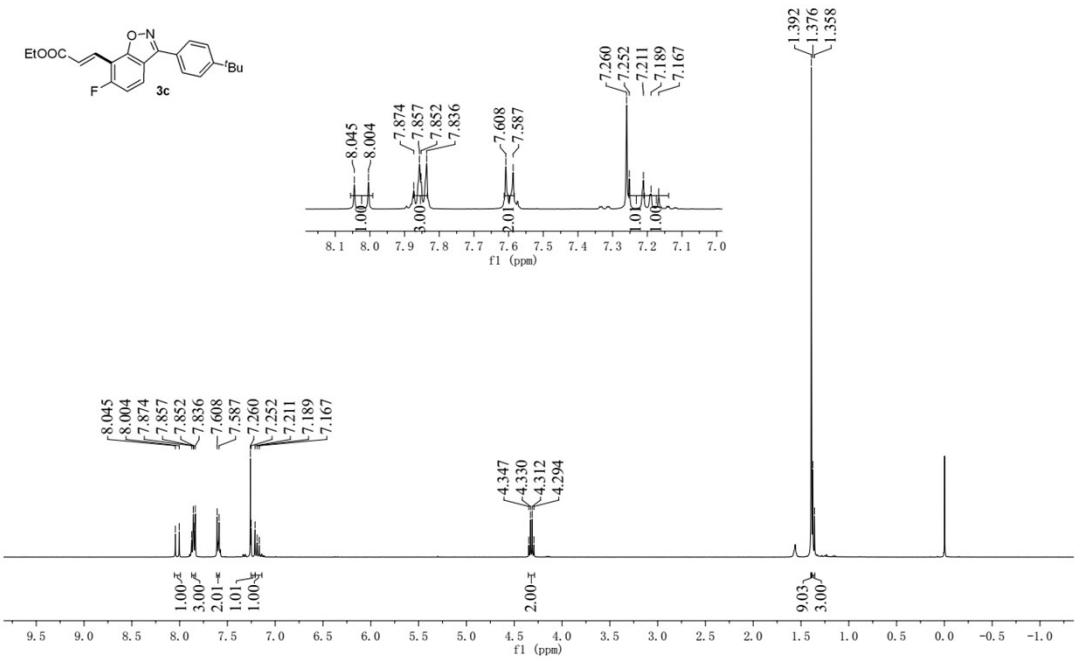
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

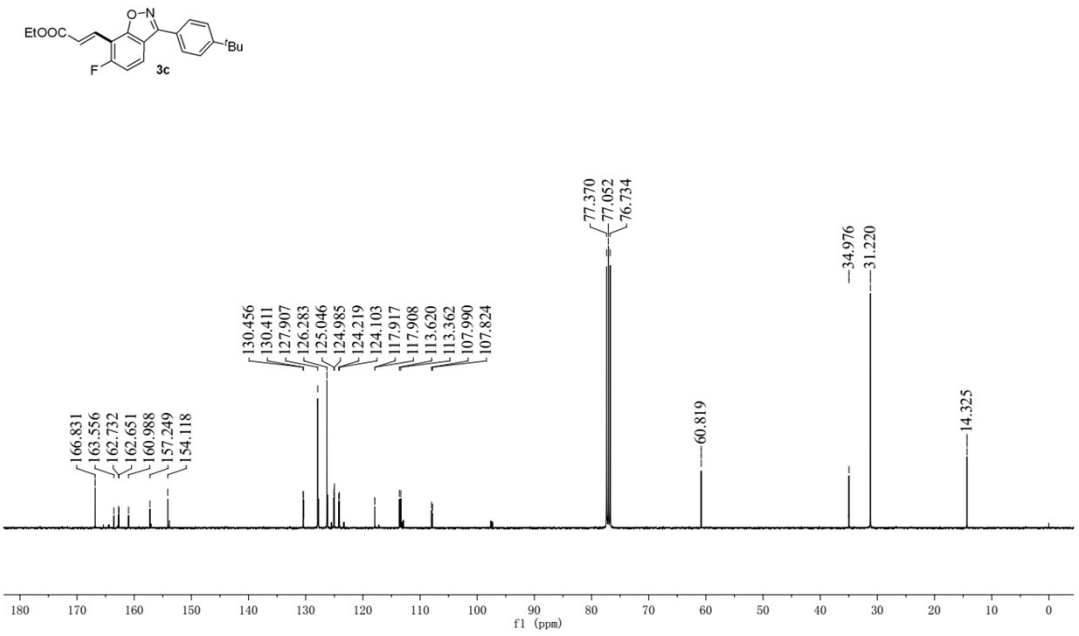


Monoisotopic Mass, Odd and Even Electron Ions
139 formula(e) evaluated with 16 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-19 H: 0-16 N: 0-1 O: 0-3 F: 0-1



Minimum:	3.00			-1.5			
Maximum:	100.00	5.0	10.0	50.0			
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
325.1113	12.23	325.1114	-0.1	-0.3	12.0	37.3	C19 H16 N O3 F

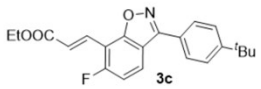

EtOOC
O
N
F
tBu
3c
8.045
8.004
7.874
7.857
7.852
7.836
7.608
7.587
7.260
7.252
7.211
7.189
7.167
1.392
1.376
1.358
4.347
4.330
4.312
4.294
1.00
3.00
2.01
1.01
1.00
2.00
9.03
3.00
f1 (ppm)


EtOOC
O
N
F
tBu
3c
166.831
163.556
162.732
162.651
160.988
157.249
154.118
130.456
130.411
127.907
126.283
125.046
124.985
124.219
124.103
117.917
117.908
113.620
113.362
107.990
107.824
77.370
77.052
76.734
60.819
34.976
31.220
14.325
f1 (ppm)

Elemental Composition Report

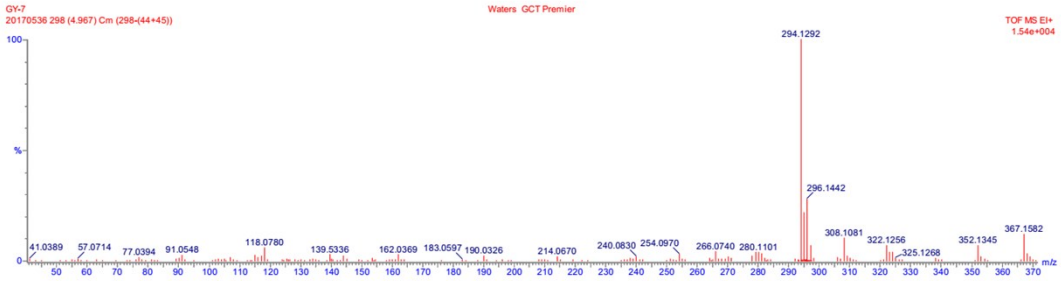
Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off



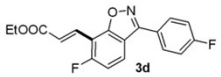
3c

Monoisotopic Mass, Odd and Even Electron Ions
345 formula(e) evaluated with 29 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-22 H: 0-22 N: 0-1 O: 0-3 F: 0-1

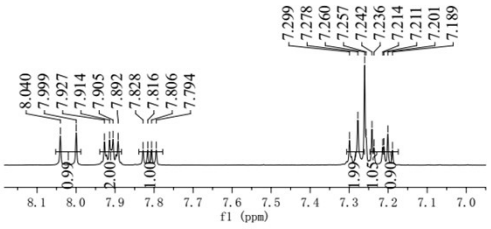


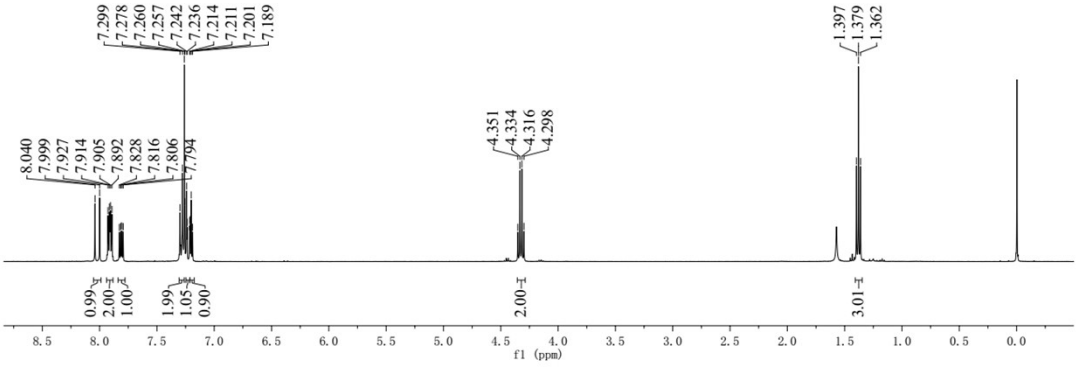
Minimum:	3.00			-1.5	
Maximum:	100.00	5.0	10.0	50.0	

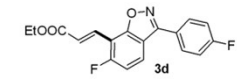
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
367.1582	11.69	367.1584	-0.2	-0.5	12.0	67.8	C22 H22 N O3 F

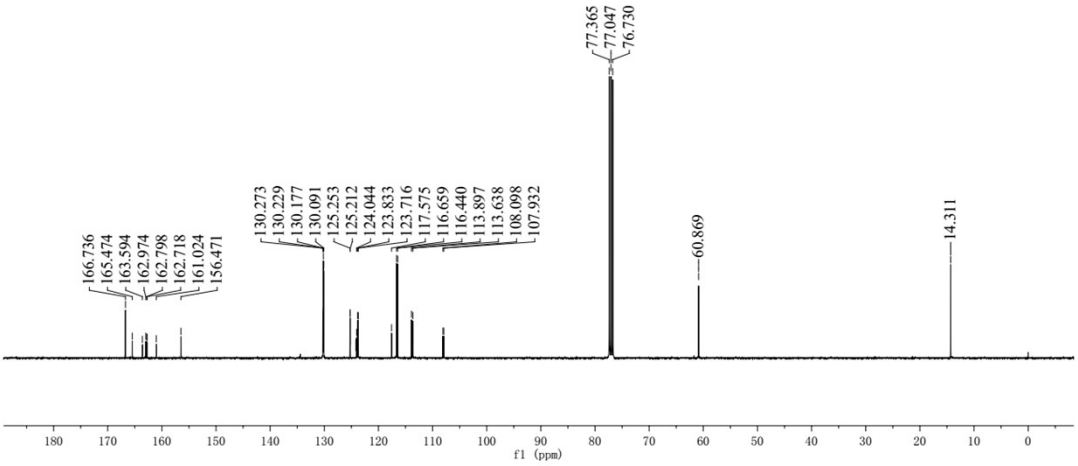


3d





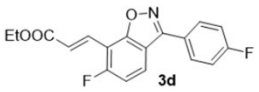




Elemental Composition Report

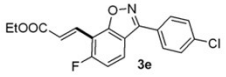
Single Mass Analysis

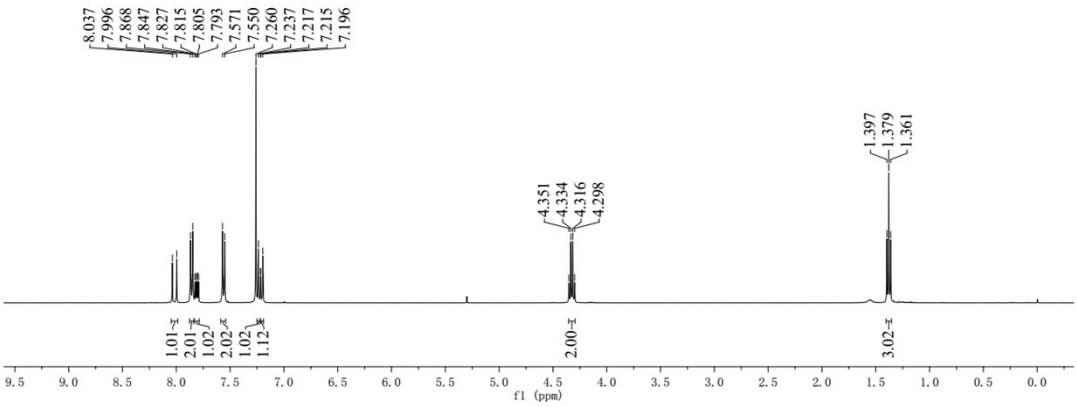
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

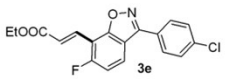


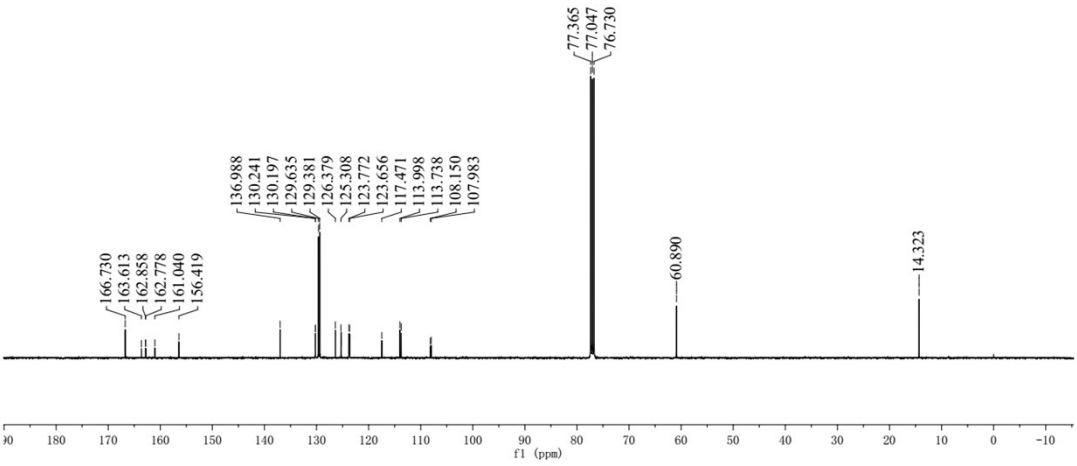
Monoisotopic Mass, Odd and Even Electron Ions
177 formula(e) evaluated with 17 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-18 H: 0-13 N: 0-1 O: 0-3 F: 0-2

Minimum:	3.00			-1.5			
Maximum:	100.00	5.0	10.0	50.0			
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
329.0864	13.43	329.0863	0.1	0.3	12.0	23.6	C18 H13 N O3 F2


EtOOC
O–N
Cl
F
3e


8.037
7.996
7.868
7.847
7.827
7.815
7.805
7.793
7.571
7.550
7.260
7.237
7.217
7.215
7.196
4.351
4.334
4.316
4.298
1.397
1.379
1.361
1.01
2.01
1.02
2.02
1.02
1.12
2.00
3.02
f1 (ppm)

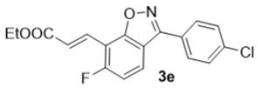

EtOOC
O–N
Cl
F
3e


77.365
77.047
76.730
136.988
130.241
130.197
129.635
129.381
126.379
125.308
123.772
123.656
117.471
113.998
113.738
108.150
107.983
166.730
163.613
162.858
162.778
161.040
156.419
60.890
14.323
f1 (ppm)

Elemental Composition Report

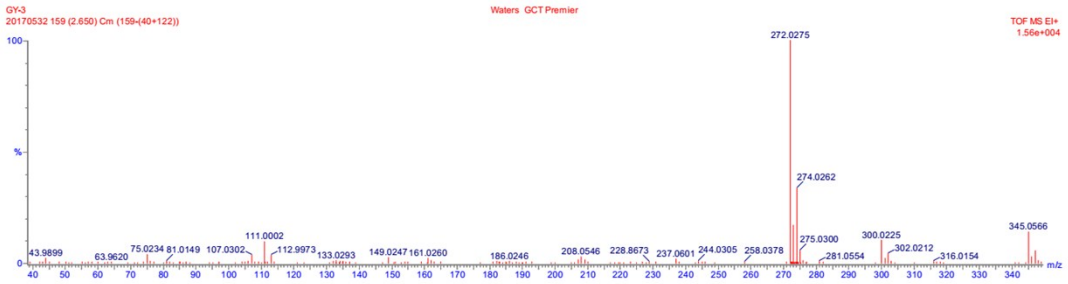
Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

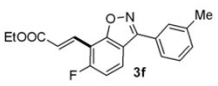


3e

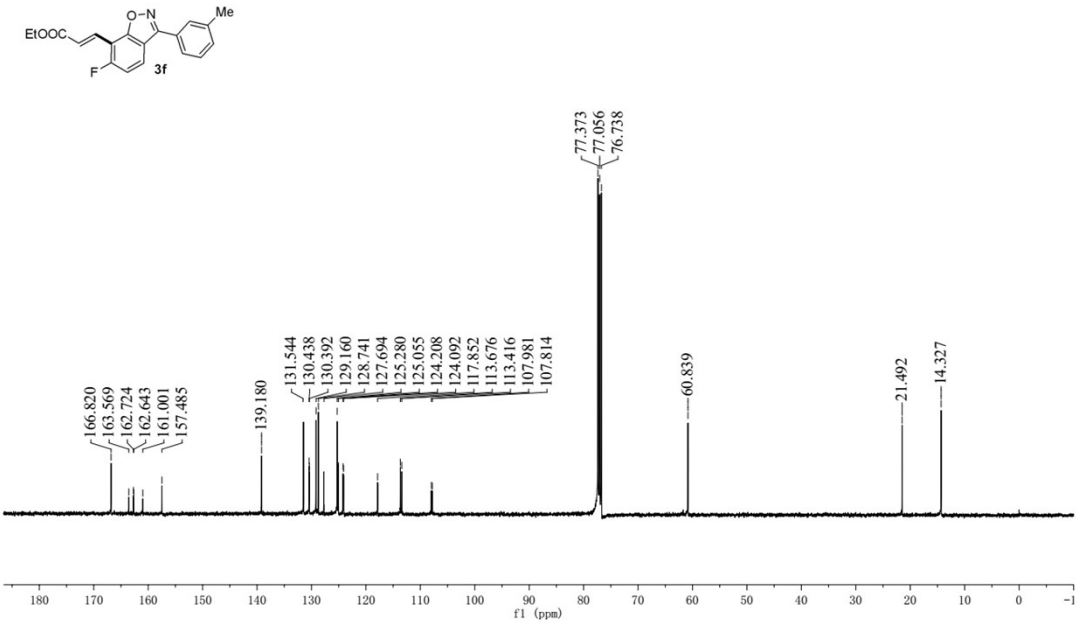
Monoisotopic Mass, Odd and Even Electron Ions
689 formula(e) evaluated with 44 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-18 H: 0-13 N: 0-1 O: 0-3 F: 0-1 35Cl: 0-1 37Cl:0-1



Minimum:	3.00			-1.5			
Maximum:	100.00	5.0	10.0	50.0			
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
345.0566	14.01	345.0568	-0.2	-0.6	12.0	3.3	C18 H13 N O3 F 35Cl



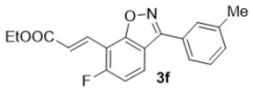
3f



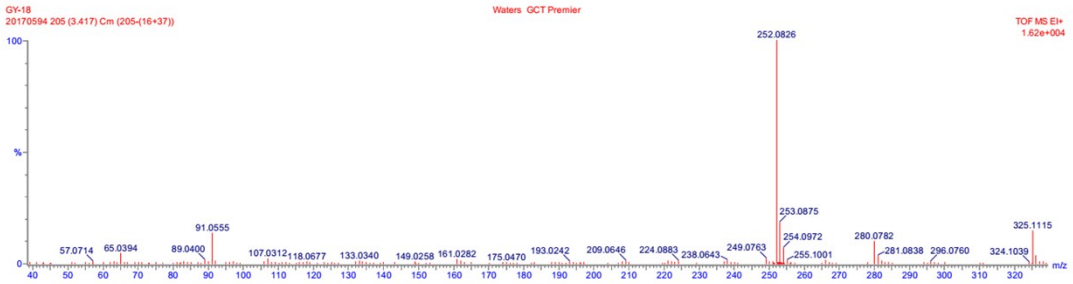
Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

