Tiosquaramide-catalysed Asymmetric Double Michael Addition of 2-(*3H*)-Furanone to Nitroolefines

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Content

General Methods

Commercially available compounds were used without further purification. The solvents and reagents were purified and dried according to standard procedures. Column chromatography was carried out using silica gel (200–300 mesh). Melting points were measured on an XT-4 melting point apparatus without correction. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on BRUKER AVANCE II 400MHz and 600MHz spectrometer. Infrared spectra were obtained on Thermo Scientific Nicolet iS5 or Bruker tensor II spectrometer. The ESI-HRMS spectra were obtained on Bruker APEX IV mass spectrometer. Elemental analysis was performed with an Elementar Vario MICRO Cube. Optical rotations were measured with Rudolph Research Analytical Autopol III. The dr value and ee value of the products were determined by chiral HPLC (Shimadzu LC-20A) analysis using a Chiralpak IC (n-hexane/EtOH as eluent). The crystal structure of **3a** was confirmed by D8 Venture X-ray crystal diffractometer.

Synthesis of organocatalysts

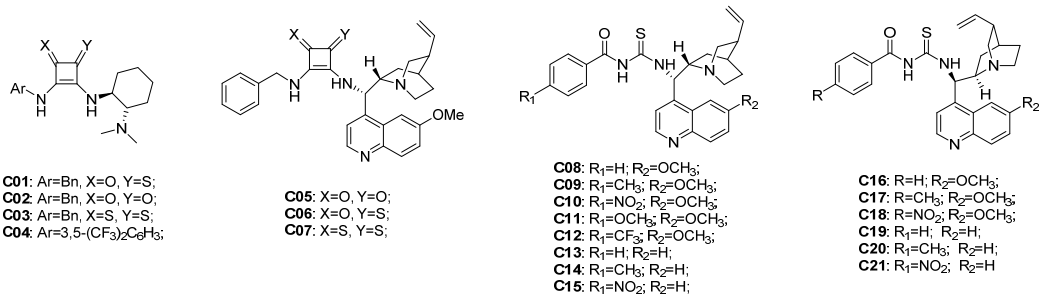
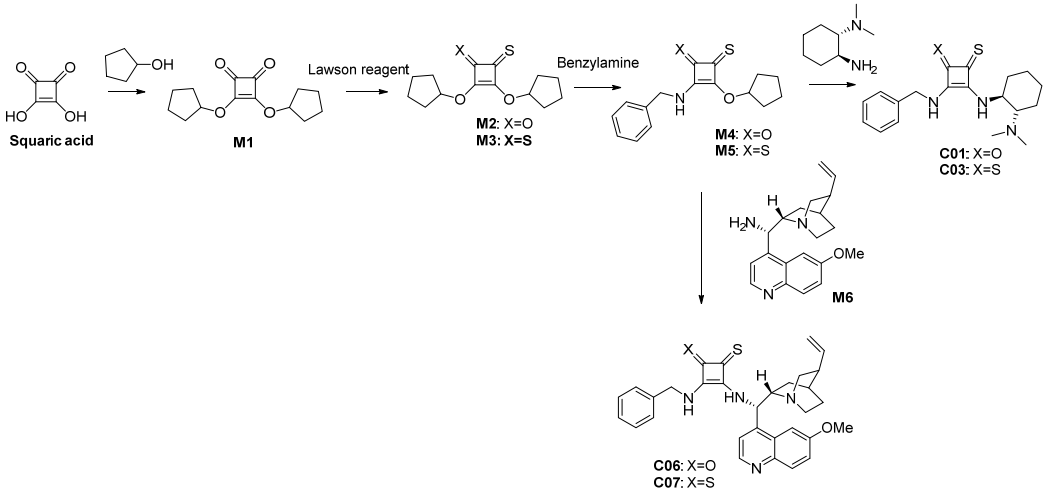


Figure S1. Structures of **C01**-**C21**.

C02, **C04** and **C05** were known compounds and prepared according to the literature procedures.[3-5] **C08**-**C21** were reported in our previous work.[2,6]

C01, **C03**, **C06** and **C07** were synthesized as followed routes in Scheme S1. Intermediates **M1**-**M5** in Scheme S1 were prepared according to the literature.[1] **M6** was prepared according to the literature.[2,6]



Scheme S1. Synthetic routes of **C01**, **C03**, **C06** and **C07**.

2-(Benzylamino)-3-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-4-Thioxocyclobut-2-en-1-one (C01). Compound **M4** (1.0 mmol, 1.0 eq.) was dissolved in DCM, and (1*S*,2*S*)-N, N-dimethylcyclohexane-1,2-diamine (1.1 mmol, 1.1 eq, commercially available) was added dropwise at 0°C. The mixture was stirred for 30 minutes at 0°C, and warmed to the room temperature for 30 minutes (monitored by TLC). The reaction mixture was then concentrated and purified by silica gel column chromatography (DCM/MeOH) to give yellow solid. 62.1% yield, m.p. 201-204 ºC, $[\alpha]_D^{30}$ = -140.40 (c = 0.11, MeOH). ^{1}H NMR (400 MHz, DMSO) δ 8.59 (s, 1H), 7.73 (s, 1H), 7.38 (m, 5H), 4.77 (s, 2H), 2.33 (s, 1H), 2.18 (s, 7H), 1.74 (m, 4H), 1.19 (m, 4H).^{13}C NMR (100 MHz, DMSO-d_6) δ 202.6, 201.1, 179.9, 171.4, 168.7, 137.4, 128.8, 128.0, 127.9, 65.8, 60.3, 52.9, 47.8, 46.3, 35.8, 33.6, 24.3, 24.0, 21.2. IR(ATR):1760.4, 1644.5, 1606.5, 1544.4 cm^{-1}. HRMS m/z calcd for $C_{19}H_{26}N_3OS$ $[M+H]^+$ 344.1791, found 344.1796.

3-(Benzylamino)-4-(((1*S*,2*S*)-2-(dimethylamino) cyclohexyl) amino) cyclobut-3-ene-1,2-dithione (C03). According to the above procedures, **C03** was prepared with **M5** and (1*S*,2*S*)-N, N-dimethylcyclohexane-1,2-diamine. Yellow solid, 47.0% yield, m.p. 133-136 ºC, $[\alpha]_D^{30}$ = -30.29 (c = 0.175, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 24.7 Hz, 5H), 5.25 (d, *J* = 85.2 Hz, 2H), 3.76 (d, *J* = 90.4 Hz, 1H), 2.28 (m, 9H), 1.25 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 170.1, 136.8, 129.9, 129.9, 128.8, 128.3, 127.9, 66.4, 54.7, 47.6, 40.1, 36.00, 31.9, 29.7, 29.3, 27.2, 25.5, 24.7, 22.7. IR(ATR):1709.8, 1635.5 cm^{-1}. HRMS m/z calcd for $C_{19}H_{26}N_3S_2$ $[M+H]^+$ 360.1563, found 360.1565.

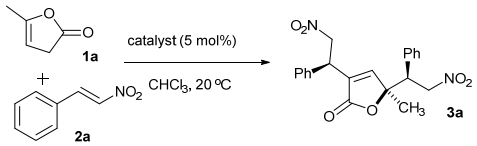
2-(Benzylamino)-3-(((1*S*)-(6-methoxyquinolin-4-yl)((2*S*)-5-vinylquinuclidin-2-yl)methyl) amino) -4-thioxocyclobut-2-en-1-one (C06). Compound **M4** (1.0 mmol, 1.0 eq) was dissolved in 5mL DCM, and amine **M6** (1.1 mmol, 1.1 eq) was added dropwise at 0°C. The mixture was stirred at 0°C for 30 minutes, and then warmed to room temperature for 10 hours (monitored by TLC). The

reaction mixture was concentrated and purified by silica gel column chromatography (DCM/MeOH) to give orange solid. 57.4% yield, m.p. 133-135ºC, $[\alpha]_D^{30}$ = 88.00 (c = 0.125, MeOH). ^{1}H NMR (400 MHz, DMSO) δ 8.81 (d, *J* = 4.3 Hz, 1H), 8.64 (s, 1H), 7.97 (d, *J* = 9.2 Hz, 2H), 7.58 (s, 1H), 7.48-7.28 (m, 7H), 5.96-5.78 (m, 1H), 4.97 (dd, *J* = 22.3, 13.8 Hz, 2H), 4.74 (s, 2H), 4.00 (s, 3H), 3.61 (s, 1H), 3.18 (s, 2H), 2.64 (m, 2H), 2.27 (s, 2H), 2.00 (m, 1H), 1.55 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 199.9, 179.7, 177.1, 174.2, 171.4, 168.3, 157.6, 147.7, 144.2, 141.8, 137.1, 131.4, 129.6, 128.8, 128.6, 128.6, 127.9, 126.9, 122.6, 114.3, 102.4, 56.0, 55.4, 47.9, 40.6, 35.1, 31.2, 30.4, 28.7, 27.1, 25.2. IR(ATR):1762.7, 1620.5, 1555.5, 1505.2 cm^{-1}. HRMS: m/z calcd for $C_{31}H_{31}N_4O_2S^-$ **[**M-H]$^-$ 523.2173, Found: 523.2166.

3-(Benzylamino) -4- (((1*S*) - (6-methoxyquinolin-4-yl) ((2*S*) -5- vinylquinuclidin-2-yl) methyl) amino) cyclobut-3-ene-1,2-dithione (C07). According to the procedures of **C06**, **C07** was obtained with the reaction of **M5** and **M6**. Yellow solid, 88.2% yield, m.p. 107-115ºC, $[\alpha]_D^{30}$ = 106.00 (c = 0.10, MeOH).^{1}H NMR (600 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.82 (d, *J* = 4.4 Hz, 1H), 8.07-7.92 (m, 2H), 7.63 (d, *J* = 4.5 Hz, 1H), 7.49-7.27 (m, 7H), 5.95-5.81 (m, 1H), 5.29 (q, *J* = 14.3 Hz, 2H), 4.99 (dd, *J* = 35.7, 13.7 Hz, 2H), 4.01 (s, 3H), 3.68 (s, 1H), 2.71 (s, 2H), 2.34 (s, 1H), 1.83 (s, 1H), 1.60 (d, *J* = 25.9 Hz, 4H), 1.25 (m, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 202.8, 171.2, 170.1, 169.8, 158.3, 148.2, 148.0, 144.8, 137.8, 132.0, 131.7, 129.3, 128.9, 128.8, 128.7, 128.3, 127.8, 127.4, 122.7, 115.1,102.8, 61.0, 56.6, 55.7, 55.4, 47.6,46.5, 41.2, 39.2, 27.5, 25.4. IR(ATR):1697.9, 1619.8, 1556.5 cm^{-1}. HRMS m/z calcd for $C_{31}H_{33}N_4OS_2$ $[M + H]^+$ 541.2090, found 541.2110.

Catalysts screening for the model reaction.

Table S1. Catalysts screening for the model reaction [a]



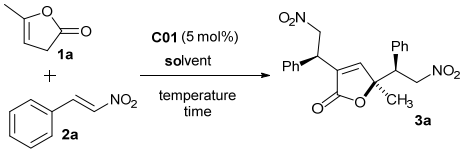
Entry	Catalyst	Equiv of **2a**	Time(h)	Yield(%)[b]	ee(%)[c]	dr[c]
1	**C01**	1.0	24	32	73	82:18
2	**C01**	**2.0**	**24**	**77**	**75**	**87:13**
3	**C02**	2.0	24	32	47	86:14
4	**C03**	2.0	24	trace	-	-
5	**C04**	2.0	24	31	71	89:11
6	**C05**	2.0	24	36	57	88:12
7	**C06**	2.0	24	51	70	82:18
8	**C07**	2.0	24	38	74	85:15
9	**C08**	2.0	72	33	41	75:25

10	**C09**	2.0	48	30	55	83:17
11	**C10**	2.0	72	19	51	87:13
12	**C11**	2.0	72	12	51	87:13
13	**C12**	2.0	72	24	37	86:14
14	**C13**	2.0	72	30	39	85:15
15	**C14**	2.0	72	22	51	86:14
16	**C15**	2.0	72	27	34	81:19
17	**C16**	2.0	72	12	-57	78:22
18	**C17**	2.0	72	23	-56	88:12
19	**C18**	2.0	72	29	-49	87:13
20	**C19**	2.0	72	38	-41	78:22
21	**C20**	2.0	80	15	-45	89:11
22	**C21**	2.0	72	21	-42	89:11

[a]All reactions were carried out with 5-methyl-2(3*H*)-furanone (**1a**, 0.3 mmol, 29.4mg), *trans*-nitrostyrene (**2a**) and the catalyst (5 mol%) in 1.0 mL $CHCl_3$ at room temperature; a minus sign of ee means that the product has the opposite configuration [b]Isolated yield. [c]Determined by chiral HPLC on Chiralpak IC column.

Optimization of reaction conditions

Table S2. Optimization of reaction conditions for the enantioselective double Michael addition of 5-methyl-2(3*H*)-furanone (**1a**) to *trans*-nitrostyrene (**2a**) [a]



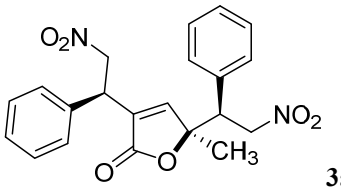
Entry	Solvent	T.(°C)	Time(h)	Yield(%)[b]	ee(%)[c]	dr[c]
1	$CHCl_3$	20	24	77	75	87:13
2	toluene	20	48	28	65	88:12
3	EtOAc	20	24	75	30	88:12
4	CH_3OH	20	30	34	14	87:13
5	CH_3CN	20	72	26	29	86:14
6	THF	20	48	38	62	87:13
7	Et_2O	20	48	50	31	88:12
8	DMF	20	48	46	13	89:11
9	DMSO	20	48	37	16	89:11
10	H_2O	20	20	51	30	88:12
11	brine	20	20	40	61	82:18

12	DCM	20	20	63	73	82:18
13	$CHCl_3$	60	24	75	41	85:15
14	$CHCl_3$	0	60	62	71	94:6
15	$CHCl_3$	-15	60	55	79	94:6
16	**$CHCl_3$**	**-30**	**70**	**77**	**86**	**93:7**
17	$CHCl_3$	-50	84	39	83	94:6
18[d]	$CHCl_3$	-30	70	70	83	93:7
19[e]	$CHCl_3$	-30	70	75	81	94:6

[a]All reactions were carried out with 5-methyl-2(3*H*)-furanone (**1a**, 0.3 mmol, 29.4 mg), *trans*-nitrostyrene (**2a**, 0.6 mmol, 89.5 mg) and the catalyst **C01**. [b]Isolated yield. [c]Determined by chiral HPLC on Chiralpak IC column. [d]2.5 mol% **C01**.[e]10 mol% **C01**.

General procedure for the asymmetric double Michael addition of 5-methyl-2(3*H*)-furanone to *β*-nitroolefins

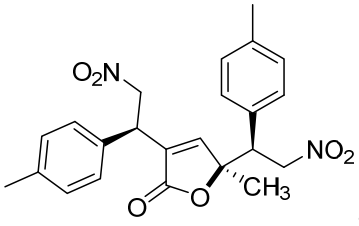
To a solution of catalyst (**C01**, 0.015 mmol, 5.2 mg) and nitroolefin (0.6 mmol) in $CHCl_3$ (2.0 ml) was added 5-methyl 2(3H)-furanone (0.3 mmol, 29.4 mg). The reaction mixture was stirred at -30 °C (monitored by TLC). After the reaction is completed, the mixture was concentrated and purified by silica gel column chromatography (ethyl acetate/petroleum).



3a

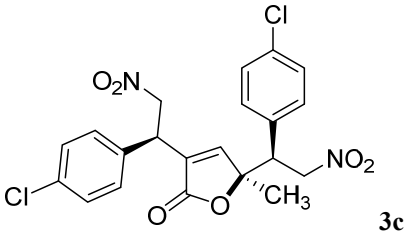
White solid, 77% yield, 86% ee, 93:7 dr, $[\alpha]_D^{20}$ = 87.69 (c = 0.325, CH_2Cl_2). m.p. 169.4-170.2°C, HPLC: Chiralpak IC column (n-hexane/EtOH = 75/25, flow rate 1.0 mL/min, λ = 210 nm), $t_R(1)$ = 9.221 min, $t_R(2)$ = 9.788 min, $t_R(3)$ = 10.793 min, $t_R(4)$ = 12.538 min. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34-7.19 (m, 6H), 7.10 (d, *J* = 7.3 Hz, 2H), 6.97 (s, 1H), 6.74 (d, *J* = 7.3 Hz, 2H), 4.92 (dd, *J* = 13.5, 4.9 Hz, 1H), 4.85-4.77 (m, 2H), 4.66 (dd, *J* = 13.3, 7.0 Hz, 1H), 4.35 (t, *J* = 7.7 Hz, 1H), 3.94 (dd, *J* = 9.8, 4.9 Hz, 1H), 1.54 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2, 152.9, 135.0, 134.4, 132.6, 129.4, 129.3, 128.9, 128.3, 127.4, 86.5, 76.6, 75.5, 50.5, 40.9, 23.6. IR(ATR): 3082.5, 2923.0, 2852.7, 1753.5, 1652.4, 1556.6, 1493.0, 1454.7, 1433.5, 1382.0, 1272.1, 1240.4, 1113.7, 1028.2, 950.4, 798.2, 768.9, 702.9 cm^{-1}. HRMS m/z calcd for $C_{21}H_{19}N_2O_6$ $[M-H]^-$ 395.1249, found

395.1241.



3b

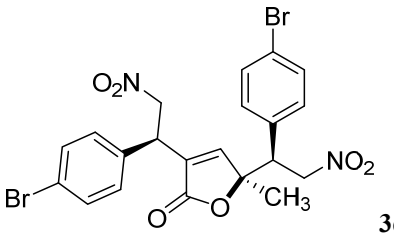
White solid, 86% yield, 86% ee, >99:1 dr, $[\alpha]_D^{20}$ = 90.86 (c = 0.35, CH_2Cl_2). m.p. 166-167.3ºC, HPLC: Chiralpak IC column (n-hexane/EtOH = 75/25, flow rate 1.0 mL/min, λ = 210 nm), $t_R(1)$ = 9.288 min, $t_R(2)$ = 9.799 min, $t_R(3)$ = 11.127 min, $t_R(4)$ = 11.820 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 7.9 Hz, 2H), 7.00 (dd, *J* = 14.8, 7.7 Hz, 5H), 6.68 (d, *J* = 8.0 Hz, 2H), 4.91-4.72 (m, 3H), 4.63 (dd, *J* = 13.2, 7.0 Hz, 1H), 4.34 (dd, *J* = 14.1, 6.5 Hz, 1H), 3.90 (dd, *J* = 9.9, 5.0 Hz, 1H), 2.33 (s, 3H), 2.30 (s, 3H), 1.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 152.9, 138.7, 138.1, 132.7, 132.1, 131.3, 130.1, 129.9, 128.2, 127.4, 86.7, 75.7, 50.3, 40.6, 23.7, 21.3, 21.2. IR(ATR): 3028.9, 2922.3, 2852.3, 1753.6, 1613.2, 1553.9, 1512.8, 1453.7, 1433.0, 1374.3, 1252.8, 1177.3, 1115.6, 1031.4, 983.7, 816.9, 648.5, 517.9 cm^{-1}. Anal. Calcd for $C_{23}H_{24}N_2O_6$: C, 65.08; H, 5.70; N, 6.60. Found: C, 65.25; H, 5.69; N, 6.68.