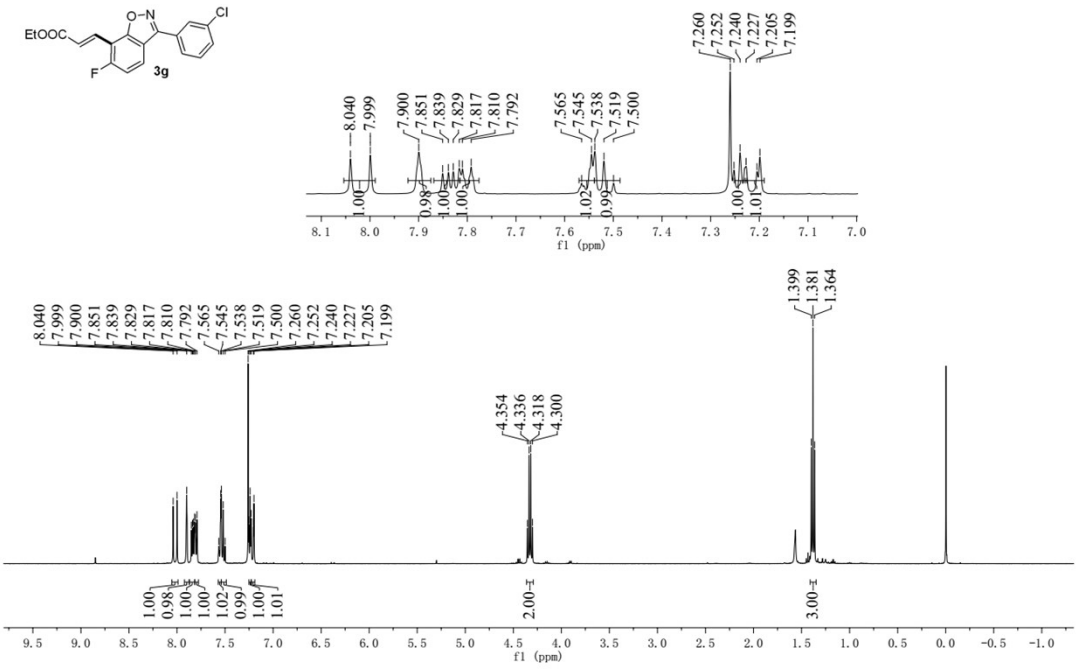


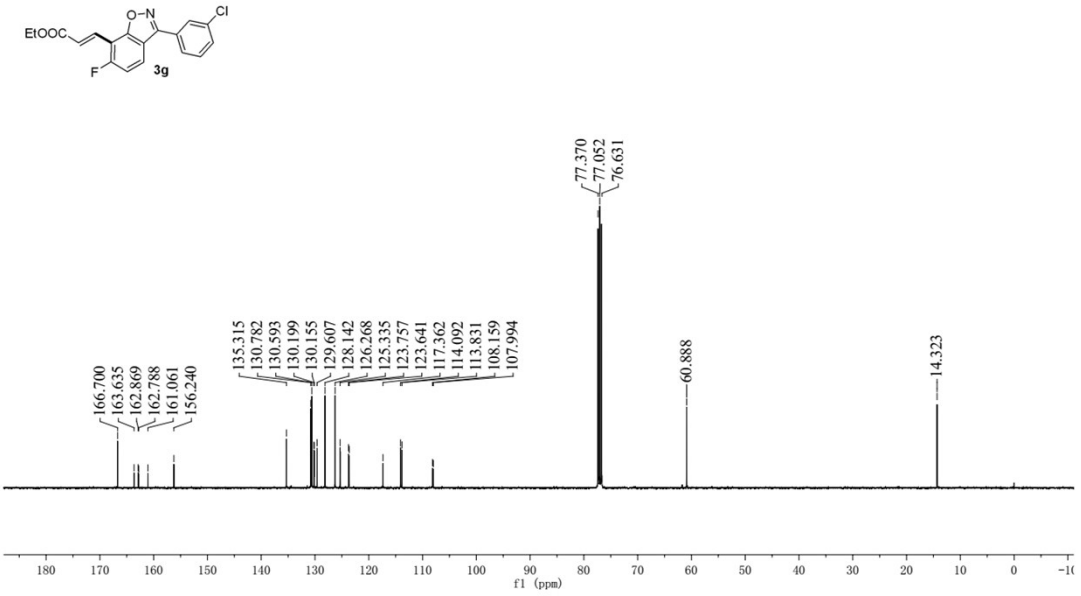
Monoisotopic Mass, Odd and Even Electron Ions
148 formula(e) evaluated with 16 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-19 H: 0-16 N: 0-1 O: 0-3 F: 0-1



Minimum:	3.00			-1.5			
Maximum:	100.00	5.0	10.0	50.0			

Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
325.1115	14.39	325.1114	0.1	0.3	12.0	16.7	C19 H16 N O3 F

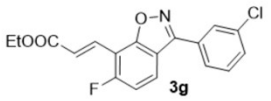

EtOOC
O–N
Cl
F
3g
8.040
7.999
7.900
7.851
7.839
7.829
7.817
7.810
7.792
7.565
7.545
7.538
7.519
7.500
7.260
7.252
7.240
7.227
7.205
7.199
4.354
4.336
4.318
4.300
1.399
1.381
1.364
f1 (ppm)


EtOOC
O–N
Cl
F
3g
166.700
163.635
162.869
162.788
161.061
156.240
135.315
130.782
130.593
130.199
130.155
129.607
128.142
126.268
125.335
123.757
123.641
117.362
114.092
113.831
108.159
107.994
77.370
77.052
76.631
60.888
14.323
f1 (ppm)

Elemental Composition Report

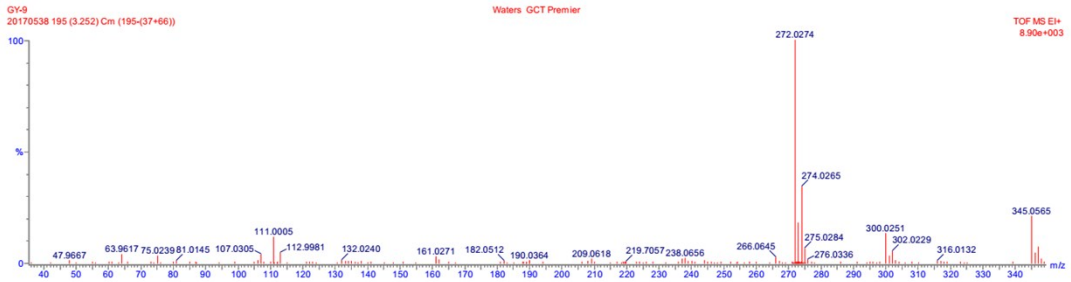
Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

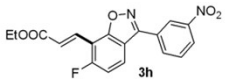


3g

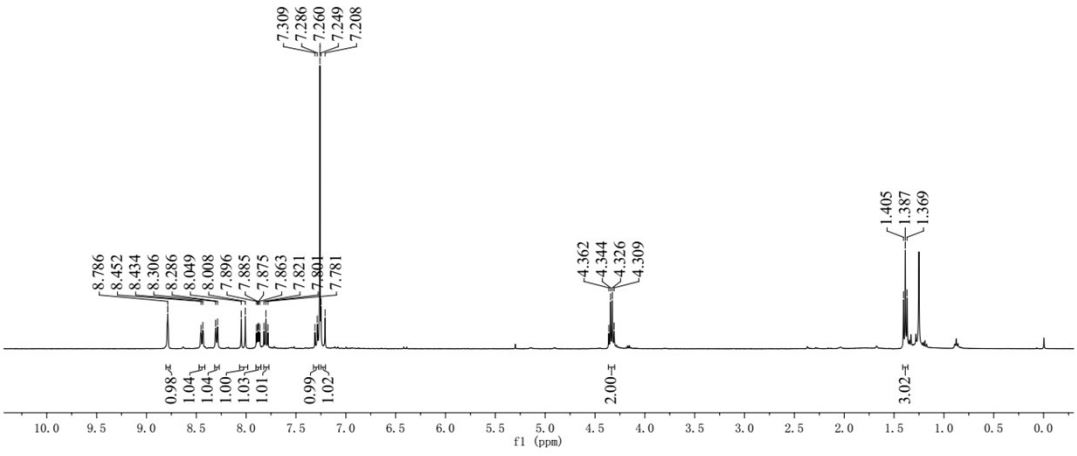
Monoisotopic Mass, Odd and Even Electron Ions
718 formula(e) evaluated with 44 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-18 H: 0-13 N: 0-1 O: 0-3 F: 0-1 35Cl: 0-1 37Cl:0-1

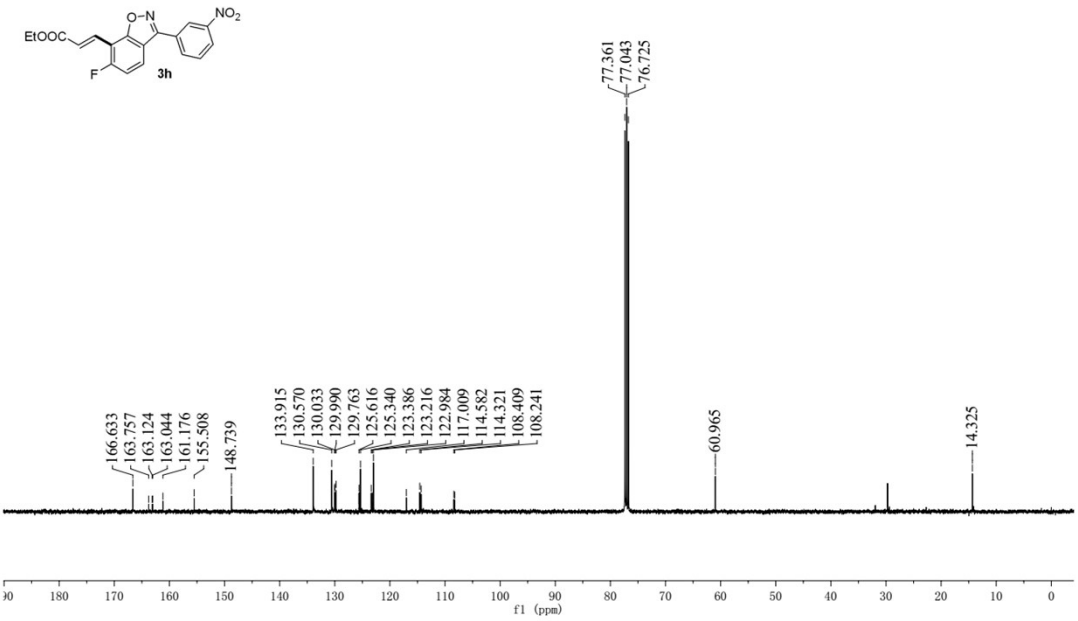


Minimum:	3.00			-1.5			
Maximum:	100.00	5.0	10.0	50.0			
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
345.0565	21.10	345.0568	-0.3	-0.9	12.0	0.5	C18 H13 N O3 F 35Cl



3h

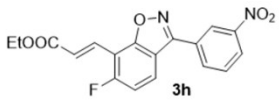




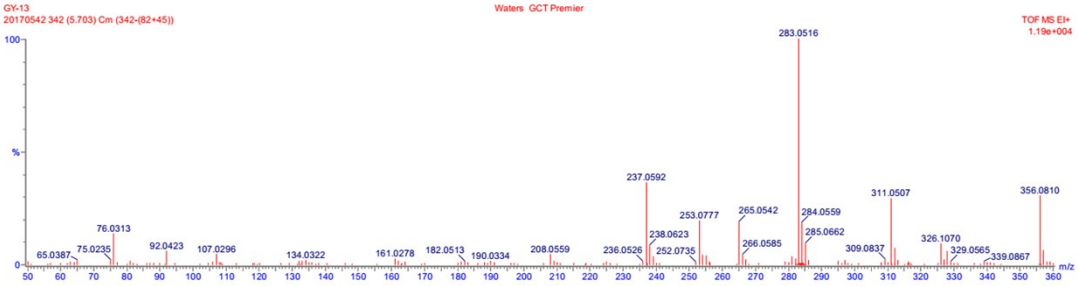
Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

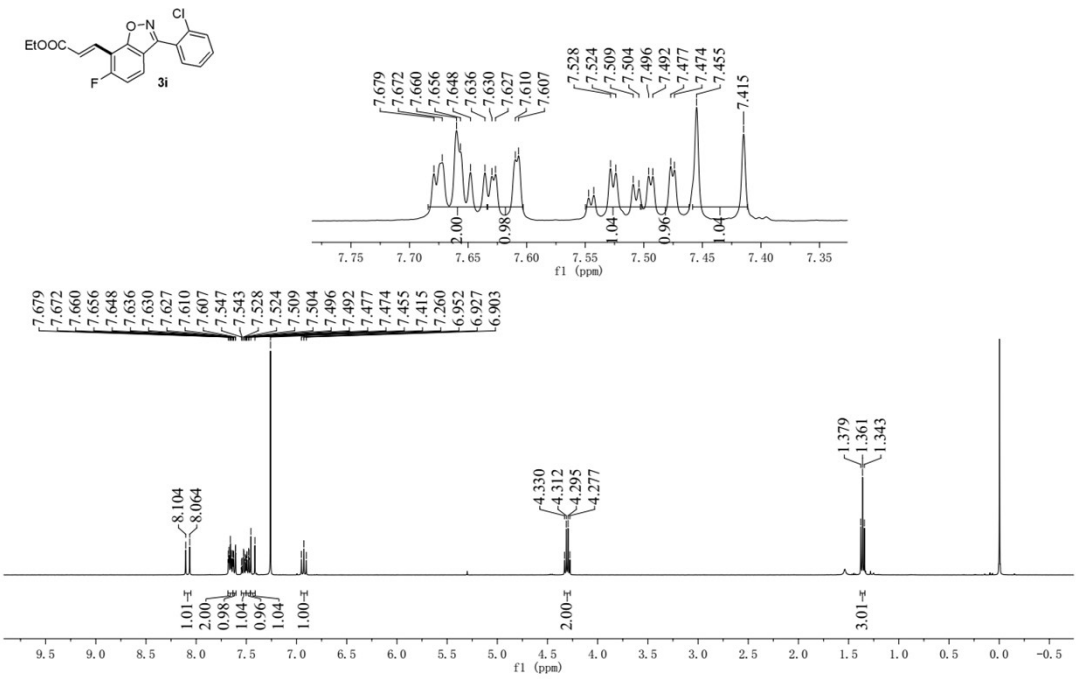


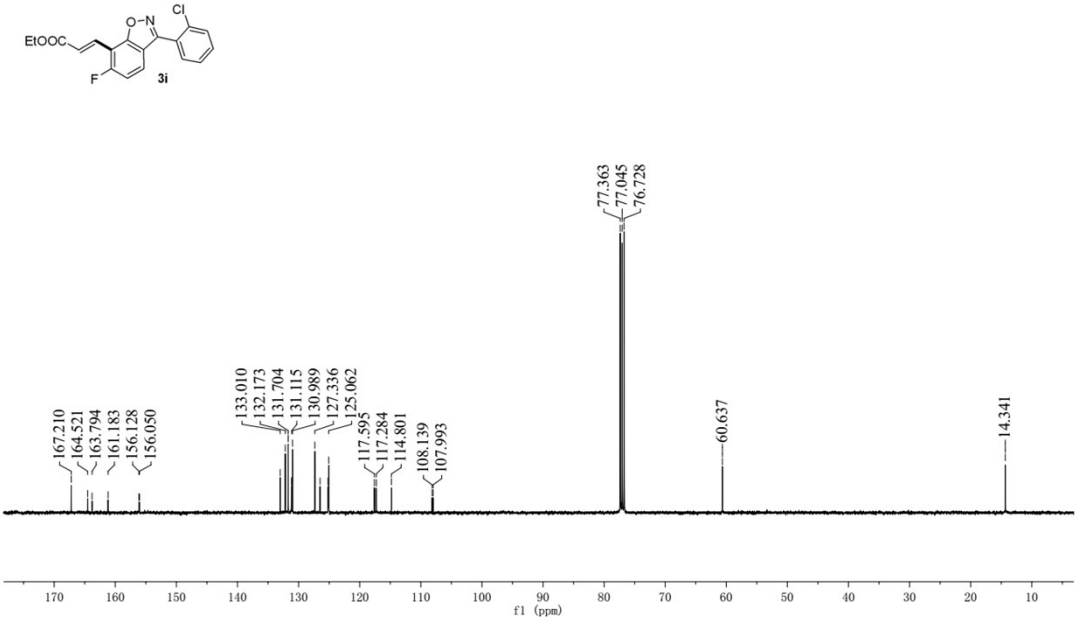
Monoisotopic Mass, Odd and Even Electron Ions
731 formula(e) evaluated with 60 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-18 H: 0-13 N: 0-2 O: 0-5 F: 0-1



Minimum:	3.00			-1.5			
Maximum:	100.00	5.0	10.0	50.0			

Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
356.0810	30.55	356.0808	0.2	0.6	13.0	1.2	C18 H13 N2 O5 F1

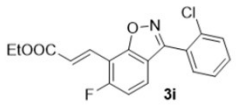

EtOOC
O–N
Cl
F
3i
7.679
7.672
7.660
7.656
7.648
7.636
7.630
7.627
7.610
7.607
7.528
7.524
7.509
7.504
7.496
7.492
7.477
7.474
7.455
7.415
2.00
0.98
1.04
0.96
1.04
f1 (ppm)
7.679
7.672
7.660
7.656
7.648
7.636
7.630
7.627
7.610
7.607
7.547
7.543
7.528
7.524
7.509
7.504
7.496
7.492
7.477
7.474
7.455
7.415
7.260
6.952
6.927
6.903
8.104
8.064
4.330
4.312
4.295
4.277
1.379
1.361
1.343
1.01
2.00
0.98
1.04
0.96
1.04
1.00
2.00
3.01
f1 (ppm)


EtOOC
O–N
Cl
F
3i
77.363
77.045
76.728
167.210
164.521
163.794
161.183
156.128
156.050
133.010
132.173
131.704
131.115
130.989
127.336
125.062
117.595
117.284
114.801
108.139
107.993
60.637
14.341
f1 (ppm)

Elemental Composition Report

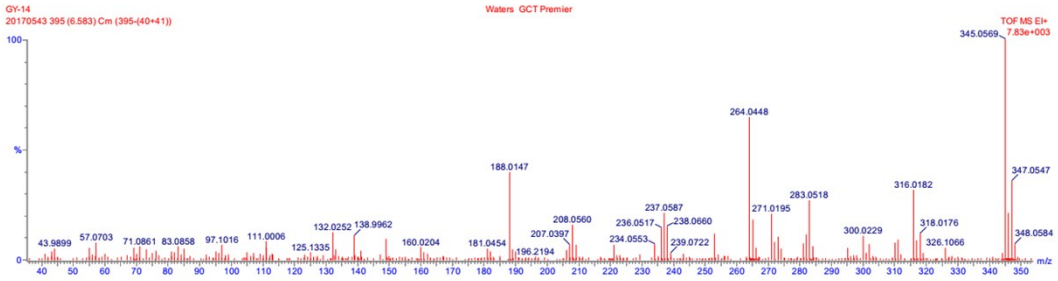
Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 100.0
Element prediction: Off

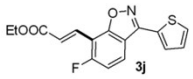


3i

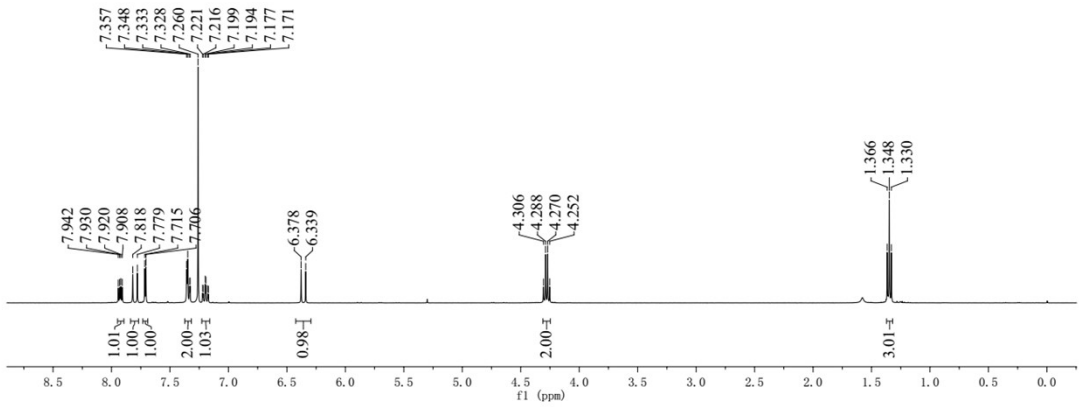
Monoisotopic Mass, Odd and Even Electron Ions
3682 formula(e) evaluated with 188 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-18 H: 0-13 N: 0-1 O: 0-3 35Cl: 0-1 37Cl:0-1 F: 0-1

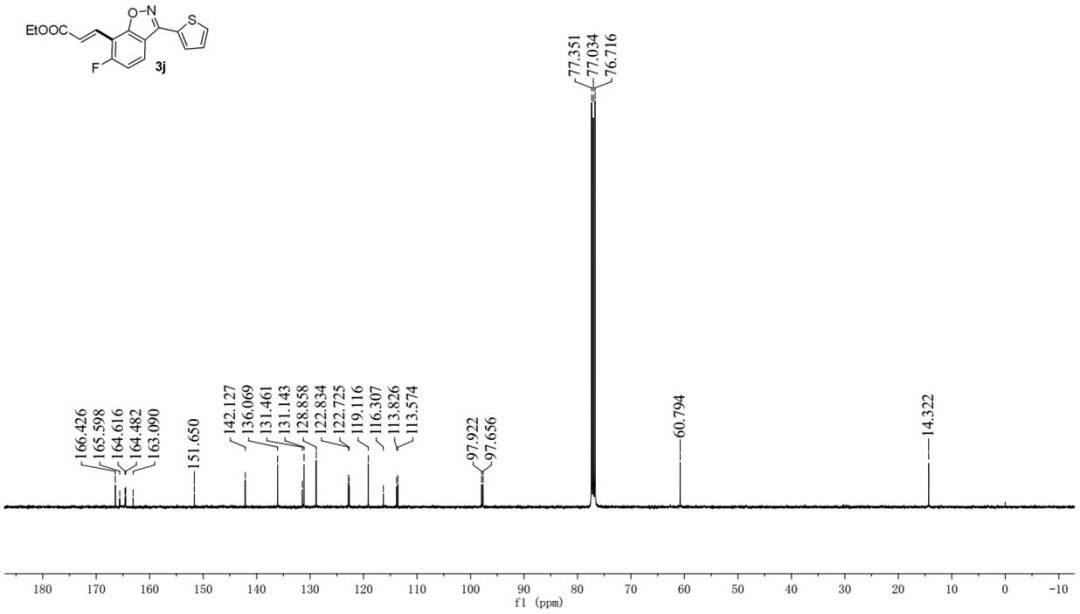


Minimum:	3.00			-1.5									
Maximum:	100.00	5.0	10.0	50.0									
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula						
345.0569	100.0	345.0568	0.1	0.3	12.0	1.0	C18	H13	N	O3	35Cl	F	