3c

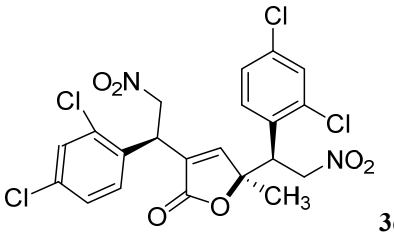
White solid, 67% yield, 94% ee, 99:1 dr, $[\alpha]_D^{20}$ = -23.20 (c = 0.125, CH_2Cl_2). m.p. 65-67.1ºC, HPLC: Chiralpak IC column (n-hexane/EtOH = 75/25, flow rate 1.0 mL/min, λ = 210 nm), $t_R(1)$ = 7.205 min, $t_R(2)$ = 8.032 min, $t_R(3)$ = 9.071 min, $t_R(4)$ = 9.694 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.22 (m, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.93-6.85 (m, 3H), 4.94 (ddd, *J* = 15.3, 13.4, 6.8 Hz, 2H), 4.84-4.73 (m, 1H), 4.45 (dd, *J* = 13.0, 7.0 Hz, 1H), 4.32 (t, *J* = 7.8 Hz, 1H), 3.88 (dd, *J* = 9.9, 5.0 Hz, 1H), 1.57 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 153.9, 135.2, 134.8, 133.7, 132.8, 132.4, 129.9, 129.7, 129.6, 129.5, 129.3, 129.2, 128.8, 86.3, 75.8, 75.3, 50.0, 40.9, 23.19. IR(ATR): 2921.3, 2851.7, 1753.8, 1651.3, 1593.6, 1550.5, 1492.6, 1433.7, 1376.3, 1260.9, 1199.3,

1091.8, 1014.7, 983.5, 825.2, 754.9, 719.1, 640.9 cm^{-1}. Anal. Calcd for $C_{21}H_{18}Cl_2N_2O_6$: C, 54.21; H, 3.90; N, 6.02. Found: C, 54.32; H, 3.82; N, 6.25.



3d

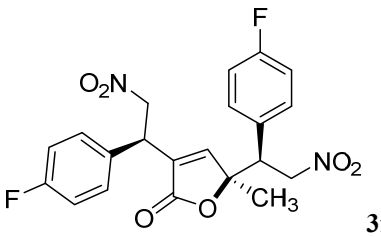
White solid, 63% yield, 95% ee, 97:3 dr, $[\alpha]_D^{20}$ = -18.75 (c = 0.16, CH_2Cl_2). m.p. 65.8-68.1ºC, HPLC: Chiralpak IC column (n-hexane/EtOH = 75/25, flow rate 1.0 mL/min, λ = 210 nm), $t_R(1)$ = 7.536 min, $t_R(2)$ = 8.321 min, $t_R(3)$ = 8.813 min, $t_R(4)$ = 9.372 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.43 (m, 2H), 7.42-7.36 (m, 2H), 6.93 (dd, *J* = 16.1, 4.7 Hz, 3H), 6.82 (d, *J* = 8.5 Hz, 2H), 4.93 (ddd, *J* = 13.5, 12.6, 6.8 Hz, 2H), 4.80-4.75 (m, 1H), 4.43 (dd, *J* = 13.0, 7.0 Hz, 1H), 4.32 (t, *J* = 7.7 Hz, 1H), 3.87 (dd, *J* = 9.8, 5.0 Hz, 1H), 1.56 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 153.9, 134.2, 133.3, 132.7, 132.5, 132.3, 129.9, 129.1, 123.3, 122.9, 86.2, 75.8, 75.2, 50.0, 40.9, 23.18. IR(ATR): 2920.3, 2851.4, 1753.9, 1658.2, 1632.5, 1550.6, 1489.9, 1434.3, 1411.0, 1376.4, 1259.7, 1074.2, 1011.2, 960.0, 884.6, 795.4, 717.4, 642.6, 516.4 cm^{-1}. Anal. Calcd for $C_{21}H_{18}Br_2N_2O_6$: C, 45.51; H, 3.27; N, 5.05. Found: C, 45.32; H, 3.32; N, 5.25.



3e

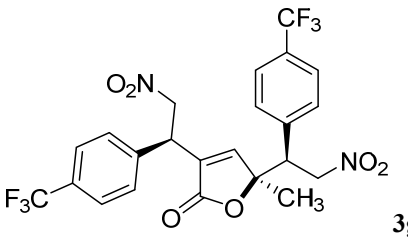
White solid, 61% yield, 63% ee, >99:1 dr, $[\alpha]_D^{20}$ = -16.53 (c = 0.375, CH_2Cl_2). m.p. 72.6-73.7ºC, HPLC: Chiralpak IC column (n-hexane/EtOH = 75/25, flow rate 1.0 mL/min, λ = 210 nm), $t_R(1)$ = 6.969 min, $t_R(2)$ = 7.404 min, $t_R(3)$ = 8.620 min, $t_R(4)$ = 9.305 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 1.8 Hz, 1H), 7.28 (d, *J* = 14.6 Hz, 2H), 7.19 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.96 (dd, *J* = 18.5, 8.4 Hz, 2H), 5.09 (dd, *J* = 13.2, 9.2 Hz, 1H), 5.00 (dd, *J* = 13.9, 4.9 Hz, 1H), 4.85 (dt, *J* = 18.7, 8.5 Hz, 2H), 4.63-4.54 (m, 2H), 1.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$)

δ 170.0, 154.3, 135.5, 135.3, 134.3, 131.1, 130.8, 130.5, 130.3, 130.2, 128.9, 128.3, 128.0, 127.5, 121.9, 86.4, 74.9, 74.2, 44.5, 37.0, 29.84. IR(ATR): 3081.5, 2920.5, 2851.3, 1756.2, 1658.2, 1632.5, 1589.0, 1552.0, 1472.4, 1375.9, 1260.2, 1175.4, 1104.0, 1054.6, 916.1, 866.7, 819.7, 797.0, 639.5 cm^{-1}. Anal. Calcd for $C_{21}H_{16}Cl_4N_2O_6$: C, 47.22; H, 3.02; N, 5.24. Found: C, 47.12; H, 3.23; N, 5.35.



3f

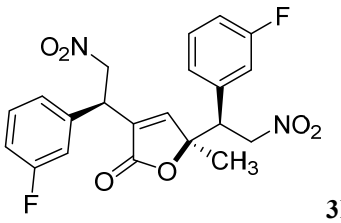
White solid, 62% yield, 93% ee, 98:2 dr, $[\alpha]_D^{20}$ = -10.91 (c = 0.275, CH_2Cl_2). m.p. 51.6-53.8°C, HPLC: Chiralpak IC column (n-hexane/EtOH = 75/25, flow rate 1.0 mL/min, λ = 210 nm), $t_R(1)$ = 7.009 min, $t_R(2)$ = 7.905 min, $t_R(3)$ = 9.119 min, $t_R(4)$ = 9.719 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06-7.02 (m, 2H), 6.98 (s, 1H), 6.95 (dd, *J* = 5.4, 2.0 Hz, 3H), 6.94-6.90 (m, 3H), 4.93 (ddd, *J* = 16.0, 13.2, 6.8 Hz, 2H), 4.79 (dd, *J* = 9.7, 3.8 Hz, 1H), 4.45 (dd, *J* = 13.0, 7.1 Hz, 1H), 4.33 (t, *J* = 7.8 Hz, 1H), 3.90 (dd, *J* = 9.9, 5.1 Hz, 1H), 1.56 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 163.9, 161.6, 153.8, 132.6, 131.1, 130.0, 129.9, 129.3, 129.2, 116.6, 116.5, 116.3, 116.2, 86.4, 76.1, 75.4, 49.9, 40.8, 23.14. IR(ATR): 2920.5, 2851.1, 1754.2, 1658.1, 1632.5, 1605.0, 1550.7, 1509.7, 1434.1, 1377.3, 1302.1, 1226.1, 1162.4, 1102.1, 1031.7, 917.5, 821.1, 797.4, 719.5, 643.3, 526.8 cm^{-1}. Anal. Calcd for $C_{21}H_{18}F_2N_2O_6$: C, 58.34; H, 4.20; N, 6.48. Found: C, 58.13; H, 4.09; N, 6.58.



3g

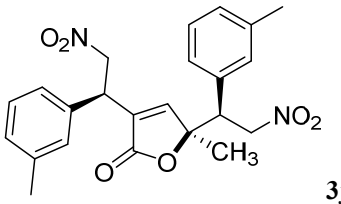
White solid, 75% yield, 92% ee, 99:1 dr, $[\alpha]_D^{20}$ = -17.00 (c = 0.100, CH_2Cl_2). m.p. 60.3-62.1°C, HPLC: Chiralpak IC column (n-hexane/EtOH = 90/10, flow rate 1.0 mL/min, λ = 210 nm), $t_R(1)$ = 9.634 min, $t_R(2)$ = 10.720 min, $t_R(3)$ = 12.140 min, $t_R(4)$ = 13.066 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.3 Hz, 3H), 7.52-7.46 (m, 1H), 7.23 (s, 1H), 7.17-7.11 (m, 1H), 7.08 (d, *J* = 8.0 Hz,

2H), 6.96 (d, *J* = 0.8 Hz, 1H), 4.93 (ddd, *J* = 26.6, 14.5, 4.6 Hz, 2H), 4.86-4.63 (m, 2H), 4.43-4.40 (m, 1H), 4.00 (dt, *J* = 10.3, 5.2 Hz, 1H), 1.60 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.7, 153.7, 139.0, 138.4, 132.3, 131.6, 131.4, 129.8, 128.8, 128.5, 128.3, 128.0, 126.7, 126.5, 126.4, 86.3, 75.7, 75.1, 50.3, 41.1, 23.39. IR(ATR): 3194.0, 2920.7, 2850.9, 1757.6, 1658.5, 1620.8, 1554.2, 1423.3, 1377.9, 1323.7, 1260.6, 1165.5, 1112.8, 1068.3, 1017.7, 957.0, 839.4, 794.2, 707.2, 645.6 cm^{-1}. Anal. Calcd for $C_{23}H_{18}F_6N_2O_6$: C, 51.89; H, 3.41; N, 5.26. Found: C, 51.67; H, 3.53; N, 5.38.



3h

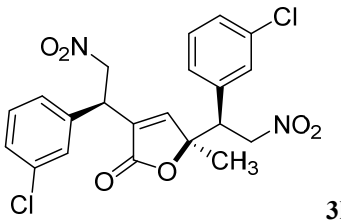
White solid, 59% yield, 94% ee, 98:2 dr, $[\alpha]_D^{20}$ = -12.00 (c = 0.100, CH_2Cl_2). m.p. 56.1-58.6ºC, HPLC: Chiralpak IC column (n-hexane/EtOH = 90/10, flow rate 1.0 mL/min, λ = 210 nm), $t_R(1)$ = 20.089 min, $t_R(2)$ = 21.572 min, $t_R(3)$ = 24.934 min, $t_R(4)$ = 25.696 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (m, 1H), 7.06 (d, *J* = 5.9 Hz, 1H), 7.04-7.00 (m, 1H), 6.98-6.93 (m, 1H), 6.91 (s, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 6.82-6.76 (m, 2H), 6.67 (dd, *J* = 9.4, 1.9 Hz, 1H), 5.00-4.88 (m, 2H), 4.86-4.76 (m, 1H), 4.44-4.31 (m, 2H), 3.91 (dd, *J* = 9.7, 5.0 Hz, 1H), 1.57 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 164.3, 164.2, 161.9, 161.7, 154.1, 137.7, 137.6, 136.8, 136.7, 132.2, 131.2, 131.1, 131.1, 131.0, 123.7, 123.2, 116.2, 116.1, 116.0, 115.9, 115.7, 115.5, 114.9, 114.7, 86.3, 75.7, 75.2, 50.3, 41.1, 23.17. IR(ATR): 3188.2, 2918.8, 2849.8, 1754.0, 1658.3, 1632.1, 1591.3, 1551.4, 1452.1, 1431.6, 1377.1, 1259.1, 1146.1, 1089.6, 1014.1, 875.7, 791.6, 698.0, 651.6, 521.9 cm^{-1}. Anal. Calcd for $C_{21}H_{18}F_2N_2O_6$: C, 58.34; H, 4.20; N, 6.48. Found: C, 58.45; H, 4.32; N, 6.29.



3j

White solid, 69% yield, 91% ee, 99:1 dr, $[\alpha]_D^{20}$ = 92.71 (c = 0.325, CH_2Cl_2). m.p. 122.7-124.2ºC, HPLC: Chiralpak IC column (n-hexane/EtOH = 93/7, flow rate 1.0 mL/min, λ = 210 nm), $t_R(1)$ = 33.571 min, $t_R(2)$ = 36.698 min, $t_R(3)$ = 41.158 min, $t_R(4)$ = 41.963 min. ^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.17 (t, *J* = 7.5 Hz, 1H), 7.13-7.05 (m, 3H), 6.93 (m, 1H), 6.87 (m, 3H), 6.43 (d, *J* = 6.4 Hz, 1H), 4.92-4.72 (m, 3H), 4.66 (dd, *J* = 13.3, 7.1 Hz, 1H), 4.32 (t, *J* = 7.7 Hz, 1H), 3.89 (dd, *J* = 9.7, 5.0 Hz, 1H), 2.30 (s, 3H), 2.25 (s, 3H), 1.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 153.1, 139.2, 139.1, 135.2, 134.4, 132.7, 129.7, 129.2, 129.0, 128.5, 125.3, 124.1, 86.7, 76.6, 75.6, 50.7, 41.0, 29.8, 23.7, 21.51. IR(ATR): 3084.1, 2920.9, 2852.2, 1749.1, 1651.9, 1606.3, 1549.5, 1489.1, 1456.8, 1375.3, 1308.8, 1256.1, 1196.9, 1116.1, 1040.4, 987.2, 905.2, 799.0, 709.3, 653.2 cm^{-1}. Anal. Calcd for $C_{23}H_{24}N_2O_6$: C, 65.08; H, 5.70; N, 6.60. Found: C, 64.93; H, 5.58; N, 6.43.



3l

White solid, 65% yield, 90% ee, 97:3 dr, $[\alpha]_D^{20}$ = -10.11 (c = 0.150, CH_2Cl_2). m.p. 63.4-65.6ºC, HPLC: Chiralpak IC column (n-hexane/EtOH = 93/7, flow rate 1.0 mL/min, λ = 210 nm), $t_R(1)$ = 23.533 min, $t_R(2)$ = 28.138 min, $t_R(3)$ = 31.978 min, $t_R(4)$ = 34.295 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.27 (m, 1H), 7.21 (m, 1H), 7.05 (q, *J* = 4.5 Hz, 2H), 6.98 (dt, *J* = 5.6, 2.7 Hz, 2H), 6.88 (dd, *J* = 13.5, 3.6 Hz, 3H), 4.95 (ddd, *J* = 15.6, 13.0, 5.9 Hz, 2H), 4.85-4.76 (m, 2H), 4.31 (dd, *J* = 12.0, 4.5 Hz, 1H), 3.88 (dd, *J* = 9.7, 5.0 Hz, 1H), 1.57 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 154.3, 137.3, 136.4, 135.7, 135.3, 135.3, 132.2, 130.8, 130.6, 129.3, 129.0, 128.7, 127.8, 125.7, 86.2, 75.6, 75.1, 50.2, 41.1, 23.07. IR(ATR): 2920.1, 2851.4, 1753.6, 1596.2, 1550.4, 1477.0, 1433.5, 1376.5, 1260.5, 1197.9, 1169.6, 1083.4, 1035.8, 960.1, 880.8, 791.0, 697.7 cm^{-1}. Anal. Calcd for $C_{21}H_{18}Cl_2N_2O_6$: C, 54.21; H, 3.90; N, 6.02. Found: C, 54.03; H, 3.99; N, 5.85.

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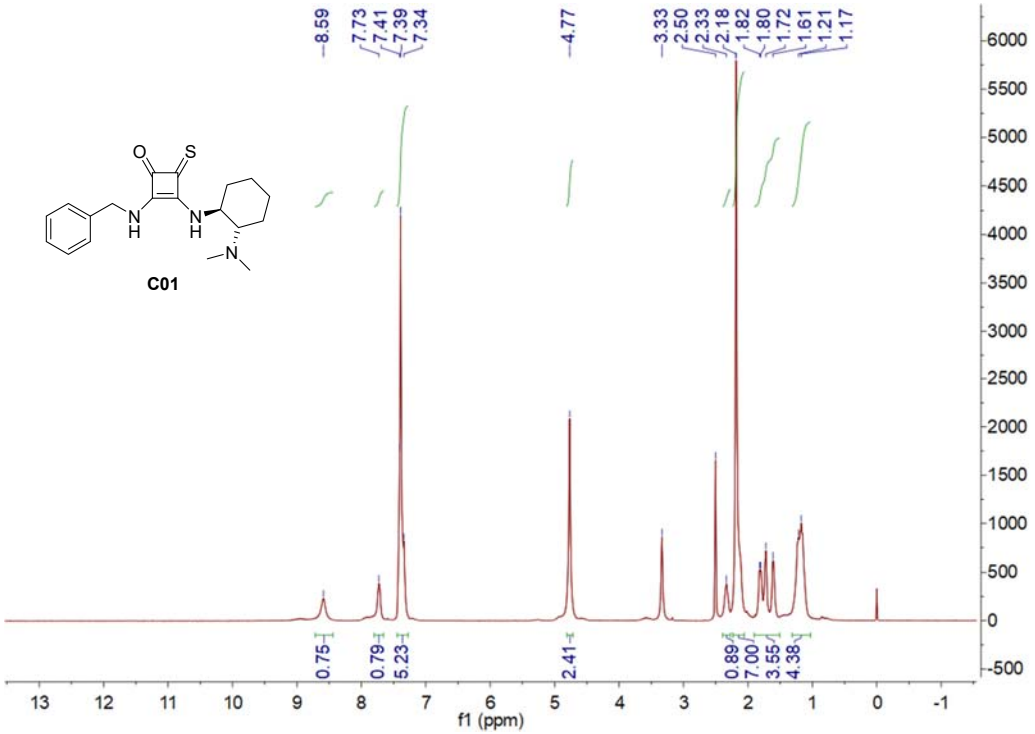
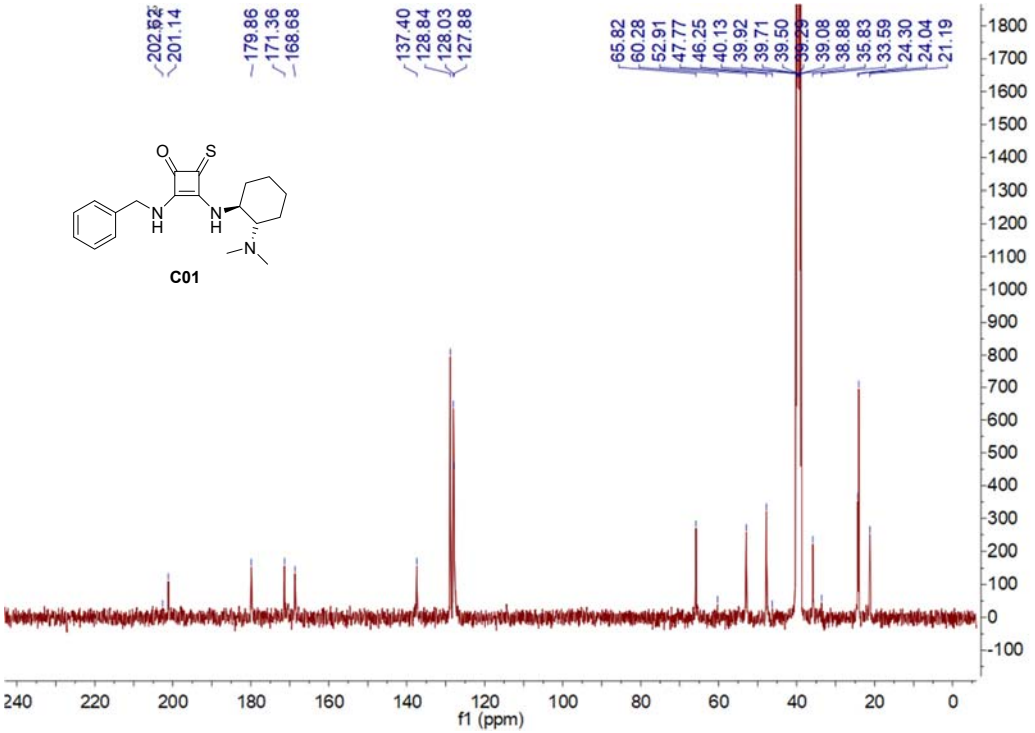
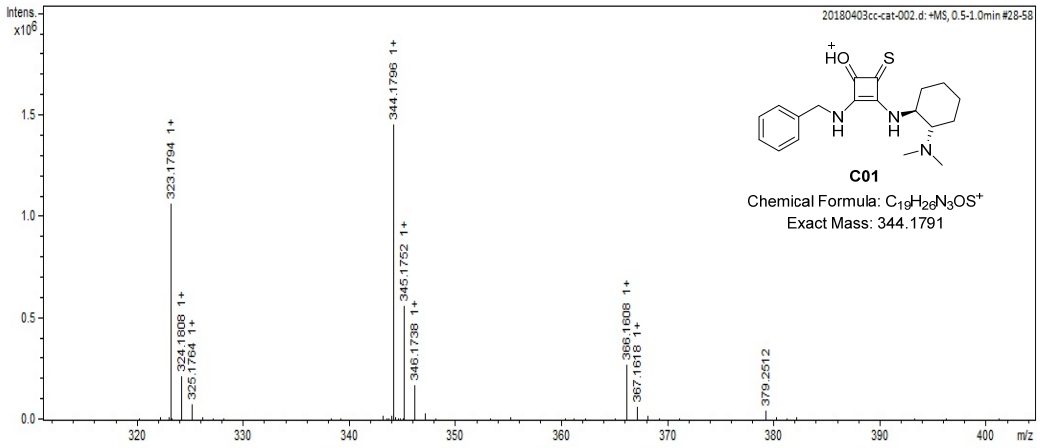
Copies of ^{1}H NMR,^{13}C NMR, HRMS and IR spectra of organocatalysts



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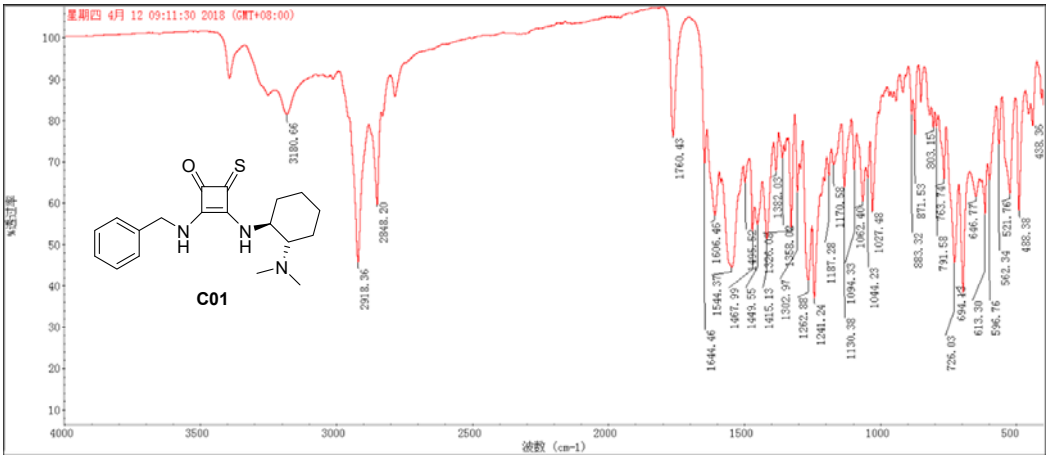
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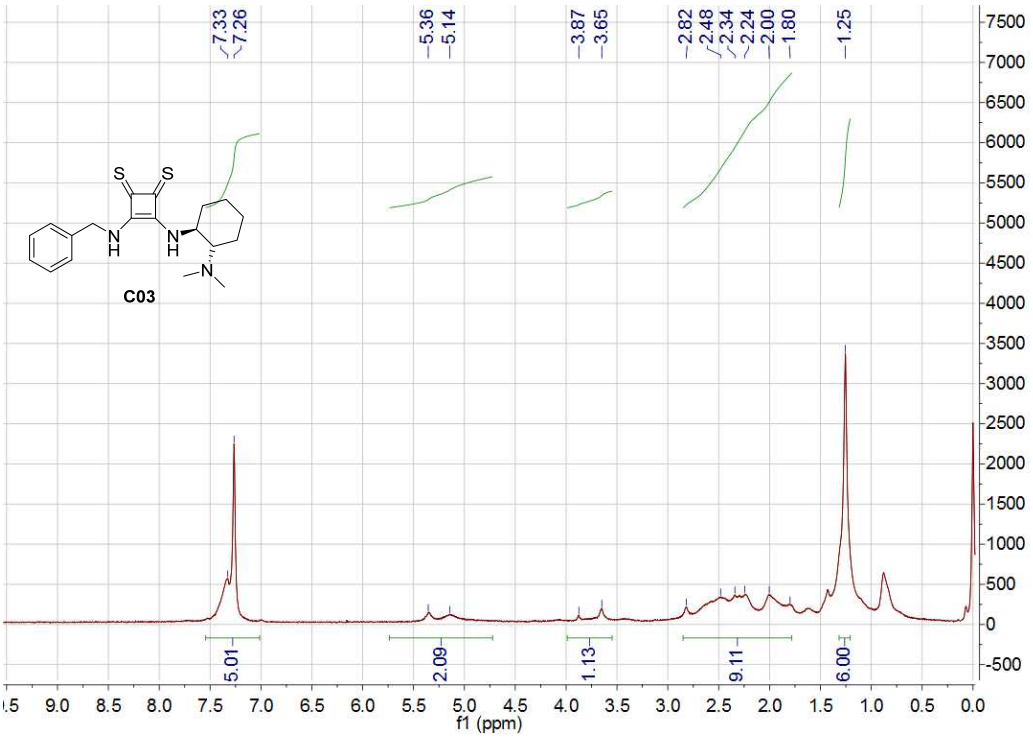
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C03
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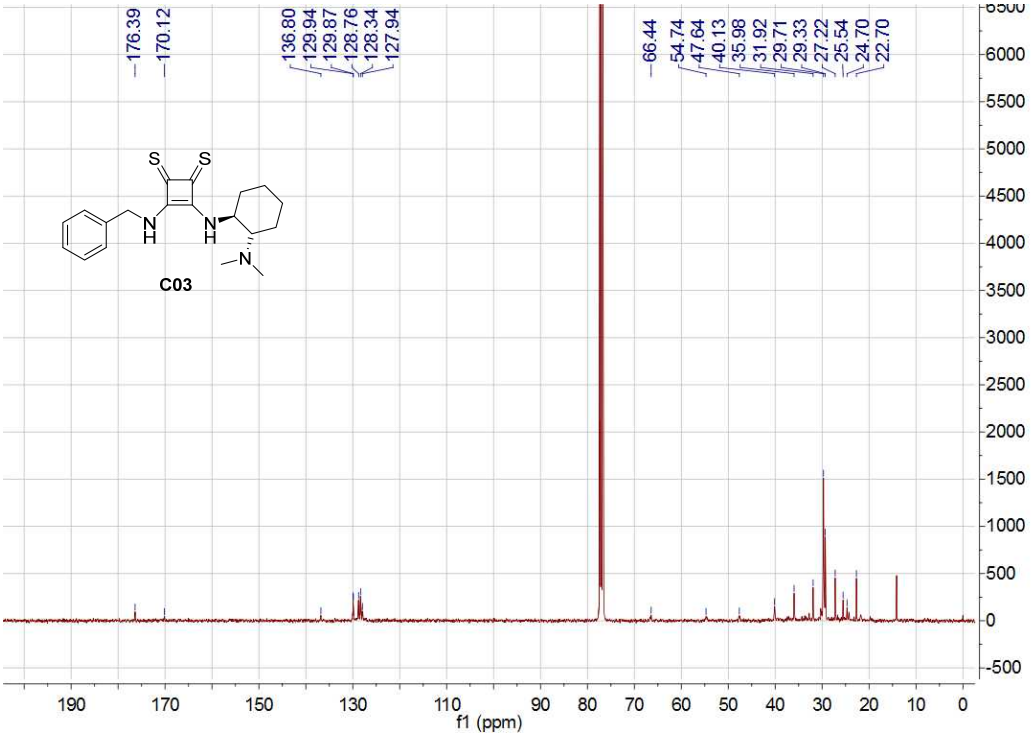
f1 (ppm)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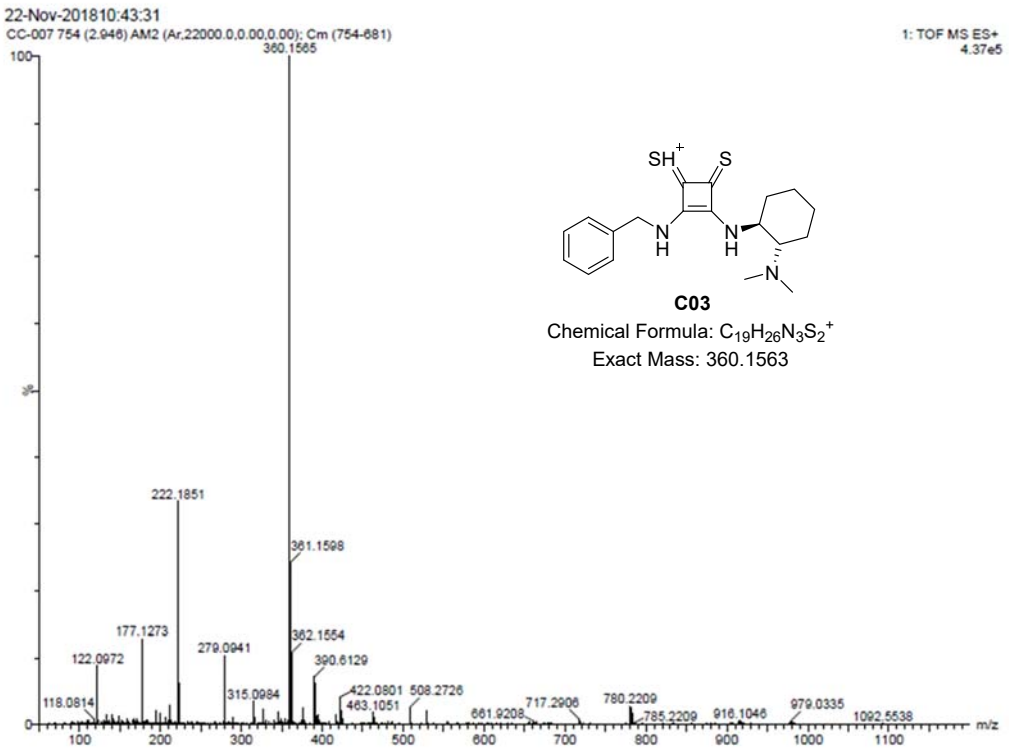
N
C03
f1 (ppm)



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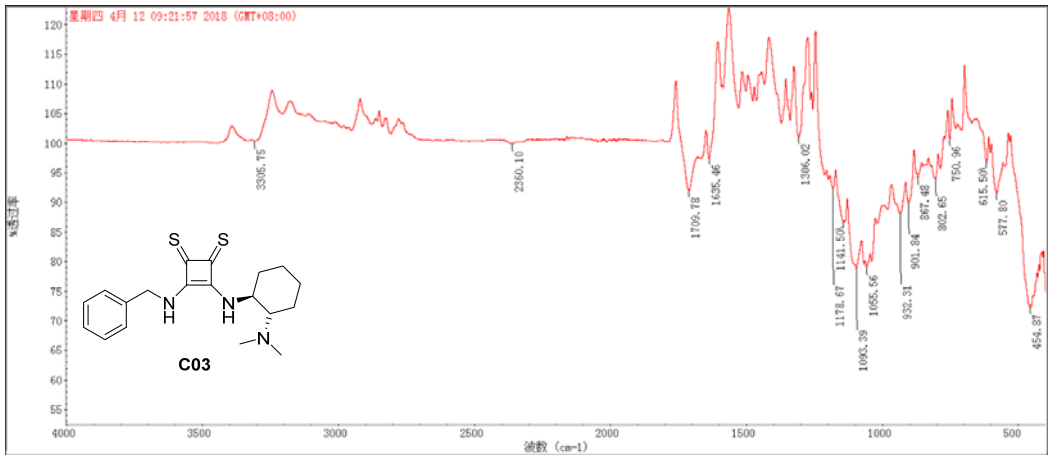