3j

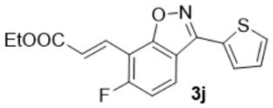




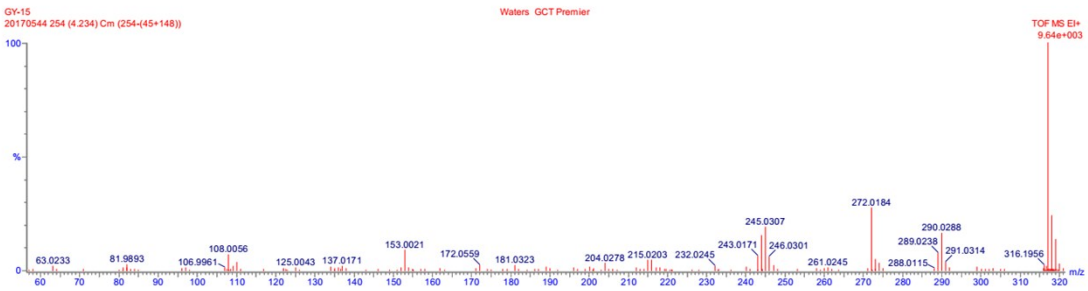
Elemental Composition Report

Single Mass Analysis

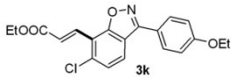
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

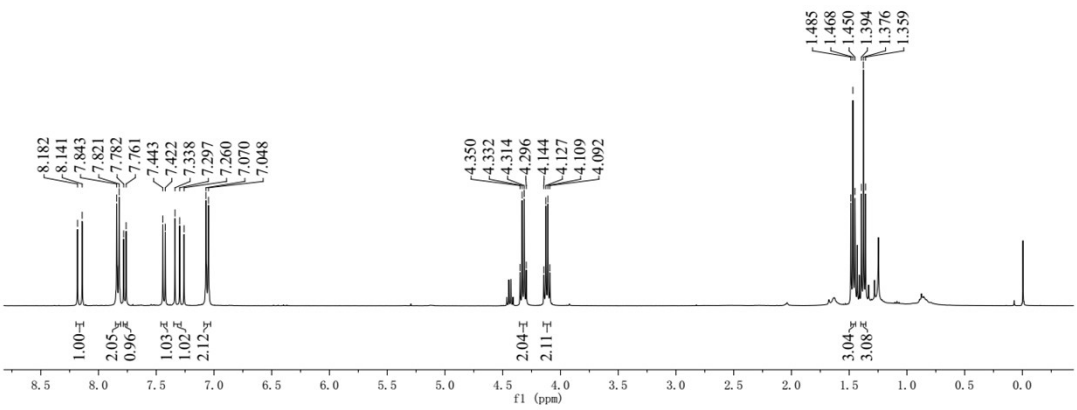


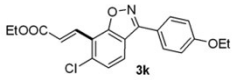
Monoisotopic Mass, Odd and Even Electron Ions
477 formula(e) evaluated with 40 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-16 H: 0-12 N: 0-1 O: 0-3 S: 0-1 F: 0-1

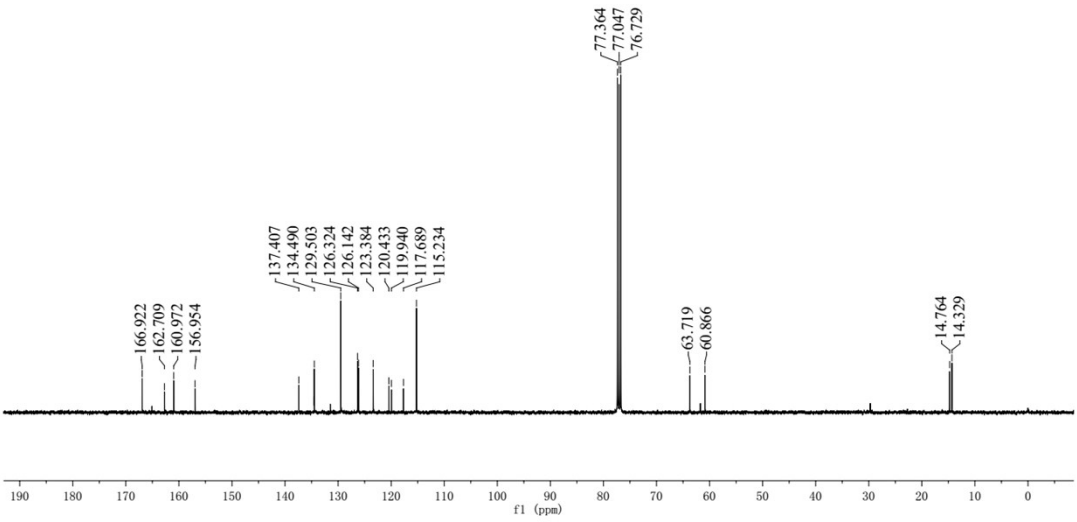


Minimum:	3.00			-1.5			
Maximum:	100.00	5.0	10.0	50.0			
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
317.0520	100.00	317.0522	-0.2	-0.6	11.0	188.9	C16 H12 N O3 S F


EtOOC
O–N
OEt
Cl
3k


8.182
8.141
7.843
7.821
7.782
7.761
7.443
7.422
7.338
7.297
7.260
7.070
7.048
4.350
4.332
4.314
4.296
4.144
4.127
4.109
4.092
1.485
1.468
1.450
1.394
1.376
1.359
1.00
2.05
0.96
1.03
1.02
2.12
2.04
2.11
3.04
3.08
f1 (ppm)

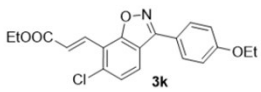

EtOOC
O–N
OEt
Cl
3k


77.364
77.047
76.729
137.407
134.490
129.503
126.324
126.142
123.384
120.433
119.940
117.689
115.234
166.922
162.709
160.972
156.954
63.719
60.866
14.764
14.329
f1 (ppm)

Elemental Composition Report

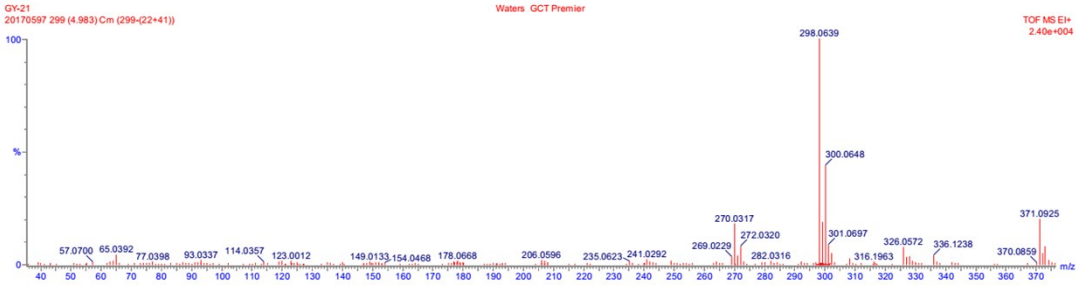
Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

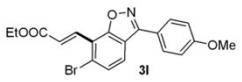


3k

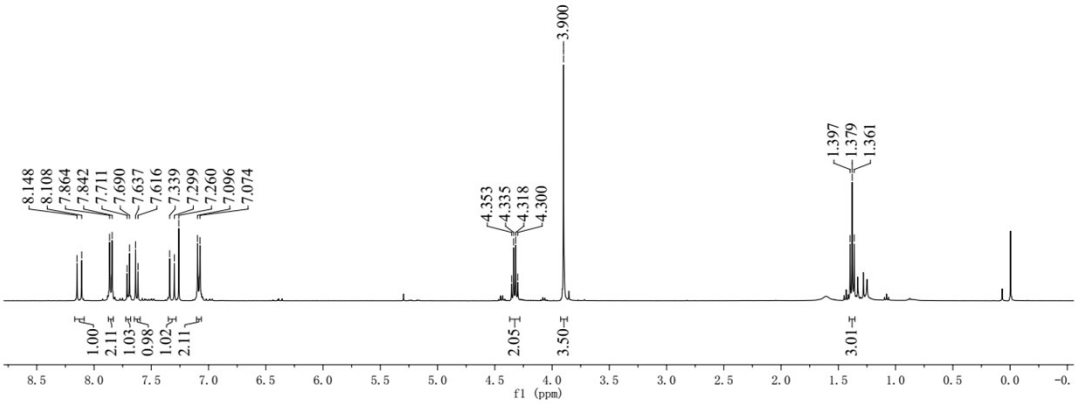
Monoisotopic Mass, Odd and Even Electron Ions
710 formula(e) evaluated with 38 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-20 H: 0-18 N: 0-1 O: 0-4 35Cl: 0-1 37Cl:0-1

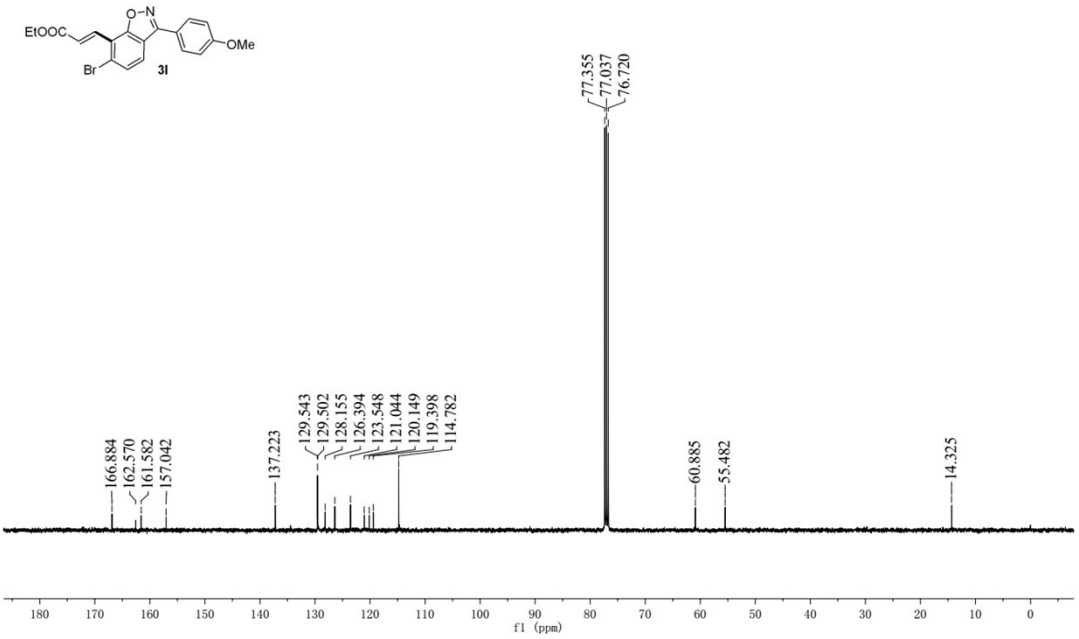


Minimum:	3.00			-1.5			
Maximum:	100.00	5.0	10.0	50.0			
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
371.0925	19.95	371.0924	0.1	0.3	12.0	6.8	C20 H18 N O4 35C



3l

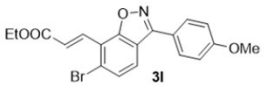




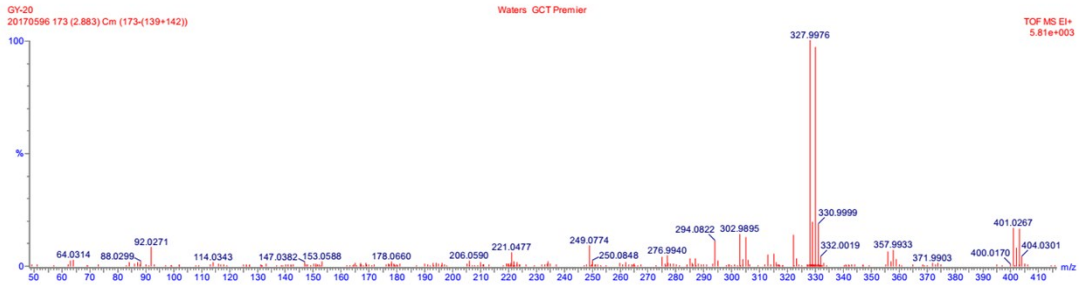
Elemental Composition Report

Single Mass Analysis

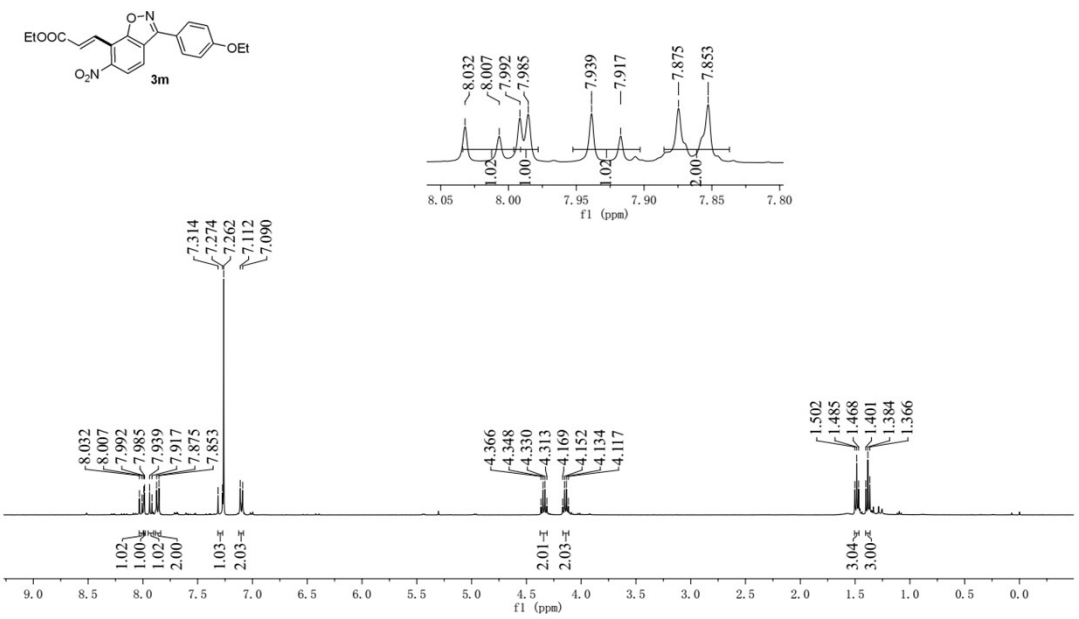
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

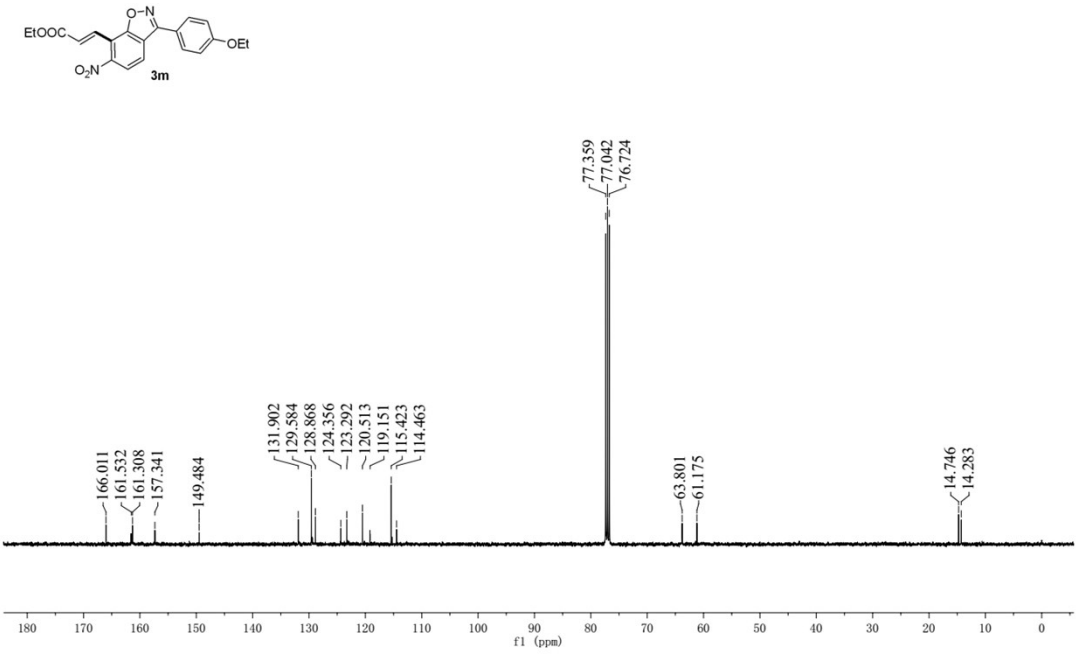


Monoisotopic Mass, Odd and Even Electron Ions
1056 formula(e) evaluated with 37 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-19 H: 0-16 N: 0-1 O: 0-4 79Br: 0-1 81Br:0-1



Minimum:	3.00			-1.5			
Maximum:	100.00	5.0	10.0	50.0			
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
401.0267	16.66	401.0263	0.4	1.0	12.0	65.7	C19 H16 N O4 79Br

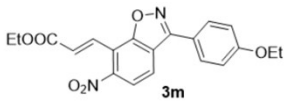

EtOOC
OEt
O2N
3m
8.032
8.007
7.992
7.985
7.939
7.917
7.875
7.853
7.314
7.274
7.262
7.112
7.090
4.366
4.348
4.330
4.313
4.169
4.152
4.134
4.117
1.502
1.485
1.468
1.401
1.384
1.366
f1 (ppm)


EtOOC
OEt
O2N
3m
166.011
161.532
161.308
157.341
149.484
131.902
129.584
128.868
124.356
123.292
120.513
119.151
115.423
114.463
77.359
77.042
76.724
63.801
61.175
14.746
14.283
f1 (ppm)

Elemental Composition Report

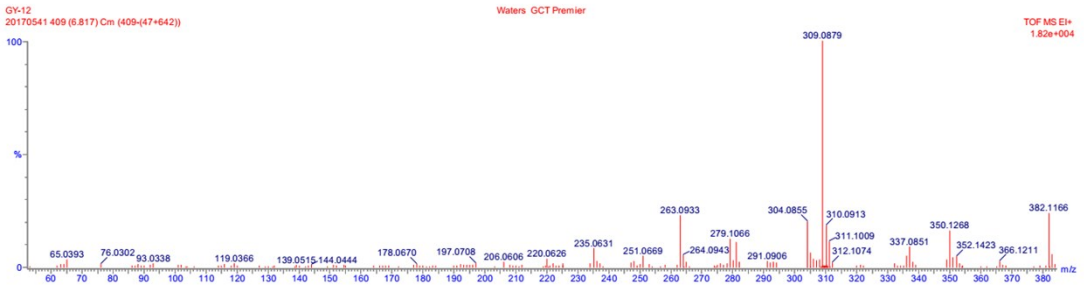
Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off



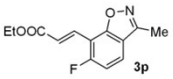
3m

Monoisotopic Mass, Odd and Even Electron Ions
500 formula(e) evaluated with 28 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-20 H: 0-18 N: 0-2 O: 0-6

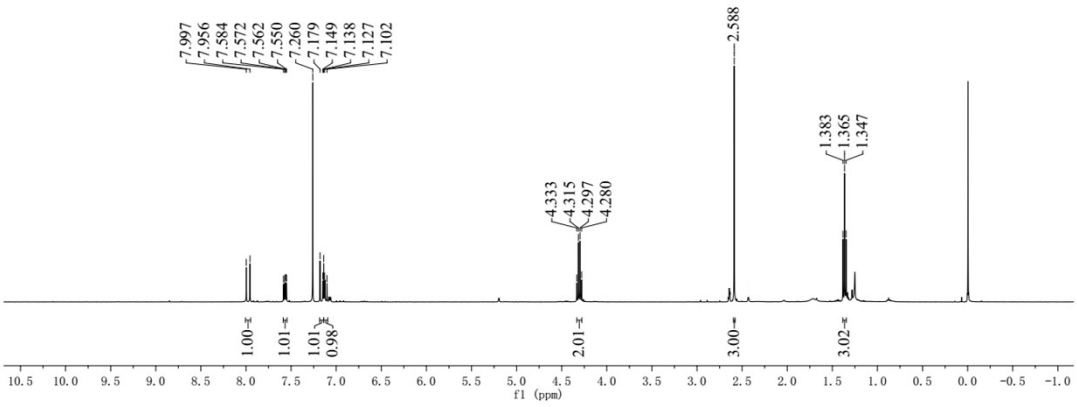


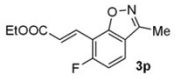
Minimum:	3.00			-1.5	
Maximum:	100.00	5.0	10.0	50.0	

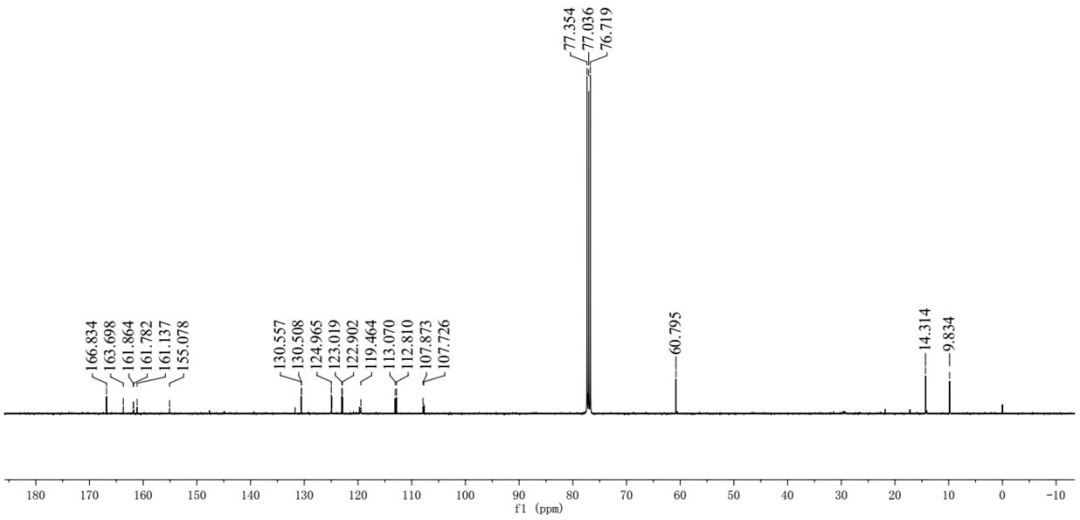
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
382.1166	23.70	382.1165	0.1	0.3	13.0	3.3	C20 H18 N2 O6