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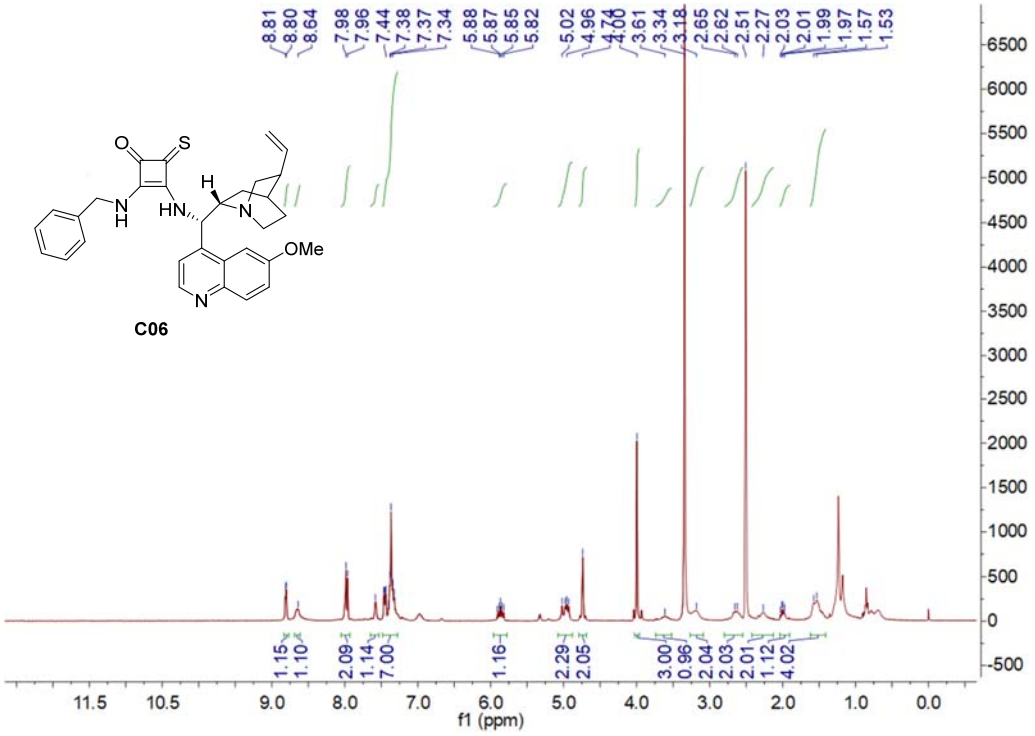
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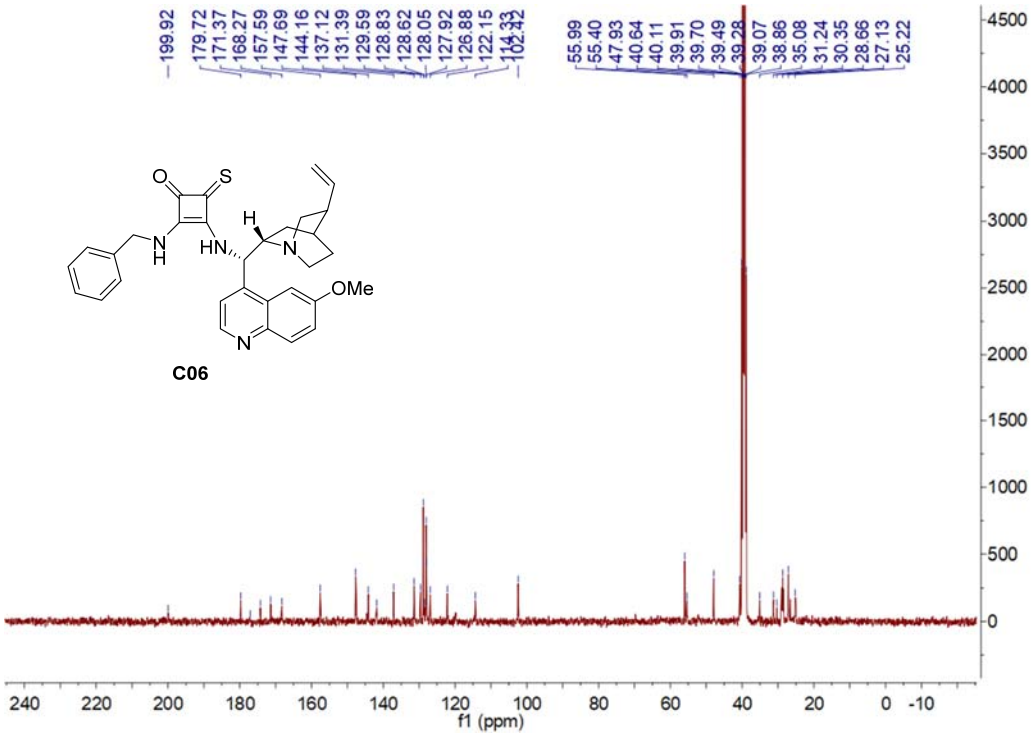
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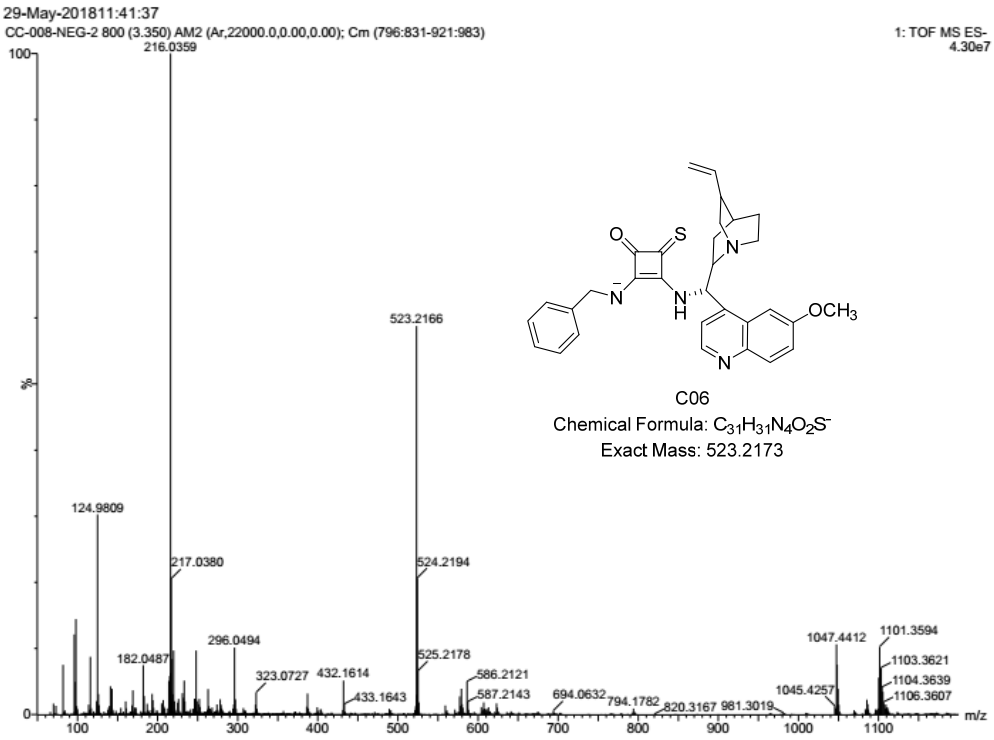
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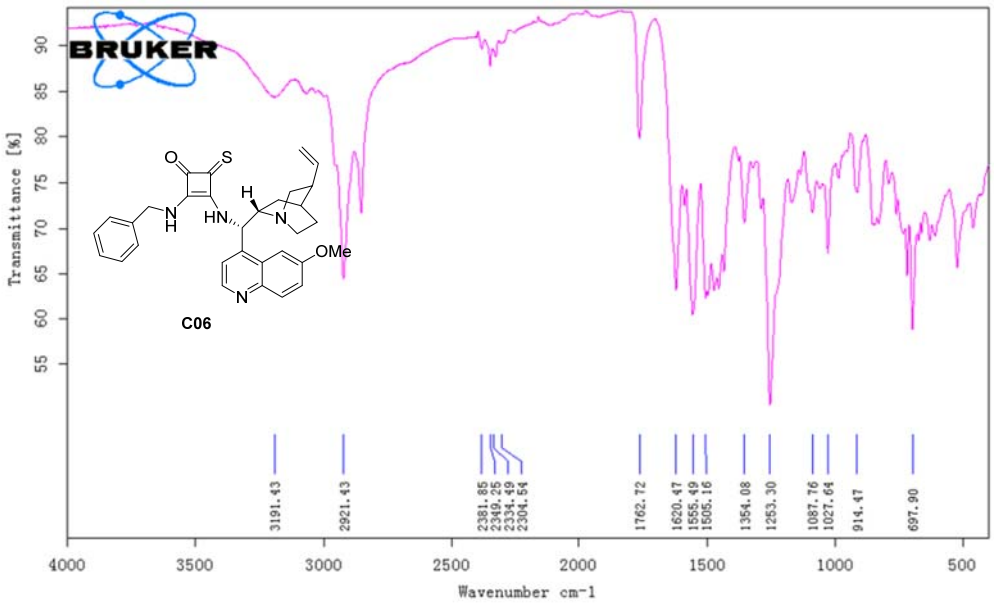
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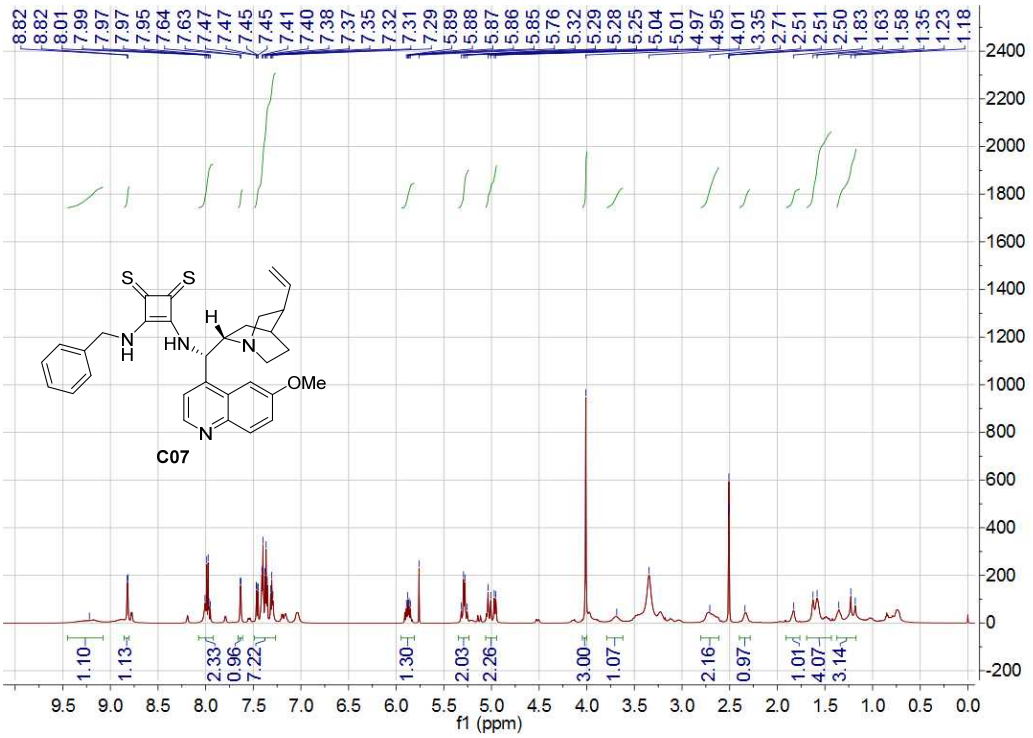
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S
N
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OMe
N
C07
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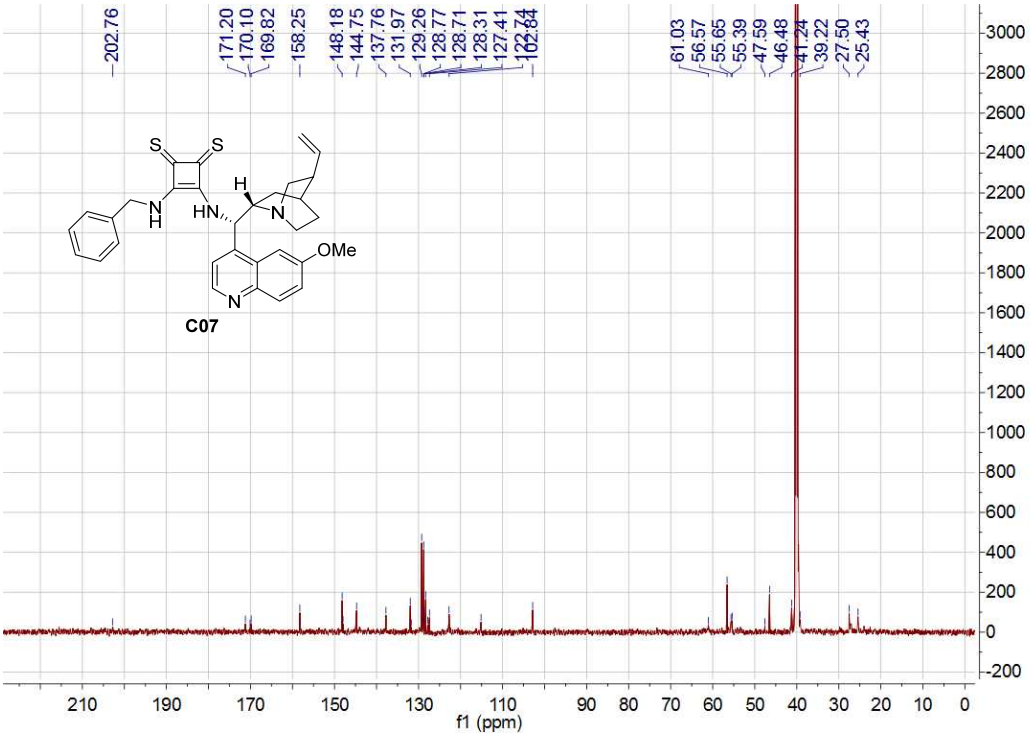
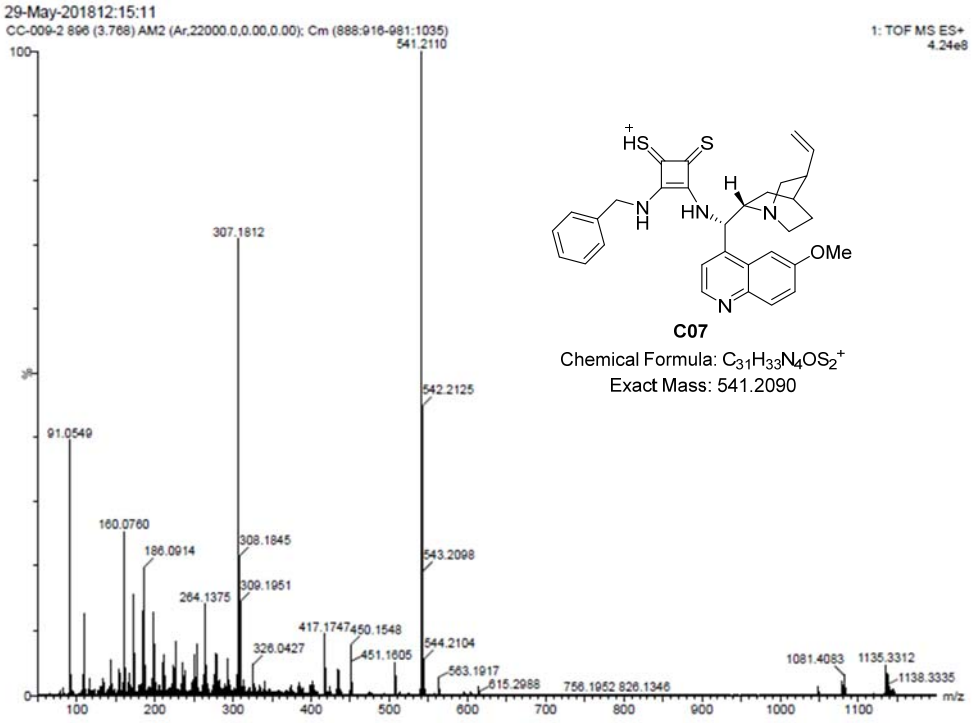
f1 (ppm)

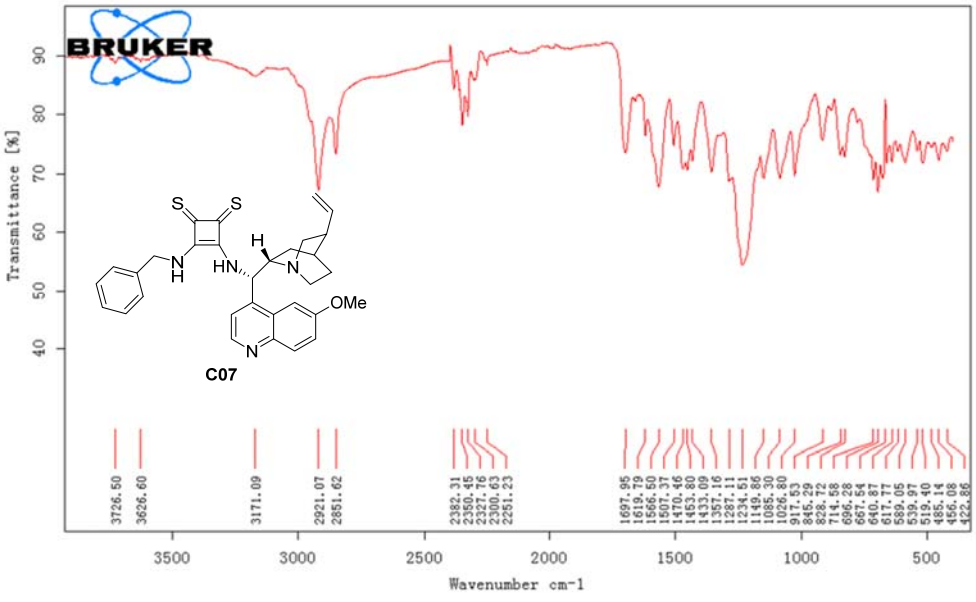

202.76
171.20 170.10 169.82 158.25 148.18 144.75 137.76 131.97 129.26 128.77 128.71 128.31 127.41 122.74 102.84
61.03 56.57 55.65 55.39 47.59 46.48 41.24 39.22 27.50 25.43
S
S
N
H
HN
H
N
OMe
N
C07
f1 (ppm)



C07

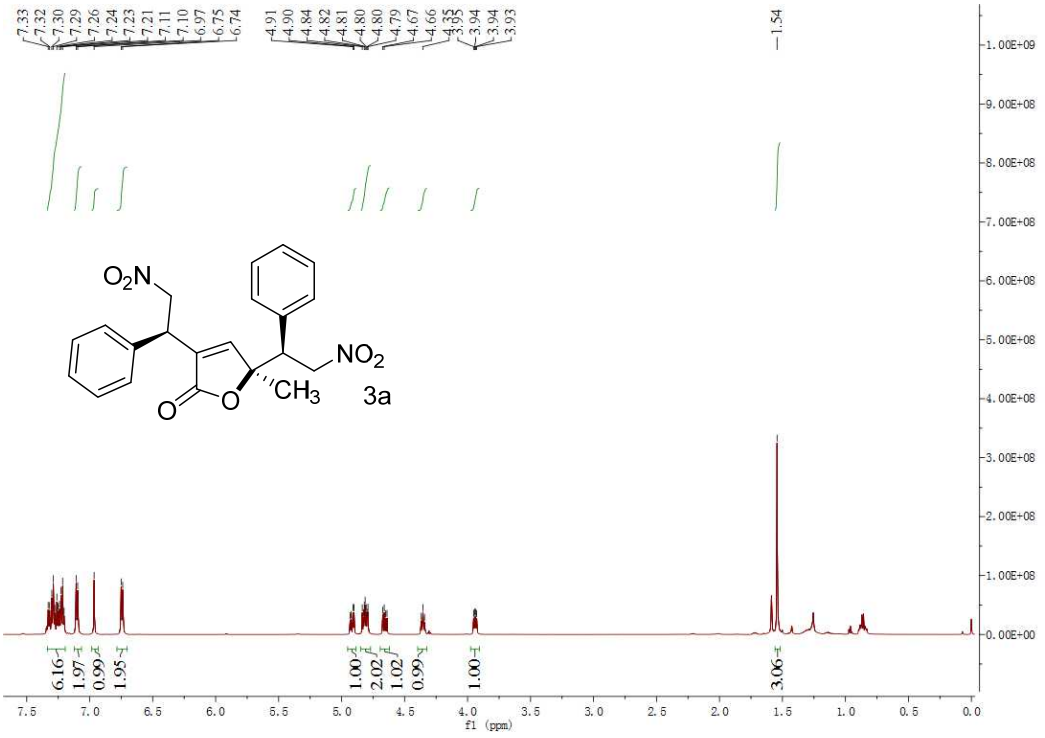
Chemical Formula: $C_{31}H_{33}N_4OS_2^+$

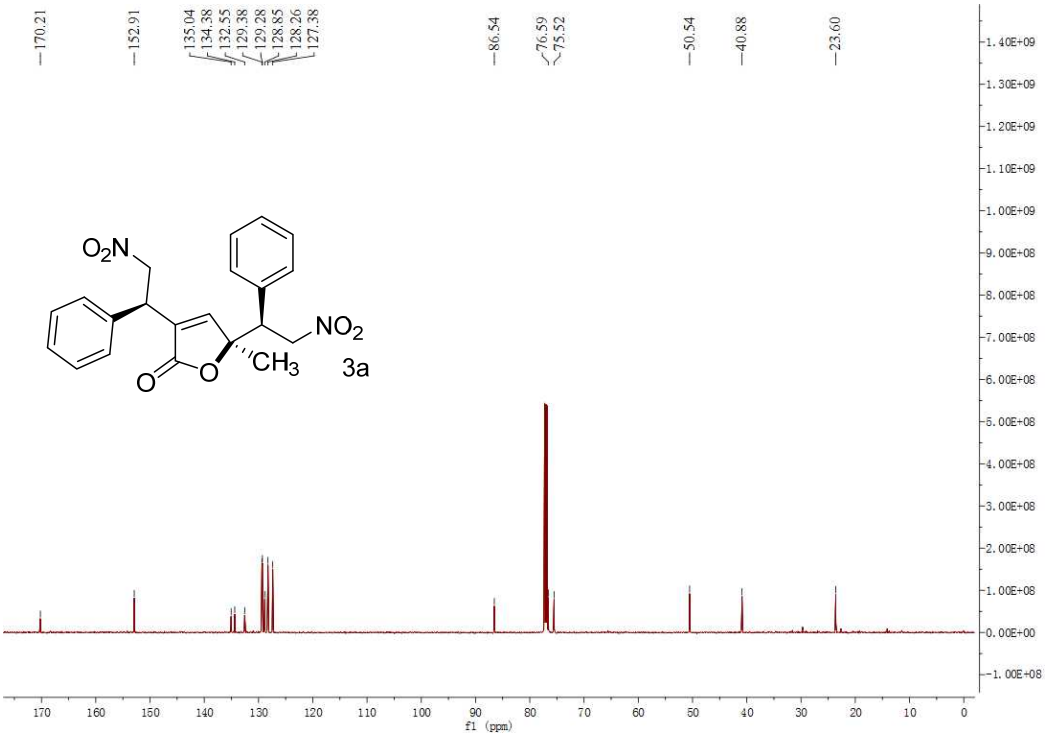
Exact Mass: 541.2090

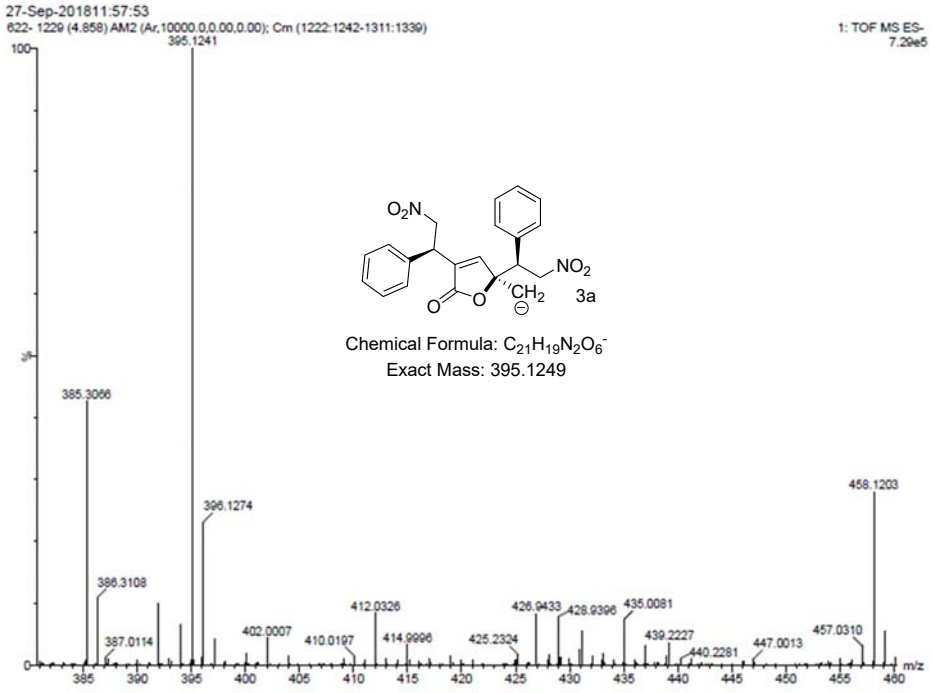


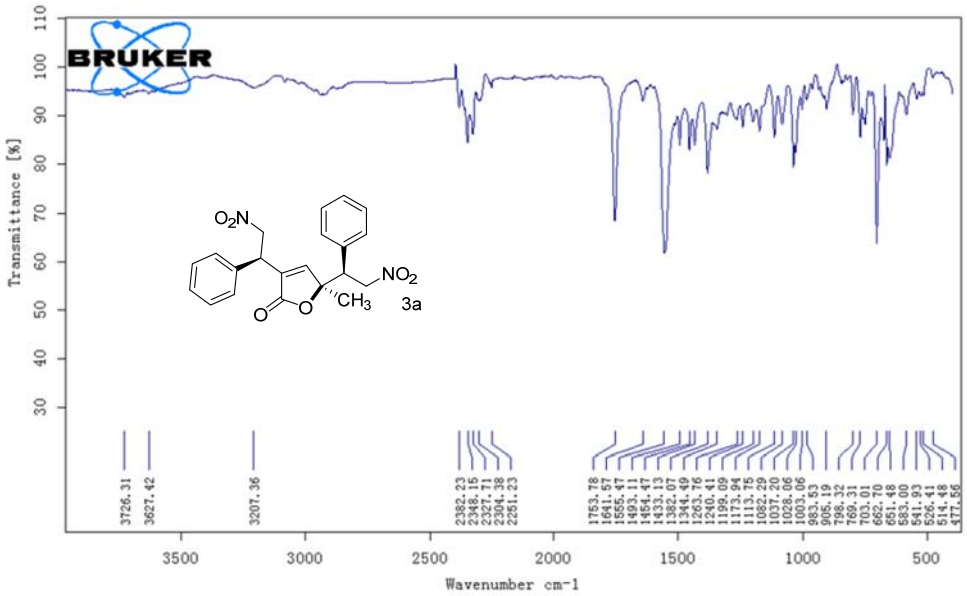
C07

Copies of ^{1}H NMR,^{13}C NMR, HRMS and IR spectra of selected Michael addition products