3p



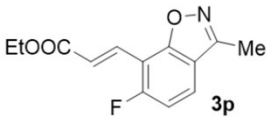




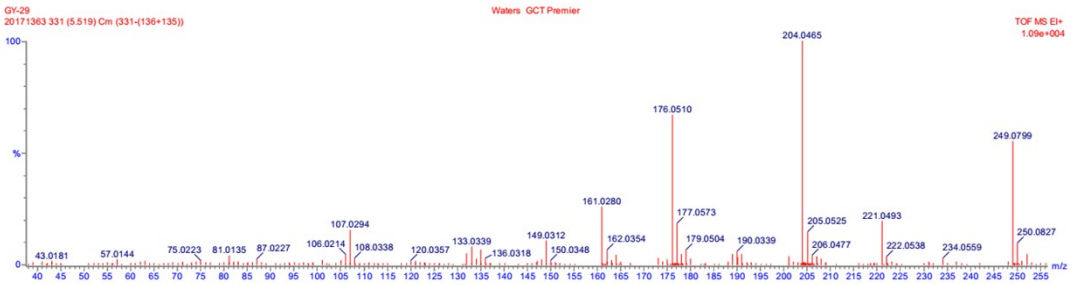
Elemental Composition Report

Single Mass Analysis

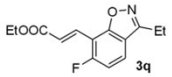
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

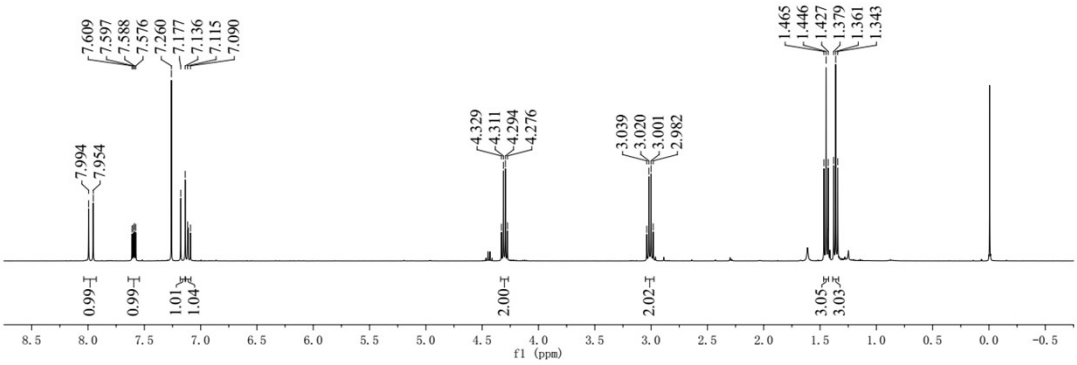


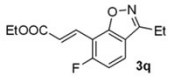
Monoisotopic Mass, Odd and Even Electron Ions
440 formula(e) evaluated with 46 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-13 H: 0-12 N: 0-1 O: 0-3 F: 0-1

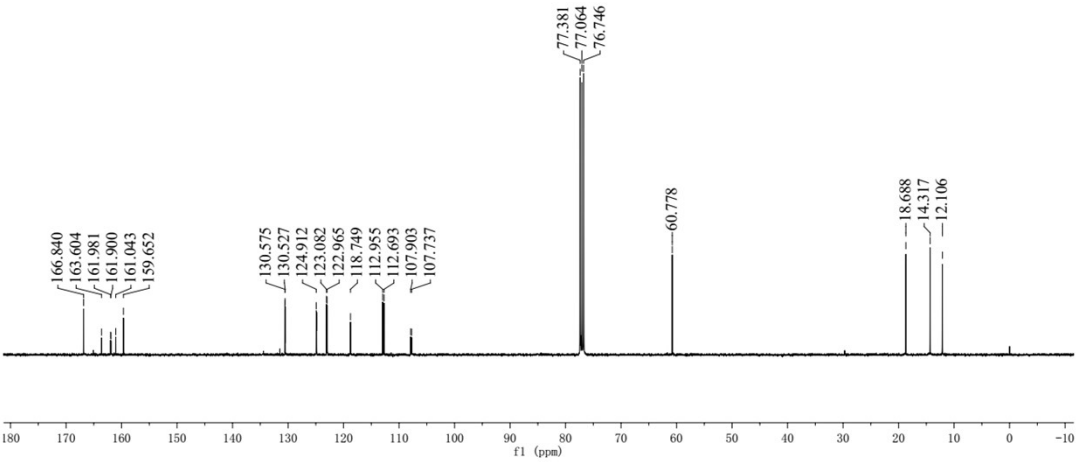


Minimum:	3.00			-1.5			
Maximum:	100.00	5.0	10.0	50.0			
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
249.0799	55.14	249.0801	-0.2	-0.8	8.0	9.0	C13 H12 N O3 F


EtOOC
O
N
Et
F
3q


7.609
7.597
7.588
7.576
7.260
7.177
7.136
7.115
7.090
7.994
7.954
4.329
4.311
4.294
4.276
3.039
3.020
3.001
2.982
1.465
1.446
1.427
1.379
1.361
1.343
0.99
0.99
1.01
1.04
2.00
2.02
3.05
3.03
f1 (ppm)

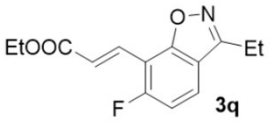

EtOOC
O
N
Et
F
3q


166.840
163.604
161.981
161.900
161.043
159.652
130.575
130.527
124.912
123.082
122.965
118.749
112.955
112.693
107.903
107.737
77.381
77.064
76.746
60.778
18.688
14.317
12.106
f1 (ppm)

Elemental Composition Report

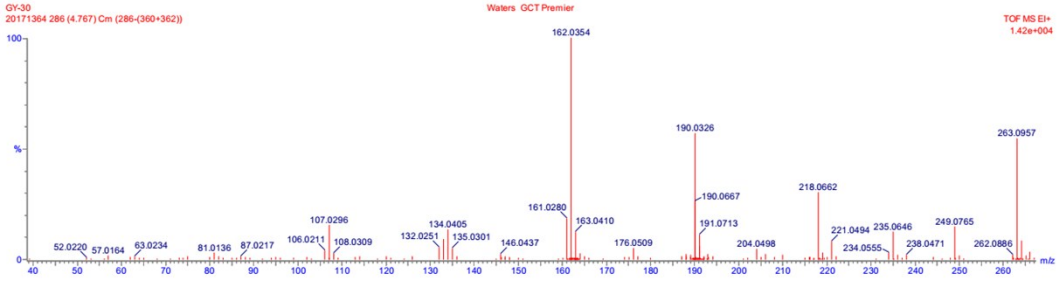
Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off



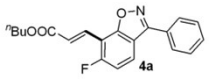
3q

Monoisotopic Mass, Odd and Even Electron Ions
440 formula(e) evaluated with 46 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-14 H: 0-14 N: 0-1 O: 0-3 F: 0-1

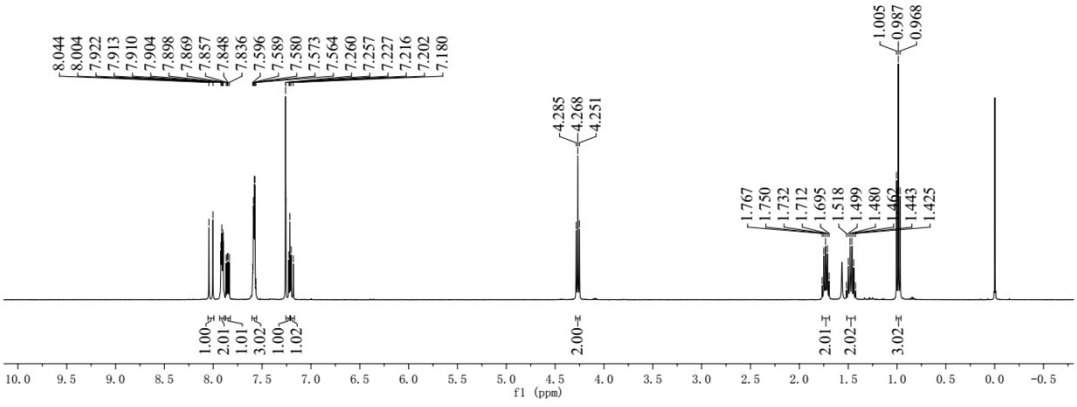


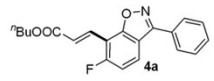
Minimum:	3.00			-1.5	
Maximum:	100.00	5.0	10.0	50.0	

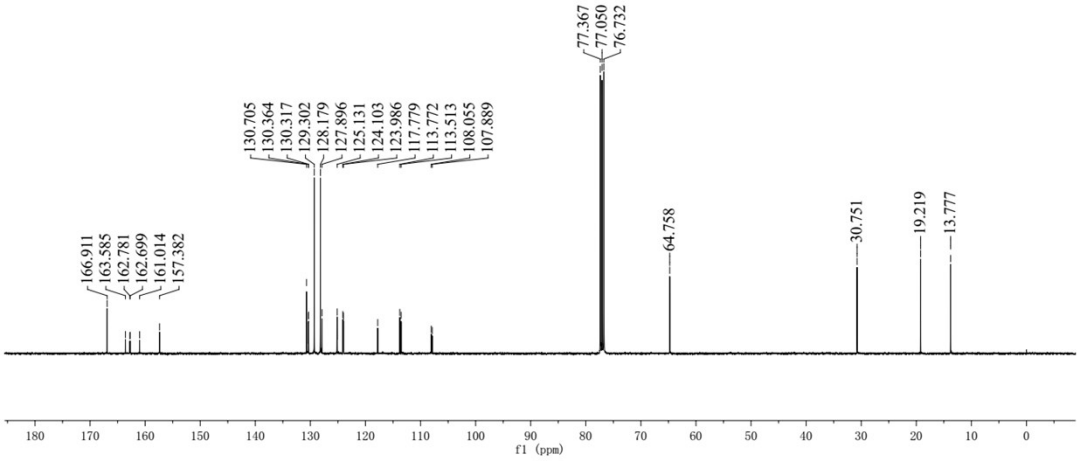
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
263.0957	54.27	263.0958	-0.1	-0.4	8.0	17.9	C14 H14 N O3 F



4a



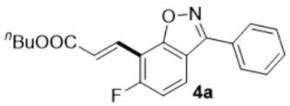




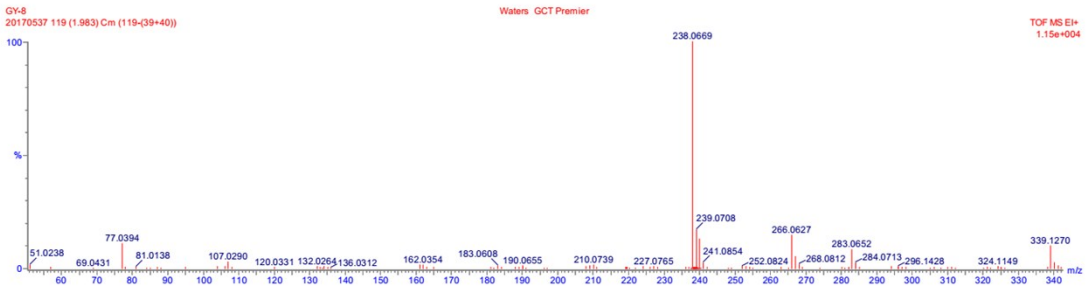
Elemental Composition Report

Single Mass Analysis

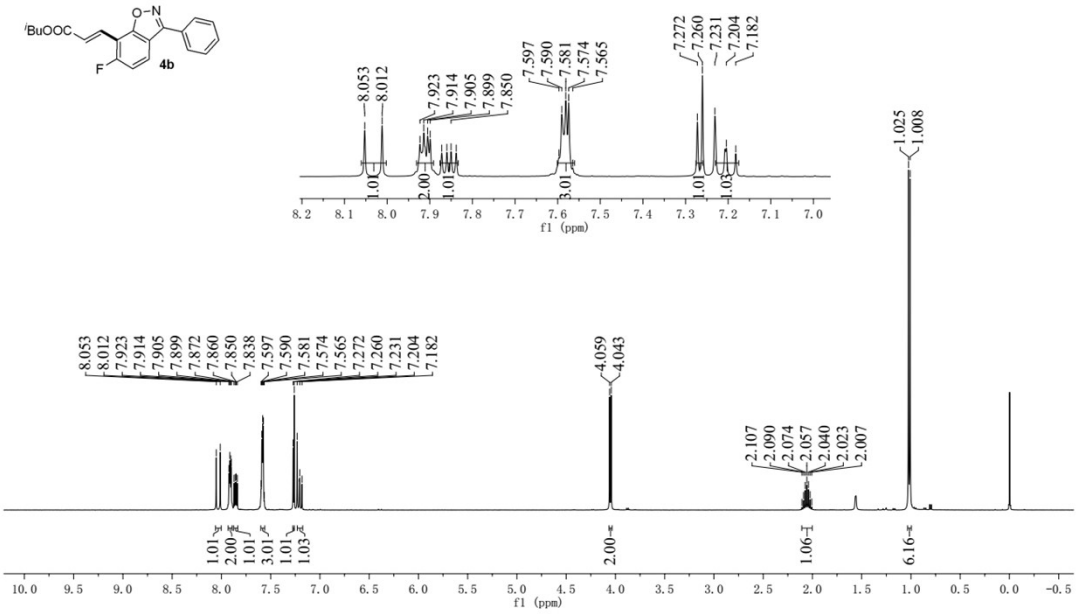
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

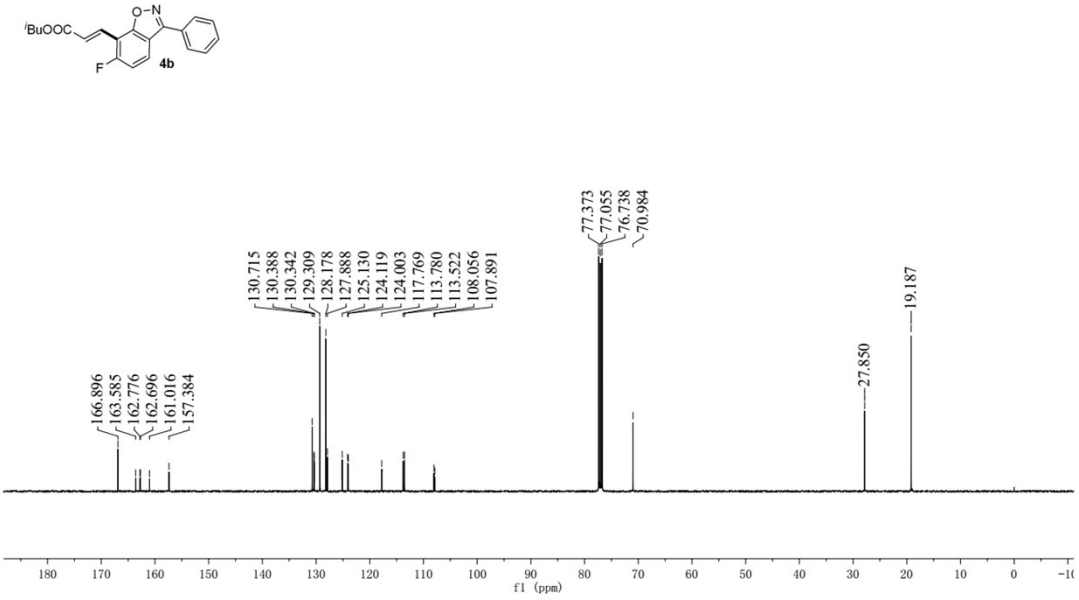


Monoisotopic Mass, Odd and Even Electron Ions
172 formula(e) evaluated with 17 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-20 H: 0-18 N: 0-1 O: 0-3 F: 0-1



Minimum:	3.00			-1.5			
Maximum:	100.00	5.0	10.0	50.0			
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
339.1270	9.68	339.1271	-0.1	-0.3	20.0	20.5	C20 H18 N O3 F

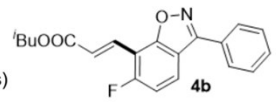

tBuOOC
F
4b
8.053
8.012
7.923
7.914
7.905
7.899
7.850
7.597
7.590
7.581
7.574
7.565
7.272
7.260
7.231
7.204
7.182
1.025
1.008
4.059
4.043
2.107
2.090
2.074
2.057
2.040
2.023
2.007
f1 (ppm)


tBuOOC
F
4b
166.896
163.585
162.776
162.696
161.016
157.384
130.715
130.388
130.342
129.309
128.178
127.888
125.130
124.119
124.003
117.769
113.780
113.522
108.056
107.891
77.373
77.055
76.738
70.984
27.850
19.187
f1 (ppm)

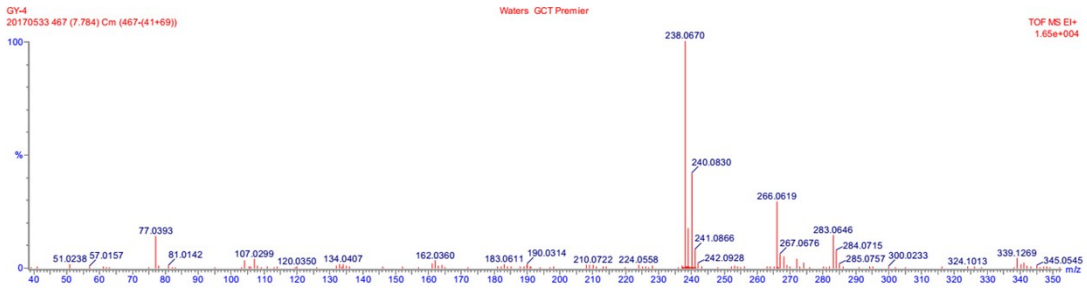
Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

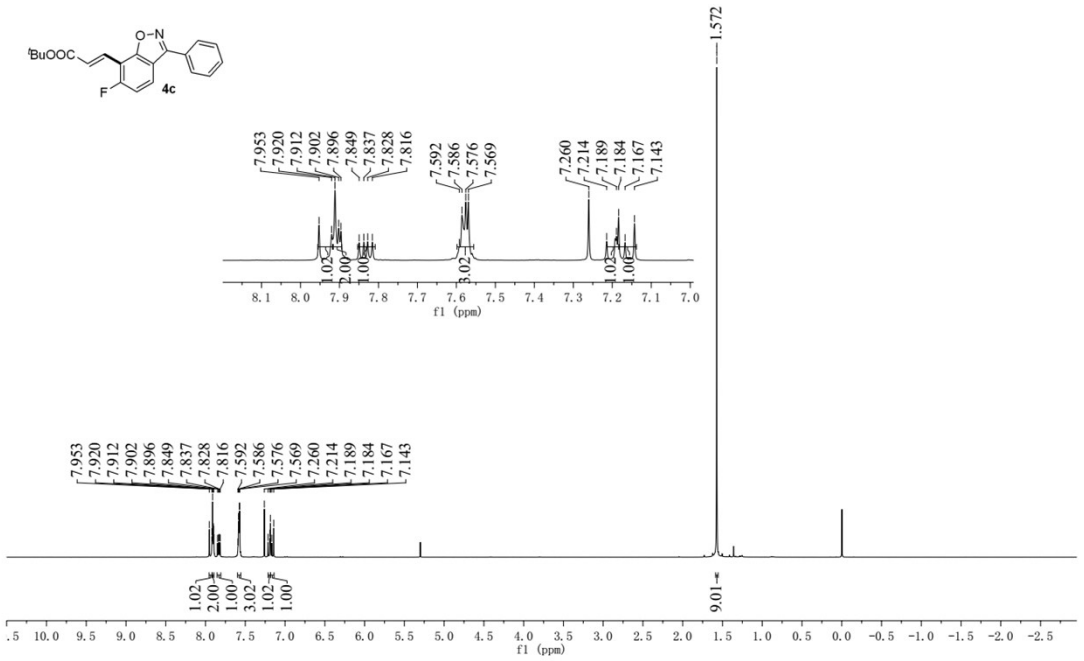


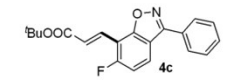
Monoisotopic Mass, Odd and Even Electron Ions
287 formula(e) evaluated with 27 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-20 H: 0-18 N: 0-1 O: 0-3 F: 0-1

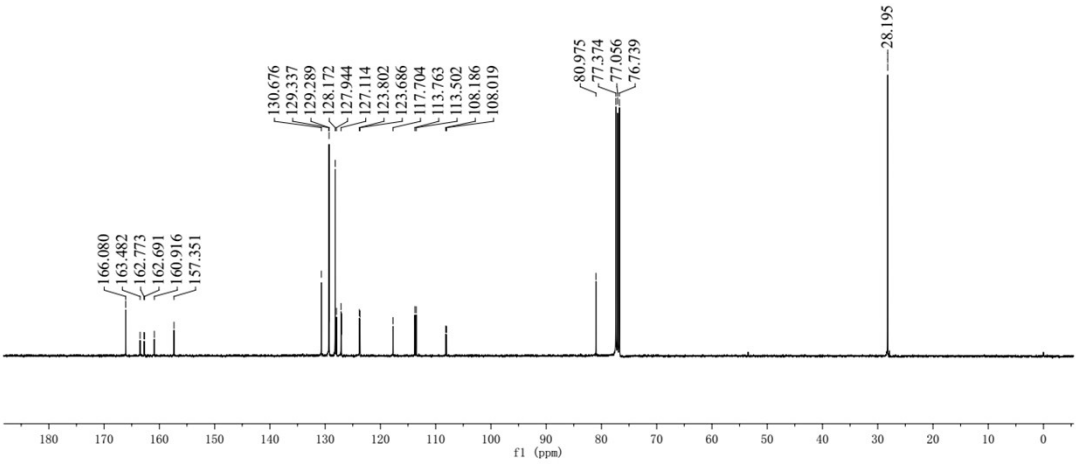


Minimum:	3.00			-1.5	
Maximum:	100.00	5.0	10.0	50.0	

Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
339.1269	4.04	339.1271	-0.2	-0.6	12.0	150.4	C20 H18 N O3 F



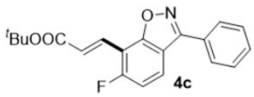




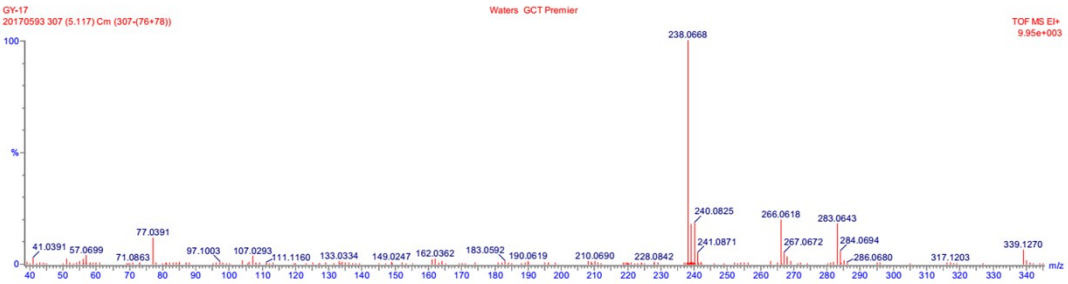
Elemental Composition Report

Single Mass Analysis

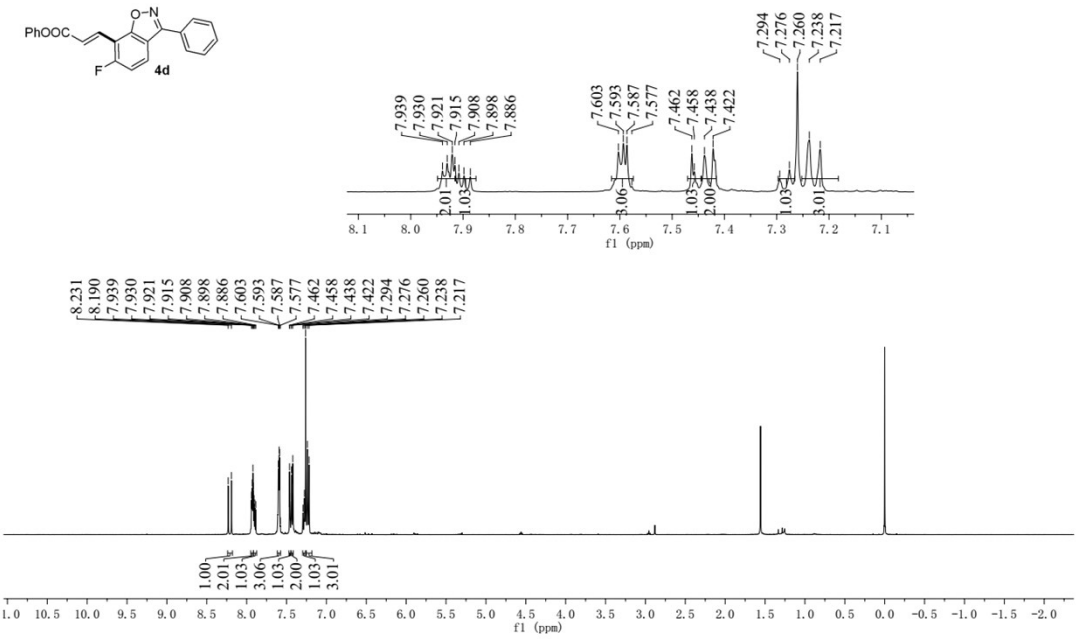
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

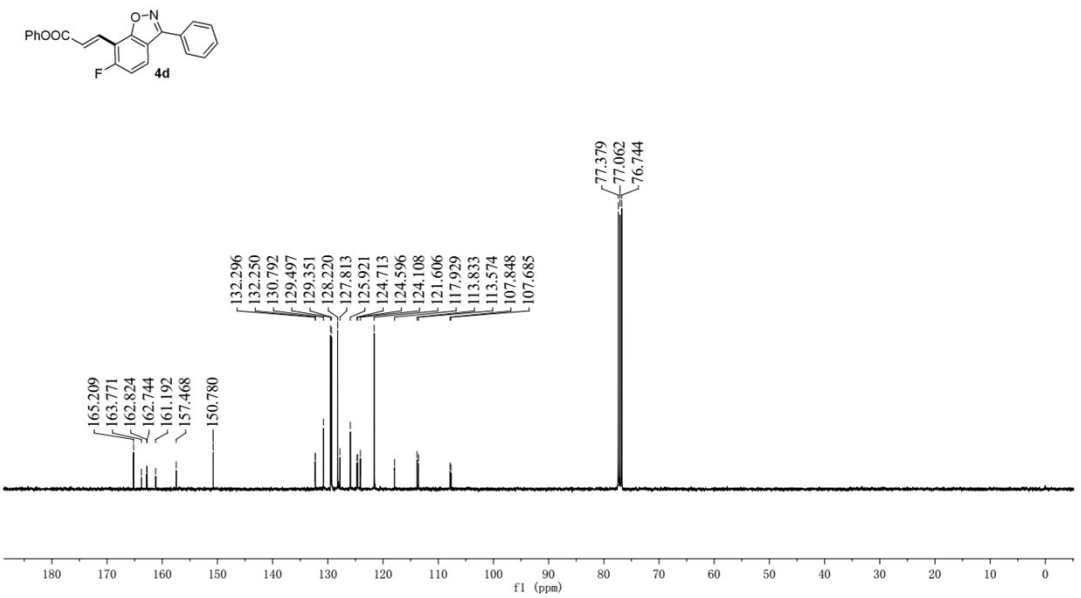


Monoisotopic Mass, Odd and Even Electron Ions
258 formula(e) evaluated with 25 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-20 H: 0-18 N: 0-1 O: 0-3 F: 0-1



Minimum:	3.00			-1.5			
Maximum:	100.00	5.0	10.0	50.0			
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
339.1270	6.07	339.1271	-0.1	-0.3	12.0	7.8	C20 H18 N O3 F

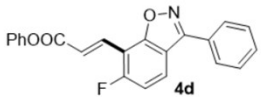

PhOOC
F
4d
7.939
7.930
7.921
7.915
7.908
7.898
7.886
7.603
7.593
7.587
7.577
7.462
7.458
7.438
7.422
7.294
7.276
7.260
7.238
7.217
f1 (ppm)


PhOOC
F
4d
77.379
77.062
76.744
132.296
132.250
130.792
129.497
129.351
128.220
127.813
125.921
124.713
124.596
124.108
121.606
117.929
113.833
113.574
107.848
107.685
165.209
163.771
162.824
162.744
161.192
157.468
150.780
f1 (ppm)

Elemental Composition Report

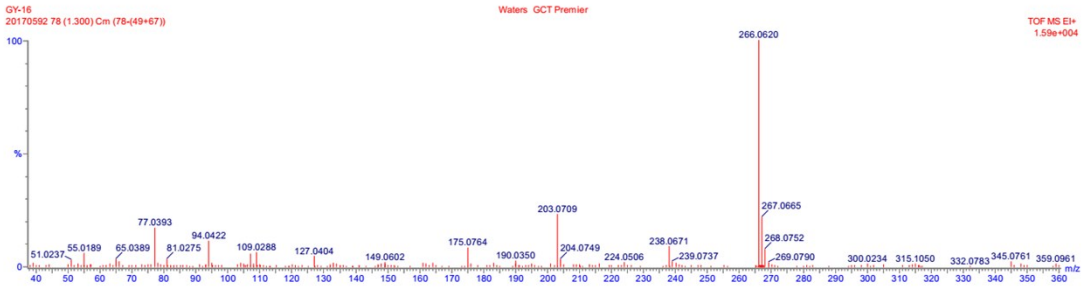
Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off



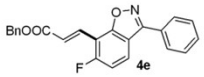
4d

Monoisotopic Mass, Odd and Even Electron Ions
631 formula(e) evaluated with 71 results within limits (up to 50 closest results for each mass
Elements Used:
C: 0-22 H: 0-14 N: 0-1 O: 0-3 F: 0-1

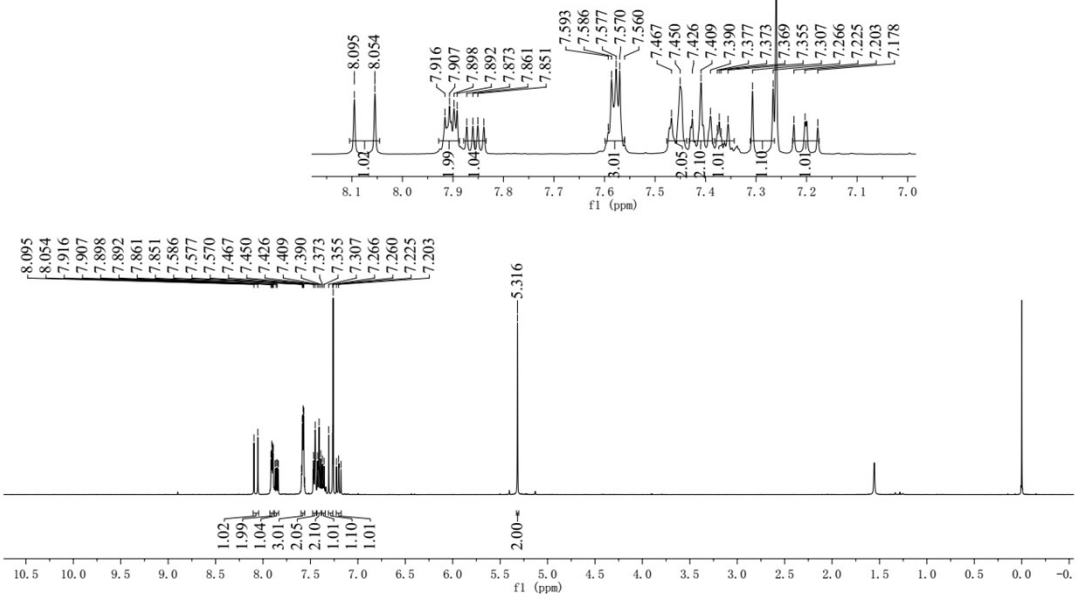


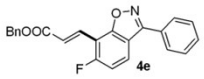
Minimum:	3.00			-1.5	
Maximum:	100.00	5.0	10.0	50.0	

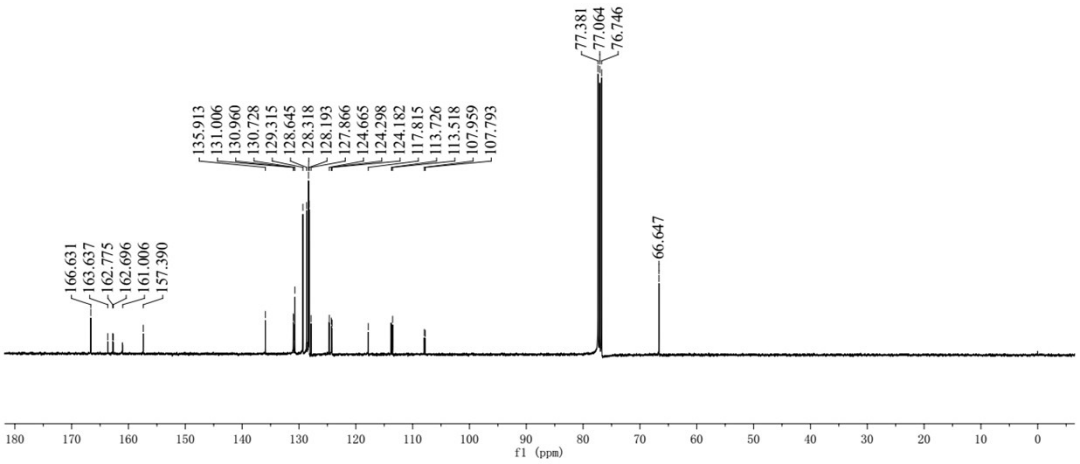
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
359.0961	1.12	359.0958	0.3	0.8	16.0	2773.5	C22 H14 N O3 F



4e



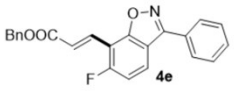




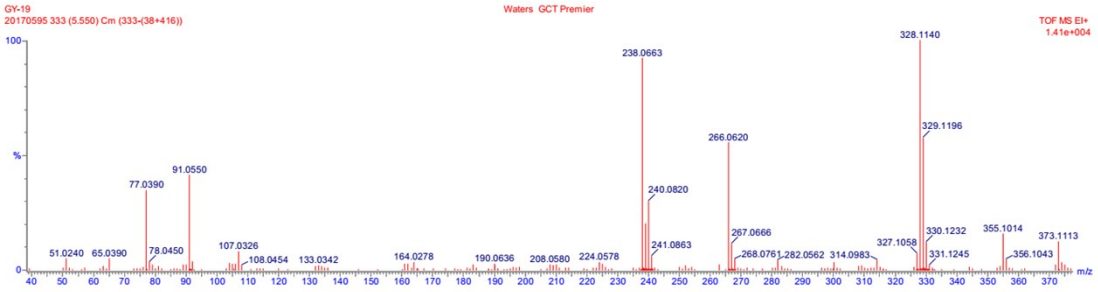
Elemental Composition Report

Single Mass Analysis

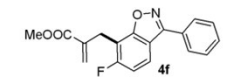
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

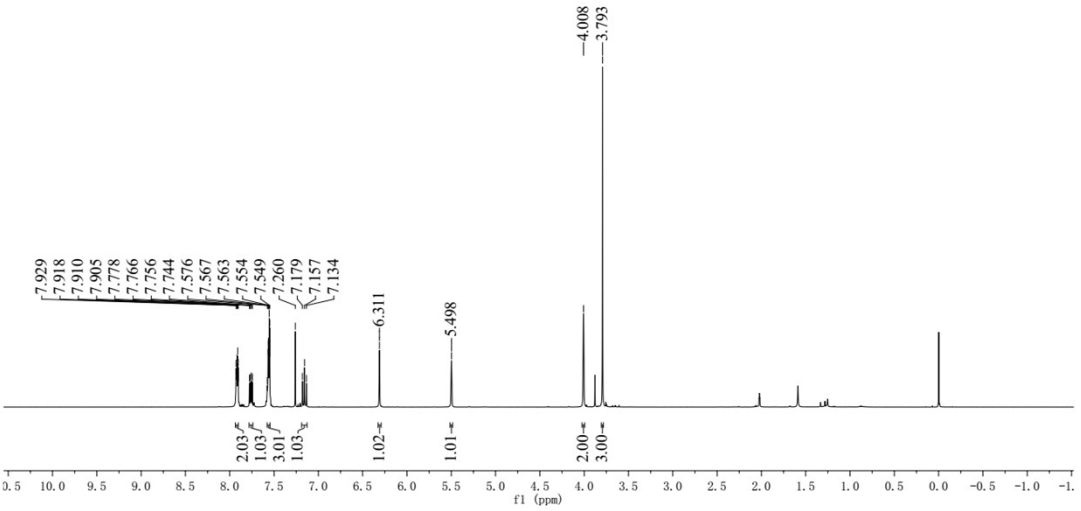


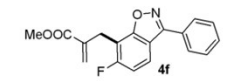
Monoisotopic Mass, Odd and Even Electron Ions
446 formula(e) evaluated with 46 results within limits (up to 1000 closest results for each mass
Elements Used:
C: 0-23 H: 0-16 N: 0-1 O: 0-3 F: 0-1

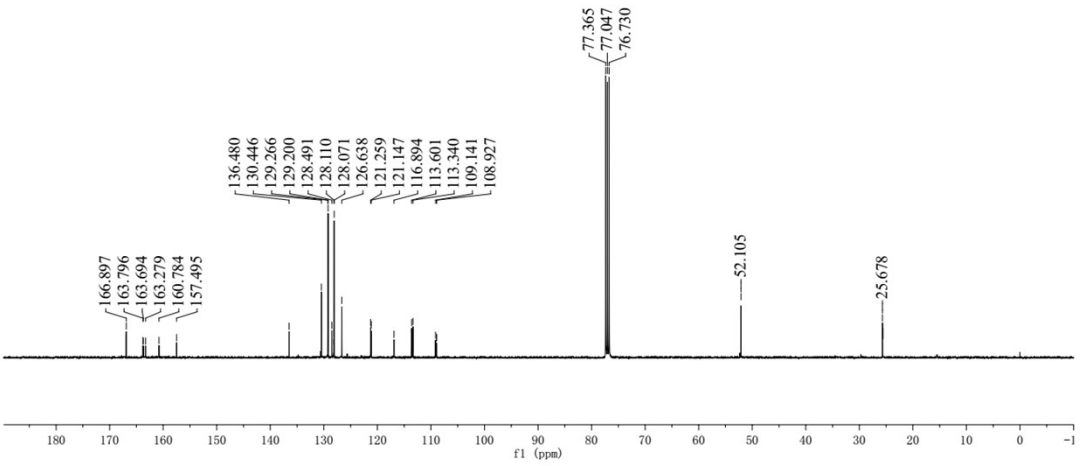


Minimum:	3.00			-1.5			
Maximum:	100.00	5.0	10.0	50.0			
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
373.1113	12.25	373.1114	-0.1	-0.3	16.0	85.5	C23 H16 N O3 F


MeOOC
O–N
F
4f


4.008
3.793
7.929
7.918
7.910
7.905
7.778
7.766
7.756
7.744
7.576
7.567
7.563
7.554
7.549
7.260
7.179
7.157
7.134
6.311
5.498
2.03
1.03
3.01
1.03
1.02
1.01
2.00
3.00
f1 (ppm)

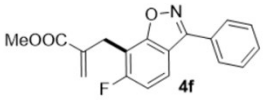

MeOOC
O–N
F
4f


77.365
77.047
76.730
136.480
130.446
129.266
129.200
128.491
128.110
128.071
126.638
121.259
121.147
116.894
113.601
113.340
109.141
108.927
166.897
163.796
163.694
163.279
160.784
157.495
52.105
25.678
f1 (ppm)

Elemental Composition Report

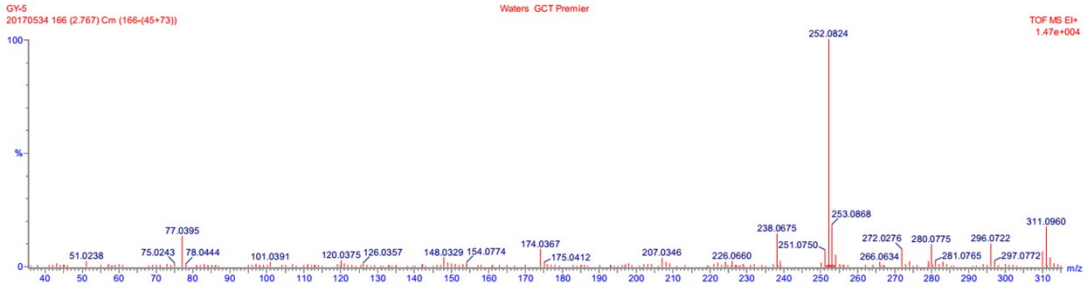
Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off



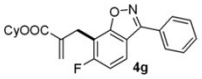
4f

Monoisotopic Mass, Odd and Even Electron Ions
220 formula(e) evaluated with 24 results within limits (up to 50 closest results for each mass
Elements Used:
C: 0-18 H: 0-14 N: 0-1 O: 0-3 F: 0-1

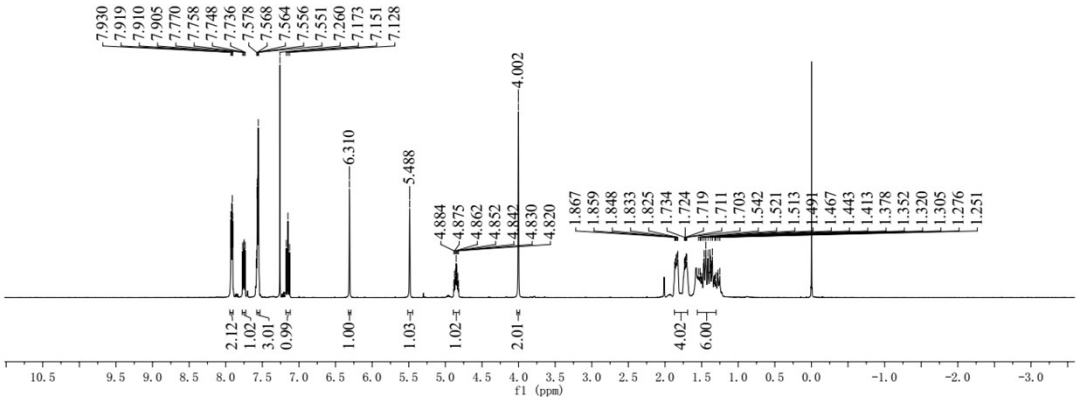


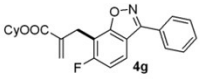
Minimum:	3.00			-1.5	
Maximum:	100.00	5.0	10.0	50.0	

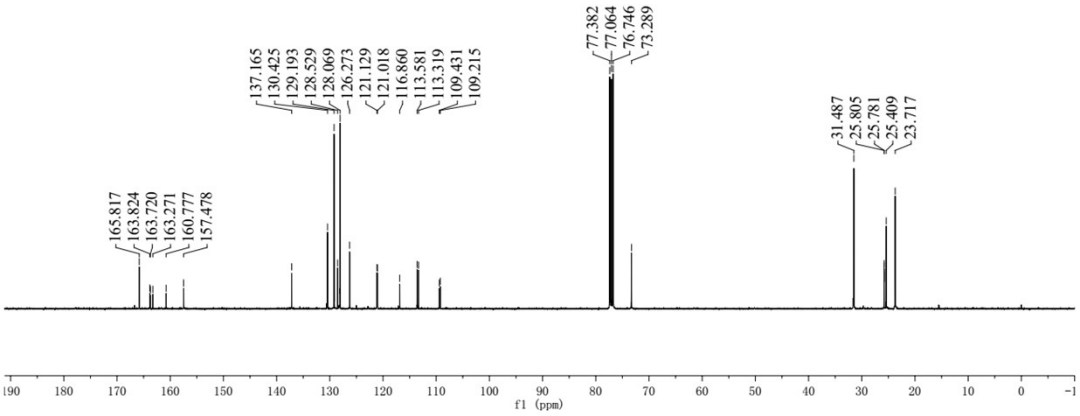
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
311.0960	17.35	311.0958	0.2	0.6	12.0	13.9	C18 H14 N O3 F