27-Sep-201811:57:53
622- 1229 (4.858) AM2 (Ar,10000.0,0.00,0.00); Cm (1222:1242-1311:1339)
1: TOF MS ES-
7.29e5
395.1241
385.3066
396.1274
386.3108
458.1203
412.0326
426.9433
428.9396
435.0081
402.0007
410.0197
414.9996
425.2324
439.2227
457.0310
387.0114
440.2281
447.0013
m/z
O2N
NO2
CH2
3a
Chemical Formula: C21H19N2O6-
Exact Mass: 395.1249


BRUKER
Transmittance [%]
Wavenumber cm-1
O2N
NO2
CH3
3a
3726.31
3627.42
3207.36
2382.23
2348.15
2327.71
2304.38
2251.23
1753.78
1641.57
1555.47
1495.11
1454.47
1433.13
1382.07
1344.49
1263.76
1240.41
1199.09
1173.94
1113.75
1082.29
1037.20
1023.06
1000.06
983.53
905.19
798.32
769.31
703.01
662.70
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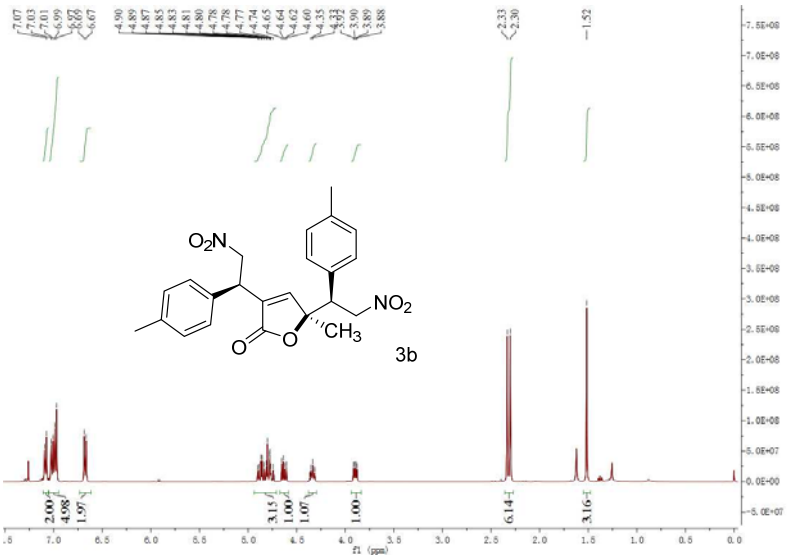
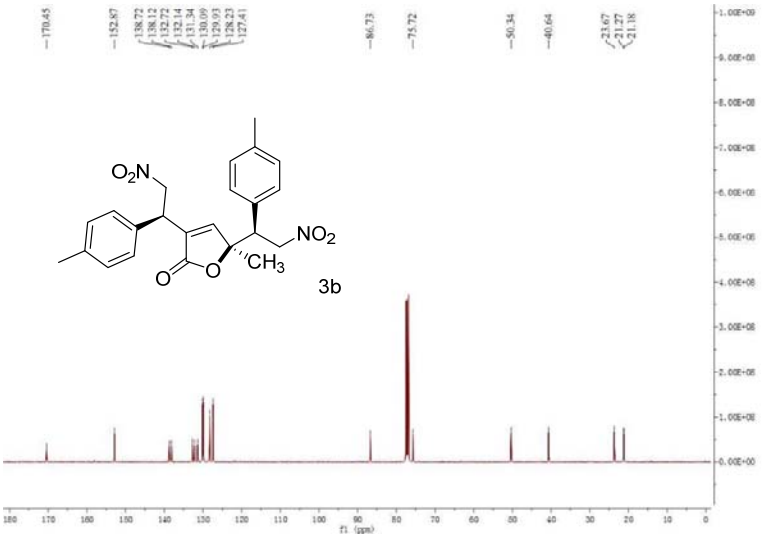
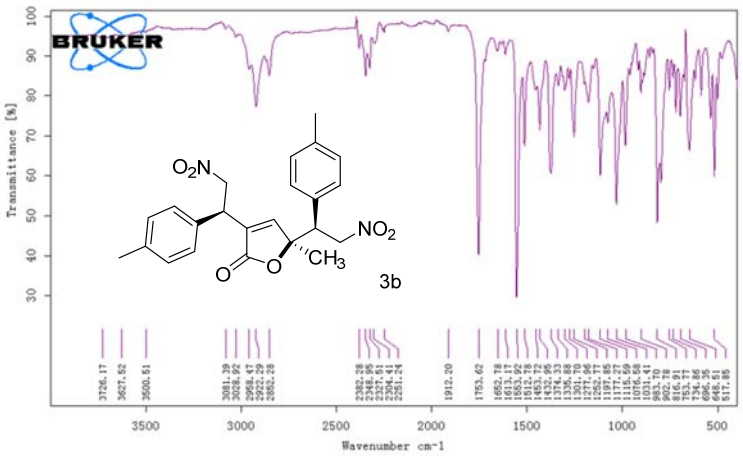
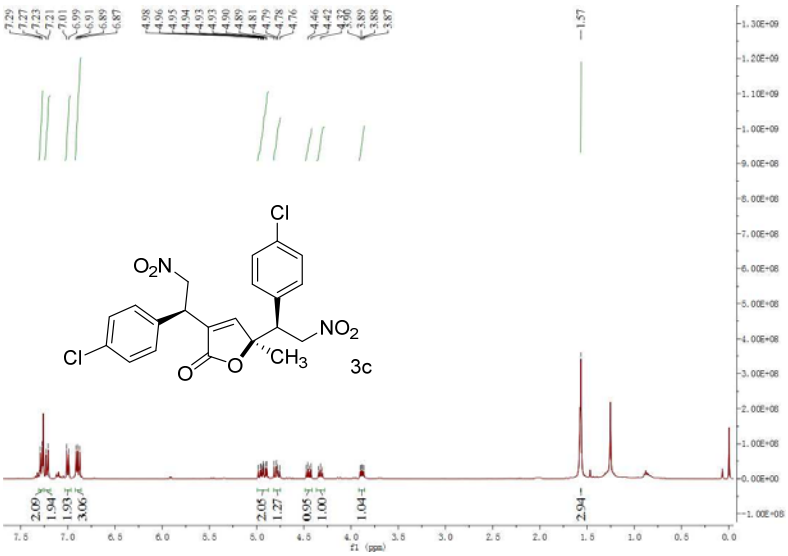
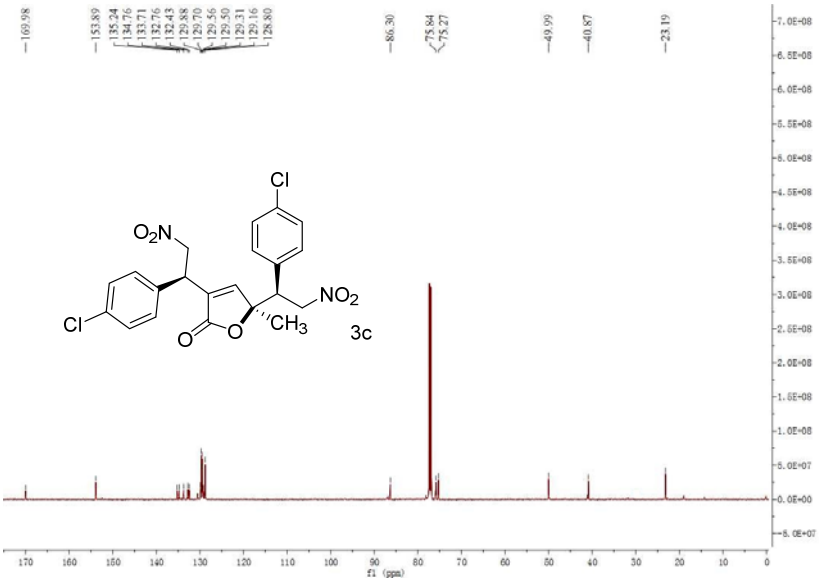
541.93
526.41
514.48
477.56

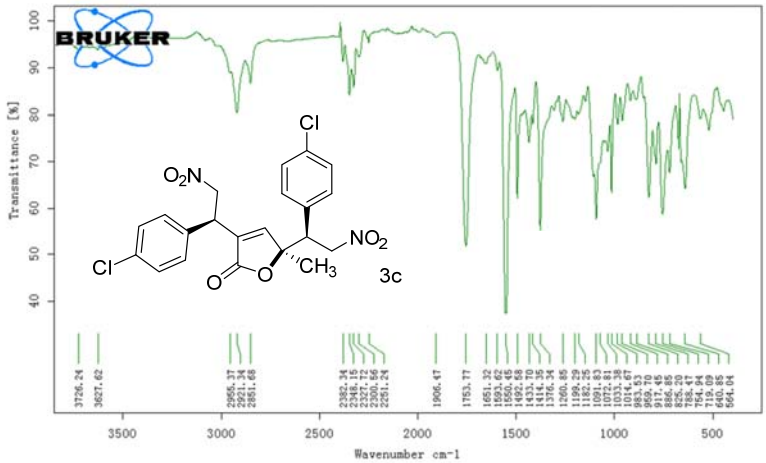

O2N
NO2
CH3
O
O
3b
f1 (ppm)

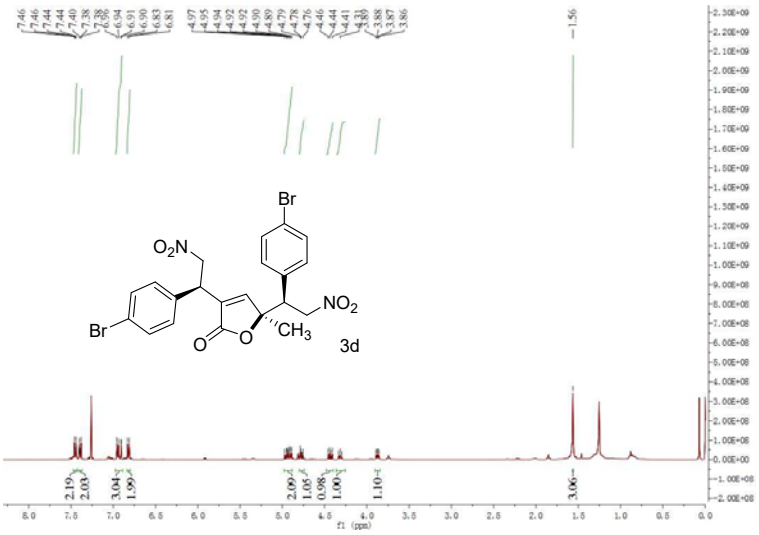

O2N
NO2
CH3
O
O
3b
f1 (ppm)

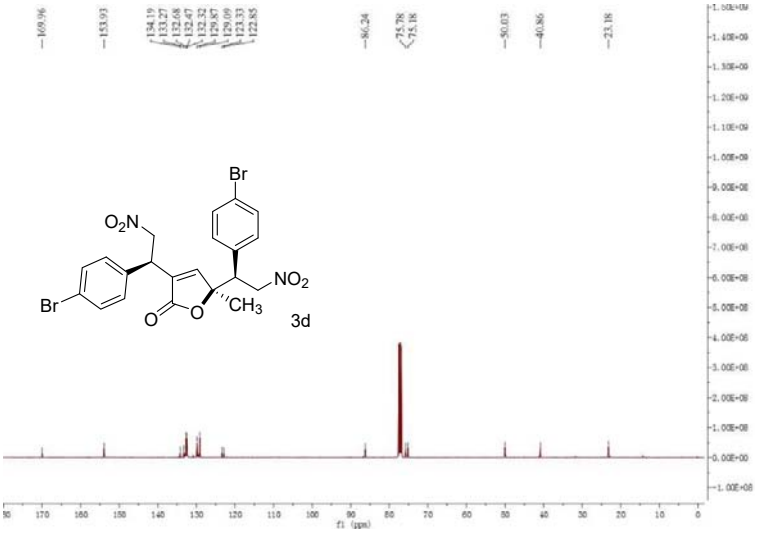

BRUKER
Transmittance [%]
O2N
NO2
CH3
O
O
3b
Wavenumber cm-1

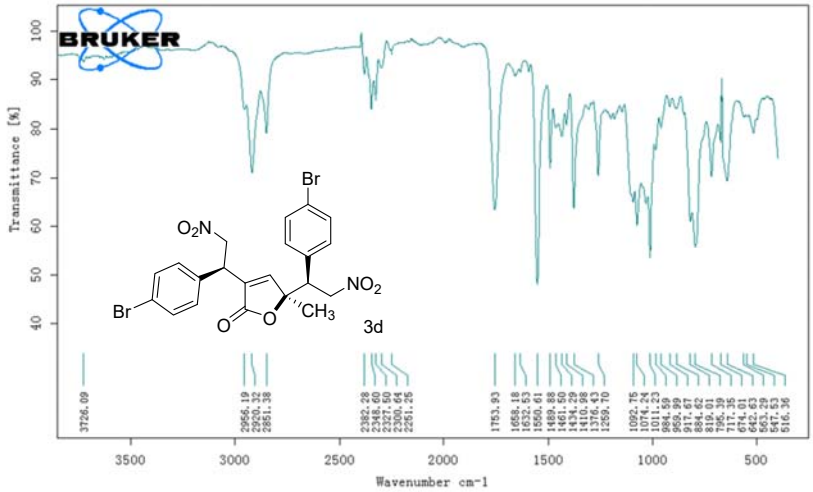

Cl
O2N
NO2
Cl
CH3
O
O
3c
f1 (ppm)

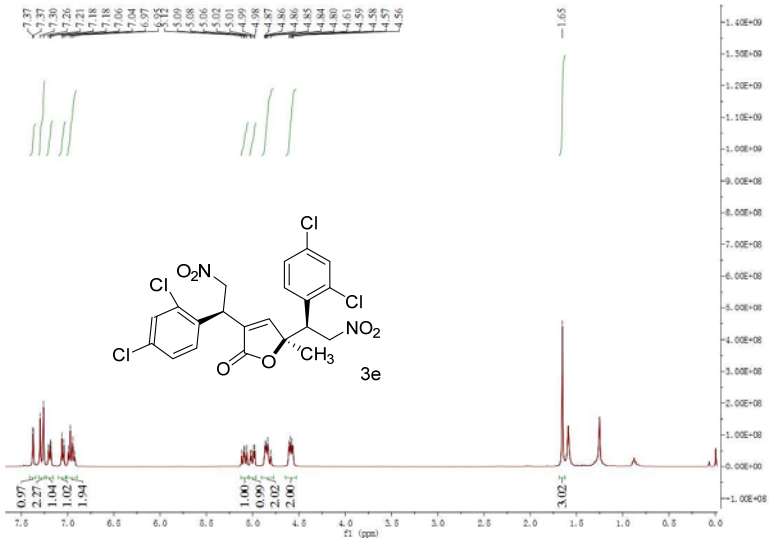

Cl
O2N
NO2
Cl
CH3
O
O
3c
f1 (ppm)