4g



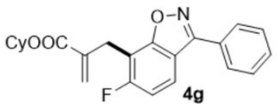




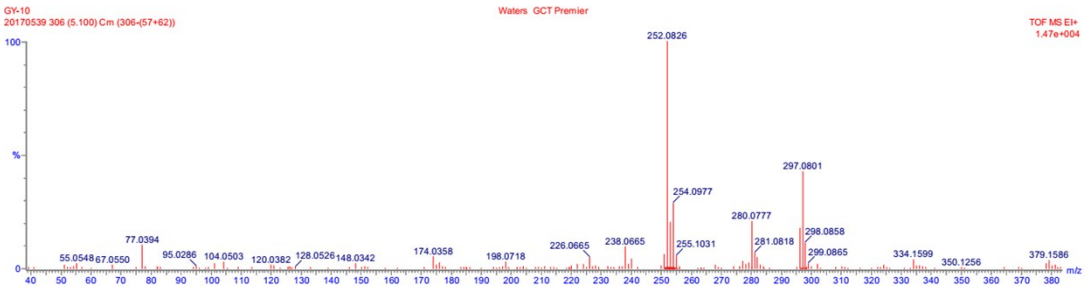
Elemental Composition Report

Single Mass Analysis

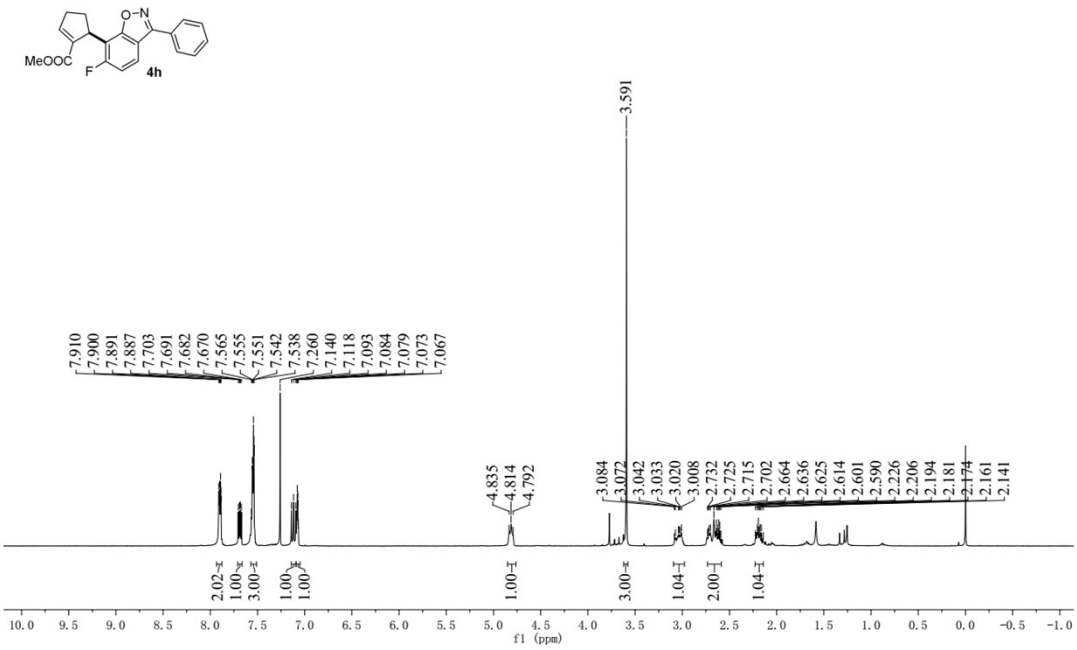
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

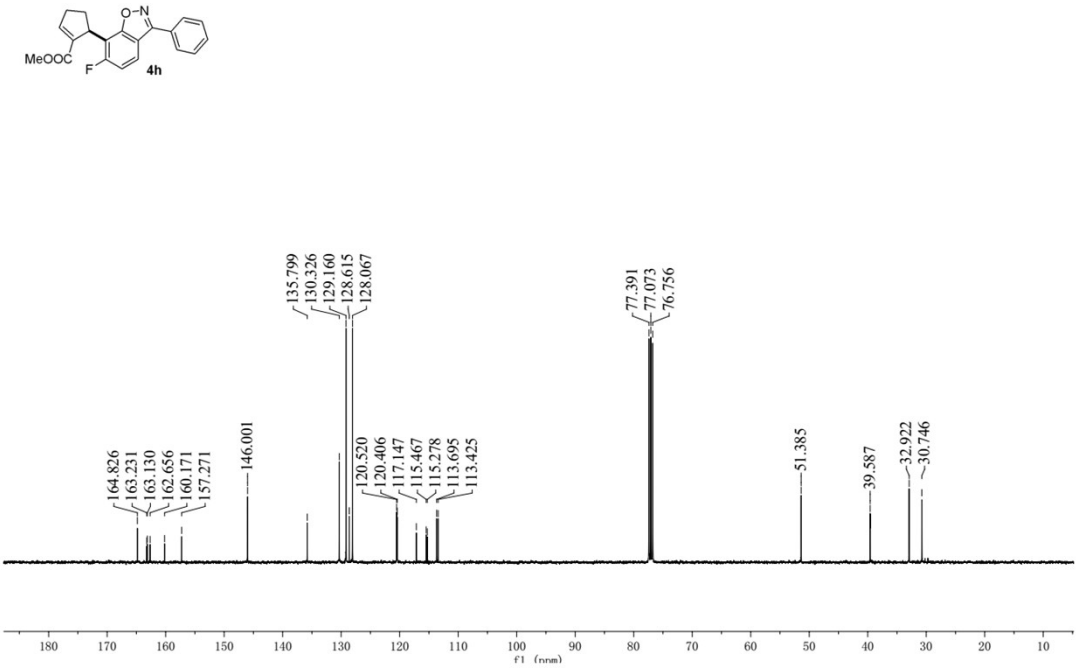


Monoisotopic Mass, Odd and Even Electron Ions
774 formula(e) evaluated with 60 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-23 H: 0-22 N: 0-1 O: 0-3 F: 0-1



Minimum:	3.00			-1.5			
Maximum:	100.00	5.0	10.0	50.0			
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
379.1586	3.34	378.1584	0.2	0.5	13.0	79.2	C23 H22 N O3 F

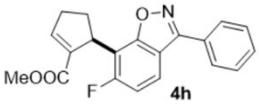

MeOOC
F
4h
7.910
7.900
7.891
7.887
7.703
7.691
7.682
7.670
7.565
7.555
7.551
7.542
7.538
7.260
7.140
7.118
7.093
7.084
7.079
7.073
7.067
4.835
4.814
4.792
3.591
3.084
3.072
3.042
3.033
3.020
3.008
2.732
2.725
2.715
2.702
2.664
2.636
2.625
2.614
2.601
2.590
2.226
2.206
2.194
2.181
2.174
2.161
2.141
2.02
1.00
3.00
1.00
1.00
1.00
3.00
1.04
2.00
1.04
f1 (ppm)


MeOOC
F
4h
164.826
163.231
163.130
162.656
160.171
157.271
146.001
135.799
130.326
129.160
128.615
128.067
120.520
120.406
117.147
115.467
115.278
113.695
113.425
77.391
77.073
76.756
51.385
39.587
32.922
30.746
f1 (ppm)

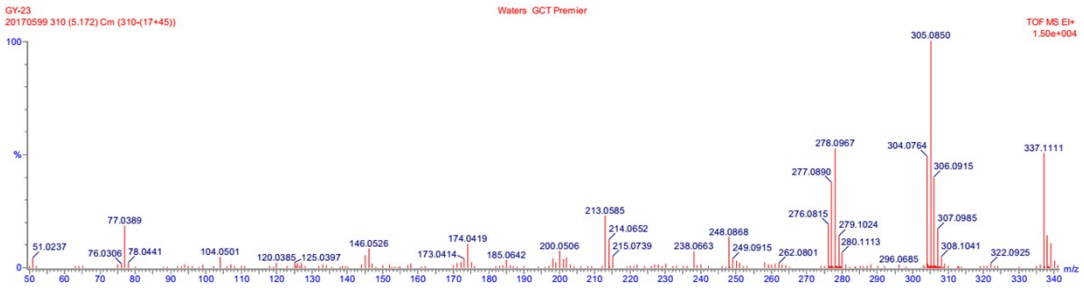
Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

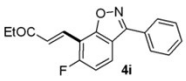


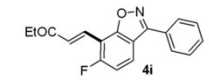
Monoisotopic Mass, Odd and Even Electron Ions
577 formula(e) evaluated with 58 results within limits (up to 50 closest results for each mass
Elements Used:
C: 0-20 H: 0-16 N: 0-1 O: 0-3 F: 0-1



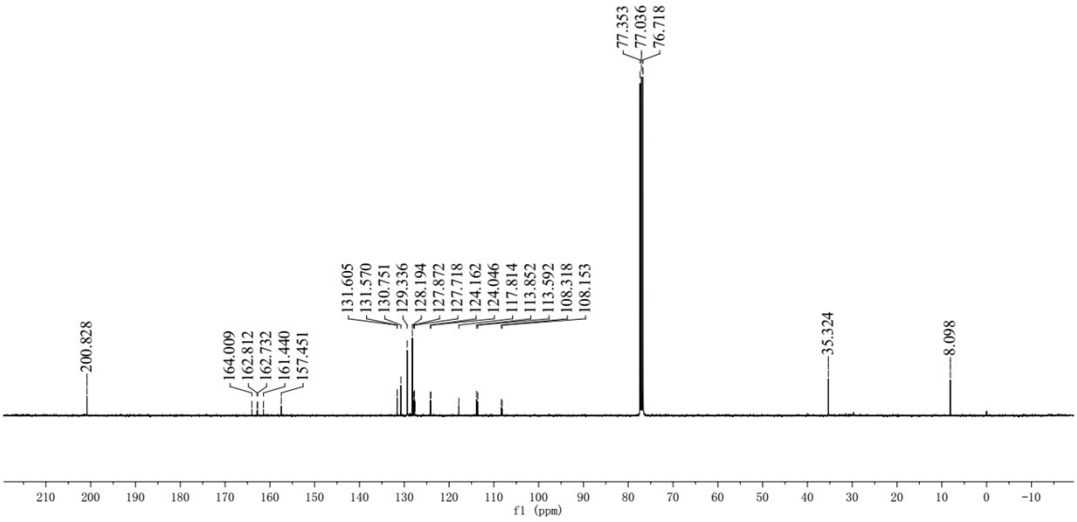
Minimum:	3.00			-1.5
Maximum:	100.00	5.0	10.0	50.0

Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
337.1111	50.32	337.1114	-0.3	-0.9	13.0	576.7	C20 H16 N O3 F



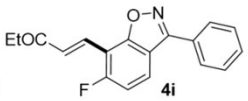


4i



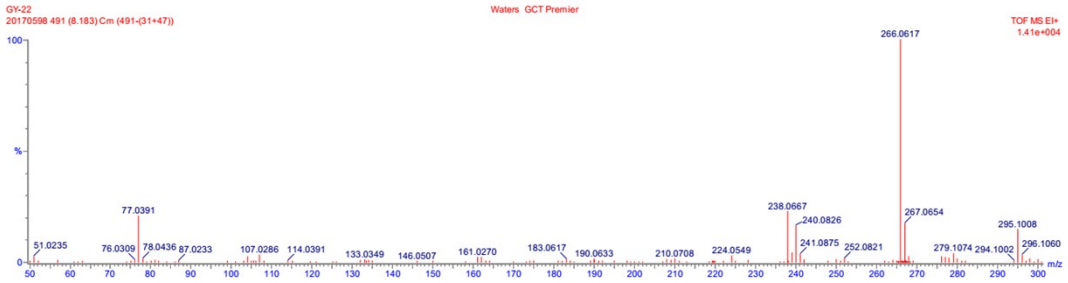
Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

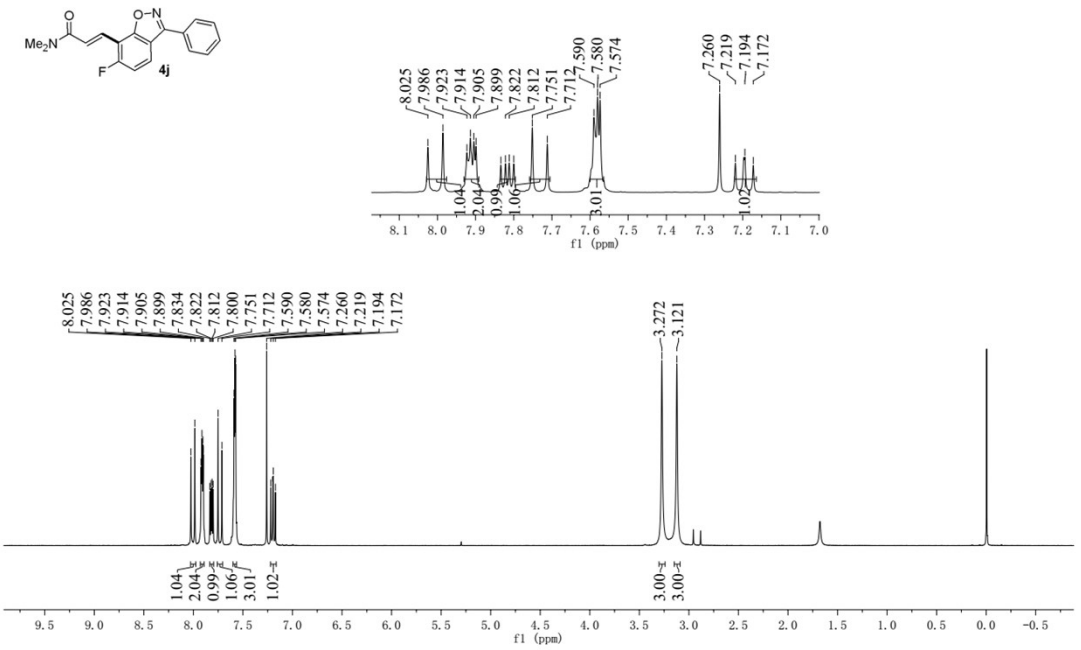


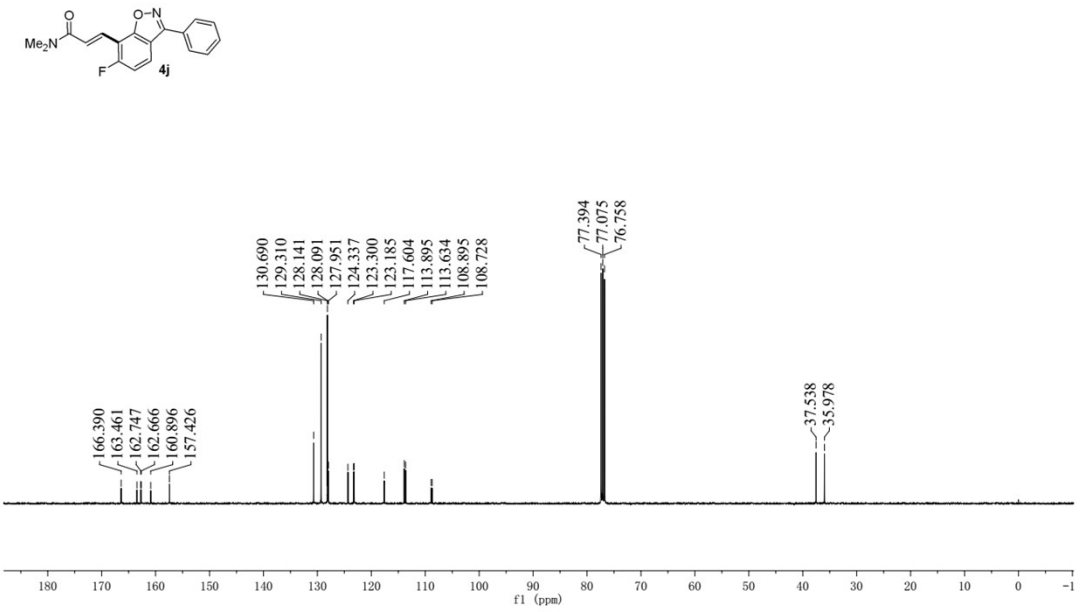
4i

Monoisotopic Mass, Odd and Even Electron Ions
98 formula(e) evaluated with 14 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-18 H: 0-14 N: 0-1 O: 0-2 F: 0-1



Minimum:	3.00			-1.5			
Maximum:	100.00	5.0	10.0	50.0			
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
295.1008	14.47	295.1009	-0.1	-0.3	12.0	3.2	C18 H14 N O2 F

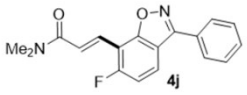

4j
8.025
7.986
7.923
7.914
7.905
7.899
7.834
7.822
7.812
7.800
7.751
7.712
7.590
7.580
7.574
7.260
7.219
7.194
7.172
3.272
3.121
1.04
2.04
0.99
1.06
3.01
1.02
3.00
3.00
f1 (ppm)


4j
166.390
163.461
162.747
162.666
160.896
157.426
130.690
129.310
128.141
128.091
127.951
124.337
123.300
123.185
117.604
113.895
113.634
108.895
108.728
77.394
77.075
76.758
37.538
35.978
f1 (ppm)

Elemental Composition Report

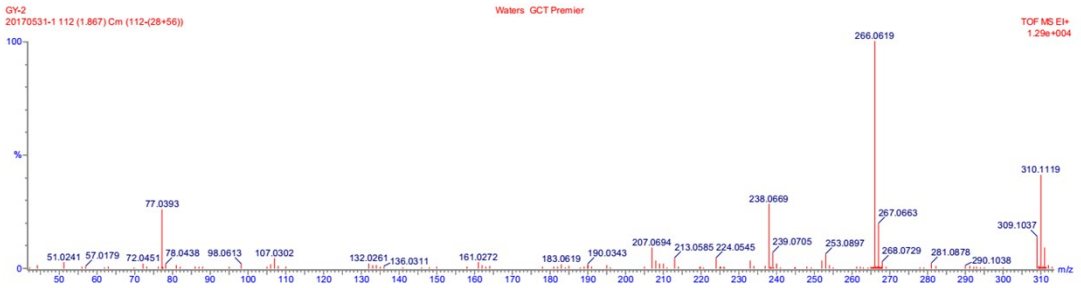
Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

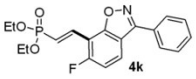


4j

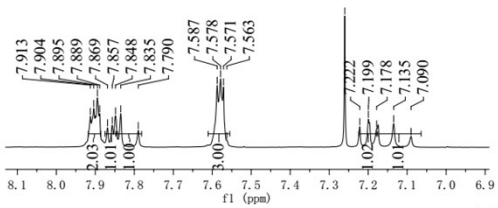
Monoisotopic Mass, Odd and Even Electron Ions
295 formula(e) evaluated with 25 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-18 H: 0-15 N: 0-2 O: 0-2 F: 0-1

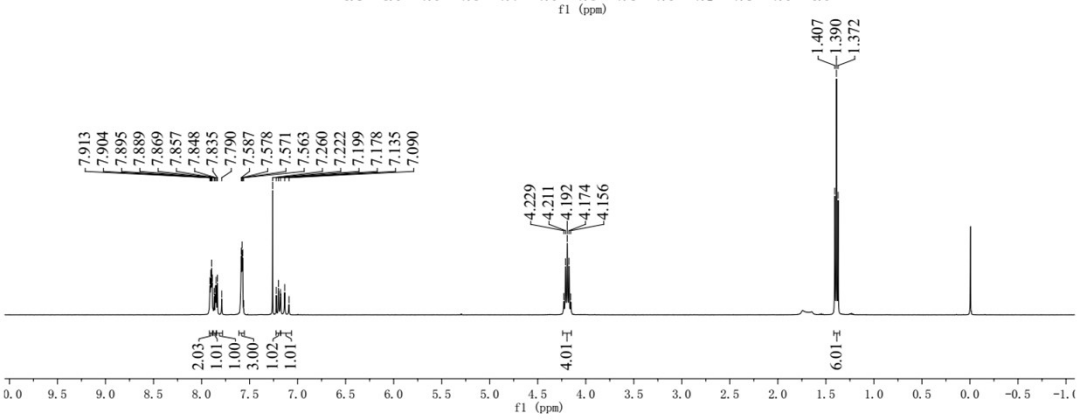


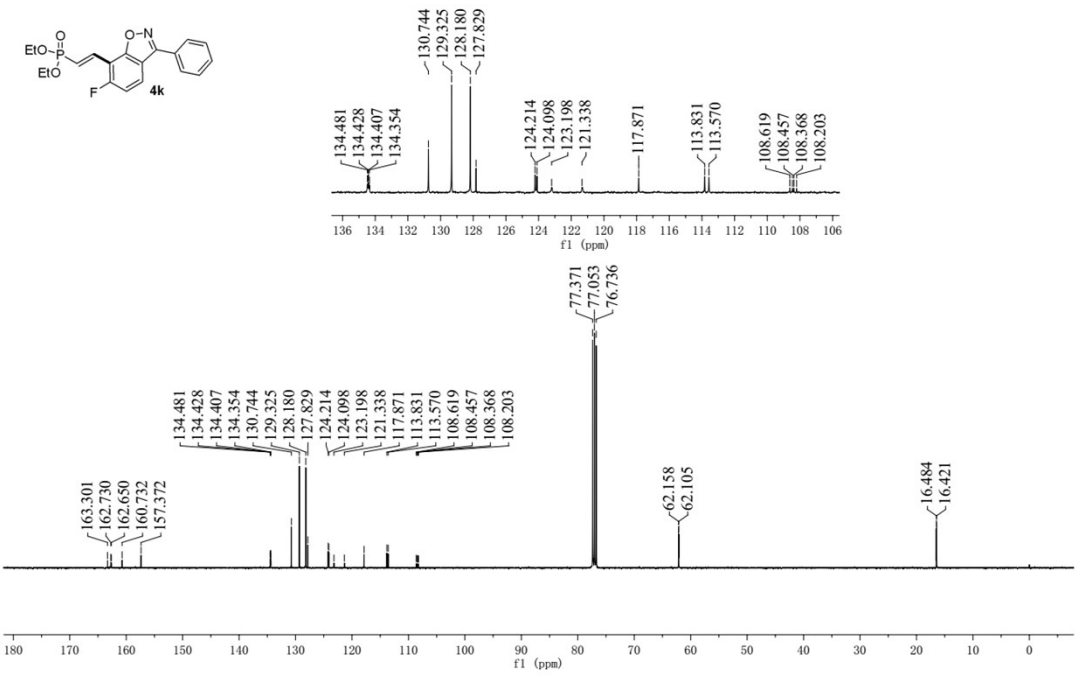
Minimum:	3.00			-1.5			
Maximum:	100.00	5.0	10.0	50.0			
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
310.1119	40.90	310.1118	0.1	0.3	12.0	0.4	C18 H15 N2 O2 F



4k



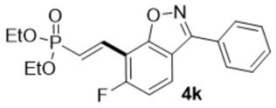




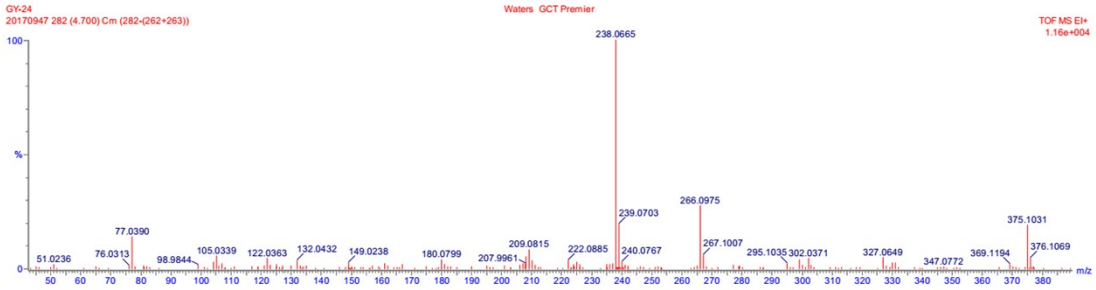
Elemental Composition Report

Single Mass Analysis

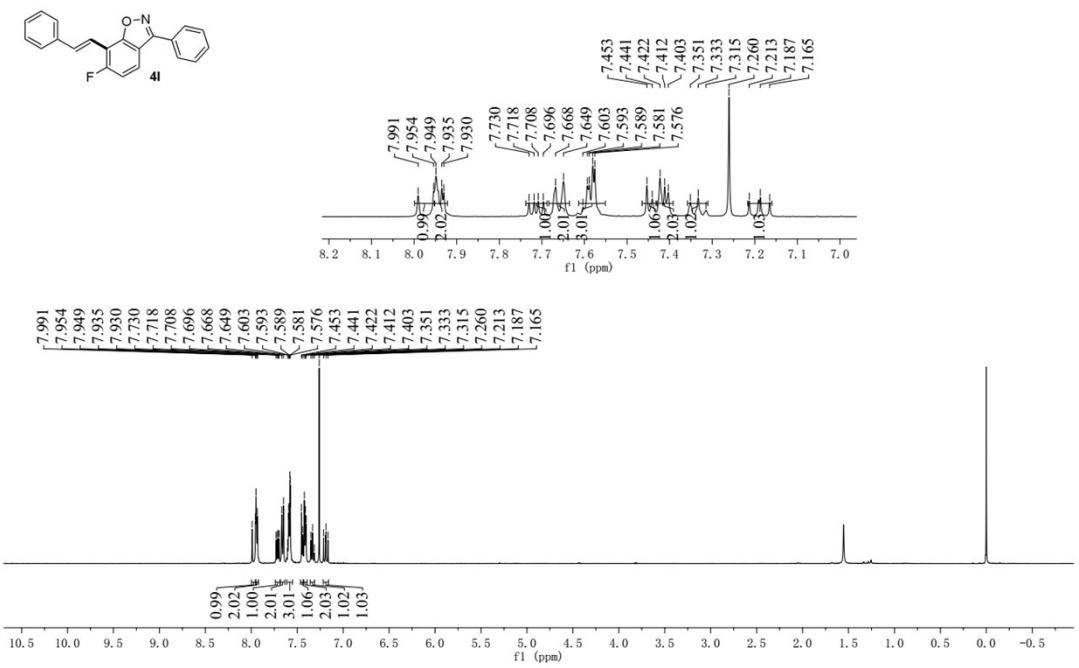
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

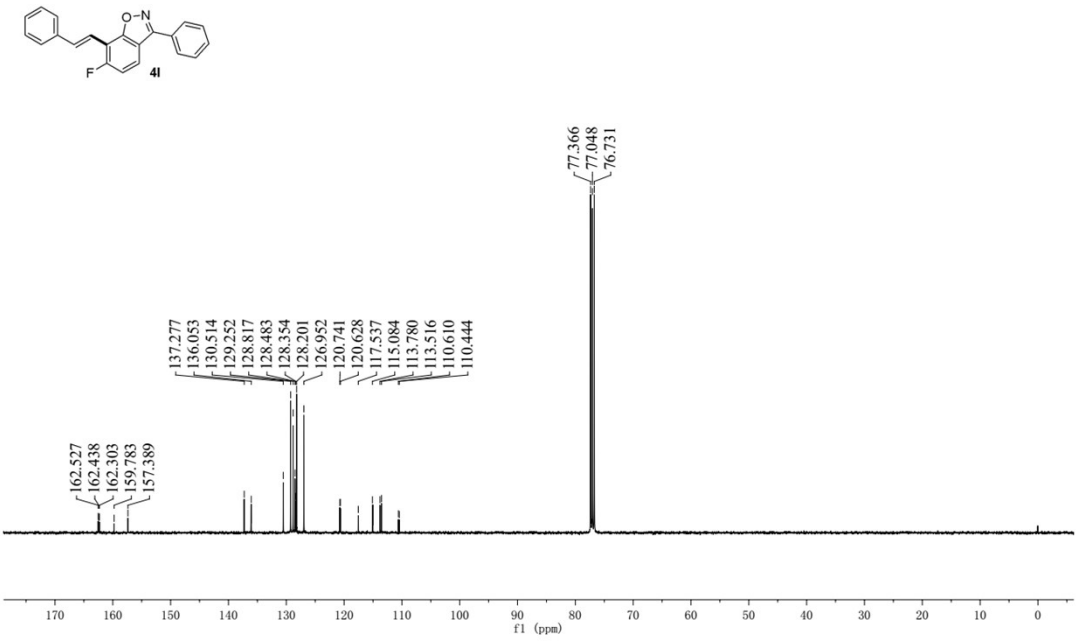


Monoisotopic Mass, Odd and Even Electron Ions
1021 formula(e) evaluated with 67 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-19 H: 0-19 N: 0-1 O: 0-4 P: 0-1 F: 0-1



Minimum:	3.00			-1.5			
Maximum:	100.00	5.0	10.0	50.0			
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
375.1031	19.04	375.1036	-0.5	-1.3	11.0	1.0	C19 H19 N O4 P F

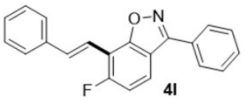

4l
7.991
7.954
7.949
7.935
7.930
7.730
7.718
7.708
7.696
7.668
7.649
7.603
7.593
7.589
7.581
7.576
7.453
7.441
7.422
7.412
7.403
7.351
7.333
7.315
7.260
7.213
7.187
7.165
0.99
2.02
1.00
2.01
3.01
1.06
2.03
1.02
1.03
f1 (ppm)


4l
77.366
77.048
76.731
137.277
136.053
130.514
129.252
128.817
128.483
128.354
128.201
126.952
120.741
120.628
117.537
115.084
113.780
113.516
110.610
110.444
162.527
162.438
162.303
159.783
157.389
f1 (ppm)

Elemental Composition Report

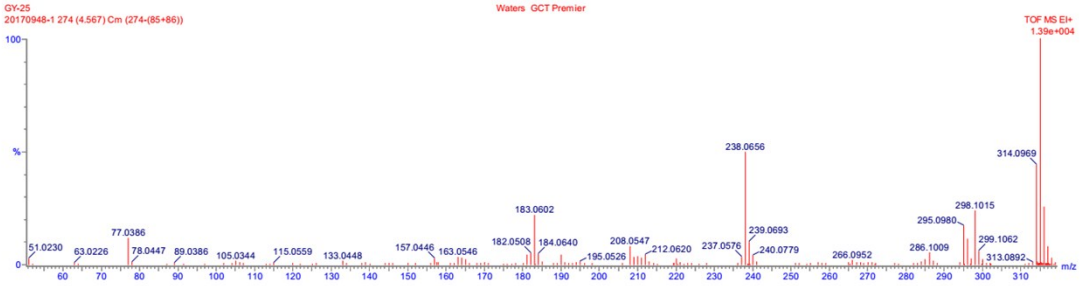
Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

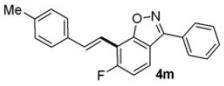


4l

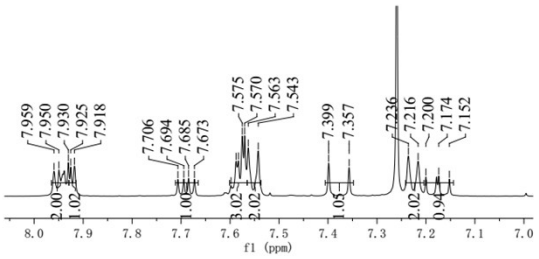
Monoisotopic Mass, Odd and Even Electron Ions
184 formula(e) evaluated with 29 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-21 H: 0-14 N: 0-1 O: 0-1 F: 0-1

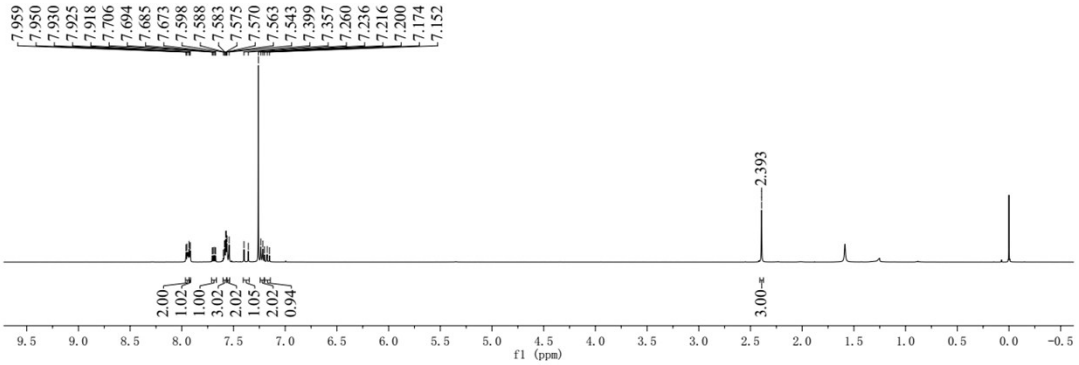


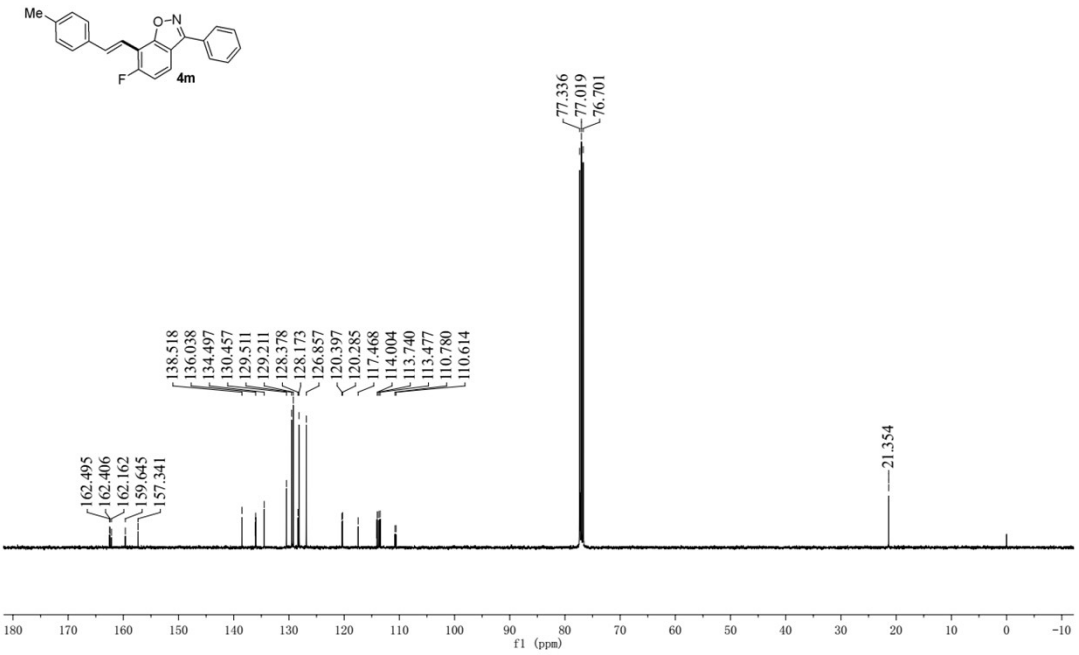
Minimum:	3.00			-1.5			
Maximum:	100.00	5.0	10.0	50.0			
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
315.1060	100.00	315.1059	0.1	0.3	15.0	202.2	C21 H14 N O F



4m



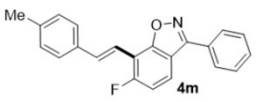




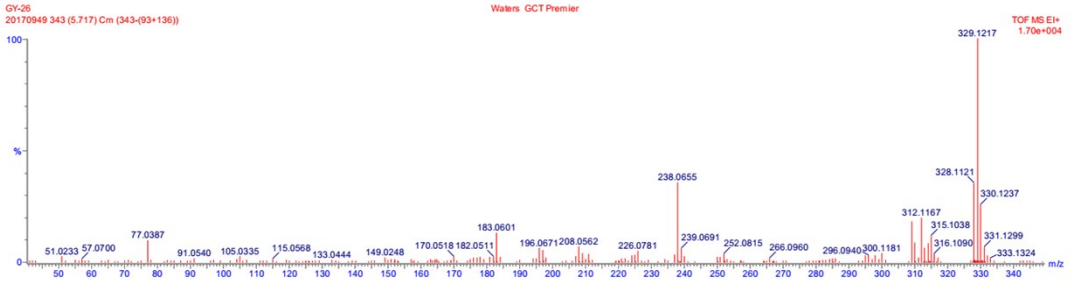
Elemental Composition Report

Single Mass Analysis

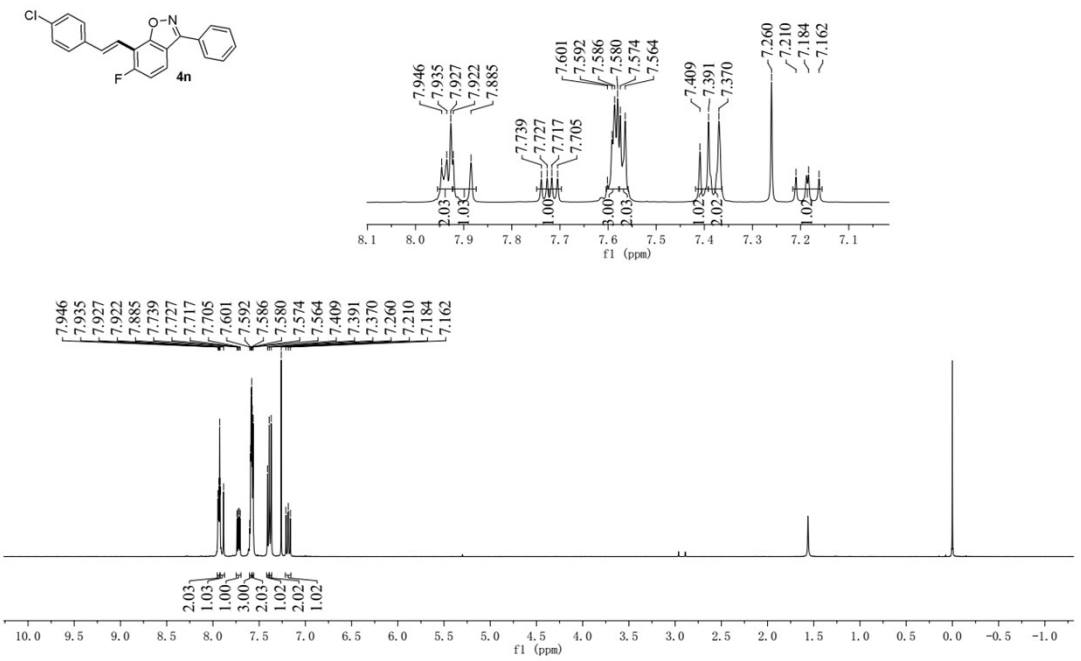
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off



Monoisotopic Mass, Odd and Even Electron Ions
190 formula(e) evaluated with 29 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-22 H: 0-16 N: 0-1 O: 0-1 F: 0-1



Minimum:	3.00			-1.5			
Maximum:	100.00	5.0	10.0	50.0			
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
329.1217	100.00	329.1216	0.1	0.3	15.0	135.4	C22 H16 N O F


4n
7.946
7.935
7.927
7.922
7.885
7.739
7.727
7.717
7.705
7.601
7.592
7.586
7.580
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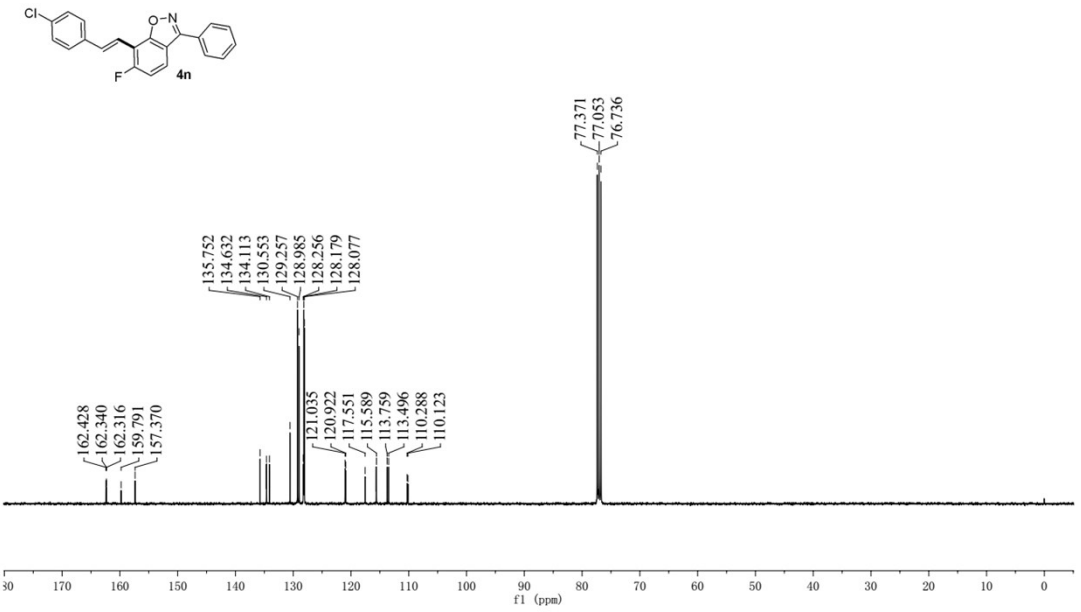
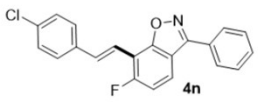
7.391
7.370
7.260
7.210
7.184
7.162
f1 (ppm)


4n
77.371
77.053
76.736
135.752
134.632
134.113
130.553
129.257
128.985
128.256
128.179
128.077
121.035
120.922
117.551
115.589
113.759
113.496
110.288
110.123
162.428
162.340
162.316
159.791
157.370
f1 (ppm)

Elemental Composition Report

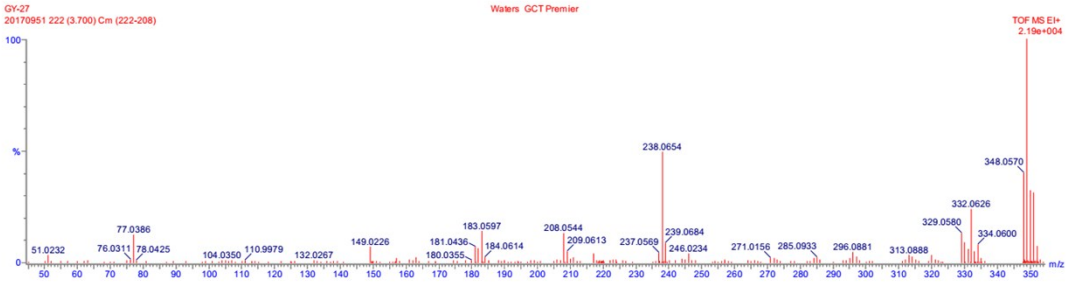
Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