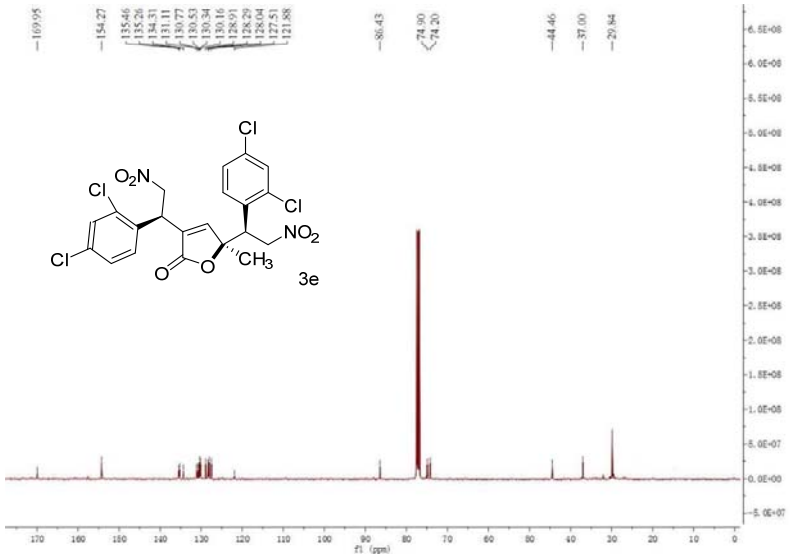

BRUKER
Transmittance [%]
Cl
O2N
NO2
Cl
CH3
O
O
3c
Wavenumber cm-1

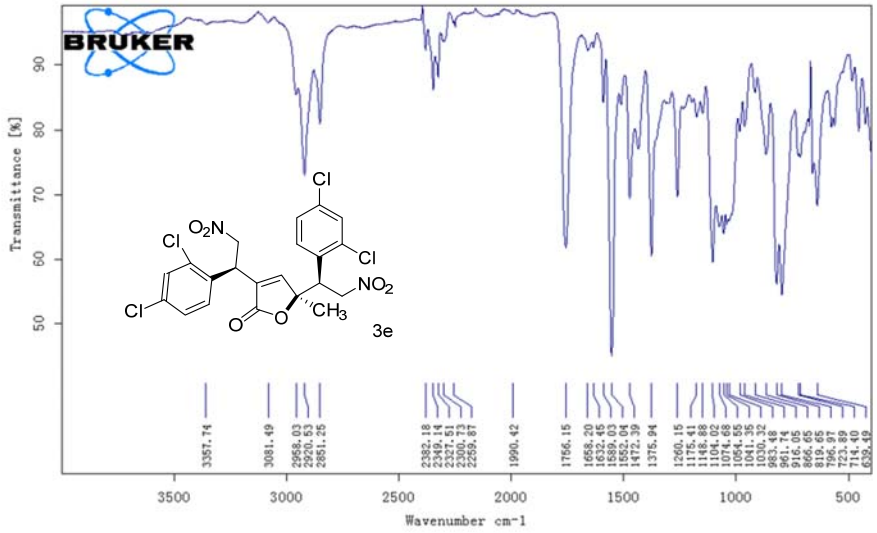

Br
O_2N
NO_2
Br
CH_3
O
O
3d

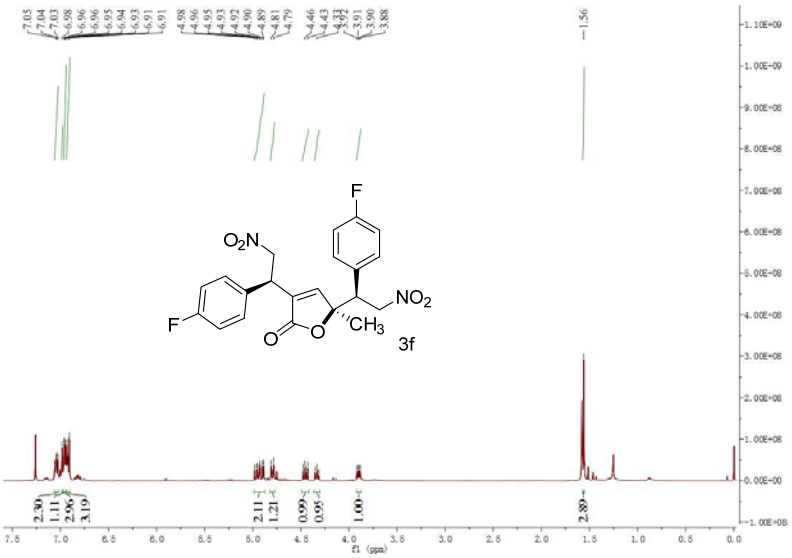

Br
O_2N
NO_2
Br
CH_3
O
O
3d

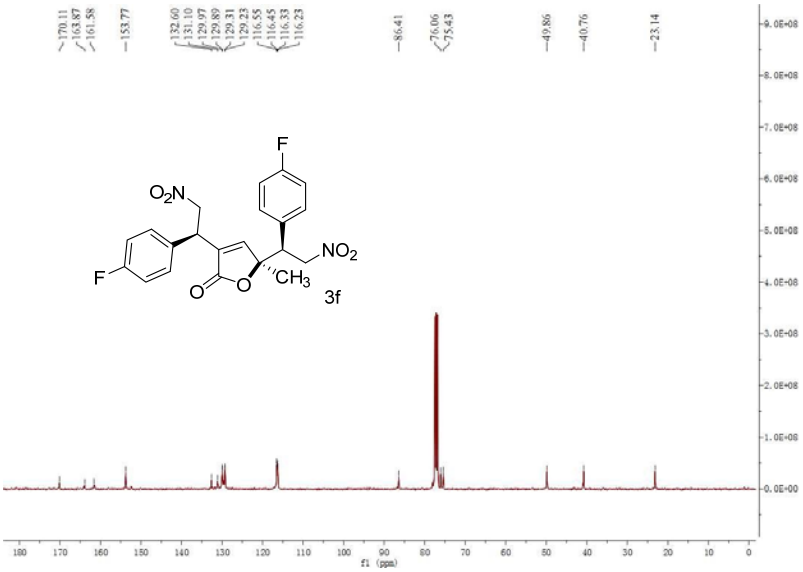

BRUKER
Transmittance [%]
Wavenumber cm-1
Br
O_2N
NO_2
Br
CH_3
O
O
3d

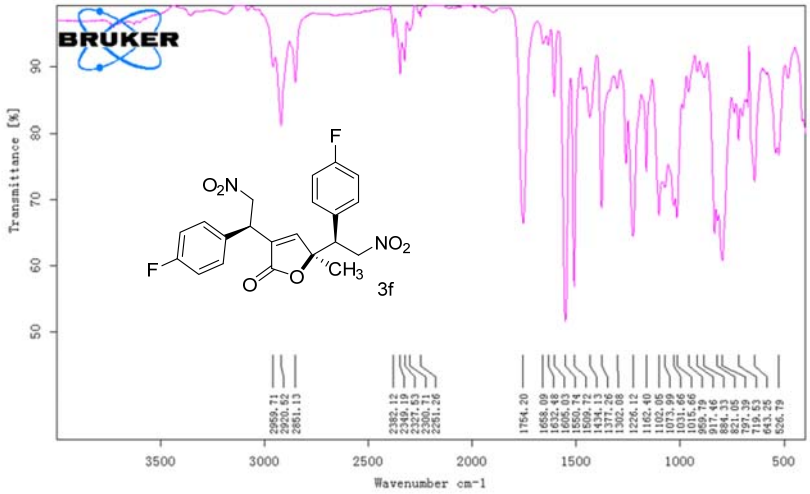

3e

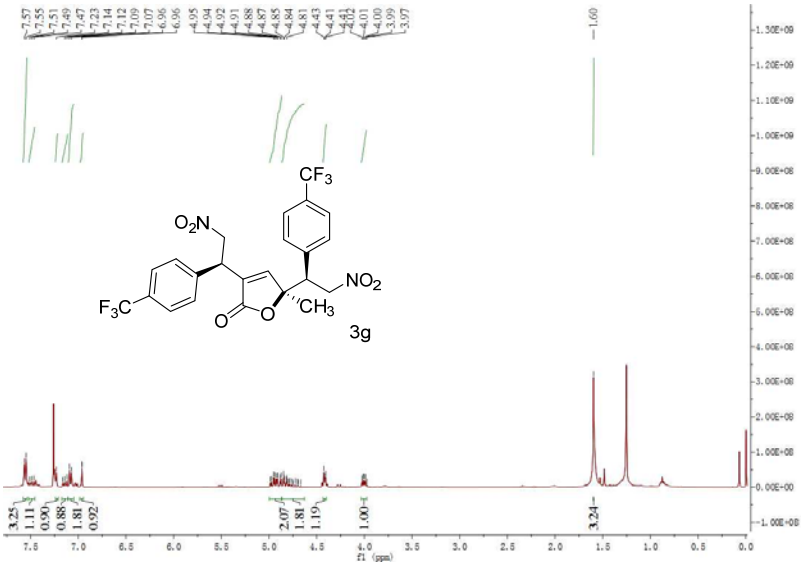

3e

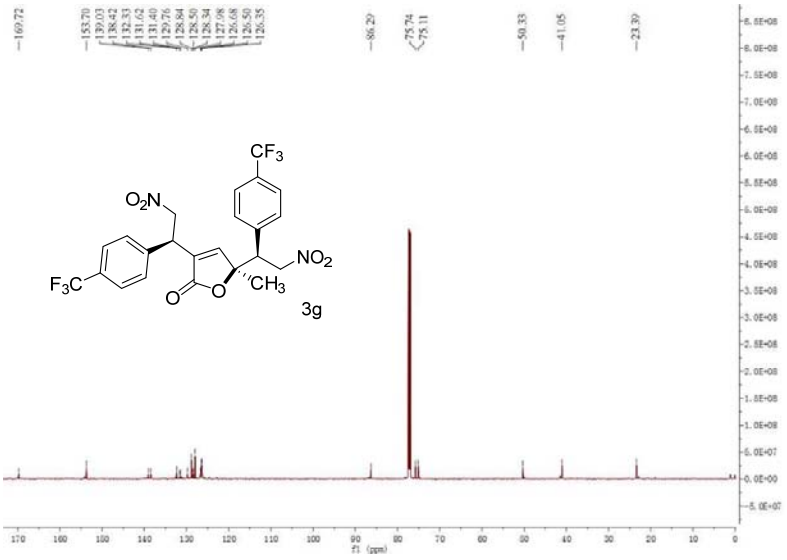

BRUKER
Transmittance [%]
Wavenumber cm-1
3e

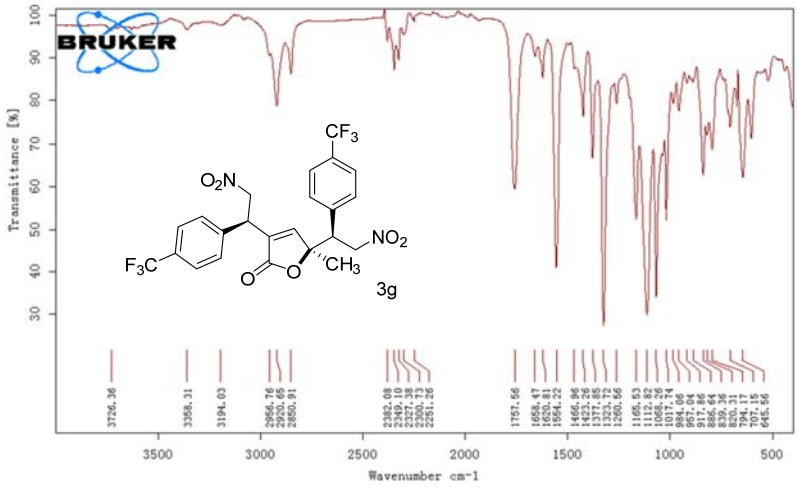

F
O2N
NO2
F
CH3
O
O
3f

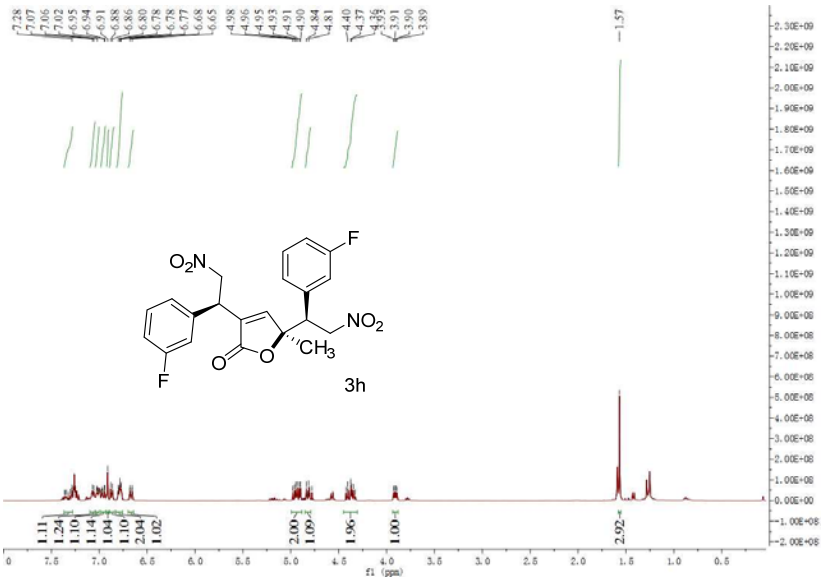

F
O2N
NO2
F
CH3
O
O
3f

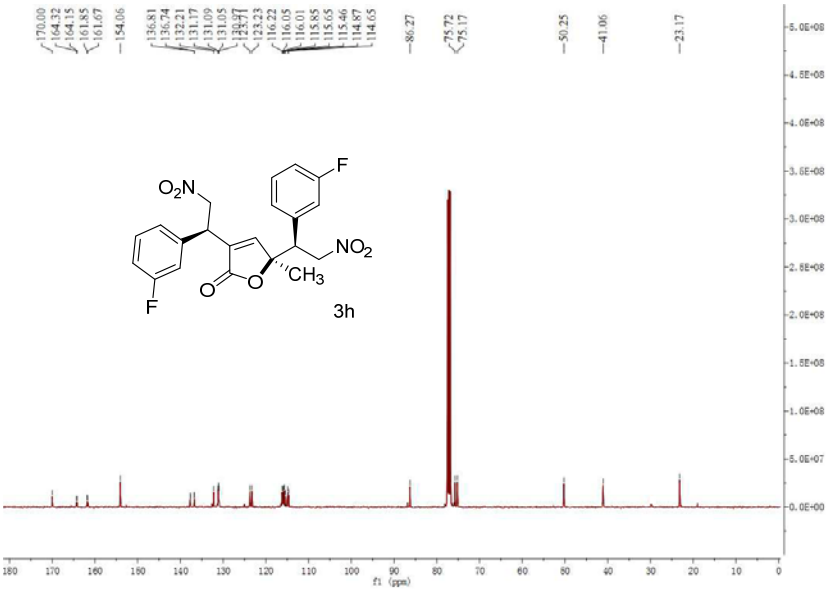

BRUKER
Transmittance [%]
Wavenumber cm-1
F
O2N
NO2
F
CH3
O
O
3f

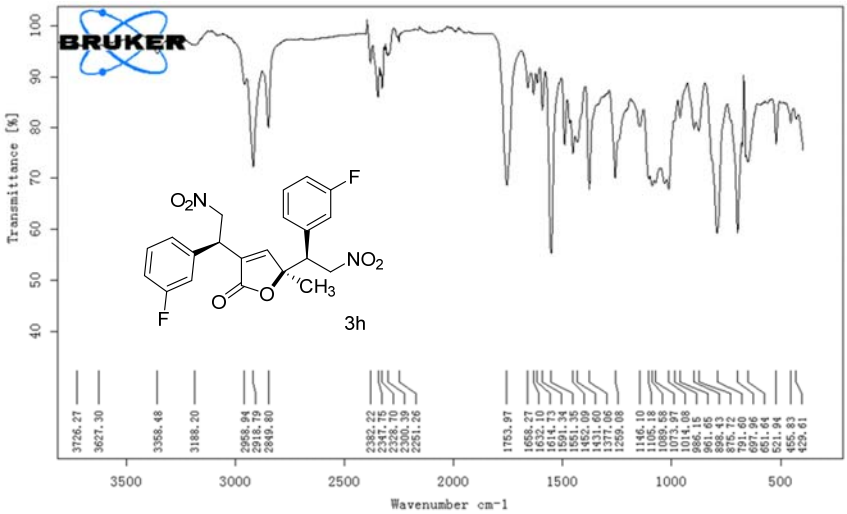

CF3
O2N
NO2
F3C
O
O
CH3
3g

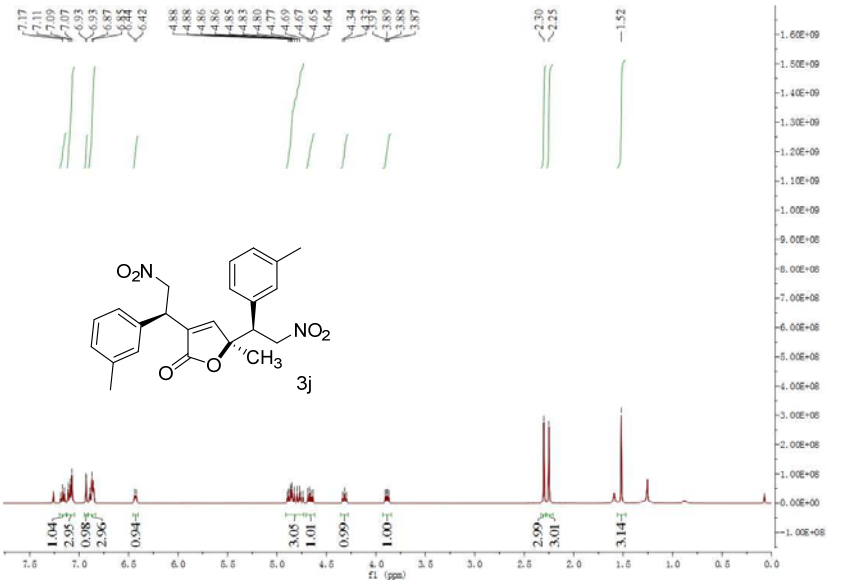

CF3
O2N
NO2
F3C
O
O
CH3
3g

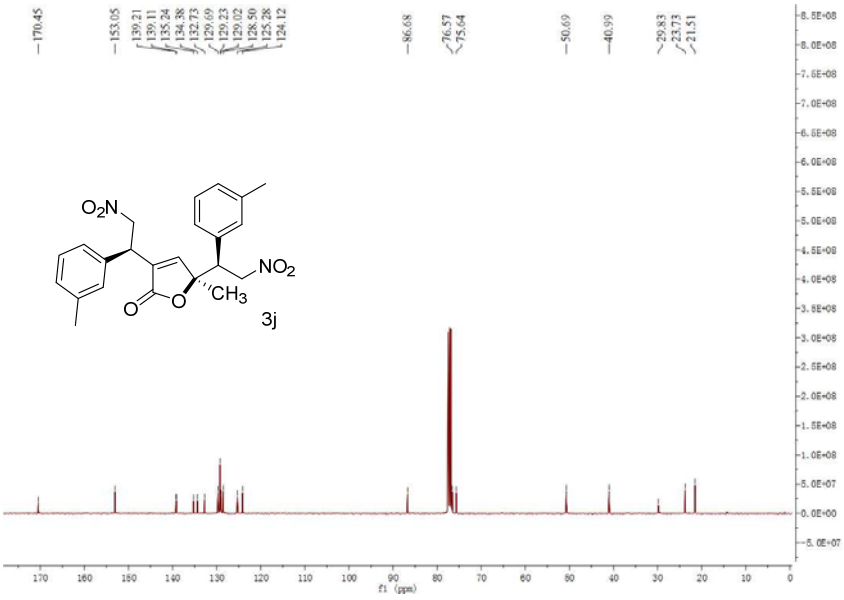

BRUKER
Transmittance [%]
CF3
O2N
NO2
F3C
O
O
CH3
3g
Wavenumber cm-1

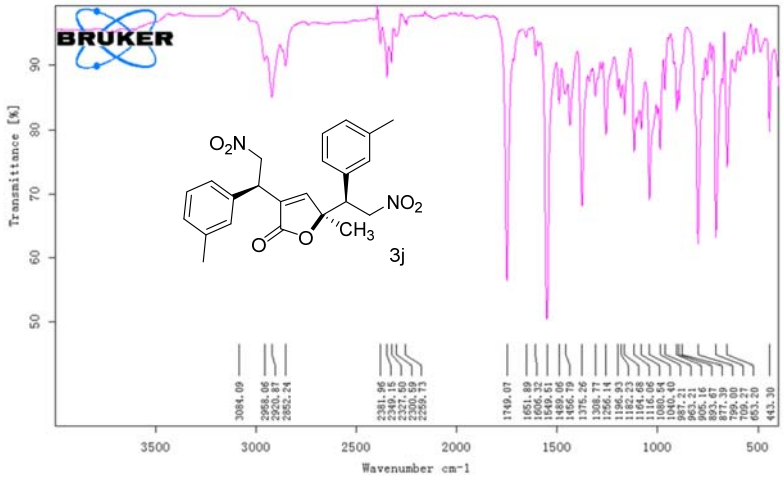

3h

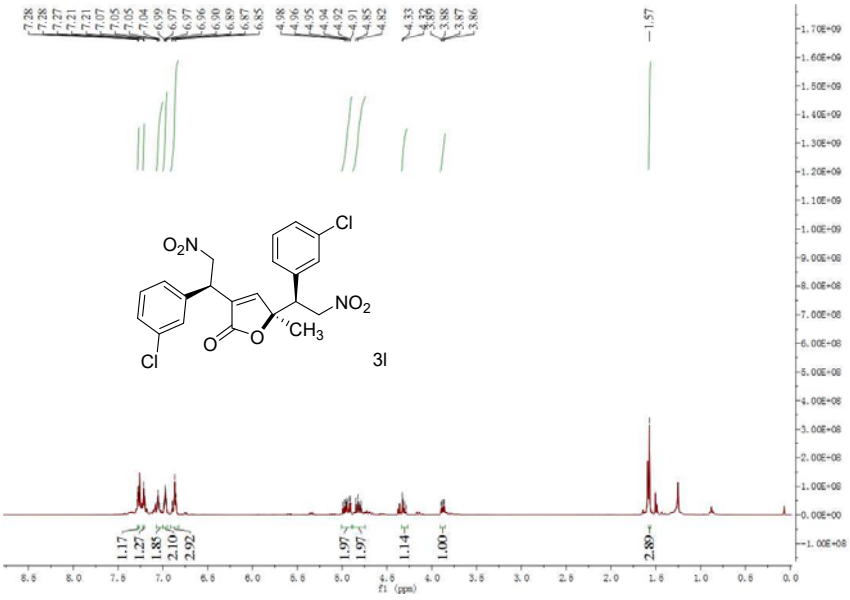

3h

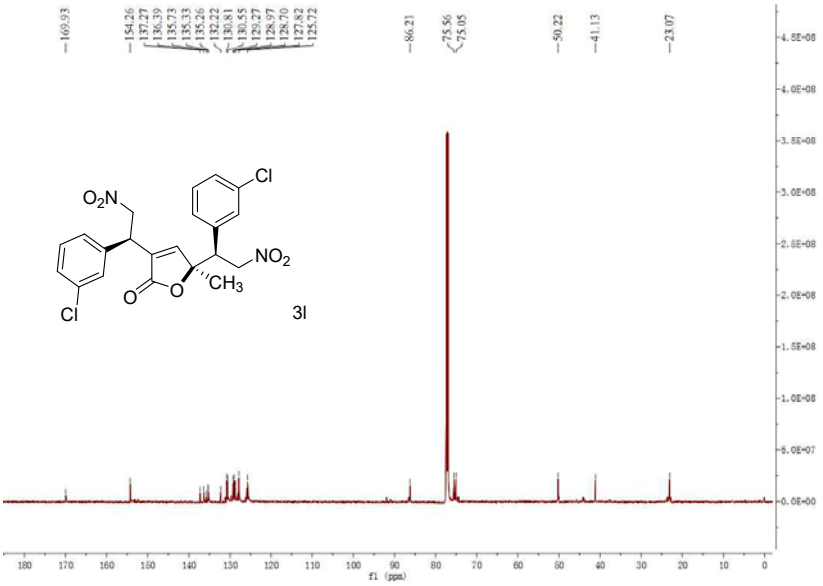

BRUKER
Transmittance [%]
Wavenumber cm-1
3h

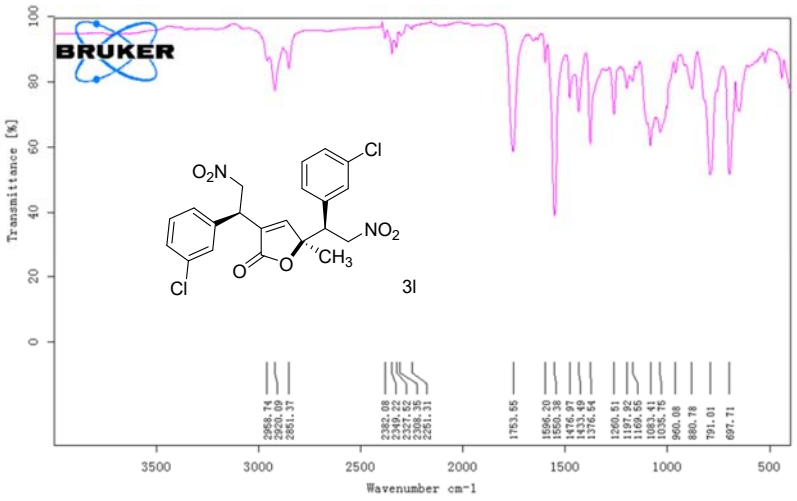

O_2N
NO_2
CH_3
O
O
3j
f1 (ppm)


O_2N
NO_2
CH_3
O
O
3j
f1 (ppm)

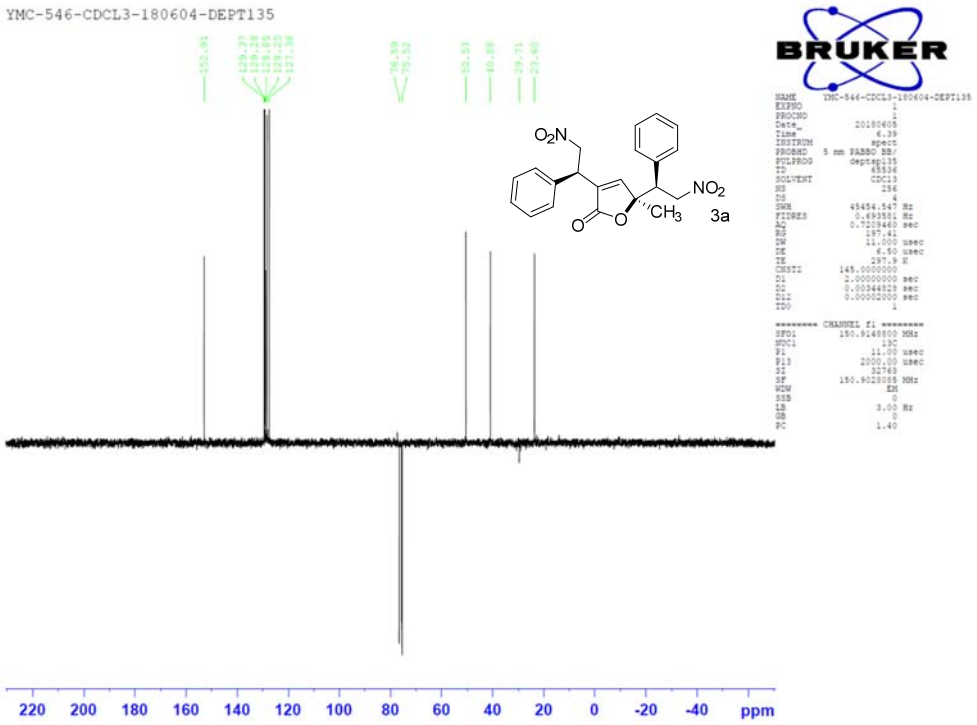

BRUKER
O_2N
NO_2
CH_3
O
O
3j
Transmittance [%]
Wavenumber cm-1


O2N
Cl
NO2
CH3
O
O
Cl
3l

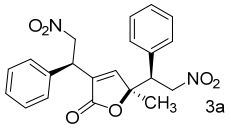

O2N
Cl
NO2
CH3
O
O
Cl
3l

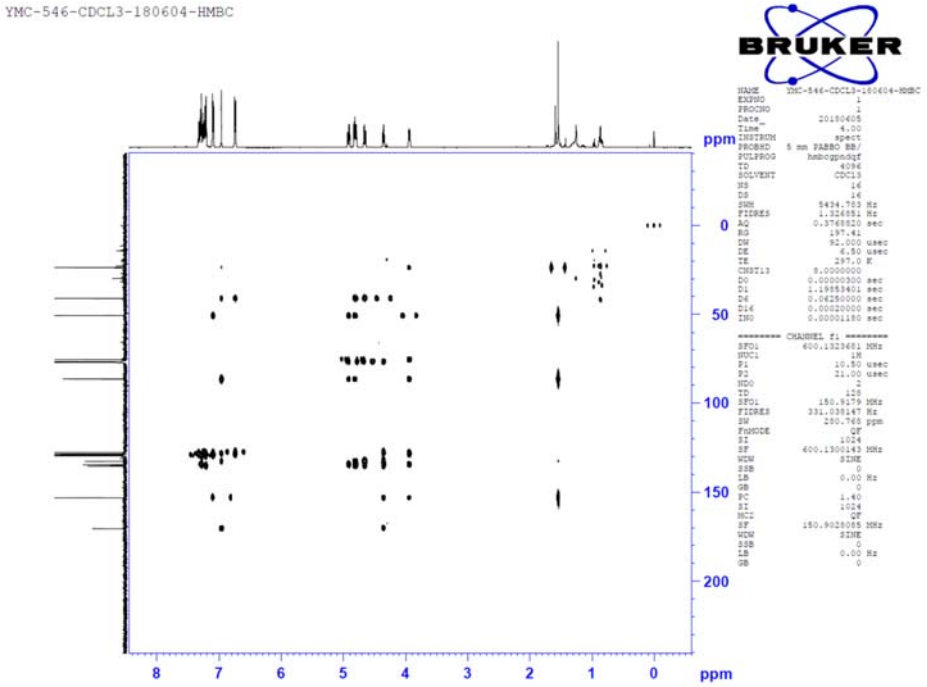

BRUKER
Transmittance [%]
Wavenumber cm-1
O2N
Cl
NO2
CH3
O
O
Cl
3l

135-DEPTNMR spectrum of 3a

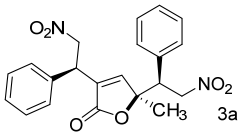


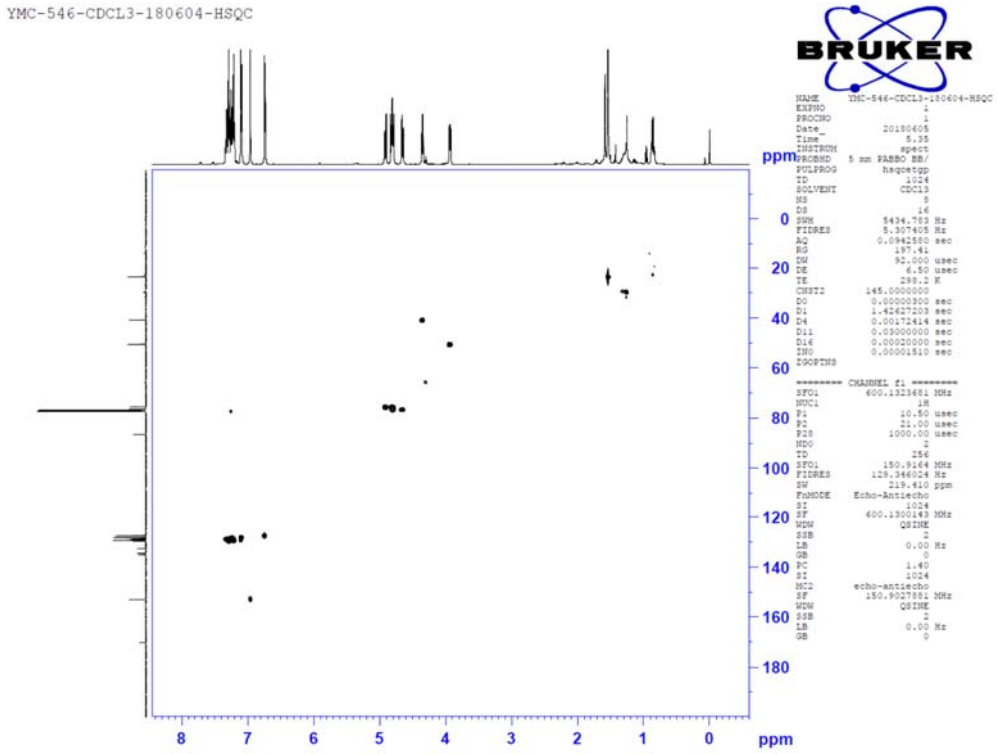
HMBC spectrum of 3a



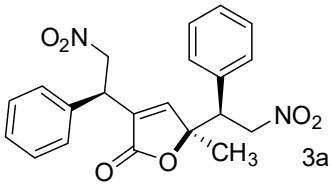


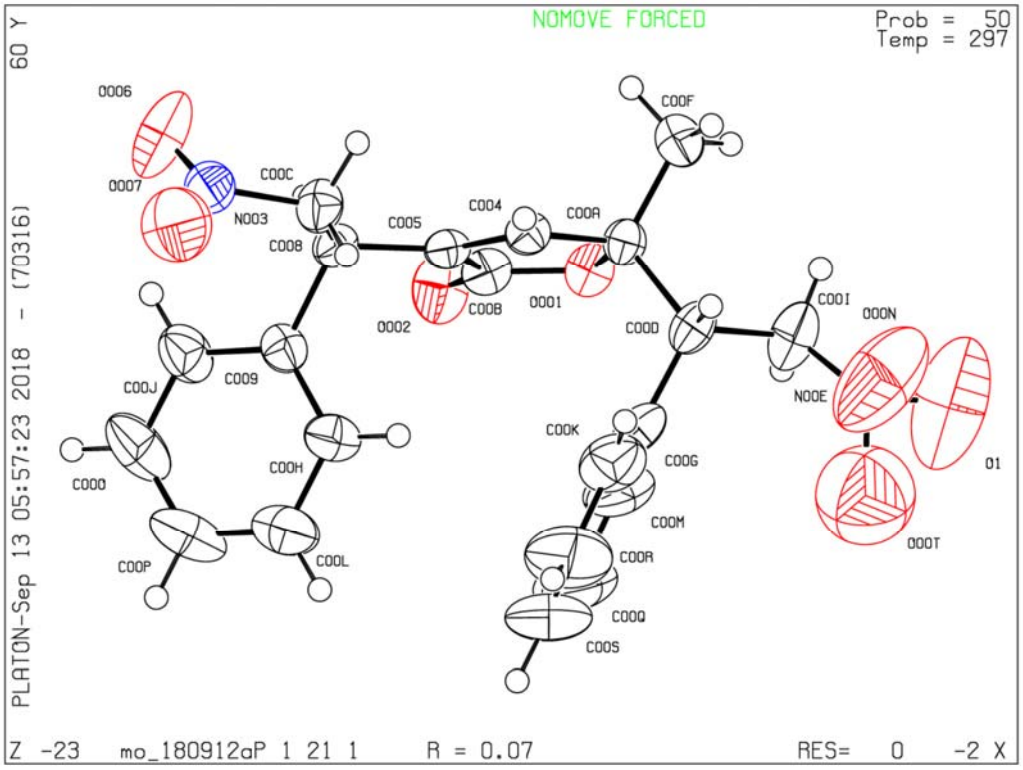
HSQC spectrum of 3a





Crystallographic data for 3a





checkCIF/PLATON report

You have not supplied any structure factors. As a result the full set of tests cannot be run.

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: mo_180912a_0m

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Bond precision:  C-C = 0.0090 A          Wavelength=0.71073

Cell:            a=6.5334(7)     b=16.5353(19)      c=9.6045(11)
                 alpha=90        beta=99.396(4)     gamma=90
Temperature:     297 K

                 Calculated                Reported
Volume           1023.7(2)                 1023.7(2)
Space group      P 21                      P 1 21 1
Hall group       P 2yb                     P 2yb
Moiety formula   C21 H20 N2 O7             0.5(C21 H20 N2 O7)
Sum formula      C21 H20 N2 O7             C10.50 H10 N O3.50
Mr               412.39                    206.19
Dx,g cm-3        1.338                     1.338
Z                2                         4
Mu (mm-1)        0.102                     0.102
F000             432.0                     432.0
F000'            432.25
h,k,lmax         7,19,11                   7,19,11
Nref             3614[ 1875]               3446
Tmin,Tmax                                  0.674,0.747
Tmin'

Correction method= # Reported T Limits: Tmin=0.674 Tmax=0.747
AbsCorr = MULTI-SCAN

Data completeness= 1.84/0.95       Theta(max)= 25.000

R(reflections)= 0.0663( 3325)      wR2(reflections)= 0.1842( 3446)

S = 1.071                  Npar= 272
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level B

```
PLAT035_ALERT_1_B _chemical_absolute_configuration Info  Not Given     Please Do !
PLAT230_ALERT_2_B Hirshfeld Test Diff for   O1       --O00T      .       8.0 s.u.
PLAT230_ALERT_2_B Hirshfeld Test Diff for   O00T     --N00E      .      15.2 s.u.
PLAT242_ALERT_2_B Low    'MainMol' Ueq as Compared to Neighbors of      N00E Check
```

Alert level C

```
STRVA01_ALERT_4_C           Flack test results are ambiguous.
          From the CIF: _refine_ls_abs_structure_Flack    0.600
          From the CIF: _refine_ls_abs_structure_Flack_su    0.300
PLAT029_ALERT_3_C _diffrn_measured_fraction_theta_full value Low .      0.975 Why?
PLAT053_ALERT_1_C Minimum Crystal Dimension Missing (or Error) ...     Please Check
PLAT054_ALERT_1_C Medium  Crystal Dimension Missing (or Error) ...     Please Check
PLAT055_ALERT_1_C Maximum Crystal Dimension Missing (or Error) ...     Please Check
PLAT089_ALERT_3_C Poor Data / Parameter Ratio (Zmax < 18) ........      6.89 Note
PLAT220_ALERT_2_C Non-Solvent  Resd 1  C   Ueq(max)/Ueq(min) Range      3.7 Ratio
PLAT220_ALERT_2_C Non-Solvent  Resd 1  O   Ueq(max)/Ueq(min) Range      5.0 Ratio
PLAT234_ALERT_4_C Large Hirshfeld Difference O1       --N00E           0.23 Ang.
PLAT234_ALERT_4_C Large Hirshfeld Difference C00R     --C00S           0.16 Ang.
PLAT241_ALERT_2_C High   'MainMol' Ueq as Compared to Neighbors of      C00S Check
PLAT242_ALERT_2_C Low    'MainMol' Ueq as Compared to Neighbors of      N003 Check
PLAT340_ALERT_3_C Low Bond Precision on  C-C Bonds ...............   0.00895 Ang.
PLAT907_ALERT_2_C Flack x > 0.5, Structure Needs to be Inverted? .      0.60 Check
```

Alert level G

```
PLAT003_ALERT_2_G Number of Uiso or Uij Restrained non-H Atoms ...        1 Report
PLAT032_ALERT_4_G Std. Uncertainty on Flack Parameter Value High .    0.300 Report
PLAT042_ALERT_1_G Calc. and Reported MoietyFormula Strings  Differ    Please Check
PLAT045_ALERT_1_G Calculated and Reported Z Differ by a Factor ...     0.50 Check
PLAT072_ALERT_2_G SHELXL First  Parameter in WGHT  Unusually Large     0.11 Report
PLAT186_ALERT_4_G The CIF-Embedded .res File Contains ISOR Records        1 Report
PLAT398_ALERT_2_G Deviating  C-O-C    Angle From 120 for O001         109.7 Degree
PLAT720_ALERT_4_G Number of Unusual/Non-Standard Labels .........       49 Note
PLAT789_ALERT_4_G Atoms with Negative _atom_site_disorder_group  #      1 Check
PLAT791_ALERT_4_G Model has Chirality at C008        (Chiral SPGR)      R Verify
PLAT791_ALERT_4_G Model has Chirality at C00A        (Chiral SPGR)      S Verify
PLAT791_ALERT_4_G Model has Chirality at C00D        (Chiral SPGR)      S Verify
PLAT860_ALERT_3_G Number of Least-Squares Restraints ............      7 Note
```

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  0 ALERT level A = Most likely a serious problem - resolve or explain
  4 ALERT level B = A potentially serious problem, consider carefully
 14 ALERT level C = Check. Ensure it is not caused by an omission or oversight
 13 ALERT level G = General information/check it is not something unexpected