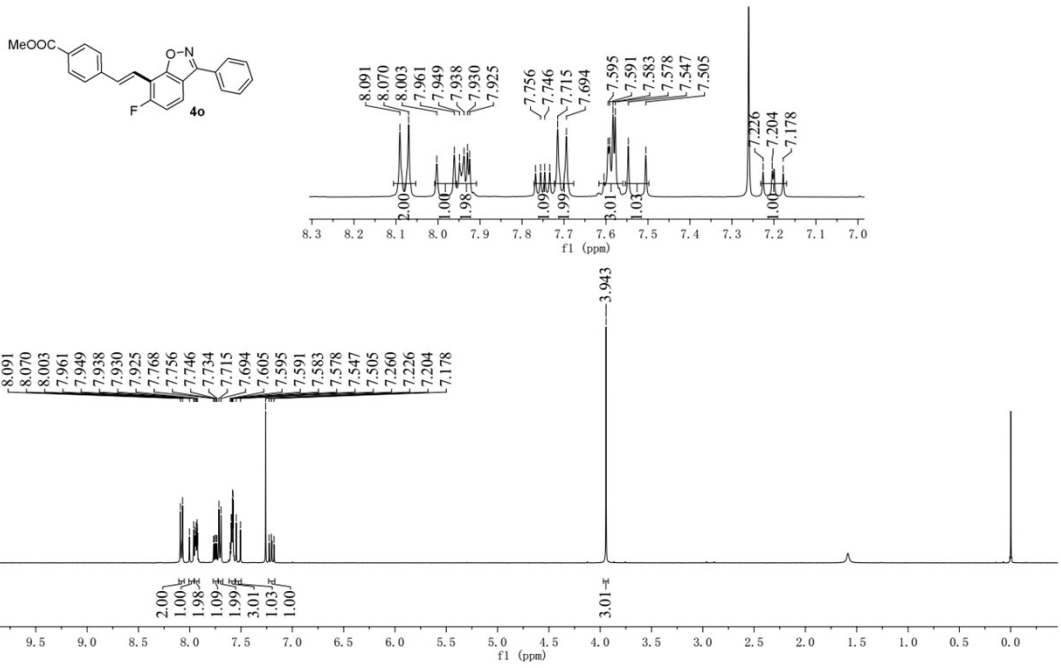


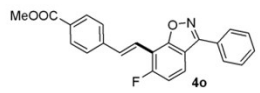
4n

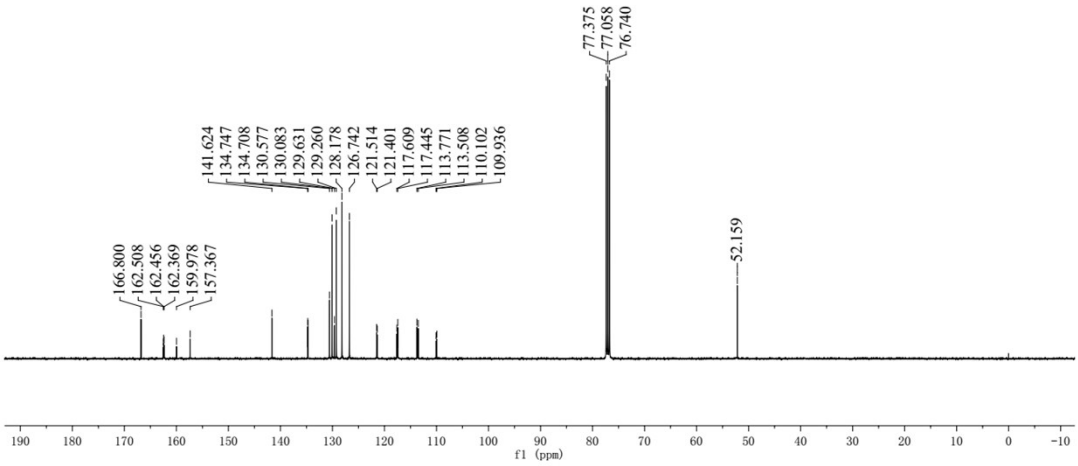
Monoisotopic Mass, Odd and Even Electron Ions
77 formula(e) evaluated with 48 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-21 H: 0-13 N: 0-1 O: 0-1 F: 0-1 35Cl: 0-1 37Cl:0-1



Minimum:	3.00			-1.5			
Maximum:	100.00	5.0	10.0	50.0			
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
349.0672	100.00	349.0670	0.2	0.6	15.0	281.5	C21 H13 N O 35Cl F



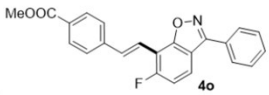




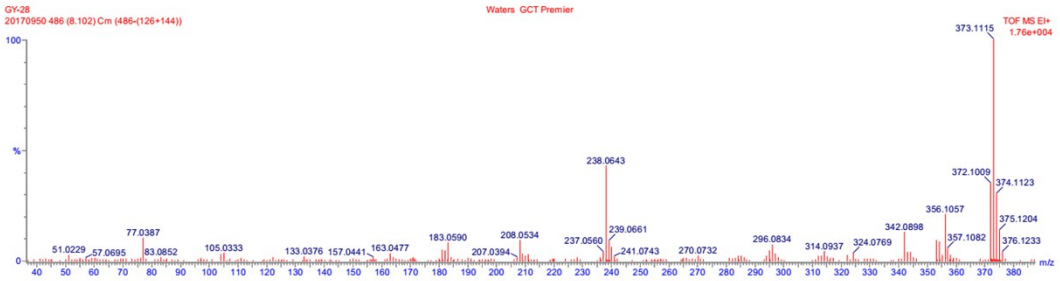
Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

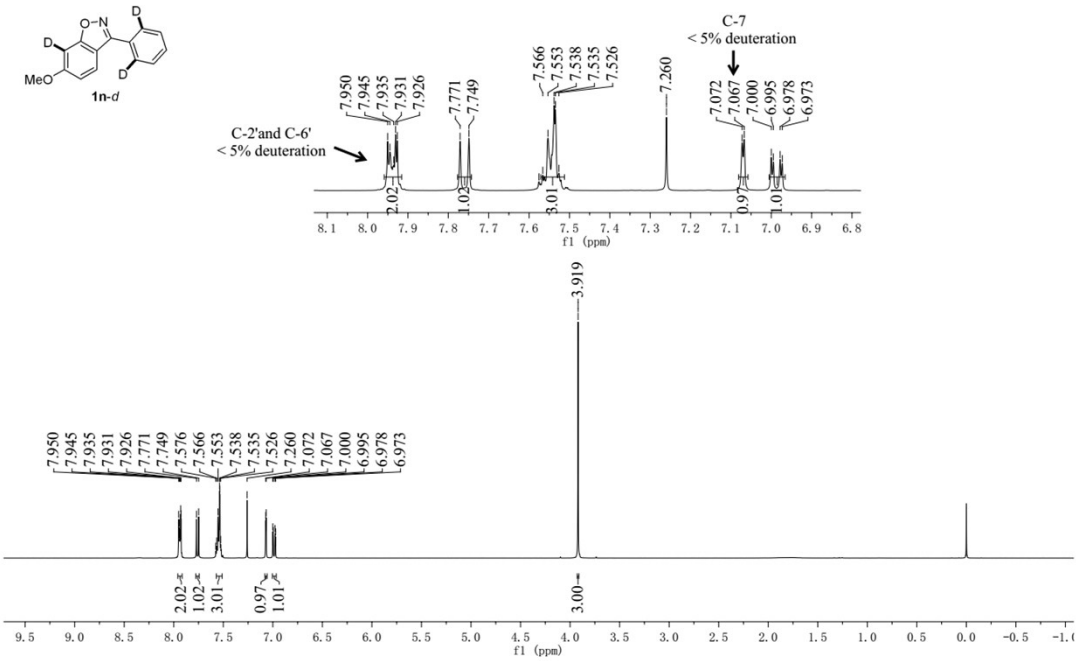


Monoisotopic Mass, Odd and Even Electron Ions
482 formula(e) evaluated with 38 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-23 H: 0-16 N: 0-1 O: 0-3 F: 0-1

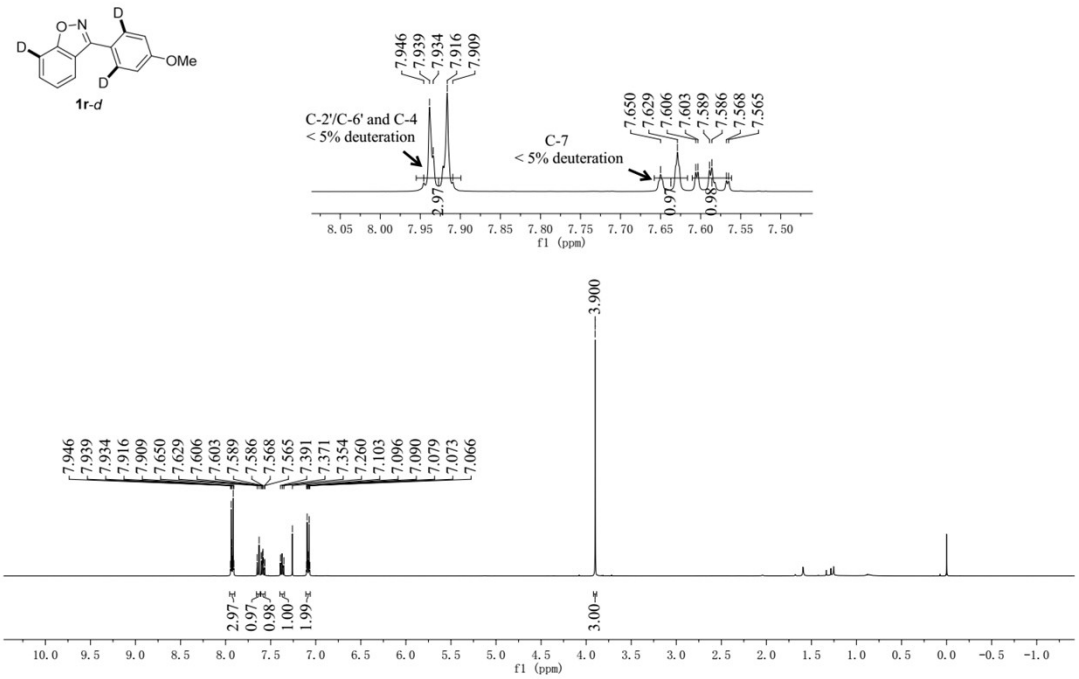


Minimum:	3.00			-1.5			
Maximum:	100.00	5.0	10.0	50.0			
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
373.1115	100.00	373.1114	0.1	0.3	16.0	601.1	C23 H16 N O3 F

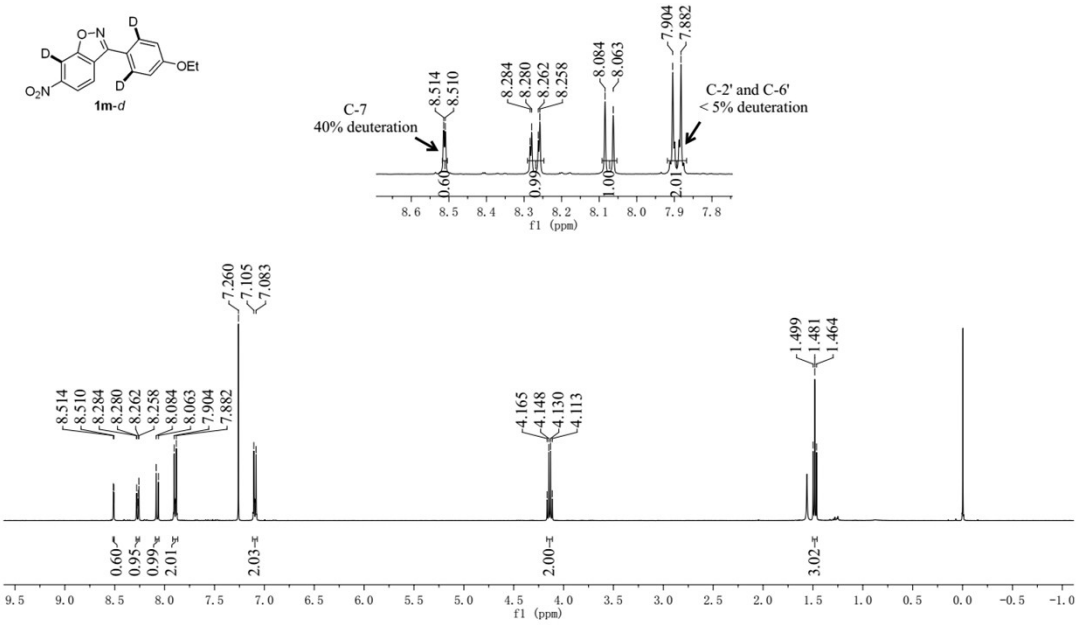
4.2 Copies of the spectra for Scheme 2



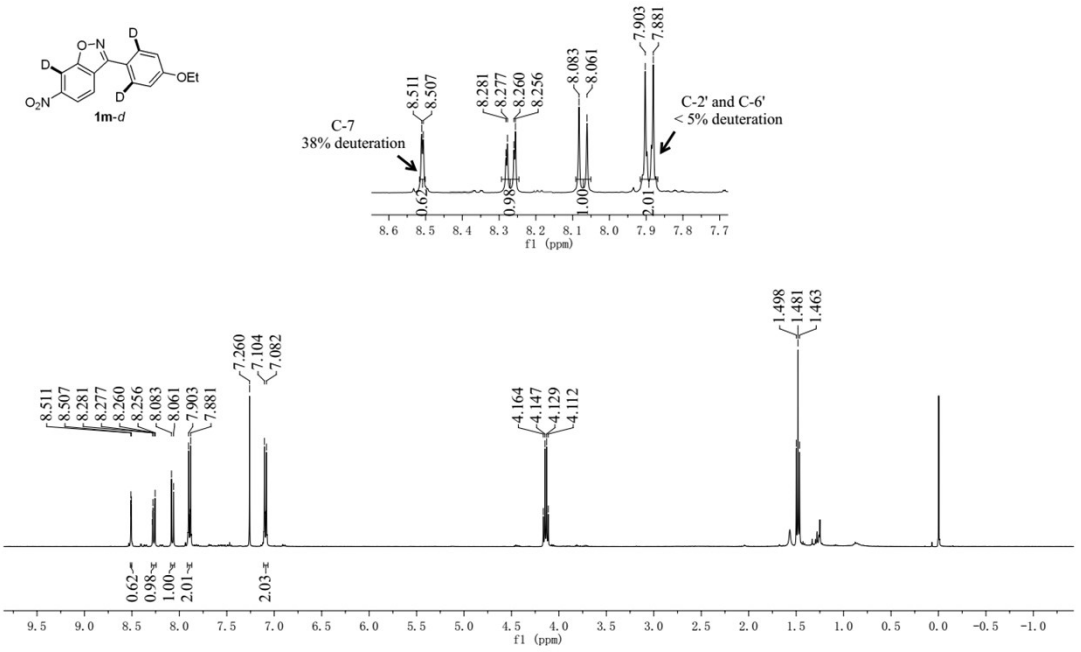
^{1}H NMR spectra for Scheme 2A



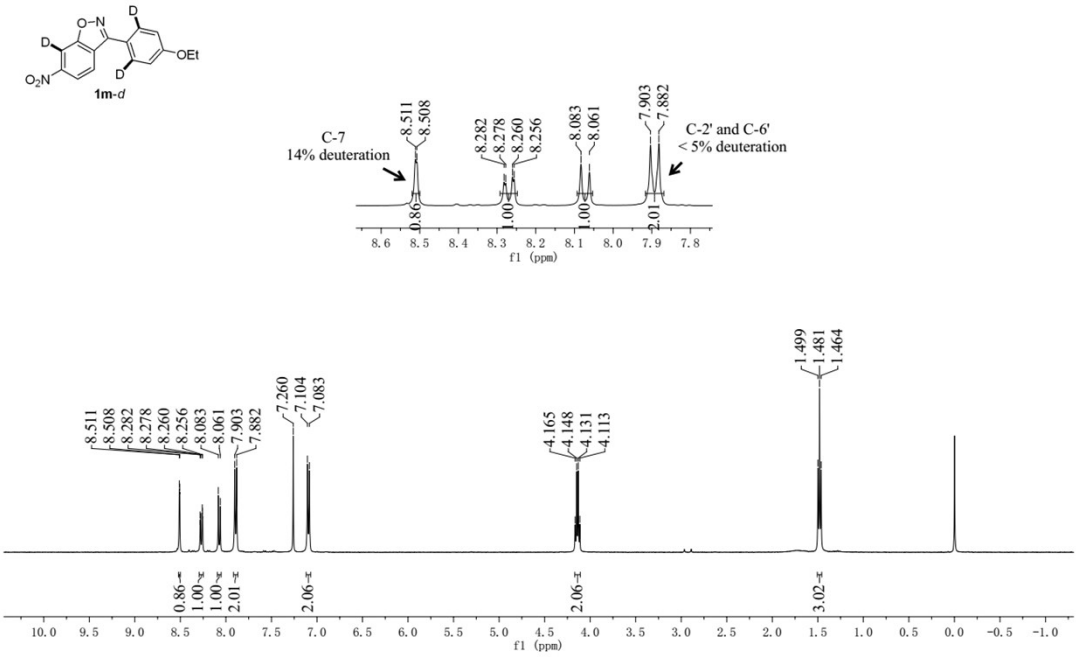
^{1}H NMR spectra for Scheme 2B



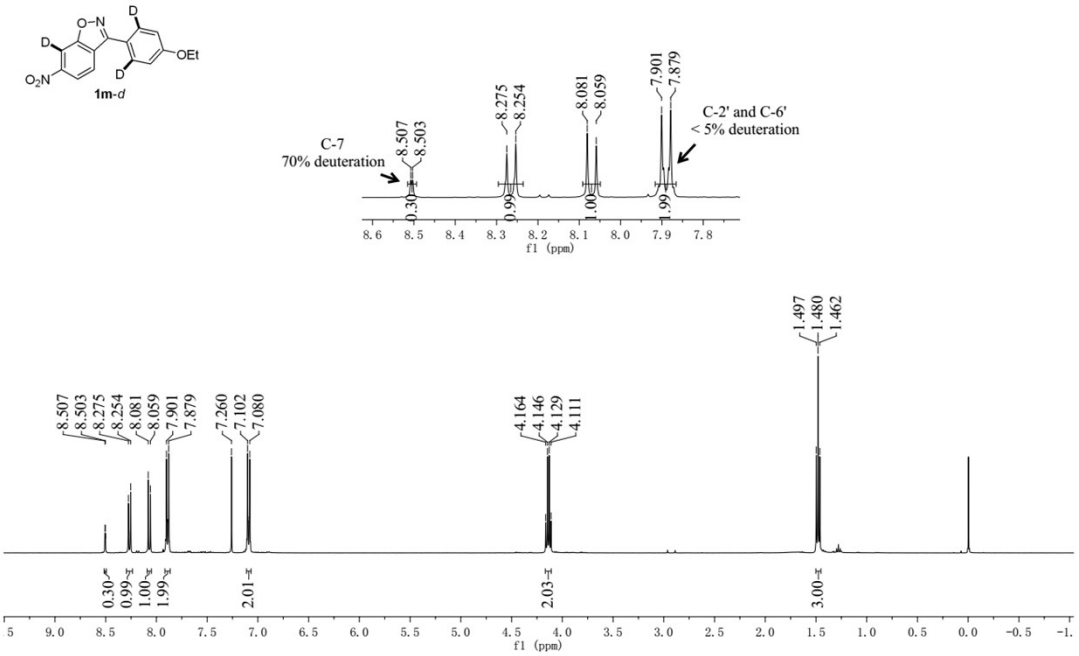
^{1}H NMR spectra for Scheme 2C



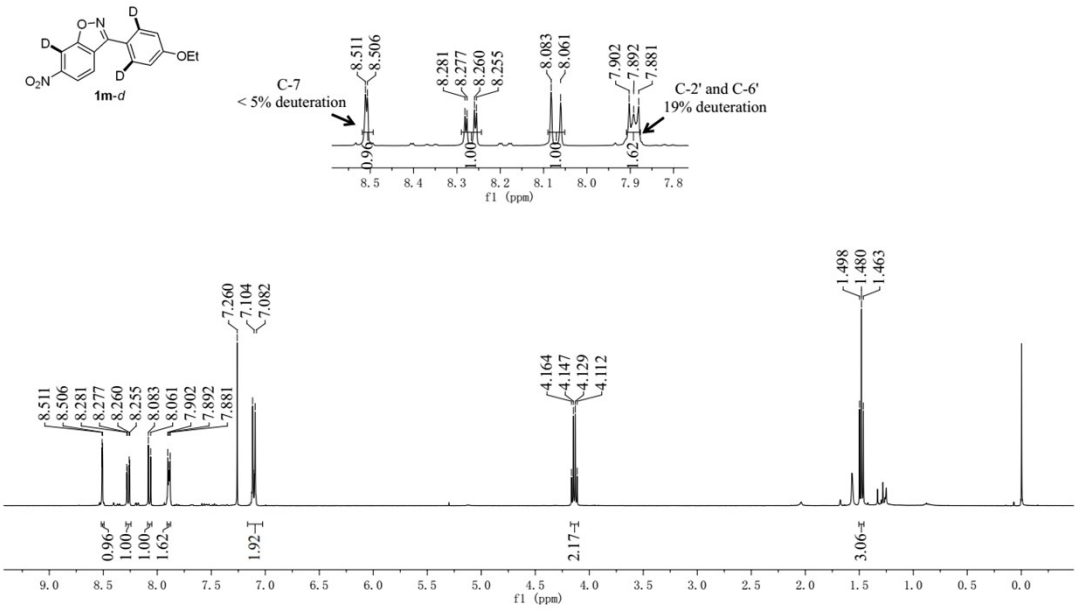
^{1}H NMR spectra for Scheme 2D



^{1}H NMR spectra for Scheme 2E



^{1}H NMR spectra for Scheme 2F



^{1}H NMR spectra for Scheme 2G