  6 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
 11 ALERT type 2 Indicator that the structure model may be wrong or deficient
  4 ALERT type 3 Indicator that the structure quality may be low
 10 ALERT type 4 Improvement, methodology, query or suggestion
  0 ALERT type 5 Informative message, check
```

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

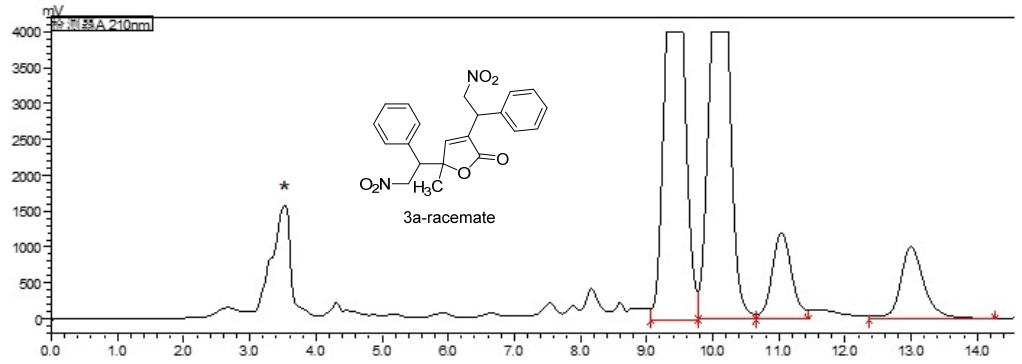
A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E* or *IUCrData*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 20/08/2018; check.def file version of 20/08/2018

Copies of HPLC profiles of Michael addition products (impurities associated to the solvent were indicated by *).



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3	11.039	25283537	1208183	9.900
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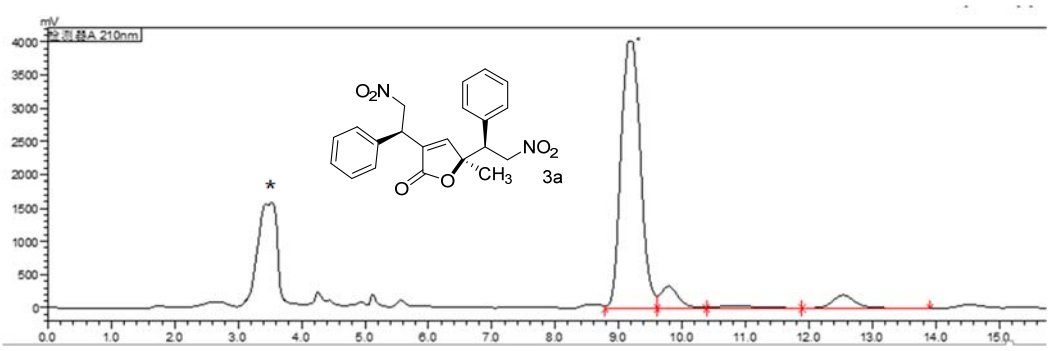

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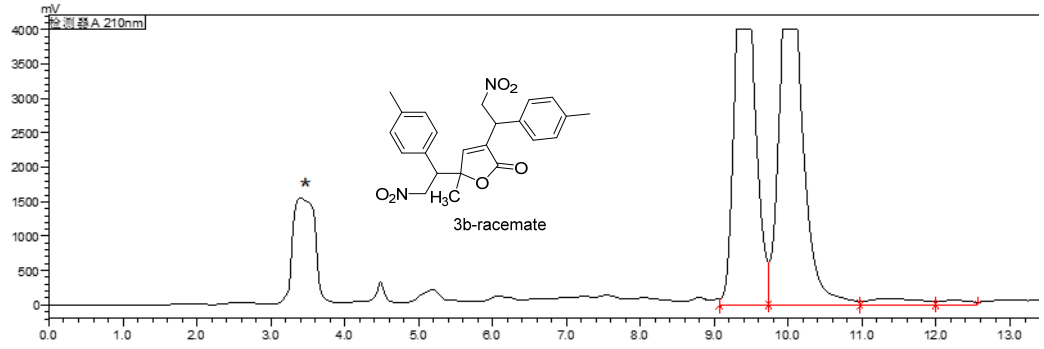

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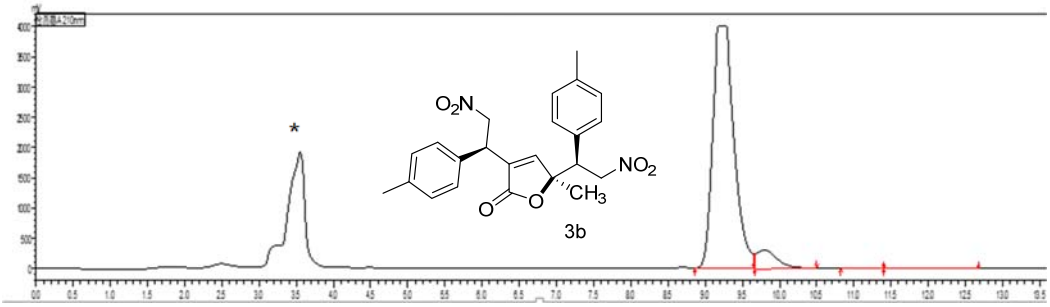

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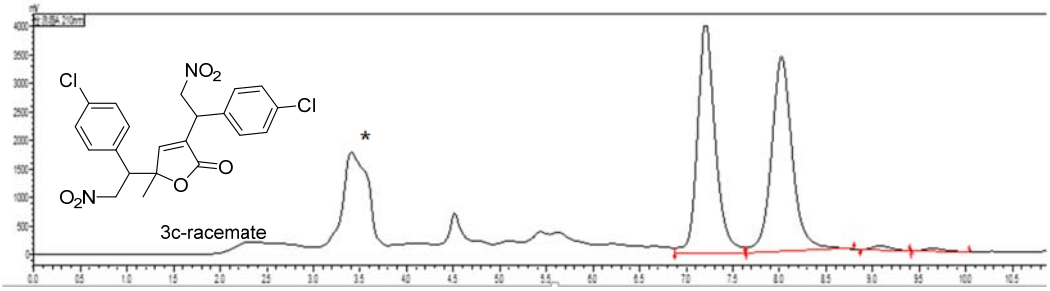

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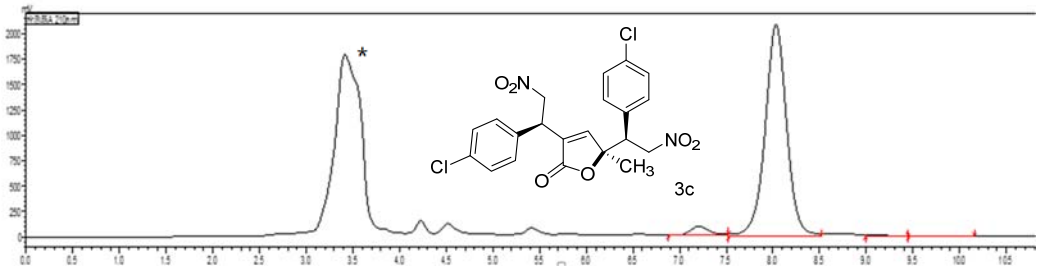

NO.	Time	Area	Height	Area%
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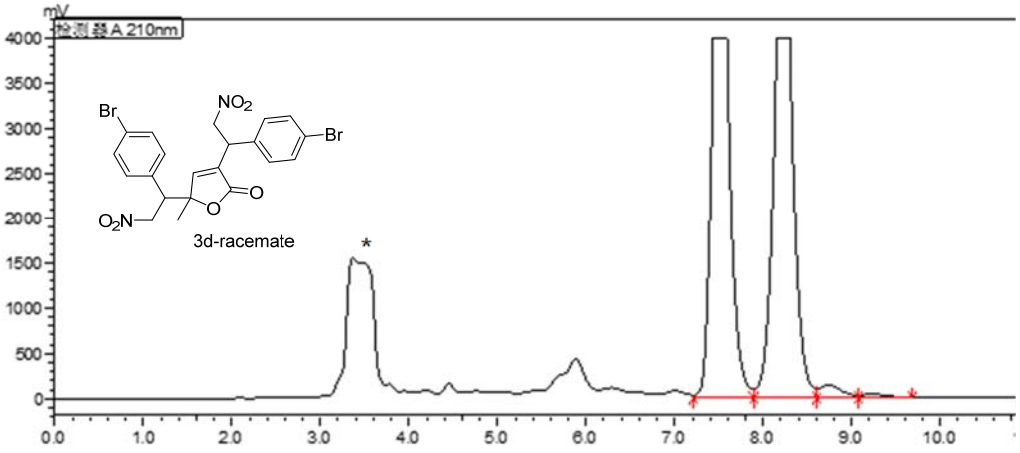

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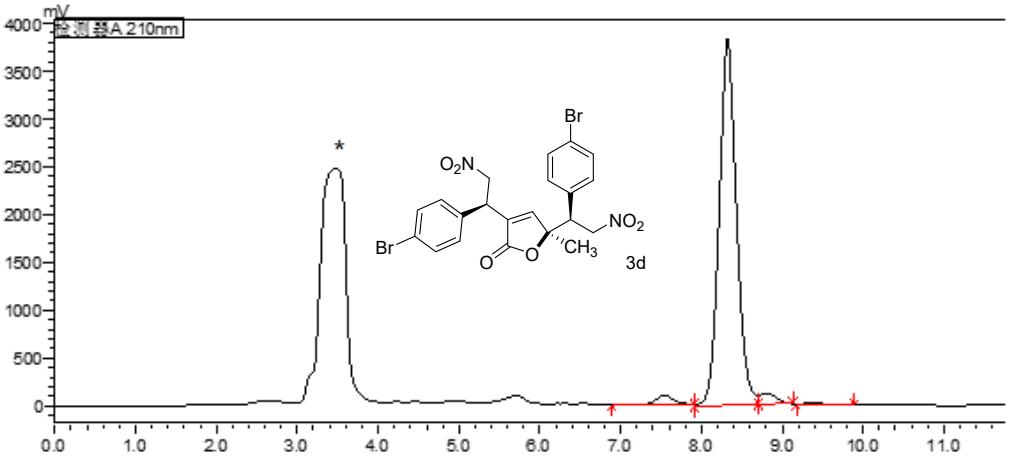

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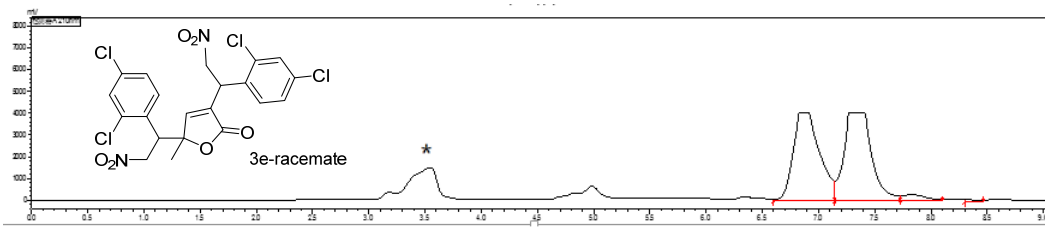

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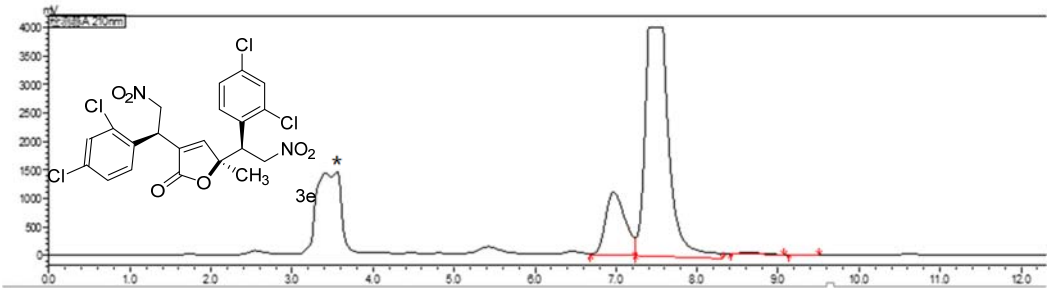

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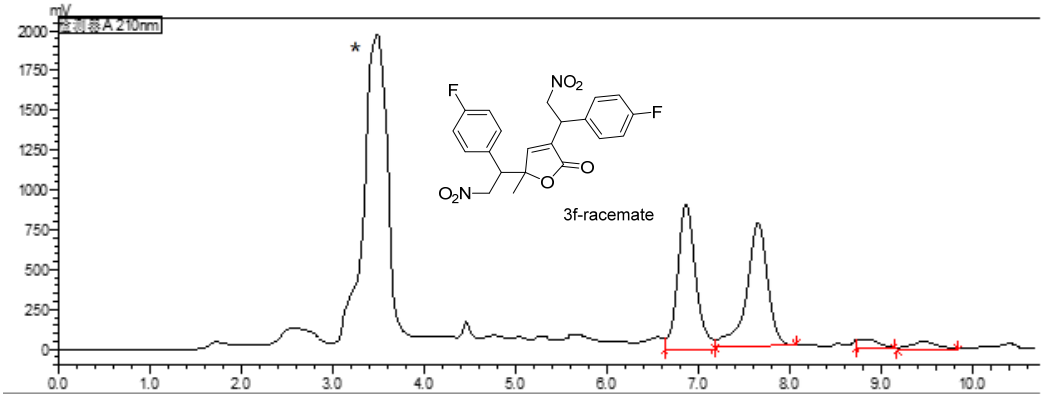

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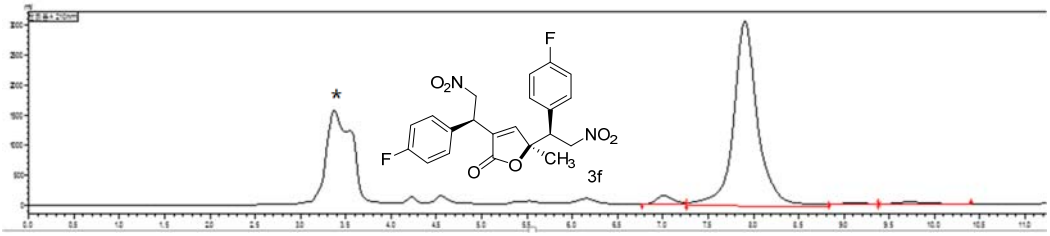

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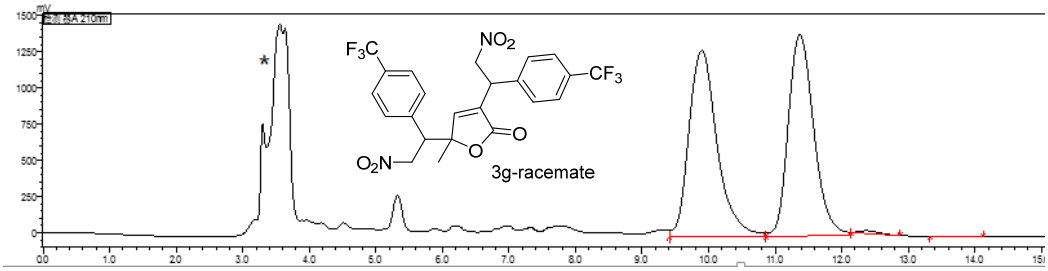

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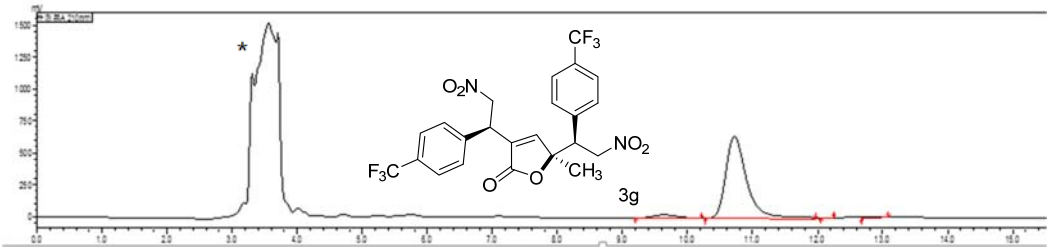

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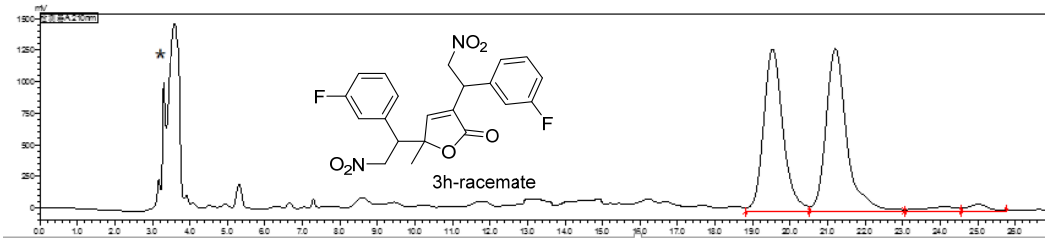

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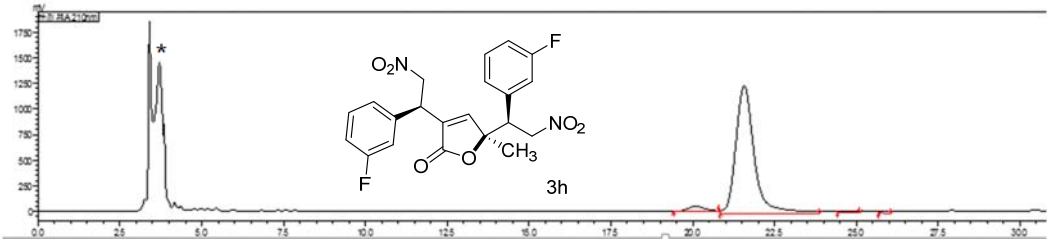

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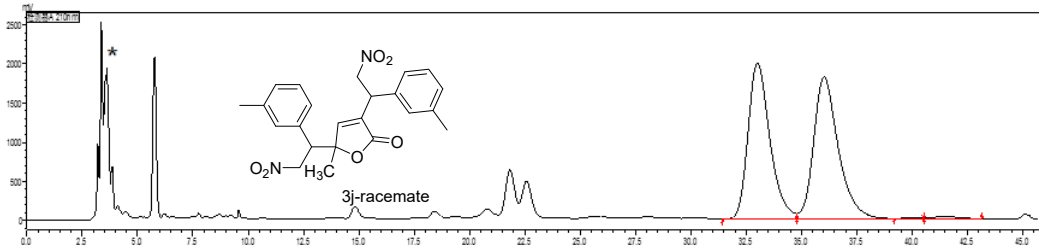

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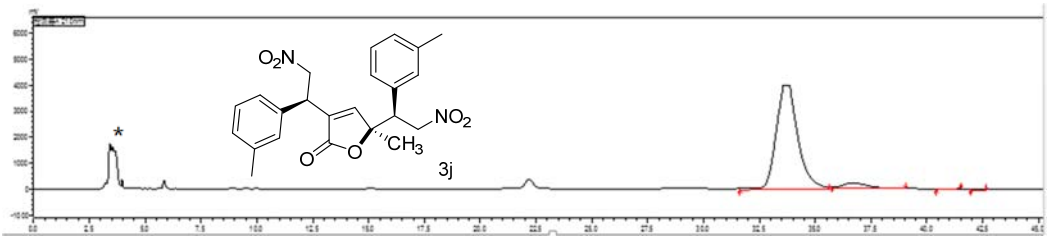

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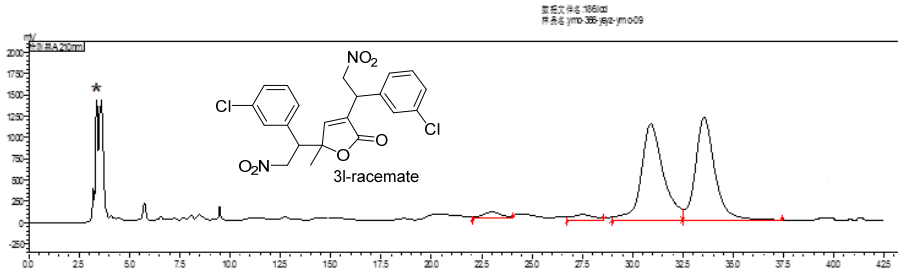

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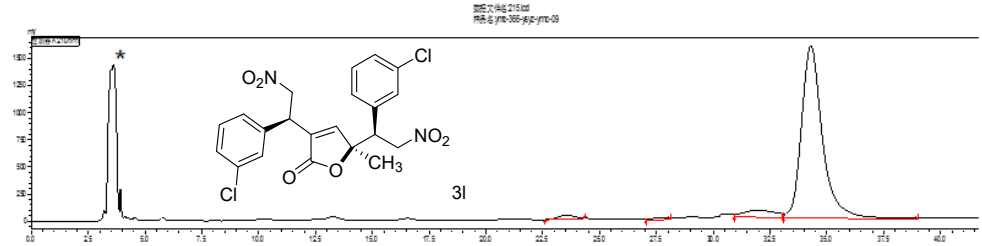

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